DESIGN, SYNTHESIS AND EVALUATION OF CHIRAL NONRACEMIC LIGANDS AND CATALYSTS FOR ASYMMETRIC SYNTHESIS

by

Michael P. A. Lyle
Bachelor of Science, Simon Fraser University, 2000

THESIS SUBMITTTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

In the
Department
of
Chemistry

SIMON FRASER UNIVERSITY

Summer 2005

APPROVAL

Name: **Michael P. A. Lyle**

Degree: Doctor of Philosophy

Title of Dissertation: ***Design, Synthesis and Evaluation of Chiral Nonracemic Ligands and Catalysts for Asymmetric Synthesis***

Examining Committee:

Chair: **Dr. Neil R. Branda**
Professor

Dr. Peter D. Wilson
Assistant Professor, Senior Supervisor

Dr. Keith N. Slessor
Professor Emeritus, Supervisory Committee

Dr. Vance E. Williams
Assistant Professor, Supervisory Committee

Dr. Daniel B. Leznoff
Associate Professor, Internal Examiner

Dr. Michael A. Kerr
External Examiner
Associate Professor
Department of Chemistry, University of Western Ontario

Date Approved: August 8, 2005

ABSTRACT

The work described in this thesis concerns the design, synthesis and evaluation of new chiral nonracemic ligands and catalysts for use in asymmetric reactions.

A series of chiral nonracemic chloroacetals were prepared from 2-chloro-4-methyl-6,7-dihydro-5*H*-[1]pyrindine-7-one and a variety of C_2-symmetric and chiral nonracemic 1,2-ethanediols (R = Me, *i*-Pr and Ph). These chloroacetals were further elaborated, in a modular fashion, to provide a series of chiral ligands and catalysts.

A new class of C_2-symmetric 2,2′-bipyridyl ligands were prepared in one step from the chloroacetals *via* a nickel(0)-mediated *homo*-coupling reaction. These ligands were then evaluated as chiral directors in copper(I)-catalyzed asymmetric cyclopropanation reactions of styrene and diazoesters (up to 44% ee).

A chiral pyridine *N*-oxide and a C_2-symmetric 2,2′-bipyridyl *N*,*N*′-dioxide were also prepared by direct oxidation of the corresponding pyridine and the 2,2′-bipyridine, respectively. These chiral *N*-oxides were evaluated as chiral catalysts in desymmeterization reactions of *cis*-stilbene oxide (up to 20% ee).

A series of pyridylphosphine ligands (*P*,*N*-ligands) were subsequently prepared in two steps from the chloroacetals *via* a Suzuki coupling reaction with *ortho*-fluorophenylboronic and on subsequent displacement of the fluoride with the potassium anion of diphenylphosphine. These ligands were then evaluated in palladium-catalyzed asymmetric allylic substitution reactions of racemic 3-acetoxy-1,3-diphenyl-1-propene with dimethyl malonate. Optimization of the reaction conditions resulted in the formation of the alkylated product in excellent yield (91%) and in high enantiomeric excess (90%).

A related chiral nonracemic and C_2-symmetric 2,2′-bipyridyl ligand was prepared from 2-chloro-4-methyl-5*H*-[1]pyrindine. This pyrindine was prepared from a common intermediate that was used in the synthesis of the first generation of ligands. The chirality of this second generation ligand was installed by a Sharpless asymmetric dihydroxylation reaction (90% ee). The subsequently elaborated 2,2′-bipyridyl ligand (enriched to >99% ee) was then evaluated in copper(I)-catalyzed asymmetric cyclopropanation reactions of alkenes and diazoesters. In the case of the reaction of *para*-fluorostyrene and *tert*-butyl diazoacetate, the corresponding cyclopropane was formed in good diastereoselectivity (92:8) and in excellent enantioselectivity (99% ee). This ligand was also evaluated in copper(II)-catalyzed asymmetric Friedel-Crafts alkylation reactions of various substituted indoles (up to 90% ee) and in copper(I)-catalyzed asymmetric allylic oxidation reactions of cyclic alkenes with *tert*-butyl peroxybenzoate (up to 91% ee).

DEDICATION

For Litsa, my parents Robert and Heather, and my brother Eric.

ACKNOWLEDGEMENTS

I would like to thank my supervisor, mentor and friend Dr. Peter D. Wilson for his support and guidance during the course of my doctoral studies. I am extremely grateful for the training he has provided me with in synthetic organic chemistry.

The members of my supervisory committee, Dr. Keith N. Slessor and Dr. Vance E. Williams are thanked for their helpful suggestions and encouragement throughout my doctoral studies.

My past and present colleagues, Jeremy Pettigrew, Peggy Paduraru, Dr. Summon Koul, Dr. Arun Narine, Dr. Jay Cadieux, Dr. Hongjuan Hu, Patrick Chen and Darren McMurtrie are all thanked for their friendship as well as for many helpful and insightful discussions.

For their technical assistance, Mrs. Marcy Tracey (NMR), Mr. Greg Owen (MS), Mr. Phillip Ferreira (MS) and Mr. M. K. Yang (CHN microanalysis), are gratefully acknowledged.

Mr. Neil D. Draper is thanked for performing all of the X-ray crystallography described in this thesis. The results from these structure determinations were critical to our research program.

Finally, the National Sciences and Engineering Research Council of Canada and Simon Fraser University are thanked for financial support.

TABLE OF CONTENTS

LIST OF SCHEMES

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

°	degree(s)
1D	one dimensional
^{13}C NMR	carbon nuclear magnetic resonance
^{1}H NMR	proton nuclear magnetic resonance
aq.	aqueous
Ac	acetate
acac	acetoacetate
AAS	asymmetric allylic substitution
AC	asymmetric cyclopropanation
AD	asymmetric dihydroxylation
Anal.	analytical
Ar	aryl
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
Bn	benzyl
BSA	*N,O-bis*trimethylsilylacetamide
c	concentration
Calcd	calculated
CD	circular dichroism
CI	chemical ionization
COD	1,5-cyclooctadiene
Conf.	absolute configuration
COSY	^{1}H-^{1}H correlation NMR spectroscopy
CH_2Cl_2	dichloromethane
CH_3CN	acetonitrile
Cp*	1,2,3,4,5-pentamethylcyclopentadienyl
d	distance
D	deuterium
dba	dibenzylideneacetone
de	diastereoisomeric excess
DET	diethyl tartrate
dr	diastereoisomeric ratio
DMAP	*N,N*-dimethyl-4-aminopyridine

DMSO	dimethylsulfoxide
dppb	1,4-*bis*(diphenylphosphino)butane
dppe	1,5-*bis*(diphenylphosphino)pentane
ε	molar absorptivity
ee	enantiomeric excess
EI	electron impact
ent	enantiomer
equiv	equivalent(s)
er	enantiomeric ratio
Et	ethyl
ether	diethyl ether
EtOAc	ethyl acetate
FAB	fast atom bombardment
GC	gas chromatography
h	hour
HR	high resolution
Hz	Hertz
IR	infrared
J	coupling constant
L*	chiral ligand
LUMO	lowest unoccupied molecular orbital
M	molarity
MALDI-TOF	matrix-assisted laser desorption ionization-time of flight
m-CPBA	*m*-chloroperoxybenzoic acid
Me	methyl
MeOH	methanol
min	minute
mL	milliliter
mol	mole(s)
MS	mass spectrometry
m/z	mass to charge ratio
NCS	*N*-chlorosuccinimide
NMO	*N*-methylmorpholine *N*-oxide
nOe	nuclear Overhauser effect

Np	naphthyl
[O]	oxidation
ORD	optical rotary dispersion
ORTEP	Oakridge thermal ellipsoid plot
Ph	phenyl
pKa	acid dissociation constant
p.s.i.	pounds per square inch
PPTS	pyridinium *p*-toluenesulfonate
rac	racemic
rt	room temperature
TADDOL	$\alpha,\alpha,\alpha',\alpha'$-tetraaryl-2,2-dimethyl-1,3-dioxolan-4,5-dimethanol
TBS	*t*-butyldimethylsilyl
temp	temperature
Tf	trifluoromethane sulfonyl
TFPB	*tetrakis*[2,6-*bis*(trifluoromethyl)phenyl]borate
THF	tetrahydrofuran
THQ	tetrahydroquinoline
TMS	trimethylsilyl
p-TsOH	*p*-toluenesulfonic acid
TS	transition state
UV	ultraviolet
Vis	visible
W	Watts

CHAPTER 1: INTRODUCTION

DESIGN, SYNTHESIS AND EVALUATION OF CHIRAL NONRACEMIC LIGANDS AND CATALYSTS FOR ASYMMETRIC SYNTHESIS

1.1. General Overview

The development of catalytic asymmetric synthesis is one of the major aspects of modern synthetic organic chemistry. This thesis concerns the design, synthesis and evaluation of new chiral nonracemic 2,2′-bipyridyl ligands (both C_2-symmetric and unsymmetric), pyridine *N*-oxides and pyridylphosphine ligands for use in catalytic asymmetric reactions.

In the first section of this introductory chapter, a brief overview of the central principles of asymmetric synthesis as well as the major achievements in this field are discussed. Particular emphasis is placed on topics that relate to our original research program. Following this general introduction, the design concepts and objectives of the research discussed in this thesis are presented.

Chiral 2,2′-bipyridine ligands and *P*,*N*-ligands have played an important role in the field of asymmetric synthesis and so a detailed discussion of these classes of ligands, including their syntheses and use in catalytic asymmetric reactions, is presented. This discussion is provided in order to place the research results described in this thesis in perspective.

1.2. Asymmetric Synthesis

In 1904, Marckwald defined asymmetric synthesis as "reactions which produce optically active substances from symmetrically constituted compounds with the intermediate use of optically active material but with the exclusion of all analytical processes".[1] The asymmetric synthesis of both natural and unnatural organic compounds in *chiral nonracemic* form is a central challenge and objective in chemistry. As such, the development of new chiral auxiliaries, reagents, ligands and catalysts for use in asymmetric synthesis is at the forefront of chemical research.

Chirality is an intrinsic feature of all matter which cannot be superimposed on its mirror image.[2] The word *chiral* "handedness" is derived from the Greek word *cheir*, which means hand. Our left and right hands are mirror images of each other and are not superimposible, which is the minimum criterion for chirality.

The first evidence of molecular chirality came in 1848 when Louis Pasteur noted the spontaneous crystallization of the sodium ammonium salt of racemic tartaric acid, which is found in wine caskets, into enantiomorphic crystals.[3] After careful physical separation of the two types of crystals with tweezers, Pasteur made the discovery that solutions of the crystals rotated plane polarized light in equal but opposite directions. The only explanation for this observation was that the molecules in each of the crystals were nonsuperimposable mirror images of one another.

---

(1) Marckwald, W. Asymmetric Synthesis. *Ber. Dtsh. Chem. Ges.* **1904**, *37*, 1368.

(2) See, for example: (a) Gardner, M. In *The New Ambidextrous Universe, 3rd ed.*, W. H. Freeman & Co., New York, 1990. (b) Heilbronner, E.; Dunitz, J. D. In *Reflections on Symmetry*, VHCA, Basel, 1993. (c) Hoffmann, R. In *The Same and Not the Same*, Columbia University Press, New York, 1995.

(3) Pasteur, L. *Ann. Chim. Phys.* **1848**, *24*, 442.

In 1874, J. H. Van't Hoff and J. A. LeBel independently proposed the tetrahedral arrangement of atoms around the central carbon atom in organic compounds. One of the consequences of this tetrahedral arrangement is that when four different substituents are attached to the central carbon, two mirror-image configurations of the central carbon are possible and this stereogenic carbon atom (or molecule) is said to be *chiral* (Figure 1.2.1.).

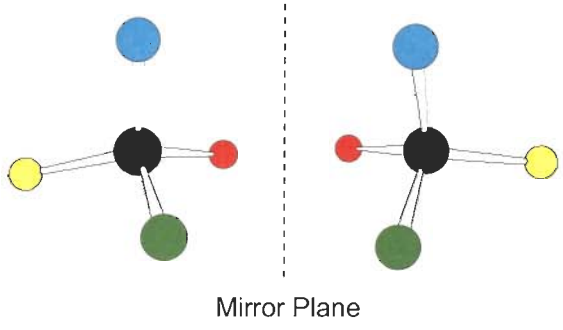


Figure 1.2.1. The two mirror-image forms of a stereogenic tetrahedral carbon atom.

There is a relationship between molecular chirality and living systems since many of the molecules essential to life such as DNA, proteins and carbohydrates are composed of *chiral nonracemic* compounds (single enantiomers/mirror-image forms). Many physiological responses are the result of highly specific interactions between these chiral molecules. In Lewis Carroll's "Through the Looking Glass" which was published in 1872 and was a sequel to "Alice in Wonderland", Alice ponders "How would you like to live in a looking-glass house, Kitty? I wonder if they'd give you milk in there? Perhaps looking-glass milk isn't good to drink". Alice was correct, if all the chiral molecules in the milk, such as lactose, were present in their mirror image form then the milk would "not be good to drink".

Since the seminal discoveries of Pasteur, Van't Hoff and LeBel in the mid-1800's organic chemists have been fascinated with chiral molecules and the creation of

molecular asymmetry. Natural products often contain amazingly intricate structures and can be rich in stereochemical features. As an illustrative example, one of the most complex natural products ever synthesized is the highly toxic marine natural product palytoxin **1** which contains sixty four stereogenic centres (Figure 1.2.2.). This compound could in principle exist as $2^{64} = 1.8 \times 10^{19}$ stereoisomers. In 1994, Kishi and co-workers reported the total synthesis of *one* of the possible stereoisomers of palytoxin **1**, the naturally occurring stereoisomer.[4]

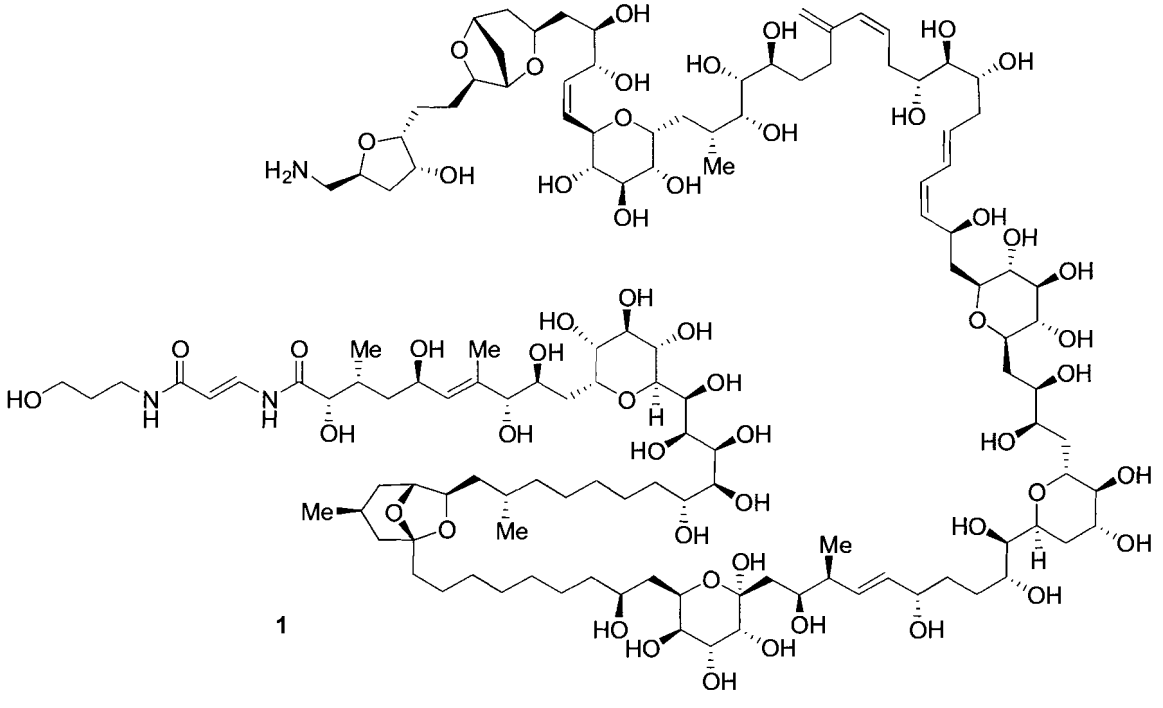
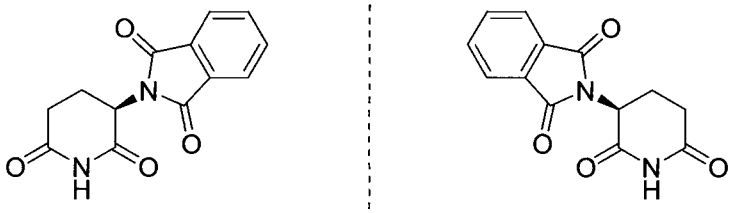


Figure 1.2.2. The highly toxic marine natural product palytoxin **1** which contains sixty four stereogenic centres.

(4) Armstrong, R. W.; Beau, J.-M.; Cheon, S. H.; Christ, W. J.; Fujioka, H.; Ham, W.-H.; Hawkins, L. D.; Jin, H.; Kang, S. H.; Kishi, Y.; Martinelli, M. J.; McWhorter, W. W.; Mizuno, M.; Nakata, M.; Stutz, A. E.; Talamas, F. X.; Taniguchi, M.; Tino, J. A.; Ueda, K.; Uenishi, J.; White, J. B.; Yonaga, M. Total Synthesis of Palytoxin Carboxylic Acid and Palytoxin Amide. *J. Am. Chem. Soc.* **1989**, *111*, 7530. (b) Suh, E. M.; Kishi, Y. Synthesis of Palytoxin from Palytoxin Carboxylic Acid. *J. Am. Chem. Soc.* **1994**, *116*, 11205.

Asymmetric synthesis is very important to the pharmaceutical industry because the structural differences between two enantiomeric drug molecules can have serious consequences with respect to biological activity. A tragic example of this came with the administration of racemic thalidomide to pregnant women in the 1960's. Unkonwn at the time, (*R*)-thalidomide (*R*)-**2** contained the desirable sedative properties while its enantiomer (*S*)-thalidomide (*S*)-**2**, was a teratogen and induced fetal abnormalities (Figure 1.2.3.).



(*R*)-**2** (*S*)-**2**

Figure 1.2.3. The structures of (*R*)-thalidomide (*R*)-**2** and (*S*)-thalidomide (*S*)-**2**.

The thalidomide tragedies increased awareness of the stereochemistry in the action of drugs and as a result, the number of drugs administered as racemic compounds has steadily decreased. In 2001, over 70% of the new chiral drugs approved were single enantiomers.[5]

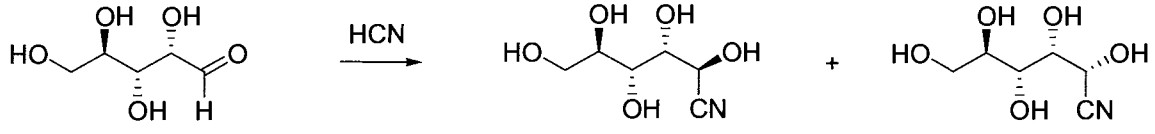
1.3. Strategies for Asymmetric Induction *via* Substrate, Auxiliary and Reagent Control

The strategies for the controlled formation of new stereogenic centres in molecules may be grouped into three categories: (a) substrate-control; (b) auxiliary-

(5) Agranat, I.; Caner, H.; Caldwell, J. Putting Chirality to Work: The Strategy of Chiral Switches. *Nat. Rev. Drug Discovery* **2002**, *1*, 753.

control; and (c) reagent-control. In an asymmetric substrate-controlled reaction, an existing stereogenic centre(s) in the reaction substrate directs the selective formation of the new stereogenic centre during a reaction with an achiral reagent. Asymmetric substrate-controlled reactions were the first type of asymmetric reactions to be conducted. In 1894, Emil Fischer observed that the addition of hydrogen cyanide to D-arabinose **3** formed the mannononitriles **4** and **5** in a diastereoselective manner (66:34, respectively) (Scheme 1.3.1.).[6]

Scheme 1.3.1. The Diastereoselective Addition of Hydrogen Cyanide to D-Arabinose **3**



3 **4** **5**

Following Fischer's observations, progress was slow in gaining a deeper understanding of asymmetric induction in substrate-controlled reactions. In 1952, Cram and Abd Elhafez reported their studies on the stereochemistry of addition reactions to aldehydes and ketones that contain a stereogenic centre adjacent to the carbonyl moiety.[7] This study formed the basis for the now well-known concept of *steric control of asymmetric induction* and the foundations were thus laid for the rational interpretation and control of the stereochemical outcome of asymmetric substrate-controlled reactions.

A more recent approach to the asymmetric formation of new stereogenic centres has involved the use of chiral auxiliaries. This method involves the temporary covalent attachment of a chiral nonracemic compound (the chiral auxiliary) to the reaction

(6) Fischer, E. *Dtsh. Chem. Ges.* **1894**, *27*, 3189.

(7) Cram, D. J.; Abd Elhafez, F. A. Studies in Stereochemistry. The Rule of "Steric Control of Asymmetric Induction" in the Syntheses of Acyclic Systems. *J. Am. Chem. Soc.* **1952**, *74*, 5828.

substrate. The temporary chiral environment imposed on the substrate by the chiral auxiliary can then control the stereochemical outcome of a subsequent reaction with an achiral substrate. In the final step of the three-step reaction sequence, the chiral auxiliary is removed from the substrate to liberate the desired enantiomerically enriched product. The auxiliary can then be recovered for use in additional asymmetric transformations.

For example, Evans' oxazolidinone-derived chiral auxiliaries have been used in the asymmetric *syn*-aldol reaction of boron enolates (Figure 1.3.1.).[8] In this reaction sequence, the oxazolidinone auxiliary **6** was reacted with propionyl chloride **7** to afford the *N*-acyl derivative **8** that was then converted to the corresponding (*Z*)-di-*n*-butylboron enolate **8** upon treatment with di-*n*-butylboron triflate. The enolate **8** was then reacted with acetaldehyde to form the *syn*-aldol addition product **10** *via* the "chair-like" transition state **9** with high diastereoselectivity (>99% de). Of note, it is sometimes possible to remove the minor diastereoisomeric impurity by recrystallization or chromatography at this stage. In the final step, the desired enantiomerically enriched product **11** is removed from the auxiliary by hydrolysis and the auxiliary **6** is recovered.

(8) Evans, D. A.; Bartroli, J.; Shih, T. L. Enantioselective Aldol Condensations. 2. *Erythro*-selective Chiral Aldol Condensations *via* Boron Enolates. *J. Am. Chem. Soc.* **1981**, *103*, 2127.

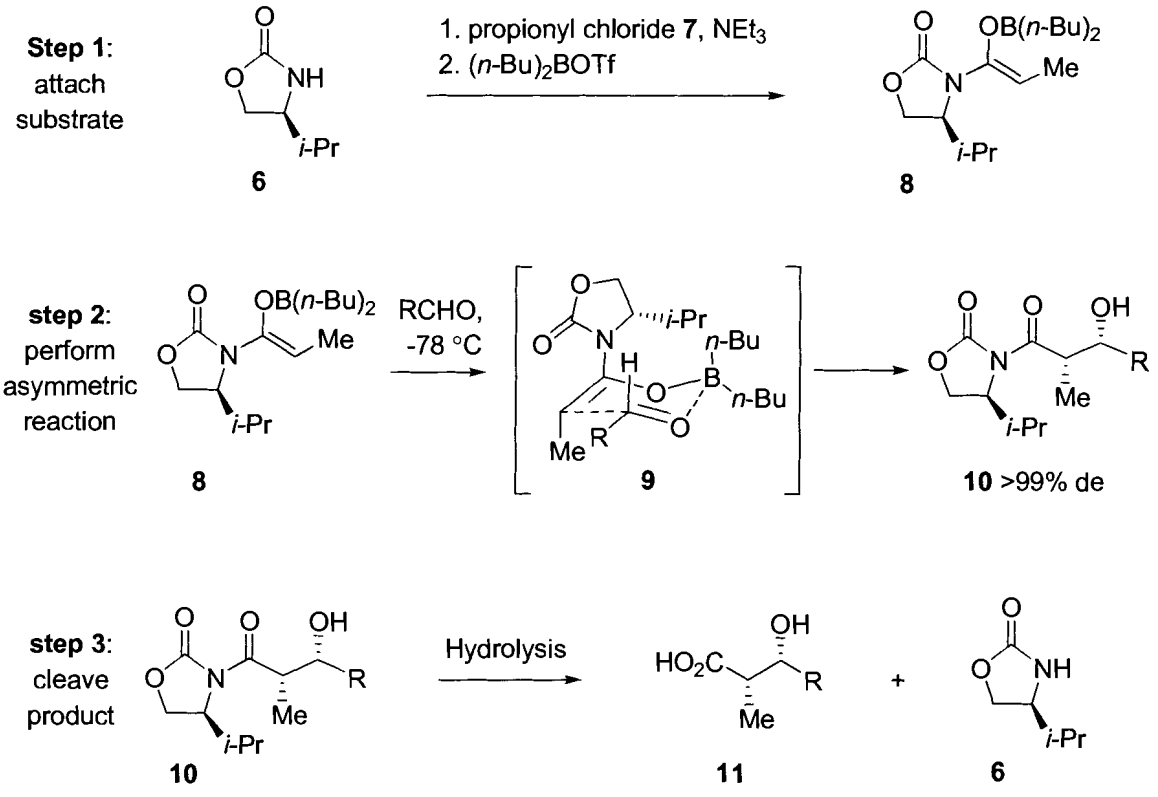
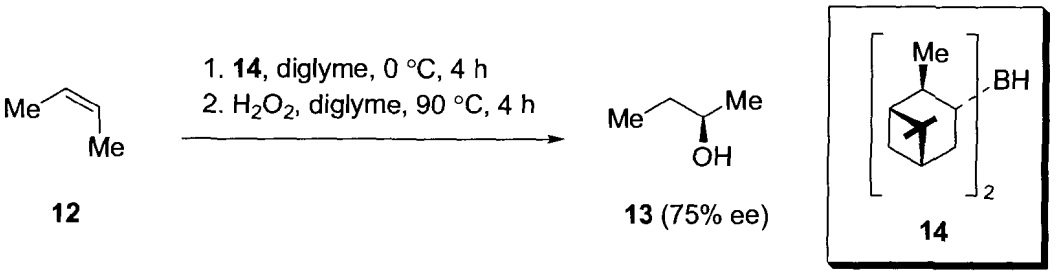


Figure 1.3.1. Application of Evans' oxazolidinone chiral auxiliary in an asymmetric aldol reaction.

The major drawback to the use of a chiral auxiliary is that it adds two extra steps to a synthetic sequence (the attachment of the auxiliary to the substrate and the removal of the auxiliary from the product). However, the use of a chiral auxiliary can serve simultaneously to protect reactive functional groups during the asymmetric transformation.

The use of chiral reagents in asymmetric reactions can be divided into two types: (a) chiral compounds used in a stoichiometric quantity; and (b) chiral compounds used in sub-stoichiometric quantities (chiral catalysts). In these types of asymmetric reactions, the chirality of the reagent controls the stereochemical outcome of the reaction with a prochiral or chiral substrate. For example, in 1951 Brown and co-workers reported the

chiral borane reagent diisopinocamphenylborane **14** which is readily synthesized by the diastereoselective reaction of diborane with the chiral nonracemic natural product α-pinene.[9] This chiral reagent **14** has been shown to be effective in several reactions including the asymmetric hydroboration/oxidation reaction of alkenes, such as (*Z*)-2-butene **12**, which affords the chiral alcohol **13** (Figure 1.3.2.).[10]



12 **13** (75% ee) **14**

Figure 1.3.2. Asymmetric hydroboration/oxidation reaction of alkenes using the chiral borane reagent **14**.

The use of substoichiometric amounts of a chiral reagent to control the formation of a new stereogenic centre(s) is referred to as a catalytic asymmetric process. Evidence suggests that asymmetric reactions catalyzed by chiral molecules dates back to the formation of key prebiotic building blocks such as carbohydrates. Chemists have theorized that amino acids such as L-alanine and L-isovaline catalyzed enantioselective condensation reactions between glycal and formaldehyde which afforded chiral carbohydrate derivatives and resulted in the proliferation of chiral nonracemic molecules in nature.[11] In modern synthetic organic chemistry, the majority of chiral catalysts

(9) Brown, H. C.; Zweifel, G. A Stereospecific Double Bond Hydration of the Double Bond in Cyclic Systems. *J. Am. Chem. Soc.* **1959**, *81*, 247.

(10) Verbit, L.; Heffron, P. J. Optically Active *sec*-Butylamine *via* Hydroboration. *J. Org. Chem.* **1967**, *32*, 3199.

(11) Pizzarello, S.; Weber, A. L. Prebiotic Amino Acids as Asymmetric Catalysts. *Science* **2004**, *303*, 1151.

developed have been transition metal complexes of chiral nonracemic organic ligands. However, the use of chiral nonracemic organic compounds in catalytic asymmetric synthesis "Organocatalysis" is a rapidly advancing technology.

In asymmetric transition metal-catalyzed reactions, the chirality of the complex is transferred to the reaction product *via* the energy difference between all the possible diastereoisomeric reaction transition states. The general mechanistic scheme shown below involves three fundamental steps: (1) the coordination of reactants A and B to the chiral transition metal complex (ML*); (2) the reaction of A and B to generate the chiral reaction product (AB); and (3) the decomplexation of the reaction product from the chiral transition metal complex (Figure 1.3.3.).

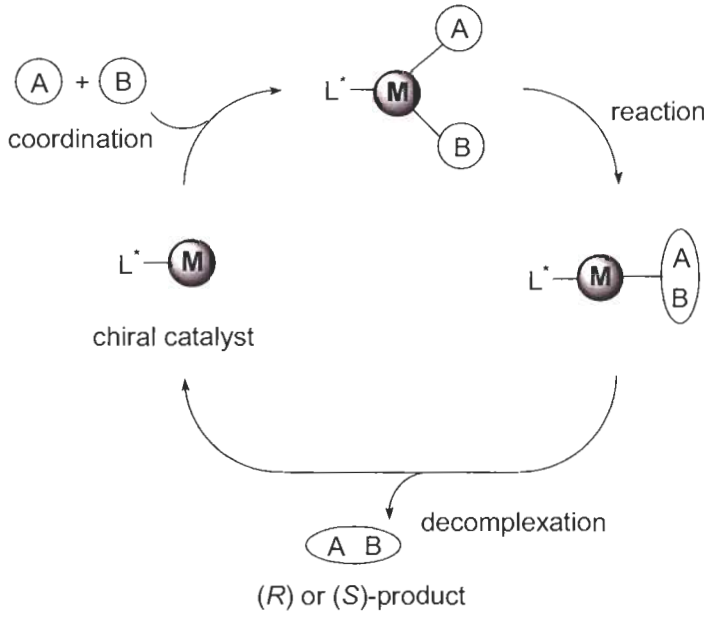


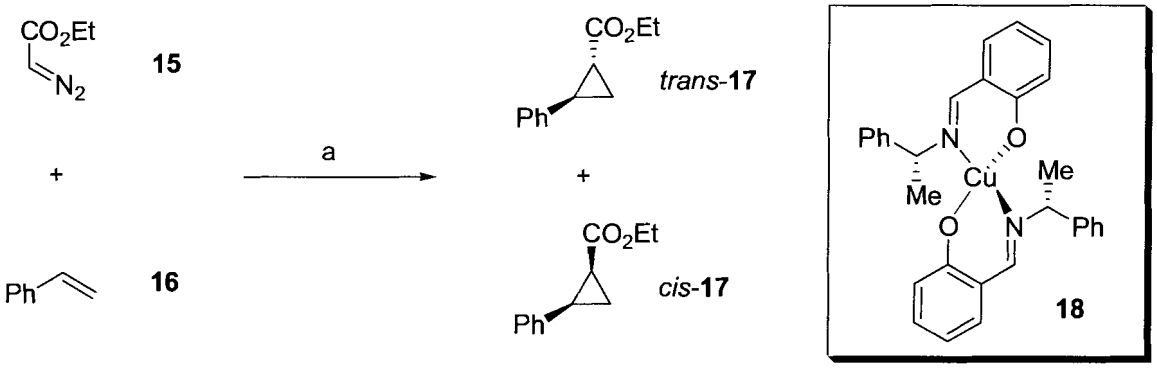
Figure 1.3.3. The general mechanistic principle of asymmetric catalysis.

In a landmark paper in 1966, Nozaki, Moriuti, Takaya and Noyori reported the first example of the use of a chiral metal complex in asymmetric synthesis.[12] The copper

(12) Nozaki, H.; Moriuti, S.; Takaya, H.; Noyori, R. Asymmetric Induction in Carbenoid Reaction by means of a Dissymetric Copper Chelate. *Tetrahedron Lett.* **1966**, *43*, 5239.

complex **18** of a chiral bidentate ligand, which was derived from salicylaldehyde and (*R*)-α-phenylethylamine, was found to catalyze the reaction between styrene **16** and ethyl diazoacetate **15** and form the diastereoisomeric *trans*-cyclopropane *trans*-**17** and *cis*-cyclopropane *cis*-**17** in 6% and 10% enantiomeric excess, respectively (Scheme 1.3.2.). Although the stereoselectivity of the reaction was low, the concept of using chiral transition metal complexes in catalytic asymmetric synthesis had been established.

Scheme 1.3.2. The First Metal-Catalyzed Asymmetric Reaction: The Copper(I)-Catalyzed Cyclopropanation Reaction of Styrene (1966)



Reagents and conditions: (a) 1 mol % copper complex **18**, CH_2Cl_2, 58-60 °C, 72% (*trans*:*cis* = 70:30).

The following three sections of this chapter concern the major achievements in catalytic asymmetric synthesis from 1966 to present day.

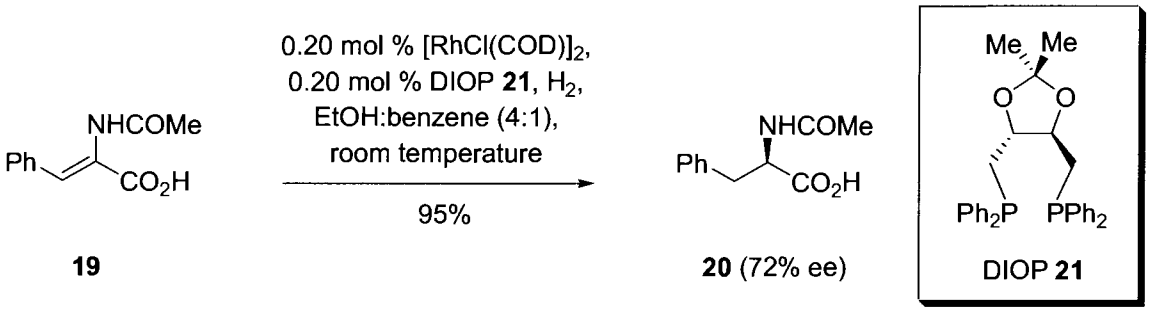
1.4. Catalytic Asymmetric Hydrogenation and Oxidation Reactions (Asymmetric C-H and C-O Bond Formation)

In 1971, Dang and Kagan reported the synthesis of the C_2-symmetric bidentate diphosphine ligand DIOP **21**.[13] Their reason for choosing a C_2-symmetric ligand with

(13) Dang, T. P.; Kagan, H. B. The Asymmetric Synthesis of Hydratropic Acid and Amino-Acids by Homogenous Catalytic Hydrogenation. *J. Chem. Soc., Chem. Commun.* **1971**, 481.

two equivalent phosphorus donor atoms was to reduce the number of possible isomeric metal complexes that could form with respect to an unsymmetrical ligand.[14] This can have a beneficial effect on the stereoselectivity of a reaction by eliminating competing and possibly less selective reaction pathways. In addition, the C_2-symmetry of the ligand can help to facilitate or simplify the interpretation of the results obtained in these experiments. A complex formed between DIOP **21** and rhodium chloride cyclooctadiene dimer was found to catalyze the asymmetric hydrogenation reaction of the *N*-acetylaminoacrylic acid **19** and afford the D-phenylalanine derivative **20** in good enantiomeric excess (72%) (Scheme 1.4.1.). Notably, this was the first catalytic asymmetric reaction to achieve relatively high levels of asymmetric induction.

Scheme 1.4.1. Asymmetric Hydrogenation Reaction of the *N*-Acetylaminoacrylic Acid **19** using the Chiral C_2-Symmetric Ligand DIOP **21** (1971)



19

20 (72% ee)

DIOP **21**

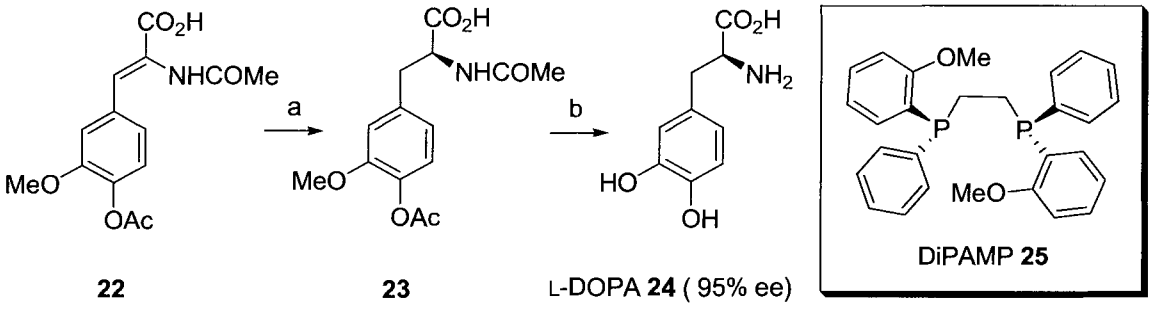
The design principles that led Dang and Kagan to synthesize DIOP **21**, particularly that of the employment of an element of C_2-symmetry, had a strong influence on the course of further research in catalytic asymmetric synthesis.

In 1974 Knowles and co-workers reported that a rhodium(I) complex containing the C_2-symmetric bidentate diphosphine ligand DiPAMP **25** which contained two

(14) For a review on C_2-symmetry, see: Whitesell, J. K. C_2-Symmetry and Asymmetric Induction. *Chem. Rev.* **1989**, *89*, 1581.

stereogenic phosphorus atoms catalyzed highly enantioselective hydrogenation reactions of unsaturated amides.[15] Based on these results, Knowles and co-workers developed the first industrial catalytic asymmetric process, a rhodium(I)-catalyzed asymmetric hydrogenation reaction of the unsaturated amide **22** that afforded the phenylalanine derivative **23**, which is a key intermediate in the synthesis of L-DOPA **24** (Scheme 1.4.2.).[15]

Scheme 1.4.2. The First Industrial Catalytic Asymmetric Process: The Asymmetric Synthesis of L-DOPA **24** using the Chiral C_2-Symmetric Ligand DiPAMP **25** (1974)



22 **23** L-DOPA **24** (95% ee)

Reagents and conditions: (a) Rh[(DiPAMP **25**)COD]BF_4, H_2, 100%; (b) H^+/H_2O.

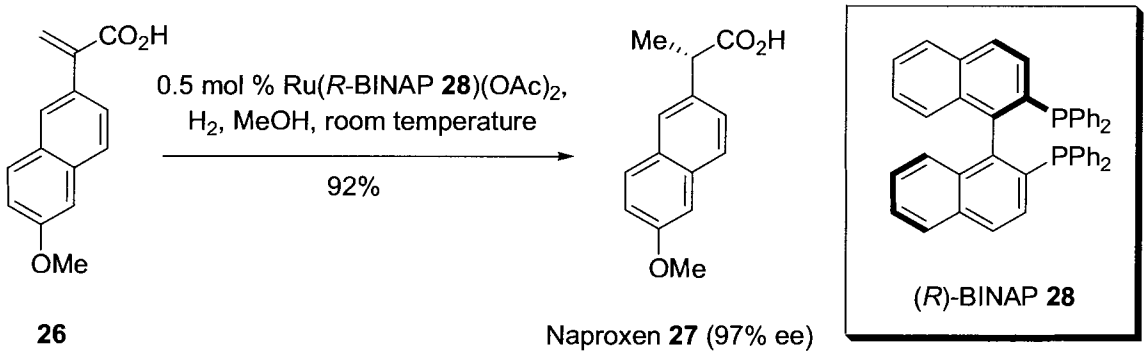
In 1980, Noyori and co-workers reported the synthesis of the axially chiral C_2-symmetric bidentate diphosphine ligand BINAP **28**.[16] Both rhodium(I) and ruthenium(II) complexes of BINAP **28** were found to be remarkable catalysts for asymmetric hydrogenation reactions of a wide range of alkene substrates. These hydrogenation catalysts are currently used in the asymmetric syntheses of several chiral drugs. For

(15) Knowles, W. S. Asymmetric Hydrogenation. *Acc. Chem. Res.* **1983**, *16*, 106.

(16) Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. Synthesis of 2,2′-*bis*(Diphenylphosphino)-1,1'-binapthyl (BINAP), an Atropisomeric Chiral *bis*(Triaryl)phosphine, and its use in the Rhodium(I)-Catalyzed Asymmetric Hydrogenation of Alpha-(acylamino)acrylic acids. *J. Am. Chem. Soc.* **1980**, *102*, 7932.

example, the anti-inflammatory drug naproxen **27** is prepared in high enantiomeric excess (97%) from the α-arylacrylic acid **26** (Scheme 1.4.3.).[17]

Scheme 1.4.3. Asymmetric Synthesis of the Anti-Inflammatory Drug Naproxen using the C_2-Symmetric Chiral Ligand BINAP **28** (1987)



In 1980, Sharpless and Katsuki reported a catalytic system for the asymmetric epoxidation of allylic alcohols using titanium(IV) tetra-isopropoxide, a chiral C_2-symmetric dialkyl tartrate derivative **31** and *tert*-butyl hydroperoxide.[18] Using this catalytic system, a wide array of allylic alcohol substrates **29** were oxidized in high enantiomeric excess (>90%) (Scheme 1.4.4.).[19]

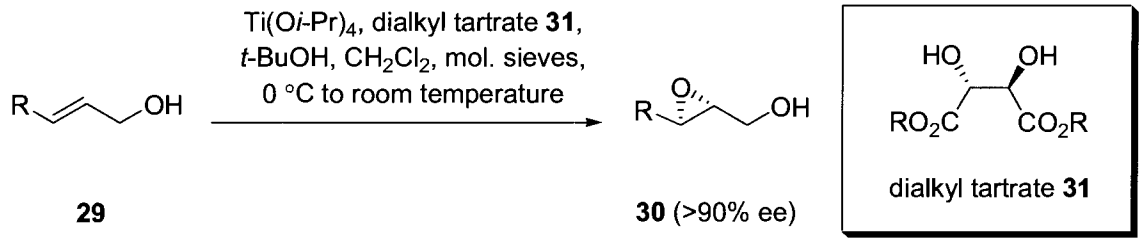
---

(17) (a) Ohta, T.; Takaya, H.; Noyori, R. Asymmetric Hydrogenation of Unsaturated Carboxylic Acids Catalyzed by BINAP-Ruthenium(II) Complexes. *J. Org. Chem.* **1987**, *52*, 3174. (b) Kitamura, M.; Yoshimura, M.; Tsukamoto, M.; Noyori, R. Synthesis of α-Amino Phosphonic Acids by Asymmetric Hydrogenation. *Enantiomer* **1996**, *1*, 281.

(18) Katsuki, T.; Sharpless, K. B. The First Practical Method for Asymmetric Epoxidation. *J. Am. Chem. Soc.* **1980**, *102*, 5974.

(19) For a review on the asymmetric epoxidation of allylic alcohols, see: Johnson, R. A.; Sharpless, K. B. Catalytic Asymmetric Epoxidation of Allylic Alcohols. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000, Chapter 6A.

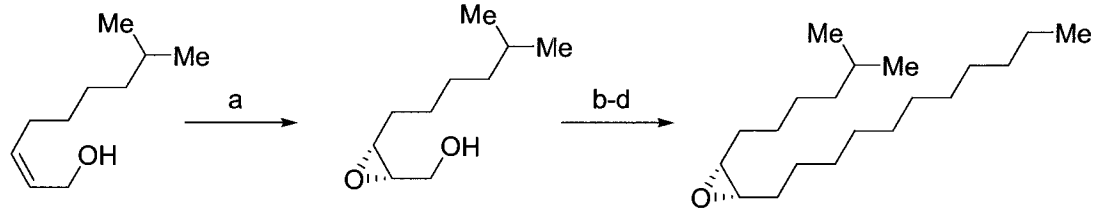
Scheme 1.4.4. Sharpless-Katsuki Asymmetric Epoxidation of Allylic Alcohols using C_2-Symmetric Dialkyl Tartrates **31** as the Chiral Ligand (1980)



29 **30** (>90% ee)

Since this initial report, the Sharpless-Katsuki protocol has been implemented industrially for the asymmetric synthesis of several important chiral molecules including (7*R*,8*S*)-disparlure **34**, the pheromone of the gypsy moth (Figure 1.4.5.).[20]

Scheme 1.4.5. The Asymmetric Synthesis of the Gypsy Moth Phermone Disparlure **34** (1981)



32 **33** (7*R*,8*S*)-disparlure **34**

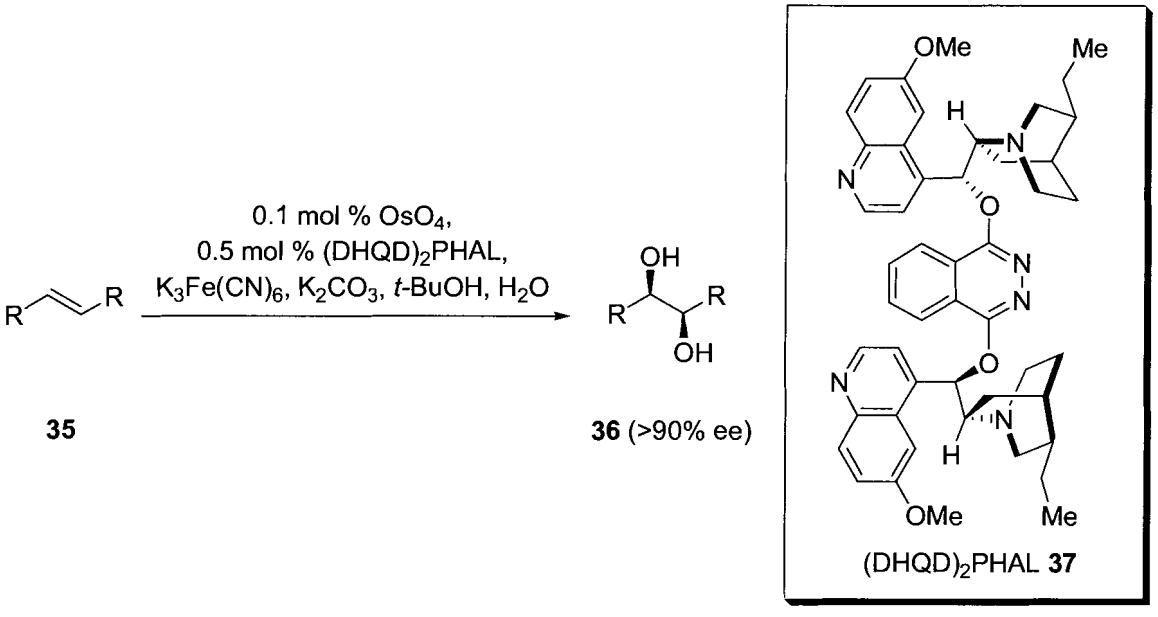
Reagents and conditions: (a) (-)-DET, Ti(O*i*-Pr)$_4$, *t*-BuOH, CH_2Cl_2, 4 Å mol. sieves, -40 °C, 4 days, 80%, 91% ee; (b) CrO_3(pyridine)$_2$, CH_2Cl_2; (c) $Ph_3P(n\text{-}C_{10}H_{21})Br$, *n*-BuLi, THF; (d) $(Ph_3P)_3RhCl$, H_2, benzene, room temperature, 24 h, 47% (over three steps).

Sharpless and co-workers made another important contribution to the field of catalytic asymmetric synthesis in 1991 when they reported the asymmetric *cis*-dihydroxylation reaction of alkenes **35** using catalytic amounts of osmium tetraoxide and a chiral C_2-symmetric *bis*cinchona alkaloid-derived ligand **37** in the presence of a

(20) Rossiter, B. E.; Katsuki, T.; Sharpless, K. B. Asymmetric Epoxidation Provides Shortest Routes to Four Chiral Epoxy Alcohols which are Key Intermediates in Syntheses of Methymycin, Erythromycin, Leukotriene C-1 and Disparlure. *J. Am. Chem. Soc.* **1981**, *103*, 464.

stoichiometric amount of a co-oxidant such as potassium ferricyanide(III) or *N*-methylmorpholine *N*-oxide (Scheme 1.4.6.).[21]

Scheme 1.4.6. Sharpless Catalytic Asymmetric *cis*-Dihydroxylation of Alkenes using C_2-Symmetric *bis*Cinchona Alkaloid-Derived Chiral Ligand **37** (1991)



35 **36** (>90% ee) (DHQD)$_2$PHAL **37**

Of note, for their contributions to asymmetric synthesis, the Nobel Prize in Chemistry for the year 2001 was awarded to K. Barry Sharpless[22] for his work on the asymmetric oxidation reactions of alkenes and to Ryoji Noyori[23] and William S. Knowles[24] for their work on the asymmetric hydrogenation reactions of alkenes.

Until the mid-1980's, the majority of research in catalytic asymmetric synthesis involved reactions which formed either carbon-hydrogen bonds (hydrogenation) or

(21) For a review on catalytic asymmetric dihydroxylation reactions, see: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. Catalytic Asymmetric Dihydroxylation. *Chem Rev.* **1994**, *94*, 2483.

(22) Sharpless, K. B. Searching for New Reactivity (Nobel Lecture). *Angew. Chem., Int. Ed.* **2002**, *41*, 2024.

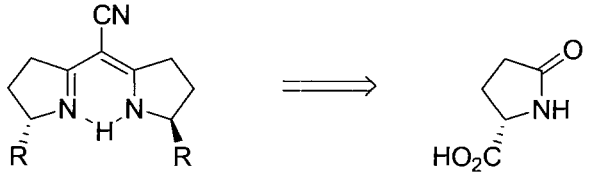
(23) Noyori, R. Asymmetric Catalysis: Science and Opportunities (Nobel Lecture). *Angew. Chem., Int. Ed.* **2002**, *41*, 2008.

(24) Knowles, W. S. Asymmetric Hydrogenations (Nobel Lecture). *Angew. Chem., Int. Ed.* **2002**, *41*, 1998.

carbon-oxygen bonds (oxidation) which are commonly referred to as "atom-transfer reactions". The next frontier for development of catalytic asymmetric synthesis was and continues to be the asymmetric construction of carbon-carbon bonds which is the focus of the brief review in the following section.

1.5. Catalytic Asymmetric Carbon-Carbon Bond Formation Reactions

Inspired by the structures of natural corrinoid and porphinoid metal complexes, which play a fundamental role in biocatalysis, Pfaltz and co-workers reported the synthesis of a class of *pseudo* C_2-symmetric bidentate dinitrogen ligands **38** that are known as semicorrins.[25] The semicorrin ligands **38** were prepared from L-pyroglutamic acid **39** which is commercially available (Figure 1.5.1.).



38 **39**

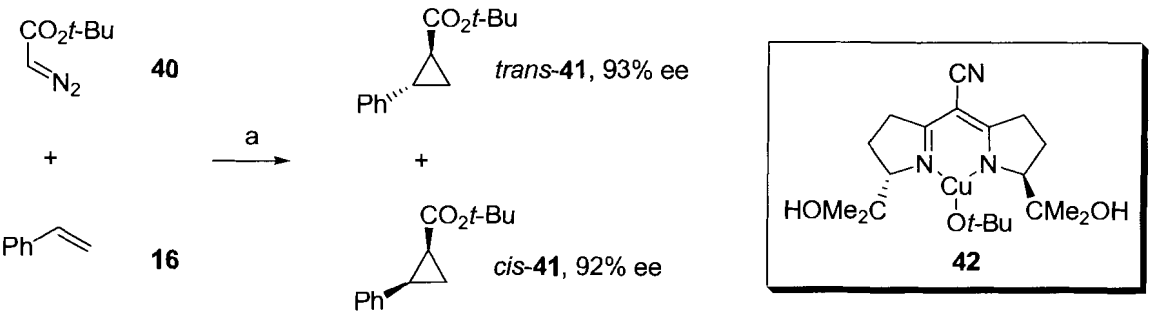
Figure 1.5.1. *Pseudo* C_2-symmetric chiral semincorrin ligands **38** (1988).

Pfaltz and co-workers first successful application of a chiral semmicorrin metal complex was in the copper(I)-catalyzed asymmetric cyclopropanation reaction of styrene **16** and *tert*-butyl diazoacetate **40**, the reaction that Nozaki, Moriuti, Takaya and Noyori had reported over 30 years earlier. However, in this instance, the semicorrin ligand

(25) Fritschi, H.; Leutenegger, U.; Siegmann, K.; Pfaltz, A. Synthesis of Chiral Semicorrin Ligands and General Concepts. *Helv. Chim. Acta* **1988**, *71*, 1541.

copper(I) *t*-butoxide complex **42** induced high levels of enantioselectivity (92-93% ee) (Scheme 1.5.1.).[26]

Scheme 1.5.1. Catalytic Asymmetric Cyclopropanation Reaction of Styrene using the *pseudo* C_2-Symmetric Chiral Semicorrin Copper(I) Complex **42** (1988)



Reagents and conditions: (a) 1 mol % **42**, $ClCH_2CH_2Cl$, room temperature, 65% (*trans*:*cis* = 81:19).

The results of these cyclopropanation reactions confirmed the usefulness of the semicorrin ligands in catalytic asymmetric carbon-carbon bond formation reactions and formed the basis of a major area of research into the use of chiral bidentate dinitrogen ligands in catalytic asymmetric reactions. In 1990 and 1991, Masamune and co-workers reported the synthesis of the C_2-symmetric *bis*oxazoline ligands **43**, **44** and **45** while Evans and co-workers reported the synthesis of the dimethyl substituted C_2-symmetric *bis*oxazoline ligands **46** (Figure 1.5.2.).[27,28,29]

(26) Fritschi, H.; Leutenegger, U.; Pfaltz, A. Enantioselective Cyclopropane Formation from Olefins with Diazo Compounds Catalyzed by Chiral (Semicorrinato)copper Complexes. *Helv. Chim. Acta.* **1988**, *71*, 1553.

(27) (a) Lowenthal, R. E.; Abiko, A.; Masamune, S. Asymmetric Catalytic Cyclopropanation of Olefins: *bis*-Oxazoline Copper Complexes. *Tetrahedron Lett.* **1990**, *31*, 6005. (b) Lowenthal, R. E.; Masamune, S. Asymmetric Copper-Catalyzed Cyclopropanation of Trisubstituted and Unsymmetrical *cis*-1,2-Disubstituted Olefins: Modified *bis*-Oxazoline Ligands. *Tetrahedron Lett.* **1991**, *32*, 7373.

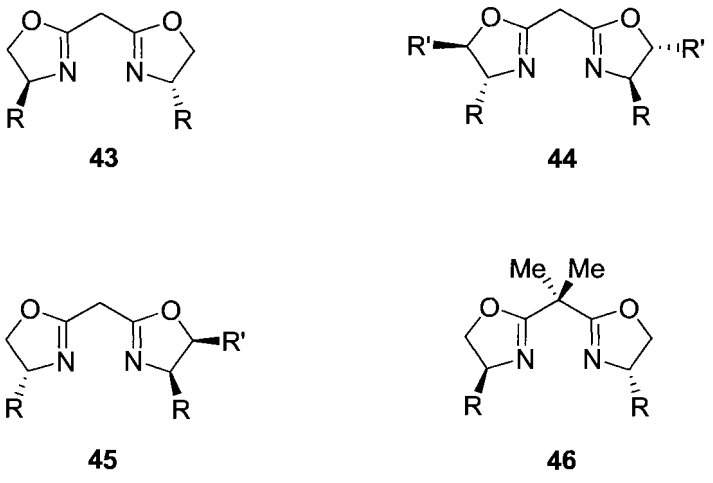


Figure 1.5.2. The C_2-symmetric chiral *bis*oxazoline ligands **43-46** reported by Masamune and Evans (1990 and 1991, respectively).

The use of chiral C_2-symmetric *bis*oxazoline ligands has resulted in remarkarble success in catalytic asymmetric synthesis in that exceptional levels of asymmetric induction in a variety of reactions such as cyclopropanations, Diels-Alder cycloadditions, ene reactions, aldol condensations, conjugate additions and Friedel-Crafts alkylations.[30] These are important reactions in organic synthesis and these accomplishments have greatly advanced the application of catalytic asymmetric synthesis in target-oriented

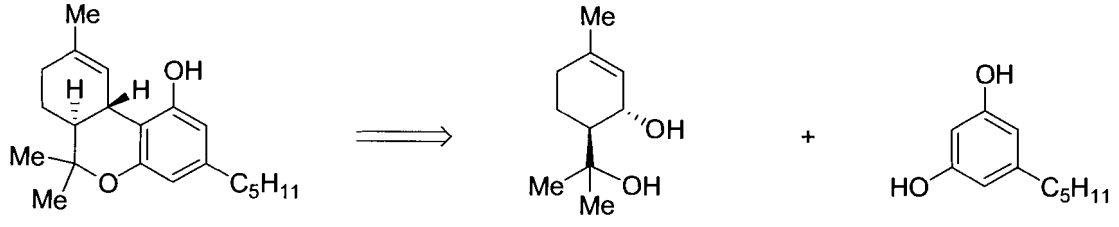
---

(28) Evans, D. A.; Woerpel, K. A.; Hinman, M. M. *bis*(Oxazolines) as Chiral Ligands in Metal-Catalyzed Asymmetric Reactions. Catalytic Asymmetric Cyclopropanation of Olefins. *J. Am. Chem. Soc.* **1991**, *113*, 726.

(29) See also: Corey, E. J.; Imai, N.; Zhang, H.-Y. Designed Catalyst for Enantioselective Diels-Alder Addition from a C_2-Symmetric Chiral *bis*(Oxazoline)-Iron(III) Complex. *J. Am. Chem. Soc.* **1991**, *113*, 729.

(30) For reviews on chiral semicorrin and *bis*oxazoline ligands, see: (a) Pfaltz, A. Chiral Semicorrins and Related Nitrogen Heterocycles as Ligands in Asymmetric Catalysis. *Acc. Chem. Res.* **1993**, *26*, 339. (b) Johnson, J. S.; Evans, D. A. Chiral *bis*(oxazoline) Copper(II) Complexes: Versatile Catalysts for Enantioselective Cycloaddition, Aldol, Michael and Carbonyl Ene Reactions. *Acc. Chem. Res.* **2000**, *33*, 325.

synthesis.[31] For example, in 1997 Evans and co-workers employed a *bis*oxazoline copper(II) complex to catalyze an asymmetric Diels-Alder reaction which was a key-step in the enantioselective synthesis of *ent*-Δ^1-tetrahydrocannabinol **47**.[32] Evans and co-worker's retrosynthetic analysis of *ent*-Δ^1-tetrahydrocannabinol **47** revealed that it could be synthesized from the chiral nonracemic allylic alcohol **48** and olivetol **49** (Figure 1.5.3.).



ent-Δ^1-tetrahydrocannabinol **47** **48** **49**

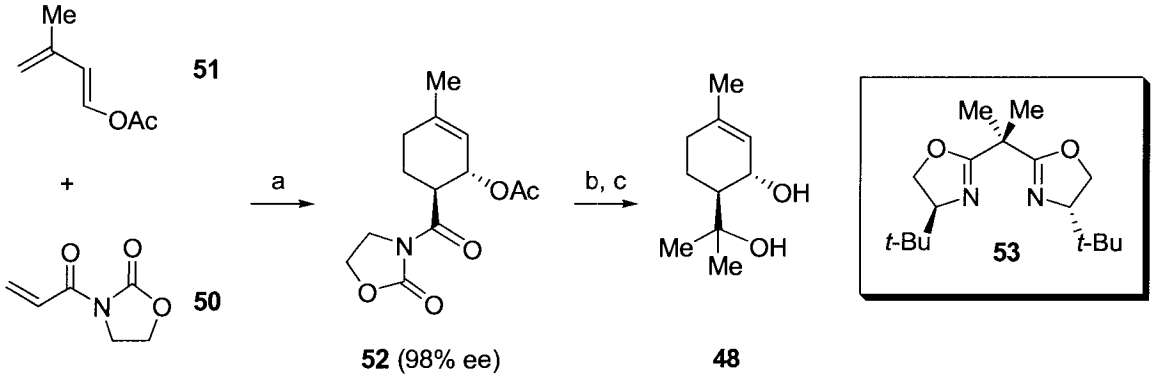
Figure 1.5.3. Evans and co-worker's retrosynthetic analysis of *ent*-Δ^1-tetrahydrocannabinol **47**.

An enantioselective Diels-Alder reaction of the oxazolidinone **50** and (*E*)-3-methyl-buta-1,3-dienylacetate **51** catalyzed by the complex formed between 2 mol % of the chiral *bis*oxazoline ligand **53** and 2 mol % of copper(II) hexafluoroantimonate afforded the allylic acetate **52** in high enantiomeric excess (98%). Treatment of this compound with lithium benzoate followed by six equivalents of methyl magnesium bromide afforded the required chiral nonracemic allylic alcohol **48** (Scheme 1.5.2.).

(31) Taylor, M. S.; Jacobsen, E. N. Asymmetric Catalysis in Complex Target Synthesis. *Proc. Nat. Acad. Sci.* **2004**, *101*, 5368.

(32) Evans, D. A.; Shaughnessy, E. A.; Barnes, D. Cationic *bis*(oxazoline)Cu(II) Lewis Acid Catalysts. Applications to the Asymmetric Synthesis of *ent*-Δ^1-Tetrahydrocannabinol. *Tetrahedron Lett.* **1997**, *38*, 3193.

Scheme 1.5.2. Evans and Co-worker's Asymmetric Synthesis of the Key Intermediate **48** used in the Synthesis of *ent*-Δ^1-Tetrahydrocannabinol **47** (1997)



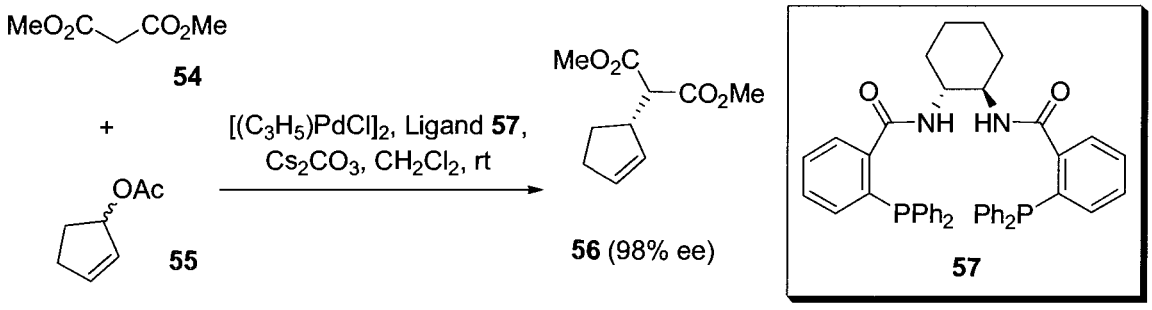
Reagents and conditions: (a) 2 mol % *bis*oxazoline ligand **53**, 2 mol % $Cu(SbF_6)_2$, - 20 °C, 18 h, 57%; (b) LiOBn, THF, - 20 °C, 3 h, 82%; (c) MeMgBr (6.0 equiv), ether 0 °C, 2 h, 80%.

Trost and co-workers C_2-symmetric bidentate diphosphine ligand **57** derived from chiral nonracemic *trans*-1,2-diaminocyclohexane has been shown to be an excellent ligand for palladium-catalyzed allylic substitution reactions.[33] An illustrative example is the catalytic asymmetric allylic substitution reaction of racemic 3-acetoxycyclopentene **55** with the cesium anion of dimethyl malonate **54** which afforded the chiral cyclopentene derivative **56** in excellent enantiomeric excess (98%) (Scheme 1.5.3.).[34]

(33) For reviews on the palladium-catalyzed asymmetric allylic substitution reaction, see: (a) Trost, B. M. Asymmetric Allylic Alkylation, an Enabling Methodology. *J. Org. Chem.* **2004**, *69*, 5813. (b) Trost, B. M. Asymmetric Transition Metal-Catalyzed Allylic Alkylations. *Chem. Rev.* **1996**, *96*, 395.

(34) Trost, B. M.; Bunt, R. C. Asymmetric Induction in Allylic Alkylations of 3-(Acyloxy)cyclopentenes. *J. Am. Chem. Soc.* **1994**, *116*, 4089.

Scheme 1.5.3. Trost and Co-worker's Palladium-Catalyzed Asymmetric Allylic Substitution Reaction (1994)



1.6. Asymmetric Organocatalysis

One of the most exciting developments in the field of catalytic asymmetric synthesis in recent years is "asymmetric organocatalysis" which concerns the acceleration of an asymmetric chemical reaction with a substoichiometric amount of a chiral nonracemic organic compound that does not contain a metal ion.[35] Research in the field of asymmetric organocatalysis has been driven by the problem of removal of traces of metal contaminants from reaction products, the high costs of some transition metal catalysts such as palladium and rhodium as well as the potential ability to use substrates that contain unprotected functional groups such as alcohols and carboxylic acids in catalytic asymmetric synthesis.

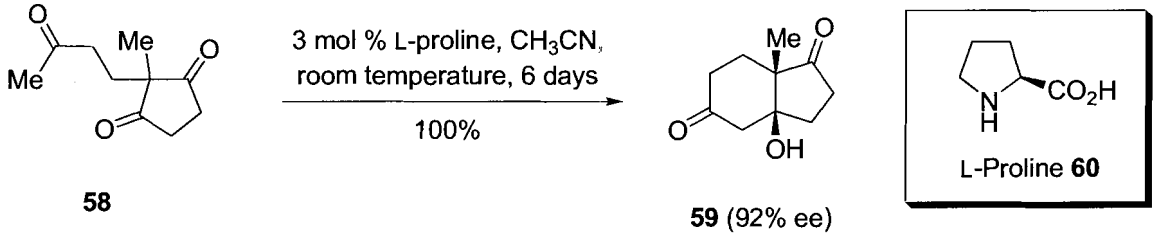
In 1974, Hajos and Parish demonstrated that L-proline **60** was a highly effective catalyst for the intramolecular aldol reaction of the triketone **58** that afforded the bicyclic product **59** in high enantiomeric excess (92%) (Scheme 1.6.1.).[36]

---

(35) For reviews on asymmetric organocatalysis, see: (a) Dalko, P. I.; Moisan, L. In the Golden Age of Organocatalysis. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (b) Special Issue: Asymmetric Organocatalysis. *Acc. Chem. Res.* **2004**, *37*, pp 487-631.

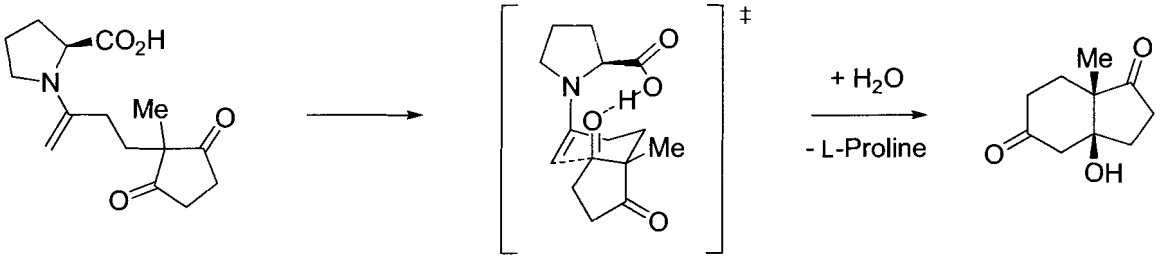
(36) Hajos, Z. G.; Parrish, D. R. Asymmetric Synthesis of Bicyclic Intermediates of Natural Product Chemistry. *J. Org. Chem.* **1974**, *39*, 1615.

Scheme 1.6.1. L-Proline Catalyzed Asymmetric Intramolecular Aldol Reaction (1974)



58 **59** (92% ee)

Bahmanyar and Houk have postulated, based upon computational studies, that L-proline **60** acts as a bifunctional catalyst in intra- and intermolecular aldol condensation reactions.[37] In the proposed mechanism, L-proline **60** undergoes a condensation reaction with the donor ketone **58** to afford the enamine **61** (Figure 1.6.1.). The enamine **61** then adds nucleophilically *via* a "chair-like" transition state **62** to the acceptor carbonyl which is activated by the formation of an intramolecular hydrogen bond interaction with the carboxylate moiety of L-proline.



61 **62** **60**

Figure 1.6.1. Bahmanyar and Houk's proposed transition state for the L-proline-catalyzed asymmetric aldol reaction.

Only recently has the potential of L-proline been more fully appreciated and it has been used to catalyze a variety of asymmetric reactions with high enantioselectivities.

(37) (a) Cannizzaro, C. E.; Houk, K. N. Magnitudes and Chemical Consequences of R_3N^+-C-H···O=C Hydrogen Bonding. *J. Am. Chem. Soc.* **2002**, *124*, 7163. (b) Bahmanyar, S.; Houk, K. N.; Martin, H. J.; List, B. Quantum Mechanical Predictions of the Stereoselectivities of Proline-Catalyzed Asymmetric Intermolecular Aldol Reactions. *J. Am. Chem. Soc.* **2003**, *125*, 2475.

These reactions include intra- and inter-molecular aldol reactions,[38] Mannich reactions,[39] α-amination reactions[40] and conjugate addition reactions.[41]

MacMillan and co-workers have recently developed a new strategy for asymmetric organocatalysis based on the activation of α,β-unsaturated carbonyl compounds *via* the reversible formation of iminium ions with a chiral nonracemic secondary amine catalyst. For example, in the presence of 5 mol % of the chiral amine **65**, the Diels-Alder reaction of cyclopentadiene and substituted α,β-unsaturated aldehydes **63** afforded the cycloadducts *exo*-**64** and *endo*-**64** in high enantiomeric excess (84-93%) (Scheme 1.6.2.).[42]

---

(38) (a) Córdova, A.; Notz, W.; Barbas III, C. F. Direct Organocatalytic Aldol Reactions in Buffered Aqueous Media. *Chem. Commun.* **2002**, 3024. (b) Córdova, A.; Notz, W.; Barbas III, C. F. Proline-Catalyzed One-Step Asymmetric Synthesis of 5-Hydroxy-(2*E*)-hexenal from Acetaldehyde. *J. Org. Chem.* **2002**, *67*, 301.

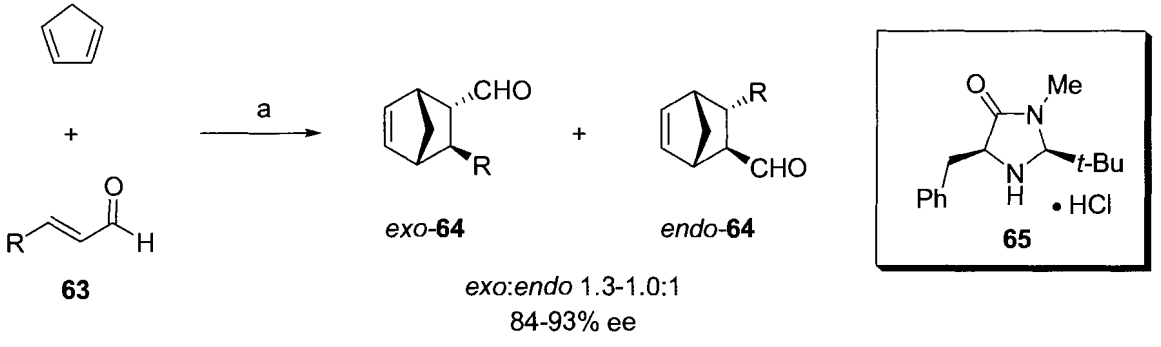
(39) Córdova, A. The Direct Catalytic Asymmetric Mannich Reaction. *Acc. Chem. Res.* **2004**, *37*, 102. (b) List, B. The Direct Catalytic Asymmetric Three-Component Mannich Reaction. *J. Am. Chem. Soc.* **2000**, *122*, 9336. (c) List, B.; Pojarliev. P.; Biller, W. T.; Martin, H. J. The Proline-Catalyzed Direct Asymmetric Three-Component Mannich Reaction: Scope, Optimization and Application to the Highly Enantioselective Synthesis of 1,2-Aminoalcohols. *J. Am. Chem. Soc.* **2002**, *124*, 827.

(40) (a) List, B. Direct Catalytic Asymmetric α-Amination of Aldehydes. *J. Am. Chem. Soc.* **2002**, *124*, 5656. (b) Kumaragurubaran, N.; Juhl, K.; Zhuang, W.; Bøgevig, A.; Jørgensen, K. A. Direct L-Proline Catalyzed Asymmetric α-Amination of Ketones. *J. Am. Chem. Soc.* **2002**, *124*, 6254.

(41) (a) Sakthivel, K.; Notz, W.; Bui, T.; Barbas III, C. F. Amino Acid Catalyzed Direct Asymmetric Aldol Reactions: A Bioorganic Approach to Catalytic Asymmetric Carbon-Carbon Bond Forming Reactions. *J. Am. Chem. Soc.* **2001**, *123*, 5260. (b) Betancort, J. M.; Barbas III, C. F. Catalytic Direct Asymmetric Michael Reactions: Taming Naked Aldehyde Donors. *Org. Lett.* **2001**, *3*, 3737.

(42) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. New Strategies for Organic Synthesis: The First Highly Enantioselective Organocatalytic Diels-Alder Reaction. *J. Am. Chem. Soc.* **2000**, *122*, 4243.

Scheme 1.6.2. Chiral Amine-Catalyzed Asymmetric Diels-Alder Reaction (2000)



Reagents and conditions: (a) 5 mol % **65**, MeOH/H_2O (95:5), room temperature.

MacMillan and co-workers have postulated that the reaction proceeds *via* the formation of a chiral iminium ion **66** between the chiral amine catalyst **65** and the α,β-unsaturated aldehyde substrate **63** that lowers the energy of the LUMO relative to that of the achiral α,β-unsaturated aldehyde (Figure 1.6.2.).

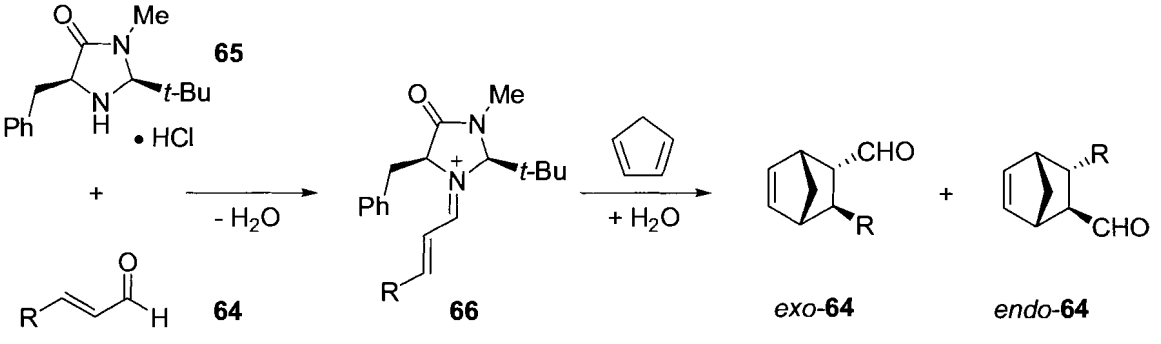


Figure 1.6.2. Diels-Alder reaction proceeds *via* the formation of a chiral iminium ion **66** between the chiral amine catalyst **65** and the α,β-unsaturated aldehyde substrate **63**.

MacMillan and co-workers have subsequently used their chiral amine catalyst **65** and related chiral amines to catalyze a variety of highly enantioselective asymmetric reactions such as Friedel-Crafts alkylation reactions,[43] Mukaiyama-Michael reactions,[44] α-chlorination of aldehydes,[45] and hydride reductions.[46]

(43) Paras, N. A.; MacMillan, D. W. C. New Strategies in Organic Catalysis: The First Asymmetric Organocatalytic Friedel-Crafts Alkylation. *J. Am. Chem. Soc.* **2001**, *123*, 4370.

1.7. Chiral Cyclic Acetals in Asymmetric Synthesis

We are currently involved in a research program that has concerned the design and synthesis of novel chiral auxiliaries, ligands and catalysts that incorporate chiral cyclic acetals as an element of chirality. This structural motif is the basis of the design concept employed in the research project described in this thesis. In this section an introduction to the use of chiral cyclic acetals in asymmetric synthesis is outlined.

Cyclic acetals can be formed by a simple acid-catalyzed condensation reaction of an aldehyde or ketone with a 1,2- or 1,3-diol. The resultant acetals are stable under a variety of reaction conditions and have thus found considerable use as common protecting groups for carbonyl moieties.

More recently, chiral cyclic acetals have been applied in asymmetric synthesis for the preparation of a variety of chiral nonracemic products.[47,48] For example, in the

---

(44) Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. C. The First Enantioselective Organocatalytic Mukaiyama-Michael Reaction: A Direct Method for the Synthesis of Enantioenriched γ-Butenolide Architecture. *J. Am. Chem. Soc.* **2003**, *125*, 1192.

(45) Brochu, M. P.; Brown, S. P.; MacMillan, D. W. C. The Direct Enantioselective Organocatalytic α-Chlorination of Aldehydes. *J. Am. Chem. Soc.* **2004**, *126*, 4108.

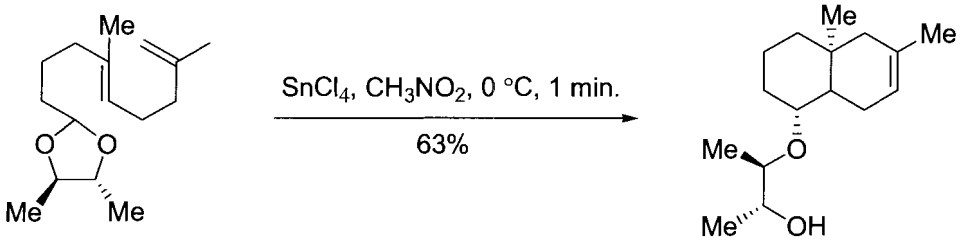
(46) Ouellet, S. G.; Tuttle, J. B.; MacMillan, D. W. C. Enantioselective Organocatalytic Hydride Reduction. *J. Am. Chem. Soc.* **2005**, *127*, 32.

(47) (a) Alibés, R.; Busquè, F.; de March P.; Figueredo, M.; Font, J.; Gambino, M. E.; Keay, B. A. Acetals of γ-Oxo-α,β-unsaturated Esters in Nitrone Cycloadditions. Regio- and Stereo-chemical Implications. *Tetrahedron*: *Asymmetry* **2001**, *12*, 1747. (b) Cossy J.; BouzBouz, S. A Short Access to (+)-Ptilocaulin. *Tetrahedron Lett.* **1996**, *37*, 5091. (c) Alexakis, A.; Mangeney, P. Chiral Acetals in Asymmetric Synthesis. *Tetrahedron*: *Asymmetry* **1990**, *1*, 477.

(48) For reviews on the applications of two prominent classes of chiral acetals (Seebach's TADDOLs and Ley's 1,2-diacetals) in asymmetric synthesis, see: (a) Seebach, D.; Beck, A. K.; Heckel, A. TADDOLs, Their Derivatives, and TADDOL Analogues: Versatile Chiral Auxiliaries. *Angew. Chem., Int. Ed.* **2001**, *40*, 92. (b) Ley, S. V.; Baeschlin, D. K.; Dixon, D. J.; Foster, A. C.; Ince, S. J.; Priepke, H. W. M.; Reynolds, D. J. 1,2-Diacetals: A New Opportunity for Organic Synthesis. *Chem. Rev.* **2001**, *101*, 53.

presence of strong Lewis acids, the ring of chiral cyclic acetals can be opened with nucleophiles. For instance, Johnson and co-workers have reported the intramolecular cationic cyclization reaction of the chiral nonracemic acetal **67** in the presence of tin tetrachloride which afforded the bicyclic compound **68** in good diastereoselectivity (85% de) (Scheme 1.7.1.).[49]

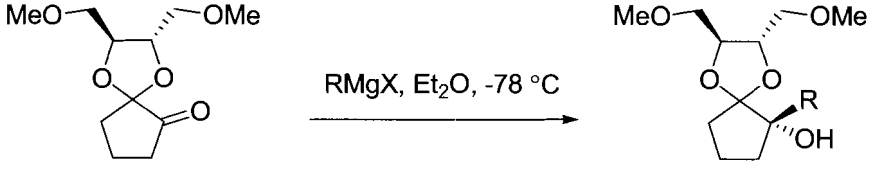
Scheme 1.7.1. Intramolecular Stereoselective Ring-Opening Reaction of the Chiral Acetal **67**.



67 **68** (85% de)

Chiral cyclic acetals have been installed in close proximity to prochiral centres to direct subsequent substrate-controlled asymmetric reactions. For example, the addition of Grignard reagents to the chiral cyclic acetal **69** afforded the chiral alcohols **70** in high diastereoselectivity (>90% de) (Scheme 1.7.2.).[50]

Scheme 1.7.2. A Chiral Cyclic Acetal as a Chiral Auxiliary for the Addition of Grignard Reagents to Ketones



69 **70** (>90% ee)

(49) Johnson, W. S. Biomimetic Polyene Cyclizations. *Angew. Chem., Int. Ed.* **1976**, *15*, 9

(50) Tamura, Y.; Kondo, H.; Annoura, H.; Takeuchi, R.; Fujioka, F. Diastereoselective Nucleophilic Addition to Chiral Open-Chain α-Ketoacetals: Synthesis of (*R*)- and (*S*)-Mevalolactone. *Tetrahedron Lett.* **1986**, *27*, 2117.

The relatively rigid nature of chiral cyclic acetals is a key feature in regard to their use as chiral directors.[51] The acetal subunit has the ability to restrict the conformational flexibility within a substrate or reagent and thus can reduce the number of competing diastereoisomeric transition states in an asymmetric reaction.

Our research program has involved the design and synthesis of novel chiral auxiliaries, ligands and catalysts that incorporate cyclic acetals as chiral directors. The general concept involves using the achiral parent ketones **72** and chiral nonracemic C_2-symmetric 1,2-diols **73** to synthesize, in a modular fashion, a structurally diverse series of novel chiral auxiliaries, ligands and catalysts (Figure 1.7.1.).* The fused bicyclic acetals **71** incorporate a site (Z) at which a substrate could be attached in the case of a chiral auxiliary or to which a metal could bind in the case of a chiral ligand as well as a reaction site in the case of a chiral catalyst.

(51) Mulzer, J.; Altenback, H.-J.; Braun, M.; Krohn, K.; Reissig, H.-U. In *Organic Synthesis Highlights*, Wiley-VCH, Weinheim, 1991, p 19.

(*) Modular: to be constructed with common units allowing flexibility and variety in use.

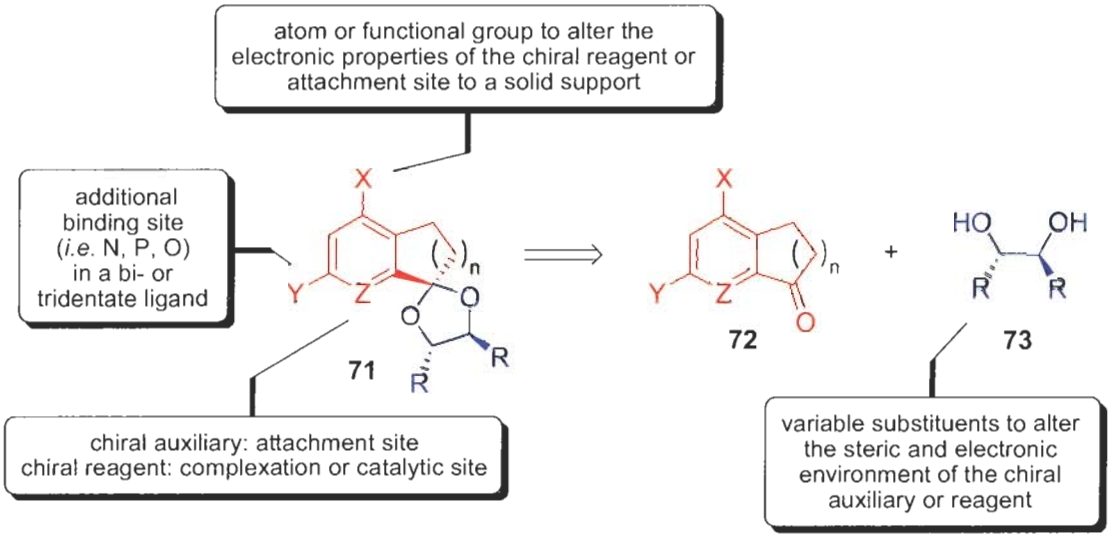
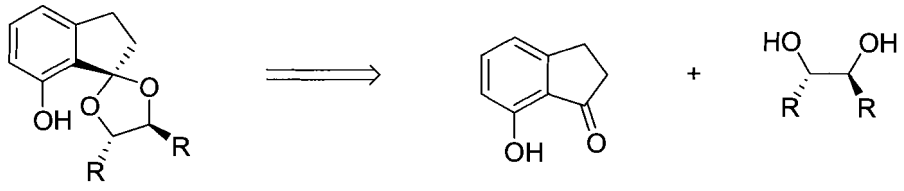


Figure 1.7.1. General concept for the modular synthesis of structurally diverse chiral auxiliaries, ligands and catalysts from the achiral ketones **72** and chiral nonracemic C_2-symmetric 1,2-diols **73**.

The use of C_2-symmetric diols ensures that only a single diastereoisomer of the acetals **71** is formed upon condensation. Moreover, one of the substituents (R) of the orthogonally fused acetal moiety blocks one of the diastereotopic faces of these molecules. The steric and electronic properties of the auxiliary or reagent could be varied by condensing the ketone **72** with a variety of chiral nonracemic C_2-symmetric 1,2-diols **73**. The substituent (X) could also be modified to alter the electronic properties of these potential chiral directors and thus enable the optimization of the structure for a particular asymmetric reaction.

Narine and Wilson have demonstrated the potential of this concept by preparing and evaluating a series of 7-hydroxyindan-1-one derived chiral auxiliaries **74** (Figure

1.7.2.).[52] These structurally rigid chiral auxiliaries **74** [R = Me, *i*-Pr, Ph, CH_2OMe, CH_2OBn, $CH_2O(1\text{-Np})$] were synthesized in a convergent manner from readily available 7-hydroxyindan-1-one **75** and a series of corresponding chiral nonracemic C_2-symmetric 1,2-diols **73**.

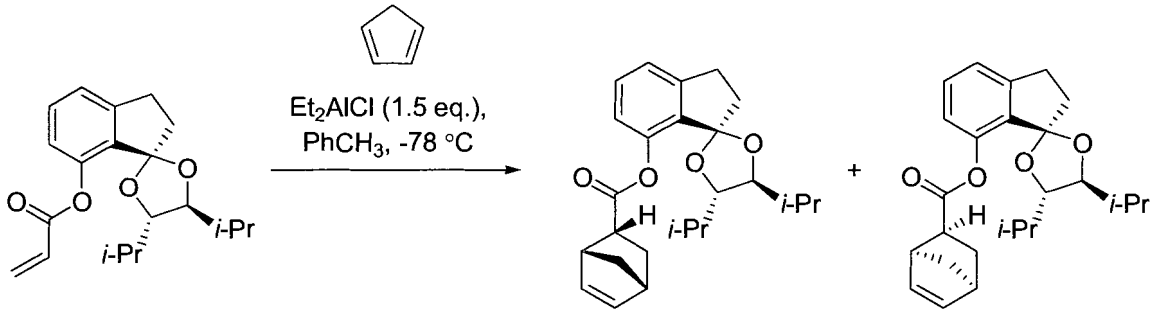


74 **75** **73**

Figure 1.7.2. 7-Hydroxyindan-1-one derived chiral auxiliaries **74**.

In the case of the acrylate derivative of the 7-hydroxyindan-1-one derived chiral auxiliary **76** (R = *i*-Pr), a high degree of stereochemical induction was observed in a diethylaluminum chloride-promoted Diels-Alder reaction with cyclopentadiene (dr = 91:9) (Scheme 1.7.3.).

Scheme 1.7.3. Diethylaluminum Chloride-Promoted Diels-Alder Reaction

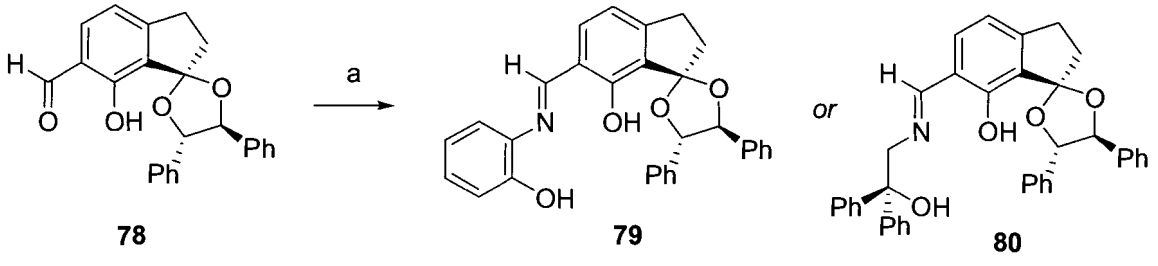


76 **77** (91:9 dr)

(52) Narine, A. A.; Wilson, P. D. Synthesis and Evaluation of 7-Hydroxyindan-1-one-Derived Chiral Auxiliaries. *Can J. Chem.* **2005**, *83*, 413.

Narine has also described the preparation of a series of related 7-hydroxyindan-1-one derived chiral ligands **79** and **80**.[53] These ligands were elaborated from the chiral auxiliary **74** by *ortho*-formylation to afford the chiral salicylaldehyde **78** which was subsequently condensed with 2-aminophenol or 1,1-diphenyl-2-aminoethanol to provide the chiral tridentate ligands **79** and **80** (Scheme 1.7.4.). These ligands were evaluated in vanadium(III)-catalyzed asymmetric sulfur oxidation reactions. However, in this case, low enantioselectivities were obtained.

Scheme 1.7.4. Synthesis of the Chiral Tridentate Ligands **79** and **80**



78 **79** **80**

Reagents and conditions: (a) 2-aminophenol, EtOH, room temperature, 18 h, 97% *or* 1,1-diphenyl-2-aminoethanol, EtOH, room temperature, 18 h, 96%.

1.8. Proposed Studies

The goal of this research project was to synthesize heterocyclic analogues **81** of the general structure **71** (Figure 1.8.1.). These analogues would then be further elaborated to provide a structurally diverse group of chiral ligands and catalysts for evaluation in catalytic asymmetric reactions. In this case, the analogues **81** contain a nitrogen atom as a binding site for a transition metal. The substituent (X) could be altered to tune the electronic properties of the ligand or catalyst. Alternatively, the substituent could be selected to facilitate the synthesis of the target compounds. The

(53) Narine, A. A. Design, Synthesis and Evaluation of Chiral Auxiliaries, Ligands and Catalysts for Asymmetric Synthesis. *Ph. D. Thesis, Simon Fraser University*, **2004**.

chlorine atom, at C-2 (the position of the substituent, Y), could act as a reaction site for further elaboration of these heterocyclic compounds to a series of ligands and catalysts.

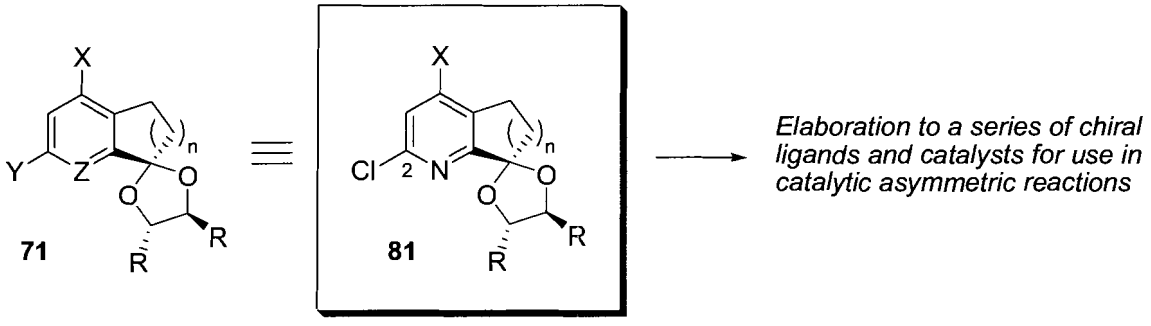


Figure 1.8.1. Heterocyclic analogues **81** of the general design structure **71**.

Retrosynthetic analysis of a proposed new class of chiral nonracemic C_2-symmetric 2,2′-bipyridyl ligands **82** is shown below (Figure 1.8.2.). These ligands should be available from the chiral nonracemic 2-chloropyridines **81** *via* a *homo*-coupling reaction. The chiral 2-chloropyridines **81** should in turn be available from the ketone **83** and a series of chiral nonracemic C_2-symmetric 1,2-diols **73**.

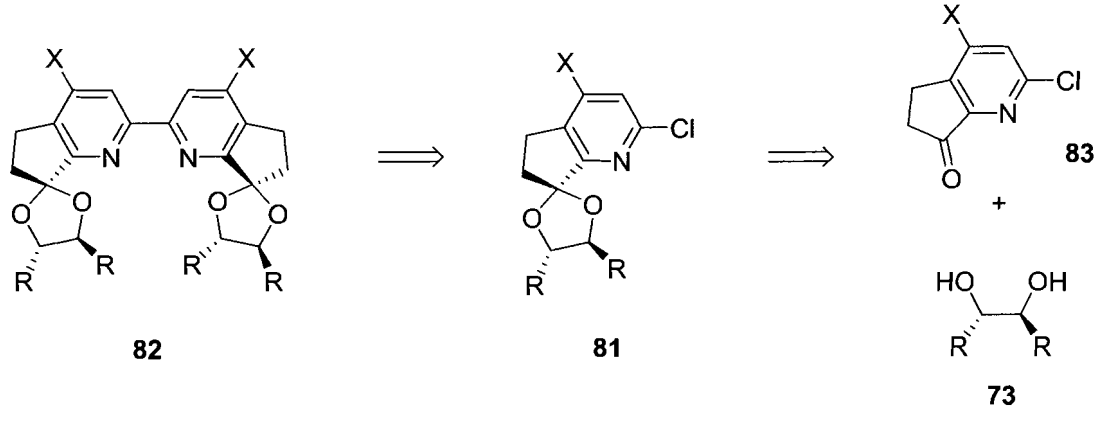
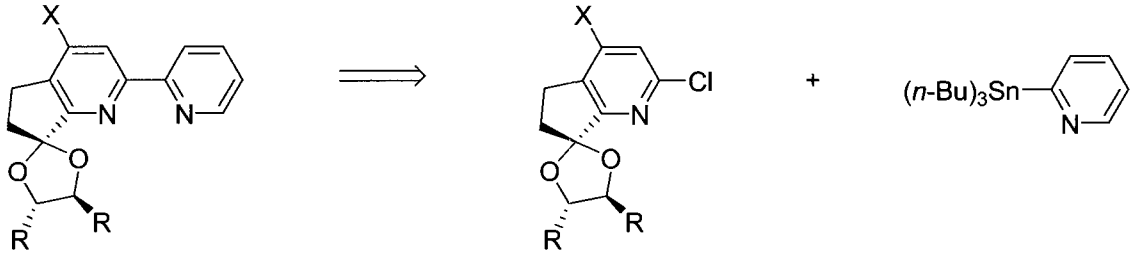


Figure 1.8.2. Retrosynthetic analysis of the new chiral nonracemic C_2-symmetric 2,2′-bipyridyl ligands **82**.

In a similar fashion, we proposed to synthesize and evaluate a series of corresponding chiral nonracemic and unsymmetric 2,2′-bipyridyl ligands **84**. These

ligands would be available by coupling the chiral nonracemic 2-chloropyridines **81** with the known 2-tri-*n*-butylstannylpyridine **85** (Figure 1.8.3.).[54]



84 **81** **85**

Figure 1.8.3. Retrosynthetic analysis of the chiral nonracemic unsymmetric 2,2′-bipyridyl ligands **84**.

Furthermore, the chiral pyridine *N*-oxide **86** and the 2,2′-bipyridyl *N,N′*-dioxide **87** could be synthesized by direct oxidation of the corresponding pyridines **71** and 2,2′-bipyridines **82**, respectively.

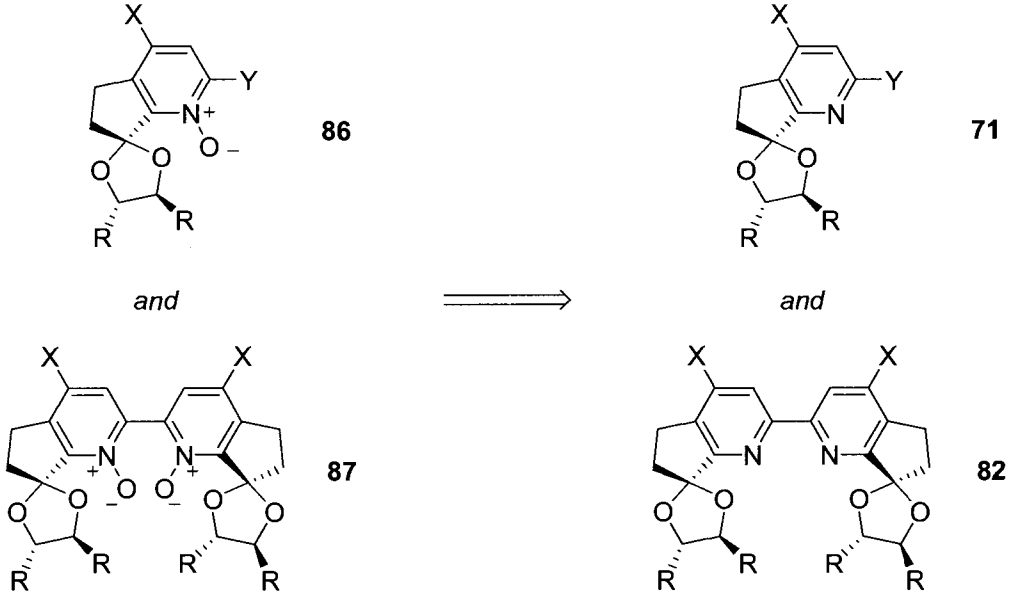
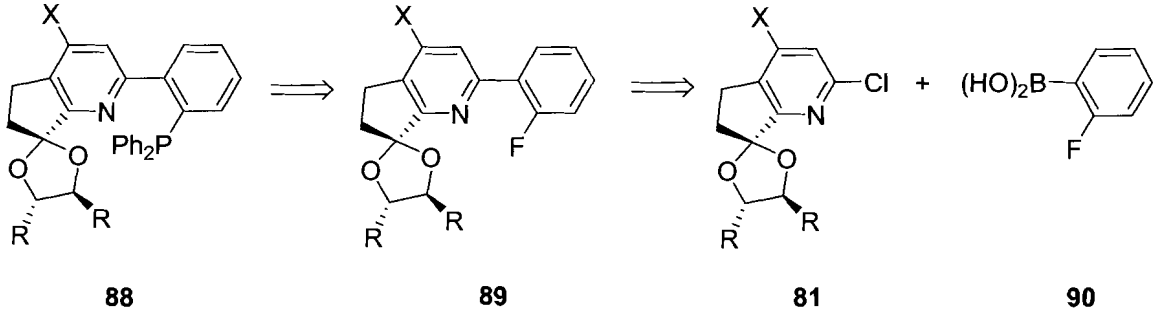


Figure 1.8.4. Retrosynthetic analysis of the chiral nonracemic pyridine *N*-oxides **86** and **87**.

(54) McWhinnie, W. R.; Poller, R. C.; Thevarasa, M. An Inclusion Compound from Hexaphenylditin and Tetraphenylditin. *J. Organomet. Chem.* **1968**, *11*, 499.

In order to further demonstrate the modular nature of our synthetic design, we also proposed to synthesize and evaluate a series of chiral nonracemic pyridylphosphine ligands **88**. These *P,N*-ligands should be available from the 2-chloropyridines **81** *via* a coupling reaction with *ortho*-fluorophenylboronic acid **90** to afford the corresponding fluorobiaryl compounds **89** followed by subsequent installation of the diphenylphosphino moiety by the displacement of the fluoride atom with the anion of diphenylphosphine (Figure 1.8.5.).



88 **89** **81** **90**

Figure 1.8.5. Retrosynthetic analysis of the chiral nonracemic pyridylphosphine ligands **88**.

An alternative strategy based on a subtle structural modification of the chiral cyclic acetal moiety was also considered. We proposed to synthesize and evaluate a series of related chiral nonracemic C_2-symmetric 2,2′-bipyridyl ligands **91**. We envisioned the synthesis of these 2,2′-bipyridyl ligands *via* an asymmetric dihydroxylation reaction of the 2-chloropyrindine **94** followed by condensation of the resultant diol **92** with a symmetrical ketone **93** (Figure 1.8.6.). The required 2-chloropyrindine **94** could in principle be prepared from a common intermediate used in the synthesis of the 2-chloroketone **83** (see: Scheme 1.8.2.). In contrast to the ligands and catalysts described above which would require the synthesis of an achiral heterocyclic ketone **83**, this ligand would require the synthesis of the chiral nonracemic heterocyclic diol **92**.

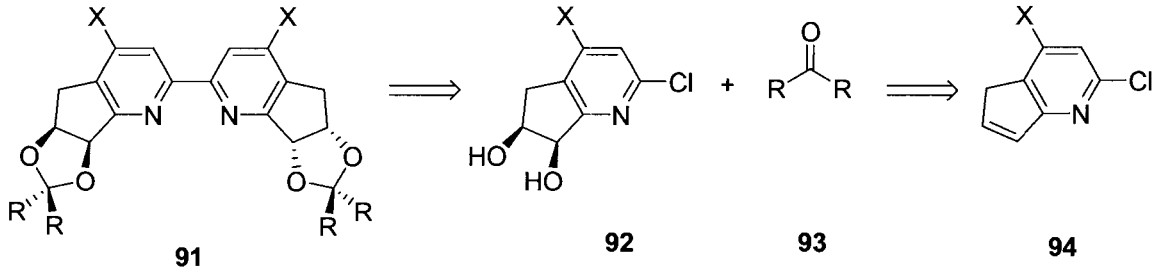


Figure 1.8.6. Retrosynthetic analysis of a related chiral nonracemic C_2-symmetric 2,2′-bipyridyl ligand **91**.

We considered that the chiral nonracemic C_2-symmetric 2,2′-bipyridyl ligands **82**, **84** and **91** could offer some advantages over the chiral *bis*oxazoline ligands that have been used successfully in many asymmetric transformations. In particular, the rigid structure provided by the chiral cyclic acetal moiety would create a sterically "well-defined" binding pocket around the transition metal centre. Moreover, we could make structural modifications to the 2,2′-bipyridyl ligands by simply condensing the ketone **83** with a variety of chiral 1,2-diols **73** or conversely by condensing the chiral diol **92** with a variety of achiral ketones **93**.

The following section concerns a brief literature review of the syntheses and reactions of chiral nonracemic 2,2′-bipyridyl ligands, pyridine *N*-oxides and pyridylphosphine ligands that relate to the results of the research described in this thesis.

1.9. Chiral Nonracemic 2,2′-Bipyridyl Ligands: Syntheses and Reactions

Of the many types of chiral ligands that have been developed for catalytic asymmetric synthesis, chiral nonracemic 2,2′-bipyridines and 1,10-phenanthrolines have

received considerable attention.[55,56] The 2,2′-bipyridine unit offers the potential for a broad range of structural modifications that include the incorporation of stereogenic centres as well as elements of planar and axial chirality. In addition, the electronic properties of this type of ligand may be adjusted by appropriate functionalization of the pyridine moieties. This class of bidentate ligands, as mentioned earlier, complements the prominent class of chiral ligands, the *bis*oxazolines that have been employed with a great degree of success in many asymmetric transformations.[57]

This section is divided into subsections that include brief reviews of 2,2′-bipyridyl ligands with stereogenic centres, 2,2′-bipyridyl ligands with axial chirality and 2,2′-bipyridyl ligands with planar chirality. A review of the common reaction types that these ligands have been employed in is also presented.

---

(55) (a) Malkov, A. V.; Kočovský, P. Chiral Bipyridine Derivatives in Asymmetric Catalysis. *Curr. Org. Chem.* **2003**, *7*, 1737. (b) Chelucci, G.; Thummel, R. P. Chiral 2,2′-Bipyridines, 1,10-Phenanthrolines, and 2,2′:6′,2′′-Terpyridines: Synthesis and Applications in Asymmetric Homogenous Catalysis. *Chem. Rev.* **2002**, *102*, 3129. (c) Fletcher, N. C. Chiral 2,2-Bipyridines: Ligands for Asymmetric Induction. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1831.

(56) (a) Reedijk, J. In *Comprehensive Coordination Chemistry*; Wilkinson, G., Gillard, R. D., McCleverty, J. A., Eds; Pergamon Press: Oxford, 1987; Vol. 2, pp 73-98. (b) Kaes, C.; Katz, A.; Hosseini, M. W. Bipyridine: The Most Widely Used Ligand. A Review of Molecules Containing at Least Two 2,2′-Bipyridine Units. *Chem. Rev.* **2000**, *100*, 3553.

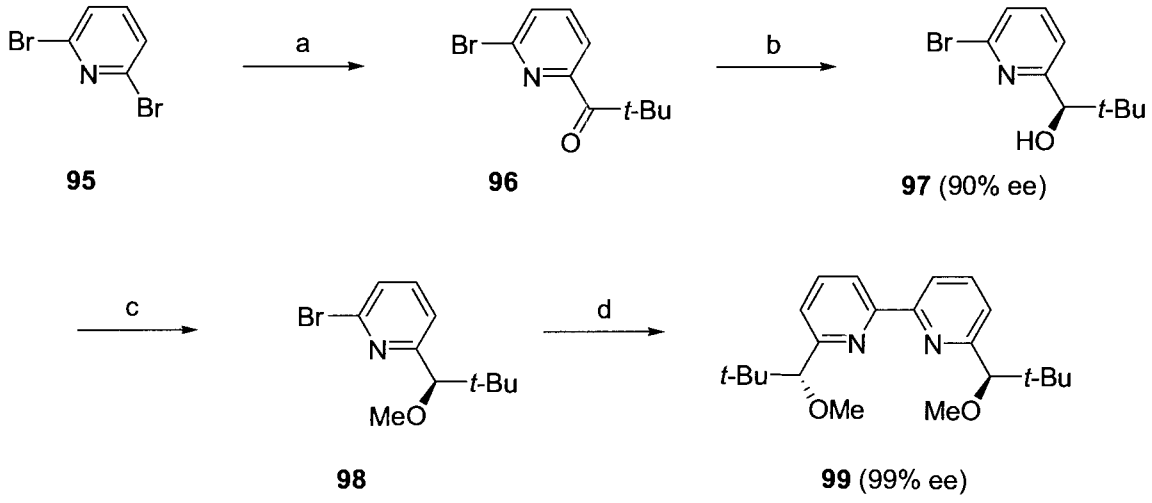
(57) For a recent review on chiral *bis*oxazolines in asymmetric transition metal catalyzed reactions, see for example: Johnson, J. S.; Evans, D. A. Chiral *bis*(oxazoline) Copper(II) Complexes: Versatile Catalysts for Enantioselective Cycloaddition, Aldol, Michael and Carbonyl Ene Reactions. *Acc. Chem. Res.* **2000**, *33*, 325.

1.9.1. 2,2′-Bipyridines with Stereogenic Centres

In 1990, Bolm and co-workers reported the synthesis of the chiral nonracemic C_2-symmetric 2,2′-bipyridyl ligand **99** (Scheme 1.9.1.).[58] The synthesis of this ligand began by monolithiation of 2,6-dibromopyridine **95** with *n*-butyllithium followed by condensation with methyl 2,2-dimethylpropionate that afforded the ketone **96** in 80% yield. Asymmetric reduction of the prochiral ketone **96** with (-)-*β*-chlorodiisopinocamphenylborane afforded the chiral alcohol **97** in high enantiomeric excess (90%). Following alkylation of the chiral alcohol **97** with methyl iodide, the chiral 2-bromopyridine **98** was subjected to a nickel(0)-mediated *homo*-coupling reaction that afforded the desired C_2-symmetric 2,2′-bipyridyl ligand **99** in 65% yield and in high enantiomeric excess (>99%).

