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DISSERTATION

ENANTIO- AND DIASTEREOSELECTIVE SMALL RING FORMATION

Submitted by
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Department of Chemistry

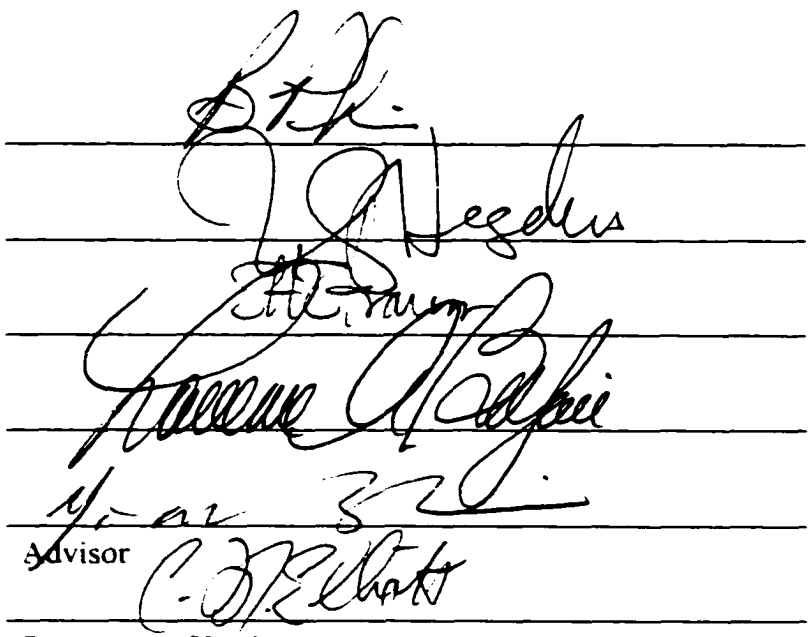
In partial fulfillment of the requirements
For the Degree of Doctor of Philosophy
Colorado State University
Fort Collins, Colorado
Summer 2002

COLORADO STATE UNIVERISITY

March 28, 2002

WE HEREBY RECOMMEND THAT THE DISSERTATION PROPARED UNDER OUR SUPERVISION BY JON CHARLES LORENZ ENTITLED ENANTIO- AND DIASTEREOSELECTIVE SMALL RING FORMATION BE ACCEPTED AS FULFILLING IN PART REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY.

Committee on Graduate Work



Advisor

Department Head

ABSTRACT OF DISSERTATION
ENANTIO- AND DIASTEREOSELECTIVE SMALL RING FORMATION

Small rings are useful reactive building blocks. Three membered rings have a large amount of strain and can be opened or rearranged to form more complex molecules. Our group has been active in the areas of catalytic asymmetric epoxidation and zinc mediated cyclopropanation.

Epoxidation of nitrogen-containing olefins was studied using the fructose-derived chiral ketone catalyst developed in our laboratory. A number of methods for preventing nitrogen oxidation were surveyed, showing that electron-poor nitrogens are compatible with dioxirane-mediated epoxidation. The epoxides were obtained in good optical purity and yield. These simple epoxides could be cyclized to form α hydroxy nitrogen heterocycles with little or no loss of enantiomeric excess. This method is complementary to other catalytic asymmetric epoxidation reactions, and is able to tolerate a variety of nitrogen-containing substituents.

Desymmetrization of cyclic dienes was studied. Symmetrical cyclic dienes with a prochiral directing group were epoxidized using the fructose-derived catalyst. Initial enantioselectivities and yields were good. If the reaction was continued a kinetic resolution occurred improving the enantiopurity of the mono epoxide. Very few catalytic reactions have shown the ability to perform this two step process. Symmetrical cyclic dienes without a prochiral-directing group were also found to be suitable substrates for this desymmetrization-kinetic resolution procedure. The change in ee of the mono epoxides with conversion to the bis epoxide can be explained using a simple transition state model based on sterics. These results provide further validation of the transition state model developed in our group.

The use of zinc carbenoids to cyclopropanate electron rich olefins has been known for some time. In the interest of gaining further understanding of the reactivity of

these zinc species for application to chiral cyclopropanation reactions, ligand effects were studied. Both the electronic and steric properties of the ligand on zinc affect the rate of cyclopropanation. A very reactive cyclopropanation reagent was developed using trifluoroacetic acid as the ligand. Variation of the leaving group on the carbenoid carbon produced a number of new carbenoid precursors which were able to cyclopropanate olefins with trifluoroacetic acid as the ligand on zinc. These new carbenoid precursors open up the opportunity for chiral Lewis acid or chiral leaving group controlled asymmetric cyclopropanation.

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CHAPTER ONE

CATALYTIC ASYMMETRIC EPOXIDATION OF NITROGEN-CONTAINING OLEFINS

1.A Introduction

Many molecules found in nature and of research interest contain chiral centers. Efficient construction of chiral compounds has long been a goal of synthetic chemists. Chiral epoxides have proven to be very versatile building blocks for organic synthesis. The ring strain allows epoxides to be opened with a variety of reagents. Complicated molecules have stereocenters that can be derived from chiral epoxides, or in some cases molecules of interest contain chiral epoxies. Due to the reactive nature of epoxides a large body of work has been compiled for the further transformation of epoxides. Neighboring groups can modulate the epoxide's reactivity, or direct addition of nucleophiles.

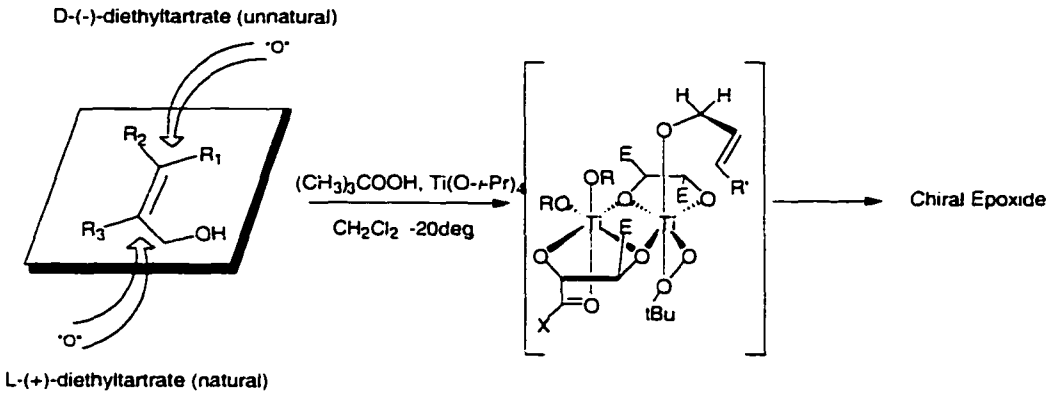
The most desirable technique for generating epoxides is catalytic asymmetric formation of epoxides from achiral starting materials. The synthesis of chiral epoxides has been the focus of extensive research efforts in the Shi group for several years.

1.B Methods for Catalytic Asymmetric Epoxidation

A number of very successful catalytic epoxidation methods have been reported over the last twenty years. There are still many situations for which there is no ideal reaction for chiral epoxide formation. Fortunately, the known methods are complementary in many cases, giving the chemist a toolbox of reactions for the formation of chiral centers.

1.B.1 Sharpless Asymmetric Epoxidation

The first successful catalytic asymmetric epoxidation method was reported by Sharpless and Katsuki using a titanium tartrate system for the epoxidation of allylic alcohols.[1,2] Further improvements were realized in 1986 when it was found that the addition of molecular sieves accelerated the reaction, allowing most substrates to be epoxidized using only 5-10 mol% of the catalyst.[3] The stereochemical outcome for the Sharpless asymmetric epoxidation can be predicted using a simple transition state model (Figure 1.1).



Scheme 1.1 Transition State Model for the Sharpless Epoxidation

The predictive power of this model has been proven to be so great that it is often used to prepare standards for the determination of absolute stereochemistry. One of the titanium atoms coordinates both the allylic alcohol and the oxygen source, holding them in a chiral environment. This highly structured transition state provides epoxides with ee greater than 95% in most cases. Since its first report the Sharpless Asymmetric Epoxidation has been applied to multiple projects throughout organic chemistry.

1.B.2 Metal Salen Systems

Successful catalytic asymmetric epoxidation of unfunctionalized olefins in high ee remained a largely unsolved problem until the 1990's.[4] Jacobsen and coworkers reported a chiral manganese salen catalyst for the epoxidation of *cis* and conjugated olefins (Figure 1.2).[5] This catalyst uses a chiral bridge at the top of the salen to control the approach of the olefin to the metal center. Both electronic and steric factors affect the rate and stereochemical outcome of the reaction. Mechanistic studies indicated that the addition was a two step process, allowing some conjugated *cis* double bonds to isomerize to form *trans* epoxides. Salen systems have been most successful with electron-rich,

conjugated olefins which can stabilize this radical or charge separated transition state. Only *cis* olefins have been epoxidized successfully due to their ability to approach the active metal center held in the flat salen ligand. More sterically congested olefins are not able to approach the active metal center, so reactions are very slow or do not proceed. There is no tightly coordinated transition state in salen-catalyzed epoxidation so substrate geometry plays a large role in selectivity.

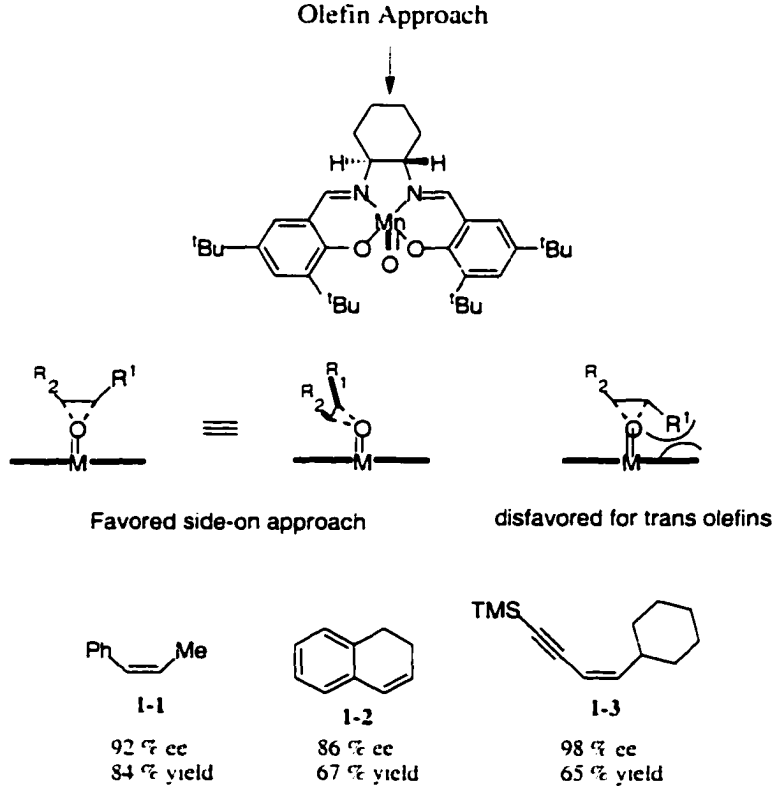


Figure 1.2 Jacobsen Epoxidation

In Figure 1.2 the effectiveness of this catalyst is shown. Extremely high ee's can be obtained with *cis* conjugated olefins. The substrate scope for the manganese salen system is more limited than for the Sharpless epoxidation, but it complementary in suitable substrates. Extremely low catalyst loading and the ability to recycle the catalyst has made is suitable for large-scale synthesis of chiral *cis* epoxides.

1.B.3 Porphyrin Systems

Porphyrin catalysts have been seen as a biomimetic approach to catalytic oxidation reactions.[6] Many of the enzymes that perform oxidations in living creatures contain a planar porphyrin in a chiral pocket. The first example of a porphyrin-catalyzed asymmetric epoxidation of a simple olefin was reported by Groves and Meyers, using a metal porphyrin.[7] A number of metals have proven competent in the oxidation of olefins to epoxides including iron, ruthenium and, manganese. For some time Collman has been at the forefront of chiral metal-porphyrin catalyzed epoxidation of olefins. A recently reported, sterically dense prophyrin system has been successfully applied to epoxidation of terminal olefins, (Figure 1.3).[8]

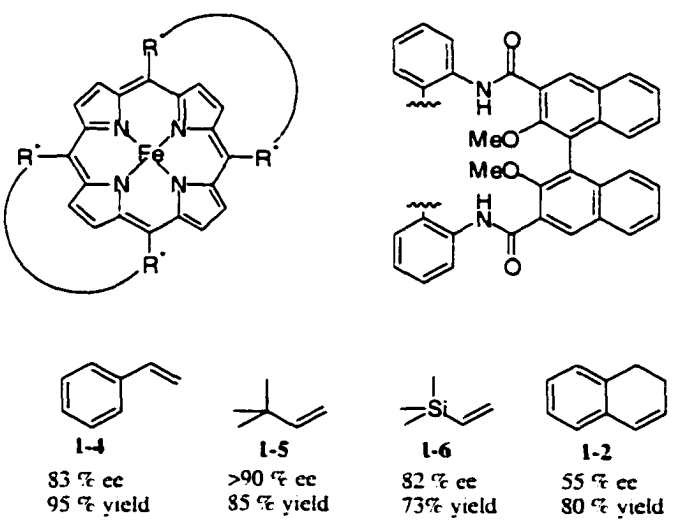


Figure 1.3 Collman's Catalysts for Terminal Olefins

The prophyrin system derives its selectivity from the steric interaction of the olefin with the chiral wings attached to the central planar core. The most successful substrates have been terminal olefins, which have a very large group on one side and a very small group on the other side of the olefin. Due to the sterically demanding nature of the catalyst, in general only terminal olefins are epoxidized in high ee.

Another successful porphyrin catalyst has recently been reported by Che and coworkers, (Figure 1.4).[9] One of the added features of ruthenium porphyrin complexes is that they can epoxidize electron-deficient olefins, although the enantioselectivities are still rather modest. Based on this behavior the possibility for nucleophilic epoxidation has been investigated.

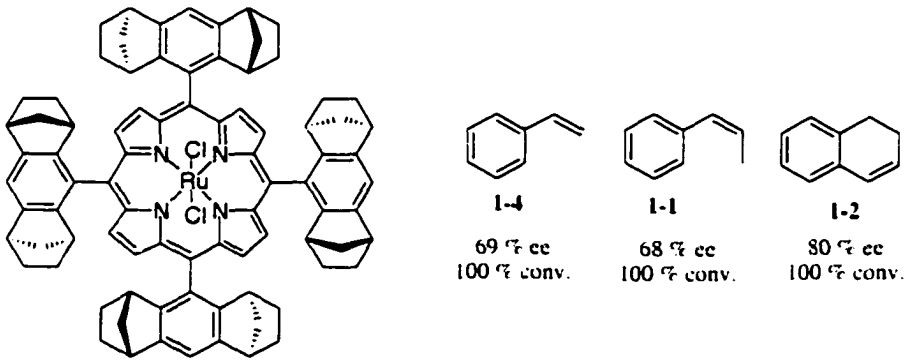
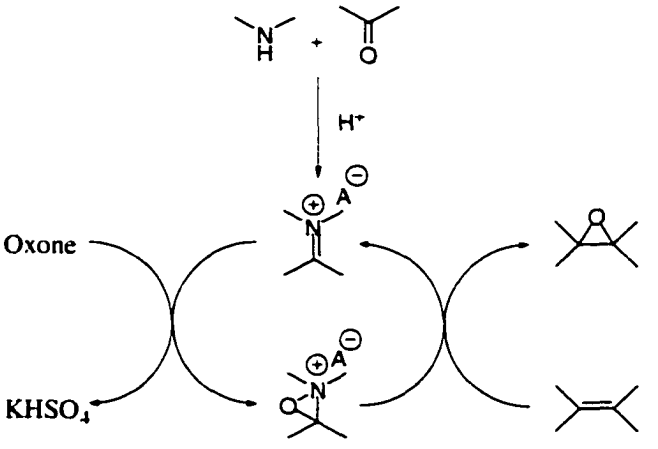


Figure 1.4 Che's Porphorin Catalyst

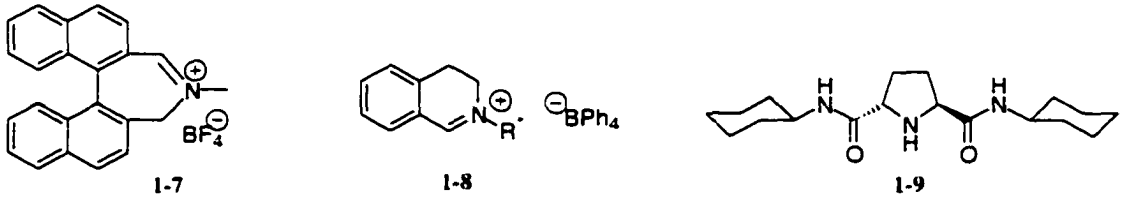
1.B.4 N-Oxide Epoxdiation of Olefins

A relatively new system for the chiral epoxidation of olefins are the imine or iminium salt catalysts.[10] An imine or iminium salt formed *in situ* or preformed can be oxidized to an oxaziridine which serves as the oxygen transfer agent, Scheme 1.1.



Scheme 1.1 Oxaziridine Epoxidation of Olefins

Catalytic asymmetric versions of oxaziridine epoxidations are still in their infancy, and the factors affecting the reactivity and selectivity are not fully understood. The initial reports are very promising, with a wide variety of structural diversity reported (Figure 1.5). Each of these catalysts has been reported by a different research group.



1-7 up to 71% ee

1-8 up to 73% ee

1-9 up to 65% ee

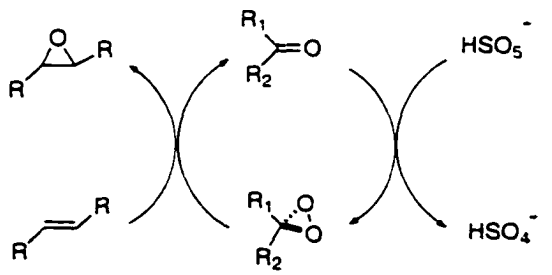
Figure 1.5 Examples of Oxaziridinium Oxygen Transfer Catalysts

One of the areas of great interest for oxaziridine-catalyzed epoxidation is the asymmetric epoxidation of terminal olefins. The catalysts could conceivably have chirality both on the nitrogen and on its ketone or aldehyde counterpart, creating a chiral pocket. A densely-packed chiral environment has been shown to be efficient in porphyrin systems for the epoxidation of terminal olefins, and could be used as a model for the oxaziridine epoxidation.

During this work it was found that amines themselves can epoxidize olefins in the presence of Oxone.[11] Initial mechanistic work has implicated a radical ion type intermediate in the epoxidation. Although Oxone is the oxidant of choice, other oxidants hold possibilities if a radical ion type intermediate is operative.

1.B.5 Dioxirane-Catalyzed Epoxidation of Olefins

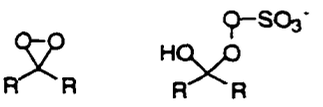
Dioxiraines can be generated in situ from Oxone or hydrogen peroxide and a ketone, Scheme 1.2. Examination of the cycle indicates that a catalytic amount of a chiral ketone could carry out the oxygen transfer. Chiral ketones have proven to be very efficient catalysts for the formation for chiral epoxides from unfunctionalized olefins.[12] Chiral ketone catalyzed epoxidation of olefins was first reported by Curci in 1984,[13] and in the 1990's many groups reported successful chiral ketone catalysts.



Scheme 1.2 Ketone Catalyzed Epoxidation

1.B.5.a Reactive Intermediate

Until recently the exact nature of the reactive intermediate formed was not known. Several papers have been published concerning the reactive intermediate for the epoxidation of olefins with Oxone and a ketone. The debate centered around the actual reactive intermediate; dioxirane **1-11**, or tetrahedral intermediate **1-12** (Scheme 1.3).



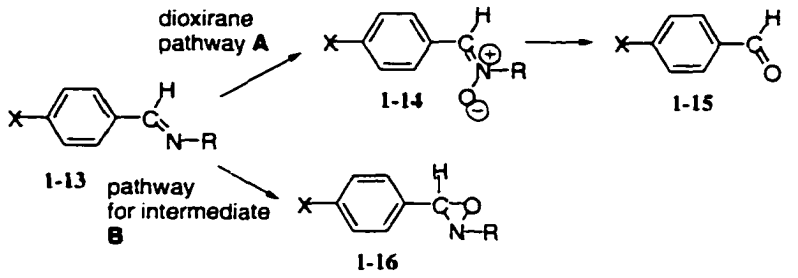
1-11 1-12

Scheme 1.3 Possible Reactive Species

The form of the actual reactive species is important to consider when designing a catalyst. The dioxirane lends itself to C_2 and pseudo C_2 symmetric catalyst design.

The first paper to appear on this subject suggested that the open form **1-12** was the reactive intermediate on the basis of an ^{18}O labeling study.[14] Armstrong used ^{18}O labeled 4-t-butyl cyclohexanone as the catalyst to epoxidize cylohexene. Since none of the isolated epoxide contained label it was concluded that intermediate **1-12** was responsible for the epoxidation. Their study was questioned on the basis of their low yield, 15%, and the poor ability of their catalyst to move between the organic and aqueous layers to participate in the catalytic cycle. Subsequent reports mentioned a substantial amount of background reaction with Armstrong's system, so the ketone may not have participated at all. Oxone is known to epoxidize olefins, but at a very slow rate in the absence of a ketone. The rigid conformation of the 4-t-butyl cyclohexanone sterically blocks one face of the ketone, allowing only one face of the ketone to interact with Oxone and subsequently react with the olefin. This may also explain why no label was seen in the product. This report provided more confusion than clarification on the mode of reaction.

A subsequent paper by Adam and coworkers in Germany tried to show the existence of **1-11** via a competition study, Scheme 1.4.[15] Nitrogen acts as a nucleophile in pathway A, while the open intermediate is expected to electrophilically oxidize the imine double bond in pathway B.

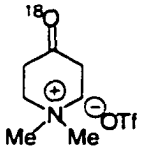


Scheme 1.4 Adam's Competition Study

Both products were observed suggesting that a dioxirane is generated under the reaction conditions, but providing little clarification about the reaction pathway.

Subsequently an ^{18}O labeled acetone catalyzed epoxidation of *trans*-β methylstyrene was performed. The isolated epoxide contained a small amount of label, suggesting that the dioxirane intermediate is involved in the epoxidation of olefins.

In late 1997 Denmark published a paper looking at the participation of dioxiranes in the epoxidation of olefins.[16] Denmark used ^{18}O labeled 1,1-dimethyl-4-oxopiperidinium triflate, ketone **1-17**, under phase-transfer conditions to epoxidize 1-phenyl cyclohexene in the presence of Oxone.



1-17

Figure 1.6 Denmark's ^{18}O Epoxidation Catalyst

When 1 equivalent of ketone **1-17** with 90% ^{18}O label was used to epoxidize cyclohexene 34% of the epoxide contained label. As the amount of ketone was increased the amount of label incorporated into the epoxide increased, suggesting that intermediate **1-11** is involved. Denmark was able to account for the majority of the ^{18}O at the end of the

reaction, and the epoxidation went in high yield, 90%, with very little background reaction observed, providing strong evidence for a dioxirane intermediate.

1.B.5.b Transition State Geometry

One of the more important issues when designing a catalyst is how will the dioxirane ring approach the olefin to transfer the oxygen. Two extreme transition states can be envisioned for oxygen transfer, spiro and planar (Figure 1.7). Baumstark and coworkers observed that *cis* hexenes were 7-9 fold more reactive than *trans* hexenes when epoxidized by dimethyl dioxirane.[17]

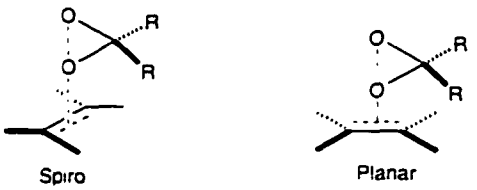


Figure 1.7 Transition State Geometry

Analysis of the possible transition state geometries showed that *cis* olefins had little steric interaction with dimethyl dioxirane in the spiro transition state, while the *trans* olefins have steric interactions. In the planar transition state both *cis* and *trans* olefins have roughly equivalent steric interactions with dimethyl dioxirane, suggesting that the primary mode of reaction is via the spiro transition state.

High level computational studies have been done by a number of groups concerning the transition state geometry.[18] In all of the cases the spiro transition state has been favored by several kilocalories. In the spiro transition state, the oxygen lone pairs line up with the olefin π^* orbital in preparation for bond formation (Figure 1.8). The orbital overlap expected in the spiro transition state lowers it energy, favoring the spiro over the planar transition state.

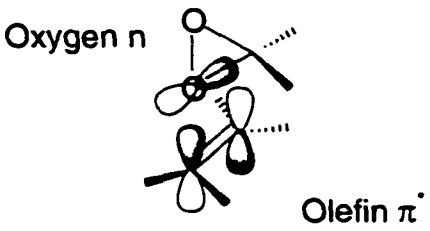
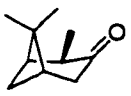


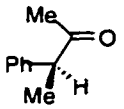
Figure 1.8 Orbital Overlap in the Spiro Transition State

1.B.5.c Chiral Ketone Catalysts

Reports of asymmetric epoxidation of olefins using dioxiranes have been made with a number of ketone catalysts. Initial success in the epoxidation of olefins using chiral ketones was reported by Curci and coworkers in 1984.[9] They obtained ee's of 6 - 12 % in low yield after long reaction times (days up to a week) for the epoxidation of unfunctionalized olefins using ketone catalysts **1-18** and **1-19**.



1-18



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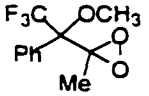
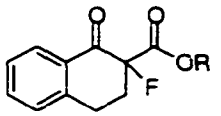


1-20

These modest results encouraged an extensive amount of effort to find a viable chiral ketone catalyzed asymmetric epoxidation reaction. Little was seen on chiral epoxidation with dioxiranes until 1995 when a number of reports appeared. Curci and coworkers developed a much more reactive and selective catalyst **1-20**, which gave ee's of about 20% and respectable yields, 80-85%, for both the S and R isomers of the ketone.[19]

The same year Marples published attempts with tetralone and indanone derived chiral ketones **1-21** and **1-22**.[20] Unfortunately they were not able to observe any enantioselectivity.



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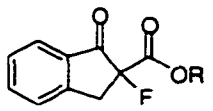
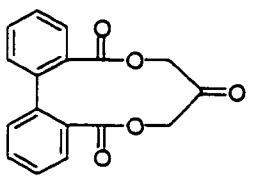


1-22

The following year Yang and coworkers published a series of ketone catalysts designed from information derived from the chiral and achiral epoxidation of olefins with dioxiranes.[21] Electron-withdrawing groups were incorporated to increase the reactivity of the ketone and subsequent dioxirane. Bulky steric groups designed to communicate stereochemistry were also incorporated, but far enough away so as not to inhibit the reactivity. A series of biphenyl **1-23** and binapthyl **1-24** ketones which showed good ee's and good yields for sterically demanding aromatic olefins were synthesized.



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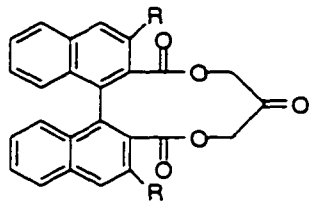
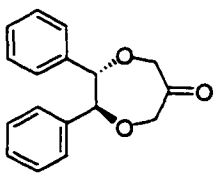


1-24 R = H

1-25 R =

In a following paper "feelers" were attached to the skeleton **1-25** to help orient the substrate as it approached the catalyst and higher ee's ranging from 84 - 95% for a variety of aromatic substrates were obtained.[22] In 1997 Song's group reported ketone catalysts **1-26** and **1-27**, similar to those of Yang's group, but the ester functionality in the tether was replaced with an ether linkage. When these ketones were used for the epoxidation they showed a marked decrease in ee and yield compared to Yang's ketones.



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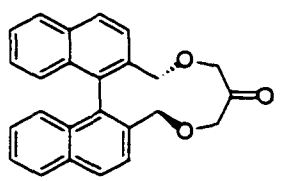
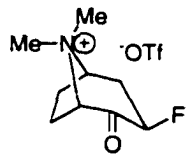


1-27

In 1997 Denmark reported limited chiral induction, 35% ee, for the epoxidation of *trans*-β-methylstyrene with a tropanone-derived catalyst **1-28**.[23] More important than this modest result is the fact that this paper showed the electronic effects on the rate of epoxidation. The axial or equatorial orientation of the fluorine greatly affected the rate of epoxidation. Fluorine in the equatorial position greatly increased the reactivity and two equatorial fluorines further increased the reactivity, probably due to an anomeric effect.

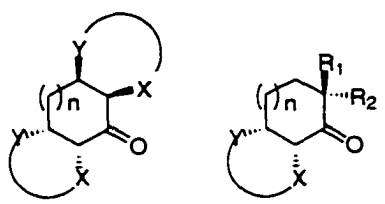


1-28

Several recent reports of ketone-catalyzed epoxidation have appeared, but the best results with their systems gave ee's in the 70's.[24] These results illustrate the sensitivity of dioxiranes to steric and electronic effects.

1.B.5.d Fructose-Derived Chiral Ketone Catalyst

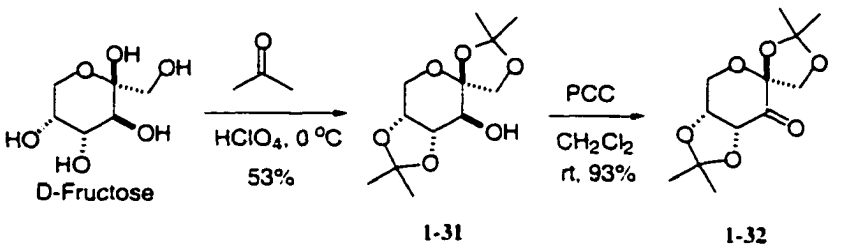
In 1996 Work in the Shi lab to find a suitable ketone catalyst for epoxidation of unfunctionalized olefins centered on a compact pseudo-C_2 symmetric design (Figure 1.9).



1-29 **1-30**

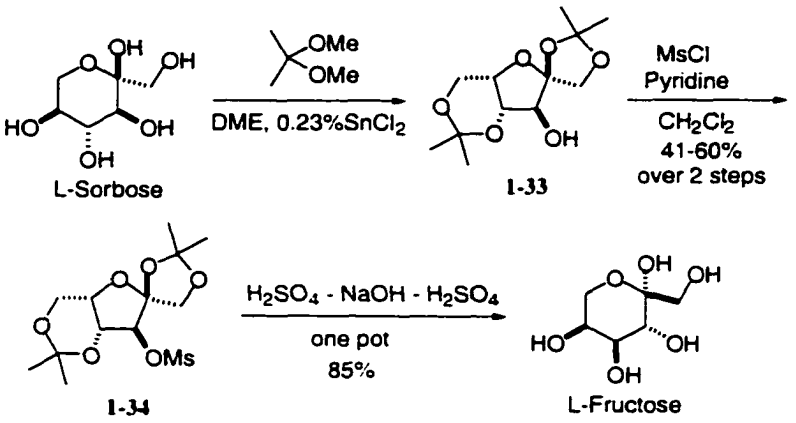
Figure 1.9 C_2 and pseudo C_2 Symmetric Ketone Design

This ketone has the stereo centers in close proximity to the reactive ketone. Epimerization of these centers is prevented by having them tied up in a fused ring, or as quaternary carbons. In a search for suitable starting materials carbohydrates were found to already posses the desired stereochemical environment. Ketone **1-32** was synthesized from readily available D-fructose in two steps Scheme 1.5



Scheme 1.5 Synthesis of Ketone 1-32

Ketone **1-32** has the desired stable chirality and chiral centers proximal to the ketone. In addition, the electron-withdrawing oxygens α to the ketone activate it for nucleophilic attack. The spiroketal helps to hold the ketone in a rigid conformation by the anomeric effect. Anytime a molecule from the chiral pool is used to synthesize a chiral catalyst there is concern over the availability of the opposite enantiomer. In this case L-fructose is very expensive. However it can be prepared from naturally-occurring, and inexpensive L-sorbose by ketalization, mesylation and acid base treatment, Scheme 1.6.



Scheme 1.6 Preparation of L-Fructose

The straightforward access to both enantiomers of ketone catalyst **1-32** makes it an attractive prospect for synthetic use.

Initial studies with ketone **1-32** showed that it could successfully epoxidize unfuntionalized *trans* and tri-substituted olefins (Figure 1.10) in high ee and good yield.[25] In order to obtain the epoxides in high ee, 300 mol% of catalyst **1-32** had to be used.

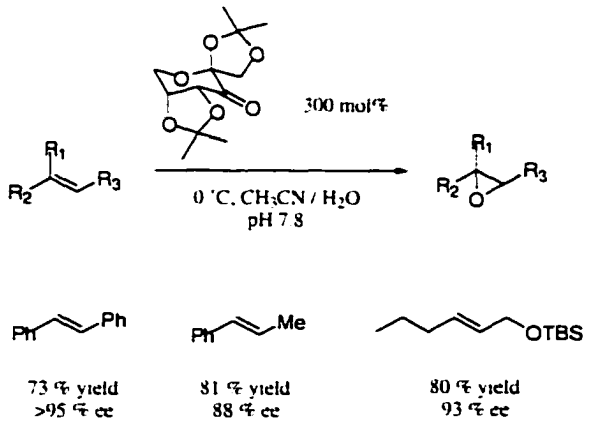
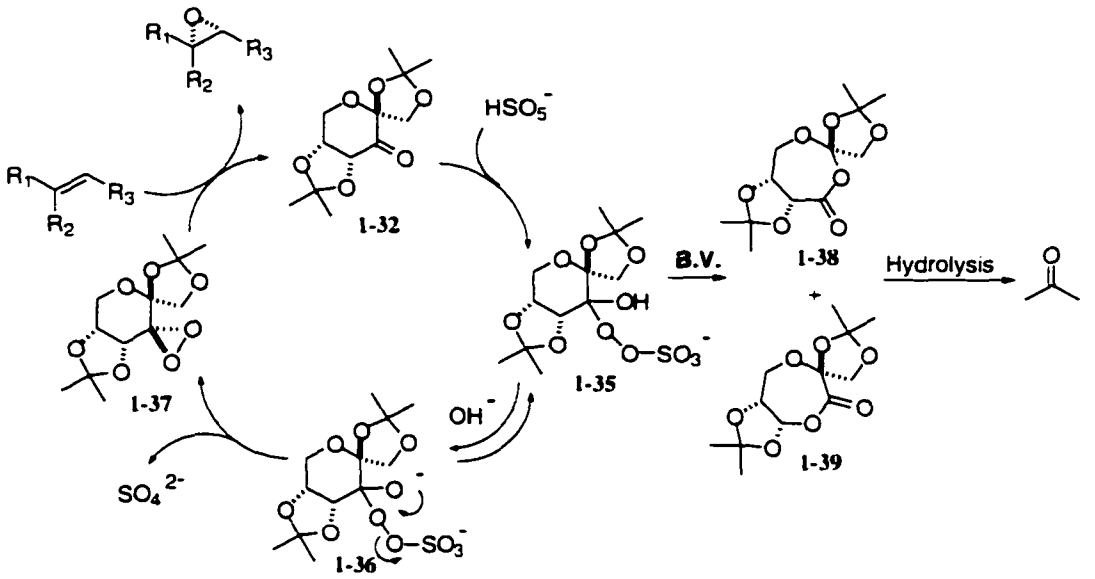


Figure 1.10 Initial Epoxidation Results

These results were both encouraging and troubling. The enatioselectivies were extremely high, better than other catalyst system reported at this time, however the extremely high catalyst loading was troubling. It seemed that the catalyst must be decomposing under

the reaction conditions. The complete catalytic cycle was analyzed for a place where the decomposition could occur Scheme 1.7.



Scheme 1.7 Proposed Catalytic Cycle

The possibility of a Baeyer-Villiger reaction of tetrahedral intermediate **1-35** before dioxirane formation seemed a feasible decomposition pathway. Raising the pH of the reaction from 7.8 to a more basic pH should favor formation of the dioxirane, diminishing the possibility of the Baeyer-Villiger reaction.

A study of the epoxide formation vs. the reaction pH using 20 mol% catalyst was carried out.[26] As the pH increased from 7.5 to 10 the conversion increased dramatically from under 10% to about 80%. With only 20 mol% of ketone catalyst used an 80% conversion showed that ketone **1-32** was truly acting as a catalyst (Figure 1.11). In addition, changing to a mixed solvent system of CH_3CN/DMM/Buffer provided a further increase in conversion.

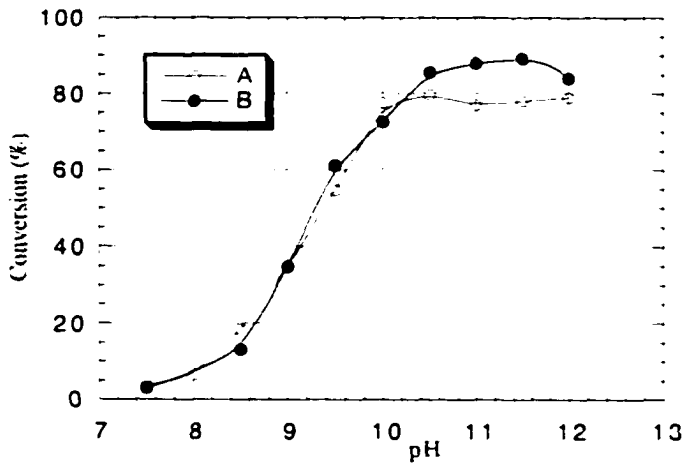


Figure 1.11. Plot of the conversion of *trans*-β-methylstyrene against pH using ketone **1-32** (0.2 eq.) as catalyst in two solvent systems, H_2O-CH_3CN (1 : 1.5, V/V) (**A**), H_2O-CH_3CN-DMM (2 : 1 : 2, V/V) (**B**)

When the new high pH epoxidation conditions were used, the amount of ketone required was lowered from 300 mol% to 30 mol%, a remarkable order of magnitude reduction. The lowering of catalyst loading maintained the good yields and high ee seen in the previous work(Figure 1.12).

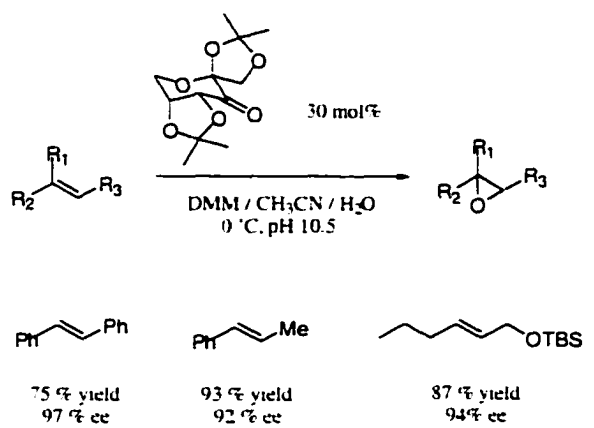


Figure 1.12 Epoxidation at High pH

The source of the enantioselectivity in dioxirane epoxidations is based on a balance of two factors, sterics, (the approach of the catalyst to the olefin), and electronics,

(the spiro vs. planar transition states.) A balance must be maintained in order to obtain good conversion and enantioselectivity.[27] These two factors can be used to build possible transition states for predicting the stereochemical outcome (Figure 1.13).

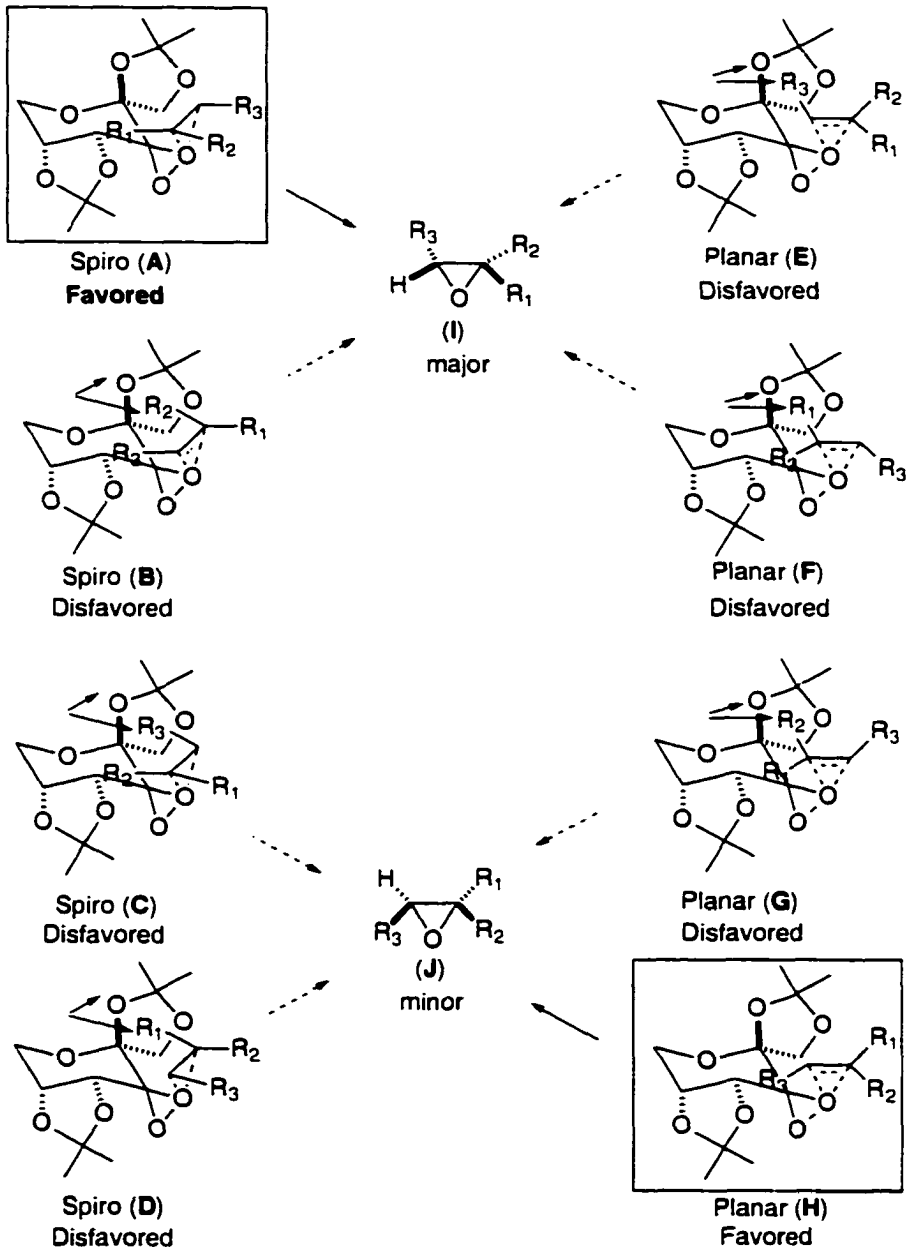
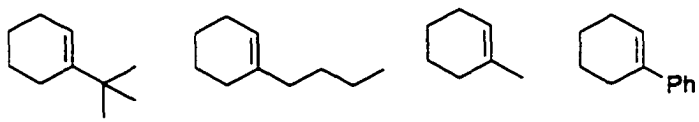


Figure 1.13 Possible Transition States for Chiral Epoxidation

A number of the transition states in Figure 1.13 can be ruled out immediately based on steric repulsion between the ketone catalyst and the olefin. After eliminating the

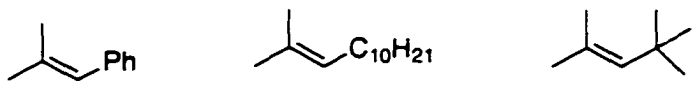
sterically-disfavored transition states, spiro A and planar H are left. According to previous experimental and computational work the spiro transition state should be favored. This competition can be followed experimentally since the planar and spiro transition states give opposite enantiomers. Examination of the absolute configuration of the products shows which transition state predominates. If there is some leakage via the planar transition state it would result in a lowering of the ee. By adjusting the size of groups R_1, R_2 and R_3 the effects of sterics on selectivity can be evaluated.

As the size of R_1increases, spiro A becomes disfavored, and the ee will decrease due to the steric repulsion of the R group and the pyran ring on the catalyst favoring the planar H transition state (Figure 1.14).



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

The effect of the size of R_1 on enantioselectivities
(Decreasing the size of R_1 results in a higher ee)



76.4% ee 86.5% ee 91% ee

The effect of the size of R_3 on enantioselectivities
(Increasing the size of R_3 results in a higher ee)

76.4% ee 96.8% ee

The effect of the size of R_1 & R_3 on enantioselectivities
(Decreasing the size of R_1 and increasing the size of R_3 enhance the ee)

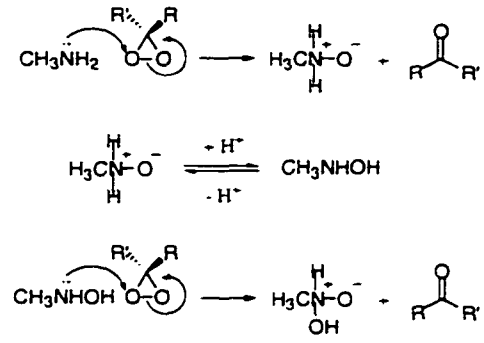
Figure 1.14 The Effect of Sterics on the Enantiomer Excess

As the size of R_3 increases, planar H is disfavored, due to the steric repulsion of R_3 sitting over the pyran ring, and spiro A is favored. When the steric effects of R_1 and R_3 are combined synergistically, the epoxide's ee is very high due to the predominance of the spiro A transition state. This transition state model can be used to predict the stereochemical outcome of a reaction, along with an estimation of the ee of the epoxide. In all of the cases seen in our labs the spiro transition state is dominant, based on the absolute configuration of the epoxides produced.[28]

1.C Epoxidation of Nitrogen Containing Molecules

1.C.1 Introduction

Nitrogen is found in a variety of molecules of chemical and biological interest, from the alkaloids to peptide-based antibiotics. If epoxidation methods developed in the Shi group could be applied to nitrogen-containing molecules it could provide another method to selectively synthesize these important molecules. Earlier work in other laboratories showed that dimethyl dioxirane (DMD) is very efficient at oxidizing primary, secondary, tertiary, aromatic, azo and isocyanate nitrogens to the nitro, nitroso or azoxy group, depending on the starting material.[29] Electron-rich nitrogens are better substrates for DMD, but electron-poor nitrogens will react in some cases. In a competition study, aniline was oxidized preferentially in the presence of furan, a very electron-rich olefin, and since epoxidation reaction is of interest the favored oxidation of nitrogen must be prevented, Scheme 1.8.



Scheme 1.8 Dioxirane Oxidation of Nitrogen

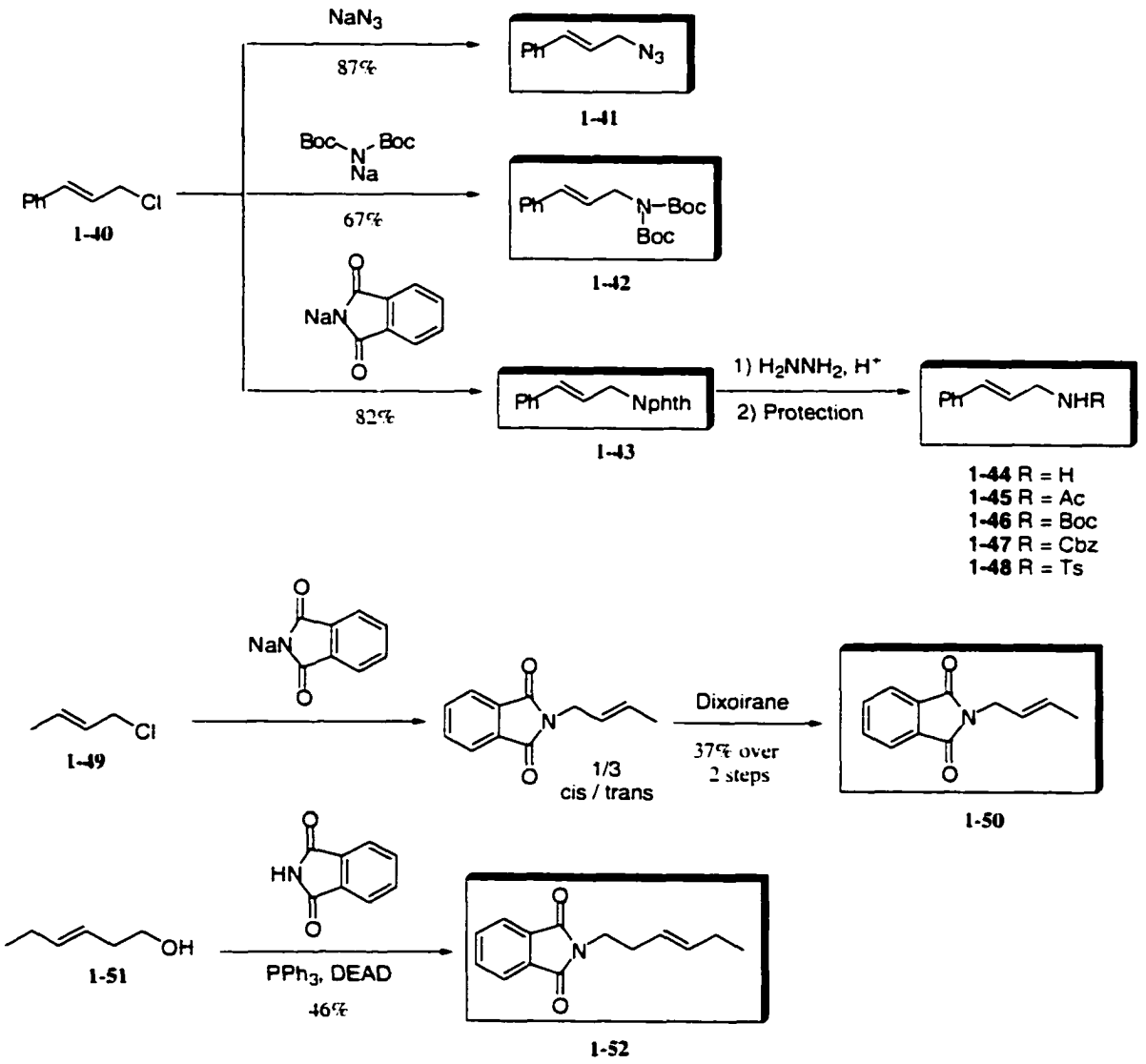
Nitrogen's nucleophilic lone pair of electrons rapidly attacks the electrophilic dioxirane ring decomposing the dioxirane and forming ammonium oxides. The nitrogen can continue to be oxidized until all of its hydrogens are replaced with oxygens if there is enough dioxirane present. Nitrogen can consume the Oxone before the dioxirane is formed resulting in sluggish and incomplete reactions. Oxone itself can oxidize nitrogens before it forms a dioxirane. An added concern is preventing nitrogen itself from acting as an epoxidation catalyst. If an achiral nitrogen acts as an epoxidation catalyst under the reaction conditions it would lower the overall selectivity of the reaction. There have been reports on reductive work-up conditions for epoxidations of compounds containing 3° amines, but they have not been shown to be very general.

1.C.1 Results

Initial studies focused on finding protected or masked nitrogens that were compatible with the epoxidation conditions. In order to prevent oxidation of the nitrogen electron-withdrawing protecting groups can be employed, or the ammonium salts can be used.[30] Due to the high pH (10-11) necessary for the selective epoxidation reaction, conversion of the amine to its ammonium salt is not a viable protection method. A number of common nitrogen protecting groups were surveyed for their compatibility with

the epoxidation method. In addition, molecules containing nitrogen masked as a phthalimide or azide were tested.

A series of cinnamyl amines were prepared from commercially available cinnamyl chloride as outlined in Scheme 1.9.



Scheme 1.9 Preparation of Nitrogen containing olefins

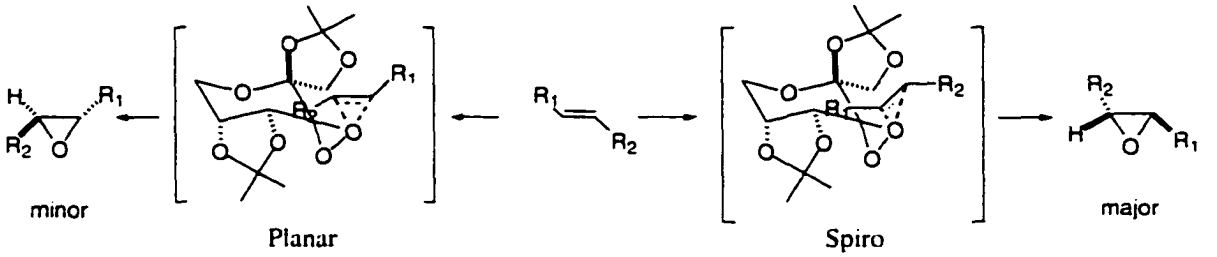
Cinnamyl chloride was directly converted to azide **1-41**. Other cinnamyl amines were derived from the Gabriel reaction, **1-42** and **1-43**. Phthalimide **1-43** was hydrolyzed to the free amine and protected with a variety of common electron-withdrawing protective groups under standard conditions. Cinnamyl azide **1-41** could be converted to cinnamyl amine by hydrogenolysis using Lindlar's catalyst, this was the preferred method.

Aliphatic phthalimide **1-50** was formed by the Gabriel reaction with crotyl chloride resulting in a mixture of the (1/3) *cis* and *trans* olefins. The minor *cis* isomer was removed by exploiting the faster rate for dioxirane epoxidation of *cis* vs. *trans* olefins. By running a short dioxirane epoxidation of **1-50** the *cis* isomer was removed leaving the desired *trans* isomer. Homo-allylic phthalimide **1-52** was prepared from the alcohol using the Mitsunobu reaction.[31]

The cinnamyl derivatives were subjected to standard epoxidation conditions with 30 mol% catalyst using Oxone as the oxidant at pH 10.5. Most common nitrogen protecting groups proved to be compatible with the epoxidation, (Table 1) notably Cbz, acetate, azide and bis-Boc groups provided an efficient means of masking nitrogen. Efforts to epoxidize molecules containing 1° and 3° allylic amines resulted in mixtures of N-oxide products. Attempts to use a reductive work-up to isolate the amine epoxide were not successful. The absolute configuration of cinnamyl azide epoxide was determined after hydrogenation with Lindlar's catalyst to the primary amine by comparing the optical rotation to the literature value.[32] One of the most important factors in the choice of the masked nitrogen is solubility, since the reaction is carried out in a very polar solvent combination starting at a ratio of H_2O/DMM/CH_3CN (1.5/2/1) with the percentage of water increasing as the reaction progresses. When cinnamyl phthalimide was used, poor conversions were obtained due to lack of solubility; similar problems were encountered when N-methyl Cbz-cinnamyl amine and Boc,Cbz bis protected amine were used, (not

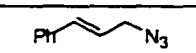
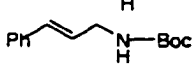
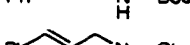
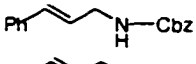
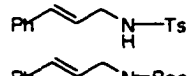
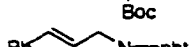
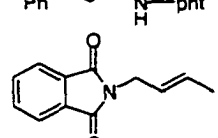
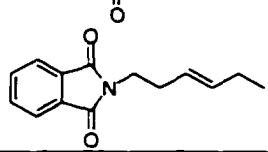
shown). If aliphatic phthalimides were used the solubility problems diminished and respectable ees were obtained (Table 1.1, entries 8,9).

The ee's obtained for the various epoxides have a wide range due to competition between the spiro and planar transition states, although nitrogen mediated epoxidation may erode the intrinsic selectivity of the process, Scheme 1.10.



