DISSERTATION

OXIDATION OF UNFUNCTIONALIZED OLEFINS INVOLVING THREE-MEMBERED HETEROCYCLES AND ITS RELATED APPLICATIONS

Submitted by

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Department of Chemistry

In partial fulfillment of the requirements

For the Degree of Doctor of Philosophy

Colorado State University

Fort Collins, Colorado

Fall 2008

COLORADO STATE UNIVERSITY

September 29, 2008

WE HEREBY RECOMMEND THAT THE DISSERTATION PREPARED UNDER OUR SUPERVISION BY BIN WANG ENTITILED OXIDATION OF UNFUNCTIONALIZED OLEFINS INVOLVING THREE-MEMBERED HETEROCYCLES AND IT'S RELATED APPLICATIONS BE ACCEPTED AS FULFILLING IN PART REQUIREMENTS OF THE DEGREE OF DOCTOR OF PHILOSOPHY.

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ABSTRACT OF DISSERTATION

OXIDATION OF UNFUNCTIONALIZED OLEFINS INVOLVING THREE-MEMBERED HETEROCYCLES AND ITS RELATED APPLICATIONS

Typically three-membered heterocycles are highly strained molecules. They can exist as stable functional groups or very reactive intermediates. This dissertation discusses three types of three-membered heterocycles including dioxiranes, epoxides, and diaziridines.

Dioxirane, a three-membered ring peroxide, is a very powerful oxidant which transfers an oxygen atom to a variety of functional groups including heteroatoms, π-bonds, X-H σ-bonds (X = C or Si), and organometallic compounds. Our group has been interested in the asymmetric epoxidation of unfuctionalized olefins using chiral dioxiranes generated from chiral ketones and Oxone. Asymmetric epoxidation produces chiral epoxides, a very useful three-membered heterocycle, which can be opened and rearranged to form more complex chiral molecules.

A glucose-derived ketone with an oxazolidinone moiety has been employed in asymmetric epoxidation of conjugated tri- and tetrasubstituted olefins. The asymmetric epoxidation and subsequent epoxide rearrangement produced the enantioenriched aryl-substituted epoxides, cyclopentanones, cyclobutanones, and γ-butyrolactones in good yields and enantioselectivities. In addition to the above chiral products, chiral allylic alcohols can also be produced via asymmetric epoxidation catalyzed by fructose-derived ketone and base-mediated epoxide isomerization in good yields, high enantioselectivities, and high stereoselectivities. It was proposed that the isomerization of acyclic silyl epoxides to give the (*Z*)-allylic alcohols proceeds through an unusual silicon-assisted E1cb mechanism based on deuterium-labeling experiments and other observations.

A practical synthesis of a diacetate chiral ketone was developed. The application of this diacetate ketone in asymmetric epoxidation of *trans*– and trisubstituted olefins, as well as its related mechanism, are discussed. A ketone with two oxazolidinone rings proved to be a robust catalyst for asymmetric epoxidation. The catalyst loading can be reduced to 1 mol %, and high enantioselectivities can still be achieved.

A glucose-derived ketone with a lactam ring has been employed in the epoxidation of 1,1-disubstituted olefins with good enantioselectivities. Studies indicated that the epoxidation of 1,1-disubstituted olefins with the lactam ketone proceeds mainly via a planar-like transition state. The α, α-dimethyl substituted lactam ketone shows different reactivity from those without substitutions. It is an effective catalyst for asymmetric epoxidation of *trans*– and trisubstituted olefins.

A study on the structural effect of ketone catalysts on asymmetric epoxidation revealed that the nitrogen atom in the spiro ring of the oxazolidinone-containing ketone is an important structural element in asymmetric epoxidation of *cis*-olefins.

N,N'-di-*t*-butylthiadiaziridine 1,1-dioxide, a nitrogen analogue of dioxiranes, was explored as a nitrogen source for Pd-catalyzed dehydrogenative diamination of unfunctionalized olefin. The diamination is likely to proceed via Pd-catalyzed allylic amination and subsequent cyclization. This diamination is mechanistically distinct from the previously studied process using di-*t*-butyldiaziridinone as nitrogen source, thus resulting in different regioselectivity.

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ACKNOWLEDGEMENTS

I would first like to thank my advisor, Dr. Yian Shi, for his guidance and support. I need to thank the past and present members of Shi groups for their helps in many ways, especially the coworkers in each project including O. Andrea Wong, Dr. Haifeng Du, Dr. Meixing Zhao, Dr. Yumei Shen, Dr. Xinyan Wu, Brian Nettles, Dr. Dajun Chen, Dr. Lianhe Shu, Dr. Yong Tang, and Dr. Jiaxi Xu.

TABLE OF CONTENTS

CHAPTER 1.0 : THREE-MEMBERED RING PEROXIDES

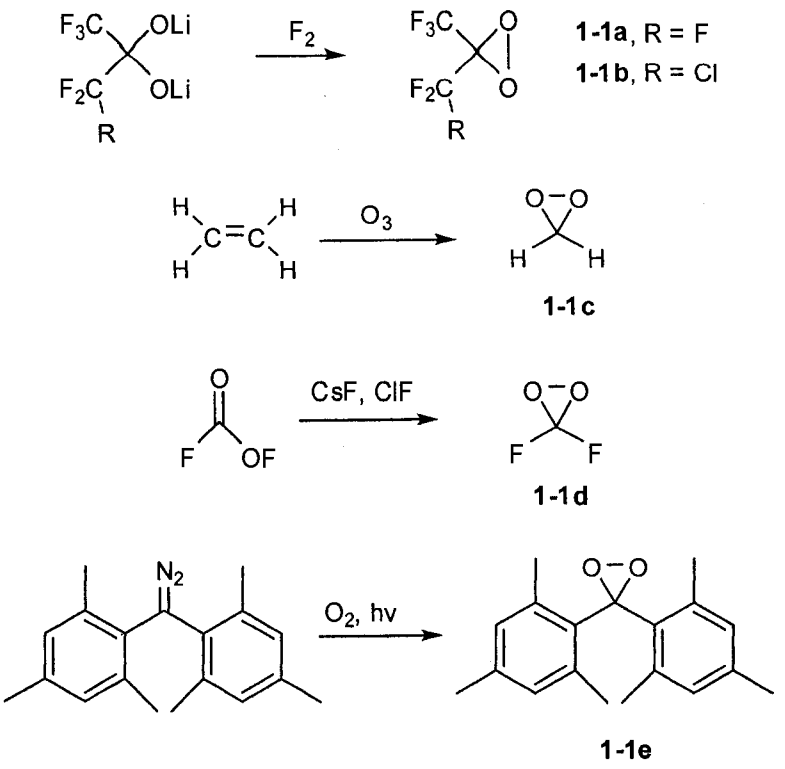
1.1 GENERAL INTRODUCTION

Three-membered ring peroxides are heterocycles consisting of two oxygens and one other atom besides oxygen. They include dioxirane and heteroatom-containing dioxiranes[1]. This review will only focus on synthetic chemistry of dioxirane, a class of highly-strained three-membered ring organic peroxides containing a carbon and two oxygen atoms. In 1899, Baeyer and Villiger suggested that the dioxirane might be an intermediate when menthone was oxidized to its corresponding lactone by $KHSO_5$.[2] Since then, dioxiranes have been proposed or shown to be involved in a number of chemical processes. During the last two or three decades, dioxiranes have been demonstrated to be very powerful and remarkably versatile oxidants which transfer oxygen atoms to a variety of functional groups including heteroatoms, π-bonds, X-H σ-bonds (X = C or Si), and organometallic compounds. Numerous excellent reviews on the chemistry of dioxiranes have appeared that are complementary to this contribution in subject and scope.[3-19]

SAFETY: Dioxiranes are peroxides and should be treated with all safety precautions.

1.2 PREPARATION OF DIOXIRANES

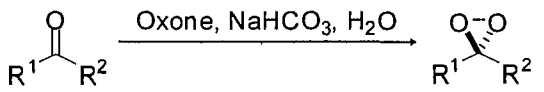
In 1972, the generation of two fluoro-substituted dioxiranes **1-1a** and **1-1b** by the F_2 oxidation of the corresponding dialkoxides was reported (Scheme 1.1).[20] Since then, a number of dioxiranes, such as dioxirane **1-1c**,[21] difluorodioxirane **1-1d**[22] and dimesityldioxirane **1-1e**,[23,24] have been formed via ozonolysis of ethene at low temperature, reaction of ClF, CsF, and FCOOF, and oxidation of carbenes by molecular oxygen, respectively. The X-ray structure of **1-1e** was obtained. A more practical and widely utilized method for preparation of dioxiranes uses suitable ketones and potassium monoperoxysulfate (Oxone), a cheap industrial bulk chemical. Dioxiranes can be generated *in situ* by simply adding Oxone to a buffered ketone solution, and can be used directly while they are formed. Certain dioxiranes have been isolated by distillation at reduced pressure from buffered ketone-Oxone mixtures and characterized spectroscopically (Table 1.1, Entries 1-4).[25-28] The distillation method is more suitable for relatively volatile dioxiranes, and usually produces dioxiranes in low concentrations. If dioxiranes are not volatile or higher concentrations of dioxiranes are needed, a salting-out procedure can be used (Table 1.1, Entries 5-10).[29,30] The peroxide content of the dioxirane solutions can be assayed by reaction with triphenylphosphine[25] or phenyl methyl sulfide[26] to yield the corresponding oxide or by iodometry[14,26] and quantitative UV-visible spectrophotometry[14].

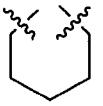
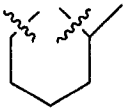
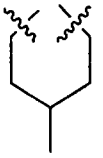
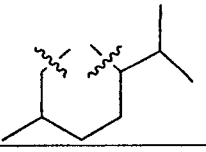


Scheme 1.1 Preparation of Dioxiranes[20-24]

Isolated dimethyldioxirane (DMDO)[34] and methyl(trifluoromethyl)dioxirane (TFDO)[35] are widely used for various electrophilic oxidation processes. TFDO is generally >1000 fold more reactive than DMDO[27], thus requiring significantly shortened reaction times. DMDO and TFDO are usually used as a solution in acetone and a solution in trifluoroacetone respectively. TFDO can also be prepared as a solution in inert solvents, such as CCl_4, DCM, or CCl_2FCCl_2F, by diluting the freshly prepared TFDO solution in trifluoroacetone with these inert solvents and washing with doubly distilled water at 0 °C to remove trifluoroacetone.[28]

Table 1.1 Preparation of Isolated Dioxiranes[25-29,31-33]



Entry	R^1	R^2	Ref	Entry	R^1	R^2	Ref
1	Me	Me	25,26,31,32	6	Me	*n*-Bu	29
2	Me	*n*-Pr	25	7			29
3	Me	*n*-Bu	25	8			29
4	Me	CF_3	27,28,33	9			29
5	Me	*i*-Pr	29	10			29

Dimethyldioxirane (DMDO) (Table 1.1, Entry 1); Typical Procedure:[32]

To a mixture of $NaHCO_3$ (58 g) in acetone (192 mL) and water (254 mL) at 5-10 °C (ice/water) in a 4-L three-necked flask [the three-necked flask was connected by a U tube (i.d. of 25 mm) to a two-necked receiving flask cooled at -78 °C with a dry ice/ethanol bath], was added Oxone (120 g, 0.195 mol) through an addition funnel for solids in 5 portions at 3 min intervals with vigorous mechanical stirring and cooling. After the mixture was stirred for 3 min upon the last addition of Oxone, a moderate vacuum (80-100 mm Hg) was applied, and the 5-10 °C cooling bath was removed. While the reaction mixture was vigorously stirred, the DMDO/acetone soln was collected in a

cooled (-78 °C) receiving flask (150 mL 0.09-0.11 M, ca. 5% yield). The soln was dried (K_2CO_3) and stored in a freezer (-20 °C) over molecular sieves (4Å).

Characterization data[6]: UV (nm) 335 (ε 13); IR (cm^{-1}) 3012, 3005, 2999, 1209, 1196, 1094, 1080, 1059, 1034, 899, 784; ^1H NMR δ 1.65; ^{13}C NMR δ 22.7, 102.0.

Methyl(trifluoromethyl)dioxirane (TFDO) (Table 1.1, Entry 4); Typical Procedure:[14]

To a slurry of $NaHCO_3$ (13 g, 155 mmol) in water (13 mL) at 0 °C in a 250-mL four-necked round bottom flask equipped with an addition funnel for solid, an additional funnel for low-boiling liquid, an efficient mechanical stirrer, and a gas inlet tube which was connected to the top inlet of a double-jacketed high-efficiency spiral condenser with -80 °C cooling (a 50 mL receiving flask cooled to -60 to -50 °C was connected to the bottom exit of the condenser) (a sidearm from the condenser was available for a water aspirator), Oxone (24 g, 0.039 mol) was added through a solid addition funnel to the vigorously stirred slurry with releasing of CO_2 gas. After 80 seconds of CO_2 evolution, trifluoroacetone (12 mL, 134 mmol) was quickly added via a precooled addition funnel, then into the reaction mixture within 1 min. After another 20 seconds, the reaction system was applied with reduced pressure (650 mm Hg) by water aspirator. A pale yellow soln of TFDO in trifluoroacetone was collected in the receiving flask (cooled at -60 to -50 °C). After 8 min, another batch of Oxone (8.0 g, 13 mmol) was added and reaction mixture was stirred for another 8 min. At this point, the aspirator was disconnected and the receiving flask was removed from condenser after it was allowed to warm to -25 °C for 5 min (to release CO_2). The receiving flask containing a pale yellow soln of TFDO in

trifluoroacetone was tightly closed by plastic stopper, wrapped with aluminum foil, and stored at -20 °C.

Characterization data[6]: UV (nm) 347 (ε 9); IR (cm^{-1}) 3020, 1447, 1427, 1402, 1330, 755, 745, 715, 615; ^{1}H NMR δ 1.97; ^{13}C NMR δ 14.5, 97.3, 122.2; ^{19}F NMR δ -81.5.

1.3 APPLICATIONS OF DIOXIRANES IN ORGANIC SYNTHESIS

Dioxiranes, a class of powerful electrophilic oxidants, can oxidize various functional groups such as, heteroatoms, π-bonds, X-H σ-bonds (X = C or Si), and organometallic compounds. When different functional groups are present, good chemoselectivity can often be obtained with the general reactivity order of heteroatoms > π-bonds > X-H σ-bonds. Oxidations may be carried out with either *in situ* generated or isolated dioxiranes. Isolated dioxiranes can be used for many acid- or base-sensitive or hydrolytically-labile substrates due to the neutral reaction conditions and easy workups (by simple removal of the volatile DMDO or TFDO under reduced pressure).

1.3.1 Oxidation of Heteroatoms by Dioxiranes

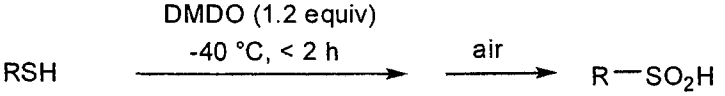
Dioxiranes are electrophilic oxidants and are very reactive toward various heteroatoms (the lone-pair electrons act as the nucleophiles), including sulfur, nitrogen, selenium, phosphorus, oxygen, chlorine, and iodine. Oxidations of sp^3-hybridized heteroatoms or sp^2-hybridized heteroatoms in aromatic rings by dioxiranes usually

produce oxyfunctionalized products, such as sulfinic acids,[36] sulfoxides or sulfones,[25,37-56] sulfoximines,[57,58] N-oxides,[25,59-64] nitro compounds,[57,65-71] hydroxylamines,[72-76] nitrones,[69,77-84] nitroxides,[85] hydroxamic acids,[79] selenoxides,[86] selenophene oxides,[87-89] phosphine oxides,[25,90] phosphates,[91,92] molecular oxygen,[93-98] hypochlorite ions,[99] and hypervalent iodines.[100-103] On the other hand, oxidations of sp^2-hybridized heteroatoms in π bonds such as C=N,[104-115] C=P,[116,117] C=S,[118,119] and P=S[120,121] often results in the cleavage of the heteroatom π bonds to generate of C=O,[104-111,113-119] C≡ N,[112] and P=O[120,121] bonds. In general, sulfur-containing substrates are more reactive toward dioxirane oxidations than nitrogen-containing compounds.[18]

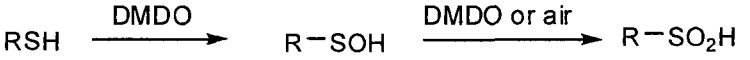
1.3.1.1 Synthesis of Sulfinic Acids

Oxidation of thiols by DMDO at low temperature produces sulfinic acid in good yield (Table 1.2).[36] A slight excess of DMDO (1.2 equv) is sufficient for this transformation and two equivalents of DMDO lead to the formation of sulfonic acid. The reaction likely proceeds via oxidation of the thiol to the sulfenic acid followed by further oxidation of the sulfenic acid to the sulfinic acid by either DMDO or air (Scheme 1.2). Aliphatic thiols are effective substrates for this transformation. Oxidation of benzylmercaptan and *p*-thiocresol gives additional products besides the corresponding sulfinic acids.

Table 1.2 Synthesis of Sulfinic Acids[36]



Entry	Starting Material	Yield (%)	Ref
1	EtSH	73	36
2	*n*-PrSH	74	36
3	*i*-PrSH	90	36
4	*n*-BuSH	84	36
5	$CH_3(CH_2)_4SH$	96	36



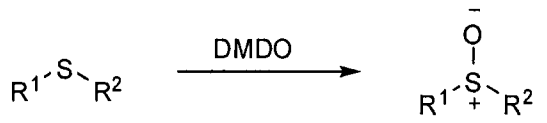
Scheme 1.2 Oxidation of Thiol to Sulfinic Acid by DMDO[36]

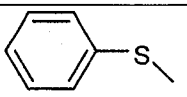
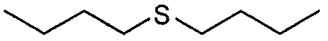
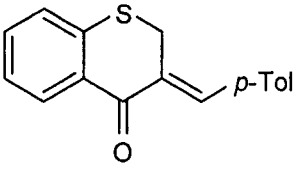
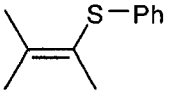
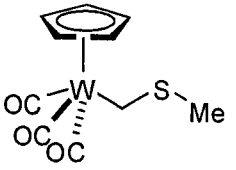
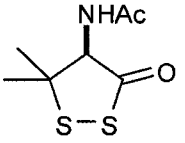
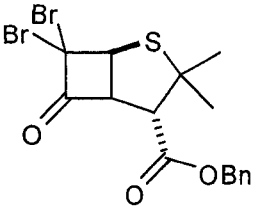
1.3.1.2 Synthesis of Sulfoxides and Sulfones

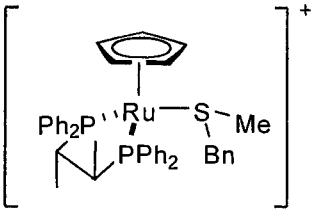
Sulfides can be readily oxidized to sulfoxides and sulfones by DMDO.[25,37-56] One equivalent of DMDO is generally used to synthesize sulfoxides (Table 1.3). Excess DMDO may further oxidize sulfoxides to sulfones. For the synthesis of sulfones (Table 1.4), more than two equivalents of DMDO are used with a slightly longer reaction time to ensure complete conversion. Oxidation of sulfides by TFDO usually goes through a slightly different mechanism to give the mixture of sulfoxides and sulfones (major) even when a large excess of sulfides as compared to TFDO are used.[53] When chiral sulfides are oxidized with DMDO, good diastereoselectivity can be obtained in some cases, particularly with some five-membered ring chiral sulfides and chiral metal-coordinated sulfides (Table 1.3, Entries 5-8).[44,47,48] However, oxidation of some six-membered ring and acyclic chiral sulfides appears to be less diastereoselective.[42,49] The neutral reaction conditions and easy work-up with dioxiranes also allow the isolation of some unstable compounds. For example, thiophene dioxide can be prepared in pure form by oxidizing thiophene with 3.0 equivalents of DMDO at -20 °C under dilute conditions followed by

simple removal of remaining DMDO and thiophene at low temperature under reduced pressure (Table 1.4, Entry 7).[52]

Table 1.3 Preparation of Sulfoxides by Oxidation of Sulfides with DMDO[25,41,44,46-48,53]

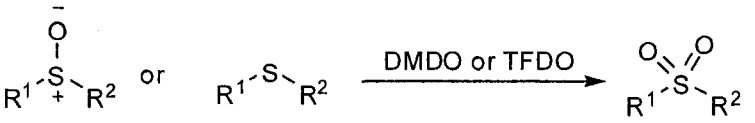


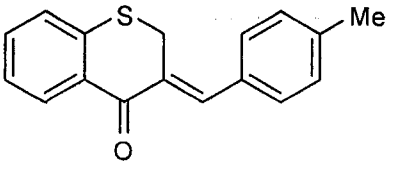
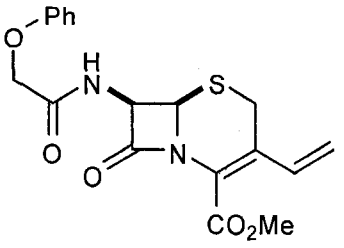
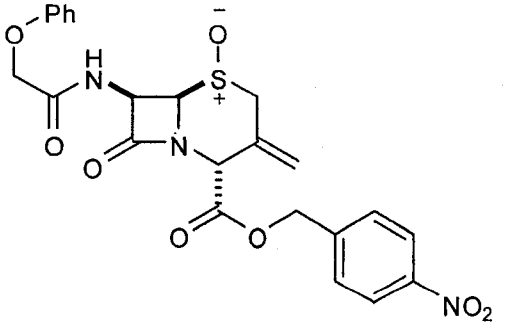
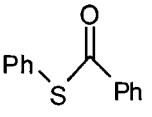
En.	Starting Material	Conditions	Yield (%)	Ref
1		1.0 equiv DMDO, rt	65	25
2		1.0 equiv DMDO, 0 °C	94[a]	53
3		1.3 equiv DMDO, 20 °C, 1 h	73	46
4		1.0 equiv DMDO, -35 °C, 1 h	81	46
5		1.0 equiv DMDO, -65 °C, 10 min	88	41
6		1.0 equiv DMDO, -78 °C	53[b]	47
7		1.5 equiv DMDO, rt, 10 min	100	44

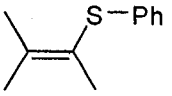
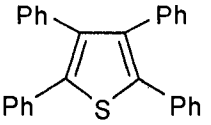
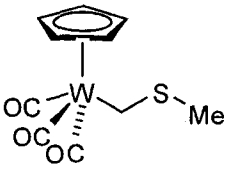
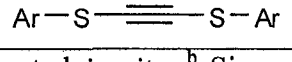
8		PF_6^-	4.0 equiv DMDO, 0 °C, 45 min	90[c]	48

[a] GC yield. [b] The sulfur close to two methyl group was selectively oxidized; Pure (*S*)-sulfoxide was obtained from recrystallization of crude product with 8/1 diastereoselectivity. [c] The product was obtained with 99/1 diastereoselectivity.

Table 1.4 Synthesis of Sulfones by Oxidation of Sulfides and Sulfoxides with Dioxiranes[38,40,41,43,46,49,51,52]

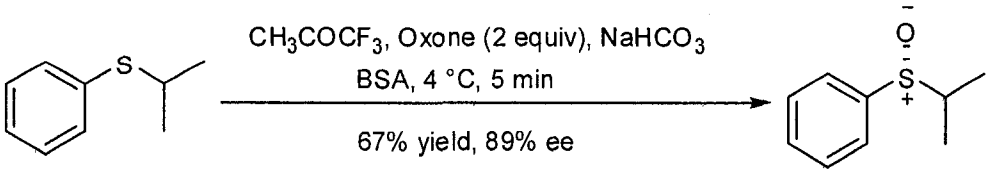


Entry	Starting Material	Conditions	Yield (%)	Ref
1		2.2 equiv DMDO, 20 °C, 1 h	100	46
2		DMDO, 0-5 °C, 2-3 h	95	49
3		DMDO, 0-5 °C, 2-3 h	100	49
4		≈ 2.6 equiv DMDO, -30 °C, 2-4 h	100	43

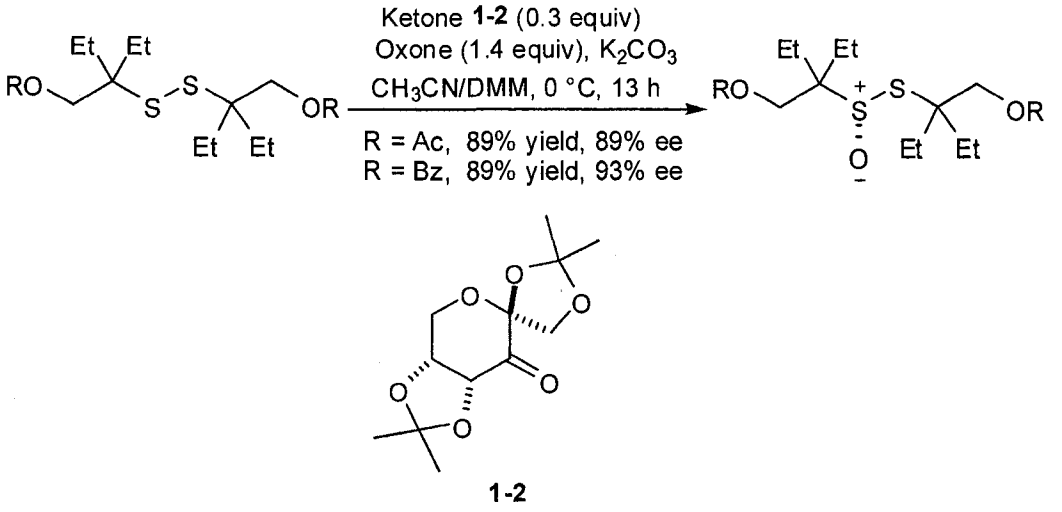
5		3.0 equiv DMDO, -35 °C, 1 h	91	46
6[a]		11 equiv CF_3COCH_3, 5.0 equiv Oxone, $NaHCO_3$, CH_3CN 0 °C, 3 h	95	51
7		3.0 equiv DMDO, -20 °C, 36 h	100	52
8		DMDO, rt, several hours	99	38
9		2.0 equiv DMDO, -65 °C, 10 min	70	41
10		DMDO, 20 °C	65-75[b]	40

[a] TFDO was generated *in situ*. [b] Since the product is unstable, the yield was based on their derivatives.

Chiral sulfoxides can be obtained in up to 89% ee when prochiral sulfides are oxidized with *in situ* generated achiral dioxiranes using bovine serum albumin (BSA) as a chiral auxiliary (Scheme 1.3).[37,39] While low ee's are obtained for the oxidation of prochiral sulfides with chiral dioxirane generated *in situ*,[55] prochiral disulfides appear to be more effective substrates.[54,56] Up to 96% ee has been obtained for functionalized disulfides with the chiral dioxirane generated *in situ* from ketone **1-2** and Oxone (Scheme 1.4).[56] The structure of disulfides has a crucial influence on the enantioselectivity.



Scheme 1.3 Enantioselective Oxidation of Sulfides by Achiral Dioxiranes[37,39]



Scheme 1.4 Enantioselective Oxidation of Sulfides by Chiral Dioxiranes[56]

(*Z*)-3-(4-Methylbenzylidene)thiochroman-4-one-1,1-dioxide (Table 1.4, Entry 1); Typical Procedure:[46]

To a soln of the sulfide (0.776 g, 2.92 mmol) in dry DCM (10 mL) at 20 °C, 0.07-0.08 M dry DMDO (2.2 equiv) in acetone was rapidly added in portions. The reaction progress was monitored by the peroxide test (KI/HOAc) and TLC (only one product could be detected at the end of reaction). Removal of the solvent affords the corresponding sulfone; yield: 0.871 g (100 %).

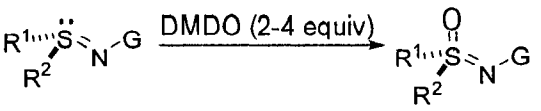
2,2,5,5-Tetraethyl-1,6-diacetate-3,4-dithiahexane-3-oxide (Scheme 1.4, R = Ac); Typical Procedure:[56]

A mixture of tetrabutylammonium hydrogen sulfate (0.015 g, 0.04 mmol) and ketone **1-2** (0.077 g, 0.3 mmol) in a alkaline buffer soln (pH = 9.3) (10 mL) was added to a soln of the 2,2,5,5-tetraethyl-3,4-dithiahexane-1,6-diacetate (0.534 g, 1 mmol) in CH_3CN/DMM (1:2) (15 mL) with stirring at 0 °C. A soln of Oxone (0.85 g, 1.38 mmol) in Na_2(EDTA) soln (6.5 mL) and a soln of K_2CO_3 (0.8 g, 5.8 mmol) in distilled water (6.5 mL) were added dropwise separately for 1 h. The resulting mixture was stirred at 0 °C for 12 h. Then the mixture was diluted with water, extracted with ether, dried over Na_2SO_4, concentrated, and purified by flash chromatography to give the product; yield: 0.489 g (89%, 89%ee).

1.3.1.3 Synthesis of Sulfoximines

Oxidation of a sulfilimine by DMDO gives a sulfoximine as the major product along with a nitro compound and a sulfone resulting from the oxidative cleavage of the N=S bond.[57] However, oxidative cleavage of N=S appears to be negligible for a sulfilimine substituted with electron-withdrawing group such as an acetyl or tosyl group on the nitrogen. *N*-tosylated and -acetylated sulfilimines can be efficiently oxidized by DMDO to give sulfoximines in good yields (Table 1.5).[58] The oxidation is also stereospecific. Oxidation of a chiral sulfilimine by DMDO gives the sulfoximine with complete retention of configuration and no loss of ee (Table 1.5, Entry 5). The oxidation of sulfilimines by TFDO is less selective, giving sulfoximines along with sulfoxides and sulfones resulting from the oxidative cleavage of the N=S bond.

Table 1.5 Oxidation of Sulfilimines by DMDO[58]



Entry	Starting Material	Condition	Yield (%)	Ref
1	Ph_2S=NTs	rt, 6 h	92	[58]
2	PhMeS=NTs	rt, 6 h	90	[58]
3	EtMeS=NTs	rt, 4 h	91	[58]
4	EtMeS=NAc	rt, 2 h	90	[58]
5		0-25 °C	90	[58]

_S_-Ethyl-_S_-methyl-_N_-(_p_-toluenesulfonyl)sulfoximine (Table 1.5, Entry 3); Typical Procedure:[58]

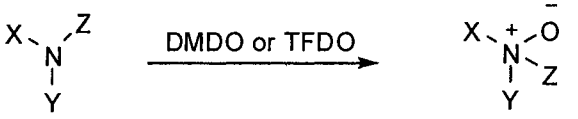
To a soln of the sulfilimine (0.037 g, 0.150 mmol) in acetone (5 mL), a cold (0 °C) DMDO soln in acetone (0.64 mmol) was added in two portions during 10-15 min. The resulting mixture was left at rt for 2 h (the reaction progress was monitored by TLC). Solvent was removed under reduced pressure and the residue was purified by flash chromatography (silica gel, Et_2O/MeOH = 95/5) to give product; yield: 0.036 g (91%).

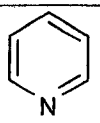
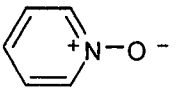
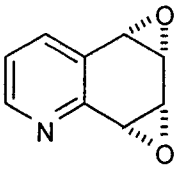
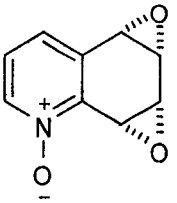
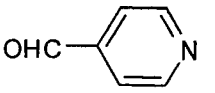
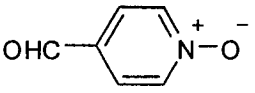
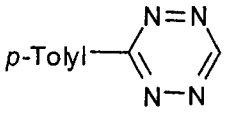
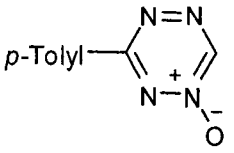
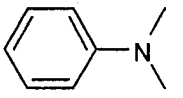
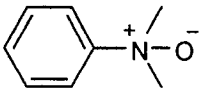
1.3.1.4 Synthesis of *N*-oxide and Nitro Compounds

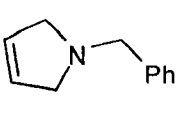
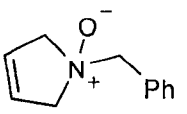
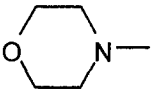
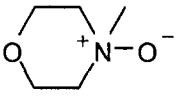
Heterocyclic aromatic amines (Table 1.6, Entries 1-4) [25,59,60,64] and alkyl tertiary amines (Table 1.6, Entries 5-7)[61,63] can be efficiently oxidized by dioxiranes (usually DMDO) to form the corresponding *N*-oxides. Functional groups such as alkenes and aldehydes can survive this transformation. Although the reaction is often complete within

a couple of hours at rt in many cases, the oxidation of 1, 2, 4, 5-tetrazines by DMDO is sluggish (Table 1.6, Entry 4).[62] However, the rate of oxidation can be significantly increased with more reactive TFDO (both isolated and generated *in situ*), reducing the reaction time from days to within an hour.[62] This oxidation is also highly regioselective with oxidation occurring exclusively at sterically less-hindered positions (Table 1.6, Entry 4).

Table 1.6 Synthesis of *N*-oxides Compounds by Dioxiranes[25,29,59,60,62-64]

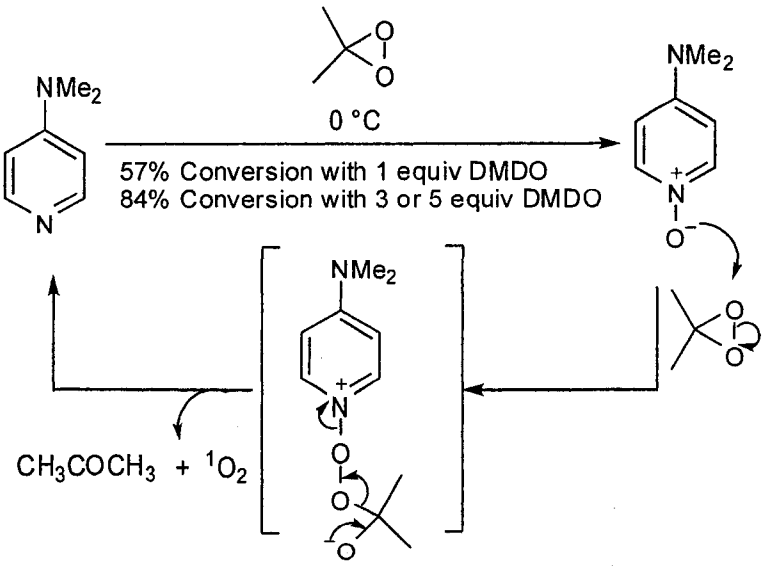


En.	Starting Material	Product	Condition	Yield (%)	Ref
1			DMDO[a], rt, 2 h	93	25,29,59
2			6 equiv DMDO, 10 °C, 3 h	99	60
3			1 equiv DMDO, 20 °C, 1 h	98	64
4			1.1 equiv TFDO, 0 °C, 20 min	90	62
5			1.5 equiv DMDO, 0 °C, < 1 h	100	63

6			2.0 equiv DMDO, 0 °C, < 1 h	100	63
7			1.2 equiv DMDO, 0 °C, < 1 h	100	63

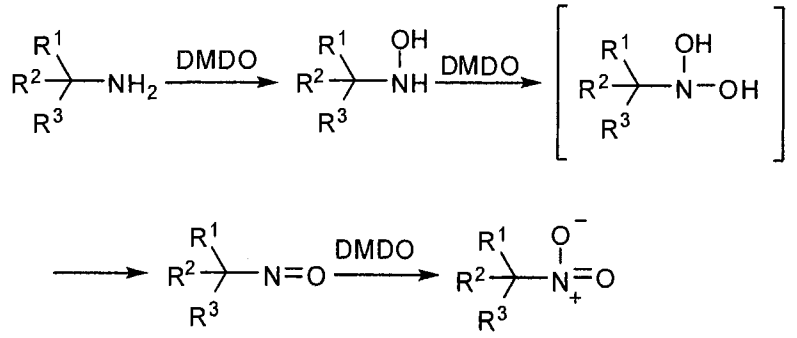
[a] DMDO was generated *in situ*.

The yields for the preparation of *N*-oxides by dioxiranes are often quantitative. Nevertheless, in some cases, such as oxidation of 4-dimethyl-aminopyridine by DMDO, maximum conversion is only 84% and can not be improved by increasing the amount of DMDO because the oxidation product, *N*-oxide, can react with DMDO to form oxygen gas and revert back to starting material (Scheme 1.5).[95]



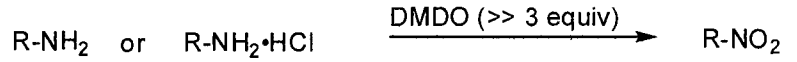
Scheme 1.5 Oxidation of 4-Dimethyl-aminopyridine by DMDO[95]

Primary amines with aryl and tertiary alkyl substituents can also be efficiently oxidized by DMDO to form nitro compounds often in high yields (Table 1.7, Entries 1-5).[57,65,66,68] The process is believed to go through hydroxylamine and nitroso compounds (Scheme 1.6). However, oxidation of primary amines bearing primary or secondary alkyl substituents by DMDO often leads to a complex mixture containing varying amounts of oximes, nitroso dimers, nitroalkanes, oxaziridines, and nitrones depending on reaction conditions and amines used.[69,70] Higher yields of nitro compounds are often obtained when both aryl and alkyl (including non-tertiary) amine hydrochloride salts are oxidized directly by DMDO (Table 1.7, Entries 6-10). [67,68,71] This method avoids the need to isolate the sensitive free amine and increases the yields of nitro compounds by reducing the side reaction between free amines and the reaction intermediates.[67]

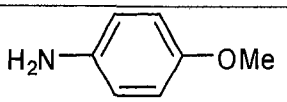
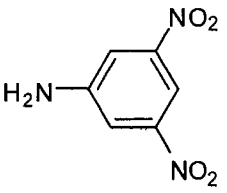
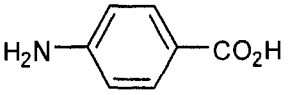
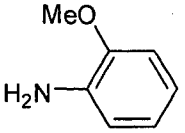
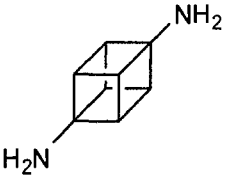
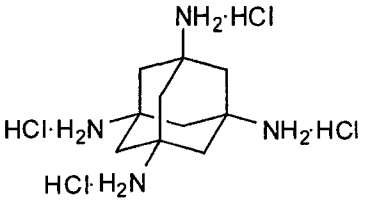
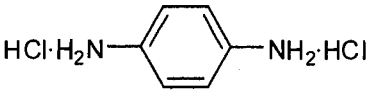
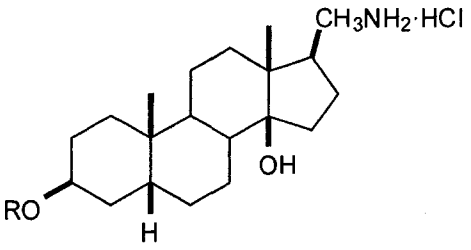


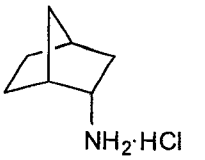
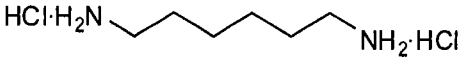
Scheme 1.6 Oxidation of Amine to Nitro Compound by DMDO[65]

Table 1.7 Oxidation of Amines or Amine Hydrochloride Salts by DMDO[65,66,68,71]



Entry	Starting Material	Condition	Yield (%)	Ref

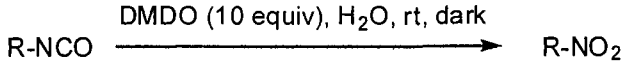
1		rt, 30 min	94[a]	65
2		rt, 3 h	94	68
3		22 °C, 30 min	95	68
4		0 °C, 45 min	100[b]	66
5		rt, 48 h	80	68
6		rt, 4 h	91	68
7		rt, 23 h	82	68
8	 R = α-L-rhamnoside	rt, 30 min	71	71

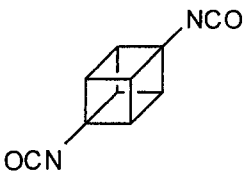
9		rt, 7 h	58	[68]
10		rt, 24 h	60	[68]

[a] GC yield. [b] DMDO was generated *in situ.*

A variety of isocyanates can also be cleanly oxidized to the corresponding nitro compounds by DMDO in acetone solution while other oxidants, such as Ozone, potassium permanganate, MCPBA, and RuO_4, often give little or a mixture of nitro compounds (Table 1.8).[67] Water is essential for the transformation. The rate of the overall reaction can be dramatically accelerated by addition of a catalytic amount of benzyltrimethylammonium hydroxide (Table 1.8, Entries 3-5). The reaction presumably proceeds through *in situ* hydrolysis of the isocyanate to the amine followed by oxidation of the amine to a nitro compound.

Table 1.8 Preparation of Nitro Compounds from Isocyanates by DMDO[67]



Entry	Starting Material	Reaction Time	Yield (%)	Ref
1	PhNCO	30 min	65	[67]
2		1.5 h	85	[67]

3	*n*-BuNCO	1 h	89[a,b]	67
4	*c*-HexNCO	3 h	94[a,b]	67
5	*t*-BuNCO	8 h	83[a,b]	67

[a] Catalytic amount of $BnMe_3N^+OH^-$ was added; [b] Calibrated GLC yield.

3-(4-Methylphenyl)-1,2,4,5-tetrazine-*N*-oxides (Table 1.6, Entry 4); Typical Procedure:[62]

A soln of TFDO (1.05 equiv) in trifluoroacetone soln (0.4-0.6 M) was added into a soln of tetrazine (0.088 g, 0.51 mmol) in dry DCM (5-10 mL) at 0 °C. After the resulting mixture was stirred at 0 °C for 20 min, the solvent was removed under reduced pressure (25 °C, 12 Torr), and the residue was purified by recrystallization from *n*-hexane to give the *N*-oxide; yield: 0.087 g (90 %).

2-Nitroanisole (Table 1.7, Entry 4); Typical Procedure:[66]

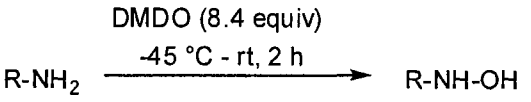
To a three-neck round bottom flask equipped with two addition funnels, a pH electrode, and a stirring bar, was added DCM (100 mL), acetone (100 mL), sodium phosphate soln (50 mL, 0.8 M), tetrabutylammonium hydrogen sulfate (0.5 mmol), and 2-anisidine (10 mmol). One addition funnel was charged with a soln of Oxone (32 mmol) in water (150 mL) while the other contained a KOH soln (2 N, 100 mL). After cooling the mixture to 0 °C, Oxone soln was added dropwise over 30 min while maintaining a pH of 7.5-8.5 by the addition of a KOH soln. Then the mixture was stirred for another 15 min and quenched by methylsulfide (1 mL). The resulting mixture was filtered. The organic layer was washed with water (50 mL), dried by $MgSO_4$, filtered, and concentrated under

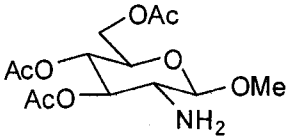
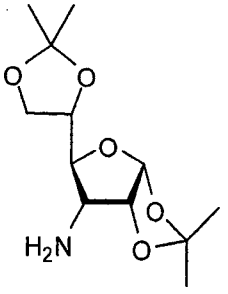
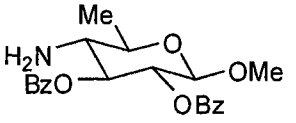
reduced pressure. The resulting residue was filtered through a 50 g plug of silica gel (DCM) to give 2-nitroanisole; yield: 1.5 g (100 %).

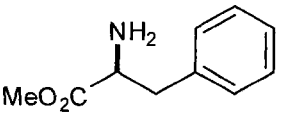
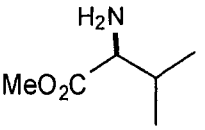
1.3.1.5 Synthesis of Hydroxylamines

As described in Scheme 1.6, oxidation of primary amines by DMDO to nitro compound involves hydroxylamines as intermediates.[65] It has been observed that hydroxylamines can be prepared from primary amines by oxidation with DMDO at low temperature (Table 1.9).[73] Chiral amino sugars and amino esters can be converted to hydroxylamines without racemization of stereocenters.

Table 1.9 Preparation of Hydroxylamines from Primary Amines by DMDO[73]

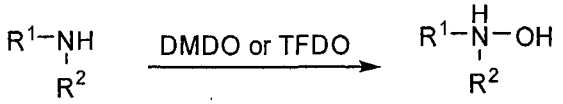


Entry	Starting Material	Yield (%)	Ref
1		76	73
2		70	73
3		75	73

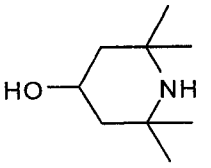
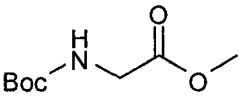
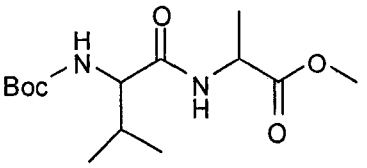
4		54	[73]
5		82	[73]

Secondary amines can be efficiently oxidized to hydroxylamines in high yields using one equivalent of DMDO at 0 °C (Table 1.10, Entries 1-3).[72] Excess amount of DMDO may further oxidize the secondary amines to nitroxide radicals (Table 1.10, Entry 3 vs Table 1.12, Entry 4) or nitrones (Table 1.10, Entry 1 vs Table 1.11, Entry 5). Oxidation of Boc protected primary amino acids by DMDO produces little *N*-hydroxylation products due to the electronic and steric effects of the Boc group. However, the oxidation can be achieved with more reactive TFDO (Table 1.10, Entry 4 and 5).[75,76] Chiral *N*-hydroxylamino acids can be obtained in good yields without racemization of stereocenters.

Table 1.10 Preparation of Hydroxylamines from Secondary Amines by Dioxiranes[72,75,76]



Entry	Starting Material	Condition	Yield (%)	Ref
1	Bn_2NH	1.0 equiv DMDO, 0 °C, 15 min	98	[72]

2	*c*-Hex_2NH	1.0 equiv DMDO, 0 °C, 10 min	83	[72]
3		1.0 equiv DMDO, 0 °C, 2 h	99	[72]
4		2.0 equiv TFDO, -20-0 °C, 5 h	82	[75]
5		2.4 equiv TFDO, 0 °C, 4 h	81[a]	[76]

[a] The yield is for the product of *N*-hydroxylation on the Boc protected amine.

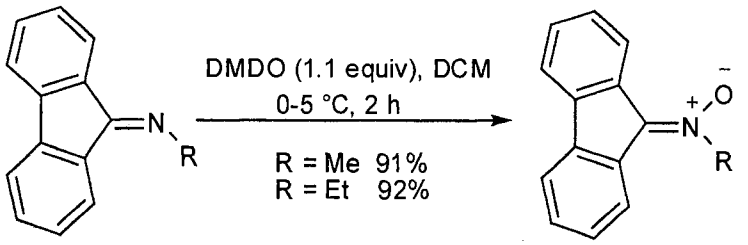
_N,N_-Dicyclohexylhydroxylamine (Table 1.10, Entry 2); Typical Procedure:[72]

A soln of DMDO (3.317 mmol) in acetone was added into a magnetically stirred *N,N*-dicyclohexylamine (0.508 g, 3.317 mmol) soln in acetone (5 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 10 min, dried over Na_2SO_4, filtered, concentrated, and purified by flash chromatography (silica gel, EtOAc/petroleum ether = 1/4) to give a white solid; yield: 0.457 g (83 %).

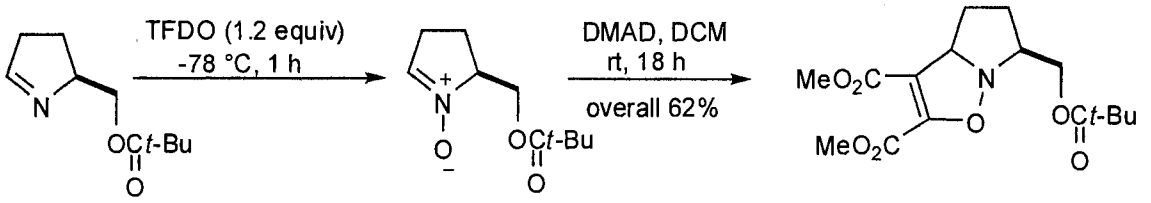
1.3.1.6 Synthesis of Nitrones and Nitroxide Radicals

Imines are oxidized by dioxiranes to produce nitrones in varied yields depending on the structure of imines and reaction conditions.[69,78,84] The oxidation usually gives a mixture of nitrones and carbonyl compounds resulting from the oxidative cleavage of C=N bonds.[78] Higher yields of isolated nitrones are obtained for imines with *C,C*-diaryl groups and imines with small *N*-alkyl substituents (Scheme 1.7).[78] The imine derived

from ethyl L-pyroglutamate is oxidized by TFDO at -78 °C to give the corresponding nitrone, which is then trapped by dimethyl acetylenedicarboxylate (DMAD) to yield a cycloaddition product in 62% overall yield (Scheme 1.8).[84]

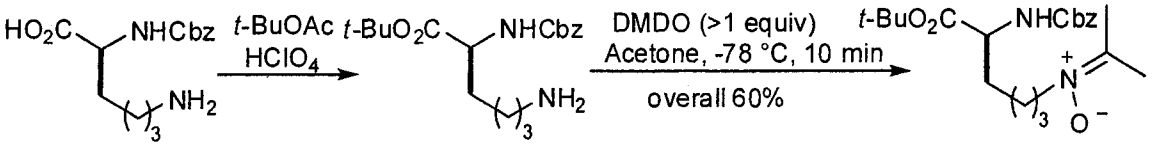


Scheme 1.7 Synthesis of Nitrones from Imines by DMDO[78]



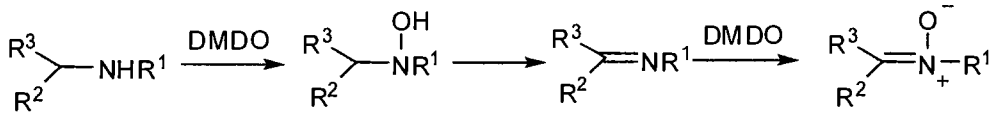
Scheme 1.8 Synthesis of Nitrone from Imine by TFDO[84]

DMDO oxidation of the primary amine of Cbz protected lysine ester can yield the nitrones at -78 °C (Scheme 1.9).[80,81,83] The reaction may go through oxidation of the dimethyl imine generated *in situ* from the primary amine and acetone. Alternatively, dimethyl nitrones may come from the rapid reaction of acetone and hydroxylamine generated *in situ* from oxidation of the amine.[80]



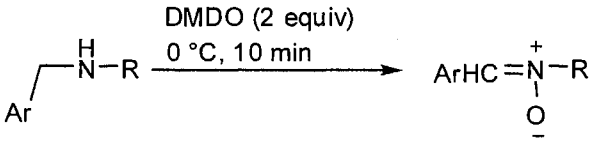
Scheme 1.9 Synthesis of Nitrone from Primary Amine and Acetone by DMDO[80,81,83]

Secondary amines having α hydrogens (often at the benzylic positions) can be oxidized to nitrones by DMDO.[77,79,82] A variety of aryl substituted nitrones can be readily prepared by this method in high yields (Table 1.11). The transformation likely involves formation of hydroxylamines, imines, then nitrones (Scheme 1.10). Using exactly 2.0 equivalents of DMDO is desirable for the synthesis of nitrones since excess dioxirane may further react with nitrones. When secondary amines having no α hydrogens are treated with 2.0 equivalents of DMDO, nitroxide radicals are formed in high yields (Scheme 1.11) (Table 1.12).[85]

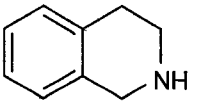


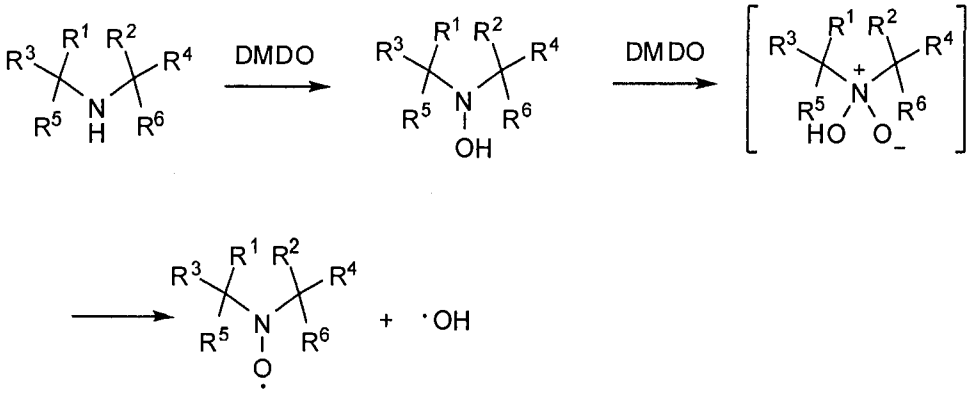
Scheme 1.10 Oxidation of Secondary Amines to Nitrone by DMDO[77]

Table 1.11 Preparation of Nitrones from Second Amines by DMDO[77,79]



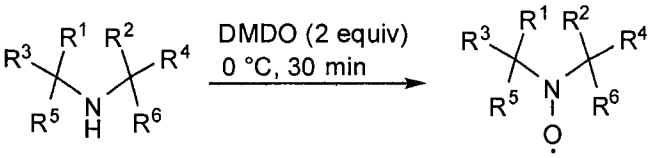
Entry	Starting Material	Yield (%)	Ref
1	BnNH-*t*-Bu	96	77
2	*p*-Tol-CH_2NH- *t*-Bu	99	77
3	*p*-$CF_3C_6H_4$-CH_2NH-*t*-Bu	98	77

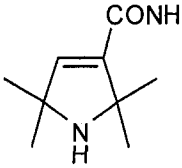
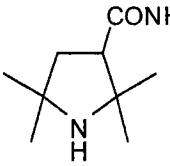
4	BnNHPh	98	[77]
5	$(Bn)_2NH$	96	[77]
6		48	[79]

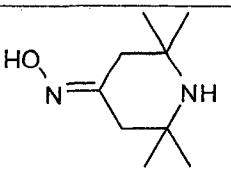
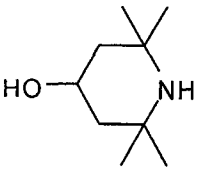
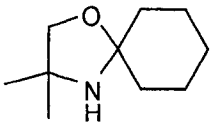


Scheme 1.11 Oxidation of Secondary Amines to Nitroxide Radicals by DMDO[85]

Table 1.12 Preparation of Nitroxide Radicals from Secondary Amines by DMDO[85]



Entry	Starting Material	Yield (%)	Ref
1		98	[85]
2		100	[85]

3		99	85
4		100	85
5		100	85

_N_-(Phenylmethylene)-2-methyl-2-proanamine _N_-oxide (Table 1.11, Entry 1); Typical Procedure:[77]

A soln of DMDO (2.99 mmol, 63.7 mL) in acetone was added into a magnetically stirred *tert*-butybenzylamine (0.244 g, 1.49 mmol) soln in acetone (5 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 10 min, concentrated, and purified by flash chromatography (silica gel, EtOAc/petroleum ether = 1/4) to give white needles; yield: 0.256 g (96 %).

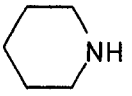
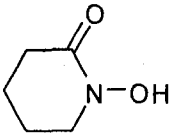
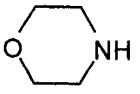
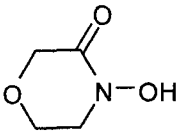
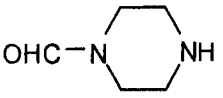
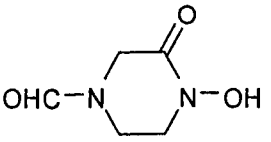
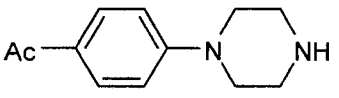
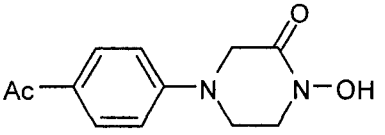
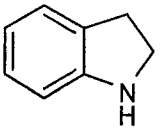
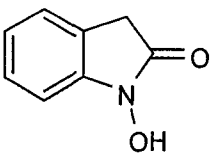
3-Carbamyl-2, 2, 5, 5-tetramethyl-3-pyrroline-1-yloxy (Table 1.12, Entry 2); Typical Procedure:[85]

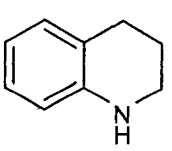
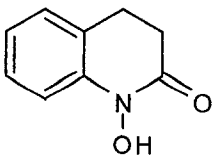
To a soln of 2, 2, 5, 5-tetramethyl-pyrrolidine-3-carboxamide (2 mmol) in acetone (20 mL) at 0 °C, was added a soln of DMDO (0.067 M, 60 mL, 4 mmol) in acetone slowly. The resulting mixture was stirred at 0 °C for 30 min and concentrated to give a bright yellow solid; yield: 0.37 g (100 %).

1.3.1.7 Synthesis of Hydroxamic Acids

Cyclic secondary amines such as piperidine, morpholine, and their derivatives are oxidized by DMDO (3.2-3.5 equiv) to form the corresponding cyclic hydroxamic acids (Table 1.13).[79] This transformation can also be extended to fused cyclic secondary amines with no benzylic hydrogens α to the nitrogen (Table 1.13, Entry 6). Amines bearing an α-benzylic hydrogen often lead to a complex mixture of nitrones and hydroxamic acid under reaction conditions (Table 1.11, Entry 6).

Table 1.13 Synthesis of Cyclic Hydroxamic Acids by Oxidation of Secondary Amines with DMDO[a79]

Entry	Starting Material	Product	Yield (%)	Ref
1			71	79
2			67	79
3			89	79
4			85	79
5			54	79

6			83	[79]

[a] All the reactions were carried out with 1 equiv amine and 3.2-3.5 equiv DMDO in acetone at 0 °C for 20-30 min.

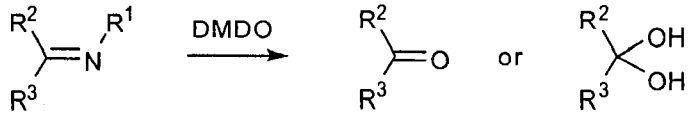
1-Hydroxy-2-pyrrolidone (Table 1.13, Entry 1); Typical Procedure:[79]

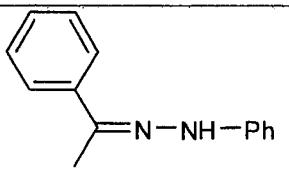
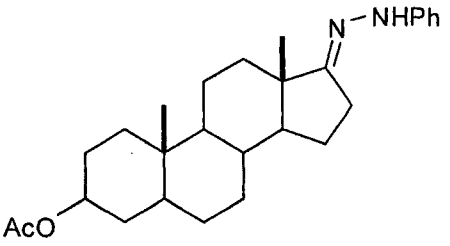
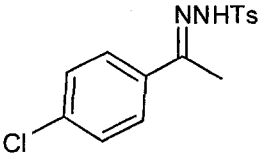
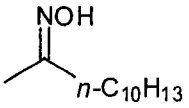
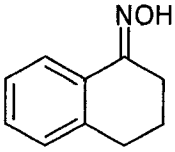
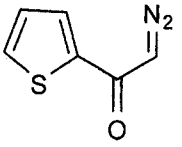
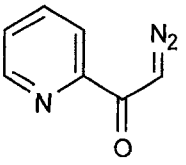
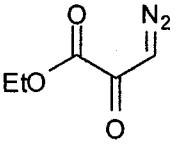
To a soln of piperidine (1.40 mmol) in acetone (5 mL), was added DMDO (4.48-4.89 mmol) soln in acetone at 0 °C. After the resulting mixture was stirred at 0 °C for 20-30 min, the solvent was removed and the resulting residue was purified by flash chromatography (methanol/acetonitrile = 1/2) to give 1-hydroxy-2-pyrrolidone; yield: 0.114 g (71 %).

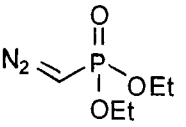
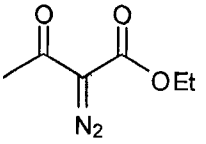
1.3.1.8 Cleavage of C=N Bonds

Dioxiranes can oxidatively cleave C=N bonds. The substrate scope includes ketone hydrazones (Table 1.14, Entries 1-3),[105,106] ketoximes (Table 1.14, Entries 4-5),[107] α-diazo ketones (Table 1.14, Entries 6-8),[104,108] diazomethylphosphonates (Table 1.14, Entry 9),[109] 2-diazo-1,3-dioxo derivatives (Table 1.14, Entry 10),[104,110] nitronate anions (Table 1.15),[113-115] and aryl oxazolines (Table 1.16).[111] In these cases, the carbonyl compounds are often generated in high yields. DMDO is usually used for this transformation while TFDO is used in some cases.[106,111]

Table 1.14 Cleavage of C=N Bonds by DMDO[104-107,109,110]

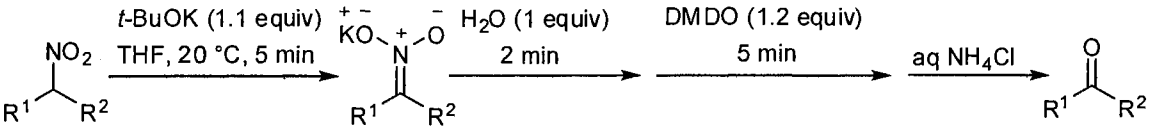


En.	Starting Material	Condition	Yield (%)	Ref
1		3.0 equiv DMDO, 20 °C, 30 min	92	106
2		3.0 equiv DMDO, 20 °C, 15 min	98[a]	106
3[b]		6.0 equiv Oxone, acetone, 25 °C, 24 h	98	105
4		1.1 equiv DMDO, 0 °C, 10 min	94	107
5		2.0 equiv DMDO, 25 °C, 24 h	100	107
6[c]		1.0 equiv DMDO, rt, a few min	85	104
7[c]		1.0 equiv DMDO, rt, a few min	100	104
8[c]		1.0 equiv DMDO, rt, a few min	100	104

9[c]		DMDO, rt	100	109
10		5.0 equiv DMDO, rt, 10 h	100	110

[a] GC Yield. [b] DMDO was generated *in situ*. [c] The products existed as hydrates.

Table 1.15 Cleavage of Nitronate Anions by DMDO[113]



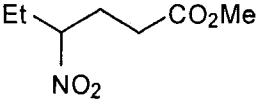
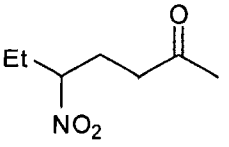
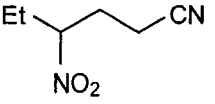
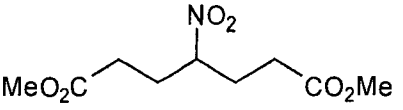
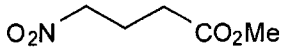
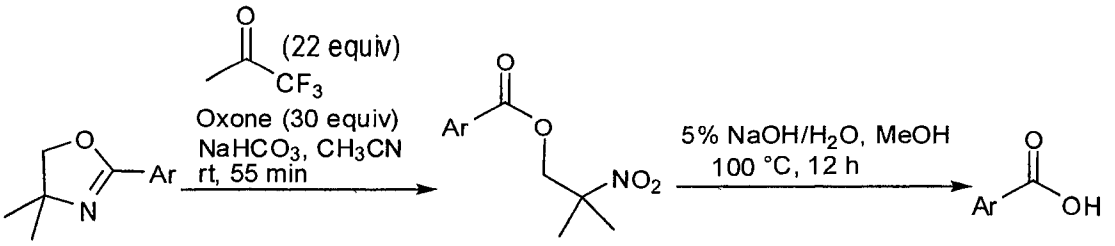
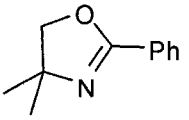
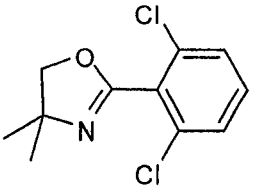
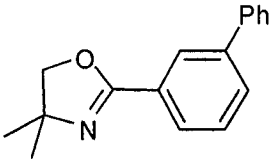
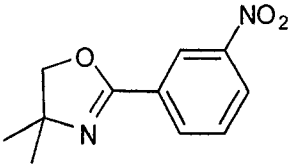
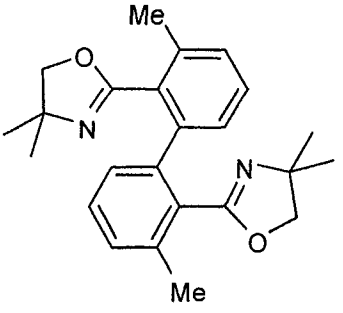
Entry	Starting Material	Yield (%)	Ref
1		90	113
2		99	113
3		86	113
4		83	113
5		73	113

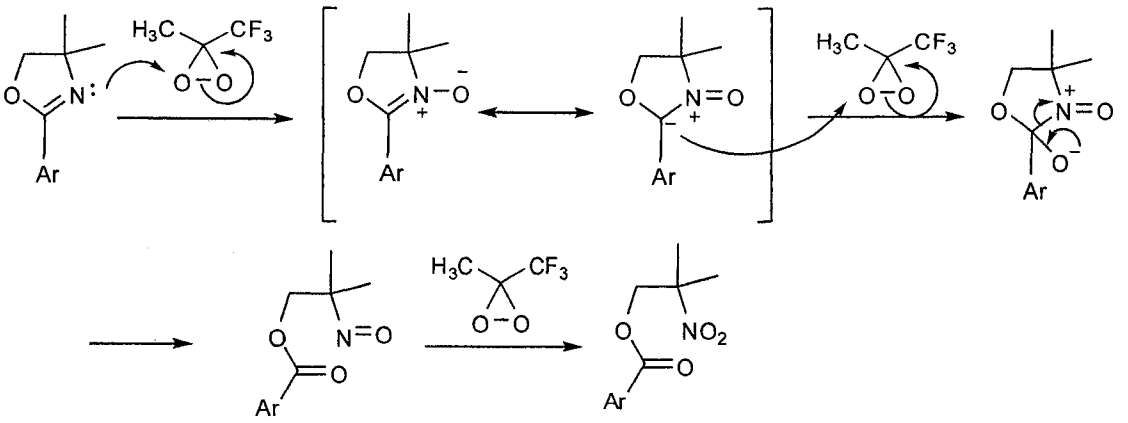
Table 1.16 Cleavage of Aryl Oxazolines by TFDO[111]



Entry	Starting Material	Yield (%)	Ref
1		91	111
2		90	111
3		95	111
4		88	111
5		80	111

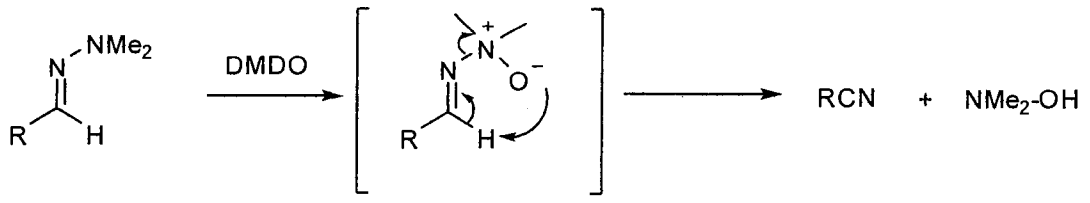
The mechanism for the cleavage of C=N bonds is likely to involve the electrophilic oxidation of the imines by dioxirane to form nitrones which is further

oxidized to produce the C=O bonds and nitroso compounds. The nitroso compounds can be further oxidized to nitro compounds.[106,111] In the case of oxidation of aryl oxazolines by TFDO, the nitroester intermediates are stable and can be isolated (Scheme 1.12).[111]



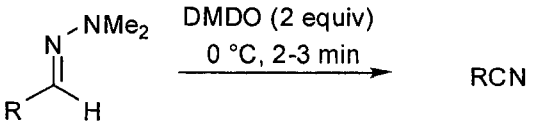
Scheme 1.12 Cleavage of Aryl Oxazolines by TFDO[111]

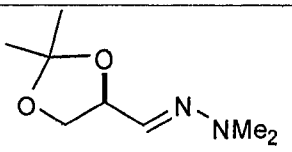
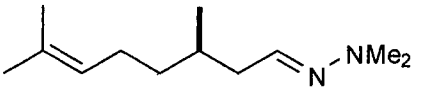
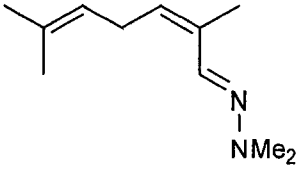
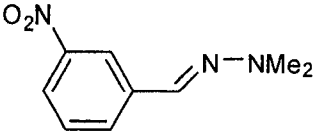
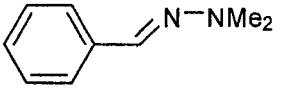
Aldehyde *N*,*N*-dimethylhydrazones can be efficiently oxidized by DMDO to produce nitriles in high yield (Table 1.17).[112] More reactive TFDO gives less satisfactory results for this transformation. The reaction likely proceeds through oxidation of the nitrogen atom of the $-NMe_2$ group by DMDO to form an *N*-oxide intermediate which undergoes an intramolecular elimination to generate the nitrile and hydroxylamine (Scheme 1.13)



Scheme 1.13 Oxidation of Aldehyde Hydrazones to Nitriles by DMDO[112]

Table 1.17 Oxidation of Aldehyde Hydrazones by DMDO[112]



Entry	Starting Material	Yield (%)	Ref
1		92	112
2		92	112
3		97	112
4		97	112
5		97	112

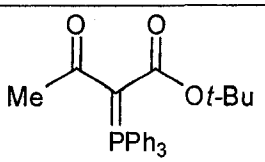
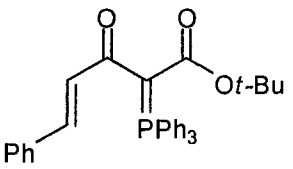
Acetophenone (Table 1.14, Entry 1); Typical Procedure:[106]

A DMDO (3 equiv) soln in acetone was added into a soln of the hydrazone (0.5 g) in acetone (4-6 mL) at 20 °C with stirring. The resulting mixture was stirred at 20 °C for 30 min. After the reaction was completed (monitored by TLC), the solvent was removed, and the resulting residue was purified by chromatography to give acetophenone; yield: 0.262 g (92 %).

1.3.1.9 Cleavage of C=P Bonds

Dioxiranes have also been used for the oxidative cleavage of C=P bonds to synthesize vicinal tricarbonyl compounds (Table 1.18),[116] α-keto esters, and α-keto amides (Table 1.19).[116,117] The oxidation can proceed rapidly at low temperature under neutral conditions. As shown in Table 1.18, the C=P bonds can be selectively cleaved to form vicinal tricarbonyl compounds without affecting functional groups such as alkene, thiophene, and vinyl ether by running the reaction at low temperature and controlling amount of dioxirane used.[116] In the case of cyanoketophosphoranes, the C=P bonds are initially oxidized to form α, β-diketo nitriles which are subsequently trapped by amines or alcohols to produce α-keto esters or α-keto amides in good yield (Table 1.19). [116,117] The transformation takes less than 5 minutes at room temperature.

Table 1.18 Synthesis of Vicinal Tricarbonyl Compounds via Cleavage of C=P Bonds by DMDO[116]

Entry	Starting Material	Condition	Yield (%)	Ref
1		3.0 equiv DMDO, 25 °C, 1 h	100	116
2		2.0 equiv DMDO, -78-25 °C, 4 h	85	116

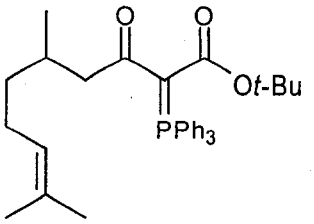
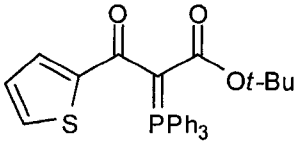
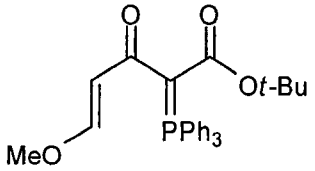
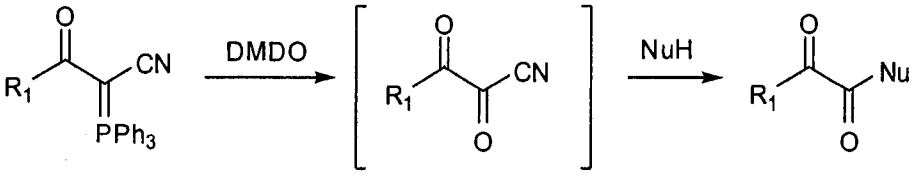
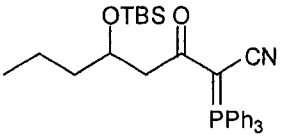
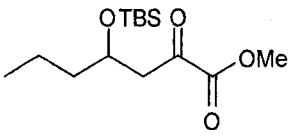
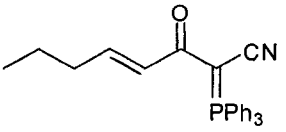
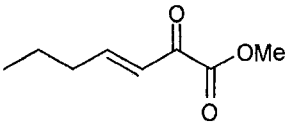
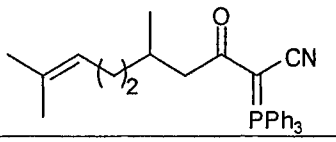
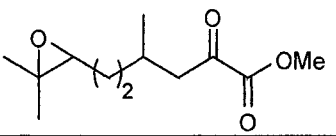
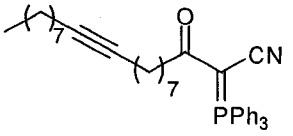
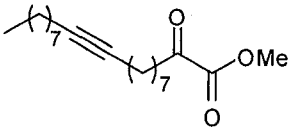
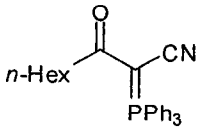
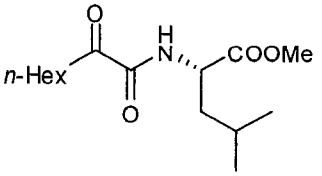
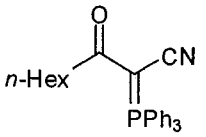
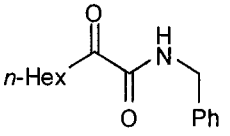
3		1.8 equiv DMDO, -78-25 °C, 4 h	83	116
4		2.0 equiv DMDO, -78-25 °C, 4 h	97	116
5		2.0 equiv DMDO, -78-25 °C, 4 h	70	116

Table 1.19 Synthesis of α-Keto Esters and Amides via Cleavage of C=P Bonds by DMDO[117]



En.	Starting Material	Product	Condition	Yield (%)	Ref
1			2.0 equiv DMDO, MeOH, rt , 5 min	88	117
2			2.0 equiv DMDO, MeOH, rt, 5 min	85	117
3			2.4 equiv DMDO,	79	117

4			MeOH, 0 °C, 5 min 2.0 equiv DMDO, MeOH, 0 °C, 5 min	87	[117]
5			2.0 equiv DMDO, L-leucine methyl ester, -78 °C, 15 min	72	[117]
6			2.0 equiv DMDO, $BnNH_2$, -78 °C, 15 min	81	[117]

***tert*-Butyl-2,3-dioxobutanoate (Table 1.18, Entry 1);Typical Procedure:**[116]

A soln of DMDO in acetone (0.1 M, 3.0 equiv) was added into a soln of *tert*-butyl-3-oxo-2-(triphenylphosphoranylidene)butanoate (0.243 g, 0.58 mmol) in DCM (2.0 mL). After the reaction mixture was stirred at 25 °C for 1 h, the crude mixture was concentrated and purified by flash chromatography (silica gel, EtOAc/*n*-hexane=1/4) to provide *tert*-butyl 2,3-dioxobutanoate as a white solid; yield: 0.1 g (100 %).

***N*-Benzyl-2-oxooctanamide (Table 1.19, Entry 6); Typical Procedure:**[117]

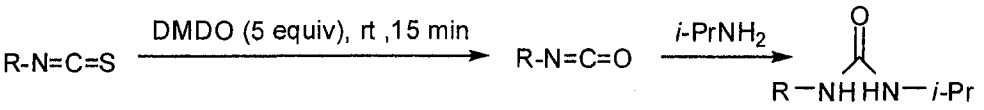
A soln of DMDO (0.04 M, 12 mL, 0.48 mmol) was added to a soln of the cyanoketophosphorane (0.10 g, 0.24 mmol) in DCM (5 mL) at -78 °C. After stirring for 5 min (complete conversion of cyanoketophosphorane as judged by TLC analysis), a soln

of benzylamine (0.026 g, 0.24 mmol) in DCM (2 mL) was added to the reaction mixture. After the reaction mixture was stirred for 10 min, the solvent was removed under reduced pressure, and the resulting residue was purified by flash chromatography (silica gel, EtOAc/*n*-hexane = 1/20) to provide the product as colorless oil; yield: 0.048 g (81 %).

1.3.1.10 Cleavage of C=S Bonds

DMDO can also be used in oxidative cleavage of C=S bond. Isothiocyanates are readily oxidized to isocyanates which can be trapped by amines to form ureas in good yields (Table 1.20).[119] The mild non-nucleophilic nature of DMDO makes it a better reagent than other oxidants such as MCPBA, trifluoroperacetic acid, and ozone for this transformation. Since the reaction is carried out in dry DMDO solution, further oxidation of isocyanates to nitro compounds as described in Table 1.8[67] is avoided.

Table 1.20 Synthesis of Isocyanates via Cleavage of C=S Bonds by DMDO[119]

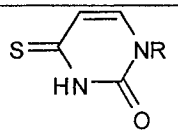
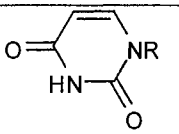
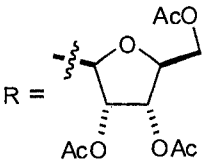
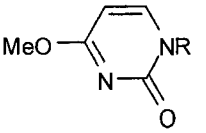
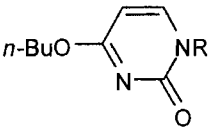
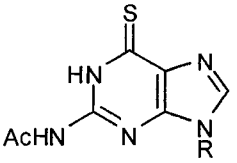
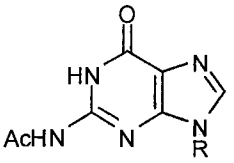
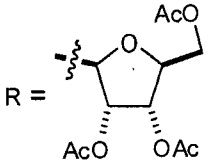
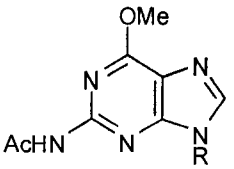


Entry	R	Yield (%)[a]	Ref
1	$PhCH_2$	84	119
2	$PhCH_2CH_2$	67	119
3	Ph	89	119
4	*n*-Bu	71	119

[a] Yield was based on urea by trapping the isocyanate *in situ* with isopropylamine.

Besides isothiocyanates, thioamides can also be efficiently oxidized by DMDO to the corresponding amides (Table 1.21, Entries 1 and 4).[118] DMDO solutions containing moisture give higher yields than dried DMDO for this transformation. If the reaction is carried out with dry DMDO acetone solution in the presence of alcohols, the alkoxy derivatives are produced in good yields (Table 1.21, Entries 2, 3, and 5).[118]

Table 1.21 Cleavage of C=S Bonds of Thioamides by DMDO[118]

En.	Starting Material	Product	Condition	Yield (%)	Ref
1			1.0 equiv wet DMDO, DCM, rt	95	118
2			1.0 equiv dry DMDO, DCM/MeOH (1/1), rt	70	118
3			1.0 equiv dry DMDO, DCM/*n*-BuOH (1/1), rt	75	118
4			1.0 equiv wet DMDO, DCM, rt	97	118
5			1.0 equiv dry DMDO, DCM/MeOH (1/1), rt	78	118

Phenyl isocyanate (Table 1.20, Entry 3); Typical Procedure: [119]

Phenyl isothiocyanate (0.15 g, 1.11 mmol) was added into a soln of dry DMDO (0.44 g, 6.0 mmol) in acetone (180 mL). The resulting mixture was stirred under N_2 at rt for 15 min to form phenyl isocyanate with complete conversion as judged by GCMS

analysis. Isopropylamine (1.12 g, 18.9 mmol) was added at 0 °C. The resulting mixture was stirred under N_2 for 1.5 h, filtered, concentrated under reduced pressure, and purified by flash column (silica gel, petroleum ether/EtOAc = 7/3) to give a white solid; yield: 0.20 g (89 %).

1.3.2 Oxidation of π-bonds by Dioxiranes

One of the most useful applications of dioxiranes is the oxidation of π bonds. Since the epoxidation of simple alkenes has been extensively described by Dr. David Goeddel in his dissertation, this section will mainly discuss the oxidation of allenes,[122-131] enols,[132-134] arenes,[135-149] and alkynes.[150-153]

1.3.2.1 Oxidation of Alkenes

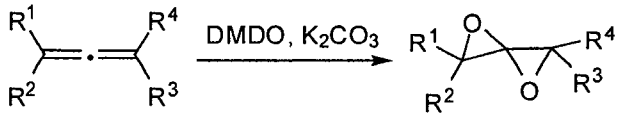
This part of the content has already been reviewed in Dr. David Goeddel's dissertation.

