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STUDIES DIRECTED TOWARD ENANTIOSELECTIVE CATALYSIS

by

Brian E. Jones

A THESIS

Presented to the Faculty of
The Graduate College at the University of Nebraska
In Partial Fulfillment of the Requirements
For the Degree of Master of Science

Major: Chemistry

Under the Supervision of Professor James M. Takacs

Lincoln, Nebraska

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STUDIES DIRECTED TOWARD ENANTIOSELECTIVE CATALYSIS

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University of Nebraska, 1995

Adviser: James M. Takacs

Many organic molecules of modest size and complexity have chirality. That is, these molecules can exist in more than one stereoisomeric form. There is a strong desire to synthesize chiral compounds that exist in the form of a single stereoisomer. The method of synthesizing chiral compounds that was studied in our research employed a less than stoichiometric amount of chiral catalyst to both catalyze and control the stereochemical outcome of the reactions attempted.

A new chiral ligand was developed to be used as part of the chiral catalyst. This new ligand was used in the enantioselective Diels-Alder cycloaddition reaction and the enantioselective allylation reaction in the attempt to synthesize products of high enantiomeric purity.

Acknowledgements

To Dr. James M. Takacs and his research group members that I've worked next to past (Dr. Sithamalli "Mouli" V. Chandramouli, Dr. John J. Weidner) and present (Lei Zhang, Francis Clement, Scott C. Boito, Ed C. Lawson, Rajan V. Athalye, Steve J. Mehrman, Dave A. Quincy), including the undergraduates (John "Chad" Byrd, Greg S. Timm, Mark A. Youngman, Kevin L. Reiman), the post-doctoral fellows (Dr. Bill R. Shay, Dr. Adrian "Sam" Vellekoop, Dr. Kevin J. Koeller), and the new members (Carol L. Walters, John A. Dickmeyer) for freely giving advice and giving my research results even more meaning. I also gratefully acknowledge Dr. Charles Ross for determining the structure of ligand **6**, via xray crystallography using the facilities in the UNL laboratory of Professor John J. Stezowski, which is shown in Figure 4 of the text.

For helping me to cope with problems seemingly on a daily basis, I wish to thank these fine ladies: Jasmine R. Mayhew, for reading very rough drafts of this thesis and for telling me that when I least expect it ...; Terry Schneider, for being there, listening, and giving me something good to look at; Marijean Nelson Eggen, for giving great professional advice and being fun to work with; Laura Elizabeth "Bess" Ingalls Wilder, I am very proud to have met you and your world through the "Little House" books.

Dedications

To Elissa W. Johnson, whose support for me to "go back to" and "stay in" school may have cost her a mate. Words are not enough, but thanks for everything.

To Dr. Leo A. Paquette of The Ohio State University, who lit the fire of desire to enjoy chemistry within me, thanks for getting me started.

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I. Introduction

As a consequence of the tetrahedral nature of carbon, most organic molecules of even modest complexity are chiral; that is, they can exist in two mirror image (enantiomeric) forms. In the case of pharmaceuticals and agrochemicals, one enantiomer of the compound is often largely responsible for the desired biological activity of the substance. Furthermore, harmful side-effects are sometimes associated with the "wrong" enantiomer.^{1,2} It is now recognized that in most cases single enantiomer drugs and agrochemicals will be the standard for the industry. Therefore, efficient, reliable, general synthetic methods for the synthesis of enantiomerically pure compounds are needed.

A number of approaches toward asymmetric synthesis have been defined.^{3,4} Among these, methods to synthesize compounds in high yield and high enantiopurity from *achiral starting materials* have long attracted interest.^{5,6,7,8,9} Two general approaches have been defined. One employs a chiral reagent in stoichiometric amounts to control the stereochemical course of the reaction. The second approach, the one that is commonly exploited in nature through the use of enzymes, employs a sub-stoichiometric amount of a chiral catalyst to both catalyze and control the stereochemical course of the organic reaction. The latter approach, termed enantioselective or asymmetric catalysis, is a rapidly growing field of research.

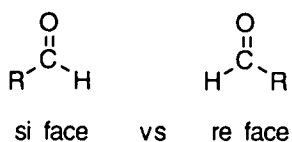
The advantages of the enantioselective catalysis approach are clear. Catalytic versus stoichiometric amounts of chiral reagent lowers the cost. In theory, it is possible to recover and reuse the chiral catalyst. Fewer side products should be formed compared to stoichiometric reagents thus reducing the amount of waste generated by the reaction. The

only disadvantage of asymmetric catalysis is that it proves difficult to design efficient catalysts and predict the stereochemical outcome. In part the difficulty lies in the lack of mechanistic detail known for the catalyzed reaction.¹ Furthermore, there are no well-defined general rules for the design of efficient chiral catalysts.¹ In the Takacs research group, the research on enantioselective catalysis seeks to develop efficient chiral metal catalysts for a variety of organic reactions. Although to date there is no general set of design requirements for such catalyst systems, several attempts to define approaches have been made.

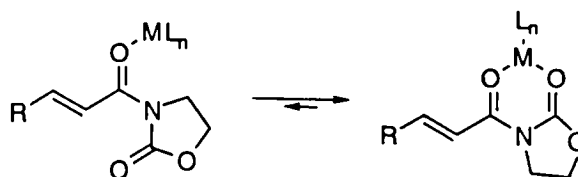
It suggested two requirements that should be met in order to achieve a highly enantioselective reaction when using chiral metal catalysts¹⁰: 1) The prochiral center that undergoes reaction in the achiral substrate should be held close proximity to the chiral metal center. A prochiral molecule is defined as an achiral molecule possessing enantiotopic groups or faces. An example relevant to our studies is the aldehyde shown in Figure 1. The aldehyde is planar and the two sides or faces of the pi-system are reflected through the plane. 2) The reacting substrate should have two coordination sites and form a chelate complex with the chiral metal in the enantiodifferentiating transition state. Chelation of the reacting substrate about the central metal reduces the number of degrees of freedom (i.e. free rotation) in the transition state, and as a consequence, it becomes easier for the asymmetric environment imposed by the chiral ligand to be translated to control of the stereochemistry of the product.

Figure 1. Prochirality and chelation.

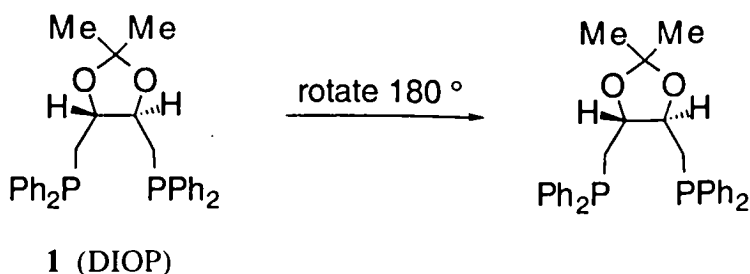
The enantiotopic faces of an aldehyde



The formation of a metal chelate

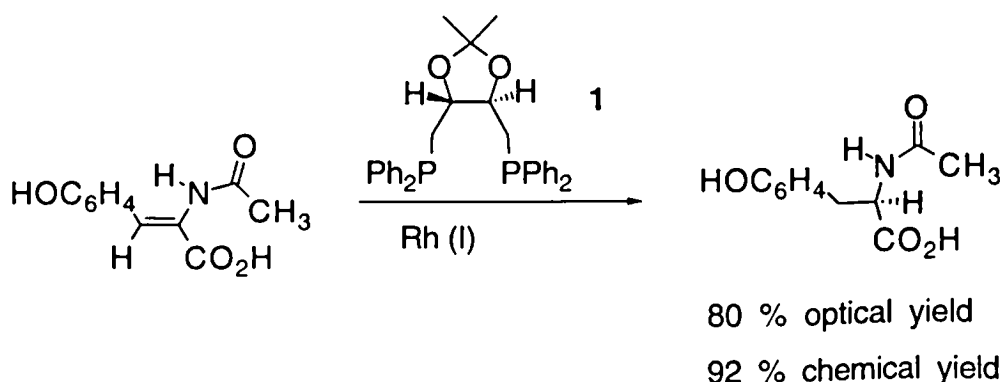


A third design criterion, championed by Whitesell, advocates the use of chiral ligands possessing a C_2 axis of symmetry.¹¹ C_2 -symmetry is present when simple rotation about an axis passing through the molecule by a 180° angle gives a structure that is identical to the structure prior to the rotation. Ligands possessing C_2 -symmetry, it is argued, have fewer diastereomeric modes of complexation, and thus reduce the number of possible competing diastereomeric transition states.¹¹ With fewer competing diastereomeric reaction pathways, it is reasonable that products may be formed with higher enantioselectivity. An example of a famous C_2 -symmetric ligand is the 2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenyl-phosphino)butane (DIOP) ligand **1** developed by Kagan and coworkers.¹² DIOP was the first chiral ligand to achieve high selectivity for one enantiomer over the other in a hydrogenation reaction.

Figure 2. A C_2 -symmetric ligand, the bis-phosphine DIOP.

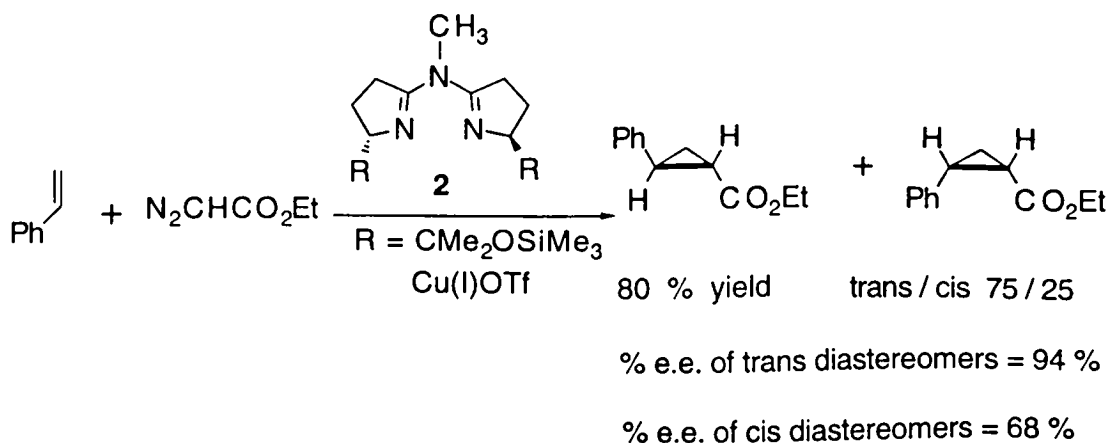
By way of definitions, the excess of one enantiomer over the other is described by the ratio of R:S, or more commonly by the percent optical purity (% o.p.) or equivalently by the percent enantiomer excess (% ee). The formula for calculating the per cent optical purity is: % o.p. = $[\alpha]_D$ of the mixture of enantiomers / $[\alpha]_D$ pure enantiomer x 100 %), with $[\alpha]_D$ being the specific optical rotation. The formula for calculating the per cent enantiomeric excess is % e.e. = $|R - S| / (R + S)$, with R being the amount of the R enantiomer and S being the amount of the S enantiomer.¹³ The DIOP ligand was used for the hydrogenation of a double bond to a single bond as shown in Scheme 1. An % ee of 90 % was obtained at the time, even more efficient catalysts have since been discovered.

Scheme 1. The asymmetric effect of DIOP (**1**) and other C_2 -symmetric chiral ligands.



A second example of a C_2 -symmetric ligand that has afforded interesting results is the chiral aza-semicorrin ligands developed by Pfaltz and coworkers.¹⁴ As illustrated below, ligand **2** was used in the catalysis of the efficient asymmetric cyclopropanation of alkenes such as styrene.¹⁴ These reactions proceed in high enantiomeric excess, 94 % ee for the *trans*-diastereomer. The ligand is C_2 -symmetric, chelates to the catalytic metal center through the nitrogens, and has a substituent alpha to the nitrogen that points toward

the metal center defining a chiral environment at the metal center. The substituent on the carbon alpha to the nitrogen is thought to have a strong influence on any chirality generated in the reaction product. This is because the chiral group blocks the approach of other molecules from that one side. Note that the ligand is relatively rigid and this characteristic may further suppress the number of conformations available to the reaction transition state.



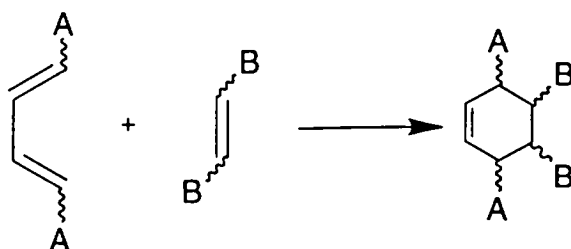
These two examples illustrate the design concepts defined by Ito and by Whitesell and serve to acquaint the reader with the very active field of enantioselective catalysis, which is the general field of this thesis. Furthermore, the Pfaltz ligand is structurally related to the ligands examined in the course of this research as described in the following section of this thesis. The precise chemical reactions investigated however were quite distinct. A new, bidentate nitrogen ligand was synthesized and its effectiveness in promoting asymmetric Diels-Alder cycloaddition and allylstannane addition reactions with zinc triflate, copper triflate, and magnesium triflate was investigated. A detailed rationale for its synthesis and the results obtained with this new ligand are described below.

II. Results and Discussion

This research deals with the challenges of enantioselective catalysis. A new, bidentate nitrogen ligand was synthesized. Its design was based on the postulate that while the known chiral bidentate bisoxazoline ligands reported to date are C_2 -symmetric as the free ligand, their metal complexes lack C_2 -symmetry because the nitrogen-to-nitrogen distance is too close. The new ligand is constrained to a bigger bite angle. Two chemical reactions that are susceptible to Lewis acid catalysis were chosen to evaluate the efficacy of the chiral Lewis acid complexes formed by complexing the ligand to magnesium-, zinc- and copper triflate salts. The results obtained in the Diels Alder cycloaddition reaction between cyclopentadiene and a chelating dienophile (the N-acyloxazolidinones derived from acrylic and crotonic acids) will be discussed first. Later in this section, the corresponding chiral Lewis acid catalyzed reaction of benzaldehyde with allyltributylstannane will be discussed.

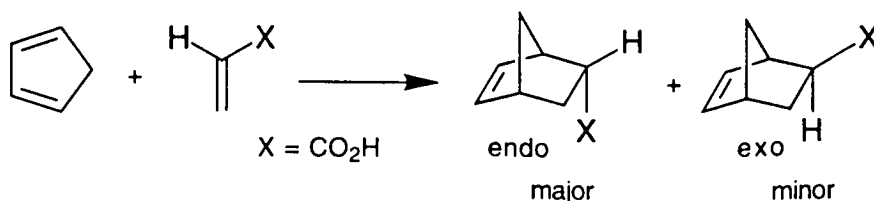
Enantioselective Diels-Alder Cycloaddition Reactions. The Diels-Alder reaction (shown in Equation 1) has long been an important carbon-carbon bond forming reaction. There are two new carbon-carbon single bonds formed resulting in a new six member ring, a new carbon-carbon double bond, and up to four new stereocenters at the atoms where the carbon-carbon bonds are formed (Equation 1). In normal electron demand Diels-Alder reactions (the type we will be discussing below), the diene will have an electron donating group(s) and the dienophile will have an electron withdrawing activating group(s).

Equation 1. The Diels-Alder cycloaddition reaction and its potential sites for stereochemical control.



In the Diels-Alder reaction of cyclopentadiene with an unsymmetrical dienophile, two stereoisomeric modes of cycloaddition are possible. In the example shown below in Equation 2, these stereoisomeric products differ with respect to whether the dienophile activating substituent, X (*e.g.*, X = CO₂H, N-acyl oxazolidinone, or other carbonyl derivative) ends up in the *endo* or *exo* orientation within the bicyclic ring system. The two addition modes have been termed *endo* and *exo*. It has been observed that the *endo* product generally forms in greater amounts than the *exo* product.^{13,15} The *endo* mode is favored over the *exo* mode by secondary orbital overlap of the pi bonds within the transition state.

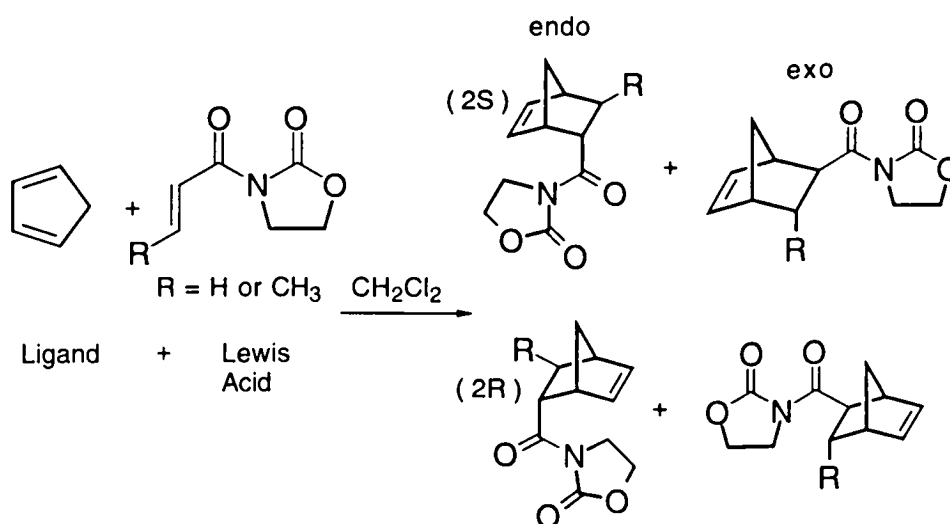
Equation 2. Endo and *exo* product formation in the Diels-Alder reaction.