Scheme 1.10 Transition States

Table 1.1 Epoxidation of *trans* Nitrogen Containing Olefins

Entry	Substrate	Yield[a] (Conv.)[b]	% ee	α_D	Abs. conf.
1		50(51)[c]	94[d]	+37.8	R.S'
2		81(95)	88[d]	+53.9	
3		48(80)	62[d](98)[e]	+49.6	
4		56(81)	84[d]	+40.0	
5		34(87)	84[g]	+46.4	
6		63(76)	>98[f]	+7.4	
7		<10(nd)	nd	nd	
8		25(33)	87[d]	-13.1	
9		63(73)	90[h]	-1.82	

Typical epoxidation procedure: To a mixture of olefin (1 mmole), tetrabutyl ammonium hydrogen sulfate (0.015g, 0.04mmol) and ketone **1** in CH_3CN/dimethoxymethane (15mL

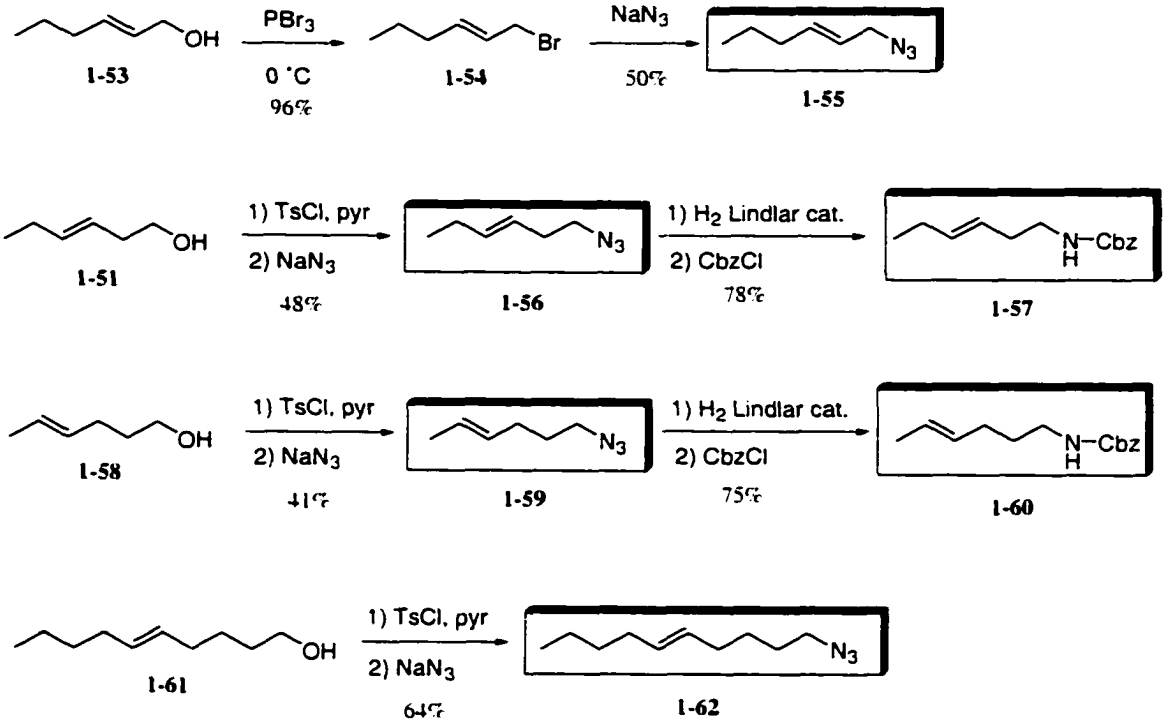
1/2 v/v) was added 10mL buffer (0.05M $Na_2B_4O_7 \cdot 10H_2O$ in 10^{-4}M disodium-EDTA) and the mixture cooled in an ice bath. A solution of Oxone (0.85g 1.38eq.) in 6.5mL 10^{-4}M EDTA and a solution of K_2CO_3 (0.80g 5.8eq) in 6.5mL H_2O are added over 1.5 hours via syringe pump. After the addition is complete the reaction is stirred an additional 30 minutes then the epoxide is isolated.
a) Many of these epoxides are very acid sensitive and decompose upon purification. Great care must be taken in buffering the silica gel used.b) Based on crude ^{1}H NMR unless otherwise noted.c) reaction carried out at −10°C with oxidant added over 3 hours d)ee determined using a Chiracel OD column e) ee after single recrystalization f) ee determined using a Chiracel OJ column g) ee determined using a Chiralpak AD h) ee determined using a Chiracel OB column i) by comparison to literature value

All of the cinnamyl compounds have a small R_1 since the aromatic ring is flat and can lay over the pyran ring of the catalyst with little steric interaction. The most notable differences are in R_2. A comparison between the small azide (Table 1 entry 1) and very large bis Boc (Table 1 entry 6) is a good example of R_2's effect on optical purity. A very large R_2 strongly disfavors the planar reaction mode, while a small R_2 allows some leakage via the planar transition state, lowering the ee. Some of the compounds are crystalline solids that can be recrystalized to improve the ee, such as N-Boc cinnamyl amine (Table 1, entry 3).

Both the Cbz and azide compounds were epoxidized in good ee and isolated in respectable yield. Additionally, the resulting epoxides can be transformed to the free epoxy amines under a variety of mild conditions without harming the epoxide. A series of aliphatic azides and N-Cbz amino olefins were prepared for further studies, Scheme 1.11.

Alcohol **1-53** was converted to the bromide then displaced with NaN_3. When the tosylate was used, there was a mixture of S_n2 and S_N2' additions. The other alcohols were activated for nucleophilic attack as their tosylates, and the crude tosylates were converted to the azides which could be isolated cleanly by simple column chromatography. The azides could be reduced to the free amine using Lindlar's catalyst

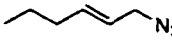
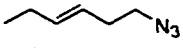
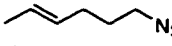
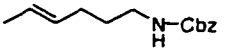
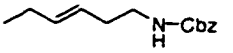
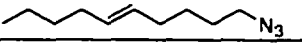
under 1 atm of H_2. The free amines were promptly protected with CbzCl under standard conditions to prevent decomposition.



Scheme 1.11 Aliphatic Olefins

Epoxidation of the aliphatic compounds proceeded with ee's of 90% or greater, similar to non-nitrogen containing *trans* olefins (Table 1.2). The volatile nature of the hexene azides causes lower yields than for the higher boiling molecules due to loss of product on work-up. Conversion of the azide to the Cbz did not substantially lower the ee of the epoxides, and volatility was no longer a problem. The absolute configuration of entry 3 was determined after cyclization and comparison of the optical rotation to a known compound.

Table 1.2 Epoxidation of *trans* Aliphatic Nitrogen Containing Olefins

Entry	Substrate	Yield[a] (Conv.)[b]	% ee	α_D	Abs. conf.
1		21(67)	93[d]	+34.2	
2		46(52)	93[d]	+37.6	
3		97(100)	91[d]	+32.8	R,S[j]
4		47	90[c]	+14.3	
5		90(96)	90[c]	+22.2	
6		69(75)	90[h]	+26.3	

Typical epoxidation procedure: To a mixture of olefin (1 mmole), tetrabutyl ammonium hydrogen sulfate (0.015g, 0.04mmol) and ketone **1** in CH_3CN/dimethoxymethane (15mL 1/2 v/v) was added 10mL buffer (0.05M $Na_2B_4O_7 \cdot 10H_2O$ in 10^{-4}M disodium-EDTA) and the mixture cooled in an ice bath. A solution of Oxone (0.85g 1.38eq.) in 6.5mL 10^{-4}M EDTA and a solution of K_2CO_3 (0.80g 5.8eq) in 6.5mL H_2O are added over 1.5 hours via syringe pump. a) Many of these epoxides are very acid sensitive and decompose upon purification. Great care must be taken in buffering the silica gel used.b) Based on crude ^{1}H NMR unless otherwise noted.c) ee determined using a chiracel OD d) ee determined using a GTA column h) ee determined using a chiralpak AD column after reduction, cyclization and N-Boc protection.

1.C.1.A H_2O_2 Oxidation

Solubility proved to be a big problem for some of the nitrogen containing substrates (Table 1 entry 7). Recent efforts to find alternative oxidants for dioxirane epoxidations have shown that hydrogen peroxide can serve as the primary oxidant at high pH in nitrile-containing solutions (Figure 1.15).[33] By replacing the inorganic salt Oxone with hydrogen peroxide the amount of water required for the reaction can be decreased and other organic solvents, such as dichloromethane mixtures, can be used.

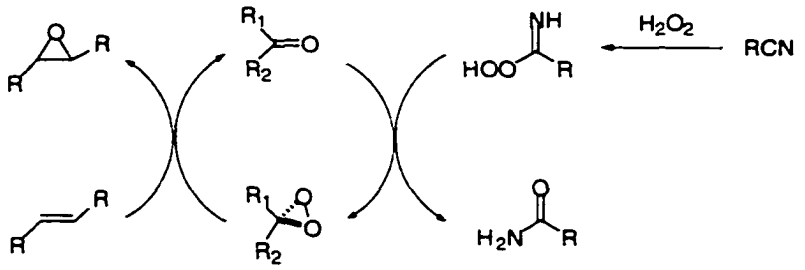
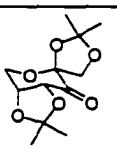
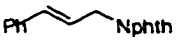
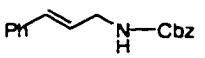
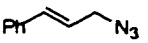
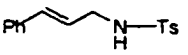
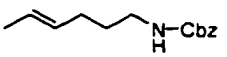
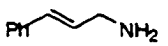


Figure 1.15 H_2O_2 as the Primary Oxidant

Under the basic reaction conditions the peroxy anion can attack the nitrile forming a peroxy imidic acid. The peroxy imidic acid can transfer its oxygen to the ketone forming a dioxirane. A variety of nitrogen-containing compounds were epoxidized using the new conditions to see if some of the more stubborn substrates would react. Unfortunately the cinnamyl phthalimide did not prove any more reactive under a variety of conditions, even under high dilution (Table 3). The peroxide reactions proved to be less general than the Oxone procedure, which is in line with the observation of H_2O_2 epoxidations of non-nitrogen containing compounds. Simple unfunctionalized olefins, such as β-methyl styrene, gave the best ee with only CH_3CN as the organic solvent. The use of CH_2Cl_2 was essential for good conversions with all of the nitrogen containing olefins surveyed.

All of the reaction times are substantially longer than under the Oxone conditions, (see Tables 1 and 2), but the reaction is a simple mix and stir procedure which does not require the use of a syringe pump. Attempts to epoxidize the free cinnamyl amine were not successful under the H_2O_2 conditions, resulting in a complex mixture of products. However the reduced solvent volume and operational simplicity of the hydrogen peroxide reactions make them ideal for scaling up for large scale preparations.

Table 1.3 Epoxidation of Nitrogen Containing Olefins using H_2O_2 as the Oxidant

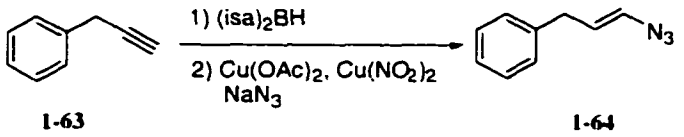
#	substrate	conditions		hr	conv.	yield	ee
1		B	60%	20	NR	ND	ND
		B*[a]	60%	12	17	ND	ND
2		A	30%	8	NR	ND	ND
		B	30%	22	100	96	71[b]
3		A	30%	24	12	ND	ND
		B	30%	24	60	53	92[c]
4		B	30%	22	51	50	85[c]
5		B	30%	25	15	ND	ND
6		B	30%	28	Decom	ND	ND

Method A The reactions were carried out at 0°C (bath temp.) with substrate (1.0 mmol) ketone **1-32**, and H_2O_2 (4.0 mmol) in CH_3CN (1.5 mL) 2.0M K_2CO_3 in 4 x 10^{-4} M EDTA (1.5 mL). Method B The reactions were carried out at 0°C (bath temp.) with substrate (1.0 mmol), ketone **1-32**, and H_2O_2 (4.0 mmol) in CH_3CN-EtOH-CH_2Cl_2 (1:1:2, v/v) (2.0 mL) 2.0M K_2CO_3 in 4 x 10^{-4} M EDTA (1.5 mL). a) Method B with an addition of 5.0 mL of CH_2Cl_2 was used. b) enantioselectivity was determined by chiral HPLC (Chiralcel OD) c) enantioselectivity was determined by chiral HPLC (Chiralpak AD)

1.C.2 Vinyl Azides

Vinyl azides can be formed with high E/Z ratios from alkynes by hydroboration followed by conversion to the vinyl azide.[34] The source of the E/Z selectivity is the large diisoamyl borane, which gives almost exclusively syn addition to the triple bond. There have been no reports of successful formation of vinyl azide epoxides, much less the

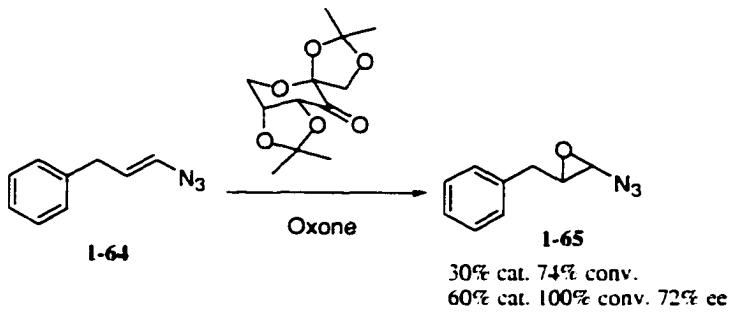
formation of chiral vinyl azide epoxides. The usefulness of these compounds is yet to be fully explored, but they could lead to chiral amino alcohols.



1-63 1-64

Scheme 1.12 Formation of *trans* Vinyl Azide

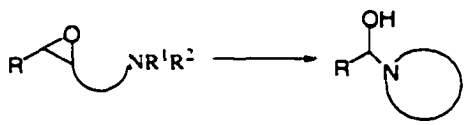
The formation of vinyl azide epoxides must be done at high pH. If the racemic epoxidation is carried out at pH 7 – 8 none of the desired product is recovered. If the reaction is run at high pH with trifluoroacetone and H_2O_2 there is no reaction and the starting material is recovered almost quantitatively. With acetone used as the catalysts as detailed for acid sensitive epoxides the reaction is clean and complete in a few hours.[35] Chiral and racemic epoxidations at pH 10.5 are very clean with very little evidence of decomposition by ^{1}H NMR of the crude reaction mixture. Unfortunately there has been little success in removal of the chiral catalysts by column chromatography. Silica gel causes decomposition of the epoxide, buffering it with triethyl amine does not alleviate the problem. Alumina chromatography has not proved successful in removing the catalysts from the epoxide. For this reason the chiral epoxidation was pushed to 100% conversion (^{1}H NMR) so that an ee could be obtained on the crude reaction mixture before attempts at purification, Scheme 1.13. With the crude reaction mixture a 72% ee was observed by chiral HPLC (Chiralcel OD-H), a little bit lower than expected, but a promising lead for further investigations. Attempts to determine the ee by GC were not successful because the epoxide decomposes in the injector.



Scheme 1.13 Vinyl Azide Epoxide Formation

1.C.3 Cyclization

Epoxy-amines contain a nucleophile and electrophile which, if judiciously placed, can be brought together to form chiral α-hydroxy nitrogen-containing heterocycles (Scheme1.14). Baldwin's rules predict that the exo mode of atttack will be favored for epoxide ring opening and this is what was observed (Figure 1.16).



Scheme 1.14 Cyclization

Aziridines can be formed from the free amine or the protected nitrogen via an Aza-Payne rearrangement as shown by Yamamoto and co-workers.[36] Azetidines, can be formed from epoxyazides by first reducing the azide to the free amine followed by treatment with butyllithium and trapping with acetic anhydride. Azetidines have been used as unnatural amino acids and in a number of candidate drugs.

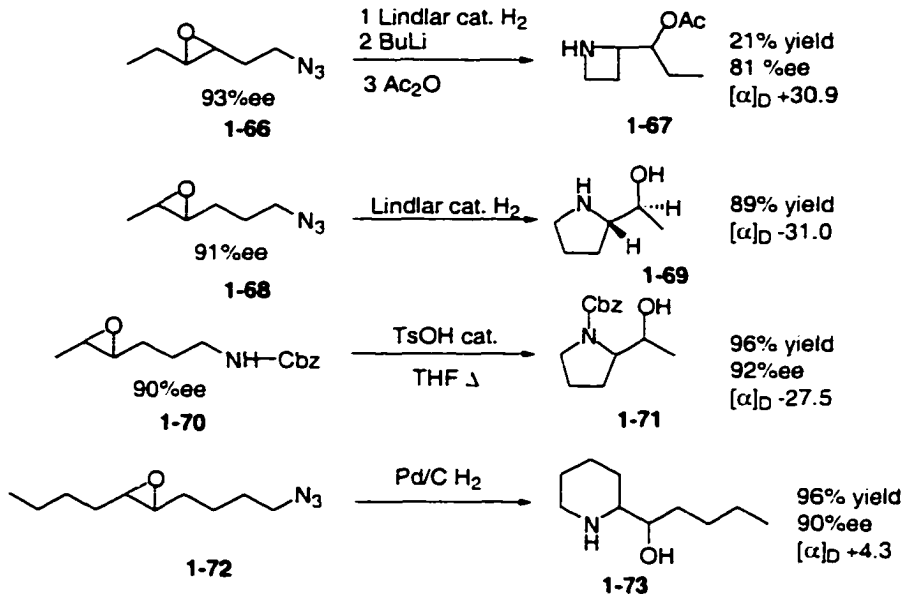


Figure 1.16 Cyclization

Piperidines and pyrrolidines can be formed in one pot from azides using reductive hydrogenation with Lindlar's catalyst, although piperidines are formed more quickly using 10% Pd/C. This mild and efficient transformation is compatible with a variety of functionality. Protected pyrrolidines can be formed with the Cbz epoxyamines using a catalytic amount of TsOH. Although the unprotected 4 and 5 membered rings can be isolated they decompose rapidly. The absolute configuration of pyrrolidine **1-69** agrees with epoxidation via a spiro transition state and was confirmed after comparing the optical rotation to the literature value.[37] Compound **1-69** is a white crystalline solid, which decomposes within minutes on exposure to air. However the Cbz-protected derivative **1-71** is much more stable and able to be stored for extended periods. Pyrrolidine **1-71** has a higher ee than that measured for starting epoxide **1-70** due to a minor *cis* impurity in the starting material, which elutes at the same time as the *trans* epoxide, but the isomers can be separated after cyclization. The minor *cis* isomer of **1-71** has an ee of 18%, which is not unexpected for this ketone catalyst. The ee of **1-72** could

not be determined by HPLC, GC or chiral shift ^{1}H NMR spectroscopy. Piperidine **1-73** is very stable, and its ee was determined after N-Boc protection.

1.D Conclusions

The chiral epoxidation method developed in the Shi labs has proven to be very effective in forming chiral epoxides with nitrogens present in the molecule. The nitrogen needs to be masked, or protected with an electron-withdrawing protective group. The success with azide-containing olefins is very encouraging since azides can be converted to free amines under a variety of mild conditions that will not affect the epoxide. Once the chiral epoxide has been formed it can be efficiently converted to a number of chiral nitrogen heterocycles of synthetic interest.

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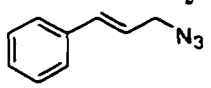
1.E EPERIMENTAL

General Methods

Column chromatography was performed with 60Å 230-400 mesh Whatman or Merck silica gel. The Merck silica gel was buffered with 1% triethyl amine on loading, or was deactivated with Na_2HCO_3. The 300 MHz ^1H NMR and 75.5 MHz ^{13}C NMR spectra were measured on a Varian Inova-300 spectrometer in $CDCl_3$. Proton chemical shifts are given relative to internal TMS (0.00 ppm), and carbon chemical shifts are given relative to $CDCl_3$ (77.16 ppm). Infrared spectra were recorded on a Perkin-Elmer 1600 Series FT-IR spectrometer. High resolution mass spectra were performed at the mass spectrometry facility of Colorado State University. Elemental analyses were performed by M-H-W Laboratories (Phoenix, AZ). Optical rotations were measured on an Autopol III automatic polarimeter in a 10 cm cell. Melting points were recorded on a Mel-Temp and are uncorrected.

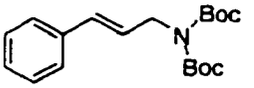
***trans*-cinnamyl azide (1-41)** (jcl-01-12)[1]



Cinnamyl chloride (0.5 g 3.3 mmol) was dissolved in acetone (15 mL). A solution of NaN_3 (0.43 g 6.6 mmol) in H_2O (7.5 mL) was added and the solution stirred rapidly for 30 min. The acetone was removed by rotary evaporation and the aqueous layer was extracted with hexane (2x). The organic layers were combined, washed with brine, dried over Na_2SO_4, and concetrated, yielding a syrup. The syrup was purified by column chromatography (silica gel, 10/1 hexane/ether) to yield azide **1-41** as a clear liquid (0.456 g, 86.7% yield) IR 2096 cm^{-1}; ^1H NMR δ 7.37-7.24 (m, 5H), 6.64 (d, J = 15.9 Hz 1H),

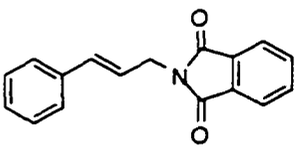
6.24 (dt J = 15.9, 6.6 Hz 1H), 3.92 (d J = 6.6Hz 2H); ^{13}C NMR δ 136.2, 134.7, 128.8, 128.4, 126.8, 122.6, 53.2.

***trans*-cinnamyl-di-*t*-butyl carboximide (1-42)** (jcl-01-03)[2]



Di-t-butyl iminodicarboxylate (1.5 g 6.9 mmol) and dry DMF (40 mL) were added to NaH (0.36 g 9.0 mmol) rinsed with hexane under N_2. After 30 min. cinnamyl chloride (1.07 g 7.0 mmol) was added in DMF (5 mL). When the reaction was complete by TLC 30 mL of ether was added, and the mixture was washed with 30 mL H_2O. The aqueous layer was extracted with 30 mL ether and the organic layers were combined, washed with $NaHCO_3$, brine and dried over Na_2SO_4. After removal of the solvent an off white solid was obtained (1.67 g). The compound was purified by column chromatography (silica gel, 10/1 hexane/ether) to yield a white solid (1.55g, 67% yield). mp = 49-50 °C; IR (NaCl) 1787, 1728 cm^{-1}; ^{1}H NMR δ 7.39-7.17 (m, 5H), 6.53 (d, J = 15.9, 1H), 6.21 (dt, J = 15.9, 6.3, 1H), 4.33 (d, J = 6.3 2H), 1.51 (s, 18H); ^{13}C NMR δ 152.5, 136.9, 132.4, 128.6, 127.7, 126.5, 125.2, 82.5, 48.3, 28.2

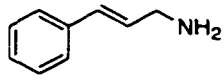
***trans*-cinnamyl phthalimide (1-43)** (jcl-01-05)



Phthalimide (2.0 g, 13.6 mmol) was added to rinsed NaH (0.54 g, 13.6 mmol), in DMF (50 mL) and heated to 60 °C under N_2. Cinnamyl chloride (2.07 g, 13.6 mmol) in DMF (30 mL) was added and the reaction mixture was heated overnight. After cooling the reaction to rt, 150 mL ether and 100 mL H_2O were added and a white precipitate formed. The solid was collected by vacuum filtration and dried under vacuum. The white solid was purified by column chromatography (silica gel, 10/1 hexane/ether) to yield **1-43** as fluffy white crystals (2.92 g, 82% yield). mp = 125-126 °C; IR ν (NaCl) 1703 cm^{-1}; ^{1}H

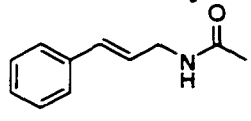
NMR δ 7.87 (m, 2H), 7.72 (m, 2H), 7.37-7.19 (m, 5H), 6.66 (d, J = 15.9Hz 1H), 6.26 (dt, J = 15.9, 6.6Hz 1H), 4.45 (dd, J = 6.6, 1.2Hz 2H); ^{13}C NMR δ 168.1, 136.3, 134.4, 134.1, 133.9, 132.3, 128.6, 128.0, 126.6, 123.4, 122.8, 39.81

***trans*-cinnamyl amine (1-44)** (jcl-01-49)



A solution of phthalimide-protected cinnamyl amine (1.5 g 5.7 mmol) in EtOH (120mL) and hydrazine monohydrate (0.285 g 5.7 mmol) was heated at reflux under N_2 for 16 hr. The reaction mixture was cooled in ice and the white precipitate was collected by vacuum filtration and washed with cold EtOH. The crystals were stirred in 150 mL 5% HCl under N_2. Once again a white precipitate formed and was removed by vacuum filtration. The filtrate was made alkaline with 6M NaOH, extracted 4x with dichloromethane. The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated to give 1.15 g of light yellow oil. The crude oil was purifed by column chromatography (silica gel eluted with 95/5 CH_2Cl_2/MeOH) to yield **1-44**as a clear liquid (0.63g, 83% yield). IR 3264, 3029, 1632, 1572 cm^{-1}; ^{1}H NMR δ 7.38-7.17 (m, 5H), 6.48 (d, J = 15.9Hz 1H), 6.29 (dt, J = 15.9, 5.7Hz 1H), 3.44 (d, J = 5.7Hz 2H), 1.25 (s, 2H, NH) ^{13}C NMR δ 136.9, 130.9, 129.3, 128.4, 127.1, 126.0, 44.1

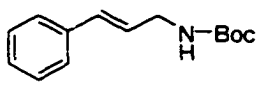
***trans*-cinnamyl acetamide (1-45)** (jcl-01-18)



Cinnamyl amine (0.5g, 3.75 mmol) and DMAP (cat) were added to a solution of acetic anhydride (0.383g, 3.75 mmol) in THF (10mL). After 5 hours 20 mL ether was added and the organic layer was washed with 50mL sat. $NaHCO_3$, 30 mL brine, dried over Na_2SO_4, and concentrated. The crude white solid was purified by column chromatography (silica gel, 95/5 CH_2Cl_2/MeOH), to yield 1-45 as a white crystaline solid

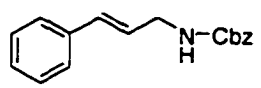
(0.331g, 50.3% yield). mp = 86-87 °C; IR (NaCl) 3293, 1636, 1555 cm^{-1}; ^1H NMR δ 7.41-7.18 (m, 5H), 6.51 (d, *J* = 15.9Hz 1H), 6.18 (dt, *J* = 15.9, 6.6Hz 1H), 5.78 (br. s, 1H, NH), 4.03 (td, *J* = 6.6, 1.2Hz 2H), 2.03 (s, 3H); ^{13}C NMR δ 163.3, 132.4, 128.8, 128.7, 127.9, 126.5, 125.6, 41.9, 23.5

***trans*-cinnamyl-*t*-butyl carbamate (1-46)** (jcl-02-46)



Solid *t*-butyl carboxylate anhydride (0.654g, 3.0 mmol) was added to a solution of Cinnamyl amine (0.40g, 3.0 mmol) in THF (15 mL). After 4 hours ether (20 mL) was added and the reaction was washed with sat. $NaHCO_3$, H_2O, brine and dried over Na_2SO_4. Removal of the solvent yielded a white solid (0.715g, quant. yield) which could be used without further purification. mp = 74-75 °C; IR ν (NaCl) 3358, 1693 cm^{-1}; ^1H NMR δ 7.38 (m, 5H), 6.50 (d, *J* = 15.9Hz 1H), 6.19 (dt, *J* = 15.9, 6.0Hz 1H), 4.67 (br. s, 1H, NH), 3.91 (m, 2H), 1.47 (s, 9H); ^{13}C NMR δ 155.9, 136.8, 131.5, 128.6, 127.7, 126.4, 79.6, 42.8, 28.5.

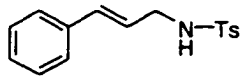
***t*-cinnamyl benzyl cabamide (1-47)** (jcl-02-07)[3]



Benzyl chloroformate (0.188g, 1.1 mmol) was added dropwise over 5 min to a solution of cinnamyl amine (0.133g, 1.0 mmol) and $NaHCO_3$ (0.210g, 2.5 mmol) in H_2O (10mL). A white precipitate formed. The reaction mixture was extracted with Et_2O, the organic layers combined, washed with brine and dried over Na_2SO_4. Removal of the solvent yielded white crystals (0.136g, 53% yield), which could be used without further purification. mp = 55-57 °C; IR ν (NaCl) 3329, 3030, 1705 cm^{-1}; ^1H NMR δ 7.40-7.18 (m, 10H), 6.51 (d, *J* = 15.9Hz 1H), 6.18 (dt, *J* = 15.9, 5.7Hz 1H), 5.13 (s, 2H), 4.92 (br, s,

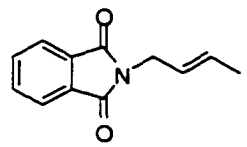
1H, NH), 3.97 (t, J = 5.7Hz 2H); ^{13}C NMR δ 156.2, 136.4, 131.4, 128.4, 128.3, 128.2, 128.0, 127.5, 126.2, 125.7, 66.7, 43.1

N-tosyl-*trans*-cinnamyl amine (1-48) (jcl-02-18)



Tosyl chloride (0.273 g, 1.43 mmol) was added to a solution. of cinnamyl amine (0.20 g, 1.5 mmol) and triethyl amine (0.152 g, 1.5 mmol) in Et_2O (10mL). After 2.5 hours 20mL of H_2O was added and the reaction was extracted 3x with 25mL EtOAc. The organic layers were combined, washed with sat. $NaHCO_3$, brine, dried over Na_2SO_4, and concentrated. The crude solid was purified by column chromatography (silica gel eluted with 1/1 hexane/ether) to yield **1-48** as a white solid (0.297 g, 69%yield). ^{1}H NMR δ 7.77 (d, J= 8.1Hz 2H), 7.32-7.19 (m, 7H), 6.42 (d, J = 15.9Hz 1H), 5.99 (dt, J = 15.9, 6.3Hz 1H), 3.74 (dd, J = 6.3, 1.2Hz 2H), 2.39 (s, 3H) ^{13}C NMR δ 143.5, 137.1, 136.2, 133.0, 129.8, 128.6, 127.9, 127.2, 126.4, 124.2, 45.6, 21.6

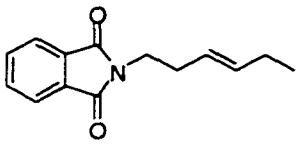
***trans*-crotyl phthalimide (1-50)** (jcl-03-08)



Phthalimide (1.47 g, 10.0 mmol) was added to rinsed NaH (0.40 g, 13.0 mmol) in DMF (35mL) and stirred 2 hr. Crotyl chloride (0.906 g, 10.0 mmol) was added and the reaction heated to 75°C in an oil bath for 4 hours. After the reaction cooled to rt 50mL H_2O was added and the reaction extracted was with 50mL Et_2O 3x. The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated. The crude white solid was recrystalized from boiling Et_2O. The small amount of *cis* isomer was removed by an incomplete epoxidation with the fructose derived ketone followed by recovery of the unreacted *trans* olefin by crystalization (0.725g 37% over two steps). mp = 75-76 °C; IR (NaCl) 1766, 1724, 1610 cm^{-1}; ^{1}H NMR δ 7.85 (dd, J = 5.4, 3.0Hz 2H),

7.71 (dd,J = 5.4, 3.6Hz 2H), 5.76 (dqt, J = 21.6, 6.3, 1.5Hz 1H), 5.54 (dtq, J = 15.3, 6.3, 1.5Hz 1H), 4.22 (dt, J = 6.0, 1.2Hz 2H), 1.67 (dq, J = 6.6, 1.2Hz 3H); ^{13}C NMR δ 168.1, 134.0, 132.3, 129.9, 124.5, 123.3, 39.58, 17.72

1-phthalimide-*trans*-3-hexene (1-52) (jcl-03-42)



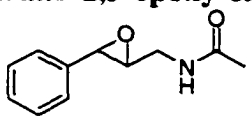
A solution of *trans*-3-hexene-1-ol (2.00 g, 20.0 mmol) in THF (30 mL) was added to phthalimide (2.95 g, 20.0 mmol) and triphenylphosphine (5.25 g, 20mmol) in THF (20 mL). A solution of diethyl azodicarboxylate (0.348 g, 20.0 mmol) in 20 mL THF was dripped into the reaction. After 4 hours the solvent was removed by rotary evaporation and the off-white sludge was purified on a short wide silica gel column eluted with 10/1 hexane/Et_2O. The product was a white solid (2.10 g, 46% yield). mp = 52 °C; IR (NaCl) ν 1706 cm^{-1},^{1}H NMR δ 7.83 (m, 2H), 7.70 (m, 2H), 5.49 (dt, J = 15.3, 6.6Hz 1H), 5.36 (dt, J = 15.0, 6.9Hz 1H), 3.72 (t, J = 6.9Hz 2H), 2.37 (dt, J = 6.9, 6.6Hz 2H), 1.94 (m, 2H), 0.85 (t, J = 7.3, 3H), ^{13}C NMR δ 168.5, 135.5, 134.0, 132.3, 124.8, 123.3, 38.0, 31.8, 25.7, 13.8

General Racemic Epoxidation Procedure (jcl-01-39)

Cinnamyl amine acetate (0.088g 0.50 mmol) and 1,3-dichloroacetone (0.064 g 0.50 mmol) were dissolved in acetonitrile (7.5 mL) and water (3.75 mL). A mixture of powdered Oxone (1.50 g, 2.46 mmol) and $NaHCO_3$ (0.75 g, 8.9 mmol) was added in small portions over 1 hour. The reaction was poured into 25 mL of H_2O, extracted with EtOAc, washed with H_2O, brine, dried over Na_2SO_4, filtered, concentrated, yielding a white solid (0.0918g 96% yield) which could be used without further purification.

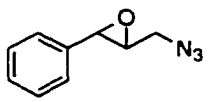
Representative Epoxidation Procedure A

***trans*-2,3-epoxy-cinnamyl acetamide** (Table 1 entry 2) (jcl-01-40)



A solution of cinnamyl amine acetate (0.088g 0.50 mmol) ketone **1-32** (0.038 g, 0.15 mmol), and tetrabutylammonium hydrogen sulfate (0.007g, 0.02 mmol) in acetonitrile-DMM (7.5 mL, 1:2, v/v) and buffer (3.75 mL), [0.05 M solution of $Na_2B_4O_7 \cdot 10H_2O$ in 4 x 10^{-4} M aqueous Na_2(EDTA)] was chilled in an ice bath. A solution of Oxone (0.425 g, 0.69 mmol) in aqueous Na_2(EDTA) (4 x 10^{-4} M, 3.25 mL) and a solution of K_2CO_3 (0.40 g, 5.8 mmol) in water (3.25 mL) were added separately via syringe pump over a period of 1.5 h. The reaction was poured into 25 mL H_2O and extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried over Na_2SO_4, filtered, concentrated, and purified by column chromatography (silica gel eluted with 4/1 EtOAc/hexane) to give the epoxide as a white solid (0.077 g, 81% yield, 88%ee). $[\alpha]_D$ = +53.9° (c 0.48, $CHCl_3$); mp = 71°C; IR ν (NaCl) 3283, 1654, 1549 cm^{-1}, ^1H NMR δ 7.47-7.18 (m, 4H), 6.0 (br. s, 1H, NH), 3.78 (ddd, *J* = 14.7, 5.7, 3.3Hz 1H), 3.72 (d, *J* = 2.4Hz 1H), 3.45 (ddd, *J* = 14.7, 6.0, 5.4Hz 1H), 3.18 (ddd *J* = 5.4, 3.3, 2.4Hz 1H), 2.03 (s 3H); ^{13}C NMR δ 170.5, 136.4, 128.6, 128.5, 125.8, 60.7, 57.0, 40.4, 23.3; Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found C, 69.20; H, 6.92; N, 7.42

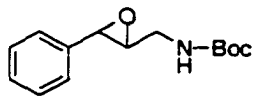
***trans*-2,3-epoxy-cinnamyl azide** (Table 1 entry 1) (jcl-01-44)[4]



Epoxidized using method A. Isolated as golden liquid by column chromatography (Whatman silica gel, eluted with 20/1 hexane/Et_2O) to yield (0.0889g, 50% yield), unreacted starting material was recovered near quantitativly. $[\alpha]_D$ +37.8° (c 2.7, $CHCl_3$); IR ν (NaCl) 2102, 1604 cm^{-1}, ^1H NMR 7.37-7.24 (m, 5H), 3.85 (d *J* = 2.1Hz 1H), 3.64

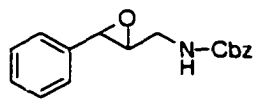
(dd, J = 13.8, 3.6Hz 1H), 3.44 (dd, J = 13.8, 5.1Hz 1H), 3.22 (ddd, J = 4.8, 3.3, 2.1Hz 1H), ^{13}C NMR δ 136.1, 128.6, 128.5, 125.7, 60.4, 56.4, 51.8; Anal.Calcd for $C_9H_9N_3O$: C, 61.70; H, 5.18; N, 23.99. Found C, 61.80; H 5.17; N, 24.00.

***trans*- 2,3- epoxy-cinnamyl-N-*tert*-butyl carbamate** (Table 1 entry 3) (jcl-02-28)



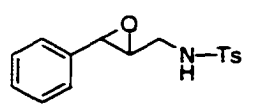
Epoxidized using method A. Isolated as a white solid (0.0597g, 48% yield) by column chromatography (silica gel buffered with 1% TEA eluted with 9/1 hexane/Et_2O). mp = 145-146°C; IR ν (NaCl) 3360, 1698 cm^{-1}, ^{1}H NMR δ 7.37-7.22 (m, 4H), 4.9 (br. s, 1H, NH), 3.74 (d, J = 1.8Hz 1H), 3.60 (m, 1H), 3.39 (ddd J = 14.7, 6.3, 4.8Hz 1H), 3.14 (m, 1H), 1.46 (s, 9H); ^{13}C NMR δ 155.9, 136.6, 128.3, 128.4, 125.6, 79.8, 60.9, 56.6, 41.4, 28.5. Anal. Calcd. for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N,5.62. Found C, 67.37; H, 7.63; N, 5.59

***trans*-2,3-epoxy cinnamyl-N-benzyl carbamate** (Table 1 entry 4) (jcl-02-30)



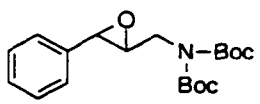
Epoxidized using method A. Isolated as a white solid (0.0762 g 56% yield) by column chromatography (silica gel buffered with 1% TEA eluted with 3/1 hexane/Et_2O). $[\alpha]_D$ = +40.0° (c 0.42, $CHCl_3$); mp = 61-62 °C; IR ν (NaCl) 3344, 1706 cm^{-1}. ^{1}H NMR δ 7.40-7.13 (m, 10H), 5.13 (s, 2H), 5.10 (br. s, 1H, NH), 3.72 (d, J = 1.5Hz 1H), 3.67 (m, 1H), 3.44 (ddd, J = 15.0, 6.6, 5.1Hz 1H), 3.15 (m, 1H); ^{13}C NMR δ 156.5, 136.4, 128.51, 128.45, 128.31, 128.16, 128.09, 125.7, 66.7, 60.7, 56.6, 41.9, 20.3; Anal. Calcd. For $C_{17}H_{17}NO_3$: C, 72.07; H, 6.04; N, 4.94. Found: C, 72.14; H, 6.28; N, 4.79.

***trans*-2,3-epoxy-cinnamyl-N-*p*-toluene sulfonate** (Table 1 entry 5) (jcl-27-26)



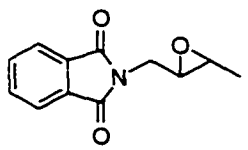
Epoxidized using method A. Isolated as a white solid (0.1166g 38.5% yield) by column chromatography (silica gel buffered with 1% TEA eluted with 1/1 hexane/Et_2O). $[\alpha]_D$ = +46.4° (c 0.14, $CHCl_3$) IR ν (NaCl) 3271cm^{-1} ^{1}H NMR δ 7.76 (d *J* = 8.1Hz 2H), 7.35-7.30 (m, 5 H), 7.72-7.15 (m, 2 H),4.68 (t, *J* = 6.0Hz 1H, NH), 3.76 (d, *J* = 2.1Hz 1H), 3.41 (ddd, *J* = 14.1, 6.0, 3.6Hz 1 H), 3.26 (ddd, *J* = 14.1, 6.9, 4.5Hz 1H), 3.12 (ddd *J* = 4.5, 3.6, 2.1Hz 1H), 2.43 (s, 3H). ^{13}C NMR δ 130.0, 128.7, 127.2, 125.8, 60.3, 56.7, 43.8, 21.7: Anal. Calcd. For $C_{16}H_{17}NO_3S$: C, 63.34; H, 5.65: N, 4.62. Found: C, 63.33; H, 5.49; N, 4.64.

***trans*-2,3-epoxy-cinnamyl-di-*tert*-butyl carboximide** (Table 1 entry 6) (jcl-02-30)



Epoxidized by method A. Isolated as a white solid (0.1106 g 63% yield) by column chromatography (silica gel buffered with TEA and eluted with 4/1 hexane/Et_2O). $[\alpha]_D$ = +7.39° (c 0.46, $CHCl_3$); mp = 77-78 °C; IR ν (NaCl) 1790, 1744, 1700 cm^{-1}; ^{1}H NMR δ 7.38-7.23 (m, 5H), 4.02 (dd, *J* = 14.4, 3.9Hz 1H), 3.79 (dd, *J* = 14.4, 5.7Hz 1H), 3.79 (d, *J* = 1.5Hz 1H), 3.17 (m, 1H), 1.53 (s, 18H); ^{13}C NMR δ 152.5, 137.2, 128.6, 128.3, 125.7, 82.98, 60.24, 57.97, 47.26, 28.21; Anal.Calcd for $C_{19}H_{27}NO_5$: C, 65.31; H, 7.79; N, 4.01. Found C, 65.21; H 7.73; N, 4.15.

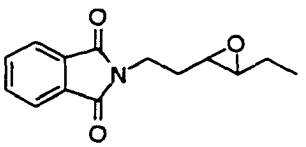
***trans*-2,3-epoxy-crotyl-phthalimide** (Table 1 entry 8)(jcl-03-37)



Epoxidized using method A. Isolated as a clear syrup (0.0133g 25% yield) by column chromatography (silica gel buffered with 1% TEA, 5/1 hexane/EtOAc). $[\alpha]_D$ = -13.1° (c 0.73, $CHCl_3$); ^{1}H NMR δ 7.87 (dd, *J* = 5.7, 3.0Hz 2H), 7.74 (dd, *J* = 5.4, 3.0Hz 2H), 3.95 (dd, *J* = 14.1, 5.1Hz 1H), 3.76 (dd, *J* = 14.4, 5.1Hz 1H), 2.97 (m, 2H), 1.30 (d, *J* = 5.1Hz

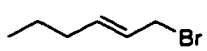
3H); ^{13}C NMR δ 168.0, 134.1, 132.0, 123.4, 55.89, 54.08, 39.34, 20.34. Anal. Calcd. for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found C, 67.01; H, 5.21; N, 6.52

1-phthalimide-*trans*-3,4-epoxy hexane (Table 1 entry 9) (jcl-11-29)



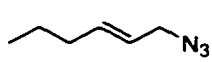
Epoxidized using method A. Isolated as a clear liquid (0.1545g 63% yield) by column chromatography chromatography (silica gel eluted with 4/1 hexane/ether). $[\alpha]_D$ = -1.82° (c 1.1, $CHCl_3$) IR ν (NaCl) 1772, 1712, cm^{-1}, ^1H NMR δ 7.85 (m, 2H), 7.72 (m, 2H), 3.86 (td, *J* = 7.2, 2.1Hz 2H), 2.77 (ddd, *J* = 6.3, 5.4, 2.4Hz 1H), 2.62 (td, *J* = 5.7, 2.4Hz 1H), 1.92 (m, 2H), 1.52 (qd, *J* = 7.5, 5.4Hz 2H), 0.93 (t, *J* = 7.5Hz 3H); ^{13}C NMR δ 168.2, 134.0, 132.1, 123.3, 59.5, 56.2, 35.3, 31.5, 25.1, 10.0. Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found C, 68.66; H, 6.07; N, 5.84

1-bromo-*trans*-2-hexene (1-54)



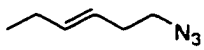
Phosphorus tribromide (10.83 g, 40 mmol) was dripped into a solution *trans*-2-hexene-1-ol (10.0g, 100mmol) in THF (50mL) in a darkened flask at 0°C. After stirring 20 min the reaction vessel was fitted with a N_2 balloon and placed in the freezer overnight. After 20 hours hexane (50 mL) was added, the reaction was washed with sat. $NaHCO_3$, H_2O, brine, dried over Na_2SO_4 and concentrated. The crude liquid was purified by column chromatography (silica gel eluted with 25/1 hexane/ether) to give a clear liquid (15.72g, 96% yield). The allyl bromide was stored in the freezer under N_2. ^1H NMR δ 5.78-5.60 (m, 2H), 3.95 (d, *J* = 6.9 Hz 2H), 2.04 (q, *J* = 7.2 Hz 2H), 1.41 (q, *J* = 7.2 Hz 2H), 0.91 (t, *J* = 7.4 Hz 3H), ^{13}C NMR δ 136.5, 126.5, 34.1, 33.6, 22.0, 13.6

1-azido-*trans*-2-hexene (1-55) (jcl-03-22)



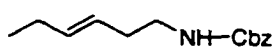
Azide **1-55** was prepared in the same manner as detailed for **1-41**, and isolated as a mixture of isomers by column chromatography (silica gel eluted with 100/1 pentane/ether) clear liquid (0.477g, 50% yield). Azide **1-55** was stored in the freezer under N_2. IR ν 2101 cm^{-1}; ^1H NMR δ 5.75 (dt, *J* = 15.0, 8.1 Hz 1H), 5.51 (dt, *J* = 15.6, 6.6 Hz 1H), 3.70 (d, *J* = 6.6 Hz 2H), 2.06 (q, *J* = 6.9 Hz 2H), 1.43 (m, 2H), 0.92 (t, *J* = 7.3 Hz 3H); ^{13}C NMR δ137.0, 122.8, 52.9, 34.2, 22.3, 13.6

1-azido-*trans*-3-hexene (1-56)



To a solution of *trans*-3-hexene-1-ol (1.00g, 10.0 mmol) in CH_2Cl_2 (50mL) was added TsCl (2.0g, 10.5 mmol) and pyridine (2.0 mL). The reaction was stirred under N_2 for 5 h and then the solvent was removed by rotary evaporation. The crude reaction mixture was dissolved in DMF (30 mL) and NaN_3 (1.30g, 20.0 mmol) was added. After 2.5h H_2O was added and the mixture was extracted 3x 25mL pentane. The organic layers were combined, washed with H_2O, brine, dried over Na_2SO_4, and concentrated. The clear liquid was purified using a short column (silica gel eluted with 100/1 pentane/ether) to yield a volatile clear liquid (0.598g, 48% yield). IR ν (NaCl) 2097 cm^{-1}, ^1H NMR δ 5.60 (dt, *J* = 15.3, 6.3Hz 1H), 5.38 (dt, *J* = 15.3, 6.9Hz 1H), 3.26 (t, *J* = 6.9Hz 2H), 2.29 (m, 2H), 2.03 (m, 2H), 0.98 (t, *J* = 7.5Hz 3H); ^{13}C NMR δ 135.6, 124.6, 51.32, 32.35, 25.72, 13.67

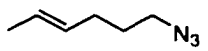
***trans*-3-hexen-1-benzyl carbamate (1-57)** (jcl-27-22)



Azide **1-56** (1.25 g 10.0 mmol) and Lindlar's catalyst (0.10 g, 10 mol%) were taken up in MeOH (10.0 mL) in a pressure tube. The tube was flushed 3x with H_2 and filled to 60 psi. After 4 hours the reaction was filtered through Celite, the plug was rinsed with EtOAc and the filtrate concentrated. The crude amine (0.258 g, 2.25 mmol) was treated with CbzCl (1.70 g, 10.0 mmol) CH_2Cl_2 (20.0 mL). The reaction poured into water.

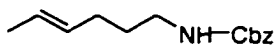
extracted 3x with ether, the organic layers were combined, washed with H_2O, brine, dried over Na_2SO_4, filtered, and concentrated. The crude liquid was purifed by column chromatography (silica gel eluted with 10/1 - 4/1 hexane/Et_2O) to yield a white solid (1.59 g, 72% yield). IR ν 3335 1700 cm^{-1}; ^1H NMR δ 7.38-7.29 (m, 5H), 5.51 (dt, *J* = 15.3, 6.3Hz 1H), 5.30 (dt, *J* = 15.3, 6.6Hz 1H), 5.07 (s, 2H), 5.0 (s br 1H), 3.20 (m, 2H), 2.19 (m, 2H), 2.01 (m, 2H), 0.95 (t, *J* = 7.3Hz 3H); ^{13}C NMR δ 156.3, 136.7, 135.2, 128.5, 128.1, 125.2, 66.7, 40.8, 33.1, 25.75, 13.9

***trans*-4-hexene azide (1-59)** (jcl-12-13)



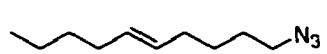
Prepared by the same method as *trans*-3-hexene azide starting with *trans*-4-hexene-1-ol (0.75 g, 7.5 mmol), and purified with a short silica column (silica gel eluted with 100/1 pentane/ether) to yield a volatile clear liquid (0.481 g 51% yield). IR ν 2098 cm^{-1}, ^1H NMR δ 5.54-5.32 (m, 2H), 3.26 (t, *J* = 6.9Hz, 2H), 2.07 (q, *J* = 7.2Hz, 2H), 1.66 (m, 5H); ^{13}C NMR δ 129.7, 126.4, 50.9, 29.7, 28.8, 18.0

***trans*-4-hexene benzyl carbamate (1-60)** (jcl-13-31)



Prepared by the same method as **1-57**, and purifed by column chromatography (silica gel eluted with 4/1 hexane/Et_2O) to yield a clear liquid (0.273 1.2 mmol 73% yield). ^1H NMR δ 7.38-7.29 (m, 5H), 5.41 (m, 2H), 5.09 (s, 2H), 4.8 (s br, 1H), 3.17 (m, 2H), 2.01 (m, 2H), 1.63 (d, *J* = 4.8 Hz 3H), 1.54 (m, 2H) ^{13}C NMR δ156.4, 136.7, 130.2, 128.5, 128.2, 125.8, 66.7, 40.7, 29.8, 18.1

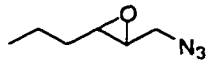
***trans*-5-decene azide (1-62)** (jcl-12-35)



Prepared from *trans*-5-decenol using the method described for **1-56**, and the crude liquid was purified by column chromatography (silica gel eluted with 100/1 hexane/Et_2O) to yield a clear oil (0.737 g 4.1mmol 64% yield). IR ν 2096.cm^{-1}; ^1H NMR δ 5.39 (m, 2H),

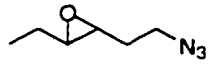
3.26 (t, J = 6.9Hz, 2H), 1.93-2.06 (m, 4H), 1.65 (m, 2H), 1.33 (m, 6H), 0.89 (t, J = 7.0Hz, 3H); ^{13}C NMR δ 131.3, 129.4, 51.6, 32.4, 32.2, 32.0, 28.5, 26.8, 22.4, 14.2

***trans*-1-azido-2,3-epoxy hexane** (Table 2, entry 1) (jcl-11-36)



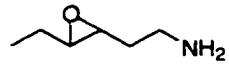
Epoxidized by method A starting with primarily *trans*-2 hexene azide (0.155g 1.3 mmol). Purified by column chromatography (silica gel deactivated with $NaHCO_3$ eluted with 15/1 pentane/Et_2O) to give a clear liquid (0.038g 0.27 mmol 21% yield). $[\alpha]_D$ +34.2° (c 0.31, $CHCl_3$), IR ν 2098 cm^{-1}; ^{1}H NMR δ 3.47 (dd, J = 135., 4.2Hz 1H), 3.31 (dd, J = 13.2, 5.1Hz 1H), 2.94 (m, 1H), 2.89 (td, J = 6.0, 2.4Hz 1H), 1.56 (m, 4H), 0.97 (t, J = 7.2Hz 3H); ^{13}C NMR δ 56.6, 56.1, 52.1, 33.5, 19.2, 13.9

***trans*-1-azido -3,4-epoxy-hexane** (Table 1.2, entry 2) **1-66** (jcl-12-10)



Epoxidized by method A starting with *trans*-3-hexene azide, purified by column chromatography (silica gel deactivated with $NaHCO_3$ eluted with 10/1 pentane/ether) to give a clear liquid (0.0462g 33% yield), 50% of SM recovered. $[\alpha]_D$ +37.6° (c 1.08, $CHCl_3$), IR ν 2098 cm^{-1}, ^{1}H NMR δ 3.44 (m, 2H), 2.8-2.7 (m, 2H), 1.89 (m, 1H), 1.74 (m, 1H), 1.59 (m, 2H), 1.00 (t, J = 7.5Hz 3H); ^{13}C NMR δ 60.0, 55.8, 48.5, 31.8, 25.1, 9.9 Anal. Calcd for $C_6H_{11}N_3O$: C, 51.05; H, 7.85; N, 29.77. Found C, 51.38; H, 7.41; N, 29.71

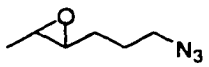
***trans*-1-amino-3,4-epoxy-hexane** (jcl-12-33)



Lindlar's catalyst (0.0025 g, 5.0 wt.%) was added to a solution of epoxy azide **1-66** (0.0473 g) in methanol (2.0 mL). The reaction was stirred under 1 atmosphere of H_2 for 5 hours then filtered through Celite, rinsed with pentane and concentrated to give the free amine as a clear liquid (0.0409 g .quantitative yield). IR ν 3364 cm^{-1}; ^{1}H NMR δ 5.17 (br.

