SYNTHESIS OF CHIRAL NONRACEMIC C_2-SYMMETRIC 2,2'-BIPYRIDINES AND THEIR EVALUATION AS LIGANDS IN COPPER-CATALYZED ASYMMETRIC REACTIONS

by

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ABSTRACT

This thesis concerns the synthesis and evaluation of a series of new chiral nonracemic C_2-symmetric 2,2'-bipyridines for use as ligands in catalytic asymmetric reactions. The 2,2'-bipyridines were prepared using a divergent synthetic strategy which employed an asymmetric dihydroxylation reaction of a 2-chloropyrindine as the key step. The resultant chiral diol was condensed with a series of symmetrical ketones to afford chiral acetals which were then converted into the requisite ligand series. These ligands were evaluated in the asymmetric copper(I)-catalyzed cyclopropanation reaction of styrene and ethyldiazoacetate. The expected major *trans*-cyclopropane products were isolated in good yield and very high enantioselectivities were achieved (up to 94% ee). These are amongst the highest enantioselectivities reported for a chiral 2,2'-bipyridyl ligand. The most effective ligand, an adamantanone derivative, was evaluated in the copper(I)-catalyzed asymmetric allylic oxidation of cyclic alkenes with *tert*-butyl peroxybenzoate. High enantioselectivities were also obtained in these reactions (up to 91% ee).

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LIST OF ABBREVIATIONS

$[\alpha]_D$	specific rotation
α	top face of molecule (as illustrated)
β	bottom face of molecule (as illustrated)
δ	chemical shift (NMR spectroscopy)
(+)-	dextrotatory
(-)-	levorotatory
(±)-	racemic
1D	one-dimensional
2D	two-dimensional
3D	three-dimensional
Ac	acetyl
AcOH	acetic acid
Ac_2O	acetic anhydride
amu	atomic mass units (mass spectroscopy)
Anal.	elemental analysis
ax	axial
aq	aqueous
Ar	aromatic group

BINAP	[1,1'-binaphthyl]-2,2'-diyl*bis*(diphenylphosphine)
Bn	benzyl (phenylmethyl)
b.p.	boiling point
br	broad
brsm	based on recovered starting material
˚C	degrees Celsius
c	concentration
calcd.	calculated (elemental analysis and mass spectrometry)
cat.	catalytic (amount)
conc.	concentrated
Cp	cyclopentadienyl
CI	chemical ionization
cm^{-1}	wavenumbers (IR spectroscopy)
^{13}C NMR	carbon nuclear magnetic resonance spectroscopy
COSY	^{1}H-^{1}H correlation spectroscopy
D	sodium *D*-line (589 nm, optical rotation)
d	doublet
dd	doublet of doublets
ddd	doublet of doublet of doublets

ddt	doublet of doublet of triplets
de	diastereomeric excess
dec.	decomposition
$(DHQ)_2PHAL$	hydroquinine 1,4-phthalazinediyl diether
$(DHQD)_2PHAL$	hydroquinidine 1,4-phthalazinediyl diether
dt	doublet of triplets
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMAP	*N*,*N*-dimethyl-4-aminopyridine
DMP	2,2'- dimethoxypropane
DMSO	dimethyl sulfoxide
eq	equatorial
equiv.	equivalent(s)
Et	ethyl
EtOAc	ethyl acetate
Et_2O	diethyl ether (ether)
h	hours
HREIMS	high-resolution electrospray ionization mass spectrometry
^1H NMR	proton nuclear magnetic resonance spectroscopy

HPLC	high performance liquid chromatography
HRMS	high-resolution mass spectrometry
Hz	Hertz (cycles per second)
i-Pr	isopropyl
IR	infrared spectroscopy
i.r.	isotopic ratio
J	coupling constant (NMR spectroscopy)
KBr	potassium bromide disc (IR spectroscopy)
LDA	lithium *N*,*N*-diisopropylamide
lit.	literature
m	multiplet (NMR spectroscopy)
M	molarity of a solution
MALDI-TOF	matrix assisted laser desorption ionization-time of flight (mass spectrometry)
MCPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MeCN	acetonitrile
MeOH	methanol
mg	milligram(s)
MHz	megahertz (NMR spectrometry)

min	minute(s)
mL	milliliter(s)
mm Hg	millimeters of mercury
mmol	millimole(s)
m.p.	melting point
mol	mole(s)
MS	mass spectrometry
m/*z*	mass to charge ratio
*μ*L	microliter(s)
N/A	not applicable
n-BuLi	*n*-butyl lithium
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
OAc	acetate
Ph	phenyl
PhH	benzene
PhMe	toluene
ppm	parts per million (NMR spectroscopy)

ppt	parts per trillion
PPTS	pyridinium *p*-toluenesulfonate
PTSA	*p*-toluenesulfonic acid monohydrate
q	quartet
rel.	relative
R_f	retention factor (thin-layer chromatography)
rt	room temperature
s	singlet (NMR spectroscopy)
t	triplet (NMR spectroscopy)
TADDOL	*α,α,α',α'*-tetraaryl-2,2-dimethyl-1,3-dioxolan-4,5-dimethanol
TBS	*tert*-butyldimethylsilyl
TBSCl	*tert*-butyldimethylsilyl chloride
t-Bu	*tert*-butyl
td	triplet of doublets (NMR spectroscopy)
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TsCl	tosyl chloride
UV	ultraviolet
w/v	weight by volume

w/w	weight by weight

CHAPTER 1: INTRODUCTION

Introduction to Chiral 2,2'-Bipyridines and Their Use in Catalytic Asymmetric Synthesis

1.1 Thesis Introduction

1.1.1 Brief Overview

This thesis concerns the synthesis of six new chiral nonracemic C_2-symmetric 2,2'-bipyridyl ligands **1b-g** and their evaluation in copper-catalyzed asymmetric reactions (Figure 1.1.1.1). These ligands were synthesized as a means of improving the overall asymmetric induction exhibited by the known 2,2'-bipyridine **1a** in various copper-catalyzed reactions, particularly the asymmetric cyclopropanation reaction of styrene and the allylic oxidation of cycloalkenes.[1]

In the following sections a brief overview of asymmetric synthesis is provided. This leads to a description of the design, synthesis and evaluation of chiral nonracemic 2,2'-bipyridines as ligands for catalytic asymmetric synthesis which is the focus of the study discussed here-in.