In normal electron demand Diels-Alder reactions, Lewis acids catalyze the reaction permitting the reaction to be carried out by allowing the reagents to react under milder, even very low temperature (-100 °C) conditions. Lewis acid catalyzed reactions often have

the added benefit over thermal conditions of improving the endo selectivity of the reaction.^{13,15} The catalysts presumably complex to a Lewis basic site on the dienophile (usually, the carbonyl oxygen). N-acyloxazolidinone derived from α,β -unsaturated acids have been popular dienophiles for Diels-Alder cycloadditions, particularly in the context of investigations into enantioselective catalysis. The reason for the popularity stems at least in part from the fact that they form chelated complexes with bidentate Lewis acids.^{16,17} That chelation to the Lewis acid defines the position of a (chiral) Lewis acid to the reacting sites in the cycloaddition reaction. We have used the N-acyloxazolidinones shown below during the course of our studies. Equation 3 shows the two enantiomeric endo products and two enantiomeric exo products possible in the reaction of cyclopentadiene with simple N-acyloxazolidinones.

Equation 3. The possible products of this Diels-Alder reaction.

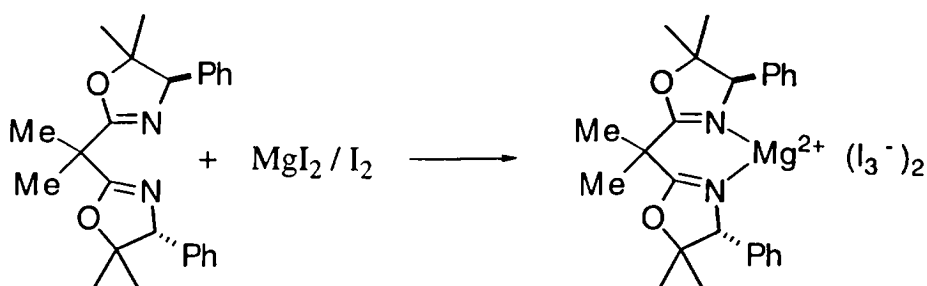


Recently, Corey and Evans have developed chiral bisoxazoline-Lewis acid complexes to catalyze the Diels-Alder reaction of cyclopentadiene (and certain other dienes) with N-acyloxazolidinones (Scheme 2).^{18,19} Note that for simplicity only the major

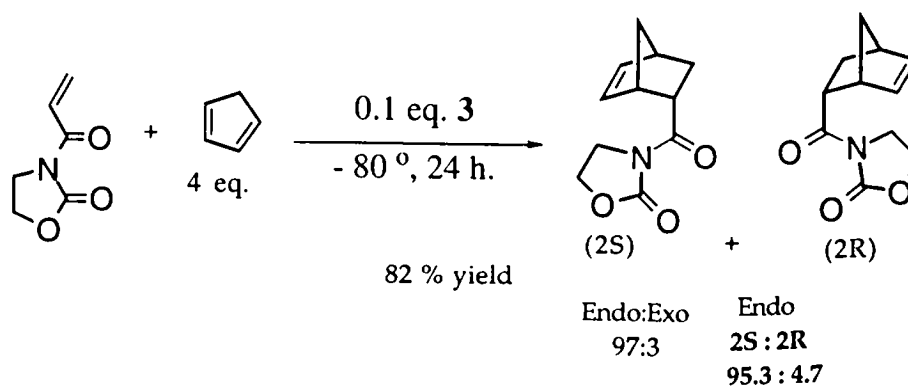
products, the enantiomeric endo isomers, are shown. There are a number of similarities between the catalysts systems. Both systems afford high levels of endo-to exo selectivity and as well produce the endo isomer with a high level of enantioselectivity (> 90 % ee). Both use simple cationic metal salts as the Lewis acids and stable anion counter ions. It is important to note that the anion must dissociate from the metal to accommodate dienophile binding. Although the two catalyst systems use very different counter ions, they share a common feature in that the anions are stable and should readily dissociate as required. The ligands employed are also quite similar. Note that while the substituents adjacent to nitrogen (the substituents that should provide the chiral environment about the metal center) are different (phenyl vs *tert*-butyl), the absolute configurations are the same. This point highlights the biggest difference between the two systems. The Corey catalyst gives predominantly the 2S product; the Evans the 2R!

Scheme 2. The enantioselective Diels-Alder reactions catalyzed by chiral Lewis acids using:

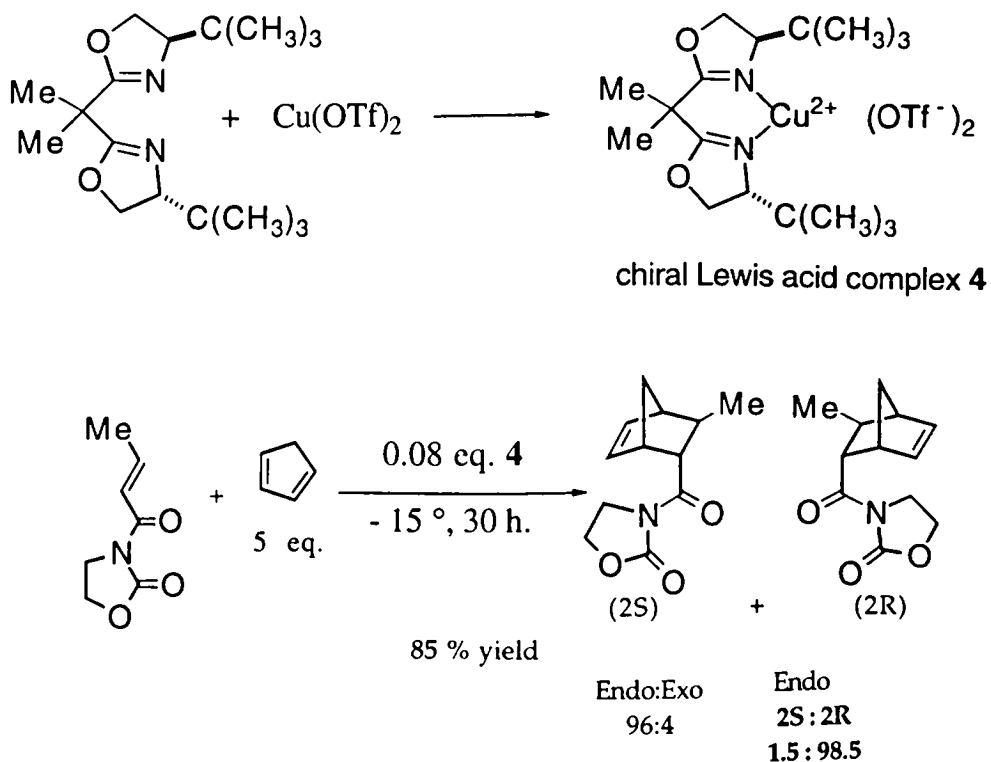
a) the Corey system;



chiral Lewis acid complex **3**



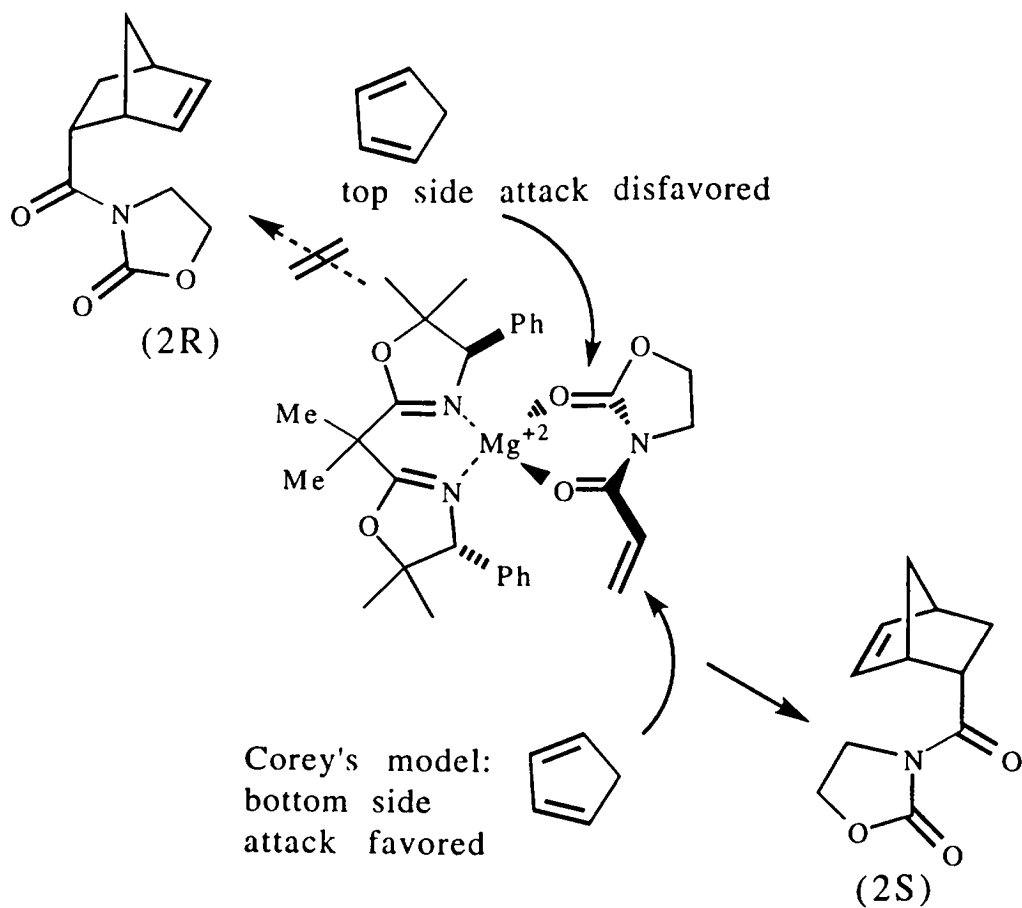
b) the Evans system.



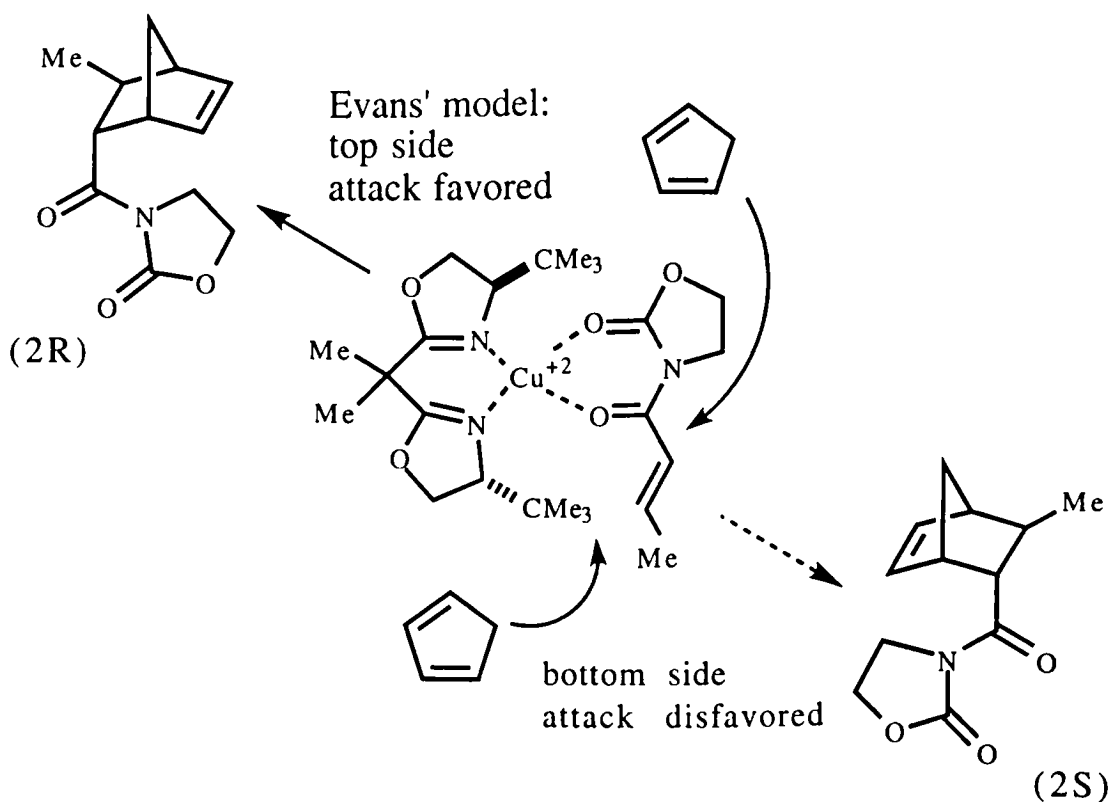
Scheme 3 shows the proposed models that are used to explain the stereoselectivities observed in the reactions of Scheme 2. The difference in the 2R versus 2S sense of stereoinduction is thought to arise from the different preferred geometries of the two chiral Lewis acid complexes **3** and **4**. Corey's model proposes a tetrahedral complex for ligand **3**. The tetrahedral complex should orient the phenyl substituents so as to block approach of the diene to the bottom face of the dienophile as drawn.¹⁸ Such an approach would lead to formation of the 2S endo product.

Scheme 3. Models for the origin of the stereoinduction observed in:

a) the Corey catalyst system;



b) the Evans catalyst system.

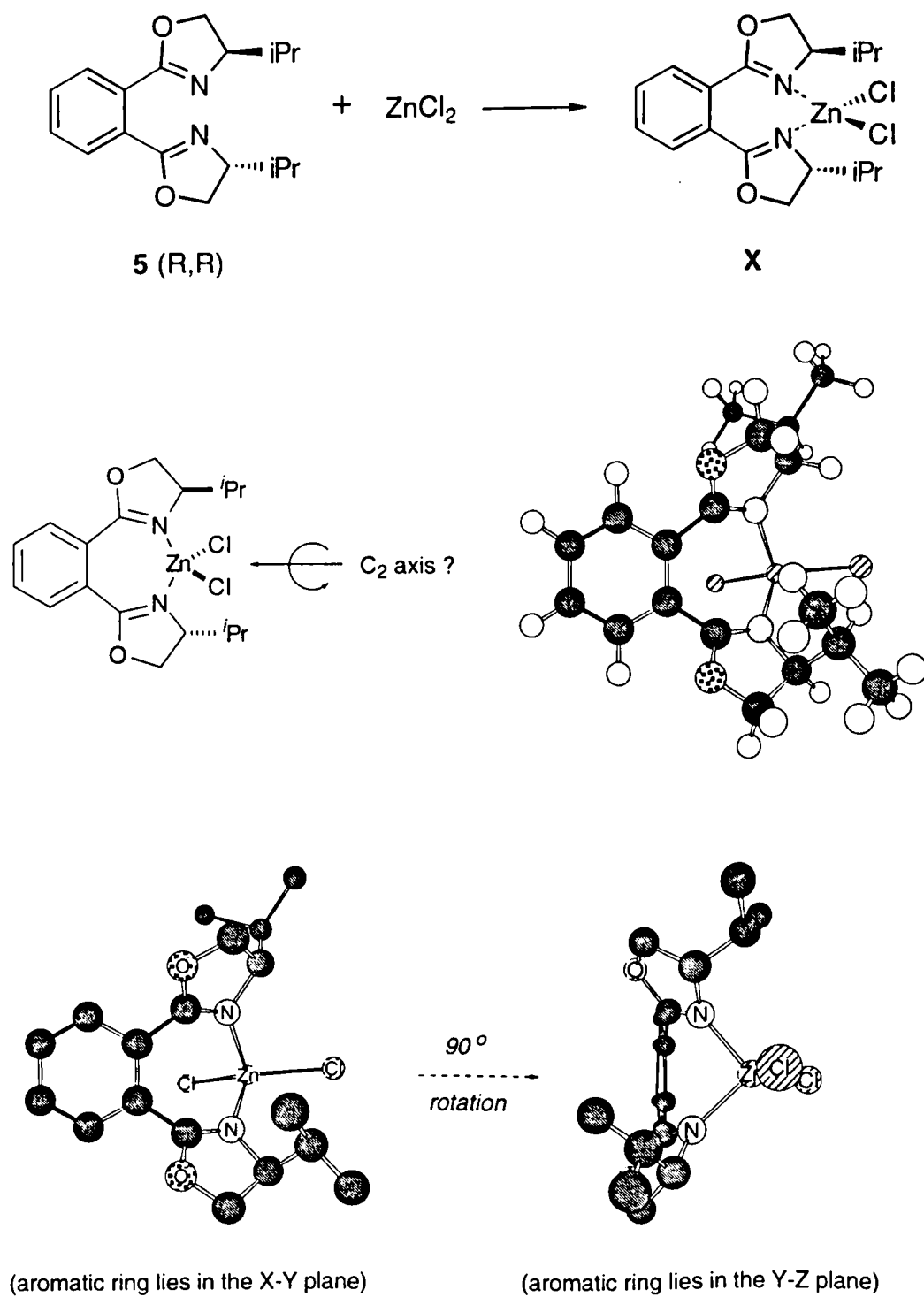


The Evans model presumes a square-planar complex **4**; the copper, nitrogens and oxygen atoms all lie in the plane. In the square planar complex, the *tert*-butyl substituent is oriented so as to block approach to the top face of the dienophile as drawn. The 2R endo product would arise from such an approach.¹⁹ It should be noted at this point that both the Evans and the Corey model are predicated on the assumption that the C₂-symmetric ligands will form C₂-symmetric metal complexes. The question was raised by Dr. Takacs about whether or not this had to be the case and we went to the literature to learn what was known at the time about the structure of bisoxazoline-metal complexes.