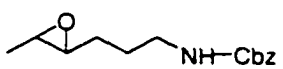
s, 2H NH), 3.00 (m, 1H), 2.83 (m, 1H), 2.75 (m, 1H), 2.03 (m, 1H), 1.73 (m, 1H), 1.56 (m, 2H), 0.99 (t, J = 7.5Hz 3H); ^{13}C NMR δ 59.54, 56.4, 38.4, 32.8, 25.0, 9.9

***trans*-1-azido-4,5-epoxy-hexane** (Table 1.2, entry 3) **1-68** (jcl-11-16)



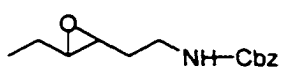
Epoxidized by method A, after work-up the material was clean (0.154 g 97% yield) the clear liquid was carried on. $[\alpha]_D$ +32.8° (c 0.79, $CHCl_3$) IR ν 2098 cm^{-1} ^{1}H NMR δ 3.34 (td J = 6.6, 2.1Hz 2H), 2.77 (qd J = 5.1, 2.1Hz 1H), 2.6 (m, 1H), 1.75 (m, 4H), 1.30 (d J = 5.1Hz 3H); ^{13}C NMR δ 59.1, 54.6, 51.2, 29.3, 25.6, 17.7 Anal. Calcd for $C_6H_{11}N_3O$: C, 51.05; H, 7.85; N, 29.77. Found C, 51.97; H, 7.83; N, 27.83

***trans*-4,5-epoxy hexane benzyl carbamate** (Table 1.2, entry 4) (**1-70**) (jcl-13-32)



Epoxidized by method A starting with *t*-4-hexene benzyl carbamate (0.169g 0.73 mmol). The epoxide was purified by column chromatography (silica gel eluted with 3/1 heaxne/EtOAc) to yield of clear liquid (0.0831 g, 0.33 mmol, 45 % yield). $[\alpha]_D$ = +14.3° (c 1.22 .$CHCl_3$); IR ν 3336, 1703, 1533, 1251 cm^{-1}; ^{1}H NMR δ 7.27-7.40 (m, 5H), 5.09 (s, 2H), 4.91 (br. s, 1H, NH), 3.24 (q, J = 6.6Hz, 2H), 2.75 (qd, J = 5.1, 2.1Hz, 1H), 2.64 (m, 1H), 1.61-1.74 (m, 4H), 1.28(d, J = 5.1Hz, 3H); ^{13}C NMR δ 156.4, 136.6, 128.5, 128.1, 66.6, 59.3, 54.7, 40.7, 29.3, 26.6, 17.7 Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.44; H, 7.68; N, 5.62. Found C, 67.31; H, 7.50; N, 5.56

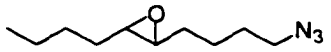
***trans*-3,4-epoxy-1-benzyl carbamate** (Table 1.2, entry 5) (jcl-13-39)



Epoxidized by method A to yield a clear liquid purified by column chromatography (silica gel eluted with 4/1 hexane/ether) (0.205g 90% yield). $[\alpha]_D$ = +22.2° (c 0.76, $CHCl_3$); IR ν 3334, 2934, 1698 cm^{-1}; ^{1}H NMR δ 7.28-7.35 (m, 5H), 5.16 (br. s, 1H, NH), 5.09 (s, 2H), 3.34 (q, J = 6.3Hz, 2H), 2.74 (m, 1H), 2.68 (m, 1H), 1.48-1.68 (m, 4H), 0.97

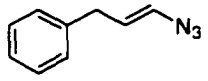
(t, J = 7.2Hz, 3H); ^{13}C NMR δ 156.4, 136.6, 128.5, 128.1, 66.7, 59.4, 56.7, 38.5, 32.0, 25.0, 9.9

***trans*-1-azido-5,6-epoxy-decane** (Table 1.2, entry 6) (**1-72**) (jcl-12-38)



Epoxidized using method A on starting with *trans*-5-decene azide (0.181g 1.0 mmol). The epoxide was purified by column chromatography (silica gel eluted with 20/1 hexane/Et_2O) to yield a clear liquid (0.155g 0.78 mmol 78% yield). $[\alpha]_D$ = 26.3° (c 1.86, $CHCl_3$); IR ν 2096 cm^{-1}; ^{1}H NMR δ 3.29 (t, J = 6.6Hz, 2H), 2.67 (m, 2H), 1.65 (m, 2H), 1.54 (m, 5H), 1.40 (m, 5H), 0.91 (t, J = 6.8Hz, 3H); ^{13}C NMR δ 58.8, 58.5, 51.4, 31.9, 31.8, 28.8, 28.3, 23.5, 22.7, 14.2

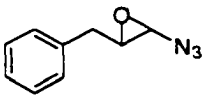
3-phenyl-*trans*-1-proply-vinyl azide (**1-64**) (jcl-27-28)[5]



A solution of diisoamyl borane was prepared by addition of 2-methyl-2-butene (2.81g 40.0 mmol) to BH_3•THF (20.0 mL 20.0 mmol 1.0 M in THF) in THF (10.0 mL) and stirred at –15°C for 30 min. followed 2 hours at 0°C. A solution of 3-phenyl-1-propyne (2.32g 20.0 mmol) in THF (5.0 mL) was added to the reaction at –15°C, after 30 min. the reaction was stirred at 0°C for 3 hours. The reaction was cooled to –25°C and *N,N* – dimethylacetamide (30.0 mL), $Cu(OAc)_2$ (3.65g 20 mmol), $Cu(NO_3)_2$•2.5 H_2O (9.70g 40 mmol), sodium azide (5.20g 80 mmol), H_2O (0.36 mL 20 mmol), and THF (30.0 mL) were added followed by stirring at –15°C for 1.5 hour, then at 0°C for 2.5 hours, and then at 25°C for 10 hours. The crude reaction mixture was filtered through a pad of Celite, washed with 75 mL of ether, the organic layer was washed with 75mL brine, he aqueous layer was washed 3x with ether, the organic layers were combined and concentrated to give a brown liquid. A solution of sodium perborate (10.0g 65.0 mmol) in H_2O (20 mL) and THF (20 mL) were added to the crude reaction mixture at 0°C and which was

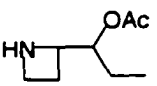
allowed to warm to 25°C over 4 hours. The reaction mixture was poured into brine (75 mL), extracted with ether 4x, the organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated to give a yellow oil. The crude azide was purified by column chromatography (silica gel eluted with pentane) to give a clear liquid (2.16g 13.6 mmol 68% yield). IR ν (film) 2109 cm^{-1}; ^1H NMR δ 7.36-7.15 (m, 5H), 5.92 (d, J = 13.2Hz 1H), 5.53 (dt, J = 13.5, 7.2Hz, 1H), 3.36 (d, J = 7.2Hz, 2H); ^{13}C NMR δ 139.5, 128.6, 128.4, 127.6, 126.4, 119.2, 35.8

1-azide-*trans*-1,2-epoxy-3-phenyl propane (1-65) (jcl-30-19)



clear liquid $[\alpha]_D$ = IR ν (film) 2112 cm^{-1}; ^1H NMR δ 7.37-7.19 (m, 5H), 4.13 (s, 1H), 3.30 (td, J = 5.4, 1.5Hz, 1H), 2.91 (d, J = 5.4Hz, 2H); ^{13}C NMR δ 135.5, 129.0, 128.7, 127.1, 67.8, 58.3, 36.36 Anal. Calcd for $C_9H_9N_3O$: C, 61.70; H, 5.18; N, 23.99. Found C, 61.95; H, 5.22; N, 23.64

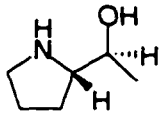
2-(1-acetyl-propane) azitidine (1-67) (jcl-13-49)



Butyllithium (0.17 mL 2.5M in hexanes, 0.42mmol) was added to a stirred solution of *trans*-3-epoxy-hexane amine (0.049g 0.42 mmol) in THF (2.0 mL) at -78°. After 2 hours at -78° acetic anhydride (0.08 mL 0.85 mmol) was added, and after an additional 30 min. the reaction allowed to warm to 25°C. After 20 min. at 25°C H_2O (10 mL) and CH_2Cl_2 (15 mL) were added, the layers were separated, the organic layer was washed with sat. NH_4Cl, brine, dried over $MgSO_4$, concentrated and the pale yellow liquid purified by column chromatography (silica gel eluted with 100/1 CH_2Cl_2/MeOH) to give a clear liquid (0.0142g 21% yield). $[\alpha]_D$ = + 30.9° ^1H NMR δ 5.88 (br. s, 1H, NH), 3.41 (dtd, J = 6.3, 5.7, 2.4Hz, 2H), 2.78 (ddd, J = 7.2, 3.6, 2.4Hz, 1H), 2.72 (ddd, J = 5.7, 5.4, 2.4Hz,

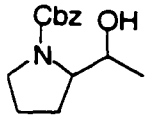
1H), 1.99-2.09 (m, 1H), 1.98 (s, 3H), 1.50-1.63 (m 2H), 1.00 (t, J = 7.4Hz, 3H); Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found C, 61.57; H, 7.91; N, 5.48

2-(1-hydroxy ethyl)-pyrrolidine (1-69)[6] (jcl-12-22)



Lindlar catatlyst (0.010g, 11 wt%) was added to a solution of *trans*-4-epoxy hexane azide (0.093 g, 0.66 mmol) in methanol (3.0 mL) in a pressure tube. The pressure tube was flushed with H_2 three times and then pressurized to 20 psi. After stirring 4.5 hours the reaction mixture was filtered through Celite, washed with Et_2O, and the filtrate was concentrated to yield a white solid (0.0683g, 0.59mmol, 89% yield). The white solid started to decompose to a brown oil upon exposure to air. $[\alpha]_D$ = -31.0° (c 0.40, $CHCl_3$); IR ν 3339 cm^{-1}; ^1H NMR δ 4.07 (br. s, 2H), 3.95 (dq, J = 6.6, 3.3Hz, 1H), 3.20 (m, 1H), 3.03 (m, 2H), 1.70-1.89 (m, 4H), 1.17 (d, J = 6.3Hz, 3H); ^{13}C NMR δ 67.0, 64.0, 46.7, 25.6, 24.1, 19.7

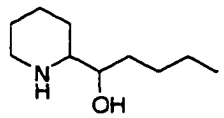
2-(1-hydroxy ethyl)-pyrrolidine benzyl carbamate (1-71) (jcl-13-34)



A solution of *trans*-4,5-epoxy-hexane benzyl carbamate 9/1 *trans/cis* (0.020 g, 0.08 mmol) and *p*-toluene sulfonic acid (0.005 g, 0.02 mmol) in THF (1.0 mL) was refluxed for 3 hr. After cooling to rt. of H_2O (10 mL) was added and the mixture was extracted 3x with Et_2O, the organic layers were combined, washed with H_2O, sat. $NaHCO_3$, brine, dried over Na_2SO_4, and concentrated to yield a clear liquid which was purified by column chromatography (silica gel eluted with 2/1 hexane/EtOAc) to give a clear liquid (0.0193 g 96% yield) as a 9/1 *trans/cis* mixture. $[\alpha]_D$ = -27.5° (c 0.26, $CHCl_3$); IR ν 3429, 1682 cm^{-1}; ^1H NMR δ 7.29-7.40 (m, 5H), 5.15 (s, 2H), 4.00 (m, 1H), 3.64 (m, 1H), 3.34 (m, 1H),

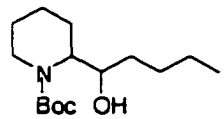
3.19 (m, 1H), 2.01 (m, 1H), 1.90 (m, 1H), 1.75 (m, 1H) 1.55 (m, 1H), 1.10 (d, J = 6.3 Hz 3H); 100MHz ^{13}C NMR (exists as rotamers) δ 136.7, 128.7, 128.2, 128.1, 69.6, 67.3, 64.2, 27.8, 24.3, 17.8 Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found C, 66.76; H, 7.21; N, 5.39

2-(-1-hydroxypentane)-piperidine (1-73) (jcl-13-05)



A solution of **1-72** (0.040 g 0.23 mmol) and Lindlar's catalyst (0.008 g) in methanol (2.0 mL) was stirred in a pressure tube under H_2 (40 psi) for 72 hours. The reaction mixture was filtered through Celite, rinsed with ether, and concentrated to give a white (0.0381 g 96% yield) mp = 74°C; $[\alpha]_D$ = +4.3° (c 0.51, $CHCl_3$); IR ν 3396 cm^{-1}; ^1H NMR δ 3.52 (m, 1H), 3.12 (m, 1H), 2.69 (td, J = 11.7, 2.7Hz, 1H), 2.56 (m, 3H), 1.85 (m, 1H), 1.58 (m, 2H), 1.22 –1.54 (m, 9H), 0.91 (t, J = 7.2Hz, 3H); ^{13}C NMR δ 74.1, 60.8, 47.1, 32.6, 28.6, 26.5, 25.2, 24.5, 23.0, 14.24

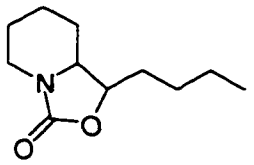
2-(-1-hydroxypentane)-piperidine *t*-butyl carbamate (jcl-13-05)



A solution of **1-73** (0.0381 g 0.23 mmol), Boc_2O (0.055 g 0.25 mmol), and triethyl amine (4 μL 0.07 mmol) in methanol (2.0 mL) was heated at reflux for 2 hours. The reaction was poured into H_2O, extracted with hexane, the organic layers were combined, washed with brine, dried over Na_2SO_4, concentrated, and purified by column chromatography (silica gel eluted with 4/1 hexane/ether) to yield a clear liquid (0.0231g 37% yield) $[\alpha]_D$ = -24.2° (c 1.0, $CHCl_3$); IR ν 3434, 1666 cm^{-1}; ^1H NMR δ 4.00 (br. s, 1H, OH), 3.83-3.97 (m, 2H), 2.72 (td, J = 13.5, 2.7Hz, 1H), 2.03 (dm, J = 12.3Hz, 1H), 1.48-1.65 (m, 6H), 1.45(s, 9H), 1.25-1.43 (m, 6H), 0.91 (t, J = 7.0Hz, 3H); ^{13}C NMR δ 155.3, 79.6, 69.7,

55.8, 40.5, 33.8, 31.8, 28.6, 28.1, 25.4, 24.7, 23.0, 22.8, 19.7, 14.2. Calcd for $C_{15}H_{29}NO_3$: C, 66.38; H, 10.77; N, 5.16. Found C, 66.58; H, 10.58; N, 5.13

1-buty-hexahydro-oxazolo[3,4 – a] pyridin-3-one[7]



A solution of 2-(-1-hydroxypentane)-piperidine *t*-butyl carbamate (0.068g, 0.25 mmol) and KO*t*Bu (0.028g, 0.25 mmol) in THF (1.5mL) was refluxed for 6.5hr. After cooling to rt. H_2O (10mL) was added and the reaction was extracted 3x with Et_2O, the organic layers were combined, washed with H_2O, brine, dried over Na_2SO_4, and concentrated. The crude liquid was purified by column chromatography (silica gel eluted with 4/1 hexane/Et_2O) to give a clear oil (0.037mg, 19 mmol, 76% yield). IR ν 2939, 2860, 1750 cm^{-1}; ^1H NMR δ 4.44 (ddd, *J* = 9.3, 7.8, 3.9Hz, 1H), 3.88 (dd, *J* = 13.3, 4.3Hz, 1H), 3.58(ddd, *J* = 14.7, 7.5, 3.6Hz, 1H), 2.84 (td, *J* = 12.6, 3.6Hz, 1H), 1.96 (m, 1H), 1.30-1.74 (m, 11H), 0.91 (t, *J* = 7.2Hz, 3H); ^{13}C NMR δ 157.3, 58.2, 42.2, 29.2, 28.2, 25.2, 24.5, 23.2, 22.7, 14.1.

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CHAPTER TWO

DESYMMETRIZATION AND KINETIC RESOLUTION OF OLEFINS BY CHIRAL DIOXIRANES

2.A. INTRODUCTION

Obtaining compounds in high optical purity from sources other than nature has always been a challenge for synthetic chemists. Generally it is much less expensive and time consuming to form compounds which are racemic or achiral. The ability to convert these inexpensive compounds into high value chiral compounds has been an area of active interest since Pasteur's time. Resolution or desymmetrization of non-optically pure compounds is one reaction manifold for the conversion of these less-expensive starting materials into desired optically enriched compounds.

2.A.1. Kinetic Resolution

Kinetic resolution involves some chiral probe interacting with a racemic mixture for which the rate of one enantiomer's interaction with the chiral probe is different from the other's. This results in the removal or alteration of the more reactive enantiomer leaving the less reactive enantiomer optically enriched.[1] This process can be carried out enzymatically, using chiral reagents, or chiral catalysts. Chiral catalysts are a very

attractive option, especially if they are inexpensive and can be used at very low loading. Unfortunately the maximum yield is 50% from a racemic mixture, since one enantiomer has to be removed. If the starting material is inexpensive and there is a suitable method for differentiating enantiomers, then kinetic resolution is a viable choice.

2.A.2. Kinetic Theory

The feasibility of kinetic resolution for a particular process or substrate is dictated by the relative rates of reaction of the two enantiomers.[1a] The two reactions can be described as a racemic mixture *R* and *S* interacting with a chiral catalyst forming products P and Q, eq.2.1 & 2.2.

$$R \xrightarrow{k_R} P \qquad \text{(eq 2.1)}$$

$$S \xrightarrow{k_S} Q \qquad \text{(eq 2.2)}$$

If we assume that *R* and *S* exist as a 50/50 mixture then $[R]_0 = [S]_0 = 0.5$ at t = 0 and conversion is represented as *C* ($0 < C < 1$). At some time *t* the amount of recovered starting material is $[R] + [S] = 1 - C$, and the enantimeric excess is $([S] - [R])/([S] + [R])$ and ee > 0 if $k_R > k_S$, giving an enrichment in *S*. Combining equations 2.1, 2.2 and these definitions the amounts of *R* and *S* can be expressed as:

$$[S] = \frac{(1 - C)(1 + ee)}{2} \qquad [R] = \frac{(1 - C)(1 - ee)}{2} \qquad \text{(eq 2.3; eq.2.4)}$$

The results of a kinetic resolution at conversion C for the ee of recovered starting material is related to the stereoselectivity factor $\mathbf{s} = k_R / k_S$. If it is assumed that the reaction is first order or pseudo first order with respect to R and S then

$$- k_R[R] = \frac{d[R]}{dt} \qquad \text{(eq 2.5)}$$

$$- k_S[S] = \frac{d[S]}{dt} \qquad \text{(eq 2.6)}$$

After integration and combination of these equations the stereoselectivity factor **s** is given by eq. 2.7.

$$\mathbf{s} = \frac{\ln([R]/[R]_0)}{\ln([S]/[S]_0)} = \frac{\ln 2\,[R]}{\ln 2\,[S]} \qquad \text{(eq 2.7)}$$

Substitution of equations 2.3 and 2.4 into equation 2.7 gives equation 2.8, which describes the selectivity in terms of ee of recovered starting material at conversion C.

$$\mathbf{s} = \frac{\ln[(1 - C)(1 - ee)]}{\ln[(1 - C)(1 + ee)]} \qquad \text{(eq 2.8)}$$

If the product is also chiral eq. 2.8 can be converted to use the optical purity of the product (ee'), eq 2.9

$$\mathbf{s} = \frac{\ln[(1 - C)(1 + ee')]}{\ln[(1 - C)(1 - ee')]} \qquad \text{(eq 2.9)}$$

These two equations allow for determination of the selectivity factor **s** from either the recovered starting material or the product. A graphical representation of the selectivity factors impact is displayed in Figure 2.1.

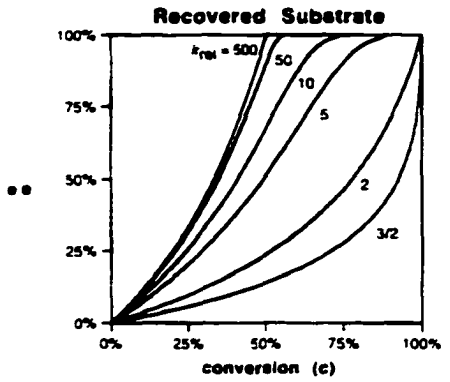


Figure 2.1 Recovered Starting Material ee vs. Conversion for a Number of s Values[1b]

Examination of this graph shows that an s value of 10 can give recovered starting material in 90% ee at 62% conversion. Evaluation of a process's viability for production of optically-enriched starting material is gauged by its selectivity factor. In general a process with an s value greater than 10 is seen as very synthetically useful. In figure 2.1 it is apparent that an s value greater than 10 quickly approaches the theoretical limit of complete selectivity.

If the product of the kinetic resolution is desired in high ee, then the process must have a higher selectivity factor than is required for recovering the starting material in high ee, Figure 2.2.

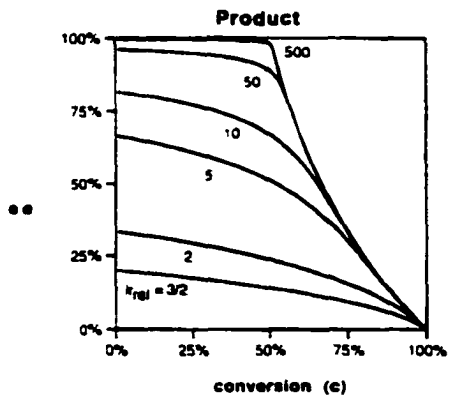
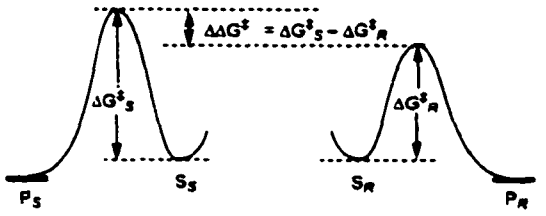


Figure 2.2 Product ee vs. Conversion for a Number of s Values[1b]

As demonstrated in Figure 2.2 kinetic resolution is not as well suited to recovery of the product in high ee. For the recovery of starting material an s value of 10 gives a

maximum optical purity of about 80% ee. The optical purity is greatly affected by the concentration of the reactant. As the concentration of the more-reactive enantiomer decreases a less-selective process will begin to consume the less-reactive enantiomer, resulting in a lowering of product ee.

A thermodynamic representation for kinetic resolution is given in Figure 2.3.



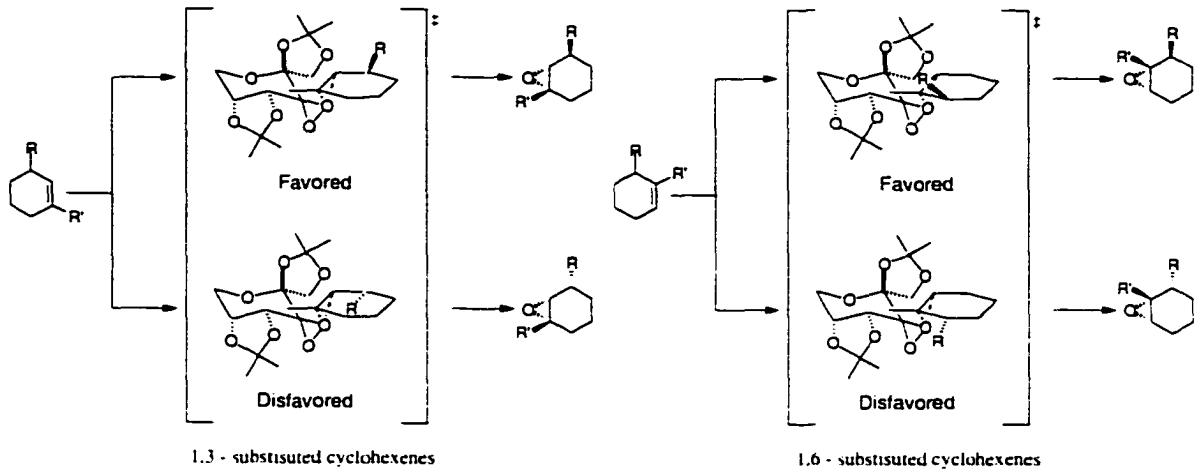
$$k_{rel} = s = k_{fast}/k_{slow} = e^{\Delta\Delta G^{\ddagger}/RT}$$

Figure 2.3 Selectivity Factor by Transition State Energy[1b]

If the products of the reaction are enantiomers there is no difference in driving force from product stability since by definition enantiomers have the same energy. The difference between rates is determined by the difference in transition state energies, similar to enantioselective processes involving achiral substrates.

2.A.3. Kinetic Resolution of Olefins with a Chiral Fructose Catalyst

The Shi group has explored the ability of chiral dioxiranes to kinetically resolve olefins.[2] It was found that substituted cyclic olefins could be resolved with selectivity factors >>10 in many cases, especially for substituted cyclohexene systems. Two factors were found to influence the selectivity factor, the substituent on the olefin itself and the chiral center needed to be adjacent to a tri-substituted olefin, Scheme 2.1.



Scheme 2.1 Kinetic Resolution of Cyclohexenes

Experiments showed that the oxygen was being delivered to the face opposite the directing group. Using the favored spiro transition state, two models were developed for 1,3 and 1,6 disubstituted cyclohexenes. The possible planar transition states are not included for clarity, however they will contribute to the overall outcome.

2.A.4. Desymmetrization Coupled with Kinetic Resolution

Symmetrical bifunctional molecules provide the opportunity for selective formation of multiple chiral centers in a single operation via an enantioselective desymmetrization. A small number of catalysts have shown the ability to differentiate between two equivalent reactive centers with high enantioselectivity.[3-4] In most cases the initial desymmetrization does not result in an enantio-pure product. If the desymmetrization can be coupled to a subsequent kinetic resolution step the optical purity can be improved with only a slight sacrifice of material. Fortunately the selectivity of the resolution need not be extremely high since only a minor amount of "starting material" will be of the undesired enantiomer. In this case the kinetic resolution does not start with

a 50/50 mixture of enantiomers, so the theoretical yield is greater than 50%. Sih and coworkers reported the first example of this phenomenon in 1984 in an enzymatic desymmetrization and kinetic resolution.[5] The combination of an enantioselective desymmetrization followed by kinetic resolution has been shown in enzyme-catalyzed and in traditional catalytic systems.

A mathematical model for desymmetrization followed by kinetic resolution has been developed. The reaction of a chiral reagent *C*, with an achiral substrate *S*, which has two possible sites of reactivity, forms the initial product *X*, eq. 2.10. The kinetic resolution of *X* under the same reaction conditions forming product *Z* is represented by eq 2.11.

$$C + S \xrightarrow{k_i} X_i \qquad i = 1, 2, 3, 4 \qquad \text{(eq 2.10)}$$

$$C + X_i \xrightarrow{\beta_i} Z_i \qquad i = 1, 2, 3, 4 \qquad \text{(eq 2.11)}$$

The initial products X_1 and X_3 are enatiomers, their diastereomers are the pair of enantiomers X_2 and X_4. If in the initial reaction $k_1 > k_j$ (j = 2, 3, 4) the major enantiomer will be X_1. The ratio of X_1/X_j is related to the ee, and this ratio will vary with time as the X_1 is converted to Z_1. For the optical purity to increase β_3, the rate of destruction of the minor enantiomer, must be faster than β_1. The change in concentration of the starting material and initial products are represented by equations 2.12 and 2.13.

$$dS / dt = -kSR \qquad \text{(eq 2.12)}$$

$$dX_i / dt = k_i S - \beta_i X_i \qquad \text{(eq. 2.13)}$$

If it assumed that the rate of the second reaction is not affected by the first reaction and that the reaction is first order in substrate equations 2.12 and 2.13 can be combined using differential equations and solving for the ratio of enantiomers gives equation 2.14.

$$\frac{X_1}{X_3} = \left[\frac{\delta_1(\delta_3 + \delta_4)}{\delta_3(\delta_1 + \delta_2)}\right]\left[\frac{s^{\cdot\delta_1 + \delta_2 - 1}}{s^{\cdot\delta_3 + \delta_4 - 1}}\right] \qquad \text{(eq 2.14)}$$

Where $\delta_1 = k_1 / k$ (fractional rate constant) and $s = [S] / [S]_{int.}$ equation 2.14 can be simplified to equations 2.15 and 2.16 giving the ratio of enantiomers at two extremes in the reaction.

$$\frac{X_1}{X_3} = \frac{\delta_1}{\delta_3} = \frac{k_1}{k_3} \qquad \text{low conversion (eq 2.15)}$$

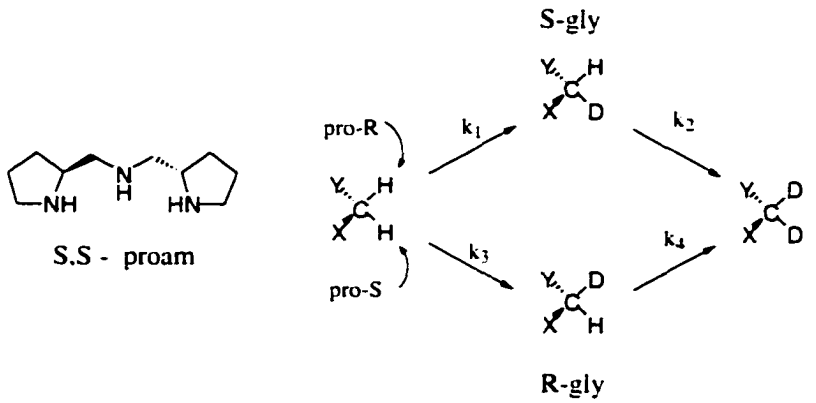
$$\frac{X_1}{X_3} = \left[\frac{\delta_1(\delta_3 + \delta_4)}{\delta_3(\delta_1 + \delta_2)}\right] s^{\cdot(\delta_1 + \delta_2 - \delta_3 - \delta_4)} \quad \text{high conversion (eq 2.16)}$$

Evaluating equation 2.16 shows that as the reaction proceeds the ee of X_1 approaches infinity. This should be no surprise since the second reaction behaves as a kinetic resolution, boosting the ee of the products from the initial transformation.

2.A.5. Previous Examples of Desymmetrization Followed by Kinetic Resolution

There are very few catalytic systems that lend themselves to desymmetrizing and kinetically resolving achiral compounds. The starting material must have two enantiotropic reactive sites, and the catalysts must be able to discriminate between them. The diastereomeric selectivity needs to be extremely high so that there is only one major product. After the first reaction the second reaction needs to be able to discriminate between the remaining reactive sites of the two enatiomers.

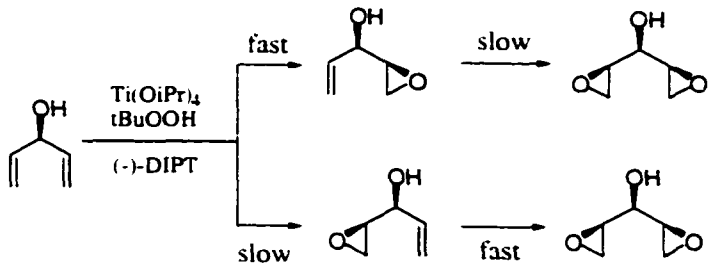
Bosnich and coworkers described the first case of a catalyst converting an achiral compound into a chiral compound followed by kinetic resolution.[6] Bosnich used a cobalt catalyst with chiral tridentate S,S proam ligands to exchange the α protons on a modified glycine for deuterium, Scheme 2.2.



Scheme 2.2 Desymmetrization of Glycine

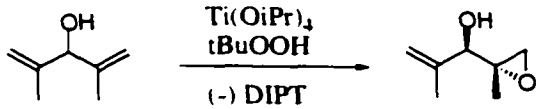
Cobalt tricarbonate was mixed with S,S proam, and the modified glycine to form a stable complex. When this complex was placed in D_2O at high pH, cobalt catalyzed selective deuterium exchange. The first reaction created the chiral glycine derivative then the minor enantiomer underwent a second exchange forming the achiral deuteroglycine, increasing the ee of the chiral deuteroglycine.

Schrieber and Ward have been very active in the application of the Sharpless asymmetric epoxidation to symmetrical and d,l,meso mixtures of bis allylic alcohols, Scheme 2.3.[7] The coordination of the titanium tartrate catalyst to the alcohol of the diene produces a very tight transition state complex which gives good initial selectivities. The second olefin can then be selectively epoxidized, kinetically resolving the mono epoxide.



Scheme 2.3 Desymmetrization using the Sharpless Asymmetric Epoxidation

In most cases the mono epoxide can be recovered with an ee greater than 95%. Figure 2.3 shows an example in which the initial desymmetrization occurs with a good ee, but the ee can be improved to > 99.3% by allowing the reaction to continue and kinetically resolve the desired mono epoxide.



80 - 85% yield

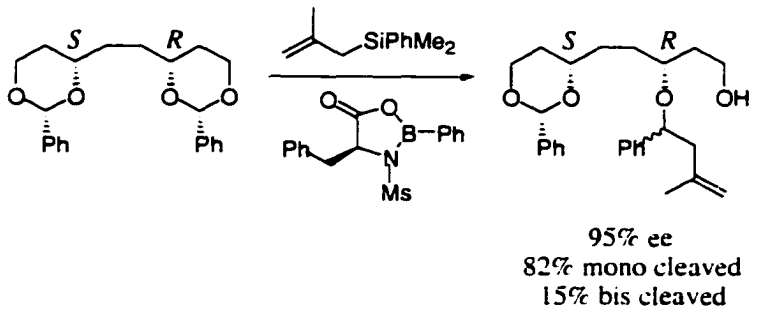
Time	% ee	% de
0.5 h	88	> 99
1.0 h	94	> 99
1.5 h	> 99.3	> 99

Figure 2.3 Sharpless Epoxidation in Desymmetrization and Kinetic Resolution

Recently a zirconium based modification of the Sharpless Asymmetric Epoxidation has been developed which can be used for tertiary alcohols, which are difficult substrates for the titanium system.[8] This advancement allows the resolution of decalin-type systems that were previously inaccessible.

Lewis acid catalyzed opening of bis acetals using a chiral Oxazaborolidine was shown to produce the mono-opened product in high ee. If the reaction was run to

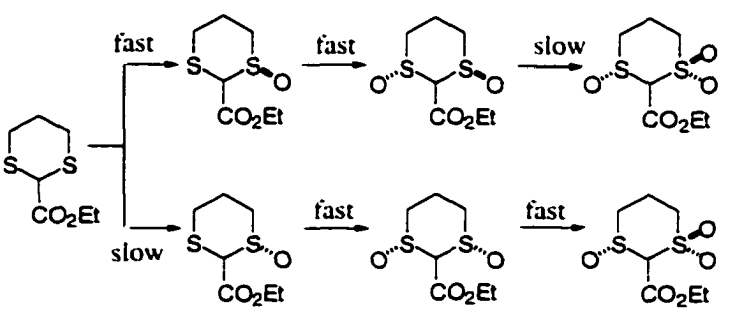
conversions where the bis-opened product was formed, the ee of the mono-opened was improved, Scheme 2.5.[9]



Scheme 2.5 Lewis Acid Catalyzed Acetal Opening

Two cases were reported for this transformation and both gave excellent ees with only a slight sacrifice of the desired mono acetal.

A slightly different case in which along with kinetic resolution of the initial product, a meso compound is removed from a mixture was demonstrated by Aggarwal in the oxidation of dithiols to *trans*-1,3-dithiane-1,3-dioxide using a chiral titanium tartrate complex with peroxide as the oxidant Scheme 2.5.[10]



Scheme 2.6 Formation of *trans* Dithiane Dioxides

Scheme 2.6 shows a simplification of all the reactions and products possible. The initial oxidation proceeds in 84 - 85% ee, but over oxidation allows the bis oxide to be isolated in 55 – 60% yield with an ee > 97% with no meso compound.

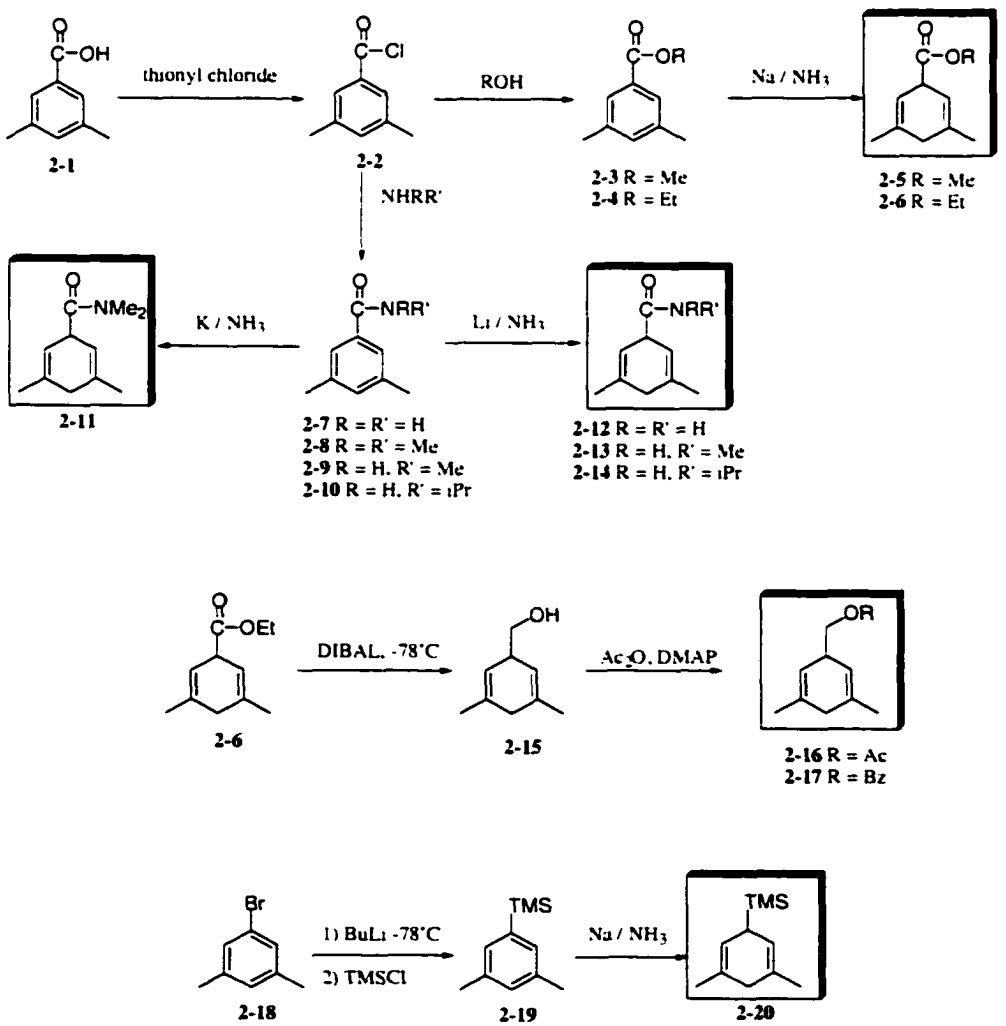
2.B. RESULTS AND DISCUSSION

2.B.1. Desymmetrization and Kinetic Resolution of Trisubstituted Cyclohexadienes

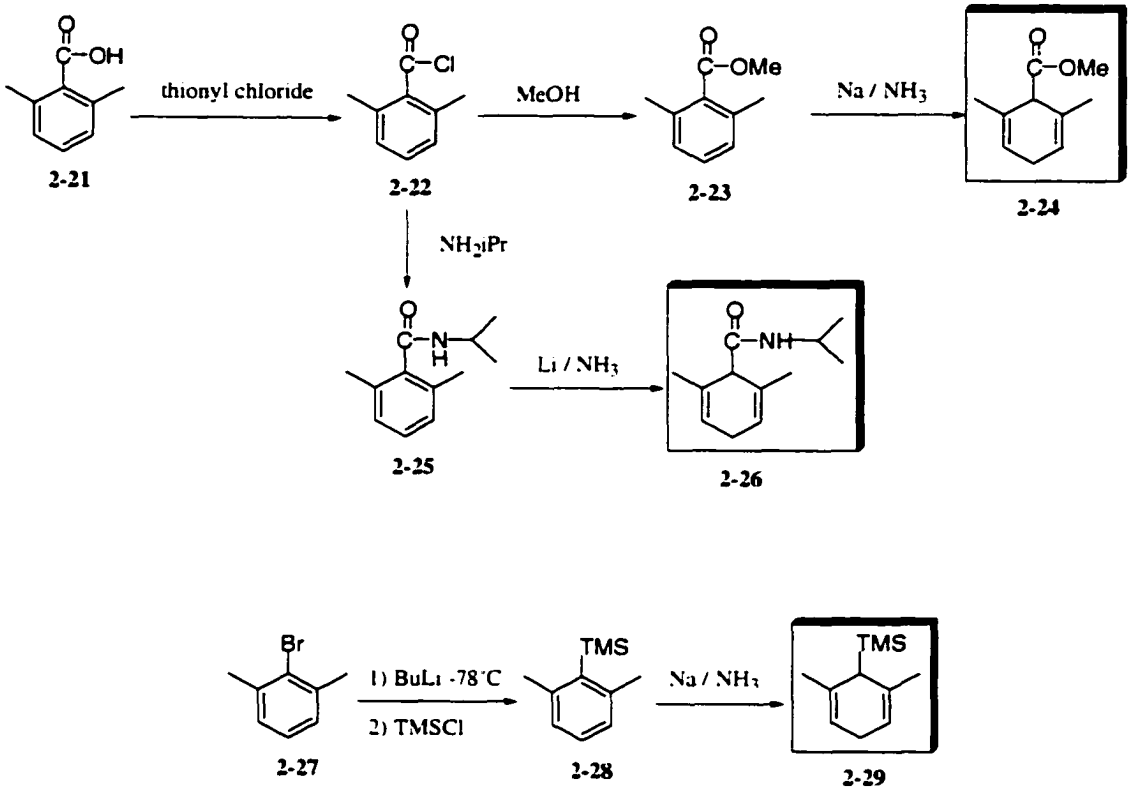
The successful kinetic resolution of conformationally constrained alkenes prompted investigation of symmetrical substrates. With a symmetrical compound the theoretical yield of the mono epoxide is 100%, whereas in kinetic resolution the theoretical yield is only 50%. In addition, if the initial epoxidation proceeds in less than 100% ee, there is the potential for increasing the optical purity by kinetic resolution of the mono epoxide. Cyclic alkenes with a methyl group on the olefin are epoxidized in good enantiomeric excess using catalysts **1-32** (ie. 1-methyl cyclohexene gives an 80%ee) making them ideal candidates for using a coupled reaction to further improve the optical purity.

Initial studies focused on the readily accessible 1,3,5-substitued–2,4-cyclohexadienes and 1,2,6-substitued–2,4-cyclohexadienes. Both of these classes of trisubstituted dienes are conformationally restricted, and they have a prochiral group proximal to the reactive olefins. This family of dienes can be accessed by Birch reduction of the appropriate aromatic derivatives, Scheme 2.7 and Scheme 2.8.[11]

Commercially-available substituted benzoic acid derivatives were converted to the acid chloride and then esterified, or aminated. The benzoic acid derivatives then underwent a Birch reduction to form the required diene. The anion-stabilizing carbonyls gave 1,4-dihydro-benzoate derivatives as the only reduction product. In all cases a proton source was used to prevent hydrolysis of the ester or amide. Esters **2-3**, **2-4**, and **2-23** were reduced with Na° in NH_3 at –78°C using H_2O as the proton source. The amides were reduced with Li° in NH_3 at reflux using EtOH or tBuOH as the proton source. The one exception was benzamide **2-8**, which was reduced with K° in NH_3 at reflux.



Scheme 2.7 Preparation of 1,3,5 Substituted Dienes



Scheme 2.8 Preparation of 1,2,6 Substituted Dienes

All of the amides were relatively stable and could be stored for extended periods in the freezer. The α proton of the ester dienes was more acid than on the amides, and as a result, the ester dienes could only be stored for a few days in the freezer before the aromatic decomposition products had accumulated. In an attempt to mitigate the rearromatization problem, diene **2-6** was reduced to the alcohol with DIBAL at low temperature and then protected as the acetate or benzoate. Both **2-16** and **2-17** were stable dienes, which could be stored in the freezer for an extended period. Trimethylsilyl dienes **2-20** and **2-29** were prepared from the commercially-available bromo xylenes by lithium-halogen exchange followed by quenching of the anion with TMSCl.

Dimethylcyclohexadiene **2-16** with its rigid conformation and prochiral center proximal to the two olefins became the initial substrate for studies. Diene **2-16** was

subjected to the standard epoxidation conditions using 1 molar equivalent of catalyst. The reaction was followed by GC analysis to determine the reaction composition and the ee of monoepoxide **2-30** at different reaction times. As shown in Figure **2.4**, the ee of the monoepoxide **2-30** indeed gradually increased with reaction time (81% to 95%).

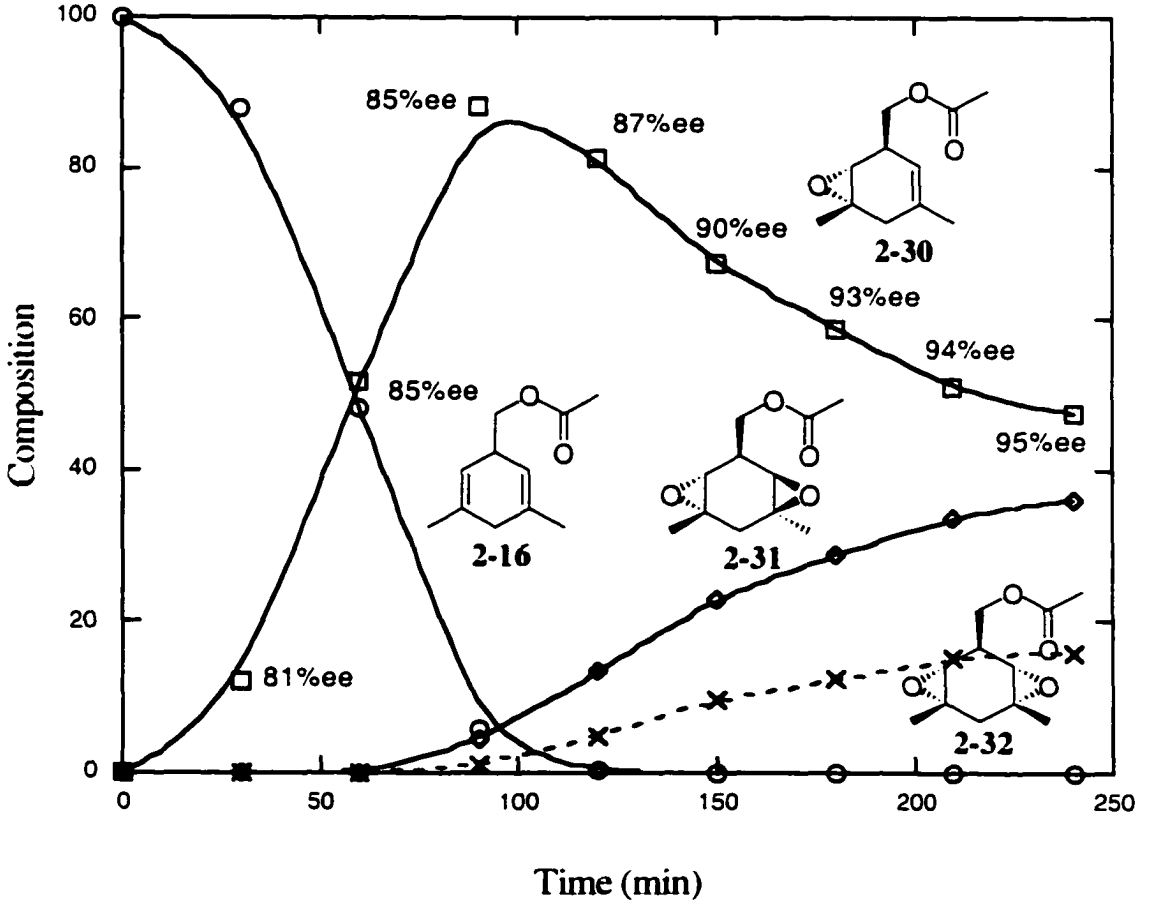
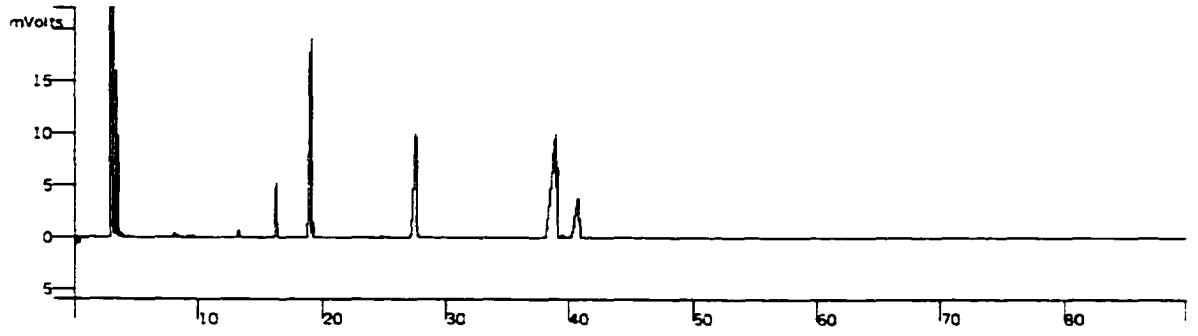


Figure 2.4 Change in ee vs Time for **2-30**

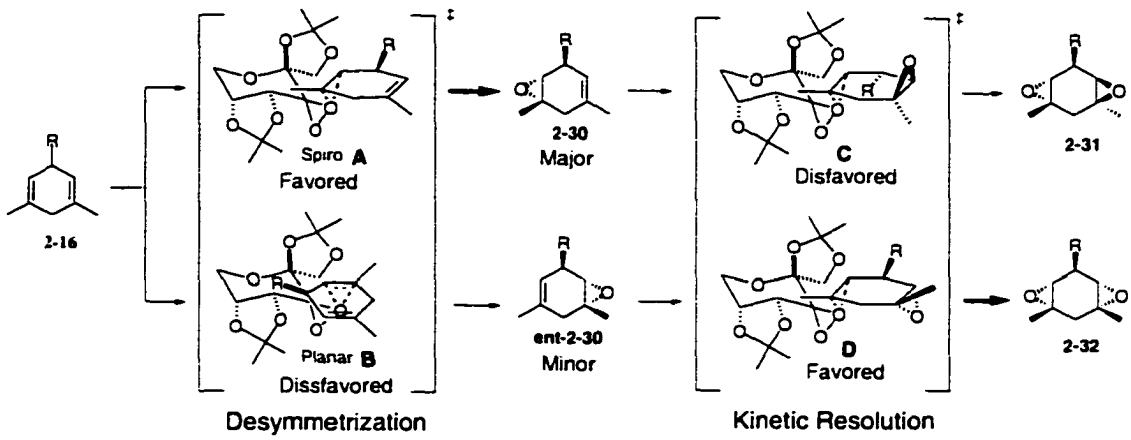
A sample GC trance for following reaction composition is shown below.

Sample Name: jcl-30-16 200°c ketone
Column VA-5MS 30m x 0.250mm 0.25um film Carrier Gas: He Position: Front
int. temp 125 int. time final temp final time rate
psi 10 lin. vel. 28 split 100 range 12
det. temp 250 inj. temp 250



Peak No	Result ()	Ret. Time (min)	Peak Name	Area (counts)
1	27.7384	19.142	Mono	211495
2	22.2223	27.577	Bis-t	169436
3	38.1356	38.958	ketone	290770
4	11.9038	40.770	Bis-c	90762
	100.0001		Totals	762463

A rationalization for this observation is outlined in Scheme 2.9. The initial desymmetrization for which the spiro (**A**) and planar (**B**) transition states delivered the oxygen preferentially *anti* to the R group gave monoepoxide **2-30** in 81% ee, which is in agreement with the epoxidation of 1-methyl cyclohexene. In a second epoxidation, the minor enantiomer (**ent-2-30**) was preferentially epoxidized due to the sterics, resulting in an increase of the optical purity of monoepoxide **2-30**. Both the *trans* and *cis* bis epoxides can be seen in the GC. Both the selectivity and the rate of the second reaction are much lower than the initial reaction. The rate of the consumption of the minor enantiomer must be greater than the consumption of the major enantiomer in order for the ee to increase. If the selectivity factor is only slightly greater than 1 the mono epoxide ee will increase with time. This result showed that the monoepoxide could be obtained in high ee (95%) from an initially less enantioselective epoxidation (81% ee) by a slight sacrifice of the monoepoxide.



Scheme 2.9 Possible Explanation of ee Enhancement for **2-30**

Additional support for the transition state model in Scheme 2.9 was gained when a crystal structure of the chiral mono epoxide of **2-14**. The crystal structure showed that the epoxide was *trans* to the directing group.

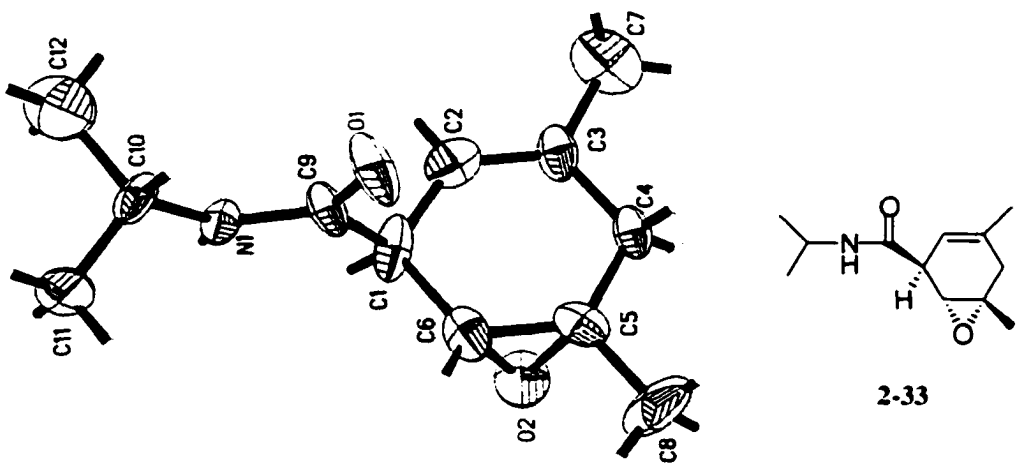
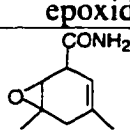
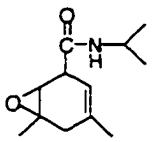
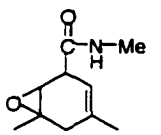
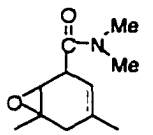
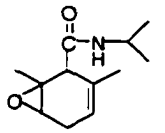
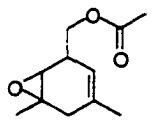
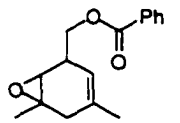
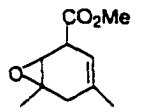
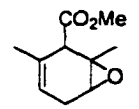
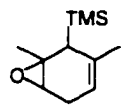
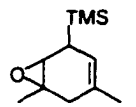


Figure 2.5 X-ray Crystal of chiral **2-33** Mono Epoxide

Studies of additional dienes examined also showed that the ee's of the monoepoxides improved using a longer reaction time, and the monoepoxides could be isolated in good yield and high ee (Table 2.1). In general, the ee of the mono epoxide increases with conversion (Table 2.1 entries 1-7). This result suggests that the minor

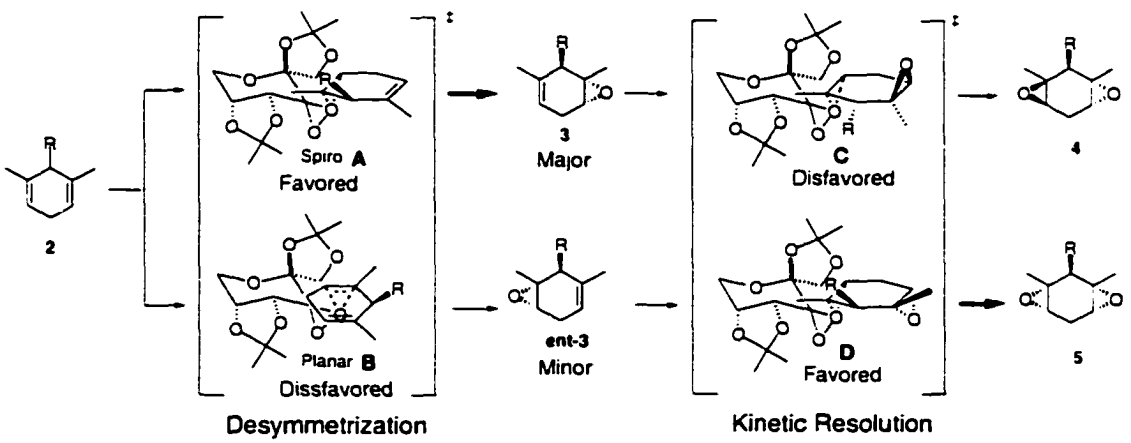
epoxide is converted to the bis epoxide in preference to the major mono epoxide. In all cases the second epoxidation proceeds at a much slower rate than the initial epoxidation. The chiral dioxirane must approach the olefin syn to either the epoxide or the chiral R group. Both of these trajectories are disfavored by sterics. Since the catalyst slowly decomposes under the reaction conditions and the second epoxidation is much less favorable the amount of catalyst, oxidant, and reaction time must be at least doubled to give an improvement in ee. Entries 8 and 9 were not able to be kinetically resolved successfully because the acidic α proton was labile under extended reaction conditions leading to rearromatization, resulting in isolation of the benzoate as the major product.

Table 2.1

entry	epoxide	time	cat (%)	yield[a]	ee (%)
1		1.5h	30	78	89[b]
		4h	60	69	95
2		1.5h	30	73	89[b]
		4h	60	68	95
3		1.5h	30	48	85[b]
		4h	60	51	91
4		1.5h	30	63	83[b]
		3h	60	57	91
5		1.5h	30	86	dr (15/1) ee 82[c]/93
		3h	60	84	dr (5.5/1) ee 91/89
6		1.5h	30	87	79[c]
		4h	100	53	95
7		1.5h	30	50	53[d]
		4h	60	42	58
8		1.5h	30	57	86[e]
9		1.5h	30	45	89[b]
10		1.5h	30	0	ND
11		1.5h	30	0	ND

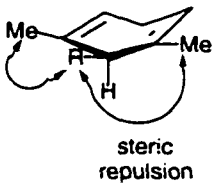
a)Typical procedure: one mmole of substrate was mixed with the 30mol% (77.4mg) ketone catalyst and 15 mg tetrabutylammonium hydrogen sulfate. This was dissolved in 10mL dimethoxymethane 5mL acetonitrile, 7.5 mL borate buffer and chilled in an ice bath. To this was added Oxone 850mg (1.38 eq.) dissolved in 6.5 mL 10^{-4} M EDTA soln. and 800mg (5.8 eq.) K_2CO_3 in 6.5 mL water over 1.5 hours. For 60mol% cat. The amount of Oxone and K_2CO_3 soln. was doubled and added over the time indicated. b) determined by HPLC Chiralpak AD. c) determined by GC Chiraldex GTA. d) determined by HPLC Chiracel OB. e)) determined by HPLC Chiracel OD

The 2-6 dimethyl substrates were also successfully taken through this process. Scheme 2.10



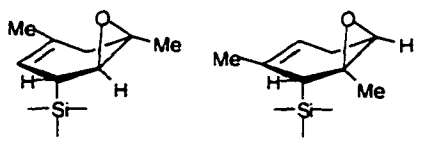
Scheme 2.10 Possible Explanation of ee Enhancement for 2,6 Substituted Dienes

Amide **2-26** was the only substrate to show a significant amount of a cis diastereomer. This is probably due to conformational differences between the 3,5 and 2,6 substituted compounds. The 3,5 compounds are almost flat with the R group occupying a pseudo equatorial position. In the 2,6 case the two methyl groups and the R are so close that there is some steric repulsion resulting in a twist in the ring, reducing the steric influence of the R group, Scheme 2.11.



Scheme 2.11 Possible Steric Interactions

Attempts to isolate the mono epoxide of trimethylsilyl dienes **2-20** and **2-29** were unsuccessful. TLC of the reaction showed that the starting diene was consumed, but the new spot quickly disappeared, forming a spot that was identical to the aromatic silane, before the epoxide could be isolated. Proton NMR spectroscopic analysis of the crude reaction mixture showed a clean conversion of the diene to the TMS xylene with no other products present. A possible explanation of the instability of the epoxides is due to the presumed *trans* arrangement of the silyl group to the epoxide as shown in Scheme 2.12.

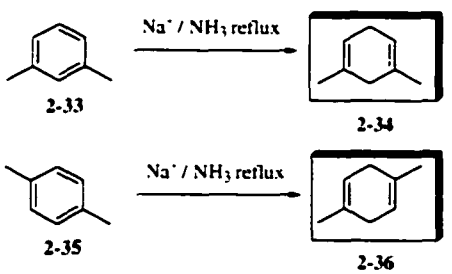


Scheme 2.12 Conformation of 1-trimethyl silyl mono epoxides

The silyl group stabilizes epoxide ring opening. Once the epoxide opens it can rapidly eliminate under the aqueous reaction conditions. The instability of allylic silyl epoxides has been seen in other cases with this catalytic system.

2.B.2. Desymmetrization and Kinetic Resolution of Cyclic Dienes Without a Prochiral Center

Previous desymmetrization and kinetic resolution of bifunctional molecules required an existing prochiral center proximal to the reacting sites to help direct the transformations. Would it be possible for the chiral center formed in the initial desymmetrization to direct the second reaction resulting in a kinetic resolution? The great difference in rates of initial and subsequent epoxidation suggested that the epoxide or methyl group must be interfering with the dioxiranes approach to the olefin. There is potential for the methyl group or initial epoxide of a symmetrical dimethyl-1,4-cyclohexadiene to influence the second epoxidation. Initial substrates were prepared from the requisite xylenes by Birch reduction, Scheme 2.11. Racemic epoxidation studies done on unsubstituted 1,4-cyclohexadiene have shown that under a variety of racemic epoxidation conditions the *trans* bis-epoxide is preferred.[12]



Scheme 2.11 Preparation of Disubstituted Cyclohexadienes

Both dienes were prepared by simple Birch reduction using Na° in NH_3 at reflux and could be stored in the freezer under an inert atmosphere. Diene **2-36** was epoxidized under standard reaction conditions and the conversion monitored by GC. The ee of the mono epoxide was determined by chiral HPLC after work-up and purification. Reactions were stopped at different times to get an idea of how the ee of the mono-epoxide changed with formation of the bis-epoxide. These studies showed that the desymmetrization-kinetic resolution proceeded efficiently for diene **2-33** (Figure 2.5).