(58) Bolm, C.; Zehnder, M.; Bur, D. Optically Active Bipyridines in Asymmetric Synthesis. *Angew. Chem., Int. Ed.* **1990**, *29*, 205.

Scheme 1.9.1. Bolm and Co-worker's Chiral Nonracemic C_2-Symmetric 2,2′-Bipyridyl Ligand **99** (1990)



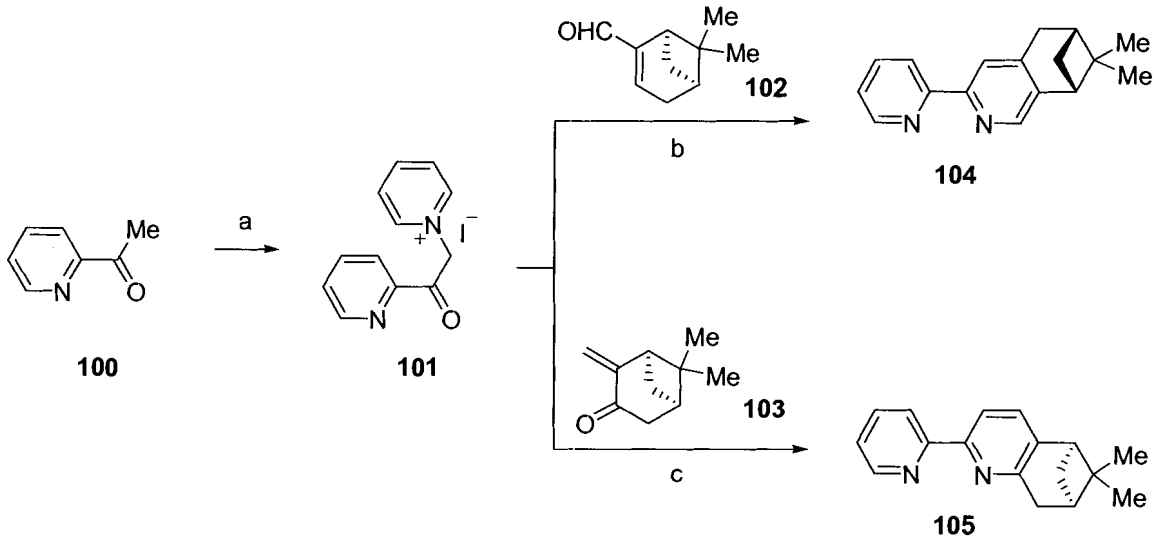
Reagents and conditions: (a) *n*-BuLi, THF, -78 °C; then *t*-$BuCO_2CH_3$, -78 °C to room temperature, 3 h 80%; (b) (-)-β-chlorodiisopinocamphenylborane (1.2 equiv), neat, room temperature, 2 days; then iminodiethanol (3.6 equiv), ether, 3 h, 59%; (c) NaH, CH_3I, THF, 0 °C to rt, 1.5 h, 85%; (d) $NiCl_2(H_2O)_6$ (1.2 equiv), Zn dust (1.3 equiv), PPh_3 (4.8 equiv), DMF, 72 °C, 3.5 h, 65%.

In 1992, von Zelewsky and co-workers reported a general approach to chiral nonracemic [4,5]- and [5,6]-cycloalkeno-fused 2,2′-bipyridyl ligands **104** and **105** that involved Kröhnke-type[59] condensation reactions of 2-acetylpyridinepyridinium iodide **101** with the terpene-derived α,β-unsaturated carbonyl compounds (-)-myrtenal **102** and (+)-pinocarvone **103** in the presence of ammonium acetate which afforded the chiral nonracemic 2,2′-bipyridyl ligands **104** and **105**, respectively (Scheme 1.9.2.).[60]

(59) Kröhnke, F. Neuere Methoden der Praparativen Organischen Chemie Synthesen mit hilfe von Pyridiniumsalzen. *Angew. Chem., Int. Ed.* **1963**, *2*, 386.

(60) Hayoz, P.; von Zelewsky, A. New Versatile Optically Active Bipyridines as Building Blocks for Helicating and Caging Ligands. *Tetrahedron Lett.* **1992**, *33*, 5165.

Scheme 1.9.2. von Zelewsky and Co-Worker's Chiral Nonracemic [4,5]- and [5,6]-Cycloalkeno-Fused 2,2′-Bipyridyl Ligands **104** and **105** (1992)



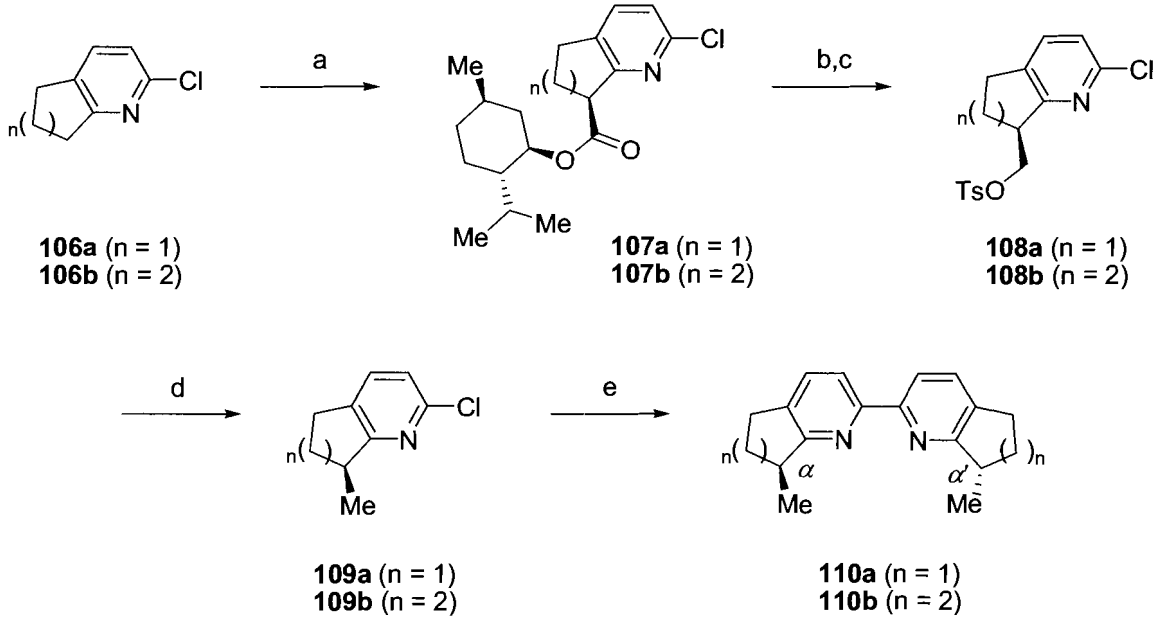
Reagents and conditions: (a) I_2, pyridine; (b) NH_4OAc, formamide, 100 °C, 12 h, 55% (c) NH_4OAc, formamide, 70 °C, 6 h, 75%.

Beginning in 1992, Katsuki and co-workers published a series of papers that described the syntheses of a number of chiral nonracemic C_2-symmetric 2,2′-bipyridyl ligands that contained [5,6]-cycloalkeno-fused bipyridine units with stereogenic centres at the α,α'-positions of the fused rings. In the first paper, they reported the syntheses of the α,α'-dimethyl substituted bipyridine ligands **110a,b** (Scheme 1.9.3.).[61] The syntheses began from the commercially available 2-chloropyridines **106a,b** that were deprotonated with lithium *N,N*-diisopropylamide and the resultant anions were subsequently condensed with (-)-menthyl chloroformate to afford the carbonates **107a,b** as mixtures of diastereoisomers. The more polar compound of each of the pairs of diastereoisomers, that had (*S*)-configuration at the newly established stereogenic centre, were isolated by

(61) Ito, K.; Tabuchi, S.; Katsuki, T. Synthesis of New Chiral Bipyridine Ligands and Their Application to Asymmetric Cyclopropanation. *Synlett* **1992**, 575.

flash chromatography and then converted to the tosylates **108a,b** by reduction with alane followed by treatment with tosyl chloride. The tosylates **108a,b** were then reduced with lithium triethylborohydride to afford the 2-chloropyridines **109a,b**. These compounds were then subjected to a nickel(0)-mediated *homo*-coupling reaction that afforded the chiral nonracemic C_2-symmetric 2,2′-bipyridyl ligands **110a,b**.

Scheme 1.9.3. Katsuki and Co-Worker's Chiral Nonracemic C_2-Symmetric 2,2′-Bipyridyl Ligands **110a,b** (1992)



106a (n = 1)
106b (n = 2)

107a (n = 1)
107b (n = 2)

108a (n = 1)
108b (n = 2)

109a (n = 1)
109b (n = 2)

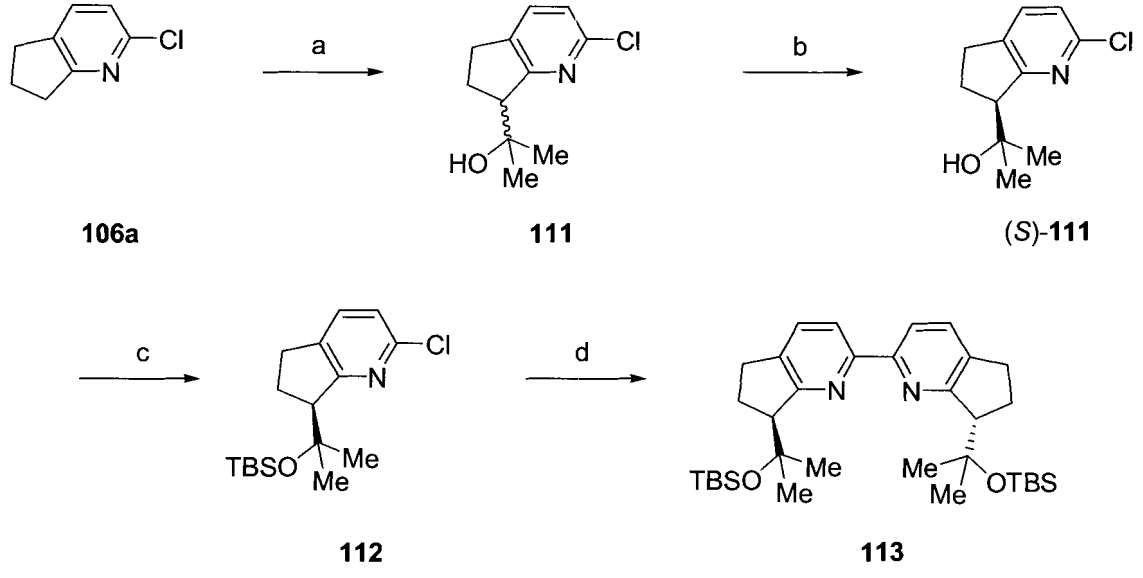
110a (n = 1)
110b (n = 2)

Reagents and conditions: (a) LDA, (-)-menthyl chloroformate, -78 °C, then chromatographic separation of the diastereoisomers, 43% (**107a**), 37% (**107b**); (b) AlH_3, THF; (c) TsCl, NEt_3, DMAP (cat.); (d) $LiBEt_3H$, THF; (e) $NiCl_2(H_2O)_6$, Zn dust, PPh_3, DMF, 47% (over four steps) (**110a**), 33% (over four steps) (**110b**).

Katsuki and co-workers subsequently reported the synthesis of a related 2,2′-bipyridine ligand **113** that contained larger substituents than methyl groups at the α and

α' positions (Scheme 1.9.4.).[62] The starting material was again the commercially available 2-chloropyridine **106a** which was deprotonated regioselectively with lithium *N*,*N*-diisopropylamide and the resultant anion was reacted with acetone to afford the racemic tertiary alcohol **111** which was then resolved by preparative chiral HPLC (Daicel Chiracel OF column). The tertiary alcohol that eluted first from the chiral column, which had (*S*) stereochemistry, was then reacted with *tert*-butyldimethylsilyl triflate. The resultant 2-chloropyridine **112** was then subjected to a nickel(0)-mediated *homo*-coupling reaction to afford the C_2-symmetric chiral nonracemic 2,2′-bipyridyl ligand **113**.

Scheme 1.9.4. Katsuki and Co-Worker's Chiral Nonracemic C_2-Symmetric 2,2′-Bipyridyl Ligand **113** (1994)



Reagents and conditions: (a) LDA, THF, -78 °C then acetone; (b) chiral HPLC resolution (Daicel Chiracel OF column); (c) TBSOTf, 2,6-lutidine; (d) $NiCl_2(H_2O)_6$, Zn dust, PPh_3, DMF.

In an effort to achieve a more efficient synthesis of the ligand **113** that would facilitate the preparation of this compound on a larger scale, Katsuki and co-workers have

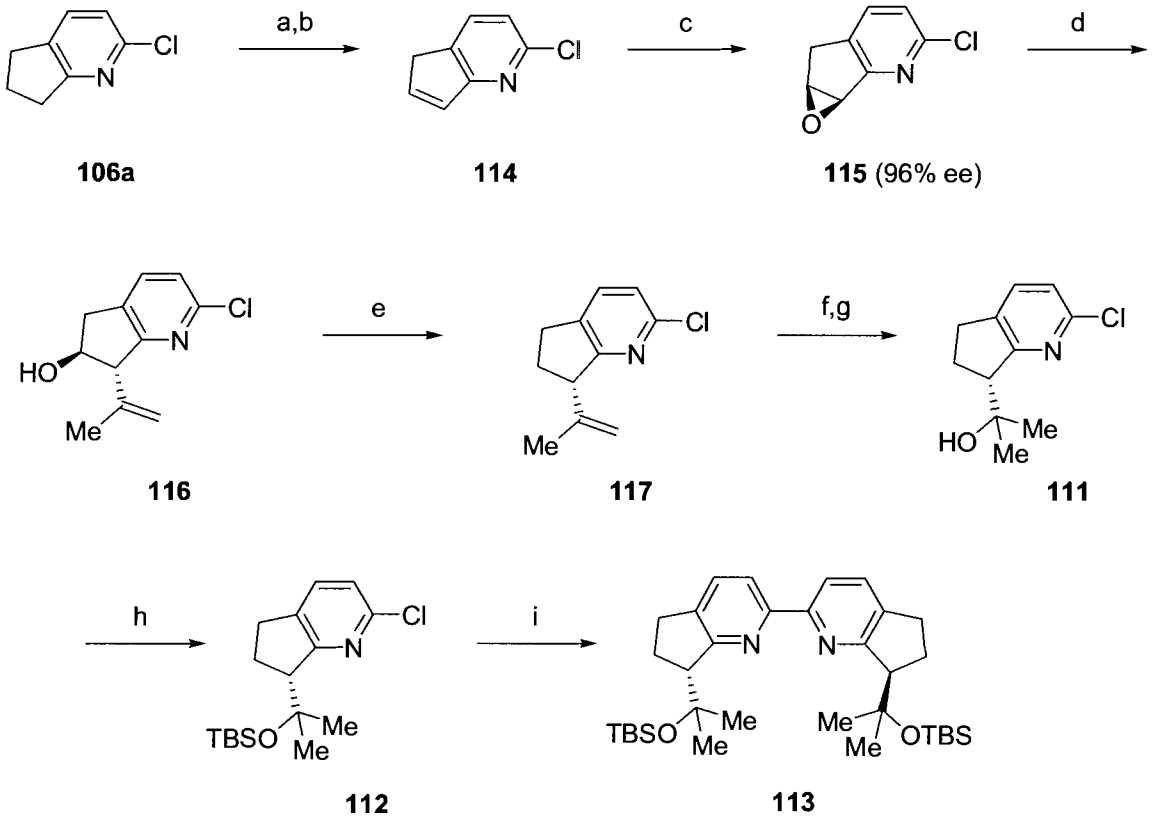
(62) Ito, K.; Katsuki, T. Synthesis of New Chiral Bipyridine Ligands and Their Application to Asymmetric Cyclopropanation. *Chem. Lett.* **1994**, 1857.

reported an asymmetric synthesis that did not rely on tedious resolution procedures (Scheme 1.9.5.).[63] The synthetic route began with the 2-chloropyridine **106a** which was deprotonated with lithium *N,N*-diisopropylamide and the resultant anion was reacted with diphenyldiselenide. The product of this reaction was then oxidized with hydrogen peroxide to the corresponding selenoxide that underwent elimination of phenylselenic acid and afforded the 2-chloropyrindine **114**. A subsequent manganese(III)-catalyzed asymmetric epoxidation reaction afforded the epoxide **115** in high enantiomeric excess (96%).[64] Treatment of this epoxide with 1-methylvinylcuprate provided the alcohol **116** as a single regioisomeric product. The alcohol **116** was then reacted with phenyl chlorothioformate in the presence of *N,N*-dimethyl-4-aminopyridine to afford the corresponding thiocarbonate. This compound was then reduced upon treatment with tri-*n*-butyltin hydride and triethylborane to afford the alkene **117**. The alkene **117** was then reacted with *m*-chloroperoxybenzoic acid and the resultant epoxide was in turn reacted with lithium triethylborohydride to afford the ring-opened tertiary alcohol **111**. This compound was then converted to the silylether **112** upon treatment with *tert*-butyldimethylsilyl triflate. A subsequent nickel(0)-mediated *homo*-coupling reaction afforded the C_2-symmetric chiral nonracemic 2,2′-bipyridyl ligand **113** in high enantiomeric excess (99.9%).

(63) Ito, K.; Yoshitake, M.; Katsuki, T. Chiral Bipyridine and Biquinoline Ligands: Their Asymmetric Synthesis and Application to the Synthesis of *trans*-Whisky Lactone. *Tetrahedron* **1996**, *52*, 3905.

(64) Fukuda, T.; Irie, R.; Katsuki, T. Mn-Salen Catalyzed Asymmetric Epoxidation of Conjugated Trisubstituted Olefins. *Synlett* **1995**, 197.

Scheme 1.9.5. Katsuki and Co-Worker's Asymmetric Synthesis of the Chiral Nonracemic C_2-Symmetric 2,2′-Bipyridyl Ligand **113** using a Manganese(III)-Catalyzed Asymmetric Epoxidation Reaction(1996)

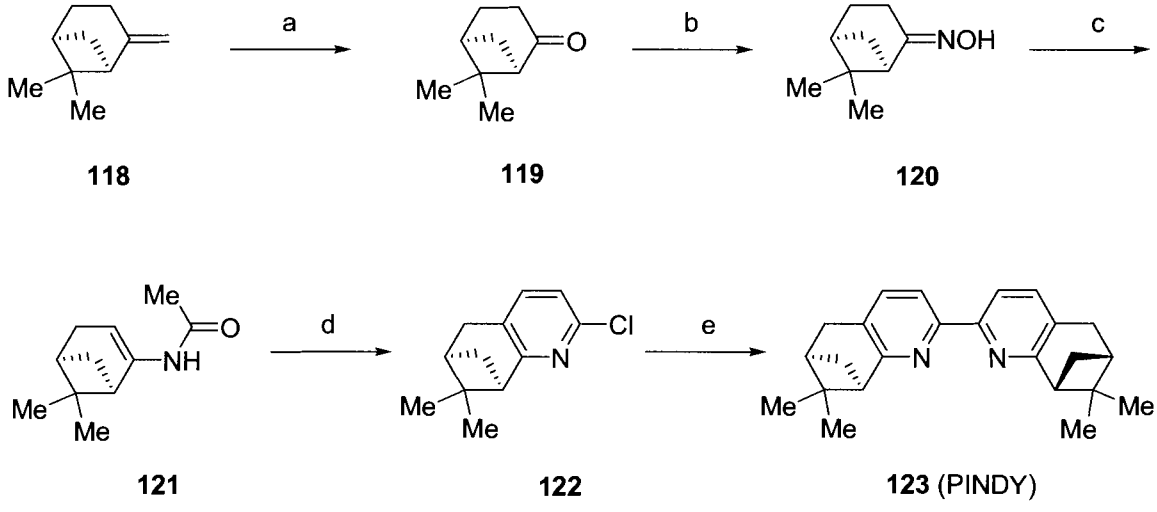


Reagents and conditions: (a) LDA, THF, -78 °C to -20 °C, 1 h then PhSeSePh, 10 min; (b) 31% H_2O_2, $NaHCO_3$, EtOAc/THF (2:1), 0 °C, 30 min, 72% (over two steps); (c) chiral Mn-salen complex, NaClO, 4-phenylpyridine-*N*-oxide, CH_2Cl_2, 0 °C, 3 h, 89%; (d) *t*-BuLi, 2-bromopropene, CuCN, THF, -78 °C, 10 min, 90%; (e) PhOC(S)Cl, DMAP, MeCN, room temperature, 3 h; purification by chromatography then *n*-Bu_3SnH, BEt_3, PhH, room temperature, 12 h, 40% (over two steps); (f) *m*-CPBA, CH_2Cl_2, 0 °C, 2.5 h, 76%; (g) $LiBEt_3H$, THF, 0 °C, 1 h, 79%; (h) TBSOTf, 2,6-lutidine, CH_2Cl_2, room temperature, 2 h, 91%; (i) $NiCl_2(H_2O)_6$, Zn dust, PPh_3, DMF, 50 °C, 12 h, 91%.

In 2000, Malkov and co-workers reported the synthesis of the chiral nonracemic C_2-symmetric 2,2′-bipyridyl ligand **123** using building blocks from the chiral pool

(Scheme 1.9.6.).[65] (+)-Nopinone **119**, which was prepared from (-)-β-pinene **118** by ozonolysis, was converted to the oxime **120**. The oxime **120** was then reduced with zinc dust in the presence of acetic anhydride to afford the enamide **121**. Subsequent reaction of this compound with *N*,*N*-dimethylformamide and phosphoryl chloride (Vilsmeier-Haack conditions) afforded the 2-chloropyridine **122**. A nickel(0)-mediated *homo*-coupling reaction then provided the desired 2,2′-bipyridyl ligand **123**.

Scheme 1.9.6. Malkov and Co-worker's Pinene-Derived Chiral C_2-Symmetric 2,2′-Bipyridyl Ligand **123** (PINDY) (2000)



Reagents and conditions: (a) OsO_4, $NaIO_4$, Me_3NO, *t*-BuOH, 80 °C, 2 h, 64%; (b) $NH_2OH{\cdot}HCl$, pyridine, EtOH; (c) Fe powder, Ac_2O, AcOH, toluene, 0 °C, 10 min, 90%; (d) DMF, $POCl_3$, 0 °C, 1 h; (e) $NiCl_2(H_2O)_6$, Zn dust, PPh_3, DMF, 60 °C, 18 h, 32 %.

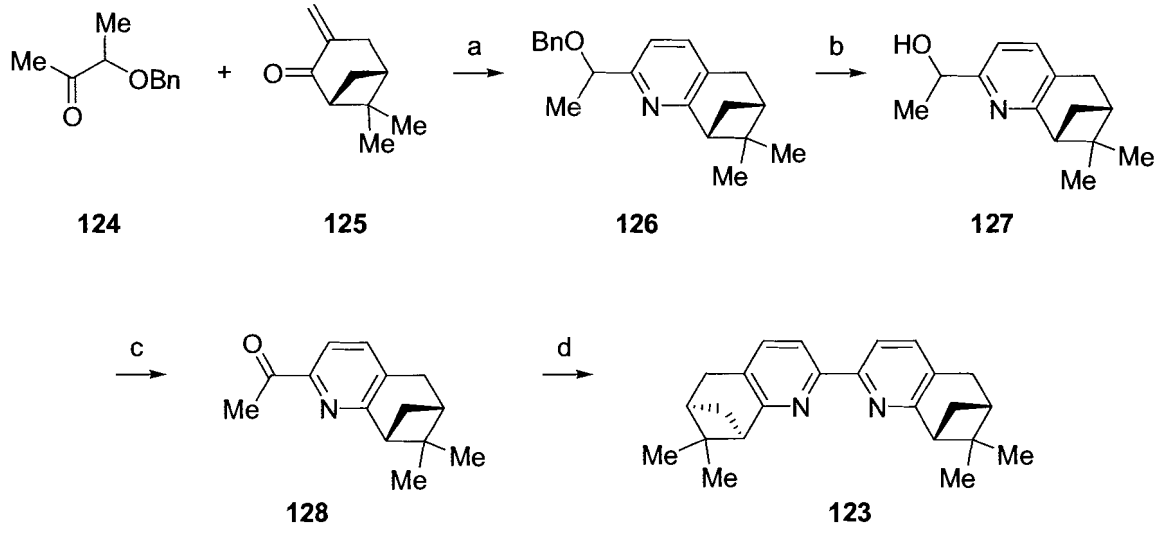
In 2001, Chelucci and co-workers reported an alternative synthesis of the 2,2′-bipyridine ligand **123** that negated the need for the metal-mediated *homo*-coupling

(65) Malkov, A. V.; Bella, M.; Langer, V.; Kočovský, P. PINDY: A Novel, Pinene-Derived Bipyridine and its Application in Asymmetric, Copper(I)-Catalyzed Allylic Oxidation. *Org. Lett.* **2000**, *2*, 3047.

reaction (Scheme 1.9.7.).[66] The difficulties often encountered in obtaining 2-halopyridines such as the requirement for relatively harsh reaction conditions and low reaction yields makes this report an important synthetic contribution. The synthetic strategy involved sequential construction of the two pyridine rings. The synthetic route began from racemic 3-benzyloxy-2-butanone **124**. The pyridine **126** was obtained upon addition of the lithium enolate of the benzylketone **124** to (*1R,5R*)-3-methylenenopinone **125**, which was prepared from (-)-β-pinene **118**, followed by aza-anulation of the resultant 1,5-dicarbonyl compound with ammonium acetate. The benzyl group was then removed by a catalytic hydrogenolysis reaction to afford the alcohol **127** which was subsequently oxidized under Swern conditions to afford the ketone **128**. The second pyridine ring was then constructed in an analogous fashion to afford the C_2-symmetric 2,2′-bipyridine ligand **123** in 35% overall yield.

(66) Chelucci, G.; Saba, A. New Synthetic Route to C_2-Symmetric 2,2′-Bipyridines: Synthesis of (6*R*,6′*R*,8*R*,8*R*′)-6,8,6′,8′-Bismethano-7,7,7′,7′-tetramethyl-5,5′,6,6′,7,7′-octahydro-2,2′-biquinoline. *Synth. Commun.* **2001**, *31*, 3161.

Scheme 1.9.7. Chelucci and Co-Worker's Route to the Pinene-Derived Chiral C_2-Symmetric 2,2′-Bipyridyl Ligand **123** (2001)



Reagents and conditions: (a) LDA, THF, -40 °C, 2 h then NH_4OAc, AcOH, reflux, 3 h, 23%; (b) H_2 (3 atm), Pd/C, EtOH, room temperature, 92%; (c) DMSO, $(COCl)_2$, NEt_3, -60 °C to room temperature, 93%; (d) LDA, THF, -40 °C, 2 h then 3-methylenenopinone **125** then NH_4OAc, AcOH, reflux, 35%.

1.9.2. 2,2′-Bipyridines with Axial Chirality

Molecules in which the chirality is due to restricted rotation about a single bond are said to contain axial chirality (atropisomeric). This type of chirality has been incorporated successfully into ligands based on the 1,1′-binapthalene framework such as BINOL[67] and BINAP.[68]

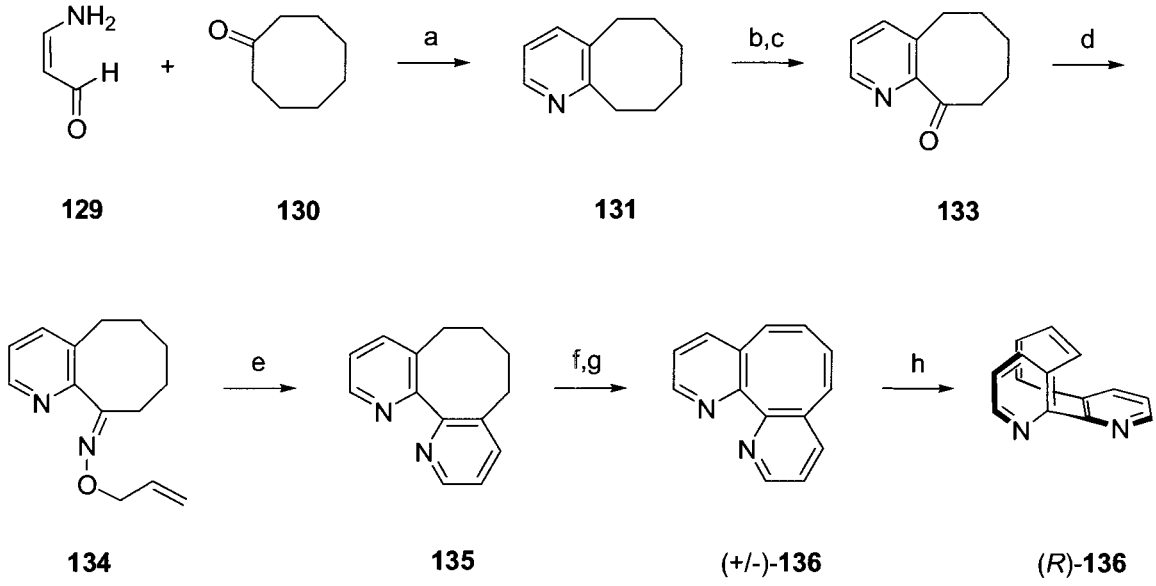
(67) (a) Noyori, R. Centenary Lecture. Chemical Multiplication of Chirality: Science and Applications. *Chem. Soc. Rev.* **1989**, *18*, 187. (b) Pu, L. 1,1′-Binapthyl Dimers, Oligomers, and Polymers: Molecular Recognition, Asymmetric Catalysis and New Materials. *Chem. Rev.* **1998**, *98*, 2405.

(68) Noyori, R. BINAP: An Efficient Chiral Element for Asymmetric Catalysis. *Acc. Chem. Res.* **1990**, *23*, 345.

The first synthesis of an axially chiral 2,2′-bipyridyl ligand **136** was reported by Wong and co-workers in 1990 (Scheme 1.9.8.).[69] The chirality of this novel ligand **136** is due to the rigidity of the cyclooctatetraene core that has a high barrier to interconversion of ring conformation. The synthesis of the ligand **136** began with the preparation of the cyclooctenopyridine **131** by the condensation reaction of *β*-aminoacrolein **129** with cyclooctanone **130** in the presence of ammonium acetate and triethylamine. The cyclooctenopyridine **131** was then converted to the benzylidene **132** upon condensation with benzaldehyde. The benzylidene **132** was then converted to the ketone **133** by ozonolysis. The second pyridine ring was then constructed by thermolysis of the corresponding *O*-allyloxime **134**, that was prepared by condensation of the ketone **133** with *O*-allylhydroxylamine. Double benzylic bromination of the resultant 2,2′-bipyridine **135** with *N*-bromosuccinimide in carbon tetrachloride afforded a diastereoisomeric mixture of dibromides. These compounds were then dehydrobrominated with alcoholic potassium hydroxide to afford the racemic axially chiral 2,2′-bipyridyl ligand **136**. Resolution of this compound was accomplished by treatment of the racemic ligand **136** with a chiral palladium complex followed by fractional crystallization to afford a single diastereoisomeric complex.

(69) Wang, X. C.; Cui, Y. X.; Mak, T. C. W.; Wong, H. N. C. Synthesis, Metal Complex Formation, and Resolution of a New C_2 Diazabiaryl Ligand: Cyclo-octa[2,1-*b*:3,4-*b*′]dipyridine. *J. Chem. Soc., Chem. Commun.* **1990**, 167.

Scheme 1.9.8. Wong and Co-Worker's Novel Axially Chiral 2,2′-Bipyridyl Ligand **136** (1990)

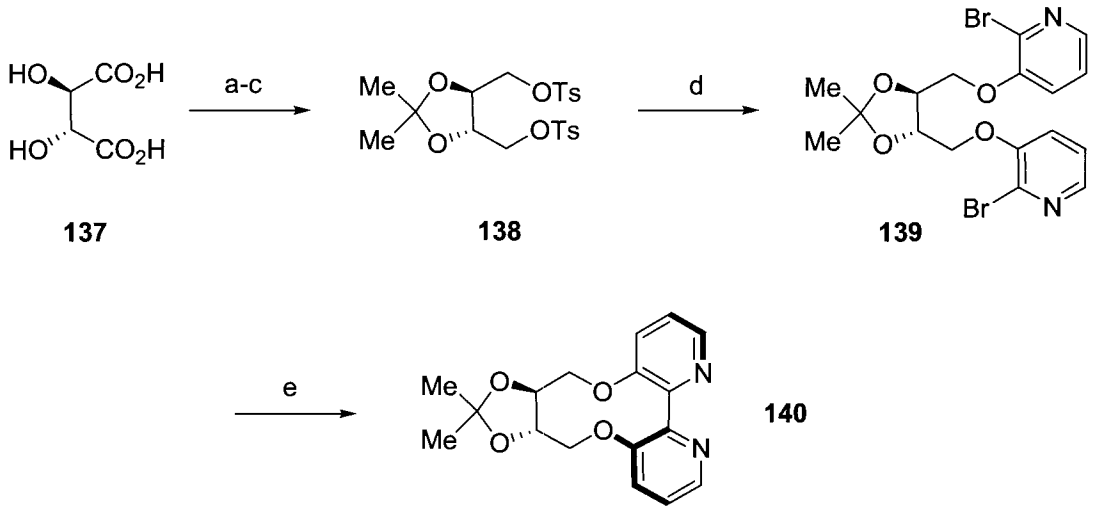


Reagents and conditions: (a) NH_4OAc, NEt_3, 120 °C, 25%; (b) PhCHO, Ac_2O, reflux, 8 days, 83%; (c) O_3, CH_2Cl_2, -40 °C then Me_2S, 40%; (d) *O*-allylhydroxylamine·HCl, NaOAc, Na_2CO_3, EtOH, reflux, 87%; (e) 180 °C, sealed tube, 52 h, 60%; (f) NBS, CCl_4, reflux; (g) KOH, EtOH, reflux, 70% (over two steps); (h) resolution by coordination to a chiral palladium complex.

In 1993, Botteghi and co-workers reported the synthesis of the axially chiral 2,2′-bipyridyl ligand **140** in which the chirality is due to the restricted rotation about the biaryl bond created by a chiral tartaric acid-derived macrocycle (Scheme 1.9.9.).[70] The synthesis of this ligand began with a double nucleophilic displacement reaction of the readily available ditosylate **138** with 2-bromo-3-hydroxypyridine that afforded the *bis*pyridine **139**. A nickel(0)-mediated *homo*-coupling reaction then provided the axially chiral 2,2′-bipyridine ligand **140** as a single atropisomer.

(70) Botteghi, C.; Schionato, A.; De Lucchi, O. A C_2-symmetric Chiral 2,2′-Bipyridine Derived from Tartaric Acid. *Synth. Commun.* **1991**, *21*, 1819.

Scheme 1.9.9. Botteghi and Co-Worker's Tartrate Derived Axially Chiral 2,2′-Bipyridyl Ligand **140** (1993)



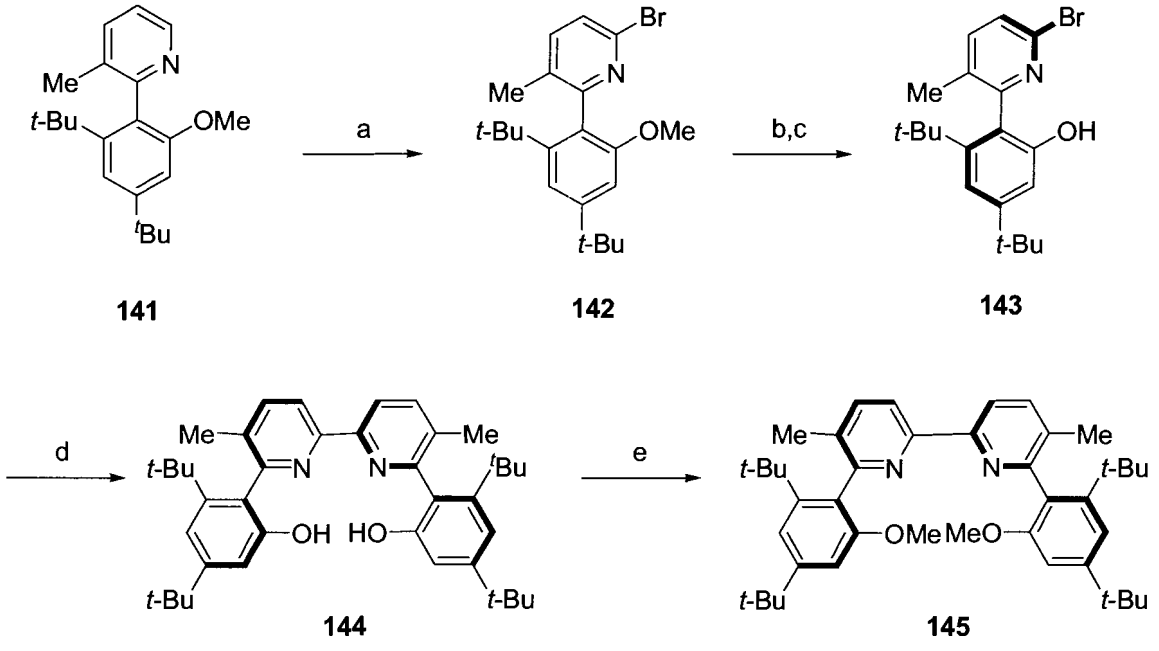
137 **138** **139** **140**

Reagents and conditions: (a) 2,2-dimethoxypropane, *p*-TsOH (cat.) reflux; (b) $LiAlH_4$, Et_2O, reflux; (c) TsCl, 2,6-lutidine, CH_2Cl_2; (d) 2-bromo-3-hydroxypyridine, NaOH, H_2O, *n*-Bu_4NBr, 85 °C, 48 h, 95%; (e) $NiCl_2(H_2O)_6$, Zn dust, PPh_3, DMF, 50 °C, 20 h, 38%.

Chan and co-workers have described the synthesis of the axially chiral 2,2′-bipyridyl ligands **144** and **145** (Scheme 1.9.10.).[71] In this case, the substituted pyridine **141** was brominated in the *ortho*-position on deprotonation with *tert*-butyllithium and subsequent treatment with 1,2-dibromoethane. Demethylation of the resultant 2-bromopyridylanisole **142** with 48% hydrogen bromide in acetic acid afforded the axially chiral racemic phenol **143** which was then separated into its atropoisomers by preparative chiral HPLC. A subsequent nickel(0)-mediated *homo*-coupling reaction of the chiral nonracemic phenol **143** afforded the 2,2′-bipyridyl ligand **144** as a single stereoisomer. Finally, methylation of the 2,2′-bipyridine **144** with dimethyl sulfate afforded the 2,2′-bipyridyl ligand **145**.

(71) Wong, H. L.; Tian, Y.; Chan, K. S. Electronically Controlled Asymmetric Cyclopropanation Catalyzed by a New Type of Chiral 2,2′-Bipyridine. *Tetrahedron Lett.* **2000**, *41*, 7723.

Scheme 1.9.10 Chan and Co-Worker's Axially Chiral 2,2′-Bipyridyl Ligands **144** and **145** (2000)



141 **142** **143**

144 **145**

Reagents and conditions: (a) *t*-BuLi (1.5 equiv), THF, -78 °C, 1 h then 1,2-dibromoethane, -78 °C to room temperature, 4 h, 71%; (b) 48% HBr/AcOH, 120 °C, 8 h, 95%; (c) HPLC resolution (Daicel Chiracel OD column); (d) $Ni(PPh_3)_2Cl_2$ (1 equiv), Zn dust (2 equiv), Et_4NI (1.5 equiv), THF, 60 °C, 8 h, 89%; (e) NaOH (2 equiv), MeOH, room temperature, 1 h then Me_2SO_4 (2 equiv), 40 °C, 2 h, 90%.

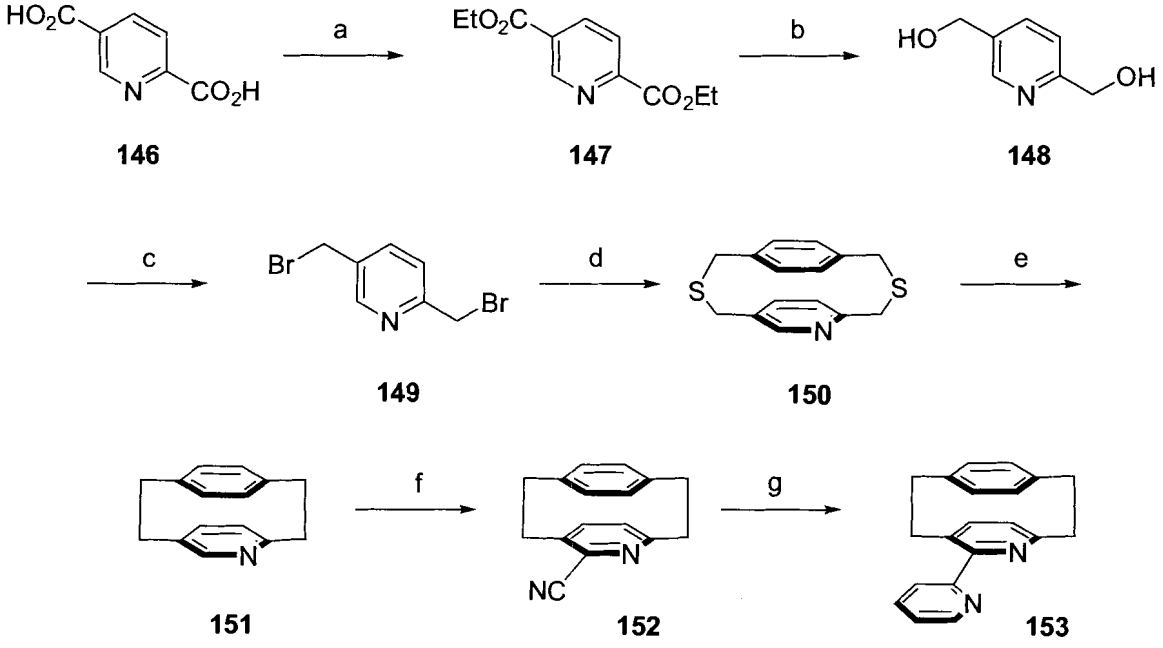
1.9.3. 2,2′-Bipyridines with Planar Chirality

Molecules with chirality that originates from the arrangement of out-of-the-plane substituents relative to a reference plane are said to have "planar chirality". There are several examples of 2,2′-bipyridyl ligands that contain elements of planar chirality. In 1999, Vögtle and co-workers reported the synthesis of the planar chiral 2,2′-bipyridyl ligand **153** (Scheme 1.9.11.).[72] The synthesis began from 2,5-pyridinedicarboxylic acid **145** which was converted to the diethyl ester **147** *via* the diacid chloride. The diester **147**

(72) Wörsdörfer, E.; Vögtle, F.; Nieger, M.; Waletzke, M.; Grimme, S.; Glorius, F.; Pfaltz, A. A New Planar Chiral Bipyridine Ligand. *Synthesis* **1999**, 597.

was then reduced with sodium borohydride in the presence of calcium chloride to afford the diol **148** which was then converted to the dibromide **149** upon treatment with 30% hydrogen bromide in acetic acid. The dibromide **149** was then coupled with 1,4-*bis*(sulfanylmethyl)benzene, under high dilution and taking advantage of the cesium template effect, to afford the *bis*(thioether) **150**. Irradiation of the *bis*(thioether) **150** with UV light (Hg, 180 W) in the presence of trimethoxyphosphine provided the cyclophane **151**. This material was then oxidized with *m*-chloroperoxybenzoic acid to the corresponding *N*-oxide which was then converted to the nitrile **152** upon reaction with trimethylsilyl cyanide and dimethylcarbamyl chloride. The final step in the synthesis was a cobalt(I)-catalyzed cyclotrimerization of the nitrile **152** with acetylene that afforded the racemic 2,2′-bipyridyl ligand **153**. The racemic compound **153** was resolved by preparative chiral HPLC. The absolute stereochemistry was then assigned by comparison of the experimental and theoretical CD spectra.

Scheme 1.9.11. Vögtle and Co-Worker's Planar Chiral 2,2′-Bipyridyl Ligand **153** (1999)



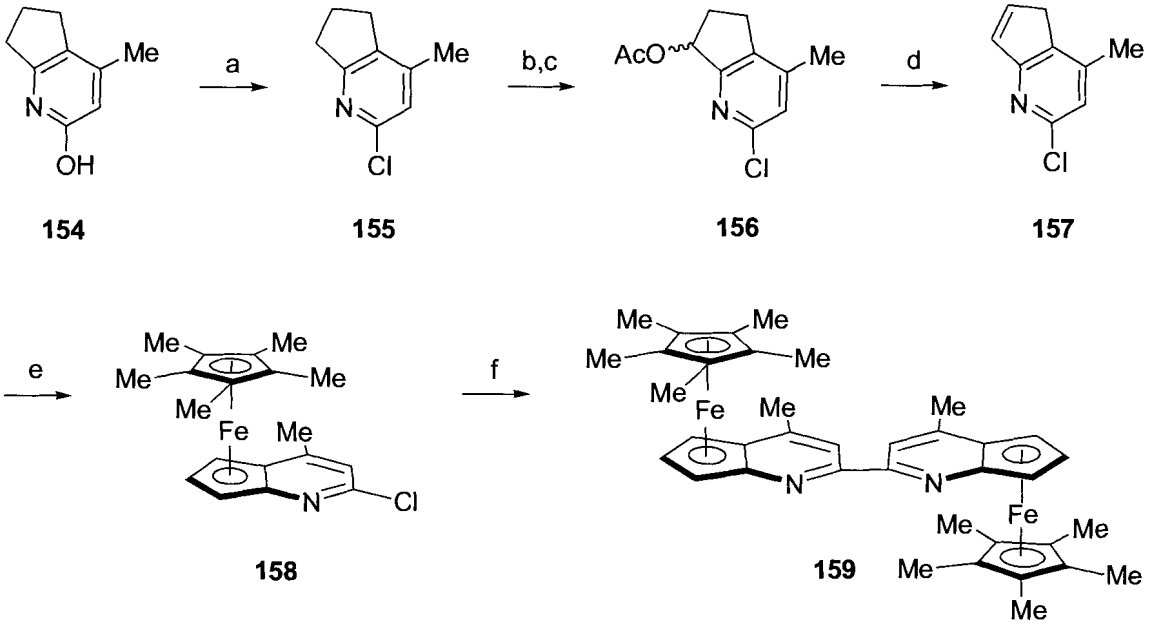
Reagents and conditions: (a) $SOCl_2$, reflux, 8 h, then EtOH, reflux, 2 h, 82%; (b) $NaBH_4$ (2 equiv), $CaCl_2$ (1 equiv), EtOH, room temperature, 16 h, 67%; (c) 30% HBr/AcOH, room temperature, 6 days; (d) 1,4-*bis*(sulfanylmethyl)benzene (1 equiv), KO*t*-Bu (2.3 equiv), Cs_2CO_3, EtOH, reflux, 16 h, 62%; (e) $P(OMe)_3$, *hv* (Hg, 180W), room temperature, 18 h, 84%; (f) *m*-CPBA (2 equiv), CH_2Cl_2, room temperature, 20 h then *N,N*-dimethylcarbamoyl chloride (1.3 equiv), TMSCN (1.3 equiv), CH_2Cl_2, room temperature, 16 h, 75%; (g) cyclopenatdienylcycloocta-1,5-dienecobalt (2 equiv), C_2H_2 (1.5 bar), $PhCH_3$, 120 °C, 20 h, 23% then resolution by chiral HPLC.

In 2000, the synthesis of a novel C_2-symmetric 2,2′-bipyridyl ligand **159** with planar chirality was reported by Fu and co-workers (Scheme 1.9.12.).[73] The synthesis of the ligand **159** began from the known pyridine-2-ol **154** which was converted to the chloride **155** upon reaction with phosphoryl chloride. The chloride **155** was then oxidized to the corresponding *N*-oxide which upon heating with acetic anhydride afforded the acetate **156**. Elimination of the acetate with sulfuric acid afforded the

(73) Rios, R.; Liang, J.; Lo, M. M.-C.; Fu, G. C. Synthesis, Resolution and Crystallographic Characterization of a New C_2-Symmetric Planar-Chiral Bipyridine Ligand: Application to the Catalytic Enantioselective Cyclopropanation of Olefins. *Chem. Commun.* **2000**, 377.

pyrindine **157** as a mixture of regioisomers. The pyrindine **157** was then complexed with iron(II) *via* reaction of its lithium salt, obtained by deprotonation with *n*-butyllithium, with Cp*FeCl to afford the ferrocene derivative **158**. This compound then underwent a nickel(0)-mediated *homo*-coupling reaction to afford the desired C_2-symmetric planar chiral 2,2′-bipyridine ligand **159** as a single diastereoisomer in racemic form. Resolution was accomplished by preparative chiral HPLC and the absolute stereochemistry was established by X-ray crystallography.

Scheme 1.9.12 Fu and Co-Worker's Novel Planar Chiral 2,2′-Bipyridyl Ligand **159** (2000)



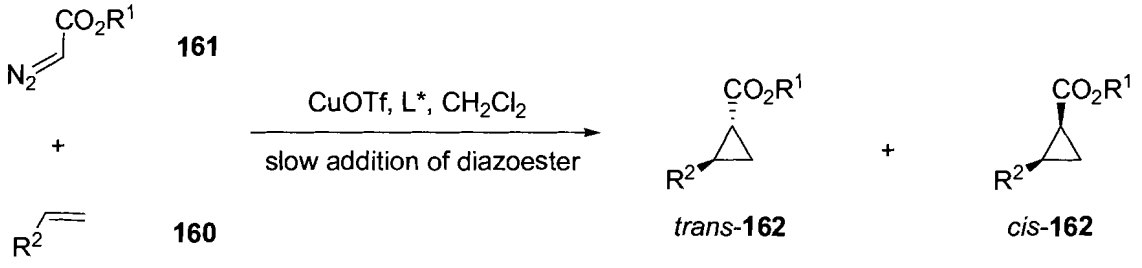
Reagents and Conditions: (a) $POCl_3$, 74 %; (b) H_2O_2, AcOH, 88%; (c) Ac_2O, 58%; (d) H_2SO_4, 79%; (e) *n*-BuLi then Cp*FeCl, 58%; (f) $Ni(PPh_3)Br_2$, Zn dust, Et_4NI, 58% then resolution by chiral HPLC (Regis Whelk-O column).

1.9.4. Catalytic Asymmetric Cyclopropanation Reactions

The copper(I)-catalyzed asymmetric cyclopropanation reaction (AC) of alkenes **160** with diazoesters **161** to afford the diastereoisomeric *trans*- and *cis*-cyclopropanes **162** has become the standard "benchmark" reaction by which new chiral 2,2′-bipyridyl

ligands are evaluated (Scheme 1.9.13.).[74] The two main driving forces for the use of the copper(I)-catalyzed AC reaction are the excellent results that have been obtained in this reaction with the structurally related chiral *bis*oxazoline ligands as well as the high affinity of 2,2′-bipyridine ligands for copper salts.

Scheme 1.9.13. Copper(I)-Catalyzed Asymmetric Cyclopropanation Reactions of Alkenes



The catalytic AC reaction of alkenes is a reaction which is used extensively in synthesis.[75] For instance, Aratani who was a student of Nozaki (one of the pioneers of catalytic asymmetric synthesis) developed a highly enantioselective synthesis of 2,2′-dimethyl-cyclopropane-1-carboxylic acid ethyl ester **165** at the Sumitomo Chemical Company that was incorporated into the commercial production process of Merck's antiobiotic drug, cilastatin **166** (Scheme 1.9.14.).[76]

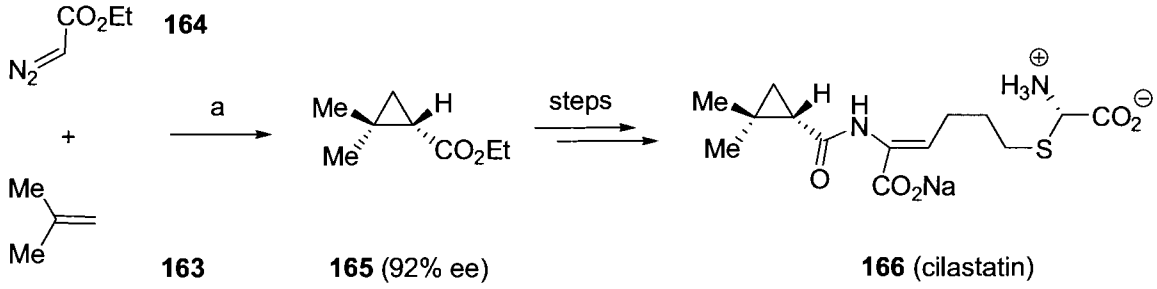
---

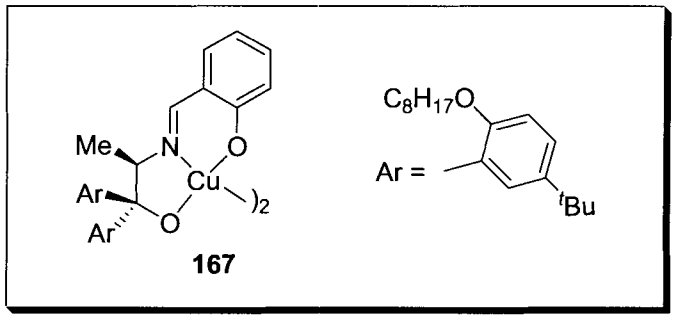
(74) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; J. Wiley: New York, 1998.

(75) For recent reviews on AC reactions, see: (a) Doyle, M. P.; Forbes, D. C. Recent Advances in Asymmetric Catalytic Metal Carbene Transformations. *Chem. Rev.* **1998**, *98*, 911. (b) Doyle, M. P.; Protopopova, M. N. New Aspects of Catalytic Asymmetric Cyclopropanation. *Tetrahedron* **1998**, *54*, 7919.

(76) (a) Aratani, T.; Yoneyoshi, Y.; Nagase, T. Asymmetric Synthesis of Chrysanthemic Acid. An Application of Copper Carbenoid Reaction. *Tetrahedron Lett.* **1975**, 1707. (b) Aratani, T.; Yoneyoshi, Y.; Nagase, T. Asymmetric Synthesis of Permethric Acid. Stereochemistry of Chiral Copper Carbenoid Reaction. *Tetrahedron Lett.* **1982**, *23*, 685. (c) Aratani, T. Catalytic Asymmetric-Synthesis of Cyclopropane-Carboxylic Acids - An Application of Chiral Copper Carbenoid Reaction. *Pure Appl. Chem.* **1985**, *57*, 1839.

Scheme 1.9.14. Industrial Synthesis of Cilastatin **166** using a Catalytic Asymmetric Cyclopropanation Reaction





Reagents and conditions: (a) 1.0 mol % copper-complex **167**, CH_2Cl_2, room temperature.

The generally accepted mechanism for the copper(I)-catalyzed AC reaction of alkenes with diazo compounds involves three fundamental steps (Figure 1.9.1.). The first step is the nucleophilic addition of the diazo compound to an electrophilic copper(I)-catalyst that affords the diazonium ion **168**. The second step is the elimination of dinitrogen to form a copper stabilized carbene **169** which, in the third step, is transferred to an alkene **160** (electron-rich substrate) to form a cyclopropane **170** and regenerate the copper(I)-catalyst **171**.

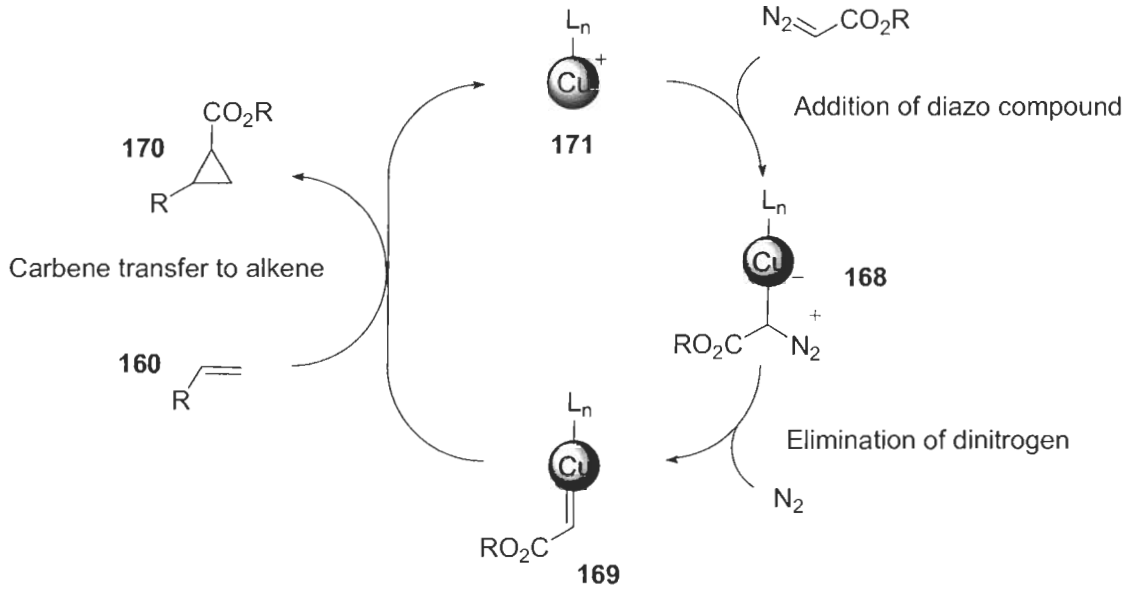


Figure 1.9.1. Mechanism of copper(I)-catalyzed cyclopropanation reactions of alkenes with diazo compounds.

The catalytic activity of a transition metal complex towards diazo compound decomposition is dependant on both the electrophilicity of the transition metal complex as well as the stability of the diazo compound. Diazo compounds with α-carbonyl moities are the preferred substrates for catalytic reactions with transition metal complexes.[77] Amongst diazocarbonyl compounds, those with two carbonyl groups that are adjacent to the diazomethane carbon are more stable towards transition metal-catalyzed decomposition than those with only one adjacent carbonyl (Figure 1.9.2.).[78] For instance, diazoacetoacetates **172** and diazomalonates **173** require elevated temperatures for reaction with transition metals, while diazoacetates **174** can undergo catalytic loss of dinitrogen at or below room temperature.

---

(77) Doyle, M. P. Catalytic Methods for Metal Carbene Transformations. *Chem. Rev.* **1986**, *86*, 919.

(78) Doyle, M. P. Metal Carbene Complexes in Organic Synthesis: Diazodecomposition-Insertion and Ylide Chemistry. In *Comprehensive Organometallic Chemistry II*; Hegedus, L. S., Ed.; Pergamon Press, New York, 1995; Vol. 12, Chapter 5.2.

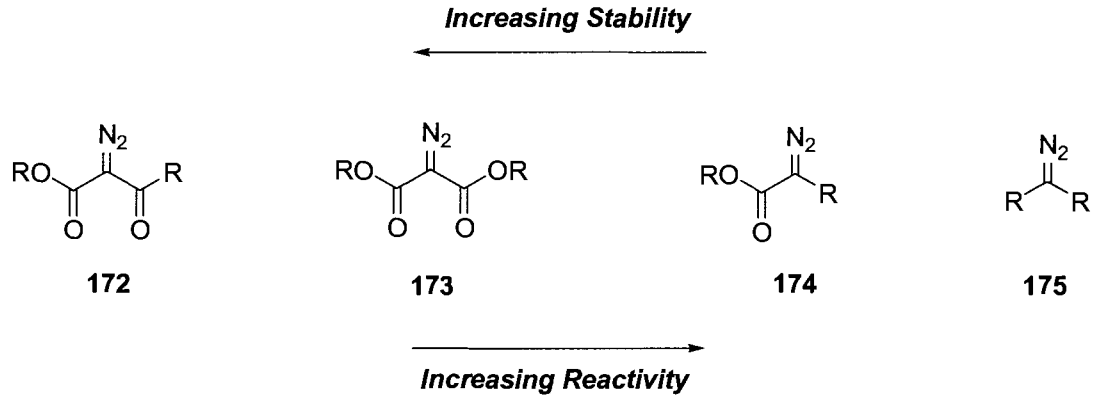


Figure 1.9.2. The relationship between diazo compound structure and reactivity (R = alkyl).

Transition metal carbene intermediates react readily with electron rich substrates such as alkenes. These intermediates may be depicted by three resonance structures: a formal metal carbene **176**; an ylide or metal stabilized carbocation **177**; and a metal stabilized carbene **178**, that illustrate the electrophilic nature of these transition metal carbenes (Figure 1.9.3.).

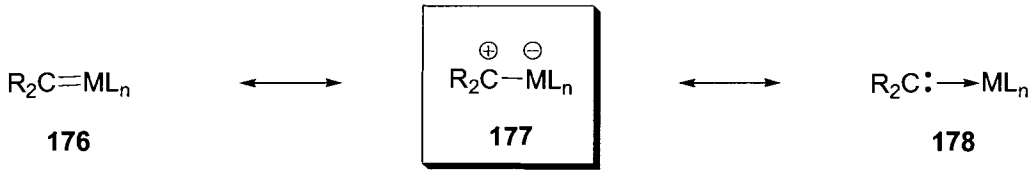


Figure 1.9.3. The contributing resonance structures of a metal carbene complex.

Three methods have been employed to carry out copper(I)-catalyzed cyclopropanation reactions. The first and most direct method involves the use of copper(I) trifluoromethanesulfonate as the copper(I) source. However, this method requires considerable experimental care to ensure the integrity of this highly air and moisture sensitive reagent (Method A).[79] The second method uses the more stable copper(II) trifluoromethanesulfonate as the copper source, that is reduced to the

(79) Salomon, R. G.; Kochi, J. K. Copper(I) Catalysis in Cyclopropanations with Diazo Compounds. The Role of Olefin Coordination. *J. Am. Chem. Soc.* **1973**, *95*, 3300.

corresponding catalytically active copper(I) species with either phenylhydrazine or a slight excess of the diazoester (Method B).[80,81] In the third method, a copper(II) chloride ligand complex is synthesized and then converted into the corresponding *bis*(trifluoromethanesulfonate) on treatment with silver trifluoromethanesulfonate. The catalytically active copper(I) species is then obtained by reduction with either phenylhydrazine or a slight excess of the diazoester (Method C).[82] In all instances, the diazoester is added slowly over the course of several hours to the reaction mixture, which contains an excess of the alkene, to avoid the undesired coupling reaction of two molecules of the diazoester to afford the corresponding fumarates.

For C_1-symmetric 2,2′-bipyridine ligands, the enantioselectivities and diastereoselectivities that have been achieved in copper(I)-catalyzed asymmetric cyclopropanation reactions of styrene with diazocompounds have been low. For instance, the planar chiral cyclophane-derived 2,2′-bipyridine ligand **153** that was reported by Vögtle and co-workers effected reactions with low enantioselectivities (≤ 26% ee).[72]

C_2-symmetric 2,2′-bipyridyl ligands have been found to perform well in cyclopropanation reactions. Bolm and co-worker's ligand **99** afforded the *trans*-cyclopropane in high enantiomeric excess (up to 92%).[58] In the case of the series of

---

(80) Fritschi, H.; Leutenegger, U.; Pfaltz, A. Semicorrin Metal Complexes as Enantioselective Catalysts. Part 2. Enantioselective Cyclopropane Formation from Olefins with Diazo Compounds Catalyzed by Chiral (Semicorrinato)copper Complexes. *Helv. Chim. Acta.* **1988**, *71*, 1553.

(81) Lowenthal, R. E.; Abiko, A.; Masamune, S. Asymmetric Catalytic Cyclopropanation of Olefins: *bis*(Oxazoline) Copper Complexes. *Tetrahedron Lett.* **1990**, *31*, 6005.

(82) Kwong, H.-L.; Lee, W.-S.; Ng, H.-F.; Chiu, W.-H.; Wong, W.-T. Chiral Bipyridine-Copper(II) Complex. Crystal Structure and Catalytic Activity in Asymmetric Cyclopropanation. *J. Chem. Soc., Dalton Trans.* **1998**, 1043.

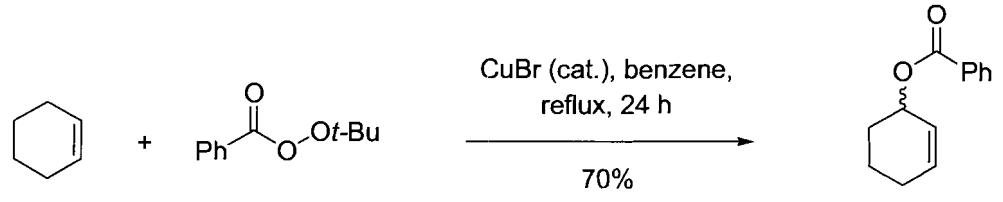
ligands **110a,b** and **113** reported by Katsuki and co-workers, high enantioselectivities were also achieved.[61,62,63] Employment of the α,α'-dimethyl substituted ligand **110a** afforded the *trans*-cyclopropane in good enantioselectivity (77% ee) while employment of the bulkier ligand **113** afforded the *trans*-cyclopropane with improved enantioselectvity (83% ee). The C_2-symmetric axially chiral 2,2′-bipyridine ligand **145** reported by Chan and co-workers was applied to the cyclopropanation reaction of styrene with ethyl diazoacetate.[69] At room temperature, the *trans*-cyclopropane was obtained in good enantiomeric excess (79%), which was improved (86% ee) upon decreasing the reaction temperature to 0 °C. A strong electronic effect was also noted with the ligand **145** in which *p*-substituted styrenes with electron withdrawing groups underwent cyclopropanation reactions in higher enantioselectivities than those with electron donating groups. Fu and co-worker's C_2-symmetric planar chiral 2,2′-bipyridine ligand **159** was also evaluated in the cyclopropanation reaction of styrene and 2,6-di-*t*-butyl-4-methylphenyl diazoacetate which afforded the *trans*-cyclopropane product in high diastereoisomeric and enantiomeric excess (94% de, 87% ee).[71] Of note, the high diastereoselectivity in this particular reaction can be attributed to the large size of the 2,6-di-*t*-butyl-4-methylphenyl substituent of the diazo compound.

1.9.5. Catalytic Asymmetric Allylic Oxidation Reactions

In 1959, Kharasch and Sosnovsky reported the allylic oxidation reaction of alkenes, such as cyclohexene, using a catalytic amount of copper(I) bromide and *tert*-

butyl peroxybenzoate **179** as the stoichiometric oxidant in benzene at reflux. This afforded the allylic ester product **180** in good yield (70%) (Scheme 1.9.15.).[83]

Scheme 1.9.15. The Copper(I)-Catalyzed Allylic Oxidation Reaction



(excess) **179** **180**

The generally accepted mechanism for this copper(I)-catalyzed allylic oxidation reaction involves four steps (Figure 1.9.4.). The first step is a copper-mediated homolytic cleavage of the oxygen-oxygen bond in the *tert*-butyl peroxybenzoate **179** that generates the copper(II) carboxylate **181** and the *tert*-butoxy radical **182**. The next step is the abstraction of the hydrogen atom from the alkene substrate **183** by the *tert*-butoxy radical that affords the thermodynamically more stable allylic radical **184** and *tert*-butanol. While no detailed kinetic measurements have been made, these first two steps are thought to be rapid and essentially diffusion controlled.[84] The third step is the addition of the allylic radical **184** to the copper(II) carboxylate **181** that affords the copper(III) species **185**. The final step of the reaction involves a pericyclic rearrangement or a reductive elimination process that affords the reaction product **186** and regenerates the active copper(I) catalyst **187**.

(83) Kharasch, M. S.; Sosnovsky, G.; Yang, N. C. Reactions of *tert*-Butyl Peresters I. The Reaction of Peresters With Olefins. *J. Am. Chem. Soc.* **1959**, *81*, 5819.

(84) Andrus, M. B.; Chen, X. Catalytic Enantioselective Allylic Oxidation of Olefins with Copper(I) Catalysts and New Perester Oxidants. *Tetrahedron* **1997**, *53*, 16229.

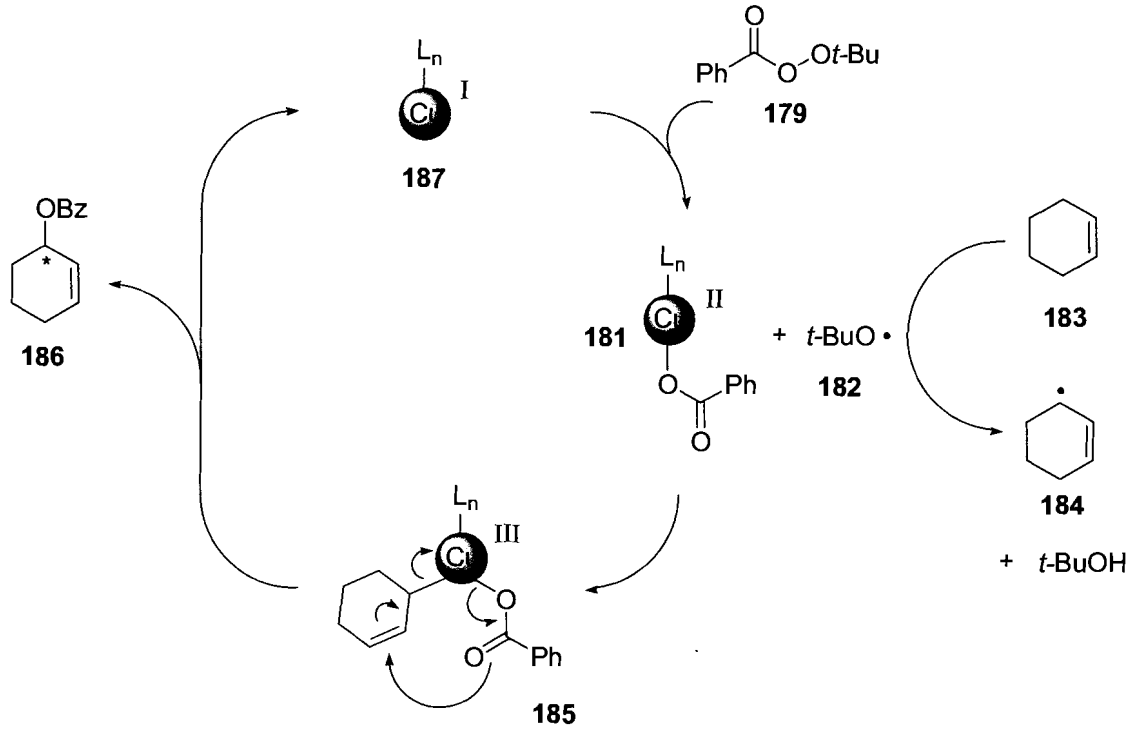


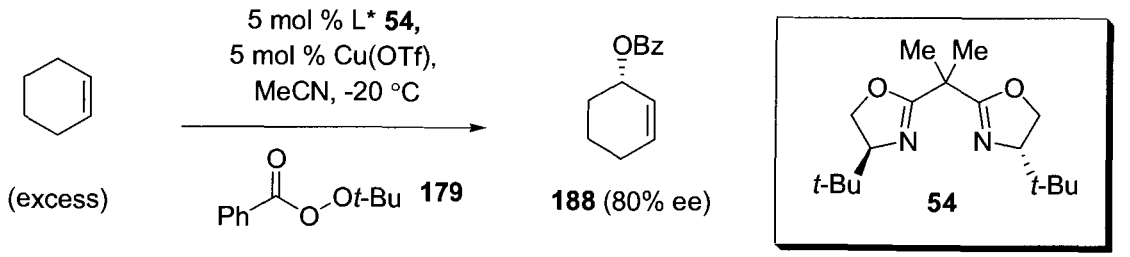
Figure 1.9.4. Mechanism for the copper(I)-catalyzed asymmetric allylic oxidation reaction of alkenes.

Asymmetric versions of this allylic oxidation reaction using chiral *bis*oxazoline copper(I)-complexes were reported independently in 1995 by Pfaltz and co-workers and Andrus and co-workers (Scheme 1.9.16.).[85,86] Enantioselectivities of up to 80% ee for the oxidation reaction of cyclic alkenes were achieved when the reactions were performed in acetonitrile at relatively low temperatures (-20 °C).

(85) Gokhale, A. S.; Minidis, A. B. E.; Pfaltz, A. Enantioselective Allylic Oxidation Catalyzed by Chiral *bis*(Oxazoline)-Copper Complexes. *Tetrahedron Lett.* **1995**, *36*, 1831.

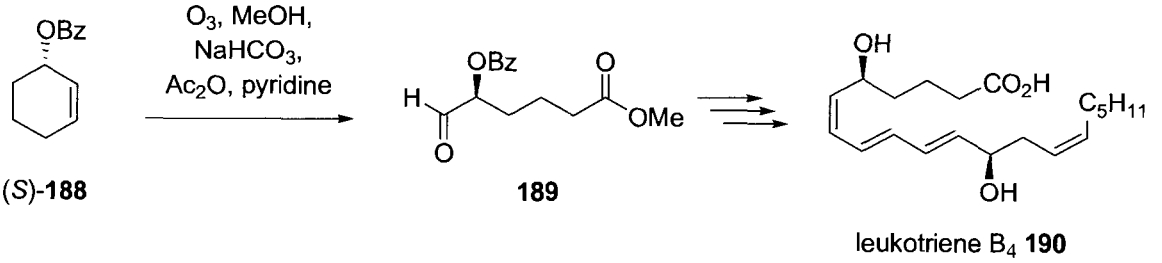
(86) Andrus, M. B.; Argade, A. B.; Chen, X.; Pamment, M. G. The Asymmetric Kharasch Reaction. Catalytic Enantioselective Allylic Acyloxylation of Olefins with Chiral Copper(I) Complexes and *tert*-Butyl Perbenzoate. *Tetrahedron Lett.* **1995**, *36*, 2945.

Scheme 1.9.16. Asymmetric Allylic Oxidation Reaction Catalyzed by the Chiral Copper(I) Triflate *bis*(Oxazoline) Complex **54**



One of the most attractive features of this asymmetric copper(I)-catalyzed allylic oxidation reaction is the usefulness of the reaction products in target-oriented synthesis. A notable example, reported by Wallace and co-workers, is the use of (*S*)-cyclohexenyl benzoate **188** to synthesize the chiral aldehyde **189** which is a key intermediate in the synthesis of the inflammation mediator leukotriene B_4 **190** (Scheme 1.9.17.).[87] The two-step asymmetric preparation of the chiral aldehyde **189** by catalytic means represents a marked improvement over previous routes which required multiple steps from carbohydrate based starting materials.

Scheme 1.9.17. Synthesis of Leukotriene B_4 **190**



High enantioselectivities have subsequently been achieved in this reaction (up to 99% ee). However, there remains a significant problem in that the catalytic systems suffer from very sluggish reaction rates.[84] In some cases, the reaction has taken up to one

(87) Hayes, R.; Wallace, T. W. A Simple Route to Methyl (5*S*)-Benzoyloxy-6-oxohexanoate, a Key Intermediate in Leukotriene Synthesis. *Tetrahedron Lett.* **1990**, *31*, 3355.

month to reach a satisfactory level of conversion.[88] It has been found that chiral C_2-symmetric 2,2′-bipyridine copper(I)-complexes are very active catalytic systems for this reaction in that they provide much faster reaction rates although the enantioselectivities obtained thus far have been somewhat lower than with *bis*oxazoline complexes.

Malkov and co-worker's chiral C_2-symmetric 2,2′-bipyridine ligand (PINDY) **123** formed an extremely active catalytic system which was able to oxidize cyclohexene with 1 mol % catalyst loading in less than 30 min at room temperature, to afford the benzoate product **188** in high yield (96%) and in moderate enantioselectivity (49% ee).[65] The enantioselectivity was improved (55% ee) when the reaction was conducted at 0 °C, but the reaction required 5 h in this instance. Similar results were obtained in the asymmetric oxidation of cyclopentene (48% ee at room temperature and 59% ee at 0 °). When cycloheptene was used as the substrate, substantially increased enantioselectivities were observed (62% ee at room temperature and 75% ee at 0 °C). Thus, with optimization of the ligand structure, a catalyst system based on a 2,2′-bipyridine framework may be capable of providing excellent enantioselectivities and reaction rates in this enantioselective allylic oxidation reaction.

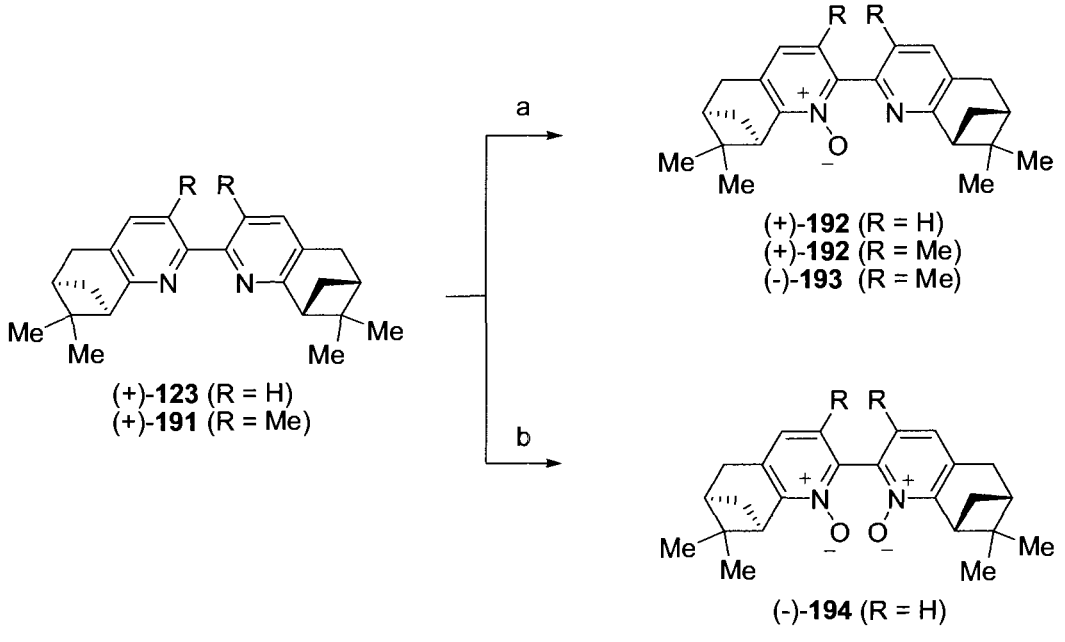
1.10. Chiral 2,2′-Bipyridine *Mono*- and *Bis*-*N*-Oxides

Recently, several examples of the *mono*- and *bis*-*N*-oxides of chiral 2,2′-bipyridine ligands have been reported. Malkov and co-workers have reported the preparation of both the corresponding *mono*- and *bis*-*N*-oxides of their chiral 2,2′-

(88) Andrus, M. B.; Zhou, Z. Highly Enantioselective Copper-*bis*Oxazoline-Catalyzed Allylic Oxidation of Cyclic Olefins with *tert*-Butyl *p*-Nitroperbenzoate. *J. Am. Chem. Soc.* **2002**, *124*, 8806.

bipyridine ligand PINDY **123** (Scheme 1.10.1.).[89] Oxidation of PINDY **123** with *m*-chloroperoxybenzoic acid at lower temperature (0 °C, 45 min) led exclusively to the *mono-N*-oxide **192** while oxidation at room temperature led to the *bis-N*-oxide **194**. In this paper the preparation of 3,3′-dimethyl-PINDY **191** and its oxidation to the *bis-N*-oxide **193** was also reported. Of note, this ligand now contains both stereogenic centres and an element of axial chirality. The two diastereoisomers of these atropisomers were separated by chromatography on silica gel.

Scheme 1.10.1. Synthesis of *Mono-* and *Bis-N*-Oxides of the Chiral Nonracemic C_2-Symmetric 2,2′-Bipyridyl Ligand **123** (2002)



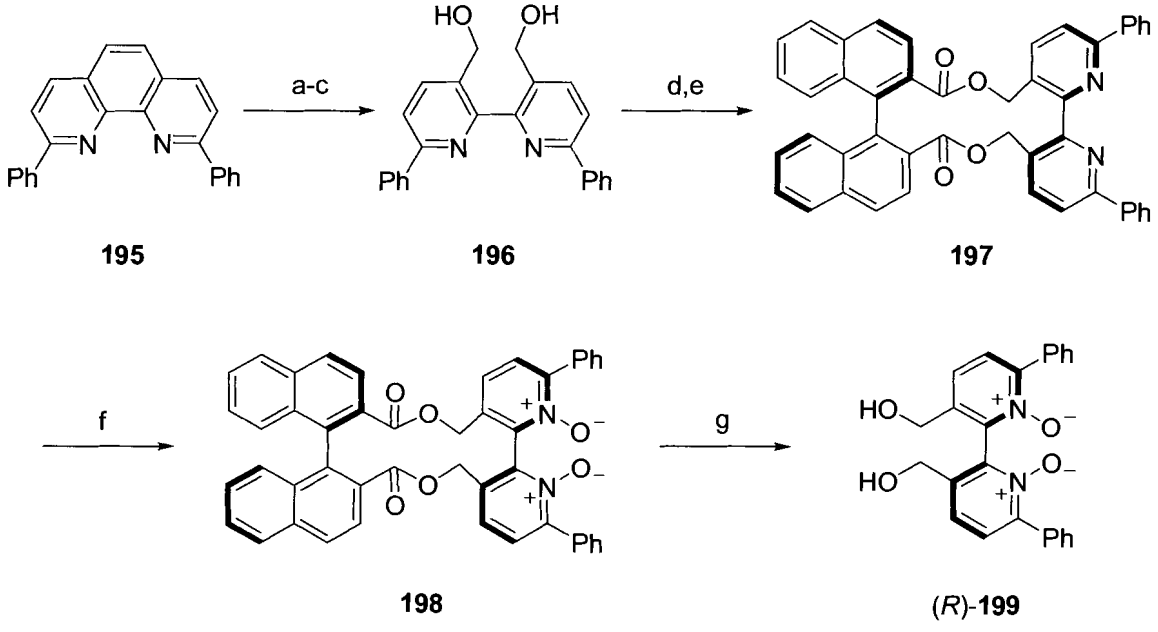
Reagents and conditions: (a) *m*-CPBA, CH_2Cl_2, 0 °C, 30 min, 96% [(+)-**192**]; (b) *m*-CPBA, CH_2Cl_2, room temperature, 24 h, 62% [(-)-**194**].

(89) Malkov, A. V.; Orsini, M.; Pernazza, D.; Muir, K. W.; Langer, V.; Meghani, P.; Kočovský, P. Chiral 2,2′-Bipyridine-Type *N*-Monoxides as Organocatalysts in the Enantioselective Allylation of Aldehydes with Allyltrichlorosilane. *Org. Lett.* **2002**, *4*, 1047.

In 2002, Hayashi and co-workers reported the synthesis of the novel axially chiral 2,2′-bipyridyl *bis*-*N*-oxide **199** (Scheme 1.10.2.).[90] For the preparation of compound **199**, a new method of introducing and fixing the axial chirality by oxidation of the cyclic diester **197** was developed. The bipyridine-diol **196** was prepared by oxidation of 2,9-diphenylphenanthroline **195** with potassium permanganate and sodium periodate followed by esterification of the resultant dicarboxylic acid and subsequent reduction with lithium aluminum hydride. The diol **196** was then coupled with (*R*)-2,2′-*bis*(chlorocarbonyl)-1,1′-binapthalene in the presence of triethylamine to afford the cyclic diester **197** in high yield. On heating the cyclic diester **197** in toluene, the thermodynamically more stable diastereoisomer **197** was obtained as a single stereoisomer. The absolute configuration of this 2,2′-bipyridine was assigned as (*R*) by X-ray crystallography. Oxidation of the 2,2′-bipyridine **197** with *m*-chloroperoxybenzoic acid followed by alkaline hydrolysis of the esters gave the enantiomerically pure *bis*-*N*-oxide (*R*)-**199**. Here, the axial chirality was now fixed by the restricted rotation about the 2,2′-bipyridine axis that was imposed by the two *N*-oxide moieties.

(90) Shimada, T.; Kina, A.; Ikeda, S.; Hayashi, T. A Novel Axially Chiral 2,2′-Bipyridine *N,N′*-Dioxide. Its Preparation and use for Asymmetric Allylation of Aldehydes with Allyl(trichloro)silane as a Highly Efficient Catalyst. *Org. Lett.* **2002**, *4*, 2799.

Scheme 1.10.2. Hayashi and Co-Worker's Novel Synthesis of the Axially Chiral 2,2′-Bipyridyl *bis*-*N*-Oxide **199** (2002)

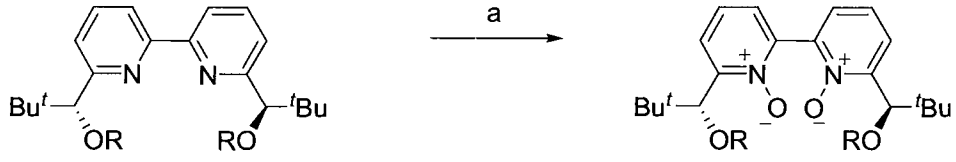


Reagents and Conditions: (a) $KMnO_4$, $NaIO_4$, K_2CO_3, *t*-BuOH, H_2O, reflux, 14 h, 39%; (b) CH_2N_2, Et_2O, room temperature, <10 min, 35%; (c) $LiAlH_4$, THF, room temperature, 2 h, 88%; (d) (*R*)-2,2′-*bis*(chlorocarbonyl)-1,1'-binapthalene, NEt_3, $CHCl_3$, room temperature, 24 h; (e) PhMe, reflux, 48 h, 75% (over two-steps); (f) *m*-CPBA, CH_2Cl_2, room temperature, 64 h, 71%; (g) 6 M NaOH, MeOH, room temperature, 31 h, 100%.

Denmark and co-workers have reported the synthesis of several chiral 2,2′-bipyridyl *bis*-*N*-oxides related to the bipyridine ligand **99** and **200** that were first reported by Bolm and co-workers (Scheme 1.10.3.).[91] The target *bis*-*N*-oxides **201** and **202** were obtained upon oxidation with *m*-chloroperoxybenzoic acid.

(91) Denmark, S. E.; Fan, Y. Catalytic, Enantioselective Aldol Additions to Ketones. *J. Am. Chem. Soc.* **2002**, *124*, 4233.

Scheme 1.10.3. Denmark and Co-Worker's Chiral Nonracemic C_2-Symmetric 2,2′-Bipyridyl Ligand *Bis-N*-Oxide **201** and **202** (2002)



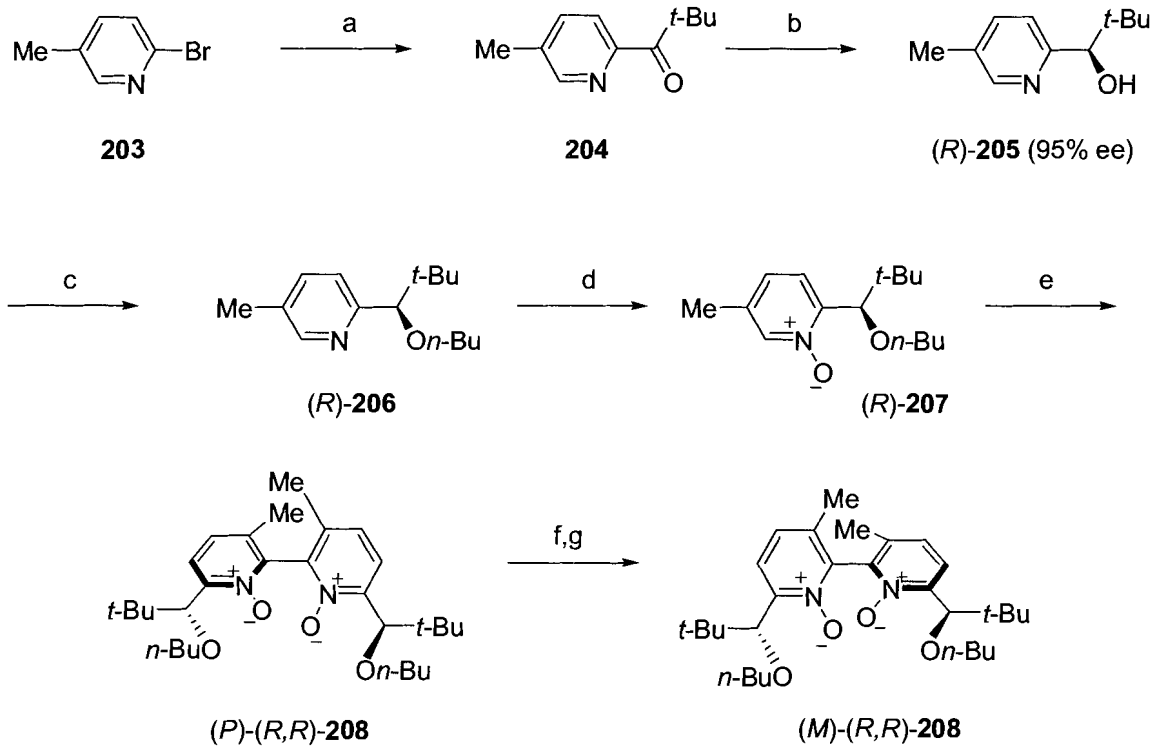
(*R,R*)-**99** (R = Me)
(*R,R*)-**200** (R = *n*-Bu)

(*R,R*)-**201** (R = Me)
(*R,R*)-**202** (R = *n*-Bu)

Reagents and conditions: (a) *m*-CPBA, CH_2Cl_2, room temperature, 12 h, 95% [(*R,R*)-**201**], 96% [(*R,R*)-**202**].

In the same paper, Denmark also reported the synthesis of the related axially chiral 3,3′-dimethyl *bis-N*-oxides **208** (Scheme 1.10.4.). The key step in the synthesis was a novel anionic coupling reaction of the *mono-N*-oxide **207**. Directed lithiation with lithium tetramethylpiperamide at -78 °C at the 2-position of the pyridine was directed by the *N*-oxide moiety. Subsequent addition of half an equivalent of iodine afforded the axially chiral *bis-N*-oxide **208** as a single atropisomer in 48% yield. To obtain the other atropisomer, the *N*-oxide moieties of **208** were reduced with zinc in acetic acid to afford the corresponding 3,3′-dimethyl-2,2′-bipyridine which was subsequently re-oxidized with *m*-chloroperoxybenzoic acid to afford a mixture of diastereoisomers which were separated by flash column chromatography.

Scheme 1.10.4. Denmark and Co-Worker's Axially Chiral 2,2′-Bipyridyl *bis*-*N*-Oxides **208** (2002)



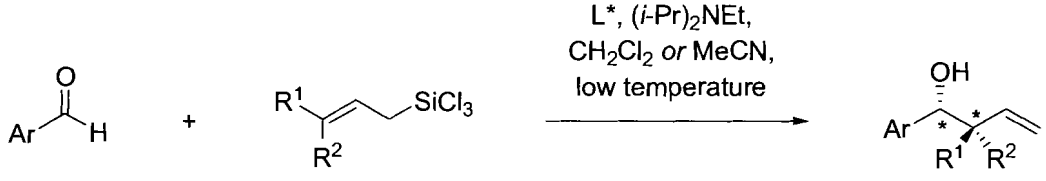
Reagents and conditions: (a) *n*-BuLi, Et_2O, -78 °C, 1 h then pivaloyl chloride (2.0 equiv), -78 °C to room temperature, 90%; (b) (-)-$(ipc)_2BCl$ (1.5 equiv), neat, room temperature, 2 h, 84%; (c) *n*-BuBr, KOH, THF, 18-crown-6, DMF, room temperature, 84%; (d) *m*-CPBA, CH_2Cl_2, room temperature, 12 h, 84%; (e) LiTMP, -73 °C, 16 h then I_2 (0.5 equiv), -73 °C to room temperature, 48%; (f) Zn dust, AcOH, room temperature, 12 h, 91%; (g) *m*-CPBA. CH_2Cl_2, room temperature, 12 h then chromatographic separation of the diastereoisomers afforded 27% [(*M*)-(*R,R*)-**208**] and 67% [(*P*)-(*R,R*)-**208**].

Chiral 2,2′-bipyridine *mono*- and *bis*-*N*-oxides have been used as organocatalysts in asymmetric synthesis. In the following section, a brief discussion of these applications is presented.

1.11. Asymmetric Allylation and Aldol Reactions with 2,2′-Bipyridine *Mono-* and *bis-N*-Oxides

Chiral nonracemic 2,2′-bipyridine *mono-* and *bis-N*-oxides have been found to be excellent asymmetric organocatalysts for the activation of silicon reagents towards reaction with electrophiles (Scheme 1.11.1.).[90]

Scheme 1.11.1. Catalytic Asymmetric Allylation Reactions of Aldehydes



209 **210** **211**

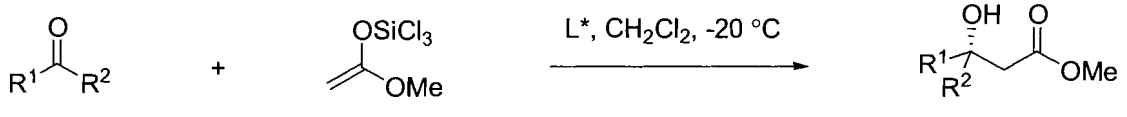
Malkov and co-worker's chiral 2,2′-bipyridine *bis-N*-oxide **194** was found to catalyze the addition of allyltrichlorosilane **210** (R^1 and R^2 = H) to benzaldehyde **209** and afforded the product (*R*)-**211** in moderate enantiomeric excess (41%) when the reaction was performed at -90 °C.[89] A considerable improvement in enantioselectivity (92% ee) was obtained when the Malkov and co-worker's chiral 2,2′-bipyridine *mono-N*-oxide **192** was used as the catalyst at -90 °C. Further studies with this catalyst **192** revealed that the enantioselectivity is highly dependant on the nature of the aldehyde substrate. In particular, aromatic aldehydes were found to be much better substrates than aliphatic aldehydes. Malkov and co-workers envisioned that the efficiency of the reaction could be improved if the rotation about the 2,2′-bipyridine bond was restricted. As such, the chiral 3,3′-dimethyl-2,2′-bipyridine *mono-N*-oxide **192** was prepared and as expected the rotation barrier about the bipyridine bond was high and the atropisomers could be isolated by chromatography. In the reaction of allyltrichlorosilane **210** with

benzaldehyde **209**, the atropisomer (R_{ax})-(+)-**192** induced the formation of the product (*S*)-**211** in excellent enantiomeric excess (98%) at -60 °C.* In contrast, the opposite atropisomer (S_{ax})-(-)-**192** gave the product (*R*)-**211** in lower enantiomeric excess (82%). This demonstrated that the sense of asymmetric induction was controlled mainly by the chiral axis in the ligand and then amplified by the matched chirality of the pinene moiety in the former case.

Hayashi and co-worker's axially chiral phenyl substituted 2,2′-bipyridine *bis-N*-oxide (*R*)-**199** has been shown to have a remarkably high catalytic activity in the allylation reaction of aromatic aldehydes.[90] When 1 mol % of this catalyst was employed, the allylation of *p*-methoxybenzaldehyde was complete in just 15 min and afforded the corresponding product in high enantiomeric excess (94%). The catalyst loading can be reduced to 0.01 mol % without significant loss in enantioselectivity. However, in this case, the reaction time required was 12 h. It was suggested that π-π stacking interactions between the aromatic group on the aldehyde substrate and the phenyl ring on the catalyst could account for the high catalytic activity because aliphatic aldehydes proved to be much less reactive under identical conditions.

Chiral 2,2′-bipyridine *bis-N*-oxides have also been shown to perform well in the asymmetric addition reaction of silyl enol ethers **213** to ketones **212** (Scheme 1.11.2.).[91]

Scheme 1.11.2. Catalytic Asymmetric Addition Reactions of Silyl Enol Ethers to Ketones



212 **213** **214**

(*) The abbreviations (R_{ax}) and (S_{ax}) refer to the absolute stereochemistry of the 2,2′-bipyridine axis.

The chiral 2,2′-bipyridine *bis*-*N*-oxide **202** reported by Denmark and co-workers was found to catalyze the addition of trichlorosilyl ketene acetal **213** to acetophenone **212** and afforded the β-hydroxyester **214** in good enantiomeric excess (64%). Restriction of the rotation about the 2,2′-bipyridine bond *via* the installation of methyl groups at the 3 and 3′ positions to afford the atropisomeric 3,3′-dimethyl-2,2′-bipyridine *bis*-*N*-oxides **208** was found to improve the catalyst efficiency. This again indicated that the reaction is controlled mainly by the axial chirality of the ligand. As such, the atropisomer (S_{ax})-**208** with matched stereogenic centres and axial chirality afforded the product in good enantiomeric excess (84%) while the mismatched catalyst (R_{ax})-**208** afforded the opposite enantiomer of the product in much lower enantiomeric excess (43%).

1.12. Chiral Nonracemic Pyridylphosphine Ligands (*P,N*-Ligands)

To date, a diverse group of chiral *P,N*-ligands that contain nitrogen and phosphorus donor atoms have been synthesized and evaluated in catalytic asymmetric reactions.[92] *P,N*-ligands are of considerable interest in catalysis because of the unique reactivity of their metal complexes which results from the electronic differences between the two donor atoms. The strong *trans*-effect is well established in *P,N*-ligands.[93] The following sections concern a brief review of the syntheses of several known chiral nonracemic pyridylphosphine ligands and their applications in catalytic asymmetric reactions.

---

(92) For a review on chiral pyridylphosphine ligands, see: Chelucci, G.; Orrù, G.; Pinna, G. A. Chiral *P,N*-Ligands with Pyridine-Nitrogen and Phosphorus Donor Atoms. Syntheses and Applications in Asymmetric Catalysis. *Tetrahedron* **2003**, *59*, 9471.

(93) For a detailed discussion on the *trans*-effect in *P,N*-ligands, see: Helmchen, G.; Pfaltz, A. Phosphinooxazolines - A New Class of Versatile, Modular *P,N*-Ligands for Asymmetric Catalysis. *Acc. Chem. Res.* **2000**, *33*, 336.

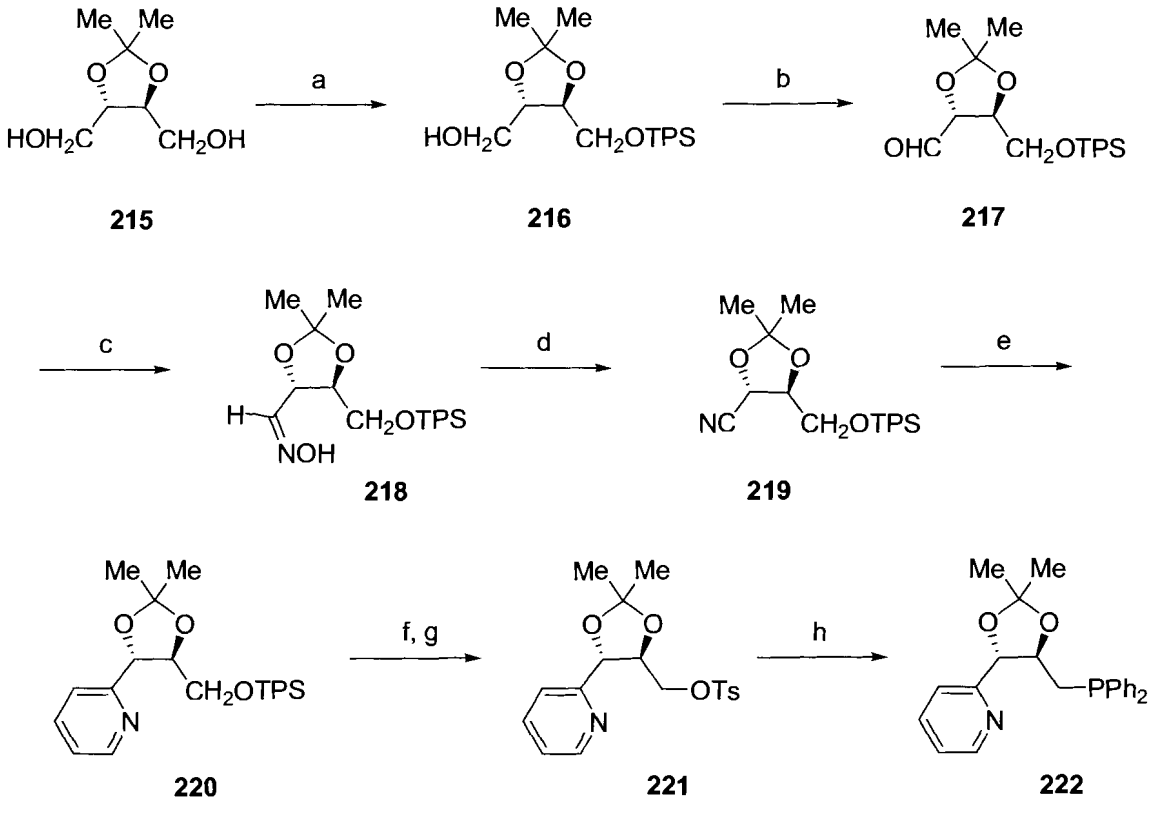
1.12.1. Chiral Pyridylphosphine Ligands With Stereogenic Centres

In 1996, Chelucci and co-workers reported the synthesis of PYDIPHOS **222**, a chiral nonracemic *P,N*-ligand derived from L-(+)-tartaric acid (Scheme 1.12.1.).[94] The synthesis began from the diol **215** which was prepared according to a literature procedure and was subsequently *mono*-protected with *tert*-butyldiphenylsilyl chloride to furnish the alcohol **216**. Following Swern oxidation, the aldehyde **217** was converted to the nitrile **219** *via* treatment of the corresponding oxime **218** with *N,N'*-carbonyldiimidazole. A cobalt(I)-catalyzed cyclotrimerization reaction of the nitrile **219** with two equivalents of acetylene afforded the pyridine **220**.[95] The hydroxyl moiety was then deprotected using a solution of tetra-*n*-butylammonium fluoride in tetrahydrofuran to afford the corresponding alcohol which was subsequently converted to the tosylate **221**. Nucleophillic displacement of the tosylate with potassium diphenylphosphide afforded the chiral nonracemic pyridylphosphine ligand **222**.

(94) Chelucci, G.; Cabras, M. A.; Botteghi, C.; Basoli, C.; Marchetti, M. Synthesis of Homochiral Pyridyl, Bipyridyl and Phosphino Derivatives of 2,2-Dimethyl-1,3-dioxolane: Use in Asymmetric Catalysis. *Tetrahedron: Asymmetry* **1996**, *7*, 885

(95) Varela, J. A.; Saá, C. Construction of Pyridine Rings by Metal-Mediated [2+2+2] Cycloaddition. *Chem. Rev.* **2003**, *103*, 3787.

Scheme 1.12.1. Chelucci and Co-Worker's Chiral *P,N*-Ligand PYDIPHOS **222** derived from Tartaric Acid (1996)



215 **216** **217** **218** **219** **220** **221** **222**

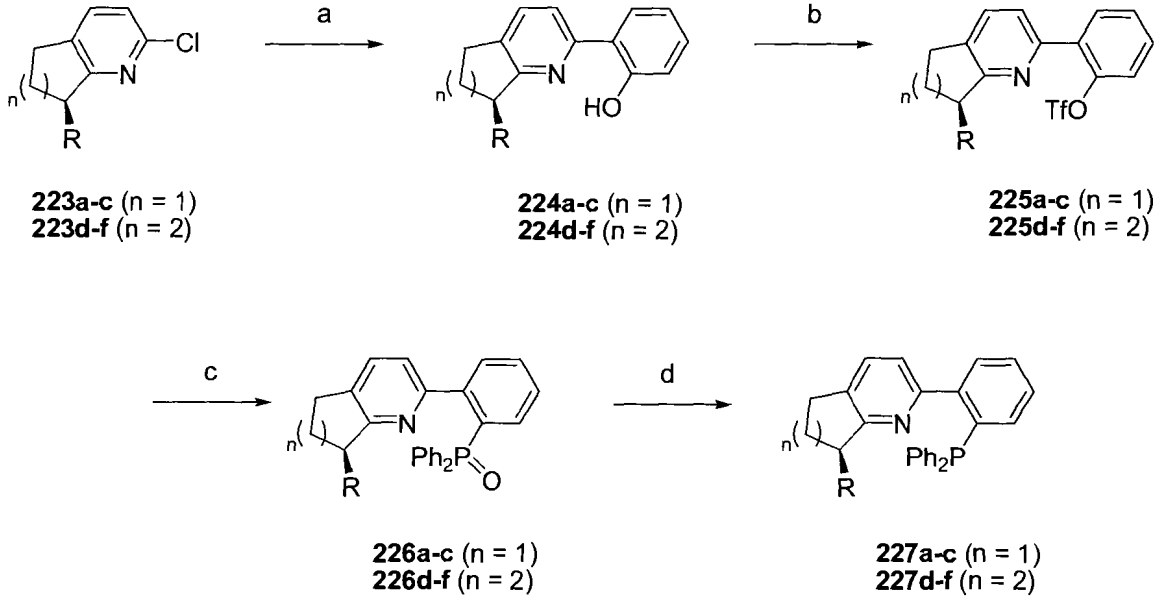
Reagents and conditions: (a) NaH (1 equiv), TPSCl, 75%; (b) $(COCl)_2$, DMSO; NEt_3, -78 °C to room temperature, 89%; (c) $NH_2OH{\cdot}HCl$, 10% K_2CO_3; (d) *N,N'*-carbonyldiimidazole, 89% (over two steps); (e) CpCo(COD), acetylene (14 atm), toluene, 120 °C, 94%; (f) *n*-Bu_4NF, THF, 83%; (g) TsCl, NEt_3, DMAP, CH_2Cl_2; (h) PPh_3, Na/K, dioxane, 67%.

Katsuki and co-workers have reported the synthesis of the chiral nonracemic 2-(phosphinoaryl)pyridine ligands **227a-f** (n = 1 or 2 *and* R = Ph, *i*-Pr and CMe_2OTBS) (Scheme 1.12.2.).[96] The syntheses began from the chiral 2-chloropyridines **223a-f**, which had been previously used in the preparation of chiral 2,2′-bipyridine ligands.[61] A Suzuki coupling reaction with *o*-hydroxyphenylboronic acid afforded the pyridylphenols **224a-f**

(96) Ito, K.; Kashiwagi, R.; Iwasaki, K.; Katsuki, T. Asymmetric Allylic Alkylation using a Palladium Complex of Chiral 2-(Phosphinoaryl)pyridine Ligands. *Synlett* **1999**, *10*, 1563.

which were then converted to the triflates **225a-f** upon reaction with triflic anhydride in the presence of 2,6-lutidine. A palladium-catalyzed coupling reaction of the triflates **225a-f** with diphenylphosphine oxide furnished the phosphine oxides **226a-f** which were converted to the desired chiral 2-(phosphinoaryl)pyridine ligands **227a-f** on reduction with trichlorosilane and triethylamine.

Scheme 1.12.2. Katsuki and Co-Worker's Chiral *P,N*-Ligands **227a-f** (1999)



223a-c (n = 1)
223d-f (n = 2)

224a-c (n = 1)
224d-f (n = 2)

225a-c (n = 1)
225d-f (n = 2)

226a-c (n = 1)
226d-f (n = 2)

227a-c (n = 1)
227d-f (n = 2)

Reagents and conditions: (a) 2-hydroxyphenylboronic acid, $Pd(PPh_3)_4$, Na_2CO_3, dioxane/H_2O (6:1); (b) Tf_2O, 2,6-lutidine; (c) $HPOPh_2$, $Pd(OAc)_2$, dppb, *i*-Pr_2NEt, DMSO; (d) $HSiCl_3$, NEt_3, $PhCH_3$.