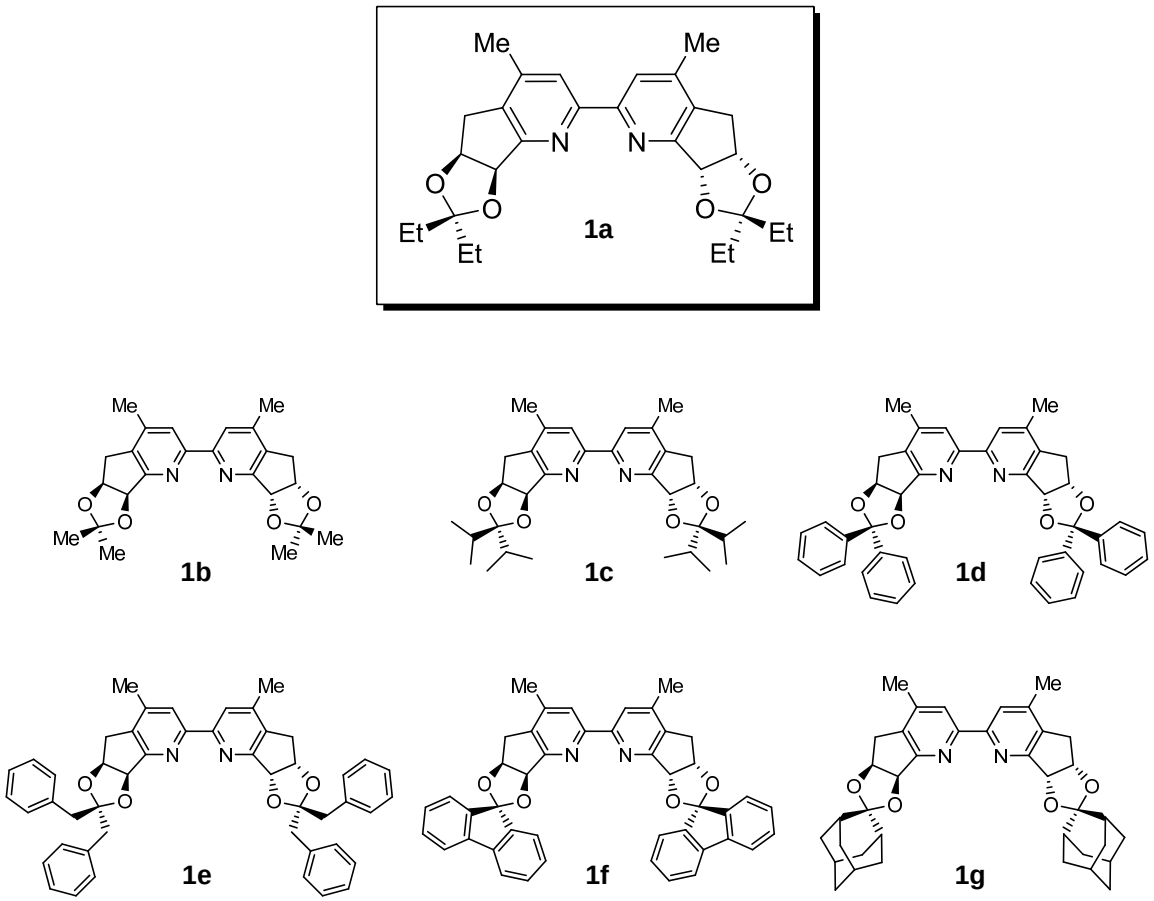


Figure 1.1.1.1: Chiral nonracemic C_2-symmetric 2,2'-bipyridine ligand series (1a-g).

1.2 Asymmetric Synthesis

1.2.1 Introduction to the Chirality of Molecules

Chirality is a phenomenon that pervades the Universe.[2] It is the fact that some objects - hands for instance - have non-superimposable mirror images. The chirality of an object is not always important, you can tie your shoes with either a left- or right-handed knot. However, when two chiral objects interact with each other, their "handedness" becomes immediately apparent; attempt to wear your left shoe on your right foot. On a molecular scale chirality may not be as obvious, yet molecular chirality dramatically affects our lives.

Many molecules exhibit chirality, which chirality can be derived from several different sources: tetrahedral atoms bearing four unique substituents (this is the most common source of molecular chirality encountered organic chemistry), chiral axes and chiral planes (shown in this order in Figure 1.2.1.1).[3] The nomenclature used to assign the stereochemistry associated with these forms of chirality was first defined for universal adoption by R. S. Cahn, C. Ingold and V. Prelog in 1951 and has since been expanded and revised several times.[4-7]

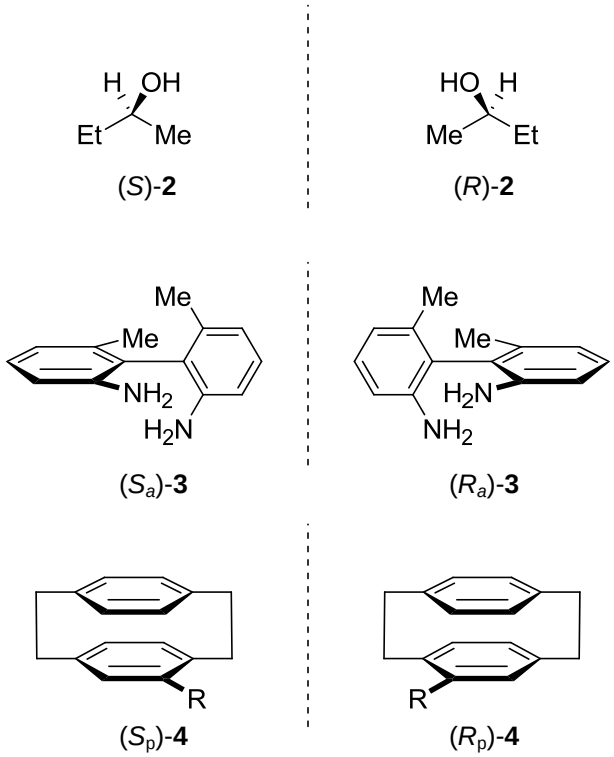
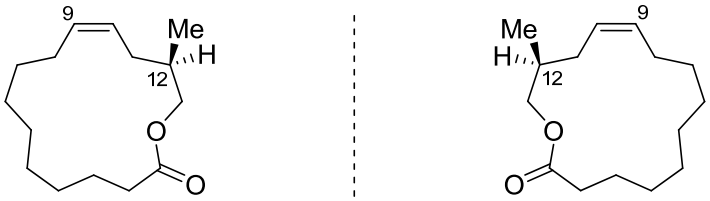


Figure 1.2.1.1: Three sources of chirality in organic chemistry: Tetrahedral chirality (2), axial chirality (3), and planar chirality (4).

Pairs of molecules that are non-superimposable mirror images, such as those illustrated above, are known as enantiomers. Such structurally-related compounds share nearly all of the same physical properties as one another: they have identical boiling points, melting points, densities, infrared absorption bands and nuclear magnetic

resonances. In fact, the only physical property in which a pair of enantiomers differ from one another is that they rotate the plane of polarized light in equal yet opposite directions. Due to these physical similarities they are difficult to separate, and are very difficult to synthesize individually.

Despite the similarities that two enantiomers share, when they are placed in a chiral environment such as an enzyme or receptor, they exhibit markedly different properties.[8] An example of this is nirvanolide **5**.[9] To the human nose (*R*)-nirvanolide (-)-**5** is noticeable by its "intense musky, fruity, powdery odour with lactonic nuances" and has a very low odour threshold; 42 ppt in air.[9] In spite of the tiny odour threshold and poetic adjectives attributed to the scent of (*R*)-nirvanolide, its enantiomer, (*S*)-nirvanolide (+)-**5**, is odourless. It may seem trivial that two enantiomers can have different scents - creating a better perfume is not going to make or break humanity - but to an insect scent may make all the difference in the world.[10]



(-)-(12*R*,9Z)-Nirvanolide (**5**)
"Intense musky, fruity, powdery odour with lactonic nuances"

(+)-(12*S*,9Z)-Nirvanolide (**5**)
Odourless

Figure 1.2.1.2: (-)-Nirvanolide (5) the musk odourant and its scentless enantiomer.

1.2.2 Molecular Chirality and Insects: Pheromones

Insects communicate in a variety of ways, possibly the most important of which is through chemical signaling using pheromones. Pheromones often contain specific enantiomers, or mixtures of enantiomers with precise enantiomeric ratios. Thus, the

ability of any particular insect to detect and produce these molecules stereospecifically is often essential to its species' survival.[8,10] Of course, to humans, the survival of some species of insects isn't always desirable.

A particularly destructive insect, the southern pine bark beetle (*Dendroctonus frontalis Zimmermann*), produces a pheromone which contains the (1*S*,5*R*) stereoisomer of frontalin (-)-**6**.[11] This pest uses the pheromone as an aggregation signal, drawing beetles from the surrounding area to infest a pine tree, which results in the death of the tree. Economic losses of 200 million USD annually are attributed these infestations.

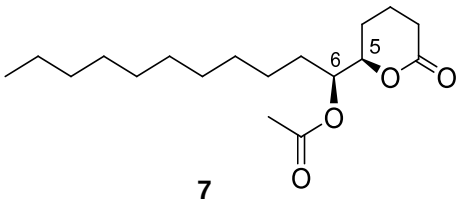
One strategy for pest control is to use artificial pheromones to trick beetles into aggregating in a trap, preventing tree infestations. However, when artificial pheromone employing (1*R*,5*S*)-frontalin (+)-**6** is used in place of (1*S*,5*R*)-frontalin (-)-**6**, no beetles are attracted.[12] Thus, if synthetic pheromone were to be used as a lure to trap these destructive insects, the proper stereochemistry of its components would be essential.