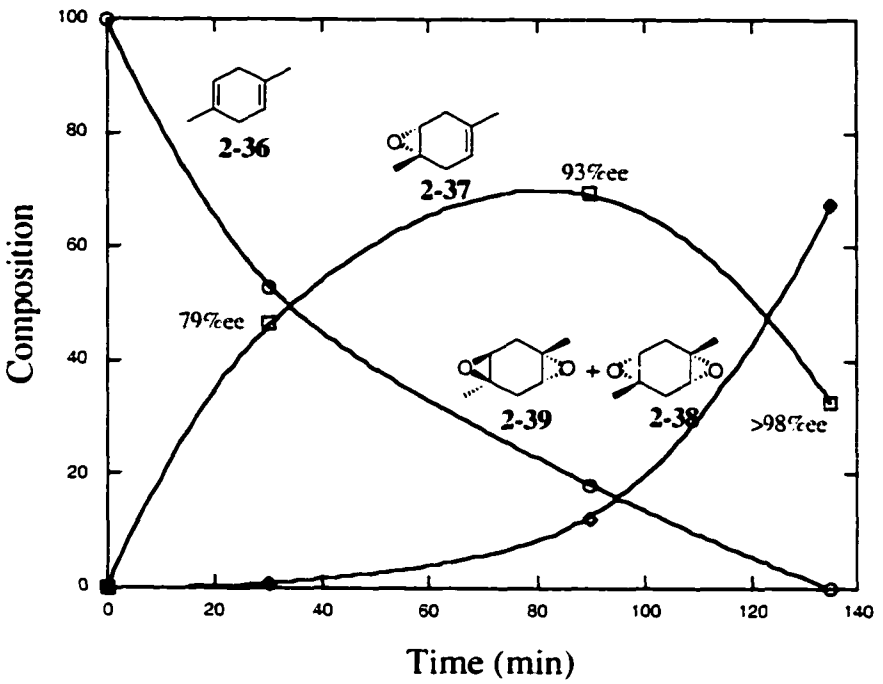


Figure 2.5. Change in ee vs conversion for **2-33**

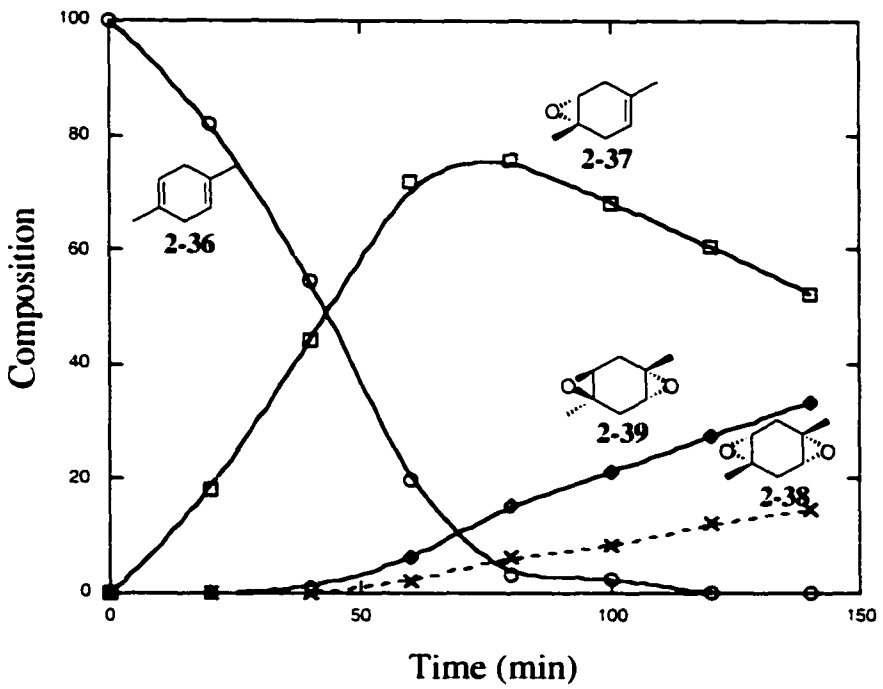
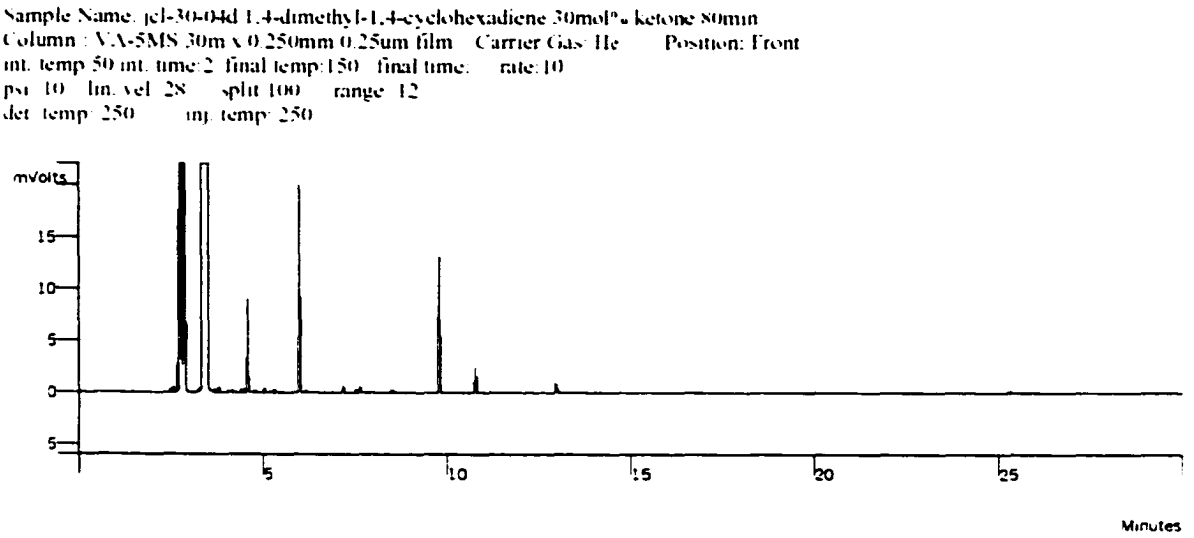


Figure 2.6 Change in Composition vs. Time for **2-36**

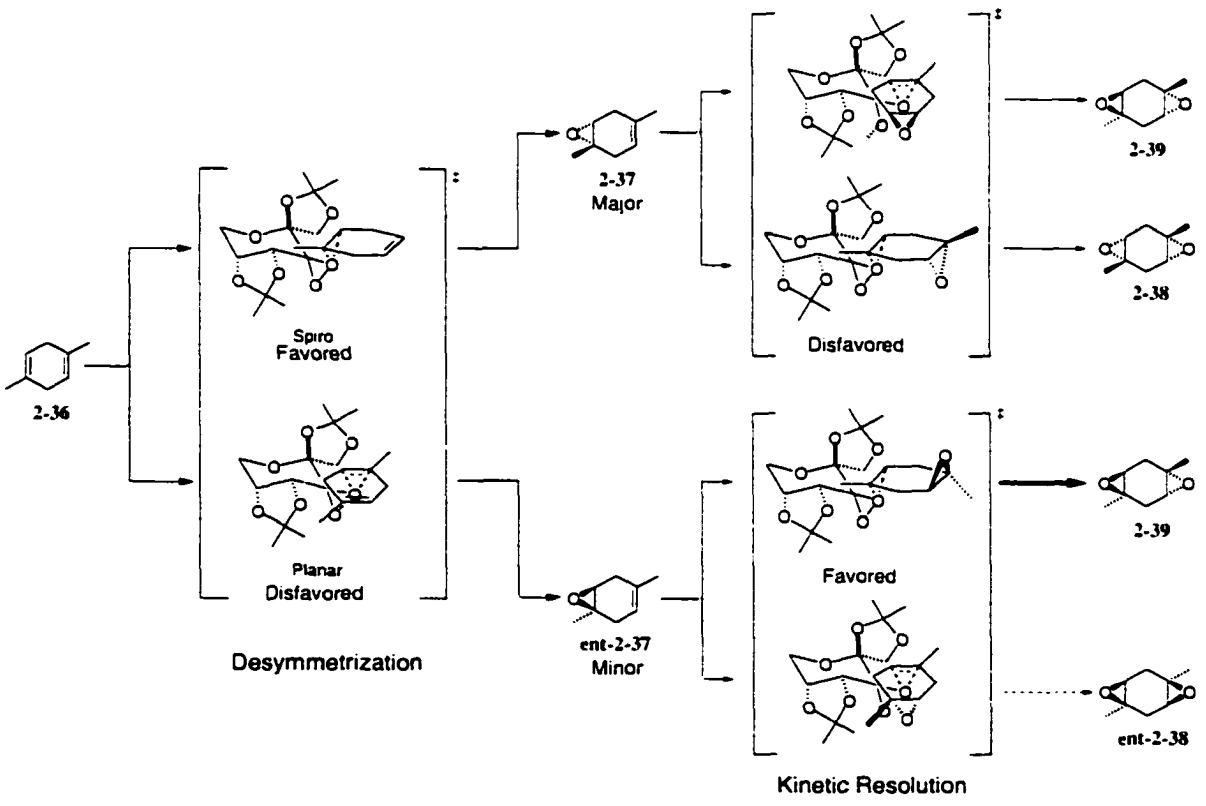
The ee of monoepoxide **2-37** increased from 79% to 98% with reaction time. This result was rather interesting, considering diene **2-33** contains no prochiral center adjacent to the reacting olefins. The chiral centers from the first epoxidation must help to direct the second epoxidation. A plot of the change in composition vs. time for a single epoxidation reaction is shown in Figure 2.6.



Peak No	Result ()	Ret. Time (min)	Peak Name	Area (counts)
1	3.0300	7.635	SM	1249
2	75.6752	9.795	Mono	31198
3	15.1904	10.783	Bis-t	6262
4	6.1044	12.941	Bis-c	2517
	100.0000		**Totals**	**41226**

Both bis-epoxides were isolated from the reaction mixture and identified by NMR spectroscopy. The seemingly large amount of *cis* bis-epoxide is deceptive. The rate of the reaction is controlled by the rate constant and concentration of the reactant. Since the ee of the mono epoxide increases, the rate constant for consumption of the minor epoxide must be larger than the rate constant for consumption of the major epoxide. However there is a large difference in the concentration of the reactants, so a moderately selective process will consume some of the major epoxide resulting in some *cis* bis-epoxide.

A possible rationalization for this increase in optical purity with reaction time is shown in Scheme 2.12. The initial epoxidation desymmetrizes the diene to give the mono epoxide **2-37** in about 80% ee, as expected. The first epoxide directs the second epoxidation to the opposite face of the diene, preferentially consuming the minor enantiomer (**ent-2-37**). Compared to the previously discussed tri-substituted cases, the second epoxidation of **2-36** was much more rapid due to the lack of steric crowding of the mono-epoxide from a directing group. The increased reactivity allows an ee > 98% to be achieved with 30 mol% of catalyst **1-32**.



Scheme 2.12 Transition State Analysis for Diene **2.36**

Interestingly, diene **2-34** displayed a different behavior when it was subjected to the epoxidation conditions (Figure 2.7), and the ee of mono-epoxide **2-40** dropped as the reaction progressed. The data points in Figure 2.7 are individual reactions for which the

composition was determined by GC and the ee was determined by chiral shift ^{1}H NMR spectroscopy after purification.

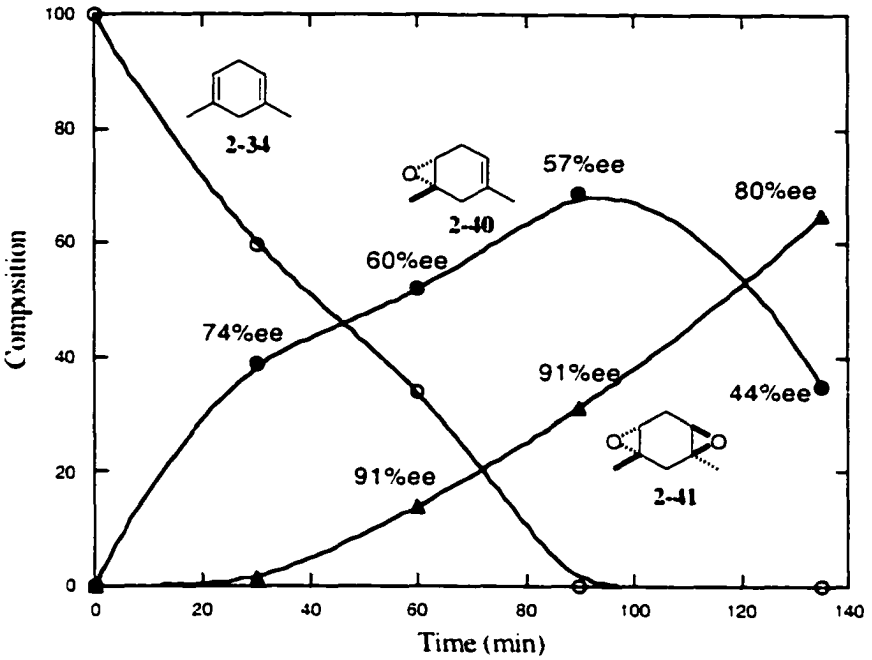


Figure 2.7 Change in ee vs Conversion for **2-34**

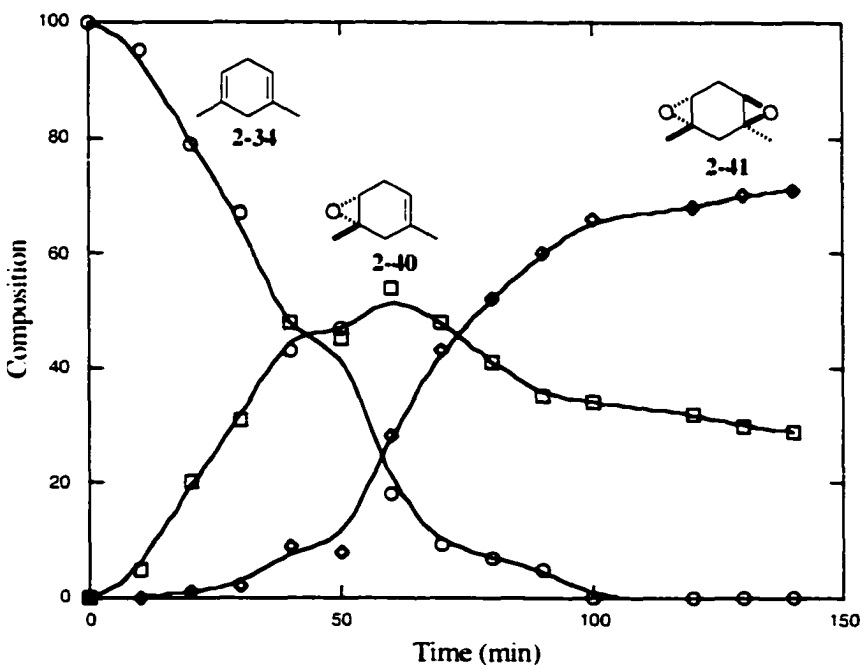
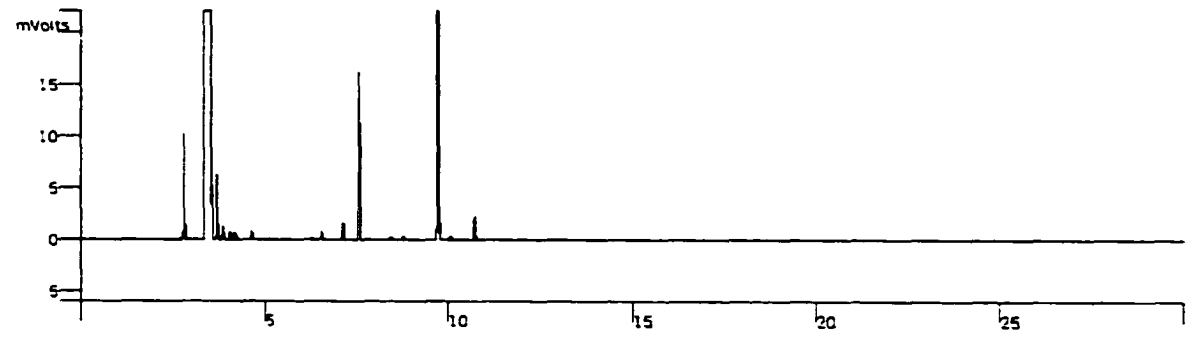


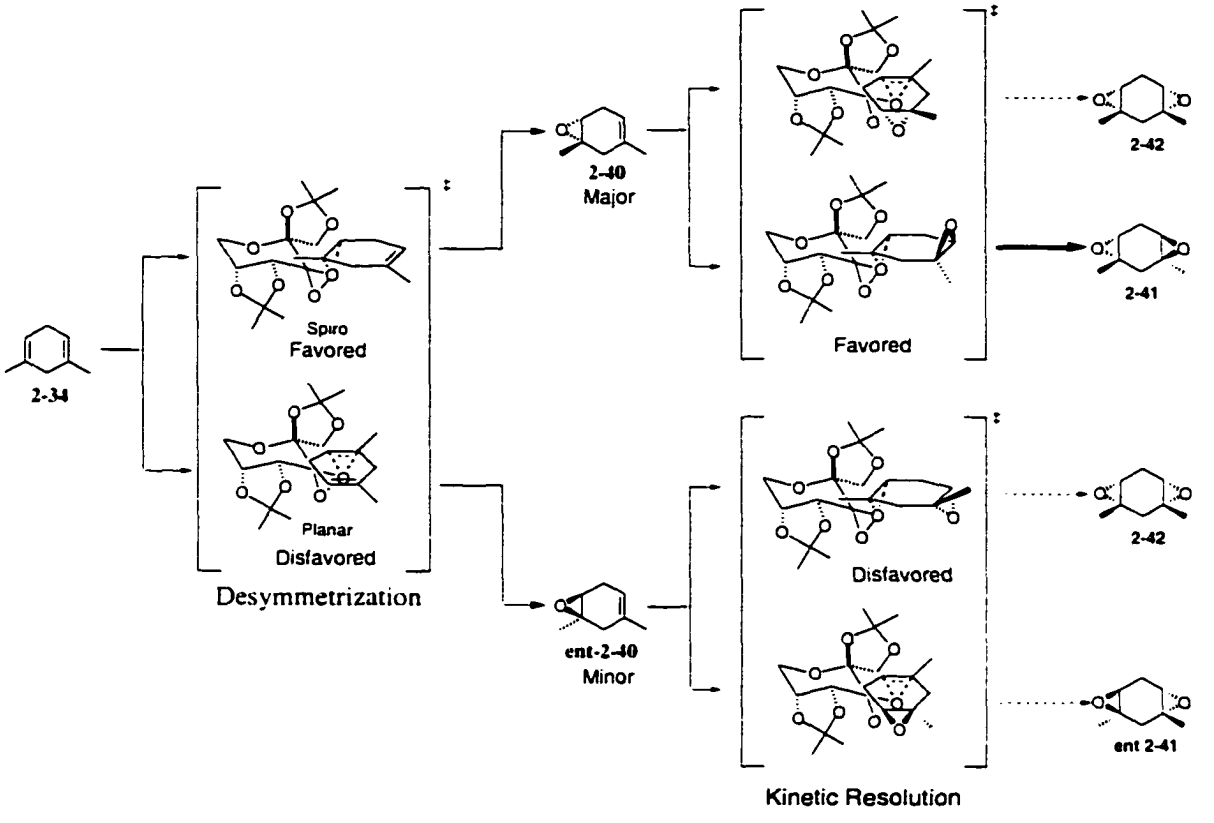
Figure 2.8 Change in Composition for **2-34** from a Single Reaction

Sample Name: jel-28-38 1,5-dimethyl-1,4-cyclohexadiene 10mol% ketone 1.5 hr
Column: VA-5MS 30m x 0.250mm 0.25um film Carrier Gas: He Position: Front
int. temp 50 int. time 2 final temp 150 final time rate 10
pst: 10 lin. vel. 28 split:100 range: 12
det. temp: 250 inj temp: 250



Peak No	Result ()	Ret. Time (min)	Peak Name	Area (counts)
1	33.7085	7.589	SM	35704
2	61.0668	9.735	Mono	64510
3	5.1347	10.725	Bis-t	5424
	100.0000		Totals	105638

An explanation for the change in ee for the mono-epoxide and bis-epoxide as the reaction progressed is provided in Scheme 2.13. The *trans* epoxidation was favored in the second step, and the major enantiomer of mono-epoxide **2-40** was preferentially epoxidized, leading to the decrease of its ee as the reaction proceeded. The fact that the bis-epoxide was found to be optically active indicated that the epoxide rings must be *trans* to each other, since the *cis*-bis-epoxide is a meso compound. As the reaction proceeded, the ee of the bis-epoxide also decreased, as the pool of mono-epoxide became deficient in the major mono-epoxide.



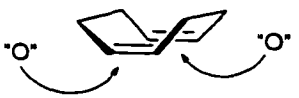
Scheme 2.13 Transition State Analysis for Diene **2.34**

Formation of the bis-epoxide from the minor enantiomer can proceed through the planar and spiro transition states. The spiro transition state is disfavored by sterics, but the planar transition state is disfavored by electronics. The spiro transition state would produce a *cis* bis-epoxide, however very little if any of the *cis* bis-epoxide is observed in the crude reaction mixture. The planar transition state produces the *trans*-bis-epoxide, but opposite to the enantiomer produced from the major product. This result suggests that the planar transition state plays an important role in the consumption of the minor enantiomer. In this case the steric interaction between the ketone and olefin overrides the electronic effect.

Attempts to apply this process to 1,4-dimethylether-1,4-cyclohexadienes were not successful. Following the reaction by TLC showed that the starting material was rapidly

converted to a second spot, but this new spot rapidly decomposed to the dimethoxy aromatic compound. The two cyclic enol ethers tested were quantitatively converted to the methoxy aromatic compounds.

Symmetrical 1,5-cyclooctadiene has been shown to exhibit a strong substrate bias for the second epoxidation to occur *cis* to the first[13]. The boat type conformation of 1,5-cyclooctadiene favors addition of both oxygens from the "bottom" of the boat. Scheme 2.14.



Scheme 2.14 Epoxidation of Cyclooctadiene

A 3/1 mixture of symmetrical 1,5- and 1,6-dimethyl-1,5-cyclooctadienes (**2-43** & **2-44**) was subjected to the desymmetrization-resolution conditions, and the composition and ee of the mono epoxide from **2-43** was monitored by GC (Figure 2.9).

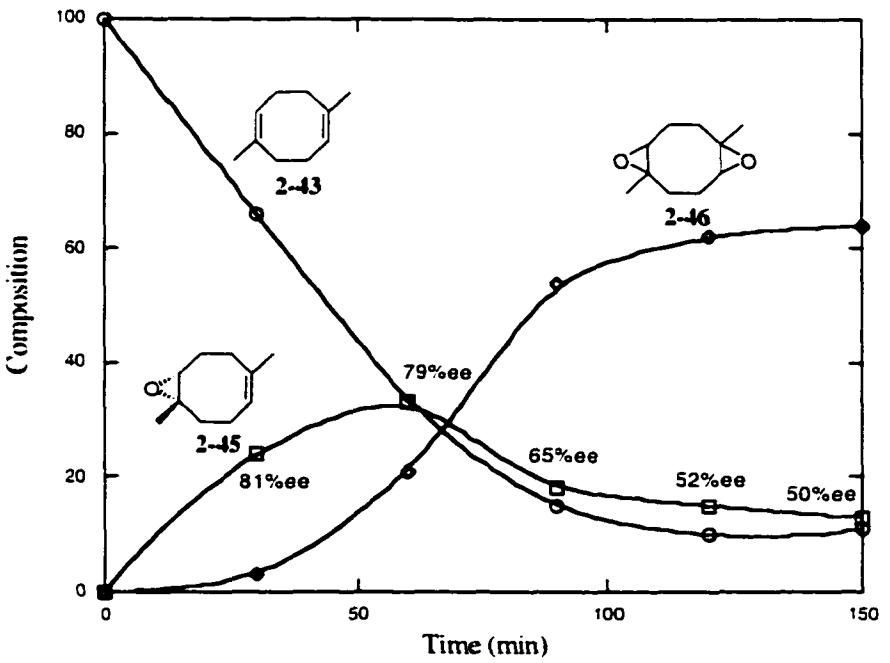
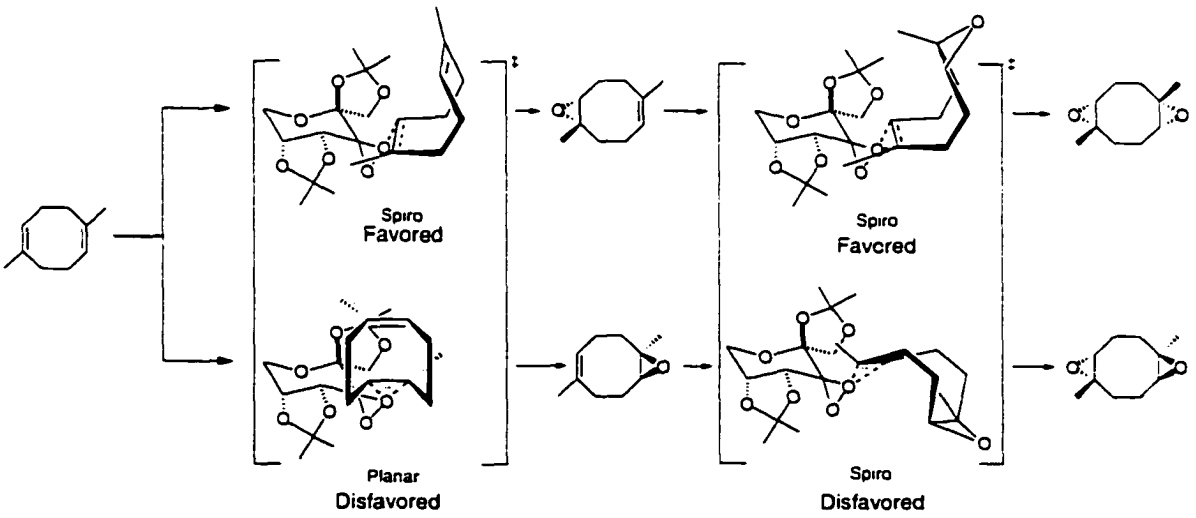


Figure 2.9 1,5-dimethyl-1,5-cyclooctadiene with 30mol% ketone **2-43**

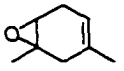
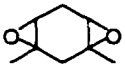
With **2-43** the optical purity of the mono-epoxide decays as the reaction proceeds due to the major enantiomer being consumed, similar to the decay in optical purity of 1-epoxy-1,5-dimethyl-4-cyclohexene (**2-34**). Scheme 2-15 shows the transition state analysis for the desymmetrization/kinetic resolution of cyclooctadienes. The initial epoxidation occurs in about 80% ee as was seen previously for methyl cyclohexene. If the second epoxidation occurs *cis* to the first, the major enantiomer will be consumed assuming that the spiro transition state predominates. The drastic decrees in ee accompanying the formation of the bis epoxide supports the transition state model presented.

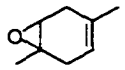
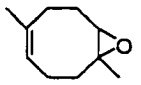
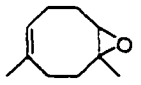


Scheme 2.15 Selectivity

Table 2.2 lists the results for the coupled desymmetrization kinetic resolution of achiral di-substituted dienes.

Table 2.2

Entry	Epoxide	ee	Time(%cat.)	Yield[a](composition)[b]
1		74[c]	30min (30)	26(39)
		61	60min (30)	29(40)
		57	90min (30)	58(69)
		44	135min (30)	20(35)
2		91[c]	60min (30)	13(16)
		94	90min (30)	27(31)

		80	135min (30)	54(65)
3		79[d] 93 >98	30min (30) 90min (30) 135min (30)	36(52/46/0.8) 51(18/69/12) 19(0/37/63)
4		81[e] 79 65 52 50	30min (30) 60min (30) 90min (30) 120min (30) 150min (30)	(31) (45) (26) (21) (18)
5		70 80 80 78 74	30min (30) 60min (30) 90min (30) 120min (30) 150min (30)	(7) (12) (8) (6) (5)

Typical experimental conditions (a) yield after purification by column chromatography. (b) determined by GC of the crude reaction mixture using a 30m x 250μm VA-5 MS column. (c) ee determined by chiral shift ^{1}H NMR (d) ee determined by chiral HPLC Chiracel OB (e) ee determined by chiral GC Chiraldex GTA

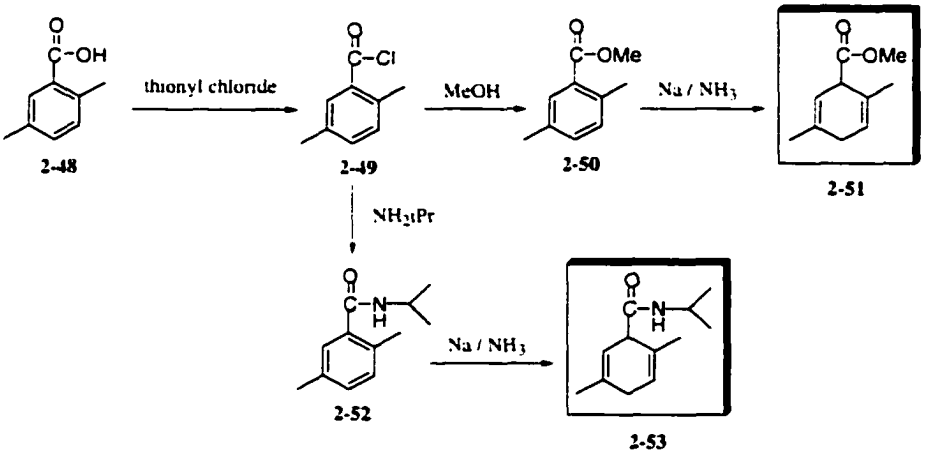
In both the achiral cyclohexadiene and cycooctadiene cases the second epoxidation is much more rapid than in the previously discussed trisubstituted compounds. This is most likely due to the lack of steric crowding on one face of the mono-epoxide allowing the resolution to take place with much more efficiency.

In summary, we have shown that ketone catalyst **1-32** can successfully desymmetrize cyclohexadienes, and kinetically resolve the monoepoxides, leading to the increase or decrease of the ee of the mono-epoxides, depending on the diene system. In some cases, a prochiral directing group is not required and the first epoxide, formed selectively, directs the second epoxidation. When the coupled desymmetrization and kinetic resolution is used synergistically, high enantiopurity can be obtained for the epoxides from an intrinsically less enantioselective substrates. In the cases studied, the transition state model provides very effective rationalizations for the observed absolute

and relative stereochemistry and optical purity. The current study will provide us useful insights to analyze and predict stereochemical outcomes for various olefin systems.

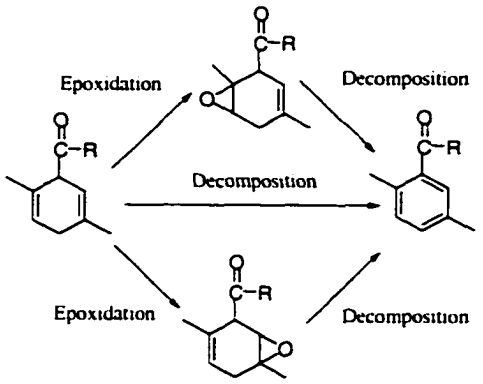
2.B.3. Miscellaneous Kinetic Resolutions

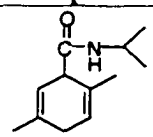
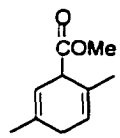
After the initial success with desymmetrization followed by kinetic resolution with trisubstituted cyclohexadienes, a number of racemic 1 substituted 2,5-dimethyl-2,5-cyclohexadienes were subjected to kinetic resolution via chiral dioxirane. These racemic compounds were prepared from the appropriate benzoate derivatives, Scheme 2.16.



Scheme 2.16 Trisubstituted Cyclohexadienes

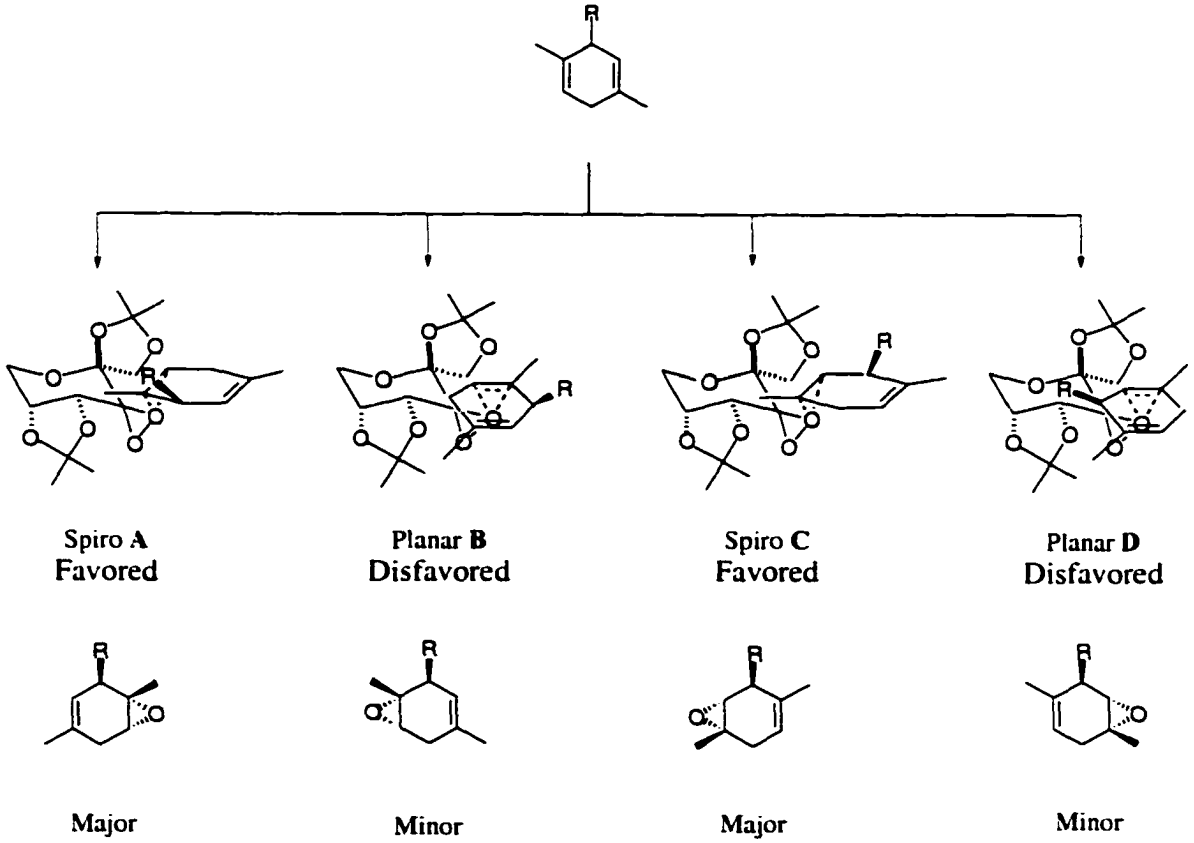
For racemic trisubstituted cyclohexadienes, kinetic resolution is possible. Unfortunately it is not possible to calculate **s**, selectivity factor, with confidence since there is a slow decomposition of both the starting diene and epoxide to the substituted aromatic ester or amide. As a result only optical purities and yields are reported in Figure 2.10. In both cases a high ee for the recovered starting material can be obtained via kinetic resolution, and the yields are respectable since the maximum possible is 50%.



Compound	yield	ee
	20	98.8[a]
	23	98.9

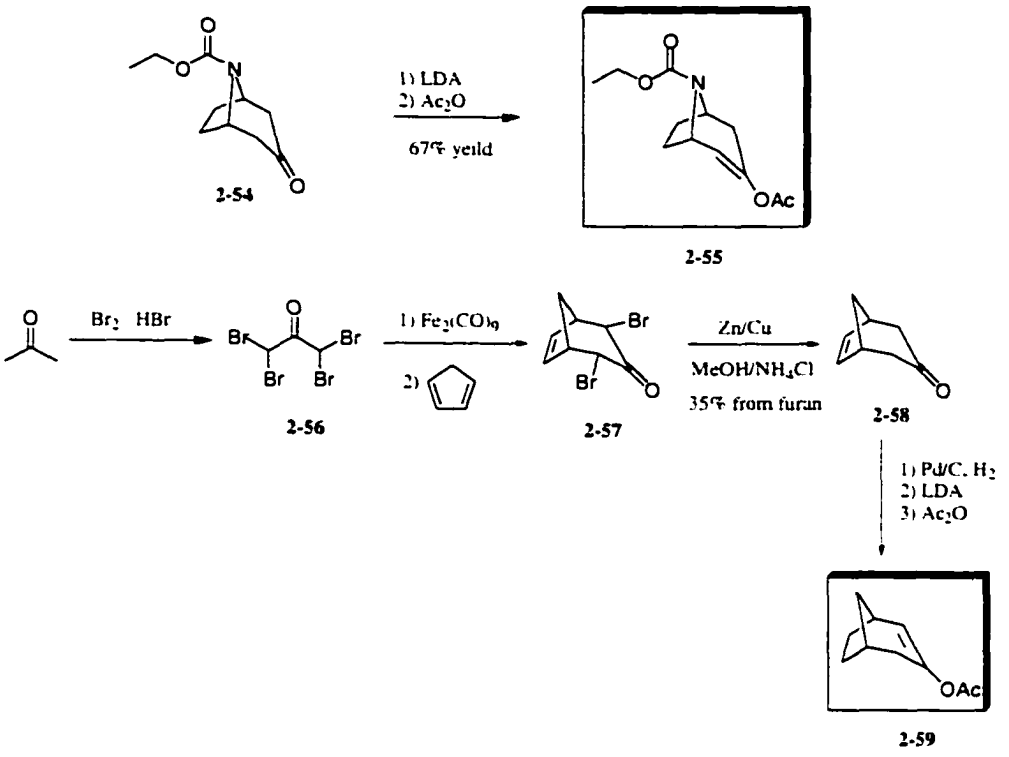
a) after recrystalization

Figure 2.10 Kinetic resolution of Tri-Substituted Hexadienes



Scheme 2.17 Kinetic Resolution of 1,2,5-Substituted Cyclohexadiene

A short time was spent investigating the possibility for the kinetic resolution of [3.2.1] bicyclic enol esters. These potentially interesting molecules were prepared following literature methods as outlined in Scheme 2.18.

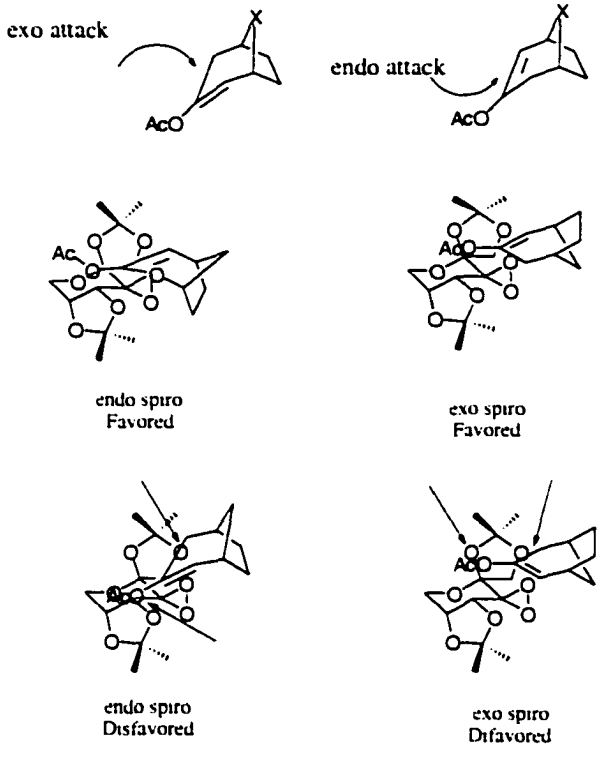


Scheme 2.18 Preparation of Racemic [3.2.1] Bicycles

Tropinone-derived bicycle **2-55** was made from the commercially available ketone by simple deprotonation and acetylation. A [3+4] cyclization from the tetrabromino acetone and cycolpentadiene gave dibromo ketone 2-57.[14] The bromines were removed with Zn/Cu in dry methanol saturated with ammonium chloride. Hydrogenation of the double followed by deprotonation with LDA and trapping with acetic anhydride gave bicycle 2-59.

When compounds **2-55** and **2-59** were subjected to kinetic resolution by ketone catalyst **1-32** the results were not as expected. The ee was low for the recovered starting material. However upon examining the epoxides formed the probable reason for the low

selectivity was identified, Scheme 2.19. The four possible spiro transition states are shown, with two of them being sterically plausible. The problem is that one delivers the oxygen in an endo fashion to one enantiomer of the racemate and the other in an exo fashion to the opposite enantiomer of the racemante.



Scheme 2.19 Modes of Attack

Examination of the epoxides formed showed that both endo and exo epoxides were formed. This lack of diastereoslectivity results in a poor enantioselectivty of the recovered starting material. However, there is some selectivity since the recovered starting material is optically enriched, but not to the extent desired (Figure 2.11).

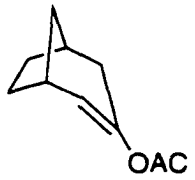
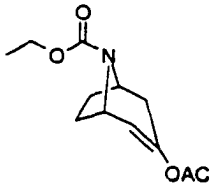
Compound	yield (conv.)	%ee	optical rotation
	39 (62)	55%	+ 28°
	29 (59)	ND	- 27°

Figure 2.11 Bicycle Kinetic Resolution Results

While these results are interesting mechanistically they were not pursued. The sterics of the olefin must produce a single favored transition state in order for a reasonable selectivity factor to be obtained. These systems are still open for further studies related to controlling the dioxirane's approach to the olefin.

2.C CONCLUSIONS

These studies show the power of the spiro transition state model in predicting the stereochemical outcome of the epoxidation. The ketone catalyst is able to successfully desymmetrize conformationally restricted dienes with prochiral directing groups. Noteworthy is the ability to desymmetrize and kinetically resolve dienes without a prochiral directing group. Kinetic resolution of racemic olefins has expanded the understanding of the transition state model. All of the results seen in the cyclic diene cases could be explained using this simple transition state model. Further areas of work include extending the desymmetrization reaction to acyclic dienes, or other less conformationally restrained molecules.

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

[3] For reviews see (a)Ward, R.S.; *Chem Soc. Rev.* **1190**, *19*, 1. (b) Willis, M. C.; *J. Chem. Soc. Perkin Trans. 1*, **1999**, 1765. (c) Spivey, A.C.; Andrews, B.I. *Angew. Chem. Int. Ed.* **2001**, *40*, 3131

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[14] (a) H.Takaya, S. Makino, Y. Hayakawa, R. Noyori; *J. Am. Chem.Soc.*, **1978**, 1765-1777. (b) ibid. p 1778-1785. (c) ibid. p. 1786-1791

2.D EXPERIMENTAL

General Methods

Reaction conversion was determined using a Varian 3800 GC with a 30m x 0.25mm VA-5 column. Column chromatography was performed with 60Å 230-400 mesh Whatman silica gel. The quality and acidity of the silica gel is very important for repeatable yields (Buffering acidic silica gel with base results in deprotonation of the mono epoxide leading to rearomatization). The 300 MHz ^{1}H NMR and 75.5 MHz ^{13}C NMR spectra were measured on a Varian Inova-300 spectrometer in $CDCl_3$. Proton chemical shifts are given relative to internal TMS (0.00 ppm), and carbon chemical shifts are given relative to $CDCl_3$ (77.16 ppm). Infrared spectra were recorded on a Perkin-Elmer 1600 Series FT-IR spectrometer. High resolution mass spectra were performed at the mass spectrometry facility of Colorado State University. Elemental analyses were performed by M-H-W Laboratories (Phoenix, AZ). Optical rotations were measured on an Autopol III automatic polarimeter in a 10 cm cell. X-ray crystallographic analyses of epoxide **2-33** was performed at the X-ray Crystallographic Laboratory of Colorado State University. Melting points were recorded on a Mel-Temp and are uncorrected.

Racemic Epoxidation

Diene **2-16** (0.180g 1.0 mmol) and 1,3-dichloroacetone (0.127 g 1.0 mmol) were dissolved in acetonitrile (15 mL) and water (7.5 mL). A mixture of powdered Oxone (3.03 g, 4.93 mmol) and $NaHCO_3$ (1.5 g, 17.8 mmol) was added in small portions, and the reaction monitored by TLC. Once the diene had been consumed the reaction was poured into 25 mL of H_2O, extracted with hexane, washed with H_2O, brine, dried over Na_2SO_4, filtered, concentrated, and purified by column chromatography (silica gel eluted with 10/1 – 4/1 hexane/ether) to yield the mono-epoxide as a clear liquid (0.140g 72%

yield), and the *trans* bis-epoxide as a clear liquid (0.038g 18% yield). (In some cases a small amount of *cis* epoxide was isolated with the *trans* monoepoxide for racemic epoxidation of tri-substituted dienes)

Representative Epoxidation Procedure A

A solution of diene **2-16** (0.180 g, 1.0 mmol), ketone **1-32** (0.077 g, 0.30 mmol), and tetrabutylammonium hydrogen sulfate (0.015g, 0.04 mmol) in acetonitrile-DMM (15 mL, 1:2, v/v) and buffer [7.5 mL, 0.05 M solution of $Na_2B_4O_7 \cdot 10H_2O$ in 4 x 10^{-4} M aqueous $Na_2(EDTA)$] was chilled in an ice bath. A solution of Oxone (0.85 g, 1.38 mmol) in aqueous $Na_2(EDTA)$ (4 x 10^{-4} M, 6.5 mL) and a solution of K_2CO_3 (0.8 g, 5.8 mmol) in water (6.5 mL) were added separately via syringe pump over a period of 1.5 h. The reaction was poured into 25 mL H_2O and extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried over Na_2SO_4, filtered, concentrated, and purified by column chromatography (silica gel eluted with 4/1 hexane/ether) to give **2-30** as a clear liquid (0.17 g, 87% yield, 79%ee).

Representative Epoxidation Procedure B

A solution of diene **2-16** (0.180 g, 1.0 mmol), ketone **1-32** (0.155 g, 0.60 mmol), and tetrabutylammonium hydrogen sulfate (0.015g, 0.04 mmol) in acetonitrile-DMM (15 mL, 1:2, v/v) and buffer [7.5 mL, 0.05 M solution of $Na_2B_4O_7 \cdot 10H_2O$ in 4 x 10^{-4} M aqueous $Na_2(EDTA)$] was chilled in an ice bath. A solution of Oxone (1.7 g, 2.76 mmol) in aqueous $Na_2(EDTA)$ (4 x 10^{-4} M, 13 mL) and a solution of K_2CO_3 (1.6 g, 11.6 mmol) in water (13 mL) were added separately via syringe pump over a period of 4 h. The reaction was poured into 25 mL H_2O and extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried over Na_2SO_4, filtered, concentrated,

and purified by column chromatography (silica gel eluted with 4/1 hexane/ether) to give **2-30** as a clear liquid (0.104 g, 53% yield, 95%ee)

Experimental Procedure for Figure 2.4

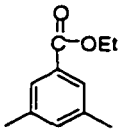
The reaction was carried out as described in Representative Procedure B, but with 1 equivalent of ketone. At thirty minute intervals small aliquots of the reaction mixture were taken, extracted with EtOAc, and dried over $MgSO_4$. Conversions were determined by GC analysis using a 30m x 0.25mm VA-5 column, and enantioselectivities were determined by GC analysis using a 30m x 0.25mm Chiraldex GTA column.

Experimental Procedure for Figures 2.5 and 2.7

A solution of diene (**2-34** or **2-36**) (0.108 g, 1 mmol), ketone **1-32** (0.077 g, 0.30 mmol), and tetrabutylammonium hydrogen sulfate (0.015 g, 0.04 mmol) in acetonitrile-DMM (15 mL, 1:2, v/v) and buffer [7.5 mL, 0.05 M solution of $Na_2B_4O_7 \cdot 10H_2O$ in 4 x 10^{-4} M aqueous $Na_2(EDTA)$] was chilled in an ice bath. A solution of Oxone (1.275 g, 2.07 mmol) in aqueous $Na_2(EDTA)$ (4 x 10^{-4} M, 9.75 mL) and a solution of K_2CO_3 (1.2 g, 8.7 mmol) in water (9.75 mL) were added separately via syringe pump over a period of 2.25 h. The reaction was poured into 25 mL H_2O and extracted with pentane. The combined organic layers were washed with water, brine, dried over Na_2SO_4, filtered, and a sample taken for GC analysis to determine the composition. Then the extracts were concentrated and purified by column chromatography (silica gel eluted with 4/1 pentane/ether) to give the mono- and bis-epoxides which were used to determine the ee's. (Each data point in Figures **2.5** & **2.7** represents one separate reaction. The epoxidations were stopped at the time specified and the epoxides were isolated for the determination of the ee's).

Representative Procedure for Benzyl Ester Formation

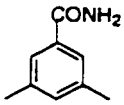
3,5-dimethyl ethyl benzoate (2-4) (jcl-29-39)



Thionyl chloride (6.54g 55 mmol) was added to a solution of 3,5-dimethyl benzoic acid (7.5g 50 mmol) in CH_2Cl_2 (200 mL) chilled in an ice bath. After 30 min the reaction was allowed to warm to rt then stirred an additional 45 min, the solvent removed by rotary evaporation. The crude acid chloride was taken up in ethanol (150 mL) and heated at reflux overnight. The ethanol was removed by rotary evaporation and the crude reaction product taken up in 100 mL H_2O and extracted 3 x 125 mL hexane. The organic layers were combined, washed with H_2O, brine, dried over Na_2SO_4 and concentrated. The clear liquid was clean enough to take on to the next step. IR ν (film) 2980,1719,1609 cm^{-1}; ^1H NMR δ = 7.66 (s, 2H), 7.19 (s, 1H), 4.36 (q, J = 7.5Hz 2H), 2.36 (s, 6H), 1.39 (t, J = 7.2Hz 3H).

Representative Procedure for Benzamide Formation

3,5-dimethyl-benzamide (2-7) (jcl-08-32)

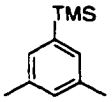


Thionyl chloride (2.379g, 20.0 mmol) was added to a flask containing 3,5-dimethylbenzoic acid (2.0g, 13.3 mmol) and DMF (0.5 mL) dissolved in CH_2Cl_2 40 mL) and refluxed for 1 h. The crude mixture was concentratated, and chilled in an ice bath. Concentrated ammonium hydroxide (40 mL) was added dropwise to control the reaction. After 3 hours the white precipatate was filtered off, washed twice with H_2O and dried under high vacuum to yield a white solid (0.9 g 45% yield) and acid was recovered from

the washes. IR ν (NaCl) 3371, 3187, 1647, 1599, 1402 cm^{-1}; ^1H NMR δ 7.42 (s, 2H), 7.16 (s, 1H), 6.05 (br. s, 1H), 5.79 (br. s, 1H), 2.36 (s, 6H)

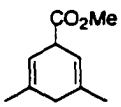
Representative Procedure foe Silyl Xylene Formation

3,5-dimethyl-1-trimethylsilylbenzene (2-19) (jcl-28-14)[1]



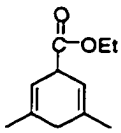
A solution of 5-bromo-m-xylene (3.70g, 20 mmol) in diethyl ether (30 mL) was cooled to -78°C and tert-butyl lithium (23.0 mL, 1.7M in pentane, 40.0 mmol) was added slowly. After stirring 30 min. at -78°C dry trimethyl silylchloride freshly distilled from CaH_2, was added (3.2 mL 25 mmol) in diethyl ether (10 mL) and the reaction warmed to room temperature. After stirring 12 hr. at room temp the reaction was poured into 100 mL of sat. aq NH_4Cl and extracted 3 x with ether. The organic layers were combined, washed with H_2O, brine, dried over $MgSO_4$, filtered, and concentrated. The crude yellow liquid was purified by column chromatography (silica gel eluted with hexanes) to give a clear liquid 5-trimethyl silyl-m-xylene (3.132g 17.57 mmol 88% yield).

3-carboxymethyl-1,5-dimethyl-1,4-cyclohexadiene (2-5) (jcl-07-11)



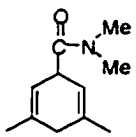
Isolated as a clear liquid by column chromatography (silica gel eluted with 20/1 hexane/ether) to yield (0.569g 25% yield) and recovered starting material (0.686g 25%). The diene can be stored in freezer under N_2 for several days, but slowly rearomatizes. IR ν (film) 2967, 2870, 2812, 1739, 1434, 1170 cm^{-1}; ^1H NMR δ 5.51 (m, 2H), 3.7 (m, 1H), 3.69 (s, 3H), 2.49 (m, 2H) 1.75 (s 6H); ^{13}C NMR δ 174.0, 134.0, 116.4, 52.1, 44.2, 35.8, 23.2

3-carboxyethyl-1,5-dimethyl-1,4-cyclohexadiene (2-6) (jcl-29-39)



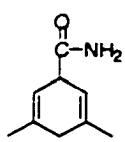
Isolated as a clear liquid by column chromatography (silica gel eluted with 25/1 hexanes/ether) (6.6g, 36.7mmol 87% yield) IR ν 2980, 1719 cm^{-1}; ^1H NMR δ 5.51 (m, 2H), 4.15 (q, J = 7.2Hz 2H), 3.70 (m, 1H), 2.49 (m, 2H), 1.74 (s, 6H), 1.27 (t, J = 7.2Hz, 3H)

3-(*N,N*-dimethylcarbamide)-1,5-dimethyl-1,4-cyclohexadiene (2-11) (jcl-29-14)[2]



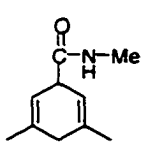
Reduced using K° in NH_3 at reflux. Isolated as a clear liquid, purified by column chromatography (silica gel eluted with 1/1 hexane/ethyl acetate) (1.27g 71% yield). IR ν 2.920, 1634, 1601 cm^{-1}; ^1H NMR δ 5.38 (m, 2H), 4.00 (m, 1H), 3.08 (s, br 3H), 2.95 (s, br 3H), 2.6-2.4 (m, 2H), 1.74 (s, 6H); ^{13}C NMR δ 172.9, 133.5, 116.7, 43.1, 37.2, 36.1, 35.6, 23.1

3-carbamide-1,5-dimethyl-1,4-cyclohexadiene (2-12) (jcl-08-35)[3]



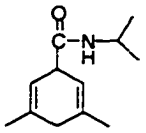
Isolated as a white solid. mp 130-131 °C; IR ν 3367, 3176, 1651 cm^{-1}; ^1H NMR δ 5.26 (br. s, 1H), 5.33 (s, 2H), 3.60 (br. s, 1H), 2.54 (d, J = 6Hz 2H), 1.79 (s, 6H)

3-(*N*-methylcarbamide)-1,5-dimethyl-1,4-cyclohexadiene (2-13) (jcl-09-06)[3]



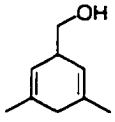
Isolated as a white solid by column chromatography (silica gel eluted with 98/2 CH_2Cl_2) to yield (0.654g 47% yield); mp 97-100; IR ν (NaCl) 3269, 1647, 1560 cm^{-1}; ^1H NMR δ 5.63 (br. s, 1H), 5.50 (m, 1H), 3.61 (m, 1H), 2.78 (d, J = 4.8Hz 2H), 2.53 (d, J = 7.5Hz 3H), 1.75 (s, 6H); ^{13}C NMR 174.2, 134.4, 117.8, 47.1, 35.8, 26.5, 23.2

3-(*N*-isopropylcarbamide)-1,5-dimethyl-1,4-cyclohexadiene (2-14) (jcl-09-03)



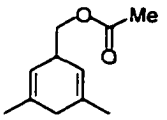
Isolated as a white solid by column chromatography (silica gel eluted with 100/1 CH_2Cl_2/MeOH) to yield (0.898g 77% yield), mp 136-138; IR ν 3264, 2969, 1646 cm^{-1}; ^1H NMR δ 5.47 (br. s, 2H), 5.36 (br. s, 1H), 4.02 (oct, J = 6.6Hz 1H), 3.55(m, 1H), 2.52 (m, 2H), 1.112 (d, J = 6.6Hz 6H); ^{13}C NMR δ 172.7, 134.3, 117.9, 47.3, 41.4, 35.9, 23.2, 22.9

3-hydroxymethyl-1,5-dimethyl-1,4-cyclohexadiene (2-15) (jcl-28-13)



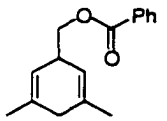
A solution of of DIBAL-H (6.47mL, 1.5M in toluene, 9.7 mmol) was added to a solution of ethyl-3,5-dimethyl-1,4-dihydro benzoate (0.874g, 4.85 mmol) in THF (20mL) at –78°. The reaction was stirred for 30min. then quenched at –78°C with sat. NH_4Cl. (1.0 mL). After warming to rt the reaction was filtered and the solid washed 3x with Et_2O. The filtrate was dried over $MgSO_4$, filtered, concentrated, and the crude oil purifed by column chromatography (siiica gel eluted with 4/1 hexane/ether) to yeild 3,5-dimethyl-1,4-dehydro bezyl alcohol (0.302g, 2.187 mmol 45% yield) as a clear liquid. Note: longer reaction times result in lower yield due to rearromatization. IR ν (film) 3333, 2963, 2925, 2866, 1608cm^{-1}; ^1H NMR δ 5.37 (s, br 2H), 3.57 (s, J = 4.2Hz 2H), 2.92 (m, 1H), 2.51 (s, 1H), 2.48 (s, 1H), 1.74 (s, 6H); ^{13}C NMR δ 124.7, 119.7, 66.5, 40.8, 36.2, 23.2

3-(hydroxymethyl acetate)-1,5-dimethyl-1,4-cyclohexadiene (2-16) (jcl-29-40)



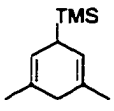
A solution of 3,5-dimethyl-1,4-dihydro benzyl alcohol (2.46mg, 17.8 mmol) and acetic anhydride (3.63g, 35.6 mmol) in THF(80mL) with DMAP (cat.) was stirred at rt for 4 hr. The reaction was poured into H_2O (75 mL) and extracted 3x with hexanes. The organic layers were combined, washed with sat. $NaHCO_3$, H_2O, brine, dried over Na_2SO_4, and concetrated. The crude yellow liquid was purified by column chromatography (silica gel eluted with 20/1 hexanes/ether) to give a clear liquid (2.56g 14.2 mmol 86% yield). IR ν (film) 2966, 1741 cm^{-1}; ^1H NMR δ 5.36 (s, br. 2H), 3.93 (d, J = 7.2Hz 2H), 3.0 (m, 1H), 2.48 (s, 1H), 2.46 (s, 1H), 2.06 (s, 3H), 1.71 (s, 6H); ^{13}C NMR δ = 171.0, 133.3, 119.1, 68.5, 37.4, 36.2, 23.2, 21.1

3-(hydroxymethyl benzoate)-1,5-dimethyl-1,4-cyclohexadiene (2-17) (jcl-28-26)



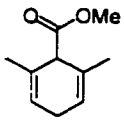
Benzoyl chloride (0.552g, 4.0 mmol) was added to a solution of 3,5-dimethyl-1,4-dihydro-benzyl alcohol (0.552g 4.0 mmol) DMAP (cat) and $NaHCO_3$ (0.336g 4.0 mmol) in THF (15.0 mL). The reaction was poured into H_2O, extracted 3x EtOAc, washed with H_2O, brine, dried over Na_2SO_4, filtered, and concentrated to give a yellow oil. Purified by column chromatography (silica gel eluted with 10/1 hexanes/ether) to yield a clear liquid (0.782g, 3.23 mmol 81% yield). In order to prevent decomposition the diene must be stored in the freezer under an inert atmospher. IR ν (film) 2965, 1719, 1602 cm^{-1}. ^1H NMR δ 8 .05 (d, J = 4.2Hz 2H), 7.56 (t, J = 7.2Hz 1H), 7.45 (t, J = 7.5Hz 2H), 5.46 (s, 2H), 4.18 (d, J = 6.6Hz 2H), 3.17 (m, 1H), 2.51 (s, 1H), 2.49 (s, 1H), 1.73 (s, 6H).