At the time this thesis project was initiated, only one bisoxazoline-metal complex structure was published. The complex was formed by reaction of the C₂-symmetric

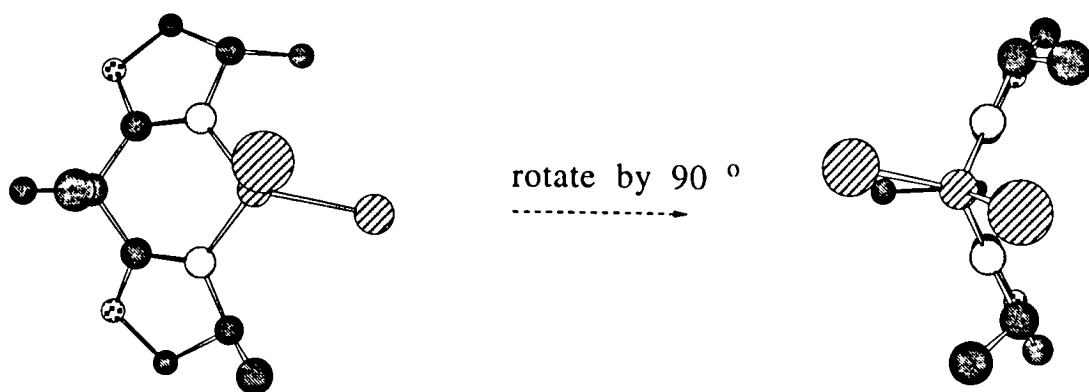
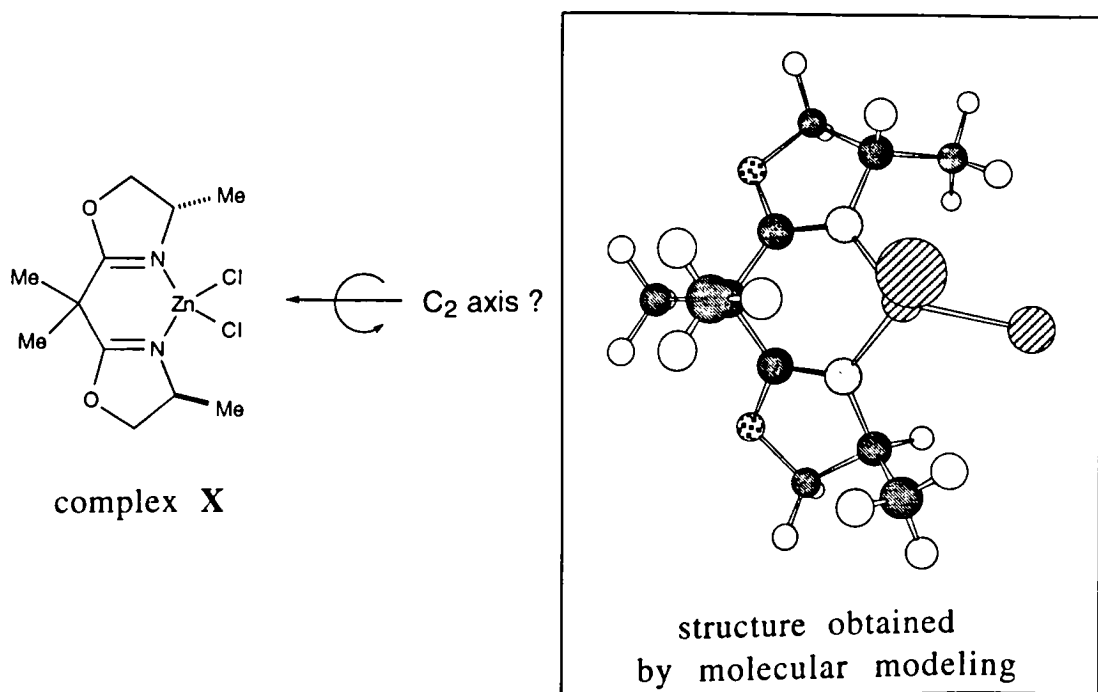
bisoxazoline ligand **5** with zinc chloride.²⁰ The zinc-bisoxazoline complex **X** has been characterized crystallographically and reported by Carsten Bolm. Scheme 4 shows the full crystal structure and two views of the complex shown without the attached hydrogens for clarity. The complex has a tetrahedral geometry about the zinc atom, but is significantly distorted from C_2 -symmetry. The nitrogen-to-nitrogen distance is too short to permit binding to the metal while preserving the C_2 -symmetry. As shown in Scheme 4, the zinc atom sits well below the plane defined by the nitrogens and aromatic ring. Bolm also reported NMR studies that are consistent with two diastereomeric non- C_2 -symmetric complexes in solution. In preparation for our subsequent studies, We asked the question whether a simple molecular modeling program (MMX in PCModel v 2.1) would give useful preliminary indications of structure for the de novo design of other ligands. Dr. Takacs therefore performed molecular modelling studies on complex **xb** and found that molecular modelling reproduced the crystal structure of complex **x** quite well.

Scheme 4. The Carsten Bolm C_2 -symmetry bisoxazoline ligand and its non- C_2 -symmetric zinc chloride complex.



This analysis raised two new questions. (1) Was the Corey complex C_2 -symmetric as his model required? (2) If not, could a ligand be designed that would indeed afford a C_2 -symmetric zinc complex? To answer the first question, Dr. Takacs performed molecular modeling studies on a bisoxazoline-zinc chloride complex (**X**) related to the one Corey employed. The modelled structure is shown in Scheme 5. The analysis again suggests the nitrogen to nitrogen distance is too small to bind $Zn(II)$ in a tetrahedral geometry and preserve C_2 -symmetry. The metal may adopt a different geometry to accept the smaller available bite angle of the bisoxazoline which is explained by the Evans model, where the results are rationalized by a square-planar geometry.

Scheme 5. Molecular modeling of a (1,3)-bisoxazoline-zinc chloride complex.

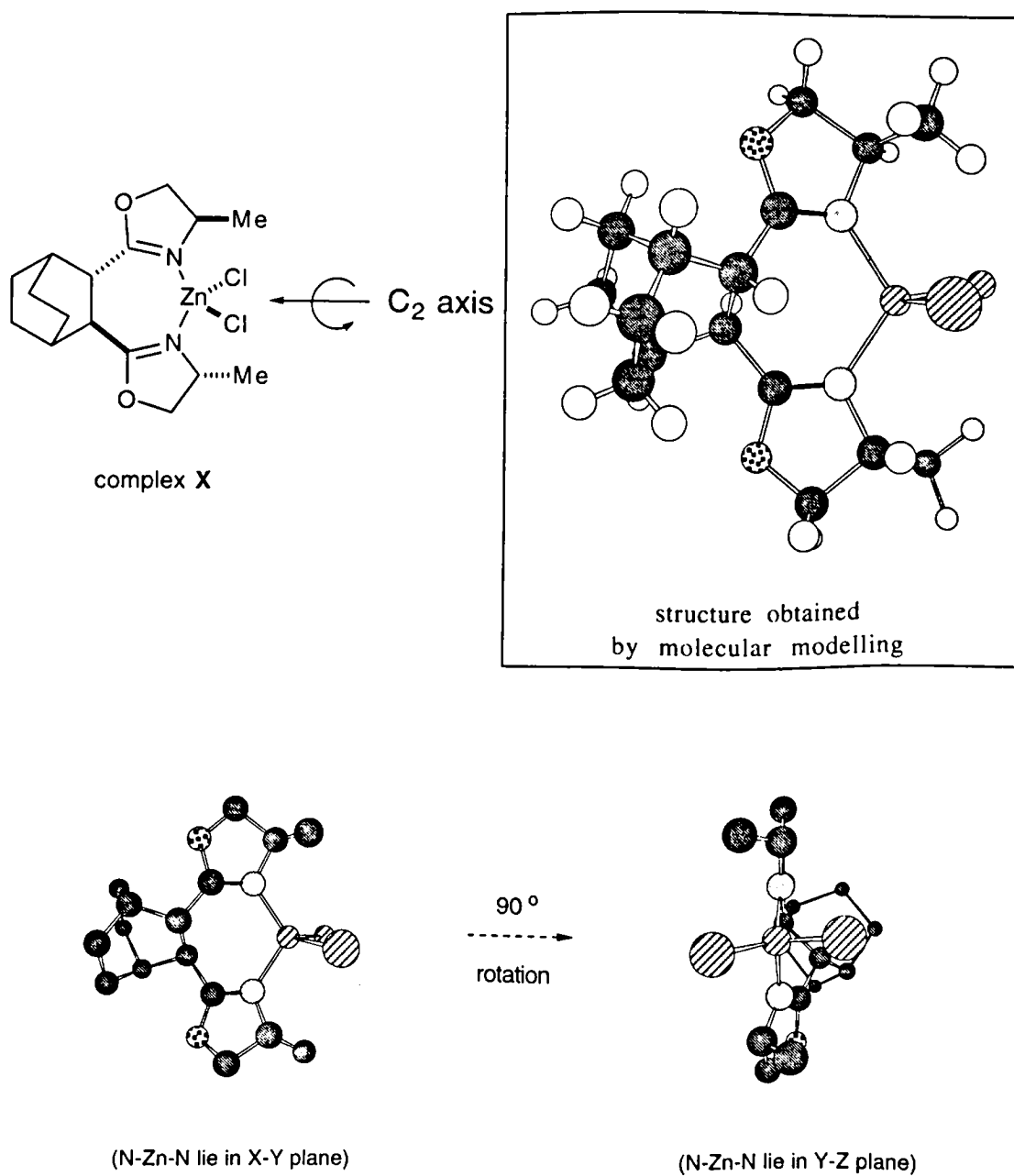


If the Corey ligand fails to give a C_2 -symmetric complex, can one be designed?

Considering molecular models it seemed plausible that a ligand based on the bicyclo[2.2.2]-backbone could orient the nitrogens far enough apart to meet the

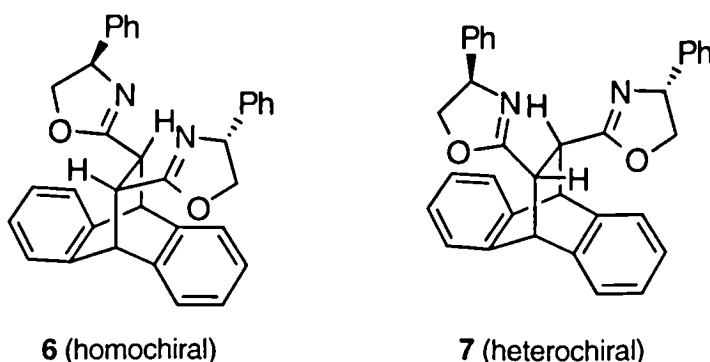
requirement. Dr. Takacs carried out molecular modeling studies as shown in Scheme 6. This analysis supported the idea that such a ligand form more nearly C_2 -symmetric tetrahedral Zn (II)-complex.

Scheme 6. Molecular modeling of a (1,4)-bisoxazoline-zinc chloride complex.



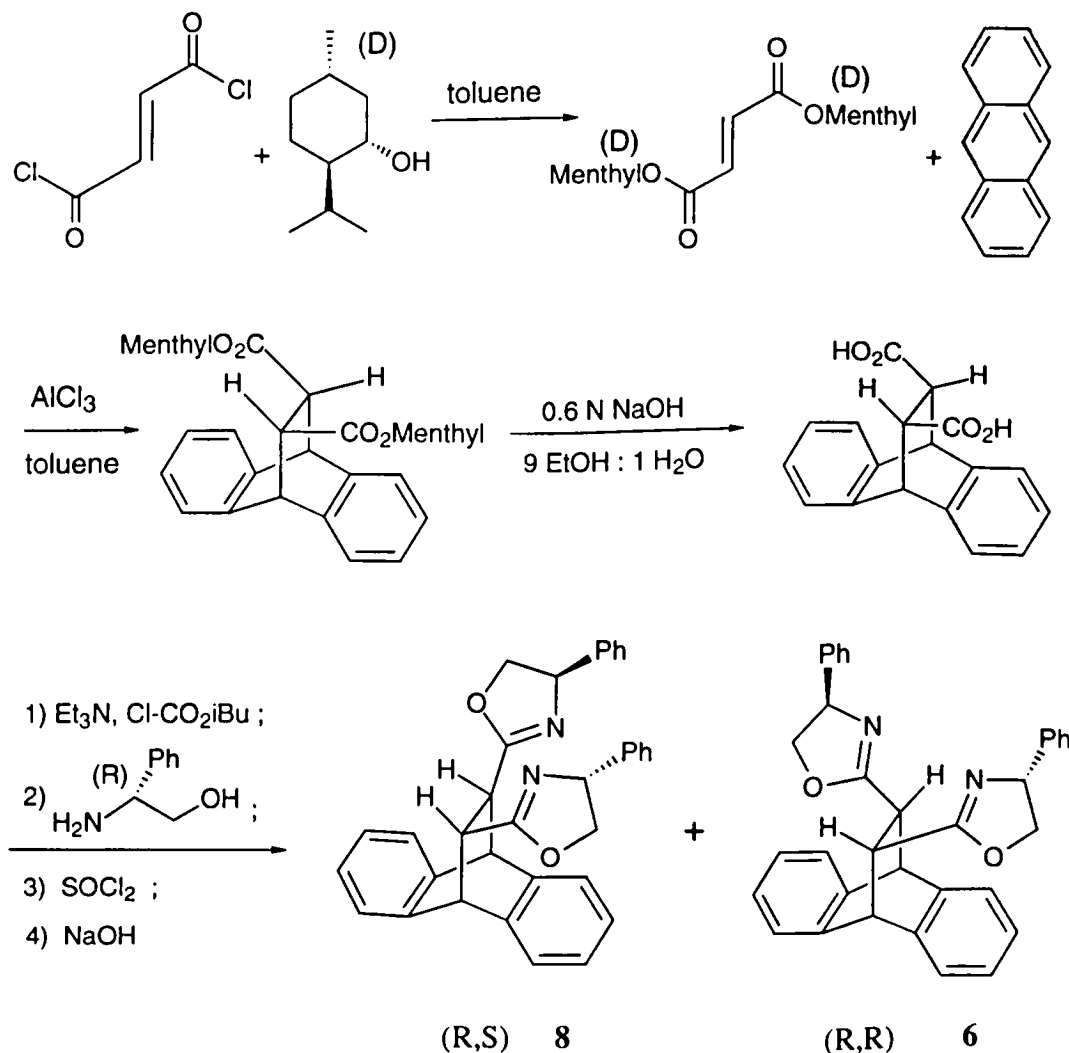
We therefore set out to design an accessible ligand based on the bicyclo[2.2.2]-backbone. It should be noted that such a ligand has an additional complication compared to the Corey or Evans ligand. That complication is that the backbone is itself chiral and bisoxazoline ligands derived from these backbones will have a total of four stereogenic centers that need to be controlled. Our target ligands are shown in Figure 3. The left hand structure (**6**), in which all of the stereogenic centers are of the R absolute configuration, will be termed the homochiral ligand. The right hand structure (**7**), in which the backbone stereocenters are of the S absolute configuration and the oxazoline stereocenters of the R absolute configuration, will be termed the heterochiral ligand.

Figure 3. Target C₂-symmetric chiral bisoxazolines used in this research.



The reactions to synthesize the homochiral ligand **6** are shown in Scheme 7. In this case the initial Diels-Alder reaction employed the dimethyl fumarate derived from D-menthol and anthracene to form the dimethyl ester. This reaction establishes the R,R-absolute configuration of the backbone as required. This dimethyl ester was treated with base to afford the dicarboxylic acid. This dicarboxylic acid was converted to a mixed

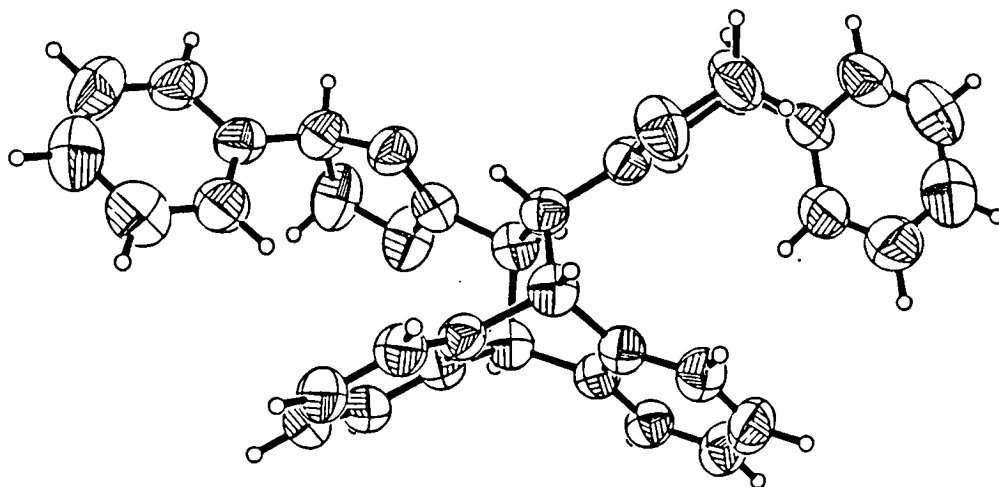
anhydride via isobutyl chloroformate and base. This occurred by the addition of the carboxylate anion to the chloroester carbonyl, followed by the leaving of chlorine. The bis mixed anhydride was added directly to a solution of (R)-phenylglycinol to afford the bis amide alcohol. This occurred by the addition of the nitrogen to the carbonyl which used to belong to the carboxylic acid, followed by the leaving of the group containing isobutyl. The bis amide alcohol was treated with thionyl chloride to afford the bis amide chloride. The bis amide chloride was cyclized to form a bisoxazoline by the addition of base. This occurred by the anionic oxygen of the amide adding to the carbon containing the chlorine, followed by the loss of this chlorine. Ligand **8** was separated by column chromatography, 75 : 25 hexane : ethyl acetate after the cyclizations of the bis-amide chloride intermediates to form ligands **6** and **8**. Bisoxazoline **8** has a R,S configuration (meso) backbone. This meso compound comes about by epimerization during the formation and / or reaction of the mixed anhydride. The yields are shown in the experimental section.