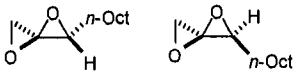
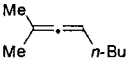
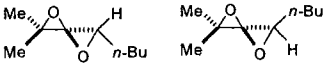
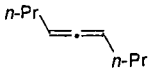
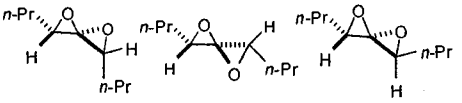
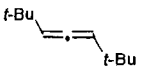
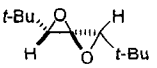
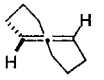
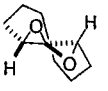
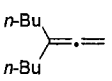
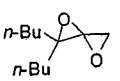
1.3.2.2 Oxidation of Allenes

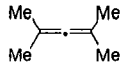
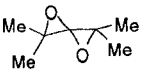
Oxidation of simple allenes by dry DMDO solution in the presence of a solid base such as K_2CO_3 can produce the corresponding 1,4-dioxaspiro [2,2] pentanes (Table 1.22) in good yields.[122,125] The initial epoxidation usually occurs at the more-substituted double bond from the face opposite to the substituent on the second double bond. The diastereoselectivity is highly dependent on the structure of allene. Acyclic mono- and trisubstituted allenes (Table 1.22, Entries 1-2) usually give good *anti* selectivity while the selectivity for acyclic symmetric 1,3-disubstituted allenes varies dramatically with the

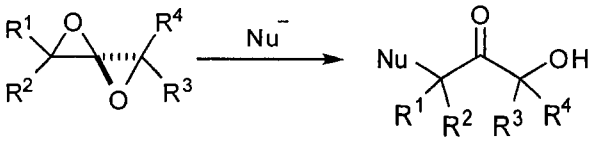
size of the substituent on the allene (Table 1.22, Entries 3-4). The oxidation of cyclic 1,3-disubstituted allene yields the *anti*, *anti* bisepoxide exclusively (Table 1.22, Entry 5). Oxidation of 1,1-disubstituted and tetrasubstituted allenes by DMDO produces bisepoxides in good yields (Table 1.22, Entries 6-7). These highly-strained spirodioxides can be smoothly transformed into highly functionalized α-hydroxy ketones by addition of a variety of nucleophiles including H_2O, alcohol, amine, thiophenol, acetate, halide, and organocuprate (Scheme 1.14).[125,131]

Table 1.22 Oxidation of Allenes with DMDO[122,125]



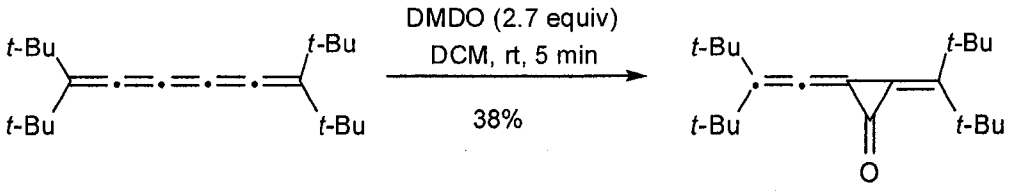
En.	Starting Material	Product	Condition	Yield (%)	Ref
1		 5 / 1	10 equiv DMDO, -40 °C, 2.5 h	50	122
2		 9 / 1	3.5 equiv DMDO, rt, 10 min	95	122
3		 1 / 1 / 0.15	4.4 equiv DMDO, rt, 20 min	99	125
4			6.9 equiv DMDO, 25 min	98	125
5			4.4 equiv DMDO, 20 min	95	125
6			10 equiv DMDO, -40 °C, 1.5h	80	122

7			4 equiv DMDO, -50 °C, 0.5 h	44	122



Scheme 1.14 Functionalization of Allene Epoxides[125,131]

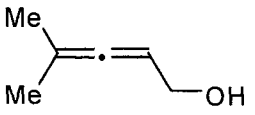
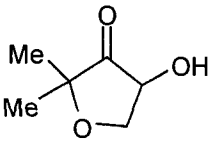
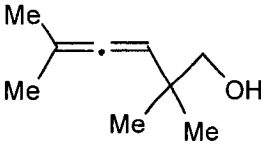
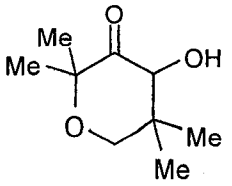
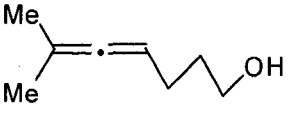
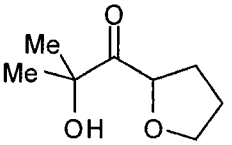
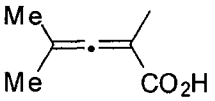
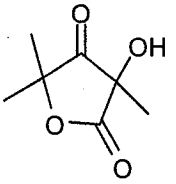
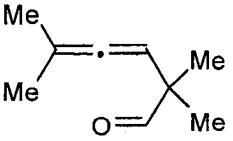
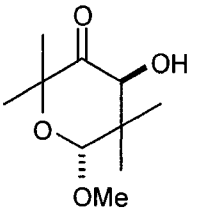
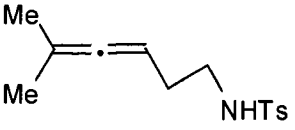
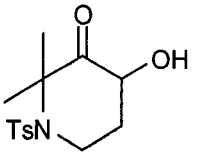
Oxidations of bisallenes[126] and cumulenes[127] have also been investigated. Sterically hindered higher-order cumulene is oxidized by DMDO to form a possible cumulene oxide intermediate which rapidly isomerizes to an uncommon cyclopropanone in overall moderate yield (Scheme 1.15).[127]



Scheme 1.15 Oxidation of Cumulenes by DMDO[127]

Allenyl alcohols (Table 1.23, Entries 1-3),[123,128] allenyl acids (Table 1.23, Entry 4),[124] allenyl aldehydes (Table 1.23, Entry 5),[129] and allenyl sulfonamides (Table 1.23, Entry 6)[130] can be oxidized by DMDO to form spirodiepoxides, which undergo an intramolecular nucleophilic addition *in situ* to produce the highly-functionalized tetrahydrofurans, tetrahydropyran derivatives, lactones, cyclic acetals and hemiacetals, and nitrogen heterocycles (Table 1.23).

Table 1.23 Oxidative Cyclization of Allenyl Derivatives with DMDO[123,124,128-130]

Entry	Starting Material	Product	Condition	Yield (%)	Ref
1			≥ 3.0 equiv DMDO	55	123 128
2			≥ 3.0 equiv DMDO	72	128
3			≥ 3.0 equiv DMDO	88	123 128
4			10 equiv DMDO	73	124
5			Excess DMDO, MeOH, K_2CO_3	83	129
6			7.5 equiv DMDO	52	130

2,5-Hexamethylene-1,4-dioxaspiro[2.2]pentane (Table 1.22, Entry 5); Typical Procedure: [125]

The cyclic allene (0.112 g, 0.9 mmol) was added into a stirred soln of DMDO (4 mmol) in acetone (40 mL) containing K_2CO_3. The mixture was stirred for 20 min, concentrated, diluted with ether, filtered, dried, and concentrated again to give the product as colorless oil; yield: 0.135 g (95%).

6-Hydroxy-2, 2, 5, 5-tetramethyl-3-oxacyclohexanone (Table 1.23, Entry 2); Typical Procedure: [128]

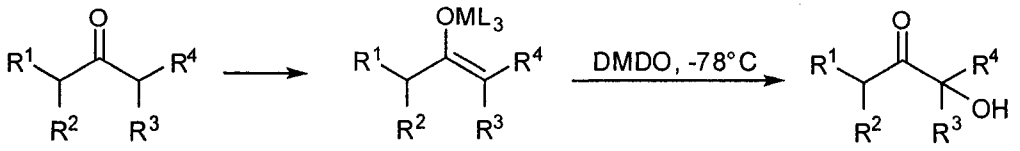
2,2,5-Trimethyl-3,4 –hexadien-1-ol (0.084 g, 0.60 mmol) was added into a DMDO soln in acetone (20 mL, more than 1.8 mmol). Upon consumption of allenyl alcohol, as monitored by TLC, the removal of solvent and excess oxidant gave 6-hydroxy-2, 2, 5, 5-tetramethyl-3-oxacyclohexanone as a white crystalline solid; yield: 0.074 g (72%).

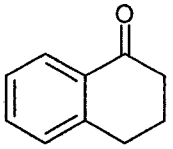
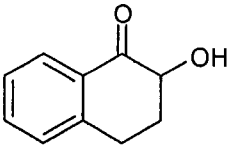
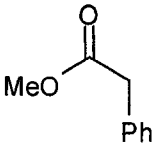
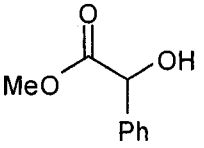
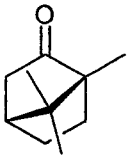
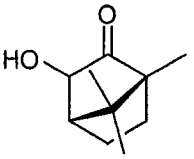
1.3.2.3 Oxidation of Enolates

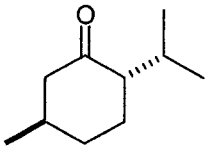
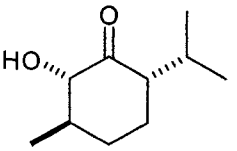
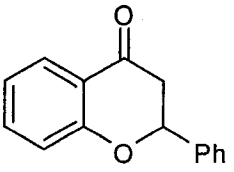
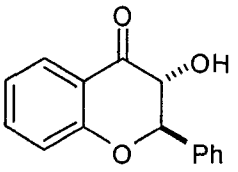
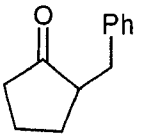
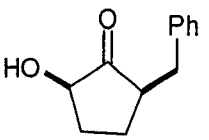
The direct oxidation of enolates by DMDO can produce α-hydroxyl carbonyl compounds. Both lithium enolates, generated with LDA,[132] and sodium enolates, generated with $NaN(TMS)_2$, [133] are good substrates for this oxidative process (Table 1.24, Entries 1-4). Higher yields of oxidation products are often obtained with sodium enolates as compared to lithium enolates, possibly due to higher reactivity of dissociated sodium enolates toward DMDO.[133] The inverse addition of enolates to a dry acetone solution of DMDO at low temperature also increases the yields of α-hydroxyl carbonyl compounds by minimizing the protonation of the enolates by acetone. Titanium enolates and silyl enol ethers, generated by transmetalation of the corresponding lithium enolates with

chlorotitanium or chlorosilane reagents, can also be oxidized by DMDO to form α-hydroxyl carbonyl compounds.[134] In general, oxidations of chiral chlorotitanocene enolates and silyl enol ethers give higher diastereoselectivity than that of sodium and lithium enolates (Table 1.24, Entries 3-6).[134] Overall, chiral chlorotitanocene enolates give the highest diastereoselectivity.[134]

Table 1.24 Oxidation of Enolates by DMDO [132-134]



En.	Substrate	Product	ML_3	Condition	Yield (%)	De (%)	Ref
1			Li	1.4 equiv DMDO, 10 min	82		132
2			Na	1.2 equiv DMDO, 2 min	60		133
3			Na	1.2 equiv DMDO, 2 min	57	29	133
4			Li	1.2 equiv DMDO, 2 min	70	50	133
5			$TiCp_2Cl$	1.2 equiv DMDO, 1 min[a]	67	84	134

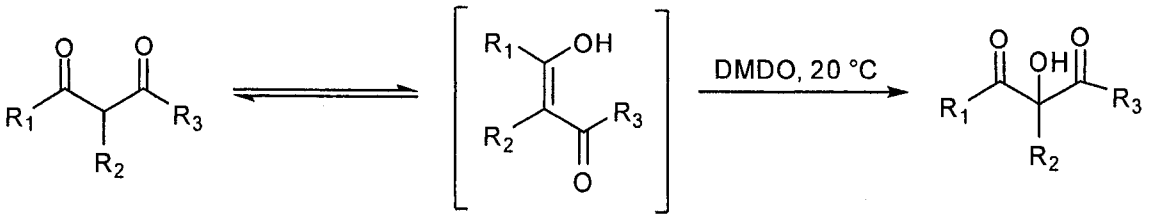
6			TMS	1.2 equiv DMDO, 30 min[b]	91	86 [134]
7			$TiCp_2Cl$	1.2 equiv DMDO, 1 min[a]	54	92 [134]
8			TMS	1.2 equiv DMDO, 30 min[b]	97	52 [134]
9			$TiCp_2Cl$	1.2 equiv DMDO, 1 min[a]	53	96 [134]
10			TMS	1.2 equiv DMDO, 30 min[b]	85	96 [134]
11			$TiCp_2Cl$	1.2 equiv DMDO, 1 min[a]	50	66 [134]
12			TMS	1.2 equiv DMDO, 30 min[b]	96	30 [134]

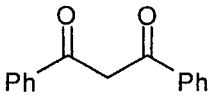
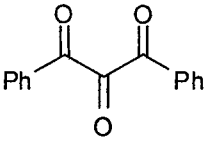
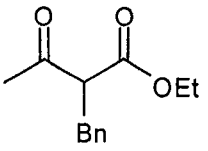
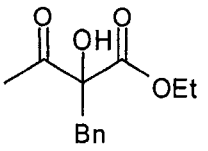
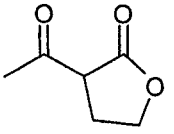
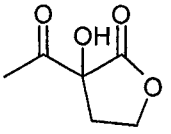
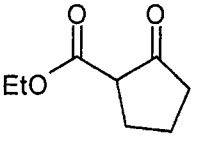
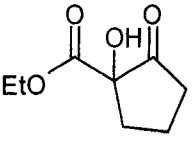
[a] The reaction mixture was quenched by sat. aq NH_4F soln and was stirred for 12 h at rt; [b] The reaction mixture was quenched by a suspension of NH_4F in MeOH and was stirred for 3 h at rt.

1,3-Dicarbonyl compounds can be directly oxidized by DMDO to form hydroxyl derivatives in high yields possibly via the enol intermediates. The oxidation usually requires long reaction times, higher temperature, and large excess of DMDO to achieve complete conversion (Table 1.25).[133] A significant rate acceleration is observed by

adding a fluoride ion, such as KF, possibly as a catalyst for the formation of enols, thus reducing the reaction times from days to an hour.

Table 1.25 Direct Oxidation of Enols with DMDO[133]



Entry	Substrate	Product	DMDO (equiv)	Time	Yield (%)	Ref
1			4	4 d	98	133
2			4	3 d	100	133
			3[a]	1 h	76	133
3			3	3 d	98	133
			1.1[a]	1 h	85	133
4			3	3 d	100	133
			3[a]	1 h	85	133

[a] Equivalents of Oxone. DMDO was generated *in situ* from Oxone and acetone. 1 equiv KF was used as catalyst to generate the enols.

2-Hydroxy-3,4-dihydronaphthalen-1(2H)-one (Table 1.24, Entry 1); Typical Procedure:[132]

A dry THF (0.5 mL) soln of α-tetralone (40 mg, 0.27 mmol) was added dropwise via a cannula to a soln of LDA freshly prepared by treating *i*-Pr_2NH (0.087 mL, 0.62 mmol) with *n*-BuLi (0.32 mL, 1.7 M, 0.54 mmol) in dry THF (2.0 mL) under argon at -78 °C for 10 min (the cannula was washed twice with 1 mL portions of dry THF to ensure complete transfer of α-tetralone). Upon stirring at -78 °C for 1 h, the mixture was added dropwise via a cannula to a flask containing dry DMDO acetone soln (5.8 mL, 0.062 M, 0.36 mmol) at -78 °C. The resulting mixture was stirred at -78 °C for 10 min, quenched by a buffer soln (pH = 7) at -78°C, and warmed to rt. The mixture was concentrated and redissolved in DCM (10 mL) and washed with water (5 mL). The aqueous layer was further extracted with DCM (2×5 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated, and purified by flash chromatography (silica gel, hexane/diethyl ether = 6.5/3.5) to give the product as light yellow oil; yield: 0.0364 g (80%).

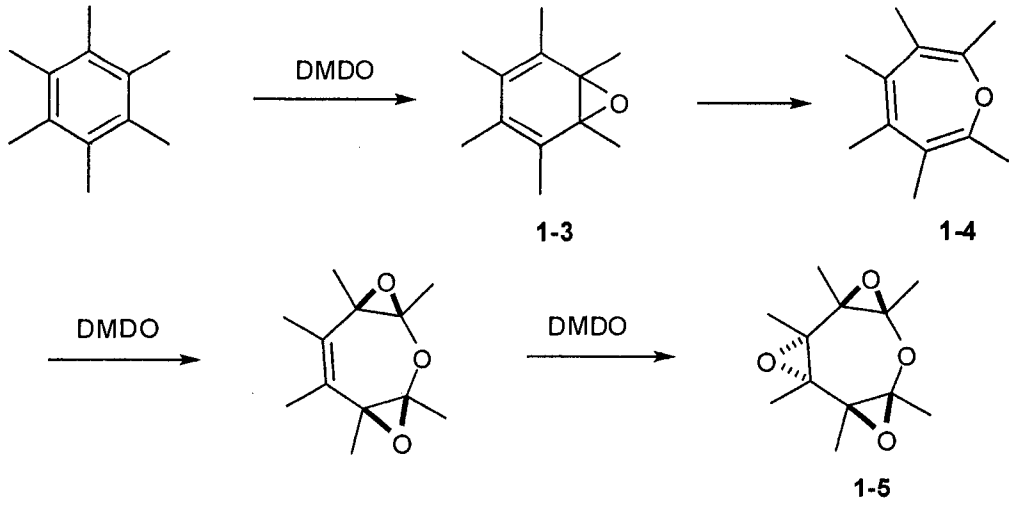
Ethyl 1-hydroxy-2-oxocyclopentanecarboxylate (Table 1.25, Entry 4); Typical Procedure:[133]

A 15% water soln of Oxone (10.2 g, 30 mmol) was added slowly within 1 h to a vigorously stirred mixture of the dicarbonyl compound (1.56 g, 10.0 mmol), acetone (8 mL), phosphate buffer (prepared from 0.059 g KH_2PO_4, 0.216 g Na_2HPO_4 in 50 mL of water), and KF (0.58 g, 10 mmol). The pH of the mixture was maintained constantly at 7.3-7.5 by adding a 10% aqueous KOH soln throughout the reaction. After all Oxone was added, the resulting mixture was stirred for an additional 15 min. The solid NaCl was added to saturation and the mixture was extracted by *t*-BuOMe (3×100 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated, and purified by

flash chromatography (silica gel, DCM) to give product as colorless oil; yield: 1.46 g (85%).

1.3.2.4 Variation 4: Oxidation of Arenes

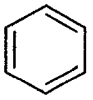
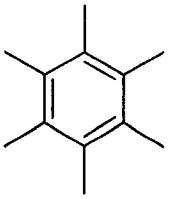
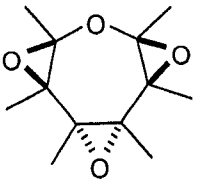
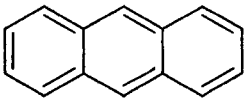
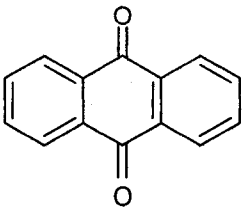
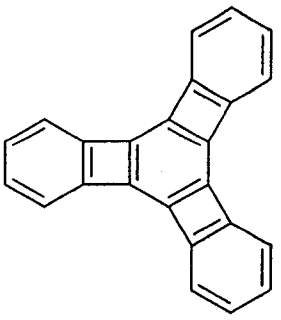
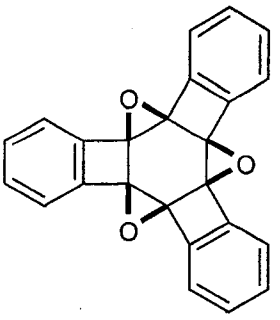
Dioxiranes can also oxidize certain arenes particularly for electron-rich aromatics such as phenols and anisoles.[135-149] In many cases, the epoxides from initial oxidation of arenes can undergo rearrangement to form certain intermediates which are further oxidized by dioxiranes. For example, hexamethylbenzene is initially oxidized by DMDO to form epoxide **1-3**, which readily tautomerizes to 2,3,4,5,6,7-hexamethyloxepin **1-4**. Further oxidation of **1-4** by DMDO gives triepoxide **1-5** (Scheme 1.16).[144,146] Thus, the products formed from oxidation of arenes by dioxiranes often vary with the structure of arenes and the reaction conditions.

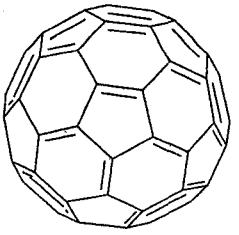
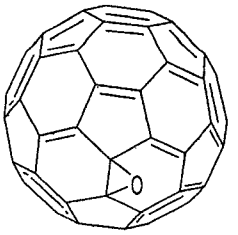


Scheme 1.16 Oxidation of Hexamethylbenzene by DMDO[144,146]

Among various arenes, benzene is difficult to oxidize and is inert towards DMDO. However, benzene has been oxidized by more reactive TFDO in a fluorinated solvent, giving two isomeric dialdehydes in 35% yield (Table 1.26, Entry 1).[137] The alkyl-substituted benzenes, naphthalene, and polycyclic arenes are more reactive substrates for the oxidation, giving the resulting products in moderate to good yields (Table 1.26).[137,140,143,144,146,147]

Table 1.26 Oxidation of Aromatic Hydrocarbons with Dioxiranes[137,140,143,144,146,147]

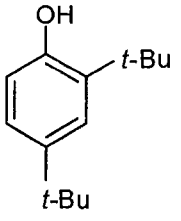
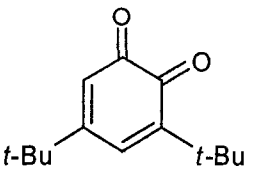
En.	Substrate	Product	Condition	Yield (%)	Ref
1		O=CHCH=CHCH=CHCH=O (*Z,Z-/E,E-* = 1:1.5)	0.2 equiv TFDO, F113, 0 °C, 6 h	35[a]	137
2			4.0 equiv DMDO, rt, 2 d	51	144,146
3			4.5 equiv TFDO, 0 °C, 30 min	80	137
4			DMDO	84	143

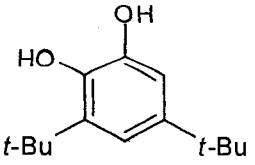
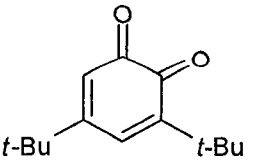
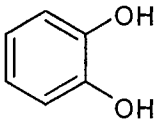
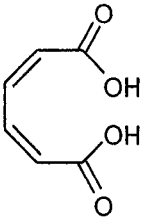
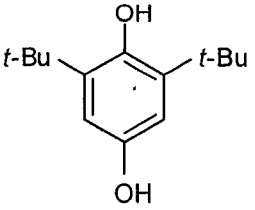
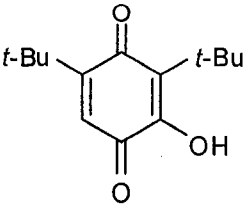
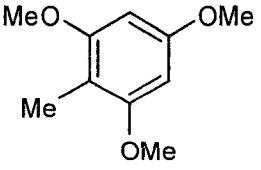
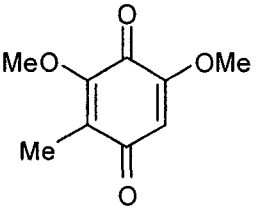
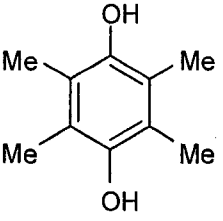
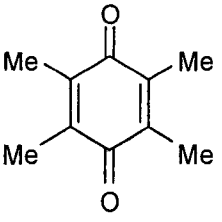
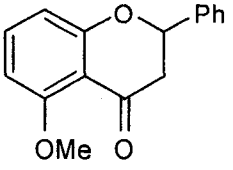
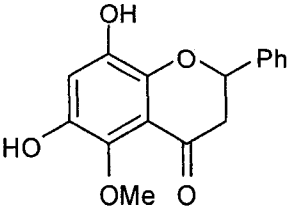
5			4.0 equiv TFDO, 0 °C, 5 min	20	[140,147]

[a] Yield is based on TFDO.

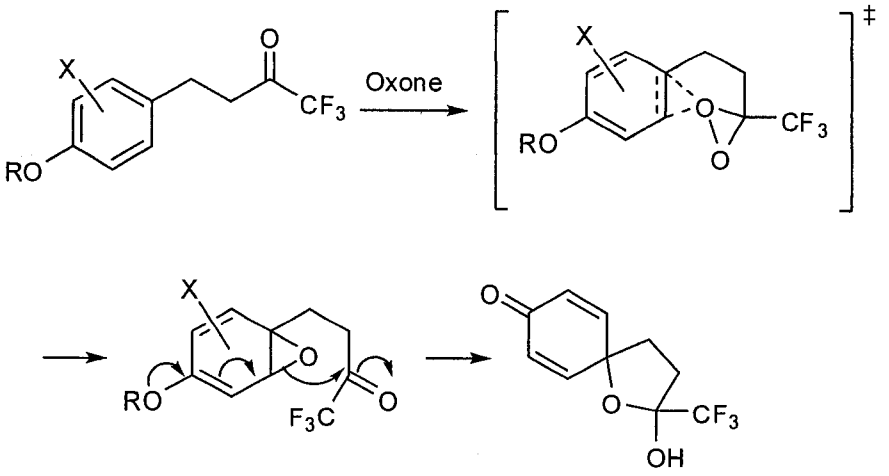
Electron-rich substituted aromatic rings, such as phenols,[138,141] catechols,[138,139] and anisoles,[142] are reactive to dioxirane oxidation. However, such oxidations often give low regioselectivity and yield complex product mixtures, which have been improved by using hindered substrates[138] and/or performing the reaction under acidic conditions in some cases (Table 1.27).[139,148] The regioselective oxidation of phenols and anisoles by dioxirane can be achieved in an intramolecular fashion to form spiro 2-hydroxydienones regardless of the presence of other substituents on the phenyl ring (Table 1.28).[149] In those cases, electron-rich aromatic rings are connected with electrophilic carbonyl groups which are converted to dioxiranes *in situ* with Oxone. The reaction process may involve intramolecular epoxidation of the aryl ring followed by epoxide rearrangement and hemiketal formation (Scheme 1.17).

Table 1.27 Oxidation of Phenols and Anisoles with Dioxiranes[138,139,141,142,148]

En.	Substrate	Product	Condition	Yield (%)	Ref
1			4.0 equiv DMDO	55	[138]

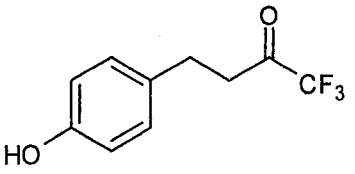
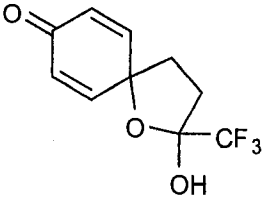
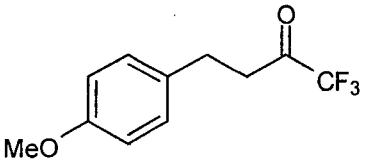
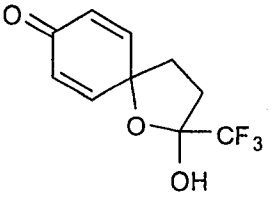
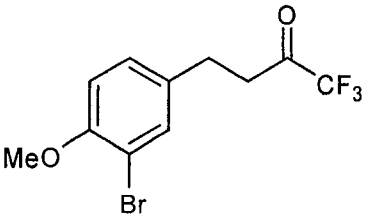
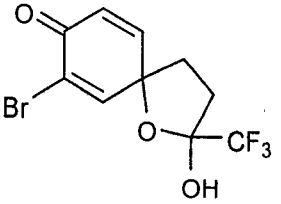
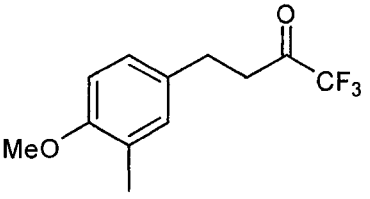
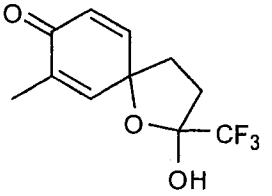
2			4.0 equiv DMDO	100	[138]
3			2.2 equiv TFDO, Acetone/TFP(1/1), -20 °C, 60 min	88	[139]
4			4.0 equiv TFDO DCM/TFP, 0 °C, 1 min	70[a]	[139]
5			2.0 equiv DMDO H_2SO_4, 0 °C, 60 min	50	[142]
6			3.0 equiv DMDO, 20 °C	87	[141]
7			3.0 equiv DMDO, 2 N HCl, -30 °C	100	[148]

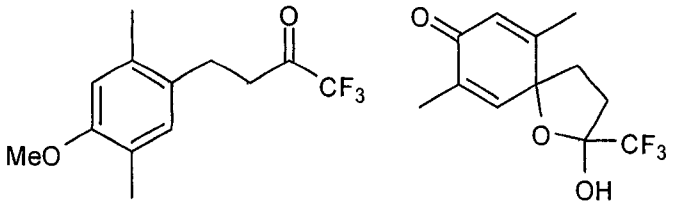
[a] GC yield.



Scheme 1.17 Intramolecular Oxidation of Phenols and Anisoles[149]

Table 1.28 Intramolecular Oxidation of Phenols and Anisoles[a149]

En.	Substrate	Product	Time	Yield (%)	Ref
1			15 min	53	149
2			30 min	55	149
3			2 h	47[b]	149
4			1 h	55[b]	149

5			1 h	50[b]	149

[a] All the reactions were in a mixture of CH_3CN and aq Na_2EDTA soln (v/v, 1.5/1) with 5 equiv Oxone and 16 equiv $NaHCO_3$ at rt. [b] Combined yield of the 1:1 mixture of diastereomers.

2,3:4,5:6,7-Triepoxy-2,3,4,5,6,7-hexamethyloxepane (Table 1.26, Entry 2); Typical Procedure:[144,146]

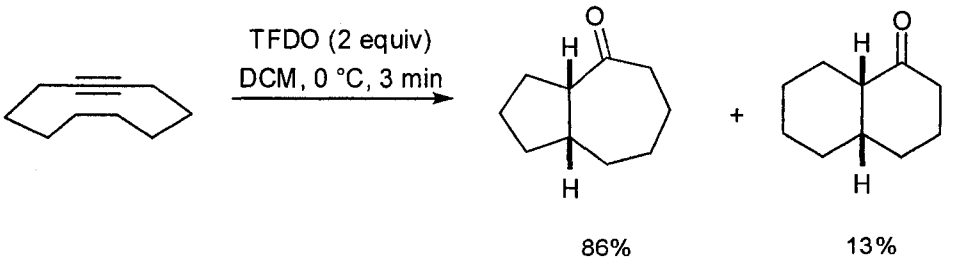
A soln of DMDO in acetone (38 mL, 0.074 M, 2.8 mmol) was added to a soln of hexamethylbenzene (0.114 g, 0.7 mmol) in acetone (3 mL) with magnetic stirring. The reaction mixture was stirred at rt for 24 h to give an orange-yellow soln. An additional aliquot of the DMDO soln (10 mL) was added and stirring continued for an additional 24 h. Solvent was removed to give a colorless residue (0.148 g), which was purified on the Chromatotron using acetone (5-10%) in hexane as eluent to afford 2,3:4,5:6,7-triepoxy-2,3,4,5,6,7-hexamethyloxepane as a colorless crystalline solid; yield: 0.081g (51%).

2-Hydroxy-2-(trifluoromethyl)-1-oxaspiro[4.5]deca-6,9-dien-8-one (Table 1.28, Entry 2); Typical Procedure:[149]

To a mixture of the ketone (0.232 g, 1.0 mmol) in CH_3CN (60 mL) and an aqueous Na_2·EDTA soln (40 mL, 4×10^{-4} M) was added a mixture of Oxone (3.07 g, 5.0 mmol) and $NaHCO_3$ (1.30 g, 15.5 mmol) at rt. Upon stirring at rt for 30 min, the reaction mixture was poured into brine and extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$, filtered, concentrated, and purified by flash column chromatography (silica gel, EtOAc/*n*-hexane = 3/7) to give the spiro-dienone as colorless syrup; yield: 0.129 g (55%).

1.3.2.5 Oxidation of Alkynes

Unlike alkenes, the oxidation of alkynes by dioxiranes is often sluggish and yields a complex mixture of products.[150-153] The reaction presumably goes through an oxirene intermediate, which is unstable and easily undergoes several transformations under the reaction conditions to form various products. Nevertheless, a well-defined bicyclic product is obtained in good yield when a cyclic alkyne is oxidized by isolated TFDO (Scheme 1.18).[150]



Scheme 1.18 Oxidation of Alkynes by TFDO[150]

1.3.3 Oxidation of X-H σ Bonds by Dioxiranes

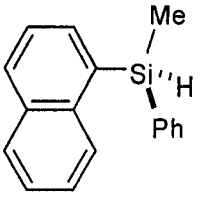
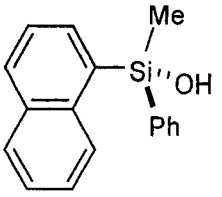
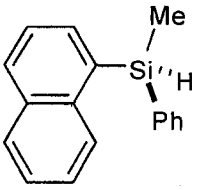
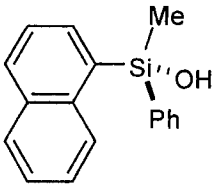
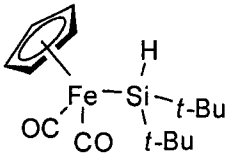
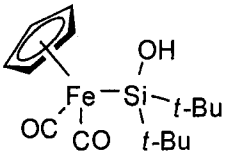
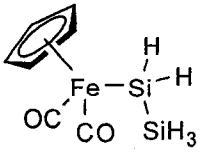
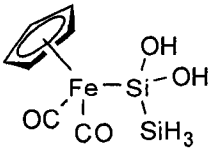
One of the highlights of dioxirane chemistry is the effective oxidation of C-H and Si-H σ bonds to form the corresponding alcohols, ketones, and silanols.

1.3.3.1 Oxidation of Si-H σ Bonds

Si-H σ bonds are weaker than C-H σ bonds and can be more readily oxidized by DMDO or TFDO to produce the silanols in high yields (Table 1.29).[154-158] The oxidation

is stereospecific, likely via a concerted O-atom insertion mechanism, and the original configurations of chiral silanes are maintained during the process (Table 1.29, Entries 3-4).

Table 1.29 Oxidation of Silanes by Dioxiranes[154,155,158]

En.	Starting Material	Product	Condition	Yield (%)	Ref
1	Et_3SiH	Et_3SiOH	1.0 equiv TFDO, -20 °C, < 1 min	≥ 98[a]	154
2	$PhMe_2SiH$	$PhMe_2SiOH$	1.0 equiv TFDO, -20 °C, < 1 min	≥ 98[a]	154
3			1.0 equiv TFDO, -20 °C, < 1 min	≥ 98[a]	154
4			1.2 equiv DMDO, 0 °C, 18 min	≥ 98[a]	154
5			1.9 equiv DMDO, -78 °C, 18 min	98	155
6			2.0 equiv DMDO, -78 °C - rt, 50 min	89	158

[a] GC yield.

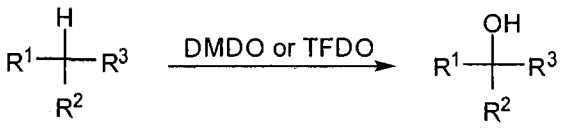
[Di-*tert*-butyl(hydroxy)silyl]dicarbonyl(η-cyclopentadienyl)iron(II) (Table 1.29, Entry 5); Typical Procedure:[155]

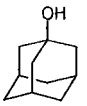
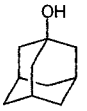
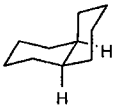
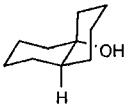
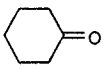
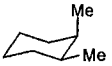
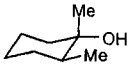
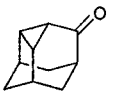
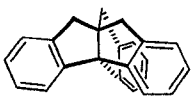
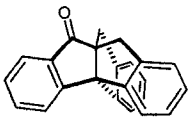
To a soln of silane (0.216 g, 0.68 mmol) in acetone (1 mL) at -78 °C, DMDO soln (14.9 mL, 12.8 mmol) was added rapidly. The resulting mixture was stirred at -78 °C until complete disappearance of DMDO (18 min, monitored by negative KI test). After filtration over celite, the mixture was concentrated and purified by column chromatography (silylated silica gel, cyclohexene/toluene = 20/1) to give a brown oil; yield: 0.233 g (98%).

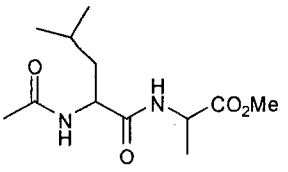
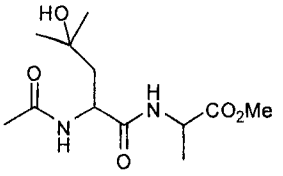
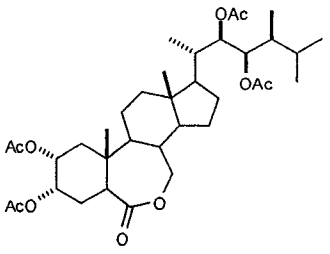
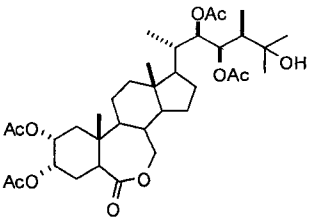
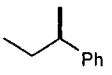
1.3.3.2 Oxidation of C-H σ Bonds in Saturated Alkanes

Direct insertion of an oxygen atom into C-H σ bonds is another important reaction of dioxiranes.[15,17,159] A wide variety of saturated alkanes can be effectively converted to oxyfunctionalized compounds such as alcohols and ketones (Table 1.30).[76,159-171] The C-H oxidation is often regioselective due to the different reactivity of various C-H σ bonds, generally following on the order of tertiary > α-cyclopropyl > benzylic ≈ secondary > primary C-H bonds.[17] For oxidation of secondary C-H bonds, the alcohols initially formed usually are further oxidized to ketones since C-H bonds adjacent to an oxygen atom are activated and more prone to dioxirane oxidation. The dioxirane C-H oxidation generally proceeds via a concerted, spiro-structured oxenoid-type mechanism, which has been supported by theoretical and experimental evidence.[160,172-175] As a result, the C-H oxidation is stereospecific and the configuration of C-H bond is therefore maintained during the reaction (Table 1.30, Entry 10).[161] TFDO oxidizes C-H bond at much faster rate than DMDO.[160]

Table 1.30 Oxidation of C-H Bonds of Saturated Alkanes with Dioxiranes[76,159-161,163,164,168]



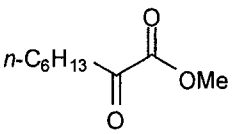
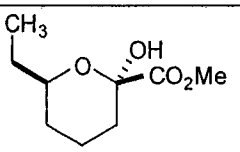
En.	Starting Material	Major Product	Condition	Yield (%)	Ref
1			0.6 equiv DMDO, 22 °C, 18 h	87[a]	159
2			2.0 equiv TFDO, -22 °C, 1 min	86	160
3			1.1 equiv TFDO, -22 °C, 5 min	88	160
4			1.1 equiv TFDO, -22 °C, 18 min	99[b]	160
5			1.1 equiv TFDO, -22 °C, 4 min	92	160
6			4.0 equiv TFDO, 0 °C, 1.5 h	66	168
7			5.0 equiv TFDO, 0 °C, 40 min	76	163

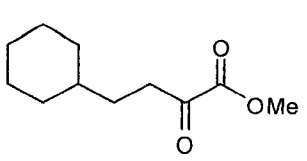
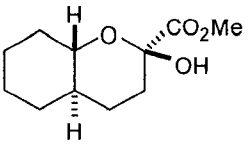
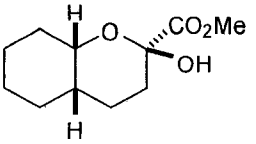
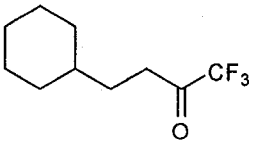
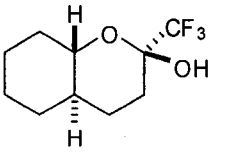
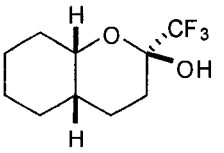
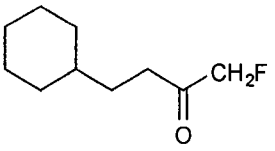
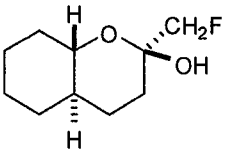
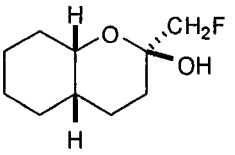
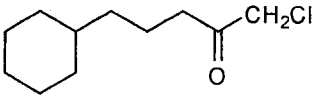
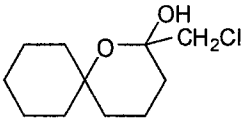
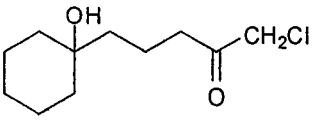
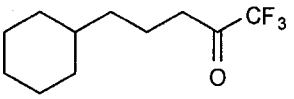
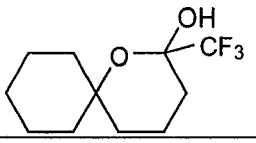
8			5.0 equiv TFDO, 0 °C, 6 h	73	76
9			1.2 equiv TFDO, 0 °C, 40 h	71	164
10			2.0 equiv TFDO, -24 °C, 1 h	95	161

[a] Yield is based on DMDO. [b] GC yield.

Dioxiranes generated *in situ* from various activated carbonyl groups and Oxone can regioselectively oxidize secondary or tertiary C-H bonds at the δ carbons in an intramolecular fashion, and the resulting alcohols further cyclize to the carbonyl groups to produce tetrahydropyrans in good yields (Table 1.31).[176] Since the primary C-H bond is most unreactive to dioxirane oxidation, no C-H oxidation was observed for methyl 2-oxohexanoate which only has primary δ C-H bonds. The diastereoselectivity observed for oxidation products can be rationalized based on the concerted spiro transition states.

Table 1.31 Intramolecular Oxidation of Unactivated C-H Bonds[a] [176]

En.	Starting Material	Product (Ratio)	Yield (%)	Ref
1			70	176

2		 4 / 1		83	176
3		 4.8 / 1		87	176
4[b]		 4.2 / 1		70	176
5		 2.6 / 1		77	176
6				78	176

[a] All the reactions were in a mixture of CH_3CN and aq Na_2EDTA soln (v/v, 1.5/1) with 5 equiv Oxone and 15 equiv $NaHCO_3$ at rt for 24 h; [b] Reaction time is 120 h.

(*S*)-2-Phenyl-2-butanol (Table 1.30, Entry 10); Typical Procedure:[161]

A TFDO soln (6.6 mmol) in 1, 1, 1-trifluoro-2-propanone was added to a soln of (*R*)-2-phenylbutane (0.44 g, 3.3 mmol) in DCM (20 mL) at -24 °C in one portion. The resulting mixture was stirred at -24 °C for 1 h (complete conversion of substrate as monitored by GC). The solvent was removed and the residue was purified by

chromatography (silica gel, hexane/ether = 7/3) to give pure (*S*)-2-phenyl-2-butanol as colorless oil; yield: 0.47 g (95%).

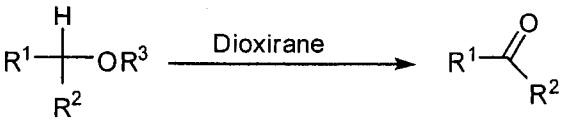
2-(Trifluoromethyl)-1-oxaspiro[5.5]undecan-2-ol (Table 1.31, Entry 6); Typical Procedure: [176]

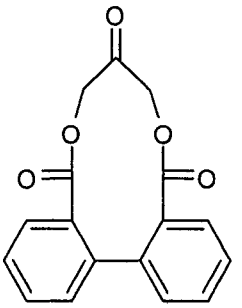
An aq Na_2·EDTA soln (20 mL, 4×10^{-4} M) was added to a soln of ketone (0.111 g, 0.5 mmol) in CH_3CN (30 mL) at rt, followed by addition of a mixture of Oxone (1.54 g, 2.5 mmol) and $NaHCO_3$ (0.65 g, 7.75 mmol). After stirring at rt for 24 h, the reaction mixture was poured into brine and extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$, concentrated, and purified by flash column (silica gel, EtOAc/*n*-hexane=1/9) to give product as a colorless oil; yield: 0.093 g, (78%).

1.3.3.3 Oxidation of Activated C-H σ Bonds

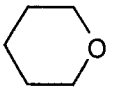
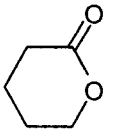
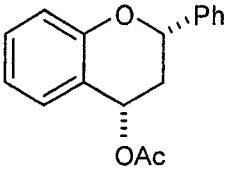
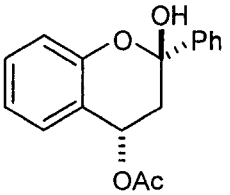
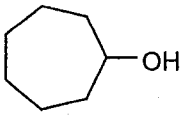
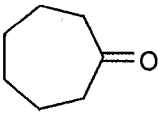
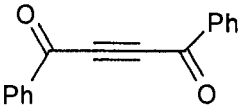
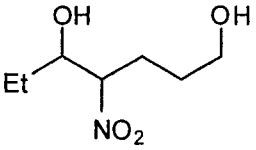
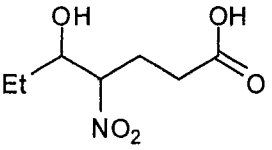
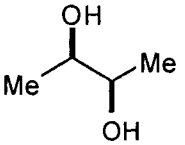
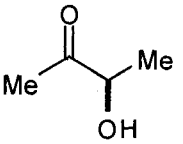
The C-H bonds adjacent to oxygen atoms are activated for the oxidation by dioxiranes. Such oxidation has lead to various synthetic transformations such as, hydropyranes to lactones or hemiketals (Table 1.32, Entries 1 and 2),[177,178] *tert*-butyl ethers to alcohols and carbonyl compounds (Table 1.32, Entry 3),[179] alcohols to ketones and acids (Table 1.32, Entries 4, 5, and 6),[153,180,181] diols[182,183] or ketals[177,183,184] to hydroxy ketones (Table 1.32, Entries 7-11). Since the oxidation is carried out under neutral conditions with high efficiency, optical purities of the resulting products are maintained when optically active starting materials are used (Table 1.32, Entries 7, 8, and 11).[182,184]

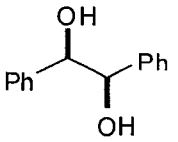
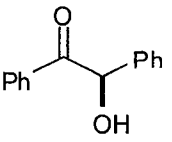
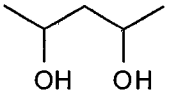
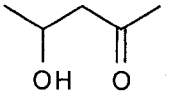
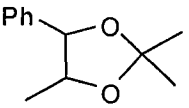
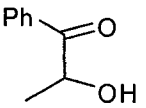
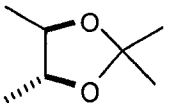
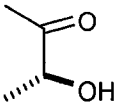
Table 1.32 Oxidation of Activated C-H Bonds with Dioxiranes[153,177-184]





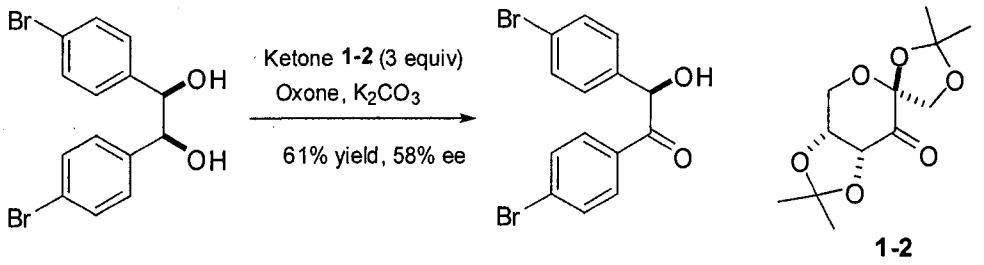
1-6

En.	Starting Material	Product	Condition	Yield (%)	Ref
1			2.2 equiv TFDO, 0 °C, 15 min	77[a]	177
2			DMDO, rt	63	178
3	*t*-BuOEt	*t*-BuOH, CH_3CHO	DMDO, rt	> 97[a,b]	179
4			0.2 equiv ketone **1-6**, 2 equiv Oxone, $NaHCO_3$, CH_3CN, rt, 3.5 h	91	180
5			3 equiv TFDO, 0 °C, 0.3 h	96	153
6			1.5 equiv DMDO, rt, overnight	80[a]	181
7	 > 98% ee	 > 98% ee	1.2 equiv DMDO, 0 °C, 4 h	> 96[a]	182

8	 96% ee	 92% ee	1.2 equiv TFDO, 0 °C, 100 min	96[a]	182
9			1.5 equiv DMDO, rt , overnight	95	183
10			1.5 equiv DMDO, rt, overnight	85	183
11	 98% ee	 98% ee	1.2 equiv TFDO, 0 °C, 40 min	> 96[a]	184

[a] GC yield; [b] Yield was based on DMDO.

The enantioselective C-H oxidation of *vic*-diols had been achieved by chiral dioxiranes generated *in situ* from Oxone and chiral ketones (Scheme 1.19).[185,186,187] Although the enantioselectivity and substrate scope awaits improvement, this enantioselective transformation has illustrated its potential synthetic value.



Scheme 1.19 Selected Examples of Enantioselective C-H Oxidation of *vic*-diols[185-187]

Cycloheptanone (Table 1.32, Entry 4); Typical Procedure:[180]

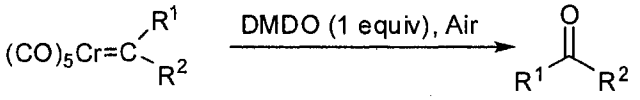
An aq Na_2EDTA soln (1 mL, 4×10^{-4} M) was added to a soln of ketone catalyst **1-6** (0.06 mmol) and cycloheptanol (0.3 mmol) in CH_3CN (1.5 mL) at rt, followed by addition of a mixture of Oxone (0.6 mmol) and $NaHCO_3$ (1.86 mmol) in portions. After stirring at rt for 3.5 h, the reaction mixture was poured into water and extracted with DCM three times. The combined organic layers were dried over Na_2SO_4, concentrated, and purified by flash column to give cycloheptanone; yield: 0.031 g (91%).

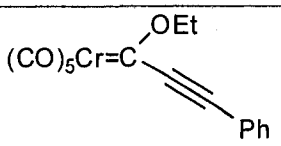
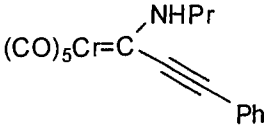
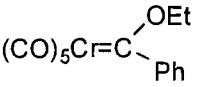
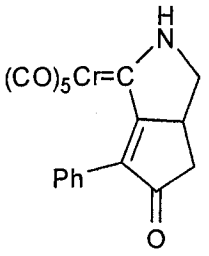
1.3.4 Oxidation of Organometallic Compounds by Dioxiranes

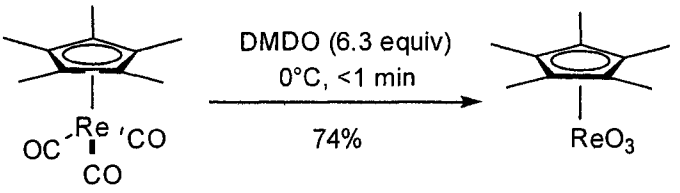
Oxidation of organometallic compounds by dioxiranes can occur at organic ligands and/or metal centers. Organic ligands often are oxidized before metal centers due to their electron richness. Examples include oxidation of heteroatoms (sulfur,[41,45,48,50] phosphorous,[90,188] and nitrogen[189]), epoxidation of π bonds (alkene,[190,191] alkyne,[152] and enolate[134]), and oxidation of X-H σ bonds (C-H bond[191] and Si-H bond[155-158]) as described in Chapter 1.3.1-1.3.3. Fisher carbenes can also be oxidized by DMDO to form esters or amides and chromium(III) oxide (Table 1.33).[192,193] The reaction may involve an initial oxidation of CO ligand by DMDO to CO_2. The resulting unstable chromium tetracarbonyl intermediate would react with O_2 to form the carbonyl product and chromium(III) oxide.[194] Rhenium and molybdenum carbonyl complexes have been shown to be oxidatively decarbonylated by DMDO in good yields (Scheme 1.20).[195] Arenechromium tricarbonyl complexes can also be converted to the corresponding arenes and chromium(III) oxide by DMDO with quantitative yields (Scheme 1.21).[196] A metal center can also be oxidized by DMDO to a higher oxidation state. For example, DMDO

is used as a stoichiometric oxidant in asymmetric epoxidation catalyzed by Jacobsen's Mn(III)salen catalyst.[197,198] In this reaction process DMDO oxidizes Mn(III) is oxidized to Mn(IV). It appears that DMDO oxidizes the Mn(III)salen complex faster than olefins since high ee is obtained for the epoxidation.

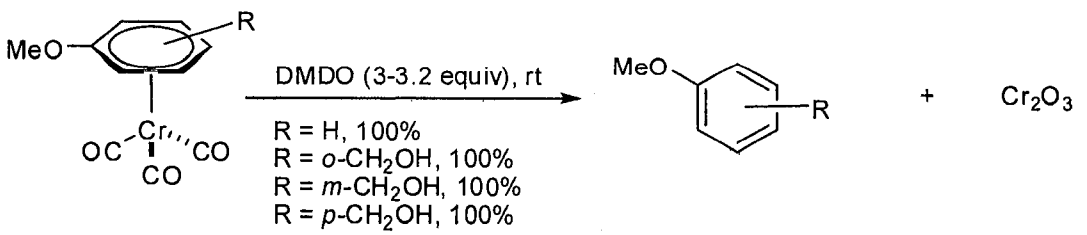
Table 1.33 Oxidation of Fisher Carbenes by DMDO[192,194]



Entry	Starting Material	Condition	Yield (%)	Ref
1		-20 °C, 4 h	90	192,194
2		-20 °C, 4 h	94	192
3		20 °C, 3 h	97	192
4		20 °C, 24 h	63	192



Scheme 1.20 Oxidative Decarbonylation of Rhenium Carbonyl Complex by DMDO[195]



Scheme 1.21 Decomplexation of Arene Chromium Compound by DMDO[196]

Ethyl 3-phenylpropiolate (Table 1.33, Entry 1); Typical Procedure:[194]

Two portions of dry DMDO soln (6.8 mL, 0.56 mmol) were added dropwise into a clear soln of Fisher carbene (0.099 g, 0.28 mmol) in acetone (10 mL) at -20 °C within 4 h under darkness. After the reaction was completed (TLC monitoring), the resulting mixture was concentrated under vacuum (25 °C, 20 Torr), resuspended in DCM, and filtered through celite to remove the chromium oxides. The filtrate was concentrated to give pure ethyl phenylpropiolate; yield: 0.044 g (90%).

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CHAPTER 2.0 : ENANTIOSELECTIVE EPOXIDATION OF TRISUBSTITUTED AND TETRASUBSTITUTED OLEFINS WITH A CONJUGATED ARYL GROUP AND RELATED APPLICATION

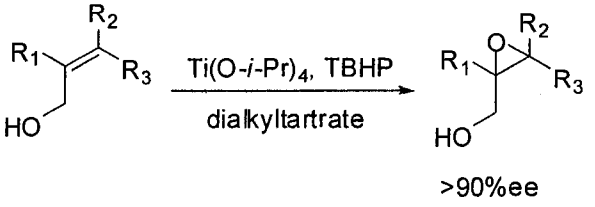
2.1 INTRODUCTION

2.1.1 Background of Asymmetric Epoxidation

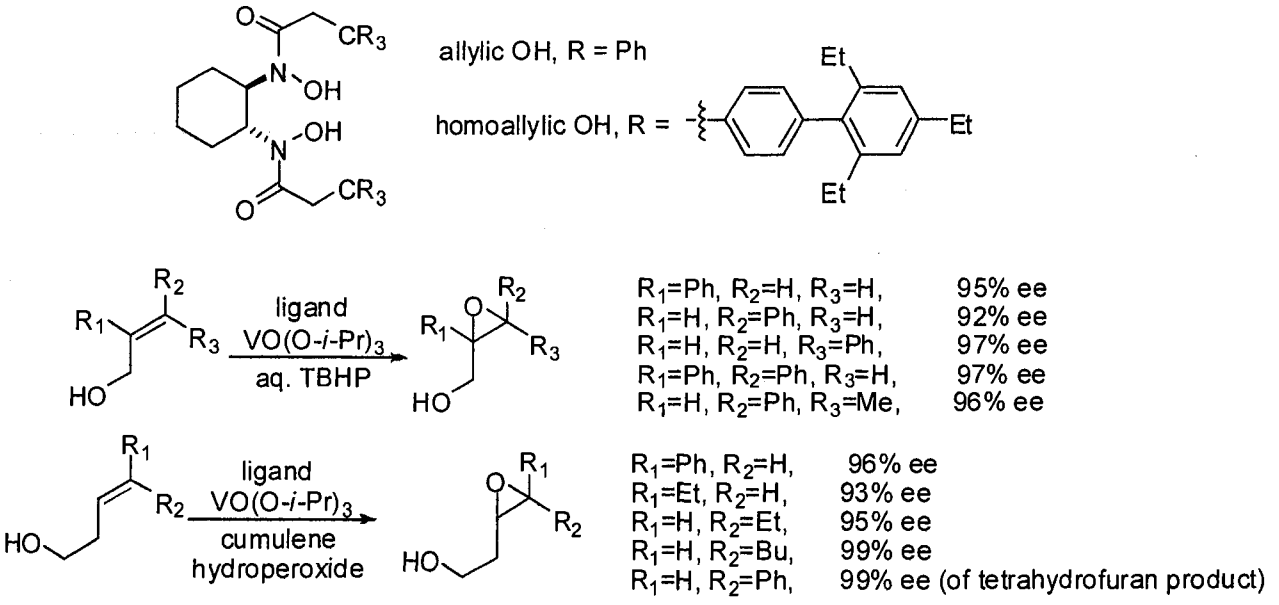
Epoxides are important intermediates and building blocks in the synthesis of complex molecules. As a functional group, epoxides are also broadly present in many biologically active compounds. Therefore, effective methods for synthesizing chiral, non-racemic epoxides are highly desirable. Various effective systems have been developed over the years for the preparation of chiral epoxides,[1-4] and asymmetric epoxidation of olefins has proven to be one of the most powerful and convenient approaches for their synthesis.

In the 1980's, Sharpless reported the first synthetically useful and highly enantioselective epoxidation method: the epoxidation of allylic alcohols with chiral titanium dialkyltartrate complex (Scheme 2.1).[5-8] Recently Yamamoto described that

chiral complexes of vanadium and bishydroxamic acids can catalyze asymmetric epoxidation of both allylic[9-12] and homoallylic[12-14] alcohols with high enantioselectivity (Scheme 2.2). The drawback of the Sharpless and Yamamoto methods is that the substrates have to be functionalized and require an alcohol group as a directing group at allylic and homoallylic positions of the olefin.



Scheme 2.1



Scheme 2.2

The first successful approach to the asymmetric epoxidation of unfunctionalized olefins was independently developed by Jacobsen (Figure 2.1)[15] and Katsuki (Figure 2.2)[16] in the 1990's. These methods utilize Mn-salen complexes as catalysts in the epoxidation of a variety of unfunctionalized conjugated olefins (especially for *cis*-olefins) with good enantioselectivities (Figures 2.1 and 2.2). Recently this approach has further evolved to a new level. Chiral Ru-salen complexes (Figure 2.3),[17] chiral titanium dimer complexes (Figures 2.4 and 2.5),[18-21] and chiral molybdenum bishydroxamic acid complexes (Figure 2.6)[12,22] were developed as catalysts for asymmetric epoxidation with broader substrate scope including some unconjugated *cis*- and terminal olefins.[20]

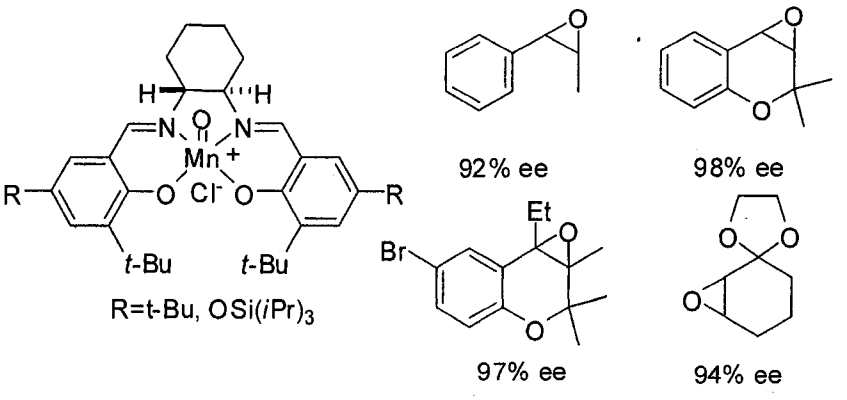


Figure 2.1

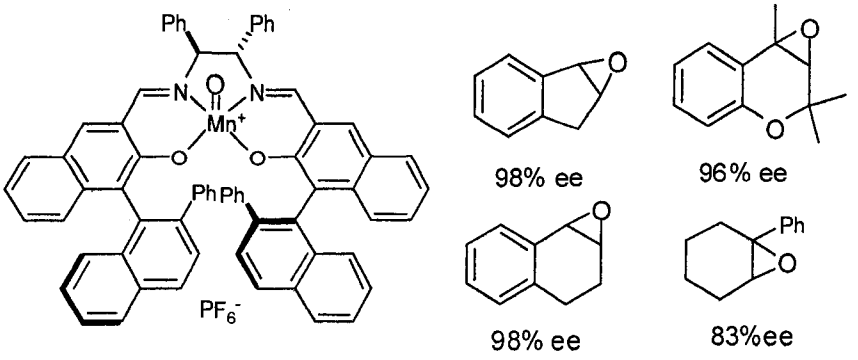


Figure 2.2

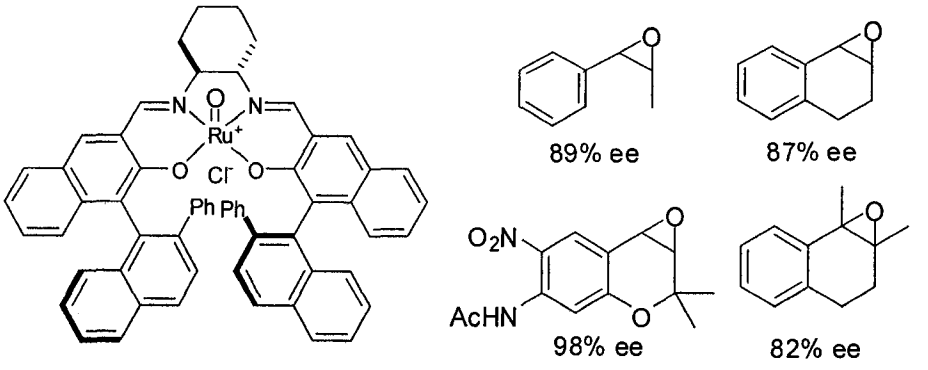


Figure 2.3

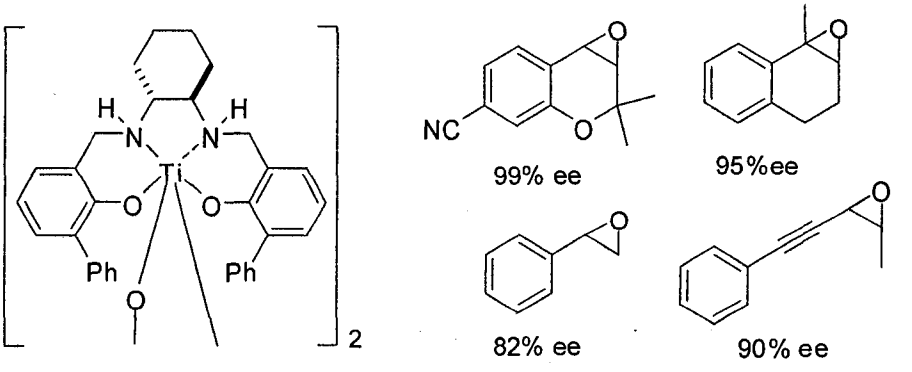


Figure 2.4

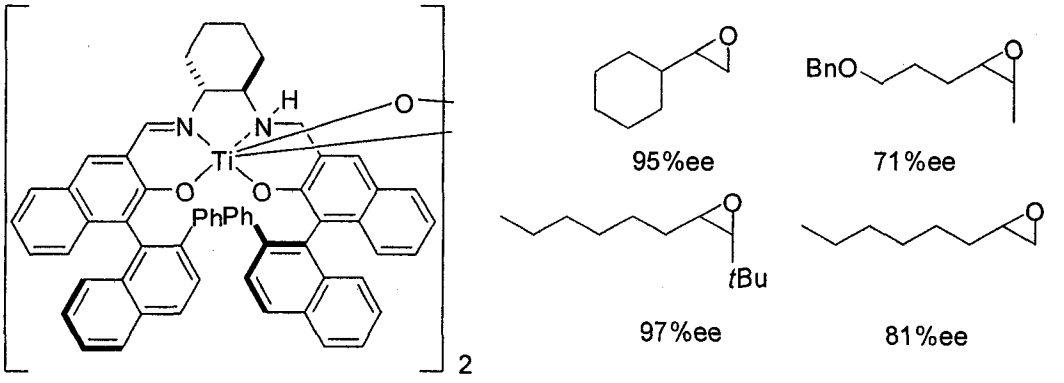


Figure 2.5

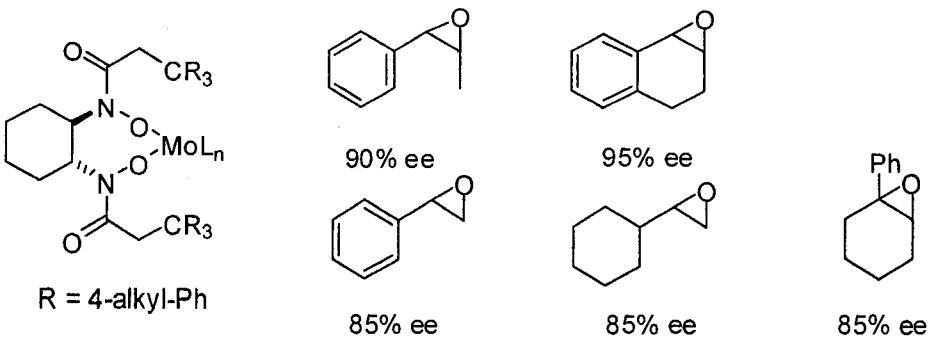
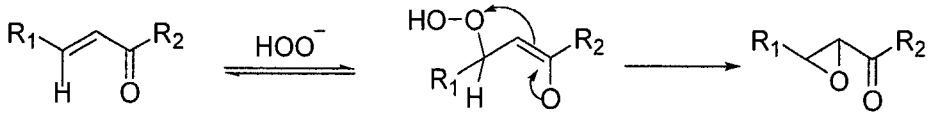


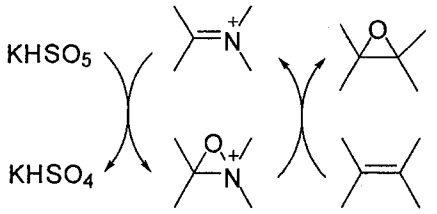
Figure 2.6

Different from the epoxidation of unfunctionalized olefins and allylic or homoallylic alcohols, most methods for the enantioselective epoxidation of electron-deficient olefins such as enones are essentially asymmetric variants of the Weitz-Scheffer epoxidation using alkaline H_2O_2.[23] The mechanism of Weitz–Scheffer epoxidation proceeds *via* reversible addition of hydroperoxide, followed by irreversible intramolecular nucleophilic displacement of hydroxide (Scheme 2.3). For this reason it was also termed as nucleophilic epoxidation. Efficient catalysts for nucleophilic epoxidation have been developed, including epoxidation with chiral metal BINOL complexes,[24] chiral phase-transfer catalysts,[25] and polyamino acid catalysts.[26]

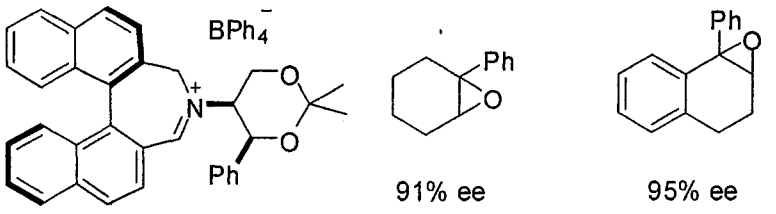


Scheme 2.3

In addition to metal-catalyzed epoxidation, organocatalytic epoxidation has also been extensively studied.[27] Much research has been focused on asymmetric epoxidation catalyzed by chiral iminium salts.[28] The mechanism of iminium salt-catalyzed epoxidation is shown in Scheme 2.4. When a chiral iminium salt reacts with Oxone (a source of peroxymonosulfate), a chiral oxaziridinium salt is generated and transfers an oxygen atom to an olefin to form a chiral epoxide. The scope and enantioselectivity of epoxidation catalyzed by chiral iminium salts have seen much progress during recent years. Iminium salts **2-1** (Figure 2.7)[29] and **2-2** (Figure 2.8)[30] catalyzed asymmetric epoxidation of some olefins with high enantioselectivity.



Scheme 2.4



2-1

Figure 2.7

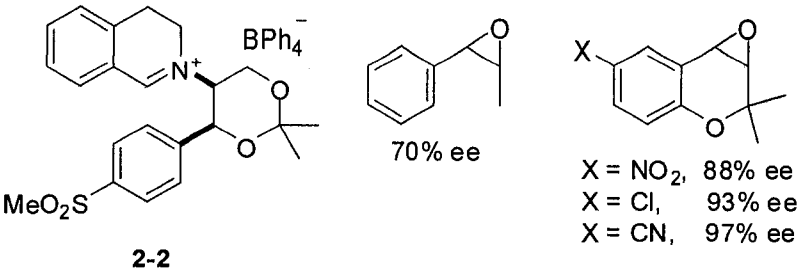
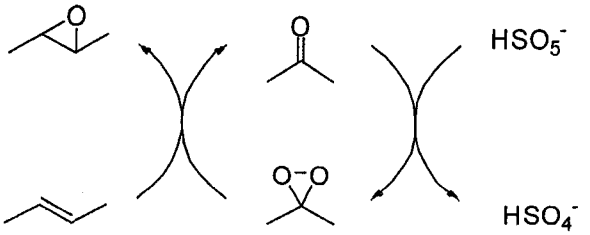


Figure 2.8

Chiral ketone catalyzed epoxidation has been studied in great depth with much success.[28,31-34] Similar to the catalytic cycle of the iminium salt-catalyzed epoxidation, chiral ketones react with peroxymonosulfate to generate chiral dioxiranes which transfer oxygen atoms to olefins to form chiral epoxides (Scheme 2.5).



Scheme 2.5

For the epoxidation with dioxirane, there are two extreme transition state geometries, spiro and planar (Figure 2.9). 'Spiro' indicates that the plane of the dioxirane is orthogonal to the plane of the olefin, while 'planar' indicates that the C=C bond of the olefin is in the plane of the dioxirane. Based on the experimental[35,36] and theoretical studies,[37-39] the spiro transition state is generally favored over planar due to secondary orbital interaction between the π^*-orbital of the olefin and the n-orbital of the dioxirane (Figure 2.10).

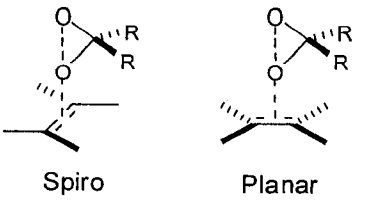


Figure 2.9

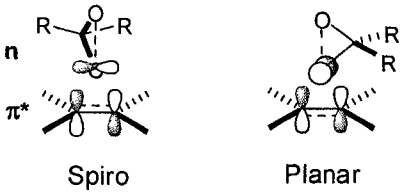
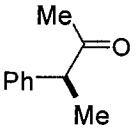
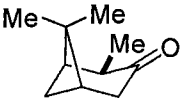
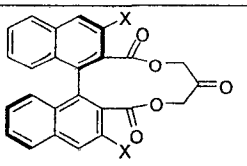
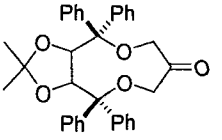
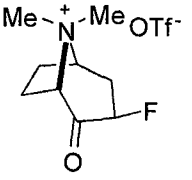
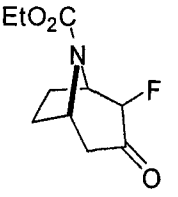
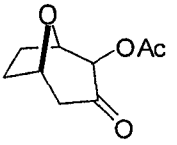
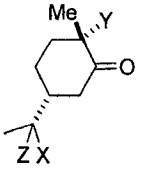
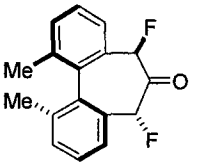


Figure 2.10

During the past three decades, various chiral ketones have been studied and reported by a number of groups (Table 2.1).[40-55] Among those ketones, the fructose-derived ketone **1-2**, reported by our group and readily prepared from L-fructose in two steps, has proven to be an effective ketone catalyst in asymmetric epoxidation of unfuctionalized *trans*- and trisubstituted olefins (Figure 2.11).[56,57] On the other hand, *cis*-, terminal and 1,1-disubstituted olefins are not effective substrates for this ketone.

Table 2.1

Entry	Ketone	Ph	Ph Ph	Ref
1		10% ee	--	40
2		13% ee	--	40

3		--	32-84% ee	41-43
4		--	65% ee	44
7		35% ee	58% ee	45
8		--	76% ee	46,47
9		70% ee	93% ee	48,49
10		--	42-90% ee	50-54
11		88% ee	94% ee	55

The stereochemistry of the epoxide obtained from ketone **1-2** catalyzed epoxidation of *trans*- and trisubstituted olefins can be rationalized based on the analysis of transition states. Assuming that the equatorial oxygen atom in the dioxirane formed from Oxone and ketone **1-2** is more accessible to olefins than the axial one,[58-60] there are eight possible transition states in the epoxidation of *trans*- and trisubstituted olefin (Figure 2.12). Among them, transition states **B-G** are disfavored due to unfavorable steric

interactions. There are only two sterically-favorable transition states, spiro **A** and planar **H**, which give opposite enantiomers of epoxide. With the preference of spiro over planar transition states, the major enantiomer of the epoxide results from spiro **A** with high ee.

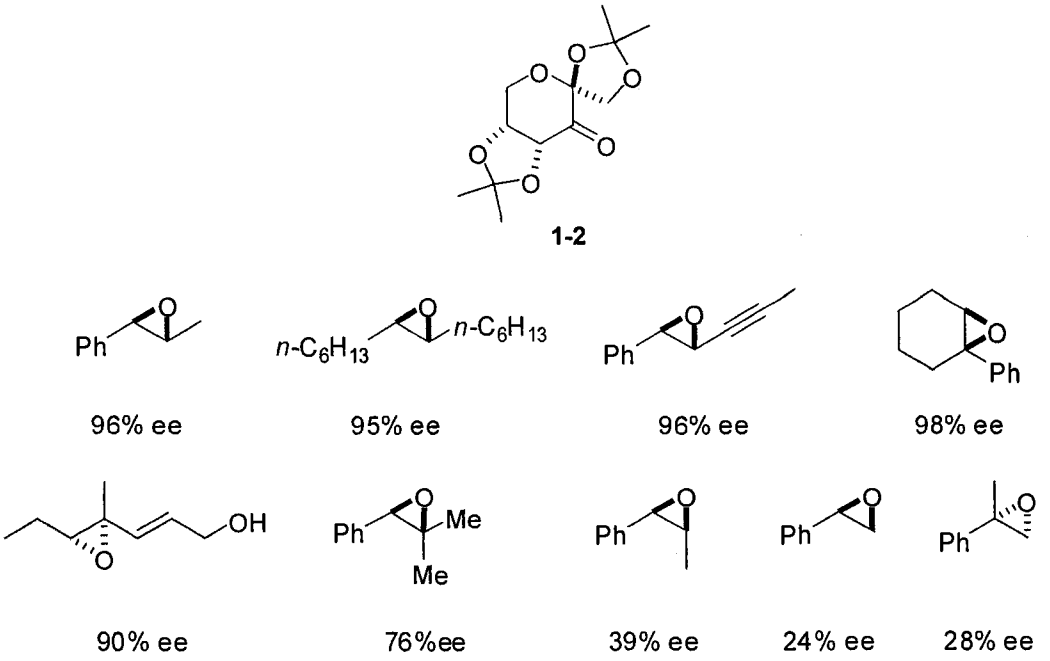


Figure 2.11

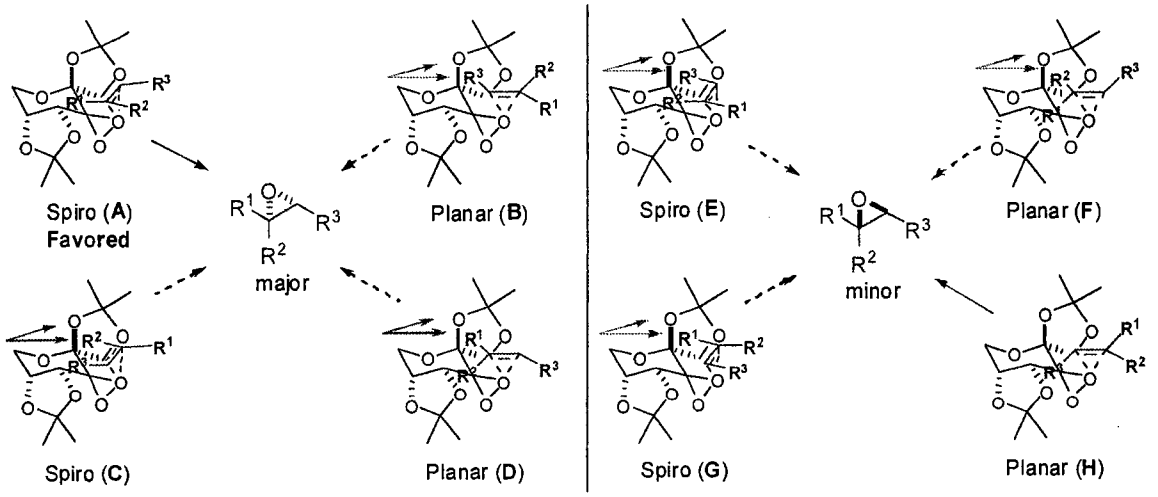


Figure 2.12

Further changing the structure of ketone **1-2** led to the discovery of ketone **2-3a**,[61,62] which efficiently catalyzed enantioselective epoxidation of a variety of conjugated *cis*-olefins and styrenes (Figure 2.13). Similar to ketone **1-2**, 1,1-disubstituted olefins, however, remain ineffective substrates with ketone **2-3a**.

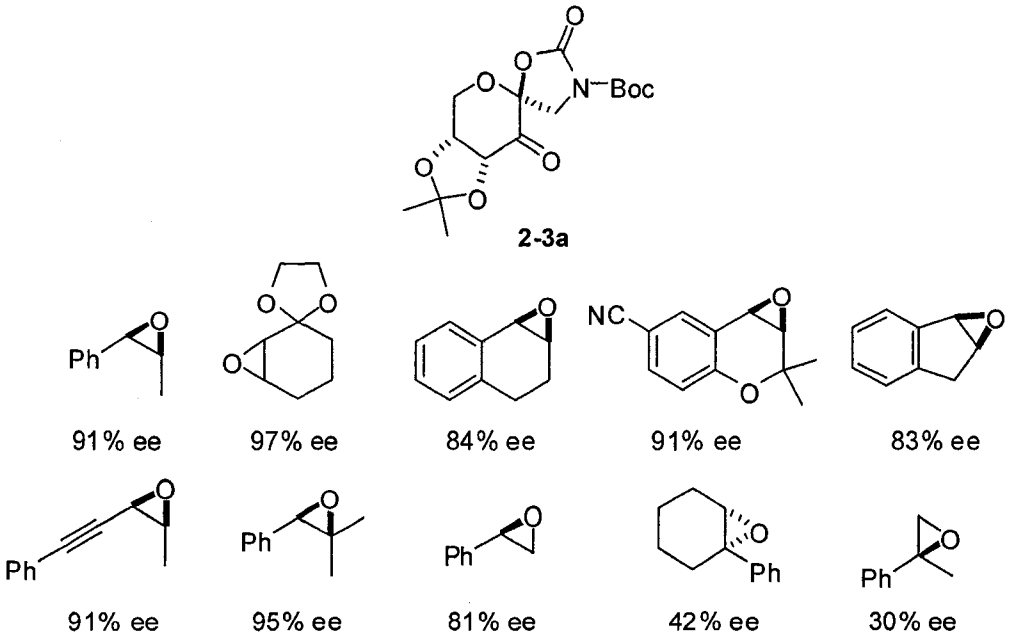


Figure 2.13

In the ketone **2-3a**-catalyzed epoxidation of *cis*-olefins, two sterically favorable spiro transition states, **I** and **J**, are most likely the major competing transition states (Figure 2.14). The configuration of the major isomer of the epoxide indicates that spiro **I**, where the R_π group is proximate to the oxazolidinone of ketone **2-3a**, is favored over spiro **J**. Therefore, an apparent interaction seems to exist between the R_π group and the oxazolidinone. The exact nature of the interaction is unclear but may be due to a van der Waals interaction, a hydrophobic interaction, or a combination thereof.