3,5-dimethyl-1-trimethylsilyl-2,4-cyclohexadiene (2-20) (jcl-28-16)[4]



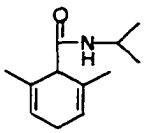
Ammonia (200mL) was condensed into a flask containing 5-trimethyl silyl-m-xylene (3.95g 16.5 mmol) dry ethanol (20 mL) -78°C. Lithium metal (0.5g 72 mmol) was added in small pieces until the blue color persisted. After 1.5 hours the cold bath and condenser were removed and the ammonia was allowed to evaporate. When there was only a small amount of solvent left sat. NH_4Cl (75 mL) was added and the flask rinsed with diethyl ether (75 mL). The layers were separated and the aqueous layer was extracted 3 x with hexane. The organic layers were combined, washed with H_2O, brine, dried over $MgSO_4$, filtered and concentrated. Attempts to purify the diene by vacuum distillation with a fractionation column distillation at 7mmHg 45°C, only enriched one fraction in diene. Gravity and flash chromatography using hexane as the eluent only gave slight enrichment, so the diene was used with a small amount of aromatic compound.

6-carboxymethyl-1,5-dimethyl-1,4-cyclohexadiene (2-24) (jcl-07-41)



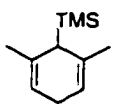
A solution of the methyl benzoate (2.43 g, 14 mmol) and H_2O (370 mL, 21 mmol) in THF (23 mL) was added to ammonia (50 mL) in a 2-neck flask under N_2 at -78°C. Sodium metal (0.820g, 35 mmol) was added in small portions to control the reaction. After 40 min. the reaction was poured into sat. NH_4Cl (50 mL) stirred 5 min. and extracted 3x with hexane. The organic layers were combined, washed with H_2O, brine, dried over Na_2SO_4, filtered, and concentrated to give a clear liquid. Crude ^1H NMR showed a 62% conversion. The diene was isolated by column chromatography (silica gel, 30/1 Hex/ Et_2O) to yield a clear liquid (0.389 g 2.34 mmol, 17% yield) along with recovered starting material. The diene was stored in the freezer under an inert atmosphere. IR ν (film) 2967, 2951, 2914, 2859, 1734, 1699, 1433 cm^{-1}; ^1H NMR δ 5.63 (br. s, 2H), 3.71 (s, 3H), 3.49 (t, J = 5.1Hz 1H), 2.72 (br. q, J = 18.9Hz 2H), 1.71 (s, 6H); ^{13}C NMR δ 173.4, 128.8, 122.0, 52.5, 52.3, 27.6, 21.9

6-(*N*-isopropylcarbamide)-1,5-dimethyl-1,4-cyclohexadiene (2-26) (jcl-10-15)



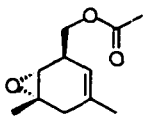
A mixture of 2,6-dimethyl-*N*-isopropyl benzamide (2.54g 13.3 mmol) and *tert*-butanol (0.93g, 13.5 mmol) was added to ammonia at reflux. Sodium metal (1.35g, 60 mmol) was added in small pieces to control the reaction. The reaction was poured into sat. NH_4Cl and extracted with ethyl acetate. The organic layers were combined, washed with water, brine, dried over Na_2SO_4, filtered and concentrated to give a white solid which was purified by column chromatography (silica gel eluted with 1/1 hexanes/ethyl acetate) to give a white crystalline solid (1.31g 51% yield). mp 155-156; IR ν (film) 3269, 2964, 1639, 1544 cm^{-1}; ^1H NMR δ 5.61 (br. s, 2H), 5.36 (br. s, 1H, NH), 4.05 (hd, J = 6.6, 2.1Hz 1H), 3.27 (t, J = 6.9, 1H), 2.75 (m, 2H), 1.73 (s, 6H), 1.10 (d, J = 6.6Hz 6H); ^{13}C NMR δ 171.4, 131.1, 121.1, 55.2, 41.3, 27.6, 22.7, 21.7

2,6-dimethyl-1-trimethylsilyl-2,4-cyclohexadiene (2-29) (jcl-28-08)[3]



Ammonia (200 mL) was condensed into a flask containing 2,6-dimethyl-1-trimethylsilyl benzene (1.62g 9.1 mmol) and dry ethanol (10 mL) at –78°C. Lithium metal (0.28g 40 mmol) was added in small pieces to control the reaction. After the addition was complete the reaction was stirred for 15 min at -78°C and then the dry ice bath was removed and the ammonia allowed to evaporate. Water (30 mL) was added, extracted 3x with ether, the organic layers were combined, washed with H_2O, brine, dried over Na_2SO_4, filtered and concentrated to give a yellow liquid which was purified by disillation under vacuum to give a clear liquid which gave spectra identical to literature values.

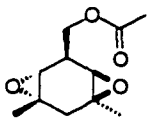
3-(hydroxymethyl acetate)-1,5-dimethyl-1,4-cyclohexadiene oxide (2-30) (jcl-29-49)



Isolated as a clear liquid by column chromatography (silica gel eluted with 4/1 hexanes/ether). $[\alpha]_D^{25}$ = +25.6° (*c* 1.47, $CHCl_3$); IR ν (film) 1742 cm^{-1}; ^1H NMR δ 5.11 (m, 1H), 4.18 (dd, *J* = 11.1, 4.5 Hz, 1H), 4.00 (dd, *J* = 11.1, 7.5 Hz, 1H), 3.04 (m, 1H), 2.93 (m, 1H), 2.41-2.23 (m, 2H), 2.06 (s, 3H), 1.65 (s, 3H), 1.38 (s, 3H); ^{13}C NMR δ 170.6, 132.2, 116.3, 65.0, 59.6, 57.2, 37.1, 35.3, 23.5, 23.0, 20.9; HRMS FAB Calcd (M + 1) for $C_{11}H_{16}O_3$: 197.1178. Found: 197.1184.

(anti) 3-(hydroxymethyl acetate)-1,5-dimethyl-1,4-cyclohexadiene bis epoxide (2-31)

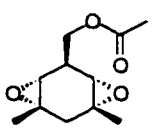
(jcl-29-49)



Isolated as a clear liquid by column chromatography (silica gel eluted with 4/1 hexanes/ether). $[\alpha]_D^{25}$ = +12.8° (*c* 0.54, $CHCl_3$); IR ν (film) 2962, 2925, 1744 cm^{-1}; ^1H NMR δ 4.31 (dd, *J* = 11.1, 6.9 Hz, 1H), 4.17 (dd, *J* = 11.1, 7.8 Hz, 1H), 2.94 (dd, *J* = 3.3, 1.8 Hz, 1H), 2.75 (d, *J* = 1.5 Hz, 1H), 2.68 (td, *J* = 7.8, 3.9 Hz, 1H), 2.15 (s, 2H), 2.10 (s, 3H), 1.32 (s, 3H), 1.315 (s, 3H); ^{13}C NMR δ 170.8, 63.2, 57.6, 57.5, 56.5, 56.2, 35.3, 34.3, 23.6, 23.2, 20.9; HRMS FAB Calcd (M + 1) for $C_{11}H_{16}O_4$: 213.1126. Found: 213.1123

(syn) 3-(hydroxymethyl acetate)-1,5-dimethyl-1,4-cyclohexadiene bis epoxide (2-32)

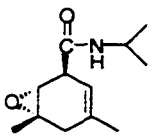
(jcl-30-16)



Isolated as a clear liquid by column chromatography (silica gel eluted with 1/1 hexanes/ethyl acetate). IR ν (film) 2962, 1742 cm^{-1}; ^1H NMR δ 4.32 (d, *J* = 4.5 Hz, 2H), 2.97 (m, 1H), 2.84 (s, 2H), 2.50 (d, *J* = 16.5 Hz, 1H), 2.10 (s, 3H), 2.00 (d, *J* = 17.1 Hz,

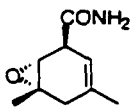
1H), 1.28 (s, 6H); ^{13}C NMR δ 170.5, 63.5, 58.7, 55.2, 34.5, 32.9, 23.4, 20.7. HRMS FAB Calcd (M + 1) for $C_{11}H_{16}O_4$: 213.1126. Found: 213.1124.

3-(*N*-isopropylcarbamide)-1,5-dimethyl-1,4-cyclohexadiene oxide (2-33) (Table 2.1, entry 2) (jcl-10-11)



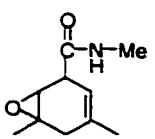
Isolated as a white solid by column chromatography (silica gel eluted with 100/1 CH_2Cl_2/MeOH). mp 124-127 °C; $[\alpha]_D^{25}$ = +87.9° (*c* 0.72, $CHCl_3$); IR ν 3310, 1646, 1545 cm^{-1}; ^1H NMR δ 5.52 (m, 1H), 5.20 (m, *J* = 1.5 Hz, 1H), 4.07 (m, *J* = 6.6 Hz, 1H), 3.41 (m, 1H), 3.31 (m, 1H), 2.40 (s, 2H), 1.73 (s, 2H), 1.40 (s, 3H), 1.17 (d, *J* = 6.6 Hz, 3H), 1.14 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR δ 170.0, 135.0, 114.8, 59.7, 57.2, 46.2, 41.7, 35.5, 23.8, 22.9, 22.8; Anal Calcd. for $C_{12}H_{19}NO_2$: C, 69.20; H, 8.71; N, 6.72. Found: C, 69.12; H, 8.86; N, 6.52.

3-carbamide-1,5-dimethyl-1,4-cyclohexadiene oxide (Table 2.1, entry 1) (jcl-10-13)



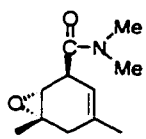
Isolated as a white solid by column chromatography (silica gel eluted with 95/5 CH_2Cl_2/MeOH) mp 122-124 °C; $[\alpha]_D^{25}$ = +63. 2° (*c* 0.50, $CHCl_3$); IR ν 1668, 1615 cm^{-1}; ^1H NMR δ 5.72 (m, 2H), 5.27 (m, 1H), 3.49 (m, 1H), 3.33 (s, 1H), 2.41 (s, 2H), 1.73 (s, 3H), 1.42 (s, 1H); ^{13}C NMR δ 173.7, 135.0, 114.8, 59.4, 57.2, 45.6, 35.4, 23.8, 22.7. Anal Calcd. for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.45; H, 7.66; N, 8.18.

3-(*N*-methylcarbamide)-1,5-dimethyl-1,4-cyclohexadiene oxide (Table 2.1, entry 3) (jcl-10-12)



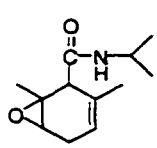
Isolated as a white solid by column chromatography (silica gel eluted with 100/1 CH_2Cl_2/MeOH) (0.0227g 50% yield) $[\alpha]_D$ =+56.8° (*c* 0.96, $CHCl_3$); mp 88-89°C; IR ν (film) 3304, 3099, 2965, 2882, 1649, 1549 cm^{-1}; ^1H NMR δ 6.05 (s, 1H), 5.22 (m 1H), 3.48 (m, 1H), 3.31 (s, 1H), 2.82 (d, *J* =5.1Hz 3H), 2.40 (s, 2H), 1.73 (s, 3H), 1.40 (s, 3H), ^{13}C NMR δ 171.6, 134.9, 114.7, 59.5, 57.2, 45.8, 35.4, 26.5, 23.7, 22.7; Anal. Calcd. for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found C, 66.18; H, 8.25; N, 7.62.

3-(*N,N*-diemethylcarbamide)-1,5-dimethyl-1,4-cyclohexadiene oxide (Table 2.1, entry 4) (jcl-29-17)



Isolated as a clear liquid by column chromatography (silica gel eluted with 1/1 hexane/EtOAc). $[\alpha]_D^{25}$ = +120.4° (*c* 1.7, $CHCl_3$); IR ν (film) 1647 cm^{-1}; ^1H NMR δ 5.18 (m, 1H), 3.88 (m, 1H), 3.18 (s 1H), 3.14 (s, 3H), 2.96 (s, 3H), 2.5-2.3 (m 2H), 1.68 (s, 3H), 1.46 (s, 3H); ^{13}C NMR δ 171.2, 133.8, 112.8, 59.4, 57.2, 41.3, 37.3, 35.4, 35.0, 23.6, 22.7. HRMS FAB Calcd. (M+1) for $C_{11}H_{17}NO_2$: 196.1338. Found: 196.1331.

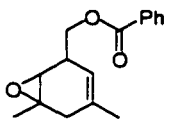
6-(*N*-isopropylcarbamide)-1,5-dimethyl-1,4-cyclohexadiene oxide (Table 2.1, entry 5) (jcl-10-17)



Isolated as a white solid by column chromatography (silica gel eluted with 1/1 hexane/EtOAc) (0.0882g 84% yield), exists as rotamers. mp 182-184°C; $[\alpha]_D$ = -117° (*c* 0.26, $CHCl_3$); IR ν 3285, 1639, 1542 cm^{-1}; ^1H NMR (in DMSO) δ 8.07 (d, *J* = 7.2Hz 0.84H), 7.68 (d, *J* = 8.1Hz 0.16H), 5.16 (br s, 1H), 3.84 (hex, *J* = 6.6Hz 0.84H), 3.88 (m, 0.16H), 3.344 (s, 0.16H), 3.341 (s, 0.84H), 3.07 (br. s, 2H), 2.94-2.78 (m, 0.41H), 2.55-2.13 (m, 1.59H), 1.52 (s, 3H), 1.21 (s, 3H), 1.08 (d, *J* = 3.0Hz 5H), 1.06 (d, *J* = 3.0Hz

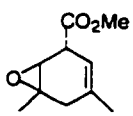
1H); ^{13}C NMR (in DMSO) major rotamer δ 169.2, 128.8, 117.9, 57.97, 56.66, 52.91, 26.19, 22.30, 22.22, 21.97, 20.73; Anal. Calcd. for $C_{12}H_{19}NO_2$: C, 69.20; H, 8.71; N, 6.72. Found C, 69.16; H, 8..62; N, 6.74

3-(hydroxymethyl benzoate)-1,5-dimethyl-1,4-cyclohexadiene oxide (Table 2.1, entry 7) (jcl-28-31)



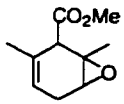
Isolated as a clear liquid column chromatography (silica gel eluted with 4/1 hexane/ether). IR ν (film) 2964, 1720, 1600 cm^{-1}; ^1H NMR δ 8.02 (d, J = 8.4Hz 2H), 7.58 (t, J = 7.2Hz 1H), 7.45 (t, J = 7.5Hz 2H), 5.19 (s, 1H), 4.46 (dd, J = 10.8, 4.2Hz 1H), 4.29 (dd J = 11.1, 6.9Hz 1H), 3.15 (s, 1H), 3.07 (m, 1H), 2.42-2.23 (m, 2H), 1.66 (s, 3H), 1.38 (s, 3H); ^{13}C NMR δ 166.2, 133.0, 132.4, 129.9, 129.4, 128.3, 116.4, 65.4, 59.8, 57.3, 37.4, 35.4, 23.5, 23.1; HRMS FAB (M + 1) for $C_{16}H_{18}O_3$ calc. 259.1334 found 259.1338.

3-carboxymethyl-1,5-dimethyl-1,4-cyclohexadiene oxide (Table 2.1, entry 8) (jcl-07-19)



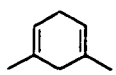
Purified by column chromatography (silica gel eluted with 10/1 hex/Et_2O) to yield a clear liquid (0.166g 57.3% yield) which must be stored in the freezer under N_2. $[\alpha]_D$ +91.2° (*c* 1.09 $CHCl_3$), IR ν 2961, 2918, 2887, 1737 cm^{-1}; ^1H NMR δ 5.26 (m, 1H), 3.73 (s, 3H), 3.61, (m, 1H), 3.28 (s, 1H), 2.37 (m, 2H), 1.68 (s, 3H), 1.43 (s, 3H); ^{13}C NMR δ 172.2, 133.3, 113.8, 58.1, 57.2, 52.3, 43.6, 35.2, 23.6, 22.8; HRMS (EI+) for $C_{10}H_{14}O_3$ calc. 182.0943 found 182.0941

6-carboxymethyl-1,5-dimethyl-1,4-cyclohexadiene oxide (Table 2.1, entry 9) (jcl-07-44)



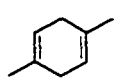
Purified by column chromatography (silica gel eluted with 5/1 hex/Et_2O) to yield a clear liquid (0.0827g 45.5% yield) which must be store under N_2 in the freezer. $[\alpha]_D$= -93.5° (*c* 0.88, $CHCl_3$). ^1H NMR δ 5.33 (br. s, 1H), 3.73 (s, 3H), 3.34 (s, 1H), 3.17 (s, 1H), 2.60 (s, 2H), 1.68 (s, 3H), 1.37 (s, 3H); ^{13}C NMR δ 172.4, 119.4, 58.3, 57.7, 53.1, 52.4, 26.6, 22.5, 21.2, 3.74; HRMS (EI+) for $C_{10}H_{14}O_3$ calc. 182.0943 found 182.0946

1,5-dimethyl-1,4-cyclohexadiene (2-34) (jcl-28-27)[5]



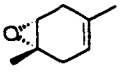
Ethanol (3.5 mL 60 mmol) and m-xyxlene (3.66g 30 mmol) were added to ammonia (200 mL) at reflux, followed by the addition of lithium wire in small pieces(1.25g 180 mmol). The reaction was stirred at reflux for 3.5 hours at which point the consensor was removed and the ammonia allowed to evaporate. When the reaction was about half of it original volumn diethyl ether was added in portions to maintain the reaction volumn at 200mL. After the reaction reached room tempurature it was poured into sat. NH_4Cl (150 mL) and the layers separated. The aquious layer was washed 3x with ether, the organic layers combined, washed 2x 100mL H_2O, brine, dried over $MgSO_4$, filtered, and the concentrated to give a yellow oil that was purified using a short column (silica gel eluted with pentane) to give a clear liquid (1.51g 14.0 mmo 47% yield). IR ν (film) 3030, 2964, 1446 cm^{-1}; ^1H NMR δ 5.41 (m, 2H), 2.69-2.64 (m, 2H), 2.46 (dd, *J* = 8.4, 8.1Hz 2H), 1.68 (s, 6H); ^{13}C NMR δ 131.1, 118.3, 35.7, 27.9, 23.3

1,4-diemethyl-1,4-cyclohexadiene (2-36) (jcl-29-39)[6]



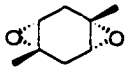
Prepared by the same method as **2-34**. IR ν 2964, 1447 cm^{-1}; ^1H NMR δ 5.41 (m, 2H), 2.57 (m, 4H), 1.67 (s, 6H); ^{13}C NMR δ 131.1, 118.5, 31.8, 23.2

1,4-dimethyl-7-oxa-bicyclo[4.1.0]hept-3-ene (**2-37**) (jcl-29-06)[6]



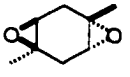
Isolated as a clear liquid by column chromatography (silica gel eluted with 4/1 pentane/ether). $[\alpha]_D^{25}$ = +41.0° (*c* 0.32, $CHCl_3$); IR ν (film) 2966, 2883, 2819, 853 cm^{-1}; ^1H NMR δ 5.15 (m, 1 H), 3.09 (s, 1H), 2.52-2.28 (m 4H), 1.64 (s, 3H), 1.37 (s, 3H); ^{13}C NMR δ 128.3, 116.5, 58.9, 56.3, 30.9, 30.7, 23.4, 23.2; HRMS EI+ Calcd. for $C_8H_{12}O$: 124.0888. Found: 124.0885

(syn)-1,4-dimethyl-4,8-dioxa-tricyclo[5.1.0.0^{OO}]octane (**2-38**) (jcl-30-09)



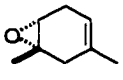
Isolated as a white solid by column chromatography (silica gel eluted with 100/1 CH_2Cl_2). $[\alpha]_D^{25}$ = +42.5° (*c* 0.19, $CHCl_3$); ^1H NMR δ 2.91 (d, *J* = 3.0 Hz, 2H), 2.58 (d, *J* = 17.1 Hz, 2H), 2.15 (dd, *J* = 16.8, 3.3 Hz, 2H), 1.29 (s, 6H); ^{13}C NMR δ 57.3, 54.6, 28.9, 23.5

(anti)-1,4-dimethyl-4,8-dioxa-tricyclo[5.1.0.0^{OO}]octane (**2-39**) (jcl-30-09)[6]



Isolated as a white solid by column chromatography (silica gel eluted with 4/1-1/1 pentane/ether). IR ν 2978, 2918, cm^{-1}; ^1H NMR δ 2.89 (d, *J* = 3.3 Hz, 2H), 2.32 (dd, *J* = 16.8, 3.6 Hz, 2H), 2.16 (d, *J* = 16.8 Hz, 2H), 1.32 (s, 6H); ^{13}C NMR δ 57.4, 55.0, 30.0, 23.5

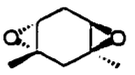
1,4-dimethyl-7-oxa-bicyclo[4.1.0]hept-3-ene (**2-40**) (jcl-29-50)



Isolated as a clear liquid by column chromatography (silica gel eluted with 4/1 pentane/ether). $[\alpha]_D^{25}$ = +3.8° (*c* 0.63, $CHCl_3$); IR ν 2964, 2882 cm^{-1}; ^1H NMR δ 5.15

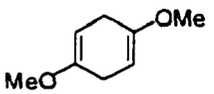
(m, 1H), 3.07 (m, 1H), 2.59-2.39 (m, 2H), 2.40-2.20 (m, 2H), 1.63 (s, 3H), 1.39 (s, 3H); ^{13}C NMR δ 129.3, 115.3, 65.8, 58.0, 35.2, 26.5, 23.4, 23.2; HRMS EI+ Calcd for $C_8H_{12}O$: 124.0888. Found: 124.0887.

(anti)-1,3-dimethyl-4,8-dioxa-tricyclo[5.1.0.0^{oo}]octane (2-41) (jcl-29-04)



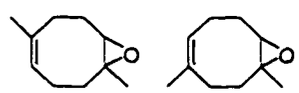
Isolated as a clear liquid by column chromatography (silica gel eluted with 4/1 pentane/ether). $[\alpha]_D^{25}$ = +11.0° (*c* 0.13, $CHCl_3$); IR ν 2981, 2925 cm^{-1}; ^1H NMR δ 2.89 (dd *J* = 2.7, 2.1 Hz, 2H), 2.32 (dd, *J* = 2.4, 2.4 Hz, 2H), 2.14 (s, 2H), 1.31 (s, 6H); ^{13}C NMR δ 56.3, 56.1, 34.4, 25.8, 23.6; Anal Calcd. for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.53; H, 8.77.

1,4-dimethoxy-1,4-cyclohexadiene (jcl-28-41)



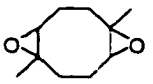
A solution of 1,4-dimethoxy benzene (4.14g 30 mmol) in ether (40 mL) was added to ammonia (200 mL) at reflux followed by the addition of Li° (0.625g 90 mmol). After 7.5 hours the reaction was quenched by slow addition of EtOH until the blue color dissipated. The reaction was poured in to water, extracted 3x with ether, the organic layers were combined, washed with H_2O, brine, dired over $MgSO_4$, filtered, and concentrated ^1H NMR δ 4.51 (s, 2H), 3.51 (s, 6H), 2.79 (s, 4H); ^{13}C NMR δ 153.7, 89.7, 54.0, 29.0

1,5-dimethyl-9-oxa-bicyclo[6.1.0]non-4-ene (2-45) (jcl-28-48)



The mixture of isomers was isolated by column chromatography (silica gel eluted with 10/1 – 4/1 hexane/ether) as a clear liquid. HRMS EI+ for $C_{10}H_{16}O_1$ calc. 152.1201 found 152.1196

1,6-dimethyl-5,10-dioxa-tricyclo[7.1.0.0^{0,0}]decane (2-46) (jcl-28-48)

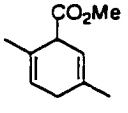


Isolated by column chromatography (silica gel eluted with 4/1 hexane/ether) as a clear liquid. ^{1}H NMR δ 2.82 (dd, J = 6.0, 4.5Hz 2H), 2.12-1.98 (m, 2H), 1.97-1.80 (m, 6H), 1.30 (s, 6H); ^{13}C NMR δ 62.6, 60.4, 28.3, 24.8, 23.7; HRMS EI+ for $C_{10}H_{16}O_2$ calc. 168.1150 found 168.1151

Kinetic Resolution

In a round bottom flask olefin (1mmol), potassium tetrabutyl ammonium hydrogen sulfate (15mg) and the chiral ketone (38 mg, 15mol%) are dissolved in 10mL dimethoxy methane (DMM), 5mL CH_3CN. A borate buffer is added and then the mixture is chilled in an ice bath and maintained at 0 °C. Oxone (0.425g 0.69eq) dissolved in 3.25mL $1x10^{-4}$ EDTA soln and K_2CO_3 (0.4 g, 2.9 eq.) dissolved in 3.25mL H_2O are added over 2 h. via syringe pump. After 4 h 20mL of H_2O is added and the reaction mixture extracted x3 with 25mL EtOAc. The organic layers are combined, washed with H_2O, brine and dried. The solvent is removed by rotary evaporation and the resulting crude product is purified by column chromatography.

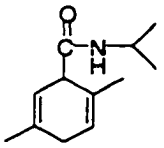
3-carboxymethyl-1,4-dimethyl-1,4-cyclohexadiene (2-51) (jcl-07-36)



Kinetically resolved with 30% ketone (0.166g 1.0 mmol), diene purified by column chromatography (silica gel eluted with 10/1 hex/Et_2O) to yield aclear liquid (0.0374g 23% yield) which must be stored under N_2 in the freezer. $[\alpha]_D$ +48.2 (c 0.82, $CHCl_3$) 98.9%ee Chirapak AD column IR (NaCl) 2956, 2868, 1730 cm^{-1}, ^{1}H NMR δ 5.64 (s, 1 H), 5.41 (s, 1 H), 3.70 (s, 3 H), 3.62 (m br, 1 H), 2.61 (q br, 2 H), 1.73 (s, 6 H); ^{13}C NMR

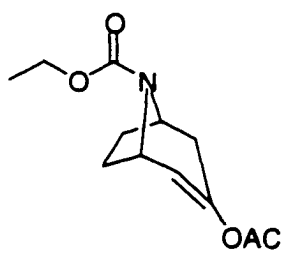
δ 173.5, 134.4, 128.5, 122.4, 116.8, 52.2, 48.4, 31.7, 23.0, 21.8 HRMS (EI+) for $C_{10}H_{14}O_2$ calc. 166.0994 found 166.0992

3-(*N*-isopropylcarbamide)-1,4-dimethyl-1,4-cyclohexadiene (2-53) (jcl-09-23)



mp 106-108 °C; $[\alpha]_D$ +50° (*c* 0.03 $CHCl_3$) 65%ee recrystalized from hexane 97%ee 97/3 hexane/IPA 1.0mL/min. λ=210 nm. IR ν (NaCl) 3277, 2969, 1643, 1546 cm^{-1}, ^1H NMR δ 5.63 (nonet *J* =1.5Hz 1H), 5.46 (oct. *J* =2.1Hz 1H), 5.32 (s br, 1H), 4.03 (d,oct, *J* = 1.5, 6.6Hz 1H), 3.41(m, 1H), 2.64 (m, 2H), 1.73 (s, 6H), 1.11 (d, *J* = 6.6Hz 6H); ^{13}C NMR δ 172.0, 133.5, 130.4, 122.0, 118.8, 51.4, 41.4, 31.8, 23.0, 22.8, 21.6; Anal. Calcd. for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.25. Found C, 74.39; H, 10.01; N, 7.32.

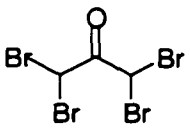
3-acetoxy-8-aza-bicyclo[3.2.1]ocy-2-ene-8-carboxylic acid ethyl ester (2-55) (jcl-05-35)



A solution of *N*-carbethoxy-4-tropinone (1.0 g 5.07 mmol) in THF (10 mL) was added to a solution of LDA prepared from diisopropyl amine (0.8 mL 5.6 mmol) and n-butyllithium (2.4 mL 2.3 M, 5.5 mmol) in THF (15 mL) at –78°C. The reaction was stirred 1 hour, then acetic anhydride (2.0 mL) was added and the reaction was stirred an additional 45 minutes, then quenched with sat NH_4Cl (3 mL) and allowed to warm to rt. After warming to room temp. EtOAc (10 mL) was added and washed with H_2O, brine, dried over Na_2SO_4 and concentrated. Purification by column chromatography (silica gel eluted with 2/1 hexane/ EtOAc) to give a clear liquid (0.160g 67% yield). ^1H NMR δ 5.73

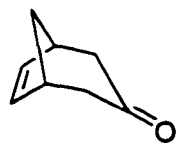
(d, J = 5.4, 1 H), 4.57 (s, br, 2H), 4.13 (m, 4H), 2.88 (s, br, 1 H), 2.10 (s, 3 H), 2.04 (s, 2 H), 2.01 (m, 4 H), 1.26 (t, 7 H); ^{13}C NMR δ 168.9, 154.1, 118.9, 61.3, 61.0, 52.5, 51.7, 51.3, 34.7, 35.2, 34.6, 34.3, 29.7, 28.9, 22.0, 20.9, 14.5; ^{1}H NMR *d*-DMSO 75°C δ 6.33 (d, J = 5.4Hz), 4.95 (dm,J = 17.4Hz), 4.65 (q,d, J = 6.9, 2.1Hz), 3.34 (d,m), 2.73 (m.), 2.65 (s.), 2.50 (m.), 2.29 (m), 1.78 (t.) ; ^{13}C NMR *d*-DMSO 75°C δ 167.9, 153.2, 145.7, 118.3, 60.0, 51.3, 38.7, 35.3, 34.1, 28.6, 20.2, 14.1

1,1,3,3-tetrabromoacetone (2-56) (jcl-05-39/40)



A solution of HBr (50mL, 48% in H_2O) was added to acetone (29g 0.5 mol) in a three neck flask chilled in ice under N_2 and bromine (103 mL, 320g, 2.0 mol) was added via addition funnel over 0.5 hr. and stirred an additional hour. The reaction was quenched with water, and the heavy red organic layer was removed and distilled under reduced pressure (72-80 °C 3mmHg). After the mono,di and tribrominated products were removed by distillation the residue was allowed to crystalize yielding the tetrabromo acetone as white needles. SEVERE LACHRIMATOR ^{1}H NMR δ 6.38 (s); ^{13}C NMR δ 183.3, 33.9

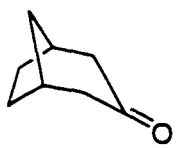
Bicyclo[3.2.1]oct-6-ene-3-one (2-58) (jcl-05-48)[7]



THF (4 mL) was added to $Fe_2(CO)_9$ (2.34 g, 12 mmol) in a dry 3 neck flask fitted with a condensor and addition funnel. The flask was flushed with N_2 benzene (20 mL) and freshly distilled cyclopentadiene (2.0 mL) was added. The reaction was stirred and heated to 80°C in an oil bath. A solution of tetrabromoacetone (3.47 g) benzene (7.5mL) and cyclopentadiene (7.5 mL) was added dropwise to the reaction over 15 min and the

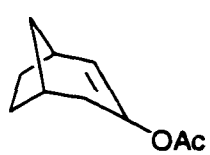
resultant mixture stirred an additional 25 min. at 80°C. After cooling benzene (30 mL) MeOH sat. with NH_4Cl (24 mL) and Zn/Cu couple (7.6 g) were added and the mixture stirred 40 min. Dichloromethane (200 mL) and saturated EDTA solution (100 mL) were added to the mixture and filtered through Celite The layers were separated and the aqueous layer was extracted twice with CH_2Cl_2 (50mL) . The organic layers were combined washed with brine, dried over Na_2SO_4 and concentrated to give a thick red oil (8.29 g). The oil was dissolved in CH_2Cl_2 (40mL) and dripped into 400 mL of rapidly stirring pentane which was then concentrated to yield a red oil (3.89 g). Purification by column chromatography (silica gel 5 1/2" x 1 3/4" plug of silica eluted with 500 mL 1/1 hexane/benzene followed by CH_2Cl_2) yielded a white solid (0.448 g). ^{1}H NMR δ 6.0 (s, 2 H), 2.87 (s, 2 H), 2.38 (q, 4 H), 2.10 (d, 1 H), 1.72 (d, 1 H); ^{13}C NMR δ 210.2, 135.4, 46.2, 41.6, 38.2

Bicylo[3.2.1]octan-3-one (jcl-05-49)[7]



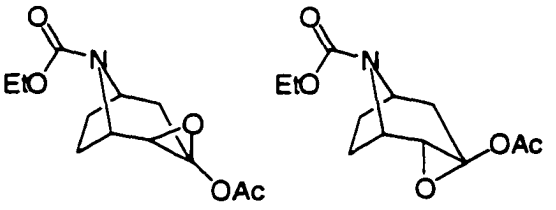
A pressure tube containing a solution of **2-58** (0.448g 3.67 mmol) and Pd/C (30mg 10% Pd, 5% w/w) in CH_2Cl_2 was flushed 3 times with H_2 and presurized to 45 psi. After 5 h. the reaction mixture was filtered through a plug of Celite and silica gel and concentrated to yield white crystals (0.361g 79% yield). ^{1}H NMR δ 2.53 (d, br J =2.7Hz 2H), 2.35 (q, J = 4.9Hz 4 H), 1.78 (m, 4 H), 1.53 (q, J =11.1Hz 2 H)

Acetic acid bicyclo[3.2.1]oct-2-en-3-yl-ester (**2-59**) (jcl-05-50)



A solution of Bicylo[3.2.1]octan-3-one (0.361g 2.91 mmol) in THF (5.0 mL) was added to a solution of LDA prepared from diisopropyl amine (0.45 mL 3.2 mmol) and n-butyllithium (1.2 mL 2.5 M, 3.05 mmol) in THF (8.0 mL) at –78°C. The reaction was stirred 1 hour, then acetic anhydride (2.0 mL) was added and the reaction was stirred an additional 45 minutes, then quenched with sat NH_4Cl (3 mL) and allowed to warm to rt. After warming to room temp. EtOAc (10 mL) was added and washed with H_2O, brine, dried over Na_2SO_4 and concentrated. The brown liquid was purified by column chromatography (20/1 hexane/Et_2O) to yield a clear liquid (0.233g 48% yield). ^1H NMR δ 5.56 (d, J = 6.9Hz 1 H), 2.5 (m, 3 H), 2.04 (s, 3 H), 1.9 (m, 4 H), 1.6 (m, 4 H); ^{13}C NMR δ 169.2, 146.7, 120.6, 38.2, 35.1, 33.8, 33.1, 30.0, 21.0

4-acetoxy-3-oxa-9-aza-tricyclo[4.2.1.$0^{4,9}$]nonane-9-carboxylic acid ethyl ester



Purification by column chromatography (silica gel deactivated with $NaHCO_3$ 3/1 hexane/ EtOAc) 59% conv. 39.0mg starting materal recovered (28.7 % of original material) and 59.9 mg of epoxide 41% optical rotation. $[\alpha]_D$ = -27.17° in $CHCl_3$ ^1H NMR ($CDCl_3$) 4.44 (d. br. 0.7 H), 4.15 (m. 2 H), 3.20 (d. J = 9.9Hz 0.5 H), 2.80 (dd. J = 14.7, 5.7Hz 0.4 H), 2.66 (dd. J = 14.1,5.4Hz 0.4 H), 2.36 (d. J =15Hz 0.2 H), 2.06 (s. 2 H), 2.04 (s. 1 H), 2.03 (m. 1.6 H), 1.74 (m. 0.87 H), 1.26 (diasteriomeric t. 3 H) ^{13}C NMR (benzene 75°C) δ 123.8, 79.0, 61.3, 59.5, 53.2, 50.2, 49.1, 29.4, 20.6, 15.1

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[1] Hevesi, L.; Dehon, M.; Crutzen, R.; Lazarescu-Grigore, A *J. Org. Chem.* **1997**, *62*, 2011

[2] Schultz, A.G; Macielag, M. *J. Org. Chem.* **1986**, *51*, 4983

[3] Dickson, L.; Matuszak, C. A.; Qazi, A. H. *J. Org. Chem.* **1978**, *43*, 1007

[4] Eaborn, C.; Jackson, R. A.; Pearce, R. *J. Chem. Soc. Perkin 1*, **1975**, 470

[5] *J. Am. Chem. Soc.* **1952**, 3658

[6] Fehnel, E. A. *J. Am. Chem. Soc.* **1972**, *94*, 3961

[7] Takaya, H.; Makino, S.; Hayakawa, Y.; Noyori, R. *J. Am. Chem. Soc.* **1978**, 1765

CHAPTER THREE

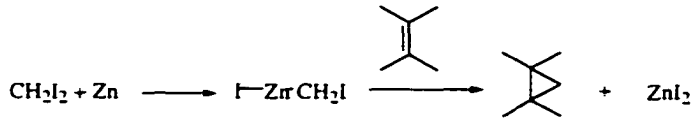
CYCLOPROPANATION USING MODIFIED ZINC CARBENOIDS

3.A. INTRODUCTION

Formation of a cyclopropane by addition of H_2C: to an olefin is the most direct method. Operationally controlling carbene or carbenoid species has not proved a simple problem to solve. Over 40 years ago Simmons and Smith reported a cyclopropanation reaction using Zn/Cu and CH_2I_2, and today it is still the focus of research.[1] This electrophillic carbenoid can cleanly form cyclopropanes with electron-rich olefins under mild conditions, and is one of the most popular methods for cyclopropane formation.[2]

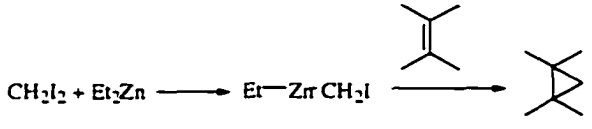
3.A.1 Reaction Development

Early work on the zinc-mediated cyclopropanation of olefins used a mixture of Zn/Cu and diiodomethane in an ethereal solvent. It was believed that the zinc metal would oxidativly add to the diiodomethane, forming I-Zn-CH_2I.



Scheme 3.1 Simmons Smith Reaction

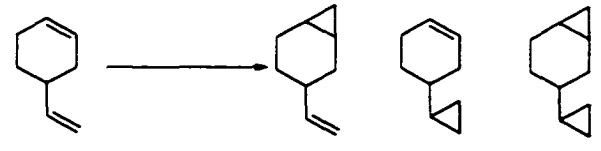
Controlling the stoichiometry of these reactions was difficult, especially with the variable reactivity of the Zn/Cu. Furukawa and coworkers reported a variation on the Simmons Smith reaction in which Zn/Cu was replaced by diethylzinc. Diethylzinc is much more air sensitive than Zn/Cu, but it is a liquid and can be measured out by syringe using a solution, or neat Et_2Zn.[3] Using Et_2Zn as the zinc source allows better control of the stoichiometry, and lends itself to chemoselective cyclopropanation reactions.



Scheme 3.2 Furukawa's Modification

Insertion of diazomethane into zinc iodide has also been used to form the reactive carbenoid, but has found little synthetic use due to the hazards involved.

The electrophilic nature of the Simmons Smith reaction can be seen in competition studies.

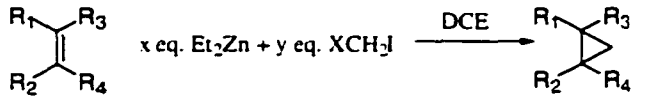


	3-1	3-2	3-3	3-4
Zn/Cu, CH_2I_2, AcCl, Et_2O		18%	9%	1%
Et_2Zn, CH_2I_2, PhMe		34%	5%	1%

Scheme 3.3 Chemoselectivity

Using the two most common methods for cyclopropanation, the more electron-rich internal olefin is cyclopropanated in preference to the external olefin. In general the more electron-rich the olefin the more favorable the reaction.

Less electron-rich olefins are not very reactive, especially when they are not adjacent to basic heteroatoms that can direct the reaction. Denmark and coworkers studied the use of chloroiodomethane as the CH_2 source for the Furukawa modification.[4] It was found that a 2:1 stoichiometry of CH_2ClI : Et_2Zn produced the best results and was capable of cyclopropanation of less electron-rich olefins.



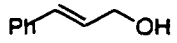
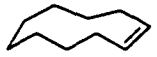
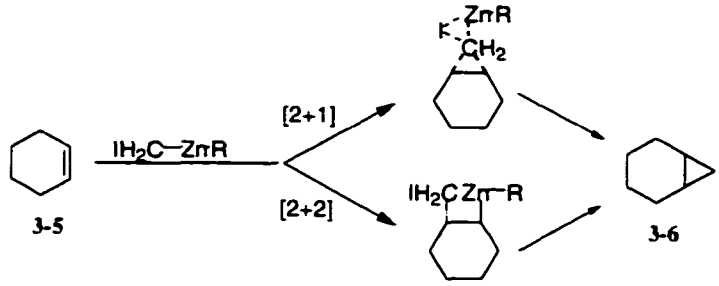
Olefin	Et_2Zn/XCH_2I	min. (temp)	conv.	yield
	2 / 4 X = Cl	15 (0)	94%	85%
	2 / 4 X = I	15 (0)	12%	ND
	2 / 4 X = Cl	30 (0)	96%	93%
	2 / 4 X = I	30 (0)	16%	ND

Figure 3.1 ICH_2Cl

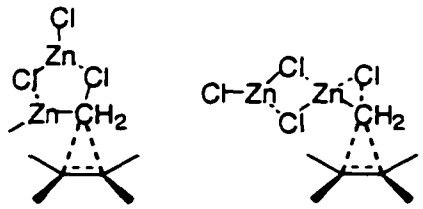
The dramatic effect of an electron-poor carbenoid can be seen in the rates of reaction in Figure 3.1. Even with the basic heteroatom in cinnamyl alcohol the rate of reaction for the Furukawa modification is substantially slower than when using CH_2ClI as the CH_2 source

The exact nature of the cyclopropanation reagent formed upon mixing Zn/Cu and CH_2I_2 or using one of the other modifications has been the focus of many papers. Both solution and solid state studies have suggested that the active species is R-Zn-CH_2X. The mechanism for the reaction was studies extensively by Wittig in the 60's and he concluded that the reaction proceeded via a "butterfly" type intermediate in a 2 +1 fashion.



Scheme 3.4 Transition State

The Simmons Smith reaction is not reported to isomerize double bonds, providing support for the 2 + 1 model. Recently, computational studies on the transition state for Lewis acid-accelerated reactions have suggested that there may be two possible transition states for the 2 + 1 mode of reaction. All of the cyclopropanation reactions produce Lewis acid as they proceed, so both of the transition states are feasible.

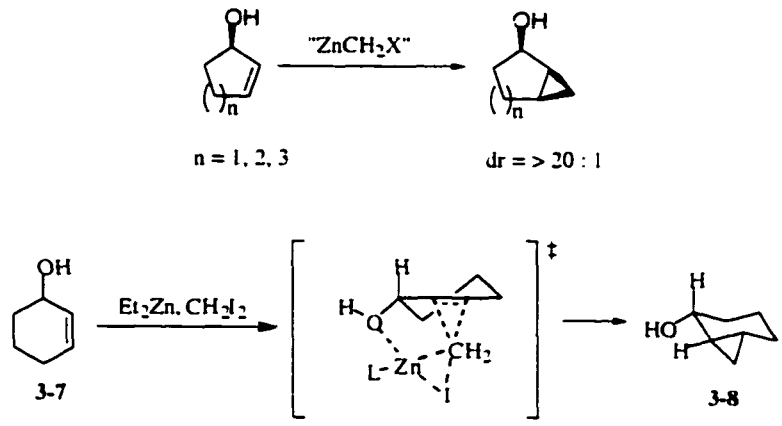


Scheme 3.5 Computational Models

Since current studies have not provided evidence to clearly support either of these models, further work is needed to elucidate the reaction mode. In all of the computational studies, the 2 + 1 mode of reaction is much more favored than the 2 + 2 mode for the Simmons Smith reaction.

3.A.2 Diastereoselectivity

Basic functional groups adjacent to olefins can direct cyclopropanation by coordinating to the electron-poor zinc. The Simmons Smith reaction gives extremely high selectivity, especially when using the Furukawa modification.



Scheme 3.6 syn Cyclopropanation

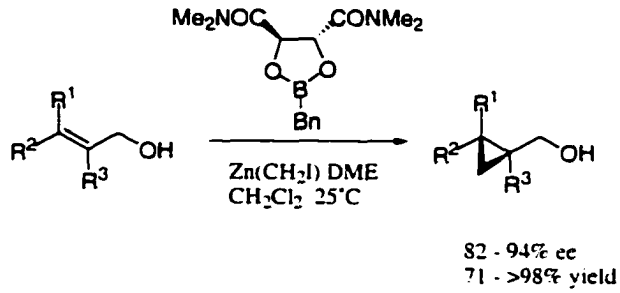
Ethers, alcohols and other functional groups with a donatable lone pair of electrons adjacent to cyclic olefins have shown diastereoselective control in a variety of synthetic and mechanistic studies. The basic functionality coordinates to the zinc and directs the cyclopropanation in a *syn* fashion.

Acyclic cases have also shown high diastereoselectivity, especially *cis* and tri-substituted allylic alcohols.

3.A.3 Chiral Cyclopropanation

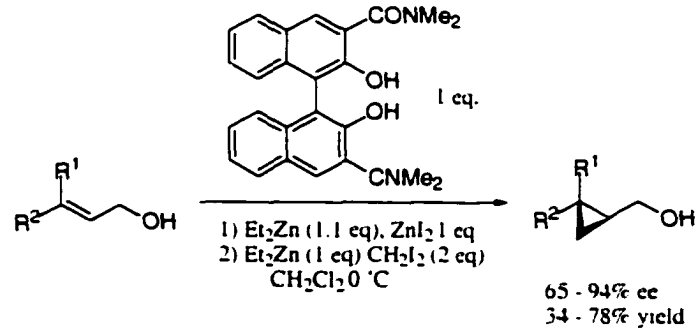
There have been very few successful systems for enantioselective cyclopropanation. The only successful substrates have been allylic alcohols, most likely

due to a coordination of zinc to the alcohol to form a cyclic transition state. Chiral boronates have been shown to be successful additives for selective cyclopropanation.[5]



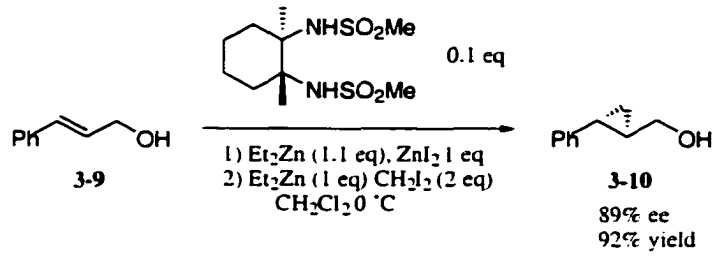
Scheme 3.7 Chiral Cyclopropantion via boranates

Another successful strategy has been to use binapthol-derived ligands as the source of selectivity.[6] The large excess of zinc probably serves as a Lewis acid in a complex transition state. Scheme **3.8**. Unfortunately this method has only found success with (E)-substituted allylic alcohols, and limited R groups.



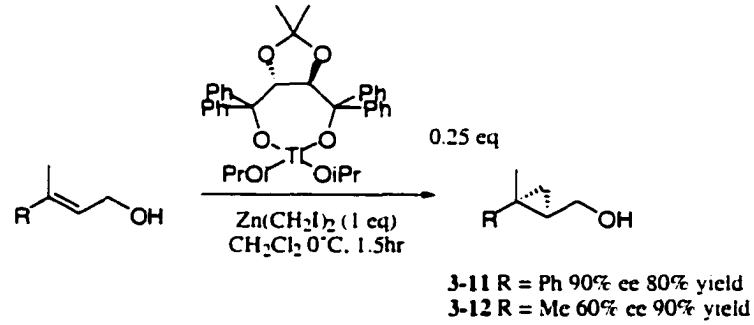
Scheme 3.8 Binapthol as a Chiral Addative

Both of these methods use a chiral additive, not a chiral catalysts to induce a chiral cyclopropanation. The search for a chiral catalyst for zinc cyclopropanations has been a long-fought battle. Only two examples of successful chiral catalysts have been reported in the literature, but some lessons can be garnered from their success.



Scheme 3.9 Chiral Sulfonamide Catalyst

Chiral disulfonamide-catalyzed cyclopropanation of allylic alcohols has been reported.[7] The sulfonamides reduce the Lewis basicity of the nitrogen atoms, avoiding complete lack of reactivity. Only 10 mol% of the chiral catalyst is needed to obtain a very respectable ee with a limited class of allylic alcohols. Both di- and tri-substituted allylic alcohols have shown promise with this system. The other successful chiral catalytic system the TADDOL derived Lewis acid acceleration.[8]



Scheme 3.10 TADDOL Accelerated Cyclopropanation

The order of addition is crucial for this reaction to be successful. The zinc carbenoid is formed in a non-coordinating solvent followed by addition of the allylic alcohol. This presumably forms a zinc-alcoxy complex, with is slow to react since the olefin is not electron rich. Addition of the Lewis acid accelerates the reaction, and provides the chiral induction. The Lewis acid may break up an unreactive alcoxyzinc complex allowing the reaction to proceed. The moderation of zinc alcoxide reactivity with a Lewis acid is a promising base on which to build a cyclopropanation reaction.

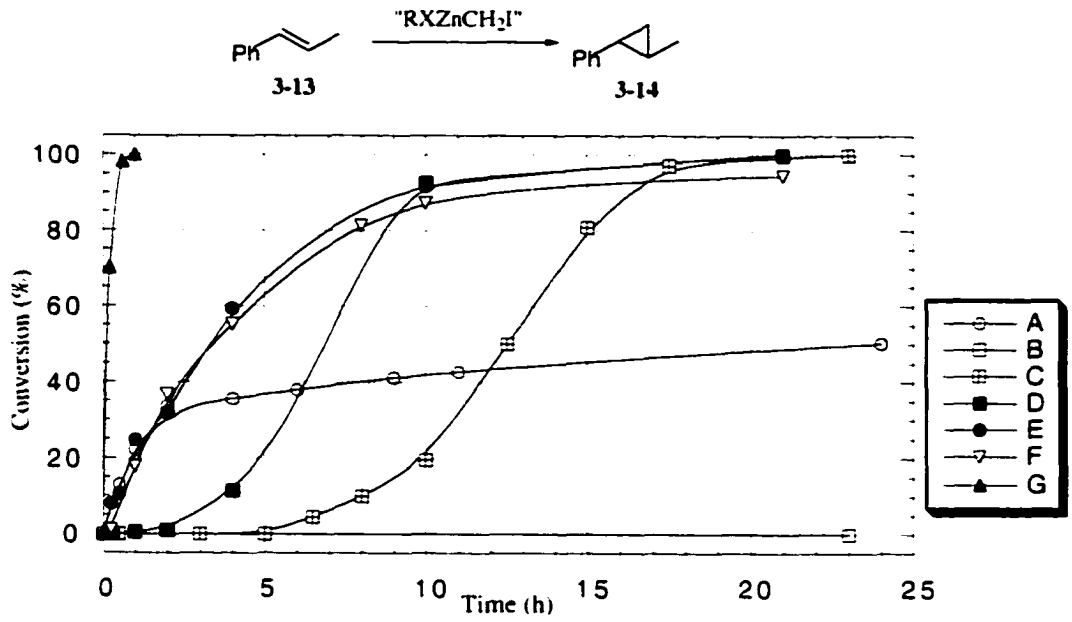
3.B Results

Initial investigations into modified zinc cyclopropanation reagents were carried out by Zhiqiang (George) Yang, a post-doc in the Shi lab. Studies were begun by generating a series of new (iodomethyl)zinc species from alcohols and acids to study their reactivities. The active reagent $RXZnCH_2I$ could be generated by two methods, shown in eqs. 3.1 and 3.2, differing in order of reagent addition. The method outlined in eq. 3.2 requires less CH_2I_2. For George's initial studies, the method outlined in eq. 3.1 was used, with *trans*-β-methylstyrene as the substrate.

$$Et_2Zn + 2\,CH_2I_2 \longrightarrow 2EtI + (ICH_2)_2Zn \xrightarrow{RXH} RXZnCH_2I + CH_3I \qquad \textbf{(eq. 3.1)}$$

$$Et_2Zn + RXH \longrightarrow EtH + RXZnEt \xrightarrow{CH_2I_2} RXZnCH_2I + EtI \qquad \textbf{(eq. 3.2)}$$

The results obtained (Figure 3.2) show that the reactivity of $RXZnCH_2I$ is highly dependent upon the R group. These initial studies were carried out at room temperature using 2 eq. of zinc reagent in dichloromethane. When RXH was EtOH or $ClCH_2CH_2OH$, no reaction occurred after stirring 24 h at room temperature.



The curves presented are: (**A**) No RXH, (**B**) EtOH or $ClCH_2CH_2OH$, (**C**) Cl_2CHCH_2OH, (**D**) CCl_3CH_2OH, (**E**) CF_3CH_2OH, (**F**) $PhCO_2H$, (**G**) CF_3CO_2H.

Figure 3.2 Plot of the conversion of *trans*-β-methylstyrene against time

A visual examination of the reaction curves shows that some of the complexes have an induction period before the reaction occurs. This induction period is of interest because it may be that the reactions are Lewis-acid catalyzed, and a minimum amount of free Lewis acid is needed for the reaction to progress. It was found that, in general, as RXH became more acidic, the reactivity increased.

Among the RXH investigated, CF_3CO_2H accelerated the cyclopropanation reaction dramatically compared to the typical cyclopropanation conditions (i.e. no RXH was added). The reaction was complete within 30 min at room temperature for *trans*-β-methylstyrene, and was very clean as judged by the ^1H NMR spectrum of the crude

reaction mixture. The dramatic acceleration of the reaction when TFA is used can be seen in Scheme 3.11, the cyclopropanation of *trans*-stilbene.

3-15 **3-16**

$CF_3CO_2ZnCH_2I$, CH_2Cl_2, 1 hr, rt — 70% yield > 90% conv.

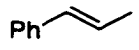
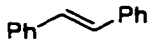
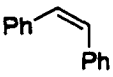
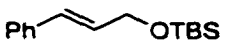
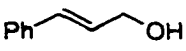
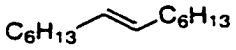
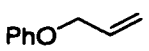
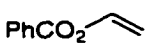
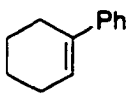
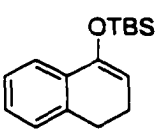
EtZnI, CH_2I_2, Et_2O, 1hr, 30-35 °C — 13% yield

Scheme 3.11 Cyclopropanation of *trans*-stilbene

The traditional method only gives a 13% yield after 1 hour, while the modified reaction gives a conversion of over 90% by ^1H NMR spectroscopy, and a 70% yield.[9] Having reactions go in high conversion is extremely valuable in cyclopropanation because it is often difficult to separate the starting olefin from the cyclopropane. Generally, distillation has to be employed, because the polarities are too similar to provide good separation by column chromatography.

With the drastic increase in reactivity observed for the cyclopropanation of *trans*-β-methylstyrene, a number of other olefins were cyclopropanated to gain an idea of the scope of reactivity of this new reagent. The results, summarized in Table 3.1, show that a variety of substrates can be converted into cyclopropanes efficiently within a short period of time. All of these reactions were carried out at room temperature in dichloromethane using 2 eq. of zinc reagent except where noted. For CF_3CO_2H, the reagents generated by both methods provided similar results.

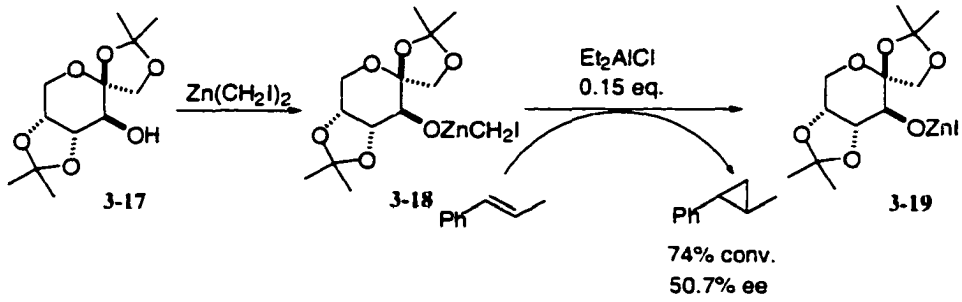
Table 3.1. Cyclopropanation of Representative Olefins Accelerated by CF_3CO_2H[a]

Entry	Olefin	time (min.)	Conv.[b]	Yield[c]
1		30	100	77
2		60	> 90	70[d]
3		60	Nd	72[d]
4		30	100	95
5		40	100	80
6		40	100	99
7		20	100	85
8		30	> 97	88
9		150	> 90	90
10		30	100	78
11		25	100	50[e]

[a] All reactions were carried out at rt with a 2/1 ratio of Zn/olefin except entries 2 & 3 where the Zn/olefin ratio was 4/1. [b] The conversion was determined from the crude reaction mixture either by GC or ^1H NMR. [c] Isolated yield. [d] *Trans*-stilbene gave *trans*-cyclopropane and *cis*-stilbene gave *cis*-cyclopropane. [e] The yield was for the product after desilylation by TBAF.