(-)-(1*S*,5*R*)-Frontalin (**6**) (+)-(1*R*,5*S*)-Frontalin (**6**)

Figure 1.2.2.1: The aggregation pheromone (-)-Frontalin [(-)-6] and its inactive enantiomer.

Yet another example of this involves female mosquitoes of the species *Culex pipiens futigans*. These insects tend to lay their eggs in a common pool of water.[13] Once a suitable pool has been found they emit the pheromone 6-acetoxy-5-hexadecanolide **7** to attract other mosquitoes. All four diastereoisomers of this compound have been synthesized, and it was found that only the (5*R*, 6*S*) diastereoisomer **7** attracted the

insect.[14] Once again, the proper chirality of a synthetic pheromone to be used as a lure to trick the mosquitoes into laying their eggs in unsuitable water would be essential.



7

Figure 1.2.2.2: The oviposition attractant pheromone (-)-(5*R*,6*S*)-6-acetoxy-5-hexadecanolide (7).

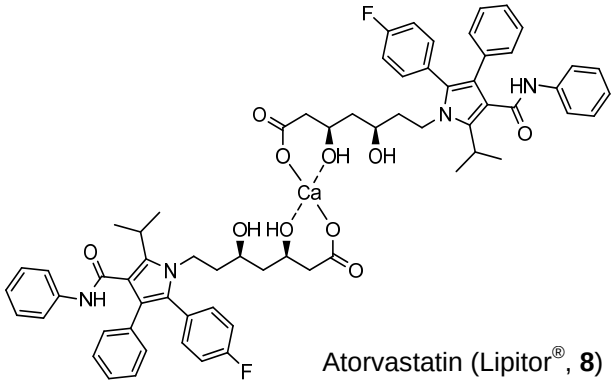
These two examples represent only a small proportion of the information that has been gathered concerning insect pheromones and their chirality.[15,16] We won't dwell on insects, as there are other fields where chirality is of concern, probably the most relevant of which is the pharmaceutical industry. With recent advances in chiral technologies, pharmaceutical companies are become increasingly conscious of chirality in the drugs they produce. The desire to investigate the individual effects of enantiomeric drugs was escalated to a legal responsibility by the passing of legislation by the FDA in 1991 that requires pharmaceutical companies to separately evaluate both enantiomers of all chiral drugs.

1.2.3 Pharmaceutical Chirality

Approximately half of all pharmaceutical drugs on the market today are chiral and of these, approximately half are sold as single enantiomers.[17] In 2006, 80% of small-molecule drugs approved by FDA were chiral and 75% were single enantiomers.[18] Notably, of the top ten pharmaceutical drugs sold in 2007, five were chiral small molecules and all of these were sold as single enantiomers, representing 39.6 billion USD in worldwide sales - six percent of the total pharmaceutical drug market that year.[19] Due

to the economic and medical significance of these blockbuster drugs we shall briefly introduce four of them, and discuss the importance of their chirality.

Lipitor® is the world's best-selling drug having worldwide sales of 13.3 billion USD in 2007.[19] It has been found that the single enantiomer form of the drug (the form currently on the market) is twice as potent as the racemic mixture.[*20] By providing the drug as single enantiomer, necessary dosages are half that of the racemic form. This is desirable as it lowers metabolic load of the drug in the body.

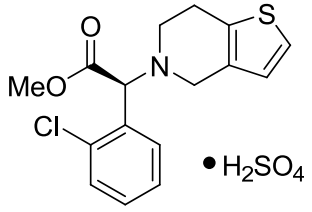


Atorvastatin (Lipitor®, **8**)

Figure 1.2.3.1: The blockbuster drug atorvastatin (8), as its calcium salt dimer. It is the #1 selling drug in the world with annual sales above 13 billion USD.

* Pfizer, in their original single enantiomer Australian patent application, had claimed that the (*R*,*R*) enantiomer was approximately ten-times as active as the racemate. However, in court they failed to prove this. In fact, it was shown that the (*R*,*R*) enantiomer was only twice as active as the racemate. Thus, the Australian patent for the single enantiomer version of the drug was revoked, which resulted in a year less of patent protection in Australia for this immensely profitable product.

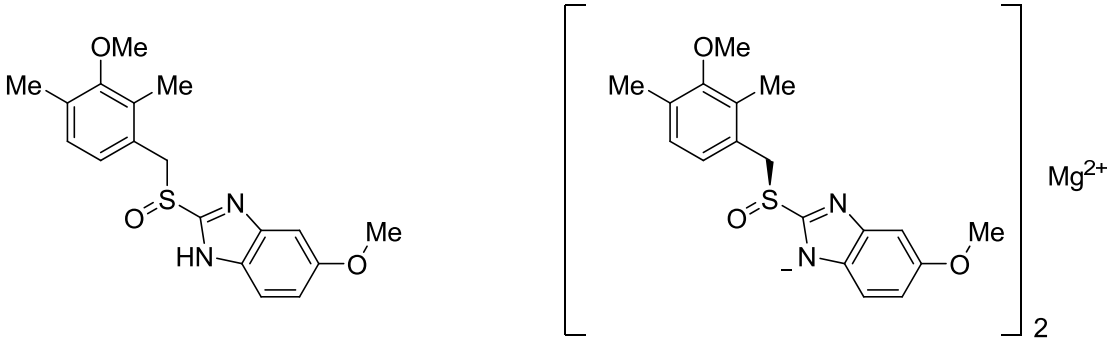
Clopidogrel (plavix®, **9**) is sold as an anti-blood clotting agent.[21] Following its initial discovery, the compound was nearly discontinued as a drug candidate when the racemate was found to be highly toxic. However, through a difficult separation, the enantiomers were separated and evaluated individually. These studies showed that the (*S*)-enantiomer was more effective as an anti-blood clotting agent and far less toxic than the racemate. In addition, the (*R*)-enantiomer was found to be ineffective and toxic.[22] Currently, the drug is sold only as the (*S*)-enantiomer.



(*S*)-Clopidogrel (Plavix®, **9**)

Figure 1.2.3.2: Clopidogrel (9), an anti-blood clotting agent used to help combat coronary artery disease. It is the #2 best-selling drug with 7.3 billion USD in sales in 2007.

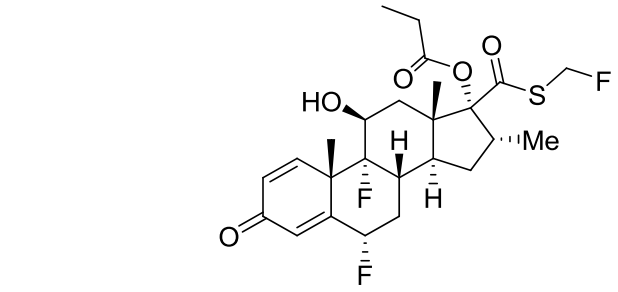
Omeprazole **10** was introduced in 1988 for the treatment of gastric ulcers. For a number of years it was the best-selling drug on the market, until its patent expiration in 2001. Coincidentally, the magnesium salt dimer of the anionic (*S*)-enantiomer of omeprazole, esomeprazole **11**, went on the market in 2000.[21] This new drug was found to have a better efficacy in controlling acid secretion than the racemate (omeprazole), and was thus an improvement. In addition, the switch from omeprazole to esomeprazole allowed AstraZeneca to extend their patent of this profitable pharmaceutical line until 2015. Thus, the impact of the chirality of pharmaceuticals extends beyond clinical effectiveness to the financial stability of multi-billion dollar corporations.



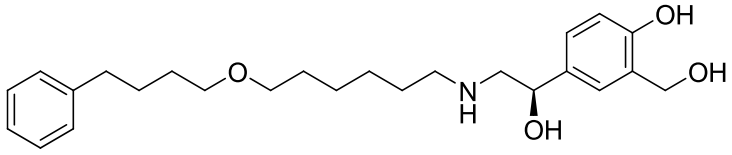
Omeprazole (Prilosec®, **10**) Esomeprazole (Nexium®, **11**)

Figure 1.2.3.3: Esomeprazole (11), a drug prescribed to treat stomach ulcers, is the #3 best-selling drug with sales of 7.2 billion USD in 2007.