Scheme 7. Synthesis of the C₂-symmetric homochiral bisoxazoline **6**.

A sample of the homochiral ligand was crystallized under nitrogen gas by swirling in a minimum amount of diethyl ether. A yellow liquid was pipetted away. The remaining solid was evaporated to dryness with nitrogen gas. This solid was then dissolved in a minimum amount of ethyl acetate. In a vial surrounding the dissolved ligand, a similar volume of cyclohexane was placed. This vial was wrapped with parafilm. The liquid in the vial surrounding the ligand was replaced with fresh cyclohexane approximately every 48 hours to afford xray quality crystals after approximately 20 days. The structure was

determined by Dr. Charles Ross using the facilities in the UNL laboratory of Professor John J. Stezowski. The crystal of **6**, along with the list of fractional coordinates, shown in Figure 4. The structure shows the C_2 -symmetry of the ligand, but is somewhat surprising in that the nitrogen-to-nitrogen distance is longer than was anticipated from molecular modelling and Drieding model analysis.

Figure 4. Crystal structure and fractional coordinates for the homochiral ligand **6**.

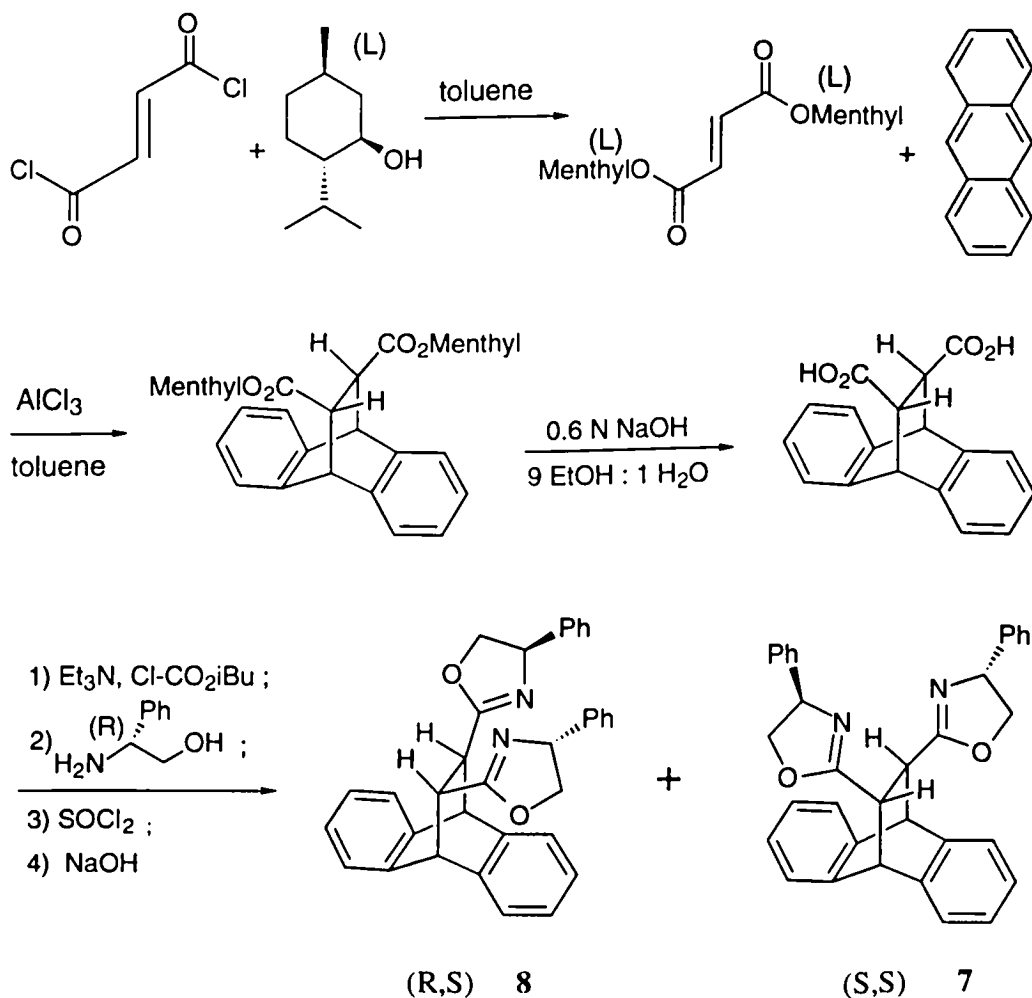


Homochiral Bicyclo[2.2.2]BO (R = (R) Ph)		
11.8261000	16.6035000	13.9864000
90.0000000	98.690000	90.0
00.7467000	00.6033000	00.8283000 O
00.6531000	00.6437000	00.6853000 N
00.8247000	00.6555000	00.6043000 C
00.8839000	00.7109000	00.5585000 C
00.8855000	00.7658000	00.5803000 H
00.9376000	00.6902000	00.4824000 C
00.9814000	00.7292000	00.4530000 H
00.9319000	00.6131000	00.4505000 C
00.9697000	00.5986000	00.3969000 H
00.8721000	00.5569000	00.4938000 C

00.8680000	00.5026000	00.4701000 H
00.8179000	00.5782000	00.5700000 C
00.7747000	00.5393000	00.6003000 H
00.7686000	00.6785000	00.6892000 C
00.7630000	00.7361000	00.6917000 H
00.8309000	00.6480000	00.7870000 C
00.8922000	00.6130000	00.7759000 H
00.8614000	00.6914000	00.8284000 H
00.6500000	00.6055000	00.7617000 C
00.5520000	00.5601000	00.7907000 C
00.5287000	00.5872000	00.8451000 H
00.5841000	00.4708000	00.8207000 C
00.6465000	00.4678000	00.8731000 H
00.4773000	00.4322000	00.8464000 C
00.4632000	00.4006000	00.9353000 C
00.5252000	00.4023000	00.9882000 H
00.3598000	00.3673000	00.9469000 C
00.3491000	00.3456000	01.0085000 H
00.2701000	00.3652000	00.8711000 C
00.1988000	00.3409000	00.8800000 H
00.2830000	00.3975000	00.7822000 C
00.2211000	00.3971000	00.7293000 H
00.3871000	00.4308000	00.7699000 C
00.2533000	00.6033000	00.6717000 O
00.3469000	00.6437000	00.8147000 N
00.1753000	00.6555000	00.8957000 C
00.1161000	00.7109000	00.9415000 C
00.1145000	00.7658000	00.9197000 H
00.0624000	00.6902000	01.0176000 C
00.0186000	00.7292000	01.0470000 H
00.0681000	00.6131000	01.0495000 C
00.0303000	00.5986000	01.1031000 H
00.1279000	00.5569000	01.0062000 C
00.1320000	00.5026000	01.0299000 H
00.1821000	00.5782000	00.9300000 C
00.2253000	00.5393000	00.8997000 H
00.2314000	00.6785000	00.8108000 C
00.2370000	00.7361000	00.8083000 H
00.1691000	00.6480000	00.7130000 C
00.1078000	00.6130000	00.7241000 H
00.1386000	00.6914000	00.6716000 H
00.3500000	00.6055000	00.7383000 C
00.4480000	00.5601000	00.7093000 C
00.4713000	00.5872000	00.6549000 H
00.4159000	00.4708000	00.6793000 C
00.3535000	00.4678000	00.6269000 H
00.5227000	00.4322000	00.6536000 C
00.5368000	00.4006000	00.5647000 C
00.4748000	00.4023000	00.5118000 H
00.6402000	00.3673000	00.5531000 C
00.6509000	00.3456000	00.4915000 H
00.7299000	00.3652000	00.6289000 C

00.8012000	00.3409000	00.6200000 H
00.7170000	00.3975000	00.7178000 C
00.7789000	00.3971000	00.7707000 H
00.6129000	00.4308000	00.7301000 C

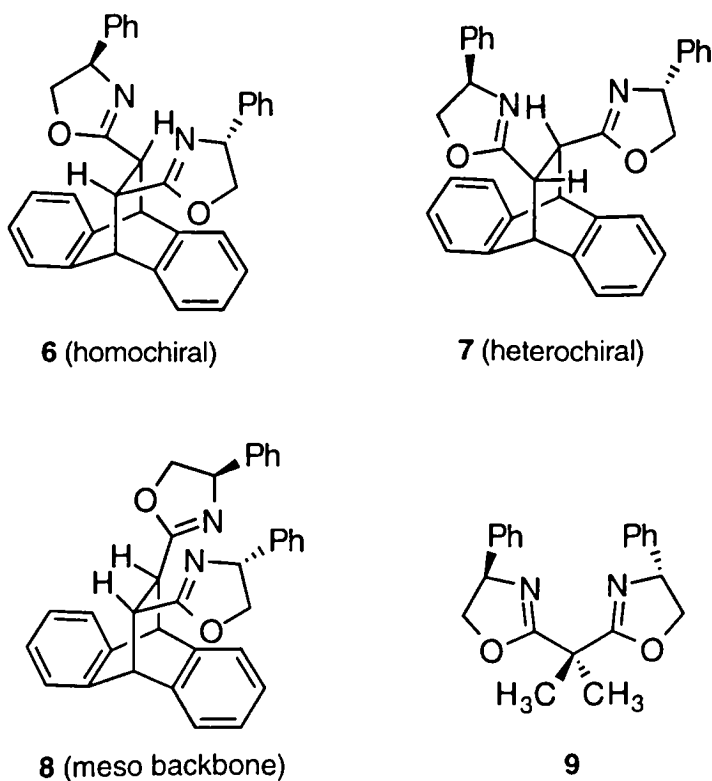
In a similar fashion to that described for the homochiral ligand **6**, the heterochiral ligand **7** was prepared as shown in Scheme 8. In this case the initial Diels-Alder reaction employed the dimethyl fumarate derived from L-menthol and anthracene to afford the diester. This reaction establishes the S,S-absolute configuration of the backbone as required. This dimethyl ester was treated with base to afford the dicarboxylic acid. This dicarboxylic acid was converted to a bis mixed anhydride via isobutyl chloroformate and base. This bis mixed anhydride was added to (R)-phenylglycinol to afford the bis amide alcohol. This bis amide alcohol was treated with thionyl chloride to afford the bis amide chloride. This bis amide chloride was cyclized to a bisoxazoline by the addition of base. Ligand **8** was separated by column chromatography, 75 : 25 hexane : ethyl acetate after the cyclizations of the bis-amide chloride intermediates to form ligands **7** and **8**. Bisoxazoline **8** has a meso backbone. This meso compound again comes about by epimerization during the formation and / or reaction of the mixed anhydride. The yields are shown in the experimental section.

Scheme 8. Synthesis of the C₂-symmetric heterochiral bisoxazoline **7**.

Having prepared the two desired chiral bisoxazoline ligands described above, we turned our attention to evaluating their effectiveness in the Diels-Alder cycloaddition of cyclopentadiene with the α,β -unsaturated N-acyloxazolidinones derived from acrylic acid and from crotonic acid. We screened three Lewis acidic metal salts in the course of our investigation: zinc(II)-, magnesium(II)- and copper(II) trifluoromethanesulfonate (triflate). The triflates were chosen because this stable anion is known to form largely dissociated metal complexes. We can compare the results of our study to those reported by Corey¹⁸

and by Evans¹⁹ (discussed above), and in addition, we carried out parallel reactions with the (1,3) bisoxazoline ligand **9** (purchased from Aldrich). We also decided to screen the bisoxazoline derived from the meso diacid, ligand **8**, that is formed as a side product in the syntheses of **6** and **7**. It cannot form a C_2 -symmetric metal complex, and we thought that the results might prove to be an interesting comparison. A much greater quantity of the homochiral bisoxazoline ligand **6** was synthesized than the corresponding heterochiral ligand **7**. As a consequence, the reader will notice that ligand **6** was the more highly studied ligand. These ligands are shown below in Figure 5.

Figure 5. Chiral bisoxazoline ligands investigated in our research.



The results of these investigations are summarized in Table 1. Several points are of note. The reactions of Table 1 investigating the effect of bisoxazolines were carried out in

dichloromethane at room temperature. We felt that in designing a new chiral catalyst, an important goal should be to find a catalyst that is effective at higher temperatures. In our studies, the metal-ligand complex was generated in situ allowing 45 minutes prior to addition of substrate for precomplexing the ligand and Lewis acid. The yields of the Diels-Alder reactions shown in Table 1 were determined by considering the weight of recovered material and comparing the remaining starting material and the formation of endo plus exo product by ^1H NMR integration. For the acryloyloxazolidinone system, a key starting material proton resonates at δ 5.96 ppm and its integration was compared to the endo plus exo protons of the product. For the (E)-crotonyloxazolidinone system, the starting material methyl group resonates at δ 1.97 ppm and its integration was compared to the endo plus exo methyl groups of the product. The endo / exo ratios were also determined by ^1H NMR integration. For the acryloyloxazolidinone derived products, the endo isomer has a signal at δ 3.03 ppm and the exo at δ 2.94 ppm. For the (E)-crotonyloxazolidinone derived product, the signals at δ 1.15 ppm and δ 0.88 ppm were integrated to assess the endo / exo ratio. The 2R / 2S enantiomeric ratio of the pure endo products (separated by chromatography, 75 : 25 hexane : ethyl acetate) were determined by chiral GC on a Daicel cyclodex- β column.

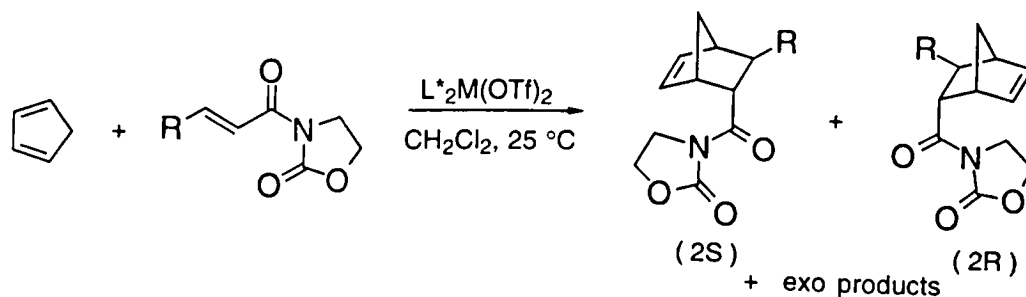


Table 1. The effect of (R)-phenyl bisoxazolines and certain metal triflates on the asymmetric Diels-Alder reaction.

entry ^a	oxazolidinone	Ligand	M(OTf) ₂	endo / exo	% yield	2S / 2R ^b	% ee ^b
R = H or Me							
1	H	6	Zn	90 / 10	93	28.5 / 71.5	43
2	H	6	Cu	80 / 20	81	69.5 / 30.5	39
3	H	6	Mg	90.5 / 9.5	92	54 / 46	8
4	H	8	Zn	90 / 10	87	27 / 73	46
5	H	8	Cu	91 / 9	88	12.5 / 87.5	75
6	H	8	Mg	89 / 11	82	52 / 48	4
7	H	9	Zn	89 / 11	82	47 / 53	6
8	H	9	Cu	87 / 13	79	53.5 / 46.5	7
9	H	9	Mg	82 / 18	78	25.5 / 74.5	49
10 ^c	Me	6	Zn	87 / 13	nd	21 / 79	58
11 ^c	Me	6	Cu	69 / 31	nd	62 / 38	24
12	Me	6	Mg	65 / 35	55	57.5 / 42.5	15
13 ^c	Me	7	Zn	86 / 14	nd	26 / 74	48
14 ^c	Me	7	Cu	65 / 35	nd	64 / 36	28
15 ^c	Me	9	Zn	77 / 23	nd	38 / 62	24
16 ^c	Me	9	Cu	79 / 21	nd	47 / 53	6
17	Me	9	Mg	76 / 24	88	25.5 / 74.5	49

^a all entries were done in CH₂Cl₂, under N₂, at room temperature, 45 minutes precomplexing the ligand and metal triflate, 10 minutes stirring the catalyst and oxazolidinone, 15 mole % of metal triflate, 20 mole % of ligand, 8 mole equivalents of cyclopentadiene, and stirred overnight.

^b the enantiomeric composition of the Diels-Alder adducts were determined by a chiral gas-chromatograph (Daicel cyclodex-β column).

^c entries done by Dave A. Quincy in the Takacs research group. These reaction yields were not determined.

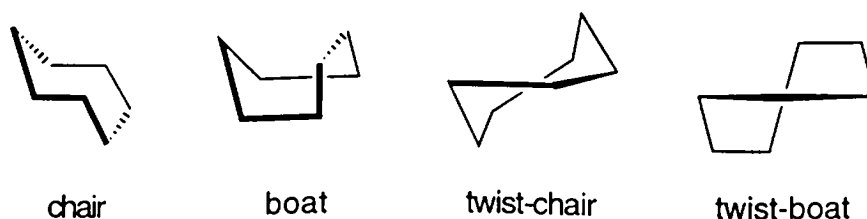
The Corey and Evans reactions described above in Scheme 2 gave yields greater than 82 % and the enantioselectivities were greater than 90 % ee. Our results were not as spectacular, but nonetheless had some interesting aspects. The yields of these reactions were greater than 78 %, except for entry 12 (magnesium triflate and ligand **6** with (E)-crotonyloxazolidinone) which shows a yield of 55 %. The enantioselectivities were greater than 43 % ee in reactions catalyzed by zinc triflate and (1,4)-bisoxazoline ligands **6**, **7**, and **8**. The (1,3)-bisoxazoline ligand **9** with magnesium triflate gave the (2R) product in 49 % ee. The most interesting example of enantioselectivity was entry 5 of Table 1 (copper triflate and ligand **8** with acryloyloxazolidinone), which shows an 87 % yield, a 91 / 9 endo / exo ratio, and a 75 % ee with the (2R) product selectively formed. Other entries catalyzed by copper triflate show the (2S) enantiomeric product being favored.