Having discovered that $RXZnCH_2I$ was effective for cyclopropanation, investigations using a chiral (iodomethyl)zinc species (RX^*ZnCH_2I) to induce

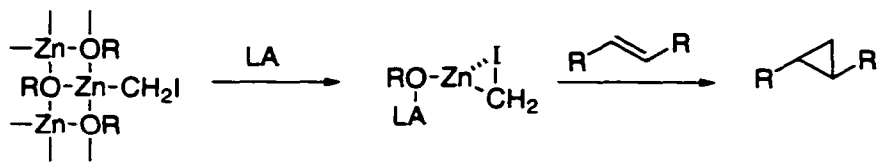
enantioselectivity for the cyclopropanation were carried out. The first case tried was, chiral (iodomethyl)zinc reagent **3-18** was prepared from alcohol **3-17**, which was prepared in one step from fructose.[10] With *trans*-β-methylstyrene as the substrate no cyclopropanation occurred, but upon addition of a Lewis acid the reaction took place.[11] A 50.7% ee was obtained for the cyclopropane product.



Scheme 3-12 Chiral Cyclopropantion of Unfunctionalized Olefins

Great progress has been made in the asymmetric cyclopropanation of allylic alcohols however, a direct asymmetric cyclopropanation of unfunctionalized olefins by transferring a simple methylene group from (halomethyl)zinc reagents is an unsolved, yet challenging, problem. Only two reports have appeared in the literature for asymmetric cyclopropanation of olefins in the absence of hydroxy groups using (halomethyl)zinc reagents. In one case, (-)-menthol was used as chiral inducer, and <4% ee was obtained.[12] In the other case L-leucine was used as chiral inducer, and a $[\alpha]^{25}_{D}$ of -0.77 was reported (no ee was mentioned).[13]

Zinc alkoxides (ROZnR') are likely to form aggregates,[14] and the Lewis acids may facilitate the reaction by breaking down the proposed $(ROZnCH_2I)_n$ aggregates. After the aggregate is broken, the zinc has a vacant orbital for iodine to coordinate, thus activating the methylene group toward cyclopropanation Scheme 3.13.



Scheme 3.13 Lewis Acid Accelerated Cyclopropanation

The ability to accelerate the cyclopropanation reaction using a Lewis acid, perhaps coordinating to the RX group on zinc, opens up the opportunity for chiral Lewis acid mediated cyclopropanation of unfuntionalized olefins.

3.B.1 Ligand Studies

From this foundation, efforts were made to explore other reactive species, especially those with potential for building chiral scaffolds. Additionally, the use of large RX groups was of interest for diastereoselectivity, and for the possible chiral Lewis-acid acceleration of the cyclopropanation. Phenols and bulky acids were chosen for three reasons: first, to examine the ability of their steric bulk adjacent to the zinc center to induce diastereo-selectivity in the cyclopropanation; second, in previous attempts to cyclopropanate allylic alcohols, the ligand had been displaced by coordination with the oxygen of the substrate in some cases. A tight coordination to a sterically-demanding, electron-withdrawing ligand could reduce this loss of activity and increase conversion. Third, if the phenols proved to be effective ligands for zinc in the cyclopropanation reaction they could be used as platforms on which to build chirality for an enantioselective cyclopropanation. Initial results are shown in Table 3.2 using 2 eq. of zinc reagent at room temperature in dichloromethane.

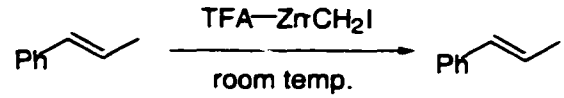
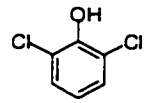
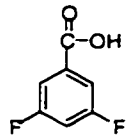
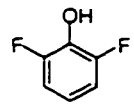
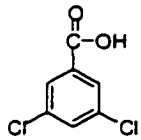
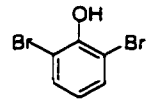
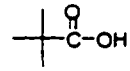
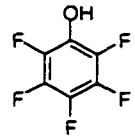
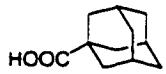


Table 3.2

Ligand	conv.[a]	Time	Ligand	conv.	Time
TFA	100	45min	TfOH	75%	8hr
	80%	18hr		72%	8hr
	78%	18hr		12%	8hr
	36%	9hr		60%	3.5hr
	50%	5.75hr		85%	6.5hr

Reactions were carried out using 2 eq of zinc reagent in CH_2Cl_2 at room temperature.
a) Conversion determined by GC

A graphical representation of the reactivities is given in Figure 3.3. The cyclopropanation of *trans*-β-methylstyrene with 1 eq. of the zinc complex using some of the new ligands is shown. While these investigations were waiting to be published a report from Charette's lab was published using some of the same phenols that were under investigation.[15]

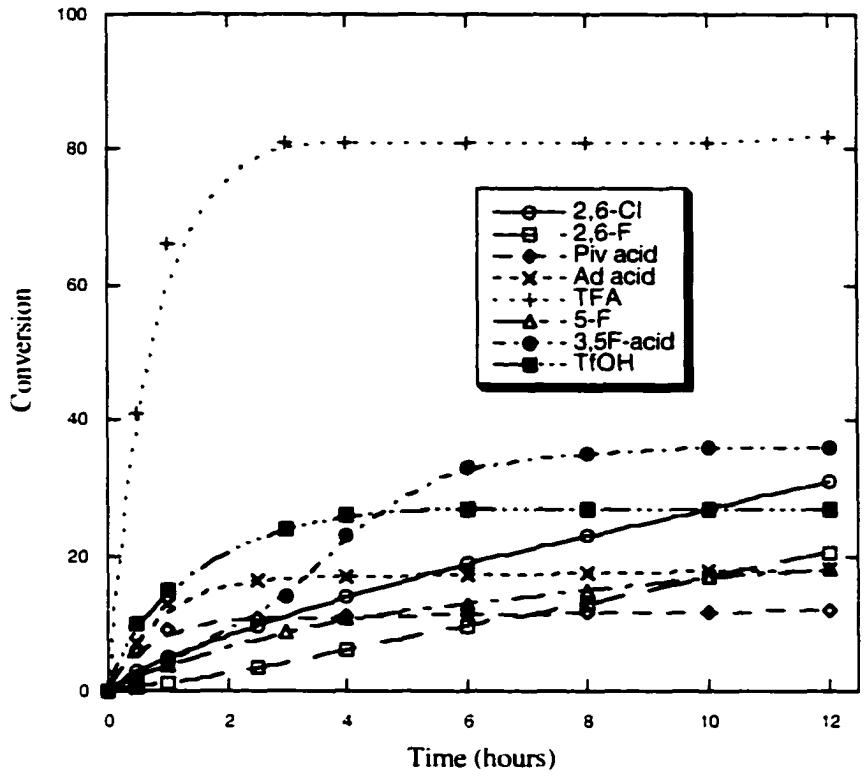


Figure 3.3 Cyclopropanation of *trans*-β-methylstyrene with 1 eq. of Zinc Reagent

The general trend remains the same as what was seen before, the more electron-withdrawing the ligand the more reactive the carbenoid, in most cases. A second demanding substrate was chosen, *trans*-stilbene, and identical reaction conditions 2 eq. RX-Zn-CH_2I, rt, 1 hour in dichloromethane, were used for each ligand (Table 3.3).

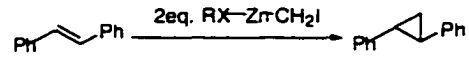
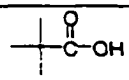
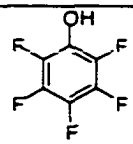
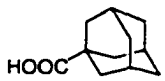
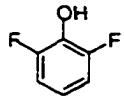
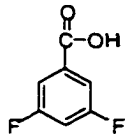
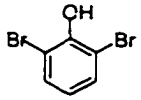
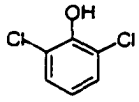
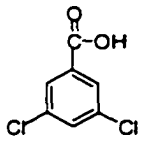
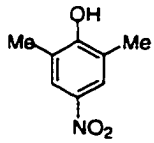


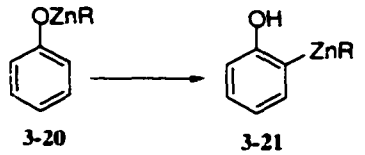
Table 3.3

Ligand	conv.	Ligand	conv.	Ligand	conv.
none	0%		18%		56%

TFA	65.6%		10%		26%
TfOH	16%		17%		0%
	26%		2%		0%

Conversion determined by GC using a 15 m rtx-5 column

Some ligands with strong electron-withdrawing ability were found to be unsuitable for formation of reactive zinc carbenoids, primarily due to solubility problems. Repeated attempts to use substituted nitrophenols met with frustration. The complexes were not soluble in a variety of polar and non-polar solvents. The use of nitrophenols with alkyl substituents to try and increase solubility did not mitigate the problem. The poor conversion seen with triflate as the ligand is due to lack of solubility in the non-coordinating solvents required for this reaction. The complex is soluble in solvents such as ether and DMF, however these solvents are able to donate electron density to zinc and defeat any benefits gained from use of the electron-withdrawing ligands. Reactions that come to a halt after a short time may also suffer from solubility, or aggregation problems, since in all cases there is a white precipitate formed as the reaction progresses. We have previously shown that with TFA as the ligand, and with 4 eq. of zinc, *trans*-stilbene can be completely converted to its cyclopropane in only 2 hours at room temperature. To date this remains the most reactive Simmons-Smith-type cyclopropanation reagent, to the best of our knowledge. All of the phenols examined have ortho substitutents, to prevent the formation of arylzinc complexes.

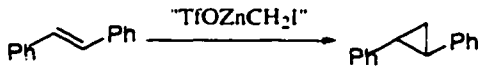


3-20 3-21

Scheme 3.14 Zinc Migration

It has been reported that phenoxy-zinc can insert into the C-H bond on an ortho carbon.[16] When 2-chloro phenol, which has only one ortho substituent, was used as the ligand on zinc olefins were successfully cyclopropanated. This is probably due to the rate difference between C-H insertion and cyclopropanation of the electron-rich substrate that was used.

One observation with the TfOH ligands is that the zinc reagent is heterogeneous, where as most of the other reagents are homogeneous or only slightly heterogeneous. A solvent study was undertaken to see if a homogeneous TfOH reagent could cyclopropanate *trans*-stilbene.



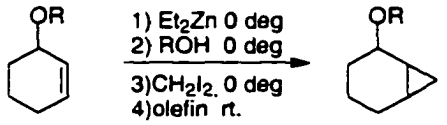
3-15 3-16

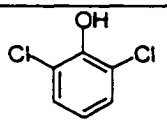
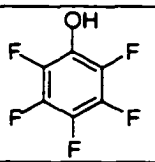
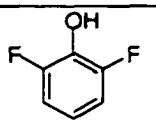
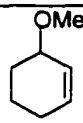
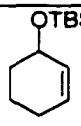
Solvent	rxn	Conv.
DMF	clear	0%
Et_2O	clear	0%
CH_2Cl_2	cloudy	15-17%
Hexane	cloudy	16%

Figure 3.4 Solvent Effects

The results confirm that the electron-poor zinc reagent is solvated by the more polar solvents, but they also deactivate the zinc reagent towards cyclopropanation.

To further explore the behavior of these new reagents a set of 2,3-cyclohexene-1-ols were used as substrates. Under the standard Furukawa reaction conditions extremely high diastereoselectivity for the syn product is observed.

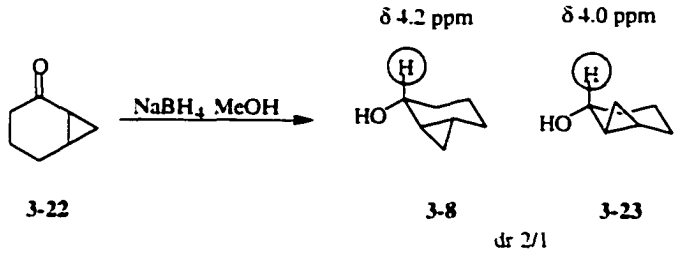


Olefin				TFA
	78% conv. syn	78.7% conv. syn **3-8/ 3-26** 6/1		81.5% conv. syn **3-8/ 3-26** 1/1.5
	~100%conv. syn **3-8/ 3-26** 5.8/1	conv. 73.5% syn **3-8/ 3-26** 1/3.5	conv. 60% syn **3-8**	71.8% conv. syn **3-8/ 3-26** 1/6.9 dr

Ratios determined by ^{1}H NMR

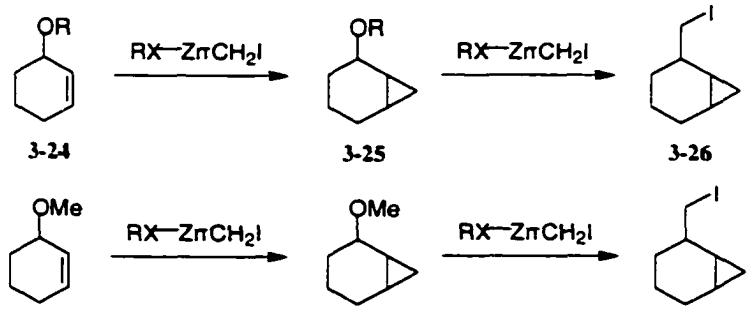
Figure 3.5 Diastereoslectivity

Simple ^{1}H NMR analysis of the chemical shift of the proton on the carbon with the oxygen substituent reveals the selectivity.



Scheme 3.15 Determination of Diastereoselectivity[17]

In none of the cases examined was the anti product observed, however there was a second set of product peaks. If two equivalents of a carbenoid with TFA or pentafluorophenol as the ligand are used to cyclopropanate the TBS ether of 2-cyclohexenol, two reactions take place. First the cyclopropane is formed, then the second equivalent of zinc reagent does a substitution reaction.



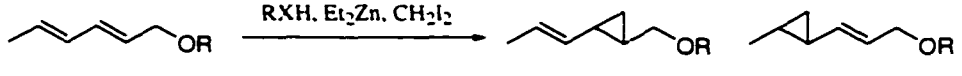
entry	conv.	temp	dr **3-26**
1	77%	Rt	3.2/1
2	72%	0 °C	12.5/1
3	57%	-10 ° C	15.1/1

Scheme 3.16 S_N1 Displacement

Work by a post-doc showed that this reaction proceeds via an S_N1 type mechanism. Since cyclopropanes are known to be able to stabilize cations by donation from the Walsh

orbitals, this is a plausible mechanism. Less electron-withdrawing ligands on the zinc display less of this behavior. Since they form much weaker Lewis acids they are not as able to activate the ether as a leaving group. The same behavior was seen for R = OMe and OAc. In fact, with OAc the substitution occurs before the cyclopropanation.

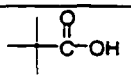
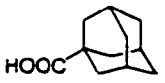
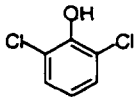
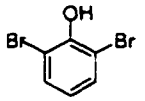
Since zinc is known to be very oxophillic, these modified zinc reagents were tested against hexadienol for chemoselectivity. Initially the parent compound *trans,trans*-2,4 hexandienol **3-27** was used as the substrate. Cyclopropanation at the proximal olefin was the only mono cyclopropane observed. If the alcohol was made into an ether, would the bulk of the ligands favor cyclopropanation of the distal olefin. With the bulkier TBDMS derivative **3-28**, no change in chemoselectivity was observed. However the extremely sterically-demanding TBDPS ether **3-29** forced cyclopropanation at the distal olefin in some cases, (Figure 3.6).

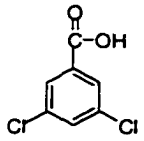


3-27 R = H
3-28 R = TBS
3-29 R = TBDPS

3-30 R = TBDPS

3-31 R = TBDPS

Ligand	prox./dist.[a]	Ligand	prox./dist.
None	1.75/1		1.1/1
TFA	11.5/1		1.2/1
	1.1/1		1.1/1



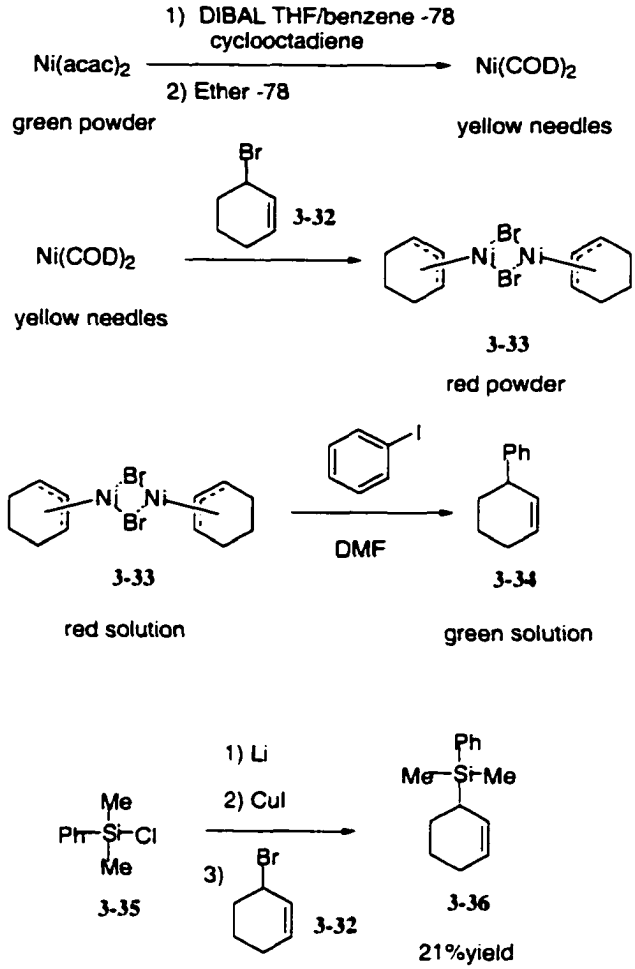
5.6/1

Et_2Zn (1.0 M in hexanes)(2.0 mL, 2 mmol) under N_2 in CH_2Cl_2 (2.4 mL) was cooled in an ice bath, and a solution of ligand (2.0 mmol) in CH_2Cl_2 (1.0 mL) was added. After stirring for 15 min. a solution of CH_2I_2 (161 μL, 2.0 mmol) in CH_2Cl_2 (0.5 mL) was added and the reaction stirred an additional 15 min. A solution of the olefin (1.0 mmol) in CH_2Cl_2 (1.0 mL) was added and the ice bath removed. After an additional 30 min. of stirring the reaction was quenched and analyzed by ^1H NMR spectroscopy and GC. a) Determined by GC analysis after desilation with TBAF.

Figure 3.6 Cyclopropanation of *trans,trans*-2,4 hexandienol TBDPS ether

Unfortunately selectivity for the distal olefin is very poor in all cases. One result that is rather intriguing is that the TFA-modified reagent still gave very good selectivity for the proximal olefin, despite the large steric disadvantage. This reagent is so electron-poor that it will burrow its way into the stertic bulk of the molecule to associate with the ether oxygen. This provides a tool to control chemoselective cyclopropanation with heteroatoms, even in sterically-demanding environments.

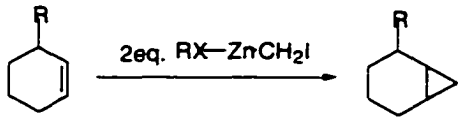
These sterically demanding zinc reagents were next tested for their ability to diastereoselectivly cyclopropanate olefins without coordinating groups. Two 1-substituted cyclohexenes with non-coordinating groups were prepared following literature procedures, Scheme 3.17.

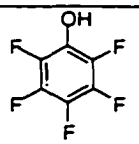
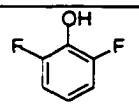
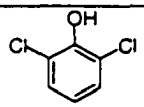
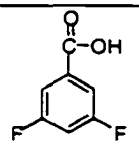


Scheme 3.17 Preparation of Substituted Cyclohexenes

Compound **3-34** 1-phenyl-2,3-cyclohexene was prepared from the π-allyl Ni complex. This series of reactions start with the formation of $Ni(COD)_2$ from inexpensive $Ni(acac)_2$.[18] The very air sensitive $Ni(COD)_2$ is then treated with 1-bromo-2-cyclohexene to form the π-allyl Ni dimer, a brick red dusty solid.[19] This π-allyl Ni dimer will add to alkyl and aryl iodides giving the desired compound **3-34**. Since these transformations must all be carried out using Schlenk techniques, it is very fortunate that the reaction can be followed by the color changes, displacing TLC as a reaction monitoring device. Silyl-substituted compound **3-36** was prepared from the silyllithiate by copper-assisted

nucleophilic attack on 1-bromo-2-cyclohexene.[20] The diastereoselectivity of these transformations using several ligand systems is shown in Figure 3.7.

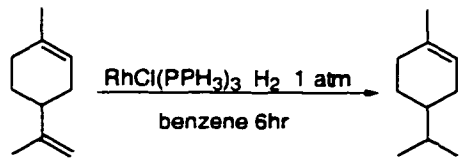


Ligand	R = Ph	R = $SiMe_2Ph$	Ligand	R = Ph	R = $SiMe_2Ph$
none		19hr 36% conv		8.3/1	2hr 89% conv. 16/1
TFA	5.5/1	45min 100%conv. 17/1		6.8/1	1.5hr 100%conv. 21/1
	8.2/1	2.5hr 100% conv 18/1		–	2.5hr 100%conv. 17/1

Et_2Zn (1.0 M in hexanes)(2.0 mL, 2 mmol) under N_2 in CH_2Cl_2 (2.4 mL) was cooled in an ice bath, and a solution of ligand (2.0 mmol) in CH_2Cl_2 (1.0 mL) was added. After stirring for 15 min. a solution of CH_2I_2 (161 μL, 2.0 mmol) in CH_2Cl_2 (0.5 mL) was added and the reaction stirred an additional 15 min. A solution of the olefin (1.0 mmol) in CH_2Cl_2 (1.0 mL) was added and the ice bath removed. The reaction was quenched and analyzed by ^1H NMR spectroscopy.

Figure 3.7 Cyclopropanation of Substituted Cyclohexenes

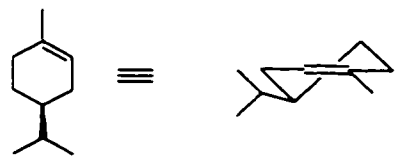
In these semi-rigid ring systems the attack is biased by the large allylic group holding the ring in a single conformation. This may be why there is little effect of the ligands in diastereoselectivity on substituted cyclohexenes. A more challenging cyclohexene derived from limonene **3-38** was chosen.



3-37 3-38

Scheme 3-18 Selective Reduction of Limonene

With TFA and 2,6-dichlorophenol as the ligands a 1-1 mixture of diastereomers was obtained, and the reaction was rapid and complete by GC. Examination of the conformation for this cyclohexene explains the lack of diastereoselectivity, Scheme 3-19.

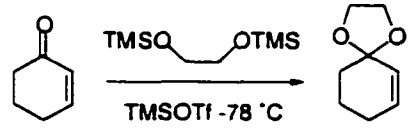


Scheme 3-19 Conformation of **3-38**

The remote isopropyl group holds the olefin so that attack seems feasible from either face.

3.B.2 Moderating Reactivity

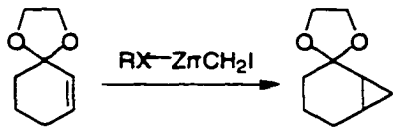
Chiral ketals are one class of the successful chiral auxilaries for selective cyclopropanation of cyclic olefins with the Simmons-Smith reaction. The modified zinc reagents produce strongly Lewis acidic bi-products, and since ketals are acid sensitive, their compatibility with ketals was examined.



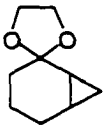
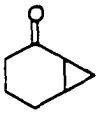
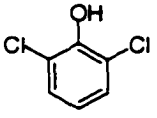
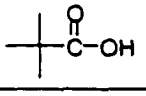
3-39 3-40

Scheme 3.20 Preparation of Cyclohexenone Ketal

The required cyclohexene ketal was prepared following the literature proceedure for electron-poor ketones.[21] Olefin **3-40** was cyclopropanated with 2 eq. of RX-Zn-CH_2I (Figure 3.8).



3-40 3-41

Ligand	conv.[a]		
none	100% 45min	12	1
TFA	10min 100% conv.	1.0	1.6
	100% 60 min.	1	0
	1 hr. 72% conv.	26.6	1

Et_2Zn (1.0 M in hexanes)(2.0 mL, 2 mmol) under N_2 in CH_2Cl_2 (2.4 mL) was cooled in an ice bath, and a solution of ligand (2.0 mmol) in CH_2Cl_2 (1.0 mL) was added. After stirring for 15 min. a solution of CH_2I_2 (161 μL, 2.0 mmol) in CH_2Cl_2 (0.5 mL) was added and the reaction stirred an additional 15 min. A solution of the olefin (1.0 mmol) in CH_2Cl_2 (1.0 mL) was added and the ice bath removed. The reaction was quenched and analyzed by ^1H NMR spectroscopy.a) Conversion and product ratios determined by GC

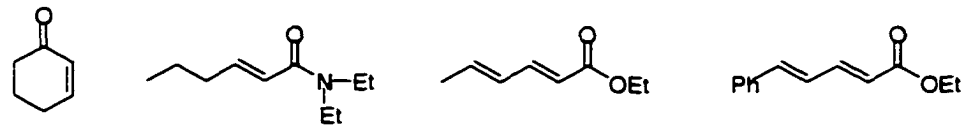
Figure 3.8 Acid Sensitive Substrate

The vast difference in reactivity can be seen in this small group of ligands, but more importantly there is a large difference in decomposition of the starting material and product. This substrate is a nice test because once the ketal is removed no cyclopropanation can occur. Any cyclopropane of cyclohexenone must have been formed by deprotection of a cyclopropanated ketal. The work-up conditions were mild, H_2O and

NH_4Cl so most of the decomposition to cyclopropyl cyclohexanone must occur during the reaction. If this reaction was run at room temperature with 2 eq. of TFA-Zn-CH_2I, a complex mixture of products was observed in less than 15 minutes, suggesting that the strongly Lewis-acidic zinc was causing decomposition. Analysis of the crude reaction mixtures by ^1H NMR spectroscopy showed at least a small amount of unidentified decomposition products in all cases. The tables of reactivity given for *trans*-β-methylstyrene and *trans*-stilbene can be used as a guide for moderating the reactivity of the cyclopropanating reagents to fit the needs of the substrate.

3.B.3 Mechanistic Study

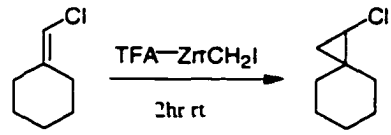
Due to the drastic difference in reactivity observed for the traditional zinc carbenoids and the TFA-modified carbenoid, a short mechanistic study was undertaken following the work of Wittig and coworker on the Zn/Cu Simmons Smith reaction.[22] Of interest was how would the increased electron-withdrawing ability of the ligand on zinc affect the bonds of the carbenoid and its reactivity towards an olefin. It was presumed that the zinc-iodine coordination would be much stronger due to the electron-poor nature of the zinc, and would this lead to a more nucleophilic species. A number of α,β-unsaturated substrates were tested and none were successfully cyclopropanated, Scheme 3.20.



3-39 3-42 3-43 3-44

Scheme 3.20 Electron-Poor Olefins

In the case of ethyl sorbate the substrate was untouched except when the very reactive TFA-Zn-CH_2I is used. The substrate was polymerized, probably in a cationic polymerization initiated by the strong Lewis acidity of the reagent. In an attempt to mask the Lewis acidity of the reagent, coordinating and non-coordinating solvents were tested with no success. These results suggest that the modified carbenoids are not nucleophilic in nature. One successful case of cyclopropanation of electron-poor olefins is vinyl chloride, Scheme 3.21.

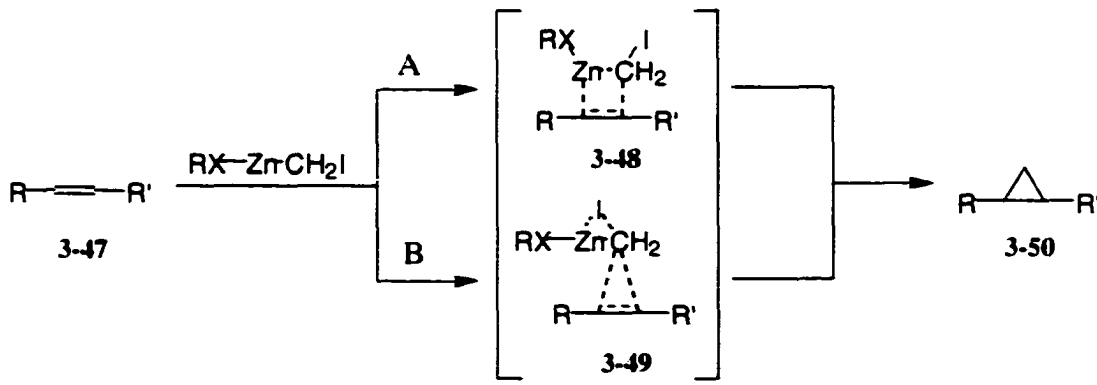


3-45 3-46

Scheme 3.21 Cyclopropanation of Vinyl Chloride

There is one example in the literature where the TFA-Zn-CH_2I reagent was used to cyclopropanate a vinyl chloride where other reagents had failed, in the synthesis of the side chain of Callipeltoside.[23] Other electron-poor olefins have been cyclopropananted where other methods failed using these modified conditions.[24]

The two possible modes of cyclopropanation possible have been of theoretical interest recently.[25] Further understanding of the mode of reaction would be useful to further expanding this methodology to diastereo and enatioselective versions.

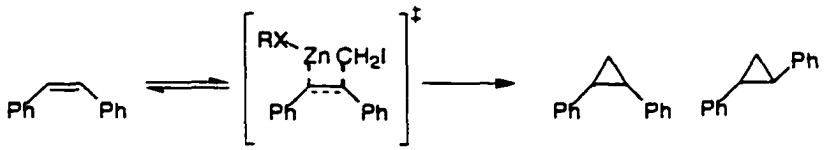


3-47

Scheme 3.22 Reaction Mode

Two pathways are shown in scheme 3.22, A involving a 2+2 type addition followed by collapse to the cyclopropane, and B a 2+1 reaction mode involving more of a concerted reaction. The traditional Simmons-Smith reaction is believed to proceed in a 2+1 manner.[3]

Isomerization of double bonds and reversibility of the reaction was initially studied with *cis*-stilbene as the substrate. Reactions were run to partial completion and analyzed for isomerization of the starting material and formation of *trans*-1,2-diphenyl-cyclopropane, both of which would be formed via pathway A. In all of the cases studied only the *cis*-cyclopropane was produced and unreacted *cis* stilbene was recovered (Figure 3.9).



3-51 3-52 3-53 3-16

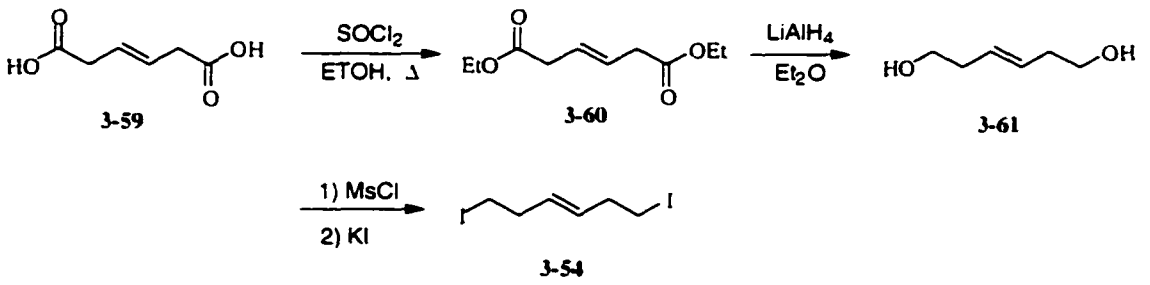
Ligand	conv.[a]	time	*t*-stilbene	*t*-cyclopropane
TFA	79%	1.5hr	none	none
Et_2Zn/CH_2I_2	0	refluxed in ether	none	none
2,6-dichloro phenol	1.5%	1.5hr	none	none
	46%	24	none	none
pentafluoro phenol	13%	1hr	none	none

Et_2Zn (1.0 M in hexanes)(2.0 mL, 2 mmol) under N_2 in CH_2Cl_2 (2.4 mL) was cooled in an ice bath, and a solution of ligand (2.0 mmol) in CH_2Cl_2 (1.0 mL) was added. After stirring for 15 min. a solution of CH_2I_2 (161 μL, 2.0 mmol) in CH_2Cl_2 (0.5 mL) was added and the reaction stirred an additional 15 min. A solution of the olefin (1.0 mmol) in CH_2Cl_2 (1.0 mL) was added and the ice bath removed. The reaction was quenched and analyzed by ^1H NMR spectroscopy. A) Conversion was determined by GC using a rtx-5 column 15 m x 0.25 mm

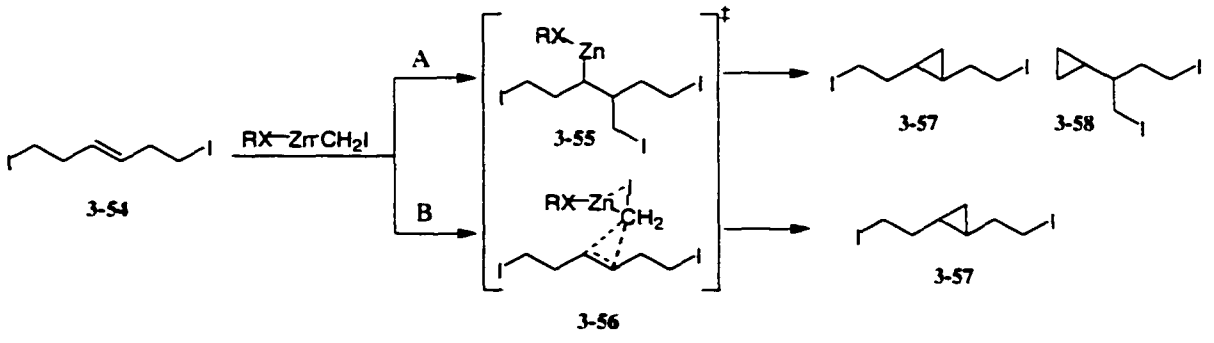
Figure 3.9 cyclopropanation of *cis* Stilbene

The reactions were relatively slow with *cis*-stilbene, as seen previously with *trans*-stilbene, but no product from isomerization of the double bond was observed by GC analysis of the crude reaction mixture. Another possibility is isomerization of the starting material if the carbene addition is reversible, however no isomerization of starting material was observed by GC. These results support a 2 + 1 type mode of reaction.

If the transition state is short-lived, or there is some coordination inhibiting rotation about the central bond no isomerization would be observed, even if a 2 + 2 mode of reaction were occurring. A second test was applied in which the substrate was 1,6-diiodo-*trans*-3-hexene. The required substrate was synthesized in a straightforward fashion from commercially available *trans*-β-hydromuconic acid 3-59, Scheme 3.24.[26]

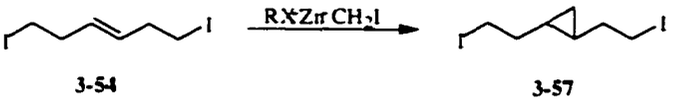


Scheme 3.24 Preparation of 1,6-diiodo-*t*-3-hexene



Scheme 3.25 Probing Reaction Mechanism

If the reaction proceeds in a 2+2 manner, pathway A, then the transition state should have two roughly equivalent carbons which could form a cyclopropane, and a distribution of products should result. The concerted pathway B should give a single product easily recognizable in the ^{1}H and ^{13}C NMR spectroscopy by its symmetry. Only a single symmetrical product and unaltered starting material was observed by ^{1}H and ^{13}C NMR spectroscopy, suggesting the prevalence of pathway B. Substrate **3-54** was cyclopropanated under standard conditions .

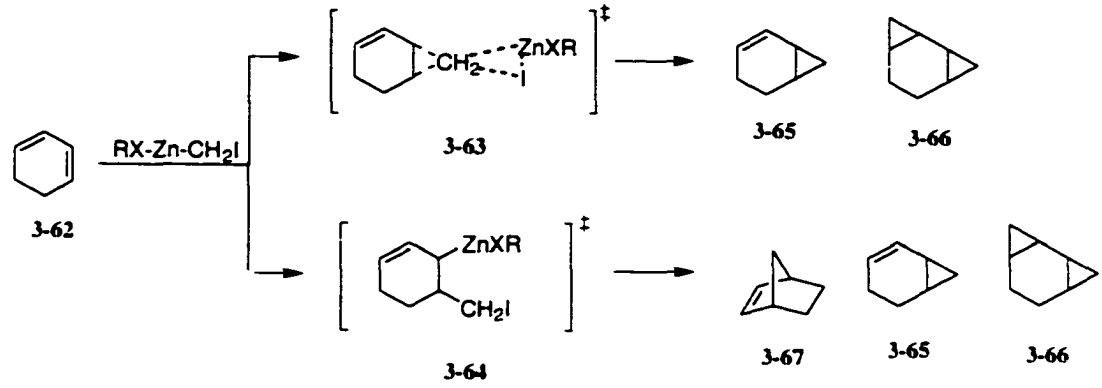


3-54 3-57

Scheme 3.26 Mechanistic Result

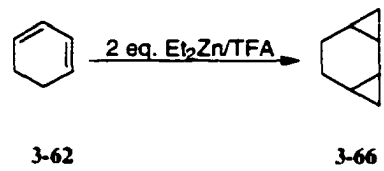
When trifluoroacetic acid was used as the ligand, a clean reaction product was obtained and determined to be the symmetrical cyclopropane by ^{1}H and ^{13}C NMR spectroscopy. This supports earlier results suggesting that our modified zinc carbenoid behave in a manner similar to the typical Simmons-Smith carbenoid by addition in a 2+1 fashion. The poor reactivity of the bulkier 2,6-dichlorophenol ligand may be attributed to the steric hindrance of the two homoallylic iodine atoms, or the electron-poor olefin. Lack of reactivity in the standard Simmons-Smith case at room temperature may be due to the inductive electron withdrawing effects of the iodines, since it is known to be very sensitive to electronics of the olefin.

If the reaction is not completely concerted and involves a charged or radical intermediate then neither of the previous tests would necessarily detect them. The substrate used to look for charged, or radical intermediates was 1,3-cyclohexadiene, **3-62**. If there is some intermediate with a charge or radical involved in the reaction then the norbornene should be observed via collapse of the charge-separated intermediate.



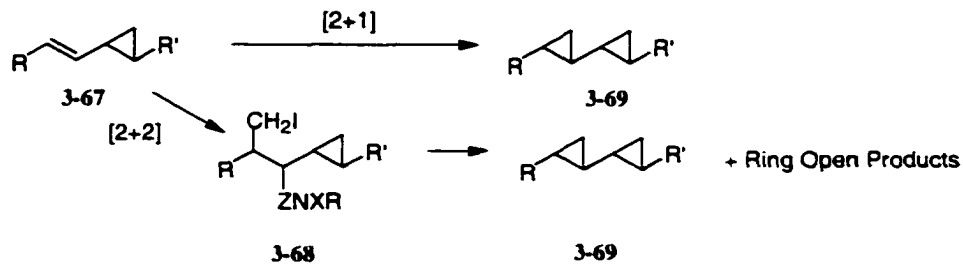
Scheme 27 Reaction of Cyclohexadiene

If two equivalents of TFA-Zn-CH_2I were used, the reaction was almost complete after 2.5 hr and a single diasteriomer of the bis-cyclopropane was observed, along with what apeared to be a small amount of mono- cyclopropane.



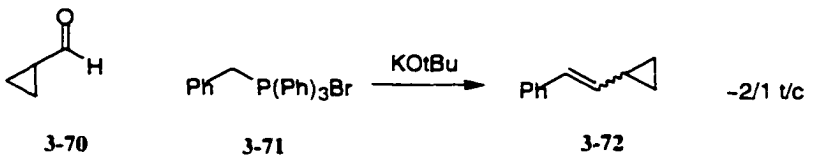
Scheme 3.28 Cyclopropanation of 1,3-Cyclohexadiene

The final test probed the stability of allylic or vinylic cyclopropanes during the cyclopropanation reaction Scheme **3.29**. There is the possibility of ring opening due to charged intermediates, or via a 2 + 2 addition. A 2 + 1 reaction should avoid these problems (Scheme 3.29).



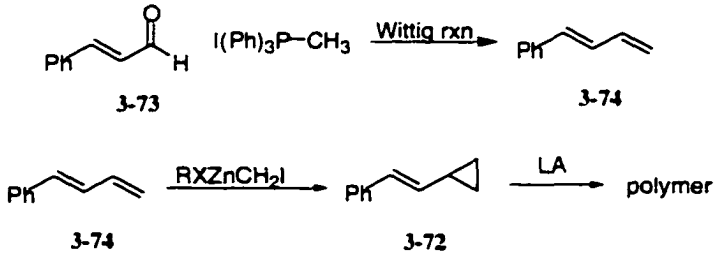
Scheme 3.29 Stability of Vinyl Cyclopropanes

The initial substrate targeted was 1-phenyl-3-cyclopropane-*trans*-1-butene **3.72**. Attempts to synthesize the product via olefination reactions resulted in E/Z mixtures



Scheme 3.30 Substrate Preparation

The mixture of isomers was almost inseperable by tradtional silica gel chromatography. Silica gel treated with 5%, 10% and 20% $AgNO_3$ (w/w) was employed with very limited success, so an alternate substrate was synthesized. Cinnamaldehyde was treated with methyl triphenylphosphonium bromide to form 1-phenyl-*trans*-1,3-butadiene. When BuLi was used to form the ylid, a large amount of Michael addition product was obtained. When KOtBu was used as the base the diene was obtained cleanly.

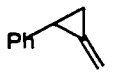


Scheme 3.21 Preparation of **3-72**

Upon cyclopropanation with TFA as the ligand at room temperature the substrate polymerized almost immediately. Upon repeating the reaction, the polymer was again observed. However when 2,6-dichloro phenol was used as the ligand, the terminal and bis-cyclopropanes were obtained cleanly. The product formed can be controlled by adjusting the amount of zinc used. The difference in results was postulated to be due to cationic polymerization initialized by the more Lewis-acidic zinc iodide by-product when

TFA is the ligand. When two equivalents of Et_2Zn with TFA as the ligand is allowed to react with the diene for only 4 minutes, the diene, terminal and bis-cyclopropanes can be isolated.

Commercially available vinyl cyclopropane 3-75 was subjected to the reaction conditions and only spirocyclopentane and recovered starting were observed in the NMR spectrum of the crude reaction mixtures.



3-75

30min 97%conv.w/TFA
65% yield

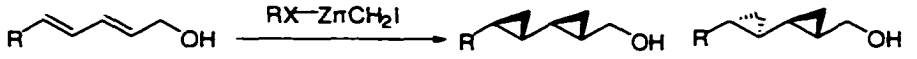
Scheme 3.32 Preparation of spiro Cyclopropane

When all of these results are put together, they strongly support the tight 2+1 mode of cyclopropanation, the same as that found by Wittig in the Zn/Cu CH_2I_2 cyclopropanation reaction.[21] This tight transition state suggests the possibility of successful chiral cyclopropanation by modifying the RX group on zinc. The close transition state is also of possible benefit in diastereoselective cyclopropanation in which RX can be a large group. Alternatively, if a large electron-rich R group is used, a chiral Lewis acid may be able to activate the carbenoid and induce chirality. Work is being carried out in this area.

3.B.4 Substrate-Directed Cyclopropanation.

During the bis-cyclopropanation of 2,4 diene-1-ol substrates examination of the ^1H and ^{13}C NMR spectra showed that one diastereomer was formed. Formation of bis-

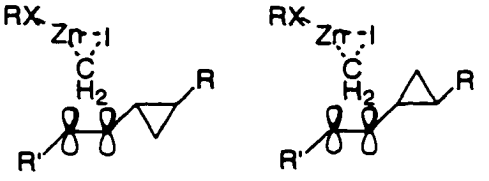
cyclopropanes from achiral conjugated dienes should produce two possible diastereomers (Scheme 3.33).



3-76 syn 3-77 anti 3-78

Scheme 3.33 Selective Cyclopropanation

A search of the literature showed that this substrate-directed diastereoselectivity had been seen before by Barrett[27] and Zercher.[28] Barrett proposed the an orbital overlap model to explain the selectivity Scheme **3-34**.

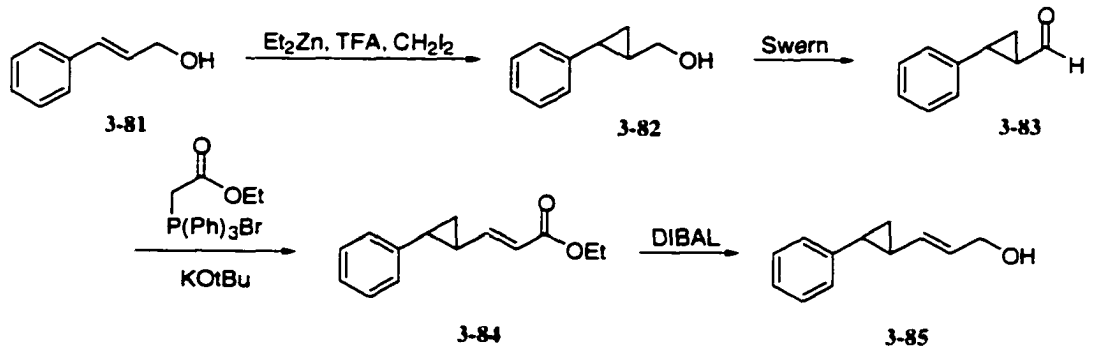


3-79 3-80

Scheme 3.34 Substrate Direction

Cyclopropanes are known for their ability to stabilize cations, donating electrons from the Walsh orbitals to the p-orbital of the adjacent carbon. These cations are stabilized enough that crystal structures have been obtained and distortion of the bond lengths show that the bond between the cyclopropane carbon and the carbons adjacent have donated some of their electron density to a p-orbital.[29] The cation-stabilizing ability of cyclopropanes had been seen in the S_N1 type displacement of allylic ethers. If this behavior is applied to bis-cyclopropanation, the existing cyclopropane will donate electrons to the opposite face of the adjacent double bond, creating an electron-rich face. Since these zinc reagents are electrophilic, anti-cyclopropanation should result, as in transition state **3-79**.

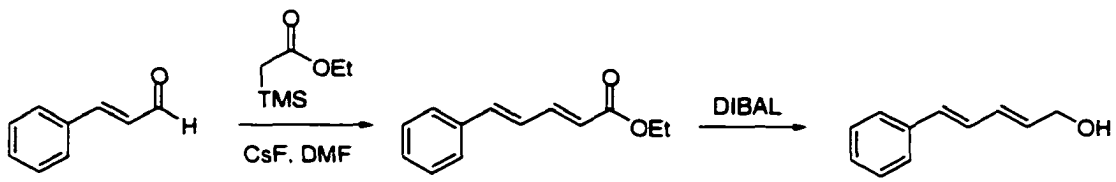
A new substrate with a distal cyclopropane was synthesized, Scheme **3-35**. Cinnamyl alcohol **3-81** was cyclopropanated then oxidized to the aldehyde. Olefin **3-84** was formed by a Horner-Emmonds-Wadsworth reaction followed by reduction to the desired alcohol **3-85**.



Scheme 3.35 Preparation of a Distal Mono Cyclopropane

Cyclopropanation of this substrate under three conditions; Furakawa's conditions, Et_2Zn/CH_2I_2, and with the modified reagent using TFA and 2,6-dichlorophenol as the ligand, at room temperature all yielded 1:1 to 1:2 mixtures of *syn* and *anti* products. The only way to determine the diastereomeric ratios was by ^{13}C NMR (100MHz) spectroscopy, as has been reported in the literature. Extensive attempts to separate the *syn* and *anti* compounds or their ester and ether derivatives by GC and HPLC were unsuccessful. There is no difference observable by ^{1}H NMR. Only the ^{13}C chemical shifts of the cyclopropane carbons are different enough to determine diastereomeric ratios. If the model put forth by Barrett is the source of the selectivity in the 2,4 diene-1-ol cases then the lack of selectivity for **3-85** substrate is explainable. The Lewis-basic alcohol can coordinate to the zinc, overwhelming any electronic effects from donation of the Walsh orbitals. Similar results are seen for the TBDPS derivative of this substrate. The Lewis-basic oxygen is a much better electron donor than the cyclopropane ring, resulting in little effective substrate-directed selectivity.

To provide further evidence about the *anti* nature of the cyclopropanation of the hexadienes, 5-phenyl-*trans,trans*-2,4-pentadienol **3-88** was synthesized Scheme 3.36. This substrate was chosen because the chemical shifts of its two diastereomers in the ^{13}C NMR spectrum are known. Olefination was accomplished using a modified Peterson olefination,[30] followed by DIBAL reduction to alcohol **3-88**.



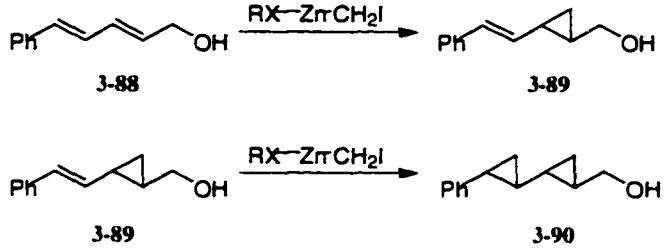
3-86 **3-87** **3-88**

Scheme 3.36 Preparation of 5-phenyl-t,t-2,4 pentadiene-1-ol

The same three conditions were used to form the bis-cyclopropanes, all at room temperature. Quantitative 100MHz ^{13}C NMR spectroscopy was used to determine the dr by adjusting the pulse sequence to decrease the NOE and a relaxation reagent was used to mitigate the affect of the T_1 value on peak intensity.[31] The drawback to this technique is that the sensitivity is significantly lowered, so a large amount of analyte and large data sets are needed.

The ability of substrates to direct allylic cyclopropanation was investigated with a number of known substrates (Figure 3.9). In the first case, the diastereoselectivity improves with the more electrophilic TFA derived reagent, but further improvement is seen with the slightly less reactive reagent derived from 2,6-dichloro phenol. If the diastereoselectivity is truly derived from cyclopropane electron donation, then a more electrophilic reagent should give better selectivity, but the reactivity/selectivity principle comes into play. The TFA-modified reagent is so reactive it has little time to be influenced by the electronics of the double bond, resulting in good, but not excellent

diastereoselectivity. The 2,6-dichlorophenol-modified reagent is more electrophilic than the Simmons-Smith reagent derived from diiodomethane, but is not as reactive as the TFA derivative so it can be more selective.



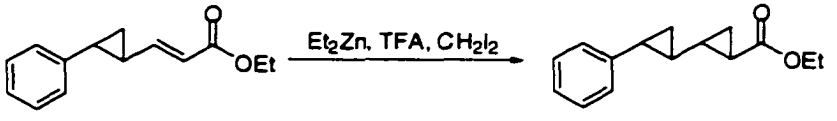
Ligand	Ph, OH [1]
Et_2Zn/CH_2I_2	4/1 anti/syn
TFA	9/1 anti/syn
OH, Cl, Cl	anti

a.All reactions were carried out at room temperature in CH_2Cl_2 with 2 eq. of zinc reagent.
b. Diastereoselectivity was determined by quantitative ^{13}C NMR in $CDCl_3$ with $Cr(acac)_3$ at 100MHz.

Figure 3.9 Substrate Directed Cyclopropanation

This work has been extended to triene derivatives and diastereoselectivity remains high. In addition, the initial cyclopropanation seems to direct cyclopropanation to the adjacent olefin so in the triene cases the order of cyclopropanation seems to go proximal to the alcohol, internal and then distal. By ^{13}C NMR spectroscopy there is one major diastereomer formed, providing further evidence that cyclopropanes can donate electron density to adjacent olefins.

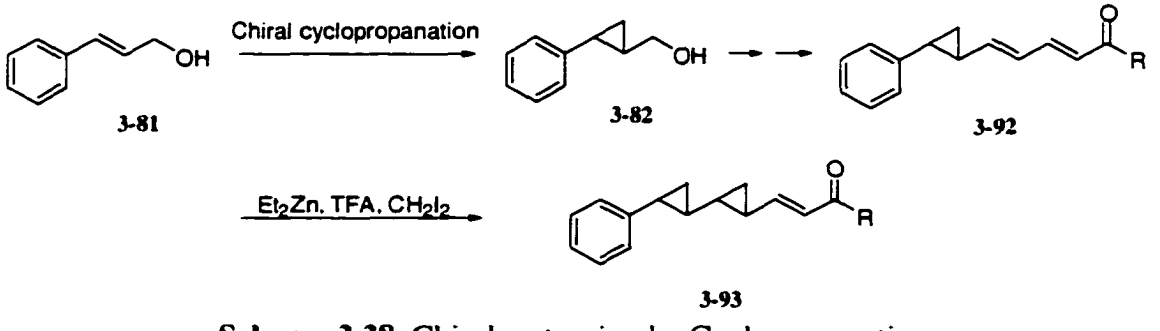
In the bis- and tris-cyclopropanations, for which there was high diastereoselectivity, it was believed that donation from the Walsh orbitals into the olefin directed the cyclopropanation. Attempts to cyclopropanate an α,β-unsaturared-δ,γ-cyclopropane **3-84** were not successful even with the TFA-Zn-CH_2I reagent. The donating power of the cyclopropane seems to be nullified by the electron-withdrawing ability of the ester.



3-84 3-91

Scheme 3.37 Cyclopropanation of Electron Poor Vivnyl Cyclopropane

If anti-cyclopropanes are a result of orbital overlap with the allylic cyclopropane, this offers an interesting opportunity. If an initial cyclopropane can be used to provide enough electron density to allow the formation of the second cyclopropane it should be anti. This would allow for the formation of enantiopure tris-cyclopropanes from a single chiral reaction followed by use of the modified cyclopropanation reagents.



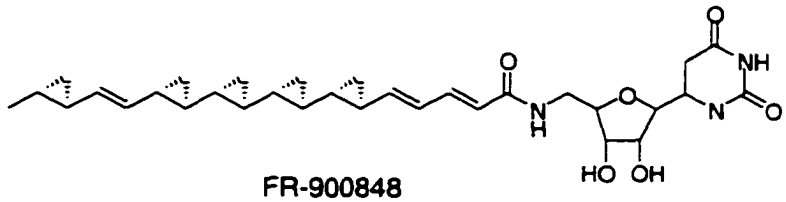
3-81 3-82 3-92

3-93

Scheme 3.38 Chiral extension by Cyclopropanation

Progress towards the formation of the bis-cyclopropane ester has been slow. New cyclopropanes are seen in the ^1H NMR but the products are not separable from the starting material. The only polycyclopropanated natural products identified to date, such

as FR-900848, have syn-cyclopropanes. The application of modified zinc reagents would be suitable for anti-polycyclopropanated compounds.

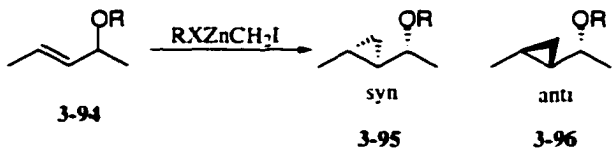


FR-900848

3.B.5 2° Allylic Alcohols

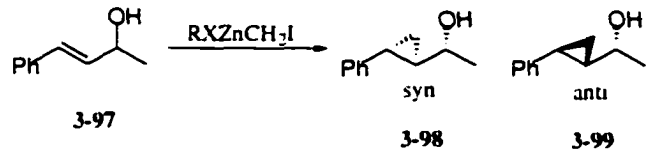
Zinc carbenoids are known to be very oxophilic reagents, and alcohols and ethers have been used as directing groups for diastereoselective cyclopropanation.[32] Great success has been achieved in the cyclopropanation of *cis* and trisubstitued 2° allylic alcohols and ethers. Only limited success has been achieved in the zinc-mediated cyclopropanation of *trans* 2° allylic alcohols. Molander and co-workers have had success with these substrates with the Sm-promoted cyclopropanation obtaining the syn-cyclopropane.[33] Charette has reported the diastereoselective cyclopropanation of some *trans* 2° allylic benzylic ethers.[34]

The selectivity of the modified carbenoids in cyclopropanation of *trans* 2° allylic alcohols was examined. The initial substrate, *trans*-3-pentenol (**3-94**) and its TBS ether were prepared from *trans*-2-butenal via a Grignard reaction.

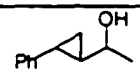
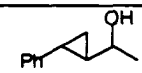
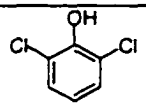
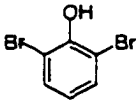


Scheme 3.39 Diastereoselective Cyclopropanation

The free alcohol proved to be an unsuitable substrate for cyclopropanation with the TFA-modified carbenoid. Only complex reaction mixtures with none of the desired cyclopropanes or starting material were formed. In an attempt to alleviate this problem, the TBS ether was used instead. There was virtually no diastereoselectivity observed when no ligand, TFA or 2,6-dichlorophenol was used in the cyclopropanation. The very small methyl group adjacent to the olefin may not provide enough steric bias to enhance diastereoselectivity so it was replaced by a phenyl group. Cyclopropanation of **3-97** proved successful, Scheme 3-10.