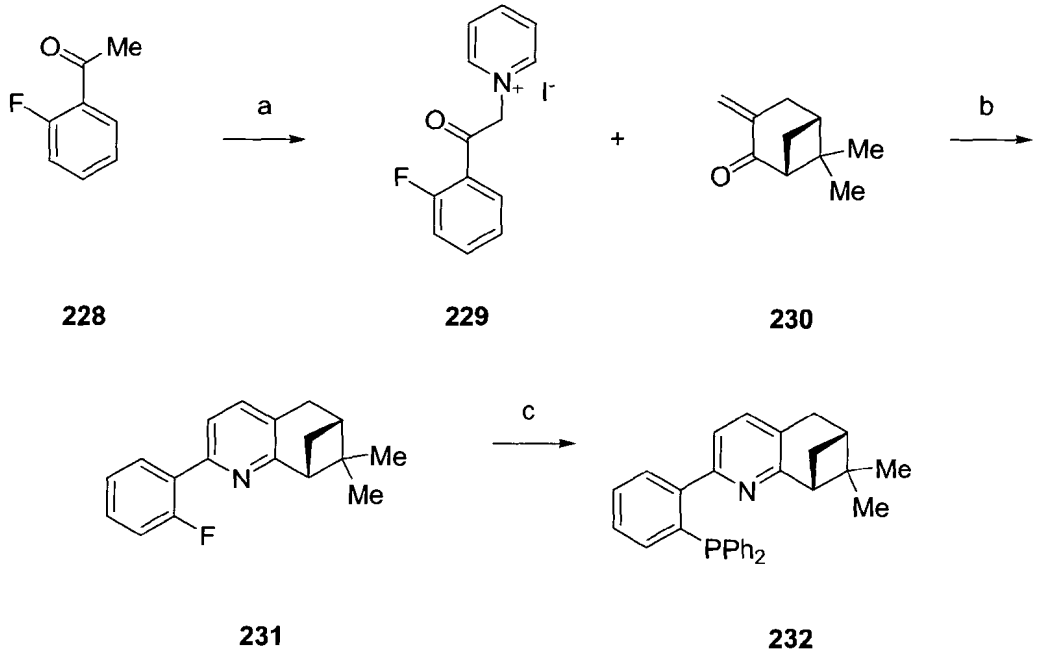
In 2001, synthetic routes to the terpene-derived *P,N*-ligand **232** were reported independently by Kočovský and co-workers and Chelucci and co-workers.[97,98] Each synthetic route used the Kröhnke cyclization reaction to install the pyridine ring by

(97) Malkov, A. V.; Bella, M.; Stará, G.; Kočovský, P. Modular Pyridine-Type *P,N*-Ligands Derived from Monoterpenes: Application in Asymmetric Heck Addition. *Tetrahedron Lett.* **2001**, *42*, 3045.

(98) Chelucci, G.; Saba, A.; Soccolini, F. Chiral 2-(2-Diphenylphosphinophenyl)-5,6,7,8-tetrahydroquinolines: New *P,N*-Ligands for Asymmetric Catalysis. *Tetrahedron* **2001**, *57*, 9989.

reaction of the terpene derived α,β-unsaturated ketone **230** with the pyridinium salts **229** or **234**. The major difference between the two synthetic routes that were described was in the way in which the diphenylphosphino moiety was installed. In the route reported by Kočovský, a nucleophilic displacement of the aromatic fluoride **231** with potassium diphenylphosphide was used to afford the chiral nonracemic *P,N*-ligand **232** in 49% yield (Scheme 1.12.3.).

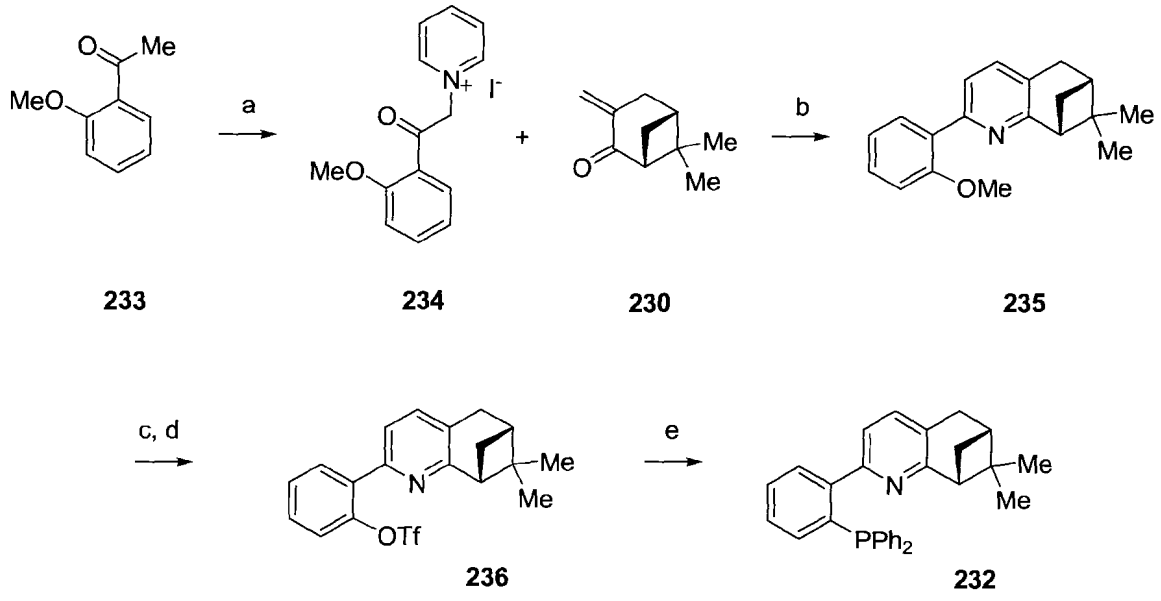
Scheme 1.12.3. Kočovský and Co-Worker's Terpene-Derived *P,N*-Ligand **232** (2002)



Reagents and conditions: (a) I_2, pyridine; (b) NH_4OAc, AcOH, 90 °C, 3 h, 47%; (c) $KPPh_2$, 18-crown-6, THF, room temperature, 48 h, 49%.

The route described by Chelucci featured a nickel(II)-catalyzed coupling reaction between the aromatic triflate **236** and diphenylphosphine in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) that afforded the desired *P,N*-ligand **232** in 43% yield (Scheme 1.12.4.).

Scheme 1.12.4. Chelucci and Co-Worker's Terpene-derived *P,N*-Ligand **232** (2002)



Reagents and conditions: (a) I_2, pyridine; (b) NH_4OAc, AcOH, 100 °C, 4 h, 24%; (c) BBr_3, CH_2Cl_2, 86%; (d) Tf_2O, pyridine, CH_2Cl_2, 82%; (e) $HPPh_2$, 10 mol % of $NiCl_2$(dppe), DABCO (2 equiv), DMF, 100 °C, 43%.

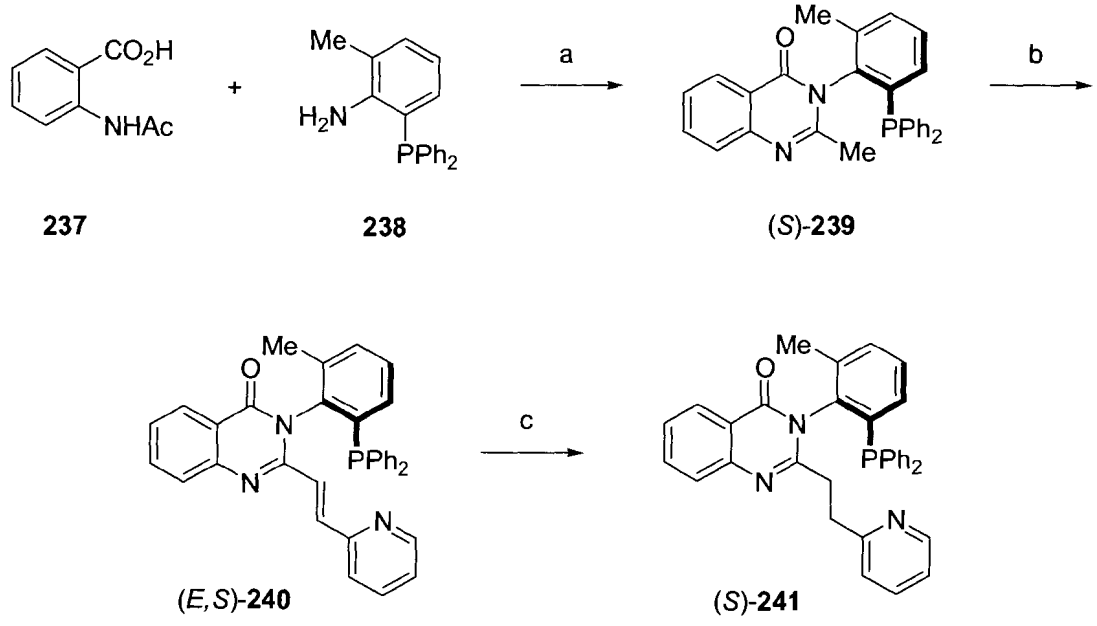
1.12.2. Chiral Pyridylphosphine Ligands With Axial Chirality

To date, there have only been a few syntheses of pyridylphosphine ligands reported which contain axial chirality. In 1998, Dai and co-workers reported the synthesis of the atropisomeric quinazolinone *P,N*-ligand (*S*)-**241** (Scheme 1.12.5.).[99] The starting material employed was (*S*)-2-methyl-3-(2-diphenylphosphino-6-methylphenyl)-4(3*H*)-quinazolinone (*S*)-**239**. This compound was prepared in racemic form by condensation of *N*-acetylanthranillic acid **237** and 2-(diphenylphosphino)-6-methylaniline **238**. The atropisomers were then resolved by coordination of this phosphine to a chiral

(99) (a) Dai, X.; Wong, A.; Virgil, S. Synthesis and Resolution of Quinazolinone Atropisomeric Phosphine Ligands. *J. Org. Chem.* **1998**, *63*, 2597. (b) Dai, X.; Virgil, S. Asymmetric Allylic Alkylation by Palladium Complexes with Atropisomeric Quinazolinone Phosphine Ligands. *Tetrahedron Lett.* **1999**, *40*, 1245.

palladium complex and subsequent fractional crystallization. The methyl group of the product (*S*)-**239** was then deprotonated with *n*-butyllithium in tetrahydrofuran and the resultant anion was reacted with 2-pyridinecarboxaldehyde to afford, after aqueous workup, the unsaturated *P,N*-ligand (*E,S*)-**240**. The saturated *P,N*-ligand (*S*)-**241** was obtained following a hydrogenation reaction.

Scheme 1.12.5. Dai and Co-Worker's Axially Chiral Quinazolinone *P,N*-Ligands **240** and **241** (1998)



237 **238** (*S*)-**239** (*E,S*)-**240** (*S*)-**241**

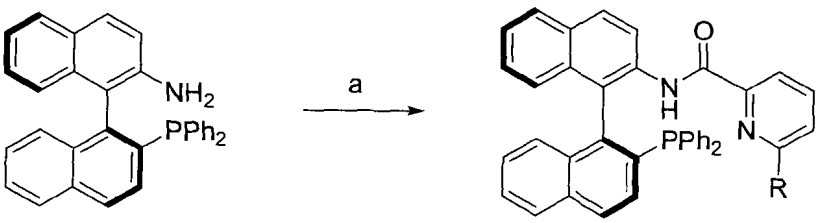
Reagents and conditions: (a) $PhSO_2Cl$, DMAP, pyridine, benzene, 80 °C, 36 h, 77%, then resolution of atropisomers; (b) *n*-BuLi, THF, -78 °C then 2-pyridinecarboxaldehyde, 78%; (b) H_2, 10% Pd/C, 95%.

In 1999, Zhang and co-workers reported the synthesis of two axially chiral *P,N*-ligands (*S*)-**243** which contained a 1,1'-binapthalene backbone (Scheme 1.12.6.).[100] The ligands were prepared from the known aminophosphine (*S*)-**242** by reaction with 2-pyridinecarboxylic acid or 6-methyl-2-pyridinecarboxylic acid in the presence of the

(100) Hu, W.; Chen, C.-C.; Zhang, X. Development of New Chiral *P,N* Ligands and Their Application in the Cu-Catalyzed Conjugate Addition of Diethylzinc to Enones. *Angew. Chem., Int. Ed.* **1999**, *38*, 3518.

coupling reagents *N,N'*-dicyclohexylcarbodiimide and *N,N*-dimethyl-4-aminopyridine in dichloromethane.

Scheme 1.12.6. Zhang and Co-Worker's Axially Chiral *P,N*-Ligand **243** (1999)



(*S*)-**242** (*S*)-**243a,b**

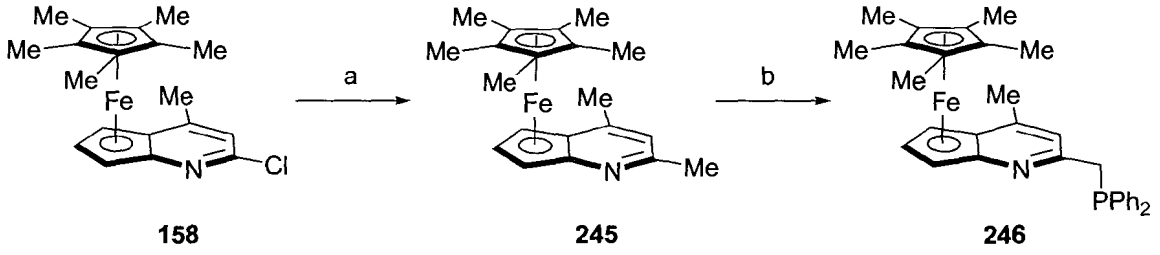
Reagents and conditions: (a) *N,N*-dicyclohexylcarbodiimide, DMAP, 2-pyrdinecarboxylic acid *or* 6-methyl-2-pyridine carboxylic acid.

1.12.3. Chiral Pyridylphosphine Ligands with Planar Chirality

In 2002, Fu and co-workers reported the synthesis of the novel planar chiral *P,N*-ligand **246** (Scheme 1.12.7.).[101] The synthesis began by sequential treatment of iron(II) chloride with Cp*Li and then the anion obtained on deprotonation of 2-chloro-4-methyl-pyrindine **157** with *n*-butyllithium which afforded the racemic planar chiral 2-chloropyridine **158**. A nickel(II)-catalyzed coupling reaction of the 2-chloropyridine **158** with methylmagnesium bromide afforded the 2-methylpyridine **245**. Regioselective deprotonation of the 2-methyl group with *n*-butyllithium followed by reaction with chlorodiphenylphosphine afforded the desired planar chiral *P,N*-ligand **246** which was resolved by chiral HPLC.

(101) Tao, B.; Fu, G. C. Application of a New Family of *P,N*-Ligands to the Highly Enantioselective Hydrosilylation of Aryl Alkyl and Dialkyl Ketones. *Angew. Chem., Int. Ed.* **2002**, *41*, 3892.

Scheme 1.12.7. Fu and Co-Worker's Planar Chiral *P,N*-Ligand **246** (2002)



158 **245** **246**

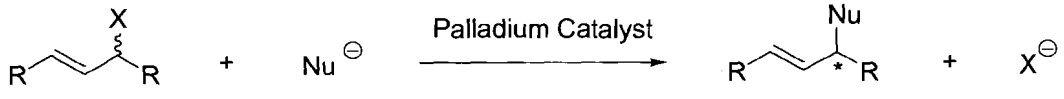
Reagents and conditions: MeMgBr, $NiCl_2$(dppp), 80%; (b) *n*-BuLi then $ClPPh_2$, 71%.

The application of some of the chiral pyridylphosphine ligands described above in palladium-catalyzed asymmetric allylic substitution reactions and palladium-catalyzed asymmetric Heck reactions is reviewed in the following sections.

1.12.4. Catalytic Asymmetric Allylic Substitution Reactions

The palladium-catalyzed asymmetric allylic substitution (AAS) reaction involves the displacement of an allylic leaving group with a nucleophile (Scheme 1.12.8.).[102] This reaction has received a great deal of attention due to its synthetic versatility which is demonstrated by its extensive application in target-oriented synthesis.[103]

Scheme 1.12.8. Palladium-Catalyzed Asymmetric Allylic Substitution Reaction



247 **248**

(102) For reviews on the AAS reaction, see: (a) Trost, B. M. Asymmetric Allylic Alkylation, an Enabling Methodology. *J. Org. Chem.* **2004**, *69*, 5813. (b) Trost, B. M. Pd Asymmetric Allylic Alkylation (AAA). A Powerful Synthetic Tool. *Chem. Pharm. Bull.* **2002**, *50*, 1. (c) Trost, B. M.; Van Vranken, D. L. Asymmetric Transition Metal-Catalyzed Allylic Alkylations. *Chem. Rev.* **1996**, *96*, 395.

(103) Trost, B. M.; Crawley, M. L. Asymmetric Transition-Metal-Catalyzed Allylic Alkylations: Applications in Total Synthesis. *Chem. Rev.* **2003**, *103*, 2921.

The proposed mechanism of the AAS reaction is shown below (Figure 1.12.1.). In the first step, the allylic substrate **247** undergoes coordination to the palladium catalyst **252** to form the π-complex **249**. Subsequent oxidative addition of the palladium centre to the C-X bond with inversion of configuration generates the cationic (π-allyl)palladium intermediates *W*-**250** and *M*-**250**. These intermediates are in conformational equilibrium and have been observed spectroscopically[104] and crystallographically.[105] A nucleophile then attacks these electrophilic intermediates and displaces the palladium with inversion of configuration to generate complex **251**. In the final step of the mechanism, the reaction product **248** is decomplexed from the palladium catalyst. This mechanism only holds for nucleophiles with a pK_a that is less than 25. Nucleophiles with a pK_a that is greater than 25 undergo an alternative reaction pathway that involves coordination of the nucleophile to the palladium centre followed by a reductive elimination process.

(104) Moberg, C.; Brember, U.; Hallman, K.; Svensson, M.; Norrby, P.; Hallberg, A.; Larhed, M.; Csoregh, I. Selectivity and Reactivity in Asymmetric Allylic Alkylation. *Pure Appl. Chem.* **1999**, *71*, 1477.

(105) Sauthier, N.; Fornies, J.; Toupet, L.; Reau, R. Palladium(II) Complexes of Chiral 1,2-Diiminophosphoranes: Synthesis, Structural Characterization, and Catalytic Activity for the Allylic Alkylation. *Organometallics* **2000**, *19*, 553.

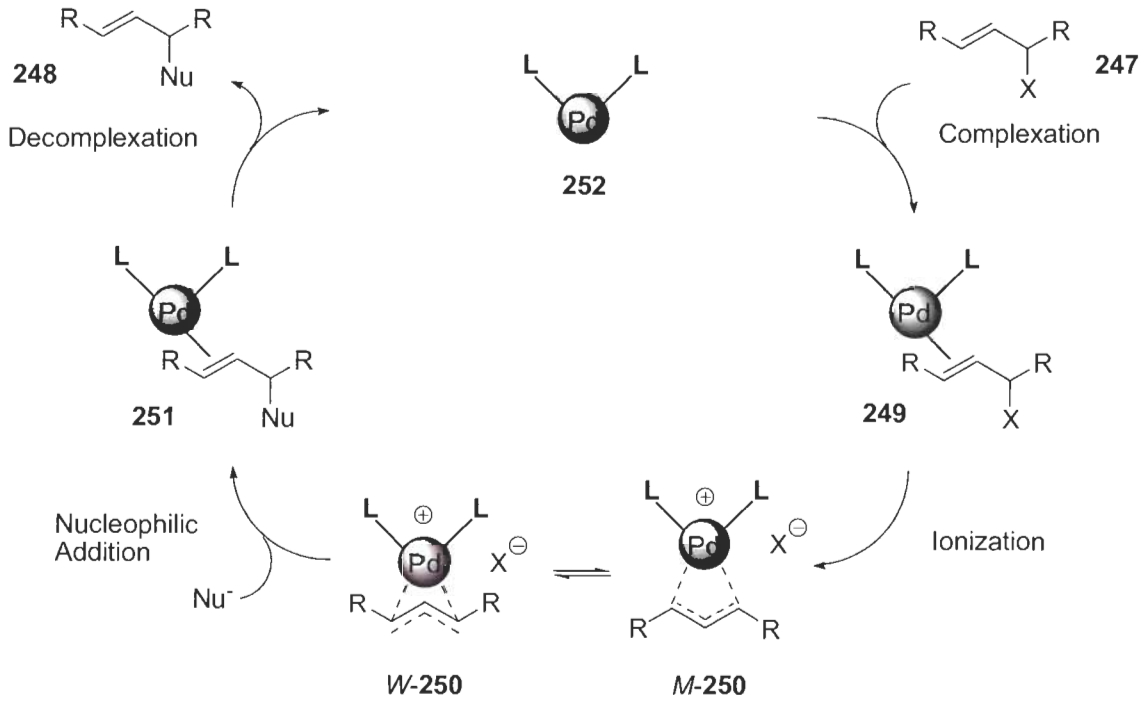


Figure 1.12.1. Mechanism for palladium-catalyzed allylic substitution reactions.

An important aspect of this proposed mechanism is that the cationic (π-allyl)palladium complex exists in a dynamic equilibrium during which its conformation and structure may change by dissociation and reassociation processes.[106] In the above mechanism, only the *M*- and *W*-isomers of the cationic (π-allyl)palladium complex are shown. However, it is important to note that the *anti,syn* isomers are also possible *via* isomerization of both the *M*- and *W*-isomers (Figure 1.12.2.).

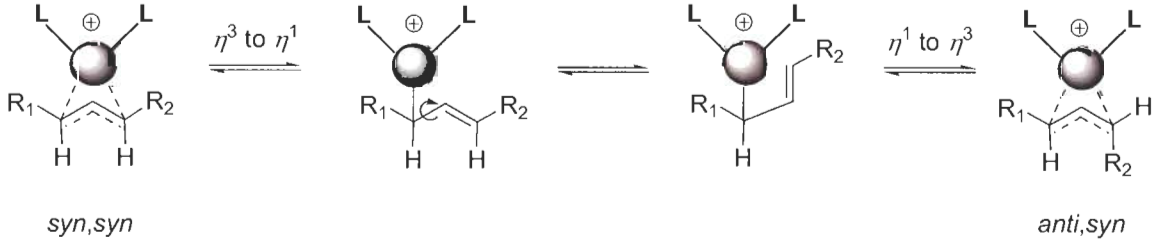
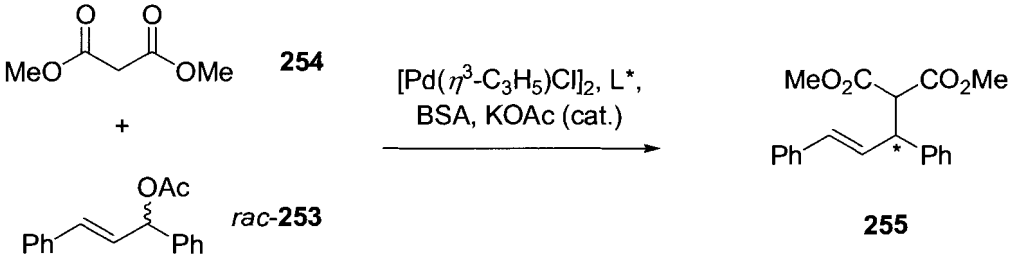


Figure 1.12.2. Dynamic conformational equilibria of cationic π-allyl metal complexes.

(106) Trost, B. M.; Toste, F. D. Regio- and Enantioselective Allylic Alkylation of an Unsymmetrical Substrate: A Working Model. *J. Am. Chem. Soc.* **1999**, *121*, 4545.

The benchmark reaction for evaluating new chiral ligands in the AAS reaction is the palladium-catalyzed nucleophilic attack of the anion of dimethyl malonate **254** on racemic 1,3-diphenylprop-2-enyl acetate *rac*-**253** (Scheme 1.12.9.). This reaction is typically performed by coordinating the chiral ligand to allylpalladiumchloride dimer *in situ* followed by the addition of dimethyl malonate, *N,O-bis*trimethylsilyl acetamide (BSA) and a catalytic amount of potassium acetate (Trost's procedure).[107]

Scheme 1.12.9. Palladium-Catalyzed Asymmetric Allylic Substitution Reaction of Racemic 1,3-Diphenylprop-2-enyl acetate *rac*-**253** with Dimethyl Malonate **254**



The palladium complexes of the chiral 2-(phosphinoaryl)pyridine ligands **227a-f** reported by Kastsuki and co-workers were evaluated in this reaction using Trost's procedure.[97] Each of the ligands afforded the product **255** in less than three hours at room temperature and in high yields. The enantioselectivities ranged from good to excellent (64 to 97% ee). The best result was obtained with ligand **227b** which showed a very high catalytic activity (reaction time ~30 min) and afforded the product in excellent enantiomeric excess (97%).

The terpene-derived *P,N*-ligands **232** reported by Chelucci and Kočovský have also been evaluated using Trost's procedure.[98,99] The ligands provided a high degree of

(107) Trost, B. M.; Murphy, D. J. A Model for Metal-Templated Catalytic Asymmetric Synthesis *via* π-Allyl Fragments. *Organometallics* **1985**, *4*, 1143.

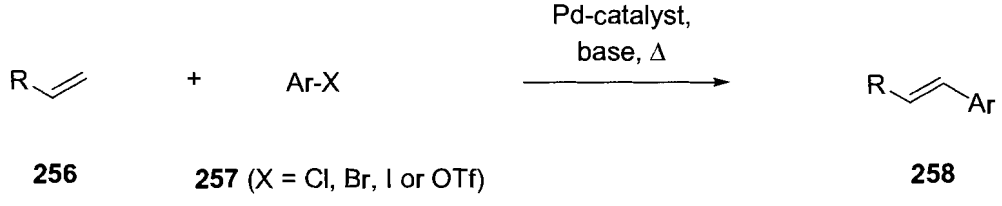
catalytic activity and afforded the product **255** in high yield. The enantioselectivities observed were moderate to good in these reactions (37 to 70% ee).

The axially chiral ligands (*S*)-**240** and (*S*)-**241** reported by Dai and co-workers have been evaluated in the allylic substitution reaction under a variety of conditions.[100] The optimal conditions involved the use of sodium hydride as the base in the presence of 15-crown-5 in dichloromethane. Under these conditions the product **255** was obtained in good enantiomeric excess (85%) with the unsaturated ligand (*S*)-**240** and in lower enantiomeric excess (78%) with the saturated ligand (*S*)-**241**. This suggested that the palladium-complex formed with the saturated ligand (*S*)-**241** is less conformationally rigid and that this resulted in a loss of stereoselectivity.

1.12.5. Catalytic Asymmetric Heck Reaction

The palladium-catalyzed Heck reaction is a particularly versatile carbon-carbon bond formation reaction in organic synthesis.[108] The overall reaction involves the coupling of an aryl (or vinyl) halide or triflate **257** with an alkene substrate **256** (Scheme 1.12.10.).

Scheme 1.12.10 Palladium-Catalyzed Heck Reaction



256 **257** (X = Cl, Br, I or OTf) **258**

(108) For a review on the Heck reaction, see: Shibasaki, M.; Vogl, E. M.; Ohshima, T. Asymmetric Heck Reaction. *Adv. Synth. Catal.* **2004**, *346*, 1533.

The first examples of asymmetric Heck reactions were reported independently in 1989 by Shibasaki and co-workers and Overman and co-workers (Figure 1.12.3.).[109,110] Here, the achiral vinyl iodide **259** and triflate **261** underwent asymmetric intramolecular cyclization reactions to afford the products **260** and **262**, respectively. Although the enantioselectivities achieved in these initial reactions were only moderate (45 to 46% ee), the potential of this reaction as a powerful asymmetric carbon-carbon bond formation reaction was clearly demonstrated.

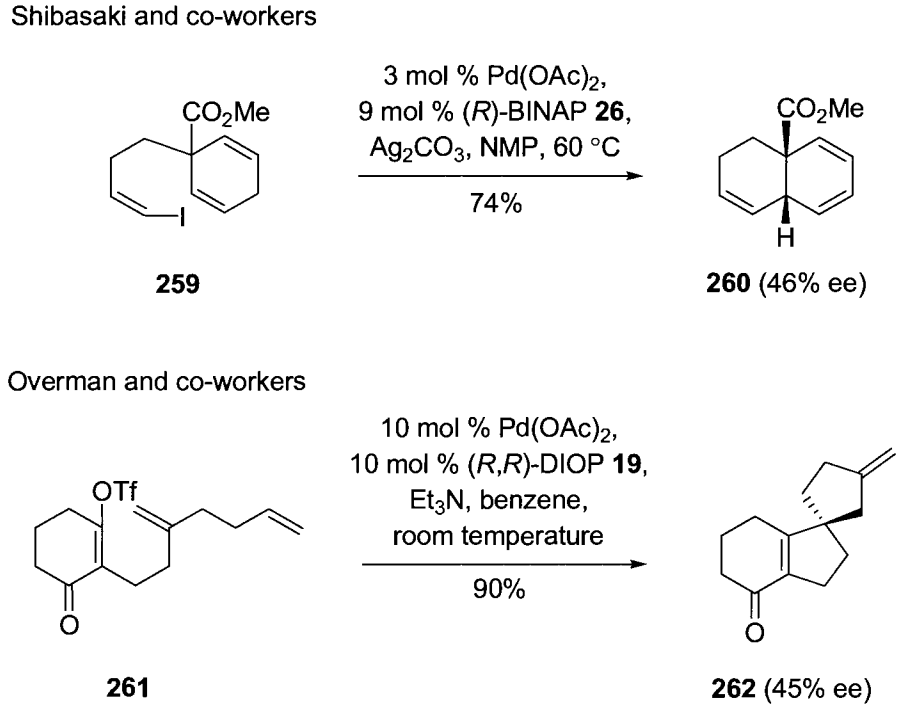


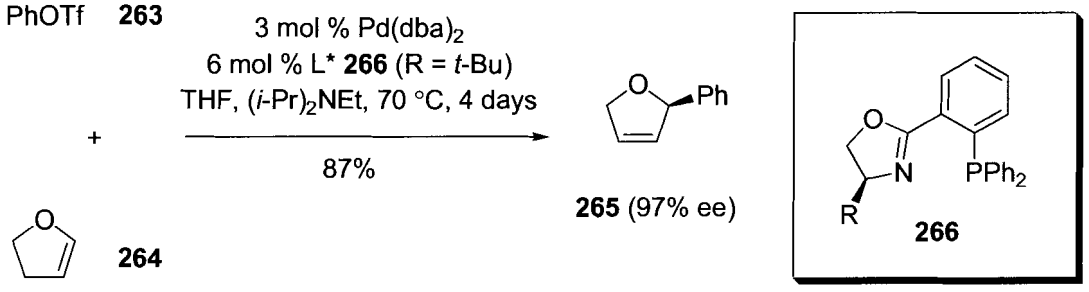
Figure 1.12.3. Asymmetric Heck reactions reported by Shibasaki and co-workers and Overman and co-workers (1989).

(109) Sato, Y.; Sodeoka, M.; Shibasaki, M. Catalytic Asymmetric Carbon-Carbon Bond Formation: Asymmetric Synthesis of *cis*-Decalin Derivatives by Palladium-Catalyzed Cyclization of Prochiral Alkenyl Iodides. *J. Org. Chem.* **1989**, *54*, 4738.

(110) Carpenter, N. E.; Kucera, D. J.; Overman, L. E. Palladium-Catalyzed Polyene Cyclizations of Trienyl Triflates. *J. Org. Chem.* **1989**, *54*, 5846.

Recently, Pfaltz and co-workers have shown the effectiveness of chiral *P,N*-ligands, particularly phosphinooxazolines **266**, in catalytic asymmetric Heck reactions.[111] High enantioselectivities (up to 97% ee) were observed in the asymmetric Heck reaction of phenyl triflate **263** with 2,3-dihydrofuran **264** (Scheme 1.12.11.).

Scheme 1.12.11. Palladium-Catalyzed Asymmetric Heck Reaction



The chiral pyridylphosphine ligands **232** reported by Kočovský and co-workers have also been evaluated in the asymmetric Heck reaction of phenyltriflate and dihydrofuran. In this case, the reaction product was isolated in moderate to good enantiomeric excess (up to 70%).[98] This is the only report in the literature of a chiral pyridylphosphine ligand being evaluated in a catalytic asymmetric Heck reaction.

1.13. Thesis Overview

In Chapter 2 of this thesis, the synthesis of a series of chiral nonracemic C_2-symmetric 2,2′-bipyridyl ligands is described. These ligands were evaluated as chiral directors in copper(I)-catalyzed asymmetric cyclopropanation reactions of alkenes and diazoesters.

(111) For a review on the use of chiral phosphinooxazoline ligands in the asymmetric Heck reaction, see: Loiseleur, O.; Hayashi, M.; Keenan, M.; Schmees, N.; Pfaltz, A. *J. Organomet. Chem.* **1999**, *576*, 16.

In Chapter 3, the synthesis of a related chiral nonracemic pyridine *N*-oxide as well as a C_2-symmetric 2,2′-bipyridine *N*,*N*′-dioxide is described. These *N*-oxides were evaluated as catalysts in a desymmeterization reaction of *cis*-stilbene oxide.

In Chapter 4, the synthesis of a series of chiral nonracemic pyridylphosphine ligands is described. These ligands were constructed based on the same design concept that was used for the 2,2′-bipyridine ligands and the *N*-oxides. These *P*,*N*-ligands were then evaluated for use as chiral directors in palladium-catalyzed asymmetric Heck reactions, in palladium(II)-catalyzed asymmetric allylic substitution reactions and in iridium(I)-catalyzed asymmetric hydrogenation reactions.

In Chapter 5, the synthesis of a chiral nonracemic C_2-symmetric 2,2′-bipyridyl ligand that originated from a subtle modification of the 2,2′-bipyridyl ligands, described in Chapter 2, is described. This ligand was evaluated in copper(I)-catalyzed asymmetric cyclopropanation reactions of alkenes and diazoesters, in copper(II)-catalyzed asymmetric Friedel-Crafts alkylation reactions and in copper(I)-catalyzed asymmetric allylic oxidation reactions.

In Chapter 6, an outline of the future development of this research project in asymmetric synthesis is outlined and in Chapter 7, an overall conclusion section on the research described in this thesis is presented.

In the final chapter of this thesis, Chapter 8, the experimental procedures and full characterization data (including elemental analyses or high-resolution mass spectrometry) concerning all of the compounds discussed in this thesis are provided.

CHAPTER 2: RESULTS AND DISCUSSION

SYNTHESIS AND EVALUATION OF A SERIES OF NEW CHIRAL NONRACEMIC C_2-SYMMETRIC AND UNSYMMETRIC 2,2′-BIPYRIDYL LIGANDS

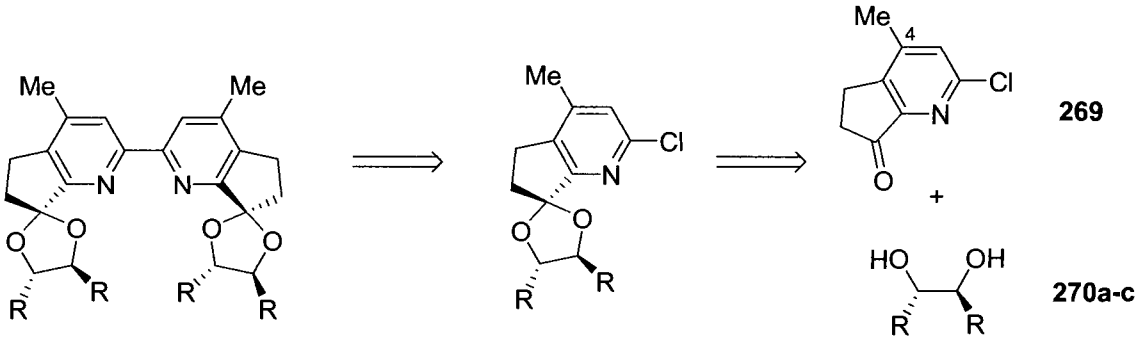
2.1. Introduction

In this chapter, a modular synthesis of a series of new chiral nonracemic and C_2-symmetric 2,2′-bipyridyl ligands as well as the synthesis of the corresponding unsymmetric 2,2′-bipyridyl ligands is described. The design concept that was conceived for the construction of these new 2,2′-bipyridyl ligands was discussed earlier in this thesis (Chapter 1, Section 1.8.).* The objective of this research project was to evaluate the effect of the chiral cyclic acetal substituent of these ligands in various catalytic asymmetric reactions.

We envisioned modular syntheses of the C_2-symmetric 2,2′-bipyridyl ligands **267a-c** (R = Me, *i*-Pr and Ph) *via* condensation of the chloroketone **269** and the corresponding chiral nonracemic C_2-symmetric 1,2-diols **270a-c**. The resultant chiral acetals **268a-c** would then be converted to the C_2-symmetric ligands **267a-c** by a nickel(0)-mediated *homo*-coupling reaction (Figure 2.1.1.). In this manner, a series of ligands could potentially be prepared from a common intermediate (the chloroketone **269**). Moreover, the substitution pattern of the chiral acetal could be varied by selection of an appropriate 1,2-diol so that the ligand could be modified for optimization in a particular asymmetric reaction. The methyl substituent at C-4 of these ligands was

(*) Part of the research described in this Chapter has been submitted for publication: Lyle, M. P. A.; Draper, N. D.; Wilson, P. D. Synthesis and Evaluation of New Chiral Nonracemic C_2-Symmetric and Unsymmetric 2,2′-Bipyridyl Ligands. *J. Org. Chem.* **2005**, *70*, 0000.

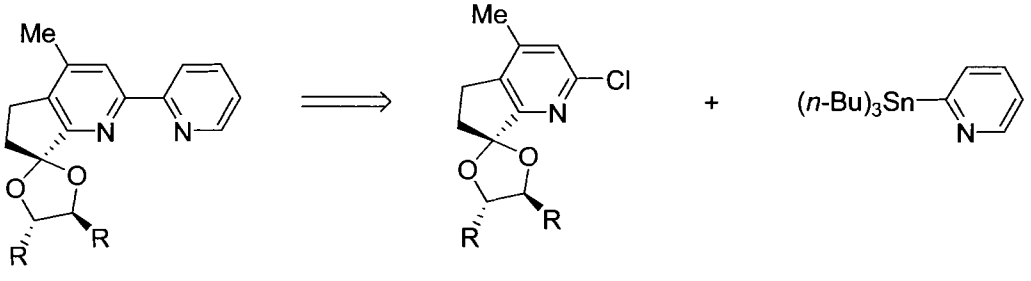
selected to facilitate the synthesis of the heterocyclic precursors from readily available starting materials.



267a-c (R = Me, *i*-Pr and Ph) **268a-c** (R = Me, *i*-Pr and Ph)

Figure 2.1.1. Retrosynthetic analysis of the chiral nonracemic C_2-symmetric 2,2′-bipyridyl ligands **267a-c** (R = Me, *i*-Pr and Ph).

In a similar fashion, the chiral nonracemic unsymmetric 2,2′-bipyridyl ligands **271a-c** (R = Me, *i*-Pr and Ph) could be prepared by a Stille coupling reaction of the chiral acetals **268a-c** (R = Me, *i*-Pr and Ph) and the known 2-(tri-*n*-butylstannyl)pyridine **272** (Figure 2.1.2.).[54]

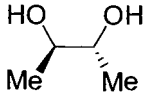


271a-c (R = Me, *i*-Pr and Ph) **268a-c** (R = Me, *i*-Pr and Ph) **272**

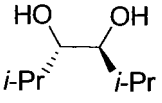
Figure 2.1.2. Retrosynthetic analysis of the chiral nonracemic unsymmetric 2,2′-bipyridyl ligands **271a-c** (R = Me, *i*-Pr and Ph).

2.2. Chiral Nonracemic C_2-Symmetric 1,2-Diols (270a-c)

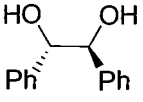
A variety of chiral nonracemic C_2-symmetric diols are commercially available or can be readily prepared from achiral or chiral nonracemic precursors. For our investigations, we selected three C_2-symmetric 1,2-diols that would provide a series of bipyridine ligands with varying steric properties around the binding site of the chiral ligands. These were: (2*R*,3*R*)-2,3-butanediol **270a** (R = Me); (1*S*,2*S*)-1,2-diisopropyl-1,2-ethanediol **270b** (R = *i*-Pr); and (1*S*,2*S*)-1,2-diphenyl-1,2-ethanediol **270c** (R = Ph) (Figure 2.2.1.).



(*R*,*R*)-**270a**



(*S*,*S*)-**270b**



(*S*,*S*)-**270c**

Figure 2.2.1. Chiral nonracemic C_2-symmetric 1,2-diols **270a-c**.

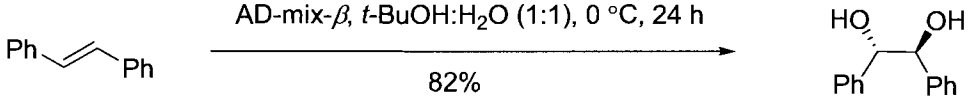
Of the three chiral diols, the diols **270a** (R = Me) and **270c** (R = Ph) are currently commercially available in both enantiomeric forms.* However, when this research project was initiated, the chiral diol **270c** (R = Ph) was not commercially available and so it was prepared on a large scale *via* the Sharpless asymmetric dihydroxylation reaction of (*E*)-stilbene **273** (Scheme 2.2.1.).[112] This involved the reaction of (*E*)-stilbene **273** and AD-mix-β in a mixture of *tert*-butanol and water (1:1) at 0 °C for 24 h that afforded the desired chiral nonracemic diol **270c** (R = Ph) in good yield (82%) and in high enantiomeric excess (>99%) after a single recrystallization from ether. The enantiomeric

(*) (2*R*,3*R*)-2,3-Butanediol is significantly less expensive than the corresponding (2*S*,3*S*)-enantiomer and so it was purchased for use in these studies.

(112) Sharpless, K.; Amberg, Y.; Bannani, G.; Crispino, J.; Hartung, K.; Jeong, H.; Kwong, K.; Morikawa, Z.; Wang, D. Xu, X.; Zhang, X.-L. The Osmium-Catalyzed Asymmetric Dihydroxylation: A New Ligand Class and a Process Improvement. *J. Org. Chem.* **1992**, *57*, 2768.

purity of the diol **270c** was determined by comparison of the optical rotation ($[\alpha]_D^{20}$ - 94.0 [*c* 2.5, ethanol]) with a literature value ($[\alpha]_D^{20}$ - 94.1 [*c* 1.0, ethanol]).[113]

Scheme 2.2.1. Preparation of the Chiral Nonracemic 1,2-Diol **270c** (R = Ph) *via* a Sharpless Asymmetric Dihydroxylation Reaction



273 **270c** (>99% ee)

The non-commercially available diol **270b** (R = *i*-Pr) was synthesized from (2*R*,3*R*)-(+)-tartaric acid ethyl ester **274** according to a five-step literature procedure (Scheme 2.2.2.).[114] The first step of the sequence involved the reaction of (2*R*,3*R*)-(+)-tartaric acid ethyl ester **274** with cylcopentanone in the presence of a catalytic amount of *p*-toluenesulfonic acid in benzene at reflux for 3 days which afforded the acetal **275** in good yield (91%). The acetal **275** was then reacted with four equivalents of methyl magnesium bromide in tetrahydrofuran at 0 °C to afford the diol **276** in good yield (89%). The dimesylate was then prepared on treatment of the diol **276** with excess methanesulfonyl chloride in dichloromethane in the presence of triethylamine and *N,N*-dimethyl-4-aminopyridine at 0 °C for 30 min. After removal of the volatiles, the crude dimesylate was taken up in dimethyl sulfoxide and treated with potassium *tert*-butoxide at room temperature for 16 h to afford the diene **277** in good yield (55%, over two steps).

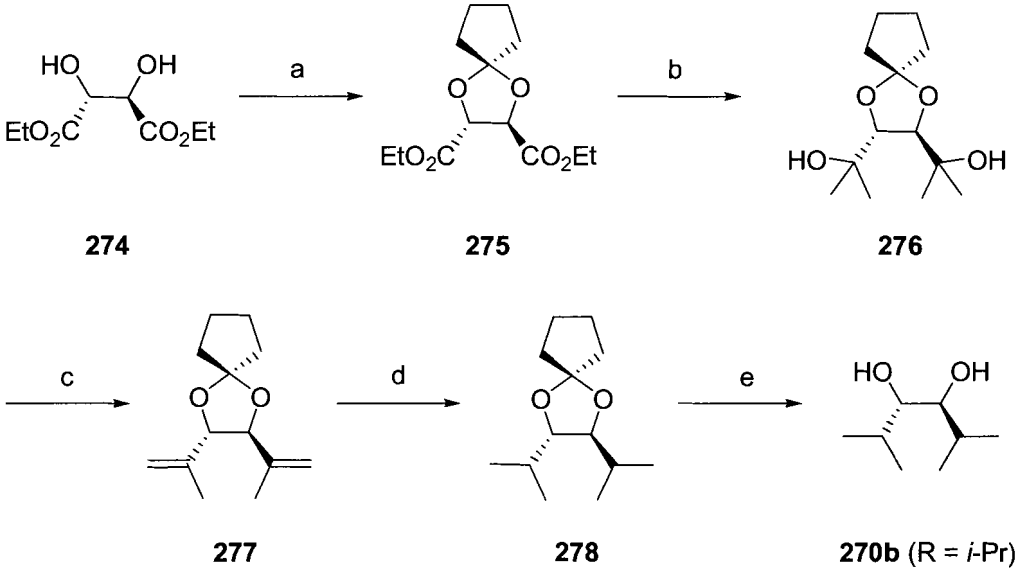
---

(113) Prasad, K. R. K.; Joshi, N. N. Stereoselective Reduction of Benzils: A New Convenient Route to Enantiomerically Pure 1,2-Diarylethanediols. *J. Org. Chem.* **1996**, *61*, 3888.

(114) (a) Wang, X.; Erickson, S. D.; Iimori, T.; Still, W. C. Enantioselective Complexation of Organic Ammonium Ions By Simple Tetracyclic Podand Ionophores. *J. Am. Chem. Soc.* **1992**, *114*, 4128. (b) Matteson, D. S.; Beedle, E. C.; Kandil, A. A. Preparation of (3*S*,4*S*)-2,5-Dimethyl-3,4-hexane diol [(*S*)-DIPED] from (*R*,*R*)-Tartaric Acid *via* Trimethylsilyl Chloride Catalyzed Acetylation of a Hindered 1,4-Diol. *J. Org. Chem.* **1987**, *52*, 5034.

The diene was then reduced using a Raney nickel-catalyzed hydrogenation reaction (40 psi H_2) in ethanol to afford the acetal **278** in excellent yield (95%). The acetal **278** was then hydrolyzed with aqueous hydrochloric acid (2 M) in tetrahydrofuran at room temperature that afforded the desired chiral diol **270b** (R = *i*-Pr) in good yield (87%). This synthetic procedure was performed on a large scale that allowed for the preparation of multi-gram quantities of this diol.

Scheme 2.2.2. Synthesis of (1*S*,2*S*)-1,2-Diisopropyl-1,2-ethanediol **270b**



274 **275** **276**

277 **278** **270b** (R = *i*-Pr)

Reagents and Conditions: (a) cyclopentanone, *p*-TsOH (cat.), benzene, reflux, 3 days, 91%; (b) MeMgBr, THF, 0 °C, 3 h, 89%; (c) MsCl, DMAP, Et_3N, CH_2Cl_2, 0 °C, 30 min, volatiles removed then; KO*t*-Bu, DMSO, room temperature, 16 h, 55% (over two steps); (d) Raney-Ni, H_2 (40 psi), EtOH, 95%; (e) HCl (2 M aq), THF, room temperature, 3 days, 87%.

2.3. Synthesis of the Chloroketone (269)

The synthesis of the chloroketone **269** was accomplished in six steps from the known 2-hydroxypyridine **280** (Scheme 2.3.1.).[115] The 2-hydroxypyridine **280** was prepared on a multi-gram scale by heating equimolar amounts of cyclopentanone, ethyl acetoacetate and ammonium acetate at reflux for 8 hours. The crystalline product that was precipitated from the crude reaction mixture was subsequently recrystallized from ethanol to afford the 2-hydroxypyridine **280** in 23% yield. The relatively low yield of this reaction does not take away from the overall efficiency of the synthetic route as it is the first step in the sequence. Moreover, the reaction was performed on a large scale and inexpensive starting materials were employed. The IR spectrum of the 2-hydroxypyridine **280** had a characteristic broad O-H peak at 2912 cm^{-1}. Moreover, in the ^1H NMR spectrum, the C-3 aromatic proton resonance appeared at δ = 6.22 ppm which indicated that the 2-hydroxypyridine **280** existed mainly as the aromatic tautomer. The first attempt at the conversion of the 2-hydroxypyridine **280** to the 2-chloropyridine **281** involved heating the 2-hydroxypyridine **280** in phosphoryl chloride at reflux (bp. 106 °C) for 24 hours. However, in this instance only starting material was recovered.[116] It was subsequently inferred that the chlorination reaction needed to be run at a higher temperature. In order to avoid the need to repeat this reaction in a sealed-tube, phenylphosphonic dichloride was selected as an alternative chlorinating agent. This substance has a relatively high boiling point (bp. 258 °C). Accordingly, the 2-

(115) Sakurai, A.; Midorikawa, H. The Cyclization of Ethyl Acetoacetate and Ketones by Ammonium Acetate. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 165.

(116) Ruble, J. C.; Fu, G. C. Chiral π-Complexes of Heterocycles with Transition Metals: A Versatile New Family of Nucleophilic Catalysts. *J. Org. Chem.* **1996**, *61*, 7230.

hydroxypyridine **280** was heated at 160 °C with phenylphosphonic dichloride for 16 h which afforded the 2-chloropyridine **281** in good yield (83%).[117] The mass spectrum of this compound displayed molecular ion peaks for M(^{35}Cl) and M(^{37}Cl) in a 3:1 ratio which is diagnostic of the incorporation of a chlorine atom. Subsequent oxidation of this compound with 30% aqueous hydrogen peroxide in acetic acid at 80 °C for 16 hours afforded the corresponding pyridine *N*-oxide. This compound was then heated with acetic anhydride at 100 °C to afford the acetate **282** in good yield (60%, over two steps).[118] Hydrolysis of the acetate **282** with lithium hydroxide in a mixture of tetrahydrofuran and water (3:1) at room temperature for 4 hours afforded the corresponding alcohol **283** in excellent yield (94%). Subsequent Swern oxidation afforded the desired chloroketone **269** in high yield (90%).[119] The IR spectrum of the chloroketone **269** displayed a characteristic carbonyl peak at 1714 cm^{-1} and a resonance for the carbonyl carbon at δ = 203.7 ppm was observed in the ^{13}C NMR spectrum.

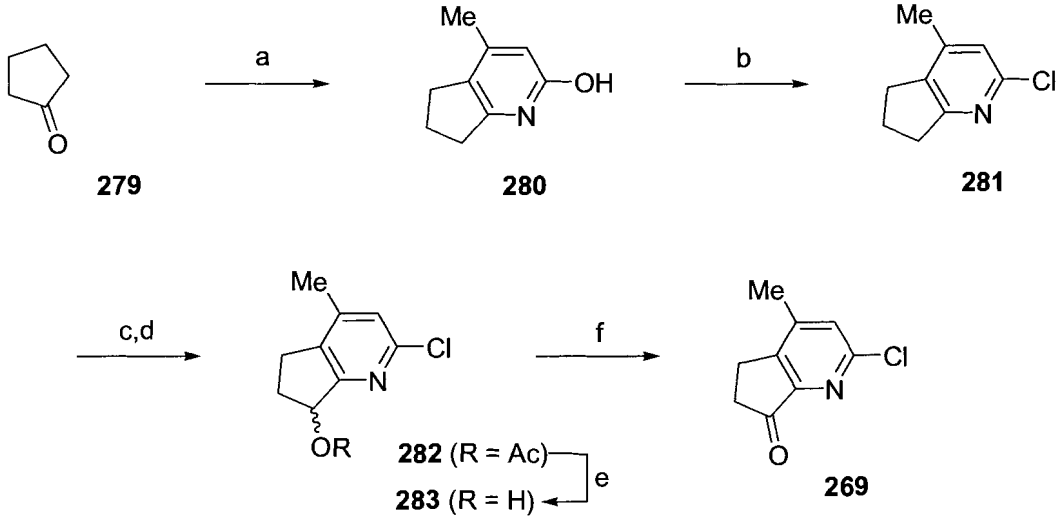
---

(117) Robison, M. M. The Preparation of 1,5-Pyrindene. *J. Am. Chem. Soc.* **1958**, *80*, 6254.

(118) The synthesis of the acetate **282** by similar methods has been reported by Fu and co-workers, see: Rios, R.; Liang, J.; Lo, M. M.-C.; Fu, G. C. Synthesis, Resolution and Crystallographic Characterication of a New C_2-Symmetric Planar-Chiral Bipyridine Ligand: Application to the Catalytic Enantioselective Cyclopropanation of Olefins. *Chem. Commun.* **2000**, 377.

(119) Mancuso, A. J.; Huang, S. L.; Swern, D. Oxidation of Long Chain and Related Alcohols to Carbonyls by Dimethyl Sulfoxide "Activated" by Oxalyl Chloride. *J. Org. Chem.* **1978**, *43*, 2480.

Scheme 2.3.1. Synthesis of the Chloroketone **269**

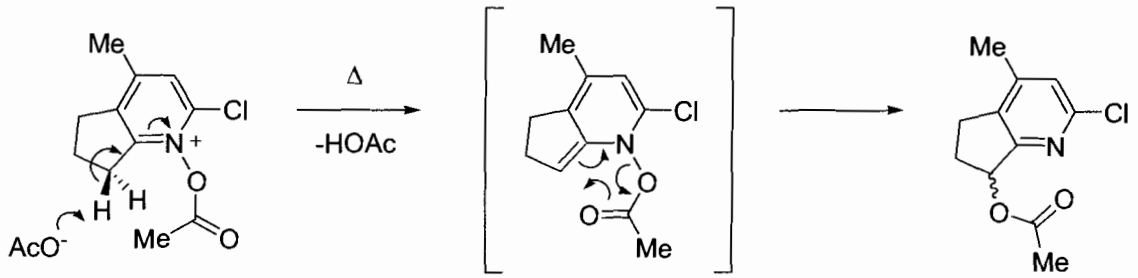


Reagents and Conditions: (a) ethyl acetoacetate, NH_4OAc, reflux, 8 h, 23%; (b) $PhP(O)Cl_2$, 160 °C, 16 h, 83%; (c) H_2O_2, H_2O, AcOH, 80 °C, 16 h; (d) Ac_2O, room temperature, 1 h then 100 °C, 4 h, 60% (over two steps); (e) LiOH, THF, H_2O, room temperature, 16 h, 94%; (f) $(COCl)_2$, DMSO, CH_2Cl_2; NEt_3, -78 °C to rt, 90%.

The *N*-oxide acetylation/migration sequence, employed in this synthetic route, is referred to as the "Boekelheide reaction" and it is formally a [3.3]-sigmatropic rearrangement of the acetylated *N*-oxide. This reaction provides a useful method for functionalization of the benzylic position of 2-alkylpyridines (Figure 2.3.1.).[120] In the proposed mechanism, the acetylated pyridine *N*-oxide **284** is deprotonated with acetate ion to afford the non-aromatic acetylated *N*-oxide **285**. This intermediate then undergoes a [3.3]-sigmatropic rearrangement to afford the acetate **282**.[121]

(120) (a) Katada, M. *J. Pharm. Soc. Jpn.* **1947**, *67*, 51. (b) Boekelheide, V.; Linn, W. J. Rearrangements of *N*-Oxides. A Novel Synthesis of Pyridyl Carbinols and Aldehydes. *J. Am. Chem. Soc.* **1954**, *76*, 1286.

(121) Oae, S.; Tamagaki, S.; Negoro, T.; Ogino, K.; Kozuka, S. Kinetic Studies on the Reactions of 2- and 4-Alkyl-Substituted Heteroaromatic *N*-Oxides with Acetic Anhydride. *Tetrahedron Lett.* **1968**, 917.



284 **285** **282**

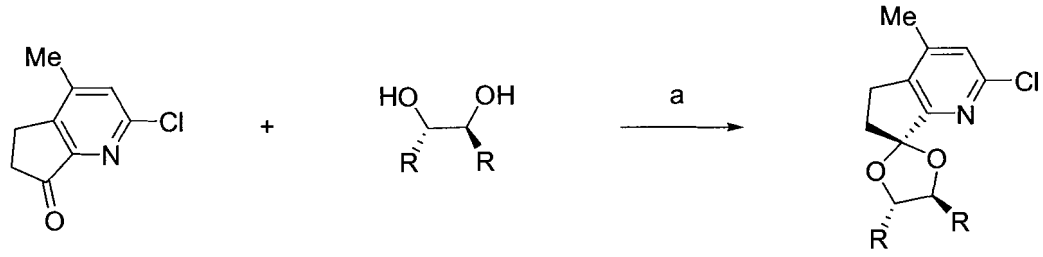
Figure 2.3.1. Mechanism for the Boekelheide reaction used for the preparation of the acetate **282**.

2.4. Synthesis of the Chiral Nonracemic Cyclic Acetals (268a-c)

The chiral acetals **268a-c** (R = Me, *i*-Pr and Ph) were prepared in good yield on condensation of the chloroketone **269** with the corresponding chiral nonracemic C_2-symmetric 1,2-diols **270a-c** on heating at reflux in benzene in the presence of a catalytic amount of *p*-toluenesulfonic acid (Scheme 2.4.1.).* These compounds were fully characterized by spectroscopic means and gave satisfactory elemental analyses.

(*) The reactions of the 2-chloroketone **269** with the chiral diols **270a-c** proceeded smoothly in the presence of 15 mol % of *p*-toluenesulfonic acid monohydrate. In our experience, related ketones that do not possess the 2-chloro substituent have required greater than one equivalent of an acid catalyst (see: ref. 53). Thus, it appears that the electron withdrawing chlorine atom lowers the basicity of the pyridine nitrogen relative to non-chlorinated pyridines.

Scheme 2.4.1. Synthesis of the Chiral Nonracemic Acetals **268a-c**



269 **270a-c** (R = Me*, *i*-Pr and Ph) **268a-c** (R = Me*, *i*-Pr and Ph)

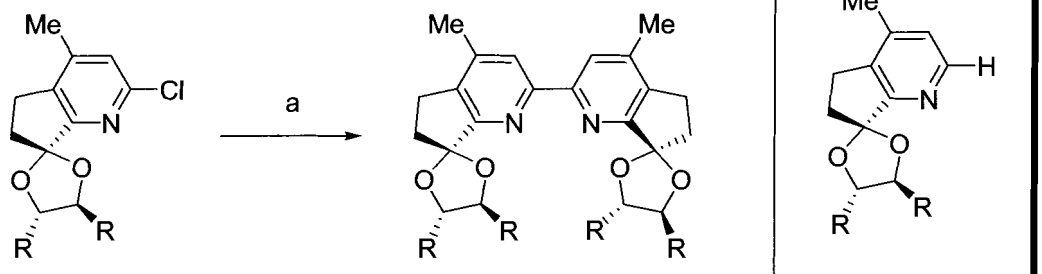
Reagents and Conditions: (a) 1,2-diols **270a-c** (R = Me, *i*-Pr and Ph), *p*-TsOH (cat.), benzene, reflux, 16 h, 85% (**268a**), 89% (**268b**), 79% (**268c**). * The compound used in this study was the enantiomer of that indicated in the reaction scheme.

2.5. Synthesis of the Chiral Nonracemic C_2-Symmetric 2,2′-Bipyridyl Ligands [267a-c (R = Me, *i*-Pr and Ph)]

The acetals **268a-c** were converted to the chiral nonracemic C_2-symmetric 2,2′-bipyridyl ligands **267a-c** by a nickel(0)-mediated *homo*-coupling reaction upon heating in tetrahydrofuran with dibromo*bis*(triphenylphosphine)nickel(II), tetraethylammonium iodide and zinc dust.[122] The reactions of the chiral acetals **268b** (R = *i*-Pr) and **268c** (R = Ph) both afforded the corresponding 2,2′-bipyridyl ligand in good yield (72% and 73%, respectively). However, in the case of the reaction of the chiral acetal **268a** (R = Me), a significant amount of the reductively dehalogenated product **286a** (35%) was obtained along with the desired 2,2′-bipyridyl ligand (41%) (Scheme 2.5.1.).

(122) (a) Dehmlow, E. V.; Sleegers, A. Synthesis of Unsymmetrically and Symmetrically Structured Dihydroxybipyridines. *Liebigs Ann. Chem.* **1992**, 953. (b) Iyoda, M.; Otsuka, H.; Sato, K.; Nisato, N.; Oda, M. Homocoupling of Aryl Halides using Nickel(II) Complex and Zinc in the Presence of Et_4NI. An Efficient Method for the Synthesis of Biaryls and Bipyridines. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 80.

Scheme 2.5.1. Synthesis of the C_2-Symmetric 2,2′-Bipyridyl Ligands **267a-c**

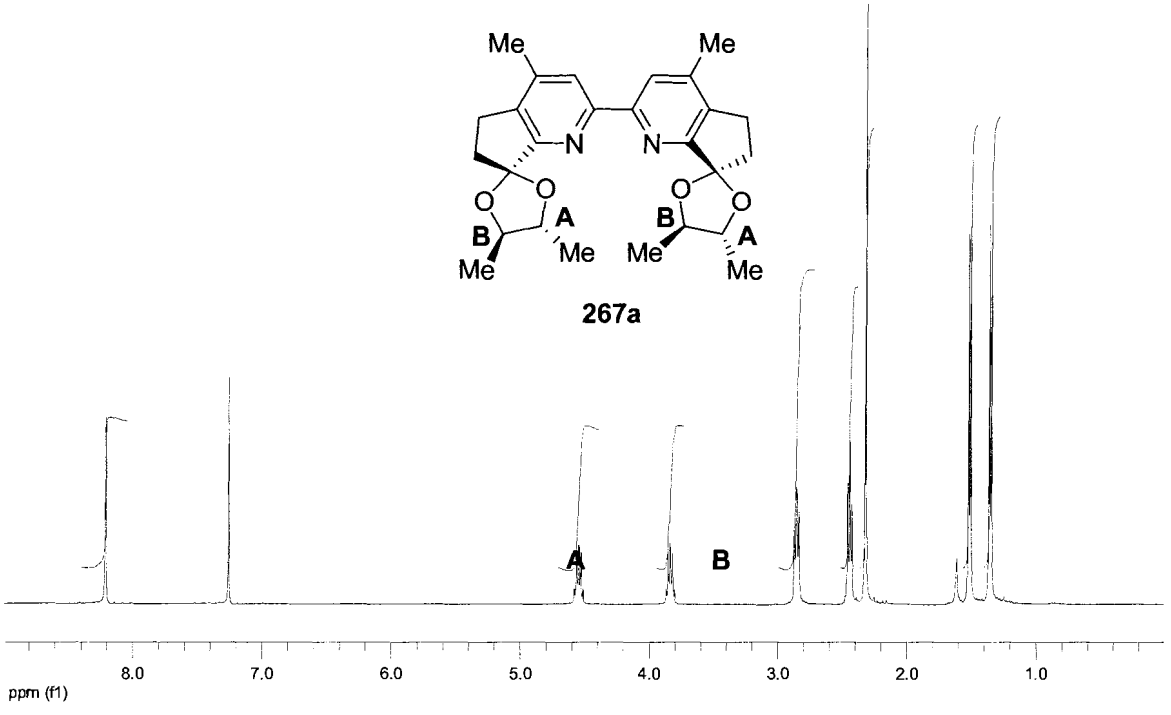


268a-c (R = Me*, *i*-Pr and Ph) **267a-c** (R = Me*, *i*-Pr and Ph) **286a** (R = Me*)

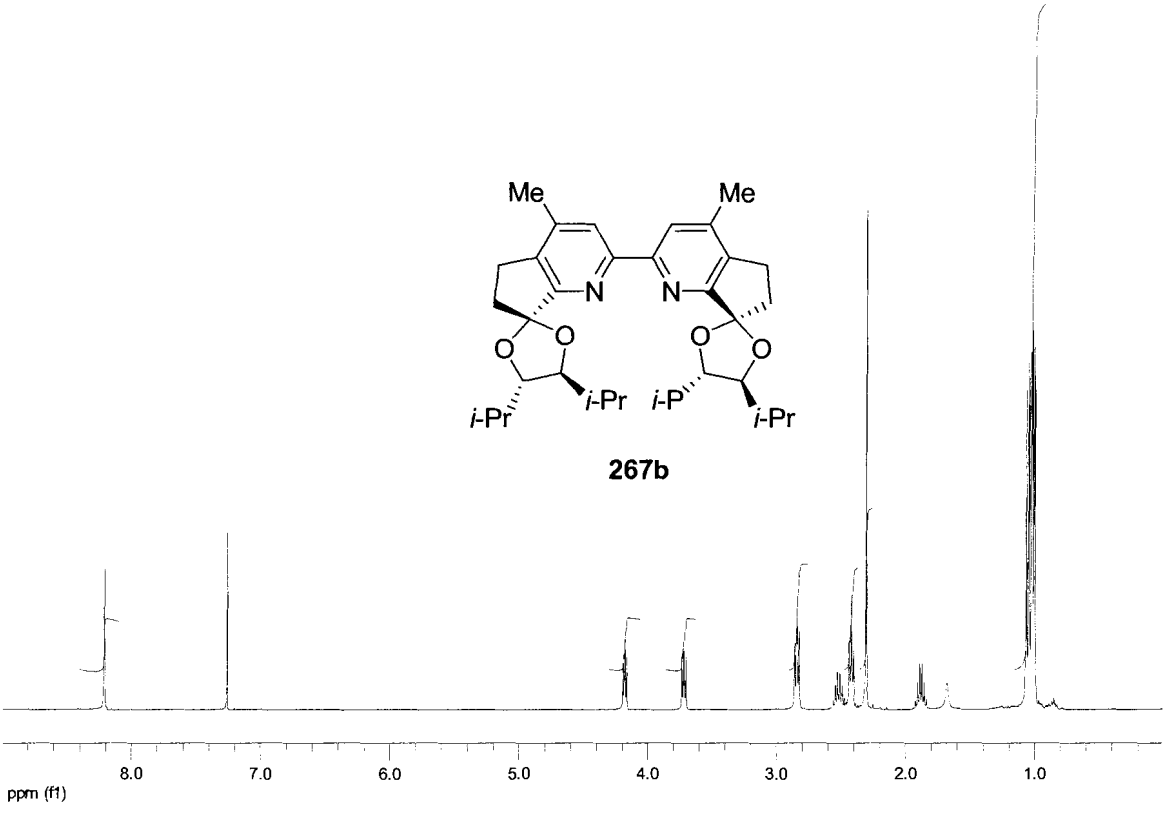
Reagents and conditions: (a) $NiBr_2(PPh_3)_2$, Zn dust, Et_4NI, THF, 60 °C, 4 days, 41% (**267a**), and 35% (**286a**), 72% (**267b**), 79% (**267c**). * The compound used in this study was the enantiomer of that indicated in the reaction scheme.

The structures of the products isolated from the above *homo*-coupling reactions were confirmed on the basis of spectroscopic evidence. In particular, the mass spectra of the 2,2′-bipyridyl ligands **267a-c** each showed the expected molecular ion peaks for M(**267a** + H) at 437, for M(**267b** + H) at 550 and for M(**267c** + H) at 686, respectively.

The ^{1}H NMR spectra for each of the C_2-symmetric 2,2′-bipyridyl ligands **267a-c** (R = Me, *i*-Pr and Ph) is shown below (Figure 2.5.1.). Of note, the distinct chemical environment of the two diastereotopic faces of these molecules was indicated by the proton signals of the chiral cyclic acetal moieties. The signal for the interior hydrogen (**A**) is shifted downfield with respect to the signal for the exterior hydrogen (**B**). This results from the proximity of the interior proton to the aromatic π-system of the pyridine moiety. In addition, the relative simplicity of the ^{1}H NMR spectra clearly indicated the C_2-symmetry of the ligands.


Me
Me
N
N
O
O
A
B
Me
Me
Me
Me
A
B
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

267a


Me
Me
N
N
O
O
O
O
i-Pr
i-Pr
i-Pr
i-Pr
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

267b

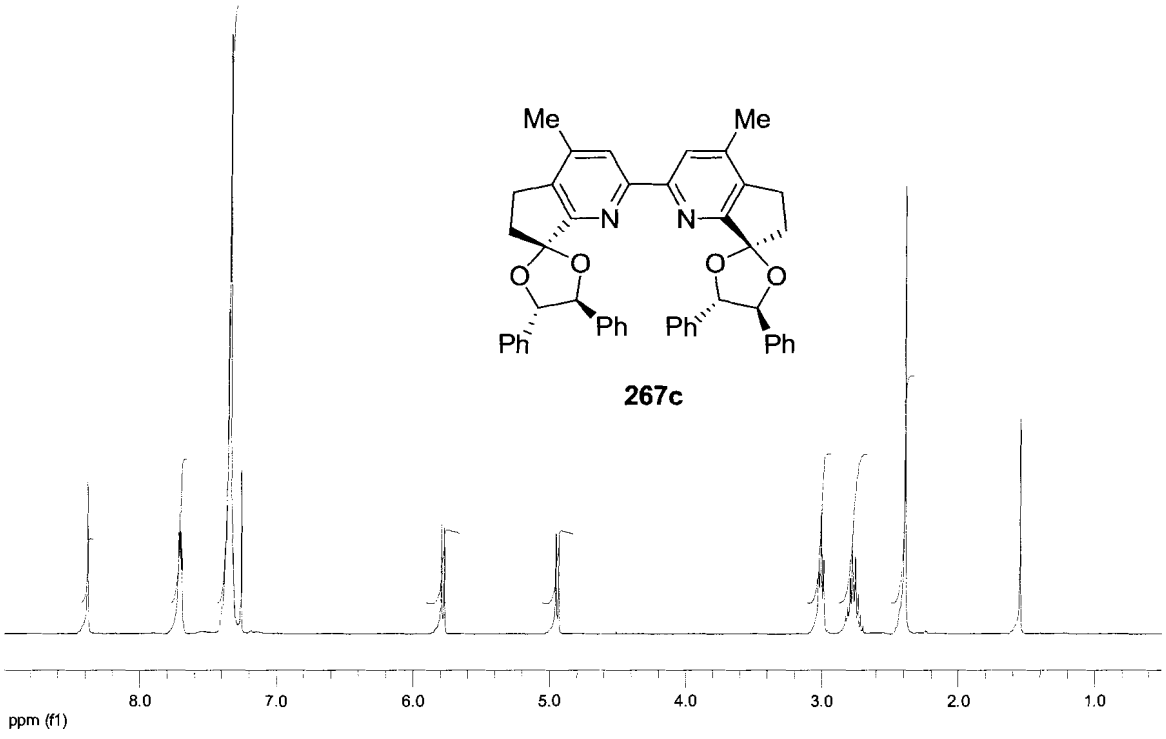
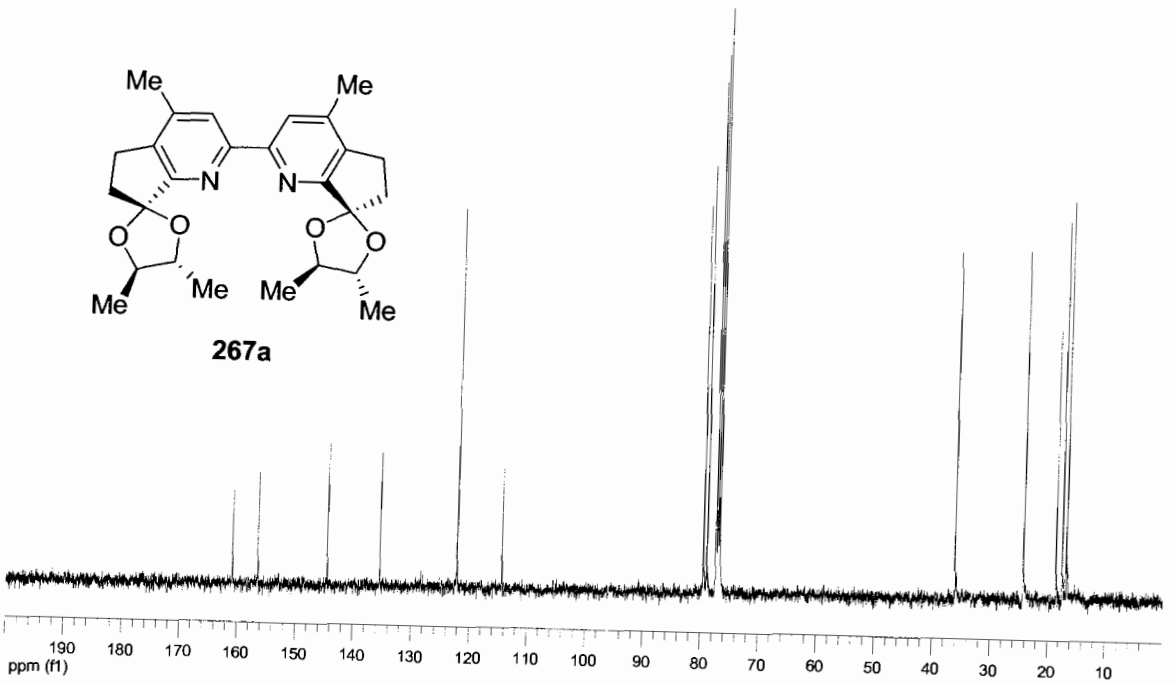
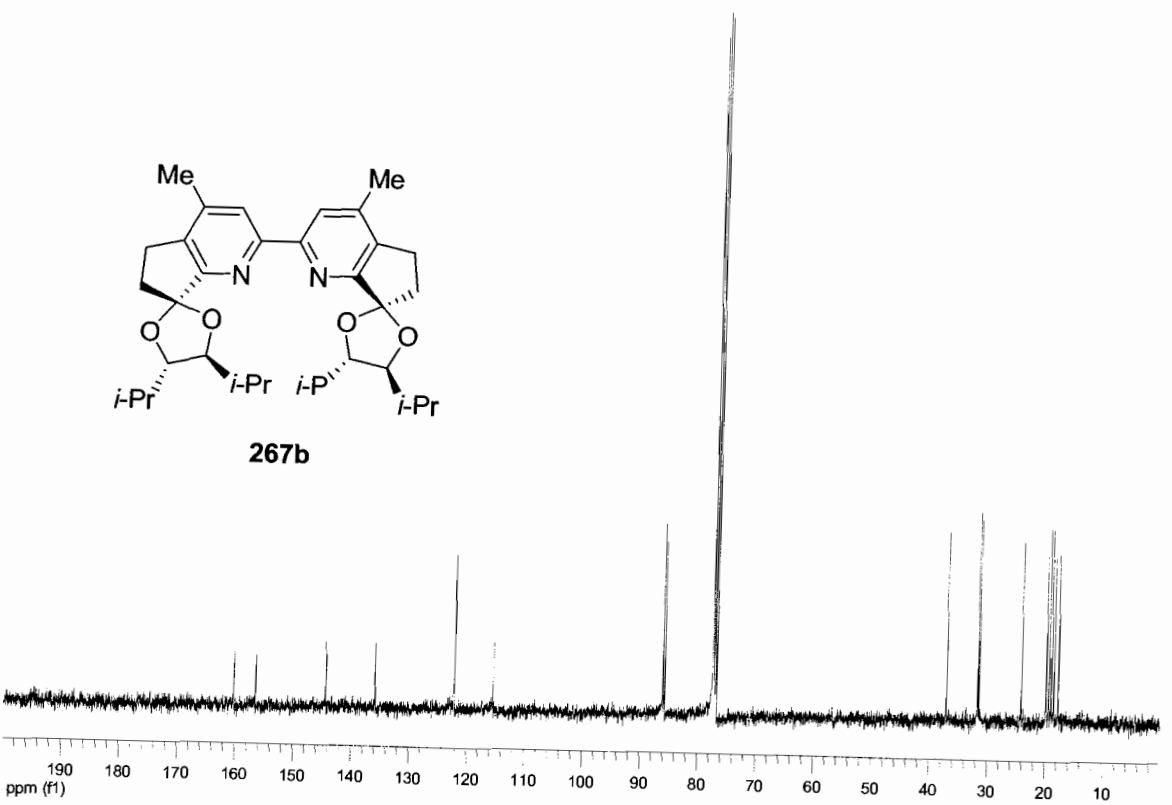


Figure 2.5.1. ^{1}H NMR spectra of the C_2-symmetric 2,2′-bipyridyl ligands **267a-c** (R = Me, *i*-Pr Ph).

The ^{13}C NMR spectra for each of the 2,2′-bipyridyl ligands **267a-c** (R = Me, *i*-Pr and Ph) is shown below (Figure 2.5.2.). The simplicity of the ^{13}C NMR spectra further indicated the C_2-symmetry of these molecules. For instance, the ^{13}C NMR spectrum of the 2,2′-bipyridyl ligand **267a** (R = Me), which has a molecular formula of $C_{26}H_{32}N_2O_4$, displayed thirteen signals.


Me
Me
N
N
O
O
O
O
Me
Me
Me
Me
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm (f1)

267a


Me
Me
N
N
O
O
O
O
i-Pr
i-Pr
i-P
i-Pr
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm (f1)

267b

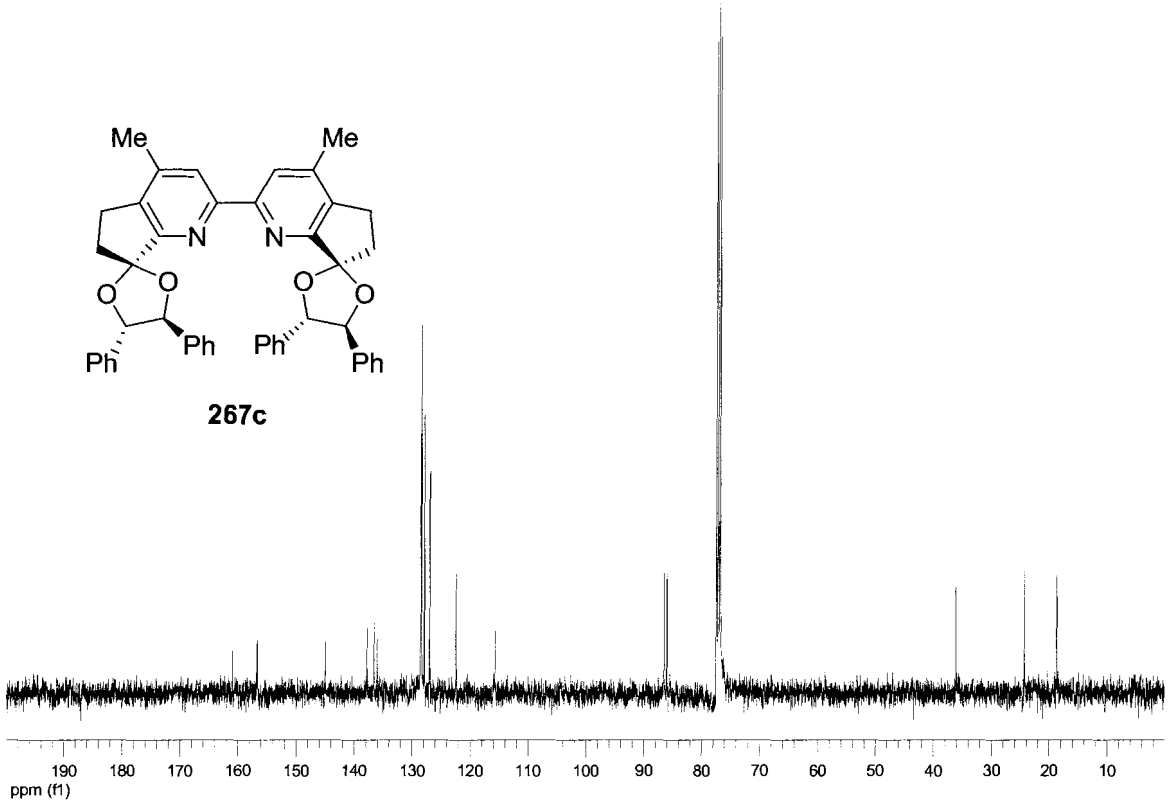


Figure 2.5.2. ^{13}C NMR spectra of the C_2-symmetric 2,2′-bipyridyl ligands **267a-c** (R = Me, *i*-Pr Ph).

The reductively dehalogenated product **286a** was assigned based upon the mass spectrum which displayed a molecular ion peak for M(**286a** + H) at 220 and the ^1H NMR spectrum which displayed C-2 and C-3 aromatic proton resonances as doublets with identical coupling constants (J = 4.9 Hz) at δ = 7.00 ppm and δ = 8.40 ppm (Figure 2.5.3.).

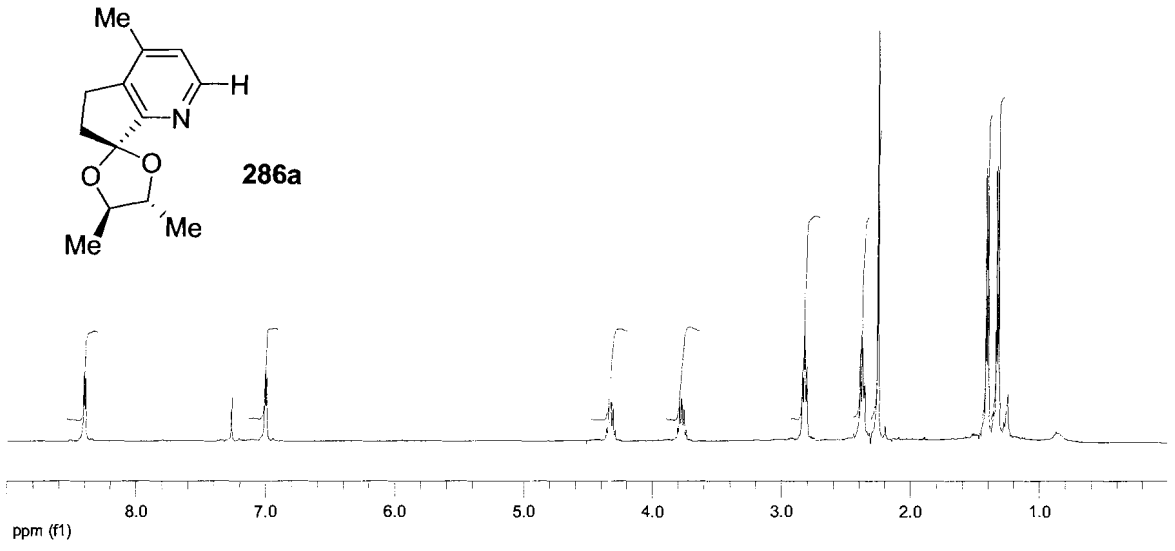


Figure 2.5.3. ^{1}H NMR spectrum of the reductively dehalogenated product **286a**.

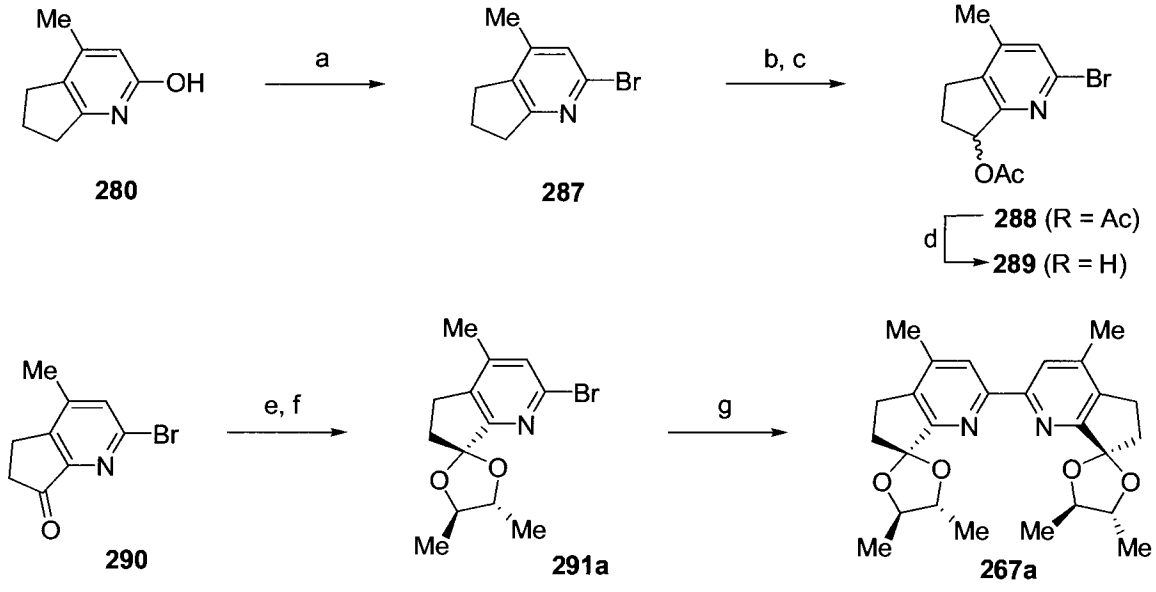
The formation of a significant quantity of the reductively dehalogenated product **286a** in the nickel(0)-mediated *homo*-coupling reaction of the 2-chloroacetal **268a** (R = Me) was problematic because it occurred in the last step of the synthetic sequence after the valuable chiral portion of the molecule had been installed. In order to circumvent this problem, it was decided to prepare the corresponding 2-bromoacetal **291a** (R = Me) (Scheme 2.5.2.). Here, it was considered that the increased reactivity of the pyridyl-bromide bond would lead to a higher yield of the desired 2,2′-bipyridine ligand **267a** (R = Me). The lower reactivity of aryl-chloride bonds relative to aryl-bromide bonds in metal-catalyzed coupling reactions is generally attributed to their reluctance to undergo oxidative addition to the metal catalyst.[123] This is in agreement with the bond dissociation energies for aryl halide bonds [at 298 K, Ph-Cl (96 kcal mol^{-1}) > Ph-Br (81 kcal mol^{-1})].[124]

(123) Grushin, V. V.; Alper, H. Transformation of Chloroarenes, Catalyzed by Transition-Metal Complexes. *Chem. Rev.* **1994**, *94*, 1047.

(124) Cox, J. D.; Pilcher, G. *Thermochemistry of Organic and Organometallic Compounds*; Academic Press: London, 1970.

The bromoacetal **291a** was prepared in a similar fashion as to that used to prepare the corresponding chloroacetal **268a** (Scheme 2.5.2.). The 2-hydroxypyridine **280** was converted in 52% yield to the 2-bromopyridine **287** upon heating at reflux in phosphorus tribromide (bp. 175 °C). However, we found that the yield of this reaction was not consistently reproducible and that the desired product was often isolated in much lower yield. Moreover, the reaction was not particularly amenable to scale-up as emulsification occurred during the work-up of the reaction mixture. The mass spectrum of the 2-bromopyridine **287** showed molecular ion peaks for M(^{81}Br) and M(^{79}Br) in a 1:1 ratio that confirmed the incorporation of a bromine atom. Treatment of the 2-bromopyridine **287** with 30% aqueous hydrogen peroxide in glacial acetic acid at 80 °C for 16 h afforded the corresponding pyridine *N*-oxide. This compound was then heated in acetic anhydride at 100 °C for 4 hours to afford the acetate **288** in good yield (54%, over two steps). Hydrolysis of the acetate **288** with lithium hydroxide monohydrate in a mixture of tetrahydrofuran and water (3:1) at room temperature for 16 h then afforded the alcohol **289** in excellent yield (95%). Subsequent Swern oxidation afforded the bromoketone **290** in 90% yield. The IR spectrum of the bromoketone **290** displayed a strong and characteristic carbonyl stretch at 1718 cm^{-1}. Condensation of the bromoketone **290** with (2*R*,3*R*)-2,3-butanediol **270a** in the presence of a catalytic amount of *p*-toluenesulfonic acid monohydrate in benzene at reflux afforded the bromoacetal **291a** (R = Me) in high yield (89%). The bromoacetal **291a** (R = Me) was then subjected to the nickel(0)-mediated *homo*-coupling reaction to afford the chiral 2,2′-bipyridyl ligand **267a** (R = Me) in good yield (83%). In this case, as anticipated, none of the reductively dehalogenated product **286a** was detected.

Scheme 2.5.2. Synthesis of the 2,2′-Bipyridyl Ligand **267a** from the 2-Bromopyridine **291**



Reagents and Conditions: (a) PBr_3, reflux, 12 h, 52%; (b) H_2O_2, H_2O, AcOH, 80 °C, 16 h; (c) Ac_2O, rt, 1 h then 100 °C, 4 h, 54% (over two steps); (d) LiOH, THF, H_2O, rt, 16 h, 95%; (e) $(COCl)_2$, DMSO, CH_2Cl_2; NEt_3, -78 °C to rt, 90%; (f) (2*R*,3*R*)-2,3-butanediol **270a**, *p*-TsOH (cat.), benzene, reflux, 20 h, 89%; (g) $NiBr_2(PPh_3)_2$, Zn, Et_4NI, THF, 60 °C, 72 h, 83%.

The mechanism by which reduction of the aryl-chloride bond occurred in the case of the acetal **268a** (R = Me) is unclear. However, if this coupling reaction proceeds *via* radical intermediates then the tetrahydrofuran reaction solvent or tetraethylammonium iodide are the most likely sources of the hydrogen atoms as the reactions were performed under strictly anhydrous conditions. The observation that this reductive process only occurred during the *homo*-coupling reaction of the acetal **268a** (R = Me) can be attributed to the fact that this less sterically encumbered molecule was more reactive than the chloroacetals **268b** (R = *i*-Pr) and **268c** (R = Ph).

2.6. Synthesis of the Chiral Nonracemic Unsymmetric 2,2′-Bipyridyl Ligands [271a (R = Me) and 271b (R = Ph)]

The unsymmetric 2,2′-bipyridyl ligands **271a** (R = Me) and **271b** (R = Ph) were prepared from the chiral acetals **268a** (R= Me) and **268c** (R = Ph) by a palladium-catalyzed Stille coupling reaction with 2-(tri-*n*-butylstannyl)pyridine **272** (Scheme 2.6.1.).[125,126] The chiral acetal **268b** (R = *i*-Pr) was not employed in this reaction because of the relatively limited quantity of the chiral diol **270b** at hand. It was found that the chiral acetals **268a** (R = Me) and **268b** (R = Ph) reacted exceedingly slowly under standard Stille coupling reaction conditions when *tetrakis*(triphenylphosphine) palladium(0) was employed as the catalyst on heating at reflux in benzene or toluene with potassium carbonate as the base.[127] However, the reactions proceeded smoothly upon employment of the reaction conditions recently reported by Fu and co-workers to afford the unsymmetric 2,2′-bipyridyl ligands **271a** and **271b** in good yield (72 and 83%, respectively).[128] These conditions involved heating a mixture of the acetal **268a** (R = Me) or **268b** (R = Ph), the 2-(tri-*n*-butylstannyl)pyridine **272** and anhydrous cesium fluoride in dioxane at reflux in the presence of catalytic amounts of *tris*(dibenzylideneacetone)dipalladium(II) and tri-*tert*-butyl phosphine. From a practical

---

(125) Milstein, D.; Stille, J. K. A General, Selective and Fascile Method for Ketone Synthesis from Acid Chlorides and Organotin Compounds Catalyzed by Palladium. *J. Am. Chem. Soc.* **1978**, *100*, 3636.

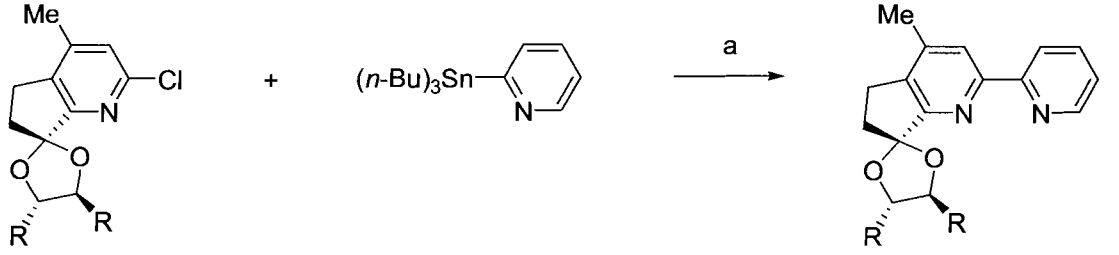
(126) For reviews on the Stille reaction, see: (a) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, 50, 1. (b) Mitchell, T. N. In *Metal Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998, Chapter 4.

(127) Echavarren, A. M.; Stille, J. K. Palladium-Catalyzed Coupling of Aryltriflates with Organostannanes. *J. Am. Chem. Soc.* **1987**, *109*, 5478.

(128) Littke, A. F.; Schwarz, L.; Fu, G. C. Pd/P(*t*-Bu)$_3$: A Mild and General Catalyst for Stille Reactions of Aryl Chlorides and Aryl Bromides. *J. Am. Chem. Soc.* **2002**, *124*, 6343.

point of view, it is important to note that Stille coupling reactions are often plagued by the difficulties in separating the desired reaction product from the trialkyltin halide byproduct. This is not a problem under these conditions due to the *in situ* formation of insoluble tri-*n*-butyltin fluoride.

Scheme 2.6.1. Synthesis of the Unsymmetric 2,2′-Bipyridyl Ligands **271a** (R = Me) and **271b** (R = Ph)



268a,c (R = Me*, Ph) **272** **271a,b** (R = Me*, Ph)

Reagents and Conditions: (a) 5 mol % Pd_2dba_3, 10 mol % P(*t*-Bu)$_3$, CsF, dioxane, reflux, 24 h, 72% (**271a**), 83% (**271b**). * The compound used in this study was the enantiomer of that indicated in the reaction scheme.

The structure of the unsymmetric 2,2′-bipyridyl ligands **271a** (R = Me) and **271b** (R = Ph) was confirmed on the basis of spectroscopic evidence. In particular, the mass spectra displayed the expected molecular ion peaks for M(**271a** + H) at 297 and for M(**271b** + H) at 421.

The ^{1}H NMR spectra for each of the unsymmetric 2,2′-bipyridyl ligands **271a** (R = Me) and **271b** (R = Ph) is shown below (Figure 2.6.1.). One of the diagnostic features of the spectra, which revealed the 2-chloro moiety had been substituted with the 2-pyridyl moiety, was the four additional low field aromatic resonances relative to the ^{1}H NMR spectra of the starting materials.

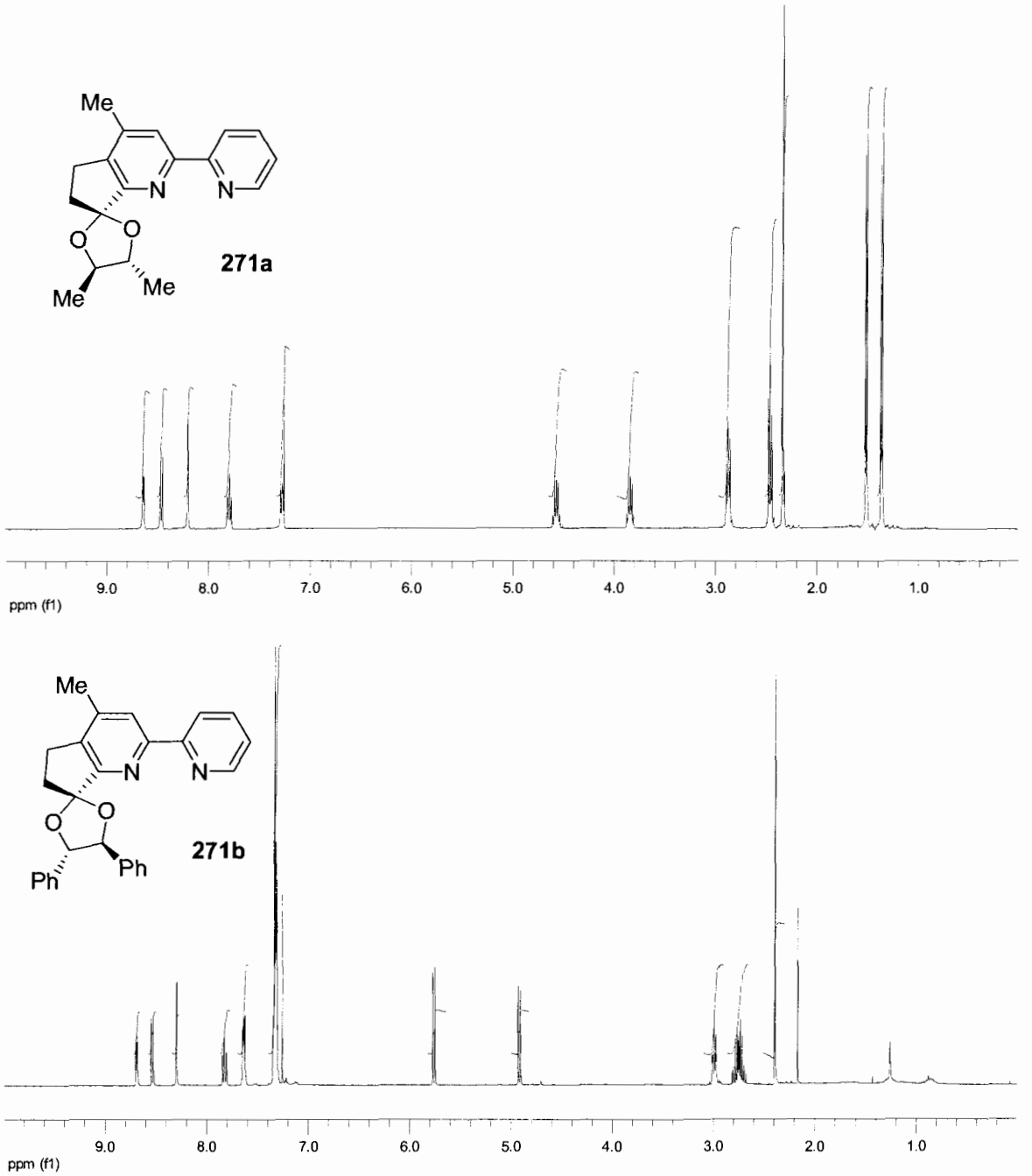


Figure 2.6.1. ^{1}H NMR spectra of the unsymmetric 2,2′-bipyridyl ligands **271a,b** (R = Me and Ph).

The ^{13}C NMR spectra for each of the unsymmetric 2,2′-bipyridyl ligands **271a** (R = Me) and **271b** (R = Ph) is shown below (Figure 2.6.2.). These spectra clearly display the lack of symmetry in these molecules. For instance, the molecular formula for the

bipyridine ligand **271a** (R = Me) is $C_{18}H_{20}N_2O_2$ and the ^{13}C NMR spectrum shows eighteen signals.

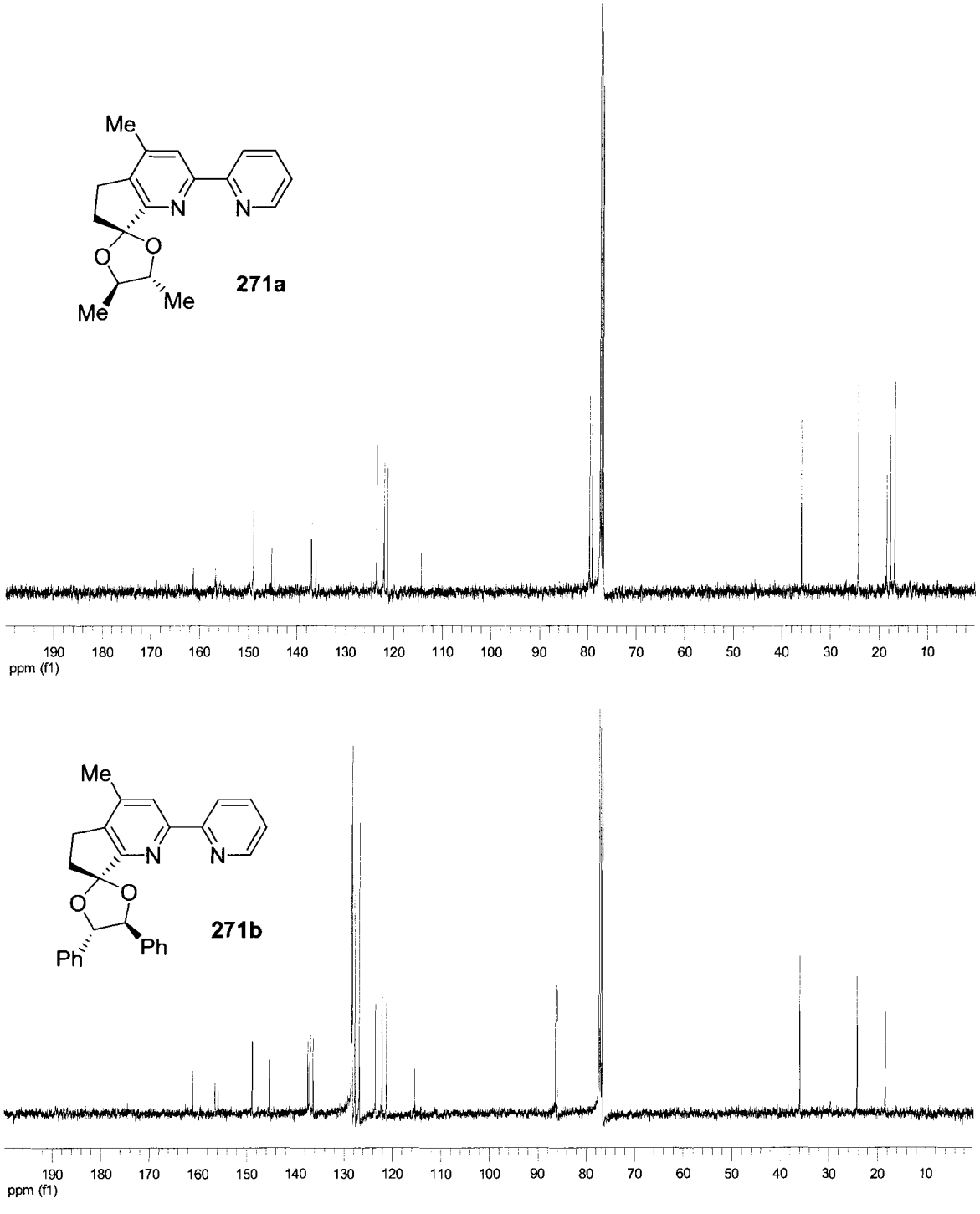
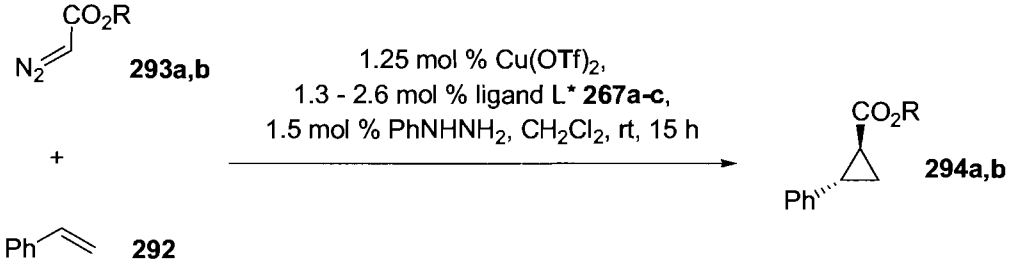


Figure 2.6.2. ^{13}C NMR spectra of the unsymmetric 2,2′-bipyridyl ligands **271a,b** (R = Me and Ph).

2.7. Evaluation of the C_2-Symmetric 2,2′-Bipyridyl Ligands (267a-c) in the Copper(I)-Catalyzed Asymmetric Cyclopropanation Reactions of Styrene and Diazoesters

With a series of three chiral nonracemic C_2-symmetric 2,2′-bipyridyl ligands **267a-c** (R = Me, *i*-Pr and Ph) in hand, the evaluation of these ligands in the copper(I)-catalyzed asymmetric cyclopropanation (AC) reaction of styrene and diazoesters was undertaken (Table 2.7.1.). These reactions were performed under a standard set of reaction conditions that were reviewed earlier in this thesis (Chapter 1, Section 1.9.4.).

Table 2.7.1. Asymmetric Cyclopropanation of Styrene **292**



entry	L*	R	L*:Cu ratio	product	*trans*:*cis*	yield (%)	ee (*trans*)
1	**267a**	Et	1:1	*ent*-**294a**	63:37	55	9
2	**267a**	*t*-Bu	1:1	*ent*-**294b**	80:20	67	7
3	**267a**	Et	2:1	*ent*-**294a**	51:49	48	24
4	**267a**	*t*-Bu	2:1	*ent*-**294b**	73:27	47	38
5	**267b**	Et	1:1	**294a**	68:32	62	25
6	**267b**	*t*-Bu	1:1	**294b**	83:17	59	44
7	**267b**	Et	2:1	**294a**	68:32	53	34
8	**267b**	*t*-Bu	2:1	**294b**	75:25	57	42
9	**267c**	Et	1:1	(±)-**294a**	63:37	58	0
10	**267c**	Et	2:1	-	-	No Reaction	-

The active copper catalyst in these reactions was generated *in situ* by reduction of the complex formed between 1.25 mol % of copper(II) triflate and 1.3 or 2.6 mol % of

the C_2-symmetric ligands **267a-c** with phenylhydrazine.[129] In all cases, the solutions of the copper(II) complexes formed between copper(II) triflate and 2,2′-bipyridyl ligands **267a-c** were light green in colour that turned deep red instantaneously when the phenylhydrazine was added. This indicated that a reduction process to form the corresponding copper(I) complexes had occurred.

The AC reactions were carried out at room temperature in dichloromethane and involved the slow addition (over ~3 h) of the ethyl and *tert*-butyl esters of diazoacetic acid **293a** (R = Et) and **293b** (R = *t*-Bu) to a solution of 2.2 equivalents styrene **292** and the preformed catalyst. The diastereoselectivity of the cyclopropanation reactions was determined by analysis of the ^{1}H NMR spectra of the crude reaction products. The yields listed in the table are the combined yields of the chromatographically separated *trans*- and *cis*-cyclopropanes. The enantiomeric excess of the *trans*-cyclopropanes was determined by analytical chiral HPLC (Daicel Chiracel OD column) following reduction to the corresponding primary alcohols with lithium aluminum hydride. The enantiomeric excess of the *cis*-cyclopropanes was not determined due to the fact that it was the minor reaction product and that it was difficult to separate the enantiomers of this compound on the analytical Daicel chiral HPLC column.

It was found that both the yields and stereoselectivities of the AC reactions were highly dependant on which ligand was employed and the ratio of the ligand and copper(II) triflate that was employed.

---

(129) For example, see: Malkov, A. V.; Pernazza, D.; Bell, M.; Bella, M.; Massa, A.; Teplý, F.; Meghani, P.; Kočovský, P. Synthesis of New Chiral 2,2′-Bipyridyl Ligands and their Application in Copper-Catalyzed Asymmetric Allylic Oxidation and Cyclopropanation. *J. Org. Chem.* **2003**, *68*, 4727.

The AC reaction of styrene **292** with ethyl diazoacetate using a 1:1 ratio of ligand **267a** (R = Me) and copper(II) triflate afforded the cyclopropane **294a** in a *trans*:*cis* ratio of 63:37 and in low enantioselectivity (9% ee) (Entry 1). Employment of the larger reaction substrate, *tert*-butyl diazoacetate, under identical reaction conditions afforded the cyclopropane **294b** in an improved *trans*:*cis* ratio of 80:20. However, the enantioselectivity of the reaction remained low (7% ee) (Entry 2). These results led to the consideration that the ligand **267a** (R = Me) was not completely bound to the copper(I) salt or that a *bis*-ligated copper(I) species had formed.[130] To attempt to improve the stereoselectivities of these initial experiments, the above AC reactions were repeated using a 2:1 ratio of ligand **267a** (R = Me) to copper(II) triflate. The reaction with ethyl diazoacetate afforded the cyclopropane **294a** in an improved enantiomeric excess (24%) as did the reaction with *tert*-butyl diazoacetate which afforded the cyclopropane **294b** in moderate enantiomeric excess (38%) (Entries 3 and 4, respectively).

Similar trends were observed in the AC reactions of styrene with the second ligand **267b** (R = *i*-Pr) that was studied. Using a 1:1 ratio of ligand **267b** (R = *i*-Pr) to copper(II) triflate, the AC reaction of styrene using ethyl diazoacetate afforded the cyclopropane **294a** in similar enantioselectivity (25% ee) whereas *tert*-butyl diazoacetate afforded cyclopropane **294b** in slighly higher enantioselectivity (44% ee) (Entries 5 and 6, respectively). The use of a 2:1 ratio of ligand **267b** (R = *i*-Pr) to copper(II) triflate in the AC reaction of styrene with ethyl diazoacetate improved the enantioselectivity of the

(130) Fritschi, H.; Leutenegger, U.; Siegmann, K.; Pfaltz, A. Semicorrin Metal Complexes as Enantioselective Catalysts. *Helv. Chim. Acta* **1988**, *71*, 1541.

reaction (34% ee) (Entry 7). However, in the case of *tert*-butyl diazoacetate the enantiomeric excess remained essentially the same (42%) (Entry 8).