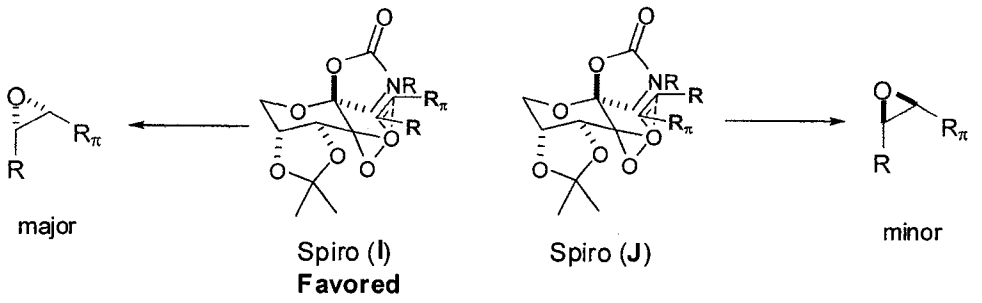


Figure 2.14

2.1.2 Research Proposal

The initial research proposal came from an interesting observation of the epoxidation using ketone **1-2** and **2-3a**. Ketone **1-2** catalyzed epoxidation of β-dimethylstyrene gave the corresponding epoxide with 76% ee (Figure 2.15), while a dramatic increase in ee was obtained with ketone **2-3a** (95% ee) (Figure 2.16). The reason is likely because of the additional attractive interaction between the phenyl group and the oxazolidinone. For ketone **1-2** catalyzed epoxidation, the two major competing transition states are the spiro **K** and planar **L** which are both sterically favorable. The major isomer of the epoxide is produced through the spiro **C** with 77% ee (Figure 2.17). For ketone **2-3a**, an additional interaction between the phenyl group and the oxazolidinone of the catalyst likely further favors spiro **M** over planar **N**, resulting much higher enantioselectivity compared to ketone **1-2** (Figure 2.17).

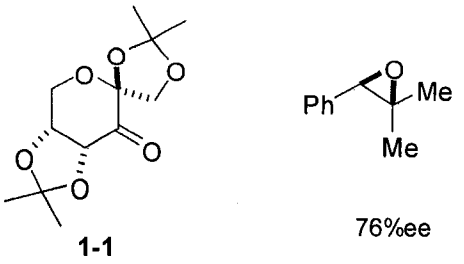


Figure 2.15

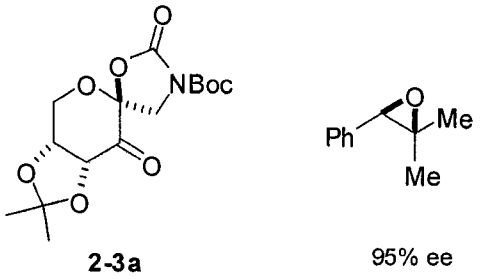


Figure 2.16

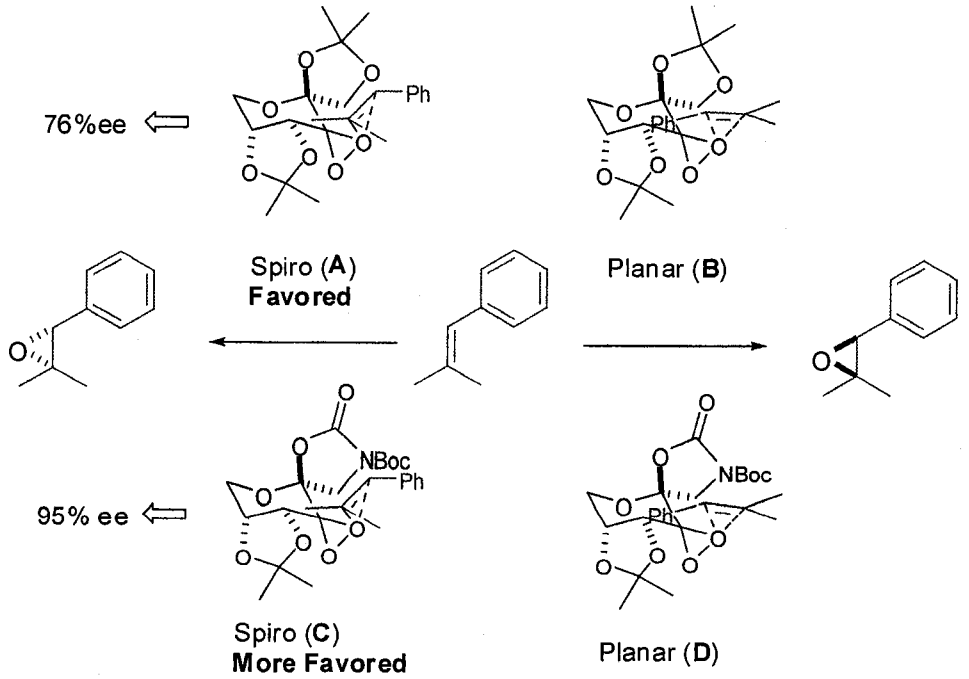
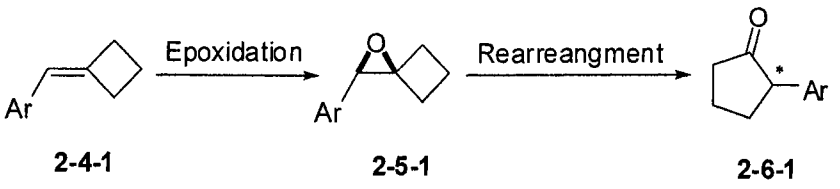


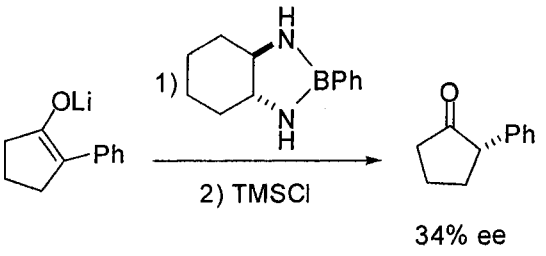
Figure 2.17

From this analysis of transition states, we want to further extend this result to other similar olefin substrates, such as olefins **2-4** (Scheme 2.6). It is reasonable to expect that the asymmetric epoxidation of **2-4-1** using ketone **2-3a** or it's analogs could produce chiral epoxide **2-5-1**, which may stereospecifically rearrange to chiral cyclopentanone **2-6-1** (Figure 2.6).[63] Currently there are no effective methods to synthesize chiral cyclopentanones with good enantioselectivity. Yamamoto reported the best result (34% ee) through asymmetric protonation of the corresponding lithium enolates (Scheme 2.7).[64]



2-4-1 **2-5-1** **2-6-1**

Scheme 2.6



34% ee

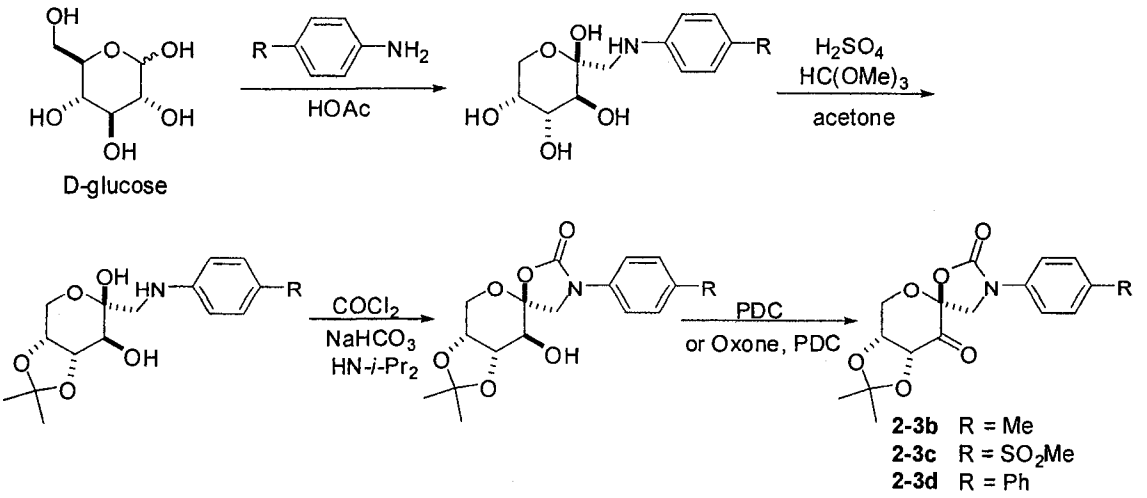
Scheme 2.7

2.2 RESULTS AND DISCUSSION

The accomplishments in Chapter 2 were completed in cooperation with Dr. Yumei Shen.

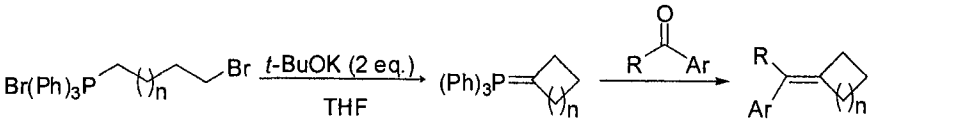
2.2.1 Preparation of Ketone Catalysts and Substrates

Before studies of epoxidation and subsequent rearrangement could begin, it was necessary to make sufficient amount of ketone catalysts and olefins. When the project began, some analogs of ketone **2-3a** via a straightforward four-step synthesis were being developed by Dr. Lianhe Shu (Scheme 2.8).[65] The ketone catalysts **2-3b** and **2-3c** had shown the similar reactivity to ketone **2-3a** in the asymmetric epoxidation *cis*-olefins.[65,66] Therefore, ketones **2-3b-d** were prepared based on the reported procedure[63,67] and investigated in the following asymmetric epoxidation along with ketone **2-3a**.



Scheme 2.8

A variety of olefins with different functional groups substituted on the different positions of the phenyl group and with three- or four-membered rings were synthesized by the Wittig reaction with reasonable yields (Scheme 2.9).[68,69]



2-4-1, n = 1, R = H
2-4-2, n = 1, R = Alkyl
2-4-3, n = 0

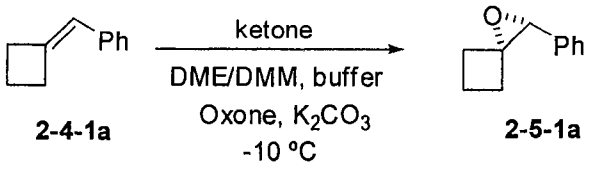
Scheme 2.9

2.2.2 Optimization of Ketone Catalyst and Epoxidation Conditions

With ketones **2-3a-d** and many substrates in hand, epoxidation was explored. Olefin **2-4-1a** was used as standard substrate to initially screen the different ketone catalysts. The results are shown in Table 2.2. Compared to 42% ee for epoxidation catalyzed by ketone **1-2** (Table 2.2, entry 1), the enantioselectivity of ketone **2-3** catalyzed epoxidation (Table 2.2, entries 2-5) showed a big improvement. The best ee (93%) was obtained from ketone **2-3a** while the ee for ketone **2-3b** catalyzed epoxidation was also more than 90%. The synthesis of ketone **2-3a** takes at least six steps and involves one column chromatography,[70] while the synthesis of ketone **2-3b** uses the inexpensive starting materials and takes only four steps without any column

chromatography.[71] Thus, it is reasonable to chose ketone **2-3b** to subsequently investigate the project.

Table 2.2[a]



2-4-1a **2-5-1a**

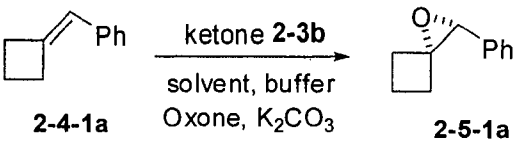
Entry	Ketone	Ee (%)	Conversion (%)
1	**1-2**	42	99
2[b]	**2-3a**	93	94
3	**2-3b**	91	99
4	**2-3c**	89	100
5	**2-4d**	81	69

[a] All reactions except entry 2 were carried out with olefin (0.2 mmol), ketone (0.04 mmol), Oxone (0.2M, 1.6 mL, 0.32 mmol), and K_2CO_3 (0.84M, 1.6 mL, 1.344 mmol) in DME/DMM (3:1, v/v) (3 mL) and buffer (0.1M K_2CO_3-AcOH, pH 9.3) (2 mL) at -10 °C. The reactions were stopped after 4 h. [b] The reaction was carried out with olefin (0.5 mmol), ketone (0.1 mmol), Oxone (0.212M, 4.2 mL, 0.89 mmol), and K_2CO_3 (0.479M, 4.2 mL, 2.01 mmol) in DME/DMM (3:1, v/v) (7.5 mL) and buffer (0.1M K_2CO_3-AcOH, pH 9.3) (5 mL) at -10 °C. The reaction was stopped after 3.5 h.

A study of reaction solvent was also conducted to ensure that the best solvent system for epoxidation had been found. It was previously determined that DME-DMM (v/v, 3/1) was the best solvent for ketone **2-3a**-catalyzed epoxidation of conjugated *cis*-olefins.[62] Other solvent conditions were screened for ketone **2-3b**-catalyzed epoxidation (Table 2.3); however, they did not result an improvement in enantioselectivity and reactivity. Thus the best solvent for this epoxidation remained to be DME-DMM (v/v,

3/1). It was also found that the best pH for the epoxidation catalyzed by ketone **2-3b** is in the pH region of 10 to 12.5, which was similar to epoxidation with ketone **1-2**.[72]

Table 2.3 [a]



2-4-1a **2-5-1a**

Entry	Solvent (v/v)	Temperature (°C)	Ee (%)	Conversion (%)
1	DME	0	89.1	99
2	DME/DMM(3/1)	0	89.5	100
3	DME/DMM(1/1)	0	89.5	100
4	DME/DMM(1/3)	0	88.4	98
5	DMM	0	86.5	66
6	DMM/CH_3CN(4/1)	0	87.9	100
7	DMM/CH_3CN(2/1)	0	77.7	99
8	DME/CH_3CN(2/1)	0	79.0	100
9	**DME/DMM(3/1)**	-10	**90.5**	**99**
10	DME/DMM(1/1)	-10	87.8	93

[a] All reactions were carried out with olefin (0.2 mmol), ketone **2-3b** (0.04 mmol), Oxone (0.2M, 1.6 mL, 0.32 mmol), and K_2CO_3 (0.84M, 1.6 mL, 1.344 mmol) in organic solvent (3 mL) and buffer (0.1M K_2CO_3-AcOH, pH 9.3) (2 mL) at 0 °C or -10 °C. The reactions were stopped after 4 h.

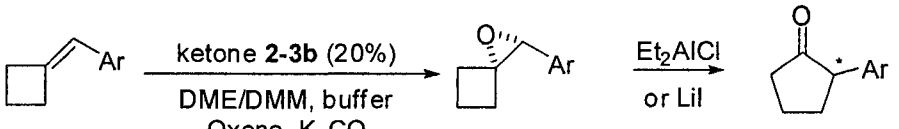
2.2.3 Synthesis of Chiral 2-Aryl Cyclopentanones

Using ketone **2-3b** under the optimized reaction conditions, we began to investigate the epoxidation of the trisubstituted olefins **2-4-1**. The results are shown in Table 2.4. Good enantioselectivity was obtained for the epoxidation of this class of trisubstituted olefins with a conjugated aryl group. Generally, higher ees were obtained for the olefins which had substituents on the phenyl group, which is consistent with an earlier observation that substituents on the phenyl group of cis-β-methylstyrene had positive effects on the enantioselectivity of the epoxidation.[66]

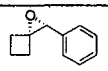
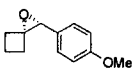
With optically active epoxides in hand, the Lewis acid-catalyzed epoxide rearrangement was explored. The stereoselectivity of the rearrangement was found to be highly sensitive to the Lewis acid and solvent. After optimization, the rearrangement was effectively achieved with Et_2AlCl in toluene at -78 ° C. The cyclopentanone product was obtained cleanly after careful work up, and high ee values were generally maintained (Table 2.4). It was found that α-Aryl cyclopentanones (**2-6-1**) readily underwent racemization on silica gel; Thus, ketones **2-6-1** were not purified by column chromatography on silica gel and were clean as judged by NMR spectroscopy. The rearrangement with Et_2AlCl is likely to go through a concerted process with inversion of the configuration (Pathway A; Scheme 2.10). Slightly more enantioselectivity is lost for epoxides with electron-donating groups, such as the 4-MeO moiety (Table 2.4, entry 2), during the rearrangement. This lowered enantioselectivity could be a result of the competition from a stepwise S_N1-type process via a carbocation which is stabilized by electron-donating groups. To probe the reaction mechanism further, the rearrangement

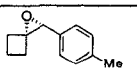
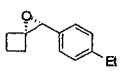
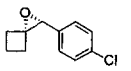
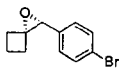
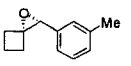
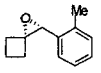
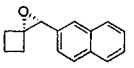
was then carried out with LiI.[73-78] The opposite enantiomer of the rearrangement product was obtained under these conditions (Table 2.4), and good ee values were also obtained in most cases. For the rearrangement with LiI, the epoxide ring was likely first opened by nucleophilic attack of I^-, followed by a pinacol-type rearrangement with double inversion of the stereocenter (Pathway B; Scheme 2.10). The low ee value obtained with the 4-MeO-substituted epoxide (Table 2.4, entry 2) could be because of the competition from pathway A and/or the S_N1-type process. To support the above mechanistic pathways further, the configurations of the 4-Cl substituted epoxide (Table 2.4, entry 5) and the corresponding rearranged cyclopentanone product with Et_2AlCl were determined by using vibrational circular dichroism (VCD; BioTools).[79] It is shown that the epoxide has an *R* configuration and the rearranged cyclopentanone has an *S* configuration. The configuration of the rearranged cyclopentanone was also determined for entry 1 by comparison with the measured optical-rotation value of the lactone product (obtained from the Baeyer-Villiger oxidation of the ketone with *m*CPBA[80]) with the reported value.[81]

Table 2.4

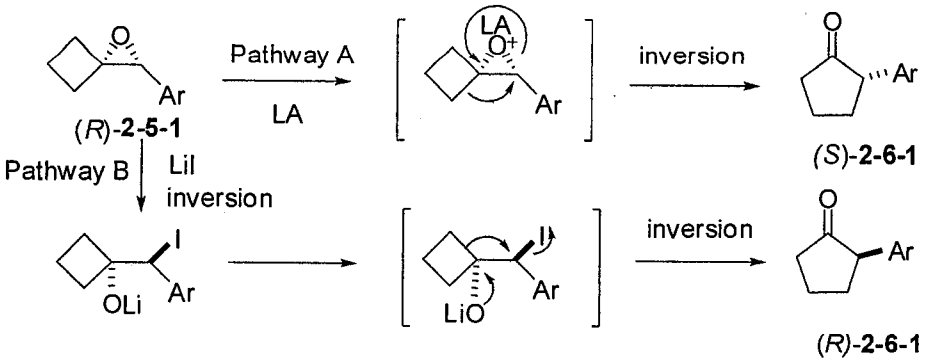


2-4-1 **2-5-1** **2-6-1**

Entry	Epoxide (**2-5-1**)	Yield of **2-5-1**[a] (ee)[d]	Yield of **2-6-1**[b] (ee)[e] with Et_2AlCl	Yield of **2-6-1**[c] (ee)[e] with LiI
1		93 (90)	90 (90) (*S*)	81 (90) (*R*)
2		95 (91)	98 (82) (*S*)	81 (40) (*R*)

3		84 (93)	82 (88) (*S*)	91 (92) (*R*)
4		67 (94)	99 (91) (*S*)	86 (92) (*R*)
5		78 (96)	89 (94) (*S*)	87 (84) (*R*)
6		80 (96)	94 (93) (*S*)	87 (84) (*R*)
7		80 (95)	82 (92) (*S*)	92 (93) (*R*)
8		77 (86)	83 (84) (*S*)	90 (80) (*R*)
9		88 (95)	94 (96) (*S*)	84 (87) (*R*)

[a] All epoxidations were carried out with substrate (0.5 mmol), ketone **2-3b** (0.1 mmol), Oxone (0.8 mmol), and K_2CO_3 (3.36 mmol) in DME/DMM (3:1, v/v) (7.5 mL) and buffer (0.1 M K_2CO_3-AcOH, pH 9.3) (5 mL) at -10 or 0 °C for 4 to 12 h except for entry 9 where the reaction was carried out in DME/DMM (1:1, v/v) (9.4 mL) and buffer (3.1 mL) at 0 °C for 8 h. The epoxides in entries 4, 5, 6, 8, & 9 were purified by silica gel column (buffered with Et_3N). [b] All rearrangements were carried out with epoxide (1.0 eq.) and Et_2AlCl (0.25 or 1.0 eq.) in $PhCH_3$ at -78 °C for 0.25 h to 3 h. The ketone products were not purified by silica gel and were clean as judged by NMR. [c] All rearrangements were carried out with LiI (1.0-3.0 eq.) in CH_2Cl_2 at rt for 5 to 30 min except entry 2 where the reaction was carried out at 0 °C. [d] The ee value (%) of the epoxide was determined by chiral GC (Chiraldex B-DM), except for entry 2, for which the ee value was determined by chiral HPLC (Chiralcel AD). The absolute configuration was tentatively assigned based on the spiro reaction mode. The absolute configuration of entry 5 was determined by using the VCD spectra (BioTools).[79] [e] The ee value (%) of the cyclopentanone was determined by chiral HPLC (Chiralcel AD). The absolute configuration was tentatively assigned based on the mechanistic consideration. The absolute configuration was determined for entry 1 by comparison of the measured optical-rotation value of the lactone product (obtained from the Baeyer-Villiger oxidation of the ketone with *m*-CPBA) with the reported value.[81] The absolute configuration of entry 5 was determined by using the VCD spectra (BioTools).



Scheme 2.10

2.2.4 Synthesis of Chiral 2-Alkyl-2-aryl Cyclopentanones and Asymmetric Epoxidation of Tetrasubstituted Olefins

With the interesting observations of epoxidation and isomerization in hand, we decided to investigate whether 2-alkyl-2-aryl cyclopentanones could also be obtained by this approach. However, the feasibility of this route requires a highly enantioselective asymmetric epoxidation of unfunctionalized tetrasubstituted olefins, which is still a challenging problem.[17,82] Jacobsen has shown that Mn-salen complex can effectively catalyze epoxidation of several unfunctionalized tetrasubstituted olefins with good enantioselecitivty, however, substrate scope was limited to chromenes (Figure 2.18).[82]

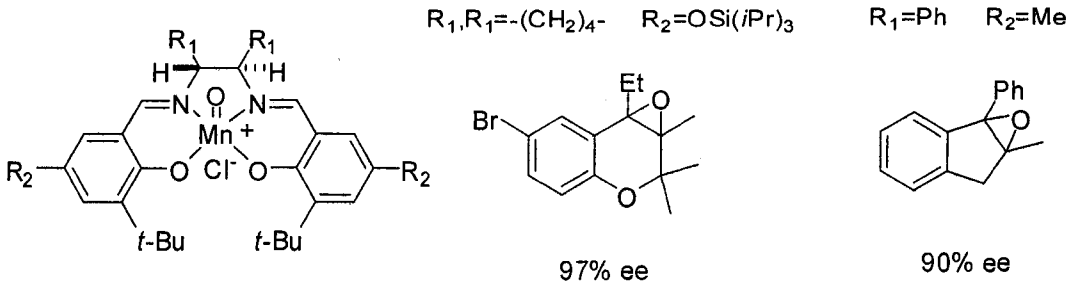
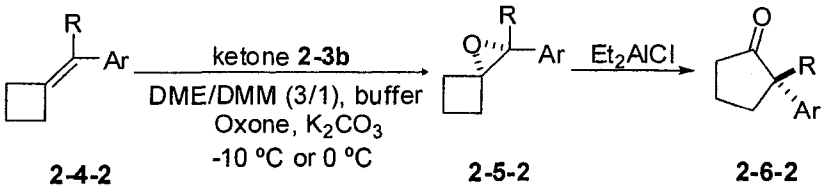


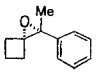
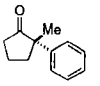
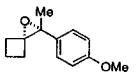
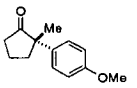
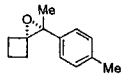
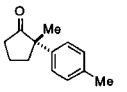
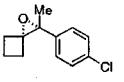
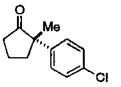
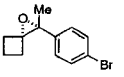
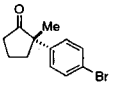
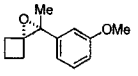
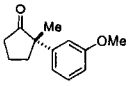
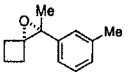
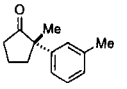
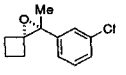
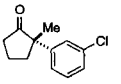
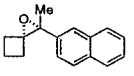
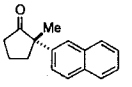
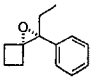
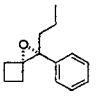
Figure 2.18

Upon synthesizing substrates using the method described in Scheme 2.9, a study of asymmetric epoxidation of tetrasubstituted olefins **2-4-2** was carried out (Table 2.5). The results are shown in Table 2.5. Epoxidation of 1-cyclobutylidene-1-phenylethane with ketone **2-3b** encouragingly gave 84% ee (Table 2.5, entry 1) while only 58%ee was obtained with ketone **1-2**. Further studies shown that the epoxidation could also be extended to a variety of phenyl-substituted olefins (Table 2.5, entries 2–9), and up to 91% ee was obtained. Epoxidation tended to give a lower enantioselectivity as the size of the R group increased (Table 2.5, entries 10 and 11 vs entry 1). Similar to the observation with trisubstituted olefins (Table 2.4), substituents on the phenyl group had positive effects on the enantioselectivity of epoxidation. Better ees were obtained with the olefins having substituents on the phenyl group (Table 2.5, entries 2-8 vs entry 1). Some of the epoxide products were purified by column chromatography on silica gel, but some underwent rearrangement on silica gel, thus they were used directly for the subsequent rearrangement without purification.

Table 2.5



Entry	Epoxide (**2-5-2**)[a,c]	Yield (ee) (%)	Ketone (**2-6-2**)[b,d]	Yield (ee) (%)

1		94[e] (84)[h]		93[g] (84)[h]
2		95[e] (87)[i]		92[g] (88)[h]
3		86[f] (88)[h]		78[g] (88)[h]
4		77[g] (89)[h]		98[g] (90)[h]
5		78[g] (91)[h]		99[g] (90)[h]
6		98[f] (88)[h]		73[g] (87)[j]
7		96[e] (87)[h]		93[g] (88)[h]
8		79[g] (88)[h]		99[g] (89)[h]
9		nd		65[g] (90)[j]
10		67[g] (77)[h]		88[g] (77)[j]
11		48[g] (70)[h]		99[g] (70)[i]

[a] All epoxidations were carried out with substrate (0.5 mmol), ketone **5** (0.1 mmol), Oxone (0.8 mmol), and K_2CO_3 (3.36 mmol) in DME/DMM (3:1, v/v) (7.5 mL) and buffer (0.1 M K_2CO_3-AcOH, pH 9.3) (5 mL) at -10 °C. [b] All rearrangements were carried out with epoxide (1.0 eq.) and Et_2AlCl (0.25 eq.) in $PhCH_3$ at -78 °C for 15 to 30 min unless otherwise noted. For entry 10, 0.5 eq. Et_2AlCl used (60 min); For entry 11, 0.75 eq. Et_2AlCl used (25 min). [c] The absolute configuration was tentatively assigned based on the spiro reaction mode. The absolute configurations of entries 1 and 5 were determined using the VCD spectra by BioTools.[79] [d] The cyclopentanone products were purified by silica gel column. For entries 3, 6, and 9, the yield is the two-step overall yield after purification. The absolute configuration was tentatively assigned based on the mechanistic consideration. For entries 1 and 5, the absolute configuration was determined using the VCD spectra by BioTools.[79] For entries 1, 3, and 6, the configuration was

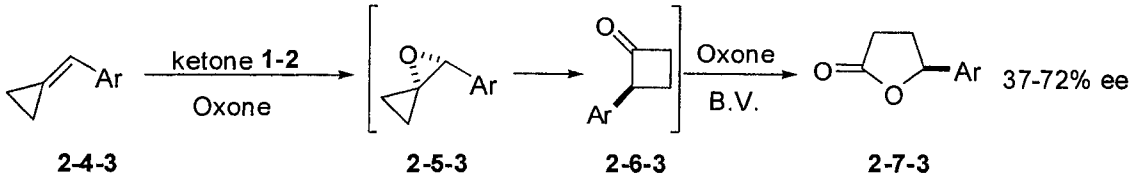
determined by comparing the measured optical rotations with the reported ones.[83,84] [e] Crude yield. [f] Conversion as determined by GC. [g] Isolated yield. [h] The enantioselectivity was determined by chiral GC (Chiraldex B-DM). [i] The enantioselectivity was determined by chiral HPLC (Chiralcel OJ). [j] The enantioselectivity was determined by chiral HPLC (Chiralpak AD).

Upon treating the epoxides **2-5-2** in Table 2.5 with Et_2AlCl in toluene, the rearrangement gave 2-methyl-2-aryl cyclopentanones in high enantioselectivity with little lost of chiralty (Table 2.5). The absolute configurations of the epoxides and rearranged products of entries 1 and 5 were determined using vibrational circular dichroism (VCD).[79] The epoxide is of an *R* configuration and the rearranged cyclopentanone has an *S* configuration. For entries 1, 3, and 6, the *S* configuration of the cyclopentanone was further confirmed by comparing the measured optical rotations with the reported ones.[83,84] Thus, the rearrangement proceeds in a concerted fashion with inversion of configuration, which is similar to pathway A described in Scheme 2.10.

2.2.5 Synthesis of Chiral γ-butyrolactones and 2-Aryl Cyclobutanones

Optically active γ-butyrolactones are a useful class of chiral building blocks for the synthesis of biologically important molecules. A number of methods have been reported for the preparation of chiral γ-lactones. Earlier, Ihara and co-workers reported that chiral γ-aryl-γ-butyrolactones were obtained in 37% to 72% ee by asymmetric epoxidation of trisubstituted benzylidenecyclopropane derivatives using ketone **1-2** and

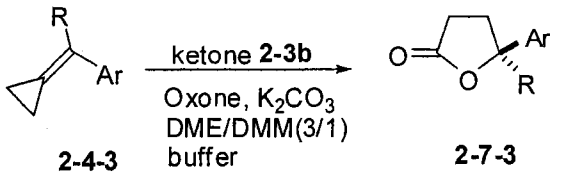
Oxone, followed by in situ epoxide rearrangement and Baeyer-Villiger oxidation (Scheme 2.11).[85,86]



Scheme 2.11

The epoxidation of a variety of benzylidenecyclopropanes with ketone **2-3b** were thus investigated. As shown in Table 2.6, 4-aryl-γ-butyrolactones can be obtained in reasonable overall yields and good ee's (up to 91% ee) for the three-step transformation. Tetrasubstituted benzylidenecyclopropanes can also be effectively epoxidized and transformed into 4-aryl-4-methyl-γ-butyrolactones in good ee (Table 2.6, entries 7-13). The absolute configurations of the products in entries 2, 3, 6, 10, and 13 of Table 2.6 were an *S* configuration by comparing the measured optical rotations with the reported ones.[87-89] Since the rearrangement from **2-5-3** to **2-6-3** likely proceeds in a concerted fashion with inversion of configuration and there is no change of configuration in the Baeyer-Villiger oxidation, it is reasonable to conclude that the configuration of corresponding epoxides is *R*.

Table 2.6 [a]



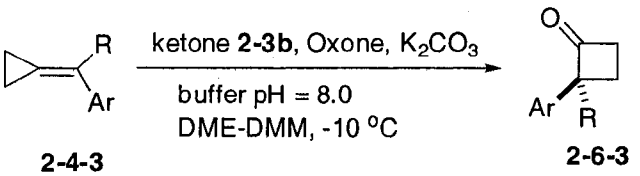
En.	Lactones **2-7-3**	Temperature (°C)	Time (h)	Yield[b] (%)	ee (%)	Config.[g]
1	Ar = *o*-MeC_6H_5, R = H	-10 to 0	8	54	80[c]	(-)
2	Ar = *p*-$MeOC_6H_5$, R = H	-10 to 0	8	49	89[d]	(-)-(*S*)[87]
3	Ar = *p*-MeC_6H_5, R = H	-10 to 0	8	68	90[e]	(-)-(*S*)[87]
4	Ar = *p*-*t*-BuC_6H_5, R = H	-10	12	52	91[e]	(-)
5	Ar = 2-Nap, R = H	-10	12	48	91[e]	(-)
6	Ar = Ph, R = Me	-10 to 0	8	50	84[f]	(-)-(*S*)[88]
7	Ar = *o*-$MeOC_6H_5$, R = Me	-10	8	73	71[c]	(-)
8	Ar = *m*-$MeOC_6H_5$, R = Me	-10 to 0	8	48	87[c]	(-)
9	Ar = *p*-$MeOC_6H_5$, R = Me	-10 to 0	8	56	82[c]	(-)
10	Ar = *p*-MeC_6H_5, R = Me	-10	8	64	79[c]	(-)-(*S*)[89]
11	Ar = *p*-ClC_6H_5, R = Me	-10 to 0	8	45	84[c]	(-)
12	Ar = *p*-BrC_6H_5, R = Me	-10	8	54	86[c]	(-)
13	Ar = 2-Nap, R = Me	-10 to 0	8	54	87[c]	(-)-(*S*)[88]

[a] All reactions were carried out with substrate (0.5 mmol), ketone **2-3b** (0.1 mmol), Oxone (1.6 mmol), and K_2CO_3 (6.72 mmol) in DME/DMM (3:1, v/v) (7.5 mL) and buffer (0.1 M K_2CO_3-AcOH in 4×10^{-4} M aqueous EDTA, pH 9.3) (5 mL). For entries 1, 2, 3, 6, 8, 9, 11, and 13, the reaction was carried out at -10 °C for 6 h, then 0 °C for 2 h. [b] Isolated yield. [c] The enantioselectivity was determined by chiral HPLC (chiralcel OJ). [d] The enantioselectivity was determined by chiral HPLC (chiralcel AD). [e] The enantioselectivity was determined by chiral HPLC (chiralcel OD). [f] The enantioselectivity was determined by chiral GC (chiraldex B-DM). [g] The absolute configurations were determined by comparing the measured optical rotations with the reported ones. The absolute configurations of the remaining lactones were tentatively assigned by analogy based on mechanistic considerations.

Further studies with selected examples showed that the Baeyer-Villiger oxidation can be suppressed using additional ketone **2-3b** and less Oxone with lower reaction pH,

giving synthetically useful 2-aryl cyclobutanones in good ee (Table 2.7). The absolute configuration of the cyclobutanone in entry 2 was determined as *S* based on the measured optical rotation as compared to the reported one,[90] which is consistent with the configuration of the corresponding lactones **2-7-3** and further confirms the mechanism described in Scheme 2.11. For the entry 1 in Table 2.7, the chiral cyclobutanone was easily racemerized under acidic condition. Thus, the purification with normal silica Gel (60 Å 230-4—mesh Whatman silica gel) resulted in lower enantioselectivity. The best result was obtained after purification with a neutral silica gel (Iatrobeads 6RS-8060).

Table 2.7



2-4-3 **2-6-3**

Entry	Cyclobutanone **2-6-3**[a]	Oxone (eq.)	K_2CO_3 (eq.)	**2-3b** (eq.)	Yield[b] (%)	ee[c] (%)	Config.[d]
1	Ar = *p*-*t*-Bu-C_6H_5, R = H	0.75	1.70	0.72	68	90	(+)
2	Ar = *p*-MeC_6H_5, R = Me	0.66	1.49	0.63	51	84	(-)-(*S*)[90]

[a] All reactions were carried out with olefin (0.5 mmol), ketone **2-3b**, Oxone, and K_2CO_3 in DME/DMM (3:1, v/v) (7.5 mL) and buffer (0.1 M K_2CO_3-AcOH in 4 × 10^{-4} M aqueous EDTA, pH 9.3) (5 mL). The reaction was carried out at -10 °C for 4 h. [b] Isolated yield. [c] The enantioselectivity was determined by chiral GC (chiraldex B-DM). [d] The absolute configuration of entry 2 was determined by comparing the measured optical rotation with the reported one. The absolute configuration of entry 1 was tentatively assigned based on mechanistic considerations.

2.2.6 Transition State Analysis

For asymmetric epoxidation of trisubstituted olefins with a conjugated aryl group, as already discussed in Figure 2.17, the two major competing transition states are likely to be spiro **O** and planar **P** (Figure 2.19). The absolute configuration and high enantiomeric excess of epoxides (Table 2.4), γ-butyrolactones (Table 2.6, entries 1-6), and cyclobutanone (Table 2.7, entry 1) show that spiro **O** is greatly favored over spiro **P,** which is likely due to additional attraction between the aryl group and the oxazolidinone moiety of ketone **2-3b**. Based on this mode, the unknown stereochemistry of remaining entries in Tables 2.4, 2.6 and 2.7 was tentatively assigned.

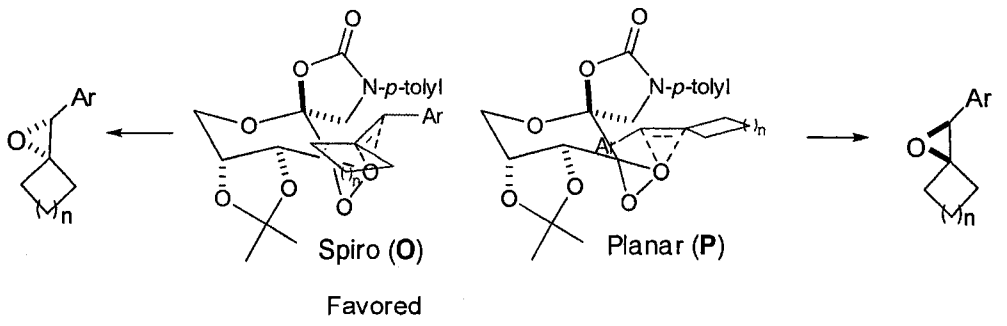


Figure 2.19

For asymmetric epoxidation of tetrasubstituted olefins with a conjugated aryl group, the two major competing transition states are likely spiro **Q** and planar **R**, which are both have a attraction between the aryl group and the oxazolidinone moiety of ketone **2-3b.** The configuration and good ees of the epoxides (Table 2.5), γ-butyrolactones (Table 2.6, entries 6-13), and cyclobutanone (Table 2.7, entry 2) indicated that spiro **Q** is likely favored over planar **R**. This mode rationalizes the observation that highly enantioselective epoxidation of tetrasubstituted olefins, **2-4-2** and **2-4-3** (R = alkyl),

requires a small R group since the inevitable steric interaction between a big R group and the oxazolidinone ring will reduce the advantage of spiro **Q** over planar **R** (Table 2.5, entries 1, 10 and 11). The unknown stereochemistry of remaining entries in Table 2.5 and Table 2.6 was also tentatively assigned based on this mode.

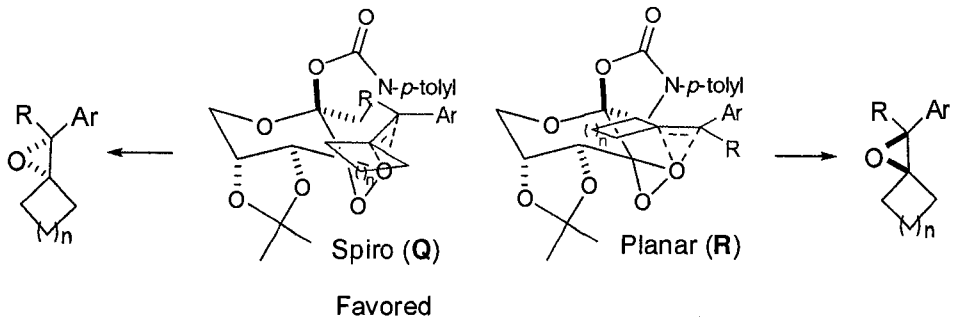


Figure 2.20

2.3 CONCLUSION

In summary, a method for symmetric epoxidation of trisubstituted and tetrasubstituted olefins with a conjugated aryl group has been described. This method utilizes the readily available ketone **2-3b** as catalyst and Oxone as stoichmetric oxidant. Using this method, a variety of enantioenriched aryl-substituted epoxides, cyclopentanones, cyclobutanones, and γ-butyrolactones were obtained in good yields and high enantioselectivity.

2.4 EXPERIMENTAL

General methods. Oxone was purchased from Aldrich. All glassware used for the epoxidation was carefully washed to be free from any trace metals which may catalyze the decomposition of Oxone. Unless stated otherwise, column chromatography was carried out with 60 Å 230-400 mesh Whatman silica gel. Infrared spectra were recorded on a Nicolet Avatar 320 FT-IR spectrometer. High resolution mass spectra were performed at the mass spectrometry facility of Colorado State University. Elemental analysis was performed by M-H-W Laboratories (Phoenix, AZ).

2.4.1 Chiral 2-Aryl Cyclopentanones

Representative procedure for asymmetric epoxidation (Table 2.4, entry 5). To a solution of the olefin (0.089 g, 0.5 mmol) and ketone **2-3b** (0.033 g, 0.1 mmol) in DME-DMM (3:1, v/v) (7.5 mL) were added buffer (0.1 M K_2CO_3-AcOH in 4 x 10^{-4} M aqueous EDTA, pH = 9.3) (5 mL) with stirring. After the mixture was cooled to -10 °C (bath temperature) via NaCl-ice bath, a solution of Oxone (0.20 M in 4 x 10^{-4} M aqueous EDTA, 4.0 mL) (0.492 g, 0.80 mmol) and a solution of K_2CO_3 (0.84 M in 4 x 10^{-4} M aqueous EDTA, 4.0 mL) (0.464 g, 3.36 mmol) were added separately and simultaneously via a syringe pump over a period of 10 h. The reaction mixture was quenched with hexane, extracted with hexane, washed with brine, dried over Na_2SO_4, filtered, concentrated, and purified by flash chromatography (the silica gel was buffered with 1% Et_3N in organic solvent; hexane/EtOAc = 50/1) to give the epoxide as a colorless oil (0.076 g, 78% yield, 96% ee).

(Entry 1, -10 °C 4 h; entry 2, -10 °C 6 h; entry 3, -10 °C, 4 h; entry 4, -10 °C, 8 h; entry 6, -10 °C, 8 h; entry 7, -10 °C, 4 h; entry 8, 0 °C, 12 h; entry 9, 0 °C, 8 h.)

Representative procedure for the epoxide rearrangement with Et_2AlCl (Table 2.4, entry 1). To a solution of the epoxide (0.032 g, 0.2 mmol) (90% ee) in dry toluene (2 mL) at -78 °C was added a solution of Et_2AlCl (1.0 M in hexane, 50 uL, 0.05 mmol). Upon stirring at -78 °C to completion (about 3 h), the reaction was quenched with saturated aqueous $NaHCO_3$ (0.10 mL) at -78 °C. Upon warming up to 0 °C, the reaction mixture was diluted with hexane, washed by brine, dried over Na_2SO_4, filtered, and concentrated to give the ketone product as a colorless oil (0.029 g, 90% yield, 90% ee). (Entry 2, 0.25 eq. Et_2AlCl, 45 min; entry 3, 0.25 eq. Et_2AlCl, 15 min; entry 4, 0.25 eq. Et_2AlCl, 15 min; entry 5, 1.0 eq. Et_2AlCl, 40 min; entry 6, 1.0 eq. Et_2AlCl, 40 min; entry 7, 1.0 eq. Et_2AlCl, 2.5 h; entry 8, 1.0 eq. Et_2AlCl, 30 min; entry 9, 0.25 eq. Et_2AlCl, 45 min.)

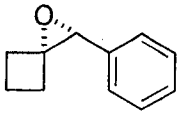
Representative procedure for the epoxide rearrangement with LiI (Table 2.4, entry 1). To a solution of the epoxide (0.032 g, 0.2 mmol) in dry CH_2Cl_2 (0.2 mL) was added LiI (beads, Aldrich) (0.080 g, 0.6 mmol). The mixture was stirred in the dark and carefully monitored by TLC until a tiny amount of the epoxide was left (ca. 20 min). The mixture was quenched immediately by adding hexane, quickly followed by addition of brine (it is extremely important to stop the reaction at the right time. Any delay could lead to significant decrease of ee). The reaction vessel was washed with hexane and brine twice. The organic layer of the combined mixture was dried (Na_2SO_4), filtered, and

concentrated to give the ketone as a light yellow oil (0.026 g, 81% yield, 90% ee) (the ee was determined immediately).

(1.0 eq. LiI used for entry 2; 2.0 eq. LiI used for entries 3, 4, and 9; 3.0 eq. LiI used for entries 5, 6, 7, and 8)

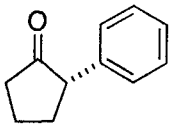
(Table 2.4, entry 1)

Epoxide[63] (b0335e).



Colorless oil; $[\alpha]_D^{25}$ = 78.0 (*c* 0.94, $CHCl_3$); IR (film) 1497 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38-7.10 (m, 5 H), 3.86 (s, 1 H), 2.70-2.34 (m, 3 H), 2.06-1.80 (m, 2H), 1.73-1.64 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.7, 128.2, 127.8, 126.2, 66.8, 62.6, 31.6, 28.6, 12.7; Anal. Calcd. for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.61; H, 7.38.

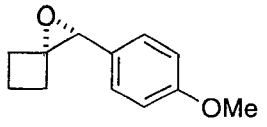
Cyclopentanone[63] (b0336d, b0540)



Colorless oil; $[\alpha]_D^{25}$ = -54.6 (*c* 0.92, $CHCl_3$); IR (film) 1738 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38-7.20 (m, 5 H), 3.36-3.30 (m, 1 H), 2.55-2.42 (m, 2 H), 2.36-1.89 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.9, 138.4, 128.5, 128.1, 126.8, 55.4, 38.6, 31.9, 21.0.; Anal. Calcd. for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.68; H, 7.44.

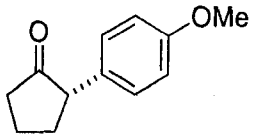
(Table 2.4, Entry 2)

Epoxide (b0335f).



Colorless oil; $[\alpha]_D^{25}$ = 72.6 (*c* 1.24, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.13-7.08 (m, 2H), 6.91-6.89 (m, 2H), 3.82 (s, 3H), 3.82 (s, 1H), 2.67-2.56 (m, 1H), 2.53-2.37 (m, 2H), 2.07-1.98 (m, 1H), 1.95-1.84 (m, 1H), 1.75-1.64 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 128.7, 127.6, 113.9, 66.7, 62.5, 55.5, 31.6, 28.6, 12.6; HRMS calcd for $C_{12}H_{14}O_2$ (M^+) 191.1072, found 191.1068.

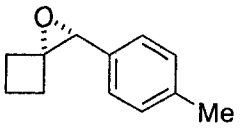
Cyclopentanone (b0336g, b0537).



Colorelss oil; $[\alpha]_D^{25}$ = -39.7 (*c* 1.23, $CHCl_3$); IR (film) 1735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.13-7.10 (m, 2 H), 6.89-6.86 (m, 2 H), 3.78 (s, 3 H), 3.30-3.23 (m, 1 H), 2.56-2.40 (m, 2 H), 2.36-1.84 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.3, 158.4, 130.5, 129.1, 114.1, 55.4, 54.7, 38.5, 32.0, 21.0; Anal. Calcd. for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.94; H, 7.56.

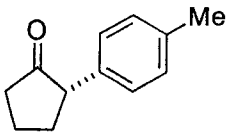
(Table 2.4, Entry 3)

Epoxide (b0335a).



Colorless oil; $[\alpha]_D^{25}$ = 101.1 (*c* 1.0, $CHCl_3$); IR (film) 1516 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.16 (d, *J* = 8.1 Hz, 2 H), 7.07 (d, *J* = 8.1 Hz, 2 H), 3.83 (s, 1 H), 2.68-2.40 (m, 3 H), 2.36 (s, 3 H), 2.12-1.82 (m, 2 H), 1.75-1.62 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.6, 133.7, 129.0, 126.3, 66.7, 62.7, 31.7, 28.8, 21.5, 12.7; HRMS calcd for $C_{12}H_{14}O$ (M^+) 174.1045, found 174.1046.

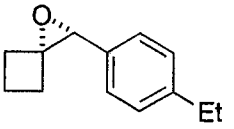
Cyclopentanone (b0336a, b0547a, b0548).



Colorless oil; $[\alpha]_D^{25}$ = -52.2 (*c* 1.44, $CHCl_3$); IR (film) 1741 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.17-7.07 (m, 4 H), 3.34-3.24 (m, 1 H), 2.54-2.43 (m, 2 H), 2.34 (s, 3 H), 2.34-2.29 (m, 1 H), 2.23-2.04 (m, 2 H), 2.00-1.90 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.3, 136.6, 135.5, 129.4, 128.1, 55.2, 38.6, 32.0, 21.3, 21.1; Anal. Calcd. for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.38; H, 7.89.

(Table 2.4, Entry 4)

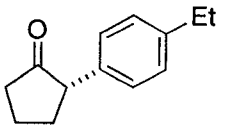
Epoxide (yms2612, b0143, b0148).



Colorless oil; $[\alpha]_D^{25}$ = 106.9 (*c* 1.0, $CHCl_3$); IR (film) 1515 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.21-7.10 (m, 4 H), 3.84 (s, 1 H), 2.70-2.62 (m, 2 H), 2.58-2.39 (m, 3H), 2.09-1.99 (m, 1 H), 1.96-1.84 (m, 1 H), 1.76-1.64 (m, 1 H), 1.25 (t, *J* = 7.8 Hz, 3 H); ^{13}C

NMR (75 MHz, $CDCl_3$) δ 143.9, 133.9, 127.7, 126.3, 66.7, 62.7, 31.6, 28.8, 28.7, 15.8, 12.7; Anal. Calcd. for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 83.00; H, 8.70.

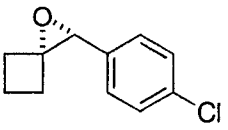
Cyclopentanone (b0209, yms2612, b0546a, b0549).



Colorless oil; $[\alpha]_D^{25}$ = -44.6 (*c* 0.9, $CHCl_3$); IR (film) 1741 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.18 (d, *J* = 7.8 Hz, 2 H), 7.12 (d, *J* = 7.8 Hz, 2 H), 3.32 (dd, *J* = 10.5, 9.3 Hz, 1 H), 2.64 (q, *J* = 7.5 Hz, 2 H), 2.54-2.46 (m, 2 H), 2.37-2.24 (m, 1 H), 2.21-2.05 (m, 2 H), 1.97-1.90 (m, 1 H), 1.24 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 219.2, 142.9, 135.5, 128.2, 128.1, 55.3, 38.7, 32.0, 28.7, 21.1, 15.8; Anal. Calcd. for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 82.85; H, 8.48.

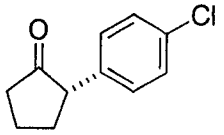
(Table 2.4, Entry 5)

Epoxide (yms2619).



Colorless oil; $[\alpha]_D^{25}$ = 106.3 (*c* 1.1, $CHCl_3$); IR (film) 1793 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31-7.28 (m, 2 H), 7.11-7.08 (m, 2 H), 3.81 (s, 1 H), 2.66-2.57 (m, 1 H), 2.50-2.35 (m, 2 H), 1.98-1.81 (m, 2 H), 1.75-1.59 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.3, 133.6, 128.4, 127.5, 66.9, 61.9, 31.6, 28.5, 12.7; Anal. Calcd. for $C_{11}H_{11}OCl$: C, 67.87; H, 5.70. Found: C, 67.62; H, 5.76.

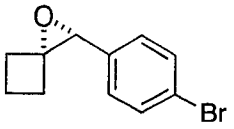
Cyclopentanone (yms2619, b0542).



Colorless oil; $[\alpha]_D^{25}$ = -46.2 (*c* 0.6, $CHCl_3$); IR (film) 1741 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31-7.29 (m, 2 H), 7.13 (d, *J* = 8.4 Hz, 2 H), 3.30-3.27 (m, 1 H), 2.53-2.44 (m, 2 H), 2.34-1.89 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.3, 136.8, 132.8, 129.6, 128.8, 54.9, 38.5, 31.8, 21.0; Anal. Calcd. for $C_{11}H_{11}OCl$: C, 67.87; H, 5.70. Found: C, 68.08; H, 5.88.

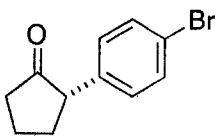
(Table 2.4, Entry 6)

Epoxide (yms2550).



Colorless oil; $[\alpha]_D^{25}$ = 93.2 (*c* 1.0, $CHCl_3$); IR (film) 1488 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46-7.43 (m, 2 H), 7.05-7.02 (m, 2 H), 3.79 (s, 1 H), 2.66-2.55 (m, 1 H), 2.49-2.35 (m, 2 H), 1.97-1.81 (m, 2 H), 1.74-1.59 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.9, 131.3, 127.9, 121.7, 66.8, 61.9, 31.6, 28.5, 12.7; Anal. Calcd. for $C_{11}H_{11}OBr$: C, 55.25; H, 4.64. Found: C, 55.05; H, 4.76.

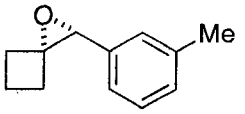
Cyclopentanone (yms2550, b0528a, b0530).



Colorless oil; $[\alpha]_D^{25}$ = -36.2 (*c* 1.0, $CHCl_3$); IR (film) 1736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46-7.44 (m, 2 H), 7.07 (d, *J* = 8.7 Hz, 2 H), 3.31-3.25 (m, 1 H), 2.54-2.44 (m, 2 H), 2.34-1.89 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.2, 137.3, 131.7, 129.9, 121.0, 54.9, 38.5, 31.7, 21.0; Anal. Calcd. for $C_{11}H_{11}OBr$: C, 55.25; H, 4.64. Found: C, 55.30; H, 4.55.

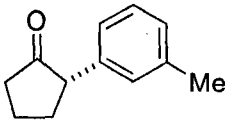
(Table 2.4, Entry 7)

Epoxide (b0335d).



Colorless oil; $[\alpha]_D^{25}$ = 98.3 (*c* 1.2, $CHCl_3$); IR (film) 1609, 1490 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26-7.21 (m, 1 H), 7.12-7.06 (m, 1 H), 7.02-6.94 (m, 2 H), 3.83 (s, 3 H), 2.68-2.54 (m, 1 H), 2.51-2.37 (m, 2 H), 2.36 (s, 3 H), 2.05-1.82 (m, 2 H), 1.76-1.63 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.7, 136.7, 128.6, 128.1, 126.9, 123.3, 66.7, 62.7, 31.7, 28.7, 21.7, 12.7; Anal. Calcd. for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.58; H, 7.94.

Cyclopentanone (b0336b, b0541).

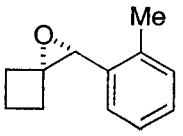


Colorless oil; $[\alpha]_D^{25}$ = -51.9 (*c* 0.84, $CHCl_3$); IR (film) 1741 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28-7.21 (m, 1 H), 7.12-7.06 (m, 1 H), 7.04-6.98 (m, 2 H), 3.35-3.26 (m, 1 H), 2.56-2.44 (m, 2 H), 2.36 (s, 3 H), 2.34-2.24 (m, 1 H), 2.22-2.06 (m, 2H), 2.01-1.90 (m, 1

H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.1, 138.5, 138.2, 129.0, 128.5, 127.7, 125.2, 55.5, 38.7, 32.1, 21.7, 21.1; Anal. Calcd. for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.50; H, 7.83.

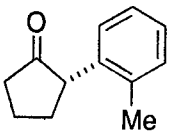
(Table 2.4, Entry 8)

Epoxide (yms2640).



Colorless oil; $[\alpha]_D^{25}$ = 4.7 (*c* 1.2, $CHCl_3$); IR (film) 1491 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.20-7.16 (m, 3 H), 7.10-7.08 (m, 1 H), 3.97 (s, 1 H), 2.73-2.62 (m, 1 H), 2.50-2.30 (m, 2 H), 2.41 (s, 3 H), 1.93-1.67 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.5, 134.9, 129.6, 127.3, 125.8, 125.1, 66.2, 60.8, 31.8, 28.8, 19.1, 13.1; HRMS calcd for $C_{12}H_{14}O$ (M^+) 174.1045, Found 174.1049.

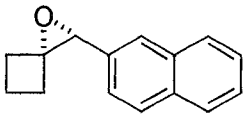
Cyclopentanone (yms2640, b0550).



Colorless oil; $[\alpha]_D^{25}$ = -91.9 (*c* 0.9, $CHCl_3$); IR (film) 1740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.20-7.15 (m, 3 H), 7.03-7.00 (m, 1 H), 3.57-3.51 (m, 1 H), 2.53-2.47 (m, 2 H), 2.40-2.28 (m, 1 H), 2.33 (s, 3 H), 2.22-2.12 (m, 1 H), 2.08-1.92 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.6, 137.6, 136.8, 130.6, 127.4, 126.9, 126.3, 53.2, 38.9, 31.9, 21.3, 20.2; HRMS calcd for $C_{12}H_{15}O$ (M^++1) 175.1123, Found 175.1123.

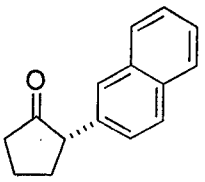
(Table 2.4, Entry 9)

Epoxide (b0335g).



White solid; mp = 75-76 °C; IR (film) 1491 cm^{-1}; IR (film) 1508 cm^{-1}; $[\alpha]_D^{25}$ = 106.6 (*c* 1.15, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.88-7.80 (m, 3 H), 7.69 (s, 1 H), 7.53-7.44 (m, 2 H), 7.32-7.24 (m, 1 H), 4.03 (s, 1 H), 2.74-2.44 (m, 3 H), 2.07-1.84 (m, 2 H), 1.78-1.62 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.4, 133.1, 127.9, 127.9, 126.3, 126.0, 125.4, 123.9, 67.1, 62.8, 31.8, 28.8, 12.8; Anal. Calcd. for $C_{15}H_{14}O$: C, 85.88; H, 6.71. Found: C, 86.08; H, 6.52.

Cyclopentanone (b0336c, b0544).



White solid; mp = 106-107 °C; $[\alpha]_D^{25}$ = -53.8 (*c* 0.89, $CHCl_3$); IR (film) 1736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.84-7.79 (m, 3 H), 7.66 (s, 1 H), 7.50-7.43 (m, 2 H), 7.34-7.31 (m, 1 H), 3.53-3.47 (m, 1 H), 2.62-2.48 (m, 2 H), 2.42-2.15 (m, 3 H), 2.04-1.93 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.4, 136.1, 133.7, 132.7, 128.5, 127.9, 127.8, 127.0, 126.6, 126.3, 125.9, 55.6, 38.7, 32.0, 21.1; Anal. Calcd. for $C_{15}H_{14}O$: C, 85.68; H, 6.71. Found: C, 85.79; H, 6.82.

2.4.2 Chiral 2-Alkyl-2-aryl Cyclopentanones

Representative procedure for asymmetric epoxidation (Table 2.5, entry 4). To a solution of the olefin (0.096 g, 0.5 mmol) and ketone **2-3b** (0.033 g, 0.1 mmol) in DME-DMM (3:1, v/v) (7.5 mL) were added buffer (0.1 M K_2CO_3-AcOH in 4 x 10^{-4} M aqueous EDTA, pH 9.3) (5 mL) with stirring. After the mixture was cooled to -10 °C (bath temperature) via NaCl-ice bath, a solution of Oxone (0.20 M in 4 x 10^{-4} M aqueous EDTA, 4.0 mL) (0.492 g, 0.80 mmol) and a solution of K_2CO_3 (0.84 M in 4 x 10^{-4} M aqueous EDTA, 4.0 mL) (0.464 g, 3.36 mmol) were added separately and simultaneously via a syringe pump over a period of 8 h. The reaction mixture was quenched with hexane, extracted with hexane, washed with brine, dried (Na_2SO_4), filtered, concentrated, and purified by flash chromatography [the silica gel was buffered with 1% Et_3N in organic solvent; Hexane-EtOAc (1/0 to 50/1) was used as eluent] to give the epoxide as a colorless oil (0.080 g, 77% yield, 90% ee).

(Entry 1, -10 °C, 8 h; Entry 2, -10 °C, 4 h; entry 3, -10 °C, 6 h; entry 5, 0 °C, 8 h; entry 6, -10 °C, 4 h; entry 7, -10 °C, 8 h; entry 8, -10 °C, 8 h; entry 9, -10 °C, 8 h; entry 10, -10 °C, 8 h; entry 11, 0 °C, 10 h.)

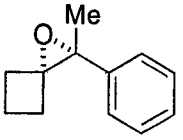
Representative procedure for the epoxide rearrangement with Et_2AlCl (Table 2.5, entry 1). To a solution of the epoxide (0.035 g, 0.2 mmol) (84% ee) in dry toluene (2 mL) at -78 °C was added a solution of Et_2AlCl (1.0 M in hexane, 50 uL, 0.05 mmol). Upon stirring at -78 °C to completion (about 15 min), the reaction was quenched with saturated aqueous $NaHCO_3$ (0.10 mL) at -78 °C. Upon warming up to 0 °C, the reaction

mixture was diluted with hexane, washed with brine, dried over Na_2SO_4, filtered, concentrated, and purified by flash chromatography [silica gel, hexane-EtOAc (20:1) as eluent] to give the ketone product as a colorless oil (0.032 g, 93% yield, 84% ee).

(Entries 2, 3, 6, 7, & 9, 0.25 eq. Et_2AlCl, 15 min; entries 4, 5, 0.25 eq. Et_2AlCl, 20 min; entry 10, 0.5 eq. Et_2AlCl, 60 min; entry 11, 0.75 eq. Et_2AlCl, 25 min.)

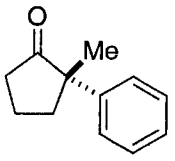
(Table 2.5, Entry 1)

Epoxide (b0337a).



Colorless oil; $[\alpha]_D^{25}$ = + 40.7 (*c* 1.1, $CHCl_3$); IR (film) 1497 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38-7.22 (m, 5H), 2.53-2.28 (m, 3H), 1.94-1.74 (m, 2H), 1.72-1.55 (m, 1H), 1.63 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.3, 128.1, 127.1, 126.0, 70.3, 63.9, 29.7, 29.4, 19.2, 12.5; HRMS calcd for $C_{12}H_{14}O$ (M^+) 174.1045, found 174.1040.

Cyclopentanone (b0338a).

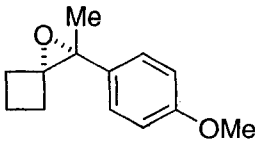


Colorless oil; $[\alpha]_D^{25}$ = -76.8 (*c* 1.0, $CHCl_3$); IR (film) 1737 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38-7.19 (m, 5H), 2.59-2.50 (m, 1H), 2.38-2.30 (m, 2H), 2.06-1.82 (m, 3H), 1.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 220.5, 142.6, 128.6, 126.7, 126.3, 53.2, 38.3,

37.8, 25.2, 18.9; Anal. Calcd. for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.85; H, 8.11.

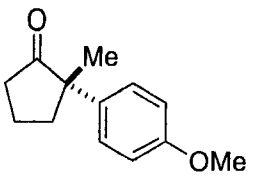
(Table 2.5, Entry 2)

Epoxide (b0337b).



Colorless oil; IR (film) 1513 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.22-7.17 (m, 2H), 6.90-6.84 (m, 2H), 3.81 (s, 3H), 2.52-2.28 (m, 3H), 1.94-1.78 (m, 2H), 1.70-1.56 (m, 1H), 1.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.8, 128.8, 127.3, 113.6, 70.3, 63.7, 55.5, 29.6, 29.3, 19.9, 12.4.

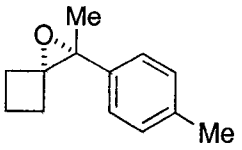
Cyclopentanone (b0338b).



Colorless oil; $[\alpha]_D^{25}$ = - 60.4 (*c* 1.3, $CHCl_3$); IR (film) 1737 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 3.77 (s, 3H), 2.55-2.47 (m, 1H), 2.35-2.30 (m, 2H), 2.04-1.82 (m, 3H), 1.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 220.7, 158.3, 134.4, 127.5, 114.0, 55.4, 52.6, 38.2, 37.7, 25.4, 18.9; Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.23; H, 7.73.

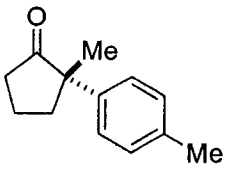
(Table 2.5, Entry 3)

Epoxide (b0337d, yms2709).



Colorless oil; IR (film) 1515 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.18-7.15 (m, 4H), 2.50-2.40 (m, 2H), 2.36-2.33 (m, 1H), 2.35 (s, 3H), 1.90-1.78 (m, 2H), 1.67-1.59 (m, 1H), 1.61 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.3, 136.7, 128.8, 126.0, 70.3, 63.9, 29.7, 29.4, 21.4, 20.0, 12.6; HRMS calcd. for $C_{13}H_{16}O$ (M^+) 188.1201, found 188.1204.

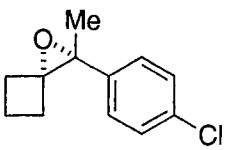
Cyclopentanone (yms2709).



Colorless oil; $[\alpha]_D^{25}$ = - 72.6 (*c* 1.0, $CHCl_3$); IR (film) 1736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25-7.12 (m, 4H), 2.58-2.50 (m, 1H), 2.36-2.31 (m, 2H), 2.32 (s, 3H), 2.05-1.83 (m, 3H), 1.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 220.8, 139.5, 136.3, 129.4, 126.3, 53.0, 38.3, 37.8, 25.3, 21.2, 19.0; Anal. Calcd. for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 83.01; H, 8.63.

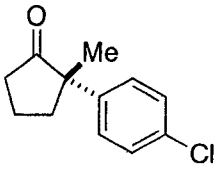
(Table 2.5, Entry 4)

Epoxide (yms2604).



Colorless oil; $[\alpha]_D^{25}$ = + 55.0 (*c* 1.0, $CHCl_3$); IR (film) 1492 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30-7.27 (m, 2H), 7.21-7.18 (m, 2H), 2.50-2.26 (m, 3H), 1.91-1.73 (m, 2H), 1.70-1.60 (m, 1H), 1.59 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.9, 133.0, 128.3, 127.5, 70.4, 63.4, 29.6, 29.2, 19.7, 12.5; Anal. Calcd. for $C_{12}H_{13}ClO$: C, 69.07; H, 6.28. Found: C, 68.80; H, 6.11.

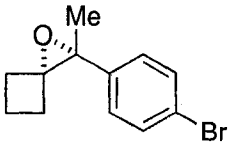
Cyclopentanone (yms2604).



Colorless oil; $[\alpha]_D^{25}$ = - 75.4 (*c* 2.1, $CHCl_3$); IR (film) 1735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 4H), 2.54-2.47 (m, 1H), 2.41-2.34 (m, 2H), 2.09-1.84 (m, 3H), 1 37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 220.4, 141.2, 132.6, 128.7, 127.9, 52.8, 38.2, 37.8, 25.3, 19.0; Anal. Calcd. for $C_{12}H_{13}ClO$: C, 69.07; H, 6.28. Found: C, 68.80; H, 6.12.

(Table 2.5, Entry 5)

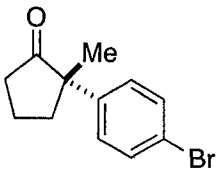
Epoxide (yms2505).



Colorless oil; $[\alpha]_D^{25}$ = + 40.8 (*c* 1.1, $CHCl_3$); IR (film) 1489 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45-7.42 (m, 2H), 7.15-7.12 (m, 2H), 2.49-2.40 (m, 2H), 2.36-2.26 (m, 1H), 1.92-1.72 (m, 2H), 1.69-1.51 (m, 1H), 1.58 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.4,

131.2, 127.8, 121.1, 70.3, 63.4, 29.5, 29.2, 19.7, 12.5; Anal. Calcd. for $C_{12}H_{13}BrO$: C, 56.94; H, 5.18. Found: C, 56.78; H, 4.91.

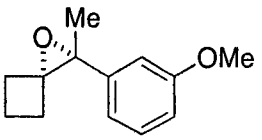
Cyclopentanone (yms2505).



Colorless oil; $[\alpha]_D^{25}$ = - 58.9 (*c* 1.1, $CHCl_3$); IR (film) 1736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44-7.42 (m, 2H), 7.24-7.21 (m, 2H), 2.52-2.42 (m, 1H), 2.38-2.32 (m, 2H), 2.07-1.81 (m, 3H), 1.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 220.1, 141.7, 131.6, 128.2, 120.8, 52.9, 38.1, 37.8, 25.3, 19.0; Anal. Calcd. for $C_{12}H_{13}BrO$: C, 56.94; H, 5.18. Found: C, 56.70; H, 5.09.

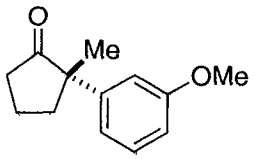
(Table 2.5, Entry 6)

Epoxide (yms2608).



Colorless oil; IR (film) 1603, 1489 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.24 (dd, *J* = 7.8, 7.5 Hz, 1H), 6.87 (d, *J* = 7.8 Hz, 1H), 6.82-6.77 (m, 2H), 3.79 (s, 3H), 2.53-2.27 (m, 3H), 1.91-1.78 (m, 2H), 1.71-1.55 (m, 1H), 1.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 142.0, 129.1, 118.5, 112.6, 111.6, 70.2, 63.8, 55.4, 29.6, 29.4, 19.9, 12.5; HRMS calcd for $C_{13}H_6O_2$ (M^+) 204.1150, found 204.1153.

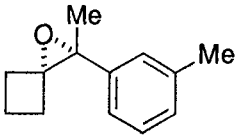
Cyclopentanone (yms2608).



Colorless oil; $[\alpha]_D^{25}$ = - 77.4 (*c* 1.0, $CHCl_3$); IR (film) 1737 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30-7.24 (m, 1H), 6.96-6.94 (m, 2H), 6.81-6.78 (m, 1H), 3.82 (s, 3 H), 2.60-2.52 (m, 1H), 2.40-2.35 (m, 2H), 2.07-1.86 (m, 3H), 1.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 220.3, 159.7, 144.3, 129.6, 118.7, 112.8, 111.7, 55.4, 53.3, 38.3, 37.8, 25.3, 19.0; Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.30; H, 7.72.

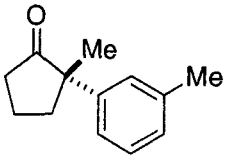
(Table 2.5, Entry 7)

Epoxide (b0337c).



Colorless oil; $[\alpha]_D^{25}$ = + 42.1 (*c* 1.0, $CHCl_3$); IR (film) 1490 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26-7.19 (m, 1H), 7.12-7.04 (m, 3H), 2.52-2.42 (m, 2H), 2.40-2.29 (m, 1H), 2.36 (s, 3H), 1.89-1.78 (m, 2H), 1.68-1.59 (m, 1H), 1.61 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.2, 137.6, 128.0, 127.8, 126.6, 123.1, 70.2, 63.9, 29.6, 29.4, 21.8, 20.0, 12.5; Anal. Calcd. for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 83.12; H, 8.42.

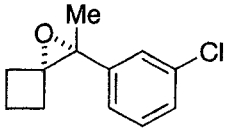
Cyclopentanone (b0338c).



Colorless oil; $[\alpha]_D^{25}$ = - 81.2 (*c* 1.1, $CHCl_3$); IR (film) 1737 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28-7.04 (m, 4H), 2.62-2.53 (m, 1H), 2.41-2.37 (m, 2H), 2.37 (s, 3H), 2.07-1.84 (m, 3H), 1.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 221.2, 142.5, 138.2, 128.5, 127.5, 127.1, 123.3, 53.3, 38.4, 37.9, 25.2, 21.9, 19.0; Anal. Calcd. for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 83.16; H, 8.77.

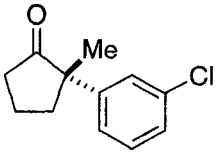
(Table 2.5, Entry 8)

Epoxide (yms2605).



Colorless oil; $[\alpha]_D^{25}$ = + 46.3 (*c* 1.0, $CHCl_3$); IR (film) 1598, 1478 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26-7.21 (m, 3H), 7.16-7.12 (m, 1H), 2.50-2.28 (m, 3H), 1.89-1.61 (m, 3H), 1.58 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.5, 134.2, 129.4, 127.3, 126.3, 124.2, 70.4, 63.4, 29.5, 29.2, 19.7, 12.5; Anal. Calcd. for $C_{12}H_{13}ClO$: C, 69.07; H, 6.28. Found: C, 69.30; H, 6.10.

Cyclopentanone (yms2605).

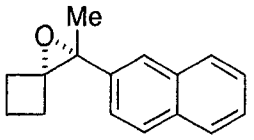


Colorless oil; $[\alpha]_D^{25}$ = - 68.7 (*c* 1.0, $CHCl_3$); IR (film) 1735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34 (s, 1H), 7.26-7.18 (m, 3H), 2.53-2.45 (m, 1H), 2.39-2.33 (m, 2H), 2.08-1.83 (m, 3H), 1 37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 219.8, 144.9, 134.5, 129.8,

127.0, 126.7, 124.7, 53.1, 38.2, 37.9, 25.2, 19.0; Anal. Calcd. for $C_{12}H_{13}ClO$: C, 69.07; H, 6.28. Found: C, 69.20; H, 6.14.

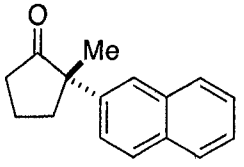
(Table 2.5, Entry 9)

Epoxide (yms2603).



Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84-7.77 (m, 4H), 7.49-7.38 (m, 3H), 2.57-2.48 (m, 2H), 2.44-2.33 (m, 1H), 1.95-1.77 (m, 2H), 1.72 (s, 3H), 1.70-1.60 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.9, 133.2, 132.6, 128.0, 127.7, 127.73, 126.2, 125.9, 124.9, 124.1, 70.5, 64.2, 29.7, 29.4, 20.1, 12.6; Anal. Calcd. for $C_{16}H_{16}O$: C, 85.68; H, 7.19. Found: C, 85.75; H, 7.17.

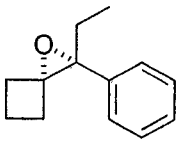
Cyclopentanone (yms2603).



Colorless oil; $[\alpha]_D^{25}$ = - 114.0 (*c* 1.0, $CHCl_3$); IR (film) 1735 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80-7.71 (m, 4H), 7.47-7.40 (m, 3H), 2.67-2.58 (m, 1H), 2.39-2.34 (m, 2H), 2.08-1.85 (m, 3H), 1.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 221.1, 139.9, 133.3, 132.2, 128.5, 128.0, 127.5, 126.2, 125.9, 124.9, 124.8, 53.6, 38.3, 38.0, 25.1, 19.0; Anal. Calcd. for $C_{16}H_{16}O$: C, 85.68; H, 7.19. Found: C, 85.50; H, 6.91.

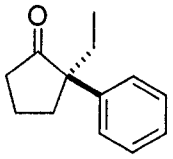
(Table 2.5, Entry 10)

Epoxide (b0337a).



Colorless oil; $[\alpha]_D^{25}$ = + 2.9 (*c* 1.0, $CHCl_3$); IR (film) 1495 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32-7.17 (m, 5H), 2.46-2.36 (m, 2H), 2.25-2.13 (m, 2H), 1.84-1.68 (m, 2H), 1.65-1.54 (m, 1H), 1.50-1.38 (m, 1H), 0.91-0.86 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 128.1, 127.0, 126.6, 70.5, 68.1, 29.7, 29.5, 26.4, 12.8, 9.4; Anal. Calcd. for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 82.74; H, 8.59.

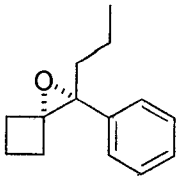
Cyclopentanone (b0338a).



Colorless oil; $[\alpha]_D^{25}$ = - 45.8 (*c* 1.0, $CHCl_3$); IR (film) 1733 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44-7.20 (m, 5H), 2.65-2.55 (m, 1H), 2.38-2.30 (m, 2H), 2.08-1.78 (m, 4H), 1.75-1.63 (m, 1H), 0.72 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 221.6, 139.4, 128.5, 127.0, 126.8, 57.6, 38.1, 33.5, 31.8, 18.9, 9.3; Anal. Calcd. for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 83.17; H, 8.48.

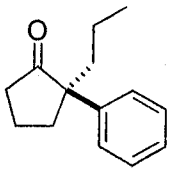
(Table 2.5, Entry 11)

Epoxide (yms2613).



Colorless oil; $[\alpha]_D^{25}$ = - 7.5 (*c* 1.3, $CHCl_3$) (77% ee); IR (film) 1466 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35-7.21 (m, 5H), 2.50-2.40 (m, 2H), 2.28-2.13 (m, 2H), 1.90-1.56 (m, 3H), 1.46-1.23 (m, 3H), 0.89 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.8, 128.1, 126.9, 126.5, 69.9, 67.5, 35.5, 29.7, 29.5, 18.6, 14.5, 12.8; Anal. Calcd. for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 82.98; H, 8.79.

Cyclopentanone (yms2613).



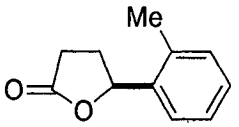
Colorless oil; $[\alpha]_D^{25}$ = - 46.4 (*c* 1.4, $CHCl_3$) (77% ee); IR (film) 1735 cm^{-1}; ^1H NMR (300 MHZ, $CDCl_3$) δ 7.42-7.20 (m, 5H), 2.65-2.58 (m, 1H), 2.31-2.24 (m, 2H), 2.07-1.79 (m, 4H), 1.64-1.54 (m, 1H), 1.17-1.01 (m, 2H), 0.81 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 219.8, 139.9, 128.6, 127.0, 126.7, 57.1, 41.5, 37.8, 34.1, 19.0, 18.3, 14.8; Anal. Calcd. for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.11; H, 9.18.

2.4.3 Chiral γ-Aryl-γ-butyrolactones and 2-Aryl Cyclobutanones

Representative procedure of asymmetric epoxidations (Table 2.6, entry 5). To a solution of the freshly prepared olefin (0.090 g, 0.50 mmol) and ketone **2-3b** (0.033 g,

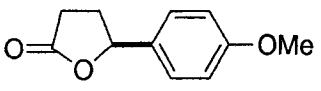
0.10 mmol) in DME-DMM (3:1, v/v) (7.5 mL) was added buffer (0.1 M K_2CO_3-AcOH in 4×10^{-4} M aqueous EDTA, pH = 9.3) (5.0 mL) with stirring. After the mixture was cooled to -10 °C (bath temperature) via NaCl-ice bath, a solution of Oxone (0.20 M in 4×10^{-4} M aqueous EDTA, 8.0 mL) (0.984 g, 1.60 mmol) and a solution of K_2CO_3 (0.84 M in 4×10^{-4} M aqueous EDTA, 8.0 mL) (0.928 g, 6.72 mmol) was added separately and simultaneously via a syringe pump over a period of 12 h. The reaction mixture was quenched with EtOAc, extracted with EtOAc, washed with brine, dried (Na_2SO_4), filtered, concentrated, and purified by flash chromatography [silica gel, hexane-EtOAc (20/1 to 4/1 to 2/1) was used as eluent] to give the lactone as a white solid (0.051 g, 48 % yield, 91 % ee).

(Table 2.6, Entry 1) (b0423).



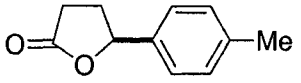
Colorless oil; $[\alpha]_D^{25} = -46.3$ (*c*1.8, $CHCl_3$) (80% ee). IR (film) 1770 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.20 (m, 4 H), 5.75-5.70 (m, 1H), 2.74-2.64 (m, 3H), 2.36 (s, 3H), 2.18-2.10 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.1, 137.6, 134.3, 130.8, 128.2, 126.5, 124.3, 79.0, 29.8, 28.9, 19.3; Anal. Calcd. for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.76; H, 6.68.

(Table 2.6, Entry 2) (b0430).



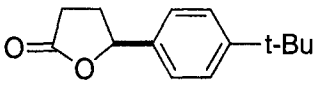
White solid; mp = 59-60°C; $[\alpha]_D^{25}$ = -11.9 (*c* 1.1, $CHCl_3$) (89% ee). IR (film) 1766 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30-7.24 (m, 2H), 6.94-6.88 (m, 2H), 5.48-5.44 (m, 1H), 3.82 (s, 3H), 2.68-2.58 (m, 3H), 2.26-2.15 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.9, 159.7, 131.2, 127.0, 114.2, 81.5, 55.5, 31.1, 29.4; Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 69.00; H, 6.20.

(Table 2.6, Entry 3) (yms2723).



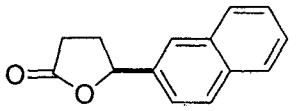
Colorless oil; $[\alpha]_D^{25}$ = -21.1 (*c* 1.0, $CHCl_3$) (90% ee); IR (film) 1767 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28-7.18 (m, 4 H), 5.47 (dd, *J* = 8.0, 6.0 Hz 1H), 2.70-2.56 (m, 3H), 2.36 (s, 3H), 2.26-2.12 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0, 138.3, 136.4, 129.4, 125.4, 81.5, 31.1, 29.3, 21.4; HRMS calcd for $C_{11}H_{13}O_2$ (M^++1): 177.0916. Found 177.0919.

(Table 2.6, Entry 4) (yms2731, b0432).



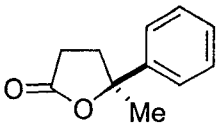
Colorless oil; $[\alpha]_D^{25}$ = -16.7, (*c* 1.2, $CHCl_3$) (91% ee); IR (film) 1761 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43-7.38 (m, 2H), 7.29-7.24 (m, 2H), 5.49 (dd, *J* = 8.1, 6.3 Hz, 1 H), 2.70-2.58 (m, 3H), 2.29-2.16 (m, 1H), 1.32 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0, 151.6, 136.3, 125.8, 125.3, 81.5, 34.9, 31.6, 31.1, 29.3; Anal. Calcd. for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.13; H, 8.19.

