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COPPER CATALYZED CYCLOPROPANATION USING CHIRAL [2.2]PARACYCLOPHANE LIGANDS AND ACTIVATION OF NAPHTHALENES TOWARD CATALYTIC HYDROGENATION BY COORDINATION OF METAL MOIETIES

A Dissertation

SUBMITTED TO THE GRADUATE FACULTY

in partial fulfillment of the requirements for the

degree of

DOCTOR OF PHILOSOPHY

By

DOUGLAS S. MASTERSON

Norman, Oklahoma

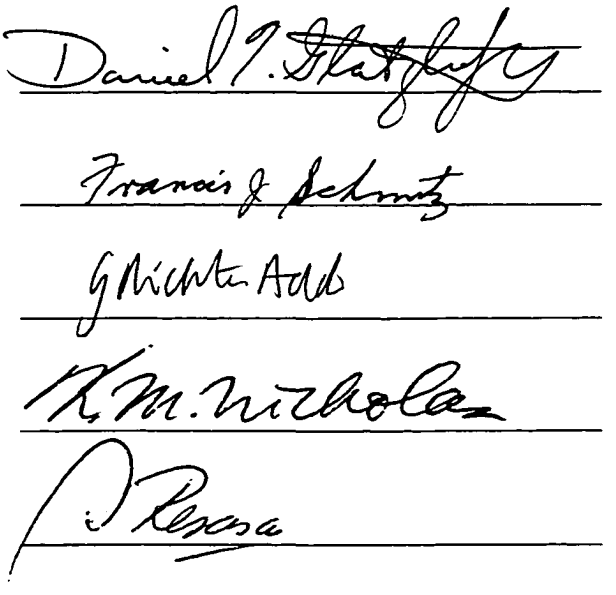
1999

COPPER CATALYZED CYCLOPROPANATION USING CHIRAL [2.2]PARACYCLOPHANE LIGANDS AND ACTIVATION OF NAPHTHALENES TOWARD CATALYTIC HYDROGENATION BY COORDINATION OF METAL MOIETIES

A Dissertation APPROVED FOR THE

DEPARTMENT OF CHEMISTRY AND BIOCHEMISTRY

BY



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ABSTRACT

The synthesis, resolution, absolute configuration, and utilization in the copper catalyzed cyclopropanation reaction of several ligands based on the chiral mono-substituted [2.2]paracyclophane moiety are presented. Schiff-base ligands based on 4-amino[2.2]paracyclophane induced enantioselectivity in the copper catalyzed cyclopropanation of olefins with diazoesters. When N-salicylidene-4-amino[2.2]paracyclophane (**5**) was used as the asymmetric ligand in the cyclopropanation of styrene with *tert*-butyldiazoacetate (TBDA), a 96% conversion to product was observed and a 40% ee for the trans isomer was obtained. When the more bulky N-(2',4'-di-*tert*-butyl)salicylidene-4-amino[2.2]paracyclophane (**14**) was used as the asymmetric ligand, an improved enantioselectivity of 67% was observed for the trans isomer in the cyclopropanation of styrene with ethyldiazoacetate (EDA). The best results were obtained using N-(4-paracyclophanyl)-2'-hydroxyacetophenone imine (**17**) as the asymmetric ligand. When (*R*)-**17** was used as the ligand a 76% ee was observed for the trans isomer in the cyclopropanation of styrene with EDA. All three ligands (**5**, **14**, and **17**) were capable of inducing significant enantioselectivity, for both the cis and trans isomers, with each of the following substrates: styrene, α-methylstyrene, 1,1-diphenylethylene. The copper catalyst derived from ligand **14** was unable to convert *trans*-stilbene and *trans*-4,4'-dimethylstilbene to cyclopropane products. This is attributed to steric interference between the bulky ortho substituent in **14** and the approaching substrate.

Mechanistic experiments were carried out which suggest that the cyclopropanation reaction using [2.2]paracyclophane based ligands proceeds by the same

mechanism as other copper catalyzed cyclopropanation reactions of olefins with diazoesters. The active state of copper was found to be the +1 oxidation state and the reactive carbenoid species was found to have considerable electrophilic character. It was found that ligands **5** and **14** had similar abilities to control olefin approach to the active carbenoid site. This suggests that the enhanced enantioselectivity observed for ligand **14** relative to **5** is probably due to the electron donating ability of the added *tert*-butyl groups.

The coordination of an iron cyclopentadienyl cation to the naphthalene moiety resulted in activation of the naphthalene ligand toward catalytic hydrogenation. Napthalene, and several dimethylnaphthalenes, when coordinated to the iron cyclopentadienyl cation, were readily reduced to their corresponding tetralin derivatives when subjected to mild catalytic hydrogenation conditions (1 atm. H_2, MeOH, RT). The rate enhancement between complexed naphthalene and non-complexed naphthalene was >> 25X. Interestingly, the reduction proved selective with the methylnaphthalenes when the methyl groups were placed in the 1 or 4 position. When a mixture of 1,4-dimethylnaphthalene iron complexes (1:1.46, iron on unsubstituted:substituted ring) was subjected to catalytic hydrogenation conditions a 88% conversion to the corresponding tetralin products was observed with a selectivity of 1:26.20 (unsubstituted ring:substituted ring). Similar selectivities in the reduction products were observed for the following substrates: 1-methylnaphthalene (1:4.90), and 1,2-dimethylnaphthalene (1:13.90). A model which accounts for the observed selectivity of the iron moiety protecting the more substituted ring in the catalytic reduction of the dimethylnaphthalenes is presented.

Attempted hydrogenation of (η^6-naphthalene)chromium tricarbonyl complexes is presented. The attempted hydrogenation of chromium complexed naphthalenes failed to produce complexed tetralin products under catalytic hydrogenation conditions. The failure to undergo catalytic reduction is attributed to the chromium tricarbonyl moieties affinity for molecular hydrogen.

CHAPTER 1: Introduction To Part I

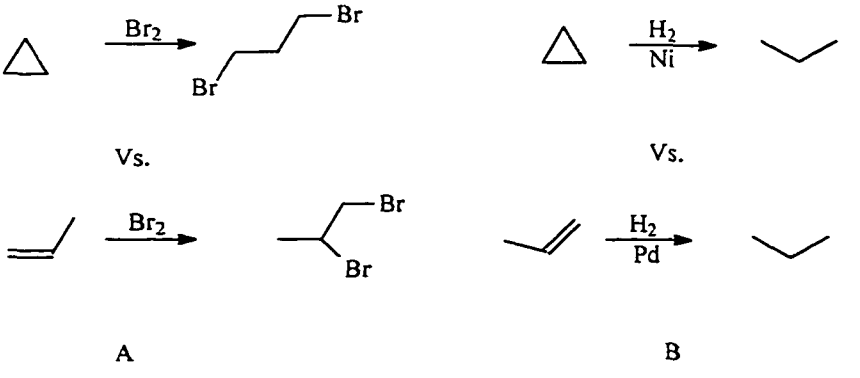
Cyclopropane, the smallest possible carbocycle, has been of great theoretical, synthetic, and biological importance. Cyclopropane derivatives have been used as: 1) probes in physical organic experiments dealing with radical mechanism elucidation,[1] 2) as both chiral and achiral building blocks in the synthesis of natural and unnatural compounds which contain no cyclopropane ring, and 3) as compounds with remarkable biological activity.

The bonding properties inherent in the cyclopropane ring have been of great interest for many years. Initially one might predict that cyclopropane derivatives could be highly unstable molecules which are difficult to isolate. Given that the geometric configuration of a cyclopropyl group demands that the internuclear C-C bond angles be 60°,[2] it would be quite rational to expect that the cyclopropyl C-C bonds would be weaker than a "normal" (i.e. sp^3) C-C bond. The reactivity of the cyclopropyl group is in accord with the "weaker" C-C bond, but in most instances cyclopropyl derivatives can be easily synthesized and isolated.

Two bonding models for cyclopropane have been proposed in an attempt to better understand the reactivity and stability of the cyclopropyl group. Both the bent bond,[2] and Walsh[2] models explain the C-C bond angles and reactivity of cyclopropane (see Figure 1).

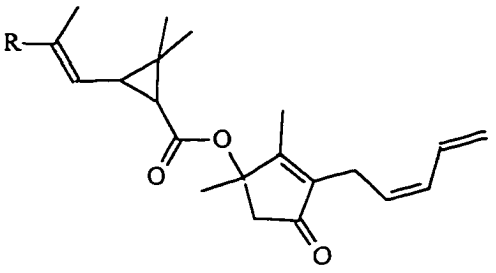
Figure 1: Cyclopropane models

The bent bond model has been shown to be the most accurate representation of cyclopropane C-C bonding. An NMR experiment was reported which confirms the bent bond model over the Walsh representation.[3] By using NMR ^{13}C-^{13}C coupling constants the hybridization of the cyclopropyl C-C bond was experimentally determined to have approximately 1/6 *s* character.[3] The 1/6 *s* character corresponds to a bond of sp^5 hybridization, giving evidence of the increased *p* character necessary for the bent bond model. The increased *p* character of the cyclopropane C-C bonds suggest that the reactivity of the cyclopropyl group should mimic that of an alkene. The reactivity of the cyclopropyl group is in accord with the increased *p* character of the C-C bond as represented in Scheme 1.[4,5]



Scheme 1: Reactivity of cyclopropane

Along with its unusual bonding and reactivity characteristics, the cyclopropyl group has found use in agriculturally and medicinally important compounds. A widely used class of insecticides, the chrysanthemic and pyrethric acid derivatives,[6] have found important use in agriculture due to their low mammalian toxicity and high insecticidal activity (Figure 2).



$R=CH_3$ (Chrysanthemic)
$R=CO_2CH_3$ (Pyrethric)

Figure 2: Cyclopropane insecticides

Many cyclopropane containing natural products have shown potent anti-tumor and anti-proliferative activity against a wide variety of cancer cell lines. Anthoplalone, isolated from the Okinawan actinia *Anthopleura pacifica*, has shown potent cytotoxicities against B-16 murine melanoma cells (Figure 3).[7]

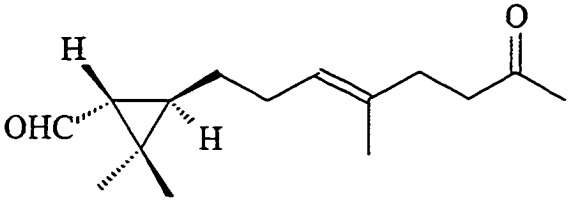


Figure 3: Anthoplalone

Curacin A, isolated from the Curacao collection of *Lyngbya majuscula*, is a cyclopropane containing lipid which has shown potent antiproliferative activity (Figure 4).[8]

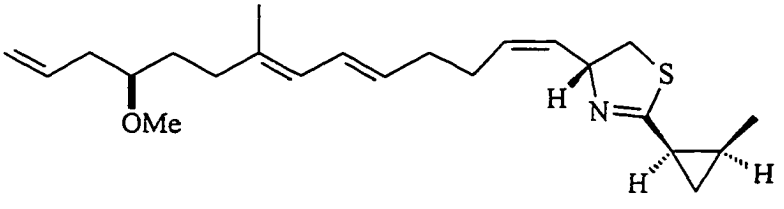
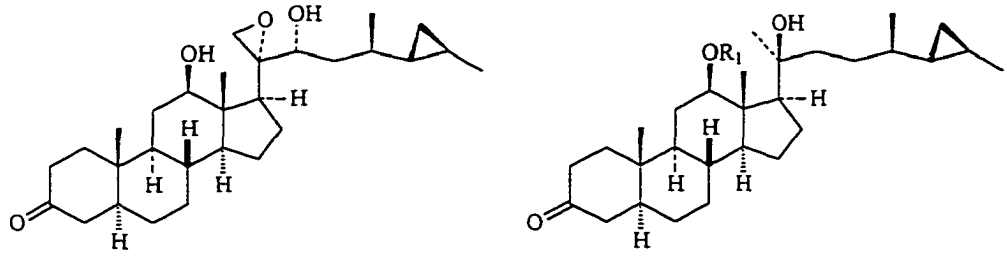


Figure 4: Curacin A

Aragusterol A and B, which were isolated from a marine sponge from the *Xestospongia* genus, have shown antiproliferative activity against KB cells. Aragusterol B demonstrated

an IC_{50} of 3.3 μg/mL toward the KB cell line *in vitro* (Figure 5).[9]



Aragusterol A Aragusterol B

Figure 5: Aragusterol A&B

Callipeltoside A, isolated from the methylene chloride extract of the shallow water lithistid sponge *Callipelta sp.*, has shown both antiproliferative activity against the KB and P388 cell lines. Callipeltoside A also demonstrated its ability to protect cells which were infected with the HIV virus (Figure 6)![10]

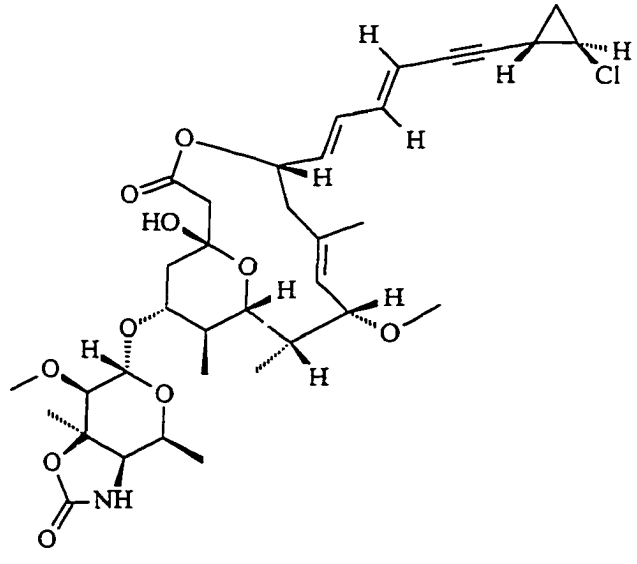


Figure 6: Callipeltoside A

It has been demonstrated that high levels of low-density lipoproteins correlates

well with coronary heart disease, a major cause of death in industrialized nations.[11] Animals which do not have the cholesteryl ester transfer protein (CETP) have relatively high levels of high-density lipoproteins which seems to correlate with reduced risk for developing coronary heart disease.[11] U-106305, a cholesteryl ester transfer protein inhibitor isolated from fermentation broths, has shown inhibition of CETP activity (Figure 7). It has been suggested that the inhibition of CETP activity may retard the progression of atherosclerosis and function as a therapeutic agent in the prevention of coronary heart disease.[11]

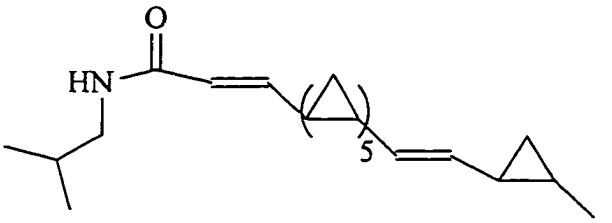


Figure 7: U-106305

Cyclopropane-containing fatty acid metabolites, halicholactone and neohalicholactone, were isolated from the marine sponge *Halchondria okadai*. Halicholactone demonstrated enzyme inhibiting activity against 5-lipoxygenase of the guinea pig polymorphonuclear leukocytes (IC_{50} = 630 μM) (Figure 8).[12]

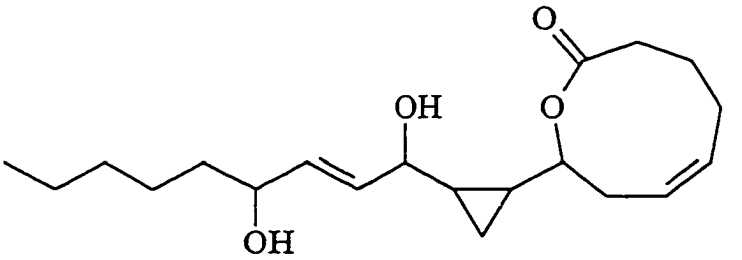


Figure 8: Halicholactone

Cyclopropane containing compounds have shown antibiotic activity. A novel, cyclopropane-containing antifungal antibiotic, FR-900848, has been isolated from fermentation broths.[13] FR-900848 has shown antifungal activity with specificity for filamentous fungi in the 0.05-0.5 μg/mL concentration range both *in vitro* and *in vivo*, and has shown effectiveness against pathogenic fungi in plants (Figure 9).[13]

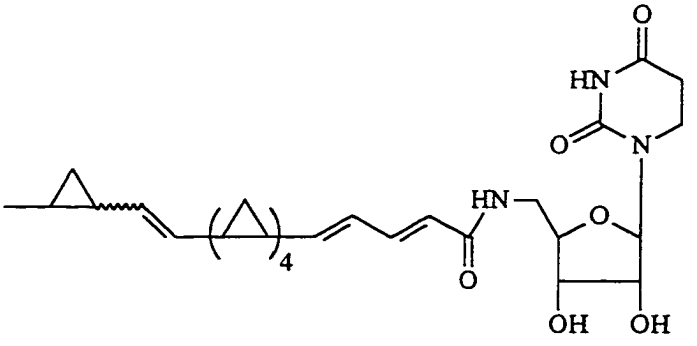
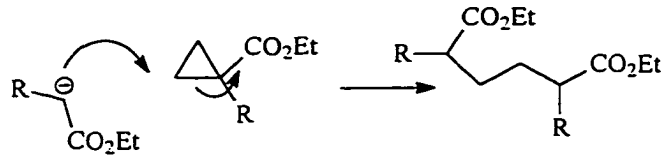


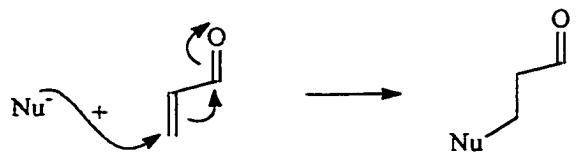
Figure 9: FR-900848

Cyclopropane derivatives have been extensively utilized in synthesis not only for their interesting structure, but also for their interesting reactivity. Cyclopropanes have been used in synthetic sequences to produce compounds which contain no cyclopropane component. Electron deficient cyclopropane derivatives have been extensively reviewed for their ability to undergo electrophilic reactions.[14] It is well known that electrophilic cyclopropane derivatives can be readily attacked by nucleophiles in a Michael fashion (Scheme 2).[14]



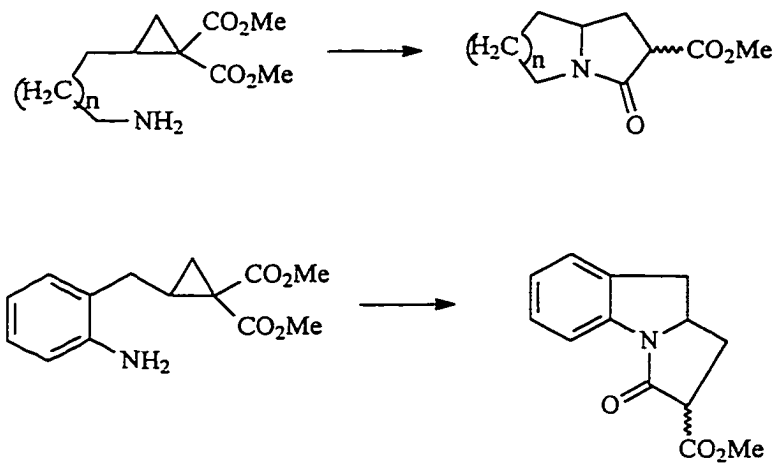
R= CO_2Et or CN

Vs.



Scheme 2: Michael addition reactions

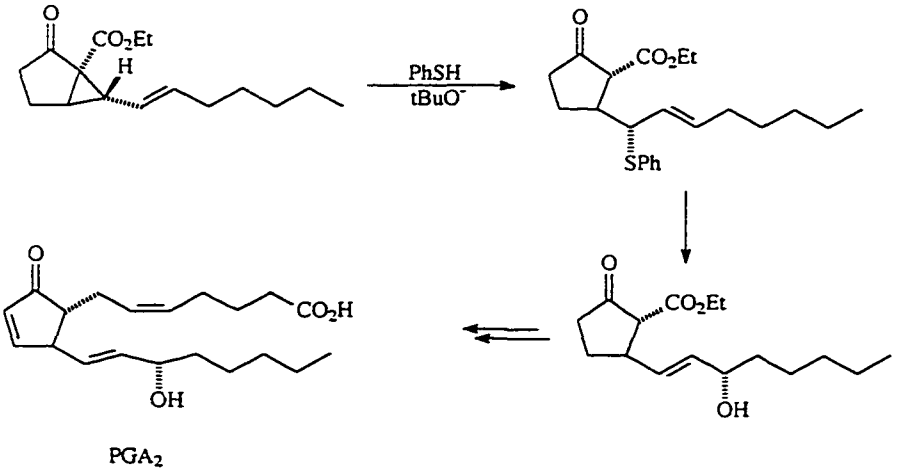
Electrophilic cyclopropane derivatives have been used successfully in annulation reactions (Scheme 3).[14]



Scheme 3: Ring annulation

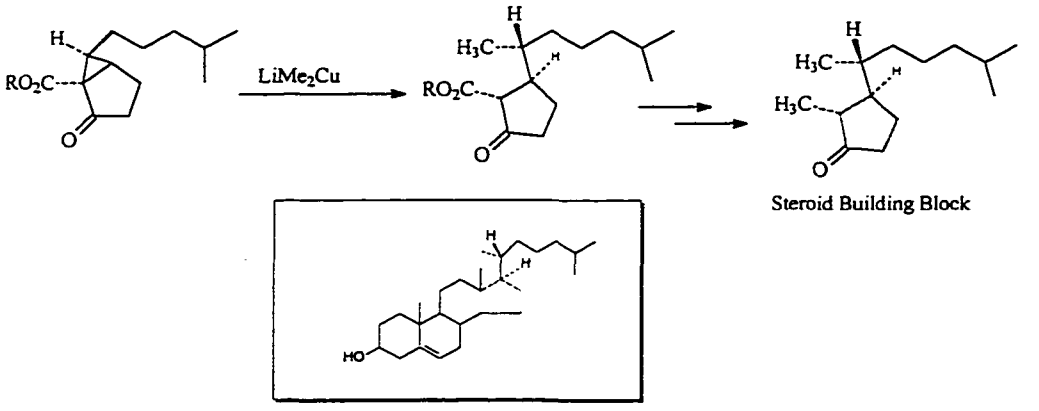
Building blocks for prostaglandins have been devised by Corey and Taber which were based on electrophilic cyclopropane derivatives.[15,16] These cyclopropane derivatives were utilized in hopes of controlling the relative stereochemistry of asymmetric centers

removed from the prostaglandin ring (Scheme 4).[16]



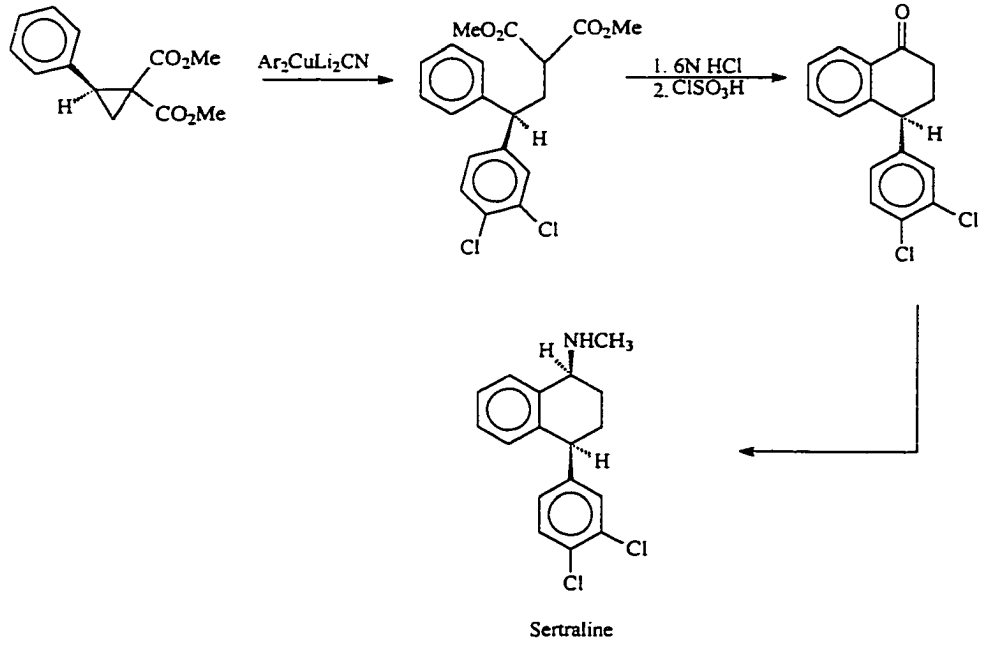
Scheme 4: Prostaglandin stereocontrol

Trost et al. reported the utilization of an electrophilic cyclopropane for steroid stereocontrol of acyclic carbon relative to ring geometry (Scheme 5).[17]



Scheme 5: Steroid stereocontrol

In 1994 E. J. Corey reported a highly efficient, asymmetric synthesis of sertraline (Zoloft®) using an electrophilic cyclopropane intermediate.[18] This synthesis afforded the highly prescribed anti-depressant drug in optically pure form and in good yield (Scheme 6).



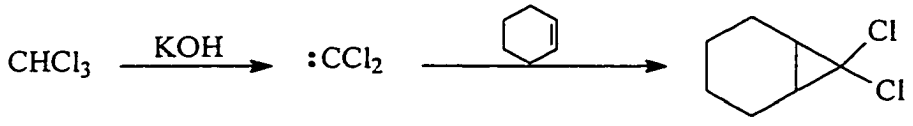
Sertraline

Scheme 6: Zoloft synthesis

The above figures and schemes illustrate the importance of the cyclopropane functional group. The cyclopropane moiety has been found in numerous natural products and has been exploited for its unusual bonding and reactivity. Many methods, both stoichiometric and catalytic, have been developed over the last several decades to construct the cyclopropane moiety, but perhaps the most effective method has been the cyclopropanation of olefins with carbenes or carbenoids.

Most students of chemistry first learn of the stoichiometric cyclopropanation

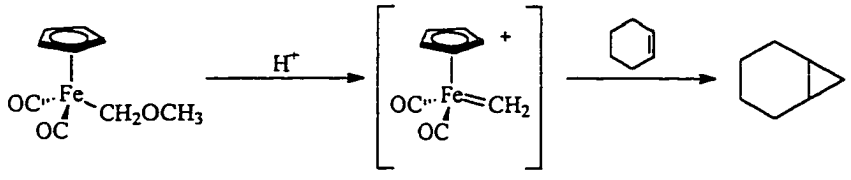
reaction in their undergraduate organic courses. Most undergraduate texts introduce the cyclopropanation reaction as a reaction between a free carbene and an olefin.[19] Typically these free carbenes are generated by an α-elimination reaction (Scheme 7).[19]



Scheme 7: α-Elimination reaction

Unfortunately, the "free" carbene cyclopropanation reaction is rather limited in synthetic scope to those compounds which readily undergo α-elimination reactions.

Fortunately it was discovered that metals and heteroatoms could be utilized to stabilize a carbene. Pettit and Jolly discovered that treatment of certain iron complexes with acid in the presence of olefin produced cyclopropane products.[20] It was initially suggested, and later confirmed, that the cyclopropanating agent in this reaction was a metal stabilized carbene (carbenoid) (Scheme 8).[20]



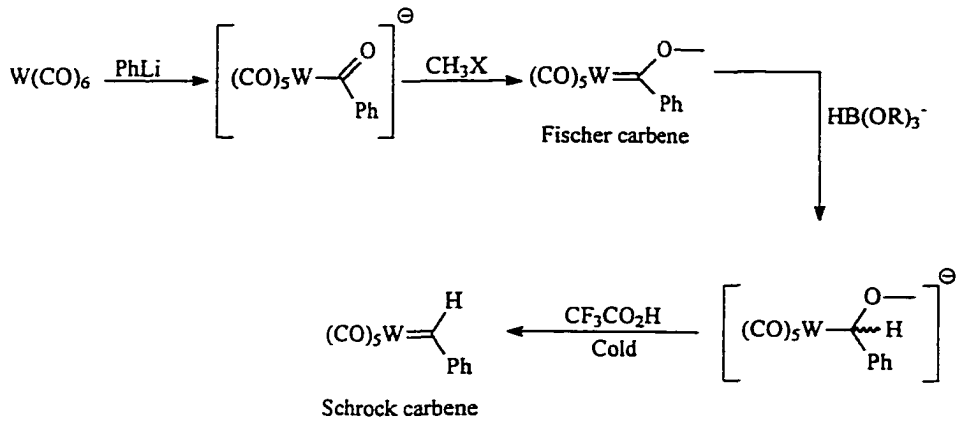
Scheme 8: Metal stabilized carbene

In the early days of these metal carbenes, it was speculated that the cyclopropanating agent may be a free carbene. Fischer demonstrated that free carbenes were indeed not the cyclopropanating agents since the syn:anti ratio was highly dependant on the metal used and that the use of optically active ligands around the metal produced some optical activity in the cyclopropane products.[20]

Fischer et al. explored the use of other metal complexes for use in the cyclopropanation of olefins. It was discovered that complexes of the type $(CO)_5M=C(OMe)Ph$ (M= Cr, Mo, W) reacted with olefins to give moderate yields of cyclopropane products.[20] It was noted in these reactions that the olefins used must contain electron withdrawing or electron donating groups for the cyclopropanation reaction to occur.

It was later reported that complexes of the type $(CO)_5W=C(Ph)H$ could also produce cyclopropane products at low reaction temperatures. The significance of this finding was that heteroatoms adjacent to the carbene were not necessary for the cyclopropanation reaction to occur and it was not necessary for the olefins to contain electronic altering groups.[20]

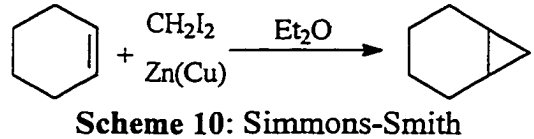
The problem with using the carbene complexes is the synthesis of a stoichiometric amount of the cyclopropanating agent.[20] Scheme 9 illustrates the synthesis of both the Fischer and Schrock type carbenes.



Scheme 9: Fischer/Schrock carbenes

It is clear from Scheme 9 that several steps are necessary for the synthesis of both the Fischer and Schrock carbene complexes.

In the late 1950's Howard Simmons and Ronald Smith reported a stoichiometric cyclopropanation reaction between methylene iodide and olefins in the presence of a zinc copper couple.[21] The advantage of this reaction is that one can utilize the readily available methylene iodide which does not undergo the α-elimination reaction with base to produce free carbene. Also this reaction does not require a tedious preparation of the carbene complex (as is required in the Fischer and Schrock systems). Scheme 10 demonstrates the use of the Simmons-Smith cyclopropanation reaction.

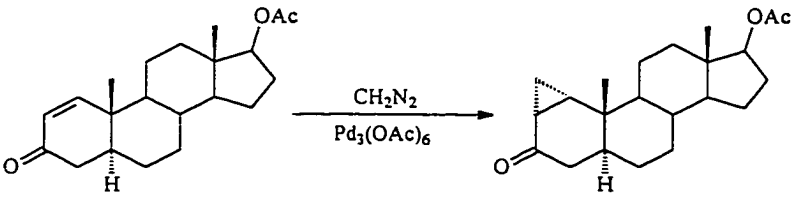


Scheme 10: Simmons-Smith

Although the use of the Simmons-Smith, Fischer, and Schrock-type

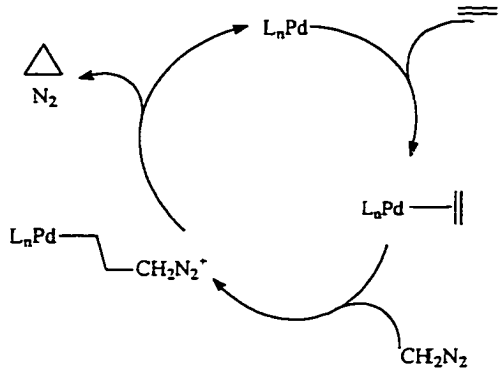
cyclopropanating agents have proven to be quite effective for the cyclopropanation of various olefin systems, one drawback to their use remains. All the above mentioned systems are stoichiometric with respect to the metal which is used in generating the cyclopropanating agent. Fortunately several transition metals have proven to be useful as catalysts in the generation of carbenoid species for the cyclopropanation of olefins. Among the best transition metals for this purpose are palladium, copper and rhodium.[22]

Palladium catalysts have proven to be extremely effective in the cyclopropanation of α,β-unsaturated carbonyl compounds with diazomethane as shown in Scheme 11.[22]



Scheme 11: Palladium catalyzed cyclopropanation

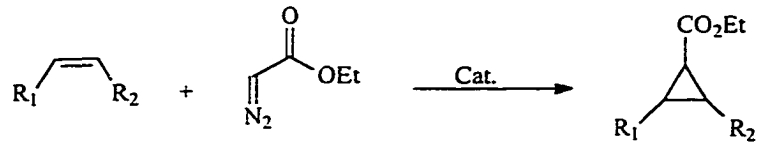
It has been proposed that the use of palladium catalyst with diazoalkanes does not proceed through a metal carbene intermediate but rather proceeds through a coordinated alkene[22] as shown in Scheme 12.



Scheme 12: Palladium catalytic cycle

It is well known that the palladium catalysts are extremely selective for diazoalkanes and reactions with diazoesters does not effectively occur.[22] The palladium catalysts are essentially an alternative to the Simmons-Smith cyclopropanation reaction.

Several catalysts have been developed around the use of copper (I) and copper (II) for the activation of diazoesters in the cyclopropanation reaction.[22] Literature examples of copper based catalysts in both inter- and intramolecular cyclopropanation reactions between diazoesters and olefins are numerous (Scheme 13). One advantage of copper based catalysts over other metals is that the initial oxidation state of the metal is of little concern. Copper has been utilized in the 0, +1, and +2 oxidation states although it has been determined that the active cyclopropanation catalyst is copper(I).[22]



Cat. = CuCl, $CuSO_4$, Cu (metal), etc.

Scheme 13: Copper catalysts

The use of dirhodium based catalysts have received considerable attention in recent years. Unlike the copper based catalysts, dirhodium catalysts are active in the +2 oxidation state of the metal.[22] These catalysts have demonstrated good catalytic properties similar to that of the copper based systems. Unfortunately, dirhodium is considerably more toxic and less cost effective than the copper based systems.

Fortunately, the copper and rhodium based catalysts perform the cyclopropanation reaction between diazoesters and olefins from essentially the same catalytic cycle as shown in Figure 10.[22]

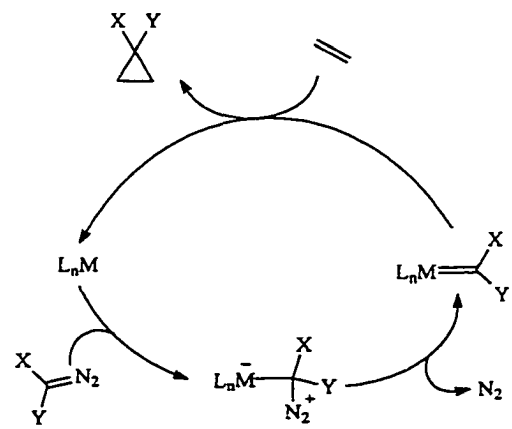
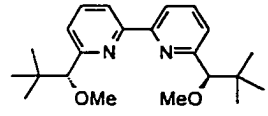


Figure 10: Copper/Rhodium catalytic cycle

Essentially the only difference between the copper based and dirhodium based catalysts as shown in Figure 10 is the active oxidation state of the metal. The dirhodium based catalysts remain in the +2 oxidation state whereas the copper based systems are active in the +1 oxidation state. There is a plethora of evidence which indicates that the +1 state is the active state of the copper based catalysts. For example, it is known that when copper(I) based catalysts are used the cyclopropanation reaction at room temperature occurs readily whereas copper(II) based catalysts require elevated temperatures or preactivation by a reducing agent to proceed.[23] When chiral bipyridine ligands are utilized, essentially the same enantioselectivities are observed between copper(I) and copper(II) based precatalysts which gives additional evidence that the active cyclopropanation catalyst is indeed copper in the +1 oxidation state (Table 1).[24]

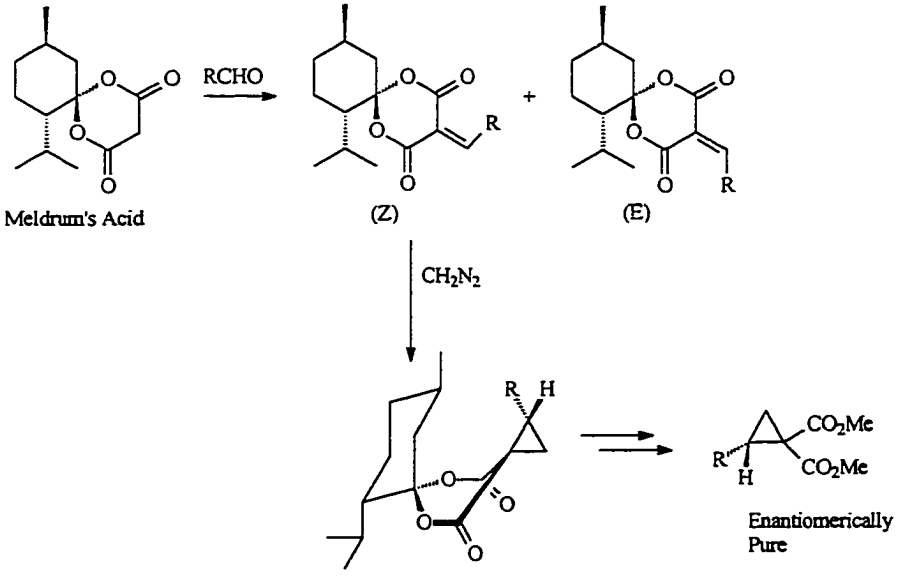


Copper (II) catalyst results				
Substrate	**Diazoester**	***trans/cis***	**%ee *trans***	**%ee *cis***
Styrene	EDA	80:20	91	92
4-Methylstyrene	EDA	80:20	88	83
Copper (I) catalyst results				
Styrene	EDA	80:20	89	74
4-Methylstyrene	EDA	80:20	88	83

Table 1: Cyclopropanation by Copper Catalysts

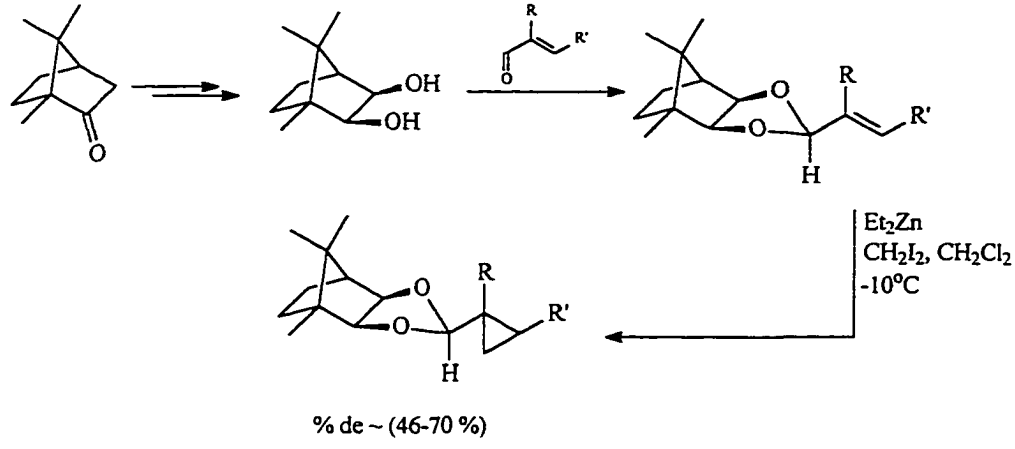
Since it is now known that the active species in the cyclopropanation of olefins with diazo compounds is a metal carbene complex, it is possible to imagine the utilization of chiral carbene complexes and chiral auxiliaries to perform asymmetric cyclopropanation reactions. Since many medicinal compounds either contain or can be derived from enantiomerically pure cyclopropanes, it would be advantageous to be able to produce the exact enantiomer of interest. There have been two main areas of interest with respect to asymmetric cyclopropanation reactions (and other asymmetric reactions): 1) the use of stoichiometric quantities of chiral auxiliaries and 2) the utilization of chiral ligands in the catalytic cyclopropanation reactions.