Particularly interesting results were obtained with ligand **267c** (R = Ph) in this AC reaction. Using a 1:1 ratio of ligand **267c** (R = Ph) and copper(II) triflate in the reaction of styrene **292** with ethyl diazoacetate **293a**, the cyclopropane **294a** was isolated in racemic form (0% ee) (Entry 9). This was very surprising since it was expected that the ligand **267c** (R = Ph) would be the most efficient chiral director of the series because of the size of the chiral cyclic acetal moiety (R = Ph). Remarkably, when the AC reaction of styrene with ethyl diazoacetate was repeated with a 2:1 ratio of ligand **267c** (R = Ph) and copper(II) triflate, the cyclopropane product was not formed (Entry 10).

The absolute stereochemistry of the major *trans*-cyclopropanation products **294a,b** when ligand **267a** (R = Me) was employed was determined to be (1*R*,2*R*) by comparison of the optical rotation with a literature value.[131] As would be expected, the *pseudo*-enantiomeric ligand **267b** (R = *i*-Pr) afforded the enantiomeric cyclopropanation products (1*S*,2*S*)-**294a,b**. These stereochemical outcome of these reactions can be rationalized in terms of the minimization of steric interactions between the reacting species and the copper(I) complex of the 2,2′-bipyridyl ligands **267a** (R = Me) and **267b** (R = *i*-Pr). A schematic representation that depicts the proposed low and high energy modes for the reaction of styrene **292** with the copper-carbene intermediate **295** [with ligand **267a** (R = Me)] that would afford the four possible isomeric cyclopropane reaction products is shown below (Figure 2.7.1.). The lower energy reaction modes can be

(131) Niimi, T.; Uchida, T.; Irie, R.; Katsuki, T. Highly Enantioselective Cyclopropanation with Co(II)-Salen Complexes: Control of *cis*- and *trans*-Selectivity by Rational Ligand Design. *Adv. Synth. Catal.* **2001**, *343*, 79.

attributed to the minimization of the steric interactions between the chiral acetal substituents (R) and the styrene **292**. Also to note in the figure, attack along reaction pathway (a) would lead to the major *trans*-cyclopropane **294** reaction product while attack along reaction pathway (b) would lead to the minor *cis*-cyclopropane **294** reaction product.

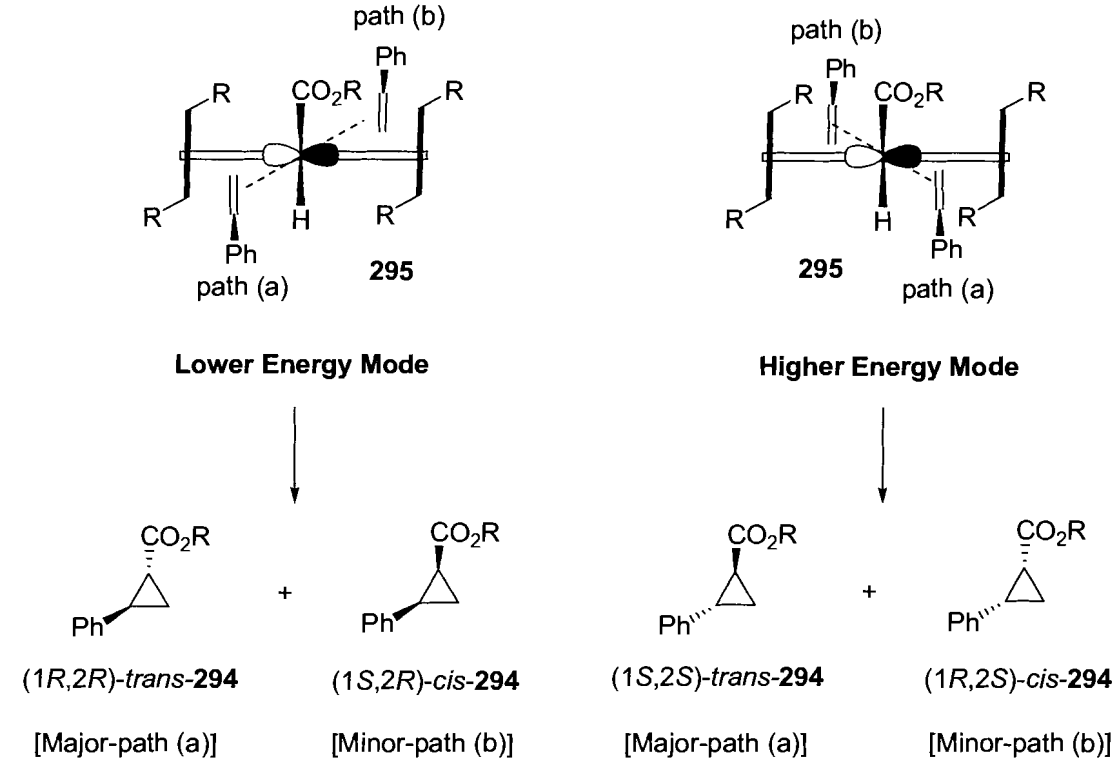


Figure 2.7.1. Rationalization of the stereochemical outcome of the AC reactions based on the minimization of steric interactions between the catalyst and the reacting species.

It was decided to undertake a crystallographic study to probe the structure of the active catalyst in these AC reactions. The ligand **267c** (R = Ph) was selected as particularly interesting results had been obtained in this case.

Due to the air and moisture sensitivity of copper(I) triflate complexes it was decided to prepare the corresponding copper(I) chloride complex of the ligand **267c** (R = Ph). Coordination of equimolar amounts of the ligand **267c** (R = Ph) and anhydrous

copper(I) chloride in a mixture of ethanol and dichloromethane (1:1) at room temperature for 4 h did not afford the expected *mono*-ligated CuCl(**267c**) complex but afforded the *bis*-ligated Cu(**267c**)$_2$·CuCl$_2$ complex in quantitative yield. The initial structural assignment of the Cu(**267c**)$_2$·CuCl$_2$ complex was based on the mass spectrum which displayed a molecular ion peak that indicated two bipyridine ligands were bound to the copper centre [1431 (M - CuCl$_2$)]. Bright red X-ray quality crystals were then obtained by recrystallization of the complex upon the slow evaporation of a solution of the complex Cu(**267c**)$_2$·CuCl$_2$ in ether and dichloromethane (1:1). Analysis of the X-ray data revealed that two 2,2′-bipyridyl ligands **267c** (R = Ph) were coordinated to the copper(I) centre in a tetrahedral geometry. In addition, the chloride counter ion had been displaced from the coordination sphere of the complex and had combined with the remaining copper(I) chloride to form a copper(I) dichloride counterion ($CuCl_2^-$).* An *ORTEP* representation of this complex is shown below (Figure 2.7.2.). Around the copper(I) centre, the following bond angles were observed: N1-Cu1-N2 = 82.2° and N2-Cu1-N1* = 131.2°. The N1-Cu1 bond length was 2.057 Å and the N2-Cu1 bond length was 2.052 Å. Complete tabulated data of bond angles and bond lengths from the X-ray structure determination of the Cu(**267c**)$_2$·CuCl$_2$ complex are provided in the experimental section of this thesis.

(*) X-ray crystal structure analysis of the Cu(**267c**)$_2$·CuCl$_2$ complex was performed by Mr. Neil D. Draper at Simon Fraser University.

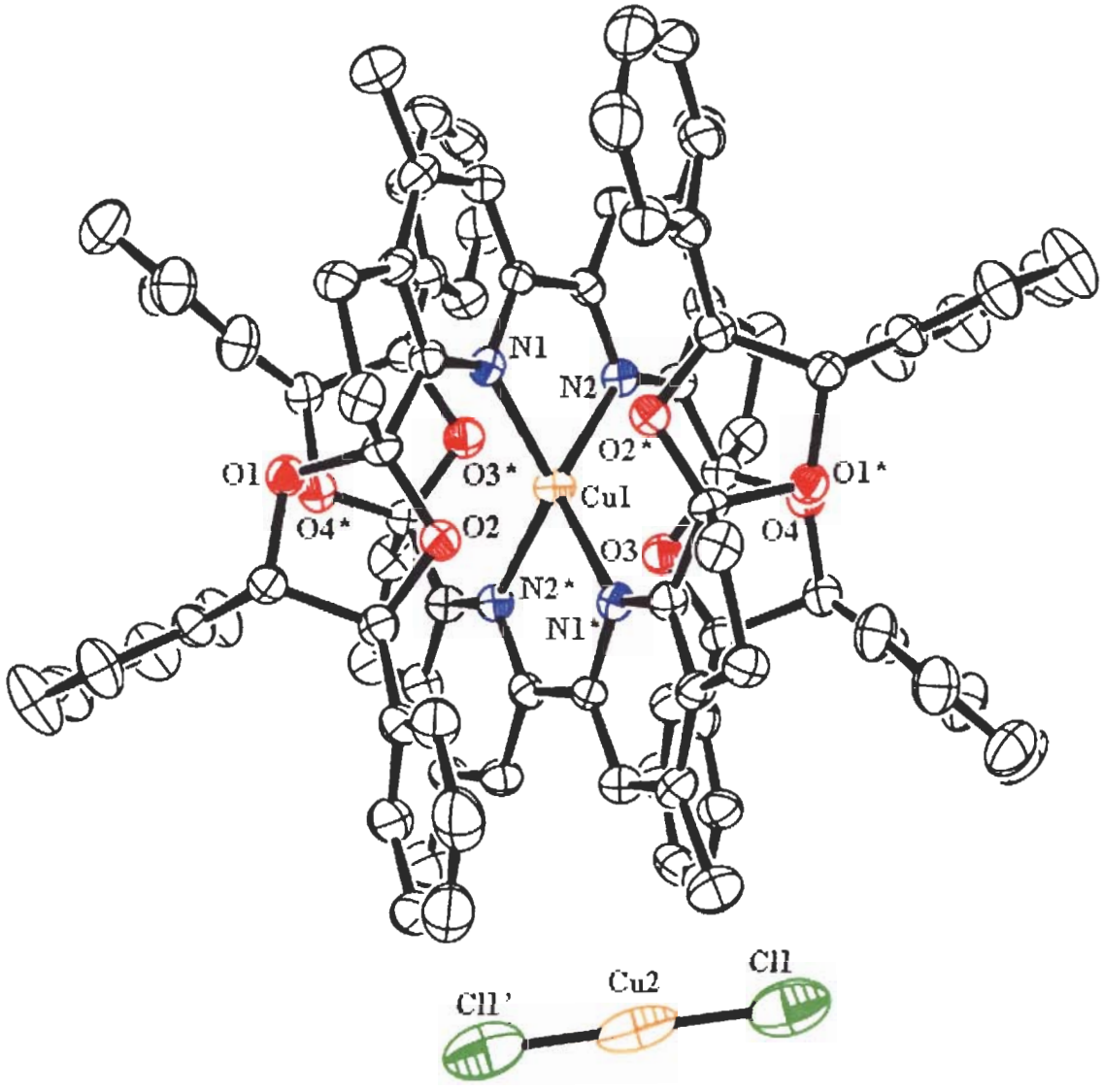
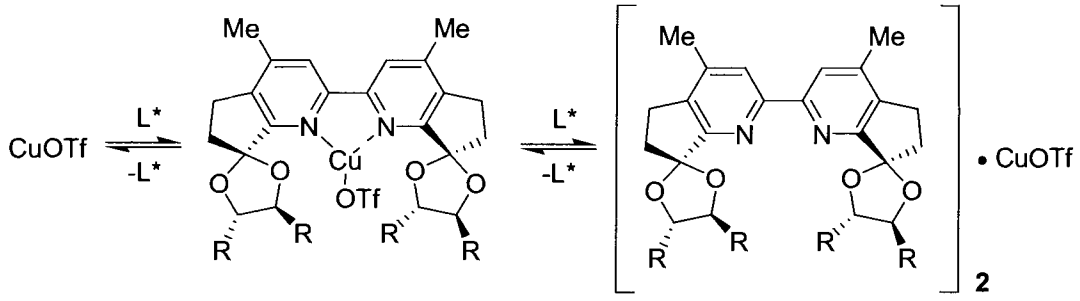


Figure 2.7.2. *ORTEP* representation of the Cu(**267c**)$_2$·$CuCl_2$ complex.*

To rationalize the results from the AC reactions of styrene **292**, and particularly the dependence of the enantioselectivity on the ratio of ligand to copper used in the reaction, it is proposed that the ligands **267a-c** have a propensity to form *bis*-ligated copper(I) complexes in solution and thus an equilibrium is established between free

(*) The thermal ellipsoids are drawn at a 25% probability and the hydrogen atoms have been removed for clarity

copper(I) triflate **296**, *mono*-ligated copper(I) triflate complexes **297**, and *bis*-ligated copper(I) triflate complexes **298** (Figure 2.7.3.).



296 (active catalyst) **297** (active catalyst) **298** (inactive catalyst)

Figure 2.7.3. The proposed equilibrium established in solution of copper(I) triflate and the 2,2′-bipyridyl ligands **267a-c** (R = Me, *i*-Pr and Ph).

The *bis*-ligated complexes are presumably inactive cyclopropanation catalysts since all possible coordination sites on the copper centre are occupied. However, the free copper(I) triflate **296**, and the *mono*-ligated copper(I) triflate complexes **297** would be active catalysts and thus the enantioselectivity observed in the AC reactions was a result of the relative rates of catalysis by these two species. It is possible that the *mono*-ligated copper(I) triflate complexes **297** could be very effective chiral directors in the AC reactions but the free copper(I) triflate in solution had diminished the enantioselectivity observed in these reactions.

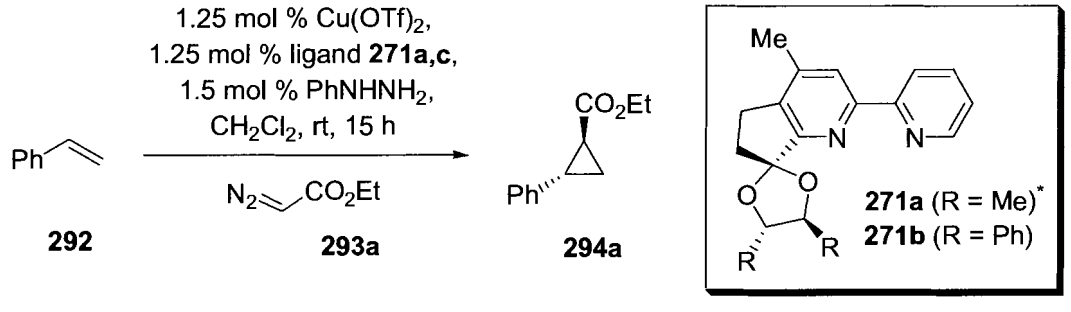
In the case of ligand **267c** (R = Ph), the *bis*-ligated complex appears to be the major complex in solution. The apparent kinetic and thermodynamic stability of this particular complex could be due to favorable π-π interactions or that the two ligands are sterically interlocked once positioned around the copper(I) centre (see, Figure 2.7.2.). Thus, when a 1:1 ratio of ligand **267c** to copper was employed in the AC reaction, the two species in solution were catalytically active free copper(I) triflate and the

catalytically inactive *bis*-ligated complex Cu(OTf)(**267c**)$_2$ and so the cyclopropane product was isolated in racemic form. Moreover, when the AC reaction was performed with a 2:1 ratio of ligand **267c** (R = Ph) and copper, the copper was entirely sequestered as the *bis*-ligated complex Cu(OTf)(**267c**)$_2$ and the cyclopropanation reaction was shut down completely.

2.8. Evaluation of the Unsymmetric 2,2′-Bipyridyl Ligands [271a,b (R = Me and Ph)] in Copper(I)-Catalyzed Asymmetric Cyclopropanation Reactions of Styrene and Ethyl Diazoacetate

The unsymmetric 2,2′-bipyridyl ligands **271a,b** (R = Me and Ph) were also evaluated in the AC reaction of styrene **292** (Scheme 2.8.1.). The AC reaction of styrene **292** with ethyl diazoacetate **293a** using a 1:1 ratio of ligands **271a,b** (R = Me and Ph) to copper(II) triflate afforded the cyclopropane **294a** in good yields (74 and 75%, respectively). However, these reactions proceeded with very low enantioselectivity in each instance (2 and 3% ee, respectively). The low enantioselectivities obtained with the unsymmetric ligands is presumably due to the lack of sufficient steric bulk on one side of the chiral ligands.

Scheme 2.8.1. Asymmetric Cyclopropanation Reactions using the Unsymmetric 2,2′-Bipyridyl Ligands **271a,b** (R = Me and Ph)



292 **293a** **294a**

* The compound used in this study was the enantiomer to that shown in the reaction scheme.

2.9. Optical Rotary Dispersion Spectrum of the $Cu(267c)_2 \cdot CuCl_2$ Complex

In the process of undertaking the full spectroscopic characterization of the $Cu(\mathbf{267c})_2 \cdot CuCl_2$ complex, it was observed that this compound possessed a particularly large optical rotation ($[\alpha]_D^{20}$ - 1300 [*c* 0.003, chloroform]). Pfaltz and co-workers have reported a similarly large optical rotation ($[\alpha]_{436}^{20}$ - 1574 [*c* 0.01, ethanol]) for a *bis*-ligated copper(II) semicorrin complex.[131] This result led us to record the optical rotary dispersion spectrum of the complex (Figure 2.9.1.). The spectrum was recorded at a concentration of 3.0 mg $Cu(\mathbf{267c})_2 \cdot CuCl_2$ complex in 100 mL of chloroform (1.9×10^{-5} M) and across a wavelength range of 200 nm to 800 nm. The maximum positive specific rotation was + 1.1×10^4 at a wavelength of 304 nm. The maximum negative specific rotation was - 1.3×10^4 at a wavelength of 329 nm (the corresponding circular dichroism spectrum is provided in the appendices of this thesis, see: Section 9.1.). To put these values in context, the classic hydrocarbon helicenes have extraordinarily high specific rotation values ($[\alpha]_D^{20}$) that range from 3640 ° for [6]-helicene to 9620 ° for [13]-helicene.[132]

(132) For a review on the synthesis of helicenes and their physical properties, see: Hopf, H. In *Classics in Hydrocarbon Chemistry*; Wiley-VCH: Weinheim, 2000, pp 321-368.

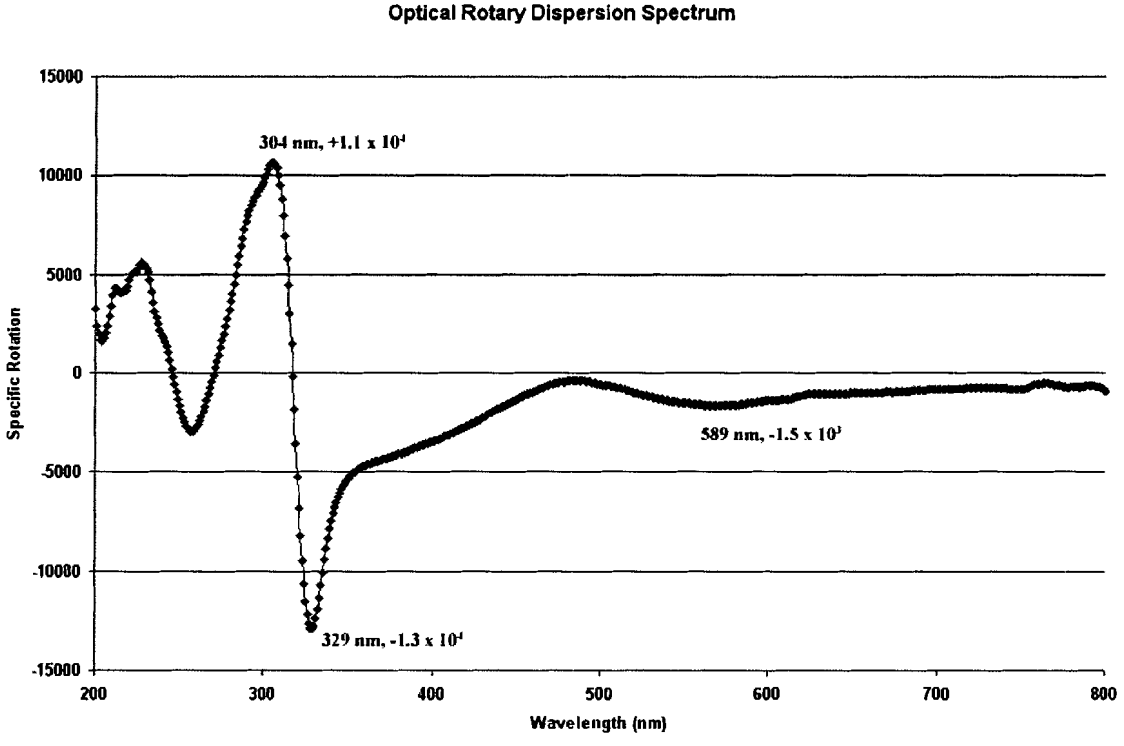


Figure 2.9.1. The optical rotary dispersion spectrum of the Cu(**267c**)$_2$·$CuCl_2$ complex.

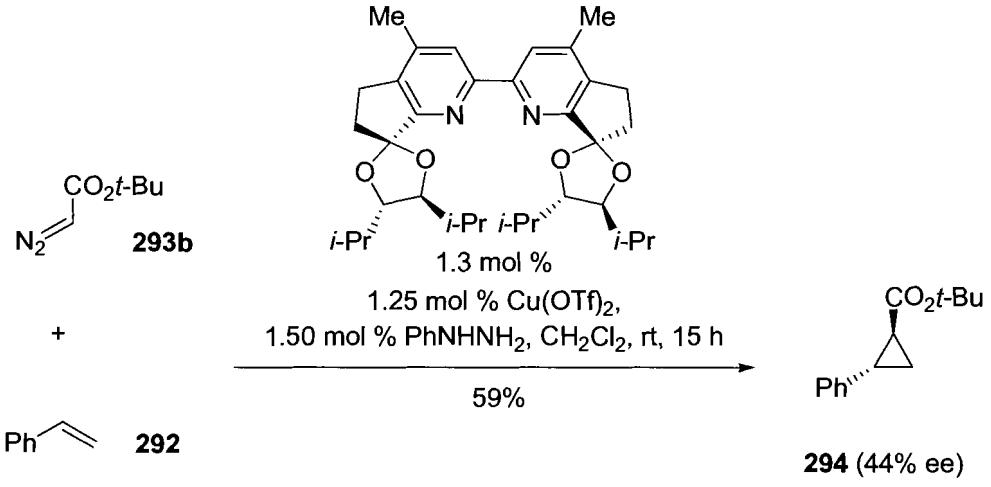
A UV spectrum of the Cu(**267c**)$_2$·$CuCl_2$ complex was also recorded on the same sample as that used to obtain the ORD spectrum. Strong UV absorbances at 287 nm (ε = 3.8 x 10^4 M^{-1} cm^{-1}), 309 (ε = 3.9 x 10^4 M^{-1} cm^{-1}) and 472 nm (ε = 6.2 x 10^3 M^{-1} cm^{-1}) were observed. The absorbance at 472 nm is in the blue-visible region of the electromagnetic spectrum which accounts for the red colour of the Cu(**267c**)$_2$·$CuCl_2$ complex.

2.10. Conclusions

The efficient and modular synthesis of a series of three chiral nonracemic C_2-symmetric 2,2′-bipyridyl ligands **267a-c** (R = Me, *i*-Pr and Ph) and two unsymmetric 2,2′-bipyridyl ligands **271a,b** (R = Me and Ph) was developed. These novel ligands were prepared in two steps from 2-chloro-4-methyl-6,7-dihydro-5H-[1]pyridine-7-one **269** and a series of chiral C_2-symmetric 1,2-diols **270a-c** (R = Me, *i*-Pr and Ph). This demonstrated the versatility of the design concept that underlies this research program in asymmetric synthesis.

The C_2-symmetric 2,2′-bipyridyl ligands **267a-c** and the corresponding unsymmetric 2,2′-bipyridyl ligands **271a,b** were evaluated in the copper(I)-catalyzed asymmetric cyclopropanation reactions of styrene **292** and diazoesters **293a-c**. The reaction conditions involved the formation of the asymmetric catalyst by reduction of the complex formed between 1.25 mol % of copper(II) triflate and 1.3 or 2.6 mol % of the C_2-symmetric ligands **267a-c** or the unsymmetric ligands **271a,b** with phenylhydrazine in dichloromethane. Following catalyst formation, styrene **292** was added to the reaction mixture followed by the slow addition of the diazoester **293a,b** over the course of 4 h. The best result was obtained in the asymmetric cyclopropanation reaction of styrene **292** and *tert*-butyl diazoacetate **267b** when the ligand **271b** (R = *i*-Pr) was employed. This afforded the reaction product **294** in good diastereoselectivity (83:17) and in moderate enantioselectivity (44% ee) (Scheme 2.10.1.).

Scheme 2.10.1. Asymmetric Cyclopropanation Reaction of Styrene employing the C_2-Symmetric 2,2′-Bipyridine Ligand **267b** (R = *i*-Pr)



In the course of these investigations it was observed that the stereoselectivities as well as the yields of the asymmetric cyclopropanation reactions were heavily dependant upon the ratio of the ligand **267a-c** and copper(II) triflate employed. The X-ray structure determination of the complex formed between the C_2-symmetric 2,2′-bipyridyl ligand **267c** (R = Ph) and copper(I) chloride showed that two bipyridyl ligands had coordinated to a copper(I) ion. This information, along with the results from the AC reactions, led to the conclusion that the 2,2′-bipyridyl ligands **267a-c** had the propensity to form catalytically inactive *bis*-ligated copper(I) species in solution that were in equilibrium with a catalytically active free copper(I) species and a *mono*-ligated copper(I) species. It was also inferred that the *mono*-ligated copper(I) species could possibly be very selective in the AC reactions and that the observed enantioselectivities were significantly eroded by the free copper(I) species in solution. For this reason, future studies with these ligands will involve their application in asymmetric reactions which are catalyzed by transition metals other than copper.

In the process of characterizing the Cu(**267c**)$_2$·$CuCl_2$ complex it was observed that it had a very large specific optical rotation. An optical rotary dispersion spectrum was recorded at a high dilution so that it was in the linear range of the instrument (1.9×10^{-5} M). The maximum positive optical rotation was $+1.1 \times 10^4$ at a wavelength of 304 nm. The maximum negative optical rotation was -1.3×10^4 at a wavelength of 329 nm. These are exceptionally high values and a future study has been considered that will involve the detection of trace quantities of copper salts and other transition metal salts in solution *via* optical rotation measurements (optical-sensing).

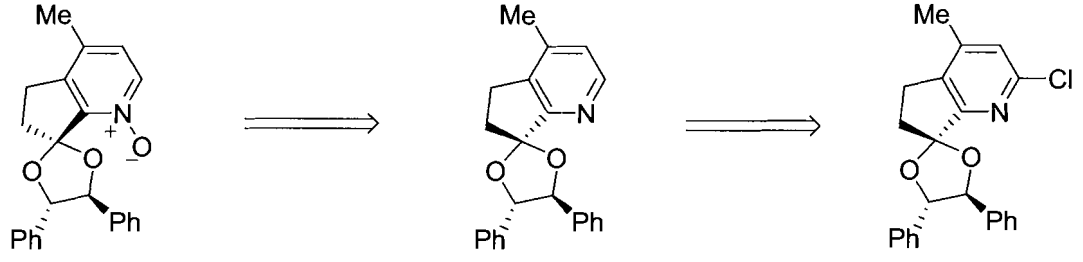
CHAPTER 3: RESULTS AND DISCUSSION

SYNTHESIS AND EVALUATION OF NEW CHIRAL NONRACEMIC PYRIDINE N-*OXIDES AND BIPYRIDINE* N,N′-*DIOXIDES*

3.1. Introduction

In this chapter, the syntheses of a chiral nonracemic pyridine *N*-oxide and a related chiral nonracemic C_2-symmetric 2,2′-bipyridyl *N,N′*-dioxide are described. The evaluation of these two chiral *N*-oxides in the catalytic desymmeterization reaction of *cis*-stilbene oxide with silicon tetrachloride is also described.

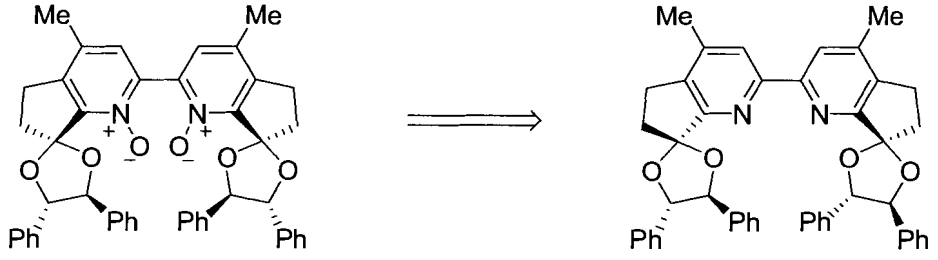
We envisioned that the chiral nonracemic pyridine *N*-oxide **299** could be prepared by simple oxidation of the corresponding pyridine **300**. This pyridine **300** could be prepared by the reduction of the chiral nonracemic 2-chloroacetal **268c** (Figure 3.1.1.). The 2-chloroacetal **268c** had previously been used to synthesize the 2,2′-bipyridyl ligands **267a-c** (see, Chapter 2).



299 **300** **268c**

Figure 3.1.1. Retrosynthetic analysis of the chiral pyridine *N*-oxide **299**.

In a similar fashion, the C_2-symmetric 2,2′-bipyridyl *N,N′*-dioxide **301** could be prepared by direct oxidation of the corresponding C_2-symmetric 2,2′-bipyridyl ligand **267c** (Figure 3.1.2.).



301 **267c**

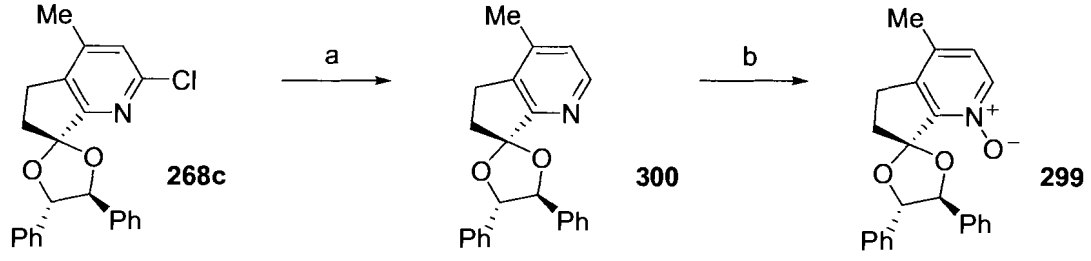
Figure 3.1.2. Retrosynthetic analysis of the chiral nonracemic C_2-symmetric 2,2′-bipyridyl *N,N′*-dioxide **301**.

3.2. Synthesis of the Chiral Nonracemic Pyridine *N*-Oxide (299)

The chiral nonracemic pyridine **300** was prepared by reduction of the 2-chloropyridine **268c** (Scheme 3.2.1.). This reaction involved heating the 2-chloropyridine **268** with borane dimethylamine complex in the presence of a catalytic amount of dibromo*bis*(triphenylphosphine)nickel(II) and potassium carbonate in acetonitrile at 50 °C which afforded the pyridine **300** in good yield (87%).[133] The pyridine **300** was then converted to the pyridine *N*-oxide **299** in excellent yield (93%) upon oxidation with *m*-chloroperoxybenzoic acid in dichloromethane at room temperature.

(133) Lipshutz, B. H.; Tomioka, T.; Pfeiffer, S. S. Mild and Selective Reductions of Aryl Halides Catalyzed by Low-Valent Nickel Complexes. *Tetrahedron Lett.* **2001**, *42*, 7737.

Scheme 3.2.1. Synthesis of the Chiral Nonracemic Pyridine *N*-Oxide **299**



Reagents and Conditions: (a) $NiBr_2(PPh_3)_2$, $BH_3{\cdot}(Me)_2NH$, MeCN, 50 °C, 12 h, 87%; (b) *m*-CPBA, CH_2Cl_2, room temperature, 24 h, 93%.

The structure of the pyridine *N*-oxide **299** was confirmed on the basis of spectroscopic evidence. The mass spectrum was not particularly useful because the compound fragmented and evidence of the *N*-oxide moiety was lost. However, elemental analysis confirmed the molecular formula $C_{23}H_{21}NO_3$. In addition, the infrared spectrum displayed a characteristic pyridine *N*-oxide stretch at 1258 cm^{-1}.[134] The ^1H NMR spectrum of the pyridine *N*-oxide **299** is shown below (Figure 3.2.1.).

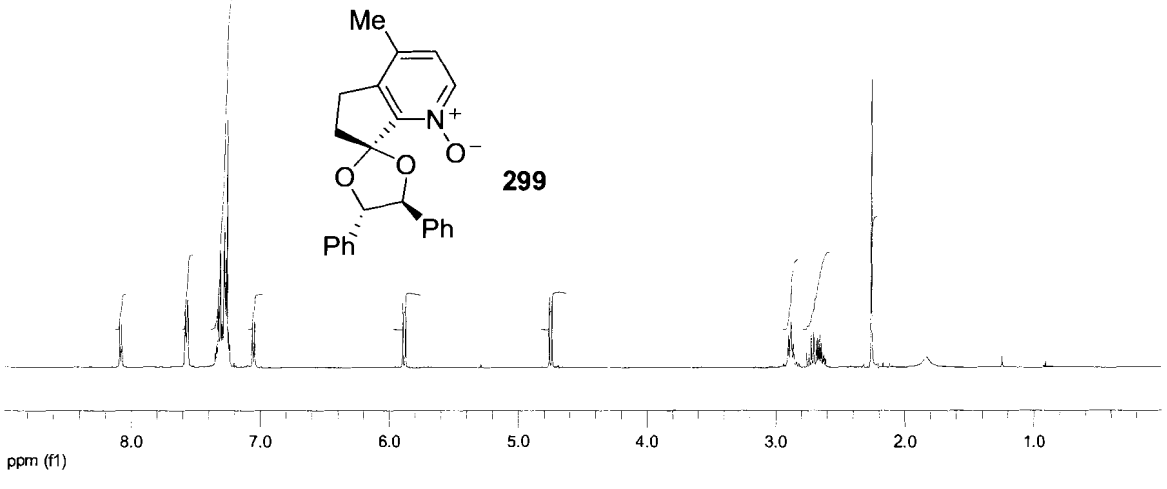


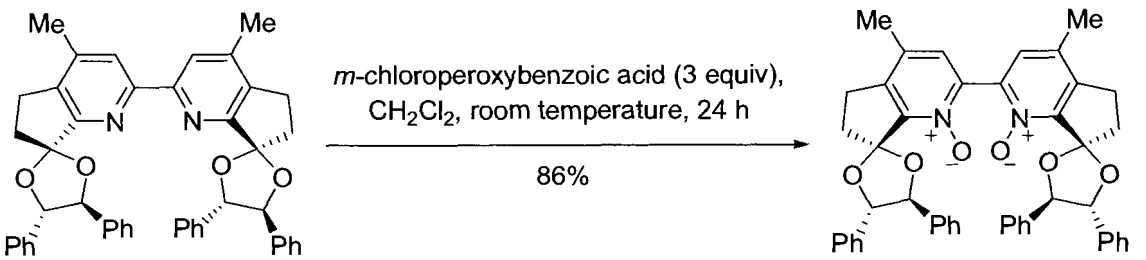
Figure 3.2.1. ^1H NMR spectrum of the chiral pyridine *N*-oxide **299**.

(134) Silverstein, R. M.; Webster, F. X. Infrared Spectrometry. In *Spectrometric Identification of Organic Compounds*, 6th ed.; John Wiley & Sons, Inc. New York, 1998; Chapter 3.

3.3. Synthesis of the Chiral Nonracemic C_2-Symmetric 2,2′-Bipyridyl *N,N′*-Dioxide (301)

The chiral 2,2′-bipyridyl *N,N*-dioxide **301** was prepared from the corresponding 2,2′-bipyridyl ligand **267c** on oxidation with three equivalents of *m*-chloroperoxybenzoic acid in dichloromethane at room temperature (Scheme 3.3.1.).

Scheme 3.3.1. Preparation of the Chiral Nonracemic C_2-Symmetric 2,2′-Bipyridyl *N,N′*-Dioxide **301**



267c **301**

The structure of the bipyridine *N,N′*-dioxide **301** was again confirmed on the basis of full spectroscopic evidence. In particular, the mass spectrum displayed a molecular ion peak for M(**301** + H) at 717 which indicated both pyridine nitrogen atoms had been oxidized. The ^{1}H NMR spectrum displayed broadened peaks which suggested that the barrier to rotation about the biaryl bond was relatively high.

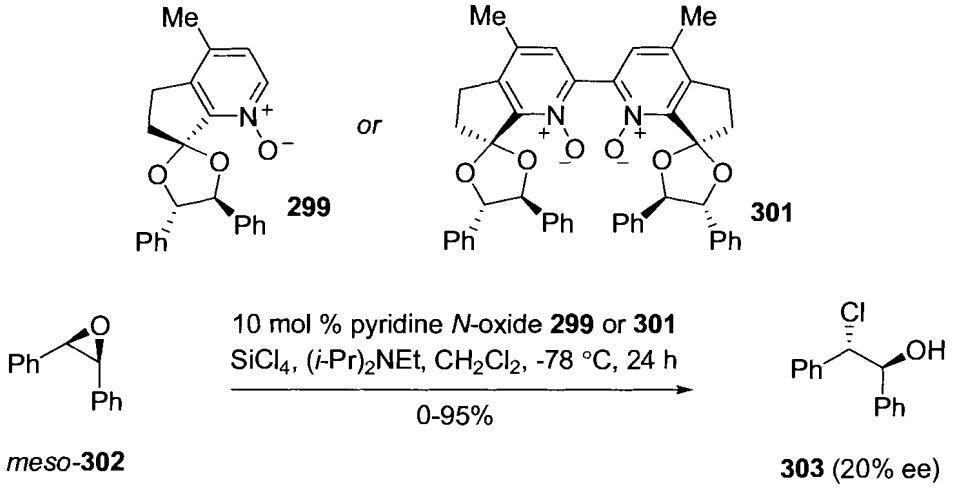
3.4. Evaluation of the Chiral Nonracemic Pyridine *N*-Oxide (299) and the C_2-Symmetric 2,2′-Bipyridyl *N,N′*-Dioxide (301) in a Catalytic Desymmeterization Reaction of *cis*-Stilbene Oxide

The chiral nonracemic pyridine *N*-oxide **299** and the C_2-symmetric 2,2′-bipyridyl *N,N′*-dioxide **301** were evaluated as chiral directors in the catalytic desymmeterization reaction of a *meso* compound, *cis*-stilbene oxide **302**, with silicon tetrachloride (Figure

3.4.1.).[135] The reaction conditions involved the addition of silicon tetrachloride to a solution of 10 mol % of the chiral pyridine *N*-oxide (**299** *or* **301**), *N,N*-diisopropylethylamine and *cis*-stilbeneoxide **302** in dichloromethane at -78 °C. The chiral pyridine *N*-oxide **299** was catalytically active and afforded the desired chiral chlorohydrin **303** in excellent yield (95%) and moderate enantiomeric excess (20%). However, in the case of the 2,2′-bipyridyl *N,N′*-dioxide **301**, no reaction occurred and only starting material was recovered after 24 h. The catalytic inactivity of the 2,2′-bipyridyl *N,N′*-dioxide **301** can be attributed to the high degree of steric hindrance around the complexation pocket of the catalyst. Due to the lack of reactivity and the low enantioselectivity, these chiral *N*-oxides were not evaluated in asymmetric aldol reactions (see, section 1.11.) and it was decided to pursue the synthesis and evaluation of other chiral ligands.

(135) (a) Nakajima, M.; Saito, M.; Uemura, M.; Hashimoto, H. Enantioselective Ring-Opening of *meso*-Epoxides with Tetrachlorosilane Catalyzed by Chiral Bipyridine *N,N′*-Dioxide Derivatives. *Tetrahedron Lett.* **2002**, *43*, 8827. (b) Garrett, C. E.; Fu, G. C. π-Bound Phosphorus Heterocycles as Catalysts: Ring-Opening of Expoxides with TMSCl in the Presence of a Phosphaferrocene. *J. Org. Chem.* **1997**, *62*, 4534. (c) Denmark, S. E.; Barsanti, P. A.; Wong, K.-T.; Stavenger, R. A. Enantioselective Ring-Opening of Epoxides with Silicon Tetrachloride in the Presence of a Chiral Lewis Base. *J. Org. Chem.* **1998**, *63*, 2428.

Scheme 3.4.1. The Desymmeterization Reactions of *cis*-Stilbene oxide **302**



3.5. Conclusions

The chiral nonracemic pyridine *N*-oxide **299** and the C_2-symmetric 2,2′-bipyridyl *N,N′*-dioxide **301** were prepared by direct oxidation of the corresponding chiral pyridine **300** and C_2-symmetric 2,2′-bipyridyl **267c**, respectively. These *N*-oxides were evaluated as chiral catalysts in the asymmetric desymmeterization reaction of *cis*-stilbene oxide with silicon tetrachloride. The pyridine *N*-oxide **299** was an active catalyst in this reaction and afforded the reaction product in excellent yield but in low enantioselectivity. The C_2-symmetric 2,2′-bipyridyl *N,N′*-dioxide **301** was found to be catalytically inactive in this reaction.

CHAPTER 4: RESULTS AND DISCUSSION

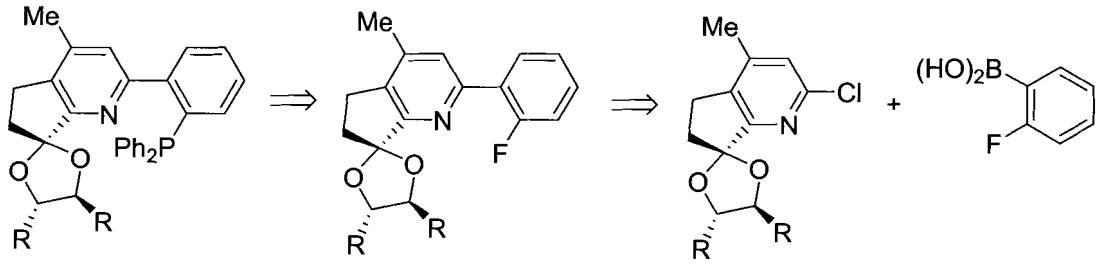
SYNTHESIS AND EVALUATION OF A SERIES OF NEW CHIRAL NONRACEMIC PYRIDYLPHOSPHINE LIGANDS

4.1. Introduction

In this chapter, the efficient and modular synthesis of a new class of chiral nonracemic pyridylphosphine ligands (*P,N*-ligands) is described.* The syntheses of these ligands represents an extension of the general design concept described in Chapter 1. Their syntheses were pursued in order to further demonstrate the modular nature of this approach as well as to identify a highly effective chiral director. The evaluation of these *P,N*-ligands in palladium-catalyzed asymmetric Heck reactions, in palladium-catalyzed asymmetric allylic substitution reactions as well as in the iridium(I)-catalyzed asymmetric hydrogenation reactions is also presented.

The chiral nonracemic *P,N*-ligands **304a-c** (R = Me, *i*-Pr and Ph) could in principle be synthesized from the corresponding chiral chloroacetals **268a-c**, the same precursors that were used in the synthesis of the chiral 2,2′-bipyridyl ligands **267a-c** (see, Chapter 2). We envisioned that a Suzuki coupling reaction of the chloroacetals **268a-c** with *ortho*-fluorophenylboronic acid **306** would afford the biaryl fluorides **305a-c** that on displacement of fluoride ion with the anion of diphenylphosphine would afford the desired *P,N*-ligands **304a-c** (Figure 4.1.1.).

(*) Part of the research described in this chapter has been published, see: Lyle, M. P. A.; Narine, A. A.; Wilson, P. D. A New Class of Chiral *P,N*-Ligands and their Application in Palladium-Catalyzed Asymmetric Allylic Substitution Reactions. *J. Org. Chem.* **2004**, *69*, 5060.



304a-c (R = Me, *i*-Pr and Ph) **305a-c** **268a-c** **306**

Figure 4.1.1. Retrosynthetic analysis of the chiral *P,N*-Ligands **304a-c** (R = Me, *i*-Pr and Ph).

4.2. Synthesis of the Chiral Nonracemic *P,N*-Ligands [304a-c (R = Me, *i*-Pr and Ph)] from the Chiral Acetals (268a-c)

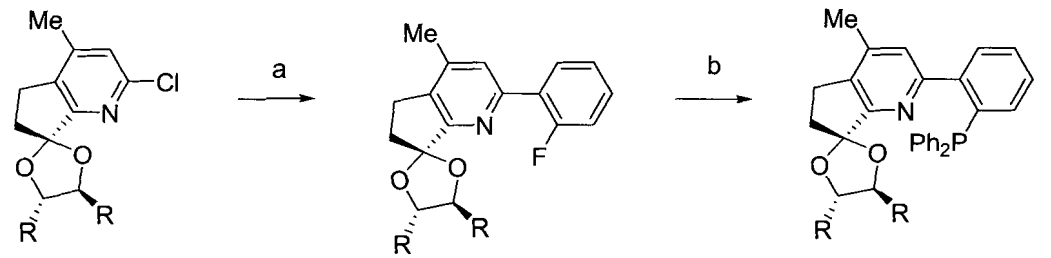
The chiral nonracemic chloroacetals **268a-c** (R = Me, *i*-Pr and Ph) were each subjected to a Suzuki coupling reaction with *o*-fluorophenylboronic acid **306** (Scheme 4.2.1.).[136] It was again found that the 2-chloropyridine moiety of these acetals reacted exceedingly slowly with this boronic acid under standard Suzuki reaction conditions which involved heating a mixture of the chloroacetals **268a-c**, the boronic acid **306** and potassium carbonate in toluene in the presence of 10 mol % *tetrakis*(triphenylphosphine)palladium(0). However, the reactions proceeded smoothly when the reaction conditions reported by Fu and co-workers were employed and afforded the desired reaction products, the aromatic fluorides **305a-c** (R = Me, *i*-Pr and Ph), in good yield (81-93%).[137] These reaction conditions involved heating a mixture of the acetals **268a-c** (R = Me, *i*-Pr and Ph), the boronic acid **306** and anhydrous cesium

(136) For a review on the Suzuki reaction, see: Miyaura, N.; Suzuki, A. Palladium-Catalyzed Cross Coupling Reactions of Organoboron Compounds. *Chem. Rev.* **1995**, *95*, 2457.

(137) Littke, A. F.; Dai, C.; Fu, G. C. Versatile Catalysts for the Suzuki Cross-Coupling of Arylboronic Acids with Aryl and Vinyl Halides and Triflates under Mild Conditions. *J. Am. Chem. Soc.* **2000**, *122*, 4020.

carbonate in tetrahydrofuran at reflux in the presence of catalytic amounts of *tris*(dibenzylideneacetone)dipalladium(0) (5 mol %) and tri-*t*-butylphosphine (10 mol %).

Scheme 4.2.1. Synthesis of the *P,N*-Ligands **304a-c** (R = Me, *i*-Pr and Ph)



268a-c (R = Me*, *i*-Pr and Ph) **305a-c** (R = Me*, *i*-Pr and Ph) **304a-c** (R = Me*, *i*-Pr and Ph)

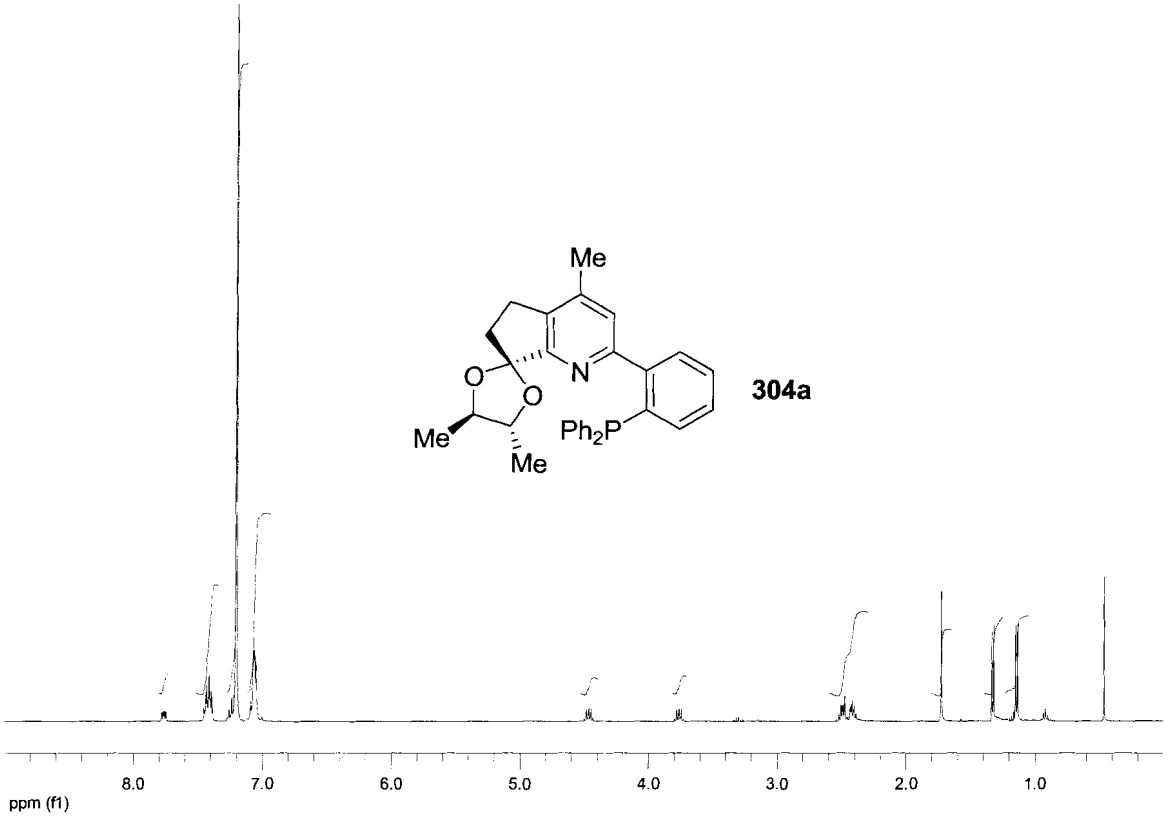
Reagents and conditions: (a) *o*-fluorophenylboronic acid **306**, 5 mol% of Pd_2dba_3, 10 mol% of $P(t\text{-}Bu)_3$, Cs_2CO_3, THF, reflux, 16 h, 93% (**305a**), 81% (**305b**), 88% (**305c**); (b) $HPPh_2$, KO*t*-Bu, 18-crown-6, THF, room temperature, 24 h, 72% (**304a**), 66% (**304b**), 63% (**304c**). * The compound used in this study was the enantiomer of that shown in the reaction scheme.

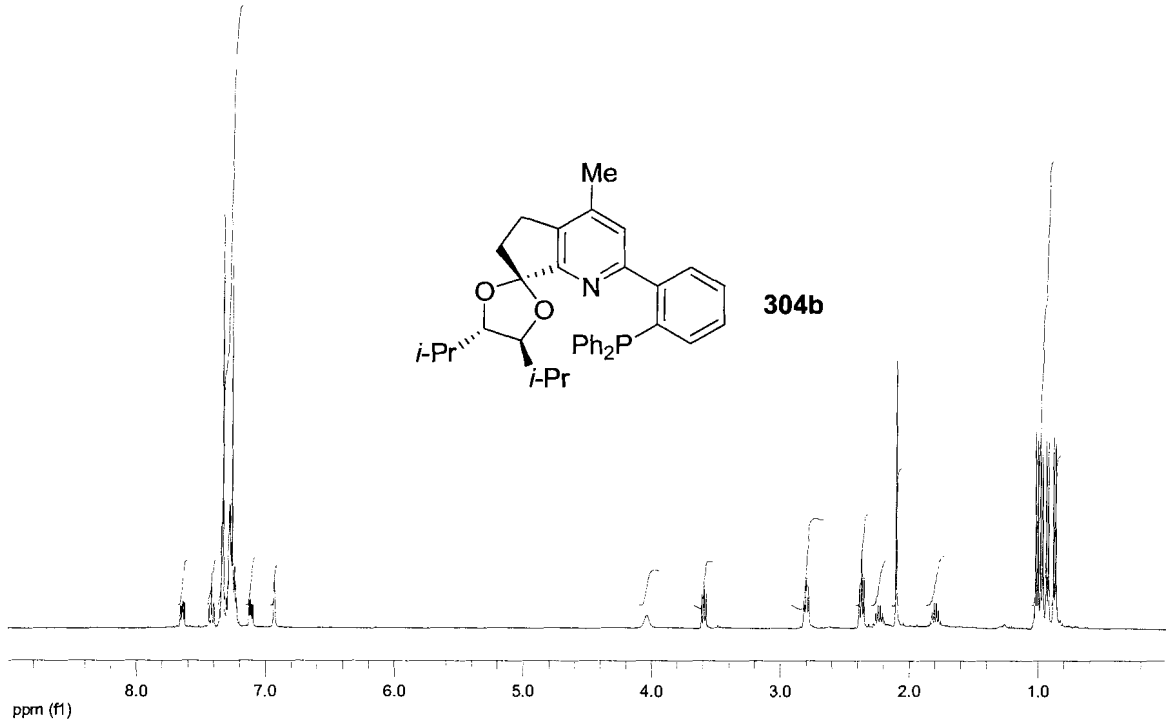
The products of the Suzuki reactions were then converted efficiently to the desired target compounds, the chiral nonracemic *P,N*-ligands **304a-c** (R = Me, *i*-Pr and Ph), on reaction of the potassium salt of diphenylphosphine in the presence of 18-crown-6 in tetrahydrofuran at room temperature for 24 hours.[138] The potassium salt of diphenylphosphine was prepared by treatment of a colourless solution of diphenylphosphine in tetrahydrofuran with potassium *tert*-butoxide. This afforded a bright red solution of the anion that faded to yellow over the course of the reaction, once the aromatic fluorides **305a-c** were added.

The mass spectra for each of the *P,N*-ligands **304a-c** (R = Me, *i*-Pr and Ph) displayed the expected molecular ion peaks for M(**304a** + H) at 480, for M(**304b** + H) at 536 and for M(**304c** + H) at 604. The ^1H NMR spectra of the *P,N*-ligands **304a-c** (R =

(138) Kündig, E. P.; Meier, P. Synthesis of New Chiral Bidentate (Phosphinophenyl)benzooxazine *P,N*-Ligands. *Helv. Chim. Acta* **1999**, *82*, 1360.

Me, *i*-Pr and Ph) are shown below (Figure 4.2.1.). These sharp, well-resolved spectra suggested that there was free rotation about the biaryl bond in each of the *P,N*-ligands **304a-c** and thus there were no atropisomeric forms of these molecules. In addition, the ^{13}C NMR spectra of these unsymmetrical molecules contained the appropriate number of signals.





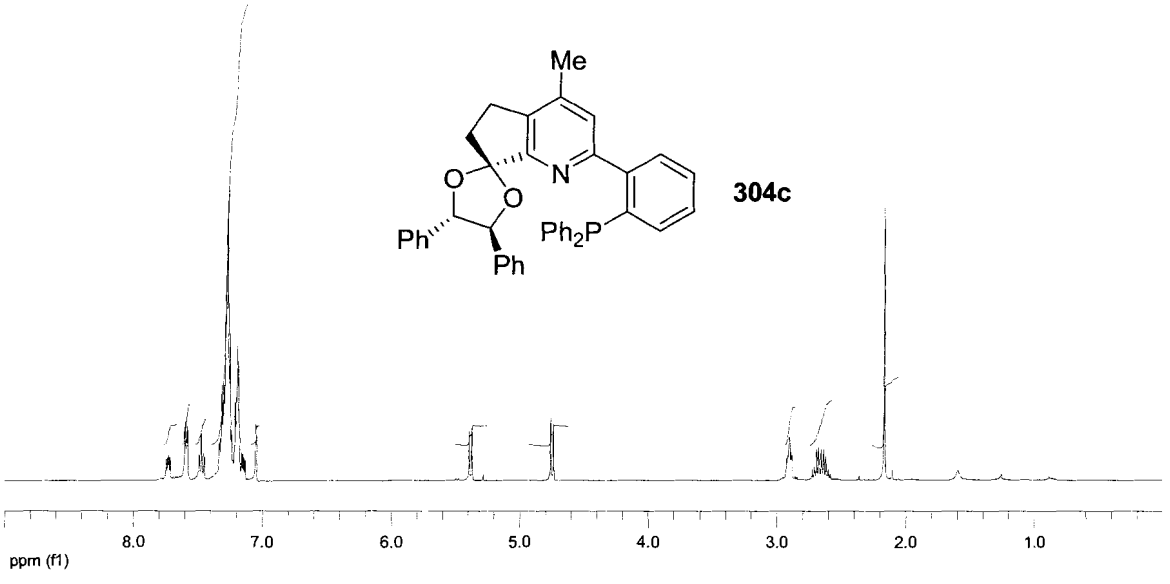


Figure 4.2.1. ^{1}H NMR spectra of the *P*,*N*-ligands **304a-c** (R = Me, *i*-Pr and Ph).

4.3. X-Ray Crystallographic Analysis of the Chiral *P,N*-Ligand [304c (R = Ph)]

In the course of these investigations, a sample of the chiral *P,N*-ligand **304c** (R = Ph) was provided to Mr. Neil D. Draper of Professor Daniel B. Leznoff's research group at Simon Fraser University who was interested in synthesizing chiral coordination polymers of this *P,N*-ligand and mercury(II) cyanide.[139] In one experiment, equimolar amounts of the *P,N*-ligand **304c** (R = Ph) and mercury(II) cyanide were dissolved in a mixture of ethanol and dichloromethane (1:1). Colourless crystals that were suitable for X-ray crystallography were obtained on slow evaporation of the solvent mixture. When the crystals were collected and analyzed by X-ray crystallography it was revealed that the crystals were not a coordination polymer but were crystals of the non-complexed *P,N*-ligand **304c** (R = Ph).

An *ORTEP* representation of the crystal structure of the ligand **304c** is shown below (Figure 4.3.1.). Notably, in the solid state, the chiral *P,N*-ligand **304c** (R = Ph) showed a preference for one atropisomeric state in which the biaryl bond was rotated such that the phosphorus atom (P1) was oriented on the same side of the molecule as the oxygen atom (O1). A complete list of tabulated bond angles and bond lengths from the X-ray structure determination of the *P,N*-ligand **304c** (R = Ph) is provided in the experimental section of this thesis.

---

(139) (a) Draper, N. D.; Batchelor, R. J.; Leznoff, D. B. Tuning the Structures of Mercury Cyanide-Based Coordination Polymers with Transition Metal Cations. *Crystal Growth and Design* **2004**, *4*, 621. (b) Haftbaradaran, F.; Draper, N. D.; Leznoff, D. B.; Williams, V. E. A Strained Silver(I) Coordination Polymer of 1,4-Diazatriphenylene. *J. Chem. Soc., Dalton Trans.* **2003**, 2105. (c) Draper, N. D.; Batchelor, R. J.; Leznoff, D. B. Using HgX_2 Units (X = CN, Cl) to Increase Structural and Magnetic Dimensionality in Conjunction with (2,2′-Bipyridyl)copper(II) Building Blocks. *Polyhedron* **2003**, *22*, 1735.

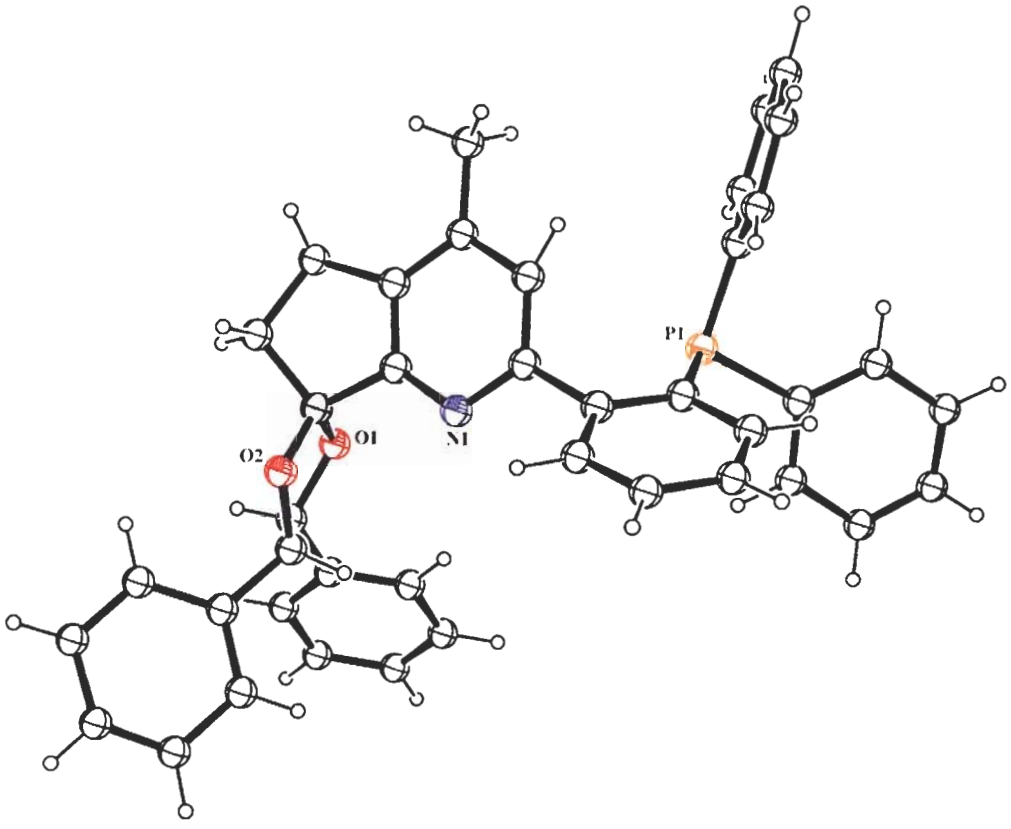


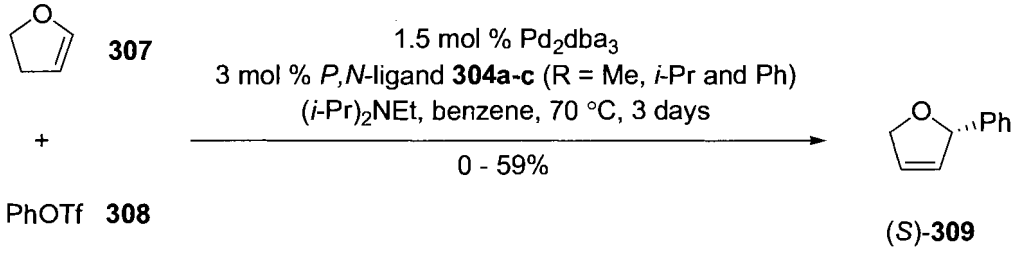
Figure 4.3.1. *ORTEP* representation of the chiral *P,N*-ligand **304c** (R = Ph).*

4.4. Evaluation of the *P,N*-Ligands (304a-c) in Palladium-Catalyzed Asymmetric Heck Reactions of 2,3-Dihydrofuran (307)

With a series of three chiral nonracemic *P,N*-ligands **304a-c** (R = Me, *i*-Pr and Ph) in hand, the evaluation of the ligands in the palladium(0)-catalyzed asymmetric Heck reactions of phenyl triflate **308** with 2,3-dihydrofuran **307** were undertaken (Table 4.4.1.). These asymmetric carbon-carbon bond forming reactions were performed under standard reaction conditions that were reviewed earlier in this thesis (see, Chapter 1 - Section 1.12.5.).

(*) The thermal ellipsoids are drawn at the 25% probability level for clarity.

Table 4.4.1. Palladium-Catalyzed Asymmetric Heck Reactions



entry	ligand	yield (%)	%ee
1	**304a** (R = Me)	59	22
2	**304b** (R = *i*-Pr)	0	-
3	**304c** (R = Ph)	0	-

The catalysts were formed *in situ* on reaction of 1.5 mol % of *tris*benzylideneacetonedipalladium(0) with 3 mol % of the chiral *P,N*-ligand **304a-c** (R = Me, *i*-Pr and Ph) in anhydrous and degassed benzene which afforded deep purple solutions. Following the formation of the catalysts, 2,3-dihydrofuran **307**, phenyl triflate **308** and *N,N*-diisopropylethylamine were added to the reaction mixture which was then heated at 70 °C for 3 days.

In the case of the *P,N*-ligand **304a** (R = Me), the system proved to be catalytically active and afforded the desired Heck reaction product **309** in moderate yield (59%) but in low enantiomeric excess (22%) (entry 1). The absolute stereochemistry of the reaction product **309** was assigned as (*S*) based on comparison of the optical rotation to a literature value.[140] The palladium(0)-catalysts derived from the *P,N*-ligands **304b,c** (R = *i*-Pr and Ph) did not catalyze the reaction under these conditions and none of the desired reaction product was isolated. The lack of reactivity of the *P,N*-ligands **304b,c** (R = *i*-Pr and Ph)

(140) Gilbertson, S. R.; Xie, D.; Fu, Z. Proline-Based *P,N* Ligands in Asymmetric Allylation and the Heck Reaction. *J. Org. Chem.* **2001**, *66*, 7240.

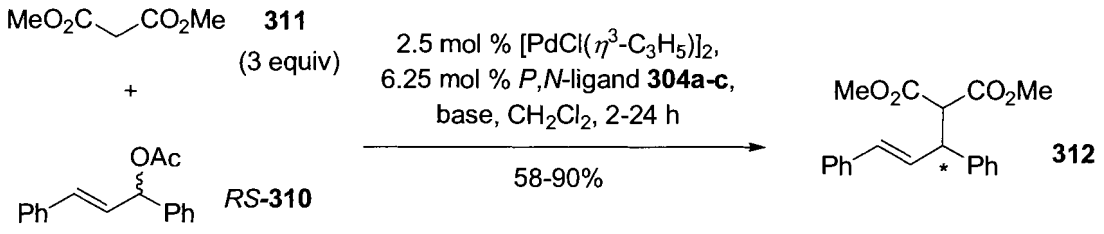
was attributed to steric hindrance around the complexation pocket of the palladium(0) centre.

In view of the low enantiomeric excess (22%) recorded with ligand **304a** (R = Me) and the catalytic inactivity of the other systems, it was concluded that the chiral nonracemic *P,N*-ligands **304a-c** were not well suited to application in asymmetric Heck reactions and so it was decided to evaluate these ligands in other asymmetric reactions.

4.5. Evaluation of the *P,N*-Ligands (304a-c) in Palladium-Catalyzed Asymmetric Allylic Substitution Reactions

The evaluation of the series of three chiral *P,N*-ligands **304a-c** (R = Me, *i*-Pr and Ph) in the palladium(II)-catalyzed asymmetric allylic substitution (AAS) reaction of racemic 3-acetoxy-1,3-diphenyl-1-propene *RS*-**310** with dimethyl malonate **311** was undertaken (Table 4.5.1.). These reactions were again performed under standard reaction conditions that were reviewed earlier in this thesis (Chapter 1, Section 1.12.4.).

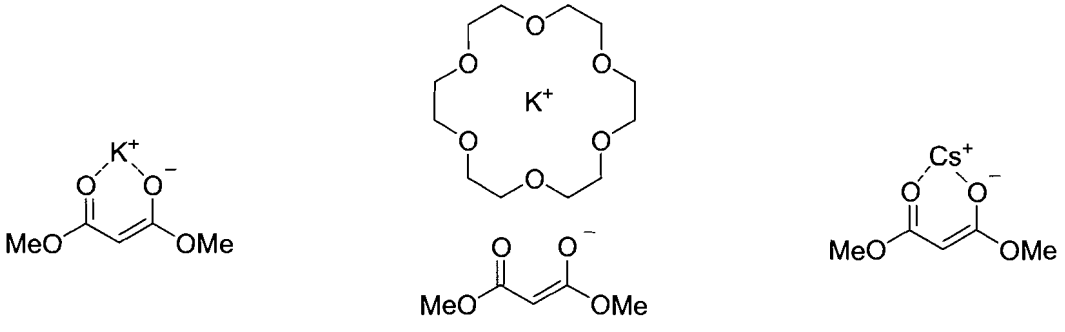
Table 4.5.1. Palladium-Catalyzed Asymmetric Allylic Substitution Reactions



entry	ligand	base	temp. (°C)	yield (%)	ee (%)	conf.
1	**304a**	BSA/KOAc (cat.)	rt	97	65	S
2	**304a**	K_2CO_3, 18-crown-6	rt	97	60	S
3	**304a**	Cs_2CO_3	rt	97	60	S
4	**304b**	BSA/KOAc (cat.)	rt	92	43	R
5	**304b**	K_2CO_3, 18-crown-6	rt	93	54	R
6	**304b**	Cs_2CO_3	rt	97	60	R
7	**304c**	BSA/KOAc (cat.)	rt	71	58	R
8	**304c**	K_2CO_3, 18-crown-6	rt	97	62	R
9	**304c**	Cs_2CO_3	rt	97	86	R
10	**304c**	Cs_2CO_3	12	97	88	R
11	**340c**	Cs_2CO_3	0	91	90	R
12	**304c**	Cs_2CO_3	-12	83	90	R

The active chiral palladium(II)-catalysts were generated by the reaction of 6.25 mol % of the chiral *P,N*-ligand **304a-c** (R = Me, *i*-Pr and Ph) with 2.5 mol % of allylpalladium chloride dimer in anhydrous dichloromethane at room temperature for 30 min which afforded pale yellow solutions. On subsequent addition of racemic 3-acetoxy-1,3-diphenyl-1-propene *RS*-**310** (1 equiv) and dimethyl malonate **311** (3 equiv) a range of bases and associated reagents were then added. The bases and associated reagents used in these reactions were as follows: (1) *N,O-bis*(trimethylsilyl)acetamide (BSA, 3 equiv) and a catalytic amount of potassium acetate; (2) anhydrous potassium carbonate (3 equiv) and 18-crown-6 (3 equiv); and (3) anhydrous cesium carbonate (3 equiv). These bases and associated reagents were chosen so that we could evaluate the effect of the

counterion of the anion of dimethyl malonate on the stereoselectivity of the reaction.[141] The nucleophilic species generated from each of these sets of reagents are shown below (Figure 4.5.1.).



313 **314** **315**

Figure 4.5.1. The nucleophilic species associated with each of the reagents used in the AAS reactions.

The yields reported in the table are of the analytically pure reaction product that was isolated by flash chromatography. The enantioselectivity of the reactions were determined by analytical chiral HPLC (Daicel Chiracel OD column) using hexane:*iso*-propanol (97:3) as the eluant with a flow rate of 0.5 mL/minute and UV detection at 245 nm.

In all cases, these catalytic systems proved to be active and afforded the desired product, 1,3-(diphenylallyl)malonic acid dimethyl ester **312** in excellent yield (up to 97%). The ^{1}H NMR spectrum of the reaction product **312** clearly showed that the acetate moiety had been displaced by the anion of dimethyl malonate. In particular, the spectrum

(141) For discussions on the effect of the counter-ion on the enantioselectivity in AAS reactions, see: (a) Brown, J. M.; Hulmes, D. I.; Guiry, P. J. Mechanistic and Synthetic Studies in Catalytic Allylic Alkylation with Palladium Complexes of 1-(2-Diphenylphosphino-1-napthyl)isoquinoline. *Tetrahedron* **1994**, *50*, 4493. (b) Bovens, M.; Togni, A.; Venanzi, L. M. Asymmetric Allylic Alkylation with Palladium Coordinated to a New Optically Active Pyrazolylmethane Ligand. *J. Organomet. Chem.* **1993**, *451*, C28.

contained two 3H singlets at 3.52 ppm and 3.72 ppm, respectively, which correspond to the two diastereotopic methyl ester moieties.

It was found that the enantioselectivities of these reactions varied depending on which *P,N*-ligand as well as which set of reaction conditions were employed. The use of the *P,N*-ligand **304a** (R = Me), derived from (2*R*,3*R*)-2,3-butanediol **270a**, afforded the product *S*-**312** in good enantiomeric excess (60-65%) (entries 1, 2 and 3) with the three individual sets of reaction conditions. These results were particularly encouraging when one considers that these asymmetric reactions were directed by the steric influence of a methyl group. The use of the *pseudo*-enantiomeric *P,N*-ligand **304b** (R = *i*-Pr), derived from (1*S*,2*S*)-1.2-diisopropyl-1,2-ethanediol **270b**, afforded the enantiomeric product *R*-**312** in similar enantiomeric excess (43-60%) (entries 4, 5 and 6). It was somewhat surprising that the use of ligand **304b** (R = *i*-Pr) showed, in general, slightly lower enantioselectivity (in view of of the presumed greater steric influence of an isopropyl group relative to a methyl group). The superior result (60% ee) was achieved when cesium carbonate was used as the base (entry 6). The use of *P,N*-ligand **304c** (R = Ph), derived from (1*S*,2*S*)-1,2-diphenyl-1,2-ethanediol **270c**, again afforded the product in moderate enantiomeric excess (58 and 62%) when BSA and a catalytic amount of potassium acetate or potassium carbonate and 18-crown-6 were employed (entries 7 and 8). However, and to our delight, the product *R*-**312** was formed in high enantiomeric excess (86%) and in excellent yield (97%) when cesium carbonate was used as the base in this room temperature reaction (entry 9). On decreasing the temperature to 12 °C a further enhancement of the enantioselectivity of the reaction was observed (88% ee) (entry 10). The optimal conditions involved performing the reaction with cesium

carbonate as the base at 0 °C for 4 h. This afforded the product *R*-**312** in good yield (91%) and in high enantiomeric excess (90%) (entry 11). A further decrease in the reaction temperature to -12 °C did not result in any further improvement in the enantioselectivity of the reaction (90%) and the yield of the reaction was compromised (83%) (entry 12).

4.6. Mechanistic Analysis of the Asymmetric Allylic Substitution Reaction using the *P,N*-Ligand [304c (R = Ph)]

In order to postulate a plausible mechanism for this highly enantioselective reaction (90% ee), a ^{31}P NMR study of the corresponding cationic π-allyl palladium complex was undertaken.

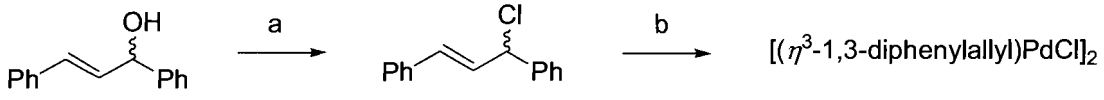
3-Chloro-1,3-diphenyl-1-propene **317** was prepared by the reaction of 1,3-diphenyl-1-propene-3-ol **316** with concentrated hydrochloric acid at room temperature followed by purification of the crude reaction product by short path distillation.[142] (1,3-Diphenylallyl)palladium chloride dimer **318** was then prepared according to a literature procedure described by Bosnich and co-workers.[143] This involved the reaction of 3-chloro-1,3-diphenyl-1-propene **317** with palladium(II) chloride under an atmosphere of carbon monoxide and in the presence of lithium chloride (Scheme 4.6.1.).

---

(142) Hayashi, T.; Yamamoto, A.; Ito, Y.; Nishioka, E.; Miura, H.; Yanagi, K. Asymmetric Synthesis Catalyzed by Chiral Ferrocenylphosphine-Transition-Metal Complexes. Palladium Catalyzed Asymmetric Allylic Amination. *J. Am. Chem. Soc.* **1989**, *111*, 6301.

(143) (a) Auburn, P. R.; Mackenzie, P. B.; Bosnich, B. Asymmetric Synthesis. Asymmetric Catalytic Allylation using Palladium Chiral Phosphine Complexes. *J. Am. Chem. Soc.* **1985**, *107*, 2033. (b) Mackenzie, P. B.; Whelan, J.; Bosnich, B. Asymmetric Synthesis. Mechanism of Asymmetric Catalytic Allylation. *J. Am. Chem. Soc.* **1985**, *107*, 2046.

Scheme 4.6.1. Preparation of (1,3-Diphenyl)allylpalladium Chloride Dimer

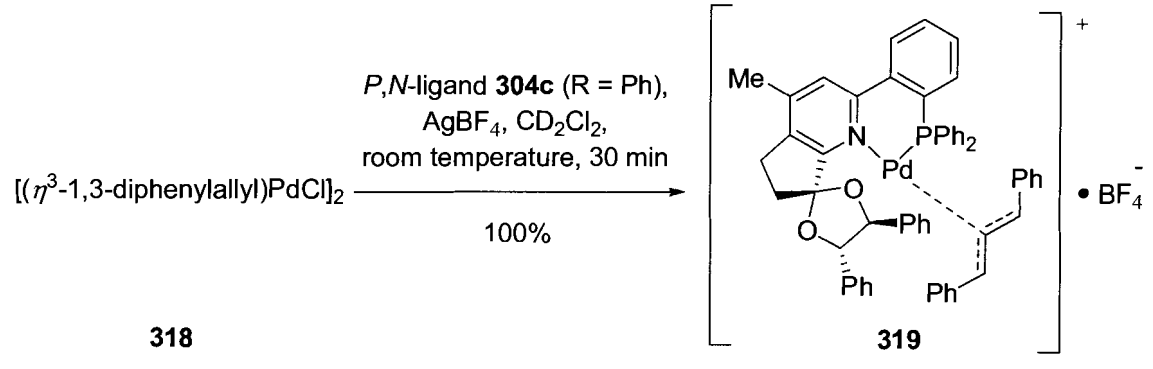


316 **317** **318**

Reagents and conditions: (a) concentrated HCl, room temperature, 30 min, 65%; (b) $PdCl_2$, LiCl, H_2O, EtOH, CO (1 atm), 45 °C for 3 h then room temperature for 24 h, 100%.

The corresponding cationic π-allyl palladium complex **319** was prepared in deuterated dichloromethane by the reaction of (1,3-diphenylallyl)palladium chloride dimer **318** and the *P,N*-ligand **304c** (R = Ph) in the presence of silver tetrafluoroborate which afforded a light yellow solution (Scheme 4.6.2.).[144]

Scheme 4.6.2. Synthesis of the Cationic π-Allyl Palladium Complex **319**



318 **319**

Examination of the ^{31}P NMR spectrum of the cationic π-allyl palladium complex **319** in deuterated dichloromethane at room temperature indicated the formation of two isomeric complexes in approximately a 2:1 ratio (Figure 4.6.1.).

(144) Gilbertson, S. R.; Lan, P. Kinetic Resolution in Palladium-Catalyzed Asymmetric Allylic Alkylations by a *P,O* Ligand System. *Org. Lett.* **2001**, *3*, 2237.

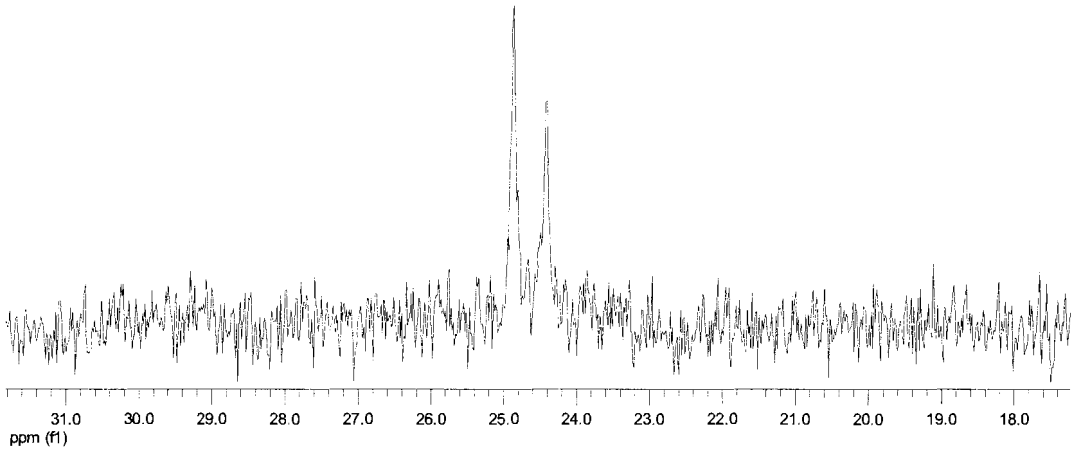


Figure 4.6.1. ^{31}P NMR spectrum of the cationic π-allyl palladium complex **319**.

These isomeric π-allyl palladium complexes were assigned as the *W*- and *M*-isomers (*W*- and *M*-**320c**), respectively (Figure 4.6.2.).[145] This assignment was made upon careful inspection of molecular models of the *M*- and *W*-isomers of the π-allyl intermediate. It was observed that the isomer *M*-**320c** was more sterically encumbered, and presumably less stable, than the corresponding isomer *W*-**320c**. This would be due to the close proximity of the 1,3-diphenylallyl moiety and one of the phenyl rings on the acetal moiety as indicated by the double headed arrow in the figure. It was attempted to make a definitive assignment of the *M*- and *W*-isomers based on ^{1}H NMR data. However, this was not possible due to the complexity of the spectra. Of note, other isomeric forms of the π-allyl complexes are possible. However, the *M*- and *W*-isomers are presumed to be the mechanistically relevant and predominant π-allyl intermediates.[146]

---

(145) For discussions on the assignment of the *M*- and *W*-isomers in related catalytic systems, see: (a) Mancherio, O. G.; Priego, J.; Ramón, S. C.; Arrayás, R. G.; Liamas, T.; Carretero, C. 1-Phosphino-2-sulfenylferrocenes as Planar Chiral Ligands in Enantioselective Palladium-Catalyzed Allylic Substitutions. *J. Org. Chem.* **2003**, *68*, 3679. (b) Evans, D. A.; Campos, K. R.; Tedrow, J. S.; Michael, F. E.; Gagné, M. R. Application of Chiral Mixed Phosphorus/Sulfur Ligands to Palladium-Catalyzed Allylic Substitutions. *J. Am. Chem. Soc.* **2000**, *122*, 7905.

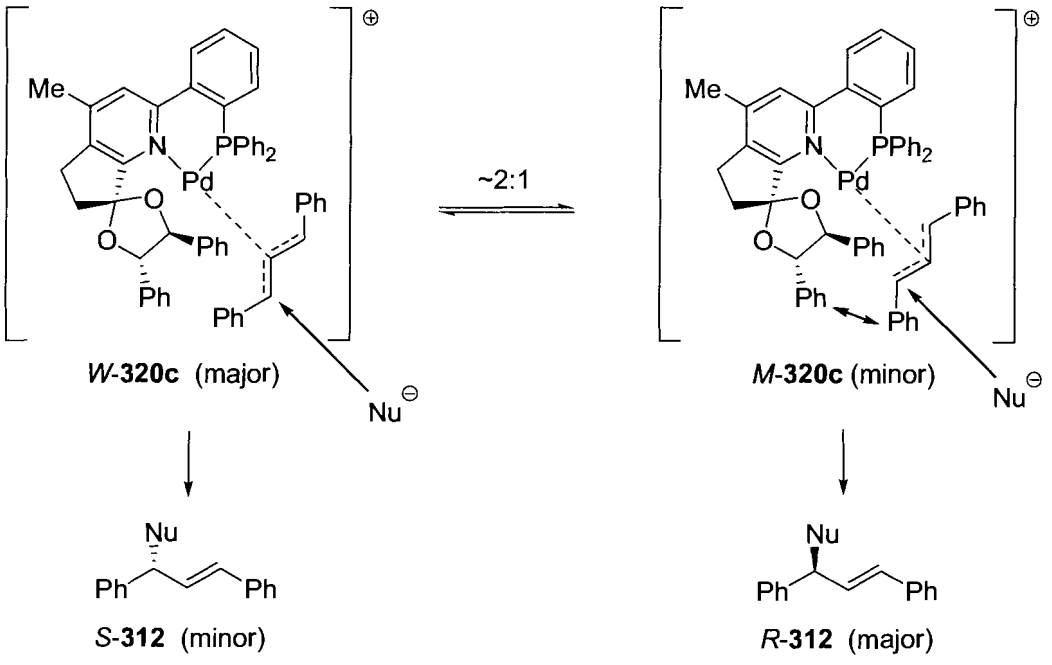


Figure 4.6.2. Isomeric π-allyl intermediates *W*- and *M*-**320c** and stereochemical rationale [Nu = $CH(COMe)_2$].

Assuming that these intermediates are involved in the reaction of racemic 3-acetoxy-1,3-diphenyl-1-propene *RS*-**310** with dimethyl malonate **311** in the presence of the *P,N*-ligand **304c** (R = Ph) and allylpalladium(II) chloride dimer, the reaction pathway can be described by a Curtin Hammett scheme.[146]

The Curtin-Hammett kinetic scheme describes a common situation in organic chemistry in which a molecule can exist in two interconverting conformational forms, each of which reacts to give a different reaction product. Recently, a definition of the Curtin-Hammett principle has been outlined by the International Union of Pure and Applied Chemistry (IUPAC) and it reads as follows; "Curtin-Hammett Principle: In a chemical reaction that yields one product from one conformational isomer and a different product from another conformational isomer (and provided these two isomers are rapidly

(146) Seeman, J. I. Effect of Conformational Change on Reactivity in Organic Chemistry. Evaluations, Applications, and Extensions of Curtin-Hammett Winstein-Holness Kinetics. *Chem. Rev.* **1983**, *83*, 83.

interconvertible relative to the rate of product formation, whereas the products do not interconvert), the product composition is not solely dependant on the relative proportions of the conformational isomers in the substrate; it is controlled by the differences in standard Gibbs energies of the respective transition states".[147]

Thus, in this AAS reaction, the interconversion of the *W*- and *M*-isomers (*W*- and *M*-**320c**) can be assumed to be rapid with respect to nucleophilic attack of the anion of dimethyl malonate (approximately a 2:1 ratio of π-allyl intermediates led to a 95:5 ratio of enantiomeric products).

It would be expected that nucleophilic attack of the anion of dimethyl malonate on these π-allyl intermediates *W*- and *M*-**320c** would occur regioselectively *trans* to the phosphine moiety because of the strong *trans*-effect for the phosphorus donor atom relative to the pyridine nitrogen.[94] The *trans*-effect lengthens the palladium-carbon bond that is *trans* to the phosphorus donor atom relative to the bond that is *trans* to the nitrogen donor atom. It would also be expected that the nucleophile would attack the exterior (more open) face of the allyl moiety (for additional clarification, see: Chapter 1, Figure 1.12.1.). Thus, to account for the observed absolute stereochemistry of the major reaction product, (1*R*)-(1,3-diphenylally)malonic acid dimethyl ester *R*-**312**, it was concluded that the π-allyl intermediate *M*-**320c** reacted at a faster rate with the anion of dimethyl malonate from the angle of attack shown in the figure. In support of these arguments, a related stereochemical interpretation has recently been reported by Helmchen and Pfaltz for a related *P,N*-ligand.[148]

---

(147) Gold, V. Glossary of Terms used in Physical Organic Chemistry. *Pure Appl. Chem.* **1979**, *51*, 1725.

(148) (a) Helmchen, G.; Pfaltz, A. Phosphinooxazolines - A New Class of Versatile, Modular *P,N*-Ligands for Asymmetric Catalysis. *Acc. Chem. Res.* **2000**, *33*, 336. (b) Pfaltz, A.; Drury III, W. J. Design of Chiral

4.7. X-Ray Crystallographic Analysis of the Palladium(II) Chloride Complex of the *P,N*-Ligand [304a (R = Me)]

To probe the structure of the active catalytic species in these AAS reactions, the palladium(II) chloride complex of the *P,N*-ligand **304a** was prepared by heating a mixture of equimolar amounts of palladium(II) chloride and the ligand **304a** in a mixture of ethanol and dichloromethane (1:1). Recrystallization of the resultant palladium complex from ethanol afforded orange X-ray quality crystals.

The X-ray crystallographic analysis of the palladium(II) chloride *P,N*-ligand **304a** complex clearly illustrated the orthogonal relationship of the acetal ring and the pyridine ring that results in the shielding of one of the diastereotopic faces of the complexes of the chiral *P,N*-ligands **304a-c** (R = Me, *i*-Pr and Ph) (Figure 4.7.1.).* A distorted square-planar geometry around the palladium centre was also noted. An interaction between the acetal oxygen atom (O2) and the palladium centre (Pd1) with an interatomic distance of 2.846 Å was observed. It is unclear if this interaction occurs in solution and what effect it may have on the reactivity of the complex. The complex, in the solid-state, is locked in one atropisomeric form with a torsion angle of 35.8 ° around the biaryl bond which is controlled by the chirality of the cyclic acetal. As expected, the Pd-Cl bond that is *trans* to the phosphine moiety is substantially longer than the Pd-Cl bond that is *trans* to the pyridine nitrogen (2.377 and 2.299 Å, respectively). This clearly reflected the stronger *trans* effect of the phosphine moiety and supported the mechanistic assumption that

---

Ligands for Asymmetric Catalysis. From C_2-Symmetric *P,P* and *N,N*-Ligands to Sterically and Electronically Nonsymmetrical *P,N*-Ligands. *Proc. Nat. Acad. Sci.* **2004**, *101*, 5723.

(*) X-ray crystallographic analysis of the $PdCl_2$·*P,N*-ligand **304a** complex was performed by Mr. Neil D. Draper at Simon Fraser University.

nucleophilic addition of the anion of dimethyl malonate to the π-allyl intermediate occurred regioselectively *trans* to the phosphine moiety. Complete tabulated bond lengths and bond angles from the X-ray structure determination of the palladium(II) chloride *P,N*-ligand **304a** complex are listed in the experimental section of this thesis.

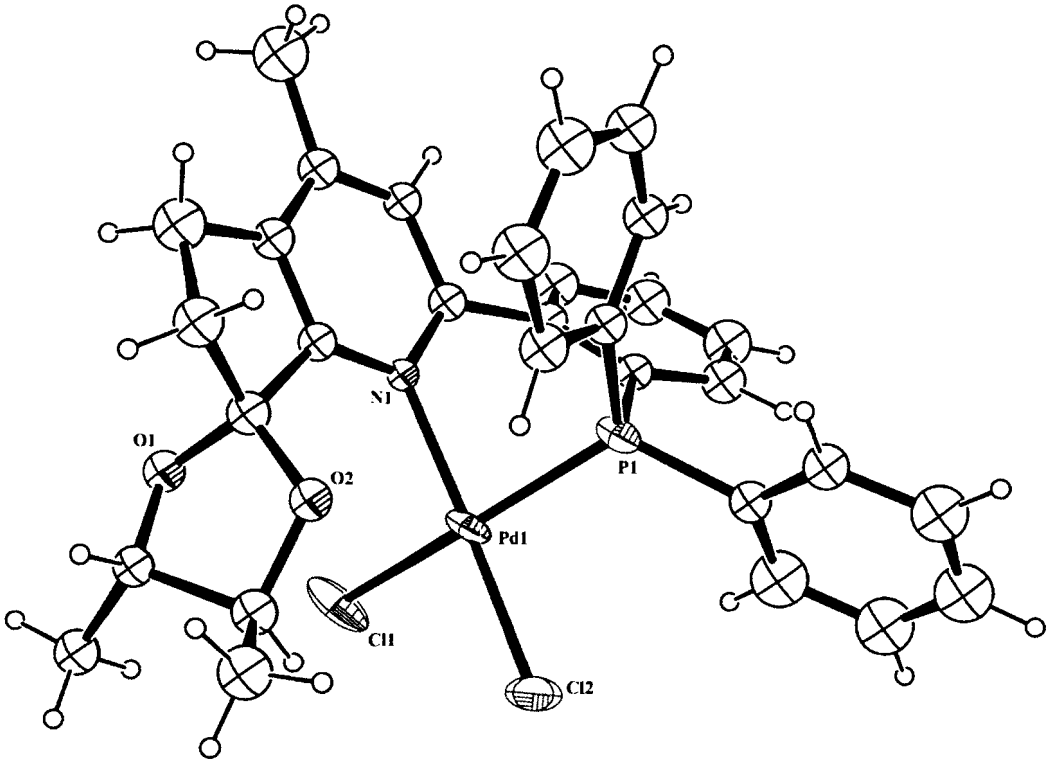


Figure 4.7.1. *ORTEP* representation of the $PdCl_2$·*P,N*-ligand **304a** complex.*

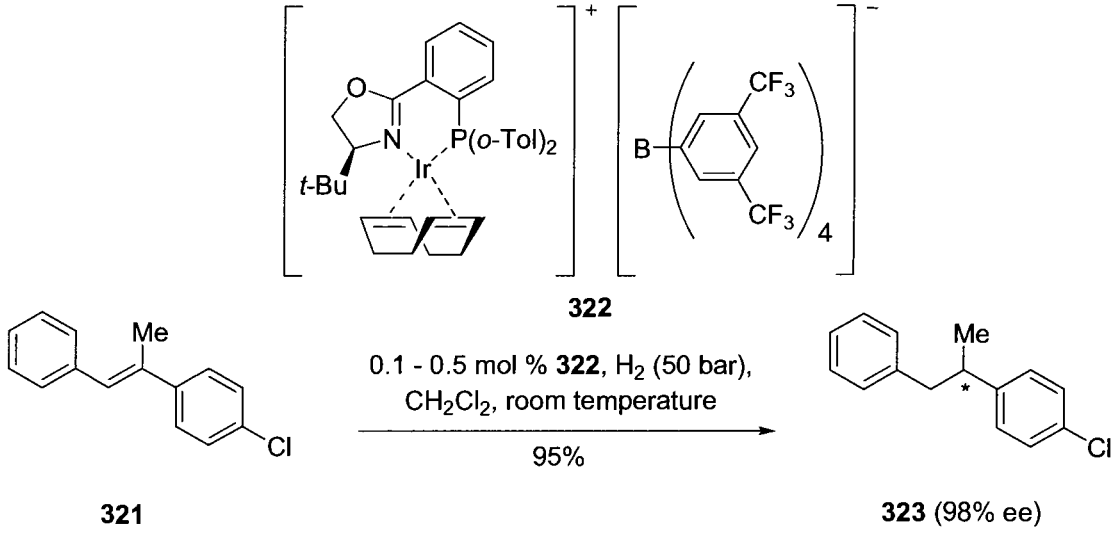
4.8. Attempted Application of the *P,N*-Ligands 304a-c in Iridium-Catalyzed Asymmetric Hydrogenation Reactions

Iridium(I) complexes with chiral phosphinooxazoline ligands have emerged as promising asymmetric hydrogenation catalysts. For example, Pfaltz and co-workers have

(*) The thermal ellipsoids are drawn at the 25% probability level for clarity.

recently reported the asymmetric hydrogenation reactions of trisubstituted 1,2-diarylalkenes.[149] Using the iridium(I) phosphinooxazoline COD complex **322** with a tetrakis[2,6-bis(trifluoromethyl)phenyl]borate (TFPB) counterion, high enantioselectivities (91-98% ee) were achieved with very low catalyst loadings (0.1-0.5 mol %) in dichloromethane at room temperature (Scheme 4.8.1.).

Scheme 4.8.1. An Asymmetric Hydrogenation Reaction with the Chiral Iridium(I) Phosphinooxazoline Complex **322**

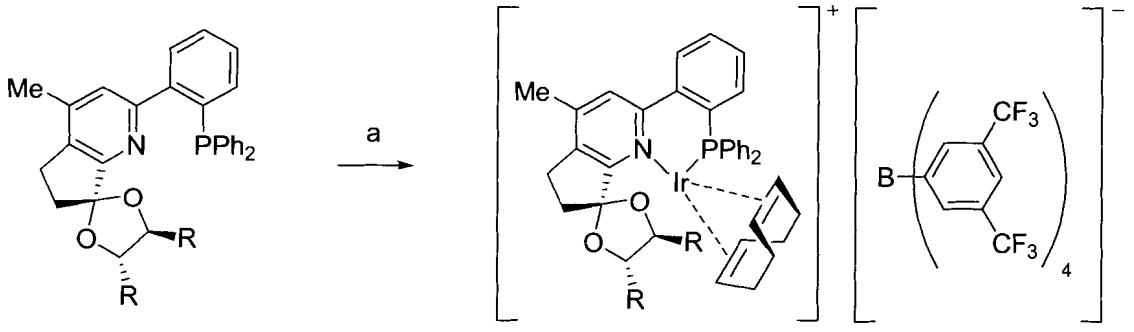


In order to evaluate the *P,N*-ligands **304a-c** (R = Me, *i*-Pr and Ph) in the above hydrogenation reaction, the corresponding Ir(I)(*P,N*-ligand **304a-c**)(COD)(TFPB) complexes **324a**-c were prepared. This was achieved by heating the *P,N*-ligands **304a-c** with iridium cyclooctadiene chloride dimer **325** in dichloromethane at reflux for 1 h. The reaction mixtures were then treated with NaTFPB and water at room temperature for 15 min. The resultant complexes were purified by crystallization from ethanol upon the slow addition of water which afforded the Ir(I)(*P,N*-ligand **304a-c**)(COD)(TFPB)

(149) Lightfoot, A.; Schnider, P.; Pfaltz, A. Enantioselective Hydrogenation of Olefins with Iridium-Phosphanodihydrooxazole Catalysts. *Angew. Chem., Int. Ed.* **1998**, *37*, 2897.

complexes **324a-c** as orange crystalline solids which were air stable (Scheme 4.8.2.).[150] Satisfactory elemental analyses for each of these compounds was obtained.

Scheme 4.8.2. Synthesis of the Chiral Iridium(I)-Complexes **324a-c**



304a-c (R = Me, *i*-Pr and Ph) **324a-c** (R = Me, *i*-Pr and Ph)

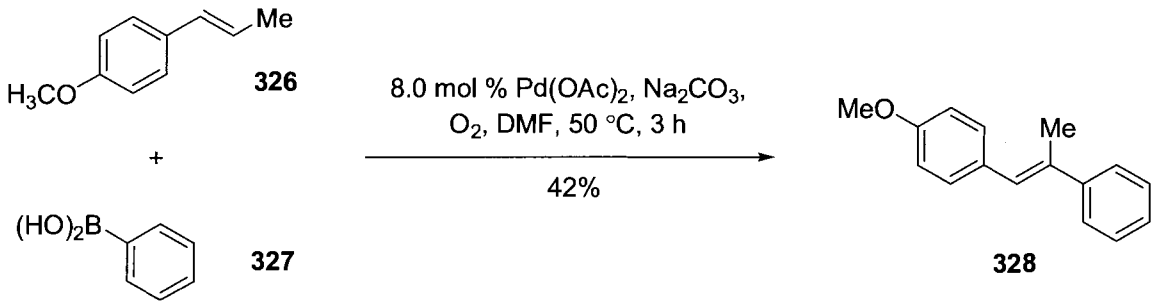
Reagents and conditions: (a) $[Ir(COD)Cl]_2$ **325**, CH_2Cl_2, reflux, 1 h then NaTFPB, H_2O, room temperature, 15 min, 91% (**324a**), 94% (**324b**), 90% (**324c**).

The Ir(I)(*P*,*N*-ligand **304a-c**)(COD)(TFPB) complexes **324a-c** were first evaluated in the asymmetric hydrogenation reaction of 1-methoxy-4-[(*E*)-2-phenylprop-1-enyl]benzene **328**. This substrate was prepared by a palladium(II) acetate-catalyzed reaction of phenylboronic acid **327** and *trans*-anethole **326** in dimethylformamide under an oxygen atmosphere (balloon pressure) and in the presence of sodium carbonate (Scheme 4.8.3.).[151]

(150) (a) Kainz, S.; Brinkmann, A.; Leitner, W.; Pfaltz, A. Iridium-Catalyzed Enantioselective Hydrogenation of Imines in Supercritical Carbon Dioxide. *J. Am. Chem. Soc.* **1999**, *121*, 6421.

(151) Jung, Y. J.; Mishra, R. K.; Yoon, C. H.; Jung, K. W. Oxygen-Promoted Pd(II) Catalysis for the Coupling of Organoboron Compounds and Olefins. *Org. Lett.* **2003**, *5*, 2231.

Scheme 4.8.3. Synthesis of the Asymmetric Hydrogenation Reaction Substrate **328**



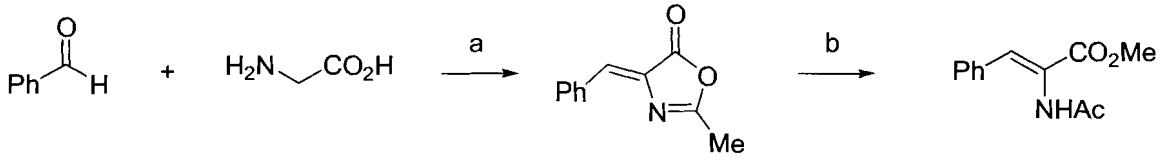
The asymmetric hydrogenation reaction of the alkene **328** was first attempted with 1 mol % of the Ir(I)(*P*,*N*-ligand **304a**)(COD)(TFPB) complex **324a** in dichloromethane at room temperature in a high-pressure reaction vessel under an atmosphere of hydrogen (50 bar). After 24 hours, none of the desired reduction product was isolated. The reaction conditions were then modified and this reaction was performed with 5 mol % of the Ir(I)(*P*,*N*-ligand **304a**)(COD)(TFPB) complex **324a** in dichloromethane at room temperature in a high-pressure reaction vessel under an atmosphere of hydrogen (100 bar). However, after 24 hours of reaction time, none of the desired product was isolated.

The reduction of the alkene **328** was also attempted with the other two chiral Ir(I)(*P*,*N*-ligand)(COD)(TFPB) complexes **324b,c** under the latter set of conditions. Again, none of the desired reduction products were isolated.

It was then decided to attempt the hydrogenation of a more reactive alkene in order to determine if the lack of catalytic activity of the Ir(I)(*P*,*N*-ligand)(COD)(TFPB) complexes **324a-c** was substrate dependant. The alkene substrate chosen was methyl α-acetamidocinnamate **332**. This substrate was prepared by heating a mixture of benzaldehyde **329** and glycine **330** in acetic anhydride to afford the oxazolone **331** in

74% yield.[152] This compound was then heated in methanol at reflux in the presence of sodium acetate to afford the methyl α-acetamidocinnamate **332** in 75% yield (Scheme 4.8.4.).

Scheme 4.8.4. Synthesis of Methyl α-acetamidocinnamate **332**



329 **330** **331** **332**

Reagents and conditions: (a) Ac_2O, NaOAc, reflux, 1 h, 74%. (b) CH_3OH, NaOAc, reflux, 3.5 h, 75%.

Unfortunately, the attempted asymmetric hydrogenation reaction of the substrate **332** with 5 mol % of the iridium(I) complexes **324a-c** in dichloromethane at room temperature in a high-pressure reaction vessel under an atmosphere of hydrogen (100 bar) for 24 hours did not afford any of the desired reaction product.

4.9. Conclusions

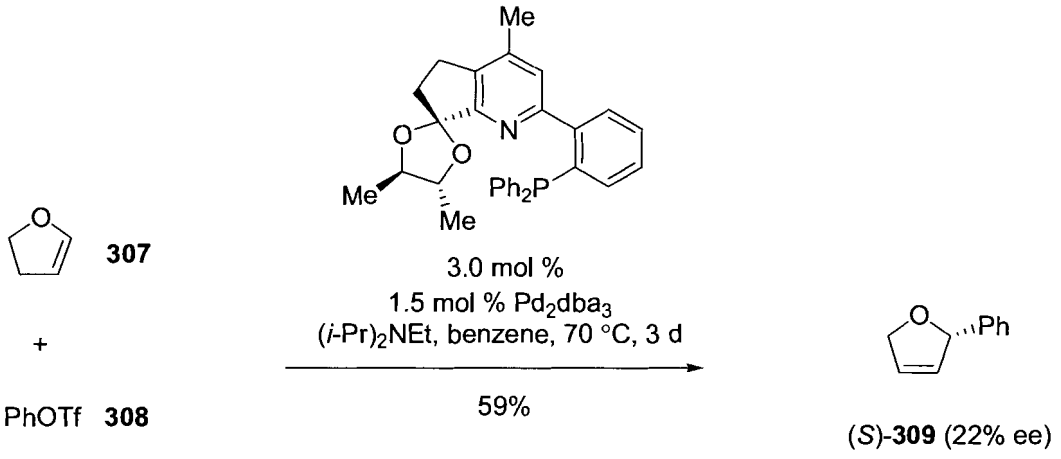
An efficient and modular synthesis of a series of three chiral nonracemic *P,N*-ligands **304a-c** (R = Me, *i*-Pr and Ph) was developed. These novel ligands were prepared in three steps from 2-chloro-4-methyl-6,7-dihydro-*5H*-[1]-pyridine-7-one **269** and a series of chiral C_2-symmetric 1,2-diols **270a-c** (R = Me, *i*-Pr and Ph).

The *P,N*-ligands **304a-c** were first evaluated in the palladium(0)-catalyzed asymmetric Heck reaction of 2,3-dihydrofuran **307** and phenyltriflate **308**. The best and only successful result was obtained with the *P,N*-ligand **304a** (R = Me). In this case, the desired reaction product **309** was isolated in reasonable yield (59%) and in moderate

(152) Vineyard, B. D.; Knowles, W. S.; Saback, M. J.; Bachman, G. L.; Weinkauff, D. J. Asymmetric Hydrogenation. Rhodium Chiral Biphosphine Catalyst. *J. Am. Chem. Soc.* **1977**, *99*, 5946.

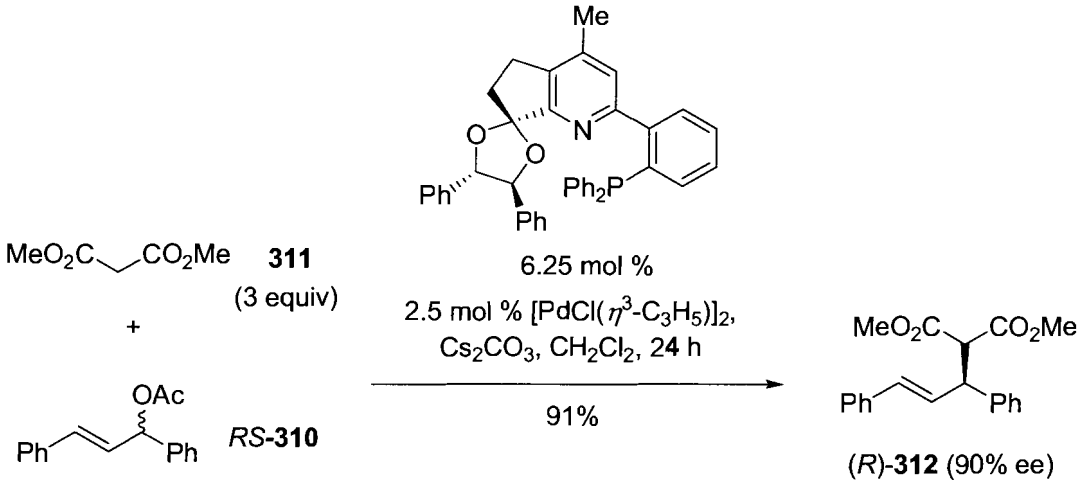
enantioselectivity (20% ee) (Scheme 4.9.1.). The remaining two *P,N*-ligands **304a,b** (R = *i*-Pr and Ph) did not catalyze this reaction.

Scheme 4.9.1. Asymmetric Heck Reaction employing the *P,N*-ligand **304a** (R = Me)



The *P,N*-ligands **304a-c** were subsequently evaluated in the palladium-catalyzed asymmetric allylic substitution reaction of racemic 3-acetoxy-1,3-diphenyl-1-propene *RS*-**310** with dimethyl malonate **311**. The *P,N*-ligands **304a-c** were evaluated with three different sets of reagents that enabled the counter ion of the nucleophile to be varied. The best result was obtained when the *P,N*-ligand **304c** (R = Ph) was used with cesium carbonate as the base at 0 °C which afforded the reaction product (*R*)-**312** in high enantiomeric excess (90%) (Scheme 4.9.2.).