The drug advair® is comprised of two constituent compounds, fluticasone **12** and salmeterol **13**, that act synergistically when used on an ongoing basis to control asthma symptoms. Fluticasone is derived from a naturally occurring steroid and is only sold as the enantiomer shown (Figure 1.2.3.4). Salmeterol is included in advair® as a racemate. Although the (*R*)-enantiomer of this molecule is more potent than the (*S*)-enantiomer, the desirability of the use of a single enantiomer of salmeterol is complicated by claims that the (*S*)-enantiomer is more selective, and thus produces fewer side effects.[23,24]



Fluticasone (**12**)



(*R*)-Salmeterol (Serevent®, **13**)

Figure 1.2.3.4: The two components of the anti-asthma drug Advair®, the #4 best-selling drug: fluticasone (12) and salmeterol (Serevent®, 13). Advair sales were 7.1 billion USD in 2007.

As was illustrated in the brief descriptions above, within a pair of enantiomeric chiral pharmaceuticals one enantiomer may elicit the desired effect, whereas the other enantiomer could either be inactive, an antagonist of the active enantiomer, or have a separate activity that could be desirable or undesirable.[25] Thus, having a drug available as its effective single enantiomer can decrease the metabolic load of a drug by decreasing the required dose. Also, it precludes off-target effects attributed to the unwanted enantiomer.[26] Once again, beyond the clinical effectiveness of a drug, the sale of *homo-*

chiral drugs can lead to tens of billions of dollars in sales. With such a drive for homochiral compounds, it may be surprising that it was only relatively recently that synthetic chemistry began to emulate nature's ability to generate optically pure material.[27]

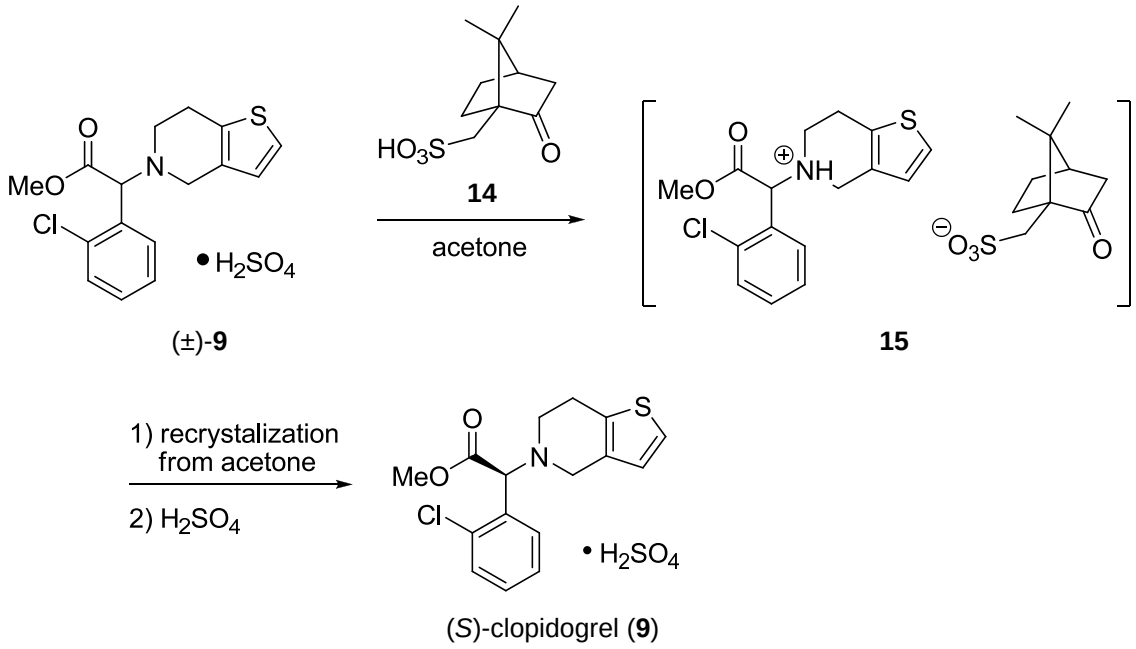
Biological systems use enzymes to catalyze chemical transformations. Enzymes are composed of chiral amino acids, making the enzymes themselves chiral. The use of these asymmetric compounds as catalysts enables Nature to generate enantiopure material. For many decades, synthetic organic chemistry did not have access to its own set of asymmetric catalysts and instead relied on various non-ideal methods to generate optically active material. These established methods generally depend on separation of racemic materials, or use of natural sources of chirality in chiral syntheses.

1.2.4 Resolution of Racemic Compounds

The separation of racemic materials can be achieved using a variety of methods, including enantioselective crystallization, separation *via* diastereomeric analogues and chiral HPLC. Such methods typically result in the loss of 50% of material as the unwanted enantiomer. In addition to this drawback these methods are generally not amenable to large scale synthesis. However, the resolution of racemic materials has been used effectively in the generation of enantiopure (*S*)-clopidogrel **9** (Scheme 1.2.4.1).[21]

In order to achieve this separation, racemic clopidogrel is treated with levorotary camphor-10-sulphonic acid **14** in acetone. This generates a diastereomeric salt **15** which is then recrystallized from acetone to afford enantiopure (*S*)-clopidogrel **9**. Fortunately, in this case the undesired (*R*)-enantiomer is easily racemized, allowing it to be recycled.

Scheme 1.2.4.1: Separation of Racemic Clopidogrel (9) by Diastereomeric Salt Formation and Recrystallization to afford Enantiopure (*S*)-Clopidogrel



1.2.5 The Use of Naturally Occurring Chirality to Access Chiral Targets

The highly abundant and readily accessible group of small, chiral nonracemic natural products is referred to as the "chiral pool". Some important constituents of this group include amino acids, sugars, steroids and terpenes. This chiral pool has historically served as a useful reservoir of starting materials in asymmetric synthesis. The commercial synthesis of fluticasone **12** uses this chiral pool strategy (Figure 1.2.5.1).[21]

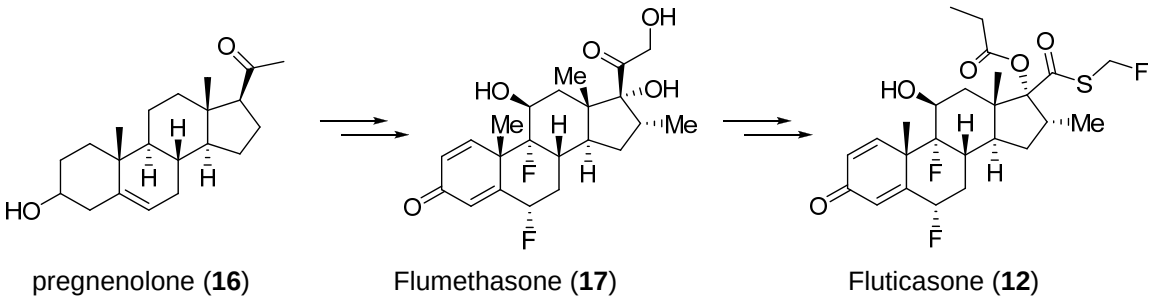


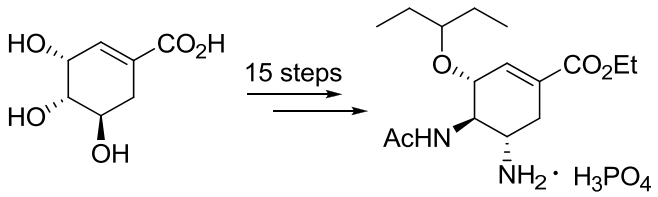
Figure 1.2.5.1: The steroidal pharmaceutical fluticasone (12) is derived from natural pregnenolone (16).

The synthesis of fluticasone **12** begins with optically pure pregnenolone **16**, a steroid which is isolated from biological sources. Using the initial asymmetric centres as a scaffold upon which to build subsequent asymmetric centres, optically pure flumethasone **17** (a commercially available intermediate used in the synthesis of fluticasone) is accessed in eleven steps.[*28] Flumethasone is then transformed in six synthetic steps to fluticasone **12**.[21] There are nine stereocentres in fluticasone **12**, leading to 5632 possible stereoisomers. In order to synthesize the desired single stereoisomer from this wide array of possible products it may very well be essential to start from naturally-derived enantiopure material, and in this case it is completely feasible.