(Table 2.6, Entry 5) (yms2734).



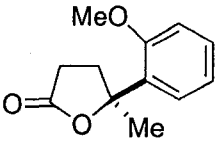
White solid; mp = 98-100°C; $[\alpha]_D^{25}$ = -19.0 (*c* 1.1, $CHCl_3$) (91% ee); IR (film) 1771 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.89-7.81 (m, 4H), 7.53-7.39 (m, 3H), 5.70-5.66 (m, 1H), 2.77-2.67 (m, 3H), 2.34-2.25 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.9, 136.7, 133.1, 133.0, 128.7, 128.0, 127.7, 126.5, 126.4, 124.3, 122.9, 81.3, 30.9, 29.0; Anal. Calcd. for $C_{14}H_{12}O_2$: C, 79.22; H, 5.70. Found: C, 79.46; H, 5.88.

(Table 2.6, Entry 6) (yms2724).



Colorless oil; $[\alpha]_D^{25}$ = -32.1 (*c* 1.0, $CHCl_3$) (84% ee); IR (film) 1770 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.28 (m, 5H), 2.67-2.38 (m, 4H), 1.71 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.5, 144.4, 128.7, 127.7, 124.2, 87.1, 36.4, 29.7, 29.2; Anal. Calcd. for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.75; H 6.71.

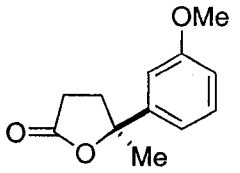
(Table 2.6, Entry 7) (yms2729).



Colorless oil; $[\alpha]_D^{25}$ = -63.8 (*c* 1.1, $CHCl_3$) (71% ee); IR (film) 1770 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49-7.46 (m, 1H), 7.31-7.26 (m, 1H), 6.98-6.90 (m, 2H), 3.86 (s,

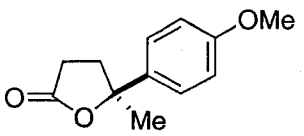
3H), 2.65-2.55 (m, 2H), 2.51-2.41 (m, 2H), 1.75 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.9, 155.3, 132.1, 129.0, 125.3, 120.6, 111.3, 86.9, 55.3, 34.5, 29.1, 27.0; Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 70.09; H, 6.90.

(Table 2.6, Entry 8) (b0424).



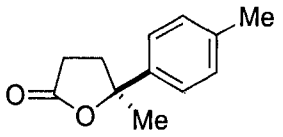
Colorless oil; $[\alpha]_D^{25}$ = -32.6 (*c* 1.0, $CHCl_3$) (87% ee); IR (film) 1770 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31-7.26 (m, 1H), 6.95-6.92 (m, 2H), 6.85-6.82 (m, 1H), 3.82 (s, 3H), 2.68-2.28 (m, 4H), 1.71 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.5, 159.7, 146.0, 129.8, 116.5, 112.8, 110.3, 87.0, 55.5, 36.4, 29.6, 29.2; Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.77; H, 6.66.

(Table 2.6, Entry 9) (b0437).



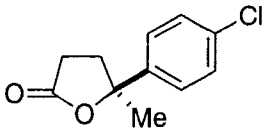
White solid; mp = 35-36 °C; $[\alpha]_D^{25}$ = -35.3 (*c* 1.0, $CHCl_3$) (82% ee). IR (film) 1774 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31-7.27 (m, 2H), 6.91-6.87 (m, 2H), 3.81 (s, 3H), 2.69-2.35 (m, 4H), 1.70 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6, 159.0, 136.4, 125.5, 114.0, 87.1, 55.5, 36.4, 29.7, 29.3; Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.85; H, 6.68.

(Table 2.6, Entry 10) (yms2727).



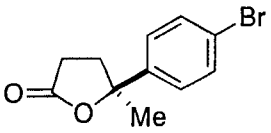
Colorless oil; $[\alpha]_D^{25}$ = -37.7 (*c* 1.1, $CHCl_3$) (79% ee); IR (film) 1774 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29-7.23 (m, 2H), 7.20-7.16 (m, 2H), 2.66-2.58 (m, 1H), 2.54-2.42 (m, 2H), 2.40-2.34 (m, 1H), 2.35 (s, 3H), 1.71 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6, 141.4, 137.4, 129.3, 124.1, 87.2, 36.4, 29.7, 29.2, 21.2; Anal. Calcd. for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.55; H, 7.20.

(Table 2.6, Entry 11) (b0426).



Colorless oil; $[\alpha]_D^{25}$ = -39.3 (*c* 1.0, $CHCl_3$) (84% ee); IR (film) 1771 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36-7.30 (m, 4H), 2.70-2.38 (m, 4H), 1.69 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.1, 142.9, 133.6, 128.8, 125.7, 86.6, 36.3, 29.6, 29.1; Anal. Calcd. for $C_{11}H_{11}ClO_2$: C, 62.72; H, 5.26. Found: C, 62.92; H, 5.10.

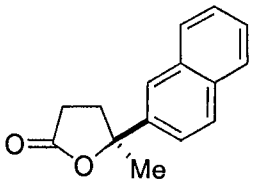
(Table 2.6, Entry 12) (yms2728).



White solid; mp = 40-43 °C; $[\alpha]_D^{25}$ = -31.9 (*c* 1.0, $CHCl_3$) (86% ee); IR (film) 1774 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 2.70-

2.37 (m, 4H), 1.69 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.1, 143.4, 131.8, 126.0, 121.7, 86.6, 36.2, 29.5, 29.1; Anal. Calcd. for $C_{11}H_{11}BrO_2$: C, 51.79; H, 4.35. Found: C, 51.86; H 4.42.

(Table 2.6, Entry 13) (b0428).



White solid; mp = 79-80 °C; $[\alpha]_D^{25}$ = -28.6 (*c* 0.8, $CHCl_3$) (87% ee); IR (film) 1774 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.90-7.80 (m, 4H), 7.52-7.40 (m, 3H), 2.70-2.42 (m, 4H), 1.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6, 141.4, 132.9, 132.6, 128.7, 128.2, 127.6, 126.6, 126.4, 122.7, 122.5, 87.2, 36.2, 29.5, 29.2; Anal. Calcd. for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.49; H, 6.50.

Procedure for the synthesis of (*S*)-2-(*p*-*t*-butylphenyl)cyclobutanone (Table 2.7, entry 1). To a solution of the freshly prepared olefin (0.093 g, 0.5 mmol) and ketone **2-3b** (0.125 g, 0.375 mmol) in DME-DMM (3:1, v/v) (7.5 mL) was added buffer (0.1 M K_2CO_3-AcOH in 4×10^{-4} M aqueous EDTA, pH = 8.0) (5.0 mL) with stirring. After the mixture was cooled to -10 °C (bath temperature) via NaCl-ice bath, a solution of Oxone (0.202 M in 4×10^{-4} M aqueous EDTA, 1.77 mL) (0.220 g, 0.36 mmol) and a solution of K_2CO_3 (0.479 M in 4×10^{-4} M aqueous EDTA, 1.77 mL) (0.117 g, 0.85 mmol) was added separately and simultaneously via a syringe pump over a period of 4 h. Then the reaction mixture was immediately quenched with hexane, extracted with hexane, dried

(Na_2SO_4), filtered, concentrated, and purified by flash chromatography [Iatrobeads 6RS-8060; hexane-EtOAc (1/0 to 20/1) was used as eluent] to give the cyclobutanone product as a colorless oil (0.069 g, 68 % yield, 90 % ee). $[\alpha]_D^{25}$ = +38.1 (*c* 1.1 $CHCl_3$) (90% ee); IR (film) 1784 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.4 Hz, 2 H), 7.20 (d, *J* = 8.4 Hz, 2H), 4.56-4.50 (m, 1H), 3.30-3.18 (m, 1H), 3.10-2.98 (m, 1H), 2.60-2.48 (m, 1H), 2.31-2.19 (m, 1H), 1.32 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.5, 150.1, 133.7, 126.9, 125.8, 64.5, 45.0, 34.7, 31.5, 17.9; HRMS Calcd for $C_{14}H_{18}O$ (M^+) 202.1358; found: 202.1353.

Procedure for the synthesis of (*S*)-2-methyl-2-*p*-tolylcyclobutanone (Table 2.7, entry 2). To a solution of the freshly prepared olefin (0.080 g, 0.5 mmol) and ketone **2-3b** (0.110 g, 0.33 mmol) in DME-DMM (3:1, v/v) (7.5 mL) was added buffer (0.1 M K_2CO_3-AcOH in 4 × 10^{-4} M aqueous EDTA, pH = 8.0) (5.0 mL) with stirring. After the mixture was cooled to -10 °C (bath temperature) via NaCl-ice bath, a solution of Oxone (0.202 M in 4 × 10^{-4} M aqueous EDTA, 1.56 mL) (0.194 g, 0.32 mmol) and a solution of K_2CO_3 (0.479 M in 4 × 10^{-4} M aqueous EDTA, 1.56 mL) (0.103 g, 0.75 mmol) was added separately and simultaneously via a syringe pump over a period of 4 h. Then the reaction mixture was immediately quenched with hexane, extracted with hexane, dried (Na_2SO_4), filtered, concentrated, and purified by flash chromatography [silica gel, hexane-EtOAc (1/0 to 20/1) was used as eluent] to give the cyclobutanone as a colorless oil (0.044 g, 51 % yield, 85 % ee). $[\alpha]_D^{25}$ = -58.2 (*c* 1.0, $CHCl_3$) (85% ee); IR (film) 1775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.1 Hz, 2H), 7.16 (d, *J* = 8.1 Hz, 2H), 3.23-2.99 (m, 2H), 2.56-2.46 (m, 1H), 2.34 (s, 3H), 2.19-2.10 (m, 1H), 1.54 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 212.7, 139.6, 136.6, 129.5, 125.7, 68.0, 42.8, 26.5, 25.7, 21.2; Anal. Calcd. for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.88; H, 7.99.

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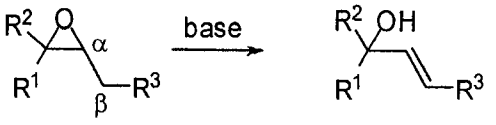
CHAPTER 3.0 : SYNTHESIS OF CHIRAL SILYL ALLYLIC ALCOHOLS BY KETONE CATALYZED ASYMMETRIC EPOXIDATION AND UNUSUAL EPOXIDE ISOMERIZATION

3.1 INTRODUCTION

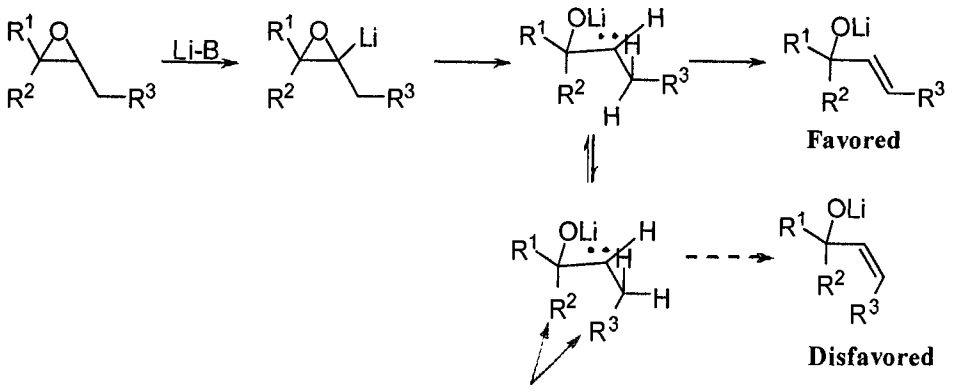
The base-mediated rearrangement of epoxides into allylic alcohols is a well-known synthetic transformation which has received a lot of attention mostly due to the interesting mechanistic features[1-11] and great usefulness of allylic alcohols in organic synthesis (Scheme 3.1).



Scheme 3.1

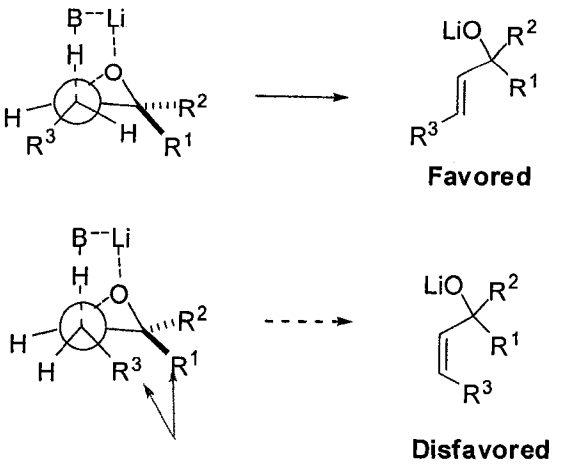
Mechanistically there are two reaction pathways to produce an allylic alcohol in a base-mediated epoxide isomerization. One is the abstraction of the α-hydrogen on the

epoxide ring, giving rise to a reactive carbene intermediate which undergoes C–H insertion to the β-position, produces an allylic alcohol (Scheme 3.2). Formation of (*Z*)-allylic alcohol is disfavored because of the steric interaction between R^1 and R^2. Instead, (*E*)-allylic alcohols are obtained as the major stereoisomer in the isomerization of acyclic epoxides.[1]



Scheme 3.2

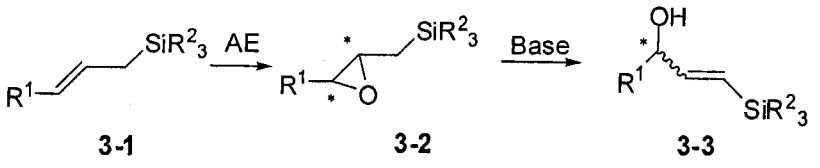
Another pathway is through the removal of a hydrogen atom at the β position of epoxide ring which is often a stereospecific *syn*-elimination (Scheme 3.3). The isomerization of acyclic epoxides will lead to formation of (*E*)-allylic alcohols due to the disfavorable stereointeraction between R^1 and R^3 in the transition state, which would form the (*Z*)-allylic alcohols.[1]



Scheme 3.3

The first enantioselective version of this isomerization using a chiral base was described in 1980.[12] Since then, many efforts have been made to establish an efficient isomerization method to enantioenriched allylic alcohols.[13-21]

Our group is interested in asymmetric epoxidation of all types of olefins by chiral dioxiranes.[22-25] Allylsilane **3-1** is one of our targets. We expect that, via asymmetric epoxidation, a chiral epoxide can be produced and further isomerized to a chiral allylic alcohol with a synthetically useful vinyl silane functionality[26-29] (Scheme 3.4).



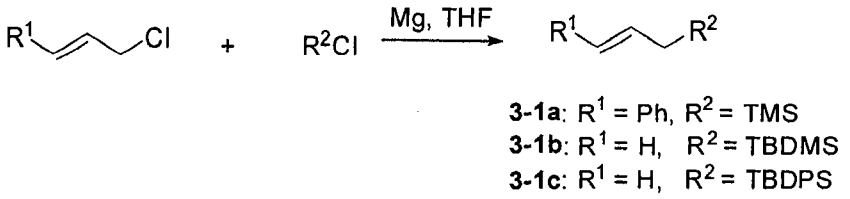
Scheme 3.4

3.2 RESULTS AND DISCUSSION

The project was initiated by Dr. Yong Tang.

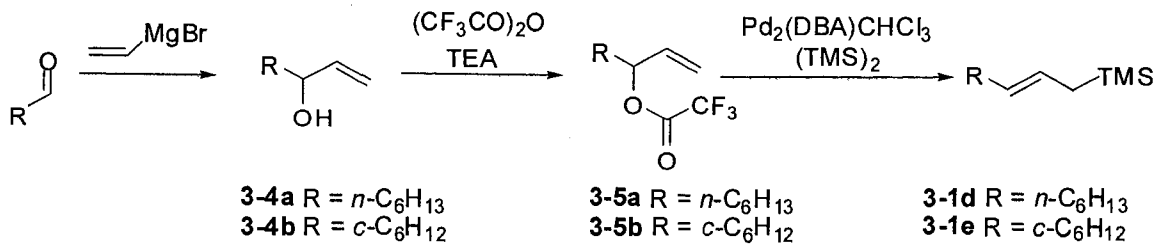
3.2.1 Synthesis of Allylsilanes

A variety of allylsilanes with different steric properties, C=C geometries, and silyl groups were synthesized through the joint efforts with Dr. Yong Tang and Dr. Jiaxi Xu. *trans*-Allylsilane **3-1a** was obtained in one step via Grignard reaction from commericially available TMSCl and *trans*-cinnamoyl chloride (Scheme 3.5).[30,31] Utilization of same method also allowed for preparation of allysilanes **3-1b** and **3-1c** in good yields (Scheme 3.5).



Scheme 3.5

trans-Allylsilanes **3-1d** and **3-1e** were synthesized by Tsuji-Trost reaction from hexamethyldisilane and the corresponding trifluoroacetate,[32] which was prepared from addition of vinyl Grignard to the corresponding aldehyde followed by esterfication with $(CF_3CO)_2O$ (Scheme 3.6).



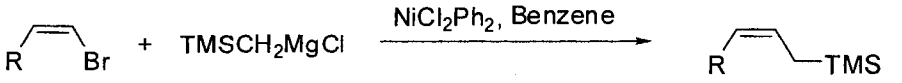
3-4a R = *n*-C_6H_{13}
3-4b R = *c*-C_6H_{12}

3-5a R = *n*-C_6H_{13}
3-5b R = *c*-C_6H_{12}

3-1d R = *n*-C_6H_{13}
3-1e R = *c*-C_6H_{12}

Scheme 3.6

cis-Allylsilanes **3-1f** and **3-1g** were prepared by Kumada coupling of $TMSCH_2MgCl$ and vinyl bromide,[33] which was synthesized from hydrobromination of the commercially available terminal alkyne (Scheme 3.7).[34]

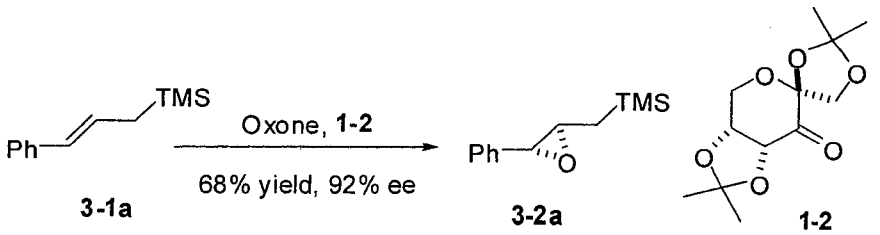


3-1f R= Ph
3-1g R= *n*-C_6H_{13}

Scheme 3.7

3.2.2 Primary Results of Epoxidation and Epoxide Isomerization

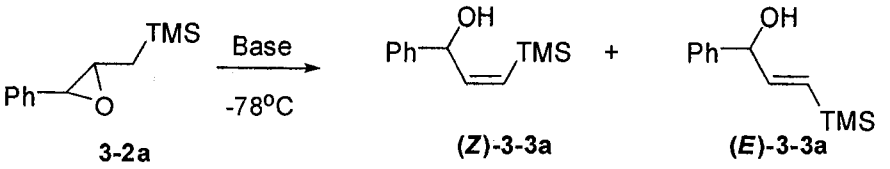
Initial results for epoxidation and isomerization were obtained from *trans*-trimethyl-cinnamylsilane **3-1a**. The asymmetric epoxidation of **3-1a** using ketone **1-2** as catalyst gave the corresponding epoxide in 92% ee and 68% yield (Scheme 3.8).



Scheme 3.8

The following base-mediated epoxide isomerization surprisingly produced either (*Z*)- or (*E*)-allylic alcohol products depending on the base used in the reaction (Table 3.1). With alkyllithiums, such as *t*-BuLi, *sec*-BuLi and *n*-BuLi, isomerization produced the (*Z*)-allylic alcohol, while the bulky lithium amide base such as LDA and LiTMP gave the (*E*)-allylic alcohol. It is the first example of formation of the (*Z*)-allylic alcohol through base-mediated isomerization of an acyclic epoxide.

Table 3.1

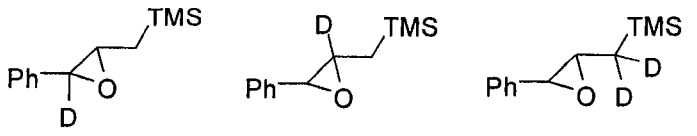


Entry	Base	Yield	*Z*/*E*
1[a]	DBU	0	--
2[a]	*t*-BuLi	21	2.1/1
3[a]	*sec*-BuLi	78	5.0/1
4[a]	*n*-BuLi	74	5.5/1
5[a,b]	*n*-BuLi	78	6.2/1
6[c]	LDA	78	1/11.5
7[c]	LiTMP	94	1/24

[a] Reactions were carried out with epoxide (0.25 mmol) and base (0.5 mmol) in THF (1.25 mL) and benzene (1.25 mL) at -78 °C for 7 h; [b] 2 eq.TMEDA was added; [c] Reactions were carried out with epoxide (0.25 mmol) and base (0.5 mmol) in THF (2.5 mL) at -78 °C for 5 h.

3.2.3 Mechanistic Study

In order to understand this unusual stereochemistry for the base mediated isomerization, three deuterium-labeled epoxides were designed (Scheme 3.9). In epoxides **3-2h** and **3-2i**, the deuterium was installed on the epoxide ring, while the deuterium labeled was at the β position adjacent to epoxide ring in epoxide **3-2j**.



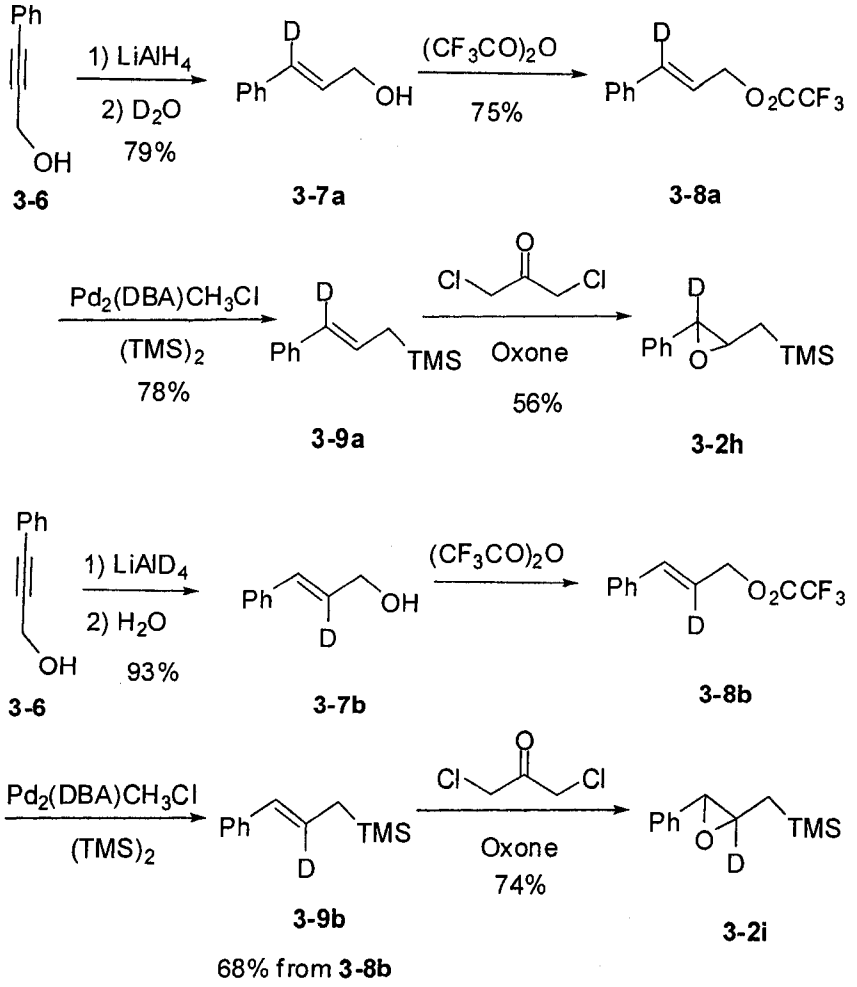
3-2h **3-2i** **3-2j**

Scheme 3.9

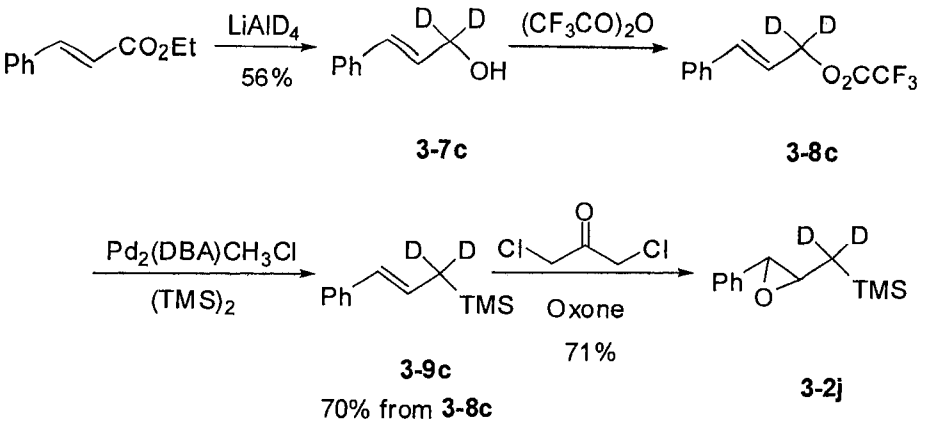
3.2.3.1 Synthesis of the Deuterium-labeled Epoxides

The synthesis of deuterium labeled epoxides **3-2h** and **3-2i** started with reduction of 3-phenyl-2-propyn-1-ol with $LiAlH_4$ or $LiAlD_4$ (Scheme 3.10).[35] By choosing D_2O and H_2O respectively as quenching reagent in the reduction, the allylic alcohols **3-7a** and **3-7b** were obtained with deuterium labeling at different positions of the C=C bond. After esterification of alcohols, Tsuji-Trost reaction, and epoxidation by Oxone, corresponding deuterium-labeled epoxides **3-2h** and **3-2i** were synthesized in good yields. The synthesis of deuterium labeled epoxide **3-2j** began with ethyl cinnamate (Scheme 3.10).

The reduction of the ester with $LiAlD_4$ gave the corresponding alcohol **3-7c** with the deuterium at the β-position of the C=C bond.[36] After similar transformations, the deuterium-labeled alcohol **3-7c** was successfully convert to the corresponding epoxide **3-2j** in good overall yields.



Scheme 3.10

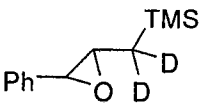
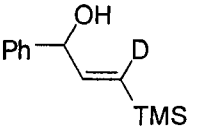


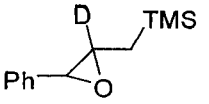
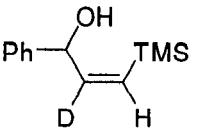
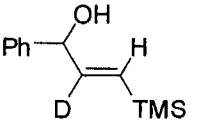
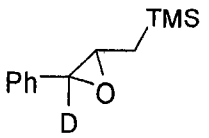
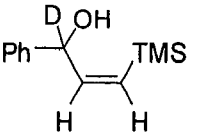
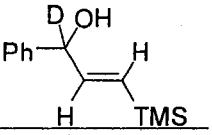
Scheme 3.10 (Continued)

3.2.3.2 Isomerization of Deuterium-labeled Silyl Epoxides

With deuterium-labeled silyl epoxides in hand, the epoxide isomerization reaction was carried out with *n*-BuLi and LiTMP. The results are summarized in the Table 3.2. For the epoxide **3-2j,** the isomerization by *n*-BuLi did not yield any detectable allylic alcohol based on the ^{1}H NMR of the crude product, while the isomerization by LiTMP produced the (*E*)-allylic alcohol as major product in relatively low yield. On the other hand, isomerization of epoxides **3-2h** and **3-2i** with *n*-BuLi and LiTMP did proceed smoothly to yield either (*Z*)- or (*E*)- allylic alcohols, respectively, in good yields.

Table 3.2

En.	Epoxides	Base	Yield	*Z*/*E*	Main products
1[a]		*n*-BuLi	No expected product	N/A	N/A
2[b]	**3-2j**	LiTMP	38	1/20	

3[a]		*n*-BuLi	85	5/1	
4[b]	**3-2i**	LiTMP	90	1/19	
5[a]		*n*-BuLi	88	6/1	
6[b]	**3-2h**	LiTMP	98	1/20	

[a] reactions were carried out with epoxide (0.25 mmol) *n*-BuLi (0.5 mmol) and TMEDA (0.5 mmol) in THF (1.25 mL) and benzene (1.25 mL) at -78 °C for 7 h; [b] reactions were carried out with epoxide (0.25 mmol), LiTMP (0.5 mmol) and in THF (2.5 mL) at -78 °C for 5 h.

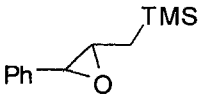
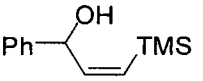
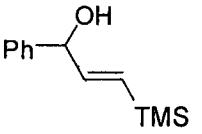
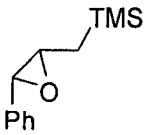
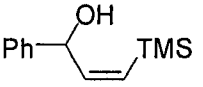
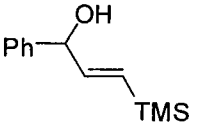
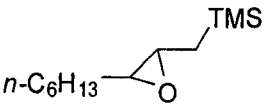
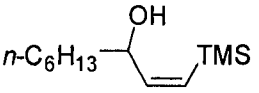
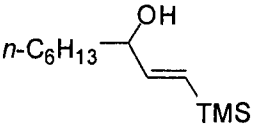
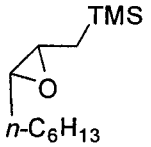
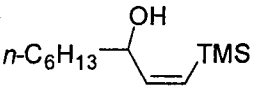
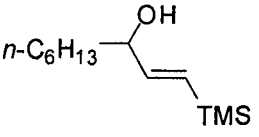
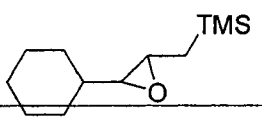
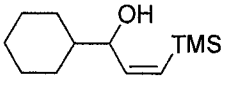
The results consistently show that both *n*-BuLi and LiTMP mediated isomerization of silyl epoxides proceed through the β deprotonation pathway. In entries 1 and 2 of Table 3.2, the yields of the epoxides isomerization were low due to the C-D bonds being much stronger than the C-H bonds. It is also understandable for silyl epoxides to first lose the hydrogen at β position adjacent to TMS since it was well known that silicon can stabilize an adjacent carbon-metal bond.[37-39]

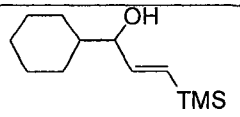
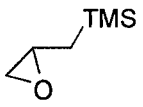
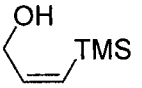
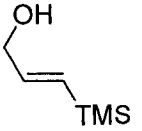
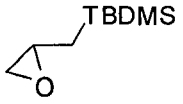
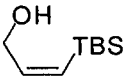
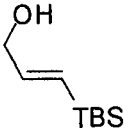
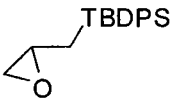
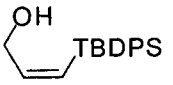
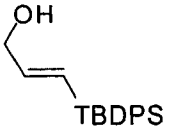
3.2.3.3 Isomerization of Other Silyl Epoxides

At this point, it was clear that the β deprotonation pathway was responsible for creating both (*Z*)- and (*E*)-allylic alcohols. However, if the reaction went through the β-deprotonation pathway, which was commonly accompanied by a stereospecific *syn*-

elimination for non silyl epoxides, the *E* stereo isomer should predominate. In order to fully understand the reaction mechanism and explored the substrate scope, epoxides **3-2b-3-2g** and **3-2k** were synthesized by epoxidation of the corresponding allylsilanes with Oxone, followed by base mediated isomerization. The results are shown in Table 3.3.

Table 3.3

	Epoxide	Base	Yield	*Z*/*E*	Main Product
1	 **3-2a**	*n*-BuLi[a]	78	6/1	
		LiTMP[b]	94	1/24	
2	 **3-2f**	*n*-BuLi[a]	22	2/1	
		LiTMP[b]	80	*E* only	
3	 **3-2d**	*n*-BuLi[a]	86	9/1	
		LiTMP[b]	97	1/18	
4	 **3-2g**	*n*-BuLi[a]	51	21	
		LiTMP[b]	80	*E* only	
5		*n*-BuLi[a]	90	7/1	

		LiTMP[b]	96	1/30	
6	 **3-2k**	*n*-BuLi[a]	62	7/1	
		LiTMP[b]	46	1/8	
7	 **3-2b**	*n*-BuLi[a]	74	3/1	
		LiTMP[b]	76	1/21	
8	 **3-2c**	*n*-BuLi[a]	98	1/1	
		LiTMP[b]	50	1/15	

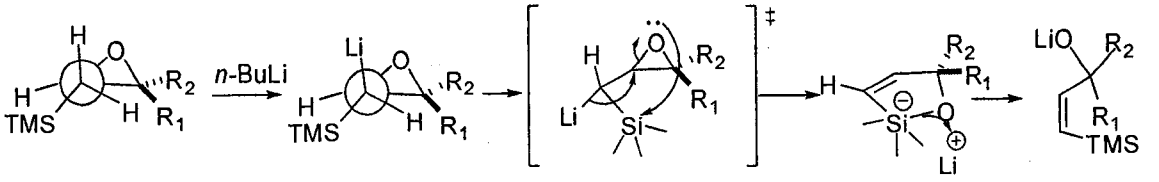
[a] Reactions were carried out with epoxide (0.25 mmol) *n*-BuLi (0.5 mmol) and TMEDA (0.5 mmol) in THF (1.25 mL) and benzene (1.25 mL) at -78 °C for 7 h. [b] Reactions were carried out with epoxide (0.25 mmol), LiTMP (0.5 mmol) and in THF (2.5 mL) at -78 °C for 5 h.

For the *trans*-trimethylsilyl epoxides **3-2a**, **3-2d**, **3-2e** and **3-2k**, the stereoselectivity to (*Z*)- and (*E*)-allylic alcohol was not significantly affected by substitution at the 1-position of silane epoxides and almost consistent *Z*/*E* selectivity was observed (Table 3.3, entries 1, 3, 5, and 6). In contrast to *trans*-silyl epoxides, the *cis*-silyl epoxides have a lower stereoselectivity and low reactivity to form (*Z*)-allylic alcohols when using the *n*-BuLi as base (Table 3.3, entries 2 and 4). On the other hand, higher stereoselectivity (only single isomer) for *cis*-silyl epoxides to (*E*)-allylic alcohols was obtained in good

yield by using the LiTMP as base (Table 3.3, entries 2 and 4). The stereoselectivity to (*Z*)-allylic alcohols is heavily dependent on the silyl group (Table 3.3, entries 6, 7, and 8). The larger the silyl groups were, the lower the selectivity was. The stereoselectivity for (*E*)-allylic alcohols was much less dependent on the size of the silyl group (Table 3.3, entries 6, 7, and 8).

3.2.3.4 Proposed Mechanism for Isomerization of Silyl Epoxides

Based on the information obtained, the reaction mechanism was proposed. There are two pathways likely for the isomerization of silyl epoxides. For the LiTMP-mediated epoxide isomerization, the reaction pathway is the well-documented E2 *syn*-elimination. For the *n*-BuLi case, the isomerization is likely to proceed thorough a silyl-promoted E1cb mechanism, which is an *anti*-elimination involving a pent-coordinated silicon specie (**3-10**) (Scheme 3.11).



3-2 **3-10** **(Z)-3-3**

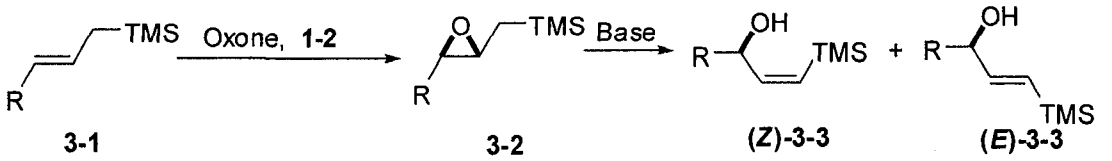
Scheme 3.11

3.2.4 Asymmetric Synthesis of Chiral Allylic Alcohols

With this unusual observation in hand, the asymmetric synthesis of chiral allylic alcohols was pursued by combining the ketone **1-2** catalyzed asymmetric epoxidation and the epoxide isomerization. The chiral silyl allylic alcohols were produced in good yield,

high enantioselectivity, and high stereoselectivity (Table 3.4). Chiral silyl allylic alcohols are useful synthetic intermediates because they contain both vinyl silane and allylic alcohol functionalities.[26]

Table 3.4



3-1 **3-2** **(Z)-3-3** **(E)-3-3**

En.	R	Epoxide Yield (%)	Epoxide Ee (%)	Base	Allylic alcohol Yield (%)	Z/E	Allylic alcohol Ee (%)	Config.
1	Ph	68[a]	92[d]	*n*-BuLi	77[b]	6/1	92[d]	
				LiTMP	94[c]	1/22	89[d]	(-)-(*S*)[40]
2	$CH_3(CH_2)_5$	58[a]	Nd	*n*-BuLi	88[b]	7/1	89[f]	
				LiTMP	94[c]	1/21	84[f]	
3	Cyclohexyl	75[a]	94[e]	*n*-BuLi	90[b]	8/1	89[f]	
				LiTMP	82[c]	1/31	88[f]	(-)-(*R*)[41]

[a] All epoxidations were carried out with the olefin (3 mmol), **1-2** (0.9 mmol), Oxone (4.14 mmol), and K_2CO_3 (17.4 mmol) in CH_3CN/dimethoxymethane (DMM) (1:2, v/v; 45 mL) and buffer (0.1 M K_2CO_3/AcOH, pH 9.3; 30 mL) at -10 °C for 3.5 h. [b] Isomerizations were carried out with epoxide (0.25 mmol), *n*-BuLi (0.5 mmol) and TMEDA (0.5 mmol) in THF (1.25 mL) and benzene (1.25 mL) at -78°C for 7 h. [c] Isomerizations were carried out with epoxide (0.25 mmol), LiTMP (0.5 mmol) and in THF (2.5ml) at -78°C for 5 h. [d] The ee was determined by chiral HPLC (Chiralcel OD). [e] The ee was determined by ^1H NMR shift analysis of the epoxide with $Eu(hfc)_3$. [f] The ee was determined by chiral GC (Chiraldex B-DM).

3.3 CONCLUSION

In summary, we found a unusual base-mediated epoxides isomerization which can selectively produce either (*Z*)- or (*E*)- silyl-substituted allylic alcohols by selecting an appropriate base. Isomerization of deuterium-labeled epoxides clearly shows that the isomerization proceeds through the β deprotonation pathway. A mechanism was proposed to be E2 for (*E*)-allylic alcohols and a silyl-promoted E1cb for (*Z*)-allylic alcohols. Combining our asymmetric epoxidation method and epoxide isomerization, chiral allylic alcohols were produced with good yields, high enantioselectivities, and high stereoselectivities. Even though epoxide isomerization has been well-documented, this unusual silyl-promoted E1cb isomerization to form acyclic (*Z*)-allylic alcohols by β deprotonation was the first reported.

3.4 EXPERIMENTAL

3.4.1 Preparation of Allylsilanes

Trimethyl-*trans*-cinnamylsilane (3-1a)[30] (b0438a). To a solution of TMSCl (6.3 g, 60 mmol) in THF (80 mL), $PhCH{=}CHCH_2Cl$ (7.6 g, 50 mmol) in THF (10 mL) was added dropwise at 0 °C over a period of 1.5 h. The resulting mixture was stirred overnight and warmed to rt. The reaction mixture was quenched by sat. NH_4Cl and 10% HCl, extracted with ether (3 × 50 mL), dried over Na_2SO_4, purified by flash chromatography (silica gel,

hexane) to give a colorless oil (9.3 g, 98% yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.07 (m, 5H), 6.37-6.14 (m, 2H), 1.72-1.62 (m, 2H), 0.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 128.7, 128.5, 128.1, 126.4, 125.7, 24.2, -1.57; HRMS calcd for $C_{12}H_{18}Si$ (M): 190.1178; found: 190.1185.

Allyl(*t*-butyl)dimethylsilane[42] (3-1b).

It was prepared through the similar procedure as **3-1a**.

Allyl(*t*-butyl)diphenylsilane[31] (3-1c).

It was prepared through the similar procedure as **3-1a**.

Non-1-en-3-ol (3-4a) (b0443). To a solution of heptaldehyde (6.850 g, 60 mmol) in THF (60 mL) with vigorous stirring, vinyl magnesium bromide (1 M, 72 mL, 72 mmol) was added dropwise by syringe at 0 °C. After the addition was complete, the mixture was stirred for 5 h at rt. Then the reaction was worked up with slow addition of water (15 mL), extracted by EtOAc (3 × 100 mL), washed by saturated NH_4Cl and brine, and dried by Na_2SO_4. After removal of solvent, the mixture was purified by flash chromatography (silica gel, hexane/EtOAc = 10/1) to give **3-4a** as a colorless oil (6.0 g, 70 % yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (ddd, J = 17.2, 10.4, 6.4 Hz, 1H), 5.22 (dt, J = 17.4, 1.2 Hz, 1H), 5.11 (dt, J = 10.4, 1.2 Hz, 1H), 4.13-4.07 (m, 1H), 1.60-1.22 (m, 10H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5, 114.7, 73.5, 37.3, 32.0, 29.5, 25.5, 22.8, 14.3;

Non-1-en-3-yl 2,2,2-trifluoroacetate (3-5a) (b0448). To a solution of allylic alcohol **3-4a** (4.26 g, 30mmol) in CH_2Cl_2 (30 mL) with stirring at 0 °C, Et_3N (4.25 g, 42 mmol), DMAP (0.367 g, 3 mmol) and $(CF_3CO)_2O$ (7.66 g, 36.5 mmol) were added in this order. The mixture was stirred for 10 h. Then water was added into reaction mixture for working up. After stirring for another 10 min, the mixture was extracted by CH_2Cl_2 (3 × 60 mL), washed by brine, dried over $NaSO_4$, and purified by flash chromatography (silica gel, hexane) to give **3-5a** as light yellow oil (3.8 g, 44% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 5.81 (ddd, J = 10.5, 10.2, 6.9 Hz., 1H), 5.43-5.25 (m, 3H), 1.86-1.62 (m, 2H),1.45-1.18 (m, 8H), 0.89 (t, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.8, 156.4, 134.4, 119.3, 116.7, 112.9, 80.0, 34.0, 31.8, 29.0, 24.9, 22.7, 14.22

(*E*)-1-trimethylsilyl-2-nonene (3-1d)[43] (b0505). A flask (150 mL) was charged with $Pd_2(DBA)CHCl_3$ (0.235 g, 0.227mmol) and dry THF (84 mL) with stirring under Ar to afford a deep purple solution. The allylic ester **3-5a** (3.6 g, 15 mmol) was added into the purple solution and stirred until the purple color of solution turned into mild purple. Then $(TMS)_2$ (4.41 g, 30.2 mmol) was added in to the mixture and stirred for 10 h at rt. After TLC showed the reaction was finished, reaction mixture was diluted with hexane (300 mL), washed with the saturated $NaHCO_3$ solution (300 mL), dried over $NaSO_4$, concentrated and purified by flash chromatography (silica gel, hexane) to give **3-1d** as a colorless oil (2.95 g, 98% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 5.41-5.32 (m, 1H), 5.28-5.20 (m, 1H), 1.96 (dd, J = 12.8, 6.4 Hz, 2H), 1.39 (dd, J = 8.0, 0.8 Hz, 2H), 1.36-1.20

(m, 8H), 0.88 (t, J = 6.8 Hz, 3H), -0.02 (s, 9H);^{13}C NMR (100 MHz, $CDCl_3$) δ 129.2, 126.1, 33.0, 32.0, 30.2, 29.0, 22.9, 22.8, 14.3, -1.8.

Cyclohexylprop-2-en-1-ol (3-4b) (b0509). The compound was synthesized through same procedure as **3-4a**. A colorless oil was obtained in 50% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 (ddd, J = 17.2, 10.4, 6.4 Hz, 1H), 5.22 (dt, J = 17.2, 1.6 Hz, 1H), 5.14 (dt, J = 10.4, 1.2 Hz, 1H), 3.85 (t, J = 6.4 Hz, 1H), 1.90-0.83 (m, 11H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.0, 115.7, 78.0, 43.6, 28.5, 26.7, 26.3.

(*E*)-(3-cyclohexylallyl)trimethylsilane (3-1e) (b0511,b0512).[44] To a solution of allylalcohol **3-4b** (4.28 g, 30 mmol) in CH_2Cl_2 (30 mL) with stirring at 0 °C, Et_3N (4.25 g, 42 mmol), DMAP (0.366 g, 3 mmol) and $(CF_3CO)_2O$ (7.6g, 36 mmol) were added in order. The mixture was stirred for 10 h. Then water was added into the reaction mixture for working up. After stirring for another 10 min, the mixture was extracted by CH_2Cl_2 (3 x 60 mL), washed by brine, dried over Na_2SO_4, concentrated, and purified by flash chromatography (silica gel, hexane) to afford allylic ester (4 g). Then a flask (300 mL) was charged with $Pd_2(DBA)CHCl_3$ (0.265 g, 0.256 mmol) and dry THF (90 mL) with stirring under Ar to afford a deep purple solution. The allylic ester (4 g) was added into the purple solution and stirred until the purple color of solution turned into mild purple. Then $(TMS)_2$ (4.97g, 34 mmol) was added in to the mixture and stirred for 10 h at rt. After TLC showed the reaction was finished, reaction mixture was diluted with hexane (200 mL), washed with saturated $NaHCO_3$ solution (200 mL), dried over Na_2SO_4, concentrated and purified by flash chromatography (silica gel, hexane) to give **3-1e** as a

colorless oil (2.98 g, 51% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.39-5.16 (m, 2H), 1.94-1.82 (m, 1H), 1.74-1.58 (m, 5H), 1.38 (m, 2H), 1.32-0.98 (m, 5H), -0.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.4, 123.5, 41.2, 33.8, 26.5, 26.4, 22.8, -1.8.

Trimethyl-*cis*-cinnamylsilane (3-1f)[30] (b0438c). It was prepared through a literature procedure.[33,34] Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.20 (m, 5H), 6.32 (d, J = 11.6 Hz., 1H), 5.72 (dt, J = 11.6, 9.2 Hz, 1H), 1.83 (dd, J = 1.2, 9.2 Hz, 2H), 0.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 129.3, 128.8, 128.3, 127.0, 126.2, 19.9, -1.32.

(*Z*)-1-trimethylsilyl-2-nonene (3-1g)[43] (b0438e). It was prepared through a literature procedure.[33,34] Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.43-5.32 (m, 1H), 5.30-5.22 (m, 1H),1.97 (dd, J = 13.6, 6.4 Hz, 2H), 1.45 (d, J = 8.4 Hz, 2H), 1.40-1.20 (m, 8H), 0.88 (t, J = 7.2 Hz, 3H), -0.01 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 127.9, 125.4, 32.1, 30.0, 29.4, 27.3, 22.9, 18.6, 14.4, -1.52.

(*E*)-3-phenylprop-2-en-1-ol-3-^{2}H (3-7a)[35] (b0446). To a solution of $LiAlH_4$ (1M, 10 mL, 10 mmol) in THF (100 mL), a solution of $PhCCCH_2OH$ (1.32 g, 10 mmol) in dry THF (50 mL) was added at rt. The mixture was stirred at rt until reaction was completed (2 h). Then D_2O was added carefully and the mixture was stirred for 1 h. The mixture was diluted with ether (50 mL). After drying over Na_2SO_4, the mixture was filtered and concentrated, purified by flash chromatography to give **3-7a** as a colorless oil (1.32 g, 97% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.20 (m, 5H), 6.39 (tt, J = 5.6, 2.4 Hz,

1H), 4.34 (d, J = 5.6 Hz, 2H), 3.69 (t, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.8, 128.8, 128.6, 128.5, 127.8, 126.6, 63.9.

(3-8a) (b0447). The compound was synthesized by a similar procedure as **3-5a**. A colorless oil was obtained in 75% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46.7.18 (m, 5H), 6.30 (tt, J = 6.8, 2.0 Hz, 1H), 5.10 (d, J = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 129.0, 128.8, 128.6, 127.1, 120.2, 77.6, 68.7.

(3-9a) (b0506). The compound was synthesized by a similar procedure as **3-1d**. Colorless oil was obtained in 78% yield. IR (film) 1629 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.05 (m, 5H), 6.26 (tt, J = 8.4, 2.0 Hz, 1H), 1.68 (m, J = 8.4 Hz, 2H), -0.06 (s, 9H, $SiMe_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 128.7, 128.5, 128.0, 126.4, 125.7, 24.1, -1.6; HRMS calcd for $C_{12}H_{17}DSi$ (M): 191.1241; found: 191.1236.

(*E*)-3-phenylprop-2-en-1-ol-2-^{2}H (3-7b)[35] (b0514b). To a solution of $PhCCCH_2OH$ (1.32 g, 10 mmol) in dry THF (90 mL), a solution of $LiAlD_4$ in THF (1 M, 11 mL, 11 mmol) was carefully added at rt. The mixture was stirred at rt until reaction was completed (4 h). Then H_2O (5 mL) was added carefully and the mixture was stirred for 1 h. The mixture was diluted with ether (50 mL). After drying over Na_2SO_4, the mixture was filtered and concentrated to give **3-7b** as a colorless oil (1.26 g, 93 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48-7.18 (m, 5H), 6.64 (s, 1H), 4.35 (s, J = 5.6 Hz, 2H), 3.69 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.3, 128.8, 128.6, 127.9, 126.7, 126.1, 63.9.

(3-9b) (b0515b). To a solution of allylalcohol **3-7b** (1.26 g, 9.3 mmol) in CH_2Cl_2 (10 mL) with stirring at 0 °C, Et_3N (1.4 g, 14 mmol), DMAP (0.122 g, 1 mmol) and $(CF_3CO)_2O$ (2.56 g, 12.7 mmol) were added in order. The mixture was stirred for 10 h. Then water (10 mL) was added into the reaction mixture for working up. After stirring for another 10 min, the mixture was extracted by CH_2Cl_2 (3 × 20 mL), washed by brine, dried over Na_2SO_4, and concentrated to afford a crude allylic ester as a colorless oil. Then a flask was charged with $Pd_2(DBA)CHCl_3$ (0.144 g, 0.140 mmol) and dry THF (56 mL) with stirring under Ar to afford a deep purple solution. The above crude allylic ester was added into the purple solution and stirred until the purple color of solution turned into mild purple. Then $(TMS)_2$ (2.72 g, 18.6 mmol) was added in to the mixture and stirred for 10 h at rt. After TLC showed the reaction was finished, reaction mixture was diluted with hexane (200 mL), washed with saturated $NaHCO_3$ solution (200 mL), dried over Na_2SO_4, concentrated and purified by flash chromatography (silica gel, hexane) to give **(3-9b)** as a colorless oil (1.2 g, 68% yield). IR (film) 1626, 1613 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-4.06 (m, 5H), 6.24 (s, 1H), 1.67 (s, 2H), -0.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 128.7, 128.5, 128.3, 126.4, 125.7, 24.0, -1.6; HRMS calcd for $C_{12}H_{17}DSi$ (M): 191.1241; found: 191.1241.

(3-7c) (b0517). The ethyl cinnamate (3.52 g, 20 mmol) was added dropwise into a solution of $LiAlD_4$ (1 M, 6 mL, 6 mmol) in dry Et_2O (60 mL) at 0 °C, The mixture was warmed to rt and stirred for 3 h and quenched by the addition of water (0.709 mL), 20% (w/v) aqueous NaOH (0.507 mL), and H_2O (12.5 mL) to give a white granular precipitate. The mixture was dried by Na_2SO_4, filtered, concentrated and purified by flash

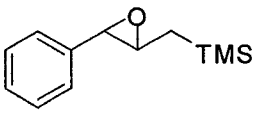
chromatography (silica gel, hexane/EtOAc = 3/1) to afford the product **3-7c** as a colorless oil (1.51 g, 56 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.20 (m, 5H), 6.63 (d, J = 15.9 Hz, 1H), 6.37 (d, J = 15.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.9, 131.5, 128.8, 128.6, 127.9, 126.7.

(3-9c) (b0535). The compound was synthesized by a similar procedure as **3-9b**. A colorless oil was obtained in 70 % yield with two steps. IR (film) 1640 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.07 (m, 5H), 6.25 (s, 2H), -0.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 128.7, 128.4, 128.0, 126.4, 125.7, 24.1, -1.7; HRMS calcd for $C_{12}H_{16}D_2Si$ (M): 192.1308; found: 192.1303.

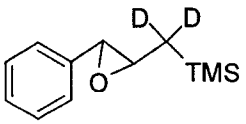
3.4.2 Epoxidation

General procedure for synthesis of racemic epoxides (Scheme 3.10): To an acetonitrile (56 mL) solution of allylsilane **3-9b** (0.765 g. 4 mmol), an aqueous Na_2(EDTA) (4 × 10^{-4} M, 36 mL) and Bu_4NHSO_4 (60 mg) was added. Then the mixture was cooled to 0 °C and 1, 3-dichloroacetone (1.17 g, 9.2 mmol) was added. A mixture of sodium bicarbonate (8.8 g, 104 mmol) and Oxone (17.2 g, 28 mmol) was added to this solution with stirring over 1.5 h. After the reaction was completed, the product was extracted by hexane, dried by Na_2SO_4, concentrated, and purified by flash chromatography (silica gel buffered by 1% Et_3N in hexane, hexane/ EtOAc = 50/1) to give the epoxide **3-2i** as colorless oil (0.609 g, 74% yield).

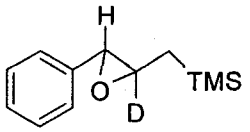
Representative procedure for asymmetric epoxidation (Table 3.4, entry 3). Olefin **3-1e** (392 mg, 94% ee, 2 mmol) was dissolved in acetonitrile-DMM (30 mL, 1:2 v/v), buffer (0.1 M K_2CO_3/AcOH, pH 9.3; 20 mL), tetrabutylammonium hydrogen sulfate (30 mg), and ketone **1-2** (154 mg, 0.6 mmol) were added with stirring. The mixture was cooled to -10 °C via a low temperature bath. A solution of Oxone (1.7 g, 2.76 mmol) in aqueous Na_2 (EDTA) (4×10^{-4}M, 13 mL) and a solution of K_2CO_3 (1.6 g, 11.6 mmol) in water (13 mL) were added dropwise separately over a period of 3.5 h (via syringe pump) at -10 °C. Then the reaction was worked up by adding hexane and was extracted with hexane. The combined organic layer was dried by Na_2SO_4, filtered, concentrated, and purified by flash chromatography (silica gel buffered by 1% Et_3N in hexane, hexane/ EtOAc = 50/1) to give the epoxide as colorless oil **3-3e** (316 mg, 75% yield).



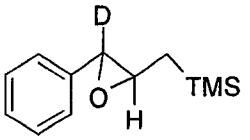
(+)-(3-2a) (b0535). Colorless oil. $[\alpha]_D^{25}$ = +6.3 (*c* 1.2, $CHCl_3$) (92 % ee); IR (film) 1496, 1250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37-7.25 (m, 5H), 3.54 (d, *J* = 2.4 Hz, 1H), 2.97 (ddd, *J* = 8.0, 5.2, 2.4 Hz, 1H), 1.27 (dd, *J* = 14.0, 5.2 Hz, 1H), 0.80 (dd, *J* = 14.0, 8.0 Hz, 1H), 0.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 128.6, 128.1, 125.6, 61.7, 60.3, 21.5, -0.9; HRMS calcd for $C_{12}H_{17}OSi$ (M-1): 205.1049; found: 205.1046.



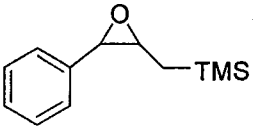
(3-2j) (b0618b). Colorless oil; IR (film) 1496, 1250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37-7.25 (m, 5H), 3.55 (d, J = 2.0Hz, 1H), 2.97 (s, 1H), 0.10 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 128.7, 128.1, 125.6, 61.6, 60.2, -0.99; HRMS calcd for $C_{12}H_{15}D_2OSi$ (M-1): 207.1174; found: 207.1178.



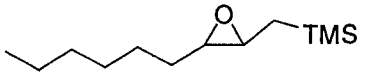
(3-2i) (b0618ap). Colorless oil; IR (film) 1496, 1250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37-7.25 (m, 5H), 3.55 (s, 1H), 1.28 (d, J = 14.4 Hz, 1H), 0.82 (d, J = 14.4 Hz, 1H), 0.10 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 128.7, 128.1, 125.6, 60.2, 21.4, -0.96; HRMS calcd for $C_{12}H_{17}DOSi$ (M): 207.1189; found: 207. 1184.



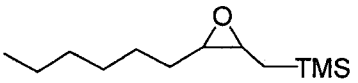
(3-2h) (b0510ap). Colorless oil; IR (film) 1496, 1250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37-7.25 (m, 5H), 2.98 (dd, J = 8.0, 5.2 Hz, 1H), 1.29 (dd, J = 14.0, 5.2 Hz, 1H), 0.81 (dd, J = 14.0, 8.0 Hz, 1H), 0.10(s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 128.7, 128.1, 125.6, 61.6, 21.5, -0.98; HRMS calcd for $C_{12}H_{16}DOSi$ (M-1): 206.1111; found: 206.1117.



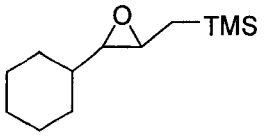
(3-2f) (b0442). Colorless oil; IR (film) 1496, 1250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.27 (m, 5H), 4.07 (d, J = 4.4 Hz, 1H), 3.35 (ddd, J = 7.6, 6.4, 4.4 Hz, 1H), 0.82 (dd, J = 14.4, 6.4 Hz, 1H), 0.80 (dd, J = 14.4, 7.6 Hz, 1H), 0.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.0, 128.1, 127.6, 127.0, 58.4, 58.2, 14.6, -0.9; Anal. Calcd. for $C_{12}H_{18}OSi$: C, 69.84. ; H, 8.79; Found: C, 70.03; H, 8.86.



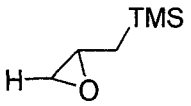
((+)-3-2d) (b0439b, b0618d). Colorless oil; $[\alpha]_D^{25}$ = +3.8 (*c* 1.0, $CHCl_3$); IR (film) 1460, 1250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.72 (ddd, J = 8.4, 5.6, 2.4 Hz, 1H), 2.62-2.59 (m, 1H), 1.53-1.27 (m, 10H), 1.11 (dd, J = 14.0, 5.6 Hz, 1H),0.88 (t, J = 6.8 Hz, 3H), 0.61 (dd, J = 14.0, 8.4 Hz, 1H), 0.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 60.6, 57.2, 32.6, 32.0, 29.5, 26.3, 22.8, 21.1, 14.3, -0.9; Anal. Calcd. for $C_{19}H_{24}OSi$: C, 67.22; H, 12.22; Found: C, 67.44; H, 12.40.



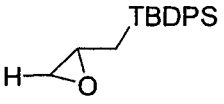
(3-2g) (b0641a). Colorless oil; IR (film) 1459, 1249 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.04 (ddd, J = 7.8, 6.4, 4.4 Hz, 1H), 2.92-2.85 (m, 1H), 1.53-1.29 (m, 10H,), 0.94 (dd, J = 14.4, 6.4 Hz, 1H), 0.89 (t, J = 6.8 Hz, 3H), 0.72 (dd, J = 14.4, 7.8 Hz, 1H), 0.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 57.9, 55.4, 32.0, 29.5, 28.1, 26.8, 22.8, 15.9, 14.3, -0.8; HRMS calcd for $C_{12}H_{26}OSi$ (M): 214.1753; found: 214.1756.



((+)-3-2e) (b0441b, b0634a). Colorless oil; $[\alpha]_D^{25}$ = +4.9 (*c* 1.2, $CHCl_3$) (94 % ee); IR (film) 1450, 1249 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.79 (ddd, *J* = 8.8, 7.2, 2.0 Hz, 1H), 2.41(dd, *J* =6.8, 2.0 Hz, 1H), 1.90-1.82 (m, 1H), 1.80-1.58 (m, 4H), 1.34-1.00 (m, 7H), 0.57 (dd, *J* = 14.0, 8.8 Hz, 1H), 0.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 64.9, 56.0, 40.8, 30.1, 29.4, 26.6, 26.0, 25.8, 21.4, -0.9; Anal. Calcd. for $C_{19}H_{24}OSi$: C, 67.86; H, 11.39; Found: C, 68.06; H, 11.58.

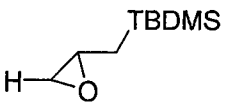


(3-2k) (b2342-A, b0627c). Colorless oil; IR (film) 1250 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.01-2.94 (m, 1H), 2.79-2.76 (m, 1H), 2.43 (dd, *J* = 4.8, 2.7 Hz, 1H), 1.16 (dd, *J* = 14.1, 4.8 Hz, 1H), 0.59 (dd, *J* = 14.1, 8.1 Hz, 1H), 0.08 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) 50.7, 48.8, 21.4, -0.91; HRMS calcd for $C_6H_{15}OSi$ (M+1): 130.0814; found: 130.0812.



(3-2c) (b027bSM). Colorless oil; IR (film) 1470 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65-7.59 (m, 4H), 7.45-7.35 (m, 6H), 3.01-2.96 (m, 1H), 2.55 (dd, *J* = 5.2, 4.0 Hz, 1H), 2.80 (dd, *J* = 4.0, 2.8 Hz, 1H), 1.94 (dd, *J* = 14.4, 4.0 Hz, 1H), 1.12 (dd, *J* = 14.4, 9.2 Hz, 1H), 1.08(s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1, 136.0, 134.4, 134.1, 129.6,

128.0, 127.9, 50.7, 49.6, 27.9, 18.2, 16.0; Anal. Calcd. for $C_{19}H_{24}OSi$: C, 76.97; H, 8.16; Found: C, 77.15; H, 8.35.

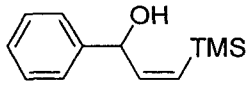


(3-2b) (b027aSM). Colorless oil; IR (film) 1471, 1390 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.03-2.97 (m, 1H), 2.81 (dd, J = 5.4, 4.5 Hz, 1H), 2.44 (dd, J = 4.8, 2.4 Hz, 1H), 1.21 (dd, J = 14.4, 2.4 Hz, 1H), 0.91 (s, 9H), 0.59 (dd, J = 14.4, 8.4 Hz, 1H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 51.0, 49.2, 26.5, 17.6, 16.6, -5.45, -5.51; HRMS calcd for $C_9H_{21}OSi$ (M+1): 172.1283; found: 172.1280.

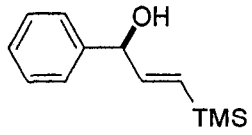
3.4.3 Epoxide Isomerization

Representative Procedure of Epoxide Isomerization with *n*-BuLi (Table 3.4, entry 2). To a solution of epoxide **3-2d** (0.25 mmol, 54 mg) in a mixture of THF (1.25 mL) and benzene (1.25 mL), TMEDA (0.5 mmol, 58 mg) was added at rt. After the mixture was cooled down to -78 °C, *n*-BuLi (0.5 mmol) in hexane was added dropwise under nitrogen at -78 °C. The resulting mixture was stirred for 7 h at -78 °C. After TLC show the reaction was finished, the reaction was quenched with water (150 ul) at -78 °C, and then warmed to rt. After drying with sodium sulfate, filtration, concentration, and purification by flash chromatography (silica gel, hexane/ EtOAc = 20/1), the product (45 mg, 88% yield) was obtained as a colorless oil.

Representative Procedure of Epoxide Isomerization with LiTMP (Table 3.4, entry 2). To a solution of 2,2,6,6-teramethylpiperidine (0.5 mmol, 70 mg) in THF (2.5 mL) at -78 °C, *n*-BuLi (0.5 mmol) in hexane was added in under N_2. After stirring for 1.5 h at -78 °C, the epoxide **3-2d** (0.25 mmol, 54 mg) was added dropwise at -78 °C. The resulting mixture was stirred for 5 h at -78° C. After TLC showed the reaction was finished, the reaction was quenched with water (150ul) at -78 °C, then warmed to rt. After drying with sodium sulfate, filtration, concentration, and purification by flash chromatography (silica gel, hexane/ EtOAc = 20/1), the product (50 mg, 94% yield) was obtained as a colorless oil.

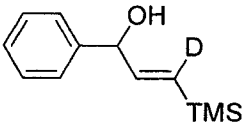


((+)-(*Z*)- 3-3a) (b0615a,b0630). Colorless oil; $[\alpha]_D^{25}$ = +166.3 (*c* 1.0, $CHCl_3$) (92 % ee); IR (film) 3335, 1602, 1248 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44-7.29 (m, 5H), 6.43 (dd, *J* =14.1, 8.7 Hz, 1H), 5.77 (d, *J* = 14.1 Hz, 1H), 5.36 (d, *J* = 8.7 Hz, 1H), 0.23 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.8, 143.0, 132.4, 128.8, 127.8, 126.2, 74.4, 0.76; HRMS calcd for $C_{12}H_{17}OSi$ (M-1): 205.1049; found: 205.1046.

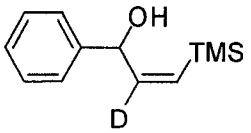


((-)-(*S*)-(*E*)-3-3a) (b0624c, b0626b, b0631c). Colorless oil; $[\alpha]_D^{25}$ = -3.0 (*c* 0.4, $CHCl_3$) (89 % ee); IR (film) 3339, 1618, 1603, 1247 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.28 (m, 5H), 6.22 (dd, *J* = 18.8, 5.6 Hz, 1H), 6.02 (dd, *J* = 18.8, 1.2 Hz, 1H), 5.20 (dd, *J*

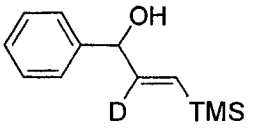
= 5.6, 1.2 Hz, 1H), 0.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.3, 142.8, 130.2, 128.8, 127.9, 126.7, 77.1, -1.12; HRMS calcd for $C_{12}H_{17}OSi$ (M-1): 205.1049; found: 205.1054.



((*E*)-3-3j) (b0625a). Colorless oil; IR (film) 3345, 1601, 1247 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.28 (m, 5H), 6.22-6,19 (m, 1H), 5.20 (d, J = 5.2 Hz, 1H), 1.96 (s, 1H), 0.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.2, 142.8, 128.8, 127.9, 126.7, 77.1, -1.12; HRMS calcd for $C_{12}H_{16}DOSi$ (M-1): 206.1111; found: 206.1107.

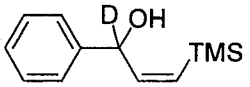


((*Z*)-3-3i) (b0621c). Colorless oil; IR (film) 3349, 1596, 1249 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.28 (m, 5H), 5.77(s, 1H), 5.36 (s, 1H), 0.23 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.0, 132.3, 128.8, 127.8, 126.3, 74.3, 0.76; HRMS calcd for $C_{12}H_{16}DOSi$ (M-1): 206.1111; found: 206.1108.

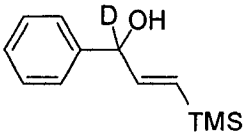


((*E*)-3-3i) (b0625b). Colorless oil; IR (film) 3345, 1597, 1248 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.28 (m, 5H), 6.01-6.00 (m, 1H), 5.20 (s, 1H), 0.09 (s, 9H); ^{13}C

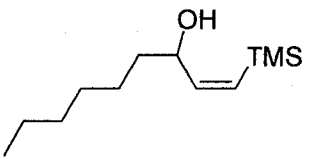
NMR (100 MHz, $CDCl_3$) δ 142.8, 130.0, 128.8, 127.9, 126.7, 77.0, -1.13; HRMS calcd for $C_{12}H_{17}DOSi$ (M): 207.1190; found: 207.1189.



((*Z*)-3-3h) (b0621d). Colorless oil; IR (film) 3335, 1601, 1249 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43-7.28 (m, 5H), 6.44 (d, J = 14.0 Hz, 1H), 5.78 (d, J = 14.0 Hz, 1H), 1.92 (s, 1H), 0.23 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.8, 143.0, 132.4, 128.8, 127.8, 126.2, 0.72; HRMS calcd for $C_{12}H_{17}DOSi$ (M): 207.1190; found: 207.1189.

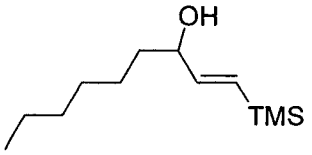


((*E*)-3-3h) (b0625c). Colorless oil; IR (film) 3345, 1616, 1603, 1449 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.28 (m, 5H), 6.21 (d, J = 18.8 Hz, 1H), 6.02 (d, J = 18.8 Hz, 1H), 1.96 (s, 1H), 0.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.2, 142.8, 130.2, 128.8, 127.9, 126.7, -1.13; HRMS calcd for $C_{12}H_{17}DOSi$ (M): 207.1190; found: 207.1195.

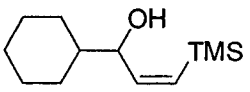


((+)-(*Z*)-3-3d) (b0621e). Colorless oil; $[\alpha]_D^{25}$ = +18.1 (*c* 1.0, $CHCl_3$) (89 % ee); IR (film) 3342, 1611, 1248 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.24 (dd, J = 14.4, 9.2 Hz,

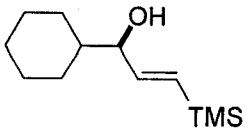
1H), 5.66 (d, J = 14.4 Hz, 1H), 4.23 (dt, J = 9.2, 6.4 Hz, 1H), 1.65-1.20 (m, 10H), 0.89 (t, J = 6.4 Hz, 3H), 0.15 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 132.0, 72.6, 37.4, 32.0, 29.5, 25.6, 22.8, 14.3, 0.68; Anal. Calcd. for $C_{12}H_{26}OSi$: C, 67.22; H, 12.22; Found: C, 67.08; H, 12.49.



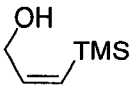
((-)-(*E*)-3-3d) (b0626c). Colorless oil; $[\alpha]_D^{25}$ = -7.1 (*c* 1.2, $CHCl_3$) (84 % ee); IR (film) 3335, 1620, 1467, 1248 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.06 (dd, J = 18.9, 5.4 Hz, 1H), 5.85 (d, J = 18.9, 1.2 Hz, 1H), 4.13-4.06 (m, 1H), 1.54-1.30(m, 10H,), 0.90 (t, J = 6.9 Hz, 3H), 0.09 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.9, 129.3, 74.9, 37.2, 32.0, 29.5, 25.6, 22.8, 14.3, -1.07; Anal. Calcd. for $C_{12}H_{26}OSi$: C, 67.22; H, 12.22; Found: C, 67.25; H, 12.12.



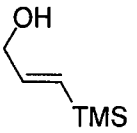
((+)-(*Z*)-3-3e) (b0623b). Colorless oil; $[\alpha]_D^{25}$ = +10.8 (*c* 1.1, $CHCl_3$) (89 % ee); IR (film) 3375, 1609, 1450 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.26 (dd, J = 14.4, 9.6 Hz, 1H), 5.72 (d, J = 14.4 Hz, 1H), 3.92 (ddd, J = 9.6, 5.4, 3.6 Hz, 1H), 1.97-0.94 (m, 12H), 0.15 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 133.1, 76.8, 43.9, 29.3, 28.9, 26.7, 26.5, 26.3, 0.79; HRMS calcd for $C_{12}H_{24}OSi$ (M): 212.1596; found: 212.1601.



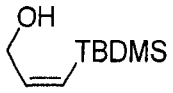
((-)-(*R*)-(*E*)-3-3e)[41] (b0626a). Colorless oil; $[\alpha]_D^{25}$ = -13.4 (*c* 1.0, $CHCl_3$) (88 % ee); IR (film) 3358, 1618, 1450 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.04 (dd, *J* = 18.6, 5.7 Hz, 1H), 5.85 (dd, *J* = 18.9, 0.9 Hz, 1H), 3.85 (q, *J* = 5.7 Hz, 1H), 1.85-0.82 (m, 12H), 0.08 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.4, 130.6, 79.4, 43.6, 29.2, 28.4, 26.7, 26.4, 26.3, -1.03; HRMS calcd for $C_{12}H_{24}OSi$ (M): 212.1596; found: 212.1596.



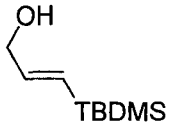
((*Z*)-3-3k) (b0628c). Colorless oil; IR (film) 3326, 1608, 1250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.46 (dt, *J* = 14.0, 6.8 Hz, 1H), 5.85 (dd, *J* = 14.0 Hz, 1H), 4.24-4.18 (m, 2H), 0.14 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.5, 132.7, 63.5, 0.39; HRMS calcd for $C_6H_{15}OSi$ (M+1): 131.0892; found: 131.0896.



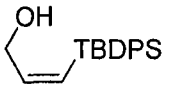
((*E*)-3-3k) (b0631d). Colorless oil; IR (film) 3325, 1621, 1248 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.19 (dt, *J* = 18.8, 4.4 Hz, 1H), 5.93 (dt, *J* = 18.8, 1.6 Hz, 1H), 4.21-4.18 (m, 2H), 1.43 (t, *J* = 6.0 Hz, 1H), 0.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9, 129.7, 65.8, -1.16; HRMS calcd for $C_6H_{15}OSi$ (M+1): 131.0892; found: 131.0893.



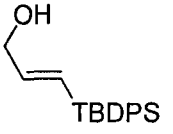
((*Z*)-3-3b) (b0628a). Colorless oil; IR (film) 3322, 1609, 1251 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.54 (dt, *J* = 14.4, 6.8 Hz, 1H), 5.73 (dt, *J* = 14.4, 1.2 Hz, 1H), 4.22-4.19 (m, 2H), 0.90 (s, 9H), 0.11 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.6, 129.9, 63.7, 26.5, 16.9, -3.9; HRMS calcd for $C_9H_{21}OSi$ (M+1): 173.1362; found; 173.1363.



((*E*)-3-3b) (0627a). Colorless oil; IR (film) 3318, 1621, 1249 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.10 (dt, *J* = 18.8, 4.4 Hz, 1H), 5.92 (dt, *J* = 18.8, 2.0 Hz, 1H), 4.20 (dd, *J* = 4.4, 2.0 Hz, 2H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.4, 126.8, 65.9, 26.6, 16.7, -5.9; HRMS calcd for $C_9H_{21}OSi$ (M+1): 173.1362; found: 173.1366.



((*Z*)-3-3c) (b0628b). Colorless oil; IR (film) 3327, 1623, 1605, 1427 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71-7.32 (m, 10H), 6.83 (dt, *J* = 14.4, 6.4 Hz, 1H), 6.19 (dt, *J* =14.4, 1.2 Hz, 1H), 3.74 (t, *J* = 6.4 Hz, 2H), 1.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.0, 135.9, 134.9, 129.5, 128.0, 125.5, 63.8, 27.4, 18.2; Anal. Calcd. for $C_{19}H_{24}OSi$: C, 76.97; H, 8.16; Found: C, 76.86; H, 7.99.



((*E*)-3-3c) (b0632a). Colorless oil; IR (film) 3317, 1624, 1249 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66-7.32 (m, 10H), 6.41-6.36 (m, 1H), 6.24-6.17 (m, 1H), 4.31-4.26 (m, 2H), 1.11 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.6, 136.4, 134.7, 129.4, 127.8, 122.4, 65.7, 27.9, 18.3; HRMS calcd for $C_{19}H_{21}OSi$ (M): 296.1596; found: 296.1589.

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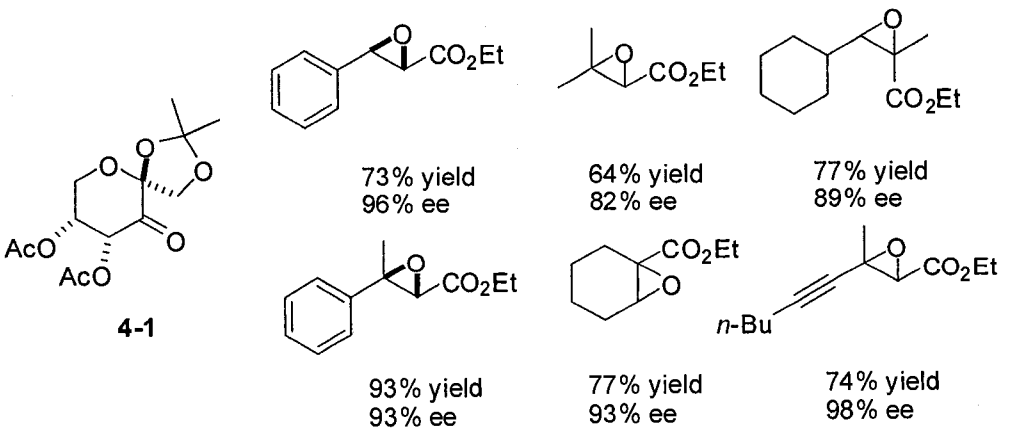
CHAPTER 4.0 : A CONTINUED STORY OF DIACETATE KETONE INCLUDING A PRACTICAL SYNTHESIS, SUBSTRATE SCOPE AND RELATED MECHANISM

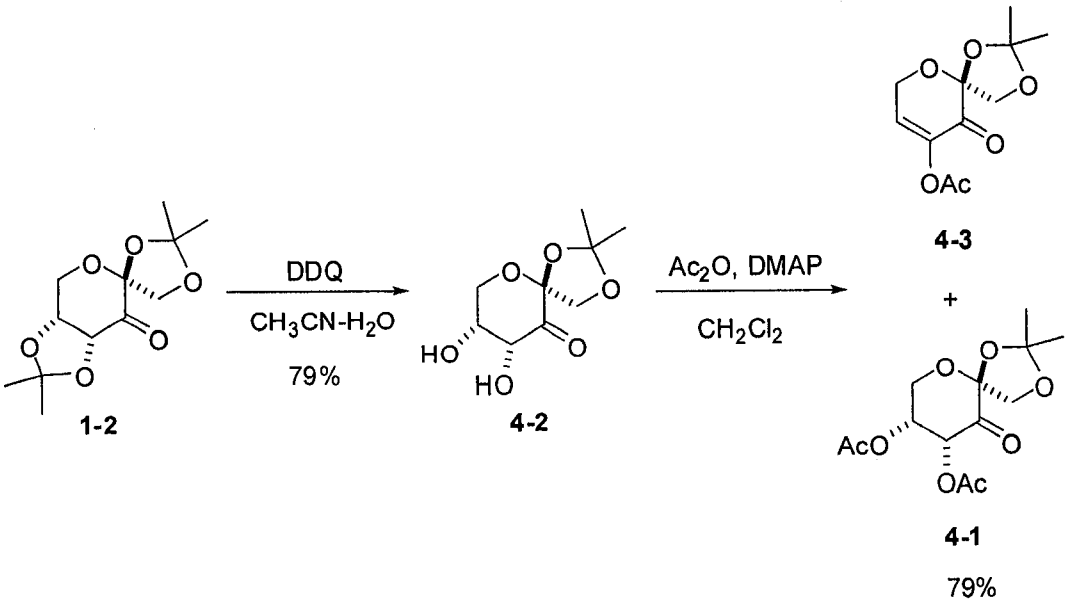
4.1 INTRODUCTION

Asymmetric epoxidation of α,β-unsaturated esters can directly produce chiral α,β-epoxy esters which are important intermediates for the organic synthesis.[1] In 2002, our group developed a highly enantioselective epoxidation of α,β-unsaturated esters using diacetate ketone **4-1** as catalyst and Oxone as oxidant (Scheme 4.1).[2] Through this method, a variety of *trans*- and trisubstituted α,β-epoxy esters can be obtained with high ee's and good yield.

Diacetate ketone **4-1** was prepared from the first generation diketal ketone **1-2** via two steps in 62% overall yield (Scheme 4.2). The problem related to this preparation method was the complexity. The process required two column purifications and was not suitable for large scale preparation. This chapter was devoted to search for the simplest way to prepare diacetate ketone **4-1** on large scale, explore its substrate scope in asymmetric epoxidation, and discuss related mechanisms.



Scheme 4.1

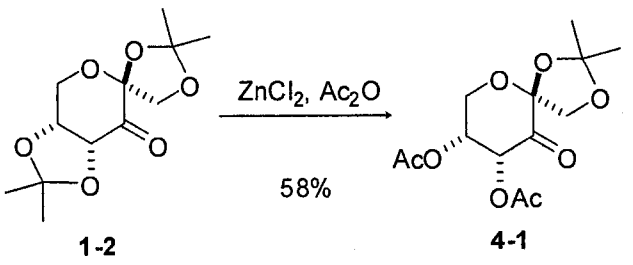


Scheme 4.2

4.2 RESULTS AND DISCUSSION

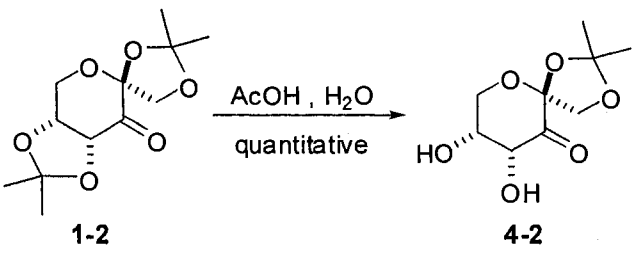
4.2.1 Searching for a Practical Synthesis of Diacetate Ketone

The initial idea was focused on a one-step reaction. In the literature, It was reported that some Lewis and Brönsted acids can catalyze both deketalization and diacetylation.[3] We used acetic anhydride as the acetyl source since it is cheap and readily available. After testing different Lewis and Brönsted acids including $TiCl_4$, $FeCl_3$, $ZnCl_2$, $Sc(OTf)_3$, $Yb(OTf)_3$,$YbCl_3$, and H_2SO_4, we found none of these acid catalyzed synthesis resulted in a clean synthesis. In most cases, reaction turned into a black mixture at the end of the reaction with a significant amount of starting ketone **1-2** left. Separation of diacetate ketone **4-1** from the reaction mixture proved to be difficult even with column chromatography since the starting material and product had very similar R_f values on TLC. The way to make separation easier was to run the reaction under solvent-free conditions and quench reaction with a suitable amount of water to help convert the starting material to the corresponding diol **4-2**, which has a much lower R_f value on TLC. The best case showed that the $ZnCl_2$ catalyzed preparation gave 58% yield after purification by flash chromatography (Scheme 4.3).