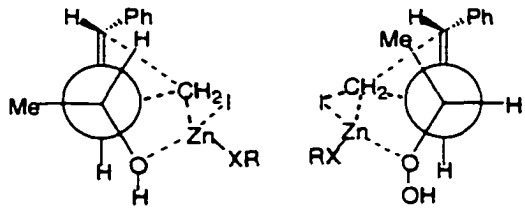
3-97 **3-98** **3-99**

Ligand	 syn/anti[a]	Ligand	 syn/anti
none	5.8/1 100% conv		rt 4.0/1 86% conv. -20 °C 11/1 37% conv.
TFA	rt Decomposition -20 °C 2.1/1		rt 4.3/1 89% conv.
TFA/CH_2ClI	1/1 98% conv.		

Et_2Zn (1.0 M in hexanes)(2.0 mL, 2 mmol) under N_2 in CH_2Cl_2 (2.4 mL) was cooled in an ice bath, and a solution of ligand (2.0 mmol) in CH_2Cl_2 (1.0 mL) was added. After stirring for 15 min. a solution of CH_2I_2 (161 μL, 2.0 mmol) in CH_2Cl_2 (0.5 mL) was added and the reaction stirred an additional 15 min. A solution of the olefin (1.0 mmol) in CH_2Cl_2 (1.0 mL) was added and the ice bath removed. The reaction was quenched and analyzed by ^1H NMR spectroscopy. a) Diasteroselectivity determined by GC using a 30m Stabilwax column

Figure 3-10 Cyclopropanation of *trans* Allylic Alcohols

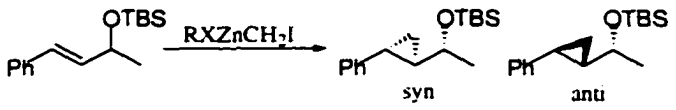
Room temperature reactions with the TFA-modified reagents produced complex reaction mixtures. If diiodomethane is replaced with chloroiodomethane the reaction is clean, but there is no selectivity. The source of the diastereoselectivity can be seen by examining the transition state models used by Molander,[35] which were proposed by Hauk[36] (Scheme 3-40).



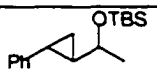
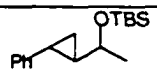
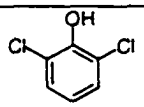
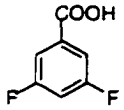
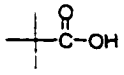
Scheme 3-40 Transition State Model

With the free alcohol, the methyl group is large enough that at lower temperatures the syn product is favored, **3-98**. The tight coordination of the electron-poor zinc to the oxygen, along with the steric bulk of the zinc imparted by the ligand, favors the syn transition state. The lack of selectivity for the TFA carbenoids is probably due to the reaction occurring with disregard for sterics as was seen in the TBDPS protected dienols. The less-reactive carbenoids provide much higher selectivity. The large 2,6-dichlorophenol ligand provides good diastereoslectivies and as the temperature is lowered, slowing the rate of the reaction, the sterics improve the diastereoselectivity to 11/1.

The bulk on the alcohol was increased using a TBS group to see if there would be an effect on the diastereoselectivity.



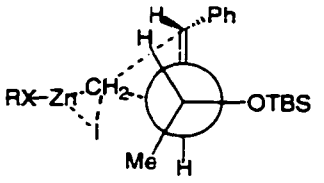
3-100 3-101 3-102

Ligand	 syn/anti[a]	Ligand	 syn/anti
none	1/16 94% conv		1/2
TFA	1/74 >98% conv		1/108 >98% conv
	1/159 96% conv		

Et_2Zn (1.0 M in hexanes)(2.0 mL, 2 mmol) under N_2 in CH_2Cl_2 (2.4 mL) was cooled in an ice bath, and a solution of ligand (2.0 mmol) in CH_2Cl_2 (1.0 mL) was added. After stirring for 15 min. a solution of CH_2I_2 (161 μL, 2.0 mmol) in CH_2Cl_2 (0.5 mL) was added and the reaction stirred an additional 15 min. A solution of the olefin (1.0 mmol) in CH_2Cl_2 (1.0 mL) was added and the ice bath removed. The reaction was quenched and analyzed by ^1H NMR spectroscopy. a)Diasteroselectivity determined by GC using a 30m Stabilwax column after treatment with TBAF. Reactions were carried out at rt in CH_2Cl_2 with 2 eq. of zinc reagent.

Figure 3.11 Cyclopropanation of *trans* Allylic Silyl Ethers

In the case of TBDMS ethers, the steric bulk of the oxygen group becomes dominant. This is amplified by adding a sterically demanding zinc complex the transition state in scheme 3.41 is the most plausible. The more sterically demanding the ligand the better the diastereoselectivity becomes, with the exception of 2,6-dichlorophenol.



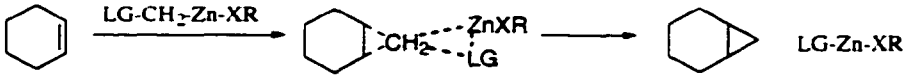
3-102

Scheme 3.41 anti Selectivity

The increase in diastereoselectivity corresponding to the size and reactivity of the zinc carbenoid was very encouraging. These results agree with the good anti selectivity seen with *tran*-2°-silyl ethers. The poor selectivity seen with 2,6-dichlorophenol is very puzzling.

3.C CH_2 Sources

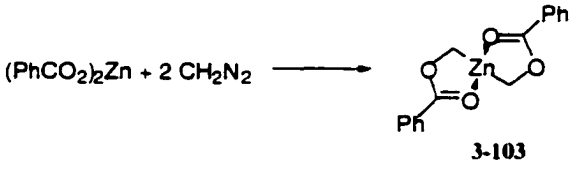
While the work on diastereoselectivity was being carried extensive studies examining the use of chiral RXH groups for the enantioselective cyclopropanation of unfunctionalized olefins were being carried out separately. Despite the initial success with a fructose-derived chiral RXH in the cyclopropanation of *t*-β-methylstyrene, a more successful system was not developed. In the interest of finding a way to selectively cyclopropanate unfunctionalized olefins, the information gathered about zinc carbenoids was examined. (Scheme 3.42).



Scheme 3.42 Leaving Group

The carbenoid is made up of zinc with a CH_2 source with a leaving group (LG), traditionally iodine or chlorine, on one side and on the other side some ligand which can moderate the reactivity. There had been a large amount of effort put forth examining the role of the ligand on zinc, but only iodine and very briefly chlorine had been examined as the leaving groups. It should be possible for other leaving groups that could coordinate zinc to be used.

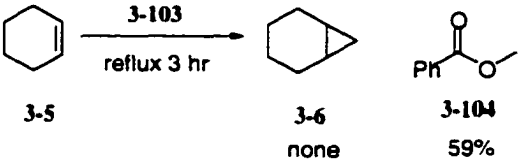
A search of the literature found two cases where alternative leaving groups on the CH_2 had been reported. Molander had examined several alternative leaving groups in his Samarium carbenoid cyclopropane reactions with no success.[37] A much more promising report was a paper by Wittig from 1967.[38] Wittig and coworkers formed zinc complex **3-103** by diazomethane insertion into Zn (II) benzoate, Scheme 3.43.



3-103

Scheme 3.43 Formation of **3-103**

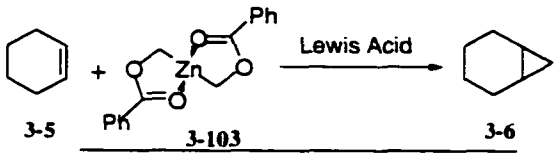
This crystalline solid was examined for its ability to cyclopropanate olefins in benzene at reflux.



3-5 **3-6** none **3-104** 59%

Scheme 3.44 Reaction of **3-103**

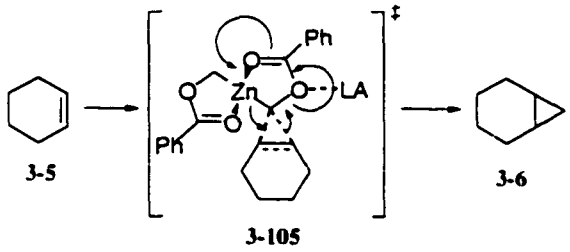
The main product of the reaction was methyl benzoate, from elimination of the zinc. When **3-103** was heated with cyclohexene to 140°C in a sealed tube for 1 hr only 6% of the cyclopropane was recovered. However, this unreactive complex could be used for cyclopropanation if Lewis acids were added to the reaction mixture,(Figure 3.12).



MX_2	conv.
ZnF_2	0% heterogeneous
$ZnCl_2$	12%
$ZnBr_2$	36%
ZnI_2	91%

Figure 3.12 Lewis Acid Mediated Cyclopropanation

Other Lewis acids were tested, but zinc halides provided the best results. Wittig proposed that the Lewis acid could coordinate to one of the ester oxygens weakening the carbon-oxygen bond, allowing the methylene to transfer to the double bond.

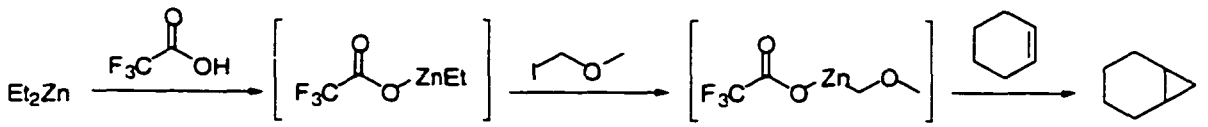


Scheme 3.45 Reaction Mechanism

Wittig tried to modify this procedure to perform nucleophilic cyclopropanations, no further work had been reported using this type of cyclopropanation reagent, most likely due to the difficulty of preparation, and handling issues. In Molander's case the desired cyclopropanation reactions did not occur. Charette has done some work on the solid state and solution reactivity of these complexes, but only very preliminary results have been reported.[39]

If the CH_2 source could be modified there would be a second handle with which to control the reactivity of the zinc carbenoids, with a strong potential for chiral Lewis acid-controlled cyclopropanation. Ligands with different electronic and steric properties

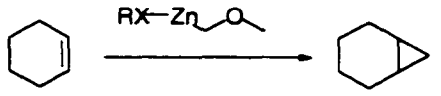
could be paired with different leaving groups on the methylene to form a new family of reagents. Initial studies began with commercially-available iodomethylmethyl ether, Scheme 2.46.



3-106 3-107 3-6

Scheme 3.46 MOMI as the CH_2 Source

After a 4 hour reaction at room temperature, a trace amount of cyclopropane was observed in the crude ^1H NMR spectrum. This exciting result lead to further studies using Lewis acids to accelerate the reaction, (Figure 3.13).

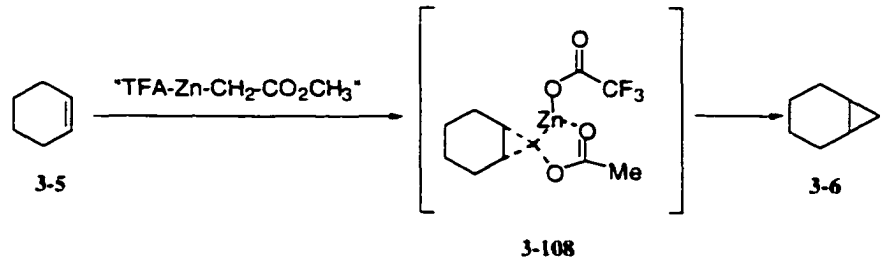


entry	RXH	CH_2	LA	Conv.
1	TFA(1 eq)	MOMI (1 eq)	$ZnCl_2$	trace
2	TFA(1 eq)	MOMI (1 eq)	Et_2AlI	trace
3	TFA(1 eq)	MOMI (1 eq)	Et_2AlCl	trace
4	TFA(1 eq)	MOMI (1 eq)	$Al(iBu)_3$	trace
5	TFA(1 eq)	MOMI (1 eq)	$ZnCl_2$	trace
6	TFA(1 eq)	MOMI (1 eq)	-	trace
7	TFA(1 eq)	MOMI (2 eq)	$ZnCl_2$	trace
8	TFA(1 eq)	MOMI (2 eq)	-	trace

Figure 3.13 MOMI as the CH_2 Source

When another ligand on zinc was used there was no reaction with MOMI as the CH_2 source. The poor reactivity is probably due to the poor leaving group used, MeO^-. This

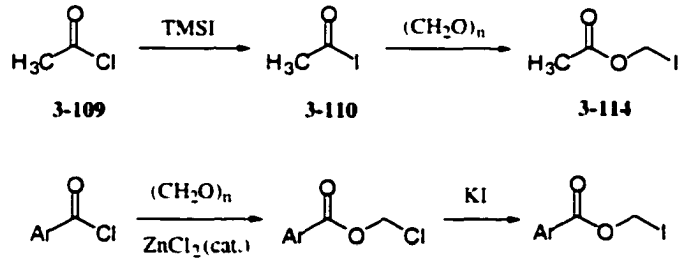
limited success encouraged the examination of other CH_2 sources. Further examination of leaving groups focused on those with oxygen carrying the negative charge since zinc is oxophilic and can coordinate to the oxygen in the transition state, Scheme 3.47.



3-5 3-108 3-6

Scheme 3.47 Possible Transition State

There is also potential for a Lewis acid to coordinate to either the RX group on zinc, or to one of the oxygens in the leaving group. This could moderate the reactivity, and potentially a chiral Lewis acid could provide asymmetric induction. This new set of CH_2 sources was prepared following literature procedures with only slight modification Scheme 3.48.

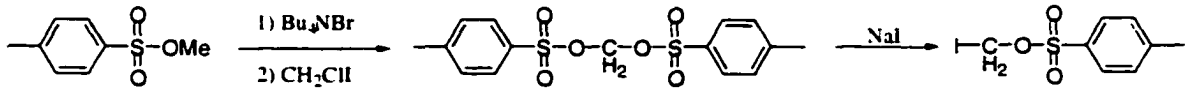


3-109 3-110 3-114

3-112 Ar = Ph
3-113 Ar = 2,6-Cl-Ph
3-114 Ar = 2,4,6-Me-Ph

3-115 Ar = Ph
3-116 Ar = 2,6-Cl-Ph
3-117 Ar = 2,4,6-Me-Ph

3-118 Ar = Ph
3-119 Ar = 2,6-Cl-Ph
3-120 Ar = 2,4,6-Me-Ph



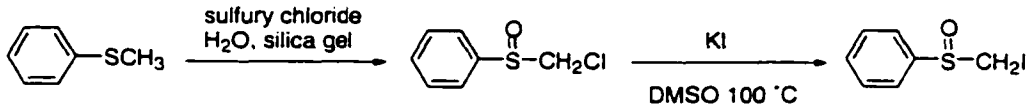
3-121 3-122 3-123

Scheme 3.48 Preparation of CH_2 Sources

Trimethylsilyl iodide was freshly prepared from iodine and hexamethyldisilane. Acetyl chloride was added and the acid iodide was collected by distillation from copper dust.[40] Treatment of the acid iodide neat with paraformaldehyde followed by distillation

from copper dust gave the desired iodomethyl acetate.[41] Conversion of aromatic acid chlorides to the acid iodides was not very successful due to their instability. A $ZnCl_2$-catalyzed insertion of formaldehyde into the acid halide bond gave the more manageable chloromethyl aryl esters.[42] A Finkelstein reaction converted the chloride to the iodide which was purified by vacuum distillation from copper dust. These iodomethyl esters can be stored over copper, under an inert atmosphere in the dark at −15°C for extended periods of time. The iodomethyl tosylate was prepared from methyl tosylate following a literature procedure, and purified by Kuglrohr distillation from copper dust at reduced pressure.[43]

The other CH_2 source which was the focus of extensive effort was **3-126** which was reported in the mid 70's, (Scheme 3.49).[44]



3-124 3-125 3-126

Scheme 3.49 Preparation of Chiral CH_2 Source

The sulfur is chiral so there is potential for chiral induction from the CH_2 source itself. Unfortunately the conversion of the chloride to the iodide is a very low-yielding, messy reaction. After repeated attempts this target was abandoned.

Methylene sources with an ester leaving groups were tested for their ability to successfully cyclopropanate alkenes. The first new CH_2 source tested was **3-114** iodomethyl acetate. Following the reaction by GC showed that we were able to use alternative CH_2 sources to successfully cyclopropanate olefins (Figure 3.14).

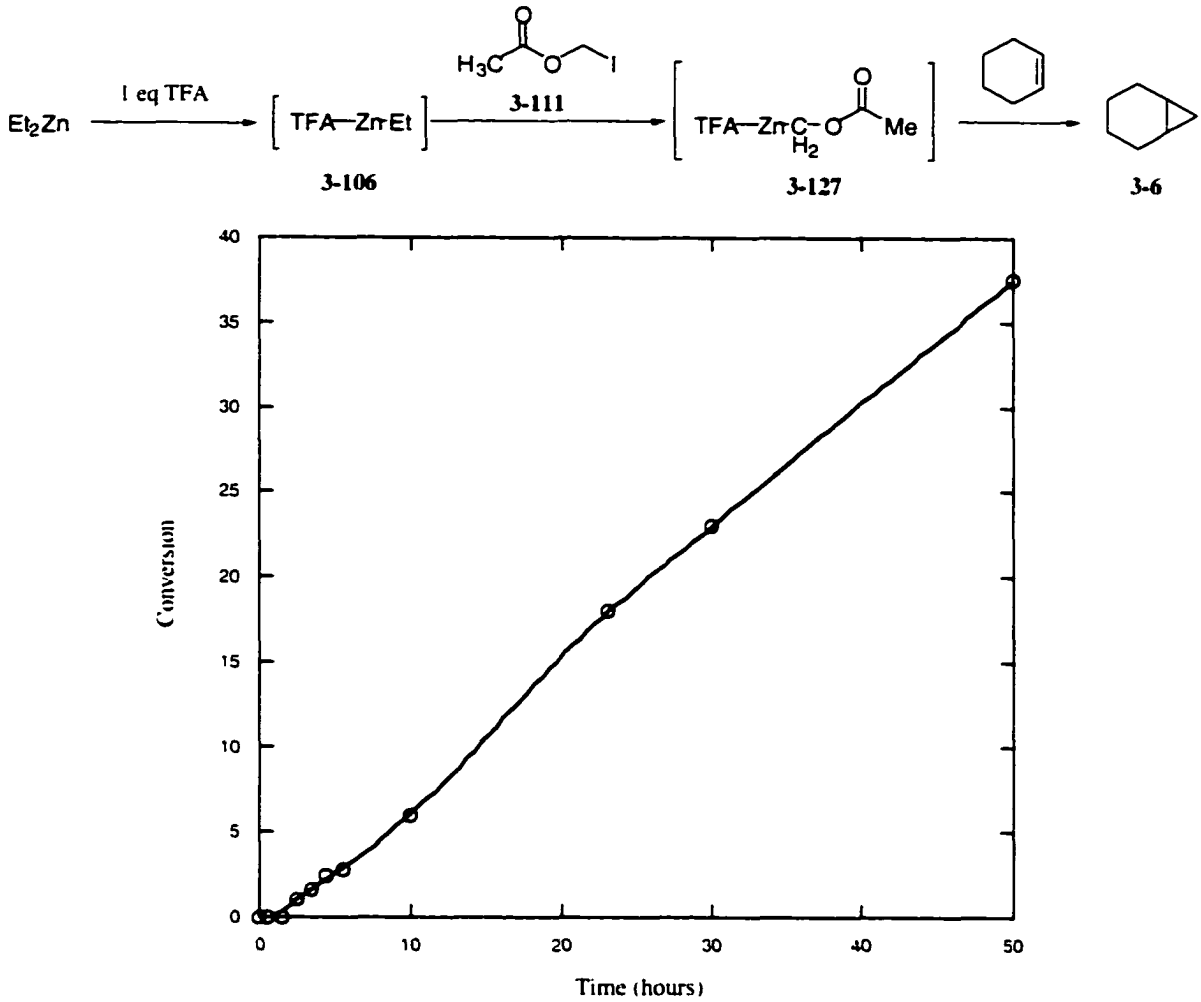
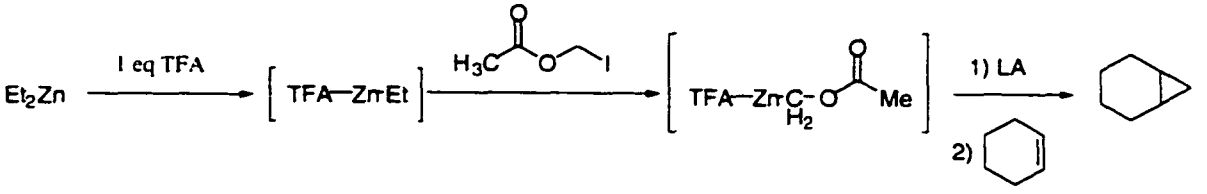


Figure 3-14 Cyclopropanation with TFA-Zn-CH_2OAc

Et_2Zn (1.0 M in hexanes)(1.0 mL, 1 mmol) under N_2 in CH_2Cl_2 (1.2 mL) was cooled in an ice bath, and a solution of ligand (1.0 mmol) in CH_2Cl_2 (1.0 mL) was added. After stirring for 15 min. a solution of CH_2 source (1.0 mmol) in CH_2Cl_2 (0.5 mL) was added and the reaction stirred an additional 15 min. A solution of the olefin (0.5 mmol) in CH_2Cl_2 (1.0 mL) was added and the ice bath removed. Samples were taken over the course of the reaction and analyzed by GC.

The reaction is much slower than when diiodomethane is used, but the reaction does proceed at room temperature. There seems to be some induction time before cyclopropanation occurs. This suggests that the reaction requires a Lewis acid to facilitate CH_2 transfer, as was seen by Wittig. To this end a series of Lewis acids was

screened for their ability to accelerate the reaction, (Figure 3-15). By far the most successful Lewis acid was zinc iodide. The reaction rate was about doubled when 10% ZnI_2, with respect to the carbenoid, was used. Some of the other Lewis acids seemed to retard the reaction, or stop it all together.



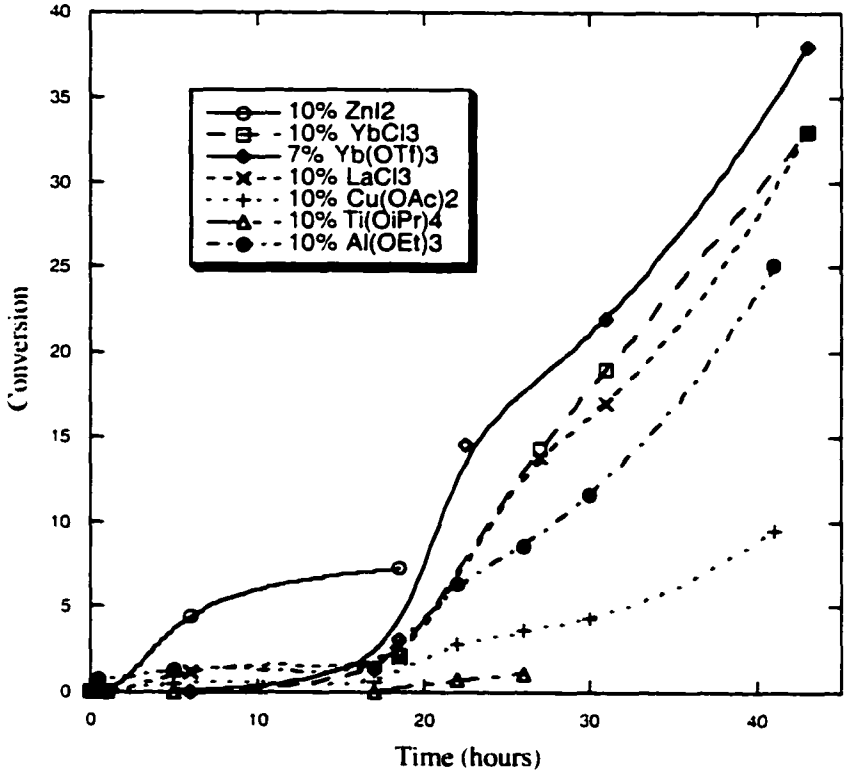


Figure 3-15 Cyclopropanation with TFA-Zn-CH_2OAc and LA

Et_2Zn (1.0 M in hexanes)(1.0 mL, 1 mmol) under N_2 in CH_2Cl_2 (1.2 mL) was cooled in an ice bath, and a solution of ligand (1.0 mmol) in CH_2Cl_2 (1.0 mL) was added. After stirring for 15 min. a solution of CH_2 source (1.0 mmol) in CH_2Cl_2 (0.5 mL) was added and the reaction stirred an additional 15 min. A solution of the olefin (0.5 mmol) in CH_2Cl_2 (1.0 mL) and Lewis acis were added and the ice bath removed. Samples were taken over the course of the reaction and analyzed by GC.

When 1-hydroxy-2-cyclohexene was used as the substrate with iodomethyl acetate as the CH_2 source and TFA as the ligand on zinc no cyclopropane is formed after 4.5 hours in CH_2Cl_2 at room temperature. Allylic alcohols are generally more reactive than simple olefins with Simmons Smith cyclopropanation. In this case, the electron-donation ability of the alcohol may be competing with the electron-withdrawing ability of the TFA ligand and retarding the reaction.

With this initial success, the CH_2 sources with aromatic esters as the leaving group were evaluated for their ability to cyclopropanate olefins. (Figure 3-16). Compound **3-118** appears to be a much better CH_2 course than iodomethyl acetate.

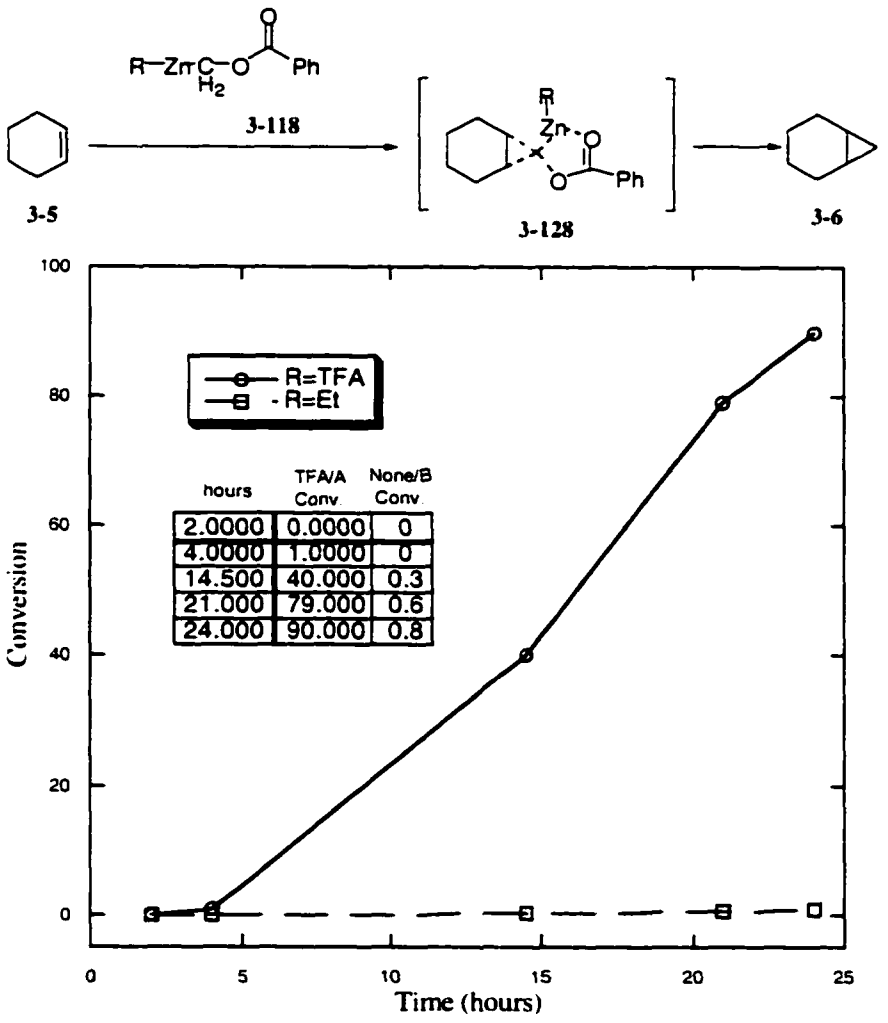
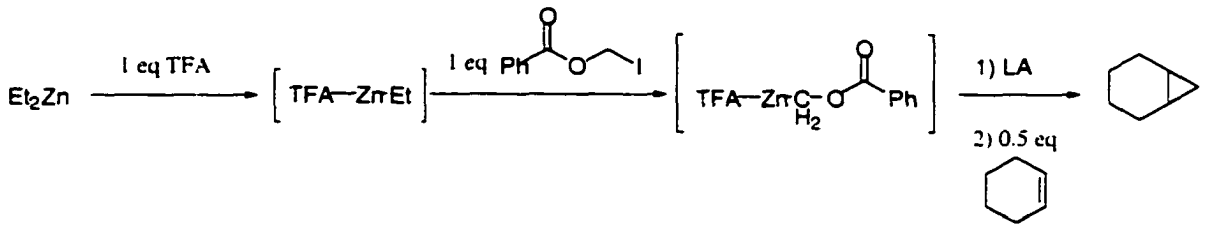


Figure 3.16 Cyclopropanation with ICH_2Obz

Et_2Zn (1.0 M in hexanes)(1.0 mL, 1 mmol) under N_2 in CH_2Cl_2 (1.2 mL) was cooled in an ice bath, and a solution of ligand (1.0 mmol) in CH_2Cl_2 (1.0 mL) was added. After stirring for 15 min. a solution of CH_2 source (1.0 mmol) in CH_2Cl_2 (0.5 mL) was added and the reaction stirred an additional 15 min. A solution of the olefin (0.5 mmol) in CH_2Cl_2 (1.0 mL) was added and the ice bath removed. Samples were taken over the course of the reaction and analyzed by GC.

The drastic effect of the ligand on the rate of reaction is shown with almost no reaction occurring in the absence of TFA. Examination of the reaction curve with TFA as the ligand on zinc shows that there is an induction period. Again this seems to indicate the need for a Lewis acid to accelerate the reaction. A variety of Lewis acids were screened for their ability to accelerate the reaction, (Figure 3-17).



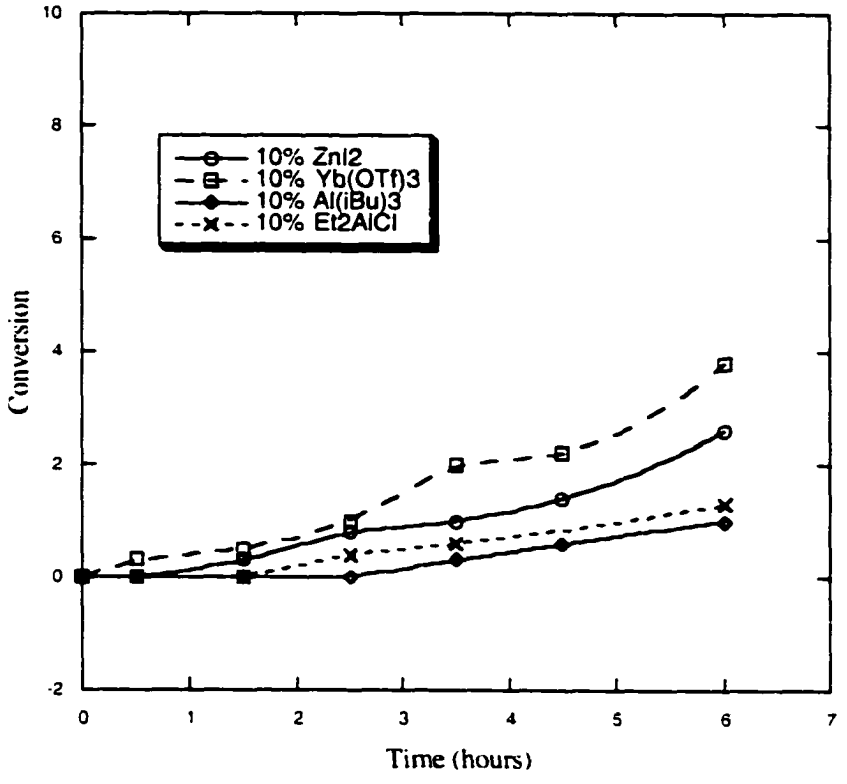


Figure 3.17 LA Accelerated Cyclopropanation

Et_2Zn (1.0 M in hexanes)(1.0 mL, 1 mmol) under N_2 in CH_2Cl_2 (1.2 mL) was cooled in an ice bath, and a solution of ligand (1.0 mmol) in CH_2Cl_2 (1.0 mL) was added. After stirring for 15 min. a solution of CH_2 source (1.0 mmol) in CH_2Cl_2 (0.5 mL) was added and the reaction stirred an additional 15 min. A solution of the olefin (0.5 mmol) in CH_2Cl_2 (1.0 mL) and Lewis acid were added and the ice bath removed. Samples were taken over the course of the reaction and analyzed by GC.

Since there was an induction period before the reaction began, the possibility of Lewis-acid acceleration was examined for the first six hours of the reaction. When 10 mol% of a Lewis acid was added, very little acceleration was seen.

In preparation for possible asymmetric versions of this reaction, a substrate which would form a chiral cyclopropane was used with different ligands and Lewis acids. (Figure 3-18).

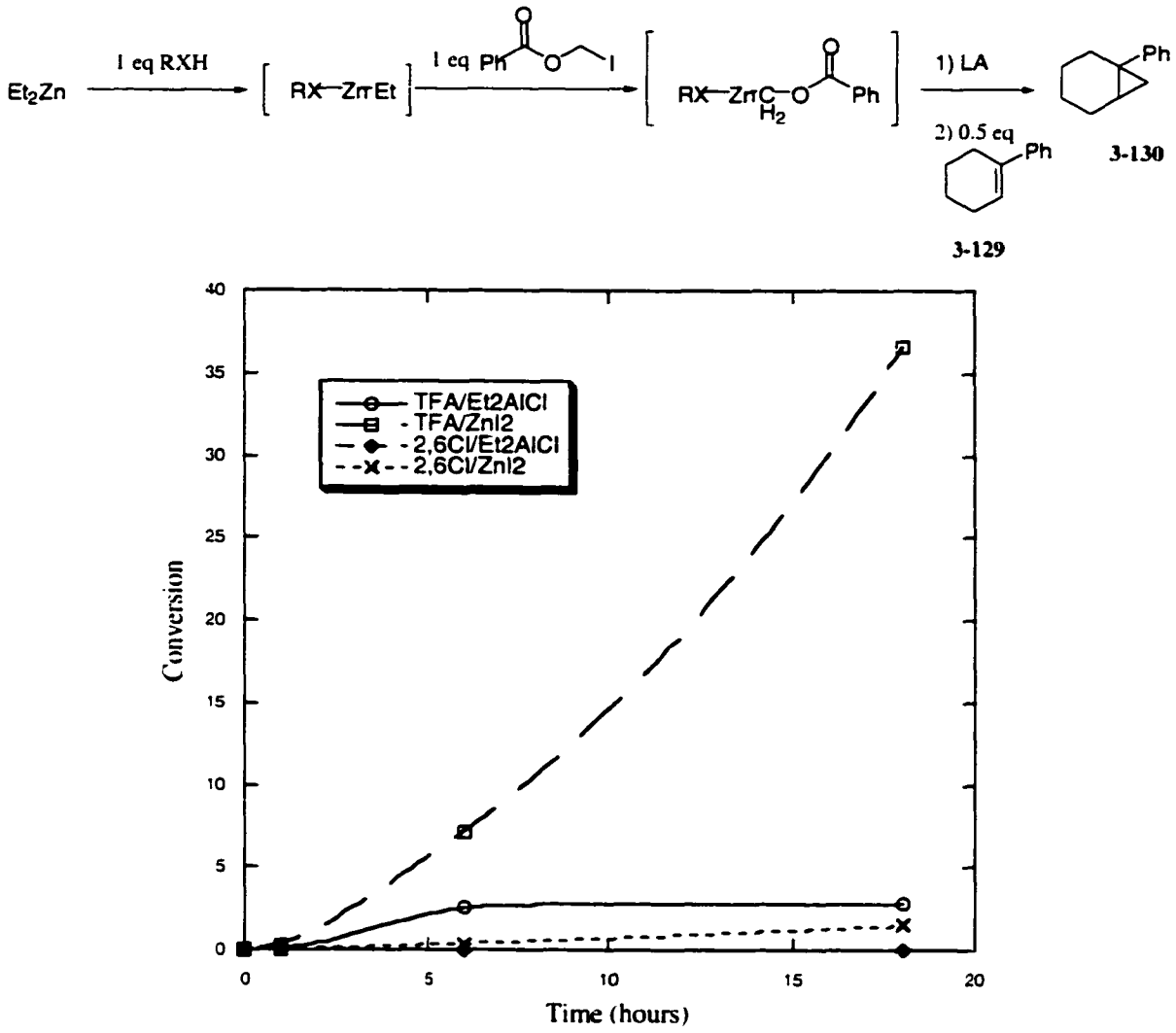


Figure 3-18 Lewis Acid and Ligand Effects

Et_2Zn (1.0 M in hexanes)(1.0 mL, 1 mmol) under N_2 in CH_2Cl_2 (1.2 mL) was cooled in an ice bath, and a solution of ligand (1.0 mmol) in CH_2Cl_2 (1.0 mL) was added. After stirring for 15 min. a solution of CH_2 source (1.0 mmol) in CH_2Cl_2 (0.5 mL) was added and the reaction stirred an additional 15 min. A solution of the olefin (0.5 mmol) in CH_2Cl_2 (1.0 mL) and Lewis acid were added and the ice bath removed. Samples were taken over the course of the reaction and analyzed by GC.

The combination of TFA as the ligand on zinc with ZnI_2 as the Lewis acid was successful in cyclopropanating 1-phenylcyclohexene. There is no induction period in the reaction curve suggesting that the ZnI_2 is acting as a Lewis acid and accelerating the reaction. The less electron-withdrawing 2,6-dichlorophenol gave a minor amount of product with ZnI_2

as the Lewis acid. The zinc Lewis acid continues to be the most consistently successful additive for the alternative CH_2 sources.

All of the reactions are still very slow and the Lewis acids are not able to yet accelerate the reaction at a rate which would allow chiral Lewis-acid catalyzed cyclopropanation. A survey of Lewis acids in benzene at 65°C was undertaken to see if a slight increase in temperature would allow the reaction to be completed in a shorter time (Figure 3-18). Since another constant problem has been solubility, perhaps a slightly elevated temperature would help to alleviate this problem.

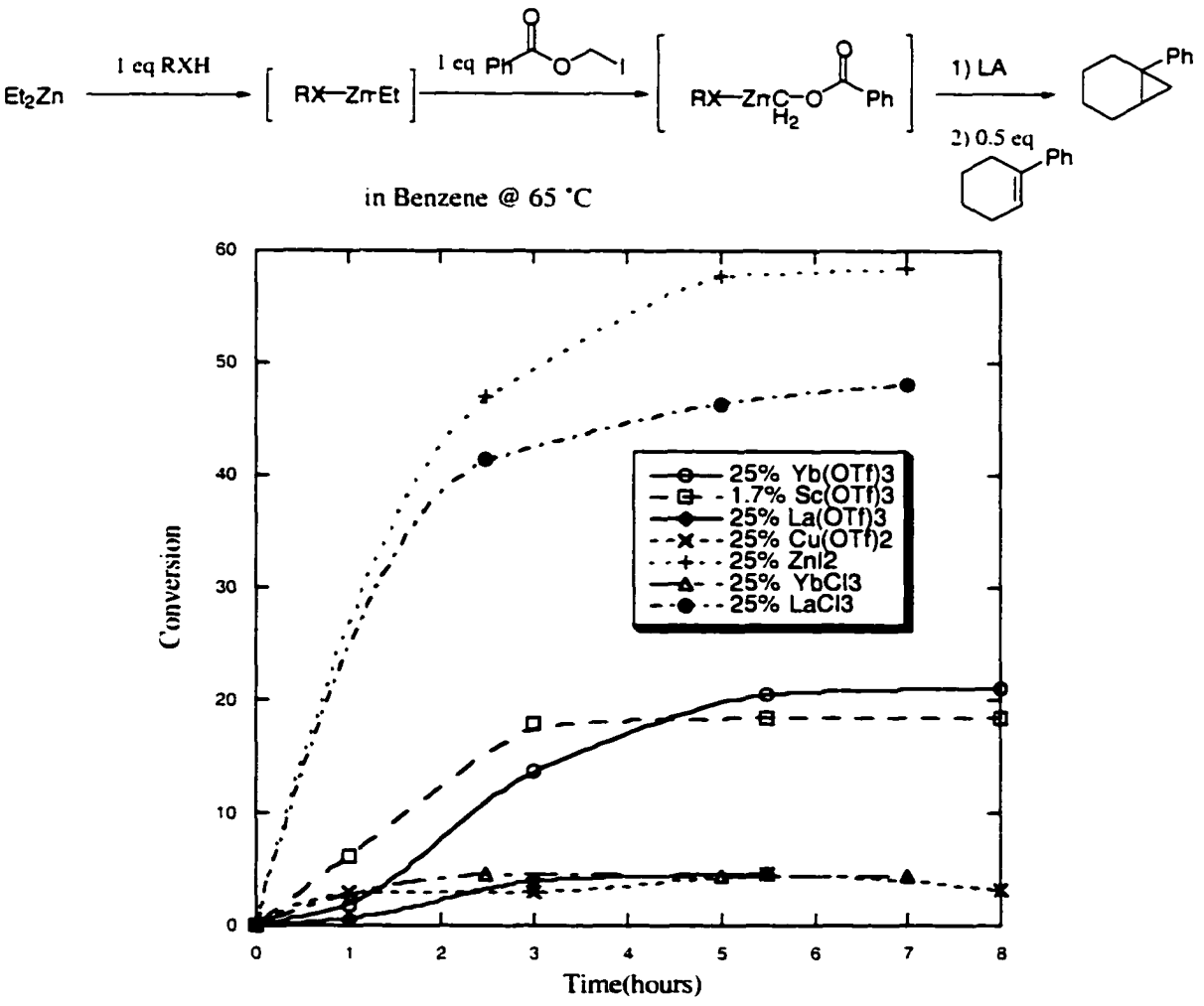
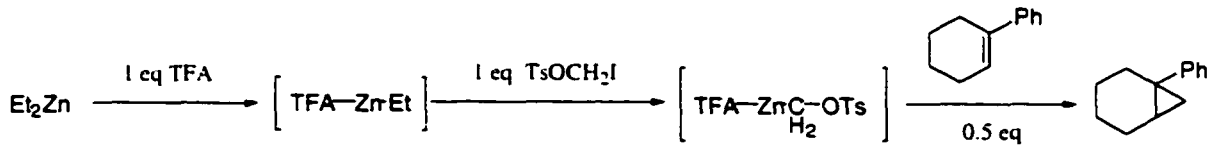


Figure 3.18 Lewis Acid Acceleration at 65 °C

Et_2Zn (1.0 M in hexanes)(1.0 mL, 1 mmol) under N_2 in benzene (1.2 mL) was cooled in an ice bath, and a solution of ligand (1.0 mmol) in CH_2Cl_2 (1.0 mL) was added. After stirring for 15 min. a solution of CH_2 source (1.0 mmol) in benzene (0.5 mL) was added and the reaction stirred an additional 15 min. A solution of the olefin (0.5 mmol) in benzene (1.0 mL) and Lewis acid were added and the ice bath removed. The reaction was heated in a 65°C oil bath Samples were taken over the course of the reaction and analyzed by GC.

Running the reaction at 65°C greatly increases the rate. Using only 25 mol% of ZnI_2, with repect to the carbenoid, a conversion of 48% can be obtained in only 2.5 hours, a large increase in reactivity. The solubility problem was reduced some. The relativly rapid cyclopropantion shows that there is no induction period for suitable Lewis acids, suggesting that they facilitate the reaction.

One other CH_2 source was examined for the cyclopropanation process, compound **3-123**. Instead of esters as the leaving group, the well-known tosylate leaving group was used. With the TFA as the ligand on zinc, a carbenoid with reactivity comparible to TFA-Zn-CH_2OBz with ZnI_2 was obtained (Figure 3.19).



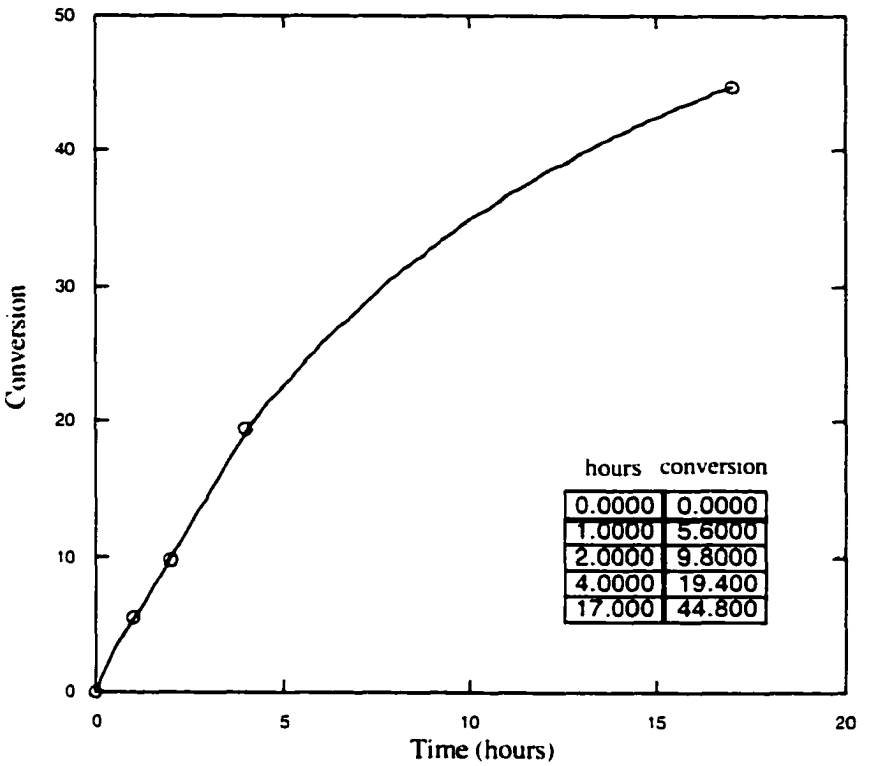
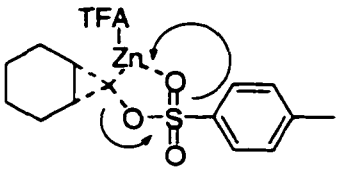


Figure 3.19 Iodomethyl Tosylate as the Leaving Group

Et_2Zn (1.0 M in hexanes)(1.0 mL, 1 mmol) under N_2 in CH_2Cl_2 (1.2 mL) was cooled in an ice bath, and a solution of ligand (1.0 mmol) in CH_2Cl_2 (1.0 mL) was added. After stirring for 15 min. a solution of CH_2 source (1.0 mmol) in CH_2Cl_2 (0.5 mL) was added and the reaction stirred an additional 15 min. A solution of the olefin (0.5 mmol) in CH_2Cl_2 (1.0 mL) and Lewis acid were added and the ice bath removed. Samples were taken over the course of the reaction and analyzed by GC.

There is no induction period in this case, suggesting that a Lewis acid is not required. The addition of a Lewis acid did not accelerate the reaction, as is expected since there is probably an internal coordination of the leaving group, similar to the use of diiodomethane, and tosylate is a very good leaving group compared to esters. (Scheme 3.50).



3-131

Scheme 3.50 Possible Transition State

The electron-poor zinc probably coordinates to one of the oxygens on the tosylate facilitating its leaving. When the reaction is run without TFA as the ligand, almost no product is observed. There were some solubility problems, and as a result complete conversion was not seen when that amount of zinc complex was increased. A large amount of work remains for this class of CH_2 sources. Solvent effects need to be studied. The construction of a chiral leaving group may be a way to address the problem chiral induction for unfunctionalized olefins. If there is a tight coordination between the zinc and oxygen a chiral group on the sulfonate may be able to induce some enantioselectivity. This could be similar to the allylic alcohol cases with chiral boraonates for which there is a chiral group coordinated to the zinc.

3.C.1 Electron-Poor Olefins

These new cyclopropanation reagents were tested for their ability to cyclopropanate electron-deficient olefins. Standard Simmons Smith-type reagents are not proficient at cyclopropanating α,β-unsaturated olefins. The first CH_2 source tested was iodomethyl acetate. When the TFA complex was stirred overnight with cyclohexenone no cyclopropane was observed. The starting material was recovered with only trace amounts of what appeared to be a Michael addition product, (Figure 3.20). When no

ligand was added no reaction occurred, even after extended reaction time. Heating the reaction in benzene at reflux did not facilitate the reaction either.

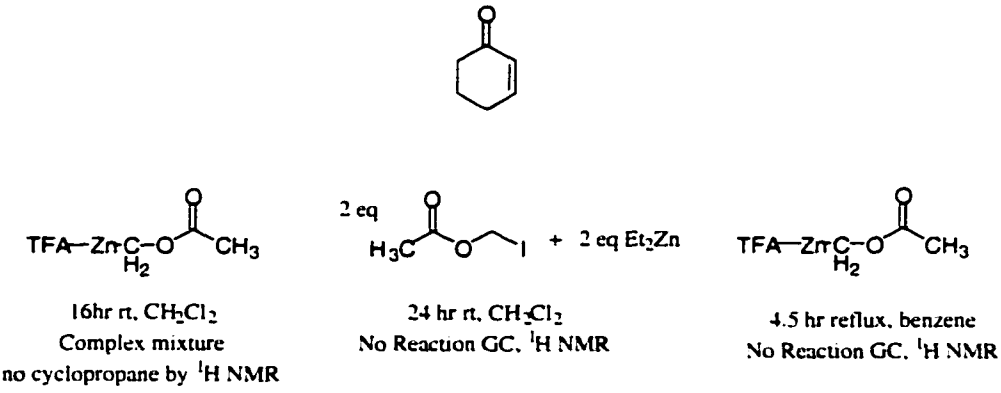


Figure 3.20 ICHOAc with Cyclohexenone

With iodomethyl benzoate, a larger selection of α,β-unsaturated olefins was surveyed but none of the desired cyclopropane was observed in any of the cases (Figure 3.22). Traces of cyclopropane were seen with cyclohexenone, but extended heating at reflux in benzene did not increase the amount of cyclopropane, by NMR spectroscopy of the crude reaction mixture.

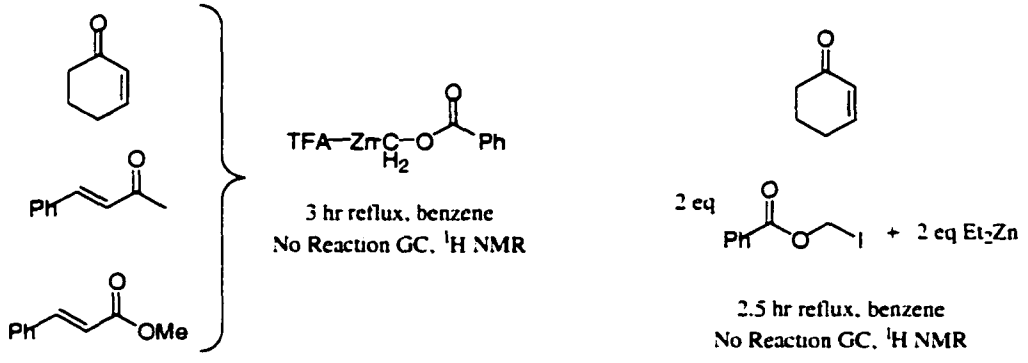


Figure 3.22 ICH_2Obz with α,β-unsaturated Olefins

Using the tosylate as a leaving group produced a reactive cyclopropanation reagent, so it was hoped that it might be able to react with electron-poor olefins while the other two reagents had failed. Stirring two equivalents of TFA-Zn-CH_2OTs with cyclohexenone or

N,N-diethyl-*t*-2-hexenamide for 3 days resulted in recovery of starting material and none of the desired cyclopropane (Figure 3.23).

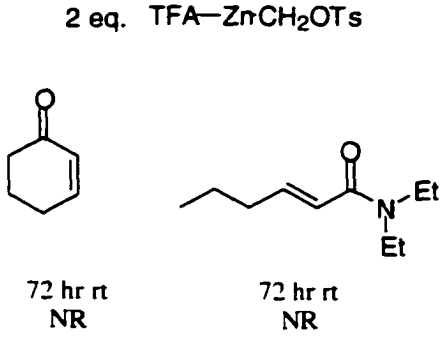


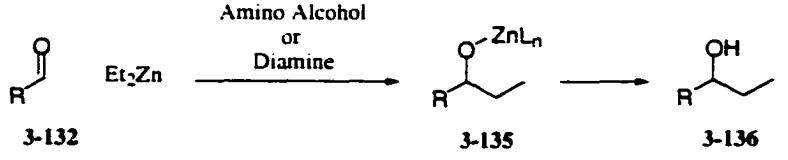
Figure 3.23 ICH_2OTs with α,β-unsaturated Olefins

The new zinc reagents are electrophilic, just like those generated from diiodomethane. There is still a need for a general method for cyclopropanation of electron poor-olefins where the ylid based approaches fail.

3.D. Other Reactions with Modified Zinc Reagents

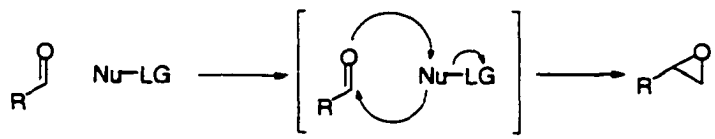
3.D.1 Reaction with Aldehydes

Organozinc reagents are known to add to electrophilic aldehydes.[45] If a chiral ligand is used, the reaction can be accelerated and there have been cases of very high enantioselectivity Scheme 3.52.



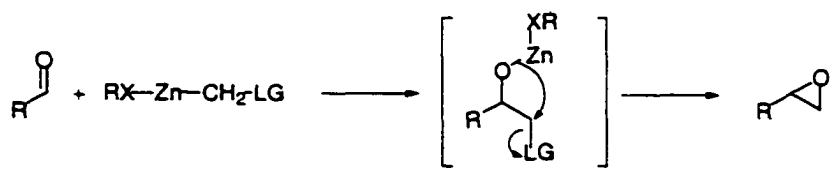
Scheme 3.52 Addition of Organozinc to Aldehydes

There is potential to form terminal epoxides by addition of organozinc reagents to aldehydes. There is currently no general method for forming chiral terminal epoxides in high ee. Sulfur ylids have been used to form epoxides both chirally and achirally, Scheme 3.53.[46] Aggarwal and coworkers have developed a catalytic method to form terminal epoxides from aldehydes.[47]



Scheme 3.53 Terminal Epoxide Formation

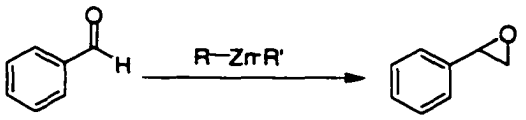
The organozinc reagents which contain a leaving group on the methylene could add to form epoxides. The electron density on the zinc can be moderated by changing the ligand on the zinc, this may affect the ability of the methylene to be added to the aldehyde. If there is addition the oxygen displace the leaving group, forming the desired epoxide, (Scheme 3.54.)



Scheme 3.54 Terminal Epoxidation with Zinc Reagents

Benzaldehyde was chosen as the test substrate since it is a very electrophilic aldehyde. A wide variety of zinc complexes were tested using different leaving groups, Lewis acids and ligands, but only trace amounts of the desired epoxide were observed by GC and

GC/MS. In most cases the unreacted aldehyde was recovered with no sign of addition. Some of the conditions tried are listed in Table 3.4.



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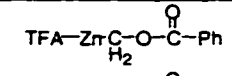
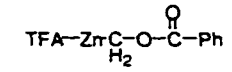
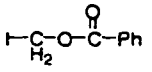
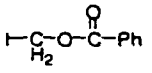
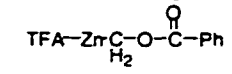
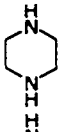
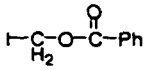
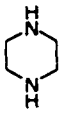
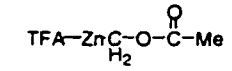
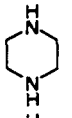
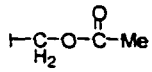
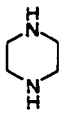
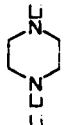
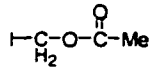
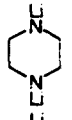
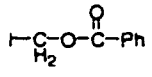
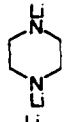
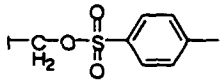
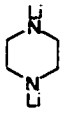
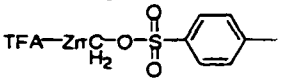
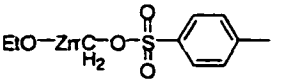
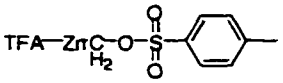
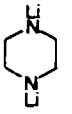
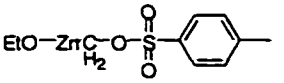
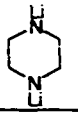
The reactions were carried out with 2 equvalents of preformed zinc reagent, in a non-coordinating solvent such as CH_2Cl_2 or toluene. The crude reaction mixtures were examined by GC and H^1 NMR spectroscopy for epoxide formation.

Organozinc addition of a methylene containing a leaving group to an aldehyde is not yet a viable method for forming terminal epoxides. However there are other leaving groups on the methylene and ligands on the zinc which could be tried. There is still room for experimentation to find a solution to this problem.