Unfortunately, large enough quantities of starting material are not available to meet the demand of the desired product, as is the case with oseltamivir (tamiflu®) **19**, an antiviral drug. The commercial synthesis[29,30] of oseltamivir **19** begins with isolated optically pure shikimic acid **18**. Shikimic acid is a naturally-occurring compound which, for synthetic uses, is isolated from the fruit of the plant star anise (*Illicium verum*). In 2005, during the avian-flu pandemic scare, the world supply of star anise was too small to supply sufficient quantities of shikimic acid to meet the demand of the drug. In addition, there was no simple way to immediately boost star anise production as the plant takes three years to mature. Although the synthesis of Tamiflu® from natural sources was initially practical, it failed to meet the demand for the drug in a potentially critical moment. This can be a major drawback to the use of a naturally occurring chiral compound as the starting point for a chiral synthesis. An additional limitation to this

[*] Interestingly, flumethasone itself is a drug prescribed for swimmer's ear.

technique lies in the finite diversity of the chiral pool - an appropriate starting material is not available for every possible target chiral molecule.



Shikimic acid Oseltamivir (Tamiflu®, **19**)

Figure 1.2.5.2: The commercial synthesis of the anti-viral drug oseltamivir (19) begins with shikimic acid (18), a compound isolated from star anise.

To meet the potential demand of oseltamivir two different approaches have been taken. New sources of shikimic acid have been sought out, such as bacterial biosynthesis,[31] and new routes towards the production of oseltamivir **19** that do not begin from shikimic acid **18** have been devised.[32-36] Of these five new synthetic routes, all introduce chirality using a technique emulating nature's enzymes, catalytic asymmetric synthesis. However, before discussing this ideal type of asymmetric transformation, two related forms of introducing chirality will be introduced. These methods are the incorporation of chiral auxiliaries and the stoichiometric use of chiral reagents.

1.2.6 Use of Chiral Auxiliaries

Chiral auxiliaries are chiral substituents which are covalently bound to a synthetic precursor of a target molecule. The stereochemistry of the auxilliary is then used as a scaffold that governs the stereoselectivity of subsequent transformations. When the auxiliary is no longer needed it is removed from the target molecule, much like a protecting group would be. One major drawback to the use of a chiral auxiliary is that it adds two steps to a synthesis: one step to install the group, and one to remove it. This is

occasionally compensated for as an auxiliary can also serve as a protecting group for a sensitive functionality.

An industrial example of a synthetic strategy which incorporates a chiral auxiliary is an early enantioselective synthesis of (+)-atorvastatin **8** (Figure 1.1.1.1). In this case the aldehyde **20** was treated with the magnesium enolate of (*S*)-2-acetoxy-1,1,2-triphenylethanol **21** at -78 ˚C. The chiral group present on this acetate is a chiral auxiliary, and due to its influence, the condensation reaction led to a product with an enantiopurity of 97% ee. Once the stereochemistry of the molecule had been established there was no longer need for this auxiliary and it was removed by saponification of the ester **22**. Following several other transformations the lactone **23** was produced, which, through hydrolysis, could easily be transformed to the calcium salt, atorvastatin **8**.

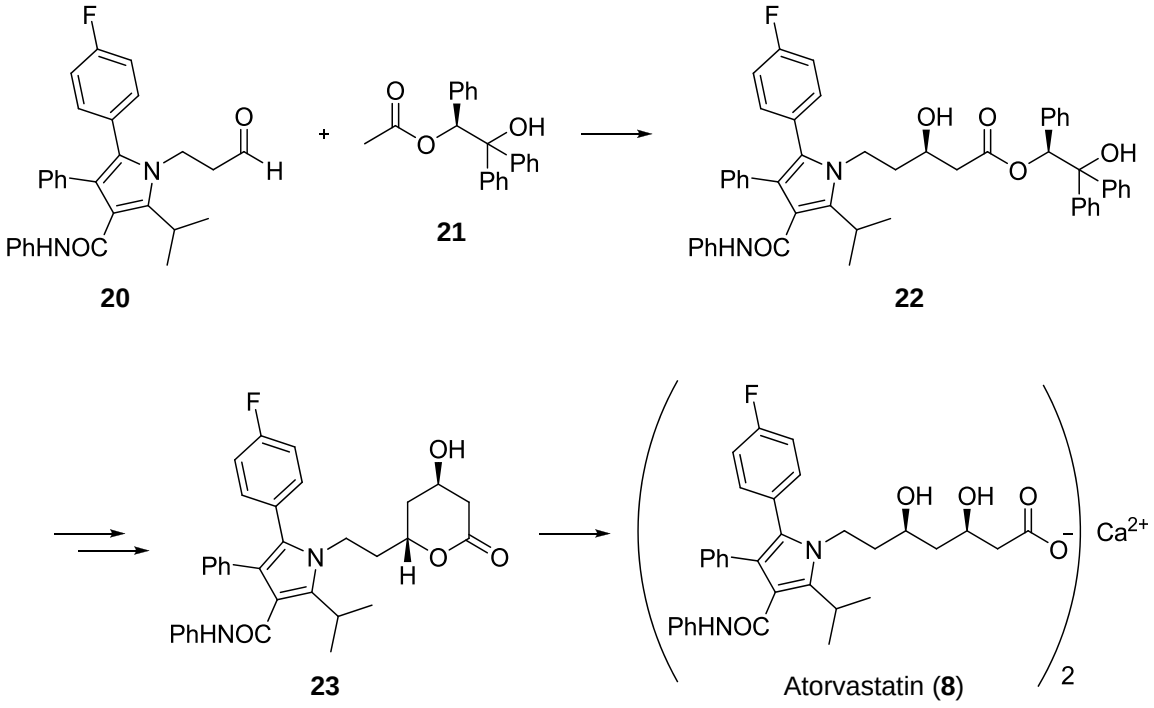


Figure 1.2.6.1: The original asymmetric synthesis of atorvastatin (8) used a chiral auxiliary to introduce stereochemistry into the molecule.

1.2.7 Use of Chiral Reagents

Another useful method of chiral induction lies not with temporarily incorporating a chiral directing unit directly onto the substrate, but rather by incorporating it into the reagent that is required for the transformation. In this way, the chirality of the reagent influences the stereochemical outcome of the reaction. An early example of this strategy was carried out by Brown and co-workers in 1959.[37] They found that hydroboration of (*Z*)-2-butene **24** using diisopinocamphenylborane **25**, followed by treatment with peroxides resulted in stereoselective hydration to give an enantio-enriched chiral alcohol **26**. While this method can be useful, it employs stoichiometric quantities of a potentially expensive chiral reagent; thus, it is not always amenable to large scale syntheses.

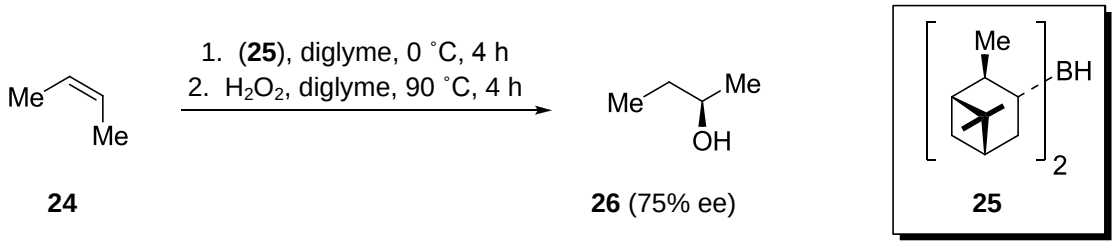


Figure 1.2.7.1: A chiral boron-hydride reducing agent can be used for the asymmetric anti-Markovnikov hydration of alkenes.