In recent years there has been an enormous amount of literature dedicated to the use of readily available chiral, non-racemic, compounds as chiral auxiliaries in various types of cyclopropanation reactions. For example, Meldrum's acid has been used successfully in the synthesis of enatiomerically pure 2-arylcyclopropane-1,1-dicarboxylates[25] as shown in Scheme 14.



Scheme 14: Meldrum's Acid auxiliary

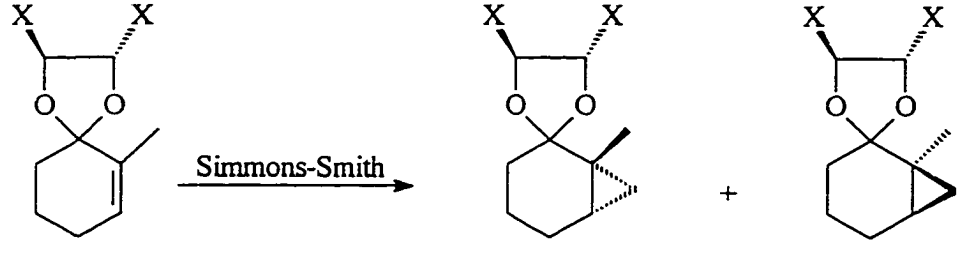
Kaye and Molema recently reported on the use of an asymmetric Simmons-Smith cyclopropanation reaction using chiral bornane-2,3-diol acetal as a chiral auxiliary (Scheme 15).[26]



% de ~ (46-70 %)

Scheme 15: Chiral acetal auxiliary

In the late 1980's Mash and Nelson reported on the diastereoselective Simmons-Smith cyclopropanation of α,β-unsaturated chiral ketals which resulted in cyclopropane products of typically greater than 70 % diastereoselectivity (Scheme 16).[27]

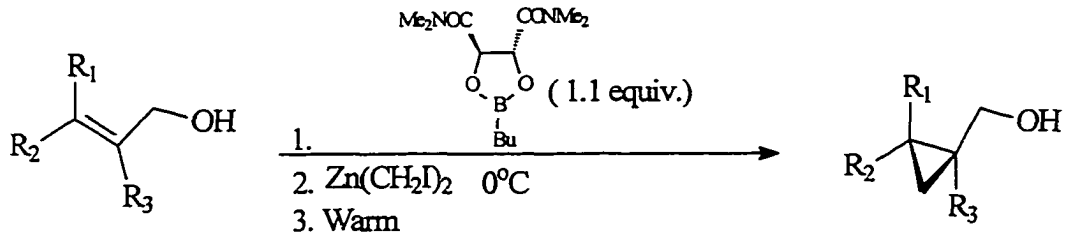


Diasteromeric Ratio = 20:1

Scheme 16: Chiral ketal auxiliary

Barrett et al. recently reported the total asymmetric synthesis of FR-900848 and U-106305 using chiral acetals as chiral auxiliaries in the Simmons-Smith cyclopropanation reaction.[28]

Charette et al. have reported on the Simmons-Smith cyclopropanation of allylic alcohols using chiral boron reagents as chiral auxiliaries. The cyclopropanation reaction occurred with conversions typically ≥ 90% and excellent enantioselectivities (≥90%) (Scheme 17).[29]



Scheme 17: Chiral boron auxiliary

One advantage of using the chiral boron derivatives in the cyclopropanation of allylic alcohols is that the reaction proceeds in a chemoselective fashion, i.e. in the presence of additional olefinic sites the allylic alcohols are the only sites which undergo cyclopropanation under Simmons-Smith conditions.[29] These reactions are believed to be controlled by a zinc alkoxide which is derived from the borane reagent, allylic alcohol, and the zinc cyclopropanating agent[29] as shown below in Figure 11.

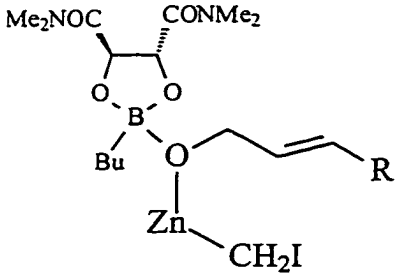
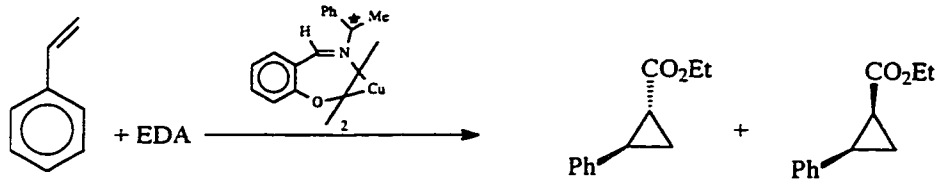


Figure 11: Proposed cyclopropanating agent

Although the use of chiral, non-racemic, auxiliaries has proven quite effective in the Simmons-Smith cyclopropanation reaction, these systems are rather limited. Unfortunately, most of the literature is based on the Simmons-Smith cyclopropanation reaction which typically (in modern versions) requires the use of the pyrophoric zinc reagents(e.g. Et_2Zn).[28] It is also worth noting that the chiral auxiliary approach requires at least a stoichiometric quantity of the auxiliary and in many instances the best enantioselectivities were achieved with a slight molar excess of the auxiliary.[28,29] The auxiliary must also be removed from the reaction medium following the reaction and this could potentially cause separation and recovery problems. Fortunately, there has been an enormous effort in designing chiral, non-racemic, ligands for use in the catalytic cyclopropanation of olefins with diazoesters.

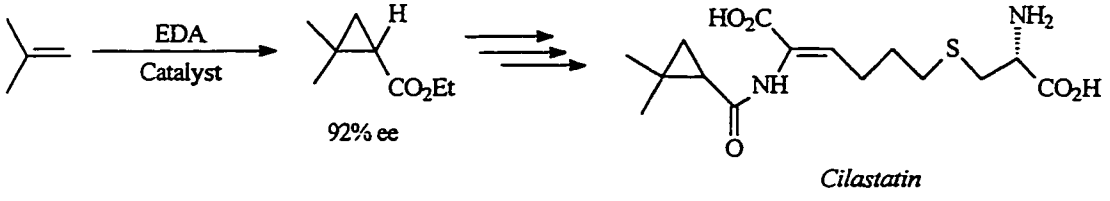
In 1966 Nozaki et al. reported the first use of a chiral homogeneous catalyst to induce enantiocontrol in a chemical transformation.[30] Nozaki et al. utilized a non-racemic Schiff-base in the presence of copper(II) to effect the transformation of styrene into the corresponding cyclopropane carboxylate as shown in Scheme 18.

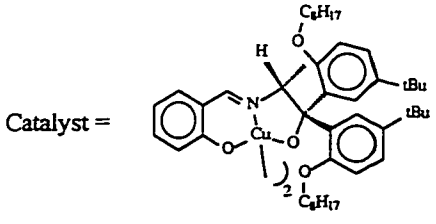


Scheme 18: 1st Asymmetric cyclopropanation

As shown in Scheme 18, the enantioselectivity was less than desirable for an effective catalyst. Although the enantioselectivity was low, this did demonstrate that chiral ligands can be utilized to induce enantioselectivity in catalytic reactions.

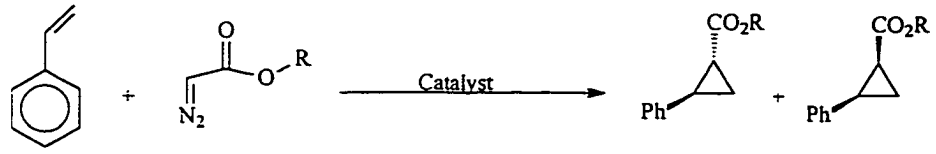
The use of chiral salicylaldimines was expanded by Aratani in the late 1970's and early 1980's.[31,32] The Aratani catalysts utilized a bulkier Schiff-base in the copper catalyzed cyclopropanation of olefins with diazoesters with greatly improved enantiocontrol relative to the Nozaki catalyst. The catalyst system that was developed by Aratani was eventually utilized in the commercial production of cilastatin (Scheme 19).[32]





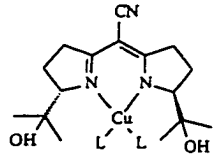
Scheme 19: Aratani improvement

In the mid 1980's Pfaltz reported on the utilization of semicorrin ligands for the copper catalyzed cyclopropanation reaction.[33,34] The semicorrin ligands were found to result in greater enantiocontrol for monosubstituted olefins (e.g. styrene) than the Aratani catalysts.[34] In the cyclopropanation of styrene with a variety of diazoesters, the semicorrin ligands showed high enantioselectivity (typically greater than 90%) for both the *cis* and *trans* diastereomers(Scheme 20).[34]



		%ee *Trans*	%ee *Cis*
R =	Et	92	80
	tBu	93	92
	d-menthyl	97	95

Catalyst =

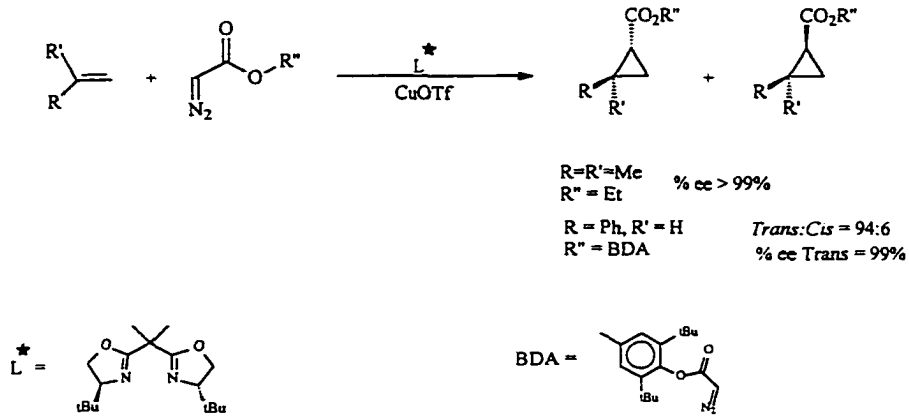


Scheme 20: Semicorrin catalysts

During the studies on the utilization of semicorrin ligands in the copper catalyzed cyclopropanation reaction, Pfaltz revealed that the active catalyst was indeed copper in the +1 oxidation state. It was found that copper(I) could be obtained from copper(II) by direct reduction of the copper(II) precatalyst with diazoesters or phenylhydrazine.[22]

Perhaps the most effective copper based catalyst is the bis-oxazoline derived copper catalyst which was introduced by Evans in the early 1990's.[22] The Evans ligand is

a C_2-symmetric ligand and has proven to be more effective than the Aratani catalyst in the cyclopropanation of isobutylene with EDA (Scheme 19). Scheme 21 below illustrates the use of Evans' ligand in the copper(I) catalyzed cyclopropanation of olefins with various diazoesters.[35]



Scheme 21: Bis-oxazoline derived catalyst

Kwong et al. recently reported on the successful use of chiral bipyridine ligands in the copper catalyzed cyclopropanation.[24] The bipyridine ligands were used in the catalytic cyclopropanation of a variety of styrene derivatives with EDA and moderate to excellent enantioselectivity was observed with all reported substrates (see Table 1 for selected results).

Chiral carboxylates have been utilized as ligands in the dirhodium catalyzed cyclopropanation of olefins with diazo esters (Figure 12).[22]

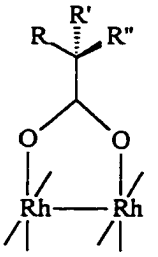
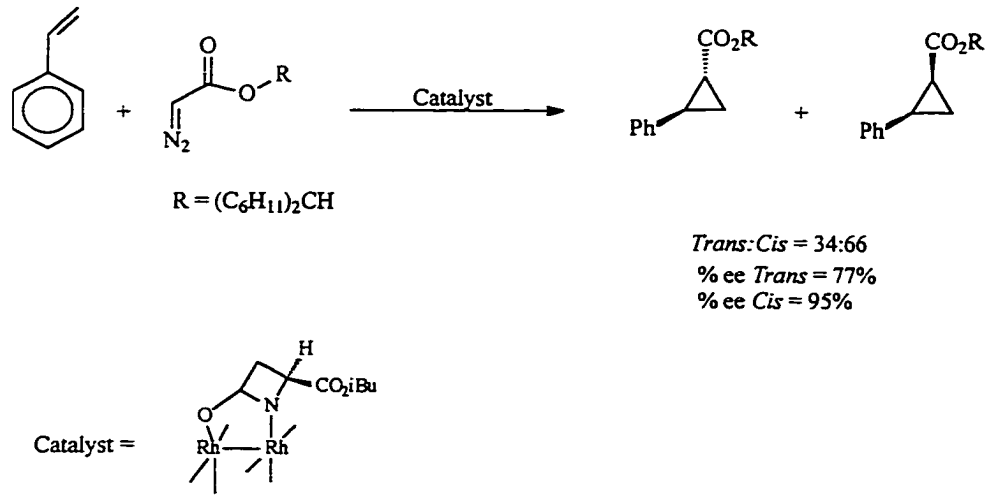


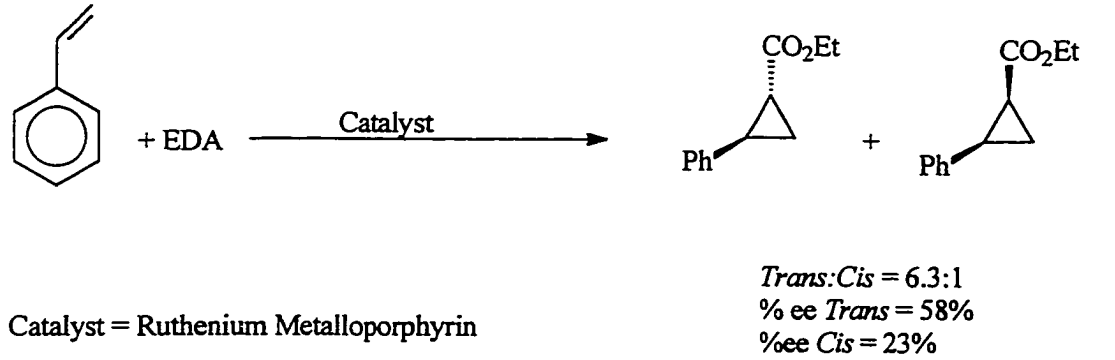
Figure 12: Rhodium catalysts

Unfortunately the utilization of chiral carboxylates in the dihrodium catalyzed cyclopropanation of olefins with diazoesters has only resulted in marginal selectivity.[22] Doyle and co-workers have reported on numerous chiral carboxamidates for use as ligands in the dirhodium catalyzed cyclopropanation reaction.[22] In many cases the use of dirhodium based catalysts have shown relatively small degrees of enantiocontrol with respect to copper catalysts, but several examples exist in which both diastereocontrol and enantiocontrol were highly selective. For example the cyclopropanation of styrene with a bulky diazoester resulted in the preferential formation of the thermodynamically less stable *cis* isomer with high enantioselectivity (Scheme 22).[22] Also the use of aryldiazoacetates[36] and vinyldiazoacetates[18] in the rhodium catalyzed cyclopropanation reactions have produced high levels of both diastereo- and enantiocontrol.



Scheme 22: Dirhodium catalysts

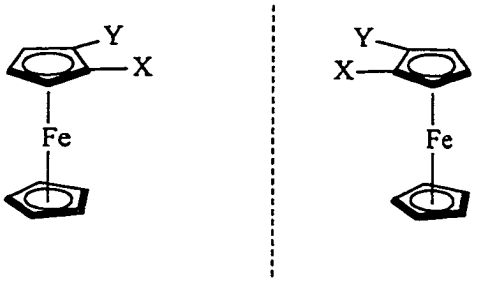
Gross et al. have recently reported on the use of chiral metalloporphyrin complexes in the asymmetric catalytic cyclopropanation of styrene with EDA.[37] The use of metalloporphyrins in these reactions has resulted in higher *trans:cis* ratios for the cyclopropane products. Interestingly, simple diazoesters (EDA) in these reactions result in high diastereocontrol thus alleviating the need for bulky diazocompounds.[37] Unfortunately, these reactions resulted at best in moderate enantioselectivity (Scheme 23).



Scheme 23: Metalloporphyrin catalyst

The above catalyst systems, both copper and rhodium based, have proven to be quite effective in the cyclopropanation of olefins with diazoesters. It is highly desirable to have catalyst systems which can give high levels of diastereo- and enantiocontrol in the synthesis of biologically relevant cyclopropane containing compounds. Unfortunately, many of the previously presented catalyst systems are extremely substrate sensitive in their enantio- and diastereocontrol (e.g. the rhodium based systems). This substrate sensitivity in the cyclopropanation reaction results in a necessity to be able to match the substrate to an appropriate catalyst system in order to obtain the desired cyclopropane product(s). It would be highly desirable to have a catalyst system which is less substrate sensitive. A catalyst system which is less substrate sensitive would be a more general purpose catalyst and could conceivably be utilized much more frequently in the synthesis of biologically relevant cyclopropane containing molecules. A class of ligands which has not been highly exploited in the catalytic cyclopropanation area is the so called planar chiral ligands.

In order for a compound to be chiral it must not be superimposable on its mirror image. Any compound which is not superimposable on its mirror image must be chiral. Many systems which contain no formal chiral center (e.g. a carbon with four unique bonds) are chiral. For example, ferrocene derivatives can be made in chiral form by simply introducing two different substituents on one ring of the ferrocene moiety (Figure 13).[38,39]



Mirror images are non-superimposable

Figure 13: Chiral ferrocene derivatives

Achiral cyclopropanations have been performed using ferrocene derivatives as ligands and future asymmetric ligands will undoubtedly be reported.[39] An all carbon version of planar chiral ligands can be based on the [2.2]paracyclophane moiety. All mono-substituted and many disubstituted [2.2]paracyclophanes possess planar chirality by virtue of atropisomerism as shown in Figure 14.

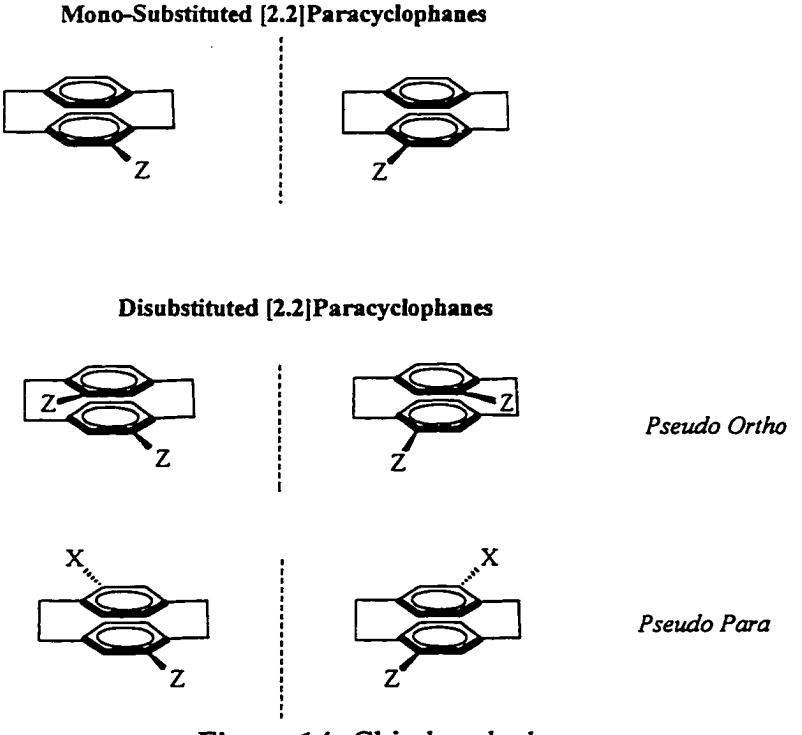
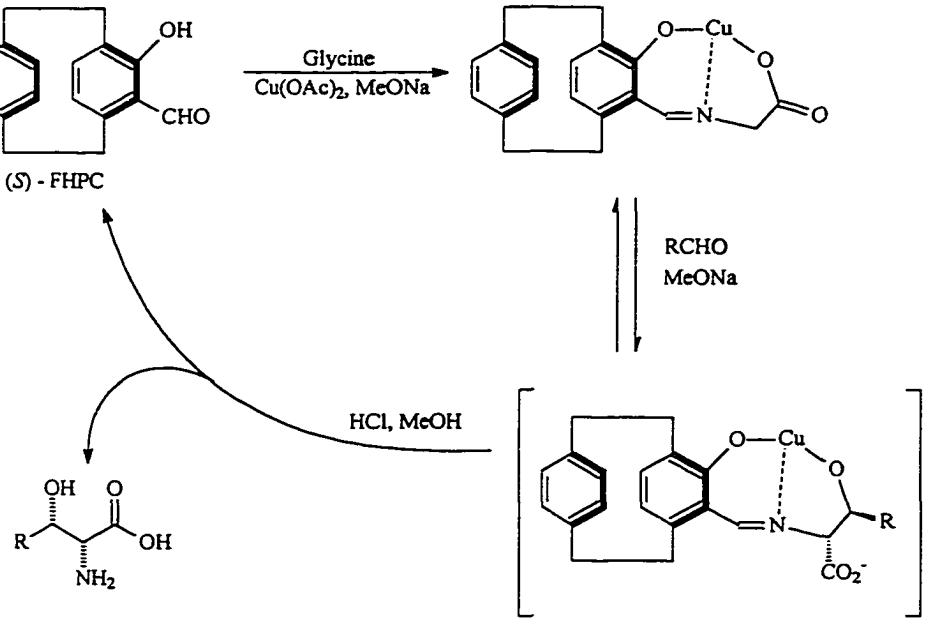


Figure 14: Chiral cyclophanes

The utilization of chiral [2.2]paracyclophane derivatives as ligands in asymmetric reactions has received little attention. The use of chiral disubstituted [2.2]paracyclophane derivatives have been utilized in the synthesis of α-amino acids,[40,41] the trimethylsilylcyanation of benzaldehyde,[42] the rhodium catalyzed asymmetric hydrogenation reaction,[43] and the copper catalyzed cyclopropanation reaction.[44]

Rozenberg et al. reported the synthesis and resolution of a salicylaldehyde type derivative of [2.2]paracyclophane which was utilized in the synthesis of β-hydroxy α-amino acids with moderate to excellent enantioselectivity (Scheme 24).[40]

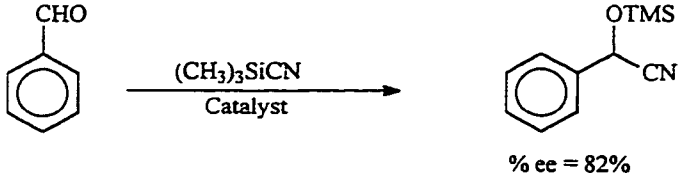


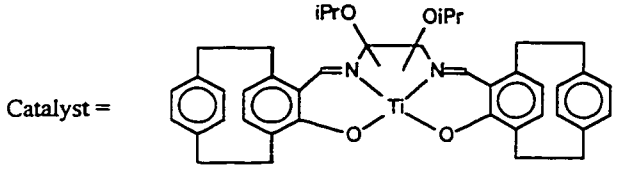
R = Ph, %ee = 77%

R = iPr, %ee = 90-98%

Scheme 24: Chiral cyclophane auxiliary

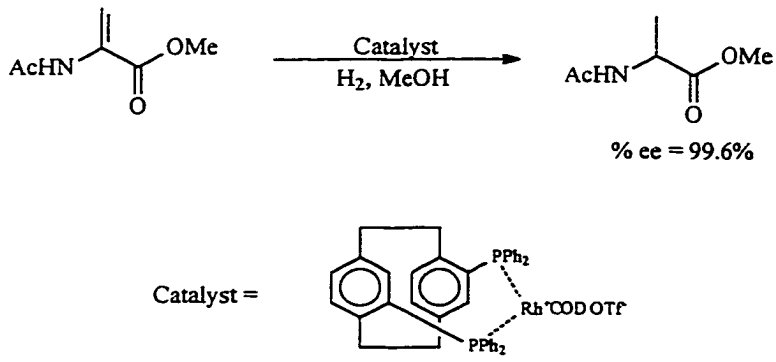
Belekon et al. have utilized the formyl hydroxy [2.2]paracyclophane depicted in Scheme 24 for use in the titanium catalyzed trimethylsilylcyanation of benzaldehyde with moderate to excellent enantioselectivity.[42] Scheme 25 below illustrates the successful use of a disubstituted chiral [2.2]paracyclophane moiety in the trimethylsilylcyanation of benzaldehyde.





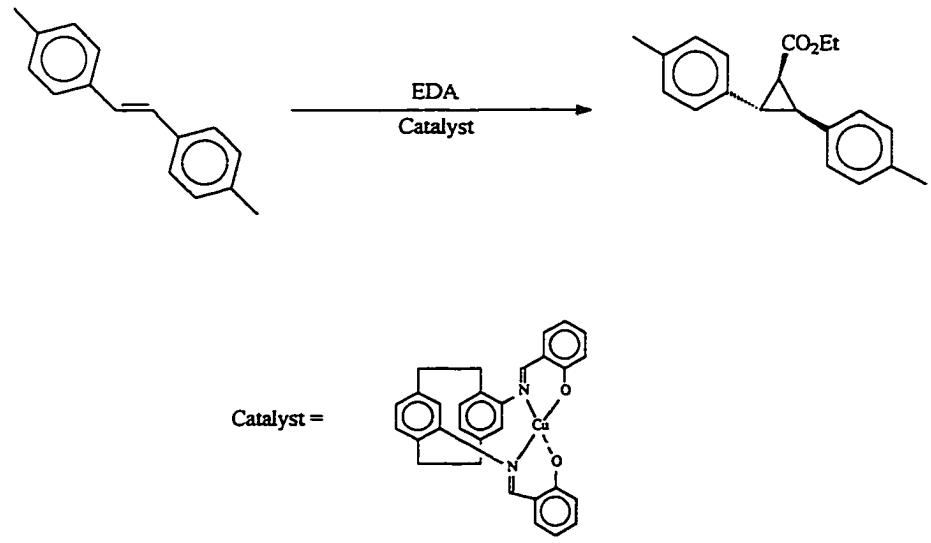
Scheme 25: Asymmetric trimethylsilylcyanation

Pye et al., at Merck Research Laboratories, reported the extremely mild asymmetric rhodium catalyzed hydrogenation of various dehydroamino acid methyl esters with good to excellent enantioselectivity.[43] The ligand which was used in the catalytic hydrogenations was a *pseudo*-ortho disubstituted [2.2]paracyclophane moiety, [2.2]PHANEPHOS. The reaction catalyst derived from [2.2]PHANEPHOS and rhodium triflate resulted in a system with remarkable reactivity. The hydrogenations went smoothly at low temperature even with substrates which are normally resistant to reduction (Scheme 26).



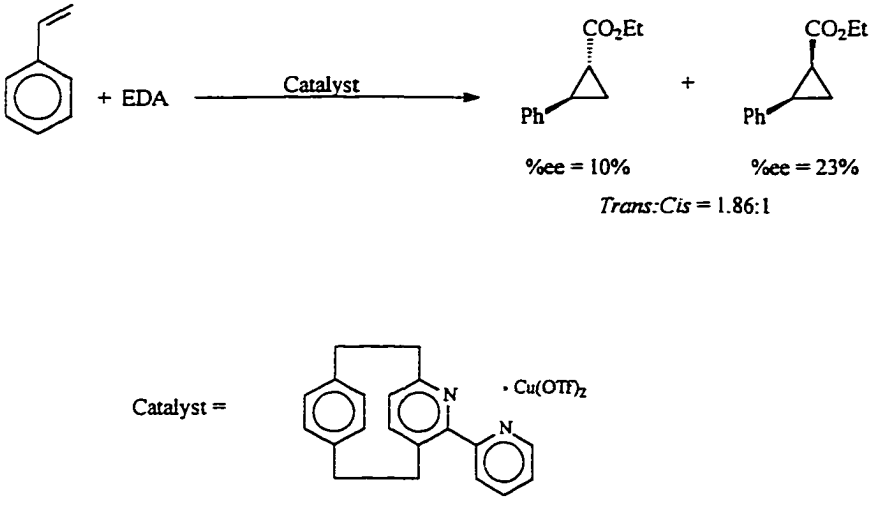
Scheme 26: [2.2]PHANEPHOS

In 1996 Morvant reported the racemic synthesis of a disubstituted chiral [2.2]paracyclophane Schiff-base and its use in the copper catalyzed cyclopropanation of 4,4'-dimethylstilbene.[45] Although the yield of cyclopropane product was low (~30%) and enantioselectivity was not explored, it was an excellent demonstration of the concept of using the [2.2]paracyclophane moiety in the copper catalyzed cyclopropanation reaction (Scheme 27).



Scheme 27: Cyclophane based cyclopropanation catalyst

A bipyridine ligand based on the [2.2]paracyclophane system has very recently been reported for use in the asymmetric copper catalyzed cyclopropanation reaction.[44] The reaction proceeded in good yield, but resulted only in low enantioselectivity (Scheme 28).



Scheme 28: Cyclophane based cyclopropanation catalyst

It is obvious that there is room for much improvement in the use of [2.2]paracyclophane moieties in asymmetric reactions in general and cyclopropanation in particular. The [2.2]paracyclophane moiety has many advantages which make it an interesting molecule to use in asymmetric reactions. The [2.2]paracyclophane moiety can be made chiral by simple aryl type chemistry (e.g. Friedel-Crafts, nitration, etc.). [2.2]Paracyclophane requires no redox active metal for chiral properties as do the ferrocene and chromium planar chiral systems. The [2.2]paracyclophane moiety is relatively stable to heat, air, and light.[43,46]

It is hoped that chiral derivatives of [2.2]paracyclophane will prove to be much more effective catalysts in the cyclopropanation reaction than other ligands. Given that the [2.2]paracyclophane unit is both chiral and bulky, it seems reasonable to exploit these properties in asymmetric reactions in general and in cyclopropanation reactions in particular. Since many catalyst systems for the catalytic asymmetric cyclopropanation reaction have proven to be substrate sensitive with respect to enantiocontrol and that the use of bulky diazoesters seem to improve enantiocontrol in these reactions,[23] it is hypothesized that using modified, structurally rigid, [2.2]paracyclophane derivatives as chiral ligands may provide a less substrate-sensitive cyclopropanation catalysts with high levels of enantiocontrol.

Chapter 2 will introduce the successful use of chiral, non-racemic, [2.2]paracyclophane Schiff-base ligands in the copper catalyzed cyclopropanation of styrene and stilbene derivatives with various diazoesters.[47] Results will be presented which show that the [2.2]paracyclophane moiety can be easily modified to give improved results over other chiral Schiff-bases. Chapter 3 will present experiments which were performed to help elucidate possible stereocontrolling factors which could be responsible for the diastereo- and enantiocontrol of the cyclopropanation reaction with chiral [2.2]paracyclophane ligands.

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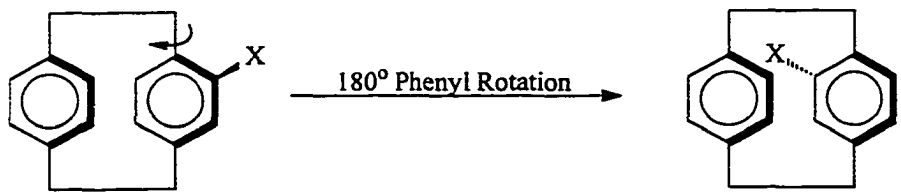
.CHAPTER 2: Chiral, Non-Racemic, [2.2]Paracyclophane Schiff-Bases

The [2.2]paracyclophane unit can be made chiral by virtue of atropisomerism.[1] Several substitution patterns exist which are chiral. For example, all mono-substituted [2.2]paracyclophane derivatives are chiral due to the restricted rotation of the phenyl rings of the [2.2]paracyclophane unit (Figure 2-1).



(*S*) (*R*)

Figure 2-1: Atropisomerization of mono-substituted [2.2]paracyclophane

Several disubstituted [2.2]paracyclophane derivatives are chiral by virtue of atropisomerism. The so called *pseudo-ortho*, *pseudo-para*, and *pseudo-meta* derivatives are all chiral as shown in Figure 2-2.

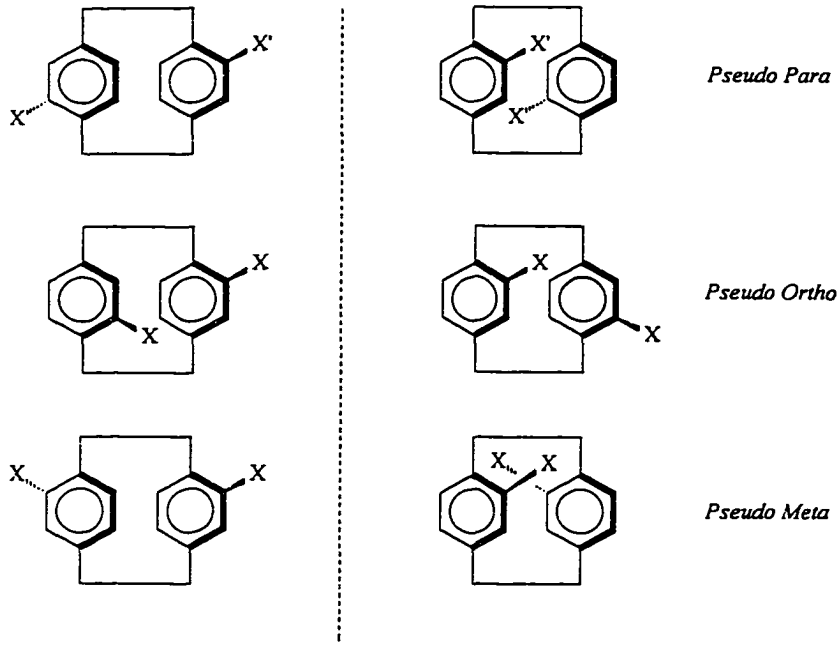


Figure 2-2: Chiral disubstituted cyclophanes

With all the possible substitution patterns of chiral [2.2]paracyclophane derivatives that are available, a substitution pattern had to be chosen that could be easily prepared in good yield, readily purified, and easily resolved into its enantiomers. The mono-substitution pattern was chosen over the disubstitution patterns since it would be easier to synthesize in high yield. The mono-substituted [2.2]paracyclophane derivatives are ideally easier to purify since only enantiomers are produced in the construction of this substitution pattern.

The first asymmetric cyclopropanation reaction, which was reported by Nozaki et al. in the late 1960's, used a chiral Schiff-base ligand as shown in Scheme 18 of the introduction. Schiff-base ligands based on the [2.2]paracyclophane moiety could potentially be constructed according to the retrosynthetic analysis which is presented in Figure 2-3.

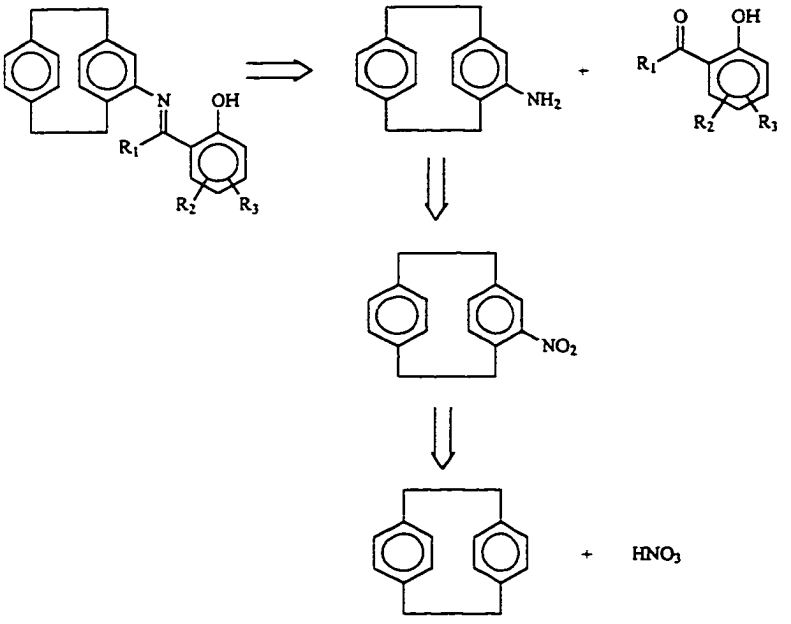
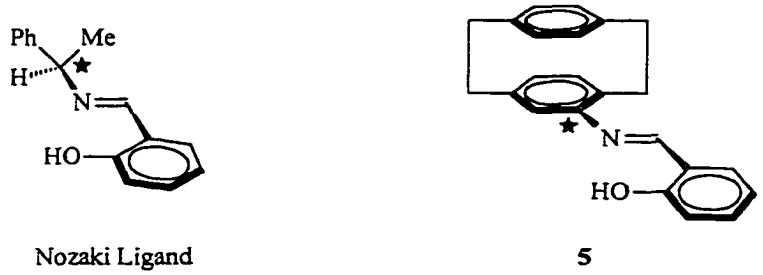


Figure 2-3: Retrosynthetic analysis of [2.2]paracyclophane Schiff-bases

Another advantage of using the mono-substituted [2.2]paracyclophane Schiff-base ligands would be that the results could be directly compared with the results of Nozaki et al. in their historical asymmetric cyclopropanation of styrene with EDA. Nozaki et al. utilized a chiral, non-racemic, amine for chiral induction.[2] The chiral amine chosen by Nozaki et al., phenethylamine, is not extremely bulky which could account for the low enantioselectivity which was observed. Replacement of phenethylamine with the more bulky [2.2]paracyclophane moiety may result in an increase in enantioselectivity relative to the ligand employed by Nozaki et al.