In order to explain the mixed results of Table 1 that show the (2S) or (2R) endo enantiomer being favored by different quantitative amounts, the possible conformations of seven atom rings should be considered. First, recall the Corey model of the approach of cyclopentadiene to the chiral catalytic complex of the dienophile shown in Scheme 3.¹⁸ Corey shows a tetrahedral complex about the magnesium ion leading selectively to the (2R) endo enantiomer. But Corey does not mention possible conformations of the complex.

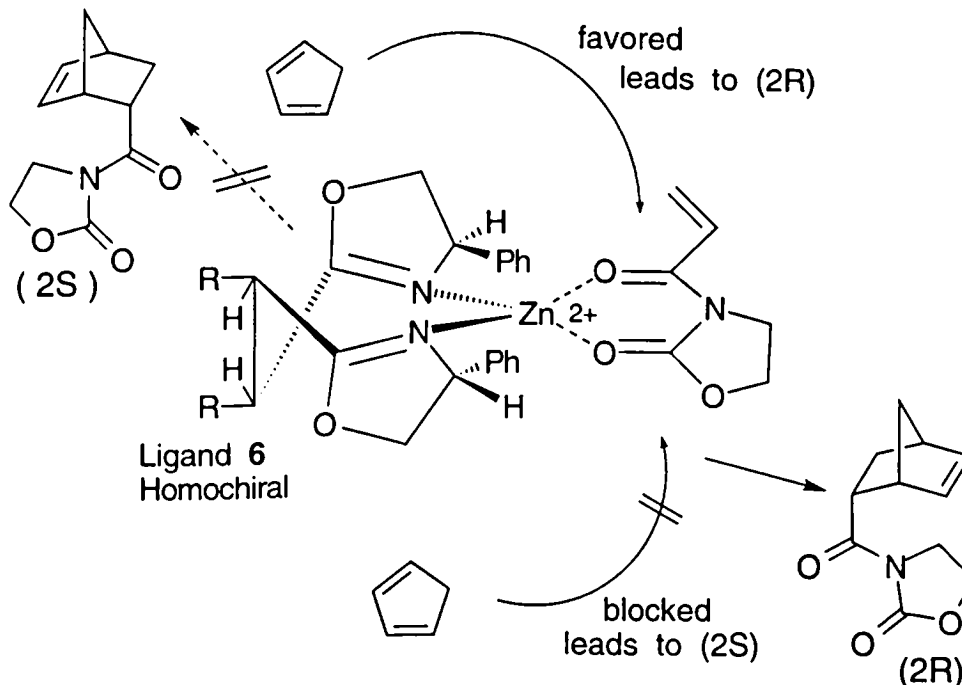
A seven atom ring containing the catalytic metal and two nitrogens of the chiral catalytic complex is hypothesized to exist. Seven atom rings can exist in different conformations as shown in Figure 6.²¹ The twist-chair is the lowest energy conformation of cycloheptane. But with two nitrogens and a metal in this seven member ring, its conformation is changed. A model of the catalytic chiral complex of entry 1 of Table 1 is shown in Scheme 9. This entry combined the homochiral ligand **6**, zinc triflate, and acryloyloxazolidinone. The catalytic metal is believed to be tetrahedral. The (R)-phenyl groups are one atom outside of this seven member ring alpha to each nitrogen. By changing the catalytic metal, this changes the conformation and moves the chiral phenyl

groups to different blocking positions. Scheme 9 shows how the approach of cyclopentadiene is favored in a way that leads to the (2R) endo enantiomer when the chiral catalytic complex is in this conformation. Note that the bisoxazoline part of the catalytic complex is C_2 -symmetric. Therefore if the carbonyl oxygens of the acryloyloxazolidinone were to line up to the catalytic metal in the opposite manner, then the other phenyl group on the bottom would do the blocking of the cyclopentadiene approach. In the case of entry 5 of Table 1, the meso ligand **8** and copper triflate together produced a seven member conformation in the catalytic complex that strongly favored the (2R) endo enantiomer being formed in 75 % ee. Other entries of Table 1 produce conformations that favor the (2S) endo enantiomer.

Figure 6. Conformations of a seven member ring.



Scheme 9. Model for the origin of the (2R) product stereoselectivity observed with the ligand 6-zinc catalytic complex.



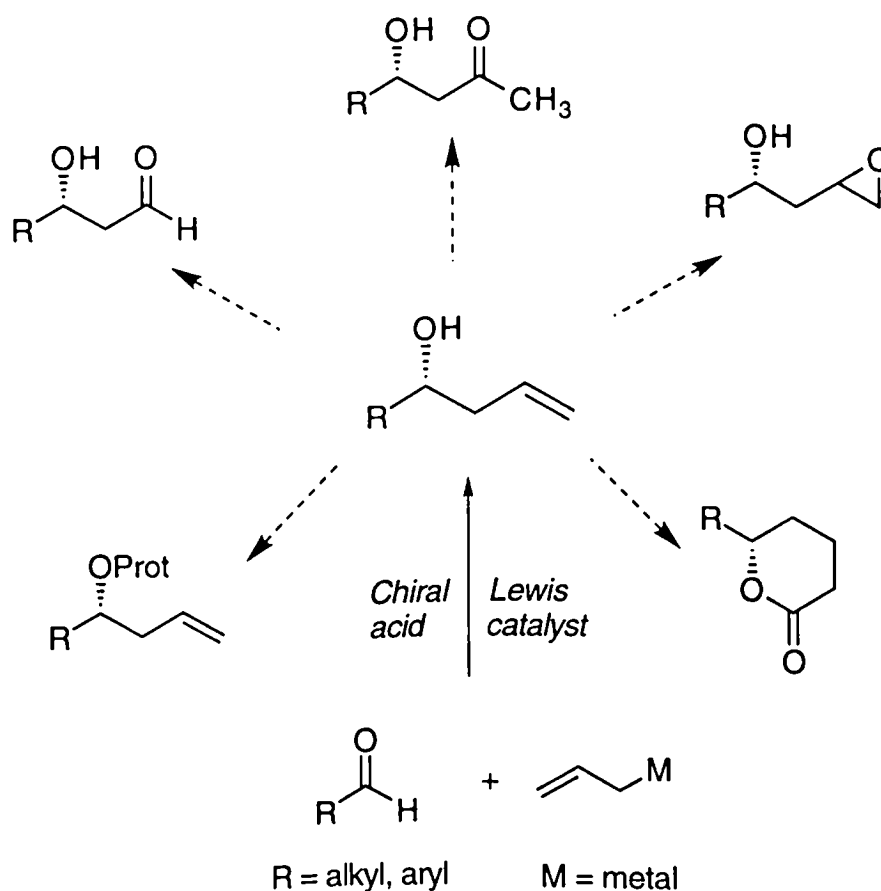
It is also hypothesized that with (1,3)-bisoxazolines and different catalytic metals, different conformations of six member rings exist to produce different product enantioselectivities. This accounts for entries 9 through 15, where the (1,3)-bisoxazoline ligand **9** and magnesium triflate catalytic complex produced six atom conformations in the catalytic complex that led to higher product % ee's than zinc or copper triflate with ligand **9**.

Furthermore, changing the amount of ligand, Lewis acid, or other conditions changes the conformation of the catalytic complex and leads to better or worse observed selectivities in the product formation. The change in the conformation of the catalytic complex diagrammed in Figure 6 is longer or shorter nitrogen-metal-nitrogen bond lengths and a bigger or smaller bite angle for the nitrogen-metal bonds.

The results of this research investigating the Diels-Alder reaction do not appear to compare well with the results of Corey and Evans.^{18,19} But considering the low temperatures used in the Corey and Evans research and that the reactions of this research were done at room temperature, the results of this research do compare well with those of Corey and Evans. Perhaps lower temperatures, different reaction times, different mole %'s of ligand and / or Lewis acid, or changing other conditions could improve the selectivity ratios observed for endo / exo isomers and for the 2S / 2R enantioselectivity of the endo isomer. The lower temperature may slow the rate of product formation and may lead to greater selectivity.

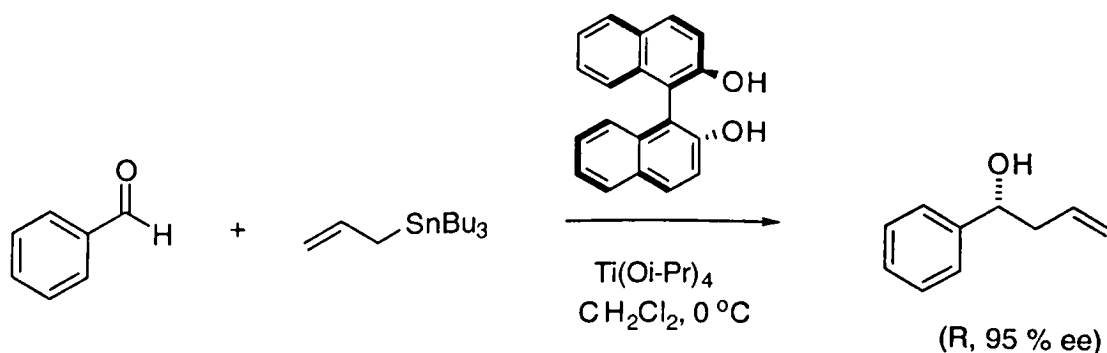
Enantioselective Allylations. The asymmetric allylation of aldehydes, as shown in Scheme 10, is another important synthetic reaction.^{22,23} Several transformations can be performed directly from this chiral β,γ -unsaturated alcohol as shown in Scheme 10.^{23,24} The chiral alcohol can be protected. The double bond can be epoxidized or ozonolyzed. The double bond can be converted to ketone or hydroformylated to synthesize a six-member chiral lactone. An efficient method for the enantioselective allylation of aldehydes would be an important contribution to the field. Adding an allylstannane to an aldehyde has been done in good (> 90 %) yield and with good (> 90 % ee) enantioselection.^{23,24,25,26,27,28} Furthermore, good diastereoselection has been achieved in the addition a crotyl stannane to aldehydes.^{24,29,30}

Scheme 10. The asymmetric allylation reaction and possible transformations subsequent to the allylation.



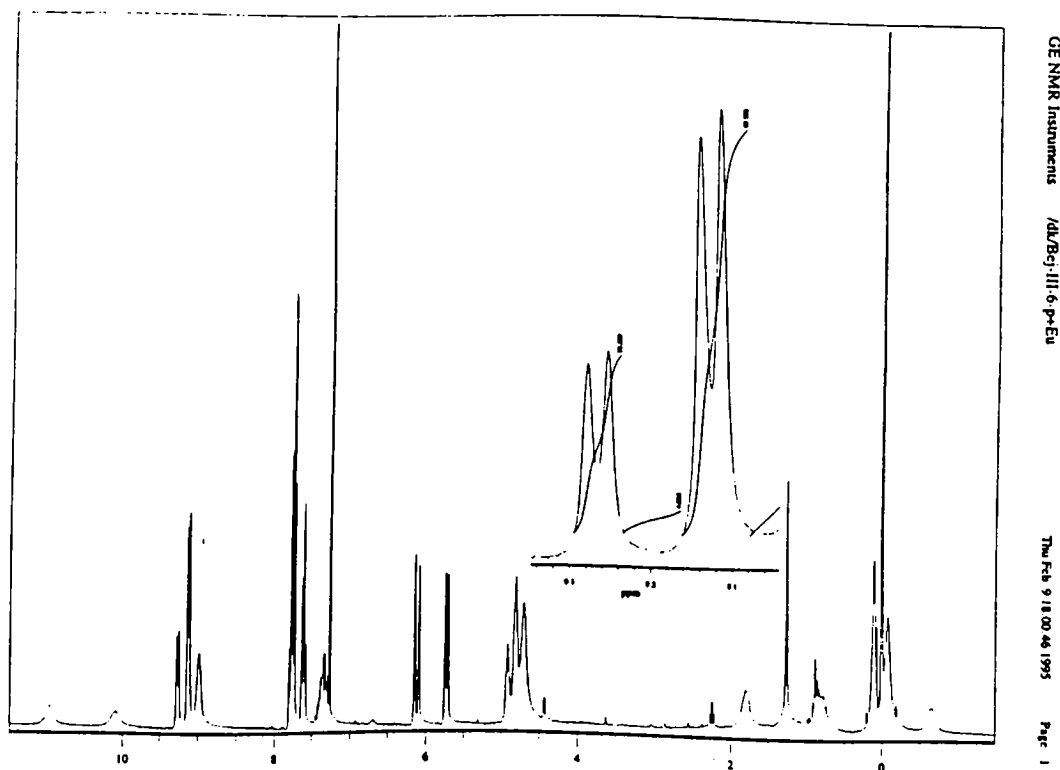
In our research, we attempted to allylate benzaldehyde with allyltributylstannane using the chiral metal catalysts described above. Keck recently reported the most effective chiral catalyst system for this allylation.²⁶ His method, shown in Equation 4 below uses a combination of (R)-binaphthol and titanium tetrakisopropoxide as the catalyst. Under his optimal conditions (CH_2Cl_2 , $0^\circ C$, 3 h) the (R)-alcohol is obtained in 94 % yield and 95 % ee.

Equation 4. The asymmetric allylation reaction catalyzed by (R)-binaphthol-titanium tetraisopropoxide using the Keck system.



Our results are summarized in Table 2. The racemic 1-phenyl-3-buten-1-ol was prepared via the Lewis acid catalyzed allylation in the absence of chiral ligand. The reactions were run by generating the chiral complex in situ. It is postulated that the chiral complex catalysts using the (1,4)-bisoxazoline, ligands **6** through **8** would generate greater enantioselectivity than the (1,3)-bisoxazoline, ligand **9**, again because of the wide bite angle of the bisoxazoline ligands. The aldehyde and allylstannane were added after sonicating a mixture of ligand and metal triflate at 0 °C for 30 minutes. The enantiomeric ratio was determined via the method described by Keck.²⁵ Two protons of both R and S enantiomers were found to shift selectively in the presence of 25 mole % chiral shift reagent Eu(hfc)₃. An example of the NMR shift experiment is shown in Figure 7.

Figure 7. Determining the enantiomer ratio of 1-phenyl-3-buten-1-ol catalyzed by ligand 6 via NMR shift reagents.



Zinc triflate was the only metal salt that we found to afford allylation product in our screen. Other Lewis acids that were attempted were $\text{Cu}(\text{OTf})_2$, $\text{Mg}(\text{OTf})_2$, and ZnCl_2 . In each of these latter cases, product was formed in a yield of less than 5 % (determined by proton NMR of the crude reaction mixture). We attempted to use allyltrimethylsilane in the place of allyltributylstannane, but the product was formed in a yield of less than 5 %. Apparently, the allyltributylstannane is a stronger nucleophile than allyltrimethylsilane. This has also been observed by Mayr and Yamamoto.^{23,31}

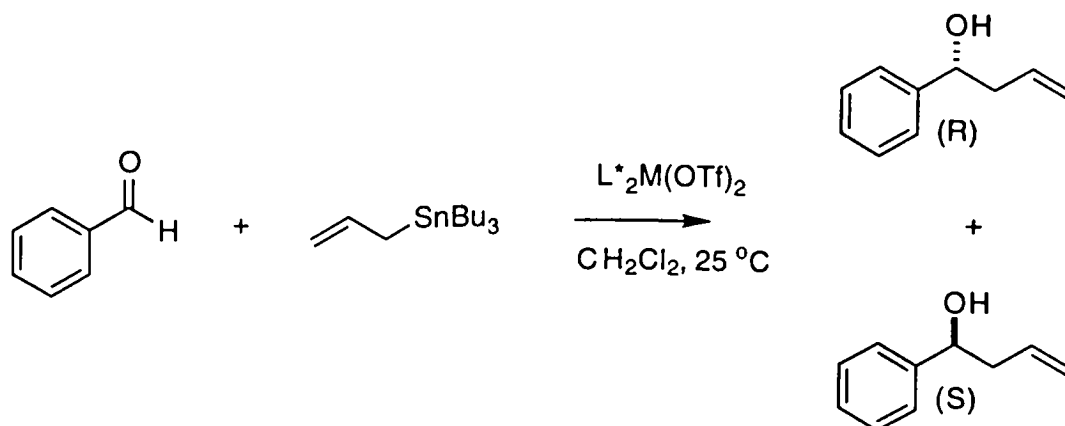


Table 2. The effect of (R)-phenyl bisoxazolines plus zinc triflate chiral catalytic complex on the allylation reaction.

entry ^a	ligand	% yield	% ee ^b	$[\alpha]_D^{(c)}$	c ^c
1	9	66	26	+ 11.2	4.60
2	7	86	31	+ 11.6	2.60
3	6	90	39	+ 13.2	2.50
4	8	70	44	+ 13.7	1.56

^a all entries were done in CH_2Cl_2 , under N_2 , 25 mole % $\text{Zn}(\text{OTf})_2$, 25 mole % ligand, 30 minutes sonication, addition of benzaldehyde at 0°C , stir for 10 minutes, addition of 1.1 mole equivalent stannane, and stirred at room temperature for 3 hours.

^b this was determined by ^1H NMR of purified product with 25 mole % $\text{Eu}(\text{hfc})_3$, chiral shift reagent, reference 25.

^c benzene was the solvent used for the specific optical rotation.