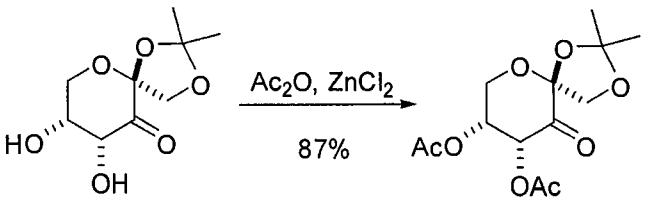
Scheme 4.3

After initial efforts, we realized the selective deketalization must be a very clean reaction to avoid the problem of separation at the end of preparation. After many experiments, we found that sulfonic acid catalyzed deketalization in MeOH, $ZnCl_2$-catalyzed deketalization in H_2O, and deketalization in AcOH-H_2O can produce diol **4-2** in high yield. Among these methods, deketalization in AcOH-H_2O is the simplest and most efficient one.[4-6] Stirring ketone **1-2** in a mixture of AcOH and H_2O quickly produced very clean deketalization product (**4-2**) in quantitative yield (Scheme 4.4).



Scheme 4.4

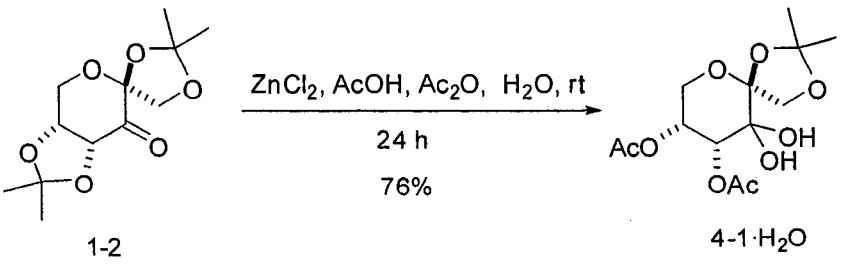
In the original two-step synthesis of ketone **4-2** (Scheme 4.1), a byproduct, enone **4-3**, was often formed by DAMP-catalyzed elimination of HOAc during the acetylating step. Thus, the acetylating step also needs to be improved. On the other hand, Lewis acid catalyzed acetylation was reported to be an efficient way to make acetyl esters in the literature.[7] After scanning different Lewis acids, $ZnCl_2$ was found to be an efficient catalyst for the acetylation of diol **4-2**. The acetylation catalyzed by $ZnCl_2$ at room temperature was quite clean, and almost no elimination byproduct was detected (**4-3**) (Scheme 4.5).



4-2 **4-1**

Scheme 4.5

Base on what was learned from the deketalization and acetylation step, a one-pot procedure to prepare the diacetate ketone **4-1** was developed by combining deketalization in AcOH-H_2O and diacetylation catalyzed by $ZnCl_2$. Through this convenient procedure, diacetate ketone **4-1** can be obtained as the hydrate (**4-1·H_2O**) in 76% yield after crystallized by the addition of water.[8-10]



1-2 4-1·H_2O

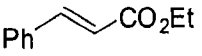
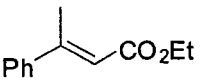
Scheme 4.6

The main advantage of this one-pot procedure is that it can be scaled up. It was easy to make 10 g of diacetate ketone **4-1** within one day without any chromatography. This method is a good candidate for chemical industry to practically synthesize the diacetate ketone catalyst since it is simple and efficient. Another advantage is that the

product obtained from this procedure is a white solid which is easier to handle than the syrup obtained from original synthesis by using DDQ and DMAP (Scheme 4.2).

With ketone **4-1·H_2O** in hand, testing its reactivity on the asymmetric epoxidation of α,β-unsaturated esters using a mixture of Oxone and $NaHCO_3$ (Method A) was carried out. The results are shown in Table 4.1. Catalyst **4-1·H_2O**, prepared by the improved one-pot procedure, gave comparable epoxidation results to **4-1**, prepared by the original sequence.

Table 4.1[a]

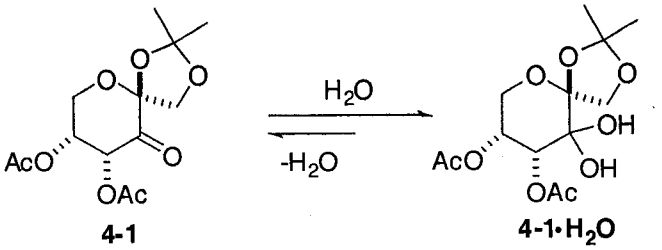
Entry	Ketone (Preparation Method)		Ee (%)	Conversion[d] (Yield)[e] (%)
1		**4-1** (DDQ-DMAP)	96 [b]	53
2		**4-1·H_2O** (one Pot)	97 [b]	51
3[11]		**4-1** (DDQ-DMAP)	96 [c]	(93)
4		**4-1·H_2O** (one Pot)	95 [c]	(90)
5		**4-1·H_2O** (one Pot)	94 [c]	(98)

[a] Method A: All reactions were carried out with substrate (0.5 mmol), ketone **4-1** (0.125 mmol), Bu_4NHSO_4 (0.03 mmol), Oxone (2.5 mmol), and $NaHCO_3$ (7.75 mmol) in CH_3CN-aq. $Na_2(EDTA)$ (4 x 10^{-4} M) (6.25 mL) (v/v, 1.5/1). A mixture of Oxone and $NaHCO_3$ was added portionwise over 4.5 h at 0 °C and stirred for another 7.5 h at 0 °C and then stirred at room temperature for 12h. For entry 5, the reaction was carried out with substrate (40 mmol), ketone **4-1** (12 mmol), Bu_4NHSO_4 (2.4 mmol), Oxone (200 mmol), and $NaHCO_3$ (620 mmol) in CH_3CN-aq. $Na_2(EDTA)$ (4 x 10^{-4} M) (500 mL) (v/v, 1.5/1). [b] Determined by chiral GC (Chiraldex G-TA). [c] Determined by chiral HPLC (Chiralcel OB). [d] Determined by chiral GC (Chiraldex G-TA). [e] Isolated Yield.

4.2.2 Equilibrium Study between Diacetate Ketone (4-1) and Diacetate Ketone Hydrate (4-1·H_2O)

4.2.2.1 ^{1}H NMR Study in CD_3CN-D_2O

Since the catalyst obtained from the one-pot procedure is a hydrate and both water and organic solvent are used in the epoxidation, it is interesting to know how fast and how much the hydrate converts to the ketone, which is the specie that actually catalyzes asymmetric epoxidation. Thus, we carried out a NMR kinetic study of the equilibrium of **4-1** and **4-1·H_2O** (Scheme 4.7).



Scheme 4.7

A solution of **4-1** or **4-1·H_2O** in CD_3CN and D_2O (v/v, 3/2) (0.024M) in an NMR tube was prepared and monitored by ^{1}H NMR as time proceeded. The results are shown in Figure 4.1. Regardless of which compound (Scheme 4.7) was used as starting material, it took about 2 h to reach the point of equilibrium which had almost same amount of ketone **4-1** in the solution. It explained why both **4-1** and **4-1·H_2O** give a comparable epoxidation results and indicated that there is only a small portion of actual ketone catalyst (**4-1**) in the ketone **4-1** catalyzed epoxidation system.

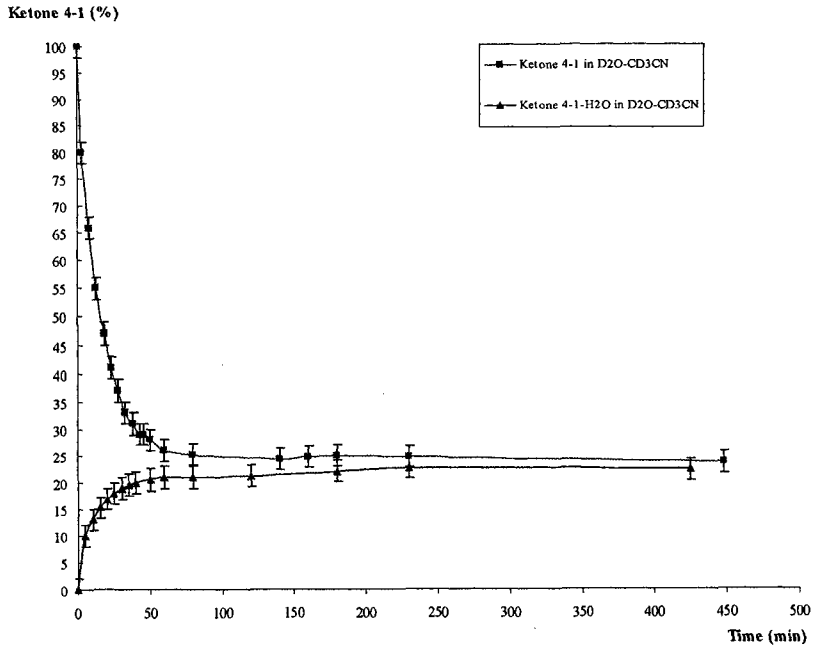


Figure 4.1

4.2.2.2 ^{1}H NMR Study of 4-1·H_2O in $CDCl_3$

We also prepared the solution of **4-1·H_2O** in $CDCl_3$ (0.095M) in an NMR tube and monitored it with ^{1}H NMR as time proceeded. The results are shown in Figure 4.2. To our surprise, **4-1·H_2O** converted to the corresponding **4-1** in 94% conversion in 160 min (Scheme 4.8). There was no **4-1·H_2O** that can be detected by ^{1}H NMR in the solution after 11 h.

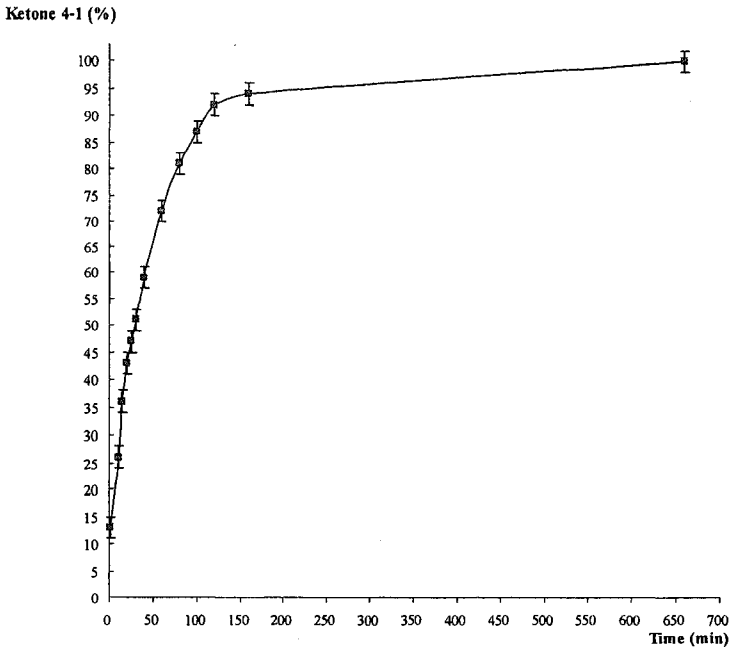
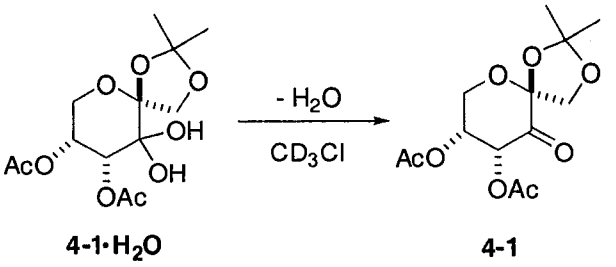


Figure 4.2



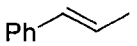
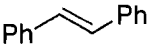
Scheme 4.8

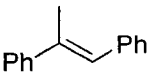
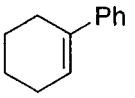
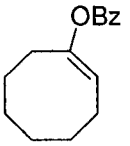
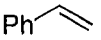
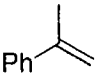
4.2.3 Exploring Substrate Scope beyond α, β-unsaturated Esters

Even though ketone **4-1** is an effective catalyst for the asymmetric epoxidation of α, β-unsaturated esters, its application on other types of olefins has not been extensively studied. Dr. Xinyan Wu did much preliminary work on optimization of pH conditions for

asymmetric epoxidation of *trans*-β-methylstyrene and showed that 8.75 to 9.50 is the optimum pH for the epoxidation using slow addition of Oxone and K_2CO_3 solution. Based on this information, an epoxidation procedure (Method B) was designed, optimized and used in exploring the substrate scope of asymmetric epoxidation along with method A. The results are shown in Table 4.2. Diacetate ketone **4-1** or **4-1·H_2O** can effectively catalyze asymmetric epoxidation of more reactive *trans*- and trisubstituted olefins with good enantioselectivity. Using the newly developed method B, Catalyst loading for asymmetric epoxidation of more reactive olefin substrates can be reduced from 30 mol % (Method A) to 10 mol % without sacrificing the enantioselectivity and yield. Comparing with epoxidation results obtained by diketal ketone (**1-2**), the diacetate ketone (**4-1** or **4-1·H_2O**) apparently is more reactive but less enantioselective for the asymmetric epoxidation of *trans*- and trisubstituted olefins.

Table 4.2 Asymmetric Epoxidation of Olefins Catalyzed by Ketone **4-1**[a, b]

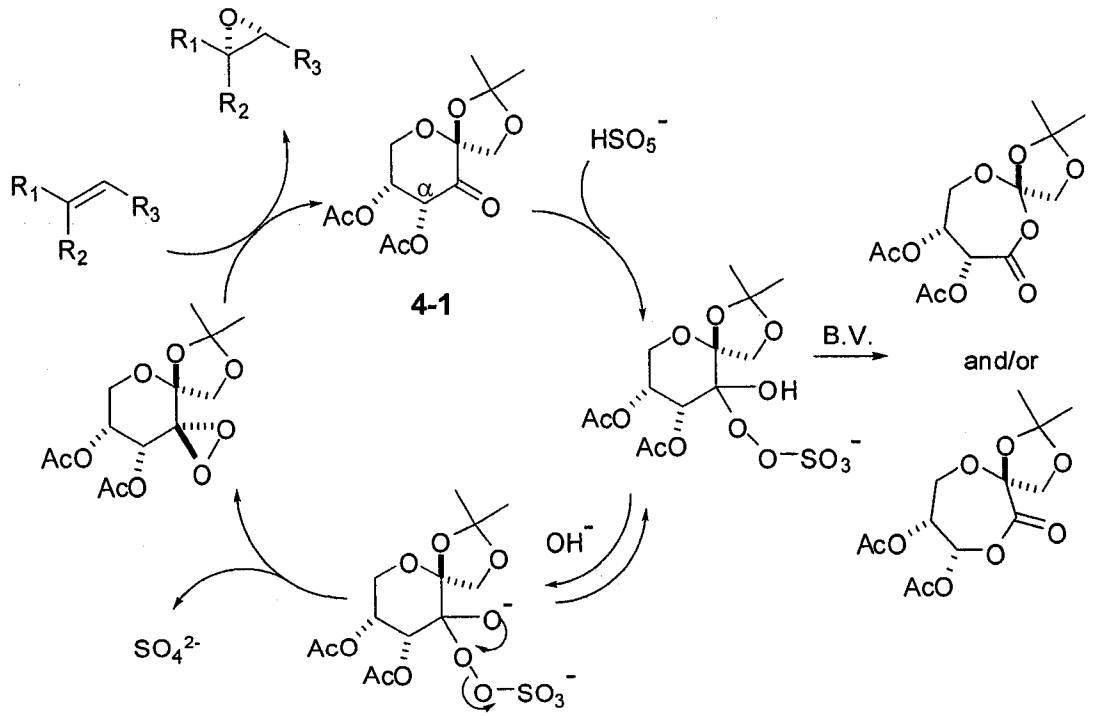
Entry	Substrate	Method (time)	Yield (%)[c]	Ee (%)	config.[d]
1		A (24 h)	75	86[e]	(+)-(R,R)[12]
		B (8 h)	81	86[e]	
2		A (24 h)	68	92[f]	(+)-(R,R)[12]
		B (16 h)	63	92[f]	
3		A (24 h)	72	84[g]	(+)-(R,R)[12]
		B (8 h)	53	88[h]	

4		A (24 h)	93	86[f]	(+)-(R,R)[12]
		B (8 h)	46	88[f]	
5		A (24 h)	92	92[e]	(+)-(R,R)[12]
		B (8 h)	82	92[e]	
6		B (8 h)	97	95[f]	(+)-(R,R)[12]
7		A (24 h)	81	26[e]	(-)-(S)[13]
		B (8 h)	77	27[e]	
8		A (24 h)	79	3[f]	(+)-(S)[14]
		B (8 h)	72	6[f]	

[a] Method A: All reactions were carried out with substrate (0.5 mmol), ketone **4-1** (0.125 mmol), Bu_4NHSO_4 (0.03 mmol), Oxone (2.5 mmol), and $NaHCO_3$ (7.75 mmol) in CH_3CN-aq. $Na_2(EDTA)$ (4 x 10^{-4} M) (6.25 mL) (v/v, 1.5:1). A mixture of Oxone and $NaHCO_3$ was added portionwise over 4.5 h at 0 °C and stirred for another 7.5 h at 0 °C and then stirred at room temperature for 12 h. [b] Method B: All epoxidations were carried out with substrate (0.5 mmol), ketone **4-1·H_2O** (0.05 mmol), Oxone (1.01 mmol), and K_2CO_3 (2.02 mmol) in CH_3CN-DMM (9 mL), and buffer (0.05 M Na_2HPO_4/0.05 M KH_2PO_4, pH 7; 3 mL) at 0 °C for 8 h, 16 h or 24 h. Oxone and K_2CO_3 were dissolved in 4 x 10^{-4} EDTA solution and added simultaneously and separately by syringe pump. [c] Isolated yields. [d] Determined by comparing the measured optical rotations and HPLC trace with the reported ones. [e] Determined by chiral GC (Chiraldex B-DM). [f] Determined by chiral HPLC (Chiralcel OD). [g] The epoxide was opened (NaOMe-MeOH), the resulting alcohol was converted to its benzoylate, enantioselectivity was determined by chiral HPLC (Chiralcel OD). [h] The epoxide was opened (NaOMe-MeOH), the resulting alcohol was converted to its benzoylate, enantioselectivity was determined by chiral HPLC (Chiralcel OD-H).

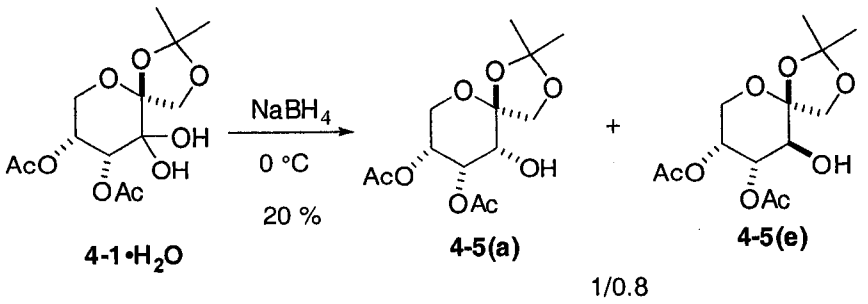
4.2.4 Transition States for Epoxidation Catalyzed by Diacetate Ketone

The better reactivity and slightly lower enantioselectivity for asymmetric epoxidation catalyzed by diacetate ketone **4-1** than diketal ketone **1-2** is due to the structural differences between them. Replacement of the fused ketal of **1-2** by two acetyl groups can increase the electron deficiency of the α-C adjacent to the carbonyl group, therefore the Baeyer-Villiger decomposition under epoxidation condition was reduced (Scheme 4.9).[10]

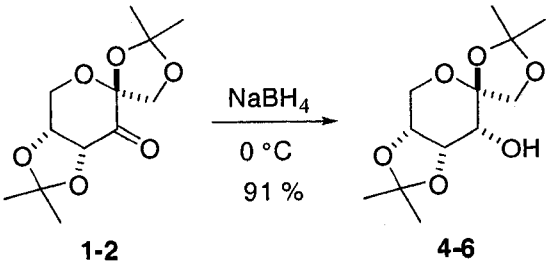


Scheme 4.9

On the other hand, the replacement of the fused ketal of **1-2** by two acetyl groups also significantly increases the possibility that the olefin can approach both the equatorial and the axial oxygen of the corresponding dioxirane. When ketone **4-1·H_2O** was subjected to reduction by $NaBH_4$, both axial and equatorial alcohols (**4-5**) were produced with a ratio of 1/0.8 (Scheme 4.10). In contrast, reduction of ketone **1-2** by $NaBH_4$ selectively yielded the corresponding axial alcohols (**4-6**) (Scheme 4.11),[5,15,16] From those results, it is reasonable to assume that the olefins likely react with both the equatorial and the axial oxygen of the chiral dioxirane for the epoxidation catalyzed by diacetate ketone **4-1** (Figure 4.3) and only the equatorial oxygen of the chiral dioxirane for epoxidation catalyzed by ketone **1-2**(Figure 4.4).



Scheme 4.10



Scheme 4.11

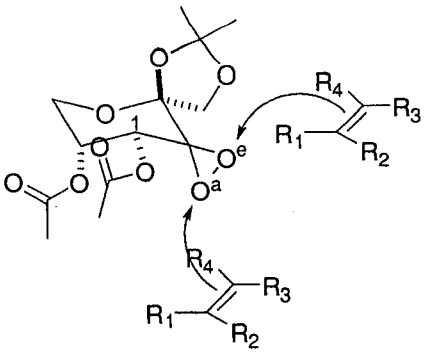


Figure 4.3

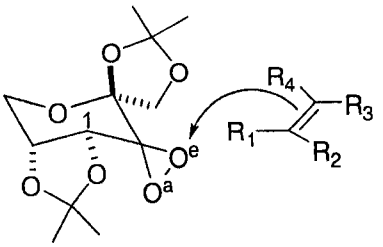


Figure 4.4

Based on the above assumption, four main competing transition states for epoxidation catalyzed by ketone **4-1** are proposed (Figure 4.5), all of which are spiro transition states since spiro transition state are generally favored over planar transition states as a result of the stabilizing interaction of an oxygen lone pair with the π^* orbital of the alkene. Among those, spiro **B** and spiro **D** are less favored than spiro **A** and spiro **C** due to the steric interaction between R_1 and ketal or acetyl group. The major enantiomer of epoxide comes from spiro **A** and spiro **C** with good enantioselectivity.

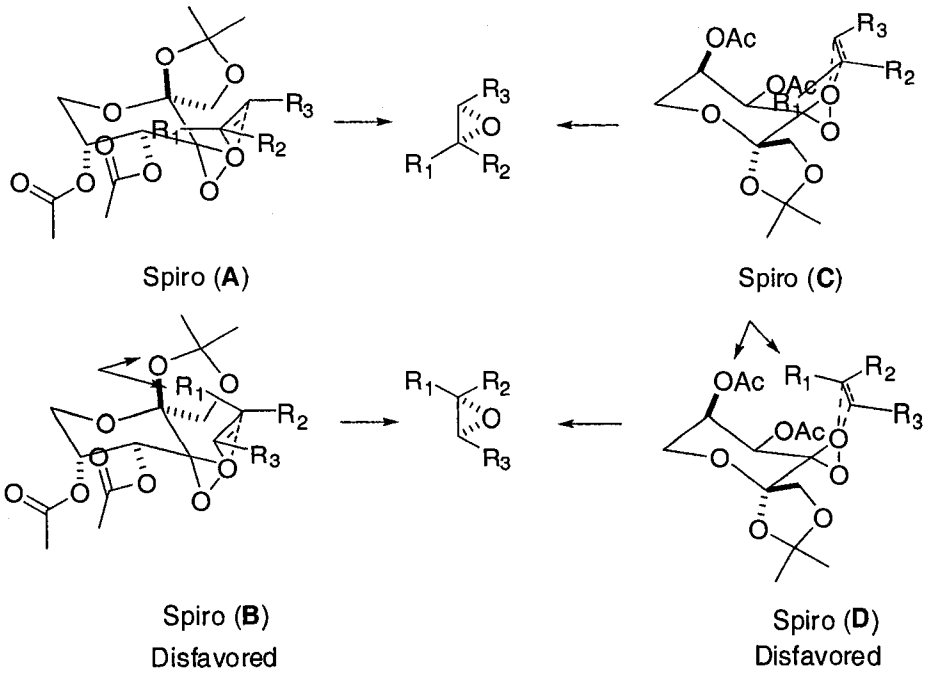
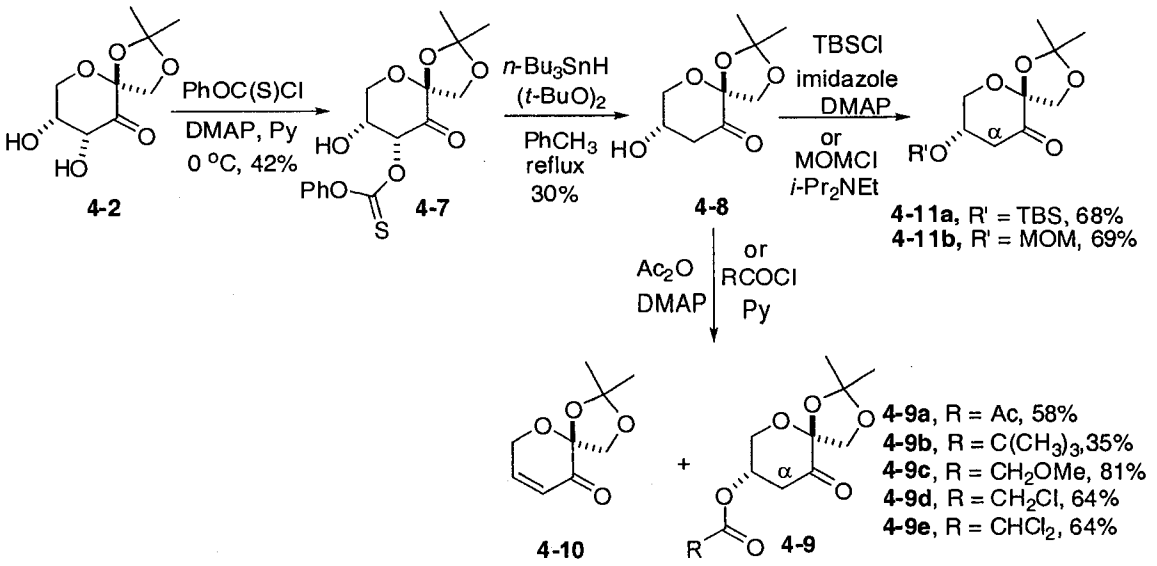


Figure 4.5 Competing Spiro Transition States for Epoxidation of Trans- and Trisubstituted Olefins with Ketone **4-1**

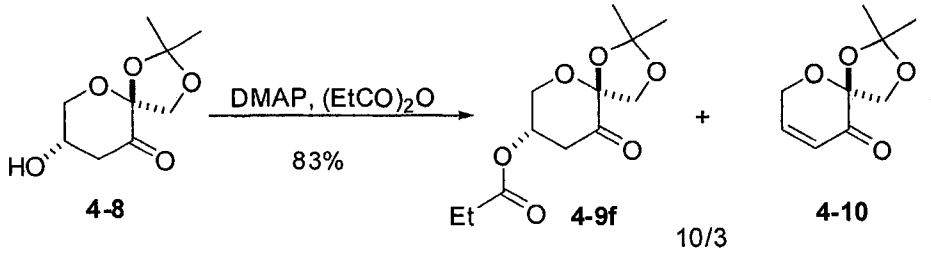
4.2.5 Synthesis of Analogs of Diacetate Ketone and Its Application on Asymmetric Epoxidation

With the early work from Dr. Dajun Chen, several diacetate ketone analogs (**4-9)** and **4-10**), which have no substitution at the α-position of the carbonyl group, were synthesized in reasonable yields through selective Barton deoxygenation[17,18] and modification of remaining alcohol with different groups (Scheme 4.12). During the synthesis of ketone **4-9**, a byproduct (**4-10)** from elimination was often produced along with the desired product in the final step. This byproduct sometimes caused problems for purification of the desired product by flash chromatograph since both **4-9** and **4-10** often have similar R_fs on the TLC plate. For example, in the synthesis of ketone **4-9f** using

DMAP and anhydride, a mixture of **4-9f** and **4-10** with a ratio of 10 to 3 was obtained after purification by flash chromatograph (Scheme 4.13).

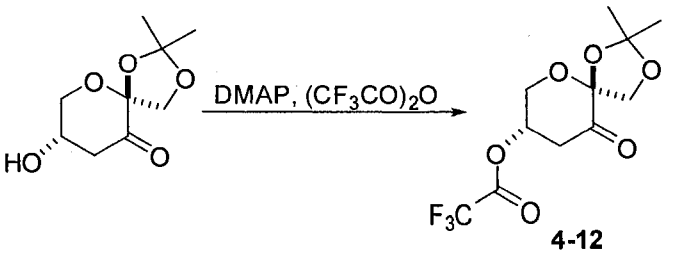


Scheme 4.12



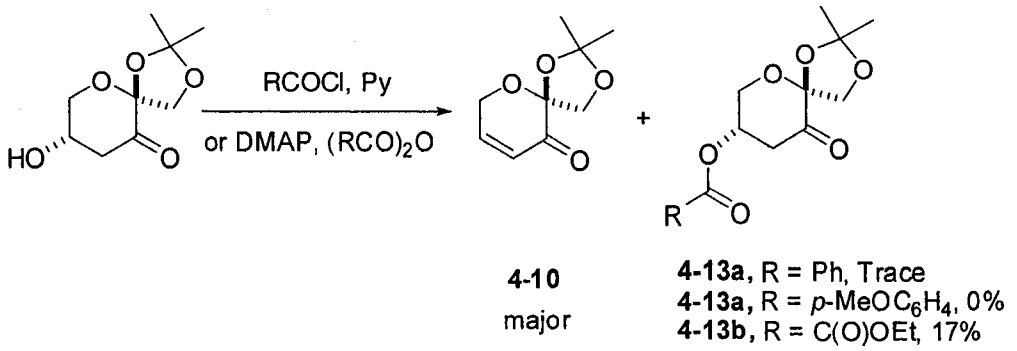
Scheme 4.13

Ketone **4-12** can be obtained with the same method as **4-9a**. However, it is unstable and decomposes before characterization can be complete (Scheme 4.14).



Scheme 4.14

The synthesis of ketone **4-13** was attempted in the same way as ketone **4-9**. However, the reaction mainly produced the elimination byproduct (**4-10**) (Scheme, 4.15). In the case of **4-13b,** the yield is only 17 %.

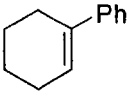
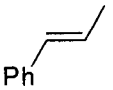


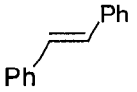
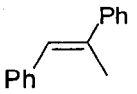
Scheme 4.15

With many ketone analogs in hands, the study of asymmetric epoxidation of *trans* and trisubstituted olefins was carried out. 1-phenyl cyclohexene and *trans*-β-methylstyrene was used as a test substrate for screening the different ketone catalysts. The results are shown in the Table 4.3. Among all the ketone catalysts, the mono ester ketones with a large electron-donating R group, such as **4-9a**, **4-9b** and **4-9f**, gave the best enantioselectivity with reasonable conversion on epoxidation of both 1-phenyl

cyclohexene and *trans*-β-methylstyrene. Overall, ketone **4-9a** and **4-9b** gave the best results. In contrast, the mono ester ketones with electron-withdrawing R groups, such as **4-9c, 4-9d, 4-9e** and **4-12,** are less reactive on the epoxidation probably due to more decomposition by elimination under the basic reaction conditions. The mono ether ketones (**4-11**) are also less reactive compared to the mono ester ketones **4-9a** and **4-9b.** This could be due to more Baeyer-Villiger decomposition on relatively electron-rich α carbon adjacent to the carbonyl group under the reaction conditions.

Table 4.3[a]

Entry	Substrate	Catalyst	Conversion[b] (Yield[c]) (%)	Ee (%)	Config[f]
1		**4-9b**	97	75[b]	(+)-(*R*,*R*)
2		**4-9f**	42	75[b]	(+)-(*R*,*R*)
3		**4-9a**	92	71[b]	(+)-(*R*,*R*)
4		**4-12**	33	57[b]	(+)-(*R*,*R*)
5		**4-9c**	16	--	--
6		**4-9d**	3	--	--
7		**4-9e**	12	--	--
8		**4-11a**	23	--	--
9		**4-11b**	58	54[b]	(+)-(*R*,*R*)
10		**4-10**	10	--	--
11		**4-9b**	100	71[b]	(+)-(*R*,*R*)
12		**4-9f**	34	64[b]	(+)-(*R*,*R*)
13		**4-9a**	85	63[b]	(+)-(*R*,*R*)
14		**4-9c**	28	--	--
15		**4-9d**	20	--	--
16		**4-9e**	12	--	--
17		**4-11a**	18	--	--

18		**4-11b**	51	56[b]	(+)-(*R*,*R*)
19		**4-9b**	(51)	83[d]	(+)-(*R*,*R*)
20		**4-9a**	(30)	76[d]	(+)-(*R*,*R*)
21		**4-9b**	(69)	75[d]	(+)-(*R*,*R*)

[a] The reactions was carried on at 0 °C with olefin (0.2 mmol), ketone (0.06 mmol), tetrabutylammonium hydrogen sulfate (0.01 mmol), Oxone (0.276 mmol) and K_2CO_3 (1.16 mmol) in acetonitrile-DMM (1:2 v/v) (3 mL), and buffer (0.1M K_2CO_3-AcOH, pH 9.2) (2 mL) for 1.5 h. [b] Determined by chiral GC (Chiraldex B-DM). [c] Isolated Yield. [d] Determined by chiral HPLC (Chiralcel OD). [e] The epoxide was opened (NaOMe-MeOH), the resulting alcohol was converted to its benzoylate, enantioselectivity was determined by chiral HPLC (Chiralcel OD). [f] Determined by comparing the GC and HPLC trace with the reported ones (Table 4.2).

Since ketone **4-9a** and **4-9b** gave the best results overall, epoxidations of more *trans*- and trisubstituted olefins were carried out with them. Good enantioselectivity (up to 83% ee) was also obtained on those substrates. Based on the configuration of the produced epoxides, four major competing spiro transition states of ketone **4-9a** and **4-9b** catalyzed epoxidation are proposed in Figure 4.6. Since there are disfavored steric interactions between R_1 and ketal or ester groups in spiro transition states **(B)** and **(D)**, the major stereo isomer is produced through the spiro **A** and **C** transition states. Bigger R groups on the ester of the ketone likely result more steric interaction and further disfavor spiro **D** transition state, therefore better enantioselectivity was obtained (Table 4.3, entries 1 vs 3, .11 vs 13, and 19 vs 20). Considering the good ees obtained from diacetate ketone (**4-1**) catalyzed epoxidation of *trans* and trisubstituted olefins, it is reasonable to conclude that the β acetate group of **4-1** plays a very important role for controlling enantioselectivity, which is consistent with the proposed transition states in Figure 4.5 where the spiro **D** is disfavored by the steric interaction between R_1 and β acetyl group.

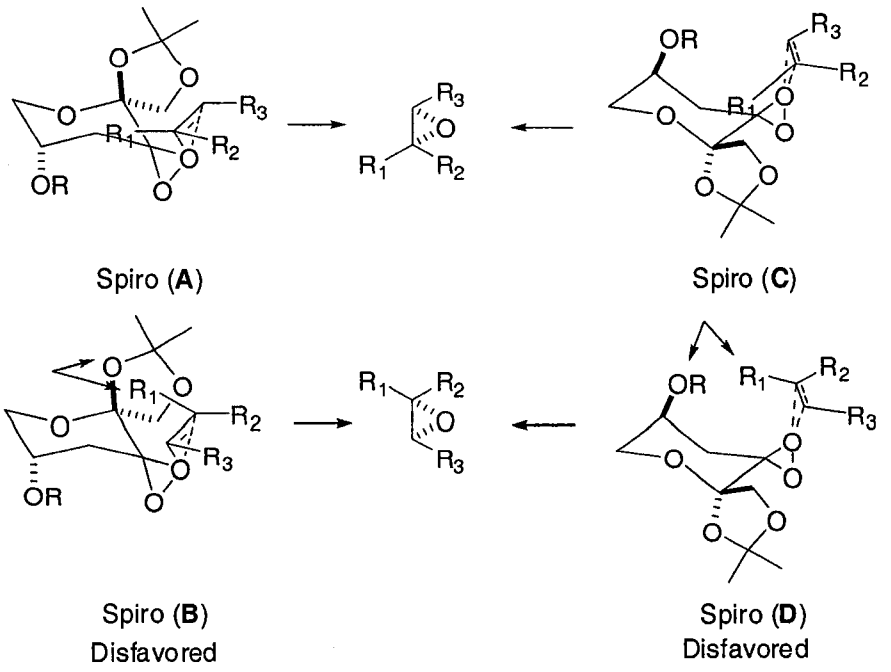


Figure 4.6 The competing spiro transition states for epoxidation of *trans*- or trisubstituted olefins with ketone **4-9a** or **4-9b**

4.3 CONCLUSION

A practical one-pot preparation of diacetate ketone has been developed. This procedure is simple, efficient, economical and scalable. ^{1}H NMR study of ketone **4-1** and ketone hydrate **4-1·H_2O** solutions revealed that no matter which compound was used in asymmetric epoxidation, there is only a small portion of actual ketone catalyst (4-1) after the equilibrium between ketone and ketone hydrate was reached in a short of period (2 h). The substrate scope of diacetate catalyzed epoxidation has been expanded to electron-rich *trans*- and trisubstituted olefins with a relatively low catalyst loading (10%). The major competing transition states for diacetate ketone catalyzed epoxidation of *trans*- and

trisubstituted olefins were proposed and consistent with the configuration of obtained chiral epoxidation and the results of asymmetric epoxidation catalyzed by it's simplified analogs.

4.4 EXPERIMENTAL

4.4.1 Practical Synthesis of Diacetate Ketone 4-1·H_2O

(Scheme 4.6)

(4-11·H_2O) (b1514). AcOH (17.5 mL) and deionized water (4.3 mL) were added to a mixture of ketone **1** (12.90 g, 50 mmol) and $ZnCl_2$ (0.170 g, 1.25 mmol) in a 250 mL round bottomed flask equipped with a Teflon-coated magnetic stir bar. After the resulting suspension was stirred at rt for 8-10 h, Ac_2O (60.0 mL, 636.0 mmol) was added into the reaction flask. After the resulting mixture was stirred at rt for 16 h, deionized water (30 mL) was added. Upon stirring at rt for 20 min, the reaction mixture was concentrated in rotvap under reduced pressure (130 mmHg, 55 °C) until about 20 mL of solution left. The resulting solution is transferred to a 100 mL beaker; and 10 mL of deionized water was used to rinse the flask and transferred to the beaker. After slightly shaking the mixture for 5 min, a clear solution was formed. The solution was then placed in an ice bath for 2 h, and the solid (mud-like) precipitates. The solid was filtered by a Büchner funnel, washed by ice-cold H_2O (5 mL) and ice-cold hexane (20 mL), and dried under vacuum pump (10-20 mmHg) overnight to give ketone **4-11·H_2O** as a white solid (12.2 g, 76% yield). mp 81-84 °C; $[\alpha]_D^{25}$ = -112.0 (*c* 1.05, $CHCl_3$); IR (film) 3436,

1736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (ketone) δ 5.89 (d, J = 4.0 Hz, 1H), 5.60-5.62 (m, 1H), 4.70 (d, J = 9.6 Hz, 1H), 4.44 (dd, J = 13.2, 1.2 Hz, 1H), 3.99 (d, J = 9.6 Hz, 1H), 3.96 (dd, J = 13.2, 2.0 Hz, 1H), 2.17 (s, 3H), 2.12 (s, 3H), 1.55 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) (ketone) δ 192.0, 170.4, 169.6, 114.1, 105.2, 74.2, 72.3, 69.6, 62.7, 26.6, 20.2, 21.0, 20.6; Anal. Calcd for $C_{13}H_{20}O_9$ (hydrate): C, 48.75; H, 6.29. Found: C, 49.14; H, 6.12.

4.4.2 NMR Study

(Figure 4.1) (b1127f). In a NMR tube **4-1** (0.009 g, 0.030 mmol) was added into the mixture of CD_3CN (0.75 mL) and D_2O (0.5 mL). The resulting solution was monitored by ^1H NMR as time proceeded. The results are shown in Table 4.4.

Table 4.4

Time (min)	0	3.0	8.0	13.0	18.0	23.0	28.0
4-1 (%)	100	80.0	66.0	55.0	47.0	41.0	37.0
Time (min)	33.0	38.0	43.0	45.0	50.0	60.0	80.0
4-1 (%)	33.0	31.0	29.0	29.0	28.0	26.0	25.2
Time (min)	140.0	160.0	180.0	230.0	448.0		
4-1 (%)	24.4	24.8	25.0	24.8	23.7		

(Figure 4.1) (b1127e). In a NMR tube **4-1·H_2O** (0.096 g, 0.030 mmol) was added into the mixture of CD_3CN (0.75 mL) and D_2O (0.5 mL). The resulting solution was monitored by ^1H NMR as time proceeded. The results are shown in Table 4.5.

Table 4.5

Time (min)	0	5.0	10.0	15.0	20.0	25.0	30.0
4-1 (%)	0	10.0	13.0	15.3	16.9	18.0	18.9
Time (min)	35.0	40.0	50.0	60.0	80.0	120.0	180.0
4-1 (%)	19.6	20.0	20.6	21.0	21.0	21.3	22.1
Time (min)	230.0	425.0					
4-1 (%)	22.7	22.4					

(Figure 4.2) (b1127a). In a NMR tube **4-1·H_2O** (0.038 g, 0.119 mmol) was added into the mixture of $CDCl_3$ (1.25 mL). The resulting solution was monitored by ^1H NMR as time proceeded. The results are shown in Table 4.4.

Table 4.6

Time (min)	1	10	15	20	25	30	40
4-1 (%)	13	26	36	43	47	51	59
Time (min)	60	80	100	120	160	660	
4-1 (%)	72	81	87	92	94	100	

4.4.3 Asymmetric Epoxidation

Representative Asymmetric Epoxidation Procedure using Oxone and $NaHCO_3$ (Method A, 40 mmol scale) (Table 4.1, Entry 5): Aqueous Na_2(EDTA) solution (1×10^{-4} M, 200 mL) and tetrabutylamminonium hydrogen sulfate (0.800 g, 2.4 mmol) was

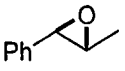
added to an acetonitrile (200 mL) solution of ethyl *trans*-β-methylcinnamate (7.6 g, 40 mmol) in 2 L 2-neck round bottom flask with vigorous mechanic stirring at 0 °C. A mixture of Oxone (122.96 g, 200 mmol) and $NaHCO_3$ (52.08 g, 620 mmol) was pulverized, and a small portion (3.24 g) of this mixture was added to the reaction mixture to bring PH to >7. Then the pulverized **4-1·H_2O** (3.636 g, 12.0 mmol) was added. The ketone left on the wall of flask was washed by acetonitrile (100 mL). The rest of Oxone and $NaHCO_3$ was added to reaction mixture portwise(3.24 g/10 min) over a period of 9 h at 0 °C. Upon stirring for additional 2 h at 0 °C and 12 h at rt, water (100 mL) was added into reaction mixture by washing the wall of reaction flask and resulting mixture was stirred for 1 h. Then the mixture was extracted with EtOAc (3 × 200 mL). The combined extracts were washed with brine (100 mL). Upon drying by anhydrous sodium sulfate (25 g), the extracts was concentrated under reduce pressure to give a 10 mL mild yellow oil. The crude oil mixture was dissolved in a mixture of DCM and hexane (v/v, 1/10, 11 mL) and filtered through a short pad of silica gel (Whatman 60 Å, 230-400 mesh, 35g) (1.5cm thin) covered by a piece of filter paper on 150 mL Pyrex Buchner funnel with fine fritted disc (Diameter = 6.0cm). The silica gel pad was washed by the mixture of hexane and ethyl acetate (hexane/EtOAc = 10/1, 550mL). Then the filtrate was concentrated under reduced pressure and dried under vacuum to give colorless oil (8.2 g, 99% yield). $[\alpha]_D^{25}$ = +121.3 (c 1.0, $CHCl_3$); IR (film) 1750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32-7.41 (m, 5H), 4.26-4.37 (m, 2H), 3.47 (s, 1H), 1.79 (s, 3H), 1.34 (t, J = 7.2, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 140.2, 128.5, 128.1, 125.3, 62.0, 61.7, 17.2, 14.5; HRMS Calcd for $C_{12}H_{15}O_3$ (M+H): 207.10212; Found:207.10232; Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84; Found C, 69.63; H, 7.09.

Representative Asymmetric Epoxidation Procedure using Oxone and $NaHCO_3$ (Method A, 0.5 mmol scale) (Table 4.2, Entry 1): Aqueous $Na_2(EDTA)$ (1×10^{-4} M, 2.5 mL) and a catalytic amount of tetrabutylammonium hydrogen sulfate (0.010 g, 0.03 mmol) were added to a solution of ethyl *trans*-β-methylstyrene (0.059 g, 0.5 mmol) in CH_3CN (2.5 mL) with vigorous stirring at 0 °C. A mixture of Oxone (1.537 g, 2.5 mmol) and $NaHCO_3$ (0.651 g, 7.75 mmol) was pulverized, and a small portion of this mixture was added to the reaction mixture to bring pH to >7. Then a solution of ketone **4-1** (0.038 g, 0.125 mmol) in CH_3CN (1.25 mL) was added. The rest of the Oxone and $NaHCO_3$ was added to the reaction mixture portionwise over a period of 4.5 h. Upon stirring for an addition 7.5 h at 0 °C and 12 h at rt, the resulting mixture was diluted with water, and extracted with ethyl acetate. The combined extracts were washed with brine, dried (Na_2SO_4), filtered, concentrated, and purified by flash chromatography (silica gel, hexane/EtOAc = 1/0 to 50/1) to give the epoxide as a colorless oil (0.050 g, 91% yield, 97% ee).

Representative Asymmetric Epoxidation Procedure using Oxone and K_2CO_3 (Method B, 0.5 mmol scale) (Table 4.2, Entry 1): To a solution of *trans*-β-methylstyrene (0.059 g, 0.5 mmol), ketone **4-1·H_2O** (0.015 g, 0.046 mmol), and tetrabutylammonium hydrogen sulfate (0.01 g, 0.03 mmol) in MeCN-DMM (v/v, 1/2) (9 mL) was added buffer (0.05 M aq Na_2HPO_4-0.05 M aq KH_2PO_4, pH 7.0) (3 mL) with stirring. Upon cooling to 0 °C, a solution of Oxone (0.212 M in 4×10^{-4} M aq EDTA, 4.8 mL) and a solution of K_2CO_3 (0.42 M in 4×10^{-4} M aq EDTA, 4.8 mL) were added

dropwise simultaneously and separately over 8 h via syringe pump. The reaction was quenched by addition of pentane and extracted with pentane. The combined organic layers were dried over Na_2SO_4, filtered, concentrated, and purified by flash chromatography (silica gel was buffered with 1% Et_3N in organic solvent, first pentane, then pentane/Et_2O = 20/1) to give the epoxide as a colorless oil (0.054 g, 81%, 86%ee).

(Table 4.2, entry 1)[12] (b0805a, b1012e, oaw2316-2).

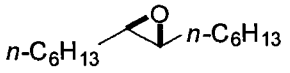


Colorless oil; $[\alpha]_D^{25}$ = +40.8 (*c* 0.92, $CHCl_3$) (86% ee); ^1H NMR (300 MHz, $CDCl_3$) δ 7.39-7.26 (m, 5H), 3.59 (d, *J* = 2.1 Hz, 1H), 3.05 (qt, *J* = 5.1, 2.1 Hz, 1H), 1.70 (d, *J* = 5.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.9, 128.6, 128.2, 125.7, 59.6, 59.2, 18.1.

(Table 4.2, entry 2)[12] (b0811c, b1012a, oaw2322-1).

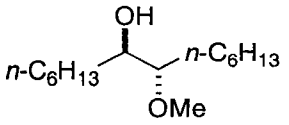
White solid; $[\alpha]_D^{25}$ = +319.8 (*c* 0.80, Benzene) (93% ee); ^1H NMR (300 MHz, $CDCl_3$) δ 7.45-7.24 (m, 10H), 3.91 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.3, 128.8, 128.5, 125.7, 63.0.

(Table 4.2, entry 3)[12] (b0811d, oaw2318-1).

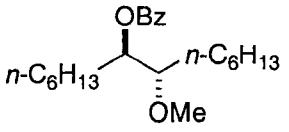


Colorless oil; $[\alpha]_D^{25}$ = +23.7 (*c* 0.90, $CHCl_3$) (88% ee); ^1H NMR (300 MHz, $CDCl_3$) δ 3.78-3.70 (m, 1H), 3.40 (d, *J* = 1.2 Hz, 3H), 3.10-3.04 (m, 1H), 2.08-2.02 (m, 1H), 1.54-

1.22 (m, 20H), 0.90-0.86 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 84.6, 71.5, 57.9, 32.1, 32.0, 29.7, 29.6, 28.7, 26.4, 26.0, 22.8, 14.3.



To a solution of the above epoxide (0.056 g, 0.26 mmol) in MeOH (0.3 mL) was added NaOMe (0.07 g, 1.32 mmol) in a small screw cap vial equipped with a stir bar. The reaction was stirred at 100 °C for 2 d. The solvent was evaporated and the residue was purified by flash chromatography (silica gel, hexane/Et_2O = 3/1) to obtain a colorless oil (0.029 g, 46% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.78-3.70 (m, 1H), 3.40 (d, J = 1.2 Hz, 3H), 3.10-3.04 (m, 1H), 2.08-2.02 (m, 1H), 1.54-1.22 (m, 20H), 0.90-0.86 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 84.6, 71.5, 57.9, 32.1, 32.0, 29.7, 29.6, 28.7, 26.4, 26.0, 22.8, 14.3.



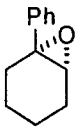
To a solution of the above alcohol (0.029 g, 0.12 mmol) in benzene (1.2 mL) was added benzoyl chloride (0.017 g, 0.014 mL, 0.12 mmol) and pyridine (0.011 g, 0.011 mL, 0.14 mmol) in a small screw cap vial equipped with a stir bar. The reaction was heated at 60 °C overnight. The solvent was evaporated and the residue was purified by flash chromatography (silica gel, hexane/Et_2O = 16/1) to obtain a colorless oil (0.025 g, 60% yield). $[\alpha]_D^{25}$ = -4.1 (*c* 0.44, $CHCl_3$) (88% ee); IR (film) 1720, 1452, 1274 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09-8.06 (m, 2H), 7.58-7.52 (m, 1H), 7.47-7.42 (m, 2H),

5.27 (dt, J = 9.6, 3.3 Hz, 1H), 3.45 (s, 3H), 3.81-3.22 (m, 1H), 1.87-1.48 (m, 5 H), 1.38-1.22 (m, 15 H), 0.91-0.84 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 133.0, 130.7, 129.8, 128.5, 83.0, 75.9, 58.7, 32.0, 31.8, 31.0, 29.6, 29.44, 29.38, 26.1, 26.0, 22.7, 14.24, 14.20; HRMS calcd for $C_{22}H_{36}O_3$ (M) 348.2665; Found: 348.2667.

(Table 4.2, entry 4)[12] (b1039, oaw2322-2, b1012b).

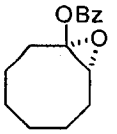
Colorless oil; $[\alpha]_D^{25}$ = +98.9 (*c* 0.98, EtOH, 88% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52-7.48 (m, 2H), 7.46-7.40 (m, 6H), 7.39-7.33 (m, 2H), 4.02 (s, 1H), 1.51 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.5, 136.1, 128.7, 128.4, 127.9, 126.7, 125.3, 67.3, 63.3, 16.9.

(Table 4.2, entry 5)[12] (b0805b, oaw2316-1, b1012c).



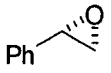
Colorless oil; $[\alpha]_D^{25}$ = +86.0 (*c* 1.11, Benzene) (92% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.25 (m, 5H), 3.09 (t, J = 1.8 Hz, 1H), 2.36-2.26 (m, 1H), 2.14 (dt, J = 15.0, 5.4 Hz, 1H), 2.04-1.98 (m, 2H), 1.70-1.45 (m, 3H), 1.41-1.27 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.6, 128.4, 127.3, 125.4, 62.0, 60.3, 29.0, 24.9, 20.3, 20.0.

(Table 4.2, entry 6)[12] (oaw2314-1).



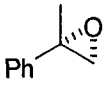
Colorless oil; $[\alpha]_D^{25}$ = +7.1 (*c* 1.09, $CHCl_3$) (95% ee); ^1H NMR (300 MHz, $CDCl_3$) δ 8.34-8.01 (m, 2H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 1H), 3.22 (dd, *J* = 9.9, 4.2 Hz, 1H), 2.92-2.87 (m, 1H), 2.29 (dq, *J* = 13.8, 4.5 Hz, 1H), 1.88-1.22 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3, 133.5, 130.2, 129.9, 128.6, 86.0, 60.5, 28.4, 28.99, 26.21, 26.17, 25.13, 24.9.

(Table 4.2, entry 7)[13] (b1039d, oaw2320-2).



Colorless oil; $[\alpha]_D^{25}$ = -8.7 (*c* 1.03, Benzene) (27% ee); ^1H NMR (300 MHz, $CDCl_3$) δ 7.41-7.28 (m, 5H), 3.89 (dd, *J* = 4.2, 2.7, 1H), 3.17 (dd, *J* = 5.7, 4.2 Hz, 1H), 2.83 (dd, *J* = 5.7, 2.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.8, 28.6, 128.3, 125.6, 55.5, 51.4.

(Table 4.2, entry 8)[14] (b1039c, oaw2324-1).



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

(Scheme 4.10) (4-5a and **4-5e) (b2427A).** A solution of sodium borohydride (0.143 g, 3.80 mmol) in EtOH (4.0 mL), was added over 30 min to a stirred solution of diester ketone **4-1·H_2O** (1.4 g, 4.37 mmol) in EtOH (15.44 mL) at 0 °C. After stirring for a further 1h, the mixture was filtered and the solvent was removed in vacuum, the residue was partitioned between ether (20 mL) and water (5 mL), and the aqueous phase was back-extracted with ether. The combined ether phases were dried by Na_2SO_4 and evaporated leaving a residue that was purified by flash chromatography (silica gel, petroleum ether-EtOAc = 5/1 to 3/1) to give a mixture of **4-5a** and **4-5e** (1/0.8) as a colorless oil (0.26 g, 20 % yield). $[\alpha]_D^{25}$ = -114.0 (*c* 1.2, $CHCl_3$); IR (film) 3483, 1747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ **4-5a**: 5.27-5.23 (m, 2H), 4.18 (d, *J* = 9.6 Hz, 1H), 4.12 (dd, *J* = 13.2, 1.2 Hz, 1H), 4.10 (d, *J* = 9.6 Hz, 1H), 3.85 (dd, *J* = 13.2, 2.0 Hz, 1H), 3.26 (dd, *J* = 13.2, 2.0 Hz, 1H), 2.17 (s, 3H), 2.10 (s, 3H), 1.49 (s, 3H), 1.40 (s, 3H); **4-5e**: 5.29-5.28 (m, 1H), 5.12 (dd, *J* = 10.4, 3.6 Hz, 1H), 4.24 (d, *J* = 8.8 Hz, 1H), 4.05-4.02 (m, 1H), 4.03 (d, *J* = 8.8 Hz, 1H), 3.90-3.85 (m, 1H), 3.74 (dd, *J* = 11.2, 3.2 Hz, 1H), 2.14 (s, 3H), 2.08 (s, 3H), 1.51 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 170.6, 170. 2, 169.7, 113.1, 112.6, 106.1, 105.8, 73.9, 72.2, 71.7, 71.7, 69.7, 69.1, 67.5, 67.4, 62.7, 62.6, 26.9, 26.6, 26.5, 21.3, 21.2, 21.12, 21.08; Anal.Calcd for $C_{13}H_{20}O_8$: C, 51.31; H, 6.62. Found: C, 51.55; H, 6.84; HRMS Calcd for $C_{13}H_{21}O_8$ (M+1): 305.1236; Found: 305.1234.

4.4.4 The Synthesis of Ketone 4-9 and 4-11

(4-7) (b0816, dc0225, dc0229). To a solution of **4-2** (2.18 g, 10 mmol), pyridine (1.03 g, 13 mmol) , DMAP (0.122 g, 1 mmol) in dry DCM (190 mL) at -35 °C, PhOC(=S)Cl (1.35 mL, 10 mmol) was added dropwise via a syringe over 5 min. The resulting mixture was stirred overnight at -35 °C. the mixture was then washed with water (3 × 60 mL) and the combined aqueous layer was extracted by DCM (60 mL). Then organic phase was combined, dried over Na_2SO_4, concentrated and purified by flash chromatography (silica gel, hexane/EtOAc = 3/1 to 1/1) to give **4-7** as a white solid (1.486 g, 42% yield). mp 75-76 °C; $[\alpha]_D^{25}$ = -81.4 (*c* 1.0, $CHCl_3$); IR (film) 3444, 1759 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48-7.42 (m, 2H), 7.35-7.30 (m, 1H), 7.22-7.16 (m, 2H), 6.32 (d, *J* = 3.3 Hz, 1H), 4.73 (d, *J* = 9.3 Hz, 1H), 4.72-4.68 (m, 1H), 4.46 (d, *J* = 12.9 Hz, 1H), 4.05 (dd, *J* = 12.9, 2.1 Hz, 1H), 4.04 (d, *J* = 9.3 Hz, 1H), 2.59 (bs, 1H), 1.57 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.9, 191.2, 153.7, 129.9, 127.1, 121.9, 114.0, 105.4, 82.9, 73.3, 69.5, 64.4, 26.6, 26.2; HRMS Calcd for $C_{16}H_{19}O_7S$ (M+H): 355.0852; Found: 355.0861.

(4-8) (dc0311, dc0216, dc0227, b0838). To a solution of **4-7** (4.15 g, 11.7 mmol) in anhydrous toluene (200 mL) under N_2, were added Bu_3SnH (5.11 g, 17.6 mmol) and *t*-butyl peroxide (0.34 g, 2.3 mmol). The mixture was heated to reflux for 2.5 h, then concentrated and purified by flash chromatography (silica gel, petroleum ester/EtOAc = 2/1 to 1/1) to afford **4-8** as a white solid (0.826 g, 35% yield). mp = 40-41 °C; $[\alpha]_D^{25}$ = -83.1 (*c* 5.3, $CHCl_3$); IR (film) 3445, 1732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.65 (d, *J*

= 9.3 Hz, 1H), 4.40-4.36 (m, 1H), 4.39 (dd, J =12.6, 1.2 Hz, 1H), 3.94 (d, J = 9.3 Hz, 1H), 3.82 (dt, J = 12.6, 2.1 Hz, 1H), 3.06 (dd, J = 15.0, 3.6 Hz, 1H), 2.67 (dt, J = 15.0, 2.7 Hz, 1H), 2.04 (d, J = 6.3 Hz, 1H), 1.55 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.3, 113.4, 104.3, 70.4, 69.9, 66.1, 44.9, 26.9, 26.4; HRMS Calcd for $C_9H_{15}O_5$ (M+H): 203.0919; Found: 203.0916.

(4-9a) (b0814, dc0312). To a solution of **4-8** (0.206 g, 1.02 mmol) and DMAP (0.004 g, 0.03 mmol) in DCM (2.5 mL), was added Ac_2O (0.156 g, 1.53 mmol). The mixture was stirred at rt for 1.5 h. TLC indicated new spot. The mixture was concentrated and purified by flash chromatography (silica gel, petroleum ester/ EtOAc = 4/1) to give **4-9a** as a white solid (0.141 g, 58%). mp 101-102 °C; $[\alpha]_D^{25}$ = -70.5 (*c* 0.6, $CHCl_3$); IR(film) 1726 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34-5.32 (m,1H), 4.66 (d, J = 9.2 Hz, 1H), 4.38 (dd, J = 12.8, 1.6 Hz, 1H), 3.94 (d, J = 9.2 Hz, 1H), 3.91 (ddd, J = 12.8, 2.4 Hz, 1H), 3.08 (dd, J = 15.6, 4.4 Hz, 1H), 2.69 (dt, J = 15.6, 2.4 Hz, 1H), 2.09 (s, 3H), 1.55 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.4, 170.5, 113.5, 104.1, 72.3, 69.8, 63.4, 41.2, 26.7, 26.3, 21.3; HRMS Calcd for $C_{11}H_{17}O_6$ (M+H): 245.1025; Found: 245.1028.

(4-9b) (b-dc0309). To a solution of **4-8** (0. 230 g, 1.14 mmol), Pyridine (0.108 g, 1.37 mmol) in DCM (4.5 mL), was added PivCl (0.166 g, 1.37 mmol). The mixture was stirred at rt for 2 days, then concentrated and purified by falsh chromatography (silica gel, petroleum ester/ EtOAc = 12/1) to give the product as a white solid (0.114 g, 35% yield). mp = 38-39 °C; $[\alpha]_D^{25}$ = -76.4 (*c* 1.4, $CHCl_3$); IR (film) 1732, 1007 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.31-5.27 (m, 1H), 4.64 (d, J = 9.0 Hz, 1H), 4.37 (dd, J = 12.9 Hz, 1.5

Hz, 1H), 3.93 (d, J = 9.0 Hz, 1H), 3.88 (ddd, J = 12.9 Hz, 2.4, 1.8 Hz, 1H), 3.09 (dd, J = 15.0 Hz, 3.9 Hz, 1H), 2.65 (ddd, J = 15.0, 3.0, 2.4 Hz, 1H), 1.55 (s, 3H), 1.39 (s, 3H), 1.19 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.3, 177.8, 113.4, 104.0, 72.0, 69.7, 63.2, 41.2, 39.0, 27.1, 26.6, 26.2; HRMS Calcd for $C_{14}H_{23}O_6$ (M+H): 287.1495; Found 287.1493.

(4-9c) (b0824a). To a solution of **4-8** (0.202 g, 1 mmol) and pyridine (0.079 g, 1 mmol) in dry DCM (10 mL), methoxyacetic chloride (0.163 g, 1.5 mmol) was added dropwise at 0 °C, then stirred for 5 h. TLC show the alcohol was disappeared. After concentration, the mixture was purified by flash chromatography (silica gel, hexane/EtOAc = 10/1 to 5/1) to give **4-9c** as a white solid (0.222 g, 81%). mp = 62-63 °C; $[\alpha]_D^{25}$ = -62.0 (*c* 1.1, $CHCl_3$); IR (film) 1745 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.46-5.42 (m, 1H), 4.64 (d, J = 9.3 Hz, 1H), 4.40 (dd, J = 13.2, 1.5 Hz, 1H), 4.05 (d, J = 1.2 Hz, 2H), 3.95-3.89 (m, 2H), 3.44 (s, 3H), 3.11 (dd, J = 15.6, 4.2 Hz, 1H), 3.73 (dt, J = 15.6, 2.7 Hz, 1H), 1.54 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.0, 169.8, 113.6, 104.1, 72.8, 69.79, 69.76, 63.2, 59.6, 41.2, 26.7, 26.3; HRMS Calcd for $C_{12}H_{19}O_7$ (M+H): 275.1131; Found 275.1129.

(4-9d) (b0821a). To a solution of **4-8** (0.202 g, 1 mmol), and DMAP (0.012 g, 0.1 mmol) in dry DCM (10 mL), was added dropwise anhydride (0.205 g, 1.2 mmol) in DCM (2 mL) at 0 °C, then stirred for 2.5 h. TLC show the alcohol was disappeared. After concentrated, mixture was purified by flash chromatography (silica gel, hexane/EtOAc = 10/1 to 5/1) to give product as a white solid (0.180 g, 64 % yield). white

solid; mp = 49-50 °C; $[\alpha]_D^{25}$ = -69.9 (c 0.90, $CHCl_3$); IR (film) 1743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.42-5.40 (m, 1H), 4.65 (d, *J* = 9.2 Hz, 1H), 4.41 (d, *J* = 13.2 Hz, 1H), 4.10 (s, 2H), 3.98-3.91 (m, *J* = 9.2 Hz, 2H),3.12 (dd, *J* = 15.6, 4.4 Hz, 1H), 3.73 (dt, *J* = 15.6, 2.4 Hz, 1H), 1.55 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 196.7, 166.9, 113.7, 104.0, 77.2, 74.3, 69.8, 63.0, 41.0, 26.7, 26.3; HRMS Calcd for $C_{11}H_{16}O_6Cl$ (M+H): 279.0635; Found 279.0641.

(4-9e) (b0830). To a solution of **4-8** (0.202 g, 1.0 mmol), and DMAP (0.012 g, 0.1 mmol) in DCM (10 mL), was added dropwise dichloroacetic anhydride (0.360 g, 1.5 mmol) at 0 °C, then stirred for 1 h. TLC show the alcohol was disappeared. After concentration, the mixture was purified by flash chromatography (silica gel, hexane/EtOAc = 10/1) to give the product as a colorless oil (0.270 g, 82% yield). colorless oil; $[\alpha]_D^{25}$ = -13.5 (*c* 1.2, $CHCl_3$); IR (film) 1747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.00 (s, 1H), 5.45-5.43 (m, 1H), 4.66 (d, *J* = 9.6 Hz, 1H), 4.44 (dd, *J* = 13.2, 1.2 Hz, 1H), 4.01-3.96 (m, 1H), 3.96 (d, *J* = 9.6 Hz, 1H), 3.15 (dd, *J* = 15.6, 4.4 Hz, 1H), 2.77 (dt, *J* = 15.6, 2.8 Hz, 1H), 1.56 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.2, 167.3, 113.8, 104.0, 75.6, 69.8, 64.1, 62.6, 40.7, 26.7, 26.2.

(4-9f and 4-10) (b0824b). To a solution of **4-8** (0.176 g, 0.87 mmol), and DMAP (0.01 g, 0.08 mmol) in 10 mL dry DCM, was added dropwise propoic anhydride(0.17 g, 1.3 mmol) at 0 °C, then stirred for 4.5 h. TLC indicates the disappearance of **4-8**. After concentration, the mixture was purified by the flash column chromatography (hexane/EtOAc = 10/1 to 5/1) to give a mixture of **4-9f** and **4-10** (10/3) as a white solid

(0.175 g, 83% yield). $[\alpha]_D^{25}$ = -74.1 (c 0.9, $CHCl_3$); IR (film) 1740, 1700 cm^{-1}; **4-9f**: ^1H NMR (300 MHz, $CDCl_3$) δ 5.35-5.33 (m, 1H), 4.66 (d, *J* = 9.3 Hz, 1H), 4.38 (dd, *J* = 13.2, 1.2 Hz, 1H), 3.93 (d, *J* = 9.3 Hz, 1H), 3.93-3.88 (m, 1H), 3.08 (dd, *J* = 15.3, 4.2 Hz, 1H), 2.68 (dt, *J* = 15.3, 2.7 Hz, 1H), 3.36 (q, *J* = 7.5 Hz, 2H), 1.55 (s, 3H), 1.39 (s, 3H), 1.13 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197, 5, 174.0, 113.5, 104.1, 72.1, 69.8, 63.4, 41.3, 27.8, 26.7, 26.3, 9.2; HRMS Calcd for $C_{12}H_{19}O_6$ (M+1): 259.1182; Found: 259.1185; **4-10**: ^{1}HNMR (300 MHz, $CDCl_3$) δ 7.07 (ddd, *J* = 10.5, 3.9, 1.8 Hz 1H), 6.20 (ddd, *J* = 10.5, 2.4, 1.8 Hz, 1H), 4.70 (ddd, *J* = 19.2, 2.7, 1.8 Hz, 1H), 4.66 (d, *J* = 9.0 Hz, 1H), 4.36 (ddd, *J*=19.2, 3.9, 1.8 Hz, 1H), 3.94 (d, *J* = 9.0 Hz, 1H), 1.57 (s, 3H), 1.42 (s, 3H); ^{13}C NMR(75 MHz, $CDCl_3$) δ 187.7, 148.3, 125.6, 113.5, 102.4, 71.0, 61.5, 26.9, 26.1.

(4-11a) (b-dc0308). To a solution of **4-8** (0.187 g, 0.93 mmol), (*i*-Pr)$_2$NEt (0.240 mL, 1.40 mmol), DMAP (0.003 g, 0.025 mmol) in DCM (3 mL), was added MOMCl (0.112 g, 1.40 mmol). The mixture was stirred overnight at rt, then concentrated, and purified by flash chromatography to give the product as a white solid (0.16 mg, 69% yield). mp = 47-48 °C; $[\alpha]_D^{23}$ = -67.8 (c 1.0, $CHCl_3$); IR (film) 1740, 1000 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.70 (s, 2H), 4.65 (d, *J* = 9.3 Hz, 1H), 4.31 (dd, *J* = 12.3, 1.2 Hz, 1H), 4.30-4.25 (m, 2H), 3.98-3.90 (m, 2H), 3.39 (s, 3H), 3.00 (dd, *J* = 14.7, 3.6 Hz, 1H), 2.74(dt, *J*=14.7, 3.0 Hz, 1H) 1.54 (s, 3H), 1.38(s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.0, 113.2, 104.3, 95.1, 74.8, 69.9, 64.3, 55.9, 42.2, 26.8, 26.4; HRMS Calcd for $C_{11}H_{19}O_6$ (M+H): 247.1182; Found 247.1176.

(4-11b) (b-dc0305). To a solution of **4-8** (0.199 g, 0.98 mmol), imidazole (0.135 g, 1.97 mmol), DMAP (0.004 g, 0.032 mmol) in dry DMF (0.4 mL), was added TBSCl (0.222 g, 1.48 mmol). The mixture was stirred at rt for 24 h. Then DCM (5 mL) was added and precipitations occurred. Upon filtration to remove white solid, the filtrate was concentrated and purified by flash chromatography (silica gel, DCM) to give **10** as colorless oil (0.216 g, 68%). $[\alpha]_D^{25} = -64.6$ (*c* 0.9, $CHCl_3$); IR(film) 1742 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.61 (d, *J* = 9.3 Hz, 1H), 4.39-4.34 (m, 1H), 4.25 (d, *J* = 12.0 Hz, 1H), 3.91 (d, *J* = 9.3 Hz, 1H), 3.69 (dt, *J* = 12.0, 2.1 Hz, 1H), 2.98 (dd, *J* = 14.4, 3.6 Hz, 1H), 2.51 (dt, *J* = 14.4, 3.0 Hz, 1H), 1.53 (s, 3H), 1.37 (s, 3H), 0.86 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.2, 112.8, 104.2, 70.9, 69.9, 66.8, 45.3, 26.8, 26.5, 25.9, 18.3, -4.5; Anal. Calcd. for $C_{15}H_{28}O_5Si$: C, 56.93; H, 8.92. Found: C, 57.10; H, 8.73.

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CHAPTER 5.0 : BIS-OXAZOLIDINONE KETONE, A HIGH TURN-OVER CATALYST FOR ASYMMETRIC EPOXIDATION

5.1 INTRODUCTION

Epoxides are very versatile intermediates, and asymmetric epoxidation of olefins is an effective approach to synthesize enantiomerically-enriched epoxides. In recent years, asymmetric epoxidations that are catalyzed by small organic molecules (ketones and iminium salts) have received intensive interest.[1] One major advantage of metal-free organic catalysts is their better environmental acceptance compared to transition-metal catalysts because most of the latter are toxic. One major disadvantage of organic catalysts is that they generally require high catalyst loadings, and decomposition of the catalyst is often observed.[1,2]

In recent years, our group focused on chiral ketone catalyzed asymmetric reactions and found that fructose-derived ketone **1-2**[3] and glucose-derived ketone **2-3**[4-15] provide high enantioselectivities for a wide range of *trans*-,[3] trisubstituted,[3,12] terminal,[5,6,10] *cis*-,[4,6-9,14,15] and certain tetrasubstituted olefins[11,13] (Figure 5.1). One drawback of these catalysts is that they decompose under oxidative reaction conditions, thus requiring a relatively high catalyst loading (typically 20-30%). It has been postulated

that the Baeyer-Villiger reaction of intermediate **5-1** is the likely decomposition pathway (Scheme 5.1).[16]

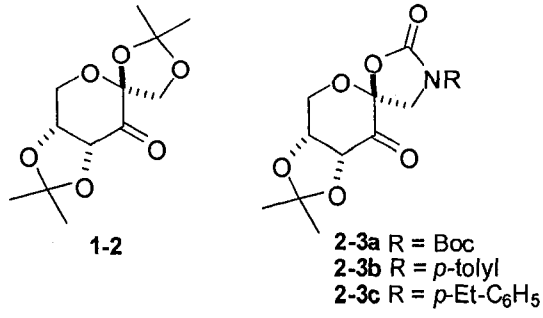
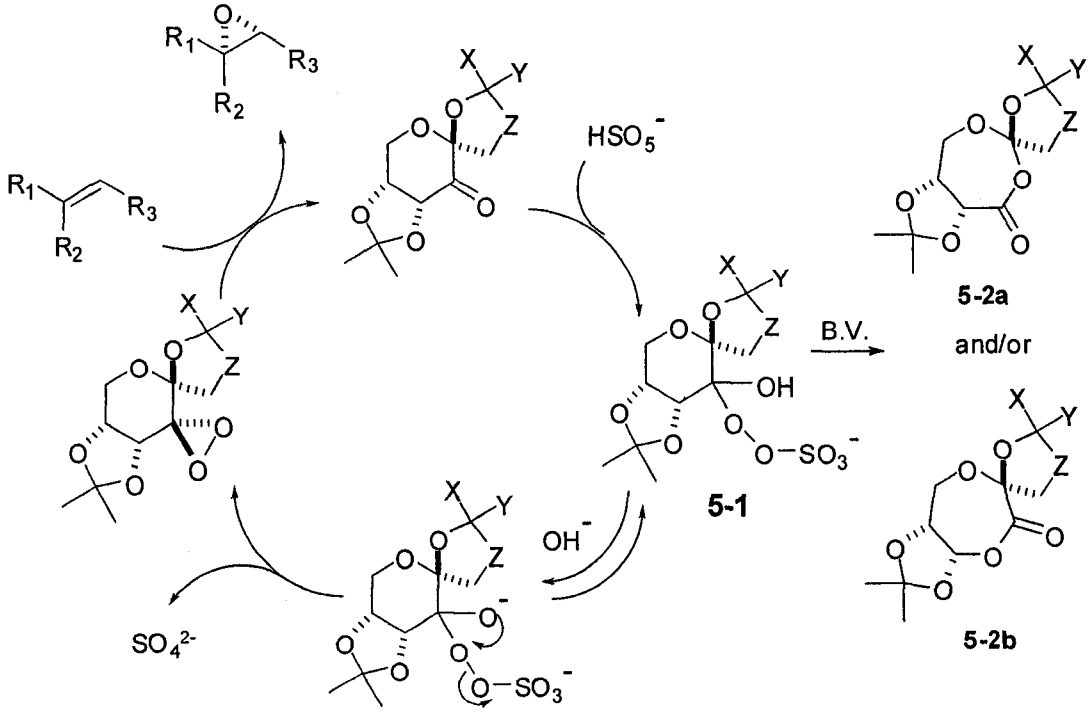
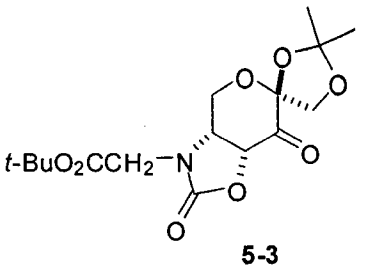


Figure 5.1

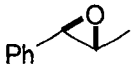


Scheme 5.1

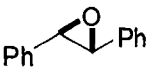
Since the migratory trend of Baeyer-Villiger oxidations could be influenced by the electronic nature of the migration group, it was envisioned that the Baeyer-Villiger oxidation of ketone **1-2** and **2-3** could possibly be reduced by increasing the electron deficiency of the α-C adjacent to the carbonyl group, thus providing more stable ketone catalysts. Ketone **5-3** (Figure 2), an analog of ketone **1-2**, was prepared and turned out to be a highly active and robust catalyst for asymmetric epoxidation of a variety of *trans*- and trisubstituted olefins. The amount of ketone catalyst could be reduced to 5 mol % without sacrificing the yield and enantioselectivity.[16]



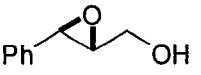
5-3



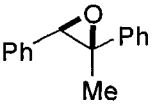
100% yield
88% ee



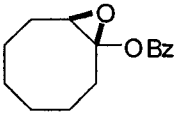
67% yield
96% ee



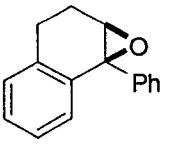
89% yield
87% ee



80% yield
93%ee



93% yield
90%ee

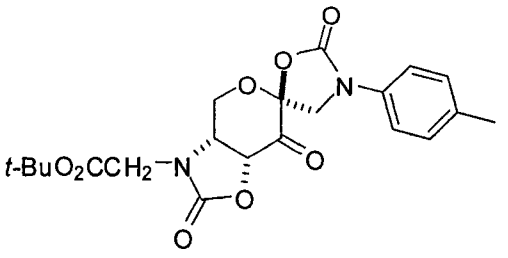


80% yield
93% ee

Figure 5.2

5.2 RESULTS AND DISCUSSION

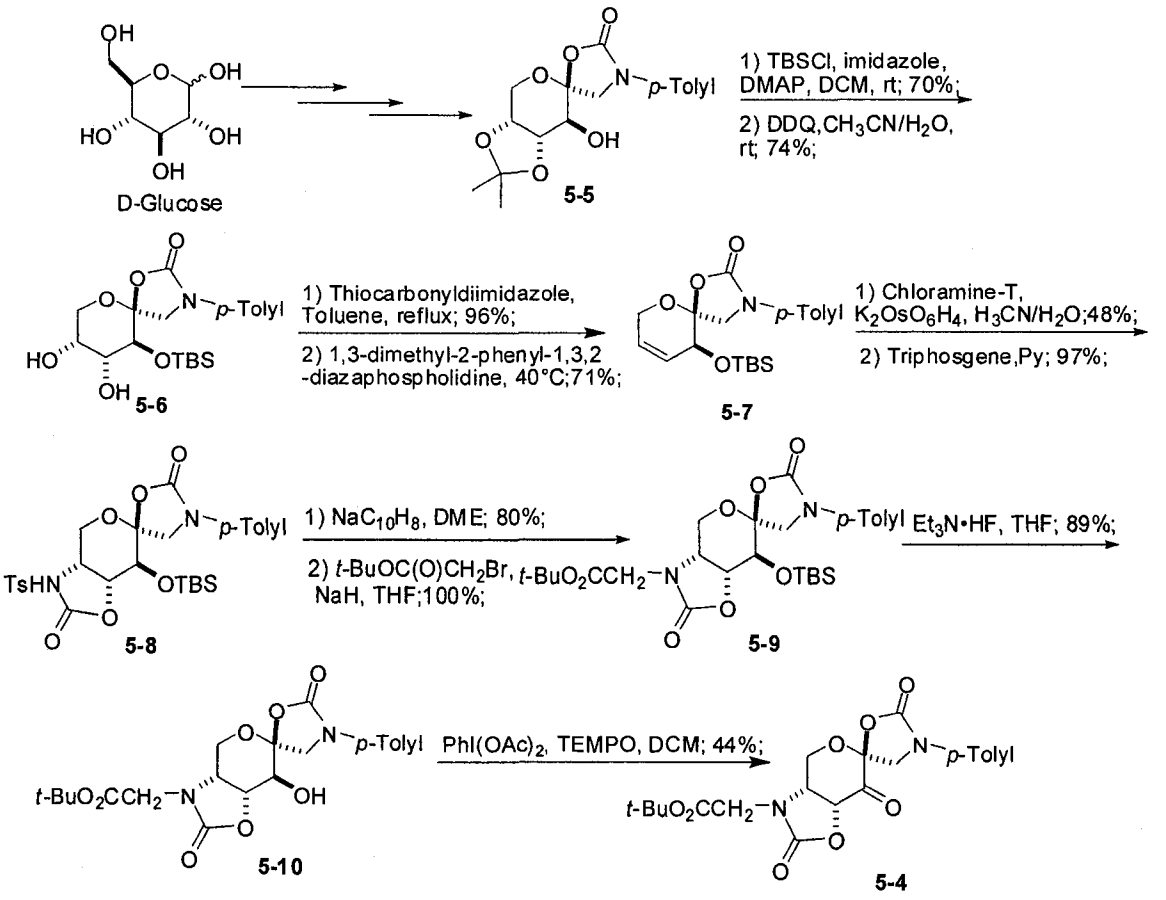
Based on the same idea, ketone **5-4** (Figure 5.3), an analog of ketone **2-4b** was designed and prepared with the joint effort with Dr. Dajun Chen and Dr. Xinyan Wu.