Scheme 4.9.2. Asymmetric Allylic Substitution Reaction employing the *P,N*-Ligand **304c** (R = Ph)



The *P,N*-ligands **304a-c** were also evaluated in asymmetric iridium(I)-catalyzed hydrogenation reactions of alkenes. The Ir(I)(*P,N*-ligand **304a-c**)(COD)(TFPB) complexes **324a-c** were prepared upon reaction of iridium cyclooctadiene chloride dimer with the *P,N*-ligands **304a-c** and then subsequent treatment with NaTFPB to afford the desired iridium complexes as air- and moisture-stable orange solids. These complexes were evaluated as chiral catalysts in the asymmetric hydrogenation reactions of 1-methoxy-4-[(*E*)-2-phenylprop-1-enyl]benzene **328** and methyl α-acetamidocinnamate **332**. However, these complexes were catalytically inactive under the reaction conditions employed.

CHAPTER 5: RESULTS AND DISCUSSION

SYNTHESIS AND EVALUATION OF A RELATED CHIRAL NONRACEMIC C_2-SYMMETRIC 2,2′-BIPYRIDYL LIGAND

5.1. Introduction

In this chapter, the synthesis of a related chiral nonracemic C_2-symmetric 2,2′-bipyridyl ligand **333** is described. In this case, the ligand design featured a subtle modification of the cyclic acetal moiety in that the chirality was installed in the heterocyclic portion of the bipyridine unit. This differed from the first generation of chiral 2,2′-bipyridyl ligands **267a-c** (Chapter 2) and the *P,N*-ligands **304a-c** (Chapter 4). In these cases, the source of the chirality of the ligands was provided by the chiral 1,2-diols **270a-c**. The evaluation of the chiral 2,2′-bipyridyl ligand **333** in copper(I)-catalyzed asymmetric cyclopropanation reactions of alkenes and diazoesters, in copper(I)-catalyzed asymmetric allylic oxidation reactions of alkenes as well as in copper(II)-catalyzed asymmetric Friedel-Crafts alkylation reactions was undertaken.*

It was envisioned that this ligand could be synthesized from the chiral nonracemic 2-chloroacetal **334** by a nickel(0)-mediated *homo*-coupling reaction. The chiral 2-

---

(*) Part of the research described in this chapter has been published (or submitted for publication), see: (a) Lyle, M. P. A.; Draper, N. D.; Wilson, P. D. Enantioselective Friedel-Crafts Alkylation Reactions Catalyzed by a Chiral Nonracemic C_2-Symmetric 2,2′-Bipyridyl Copper(II) Complex. *Org. Lett.* **2005**, *7*, 901. (b) Lyle, M. P. A.; Wilson, P. D. Synthesis of a New Chiral Nonracemic C_2-Symmetric 2,2′-Bipyridyl Ligand and its Application in Copper(I)-Catalyzed Enantioselective Cyclopropanation Reactions. *Org. Lett.* **2004**, *6*, 855. (c) Lyle, M. P. A.; Wilson, P. D. Asymmetric Allylic Oxidation Reactions Catalyzed by a Chiral Nonracemic C_2-Symmetric 2,2′-Bipyridyl Copper(I) Complex. *Org. Lett.* **2005**, *7*, 0000 (Submitted).

chloroacetal **334** could in turn be prepared from the 2-chloropyrindine **336** by an asymmetric dihydroxylation reaction and subsequent condensation with 3-pentanone. This ketone was selected because it is symmetrical and so this would ensure that only a single diastereoisomer would form upon condensation with the diol. In addition, the ethyl substituents would be somewhat larger than that would be installed if acetone was employed as a reaction partner. The 2-chloropyrindine **336** could be prepared from the acetate **282** by an elimination reaction. The acetate **282** was a key intermediate that was employed in the preparation of the chiral 2,2′-bipyridyl ligands **267a-c** (Chapter 2) and the *P*,*N*-ligands **304a-c** (Chapter 4).

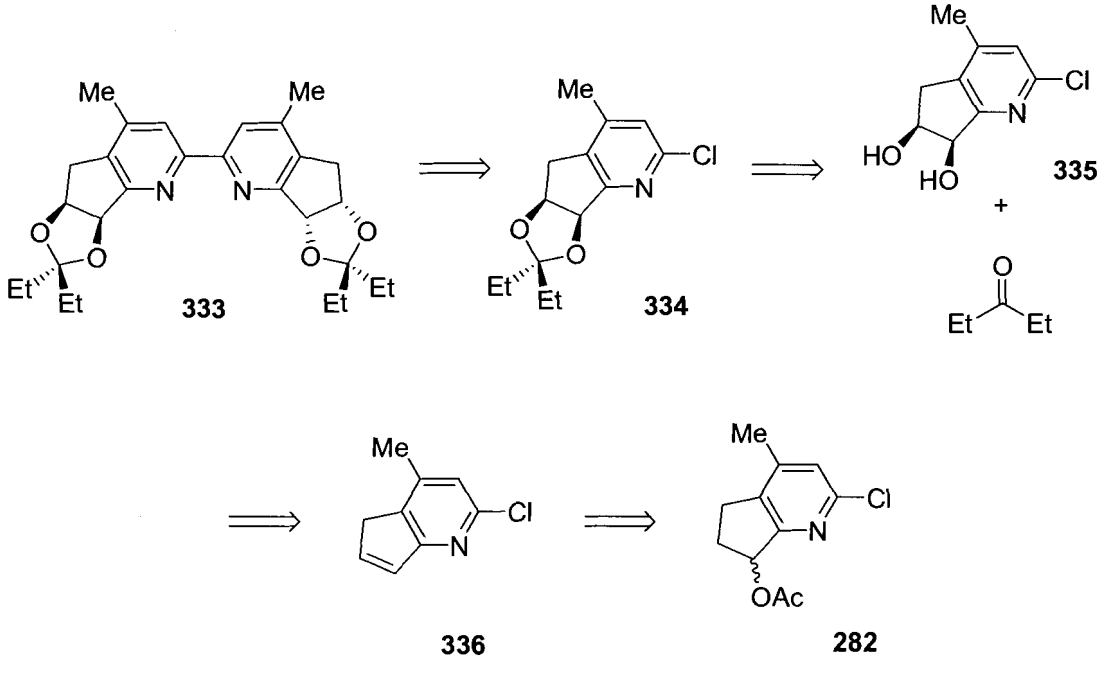


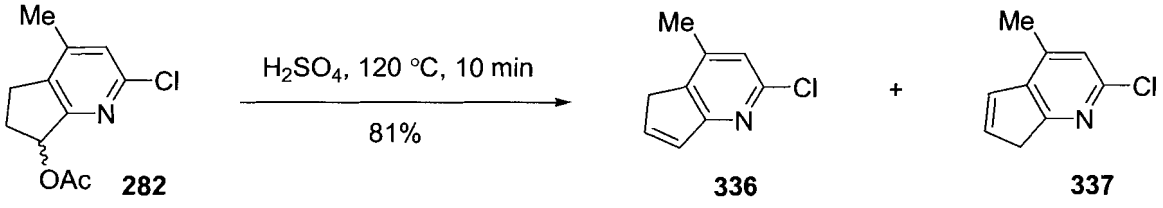
Figure 5.1.1. Retrosynthetic analysis of the chiral nonracemic C_2-symmetric 2,2′-bipyridyl ligand **333**.

5.2. Synthesis of the 2-Chloropyrindine (336)

2-Chloro-4-methyl-5*H*-[1]pyrindine **336** was prepared, as essentially a single regioisomeric product (>30:1), on heating the acetate **282** briefly in concentrated sulfuric

acid at 120 °C for 10 min. When the reaction was run for 1 h, the ratio of regioisomers decreased significantly (<10:1) which was due to an acid-catalyzed formal 1,3-hydrogen shift. The ratio of these regioisomeric products was conveniently determined by inspection of the ^{1}H NMR spectrum. Fu and co-workers have reported a related reaction in which a functionalized pyrindine was formed as a mixture of regioisomers (2:1) after heating the corresponding acetate in sulfuric acid at 125 °C for 1 h.[153]

Scheme 5.2.1. Synthesis of the 2-Chloropyrindine **336**



5.3. Catalytic Asymmetric Dihydroxylation Reaction of the 2-Chloropyrindine (336)

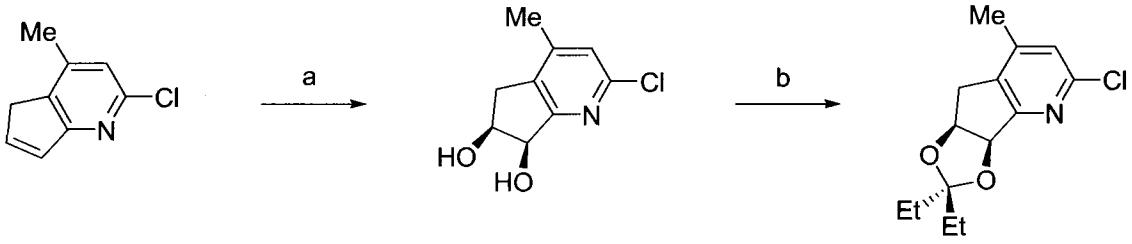
The asymmetric dihydroxylation (AD) of the pyrindine **336** with AD-mix-β afforded the diol (+)-**335**. This involved the reaction of the pyrindine **336** with AD-mix-β in a mixture of *tert*-butanol and water (1:1) at 0 °C for 12 h.[154] The crude diol (+)-**335** was then directly reacted with 3-pentanone in the presence of a catalytic amount of *p*-toluenesulfonic acid monohydrate in benzene at reflux which afforded the chiral acetal (+)-**334** in reasonable overall yield (57%, over two steps). The chiral acetal (+)-**334** was

(153) Ruble, J. C.; Fu, G. C. Chiral π-Complexes of Heterocycles with Transition Metals: A Versatile New Family of Nucleophilic Catalysts. *J. Org. Chem.* **1996**, *61*, 7230.

(154) For a review on AD reactions, see: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. Catalytic Asymmetric Dihydroxylation. *Chem. Rev.* **1994**, *94*, 2483.

found to have a high enantiomeric excess (90%) upon analytical chiral HPLC analysis (Daicel Chiracel OD column).

Scheme 5.3.1. Sharpless Asymmetric Dihydroxylation Reaction of the Pyrindine **336**



336 (+)-**335** (+)-**334** (90% ee)

Reagents and Conditions: (a) AD-mix-β, *t*-BuOH/H_2O (1:1), 0 °C, 12 h; (b) 3-pentanone, PhH, *p*-TsOH (cat.), reflux, 16 h, 57% (over two steps).

The structure of the chloroacetal (+)-**334** was assigned on the basis of spectroscopic evidence. In particular, the mass spectrum displayed the expected molecular ion peaks for M(^{35}Cl + H) and M(^{37}Cl + H) at 268 and 270, respectively. The ^{1}H NMR spectrum of the chiral chloroacetal (+)-**334** contained the expected resonances for the two diastereotopic ethyl moieties as well as a coupled C-6 proton signal at δ = 4.99 ppm and a coupled C-7 proton signal at δ = 5.41 ppm that were attributable to the cyclic acetal (Figure 5.3.1.).

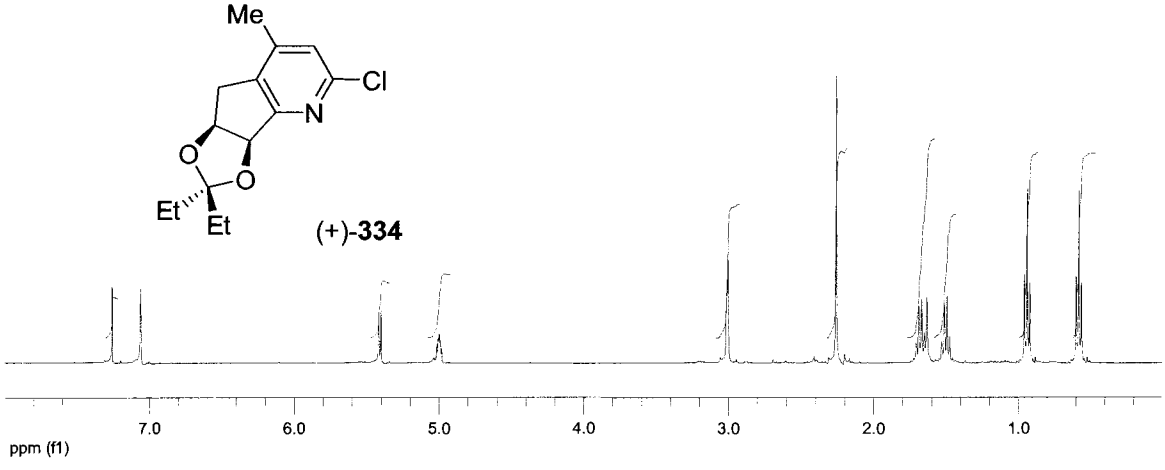


Figure 5.3.1. ^{1}H NMR spectrum of the chiral chloroacetal (+)-**334**.

The regiochemistry of the chloroacetal (+)-**334** was confirmed on inspection of the NOESY spectrum of this compound. Diagnostic nOe contacts were observed between the diastereotopic C-5 protons and the protons of the C-4 methyl substituent (Figure 5.3.2.).

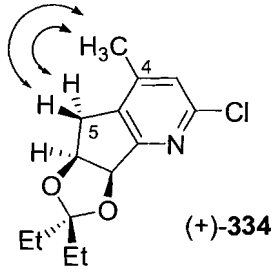


Figure 5.3.2. Diagnostic contacts observed in the NOESY spectrum of the chloroacetal (+)-**334**.

It was considered that the moderate yield of the diol (+)-**335** obtained using the standard Sharpless asymmetric dihydroxylation reaction conditions could be due to the slow reaction rate and that exposure of the pyrindine **336** to these reaction conditions for a long period of time could have led to further detrimental oxidation processes. This hypothesis was plausible as the mass recovery from the reaction work-up was low and it appeared that some very polar byproducts were formed.

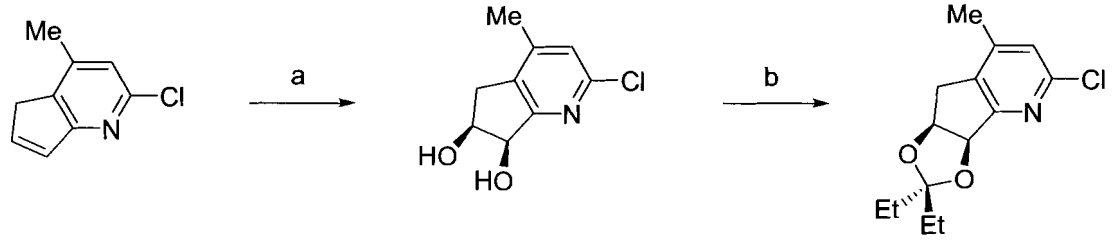
Sharpless and co-workers have reported an improvement in the rate of the AD reaction with the chiral ligand $(DHQD)_2PHAL$ using methanesulfonamide as an additive.[155] Using these reaction conditions, the rate and yield of the above reaction were not improved.

The rate and yield of this AD reaction were improved when it was modified and performed with 1 mol % of potassium osmate dihydrate and 5 mol % of the chiral ligand

(155) (a) Wang, Z.-M.; Kakiuchi, K.; Sharpless, K. B. Osmium-Catalyzed Asymmetric Dihydroxylation of Cyclic *cis*-Disubstituted Olefins. *J. Org. Chem.* **1994**, *59*, 6895. (b) Wang, L.; Sharpless, K. B. Catalytic Asymmetric Dihydroxylation of *cis*-Disubstituted Olefins. *J. Am. Chem. Soc.* **1992**, *114*, 7568.

$(DHQD)_2PHAL$ (a ten-fold higher catalyst loading than typically used in AD reactions), potassium ferricyanide and potassium carbonate in a mixture of *tert*-butanol and water (1:1) at 0 °C for 2 h. The acetal (+)-**334** was isolated in an improved yield (81%) and in the same enantiomeric excess (90%) upon reaction of the crude diol with 3-pentanone (Scheme 5.3.2.). The rate of the AD reaction was also significantly improved (2 hours vs. 12 hours reaction time).

Scheme 5.3.2. Modified Sharpless Asymmetric Dihydroxylation Reaction



336 (+)-**335** (+)-**334** (90% ee)

Reagents and Conditions: (a) 1 mol % $K_2OsO_4 \cdot 2H_2O$, 5 mol % $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH/H_2O (1:1) 2 h; (b) 3-pentanone, PhH, *p*-TsOH (cat.), reflux, 16 h, 81% (over two steps).

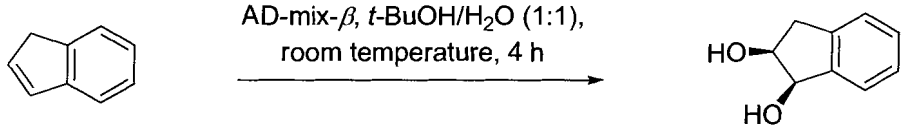
A final optimization attempt concerned the employment of *N*-methylmorpholine-*N*-oxide as the stoichiometric oxidant instead of iron ferricyanide in the latter two step procedure. In this case, the acetal (+)-**334** was isolated in excellent overall yield (89%).[156] However, the reaction time required was longer (24 h) and the enantioselectivity of the reaction was significantly compromised (61% ee).

Cyclic *cis*-alkenes are known to be one of the most challenging substrates in the Sharpless AD reactions. To the best of our knowledge, the AD reaction on the pyrindine **336** is the highest enantioselectivity (90% ee) that has been reported for a cyclic *cis*-

(156) Wang, Z.-M.; Sharpless, K. B. A Solid-to-Solid Asymmetric Dihydroxylation Procedure for Kilogram-Scale Preparation of Enantiopure Hydrobenzoin. *J. Org. Chem.* **1994**, *59*, 8302.

alkene.[155] Hanessian and co-workers have reported that indene can be dihydroxylated with a simple C_2-symmetric chiral ligand derived from (1*R*,2*R*)-*trans*-1,2-diaminocyclohexane in 80% ee (70% yield). [157] However, the chiral ligand and osmium tetraoxide were used stoichiometrically in this reaction. For additional comparison, the AD reaction of indene **338** with AD-mix-β has been reported to afford the corresponding diol **339** (6*S*,7*R* stereochemistry) in only moderate enantiomeric excess (33-40%) (Scheme 5.3.3.).[158]

Scheme 5.3.3. Sharpless Asymmetric Dihydroxylation of Indene **338**



338 **339** (33-40% ee)

The origin of the high enantioselectivity (90% ee) in the AD reaction of the pyrindine **336** are unclear. However, it is reasonable to suggest that the pyridine nitrogen causes an increase in enantioselectivity in the AD reaction of the pyrindine **336** (90% ee) relative to indene **338** (33-40% ee) because of a secondary coordinative interaction to the osmium tetraoxide of the catalytic species or to a spectator molecule of osmium tetraoxide. Enhancements in enantioselectivity have been attributed to secondary coordinative effects for AD reactions of allylic alcohol substrates.[159] In support of this hypothesis, it was observed that the regioisomeric pyrindine **337** undergoes an AD

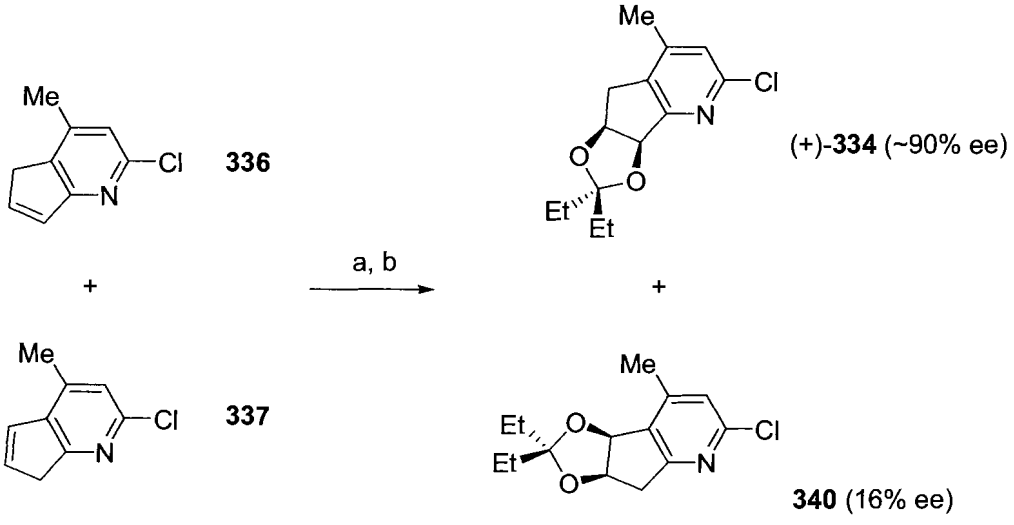
(157) Hanessian, S.; Meffre, P.; Girard, M.; Beaudoin, S.; Sancéau, J.-Y.; Bennani, Y. Asymmetric Dihydroxylation of Olefins With a Simple Chiral Ligand. *J. Org. Chem.* **1993**, *58*, 1991.

(158) Spivey, A. C.; Hanson, R.; Scorah, N.; Thorpe, S. J. Sharpless Asymmetric Dihydroxylation: Effect of Alkene Structure on Rates and Selectivity. *J. Chem. Ed.* **1999**, *76*, 655.

(159) Hale, K. J.; Manaviazar, S.; Peak, S. A. Anomalous Enantioselectivity in the Sharpless Catalytic Asymmetric Dihydroxylation Reaction of 1,1-Disubstituted Allyl Alcohol Derivatives. *Tetrahedron Lett.* **1994**, *35*, 425.

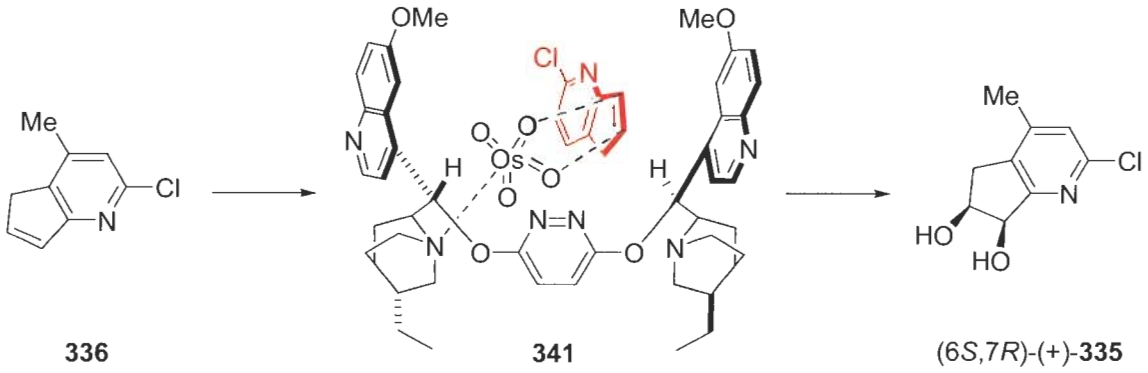
reaction in low enantiomeric excess (16%). This result was obtained when an AD reaction of a mixture of the regioisomeric pyrindines **336** and **337** (~8:1) was performed (Scheme 5.3.4.). The acetals (+)-**334** and **340** were separable by column chromatography and the enantiomeric excess of the regioisomeric acetal **340** was determined by analytical chiral HPLC (Daicel Chiracel OD column).

Scheme 5.3.4. Sharpless Asymmetric Dihydroxylation of an ~8:1 Mixture of the Regioisomeric Pyrindines **336** and **337**



Reagents and Conditions: (a) 1 mol % $K_2OsO_4 \cdot 2H_2O$, 5 mol % $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH/H2O (1:1), 0 °C, 2 h; (b) 3-pentanone, PhH, *p*-TsOH (cat.), reflux, 16 h (product yields not determined).

The absolute stereochemistry of the diol (+)-**335** was not determined definitively but the assignment (6*S*,7*R*) was based on the well-established predictability of the Sharpless AD reaction and on the stereochemical outcome of the asymmetric reactions that are described later in this chapter. In the figure below, the proposed transition state **341** for the AD reaction of the 2-chloropyrindine **336** with osmium tetraoxide and $(DHQD)_2PHAL$ is depicted (Figure 5.3.3.). The proposed transition state **341** could be rationalized on the basis of the minimization of steric interactions between the substrate and the catalyst which would lead to a product with (6*S*,7*R*)-stereochemistry.



336 **341** (6*S*,7*R*)-(+)-**335**

Figure 5.3.3. The proposed transition state for the AD reaction of the 2-chloropyridine **336**.*

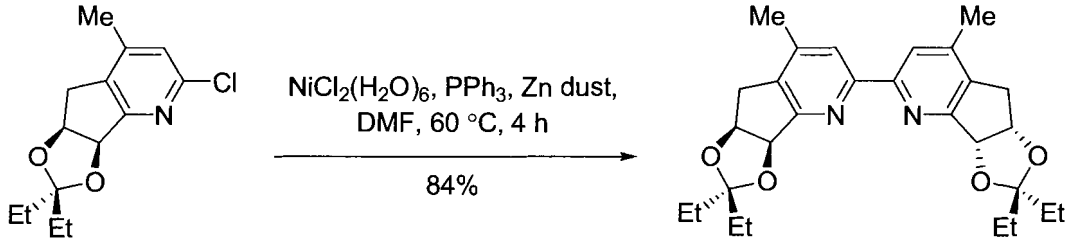
5.4. Synthesis of the Chiral Nonracemic C_2-Symmetric 2,2′-Bipyridyl Ligand [(+)-333] from the Chloroacetal [(+)-334]

The new chiral nonracemic and C_2-symmetric 2,2′-bipyridyl ligand (+)-**333** was prepared by a nickel(0)-mediated coupling reaction of the acetal (+)-**334** in 84% yield (Scheme 5.4.1.).[123] The reaction conditions involved heating a solution of the acetal (+)-**334** (90% ee) in *N*,*N*-dimethylformamide in the presence of the *tetrakis*(triphenylphosphine)nickel(0) (formed *in situ* upon reduction of nickel(II) chloride hexahydrate with zinc dust in the presence of triphenylphosphine) which afforded the 2,2′-bipyridyl ligand (+)-**333** as a white crystalline solid in good yield (84%).♣

(*) The methyl substituent of the pyrindine **336** has been removed in the transition state **341** for clarity.

(♣) The enantiomeric 2,2′-bipyridyl ligand (-)-**333** was also prepared in 53% yield (unoptimized) from the enantiomeric acetal (-)-**334** which was prepared from the pyrindine **336** using AD-mix-α in the Sharpless asymmetric dihydroxylation reaction.

Scheme 5.4.1. Synthesis of the 2,2′-Bipyridyl Ligand (+)-**333**



(+)-**334** (90% ee) (+)-**333** (>99% ee)

The mass spectrum of the chiral 2,2′-bipyridyl ligand (+)-**333** displayed the expected molecular ion peak for M[(+)-**333** + H] at 465. The ^{1}H NMR spectrum of the chiral 2,2′-bipyridyl ligand (+)-**333** displayed the expected low field resonance for the equivalent C3 and C3′ protons at δ = 8.30 ppm which is diagnostic of a 2,2′-bipyridine moiety (Figure 5.4.1.).

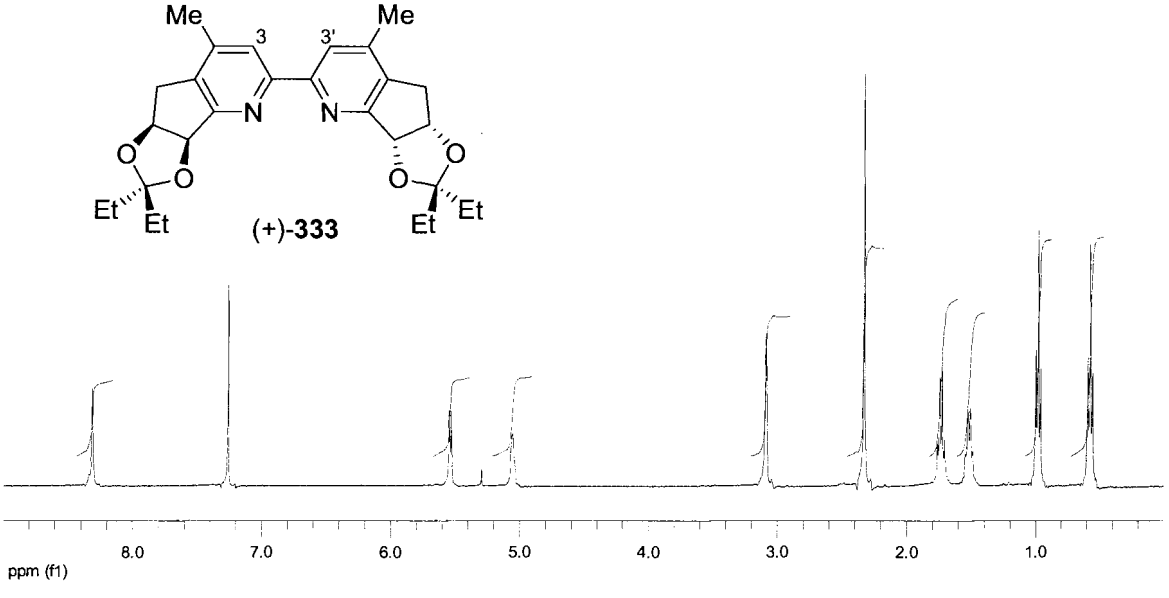


Figure 5.4.1. ^{1}H NMR spectrum of the chiral nonracemic C_2-symmetric 2,2′-bipyridyl ligand (+)-**333**.

The ^{13}C NMR spectrum again clearly indicated the C_2-symmetry of this 2,2′-bipyridyl ligand (+)-**333** (Figure 5.4.2.). This compound has a molecular formula of $C_{28}H_{36}N_2O_4$ and fourteen signals were observed in the ^{13}C NMR spectrum.

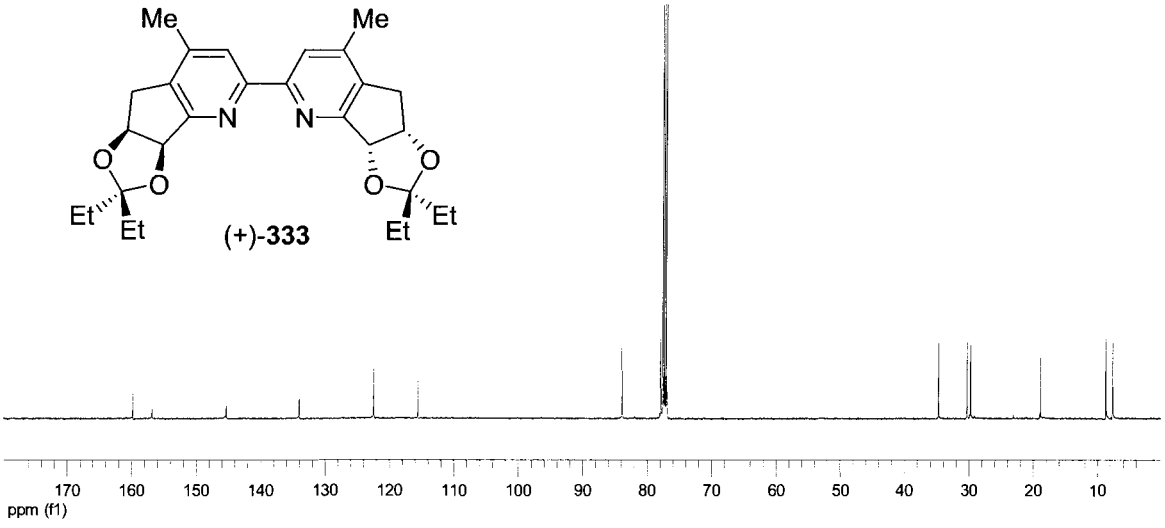


Figure 5.4.2. ^{13}C NMR spectrum of the chiral nonracemic C_2-symmetric 2,2′-bipyridyl ligand (+)-**333**.

A small amount of the corresponding *meso*-bipyridine **342** was also isolated from this reaction by flash chromatography (~5%). The enantiomeric purity of the desired bipyridyl ligand (+)-**333** was determined by analytical chiral HPLC and found to be greater than 99% ee. Since the starting chiral 2-chloroacetal (+)-**334** had an enantiomeric excess of 90%, this indicated that a significant enrichment of the enantiomeric purity of the chiral material had occurred in this coupling reaction. It was hypothesized that the enrichment was due to the conversion of the minor enantiomer of the starting material to the diastereoisomeric *meso*-bipyridine **342** which was then separated from the desired 2,2′-bipyridine (+)-**333** by flash chromatography (Figure 5.4.3.).

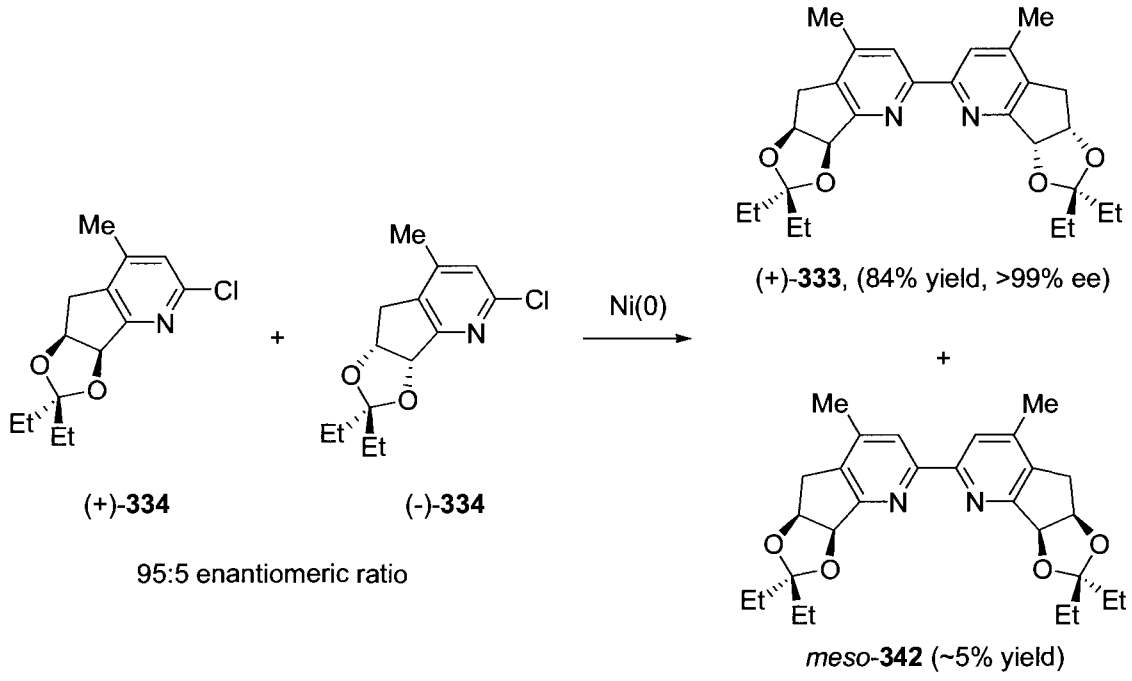


Figure 5.4.3. Enrichment of enantiomeric purity in the *homo*-coupling reaction of the 2-chloroacetal (+)-**334**.

5.5. Synthesis of the Tetrahydroquinoline (344)

Given the high enantioselectivity that was obtained in the AD reaction of the 2-chloropyrindine **336**, it was decided to prepare the corresponding dihydroquinoline, 2-chloro-4-methyl-6,7-dihydroquinoline **345**. This precursor could then be elaborated to the corresponding 2,2′-bipyridine ligand **343** using a similar synthetic route to that was used to prepare the pyrindine **336** (Figure 5.5.1.).

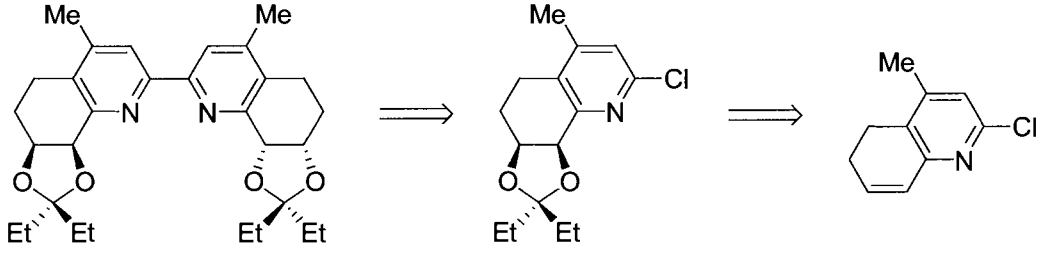
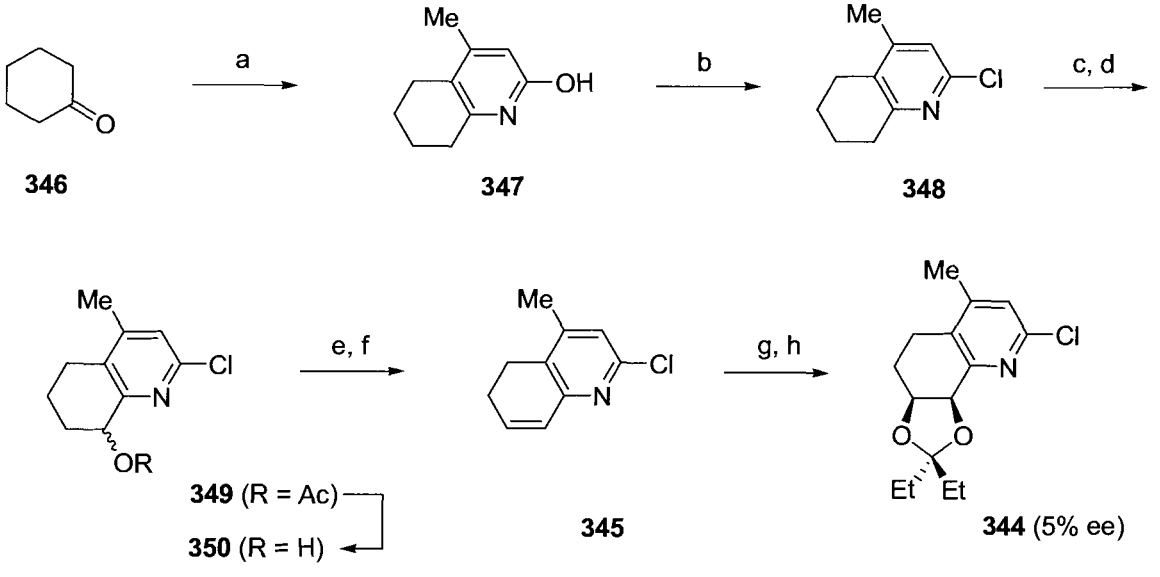


Figure 5.5.1. Retrosynthetic analysis of the 2,2′-bipyridine ligand **343**.

Thus, the 2-hydroxypyridine **347** was prepared on a multi-gram scale by heating equimolar amounts of cyclohexanone, ethyl acetoacetate and ammonium acetate at reflux for 8 hours following which the highly crystalline product crystallized from the reaction mixture (Scheme 5.5.1.).[116] Subsequent recrystallization from ethanol afforded the 2-hydroxypyridine **347** in 18% yield. The IR spectrum of the 2-hydroxypyridine **347** had a characteristic broad O-H peak at 3426 cm^{-1}. In the ^1H NMR spectrum, the C-3 aromatic proton resonance appeared at δ = 6.25 ppm which again indicated that the 2-hydroxypyridine **347** existed mainly as the aromatic tautomer.

Scheme 5.5.1. Synthesis of the Dihydroquinoline **345** and Its Sharpless Asymmetric Dihydroxylation Reaction



Reagents and Conditions: (a) ethyl acetoacetate, NH_4OAc, reflux, 8 h, 18%; (b) $PhP(O)Cl_2$, 160 °C, 16 h, 84%; (c) H_2O_2, H_2O, AcOH, 80 °C; (d) Ac_2O, rt, 1 h then 100 °C, 4 h, 77% (over two steps); (e) LiOH, THF, H_2O, rt, 16 h; (f) polyphosphoric acid, 100 °C, 30 min, 83% (over two steps); (g) AD-mix-β , *t*-BuOH/H_2O (1:1), 0 °C, 12 h; (b) 3-pentanone, PhH, *p*-TsOH (cat.), reflux, 16 h, 79% (over two steps).

The 2-hydroxypyridine **347** was then heated with phenylphosphonic dichloride at 160 °C for 16 hours which afforded the 2-chloropyridine **348** in 84% yield. The mass spectrum of this compound displayed molecular ion peaks for M(^{35}Cl + H) and M(^{37}Cl + H) at 182 and 184, respectively, in a 3:1 ratio. Subsequent oxidation of this compound with 30% aqueous hydrogen peroxide in acetic acid at 80 °C for 16 hours afforded the corresponding pyridine *N*-oxide. This compound was then heated with acetic anhydride at 100 °C for 4 hours which afforded the acetate **349** in good yield (77%, over two steps).[119] It was then attempted to convert the acetate **349** to the dihydroquinoline **345** by employment of the same reaction conditions used in the synthesis of the pyrindine **336** (concentrated sulfuric acid, 120 °C, 10 min). However, under these reaction conditions none of the desired reaction product was isolated and it appeared that a significant amount of polymeric material had formed. Thus, the acetate **349** was hydrolyzed with lithium hydroxide in a mixture of tetrahydrofuran and water (3:1) at room temperature for 16 h which afforded the alcohol **350**. The crude alcohol **350** was then heated with polyphosphoric acid at 120 °C for 30 min which afforded the desired dihydroquinoline **345** in good yield (83%, over two steps).[160] The AD reaction of the dihydroquinoline **345** with AD-mix-β in a mixture of *tert*-butanol and water (1:1) at 0 °C for 12 h afforded the corresponding diol in good yield (86%). Subsequent condensation of this diol with 3-pentanone in the presence of a catalytic amount of *p*-toluenesulfonic acid monohydrate in benzene at reflux afforded the chiral acetal **344** in very good yield (92%). However, analytical chiral HPLC analysis (Daicel Chiralcel OD column) showed that the acetal **344**

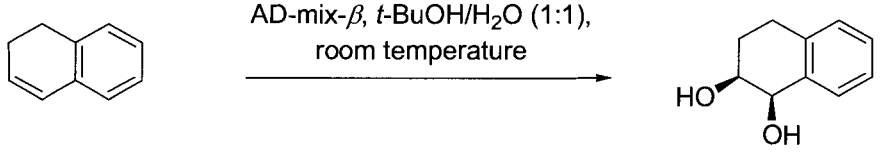
---

(160) Agarwal, S. K.; Boyd, D. R.; Davies, J. H.; Hamilton, L.; Jerina, D. M.; McCullough, J. J.; Porter, H. P. Synthesis of Arene Oxide and *trans*-Dihydrodiol Metabolites of Quinoline. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1969.

had been formed in low enantiomeric excess (5%). Thus, the AD reaction of the dihydroquinoline **345** is much less enantioselective that the AD reaction of the pyrindine **336**.

The low enantioselectivity of the AD reaction of the dihydroquinoline **345** (5% ee) is surprising when it is compared to the notably high enantioselectivity of the AD reaction of the pyrindine **336** (90% ee). For comparison, the AD reaction of dihydronapthalene **351** with AD-mix-β has been reported to afford the corresponding diol **352** in low enantiomeric excess (7%) (Scheme 5.5.2.).[155] Based on the results obtained in the AD reactions of the pyrindine **336** and the dihydroquinoline **345** as well as the literature reports for indene **338** and dihydronapthalene **351**, it appears that five-membered ring cyclic alkenes lead to dihydroxylated products in significantly higher enantioselectivities than do six-membered ring cyclic alkenes.

Scheme 5.5.2. The AD reaction of Dihydronapthalene **351** with AD-mix-β

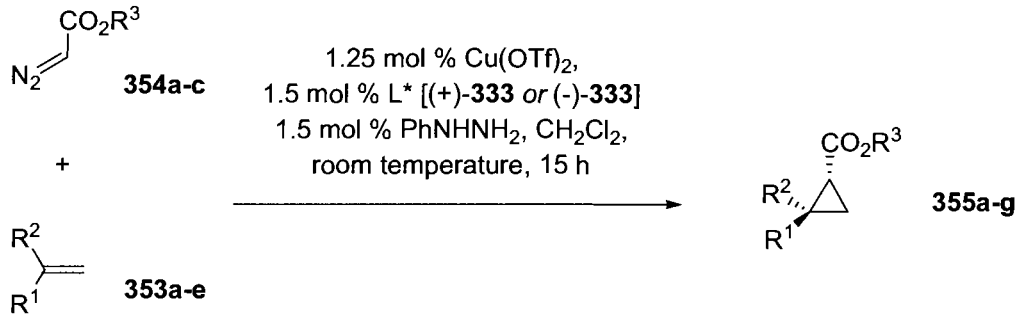


351 **352** (7% ee)

5.6. Evaluation of the 2,2′-Bipyridyl Ligand [(+)-333] in Copper(I)-Catalyzed Asymmetric Cyclopropanation Reactions of Alkenes

With the new chiral nonracemic and C_2-symmetric 2,2′-bipyridyl ligand (+)-**333** in hand, the evaluation of this chiral ligand in catalytic asymmetric synthesis was undertaken by executing a series of copper(I)-catalyzed asymmetric cyclopropanation reactions (Table 5.6.1.).

Table 5.6.1. Asymmetric Cyclopropanation Reactions of Alkenes **353a-e**



entry	L*	R^1	R^2	R^3	product	*trans*:*cis*	yield (%)	% ee (*trans*)
1	(+)-**333**	Ph	H	Et	**355a**	80:20	74	82
2	(+)-**333**	Ph	H	Bn	**355b**	92:8	49	84
3	(+)-**333**	Ph	H	*t*-Bu	**355c**	93:7	67	92
4	(-)-**333**	Ph	H	*t*-Bu	*ent*-**355c**	92:8	68	93
5	(+)-**333**	*p*-$MeOC_6H_4$	H	*t*-Bu	**355d**	>95:5	69	71
6	(+)-**333**	*p*-FC_6H_4	H	*t*-Bu	**355e**	92:8	73	99
7	(+)-**333**	$PhCH_2CH_2$	H	*t*-Bu	**355f**	>95:5	82	83
8	(+)-**333**	Ph	Ph	*t*-Bu	**355g**	--	81	72

According to standard literature procedures, the active copper(I)-catalyst was generated *in situ* by reduction of the complex formed between 1.25 mol % of copper(II) triflate and 1.5 mol % of the chiral ligand (+)-**333** with phenylhydrazine. [161] The asymmetric cyclopropanation reactions were carried out at room temperature in dichloromethane and involved the slow addition of the diazoesters **354a-c** (over ~3 h) to solutions of alkenes **353a-e** and the preformed catalyst. Of note, the diazoesters **354a-c** were again employed as the limiting reagent to minimize *homo*-coupling reactions of the diazoesters that would form the corresponding fumarates. The diastereoselectivities of

(161) For example, see: Malkov, A. V.; Pernazza, D.; Bell, M.; Bella, M.; Massa, A.; Teplý, F.; Meghani, P.; Kočovský, P. Synthesis of New Chiral 2,2′-Bipyridine Ligands and their Application in Copper-Catalyzed Asymmetric Allylic Oxidation and Cyclopropanation. *J. Org. Chem.* **2003**, *68*, 4727.

the cyclopropanation reactions were determined by analysis of the ^{1}H NMR spectra of the crude reaction products. The yields reported in the table are the combined yields of the chromatographically separated *trans*- and *cis*-cyclopropanes. The enantioselectivities of the *trans*-cyclopropanes were determined by analytical chiral HPLC (Daicel Chiracel OD column) following reduction to the corresponding primary alcohols with lithium aluminum hydride. The enantioselectivities of the *cis*-cyclopropanes were again not determined because these compounds were the minor reaction products and that the enantiomers of these particular compounds were difficult to separate by analytical chiral HPLC (Daicel Chiracel OD column).

In all instances, the catalytic system was found to be active and afforded the desired reaction products **355a-g** in good yield (49-81%). The asymmetric cyclopropanation reaction of styrene **353a** with ethyl diazoacetate **354a** afforded the cyclopropane **355a** in good yield (74%), diastereoselectivity (80:20) and enantioselectivity (82% ee) (entry 1). This result compares favorably with several other known chiral 2,2′-bipyridyl ligands.[73] An improvement of the diastereoselectivity of this reaction was achieved when benzyl and *tert*-butyl diazoacetate **354b-c** were used to prepare the corresponding cyclopropanes **355b-c** (dr = 92:8 and 93:7, respectively) (entries 2 and 3). Moreover, very high enantioselectivity (92% ee) was also recorded for the reaction of styrene **353a** with *tert*-butyl diazoacetate **354c** (entry 3). The absolute stereochemistry of the cyclopropane **355a** was assigned as (1*R*,2*R*) by comparison of the optical rotation with literature values.[162] The enantiomeric ligand (-)-**333** was used to

(162) Niimi, T.; Uchida, T.; Irie, R.; Katsuki, T. Highly Enantioselective Cyclopropanantion with Co(II)-Salen Complexes: Control of *cis*- and *trans*-Selectivity by Rational Ligand Design. *Adv. Synth. Catal.* **2001**, *343*, 79.

prepare the cyclopropane *ent*-**355c** in nearly identical enantioselectivity (93% ee), which also illustrated the observed reproducibility of these asymmetric cyclopropanation reactions (entry 4). It is known that the enantioselectivity of cyclopropanation reactions of styrene derivatives are susceptible to electronic effects.[71,73] Thus, it was found that the asymmetric cyclopropanation of an electron rich substrate, *p*-methoxystyrene **353b**, with ligand (+)-**333** afforded the corresponding cyclopropane **355d** in only moderate enantiomeric excess (71%) (entry 5). However, the electron poor substrate *p*-fluorostyrene **353c** afforded the corresponding cyclopropane **355e** in exceptionally high enantiomeric excess (99%) (entry 6). The latter result, to the best of our knowledge, is the highest reported enantioselectivity for an asymmetric cyclopropanation reaction with a chiral bipyridyl ligand. The ligand (+)-**333** was also used to cyclopropanate a terminal alkene, 4-phenyl-1-butene **353d**, in good enantiomeric excess (83%) (entry 7) as well as a 1,1-disubstituted alkene, 1,1-diphenylethene **353e**, in moderate enantiomeric excess (72%) (entry 8).

The stereochemical outcome of these asymmetric cyclopropanation reactions can be rationalized in terms of minimization of steric interactions between the reacting species and the copper(I)-complex of the bipyridyl ligand (+)-**333** (Figure 5.6.1.).[163] Four modes of approach of the styrene derivatives to the chiral copper carbene intermediate can be envisioned in the depicted *front on* view. The energetically favoured approaches of the styrene derivatives to the copper carbene intermediate **356** would be those in which the large aromatic substituents of the styrene derivatives are on the opposite face as the

(163) Doyle, M. P. Chiral Catalysts for Enantioselective Carbenoid Cyclopropanation Reactions. *Recl. Trav. Chim. Pays-Bas* **1991**, *110*, 305.

chiral acetal moieties of the ligand (+)-**333** in that this would minimize of steric interactions (as depicted by the curly arrows).

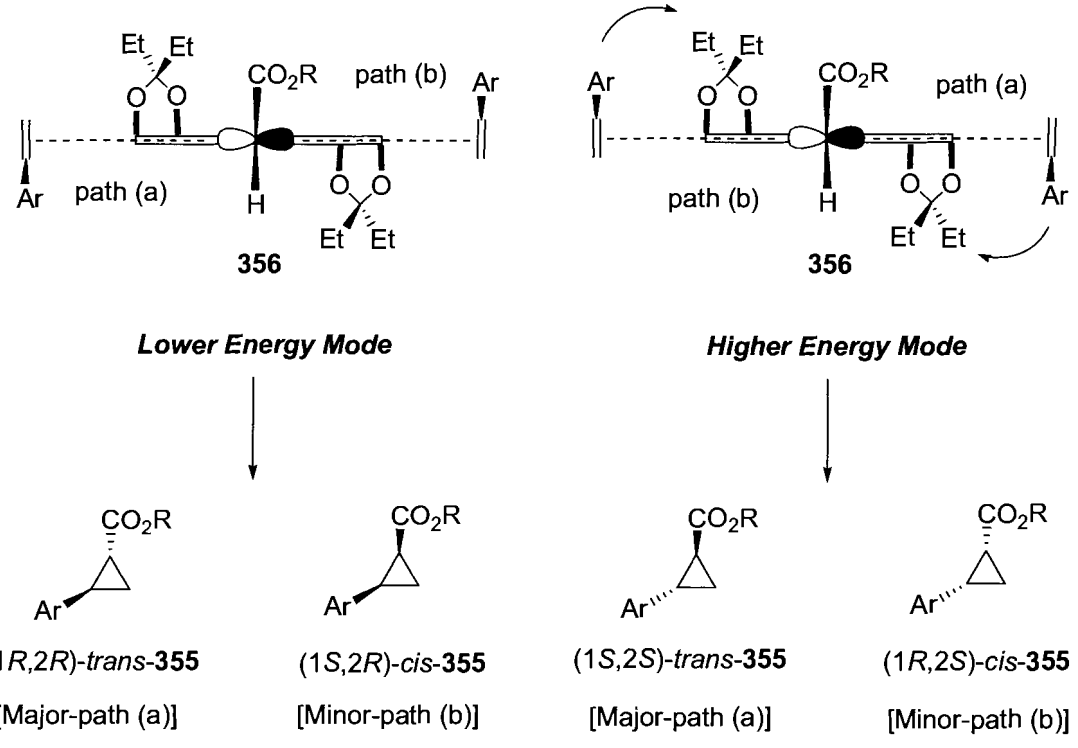


Figure 5.6.1. Rationalization of the stereochemical outcome of the asymmetric cyclopropanation reactions based on the minimization of steric interactions between the catalyst and the reacting species.

The approaches of the styrene derivative in which the aromatic substituent is on the opposite side as the ester moiety of the carbene complex would lead to the major *trans*-cyclopropane product **355** [path (a)]. Furthermore, from the depictions presented it can be appreciated that the size of the ester moiety in the copper carbene intermediate would influence the level of diastereoselectivity of these reactions (which is experimentally observed). The high levels of stereoinduction recorded can be rationalized in terms of the structural rigidity that is provided by the chiral acetal moieties of the C_2-symmetric bipyridyl ligand. Of note, disubstituted chiral *bis*oxazoline ligands

can provide improved enantioselectivities in AC reactions relative to monosubstituted *bis*oxazoline ligands.[164]

As a result of the excellent results obtained with the new chiral nonracemic C_2-symmetric 2,2′-bipyridyl ligand (+)-**333** in copper(I)-catalyzed asymmetric cyclopropanation reactions, it was decided to evaluate this ligand in other catalytic asymmetric reactions. In the following section, the evaluation of this ligand in copper(II)-catalyzed asymmetric Friedel-Crafts alkylation reactions is described.

5.7. Asymmetric Copper(II)-Catalyzed Friedel-Crafts Alkylation Reactions

The Friedel-Crafts (F-C) alkylation reaction is one of the oldest known organic transformations to employ Lewis acid catalysis and it is a particularly versatile carbon-carbon bond formation reaction.[165,166] In the mid-1980's the first examples of asymmetric F-C reactions were reported in the literature.[167] The asymmetric F-C reactions can be divided into two categories: (1) asymmetric 1,2-addition of electron rich

(164) Doyle, M. P. Asymmetric Addition and Insertion Reactions of Catalytically-Generated Metal Carbenes. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000, Chapter 5.

(165) (a) Friedel, C.; Crafts, J. M. *R. Hebd. Seances Acad. Sci.* **1877**, *84*, 1392. (b) Friedel, C.; Crafts, J. M. *R. Hebd. Seances Acad. Sci.* **1877**, *84*, 1450.

(166) Olah, G. A.; Khrisnamurti, R.; Prakash, G. K. S. In *Comprehensive Organic Synthesis*, 1st ed.; Pergamon: New York, 1991, Vol. 3, pp 293-339.

(167) (a) Bigi, F.; Casiraghi, G.; Casnati, G.; Satori, G. Asymmetric Electrophilic Substitution on Phenols. Enantioselective *ortho*-Hydroxyalkylation Mediated by Chiral Alkoxyaluminum Chlorides. *J. Org. Chem.* **1985**, *50*, 5018. (b) Erker, G.; van der Zeijden, A. A. H. Enantioselective Catalysis with a New Zirconium Trichloride Lewis Acid Containing a "Dibornacyclopentadienyl" Ligand. *Angew. Chem., Int. Ed.* **1990**, *29*, 512.

aromatic systems to carbonyl groups; and (2) asymmetric 1,4-additon of electron rich aromatic systems to α,β-unsaturated carbonyl compounds (Figure 5.7.1.).

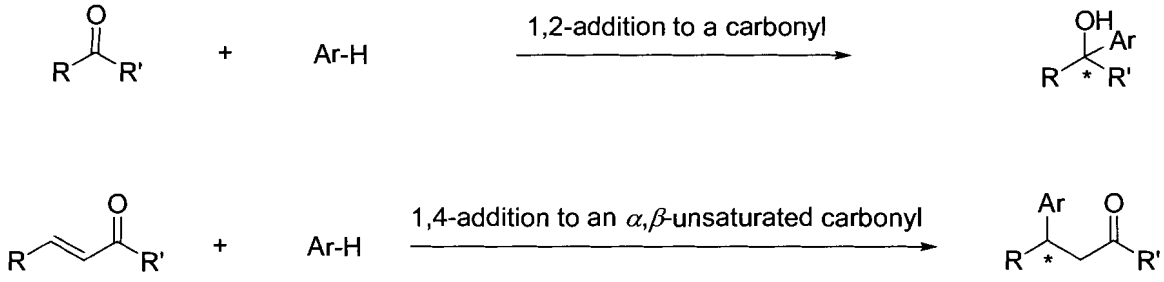
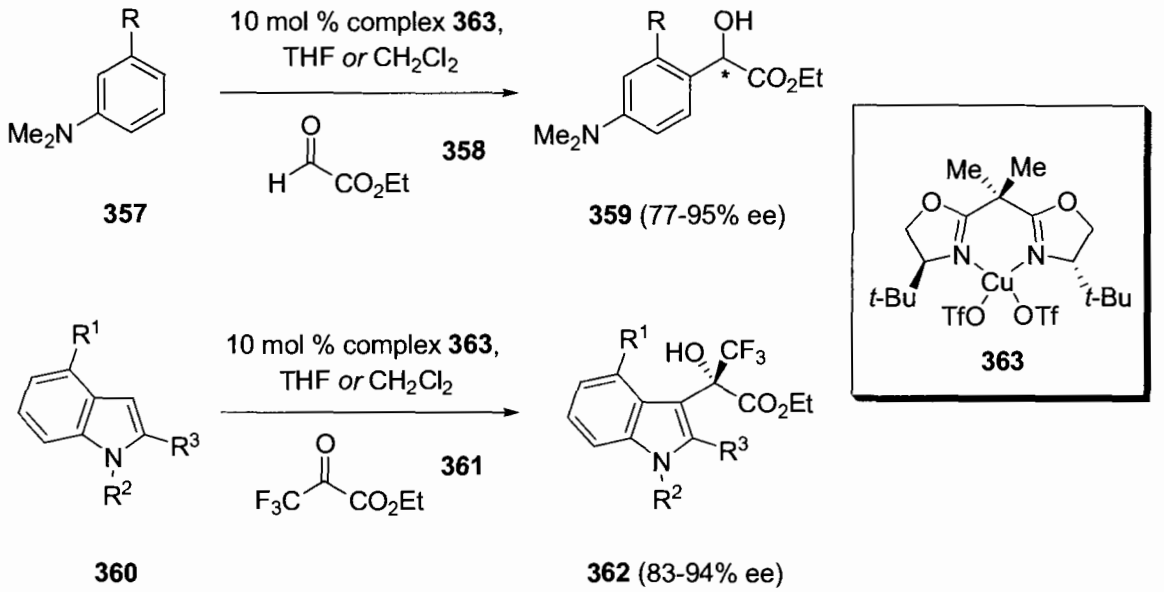


Figure 5.7.1. Possible strategies in the asymmetric Friedel-Crafts alkylation reactions of activated aromatic compounds.

Recently, Jørgensen and co-workers have pioneered the catalytic enantioselective F-C reaction of activated aromatic compounds with electron deficient carbonyl compounds using the chiral *bis*oxazoline copper(II) complex **363** as the catalyst (Scheme 5.7.1.).[168] In particular, Jørgensen has described that the F-C reactions of activated aromatic compounds **357** with ethyl glyoxylate **358** affords aromatic mandelic esters **359** in high enantiomeric excess (77-95%) and also that the F-C reactions of heteroaromatic compounds, such as indole **360**, with ethyl 3,3,3-triflouropyruvate **361** afforded the corresponding heteroaromatic hydroxytrifluoromethyl esters **362** in high enantiomeric excess (83-94%).

(168) (a) Zhuang, W.; Gathergood, N.; Hazell, R. G.; Jørgensen, K. A. Catalytic, Highly Enantioselective Friedel-Crafts Reactions of Aromatic and Heteroaromatic Compounds to Trifluoropyruvate. A Simple Approach for the Formation of Optically Active Aromatic and Heteroaromatic Hydroxy Trifluoromethyl Esters. *J. Org. Chem.* **2001**, *66*, 1009. (b) Gathergood, N.; Zhuang, W.; Jørgensen, K. A. Catalytic Enantioselective Friedel-Crafts Reactions of Aromatic Compounds with Glyoxylate: A Simple Procedure for the Synthesis of Optically Active Mandelic Acid Esters. *J. Am. Chem. Soc.* **2000**, *122*, 12517.

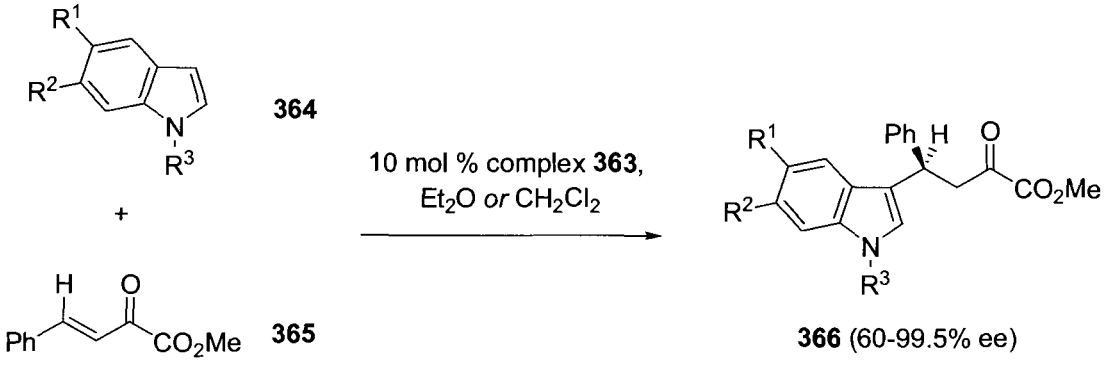
Scheme 5.7.1. Catalytic Asymmetric Friedel-Crafts Reactions of Activated Aromatic Compounds Catalyzed by the Chiral Copper(II) *bis*(Oxazoline) Complex **363** (2001)



Jørgensen and co-workers have also reported the enantioselective F-C reactions of indoles **364** with the β,γ-unsaturated-α-ketoester **365** employing the chiral *bis*oxazoline copper(II) complex **363** which afforded the 1,4-addition products **366** (Scheme 5.7.2.).[169]

(169) Jensen, K. B.; Thorhauge, J.; Hazell, R. G.; Jørgensen, K. A. Catalytic Asymmetric Friedel-Crafts Alkylation of β,γ-Unsaturated α-Ketoesters: Enantioselective Addition of Aromatic C-H Bonds to Alkenes. *Angew. Chem., Int. Ed.* **2001**, *40*, 160.

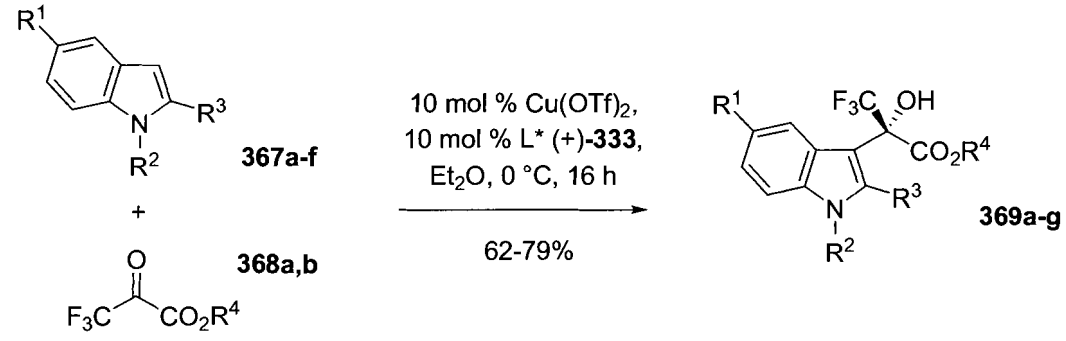
Scheme 5.7.2. Catalytic Enantioselective Michael Addition of Indoles to the β,γ-Unsaturated α-Keto Ester **365** Catalyzed by the Chiral Copper(II) *Bis*oxazoline Complex **363** (2001)



5.8. Evaluation of the 2,2′-Bipyridyl Ligand [(+)-333] in Copper(II)-Catalyzed Asymmetric Friedel-Crafts Alkylation Reactions

The ligand (+)-**333** was evaluated in the reactions of a series of commercially available indoles **367a-f** with the ethyl and methyl esters of 3,3,3-trifluoropyruvic acid **368a,b** (Table 5.8.1.). To the best of our knowledge, this is the first report of the application of a 2,2′-bipyridyl ligand in catalytic enantioselective F-C reactions.

Table 5.8.1. Asymmetric Friedel-Crafts Alkylation Reactions of Indoles **367a-f**



entry	R^1	R^2	R^3	R^4	product	temperature (°C)	yield (%)	ee (%)
1	H	H	H	Et	**369a**	0	68	74
2	H	H	H	Me	**369b**	0	77	90
3	H	H	H	Me	**369b**	-10	62	90
4	H	H	Me	Me	**369c**	0	79	86
5	OMe	H	H	Me	**369d**	0	69	72
6	NO_2	H	H	Me	**369e**	0	75	60
7	H	Me	H	Me	**369f**	0	74	18
8	H	Me	Ph	Me	**369g**	0	65	18

The active copper(II)-catalyst was generated *in situ* on reaction of 10 mol % of copper(II) triflate and 10 mol % of the 2,2′-bipyridyl ligand (+)-**333** which afforded a colourless solution. It was determined that performing the reactions in ether at 0 °C was the optimal conditions for the reaction. This was determined after performing preliminary asymmetric F-C reactions of indole **367a** with methyl 3,3,3-trifluoropyruvate **368b**. The desired product **369b**, was isolated in good yield in both dichloromethane and tetrahydrofuran at 0 °C but the enantioselectivities were relatively lower in these instances (28% and 45% ee, respectively).

Under the optimized reaction conditions, the copper(II)triflate complex of ligand (+)-**333** displayed excellent catalytic activity and the F-C reactions reached completion within 16 h in all instances. The yields reported in the table are of the pure reaction products after isolation by flash chromatography. The enantioselectivity of the reactions were determined by analytical chiral HPLC (Daicel Chiracel OD column).

The F-C reaction of indole **367a** with ethyl 3,3,3-trifluoropyruvate **368a** afforded the known product **369a** in good yield (68%) and in good enantiomeric excess (74%) (entry 1). The absolute stereochemistry of the reaction product **369a** was assigned as (*S*) on comparison of the optical rotation with a literature value.[168]

The F-C reaction of indole **367a** with methyl 3,3,3-trifluoropyruvate **368b** afforded the product **369b** in similar yield (77%) but in significantly higher enantiomeric excess (90%) (entry 2). This result compares favorably with the copper(II) triflate *bis*oxazoline complex catalyzed reactions reported by Jørgensen and co-workers for a range of substrates (83-94% ee).[168] Of note, it was assumed that the absolute stereochemistry of the reaction product **369b** was (*S*) in that it is reasonable to expect that the alternative use of the methyl ester of 3,3,3-triflouropyruvic acid **368b** would not effect the stereochemical outcome of the F-C reaction. There was no further enhancement of enantioselectivity on repeating the above experiment at a lower temperature (-10 °C) (entry 3). Thus, methyl 3,3,-trifluoropyruvate **368b** was used exclusively in the subsequent experiments and the reactions were performed at 0 °C.

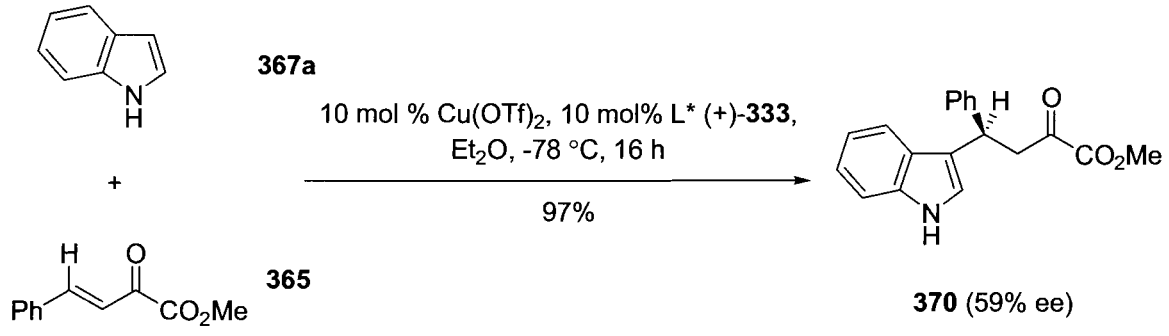
The F-C reaction of 2-methylindole **367b** again afforded the corresponding product **369c** in high enantiomeric excess (86%) (entry 4). The electron-rich substrate, 5-methoxyindole **367c**, afforded the product **369d** in good enantiomeric excess (72%)

whereas the electron-poor substrate, 5-nitroindole **367d**, afforded the product **369e** in slightly lower enantiomeric excess (60%) (entries 5 and 6, respectively). Surprisingly, 1-methylindole **367e** and 1-methyl-2-phenylindole **367f** afforded the corresponding products **369f** and **369g** in low enantiomeric excess (18%) (entries 7 and 8, respectively). Thus, it is evident that the substitution of the hydrogen atom of the indole nitrogen has a detrimental effect on the enantioselectivity of the F-C reaction. This result is in contrast to the copper(II) triflate *bis*oxazoline complex catalyzed F-C reactions in which substitution of the indole nitrogen does not lower the enantioselectivity of the reaction.[168] Further experimentation is required to determine the origin effect. However, these results do suggest that the indole N-H bond is involved in the reaction transition state or that detrimental steric factors are at play in these particular catalytic F-C reactions.

The 2,2′-bipyridine (+)-**333** was also evaluated in the conjugate addition reactions of the indole **367a** and 3-methoxyphenol **371** to (3*E*)-2-oxo-4-phenyl-3-butenoic acid methyl ester **365**.[169,170] In the case of the indole **367**, the conjugate addition product **370** was formed in excellent yield (97%) and good enantiomeric excess (59%) when the reaction was performed in ether at -78 °C for 16 hours (Scheme 5.8.1.). The absolute stereochemistry of the major conjugate addition product **370** was assigned as (*S*) based on comparison of the optical rotation with a literature value.[169]

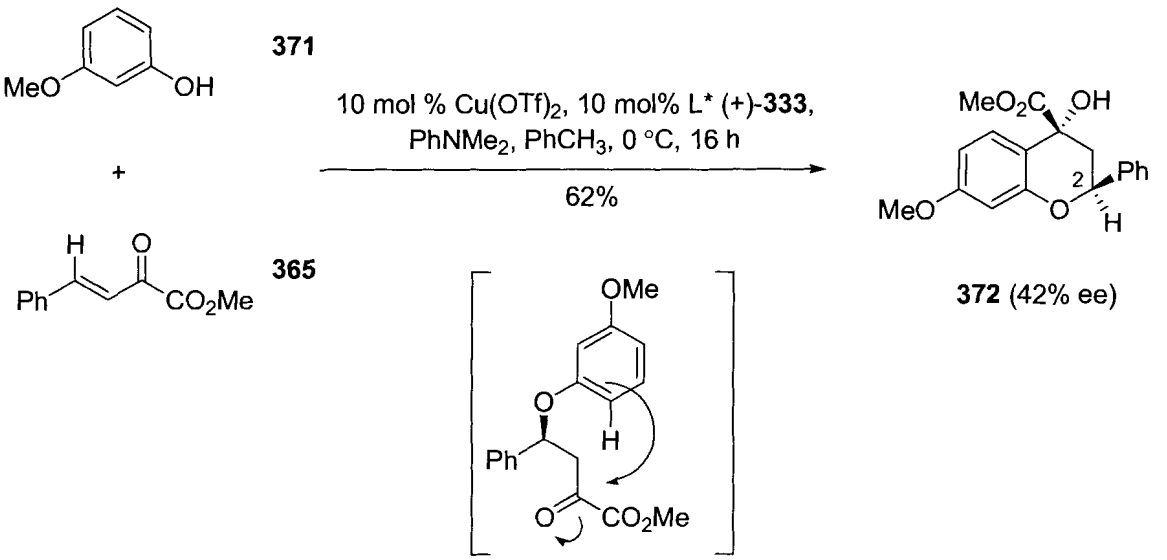
(170) van Lingen, H. L.; Zhuang, W.; Hansen, T.; Rutjes, F. P. J. T.; Jørgensen, K. A. Formation of Optically Active Chromanes by Catalytic Asymmetric Tandem oxa-Michael Addition-Friedel-Crafts Alkylation Reactions. *Org. Biomol. Chem.* **2003**, *1*, 1953.

Scheme 5.8.1. The Asymmetric Conjugate Addition Reaction of Indole **367a** to the β,γ-Unsaturated α-Keto Ester **365**



In the case of the reaction with 3-methoxyphenol, the reaction was performed in toluene in the presence of *N*,*N*-dimethylaniline at 0 °C for 16 h (Scheme 5.8.2.). In this instance, the product of the initial conjugate addition reaction underwent a subsequent intramolecular F-C reaction to afford the novel chromane derivative **372**, as a single diastereoisomer, in moderate enantiomeric excess (42%) and in good yield (62%). The absolute stereochemistry of the chromane product **372** is not known. However, it is assumed that the major product of this reaction has the same stereochemistry (at C2) as that observed for the major conjugate addition product **370**.

Scheme 5.8.2. The Conjugate Addition Reaction of 3-Methoxyphenol **371** to the β,γ-Unsaturated α-Keto Ester **365**



The product is formed *via* tandem conjugate addition/intramolecular Friedel-Crafts alkylation reactions

In order to gain insight into the structure of the active catalyst in the above reactions, a copper(II) chloride complex was prepared by heating equimolar amounts of the 2,2′-bipyridyl ligand (+)-**333** and anhydrous copper(II) chloride in a mixture of ethanol and dichloromethane (1:1). Yellow crystals of the copper(II) chloride (+)-**333** complex that were suitable for X-ray crystallography were obtained on recrystallization, by slow evaporation of the solvent, from a mixture of ethanol and dichloromethane (2:1).

An *ORTEP* representation of the copper(II) chloride (+)-**333** complex is shown below (Figure 5.8.1.).* It was found that, in the solid state, the ligands adopt a geometry that lies between tetrahedral and square-planar around the copper atom (bond angles: Cl1-Cu-N1 = 138.12°, Cl1-Cu-N2 = 103.12°, Cl2-Cu-N2 = 137.90°, Cl2-Cu-N1 = 101.38°, Cl1-Cu-Cl2 = 103.12°, N1-Cu-N2 = 80.86°) In this structure, the chloride

(*) The X-ray structure determination of the copper(II) chloride (+)-**333** complex was performed by Mr. Neil D. Draper at Simon Fraser University.

ligands are tilted away from the large cyclic acetal moieties of the C_2-symmetric 2,2′-bipyridyl ligand (+)-**333**. The bond lengths of the copper atom to the chlorine atoms (Cl1 and Cl2) were found to be 2.2100 and 2.2054 Å, respectively. Complete tabulated bond angles and bond lengths from the X-ray crystal structure of the copper(II) chloride ligand (+)-**333** complex are provided in the experimental section of this thesis.

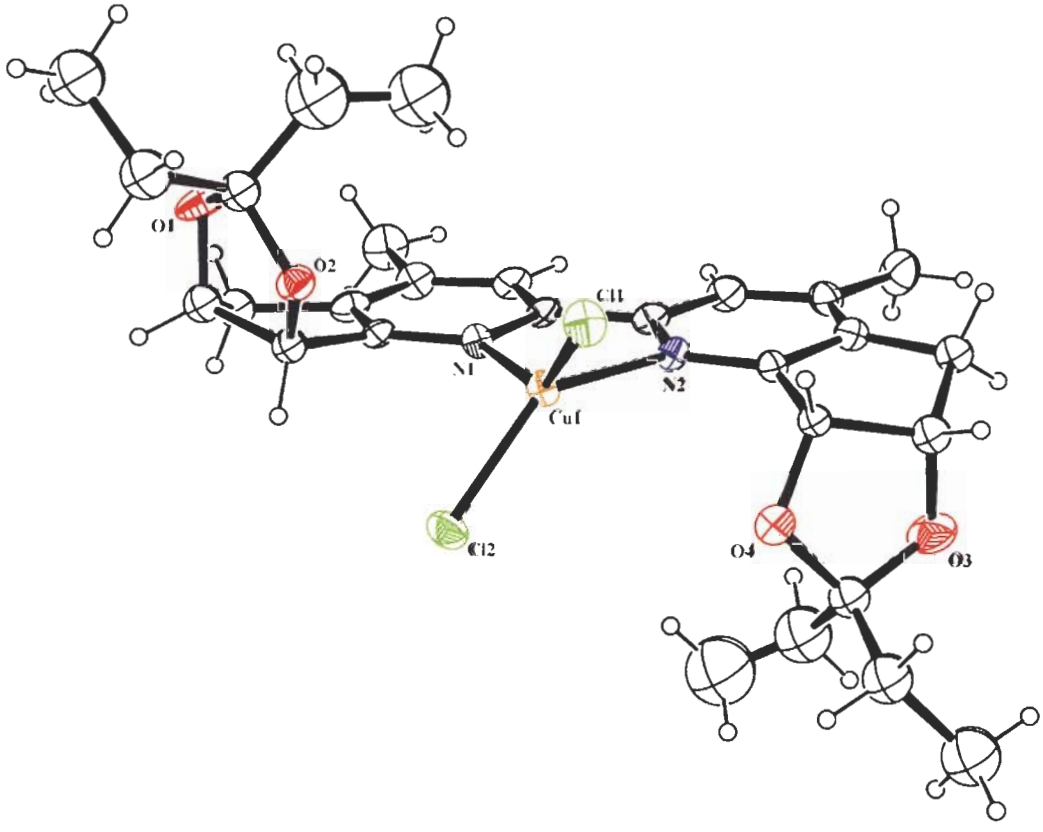


Figure 5.8.1. *ORTEP* representation of the $CuCl_2$·ligand (+)-**333** complex.*

Similar structural observations have been recorded for several copper(II) chloride *bis*oxazoline complexes.[171] For comparison, an *ORTEP* representation of the copper(II)

(*) The thermal ellipsoids are drawn at a 25% probability level for clarity.

chloride *tert*-butyl *bis*oxazoline complex prepared by Jørgensen and co-workers is shown below (Figure 5.8.2.). Again, the ligands are found to adopt a geometry around the copper atom that lies between tetrahedral and square planar. In addition, the chloride ligands in this structure are tilted away from the bulky *tert*-butyl substituents of the C_2-symmetric *bis*oxazoline ligand.

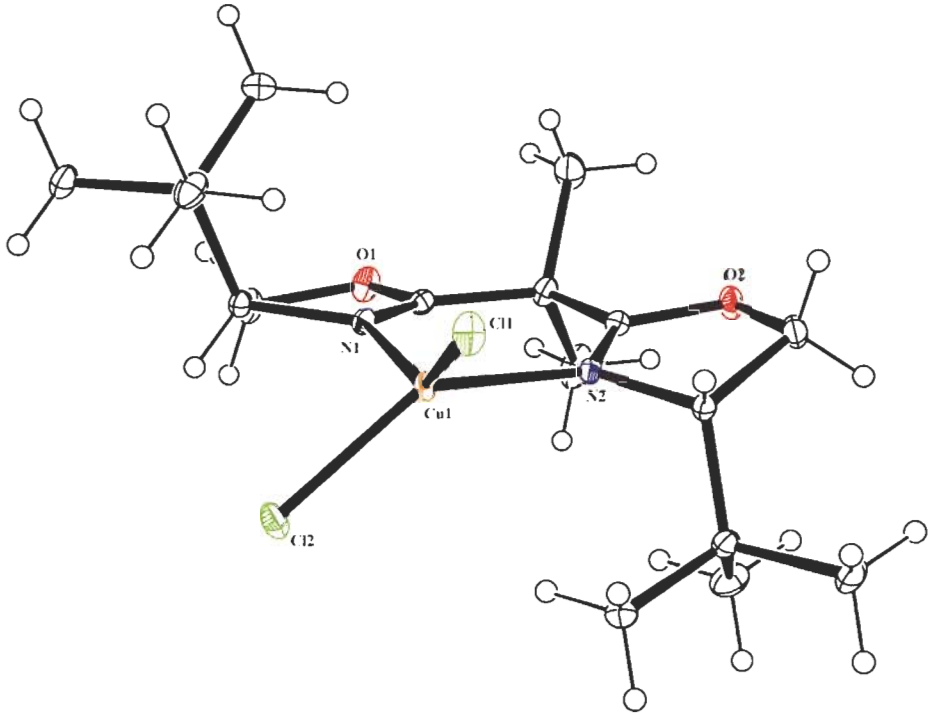


Figure 5.8.2. *ORTEP* representation of a $CuCl_2$·*tert*-butyl *bis*oxazoline complex.*

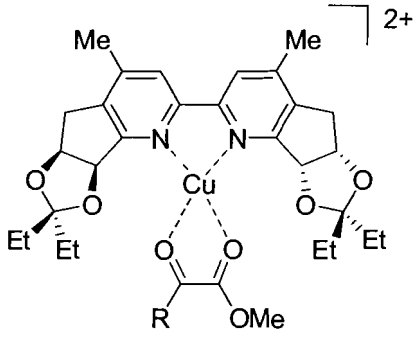
In order to rationalize the stereochemical outcome of the copper(II)-catalyzed asymmetric F-C reactions of the indoles **367a-f** with methyl 3,3,3-trifluoropyruvate **368b**,

---

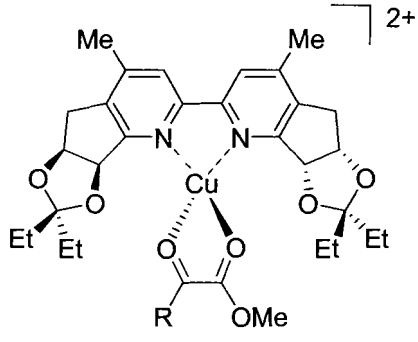
(171) Thorhauge, J.; Roberson, M.; Hazell, R. G.; Jørgensen, K. A. On the Intermediates in Chiral *bis*(Oxazoline) copper(II)-Catalyzed Enantioselective Reactions-Experimental and Theoretical Investigations. *Chem. Eur. J.* **2002**, *8*, 1888 and references therein.

(*) The thermal ellipsoids are drawn at a 25% probability level for clarity. The crystallographic data for this complex were obtained from the Cambridge Crystallographic Data Centre (see: ref. 171).

it is postulated that the relatively small α-ketoester **368b** coordinates in a bidentate fashion to the copper centre of the copper(II) triflate (+)-**333** complex in an approximately square planar geometry (Figure 5.8.3.). The indoles **367a-f** would then be expected to attack the sterically accessible *Re*-face of the carbonyl moiety. To rationalize the *opposite* facial selectivity for the reaction of indole **367a** with the β,γ-unsaturated α-ketoester **365**, it is postulated that this larger substrate coordinates in a bidentate fashion to the copper centre in an approximately tetrahedral geometry and that the β,γ-unsaturated α-ketoester moiety adopts an s-*cis* conformation. The indole would then be expected to attack the β,γ-unsaturated α-ketoester moiety from the more sterically accessible *Si*-face of the complex. The lower enantioselectivity of this process may be attributed to the conformational flexibility of the β,γ-unsaturated α-ketoester moiety or, more simply, to the fact that the reaction centre is located further from the chiral pocket of the complex.



Square-planar Coordination
(*Re*-Face approach, R = CF_3)



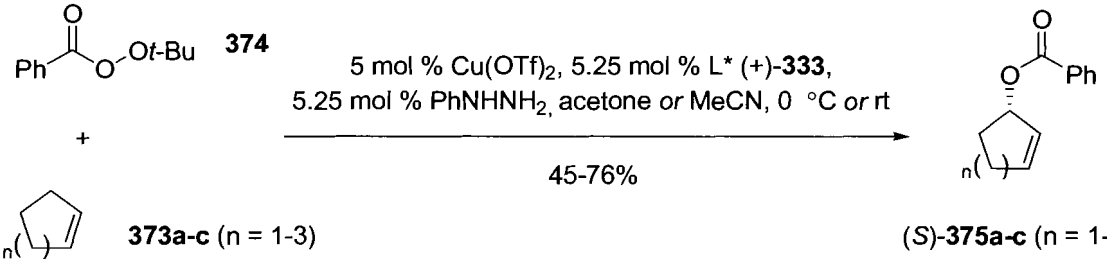
Tetrahedral Coordination
(*Si*-Face approach R = CHCHPh)

Figure 5.8.3. Square-planar and tetrahedral coordination of the α-ketoester substrates **368a,b** and **365** to the chiral catalyst.

5.9. Evaluation of the 2,2′-Bipyridyl Ligand [(+)-333] in Copper(I)-Catalyzed Asymmetric Allylic Oxidation Reactions

The chiral 2,2′-bipyridyl ligand (+)-**333** was also evaluated in copper(I)-catalyzed asymmetric allylic oxidation reactions of cyclic alkenes **373a-c** (n = 1-3) with *tert*-butylperoxy benzoate **374** as the oxidant (Table 5.9.1.).

Table 5.9.1. Asymmetric Allylic Oxidation Reactions



entry	substrate	n	solvent	temperature	yield (%)	ee (%)
1	**373a**	1	acetone	rt	64	32
2	**373a**	1	MeCN	rt	69	34
3	**373b**	2	acetone	rt	67	65
4	**373b**	2	MeCN	rt	56	84
5	**373b**	2	acetone	0 °C	51	81
6	**373b**	2	MeCN	0 °C	45	91
7	**373c**	3	acetone	rt	72	36
8	**373c**	3	MeCN	rt	76	40

The active copper(I)-catalyst for these reactions was generated *in situ* by reduction of the complex formed between 5 mol % of copper(II) triflate and 5.25 mol % of the chiral ligand (+)-**333** with phenylhydrazine in either acetone or acetonitrile. These solvents were chosen because they have provided the highest enantioselectivities in related catalytic systems.[65] Following the formation of the catalyst, the red reaction mixtures were then treated with the stoichiometric oxidant *tert*-butylperoxy benzoate **374**

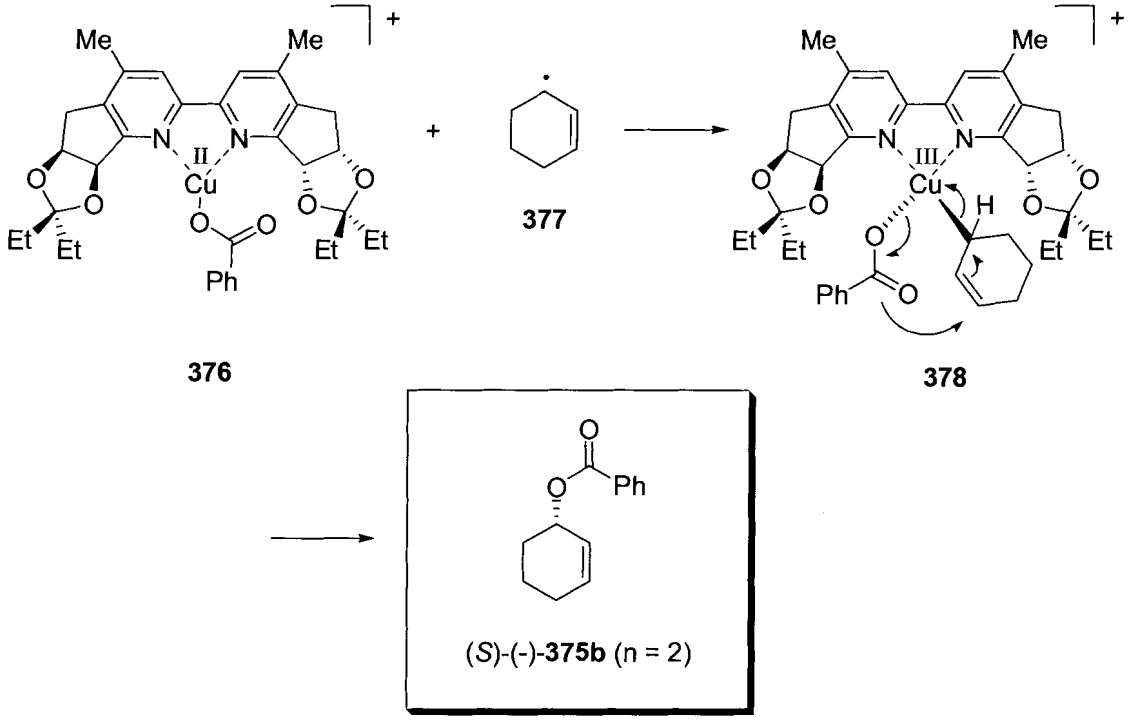
and an excess (5 equiv) of the cyclic alkenes **373a-c** (n = 1-3). The yields listed in the table are of analytically pure reaction products that were isolated by flash chromatography. The enantioselectivity of the reactions were determined by analytical chiral HPLC (Daicel Chiracel OD column) using hexane:isopropanol (250:1) as the eluant with a flow rate of 0.5 mL/minute and UV detection at λ = 220 nm.

The allylic oxidation reaction of cyclopentene **373a** (n = 1) in acetone at room temperature for 24 h afforded the reaction product **375a** (n = 1) in good yield (64%) and in moderate enantioselectivity (32% ee) (entry 1). Performing the same reaction in acetonitrile for 16 h afforded the reaction product **375a** (n = 1) in similar yield and enantioselectivity (69 and 34% ee, respectively) (entry 2). The allylic oxidation reaction of cyclohexene **373b** (n = 2) in acetone at room temperature for 16 h afforded the reaction product **375b** (n = 2) in good yield (67%) and in higher enantiomeric excess (65%) (entry 3). On switching to acetonitrile as the reaction solvent at room temperature, the enantioselectivity increased substantially (84% ee) (entry 4). However, in this instance the reaction rate was slower and the reaction product **375b** (n = 2) was isolated in slightly lower yield (56%) after 72 h reaction time. The excellent room results with cycohexene **373b** (n = 2) as the reaction substrate at room temperature led us to attempt to increase the enantioselectivity by performing the allylic oxidation reactions at a lower temperature. When the oxidation reaction of cyclohexene **373b** (n = 2) was conducted in acetone at 0 °C for 48 h, the reaction product **375b** (n = 2) was isolated in moderate yield (51%) and good enantiomeric excess (81%) (entry 5). A further enhancement of enantioselectivity was observed when the reaction was performed in acetonitrile at 0 °C for 96 h (91% ee). However, in this case, the yield was slightly compromised (45%)

(entry 6). To the best of our knowledge, these are the highest reported enantioselectivities in an asymmetric allylic oxidation reaction with a chiral 2,2′-bipyridyl ligand. The allylic oxidation reaction of cycloheptene **373b** (n = 3) in acetone for 16 h afforded the reaction product **375b** (n = 3) in good yield (72%) but only in moderate enantiomeric excess (36%) (entry 7). When the corresponding reaction was performed in acetonitrile for 16 h, the reaction product **375b** (n = 3) was formed in similar yield and enantioselectivity (72% and 40% ee, respectively) (entry 8). The absolute stereochemistry of each of the above reaction products **375a-c** (n = 1-3) was assigned as (*S*) based on comparison of the optical rotations with literature values.[65] These results demonstrated that this asymmetric allylic oxidation reaction was highly substrate dependant.

The asymmetry of the process is most likely the result of the approach of the allylic radical **377** (shown for cyclohexene) to one of the less hindered quadrants of the C_2-symmetric copper(II) benzoate complex **376** that would afford the copper(III) complex **378.** This species would then undergo a pericyclic rearrangement (or direct reductive elimination) to afford the product (*S*)-**375b** and regenerate the catalytic copper(I) complex (Scheme 5.9.1.).

Scheme 5.9.1. Rationalization of the Stereochemical Outcome of the Asymmetric Allylic Oxidation Reactions based on the Minimization of Steric Interactions between the Catalyst and the Reacting Species



5.10. Optical Rotary Dispersion Spectrum of the Copper(II) Chloride [(+)-333] Complex

In the process of undertaking the characterization of the copper(II) chloride (+)-**333** complex, we observed that it possessed a large optical rotation ($[\alpha]_D^{20}$ + 793 [*c* 0.0029, chloroform]) similar to the optical rotation observed for the Cu(**267c**)$_2$·$CuCl_2$ complex described in Chapter 2. The optical rotary dispersion spectrum for this complex was also recorded (Figure 5.10.1.). The spectrum was recorded at a concentration of 2.9 mg of the complex in 100 mL of chloroform (4.7 x 10^{-5} M) and across a wavelength range of 200 to 800 nm. The maximum positive specific rotation was + 2.3 x 10^4 at 293 nm. The maximum negative specific rotation was - 1.2 x 10^4 at 332 nm (the

corresponding circular dichroism spectrum is provided in the appendices of this thesis, see: Section 9.2.). These values are even higher than the specific rotations observed and reported for the Cu(**267c**)$_2$·$CuCl_2$ complex in Chapter 2.

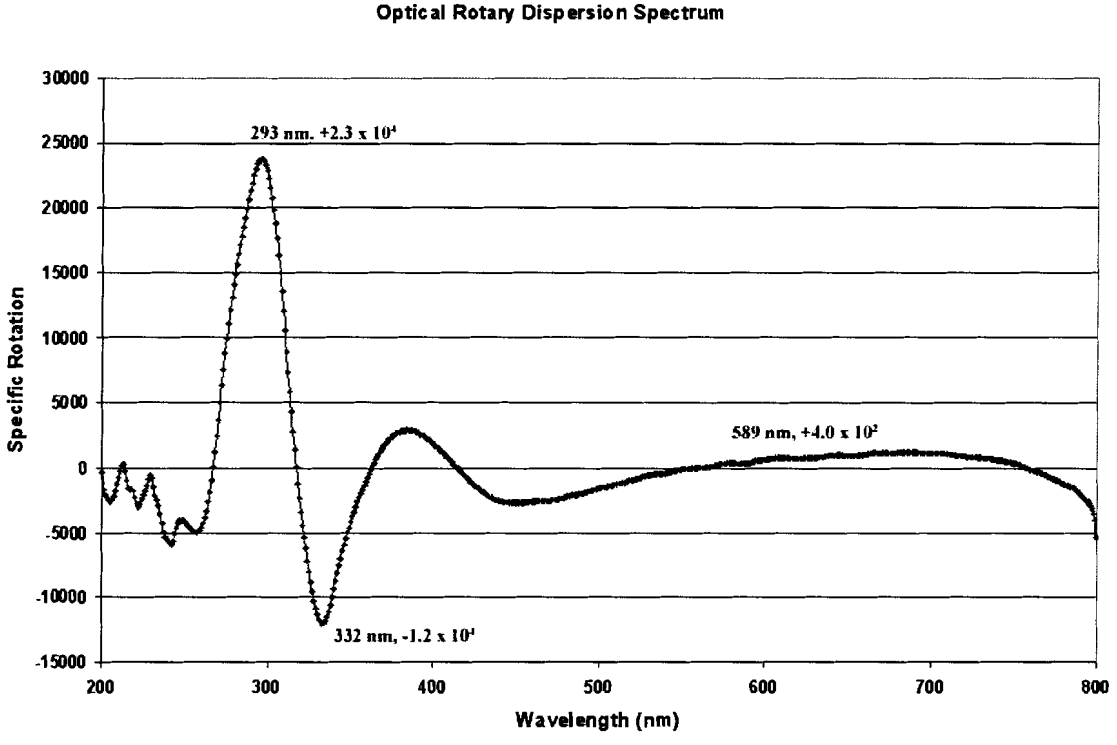


Figure 5.10.1. The optical rotary dispersion spectrum of the copper(II) chloride (+)-**333** complex.

A UV-vis spectrum of the copper(II) chloride (+)-**333** complex that was recorded on the same sample as the optical rotary dispersion spectrum showed strong absorbances at 328 nm (ε = 2.0 x 10^4 M^{-1} cm^{-1}) and 315 nm (ε = 2.0 x 10^4 M^{-1} cm^{-1}). No absorptions were observed above 400 nm in the UV-vis spectrum.

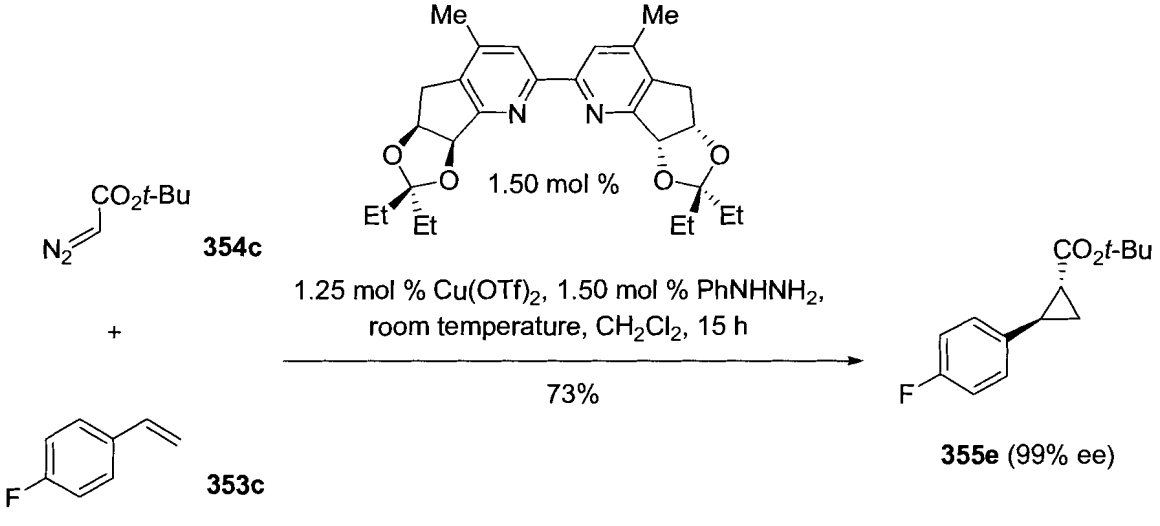
5.11. Conclusions

The efficient synthesis of the low molecular weight, chiral nonracemic and C_2-symmetric 2,2′-bipyridyl ligand (+)-**333** from readily available starting materials was developed. The chirality of the ligand was installed by a modified Sharpless asymmetric

dihydroxylation reaction of a pyrindine in high enantioselectivity (90% ee). This is the highest reported enantioselectivity for an asymmetric dihydroxylation reaction of a cyclic *cis*-alkene.

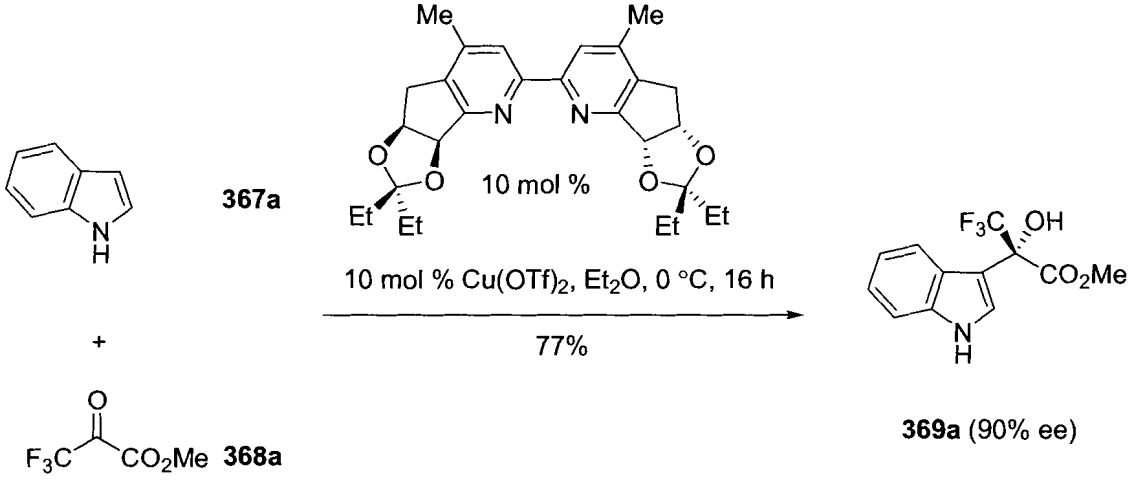
The ligand (+)-**333** was found to be a highly effective chiral director in the copper(I)-catalyzed asymmetric cyclopropanation reactions of a variety of alkenes with *tert*-butyl diazoacetate **354c**. Very high diastereoselectivities (>95:5) and enantioselectivities (up to 99% ee) were observed. The reaction conditions involved the formation of the catalyst *in situ* by reduction of the complex formed between 1.25 mol % of copper(II) triflate and 1.5 mol % of the chiral ligand (+)-**333** with phenylhydrazine. The best result was obtained in the asymmetric cyclopropanation reaction of *p*-fluorostyrene **353c** with *tert*-butyl diazoacetate **354c** which afforded the reaction product **355e** in exceptionally high enantiomeric excess (99%) (Scheme 5.11.1.). This result is the highest reported enantioselectivity for an asymmetric cyclopropanation reaction with a chiral 2,2′-bipyridine ligand.

Scheme 5.11.1. Asymmetric Cyclopropanation Reaction employing the C_2-Symmetric 2,2′-Bipyridyl Ligand (+)-**333**



The ligand (+)-**333** was also evaluated in the copper(II)-catalyzed asymmetric Friedel-Crafts alkylation reactions of a series of substituted indoles **367a-f** with the methyl and ethyl esters of 3,3,3-trifluoropyruvic acid **368a,b**. High enantioselectivities were observed (up to 90% ee). However, it was noted that substitution of the hydrogen atom of the indole nitrogen had a detrimental effect on the enantioselectivity of the reactions. The reaction conditions involved the formation of the catalyst *in situ* by reaction of 10 mol % of copper(II) triflate and 10 mol % of the 2,2′-bipyridyl ligand (+)-**333** in ether. Following catalyst formation, the solutions were cooled to 0 °C and the indole **367a-f** and the methyl or ethyl ester of 3,3,3-trifluoropyruvic acid **368a,b** were added. The best result was obtained for the asymmetric Friedel-Crafts reaction of indole **367a** with methyl 3,3,3-trifluoropyruvate **368a** which afforded the reaction product **369a** in high enantiomeric excess (90%) (Scheme 5.11.2.).

Scheme 5.11.2. Asymmetric Friedel-Crafts Reaction employing the C_2-Symmetric 2,2′-Bipyridyl Ligand (+)-**33**



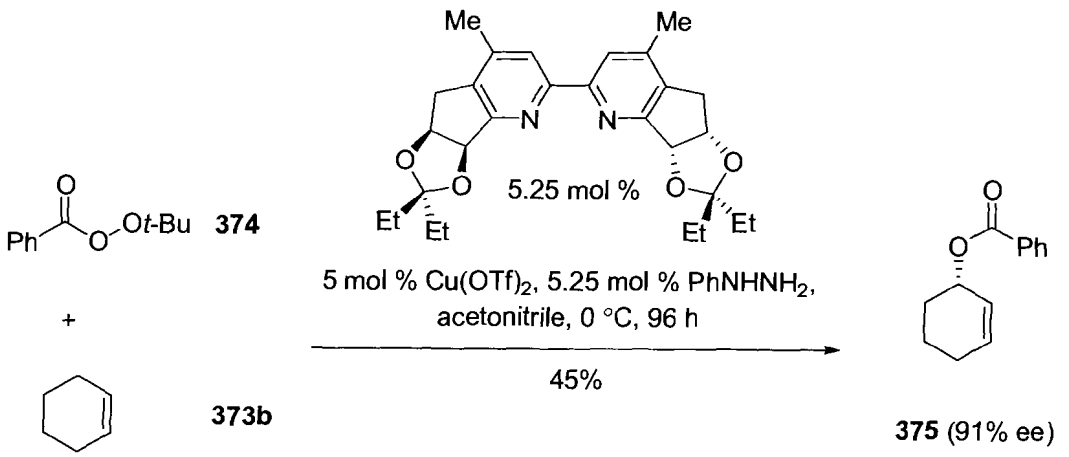
We also employed the ligand (+)-**333** in related conjugate addition reactions of the indole **367a** and 3-methoxyphenol **371** to (3*E*)-2-oxo-4-phenyl-3-butenoic acid methyl ester **365**. In the case of indole **367a**, the conjugate addition product **370** was

formed in excellent yield (97%) and good enantiomeric excess (59%). In the case of the reaction with 3-methoxyphenol, the product of the initial conjugate addition reactions underwent a subsequent intramolecular F-C reaction to afford the novel chromane derivative **372**, as a single diastereoisomer, in moderate enantiomeric excess (42%) and in good yield (62%). In order to gain insight into the active catalyst in these Friedel-Crafts alkylation reactions, the copper(II) chloride (+)-**333** complex was prepared and analyzed by X-ray crystallography. This analysis revealed a distorted square-planar geometry around the copper(II) centre. It was observed that the copper(II) chloride (+)-**333** complex had a remarkably high specific optical rotation. An optical rotary dispersion spectrum was recorded that displayed a maximum positive specific rotation was + 2.3 x 10^4 at 293 nm and a maximum negative specific rotation was - 1.2 x 10^4 at 332 nm.

Finally, the ligand (+)-**333** was evaluated in copper(I)-catalyzed asymmetric allylic oxidation reactions of a series of cyclic alkenes **373a-c** using *tert*-butyl peroxybenzoate **374**. The reaction conditions involved formation of the catalyst *in situ* by reduction of the complex formed between 5.0 mol % of copper(II) triflate and 5.25 mol % of the chiral ligand (+)-**333** with phenylhydrazine in either acetone or acetonitrile. A broad range of enantioselectivities were obtained (32 to 91% ee) that depended on the substrate and the reaction conditions employed. The best result was obtained in the asymmetric allylic oxidation reaction of cyclohexene **373b** with *tert*-butylperoxybenzoate **374** in acetonitrile at 0 °C which afforded the product **375b** in high enantiomeric excess (91%) (Scheme 5.11.3.). This result represents the highest reported enantioselectivity in an asymmetric allylic oxidation with a chiral 2,2′-bipyridyl ligand. Moreover, the rates

of these reactions were greater than have been observed for reactions with *bis*oxazoline derived catalysts.

Scheme 5.11.3. Asymmetric Allylic Oxidation Reaction employing the C_2-Symmetric 2,2′-Bipyridyl Ligand (+)-**333**



CHAPTER 6: FUTURE WORK

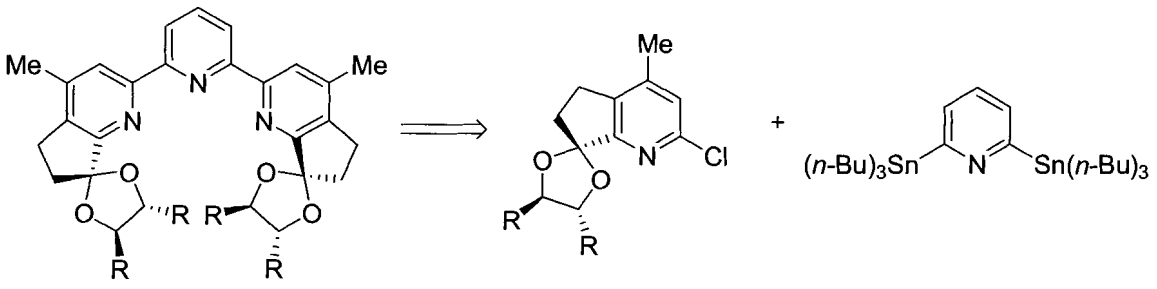
6.1. Synthesis and Evaluation of New Chiral Nonracemic C_2-Symmetric Tripyridine Ligands

In Chapter 2 of this thesis, the synthesis and evaluation of series of chiral nonracemic C_2-symmetric 2,2′-bipyridyl ligands **267a-c** (R = Me, *i*-Pr and Ph) was described. In the course of subsequent investigations into the use of the 2,2′-bipyridyl ligands **267a-c** as chiral directors it was discovered that these ligands displayed coordination properties with copper salts that were detrimental to the stereoselectivity of the copper-catalyzed asymmetric reactions. Future studies with these ligands will involve their evaluation in asymmetric reactions that are catalyzed by transition metals other than copper.