Our research shows that the zinc triflate-bisoxazoline complex catalyzes the allylation in a slightly enantiomerically enriched manner. Since the allylation reaction products directed by ligands **6**, **7**, **8**, and **9** gave positive specific rotations, it was clear that the (R) enantiomer had been selectively formed because the (S)-1-phenyl-3-buten-1-ol enantiomer gives an $[\alpha]_D = -44.92^\circ$ ($c = 7.38$, benzene).³² The chiral complex blocks the

approach of the allyl metal toward the aldehyde in such a way that leads to the (R) alcohol.^{14,23,24,33}

The yields of both of these allylation systems were between 66 and 98 %. But comparing the % ee's of Keck's system (87-96 % ee) to our zinc triflate-bisoxazoline catalytic system (26-44 % ee), the Keck system clearly shows a much greater enantioselectivity than the bisoxazoline system employed in this research, and this is preferable.²⁶

This investigation indicates that more research is needed in order to increase the % ee of this allylic alcohol product of this reaction using these bisoxazoline ligands. Perhaps changing the reaction temperature, the mole % of ligand and / or zinc triflate, or other conditions could improve the enantioselectivity of this reaction, as mentioned previously.

III. Conclusions and Future Directions

The bisoxazoline ligands **6**, **7**, **8**, and **9** that were investigated show potential for being used as chirality generating agents in carbon-carbon bond forming reactions. This research indicates that greater enantioselectivities are observed for the Diels-Alder reaction than the allylation reaction using these bisoxazoline ligands. The (1,4)-bisoxazoline ligands generated up to 75 % ee in the reactions that they catalyzed.

The chiral phenyl part of the (1,4)-bisoxazoline (i.e. the outer part of the ligand) is the greater stereochemistry inducing part of the ligand, compared to the "backbone" (i.e. the inner part of the ligand derived from anthracene). This statement is based on the % ee of the products resulting from the allylation reactions catalyzed by ligands **6**, **7**, and **8** shown in Table 2, there is only small difference in % ee (31 through 44 % ee). The (R)-1-phenyl-3-butene-1-ol product was the major enantiomer of the reactions catalyzed by ligands **6**, **7**, **8** and **9**. If the product stereochemistry was derived mainly from the inner part of these ligands, some (S) product enantioselection would be observed.

In the case of the asymmetric Diels-Alder reactions catalyzed by ligands **6**, **7**, or **8** with zinc, copper, or magnesium shown in Table 1, the conformation that the backbone (inner part) of the ligands and metal are held strongly influences the (2R) versus (2S) enantioselectivity and the magnitude of % ee. However, the (R)-phenyl groups alpha to the nitrogens binding the catalytic metal are believed to block the approach of cyclopentadiene and direct the stereochemical outcome of the product as was shown in Scheme 9.

Also note in the asymmetric allylation reactions of Table 2 that the (1,4)-bisoxazoline ligands **6**, **7**, and **8** did generate greater % ee's (31 through 44 % ee) than the (1,3)-bisoxazoline ligand **9** (26 % ee).

Zinc triflate had a greater ability to catalyze the enantioselective allylation reaction than other Lewis acids attempted ($\text{Cu}(\text{OTf})_2$, $\text{Mg}(\text{OTf})_2$, and ZnCl_2). All of the Lewis acids that were attempted to catalyze the asymmetric Diels-Alder reaction ($\text{Zn}(\text{OTf})_2$, $\text{Cu}(\text{OTf})_2$, and $\text{Mg}(\text{OTf})_2$) were able to do so. The asymmetric Diels-Alder reaction was more easily catalyzed than the asymmetric allylation reaction.

A conformational analysis of each of the (1,4)-bisoxazoline ligands **6**, **7**, and **8** with ionic zinc and with copper (II) should be performed in order to determine the differences in the conformations of the seven member rings of these catalytic complexes that exist.

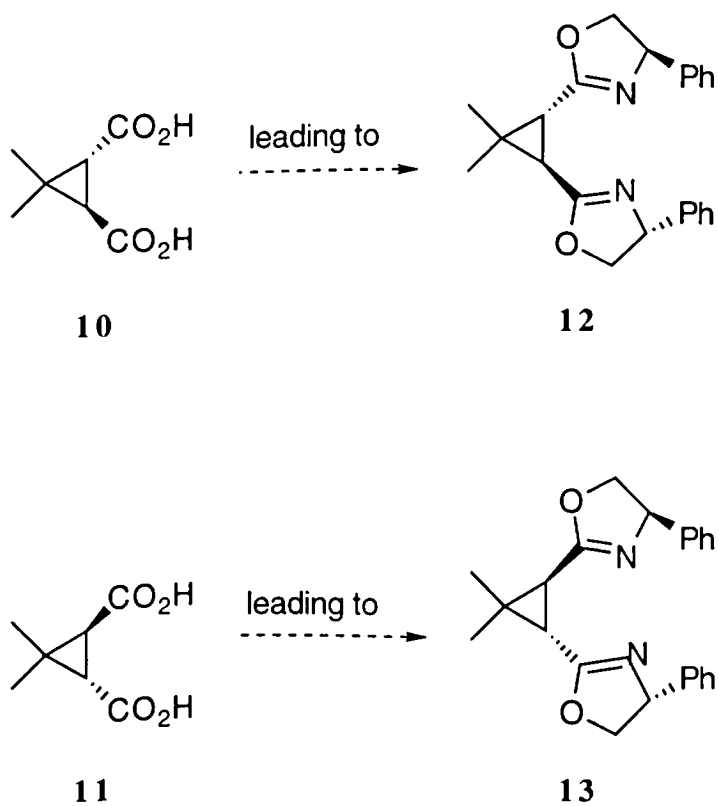
Alternative ligands worth trying would be (1,4)-bisoxazolines, ligands **12** and **13**, with the cyclopropyl backbone as shown in Scheme 11. Ligands **12** and **13** could be made from compounds **10** and **11** by the same technology used to synthesize ligands **6** and **7** from 9,10-ethane-11,12-dicarboxylic acid-9,10-dihydro anthracene. Both the (R,R) and (S,S) enantiomers of caronic acid, compounds **10** and **11** respectively, show a greater magnitude of specific optical rotations than both of the enantiomers of the dicarboxylic acid derived from anthracene. Therefore, it is postulated that the ligands **12** and **13** would have a greater chiral environment and would thus direct reactions with greater enantioselectivity than ligands **6** and **7**. These ligands which would be derived from caronic acid would also have the same advantage of having a large bite-angle that the anthracene derived ligands studied in this research have.

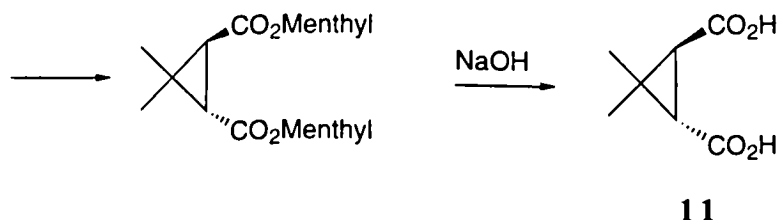
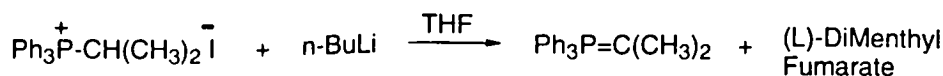
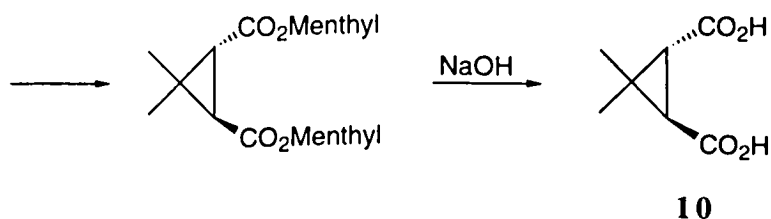
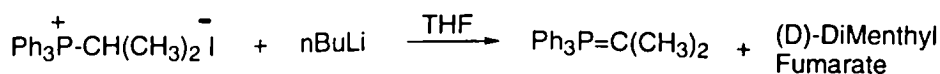
Compound **10** was synthesized in this research, as shown in Scheme 12. The ylide of isopropyltriphenylphosphonium iodide was added to the dimethyl fumarate derived from D-menthol to afford a crude dimethyl ester. This reaction occurred by the

negatively charged carbon of the ylide adding to the conjugated ester in the Michael fashion. The other carbon, that was part of the carbon-carbon double bond of dimenthyl fumarate and not bonded to the ylide, became negatively charged and then added to the carbon containing the phosphonium followed by the loss of triphenylphosphine. The crude diester was crystallized in 100 % ethanol to establish the R,R-absolute configuration of the backbone as required. This dimenthyl ester was treated with base to afford the dicarboxylic acid (caronic acid), compound **10**.

The reactions to synthesize compound **11**, as shown in Scheme 12, occurred via the same mechanisms as with the synthesis of compound **10**. The ylide of isopropyltriphenylphosphonium iodide was added to the dimenthyl fumarate derived from L-menthol to afford a crude dimenthyl ester. The crude diester was crystallized in 100 % ethanol to establish the S,S-absolute configuration of the backbone as required. This dimenthyl ester was treated with base to afford the dicarboxylic acid (caronic acid), compound **11**.

Scheme 11. (1,4)-Bisoxazolines worthy of being synthesized and attempted to be used as chirality inducing ligands.



Scheme 12. Synthesis of C₂-symmetric compounds **10** and **11**.

Also worth synthesizing would be (1,4)-bisoxazoline ligands derived from (S)-phenylglycinol to determine if opposite and equal (or better) enantioselectivity would be obtained. For example, the (R) homochiral bisoxazoline ligand **6** would not necessarily give equal and opposite sense of asymmetric induction as the enantiomeric (S)-phenyl homochiral bisoxazoline ligand. Only (R)-phenylglycinol was used to synthesize the ligands for this research. Clearly, more research is needed to synthesize other (1,4)-bisoxazoline ligands, also to investigate these ligands in some carbon-carbon bond forming reactions in order to determine just how effective the bisoxazolines can be when used in asymmetric catalysis complexes.

Research in the field of enantioselective catalysis should continue to grow with the purpose of increasing stereoselectivities of carbon-carbon bond forming reactions and synthesizing enantiomerically pure compounds. To do this, a design for a ligand capable of catalyzing organic reactions will be needed. Research chemists should continue to look for a more generalized system for selectively catalyzing more than one kind of reaction. Making large amounts of chiral product from achiral starting materials and a small amount of chiral catalyst, which can be recovered and used again, would be beneficial and cost effective.^{1,2,10,11,32,34}

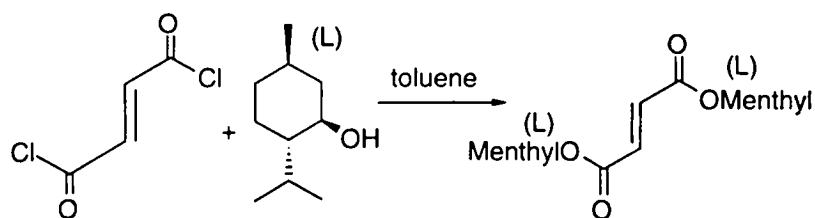
IV. Experimental Procedures

General procedures. Unless otherwise noted, all reactions were carried out under an atmosphere of nitrogen, all reactions were run at ambient temperature, all temperatures were measured externally, and all temperatures were reported in degrees Celsius (°C).

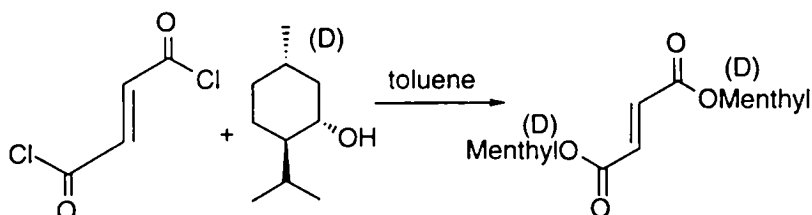
Solvents and Reagents. Tetrahydrofuran (THF) was distilled under nitrogen from sodium benzophenone ketyl prior to use. Hexanes (Hex) were purified by distillation. Dichloromethane (DCM) was passed through a column of alumina. *n*-Butyllithium (*n*-BuLi) was used as a 2.5 M solution in hexanes. All other reagents and solvents received from commercial sources were used without further purification.

Analytical Instrumentation and Data. Melting points were uncorrected. Optical rotations were measured using 10 cm cells on a Rudolph Autopol III polarimeter at ambient temperature. Thin layer chromatographic (TLC) analyses were performed on Analtech Silica Gel HLF (0.25 mm) precoated analytical plates and visualized by using a hand-held short wavelength ultra-violet lamp (254 nm) or iodine chamber. All ¹H and ¹³C NMR spectra were obtained on a GE Omega 300 MHz spectrophotometer. Unless otherwise noted, all NMR spectra were obtained on solutions in CDCl₃. All ¹H spectral data are reported in ppm from an internal standard tetramethylsilane or residual chloroform as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (reported in Hertz), interpretation. All ¹³C spectra were decoupled with waltz-16 decoupling. For most compounds, the number of attached hydrogens were determined using the DEPT pulse sequence. All ¹³C spectral data

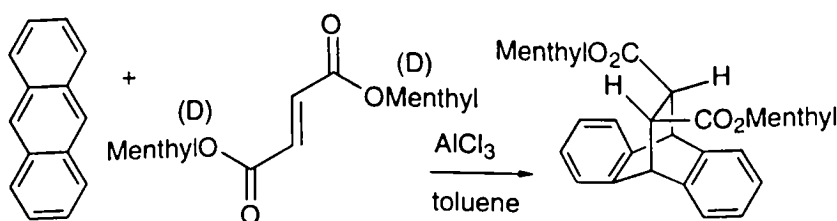
(s = no attached hydrogens, d = CH, t = CH₂, q = CH₃) were reported in ppm from an internal standard CDCl₃ unless otherwise noted. Infrared (IR) spectra were obtained on a Analect RFX-65 FT-IR spectrophotometer using the Attenuated Total Reflectance technique (ATR, neat, ZnSe crystal). Selected absorbances were reported in wavenumber (cm⁻¹). Analytical samples were purified by chromatography on silica followed by a high-vacuum drying pistol over P₂O₅. Combustion analyses were performed by M-H-W Laboratories (Phoenix, AZ).



Preparation of (L)-dimenthyl fumarate by the procedure of Scharf, reference 35, [BEJ-I-21]. To a solution of (L)-menthol (61.5 g, 394 mmol) in toluene (200 mL) was added fumaryl chloride (21.5 mL, 0.20 mol). The resulting mixture was heated to reflux. After 12 h reflux, the reaction mixture was cooled and pyridine (40 mL, 0.5 mol) added. The resulting mixture was refluxed for an additional hour, then cooled to room temperature. The mixture was washed sequentially with saturated aqueous NaCl (2 x 100 mL), 10 % aqueous HCl (2 x 100 mL), and again with saturated aqueous NaCl (2 x 100 mL). The organic layer was dried (MgSO₄), filtered, and concentrated. Bulb-to-bulb distillation (210 °C, < 0.1 torr) yielded (L)-dimenthyl fumarate (59.6 g, 77 % yield) as a pale yellow solid: mp 57-59 °C[literature³⁶ mp 59-61 °C]; [α]_D = - 99.9° (c = 1.40, CHCl₃) [literature³⁷ [α]_D = - 96.2° (c = 1.37, CHCl₃)]; ¹H NMR δ 6.81 (s, 2H, C=C-H), 4.78 (ddd, J = 4.4, 4.4, 10.9 Hz, 2H, O-C-H), 2.03 (m, 2H, CH-iPr), 1.86 (m, 2H, CH₂-CH-CH₃), 1.68 (m, 4H, CH₂-CH-iPr), 1.43 (m, 4H, CH₂-C-O), 1.04 (m, 4H, CH₂-CH₂-CH-iPr), 0.90 (m, 14H, CH₃-CH-CH₃), 0.75 (d, J = 6.9 Hz, 6H, CH₂-CH-CH₃); ¹³C NMR δ 165.3 (s, C=O), 134.5 (d, CH-C=O), 76.0 (d, O-C-H), 47.7 (d, CH-iPr), 41.4 (t, CH₂-CH₂-CH-iPr), 34.8 (t, CH₂-C-O), 32.0 (d, CHMe₂), 26.9 (d, CH₂-CH-CH₃), 24.0 (t, CH₂-CH-iPr), 22.6 (q, CH₃-CH-CH₃), 21.4 (q, CH₃-CH-CH₃), 16.9 (q, CH₂-CH-CH₃).

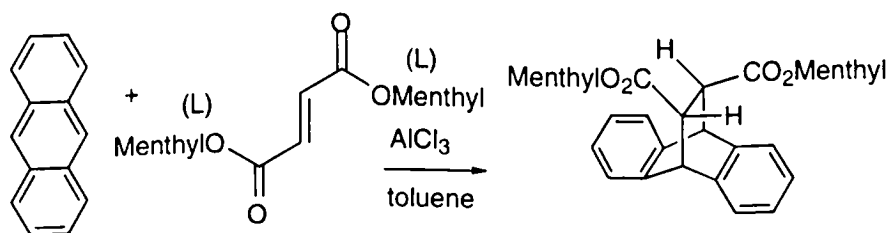


(D)-Dimenthyl fumarate [BEJ-I-20] was prepared from (D)-menthol (61.5 g, 394 mmol) similarly using the procedure described above to afford (D)-dimenthyl fumarate (74.4 g, 96 % yield) as a pale yellow solid: mp 57-59 °C; $[\alpha]_D = +99.4^\circ$ ($c = 1.39$, CHCl_3); $^1\text{H NMR}$ δ 6.82 (s, 2H, C=C-H), 4.79 (ddd, $J = 4.4, 4.4, 10.9$ Hz, 2H, O-C-H), 2.04 (m, 2H, CH-iPr), 1.86 (m, 2H, $\text{CH}_2\text{-CH-CH}_3$), 1.67 (m, 4H, $\text{CH}_2\text{-CH-iPr}$), 1.43 (m, 4H, $\text{CH}_2\text{-C-O}$), 1.02 (m, 4H, $\text{CH}_2\text{-CH}_2\text{-CH-iPr}$), 0.90 (m, 14H, $\text{CH}_3\text{-CH-CH}_3$), 0.75 (d, $J = 6.9$ Hz, 6H, $\text{CH}_2\text{-CH-CH}_3$); $^{13}\text{C NMR}$ δ 165.3 (s, C=O), 134.5 (d, CH-C=O), 76.0 (d, O-C-H), 47.7 (d, CH-iPr), 41.4 (t, $\text{CH}_2\text{-CH}_2\text{-CH-iPr}$), 34.8 (t, $\text{CH}_2\text{-C-O}$), 32.0 (d, CHMe₂), 26.9 (d, $\text{CH}_2\text{-CH-CH}_3$), 24.0 (t, $\text{CH}_2\text{-CH-iPr}$), 22.6 (q, $\text{CH}_3\text{-CH-CH}_3$), 21.4 (q, $\text{CH}_3\text{-CH-CH}_3$), 16.9 (q, $\text{CH}_2\text{-CH-CH}_3$).