5-4

Figure 5.3

The preparation of ketone **5-4** began with D-glucose (Scheme 5.2). After the Amadori rearrangement, ketalization, and oxazolidinone formation, alcohol **5-5** was prepared based on reported procedure.[7] Then TBS protection of alcohol and deketalation by DDQ gave diol **5-6** in 52% yield in two steps. After Corey-Winter olefination, compound **5-7** was obtained in 68% yield. With the selective aminohydroxylation and phosgene cyclization, another oxazolidinone ring was built in 47% yield in two steps. After carefully removing the Ts group using a mixture of sodium and naphthalene and alkylation of amide by CH_2BrCO_2t-Bu, TBS ester **5-9** was produced with 78% yield in two steps. Deprotection of silyl ester to alcohol **5-10**, which structure was confirmed by X-ray of its single crystal (Figure 5.4). The oxidization of alcohol **5-10** by TEMPO oxidation gave a ketone **5-4** which partially exists in a hydrate form.


D-Glucose
5-5
1) TBSCl, imidazole, DMAP, DCM, rt; 70%;
2) DDQ,CH3CN/H2O, rt; 74%;
5-6
1) Thiocarbonyldiimidazole, Toluene, reflux; 96%;
2) 1,3-dimethyl-2-phenyl-1,3,2 -diazaphospholidine, 40°C;71%;
5-7
1) Chloramine-T, K2OsO6H4, H3CN/H2O;48%;
2) Triphosgene,Py; 97%;
5-8
1) NaC10H8, DME; 80%;
2) t-BuOC(O)CH2Br, t-BuO2CCH2-N
NaH, THF;100%;
5-9
Et3N•HF, THF; 89%;
5-10
PhI(OAc)2, TEMPO, DCM; 44%;
5-4

Scheme 5.2

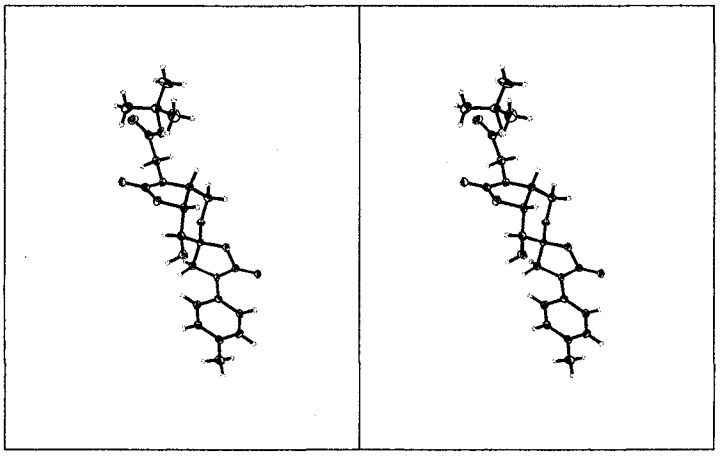
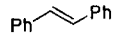
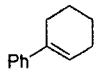
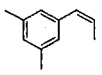
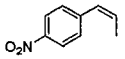
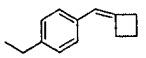
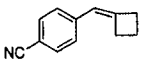
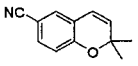


Figure 5.4 The X-ray Structure of Compound **5-10** (stereoview)

With ketone **5-4** in hand, asymmetric epoxidation of olefins were carried out. Indeed, ketone **5-2** was found indeed to be a very active catalyst (Table 5.1). When 1 mol % ketone was used, good yield and enantioselectivity (up to 93%) was obtained for the asymmetric epoxidation of conjugated *cis* and trisubstituted olefin (Table 5.1, entries 3-7).

Table 5.1 Asymmetric Epoxidation of Olefins Catalyzed by 1 mol % of Ketone **5-4**

Entry	Substrate	Temperature (°C)	Yield[d] (%)	Ee (%)	Config.[g]
1[a]		0	69	86[e]	(+)-(*R*, *R*)[3]
2[b]		-10	90	35[f]	(-)-(*S*, *S*)[7]
3[b]		-10	78	83[f]	(-)
4[c]		0	77	90[f]	(-)
5[b]		-10	87	87[f]	(+)
6[c]		0	73	93[f]	(+)
7[b]		-10	64	87[e]	(+)-(*R*, *R*)[14]

[a] The reactions was carried out with olefin (0.2 mmol), ketone (0.002 mmol, 0.86 mg), tetrabutylammonium hydrogen sulfate (3.75 mg, 0.01 mmol), Oxone (0.276 mmol) and K_2CO_3 (1.16 mmol) in CH_3CN-DMM (1:2 v/v) (3 mL), and buffer (0.1M K_2CO_3-AcOH, pH 9.3) (2 mL). The reactions were stopped after 16 h. [b] The reactions were carried out with olefin (0.2 mmol), Ketone (0.002 mmol), tetrabutylammonium hydrogen sulfate (3.75 mg, 0.01 mmol), Oxone (0.32 mmol), and K_2CO_3 (1.344 mmol) in DME-DMM (3:1, v/v) (3 mL) and buffer (0.1M K_2CO_3-AcOH, pH 9.2) (2 mL). The reactions were stopped after 16 h. [c] The reactions were carried out with olefin (0.2 mmol), Ketone

(0.002 mmol), tetrabutylammonium hydrogen sulfate (3.75 mg, 0.01 mmol), Oxone (0.32 mmol), and K_2CO_3 (1.344 mmol) in DME/DMM (3:1, v/v) (3.75 mL) and buffer (0.1M K_2CO_3-AcOH, pH 9.2) (1.25 mL). The reactions were stopped after 16 h. [d] Isolated yield. [e] The enantioselectivity was determined by chiral HPLC (Chiralcel OD). [f] The enantioselectivity was determined by chiral GC (Chiraldex B-DM). [g] Determined by comparing the measured optical rotations and HPLC or GC trace with the reported ones.

5.3 CONCLUSION

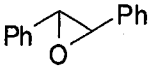
In summary, the replacement of the fused ketal of ketone **2-4b** with an oxazolidinone creates a more stable and reactive catalyst for asymmetric epoxidation due to the reduction of Baeyer-Villiger decomposition. The ketone **5-4** is highly active. It gives good yields and enantioselectivities for a variety of conjugated olefin substrates with 1 mol % catalyst loading. The information gained from this study is helpful for the further understanding of the ketone-catalyzed epoxidation and for the design of more efficient catalysts in the future.

5.4 EXPERIMENTAL

Representative Epoxidation Procedure (Table 5.1, Entry 6). To a solution of the olefin (0.034 g, 0.2 mmol), tetrabutylammonium hydrogen sulfate (0.004 g, 0.01 mmol) and ketone (0.9 mg, 0.002 mmol) in DME/DMM (v/v, 3/1) (3.75 mL) were added buffer (0.1 M K_2CO_3-AcOH in 4 x 10^{-4} M aqueous EDTA, pH = 9.3) (1.25 mL) with stirring. After the mixture was cooled to 0 °C (bath temperature), a solution of Oxone (0.20 M in 4 x 10^{-4} M aqueous EDTA, 1.6 mL) (0.197 g, 0.32 mmol) and a solution of K_2CO_3 (0.84

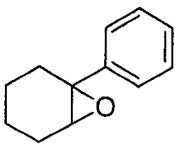
M in 4 x 10^{-4} M aqueous EDTA, 1.6 mL) (0.185 g, 1.344 mmol) were added separately and simultaneously via a syringe pump over a period of 16 h. The reaction mixture was quenched with hexane, extracted with hexane, dried Na_2SO_4, filtered, concentrated, and purified by flash chromatography [the silica gel was buffered with 1% Et_3N in organic solvent; hexane/Et_2O = 50/1 was used as eluent] to give the epoxide as colorless oil (0.028 g, 76 % yield).

(Table 5.1, Entry 1)[3](b0645a).



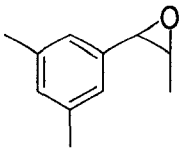
White solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44-7.34 (m, 10H), 3.90 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.3, 128.8, 128.5, 125.7, 63.1.

(Table 5.1, Entry 2)[7](b0641a).



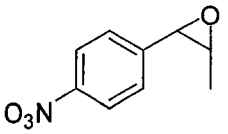
Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.22 (m, 5H), 3.07 (s, 1H), 2.33-2.24 (m, 1H), 2.12 (td, J = 14.7, 5.4 Hz, 1H), 2.02-1.96 (m, 2H), 1.64-1.41 (m, 3H), 1.38-1.26 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.7, 128.5, 127.4, 125.5, 62.1, 60.4, 29.0, 24.9, 20.3, 20.0.

(Table 5.1, Entry 3)[6] (b0646c).



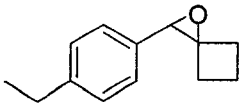
Colorless oil; $[\alpha]_D^{25}$ = -19.2 (*c* 0.9, $CHCl_3$) (83 % ee); ^1H NMR (300 MHz, $CDCl_3$) δ 6.96-6.91 (m, 3H), 4.01 (d, *J* = 4.5 Hz, 1H), 3.36-3.29 (m, 1H), 2.33 (s, 6H), 1.11 (d, *J* = 5.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ137.8, 135.6, 129.4, 124.5. 57.8, 55.3, 21.5, 12.8;

(Table 5.1, Entry 4)[7] (b0637a).



Colorless oil; $[\alpha]_D^{25}$ = -47.4 (*c* 0.7, $CHCl_3$) (90 % ee); ^1H NMR (300 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.7 Hz, 2H), 7.48 (d, *J* = 8.7 Hz, 2H), 4.13 (d, *J* = 4.2 Hz, 1H), 3.46-3.40 (m, 1H), 1.11 (d, *J* = 5.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 147.7, 143.4, 127.7, 123.5, 57.1, 55.8, 18.1, 12.7.

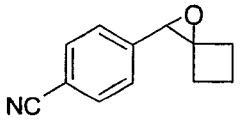
(Table 5.1, Entry 5)[12] (b0639b).



Colorless oil; $[\alpha]_D^{25}$ = +102.1 (*c* 1.0, $CHCl_3$) (87 % ee); ^1H NMR (300 MHz, $CDCl_3$) δ 7.20 (d, *J* = 7.8 Hz, 2H), 7.11 (d, *J* = 7.8 Hz, 2H), 2.66 (q, *J* = 7.8 Hz, 2H), 2.58-2.38 (m, 3H), 2.09-1.99 (m, 1H), 1.96-1.84 (m, 1H), 1.76-1.64 (m, 1H), 1.25 (t, *J* = 7.8 Hz,

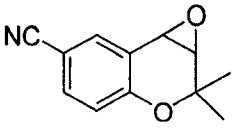
3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.9, 133.9, 127.7, 126.2, 66.7, 62.6, 31.6, 28.8, 28.7, 15.8, 12.7.

(Table 5.1, Entry 6) (b0640a).



White Solid; m.p. 49-50 °C; $[\alpha]_D^{25}$ = +114.0 (*c* 1.0, $CHCl_3$) (93 % ee); IR (film) 2228, 1610 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (m, 2H), 7.30 (m, 2H), 3.89 (s, 1H), 2.72-2.61 (m, 1H), 2.55-2.34 (m, 2H), 2.00-1.84 (m, 2H), 1.79-1.67 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$); δ .142.3, 132.0, 126.8, 118.8, 111.5, 67.5, 61.6, 31.6, 28.4, 12.7; Anal. Calcd. for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.99; H, 6.05; N, 7.41.

(Table 5.1, Entry 7)[14] (b0644b).



Colorless oil; $[\alpha]_D^{25}$ = +61.3 (*c* 1.6, $CHCl_3$) (84 % ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, *J* = 2.1 Hz, 1H), 7.53 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 3.91 (d, *J* = 4.2 Hz, 1H), 3.54 (d, *J* = 4.5 Hz, 1H), 1.60 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.7, 134.6, 134.0, 121.3, 119.2, 118.9, 104.5, 74.9, 62.5, 50.1, 25.7, 23.2.

5.5 REFERENCES

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CHAPTER 6.0 : ASYMMETRIC EPOXIDATION OF 1,1-DISUBSTITUTED OLEFINS BY CHIRAL DIOXIRANE VIA A PLANAR-LIKE TRANSITION STATE

6.1 INTRODUCTION

As introduced in Chapter 2, chiral dioxiranes are effective for asymmetric epoxidation of olefins, and a number of laboratories have extensively investigated chiral ketones of various structures.[1-5] In our own studies, we found that fructose-derived ketone **1-2** is a very effective catalyst for the epoxidation of *trans*- and trisubstituted olefins,[6-8] and oxazolidinone-bearing ketones **2-3** can give high ee's for olefins such as conjugated aromatic *cis*-olefins,[9-13] conjugated *cis*-dienes[14] and enynes,[9,10,15] styrenes,[10,11,16,17] certain trisubstituted,[18,19] and tetrasubstituted olefins[19,20] which had not been effective with ketone **1-2** (Figure 6.1). Studies have shown that the enantioselectivity afforded by ketone **2-3** results from an apparent attractive interaction between the R_π group of the olefin and the spiro oxazolidinone of the ketone catalyst.[9-20]

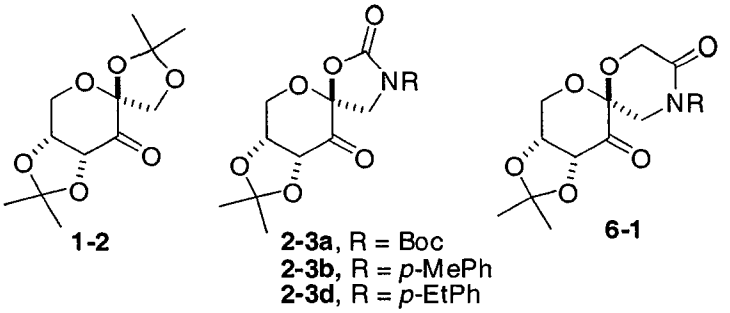


Figure 6.1

Among the six classes of olefins shown in Figure 6.2, unfuctionalized 1,1-disubstituted terminal olefins (**VI**) have generally been challenging for asymmetric epoxidation.[21] Until now, many efforts including chiral metal catalysis,[22-34] chiral dioxiranes,[7,10,16,35-45] or chiral oxaziridinium salts[46] or others[47] have been made, however, with little success.

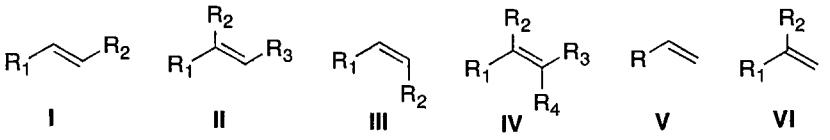


Figure 6.2

Epoxidation of α-methylstyrene and α-isopropylstyrene with ketone **2-3a** gave (*S*)-α-methylstyrene oxide in 30% ee and α-isopropylstyrene oxide in 58% ee, respectively.[10] Several possible spiro and planar transition states for epoxidation with ketone **2-3** are shown in Figure 6.3.[7,10] Spiro transition states (**A-D**) are generally favored stereoelectronically as a result of the stabilizing interaction of an oxygen lone pair with the π* orbital of the alkene.[48-54] However, planar transition states **E** and **G** appear to be

sterically more favored as compared to spiro transition states. Planar transition states **F** and **H** are disfavored both electronically and sterically, thus are unlikely to be significant contributors. Between the two planar transition states **E** and **G**, **E** is likely to be favored over **G** due to the associative interaction between the phenyl group of the olefin and the oxazolidinone of the ketone catalyst. We hypothesized that planar **E** might be the major transition state for the epoxidation of α-methylstyrene based on the *S* configuration of the resulting epoxide obtained with ketone **2-3a**. A higher ee obtained with α-isopropylstyrene could be due to disfavoring competing spiro **D** by a larger isopropyl group.[10] Based on these observations, we decided to search for ketone catalysts that can further favor planar **E**-like transition state to enhance the enantionselectivity for the epoxidation of 1,1-disubstituted terminal olefins. We have found that lactam ketones **6-1** provide very promising results (Figure 6.1).

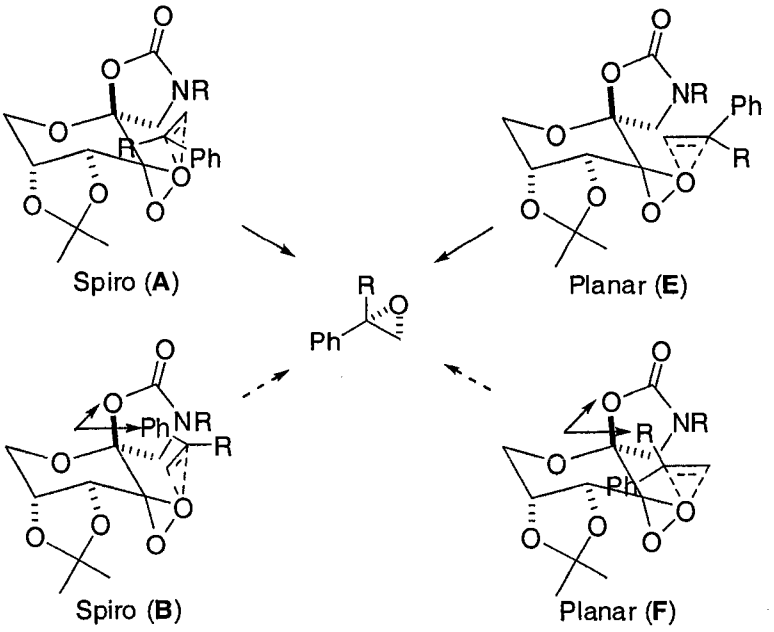


Figure 6.3

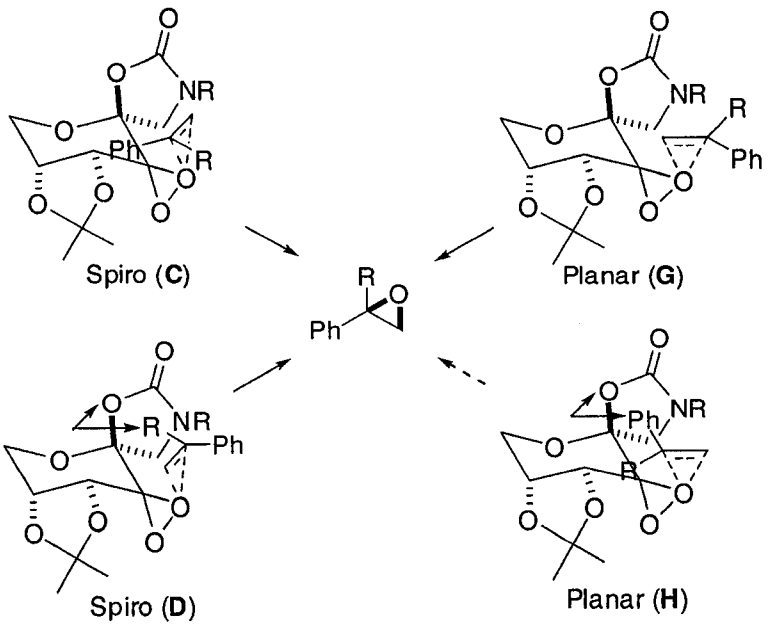
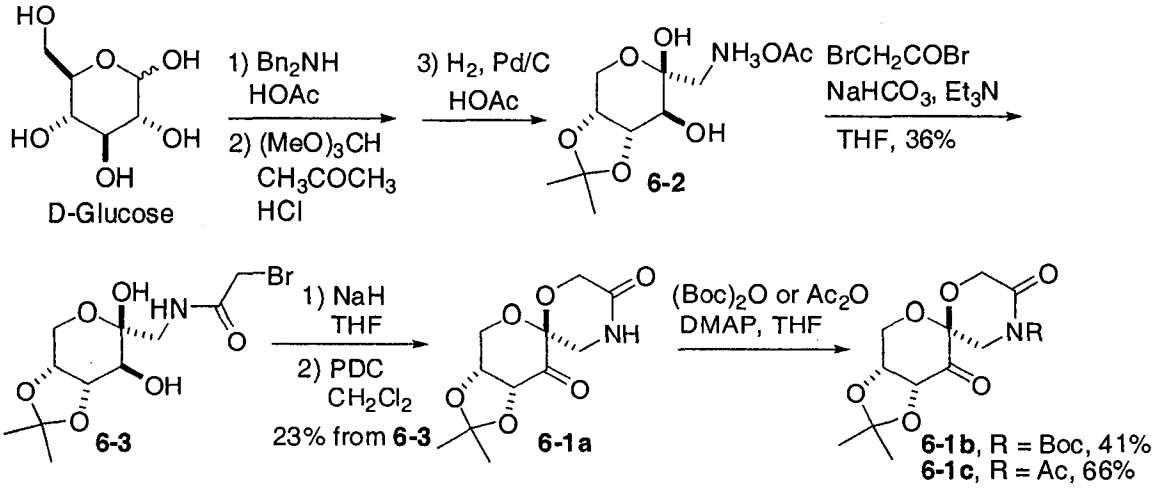


Figure 6.3 (continued)

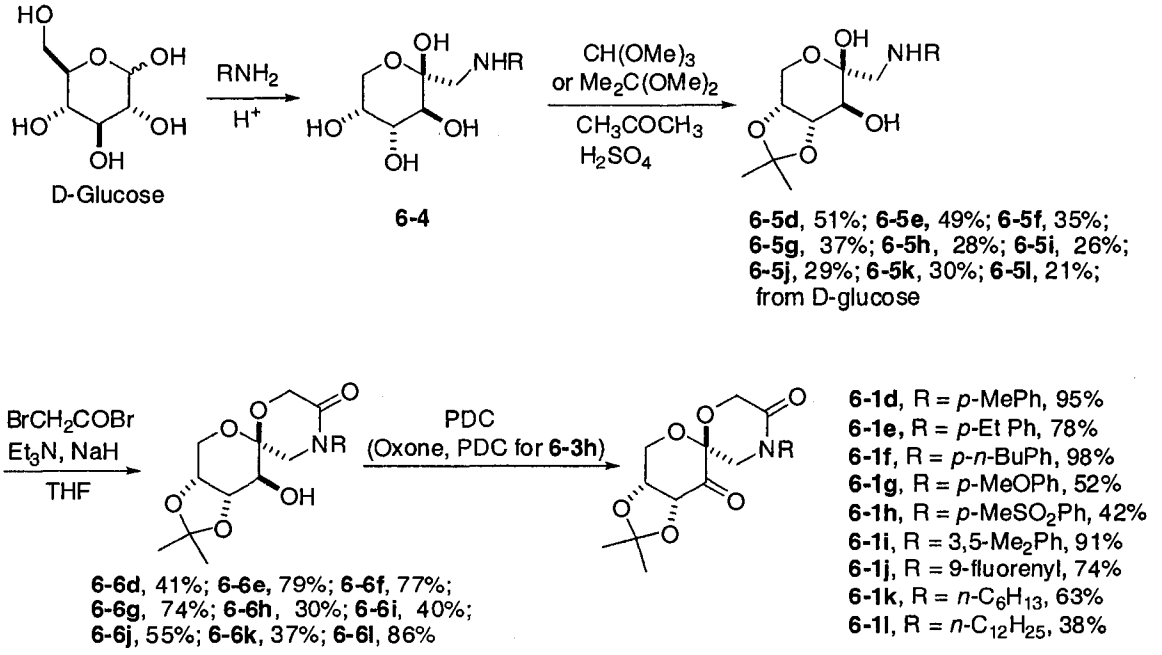
6.2 RESULTS AND DISCUSSION

The synthesis of lactam ketone **6-1** is outlined in Schemes 6.1 and 6.2. Diol **6-2**, prepared from D-glucose as previously reported,[55] was treated with $BrCH_2COBr$ to form compound **6-3**, which was then converted to ketone **6-1a** after cyclization and oxidation. Upon introduction of a Boc or Ac group, ketone **6-1a** was converted to ketones **6-1b** and **6-1c** (Scheme 6.1). Ketones **6-1d-h** were prepared from D-glucose in four steps by Amadori rearrangement,[56] ketalization,[11] formation of the six-membered lactam, and subsequent oxidation (Scheme 6.2). The X-ray structure of ketone **6-1d** is shown in Figure 6.4. An overlay of ketones **2-3b** and **6-1d** is shown in Figure 6.5. In contrast to

ketone **2-3b**,[11] the *N*-phenyl group and the lactam carbonyl group in **6-1d** are not coplanar.



Scheme 6.1



Scheme 6.2

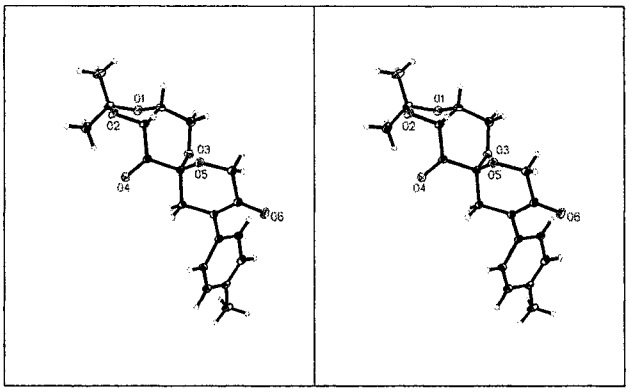


Figure 6.4 The X-ray Structure of Ketone **6-1d** (stereoview)

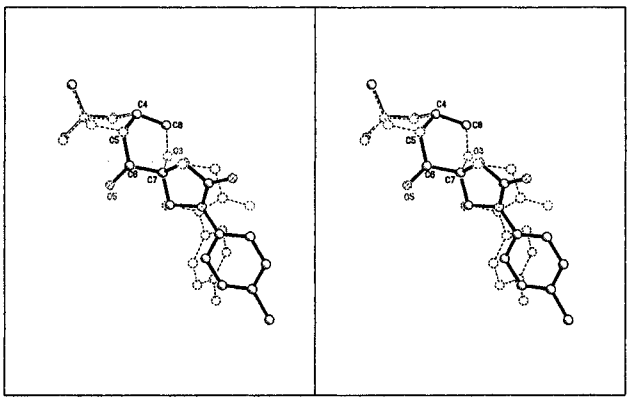
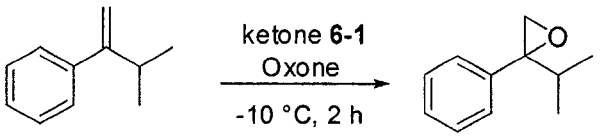


Figure 6.5 Crystal Structure Overlay of Ketones **2-3b** and **6-1d** (stereoview)

Initial studies on the epoxidation of α-isopropylstyrene with ketone **6-1d** showed that 1,4-dioxane was among the best solvents, giving 94% conversion and 84% ee (Table 6.1, entry 4). The enantioselectivity was also affected by the *N*-substituents of ketone catalysts with ketones **6-1a**, **6-1d**, **6-1e**, **6-1f**, and **6-1h** giving the highest enantioselectivity (82-84% ee) (Table 6.1, entries 7, 4, 10, 11, and 13). Ketone **6-1d**, readily synthesized from inexpensive starting materials, was subsequently investigated for the epoxidation of 1,1-disubstituted terminal olefins.

Table 6.1 Asymmetric Epoxidation of α-Isopropylstyrene with Ketones **6-1**[a]



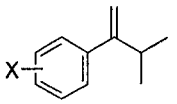
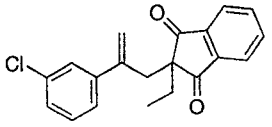
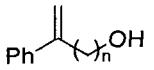
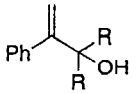
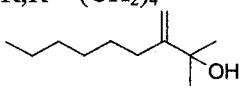
entry	ketone	solvent	conv. (%)[b]	ee (%)[b]
1	**6-1d**	CH_3CN/DMM (1/2)	97	71
2	**6-1d**	DMM	32	77
2	**6-1d**	DME	94	81
3	**6-1d**	DME/*n*-BuOH	99	76
4	**6-1d**	1,4-dioxane	94	84
5	**6-1d**	1,4-dioxane/DME (2/1)	99	80
6	**6-1d**	1,4-dioxane/*n*-BuOH (1/1)	100	78
7	**6-1a**	1.4-dioxane	91	82
8	**6-1b**	1.4-dioxane	69	71
9	**6-1c**	1.4-dioxane	10	nd
10	**6-1e**	1.4-dioxane	99	82
11	**6-1f**	1.4-dioxane	100	83
12	**6-1g**	1.4-dioxane	99	81
13	**6-1h**	1.4-dioxane	99	85
14	**6-1i**	1.4-dioxane	98	83
15	**6-1j**	1.4-dioxane	80	52
16	**6-1k**	1.4-dioxane	99	84
17	**6-1l**	1.4-dioxane	100	80

[a] All epoxidations were carried out with the olefin (0.2 mmol), ketone **6-1** (0.06 mmol), Oxone (0.32 mmol), and K_2CO_3 (1.344 mmol) in organic solvent (3 mL) and buffer (0.1 M K_2CO_3/AcOH, pH 9.3; 2 mL) at -10 °C for 2 h. [b] The conversion and ee were determined by chiral GC (B-DM column).

As shown in Table 6.2, a variety of aryl-substituted 1,1-disubstituted olefins can be effectively epoxidized with good enantioselectivities (62-88% ee). Generally speaking, substrates with bulky alkyl groups at α positions of olefins produce epoxides with higher enantioselectivity than those with small groups. The substituents on the phenyl groups of olefins also have some effects on the enantioselectivities (74-88% ee) (Table 6.2, entries 7-14). Allylic, homoallylic, and bishomoallylic alcohols are also

effective substrates (Table 6.2, entries 16-21). Up to 88% ee was obtained for 1,1-dialkyl-2-aryl allylic alcohols (Table 6.2, entries 19-21). A reasonable enantioselectivity (60% ee) was also obtained for a non-aromatic allylic alcohol (Table 6.2, entry 22).

Table 6.2 Asymmetric Epoxidation of 1,1-Disubstituted Olefins with Ketone **6-1d**[a]

entry	substrate	yield (%)[b]	ee (%)	config.[e]
				
1	R = Me	60	62[c]	(+)-(*S*)[57]
2	R = Et	71	78[d]	(+)-(*S*)[57]
3	R = *n*-Pr	90	75[d]	(+)
4	R = *i*-Bu	54	74[d]	(+)
5	R = *c*-C_6H_{11}	62	77[c]	(+)
6	R = *t*-Bu	43	86[d]	(+)
				
7	X = H	71	84[d]	(+)
8	X = *p*-*i*-Pr	51	82[c]	(+)
9	X = *p*-MeO	94	84[c]	(+)
10	X = *p*-F	78	74[d]	(+)
11	X = *p*-Br	68	78[d]	(+)
12	X = *m*-Me	57	82[c]	(+)
13	X = *m*-F	74	81[d]	(+)
14	X = *o*-F	72	88[d]	(+)
15		51	66[c]	(-)-(*S*)[58]
				
16	n = 1	93	77[c]	(+)-(*R*)[47]
17	n = 2	47	72[c]	(+)
18	n = 3	62	74[c]	(+)
				
19	R = Me	76	87[c]	(+)-(*S*)[57]
20	R = Et	85	87[d]	(+)
21	R,R = $(CH_2)_4$	86	88[d]	(+)-(*S*)[57]
22		78(81[f])	60(72[f])[d]	(+)

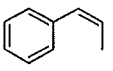
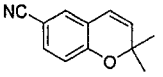
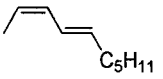
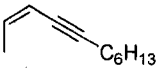
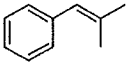
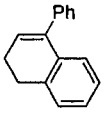
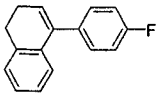
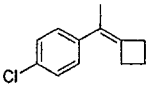
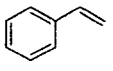
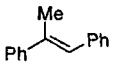
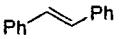
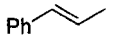
[a] Unless stated otherwise, all epoxidations were carried out with the olefin (0.2 mmol), ketone **6-1d** (0.06 mmol), Oxone (0.32 mmol), and K_2CO_3 (1.344 mmol) in 1,4-dioxane (3 mL), and buffer (0.1 M K_2CO_3/AcOH, pH 9.3; 2 mL) at -10 °C for 2 h (4 h for entries 6, 11, 13, and 14). [b] Isolated yield except entry 7 which is crude yield. [c] The ee was determined by chiral HPLC (Chiracel OD column). [d] The ee was determined by chiral GC (B-DM column). [e] The absolute configurations were determined by comparing the measured optical rotations and HPLC trace with reported ones. [f]. ketone **6-1k** (0.3 eq.) was used.

In addition to 1,1-disubstituted olefin, epoxidation of other olefins was also investigated with ketone **6-1d**, A level of enantioselectivity similar to that obtained with ketone **2-3**, was found with **6-1d** in epoxidation of conjugated *cis*- and trisubstituted olefins (Table 6.3, entries 1-5), indicating that there still exists an electronic attraction between the amide moiety and the phenyl group of the olefin in spiro transition state **I** (Figure 6.6). Nevertheless, this attraction appears to be weaker than that between ketone **2-3** and olefins, resulting in more competition from the other possible transition states.

When 1-phenylcyclohexene was epoxidized with ketone **6-1d**, the (*S*,*S*)-epoxide derived from planar **L** (Figure 6.7) was obtained with 80% ee (Table 6.3, entry 6) while the epoxidation with ketones **2-3a** and **2-3b** gave 43% ee of the (*S*,*S*)-epoxide[16] and 25% ee of the (*R*,*R*)-epoxide,[11] respectively. This observation suggests that the six-membered lactam moiety provides a more favorable environment for the attraction between the lactam moiety of the ketone and the phenyl group of the olefin in the planar transition state as compared to ketones **2-3a** and **2-3b**. In the case of 1-phenyl-3,4-dihydronaphthalene and 4-(4-fluorophenyl)-1,2-dihydronaphthalene, the epoxide resulting from the planar transition state was obtained in as high as 90% and 84% ee's respectively (Table 6.3, entries 7 and 8), further illustrating the aforementioned attraction in the planar transition state.

In the epoxidation of tetrasubstituted olefin, styrene, *trans*-olefins, and trisubstituted olefin, low ee's were obtained, likely due to the significant competition from corresponding planar-type transition states in which the phenyl group is proximate to the lactam moiety of the ketone (Table 6.3, entries 9-13).[7,17,20]

Table 6.3 Asymmetric Epoxidation of Olefins by Ketone **6-1d**

Entry	Olefin	**6-1d** (eq.)	Conv.[c] (Yield)[d] (%)	Ee[e] (%)	Config.[h]
1[a]		0.30	100 (60)	85	(-)-(1*R*,2*S*)[9]
2[a]		0.20	89 (87)	84[f]	(+)-(3*R*,4*R*)[9]
3[a]		0.20	81 (58)	68[g]	(-)-
4[a]		0.25	91 (69)	70	(-)-(2*S*,3*R*)[15]
5[a]		0.20	92 (71)	91	(+)-(*R*)[7]
6[a]		0.20	99 (89)	80	(-)-(*S*, *S*)[7,10,11]
7[a]		0.20	88 (56)	90[f]	(+)-(1*R*, 2*S*)[7]
8[a]		0.20	55 (48)	84[f]	(+)-
9[a]		0.25	87 (84)	72	(+)-
10[a]		0.30	100 (75)	44	(-)-(*R*)[17]
11[b]		0.30	90 (90)	64[f]	(+)-(*R*,*R*)[59]
12[b]		0.30	48 (45)	77[f]	(+)-(*R*,*R*)[7]
13[b]		0.30	100 (75)	34	(+)-(*R*,*R*)[8]

[a] All reactions were carried out with olefin (0.2 mmol), ketone **6-1d**, tetrabutylammonium hydrogen sulfate (3.75 mg, 0.01 mmol), 0.2M Oxone (1.6 mL, 0.32 mmol), and 0.84M K_2CO_3 (1.6 mL,1.344 mmol) in DME/DMM (3:1, v/v) (3 mL) (DME (3 mL) for entry 10), and buffer (0.1M K_2CO_3-AcOH, pH 9.2) (2 mL) at -10 °C for 4 h. For entries 2 and 4, epoxidation was carried at 0 °C for 12 h. For entry 3, epoxidation was carried at -10 °C for 8 h. [b] All reactions were carried out with olefin (0.2 mmol), ketone **6-1d** (0.06 mmol), tetrabutylammonium hydrogen sulfate (3.75 mg, 0.01 mmol), Oxone (0.276 mmol), K_2CO_3 (1.16 mmol) CH_3CN-DMM (1:2, v/v) (3 mL) and buffer (0.1M K_2CO_3-AcOH, pH 9.2) (2 mL) at -10 °C for 4 h. [c] Conversion was determined by GC (Chiraldex BD-M) except for entries 2, 3, 7, 8, 11, and 12 in which conversion was determined by ^1H NMR. [d] isolated yield. [e] unless stated otherwise, ee was determined by GC (Chiraldex BD-M). [f] ee was determined by chiral HPLC (Chiracel OD column). [g] ee was determined by chiral HPLC (Chiracel OJ column). [h] The absolute configurations were determined by comparing the measured optical rotations and GC and HPLC trace with reported ones.

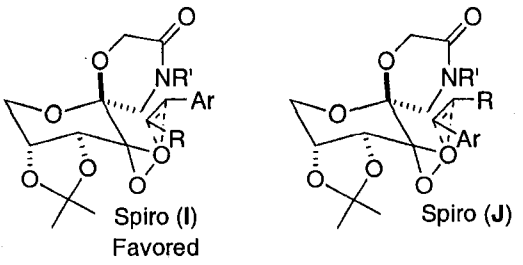


Figure 6.6

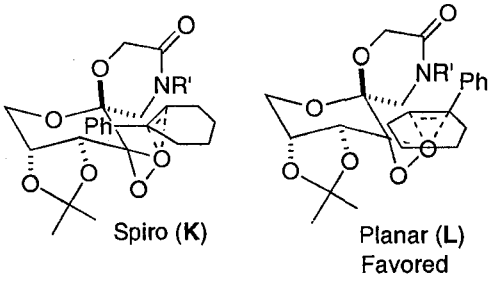


Figure 6.7

The known absolute configurations of selected epoxides (Table 6.2, entries 1, 2, 15, 16, 19, and 21) are consistent with the notion that the epoxidation proceed mainly via

planar transition state **P** (Figure 6.8). A bulky R substituent on the olefin disfavors spiro **O**, thus resulting in higher ee's, as observed. Further improvement of the enantioselectivity will require further disfavoring spiro **N** and/or planar **Q** transition states.

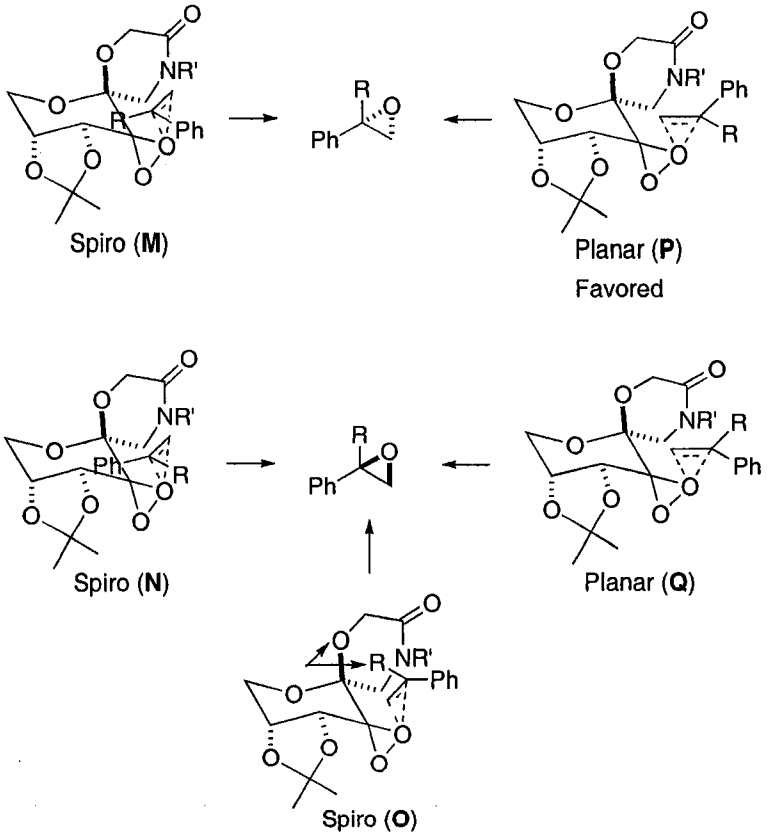


Figure 6.8 The Proposed Competing Transition States for the Epoxidation of 1,1-Disubstituted Terminal Olefins with Ketone **6-1**

6.3 CONCLUSION

In summary, a variety of 1,1-disubstituted terminal olefins can be enantioselectively epoxidized using lactam ketone **6-1d** as catalyst and Oxone as oxidant, giving up to 88% ee. Studies indicate that the epoxidation of 1,1-disubstituted terminal olefins with ketone **6-1** proceeds mainly via a planar transition state. Ketone **6-1** provides a promising lead for further improvement of the enantioselectivity for this challenging class of olefins.

6.4 EXPERIMENTAL

6.4.1 Synthesis and Characterization of Ketones 6-1a-c

(6-3) (b1148). To a mixture of the crude amino salt **6-2** (prepared from D-glucose as previously reported[55]) (14.47 g, 52.0 mmol) in THF (250 mL) was added $NaHCO_3$ (8.7 g, 104.0 mmol). After the resulting mixture was stirred at rt for 1 h, Et_3N (6.83 g, 9.46 mL, 67.6 mmol) was added, followed by a dropwise addition of 2-bromoacetyl bromide (13.65 g, 67.6 mmol) in THF (20 mL) at rt within 1 h. Upon stirring at rt for 6 h, the reaction mixture was filtered and concentrated to give a brown crude syrup which was purified by flash chromatography (silica gel, hexanes /EtOAc = 1/4 to 0/1) to give diol **6-3** as a light brown solid (6.4 g, 36% yield): mp 89-91 °C; $[\alpha]_D^{25}$ = -105.0 (*c* 0.60, MeOH); IR (film) 3343, 1733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.28-4.17 (m, 4H),

3.98 (d, J = 13.6 Hz, 1H), 3.92 (s, 2H), 3.62 (dd, J = 14.0, 7.2 Hz, 1H), 3.57-3.48 (m, 2H), 1.53 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 109.4, 96.8, 76.4, 73.4, 71.7, 60.3, 47.4, 28.6, 28.2, 26.2; HRMS Calcd for $C_{11}H_{16}BrNO_5$ (M-H_2O): 321.0212; Found: 321.0211.

(**6-1a**) (**b1209**, **b1145B**). To a solution of diol **6-3** (1.85 g, 5.4 mmol) in THF (30 mL) was carefully added NaH (95%, 0.301 g, 11.9 mmol) in portions. Upon stirring at rt for 0.5 h, the reaction mixture was quenched with MeOH (0.58 mL), concentrated, and dried under vaccum to give a yellow syrup. To a mixture of the above yellow syrup in dry DCM (50 mL) was added PDC (4.06 g, 10.8 mmol), 3Å MS (2.5 g), and 4 drops of AcOH. Upon stirring at rt for 4 d (TLC showed no alcohol left), the reaction mixture was filtered through a pad of silica gel, and the filter cake was washed by EtOAC/MeOH (10/1). Upon removal of solvent, the mixture was purified by flash chromatography (silica gel, EtOAc) to give ketone **6-1a** as a white solid (0.327 g, 23% yield): mp 186-187 °C; $[\alpha]_D^{25}$ = -61.3 (*c* 0.50, $CHCl_3$); IR (film) 3200, 1749, 1692 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.01 (s, 1H), 4.82 (d, J = 5.6 Hz, 1H), 4.63 (d, J = 5.6, Hz, 1H), 4.32 (d, J = 16.4 Hz, 1H), 4.26 (d, J = 16.4 Hz, 1H), 4.21 (s, 2H), 4.03 (d, J = 13.2 Hz, 1H), 3.37 (dd, J = 13.2, 4.4 Hz, 1H), 1.48 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.6, 166.7, 111.0, 95.1, 78.4, 75.6, 62.5, 59.9, 44.1, 27.4, 26.3; Anal. Calcd. for $C_{11}H_{15}NO_6$: C, 51.36; H, 5.88. Found: C, 51.52; H, 5.88.

(**6-1b**) (**b1213A**). To a solution of ketone **6-1a** (0.171 g, 0.67 mmol) and DMAP (0.0008 g, 0.0065 mmol) in THF (10 mL) was added Boc anhydride (0.160 g, 0.737 mmol).

After the resulting mixture was stirred at rt for 1 d, additional amount of Boc anhydride (0.160 g, 0.737 mmol) was added, and the mixture was stirred for another day at rt (TLC showed most of starting material disappeared). The reaction mixture was concentrated and purified by flash chromatography (silica gel, first hexanes/EtOAc = 2/1, then EtOAc) to give ketone **6-1b** as a colorless syrup (0.1 g, 41% yield) plus some recovered ketone **6-1a**: $[\alpha]_D^{25}$ = -68.0 (*c* 2.0, $CHCl_3$); IR (film) 1781, 1731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.80 (d, *J* = 5.6 Hz, 1H), 4.60 (ddd, *J* = 5.6, 2.0, 0.8 Hz, 1H), 4.35 (d, *J* = 14.4 Hz, 1H), 4.33 (d, *J* = 16.4 Hz, 1H), 4.28 (d, *J* = 16.4 Hz, 1H), 4.27 (dd, *J* = 12.4, 2.0 Hz, 1H), 4.19 (d, *J* = 12.4 Hz, 1H), 3.75 (d, *J* = 14.4 Hz, 1H), 1.55 (s, 9H) 1.49 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.1, 166.8, 150.4, 111.1, 97.0, 84.7, 78.2, 75.6, 64.0, 60.1, 46.0, 28.1, 27.4, 26.3; HRMS Calcd for $C_{16}H_{24}NO_8$ (M+H): 358.1502; Found: 358.1498.

(**6-1c**) (**b1213B**). To a solution of ketone **6-1a** (0.138 g, 0.54 mmol) and DMAP (0.0066 g, 0.054 mmol) in THF (20 mL) was added acetic anhydride (1.1 g, 10.8 mmol). Upon stirring at rt for 12 h, the reaction mixture was concentrated and purified by flash chromatography (silica gel, hexanes/EtOAc = 1/1) to give ketone **6-1c** as a white solid (0.106 g, 66% yield): mp 159-160 °C; $[\alpha]_D^{25}$ = -109.1 (*c* 0.80, $CHCl_3$); IR (film) 1753, 1732, 1693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.78 (d, *J* = 5.6 Hz, 1H), 4.59 (d, *J* = 5.6 Hz, 1H), 4.39 (d, *J* = 16.4 Hz, 1H), 4.33 (d, *J* = 16.4 Hz, 1H), 4.23 (dd, *J* = 13.2, 2.0 Hz, 1H), 4.22 (d, *J* = 14.8 Hz, 1H), 4.18 (d, *J* = 13.2 Hz, 1H), 3.99 (d, *J* = 14.8 Hz, 1H), 2.60 (s, 3H), 1.48 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.0, 171.8, 168.2,

111.2, 96.9, 77.9, 75.5, 63.8, 60.2, 44.1, 27.4, 27.3, 26.2; Anal.Calcd. for $C_{13}H_{17}NO_7$: C, 52.17; H, 5.73. Found: C, 52.06; H, 5.89.

6.4.2 Synthesis and Characterization of Ketones 6-1d-l

Ketone **6-1d**:

(**6-5d**)[11] (**b1329**). Conc. H_2SO_4 (98.5 g, 366 mmol) was added to a suspension of **6-4d** (prepared from D-glucose with 64% yield)[60] (29.4 mL, 529 mmol) and 2,2-dimethoxypropane (135 mL, 1098 mmol) in acetone (853 mL) at 0 °C. The mixture was then stirred at 0 °C (ice water bath) for 90 min in a rotary vaporator without vaccum but open to air. The reaction mixture was quenched by NH_4OH (99 mL), diluted by excess acetone (approximately 3 L) and DCM (approximately 3 L) and dried by Na_2SO_4 (approximately 400 g). The resulting mixture was stirred at rt for 1 h. Then the mixture was filtered through a pad of silica gel (1 cm thick). The filtrate was concentrated and recrystallized by hexane/DCM to give the product as a light yellow solid (90 g, 80 % yield) which was directly used in the next step.

(**6-6d**) (**b0922, b0931, b1036, b1413**). To a solution of amino alcohol **6-5d** (3.09 g, 10.0 mmol) and Et_3N (1.11 g, 1.54 mL, 11.0 mmol) in dry THF (50 mL), a solution of 2-bromoacetyl bromide (2.22 g, 0.95 mL, 11.0 mmol) in dry THF (10 mL) was added dropwise at rt over 2 h. After the resulting mixture was stirred at rt for 3 h, NaH (95%, 0.6 g, 23.7 mmol) was added into the reaction mixture carefully. Upon stirring at rt for 0.5 h, the reaction mixture was quenched with MeOH (0.25 mL) and filtered. The filtrate was concentrated and purified by flash chromatography (silica gel, hexanes/EtOAc = 1/6)

to give lactam **6-6d** as a white solid (1.42 g, 41% yield): mp 198-199 °C; $[\alpha]_D^{25}$ = -144.6 (*c* 1.0, $CHCl_3$); IR (film) 3410, 1661 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.21-7.14 (m, 4H), 4.40-4.36 (m, 1H), 4.30-4.21 (m, 4H), 4.12 (d, *J* = 13.2 Hz, 1H), 3.96 (dd, *J* = 13.2, 2.8 Hz, 1H), 3.62-3.59 (m, 1H), 3.53-3.48 (m, 1H), 3.10-2.88 (m, 1H), 2.33 (s, 3H), 1.51 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 138.4, 137.4, 130.1, 125.8, 109.7, 96.2, 76.5, 73.4, 71.7, 62.7, 60.5, 54.2, 28.2, 26.2, 21.2; HRMS Calcd for $C_{18}H_{24}O_6N$ (M+H): 350.1604; Found: 350.1607.

(6-1d) (b0932, b1038, b1414). AcOH (0.15 mL) was added to a slurry of lactam **6-6d** (4.8 g, 13.76 mmol), PDC (10.3 g, 27.5 mmol), and 3Å MS (6.5 g) in CH_2Cl_2 (300 mL). Upon stirring at rt for 3 d (no starting material left as judged by TLC), the reaction mixture was filtered through a pad of silica gel, and the filter cake was washed with EtOAc. The filtrate was concentrated and purified by flash chromatography (silica gel, hexanes/EtOAc = 3/1) to give ketone **6-1d** as a white solid (4.5 g, 95% yield): mp 184-185 °C; $[\alpha]_D^{25}$ = -86.5 (*c* 1.0, $CHCl_3$); IR (film) 1753, 1674 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.24-7.18 (m, 4H), 4.86 (d, *J* = 5.7 Hz, 1H), 4.66-4.64 (m, 1H), 4.49-4.23 (m, 5H), 3.64 (d, *J* = 13.8 Hz, 1H), 2.36 (s, 3H), 1.47 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.7, 165.2, 138.2, 137.7, 130.2, 125.8, 111.0, 96.1, 78.4, 75.7, 63.2, 59.9, 51.9, 27.3. 26.2, 21.3; HRMS Calcd for $C_{18}H_{22}NO_6$ (M+H): 348.1447; Found: 348.1447; Anal. Calcd. for $C_{18}H_{21}NO_6$: C, 62.24; H, 6.09. Found: C, 62.02; H, 6.01.

Ketone **6-1e**:

(**6-6e**) (**b1319**). To a solution of **6-5e** (prepared from D-glucose in two steps with about 49% yield)[17] (2.4 g, 7.4 mmol) and Et_3N (1.22 mL, 9 mmol) in dry THF (75 mL), 2-bromoacetyl bromide (0.78 mL, 9.0 mmol) was added dropwise at rt within 5 min. The resulting mixture was stirred at rt for 35 min. TLC showed that starting material was consumed, and then additional dry THF (250mL) was added into the reaction mixture. Then the first portion of NaH (60%, 1.32 g, 33 mmol) was added slowly into mixture. The resulting mixture was stirred at rt for 1 h. TLC showed that bromoamide was not completely disappeared. The second part of NaH (60%, 0.50 g, 12.5 mmol) was added into the reaction mixture. The reaction mixture was continued to be stirred at rt for 0.5 h. Then water (0.82 mL, 45.5 mmol) was added slowly into the reaction mixture. The resulting mild yellow mixture was dried by Na_2SO_4 and filtered through a pad of silica gel (1 cm thick). The filtration cake was washed by EtOAc. After solvent was removed, the mixture was purified by crystallization (Hexane/DCM) to give **6-6e** as a yellow solid (2.12 g, 79% yield). This solid product was directly used in the next step reaction. It also can be further purified by flash chromatography (silica gel, hexane/EtOAc = 1/1 to 0/1) to give a white solid; mp = 176-177 °C; $[\alpha]_D^{25}$ = -148.1 (*c* 1.0, $CHCl_3$); IR (film) 3420, 1669, 1653 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.23 (s, 4H), 4.44-4.23 (m, 5H), 4.14 (d, *J* = 13.5Hz, 1H), 3.99 (dd, *J* = 13.5, 2.7 Hz, 2H), 3.65 (m, 1H), 3.58 (d, *J* = 12.9 Hz, 1H), 2.65 (q, *J* = 7.5 Hz, 2H), 1.53 (s, 3H), 1.40 (s, 3H), 1.24 (t, *J* = 7.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.6, 143.7, 138.6, 129.0, 125.9, 109.9, 96.2, 76.6, 73.4, 71.9, 62.8, 60.6, 54.4, 28.7, 28.2, 26.2, 15.6; Anal. Calcd. for $C_{19}H_{25}NO_6$: C, 62.80; H, 6.93; Found: C, 62.90; H, 6.91.

(6-1e) (b1321). To a slurry of **6-6e** (1.08 g, 3.0 mmol), PDC (2.54 g, 6.8 mmol) and 3Å MS (1.7 g) in DCM (50 mL), 4 drops of AcOH were added. The resulting mixture was stirred as rt for 4 d. TLC show the no alcohol was left. The mixture was filtered through a pad of silica gel and the filtration cake was washed by EtOAc. After removal of solvent, the mixture was purified by flash chromatography (silica gel, hexane/EtOAc = 1/1) to give **6-1e** as a colorless oil (0.85 g, 78% yield); $[\alpha]_D^{25}$ = -71.6 (*c* 1.1, $CHCl_3$); IR (film) 1752, 1674 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (m, 4H), 4.86 (d, *J* = 5.6 Hz, 1H), 4.65 (ddd, *J* = 5.6, 2.0, 1.2 Hz, 1H), 4.48-4.24 (m, 5H), 3.65 (d, *J* = 13.6 Hz, 1H), 2.65 (q, *J* = 5.7 Hz, 2H), 1.47 (s, 3H), 1.43 (s, 3H), 1.24 (t, *J* = 5.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.7, 165.2, 142.6, 138.3, 129.6, 125.7, 111.0, 96.2, 78.5, 75.7, 63.3, 59.9, 51.9, 35.4, 33.7, 27.3, 26.3, 22.5, 14.1; Anal. Calcd. for $C_{19}H_{23}NO_6$: C, 63.15; H, 6.41. Found: C, 62.88; H, 6.29.

Ketone **6-1f**:

(6-4f) (b1316). To a mixture of D-glucose (48.2 g, 268.0 mmol), 4-*n*-butyl aniline (48 g, 322 mmol), and water (14.4 mL) was added HOAc (0.288 g, 4.8 mmol). The mixture was rotated on a rotary evaporator (sealed without vacuum) at 90–93 °C for about 0.5 h (during this time a brown solid precipitated from the reaction mixture). After cooling to room temperature, ether–ethanol (3:1, 300 mL) was added (solid on the side of flask was broken up by a spatula). Upon stirring at room temperature for an additional 1 h, the mixture was filtered, washed with ether-ethanol (14:1, 100 mL), ether–ethanol (5:1, 150

mL), ether (50 mL), and dried under vacuum to give **6-4f** as a white solid (46.15 g, 55% yield).

(6-5f) (b1318). Concentrated H_2SO_4 (12 mL, 216 mmol) was added to a suspension of **6-4f** (46 g, 148 mmol) and dimethoxypropane (54.5 mL, 444 mmol) in acetone (400 mL) at 0 °C. The mixture was then stirred at 0 °C (ice water bath) for 90 min in a rotary vaporator without vacuum but not open to air. Initially the viscous reaction mixture became fluid. After time, white product began precipitating out of the mixture, and the viscosity increased. The reaction mixture was quenched by NH_4OH (40 mL, 580 mmol), diluted by excess acetone (estimated 1000 mL) and dried over excess Na_2SO_4. The resulting mixture was stirred at rt for 1 h. Then the mixture was filtered through a pad of silica gel (1cm thick). The filtrate was concentrated and recrystallized (hexane/EtOAc) to give **6-5f** as a light yellow solid (33.5 g, 65% yield). mp = 92-93 °C; $[\alpha]_D^{25} = -115.4$ (*c* 1.1, $CHCl_3$); IR (film) 3386 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.05 (d, *J* = 8.0 Hz, 2H), 6.81 (dd, *J* = 8.0, 2.4 Hz, 2H), 4.26-4.16 (m, 3H), 4.01 (d, *J* = 13.6 Hz, 1H), 3.64-3.61 (m, 2H), 3.27 (dd, *J* = 12.8, 1.6 Hz, 1H), 2.52 (t, *J* = 7.6 Hz, 2H), 1.56 (s, 3H), 1.59-1.51 (m, 2H), 1.39 (s, 3H), 1.39-1.31 (m, 2H), 0.92 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.1, 134.6, 129.4, 115.3, 109.4, 96.4, 77.5, 77.3, 76.9, 73.7, 72.3, 59.6, 51.3, 34.9, 34.0, 28.2, 26.3, 22.5, 14.1; Anal. Calcd for $C_{19}H_{29}NO_5$: C, 64.93; H, 8.32. Found: C, 64.72; H, 8.00.

(6-6f) (b1320). To a solution of **6-5f** (5.4 g, 15.3 mmol) and Et_3N (2.43 mL, 18 mmol) in dry THF (200 mL), 2-bromoacetyl bromide (1.56 mL, 18.0 mmol) was added dropwise at

rt within 5 min. The resulting mixture was stirred at rt for 35 min. TLC showed that starting material was consumed. Then the first part of NaH (60%, 2.1 g, 53 mmol) was added slowly into the mixture. The resulting mixture was stirred at rt for 1 h. TLC showed that bromoamide was not completely converted. The second part of NaH (60%, 0.54 g, 13.5 mmol) was added into the reaction mixture. The reaction mixture was continued to be stirred at rt for 1 h. Then mild yellow mixture was filtered through a pad of silica gel (1 cm thick) and the filtration cake was washed by EtOAc. To the filtrate, MeOH (0.606 mL, 15 mmol) was added. After solvent was removed, the mixture was purified by flash chromatography (silica gel, hexane/EtOAc = 1/1 to 0/1) to give **6-6f** as a light yellow solid (4.62 g, 77% yield). mp = 112-113 °C; $[\alpha]_D^{25}$ = -142.3 (*c* 1.0, $CHCl_3$); IR (film) 3412, 1670 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.21 (s, 4H), 4.44-4.23 (m, 5H), 4.14 (d, *J* = 13.5 Hz, 1H), 3.99 (dd, *J* = 13.5, 2.7 Hz, 2H), 3.65 (d, *J* = 6.6 Hz, 1H), 3.57 (d, *J* = 12.9 Hz, 1H), 2.60 (t, *J* = 7.5 Hz, 2H), 1.64-1.53 (m, 2H), 1.53 (s, 3H), 1.42-1.30 (m, 2H), 1.39 (s, 3H), 0.93 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 142.4, 138.6, 129.5, 125.8, 109.9, 96.1, 76.6, 73.4, 71.9, 62.9, 60.6, 54.4, 35.4, 33.7, 28.2, 26.2, 22.5, 14.1; Anal. Calcd for $C_{21}H_{29}NO_6$: C, 64.43; H, 7.47; Found: C, 64.50; H, 7.34.

(6-1f) (b1323). To the slurry of **6-6f** (3.6 g, 9.2 mmol), PDC (7.18 g, 19 mmol) and 3Å MS (5.0 g) in DCM (200 mL), AcOH (0.1 mL) was added. The resulting mixture was stirred at rt for 3 d. TLC show the no alcohol was left. The mixture was filtered through a pad of silica gel and the filtration cake was washed by EtOAc. After removal of solvent, the mixture was purified by flash chromatography (silica gel, hexane/EtOAc = 2/1 to 1/1)

to give **6-1f** as a white solid (3.5 g, 98% yield); mp 84-86 °C; $[\alpha]_D^{25}$ = -87.0 (*c* 1.1, $CHCl_3$); IR (film) 1753, 1675 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23-7.22 (m, 4H), 4.85 (d, *J* = 5.6 Hz, 1H), 4.65 (d, *J* = 5.6 Hz, 1H), 4.48-4.23 (m, 5H), 3.64 (d, *J* = 13.6 Hz, 1H), 2.61 (t, *J* = 8.0 Hz, 2H), 1.63-1.55 (m, 2H), 1.46 (s, 3H), 1.42 (s, 3H), 1.40-1.31 (m, 2H), 0.93 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.7, 165.2, 142.6, 138.3, 129.6, 125.7, 111.0, 96.2, 78.5, 75.7, 63.3, 59.9, 51.9, 35.4, 33.7, 27.3, 26.3, 22.5, 14.1; Anal. Calcd. for $C_{21}H_{27}NO_6$: C, 64.77; H, 6.99; N, 3.60. Found: C, 64.57; H, 6.86; N, 3.50.

Ketone **6-1g**:

(6-6g) (b1434). To a solution of **6-5g** (prepared from D-glucose in two steps with 37% yield)[11] (3.15 g, 10 mmol) and Et_3N (1.61 mL, 11 mmol) in dry THF (200 mL), 2-bromoacetyl bromide (0.96 mL, 11 mmol) was added dropwise at rt within 5 min. The resulting mixture was stirred at rt for 1 h. TLC showed that diol was gone. Then the NaH (60%, 1.2 g, 30 mmol) was divided into 3 portions and added slowly into mixture within 1 h. The resulting mixture was stirred at rt overnight. Then resulting slurry was quenched by saturated $NaHCO_3$ (5 mL) and diluted by Et_2O (200 mL). The mixture was washed by H_2O (3 × 30 mL). The aqueous solution was extracted by Et_2O (5 × 75 mL). The combined organic layers were dried over Na_2SO_4 and concentrated until about 5 mL solution was left. Solid was crystallized out, filtered, washed with Et_2O (10 mL) and Et_2O/Hexane (1/1, 40 mL) and dried under vacuum to give **6-6g** as a light yellow solid (2.7 g, 74% yield). mp = 169-170°C; $[\alpha]_D^{25}$ = -120.0 (*c* 1.2, $CHCl_3$); IR (film): 3404,

1653 cm^{-1}; ^1H NMR (300M Hz, $CDCl_3$) δ 7.24-7.21 (m, 2H), 6.94-6.91 (m, 2H), 4.44-3.53 (m, 9H), 3.82 (s, 3H), 1.54 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 158.8, 133.8, 127.4, 114.8, 109.9, 96.2, 76.6, 73.4, 71.8, 62.7, 60.6, 55.7, 54.6, 28.2, 26.2; HRMS Calcd for $C_{18}H_{23}NO_7$ (M): 365.1475; Found: 365.1474.

(6-1g) (b1436). To a slurry of **6-6g** (1.5 g, 4.1 mmol), PDC (3.08 g, 8.2 mmol) and 3Å MS (1.8 g) in DCM (100 mL), AcOH (0.04 mL) was added. The resulting mixture was stirred as rt for 3 d. TLC show that no alcohol was left. The mixture was filtered through a pad of silica gel and the filtration cake was washed with EtOAc. After removal of solvent, the mixture was purified by flash chromatography (silica gel, hexane/EtOAc = 1/1 to 1/2) to give **6-1g** as a white solid (0.77 g, 52% yield). mp = 130-132°C; $[\alpha]_D^{25}$ = -91.6 (c 0.7, $CHCl_3$); IR (film) 1753, 1672cm^{-1}; ^1H NMR (400 M Hz, $CDCl_3$) δ 7.24 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 4.86 (d, *J* = 5.6 Hz, 1H), 4.65 (ddd, *J* = 5.6, 1.2, 0.8 Hz, 1H), 4.48-4.24 (m, 5H), 3.82 (s, 3H), 3.62 (d, *J* = 13.6 Hz, 1H), 1.47 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 197.7, 165.3, 158.8, 133.5, 127.3, 114.8, 110.9, 96.1, 78.4, 75.6, 63.2, 59.9, 55.6, 52.1, 27.3, 26.2; HRMS Calcd for $C_{18}H_{21}NO_7$ (M): 363.1318; Found: 363.1321.

Ketone **6-1h:**

(6-6h) (b1135, b0943). To a solution of **6-5h** (prepared from D-glucose in two steps with about 28% yield)[11] (3.14 g, 9.3 mmol), Et_3N (1.3 mL, 9.3 mmol) and $NaHCO_3$ (1.56 g, 18.6mmol) in dry THF (93 mL), 2-bromoacetyl bromide (0.88 mL, 10.2 mmol) in the dry THF (5 mL) was added dropwise at rt with in 1h. The resulting mixture was stirred at

rt for 1h. Then NaH (95 %, 0.446 g, 18.6 mmol) was added into the mixture carefully. The resulting mixture was stirred at rt for 0.5 h. Then the mild yellow mixture was filtered. After organic solvent was removed, the mixture was purified by the flash chromatography (silica gel, hexane/EtOAc = 2/1) to give **6-6h** as light yellow oil (1.08 g, 30% yield). This is directly used in the next step.

(6-1h) (b1142, b1144). The mixture of Oxone(4.84 g, 7.8 mmol) and $NaHCO_3$ (1.96 g, 23.4 mmol) was added in portion to solution of **6-6h** (1.0 g, 2.6 mmol) in 4×10^{-4} EDTA solution (3 mL) and CH_3CN (4.5 mL) within 1 h. The mixture was stirred for 1 h. TLC show sulfide was completely converted. The reaction mixture was extracted by EtOAc, dried over Na_2SO_4, and concentrated to give a crude sulfone. The mixture of crude sulfone, PDC (0.993 g, 2.64 mmol), 3Å MS (0.622 g) and a drop of AcOH in dry DCM (20 mL) was stirred at rt for 6 d. Then the mixture was filtered through a pad of silica gel and the filtration cake was washed with EtOAc. After removal of solvent, the mixture was purified by flash chromatography (silica gel, hexane/EtOAc = 2/1) to give **6-1h** as a colorless oil (0.45 g, 42% yield). $[\alpha]_D^{25}$ = -60.0 (c 1.3, $CHCl_3$); IR (film) 1753, 1681cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 8.8 Hz, 2H), 7.61 (d, J = 8.8 Hz, 2H), 4.86 (d, J = 5.6 Hz, 1H), 4.65 (dd, J = 5.6, 0.8 Hz, 2H), 4.46-4.43 (m, 3 H), 4.30 (m, 2H), 3.72 (d, J = 13.2 Hz, 1H), 3.06 (s, 3H), 1.46 (s, 3H), 1.42(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.5, 165.6, 145.5, 138.8, 128.8, 125.9, 111.1, 96.3, 78.3, 75.6, 63.4, 60.1, 51.1, 44.8, 27.3, 26.2; HRMS Calcd. for $C_{18}H_{21}NO_8S$ (M^+) 411.0987. Found: 411.0983.

Ketone **6-1i:**

(6-6i) (b1424). Water (28.5 mL) and acetic acid (0.566 g, 0.54 mL, 9.43 mmol) were added in to a mixture of D-glucose (95.4 g, 530 mmol) and 3,5-dimethylaniline (77 g, 636 mmol) in a 1 L round bottom flask. This mixture was stirred at 90°C (water bath temperature) by a rotary evaporator without vacuum but open to air for 1.5 h. The reaction flask was then removed from the warm water bath and allowed to cool to rt. MeOH (200 mL) was added and the mixture was stirred at rt overnight to form yellow slurry. After the resulting slurry was filtered, the filter cake was washed with EtOH/Et_2O (v/v, 1/4) and ether and dried under vacuum overnight to give **6-6i** as a light yellow solid (59 g, 39% yield).

(6-5i) (b1432). Concentrated H_2SO_4 (7.2 mL, 130 mmol) was added to a suspension of **6-6i** (28.3 g, 100 mmol) and dimethoxypropane (37 mL) in acetone (250 mL) at 0 °C. The mixture was then stirred at 0 °C (ice water bath) for 90 min in a rotary vaporator without vacuum but not open to air. Initially the viscous reaction mixture became fluid. After time, the product began precipitating out of the mixture. The reaction mixture was quenched by NH_4OH (22 mL, 315 mmol), diluted by DCM (500 mL) and dried over excess Na_2SO_4. The resulting mixture was filtered through a pad of silica gel. The filtrate was concentrated and purified by flash chromatography (silica gel, hexane/EtOAC = 3/1 to 2/1) to give **6-5i** as a yellow syrup (21.8 g, 67% yield). $[\alpha]_D^{25}$ = -91.7 (c 2.1, $CHCl_3$); IR (film) 3392 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.49 (s, 1H), 6.44 (s, 2H), 4.27-4.12 (m, 3H), 4.02 (d, J = 13.2 Hz, 1H), 3.66 (d, J = 13.2 Hz, 1H), 3.55 (d, J = 6.9 Hz, 1H), 3.22 (d, J = 13.2 Hz, 1H), 2.26 (s, 6H), 1.58 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 148.1, 139.4, 121.5, 112.7, 109.5, 96.5, 77.6, 73.8, 72.4, 59.7, 50.4, 28.4, 26.4, 21.6; HRMS Calcd for $C_{17}H_{25}NO_5$ (M^+): 323.1733; Found: 323.1732.

(6-6i) (b1439). To a solution of amino alcohol (3.8 g, 11.7 mmol) and Et_3N (1.3 g, 1.79 mL, 12.9 mmol) in dry THF (100 mL), 2-bromoacetyl bromide (2.60 g, 1.12 mL, 12.9 mmol) was added dropwise at rt within 5 min. The resulting mixture was stirred at rt for 1 h. TLC showed that diol was gone. Then NaH (60%, 1.4 g, 35.1 mmol) was divided to 2 portions and added slowly into mixture within 1 h. The resulting mixture was stirred at rt for 6 h. Then slurry mixture was quenched by 5 mL saturated $NaHCO_3$ and diluted by Et_2O (100 mL). The mixture was washed by H_2O (3 × 30 mL). The aqueous solution was extracted by Et_2O (5 × 75 mL). The combined organic layers was dried by Na_2SO_4 and concentrated until about 3mL solution was left. Solid was crystallized out, filtered, washed by Et_2O (10 mL) and Et_2O/Hexane (v/v, 1/1, 10 mL) and dried under vacuum to give **6-6i** as a light brown solid (1.7 g, 40% yield). mp = 186-188 °C; $[\alpha]_D^{25}$ = -115.3 (c 1.0, $CHCl_3$); IR (film) 3420, 1653 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.93 (s, 1H), 6.92 (s, 2H), 4.49-4.23 (m, 5H), 4.15 (d, J = 13.5 Hz, 1H), 3.99 (dd, J = 13.5, 2.7 Hz, 1H), 3.64 (t, J = 7.2 Hz, 1H), 3.55 (d, J = 12.3Hz, 1H), 2.32 (s, 6H), 1.53 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 140.9, 139.4, 129.5, 123.9, 109.9, 96.1, 76.6, 73.5, 71.9, 62.8, 60.6, 54.5, 28.2, 26.2, 21.4; Anal. Calcd. for $C_{19}H_{25}NO_6$: C, 62.80; H, 6.93. Found: C, 62.90; H, 6.78.

(6-1i) (b1442). To a slurry of **6-6i** (1.1 g, 3.03 mmol), PDC (2.27 g, 6.06 mmol) and 3Å MS (1.36 g) in DCM (100 mL), AcOH (0.04 mL) was added. The resulting mixture was

stirred as rt. for 2 d. TLC show the no alcohol was left. The mixture was filtered through a pad of silica Gel and filtration cake was washed by EtOAc. After removal of solvent, the mixture was purified by flash column (silica gel, hexane/EtOAc = 2/1 to 1/1) to give **6-1i** as a white solid (0.99 g, 91% yield). mp 153-155 °C; $[\alpha]_D^{25}$ = -95.1 (*c* 0.70, $CHCl_3$); IR (film) 1754, 1675 cm^{-1}; ^1H NMR (300 M Hz, $CDCl_3$) δ 6.94 (s, 1H), 6.93 (s, 2H), 4.85 (d, *J* = 5.4 Hz, 1H), 4.65 (d, *J* = 5.4 Hz, 1H), 4.48-4.23 (m, 5H), 3.62 (d, *J* = 13.5 Hz, 1H), 2.32 (s, 6H), 1.46 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.7, 165.1, 140.6, 139.4, 129.7, 123.8, 111.0, 96.1, 78.5, 75.7, 63.2, 59.9, 52.0, 27.4, 26.3, 21.4; Anal. Calcd. for $C_{19}H_{23}NO_6$: C, 63.15; H, 6.41. Found: C, 63.41; H, 6.60.

Ketone **6-1j**:

(6-4j)[56] (b1437, b1440, b1445). To a slurry of 9-aminoflurene hydrochloride (25.0 g, 115.0 mmol) in $CHCl_3$ (500 mL), a solution of NaOH (5.52 g, 138.0 mmol) in water (50 mL) was added. The resulting mixture was stirred at rt overnight. The layers were separated, and the aqueous layer was extracted by $CHCl_3$ (80 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to give 9-aminoflurene (20.3 g, 98% yield) which was directly used for next step without further purification.

To a mixture of D-Glucose (24.1 g, 134.0 mmol) and 9-aminoflurene (20.3 g, 112.0 mmol) were added acetic acid (3.2 g, 3.1 mL, 53.0 mmol), EtOH (21 mL), and water (13.4 mL). The mixture was rotated on a rotary evaporator open to air at rt for 6 h (a spatula was occasionally used to break the hard clumps). Upon standing at rt overnight, the mixture was diluted with EtOAc (70 mL) and stirred at rt for 1 h. The resulting slurry

was filtered and washed by a mixture of hexanes and EtOAc (1/1, v/v, 60 mL). The filter cake was dried under vacuum to give a white solid (28.0 g, 72% yield) which is directly used in next step without further purification.

To a solution of the above white solid (27.0 g, 78.6 mmol) in isopropanol (195 mL), a solution of oxalic acid (10.6 g, 117.9 mmol) in isopropanol (130 mL) was added. Upon stirring at 70 °C for 5 h, the reaction mixture was cooled to rt, filtered, and washed with ether. The filter cake was dried under vacuum to give **6-6j** as a crude light brown solid (26.0 g, 96% yield) which is directly used in next step without further purification.

(6-5j) (b1447). Concentrated H_2SO_4 (3.64 mL, 65.6 mmol) was added to a suspension of the above compound (15.0 g, 43.7 mmol) and trimethyl orthoformate (9.26 g, 9.56 mL, 87.4 mmol) in acetone (300 mL) at 0 °C. Upon stirring at 0 °C (ice-water bath) for 40 min, the reaction mixture was quenched with NH_4OH (9.0 mL), diluted with acetone (about 500 mL), and dried over excess Na_2SO_4 with stirring at rt for 1 h. The reaction mixture was filtered through a pad of silica gel, and the filtrate was concentrated until small amount of solution was left (10 mL). A solid was crystallized, filtered, and washed by acetone to give diol 6-5**j** as a white solid (7.0 g, 42% yield): mp 139-140 °C (decompose); $[\alpha]_D^{25}$ = -136.0 (*c* 1.0, $CHCl_3$); IR (film) 3068, 1601 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (t, *J* = 7.2 Hz, 2H), 7.70 (t, *J* = 7.2 Hz, 2H), 7.45 (t, *J* = 7.2 Hz, 1H), 7.42 (t, *J* = 7.2 Hz, 1H), 7.34 (t, *J* = 7.2 Hz, 1H), 7.25 (t, *J* = 7.2 Hz, 1H), 5.83 (s, 1H), 4.45 (t, *J* = 6.0 Hz, 1H), 4.15-4.12 (m, 2H), 3.72 (d, *J* = 13.2 Hz, 1H), 3.56 (d, *J* = 6.4 Hz, 1H), 2.69 (d, *J* = 12.8 Hz, 1H), 2.45 (d, *J* = 12.8 Hz, 1H), 2.18 (s, 1H), 1.29 (s, 3H), 1.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 142.0, 141.8, 138.2, 137.9, 130.1, 128.5,

128.4, 126.4, 126.1, 120.6, 109.1, 93.9, 75.8, 73.2, 60.6, 60.0, 48.6, 27.7, 25.8; HRMS. Calcd. for $C_{22}H_{26}NO_5$ (M+H): 384.1805; Found: 384.1810.

(6-6j) (b1448). To a solution of diol **6-5j** (1.5 g, 3.92 mmol) and Et_3N (0.435 g, 0.60 mL, 4.31 mmol) in dry THF (125 mL), 2-bromoacetyl bromide (0.87 g, 0.375 mL, 4.31 mmol) was added dropwise at rt within 5 min. After the resulting mixture was stirred at rt for 2 h and 10 min (TLC showed diol **6-5j** gone), NaH (60%, 0.627 g, 15.7 mmol) was added slowly. Upon stirring at rt for 2 d, the slurry mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL), diluted with Et_2O (100 mL), washed with H_2O (3×15 mL). The organic layers was dried over Na_2SO_4, concentrated, dissolved in DCM, washed with H_2O, and dried over Na_2SO_4, filtered, concentrated, and recrystallized in DCM-Et_2O-Hexanes to give alcohol **6-6j** as a white solid (0.905 g, 55% yield): mp 197-198 °C; $[\alpha]_D^{25}$ = -163.5 (*c* 0.5, $CHCl_3$); IR (film) 3364, 1646 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.74-7.69 (m, 2H), 7.52-7.29 (m, 6H), 6.91 (s, 1H), 4.50 (d, *J* = 16.5 Hz, 1H), 4.38 (d, *J* = 16.5 Hz, 1H), 4.22 (dd, *J* = 6.0, 2.1 Hz, 1H), 4.15 (t, *J* = 6.3 Hz, 1H), 4.00 (d, *J* = 13.5 Hz, 1H), 3.90 (dd, *J* = 13.5, 2.4 Hz, 1H), 3.34 (t, *J* = 6.3 Hz, 1H), 3.32 (d, *J* = 12.6 Hz, 1H), 2.43 (d, *J* = 12.6 Hz, 1H), 2.20 (d, *J* = 6.3 Hz, 1H), 1.29 (s, 3H), 1.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 141.6, 141.1, 140.9, 129.1, 129.0, 128.3, 127.9, 125.7, 125.1, 120.5, 120.1, 109.7, 95.6, 75.9, 73.2, 71.0, 62.5, 60.7, 58.1, 45.8, 27.6, 26.0; HRMS. Calcd. for $C_{24}H_{26}NO_6$ (M+H): 424.1755; Found: 424.1766.

(6-1j) (b1450). To a slurry of alcohol **6-6j** (0.905 g, 2.14 mmol), PDC (1.609 g, 4.28 mmol), and 3Å MS (1.127 g) in DCM (80 mL), AcOH (0.05 mL) was added. Upon

stirring at rt for 2 d (TLC showed no alcohol left), the reaction mixture was filtered through a pad of silica gel, and the filter cake was washed by EtOAc. The filtrate was concentrated and purified by flash chromatography (silica gel, hexanes/EtOAc = 2/1 to 1/1) to give ketone **6-1j** as a white solid (0.67 g, 74% yield): mp 225-226 °C; $[\alpha]_D^{25}$ = -114.4 (*c* 0.80, $CHCl_3$); IR (film) 1755, 1661 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (t, *J* = 6.8 Hz, 2H), 7.48-7.41 (m, 4H), 7.33 (t, *J* = 7.3 Hz, 2H), 6.91 (s, 1H), 4.72 (d, *J* = 5.6 Hz, 1H), 4.58 (d, *J* = 5.6 Hz, 1H), 4.54 (d, *J* = 16.4 Hz, 1H), 4.45 (d, *J* = 16.4 Hz, 1H), 4.22-4.10 (m, 2H), 3.40 (d, *J* = 13.2 Hz, 1H), 4.51 (d, *J* = 13.2 Hz, 1H), 1.33 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.6, 165.8, 141.7, 141.6, 140.8, 140.6, 129.3, 129.2, 128.2, 128.0, 125.5, 125.1, 120.6, 120.3, 111.0, 95.9, 78.4, 75.6, 62.6, 60.1, 58.1, 43.5, 27.1, 26.1; Anal. Calcd. for $C_{24}H_{23}NO_6$: C, 68.40; H, 5.50. Found: C, 68.55; H, 5.71.

Ketone **6-1k:**

(6-5k) (b1420).

To a mixture of D-glucose (18.0 g, 100 mmol) and 1-hexylamine (15.15 g, 150 mmol) was added acetic acid (2.4 g, 40 mmol), EtOH (10 mL) and water (10 mL). The mixture was stirred at rt for 30 min, stand at rt for 2 h. The solid was filtered, washed with EtOAc and dried under vacuum to give a white solid (20.8 g, 79%) as crude product.

To above white solid, was added *i*-PrOH (150 mL) and oxalic acid (8.5g, 94 mmol) in *i*-PrOH (100 mL). Upon stirring at 70 C for 5 h, the reaction mixture was cooled to rt,

filtered, washed with ether and dired under vaccum to get the crude **6-4k** (20 g, 71% yield)

To a suspension of **6-4k** (9.71 g, 36.9 mmol) in acetone (420 mL) was added $HC(OMe)_3$ (6.75 mL) and concentrated H_2SO_4 (2.74 mL, 49.3 mmol) at 0 °C. Upon stirring at 0 °C for 1 h, NH_4OH (27.9 mL, 404 mmol) and excess amount of Na_2SO_4 was added. Resulting slurry was filtered. The filtrate was concentrated and purified by flash chromatography (silica gel, Et_2O) to give **6-5k** as a colorless syrup (3.8 g, 34 %) which is directly used in next step.