Figure 2-4 illustrates the replacement of phenethylamine in the Nozaki ligand with the larger [2.2]paracyclophane moiety.



Nozaki Ligand **5**

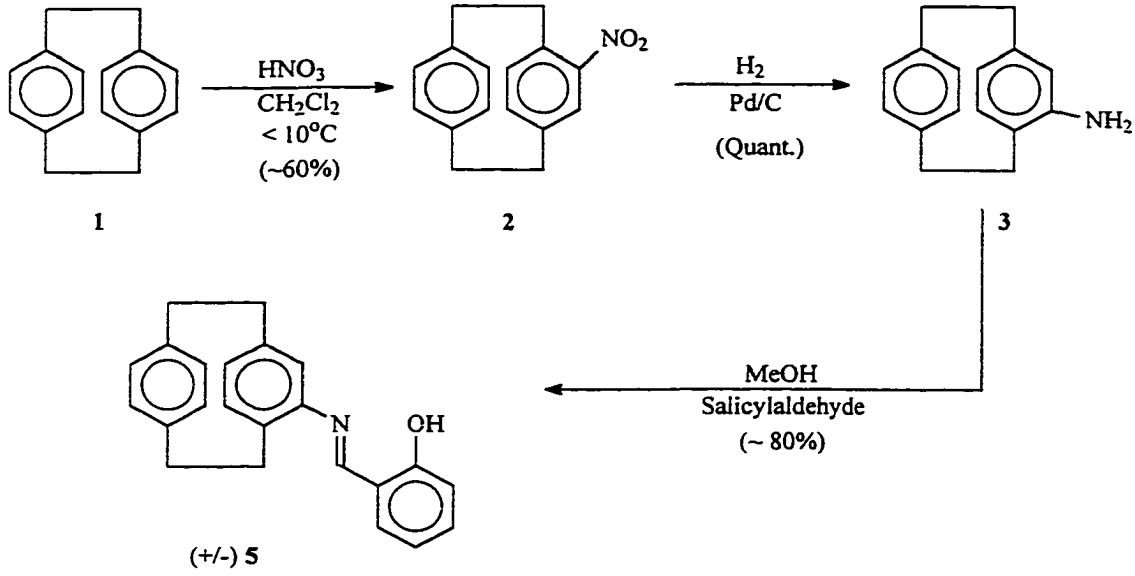
Figure 2-4: Nozaki ligand vs. **5**

Direct comparison of ligand **5** with that of the Nozaki ligand in the copper catalyzed cyclopropanation will allow for the evaluation of the chiral [2.2]paracyclophane moiety in its ability to induce enantioselectivity.

Synthesis, Resolution, and Absolute Configuration of N-Salicylidene-4-amino[2.2]paracyclophane (SAL-4-ACP) (5).

In accord with the retrosynthetic analysis, as shown in Figure 2-3, ligand **5** was synthesized by the direct condensation of 4-amino[2.2]paracyclophane (**3**)[3] with salicyladehyde (**4**). Compound **3** can be made from 4-nitro[2.2]paracyclophane (**2**) by catalytic reduction of the nitro group. Cram originally reported the synthesis of **2** by direct nitration of [2.2]paracyclophane (**1**) with nitric acid.[3] Although Cram's method afforded compound **2** it was obtained in less than desirable yield (~33%). Morvant reported an improved procedure to obtain **2** in higher yield by using cold dichloromethane as the reaction solvent.[4] This improved procedure resulted in yields of 60-70% for

compound **2**. Scheme 2-1 below illustrates the synthesis of ligand **5** from **1**.



Scheme 2-1: Synthesis of SAL-4-ACP (**5**) from [2.2]paracyclophane

With an efficient synthesis of **5** in hand, an efficient and rapid means of resolving the racemic **5** was necessary before proceeding with the cyclopropanation reaction. Fortunately, the resolution of various racemic [2.2]paracyclophane derivatives by chiral HPLC techniques is known[5]. The use of chiral HPLC is especially advantageous since both enantiomers can be isolated in optically pure form. Although ligand **5** is a previously unreported compound, the resolution of **5** using a chiral HPLC column was attempted. It was found that ligand **5** could efficiently be resolved on a semi-preparative Chiralcel AD column with complete baseline resolution as shown in Figure 2-5.

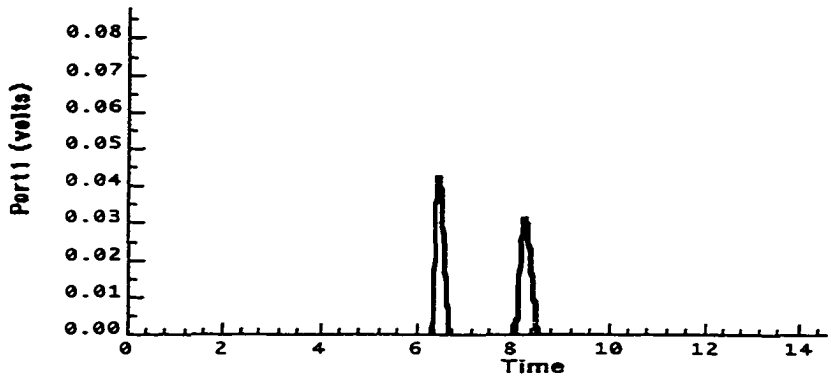


Figure 2-5: HPLC resolution of +/- **5**

Both enantiomers of racemic **5** were isolated and subjected to polarimetry to determine the sign and magnitude of their rotation of polarized light. It is desirable to know the absolute configuration of (+) or (-) **5** and a method of determining the absolute stereochemistry is available. It is known that (*R*)-**3** can be obtained by fractional crystallization of racemic **3** with (+)-camphorsulfonic acid.[6] Having an authentic sample of (*R*)-**3** available lends itself to the construction of (*R*)-**5** which then can be subjected to chiral HPLC. This sequence allows for the determination of the absolute stereochemistry of both (+) and (-) **5**. Figure 2-6 below illustrates the HPLC result of determining the absolute stereochemistry of (+) and (-) **5**.

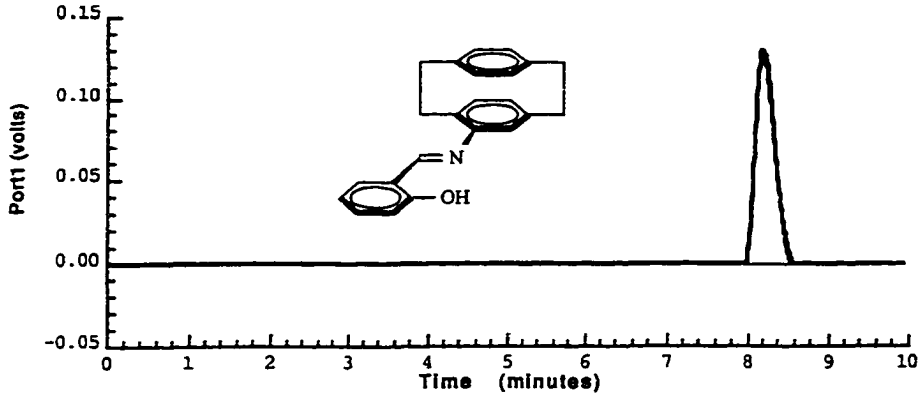


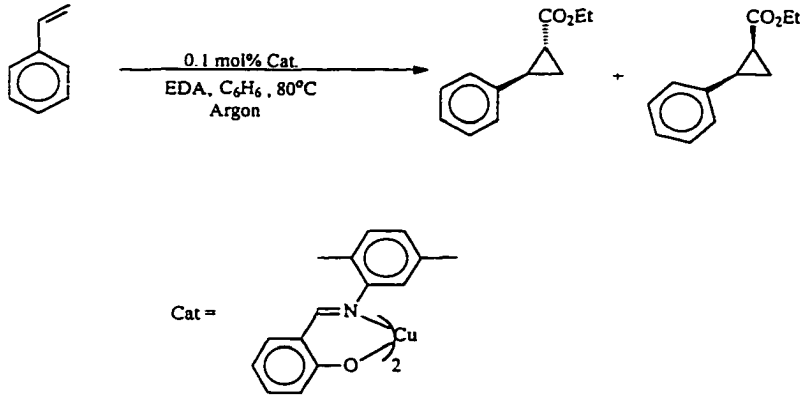
Figure 2-6: (*R*)-**5** and corresponding HPLC

Ligand **5** was characterized by ^{1}H NMR, ^{13}C NMR, MS, and X-ray crystallography. All spectroscopic techniques were consistent with the given structure of **5** (for additional details see Experimental and Appendix 1).

Copper Catalyzed Cyclopropanation of Olefins with SAL-4-ACP (5)

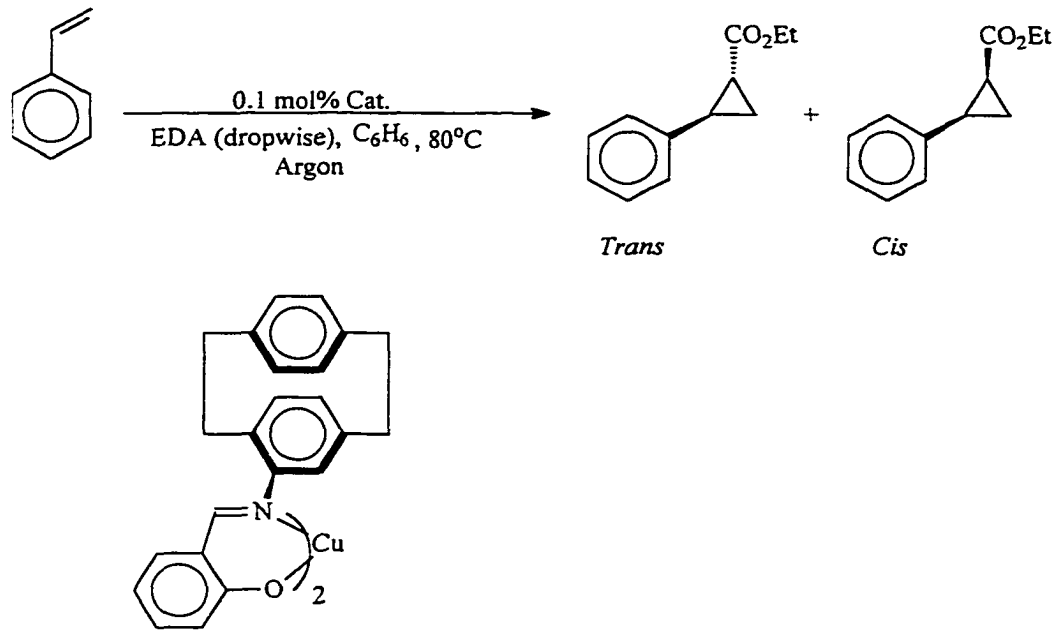
Before using the precious resolved **5**, it was decided that it would be prudent to perform an initial cyclopropanation study to produce racemic cyclopropane products with an achiral model ligand (**6**).[7] This initial study would allow for the determination of appropriate catalyst loading and reaction conditions as well as provide racemic cyclopropane products which were used in the screening of chiral HPLC columns for %ee determination. It was determined that the copper catalyst provided excellent conversion of olefins to their corresponding cyclopropane carboxylates at a catalyst loading of 0.1

mol% (copper/olefin). It was also determined that the catalyst could be generated *in situ* by mixing the appropriate amount of ligand with an excess of copper (II) acetate in methanol and allowing the solution to stir for three hours followed by precipitating the excess copper acetate with toluene. The toluene solution was then passed through a pad of filtering agent to ensure the removal of all non-complexed copper species. Copper complexed **6** was characterized by MS and ^{1}H NMR. The NMR spectra revealed diminished signals due to the paramagnetic nature of copper (II). Scheme 2-2 illustrates the cyclopropanation conditions employed with ligand **6**.



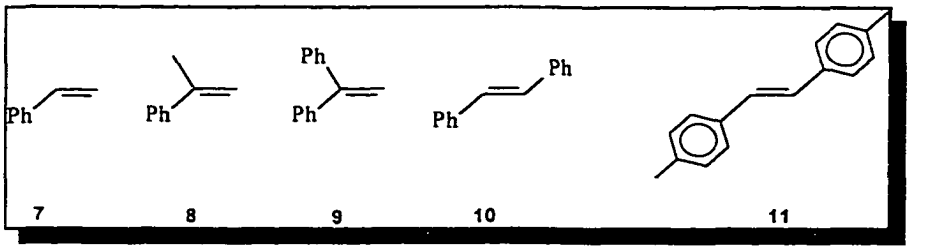
Scheme 2-2: Cyclopropanation conditions with **6**

With initial cyclopropanation reaction procedures and conditions obtained from the model ligand study, proceeding with the non-racemic **5** is straightforward. The catalyst was constructed with ligand **5** the same as with ligand **6**. The catalyst was used in the cyclopropanation of various styrene and stilbene derivatives; the results are presented in Table 2-1 below (Scheme 2-3 illustrates the reaction conditions).[8]



Scheme 2-3: Cyclopropanation reaction conditions

Table 2-1: Cyclopropanation results



Substrate	Diazo-ester[a]	% Conv.[b]	Turnover #[c]	*Cis/Trans*	% ee *Trans*	%ee *Cis*
7	EDA	96%	960	1:1.24	27.4%	12.7%
7	TBDA	96%	960	1:5.9	40.5%[d]	12.7%[d]
8	EDA	91%	910	1:1.8	18.2%	13.5%
9	EDA	93%	930	----	'9.5%'[e]	----
9	TBDA	70%	700	----	'8.3%'[e]	----
10	EDA	39%	390	----	'11.8%'[e]	----
11	EDA	32%[f]	3.2	----	'30.0%'[e]	----

a) EDA = Ethyldiazoacetate, TBDA = *tert*-Butyldiazoacetate, b) Determined by gas chromatography, c) Calculated using the following equation: (mole olefin * %conversion)/mole catalyst, d) % ee was determined on the methyl esters, e) The terms *cis* and *trans* are irrelevant, f) Reaction performed at 10 mol% catalyst loading.

From the results presented in Table 2-1, it is obvious that using non-racemic **5** resulted in significant enantioselectivity with all substrates tested. It is also worth noting that the turnover numbers for the catalyst were quite good which allows for the low catalyst loading of 0.1 mole %. Catalyst loadings this small have not been reported (typically 1 to 10 mole % is reported). It was observed that the styrene derivatives exhibited nearly quantitative reaction conversions, whereas the stilbene derivatives had

much lower conversion to cyclopropane product. The lower conversion of the *trans*-stilbene **10** has been observed for other copper catalysts and has been attributed to steric interactions between **10** and the catalyst.[9] Figure 2-7 below illustrates a steric model which explains the low reaction conversion of the stilbene derivatives.

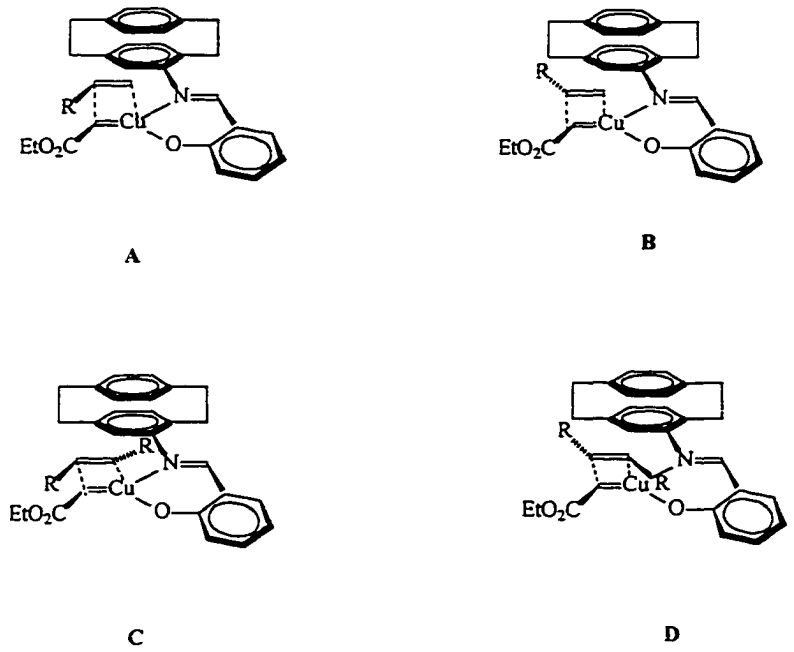


Figure 2-7: Steric rationale for conversion and enantioselectivity

From the steric interactions shown in Figure 2-7, it is hypothesized that the styrene derivatives are able to orient themselves in such a manner as to minimize steric congestion with the [2.2]paracyclophane moiety. Molecular mechanics calculations suggest that the [2.2]paracyclophane moiety can rotate easily about the cyclophane-nitrogen bond giving rise to a number of possible conformations.[10] Taking the orientations shown in Figure 2-7 as being representative of the steric environment, orientation **A** is lower in energy than **B** since orientation **A** places the phenyl group of the substrate away from the bulky [2.2]paracyclophane moiety. The *trans*-stilbene derivatives cannot adopt such an orientation with respect to the [2.2]paracyclophane unit. Orientations **C** and **D** illustrate that both possible orientations for the *trans*-stilbene derivatives have similar steric interactions with the [2.2]paracyclophane unit, both of which place a phenyl group in close proximity to the [2.2]paracyclophane moiety. This is believed to be the reason why the *trans*-stilbene derivatives experience a lower conversion to product, relative to the styrene derivatives, under identical reaction conditions.

From Table 2-1 it is observed that the order of enantioselectivity, utilizing EDA, is as follows: styrene (**7**) > α-methylstyrene (**8**) > 1,1-diphenylethylene (**9**) suggesting that olefin steric bulk in the α position and enantioselectivity are related. As the steric bulk of the olefin becomes more symmetrical, the observed enantioselectivity decreases. The enantioselectivities that were observed in this series ranged from moderate to low when compared to other copper cyclopropanation catalysts,[11] but nonetheless were a vast improvement over Nozaki's ligand (see Figure 2-4). The cyclopropanation of **7** resulted

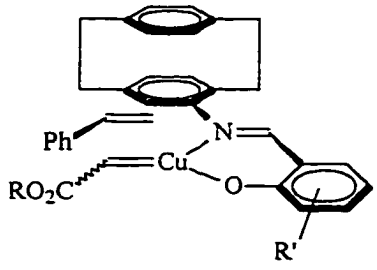
in a *trans* percent ee of 27.4% and a *cis* percent ee of 12.7%. The cyclopropanation of **8** resulted in a *trans* percent ee of 18.2% and a *cis* percent ee of 13.5%. The best result was found to be the reaction of **7** with TBDA which resulted in a 40% ee for the *trans* isomer and a 12.7%ee for the *cis* isomer. This is a considerable improvement over the 27% ee observed when EDA was utilized in the cyclopropanation of **7**. The higher enantioselectivities that are observed for the *trans* isomers relative to the *cis* isomers is in agreement with previous reports,[11,12] although the origin of this effect is uncertain. This increase in enantioselectivity is in agreement with other literature reports of increased percent ee with bulkier diazo compounds.[12] In the case of all the styrene derivatives, **7-9**, all observed diastereomeric ratios are similar to those reported in the literature for other copper catalyst systems.[2] With regard to the model shown in Figure 2-7, it should be noted that the actual conformation(s) around the active catalyst must allow for *trans*-cyclopropane products to form preferentially.

The cyclopropanation of *trans*-stilbene **10** with EDA resulted in a percent ee of 11.8%. The low enantioselectivity obtained in the cyclopropanation of **10** with EDA is in agreement with the proposed model depicted in Figure 2-7. The possible orientations for *trans*-stilbene **10**, **C** and **D** are of similar energy; there is no significant preference for one orientation over the other which results in reduced enantioselectivity. A moderate enantioselectivity of 30% was observed for the cyclopropanation of *trans*-4,4'-dimethylstilbene **11** (at 10 mole % catalyst). Two possible explanations can account for the increased enantioselectivity of **11** relative to **10**. The methyl groups of substrate **11** introduce an additional steric interaction with the bridging methylenes of the

[2.2]paracyclophane moiety of **5** which could result in increased enantioselectivity. An alternate explanation to the increase in enantioselectivity of **11** relative to **10** could be the electronic contribution of the para methyl groups in **11**. It has been reported, for other asymmetric reactions as well as cyclopropanation, that electronic effects can have an influence on the resulting enantioselectivity of the products.[13,14] It was also observed that the *trans* configuration of **10** and **11** was maintained in the cyclopropanation reaction.

The low to moderate enatioselectivities, as presented in Table 2-1, may be attributed to a non-rigid framework of **5** with respect to the putative catalytically active copper carbenoid. Given that simple molecular mechanics calculations suggest that rotation about the [2.2]paracyclophane- nitrogen bond in **5** can take place easily, it is likely that a fixed conformation of the active catalyst does not exist. The [2.2]paracyclophane unit may rotate in such a way as to minimize steric interactions with the olefin resulting in an overall reduction in enantioselectivity.

Given that ligand **5** showed significant enantioselectivity in all substrates tested; modifying ligand **5** in hopes of attaining increased enantioselectivities appeared hopeful. It is obvious, from Table 2-1, that increasing the steric bulk of the diazoester resulted in a significant increase in enatioselectivity of the *trans* cyclopropane product. It was initially hypothesized that it may be possible to incorporate additional steric bulk into the asymmetric [2.2]paracyclophane Schiff-base ligands thus enhancing the 'steric pocket' of the active catalyst. By enhancing the 'steric pocket' the number of possible orientations for substrate approach is dramatically reduced as shown in Figure 2-8 below.



R' = Bulky Group

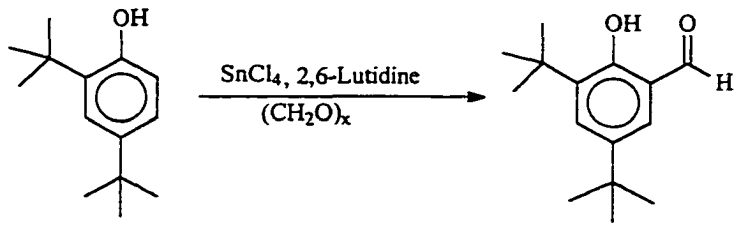
Figure 2-8: Adding steric bulk

The phenyl group of the approaching olefin should orient itself in such a manner as to avoid steric congestion with both the [2.2]paracyclophane moiety and the bulky R' group. Jacobsen has used a similar strategy to improve the enantioselectivity in the manganese promoted asymmetric epoxidation of unfunctionalized olefins with good success.[15]

Keeping with the retrosynthetic analysis as shown in Figure 2-3, it seemed reasonable to add additional bulk by way of modified salicyladehydes. Using modified salicylaldehydes simplifies the synthetic approach to obtaining modified versions of ligand **5**. The formylation of substituted phenols[16] has been known for some time and the formylation of the inexpensive 2,4-di-*tert*-butyl phenol **12** would result in the construction of a salicyladehyde moiety containing significant steric bulk.

Synthesis, Resolution, and Absolute Configuration of N-(2',4'-di-*tert*-Butyl)Salicylidene-4-amino[2.2]paracyclophane (14)

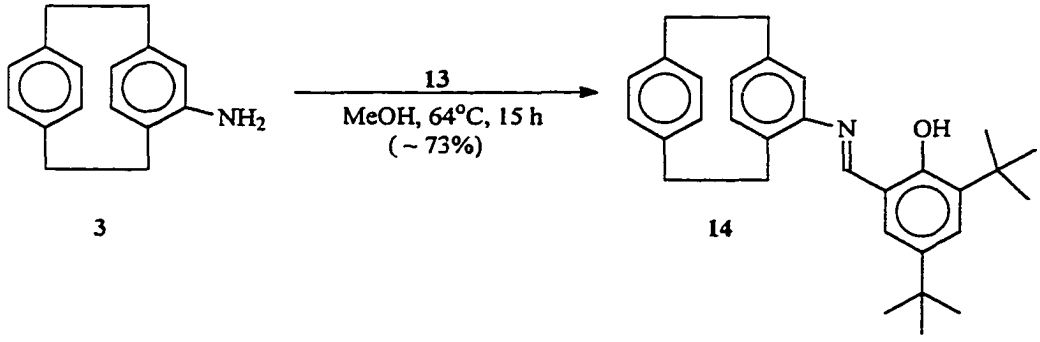
The formylation of **12** is illustrated in Scheme 2-4 below.



12 **13**

Scheme 2-4: Synthesis of a bulky salicylaldehyde

The formylation of **12** gave **13** in acceptable yields which can be used in the condensation with **3** to produce the modified Schiff-base **14**[17] as shown below in Scheme 2-5.



3 **14**

Scheme 2-5: Synthesis of +/- **14**

As with ligand **5**, the sterically modified ligand **14** was subjected to chiral HPLC resolution. Figure 2-9 below shows the resulting chiral HPLC chromatogram for racemic **14**.

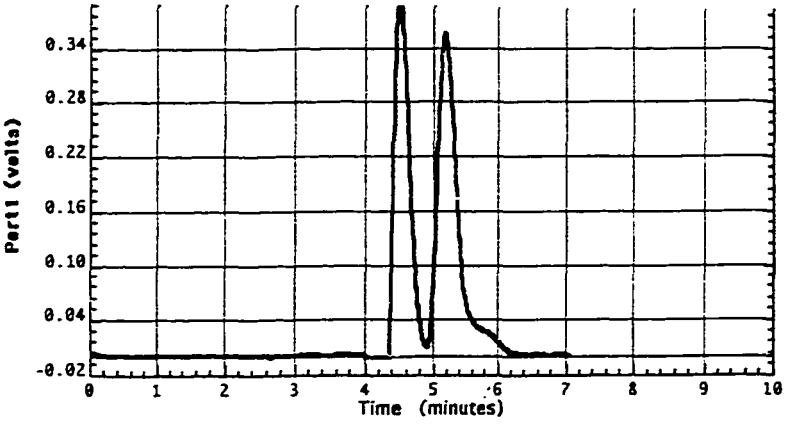


Figure 2-9: Chiral HPLC of +/- **14**

(*R*) enriched **14** was prepared by the direct condensation of (*R*)-**3** with **13**. (*R*)-**14** was subjected to chiral HPLC in order to determine the absolute stereochemistry of both enantiomers of **14** (Figure 2-10).

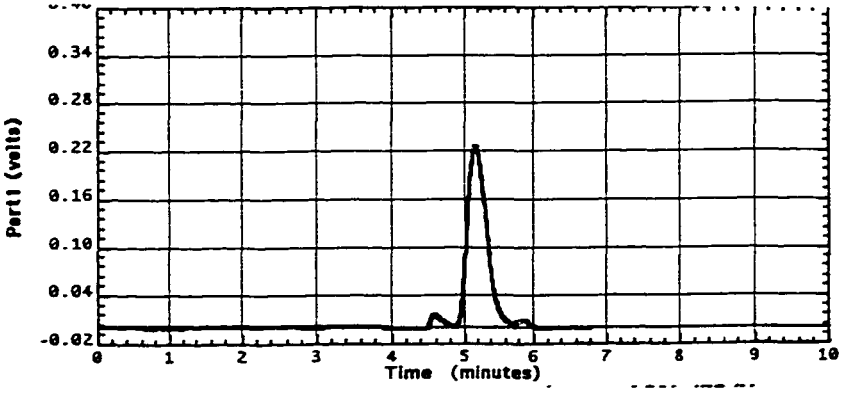
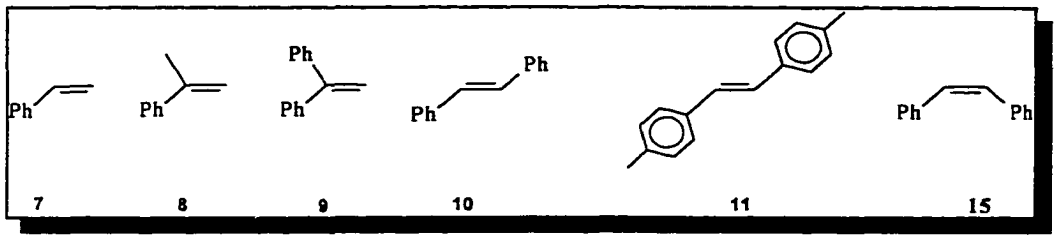


Figure 2-10: (*R*) enriched **14**

Enantiomerically pure **14** was complexed with copper (II) using the same procedure as for ligand **5**. The copper catalyst derived from **14** was used in the cyclopropanation of various styrene and stilbene derivatives, the results of which are shown in Table 2-2.

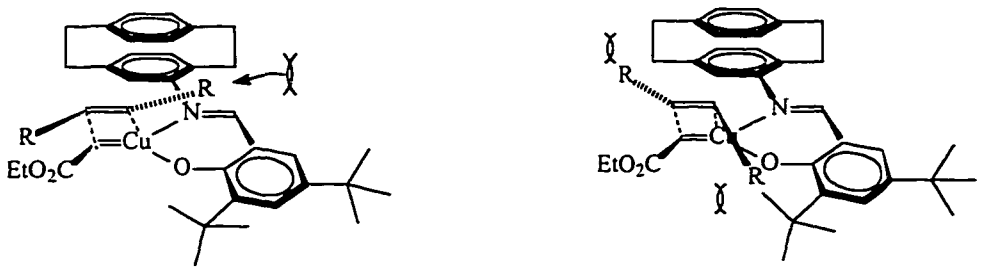
Table 2-2: Cyclopropanation results



Substrate	Diazo-Ester[a]	% Conv.[b]	Turnover #[c]	*Cis/Trans*	%ee *Trans*	%ee *Cis*
7	EDA	57%	570	1:1.90	67.1%	61.2%
7	TBDA	71%	710	1:3.14	67.8%	53.6%
8	EDA	90%	900	1:1.30	48.29%	8.0%
9	EDA	70%	700	----	'4.0%'[d]	----
10&11	EDA	0%	0	----	----	----
15	EDA	19%	190	1:7.4[e]	----	----

a) EDA = Ethyldiazoacetate, TBDA = *tert*-Butyldiazoacetate, b) Determined by gas chromatography, c) Calculated using the following equation: (mole olefin * %conversion)/mole catalyst, d) The term *cis* and *trans* are irrelevant, e) refers to the endo/exo ratio.

From Table 2-2 it is readily observed that the reactivity and selectivity was markedly different for ligand **14** relative to ligand **5** in the copper catalyzed cyclopropanation reaction. The turnover numbers for **14**, although acceptable, were generally lower than the turnover numbers for ligand **5**. Interestingly, substrates **10** and **11** showed no conversion to product. Substrate **15** underwent low conversion to the corresponding cyclopropane carboxylates, the conversion of substrate **15** is probably due to the higher reactivity of *cis* olefins relative to *trans* olefins. The inability of substrates **10** and **11** to undergo the cyclopropanation reaction is in accord with the proposed steric model presented in Figure 2-7. Figure 2-11 below illustrates the sterically modified version of Figure 2-7, which shows why the stilbene derivatives experience low reaction conversion.



Orientation 1 Orientation 2

R = Ph

Figure 2-11: Steric rational for low conversion of **10** and **11**.

Orientations 1 and 2 in Figure 2-11 above demonstrate severe interactions between the stilbene substrate and both the [2.2]paracyclophane and salicylidene moieties. These severe interactions are believed to be the reason why the stilbene substrates experience such low reaction conversions.

Under identical reaction conditions, it is apparent that ligand **14** was a vast improvement over ligand **5** with regard to enantioselectivity. The order of enantioselectivity was the same for ligand **14** as for ligand **5**: styrene (**7**) > α-methylstyrene (**8**) > 1,1-diphenylethylene (**9**). The cyclopropanation of **7** with EDA resulted in a *trans* percent ee of 67.1% and a *cis* percent ee of 61.2%. A dramatic improvement was not observed when **7** was cyclopropanated with TBDA. The cyclopropanation of **7** with TBDA resulted in a *trans* percent ee of 67.8% and a *cis* percent ee of 53.6%. This result alone showed considerable improvement over ligand **5**, illustrating that the added *tert*-butyl groups have a remarkable effect on the enantioselectivity. The cyclopropanation of **8** with EDA resulted in a *trans* percent ee of 48.29% and a *cis* percent ee of 8.0%. The cyclopropanation of **9** with EDA resulted in a low enantioselectivity of 4.0%. As with ligand **5**, it appears that steric bulk in the α position and enantioselectivity are related.

It is hypothesized that the increase in enantioselectivity could be the result of two contributing factors. The bulky nature of the added *tert*-butyl groups could help minimize the number of possible orientations that the approaching olefin can adopt resulting in creased enantioselectivity (see Figure 2-12). This is in accord with the inability of the stilbene derivatives to undergo efficient cyclopropanation with this catalyst.

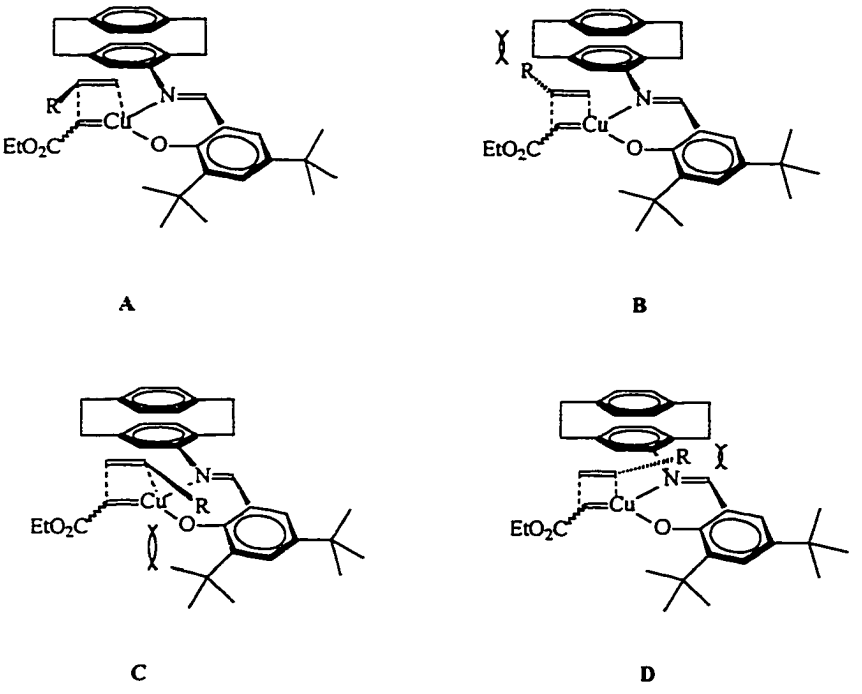


Figure 2-12: Steric rational for enantioselectivity of ligand **14**

Orientation **A** in Figure 2-12 is the only orientation which does not exhibit severe steric interactions between the substrate and catalyst.

Another possible contributing factor to the increased enantioselectivity of ligand **14** relative to ligand **5** could be an electronic effect.[13] It is known that the electronic character of a ligand can dramatically influence the enantioselective outcome of a reaction. Although the enantioselectivities and conversions which were obtained with ligand **14** which fit nicely into the steric model shown in Figure 2-7 and 2-12, electronic effects can not be ruled out at this point (the following chapter will deal with this issue in more detail).

Although ligand **14** was a considerable improvement over both ligand **5** and Nozaki's ligand, **14** demonstrated significant substrate dependance on the resulting enantioselectivities of the products. Ligand **14** demonstrated that chiral [2.2]paracyclophane derivatives could be easily modified to show enhanced enantioselectivity. Many chiral ligands, in copper catalyzed cyclopropanation, that show excellent enantioselectivities and are not substantially substrate dependant are of the C_2 symmetric type.[18] The catalyst system which was reported by Morvant was indeed a C_2 symmetric ligand based on the [2.2]paracyclophane moiety, but the construction of C_2 symmetric Schiff-base ligands based on a [2.2]paracyclophane moiety would be a low yielding process.[4] For example, the di-nitration of the parent [2.2]paracyclophane is known to give a vast mixture of products which would have to be separated from the desired *pseudo*-ortho isomer.[4] Instead of using an actual C_2 symmetric system, it was hypothesized that it may be possible to introduce *pseudo* C_2 symmetry with respect to the [2.2]paracyclophane moiety in a mono-substituted Schiff -base (see Figure 2-13).

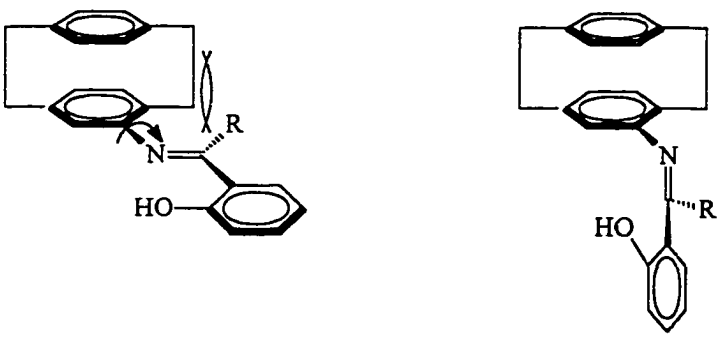
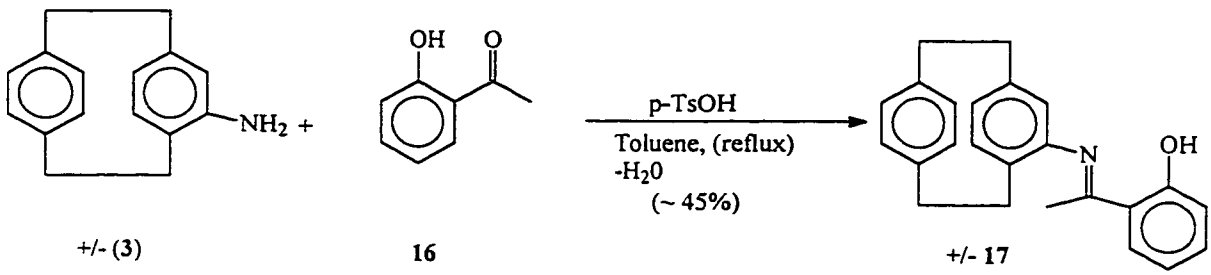


Figure 2-13: Cyclophane ligand with restricted rotation

From Figure 2-13, if R and the ethano bridges of the [2.2]paracyclophane moiety were to experience significant steric crowding, it is conceivable that a rotation about the cyclophane-nitrogen bond could occur as drawn to help relieve the steric crowding. This rotation would allow for the copper center to be placed in a *pseudo* C_2 symmetrical position with respect to the [2.2]paracyclophane unit. Models have revealed that even with R being a methyl group significant twisting about the cyclophane- nitrogen bond should occur to help relieve strain. Scheme 2-6 shows the synthesis of ligand **17** where R is a methyl group.