In order to further demonstrate the modular and divergent nature of the synthetic design described in this thesis, future work on this project will also involve the synthesis and evaluation of a series of chiral nonracemic C_2-symmetric tripyridine ligands **379a-c** (R = Me, *i*-Pr and Ph) (Figure 6.1.1.). These ligands could be prepared from the corresponding 2-chloropyridines **268a-c** and the known *bis*-stannane **380** by palladium(0)-catalyzed Stille coupling reactions.[172]

---

(172) Hanan, G. S.; Schubert, U. S.; Volkmer, D.; Riviere, E.; Lehn, J.-M.; Kyritsakas, N.; Fischer, J. Synthesis. Structure and Properties of *oligo*-Tridentate Ligands: Covalently Assembled Precursors of Coordination Arrays. *Can. J. Chem.* **1997**, *75*, 169.



379a-c (R = Me, *i*-Pr and Ph) **268a-c** (R = Me, *i*-Pr and Ph) **380**

Figure 6.1.1. Retrosynthetic analysis of the chiral nonracemic C_2-symmetric tripyridine ligands **379a-c** (R = Me, *i*-Pr and Ph).

These ligands would then be evaluated as chiral directors in scandium(III)-catalyzed asymmetric reactions. Scandium(III)-catalyzed reactions are particularly interesting because they are of broad scope and often involve the formation of carbon-carbon bonds. These reaction types include; Diels-Alder reactions, aza Diels-Alder reactions, 1,3-dipolar cycloaddition reactions, Friedel-Crafts alkylation reactions and nucleophilic ring-opening reactions of *meso*-epoxides.[173]

6.2. Modification and Optimization of the Structural Features of the Chiral Nonracemic C_2-Symmetric 2,2′-Bipyridyl Ligand [(+)-333] and Evaluation in Asymmetric Reactions

In Chapter 5 of this thesis, the synthesis and evaluation of a new chiral nonracemic C_2-symmetric 2,2′-bipyridyl ligand (+)-**333** was described. This ligand was shown to be an extremely effective chiral director in asymmetric copper(I)-catalyzed

(173) For examples of scandium(III)-catalyzed asymmetric reactions, see: (a) Kobayashi, S. Scandium Triflate in Organic Synthesis. *Eur. J. Org. Chem.* **1999**, 15. (b) Evans, D. A.; Scheidt, K. A.; Fandrick, K. R.; Lam, H. W.; Wu, J. Enantioselective Indole Friedel-Crafts Alkylations Catalyzed by *bis*(Oxazolinyl)pyridine-Scandium(III) Triflate Complexes. *J. Am. Chem. Soc.* **2003**, *125*, 10780. (c) Schneider, C.; Sreekanth, A. R.; Mai, E. Scandium-Bipyridine-Catalyzed Enantioselective Addition of Alcohols and Amines to *meso*-Epoxides. *Angew. Chem., Int. Ed.* **2004**, *43*, 5691.

cyclopropanation reactions, copper(II)-catalyzed asymmetric Friedel-Crafts alkylation reactions and copper(I)-catalyzed asymmetric allylic oxidation reactions. Future work on this project will involve the synthesis of the corresponding *mono-N*-oxide **382** and *N,N'*-dioxide **381** (Figure 6.2.1.). These *N*-oxides would then be evaluated, for example, as chiral catalysts in organocatalytic asymmetric aldol reactions.

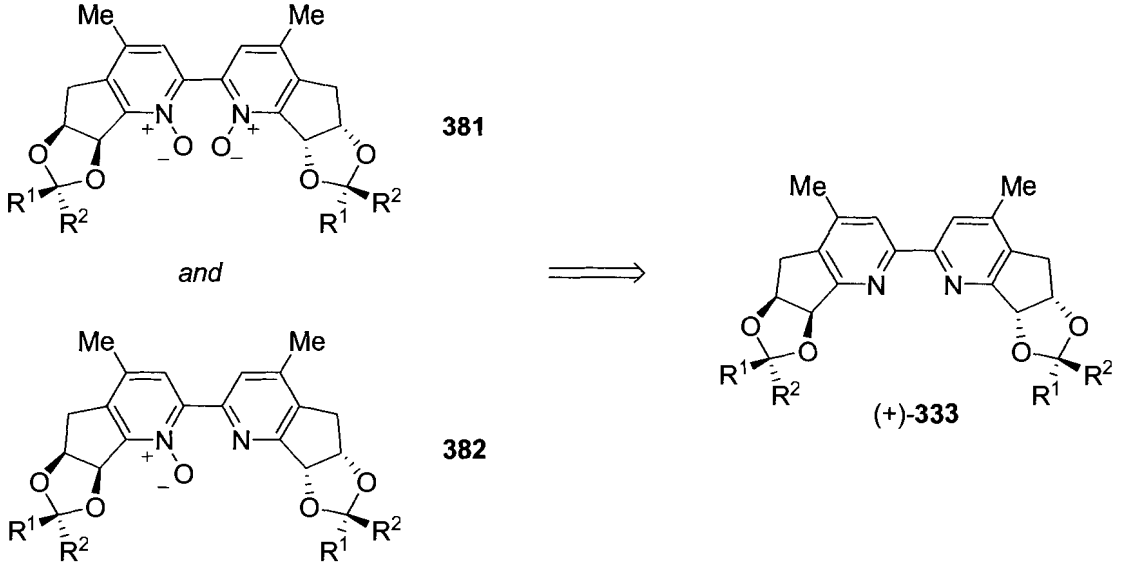


Figure 6.2.1. Retrosynthetic analysis of the chiral pyridine *N*-oxide **382** and *N,N'*-dioxide **381**.

Future work on this project will also involve the optimization of the ligand structure by undertaking the synthesis of a series of related ligands **383** in which the substituents R^1 and R^2 on the chiral cyclic acetal would be varied in order to alter the shape and electronics of the chiral pocket of the catalytic species. The objective here would be to improve the level of asymmetric induction in the reaction types that have already been investigated as well as to study new asymmetric transformations. The C_2-symmetric 2,2'-bipyridyl ligands **383** would be synthesized from the corresponding 2-chloropyridines **384** using a nickel-mediated *homo*-coupling reaction (Figure 6.2.2.). The 2-chloropyridines **384** could be prepared from the chiral diol **335** and a series of

symmetrical and unsymmetrical ketones **385** (R^1 and R^2 = various substituents). In the case of the unsymmetrical ketones **385** ($R^1 \neq R^2$), it is anticipated that their condensation reactions with the diol **335** would be diastereoselective in that the larger substituent should occupy the less sterically congested convex face of these bicyclic molecules.

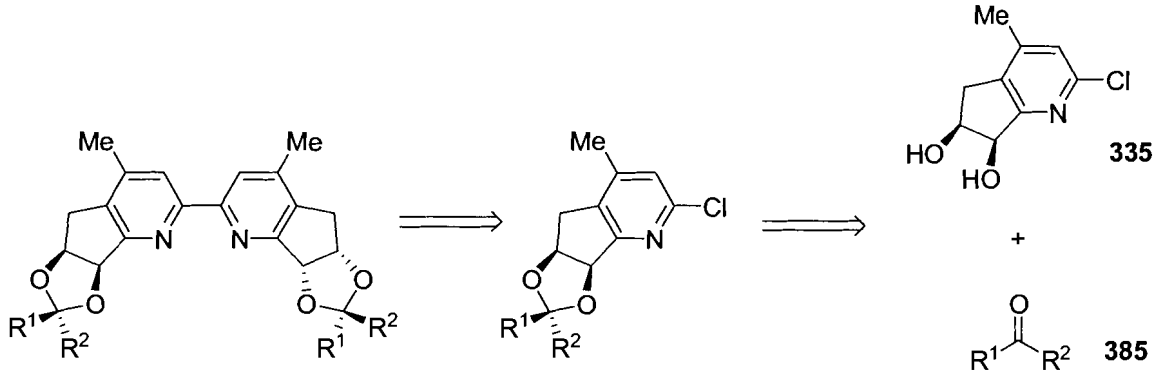


Figure 6.2.2. Retrosynthetic analysis of the chiral nonracemic C_2-symmetric 2,2′-bipyridyl ligands **383** (R^1 and R^2 = various substituents).

Future work on this project will also include the synthesis of a series of the related chiral nonracemic C_2-symmetric tripyridine ligands **386** from the 2-chloropyridines **384** (R^1 and R^2 = various substituents) and the known stannane **380** *via* palladium(0)-catalyzed Stille coupling reactions (Figure 6.2.3.).

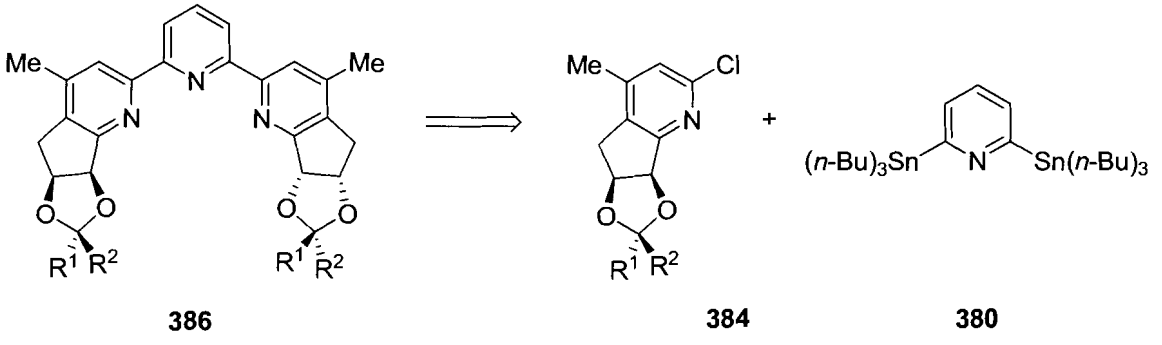


Figure 6.2.3. Retrosynthetic analysis of the chiral nonracemic C_2-symmetric tripyridine ligands **386** (R^1 and R^2 = various substituents).

CHAPTER 7: GENERAL CONCLUSIONS

The research work described in this thesis has concerned the concise and modular synthesis of several new classes of chiral nonracemic ligands and catalysts for use in asymmetric synthesis. A series of chiral nonracemic acetals **268a-c** (R = Me, *i*-Pr and Ph) were prepared from 2-chloro-4-methyl-6,7-dihydro-5*H*-[1]pyrindine-7-one **269** and a variety of C_2-symmetric 1,2-ethanediols **270a-c**. These acetals were further elaborated, in a modular fashion, to a series of chiral ligands and catalysts that were then evaluated in various catalytic asymmetric reactions.

The C_2-symmetric 2,2′-bipyridyl ligands **267a-c** were prepared in one step from the acetals **268a-c** *via* a nickel(0)-mediated *homo*-coupling reaction. Similarly, the corresponding unsymmetric 2,2′-bipyridyl ligands **271a,b** were prepared by a Stille coupling reaction with 2-(tri-*n*-butylstannyl)pyridine **272**. These ligands were then evaluated as chiral directors in copper(I)-catalyzed asymmetric cyclopropanation reactions of styrene and diazoesters. In the course of our investigations it was observed that the stereoselectivities as well as the yields of the cyclopropanation reactions were highly dependant on the ratio of the C_2-symmetric ligand to copper used. The best result was obtained in the asymmetric cyclopropanation of styrene with *tert*-butyl diazoacetate with the ligand **267b** (R = *i*-Pr) which afforded the reaction product in good diastereoselectivity (83:17) and moderate enantioselectivity (44% ee). The unsymmetric 2,2′-bipyridyl ligands **271a,b** were found to be poor chiral directors in asymmetric cyclopropanation reactions. Interestingly, a copper(I) complex of the C_2-symmetric ligand **267c** was found to have a large specific optical rotation (+ 1.1 x 10^4 at 304 nm).

The chiral pyridine *N*-oxide **299** and the C_2-symmetric 2,2′-bipyridyl *N,N′*-dioxide **301** were prepared by direct oxidation of the chiral acetal **300** and the 2,2′-bipyridyl ligand **267c**, respectively. These chiral *N*-oxides **299** and **301** were then evaluated as chiral catalysts in desymmeterization reactions of *cis*-stilbene oxide with silicon tetrachloride. The chiral pyridine *N*-oxide **299** was catalytically active in this reaction and afforded the desired product in good yield (95%) but in low enantioselectivity (20% ee). The 2,2′-bipyridyl *N,N′*-dioxide did not catalyze this desymmeterization reaction.

A series of *P,N*-ligands **304a-c** was subsequently prepared in two steps from the chiral acetals **268a-c** by a Suzuki coupling with *ortho*-fluorophenylboronic acid and subsequent displacement of the fluoride with the potassium anion of diphenylphosphine. These ligands were then evaluated as chiral directors in palladium-catalyzed asymmetric Heck reactions of 2,3-dihydrofuran and phenyltriflate. The best and only result was obtained with the *P,N*-ligand **304a** (R = Me) which afforded the desired reaction product in reasonable yield (59%) and moderate enantioselectivity (20% ee). The ligands were subsequently evaluated in palladium-catalyzed asymmetric allylic substitution reactions of racemic 3-acetoxy-1,3-diphenyl-1-propene *RS*-**310** with dimethyl malonate **311**. The best result was obtained when the *P,N*-ligand **304c** (R = Ph) was used with cesium carbonate as the base in dichloromethane at 0 °C which afforded the corresponding reaction product in excellent yield (91%) and high enantiomeric excess (90%).

A related chiral C_2-symmetric 2,2′-bipyridyl ligand (+)-**333**, that was conceived by considering a subtle modification to the cyclic acetal moiety of the first generation ligands, was prepared from 2-chloro-4-methyl-5*H*-[1]pyrindine. This pyrindine was prepared from the acetate **282** that was an intermediate used in the synthesis of the 2,2′-

bipyridines **267a-c** and the *P,N*-ligands **304a-c**. The chirality of this ligand was installed by a highly enantioselective Sharpless dihydroxylation reaction (90% ee). This is the highest enantioselectivity obtained in a catalytic asymmetric dihydroxylation of a cyclic *cis*-alkene. The subsequently elaborated 2,2′-bipyridyl ligand (+)-**333** (>99% ee) was found to be a much more efficient chiral director than the C_2-symmetric 2,2′-bipyridyl ligands **267a-c** and the corresponding unsymmetric 2,2′-bipyridyl ligands **271a,b** that were described in Chapter 2. It is inferred that the modified ligand (+)-**333** did not have a propensity to form *bis*-ligated copper(I) complexes. The ligand was evaluated in copper(I)-catalyzed asymmetric cyclopropanation reactions of various styrenes **353a-g** and diazoesters **354a-c**. The best result was obtained in the reaction of *para*-fluorostyrene **353c** and *tert*-butyl diazoacetate **354c** which afforded the reaction product in good diastereoselectivity (92:8) and in excellent enantioselectivity (99% ee). This is the highest enantioselectivity obtained in an asymmetric cyclopropanation reaction with a chiral bipyridine ligand. The ligand (+)-**333** was also evaluated in copper(II)-catalyzed asymmetric Friedel-Crafts alkylation reactions. This included the reactions of various substituted indoles **367a-g** with the methyl and ethyl esters of 3,3,3-trifluoropyruvic acid **368a,b**. The best result was observed in the reaction of indole **367a** with methyl 3,3,3-trifluoropyruvate **368a** which afforded the corresponding reaction product in good yield (77%) and in good enantioselectivity (90% ee). Finally, the ligand (+)-**333** was evaluated in the copper(I)-catalyzed asymmetric allylic oxidation reaction of cyclic alkenes **373a-c** using *tert*-butyl peroxybenzoate **374**. A broad range of enantioselectivities were obtained that depended on the substrate and reaction conditions employed. However good catalytic activity was observed in all cases. The best result was obtained in the

asymmetric allylic oxidation reaction of cyclohexene **373b** in acetonitrile which afforded the corresponding reaction product in high enantioselectivity (91% ee). A copper(II) complex of this ligand was also found to have a high specific optical rotation (+ 2.3 x 10^4 at 293 nm).

CHAPTER 8: EXPERIMENTAL SECTION

8.1. General Experimental Details

All non-aqueous reactions were performed under an atmosphere of dry nitrogen in oven- or flame-dried glassware, unless indicated otherwise. The reaction temperatures stated were those of the external bath. Diethyl ether (ether) and tetrahydrofuran (THF) were dried over sodium/benzophenone ketyl and distilled under an atmosphere of dry nitrogen immediately prior to use. Benzene, toluene, dichloromethane, pyridine, *N*,*N*-diisopropylamine and triethylamine were dried over calcium hydride and distilled under an atmosphere of dry nitrogen immediately prior to use. All other solvents and reagents were purified by standard techniques or used as supplied.[174] Brine refers to a saturated aqueous solution of sodium chloride. Silica gel column chromatography ("flash chromatography") was carried out using Merck silica gel 60 (230 to 400 mesh).[175] Melting points were measured on a Gallenkamp capillary melting point apparatus and are uncorrected. Optical rotations were recorded on a Perkin Elmer 341 polarimeter. All proton and carbon and phosphorus nuclear magnetic resonance spectra (^{1}H, ^{13}C and ^{31}P NMR, respectively) were recorded using a Bruker AMX 400 FT spectrometer (operating frequencies: ^{1}H, 400.13 MHz; ^{13}C, 100.61 MHz; ^{31}P, 161.97 MHz) at ambient temperature. The ^{1}H and ^{13}C chemical shifts (δ) for all compounds are listed in parts per million downfield from tetramethylsilane using the NMR solvent as an internal reference. The reference values used for deuterated chloroform ($CDCl_3$) were 7.26 and 77.16 ppm

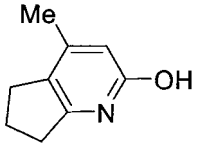
(174) Armarego, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals*, 4th ed.; Oxford: Butterworth-Heinemann, 1997.

(175) Still, W. C.; Kahn, M.; Mitra, A. Rapid Chromatographic Technique for Preparative Separations with Moderate Resolution. *J. Org. Chem.* **1978**, *43*, 2923.

for ^{1}H and ^{13}C NMR spectra, respectively. The reference values used for deuterated benzene (C_6D_6) were 7.15 and 128.02 ppm, respectively. The reference value used for deuterated acetone (acetone-D_6) was 30.83 ppm for ^{13}C NMR spectra. The ^{31}P chemical shifts (δ) are listed in parts per million downfield from phosphoric acid which was employed as an external reference. Infrared spectra (IR) were recorded as either KBr pellets (KBr), evaporated films (ef) or as films (neat) using a Perkin Elmer 599B IR spectrophotometer. Low-resolution mass spectra (MS) were recorded on a Hewlett Packard 5985 GC-mass spectrometer. The mode of ionization used was chemical ionization (CI) with isobutane. Matrix-assisted laser desorption/ionization time-of-flight mass spectra (MALDI-TOF) using 2,5-dihydroxybenzoic acid as the matrix were recorded on a PerSeptive Biosystems Voyager-DE spectrometer. High-resolution mass spectra using fast atom bombardment (FAB HRMS) were recorded on a Kratos Concept IH mass spectrometer. Microanalyses were performed on a Carlo Erba Model 1106 CHN analyzer. Analytical chiral high performance liquid chromatography (HPLC) was performed on a Hewlett Packard Series 1050 instrument. All HPLC separations were performed on a Daicel Chiracel OD column. Chiral gas chromatography (GC) was performed on a Varian 3400 instrument. All GC separations were performed on a J & W Scientific cyclosilb column. Optical rotary dispersion spectra were recorded on a Jasco J-810 spectropolarimeter. UV-Vis spectra were recorded on a Varian Cary 300 spectrophotometer. All compounds described in this experimental section were fully characterized (including elemental analyses or high-resolution mass spectrometry).

8.2. Experimental Procedures and Characterization Data Concerning Chapter 2

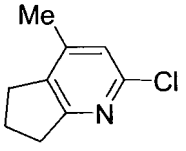
8.2.1. *4-Methyl-6,7-dihydro-5*H*-[1]pyrindine-2-ol* (280)[116]



280

A mixture of cyclopentanone (25.2 g, 300 mmol), ethyl acetoacetate (39.0 g, 300 mmol) and ammonium acetate (23.1 g, 300 mmol) was heated at reflux for 8 h. The reaction mixture was then allowed to cool to room temperature and following dilution with ether (25 mL) was allowed to stand overnight during which time the product precipitated from the reaction mixture. The product was isolated by filtration, washed with ether (50 mL) and recrystallized from ethanol (100 mL) to afford the *title compound* **280** (10.2 g, 23%) as a yellow crystalline solid. **M.p.** 243-244 °C, ethanol (lit.[116] 243-244 °C, ethanol); **^{1}H NMR** ($CDCl_3$) δ 2.05-2.15 (5H, m, $ArCH_2CH_2$ and CH_3), 2.66 (2H, apparent t, J = 7.0 Hz, $ArCH_2$), 2.92 (2H, apparent t, J = 7.6 Hz, $ArCH_2$), 6.22 (1H, s, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 20.0, 22.70, 28.7, 31.5, 115.5, 121.2, 149.0, 151.4, 166.3; **IR** (KBr) 2912 (broad), 1653, 1621, 1578, 1447, 1425, 1371, 1327, 1221, 933, 901, 860 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 150 (M + H, 100).

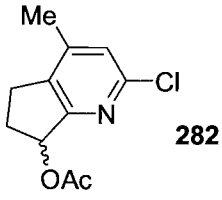
8.2.2. *2-Chloro-4-methyl-6,7-dihydro-5H-[1]pyrindine* (281)[116]



281

To phenylphosphonic dichloride (1.00 mL, 7.08 mmol) was added the pyridine-2-ol **280** (500 mg, 3.36 mmol) and the resultant mixture was heated in an oil bath at 160 °C for 16 h. The reaction mixture was then allowed to cool to room temperature and water (~5 mL) was added dropwise (*CAUTION*). The acidic reaction mixture was then diluted with an additional quantity of water (50 mL), neutralized by the careful addition of potassium carbonate (~1.0 g) and extracted with chloroform (3 x 30 mL). The combined organic extracts were washed with water (2 x 20 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford the crude product as a dark brown oil. Flash chromatography using chloroform as the eluant afforded the *title compound* **281** (465 mg, 83%) as a white crystalline solid. **M.p.** 41-42 °C, chloroform; **^{1}H NMR** ($CDCl_3$) δ 2.12 (2H, m, $ArCH_2CH_2$), 2.22 (3H, s, CH_3), 2.81 (2H, apparent t, J = 7.9 Hz, $ArCH_2$), 2.98 (2H, apparent t, J = 8.3 Hz, $ArCH_2$), 6.90 (1H, s, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 20.1, 22.7, 28.7, 31.4, 115.3, 121.6, 149.0, 151.7, 166.1; **IR** (KBr) 1654, 1621, 1578, 1425, 1327 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 168 (M + H, 100); **Anal.** Calcd. for $C_9H_{10}ClN$: C, 64.48; H, 6.01; N, 8.36. Found: C, 64.29; H, 5.92; N, 8.30.

8.2.3. *7*(RS)-*7-Acetoxy-2-chloro-4-methyl-6,7-dihydro-5H-[1]pyrindine* (282)[119]

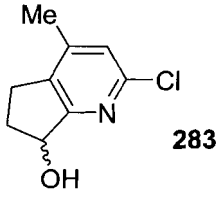


282

To a stirred solution of the chloropyridine **281** (3.00 g, 17.9 mmol) in glacial acetic acid (25 mL) was added an aqueous solution of hydrogen peroxide (30% w/w, 8.60 mL, 75.9 mmol) and the resultant mixture was heated at 80 °C for 16 h. The reaction mixture was then allowed to cool to room temperature and following concentration *in vacuo* was diluted with water (100 mL). The slightly acidic solution was neutralized by the careful addition of potassium carbonate (~1.0 g) and then extracted with chloroform (3 x 30 mL). The combined organic extracts were washed with water (3 x 15 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford the corresponding pyridine *N*-oxide (3.22 g, 98%) as a white crystalline solid. This material was taken up in acetic anhydride (25 mL) and the resultant suspension was stirred at room temperature for 1 h and then heated at 100 °C for 4 h. The reaction mixture was then allowed to cool to room temperature and was concentrated *in vacuo* to afford the crude product as a dark brown oil. Flash chromatography using hexanes:ether (1:1) as the eluant afforded the *title compound* **282** (2.42 g, 60% over two steps) as an orange oil. **^{1}H NMR** ($CDCl_3$) δ 2.01-2.10 (4H, m, CH_3 and $ArCH_2CHH$), 2.27 (3H, s, OAc), 2.58-2.68 (1H, m, $ArCH_2CHH$), 2.76 (1H, m, $ArCHH$), 2.94 (1H, m, $ArCHH$), 6.00 (1H, dd, J = 7.6, 4.6 Hz, $CHOAc$), 7.06 (1H, s, ArH); **^{13}C NMR** ($CDCl_3$) δ 18.7, 21.1, 26.0, 28.2, 30.4, 124.4, 136.1, 147.1, 150.6, 159.9, 170.6; **IR** (neat) 2946, 1738, 1592, 1571, 1443, 1370, 1235, 1193, 1106, 1050, 890 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 226 (M + H, 100), 166 (38);

Anal. Calcd. for $C_{11}H_{12}ClNO_2$: C, 58.54; H, 5.36; N, 6.21. Found: C, 58.79; H, 5.37; N, 6.11.

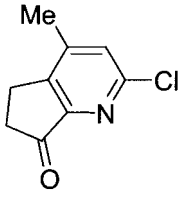
8.2.4. *7(RS)-2-Chloro-4-methyl-6,7-dihydro-5H-[1]pyrindine-7-ol* (283)



283

To a stirred solution of the acetate **282** (2.00 g, 8.88 mmol) in tetrahydrofuran:water (3:1, 20 mL) was added lithium hydroxide monohydrate (1.49 g, 35.6 mmol) and the resultant solution was stirred at room temperature for 16 h. The reaction mixture was then diluted with water (15 mL) and extracted with chloroform (3 x 25 mL). The combined organic extracts were washed with brine (15 mL) and water (15 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford the crude product. Flash chromatography using hexanes:ether (1:1) as the eluant afforded the *title compound* **283** (1.37 g, 94%) as a white crystalline solid. **M.p.** 100-102 °C; hexanes/ether; **^{1}H NMR** ($CDCl_3$) δ 1.99-2.16 (1H, m, $ArCH_2CHH$), 2.24 (3H, s, CH_3), 2.47-2.57 (1H, m, $ArCH_2CHH$), 2.67-2.72 (1H, m, ArCHH), 2.92 (1H, ddd, J = 13.1, 8.9, 4.0 Hz, ArCHH), 3.82 (1H, broad s, OH), 5.19 (1H, dd, J = 7.3, 5.8 Hz, CHOH), 6.99 (1H, s, ArH); **^{13}C NMR** ($CDCl_3$) δ 18.8, 25.9, 32.5, 74.7, 124.0, 135.0, 147.6, 150.4, 164.8; **IR** (KBr) 1594, 1567, 1445, 1374, 1298, 1191, 1094, 1064, 1019, 965, 925, 888, 861 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 184 (M + H, 100), 166 (20); **Anal.** Calcd. for $C_9H_{10}ClNO$: C, 58.86; H, 5.49; N, 7.63. Found: C, 58.62; H, 5.62; N, 7.46.

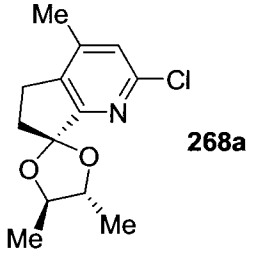
8.2.5. *2-Chloro-4-methyl-6,7-dihydro-5H-[1]pyrindine-7-one* (269)



269

To a stirred solution of oxalyl chloride (57 μL, 0.65 mmol) in dichloromethane (6 mL) at -78 °C was added dimethyl sulfoxide (150 μL, 2.18 mmol) and the resultant solution was stirred for 10 min. A solution of the alcohol **283** (100 mg, 0.545 mmol) in dichloromethane (5 mL) was then added *via* a cannula over the course of 5 min. The reaction mixture was stirred for an additional 10 min and triethylamine (380 μL, 2.73 mmol) was then added and the reaction mixture was allowed to warm slowly to room temperature. The reaction mixture was then diluted with ether (30 mL) and washed with brine (3 x 5 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford the crude product. Flash chromatography using hexanes:ether (1:1) as the eluant afforded the *title compound* **269** (89 mg, 90%) as a white crystalline solid. **M.p.** 149-152 °C; hexanes/ether; **^{1}H NMR** ($CDCl_3$) δ2.38 (3H, s, CH_3), 2.69-2.78 (2H, m, $ArCH_2CH_2$), 2.96-3.06 (2H, m, $ArCH_2$), 7.26 (1H, s, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 17.6, 21.8, 34.8, 128.4, 148.6, 149.31, 153.0, 153.5, 203.7; **IR** (KBr) 1714, 1587, 1439, 1421, 1285, 1256, 1203, 1112, 871, 570 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 182 (M + H, 100); **Anal.** Calcd. for C_9H_8ClNO: C, 59.52; H, 4.44; N, 7.71. Found: C, 59.44; H, 4.44; N, 7.67.

8.2.6. *2-Chloro-4-methyl-6,7-dihydro-5H-[1]pyrindine-7-one (2R,3R)-2,3-Butanediol Acetal* (268a)

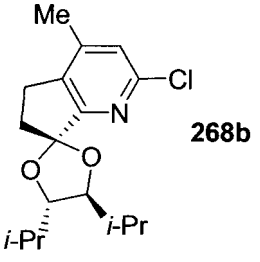


268a

To a stirred solution of the chloroketone **269** (101 mg, 0.550 mmol) in benzene (3 mL) was added (2*R*,3*R*)-2,3-butanediol **270a** (76 μL, 0.83 mmol) and *para*-toluenesulfonic acid monohydrate (16 mg, 83 μmol) and the resultant solution was heated at reflux in a Dean-Stark apparatus for 16 h. The reaction mixture was then allowed to cool to room temperature and potassium carbonate (100 mg) was added. After an additional 10 min, the reaction mixture was filtered and the filter-cake was washed with ether (10 mL). The combined filtrates were concentrated *in vacuo* to afford the crude product. Flash chromatography using hexanes:ether (2:1) as the eluant afforded the *title compound* **268a** (119 mg, 85%) as a white crystalline solid. **M.p.** 84-86 °C, hexanes/ether; $[\alpha]_D^{20}$ - 24.7 (*c* 1.15, chloroform); **^{1}H NMR** (C_6D_6) δ 1.14 (3H, d, J = 6.1 Hz, CHCH_3), 1.38 (3H, d, J = 6.1 Hz, CHCH_3), 1.47 (3H, s, CH_3), 2.19-2.25 (2H, m, ArCH$_2$CH_2), 2.37-2.43 (2H, m, ArCH_2), 3.73 (1H, dq, J = 6.1, 8.2 Hz, OC*H*), 4.68 (1H, dq, J = 6.1, 8.2 Hz, OC*H*), 6.61 (1H, s, Ar*H*); **^{13}C NMR** (C_6D_6) δ 17.1, 17.9, 18.1, 24.1, 36.7, 79.8, 80.5, 114.6, 124.9, 134.8, 147.4, 151.7, 163.6; **IR** (KBr) 2980, 2935, 2978, 1594, 1457, 1443, 1377, 1316, 1296, 1264, 1228, 1204, 1183, 1161, 1130, 1112, 1085, 1048, 978, 938, 899, 873, 865, 833 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 254 (M + H, 100),

182 (33); **Anal.** Calcd. for $C_{13}H_{16}ClNO_2$: C, 61.54; H, 6.36; N, 5.52. Found: C, 61.48; H, 6.41; N, 5.49.

8.2.7. *2-Chloro-4-methyl-6,7-dihydro-5H-[1]pyrindine-7-one (1S,2S)-1,2-Diisopropyl-1,2-ethanediol Acetal* (268b)

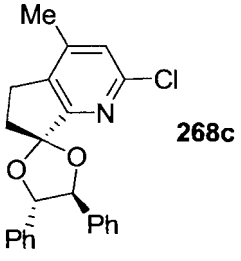


268b

To a stirred solution of the chloroketone **269** (251 mg, 1.38 mmol) in benzene (8 mL) was added (1*S*,2*S*)-1,2-diisopropyl-1,2-ethanediol **270b**[115] (221 mg, 1.52 mmol) and *para*-toluenesulfonic acid monohydrate (40 mg, 0.21 mmol) and the resultant solution was heated at reflux in a Dean-Stark apparatus for 16 h. The reaction mixture was then allowed cool to room temperature and potassium carbonate (100 mg) was added. After an additional 10 min, the reaction mixture was filtered and the filter-cake was washed with ether (25 mL). The combined filtrates were concentrated *in vacuo* to afford the crude product. Flash chromatography using hexanes:ether (4:1) as the eluant afforded the *title compound* **268b** (380 mg, 89%) as a colourless oil that crystallized upon standing. **M.p.** 34-35 °C; $[\alpha]_D^{20}$ - 30.8 (*c* 1.10, chloroform); **^{1}H NMR** ($CDCl_3$) δ 0.93 (3H, d, J = 6.9 Hz, CHCH_3), 0.95 (3H, d, J = 6.5 Hz, CHCH_3), 0.99 (3H, d, J = 6.9 Hz, CHCH_3), 1.01 (3H, d, J = 6.5 Hz, CHCH_3), 1.77-1.87 (1H, m, CH(CH$_3$)$_2$), 2.16-2.28 (4H, m, CH$_3$ and CH(CH$_3$)$_2$), 2.33-2.38 (2H, m, ArCH$_2$CH_2), 2.71-2.78 (2H, m, ArCH_2), 3.63 (1H, dd, J = 5.5, 7.6 Hz, OCH), 4.11 (1H, apparent t, J = 5.8 Hz, OCH), 7.02 (1H, s, ArH); **^{13}C NMR** ($CDCl_3$) δ 17.6, 18.4, 19.0, 19.7, 20.2, 24.0, 31.5, 31.7, 37.1, 86.0, 86.1, 114.8,

124.8, 135.1, 147.3, 151.3, 161.7; **IR** (KBr) 2961, 1594, 1442, 1384, 1318, 1299, 1202, 1170, 1056, 922, 865, 631 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 310 (M + H, 100), 182 (20); **Anal.** Calcd. for $C_{17}H_{24}ClNO_2$: C, 65.90; H, 7.81; N, 4.52. Found: C, 65.72; H, 7.85; N, 4.49.

8.2.8. *2-Chloro-4-methyl-6,7-dihydro-5H-[1]pyrindine-7-one (1S,2S)-1,2-Diphenyl-1,2-ethanediol Acetal* (268c)

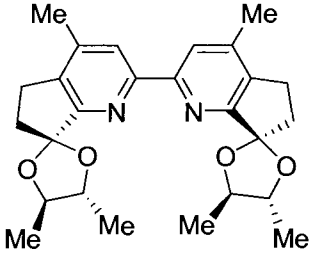


268c

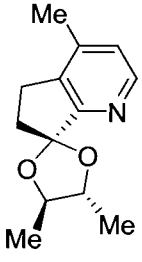
To a stirred solution of the chloroketone **269** (100 mg, 0.551 mmol) in benzene (3 mL) was added (1*S*,2*S*)-1,2-diphenyl-1,2-ethanediol **270c** (152 mg, 0.709 mmol) and *para*-toluenesulfonic acid monohydrate (16 mg, 0.083 mmol) and the resultant solution was heated at reflux in a Dean-Stark apparatus for 16 h. The reaction mixture was then allowed cool to room temperature and potassium carbonate (100 mg) was added. After an additional 10 min, the reaction mixture was filtered and the filter-cake was washed with ether (10 mL). The combined filtrates were concentrated *in vacuo* to afford the crude product. Flash chromatography using hexanes:ether (4:1) as the eluant afforded the *title compound* **268c** (163 mg, 79%) as a colourless oil that crystallized upon standing. **M.p.** 44-46 °C, hexanes/ether; $[\alpha]_D^{20}$ - 108 (*c* 0.38, chloroform); **^{1}H NMR** (C_6D_6) δ 1.54 (3H, s, CH_3), 2.26-2.32 (2H, m, $ArCH_2CH_2$), 2.51-2.65 (2H, m, $ArCH_2$), 4.99 (1H, d, *J* = 8.9 Hz, OC*H*), 5.99 (1H, d, *J* = 8.9 Hz, OC*H*), 6.68 (1H, s, Ar*H*), 7.07-7.15 (4H, m, Ar*H*), 7.18-7.29 (4H, m, Ar*H*), 7.74-7.79 (2H, m, Ar*H*); **^{13}C NMR** (C_6D_6) δ 17.4, 23.5,

36.3, 86.5, 87.2, 115.0, 124.8, 127.2, 128.5, 128.6, 130.5, 131.9, 134.8, 136.9, 137.4, 143.0, 147.1, 151.4, 162.3; **IR** (KBr) 2914, 2362, 2336, 1594, 1570, 1496, 1453, 1443, 1384, 1320, 1298, 1267, 1229, 1201, 1160, 1113, 1059, 1021, 939, 925, 879, 759, 699 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 378 (M + H, 41), 271 (27), 182 (100); **Anal.** Calcd. for $C_{23}H_{20}ClNO_2$: C, 73.11; H, 5.33; N, 3.71. Found: C, 72.96; H, 5.39; N, 3.78.

8.2.9. ***Preparation of 4,4'-Dimethyl-6,6',7,7'-tetrahydro-5H,5'H-2,2'-bi([1]pyrindinyl)-7,7'-dione (2R,3R)-2,3-Butanediol* bis-*Acetal* (267a) *and 4-Methyl-6,7-dihydro-5H-[1]pyrindin-7-one (2R,3R)-2,3-Butanediol Acetal* (286) *from the 2-Chloropyridine* (268a)**



267a *and*

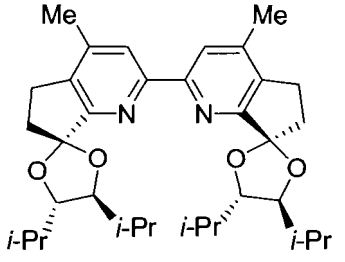


286

To a stirred solution of dibromo*bis*(triphenylphosphine)nickel(II) (1.17 g, 1.58 mmol) in degassed tetrahydrofuran (30 mL) were added zinc dust (<10 microns, 310 mg, 4.74 mmol) and tetraethylammonium iodide (812 mg, 3.16 mmol). The reaction mixture was stirred at room temperature for 30 min and then a solution of the 2-chloropyridine **268a** (800 mg, 3.16 mmol) in degassed tetrahydrofuran (12 mL) was added *via* a cannula. The resultant mixture was heated at 60 °C for 72 h and then allowed to cool to room temperature. The reaction mixture was poured into an aqueous solution of ammonium hydroxide (10% w/w, 200 mL) and was extracted with a mixture of ether and benzene (1:1, 3 x 100 mL). The combined organic extracts were washed with water (2 x 20 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo* to afford the crude

product. Flash chromatography using chloroform as the eluant afforded the *title compound* **267a** (242 mg, 35%) as white crystalline solid and the *title compound* **286** (269 mg, 39%) as a white crystalline solid. *Title compound* **286**: **M.p.** 52-54 °C, chloroform; $[\alpha]_D^{20}$ - 14.9 (*c* 1.02, chloroform); **^{1}H NMR** ($CDCl_3$) δ 1.33 (3H, d, J = 6.1 Hz, CH_3), 1.41 (3H, d, J = 6.1 Hz, CH_3), 2.25 (3H, s, ArCH_3), 2.35-2.41 (2H, m, ArCH$_2$CH_2), 2.79-2.86 (2H, m, ArCH_2), 3.77 (1H, dq, J = 6.1, 7.8 Hz, CHCH$_3$), 4.32 (1H, dq, J = 6.1, 8.0 Hz, CHCH$_3$), 7.00 (1H, d, J = 4.9 Hz, ArH), 8.40 (1H, d, J = 4.9 Hz, ArH); **^{13}C NMR** ($CDCl_3$) δ 16.7, 16.8, 18.2, 24.3, 36.2, 79.4, 114.1, 124.7, 135.9, 144.4, 149.4, 161.0; **IR** (KBr) 2974, 2921, 2862, 1602, 1448, 1378, 1331, 1303, 1192, 1162, 1094, 926 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 220 (M + H, 100), 148 (8); **Anal.** Calcd. for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.07; H, 7.84; N, 6.32. *Title compound* **267a**: **M.p.** 292-294 °C, chloroform; $[\alpha]_D^{20}$ - 53.7 (*c* 0.99, chloroform); **^{1}H NMR** ($CDCl_3$) δ 1.35 (6H, d, J = 6.1 Hz, CHCH_3), 1.57 (6H, d, J = 6.0 Hz, CHCH_3), 2.33 (6H, s, ArCH_3), 2.41-2.49 (4H, m, ArCH$_2$CH_2), 2.83-2.89 (4H, m, ArCH_2), 3.84 (2H, dq, J = 6.0, 8.0 Hz, CHCH$_3$), 4.55 (2H, dq, J = 6.0, 7.8 Hz, CHCH$_3$), 8.21 (2H, s, ArH); **^{13}C NMR** ($CDCl_3$) δ 16.8, 17.6, 18.6, 24.3, 36.1, 79.0, 79.6, 114.4, 122.1, 135.5, 144.5, 156.5, 160.8; **IR** (KBr) 2982, 2970, 2935, 2896, 1591, 1432, 1423, 1379, 1321, 1293, 1204, 1181, 1162, 1095, 1076, 1059 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 437 (M + H, 100), 365 (45), 167 (48); **Anal.** Calcd. for $C_{26}H_{32}N_2O_4$: C, 71.53; H, 7.39; N, 6.42. Found: C, 71.38; H, 7.22; N, 6.26.

8.2.10. *4,4'-Dimethyl-6,6',7,7'-tetrahydro-5H,5'H-2,2'-bi([1]pyrindinyl)-7,7'-dione (1S,2S)-1,2-Diisopropyl-1,2-ethanediol* bis-*Acetal* (267b)

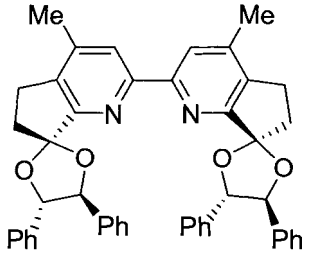


267b

To a stirred solution of dibromo*bis*(triphenylphosphine)nickel(II) (609 mg, 0.82 mmol) in degassed tetrahydrofuran (12 mL) were added zinc dust (<10 microns, 162 mg, 2.48 mmol) and tetraethylammonium iodide (424 mg, 1.65 mmol). The reaction mixture was stirred at room temperature for 30 min and then a solution of the 2-chloropyridine **268b** (511 mg, 1.65 mmol) in degassed tetrahydrofuran (6 mL) was added *via* a cannula. The resultant mixture was heated at 60 °C for 72 h and then was allowed to cool to room temperature. The reaction mixture was poured into an aqueous solution of ammonium hydroxide (10% w/w, 200 mL) and was extracted with ether (3 x 50 mL). The combined organic extracts were washed with water (2 x 20 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo* to afford the crude product. Flash chromatography using hexanes:ether (10:1) as the eluant afforded the *title compound* **267b** (326 mg, 72%) as a white crystalline solid. **M.p.** 166-167 °C, hexanes/ether; $[\alpha]_D^{20}$ - 44.3 (*c* 0.37, chloroform); **^{1}H NMR** ($CDCl_3$) δ 0.99-1.08 (24H, m, $CHCH_3$), 1.82-1.95 (2H, m, $CHCH_3$), 2.31 (6H, s, $ArCH_3$), 2.39-2.45 (4H, m, $ArCH_2CH_2$), 2.46-2.58 (2H, m, $CHCH_3$), 2.81-2.87 (4H, m, $ArCH_2$), 3.72 (2H, dd, J = 4.8, 7.8 Hz, OC*H*), 4.18 (2H, dd, J = 4.8, 6.4 Hz, OC*H*), 8.21 (2H, s, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 17.8, 18.6, 19.0, 19.4, 19.9, 24.2, 31.5, 31.8, 37.1, 85.8, 86.1, 115.5, 122.2, 135.9, 144.4, 156.5, 160.3; **IR**

(KBr) 2959, 2872, 1596, 1573, 1468, 1435, 1384, 1367, 1324, 1292, 1225, 1191, 1163, 1148, 1099, 1056, 1009, 921 cm^{-1}; **MS** (MALDI-TOF) *m/z* 550 (M + H); **Anal.** Calcd. for $C_{34}H_{48}N_2O_4$: C, 74.42; H, 8.82; N, 5.10. Found: C, 74.60; H, 8.95; N, 5.30.

8.2.11. ***4,4'-Dimethyl-6,6',7,7'-tetrahydro-5H,5'H-2,2'-bi([1]pyrindinyl)-7,7'-dione (1S,2S)-1,2-Diphenyl-1,2-ethanediol* bis-*Acetal* (267c)**

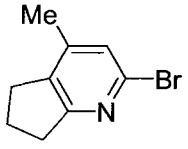


267c

To a stirred solution of dibromo*bis*(triphenylphosphine)nickel(II) (743 mg, 1.00 mmol) in degassed tetrahydrofuran (15 mL) were added zinc dust (<10 microns, 197 mg, 3.02 mmol) and tetraethylammonium iodide (517 mg, 2.01 mmol). The reaction mixture was stirred at room temperature for 30 min and then a solution of the 2-chloropyridine **268c** (760 mg, 2.01 mmol) in degassed tetrahydrofuran (12 mL) was then added *via* a cannula. The resultant mixture was heated at 60 °C for 72 h and then was allowed to cool to room temperature. The reaction was then poured into an aqueous solution of ammonium hydroxide (10% w/w, 300 mL) and was extracted with ether (3 x 50 mL). The combined organic extracts were washed with water (2 x 20 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo* to afford the crude product. Flash chromatography using hexanes:ether (6:1) as the eluant afforded the *title compound* **267c** (502 mg, 73%) as a white crystalline solid. **M.p.** 214-215 °C, hexanes/ether; $[\alpha]_D^{20}$ + 250 (*c* 1.00, chloroform); **^{1}H NMR** ($CDCl_3$) δ 2.39 (6H, s, $ArCH_3$), 2.70-2.84 (4H, m, $ArCH_2CH_2$), 2.97-3.07 (4H, m, $ArCH_2$), 4.95 (2H, d, J = 8.5 Hz, C*H*), 5.79 (2H, d, J =

8.5 Hz, C*H*), 7.28-7.45 (16H, m, Ar*H*), 7.65-7.78 (4H, m, Ar*H*), 8.39 (2H, s, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 18.7, 24.3, 36.1, 86.0, 86.5, 115.7, 122.5, 127.0, 128.0, 128.4, 128.5, 136.0, 136.6, 137.8, 145.0, 156.7, 161.0; **IR** (KBr) 2366, 2341, 1594, 1498, 1436, 1422, 1326, 1195, 1159, 1141, 1099, 1023, 938, 916, 761, 700 cm^{-1}; **MS** (MALDI-TOF) *m/z* 686 (M + H); **Anal.** Calcd. for $C_{46}H_{40}N_2O_4$: C, 80.68; H, 5.89; N, 4.09. Found: C, 80.50; H, 5.77; N, 4.06.

8.2.12. *2-Bromo-4-methyl-6,7-dihydro-5*H*-[1]pyrindine* (287)

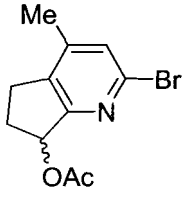


287

A solution of the 2-hydroxypyridine **280** (3.00 g, 20.1 mmol) in phosphorus tribromide (4.5 mL, 47 mmol) was heated at reflux for 12 h. The reaction mixture was then allowed to cool to room temperature and was poured into an ice-cold aqueous solution of sodium hydroxide (2 M, 300 mL). The resultant mixture was extracted (gentle agitation to avoid emulsification) with ethyl acetate (3 x 200 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated *in vacuo* to afford the crude product. Flash chromatography using chloroform as the eluant afforded the *title compound* **287** (2.20 g, 52%) as a colourless oil which crystallized upon standing. **M.p.** 35-36 °C; **^{1}H NMR** ($CDCl_3$) δ 2.04-2.16 (2H, m, $ArCH_2CH_2$), 2.21 (3H, s, CH_3), 2.80 (2H, apparent t, J = 7.5 Hz, $ArCH_2$), 2.99 (2H, apparent t, J = 7.8 Hz, $ArCH_2$), 7.05 (1H, s, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 18.7, 25.9, 32.31, 74.9, 127.7, 135.3, 141.1, 147.4, 165.2; **IR** (KBr) 2356, 2337, 1733, 1717, 1700, 1684, 1653, 1558, 1507, 1458, 1419, 1375, 1305, 1261, 1186, 1090, 865 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 213

[M(^{81}Br) + H, 97], 211 [M(^{79}Br) + H, 100]; **Anal.** Calcd. for $C_9H_{10}NBr$: C, 50.97; H, 4.75; N, 6.60. Found: C, 50.66; H, 4.73; N, 6.39.

8.2.13. ***(7RS)-7-Acetoxy-2-bromo-4-methyl-6,7-dihydro-5H-[1]pyrindine*** **(288)**

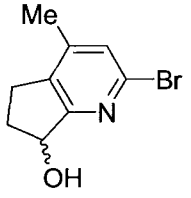


288

To a stirred solution of the 2-bromopyridine **280** (2.20 g, 10.4 mmol) in glacial acetic acid (20 mL) was added an aqueous solution of hydrogen peroxide (30% w/w, 5.0 mL, 49 mmol). The resultant solution was heated at 80 °C for 20 h and then was allowed to cool to room temperature. The reaction mixture was concentrated *in vacuo* and the residue was taken up in water (100 mL). The resultant slightly acidic mixture was neutralized by the careful addition of solid potassium carbonate which was then extracted with chloroform (3 x 50 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated *in vacuo* to afford the pyridine *N*-oxide (2.35 g, 99%) as a white crystalline solid. This material was taken up in acetic anhydride (20 mL) and the resultant mixture was heated slowly to 100 °C over 2 h. The resultant solution was heated at 100 °C for 2 h and then was allowed to cool to room temperature. The reaction mixture was then concentrated *in vacuo* and purified by flash chromatography using hexanes:ether (1:1) as the eluant to afford the *title compound* **288** (1.50 g, 54%, over two steps) as a light orange oil which crystallized upon standing. **M.p.** 68-69 °C; **^{1}H NMR** ($CDCl_3$) δ 2.00-2.11 (4H, m, $ArCH_2CHH$ and CH_3CO), 2.26 (3H, s, $ArCH_3$), 2.68-2.68 (1H, m, $ArCH_2CHH$), 2.69-2.80 (1H, m, ArCHH), 2.87-2.98 (1H, m, ArCHH), 5.98-6.02 (1H, m, CHOAc), 7.22 (1H, s, ArH); **^{13}C NMR** ($CDCl_3$) δ 18.7, 21.5, 26.3, 30.6, 62.5,

122.9, 136.9, 141.5, 147.2, 160.8, 170.8; **IR** (KBr) 2363, 2337, 1734, 1653, 1635, 1559, 1541, 1507, 1370, 1337, 1235, 1094, 1036, 856 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 272 [M(^{81}Br) + H, 97], 270 [M(^{79}Br) + H, 100], 212 (30), 101 (35); **Anal.** Calcd. for $C_{11}H_{12}NO_2Br$: C, 48.91; H, 4.48; N, 5.19. Found: C, 48.63; H, 4.43; N, 5.32.

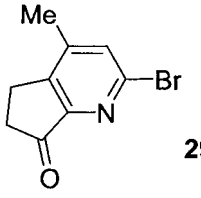
8.2.14. ***(7RS)-2-Bromo-4-methyl-6,7-dihydro-5H-[1]pyrindin-7-ol*** **(289)**



289

A stirred solution of the acetate **288** (1.50 g, 5.55 mmol) and lithium hydroxide monohydrate (932 mg, 22.2 mmol) in tetrahydrofuran (15 mL) and water (5 mL) was stirred at room temperature for 5 h. The reaction mixture was then diluted with water (25 mL) and extracted with chloroform (3 x 25 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated *in vacuo* to afford the crude product. Flash chromatography using hexanes:ether (1:1) as the eluant afforded the *title compound* **289** (1.20 g, 95%) as a white crystalline solid. **M.p.** 110-111 °C, hexanes/ether; **^{1}H NMR** ($CDCl_3$) δ 1.99-2.12 (1H, m, $ArCH_2CHH$), 2.26 (3H, s, $ArCH_3$), 2.48-2.59 (1H, m, $ArCH_2CHH$), 2.63-2.75 (1H, m, ArCHH), 2.87-2.97 (1H, m, ArCHH), 5.18 (1H, apparent t, J = 7.2 Hz, CHOH), 7.19 (1H, s, ArH); **^{13}C NMR** ($CDCl_3$) δ 18.6, 25.8, 32.2, 74.8, 127.6, 135.2, 141.0, 147.3, 165.1; **IR** (KBr) 3258, 2361, 1733, 1717, 1700, 1684, 1653, 1636, 1559, 1541, 1507, 1187, 1090, 863 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 230 [M(^{81}Br) + H, 22], 228 [M(^{79}Br) + H, 22], 201 (100), 173 (25), 118 (18), 91 (53), 77 (36), 65 (36), 51 (33), 39 (42); **Anal.** Calcd. for $C_9H_{10}NOBr$: C, 47.39; H, 4.42; N, 6.14. Found: C, 47.61; H, 4.45; N, 5.98.

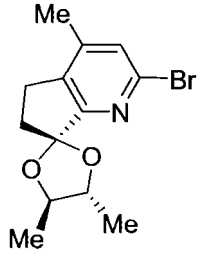
8.2.15. *2-Bromo-4-methyl-6,7-dihydro-5*H*-[1]pyrindin-7-one* (290)



290

To a stirred solution of oxalyl chloride (415 μL, 4.76 mmo) in dichloromethane (40 mL) at -78 °C was added dimethylsulfoxide (1.10 mL, 14.2 mmol) dropwise over ~5 min. The resultant solution was stirred for 10 min and then a solution of the alcohol **289** (900 mg, 3.95 mmol) in anhydrous dichloromethane (15 mL) was added *via* a cannula. After an additional 10 min, triethylamine (2.80 mL, 20.1 mmol) was added and the reaction mixture was then allowed to warm to room temperature. The resultant mixture was then diluted with additional dichloromethane (50 ml) and washed with water (50 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo* to afford the crude product. Flash chromatography using dichloromethane as the eluant afforded the bromoketone **290** (804 mg, 90%) as a white crystalline solid **M.p.** 188-189 °C, dichloromethane; **^{1}H NMR** ($CDCl_3$) δ 2.39 (3H, s, CH_3), 2.74-2.80 (2H, m, $ArCH_2CH_2$), 2.97-3.02 (2H, m, $ArCH_2$), 7.46 (1H, s, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 17.5, 21.9, 34.7, 132.0, 143.9, 148.9, 149.0, 154.2, 203.5; **IR** (KBr) 2360, 1719, 1684, 1653, 1559, 1540, 1521, 1094 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 228 [M(^{81}Br) + H, 100], 226 [M(^{79}Br) + H, 100]; **Anal.** Calcd. for C_9H_8NOBr: C, 47.82; H, 3.57; N, 6.20. Found: C, 47.71; H, 3.48; N, 6.22.

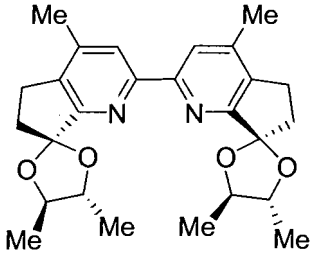
8.2.16. *2-Bromo-4-methyl-6,7-dihydro-5H-[1]pyrindin-7-one (2R,3R)-2,3-Butanediol Acetal* (291a)



291a

To a stirred solution of the bromoketone **290** (650 mg, 2.87 mmol) in benzene (15 mL) was added (2*R*,3*R*)-2,3-butanediol **270a** (0.33 mL, 3.6 mmol) and *p*-toluenesulfonic acid monohydrate (82 mg, 0.43 mmol) and the resultant solution was heated at reflux in a Dean-Stark apparatus for 20 h. The reaction mixture was then allowed to cool to room temperature and potassium carbonate (200 mg) was added. After an additional 10 min, the reaction mixture was filtered and the filter-cake was washed with ether (15 mL). The combined filtrates were concentrated *in vacuo* to afford the crude product. Flash chromatography using hexanes:ethyl acetate (2:1) as the eluant afforded the *title compound* **291a** (760 mg, 89%) as a white crystalline solid **M.p.** 128-129 °C, hexanes/ethyl acetate; $[\alpha]_D^{20}$ - 25.8 (*c* 1.07, chloroform); **^{1}H NMR** ($CDCl_3$) δ 1.31 (3H, d, J = 6.1 Hz, CHCH_3), 1.41 (3H, d, J = 6.1 Hz, CHCH_3), 2.22 (3H, s, ArCH_3), 2.35-2.40 (2H, m, ArCH$_2$CH_2), 2.72-2.78 (2H, m, ArCH_2), 3.72-3.90 (1H, m, CHCH$_3$), 4.35-4.43 (1H, m, CHCH$_3$), 7.19 (1H, s, ArH); **^{13}C NMR** ($CDCl_3$) δ 16.6, 17.1, 18.1, 23.9, 35.9, 79.2, 79.7, 113.6, 128.4, 135.0, 141.8, 147.1, 162.4; **IR** (KBr) 2985, 2933, 2361, 2331, 1588, 1441, 1376, 1314, 1263, 1204, 1107, 1077, 931, 865 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 300 [M(^{81}Br) + H, 97], 298 [M(^{79}Br) + H, 100], 226 (21), 115 (53); **Anal.** Calcd. for $C_{13}H_{16}NO_2Br$: C, 52.36; H, 5.41; N, 4.70. Found: C, 52.25; H, 5.47; N, 4.61.

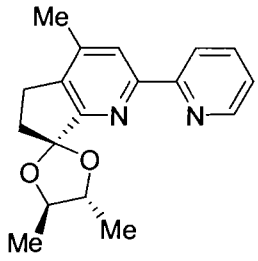
8.2.17. *Preparation of 4,4'-Dimethyl-6,6',7,7'-tetrahydro-5H,5'H-2,2'-bi([1]pyrindinyl)-7,7'-dione (2R,3R)-Butanediol* bis-*Acetal* (267a) *from the 2-Bromopyridine* (291a)



267a

To a stirred solution of dibromo*bis*(triphenylphosphine)nickel(II) (224 mg, 0.302 mmol) in degassed tetrahydrofuran (15 mL) were added zinc dust (<10 microns, 197 mg, 3.02 mmol) and tetraethylammonium iodide (517 mg, 2.01 mmol) and the resulting mixture was stirred at room temperature for 30 min. A solution of the 2-bromopyridine **291a** (600 mg, 2.01 mmol) in degassed tetrahydrofuran (6 mL) was then added *via* a cannula and the resultant mixture was heated at 60 °C for 72 h. The reaction mixture was then allowed to cool to room temperature and was poured into an aqueous solution of ammonium hydroxide (10% w/w, 150 mL). The resultant mixture was extracted with a mixture of ether and benzene (1:1, 3 x 100 mL). The combined organic extracts were washed with water (2 x 20 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo* to afford the crude product. Flash chromatography using chloroform as the eluant afforded the *title compound* **267a** (364 mg, 83%) as a white crystalline solid. The spectroscopic data were in agreement with that recorded above.

8.2.18. *4-Methyl-2-(2'-pyridyl)-6,7-dihydro-5H-[1]pyrindin-7-one (2R,3R)-2,3-Butanediol Acetal* (271a)

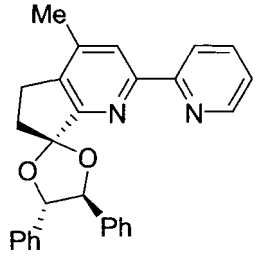


271a

To a stirred solution the 2-chloropyridine **268a** (175 mg, 0.690 mmol) and 2-(tri-*n*-butylstannyl)pyridine **272** (472 mg, 0.759 mmol) in anhydrous, degassed dioxane (3 mL) at room temperature were added *tris*(dibenzylideneacetone)dipalladium(0) (16 mg, 17 μmol), a solution of tri-*tert*-butylphosphine in tetrahydrofuran (0.10 M, 0.69 mL, 69 μmol) and anhydrous cesium fluoride (231 mg, 1.52 mmol). The resultant solution was heated at reflux for 24 h and then was allowed to cool to room temperature. The reaction mixture was filtered through a pad of silica gel using ethyl acetate as the eluant and the filtrate was then concentrated *in vacuo* to afford the crude product. Flash chromatography using hexanes:ether (4:1) as the eluant afforded the *title compound* **271a** (147 mg, 72%) as a white crystalline solid. **M.p.** 164-165 °C, hexanes/ether; $[\alpha]_D^{20}$ - 40.8 (*c* 1.04, chloroform); **^{1}H NMR** ($CDCl_3$) δ 1.37 (3H, d, J = 6.1 Hz, $CHCH_3$), 1.52 (3H, d, J = 6.0 Hz, $CHCH_3$), 2.34 (3H, s, $ArCH_3$), 2.44-2.50 (2H, m, $ArCH_2CH_2$), 2.85-2.91 (2H, m, $ArCH_2$), 3.80-3.89 (1H, m, $CHCH_3$), 4.54-4.62 (1H, m, $CHCH_3$), 7.25-7.29 (1H, m, Ar*H*), 7.76-7.84 (1H, m, Ar*H*), 8.20 (1H, s, Ar*H*), 8.45-8.49 (1H, m, Ar*H*), 8.63-8.67 (1H, m, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 16.7, 17.6, 18.4, 24.3, 36.0, 79.1, 79.7, 114.3, 121.3, 122.0, 123.5, 136.0, 136.9, 145.1, 148.9, 155.8, 156.7, 161.3; **IR** (KBr) 1586, 1565, 1441, 1376, 1316, 1191, 1096, 1079, 932, 896, 798 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 297

(M + H, 100); **Anal.** Calcd. for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 72.68; H, 7.00; N, 9.17.

8.2.19. ***4-Methyl-2-(2'-pyridyl)-6,7-dihydro-5H-[1]pyrindin-7-one (1S,2S)-1,2-Diphenyl-1,2-ethanediol Acetal*** **(271b)**

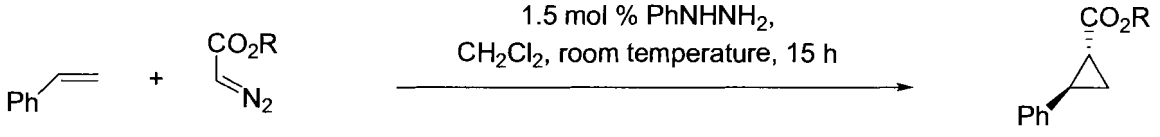


271b

To a stirred solution the 2-chloropyridine **268c** (261 mg, 0.690 mmol) and 2-(tri-*n*-butylstannyl)pyridine **272** (472 mg, 0.759 mmol) in anhydrous, degassed dioxane (5 mL) at room temperature were added *tris*(dibenzylideneacetone)dipalladium(0) (16 mg, 17 μmol), a solution of tri-*tert*-butylphosphine in tetrahydrofuran (0.10 M, 0.69 mL, 69 μmol) and anhydrous cesium fluoride (231 mg, 1.52 mmol). The resultant solution was heated at reflux for 24 h and then was allowed to cool to room temperature. The reaction mixture was filtered through a pad of silica gel using ethyl acetate as the eluant and the filtrate was then concentrated *in vacuo* to afford the crude product. Flash chromatography using hexanes:ether (4:1) as the eluant afforded the *title compound* **271b** (242 mg, 83%) as a white crystalline solid. **M.p.** 120-121 °C, hexanes/ether; $[\alpha]_D^{20}$ - 98.4 (*c* 1.00, chloroform); **^{1}H NMR** ($CDCl_3$) δ 2.40 (3H, s, CH_3), 2.68-2.82 (2H, m, ArCHCH_2), 2.96-3.03 (2H, m, ArCH_2), 4.92 (1H, d, J = 8.5 Hz, C*H*), 5.77 (1H, d, J = 8.5 Hz, C*H*), 7.29-7.37 (9H, m, Ar*H*), 7.61-7.66 (2H, m, Ar*H*), 7.80-7.86 (1H, m, Ar*H*), 8.30 (1H, s, Ar*H*), 8.52-8.56 (1H, m, Ar*H*), 8.67-8.71 (1H, m, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 18.5, 24.3, 36.1, 86.1, 86.5, 115.6, 121.4, 122.2, 123.6, 126.9, 127.9, 128.4, 128.5, 128.5,

136.5, 137.1, 137.5, 145.4, 149.0, 156.7, 161.2; **IR** (KBr) 1586, 1564, 1492, 1441, 1381, 1351, 1320, 1289, 1253, 1210, 1185, 1164, 1103, 1056, 1021, 936, 920, 796, 761, 751, 700 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 421 (M + H, 90), 314 (2), 225 (100); **Anal.** Calcd. for $C_{28}H_{24}N_2O_2$: C, 79.98; H, 5.75; N, 6.66. Found: C, 79.64; H, 6.02; N, 6.30.

8.2.20. ***General Procedure for the Copper(I)-Catalyzed Enantioselective Cyclopropanation of Styrene* (292) *with the Ethyl and* tert-*Butyl Esters of Diazoacetic Acid* (293a,b)**

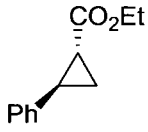


292 **293a,b** **294a,b**

To a stirred solution of copper(II) triflate (9.0 mg, 25 μmol) in dichloromethane (4 mL) was added the 2,2′-bipyridyl ligand **267a-c** *or* the unsymmetrical bipyridyl ligand **271a,b** (30 μmol *or* 55 μmol) and the resultant solution was stirred at room temperature for 30 min. Phenylhydrazine (3.0 μL, 30 μmol) and styrene **292** (0.50 mL, 4.4 mmol) were then added. A solution of the ethyl or *tert*-butyl ester of diazoacetic acid **293a,b** (2.00 mmol) in dichloromethane (3 mL) was then added over ~3 h *via* syringe pump. After the addition was complete, the reaction mixture was stirred for an additional 12 h. The resultant mixture was concentrated *in vacuo* to afford the crude product. The ratios of the *trans*- and *cis*-isomers of the cyclopropane reaction products were then determined by ^{1}H NMR spectroscopy. Flash chromatography using petroleum ether:ethyl acetate (96:4) as the eluant afforded the pure *trans*-cyclopropanes **294a,b** and the corresponding *cis*-cyclopropanes. The enantiomeric purities of the major *trans*-isomers of the

cyclopropane reaction products were determined following reduction with lithium aluminum hydride.

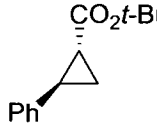
8.2.21. trans-*2-Phenyl-cyclopropane-1-carboxylic Acid Ethyl Ester* (294a)



294a

^{1}H NMR ($CDCl_3$) δ 1.25-1.34 (4H, m, C*H*$_3$ and C*H*H), 1.56-1.63 (1H, m, CH*H*), 1.87-1.93 (1H, m, C*H*CO_2Et), 2.52 (1H, ddd, J = 10.2, 6.4, 4.1 Hz, C*H*Ph), 4.17 (2H, q, J = 7.2 Hz, C*H*$_2$CH$_3$), 7.07-7.14 (2H, m, Ar*H*), 7.17-7.23 (1H, m, Ar*H*), 7.24-7.32 (2H, m, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 14.4, 17.2, 24.3, 26.3, 60.8, 126.3, 126.6, 128.6, 140.3, 173.5; **IR** (neat) 2988, 1721, 1603, 1496, 1411, 1189, 1040, 1019, 847, 761, 722, 701 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 191 (M + H, 100). Analytical chiral HPLC analysis of the corresponding primary alcohol using a Daicel Chiracel OD column [hexanes:isopropanol (90:10), flow rate at 0.5 mL/min, detection at λ = 220 nm, t_1 = 15.4 min, t_2 = 25.2 min].

8.2.22. trans-*2-Phenyl-cyclopropane-1-carboxylic Acid* tert-*Butyl Ester* (294b)

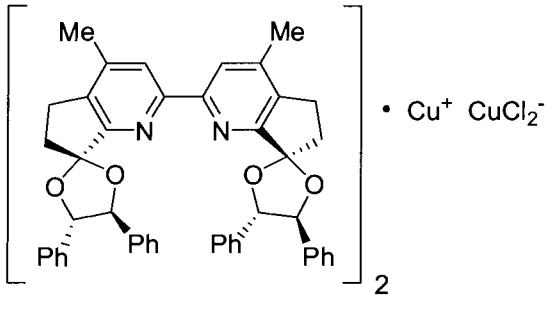


294b

^{1}H NMR ($CDCl_3$) δ 1.23 (1H, m, C*H*H), 1.47 (9H, s, *t*-Bu), 1.50-1.56 (1H, m, CH*H*), 1.84 (1H, m, C*H*CO_2*t*-Bu), 2.44 (1H, m, C*H*Ph), 7.06-7.12 (2H, m, Ar*H*), 7.16-7.22 (1H, m, Ar*H*), 7.24-7.31 (2H, m, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 17.4, 25.6, 26.1, 28.5, 80.9, 126.4, 126.7, 128.7, 140.9, 172.9; **IR** (neat) 2977, 1715, 1606, 1498, 1403, 1367, 1343, 1222, 1152, 936, 844, 783, 761, 744 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 219 (M + H, 18), 163 (100). Analytical chiral HPLC analysis of the corresponding primary alcohol using a

Daicel Chiracel OD column [hexanes:isopropanol (90:10), flow rate at 0.5 mL/min, detection at λ = 220 nm, t_1 = 15.4 min, t_2 = 25.2 min].

8.2.23. ***Procedure for the Preparation and Crystallization of bis-[4,4'-Dimethyl-6,6',7,7'-tetrahydro-5H,5'H-2,2'-bi([1]pyrindinyl)-7,7'-dione (1S,2S)-1,2-Diphenyl-1,2-ethanediol*** **bis-*Acetal]* (267c)** ***Copper(I) Chloride Complex***



A solution of the ligand **267c** (35 mg, 51 μmol) and copper(I) chloride (5.0 mg, 51 μmol) in a mixture of ethanol:dichloromethane (1:1, 3 mL) was stirred at room temperature for 4 h. The reaction mixture was then concentrated *in vacuo* to afford the crude product. This material was then taken up in dichloromethane (2 mL) and was filtered through a plug of glass wool. Ether (3 mL) was then added to the filtrate and upon slow evaporation, the *title compound* (27 mg, 68%) was obtained as X-ray quality red crystals. **M.p.** >220 °C (dec.), ether/dichloromethane; $[\alpha]_{253}^{20}$ - 2500, $[\alpha]_{365}^{20}$ - 4900, $[\alpha]_{405}^{20}$ - 3400, $[\alpha]_{546}^{20}$ - 1333, $[\alpha]_{589}^{20}$ - 1300 (*c* 0.0030, chloroform); **UV-Vis** λ_{max} (chloroform) 287 (ε = 38158), 309 (ε = 38684), 472 (ε = 6158) nm; **IR** (KBr) 1603, 1496, 1315, 1167, 1140, 1056, 1023, 951, 807, 759 cm^{-1}; **MS** (MALDI-TOF) *m/z* 1431 (M - $CuCl_2$), 747 (M - $CuCl_2$ - L); **Anal.** Calcd. for $C_{92}H_{80}Cl_2Cu_2N_4O_8$: C, 70.49; H, 5.14; N, 3.57. Found: C, 70.36; H, 5.15; N, 4.10.

8.2.24. *X-Ray Crystallographic Analysis of the* $Cu(267c)_2 \cdot CuCl_2$ *Complex*

A single crystal, a red block that had the dimensions 0.17 x 0.40 x 0.94 mm^3, was mounted on a glass fiber using epoxy adhesive. The data for this crystal of the $Cu(\mathbf{267c})_2 \cdot CuCl_2$ complex was acquired at 293 K on a *Rigaku RAXIS-RAPID* curved image plate area detector with graphite monochromated Cu Kα radiation. Indexing for the crystal was performed using four, 5 ° oscillations that were exposed for 300 seconds. The following data range was recorded: $4.65° \leq 2\theta \leq 144.25°$ and a total of fifty four images were collected. A sweep of data was then collected using ω scans from 0.0° to 180.0° in 10° steps, at $\chi = 0.0°$ and $\phi = 0.0°$. A second sweep of data was collected using ω scans from 0.0° to 180.0° in 10° steps, at $\chi = 45.0°$ and $\phi = 0.0°$. A final sweep of data was collected using ω scans from 0.0° to 180.0° in 10° steps, at $\chi = 45.0°$ and $\phi = 90.0°$. The exposure rate was 75 sec/° and in each case, the crystal-to-detector distance was 127.40 mm. A numerical absorption correction was then applied which resulted in the following transmission range: 0.4114 to 0.6854.[176] The coordinates and anisotropic displacement parameters for the non-hydrogen atoms were then refined with the exception of Cl(5), Cl(6) and C(47). Of note, hydrogen atoms were placed in calculated positions (d C-H 0.95 Å) and their coordinate shifts were linked with those of the respective carbon atoms during refinement. Isotropic thermal parameters for the hydrogen atoms were initially assigned proportionately to the equivalent isotropic thermal parameters of their respective carbon atoms. Subsequently, the isotropic thermal parameters for the hydrogen atoms were constrained to have identical shifts during

(176) de Meulenaer, J.; Tompa, H. Absorption Correction in Crystal Structure Analysis. *Acta Cryst.* **1965**, *19*, 1014.

refinement. The programs used for all absorption corrections, data reduction, and processing were from the *Rigaku CrystalClear* package. The structure was refined using *CRYSTALS*.[177] Complex scattering factors for neutral atoms were used in the calculation of structure factors.[178] An *ORTEP* representation of the Cu(**267c**)$_2$·$CuCl_2$ complex is provided below (Figure 8.2.1. and 8.2.2.). Crystallographic data, fractional atomic coordinates and equivalent isotropic thermal displacement parameters, selected bond lengths, and selected bond angles for the Cu(**267c**)$_2$·$CuCl_2$ complex are also listed below (Table 8.2.1., 8.2.2., 8.2.3. and 8.3.4., respectively).

(177) Watkin, D. J.; Prout, C. K.; Carruthers, J. R.; Betteridge, P. W.; Cooper, R. I. *CRYSTALS* Issue 12.50; Chemical Crystallography Laboratory, University of Oxford, Oxford, 2003.

(178) International Union of Crystallography. *International Tables for X-Ray Crystallography*; Kynoch Press: Birmingham, 1952.

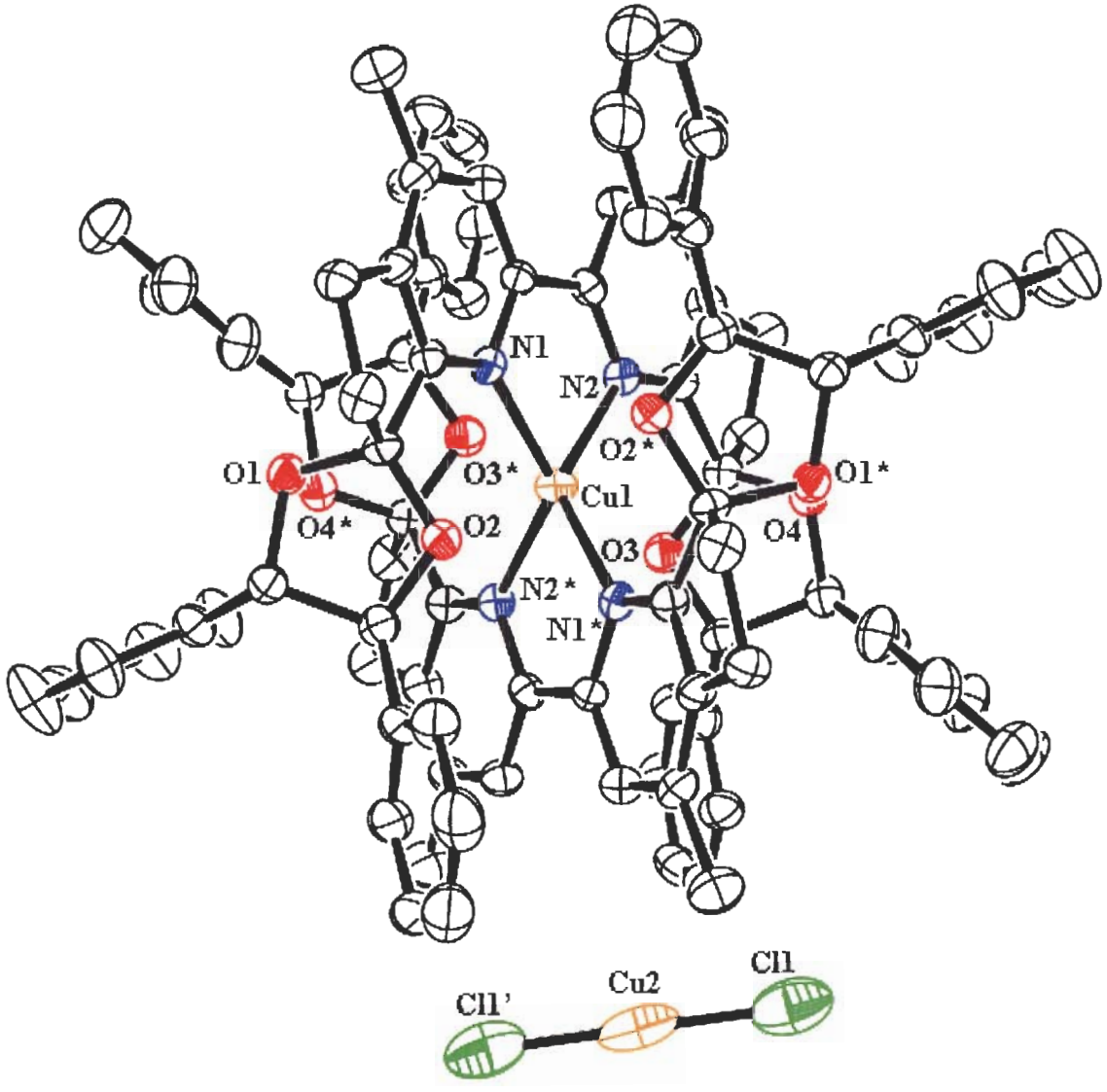


Figure 8.2.1. *ORTEP* representation of the Cu(**267c**)$_2$·$CuCl_2$ complex.*

(*) The thermal ellipsoids are drawn at a 25% probability level and the hydrogen atoms as well as the atoms of the incorporated solvent molecule (CH_2Cl_2) have been removed for clarity. Symmetry transformations: (*) $-x-2, -y-1, z$; (') $-x-3, -y-1, z$.

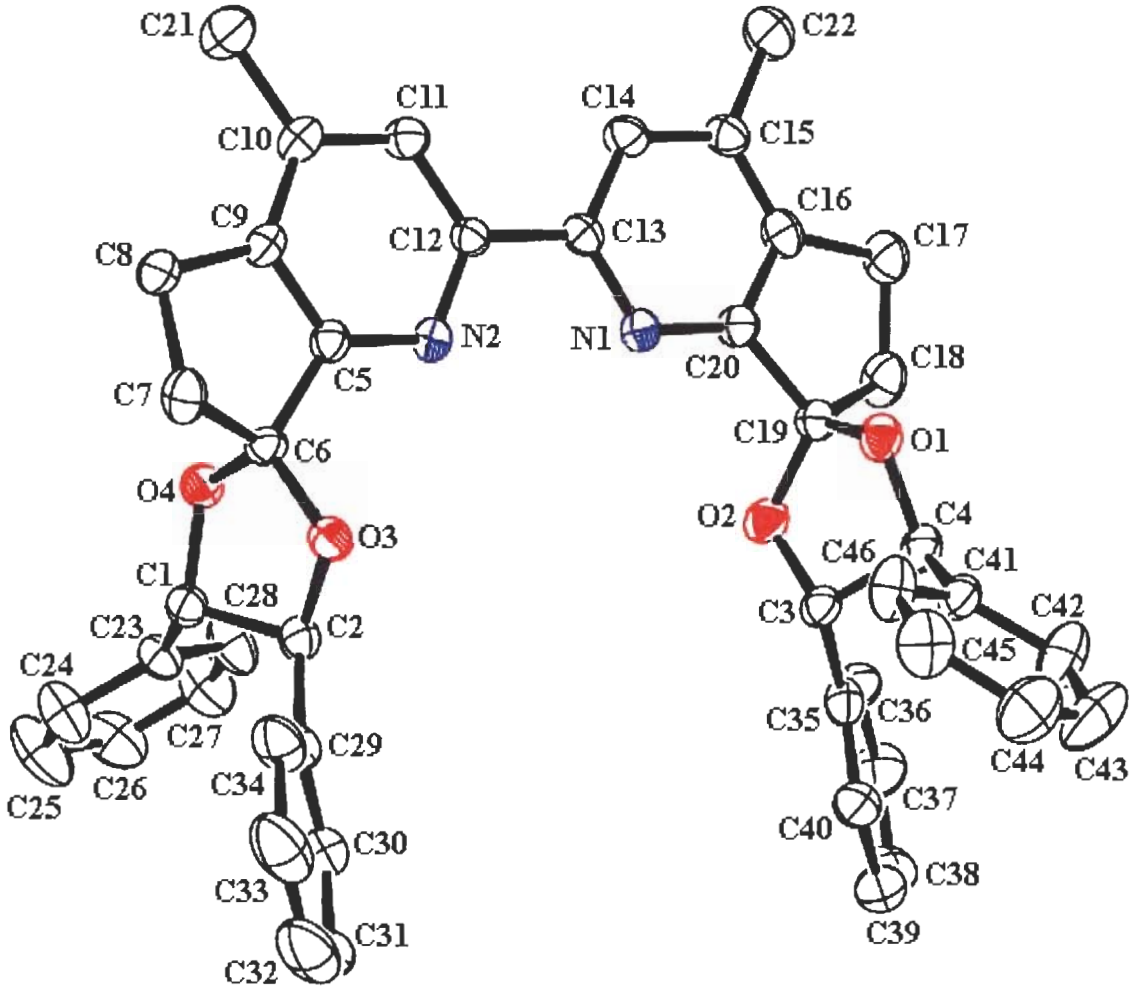


Figure 8.2.2. Partial *ORTEP* representation of the Cu(**267c**)$_2$·$CuCl_2$ complex showing the carbon atom numbering scheme of the 2,2′-bipyridyl ligand.

Table 8.2.1. Summary of Crystallographic Data for the Cu(**267c**)$_2$·$CuCl_2$ Complex

Empirical formula	$C_{93}H_{82}Cl_4Cu_2N_4O_8$
FW (g mol^{-1})	1648.35
Temperature (K)	293
Wavelength (Cu $K\alpha$, Å)	1.54180
Crystal system	Orthorhombic
Space group	$P2_12_12$

a (Å)	14.7325(4)
b (Å)	15.2366(2)
c (Å)	19.0213(3)
α (°)	90
β (°)	90
γ (°)	90
Z	2
U (Å^3)	4269.77(15)
D_{calc} (g cm^{-3})	1.285
2θ limits (°)	4.65-144.25
Reflections collected	28285
Independent reflections	6828
Reflections observed [$I = 2.5\sigma(I)$]	4566
Goodness-of-fit on F	0.601
R_1, R_w [$I = 2.5\sigma(I)$]	0.0532, 0.750

Table 8.2.2. Fractional Atomic Coordinates (Å) and Equivalent Isotropic Thermal Displacement Parameters [U(iso), (Å^2)] for the Cu(**267c**)$_2$·$CuCl_2$ Complex*

atom	x	y	z	U (iso)
Cu1	-1.0000	-0.5000	-0.74787(4)	0.0504
Cu2	-1.5000	-0.5000	-0.76716(8)	0.1386
Cl1	-1.4990(2)	-0.3648(3)	-0.76428(13)	0.1615
O1	-1.0381(3)	-0.7195(2)	-0.86114(17)	0.0593
O2	-1.0694(3)	-0.5825(2)	-0.90075(17)	0.0613

(*) The occupancies for all atoms listed in this table are 1.0.

O3	-1.0397(2)	-0.4058(2)	-0.59490(16)	0.0543
O4	-0.9617(2)	-0.2825(2)	-0.62182(17)	0.0518
N1	-0.9054(3)	-0.5703(2)	-0.80400(16)	0.0447
N2	-0.8869(3)	-0.4603(2)	-0.69351(16)	0.0436
C1	-1.0541(4)	-0.2552(3)	-0.6092(2)	0.0498
C2	-1.1043(4)	-0.3416(3)	-0.6187(2)	0.0528
C3	-1.1556(4)	-0.6226(3)	-0.8818(3)	0.0522
C4	-1.1324(4)	-0.7206(3)	-0.8795(2)	0.0588
C5	-0.8787(4)	-0.4146(3)	-0.6328(2)	0.0479
C6	-0.9538(4)	-0.3690(3)	-0.5926(2)	0.0456
C7	-0.9148(4)	-0.3654(4)	-0.5184(2)	0.0639
C8	-0.8123(4)	-0.3587(4)	-0.5281(2)	0.0575
C9	-0.7980(4)	-0.4029(3)	-0.5974(2)	0.0505
C10	-0.7165(4)	-0.4310(3)	-0.6280(2)	0.0562
C11	-0.7244(4)	-0.4797(3)	-0.6898(2)	0.0564
C12	-0.8096(3)	-0.4960(3)	-0.71947(19)	0.0436
C13	-0.8201(4)	-0.5533(3)	-0.7818(2)	0.0471
C14	-0.7439(4)	-0.5890(3)	-0.8155(2)	0.0562
C15	-0.7527(4)	-0.6406(3)	-0.8752(3)	0.0564
C16	-0.8408(4)	-0.6547(4)	-0.8990(2)	0.0622
C17	-0.8719(5)	-0.7039(4)	-0.9627(3)	0.0772
C18	-0.9695(5)	-0.6718(4)	-0.9720(3)	0.0769
C19	-1.0014(4)	-0.6468(3)	-0.8980(2)	0.0527
C20	-0.9132(4)	-0.6192(3)	-0.8625(2)	0.0500
C21	-0.6252(5)	-0.4119(5)	-0.5955(3)	0.0821
C22	-0.6701(5)	-0.6755(5)	-0.9135(4)	0.0939
C23	-1.0785(4)	-0.1816(3)	-0.6576(2)	0.0578
C24	-1.1037(5)	-0.1012(4)	-0.6337(3)	0.0868
C25	-1.1216(7)	-0.0334(5)	-0.6787(4)	0.1213

C26	-1.1185(5)	-0.0464(5)	-0.7491(4)	0.0995
C27	-1.0920(5)	-0.1243(5)	-0.7749(3)	0.0950
C28	-1.0721(5)	-0.1929(4)	-0.7297(3)	0.0836
C29	-1.1927(4)	-0.3509(3)	-0.5795(3)	0.0614
C30	-1.2741(5)	-0.3279(4)	-0.6134(4)	0.0802
C31	-1.3551(6)	-0.3402(5)	-0.5775(6)	0.1098
C32	-1.3550(9)	-0.3736(6)	-0.5123(7)	0.1232
C33	-1.2777(8)	-0.3958(5)	-0.4796(5)	0.1094
C34	-1.1962(5)	-0.3859(4)	-0.5133(3)	0.0760
C35	-1.2313(4)	-0.5953(3)	-0.9303(3)	0.0606
C36	-1.2136(5)	-0.5690(4)	-0.9990(3)	0.0710
C37	-1.2844(6)	-0.5472(5)	-1.0418(4)	0.0921
C38	-1.3726(6)	-0.5498(5)	-1.0187(4)	0.0911
C39	-1.3900(6)	-0.5756(5)	-0.9532(4)	0.0927
C40	-1.3200(5)	-0.5991(4)	-0.9075(3)	0.0717
C41	-1.1869(4)	-0.7712(3)	-0.8270(3)	0.0604
C42	-1.2522(6)	-0.8311(5)	-0.8497(4)	0.0979
C43	-1.3089(6)	-0.8702(6)	-0.7996(5)	0.1205
C44	-1.2974(6)	-0.8566(5)	-0.7308(5)	0.1054
C45	-1.2307(6)	-0.8003(4)	-0.7077(4)	0.0898
C46	-1.1760(5)	-0.7582(4)	-0.7552(3)	0.0799
Cl5	0.4148(5)	0.1049(4)	0.1749(3)	0.158(2)
Cl6	0.4107(6)	0.0982(6)	0.3254(4)	0.201(3)
C47	0.3545(16)	0.1399(16)	0.2415(12)	0.152(8)
H11	-1.0600(4)	-0.2360(3)	-0.5619(2)	0.060(7)
H21	-1.1153(4)	-0.3507(3)	-0.6674(2)	0.063(7)
H31	-1.1705(4)	-0.6042(3)	-0.8355(3)	0.063(7)
H41	-1.1397(4)	-0.7454(3)	-0.9250(2)	0.071(7)
H71	-0.9300(4)	-0.4166(4)	-0.4924(2)	0.089(5)

H72	-0.9364(4)	-0.3150(4)	-0.4942(2)	0.089(5)
H81	-0.7929(4)	-0.2993(4)	-0.5303(2)	0.084(5)
H82	-0.7805(4)	-0.3881(4)	-0.4915(2)	0.084(5)
H111	-0.6713(4)	-0.5021(3)	-0.7117(2)	0.079(5)
H141	-0.6853(4)	-0.5768(3)	-0.7971(2)	0.075(5)
H171	-0.8695(5)	-0.7654(4)	-0.9546(3)	0.108(5)
H172	-0.8358(5)	-0.6896(4)	-1.0024(3)	0.108(5)
H181	-1.0063(5)	-0.7176(4)	-0.9903(3)	0.103(5)
H182	-0.9717(5)	-0.6227(4)	-1.0028(3)	0.103(5)
H211	-0.5788(5)	-0.4363(5)	-0.6242(3)	0.109(5)
H212	-0.6226(5)	-0.4375(5)	-0.5500(3)	0.109(5)
H213	-0.6166(5)	-0.3503(5)	-0.5918(3)	0.109(5)
H221	-0.6883(5)	-0.7100(5)	-0.9526(4)	0.128(5)
H222	-0.6350(5)	-0.6271(5)	-0.9294(4)	0.128(5)
H223	-0.6347(5)	-0.7103(5)	-0.8824(4)	0.128(5)
H241	-1.1051(5)	-0.0911(4)	-0.5844(3)	0.107(6)
H251	-1.1404(7)	0.0215(5)	-0.6601(4)	0.140(6)
H261	-1.1336(5)	0.0000(5)	-0.7804(4)	0.118(6)
H271	-1.0873(5)	-0.1334(5)	-0.8242(3)	0.125(6)
H281	-1.0532(5)	-0.2481(4)	-0.7477(3)	0.110(6)
H301	-1.2722(5)	-0.3054(4)	-0.6600(4)	0.101(6)
H311	-1.4103(6)	-0.3240(5)	-0.5998(6)	0.129(6)
H321	-1.4120(9)	-0.3818(6)	-0.4898(7)	0.132(6)
H331	-1.2820(8)	-0.4176(5)	-0.4329(5)	0.118(6)
H341	-1.1423(5)	-0.4044(4)	-0.4902(3)	0.087(6)
H361	-1.1530(5)	-0.5678(4)	-1.0162(3)	0.085(6)
H371	-1.2725(6)	-0.5286(5)	-1.0886(4)	0.109(6)
H381	-1.4211(6)	-0.5335(5)	-1.0489(4)	0.120(6)
H391	-1.4511(6)	-0.5787(5)	-0.9374(4)	0.118(6)

H401	-1.3330(5)	-0.6168(4)	-0.8606(3)	0.086(6)
H421	-1.2601(6)	-0.8411(5)	-0.8987(4)	0.104(6)
H431	-1.3514(6)	-0.9129(6)	-0.8154(5)	0.144(6)
H441	-1.3394(6)	-0.8821(5)	-0.6989(5)	0.122(6)
H451	-1.2207(6)	-0.7920(4)	-0.6588(4)	0.104(6)
H461	-1.1308(5)	-0.7182(4)	-0.7396(3)	0.092(6)
H471	0.3522(16)	0.2022(16)	0.2410(12)	0.12(3)
H472	0.2948(16)	0.1170(16)	0.2379(12)	0.12(3)

Table 8.2.3. Bond Lengths (Å) for the Cu(**267c**)$_2$·$CuCl_2$ Complex

Cu1-N3*	2.057(4)
Cu1-N2*	2.052(4)
Cu1-C13*	2.846(5)
Cu1-N1	2.057(4)
Cu1-N2	2.052(4)
Cu1-C13	2.846(5)
Cu2-Cl1′	2.060(4)
Cu2-Cl1	2.060(4)
O1-C4	1.433(6)
O1-C19	1.418(6)
O2-C3	1.453(6)
O2-C19	1.402(6)
O3-C2	1.438(6)
O3-C6	1.384(6)
O4-C1	1.443(6)
O4-C6	1.435(6)
N1-C13	1.351(6)
N1-C20	1.344(6)
N2-C5	1.355(5)

N2-C12	1.355(6)
C1-C2	1.521(7)
C1-C23	1.494(7)
C2-C29	1.507(8)
C3-C4	1.533(7)
C3-C35	1.506(7)
C4-C41	1.495(8)
C5-C6	1.514(7)
C5-C9	1.378(7)
C6-C7	1.526(6)
C7-C8	1.525(8)
C8-C9	1.495(7)
C9-C10	1.402(8)
C10-C11	1.395(7)
C10-C21	1.508(8)
C11-C12	1.398(7)
C12-C13	1.480(6)
C13-C14	1.402(7)
C14-C15	1.388(7)
C15-C16	1.391(8)
C15-C22	1.514(8)
C16-C17	1.495(7)
C16-C20	1.383(7)
C17-C18	1.529(9)
C18-C19	1.532(6)
C19-C20	1.522(7)
C23-C24	1.359(8)
C23-C28	1.386(7)
C24-C25	1.368(9)

C25-C26	1.355(10)
C26-C27	1.342(9)
C27-C28	1.384(8)
C29-C30	1.407(9)
C29-C34	1.368(8)
C30-C31	1.388(11)
C31-C32	1.341(14)
C32-C33	1.342(14)
C33-C34	1.370(11)
C35-C36	1.391(8)
C35-C40	1.379(8)
C36-C37	1.365(9)
C37-C38	1.372(11)
C38-C39	1.332(10)
C39-C40	1.395(9)
C41-C42	1.395(8)
C41-C46	1.389(8)
C42-C43	1.401(11)
C43-C44	1.336(11)
C44-C45	1.376(10)
C45-C46	1.372(9)
Cl5-C47	1.64(2)
Cl6-C47	1.91(2)

Table 8.2.4. Bond Angles (°) for the Cu(**267c**)$_2$·$CuCl_2$ Complex

N1*-Cu1-N2*	82.23(15)
N1*-Cu1-C13*	26.20(14)
N2*-Cu1-C13*	56.08(14)
N1*-Cu1-N1	117.46(19)

N2*-Cu1-N1	131.17(14)
C13*-Cu1-N1	131.46(14)
N1*-Cu1-N2	131.17(14)
N2*-Cu1-N2	119.49(19)
C13*-Cu1-N2	141.85(13)
N1-Cu1-N2	82.23(15)
N1*-Cu1-C13	131.46(14)
N2*-Cu1-C13	141.85(13)
C13*-Cu1-C13	153.81(17)
N1-Cu1-C13	26.20(14)
N2-Cu1-C13	56.08(14)
Cl1′-Cu2-Cl1	176.95(17)
C4-O1-C19	105.0(4)
C3-O2-C19	108.8(4)
C2-O3-C6	109.8(4)
C1-O4-C6	106.1(3)
Cu1-N1-C13	111.6(3)
Cu1-N1-C20	131.3(3)
C13-N1-C20	116.5(4)
Cu1-N2-C5	130.8(3)
Cu1-N2-C12	112.4(3)
C5-N2-C12	116.2(4)
O4-C1-C2	100.9(4)
O4-C1-C23	109.9(4)
C2-C1-C23	117.3(4)
C1-C2-O3	103.3(4)
C1-C2-C29	116.3(4)
O3-C2-C29	110.6(4)
O2-C3-C4	102.8(4)

O2-C3-C35	112.3(4)
C4-C3-C35	116.8(4)
C3-C4-O1	102.2(4)
C3-C4-C41	113.7(5)
O1-C4-C41	111.4(4)
N2-C5-C6	127.0(4)
N2-C5-C9	124.0(4)
C6-C5-C9	109.0(4)
C5-C6-O4	106.6(4)
C5-C6-O3	117.8(4)
O4-C6-O3	106.6(4)
C5-C6-C7	102.0(4)
O4-C6-C7	110.9(4)
O3-C6-C7	112.8(4)
C6C7-C8	105.3(4)
C7-C8-C9	102.5(4)
C8-C9-C5	111.5(5)
C8-C9-C10	128.6(5)
C5-C9-C10	119.8(4)
C9-C10-C11	116.1(5)
C9-C10-C21	122.3(5)
C11-C10-C21	121.6(5)
C10-C11-C12	120.7(5)
C11-C12-N2	122.4(4)
C11-C12-C13	121.5(4)
N2-12-C13	116.1(4)
C12-C13-N1	117.5(4)
C12-C13-Cu1	75.4(3)
N1-C13-Cu1	42.2(2)

C12-C13-C14	120.7(4)
N1-C13-C14	121.8(4)
Cu1-C13-C14	163.7(4)
C13-C14-C15	121.3(5)
C14-C15-C16	116.1(5)
C14-C15-C22	121.2(6)
C16-C15-C22	122.6(5)
C15-C16-C17	128.8(5)
C15-C16-C20	119.8(4)
C17-C16-C20	111.5(5)
C16-C17-C18	102.8(5)
C17-C18-C19	105.1(5)
C18-C19-O1	112.2(4)
C18-C19-O2	111.0(4)
O1-C19-O2	106.9(4)
C18-C19-C20	102.4(5)
O1-C19-C20	108.7(4)
O2-C19-C20	115.7(4)
C19-C20-C16	109.1(4)
C19-C20-N1	126.4(4)
C16-C20-N1	124.5(5)
C1-C23-C24	122.4(5)
C1-C23-C28	120.0(4)
C24-C23-C28	117.5(5)
C23-C24-C25	121.6(6)
C24-C25-C26	120.1(6)
C25-C26-C27	120.0(6)
C26-C27-C28	120.2(6)
C23-C28-C27	120.4(5)

C2-C29-C30	119.1(5)
C2-C29-C34	121.7(6)
C30-C29-C34	119.2(6)
C29-C30-C31	118.3(7)
C30-C31-C32	120.4(9)
C31-C32-C33	121.7(9)
C32-C33-C34	120.0(9)
C33-C34-C29	120.5(8)
C3-C35-C36	121.1(5)
C3-C35-C40	119.8(5)
C36-C35-C40	119.1(5)
C35-C36-C37	119.2(7)
C36-C37-C38	121.7(7)
C37-C38-C39	119.4(6)
C38-C39-C40	121.1(7)
C39-C40-C35	119.6(6)
C4-C41-C42	120.1(5)
C4-C41-C46	121.4(5)
C42-C41-C46	118.5(6)
C41-C42-C43	118.6(7)
C42-C43-C44	121.7(7)
C43-C44-C45	120.1(7)
C44-C45-C46	120.0(6)
C41-C46-C45	120.9(6)
Cl6-C47-Cl5	107.7(13)

8.2.25. *Optical Rotary Dispersion Spectrum of the* $Cu(267c)_2 \cdot CuCl_2$ *Complex*

The following optical rotatory dispersion spectrum of the $Cu(\mathbf{267c})_2 \cdot CuCl_2$ complex was recorded at 20 °C in chloroform [*c* 0.0030 (g per 100 mL)] (Figure 8.2.3.).

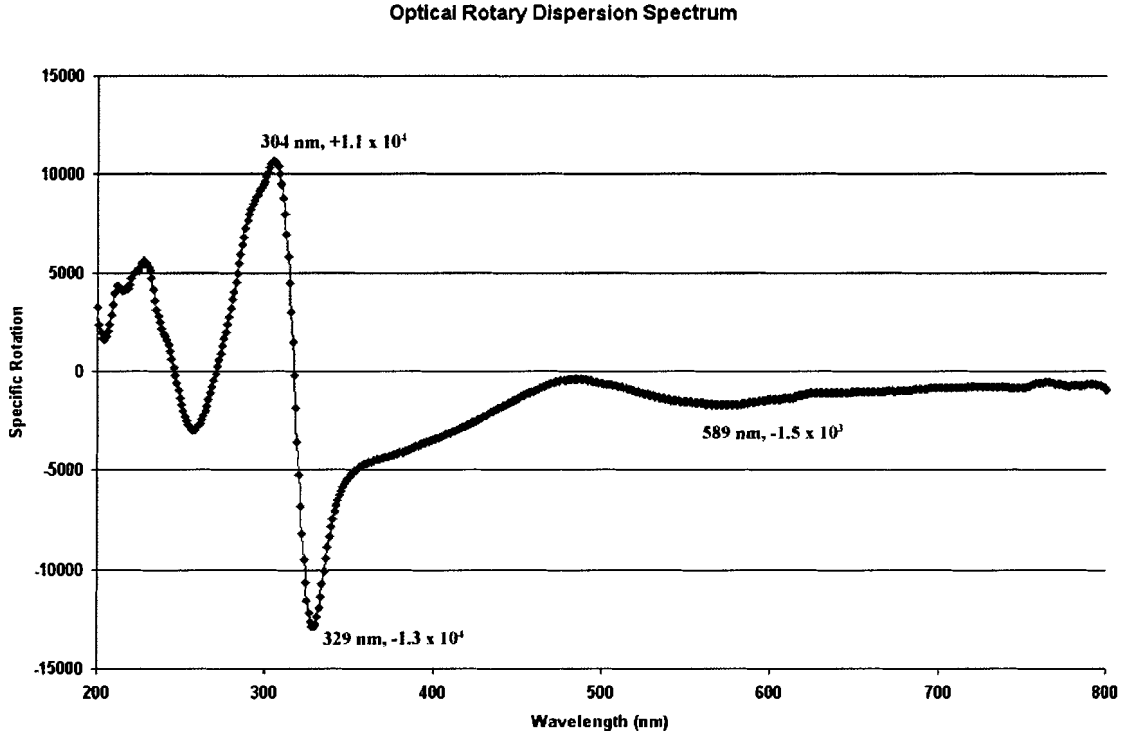
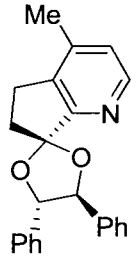


Figure 8.2.3. Optical rotary dispersion spectrum of the $Cu(\mathbf{267c})_2 \cdot CuCl_2$ Complex.

8.3. Experimental Procedures and Characterization Data Concerning Chapter 3

8.3.1. *4-Methyl-6,7-dihydro-5H-[1]pyrindine-7-one (1S,2S)-1,2-Diphenyl-1,2-ethanediol Acetal* (300)

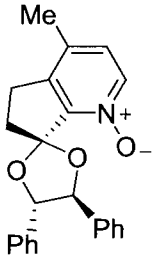


300

To a stirred solution of the 2-chloropyridine **268c** (200 mg, 0.529 mmol) and dibromo*bis*(triphenylphosphine)nickel(II) (118 mg, 0.159 mmol) in anhydrous acetonitrile (4 mL) was added potassium carbonate (80 mg, 0.58 mmol) and borane dimethylamine complex (81 mg, 1.38 mmol) and the resultant solution was heated at 50 °C for 12 h. The reaction mixture was then allowed to cool to room temperature and was filtered through a pad of celite and the filter cake was washed with ether (25 mL). The combined filtrates were concentrated *in vacuo* to afford the crude product. Flash chromatography using hexanes:ether (3:1) as the eluant afforded the *title compound* **300** (140 mg, 77%) as a colourless oil. $[\alpha]_D^{20}$ - 122 (*c* 1.4, chloroform); **^{1}H NMR** ($CDCl_3$) δ 2.31 (3H, s, C*H*$_3$), 2.62-2.70 (2H, m, ArCH$_2$C*H*$_2$), 2.90-2.97 (2H, m, ArC*H*$_2$), 4.82 (1H, d, J = 8.6 Hz, OC*H*), 5.59 (1H, d, J = 8.6 Hz, OC*H*), 7.07-7.10 (1H, m, Ar*H*), 7.10-7.15 (1H, m, Ar*H*), 7.21-7.25 (1H, m, Ar*H*), 7.26-7.36 (6H, m, Ar*H*), 7.47-7.51 (2H, m, Ar*H*), 8.53 (1H, d, J = 4.9 Hz, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 18.3, 24.3, 36.2, 86.2, 115.5, 124.9, 126.8, 127.1, 127.9, 128.3, 128.4, 128.5, 128.8, 134.0, 136.5, 136.6, 144.5, 149.5; **IR**

(neat) 1420, 1342, 1123, 1051, 780; **MS** (CI) *m/z* (rel. intensity) 344 (M + H, 100); **Anal.** Calcd. for $C_{23}H_{21}NO_2$: C, 80.44; H, 6.16; N, 4.08. Found: C, 80.52; H, 6.19; N, 3.95.

8.3.2. *4-Methyl-6,7-dihydro-5H-[1]pyrindine-7-one (1S,2S)-1,2-Diphenyl-1,2-ethanediol Acetal N-Oxide* (299)

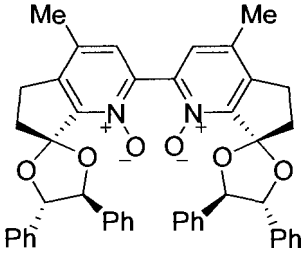


299

To a stirred solution of the pyridine **300** (125 mg, 0.364 mmol) in dichloromethane (5 mL) was added *m*-chloroperoxybenzoic acid (≤77%, 323 mg, 1.44 mmol) and the resultant solution was stirred at room temperature for 16 h. The reaction mixture was then diluted with dichloromethane (25 mL) and was washed with an aqueous solution of potassium hydroxide (20% w/w, 15 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford the crude product. Flash chromatography using chloroform:methanol (95:5) as the eluant afforded the *title compound* **299** (128 mg, 99%) as a white solid/foam. **M.p.** 63-64 °C, chloroform/methanol; $[\alpha]_D^{20}$ - 242 (*c* 0.18, chloroform); **^{1}H NMR** ($CDCl_3$) δ 2.26 (3H, s, CH_3), 2.59-2.77 (2H, m, $ArCH_2CH_2$), 2.85-2.93 (2H, m, $ArCH_2$), 4.75 (1H, d, J = 8.8 Hz, OC*H*), 5.89 (1H, d, J = 8.8 Hz, OC*H*), 7.05 (1H, d, J = 6.4 Hz, Ar*H*), 7.22-7.36 (8H, m, Ar*H*), 7.54-7.60 (2H, m, Ar*H*), 8.08 (1H, d, J = 6.4 Hz, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 17.5, 24.8, 37.7, 87.0, 87.3, 115.5, 126.7, 127.5, 128.2, 128.3, 128.4, 128.6, 128.9, 134.1, 135.8, 136.8, 138.9, 142.2; **IR** (KBr) 1461, 1327, 1258, 1202, 1174, 1139, 1086, 1062, 930, 752 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 344 (M - O + H, 100), 186 (66), 149 (69);

Anal. Calcd. for $C_{23}H_{21}NO_3 \cdot H_2O$: C, 73.19; H, 6.14; N, 3.71. Found: C, 73.19; H, 6.08; N, 3.61.