(6-6k) (b1438). To a solution of amino alcohol (1.18 g, 3.9 mmol) and Et_3N (0.595 mL, 4.28 mmol) in dry THF (50 mL), 2-bromoacetyl bromide (0.372 mL, 4.28 mmol) was added dropwise at rt within 5min. The resulting mixture was stirred at rt for 1 h10 min. TLC showed that diol was gone. Then the NaH (60%, 0.624 g, 15.6 mmol) was added slowly into mixture. The resulting mixture was stirred at rt for 2 d. Then slurry mixture was quenched by saturated $NaHCO_3$ (2.5 mL) and diluted by Et_2O (100 mL). The mixture was washed by H_2O (3 × 10mL). The aqueous solution was extracted by Et_2O (5 × 35 mL). The combined organic layers was dried by Na_2SO_4, concentrated and purified by flash chromatography (silica gel, EtOAc/hexane = 2/1 to 1/0) to give **6-6k** as a white solid (0.5 g, 37% yield); mp = 98-99 °C; $[\alpha]_D^{25}$ = -121.8 (*c* 1.1, $CHCl_3$); IR (film) 3299, 1641 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.26-4.03 (m, 5H), 3.90-3.85 (m, 2H), 3.59 (d, *J* = 6.8 Hz, 1H), 3.41-3.29 (m, 2H), 3.15 (d, *J* = 9.6 Hz, 1H), 1.60-1.41(m, 2H), 1.53 (s, 3H), 1.37 (s, 3H), 1.32-1.19 (m, 6H), 0.88-0.84 (m, *J* = 6.8 Hz, 3H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 109.7, 96.1, 76.5, 73.4, 71.7, 62.2, 60.3, 50.4, 46.5, 31.7, 28.2,

26.7, 26.5, 26.2, 22.7, 14.2. Anal Calcd. for $C_{17}H_{29}NO_6$: C, 59.46; H, 8.51; Found: C, 59.29; H, 8.59.

(b1444) (6-1k). To a slurry of **6-6k** (0.4 g, 1.16 mmol), PDC (0.872 g, 2.32 mmol) and 3Å MS (0.457 g) in DCM (40 mL), AcOH (0.013 mL) was added. The resulting mixture was stirred as rt for 3 d. TLC show the no alcohol was left. The mixture was filtered through a pad of silica gel and filtration cake was washed by EtOAc. After removal of solvent, the mixture was purified by flash chromatography (silica gel, hexane/EtOAc= 1/1) to give **6-1k** as a white solid (0.25 g, 63% yield); mp 74-75 °C; $[\alpha]_D^{25}$ = -72.9 (*c* 0.70, $CHCl_3$); IR (film) 1755, 1663 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.82 (d, *J* = 5.4 Hz, 1H), 4.62 (dd, *J* = 5.4, 1.5 Hz, 1H), 4.32-4.16 (m, 4H), 3.98 (d, *J* = 13.5 Hz, 1H), 3.41 (t, *J* = 7.5 Hz, 2H), 3.25 (d, *J* = 13.5 Hz, 1H), 1.62-1.26 (m, 8H), 1.49 (s, 3H), 1.42 (s, 3H), 0.89 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.9, 164.7, 110.9, 95.9, 78.5, 75.7, 62.6, 59.7, 48.1, 46.6, 31.7, 27.4, 26.8, 26.5, 26.3, 22.7, 14.2; Anal. Calcd. for $C_{17}H_{27}NO_6$: C, 59.81; H, 7.97. Found: C, 59.87; H, 8.12.

Ketone **6-1l:**

(6-6l) (b1608). In a 100 mL round-bottomed flask, 2-bromo acetylbromide (0.300 mL, 3.45 mmol) was dropwise added into the mixture of **6-5l** (prepared by Dr. Lianhe Shu through a reaction sequence similar to **6-5j** with 21% yield) (1.215 g, 3.14 mmol) and triethylamine (0.481 mL, 3.45 mmol) in THF (90 mL) to give a brown suspension. The resulting mixture was stirred at rt for 2 h. Then sodium hydride (60%, 0.502 g, 12.54 mmol) were added and the mixture was stirred at rt overnight. The mixture was quenched

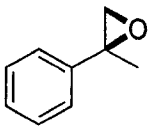
by saturated $NaHCO_3$ (5 mL) and diluted by Et_2O (100 mL). The mixture was washed with water (3 × 10 mL). The combined aqueous solution was extracted with ether (3 × 35 mL). The combined organic layer was dried over sodium sulfate, filtrated and concentrated to give **6-6l** as a yellow solid (1.15 g, 86 % yield), which was directly used for next step reaction.

(6-1l) (b1610). In a 100 mL round-bottomed flask, PDC (1.549 g, 4.12 mmol) was added into the mixture of alcohol (0.880 g, 2.058 mmol), 3Å MS (1.0g) and acetic acid (0.059 mL, 1.029 mmol) in DCM (20 mL) to give a brown suspension. The resulting mixture was stirred at rt for 4 d. Then the mixture was filtered through a pad of silica gel and filtration cake was washed by EtOAc. After solvent was removed, the residue was purified by flash chromatography (silica gel; hexane/EtOAc = 2/1 to 3/2) to give a colorless syrup (0.330 g, 38 % yield). $[\alpha]_D^{25}$ = -53.8 (*c* 0.9, $CHCl_3$); IR (film) 1755, 1662 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.82 (d, *J* = 5.7 Hz, 1H), 4.63 (dt, *J* = 5.7, 1.2 Hz, 1H), 4.26 (d, *J* = 5.1 Hz, 2H), 4.20 (s, 2H), 4.98 (d, *J* = 13.2 Hz, 1H), 3.41 (t, *J* = 7.8 Hz, 2H), 3.25 (d, *J* = 13.2 Hz, 1H), 1.64-1.20 (m, 20H), 1.49 (s, 3H), 1.43 (s, 3H), 0.90 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.9, 164.7, 110.9, 95.9, 78.6, 75.7, 62.6, 59.8, 48.1, 46.7, 32.1, 29.85, 29.78, 29.72, 29.6, 29.5, 27.4, 26.9, 26.87, 26.3, 22.9, 14.4; HRMS Calcd for $C_{23}H_{40}NO_6$ (M^++1): 426.2850; Found: 426.2843.

6.4.3 Asymmetric Epoxidation

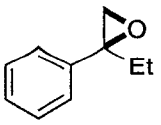
Representative Epoxidation Procedure (Table 6.2, entry 19). To a solution of the olefin (0.324 g, 0.20 mmol), tetrabutylammonium hydrogen sulfate (0.0038 g, 0.010 mmol), and ketone (0.0208 g, 0.06 mmol) in dioxane (3 mL) was added buffer (0.1 M K_2CO_3-AcOH in 4 x 10^{-4} M aqueous EDTA, pH = 9.3) (2 mL) with stirring. After the mixture was cooled to -10 °C (bath temperature), a solution of Oxone (0.20 M in 4 x 10^{-4} M aqueous EDTA, 1.6 mL) (0.197 g, 0.32 mmol) and a solution of K_2CO_3 (0.84 M in 4 x 10^{-4} M aqueous EDTA, 1.6 mL) (0.185 g, 1.344 mmol) were added separately and simultaneously via a syringe pump over a period of 2 h. The reaction mixture was quenched with hexanes, extracted with EtOAc, dried over Na_2SO_4, filtered, concentrated, and purified by flash chromatography (silica gel was buffered with 1% Et_3N in organic solvent; hexanes/Et_2O=5/1 as eluent) to give the epoxide as a white solid (0.027 g, 76% yield, 87% ee).

(Table 6.2, entry 1)[57] (b0941c, mxzhao-17-14-3).



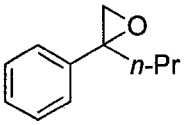
Colorless oil; $[\alpha]_D^{25}$ = +13.0 (*c* 0.80, $CHCl_3$) (62% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.27 (m, 5H), 2.99 (d, *J* = 5.4 Hz, 1H), 2.82 (d, *J* = 5.4 Hz, 1H), 1.74 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.4, 128.5, 127.7, 125.5, 57.3, 57.0, 22.0.

(Table 6.2, entry 2) (mxzhao-17-14-3).



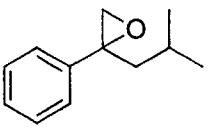
Colorless oil; $[\alpha]_D^{25}$ = +26.1 (*c* 0.70, $CHCl_3$) (78% ee); IR (film) 1496, 1463, 1448 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41-7.29 (m, 5H), 3.00 (d, *J* = 5.7 Hz, 1H), 2.76 (d, *J* = 5.7 Hz, 1H), 2.28-2.16 (m, 1H), 1.89-1.77 (m, 1H), 0.96 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.2, 128.5, 127.5, 126.2, 61.1, 55.6, 28.5, 9.2; HRMS Calcd for $C_{10}H_{12}O$ (M): 148.0888; Found: 148.0889.

(Table 6.2, entry 3) (mxzhao-17-16-4).



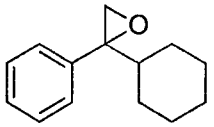
Colorless oil; $[\alpha]_D^{25}$ = +26.1 (*c* 1.4, $CHCl_3$) (75% ee); IR (film) 1496, 1465, 1448 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.25 (m, 5H), 2.96 (d, *J* = 5.4 Hz, 1H), 2.74 (d, *J* = 5.4 Hz, 1H), 2.21-2.11 (m, 1H), 1.77-1.67 (m, 1H), 1.47-1.32 (m, 2H), 0.93 (t, *J* = 7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.4, 128.5, 127.5, 126.2, 60.6, 55.6, 37.8, 18.5, 14.4; HRMS Calcd for $C_{11}H_{14}O$ (M): 162.1045; found: 162.1046; Anal. Calcd. for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.22; H, 8.80.

(Table 6.2, entry 4) (mxzhao-18-18).



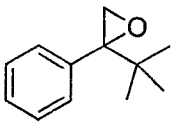
Colorless oil; $[\alpha]_D^{25}$ = +31.1 (*c* 0.90, $CHCl_3$) (74% ee); IR (film) 1496, 1466, 1448 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41-7.25 (m, 5H), 2.87 (d, *J* = 5.7 Hz, 1H), 2.72 (d, *J* = 5.7 Hz, 1H), 2.14 (dd, *J* = 13.8, 6.0 Hz, 1H), 1.66 (septet, *J* = 6.6 Hz, 1H), 1.55 (dd, *J* = 13.8, 8.1 Hz, 1H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.4, 128.5, 127.5, 126.3, 60.2, 55.1, 44.8, 25.6, 23.6, 22.9. HRMS Calcd for $C_{12}H_{16}O$ (M): 176.1201; Found: 176.1206; Anal. Calcd. for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.69; H, 9.30.

(Table 6.2, entry 5) (b1519a).



Colorless oil; $[\alpha]_D^{25}$ = +35.2 (*c* 1.0, $CHCl_3$) (77% ee); IR (film) 1495, 1447 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37-7.26 (m, 5 H), 3.02 (d, *J* = 5.7 Hz, 1 H), 2.70 (d, *J* = 5.7 Hz, 1H), 1.82-1.56 (m, 6H), 1.26-0.95 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.9, 128.1, 127.51, 127.46, 64.5, 53.1, 43.2, 29.0, 28.3, 26.5, 26.3, 26.2; Anal. Calcd. for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.33; H, 8.74.

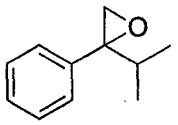
(Table 6.2, entry 6) (mxzhao-17-18-4).



Colorless oil; $[\alpha]_D^{25}$ = +53.3 (*c* 0.90, $CHCl_3$) (86% ee); IR (film) 1480, 1462, 1447 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.25 (m, 5H), 3.12 (d, *J* = 5.2 Hz, 1H), 2.66 (d, *J* =

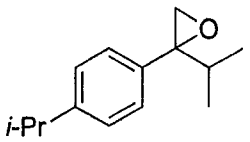
5.2 Hz, 1H), 0.99 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.7, 129.0, 127.5, 127.4, 67.0, 51.0, 34.0, 26.5; Anal. Calcd. for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.53; H, 9.10.

(Table 6.2, entry 7) (mxzhao-17-16-4).



Colorless oil; $[\alpha]_D^{25}$ = +33.5 (*c* 1.1, $CHCl_3$) (84% ee); IR (film) 1496, 1468 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39-7.26 (m, 5H), 3.00 (d, *J* = 5.4 Hz, 1H), 2.73 (d, *J* = 5.4 Hz, 1H), 2.10 (septet, *J* = 6.9 Hz, 1H), 0.98 (d, *J* = 3.6 Hz, 3H), 0.95 (d, *J* = 3.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.6, 128.1, 127.6, 127.5, 64.7, 53.4, 33.3, 18.7, 18.0; Anal. Calcd. for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.62; H, 8.62.

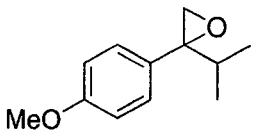
(Table 6.2, entry 8) (mxzhao-17-23-2).



Colorless oil; $[\alpha]_D^{25}$ = +23.6 (*c* 1.0, $CHCl_3$) (82% ee); IR (film) 1512, 1464 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 2.98 (d, *J* = 5.1 Hz, 1H), 2.90 (septet., *J* = 6.9 Hz, 1H), 2.72 (d, *J* = 5.1 Hz, 1H), 2.08 (septet., *J* = 6.9 Hz, 1H), 1.25 (d, *J* = 6.9 Hz, 6H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.2, 136.9, 127.4, 126.1, 64.6, 53.3, 34.0, 33.4, 24.2, 18.7,

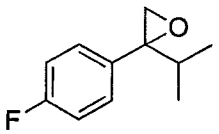
18.1; HRMS Calcd for $C_{14}H_{21}O$ (M+H): 205.1592; Found: 205.1588. Anal. Calcd. for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.42; H, 9.69.

(Table 6.2, entry 9) (b1808).



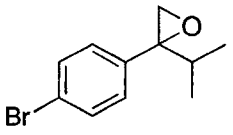
Colorless oil; $[\alpha]_D^{25}$= +22.2 (*c* 1.1, $CHCl_3$) (84% ee); IR (film) 1612 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30-7.27 (m, 2H), 6.88-6.86 (m, 2H), 3.81 (s, 3H), 2.97 (d, *J* = 5.2 Hz, 1H), 2.71 (d, *J* = 5.2 Hz, 1H), 2.03 (septet, *J* = 6.8 Hz, 1H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 131.6, 128.7, 113.5, 64.4, 55.5, 53.5, 33.6, 18.8, 18.1; Anal. Calcd. for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.78; H, 8.22.

(Table 6.2, entry 10) (b1805).



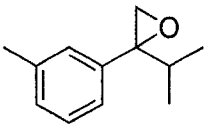
Colorless oil; $[\alpha]_D^{25}$ = +28.2 (*c* 1.1 $CHCl_3$) (74% ee); IR (film) 1606 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.32 (m, 2H), 7.04-7.00 (m, 2H), 2.99 (d, *J* = 5.2 Hz, 1H), 2.69 (d, *J* = 5.2 Hz, 1H), 2.04 (septet, *J* = 6.8 Hz, 1H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 161.0, 135.3, 129.2, 129.1, 115.1, 114.9, 64.3, 53.5, 33.4, 18.7, 18.0; Anal. Calcd. for $C_{11}H_{13}FO$: C, 73.31; H, 7.27. Found: C, 73.53; H, 7.42.

(Table 6.2, entry 11) (b1816).



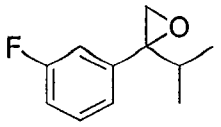
Colorless oil; $[\alpha]_D^{25}$ = +21.7 (*c* 1.2, $CHCl_3$) (78% ee); IR (film) 1593 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48-7.45 (m, 2H), 7.26-7.23 (m, 2H), 3.00 (d, *J* = 5.2 Hz, 1H), 2.66 (d, *J* = 5.2 Hz, 1H), 2.07 (septet, *J* = 6.8 Hz, 1H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ δ 138.7, 131.3, 129.2, 121.6, 64.2, 53.5, 33.1, 18.7, 17.9; Anal. Calcd. for $C_{11}H_{13}BrO$: C, 54.79; H, 5.43. Found: C, 54.72; H, 5.34.

(Table 6.2, entry 12) (b1742).



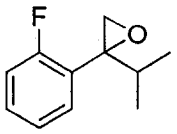
Colorless oil; $[\alpha]_D^{25}$ = +30.9 (*c* 1.0, $CHCl_3$) (82% ee); IR (film) 1608 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24-7.09 (m, 4H), 2.99 (d, *J* = 5.2 Hz, 1H), 2.71 (d, *J* = 5.2 Hz, 1H), 2.36 (s, 3H), 2.09 (septet, *J* = 6.8 Hz, 1H), 0.96 (d, *J* = 7.2 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.5, 137.7, 128.3, 128.1, 128.0, 124.6, 64.7, 53.4, 33.3, 21.7, 18.7, 18.1; Anal. Calcd. for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.96; H, 8.97.

(Table 6.2, entry 13) (b1825).



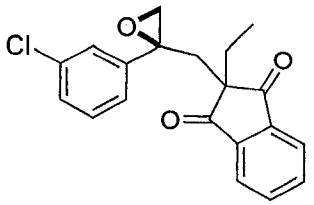
Colorless oil; $[\alpha]_D^{25}$ = +35.7 (*c* 1.4, $CHCl_3$) (81% ee); IR (film) 1616 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33-7.27 (m, 1H), 7.15 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.10-7.07 (m, 1H), 7.00-6.95 (ddd, *J* = 8.4, 2.8, 0.8 Hz, 1H), 3.01 (d, *J* = 5.2 Hz, 1H), 2.69 (d, *J* = 5.2 Hz, 1H), 2.12 (septet, *J* = 6.8 Hz, 1H), 0.97 (d, *J* = 7.2 Hz, 3H), 0.95 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0, 161.6, 142.43, 142.36, 129.8, 129.7, 122.9, 114.6, 114.5, 114.4, 114.3, 64.1, 53.6, , 32.9, 18.7, 17.8; Anal. Calcd. for $C_{11}H_{13}FO$: C, 73.31; H, 7.27. Found: C, 73.50; H, 7.39.

(Table 6.2, entry 14) (b1739).



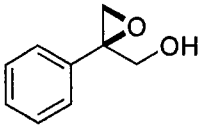
Colorless oil; $[\alpha]_D^{25}$ = +53.1 (*c* 1.5, $CHCl_3$) (88% ee); IR (film) 1617 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41-7.37 (td, *J* = 7.2, 1.2 Hz, 1H), 7.32-7.26 (m, 1H), 7.15-7.11 (td, *J* = 7.6, 1.2 Hz, 1H), 7.06-7.01 (m, 1H), 3.05 (d, *J* = 5.2 Hz, 1H), 2.81 (d, *J* = 5.2 Hz, 1H), 2.02 (septet, *J* = 6.8 Hz, 1H), 0.98-0.94 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 159.4, 130.5, 130.4, 129.6, 129.5, 126.8, 126.7, 123.9, 123.9, 115.5, 115.3, 61.4, 52.5, 33.9, 18.2, 17.9; Anal. Calcd. for $C_{11}H_{13}FO$: C, 73.31; H, 7.27. Found: C, 73.12; H, 6.93.

(Table 6.2, entry 15) (b1611).



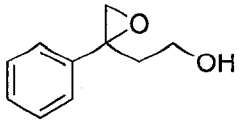
Colorless oil; $[\alpha]_D^{25}$ = -34.9 (*c* 0.80, $CHCl_3$) (66% ee); IR (film) 1744, 1708 cm^{-1}; ^1H NMR (400 MHz) δ 7.93-7.73 (m, 4H), 7.11-6.99 (m, 3H), 6.82 (s, 1H), 2.84 (d, *J* = 5.2 Hz, 1H), 2.77 (d, *J* = 14.0 Hz, 1H), 2.56 (d, *J* = 14.0 Hz, 1H), 2.48 (d, *J* = 5.2 Hz, 1H), 1.80 (q, *J* = 7.6 Hz, 2H), 0.65 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz) δ 203.4, 203.1, 142.4, 141.4, 135.7, 135.6, 134.2, 129.6, 128.1, 126.3, 124.9, 123.0, 122.9, 58.0, 57.2, 56.3, 40.1, 30.1, 8.9; Anal. Calcd. for $C_{20}H_{17}O_3Cl$: C, 70.49; H, 5.03. Found: C, 70.26; H, 5.21.

(Table 6.2, entry 16) (mxzhao-18-26-1).



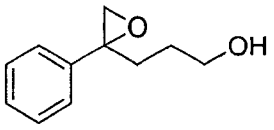
Colorless oil; $[\alpha]_D^{25}$ = +27.4 (*c* 1.3, $CHCl_3$) (77% ee); IR (film) 3420 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41-7.33 (m, 5H), 4.12 (dd, *J* = 12.3, 4.5 Hz, 1H), 4.03 (dd, *J* = 12.6, 9.0 Hz, 1H), 3.29 (d, *J* = 5.1 Hz, 1H), 2.84 (d, *J* = 5.1 Hz, 1H), 1.91 (dd, *J* = 9.0, 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5, 128.8, 128.4, 126.2, 63.2, 60.6, 52.7; HRMS Calcd for $C_9H_9O_2$ (M-H): 149.0603. Found: 149.0601

(Table 6.2, entry 17) (b1505b).



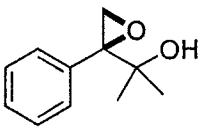
Colorless oil; $[\alpha]_D^{25}$ = +17.5 (*c* 1.3, $CHCl_3$) (72% ee); IR (film) 3411 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41-7.28 (m, 5 H), 3.80-3.68 (m, 2H), 3.14 (d, *J* = 4.8 Hz, 1H), 2.79 (d, *J* = 4.8 Hz, 1 H), 2.52 (ddd, *J* = 14.4, 6.8, 5.6 Hz, 1H), 2.12 (ddd, *J* = 14.4, 6.8, 5.6 Hz, 1H), 2.04 (t, *J* = 5.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.9, 128.7, 128.0, 125.9, 59.7, 59.4, 55.0, 37.2; HRMS Calcd for $C_{10}H_{12}O_2$ (M): 164.0837. Found: 164.0836.

(Table 6.2, entry 18) (mxzhao-18-26-2, b1513, b1511).



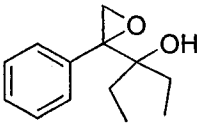
Colorless oil; $[\alpha]_D^{25}$ = +19.8 (*c* 2.1, $CHCl_3$) (74% ee); IR (film) 3396 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39-7.20 (m, 5H), 3.62 (t, *J* = 6.0 Hz, 2H), 2.99 (d, *J* = 5.1 Hz, 1H), 2.75 (d, *J* = 5.1 Hz, 1H), 2.45-2.36 (m, 1H), 2.09 (s, 1H), 1.82-1.72 (m, 1H), 1.67-1.58 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.6, 128.6, 127.6, 126.0, 62.4, 60.3, 56.3, 31.8, 28.0; HRMS Calcd for $C_{11}H_{14}O_2$ (M): 178.0994. Found: 178.0991; Anal. Calcd. for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.33 ; H, 7.90.

(Table 6.2, entry 19) (b1505a).



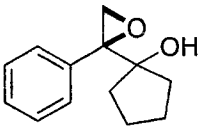
White solid; mp 55-56 °C; $[\alpha]_D^{25}$ = +55.3 (*c* 1.1, $CHCl_3$) (87% ee); IR (film) 3477 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44-7.31 (m, 5 H), 3.37 (d, *J* = 5.2 Hz, 1H), 2.75 (d, *J* = 5.2 Hz, 1 H), 2.14 (s, 1 H), 1.36 (s, 3 H), 1.22 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 128.5, 128.1, 128.0, 70.4, 67.0, 51.1, 26.9, 25.7; HRMS Calcd for $C_{11}H_{12}O$ (M-H_2O): 160.0888; found: 160.0890.

(Table 6.2, entry 20) (b1522b).



Colorless oil; $[\alpha]_D^{25}$ = +38.1 (*c* 1.4, $CHCl_3$) (87% ee); IR (film) 3505 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45-7.40 (m, 2H), 7.40-7.30 (m, 3H), 3.33 (d, *J* = 5.6 Hz, 1H), 2.68 (d, *J* = 5.6 Hz, 1H), 2.06 (s, 1H), 1.83-1.73 (m, 1H), 1.70-1.61 (m, 1H), 1.57-1.48 (m, 1H), 1.46-1.37 (m, 1H), 1.10 (t, *J* = 7.6 Hz, 3H), 0.94 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 128.2, 128.0, 127.8, 73.7, 64.8, 50.6, 30.9, 28.9, 8.4, 7.6; Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.55; H, 8.60.

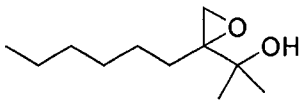
(Table 6.2, entry 21) (b1523).



Colorless oil; $[\alpha]_D^{25}$ = +48.6 (*c* 1.0, $CHCl_3$) (88% ee); IR (film) 3465 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48-7.45 (m, 2H), 7.37-7.29 (m, 3H), 3.30 (d, *J* = 5.6 Hz, 1H), 2.78 (d, *J* = 5.6 Hz, 1H), 1.92-1.70 (m, 4H), 1.65-1.52 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$)

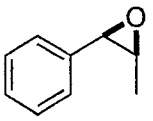
δ 138.2, 128.7, 128.1, 82.5, 64.5, 51.4, 36.30, 36.27, 23.6, 23.5; Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.33; H, 7.76.

(Table 6.2, entry 22) (b1545, b1548).



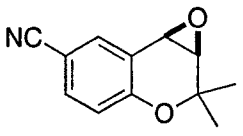
Colorless oil; $[\alpha]_D^{25}$ = +4.3 (*c* 0.80, $CHCl_3$) (60% ee); IR (film) 3473 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.99 (d, *J* = 4.8 Hz, 1H), 2.69 (d, *J* = 4.8 Hz, 1H), 2.07 (s, 1H), 1.88-1.60 (m, 2H), 1.31 (s, 3H), 1.27 (s, 3H), 1.34-1.23 (m, 8H), 0.90 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 70.3, 64.6, 48.4, 31.9, 29.8, 29.4, 26.5, 25.6, 24.6, 22.8, 14.3; Anal. Calcd. for $C_{11}H_{22}O_2$: C, 70.92; H, 11.90. Found: C, 71.09; H, 11.94.

(Table 6.3, entry 1)[9,10] (b0937c, mxzhao-17-07-2).



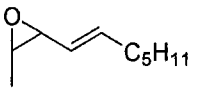
Colorless oil; $[\alpha]_D^{25}$ = -40.8 (*c* 0.75, $CHCl_3$) (85% ee); ^1H NMR (300 MHz, $CDCl_3$) δ 7.38-7.26 (m, 5H), 3.07 (d, *J* = 4.2 Hz, 1H), 3.34 (qd, *J* = 5.4, 4.5 Hz, 1H), 1.09 (d, *J* = 5.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.7, 128.2, 127.7, 126.8, 57.8, 55.4, 12.7.

(Table 6.3, entry 2)[10] (b0937g, mxzhao-17-11-2).



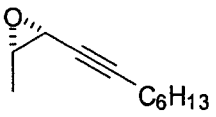
Colorless oil; $[\alpha]_D^{25}$ = +61.3 (*c* 1.6, $CHCl_3$) (84% ee); ^1H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, *J* = 2.1 Hz, 1H), 7.53 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 3.91 (d, *J* = 4.2 Hz, 1H), 3.54 (d, *J* = 4.5 Hz, 1H), 1.60 (s, 3H). 1.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.7, 134.6, 134.0, 121.3, 119.2, 118.9, 104.5, 74.9, 62.5, 50.1, 25.7, 23.2.

(Table 6.3, entry 3)[14] (mxzhao-17-12-1)



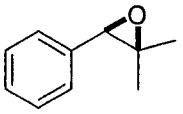
Colorless oil; $[\alpha]_D^{25}$ = -12.5 (*c* 0.8, $CHCl_3$) (68% ee); ^1H NMR (300 M Hz, $CDCl_3$) δ 5.94 (d, *J* = 15.3, 6.9 Hz, 1H), 5.31 (qt, *J* = 8.1, 1.5 Hz, 1H), 3.37 (dd, *J* = 8.1, 4.5 Hz, 1H), 3.20 (qd, *J* = 5.4, 0.9Hz, 1H), 2.10 (q, *J* = 6.6 Hz, 2H), 1.45-1.23 (m, 9H), 0.89 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5, 124.0, 57.5, 54.7, 32.8, 31.5, 28.9, 27.7, 14.2, 13.7.

(Table 6.3, entry 4)[15] (mxzhao-17-10-2)



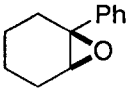
Colorless oil; $[\alpha]_D^{25}$ = -27.8 (*c* 1.15, $CHCl_3$) (70% ee); ^1H NMR (300 M Hz, $CDCl_3$) δ 3.42-3.40 (m, 1H), 3.12 (dt, *J* = 5.4, 4.2 Hz, 1H), 2.23 (td, *J* = 6.9, 1.5 Hz, 2H), 1.50 (q, *J* = 6.9 Hz, 2H), 1.43-1.23 (m, 10H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 86.9, 75.1, 54.2, 46.1, 31.5, 28.7, 28.6, 22.7, 19.0, 14.8, 14.2.

(Table 6.3, entry 5)[7] (b0937e, mxzhao-17-08-2)



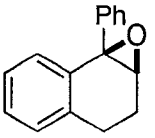
Colorless oil; $[\alpha]^{25}_D$ = +37.9 (*c* 1.2, benzene) (91% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.27 (m, 5H), 3.88 (s, 1H), 1.50 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.8, 128.2, 127.6, 126.6, 64.8, 61.3, 25.0, 18.2.

(Table 6.3, entry 6)[7,10,11] (b1217f, b0937d, mxzhao-17-13-1).



Colorless oil; $[\alpha]_D^{25}$ = -56.3 (*c* 1.4, $CHCl_3$) (80% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.22 (m, 5H), 3.07 (s, 1H), 2.33-2.24 (m, 1H), 2.12 (td, *J* = 14.7, 5.4 Hz, 1H), 2.02-1.96 (m, 2H), 1.64-1.41 (m, 3H), 1.38-1.26 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.7, 128.5, 127.4, 125.5, 62.1, 60.4, 29.0, 24.9, 20.3, 20.0.

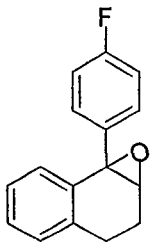
(Table 6.3, entry 7)[7] (b1236a, mxzhao-17-13-2).



Colorless oil; $[\alpha]_D^{25}$ = +54.0 (*c* 1.2, $CHCl_3$) (90% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53-7.49 (m, 2H), 7.46-7.38 (m, 3H), 7.24 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.18 (d, *J* = 7.2 Hz, 1H), 7.09 (td, *J* = 7.8, 1.2 Hz, 1H), 7.01 (dd, *J* = 7.8, 1.2 Hz, 1H), 3.65 (d, *J* = 3.0 Hz, 1H), 3.03-2.92 (m, 1H), 2.72 (dd, *J* = 15.9, 5.7 Hz, 1H), 2.55-2.46 (m, 1H), 2.06 (td, *J* =

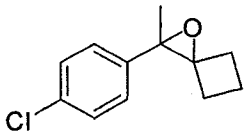
13.8, 6.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ138.8, 137.3, 135.0, 130.0, 128.8, 128.4, 128.3, 128.1, 127.9, 126.1, 63.2, 60.7, 25.6, 22.3.

(Table 6.3, entry 8) (mxzhao-17-10-1)



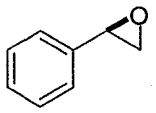
White solid; $[\alpha]_D^{25}$ = +34.7 (*c* 1.1, $CHCl_3$) (84% ee); ^1H NMR (300 MHz, $CDCl_3$) δ 7.49-7.44 (m, 2H), 7.28-7.22 (m, 1H), 7.18-7.07 (m, 4H), 6.97 (d, *J* = 8.1 Hz, 1H), 3.61 (d, *J* = 2.7 Hz, 1H), 2.95 (td, *J* = 15.9, 6.6 Hz, 1H), 2.71 (dd, *J* = 15.6, 5.7 Hz, 1H), 2.54-2.45 (m, 1H), 2.04 (td, *J* = 13.8, 5.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.1, 160.8, 137.3, 134.8, 134.6, 129.8, 129.7, 128.8, 128.4, 126.2, 115.4, 115.1, 63.3, 60.2, 25.5, 22.2.

(Table 6.3, entry 9)[20] (b0937b, mxzhao-17-08-1)



Colorless oil; $[\alpha]_D^{25}$ = +31.0 (*c* 1.75, $CHCl_3$) (72% ee); ^1H NMR (300 MHz, $CDCl_3$) δ 7.32-7.28 (m, 2H), 7.23-7.19 (m, 2H), 2.52-2.28 (m, 3H), 1.94-1.74 (m, 3H), 1.68-1.57 (m, 1H), 1.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.0, 133.1, 128.4, 127.6, 70.4, 63.4, 29.5, 29.1, 19.6, 12.4.

(Table 6.3, entry 10)[17] (b0937f, mxzhao-17-07-1)

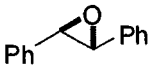


Colorless oil; $[\alpha]_D^{25}$ = -12.1 (*c* 0.80, $CHCl_3$) (44% ee); ^1H NMR (300 MHz, $CDCl_3$) δ 7.37-7.25 (m, 5H), 3.86 (dd, *J* = 3.6, 3.0 Hz, 1H), 3.15 (dd, *J* = 5.4, 3.9 Hz, 1H), 2.80 (dd, *J* = 5.4, 2.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.8, 128.7, 128.4, 125.7, 52.6, 51.4.

(Table 6.3, entry 11)[59] (mxzhao-17-12-2)

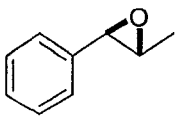
White solid; $[\alpha]_D^{25}$ = +62.0 (*c* 1.8, $CHCl_3$) (64% ee); ^1H NMR (300 MHz, $CDCl_3$) δ 7.51-7.34 (m, 10H), 4.00 (s, 1H), 1.50 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.5, 136.1, 128.7, 128.4, 127.9, 127.7, 126.7, 125.4, 67.3, 63.3, 16.9.

(Table 6.3, entry 12)[7] (b0941b)



White solid; $[\alpha]_D^{25}$ = +272.0 (*c* 0.5, Benzene) (77% ee); ^1H NMR (300 MHz, $CDCl_3$) δ 7.44-7.34 (m, 10H), 3.90(s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.3, 128.8, 128.5, 125.7, 63.1.

(Table 6.3, entry 13)[7] (b0941a, mxzhao-17-11-1)



Colorless oil; $[\alpha]_D^{25}$ = +13.1 (*c* 0.80, $CHCl_3$) (34% ee); ^1H NMR (300 MHz, $CDCl_3$) δ 7.37-7.24 (m, 5H), 3.57 (d, *J* = 1.8 Hz, 1H), 3.04 (td, *J* = 5.1, 2.1 Hz, 1H), 1.45 (d, *J* = 5.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.0, 128.6, 128.2, 125.8, 59.7, 59.2, 18.1.

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CHAPTER 7.0 : EXPLORING STRUCTURAL EFFECTS OF KETONE CATALYSTS ON ASYMMETRIC EPOXIDATION

7.1 INTRODUCTION

Looking back at the history of dioxirane-catalyzed epoxidation, especially the ketone catalysts developed in our group, the design and synthesis of the new ketone catalyst is crucial to progress in this area.[1-5] Changing the ketal functionality in ketone **1-2** to the oxazolidinone ring in ketone **2-3** (Figure 7.1)[6,7] had dramatic influence on the reactivity of the catalyst. The same result was obtained by changing the oxazolidinone ring in ketone **2-3** to a six-membered lactam in ketone **6-1,** resulting in an effective catalyst for the asymmetric epoxidation of 1,1-disubstituted olefins (Figure 7.1). Those very different results for structurally similar ketones encouraged us to further explore the structural effects of the spiro ring. This Chapter describes those efforts.

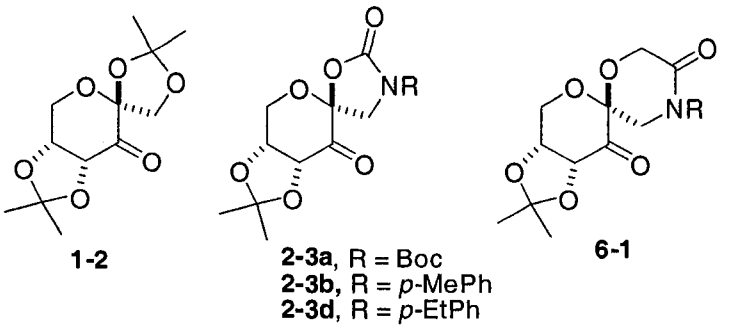


Figure 7.1

7.2 RESULTS AND DISCUSSION

7.2.1 The Structural Effect of Nitrogen Atom in Ketone 2-3

As described in Chapter 2, ketones **2-3** were effective catalysts for asymmetric epoxidation of conjugated *cis*-olefins.[8-11] The high enantioselectivity appears to arise primarily from electronic differentiation between two competing spiro transition states (Figure 7.2). Other early studies showed that ketone **7-1b** bearing carbonyl functionality in the spiro ring provided higher enantioselectivity for epoxidation of *cis*-β-methylstyrene when compared to the chiral ketone **7-1a** without carbonyl groups in its spiro rings (Figure 7.3 vs Figure 7.4).[12] Therefore, it has been concluded that the carbonyl group is partially responsible for the attraction between the phenyl group of the olefin and the spiro ring of the ketone catalysts **2–3** and **7–1b** (Figure 7.2).

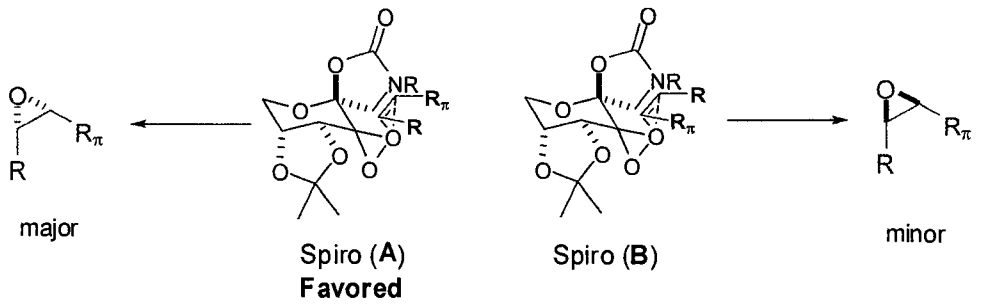


Figure 7.2

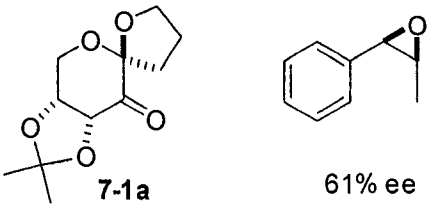


Figure 7.3

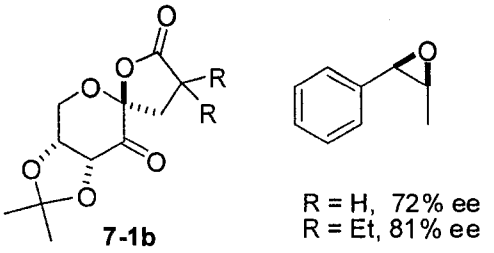


Figure 7.4

In addition to the carbonyl group, there is also a substituted nitrogen atom in the spiro ring of the ketone **2-3**. Whether the nitrogen atom of the oxazolidinone is essential for the reactivity of ketone **2-3** or not merits study. The crystal structure of ketone **2-3b** revealed that the oxazolidinone ring and the phenyl group are coplanar (Figure 7.5), and

the nitrogen atom on the oxazolidinone is likely sp^2-hybridized. In order to address the importance of the nitrogen atom, ketones **7-2a** and **7-2b** (Figure 7.6), which have a a carbonyl group and an sp^2-hybridized carbon, were designed, synthesized, and investigated in the asymmetric epoxidation.

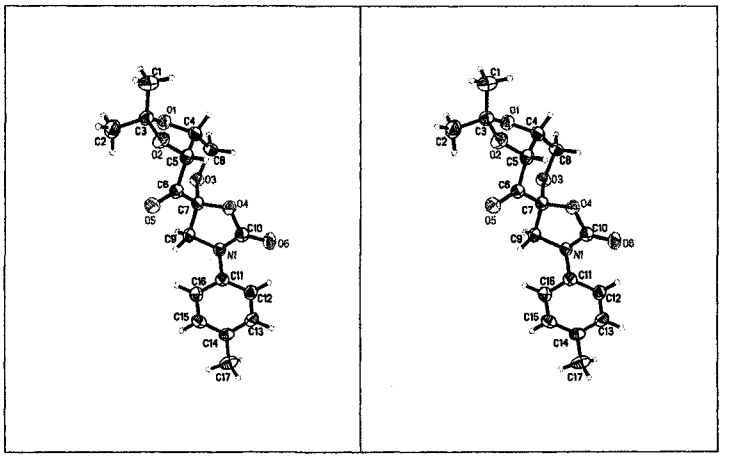
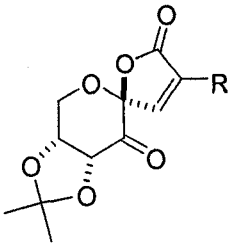


Figure 7.5

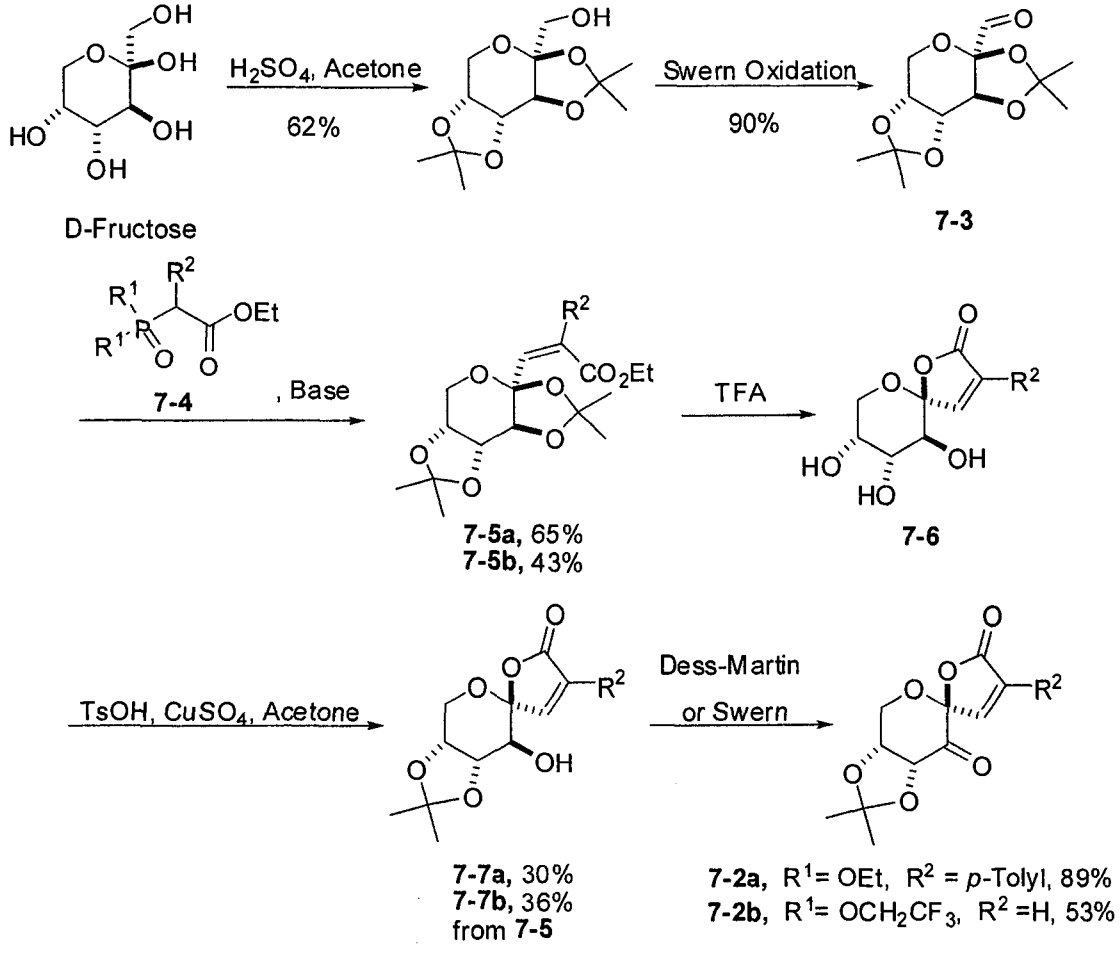


7-2a, R = *p*-Tolyl
7-2b, R = H

Figure 7.6

Ketones **7-2a** and **7-2b** were synthesized as shown in Scheme 7.1. Aldehyde **7-3** was prepared through the thermodynamic ketalization of D-fructose, followed by Swern

oxidation according the literature procedure.[13,14] Aldehyde **7-3** was converted to a (*Z*)-α,β-unsaturated ester **7-5** through a Still-Gennari modified HWE olefination.[15-17] Upon treating **7-5** with TFA, the deketalization, subsequent cyclization, and ketalization produced the alcohol **7-7**. After oxidation of alcohol **7-7**, the ketone was obtained through six steps overall. The X-ray structure (stereoview) of ketone **7-2a** and ketone **7-2b·H_2O** are shown in Figure 7.7 and Figure 7.8. Similar to ketone **2-3b**, the phenyl group and the spiro ring of ketone **7-2a** are coplanar.



Scheme 7.1

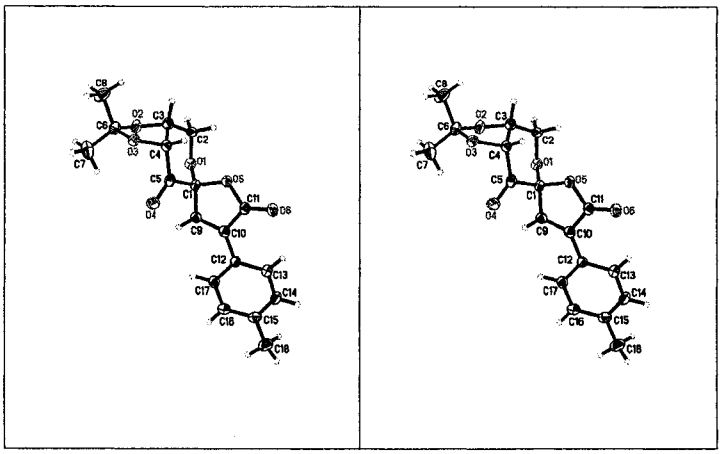


Figure 7.7

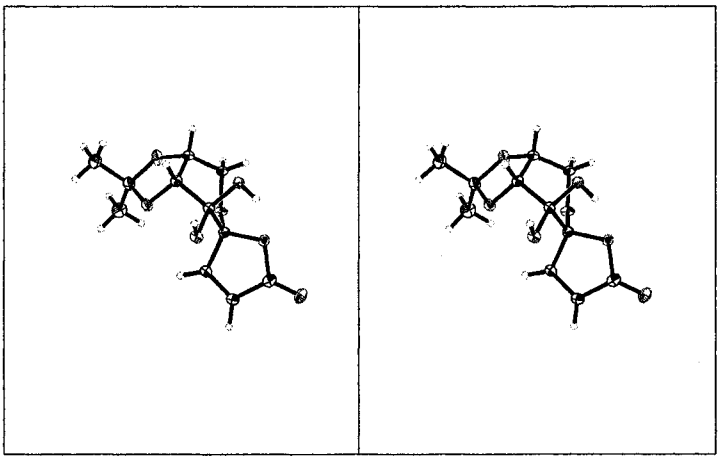
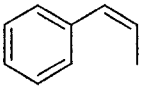
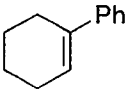
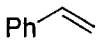
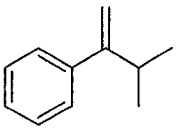


Figure 7.8

With a brief optimization of pH (Figure 7.2, entries 1 and 2), the catalytic properties of ketones **7-2a** and **7-2b** were evaluated. Epoxidation of *cis*-β-methylstyrene with ketone **7-2a** gave 59% ee which was slightly higher than ketone **7-2b.** Using ketone **7-2a** as catalyst, epoxidation of 1-phenylcyclohexene, styrene, and α–isopropyl styrene

gave low to moderate ee's and decent conversion (Figure 7.2). These results show that α,β-unsaturated ketones **7-2** are not good catalysts for asymmetric epoxidation. The low ee observed in epoxidation of *cis*-β-methylstyrene indicates that the nitrogen atom on the spiro ring of ketone catalysts **2–3** is also partially responsible for electronic attraction between the phenyl group of the olefin and the oxazolidinone moiety of the catalyst.

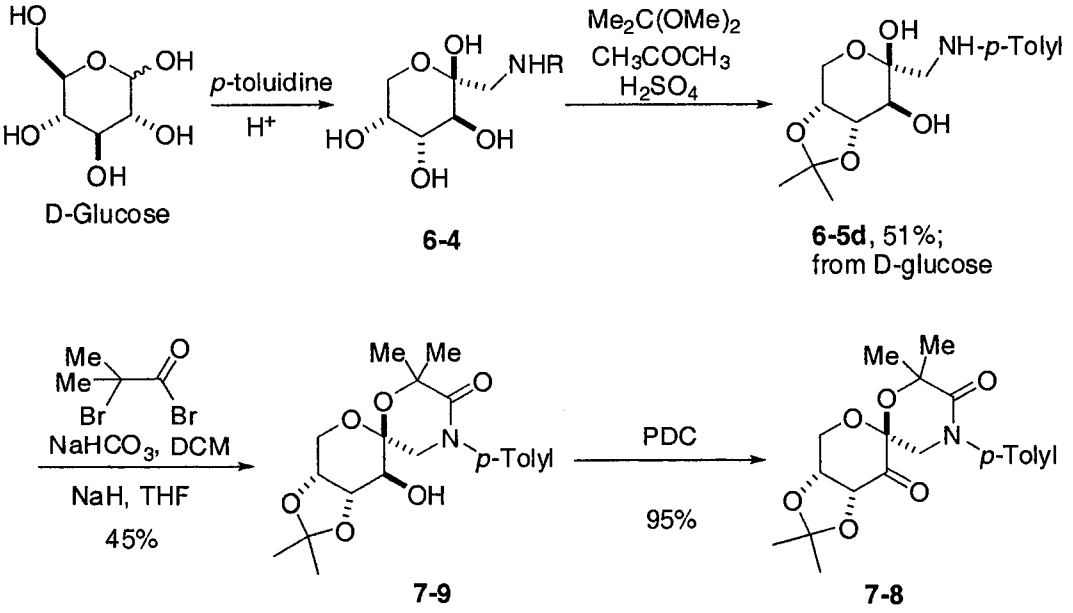
Table 7.1

En.	Substrate	Ketone	Conv. (%)[d]	Ee (%)[d]	Config.[e]
1[a]		**7-2a**	99	46	(-)-(1*R*, 2*S*)[8,9]
2[b]		**7-2a**	80	59	(-)-(1*R*, 2*S*)[8,9]
3[b]		**7-2b**	67	47	(-)-(1*R*, 2*S*)[8,9]
4[b]		**7-2a**	66	77	(+)-(*S*, *S*)[18]
5[b]		**7-2a**	93	55	(-)-(*R*)[19]
6[c]		**7-2a**	64	6	(-)

[a] The reaction was carried out with olefin (0.1 mmol), ketone (0.03 mmol), tetrabutylammonium hydrogen sulfate (2 mg, 0.005 mmol), 0.212 M Oxone (0.84 mL, 0.178 mmol), and 0.479 M K_2CO_3 (0.84 mL, 0.402 mmol) in DME/DMM (3:1, v/v) (1.5 mL) and buffer (0.1M K_2CO_3-AcOH, pH 8.0) (1 mL) at 0 °C for 3.5 h. [b] All reactions were carried out with olefin (0.1 mmol), ketone (0.03 mmol), tetrabutylammonium hydrogen sulfate (2 mg, 0.005 mmol), 0.212 M Oxone (0.84 mL, 0.178 mmol), and 0.892 M K_2CO_3 (0.84 mL,0.749 mmol) in DME/DMM (3:1, v/v) (1.5 mL) and buffer (0.1M K_2CO_3-AcOH, pH 9.3) (1 mL) at 0 °C for 3.5h. For entries 4 and 5, reaction was carried for 1.5 h. [c] The epoxidation was carried out with the olefin (0.1 mmol), ketone (0.03 mmol), 0.2 M Oxone (0.8 mL, 0.16 mmol), and 0.84 M K_2CO_3 (0.8 mL, 0.672 mmol) in 1,4-dioxane (1.5 mL), and buffer (0.1 M K_2CO_3/AcOH, pH 9.3) (1 mL) at -10 °C for 2 h. [d] Determined by GC (Chiraldex BD-M). [e] The absolute configurations were determined by comparing the GC trace with reported ones.

7.2.2 Dimethyl Lactam Ketone 7-8

In Chapter 6, we discussed that lactam ketone **6-1d** is a effective catalyst for asymmetric epoxidation of 1,1-disubstituted olefins. During the examination of ketone structure, ketone **7-8**, which has two methyl groups substituted at the α position of the lactam, was also synthesized in good yield through a four step sequence similar to that used to synthesize **6-1d** (Scheme 7.2). The X-ray structure of ketone **7-8** is shown in Figure 7.9.



Scheme 7.2

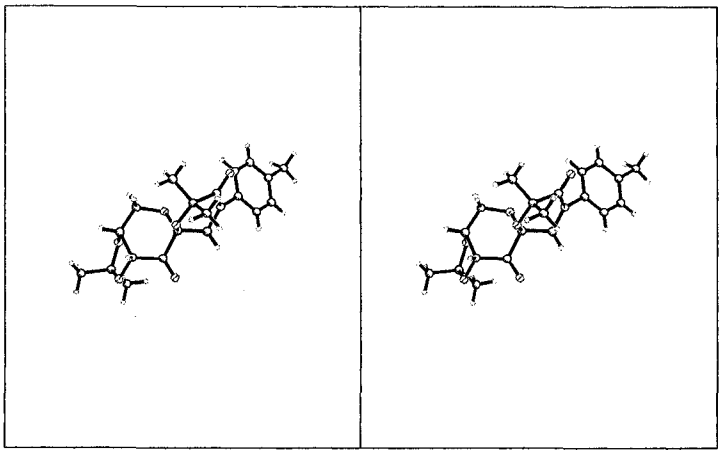
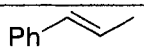
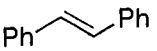
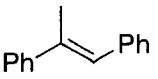
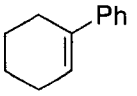
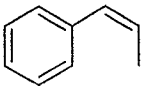
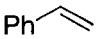
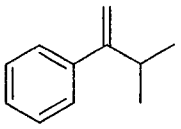
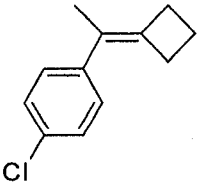


Figure 7.9

The catalytic properties of **7-8** were evaluated with a variety of ketones (Table 7.2). The epoxidation of α–isopropyl styrene only gave 45% ee (Table 7.2, entry 8). The epoxidation of 1-phenylcyclohexene with ketone **7-8** produced the (+)-(*R*,*R*)-epoxide with 86% ee (Table 7.1, entry 5). The configuration of the resulting epoxide is opposite to the one obtained with ketone **6-1**, but same as the one obtained with ketone **1-2**. High enantioselectivity was also obtained for epoxidation of *trans*-β-methylstyrene, stilbene, and methyl stilbene, which indicates that ketone **7-8** is likely a general catalyst for asymmetric epoxidation of *trans*- and trisubstituted olefins. On the other hand, epoxidation of *cis*-, terminal, and tetrasubstituted olefins with ketone 7-8 give low enantioselectivities. It was also found that ketone **7-8** was quite stable under the reaction conditions. In the case of entry 2 in Table 7.2, 36% of the catalyst was recovered after the reaction. Based on this information, epoxidation with fewer catalysts was also tested (Table 7.2, entry 3). The corresponding epoxide was also obtained in good yield and high enantioselectivity.

Table 7.2

En.	Substrate	**7-8** (eq.)	Temp. (°C)	Yield (%)[c]	Ee (%)	config.[g]
1[a]		0.30	-10	84	93[e]	(+)-(*R*, *R*)[18]
2[a]		0.30	0	56	96[f]	(+)-(*R*, *R*)[18]
3[a]		0.15	0	46	97[f]	(+)-(*R*, *R*)[18]
4[a]		0.30	-10	55	90[f]	(+)-(*R*, *R*)[18]
5[b]		0.20	-10	74	86[e]	(+)-(*R*, *R*)[8]
6[b]		0.20	-10	71	62[e]	(-)-(1*R*, 2*S*)[8,9]
7[b]		0.20	-10	88	51[e]	(-)-(*R*)[19]
8[b]		0.30	-10	83[d]	45[e]	(-)
9[b]		0.20	-10	32	65[e]	(+)[20]

[a] All reactions were carried out with olefin (0.2 mmol), ketone **7-8**, tetrabutylammonium hydrogen sulfate (3.75 mg, 0.01 mmol), Oxone (0.276 mmol), K_2CO_3 (1.16 mmol) CH_3CN-DMM (1:2, v/v) (3 mL) and buffer (0.1M K_2CO_3-AcOH, pH 9.3) (2 mL) at -10 or 0 °C for 4 h. For entry 3, epoxidation was carried for 8 h. [b] All reactions were carried out with olefin (0.2 mmol), ketone **7-8**, tetrabutylammonium hydrogen sulfate (3.75 mg, 0.01 mmol), 0.2 M Oxone (1.6 mL, 0.32 mmol), and 0.84 M K_2CO_3 (1.6 mL,1.344 mmol) in DME/DMM (3:1, v/v) (3 mL) (DME (3 mL) for entry 7 and 1.4-dioxane (3 mL) for entry 8), and buffer (0.1M K_2CO_3-AcOH, pH 9.3) (2 mL) at -10 °C for 4 h. For entries 8, epoxidation was carried for 2 h. [c] Isolated yield. [d] It is a conversion which was determined by GC (Chiraldex BD-M). [e] Unless stated otherwise, ee was determined by GC (Chiraldex BD-M). [f] ee was determined by chiral HPLC (Chiracel OD column). [g]

The absolute configurations were determined by comparing the measured optical rotations, GC trace, and HPLC trace with reported ones.

An overlay of ketones **1-2** and **7-8** (Figure 7.10) indicates that both ketones share similar steric features in the spiro ketal ring. Early studies showed that the two methyl groups of the spiro ketal ring in ketone **1-2** were crucial to successful asymmetric epoxidation of *trans*- and trisubstituted olefins.[12] In the case of ketone **7-8**, the two methyl groups at the α position of the lactam are very close to the methyl groups of ketone **1-2** in the overlay (Figure 7.10).

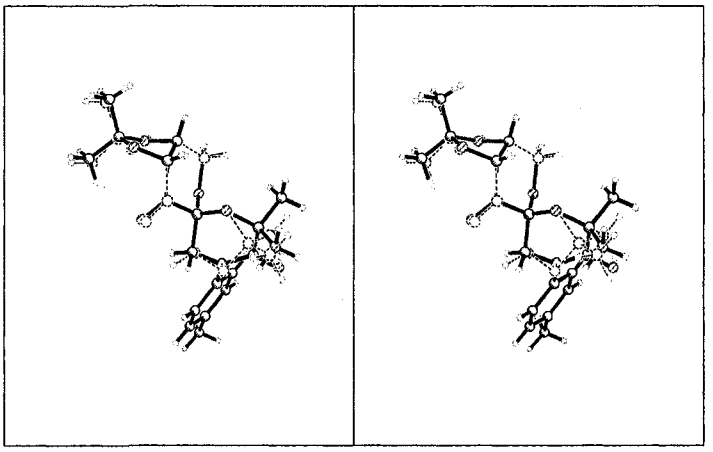


Figure 7.10

The major competing transition states for **7-8**-catalyzed epoxidation of *trans*- and trisubstituted olefins are likely spiro C and planar D (Figure 7.11) which are both sterically favored. The configuration and high enantiomeric excess of the epoxides show that spiro C is greatly favored over spiro D.[21]

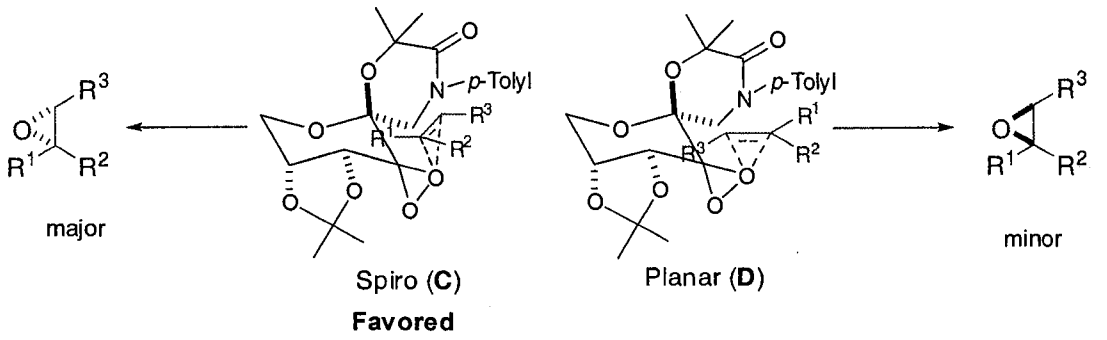


Figure 7.11

7.3 CONCLUSION

A study of α, β-unsaturated lactone ketones **7-2** revealed that the nitrogen atom in the spiro ring of ketone **2-3** is an important structural element in asymmetric epoxidation of *cis*-olefins. A very effective catalyst (**7-8**) for asymmetric epoxidation of *trans*- and trisubstituted olefins was developed through the modification of the spiro lactam ring of ketone **6-1d**. Ketone **7-8** was synthesized through a route of four steps from cheap starting material and is quite stable under epoxidation condition.

7.4 EXPERIMENTAL

7.4.1 The Synthesis of Ketone 7-2

Triethyl 2-*p*-tolylphosphonoacetate (7-4a) (b2017).

To a suspension of sodium hydride (60%) (3.20 g, 80 mmol) in DMF (16.10 mL) was added a solution of triethyl phosphonoacetate (16.01 mL, 80 mmol) at room temperature. After the solution was stirred at this temperature for 10 min, 4-iodotoluene (8.72 g, 40 mmol) and copper (I) iodide (15.24 g, 80 mmol) were added in turn, and the mixture was stirred at 100°C for 10 h. The reaction was quenched by the addition of 10 % aqueous HCl, filtered through a celite pad, extracted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel to give the triethyl 2-tolylphosphonoacetate as a colorless oil (8.1 g, 64.4 % yield). IR (film) 1732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37 (dd, J = 7.8, 2.1 Hz, 2H), 7.12 (dd, J = 7.8, 0.8 Hz, 2H), 4.22-3.95 (m, 7H), 2.30(d, J = 1.8 Hz, 3H), 1.24 (t, J = 6.9 Hz, 6H), 1.18 (dt, J = 6.9, 0.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 167.8, 137.7, 129.5, 129.4, 129.3, 127.9, 127.8, 63.4, 63.3, 63.1, 63.0, 61.8, 52.8, 51.0, 21.1, 16.4, 16.32, 16.26, 14.1; Anal. Calcd for $C_{15}H_{23}O_5P$: C, 57.32; H, 7.38. Found: C, 57.04; H, 7.14.

(7-5a) (b2022).

A mixture of lithium chloride (0.060 g, 1.404 mmol), triethyl 2-tolylphosphonoacetate (0.353 g, 1.123 mmol), and DBU (0.212 mL, 1.404 mmol) in acetonitrile (9.36 mL) was stirred at rt under argon for 10 min, and then the aldehyde (0.290 g, 1.123 mmol) in acetonitrile (9.36 mL) was added. After stirring the mixture at rt overnight, aqueous saturated NH_4Cl and $CHCl_3$ were added. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by flash chromatography (silica

gel; hexane/Et_2O = 2/1) to give the product (0.213 g, 45.3 % yield) as a colorless oil. $[\alpha]_D^{25}$ = -47.6 (*c* 2.5, $CHCl_3$); IR (film) 1731, 1651 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 4.65 (dd, *J* = 7.6, 2.8 Hz, 1H), 4.38-4.22 (m, 4H), 3.90 (dd, *J* = 12.8, 2.0 Hz, 1H), 3.85 (d, *J* = 12.8 Hz, 1H), 2.34 (s, 3H), 1.53 (s, 3H), 1.52 (s, 3H), 1.37 (s, 3H), 1.36 (s, 3H), 1.34 (t, *J* = 5.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 138.7, 136.7, 133.0, 129.5, 127.8, 126.4, 109.5, 109.3, 101.2, 74.2, 70.7, 70.5, 61.6, 61.2, 26.5, 26.1, 24.6, 24.4, 21.4, 14.4; Anal. Calcd for $C_{23}H_{30}O_7$: C, 66.01; H, 7.23. Found: C, 65.88; H, 7.12.

(b7-7a) (b2024, b2025).

The solution of ester (3.96 g, 9.46 mmol) in trifluoroacetic acid aqueous solution (v/v, 70%) (19 mL) at rt was stirred for 6 h. The solvent was concentrated by rotvap and vacuum to give a crude colorless oil. The product was taken on without further purification.

To the solution of above crude triol (2.77 g, 9.46 mmol) in acetone (40 mL) at rt was added *p*-toluenesulfonic acid monohydrate (0.126 g, 0.662 mmol) and copper (II) sulfate pentahydrate (2.87 g, 17.97 mmol). The reaction was allow to stirred at rt for 4 d, then K_2CO_3 (excess) was added until the pH of the mixture was alkaline. The reaction was then filtered through a pad of celite. After solvent was removed, the mixture was purified by flash chromatography (silica gel, diethyl ether/hexane = 1/1 to 2/1) to give a white solid (1.44 g, 46% yield). mp = 145-147 °C; $[\alpha]_D^{25}$ = -138.1 (*c* 1.0, $CHCl_3$); IR (film) 3444, 1771 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.1 Hz, 2H), 7.22 (d, *J* = 8.1 Hz, 2H), 7.21 (s, 1H), 4.36 (d, *J* = 6.0 Hz, 1H), 4.35 (d, *J* = 12.9 Hz, 1H), 4.37-4.32 (m,

1H), 4.21 (d, J = 12.9 Hz, 1H), 4.03 (d, J = 6.0 Hz, 1H), 2.38 (s, 3H), 1.60 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 142.1, 140.5, 134.4, 129.6, 127.6, 125.9, 110.2, 104.5, 76.4, 73.1, 71.0, 63.8, 28.1, 26.1, 21.7; Anal. Calcd for CHO: C, 65.05; H, 6.07. Found: C, 65.28; H, 6.09.

(7-2a) (b2031b).

To the solution of alcohol (0.332 g, 0.999 mmol) in DCM (6.69 mL), Dess-Martin periodinane (0.424 g, 0.999 mmol) was added. The resulting mixture was stirred at rt for 3h. Additional Dess-Martin periodinane (0.424 g, 0.999 mmol) was added. The mixture was stirred for another hour. The crude NMR showed that no alcohol remained. Then mixture was concentrated and purified by flash chromatography (silica gel; hexane/diethyl ether = 2/1) to give a white solid (0.308 g, 89 % yield). mp = 48-49 °C; $[\alpha]_D^{25}$ = -141.5 (*c* 0.8, $CHCl_3$); IR (film) 1782 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 8.0 Hz, 2H), 7.38 (s, 1H), 7.24 (d, J = 8.0 Hz, 2H), 4.85 (d, J = 6.0 Hz, 1H), 4.70 (dt, J = 6.0, 1.2 Hz, 1H), 4.50 (dd, J = 14.0, 2.0 Hz, 1H), 4.32 (d, J = 14.0 Hz, 1H), 2.40 (s, 3H), 1.57 (s, 3H), 1.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.9, 168.6, 141.0, 140.1, 134.9, 129.7, 127.8, 125.5, 111.9, 103.0, 77.8, 63.9, 27.2, 26.1, 21.7; HRMS Calcd for $C_{18}H_{19}O_6$ (M+1): 331.1182; Found: 331.1178.

(7-5b) (b1843, b1905, b1940).

A solution of ethyl (bis(2,2,2-trifluoroethoxy)phosphinyl)acetate (2.87 mL, 12.11 mmol) and 18-Crown-6 (16.0 g, 60.5 mmol) in THF (242 mL) was cooled to -78°C under N_2 and treated with 0.5 M potassium bis(trimethylsilyl)amide (29.1 mL, 14.53 mmol). The

aldehyde (3.13 g, 12.11 mmol) in THF (20 mL) was then added and the resulting mixture was stirred at -78 °C for 30 min. The sat. NH_4Cl (60 mL) was added into the mixture. The mixture was extracted with Et_2O (2 × 200 mL). The organic solution was dried over Na_2SO_4, concentrated, and purified by flash chromatography (silica gel, hexane/diethyl ether = 1/1) to give *cis* olefins as a colorless oil (1.7 g, 43 % yield). $[\alpha]_D^{25}$ = +36.8 (*c* 1.1, $CHCl_3$); IR (film) 1732, 1663 cm^{-1}; ^1H NMR (300 MHz, CD_3Cl) δ 5.96-5.85 (m, *J* = 12.3 Hz, 2 H), 4.63 (dd, *J* = 7.8, 2.4 Hz, 1H), 4.28-4.16 (m, 4 H), 3.87 (dd, *J* = 12.9, 1.8 Hz, 1H), 3.77 (d, *J* = 12.9 Hz, 1H), 1.52 (s, 3H), 1.51 (s, 3H), 1.36 (s, 3H), 1.33 (s, 3H), 1.32 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, CD_3Cl) δ 167.7, 134.9, 122.9, 109.5, 109.2, 101.1, 73.8, 70.6, 70.4, 61.6, 60.9, 26.5, 26.0, 24.52, 24.47, 14.4; HRMS Calcd for $C_{16}H_{24}O_7Na$ (M+Na): 351.1421; Found: 351.1414.

(7-7b) (b1847, b1849, b1908, b1910).

The solution of ester (1.7 g, 5.18 mmol) in trifluoroacetic acid aqueous solution (v/v, 70%) (10.36 mL) at rt was stirred for 6 h. The solvent was removed by rotvap (40°C water bath) and vacuum. The crude triol (white solid) was taken on next step without further purification. To the solution of crude triol in acetone (49.3 mL) at rt was added *p*-toluenesulfonic acid monohydrate (0.069 g, 0.363 mmol) and copper (II) sulfate pentahydrate (1.571 g, 9.84 mmol). The reaction was allowed to stir at rt for 56 h. K_2CO_3 (excess) was added until the pH of the mixture was alkaline. The reaction was then filtered through celite. After the solvent was removed, the mixture was purified by flash chromatography (silica gel; diethyl ether/hexane = 2/1 to 1/0) to give a white solid (0.45 g, 36 % yield). mp = 142-144°C; $[\alpha]_D^{25}$ =-191.4 (*c* 0.8, $CHCl_3$). IR (film) 3442, 1776

cm^{-1}; ^1H NMR (400 MHz, CD_3Cl) δ 7.21 (d, J = 5.6 Hz, 1H), 6.21 (d, J = 5.6 Hz, 1H), 4.37-4.28 (m, 3H), 4.19 (d, J = 13.6 Hz, 1H), 3.97 (d, J = 6.4 Hz, 1H), 1.58 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (75 MHz, CD_3Cl) δ 170.1, 152.3, 124.3, 110.2, 107.1, 76.1, 72.9, 70.5, 63.9, 28.0, 26.0; Anal. Calcd. for $C_{11}H_{14}O_6$: C, 54.54; H, 5.83. Found: C, 54.70; H, 5.65.

(7-7b) (b1921).

A solution of oxalyl chloride (0.114 mL, 1.300 mmol) in DCM (8.67 mL) was cooled to -78 °C. To this solution was added dimethylsulfoxide (0.185 mL, 2.60 mmol) slowly with caution at -78 °C. This was allowed to stir at -78 °C for 10 min. The cooling bath was then removed and the reaction mixture was allowed to stir for 3 min. The reaction was then take back to -78 °C and allowed stir at -78 °C for 10 min. A solution of alcohol (0.210 g, 0.867 mmol) in DCM (16 mL) was slowly added. The reaction was allowed to stir at -78 °C for 1 h. Triethylamine (0.580 mL, 4.16 mmol) was then added and reaction was allowed to warm to rt over 45 min. The reaction was then quenched with water (3 mL) and the aqueous layer was extracted with DCM. The organics were then combined, washed with brine (3 mL), dried over Na_2SO_4, concentrated, and purified by flash chromatography (silica gel, diethyl ether/hexane = 3/1 to 4/1) to give the product as a white solid (0.110 g, 52.8 % yield). mp = 88-89 °C; $[\alpha]_D^{25}$ = -172.7 (*c* 0.6, $CHCl_3$). IR (film) 1803, 1782, 1751 cm^{-1}; ^1H NMR (300 MHz, CD_3Cl) δ 7.10 (d, J = 5.7 Hz, 1H), 6.29 (d, J = 5.7 Hz, 1H), 4.82 (d, J = 5.7 Hz, 1H), 4.77 (m, J = 5.7 Hz, 1H), 4.48 (dd, J = 13.8, 2.1 Hz, 1H), 4.32 (d, J = 13.8 Hz, 1H), 1.54 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (75MHz, CD_3Cl) (a mixture of hydrate and ketone) δ 196.5, 169.0, 151.9, 150.7, 124.8,

123.9, 111.8, 110.6, 105.2, 91.2, 77.4, 75.9, 75.8, 73.1, 64.1, 63.8, 27.1, 26.4, 26.1, 24.8; HRMS Calcd for $C_{11}H_{13}O_6$ (M+H): 241.0712; Found: 241.0710.

7.4.2 The Synthesis of Ketone 7-8

(7-9) (b1248, b1241b).

To a slurry of amino alcohol (prepared from D-glucose in two steps)[8] (3.05 g, 10 mmol) and $NaHCO_3$ (1.68 g, 20 mmol) in DCM (400 mL), 2-bromo-2-methylpropanoyl bromide (1.48 mL, 12 mmol) was added dropwise at rt. The resulting mixture was stirred at rt for 16 h to form a brown slurry. TLC showed no starting material remained (the product was slightly less polar than the starting material). The reaction was quenched by adding 0.1 M aqueous K_2CO_3 solution (50 mL). Organic solvent was removed and dried under vacuum for 3 h to form crude brown syrup. To this crude brown syrup, THF (200 mL) and NaH (60%, 0.8 g, 20 mmol) was added. The resulting mixture was stirred at rt for 0.5 h. Then water (0.2 mL) was added. After filtration and removal of solvent, the mixtutre was purified by flash chromatography (silica gel, Hexane/EtOAc = 1/1) to give the alcohol as light yellow syrup (1.7 g, 45% yield). $[\alpha]_D^{25}$ =-54.4 (c 1.0, $CHCl_3$); IR 1659 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.22-7.16 (m, 4H), 4.30-4.23 (m, 2H), 4.19 (d, J = 12.9 Hz, 1H), 4.13 (dd, J = 13.2, 1.8 Hz, 1H), 4.00 (d, J = 13.2 Hz, 1H), 3.71 (d, J = 12.9 Hz, 1H), 3.63-3.61 (m, 1H), 2.34 (s, 3H), 1.60 (s, 3H), 1.57 (s, 3H), 1.51 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 139.6, 137.0, 130.0, 125.8, 110.0, 95.7, 77.3, 76.0, 73.3, 71.7, 60.7, 55.8, 28.3, 27.8, 27.0, 25.9, 21.3; HRMS Calcd for $C_{20}H_{28}NO_6$ (M): 378.1917; Found: 378.1907.

(7-8) (b1244, b1248).

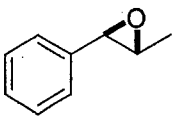
To a slurry of alcohol (1.7 g, 4.5 mmol), PDC (5.1 g, 13.6 mmol) and 3Å MS (3.3 g) in DCM (50 mL), 2 drops of AcOH was added. The resulting mixture was stirred as rt for 3 d. TLC show the no alcohol was remained. The mixture was filtered through a pad of silica gel and filtration cake was washed by EtOAc. After removal of solvent, the mixture was purified by flash chromatography (silica gel, hexane/EtOAc = 2/1) to give the ketone as a white solid (1.6 g, 95% yield). mp = 118-119 °C; $[\alpha]_D^{25}$ = -96.9 (*c* 1.2, $CHCl_3$); IR (film) 1751, 1677 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23-7.17 (m, 4H), 4.85 (d, *J* = 5.2 Hz, 1H), 4.61 (dd, *J* = 5.6, 1.6 Hz, 1H), 4.46 (dd, *J* = 13.6, 2.4Hz, 1H), 4.38 (d, *J* = 14.0 Hz, 1H), 4.18 (d, *J* = 14 Hz, 1H), 3.77(d, *J* = 13.6 Hz, 1H), 2.35 (s, 3H), 1.66 (s, 3H), 1.56 (s, 3H), 1.46 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.8, 170.8, 139.2, 137.1, 129.9, 125.7, 110.8, 96.5, 78.6, 78.4, 75.7, 59.6, 52.0, 27.7, 27.3, 26.6, 26.3, 21.3; Anal. Calcd. for $C_{20}H_{25}NO_6$: C, 63.99; H, 6.71. Found: C, 63.75; H, 6.89.

7.4.3 Asymmetric Epoxidation

Representative Epoxidation Procedure (Table 7.2, Entry 2). To a solution of the olefin (0.036 g, 0.2 mmol), tetrabutylammonium hydrogen sulfate (0.004 g) and ketone (0.023, 0.06 mmol) in acetonitrile-DMM (v/v, 1:2) (3 mL) was added buffer (0.1 M K_2CO_3-AcOH in 4 x 10^{-4} M aqueous EDTA, pH = 9.3) (2 mL) with stirring. After the mixture was cooled to 0 °C (bath temperature), a solution of Oxone (0.17 g, 0.276 mmol) in aqueous Na_2(EDTA) (4 × 10^{-4} M, 1.3 mL) and a solution of K_2CO_3 (0.16 g, 1.16

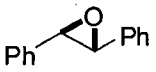
mmol) in aqueous Na_2(EDTA) (4×10^{-4} M, 1.3 mL) were added separately and simultaneously via a syringe pump over a period of 4 h at 0 °C. The reaction mixture was quenched with hexane, extracted with hexane, dried over Na_2SO_4, filtered, concentrated, and purified by flash chromatography [the silica gel was buffered with 1% Et_3N in organic solvent; hexane/Et_2O = 50/1 was used as eluent] to give the epoxide as colorless oil (0.022 g, 56% yield).

(Table 7.2, entry 1)[18](b1308a)



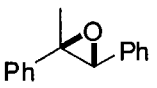
Colorless oil; $[\alpha]_D^{25}$ = +41.5 (*c* 1.1, $CHCl_3$) (93 % ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.24 (m, 5H), 3.57 (d, *J* = 1.8 Hz, 1H), 3.04 (td, *J* = 5.1, 2.1 Hz, 1H), 1.45 (d, *J* = 5.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.0, 128.6, 128.2, 125.8, 59.7, 59.2, 18.1.

(Table 7.2, entry 2)[18](b1309a, OAW2350-2)



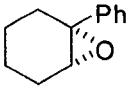
White solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44-7.34 (m, 10H), 3.90(s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.3, 128.8, 128.5, 125.7, 63.1.

(Table 7.2, entry 4)[18](b1312a)



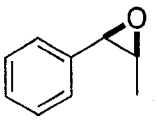
White solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51-7.34 (m, 10H), 4.00 (s, 1H), 1.50 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.5, 136.1, 128.7, 128.4, 127.9, 127.7, 126.7, 125.4, 67.3, 63.3, 16.9.

(Table 7.2, entry 5)[8] (b1217g)



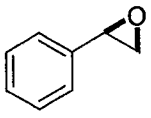
Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.22 (m, 5H), 3.07 (s, 1H), 2.33-2.24 (m, 1H), 2.12 (td, J = 14.7, 5.4 Hz, 1H), 2.02-1.96 (m, 2H), 1.64-1.41 (m, 3H), 1.38-1.26 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.7, 128.5, 127.4, 125.5, 62.1, 60.4, 29.0, 24.9, 20.3, 20.0.

(Table 7.2, entry 6)[8,9] (b1306a)



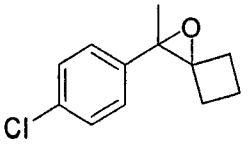
Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.26 (m, 5H), 3.07 (d, J = 4.2 Hz, 1H), 3.34 (qd, J = 5.4, 4.5 Hz, 1H), 1.09 (d, J = 5.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.7, 128.2, 127.7, 126.8, 57.8, 55.4, 12.7.

(Table 7.2, entry 7)[19] (b1307a)



Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.25 (m, 5H), 3.86 (dd, J = 3.6, 3.0 Hz, 1H), 3.15 (dd, J = 5.4, 3.9 Hz, 1H), 2.80 (dd, J = 5.4, 2.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.8, 128.7, 128.4, 125.7, 52.6, 51.4.

(Table 7.2, entry 9)[20] (b1311a)



Colorless oil; $[\alpha]_D^{25}$ = +31.9 (*c* 0.4, $CHCl_3$) (65 % ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.28 (m, 2H), 7.23-7.19 (m, 2H), 2.52-2.28 (m, 3H), 1.94-1.74 (m, 3H), 1.68-1.57 (m, 1H), 1.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.0, 133.1, 128.4, 127.6, 70.4, 63.4, 29.5, 29.1, 19.6, 12.4.