+/- (3) 16 +/- 17

Scheme 2-6: Synthesis of +/- **17** from +/- **3** and **16**

Racemic **17** was characterized by ^{1}H NMR, ^{13}C NMR, MS, and X-ray crystallography and all spectroscopic data is consistent with the structure of **17** (see experimental and appendix for additional information).

Unfortunately, racemic **17** was not resolvable using an semi-preparative Chiralcel AD chiral HPLC column. Racemic **17** was resolvable on an analytical Chiralcel OJ column, but use of this column would not allow for the separation of the necessary quantities of ligand needed. An alternative approach to obtaining enantio- enriched **17** is

to use the partially resolved (*R*)-**3**.[6] Since the ligand can be resolved on an analytical column, the percent ee of the ligand can be readily determined and the absolute configuration can be assigned. Figure 2-14 shows the resolution of racemic **17** on an Chiralcel OJ analytical HPLC column.

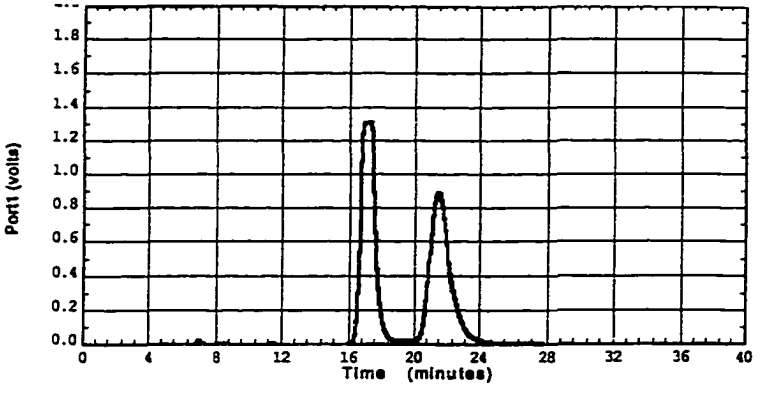


Figure 2-14: Resolution of +/- **17**.

Figure 2-15 shows the HPLC chromatogram of (*R*) enriched **17**.

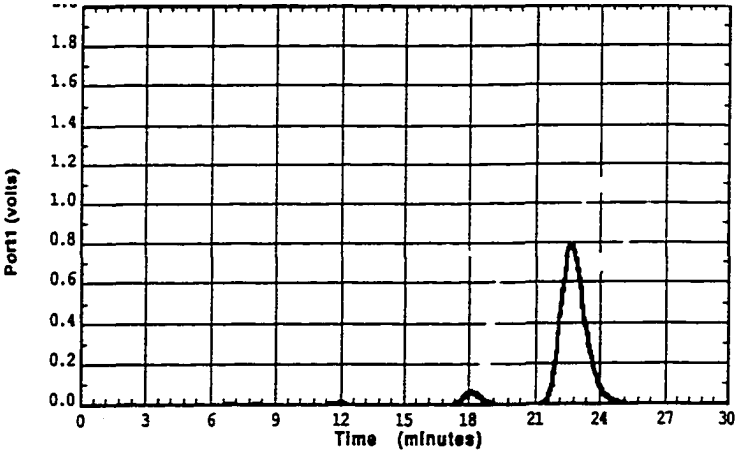
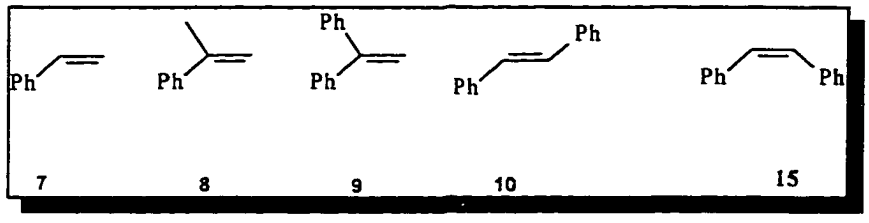


Figure 2-15: HPLC chromatogram of (*R*)-**17**

From Figure 2-15 it was found that the (R) enriched **17** had a percent ee of 86.34%. The enantiomerically enriched **17** was complexed with copper (II) acetate and the resulting copper catalyst was used in the cyclopropanation of various styrene and stilbene derivatives using the same procedure outlined in Scheme 2-3. The results of the cyclopropanation reactions utilizing **17** are listed below in Table 2-3 (results are corrected for %ee of ligand[19] assuming similar kinetics between the diastereomeric transition states).

Table 2-3: Cyclopropanation results



Substrate	Diazo-Ester[a]	% Conv.[b]	Turnover #[c]	*Cis/Trans*	%ee *Trans*	%ee *Cis*
7	EDA	92.9%	929	1:1.9	75.8%	60.5%
7	TBDA	80.7%	807	1:4.6	88.2%	77.9%
8	EDA	85.8%	858	1:3.3	84.3%	95.0%
9	EDA	84.7%	847	----	'74.4%'[d]	----
10	EDA	20.2%	202	----	'23.4%'[d]	----
15	EDA	22.02%	220	1:16.8[e]	----	----

a) EDA = Ethyldiazoacetate, TBDA = *tert*-Butyldiazoacetate, b) Determined by gas chromatography, c) Calculated using the following equation: (mole olefin * %conversion)/mole catalyst, d) The terms *cis* and *trans* are irrelevant, e) refers to endo/exo ratio.

After correcting for the %ee of ligand **17**, the results presented in Table 2-3 clearly demonstrate an improvement in enantioselectivity for **17** relative to **5** and **14**. The cyclopropanation of substrate **7** with EDA resulted in a *trans* percent ee of 75.8% and a *cis* percent ee of 60.5%. The cyclopropanation of **7** with TBDA resulted in a *trans* percent ee of 88.2% and a *cis* percent ee of 77.9%. The cyclopropanation of **7** with TBDA showed an almost identical increase in percent ee for the *trans* isomer when ligand **5** and ligand **17** were used. This result seems to suggest that ligand **17** has a more rigid conformation relative to **5** which is in accord with the initial prediction that the *pseudo* C_2 symmetry would be beneficial. Amazingly, substrate **8** showed remarkable enantioselectivity. The cyclopropanation of **8** with EDA resulted in a *trans* percent ee of 84.3% and a *cis* percent ee of 95.0%. Substrate **9**, for ligands **5** and **14**, has proven to be the least favorable substrate with respect to enantioselectivity. The cyclopropanation of substrate **9** with EDA resulted in a dramatically improved percent ee of 74.4%. The *trans*-stilbene (**10**) showed a percent ee of 23.4% which is a vast improvement over ligand **5**. The cyclopropanation of substrate **15** showed a high endo/exo ratio of 1:16.8.

The results presented in Table 2-3 clearly indicate that ligand **17** is much less substrate sensitive with respect to enantioselectivity than are ligands **5** and **14**. The introduction of the methyl group in place of an imine hydrogen shows that small modifications can have a profound effect on enatioselectivity. It is reasonable to hypothesize that the increase in enantioselectivity arises from eliminating a facial approach preference.

Figure 2-16 demonstrates a non-C_2 symmetric system and the resulting products that arise from different facial approaches of the olefin (all other factors being equal).

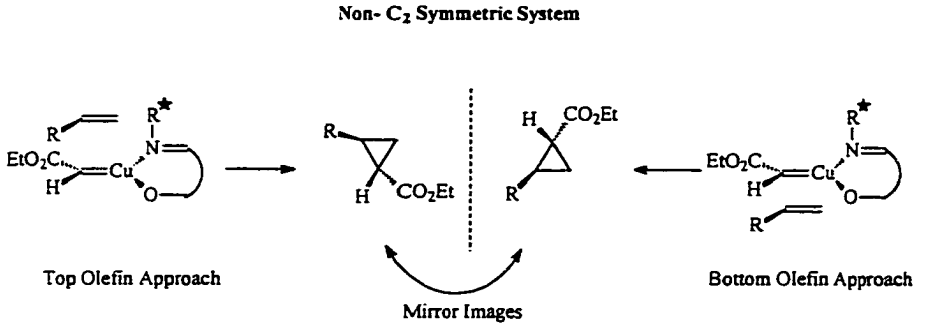


Figure 2-16: Enantiomers arising from olefin approach

It is possible to eliminate the problem of facial approach by either making the two faces equal (as in a true C_2-symmetric system) or by blocking a face such that approach from only one face is possible. The results presented in Table 2-3 suggest that the *pseudo* C_2-symmetric system is sufficient to both substantially increase enatioselectivity and create a catalyst system which is less substrate dependant.

Conclusion/Future Directions

It has been demonstrated that chiral, salen type, ligands based on the mono-substituted [2.2]paracyclophane unit can be easily constructed. It has also been demonstrated that the use of entiomerically pure **5**, **14**, and enriched **17** induce enantioselectivity in the copper catalyzed cyclopropanation reaction of diazoesters with a variety of styrene and stilbene derivatives. It has been found that the catalyst loading can be quite small (0.1 mol%) when using ligands **5**, **14**, and **17**. The low catalyst loading results in turnover numbers that approach 1000, and results in practically no diazo coupling side products.

The ease with which these ligands can be modified should lend itself to further investigation. Interestingly, simple modifications resulted in a dramatic increase in enantioselectivity of the resulting cyclopropane products. For example, for the *trans* phenyl cyclopropane carboxylate (resulting from the cyclopropanation of styrene (**7**) with EDA) the enantioselectivity increased as a function of catalyst modification: **17** > **14** > **5**. All ligands tested (**5**, **14**, and **17**) gave much improved enantioselectivity over Nozaki's chiral salen ligand (6% ee for both the *cis* and *trans* phenylcyclopropane carboxylate). Although the use of ligands **5** and **14** proved to be substrate dependant on the resulting enantioslectivity of the cyclopropane products, introducing *pseudo* C_2 symmetry with respect to the [2.2]paracyclophane moiety resulted in much less substrate dependance. Ligand **17** proved to be comparable in enantioselectivity with some of the best copper catalysts available (Evans ligand).

The utilization of chiral [2.2]paracyclophanes as chiral auxiliaries and ligands has not been extensively exploited. Given that the mono- substituted [2.2]paracyclophane salen ligands can be easily synthesized, purified, and resolved into their enantiomers suggest that this class of ligands needs to be tested in other asymmetric reactions. The use of chiral metal complexes to perform desymmetrization of *meso* compounds has recently received considerable attention. For example the use of chiral copper compounds have been utilized in the desymmetrization of meso N-sulfonylaziridines with moderate to excellent enantioselection (see Figure 2-17).[20]

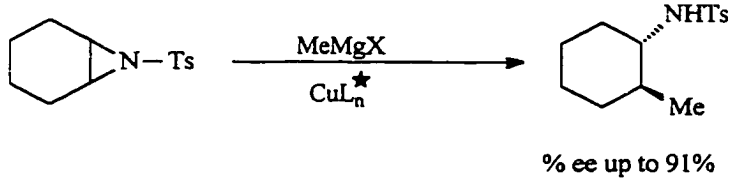


Figure 2-17: Desymmetrization

Trost et al. have used palladium complexes of chiral amides in the desymmetrization of *meso* compounds with nucleophiles in a total synthesis of L-showdomycin (Figure 2-18).[21]

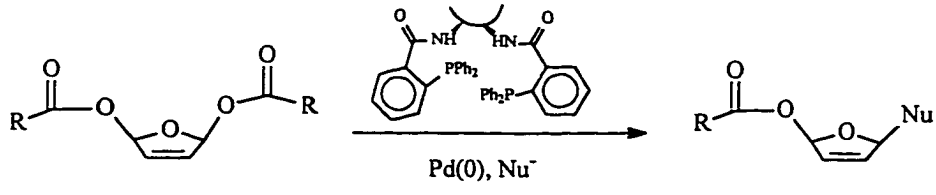


Figure 2-18: Synthesis of L-showdomycin

the *pseudo*-ortho [2.2]paracyclophane substitution pattern could be used in place of the cyclohexane diamine of Figure 2-18. It would also be possible to use a mono substituted [2.2]paracyclophane for this purpose.

Chiral copper complexes have been used in catalytic asymmetric aldol reactions with moderate to excellent success. Evans et al. have recently reported the asymmetric aldol reaction[22] as shown in Figure 2-19.

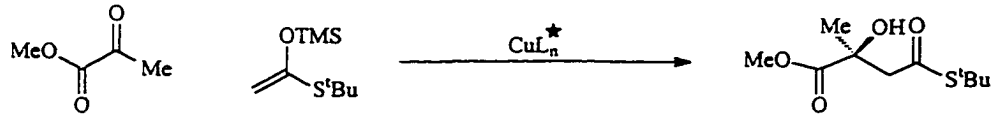


Figure 2-19: Asymmetric aldol reaction

Copper catalysts derived from ligands **5**, **14** ,and **17** could easily be screened for enantioselective induction in the aldol reactions presented in Figure 2-19.

The [2.2]paracyclophane catalysts could be used in virtually any reaction that requires a metal center as a catalyst. Future possibilities include asymmetric Diels-Alder reactions, asymmetric azirdination and epoxidation, asymmetric hydrogenation, etc.

In the following chapter, mechanistic considerations as well as use of additionally substituted [2.2]paracyclophanes in asymmetric cyclopropanation will be presented. Experiments to help elucidate the role of the [2.2]paracyclophane unit in directing olefin approach will be presented as well as other experiments to determine electronic factors in enantioselectivity with these catalyst systems.

Experimental

Benzene was distilled under a nitrogen atmosphere from CaH_2. Styrene and α-methylstyrene were obtained from Aldrich Chemical Co. and filtered through neutral alumina prior to use. *Cis*- and *trans*-stilbene were obtained from Aldrich Chemical Co. and used as received. *Trans*-4,4'-dimethylstilbene was prepared by a literature procedure and recrystallized from ethanol prior to use.[23] ^1H and ^{13}C NMR spectra were recorded on either a Varian 300 XL or Varian unity 400 spectrometer using chloroform-d as solvent, and referenced to residual $CHCl_3$. Reaction conversions were determined by gas chromatography on either an Hewlett Packard 5790A or Shimadzu gas chromatograph equipped with a flame ionization detector and a OV101 packed column. The program used to obtain gas chromatograms is as follows: initial temperature of 50°C for 5.0 minutes, 20°C/minute until 250°C is reached, and 250°C maintained for 20 minutes. The gas chromatograph used pre-purified nitrogen as the carrier gas. Enantioselectivities were determined by HPLC using either a Chiralcel AD or OJ column with 1:9 (vol/vol) i-PrOH/hexanes as solvent. HPLC was performed using either a Shodex RI detector or a BioRad uv/vis detector at 254 nm and an SSI or BioRad pump. Melting points were determined using a Meltemp apparatus and are uncorrected. Optical rotations were determined using a Rudolph Research Autopol III polarimeter. All $[\alpha]_D$ determinations were performed at room temperature unless otherwise noted and were determined from the slope of the line derived by plotting α_{obs} vs. concnetration (g/mL). Low resolution mass spectra were obtained using a Hewlett Packard HP 5985 mass spectrometer. High resolution mass spectra (FAB) were obtained on a VG ZAB-E mass spectrometer using

Xe atoms as the ionozation source and 3-nitrobenzyl alcohol as the matrix. Ethyldiazoacetate (EDA) and *tert*-butyldiazoacetate (TBDA) were prepared by literature methods.[24,25] Cyclopropanation reactions were performed in dried glassware under an ultra high purity argon atmosphere. 4-Nitro[2.2]paracyclophane (**2**) was prepared by the method outlined by Morvant.[4] 4-Amino[2.2]paracyclophane (**3**) was prepared either by palladium catalyzed reduction of **2** or by $SnCl_2$/HCl reduction of **2**.[1] The *tert*-butyl cyclopropane carboxylates were converted to their corresponding methyl esters for %ee determination. The *tert*-butyl esters were first saponified by methanolic sodium hydroxide, acidified and isolated, and the resulting acids were treated with gaseous diazomethane to yield the desired methyl esters.[26] (*R*)-4-Amino[2.2]paracyclophane, (*R*)-**3**, was prepared from (+/-) 4-amino[2.2]paracyclophane, **3**, by a literature resolution.[6]

Synthesis of (+/-)-N-Salicylidene-4-amino[2.2]paracyclophane (5). A 50 mL round bottom flask was charged with 0.3977 g of (+/-) 4-amino[2.2]paracyclophane (**3**) (1.560 mmol), 0.2247 g of salicylaldehyde (**4**) (1.830 mmol) and 20 mL of methanol. The flask was fitted with a reflux condenser and the mixture was heated to reflux solvent for 15 minutes. Solvent was removed under reduced pressure and the resulting yellow solid was dissolved in the minimum amount of methanol and placed in a freezer overnight. Crystals of **5** as yellow clusters were collected and rinsed with cold methanol to yield 0.4100 g (1.250 mmol) of isolated product (80%); mp: 126-126.5°C; ^{1}H- NMR (300 MHz, $CDCl_3$):δ 2.80 (1H,m), 3.04 (4H, m), 3.20 (2H, m), 3.62 (1H, m), 6.01 (1H,s), 6.36 (1H, dd 2Hz, 8Hz), 6.50 (4H, m), 6.82 (1H, dd 2Hz, 8Hz), 6.96 (1H, t 8Hz), 7.10 (1H, d 8Hz), 7.40 (2H, m), 8.32 (1H, s), 13.82 (1H, s, D_2O exchangeable).

^{13}C- NMR (100 MHz, $CDCl_3$):δ 32.57, 34.22, 34.94, 35.25, 117.16, 119.05, 119.58, 125.27, 129.11, 131.63, 131.78, 132.01, 132.94, 133.39, 134.70, 134.88, 138.92, 139.76, 139.80, 141.84, 146.66, 160.85, 161.10. MS (70ev): *m/z* 327.1 (M^+), 223.1, 104.0. HRMS (FAB) *m/z* calc'd for $C_{23}H_{22}NO$ ($M + H^+$) 328.1701 found 328.1713. Resolution of (+/-) **5** was achieved on a semi-preparative Chiralcel AD column (1:9 i-PrOH/hexanes @3.00 ml/min), R_t (-) 6.5 min., (+) 8.5 min. $[\alpha]_D$ (EtOH): -236.3 ± 14.9 and 248.6 ± 13.4.

Typical cyclopropanation using ligand 5: A dried 100 mL round bottom flask was charged with 3.08 g of styrene (29.0 mmol), 48 mL of freshly distilled benzene, and 0.1 mol% preformed copper catalyst. The copper catalyst was prepared by stirring 19.3 mg of **5** with an excess of copper(II) acetate in methanol for three hours, removing the methanol under reduced pressure, precipitating excess copper(II) acetate with toluene and filtering the brown toluene solution through celite and removing solvent under reduced pressure. The resulting brown solid catalyst was used immediately without further purification. The cyclopropanation flask was fitted with a reflux condenser connected to an argon inlet and a mineral oil bubbler. The solution was heated to reflux the solvent, with stirring, and 5.14 g (1.50 eq) of EDA, diluted to 20 mL with benzene, was added dropwise over a five hour period using a syringe pump and stainless steel transfer needle. After the addition of EDA was complete, heating was continued an additional 30 minutes before the solution was cooled to room temperature. The resulting solution was filtered through a 6 inch neutral alumina column, using fresh benzene as eluent, to remove the catalyst. All cyclopropane products were characterized by ^{1}H NMR, GC, GC/MS, and chiral HPLC (see Appendix 1 for chromatogram traces).

Synthesis of (+/-) N-(2',4'- di-*tert*-butyl)Salicylidene-4-amino[2.2]paracyclophane (14): In a 25 mL round bottom flask was placed 45.0 mg (1.03 mmol) of (+/-) 4-amino[2.2]paracyclophane (**3**), 44.0 mg of 2,4- di-*tert*-butyl salicylaldehyde (**13**), and 6.0 mL of methanol. The flask was fitted with a reflux condenser and the solution was allowed to reflux for 15 hours. The solvent was removed under reduced pressure and the resulting yellow solid was purified by column chromatography (silica gel) using low boiling petroleum ether as eluent to obtain 0.0648 g (1.47E-4 mol) of **14** (isolated yield 73%). Mp: 169-171°C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.34 (9H, s), 1.54 (9H, s), 2.80-3.70 (8H, m), 6.00 (1H, s), 6.35 (1H, d 7Hz), 6.53 (4H, m), 6.84 (1H, d 7Hz), 7.20 (1H, d 3Hz), 7.47 (1H, d 3Hz), 8.33 (1H, s), 14.01 (1H, bs, D_2O exchangeable). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 29.55, 31.68, 32.77, 34.26, 34.30, 35.04, 35.28, 35.34, 118.60, 125.26, 126.49, 127.66, 128.99, 131.10, 131.71, 132.84, 133.34, 134.54, 134.69, 136.92, 138.80, 139.82, 140.37, 141.57, 146.82, 158.19, 161.82. MS (70 ev): *m/z* 439.2 (M^+), 334.3, 104.0. HRMS (FAB) *m/z* calcd for $C_{31}H_{37}NO$ (M^+) 439.2875 found 439.2860. Resolution of (+/-) **14** was achieved on a semi-preparative Chiralcel AD column

(1:9 i-PrOH/hexanes @2.00 ml/min), R_t (-) 4.5 min., (+) 5.5 min. $[\alpha]_D$ (benzene): -267.9 ± 9.1 and (+) enantiomer did not give reproducible optical rotations which is believed to be due to inaccurate mass as a result of residual solvent (although the (+) enantiomer was enantiomerically pure by HPLC).

Typical cyclopropanation using ligand 14: A dried 25 mL round bottom flask was charged with 0.830 g of styrene (7.96 mmol), 10 mL of freshly distilled benzene, and 0.1 mol% preformed copper catalyst. The copper catalyst was prepared by stirring 7.10 mg of **14** with an excess of copper (II) acetate in methanol for three hours. The methanol was removed under reduced pressure and the excess copper (II) acetate was precipitated with toluene. The brown toluene solution was filtered through celite and the solvent was removed under reduced pressure to yield a brown solid. The copper catalyst was used immediately without further purification. The cyclopropanation flask was fitted with a reflux condenser connected to an argon inlet and mineral oil bubler. The solution was heated to reflux solvent and 1.320 g (1.50 eq.) of EDA, diluted to 5.0 mL with benzene, was added dropwise over a five hour period using a syringe pump and stainless steel transfer needle. After the addition of EDA was complete the solution was allowed to reflux an additional 30 minutes before being cooled to room temperature. The resulting solution was passed through a 6 inch neutral alumina column, using fresh benzene as eluent, to remove the catalyst. All cyclopropane products were characterized by ^{1}H NMR, GC, GC/MS, and chiral HPLC (see Appendix 1 for chromatogram traces).

Synthesis of (*R*)- 4-paracyclophanyl-2'-hydroxyacetophenone imine (17): A 50 mL pear shaped flask was charged with 0.3781 g (1.690 E-3 mol) of (*R*)-4-amino[2.2]paracyclophane, ca. 20 mg of *p*-TsOH, 20 mL of toluene, and a stir bar. The pear shaped flask was then fitted with a Hickman still and reflux condenser and the resulting solution was brought to reflux solvent. After all the water was azeotropically removed from the reaction vessel, fresh, dry, toluene was added to bring the volume to 20 mL. The solution was again brought to reflux and 0.2490 g (1.829 E-3 mol) of 2-hydroxy acetophenone was added by syringe over a 30 minute period. The resulting solution was heated to reflux solvent overnight. The Hickman still was removed and activated 4 Å molecular sieves were added and the solution was heated to reflux solvent an additional 24 hours. The resulting yellow mixture was removed from the heat and allowed to cool to room temperature. The mixture was then filtered through a 1 inch pad of neutral alumina which was washed with fresh toluene. The solvent was removed under reduced pressure to obtain 0.3295 g (9.650 E-4 mol) of crude (*R*)-**17** (~57% yield). The crude material was recrystallized from methanol/hexanes. The crude (*R*)-**17** was dissolved in 10 mL of boiling methanol, cooled to room temperature, and hexanes was added until the solution clouded. This mixture was placed in a freezer for 48 hours and the crystals of (*R*)-**17** were collected and rinsed with cold hexanes. The %ee of (*R*)-**17** was determined on an analytical Chiralcel OJ column (1:9 i-PrOH/hexanes @ 1.00 mL/min). The %ee was determined to be 86.34%. MP (racemic): 178-179.5°C. ^{1}H-NMR (400, $CDCl_3$): δ 2.18 (3H, s), 2.93-2.99 (1H, m), 3.06-3.23 (8H, m with 1 D_2O exchangeable proton), 5.76 (1H, s), 6.44-6.53 (4H, m), 6.60-6.62 (1H, dd 2Hz, 8Hz), 6.90 (1H, t 7Hz), 7.10 (2H, d 8Hz),

7.41 (1H, t 7Hz), 7.60 (1H, d 8Hz). ^{13}C-NMR (75 MHz, CDCl3): δ 17.46, 32.33, 34.25, 35.08, 35.41, 118.09, 118.21, 119.67, 127.68, 128.80, 128.99, 130.07, 132.06, 132.27, 132.79, 133.10, 133.30, 134.90, 138.97, 139.58, 140.84, 143.98, 162.21, 169.95.MS (70 ev): 341.1 (M+), 222.0, 107. HRMS (FAB): m/z calc'd for $C_{24}H_{24}NO$ (M + H^+) 342.1858 found 342.1873.

Typical cyclopropanation using ligand (*R*)-17: A 25 mL roundbottom flask was charged with 1.00 g styrene (9.60E-3 mol) and 0.1 mol% of preformed copper catalyst. The copper catalyst was prepared by refluxing 6.60 mg of (*R*)-**17** with an excess of copper (II) acetate for 24 hours in toluene, allowing the toluene solution to cool, and filtering the solution through celite to remove non-complexed copper species. The solvent was removed under reduced pressure to obtain a brown solid which was used without further purification. The cyclopropanation flask was fitted with a reflux condenser attached to an argon inlet and a mineral oil bubbler and the solution was heated to reflux solvent. 1.64 g (1.50 eq.) of EDA was diluted to 5 mL with benzene and added dropwise over a five hour period by syringe pump. After the addition of EDA was complete the solution was allowed to reflux an additional 30 minutes. The solution was cooled to room temperature and filtered through a 6 inch neutral alumina column using fresh benzene as eluent. All cyclopropane products were characterized by ^{1}H NMR, GC, GC/MS, and chiral HPLC (see Appendix 1 for chromatogram traces). The %ee of the resulting products were corrected for the %ee of the ligand.[19]

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Appendix 1: Supplemental Information for Chapter 2

The following pages contain chiral HPLC traces for various cyclopropane products obtained through this study. The HPLC traces were obtained at room temperature using either a Chiralcel OJ or AD analytical column. Gas chromatograph traces of the crude reaction mixtures are also included.

X-ray structures of ligands **5**, **14**, and **17** are included. The crystal structures were obtained on appropriate crystals of racemic materials. The X-ray data was collected on a Siemens P4 diffractometer located at the University of Oklahoma Analytical Services Center. The X-ray data was collected under a nitrogen atmosphere at a temperature of 77K. The data was refined by full-matrix least-squares on F^2. ^{1}H NMR of ligands **5**, **14**, and **17** are also included.

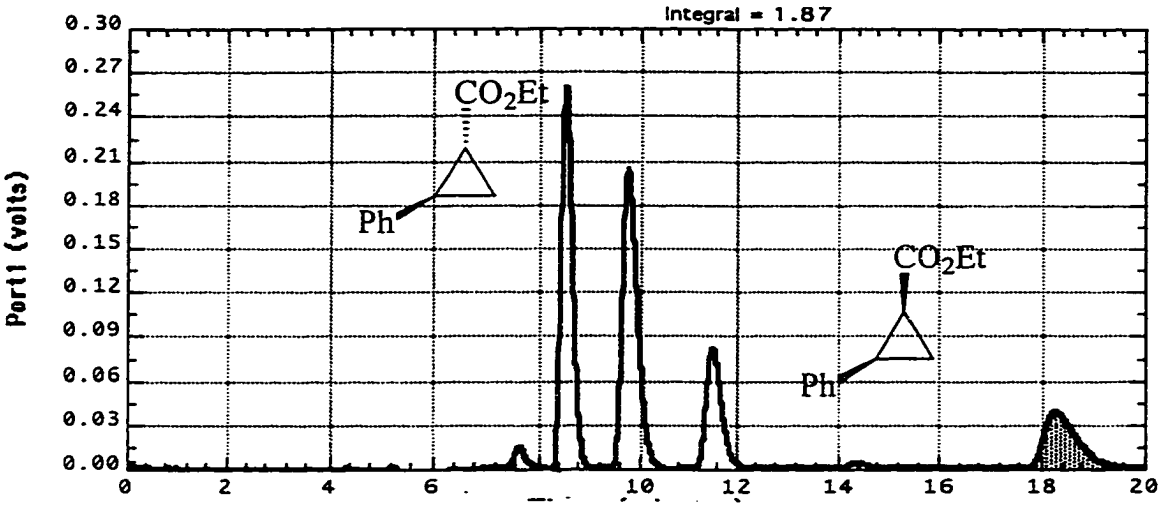


Figure 2-20a: Chiral HPLC (OJ column) of *trans*- and *cis*- phenyl cyclopropane carboxylate @0.6 mL/min (1:9 i-PrOH/hexanes)

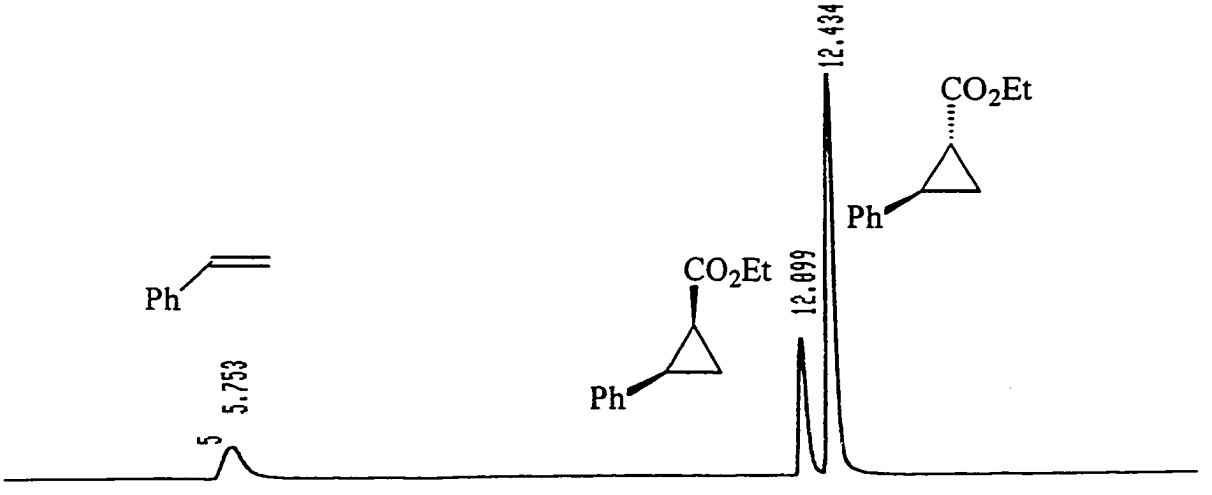


Figure 2-20b: GC trace of crude reaction mixture from the cyclopropanation of styrene with EDA.

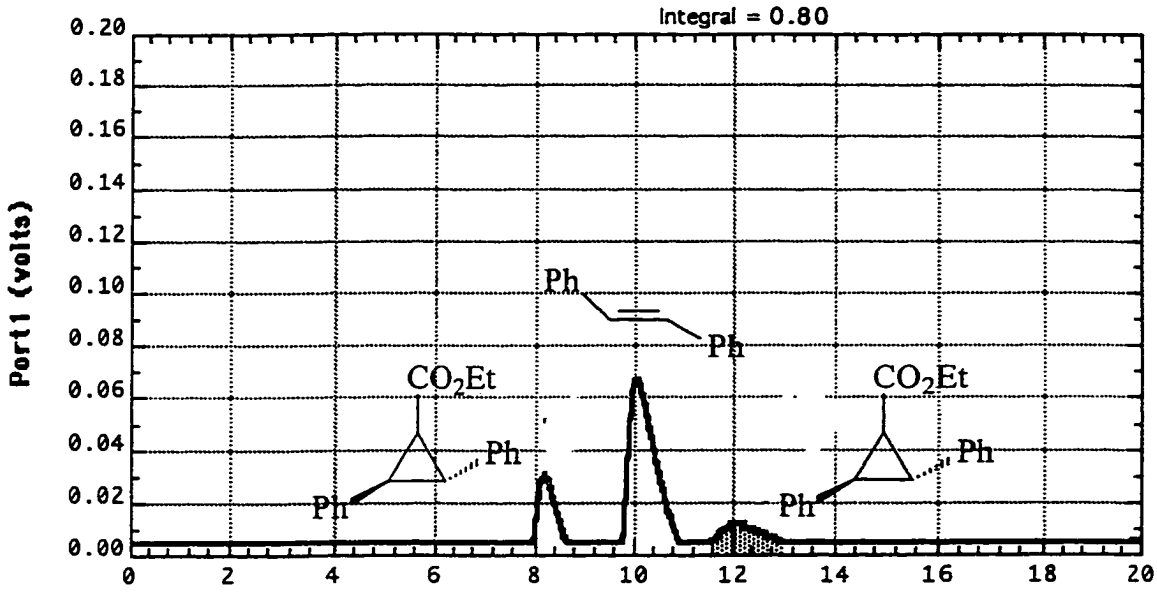


Figure 2-21a: Chiral HPLC of crude reaction mixture of the cyclopropanation of *trans*-stilbene (OJ column) @1.00 mL/min (1:9 i-PrOH/hexanes).

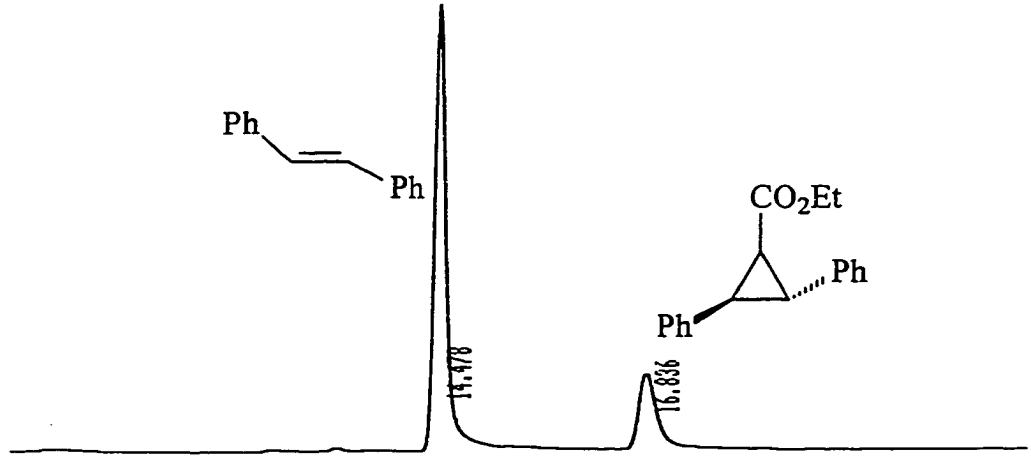


Figure2-21b: GC trace of the crude reaction mixture of the cyclopropanation of *trans*-stilbene.

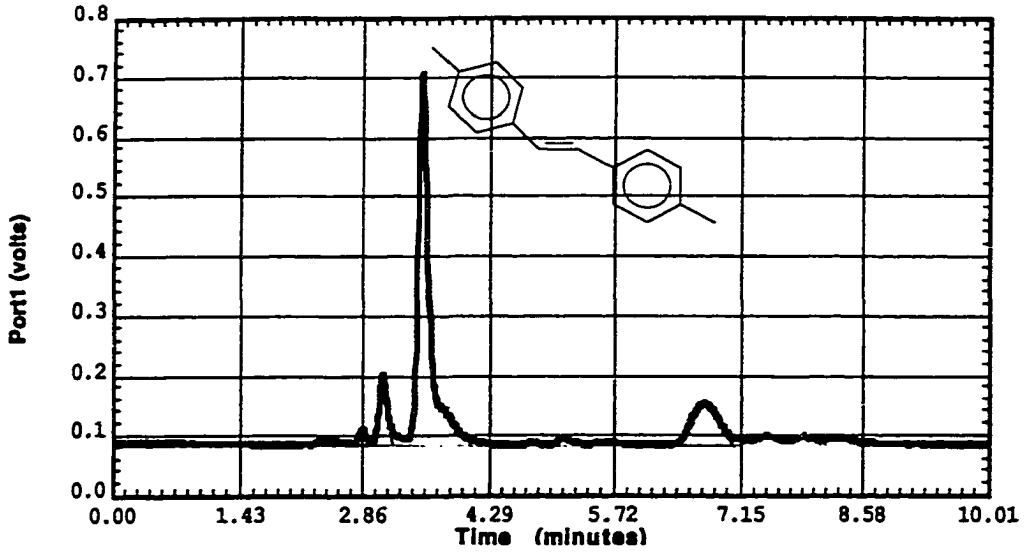


Figure 2-22a: Chiral HPLC of crude reaction mixture of the cyclopropanation of *trans*-4,4'-dimethylstilbene (AD column) @1.00 mL/min (1:9 i-PrOH/hexanes).

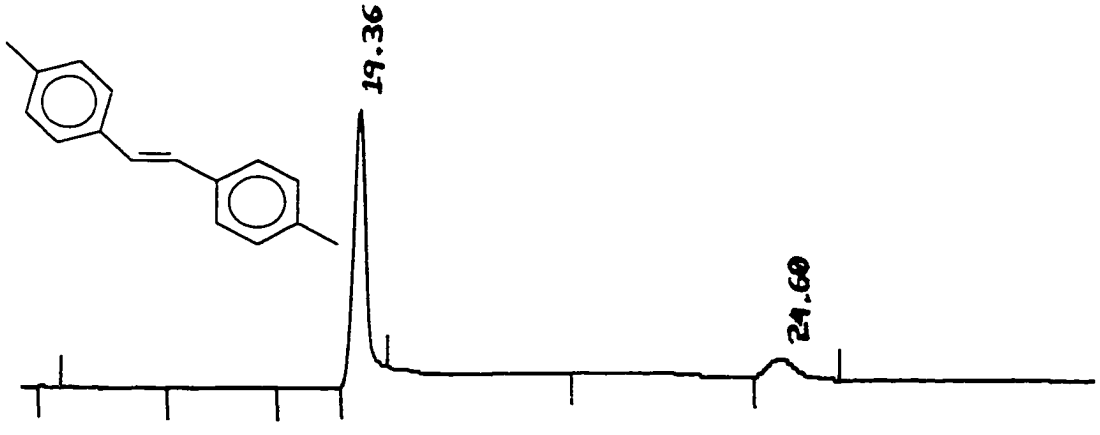


Figure 2-22b: GC trace of the crude reaction mixture of the cyclopropanation of *trans*-4,4'-dimethylstilbene.