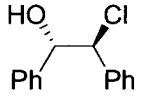
8.3.3. *4,4'-Dimethyl-6,6',7,7'-tetrahydro-5H,5'H-2,2'-bi([1]pyrindinyl)-7,7'-dione (1S,2S)-1,2-Diphenyl-1,2-ethanediol* bis-*Acetal* N-*Oxide* (301)



301

To a stirred solution of the 2,2′-bipyridine **267c** (100 mg, 0.145 mmol) in dichloromethane (5 mL) was added *m*-chloroperoxybenzoic acid (≤77%, 323 mg, 1.44 mmol) and the resultant solution was stirred at room temperature for 72 h. The reaction mixture was then diluted with dichloromethane (25 mL) and was washed with an aqueous solution of potassium hydroxide (20% w/w, 15 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford the crude product. Flash chromatography using chloroform as the eluant afforded the *title compound* **301** (57 mg, 55%) as a viscous colourless oil. $[\alpha]_D^{20}$ - 268 (*c* 0.75, chloroform); **^{1}H NMR** ($CDCl_3$) δ 2.32 (6H, broad s, C*H*$_3$), 2.57-2.82 (4H, m, ArCH$_2$C*H*$_2$), 2.84-2.98 (4H, m, ArC*H*$_2$), 4.69-4.76 (2H, m, OC*H*), 5.75-5.84 (2H, m, OC*H*), 7.17-7.37 (18H, m, Ar*H*), 7.47-7.55 (2H, m, Ar*H*), 8.07 (2H, broad s, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 21.6, 24.8, 37.9, 86.7, 87.1, 115.8, 126.7, 127.9, 128.2, 128.4, 128.6, 128.8, 129.3, 135.4; **IR** (neat) 2929, 1726, 1677, 1494, 1450, 1325, 1261, 1148, 700 cm^{-1}; **MS** (MALDI-TOF) *m/z* 717 (M + H), 701 (M - O + H); **Anal.** Calcd. for $C_{46}H_{40}N_2O_6$: C, 77.08; H, 5.62; N, 3.91. Found: C, 76.92; H, 5.93; N, 3.95.

8.3.4. *Asymmetric Synthesis of (1S,2S)-2-Chloro-1,2-diphenylethan-1-ol* (303)



303

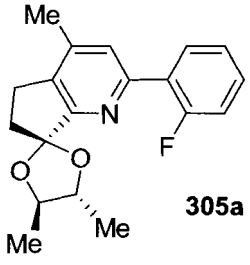
To a stirred solution of the chiral pyridine-*N*-oxide **299** (28 mg, 79 μmol), *cis*-stilbeneoxide *meso*-**302** (155 mg, 0.79 mmol) and *N,N*-diisopropylethylamine (151 μL, 0.869 mmol) in dichloromethane (3 mL) at -78 °C was added silicon tetrachloride (110 μL, 0.948 mmol) and the resultant solution was stirred at -78 °C for 24 h. The reaction mixture was then allowed to warm to 0 °C and then a mixture (1:1, 3 mL) of a saturated aqueous solution of potassium fluoride and an aqueous solution of potassium hydrogen phosphate (1.0 M) was added. The resultant mixture was then extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with water (5 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo* to afford the crude product. Flash chromatography using hexanes:ether (9:1) as the eluant afforded the *title compound* **303** (162 mg, 88%) as a colourless oil. The enantiomeric purity of this material was determined to be 22% ee by analytical chiral GC using a J & W Scientific CYCLOSILB column [column temp. 170 °C, head pressure 20 psi; t_{MINOR} = 75.97 min, t_{MAJOR} = 77.74 min]. $[\alpha]_D^{20}$ + 3.1 (*c* 1.1, ethanol) [lit.[179] - 20.2 (*c* = 5.2, ethanol) for *R,R*-enantiomer]; **^{1}H NMR** ($CDCl_3$) δ 3.02 (1H, d, *J* = 2.8 Hz, ClC*H*), 4.95 (1H, dd, *J* = 8.3, 2.7 Hz, HOC*H*), 5.01 (1H, d, *J* = 8.3 Hz, O*H*), 7.08-7.13 (2H, m, Ar*H*), 7.14-7.24 (8H, m, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 70.67, 78.76, 126.96. 127.96, 128.14, 128.20, 128.32, 128.55, 137.67, 138.68; **MS** (CI) *m/z* (rel. intensity) 215 (M - OH, 100).

---

(179) Denmark, S. E.; Barsanti, P. A.; Wong, K.-T.; Stavenger, R. A. Enantioselective Ring Opening of Epoxides with Silicon Tetrachloride in the Presence of a Chiral Lewis Base. *J. Org. Chem.* **1998**, *63*, 2428.

8.4. Experimental Procedures and Characterization Data Concerning Chapter 4

8.4.1. *2-(2-Fluorophenyl)-4-methyl-6,7-dihydro-5H-[1]pyrindine-7-one (2R,3R)-2,3-Butanediol Acetal* (305a)

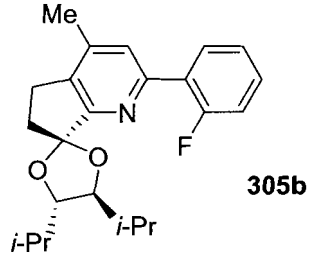


305a

To a stirred solution of the acetal **268a** (100 mg, 0.395 mmol) and *ortho*-fluorophenylboronic acid **306** (83 mg, 0.59 mmol) in degassed tetrahydrofuran (10 mL) was added *tris*(dibenzylideneacetone)dipalladium(0) (18 mg, 20 μmol), tri-*tert*-butylphosphine (395 μL of a 0.10 M solution in tetrahydrofuran, 40 μmol) and anhydrous cesium carbonate (641 mg, 1.97 mmol). The resultant suspension was heated at reflux for 16 h. The reaction mixture was then allowed to cool to room temperature and was then diluted with ethyl acetate (25 mL). The resultant solution was washed with brine (10 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford the crude product. Flash chromatography using hexanes:ether (4:1) as the eluant afforded the *title compound* **305a** (115 mg, 93%) as a white crystalline solid. **M.p.** 63-64 °C, hexanes/ether; $[\alpha]_D^{20}$ - 45.2 (*c* 0.87, chloroform); **^{1}H NMR** ($CDCl_3$) δ 1.22 (3H, d, J = 6.1 Hz, $CHCH_3$), 1.50 (3H, d, J = 6.1 Hz, $CHCH_3$), 1.73 (3H, s, CH_3), 2.40-2.46 (2H, m, $ArCH_2CH_2$), 2.50-2.56 (2H, m, $ArCH_2$), 3.86 (1H, dq, J = 5.8, 7.9 Hz, OC*H*), 4.85 (1H, dq, J = 6.1, 8.2 Hz, OC*H*), 6.95-7.01 (2H, m, Ar*H*), 7.04-7.09 (1H, m, Ar*H*), 7.50-7.53 (1H, m, Ar*H*), 8.35-8.41 (1H, m, Ar*H*); **^{13}C NMR** (C_6D_6) δ 17.4, 18.4, 18.8, 24.6, 36.7,

79.7, 80.6, 115.4, 116.8, 117.0, 125.1, 125.2, 125.86, 125.94, 130.6, 130.7, 132.30, 132.33, 135.0, 144.7, 153.4, 162.9, 163.6; **IR** (KBr) 2973, 2928, 1599, 1493, 1450, 1377, 1348, 1318, 1293, 1275, 1266, 1240, 1211, 1190, 1180, 1158, 1098, 1080, 1047, 935, 898, 882, 761 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 314 (M + H, 100), 242 (14); **Anal.** Calcd. for $C_{19}H_{20}FNO_2$: C, 72.82; H, 6.43; N, 4.47. Found: C, 72.55; H, 6.54; N, 4.33.

8.4.2. ***2-(2-Fluorophenyl)-4-methyl-6,7-dihydro-5H-[1]pyrindine-7-one (1S,2S)-1,2-Diisopropyl-1,2-ethanediol Acetal*** **(305b)**

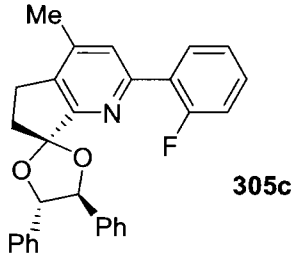


305b

To a stirred solution of the acetal **268b** (100 mg, 0.323 mmol) and *ortho*-fluorophenylboronic acid **306** (68 mg, 0.49 mmol) in degassed tetrahydrofuran (8 mL) was added *tris*(dibenzylideneacetone)dipalladium(0) (14 mg, 16 μmol), tri-*tert*-butylphosphine (325 μL of a 0.10 M solution in tetrahydrofuran, 33 μmol) and anhydrous cesium carbonate (525 mg, 1.62 mmol). The resultant suspension was then heated at reflux for 16 h. The reaction mixture was then allowed to cool to room temperature and was diluted with ethyl acetate (25 mL). The resultant solution was washed with brine (10 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford the crude product. Flash chromatography using hexanes:ether (8:1) as the eluant afforded the *title compound* **305b** (97 mg, 81%) as a colourless oil. $[\alpha]_D^{20}$ - 4.38 (*c* 0.64, chloroform); **^{1}H NMR** ($CDCl_3$) δ 0.98 (3H, d, J = 6.6 Hz, $CHCH_3$), 1.00 (3H, d, J = 7.3 Hz, $CHCH_3$), 1.02-1.07 (6H, m, 2 x $CHCH_3$), 1.83-1.91 (1H, m, $CHCH_3$), 2.32 (3H, s, CH_3), 2.38-2.45

(3H, m, $ArCH_2CH_2$ and $CHCH_3$), 2.83-2.88 (2H, m, $ArCH_2$), 3.71 (1H, dd, J = 5.9, 7.3 Hz, OC*H*), 4.15 (1H, apparent t, J = 5.1 Hz, OC*H*), 7.09-7.19 (1H, m, Ar*H*), 7.20-7.25 (1H, m, Ar*H*), 7.30-7.42 (1H, m, Ar*H*), 7.54 (1H, s, Ar*H*), 7.99-8.04 (1H, m, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 17.9, 18.7, 19.2, 19.7, 20.1, 24.3, 31.7, 31.8, 37.2, 86.0, 86.3, 115.6, 116.2, 116.4, 124.6, 125.6, 125.7, 130.07, 130.14, 131.7, 135.1, 144.5; **IR** (KBr) 2963, 1654, 1596, 1560, 1542, 1507, 1490, 1459, 1321, 1179, 1098, 1057, 924, 931, 761 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 370 (M + H, 100), 242 (19), 191 (14), 190 (13); **Anal.** Calcd. for $C_{23}H_{28}FNO_2$: C, 74.77; H, 7.64; N, 3.79. Found: C, 74.91; H, 7.52; N, 3.56.

8.4.3. ***2-(2-Fluorophenyl)-4-methyl-6,7-dihydro-5H-[1]pyrindine-7-one (1S,2S)-1,2-Diphenyl-1,2-ethanediol Acetal* (305c)**

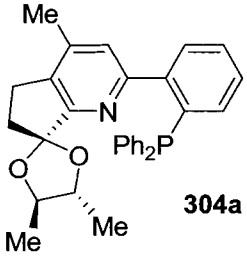


305c

To a stirred solution of the acetal **268c** (351 mg, 0.929 mmol) and *ortho*-fluorophenylboronic acid **306** (195 mg, 1.39 mmol) in degassed tetrahydrofuran (20 mL) was added *tris*(dibenzylideneacetone)dipalladium(0) (41 mg, 46 μmol), tri-*tert*-butylphosphine (925 μL of a 0.10 M solution in tetrahydrofuran, 93 μmol) and anhydrous cesium carbonate (1.51 g, 4.63 mmol). The resultant suspension was then heated at reflux for 16 h. The reaction mixture was then allowed to cool to room temperature and was diluted with ethyl acetate (15 mL). The resultant solution was washed with brine (10 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford the crude product. Flash chromatography using hexanes:ether (8:1) as the eluant afforded the

title compound **305c** (356 mg, 88%) as a white foam/solid. **M.p.** 46-48 °C, hexanes/ether; $[\alpha]_D^{20}$ + 119 (*c* 0.56, chloroform); **^{1}H NMR** ($CDCl_3$) δ2.36 (3H, s, CH_3), 2.64-2.79 (2H, m, $ArCH_2CH_2$), 2.94-3.02 (2H, m, $ArCH_2$), 4.87 (1H, d, *J* = 8.6 Hz, OC*H*), 5.72 (1H, d, *J* = 8.60 Hz, OC*H*), 7.14-7.21 (1H, m, Ar*H*), 7.27-7.34 (9H, m, Ar*H*), 7.35-7.42 (1H, m, Ar*H*), 7.62-7.69 (3H, m, Ar*H*), 8.12-8.17 (1H, m, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ41.8, 52.2, 55.4, 61.6, 75.8, 110.6, 120.9, 123.6, 127.9, 128.59, 128.62, 128.8, 128.9, 129.5, 129.9, 131.2, 134.3, 157.2, 157.9, 167.3; **MS** (CI) *m/z* (rel. intensity) 438 (M + H, 25), 331 (6), 242 (100), 197 (19), 169 (11), 146 (8), 113 (22), 81 (59); **Anal.** Calcd. for $C_{29}H_{24}FNO_2$: C, 79.61; H, 5.53; N, 3.20. Found: C, 79.90; H, 5.52; N, 3.41.

8.4.4. *2-(2-Diphenylphosphanyl-phenyl)-4-methyl-6,7-dihydro-5H-[1]pyrindine-7-one (2R,3R)-2,3-Butanediol Acetal* (304a)

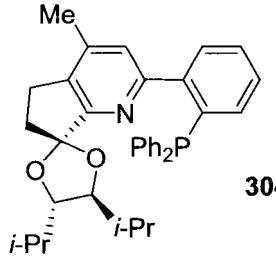


304a

To a stirred solution of potassium *tert*-butoxide (101 mg, 0.900 mmol) and 18-crown-6 (283 mg, 1.07 mmol) in tetrahydrofuran (5 mL) at 0 °C was added diphenylphosphine (166 mg, 0.892 mmol). The resultant red solution was stirred for 1 h. A solution of the aromatic fluoride **305a** (140 mg, 0.446 mmol) in tetrahydrofuran (2 mL) was then added *via* a cannula and the resultant mixture was stirred at room temperature for 24 h. Methanol (2 mL) was then added and the solution was concentrated *in vacuo* to afford the crude product. Flash chromatography using hexanes:ether (8:1) as the eluant afforded the *title compound* **304a** (155 mg, 72%) as a white foam/solid. **M.p.** 48-49 °C,

hexanes/ether; $[\alpha]_D^{20}$ + 1.96 (*c* 0.53, chloroform); **^{1}H NMR** (C_6D_6) δ 1.15 (3H, d, J = 6.1 Hz, CHCH_3), 1.33 (3H, d, J = 6.1 Hz, CHCH_3), 1.73 (3H, s, CH_3), 2.38-2.45 (2H, m, CH_2), 2.46-2.54 (2H, m, CH_2), 3.73-3.80 (1H, m, C*H*CH$_3$), 4.42-4.51 (1H, m, C*H*CH$_3$), 7.02-7.11 (8H, m, Ar*H*), 7.23-7.26 (1H, m, Ar*H*), 7.37-7.46 (5H, m, Ar*H*), 7.76 (1H, ddd, J = 1.5, 4.6, 7.9 Hz, Ar*H*); **^{13}C NMR** (C_6D_6) δ 16.6, 17.6, 17.7, 23.9, 36.5, 78.9, 79.8, 114.7, 125.7, 125.8, 127.8, 128.5, 128.6, 128.9, 129.9, 130.6, 130.7, 134.0, 134.2, 134.3, 134.4, 134.5, 135.5, 139.4, 139.6, 143.1, 159.2, 162.4; **IR** (KBr) 3050, 2970, 2928, 1597, 1585, 1477, 1433, 1374, 1347, 1315, 1277, 1137, 1190, 1157, 1126, 1100, 1081, 936, 766, 744, 697, 627 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 480 (M + H, 100), 409 (16), 402 (17); **Anal.** Calcd. for $C_{31}H_{30}NO_2P$: C, 77.64; H, 6.31; N, 2.92. Found: C, 77.39; H, 6.49; N, 2.67.

8.4.5. *2-(2-Diphenylphosphanyl-phenyl)-4-methyl-6,7-dihydro-5H-[1]pyrindine-7-one (1S,2S)-1,2-Diisopropyl-1,2-ethanediol Acetal* (304b)

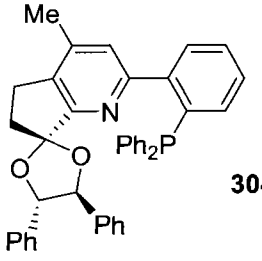


304b

To a stirred solution of potassium *tert*-butoxide (256 mg, 2.26 mmol) and 18-crown-6 (717 mg, 2.71 mmol) in tetrahydrofuran (10 mL) at 0 °C was added diphenylphosphine (421 mg, 2.26 mmol). The resultant red solution was stirred for 1 h. A solution of the aromatic fluoride **305b** (417 mg, 1.13 mmol) in tetrahydrofuran (5 mL) was then added *via* a cannula and resultant mixture was stirred at room temperature for 24 h. Methanol (5 mL) was then added and the solution was concentrated *in vacuo* to

afford the crude product. Flash chromatography using hexanes:ether (8:1) as the eluant afforded the *title compound* **304b** (402 mg, 66%) as a white foam/solid. **M.p.** 54-55 °C, hexanes/ether; $[\alpha]_D^{20}$ - 8.33 (*c* 0.60, chloroform); **^{1}H NMR** ($CDCl_3$) δ0.87 (3H, d, J = 7.0 Hz, CHCH_3), 0.93 (3H, d, J = 6.4 Hz, CHCH_3), 0.97 (3H, d, J = 7.0 Hz, CHCH_3), 1.01 (3H, d, J = 6.7 Hz, CHCH_3), 1.75-1.85 (1H, m, CH(CH_3)$_2$), 2.10 (3H, s, CH_3), 2.19-2.29 (1H, m, CH(CH_3)$_2$), 2.33-2.41 (2H, m, ArCH_2CH_2), 2.76-2.84 (2H, m, ArCH_2), 3.59 (1H, dd, J = 5.8, 7.9 Hz, OCH), 4.00-4.08 (1H, m, OCH), 6.93 (1H, s, ArH), 7.11 (1H, ddd, J = 1.2, 4.0, 7.6 Hz, ArH), 7.21-7.31 (7H, m, ArH), 7.31-7.36 (5H, m, ArH), 7.39-7.45 (1H, m, ArH), 7.62-7.67 (1H, m, ArH); **^{13}C NMR** ($CDCl_3$) δ17.8, 18.5, 19.4, 19.8, 20.2, 24.3, 31.5, 37.4, 85.9, 128.57, 128.60, 128.65, 128.76, 128.79, 129.1, 131.0, 134.1, 134.2, 134.3, 134.4, 135.2; **IR** (KBr) 3447, 2959, 2919, 2864, 2366, 2341, 1655, 1591, 1541, 1490, 1447, 1434, 1344, 1311, 1254, 1218, 1102, 1073, 921, 744, 698 cm^{-1}; **MS** (MALDI-TOF) 537 (M + H); **Anal.** Calcd. for $C_{35}H_{38}NO_2P$: C, 78.48; H, 7.15; N, 2.61. Found: C, 78.39; H, 7.25; N, 2.69.

8.4.6. *2-(2-Diphenylphosphanyl-phenyl)-4-methyl-6,7-dihydro-5H-[1]pyrindine-7-one (1S,2S)-1,2-Diphenyl-1,2-ethanediol Acetal* (304c)

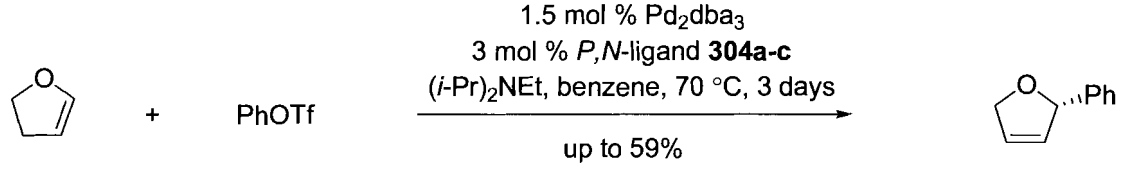


304c

To a stirred solution of potassium *tert*-butoxide (177 mg, 1.58 mmol) and 18-crown-6 (502 mg, 1.90 mmol) in tetrahydrofuran (12 mL) at 0 °C was added diphenylphosphine (294 mg, 1.58 mmol). The resultant red solution was stirred for 1 h.

A solution of the aromatic fluoride **305b** (346 mg, 0.791 mmol) in tetrahydrofuran (5 mL) was then added *via* a cannula and resultant mixture was stirred at room temperature for 24 h. Methanol (5 mL) was added and the solution was concentrated *in vacuo* to afford the crude product. Flash chromatography using hexanes:ether (8:1) as the eluant afforded the *title compound* **304c** (302 mg, 63%) as a white foam/solid. **M.p.** 79-80 °C, hexanes/ether; $[\alpha]_D^{20}$ - 129 (*c* 0.55, chloroform); **^{1}H NMR** ($CDCl_3$) δ 2.16 (3H, s, CH_3), 2.55-2.75 (2H, m, $ArCH_2CH_2$), 2.83-2.97 (2H, m, $ArCH_2$), 4.75 (1H, d, J = 8.7 Hz, OC*H*), 5.38 (1H, d, J = 8.7 Hz, OC*H*), 7.04-7.06 (1H, m, Ar*H*), 7.12-7.35 (20H, m, Ar*H*), 7.47 (1H, m, Ar*H*), 7.56-7.62 (2H, m, Ar*H*), 7.73 (1H, ddd, J = 1.1, 4.4, 7.6 Hz, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 18.4, 24.3, 36.5, 85.5, 86.5, 115.7, 126.5, 126.6, 126.9, 128.2, 128.3, 128.49, 128.53, 128.6, 128.7, 128.9, 130.6, 130.7, 134.1, 134.2, 134.3, 134.4, 134.6, 135.0, 136.2, 136.4, 137.2, 137.3, 138.5, 138.65, 138.69, 138.8, 143.6, 147.4, 147.6, 159.2, 160.7; **IR** (KBr) 3452, 3052, 2923, 1655, 1600, 1585, 1434, 1156, 1021, 760, 746, 698 cm^{-1}; **MS** (MALDI-TOF) 605 (M + H); **Anal.** Calcd. for $C_{41}H_{34}NO_2P$: C, 81.57; H, 5.68; N, 2.32. Found: C, 81.63; H, 5.72; N, 2.33.

8.4.7. *Procedure for Palladium(0)-Catalyzed Asymmetric Heck Reactions: Asymmetric Synthesis of (2S)-2,5-Dihydro-2-phenylfuran* (*S*-309)



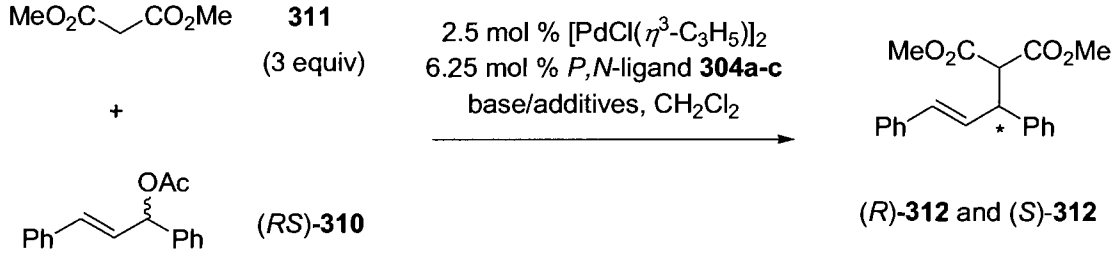
307 **308** (*S*)-**309**

A solution of *tris*(dibenzylideneacetone)dipalladium(0) (24 mg, 26 μmol) and the chiral *P,N*-ligand **304a-c** (52 μmol) in anhydrous, degassed benzene (10 mL) was stirred at room temperature for 1 h. Phenyl triflate **308** (0.28 mL, 1.7 mmol), 2,3-dihydrofuran

307 (0.66 mL, 8.7 mmol) and *N,N*-diisopropylethylamine (0.91 mL, 5.2 mmol) were then added and the resultant solution was heated at 70 °C for 72 h. The reaction mixture was then allowed to cool to room temperature and was diluted with ether (50 mL). The organic layer was washed with brine (2 x 10 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford the crude product. For the reaction that employed the *P,N*-ligand **304a** (R = Me), the crude product was purified by flash chromatography using hexanes/ether (4:1) as the eluant which afforded the *title compound* (*S*)-**309** (150 mg, 59%) as a colourless oil. The enantiomeric purity of this material was determined to be 22% ee and the absolute stereochemistry was determined to be (*S*) by comparison of the optical rotation with the literature value. $[\alpha]_D^{20}$ - 62 (*c* 1.50, chloroform) [lit.[180] -265 (c 0.925, chloroform, 91% ee by chiral GC)]; **^{1}H NMR** ($CDCl_3$) δ 4.71-4.81 (1H, m, C*H*H), 4.80-4.89 (1H, m, CH*H*), 5.76-5.82 (1H, m, OC*H*), 5.98-6.02 (2H, m, 2 x C*H*), 7.23-7.39 (5H, m, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 76.2, 88.3, 126.4, 126.5, 127.6, 127.7, 128.4, 129.9, 142.1; **IR** (neat) 2955, 2852, 1600, 1492 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 147 (M + H, 100).

(180) Kündig, P. E.; Meier, P. Synthesis of New Chiral Bidentate (Phosphinophenyl)benzoxazine *P,N*-Ligands. *Helv. Chim. Acta* **1999**, *82*, 1360.

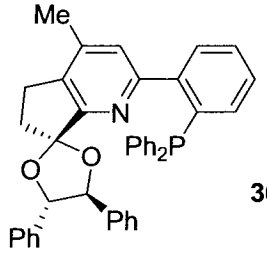
8.4.8. ***General Procedures for Palladium(II)-Catalyzed Asymmetric Allylic Substitution Reactions*: *Asymmetric Synthesis of (1R)-(1,3-Diphenylallyl)malonic Acid Dimethyl Ester* (R)-312 *and (1S)-(1,3-Diphenylallyl)malonic Acid Dimethyl Ester* (*S*)-312**



A solution of allylpalladium(II) chloride dimer (3.7 mg, 10 μmol) and the chiral *P,N*-ligand **304a-c** (25 μmol) in dichloromethane (1.5 mL) was stirred at room temperature for 1 h. A solution of (3*RS*)-3-acetoxy-1,3-diphenyl-1-propene *RS*-**310** (100 mg, 0.396 mmol) and dimethyl malonate **311** (208 mg, 1.20 mmol) in dichloromethane (1.5 mL) was then added *via* a cannula followed by one of three bases and associated reagents [(1) BSA (295 μL, 1.20 mmol) and a catalytic amount of potassium acetate (3 mg); (2) potassium carbonate (166 mg, 1.20 mmol) and 18-crown-6 (296 mg, 1.20 mmol); (3) anhydrous cesium carbonate (391 mg, 1.20 mmol)]. The reaction mixture was then stirred at the temperature specified (see Table 4.5.1., Chapter 4) and was monitored by thin-layer chromatography until the starting material had been consumed. The reaction mixture was then diluted with ether (25 mL) and washed with a saturated aqueous solution of ammonium chloride (5 mL) and water (5 mL). The organic layer was then dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford the crude product. Flash chromatography using hexanes:ether (3:1) as the eluant afforded the *title compounds* (R)-**312** or (*S*)-**312** as colourless oils. The enantiomeric purity of the

reaction products was determined by analytical chiral HPLC (Daicel Chiracel OD column) [hexanes:2-propanol (97:3), flow rate at 0.5 mL/min, detector at λ = 245 nm; t_1 = 19.4 min, t_2 = 20.5 min]. The absolute stereochemistry of the reaction products was determined by comparing the sign of the optical rotation to a literature value.[181] **^{1}H NMR** ($CDCl_3$) δ3.53 (3H, s, CO_2CH_3), 3.71 (3H, s, CO_2CH_3), 3.96 (1H, d, J = 10.7 Hz, $CH(CO_2CH_3)_2$), 4.27 (1H, dd, J = 11.0, 8.6 Hz, ArC*H*), 6.33 (1H, dd, J = 15.9, 8.6 Hz, C*H*), 6.48 (1H, d, J = 15.9 Hz, C*H*), 7.17-7.35 (10H, m, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ49.2, 52.4, 52.6, 57.6, 126.4, 127.2, 127.6, 127.9, 128.5, 128.7, 129.1, 131.8, 136.8, 140.2, 167.8, 168.2; **IR** (KBr) 1759, 1733, 1600, 1494, 1433, 1321, 1261, 1141, 1020, 968, 921, 803, 766, 745, 700 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 324 (M + H, 3), 235 (10), 193 (100).

8.4.9. *Crystallization of the* P,N-*Ligand* (304c)*



304c

The *P,N*-ligand **304c** (20 mg, 33 μmol) and mercury(II) cyanide (8.3 mg, 33 μmol) were dissolved in ethanol:dichloromethane (1:1, 5 mL). Upon slow evaporation of the solvent mixture, colourless X-ray quality crystals of the *P,N*-ligand **304c** were deposited from the solution.

---

(181) Evans, D. A.; Campos, K. R.; Tedrow, J. S.; Michael, F. E.; Gagné, M. R. Application of Chiral Mixed Phosphorus/Sulfur Ligands to Palladium-Catalyzed Allylic Substitutions. *J. Am. Chem. Soc.* **2000**, *122*, 7905.

(*) This procedure was conducted by Mr Neil D. Draper of Professor Daniel B. Leznoff's research group at Simon Fraser University in an attempt to synthesize a chiral coordination polymer of the *P,N*-ligand **304c** and mercury(II) chloride, see: Chapter 4, Section 4.3.

8.4.10. *X-Ray Crystallographic Analysis of the* P,N-*Ligand* (304c)

A single crystal, a colourless block that had the dimensions 0.43 x 0.57 x 0.68 mm^3, was mounted on a glass fiber using epoxy adhesive. The data for this crystal of the *P,N*-ligand **304c** was acquired at 293 K on an Enraf Nonius CAD4F diffractometer using graphite monochromated Mo Kα radiation. The following data range was recorded: $4^\circ \leq 2\theta \leq 50^\circ$. The data was corrected by integration for the effects of absorption using a semi-empirical psi-scan method with the following transmission range: 0.8730 - 0.9819. The data reduction included corrections for Lorentz and polarization effects. Final unit-cell dimensions were determined based on the following well-centred reflections: 42 reflections with range $38^\circ \leq 2\theta \leq 42^\circ$.

For the *P,N*-ligand **304c**, the coordinates and anisotropic displacement parameters for the non-carbon and hydrogen atoms were refined; carbon atoms were refined using isotropic thermal parameters. Hydrogen atoms were placed in calculated positions (d C-H 0.95 Å) and their coordinate shifts were linked with those of the respective carbon atoms during refinement. Isotropic thermal parameters for the hydrogen atoms were initially assigned proportionately to the equivalent isotropic thermal parameters of their respective carbon atoms. Subsequently, the isotropic thermal parameters for the C-H hydrogen atoms were constrained to have identical shifts during refinement.

The programs used for all absorption corrections, data reduction, and processing were from the *NRCVAX* Crystal Structure System.[182] The structure was refined using *CRYSTALS*. [177] An *ORTEP* representation of the *P,N*-ligand **304c** is provided below (Figure 8.4.1.). Crystallographic data, fractional atomic coordinates and equivalent

(182) Gabe, E. J.; Lepage, Y.; Charland, J. P.; Lee, F. L.; White, P. S. *J. Appl. Cryst.* **1989**, *22*, 384-387.

isotropic thermal displacement parameters, selected bond lengths, and selected bond angles for the *P,N*-ligand **304c** are also listed below (Table 8.4.1., 8.4.2., 8.4.3. and 8.4.4., respectively).

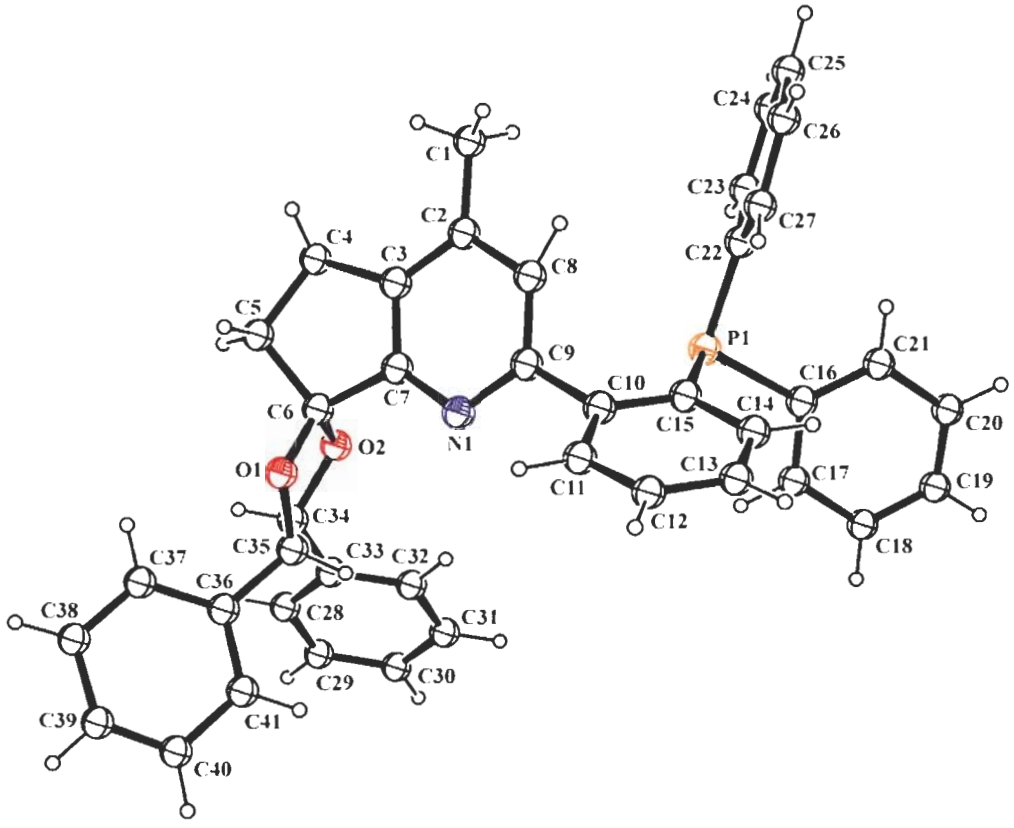


Figure 8.4.1. *ORTEP* representation of the *P,N*-ligand **304c**.*

(*) The thermal ellipsoids are drawn at a 25% probability level for clarity.

Table 8.4.1. Summary of Crystallographic Data for the *P,N*-ligand **304c**

Empirical formula	$C_{41}H_{34}NO_2P$
FW (g mol^{-1})	1206.27
Temperature (K)	293
Wavelength (Cu $K\alpha$, Å)	1.54180
Crystal system	monoclinic
Space group	$P\ 2_1$
a (Å)	14.1365(15)
b (Å)	11.0559(16)
c (Å)	21.938(3)
α (°)	90
β (°)	101.754 (9)
γ (°)	90
Z	2
U (Å^3)	3356.8(8)
D_{calc} (g cm^{-3})	1.195
2θ limits (°)	4-50
Reflections collected	8594
Independent reflections	8288
Reflections observed [$I = 2.5\sigma(I)$]	5372
Goodness-of-fit on F	2.8054
R_1, R_w [$I = 2.5\sigma(I)$]	0.053, 0.0551

Table 8.4.2. Fractional Atomic Coordinates (Å) and Equivalent Isotropic Thermal Displacement Parameters [*U*(iso), (Å^2)] for the *P,N*-Ligand **304c***

atom	*x*	*y*	*z*	*U* (iso)
P1	-0.43163(12)	-0.59752(16)	-0.75708(6)	0.0565
O1	-0.2250(3)	-0.2903(4)	-0.97644(16)	0.0673
O2	-0.2420(3)	-0.1845(4)	-0.89034(15)	0.0583
N1	-0.3259(3)	-0.4492(4)	-0.90222(19)	0.0497
C1	-0.6254(4)	-0.3389(6)	-0.9238(2)	0.0670
C2	-0.5220(4)	-0.3747(5)	-0.9170(2)	0.0421
C3	-0.4515(4)	-0.3001(5)	-0.9327(2)	0.0475
C4	-0.4597(4)	-0.1740(6)	-0.9604(3)	0.0689
C5	-0.3656(4)	-0.1629(6)	-0.9857(2)	0.0662
C6	-0.2934(4)	-0.2461(5)	-0.9438(2)	0.0549
C7	-0.3582(4)	-0.3423(5)	-0.9242(2)	0.0468
C8	-0.4893(4)	-0.4883(5)	-0.8941(2)	0.0507
C9	-0.3937(4)	-0.5234(5)	-0.8871(2)	0.0461
C10	-0.3657(4)	-0.6501(5)	-0.8664(2)	0.0456
C11	-0.3200(4)	-0.7209(6)	-0.9041(3)	0.0579
C12	-0.3028(4)	-0.8410(6)	-0.8904(3)	0.0626
C13	-0.3284(4)	-0.8922(5)	-0.8395(3)	0.0625
C14	-0.3703(4)	-0.8228(5)	-0.8005(3)	0.0576
C15	-0.3897(4)	-0.6988(5)	-0.8129(2)	0.0497
C16	-0.3859(4)	-0.6775(5)	-0.6837(2)	0.0549(14)
C17	-0.2899(4)	-0.6672(6)	-0.6595(3)	0.0724(17)
C18	-0.2470(5)	-0.7223(6)	-0.6025(3)	0.086(2)
C19	-0.3045(4)	-0.7801(6)	-0.5708(3)	0.0735(17)
C20	-0.3998(4)	-0.7945(5)	-0.5930(3)	0.0664(16)
C21	-0.4424(4)	-0.7403(5)	-0.6507(2)	0.0601(15)

(*) The occupancies for all atoms listed in this table are 1.0.

C22	-0.5605(4)	-0.6240(5)	-0.7696(2)	0.0591(15)
C23	-0.6101(4)	-0.7128(6)	-0.8073(3)	0.0678(17)
C24	-0.7106(5)	-0.7220(6)	-0.8166(3)	0.090(2)
C25	-0.7608(6)	-0.6422(7)	-0.7865(3)	0.103(2)
C26	-0.7127(6)	-0.5572(7)	-0.7493(3)	0.105(2)
C27	-0.6151(5)	-0.5437(7)	-0.7410(3)	0.086(2)
C28	-0.0152(5)	-0.0508(7)	-0.8321(3)	0.0984
C29	0.0500(6)	-0.0340(11)	-0.7766(4)	0.1331
C30	0.0518(7)	-0.1123(13)	-0.7288(5)	0.1466
C31	-0.0123(7)	-0.2075(10)	-0.7351(4)	0.1350
C32	-0.0765(5)	-0.2220(7)	-0.7904(3)	0.1015
C33	-0.0780(4)	-0.1463(6)	-0.8395(3)	0.0678
C34	-0.1467(4)	-0.1661(6)	-0.9005(2)	0.0566
C35	-0.1310(4)	-0.2758(6)	-0.9379(3)	0.0644
C36	-0.0583(5)	-0.2658(7)	-0.9785(4)	0.0890
C37	-0.0772(7)	-0.1971(10)	-1.0327(4)	0.1364
C38	-0.0083(10)	-0.1845(14)	-1.0690(5)	0.1800
C39	0.0754(9)	-0.2503(18)	-1.0508(7)	0.1989
C40	0.0972(10)	-0.3158(19)	-1.0003(7)	0.2103
C41	0.0267(7)	-0.3255(10)	-0.9622(5)	0.1475
H11	-0.6363(4)	-0.2636(6)	-0.9449(2)	0.114(9)
H12	-0.6652(4)	-0.3992(6)	-0.9469(2)	0.114(9)
H13	-0.6405(4)	-0.3318(6)	-0.8837(2)	0.114(9)
H41	-0.5151(4)	-0.1665(6)	-0.9930(3)	0.116(9)
H42	-0.4622(4)	-0.1146(6)	-0.9295(3)	0.116(9)
H51	-0.3760(4)	-0.1884(6)	-1.0279(2)	0.113(9)
H52	-0.3429(4)	-0.0818(6)	-0.9826(2)	0.113(9)
H81	-0.5538(4)	-0.5054(5)	-0.8905(2)	0.095(4)
H111	-0.3005(4)	-0.6860(6)	-0.9392(3)	0.071(4)
H121	-0.2725(4)	-0.8892(6)	-0.9167(3)	0.079(4)

H131	-0.3177(4)	-0.9760(5)	-0.8314(3)	0.077(4)
H141	-0.3861(4)	-0.8587(5)	-0.7645(3)	0.074(4)
H171	-0.2508(4)	-0.6213(6)	-0.6815(3)	0.090(4)
H181	-0.1792(5)	-0.7176(6)	-0.5871(3)	0.107(4)
H191	-0.2769(4)	-0.8137(6)	-0.5314(3)	0.092(4)
H201	-0.4382(4)	-0.8395(5)	-0.5702(3)	0.083(4)
H211	-0.5099(4)	-0.7476(5)	-0.6665(2)	0.077(4)
H231	-0.5753(4)	-0.7688(6)	-0.8271(3)	0.086(4)
H241	-0.7440(5)	-0.7823(6)	-0.8435(3)	0.111(4)
H251	-0.8290(6)	-0.6484(7)	-0.7920(3)	0.124(4)
H261	-0.7481(6)	-0.5038(7)	-0.7285(3)	0.130(4)
H271	-0.5838(5)	-0.4802(7)	-0.7154(3)	0.102(4)
H281	-0.0166(5)	0.0046(7)	-0.8653(3)	0.122(4)
H291	0.0945(6)	0.0314(11)	-0.7722(4)	0.161(4)
H301	0.0961(7)	-0.1006(13)	-0.6904(5)	0.175(4)
H311	-0.0118(7)	-0.2629(10)	-0.7019(4)	0.162(4)
H321	-0.1213(5)	-0.2870(7)	-0.7947(3)	0.122(4)
H341	-0.1463(4)	-0.0963(6)	-0.9257(2)	0.072(4)
H351	-0.1158(4)	-0.3435(6)	-0.9110(3)	0.080(4)
H371	-0.1376(7)	-0.1573(10)	-1.0450(4)	0.172(4)
H381	-0.0186(10)	-0.1342(14)	-1.1049(5)	0.231(4)
H391	0.1210(9)	-0.2481(18)	-1.0771(7)	0.250(4)
H401	0.1583(10)	-0.3544(19)	-0.9890(7)	0.262(4)
H411	0.0401(7)	-0.3740(10)	-0.9257(5)	0.178(4)

Table 8.4.3. Bond Lengths (Å) for the *P,N*-Ligand **304c**

P1-C15	1.843(5)
P1-C16	1.836(5)
P1-C22	1.810(6)
O1-C6	1.402(6)

O1-C35	1.432(6)
O2-C6	1.422(6)
O2-C34	1.424(6)
N1-C7	1.323(7)
N1-C9	1.353(7)
C1-C2	1.491(7)
C2-C3	1.390(7)
C2-C8	1.396(7)
C3-C4	1.517(8)
C3-C7	1.376(7)
C4-C5	1.547(8)
C5-C6	1.534(7)
C6-C7	1.521(7)
C8-C9	1.384(7)
C9-C10	1.501(7)
C10-C11	1.391(7)
C10-C15	1.395(7)
C11-C12	1.372(8)
C12-C13	1.364(8)
C13-C14	1.370(7)
C14-C15	1.414(7)
C16-C17	1.357(7)
C16-C21	1.371(7)
C17-C18	1.413(8)
C18-C19	1.335(8)
C19-C20	1.345(7)
C20-C21	1.419(7)
C22-C23	1.379(7)
C22-C27	1.406(8)
C23-C24	1.397(8)

C24-C25	1.381(9)
C25-C26	1.336(9)
C26-C27	1.362(8)
C28-C29	1.382(9)
C28-C33	1.367(9)
C29-C30	1.357(14)
C30-C31	1.377(14)
C31-C32	1.369(10)
C32-C33	1.361(9)
C33-C34	1.501(7)
C34-C35	1.504(8)
C35-C36	1.495(9)
C36-C37	1.392(11)
C36-C41	1.352(10)
C37-C38	1.385(11)
C38-C39	1.377(17)
C39-C40	1.31(2)
C40-C41	1.429(14)

Table 8.4.4. Bond Angles (°) for the *P,N*-Ligand **304c**

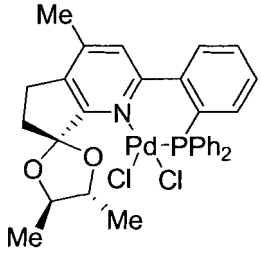
C15-P1-C16	100.7(2)
C15-P1-C22	104.5(2)
C16-P1-C22	102.7(2)
C6-O1-C35	108.2(4)
C6-O2-C34	106.3(4)
C7-N1-C9	115.0(5)
C2-C1-H12	109.2(3)
C1-C2-C3	123.7(5)
C1-C2-C8	121.4(5)
C3-C2-C8	114.9(5)

C2-C3-C4	130.2(5)
C2-C3-C7	118.8(6)
C4-C3-C7	111.0(5)
C3-C4-C5	102.4(5)
C4-C5-C6	104.7(4)
C4-C5-H51	110.6(3)
C5-C6-O2	111.9(5)
C5-C6-O1	110.3(4)
O2-C6-O1	107.4(4)
C5-C6-C7	102.9(5)
O2-C6-C7	109.8(4)
O1-C6-C7	114.7(5)
C6-C7-C3	110.0(5)
C6-C7-N1	123.0(5)
C3-C7-N1	127.0(5)
C2-C8-C9	122.4(5)
C8-C9-N1	121.9(5)
C8-C9-C10	119.1(5)
N1-C9-C10	119.0(5)
C9-C10-C11	118.1(5)
C9-C10-C15	121.4(5)
C11-C10-C15	120.4(5)
C10-C11-C12	119.8(6)
C11-C12-C13	121.1(6)
C12-C13-C14	120.0(5)
C13-C14-C15	121.0(5)
P1-C15-C14	122.5(4)
P1-C15-C10	119.4(4)
C14-C15-C10	117.7(5)
P1-C16-C17	116.6(4)

P1-C16-C21	124.6(4)
C17-C16-C21	118.7(5)
C16-C17-C18	121.6(6)
C18-C17-H171	119.3(4)
C17-C18-C19	118.0(7)
C18-C19-C20	122.7(6)
C19-C20-C21	119.0(6)
C20-C21-C16	119.8(5)
P1-C22-C23	125.4(5)
P1-C22-C27	117.2(5)
C23-C22-C27	117.3(6)
C22-C23-C24	121.1(6)
C23-C24-C25	119.3(7)
C24-C25-C26	119.6(8)
C25-C26-C27	122.3(8)
C22-C27-C26	120.3(7)
C29-C28-C33	120.6(8)
C28-C29-C30	119.9(10)
C29-C30-C31	120.1(9)
C30-C31-C32	118.9(10)
C31-C32-C33	122.0(8)
C28-C33-C32	118.4(6)
C28-C33-C34	120.4(6)
C32-C33-C34	121.2(6)
C33-C34-O2	110.0(4)
C33-C34-C35	117.6(5)
O2-C34-C35	102.7(4)
C34-C35-O1	101.0(4)
C34-C35-C36	117.4(5)
O1-C35-C36	108.9(5)

C35-C36-C37	120.9(7)
C35-C36-C41	119.2(9)
C37-C36-C41	119.9(8)
C36-C37-C38	120.8(10)
C37-C38-C39	116.3(12)
C38-C39-C40	125.4(14)
C39-C40-C41	117.8(15)
C40-C41-C36	119.8(11)

8.4.11. *Procedure for the Preparation and Crystallization of the $PdCl_2$·P,N-Ligand* (304a) *Complex*



A solution of the ligand **304a** (20 mg, 42 μmol) and palladium(II) chloride (7.4 mg, 42 μmol) in acetonitrile (2 mL) was heated at reflux for 30 min. The reaction mixture was then allowed to cool to room temperature and was concentrated *in vacuo* to afford the crude product. This material was then dissolved in hot ethanol (1 mL) and upon cooling to 5 °C, the *title compound* (21 mg, 77%) was obtained as orange X-ray quality crystals. **M.p.** >210 °C (dec.), ethanol; $[\alpha]_D^{20}$ - 55 (*c* 0.15, chloroform); **IR** (KBr) 2362, 2340, 1996, 1656, 1610, 1561, 1547, 1438, 1090, 1074 873 cm^{-1}; **MS** (MALDI-TOF) *m/z* 620 (M - Cl); **Anal.** Calcd. for $C_{31}H_{30}Cl_2NO_2PPd$: C, 56.68; H, 4.60; N, 2.13. Found: C, 56.31; H, 4.42; N, 2.27.

8.4.12. *X-Ray Crystallographic Analysis of the $PdCl_2$·P,N-Ligand* (304a) *Complex*

A single crystal, an orange platelet that had the dimensions 0.09 x 0.26 x 0.26 mm^3, was mounted on a glass fiber using epoxy adhesive. The data for this crystal of the palladium(II) chloride *P,N*-ligand **304a** complex was acquired at 293 K on an Enraf Nonius CAD4F diffractometer with graphite monochromated Mo Kα radiation. The following data range was recorded: $4^\circ \leq 2\theta \leq 46^\circ$. The data was corrected by integration for the effects of absorption using a semi-empirical psi-scan method with the following transmission range: 0.5362 – 0.9151. The data reduction included corrections for Lorentz and polarization effects. Final unit-cell dimensions were determined based on the following well-centred reflections: 56 reflections with range $30^\circ \leq 2\theta \leq 38^\circ$.

The coordinates and anisotropic displacement parameters for the non-carbon and hydrogen atoms were refined. Carbon atoms were refined using isotropic thermal parameters. Hydrogen atoms were placed in calculated positions (d C-H 0.95 Å) and their coordinate shifts were linked with those of the respective carbon atoms during refinement. Isotropic thermal parameters for the hydrogen atoms were initially assigned proportionately to the equivalent isotropic thermal parameters of their respective carbon atoms. Subsequently the isotropic thermal parameters for the C-H hydrogen atoms were constrained to have identical shifts during refinement. The programs used for all absorption corrections, data reduction, and processing were from the *NRCVAX* Crystal Structure System.[184] The structure was refined using *CRYSTALS*.[177]

An *ORTEP* representation of the palladium(II) chloride *P,N*-ligand **304a** complex is provided below (Figure 8.4.2.). Crystallographic data, fractional atomic coordinates and equivalent isotropic thermal displacement parameters, selected bond lengths, and

selected bond angles for the palladium(II) chloride *P,N*-ligand **304a** complex are also listed below (Table 8.4.5., 8.4.6., 8.4.7. and 8.4.8., respectively).

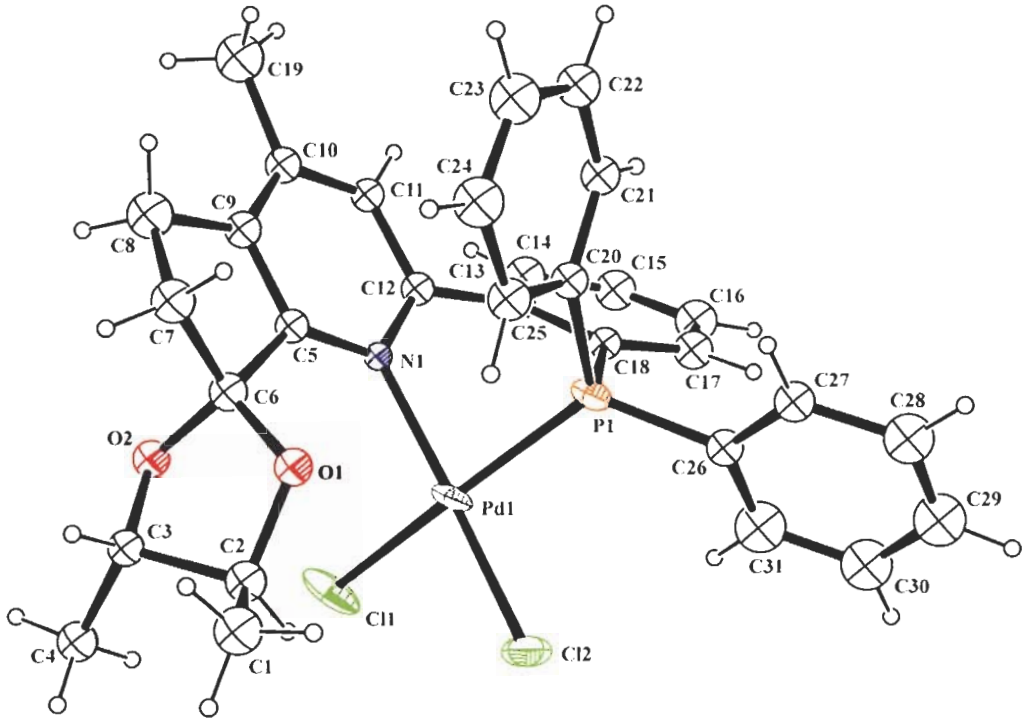


Figure 8.4.2. *ORTEP* representation of the $PdCl_2$·*P,N*-ligand **304a** complex.*

Table 8.4.5. Summary of Crystallographic Data for the $PdCl_2$·*P,N*-ligand **304a** Complex

Empirical formula	$C_{31}H_{30}NCl_2O_2PPd$
FW (g mol^{-1})	656.8746
Temperature (K)	293
Crystal system	orthorhombic
Space group	*P* 2_1 2_1 2_1
a (Å)	11.6538(13)

(*) The thermal ellipsoids are drawn at a 25% probability level for clarity.

b (Å)	13.3090(19)
c (Å)	18.802(3)
α (°)	90
β (°)	90
γ (°)	90
Z	4
U (Å^3)	2916.2(7)
D_{calc} (g cm^{-3})	1.496
2θ limits (°)	4-46
Reflections collected	2505
Independent reflections	2335
Reflections observed [$I = 2.5\sigma(I)$]	1296
Goodness-of-fit on F	1.6738
R_1, R_w [$I = 2.5\sigma(I)$]	0.066, 0.074

Table 8.4.6. Fractional Atomic Coordinates (Å) and Equivalent Isotropic Thermal Displacement Parameters [U(iso), (Å^2)] for the $PdCl_2$·*P,N*-ligand **304a** Complex*

Atom	x	y	z	U (iso)
Pd1	0.70704(12)	0.24533(17)	0.28174(8)	0.0492
Cl1	0.6244(5)	0.2590(9)	0.3969(3)	0.0940
Cl2	0.7725(7)	0.0849(5)	0.3019(4)	0.0885
P1	0.7147(5)	0.2335(6)	0.1647(3)	0.0531
O1	0.9128(12)	0.3414(11)	0.3268(7)	0.050(4)
O2	0.8292(11)	0.4447(12)	0.4074(7)	0.051(4)
N1	0.6870(11)	0.3969(11)	0.2613(7)	0.031(4)

(*) The occupancies for all atoms listed in this table are 1.0.

C1	1.0439(18)	0.248(2)	0.4016(12)	0.077(7)
C2	0.9285(19)	0.289(2)	0.3952(12)	0.059(7)
C3	0.9119(18)	0.3857(17)	0.445(1)	0.047(6)
C4	0.858(2)	0.3556(18)	0.5186(11)	0.060(7)
C5	0.7653(16)	0.4623(15)	0.2854(12)	0.043(5)
C6	0.8681(19)	0.4391(18)	0.3343(11)	0.053(6)
C7	0.9494(19)	0.5226(17)	0.3146(13)	0.068(7)
C8	0.875(2)	0.611(2)	0.2994(14)	0.079(8)
C9	0.7691(17)	0.5628(16)	0.269(1)	0.051(6)
C10	0.6781(16)	0.6011(16)	0.2285(11)	0.052(6)
C11	0.6040(17)	0.5367(15)	0.2028(11)	0.045(6)
C12	0.6045(16)	0.4331(15)	0.2178(12)	0.045(5)
C13	0.5315(17)	0.3653(16)	0.1756(11)	0.045(6)
C14	0.419(2)	0.396(2)	0.1668(13)	0.068(7)
C15	0.345(2)	0.332(2)	0.1274(14)	0.075(8)
C16	0.382(2)	0.250(2)	0.0952(12)	0.078(7)
C17	0.4931(18)	0.2205(19)	0.1050(12)	0.063(7)
C18	0.5683(16)	0.2759(17)	0.145(1)	0.042(5)
C19	0.675(2)	0.7103(19)	0.2045(14)	0.094(9)
C20	0.8137(17)	0.3187(17)	0.1214(11)	0.048(6)
C21	0.779(2)	0.3785(17)	0.0638(12)	0.055(7)
C22	0.857(2)	0.444(2)	0.0343(13)	0.066(8)
C23	0.962(2)	0.456(2)	0.0659(14)	0.086(9)
C24	0.999(2)	0.402(2)	0.1223(14)	0.083(9)
C25	0.9209(19)	0.329(2)	0.1517(13)	0.063(7)
C26	0.7267(18)	0.1145(18)	0.1192(11)	0.050(6)
C27	0.796(2)	0.1026(18)	0.0620(12)	0.058(7)
C28	0.788(2)	0.011(2)	0.0219(14)	0.089(9)
C29	0.725(3)	-0.063(3)	0.0422(15)	0.10(1)
C30	0.655(2)	-0.052(3)	0.1008(16)	0.10(1)

C31	0.655(3)	0.039(2)	0.1389(17)	0.10(1)
H11	1.0489(18)	0.213(2)	0.4455(12)	0.15(4)
H12	1.0985(18)	0.301(2)	0.4009(12)	0.15(4)
H13	1.0592(18)	0.203(2)	0.3636(12)	0.15(4)
H41	0.910(2)	0.3168(18)	0.5458(11)	0.12(4)
H42	0.837(2)	0.4142(18)	0.5445(11)	0.12(4)
H43	0.791(2)	0.3170(18)	0.5092(11)	0.12(4)
H2	0.8783(19)	0.234(2)	0.4020(12)	0.04(4)
H3	0.9831(18)	0.4175(17)	0.455(1)	0.04(4)
H71	1.0017(19)	0.5345(17)	0.3525(13)	0.07(4)
H72	0.9908(19)	0.5057(17)	0.2728(13)	0.07(4)
H81	0.859(2)	0.646(2)	0.3423(14)	0.09(4)
H82	0.909(2)	0.656(2)	0.2663(14)	0.09(4)
H111	0.5439(17)	0.5620(15)	0.1738(11)	0.05(3)
H14	0.391(2)	0.457(2)	0.1867(13)	0.06(3)
H15	0.267(2)	0.351(2)	0.1218(14)	0.09(3)
H16	0.331(2)	0.208(2)	0.0697(12)	0.08(3)
H17	0.5239(18)	0.1634(19)	0.0814(12)	0.06(3)
H191	0.607(2)	0.7217(19)	0.1779(14)	0.04(3)
H192	0.678(2)	0.7552(19)	0.2437(14)	0.04(3)
H193	0.740(2)	0.7212(19)	0.1749(14)	0.04(3)
H21	0.704(2)	0.3728(17)	0.0452(12)	0.08(3)
H22	0.838(2)	0.481(2)	-0.0073(13)	0.09(3)
H23	1.012(2)	0.505(2)	0.0456(14)	0.11(3)
H24	1.071(2)	0.415(2)	0.1432(14)	0.11(3)
H25	0.9459(19)	0.286(2)	0.1889(13)	0.09(3)
H27	0.848(2)	0.1547(18)	0.0500(12)	0.08(3)
H28	0.833(2)	0.001(2)	-0.0198(14)	0.12(3)
H29	0.726(3)	-0.125(3)	0.0181(15)	0.12(3)
H30	0.604(2)	-0.105(3)	0.1133(16)	0.14(3)

H31	0.606(3)	0.046(2)	0.1793(17)	0.12(3)

Table 8.4.7. Bond Lengths (Å) for the $PdCl_2$·*P,N*-ligand **304a** Complex

Pd1-Cl1	2.376(6)
Pd1-Cl2	2.299(7)
Pd1-P1	2.209(5)
Pd1-N1	2.067(14)
P1-C18	1.835(19)
P1-C20	1.81(2)
P1-C26	1.81(2)
O1-C2	1.47(2)
O1-C6	1.41(3)
O2-C3	1.43(2)
O2-C6	1.45(2)
N1-C5	1.34(2)
N1-C12	1.35(2)
C1-C2	1.46(3)
C2-C3	1.60(3)
C3-C4	1.57(3)
C5-C6	1.54(3)
C5-C9	1.37(3)
C6-C7	1.51(3)
C7-C8	1.49(3)
C8-C9	1.51(3)
C9-C10	1.40(2)
C10-C11	1.31(2)
C10-C19	1.52(3)
C11-C12	1.41(3)
C12-C13	1.47(3)
C13-C14	1.39(3)

C13-C18	1.39(3)
C14-C15	1.41(3)
C15-C16	1.32(3)
C16-C17	1.36(3)
C17-C18	1.37(3)
C20-C21	1.40(3)
C20-C25	1.38(3)
C21-C22	1.38(3)
C22-C23	1.37(3)
C23-C24	1.35(3)
C24-C25	1.44(3)
C26-C27	1.35(3)
C26-C31	1.37(3)
C27-C28	1.44(3)
C28-C29	1.28(3)
C29-C30	1.38(3)
C30-C31	1.41(4)

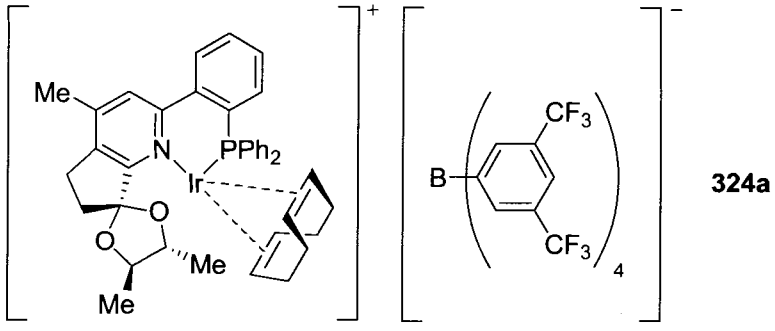
Table 8.4.8. Bond Angles (°) for the $PdCl_2 \cdot$ *P,N*-ligand **304a** Complex

Cl1-Pd1-Cl2	93.2(3)
Cl1-Pd1-P1	158.4(2)
Cl2-Pd1-P1	94.9(3)
Cl1-Pd1-N1	92.8(5)
Cl2-Pd1-N1	167.1(4)
P1-Pd1-N1	83.6(4)
Pd1-P1-C18	98.2(6)
Pd1-P1-C20	115.4(8)
C18-P1-C20	108.0(11)
Pd1-P1-C26	122.5(7)
C18-P1-C26	104.2(10)

C20-P1-C26	106.7(10)
C2-O1-C6	113.1(16)
C3-O2-C6	103.5(16)
Pd1-N1-C5	119.7(12)
Pd1-N1-C12	122.7(12)
C5-N1-C12	117.2(16)
O1-C2-C1	111.4(19)
O1-C2-C3	97.0(17)
C1-C2-C3	111.5(20)
O2-C3-C2	103.3(16)
O2-C3-C4	107.9(17)
C2-C3-C4	111.2(18)
N1-C5-C6	126.9(18)
N1-C5-C9	125.4(19)
C6-C5-C9	107.7(18)
O1-C6-O2	105.0(18)
O1-C6-C5	114.4(18)
O2-C6-C5	108.2(16)
O1-C6-C7	115.1(17)
O2-C6-C7	113.0(19)
C5-C6-C7	101.2(17)
C6-C7-C8	105.5(18)
C7-C8-C9	102.1(20)
C5-C9-C8	111.0(19)
C5-C9-C10	116.8(19)
C8-C9-C10	132.1(20)
C9-C10-C11	117.5(20)
C9-C10-C19	121.7(19)
C11-C10-C19	120.1(20)
C10-C11-C12	124.4(20)

N1-C12-C11	118.3(18)
N1-C12-C13	121.3(18)
C11-C12-C13	119.3(19)
C12-C13-C14	115.6(20)
C12-C13-C18	124.8(18)
C14-C13-C18	119.7(21)
C13-C14-C15	117.3(25)
C14-C15-C16	122.8(27)
C15-C16-C17	119.0(28)
C16-C17-C18	121.6(25)
P1-C18-C13	117.7(15)
P1-C18-C17	122.7(17)
C13-C18-C17	119.4(19)
C10-C19-H193	107.6(12)
P1-C20-C21	121.3(17)
P1-C20-C25	117.0(18)
C21-C20-C25	121.5(23)
C20-C21-C22	118.9(24)
C21-C22-C23	119.1(25)
C22-C23-C24	124.0(29)
C23-C24-C25	117.6(27)
C20-C25-C24	118.7(24)
P1-C26-C27	121.7(19)
P1-C26-C31	118.2(20)
C27-C26-C31	119.7(26)
C26-C27-C28	118.4(26)
C27-C28-C29	122.1(30)
C28-C29-C30	120.1(36)
C29-C30-C31	119.5(33)
C26-C31-C30	119.8(29)

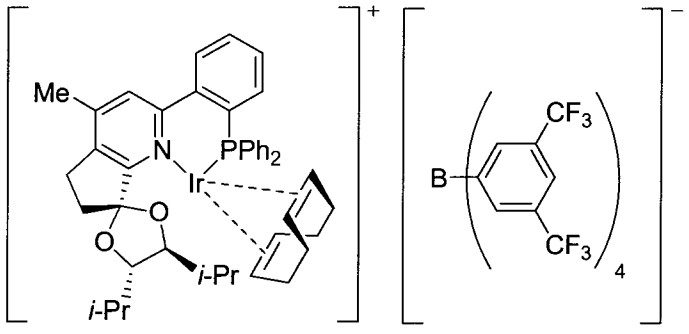
8.4.13. ***2-(2-Diphenylphosphanyl-phenyl)-4-methyl-6,7-dihydro-5H-[1]pyrindine-7-one (2R,3R)-2,3-Butanediol Acetal Iridium(I) Cyclooctadiene*** **tetrakis*[3,5-bis(Trifluoromethyl)phenyl]borate Complex* (324a)**



324a

A deep orange solution of the *P,N*-ligand **304a** (18 mg, 38 μmol) and cyclooctadieneiridium(I) chloride dimer (13 mg, 19 μmol) in anhydrous dichloromethane (3 mL) was heated at reflux for 1 h. The reaction mixture was then allowed to cool to room temperature and sodium *tetrakis*[3,5-*bis*(trifluoromethyl)phenyl]borate (50 mg, 56 μmol) and water (3 mL) were added. The resultant biphasic mixture was stirred vigorously for 15 min. The two phases were then separated and the aqueous phase was extracted with dichloromethane (2 x 10 mL). The combined organic extracts were washed with water (10 mL) and concentrated *in vacuo* to afford the crude product. This material was then taken up in ethanol (1 mL) and crystallized by the slow addition of water (1 mL) which afforded the *title compound* **324a** (56 mg, 89%) as an orange crystalline solid. **Anal.** Calcd. for $C_{71}H_{54}BF_{24}IrNO_2P$: C, 51.90; H, 3.31; N, 0.85. Found: C, 52.23; H, 3. 49; N, 0.78.

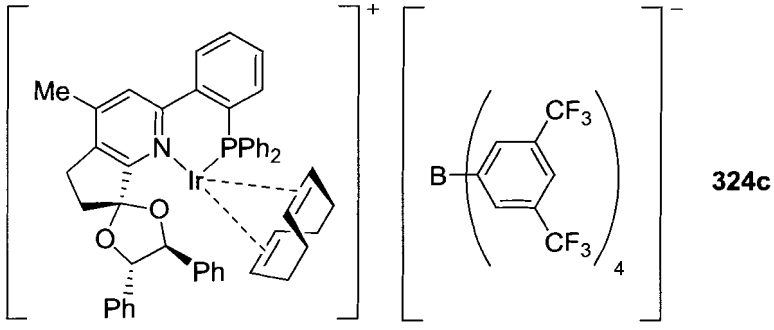
8.4.14. *2-(2-Diphenylphosphanyl-phenyl)-4-methyl-6,7-dihydro-5H-[1]pyrindine-7-one (1S,2S)-1,2-Diisopropylethanediol Acetal Iridium(I) Cyclooctadiene* tetrakis*[3,5-bis(Trifluoromethyl)phenyl]borate Complex* (324b)



324b

A deep orange solution of the *P,N*-ligand **304b** (71 mg, 0.13 mmol) and cyclooctadieneiridium(I) chloride dimer (45 mg, 65 μmol) in anhydrous dichloromethane (4 mL) was heated at reflux for 1 h. The reaction mixture was then allowed to cool to room temperature and sodium *tetrakis*[3,5-*bis*(trifluoromethyl)phenyl]borate (177 mg, 0.20 mmol) and water (4 mL) were added. The resultant biphasic mixture was stirred vigorously for 15 min. The two phases were then separated and the aqueous phase was extracted with dichloromethane (2 x 10 mL). The combined organic extracts were washed with water (10 mL) and concentrated *in vacuo* to afford the crude product. This material was then taken up in ethanol (2 mL) and crystallized by the slow addition of water (2 mL) which afforded the *title compound* **324b** (219 mg, 97%) as an orange crystalline solid. **Anal.** Calcd. for $C_{75}H_{62}BF_{24}IrNO_2P$: C, 53.01; H, 3.68; N, 0.82. Found: C, 53.26; H, 3. 53; N, 0.78.

8.4.15. ***2-(2-Diphenylphosphanyl-phenyl)-4-methyl-6,7-dihydro-5H-[1]pyrindine-7-one (1S,2S)-1,2-Diphenyl-1,2-ethanediol Acetal Iridium(I) Cyclooctadiene*** **tetrakis*[3,5-bis(Trifluoromethyl)phenyl]borate Complex* (324c)**

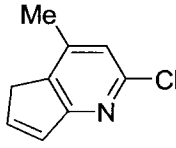


324c

A deep orange solution of the *P,N*-ligand **304c** (80 mg, 0.13 mmol) and cyclooctadieneiridium(I) chloride dimer (45 mg, 67 μmol) in anhydrous dichloromethane (4 mL) was heated at reflux for 1 h. The reaction mixture was allowed to cool to room temperature and sodium *tetrakis*[3,5-*bis*(trifluoromethyl)phenyl]borate (177 mg, 0.20 mmol) and water (4 mL) were added. The resultant biphasic mixture was stirred vigorously for 15 min. The two phases were then separated and the aqueous phase was extracted with dichloromethane (2 x 10 mL). The combined organic extracts were washed with water (10 mL) and concentrated *in vacuo* to afford the crude product. This material was then taken up in ethanol (2 mL) and crystallized by the slow addition of water (2 mL) which afforded the *title compound* **324c** (211 mg, 92%) as an orange crystalline solid. **Anal.** Calcd. for $C_{81}H_{58}BF_{24}IrNO_2P$: C, 55.05; H, 3.31; N, 0.79. Found: C, 55.17; H, 3. 20; N, 0.65.

8.5. Experimental Procedures and Characterization Data Concerning Chapter 5

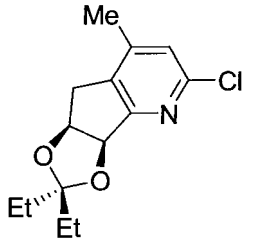
8.5.1. *2-Chloro-4-methyl-5*H*-[1]pyrindine* (336)



336

A stirred solution of the acetate **282** (901 mg, 3.99 mmol) in concentrated sulfuric acid (1.5 mL) was heated at 120 °C for 10 min. The reaction mixture was then poured on to ice (~25 g) and was basified with an aqueous solution of potassium hydroxide (40% w/v, 6 mL). The resultant mixture was extracted with dichloromethane (3 x 25 mL) and the combined organic extracts were washed with water (2 x 10 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford the crude product as a dark brown oil. Flash chromatography using hexanes:ether (1:1) as the eluant afforded the *title compound* **336** (535 mg, 81%) as a colourless oil. **^{1}H NMR** ($CDCl_3$) δ 2.36 (3H, s, CH_3), 3.29-3.32 (2H, m, ArCH_2), 6.91-6.98 (3H, m, 2 x C*H* and Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 35.5, 38.4, 120.1, 133.1, 134.6, 139.9, 144.1, 149.7, 163.9; **IR** (neat) 2919, 1595, 1576, 1550, 1430, 1375, 1333, 1261, 1179, 1116, 1032, 940, 892, 848 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 166 (M + H, 100). This material was used immediately in the subsequent dihydroxylation reactions.

8.5.2. (6S,7R)-*2-Chloro-4-methyl-6,7-dihydro-5H-[1]pyrindine-6,7-diol 3-Pentanone Acetal* [(+)-334]



(+)-**334**

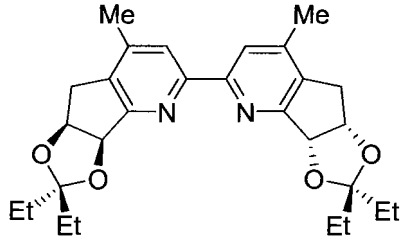
Method A: To a stirred solution of the chloropyridine **336** (101 mg, 0.604 mmol) in *tert*-butanol:water (1:1, 6 mL) at 0 °C was added AD-mix-β (840 mg) in one portion and the resultant orange suspension was stirred at 0 °C for 12 h. Sodium sulfite (300 mg) was then added to the reaction mixture. After an additional 30 min, brine (15 mL) was added and the reaction mixture was extracted with ethyl acetate (3 x 25 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford the crude diol (+)-**335** as a light brown solid. This material was taken up in benzene (6 mL) and 3-pentanone (78 μL, 0.75 mmol) and *p*-toluenesulfonic acid monohydrate (10 mg, 75 μmol) were added. The resultant solution was then heated at reflux in a Dean-Stark trap for 16 h. The reaction mixture was then allowed to cool to room temperature and potassium carbonate (20 mg) was added. The reaction mixture was filtered, the filter-cake was washed with dichloromethane (10 mL) and the combined filtrates were concentrated *in vacuo* to afford the crude product as a dark brown oil. Flash chromatography using hexanes:ethyl acetate (2:1) as the eluant afforded the *title compound* (+)-**334** (92 mg, 57%, over two steps) as a colourless oil which crystallized upon standing. The enantiomeric purity of this material was determined to be 90% ee by analytical chiral HPLC using a Daicel Chiracel OD column [hexanes:isopropanol (96:4), flow rate at 0.5 mL/min, detection at λ = 220 nm;

t_{MAJOR} = 18.99 min, t_{MINOR} = 23.10 min]. The above procedure was also carried out using AD-mix-α. The enantiomeric purity of the product of this reaction, following conversion to the acetal (-)-**334** (48% yield, over two steps), was also determined by analytical chiral HPLC (82% ee). Acetal (+)-**334**: **M.p.** 43-44 °C; $[\alpha]_D^{20}$ + 80 (*c* 0.50, chloroform); **^{1}H NMR** ($CDCl_3$) δ 0.58 (3H, t, *J* = 7.3 Hz, CH_2CH_3), 0.94 (3H, t, *J* = 7.6 Hz, CH_2CH_3), 1.50 (2H, q, *J* = 7.3 Hz, CH_2CH_3), 1.68 (2H, q, *J* = 7.6 Hz, CH_2CH_3), 2.26 (3H, s, $ArCH_3$), 2.99-3.03 (2H, m, CH_2), 4.98-5.02 (1H, m, *H*CO), 5.41 (1H, d, *J* = 5.8 Hz, *H*CO), 7.06 (1H, s, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 7.7, 8.9, 19.0, 29.6, 30.2, 34.34, 77.7, 83.3, 115.9, 124.8, 133.0, 148.0, 151.6, 160.9; **IR** (KBr) 2973, 2939, 1748, 1717, 1589, 1570, 1463, 1442, 1377, 1314, 1286, 1267, 1191, 1169, 1131, 1104, 1084, 1011, 862 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 268 (M + H, 100), 239 (48), 182 (97); **Anal.** Calcd. for $C_{14}H_{18}ClNO_2$: C, 62.80; H, 6.78; N, 5.23. Found: C, 62.65; H, 6.85; N, 5.35.

Method B: To a suspension of potassium osmate dihydrate (2.8 mg, 7.6 μmol, 1 mol %), $(DHQD)_2PHAL$ (29 mg, 38 μmol, 5 mol %), potassium ferricyanide (746 mg, 2.27 mmol) and potassium carbonate (313 mg, 2.27 mmol) in *tert*-butanol:water (1:1, 6 mL) at 0 °C was added the chloropyridine **336** (125 mg, 0.755 mmol). After 2 h, sodium sulfite (300 mg) was added to the reaction mixture. After an additional 30 min, brine (30 mL) was added, the reaction mixture was extracted with ethyl acetate (3 x 25 mL). The combined organic extracts were then washed with brine (10 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford the crude diol (+)-**335** as a light brown solid. This material was taken up in benzene (8 mL) and 3-pentanone (0.10 mL, 0.94 mmol) and *p*-toluenesulfonic acid monohydrate (18 mg, 0.094 mmol) were added. The resultant solution was then heated at reflux in a Dean-Stark trap for 16 h. The

reaction mixture was then allowed to cool to room temperature and potassium carbonate (50 mg) was added. The reaction mixture was filtered, the filter-cake was washed with dichloromethane (10 mL) and the combined filtrates were concentrated *in vacuo* to afford the crude product as a dark brown oil. Flash chromatography using hexanes:ethyl acetate (2:1) as the eluant afforded the *title compound* (+)-**334** (164 mg, 81%) as a colourless oil which crystallized upon standing. $[\alpha]_D^{20}$ + 78 (*c* 0.72, chloroform). The spectroscopic data for this compound was found to be identical in every respect to the material prepared using *Method A*. The enantiomeric purity of this material was determined to be 90% ee by analytical chiral HPLC.

8.5.3. ***(6S,6'S,7R,7'R)-4,4'-Dimethyl-6,6',7,7'-tetrahydro-5H,5'H-2,2'-bi([1]pyrindinyl)-6,6',7,7'-tetraol 3-Pentanone* bis-*Acetal* [(+)-333]**

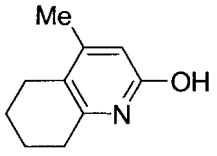


(+)-**333**

To a stirred solution of nickel(II) chloride hexahydrate (135 mg, 0.570 mmol) and triphenylphosphine (597 mg, 2.27 mmol) in anhydrous, degassed dimethylformamide (2 mL) was added zinc dust (<10 microns, 48 mg, 0.73 mmol) and the resultant suspension was heated at 60 °C for 1 h. A solution of the acetal (+)-**334** (150 mg, 0.560 mmol) in anhydrous, degassed dimethylformamide (2 mL) was then added *via* a cannula and resultant mixture was heated at 60 °C for 4 h. The reaction mixture was then allowed to cool to room temperature and was poured into an aqueous solution of ammonium hydroxide (10% w/w, 50 mL). The resultant mixture was extracted with dichloromethane (3 x 15 mL). The combined organic extracts were dried over anhydrous magnesium

sulfate and concentrated *in vacuo* to afford the crude product. Flash chromatography using hexanes:ethyl acetate (2:1) afforded the *title compound* (+)-**333** (109 mg, 84%) as a white crystalline solid. The enantiomeric purity of this material was determined to be >99% ee by analytical chiral HPLC using a Daicel Chiracel OD column [hexanes:isopropanol (60:40), flow rate at 0.5 mL/min, detection at λ = 220 nm; t = 23.59 min]. The enantiomeric ligand (-)-**333** was also prepared from the acetal (-)-**334** (53% yield, unoptimized). The enantiomeric purity of this ligand was also determined to be >99% ee by analytical chiral HPLC using a Daicel Chiracel OD column [hexanes:isopropanol (60:40), flow rate at 0.5 mL/min, detection at λ = 220 nm; t = 17.26 min]. Ligand (+)-**333**: **M.p.** 220-221 °C, hexanes/ethyl acetate; $[\alpha]_D^{20}$ + 154 (*c* 0.50, chloroform); **^{1}H NMR** ($CDCl_3$) δ 0.58 (6H, t, J = 7.6 Hz, CH_2CH_3), 0.98 (6H, t, J = 7.6 Hz, CH_2CH_3), 1.47-1.55 (4H, m, CH_2CH_3), 1.73 (4H, q, J = 7.6 Hz, CH_2CH_3), 2.32 (6H, s, $ArCH_3$), 3.07-3.11 (4H, m, $ArCH_2$), 5.02-5.08 (2H, m, *H*CO), 5.53 (2H, d, J = 5.8 Hz, *H*CO), 8.30 (2H, s, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 7.8, 8.8, 19.0, 29.9, 30.5, 34.9, 78.0, 84.0, 115.71, 122.6, 134.1, 145.4, 157.1, 160.0; **IR** (KBr) 2971, 2937, 1746, 1591, 1463, 1434, 1376, 1307, 1202, 1168, 1135, 1080, 1060, 1009, 974, 932, 841, 730 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 465 (M + H, 59) 123 (100); **FAB HRMS** Calcd. for $C_{28}H_{36}N_2O_4$: 464.2675. Found: 464.2675. **Anal.** Calcd. for $C_{28}H_{36}N_2O_4$: C, 72.39; H, 7.81; N, 6.03. Found: C, 72.28; H, 7.96; N, 5.77.

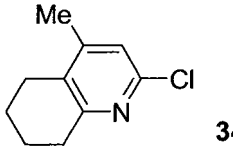
8.5.4. *5,6,7,8-Tetrahydro-4-methylquinolin-2-ol* (347)[116]



347

A mixture of cyclohexanone (50.0 g, 509 mmol), ethyl acetoacetate (66.3 g, 509 mmol) and ammonium acetate (39.2 g, 509 mmol) was heated at reflux for 16 h. The reaction mixture was then allowed to cool to room temperature and was diluted with hexanes (50 mL) which caused product to precipitate from the reaction mixture. The product was isolated by filtration, was washed with hexanes (50 mL) and then recrystallized from ethanol (100 mL) to afford the *title compound* **347** (15.0 g, 18%) as a yellow crystalline solid. **M.p.** 251-252 °C, ethanol (lit.[116] 252-253 °C, ethanol); **^{1}H NMR** ($CDCl_3$) δ 1.71-1.80 (4H, m, 2 x $ArCH_2CH_2$), 2.10 (3H, s, CH_3), 2.34-2.42 (2H, m, $ArCH_2$), 2.62-2.71 (2H, m, $ArCH_2$), 6.25 (1H, s, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 19.8, 21.7, 22.7, 23.9, 27.3, 114.8, 116.3, 142.5, 153.9, 164.5; **IR** (KBr) 3426, 1649, 1538, 1457, 1203, 925, 852 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 164 (M + H, 100)

8.5.5. *2-Chloro-5,6,7,8-tetrahydro-4-methylquinoline* (348)

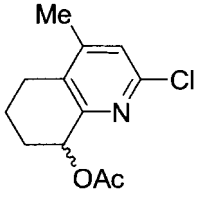


348

To phenylphosphonic dichloride (8.0 mL, 56 mmol) was added the pyridine-2-ol **347** (4.00 g, 24.5 mmol) and the resultant solution was heated in an oil bath at 160 °C for 16 h. The reaction mixture was then allowed to cool to room temperature and water (15 mL) was added dropwise (*CAUTION*). The acidic reaction mixture was then diluted with an additional quantity of water (50 mL), was neutralized by the careful addition of

potassium carbonate (~ 6 g) and extracted with chloroform (3 x 25 mL). The combined organic extracts were washed with water (30 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford the crude product. Flash chromatography using chloroform as the eluant afforded the *title compound* **348** (3.70 g, 84%) as a light yellow oil. **^{1}H NMR** ($CDCl_3$) δ 1.78-1.88 (4H, m, 2 x $ArCH_2CH_2$), 2.19 (3H, s, CH_3), 2.54-2.62 (2H, m, $ArCH_2$), 2.83-2.92 (2H, m, $ArCH_2$), 6.95 (1H, s, ArH); **^{13}C NMR** ($CDCl_3$) δ 19.0, 22.7, 22.7, 25.6, 32.9, 122.4, 130.1, 149.3, 158.0; **IR** (neat) 2937, 2384, 1578, 1556, 1445, 1313, 1270, 1110, 1093, 897 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 182 (M + H, 100); **Anal.** Calcd. for $C_{10}H_{12}ClN$: C, 66.12; H, 6.66; N, 7.71. Found: C, 66.14; H, 6.72; N, 7.69.

8.5.6. *(8RS)-8-Acetoxy-2-chloro-5,6,7,8-tetrahydro-4-methylquinoline* (349)

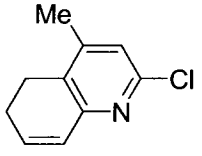


349

To a stirred solution of the chloropyridine **348** (2.70 g, 14.9 mmol) in glacial acetic acid (20 mL) was added an aqueous solution of hydrogen peroxide (30% w/w, 7.1 mL, 69 mmol) and the resultant mixture was heated at 80 °C for 16 h. The reaction mixture was then allowed to cool to room temperature and following concentration *in vacuo* was diluted with water (100 mL). The resultant slightly acidic solution was neutralized by the careful addition of potassium carbonate (~1.0 g) and then was extracted with chloroform (3 x 30 mL). The combined organic extracts were washed with water (3 x 20 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford the corresponding pyridine-*N*-oxide (2.85 g, 97%) as a white crystalline

solid. This material was taken up in acetic anhydride (20 mL) and the resultant suspension was heated slowly to 100 °C over the course of 1 h and then held at this temperature for 4 h. The resultant mixture was allowed to cool to room temperature and was then concentrated *in vacuo* to afford the crude product. Flash chromatography using hexanes:ether (1:1) as the eluant afforded the *title compound* **349** (2.80 g, 77%) as a colourless oil. **^{1}H NMR** ($CDCl_3$) δ 1.79-1.99 (4H, m, 2 x $ArCH_2CH_2$), 2.10 (3H, s, OAc), 2.22 (3H, s, CH_3), 2.45-2.78 (2H, m, $ArCH_2$), 5.83 (1H, apparent t, J = 3.9 Hz, ArCHOAc), 7.08 (1H, s, ArH); **^{13}C NMR** ($CDCl_3$) δ 17.9, 19.0, 22.3, 25.3, 28.4, 71.1, 124.9, 131.7, 149.8, 153.2, 170.3; **IR** (neat) 2358, 2339, 1757, 1650, 1557, 1513, 1369, 1206, 1075 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 240 (M + H, 100), 212 (43), 180 (18); **Anal.** Calcd. for $C_{12}H_{14}ClNO_2$: C, 60.13; H, 5.89; N, 5.84. Found: C, 59.80; H, 5.97; N, 5.49.

8.5.7. *2-Chloro-5,6-dihydro-4-methylquinoline* (345)

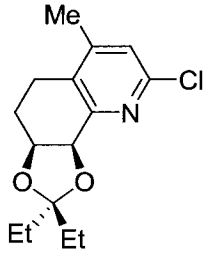


345

To a stirred solution of the acetate **349** (2.00 g, 8.34 mmol) in a mixture of tetrahydrofuran and water (3:1, 20 mL) was added lithium hydroxide monohydrate (1.75 g, 41.7 mmol) and the resultant solution was stirred at room temperature for 5 h. The reaction mixture was then diluted with ether (100 mL) and was washed with water (3 x 30 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford the corresponding alcohol **350** (1.62 g, 98%) as a light brown crystalline solid. To this material, polyphosphoric acid (11 g) was added and the resultant mixture was heated at 120 °C for 30 min. The hot reaction mixture was then

poured onto crushed ice (~250 mL) and the resultant acidic solution was basified by the addition of an aqueous solution of potassium hydroxide (20% w/w, 75 mL). The resultant mixture then was extracted with dichloromethane (3 x 40 mL) and the combined organic extracts were washed with water (30 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford the crude product. Flash chromatography using hexanes:ether (1:1) as the eluant afforded the *title compound* **345** (1.24 g, 83% over two steps) as a light yellow oil. **^{1}H NMR** ($CDCl_3$) δ 2.23 (3H, s, CH_3), 2.33-2.43 (2H, m, $ArCH_2CH_2$), 2.78 (2H, apparent t, J = 8.5 Hz, $ArCH_2$), 6.28-6.34 (1H, m, ArCHCH), 6.54 (1H, dt, J = 3.8, 1.9 Hz, ArCH), 6.93 (1H, s, ArH); **^{13}C NMR** ($CDCl_3$) δ 18.8, 22.5, 22.7, 123.4, 128.1, 129.0, 134.4, 147.2, 148.3, 153.2; **IR** (neat) 2378, 2349, 1571, 1554, 1442, 1336, 1270, 1114, 1088, 901 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 180 (M + H, 100); **Anal.** Calcd. for $C_{10}H_{10}ClN$: C, 66.86; H, 5.61; N, 7.80. Found: C, 66.57; H, 5.61; N, 7.69.

8.5.8. ***2-Chloro-5,6,7,8-tetrahydro-4-methyl-quinoline-7,8-diol 3-Pentanone Acetal* (344)**

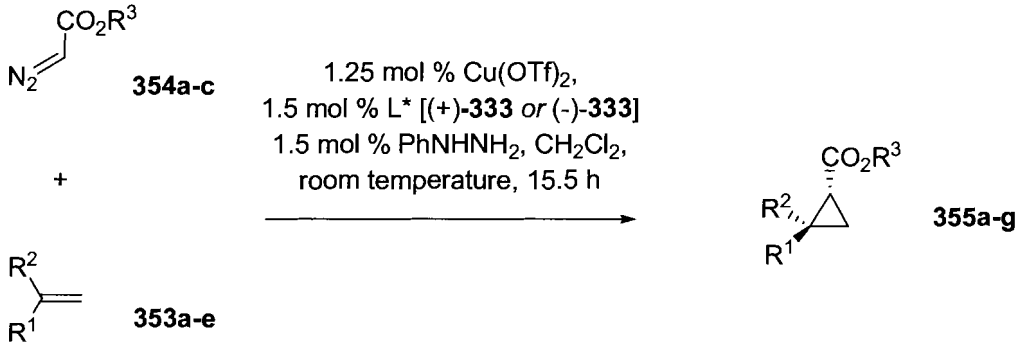


344

To a stirred solution of the chloropyridine **345** (340 mg, 1.89 mmol) in *tert*-butanol:water (1:1, 18 mL) at 0 °C was added AD-mix-β (2.63 g) in one portion and the resultant orange suspension was stirred at 0 °C for 12 h. Sodium sulfite (1.25 g) was then added to the reaction mixture. After an additional 30 min, brine (50 mL) was added and the reaction mixture was extracted with ethyl acetate (3 x 30 mL). The combined organic

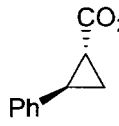
extracts were dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford the crude diol (347 mg, 86%) as a pale beige solid. This material was taken up in anhydrous benzene (10 mL) and 3-pentanone (0.25 mL, 2.4 mmol) and *p*-toluensulfonic acid monohydrate (45 mg, 0.24 mmol) were added. The resultant solution was heated in a Dean-Stark trap at reflux for 16 h. The reaction mixture was then allowed to cool to room temperature and potassium carbonate (60 mg) was added. The reaction mixture was filtered, the filter-cake was washed with dichloromethane (10 mL) and the combined filtrates were concentrated *in vacuo* to afford the crude product as a dark brown oil. Flash chromatography using hexanes:ethyl acetate (2:1) as the eluant afforded the *title compound* (+)-**344** (420 mg, 79%, over two steps) as a colourless oil. The enantiomeric purity of this material was determined to be 5% ee by analytical chiral HPLC using a Daicel Chiracel OD column [hexanes:isopropanol (96:4), flow rate at 0.5 mL/min, detection at λ = 220 nm; t_{MAJOR} = 16.24 min, t_{MINOR} = 17.95 min]. **^{1}H NMR** ($CDCl_3$) δ 0.69 (3H, t, J = 7.1 Hz, CH_2CH_3), 0.95 (3H, t, J = 7.2 Hz, CH_2CH_3), 1.57 (2H, q, J = 7.4 Hz, CH_2CH_3), 1.72 (2H, q, J = 7.5 Hz, CH_2CH_3), 2.17-2.32 (5H, m, $ArCH_3$ and $ArCH_2CH_2$), 2.53-2.64 (1H, m, ArCHH), 2.68-2.82 (1H, m, ArCHH), 4.67 (1H, m, HCO), 5.13 (1H, m, HCO), 7.07 (1H, s, ArH); **^{13}C NMR** ($CDCl_3$) δ 7.7, 8.9, 19.2, 19.8, 27.1, 29.0, 29.2, 73.3, 75.8, 112.6, 124.5, 131.5, 148.6, 154.2; **IR** (neat) 2971, 1582, 1447, 1271, 1196, 1133, 1080, 981, 893 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 282 (M + H, 100); **Anal.** Calcd. for $C_{15}H_{20}ClNO_2$: C, 63.94; H, 7.15; N, 4.97. Found: C, 63.87; H, 7.20; N, 4.76.

8.5.9. *General Procedure for Copper(I)-Catalyzed Enantioselective Cyclopropanation Reactions of Alkenes* (353a-e) *with Diazoesters* (354a-c)



To a stirred solution of copper(II) triflate (9.0 mg, 25 μmol) in anhydrous dichloromethane (3 mL) was added ligand (+)-**333** [*or* (-)-**333**] (13.9 mg, 29.9 μmol) and the resultant solution was stirred at room temperature for 30 min. Phenylhydrazine (3.0 μL, 30 μmol) and the alkene **353a-e** (styrene, *p*-methoxystyrene, *p*-fluorostyrene, 4-phenylbut-1-ene *or* 1,1-diphenylethene, 4.37 mmol) were then added. A solution of the diazoester **354a-c** (ethyl, benzyl *or* *tert*-butyl diazoacetate, 2.00 mmol) in dichloromethane (3 mL) was then added over the course of ~3 h *via* a syringe pump. After the addition was complete, the reaction was stirred for an additional 12 h. The reaction mixture was then concentrated *in vacuo* to afford the crude product. The ratios of the *trans*- and *cis*-isomers of the cyclopropane reaction products were then determined by ^{1}H NMR spectroscopy. Flash chromatography using petroleum ether:ethyl acetate (96:4) as the eluant afforded the pure *trans*-cyclopropanes **355a-g** and the corresponding *cis*-cyclopropanes. The enantiomeric purities of the major *trans*-isomers of the cyclopropane reaction products **355a-g** were determined following reduction with lithium aluminum hydride.

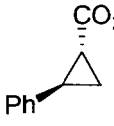
8.5.10. *(1R,2R)*-trans-*2-Phenyl-cyclopropane-1-carboxylic Acid Ethyl Ester* (355a)



355a

Combined yield of *trans*- and *cis*-isomers (282 mg, 74%, 82:18) as colourless oils. $[\alpha]_D^{20}$ - 231 (*c* 0.94, chloroform). The spectroscopic data for this compound was identical to that reported in section **8.2.20**. Analytical chiral HPLC analysis of the corresponding primary alcohol using a Daicel Chiracel OD column [hexanes:isopropanol (90:10), flow rate at 0.5 mL/min, detection at λ = 220 nm, t_{MINOR} = 15.4 min, t_{MAJOR} = 25.2 min, 82% ee].

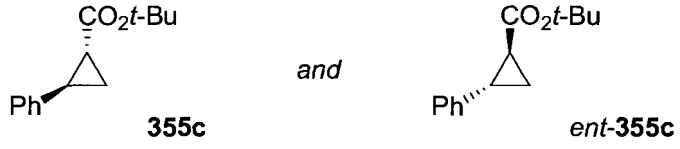
8.5.11. *(1R,2R)*-trans-*2-Phenyl-cyclopropane-1-carboxylic Acid Benzyl Ester* (355b)



355b

Combined yield of *trans*- and *cis*-isomers (247 mg, 49%, 92:8) as colourless oils. $[\alpha]_D^{20}$ - 264 (*c* 0.65, chloroform); **^{1}H NMR** ($CDCl_3$) δ 1.36 (1H, m, C*H*H), 1.67 (1H, m, CH*H*), 2.00 (1H, m, C*H*CO_2Bn), 2.59 (1H, m, C*H*Ph), 5.18 (1H, s, OC*H*H), 5.19 (1H, s, OCH*H*), 7.08-7.14 (2H, m, Ar*H*), 7.18-7.32 (3H, m, Ar*H*), 7.33-7.43 (5H, m, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 17.4, 24.2, 26.5, 66.7, 126.3, 126.6, 128.3, 128.6, 128.7, 136.1, 140.0, 173.4; **IR** (neat) 1720, 1603, 1498, 1457, 1407, 1338, 1325, 1168, 1030, 973, 934, 851, 752, 699 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 253 (M + H, 77), 91 (100). Analytical chiral HPLC analysis of the corresponding primary alcohol using a Daicel Chiracel OD column [hexanes:isopropanol (90:10), flow rate at 0.5 mL/min, detection at λ = 220 nm, t_{MINOR} = 15.4 min, t_{MAJOR} = 25.2 min, 84% ee].

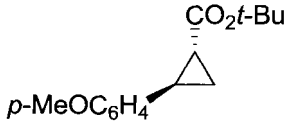
8.5.12. *(1*R,*2*R*)*-trans-*2-Phenyl-cyclopropane-1-carboxylic Acid* tert-*Butyl Esters* (355c) *and* (*ent*-355c)



355c *ent*-**355c**

Combined yield of *trans*- and *cis*-isomers (293 mg, 67%, 92:8) as colourless oils. $[\alpha]_D^{20}$ - 237 (*c* 0.92, chloroform). The spectroscopic data for this compound was identical to that reported in **8.2.21**. Analytical chiral HPLC analysis of the corresponding primary alcohol using a Daicel Chiracel OD column [hexanes:isopropanol (90:10), flow rate at 0.5 mL/min, detection at λ = 220 nm, t_{MINOR} = 15.4 min, t_{MAJOR} = 25.2 min, 92% ee]. The above procedure was also carried out, on a smaller scale, using ligand (-)-**333** to afford the cyclopropanes *ent*-**355c** (181 mg, 68%, 96:4) as colourless oils. Analytical chiral HPLC analysis of the corresponding primary alcohol using a Daicel Chiracel OD column [hexanes:isopropanol (90:10), flow rate at 0.5 mL/min, detection at λ = 220 nm, t_{MAJOR} = 15.4 min, t_{MINOR} = 25.2 min, 93% ee].

8.5.13. *(1*R,*2*R*)*-trans-*2-(4-Methoxyphenyl)-cyclopropane-1-carboxylic Acid* tert-*Butyl Ester* (355d)

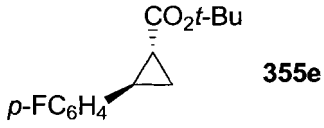


355d

Combined yield of *trans*- and *cis*-isomers (343 mg, 69%, 96:4) as colourless oils. $[\alpha]_D^{20}$ - 189 (*c* 0.75, chloroform); **^{1}H NMR** ($CDCl_3$) δ 1.18 (1H, m, C*H*H), 1.45-1.52 (10H, m, *t*-Bu and CH*H*), 1.75 (1H, m, C*H*CO_2*t*-Bu), 2.40 (1H, m, C*H*Ph), 3.78 (3H, s, OCH_3), 6.80-6.84 (2H, m, Ar*H*), 7.01-7.04 (2H, m, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 17.1,

25.3, 25.5, 28.5, 55.7, 80.8, 114.2, 127.6, 132.8, 158.5, 173.1; **IR** (neat) 2978, 2934, 1717, 1612, 1518, 1457, 1403, 1370, 1342, 1293, 1252, 1153, 1025, 845, 825, 813, 748 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 249 (M + H, 6), 193 (100). Analytical chiral HPLC analysis of the corresponding primary alcohol using a Daicel Chiracel OD column [hexanes:isopropanol (90:10), flow rate at 0.5 mL/min, detection at λ = 220 nm, t_{MINOR} = 21.2 min, t_{MAJOR} = 24.0 min, 71 % ee].

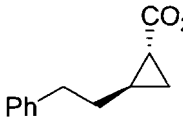
8.5.14. ***(1R,2R)*-trans-*2-(4-Fluorophenyl)-cyclopropane-1-carboxylic Acid* tert-*Butyl Ester* (355e)**



355e

Combined yield of *trans*- and *cis*-isomers (345 mg, 73%, 91:9) as colourless oils. $[\alpha]_D^{20}$ - 182 (*c* 0.64, chloroform); **^{1}H NMR** ($CDCl_3$) δ 1.18 (1H, m, C*H*H), 1.47 (9H, s, *t*-Bu), 1.48-1.53 (1H, m, CH*H*), 1.75-1.80 (1H, m, C*H*CO_2t-Bu), 2.42 (1H, m, C*H*Ph), 6.93-6.99 (2H, m, Ar*H*), 7.02-7.08 (2H, m, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 17.3, 25.3, 25.4, 28.5, 81.0, 115.5, 115.6, 127.9, 128.0, 134.9, 136.4, 162.8, 164.8, 172.8; **IR** (neat) 2980, 1719, 16708, 1515, 1457, 1398, 1368, 1334, 1312, 1218, 1152, 980, 846, 826, 767, 745 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 237 (M + H, 19), 181 (100); **Anal.** Calcd. for $C_{14}H_{17}FO_2$: C, 71.16; H, 7.25. Found: C, 70.97; H, 7.07. Analytical chiral HPLC analysis of the corresponding primary alcohol using a Daicel Chiracel OD column [hexanes:isopropanol (90:10), flow rate at 0.5 mL/min, detection at λ = 220 nm, t_{MINOR} = 14.4 min, t_{MAJOR} = 16.2 min, 99% ee].

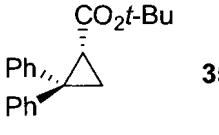
8.5.15. *(1R,2R)*-trans-*2-(2'-Phenylethyl)-cyclopropane-1-carboxylic Acid* tert-*Butyl Ester* (355f)



355f

Combined yield of *trans*- and *cis*-isomers (404 mg, 82%, 95:5) as colourless oils. $[\alpha]_D^{20}$ - 41 (*c* 0.50, chloroform); **^{1}H NMR** ($CDCl_3$) δ0.56 (1H, ddd, *J* = 10.3, 6.3, 3.9 Hz, C*H*H), 1.00-1.04 (1H, m, CH*H*), 1.18-1.28 (2H, m, $PhCH_2CHHCH$), 1.38 (9H, s, *t*-Bu), 1.50-1.57 (2H, m, $PhCH_2CHH$ and $CHCO_2t$-Bu), 2.63-2.68 (2H, m, $PhCH_2$), 7.09-7.15 (3H, m, Ar*H*), 7.18-7.24 (2H, m, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ15.5, 21.6, 22.3, 28.5, 35.3, 35.9, 80.3, 126.2, 128.7, 128.8, 142.1, 174.0; **IR** (neat) 2979, 2931, 2858, 1724, 1603, 1497, 1455, 1404, 1368, 1258, 1214, 1146, 1079, 978, 848, 748, 699 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 247 (M + H, 49), 192 (14), 191 (100); **Anal.** Calcd. for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00; Found: C, 77.78; H, 9.30. Analytical chiral HPLC analysis of the corresponding primary alcohol using a Daicel Chiracel OD column [hexanes:isopropanol (90:10), flow rate at 0.5 mL/min, detection at λ = 220 nm, t_{MINOR} = 16.2 min, t_{MAJOR} = 19.8 min, 83% ee].

8.5.16. *(1R)-2,2-Diphenyl-cyclopropane-1-carboxylic acid* tert-*Butyl Ester* (355g)

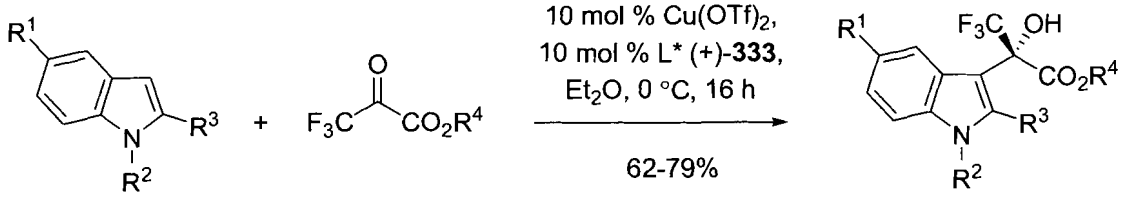


355g

Yield (477 mg, 81%) as a colourless oil. $[\alpha]_D^{20}$ - 165 (*c* 0.25, chloroform); **^{1}H NMR** ($CDCl_3$) δ1.21 (9H, s, *t*-Bu), 1.49-1.53 (1H, m, C*H*H), 2.09-2.13 (1H, m, CH*H*), 2.46 (1H, dd, *J* = 7.8, 5.9 Hz, $CHCO_2t$-Bu), 7.14-7.22 (2H, m, Ar*H*), 7.23-7.29 (6H, m, Ar*H*), 7.35-7.38 (2H, m, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ20.2, 28.0, 30.2, 39.6, 80.5, 126.5,

127.0, 127.7, 128.3, 128.5, 130.2, 140.4, 145.3, 169.8; **IR** (neat) 2977, 2934, 1719, 1662, 1601, 1496, 1448, 1390, 1367, 1293, 1250, 1150, 1028, 972, 847, 781, 747, 703 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 295 (M + H, 6), 239 (100), 183 (16). Analytical chiral HPLC analysis of the corresponding primary alcohol using a Daicel Chiracel OD column [hexanes:isopropanol (90:10), flow rate at 0.5 mL/min, detection at λ = 220 nm, t_{MINOR} = 22.6 min, t_{MAJOR} = 18.8 min, 72% ee].

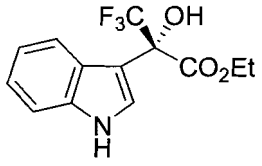
8.5.17. *General Procedure for the Copper(II)-Catalyzed Asymmetric Friedel-Crafts Reactions using Ligand* [(+)-333]



367a-f **368a,b** **369a-g**

To a flame-dried Schlenk tube was added copper(II) trifluoromethanesulfonate (3.1 mg, 8.6 μmol), ligand (+)-**333** (4.1 mg, 8.8 μmol) and ether (1.5 mL). The resultant solution was stirred at room temperature for 1 h. The catalyst solution was then cooled to 0 °C and the appropriate indole **367a-f** (94 μmol) and the ethyl *or* methyl ester of 3,3,3-trifluoropyruvic acid **368a,b** (86 μmol) were added. The Schlenk tube was then sealed and the reaction mixture was stirred at 0 °C for 16 h. The resultant mixture was then concentrated *in vacuo* to afford the crude product. Flash chromatography using hexanes:ether (1:1) as the eluant afforded the desired substituted indoles **369a-g**.

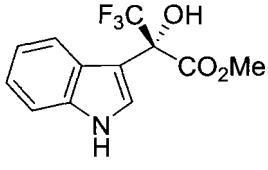
8.5.18. *(2S)-3,3,3-Trifluoro-2-hydroxy-(indole-3-yl)-propionic Acid Ethyl Ester* (369a)



369a

Indole **367a** (11.0 mg, 94 μmol) was reacted with ethyl 3,3,3-trifluoropyruvate **368a** (11 μL, 86 μmol) according to the general procedure to afford the *title compound* **369a** (17 mg, 68%) as a colourless oil. $[\alpha]_D^{20}$ + 11.3 (*c* 1.01, chloroform) [lit.[168] $[\alpha]_D^{rt}$ + 12.3 (*c* 1.91, chloroform), 83% ee]; **^{1}H NMR** ($CDCl_3$) δ 1.35 (3H, t, J = 7.1 Hz, $CO_2CH_2CH_3$), 4.33-4.39 (1H, m, CO_2CHHCH_3), 4.42-4.50 (1H, m, CO_2CHHCH_3), 7.14-7.19 (1H, m, Ar*H*), 7.21-7.26 (1H, m, Ar*H*), 7.39 (1H, d, J = 8.1 Hz, Ar*H*), 7.49 (1H, d, J = 2.6 Hz, Ar*H*), 7.91 (1H, d, J = 8.1 Hz, Ar*H*), 8.27 (1H, broad s, N*H*); **^{13}C NMR** (acetone-D_6) δ 15.2, 64.6, 79.2 (q, $^2J_{C\text{-}F}$ = 31 Hz), 110.7, 113.5, 121.4, 122.9, 123.7, 126.3 (q, $^1J_{C\text{-}F}$ = 285 Hz), 126.8, 127.4, 138.8, 170.3; **IR** (KBr) 3417 (broad), 1741, 1462, 1372, 1310, 1229, 1176, 1097, 1008, 909, 858, 751 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 270 (52), 171 (100). Analytical chiral HPLC analysis using a Daicel Chiracel OD column [hexanes:isopropanol (90:10), flow rate at 0.5 mL/min, detection at λ = 220 nm, t_{MINOR} = 32.5 min, t_{MAJOR} = 37.1 min, 74% ee].