1.3 Asymmetric Catalysis

1.3.1 Introduction to Asymmetric Catalysis

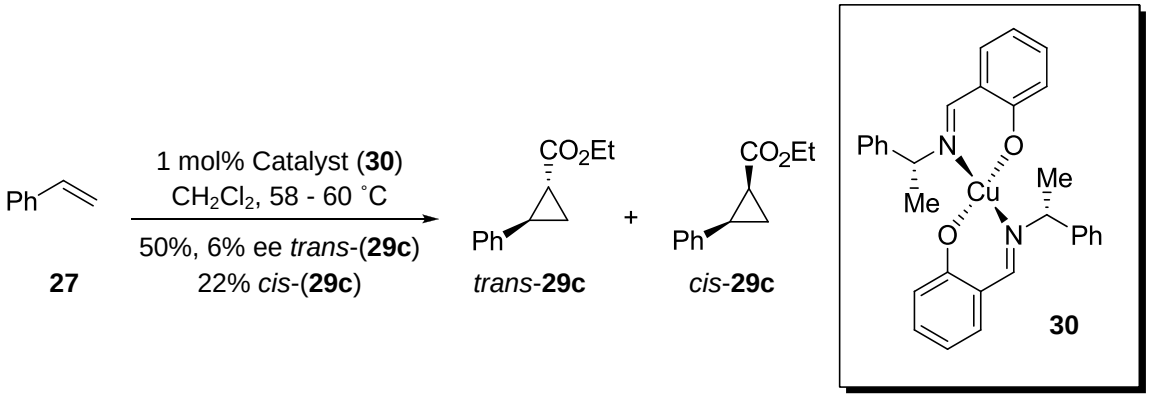
Perhaps the ideal way to generate optically enriched material is through emulation of Nature: using a sub-stoichiometric amount of a chiral compound as a catalyst. There are several forms of asymmetric catalysis: biocatalysis, such as the use of enzymes or organisms to perfom a transformation; asymmetric catalysis, which employs chiral ligand-metal complexes as catalysts; and organo-catalysis. Organo-catalysis is a field which began to gain popularity in the late 1990's and concerns the use of low molecular

weight, chiral nonracemic organic compounds as catalysts in a variety of reactions.[38] As it is not the main focus of this thesis, the interested reader is directed to several review articles on the topic.[39-42] As asymmetric catalysis using chiral ligand-metal complexes is the subject of this thesis, a brief review of asymmetric catalysis with regard to these complexes will be undertaken, followed by brief descriptions of ligand families that have found wide applicability in metal-catalyzed asymmetric transformations.

1.3.2 Asymmetric Catalysis Involving Metal Complexes

Pioneering work in the field of metal-catalyzed asymmetric catalysis was performed by Noyori in 1966.[43] He developed a catalyst **30** based on a copper-ligand complex in which the ligand imparted its chirality onto the catalyst system. He employed this catalyst in the asymmetric cyclopropanation reaction of styrene **27**. Though only modest enantioselectivity was achieved, the results were encouraging as this was one of the first examples of asymmetric catalysis performed with a synthetic catalyst.

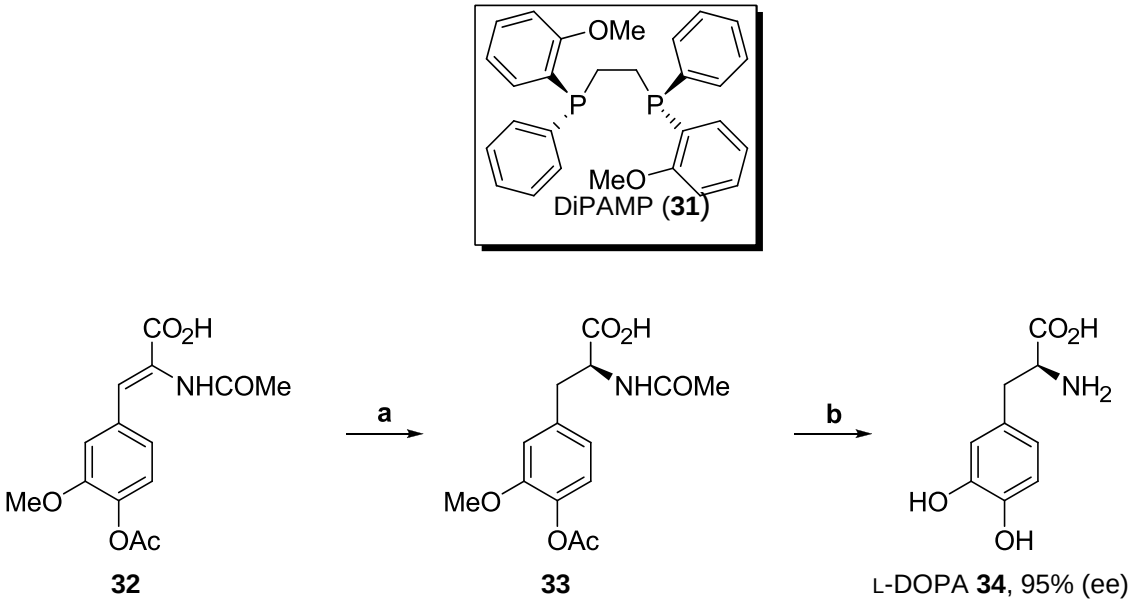
Scheme 1.3.2.1: The Copper(I)-Promoted Cyclopropanation Reaction of Styrene (27) Employing Ligand (30)[43]



The next major milestone in asymmetric catalysis was its commercialization, which demonstrated its real-world applications. This commercialized reaction was an asymmetric hydrogenation reaction that employed the ligand DiPAMP **31**, this compound

was developed by Knowles at Monsanto in 1972.[44,45] This asymmetric hydrogenation procedure was utilized in the synthesis of L-DOPA **34** (Scheme 1.3.2.2), a drug used to treat Parkinson's disease. Over time, catalysts were developed for different asymmetric transformations, most notably the asymmetric epoxidation[46-48] and dihydroxylation[49] reactions of alkenes. These advancements earned the Nobel Prize for Noyori, Knowles and Sharpless in 2001, all of whom used asymmetric ligand-metal catalyst systems.

Scheme 1.3.2.2: Commercial Application of Asymmetric Catalysis: Hydrogenation of the *α,β*-Unsaturated Amide (32) in the Synthesis of L-DOPA (34)



Reagents and Conditions: (a) Rh(DiPAMP **31**)COD]BF_4, H_2, 100%; (b) H^+/H_2O.

1.3.3 Sharpless Asymmetric Epoxidation

In 1980, a groundbreaking catalytic system for the asymmetric epoxidation of allylic alcohols was reported by Sharpless and Katsuki.[46] This system employs titanium(IV) tetra-*iso*propoxide, a chiral C_2-symmetric dialkyl tartarate derivative **37** and

tert-butyl hydroperoxide. The system was shown to oxidize a wide array of allylic alcohols in high enantiomeric excess (>90%) (Figure 1.3.3.1).[50]

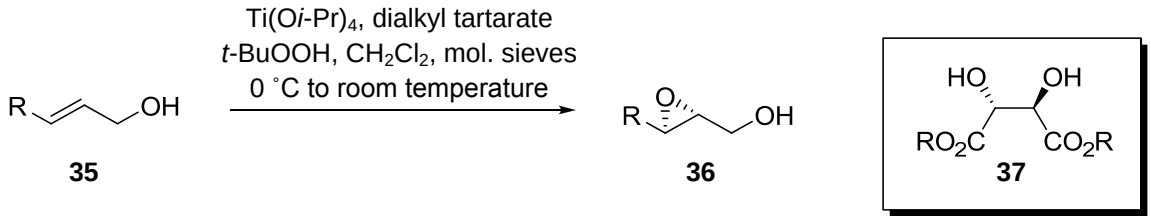


Figure 1.3.3.1: The Sharpless asymmetric epoxidation of allylic alcohols uses dialkyl tartarate (37) derivatives and titanium *tetra*-isopropoxide to catalyze the formation of chiral nonracemic epoxides.