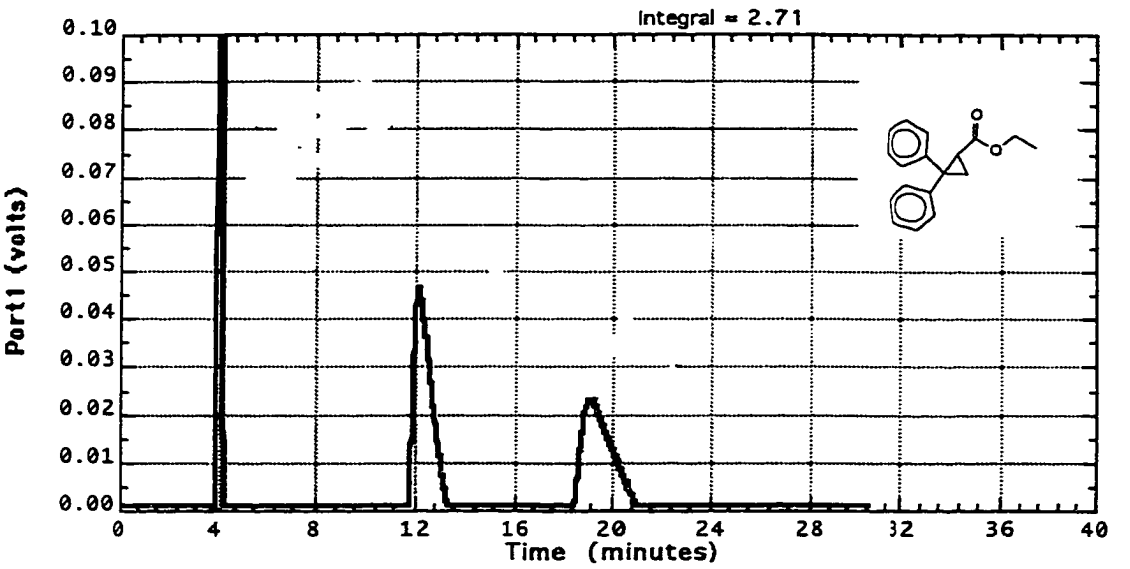


Figure 2-23a: Chiral HPLC of crude reaction mixture of the cyclopropanation of 1,1-diphenylethylene (OJ column) @1.50 mL/min (1:9 i-PrOH/hexanes).

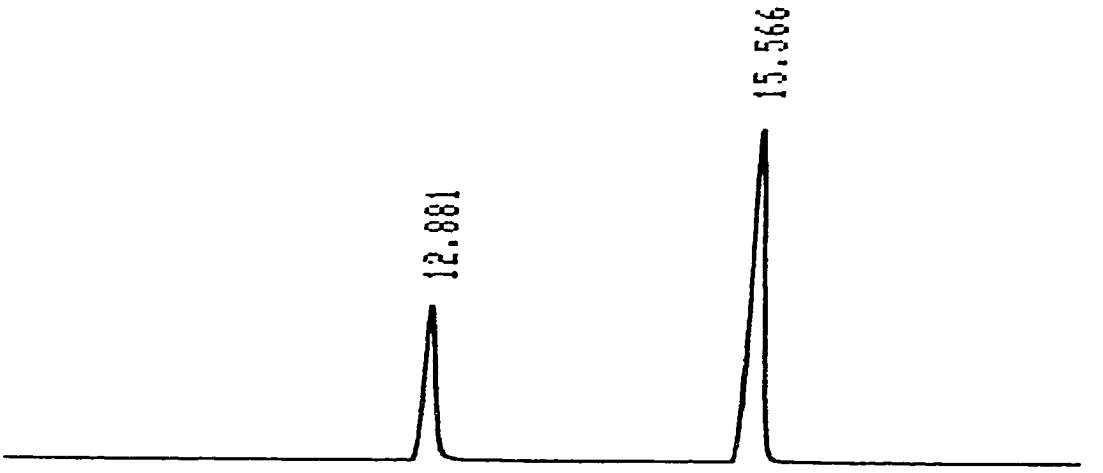


Figure 2-23b: GC trace of the crude reaction mixture of the cyclopropanation of 1,1-diphenylethylene.

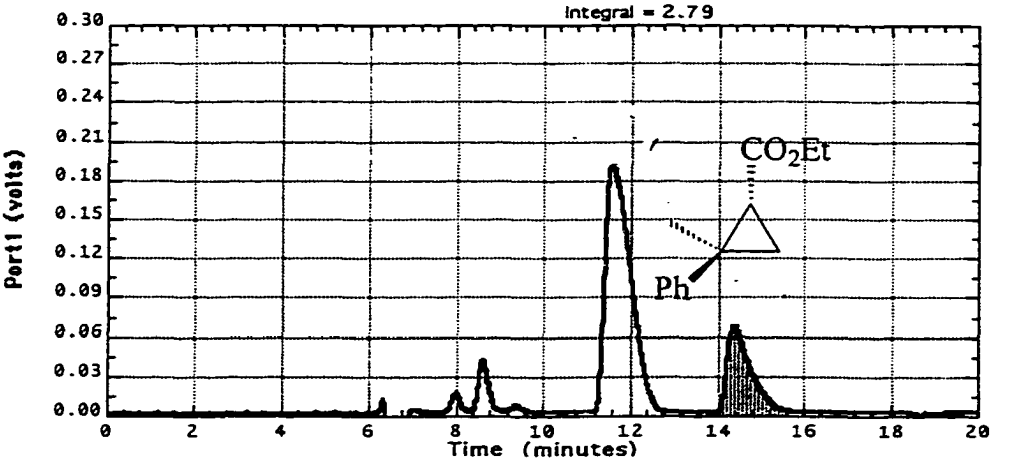


Figure 2-24a: Chiral HPLC of the *trans*-products from the cyclopropanation of α-methylstyrene (OJ column) @0.5 mL/min (1:9 i-PrOH/hexanes).

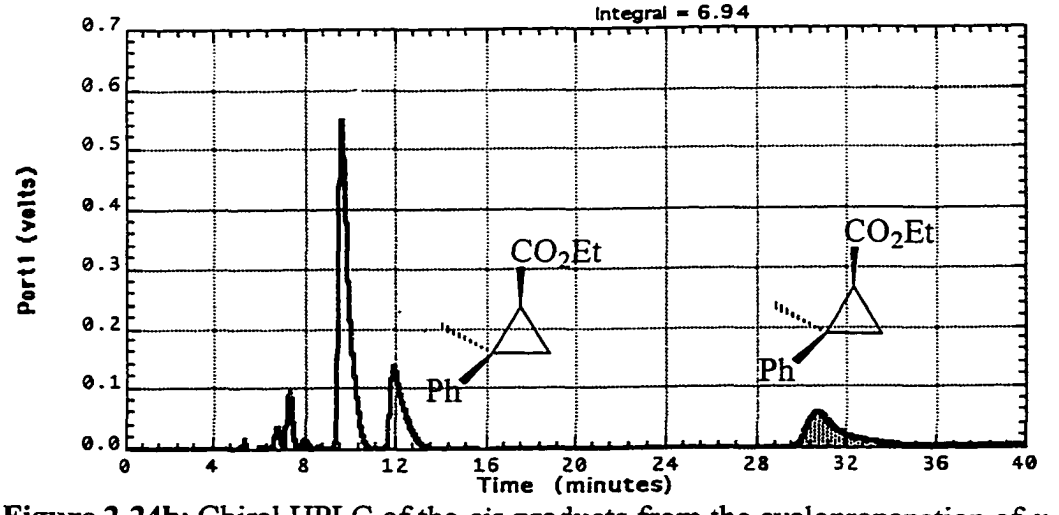


Figure 2-24b: Chiral HPLC of the *cis*-products from the cyclopropanation of α-methylstyrene (OJ column) @0.60 mL/min (1:9 i-PrOH/hexanes).

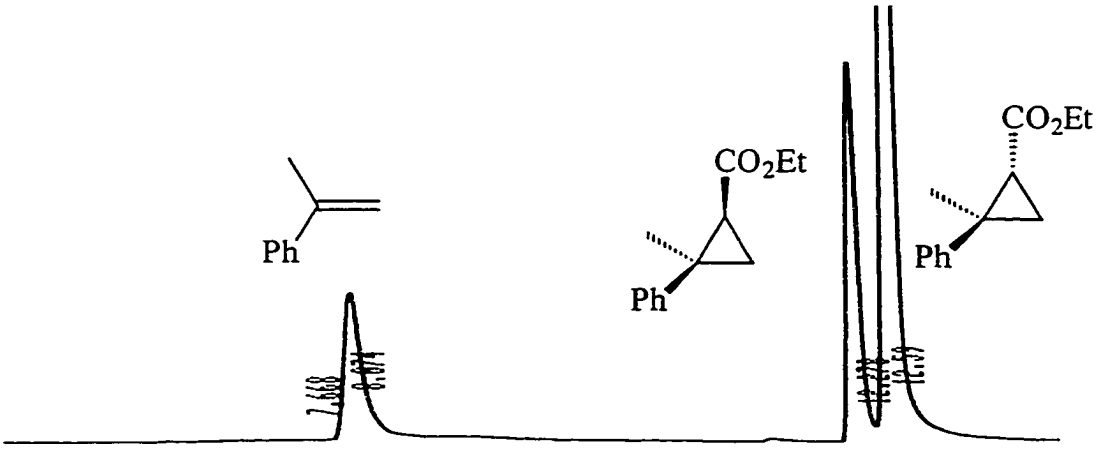


Figure 2-24c: GC trace of the crude reaction mixture of the cyclopropanation of α-methylstyrene.

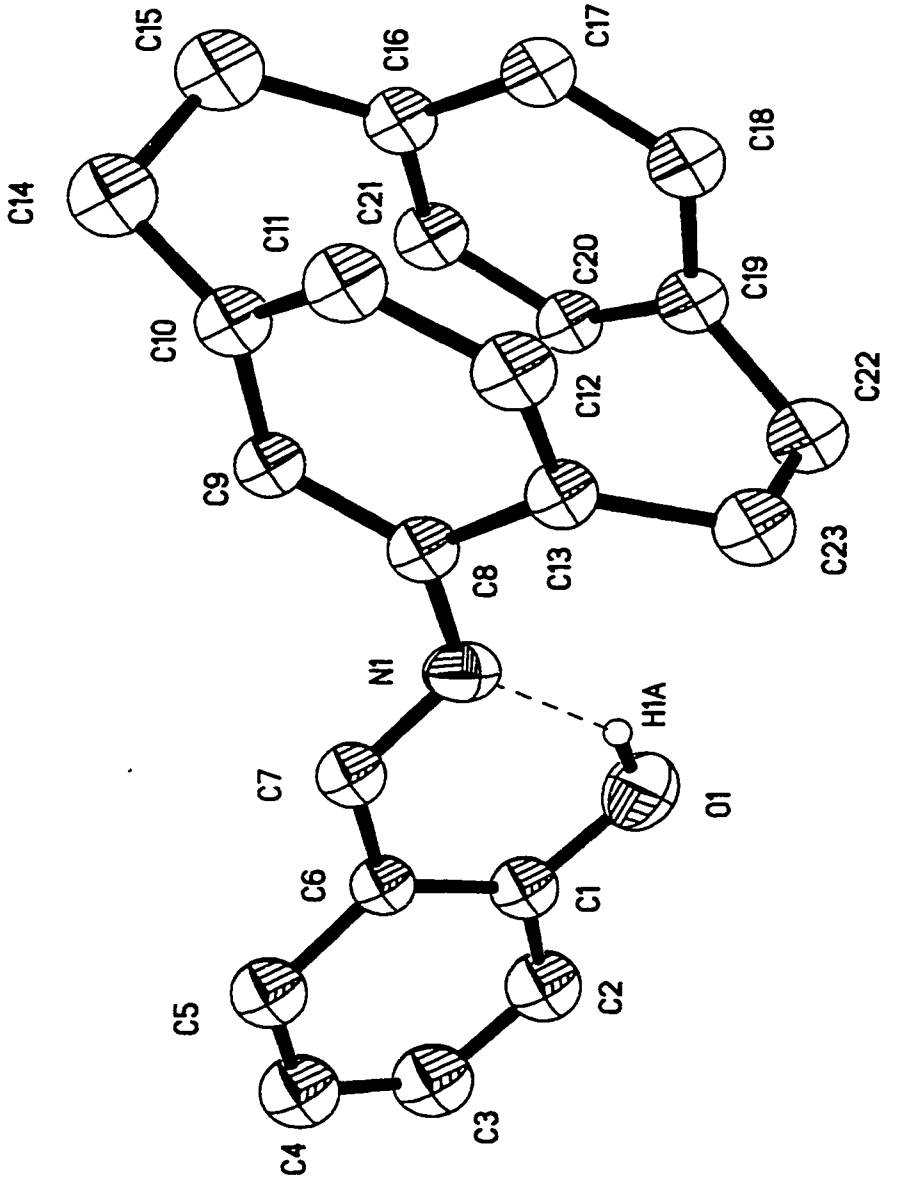


Figure 2-25: X-ray structure of ligand **5**.

Crystal data and structure refinement for ligand **5**.

Empirical formula	C23 H21 N O
Formula weight	327.41
Temperature	173(2) K
Wavelength	0.71073 A
Crystal system	Orthorhombic
Space group	Pbca
Unit cell dimensions	a = 17.9435(14) A alpha = 90 deg. b = 7.8818(6) A beta = 90 deg. c = 24.407(2) A gamma = 90 deg.
Volume, Z	3451.9(5) A^3, 8
Density (calculated)	1.260 Mg/m^3
Absorption coefficient	0.076 mm^-1
F(000)	1392
Crystal size	0.20 x 0.40 x 0.28 mm
Theta range for data collection	2.02 to 25.00 deg.
Limiting indices	-5<=h<=21, -9<=k<=9, -29<=l<=6
Reflections collected	3044
Independent reflections	3043 [R(int) = 0.0653]
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3042 / 0 / 227
Goodness-of-fit on F^2	1.035
Final R indices [I>2sigma(I)]	R1 = 0.0567, wR2 = 0.1181
R indices (all data)	R1 = 0.1056, wR2 = 0.1607
Extinction coefficient	0.0030(6)
Largest diff. peak and hole	0.191 and -0.170 e.A^-3

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for ligand **5**.

	x	y	z	U(eq)
O(1)	3426(1)	1631(3)	4763(1)	46(1)
N(1)	3094(1)	-180(3)	5617(1)	31(1)
C(1)	2694(2)	1584(4)	4632(1)	37(1)
C(2)	2456(2)	2414(4)	4160(1)	50(1)
C(3)	1711(2)	2355(5)	4018(1)	54(1)
C(4)	1204(2)	1480(5)	4329(1)	51(1)
C(5)	1432(2)	678(4)	4802(1)	44(1)
C(6)	2183(2)	731(4)	4965(1)	33(1)
C(7)	2410(2)	-122(4)	5462(1)	33(1)
C(8)	3280(2)	-1029(3)	6109(1)	30(1)
C(9)	2898(2)	-691(4)	6592(1)	30(1)
C(10)	3133(2)	-1370(4)	7088(1)	34(1)
C(11)	3662(2)	-2645(4)	7071(1)	38(1)
C(12)	4060(2)	-2941(4)	6592(1)	38(1)
C(13)	3936(2)	-1997(4)	6120(1)	32(1)
C(14)	2945(2)	-461(5)	7618(1)	45(1)
C(15)	3575(2)	819(5)	7809(1)	48(1)
C(16)	4132(2)	1180(4)	7362(1)	35(1)
C(17)	4769(2)	203(4)	7310(1)	38(1)
C(18)	5124(2)	20(4)	6808(1)	37(1)
C(19)	4833(2)	784(4)	6343(1)	34(1)
C(20)	4299(2)	2045(4)	6424(1)	33(1)
C(21)	3951(2)	2236(4)	6925(1)	35(1)
C(22)	4958(2)	33(4)	5782(1)	43(1)
C(23)	4556(2)	-1729(4)	5711(1)	40(1)

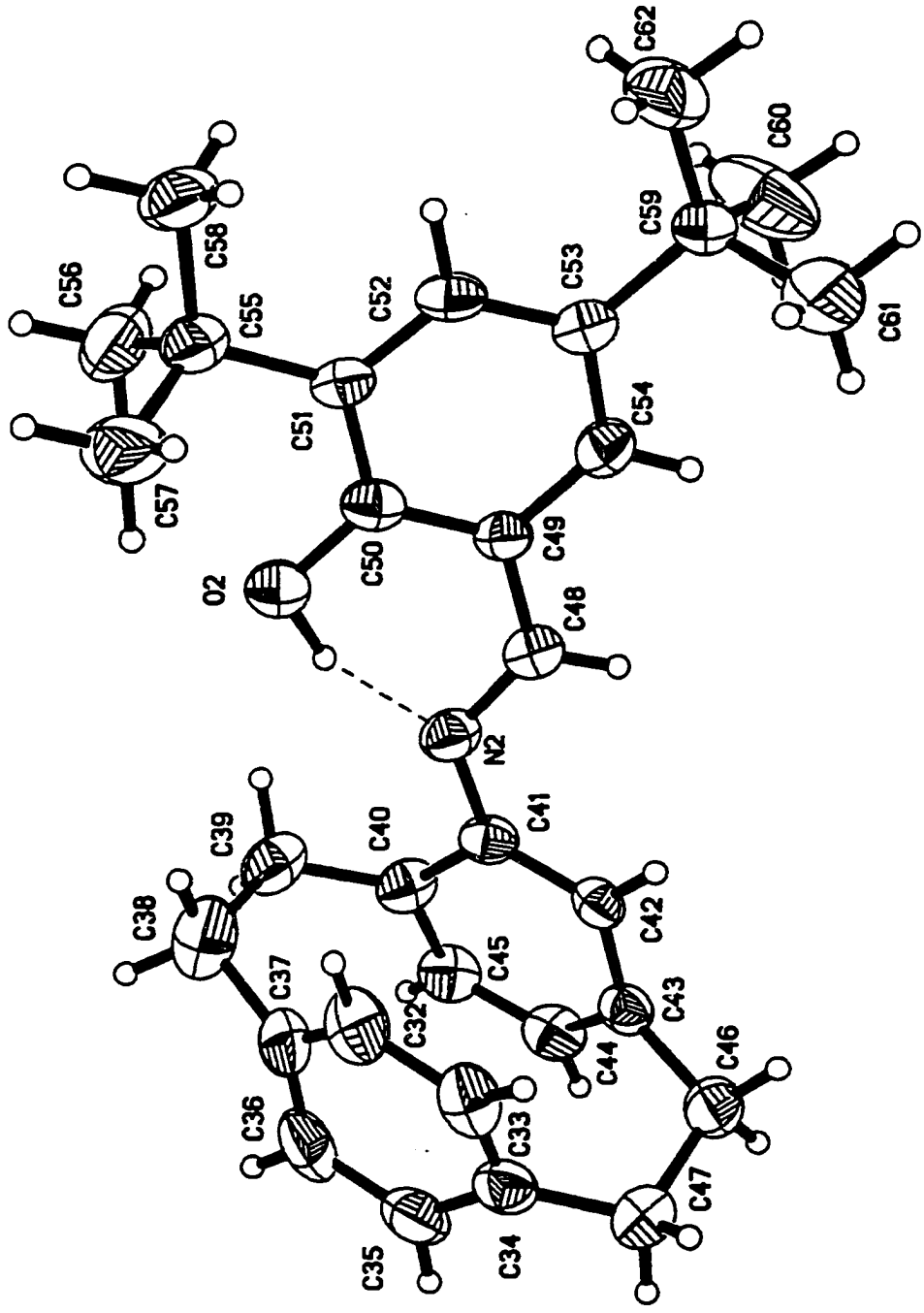


Figure 2-26: X-ray structure of ligand **14**.

Crystal data and structure refinement for ligand **14**.

Empirical formula	C27.56 H32.89 N0.89 O0.89
Formula weight	390.77
Temperature	293 (2) K
Wavelength	0.71073
Crystal system	Monoclinic
Space group	P2(1)/n
Unit cell dimensions	a = 13.629 (2) A alpha = 90 deg.
	b = 10.7220 (10) A beta = 98.62 deg.
	c = 35.802 (5) A gamma = 90 deg.
Volume, Z	5172.7 (12) A^3, 9
Density (calculated)	1.129 Mg/m^3
Absorption coefficient	0.067 mm^-1
F (000)	1904
Crystal size	0.26 x 0.42 x 0.26 mm
Theta range for data collection	1.98 to 22.00 deg.
Limiting indices	0<=h<=14, 0<=k<=11, -37<=l<=37
Reflections collected	6669
Independent reflections	6345 [R(int) = 0.0263]
Absorption correction	none
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6345 / 0 / 603
Goodness-of-fit on F^2	1.028
Final R indices [I>2sigma (I)]	R1 = 0.0581, wR2 = 0.1253
R indices (all data)	R1 = 0.1071, wR2 = 0.1527
Largest diff. Peak and hole	0.217 and -0.190 e.A^3

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for ligand **14**.

	X	Y	Z	U(eq)
O (2)	4387 (2)	5285 (3)	731 (1)	49 (1)
N (2)	3127 (2)	4337 (3)	1137 (1)	38 (1)
C (32)	1027 (3)	5648 (4)	665 (1)	50 (1)
C (33)	416 (3)	5931 (4)	933 (1)	48 (1)
C (34)	-378 (3)	5198 (4)	977 (1)	43 (1)
C (35)	-638 (3)	4329 (4)	695 (1)	52 (1)
C (36)	-71 (4)	4056 (4)	423 (1)	56 (1)
C (37)	838 (3)	4632 (4)	436 (1)	51 (1)
C (38)	1667 (4)	4011 (4)	270 (1)	67 (1)
C (39)	2130 (3)	2881 (4)	514 (1)	49 (1)
C (40)	1843 (3)	2864 (3)	903 (1)	38 (1)
C (41)	2224 (3)	3726 (3)	1183 (1)	34 (1)
C (42)	1665 (3)	4104 (3)	1458 (1)	32 (1)
C (43)	734 (3)	3593 (3)	1475 (1)	34 (1)
C (44)	477 (3)	2534 (3)	1257 (1)	41 (1)
C (45)	1020 (3)	2198 (3)	977 (1)	41 (1)
C (46)	-33 (3)	4317 (4)	1650 (1)	47 (1)
C (47)	-734 (3)	5119 (5)	1354 (1)	60 (1)
C (48)	3724 (3)	4705 (3)	1431 (1)	38 (1)
C (49)	4650 (3)	5347 (3)	1408 (1)	34 (1)
C (50)	4961 (3)	5628 (3)	1058 (1)	37 (1)
C (51)	5870 (3)	6249 (3)	1048 (1)	35 (1)
C (52)	6418 (3)	6563 (3)	1396 (1)	38 (1)
C (53)	6135 (3)	6306 (3)	1749 (1)	35 (1)
C(54)	5244 (3)	5692 (3)	1744 (1)	38 (1)
C (55)	6234 (3)	6558 (4)	674 (1)	44 (1)
C (56)	6363 (3)	5351 (4)	455 (1)	64 (1)
C (57)	5480 (3)	7406 (5)	435 (1)	71 (2)
C (58)	7229 (3)	7249 (4)	730 (1)	52 (1)
C (59)	6769 (3)	6658 (4)	2122 (1)	41 (1)
C (60)	7050 (4)	5489 (5)	2353 (1)	89 (2)
C (61)	6154 (3)	7512 (5)	2347 (1)	79 (2)
C (62)	7697 (3)	7365 (4)	2073 (1)	67 (1)

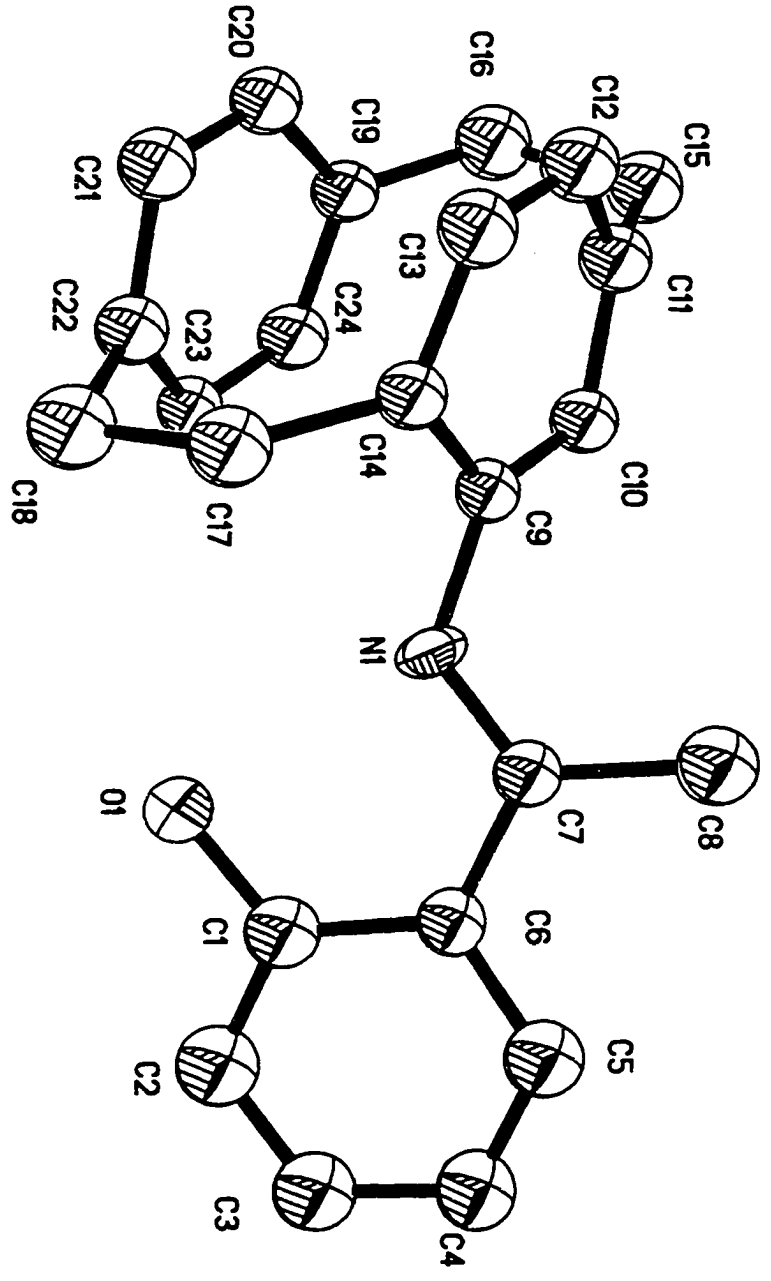


Figure 2-27: X-ray structure of ligand **17**.

Crystal data and structure refinement for ligand **17**

Empirical formula	C24 H23 N O	
Formula weight	341.43	
Temperature	173 (2) K	
Wavelength	0.71073 A	
Crystal system	Orthorhombic	
Space group	pbca	
Unit cell dimensions	a = 14.867 (3) A	alpha = 90 deg.
	b = 10.488 (4) A	beta = 90 deg.
	c = 22.764 (4) A	gamma = 90 deg.
Volume, Z	3549 (2) A^3, 8	
Density (calculated)	1.278 Mg/m^3	
Absorption coefficient	0.077 mm^-1	
F (000)	1456	
Crystal size	0.08 x 0.48 x 0.34 mm	
Theta range for data collection	1.79 to 25.00 deg.	
Limiting indices	-5<=h<=17, -12<=k<=12, -6<=l<=27	
Reflections collected	3140	
Independent reflections	3128 [R(int) = 0.0713]	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3126 / 0 / 236	
Goodness-of-fir on F^2	1.018	
Final R indices [I>2sigma(I)]	R1 = 0.0804	wR2 = 0.2007
R indices (all data)	R1 = 0.1309	wR2 = 0.2495
Extinction coefficient	0.004 (2)	
Largest diff. Peak and hole	0.366 and -0.395 e.A^-3	

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for ligand **17**.

	X	Y	Z	U(eq)
O (1)	1411 (2)	1643 (3)	5181 (1)	43 (1)
N (1)	2129 (2)	14 (3)	5824 (1)	30 (1)
C (1)	2230 (3)	1773 (4)	4927 (2)	35 (1)
C (2)	2317 (3)	2681 (4)	4481 (2)	45 (1)
C (3)	3125 (3)	2843 (5)	4201 (2)	46 (1)
C (4)	3856 (3)	2105 (5)	4355 (2)	46 (1)
C (5)	3781 (3)	1224 (4)	4798 (2)	39 (1)
C (6)	2968 (3)	1047 (4)	5105 (2)	31 (1)
C (7)	2909 (3)	159 (4)	5604 (2)	29 (1)
C (8)	3747 (3)	-520 (4)	5807 (2)	37 (1)
C (9)	1947 (2)	-751 (3)	6350 (2)	27 (1)
C (10)	2380 (2)	-452 (4)	6884 (2)	28 (1)
C (11)	2112 (3)	-1026 (4)	7404 (2)	33 (1)
C (12)	1567 (3)	-2098 (4)	7355 (2)	37 (1)
C (13)	1151 (3)	-2388 (4)	6827 (2)	36 (1)
C (14)	1266 (3)	-1624 (4)	6329 (2)	30 (1)
C (15)	2239 (3)	-337 (5)	7980 (2)	41 (1)
C (16)	1425 (3)	561 (5)	8143 (2)	46 (1)
C (17)	748 (3)	668 (4)	7651 (2)	33 (1)
C (18)	53 (3)	-204 (4)	7596 (2)	35 (1)
C (19)	-342 (3)	-445 (4)	7057 (2)	36 (1)
C (20)	-39 (3)	182 (4)	6555 (2)	34 (1)
C (21)	508 (2)	1231 (3)	6636 (2)	29 (1)
C (22)	900 (3)	1474 (4)	7175 (2)	31 (1)
C (23)	-137 (3)	-417 (5)	5955 (2)	44 (1)
C (24)	542 (3)	-1571 (4)	5864 (2)	40 (1)

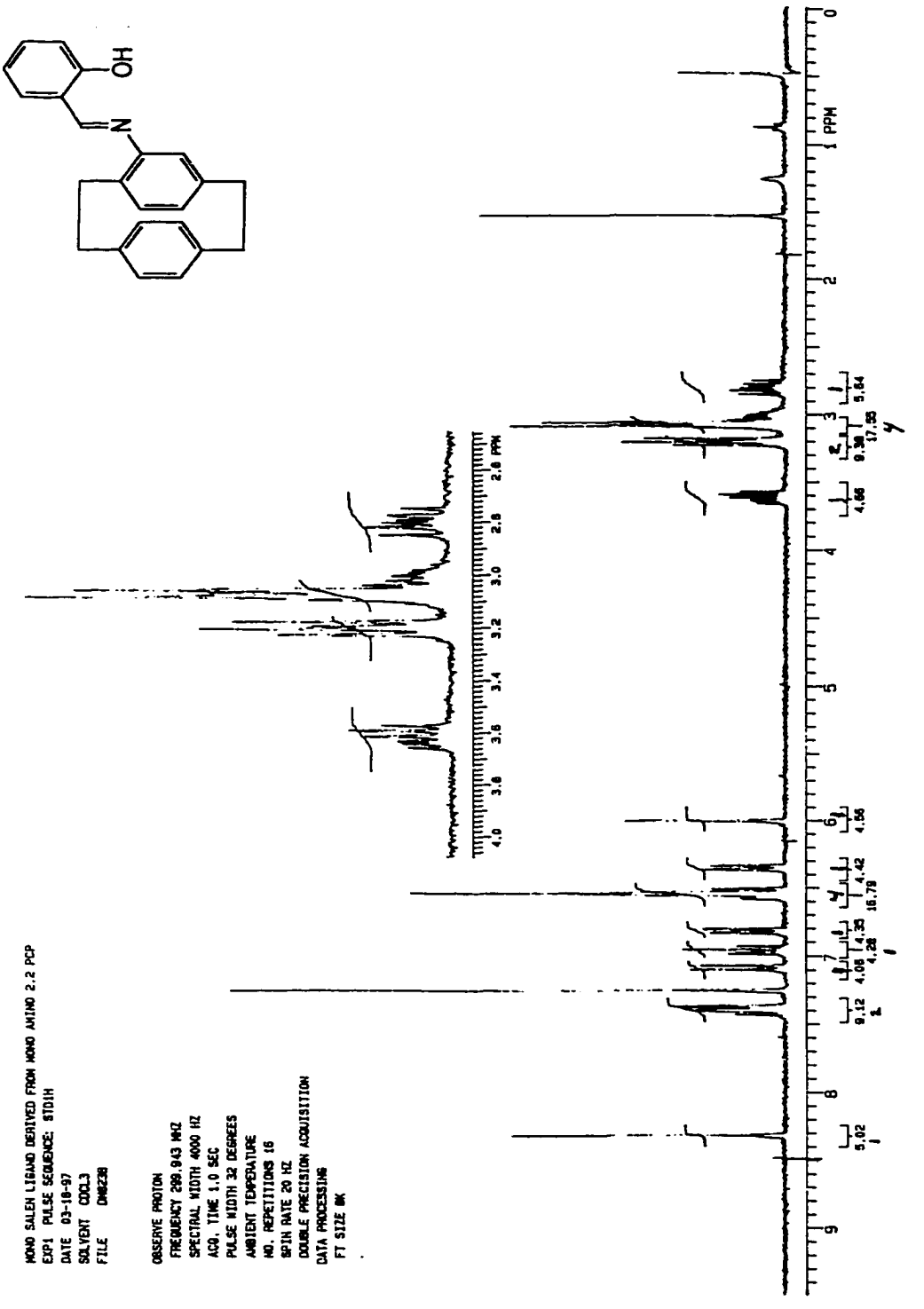


Figure 2-28: ^{1}H-NMR of ligand **5**.

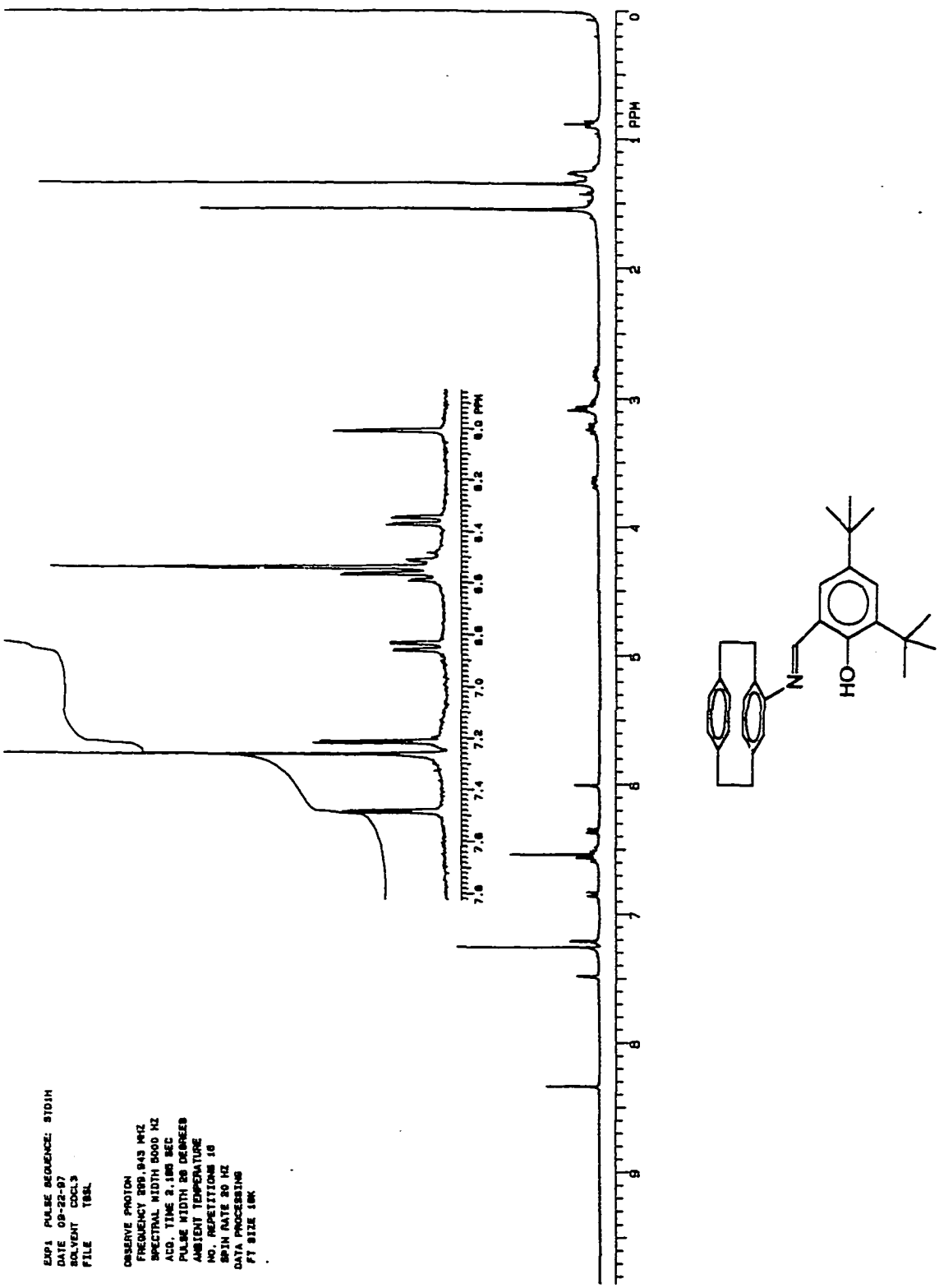


Figure 2-29: ^{1}H-NMR of ligand **14**.