8.5.19. *(2S)-3,3,3-Trifluoro-2-hydroxy-(indole-3-yl)-propionic Acid Methyl Ester* (369b)

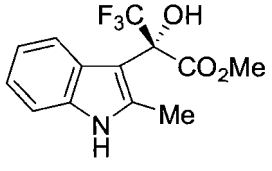


369b

Indole **367a** (11.0 mg, 94 μmol) was reacted with methyl 3,3,3-trifluoropyruvate **368b** (8.7 μL, 86 μmol) according to the general procedure to afford the *title compound*

369b (18 mg, 77%) as a colourless oil. $[\alpha]_D^{20}$ - 24.1 (*c* 0.99, chloroform); **^{1}H NMR** ($CDCl_3$) δ3.94 (3H, s, CO_2CH_3), 4.35 (1H, broad s, O*H*), 7.14-7.20 (1H, m, Ar*H*), 7.21-7.25 (1H, m, Ar*H*), 7.36-7.41 (1H, m, Ar*H*), 7.44-7.48 (1H, m, Ar*H*), 7.87 (1H, d, J = 8.0 Hz, Ar*H*), 8.29 (1H, broad s, N*H*); **^{13}C NMR** (acetone-D_6) δ58.0, 82.5 (q, $^2J_{C\text{-}F}$ = 31 Hz), 113.9, 116.8, 124.9, 126.0, 127.1, 129.5 (q, $^1J_{C\text{-}F}$ = 286 Hz), 130.1, 130.7, 142.0, 174.2; **IR** (neat) 3414 (broad), 3331 (broad), 1750, 1461, 1438, 1341, 1299, 1261, 1233, 1173, 1118, 1102, 1080, 999, 907, 753 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 273 (M + H, 12), 256 (100); **Anal.** Calcd. for $C_{12}H_{10}F_3NO_3$: C, 52.75; H, 3.69; N, 5.13. Found: C, 52.90; H, 3.69; N, 5.06. Analytical chiral HPLC analysis using a Daicel Chiracel OD column [hexanes:isopropanol (90:10), flow rate at 0.5 mL/min, detection at λ = 220 nm, t_{MINOR} = 44.2 min, t_{MAJOR} = 45.8 min, 90% ee].

8.5.20. ***(2S)-3,3,3-Trifluoro-2-hydroxy-(2-methylindole-3-yl)-propionic Acid Methyl Ester*** **(369c)**

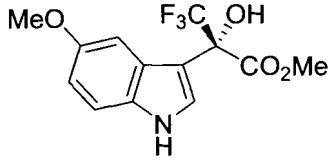


369c

2-Methylindole **367b** (12.4 mg, 94 μmol) was reacted with methyl 3,3,3-trifluoropyruvate **368b** (8.7 μL, 86 μmol) according to the general procedure to afford the *title compound* **369c** (20 mg, 79%) as a light yellow oil. $[\alpha]_D^{20}$ + 7.1 (*c* 1.70, chloroform); **^{1}H NMR** ($CDCl_3$) δ2.50 (3H, s, CH_3), 2.52 (3H, s, CO_2CH_3), 7.07-7.19 (2H, m, Ar*H*), 7.26-7.30 (1H, m, Ar*H*), 7.75 (1H, d, J = 8.0 Hz, Ar*H*), 8.03 (1H, broad s, N*H*); **^{13}C NMR** (acetone-D_6) δ 14.5, 54.1, 79.7 (q, $^2J_{C\text{-}F}$ = 30 Hz), 105.9, 112.4, 121.3, 121.4, 122.7, 126.9 (q, $^1J_{C\text{-}F}$ = 284 Hz), 129.1, 137.0, 137.5, 170.9; **IR** (neat) 3401 (broad),

1741, 1694, 1461, 1438, 1291, 1183, 1029, 748 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 287 (M + H, 100), 270 (50); **FAB HRMS** Calcd. for $C_{13}H_{12}F_3NO_3$: 287.0769. Found: 287.0774. Analytical chiral HPLC analysis using a Daicel Chiracel OD column [hexanes:isopropanol (90:10), flow rate at 0.5 mL/min, detection at λ = 220 nm, t_{MAJOR} = 43.9 min, t_{MINOR} = 63.3 min, 86% ee].

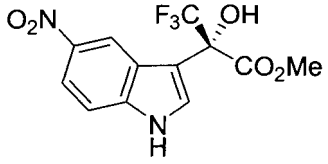
8.5.21. ***(2S)-3,3,3-Trifluoro-2-hydroxy-(5-methoxyindole-3-yl)-propionic Acid Methyl Ester*** **(369d)**



369d

5-Methoxyindole **367c** (13.9 mg, 94 μmol) was reacted with methyl 3,3,3-trifluoropyruvate **368b** (8.7 μL, 86 μmol) according to the general procedure to afford the *title compound* **369d** (18 mg, 69%) as a colourless oil. $[\alpha]_D^{20}$ - 1.7 (*c* 1.30, chloroform); **^{1}H NMR** ($CDCl_3$) δ 3.84 (3H, s, OCH_3), 3.92 (3H, s, CO_2CH_3), 6.86-6.91 (1H, m, Ar*H*), 7.18 (1H, d, *J* = 8.9 Hz, Ar*H*), 7.30-7.34 (2H, m, Ar*H*), 8.33 (1H, broad s, N*H*); **^{13}C NMR** (acetone-D_6) δ 54.8, 56.8, 79.2 (q, $^2J_{C\text{-}F}$ = 31 Hz), 104.4, 114.2, 114.9, 124.9, 127.3, 127.7 (q, $^1J_{C\text{-}F}$ = 288 Hz), 127.7, 127.9, 133.9, 170.8; **IR** (neat) 3409 (broad), 1748, 1692, 1628, 1583, 1488, 1441, 1294, 1217, 1178, 1113, 1026, 1000, 906, 794 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 303 (M + H, 100), 286 (41), 244 (16), 174 (24), 147 (67); **FAB HRMS** Calcd. for $C_{13}H_{12}F_3NO_4$: 303.0718. Found: 303.0716. Analytical chiral HPLC analysis using a Daicel Chiracel OD column [hexanes:isopropanol (90:10), flow rate at 0.5 mL/min, detection at λ = 220 nm, t_{MINOR} = 61.5 min, t_{MAJOR} = 72.5 min, 72% ee].

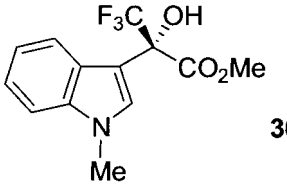
8.5.22. *(2S)-3,3,3-Trifluoro-2-hydroxy-(5-nitroindole-3-yl)-propionic Acid Methyl Ester* (369e)



369e

5-Nitroindole **367d** (15.3 mg, 94 μmol) was reacted with methyl 3,3,3-trifluoropyruvate **368b** (8.7 μL, 86 μmol) according to the general procedure to afford the *title compound* **369e** (21 mg, 75%) as a yellow crystalline solid. **M.p.** 139-140 °C, hexanes/ether; $[\alpha]_D^{20}$ - 0.5 (*c* 1.00, chloroform); **^{1}H NMR** ($CDCl_3$) δ 4.01 (3H, s, CO_2CH_3), 4.27 (1H, broad s, O*H*), 7.45 (1H, d, J = 9.0 Hz, Ar*H*), 7.67-7.70 (1H, m, Ar*H*), 8.16 (1H, dd, J = 9.0, 2.2 Hz, Ar*H*), 8.74 (1H, broad s, N*H*), 8.92-8.95 (1H, m, Ar*H*); **^{13}C NMR** (acetone-D_6) δ 55.2, 79.2 (q, $^2J_{C\text{-}F}$ = 30 Hz), 113.0, 114.1, 119.1, 120.1,125.8 (q, $^1J_{C\text{-}F}$ = 285 Hz), 126.8, 130.7, 141.7, 143.9, 170.2; **IR** (KBr) 3400 (broad), 3373 (broad), 1754, 1521, 1473, 1339, 1303, 1224, 1198, 1169, 1108, 1053, 989, 941, 660 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 319 (M + H, 100), 302 (33), 259 (51); **Anal.** Calcd. for $C_{12}H_9F_3N_2O_5$: C, 45.29; H, 2.85; N, 8.80. Found: C, 45.02; H, 3.06; N, 8.51. ^{1}H NMR analysis of the reaction product in the presence of the chiral shift reagent Eu(hfc)$_3$ indicated a 3.9:1.0 ratio of enantiomers, 60% ee.

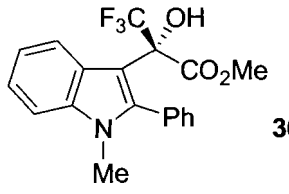
8.5.23. *(2S)-3,3,3-Trifluoro-2-hydroxy-(1-methylindole-3-yl)-propionic Acid Methyl Ester* (369f)



369f

1-Methylindole **367e** (12.3 mg, 94 μmol) was reacted with methyl 3,3,3-trifluoropyruvate **368b** (8.7 μL, 86 μmol) according to the general procedure to afford the *title compound* **369f** (18 mg, 74%) as a colourless oil. **^{1}H NMR** ($CDCl_3$) δ 3.80 (3H, s, NCH_3), 3.94 (3H, s, CO_2CH_3), 7.13-7.19 (1H, m, Ar*H*), 7.24-7.30 (1H, m, Ar*H*), 7.31-7.35 (2H, m, Ar*H*), 7.82-7.87 (1H, d, J = 8.2 Hz, Ar*H*); **^{13}C NMR** (acetone-D_6) δ 34.1, 54.8, 79.1 (q, $^2J_{C\text{-}F}$ = 31 Hz), 109.5, 111.6, 121.6, 122.9, 123.8, 126.2 (q, $^1J_{C\text{-}F}$ = 286 Hz), 127.8, 130.9, 139.2, 170.8; **IR** (neat) 3488 (broad), 1742, 1544, 1477, 1466, 1296, 1173, 1135, 745 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 288 (M + H, 46), 270 (100); **FAB HRMS** Calcd. for $C_{13}H_{12}F_3NO_3$: 287.0769. Found: 287.0769. Analytical chiral HPLC analysis using a Daicel Chiracel OD column [hexanes:isopropanol (90:10), flow rate at 0.5 mL/min, detection at λ = 220 nm, t_{MINOR} = 26.2 min, t_{MAJOR} = 37.1 min, 18% ee].

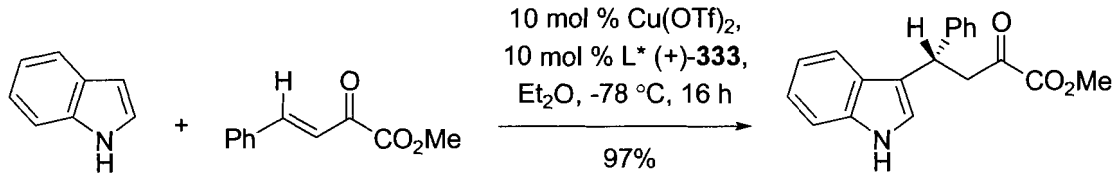
8.5.24. *(2S)-3,3,3-Trifluoro-2-hydroxy-(1-methyl-2-phenylindole-3-yl)-propionic Acid Methyl Ester* (369g)



369g

1-Methyl-2-phenylindole **369f** (19.5 mg, 94 μmol) was reacted with methyl 3,3,3-trifluoropyruvate **368b** (8.7 μL, 86 μmol) according to the general procedure to afford the *title compound* **369g** (20 mg, 65%) as a colourless oil. **^{1}H NMR** ($CDCl_3$) δ 3.26 (3H, s, NC*H*$_3$), 3.36 (3H, s, CO_2C*H*$_3$), 7.17-7.42 (5H, m, Ar*H*), 7.45-7.55 (3H, m, Ar*H*), 8.07 (1H, d, J = 8.1 Hz, Ar*H*); **^{13}C NMR** (acetone-D_6) δ 53.5, 79.7 (q, $^2J_{C\text{-}F}$ = 30 Hz), 111.4, 121.7, 123.9, 124.3, 126.5 (q, $^1J_{C\text{-}F}$ = 285 Hz), 129.7, 129.9, 130.9, 132.7, 133.0, 133.7, 138.4, 141.2, 169.7; **IR** (neat) 3445 (broad), 1736, 1467, 1442, 1294, 1238, 1188, 1106, 1069, 984, 748 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 364 (M + H, 93), 346 (100); **FAB HRMS** Calcd. for $C_{19}H_{16}F_3NO_3$: 363.1082. Found: 363.1083. Analytical chiral HPLC analysis using a Daicel Chiracel OD column [hexanes:isopropanol (96:4), flow rate at 0.5 mL/min, detection at λ = 245 nm, t_{MINOR} = 25.6 min, t_{MAJOR} = 26.4 min, 18% ee].

8.5.25. *(4S)-4-(Indole-3-yl)-4-phenyl-2-oxo-butanoic Acid Methyl Ester* (370)[169]



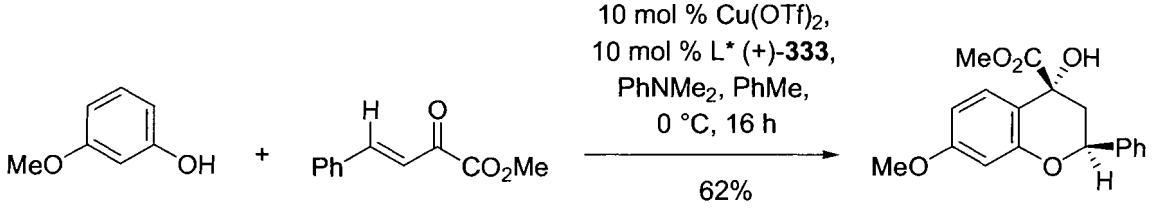
367a **365** **370**

To a flame-dried Schlenk tube was added copper(II) trifluoromethanesulfonate (3.1 mg, 8.6 μmol), ligand (+)-**333** (4.1 mg, 8.8 μmol) and ether (2.0 mL) and the resultant solution was stirred at room temperature for 1 h. The catalyst solution was then cooled to -78 °C and indole **367a** (10.0 mg, 86 μmol) and (3*E*)-2-oxo-4-phenyl-3-butenoic acid methyl ester **365**[183] (16.4 mg, 86 μmol) were then added. The resultant heterogeneous mixture was stirred at -78 °C for 16 h. The reaction mixture was then allowed to warm to room temperature and was filtered through a pad of silica gel using ether as the eluant. The filtrate was concentrated *in vacuo* to afford the desired product as the corresponding enol tautomer in pure form. The enol was smoothly converted to the desired ketone on stirring in methanol (5 mL) at room temperature for 2 h. On concentration *in vacuo*, the *title compound* **370** (25 mg, 97%) was isolated as a white crystalline solid. **M.p.** 93-94 °C, methanol (lit.[169] 98 °C, ether/pentane); $[\alpha]_D^{20}$ + 14.1 (*c* 1.00, chloroform) [lit.[169] $[\alpha]_D^{rt}$ - 23.9 (*c* 1.00, chloroform), 99.5% ee]; **^{1}H NMR** ($CDCl_3$) δ3.6 (1H, dd, *J* = 17.0, 8.0 Hz, C*H*H), 3.69 (1H, dd, *J* = 17.0, 7.1 Hz, CH*H*), 3.77 (3H, s, CO_2CH_3), 4.93 (1H, t, *J* = 7.5 Hz, PhC*H*), 6.99-7.46 (10H, m, Ar*H*), 7.99 (1H, broad s, N*H*); **^{13}C NMR** ($CDCl_3$) δ 38.9, 45.9, 53.2, 111.3, 116.5, 119.7, 120.2, 122.3, 126.7,

(183) Dujardin, G.; Leconte, S.; Benard, A.; Brown, E. A Straightforward Route to *E*-γ-Aryl-α-oxobutenoic Esters by One-Step Acid-Catalysed Crotonisation of Pyruvates. *Synlett* **2001**, 147.

128.3, 136.2, 143.3, 161.1; **IR** (KBr) 3447 (broad), 1744, 1699, 1490, 1456, 1438, 1376, 1240, 1091, 1071, 768, 747 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 290 (25), 191 (100), 118 (34). The enantiomeric purity of the reaction product was determined by comparison of the optical rotation with a literature value, 59% ee.[169]

8.5.26. ***(2S,4R)-3,4-Dihydro-4-hydroxy-7-methoxy-2-phenyl-2H-chromene-4-methyl Carboxylate* (372)**[170]

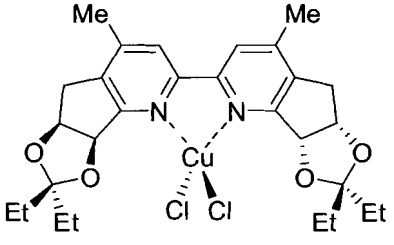


371 **365** **372**

To a flame-dried Schlenk tube was added copper(II) trifluoromethanesulfonate (9.0 mg, 25 μmol), ligand (+)-**333** (13.0 mg, 28 μmol) and toluene (1.0 mL) and the resultant solution was stirred at room temperature for 1 h. (3*E*)-2-oxo-4-phenyl-3-butenoic acid methyl ester **365** (58 mg, 0.25 mmol) and *N,N*-dimethylaniline (3.2 μL, 25 μmol) were then added and the solution was cooled to 0 °C. 3-methoxyphenol **371** (55 μL, 0.50 mmol) was added to the resultant solution which was then stirred at 0 °C for 16 h. The reaction mixture was then concentrated *in vacuo* to afford the crude product. Purification by flash chromatography using pentane:ether (5:1) as the eluant afforded the *title compound* **372** (49 mg, 62%) as a colourless oil. $[\alpha]_D^{20}$ + 0.75 (*c* 1.00, chloroform) [lit.[170] $[\alpha]_D^{rt}$ + 1.36 (*c* 1.55, chloroform), 80% ee]; **^{1}H NMR** ($CDCl_3$) δ2.26 (1H, dd, *J* = 13.4, 5.5 Hz, C*H*H), 2.45 (1H, td, *J* = 2.0, 13.2 Hz, CH*H*), 3.75 (3H, s, CO_2CH_3), 3.90 (3H, s, OCH_3), 4.28 (1H, dd, *J* = 13.2, 5.5 Hz, PhC*H*), 4.37 (1H, broad d, *J* = 2.0 Hz, O*H*), 6.40-6.47 (2H, m, Ar*H*), 6.64 (1H, d, *J* = 8.4 Hz, Ar*H*), 7.23-7.38 (5H, m, Ar*H*);

^{13}C NMR ($CDCl_3$) δ 37.1, 53.8, 55.6, 94.7, 102.0, 108.8, 118.0, 127.2, 129.0, 129.1, 130.2, 143.8, 152.4, 159.7, 170.5; **IR** (neat) 3450 (broad), 1750, 1621, 1581, 1504, 1442, 1256, 1161, 1123, 1032 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 315 (M + H, 38), 265 (100). Analytical chiral HPLC analysis using a *Daicel Chiracel OD* column [hexanes:isopropanol (98:2), flow rate at 0.75 mL/min, detection at λ = 220 nm, t_{MAJOR} = 34.4 min, t_{MINOR} = 36.7 min, 42% ee].

8.5.27. ***Procedure for the Preparation and Crystallization of the $CuCl_2$ Ligand*** **[(+)-333]** ***Complex***



A solution of the ligand (+)-**333** (12.4 mg, 26.7 μmol) and copper(II) chloride (3.8 mg, 28 μmol) in a mixture of ethanol:dichloromethane (1:1, 4 mL) was heated at reflux for 6 h. The reaction mixture was then allowed to cool to room temperature and was concentrated *in vacuo* to afford the crude product. This material was then taken up in dichloromethane (2 mL) and filtered through a pad of glass wool. Ethanol (1 mL) was then added to the filtrate and upon slow evaporation of the solvent, the *title compound* (10 mg, 62%) was obtained as X-ray quality yellow crystals. **M.p.** >210 °C (dec.), dichloromethane/ethanol; $[\alpha]_{365}^{20}$ + 759, $[\alpha]_{405}^{20}$ + 2552, $[\alpha]_{546}^{20}$ + 1207, $[\alpha]_{589}^{20}$ + 793 (*c* 0.0029, chloroform); **UV-Vis** λ_{max} (chloroform) 328 (ε = 19597), 315 (ε = 20446) nm; **IR** (KBr) 3433 (broad), 3044, 2972, 2937, 2880, 1604, 1478, 1463, 1196, 1176, 1091, 1082,

929 cm^{-1}; **MS** (MALDI-TOF) *m/z* 562 (M - Cl), 465 (M - $CuCl_2$ + H); **Anal.** Calcd. for $C_{28}H_{36}Cl_2CuN_2O_4$: C, 56.14; H, 6.06; N, 4.68. Found: C, 56.31; H, 6.12; N, 4.75.

8.5.28. *X-Ray Crystallographic Analysis of the $CuCl_2$·Ligand* [(+)-333] *Complex*

A single crystal, a yellow platelet that had the dimensions 0.06 x 0.23 x 0.28 mm^3, was mounted on a glass fiber using epoxy adhesive. The data for this crystal of the $CuCl_2$·ligand (+)-**333** complex was acquired at 293 K on a *Rigaku RAXIS-RAPID* curved image plate area detector with graphite monochromated Cu Kα radiation. Indexing for the crystal was performed using four, 5° oscillations that were exposed for 400 seconds. The following data range was recorded: $4.1° \leq 2\theta \leq 144.3°$ and a total of 54 images were collected. A sweep of data was then collected using ω scans from 0.0° to 180.0° in 10° steps, at $\chi = 0.0°$ and $\phi = 0.0°$. A second sweep of data was collected using ω scans from 0.0° to 180.0° in 10° steps, at $\chi = 45.0°$ and $\phi = 0.0°$. A final sweep of data was collected using ω scans from 0.0° to 180.0° in 10° steps, at $\chi = 45.0°$ and $\phi = 90.0°$. The exposure rate was 100 sec/° and in each case, the crystal-to-detector distance was 127.40 mm. A numerical absorption correction was then applied which resulted in the following transmission range: 0.69 to 0.83. The coordinates and anisotropic displacement parameters for the non-hydrogen atoms were then refined. Of note, hydrogen atoms were placed in calculated positions (d C-H 0.95 Å) and their coordinate shifts were linked with those of the respective carbon atoms during refinement. Isotropic thermal parameters for the hydrogen atoms were initially assigned proportionately to the equivalent isotropic thermal parameters of their respective carbon atoms. Subsequently, the isotropic thermal parameters for the hydrogen atoms were constrained to have identical shifts during refinement. The programs used for all absorption corrections, data reduction, and

processing were from the *Rigaku CrystalClear* package. The structure was refined using *CRYSTALS*.[177] Complex scattering factors for neutral atoms were used in the calculation of structure factors.[178] An *ORTEP* representation of the $CuCl_2$·ligand (+)-**333** complex is provided below (Figure 8.5.1.). Crystallographic data, fractional atomic coordinates and equivalent isotropic thermal displacement parameters, selected bond lengths, and selected bond angles for the $CuCl_2$·ligand (+)-**333** complex are listed below (Table 8.5.1., 8.5.2., 8.5.3., and 8.5.4., respectively).

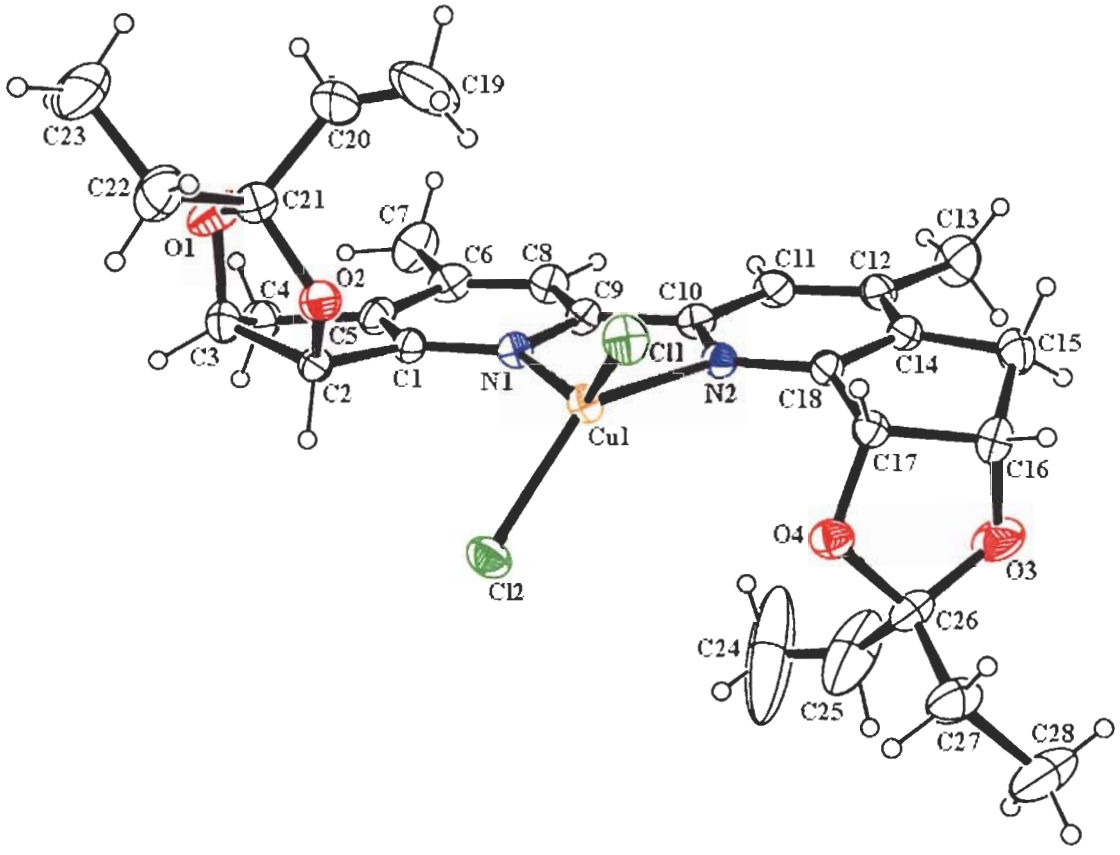


Figure 8.5.1. *ORTEP* representation of the $CuCl_2$·ligand (+)-**333** complex*

(*) The thermal ellipsoids are drawn at a 25% probability level for clarity.

Table 8.5.1. Summary of Crystallographic Data for the $CuCl_2$·Ligand (+)-**333** Complex

Empirical formula	$C_{28}H_{36}N_2Cl_2CuO_4$
FW (g mol^{-1})	599.06
Temperature (K)	293
Wavelength (Cu $K\alpha$, Å)	1.54180
Crystal system	monoclinic
Space group	$P\,2_1$
a (Å)	8.7438(6)
b (Å)	7.6589(3)
c (Å)	21.3498(9)
α (°)	90
β (°)	90.022(3)
γ (°)	90
Z	2
U ($Å^3$)	1429.75(13)
D_{calc} (g cm^{-3})	1.391
2θ limits (°)	4-145
Reflections collected	10274
Independent reflections	3461
Reflections observed [$I = 2.5\sigma(I)$]	3374
Goodness-of-fit on *F*	1.1741
R_1, R_w [$I = 2.5\sigma(I)$]	0.0436, 0.0553

Table 8.5.2. Fractional Atomic Coordinates (Å) and Equivalent Isotropic Thermal Displacement Parameters [*U*(iso), (Å^2)] for the $CuCl_2$·Ligand (+)-**333** Complex*

atom	*x*	*y*	*z*	*U* (iso)
Cu1	-0.75010(9)	-0.0208(2)	-0.25004(4)	0.0378
Cl1	-0.90802(18)	0.1773(2)	-0.28858(7)	0.0534
Cl2	-0.90612(19)	-0.2196(2)	-0.21132(8)	0.0541
O1	-0.6450(6)	-0.4482(7)	-0.4404(2)	0.0760
O2	-0.8062(5)	-0.2837(5)	-0.37837(18)	0.0509
O3	-0.6458(6)	0.4056(7)	-0.0595(2)	0.0744
O4	-0.8071(5)	0.2408(5)	-0.12236(18)	0.0475
N1	-0.5748(5)	-0.1706(6)	-0.2803(2)	0.0359
N2	-0.5728(6)	0.1282(6)	-0.2199(2)	0.0375
C1	-0.5812(7)	-0.3224(8)	-0.3120(2)	0.0402
C2	-0.7223(7)	-0.4002(7)	-0.3385(3)	0.0382
C3	-0.6599(8)	-0.5396(9)	-0.3826(3)	0.0577
C4	-0.4985(8)	-0.5821(8)	-0.3609(3)	0.0622
C5	-0.4494(8)	-0.4181(7)	-0.3264(2)	0.0428
C6	-0.3098(7)	-0.3555(8)	-0.3135(3)	0.0479
C7	-0.1639(9)	-0.4472(10)	-0.3327(4)	0.0758
C8	-0.3037(8)	-0.1964(9)	-0.2830(3)	0.0501
C9	-0.4329(7)	-0.1067(7)	-0.2666(2)	0.0370
C10	-0.4335(7)	0.0642(7)	-0.2330(3)	0.0383
C11	-0.3009(8)	0.1522(9)	-0.2167(3)	0.0512
C12	-0.3096(9)	0.3124(9)	-0.1869(3)	0.0580
C13	-0.1669(8)	0.4070(10)	-0.1675(4)	0.0750
C14	-0.4554(8)	0.3770(8)	-0.1728(3)	0.0460
C15	-0.5007(8)	0.5403(8)	-0.1393(3)	0.0554
C16	-0.6586(8)	0.4961(9)	-0.1163(3)	0.0544

(*) The occupancies for all atoms listed in this table are 1.0.

C17	-0.7272(7)	0.3574(7)	-0.1604(3)	0.0407
C18	-0.5777(7)	0.2787(7)	-0.1887(2)	0.0376
C19	-0.638(2)	-0.0177(17)	-0.4424(8)	0.2811
C20	-0.6711(19)	-0.1446(14)	-0.4632(5)	0.1753
C21	-0.7544(9)	-0.3110(10)	-0.4414(3)	0.0615
C22	-0.8884(8)	-0.3642(12)	-0.4796(3)	0.0799
C23	-0.8460(10)	-0.4058(14)	-0.5480(3)	0.1098
C24	-0.647(2)	-0.0320(16)	-0.0540(8)	0.2839
C25	-0.6678(16)	0.1087(14)	-0.0353(5)	0.1445
C26	-0.7535(9)	0.2679(10)	-0.0581(3)	0.0624
C27	-0.8975(9)	0.3198(11)	-0.0206(3)	0.0813
C28	-0.8464(12)	0.3585(14)	0.0484(4)	0.1213
H21	-0.7856(7)	-0.4475(7)	-0.3066(3)	0.050(4)
H31	-0.7222(8)	-0.6407(9)	-0.3859(3)	0.064(4)
H41	-0.4339(8)	-0.6010(8)	-0.3960(3)	0.072(4)
H42	-0.4944(8)	-0.6809(8)	-0.3340(3)	0.072(4)
H71	-0.0776(9)	-0.3829(10)	-0.3186(4)	0.085(4)
H72	-0.1614(9)	-0.4557(10)	-0.3771(4)	0.085(4)
H73	-0.1617(9)	-0.5610(10)	-0.3150(4)	0.085(4)
H81	-0.2068(8)	-0.1469(9)	-0.2733(3)	0.057(4)
H111	-0.2040(8)	0.1016(9)	-0.2255(3)	0.061(4)
H131	-0.1934(8)	0.5146(10)	-0.1482(4)	0.085(4)
H132	-0.1060(8)	0.4289(10)	-0.2034(4)	0.085(4)
H133	-0.1109(8)	0.3372(10)	-0.1387(4)	0.085(4)
H151	-0.4983(8)	0.6386(8)	-0.1664(3)	0.070(4)
H152	-0.4354(8)	0.5608(8)	-0.1045(3)	0.070(4)
H161	-0.7212(8)	0.5971(9)	-0.1130(3)	0.064(4)
H171	-0.7910(7)	0.4051(7)	-0.1921(3)	0.048(4)
H191	-0.565(2)	0.0425(17)	-0.4675(8)	0.459(4)
H192	-0.735(2)	0.0379(17)	-0.4459(8)	0.459(4)

H193	-0.606(2)	-0.0159(17)	-0.3999(8)	0.459(4)
H201	-0.6981(19)	-0.1324(14)	-0.5061(5)	0.151(4)
H202	-0.5690(19)	-0.1861(14)	-0.4601(5)	0.151(4)
H221	-0.9564(8)	-0.2675(12)	-0.4802(3)	0.097(4)
H222	-0.9378(8)	-0.4617(12)	-0.4610(3)	0.097(4)
H231	-0.9361(10)	-0.4345(14)	-0.5707(3)	0.132(4)
H232	-0.7972(10)	-0.3089(14)	-0.5673(3)	0.132(4)
H233	-0.7785(10)	-0.5031(14)	-0.5481(3)	0.132(4)
H241	-0.595(2)	-0.0981(16)	-0.0231(8)	0.397(4)
H242	-0.738(2)	-0.0910(16)	-0.0656(8)	0.397(4)
H243	-0.584(2)	-0.0183(16)	-0.0897(8)	0.397(4)
H251	-0.7255(16)	0.0803(14)	0.0009(5)	0.182(4)
H252	-0.5708(16)	0.1529(14)	-0.0232(5)	0.182(4)
H271	-0.9424(9)	0.4203(11)	-0.0391(3)	0.097(4)
H272	-0.9691(9)	0.2265(11)	-0.0210(3)	0.097(4)
H281	-0.9362(12)	0.3907(14)	0.0706(4)	0.144(4)
H282	-0.7753(12)	0.4523(14)	0.0494(4)	0.144(4)
H283	-0.8020(12)	0.2585(14)	0.0675(4)	0.144(4)

Table 8.5.3. Bond Lengths (Å) for the $CuCl_2$·Ligand (+)-**333** Complex

Cu1-Cl1	2.2100(17)
Cu1-Cl2	2.2054(19)
Cu1-N1	2.021(5)
Cu1-N2	2.029(5)
O1-C3	1.423(8)
O1-C21	1.421(9)
O2-C2	1.435(6)
O2-C21	1.436(8)
O3-C16	1.403(8)
O3-C26	1.414(9)

O4-C17	1.395(7)
O4-C26	1.463(7)
N1-C1	1.347(7)
N1-C9	1.365(7)
N2-C10	1.343(7)
N2-C18	1.332(7)
C1-C2	1.482(8)
C1-C5	1.400(8)
C2-C3	1.525(8)
C3-C4	1.521(9)
C4-C5	1.519(8)
C5-C6	1.339(8)
C6-C7	1.513(8)
C6-C8	1.383(9)
C8-C9	1.368(8)
C9-C10	1.492(7)
C10-C11	1.386(8)
C11-C12	1.384(9)
C12-C13	1.501(8)
C12-C14	1.401(9)
C14-C15	1.495(8)
C14-C18	1.351(8)
C15-C16	1.504(8)
C16-C17	1.540(8)
C17-C18	1.562(8)
C19-C20	1.107(14)
C20-C21	1.540(11)
C21-C22	1.484(9)
C22-C23	1.541(9)
C24-C25	1.162(13)

C25-C26	1.512(10)
C26-C27	1.545(10)
C27-C28	1.567(10)

Table 8.5.4. Bond Angles (°) for the $CuCl_2$·Ligand (+)-**333** Complex

Cl1-Cu1-Cl2	103.12(7)
Cl1-Cu1-N1	138.12(14)
Cl2-Cu1-N1	101.38(15)
Cl1-Cu1-N2	102.07(15)
Cl2-Cu1-N2	137.90(14)
N1-Cu1-N2	80.86(18)
C3-O1-C21	108.4(5)
C2-O2-C21	107.7(5)
C16-O3-C26	109.5(5)
C17-O4-C26	107.1(5)
Cu1-N1-C1	128.3(4)
Cu1-N1-C9	114.7(4)
C1-N1-C9	117.1(5)
Cu1-N2-C10	115.0(4)
Cu1-N2-C18	128.4(4)
C10-N2-C18	116.7(5)
N1-C1-C2	125.0(5)
N1-C1-C5	121.9(5)
C2-C1-C5	113.0(5)
C1-C2-O2	113.7(5)
C1-C2-C3	102.7(5)
O2-C2-C3	104.6(5)
C2-C3-O1	102.9(5)
C2-C3-C4	107.1(5)
O1-C3-C4	106.5(6)

C3-C4-C5	103.5(5)
C4-C5-C1	107.9(6)
C4-C5-C6	130.7(6)
C1-C5-C6	121.2(6)
C5-C6-C7	123.2(6)
C5-C6-C8	116.5(6)
C7-C6-C8	120.3(6)
C6-C8-C9	122.1(6)
C8-C9-N1	121.0(5)
C8-C9-C10	124.5(5)
N1-C9-C10	114.5(5)
C9-C10-N2	115.1(5)
C9-C10-C11	122.9(6)
N2-C10-C11	122.0(6)
C10-C11-C12	120.0(7)
C11-C12-C13	120.6(7)
C11-C12-C14	117.5(6)
C13-C12-C14	121.8(6)
C12-C14-C15	129.8(6)
C12-C14-C15	118.0(6)
C15-C14-C18	112.2(6)
C14-C15-C16	102.2(5)
C15-C16-O3	108.7(5)
C15-C16-C17	108.3(5)
O3-C16-C17	102.6(5)
C16-C17-O4	106.3(5)
C16-C17-C18	100.2(5)
O4-C17-C18	113.4(5)
C17-C18-C14	110.5(5)
C17-C18-N2	123.7(5)

C14-C18-N2	125.6(6)
C19-C20-C21	136.9(10)
C20-C21-O2	108.2(6)
C20-C21-O1	107.4(8)
O2-C21-O1	107.8(5)
C20-C21-C22	115.8(8)
O2-C21-C22	107.8(6)
O1-C21-C22	109.7(6)
C21-C22-C23	112.8(7)
C24-C25-C26	135.6(10)
C25-C26-O4	110.2(6)
C25-C26-O3	106.1(8)
O4-C26-O3	107.4(5)
C25-C26-C27	116.4(8)
O4-C26-C27	105.2(6)
O3-C26-C27	111.2(6)
C26-C27-C28	107.7(7)

8.5.29. *Optical Rotary Dispersion Spectrum of the Copper(II) Chloride·Ligand (+)-333 complex*

The following optical rotary dispersion spectrum of the copper(II) chloride·ligand (+)-**333** complex was recorded at 20 °C in chloroform [*c* 0.0029 (g per 100 mL)] (Figure 8.5.2.).

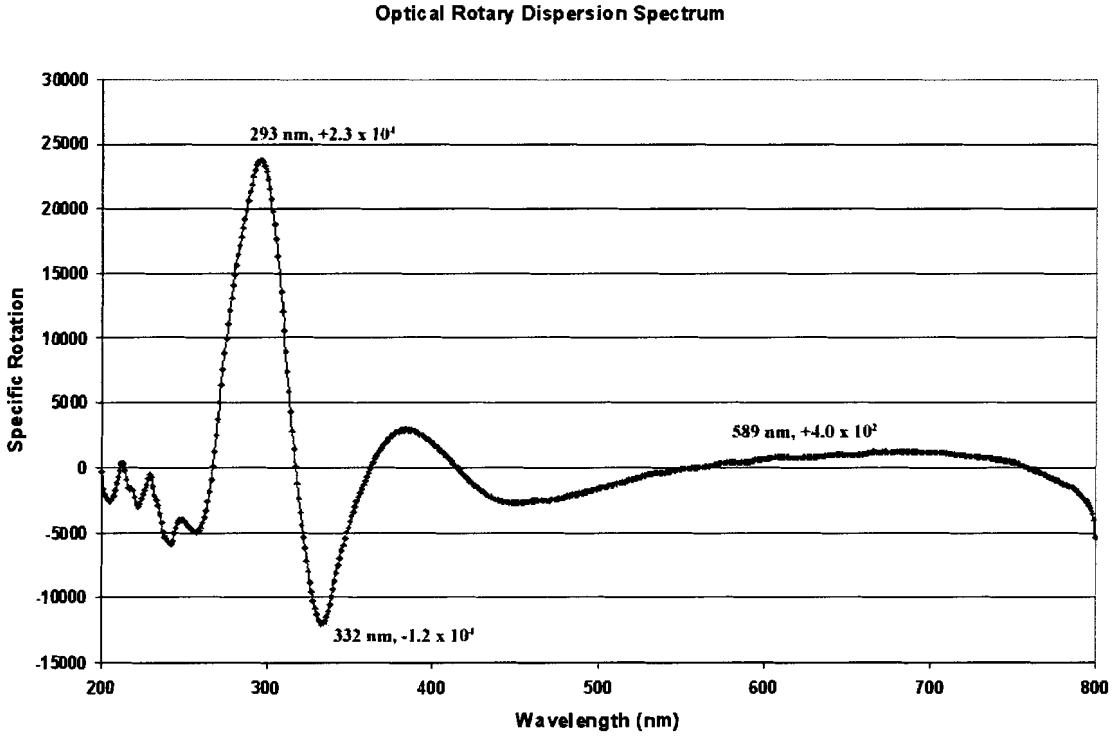
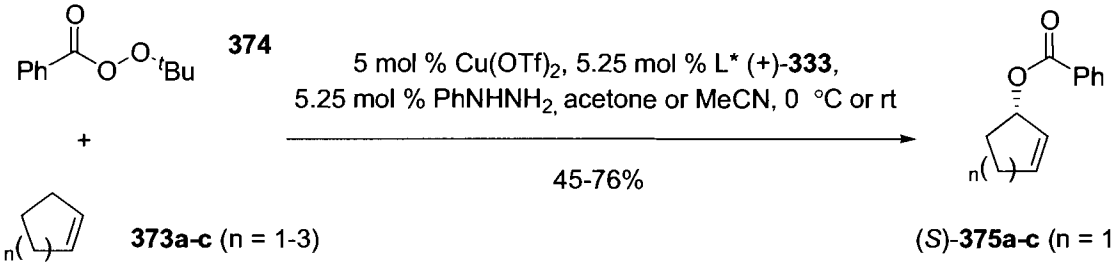


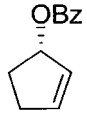
Figure 8.5.2. Optical rotary dispersion spectrum of the $CuCl_2$·ligand (+)-**333** complex.

8.5.30. ***General Procedure for Copper(I)-Catalyzed Asymmetric Allylic Oxidation Reactions of Cyclopentene*** **[373a (n = 1)],** ***Cyclohexene*** **[373b (n = 2)]** ***and Cycloheptene*** **[373c (n = 3)]** ***with*** **tert-*Butyl Peroxybenzoate* (374):** ***Asymmetric Syntheses of (1S)-Cyclopent-2-enyl Benzoate*** **[(*S*)-375a (n = 1)],** ***(1S)-Cyclohex-2-enyl Benzoate*** **[(*S*)-375b (n = 2)]** ***and (1S)-Cyclohept-2-enyl Benzoate*** **[(*S*)-375c (n = 3)].**



To a screw-cap vial was added copper(II) trifluoromethanesulfonate (6.3 mg, 17 μmol), the chiral 2,2′-bipyridine ligand (+)-**333** (8.5 mg, 18 μmol) and the reaction solvent (acetone *or* acetonitrile, 2.5 mL). The resultant solution was then stirred at room temperature for 1 h. Phenylhydrazine (2.0 μL, 20 μmol) was then added and the reaction mixture was stirred for an additional 5 min at room temperature. The reaction mixture was then heated to a specific temperature (see: Table 5.9.1, Chapter 5) and the appropriate cyclic alkene substrate was added [(1) cyclopentene **373a** (n = 1) (0.15 mL, 1.7 mmol) *or* (2) cyclohexene **373b** (n = 2) (0.18 mL, 1.8 mmol) *or* (3) cycloheptene **373c** (n = 3) (0.20 mmol, 1.7 mmol)]. The oxidant *tert*-butyl peroxybenzoate **374** (67 μL, 0.35 mmol) was then added and the reaction vial was capped. The progress of the reaction was monitored by thin-layer chromatography until the *tert*-butyl peroxybenzoate had been consumed. The reaction mixture was then concentrated *in vacuo* to afford the crude product. Flash chromatography using hexanes:ether (5:1) as the eluant afforded the *title compounds* (*S*)-**375a-c** (n = 1-3).

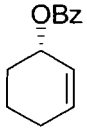
8.5.31. *(1S)-Cyclopent-2-enyl Benzoate* [(*S*)-375a]



(*S*)-**375a**

^{1}H NMR ($CDCl_3$) δ 1.98-2.02 (1H, m, CH*H*); 2.20-2.70 (3H, m CH_2 and C*H*H), 5.91-5.96 (2H, m, OC*H* and C*H*), 6.15 (1H, apparent d, J = 4.8 Hz, C*H*), 7.45-7.49 (3H, m, Ar*H*), 8.03 (2H, dd, J = 7.7, 1.8 Hz, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 29.9, 30.9, 81.1, 128.8, 129.3, 129.4, 130.4, 132.7, 134.4, 137.6, 162.3; **IR** (neat) 3062, 1714, 1270, 1116, 1026, 711 cm$^{-1;}$ **MS** (CI) *m/z* (rel. intensity) 189 (M + H, 100). Analytical chiral HPLC analysis using a Daicel Chiracel OD column [hexanes:isopropanol (250:1), flow rate at 0.50 mL/min, detection at λ = 220 nm, t_{MAJOR} = 32.4 min, t_{MINOR} = 43.6 min].

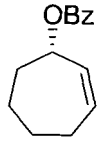
8.5.32. *(1S)-Cyclohex-2-enyl Benzoate* [(*S*)-375b]



(*S*)-**375b**

^{1}H NMR ($CDCl_3$) δ 1.65-1.76 (1H, m, C*H*H), 1.78-2.21 (5H, m, 2 x CH_2, C*H*H), 5.49-5.55 (1H, m, C*H*OBz), 5.80-5.87 (1H, m, C*H*), 5.98-6.04 (1H, m, C*H*), 7.40-7.66 (4H, m, Ar*H*), 8.06 (1H, d, J = 7.3 Hz, Ar*H*), 8.13 (1H, d, J = 7.3 Hz, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 19.1, 25.1, 28.5, 68.8, 125.8, 128.4, 128.6, 129.7, 130.4, 132.9, 133.0, 133.9, 166.4; **IR** (neat) 2941, 1713, 1602, 1584, 1453, 1428, 1326, 1271, 1178, 1112, 1070, 1026, 918 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 203 (M + H, 14), 181 (87), 159 (24), 91 (55). Analytical chiral HPLC analysis using a Daicel Chiracel OD column [hexanes:isopropanol (250:1), flow rate at 0.50 mL/min, detection at λ = 220 nm, t_{MAJOR} = 26.1 min, t_{MINOR} = 29.0 min].

8.5.33. *(1S)-Cyclohept-2-enyl Benzoate* [(*S*)-375c]



(*S*)-**375c**

^{1}H NMR ($CDCl_3$) δ 1.40-1.55 (1H, m, C*H*H), 1.65-1.91 (3H, m, CH_2 and C*H*H), 1.94-2.06 (2H, m, CH_2), 2.09-2.21 (1H, m, C*H*H), 2.21-2.31 (1H, m, C*H*H), 5.66 (1H, apparent d, J = 9.9 Hz, C*H*OBz), 5.77-5.83 (1H, m, C*H*), 5.85-5.93 (1H, m, C*H*), 7.40-7.51 (2H, m, Ar*H*), 7.52-7.64 (1H, m, Ar*H*), 7.68-7.73 (1H, m, Ar*H*), 8.04-8.09 (1H, m, Ar*H*), 8.10-8.15 (1H, m, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 26.7, 26.9, 28.7, 33.0, 74.8, 122.7, 128.4, 129.1, 129.7, 132.1, 132.9, 133.6, 166.0; **IR** (neat) 2930, 2856, 1717, 1602, 1584, 1451, 1273, 1113, 1070, 1026, 980 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 123 ($PhCO_2H$ + H, 33), 95 (M – PhCOO, 100); Analytical chiral HPLC analysis using a Daicel Chiracel OD column [hexanes:isopropanol (250:1), flow rate at 0.50 mL/min, detection at λ = 220 nm, t_{MAJOR} = 19.2 min, t_{MINOR} = 23.5 min].

APPENDICES

9.1. Circular Dichroism Spectrum of the Cu(267)$_2$·CuCl$_2$ Complex

A circular dichroism spectrum was recorded for the Cu(**267c**)$_2$·CuCl$_2$ complex (Figure 9.1.1.). The spectrum was recorded at a concentration of 3.0 mg Cu(**267c**)$_2$·CuCl$_2$ complex in 100 mL of chloroform (1.9 x 10^{-5} M) and across a wavelength range of 200 to 800 nm.

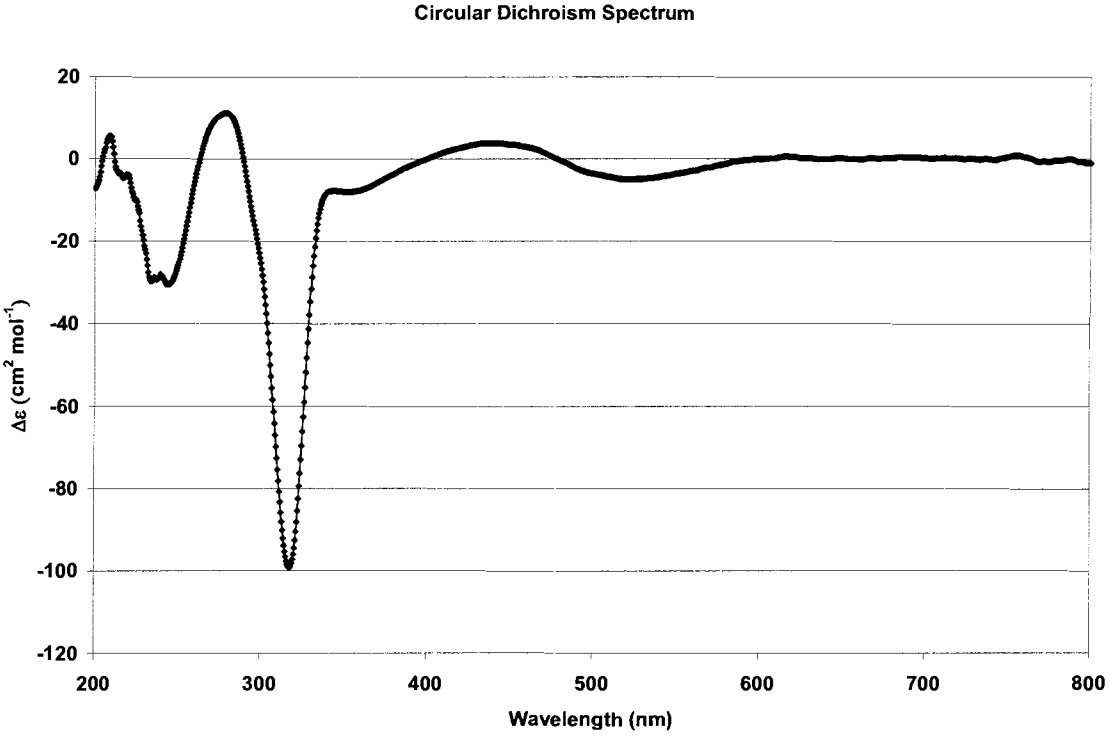


Figure 9.1.1. Circular dichroism spectrum of the Cu(**267c**)$_2$·CuCl$_2$ complex.

9.2. Circular Dichroism Spectrum of the CuCl$_2$·ligand (+)-333 Complex

A circular dichroism spectrum was recorded for the CuCl$_2$·ligand (+)-**333** complex (Figure 9.2.1.). The spectrum was recorded at a concentration of 2.9 mg CuCl$_2$·ligand (+)-**333** complex in 100 mL of chloroform (4.7 x 10^{-5} M) and across a wavelength range of 200 to 800 nm.

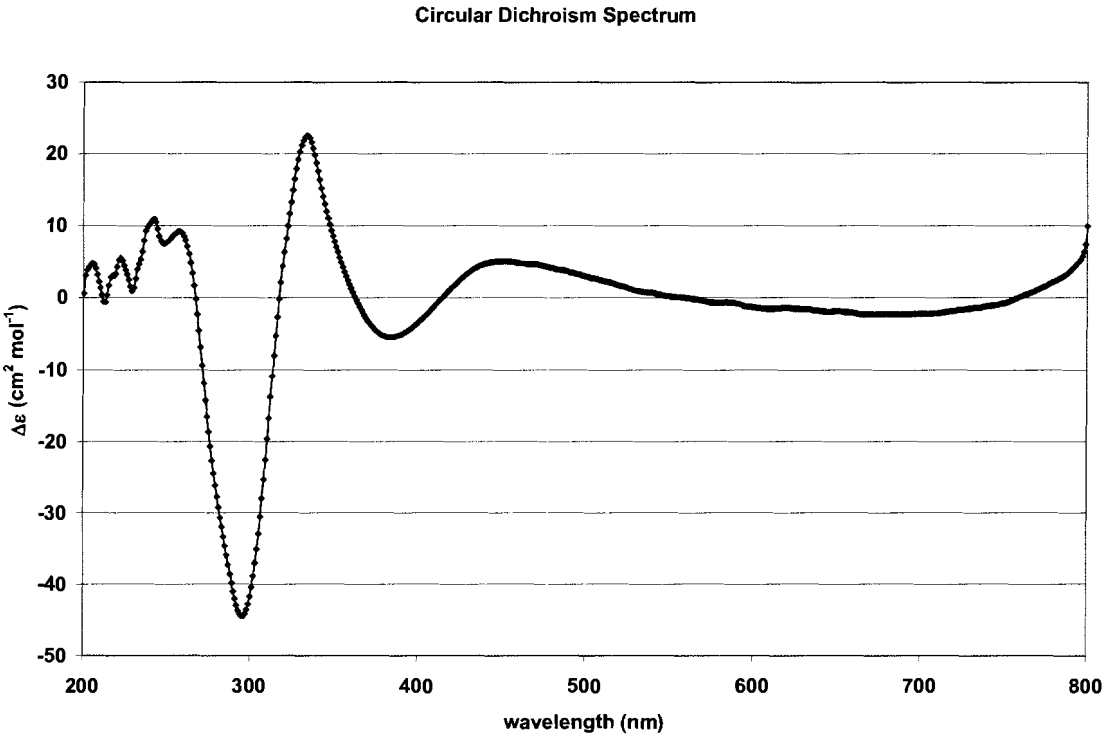


Figure 9.2.1. Circular dichroism spectrum of the $CuCl_2$·ligand (+)-**333** complex.

BIBLIOGRAPHY

(1) Marckwald, W. Asymmetric Synthesis. *Ber. Dtsh. Chem. Ges.* **1904**, *37*, 1368.

(2) (a) Gardner, M. In *The New Ambidextrous Universe, 3rd ed.*, W. H. Freeman & Co., New York, 1990. (b) Heilbronner, E.; Dunitz, J. D. In *Reflections on Symmetry*, VHCA, Basel, 1993. (c) Hoffmann, R. In *The Same and Not the Same*, Columbia University Press, New York, 1995.

(3) Pasteur, L. *Ann. Chim. Phys.* **1848**, *24*, 442.

(4) Armstrong, R. W.; Beau, J.-M.; Cheon, S. H.; Christ, W. J.; Fujioka, H.; Ham, W.-H.; Hawkins, L. D.; Jin, H.; Kang, S. H.; Kishi, Y.; Martinelli, M. J.; McWhorter, W. W.; Mizuno, M.; Nakata, M.; Stutz, A. E.; Talamas, F. X.; Taniguchi, M.; Tino, J. A.; Ueda, K.; Uenishi, J.; White, J. B.; Yonaga, M. Total Synthesis of Palytoxin Carboxylic Acid and Palytoxin Amide. *J. Am. Chem. Soc.* **1989**, *111*, 7530. (b) Suh, E. M.; Kishi, Y. Synthesis of Palytoxin from Palytoxin Carboxylic Acid. *J. Am. Chem. Soc.* **1994**, *116*, 11205.

(5) Agranat, I.; Caner, H.; Caldwell, J. Putting Chirality to Work: The Strategy of Chiral Switches. *Nat. Rev. Drug Discovery* **2002**, *1*, 753.

(6) Fischer, E. *Dtsh. Chem. Ges.* **1894**, *27*, 3189.

(7) Cram, D. J.; Abd Elhafez, F. A. Studies in Stereochemistry. The Rule of "Steric Control of Asymmetric Induction" in the Syntheses of Acyclic Systems. *J. Am. Chem. Soc.* **1952**, *74*, 5828.

(8) Evans, D. A.; Bartroli, J.; Shih, T. L. Enantioselective Aldol Condensations. 2. *Erythro*-selective Chiral Aldol Condensations *via* Boron Enolates. *J. Am. Chem. Soc.* **1981**, *103*, 2127.

(9) Brown, H. C.; Zweifel, G. A Stereospecific Double Bond Hydration of the Double Bond in Cyclic Systems. *J. Am. Chem. Soc.* **1959**, *81*, 247.

(10) Verbit, L.; Heffron, P. J. Optically Active *sec*-Butylamine *via* Hydroboration. *J. Org. Chem.* **1967**, *32*, 3199.

(11) Pizzarello, S.; Weber, A. L. Prebiotic Amino Acids as Asymmetric Catalysts. *Science* **2004**, *303*, 1151.

(12) Nozaki, H.; Moriuti, S.; Takaya, H.; Noyori, R. Asymmetric Induction in Carbenoid Reaction by means of a Dissymetric Copper Chelate. *Tetrahedron Lett.* **1966**, *43*, 5239.

(13) Dang, T. P.; Kagan, H. B. The Asymmetric Synthesis of Hydratropic Acid and Amino-Acids by Homogenous Catalytic Hydrogenation. *J. Chem. Soc., Chem. Commun.* **1971**, 481.

(14) Whitesell, J. K. C_2-Symmetry and Asymmetric Induction. *Chem. Rev.* **1989**, *89*, 1581.

(15) Knowles, W. S. Asymmetric Hydrogenation. *Acc. Chem. Res.* **1983**, *16*, 106.

(16) Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. Synthesis of 2,2′-*bis*(Diphenylphosphino)-1,1'-binapthyl (BINAP), an Atropisomeric Chiral *bis*(Triaryl)phosphine, and its use in the Rhodium(I)-Catalyzed Asymmetric Hydrogenation of Alpha-(acylamino)acrylic Acids. *J. Am. Chem. Soc.* **1980**, *102*, 7932.

(17) (a) Ohta, T.; Takaya, H.; Noyori, R. Asymmetric Hydrogenation of Unsaturated Carboxylic Acids Catalyzed by BINAP-Ruthenium(II) Complexes. *J. Org. Chem.* **1987**, *52*, 3174. (b) Kitamura, M.; Yoshimura, M.; Tsukamoto, M.; Noyori, R. Synthesis of α-Amino Phosphonic Acids by Asymmetric Hydrogenation. *Enantiomer* **1996**, *1*, 281.

(18) Katsuki, T.; Sharpless, K. B. The First Practical Method for Asymmetric Epoxidation. *J. Am. Chem. Soc.* **1980**, *102*, 5974.

(19) Johnson, R. A.; Sharpless, K. B. Catalytic Asymmetric Epoxidation of Allylic Alcohols. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000, Chapter 6A.

(20) Rossiter, B. E.; Katsuki, T.; Sharpless, K. B. Asymmetric Epoxidation Provides Shortest Routes to Four Chiral Epoxy Alcohols which are Key Intermediates in Syntheses of Methymycin, Erythromycin, Leukotriene C-1 and Disparlure. *J. Am. Chem. Soc.* **1981**, *103*, 464.

(21) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. Catalytic Asymmetric Dihydroxylation. *Chem Rev.* **1994**, *94*, 2483.

(22) Sharpless, K. B. Searching for New Reactivity (Nobel Lecture). *Angew. Chem., Int. Ed.* **2002**, *41*, 2024.

(23) Noyori, R. Asymmetric Catalysis: Science and Opportunities (Nobel Lecture). *Angew. Chem., Int. Ed.* **2002**, *41*, 2008.

(24) Knowles, W. S. Asymmetric Hydrogenations (Nobel Lecture). *Angew. Chem., Int. Ed.* **2002**, *41*, 1998.

(25) Fritschi, H.; Leutenegger, U.; Siegmann, K.; Pfaltz, A. Synthesis of Chiral Semicorrin Ligands and General Concepts. *Helv. Chim. Acta* **1988**, *71*, 1541.

(26) Fritschi, H.; Leutenegger, U.; Pfaltz, A. Enantioselective Cyclopropane Formation from Olefins with Diazo Compounds Catalyzed by Chiral (Semicorrinato)copper Complexes. *Helv. Chim. Acta.* **1988**, *71*, 1553.

(27) (a) Lowenthal, R. E.; Abiko, A.; Masamune, S. Asymmetric Catalytic Cyclopropanation of Olefins: *bis*-Oxazoline Copper Complexes. *Tetrahedron Lett.* **1990**, *31*, 6005. (b) Lowenthal, R. E.; Masamune, S. Asymmetric Copper-Catalyzed Cyclopropanation of Trisubstituted and Unsymmetrical *cis*-1,2-Disubstituted Olefins: Modified *bis*-Oxazoline Ligands. *Tetrahedron Lett.* **1991**, *32*, 7373.

(28) Evans, D. A.; Woerpel, K. A.; Hinman, M. M. *bis*(Oxazolines) as Chiral Ligands in Metal-Catalyzed Asymmetric Reactions. Catalytic Asymmetric Cyclopropanation of Olefins. *J. Am. Chem. Soc.* **1991**, *113*, 726.

(29) Corey, E. J.; Imai, N.; Zhang, H.-Y. Designed Catalyst for Enantioselective Diels-Alder Addition from a C_2-Symmetric Chiral *bis*(Oxazoline)-Iron(III) Complex. *J. Am. Chem. Soc.* **1991**, *113*, 729.

(30) (a) Pfaltz, A. Chiral Semicorrins and Related Nitrogen Heterocycles as Ligands in Asymmetric Catalysis. *Acc. Chem. Res.* **1993**, *26*, 339. (b) Johnson, J. S.; Evans, D. A. Chiral *bis*(Oxazoline) Copper(II) Complexes: Versatile Catalysts for Enantioselective Cycloaddition, Aldol, Michael and Carbonyl Ene Reactions. *Acc. Chem. Res.* **2000**, *33*, 325.

(31) Taylor, M. S.; Jacobsen, E. N. Asymmetric Catalysis in Complex Target Synthesis. *Proc. Nat. Acad. Sci.* **2004**, *101*, 5368.

(32) Evans, D. A.; Shaughnessy, E. A.; Barnes, D. Cationic *bis*(Oxazoline)Cu(II) Lewis Acid Catalysts. Applications to the Asymmetric Synthesis of *ent*-Δ^1-Tetrahydrocannabinol. *Tetrahedron Lett.* **1997**, *38*, 3193.

(33) (a) Trost, B. M. Asymmetric Allylic Alkylation, an Enabling Methodology. *J. Org. Chem.* **2004**, *69*, 5813. (b) Trost, B. M. Asymmetric Transition Metal-Catalyzed Allylic Alkylations. *Chem. Rev.* **1996**, *96*, 395.

(34) Trost, B. M.; Bunt, R. C. Asymmetric Induction in Allylic Alkylations of 3-(Acyloxy)cyclopentenes. *J. Am. Chem. Soc.* **1994**, *116*, 4089.

(35) (a) Dalko, P. I.; Moisan, L. In the Golden Age of Organocatalysis. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (b) Special Issue: Asymmetric Organocatalysis. *Acc. Chem. Res.* **2004**, *37*, pp 487-631.

(36) Hajos, Z. G.; Parrish, D. R. Asymmetric Synthesis of Bicyclic Intermediates of Natural Product Chemistry. *J. Org. Chem.* **1974**, *39*, 1615.

(37) (a) Cannizzaro, C. E.; Houk, K. N. Magnitudes and Chemical Consequences of R_3N^+-C-H···O=C Hydrogen Bonding. *J. Am. Chem. Soc.* **2002**, *124*, 7163. (b) Bahmanyar, S.; Houk, K. N.; Martin, H. J.; List, B. Quantum Mechanical Predictions of the Stereoselectivities of Proline-Catalyzed Asymmetric Intermolecular Aldol Reactions. *J. Am. Chem. Soc.* **2003**, *125*, 2475.

(38) (a) Córdova, A.; Notz, W.; Barbas III, C. F. Direct Organocatalytic Aldol Reactions in Buffered Aqueous Media. *Chem. Commun.* **2002**, 3024. (b) Córdova, A.; Notz, W.; Barbas III, C. F. Proline-Catalyzed One-Step Asymmetric Synthesis of 5-Hydroxy-(2*E*)-hexenal from Acetaldehyde. *J. Org. Chem.* **2002**, *67*, 301.

(39) Córdova, A. The Direct Catalytic Asymmetric Mannich Reaction. *Acc. Chem. Res.* **2004**, *37*, 102. (b) List, B. The Direct Catalytic Asymmetric Three-Component Mannich Reaction. *J. Am. Chem. Soc.* **2000**, *122*, 9336. (c) List, B.; Pojarliev. P.; Biller, W. T.; Martin, H. J. The Proline-Catalyzed Direct Asymmetric Three-Component Mannich Reaction: Scope, Optimization and Application to the Highly Enantioselective Synthesis of 1,2-Aminoalcohols. *J. Am. Chem. Soc.* **2002**, *124*, 827.

(40) (a) List, B. Direct Catalytic Asymmetric α-Amination of Aldehydes. *J. Am. Chem. Soc.* **2002**, *124*, 5656. (b) Kumaragurubaran, N.; Juhl, K.; Zhuang, W.; Bøgevig, A.; Jørgensen, K. A. Direct L-Proline Catalyzed Asymmetric α-Amination of Ketones. *J. Am. Chem. Soc.* **2002**, *124*, 6254.

(41) (a) Sakthivel, K.; Notz, W.; Bui, T.; Barbas III, C. F. Amino Acid Catalyzed Direct Asymmetric Aldol Reactions: A Bioorganic Approach to Catalytic Asymmetric Carbon-Carbon Bond Forming Reactions. *J. Am. Chem. Soc.* **2001**, *123*, 5260. (b) Betancort, J. M.; Barbas III, C. F. Catalytic Direct Asymmetric Michael Reactions: Taming Naked Aldehyde Donors. *Org. Lett.* **2001**, *3*, 3737.

(42) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. New Strategies for Organic Synthesis: The First Highly Enantioselective Organocatalytic Diels-Alder Reaction. *J. Am. Chem. Soc.* **2000**, *122*, 4243.

(43) Paras, N. A.; MacMillan, D. W. C. New Strategies in Organic Catalysis: The First Asymmetric Organocatalytic Friedel-Crafts Alkylation. *J. Am. Chem. Soc.* **2001**, *123*, 4370.

(44) Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. C. The First Enantioselective Organocatalytic Mukaiyama-Michael Reaction: A Direct Method for the Synthesis of Enantioenriched γ-Butenolide Architecture. *J. Am. Chem. Soc.* **2003**, *125*, 1192.

(45) Brochu, M. P.; Brown, S. P.; MacMillan, D. W. C. The Direct Enantioselective Organocatalytic α-Chlorination of Aldehydes. *J. Am. Chem. Soc.* **2004**, *126*, 4108.

(46) Ouellet, S. G.; Tuttle, J. B.; MacMillan, D. W. C. Enantioselective Organocatalytic Hydride Reduction. *J. Am. Chem. Soc.* **2005**, *127*, 32.

(47) (a) Alibés, R.; Busquè, F.; de March P.; Figueredo, M.; Font, J.; Gambino, M. E.; Keay, B. A. Acetals of γ-Oxo-α,β-unsaturated Esters in Nitrone Cycloadditions. Regio- and Stereo-chemical Implications. *Tetrahedron*: *Asymmetry* **2001**, *12*, 1747. (b) Cossy J.; BouzBouz, S. A Short Access to (+)-Ptilocaulin. *Tetrahedron Lett.* **1996**, *37*, 5091. (c) Alexakis, A.; Mangeney, P. Chiral Acetals in Asymmetric Synthesis. *Tetrahedron*: *Asymmetry* **1990**, *1*, 477.

(48) (a) Seebach, D.; Beck, A. K.; Heckel, A. TADDOLs, Their Derivatives, and TADDOL Analogues: Versatile Chiral Auxiliaries. *Angew. Chem., Int. Ed.* **2001**, *40*, 92. (b) Ley, S. V.; Baeschlin, D. K.; Dixon, D. J.; Foster, A. C.; Ince, S. J.; Priepke, H. W. M.; Reynolds, D. J. 1,2-Diacetals: A New Opportunity for Organic Synthesis. *Chem. Rev.* **2001**, *101*, 53.

(49) Johnson, W. S. Biomimetic Polyene Cyclizations. *Angew. Chem., Int. Ed.* **1976**, *15*, 9.

(50) Tamura, Y.; Kondo, H.; Annoura, H.; Takeuchi, R.; Fujioka, F. Diastereoselective Nucleophilic Addition to Chiral Open-Chain α-Ketoacetals: Synthesis of (*R*)- and (*S*)-Mevalolactone. *Tetrahedron Lett.* **1986**, *27*, 2117.

(51) Mulzer, J.; Altenback, H.-J.; Braun, M.; Krohn, K.; Reissig, H.-U. In *Organic Synthesis Highlights*, Wiley-VCH, Weinheim, 1991, p 19.

(52) Narine, A. A.; Wilson, P. D. Synthesis and Evaluation of 7-Hydroxyindan-1-one-Derived Chiral Auxiliaries. *Can J. Chem.* **2005**, *83*, 413.

(53) Narine, A. A. Design, Synthesis and Evaluation of Chiral Auxiliaries, Ligands and Catalysts for Asymmetric Synthesis. *Ph. D. Thesis, Simon Fraser University*, **2004**.

(54) McWhinnie, W. R.; Poller, R. C.; Thevarasa, M. An Inclusion Compound from Hexaphenylditin and Tetraphenylditin. *J. Organomet. Chem.* **1968**, *11*, 499.

(55) (a) Malkov, A. V.; Kočovský, P. Chiral Bipyridine Derivatives in Asymmetric Catalysis. *Curr. Org. Chem.* **2003**, *7*, 1737. (b) Chelucci, G.; Thummel, R. P. Chiral 2,2′-Bipyridines, 1,10-Phenanthrolines, and 2,2′:6′,2′′-Terpyridines: Synthesis and Applications in Asymmetric Homogenous Catalysis. *Chem. Rev.* **2002**, *102*, 3129. (c) Fletcher, N. C. Chiral 2,2-Bipyridines: Ligands for Asymmetric Induction. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1831.

(56) (a) Reedijk, J. In *Comprehensive Coordination Chemistry*; Wilkinson, G., Gillard, R. D., McCleverty, J. A., Eds; Pergamon Press: Oxford, 1987; Vol. 2, pp 73-98. (b) Kaes, C.; Katz, A.; Hosseini, M. W. Bipyridine: The Most Widely Used Ligand. A Review of Molecules Containing at Least Two 2,2′-Bipyridine Units. *Chem. Rev.* **2000**, *100*, 3553.

(57) Johnson, J. S.; Evans, D. A. Chiral *bis*(Oxazoline) Copper(II) Complexes: Versatile Catalysts for Enantioselective Cycloaddition, Aldol, Michael and Carbonyl Ene Reactions. *Acc. Chem. Res.* **2000**, *33*, 325.

(58) Bolm, C.; Zehnder, M.; Bur, D. Optically Active Bipyridines in Asymmetric Synthesis. *Angew. Chem., Int. Ed.* **1990**, *29*, 205.

(59) Kröhnke, F. Neuere Methoden der Praparativen Organischen Chemie Synthesen mit hilfe von Pyridiniumsalzen. *Angew. Chem., Int. Ed.* **1963**, *2*, 386.

(60) Hayoz, P.; von Zelewsky, A. New Versatile Optically Active Bipyridines as Building Blocks for Helicating and Caging Ligands. *Tetrahedron Lett.* **1992**, *33*, 5165.

(61) Ito, K.; Tabuchi, S.; Katsuki, T. Synthesis of New Chiral Bipyridine Ligands and Their Application to Asymmetric Cyclopropanation. *Synlett* **1992**, 575.

(62) Ito, K.; Katsuki, T. Synthesis of New Chiral Bipyridine Ligands and Their Application to Asymmetric Cyclopropanation. *Chem. Lett.* **1994**, 1857.

(63) Ito, K.; Yoshitake, M.; Katsuki, T. Chiral Bipyridine and Biquinoline Ligands: Their Asymmetric Synthesis and Application to the Synthesis of *trans*-Whisky Lactone. *Tetrahedron* **1996**, *52*, 3905.

(64) Fukuda, T.; Irie, R.; Katsuki, T. Mn-Salen Catalyzed Asymmetric Epoxidation of Conjugated Trisubstituted Olefins. *Synlett* **1995**, 197.

(65) Malkov, A. V.; Bella, M.; Langer, V.; Kočovský, P. PINDY: A Novel, Pinene-Derived Bipyridine and its Application in Asymmetric, Copper(I)-Catalyzed Allylic Oxidation. *Org. Lett.* **2000**, *2*, 3047.

(66) Chelucci, G.; Saba, A. New Synthetic Route to C_2-Symmetric 2,2′-Bipyridines: Synthesis of (6*R*,6′*R*,8*R*,8*R*′)-6,8,6′,8′-Bismethano-7,7,7′,7′-tetramethyl-5,5′,6,6′,7,7′-octahydro-2,2′-biquinoline. *Synth. Commun.* **2001**, *31*, 3161.

(67) (a) Noyori, R. Centenary Lecture. Chemical Multiplication of Chirality: Science and Applications. *Chem. Soc. Rev.* **1989**, *18*, 187. (b) Pu, L. 1,1′-Binapthyl Dimers, Oligomers, and Polymers: Molecular Recognition, Asymmetric Catalysis and New Materials. *Chem. Rev.* **1998**, *98*, 2405.

(68) Noyori, R. BINAP: An Efficient Chiral Element for Asymmetric Catalysis. *Acc. Chem. Res.* **1990**, *23*, 345.

(69) Wang, X. C.; Cui, Y. X.; Mak, T. C. W.; Wong, H. N. C. Synthesis, Metal Complex Formation, and Resolution of a New C_2 Diazabiaryl Ligand: Cyclo-octa[2,1-*b*:3,4-*b*′]dipyridine. *J. Chem. Soc., Chem. Commun.* **1990**, 167.

(70) Botteghi, C.; Schionato, A.; De Lucchi, O. A C_2-Symmetric Chiral 2,2′-Bipyridine Derived From Tartaric Acid. *Synth. Commun.* **1991**, *21*, 1819.

(71) Wong, H. L.; Tian, Y.; Chan, K. S. Electronically Controlled Asymmetric Cyclopropanation Catalyzed by a New Type of Chiral 2,2′-Bipyridine. *Tetrahedron Lett.* **2000**, *41*, 7723.

(72) Wörsdörfer, E.; Vögtle, F.; Nieger, M.; Waletzke, M.; Grimme, S.; Glorius, F.; Pfaltz, A. A New Planar Chiral Bipyridine Ligand. *Synthesis* **1999**, 597.

(73) Rios, R.; Liang, J.; Lo, M. M.-C.; Fu, G. C. Synthesis, Resolution and Crystallographic Characterization of a New C_2-Symmetric Planar-Chiral Bipyridine Ligand: Application to the Catalytic Enantioselective Cyclopropanation of Olefins. *Chem. Commun.* **2000**, 377.

(74) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; J. Wiley: New York, 1998.

(75) (a) Doyle, M. P.; Forbes, D. C. Recent Advances in Asymmetric Catalytic Metal Carbene Transformations. *Chem. Rev.* **1998**, *98*, 911. (b) Doyle, M. P.; Protopopova, M. N. New Aspects of Catalytic Asymmetric Cyclopropanation. *Tetrahedron* **1998**, *54*, 7919.

(76) (a) Aratani, T.; Yoneyoshi, Y.; Nagase, T. Asymmetric Synthesis of Chrysanthemic Acid. An Application of Copper Carbenoid Reaction. *Tetrahedron Lett.* **1975**, 1707. (b) Aratani, T.; Yoneyoshi, Y.; Nagase, T. Asymmetric Synthesis of Permethric Acid. Stereochemistry of Chiral Copper Carbenoid Reaction. *Tetrahedron Lett.* **1982**, *23*, 685. (c) Aratani, T. Catalytic Asymmetric-Synthesis of Cyclopropane-Carboxylic Acids - An Application of Chiral Copper Carbenoid Reaction. *Pure Appl. Chem.* **1985**, *57*, 1839.

(77) Doyle, M. P. Catalytic Methods for Metal Carbene Transformations. *Chem. Rev.* **1986**, *86*, 919.

(78) Doyle, M. P. Metal Carbene Complexes in Organic Synthesis: Diazodecomposition-Insertion and Ylide Chemistry. In *Comprehensive Organometallic Chemistry II*; Hegedus, L. S., Ed.; Pergamon Press; New York, 1995; Vol. 12, Chapter 5.2.

(79) Salomon, R. G.; Kochi, J. K. Copper(I) Catalysis in Cyclopropanations with Diazo Compounds. The Role of Olefin Coordination. *J. Am. Chem. Soc.* **1973**, *95*, 3300.

(80) Fritschi, H.; Leutenegger, U.; Pfaltz, A. Semicorrin Metal Complexes as Enantioselective Catalysts. Part 2. Enantioselective Cyclopropane Formation from Olefins with Diazo Compounds Catalyzed by Chiral (Semicorrinato)copper Complexes. *Helv. Chim. Acta.* **1988**, *71*, 1553.

(81) Lowenthal, R. E.; Abiko, A.; Masamune, S. Asymmetric Catalytic Cyclopropanation of Olefins: *bis*(Oxazoline) Copper Complexes. *Tetrahedron Lett.* **1990**, *31*, 6005.

(82) Kwong, H.-L.; Lee, W.-S.; Ng, H.-F.; Chiu, W.-H.; Wong, W.-T. Chiral Bipyridine-Copper(II) Complex. Crystal Structure and Catalytic Activity in Asymmetric Cyclopropanation. *J. Chem. Soc., Dalton Trans.* **1998**, 1043.

(83) Kharasch, M. S.; Sosnovsky, G.; Yang, N. C. Reactions of *tert*-Butyl Peresters I. The Reaction of Peresters With Olefins. *J. Am. Chem. Soc.* **1959**, *81*, 5819.

(84) Andrus, M. B.; Chen, X. Catalytic Enantioselective Allylic Oxidation of Olefins with Copper(I) Catalysts and New Perester Oxidants. *Tetrahedron* **1997**, *53*, 16229.

(85) Gokhale, A. S.; Minidis, A. B. E.; Pfaltz, A. Enantioselective Allylic Oxidation Catalyzed by Chiral *bis*(Oxazoline)-Copper Complexes. *Tetrahedron Lett.* **1995**, *36*, 1831.

(86) Andrus, M. B.; Argade, A. B.; Chen, X.; Pamment, M. G. The Asymmetric Kharasch Reaction. Catalytic Enantioselective Allylic Acyloxylation of Olefins with Chiral Copper(I) Complexes and *tert*-Butyl Perbenzoate. *Tetrahedron Lett.* **1995**, *36*, 2945.

(87) Hayes, R.; Wallace, T. W. A Simple Route to Methyl (5*S*)-Benzoyloxy-6-oxohexanoate, a Key Intermediate in Leukotriene Synthesis. *Tetrahedron Lett.* **1990**, *31*, 3355.

(88) Andrus, M. B.; Zhou, Z. Highly Enantioselective Copper-*bis*Oxazoline-Catalyzed Allylic Oxidation of Cyclic Olefins with *tert*-Butyl *p*-Nitroperbenzoate. *J. Am. Chem. Soc.* **2002**, *124*, 8806.

(89) Malkov, A. V.; Orsini, M.; Pernazza, D.; Muir, K. W.; Langer, V.; Meghani, P.; Kočovský, P. Chiral 2,2′-Bipyridine-Type *N*-Monoxides as Organocatalysts in the Enantioselective Allylation of Aldehydes with Allyltrichlorosilane. *Org. Lett.* **2002**, *4*, 1047.

(90) Shimada, T.; Kina, A.; Ikeda, S.; Hayashi, T. A Novel Axially Chiral 2,2′-Bipyridine *N*,*N*′-Dioxide. Its Preparation and use for Asymmetric Allylation of Aldehydes with Allyl(trichloro)silane as a Highly Efficient Catalyst. *Org. Lett.* **2002**, *4*, 2799.

(91) Denmark, S. E.; Fan, Y. Catalytic, Enantioselective Aldol Additions to Ketones. *J. Am. Chem. Soc.* **2002**, *124*, 4233.

(92) Chelucci, G.; Orrù, G.; Pinna, G. A. Chiral *P*,*N*-Ligands with Pyridine-Nitrogen and Phosphorus Donor Atoms. Syntheses and Applications in Asymmetric Catalysis. *Tetrahedron* **2003**, *59*, 9471.

(93) Helmchen, G.; Pfaltz, A. Phosphinooxazolines - A New Class of Versatile, Modular *P*,*N*-Ligands for Asymmetric Catalysis. *Acc. Chem. Res.* **2000**, *33*, 336.

(94) Chelucci, G.; Cabras, M. A.; Botteghi, C.; Basoli, C.; Marchetti, M. Synthesis of Homochiral Pyridyl, Bipyridyl and Phosphino Derivatives of 2,2-Dimethyl-1,3-dioxolane: Use in Asymmetric Catalysis. *Tetrahedron: Asymmetry* **1996**, *7*, 885

(95) Varela, J. A.; Saá, C. Construction of Pyridine Rings by Metal-Mediated [2+2+2] Cycloaddition. *Chem. Rev.* **2003**, *103*, 3787.

(96) Ito, K.; Kashiwagi, R.; Iwasaki, K.; Katsuki, T. Asymmetric Allylic Alkylation using a Palladium Complex of Chiral 2-(Phosphinoaryl)pyridine Ligands. *Synlett* **1999**, *10*, 1563.

(97) Malkov, A. V.; Bella, M.; Stará, G.; Kočovský, P. Modular Pyridine-Type *P,N*-Ligands Derived from Monoterpenes: Application in Asymmetric Heck Addition. *Tetrahedron Lett.* **2001**, *42*, 3045.

(98) Chelucci, G.; Saba, A.; Soccolini, F. Chiral 2-(2-Diphenylphosphinophenyl)-5,6,7,8-tetrahydroquinolines: New *P,N*-Ligands for Asymmetric Catalysis. *Tetrahedron* **2001**, *57*, 9989.

(99) (a) Dai, X.; Wong, A.; Virgil, S. Synthesis and Resolution of Quinazolinone Atropisomeric Phosphine Ligands. *J. Org. Chem.* **1998**, *63*, 2597. (b) Dai, X.; Virgil, S. Asymmetric Allylic Alkylation by Palladium Complexes with Atropisomeric Quinazolinone Phosphine Ligands. *Tetrahedron Lett.* **1999**, *40*, 1245.

(100) Hu, W.; Chen, C.-C.; Zhang, X. Development of New Chiral *P,N* Ligands and Their Application in the Cu-Catalyzed Conjugate Addition of Diethylzinc to Enones. *Angew. Chem., Int. Ed.* **1999**, *38*, 3518.

(101) Tao, B.; Fu, G. C. Application of a New Family of *P,N*-Ligands to the Highly Enantioselective Hydrosilylation of Aryl Alkyl and Dialkyl Ketones. *Angew. Chem., Int. Ed.* **2002**, *41*, 3892.

(102) (a) Trost, B. M. Asymmetric Allylic Alkylation, an Enabling Methodology. *J. Org. Chem.* **2004**, *69*, 5813. (b) Trost, B. M. Pd Asymmetric Allylic Alkylation (AAA). A Powerful Synthetic Tool. *Chem. Pharm. Bull.* **2002**, *50*, 1. (c) Trost, B. M.; Van Vranken, D. L. Asymmetric Transition Metal-Catalyzed Allylic Alkylations. *Chem. Rev.* **1996**, *96*, 395.

(103) Trost, B. M.; Crawley, M. L. Asymmetric Transition-Metal-Catalyzed Allylic Alkylations: Applications in Total Synthesis. *Chem. Rev.* **2003**, *103*, 2921.

(104) Moberg, C.; Brember, U.; Hallman, K.; Svensson, M.; Norrby, P.; Hallberg, A.; Larhed, M.; Csoregh, I. Selectivity and Reactivity in Asymmetric Allylic Alkylation. *Pure Appl. Chem.* **1999**, *71*, 1477.

(105) Sauthier, N.; Fornies, J.; Toupet, L.; Reau, R. Palladium(II) Complexes of Chiral 1,2-Diiminophosphoranes: Synthesis, Structural Characterization, and Catalytic Activity for the Allylic Alkylation. *Organometallics* **2000**, *19*, 553.

(106) Trost, B. M.; Toste, F. D. Regio- and Enantioselective Allylic Alkylation of an Unsymmetrical Substrate: A Working Model. *J. Am. Chem. Soc.* **1999**, *121*, 4545.

(107) Trost, B. M.; Murphy, D. J. A Model for Metal-Templated Catalytic Asymmetric Synthesis *via* π-Allyl Fragments. *Organometallics* **1985**, *4*, 1143.

(108) Shibasaki, M.; Vogl, E. M.; Ohshima, T. Asymmetric Heck Reaction. *Adv. Synth. Catal.* **2004**, *346*, 1533.

(109) Sato, Y.; Sodeoka, ,M.; Shibasaki, M. Catalytic Asymmetric Carbon-Carbon Bond Formation: Asymmetric Synthesis of *cis*-Decalin Derivatives by Palladium-Catalyzed Cyclization of Prochiral Alkenyl Iodides. *J. Org. Chem.* **1989**, *54*, 4738.

(110) Carpenter, N. E.; Kucera, D. J.; Overman, L. E. Palladium-Catalyzed Polyene Cyclizations of Trienyl Triflates. *J. Org. Chem.* **1989**, *54*, 5846.

(111) Loiseleur, O.; Hayashi, M.; Keenan, M.; Schmees, N.; Pfaltz, A. *J. Organomet. Chem.* **1999**, *576*, 16.

(112) Sharpless, K.; Amberg, Y.; Bannani, G.; Crispino, J.; Hartung, K.; Jeong, H.; Kwong, K.; Morikawa, Z.; Wang, D. Xu, X.; Zhang, X.-L. The Osmium-Catalyzed Asymmetric Dihydroxylation: A New Ligand Class and a Process Improvement. *J. Org. Chem.* **1992**, *57*, 2768.

(113) Prasad, K. R. K.; Joshi, N. N. Stereoselective Reduction of Benzils: A New Convenient Route to Enantiomerically Pure 1,2-Diarylethanediols. *J. Org. Chem.* **1996**, *61*, 3888.

(114) (a) Wang, X.; Erickson, S. D.; Iimori, T.; Still, W. C. Enantioselective Complexation of Organic Ammonium Ions By Simple Tetracyclic Podand Ionophores. *J. Am. Chem. Soc.* **1992**, *114*, 4128. (b) Matteson, D. S.; Beedle, E. C.; Kandil, A. A. Preparation of (3*S*,4*S*)-2,5-Dimethyl-3,4-hexane Diol [(*S*)-DIPED] from (*R*,*R*)-Tartaric Acid *via* Trimethylsilyl Chloride Catalyzed Acetylation of a Hindered 1,4-Diol. *J. Org. Chem.* **1987**, *52*, 5034.

(115) Sakurai, A.; Midorikawa, H. The Cyclization of Ethyl Acetoacetate and Ketones by Ammonium Acetate. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 165.

(116) Ruble, J. C.; Fu, G. C. Chiral π-Complexes of Heterocycles with Transition Metals: A Versatile New Family of Nucleophilic Catalysts. *J. Org. Chem.* **1996**, *61*, 7230.

(117) Robison, M. M. The Preparation of 1,5-Pyrindene. *J. Am. Chem. Soc.* **1958**, *80*, 6254.

(118) Rios, R.; Liang, J.; Lo, M. M.-C.; Fu, G. C. Synthesis, Resolution and Crystallographic Characterication of a New C_2-Symmetric Planar-Chiral Bipyridine Ligand: Application to the Catalytic Enantioselective Cyclopropanation of Olefins. *Chem. Commun.* **2000**, 377.

(119) Mancuso, A. J.; Huang, S. L.; Swern, D. Oxidation of Long Chain and Related Alcohols to Carbonyls by Dimethyl Sulfoxide "Activated" by Oxalyl Chloride. *J. Org. Chem.* **1978**, *43*, 2480.

(120) (a) Katada, M. *J. Pharm. Soc. Jpn.* **1947**, *67*, 51. (b) Boekelheide, V.; Linn, W. J. Rearrangements of *N*-Oxides. A Novel Synthesis of Pyridyl Carbinols and Aldehydes. *J. Am. Chem. Soc.* **1954**, *76*, 1286.

(121) Oae, S.; Tamagaki, S.; Negoro, T.; Ogino, K.; Kozuka, S. Kinetic Studies on the Reactions of 2- and 4-Alkyl-Substituted Heteroaromatic *N*-Oxides with Acetic Anhydride. *Tetrahedron Lett.* **1968**, 917.

(122) (a) Dehmlow, E. V.; Sleegers, A. Synthesis of Unsymmetrically and Symmetrically Structured Dihydroxybipyridines. *Liebigs Ann. Chem.* **1992**, 953. (b) Iyoda, M.; Otsuka, H.; Sato, K.; Nisato, N.; Oda, M. Homocoupling of Aryl Halides using Nickel(II) Complex and Zinc in the Presence of Et_4NI. An Efficient Method for the Synthesis of Biaryls and Bipyridines. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 80.

(123) Grushin, V. V.; Alper, H. Transformation of Chloroarenes, Catalyzed by Transition-Metal Complexes. *Chem. Rev.* **1994**, *94*, 1047.

(124) Cox, J. D.; Pilcher, G. *Thermochemistry of Organic and Organometallic Compounds*; Academic Press: London, 1970.

(125) Milstein, D.; Stille, J. K. A General, Selective and Fascile Method for Ketone Synthesis from Acid Chlorides and Organotin Compounds Catalyzed by Palladium. *J. Am. Chem. Soc.* **1978**, *100*, 3636.

(126) (a) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, 50, 1. (b) Mitchell, T. N. In *Metal Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; Chapter 4.

(127) Echavarren, A. M.; Stille, J. K. Palladium-Catalyzed Coupling of Aryltriflates with Organostannanes. *J. Am. Chem. Soc.* **1987**, *109*, 5478.

(128) Littke, A. F.; Schwarz, L.; Fu, G. C. Pd/P(*t*-Bu)$_3$: A Mild and General Catalyst for Stille Reactions of Aryl Chlorides and Aryl Bromides. *J. Am. Chem. Soc.* **2002**, *124*, 6343.

(129) Malkov, A. V.; Pernazza, D.; Bell, M.; Bella, M.; Massa, A.; Teplý, F.; Meghani, P.; Kočovský, P. Synthesis of New Chiral 2,2′-Bipyridyl Ligands and their Application in Copper-Catalyzed Asymmetric Allylic Oxidation and Cyclopropanation. *J. Org. Chem.* **2003**, *68*, 4727.

(130) Fritschi, H.; Leutenegger, U.; Siegmann, K.; Pfaltz, A. Semicorrin Metal Complexes as Enantioselective Catalysts. *Helv. Chim. Acta* **1988**, *71*, 1541.

(131) Niimi, T.; Uchida, T.; Irie, R.; Katsuki, T. Highly Enantioselective Cyclopropanation with Co(II)-Salen Complexes: Control of *cis*- and *trans*-Selectivity by Rational Ligand Design. *Adv. Synth. Catal.* **2001**, *343*, 79.

(132) Hopf, H. In *Classics in Hydrocarbon Chemistry*; Wiley-VCH: Weinheim, 2000; pp 321-368.

(133) Lipshutz, B. H.; Tomioka, T.; Pfeiffer, S. S. Mild and Selective Reductions of Aryl Halides Catalyzed by Low-Valent Nickel Complexes. *Tetrahedron Lett.* **2001**, *42*, 7737.

(134) Silverstein, R. M.; Webster, F. X. Infrared Spectrometry. In *Spectrometric Identification of Organic Compounds*, 6th ed.; John Wiley & Sons, Inc. New York, 1998; Chapter 3.

(135) (a) Nakajima, M.; Saito, M.; Uemura, M.; Hashimoto, H. Enantioselective Ring-Opening of *meso*-Epoxides with Tetrachlorosilane Catalyzed by Chiral Bipyridine *N,N'*-Dioxide Derivatives. *Tetrahedron Lett.* **2002**, *43*, 8827. (b) Garrett, C. E.; Fu, G. C. π-Bound Phosphorus Heterocycles as Catalysts: Ring-Opening of Expoxides with TMSCl in the Presence of a Phosphaferrocene. *J. Org. Chem.* **1997**, *62*, 4534. (c) Denmark, S. E.; Barsanti, P. A.; Wong, K.–T.; Stavenger, R. A. Enantioselective Ring-Opening of Epoxides with Silicon Tetrachloride in the Presence of a Chiral Lewis Base. *J. Org. Chem.* **1998**, *63*, 2428.

(136) Miyaura, N.; Suzuki, A. Palladium-Catalyzed Cross Coupling Reactions of Organoboron Compounds. *Chem. Rev.* **1995**, *95*, 2457.

(137) Littke, A. F.; Dai, C.; Fu, G. C. Versatile Catalysts for the Suzuki Cross-Coupling of Arylboronic Acids with Aryl and Vinyl Halides and Triflates under Mild Conditions. *J. Am. Chem. Soc.* **2000**, *122*, 4020.

(138) Kündig, E. P.; Meier, P. Synthesis of New Chiral Bidentate (Phosphinophenyl)benzooxazine *P,N*-Ligands. *Helv. Chim. Acta* **1999**, *82*, 1360.

(139) (a) Draper, N. D.; Batchelor, R. J.; Leznoff, D. B. Tuning the Structures of Mercury Cyanide-Based Coordination Polymers with Transition Metal Cations. *Crystal Growth and Design* **2004**, *4*, 621. (b) Haftbaradaran, F.; Draper, N. D.; Leznoff, D. B.; Williams, V. E. A Strained Silver(I) Coordination Polymer of 1,4-Diazatriphenylene. *J. Chem. Soc., Dalton Trans.* **2003**, 2105. (c) Draper, N. D.; Batchelor, R. J.; Leznoff, D. B. Using HgX_2 Units (X = CN, Cl) to Increase Structural and Magnetic Dimensionality in Conjunction with (2,2′-Bipyridyl)copper(II) Building Blocks. *Polyhedron* **2003**, *22*, 1735.

(140) Gilbertson, S. R.; Xie, D.; Fu, Z. Proline-Based *P,N* Ligands in Asymmetric Allylation and the Heck Reaction. *J. Org. Chem.* **2001**, *66*, 7240.

(141) (a) Brown, J. M.; Hulmes, D. I.; Guiry, P. J. Mechanistic and Synthetic Studies in Catalytic Allylic Alkylation with Palladium Complexes of 1-(2-Diphenylphosphino-1-napthyl)isoquinoline. *Tetrahedron* **1994**, *50*, 4493. (b) Bovens, M.; Togni, A.; Venanzi, L. M. Asymmetric Allylic Alkylation with Palladium Coordinated to a New Optically Active Pyrazolylmethane Ligand. *J. Organomet. Chem.* **1993**, *451*, C28.

(142) Hayashi, T.; Yamamoto, A.; Ito, Y.; Nishioka, E.; Miura, H.; Yanagi, K. Asymmetric Synthesis Catalyzed by Chiral Ferrocenylphosphine-Transition-Metal Complexes. Palladium Catalyzed Asymmetric Allylic Amination. *J. Am. Chem. Soc.* **1989**, *111*, 6301.

(143) (a) Auburn, P. R.; Mackenzie, P. B.; Bosnich, B. Asymmetric Synthesis. Asymmetric Catalytic Allylation using Palladium Chiral Phosphine Complexes. *J. Am. Chem. Soc.* **1985**, *107*, 2033. (b) Mackenzie, P. B.; Whelan, J.; Bosnich, B. Asymmetric Synthesis. Mechanism of Asymmetric Catalytic Allylation. *J. Am. Chem. Soc.* **1985**, *107*, 2046.

(144) Gilbertson, S. R.; Lan, P. Kinetic Resolution in Palladium-Catalyzed Asymmetric Allylic Alkylations by a *P,O* Ligand System. *Org. Lett.* **2001**, *3*, 2237.

(145) (a) Mancherio, O. G.; Priego, J.; Ramón, S. C.; Arrayás, R. G.; Liamas, T.; Carretero, C. 1-Phosphino-2-sulfenylferrocenes as Planar Chiral Ligands in Enantioselective Palladium-Catalyzed Allylic Substitutions. *J. Org. Chem.* **2003**, *68*, 3679. (b) Evans, D. A.; Campos, K. R.; Tedrow, J. S.; Michael, F. E.; Gagné, M. R. Application of Chiral Mixed Phosphorus/Sulfur Ligands to Palladium-Catalyzed Allylic Substitutions. *J. Am. Chem. Soc.* **2000**, *122*, 7905.

(146) Seeman, J. I. Effect of Conformational Change on Reactivity in Organic Chemistry. Evaluations, Applications, and Extensions of Curtin-Hammett Winstein-Holness Kinetics. *Chem. Rev.* **1983**, *83*, 83.

(147) Gold, V. Glossary of Terms used in Physical Organic Chemistry. *Pure Appl. Chem.* **1979**, *51*, 1725.

(148) (a) Helmchen, G.; Pfaltz, A. Phosphinooxazolines - A New Class of Versatile, Modular *P,N*-Ligands for Asymmetric Catalysis. *Acc. Chem. Res.* **2000**, *33*, 336. (b) Pfaltz, A.; Drury III, W. J. Design of Chiral Ligands for Asymmetric Catalysis. From C_2-Symmetric *P,P* and *N,N*-Ligands to Sterically and Electronically Nonsymmetrical *P,N*-Ligands. *Proc. Nat. Acad. Sci.* **2004**, *101*, 5723.

(149) Lightfoot, A.; Schnider, P.; Pfaltz, A. Enantioselective Hydrogenation of Olefins with Iridium-Phosphanodihydrooxazole Catalysts. *Angew. Chem., Int. Ed.* **1998**, *37*, 2897.

(150) (a) Kainz, S.; Brinkmann, A.; Leitner, W.; Pfaltz, A. Iridium-Catalyzed Enantioselective Hydrogenation of Imines in Supercritical Carbon Dioxide. *J. Am. Chem. Soc.* **1999**, *121*, 6421.

(151) Jung, Y. J.; Mishra, R. K.; Yoon, C. H.; Jung, K. W. Oxygen-Promoted Pd(II) Catalysis for the Coupling of Organoboron Compounds and Olefins. *Org. Lett.* **2003**, *5*, 2231.

(152) Vineyard, B. D.; Knowles, W. S.; Saback, M. J.; Bachman, G. L.; Weinkauff, D. J. Asymmetric Hydrogenation. Rhodium Chiral Biphosphine Catalyst. *J. Am. Chem. Soc.* **1977**, *99*, 5946.

(153) Ruble, J. C.; Fu, G. C. Chiral π-Complexes of Heterocycles with Transition Metals: A Versatile New Family of Nucleophilic Catalysts. *J. Org. Chem.* **1996**, *61*, 7230.

(154) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. Catalytic Asymmetric Dihydroxylation. *Chem. Rev.* **1994**, *94*, 2483.

(155) (a) Wang, Z.-M.; Kakiuchi, K.; Sharpless, K. B. Osmium-Catalyzed Asymmetric Dihydroxylation of Cyclic *cis*-Disubstituted Olefins. *J. Org. Chem.* **1994**, *59*, 6895. (b) Wang, L.; Sharpless, K. B. Catalytic Asymmetric Dihydroxylation of *cis*-Disubstituted Olefins. *J. Am. Chem. Soc.* **1992**, *114*, 7568.

(156) Wang, Z.-M.; Sharpless, K. B. A Solid-to-Solid Asymmetric Dihydroxylation Procedure for Kilogram-Scale Preparation of Enantiopure Hydrobenzoin. *J. Org. Chem.* **1994**, *59*, 8302.

(157) Hanessian, S.; Meffre, P.; Girard, M.; Beaudoin, S.; Sancéau, J.-Y.; Bennani, Y. Asymmetric Dihydroxylation of Olefins With a Simple Chiral Ligand. *J. Org. Chem.* **1993**, *58*, 1991.

(158) Spivey, A. C.; Hanson, R.; Scorah, N.; Thorpe, S. J. Sharpless Asymmetric Dihydroxylation: Effect of Alkene Structure on Rates and Selectivity. *J. Chem. Ed.* **1999**, *76*, 655.

(159) Hale, K. J.; Manaviazar, S.; Peak, S. A. Anomalous Enantioselectivity in the Sharpless Catalytic Asymmetric Dihydroxylation Reaction of 1,1-Disubstituted Allyl Alcohol Derivatives. *Tetrahedron Lett.* **1994**, *35*, 425.

(160) Agarwal, S. K.; Boyd, D. R.; Davies, J. H.; Hamilton, L.; Jerina, D. M.; McCullough, J. J.; Porter, H. P. Synthesis of Arene Oxide and *trans*-Dihydrodiol Metabolites of Quinoline. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1969.

(161) Malkov, A. V.; Pernazza, D.; Bell, M.; Bella, M.; Massa, A.; Teplý, F.; Meghani, P.; Kočovský, P. Synthesis of New Chiral 2,2′-Bipyridine Ligands and their Application in Copper-Catalyzed Asymmetric Allylic Oxidation and Cyclopropanation. *J. Org. Chem.* **2003**, *68*, 4727.

(162) Niimi, T.; Uchida, T.; Irie, R.; Katsuki, T. Highly Enantioselective Cyclopropanantion with Co(II)-Salen Complexes: Control of *cis*- and *trans*-Selectivity by Rational Ligand Design. *Adv. Synth. Catal.* **2001**, *343*, 79.

(163) Doyle, M. P. Chiral Catalysts for Enantioselective Carbenoid Cyclopropanation Reactions. *Recl. Trav. Chim. Pays-Bas* **1991**, *110*, 305.

(164) Doyle, M. P. Asymmetric Addition and Insertion Reactions of Catalytically-Generated Metal Carbenes. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; Chapter 5.

(165) (a) Friedel, C.; Crafts, J. M. *R. Hebd. Seances Acad. Sci.* **1877**, *84*, 1392. (b) Friedel, C.; Crafts, J. M. *R. Hebd. Seances Acad. Sci.* **1877**, *84*, 1450.

(166) Olah, G. A.; Khrisnamurti, R.; Prakash, G. K. S. In *Comprehensive Organic Synthesis*, 1st ed.; Pergamon: New York, 1991; Vol. 3, pp 293-339

(167) (a) Bigi, F.; Casiraghi, G.; Casnati, G.; Satori, G. Asymmetric Electrophilic Substitution on Phenols. Enantioselective *ortho*-Hydroxyalkylation Mediated by Chiral Alkoxyaluminum Chlorides. *J. Org. Chem.* **1985**, *50*, 5018. (b) Erker, G.; van der Zeijden, A. A. H. Enantioselective Catalysis with a New Zirconium Trichloride Lewis Acid Containing a "Dibornacyclopentadienyl" Ligand. *Angew. Chem., Int. Ed.* **1990**, *29*, 512.

(168) (a) Zhuang, W.; Gathergood, N.; Hazell, R. G.; Jørgensen, K. A. Catalytic, Highly Enantioselective Friedel-Crafts Reactions of Aromatic and Heteroaromatic Compounds to Trifluoropyruvate. A Simple Approach for the Formation of Optically Active Aromatic and Heteroaromatic Hydroxy Trifluoromethyl Esters. *J. Org. Chem.* **2001**, *66*, 1009. (b) Gathergood, N.; Zhuang, W.; Jørgensen, K. A. Catalytic Enantioselective Friedel-Crafts Reactions of Aromatic Compounds with Glyoxylate: A Simple Procedure for the Synthesis of Optically Active Mandelic Acid Esters. *J. Am. Chem. Soc.* **2000**, *122*, 12517.

(169) Jensen, K. B.; Thorhauge, J.; Hazell, R. G.; Jørgensen, K. A. Catalytic Asymmetric Friedel-Crafts Alkylation of β,γ-Unsaturated α-Ketoesters: Enantioselective Addition of Aromatic C-H Bonds to Alkenes. *Angew. Chem., Int. Ed.* **2001**, *40*, 160.

(170) van Lingen, H. L.; Zhuang, W.; Hansen, T.; Rutjes, F. P. J. T.; Jørgensen, K. A. Formation of Optically Active Chromanes by Catalytic Asymmetric Tandem oxa-Michael Addition-Friedel-Crafts Alkylation Reactions. *Org. Biomol. Chem.* **2003**, *1*, 1953.

(171) Thorhauge, J.; Roberson, M.; Hazell, R. G.; Jørgensen, K. A. On the Intermediates in Chiral *bis*(Oxazoline)copper(II)-Catalyzed Enantioselective Reactions-Experimental and Theoretical Investigations. *Chem. Eur. J.* **2002**, *8*, 1888.

(172) Hanan, G. S.; Schubert, U. S.; Volkmer, D.; Riviere, E.; Lehn, J.-M.; Kyritsakas, N.; Fischer, J. Synthesis. Structure and Properties of *oligo*-Tridentate Ligands: Covalently Assembled Precursors of Coordination Arrays. *Can. J. Chem.* **1997**, *75*, 169.

(173) (a) Kobayashi, S. Scandium Triflate in Organic Synthesis. *Eur. J. Org. Chem.* **1999**, 15. (b) Evans, D. A.; Scheidt, K. A.; Fandrick, K. R.; Lam, H. W.; Wu, J. Enantioselective Indole Friedel-Crafts Alkylations Catalyzed by *bis*(Oxazolinyl)pyridine-Scandium(III) Triflate Complexes. *J. Am. Chem. Soc.* **2003**, *125*, 10780. (c) Schneider, C.; Sreekanth, A. R.; Mai, E. Scandium-Bipyridine-Catalyzed Enantioselective Addition of Alcohols and Amines to *meso*-Epoxides. *Angew. Chem., Int. Ed.* **2004**, *43*, 5691.

(174) Armarego, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals*, 4th ed.; Butterworth-Heinemann: Oxford, 1997.

(175) Still, W. C.; Kahn, M.; Mitra, A. Rapid Chromatographic Technique for Preparative Separations with Moderate Resolution. *J. Org. Chem.* **1978**, *43*, 2923.

(176) de Meulenaer, J.; Tompa, H. *Acta Cryst.* **1965**, *19*, 1014.

(177) Watkin, D. J.; Prout, C. K.; Carruthers, J. R.; Betteridge, P. W.; Cooper, R. I. *CRYSTALS* Issue 12.50; Chemical Crystallography Laboratory, University of Oxford, Oxford, England, 2003.

(178) International Union of Crystallography. *International Tables for X-Ray Crystallography*; Kynoch Press: Birmingham, 1952.

(179) Denmark, S. E.; Barsanti, P. A.; Wong, K.-T.; Stavenger, R. A. Enantioselective Ring Opening of Epoxides with Silicon Tetrachloride in the Presence of a Chiral Lewis Base. *J. Org. Chem.* **1998**, *63*, 2428.

(180) Kündig, P. E.; Meier, P. Synthesis of New Chiral Bidentate (Phosphinophenyl)benzoxazine *P,N*-Ligands. *Helv. Chim. Acta* **1999**, *82*, 1360.

(181) Evans, D. A.; Campos, K. R.; Tedrow, J. S.; Michael, F. E.; Gagné, M. R. Application of Chiral Mixed Phosphorus/Sulfur Ligands to Palladium-Catalyzed Allylic Substitutions. *J. Am. Chem. Soc.* **2000**, *122*, 7905.

(182) Gabe, E. J.; Lepage, Y.; Charland, J. P.; Lee, F. L.; White, P. S. *J. Appl. Cryst.* **1989**, *22*, 384-387.

(183) Dujardin, G.; Leconte, S.; Benard, A.; Brown, E. A Straightforward Route to *E*-γ-Aryl-α-oxobutenoic Esters by One-step Acid-catalysed Crotonisation of Pyruvates. *Synlett* **2001**, 147.