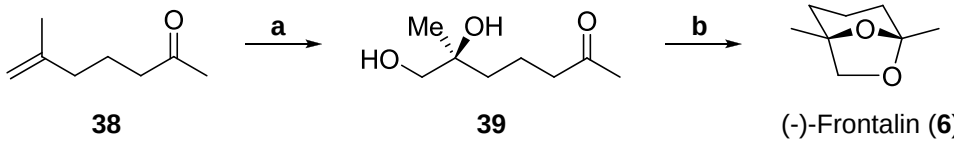
The Sharpless asymmetric epoxidation has been applied to the industrial synthesis of several important chiral molecules including (7*R*,8*S*)-disparlure.[51] This compound is the sex attractant pheromone associated with the gypsy moth, a pest whose caterpillars infest hardwood trees - particularly oak.

1.3.4 Sharpless Asymmetric Dihydroxylation

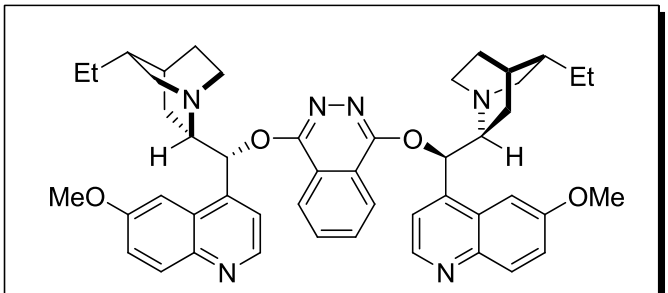
In 1991 Sharpless and co-workers reported another highly important contribution to the field of asymmetric catalysis. They reported a catalytic asymmetric system that involved osmium tetroxide for the synthesis of chiral nonracemic diols. This system uses a minute amount of catalyst, 0.1 mol% of osmium tetroxide and 0.5 mol% of the asymmetric ligand $(DHQ)_2PHAL$ **40**. The reaction is carried out in the presence of a stoichiometric amount of a co-oxidant, such as potassium ferricyanide(III) or *N*-methylmorpholine *N*-oxide.[49] This catalytic system has been optimized to the point where it can be used to generate either enantiomeric diol. Moreover, all of the necessary components are sold as a premixed formulation (AD-mix α, and AD-mix β) making this oxidation protocol exceptionally simple to carry out. The Sharpless asymmetric dihydroxylation has been applied to the synthesis of the aforementioned pine beetle

attractant frontalin **6**.[52] This synthesis afforded (-) frontalin **6** in 84% yield and in 60-70% ee after two steps.

Scheme 1.3.4.1: Asymmetric Synthesis of (-) Frontalin (6) Employing a Sharpless Asymmetric Dihydroxylation



38 **39** (-)-Frontalin (**6**)



$(DHQ)_2PHAL$ (**40**)

Reagents and Conditions: (a) Ad mix-*α* [containing the ligand $(DHQ)_2PHAL$ (**40**)], 1:1 *t*-BuOH/H_2O, 0 ˚C, 18h; (b) HCl, 25 ˚C, 84% (over two steps), 60-70% ee.

1.4 "Privileged" Ligand Classes in Catalytic Asymmetric Synthesis

1.4.1 Introduction to "Privileged" Ligands

Since the initial advancements in asymmetric catalysis, thousands of chiral ligands have been prepared, yet only a relatively small number of structural classes stand out because of their broad applicability. These "privileged" ligands allow high levels of enantioselectivity in many different metal-catalyzed reactions.[53] A short survey of some of these ligands, including BINOL, BINAP, semicorrins, *bis*-oxazolines and salen families, will be presented in the following subsections (Figure 1.4.1.1). A general trend in these "privileged" ligand systems is that they are C_2-symmetric.[54,55] This symmetry element leads to a reduction in the number of possible isomeric metal complexes as well

as the number of possible substrate-catalyst reaction pathways when compared with a nonsymmetrical ligand.[54,56]

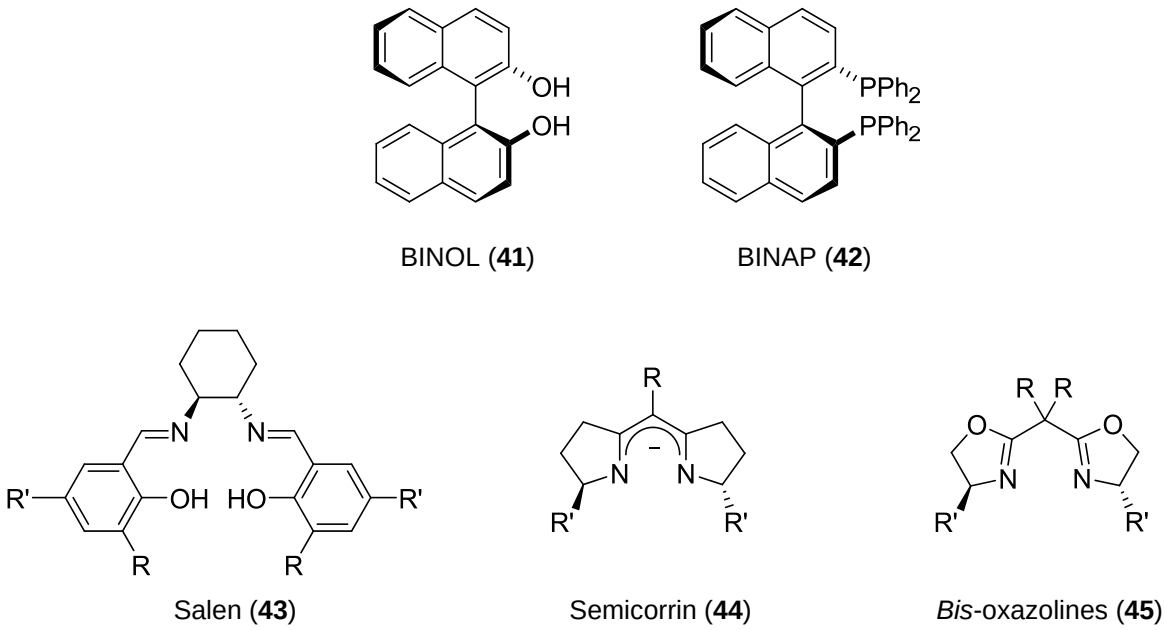
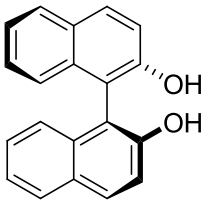


Figure 1.4.1.1: The basic framework of several "privileged" ligand classes.

1.4.2 BINOL

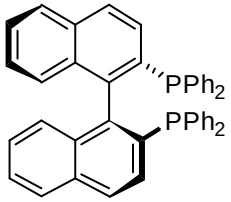


(S_a)-Binol

Oxophilic metals, such as early transition metals, have been widely used as Lewis acids in combination with oxygen-containing ligands. As such, 2,2'- binaphthol (BINOL) and its derivatives have generated particular interest because these compounds can be modified, thereby affecting the reaction environment by influencing the properties of the metal centre.[57] The first use of BINOL as a chiral ligand in metal-mediated asymmetric catalysis was reported in 1979 by Noyori in the reduction of aromatic ketones and aldehydes.[58] Since that time, BINOL and structurally-related binaphthol ligands have been used with great success in Mannich, Strecker and Reissert-type reactions as well as Diels-Alder, Ene, Aldol and Friedel-Crafts reactions, demonstrating the broad utility of

this class of ligand. All of these reaction types and others have been discussed by Yudin and co-workers and Brunel in extensive review articles.[57,59]

1.4.3 BINAP



(S_a)-BINAP

BINAP, the phosphine analogue of BINOL, was discovered in 1980 by the illustrious chemist Noyori and is a particularly versatile ligand that is used mainly in asymmetric hydrogenation reactions. In the thirty years that have followed since its discovery, more than 750 papers concerning the use and synthesis of BINAP and related compounds have been published. From a commercial standpoint, 244 patents concerning the synthesis or particular uses of BINAP were issued. In addition, it is one of the few chiral ligands that is produced on an industrial scale, and several large-scale asymmetric syntheses are now carried out with BINAP.[60] This includes the Takasako synthesis of L-menthol. This synthesis involves the asymmetric isomerisation of alkene **47** to a chiral enamine **48**, a reaction which is catalyzed by a chiral ruthenium catalyst **50** (Figure 1.4.3.1).[61] This synthesis could be considered as the first demonstration of a large-scale industrial synthesis that involves asymmetric catalysis.[61] For these reasons, BINAP has been said to be both the most often used and the most useful ligand for asymmetric catalysis.[62] As such, it has been extensively reviewed in literature.[62,63]