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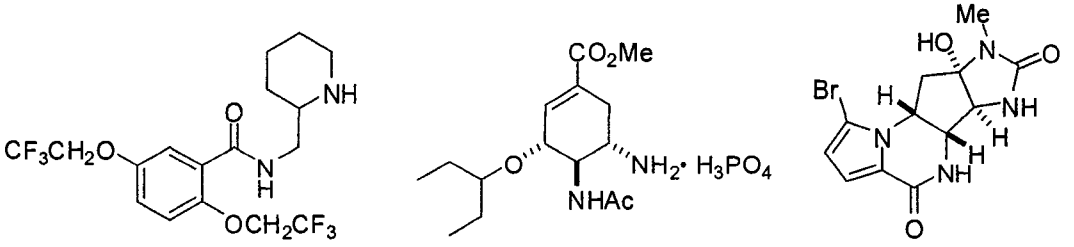
CHAPTER 8.0 : A PALLADIUM-CATALYZED DEHYDROGENATIVE DIAMINATION OF TERMINAL OLEFINS

8.1 INTRODUCTION

8.1.1 Importance of Vicinal Diamine

Vicinal diamines are very important functional moieties contained in various biologically active compounds (Figure 8.1) and widely used as chiral control elements in asymmetric synthesis (Figure 8.2).[1-3] Diamination, direct introduction of two nitrogen atoms to olefins, provides efficient and convenient approaches to the synthesis of vicinal diamines since olefins are often readily available.



Flecainide
Antiarrhythmic Agent

Tamiflu
Antiinfluenza Agent

Agelastatin A
Antitumor Agent

Figure 8.1 Selected Examples of Biologically Active Vicinal Diamines

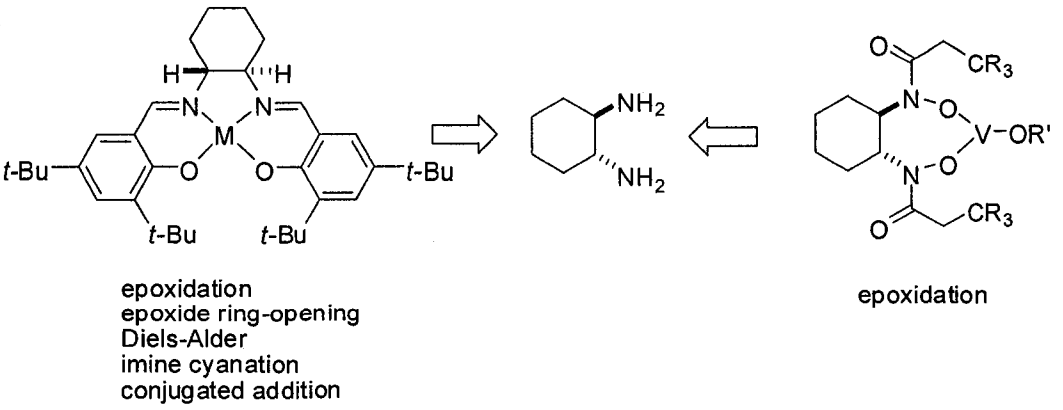
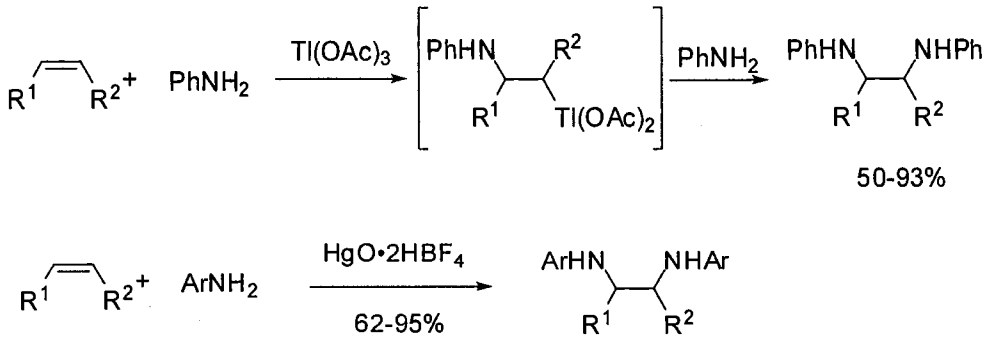


Figure 8.2 Selected Example of Vicinal Diamine Used in Asymmetric Synthesis

In the past three decades, much research has been done on diamination of olefins using metal complex. The metal complex can be used as stoichmetric or catalytic reagent.

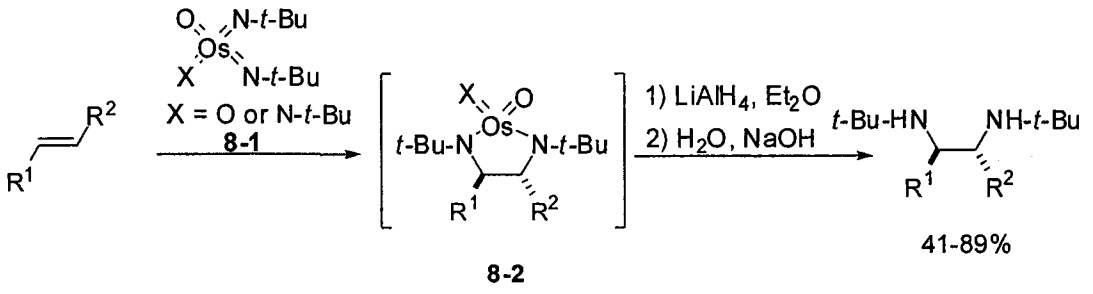
8.1.2 Stoichiometric Diamination

In 1974, Barluenga described the use of thallium acetate to promote the addition of anilines to C=C double bonds to produce the corresponding aromatic vicinal diamines with good yields (Scheme 8.1).[4] Later, mercury salts were used to mediate the reaction with more successful examples.[5] No diastereoselectivity was reported for either method.



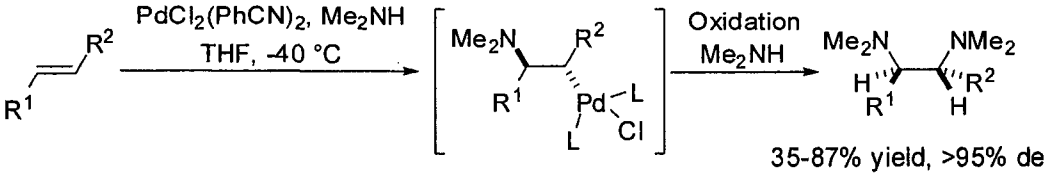
Scheme 8.1

Sharpless reported that imidoosmium complex **8-1** can stereospecifically diaminate *trans*- and terminal olefins in good yields (Scheme 8.2).[6] The reaction is believed to proceed through a *cis*-addition of **8-1** to an C=C bond to give a Os(VI)-diamine complex **8-2** which can be converted to a free vicinal diamine by reduction. Attempts to introduce enantioselectivity with chiral ligands of Os have met little success. Until now, the only successful asymmetric examples of Os-mediated diamination are through modification of the olefin by chiral auxiliary[7] or chiral Lewis acid.[8] Therefore, the substrate scope is limited.



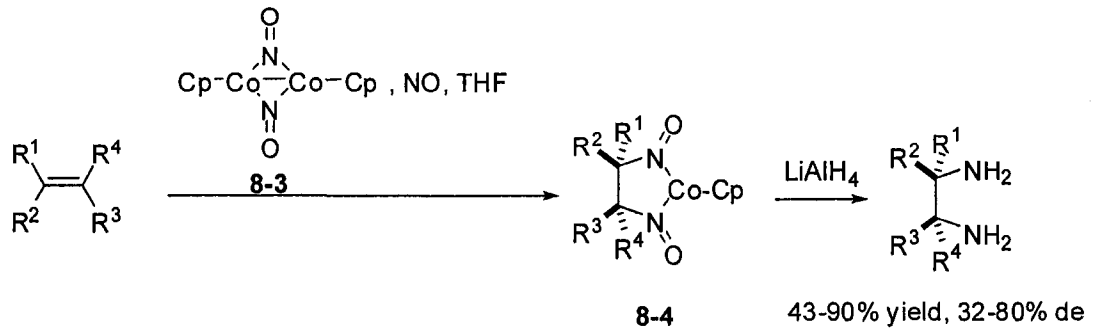
Scheme 8.2

Bäckvall showed that the diamination of *trans*-olefins can be promoted by Pd(II) complexes (Scheme 8.3).[9] The reaction likely proceeds through a *trans*-aminopalladation of C=C bonds,[10] followed by oxidation of Pd(II) to Pd(IV) and nucleophilic displacement of Pd(IV) species by an excess of dimethylamine, to produce the corresponding vicinal diamines in good yields. Therefore the diamination is overall *cis*-stereospecific with good diastereoselectivity.



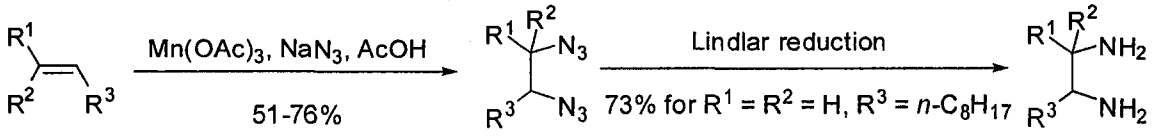
Scheme 8.3

In 1980, Bergman described a diamination approach using nitric oxide and cobalt complex **8-3** (Scheme 8.4).[11] The method has a broad substrate scope which includes terminal, *cis*-, *trans*-, trisubstituted and some tetrasubstituted olefins, however, with low diastereoselectivity. While the initial formation of **8-4** is believed to be a stereospecific *cis*-addition, the low diastereoselectivity is due to the epimerization during the reduction of Co-diamine complexes **8-4**.



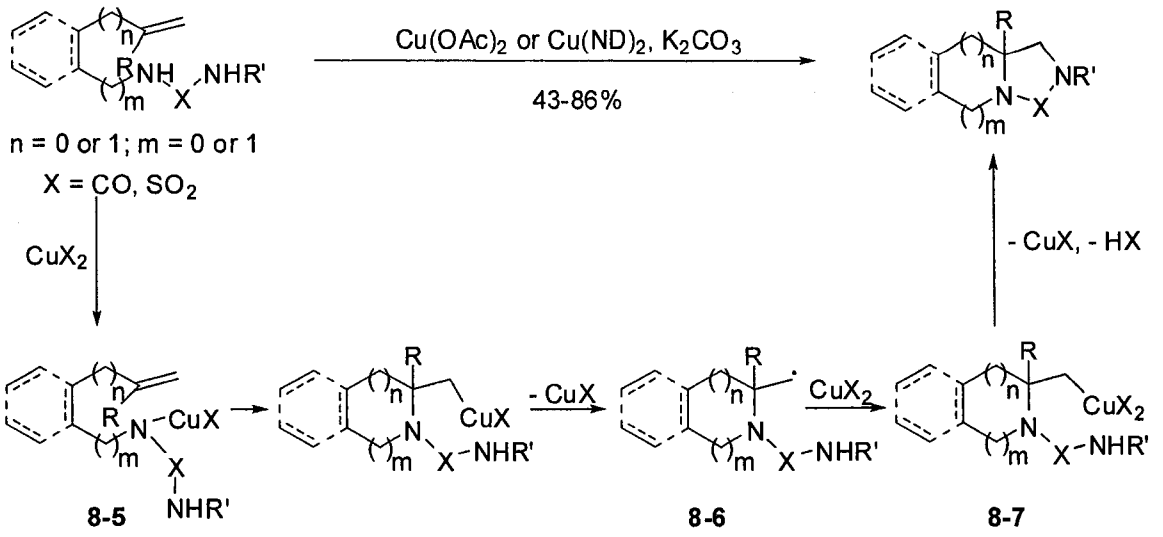
Scheme 8.4

Firstad described a $Mn(OAc)_3$-mediated diamination of a variety of olefins to produce vicinal diazides which can be reduced to free diamines (Scheme 8.5).[12] The reaction was proposed to involve a Mn (III)-N_3 species which can transfer a N_3 radical to C=C bonds. The yields of diazides were good while stereoselectivity was low (trans/cis = 4/1 to 6/1), likely due to the nature of the radical species.



Scheme 8.5

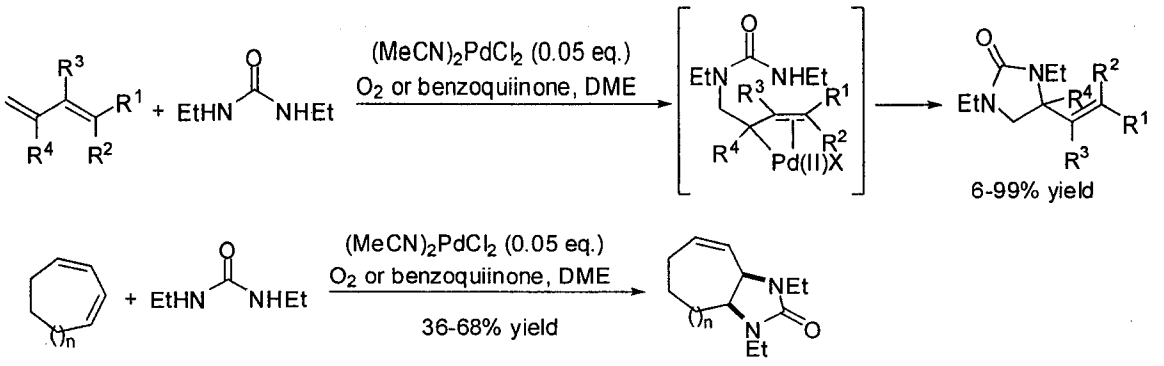
Chemler recently developed a Cu(II)-mediated intramolecular diamination in which the two nitrogens were tethered by SO_2 or CO, and the terminal C=C bonds were diaminated to produced bicyclic diamines in good yields (Scheme 8.6).[13,14] The proposed mechanism is shown in Scheme 8.6. The reaction is likely initiated by coordination of the sulfamide nitrogen to Cu(II) catalyst providing intermediate **8-5**. After aminocupration and C-Cu bond homolysis, a primary radical intermediate (**8-6**) was generated, then reacted with Cu(II) catalyst to form Cu(III) species **8-7** which underwent ligand exchange and reductive elimination or nucleophilic displacement to afford the final diamination product.



Scheme 8.6

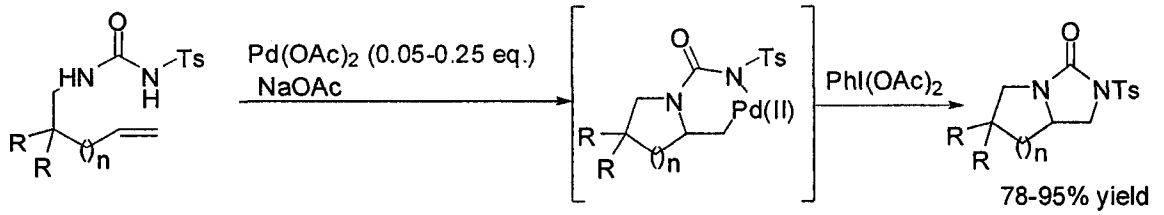
8.1.3 Catalytic Diamination

Recently Pd(II) promoted diamination has been further demonstrated in catalytic fashion by Booker-Milburn[15] and Muñiz.[16,17] Booker-Milburn has shown that the conjugated dienes were effectively diaminated in good yields with ethyl urea as nitrogen source (Scheme 8.7). A π–allyl complex was formed after initial aminopalladation and underwent intramolecular Tsuji-Trost allylic amination to afford a tethered diamine.

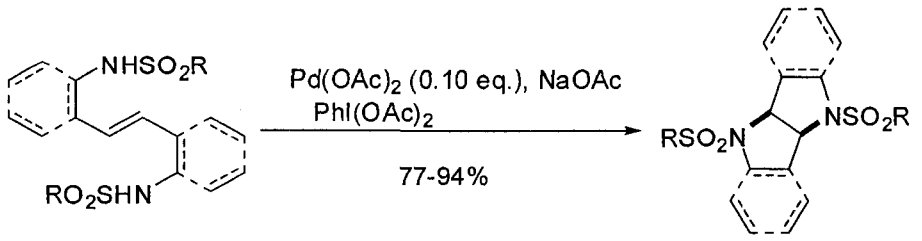


Scheme 8.7

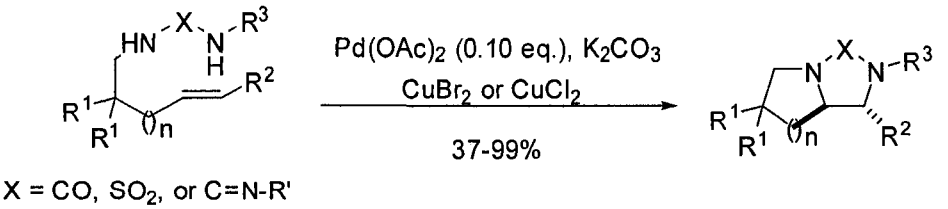
Muñiz reported that Pd-catalyzed intramolecular diamination in which two nitrogens were tethered by CO and terminal C=C bonds were diaminated (Scheme 8.8).[16,17] The reaction produces a variety of cyclic diamines in good yields though a two-steps mechanism similar to that of Bäckvall's (Scheme 8.3) except the first step which is *syn*-aminopalladation.[17] This method can be used to construct bisindoline and bipyrrolidine in good yields and with excellent diastereoselectivity (Scheme 8.9).[18] Besides $PhI(OAc)_2$, $CuBr_2$ and $CuCl_2$ can also be used as the oxidant for this Pd(II)-catalyzed process with more sustainable results and better substrate scope, including internal C=C bonds (Scheme 8.10).[19,20]



Scheme 8.8

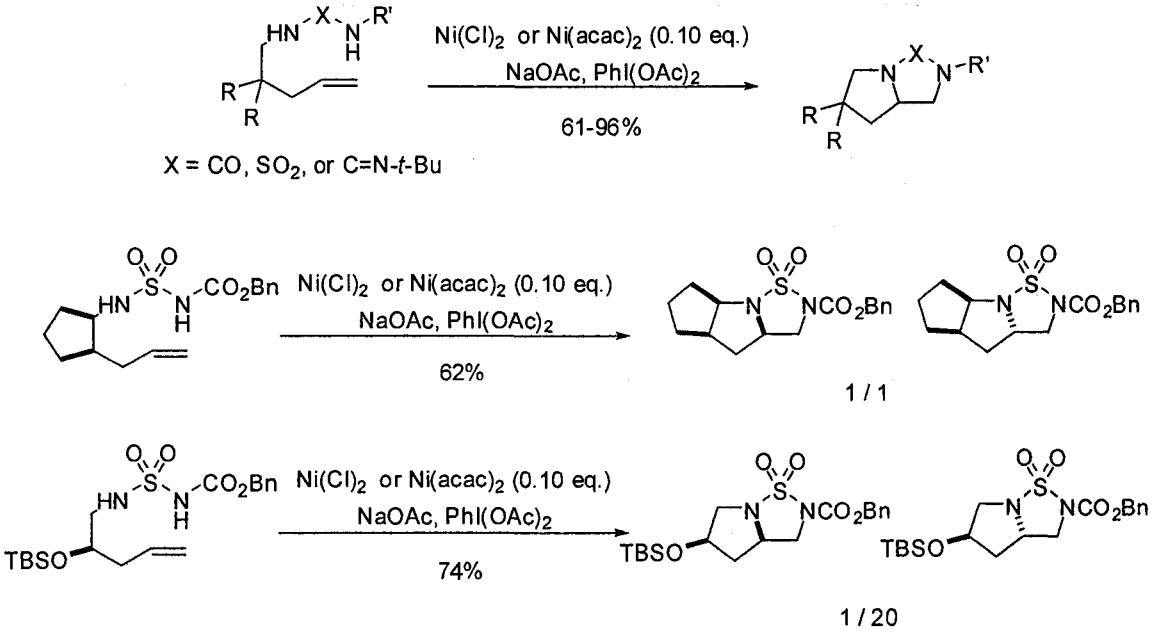


Scheme 8.9



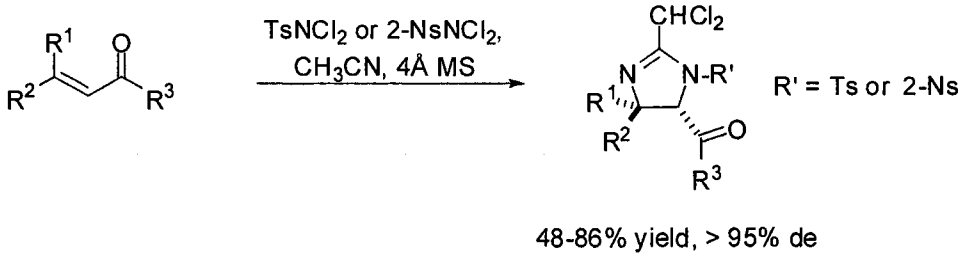
Scheme 8.10

Muñiz further showed that this intramolecular diamination can also be catalyzed by Ni(II) complex with good substrate scope and variable diastereoselectivity (Scheme 8.11).[21]

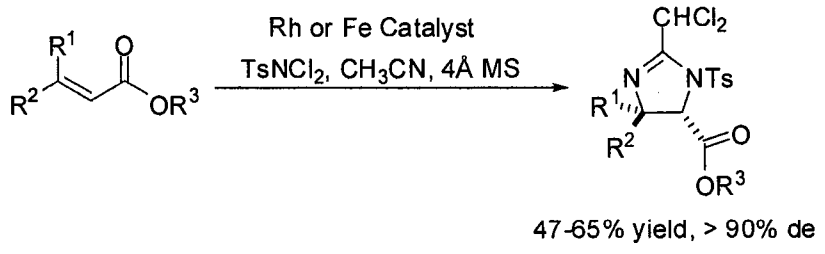


Scheme 8.11

Li reported that *p*-$TsNCl_2$ and nitrile can diaminate α, β-unsaturated ketones or esters to form the imidazolines in good yields and with good diastereoselectivities.[2,22-24] Interestingly, the reactivity of this transformation is sensitive to the type of substrate. α, β-Unsaturated ketones can be rapidly diaminated at room temperature without any metal catalyst (Scheme 8.12).[24] The diamination of α, β-unsaturated ester was promoted by Rh or Fe catalysts with a better reaction rate (Scheme 8.13).[22-24] Later the transformation was improved with another nitrogen source (2-$NsNCl_2$)[25] and with the formation of trichlorinated imidazoline[25-27] which may facilitate further transformations of imidazoline.



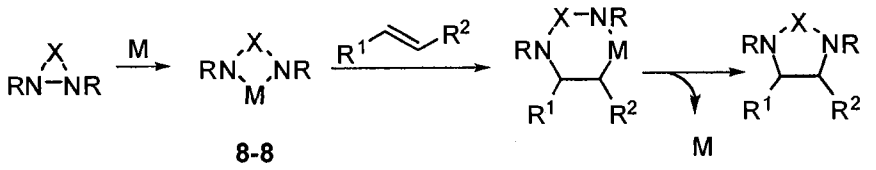
Scheme 8.12



Scheme 8.13

8.1.4 An Approach Inspired by Dioxiranes

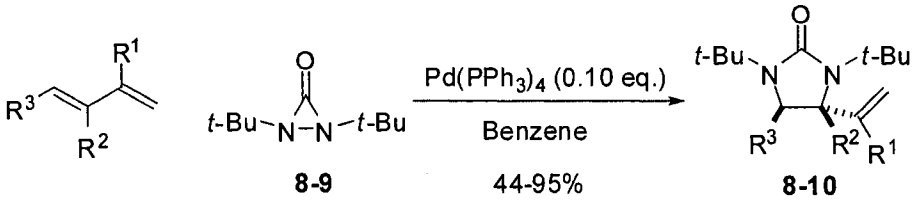
Recently, Shi group reported a Pd(0)- and Cu(I)- catalyzed stereoselective diamination of conjugated dienes and terminal olefins.[28-30] The nitrogen source used in the reaction is di-*tert*-butyldiaziridinone which is a nitrogen analogs of the aforementioned dioxiranes. The transformation utilizes the strain of the three-membered ring to rapidly form the corresponding metal-nitrogen species (**8-8**), which can effectively promote the amination of C=C bonds (Scheme 8.14).



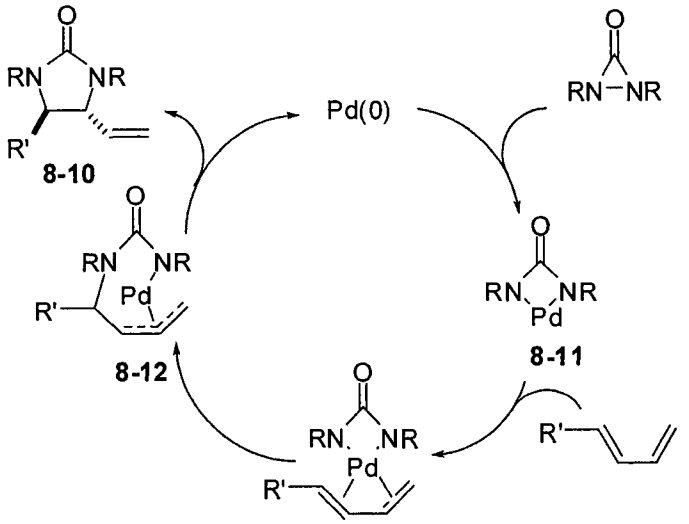
Scheme 8.14

Using $Pd(PPh_3)_4$ as the catalyst and di-*tert*-butyldiaziridinone (**8-9**)[31] as the nitrogen source,[28] the diamination of conjugated terminal dienes regioselectively produced the internal diamination products **8-10** in good yields (Scheme 8.15). The reaction likely involves initial migratory insertion of the corresponding Pd-nitrogen specie **8-11** to internal C=C bond of diene, followed by reductive elimination of the resulting π–allylic complex **8-12** to give the diamination product **8-10** (Scheme 8.16). When a chiral ligand was used, the diamination of dienes proceeded with high enantioselectivity. Chiral diamines can be obtained upon deprotection of chiral **8-10** and

the C=C bond contained in diamination product can be elaborated into other functionality.[32]



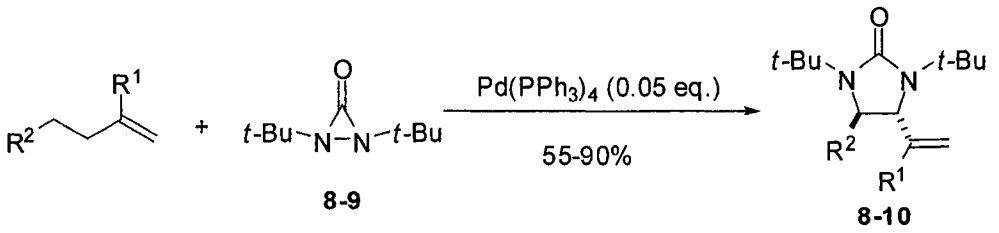
Scheme 8.15



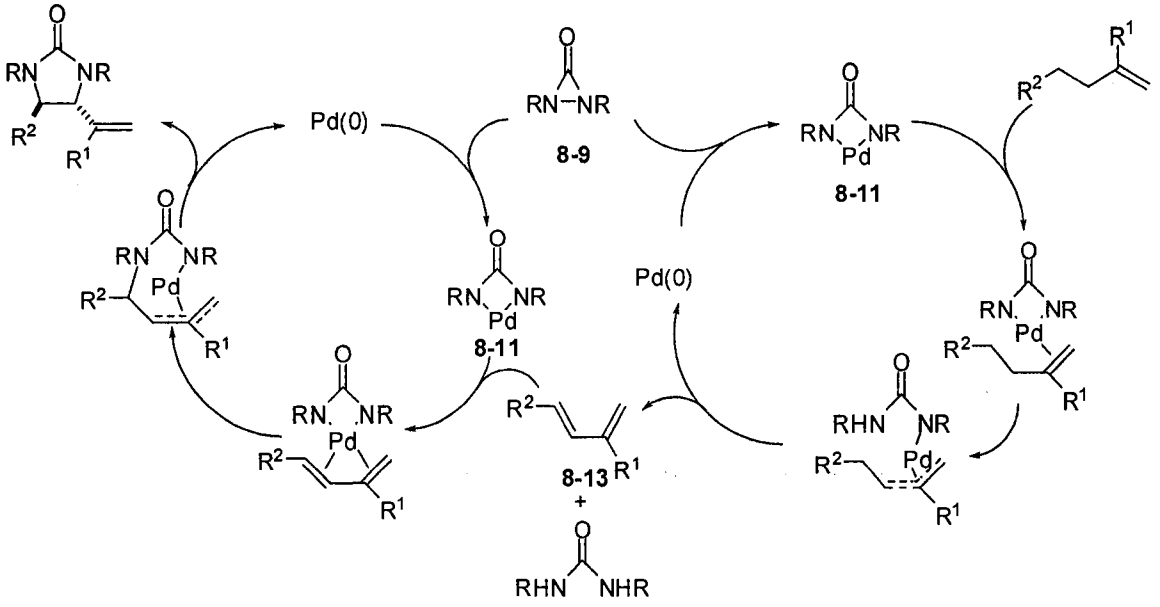
Scheme 8.16

In addition to dienes, terminal olefins also can be diaminated at allylic and homoallylic carbons to produce an internal diamination product (**8-10**) using the $Pd(PPh)_4$ as the catalyst and **8-9** as the nitrogen source under solvent-free conditions (Scheme 8.17).[29] The reaction is likely to proceed through a formation of diene **8-13** *in situ* by Pd(II)-promoted C-H activation and β-hydride elimination, followed by the

sequential diamination of diene **8-13** (Scheme 8.17). When chiral ligands were used, diamination of terminal olefins proceeded with high enantioselectivity.[33]



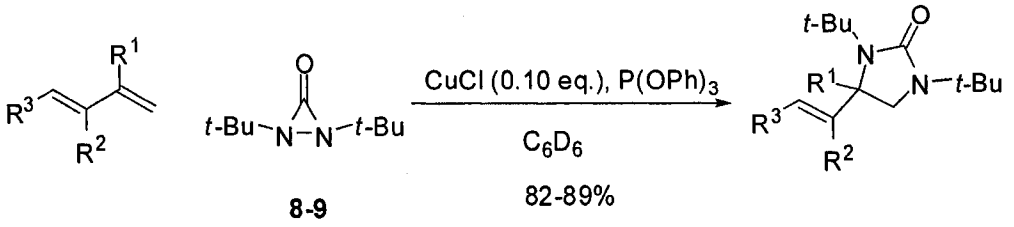
Scheme 8.17



Scheme 8.18

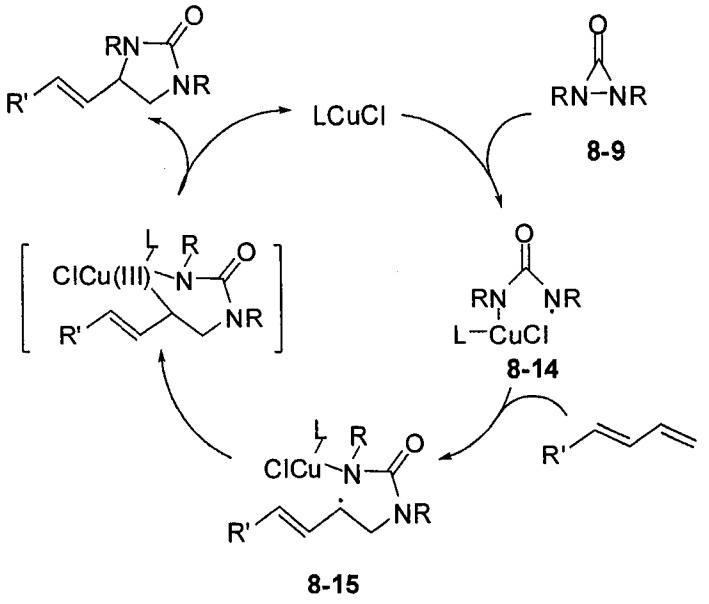
Using CuCl as a catalyst and di-*tert*-butyldiaziridinone (**8-9**)[31] as nitrogen source, Conjugated terminal dienes were regioselectively diaminated at the terminal position (Scheme 8.19).[30] The reaction mechanism likely involves the formation of radical species

8-14, which reacts with the diene at the terminal position to afford radical **8-15**. Homolytic cleavage of the Cu-N bond of **8-15** and formation of the C-N bond provides diamination product and regenerates the CuCl catalyst. Alternatively, the carbon radical of **8-15** could coordinate with the Cu to form Cu(III)-like species, which gives the product and regenerates the CuCl catalyst after reductive elimination (Scheme 8.20).



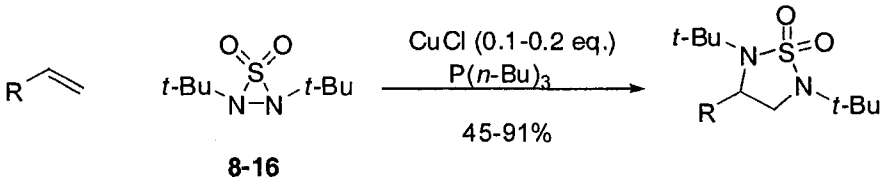
8-9

Scheme 8.19



Scheme 8.20

All the above diamination methods were developed with di-*tert*-butyldiaziridinone (**8-9**) being nitrogen source. Another readily available nitrogen analog of dioxiranes, *N*, *N'*-di-*tert*-butylthiadiaziridine 1,1-dioxide (**8-16**),[34] recently has also been used in the CuCl-catalyzed diamination of activated terminal olefin through a similar radical mechanism in Scheme 8.20 (Scheme 8.21).[35] This chapter will describe some preliminary results on **8-16**-involved dehydrogenative diamination catalyzed by Pd(0) complex.



8-16

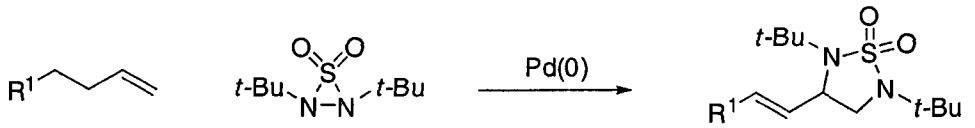
Scheme 8.21

8.2 RESULTS AND DISCUSSION

8.2.1 Reaction Conditions and Substrate Scope

When terminal olefins such as 1-nonene were treated with 5 mol% $Pd(PPh_3)_4$ and *N,N'*-di-*t*-butylthiadiaziridine 1,1-dioxide (**8-16**), no allylic and homoallylic diamination products similar to **8-12** were detected (Scheme 8.17 and Scheme 8.22). Instead, terminal diamination product **8-18** was formed in 34% conversion. After much optimization of ligands (including *N*-heterocyclic carbenes), solvents, temperature, amount of **8-16**, and catalyst loading, the diamination process was further improved using

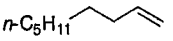
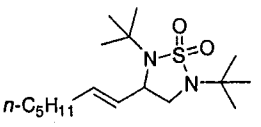
10 mol % Pd catalyst prepared from $Pd_2(dba)_3$ and tri-2-furylphosphine at higher reaction temperature. For example, treating 1-nonene (**8-17a**) with $Pd_2(dba)_3$ (0.05 eq.), tri-2-furylphosphine (0.3 eq.), and **8-16** (2.0 eq.) at 75 °C for 10 h gave terminal diamination product **8-18a** in 68% yield (Table 8.1, entry 1). The diamination can be extended to a variety of terminal olefins (Table 8.1, entries 1-11) (the X-ray structure of **8-18f** is shown in Figure 8.3). In all these cases, diamination products **8-18** were formed as major products along with small amounts of isomers. One type of isomer that was observed is (*Z*)-isomer of **8-18**. It could be isolated in the case of 4-alkoxy-1-butene (Table 8.1, entries 7 and 8). Another type of isomer could result from double bond migration. In some cases (Table 8.1, entry 4), substantial amount of this type of isomer was observed. In the case of 4-aryl substituted 1-butenes (Table 8.1, entries 5 and 6), dienes and internal diamination products were also formed.

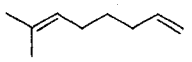
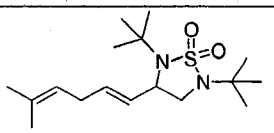
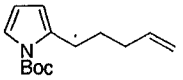
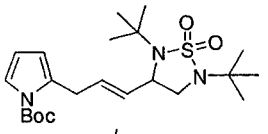
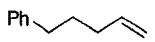
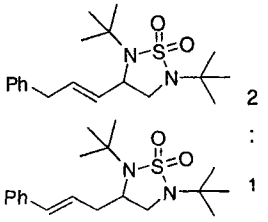
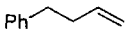
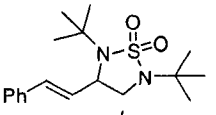
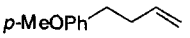
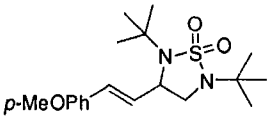
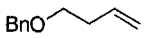
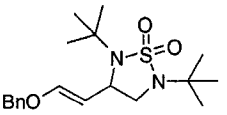
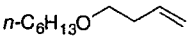
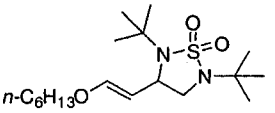
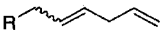
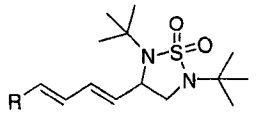


8-17 **8-16** **8-18**

Scheme 8.22

Table 8.1 Catalytic Dehydrogenative Diamination [a]

Entry	Substrate (**8-17**)	Product (**8-18**)	Yield [e] (%)
1	 **8-17a**		68

2	 **8-17b**		47
3	 **8-17c**		74
4	 **8-17d**		77
5[b]	 **8-17e**		45[f]
6	 **8-17f**		62[g]
7	 **8-17g**		61[h]
8	 **8-17h**		61[i]
9[c]	 **8-17i**, R = H (*E*)		42
10[d]	**8-17j**, R = H (*Z*)		40
11[c]	**8-17k**, R = Ph (*Z*, *E* mixture, 6:1)		66[j]

[a] All reactions were carried out with olefin (1.0 mmol), $Pd_2(dba)_3$ (0.050 mmol), tri-2-furylphosphine (0.30 mmol), and *N,N'*-di-*t*-butylthiadiaziridine 1,1-dioxide (**8-16**) (2.0 mmol) in benzene (0.25 mL) at 75 °C under argon for 10 h unless otherwise stated. [b] The reaction was carried out at 75 °C for 22 h. [c] The reaction was carried out at 65 °C for 6 h. [d] The reaction was carried out at 50 °C for 20 h. [e] Isolated yield. [f] The diene, internal diamination product, and **8-18e** were observed in ^{1}H NMR of crude reaction mixture with a ratio of 1.8/1/4.5. [g] The diene, internal diamination product, and **8-18f** were observed in ^{1}H NMR of crude reaction mixture with a ratio of 1/1.1/4.3. The internal diamination product was also isolated in 15% yield. [h] (*Z*)- and (*E*)- isomers were observed in ^{1}H NMR of crude reaction mixture with a ratio of 1/6. [i] (*Z*)- and (*E*)- isomers were observed in ^{1}H NMR of crude reaction mixture with a ratio of 1/6. The (*Z*)-isomer was also isolated in 10% yield. [j] (1*Z*, 3*E*)-isomer was also isolated in 7% yield.

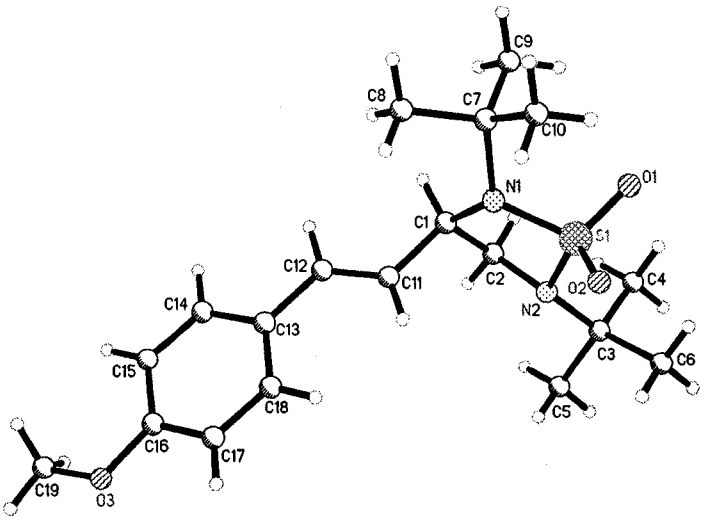


Figure 8.3

The olefins in Figure 8.4 were also investigated under the diamination condition using **8-16**. Terminal diamination product (**8-18**) was observed as the major product in ^{1}H NMR of the crude reaction mixture with good conversion; however, isolation of **8-18** in this case turned out to be difficult and a mixture of *N,N'*-di-*t*-butyl sulfamide and desired product was obtained.

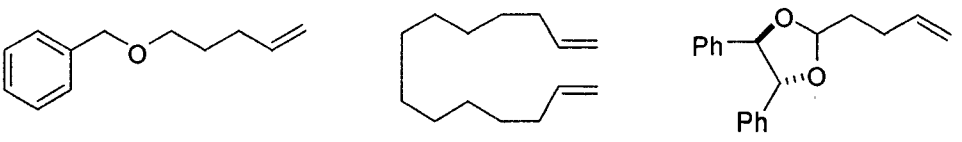


Figure 8.4

The substrates in Figure 8.5 were also screened under the diamination condition using **8-16**. However, no desired diamination product was observed in the ^{1}H NMR of

the crude reaction mixture in those cases. In the case of 1,1-disubstituted olefins, much starting material remained after the reaction.

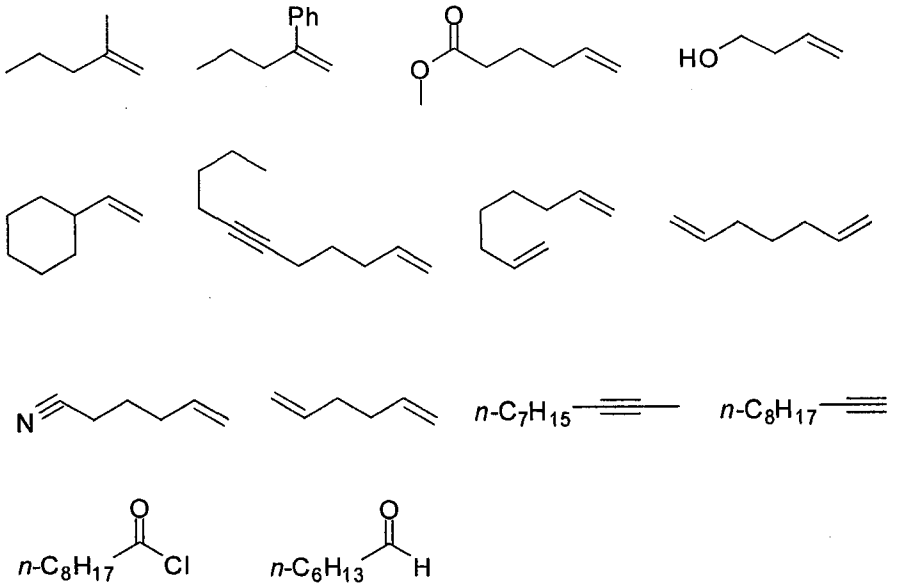


Figure 8.5

The diamination of internal C=C bonds were also tested with $Pd(PPh_3)_4$ and **8-16** (

Figure 8.6), Surprisingly, trace amount of terminal diamination product was observed in the ^1H NMR of the crude reaction mixture in the case of *cis* and *trans*-2-heptene. Those observations wait for the further study.

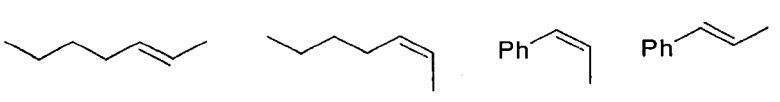
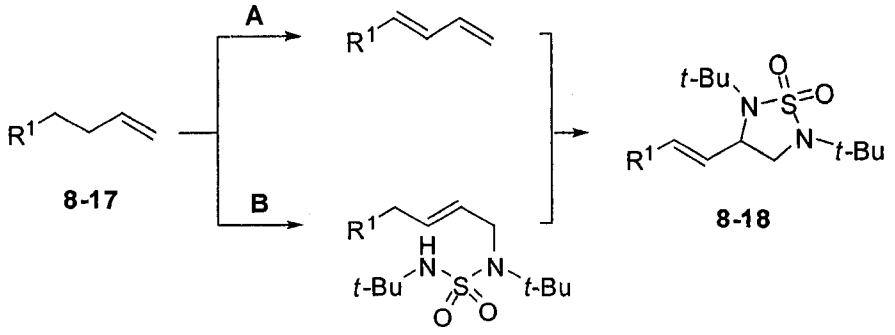


Figure 8.6

8.2.2 Mechanistic Hypothesis

Regarding the mechanism for this reaction, it could proceed through the initial allylic amination at a distal position followed by the Pd(II)-catalyzed aminopalladation of the internal C=C bond to form the terminal amination product (Scheme 8.23, Pathway B). Another alternative hypothesis for the mechanism is the first formation of dienes followed by the diamination of the diene at the terminal position (Scheme 8.23, Pathway A).

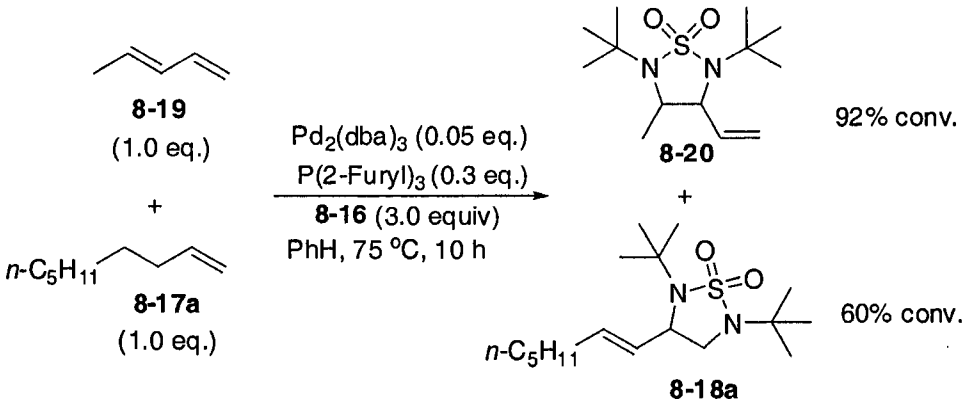


Scheme 8.23

Pathway A is the mechanism of our previous Pd(0)-catalyzed diamination of terminal olefins at allylic and homoallylic carbons (Scheme 8.17 and

Scheme 8.18).[29] However, this mechanistic hypothesis was disproved by following several experiments. First, when a mixture of 1,3-pentadiene (**8-19**) and 1-nonene (**8-17a**) was subjected to the diamination conditions (Scheme 8.24), compounds **8-20** and **8-18a** were formed, respectively. Diene **8-19** was diaminated predominately at

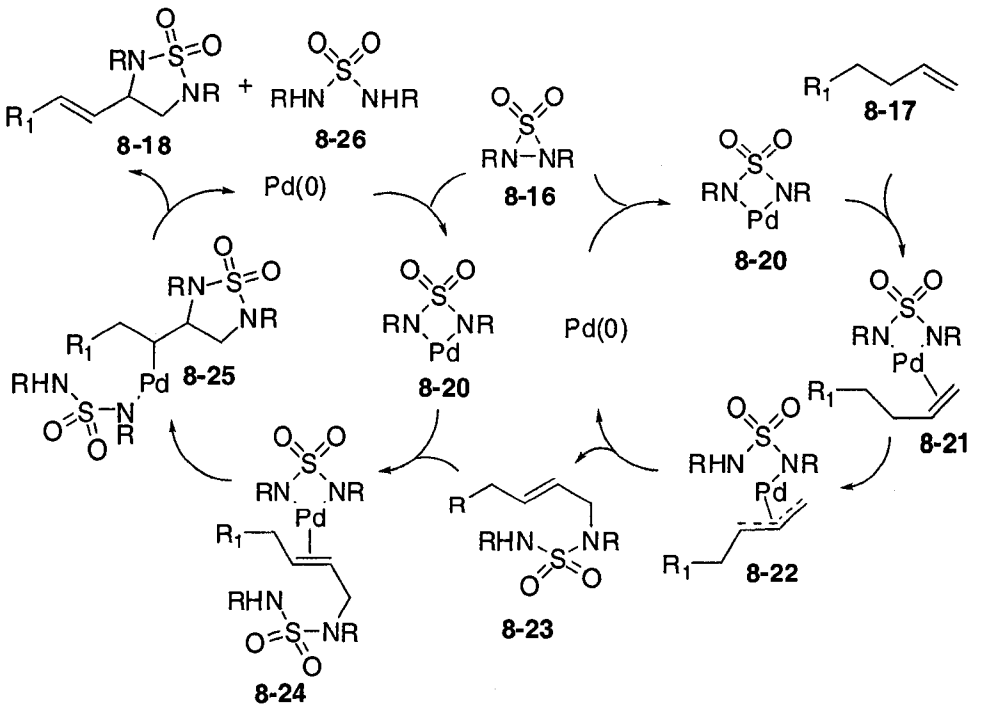
the internal C=C bonds along with trace amounts of diamination product at the terminal carbons of **8-19**, while terminal olefin **8-17a** was diaminated at the terminal carbons. Second, no inter-conversion between internal and terminal diamination product was observed under the reaction conditions. This eliminates the possibility that the product comes from the initially internal diamination of the diene and subsequent rapid inter-conversion of the internal product to the terminal one. These results indicate that this diamination is unlikely to proceed *via* an *in situ* generated diene (pathway A) as in the case when di-*t*-butyldiaziridinone (**8-9**) was used as nitrogen source (Scheme 8.17 and Scheme 8.18).



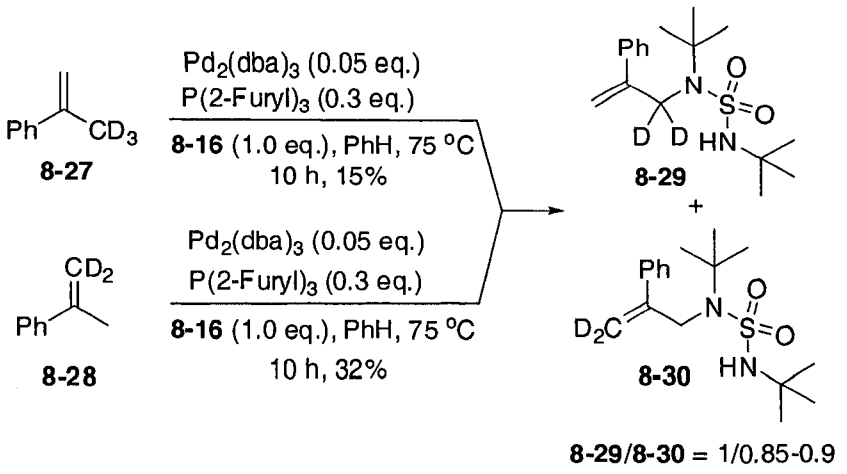
Scheme 8.24

While a precise reaction mechanism awaits further study, a plausible catalytic cycle is shown in Scheme 8.25. Pd(0) first inserts into the N-N bond of **8-16** to form a four-membered Pd(II) species **8-20**, which forms complex **8-21** with olefin **8-17**. Removal of an allylic hydrogen of **8-21** forms π-allyl Pd complex **8-22**,[36-38] which gives allyl sulfamide **8-23** and regenerates the Pd(0) catalyst after reductive elimination.[39]

Subsequently, **8-23** complexes with **8-20** to form **8-24**, which then undergoes a Pd(II)-catalyzed cyclization to form **8-25**.[40-44] Finally, **8-24** undergoes a β-hydride elimination and reductive elimination to form product **8-18** and sulfamide **8-26** with regeneration of Pd(0) catalyst. In the case of 4-phenyl substituted 1-butene (Table 8.1, entries 5 and 6), some amounts of dienes were formed from β-hydride elimination of π-allyl Pd complex **8-22**,[36,45] which is consistent with the proposed mechanism (Scheme 8.25). To further probe the allylic amination process, deuterium-labled α-methyl styrenes **8-27** and **8-28** were subjected to the reaction conditions (Scheme 8.26). Although these two substrates were less reactive due to steric effects, small amount of allylic amination products were isolated, and the deuterium was almost equally distributed at the terminal and allylic positions of the olefin in both cases (Scheme 8.26). This suggests that the initial allylic amination from π-allyl Pd complex **8-22** is a viable process (Scheme 8.25).

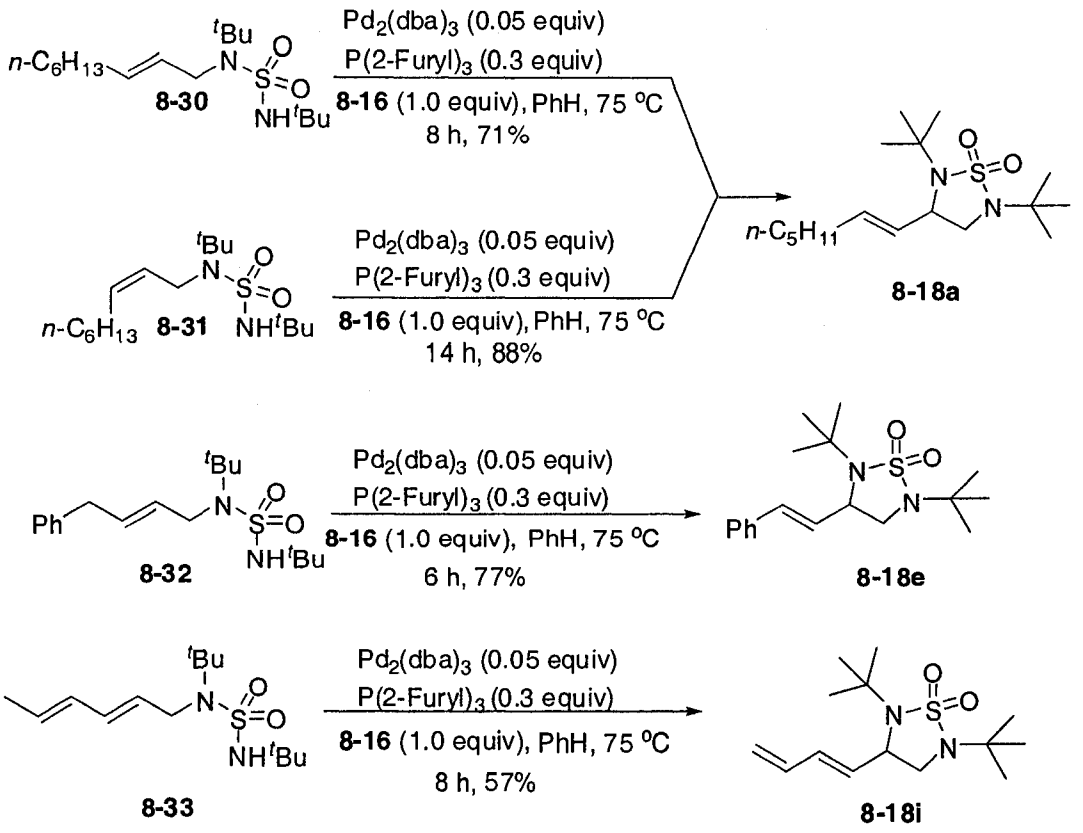


Scheme 8.25



Scheme 8.26

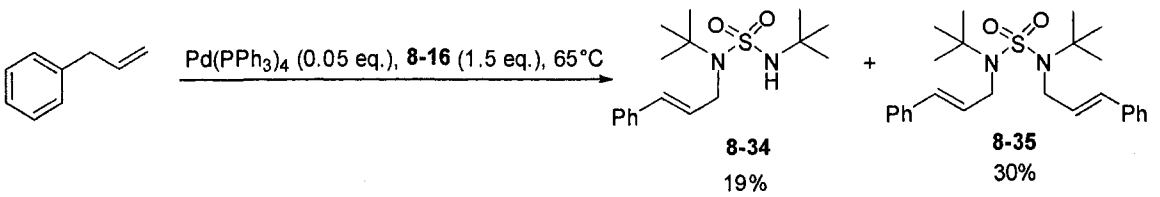
Clear identification and isolation of allyl sulfamide **8-23** from the crude reaction mixtures generally proved to be difficult. However, in the case of Table 8.1, entry 1, trace amounts of the allyl sulfamide in the reaction mixture could be detected by ^{1}H NMR and GC-MS. Thus allyl sulfamides **8-31-8-33** were prepared and subjected to the reaction condition (Scheme 8.27). Indeed these sulfamides cyclized to form compound **8-18a**, **8-18e**, and **8-18i** in good yields, respectively. However, no cyclization was observed without di-*t*-butylthiadiaziridine 1,1-dioxide (**8-16**) (Scheme 8.27). These results are in agreement with the mechanism described in Scheme 8.25. The exact mechanism for the Pd(II)-catalyzed cyclization of **8-23** to form **8-18** awaits further study.



Scheme 8.27

8.2.3 Miscellaneous

Treating allylbenzene with $Pd(PPh_3)_4$ and **8-16** under solvent-free conditions gave two allylic amination products with decent yield (Scheme 8.28). This result indicated this Pd-catalyzed amination system can be used in the generation of allylic amine.



Scheme 8.28

8.3 CONCLUSION

In summary, a variety of terminal olefins have been effectively dehydrogenatively diaminated via Pd(II) catalyzed catalytic allylic amination followed by aminopalladation and β-hydride elimination using *N,N'*-di-*tert*-butylthiadiaziridine 1,1-dioxide (**8-16**) as the nitrogen source and Pd(0) as the catalyst, giving the diamination products in good yields with high regioselectivity. This diamination uses readily available terminal olefins and provides complementary regioselectivity to the previous Pd(0)-catalyzed diamination of dienes and terminal olefins.[28,29,32,33] The allylic amination step in this transformation represents an early example of catalytic intermolecular allylic amination[39] which is very useful in functionalization of complex molecular, while the aminopalladation step shows that *N, N'*-di-*tert*-butylthiadiaziridine is a new efficient oxidant to generate very active Pd(II) species,[40-44] which provides a new opportunity to develop asymmetric Pd-catalyzed heterocyclizations.

8.4 EXPERIMENTAL

Procedure for preparation of *N, N'*-di-*t*-butylthiadiaziridine 1,1-dioxide (8-16).[34]

To a suspension of sodium hydride (60%) (2.0 g, 50.0 mmol) in hexane (400 mL) was added *N,N'*-di-*t*-butyl sulfamide (10.0 g, 48.0 mmol) over a period of 30 min. The

resulting slurry was stirred at reflux for 2 h. Upon cooling to -30 °C, *t*-butyl hypochlorite (5.43 g, 50.0 mmol) was added dropwise with lights off. The reaction mixture was stirred at -30 °C for 3 h and at 0 °C for 1 h in the dark. Cold ether (200 mL) was then added. The organic layers were washed with water (100 mL), dried over $MgSO_4$, filtered, concentrated, and distilled under reduced pressure (95 °C, 8 mmHg) to give *N,N'*-di-*t*-butylthiadiaziridine 1,1-dioxide (**8-16**) as a colorless oil which solidified at room temperature (8.5 g, 86 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 61.4, 27.7.

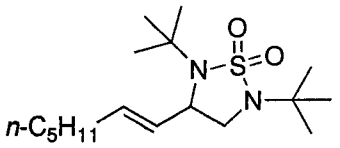
Representative Dehydrogenative Diamination Procedure (Table 8.1, Entry 1). A Pyrex tube charged with $Pd_2(dba)_3$ (0.046 g, 0.050 mmol) and tri-2-furylphosphine (0.070 g, 0.30 mmol) was evacuated and then filled with argon three times. Upon addition of benzene (0.25 mL), the resulting mixture was stirred at 75 °C for 15 min. 1-Nonene (0.126 g, 1.0 mmol) was added, followed by *N,N'*-di-*t*-butylthiadiaziridine 1,1-dioxide (**8-16**) (0.413 g, 2.00 mmol). The reaction mixture was stirred at 75 °C for 10 h, and purified by flash chromatography [silica gel; toluene first to remove the yellow dibenzylideneacetone, then petroleum ether-EtOAc (40/1 to 30/1)] to give the diamination product **8-18a** as a colorless oil (0.225 g, 68%).

Representative Procedure for Allylic Amination of α-Methyl Styrenes (Scheme 8.26). A Pyrex tube charged with $Pd_2(dba)_3$ (0.023 g, 0.025 mmol) and tri-2-furylphosphine (0.035 g, 0.150 mmol) was evacuated and then filled with argon three times, followed by addition of benzene (0.125 mL). After the resulting mixture was stirred at 75 °C for 15 min, α-methyl styrenes **8-28** (0.060 g, 0.5 mmol) and *N,N'*-di-*t*-

butylthiadiaziridine 1,1-dioxide (**8-16**) (0.103 g, 0.50 mmol) were added successively. The reaction mixture was stirred at 75 °C for 10 h and purified by flash chromatography [silica gel; toluene first to remove the yellow dibenzylideneacetone, then petroleum ether-EtOAc (30/1)] to give the allylic amination product **8-29** and **8-30** as a white solid (0.052 g, 32 %).

Representative Procedure for Cyclization of Allyl Sulfamide (Scheme 8.27). A Pyrex tube charged with $Pd_2(dba)_3$ (0.018 g, 0.020 mmol) and tri-2-furylphosphine (0.028 g, 0.120 mmol) was evacuated and then filled with argon three times, followed by addition of benzene (0.1 mL). After the resulting mixture was stirred at 75 °C for 15 min, allyl sulfamide **8-31** (0.133 g, 0.4 mmol) and *N,N'*-di-*t*-butylthiadiaziridine 1,1-dioxide (**8-16**) (0.083 g, 0.40 mmol) were added successively. The reaction mixture was stirred at 75 °C for 14 h and purified by flash chromatography [silica gel; toluene first to remove the yellow dibenzylideneacetone, then petroleum ether-EtOAc (30/1 to 20/1)] to give the cyclization product **8-18a** as a colorless oil (0.116 g, 88 %).

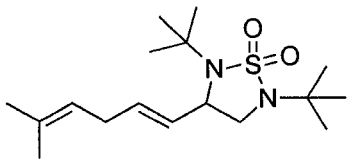
(Table 8.1, Entry 1) (b2114A).



Colorless oil; IR (film): 1668, 1623, 1252 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.75-5.61 (m, 2H), 4.01-3.95 (m, 1H), 3.42 (dd, J = 8.4, 6.0 Hz, 1H), 2.97 (dd, J = 8.4, 4.2 Hz, 1H), 2.07-2.01 (m, 2H), 1.47-1.24 (m, 6H), 1.42 (s, 9H), 1.39 (s, 9H), 0.89 (t, J = 6.6 Hz,

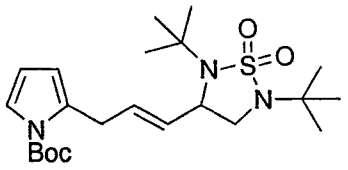
3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.4, 131.2, 57.7, 56.3, 55.6, 47.7, 32.1, 31.6, 28.8, 28.7, 27.5, 22.6, 14.3; Anal. Calcd. for $C_{17}H_{34}N_2O_2S$: C, 61.77; H, 10.37; N, 8.48. Found: C, 61.64; H, 10.36; N, 8.23.

(Table 8.1, Entry 2) (b2211A).



Colorless oil; IR (film) 1667, 1371 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.74-5.59 (m, 2H), 5.16-4.06 (m, 1H), 4.02-3.96 (m, 1H), 3.42 (dd, J = 9.0, 6.3 Hz, 1H), 2.97 (dd, J = 9.0, 4.5 Hz, 1H), 2.73 (t, J = 6.3 Hz, 2H), 1.72 (s, 3H), 1.61 (s, 3H), 1.41 (s, 9H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.6, 131.8, 131.1, 121.0, 57.8, 56.3, 55.6, 47.5, 30.9, 28.8, 27.5, 25.9, 17.9; Anal. Calcd. for $C_{17}H_{32}N_2O_2S$: C, 62.15; H, 9.82; N, 8.53. Found: C, 62.33; H, 9.82; N, 8.53.

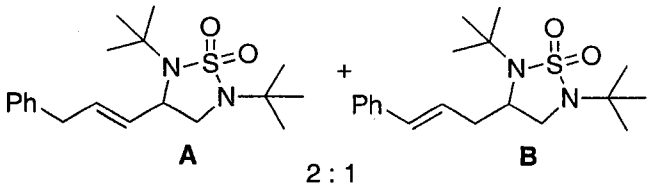
(Table 8.1, Entry 3) (b2134A).



Colorless oil; IR (film) 1740, 1371 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21-7.18 (m, 1H), 6.11-6.07 (m, 1H), 5.93-5.86 (m, 2H), 5.75 (dd, J =15.6, 8.0 Hz, 1H), 4.07-4.02 (m, 1H), 3.63 (d, J = 6.4 Hz, 2H), 3.43 (dd, J = 8.8, 6.4 Hz, 1H), 2.98 (dd, J = 8.8, 4.0 Hz, 1H), 1.59 (s, 9H), 1.41 (s, 9H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.5, 133.6, 132.8, 130.0, 121.4, 111.8, 110.3, 83.7, 57.8, 56.4, 55.3, 47.4, 31.8, 28.7, 28.3,

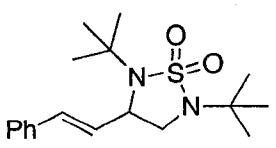
27.5; Anal. Calcd. for $C_{22}H_{37}N_3O_4S$: C, 60.11; H, 8.48; N, 9.56. Found: C, 59.89; H, 8.29; N, 9.62.

(Table 8.1, Entry 4) (b2209A).



Colorless oil; IR (film) 1602, 1371 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) A: δ 7.38-7.15 (m, 5H), 5.89-5.77 (m, 2H), 4.04-4.00 (m, 1H), 3.45 (dd, J = 8.8, 6.4 Hz, 1H), 3.41-3.39 (m, 2H), 3.00 (dd, J = 8.8, 4.0 Hz, 1H), 1.41 (s, 9H), 1.40 (s, 9H); B: δ 7.38-7.15 (m, 5H), 6.46 (d, J = 16.0 Hz, 1H), 6.20 (ddd, J = 16.0, 8.4, 6.4 Hz, 1H), 3.56-3.52 (m, 1H), 3.34 (dd, J = 8.8, 6.4 Hz, 1H), 3.17 (d, J = 8.8 Hz, 1H), 2.81-2.73 (m, 1H), 2.55-2.51 (m, 1H), 1.47 (s, 9H), 1.38 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) A & B: δ 139.8, 137.2, 133.5, 132.6, 131.6, 128.8, 128.73, 128.67, 127.7, 126.5, 126.3, 125.7, 57.8, 57.6, 56.4, 56.3, 55.2, 52.0, 47.5, 44.7, 39.5, 38.7, 28.7, 28.4, 27.8, 27.6; Anal. Calcd. for $C_{19}H_{30}N_2O_2S$: C, 65.10; H, 8.63; N, 7.99. Found: C, 65.32; H, 8.52; N, 8.11.

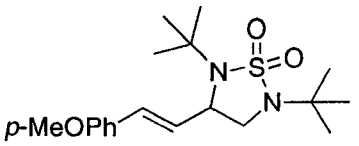
(Table 8.1, Entry 5) (b2122A).



White solid; mp 171-172 °C; IR (film) 1575, 1285 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42-7.28 (m, 5H), 6.58 (d, J = 16.0 Hz, 1H), 6.45 (dd, J = 16.0, 8.4 Hz, 1H), 4.20 (ddd, J

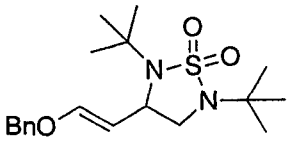
= 8.4, 6.4, 4.0 Hz, 1H), 3.55 (dd, J = 8.8, 6.4 Hz, 1H), 3.10 (dd, J = 8.8, 3.6 Hz, 1H), 1.46 (s, 9H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.3, 131.7, 130.6, 128.9, 128.3, 126.8, 57.9, 56.5, 55.7, 47.4, 28.8, 27.6; Anal. Calcd. for $C_{18}H_{28}N_2O_2S$: C, 64.25; H, 8.39; N, 8.33. Found: C, 64.36; H, 8.48; N, 8.09.

(Table 8.1, Entry 6) (b2142A).



White solid; mp 121-122 °C; IR (film) 1651, 1607, 1291 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 6.51 (d, J = 16.0 Hz, 1H), 6.29 (dd, J = 16.0, 8.8 Hz, 1H), 4.20-4.15 (m, 1H), 3.83 (s, 3H), 3.53 (dd, J = 8.8, 6.4 Hz, 1H), 3.07 (dd, J = 8.8, 4.0 Hz, 1H), 1.45 (s, 9H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 131.1, 129.0, 128.3, 128.0, 114.3, 57.8, 56.5, 55.9, 55.6, 47.5, 28.8, 27.5; Anal. Calcd. for $C_{19}H_{30}N_2O_3S$: C, 62.26; H, 8.25; N, 7.64. Found: C, 62.06; H, 8.46; N, 7.77.

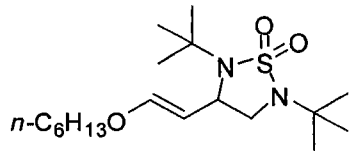
(Table 8.1, Entry 7) (b2037B).



Colorless oil; IR (film) 1671, 1652 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 5H), 6.56 (d, J = 12.6 Hz, 1H), 5.19 (dd, J = 12.6, 9.0 Hz, 1H), 4.80 (s, 2H), 3.98 (ddd, J =9.0, 6.0, 3.3 Hz, 1H), 3.47 (dd, J = 8.4, 6.0 Hz, 1H), 2.98 (dd, J = 8.4, 3.3 Hz, 1H), 1.42 (s,

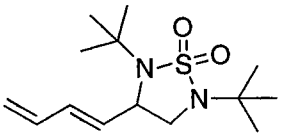
9H), 1.40 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.1, 136.7, 128.8, 128.3, 127.7, 106.2, 71.5, 57.7, 56.3, 52.8, 48.7, 28.8, 27.5; Anal. Calcd. for $C_{19}H_{30}N_2O_3S$: C, 62.26; H, 8.25; N, 7.64. Found: C, 61.90; H, 7.97; N, 7.87.

(Table 8.1, Entry 8) (b2038B).



Colorless oil; IR (film) 1671, 1652, 1369 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.47 (d, J = 12.6 Hz, 1H), 5.05 (dd, J = 12.9, 9.3 Hz, 1H), 3.69 (ddd, J = 9.3, 6.0, 3.6 Hz, 1H), 3.73-3.65 (m, 2H), 3.46 (dd, J = 8.4, 6.0 Hz, 1H), 2.98 (dd, J = 8.4, 3.6 Hz, 1H), 1.70-1.60 (m, 2H), 1.48-1.26 (m, 6H), 1.44 (s, 9H), 1.40 (s, 9H), 0.90 (t, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.7, 104.9, 69.7, 57.7, 56.3, 53.1, 48.9, 31.8, 29.3, 28.9, 27.6, 25.8, 22.8, 14.2; Anal.Calcd. for $C_{18}H_{36}N_2O_3S$: C, 59.96; H, 10.06; N, 7.77. Found: C, 59.78; H, 9.89; N, 7.90.

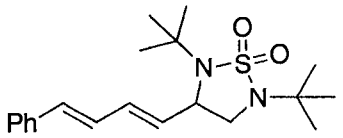
(Table 8.1, Entries 9 and 10) (b2241B).



Colorless oil; IR (film) 1604, 1370 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.34 (dt, J = 17.2, 10.0 Hz, 1H), 6.24 (dd, J = 15.2, 10.4 Hz, 1H), 5.94 (dd, J = 15.2, 8.4 Hz, 1H), 5.23 (dd, J = 17.2, 1.6 Hz, 1H), 5.15 (dd, J = 10.0, 1.6 Hz, 1H), 4.06-4.02 (m, 1H), 3.48 (dd, J = 8.8, 6.4 Hz, 1H), 3.01 (dd, J = 8.8, 3.6 Hz, 1H), 1.41 (s, 9H), 1.38 (s, 9H); ^{13}C NMR

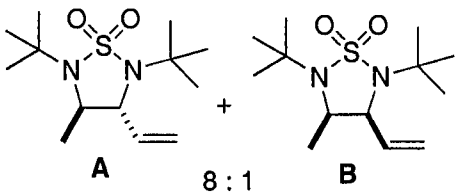
(100 MHz, $CDCl_3$) δ 135.9, 134.5, 132.4, 118.6, 57.8, 56.4, 55.0, 47.3, 28.7, 27.5; Anal. Calcd. for $C_{14}H_{26}N_2O_2S$: C, 58.70; H, 9.15; N, 9.78. Found: C, 58.69; H, 9.14; N, 9.59.

(Table 8.1, Entry 11) (b2315).



White solid; mp 129-130 °C; IR (film) 1642, 1596, 1290 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43-7.20 (m, 5H), 6.79 (dd, *J* =, 15.6, 10.2 Hz, 1H), 6.59 (d, *J* = 15.6 Hz, 1H), 6.40 (dd, *J* = 15.3, 10.2 Hz, 1H), 6.05 (dd, *J* = 15.3, 8.4 Hz, 1H), 4.11 (ddd, *J* = 8.4, 6.6, 3.3 Hz, 1H), 3.51 (dd, *J* = 8,4, 6.6 Hz, 1H), 3.05 (dd, *J* = 8.4, 3.3 Hz, 1H), 1.44 (s, 9H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.0, 134.4, 133.7, 132.1, 128.9, 128.1, 127.7, 126.6, 57.8, 56.5, 55.3, 47.5, 28.8, 27.5; Anal. Calcd. for $C_{20}H_{30}N_2O_2S$: C, 66.26; H, 8.34; N, 7.73. Found: C, 66.06; H, 8.12; N, 7.78.

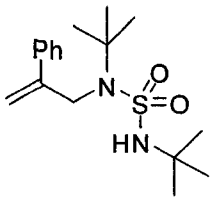
(Table 8.1, Entry 12) (b2311A).



White solid; IR (film) 1647, 1280 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) A: δ 6.07 (ddd, *J* = 17.2, 10.4, 6.8 Hz, 1H), 5.37 (d, *J* = 17.2 Hz, 1H), 5.21 (d, *J* = 10.4 Hz, 1H), 3.62 (d, *J* = 6.8 Hz, 1H), 3.34 (q, *J* = 6.4 Hz, 1H), 1.42 (d, *J* = 6.4 Hz, 3H), 1.42 (s, 9H), 1.40 (s, 9H); B: δ 5.97 (ddd, *J* = 17.2, 10.0, 9.2 Hz, 1H), 5.30 (d, *J* = 17.2 Hz, 1H), 5.26 (d, *J* =

10.0 Hz, 1H), 3.98 (dd, J = 9.2, 5.6 Hz, 1H), 3.59-3.55 (m, 1H), 1.44 (s, 9H), 1.43 (s, 9H), 1.26 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) A: δ 139.1, 116.8, 63.3, 56.9, 55.8, 29.0, 28.9, 23.0; B: δ 137.1, 118.7, 62.9, 57.8, 57.4, 54.0, 28.8, 28.6, 18.4; Anal. Calcd. for $C_{13}H_{26}N_2O_2S$: C, 56.90; H, 9.55; N, 10.21. Found: C, 57.02; H, 9.60; N, 10.30.

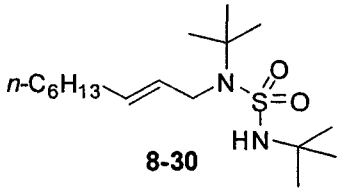
(Scheme 8.26) (b2413A, b2119A, b2421A).



White Solid; mp 85-86 °C; IR (film) 3278, 1640, 1317 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-9.29 (m, 5H), 5.46-5.42 (m, 2H), 4.30 (s, 2H), 3.53 (s, 1H), 1.49 (s, 9H), 1.34 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.2, 140.2, 128.6, 128.1, 126.7, 113.3, 59.8, 55.2, 50.4, 30.4, 29.8; HRMS Calcd for $C_{17}H_{28}N_2O_2S$ (M^+): 324.1872; Found: 324.1874.

(Scheme 8.27) (b2143B, b2139A, b2247A, b2241B)

(8-30) (b2138A).

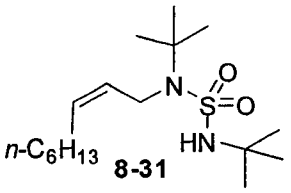


8-30

Colorless oil; IR (film) 3281, 1666, 1316 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.64-5.46 (m, 2H), 3.88 (d, J = 4.5 Hz, 2H), 3.75 (s, 1H); 2.02 (q, J = 6.6 Hz, 2H), 1.45 (s, 9H),

1.34 (s, 9H), 0.88 (t, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.3, 129.1, 59.4, 54.7, 49.1, 32.5, 31.9, 30.3, 30.2, 29.4, 29.1, 22.8, 14.3; Anal.Calcd. for $C_{17}H_{36}N_2O_2S$: C, 61.40; H, 10.91; N, 8.42. Found: C, 61.18; H, 10.68; N, 8.16.

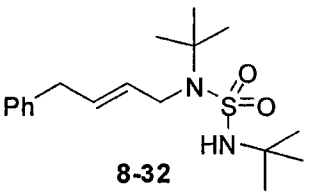
(8-31) (b2137B).



8-31

Colorless oil; IR (film) 3280, 1651, 1316 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.63-5.52 (m, 1H), 5.45-5.33 (m, 1H), 3.96 (d, J = 5.7 Hz, 2H), 3.84 (s, 1H), 2.03 (q, J = 6.9 Hz, 2H), 1.51-1.19 (m, 8H), 1.44 (s, 9H), 1.33 (s, 9H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.6, 129.5, 59.3, 54.7, 44.6, 31.9, 30.3, 30.2, 29.5, 29.2, 27.6, 22.8, 14.3; Anal. Calcd. for $C_{17}H_{36}N_2O_2S$: C, 61.40; H, 10.91; N, 8.42. Found: C, 61.25; H, 10.75; N, 8.51.

(8-32) (b2242A).

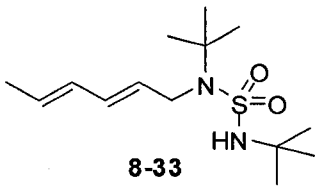


8-32

Colorless oil; IR (film) 3282, 1603, 1316 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.17 (m, 5H), 5.76-5.73 (m, 2H), 3.92 (d, J = 4.8 Hz, 2H), 3.81 (s, 1H), 3.38 (d, J = 4.8 Hz, 2H), 1.45 (s, 9H), 1.32 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.4, 131.5, 130.7,

128.8, 128.7, 126.3, 59.4, 54.7, 48.8, 38.9, 30.3, 30.2; Anal.Calcd. for $C_{18}H_{30}N_2O_2S$: C, 63.87; H, 8.93; N, 8.28. Found: C, 63.88; H, 9.01; N, 8.28.

(8-33) (b2236A).

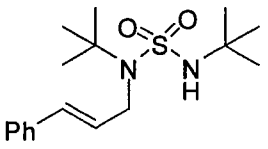


8-33

Colorless oil; IR (film) 3277, 1658, 1316 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.15-6.01 (m, 2H), 5.74-5.63 (m, 2H), 3.94 (d, J = 6.4 Hz, 2H), 3.75 (s, 1H), 1.76 (d, J = 6.8 Hz, 3H), 1.45 (s, 9H), 1.34 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.3, 131.0, 129.7, 129.6, 59.4, 54.7, 48.9, 30.3, 30.2, 18.3; Anal.Calcd. for $C_{14}H_{28}N_2O_2S$: C, 58.29; H, 9.78; N, 9.71. Found: C, 58.17; H, 9.86; N, 9.57.

(Scheme 8.28)

(8-34) (b1945A).

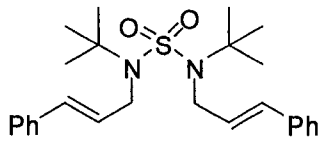


8-34

White solid; mp = 103-104 °C; IR (film) 3284, 1598, 1315 cm^{-1}; ^1H NMR (400 MHz, Benzene-d_6) δ 7.36 (d, J = 7.2Hz, 2H), 7.22 (t, J = 7.2 Hz, 2H), 7.17-7.13 (m, 1H), 6.64 (dt, J = 16.0, 6.4 Hz, 1H), 6.49 (d, J = 16.0Hz, 1H), 4.07 (dd, J = 6.4, 0.8 Hz, 2H),3.90 (s, 1H), 1.49 (s,9 H), 1.25 (s, 9H); ^{13}C NMR (100 MHz, Benzene-d_6) δ 137.3, 131.6, 129.8,

128.9, 128.5, 126.6, 59.1, 54.1, 49.4, 30.0, 29.9; Anal.Calcd. for $C_{17}H_{28}N_2O_2S$: C, 62.93; H, 8.70; N, 8.63. Found: C, 63.16; H, 8.17; N, 8.56.

(8-35) (b1945A).



8-35

White solid; mp = 98-100 °C; IR (film) 1950, 1319 cm^{-1}; ^1H NMR (300 MHz, Benzene-d_6) δ 7.37 (d, J = 7.2 Hz, 4H), 7.21 (t, J = 7.2 Hz, 4H), 7.16-7.12 (m, 2H), 6.72 (dt, J = 16.0, 6.4 Hz, 2H), 6.42 (d, J = 16.0 Hz, 2H), 4.08 (dd, J = 6.4, 0.8 Hz, 4H), 1.53 (s,18 H); ^{13}C NMR (100 MHz, Benzene-d_6) δ 137.3, 131.6, 129.6, 128.9, 126.6, 59.9, 49.2, 30.2; Anal.Calcd. for$C_{26}H_{36}N_2O_2S$: C, 70.87; H, 8.23; N, 6.36. Found: C, 70.68; H, 7.99; N, 6.51.

8.5 REFERENCES

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BIOSKETCH

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