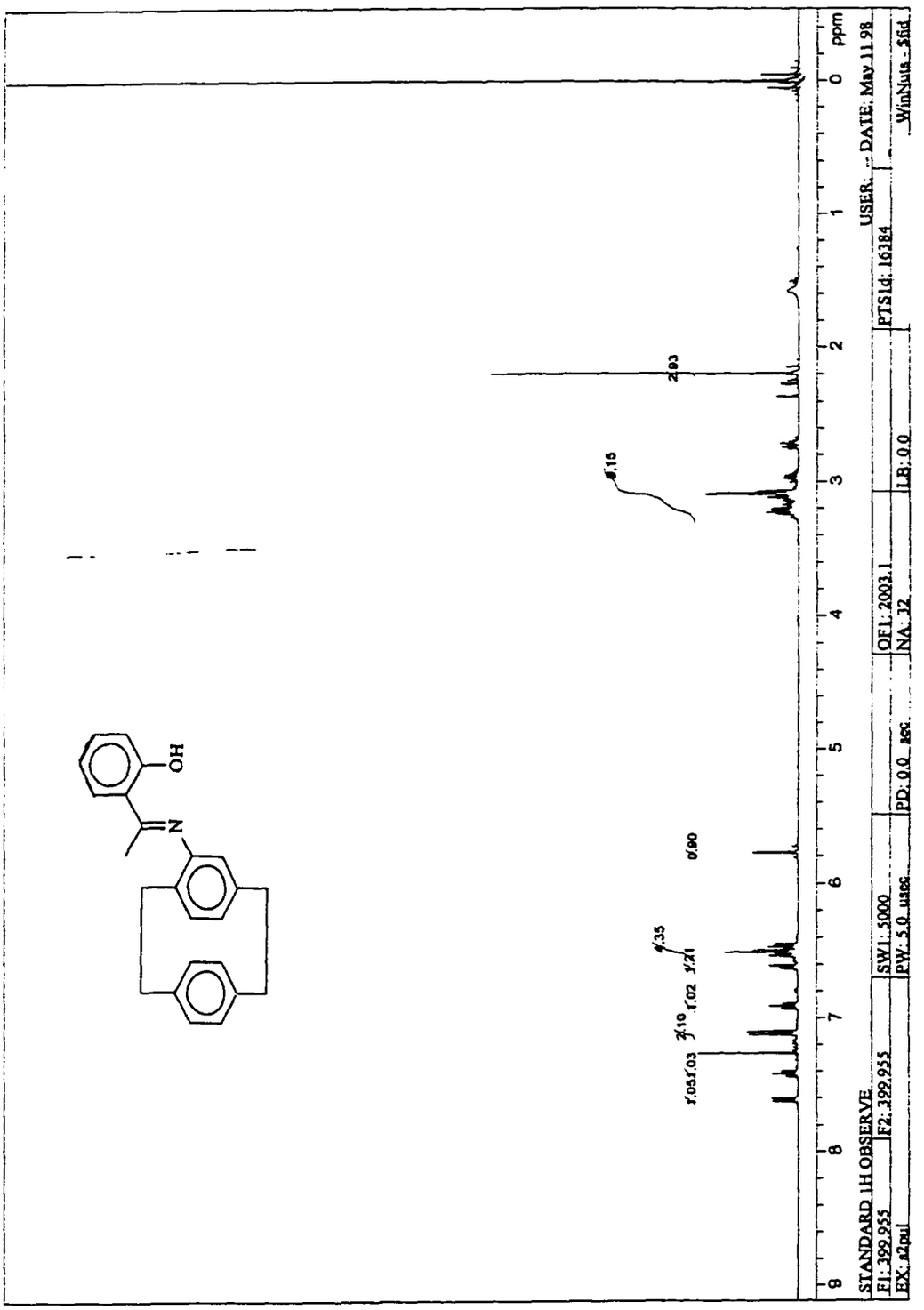


Figure 2-30: ^{1}H-NMR of ligand **17**.

CHAPTER 3: Mechanistic Considerations in the Copper Catalyzed Cyclopropanation Reaction Using Chiral [2.2]Paracyclophane Ligands.

Introduction

Many mechanistic considerations in the copper catalyzed cyclopropanation reaction need further study. The orientation of the active catalyst derived from chiral mono-substituted [2.2]paracyclophane ligands is unknown. Not knowing the exact conformation of the active catalytic species makes it difficult to predict which factors are responsible for determining the stereoselectivity in the resulting cyclopropane products. The control of olefin approach is unclear with the mono-substituted [2.2]paracyclophane ligands.

The copper catalyzed cyclopropanation reaction using chiral [2.2]paracyclophane ligands also has many electronic issues which need to be addressed. It is well known that with many ligand systems the active oxidation state of the copper metal is the +1 oxidation state,[1] but no precedent exists for the utilization of [2.2]paracyclophane ligands. It is also well known that the active carbenoid species in the copper catalyzed cyclopropanation reaction are electrophilic in character,[2,3] but the character of the carbenoid species derived from the [2.2]paracyclophane ligands is completely unknown. The extent of electronic vs. steric interactions inherent in the mono-substituted [2.2]paracyclophane ligands with the olefinic substrates is unknown.

Rather than assuming that the active catalyst is the same as in other systems, it was decided that a limited mechanistic study would be prudent. This chapter will present

results of experiments that were devised to address the mechanistic concerns of the copper catalyzed cyclopropanation reaction which are specific to the use of the [2.2]paracyclophane ligand system.

Enantiomers Arising from Olefin Approach to Carbenoid

In non- C_2 symmetric systems the approach of the olefin becomes a major mechanistic concern. In C_2 symmetric systems the terms top and bottom approach have no real meaning as shown in Figure 3-1.

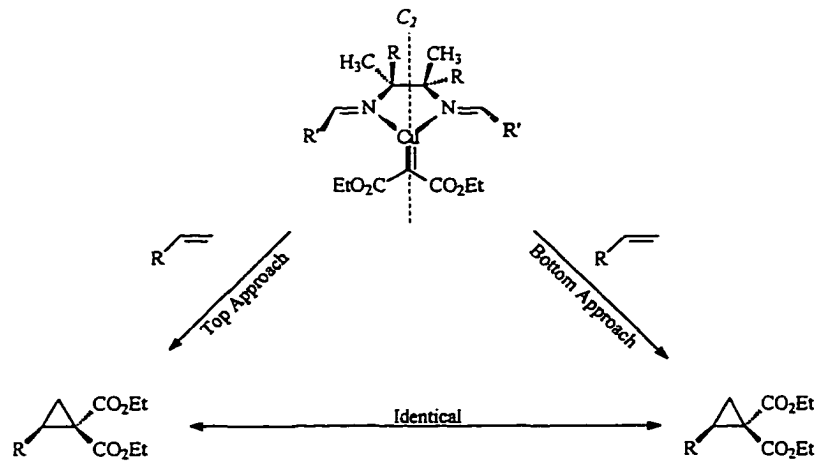


Figure 3-1: Olefin approach in C_2 symmetric systems

This is not the case in the mono-substituted [2.2]paracyclophane systems since there is no symmetry operation which demands that the two faces of the carbenoid be identical. In this case olefin approach to the carbenoid center can lead to different products. Figure 3-2 below illustrates that olefin approach in non-C_2 symmetric systems can lead to different enantiomers (all other factors being equal).

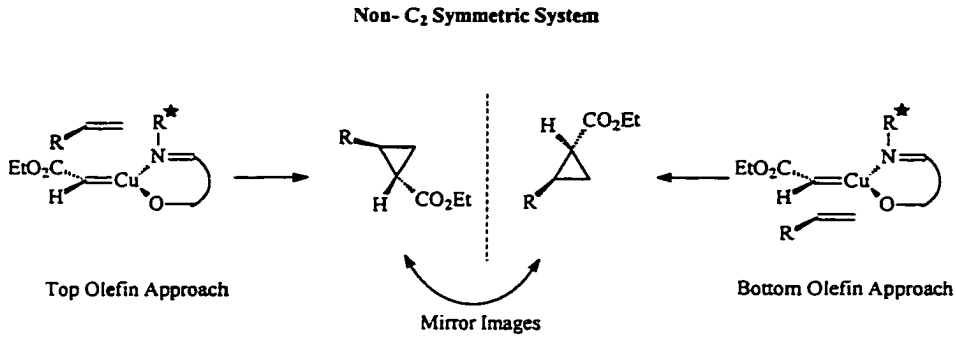


Figure 3-2: olefin approach in non-C_2 symmetric systems

In order to assess the ability of the chiral mono-substituted [2.2]paracyclophane Schiff-base ligands to direct olefin approach a system must be devised such that the resulting enantiomers are obtained from olefin approach only. Figure 3-2 above illustrates the use of EDA as the diazo ester in the formation of the active carbenoid. The problem with using EDA is that it is not a symmetric entity and can possibly give rise to two orientations with respect to the ligand as shown in Figure 3-3.

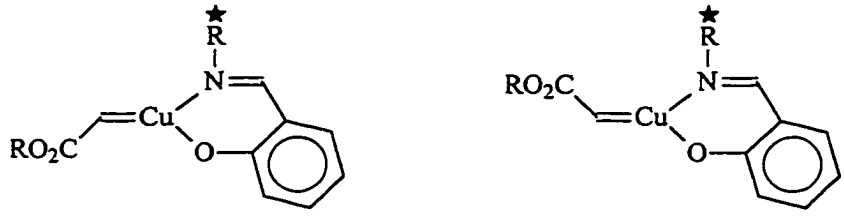
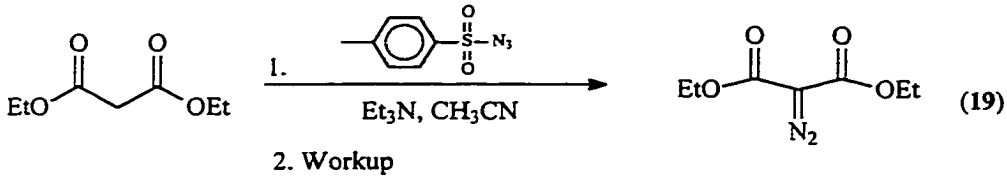


Figure 3-3: Carbenoid orientaions with EDA

Since the goal is to determine the ability of the cyclophane ligand to direct olefin approach, the problem of carbene orientation when using EDA must be eliminated. In order to eliminate carbene orientation problems a symmetrical diazo compound can be employed. Scheme 3-1 shows the construction of a symmetrical diazo diester from diethyl malonate using a diazo transfer reaction.[4]



(19)

Scheme 3-1: Synthesis of symmetrical diazo esters

Diazo compound **19** could be utilized in the construction of cyclopropane product **20**.[5] The enantiomeric excess of **20** can be determined by converting **20** to its methyl ester derivative and measuring its optical rotation.[5] The magnitude of the enantiomeric excess is a measure of the ligand's ability to direct the olefin approach to the catalytically active carbenoid. Figure 3-4 illustrates the formation of enantiomers by olefin approach with ligand **5**.

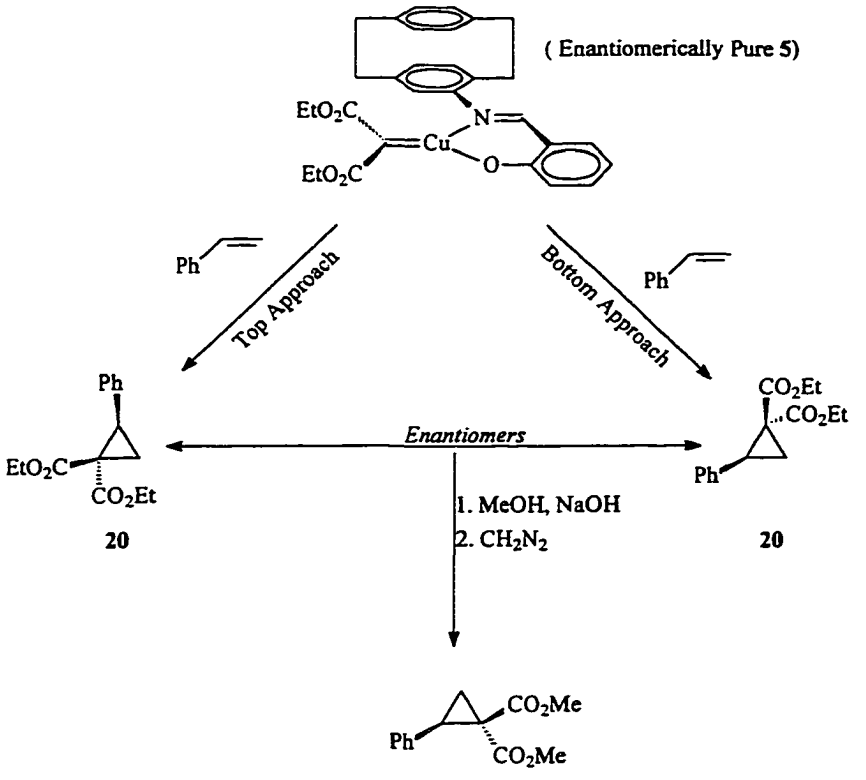


Figure 3-4: Enantiomers arising from olefin approach

From Figure 3-4, top face approach leads to the opposite enantiomer of bottom face approach and there is no chance of diastereomeric cyclopropanation products being formed. If olefin approach is significantly restricted to either the top or bottom face then one would expect a high level of enatioselective induction, but if facial selectivity is low one would expect a smaller enantioselective induction and hence lower %ee values in the resulting cyclopropane products.

Ligand **5** was complexed with copper (II) acetate (chapter 2 Experimental) and was utilized in the cyclopropanation of styrene with diazo ester **19**. It was found that use of **19** as diazo compound resulted in a sluggish reaction rate. In order to overcome the

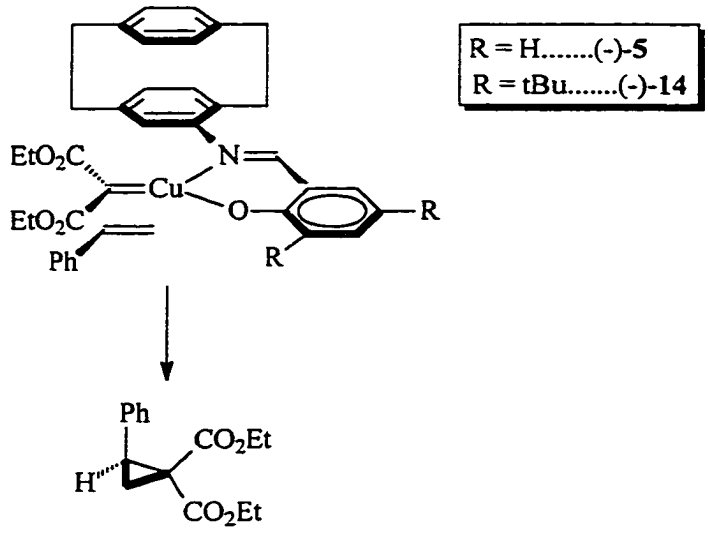
sluggish rate a longer reaction time was employed as well as a higher catalyst loading. The resulting mixture was then filtered through neutral alumina to remove the copper catalyst and the cyclopropane products were subjected to basic hydrolysis. The resulting diacid was exposed to an excess of diazomethane to obtain the methyl ester derivative of **20**. The %ee was determined by optical rotation of the methyl ester derivative of **20**. The results for both ligands **5** and **14** are listed below in Table 3-1.

Table 3-1[a]: Results of olefin approach experiment

Ligand	Substrate	% Conversion[b]	% ee[c]
(-)-**5**	styrene (**7**)	42.9 %	11.19% (*S*)
(-)-**14**	styrene (**7**)	74.6%	8.48% (*S*)

a) reaction performed using a 0.3 mol% catalyst loading and **19** as the diazoester, b) determined using gas chromatography on the crude reaction mixture, c) determined by optical rotation of the corresponding di-methyl ester derivative, product configuration shown in parentheses.

Table 3-1 illustrates that enantioselectivity with both ligands **5** and **14** is low. The low enantioselectivity is indicative of the mono-substituted [2.2]paracyclophane Schiff-base ligands having poor olefin directing ability. It is also clear from Table 3-1 that the (*S*) enantiomer of ligands **5** and **14** result in formation of the (*S*) cyclopropane product[5] which can be rationalized by a steric model as shown in Figure 3-5 below.

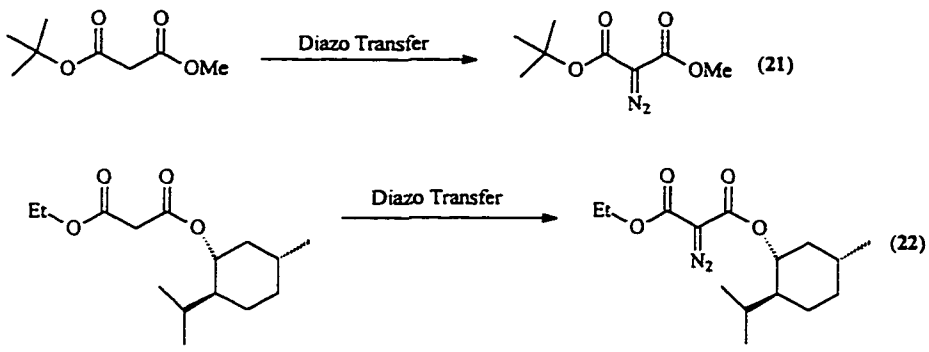


(*S*) Product

Figure 3-5: Steric model for (*S*) product formation

Figure 3-5 illustrates that formation of the (*S*) cyclopropane product must arise from bottom side olefin approach. Since the resulting **20** was not isolated in racemic form, this indicates a preference in bottom side olefin approach, albeit a small preference.

In an attempt to improve the enantioselectivity of **20,** other diazo diesters were constructed by essentially the same diazo transfer reaction that was illustrated in Scheme 3-1. Scheme 3-2 below shows the formation of diazo diesters **21** and **22.**



Scheme 3-2

Diazo esters **21** and **22** were subjected to the same conditions as diazo ester **19**. The results of using **21** and **22** are shown below in Table 3-2.

Table 3-2[a]: Results of using modified diazoesters

Ligand	Diazo Ester	Substrate	% Conv.[b]	%ee[c]
(-)-**5**	**21**	styrene (**7**)	70%	10.77% (*S*)
(-)-**5**	**22**	styrene (**7**)	0%	----

a) reaction performed using 0.3 mol% catalyst loading, b) determined by gas chromatography, c) determined by optical rotation of the di-methylester derivative, product configuration shown in parentheses.

From Table 3-2 it is clear that altering the diazoester, at least in this case, has little effect on the observed enantioselectivity of the cyclopropane products. Diazo ester **21** essentially gave the same enantiomeric enrichment of product **20** as did diazo ester **19**. Although the % ee was the same it should be pointed out that when **21** was used as the diazoester the *cis/trans* selectivity was about 1:6.35 by ^{1}H NMR (this is of little

importance since the diastereomers are destroyed during saponification).

It is apparent from tables 3-1 and 3-2 that the ability of the [2.2]paracyclophane moiety to direct olefin approach is relatively small. In order to better quantify the olefin directing ability of the [2.2]paracyclophane moiety a transition state analysis is in order.[6] Figure 3-6 illustrates the two possible diastereomeric, enantiodiscriminating, transition states which ultimately lead to the different product enantiomers.

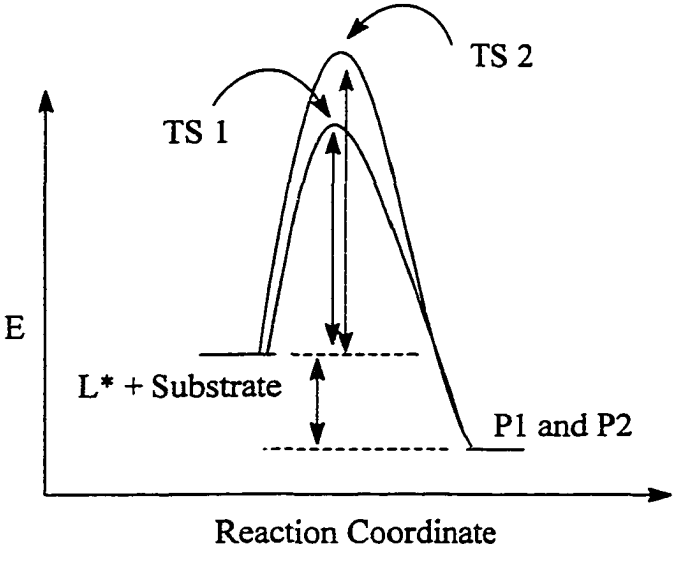


Figure 3-6: Transition state analysis

From Figure 3-6 it is possible to calculate the free energy difference of TS 1 and TS 2.[6] The reaction of styrene with **19** to produce **20** can be envisioned to occur as outlined in Figure 3-6 where TS 1 and TS 2 are the transition states which arise from either top side or bottom side olefin approach to the carbenoid center and P1 and P2 are enantiomers of one another. Knowing the enantiomeric excess of product **20** it is possible to determine

the difference in free energy of TS 1 and TS 2 and hence the energy difference in facial olefin approach. Using this information and the following relationship,[6] $P1/P2 = e^{-\Delta\Delta G/RT}$, the free energy difference for an average P1/P2 ratio of 55/45 (10% ee, the average %ee of the three reported experiments) at 80°C reaction temperature is 0.14 kcal/mol.

The above data indicate that catalysts derived from mono-substituted [2.2]paracyclophanes have low levels of control over olefin approach to the active carbenoid site. Attempts to improve olefin approach by using either ligand **14** or diazo diester **21** did not result in significant improvements in enantioselectivity. This suggests that in this case olefin approach is not restricted to a single face as would be expected if high enantioselectivities had been achieved. The calculated free energy difference of TS 1 and TS 2 (Figure 3-6) is a relatively small 0.14 kcal/mol which is indicative of poor facial selectivity.

Electronic Character of the Active Metal Center and Carbenoid

It is well accepted that the active oxidation state of the copper atom in the cyclopropanation reaction of olefins with diazoesters is the +1 oxidation state.[1] Initially it was decided to attempt a select series of experiments in order to elucidate the active state of the metal when [2.2]paracyclophane Schiff-base ligand **5** was utilized. It is known that diazo compounds can reduce copper (II) to copper (I) at elevated temperatures.[1,2] This fact allowed the design of an experiment to determine if copper (I) or copper (II) was the active oxidation state of the metal and also would allow for the exploration of changing the reaction temperature on the %ee of the cyclopropane products. The experiment was conducted by using both copper (I) and copper (II) systems. The copper (II) system was tried at both 80°C and 0°C and the copper (I) system was performed at 0°C. The experiment was set up using 1,1-diphenylethylene (**9**) as the substrate and EDA as the diazoester as shown in Figure 3-7.

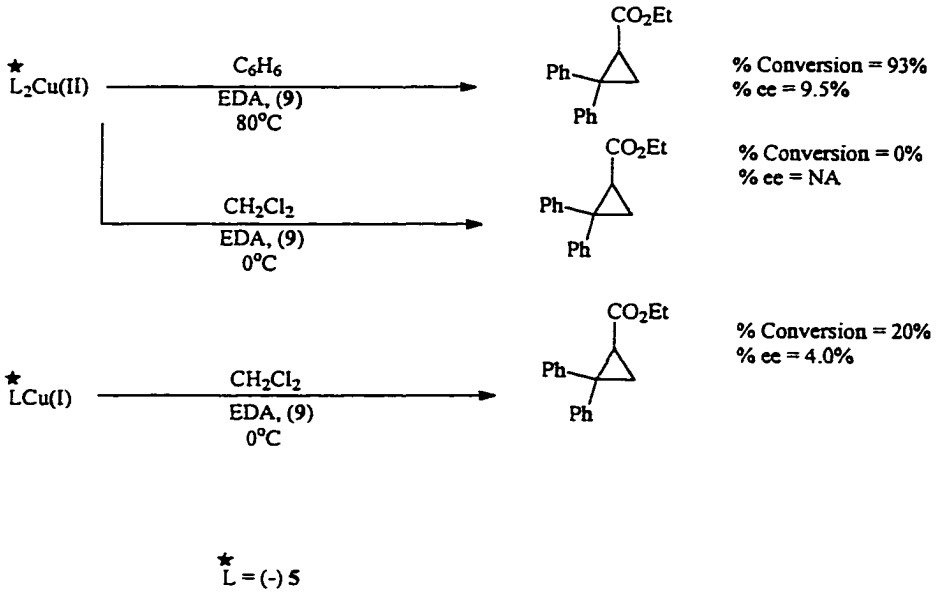


Figure 3-7: Copper oxidation state determination

From Figure 3-7 it is clear that the active oxidation state of the copper center must be the +1 state. The copper (II) system only produced product at elevated temperature where it is known that diazoesters can reduce the copper (II) species to a copper (I) species. The copper (I) system was able to perform cyclopropanation when submerged in an ice/water bath. Interestingly, it should be pointed out that lowering the temperature from 80°C to 0°C appeared to have no real significant effect on the %ee of the products (both were less than 10%). This suggests that design modifications to the ligand system are needed before attempting to fine tune the enantioselectivity of the cyclopropane products by altering reaction conditions.

The copper carbenoid systems have been shown to be electrophilic in nature.[2,3] In order to better understand the effect of the [2.2]paracyclophane moiety on the electronic character of the carbenoid a Hammett study was conducted with various para substituted styrenes. The experiment was carried out as a competition experiment between equimolar amounts of styrene and a para substituted styrene[3] as shown in Figure 3-8.

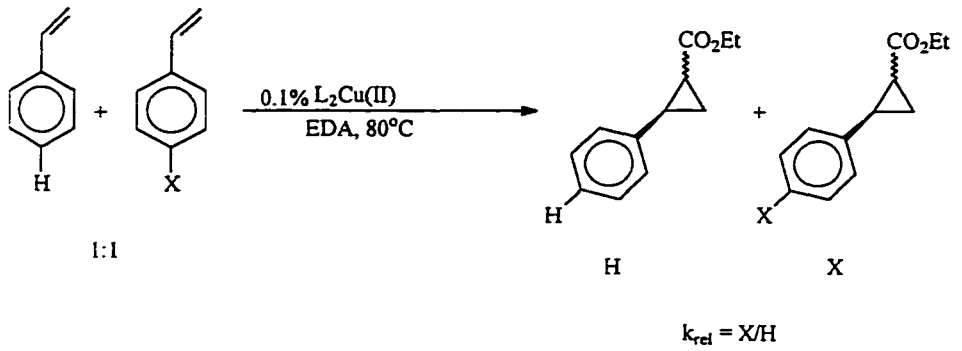


Figure 3-8: Competition experiment

If the carbenoid has significant electrophilic character one would expect small k_{rel} values for X= EWG and larger k_{rel} values for X=EDG.[7] The results of this competition experiment are listed below in Table 3-3.

Table 3-3[a]: Kinetic results

X[b]	k_{rel}[c]
H	1[d]
Me	1.95[e]
OMe	1.13[e]
Cl	1.01
CF_3	0
OAc	0

a) performed using 0.1 mol% catalyst (derived from racemic **5**), and 0.5 eq. EDA, conversions not determined b) para substituent of styrene c) determined by GC analysis and includes both *cis* and *trans* isomers d) default value for a substituent relative to itself e) average value of three runs

Table 3-3 shows that strong electron withdrawing groups such as CF_3 inhibited the formation of cyclopropane products whereas the electron donating groups such as Me promoted the formation of cyclopropane products. This behavior is indicative of an electrophilic carbenoid system. Interestingly, the value of the methoxy substituted styrene was less than that of the methyl substituted styrene. Figure 3-9 below shows the data of Table 3-3 in graphical form as a plot of log k_{rel} vs. several σ values. It is worth noting that none of the plots gave excellent fits to a line as is expected. It is obvious that the point in question is the methoxy substituted styrene. The methoxy substituted styrene should reveal larger k_{rel} values than the methyl substituted styrene for an electrophilic system,[7] but the methyl substituted styrene consistently showed larger k_{rel} values over the methoxy substituted styrene.

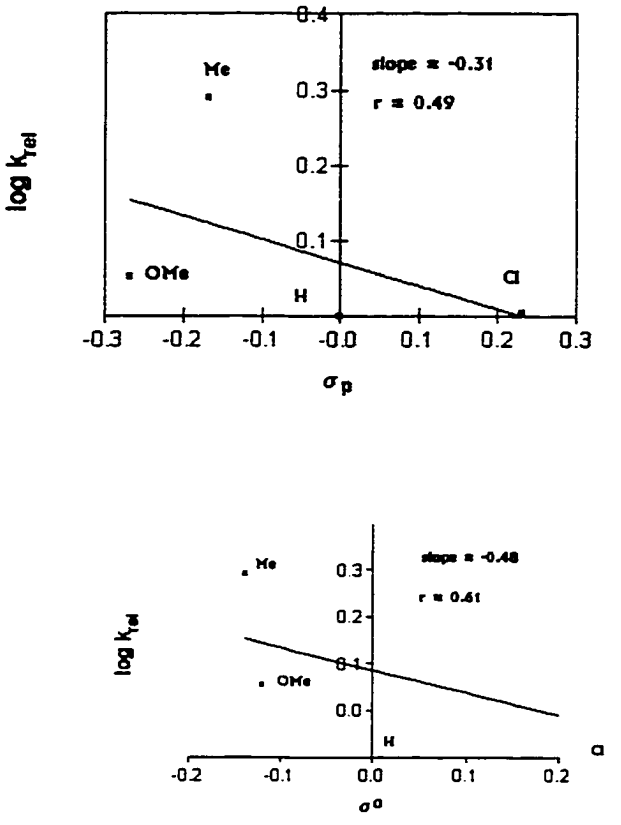


Figure 3-9: Hammett plots

Figure 3-9 above illustrates a negative slope with the best fit to σ^o constants. The negative slope is indicative of an electrophilic carbenoid center.[7] The slope of -0.48 is of similar magnitude to other reported copper carbenoid systems.[3] The fact that the data has the best fit to σ^o parameters is indicative of a mechanism which is largely concerted in nature.[8]

In conclusion it has been shown that the active oxidation state of the copper center

is the +1 oxidation state. The +1 value was determined by comparing the reactivity of copper (I) and copper(II) catalysts at low temperature which resulted in the copper(I) catalyst forming cyclopropane products. The electronic character of the catalytically active carbenoid was determined to be electrophilic in nature. The electrophilic carbenoid is consistent with both the Hammett plots presented in Figure 3-9 and with the fact that certain styrene derivatives shown in Table 3-3 failed to yield cyclopropane products (presumably due to the electron withdrawing para substituent). Unfortunately, since the styrenes with EWG failed to yield cyclopropane products these substituents had to be omitted from the Hammett plots which reduces the number of data points available for a strict statistical analysis. It was possible to determine the effect of lowering the reaction temperature on the enantioselectivity of the cyclopropane products. In the case of 1,1-diphenylethylene and EDA there was no improvement in enantioselectivity by lowering the reaction temperature from 80°C to 0°C. In fact a slight decrease in enantioselectivity was observed for the reaction at 0°C, but this is presumably due to the change in solvent composition (CH_2Cl_2 at 0°c vs. C_6H_6 at 80°C).

Electronic Tuning of Schiff-Base Ligands for Improved Enantioselectivity

Jacobsen has shown that it is possible to improve the enantioselectivity of the catalytic epoxidation reaction by altering the electronic character of the ligands which are bound to the catalytically active metal center.[9] Jacobsen found that a strong linear correlation exists between observed %ee and the EDG which was placed on the ligand (all else being equal).[9] This finding was rationalized using transition state theory. It is well accepted that catalytic reactions of non-functionalized olefins (for epoxidation and cyclopropanation) proceed through an "early" transition state.[9] Jacobsen argued that by increasing the electronic character of the ligands the transition state was shifted to a "later" more product like transition state. A "late" transition state is believed to be better situated to impose enantiodiscrimination since the reacting partners would be more closely associated with one another.[9] Jacobsen's argument for the "late" transition state can be stated graphically as shown in Figure 3-10.

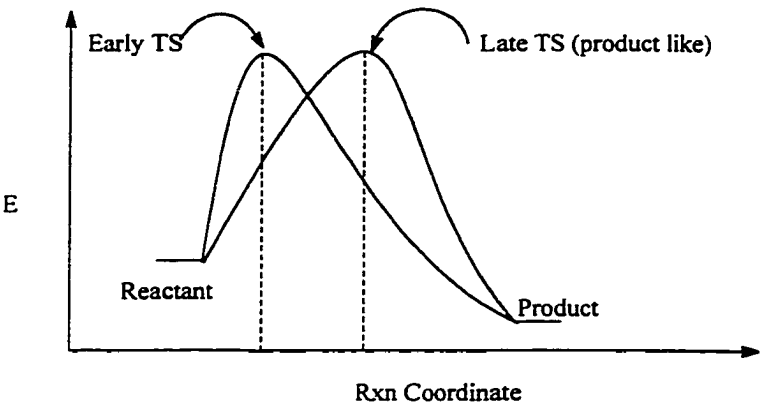
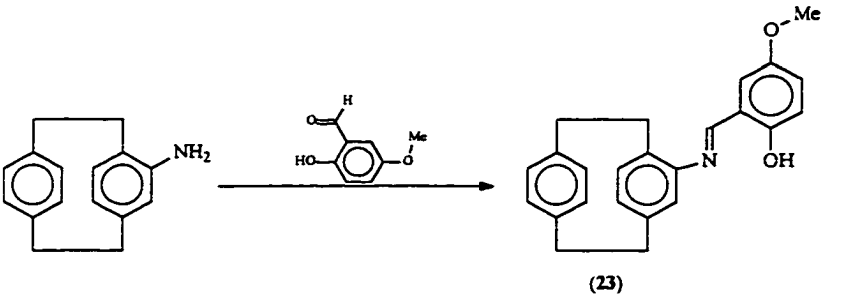


Figure 3-10

It is believed that the catalytic cyclopropanation reaction proceeds through an "early" transition state.[2] This would seem to imply that the addition of electron donating substituents on the ligands would yield better enantioselectivities. Indeed experiments have been performed which show increased enatioselectivities in the cyclopropane products when electron donating groups are present.[10] This would seem to explain why ligand **14** showed improved enantioselectivities over ligand **5** since **14** contains both an ortho and a para *tert*-butyl electron donating group ($\sigma_p = -0.15$[8]). In the case of **14** the main problem is that of the ortho *tert*-butyl group since steric interactions of this group with the approaching substrate cannot be neglected (this was shown to be the case by the inability of *trans*-stilbene to form cyclopropane products). In order to ascertain the electronic influence of the substituents on the enantioselectivity of the copper catalyzed cyclopropanation reaction using chiral [2.2]paracyclophane ligands, a *p*-methoxy group ($\sigma p = -0.28$[8]) was added, relative to the phenolic group, to ligand **5** in order to determine if the electron donating methoxy substituent would yield improved enantioselectivities

over **5** (see Figure 3-11).



(23)

Figure 3-11: Synthesis of electron rich ligand

Ligand **23** was synthesized by the condensation of the commercially available 2-hydroxy-5-methoxybenzaldehyde with racemic 4-amino[2.2]paracyclophane (**3**). Fortunately, racemic **23** was nicely resolved on a semi-preparative Chiralcel AD HPLC column. The (+) enantiomer of **23** (14.3 mg) was complexed with copper(II) by stirring with a 2X excess of copper(II) acetate in methanol for three hours. The methanol solvent was removed under reduced pressure and the resulting solid was dissolved in toluene. The toluene solution was filtered to remove non-complexed copper species and the toluene was removed under reduced pressure to yield a brown microcrystalline solid. The catalyst was used immediately without further purification.

A cyclopropanation of styrene with EDA was performed using the catalyst derived from (+) **23**. The results of this cyclopropanation reaction was a 31% conversion of the styrene substrate to the corresponding cyclopropane products. The %ee of the resulting cyclopropane products was essentially racemic for both the *cis* and *trans* isomers. This result was unexpected given the rationale of Jacobsen[9] and Rippert.[10] The low

enantioselectivity that was observed with **23** may be explained by an alteration of reaction mechanism.[8] It was evident from the Hammett studies presented above that the methoxy substituted styrene had reduced reactivity relative to the methyl substituted styrene. Perhaps the methoxy substituent forces the reaction mechanism to alter such that both reactivity and enantioselectivity are significantly reduced. It is possible that if the enantiodiscriminating event occurs in an "earlier" transition state the use of the methoxy substituent may force the transition state to be extremely "late" and hence result in poorer enantioselectivity.

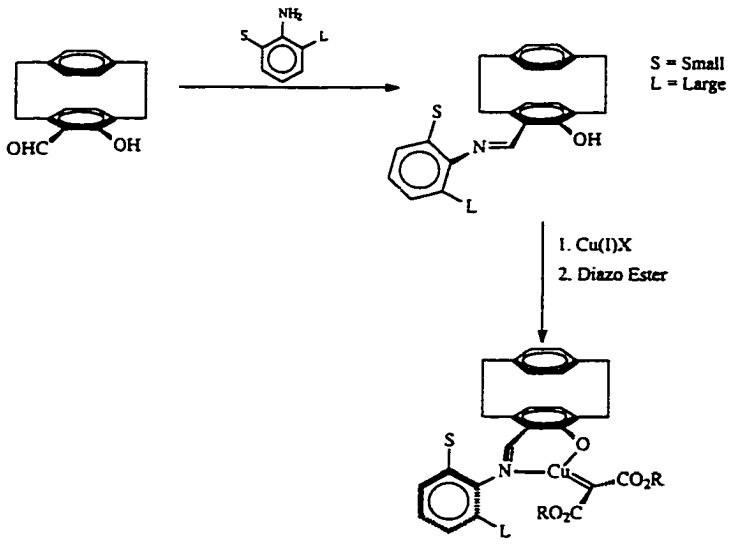
It is obvious that adding a methoxy substituent to the [2.2]paracyclophane ligand system failed to produce enhanced results relative to **5**. It is possible that when **23** is used as a ligand other factors, such as steric or mechanism alteration, could be reducing the reactivity and the selectivity of the reaction. It is possible that placing an electron donating substituent (e.g. OMe) para to the imine group, instead of the hydroxy group, may result in improved enantioselectivities. Placing an electron donating group para to the imine group can have a direct resonance effect upon the copper center; whereas when the electron donating group is para to the hydroxy group the electrons cannot be directly delocalized onto the copper, or hydroxy, center. When **5** was used as the ligand[11] moderate enantioselectivities (~27 % for the *trans* isomer with styrene and EDA) and high conversions (~90%) were obtained. It is also interesting to note that the methoxy substituent proved problematic when used as a substituent on either the ligand or the styrene. This observation suggests that the reduced reactivity/selectivity is real and additionally substituted ligands are needed in order to better quantify the effects of

substitution on the observed reactivity and selectivity in the copper catalyzed cyclopropanation reaction.

Chapter 3 Conclusion/ Future work

In conclusion, the limited mechanistic study which has been undertaken in determining the effects of the [2.2]paracyclophane moiety on the copper catalyzed cyclopropanation reaction has proven useful. It has been determined that the mono-substituted [2.2]paracyclophane moiety does not significantly control olefin approach to the active carbenoid center. It is hypothesized that perhaps true C_2 symmetric ligands based on the *pseudo*-ortho [2.2]paracyclophane substitution pattern may provide greater enantioselectivities since the approach of the olefin in these systems is irrelevant. It has been determined that copper(I) is indeed the active oxidation state of copper and that lowering the reaction temperature does not significantly alter the resulting %ee of the cyclopropane products. In the future additional *para* substituted styrenes and ligands need to be examined in order to obtain better k_{rel} data. The Hammett study which was conducted does indicate that the active carbenoid is an electrophilic one of similar magnitude to other reported copper systems.

In the future additionally substituted cyclophane ligands which can better control olefin approach need to be explored. The following illustrates the construction of such a system which should result in a more rigid framework (Scheme 3-3).



Scheme 3-3: Disubstituted cyclophane ligand

The large group (e.g. *tert*-butyl) should orient itself such as to minimize steric interations with both the cyclophane and the carbenoid which would most likely place it "underneath" the copper atom. With this orientaion of the large group olefin approach should occur from the top face and result in increased levels of enantiocontrol. Initial experiments with this concept have been shown in literature for other asymmetric reactions and moderate levels of enantiocontrol have been observed.[12,13] Initial experiments in our laboratories with S = L = Me have resulted in racemic products which are attributed to the relatively small size of the methyl group. Future experiments with S = H and L = *tert*- butyl, etc. need to be conducted to provide additional insight.