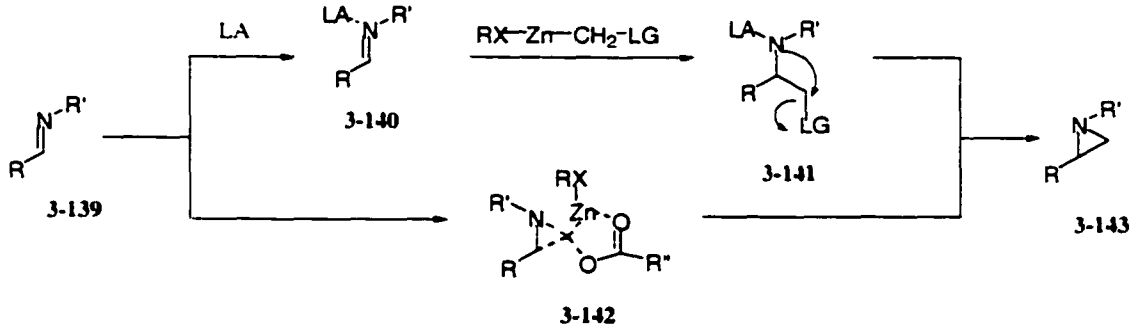
Table 3.4

Complex	solvent	LA/ligand
	CH_2Cl_2	
	CH_2Cl_2	ZnI_2 1eq.
 Et_2Zn 1/1	CH_2Cl_2	
 Et_2Zn 2/1	CH_2Cl_2	
	benzene	 10% to RCHO
 Et_2Zn 2/1	benzene	 10% to RCHO
	benzene	 10% to RCHO
 Et_2Zn 2/1	benzene	 10% to RCHO
CH_2I_2/Et_2Zn 2/1	toluene	 10% to RCHO
 Et_2Zn 2/1	toluene	 10% to RCHO
 Et_2Zn 2/1	toluene	 10% to RCHO
 Et_2Zn 2/1	toluene	 100% to RCHO
	toluene	$Ti(OiPr)_4$
	toluene	$Ti(OiPr)_4$
	toluene	 100% to RCHO
	toluene	 100% to RCHO

3.D.2 Imine Experiments

Chiral aziridines are difficult to prepare directly in high ee.[48] Compared to the vast amount of success in the formation of chiral epoxides and cyclopropanes, aziridine formation remains a largely unsolved problem. Addition of a methylene to an imine in high ee has been reported for a limited class of compounds using several methods.[49]

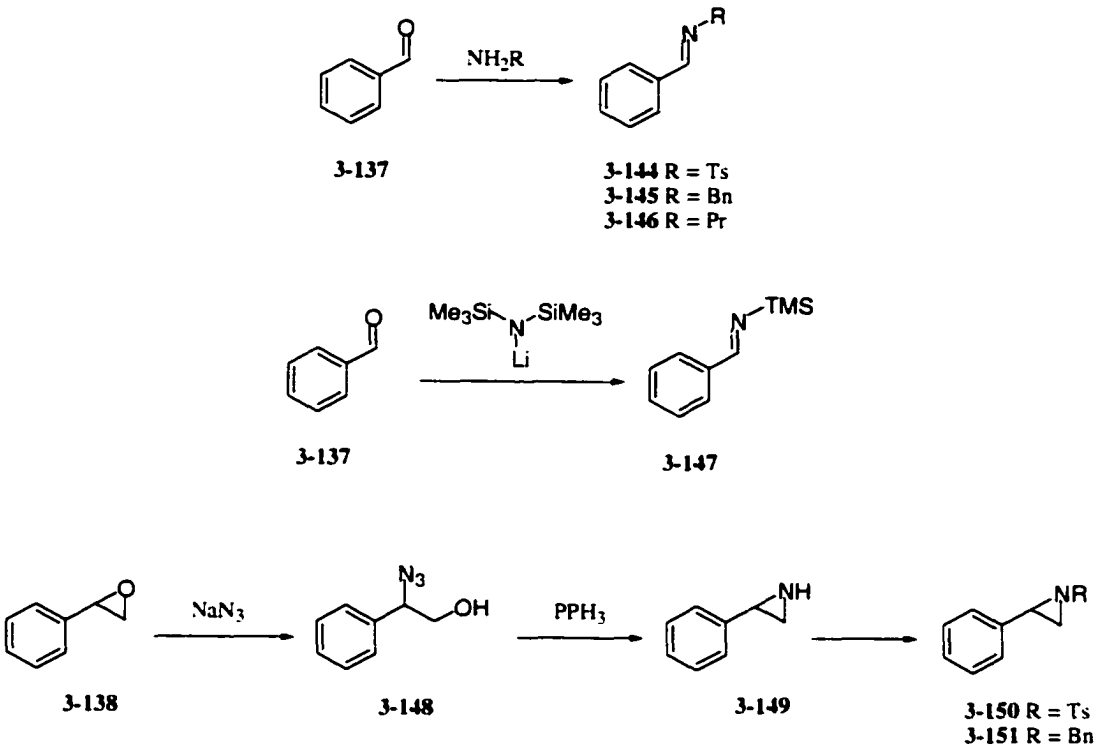
Addition of a carbenoid into the π system of an imine is conceptually similar to cyclopropanation. There is an early report of an imine with electron withdrawing groups on the nitrogen being converted to the aziridine with a Simmons-Smith reagent.[50] Two modes of reaction can be envisioned for this transformation as in cyclopropanation Scheme 3.55.



Scheme 3.55 Aziridination

The nature of both the zinc reagent and imine should contribute to the mode of reaction. The more electron-poor the imine, the more likely the nucleophilic attack. This mode of reaction could also be induced by using a Lewis acid.

Aromatic imines were used since they are stable and the group on the nitrogen was varied from electron-donating to electron-withdrawing. The preparation of the imines and aziridine standards were carried out following literature procedures Scheme (3.56.)



Scheme 3.56 Preparation of Imines and Standards

Imines 3-144, 3-145, and 3-146 were prepared from the primary amine by dehydration of the aldehyde.[51] Silyl-substituted imine 3-147 was produced by addition of lithium bis(trimethylsilyl)amide to benzaldehyde followed by elimination of the silanol.[52] The reference aziridines were formed by addition of sodium azide to styrene oxide followed by a triphenyl phosphine-mediated cyclization.[53,54]

Reactions were monitored by GC and GC/MS, or by ^{1}H NMR spectroscopy of the crude reaction mixtures. None of the cases produced more than a trace amount of aziridine. With the more electron-rich imines it was not uncommon to see decomposition of the imine in the crude ^{1}H NMR spectrum. In general the reaction were run with 2 equivalents of preformed zinc reagent at room temperature in non-coordinating solvents. Some of the cases tried are listed below.

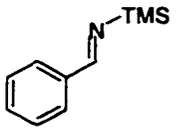
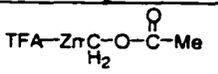
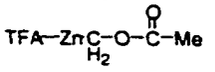
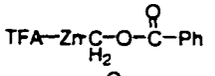
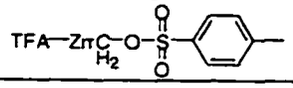


Table 3.5

complex	solvent	LA/ligand
	CH_2Cl_2	
	CH_2Cl_2	$Yb(OTf)_3$ 25%
	CH_2Cl_2	
	CH_2Cl_2	

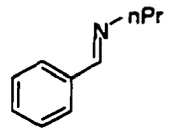
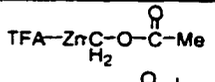
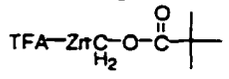
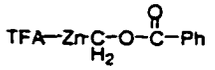
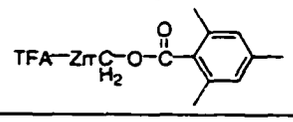


Table 3.6

complex	solvent
	CH_2Cl_2
	CH_2Cl_2
	CH_2Cl_2
	CH_2Cl_2

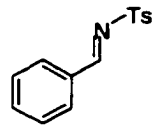
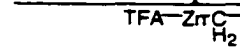
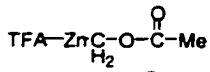
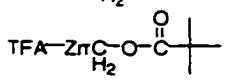
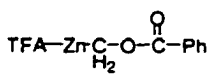
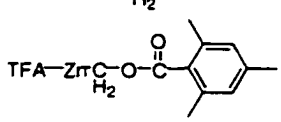
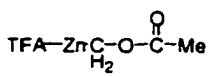
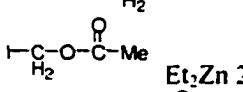
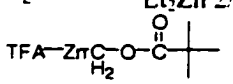
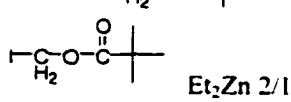
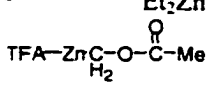
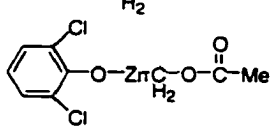
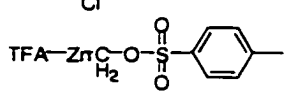
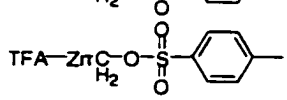


Table 3.7

Complex	solvent	LA/ligand
	CH_2Cl_2	
	CH_2Cl_2	
	CH_2Cl_2	
	CH_2Cl_2	
	CH_2Cl_2	
	CH_2Cl_2	BF_3OEt_2 25%
 Et_2Zn 2/1	CH_2Cl_2	BF_3OEt_2 25%
	CH_2Cl_2	BF_3OEt_2 25%
 Et_2Zn 2/1	CH_2Cl_2	BF_3OEt_2 25%
	toluene	Et_2AlCl 25%
	toluene	Et_2AlCl 25%
	toluene	BF_3OEt_2 10%
	toluene	Et_2AlCl 25%

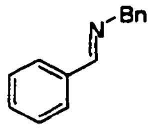
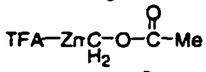
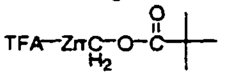
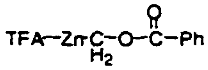
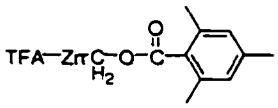
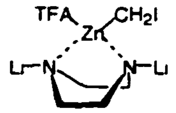
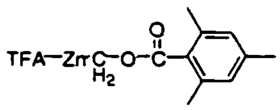
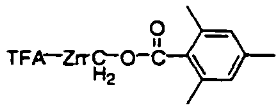
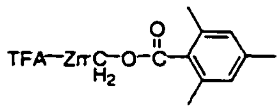
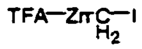
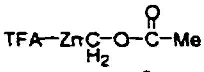
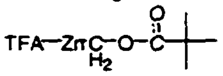
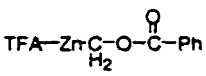
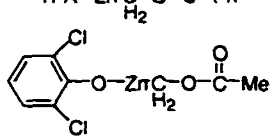
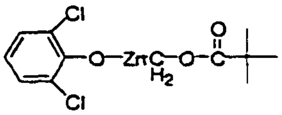
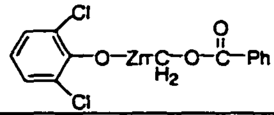
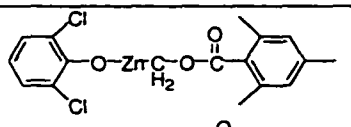
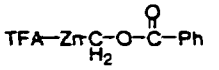
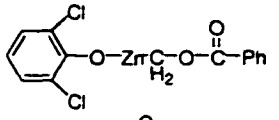
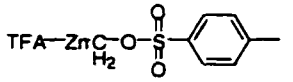
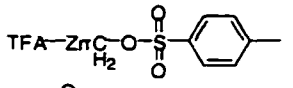
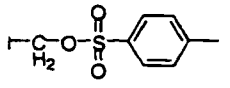
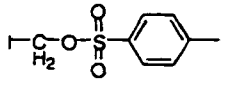
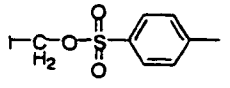
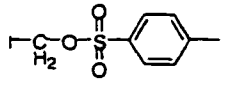
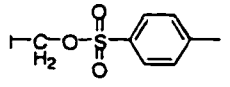
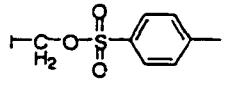
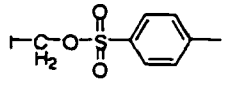
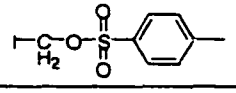


Table 3.8

Complex	solvent	LA/ligand
	CH_2Cl_2	
	CH_2Cl_2	
	CH_2Cl_2	
	CH_2Cl_2	
	toluene	100% piperazine to imine
	CH_2Cl_2	Et_2AlCl 10%
	CH_2Cl_2	BF_3OEt_2 80%
	CH_2Cl_2	BH_3THF 10%
	CH_2Cl_2	BF_3OEt_2 10%
	CH_2Cl_2	BF_3OEt_2 10%
	CH_2Cl_2	BF_3OEt_2 10%
	CH_2Cl_2	BF_3OEt_2 10%
	CH_2Cl_2	BF_3OEt_2 10%
	CH_2Cl_2	BF_3OEt_2 10%
	CH_2Cl_2	BF_3OEt_2 10%

	CH_2Cl_2	BF_3OEt_2 10%
	toluene	Et_2AlCl 25%
	toluene	Et_2AlCl 25%
	toluene	BF_3OEt_2 25%
	toluene	Et_2AlCl 25%
 Et_2Zn 2/1	toluene	BF_3OEt_2 25%
 Et_2Zn 2/1	toluene	Et_2AlCl 25%
 Et_2Zn 2/1	toluene	ZnI_2 25%
 Et_2Zn 2/1	toluene	$Yb(OTf)_3$ 25%
 Et_2Zn 2/1	CH_2Cl_2	BF_3OEt_2 25%
 Et_2Zn 2/1	CH_2Cl_2	Et_2AlCl 25%
 Et_2Zn 2/1	CH_2Cl_2	$Yb(OTf)_3$ 25%
 Et_2Zn 2/1	CH_2Cl_2	ZnI_2 25%

Even though none of the reactions tried produced more than a trace amount of the desired aziridine, the iodomethyl leaving group species could be applied to this problem with different metal systems, or different classes of imines. The use of magnesium, aluminum, samarium or other metals to do carbene, or nucleophilic type addition to imines still needs to be explored.

3.E. Conclusions

A number of new and interesting zinc reagents for cyclopropanation of olefins have been developed. The reactivity of these reagents can be modulated by adjusting the ligand on the zinc, and the leaving group on the methylene. With these two handles on the zinc reagent work is being carried out to develop chiral cyclopropanation reactions. Initial success with chiral ligands on the zinc is currently under study in our lab. The possibility of chiral Lewis-acid mediated cyclopropanation both with ligands on zinc or the leaving groups on the methylene are being investigated. The ability to use a tosylate as a leaving group on the CH_2 source opens the possibility for a chiral leaving group to induce chiral cyclopropanation. There has been little success in applying these reagents to other double bonds, such as aldehydes or imines, but there are still many untried possibilities in both areas. This work can serve as a foundation to build a family of zinc reagents for formation of chiral three membered rings.

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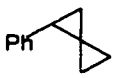
3.F EXPERIMENTAL

Typical procedures for cyclopropanation

Small scale

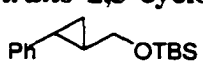
1-phenyl-spirocyclopentane (Scheme 3.32) (jcl-18-20)[1]



To freshly distilled CH_2Cl_2 (2.4 mL) was added Et_2Zn (1.0 M in hexanes)(2.0 mL, 2 mmol) under N_2. The solution was cooled in an ice bath and a solution of trifluoroacetic acid (154 μL, 2.0 mmol) in CH_2Cl_2 (1.0 mL) was added. After stirring for 15 min. a solution of CH_2I_2 (161 μL, 2.0 mmol) in CH_2Cl_2 (0.5 mL) was added and the reaction stirred an additional 15 min. A solution of the 1-methylene-2-phenylcyclopropane (0.130g, 1.0 mmol) in CH_2Cl_2 (1.0 mL) was added and the ice bath removed. After an additional 30 min. of stirring the reaction was quenched with 0.1 M HCl (10 mL) and CH_2Cl_2 (10 mL). The layers were separated and the aqueous layer extracted CH_2Cl_2. The organic layers were combined, washed with sat. $NaHCO_3$, H_2O, brine, dried over Na_2SO_4, concentrated, and purified by column chromatography (silica gel eluted with pentane) to yield a clear liquid (0.0951g, 65% yield). ^{1}H NMR δ 7.28 (m, 2H), 7.16-7.07 (m, 3H), 2.22 (dd, J = 7.8, 4.5Hz, 1H), 1.49 (dd, J = 8.1, 4.2Hz, 1H), 1.01 (t, J = 4.5z, 1H), 0.92 (s, 2H), 0.90 (dd, J = 6.6, 3.1Hz, 1H), 0.75 (d, J = 9.5Hz, 1H); ^{13}C NMR δ 143.3, 128.1, 126.1, 125.2, 22.7, 18.8, 17.9, 7.5, 5.1

Large scale

***trans*-2,3-cyclopropyl-3-phenylpropanol TBS ether** (jcl-06-24)

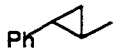


To freshly distilled CH_2Cl_2 (20 mL) was added Et_2Zn (1.0 M in hexanes)(20 mL, 20 mmol) under N_2 (it is best to use an inlet adapter for the nitrogen line since needles often become clogged). The solution was chilled in an ice bath and a solution of triflouroacetic acid (1.54 mL, 20 mmol) in CH_2Cl_2 (10 mL) was slowly dripped into the reaction mixture via syringe. Upon stirring for 20 min. a solution of CH_2I_2 (1.61 mL, 20 mmol) in CH_2Cl_2 (10 mL) was added all at once. After an additional 20 min. a soluntion of (E)-cinnamyl alcohol TBS ether (2.60 g 10 mmol) in CH_2Cl_2 (10mL) was added and the ice bath removed. After an additional 30 min. the reaction mixture was quenched with 0.1 M HCl (50 mL) and 25 mL hexanes, and the layers were separated. The aqueous layer was extracted with hexanes. The combined organic layers were washed with saturated $NaHCO_3$, H_2O, brine, dried over Na_2SO_4, filtered, concentrated, and purified by column chromatography (silica gel eluted with 50/1 hexane/ether) to yield a clear liquid (2.61 g, 95% yield): IR ν 2955, 2933, 2892, 2857, 1605 cm^{-1}; ^1H NMR δ 7.26 (m, 2H), 7.15 (m, 1H), 7.08 (m, 2H), 3.72 (dd, J = 10.8, 5.7Hz 1H), 3.61 (dd, J = 10.8, 6.0Hz 1H), 1.83 (dt, J = 8.5, 4.8Hz 1H), 1.37 (m, 1H), 0.94 (m, 2H), 0.93 (s, 9H), 0.09 (s, 6H); ^{13}C NMR δ 143.3, 128.4, 126.1, 125.5, 66.0, 26.2, 25.4, 20.9, 18.6, 13.7, -5.0. Anal. Calcd for $C_{12}H_{26}OSi$: C, 73.22; H, 9.98. Found: C, 73.19; H, 9.71.

***trans* -Stilbene cyclopropane (3-16)** (jcl-06-36)

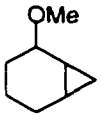
The reaction was run as detailed for the large reaction except 4 eq. of zinc reagent were used. Isolated by column chromatography (silica gel eluted with hexanes) as a clear liquid (1.56g 80% yield). ^1H NMR δ 7.2 (m, 10 H) 2.16 (t, 2 H), 1.44 (dd, J= 8.1, J= 6, 2H); ^{13}C NMR δ 142.7, 128.9, 127.8, 125.9, 28.2, 18.4

***trans*-β-methylstyrene cyclopropane** (Table 3.2)



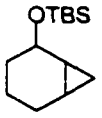
IR ν 1605 cm^{-1}; ^1H NMR δ 7.52 (m, 5H), 1.56 (dt, *J* = 8.4, 4.8Hz 1H), 1.18 (d, *J* = 5.7 Hz 3H), 1.04 (m, 1H), 0.88 (m, 1H), 0.73 (m, 1H); ^{13}C NMR δ 144.3, 128.4, 125.7, 125.4, 24.6, 19.3, 18.2, 17.8.

Bicyclo [4.1.0]heptane-2-methylether (Figure 3.5, entry 1) (jcl-06-33)



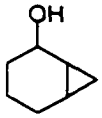
Isolated by column chromatography (silica gel eluted with 10/1 hexane/Et_2O) as a clear liquid (0.0426g 34% yield) 1/1 mixture diasteriomers (NMR), ^1H NMR δ 3.76(q, 1/2 H), 3.47(q, 1/2 H), 3.39 (s, 3 H), 2.0-1.1 (m, br), 0.62 (t d, 1/2 H), 0.35 (q, 1/2 H); ^{13}C NMR δ 75.6, 55.4, 29.9, 29.8, 29.5, 27.3, 23.5, 19.9, 14.0, 12.3, 7.2

Bicyclo [4.1.0]heptane-2-ol TBS ether(Figure 3.5, entry 2) (jcl-06-38)



Isolated by column chromatography (silica gel eluted with 100/1 hexane/ether) as a clear liquid (0.036g 16% yield) in low yield due to S_n1 replacement of the ether with iodomethane.

cis-Bicyclo [4.1.0]heptane-2-ol (3-8) (jcl-06-32)[2]

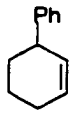


Isolated by column chromatography (silica gel eluted with 2/1 hexane/ether) as a clear liquid (0.047g 42% yield) in a dr = 2.3/1 (NMR). ^1H NMR δ 3.29 (dd, *J* = 6.3, 3.6Hz 0.6 H), 3.15 (dq, *J* = 7.5,9.3Hz 1.4 H), 2.35 (m, 1 H), 1.97 (m, 1 H), 1.88 (m, 1 H), 1.72 (m, 2 H), 1.56 (m, 1 H), 1.40 (m, 2 H), 0.90 (m, 2 H), 0.63 (m, 1H), 0.06 (m, 0.5 H)

1-hydroxy-*trans*-2-cyclopropyl-*trans*-4-hexene (Figure 3.6) (jcl-17-47)

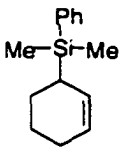
^{1}H NMR δ 5.51 (dq, J = 15.0, 6.3Hz 1H), 5.05 (ddq, J = 15.3, 8.4, 1.8Hz, 1H), 3.49 (dd, J = 6.9, 2.4Hz 2H), 1.64 (dd, J = 6.3, 1.5Hz 2H), 1.4 (s, br 1H), 1.27 (m, 1H), 1.1 (m, 1H), 0.59 (m, 2H)

1-phenyl-2-cyclohexene (3-34) (jcl-15-10)[3]



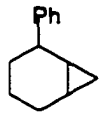
Isolated by column chromatography (silica gel treated w/ 5% w/w $AgNO_3$ eluted with pentane) to give a clear liquid (0.313 g 56%yield) ^{1}H NMR δ 7.52-7.1 (m, Ar 5H), 5.89 (dq, J = 9.9, 3.6Hz 1H), 5.71 (dm, J = 10.2Hz 1H), 3.40 (m, 1H), 2.2-1.9 (m, 3H), 1.8-1.5 (m, 3H)

1-dimethylphenylsilyl-2-cyclohexene (3-36) (jcl-17-04)[4]



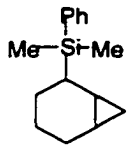
Isolated by column chromatography (silica gel eluted with hexane) to give a clear liquid (1.187g, 5.5 mmol, 61%yield) which gave spectra identical to those in the literature.

2-phenyl-bicyclo [4.1.0]heptane (Figure 3.7 entry 2)



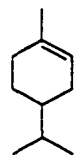
Isolated as a clear liquid after work-up major isomer ^{1}H NMR δ 7.4-7.1 (m 5H), 2.80 (ddd, J = 9.9, 5.4, 2.1Hz 1H), 1.65 (m 2H), 1.45 (m, 2H), 1.1-0.9 (m 4H), 0.66 (ddd J = 8.97, 8.9, 4.4Hz 1H), 0.17 (q, J = 4.95Hz 1H) minor diastereomer cyclopropane shifts 0.68 (ddd J = 8.97, 8.9, 4.4Hz 1H), 0.30 (q, J = 5.13Hz 1H)

2-dimethylphenylsilyl-bicyclo [4.1.0]heptane (Figure 3.7 entry 1) (jcl-17-07)



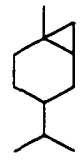
Isolated by column chromatograpy (silica gel eluted with pentane) as a clear liquid (0.097g 90%yield) ^{1}H NMR δ 7.56 (m, 2H), 7.36 (m, 3H), 1.84 (dm, *J* = 10.5Hz 1H), 1.66 (m, 1H), 1.47 (m, 1H), 1.39 (m, 1H), 1.00 (m, 2H), 0.79 (m, 2H), 0.60 (ddd, *J* = 8.7, 4.5, 3.9Hz 1H), 0.32 (s, 3H), 0.29 (s, 3H), 0.068 (dt, *J* = 5.1, 4.8Hz 1H); ^{13}C NMR δ 138.8, 134.1, 128.8, 127.7, 24.2, 23.8, 23.5, 21.8, 12.6, 10.8, 10.2, -4.3, -4.6

dihydro limonene (3-38) (jcl-16-16)



Wilkinson's catalyst (0.25 g) was placed in an argon flushed flask containing benzene (20 mL), and the flask was flusked with H_2 3x then (+)limonene (1.5g 11.0 mmol) was added. The reaction was stirred overnight under 1 atm. of H_2, filtered through a pad of Celite, washed with ether, concentrated, and purification by column chromatography (silica gel eluted with pentane) to yield a clear liquid (1.37g 91% yield). IR ν 2921 cm $^{-1}$; ^{1}H NMR δ 5.3 (m, 1H), 2.04 (m, 1H), 1.95 (m, 2H), 1.75 (m, 2H), 1.64 (s, 3H), 1.47 (hep, *J* = 3.0Hz, 1H), 1.25 (m, 3H), 0.88 (dd, *J* = 6.8, 4.2Hz 6H); ^{13}C NMR δ 134.0, 121.1, 40.2, 32.5, 31.0, 29.2, 26.7, 23.7, 20.2, 19.9

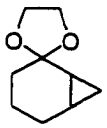
4-isopropyl-1-methyl-1-cyclopropyl cyclohexane (jcl-16-03)



Isolated by column chromatography, (silica gel eluted with pentane) as a 1/1 mixture of diasteriomers (0.053g 71% yield). ^{1}H NMR is uninformative, except for the pairs of

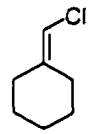
methyl peaks, 1.03 (s, 1/2 3H), 1.02 (s, 1/2 3H), and the isopropyl methyl's 0.831 (dd, J = 6.75, 3.1Hz, 1/2 6H), 0.80 (d, J = 6.75Hz 1/2 6H); ^{13}C NMR δ 41.2, 37.5, 32.8, 32.1, 31.8, 31.6, 28.6, 28.12, 28.07, 27.68, 27.59, 28.5, 24.5, 22.9, 22.6, 20.5, 20.2, 20.1, 20.0, 19.9, 19.8, 18.6, 18.5, 18.2

2-cyclopropyl-cyclohexane ethyl ketal (3-41) (jcl-23-46)



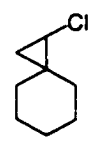
Cyclopropanated using 2,6-dichlorophenol as the ligand on zinc. Isolated by column chromatography (silica gel eluted with 15/1 hexane/ether) as a clear liquid (0.0629g 82% yield). IR ν 2869 cm^{-1}; ^{1}H NMR δ 3.91-4.09 (m, 4H), 1.88 (m, 1H), 1.48-1.59 (m, 3H), 1.31-1.47 (m, 2H), 1.06-1.23 (m, 2H), 0.72 (dt, J = 5.1 Hz 1H), 0.31 (q, J = 5.4Hz 1H) ^{13}C NMR δ 109.4, 64.6, 64.4, 32.0, 22.7, 19.8, 19.0, 12.2, 9.2

cyclohexane methylene vinyl chloride (jcl-18-06)



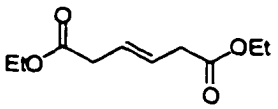
THF (65 mL) was added to dry (chloromethyl)triphenylphosphinonium (7.0 g 20 mmol) and KO*t*Bu (2.46g 21 mmol) and the orange reaction mixture was stirred 1 hour, then cyclohexanone (1.96g 20 mmol) was added and the reaction stirred an additional 4 hours. The reaction was concentrated and purified by column chromatography (silica gel eluted with 25/1 hexane/ether) to give a clear liquid (1.63g 63% yield). IR ν 3068, 1638 cm^{-1}; ^{1}H NMR δ 5.75 (s, 1H), 2.3 (m, 2H), 2.12 (m, 2H), 1.55 (s, br. 6H); ^{13}C NMR δ 142.2, 108.5, 34.3, 28.7, 28.1, 26.8, 26.5

1-chloro-1.5-spirocyclooctane (3-46) (jcl-18-08)



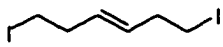
The spiro cyclopropane was seen in the crude ^{1}H NMR, but could not be separate by column chromatography with silica gel. An attempt to remove the starting material and other minor impurities using silica gel treated with 5% $AgNO_3$ resulted in decomposition of the cyclopropane. ^{1}H NMR δ 3.18 (m, 1H), 2.86 (dd J = 7.2, 3.9Hz, 2H), 1.7-1.1 (m, 8H), 0.82 (dd, J = 7.32, 5.85Hz, 1H), 0.54 (dd J = 5.85, 3.84Hz, 1H)

1,6-diethyl-*trans*-3-hexen-dioate (jcl-19-20)[5]



Thionyl chloride (5.1 mL) was added to a solution of *trans*-β-hydromuconic acid (5.0g 35 mmol) in ethanol (75 mL) and heated at reflux. After 12 hours the reaction was cooled to rt, and poured into H_2O, extracted with hexane, washed with 1.0 M NaOH, brine, dried over Na_2SO_4, filtered and concentrated to yield a clear liquid (4.8g 68% yield) which could be used without further purification. IR ν 2983, 1737 cm^{-1}; ^{1}H NMR δ5.70 (dt J = 3.6, 1.5Hz, 2H), 4.14 (q, J = 6.9Hz, 4H), 3.08 (d, J = 5.1Hz, 4H), 1.26 (t, J = 7.2Hz, 6H); ^{13}C NMR δ 171.6, 126.0, 60.8, 38.1, 14.3.

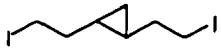
1,6-diiodo-*trans*-3-hexene (3-54) (jcl-19-21/jcl-19-37)



Lithium aluminum hydride (2.5g) was added to a solution of 1,6-diethyl-*trans*-3-hexen-dioate (4.8g 23.5 mmol) in diethyl ether (60 mL) at −15°C. After 2 hours the reaction was quenched by addition of H_2O (2.5 mL), 15% NaOH (2.5 mL) and H_2O (7.5 mL), the white precipitate was removed by filtration, washed 2x with ether, the organic layers were combined, washed with brine, dried over Na_2SO_4, filterd and concentrated to give a clear liquid (2.08g 76% yield) which was taken on directly. Triethyl amine (5 mL) was dripped into a solution of diol (1.32g 11.4 mmol), methane sulfonyl chloride (2.875g 11.4 mmol), in CH_2Cl_2 (35 mL) chilled in an ice bath. After stirring 2 hours the reaction was poured into H_2O, extracted with CH_2Cl_2, the organic layers combined, washed with H_2O,

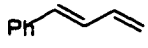
brine, dried over Na_2SO_4, filtered, and concentrated to give a clear liquid. A solution of the the crude mesylate, and dry KI (5.68g 34.2 mmol) in dry acetone (80 mL) was heated at reflux for 2 hours. The reaction was poured into H_2O (50 mL), extracted with hexane, the organic layer combined, washed with H_2O, brine, dried over Na_2SO_4, filtered, concentrated, purified by column chromatography (silica gel eluted with 100/1 hexane/ether) to yield a white solid (1.558g 40% yield). ^1H NMR δ 5.48 (m, 2H), 3.16 (t, J = 7.2Hz 4H), 2.57 (m, 2H); ^{13}C NMR δ 131.4, 36.6, 5.5. (ref : Fink, B. E.; Kym, P. R.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 4334)

1,6-diiodo-*t*-3-cyclopropyl hexane (3-57) (jcl-19-39)



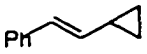
Isolated after work-up as a clean semi-solid, no further purification was required. IR ν 2954 cm^{-1}; ^1H NMR δ 3.23 (t, J = 6.9Hz 4H), 1.78 (m, 4H), 0.73-0.62 (m, 2), 0.389 (dd, J = 6.8, 6.6Hz 2H); ^{13}C NMR δ 37.9, 19.6, 11.2, 6.2

***trans*-1-phenyl-1,3-butadiene (3-74)** (jcl-17-41)



THF (80 mL) was added to a mixture of methyl trimethylphosphonium iodide (12.13g 30 mmol), KO*t*Bu (3.36g 30 mmol) and the mixture stirred for 1.5 hours. A solution of cinnamaldehyde (3.96g, 30 mmol) in THF (10 mL) was added and the reaction stirred an additional 2.5 hours, then filtered. The filtrate was concentrated, allowed to crystalize, the supernate removed and purified by column chromatography (silica gel eluted with hexane) to yield a clear liquid (2.93g 75% yield). IR ν 3028, 1632, 1602 cm^{-1}; ^1H NMR δ 7.40, (dm, J = 7.5Hz, 2H), 7.31 (t, J = 6.9, 2H), 7.24-7.19 (m, 1H), 6.78 (dd, J = 15.0, 11.1Hz 1H), 6.56 (d, J = 15.6, 1H), 6.50 (ddd, J = 17.0, 10.5, 10.0Hz 1H), 5.33 (d, J = 16.8Hz 1H), 5.17 (d, J = 10.2 1H); ^{13}C NMR 137.2, 132.9, 129.7, 128.7, 127.7, 126.5, 117.7

***trans*-1-phenyl-3-cyclopropyl-1-butene (3-72)** (jcl-17-44)

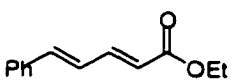


Cyclopropanated using 2,6-dichlorophenol as the ligand on zinc. Isolated by column chromatography (silica gel eluted with hexane) to yield the mono-cyclopropane (0.0563g 78% yield) and bis-cyclopropane (0.0215g 13% yield) as clear liquids. Mono cyclopropane ^{1}H NMR δ 7.3 (m, 4H), 7.15 (m, 1H), 6.46 (d, *J* = 15.9Hz, 1H), 5.72 (dd, *J* = 15.9, 9.0Hz 1H), 1.53 (m, 1H), 0.82 (dm, *J* = 6.39Hz, 2H), 0.51 (dd, *J* = 4.8, 2.0Hz 2H); ^{13}C NMR δ 137.8, 134.9, 128.5, 127.4, 126.5, 125.6, 14.8, 7.5

[1.3.1] tricyclooctane (jcl-18-44)

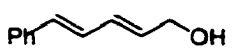
Isolated after work-up as a clear liquid without need for further purification. ^{1}H NMR δ 1.61 (s, 4H), 1.08 (m, 2H), 0.77 (m, 2H), 0.4 (m, 4H); ^{13}C NMR δ 18.1, 11.4, 11.0, 7.6

5-phenyl-*trans,trans*-2,4-pentadiene ethyl ester (jcl-19-03)[6]



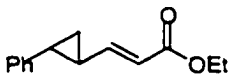
A solution of ethyl(trimethylsilyl)acetate (1.60g 10 mmol) in DMSO (2.0 mL) was slowly added to a mixture of cinnamaldehyde (1.123g 8.5 mmol) and CsF (0.152g 1.0 mmol) in DMSO (2.0 mL) over 15 min. After stirring at rt for 35 min the reaction was heated to 100 °C in an oil bath for an additional 75 min then cooled to rt. The reaction mixture was taken up in ether, washed 3x with H_2O, brine, dried over Na_2SO_4 filtered concentrated and purified by column chromatography (silica gel eluted with 10/1 hexane/ether) to yield a clear liquid (0.702g 3.47 mmol 41% yield) ^{1}H NMR δ 7.5-7.25 (m, 6H), 6.89 (s, 1H), 6.87 (d, *J* = 5.1Hz 1H), 5.99 (d, *J* = 15.6Hz 1H), 4.23 (q, *J* = 7.2Hz 2H), 1.31 (t, *J* = 7.2Hz 3H). ^{13}C NMR δ167.1, 144.6, 140.4, 136.1, 129.1, 128.9, 127.3, 126.3, 121.4, 60.5, 14.6

5-phenyl-*trans,trans*-2,4-pentadienol (jcl-20-14)[7]



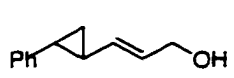
A solution of DIBAL-H (1.0 M in THF) (26 mL 26 mmol) was added to a solution of 5-phenyl-*trans,trans*-2,4-pentadiene ethyl ester (2.611g 13 mmol) in THF (35 mL) at −15°C, the reaction warmed to 0°C and stirred 30min, warmed to rt and stirred a further 30min. The reaction was chilled in an ice bath and saturated NH_4Cl (1.0 mL) was added, filtered, the solid washed with EtOAc , dried over Na_2SO_4, filtered, concentrated, and purified by column chromatography (silica gel eluted with 3/1 hexane/ether) to yield a white solid (1.02g 49% yield) along with recovering starting material. IR ν 3300, 1641 cm^{-1}; ^1H NMR δ 7.2-7.41 (m, 5H), 6.79 (dd, *J* = 15.3, 10.2Hz 1H), 6.57 (d, *J* = 15.9Hz, 1H), 6.42 (dd, *J* = 15.0, 13.8Hz 1H), 5.7 (dt, *J* = 15.0, 5.7Hz 1H), 4.26 (dd, *J* = 5.7, 5.1Hz 2H)

5-phenyl-*trans*-4-cyclopropyl-*trans*-2-pentene ethyl ester (jcl-19-50)



Ethyl(triphenylphosphonium bromide)acetate (4.81g 11.2 mmol) and KO*t*Bu (1.26g 11.2 mmol) in THF (40 mL) were stirred at rt for 1 hour, then a solution of (E)-cyclopropyl-cinnamaldehyde (1.64g 11.2 mmol) in THF (10 mL) was added and the reaction stirred an additional 2.5 hours. The reaction was concentrated, and purified by column chromatography (silica gel eluted with 25/1-10/1 hexane/ether) to yield a clear liquid (1.57g 65% yield). IR ν 1712, 1644, 1605 cm^{-1}; ^1H NMR δ 7.31-7.04 (m, 5H), 6.59 (dd, *J* = 15.3, 9.6Hz 1H), 5.89 (d, *J* = 15.0Hz 1H), 4.18 (q, *J* = 7.2Hz 2H), 2.17 (ddd, *J* = 9.6, 6.3, 3.9Hz 1H), 1.80 (m, 1H), 1.44 (ddd, *J* 9.0, 5.7, 5.4Hz 1H)1.30 (m, 1H), 1.28 (t, *J* = 6.9Hz 3H); ^{13}C NMR δ 166.8, 151.7, 140.9, 128.6, 126.3, 126.0, 119.0, 60.3, 26.97, 26.81, 17.7, 14.4

5-phenyl-*trans*-2-cyclopropyl-*trans*-4-pentenol (jcl-20-06)

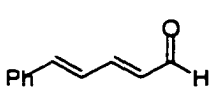


A solution of DIBAL-H (1.0 M in THF) (13.6 mL 13.6 mmol) was added to a solution of 5-phenyl-*trans*-4-cyclopropyl-*trans*-2-pentene ethyl ester (1.474g 6.8 mmol) in THF (20 mL) at –15°C, the reaction warmed to 0°C and stirred 30min, warmed to rt and stirred a further 4 hr. The reaction was chilled in an ice bath and saturated NH_4Cl (1.0 mL) was added, filtered, the solid washed with EtOAc , dried over Na_2SO_4, filtered, concentrated, and purified by column chromatography (silica gel eluted with 4/1-1/1 hexane/ether) to yield a clear liquid (0.89g 75% yield) the bulk of the unreacted starting material was recovered. ^{1}H NMR δ 7.28-7.22 (m, 2H), 7.2-7.11 (m, 1H), 7.10-7.02 (m, 2H), 5.73 (dt, *J* = 15.0, 6.3Hz 1H), 5.39 (dd, *J* 15.3, 8.7Hz 1H), 4.09 (d, *J* = 6.0Hz 2H), 1.91(ddd, *J* = 9.0, 5.7, 4.5Hz 1H), 1.68 (m, 1H), 1.61 (s, OH), 1.21 (ddd, *J* = 8.7, 5.4, 5.1Hz 1H), 1.08 (ddd, *J* = 8.7, 5.4, 5.1Hz 1H); ^{13}C NMR δ 142.1, 125.2, 128.4, 127.4, 125.7, 63.6, 26.3, 25.4, 16.9

anti-*trans,trans*-2,4-dicyclopropyl-5-phenyl-pentanol / syn-*trans,trans*-2,4-dicyclopropyl-5-phenyl-pentanol (jcl-20-16, 17, 18, 19) (jcl-20-9, 10, 11)[8]

^{1}H NMR δ 7.22 (m, 2H), 7.12 (m, 1H), 7.00 (m, 2H) 3.43 (m,2H), 1.64 (m, 2H), 1.15 (m, 1H), 1.0-0.7 (m, 4H), 0.4 (m, 2H); anti diastereomer (100 MHz) ^{13}C δ 148.1, 128.4, 125.8, 125.5, 67.0, 24.62, 22.02, 20.49, 19.57, 18.84, 14.58, 8.81. Cyclopropyl protons for the syn diastereomer (100 MHz) ^{13}C δ 24.46, 22.198, 20.08, 19.54, 18.61, 14.06, 8.018

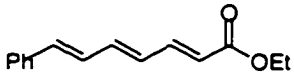
5-phenyl-*trans,trans*-2,4-pentadienal (jcl-21-42)[7]



Oxalyl chloride (2.24g 17.6 mmol) was slowly dripped into a solution of DMSO (2.5 mL 35.3 mmol) in CH_2Cl_2 (30 mL) at –78°C, stirred at –78°C for 10 min. , warmed to rt and stirred 5 min. then recooled to –78°C. A solution of 5-phenyl-*trans,trans*-2,4-pentadienol

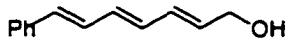
(2.36g 14.7 mmol) in CH_2Cl_2 (30 mL) was added and the reaction stirred at –78°C for 30 min. followed by addition of triethylamine (9.75 mL 73.5 mmol) and stirred an additional 15 min. The reaction was warmed to rt, poured into sat. NH_4Cl , extracted with CH_2Cl_2, the organic layers were combined, washed 2x with H_2O, brine, dried over Na_2SO_4, filtered, concentrated, and purified by column chromatography (silica gel eluted with 4/1 hexane/ether) to yield a clear liquid (2.03g 88% yield). IR ν 2815, 2745, 1678, 1619 cm^{-1}; ^1H NMR δ 9.62 (d, J = 6.9Hz 1H), 7.53-7.48 (m, 2H), 7.42-7.34 (m, 3H), 7.27 (ddd, J = 15.3, 6.9, 3.3Hz 1H), 7.02 (s, 1H), 7.01 (dd J = 3.3, 3.3Hz 1H), 6.27 (dd, J = 15.0, 7.8Hz 1H); ^{13}C NMR δ 193.6, 152.1, 142.5, 135.6, 131.7, 129.8, 129.0, 127.6, 126.2

7-phenyl-*trans,tans,trans*-2,4,6-heptatriene ethyl ester (jcl-21-43)[7]



Prepared by the same method as detailed for 5-phenyl-*trans*-4-cyclopropyl-*trans*-2-pentene ethyl ester from 5-phenyl-*trans,trans*-2,4-pentadienal. Isolated as a yellow solid after work-up and taken on without purification. IR ν 1698, 1626, 1604, 1592 cm^{-1}; ^1H NMR δ 7.45-7.40 (m, 2H), 7.37-7.22(m, 4H), 6.86 (dd, J = 14.7, 10.5Hz 1H), 6.75-6.66 (m, 2H), 6.42 (dd, J = 14.7, 11.1Hz 1H), 5.91 (d, J = 15.0Hz 1H), 4.21 (q, J = 7.2Hz 2H), 1.30 (t, J = 7.2Hz); ^{13}C NMR δ 167.1, 144.4, 140.8, 136.7, 130.3, 128.8, 128.5, 128.0, 126.9, 121.0, 60.4, 14.5

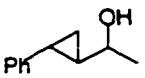
7-phenyl-*trans,trans,trans*-2,4,6-heptatrienol (jcl-21-43)[7]



Reduced following the proceedure described for 5-phenyl-*trans*-2-cyclopropyl-*trans*-4-pentenol, starting from 7-phenyl-*trans,tans,trans*-2,4,6-heptatriene ethyl ester. Isolated by column chromatography (silica gel eluted with 4/1 hexane/ether) to yield a white powder (1.00g 44% yield over two steps). mp = 115-118 °C; ^1H NMR δ 7.44-7.20 (m, 5H), 6.82 (dd, J = 15.9, 9.9Hz 1H), 6.56 (d, J = 15.6Hz 1H), 6.42-6.30 (m, 3H), 5.89 (dt,

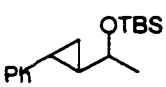
14.7, 5.7Hz 1H), 4.22 (d J = 5.7Hz 2H), 1.45 (s, OH); ^{13}C NMR δ 137.4, 133.6, 133.0, 132.52, 132.46, 131.7, 128.9, 128.8, 127.7, 126.5, 63.5

***trans*-3-cyclopropyl-4-phenyl-butan-2-ol (3-98/3-99)** (jcl-21-48, jcl-23-3,4,12)[9]



The syn/anti mixture used as a reference standard was prepared following Charette's proceedure. Isolated by column chromatography (silica gel eluted with 3/1 hexane/ether) to yield a clear liquid. syn isomer ^{1}H NMR δ 7.25 (m, 2H), 7.15 (m, 1H), 7.06 (m, 2H), 3.37 (pent. J = 6.9Hz 1H), 1.80 (ddd, J = 9.6, 5.4, 4.2Hz 1H), 1.66 (s, br. OH) 1.34 (d, J = 6.3Hz, 3H), 1.26 (m, 1H), 0.95 (m, 2H). ^{13}C NMR δ 142.5, 128.4, 126.0, 125.7, 71.9, 30.9, 22.9, 20.9, 14.0

***trans*-3-cyclopropyl-4-phenyl-butan-2-dimethyl-*t*-butyl siloxane (3-102)** (jcl-20-30)



Isolated by column chromatography (silica gel eluted with 100/1 hexane/ether) to yield a clear liquid (0.051g 37% yield). anti isomer ^{1}H NMR δ 7.4-7.2 (m, 5H), 3.74 (dd, J = 6.3, 6.0Hz 1H), 2.02 (dt, J = 8.7, 5.4Hz, 1H), 1.37 (d, J = 6.0Hz, 3H), 1.32 (m, 1H), 1.01 (s, 9H), 1.0 (m, 1H), 0.18 (d, J = 4.2H 6H) ^{13}C NMR δ 128.3, 126.2, 125.4, 113.2, 70.3, 30.8, 26.0, 24.0, 20.4, 12.7, -4.3

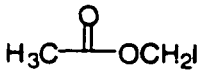
iodomethyl acetate (3-114) (jcl-24-28)[10]

Cyclopropanation with an alternative CH_2 Source

To freshly distilled CH_2Cl_2 (1.0 mL) was added Et_2Zn (1.0 M in hexanes)(0.5 mL, 0.5 mmol) under Ar. The solution was cooled in an ice bath and a solution of trifluoroacetic acid (38 μL, 0.5 mmol) in CH_2Cl_2 (0.5 mL) was added. After stirring for 15 min. a solution of iodomethyl benzoate (0.130g, 0.5 mmol) in CH_2Cl_2 (0.5 mL) was added and

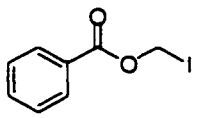
the reaction stirred an additional 15 min. A solution of the 1-phenylcyclohexene (40 μL, 0.25 mmol) in CH_2Cl_2 (0.5 mL) and diethyl aluminum chloride (1.0 M in hexane) (125 μL 0.125 mmol) was added and the ice bath removed. Aliquots were removed, taken up in $CHCl_3$, washed with H_2O, dried over $MgSO_4$ and analyzed by GC.

Iodomethyl acetate (3-144) (jcl-24-28)



Finely powdered paraformaldehyde (1.95 g, 65 mmol) was added in small portions to freshly prepared acetyl iodide (11.158 g, 66 mmol) (prepared from acetyl chloride and TMSI).[11] After the addition was complete the flask was fitted with a condenser and the reaction stirred in a 100 °C oil bath for 1 hr. After cooling to rt copper dust was added, the reaction was fractionally distilled under vacuum (1.5mm Hg) with the distillate collected at -78 °C. Iodomethyl acetate was collected at 28 °C and stored in the freezer over copper dust under argon in a dark bottle. IR ν 1762 cm^{-1}; ^1H NMR δ 5.90 (s, 2H), 2.10 (s, 3H); ^{13}C NMR δ 168.7, 30.8, 21.2.

iodomethyl benzoate (3-118) (jcl-24-24)[12]

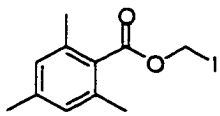


Benzoyl chloride (70.3 g 500 mmol) was added dropwise over an hour to a mixture of paraformaldehyde (dried over P_2O_5) (15.0 g 500 mmol) and dry $ZnCl_2$ (1.36 g 10 mmol) chilled in an ice bath. After the addition was complete the reaction was stirred in at 50-55°C in an oil bath for 8 hours then cooled to rt, Cu^0 dust and distilled under vacuum to yield a clear liquid which can be stored in the freezer under Ar.

In a dark room chloromethyl benzoate (7.33 g 43 mmol) was dripped into a solution of NaI(dry) (7.5 g 50 mmol) in CH_3CN(dry) (60 mL) over 25 min. and the reaction was stirred in the dark for 24 hours. The reaction was filtered, concentrated, taken up in

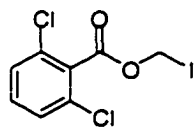
toluene (70 mL), washed 2x with 5% $NaHSO_3$, H_2O, dried over Na_2SO_4, filtered, concentrated, and purified by vacuum distillation (1.5 mm Hg) from Cu° dust, a clear liquid was collected at 78-90°C. IR ν film 1739, 1600 cm^{-1}; ^1H NMR δ 8.03 (d J = 7.2Hz 2H), 7.61 (t J = 7.2Hz 1H), 7.46 (t J = 7.5Hz 2H), 6.16 (s, 2H); ^{13}C NMR δ 164.6, 133.9, 130.0, 128.8, 128.6, 31.3

iodomethyl 2,4,6-trimethyl-benzoate (3-119) (jcl-25-24)



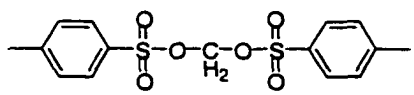
Prepared from 2,4,6-trimethyl benzoyl chloride by the same method as **3-118**. Purified by column chromatography (silica gel eluted with 15/1 hexane/ether) to yield a clear liquid (2.56 g 81% yield). IR ν film 1743, 1611 cm^{-1}; ^1H NMR δ 6.85 (s, 2H), 6.10 (s, 2H), 2.31 (s, 6H), 2.28 (s, 3H); ^{13}C NMR δ 168.0, 140.4, 136.1, 128.8, 30.7, 21.43, 20.19

iodomethyl 2,6-dichloro-benzoate (3-120) (jcl-25-23)



Prepared from 2,6-dichloro benzoyl chloride as described for **3-118**. Purified by column chromatography (silica gel eluted with 25/1 hexane/ether) to yield a clear liquid (1.225g 74% yield) which was stored in the freezer over Cu° dust. IR ν film1792, 1564 cm^{-1}; ^1H NMR δ 7.4-7.2 (m, 3H), 5.94 (s, 2H)

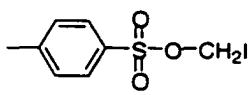
bis-tosylmethane (3-122) (jcl-25-32)[13]



A solution of tetrabutyl ammonium bromide (1.1 g, 3.4 mmol) and methyl tosylate (9.4 mL, 62.4 mmol) was heated to 85°C to form a clear solution, then the reaction was cooled to about 40°C and chloroiodomethane (10.0 g, 56.7 mmol) was added and the flask fitted for distillation. The reaction was heated at 130°C for 2 hours until no more

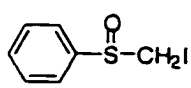
liquid came over then the reaction temperature was increased to 140°C for an additional hour. The oil bath was turned off and after the reaction cooled to rt boiling Et_2O (400 mL) was added and a white solid formed upon cooling. The crude white solid was purified by column chromatography (silica gel eluted with 1/1 hexane/EtOAc) to yield white crystals (1.947 g 18% yield). IR ν film 1597, 1371, 1193, 1178 cm^{-1}; ^1H NMR δ 7.59 (d J = 8.4Hz 4H), 7.24 (d J = 9.0Hz 4H), 5.81 (s, 2H), 2.45 (s, 6H); ^{13}C NMR δ 145.3, 133.1, 129.6, 127.8, 87.9, 21.8

iodomethyl tosylate (3-123) (jcl-25-34)[13]



A solution of dry sodium iodide (1.23 g 5.46 mmol) in dry acetone (3.75 mL) was added to a solution of bis-tosyl methane (1.95 g, 5.46 mmol) in dry acetone (11.25 mL). The flask was fitted with a condenser and heated in a 50 °C oil bath for 5 min. and a white precipitate formed. The reaction was filtered, the filtrate taken up in Et_2O (50 mL) the organic layer was washed with H_2O, sat $NaHSO_3$, H_2O, brine, dried over Na_2SO_4, filtered, concentrated, and purified by Kuglerohr distillation 153-157°C 0.5mmHg to give a light yellow oil (1.204g 71% yield). IR ν film 1570 cm^{-1}; ^1H NMR δ 7.83 (d J = 8.4Hz 2H), 7.38 (d J = 8.1Hz 2H), 5.90(s, 2H), 2.47(s, 3H); ^{13}C NMR δ 145.9, 132.2, 130.0, 128.5, 32.8, 22.0.

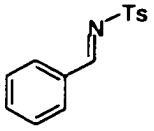
iodomethyl phenyl sulfonate (3-126)(jcl-25-46)[14]



Dry NaI (0.664g 4.4 mmol) was added to a solution of chloromethyl sulfonate (0.350g 2.0 mmol) in DMSO (2.0 mL). After stirring for 9 hours the reaction was filtered, washed with CH_3CN, concentrated and crystalized from water to give (0.063g 11%

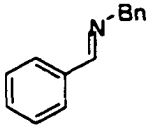
yield). IR ν film 3054, 3003, 2932 cm^{-1}; ^1H NMR δ 7.64 (m, 2H), 7.56 (m, 3H), 4.41 (d, *J* = 10.2Hz 1H), 4.16 (d, *J* = 9.9Hz 1H); ^{13}C NMR δ 142.6, 131.8, 129.1, 124.6, 25.5

benzyl-tosylsulfonate imine (3-144) (jcl-25-47)[15]



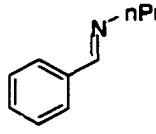
A solution of benzaldehyde (2.63g 26.52 mmol), p-toluenesulfonamide (4.54g 26.5mmol) $BF_3 \bullet OEt_2$ (50 μL) in toluene (150 mL) was refluxed with a Dien-Stark trap for 12 hr. The reaction was washed 2x with 1.0M NaOH, 2x with H_2O, dried over Na_2SO_4, filtered, concentrated, and purified by crystalization from CH_2Cl_2/pentane (5.72g 83% yield). IR ν film 1597, 1574 cm^{-1}; ^1H NMR δ 9.03 (s, 1), 7.90 (m, 4H), 7.61 (t *J* = 7.2Hz 1H), 7.48 (t *J* = 7.8Hz 2H), 7.34 (d *J* = 8.1Hz 2H), 2.43 (s, 3H); ^{13}C NMR δ 169.9, 144.4, 135.0, 134.8, 132.2, 131.2, 129.7, 129.0, 128.0, 21.7

benzyl-N-benzyl imine (3-145) (jcl-26-08)[16]



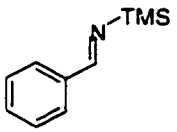
A mixture of benzaldehyde (3.18g 30 mmol) benzyl amine (3.21g 30 mmol) and $MgSO_4$ in benzene (60 mL) was stirred at rt for 2.5 hours. The reaction was filtered, concentrated and purified by vacuum distillation (104-106°C 2 mm Hg) to yield a clear liquid (5.09g 87% yield). IR ν film 3064, 3027, 2839, 1644, 1600, 1580 cm^{-1}; ^1H NMR δ 8.39 (s, 1H), 7.78 (dd, *J* = 5.7, 2.1Hz 2H), 7.42 (d, *J* = 2.4Hz 2H), 7.40 (d, *J* = 1.5Hz 1H), 7.34 (d *J* = 4.5Hz 4H), 7.26 (dd *J* = 5.4, 3.3Hz 1H), 4.83 (s 2H); ^{13}C NMR δ 161.8, 139.1, 136.0, 130.7, 128.5, 128.4, 128.2, 127.9, 126.9, 65.0

benzyl-N-propyl imine (3-146) (jcl-25-49)



Prepared by the method described for **3-145**, Purified by vacuum distillation (91-97°C 2.5 mm Hg) to yield a clear liquid (3.82g 87% yield). IR ν film, 3062, 3027, 2960, 2930, 2873, 2832, 1646, 1580 cm^{-1}; ^1H NMR δ 8.27(s, 1H), 7.72(dd J = 5.7, 2.7, 2H), 7.41(m 3H), 3.58(t J = 6.9, 2H), 1.73(hex J = 7.2, 2H), 0.96(t J = 7.5, 3H); ^{13}C NMR δ 160.7, 130.3, 128.4, 127.9, 63.5, 24.1, 12.0

benzyl-N-trimethylsilyl imine (3-147) (jcl-26-43)[17]



A solution of Lithium Hexamethyldisilazane (1.0 M in hexane) was concentrated to 1/3 of its original volume under vacuum and benzaldehyde (1.59g 15 mmol) was added at 0°C. The reaction was allowed to warm to rt over 2.5 hr then purified by vacuum distillation to yield a light yellow liquid (1.384g 51% yield). ^1H NMR δ 8.97 (s, 1H), 7.80 (m, 2H), 7.44 (m, 3H), 0.26 (s, 9H); ^{13}C NMR δ 168.3, 158.0, 131.2, 128.4, 127.1, -1.0

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