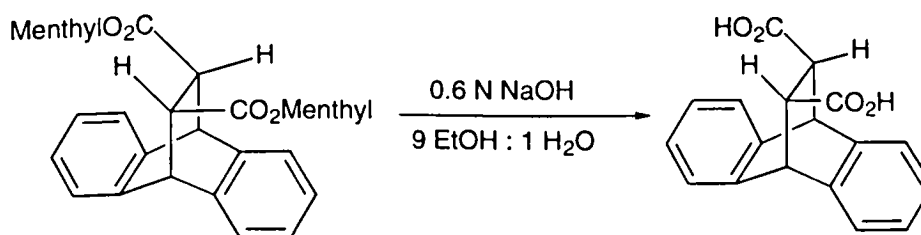
Preparation of (R,R)-9,10-ethane-11,12-dimenthyl carboxylate-9,10-dihydro anthracene by the procedure of Yamamoto, reference 38, (prepared by KLR-I-38). A mixture of aluminum trichloride (10.64 g, 80.0 mmol), anthracene (7.30 g, 40.8 mmol), and toluene (350 mL) was stirred at 0 °C. (D)-Dimenthyl fumarate (16.0 g, 40.8 mmol) was added, solution was brought to room temperature, and stirred for

4.5 hours. The resulting mixture was quenched with water (100 mL). Ethyl acetate (200 mL) was added and the mixture stirred for 24 hours. The organic layer was then washed sequentially with saturated aqueous NaCl (2 x 100 mL), 10 % aqueous NaOH (100 mL), and saturated aqueous NaCl (100 mL). The organic layer was then dried (Na_2SO_4), filtered, and concentrated. The resulting white solid was recrystallized from ethanol to give (R,R)-9,10-ethane-11,12-dimethyl carboxylate-9,10-dihydro anthracene (18.0 g, 77 % yield) as a white solid: mp 166-167 °C $[\alpha]_D = +29.4^\circ$ ($c = 4.99$, CHCl_3); ^1H NMR δ 7.37 (m, 2H), 7.23 (m, 2H), 7.12 (m, 4H), 4.72 (s, 2H, CH-Ar), 4.60 (ddd, $J = 4.4, 4.4, 10.9$ Hz, 2H, O-C-H), 3.40 (s, 2H, CH-C=O), 2.00 (m, 2H, CH-iPr), 1.84 (m, 2H, $\text{CH}_2\text{-CH-CH}_3$), 1.70 (m, 4H, $\text{CH}_2\text{-CH-iPr}$), 1.43 (m, 4H, $\text{CH}_2\text{-C-O}$), 0.98 (m, 18H), 0.76 (d, $J = 7.2$ Hz, 6H, $\text{CH}_2\text{-CH-CH}_3$); ^{13}C NMR δ 172.6 (s, C=O), 143.2 (s), 140.8 (s), 127.0 (d), 126.7 (d), 125.5 (d), 124.2 (d), 75.7 (d, O-C-H), 48.9 (d), 47.7 (d), 47.6 (d), 41.4 (t, $\text{CH}_2\text{-CH}_2\text{-CH-iPr}$), 34.9 (t, $\text{CH}_2\text{-C-O}$), 32.0 (d, CHMe_2), 26.7 (d, $\text{CH}_2\text{-CH-CH}_3$), 23.8 (t, $\text{CH}_2\text{-CH-iPr}$), 22.6 (q, $\text{CH}_3\text{-CH-CH}_3$), 21.7 (q, $\text{CH}_3\text{-CH-CH}_3$), 16.8 (q, $\text{CH}_2\text{-CH-CH}_3$).



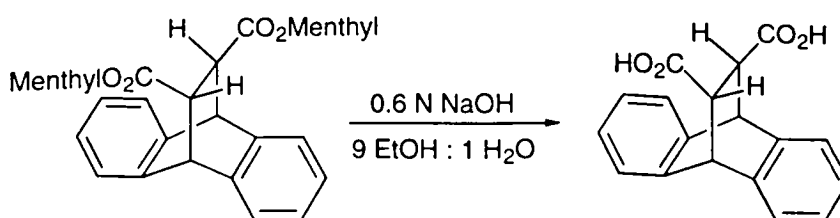
(S,S)-9,10-Ethane-11,12-dimethyl carboxylate-9,10-dihydro anthracene (prepared by KLR-I-21-2). The cycloadduct was prepared from (L)-dimethyl fumarate (5.66 g, 14.4 mmol) using the procedure described above to afford (S,S)-9,10-ethane-11,12-dimethyl carboxylate-9,10-dihydro anthracene (5.89 g, 71 % yield) as a white solid: mp 168.5-170 °C; $[\alpha]_D = -30.0^\circ$ ($c = 5.02$, CHCl_3); ^1H NMR δ

7.38 (m, 2H), 7.23 (m, 2H), 7.12 (m, 4H), 4.71 (s, 2H, CH-Ar), 4.59 (ddd, $J = 4.4$, 4.4, 10.9 Hz, 2H, O-C-H), 3.40 (s, 2H, CH-C=O), 2.00 (m, 2H, CH-iPr), 1.82 (m, 2H, CH₂-CH-CH₃), 1.67 (m, 4H, CH₂-CH-iPr), 1.43 (m, 4H, CH₂-C-O), 0.98 (m, 18H), 0.77 (d, $J = 6.9$ Hz, 6H, CH₂-CH-CH₃); ¹³C NMR d 172.6 (s, C=O), 143.2 (s), 140.8 (s), 127.0 (d), 126.7 (d), 125.5 (d), 124.2 (d), 75.7 (d, O-C-H), 48.9 (d), 47.7 (d), 47.6 (d), 41.4 (t, CH₂-CH-iPr), 34.9 (t, CH₂-C-O), 32.0 (d, CHMe₂), 26.7 (d, CH₂-CH-CH₃), 23.8 (t, CH₂-CH-iPr), 22.6 (q, CH₃-CH-CH₃), 21.7 (q, CH₃-CH-CH₃), 16.7 (q, CH₂-CH-CH₃).

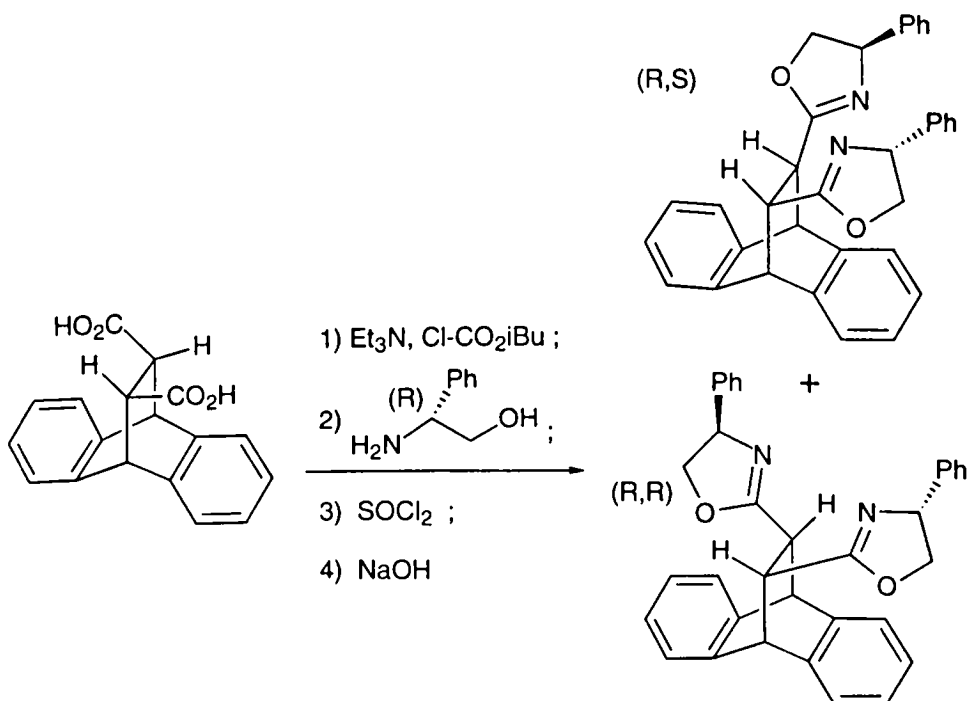


Preparation of (R,R)-9,10-ethane-11,12-dicarboxylic acid-9,10-dihydro anthracene by the procedure of Matsuda, reference 37, [BEJ-II-24]. A mixture of (R,R)-9,10-ethane-11,12-dimethyl carboxylate-9,10-dihydro anthracene (9.60 g, 16.8 mmol) and 170 mL of 0.6 N sodium hydroxide (4.0 g, 100 mmol) in 9:1 ethanol:water was heated to reflux. After 16 hours, the mixture was concentrated via rotovap, then diluted with water (100 mL) and further concentrated. The residue was slurried in water (100 mL) and some liberated white solid (menthol) separated by filtration. The filtrate was acidified with hydrochloric acid until pH < 2, then extracted with diethyl ether (3 x 75 mL). The combined organic extracts were dried (MgSO₄), filtered, and concentrated. The residue was recrystallized from acetonitrile to give (R,R)-9,10-ethane-11,12-dicarboxylic acid-9,10-dihydro anthracene (3.13 g, 63 % yield) as a white powder:

mp 253-254.5 °C [literature³⁹ mp 252.5 °C]; $[\alpha]_D = +12.1^\circ$ ($c = 5.22$, 1,4-dioxane) [literature³⁹ $[\alpha]_{578} = +11.7^\circ$ ($c = 5.00$, 1,4-dioxane)]; ^1H NMR (acetone- d_6) δ 10.87 (s, 2H, CO_2H), 7.39 (s, 2H), 7.29 (s, 2H), 7.09 (m, 4H), 4.83 (s, 2H, CH-Ar), 3.38 (s, 2H, CH-C=O); ^{13}C NMR (acetone- d_6) δ 173.5 (s, C=O), 143.6 (s), 141.6 (s), 126.8 (d), 126.7 (d), 125.5 (d), 124.2 (d), 48.2 (d), 47.3 (d); FT-IR (ZnSe, ATR) 2962, 1705 cm^{-1} .



(S,S)-9,10-Ethane-11,12-dicarboxylic acid-9,10-dihydro anthracene [BEJ-II-8] was prepared from (S,S)-9,10-ethane-11,12-dimethyl carboxylate-9,10-dihydro anthracene (8.40 g, 14.7 mmol) using the procedure described above to afford (S,S)-9,10-ethane-11,12-dicarboxylic acid-9,10-dihydro anthracene (2.28 g, 53 % yield) as a white powder: mp 252-253.5 °C [literature³⁹ mp 252.5 °C]; $[\alpha]_D = -5.05^\circ$ ($c = 2.06$, 1,4-dioxane) [literature³⁹ $[\alpha]_{578} = -15.3^\circ$ ($c = 2.00$, 1,4-dioxane)]; ^1H NMR (acetone- d_6) δ 10.67 (s, 2H, CO_2H), 7.39 (s, 2H), 7.29 (s, 2H), 7.09 (m, 4H), 4.82 (s, 2H, CH-Ar), 3.38 (s, 2H, CH-C=O); ^{13}C NMR (acetone- d_6) δ 173.4 (s, C=O), 143.6 (s), 141.4 (s), 126.8 (d), 126.6 (d), 125.4 (d), 124.2 (d), 48.2 (d), 47.3 (d); FT-IR (Zn-Se, ATR) 2966, 1730 cm^{-1} .



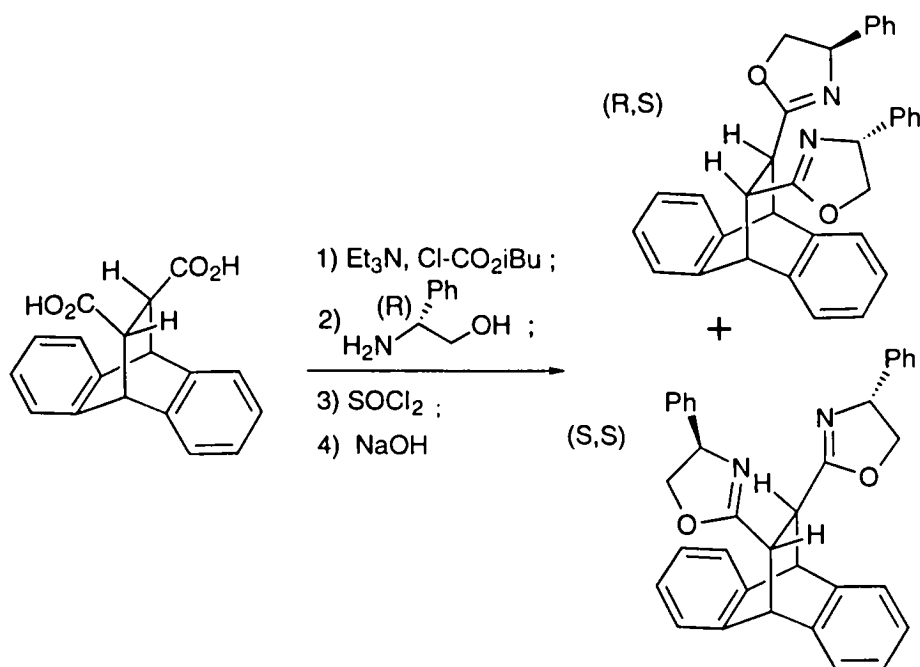
Preparation of (R,R)-9,10-ethane-11,12-((R,R)-4,4'-diphenyl-2,2'-(1,4)-bisoxazoline-9,10-dihydro anthracene, compound 6, by the procedures of Pettit, reference 40 and Nishiyama, reference 41, [BEJ-II-22, BEJ-II-26, BEJ-II-28]. To a cooled ($-5\text{ }^\circ\text{C}$) solution of (R,R)-9,10-ethane-11,12-dicarboxylic acid-9,10-dihydro anthracene (1.00 g, 3.40 mmol) and triethylamine (0.99 mL, 7.1 mmol) in THF (40 mL) was added isobutyl chloroformate (0.96 mL, 7.4 mmol). The resulting slurry was stirred for 30 minutes ($-5\text{ }^\circ\text{C}$), then filtered directly into a solution of (R)-phenylglycinol (1.0 g, 7.4 mmol) in cold ($-5\text{ }^\circ\text{C}$) THF (70 mL). The resulting mixture was stirred and slowly warmed to room temperature. After 16 hours, the mixture was concentrated and the residue partitioned between DCM (75 mL) and 10% aqueous HCl (75 mL). The organic layer was washed sequentially with 10% aqueous HCl (75 mL), saturated aqueous NaCl (75 mL), and then dried (MgSO_4), filtered, and concentrated to give a crude bis amide alcohol which was used without further purification.

This crude bis amide alcohol was dissolved in DCM (100 mL) and treated with thionyl chloride (4.9 mL, 67 mmol). After 15 min, the resulting solution was heated at reflux for 3 hours and then cooled to room temperature. The solution was washed sequentially with cold water (100 mL), 0.1 M aqueous K_2CO_3 (2 x 120 mL), and saturated aqueous NaCl (100 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by chromatography on silica (step gradient eluent: 98:2 Hex:EtOAc (300 mL); 50:50 Hex:EtOAc) to give a crude bis amide chloride which was used without further purification.

A mixture of this purified bis amide chloride and 180 mL 0.6 N sodium hydroxide (4.3 g, 108 mmol) in 7:3 methanol:water was heated under reflux for 4 hours. The mixture was then concentrated to remove methanol. Sodium chloride was added to saturate the aqueous layer, and the resulting mixture extracted with DCM (4 x 90 mL). The extracts were washed with 2 % aqueous sodium hydroxide, dried (Na_2SO_4), filtered, and concentrated. Chromatography on silica, 75:25 Hex:EtOAc, yielded the (1,4)-bisoxazoline ligand **8** (0.189 g, 11 % yield) as a pale yellow solid and the desired (R,R)-(1,4)-bisoxazoline ligand **6** (0.358 g, 21 % yield): TLC analysis (60:40 DCM:Et₂O, Iodine chamber visualization), R_f 0.76 (R,R)-9,10-ethane-11,12-((R,R)-N,N'-bis-(2-chloro-1-phenylethyl)-carboxamide)-9,10-dihydro anthracene, 0.71 **8**, 0.64 **6**.