Chapters 4 and 5 will introduce the topic of naphthalene activation by metal coordination. Chapter 4 will introduce some background of the importance of tetralin

containing compounds and how they are synthetically produced. Chapter 5 will present the results of using metal moieties complexed to the naphthalene nucleus and their effect on the catalytic hydrogenation of the naphthalene ligand to the corresponding tetralin ligand.

Chapter 3 Experimental

Benzene, toluene, triethylamine, and acetonitrile were distilled from CaH_2 under a nitrogen atmosphere prior to use. THF was distilled from Na/benzophenone ketyl under a nitrogen atmosphere prior to use. ^1H NMR and ^{13}C NMR were obtained on either a Varian XL 300 or Varian Unity 400 spectrometer. NMR spectra were referenced to the residual proton concentration of the solvent used (usually $CDCl_3$). Styrene, 4-chlorostyrene, 4-vinyl anisole, 4-acetoxy styrene, 4- trifluormethylstyrene, and 4-methylstyrene were purchased from Aldrich Chemical Co, Inc. and filtered through neutral alumina to removed polymerization inhibitors. The inhibitor free styrenes were dissolved in benzene to give equimolar solutions and were kept frozen until needed for the Hammett study. (-) Menthol was obtained from Aldrich Chemical Co, Inc. and used as received. Diethylmalonate was distilled under reduced pressure prior to use. *tert*-Butyl-methylmalonate was obtained from Fluka and used as received. Tosyl azide was prepared using a literature procedure[4]. Reaction conversions were determined by gas chromatography on a Shimadzu GC-14A gas chromatograph equipped with a flame ionization detector and an SE 54 packed column. The GC program was as follows: initial temperature of 50°C for 5.0 minutes, 20°C/minute until 250°C was reached, and 250°C was maintained for 20 minutes. Enantioselectivities were determined by HPLC using a

Chiralcel OJ column and ligand resolutions were performed using a Chiralcel AD column using 1:9 (vol/vol) i-PrOH/hexanes as solvent. Optical rotations were determined on a Rudolph Research Autopol III polarimeter. All $[\alpha]_d$ determinations were performed at the indicated temperatures from the slope of the line derived by plotting α_{obs} vs. concentration (g/ml). Low resolution mass spectra were obtained using a Hewlett Packard HP 5985 mass spectrometer. High resolution mass spectra (FAB) were obtained on a VG ZAB-E mass spectrometer using Xe atoms as the ionization source and 3-nitrobenzyl alcohol as the matrix.

Synthesis of Diethyl Diazomalonate (19): In a 1000 mL Erylenmeyer flask was placed 30.0 g (0.187 mol) of freshly distilled diethyl malonate, 18.9 g (0.187 mol) of triethylamine, and 600 mL of freshly distilled acetonitrile. The resulting solution was stirred vigorously at room temperature and 39.4 g (0.200 mol) of previously prepared tosyl azide was added dropwise over 30-40 minutes. The resulting mixture was allowed to stir for 4 hours. The solvent was removed under reduced pressure to obtain a solid mass which was triturated with 200 mL ether and the ether was washed twice with aqueous KOH and once with water. The ether layer was dried and the ether was removed under reduced pressure to yield a viscous oil which solidifies in the freezer. The yellow oil was distilled under reduced pressure using a short path distillation apparatus. Yield not determined. ^{1}H NMR (300, $CDCl_3$):δ 1.30 (t, 3H), 4.30 (q, 2H).

Synthesis of *tert*-Butyl-Methyl Diazomalonate (21): A 10 mL (5.9E-2 mol) aliquot of commercially available *tert*-butyl-methylmalonate and 5.98 g (5.91E-2 mol) of triethylamine were placed in a 250 mL erlynmeyer flask and 80 mL of freshly distilled

acetonitrile was added. The mixture was stirred vigorously at room temperature and then 11.9 g (6.03E-2 mol) of previously prepared tosyl azide was added dropwise over a 10 minute period. The reaction mixture was allowed to stir for 3 hours. The solvent was removed under reduced pressure to obtain a solid mass which was triturated with 85 ml of Et_2O and then washed twice with 80 mL of aqueous KOH (7g) and once with 100 mL of water. The ether layer was dried with $MgSO_4$ and the ether was removed under reduced pressure to yield 7.38 g (3.68 E-2 mol) (62.5% yield) of product as a yellow viscous oil. ^1H NMR (400, $CDCl_3$): δ 1.49 (s, 9H), 3.80 (s, 3H).

Synthesis of Ethyl-(-)Menthyl Diazomalonate (22): Diethylmalonate, 100g (0.624 mol), was dissolved in 400 mL of absolute ethanol in a roundbottom flask fitted with a reflux condenser and a nitrogen inlet. To this was added 35.0 g (0.623 mol) of KOH in 400 ml of absolute ethanol. The solution was allowed to stir overnight. The resulting mixture was heated to reflux solvent and the solution was filtered. The filtrate was placed in an ice bath to induce crystallization of the potassium salt. The salt was then dried and placed into 50-60 mL of water, the solution was cooled with an ice bath and 40 mL of concentrated hydrochloric acid was added dropwise such that the temperature remained below 5°C. The aqueous layer was filtered to remove the potassium chloride and the aqueous layer was extracted several times with ether. The organic layer was dried and the ether was removed under reduced pressure to obtain pure (by ^1H NMR) monoethyl malonate. A solution of 20.0 g (0.17 mol) of thionyl chloride and 100 mL of freshly distilled benzene was placed into a round bottom flask equipped with a reflux condenser and nitrogen inlet. A 21.89 g (0.166 mol) portion of monoethyl malonate was

added dropwise through the reflux condenser at room temperature. After the addition was complete (and the solution stopped evolving hydrogen chloride gas) the solution was allowed to stir for 30 minutes then it was heated to reflux the solvent until hydrogen chloride evolution had ceased. To this solution 25.90 g (0.166 mol) of commercially available (-) menthol in 75 mL of fresh benzene was added dropwise followed by the dropwise addition of 17.0 g (0.168 mol)of triethylamine. The solution became extremely thick and it was allowed to stir an additional 30 minutes then heated to reflux for 2 hours. The reaction was allowed to cool, transferred to a separatory funnel and washed twice with a 0.2N pH 3 phosphate buffer followed by an aqueous wash. The organic layer was dried and the benzene solvent was removed under reduced pressure to obtain 35.30 g of crude ethyl-(-)menthyl malonate. The crude malonate was vacuum distilled using a short path apparatus and the fraction which contained no free menthol (by GC analysis) was collected and treated with decolorizing carbon to obtain 15.14 g of pure malonate as a colorless oil (33.5% yield based on menthol).^{1}H NMR (400 MHz, $CDCl_3$): δ 0.72 (d, J = 7 Hz, 3H), 0.86 (apparent t, J = 6 Hz, 6H), 0.97 (m, 2H), 1.24 (t, J = 7Hz, 3H), 1.44 (m, 2H), 1.64 (m, 2H), 1.84 (m, 1H), 1.99 (m, 1H), 3.31 (s, 2H), 4.16 (m, 2H), 4.70 (dt, J = 4 Hz, 11 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.95, 16.10, 20.64, 21.89, 23.22, 25.94, 31.28, 34.07, 40.53, 42.00, 46.79, 61.35, 76.68, 166.08, 166.59. $[\alpha]_d^{23}$ ($CHCl_3$) = -59.08 +/- 0.455. A 7.92 g portion of this (-) ethyl-menthylmalonate was placed in 50 mL freshly distilled acetonitrile and 3.0 g triethylamine was added followed by 5.78 g of tosyl azide. After the usual basic workup a yellow oil was obtained which was used without further purification (attempted distillation of the crude diazo compound resulted in a mild

decomposition of the product). ^{1}H NMR (400 MHz, $CDCl_3$) was essentially the same as for the parent malonate except the signals were broad and the singlet at 3.31 ppm (2H) was no longer present. MS (FAB) m/z = 297.2 $(M+H)^+$, 319.2 $(M+Na)^+$, 615.4 $(M_2+Na)^+$. Gas chromatography on this diazo compound resulted in no signals even after 45 minutes elution time.

Synthesis of 1,1-*Bis*-(methoxycarbonyl)-2-phenylcyclopropane (20) (General Procedure): Ligand (-)-**5** (5.00 mg, 1.53 E-5 mol) was complexed with copper(II) as outlined in the chapter 2 experimental section. A 0.56 g (5.3 E-3 mol) aliquot of styrene was dissolved in 5 ml benzene. The catalyst and styrene solution were placed in a 25 mL roundbottom flask equipped with a nitrogen inlet and reflux condenser. The resulting solution was heated to reflux solvent under a nitrogen atmosphere. A solution of 1.50 g (8.1 E-3 mol) of **19** dissolved in 5 mL of benzene was added dropwise over a 12 hour period by syringe pump. After the addition of **19** was complete the reaction was allowed to proceed an additional 24 hours. The reaction mixture was allowed to cool to room temperature. The solution was then filtered through a short neutral alumina column and eluted with 50 mL fresh benzene. The benzene was removed under reduced pressure and the resulting oil was dissolved in 10 mL of methanol and 8 mL of 3N NaOH was added. The resulting solution was heated to reflux solvent for 24 hours. The solvent was removed under reduced pressure and the resulting solid was dissolved in 25 mL of water. The aqueous layer was tested with litmus paper and NaOH was added to keep the mixture basic (pH ~ 12). The aqueous layer was extracted once with petroleum ether to remove any material which had not been saponified. The aqueous layer was then made

acidic to litmus paper (pH ~ 1.0) with concentrated hydrochloric acid.

The acidic milky white solution was then extracted twice with 25 mL of CH_2Cl_2. The organic layer was dried with $MgSO_4$ and the solvent was removed under reduced pressure. The saponified material (0.200 g, 9.80E-4 mol) was dissolved in 4 mL freshly distilled THF, placed in a micro diazomethane generator, and subjected to about a 4X excess of diazomethane. The resulting material was placed on a preparative tlc plate and was subsequently eluted with 10% ethylacetate/hexanes. The top band of the tlc plate was isolated to provide 0.0721 g (3.08 E-4 mol, 31.4 %) of pure **20** as a white solid (di-methylester derivative). ^{1}H NMR (300 MHz, $CDCl_3$) : δ 1.74 (dd, j= 5,9 Hz, 1H), 2.20 (dd, j= 5,8 Hz, 1H), 3.21 (t, j= 8 Hz, 1H), 3.36 (s, 3H), 3.80 (s, 3H), 7.2-7.3 (m, 5H). The ^{1}H NMR closely resembled that reported by Corey and Gant.[5] The optical rotation was compared to that of Corey and Gant.[5] HRMS (FAB) calc'd for $C_{13}H_{15}O_4$ ($M + H^+$) 235.0970 found 235.0983.

Synthesis and Resolution of N-(4'-methoxy)Salicylidene-4-amino[2.2]paracyclophane (23): A 25 mL roundbottom flask was charged with 0.200 g (8.96 E-4 mol) of ± 4-amino[2.2]paracyclophane (**3**), 0.140 g (8.99 E-4 mol) of 2-hydroxy-5-methoxybenzaldehyde, a stir bar, and 15 mL of freshly distilled toluene. The reaction flask was fitted with a reflux condenser and the mixture was heated to reflux solvent for 13 hours. The mixture was allowed to cool and half the solvent was removed under reduced pressure. The resulting red solution was added to a silica gel column which was eluted with about 200 mL of toluene. The column was then eluted with methanol until a red fraction was collected (tlc R_f = 0.74 with methanol). The solvent was removed

to obtain 0.2136 g (5.980 E-4 mol) of purified product in 66.80% isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.83 (m, 1H), 3.03-3.23 (m, 6H), 3.63 (m, 1H), 3.82 (s, 3H), 6.00 (s, 1H), 6.36 (d, J = 8 Hz, 1H), 6.52-6.59 (m, 4H), 6.83 (d, J = 8 Hz, 1H), 6.89 (s, 1H), 7.04 (s, 2H), 8.27 (s, 1H), 13.36 (bs, 1H, D_2O exchangeable). ^{13}C (100 MHz, $CDCl_3$):δ 32.55, 34.18, 34.90, 35.20, 55.92, 115.10, 117.89, 119.16, 120.19, 125.20, 129.08, 131.65, 131.74, 132.95, 133.36, 134.71, 134.86, 138.89, 139.76, 141.80, 146.65, 152.25, 155.29, 160.49. HRMS (FAB): calc'd for $C_{24}H_{23}NO_2$ (M^+) 357.1729, found 357.1740. Resolution of (+/-) **23** was achieved on a semi-preparative Chiralcel AD HPLC column eluted with 1:9 (vol/vol) i-PrOH/hexanes at 3.00 ml/min. (-) enantiomer t_r = 8.90 minutes, (+) enantiomer t_r = 16.40 minutes. $[\alpha]_d^{26}$ = +163.20 +/- 2.35 for the (+) enantiomer.

Competition Experiment (General Procedure):[3] A 0.63 mg portion of racemic **5** was complexed with copper as described in the chapter 2 experimental section. The catalyst was placed in a 10 ml conical vial equipped with a reflux condenser and argon inlet. A 1.0 ml aliquot of styrene solution (.0500 g/ml in benzene) and 1.0 ml of 4-methylstyrene solution (.0567 g/ ml in benzene) was added with a stir bar to the conical vial. The resulting solution was heated to reflux solvent under an argon atmosphere. Then 0.5 equivalents of EDA (.0548 g) was added in four equal portions over a two hour period. After the EDA was added the solution was allowed to reflux an additional hour. The solution was cooled, filtered through a small plug of neutral alumina, and the solvent and volatiles were removed under reduced pressure. The crude oil was analyzed by GC to determine k_{rel}.

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CHAPTER 4: Introduction to Part II

Many biological and medicinal compounds contain a tetralin core structure upon which the rest of the molecule can be constructed (Figure 4-1).

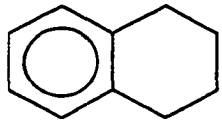


Figure 4-1:
Tetralin

Several compounds of current therapeutic importance contain a tetralin core structure. Sertraline, commercially known as Zoloft®, a highly prescribed antidepressant,[1] contains a tetralin core structure as shown in Figure 4-2.[2,3]

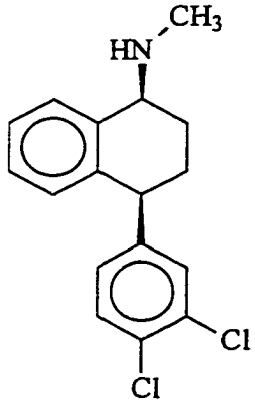


Figure 4-2:
Sertraline

Several compounds which are built upon tetralin core structures have demonstrated potent anti-infective properties against several types of pathogens. For

example, compounds which were isolated from the plant *Guardiola platyphylla*, shown in Figure 4-3, have demonstrated activity against *Staphylococcus aureus*, *Bacillus subtillis*, *Klebsiella pneumonia*, and *Candida albicans*. [4]

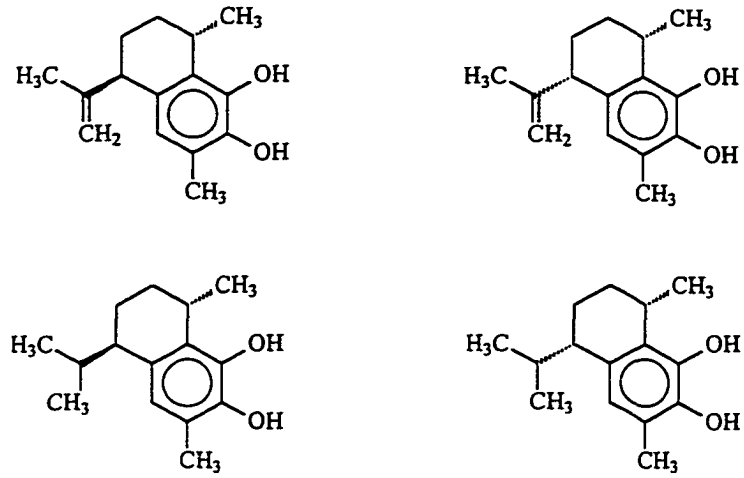


Figure 4-3: Anti-infective tetralin derivatives

A series of compounds which were based on a tetralin structure have been reported which were screened for possible antimalarial activity.[5] Figure 4-4 below illustrates one of sixteen compounds which were screened for antimalarial activity.

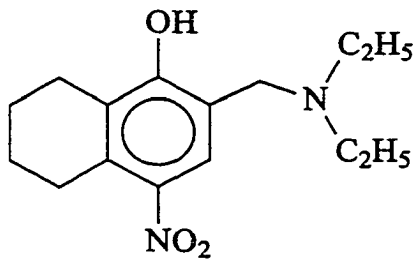


Figure 4-4

The potent anti-inflammatory class of compounds known as the pseudopterosins, contain a tetralin core structure.[6] Premature aging of the skin has been attributed to an inflammatory reaction and the pseudopterosin family of compounds is known to inhibit enzymes which trigger inflammatory chemical release.[7] *Pseudopterosin* C has been commercialized by the cosmetics industry as a skin care product which is used to reduce premature aging (Figure 4-5).[7]

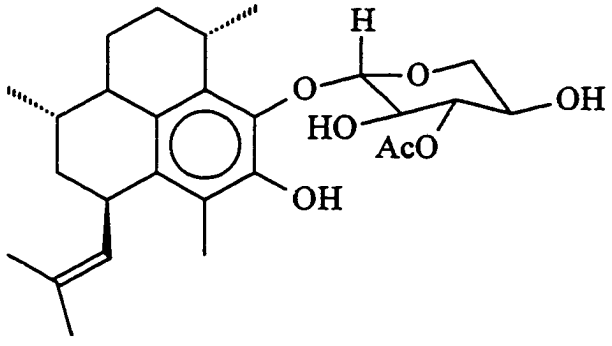


Figure 4-5: *Pseudopterosin* C

The tetralin core can be constructed by a variety of different pathways. Tetralin structures have been constructed by using acid catalyzed cyclization reactions. Corey et. al. reported a synthesis of sertraline's tetralin core by an acid catalyzed cyclization reaction of an appropriately substituted acid[3] as shown below in Figure 4-6.

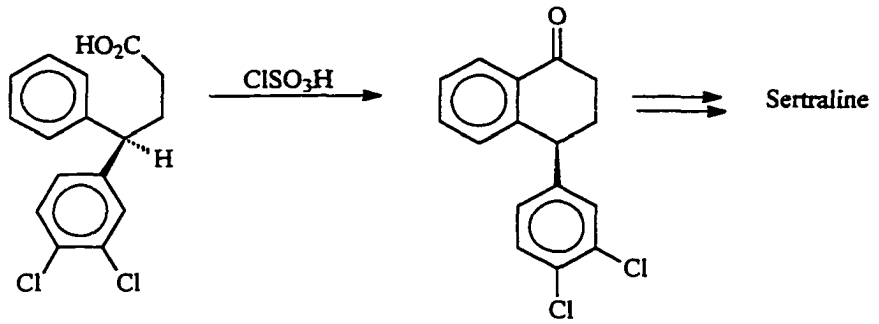


Figure 4-6: Acid catalyzed construction of a tetralin core.

Unfortunately, the acid catalyzed cyclization route requires extremely acidic conditions and several synthetic steps may be required to obtain the appropriately substituted carboxylic acid which is required for such a cyclization.

The reduction of appropriately substituted tetralone compounds[8] has also been utilized to obtain tetralin structures. This method has the drawback that the carbonyl must be reduced off at some point which can typically go rather sluggishly. Methyl substituted tetralin compounds have been constructed in this manner (Figure 4-7).

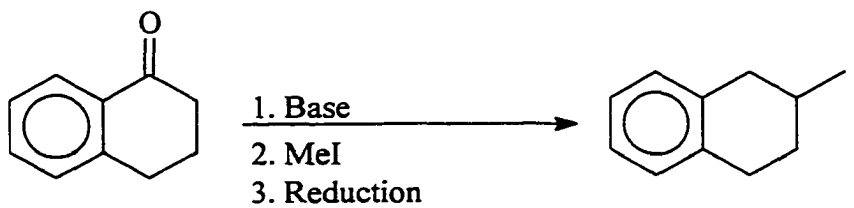
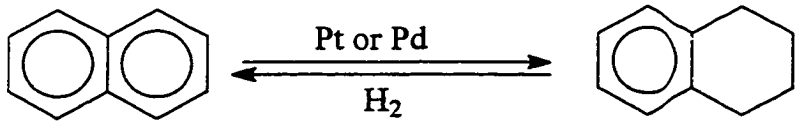


Figure 4-7: Synthesis of substituted tetralins

These methods suffer from the harsh reaction conditions which are frequently employed. It would be advantageous if the tetralin core could be easily constructed from inexpensive

starting materials in as few steps as possible under relatively mild reaction conditions.

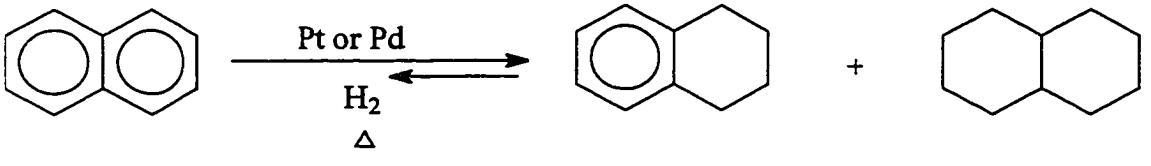
The direct reduction of naphthalenes to tetralins is well known.[9-12] Various reagents have been employed to perform the direct reduction of napthalenes such as platinum and palladium catalyzed hydrogenation (Figure 4-8).[12]



Naphthalene Tetralin

Figure 4-8: Direct reduction of naphthalene

Unfortunately the direct reduction of naphthalene to tetralin is an equilibrium process. In order to shift this equilibrium to the tetralin product several atmospheres of hydrogen are employed. The use of elevated temperature and hydrogen pressure also results in significant over-reduction to both *cis* and *trans* decalin byproducts (Figure 4-9).[10]



Naphthalene Tetralin *cis* and *trans* Decalin

Figure 4-9: Direct reduction products

The direct reduction of methyl substituted naphthalenes in refluxing acetic acid has been reported.[9] The selectivity of reduction has proven to be poor using direct reduction methodology. The reduction of 1-methylnapthalene using Pd/C catalyst, 1 atm. hydrogen pressure in refluxing acetic acid resulted in an approximate 1:2 mixture of tetralin products(Figure 4-10).[9]

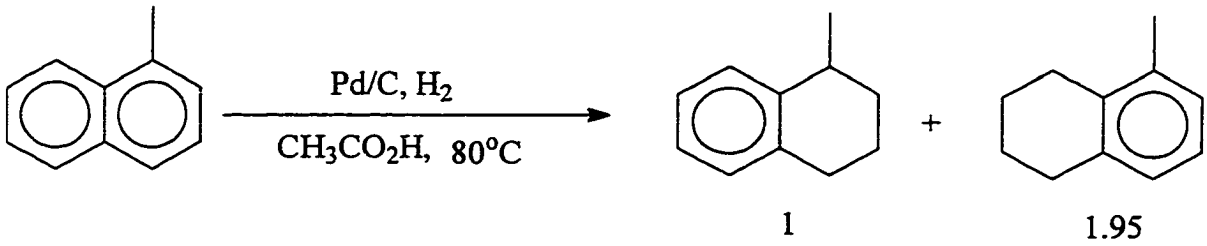
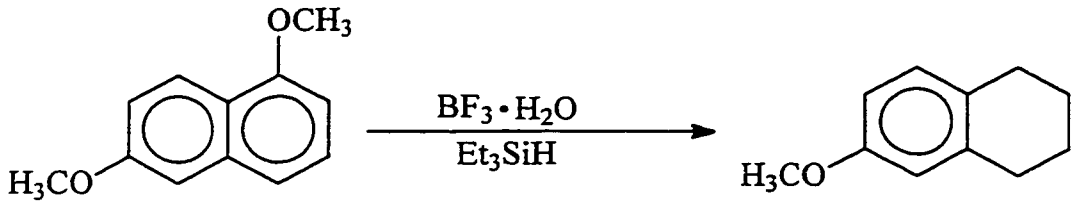


Figure 4-10: Selectivity of reduction

The reduction of electron rich naphthalenes in acidic media has been reported . The use of $BF_3 \cdot H_20$-Et_3SiH has demonstrated its ability to protonate the aromatic ring of naphthalene followed by hydride donation which formally reduces the aromatic ring.[13] A major drawback to this methodology is that the aromatic rings must be electron rich and cleavage of various functional groups has been observed (Figure 4-11).[13]



only observed reduction product

Figure 4-11: Reduction in acidic media

Borane catalyzed hydrogenation of substituted naphthalenes to tetralins has been shown to occur at elevated reaction temperature and hydrogen pressure.[14] The reaction conditions employed in the borane catalyzed reduction of naphthalenes are rather harsh and often result in significant isomerization and elimination of substituents (Figure 4-12).[14]

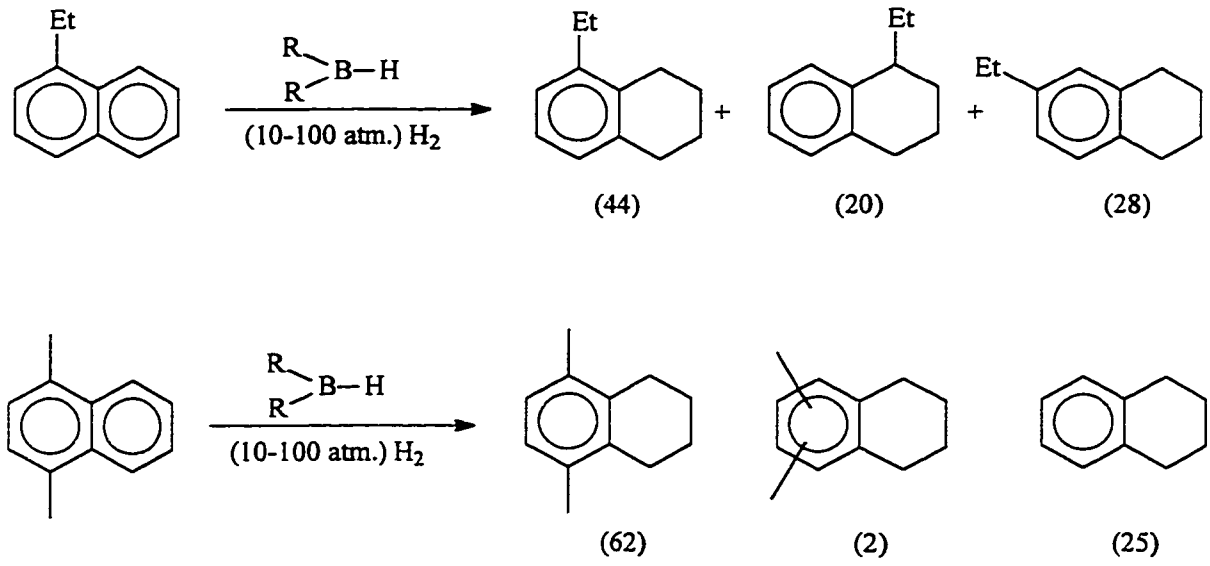


Figure 4-12: Borane catalyzed reduction of substituted naphthalenes

All the direct reduction methods listed above suffer significant reactivity, selectivity, and functional group tolerance problems. A method which can affect the direct reduction of naphthalenes to their corresponding tetralins under mild and selective conditions is highly desirable.

Conceptually, many of the problems encountered in the catalytic reduction of naphthalenes could be overcome by the η^6-coordination of a metal moiety to one ring of the naphthalene unit. By choosing the appropriate metal moiety it could be possible to view the naphthalene unit as two separate components; a 1,3-diene component and a 6π localized, by metal coordination, aromatic component (Figure 4-13).

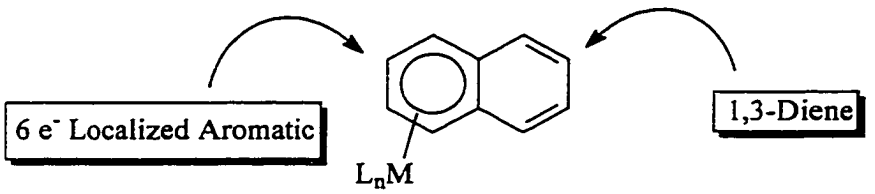


Figure 4-13: Localization of aromaticity

The hydrogenation of other metal-containing dinuclear aromatics is well known in which the metal moiety essentially protects a 6π, five member, aromatic ring. Fischer et al. reported several years ago that bisindenyliron could be catalytically hydrogenated to give bis(tetrahydroindenyl)iron[15] (Figure 4-14).

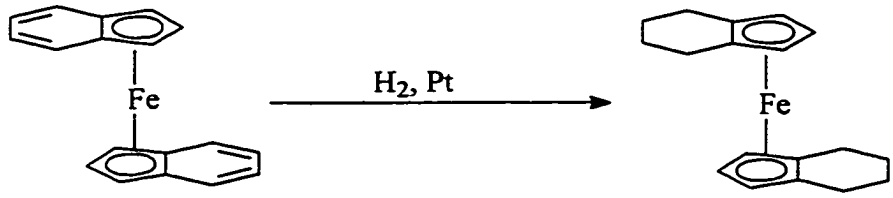


Figure 4-14

Britzinger reported the palladium catalyzed hydrogenation of bis(indenyl) titanium complexes to the corresponding tetrahydroindenyl titanium complexes[16].

If the metal moiety can effectively localize the aromatic system to a single ring of the naphthalene unit as depicted in Figure 4-13, the non-coordinated ring of the naphthalene should become activated toward catalytic hydrogenation under mild conditions since conjugated dienes can be catalytically reduced under relatively mild conditions. One potential problem with using complexation of a metal moiety to activate a naphthalene nucleus is the selectivity of the complexation when utilizing unsymmetrically substituted naphthalenes (Figure 4-15).

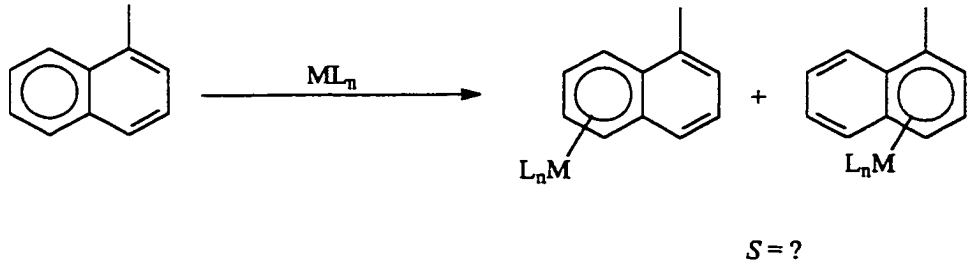


Figure 4-15

It is also possible that the selectivity of metal complexation could result in a problem with the selectivity of the reduction. Should a mixture of naphthalene metal complexes form it would be logical to expect a mixture of reduction products, the composition being directly related to the composition of the metal naphthalene complexes.

In 1994 Glatzhofer et al. reported the catalytic hydrogenation of a (η5-cyclopentadienyl) (η6-naphthalene) ruthenium cationic complex under mild conditions[17]. Unfortunately, the ruthenium moiety that was employed involved several synthetic steps to make and was also relatively expensive. In order to avoid the disadvantages of the ruthenium moiety, use of the iron cyclopentadienyl moiety in place of the isoelectronic ruthenium unit is a logical substitution.

The chemistry of the iron cyclopentadienyl cationic complexes of naphthalenes has been explored. Sutherland et al. reported that the iron cyclopentadienyl cationic complex of naphthalene underwent conversion to the corresponding tetralin when formed from naphthalene and ferrocene in refluxing decalin[18]. Sutherland also reported that the naphthalene iron complex did not undergo platinum catalyzed reduction to the complexed tetralin[18]. It is quite interesting that the ruthenium complex of naphthalene readily underwent catalytic reduction, but that the analogous iron complexes reportedly did not. Given that ruthenium and iron complexes of naphthalene are isoelectronic, further investigation of the iron moiety is warranted. The use of iron over ruthenium has several advantages from a synthetic point of view. The iron naphthalene complexes are synthesized in one step from readily available starting materials and the iron moiety is far less expensive than the ruthenium unit.

In the following chapter results will be presented on the palladium catalyzed reduction of several methyl, dimethyl, and methoxy substituted (η^5-cyclopentadienyl) (η^6-naphthalene)iron (II) hexafluorophosphate salts under mild conditions. In many instances, the regioselectivity of the catalytic reduction of several iron naphthalene complexes proved to be extremely high even when the regioselectivity of the complex formation was not.[19] Also the results of substituting the neutral chromium tricarbonyl unit for the cationic iron moiety will be presented.

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Chapter 5: Naphthalene Activation Toward Catalytic Hydrogenation by Coordination of the Iron Cyclopentadienyl Cation and Chromium Tricarbonyl Unit

Many transition metal moieties can form complexes with aromatic units. Among the most prevalent are chromium tricarbonyl, iron cyclopentadienyl cation, manganese tricarbonyl cation, and the ruthenium cyclopentadienyl cation.[1] It has been shown that a ruthenium cyclopentadienyl cationic complex of naphthalene could be hydrogenated to the corresponding tetralin complex under mild conditions.[2] This result seems to suggest that the ruthenium cationic moiety is capable of localizing the aromaticity of the naphthalene unit to a single ring of the naphthalene ligand.[2] The localization of aromaticity activates the other, non-complexed, ring toward catalytic hydrogenation. The ruthenium moiety employed in this reaction was needed in stoichiometric quantities to affect the activation toward catalytic hydrogenation. Given that ruthenium is expensive relative to other transition metals (e.g. Fe and Cr), another metal system capable of performing the same transformation as the ruthenium system is desirable. In this chapter the results of substituting the iron cyclopentadienyl cation and the chromium tricarbonyl unit for the more expensive ruthenium cation for complexing naphthalene will be presented in regard to the palladium catalyzed hydrogenation reactions.[3]

Synthesis and Hydrogenation of (η^5-cyclopentadienyl) (η^6-naphthalenyl) Iron (II) Hexafluorophosphate Salts

The cationic iron cyclopentadienyl complexes were synthesized using a literature procedure.[4] Figure 5-1 below illustrates the synthesis of the iron cyclopentadienyl naphthalene complexes. The products of this procedure were approximately 1:1 mixtures of complexed substituted naphthalenes.

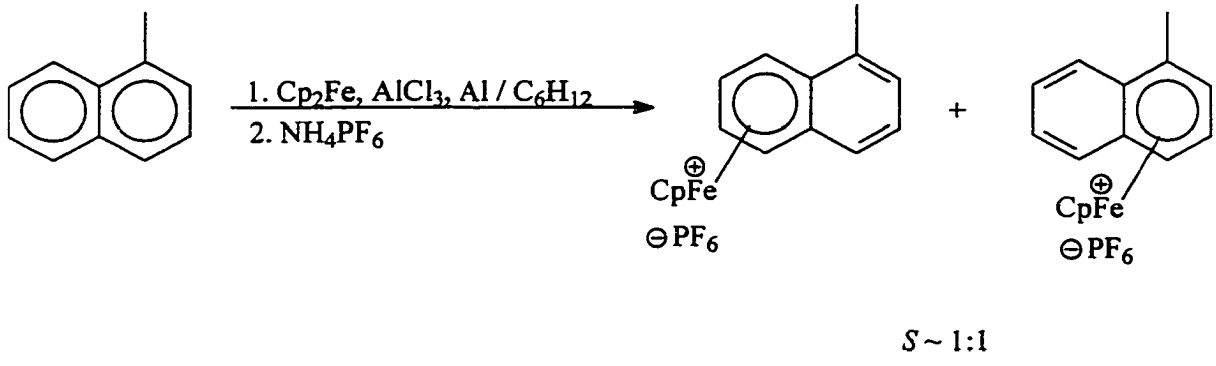


Figure 5-1: Formation of naphthalene iron complexes

The complexation of both mono- and di-methylnaphthalenes occurs with a slight preference for the iron moiety to attach to the substituted ring when a methyl substituent is placed in the 1 or 4 position. A lesser preference was observed for the substituted ring by the iron unit when a methyl substituent was placed in the 2 or 3 position. The observed preference for substitution to the more or less substituted ring is probably due to electronic differences between the substituted and unsubstituted rings with placement of the methyl substituent.[5] Attempted chromatographic separation of these mixtures proved difficult and they were used without any further workup in the subsequent hydrogenation

reactions. The complexation of 1-methoxynaphthalene proved interesting. Initially, it was expected that the iron moiety would preferentially complex to the methoxy substituted ring. It was found, after complexation, that the iron unit complexed only to the unsubstituted ring and that the methyl ether linkage was cleaved resulting in a complexed naphthol. The preferential complexation of the iron unit to the unsubstituted ring is an result identical to that previously reported for a ruthenium analog.[5]

The catalytic reduction of the naphthalene iron comlexes was performed at ambient temperature and pressure. The resulting tetralin complexes were characterized by ^{1}H NMR and by FAB mass spectrometry. The FAB mass spectra of all tetralin complexes clearly indicated the addition of four hydrogen atoms to the parent naphthalene complex. ^{1}H NMR of the known (η^5-cyclopentadienyl) (η^6-tetralin)iron (II) hexafluorophosphate[6] was used as a comparison. Figure 5-2 below illustrates the ^{1}H NMR spectra of both the naphthalene and tetralin iron complexes (acetone-d_6 solvent).

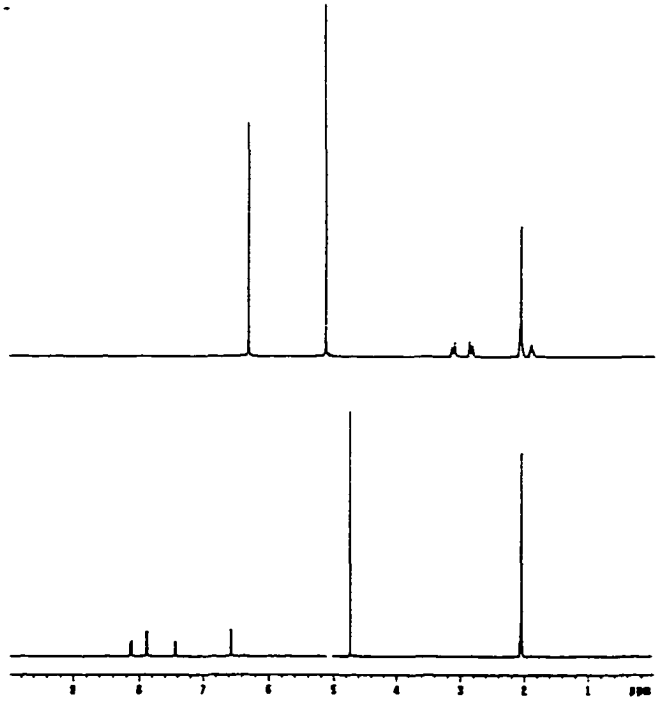


Figure 5-2: (Top) tetralin iron complex
(Bottom) naphthalene iron complex (acetone-d_6)

The hydrogenation of the (η^5-cyclopentadienyl) (η^6-naphthalene)iron (II) hexafluorophosphate was monitored by ^{1}H NMR. The disappearance of the upfield Cp signals of the naphthalene complexes was observed with new Cp signals appearing downfield for the corresponding tetralin complexes (see Figure 5-2). The appearance of aliphatic resonances in the 2.6-3.2 ppm range are observed for the tetralin complexes at the expense of the aromatic resonances of the naphthalene complexes. Comparison of the methyl signals and the Cp signals was used to assign the location of the iron moiety. Figure 5-3 illustrates the ^{1}H NMR spectra of the 1,4-dimethylnaphthalene iron complex mixture and the corresponding 1,4-dimethyltetralin iron complex mixture.

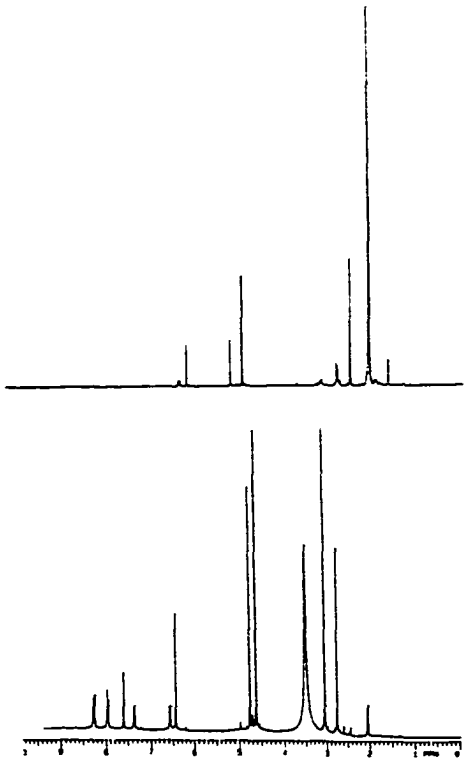
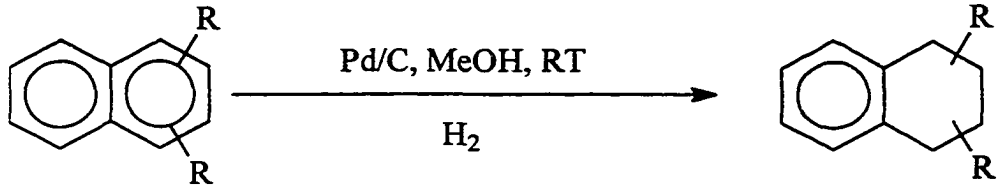


Figure 5-3: (Top): 1,4-Dimethyltetralin iron complex. (Bottom): 1,4-Dimethylnaphthalene iron complex (acetone-d_6)

Table 5-1 below illustrates attempts to catalytically reduce non-complexed naphthalenes to tetralins under mild conditions. From Table 5-1 it is clear that the reduction of many naphthalenes is difficult under ambient conditions. The catalytic reduction of naphthalene results in a 32% conversion to the corresponding tetralin after several days exposure to 1 atmosphere hydrogen, even with a large excess of palladium catalyst (by weight). This difficulty is attributed to the aromatic character of the naphthalene nucleus.[7]

Table 5-1: Naphthalene reduction



Hydrogenation of Substituted Naphthalenes[a]			
Entry	Naphthalene	Rxn. Time[b]	% Conversion[c]
1	Naphthalene	2	32%
2	1-Methylnaphthalene	2	0%
3	2-Methylnaphthalene	2	0%
4	1,2-Dimethylnaphthalene	2	64%
5	1,4-Dimethylnaphthalene	2	0%
6	2,3-Dimethylnaphthalene	2	0%
7	1-Methoxynaphthalene	2	*trace*

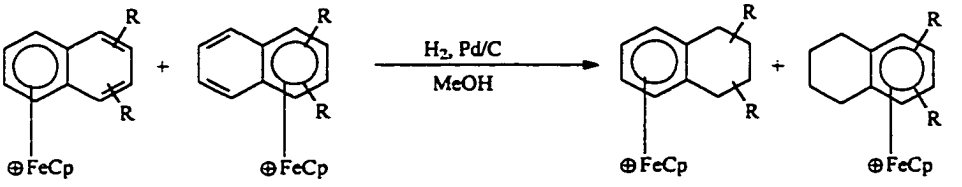
a) using 1 atm. H_2 and an equivalent of 10% Pd/c (by weight) at room temperature, b) reaction time in days, c) based on ^{1}H NMR.

By complexing naphthalene with the iron cyclopentadienyl cation, the reactivity towards catalytic reduction dramatically increases. An *in situ* competition experiment was performed between non-complexed and complexed naphthalene. The result of this *in situ* experiment was inconclusive due to the fact that the naphthalene iron complex was completely reduced before any reduction of naphthalene took place (by ^{1}H NMR). The reduction of the iron cyclopentadienyl complexed naphthalene essentially goes to completion and over-reduction to decalin is not observed.

The non-complexed mono-methylnaphthalenes did not undergo catalytic reduction under mild conditions, even after several days exposure to a hydrogen atmosphere and a large excess of palladium catalyst (by weight).

Table 5-2 shows the results of the catalytic reduction of a variety of iron cyclopentadienyl complexed naphthalenes.

Table 5-2: Reduction of iron naphthalene complexes



A B C D

Hydrogenation of Iron Cationic Naphthalene Comnplexes[a]				
Entry	Naphthalene Complex	**A/B**	% Conv.[b]	**C/D**
1	Naphthalene	----	100%	----
2	1-Methylnaphthalene	1:1.31	80%	1:4.90[c]
3	1-Methylnaphthalene	1:1.31	100%[d]	1:1.70
4	2-Methylnaphthalene	1:1.20	100%	1:1.00
5	1,2-Dimethylnaphthalene	1:1.26	77%	1:13.90
6	1,4-Dimethylnaphthalene	1:1.46	88%	1:26.20
7	1,4-Dimethylnaphthalene	1:1.46	100%[d]	1:2.70
8	2,3-Dimethylnaphthalene	1.97:1	100%	1.90:1
9	1-Hydroxynaphthalene[e]	1.00:0	100%	1.00:0

a) using 1 atm. H_2 and ~16 mg of 10% Pd/C per 80-90 mg complex at room temperature for 18 hr., b) based on ^{1}H NMR of the Cp signals, c) ratio determined by GC integration of decomplexed material, d) using a 3 fold excess (by weight) of 10% Pd/C, e) obtained after workup from the complexation of 1-methoxynaphthalene.

The results of Table 5-2 contrast those shown in Table 5-1. The complexed mono-methylnaphthalenes underwent smooth conversion to the mono-methyltetralin complexes under mild catalytic reduction conditions. Interestingly, under certain circumstances, the mono-methylnaphthalene complexes experienced a selectivity in the reduction which did

not correspond to the ratio of the starting complex (Table 5-2 entries 2 and 3). When the 1-methylnaphthalene iron cyclopentadienyl complex (mixture of isomers) underwent catalytic reduction to 80% conversion ~1:5 selectivity was observed in the resulting tetralin products. This selectivity was in favor of the iron cyclopentadienyl cation being located on the more substituted ring (Scheme 5-1).

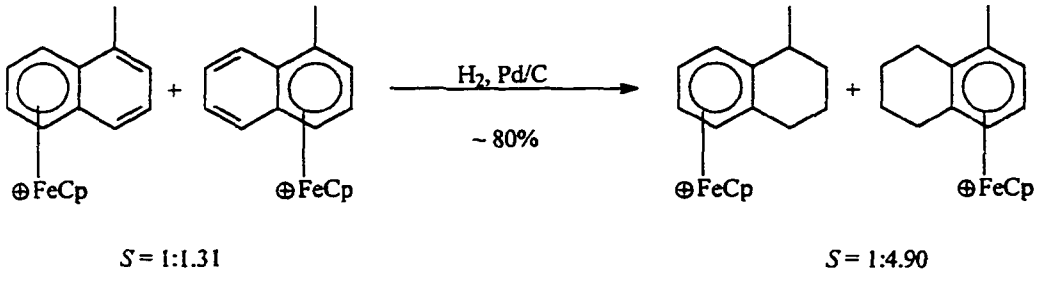


Figure 5-1: Reduction selectivity

When the reduction of the 1-methylnaphthalene iron complex was carried out with an excess of palladium catalyst, the reduction went to completion within 2-3 hours and a much lower selectivity was observed (Table 5-2 entry 3). The catalytic reduction of the 2-methylnaphthalene iron complex produced a mixture of tetralin complexes which was essentially in the same ratio as the starting 2-methylnaphthalene iron complex (Table 5-2 entry 4).

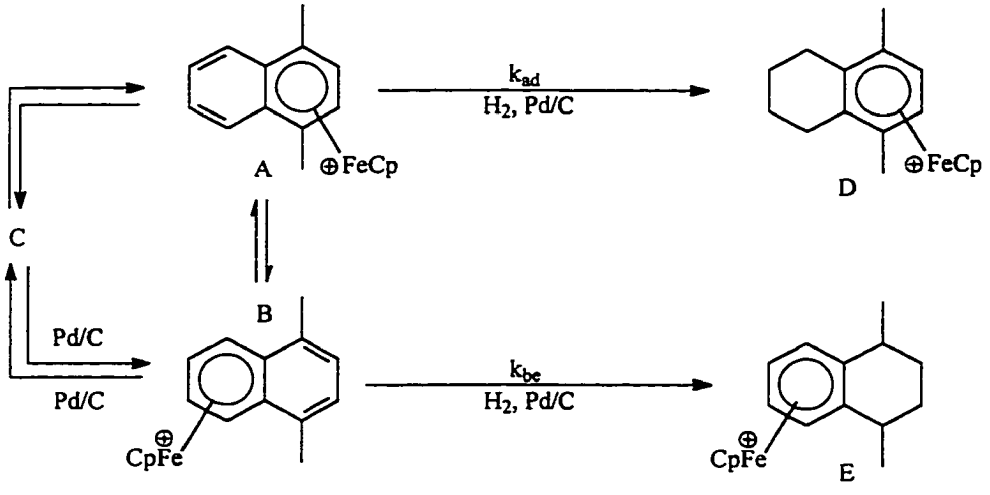
The non-complexed dimethylnaphthalenes were also difficult to reduce under mild conditions (Table 5-1 entries 4-6). Reduction of 1,4- and 2,3-dimethylnaphthalene did not occur under mild conditions although the reduction of 1,2-dimethylnaphthalene was observed to have taken place in 64% conversion (using an equivalent mass of 10% Pd/C).[8] The catalytic reduction of the 1,2-dimethylnaphthalene iron cyclopentadienyl

complex mixture underwent conversion to the tetralin complexes in 77% conversion with a high selectivity of ~ 1:14 (by ^{1}H NMR) in favor of the more substituted ring being protected by the iron cyclopentadienyl unit (Table 5-2 entry 5). Even more dramatic results were observed for the 1,4-dimethylnaphthalene iron cyclopentadienyl complex in both conversion and selectivity (Table 5-2 entry 6). Interestingly, when the 1,4-dimethylnaphthalene iron complex was reduced in the presence of a large excess of palladium catalyst, the reaction was essentially complete within 2-3 hours and a much lower selectivity of ~1:2 was observed (Table 5-2 entry 7). The catalytic reduction of the 2,3-dimethylnaphthalene iron cyclopentadienyl complex produced a mixture of tetralin complexes which was essentially in the same ratio as the starting 2,3-dimethylnaphthalene iron complex. The reduction of the 1-hydroxynaphthalene iron cyclopentadienyl complex was completely reduced under the mild conditions employed and no isomerization of the iron moiety was detected. Interestingly, the reduction of the 1-hydroxynaphthalene iron complex proceed smoothly in water (the complex itself is quite soluble in water).

In all cases presented in Table 5-2 the complexation of the aromatic naphthalene unit with the cationic iron moiety significantly increases the rate of hydrogenation and protects the complexed ring from reduction. This suggests that the iron moiety is capable of partially localizing the aromaticity of the naphthalene nucleus to the complexed ring.

The selectivity that was observed in the reduction of the 1-methyl-, 1,2-dimethyl-, and 1,4-dimethylnaphthalene iron cyclopentadienyl complexes was not expected. In order to account for the observed selectivity a model using the 1,4-dimethylnaphthalene iron

complex as an example is invoked (Scheme 5-2).



Scheme 5-2: Selectivity model

Scheme 5-2 illustrates two possible pathways by which the selectivity in the reduction of the methyl substituted naphthalenes could take place. Initially it was hypothesized that $k_{ad}>>k_{be}$ and either an equilibration between A and B was occurring or an intermediate C was formed from B which was then formally converted to A. The equilibration of A and B in solution was discounted based on results obtained from both a stop experiment (see experimental) and a VT NMR experiment. The stop experiment was performed by stopping the hydrogenation at ~ 56% conversion and performing a ^{1}H NMR analysis on the reaction mixture. It was evident from this stop experiment that complex A (iron unit on more substituted ring) had indeed hydrogenated almost exclusively to form product D with complex B (iron on less substituted ring) largely unreacted (Figure 5-4).

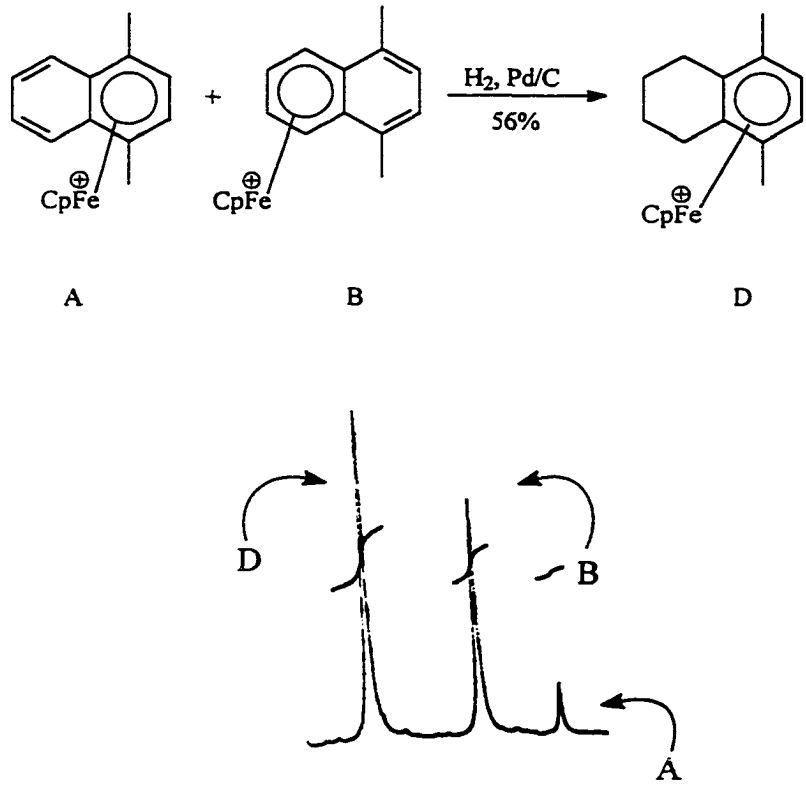
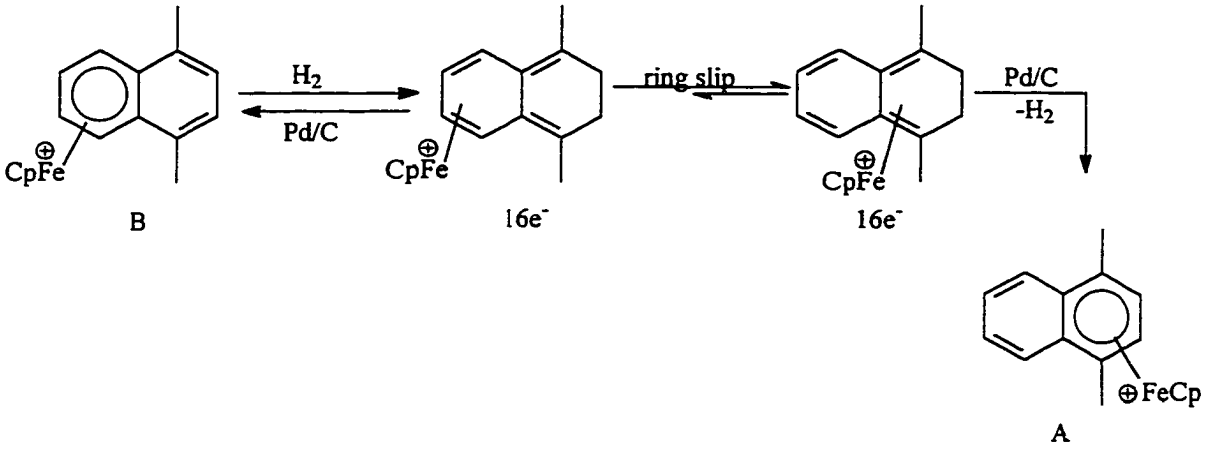


Figure 5-4: ^{1}H NMR of Cp region after stop experiment

This observation confirmed the initial hypothesis that $k_{ad}>>k_{bc}$. Continued observation of this sample by ^{1}H NMR over several days revealed no re-equilibration between A and B which was consistent with the absence of temperature dependent equilibration in the VT NMR experiment.

Given that both the VT NMR and stop experiment were consistent with a mechanism which excluded a direct equilibration of A and B, it would seem likely that the palladium catalyst was necessary for the formation of an intermediate C, which could possibly account for the conversion of B to A. Forming a 16 electron intermediate could

allow for a ring slip which would account for the conversion of B to A. As shown in Scheme 5-3, hydrogen could be added to compound B across the 2,3-bond creating an ortho-quinodimethane type 16 electron intermediate.



Scheme 5-3: Conversion of B to A

The initially formed 16 electron intermediate shown in Scheme 5-3 could then undergo a ring slip to the more electron rich diene, producing a more stabilized 16 electron intermediate. Indeed the palladium was necessary for the isomerization to proceed and it is hypothesized that the initial isomerization is due to residual hydrogen on the palladium catalyst which allows the formation of the proposed 16 electron intermediate. Following ring slip, the η^4 16 electron species can then be re-aromatized by removal of H_2 by the heterogeneous palladium catalyst[9] which would represent a formal conversion of B to A as shown in Scheme 5-2 . Another possibility could be that the less substituted double bonds could then be hydrogenated followed by re-aromatization. Control experiments were performed in which nitrogen was substituted for the hydrogen gas in hopes of determining if the palladium catalyst was playing a vital role in the isomerization. The

1,4-dimethylnaphthalene iron complex did undergo slow isomerization in the presence of the palladium catalyst, but this trend reached a maximum of approximately 68%, in favor of the iron being located on the more susbstituted ring, after ten hours exposure to the palladium catalyst in acetone solvent.

The proposed mechanism of a 16 electron intermediate is consistent with the results as shown in Table 5-2. Those complexes which contain a methyl substituent in the 1 or 4 position show high selectivity as a result of the rate difference in the hydrogenation of the two compounds and the formation of the η^4 16 electron intermediate which can ring slip to the more electron rich diene to produce a more stabilized 16 electron intermediate. Those complexes which contain a methyl substituent in the 2 or 3 position have these sites blocked such that hydrogen can not readily add across the 2,3 bond, similar to the difficulty in hydrogenating highly substituted alkenes,[8] required in generating the η^4 16 electron species suspected to be the active isomerization intermediate. It also appears that the heterogeneous nature of the catalyst is a requirement. All attempts in using the homogeneous Wilkinsons catalyst failed to yield reduction products of any kind.

Synthesis and Attempted Hydrogenation of η^6-Naphthalenyl Chromium Tricarbonyl Complexes

The neutral chromium tricarbonyl naphthalene complexes were synthesized using a general literature procedure.[10] Figure 5-4 below illustrates the synthesis of the chromium tricarbonyl naphthalene complexes.

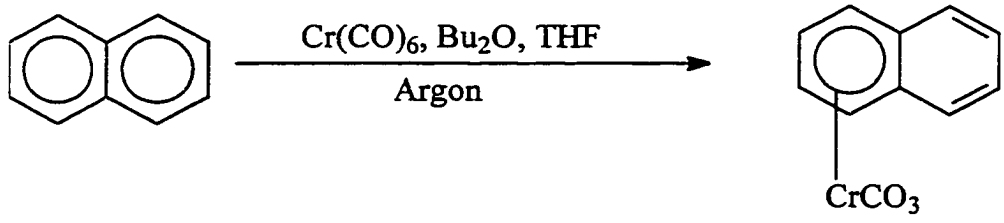
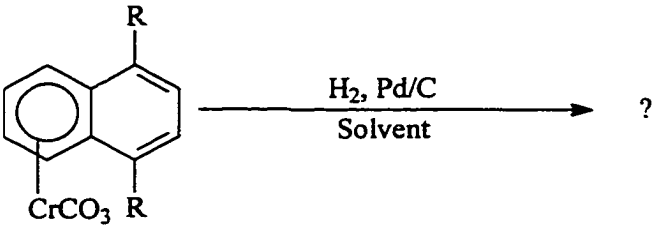


Figure 5-4: Formation of chromium tricarbonyl complexes

The complexation of 1,4-dimethylnaphthalene with the chromium tricarbonyl unit proceeded with a preference for the chromium moiety on the unsubstituted ring and the product could be purified by crystallization from hexanes/toluene to yield a single isomer (chromium on unsubstituted ring)[11].

Chromium tricarbonyl naphthalene has been used successfully as a hydrogenation catalyst in the reduction of 1,3-dienes to *cis* mono-enes.[12,13] This fact was of some concern because the chromium unit is believed to decomplex in the presence of a hydrogen atmosphere when dissolved in coordinating solvents.[12] The chromium complexes were placed under hydrogenation conditions as shown in Table 5-3.

Table 5-3: Attempted hydrogenation of chromium complexes



Attempted Hydrogenation of Chromium Complexes[a]			
R	Solvent	%Conversion[b]	Products
H	Ethanol	0%	Naphthalene
H	Hexanes	0%	Naphthalene
Me	Ethanol	0%	1,4-Dimethylnaphthalene
Me	Hexanes	0%	1,4-Dimethylnaphthalene
Me	Hexanes/Toluene	0%	Complex[c]

a) using 1 atm. H_2, and an equivalent mass of 10% Pd/C, b) with respect to tetralin products, c) the complex was only observed by ^{1}H NMR but the MS indicated a small amount of 1,4-dimethyltetralin chromium tricarbonyl complex.

From the results presented in Table 5-3 it is evident that reduction of the chromium complexes to the corresponding tetralin complexes does not occur. This is believed to be due to the affinity of the chromium unit for hydrogen. This is supported by the fact that in donor solvents decomplexed material was the only observed organic material. Although the use of chromium tricarbonyl as a complexing agent has proven useful for other transformations,[14,15] it is clearly not feasible in the activation of the naphthalene nucleus toward catalytic hydrogenation.

Conclusion/Future Directions

Coordination of the naphthalene nucleus with the iron cyclopentadienyl cation has been shown to increase the rate of reduction of the naphthalene nucleus to tetralin, which is complementary to the previously reported ruthenium analog.[2] It is well known that the catalytic reduction of aromatic compounds requires harsh reaction conditions of temperature and pressure.[7] It has also been well established that under harsh reaction conditions naphthalenes are readily hydrogenated, often resulting in over-reduction to *cis*- and *trans*-decalins.[7] Coordination of the naphthalene nucleus with the iron cyclopentadienyl cation allows the reduction to proceed under extremely mild conditions and protects the naphthalene from over-reduction.

In many instances the reductions showed remarkable selectivity. If the methyl substituents are appropriately placed (i.e. 1 or 4 position) a single reduction product is produced almost exclusively favoring the iron unit protecting the more substituted ring. Amazingly the substituents need not be strongly electron donating to effect the observed selectivity. Product selectivity can be controlled by judicious choice of substrate/catalyst ratio.

A mechanism has been proposed which accounts for the observed selectivity. Unfortunately, due to the heterogeneous nature of the reaction, the suspected intermediates have not been directly detected. Even though the η^4 16 electron intermediate has not been detected, the results of all reductions of methyl substituted naphthalenes are consistent with this intermediate.

The use of the chromium tricarbonyl naphthalene complexes proved not to activate the naphthalene nucleus toward catalytic hydrogenation. This is due to the affinity of the chromium unit toward molecular hydrogen. Attempts to use non-coordinating solvents in an attempt to suppress the chromium tricarbonyls' affinity for molecular hydrogen failed.

In the future calorimetric experiments on the iron complexes could prove useful. It is well known that ΔH_{red} data has been used to determine the stability of conjugated polyenes as well as aromatic systems.[16,17] Preliminary semi-empirical calculations performed in our laboratories suggest that the coordination of the iron moiety increases the ΔH_{red} for the naphthalene iron cyclopentadienyl cationic system. The calculated ΔH_{red} using the PM3 semi-empirical package for the (η^5-cyclopentadienyl)(η^6-naphthalene)iron(II) hexafluorophosphate salt was -44.46 kcal/mol (caution should be observed in the absolute interpretation of this numerical result with respect to experimentally determined values). The literature value for the ΔH_{red} of naphthalene to tetralin is -29.8 kcal/mol.[18] The ΔH_{red} of 1,3-cyclohexadiene is reported to be -53.6 kcal/mol.[19] Calorimetric experiments should give insight into the exact nature of the non-complexed ring. Information obtained from calorimetric studies could provide guidance toward additional transformations with naphthalene iron complexes. Efforts are currently underway in our laboratories to obtain calorimetric data.

Given that the iron can perform two possible functions also allows for the possibility of more extensive synthetic utility. The iron cyclopentadienyl cation can be used to impart chirality in a tetralin product. Figure 5-5 below illustrates a generic route

to the highly prescribed sertraline (Zoloft®).

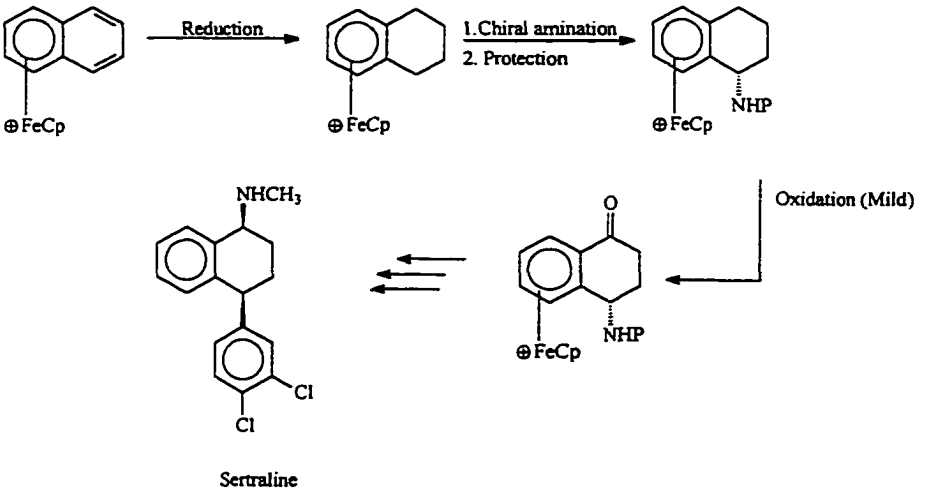


Figure 5-5: Proposed synthetic utility

a method which can give chiral amines has been reported using chiral nitrite reagents in the formation of benzylic hydroxyl-imines of iron cyclopentadienyl tetralin complex.[20] Experiments to elucidate the ability of mild benzylic oxidations of iron complexed tetralin is currently underway in our laboratories.

Experimental

General

THF was distilled from sodium/benzophenone under a nitrogen atmosphere prior to use. All other solvents were used as received unless otherwise noted. Ammonium hexafluorophosphate was prepared by neutralizing an aqueous solution of hexafluorophosphoric acid with ammonium hydroxide. $AlCl_3$ was obtained from Aldrich Chemical Company, Inc. and used as received. All naphthalene iron complexes were prepared using a known literature procedure, substituting cyclohexane for methylcyclohexane as solvent.[4] NMR spectra of all naphthalene iron complexes were consistent with literature values.[4] All naphthalene iron complexes were dried at 80°C in vacuo for 5 hours. ^1H NMR spectra of the resulting iron complexes were obtained using either a Varian unity 400 or a 300 XL spectrometer using acetone-d_6 as solvent with reference to residual solvent proton concentration. The ^{19}F spectra were obtained on a Varian Unity 400 and externally referenced to fluorobenzene.[21] VT NMR was performed on a Varian 300 XL spectrometer from -50°C to room temperature (10°C increments) allowing ~15 minutes equilibration at each temperature setting. 1-Methylnaphthalene was obtained from Aldrich Chemical Co.,Inc. and distilled under reduced pressure prior to use. 2-Methylnaphthalene was obtained from Aldrich Chemical Co.,Inc. and was recrystallized from benzene and dried under vacuum prior to use. 1,4-Dimethyl- and 1,2-dimethylnaphthalene[22] were prepared by LAH reduction of the corresponding bromomethylmethylnaphthalenes.[23] Naphthalene and ferrocene were recrystallized from methanol prior to use. 10% Pd/C was obtained form Aldrich Chemical Co., Inc. and used

as received. All hydrogenation reactions were performed at ambient temperature and pressure using a hydrogenation apparatus which consisted of a column of water as the hydrogen resevoir. FAB MS were recorded on a VG ZAB-E mass spectrometer using 3-nitrobenzylalcohol as the matrix. Decomplexation of the 1-methyltetralin iron complex was performed in a pyrex beaker using acetone as solvent in a Rayonet photochemical reactor. The chromium tricarbonyl naphthalene and 1,4-dimethylnaphthalene complexes were prepared using a literature procedure and the resulting complexes gave ^{1}H NMR identical to published values.[11] Semi-empirical calculations were performed using the PM3 method and PcSpartan 2.0[24] on an AMD-333 computer system.

Catalytic reduction of naphthalene iron complexes (typical procedure). (η^5-Cyclopentadienyl) (η^6-naphthalene)iron (II) hexafluorophosphate (80-90 mg) was dissolved in 6 mL of fresh methanol and added to a 10 mL roundbottom flask charged with 16-20 mg of 10% Pd/C and a stir bar. The charged flask was attached to a hydrogen reservoir and flushed three times with hydrogen. The mixture was allowed to stir at ambient temperature and pressure for 18 hours. The reaction mixture was removed from the hydrogen atmosphere and filtered through filtering agent to remove the Pd/C to give a yellow solution. ^{1}H NMR and mass spectra of the yellow solid were consistent with literature values for (η^5-cyclopentadienyl) (η^6-tetralin) iron(II) hexafluorophosphate, and were also identical to an authentic sample which was prepared from commercially available tetralin. ^{1}H NMR (300) showed a characteristic Cp signal at (δ 5.1, s,5H), aliphatic resonances at (δ 2.75-2.90, m, 4H) and (δ 3.05-3.20, m, 4H) and an aromatic signal at (δ 6.30, s, 4H).

1,4-Dimethyltetralin Iron Complexes: The 1,4-Dimethyltetralin complex mixture was obtained in a similar manner as described for the tetralin complex. FAB MS gave a m/z of 281.0 ($C_{17}H_{21}Fe$). The ^1H NMR spectrum showed characteristic Cp signals at: (δ 4.9, s, 5H, iron on substituted ring) and (δ 5.2, s, 5H, iron on less substituted ring). The NMR also showed characteristic signals for the methyl groups at:(δ 2.25, s, 6H) and (δ 1.61, d *J*=7.2 Hz, 6H). Aliphatic resonances of appropriate total integrations were observed at δ 2.7-3.3 and aroamtic signals appeared at (δ 6.21, s, 2H) and at (δ 6.35-6.45, m, 4H). The integration of the Cp protons and methyl protons for each diastereomer are in agreement with the given assignment.

2,3-Dimethyltetralin Iron Complexes: The 2,3-dimethyltetralin complex mixture (**3**) was obtained in a similar manner as described for the tetralin complex. FAB MS gave a m/z of 281.0 ($C_{17}H_{21}Fe$).The ^1H NMR spectrum showed characteristic Cp signals at: (δ 4.9, s, 5H, iron on substituted ring) and (δ 5.15, s, 5H, iron on less substituted ring). The NMR spectrum also revealed characteristic methyl signals at: (δ 2.50, s, 6H) and (δ 1.20,d, 6H). Aliphatic resonances of appropriate integration were observed at ca. δ 2.7-3.2. Aromatic resonances at (δ 6.2,s, 2H) and (δ 6.4, s, 4H) of appropriate intergration were observed. The integration of the Cp protons and methyl protons for each diastereomer are in agreement with the given assignment.

1,2-Dimethyltetralin Iron Complexes: The 1,2-dimethyltetralin complex mixture (**4**)was obtained in a similar manner as described for the tetralin complex. FAB MS gave a m/z of 281.2 ($C_{17}H_{21}Fe$).The ^1H NMR spectrum showed characteristic Cp signals at: (δ 4.96, s, 5H, iron on more substituted ring) and (δ 5.08, s, 5H, iron on less substituted

ring). The NMR spectrum also revealed characteristic methyl signals at (δ 2.49, s, 3H) and (δ 2.54, s, 3H), methyl doublets were not easily observed but appeared at ca. δ 1.1 and 1.6 ppm. Aliphatic resonances of appropriate integration were observed at ca.δ 2.7-3.2. Aromatic resonances at δ 6.0-6.2 of appropriate intergration were observed The integration of the Cp protons and methyl protons are in good agreement with the given assignments.

1-Methyltetralin Iron Complexes: The 1-methyltetralin iron complex mixture (**5**) was obtained in a similar manner as the tetralin complex. FAB MS gave a m/z of 267.1 ($C_{16}H_{19}Fe$). The ^{1}H NMR(400) spectrum showed characteristic Cp signals at: (δ 5.01, s, 5H, iron on more substituted ring) and (δ 5.20, s, 5H, iron on less substituted ring). The NMR also revealed characteristic methyl signals at: (δ 2.55, s, 3H) and (δ 1.61, d *J*= 6.9 , 3H). Aliphatic resonances of appropriate integration were observed at ca. δ 2.7-3.2. Aromatic resonances at δ 6.2-6.5 of appropriate integration were observed. The integration of the Cp protons and methyl protons are in good agreement with the given assignments.

2-Methyltetralin Iron Complexes: The 2-methyltetralin iron complex mixture (**6**) was obtained in a similar manner as the tetralin complex. FAB MS gave a m/z of 267.1 ($C_{16}H_{19}Fe$). The ^{1}H NMR(300) spectrum showed characteristic Cp signals at: (δ 5.08, s, 5H, iron on more substituted ring) and (δ 5.14, s, 5H, iron on less substituted ring). The NMR spectrum also revealed characteristic methyl signals at: (δ 2.45, s, 3H) and (δ 1.16, d *J*=6.1, 3H). Aliphatic resonances of appropriate integration were observed at ca.δ 2.7-3.2. Aromatic protons of appropriate integration were observed at δ 6.21-6.40.

The integration of the Cp protons and the methyl protons are in good agreement with the given assignments.

Stop Reduction Experiment: The procedure for the stop experiment was essentially the same as for the reduction of the 1,4-dimethylnaphthalene iron complexes except the reaction was removed from the hydrogen atmosphere after ~ 50-60 % conversion (about 8-10 h.).

Palladium isomerization experiment: Isomerization experiments were performed in a similar manner to the catalytic reduction of the 1,4-dimethylnaphthalene iron complexes except nitrogen was used as the atmosphere and the reaction apparatus was thermostated.

Synthesis of (η^5-cyclopentadienyl)(η^6-1-Hydroxynaphthalene) Iron (II) Hexafluorophosphate (7): In a 250 mL roundbottom flask was placed 6.00 g (3.79E-2 moles) of 1-methoxynaphthalene, 3.40 g ferrocene (3.64E-2 moles), 1.50 g (0.111 moles) aluminum powder, 24.2 g (0.181 moles) $AlCl_3$, a stir bar, and 200 mL of cyclohexane. The flask was equipped with a reflux condenser and a nitrogen inlet. The resulting solution was heated to reflux the solvent for 24 h. and then cooled to room temperature. The flask was removed from the reflux condenser and placed into an ice bath. When the contents of the flask had been cooled, about 100 mL of ice water was added slowly (excessive heat is generated with the liberation of steam and hydrogen chloride gas). The mixture is stirred and then filtered to remove unwanted solids. Additional water is added (about 50 mL) and the biphasic mixture is placed in a separatory funnel and the aqueous layer is removed and saved (the cyclohexane can be discarded). The aqueous layer was

extracted twice with 60 mL portions of fresh cyclohexane. The aqueous layer was then slowly dripped into a 2X solution of NH_4PF_6 (12.36 g in about 30 mL H_2O). The red solid was filtered and the aqueous layer is extracted 3 times with methylene chloride to obtain additional product. The product was isolated in 12.50% (1.8715 g) yield based on 1-methoxynaphthalene. ^{1}H NMR (400 MHz, 4:1 D_2O/acetone-d_6): δ 4.46 (s, 5H), 6.23 (m, 2H), 6.88 (d, J = 7.6 Hz, 1H), 7.02 (d, J = 6.4 Hz, 1H), 7.22 (d, J = 6.1 Hz, 1H), 7.24 (d, J= 8.5 Hz, 1H), 7.53 (apparent t, J= 8.1 Hz, 1H). When the ^{1}H NMR was performed in pure acetone-d_6 solvent the spectrum also revealed a D_2O exchangeable resonance at 10.61 (s, 1H). ^{13}C (100 MHz, acetone-d_6): δ 77.23, 81.15, 85.60, 86.84, 87.88, 88.89, 99.03, 109.97, 120.66, 134.68, 157.16. ^{19}F (376 MHz, acetone-d_6) : -71.52 (d, J_{PF} = 708 Hz). MS (FAB) m/z 265.1 (M - PF_6^-)$^+$. To help confirm that the methyl ether had been cleaved, it was observed that this compound underwent a color change when placed in aqueous base (NaOH). The color change was from a red/yellow to purple color and was completely reversible, This is indicative of a phenolic OH moiety.

Hydrogenation of (η^5-cyclopentadienyl)(η^6-1-Hydroxynaphthalene) Iron (II) Hexafluorophosphate (7): The hydrogenation was performed in a similar manner as for the methyl-substituted naphthalene complexes except water was used as the solvent. ^{1}H NMR (400 MHz, Acetone-d_6): δ 1.84 (m, 2H), 2.23 (m,2H), 2.84 (m, 2H), 3.15 (m, 1H), 4.75 (m broad, 1H), 5.20 (s, 5H), 6.25-6.57 (m, 4H). MS (FAB) mz/ = 265.1 (M-PF_6^-)$^+$.

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