(R,S)-bisoxazoline **8**: mp 87-89 °C; $[\alpha]_D = +40.6^\circ$ ($c = 1.06$, $CHCl_3$); 1H NMR δ 7.35 (m, 4H), 7.26 (m, 6H), 7.15 (m, 4H), 7.06 (m, 4H), 4.99 (dd, $J = 7.9, 9.8$ Hz, 2H, Ph-CH-N), 4.82 (s, 2H, CH-Ar fused), 4.57 (dd, $J = 8.6, 10.0$ Hz, 2H from 2 CH_2 's), 4.01 (t, $J = 8.0$ Hz, 2H from 2 CH_2 's), 3.68 (s, 2H, CH-BO); ^{13}C NMR δ 169.5 (s, O-C=N), 143.2 (s), 141.1 (s), 129.2 (d), 127.2 (d), 127.0 (d), 124.5 (d), 75.9 (t), 69.9 (d, Ph-CH-N), 47.6 (d, CH-Ar fused), 43.5 (d, CH-BO); FT-IR (ZnSe, ATR) 3024, 2962, 1657 cm^{-1} ; Combustion analysis ($C_{34}H_{28}N_2O_2 = 82.23\%$ C, 5.68 % H) found 82.42 % C, 5.72 % H.

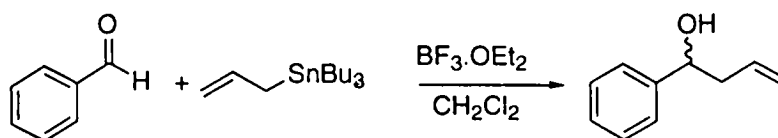
(R,R)-bisoxazoline **6**: mp 147-149 °C; $[\alpha]_D = -27.4^\circ$ ($c = 1.03$, CHCl_3); ^1H NMR δ 7.35 (m, 14H), 6.50 (m, 4H), 5.02 (t, 2H, $J = 8.9$ Hz, Ph-CH-N), 4.89 (s, 2H, CH-Ar fused), 4.60 (dd, $J = 8.1, 10.1$ Hz, 2H from 2 CH_2 's), 3.97 (t, $J = 8.2$ Hz, 2H from 2 CH_2 's), 3.93 (s, 2H, CH-BO); ^{13}C NMR δ 169.9 (s, O-C=N), 142.8 (s), 141.6 (s), 129.1 (d), 127.1 (d), 125.5 (d), 125.2 (d), 76.6 (t), 69.7 (d, Ph-CH-N), 47.2 (d, CH-Ar fused), 43.8 (d, CH-BO); FT-IR (ZnSe, ATR) 3026, 2964, 1657 cm^{-1} ; Combustion analysis ($\text{C}_{34}\text{H}_{28}\text{N}_2\text{O}_2 = 82.23\%$ C, 5.68% H) found 81.96% C, 5.46% H.



(S,S)-9,10-ethane-11,12-((R,R)-4,4'-diphenyl-2,2'-(1,4)-bisoxazoline-9,10-dihydro anthracene, compound 7, [BEJ-II-5, BEJ-II-6, BEJ-II-9]. Compound **7** was prepared from (S,S)-9,10-ethane-11,12-dicarboxylic acid-9,10-dihydro anthracene (1.00 g, 3.40 mmol) using the procedure described above to afford the

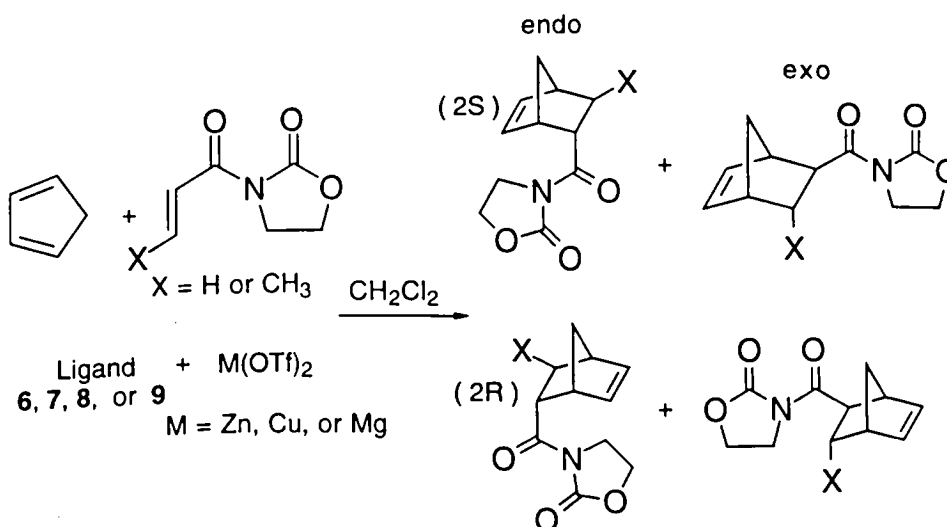
(1,4)-bisoxazoline ligand **8** (0.122 g, 7 % yield) as a pale yellow solid and the desired (S,S)-(1,4)-bisoxazoline ligand **7** (0.154 g, 9 % yield): TLC analysis (60:40 DCM:Et₂O, Iodine chamber visualization), *R_f* 0.76 (R,R)-9,10-ethane-11,12-((R,R)-N,N'-bis-(2-chloro-1-phenylethyl)-carboxamide)-9,10-dihydro anthracene, 0.71 **8**, 0.64 **7**.

(S,S)-bisoxazoline **7**: mp 158-159.5 °C; [α]_D = - 33.2° (c = 0.99, CHCl₃); ¹H NMR δ 7.54 (m, 2H), 7.24 (m, 12H), 6.49 (m, 4H), 5.02 (t, 2H, J = 9.3 Hz, Ph-CH-N), 4.87 (s, 2H, CH-Ar fused), 4.60 (dd, J = 8.1, 10.1 Hz, 2H from 2 CH₂'s), 3.96 (t, J = 8.1 Hz, 2H from 2 CH₂'s), 3.92 (s, 2H, CH-BO); ¹³C NMR δ 169.9 (s, O-C=N), 142.8 (s), 141.6 (s), 129.1 (d), 127.1 (d), 125.5 (d), 125.2 (d), 76.6 (t), 69.8 (d, Ph-CH-N), 47.2 (d, CH-Ar), 43.8 (d, CH-BO); FT IR (ZnSe, ATR) 2966, 2895, 1656 cm⁻¹; Combustion analysis (C₃₄H₂₈N₂O₂ = 82.23 % C, 5.68 % H) found 82.06 % C, 5.46 % H.



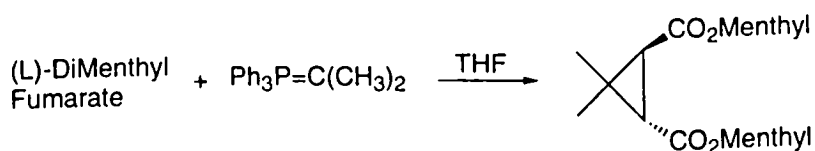
Preparation of 1-phenyl-3-buten-1-ol by the procedure of Keck, reference 26, [BEJ-II-60]. To a cooled (- 78 °C) solution of benzaldehyde (0.12 mL, 1.2 mmol) and allyltributyltin (0.34 mL, 1.1 mmol), DCM (2.0 mL), boron trifluoride diethyl etherate (0.12 mL, 1.0 mmol) was added dropwise. The reaction mixture was slowly warmed to room temperature. After 2 hours, saturated aqueous NaHCO₃ (4 mL) was added and the resulting mixture stirred rapidly (1h). DCM (20 mL) and Na₂SO₄ was added, and the organic layer was separated, dried, filtered, and concentrated. Chromatography on silica (91:9 Hex:EtOAc) yielded 1-phenyl-3-buten-1-ol (0.150 g, 84 % yield) as a clear oil: TLC analysis (91:9 Hex:EtOAc, Iodine chamber visualization) *R_f*

0.08; ^1H NMR δ 7.32 (m, 5H), 5.81 (m, 1H, $\text{CH}=\text{CH}_2$), 5.17 (m, 2H, $\text{CH}=\text{CH}_2$), 4.73 (m, 1H, benzylic), 2.53 (m, 2H), 2.29 (s, 1H, OH); ^{13}C NMR δ 144.6 (s, $\text{CH}=\text{CH}_2$), 135.2 (s), 129.1 (d), 128.2 (d), 126.5 (d), 119.0 (t, $\text{CH}=\text{CH}_2$), 74.0 (d, benzylic), 44.5 (t).



The general procedure for the Diels-Alder reactions catalyzed by bisoxazolines and metal triflates, [BEJ-III-17]. A mixture of ligand **6** (0.0639 g, 0.129 mmol), zinc triflate (0.351 g, 0.0965 mmol), and DCM (1.5 mL) was stirred at room temperature. After 45 minutes, acryloyloxazolidinone (0.0735 g, 0.521 mmol) or (E)-crotonyloxazolidinone was added. After 15 minutes, cyclopentadiene (0.34 mL, 4.2 mmol) was added. After 16 hours, the mixture was concentrated. Chloroform (2 mL) and saturated aqueous NaHCO_3 (4 mL) were added. The organic layer was dried (MgSO_4), filtered, and concentrated. The reaction yield (93 %) was determined by ^1H NMR integration comparing the remaining starting material and the formation of endo plus exo product. The endo / exo ratio (90 / 10) was determined by ^1H NMR integration. A portion of pure endo isomers, which was isolated by chromatography on silica (75:25

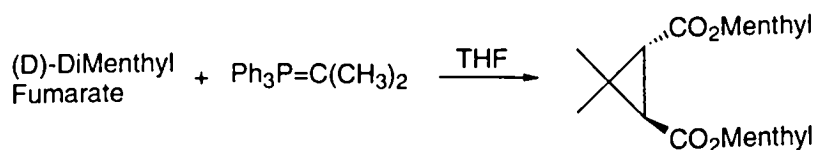
Hex:EtOAc), was injected into the chiral gas-chromatograph (Daicel cyclodex- β column, with temperature program starting at 110 °C and going to 150 °C at a rate of 0.4 degrees per minute, and then going to 220 °C at a rate of 2.0 degrees per minute). The 2S enantiomer eluted at 105.5 minutes and the 2R enantiomer eluted at 105.9 minutes to determine the 2R / 2S (71.5 / 27.5) enantiomeric composition. For the acryloyloxazolidinone system, a starting material proton occurs at δ 5.96 ppm and was integrated and compared to the endo / exo proton of the product. For the (E)-crotonyloxazolidinone system, the starting material methyl group occurs at δ 1.97 ppm and was integrated and compared to the endo / exo methyl group of the product. For the acryloyloxazolidinone plus cyclopentadiene product, the signal at δ 3.03 ppm and 2.94 ppm is the endo / exo proton and was integrated. For the (E)-crotonyloxazolidinone plus cyclopentadiene product, the signal at δ 1.15 ppm and 0.88 ppm is the endo / exo methyl group and was integrated.



Preparation of (1S,3S)-dimenthyl caronate by the procedure of Krief, reference 42, [BEJ-I-23]. To a cooled solution (0 °C) of isopropyltriphenylphosphonium iodide (15.6 g, 36.0 mmol) in THF (485 mL) nBuLi (14.4 mL, 36.0 mmol) was added.

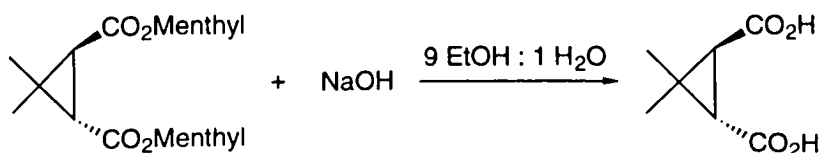
This ylide solution was slowly added via addition funnel to a cooled (-78 °C) solution of (L)-dimenthyl fumarate (11.8 g, 30.1 mmol) in THF (600 mL). The resulting mixture was stirred for 30 minutes and then brought to room temperature. The reaction

was quenched by the addition of 10% aqueous hydrochloric acid. The mixture was dried (MgSO_4), filtered, and concentrated. Chromatography on silica (step gradient eluent : 100% Hex (300 mL); 98:2 Hex:EtOAc) yielded a crude product which was crystallized in 100% ethanol (0.1 M) and letting the solution stand overnight to give (1S,3S)-dimenthyl caronate (4.88 g, 37 % yield) as white crystals: mp 138-139.5 °C; ^1H NMR δ 4.66 (ddd, $J = 4.3, 4.3, 11.0$ Hz, 2H, O-C-H), 2.19 (s, 2H, CH-CO₂CH), 1.92 (m, 4H), 1.66 (m, 4H, CH₂-CH-iPr), 1.41 (m, 4H, CH₂-C-O), 1.25 (s, 6H, CH₃-C-CH₃), 0.99 (m, 4H, CH₂-CH₂-CH-iPr), 0.88 (m, 14H, CH₃-CH-CH₃), 0.74 (d, $J = 6.9$ Hz, 6H, CH₂-CH-CH₃); ^{13}C NMR δ 170.9 (s, C=O), 75.4 (d, O-C-H), 47.6 (d, CH-iPr), 41.8 (t, CH₂-CH₂-CH-iPr), 34.9 (t, CH₂-C-O), 34.0 (q, CH₃-C-CH₃), 32.0 (d, CHMe₂), 30.2 (s, CH₃-C-CH₃), 26.7 (d, CH₂-CH-CH₃), 24.0 (t, CH₂-CH-iPr), 22.6 (q, CH₃-CH-CH₃), 21.4 (q, CH₃-CH-CH₃), 21.0 (d, CH-CO₂CH), 16.9 (q, CH₂-CH-CH₃).

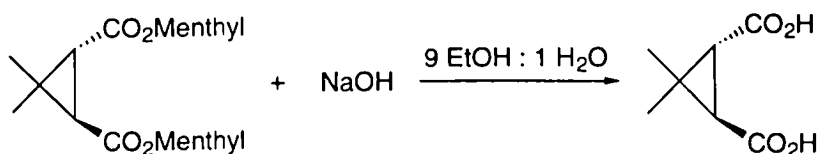


(1R,3R)-Dimenthyl caronate, [BEJ-I-16] was prepared from (D)-dimenthyl fumarate (8.93 g, 22.7 mmol) using the procedure described above to afford (1R,3R)-dimenthyl caronate (4.54 g, 46 % yield) as white crystals: mp 137-138 °C; ^1H NMR δ 4.66 (ddd, $J = 4.3, 4.3, 11.0$ Hz, 2H, O-C-H), 2.19 (s, 2H, CH-CO₂CH), 1.92 (m, 4H), 1.66 (m, 4H, CH₂-CH-iPr), 1.42 (m, 4H, CH₂-C-O), 1.25 (s, 6H, CH₃-C-CH₃), 0.99 (m, 4H, CH₂-CH₂-CH-iPr), 0.88 (m, 14H, CH₃-CH-CH₃), 0.74 (d, $J = 6.9$ Hz, 6H, CH₂-CH-CH₃); ^{13}C NMR δ 170.9 (s, C=O), 75.4 (d, O-C-H), 47.6 (d, CH-iPr), 41.8

(t, CH₂-CH₂-CH-iPr), 34.9 (t, CH₂-C-O), 34.0 (q, CH₃-C-CH₃), 32.0 (d, CHMe₂), 30.2 (s, CH₃-C-CH₃), 26.7 (d, CH₂-CH-CH₃), 24.0 (t, CH₂-CH-iPr), 22.6 (q, CH₃-CH-CH₃), 21.4 (q, CH₃-CH-CH₃), 21.0 (d, CH-CO₂CH), 16.9 (q, CH₂-CH-CH₃).



Preparation of (1S,3S)-caronic acid, compound 11, by the procedure of Matsuda, reference 37, [BEJ-I-26]. A solution of (1S,3S)-dimenthyl caronate (5.00 g, 11.5 mmol) and Sodium hydroxide (2.76 g, 69.0 mmol) in 9:1 ethanol:water (100 mL) was refluxed overnight. Water (20 mL) was added to the solution and the mixture concentrated via rotovap. This process was repeated four more times. The aqueous residue was extracted with (4 x 20 mL) ether and the aqueous layer acidified with 10 % aqueous hydrochloric acid until pH < 2. The acidic aqueous layer was extracted with ether (4 x 20 mL). The combined organic layers were concentrated to give a crude product. The crude product was dissolved in 10 % aqueous sodium hydroxide and acidified with 10 % aqueous hydrochloric acid until pH < 2. The acidic aqueous layer was extracted with ether (4 x 20 mL). The combined organic extracts were dried (MgSO₄), filtered, and concentrated to give (1S,3S)-caronic acid, compound 11, (1.55 g, 86 % yield) as a white powder: mp 208-209 °C; [α]_D = + 35.8° (c = 1.98, MeOH); ¹H NMR (acetone-d₆) δ 9.93 (s, 2H, CO₂H), 2.08 (s, 2H, CH-CO₂H), 1.27 (s, 6H, CH₃); ¹³C NMR (acetone-d₆) δ 171.8 (s, CO₂H), 33.8 (d), 30.3 (s), 20.3 (q).



(1R,3R)-Caronic acid, compound 10, [BEJ-I-19] was prepared from (1R,3R)-dimenthyl caronate (4.00 g, 9.16 mmol) using the procedure described above to afford (1R,3R)-caronic acid, compound **10**, (1.19 g, 82 % yield) as a white powder: mp 206-208 °C [literature⁴³ mp 208-208.5 °C]; $[\alpha]_D = -31.5^\circ$ ($c = 2.00$, MeOH) [literature⁴³ $[\alpha]_{546} = -34.5^\circ$ (MeOH)]; ^1H NMR (acetone- d_6) δ 10.23 (s, 2H, CO_2H), 2.08 (s, 2H, $\text{CH-CO}_2\text{H}$), 1.27 (s, 6H, CH_3); ^{13}C NMR (acetone- d_6) δ 171.8 (s, CO_2H), 33.8 (d), 30.3 (s), 20.3 (q).

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