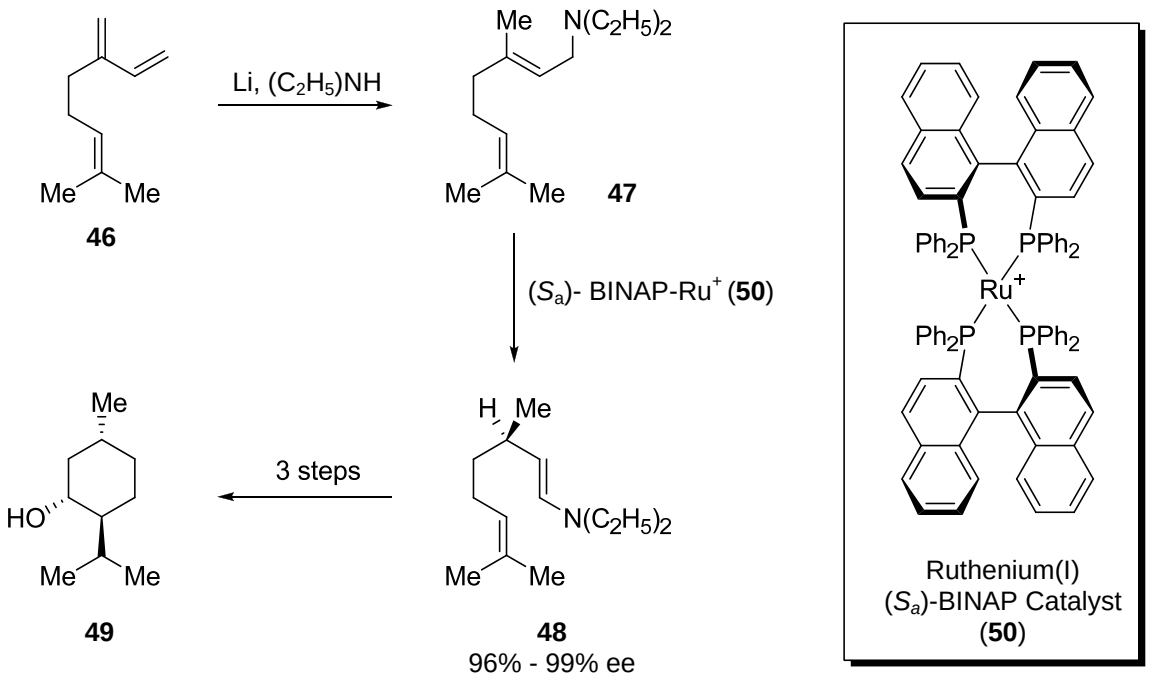
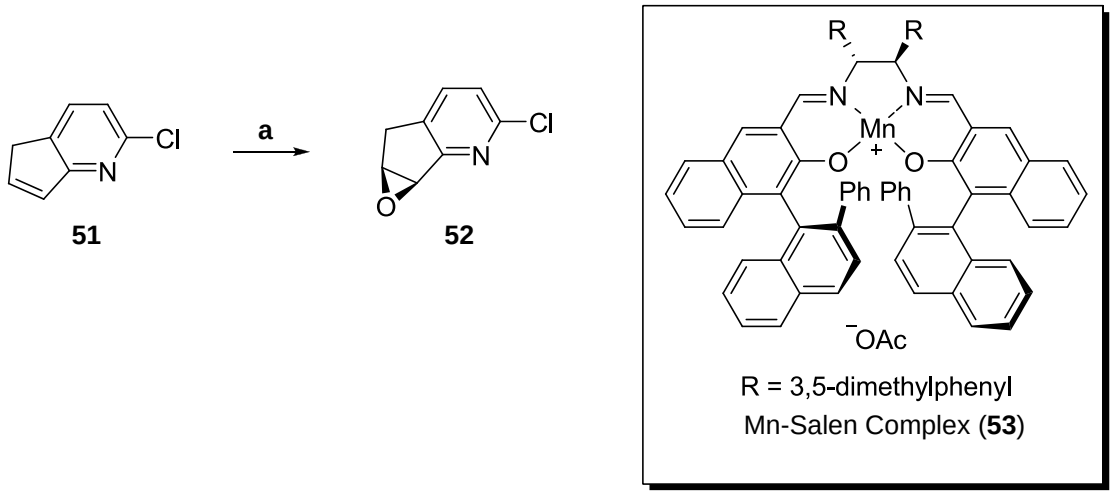


Figure 1.4.3.1: The Takasako synthesis of L-menthol involves the asymmetric isomerisation of alkene (47) to the enamine (48), a reaction which is catalyzed by the chiral ruthenium catalyst (50).[61]

1.4.4 Salen

Salen complexes are a class of tetradentate Schiff bases that attained widespread attention in the early 1990s.[64,65] This class of ligand is best known for its efficient and widespread use in asymmetric epoxidation reactions of unfunctionalized olefins. This asymmetric catalytic transformation was exploited by Katsuki using the chiral nonracemic salen-Mn complex **53** to afford the chiral pyridyl compound **52** (Scheme 1.4.4.1).[66] This epoxidation protocol is a major improvement over Sharpless asymmetric epoxidation which typically only gives favourable results when performed on terminal allylic alcohols. In addition to this major success, ligands of this class have also been employed with success in the kinetic resolution of racemic allenes[67] and epoxides.[68,69] They have also been applied towards asymmetric Strecker,[70] hetero-Diels Alder,[71] allylation of aldehydes[72] and cyclopropanation[73] reactions as well as in the asymmetric allylation reactions of aldehydes.[74,75]

Scheme 1.4.4.1: Katsuki's Catalytic Asymmetric Epoxidation of a Pyridyl Alkene (51) Using the Chiral Nonracemic Manganese-Salen Complex (53)



51 **52**

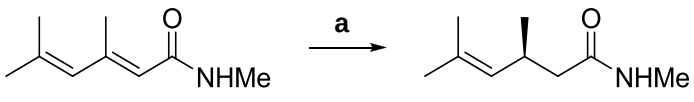
R = 3,5-dimethylphenyl
Mn-Salen Complex (**53**)

Reagents and Conditions: (a) Chiral nonracemic Mn-salen complex **53**, NaClO, 4-phenylpyridine-*N*-oxide, CH_2Cl_2, 0 ˚C, 3 h, 89%, 97% ee.

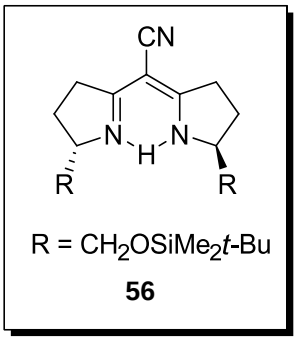
1.4.5 Semicorrins

In the mid-1980s semicorrins emerged as a new class of prominent ligands and were extensively investigated.[76,77] Compounds of this class are *pseudo*-C_2 symmetric and the two substituent groups at the stereogenic centres are held in close proximity to the coordination site by the rigid structure of the molecule. Thus, these groups exhibit a strong influence on the stereochemical course of metal-catalyzed reactions. This family of ligands was proven to be particularly useful in two particular reaction classes: the enantioselective copper-catalyzed cyclopropanation reactions of alkenes, and in the cobalt-catalyzed conjugate reduction of *α,β*-unsaturated esters and amides. This protocol was employed towards the conjugate addition of a hydride ion to the conjugated amide **54**, affording the amide **55** in high enantiopurity (Scheme 1.4.5.1).[78,79] As these ligands are anionic in character, they act as pi- and sigma-donors, this has the effect of reducing the electrophilicity of the chelated metal ion. For applications requiring a more electrophilic metal centre, the *bis*-oxazoline class of ligands were developed.

Scheme 1.4.5.1: Cobalt-Catalyzed Enantioselective Reduction of an of *α,β*-Unsaturated Amide (54)



54 **55**, 97% ee



R = CH_2OSiMe_2*t*-Bu

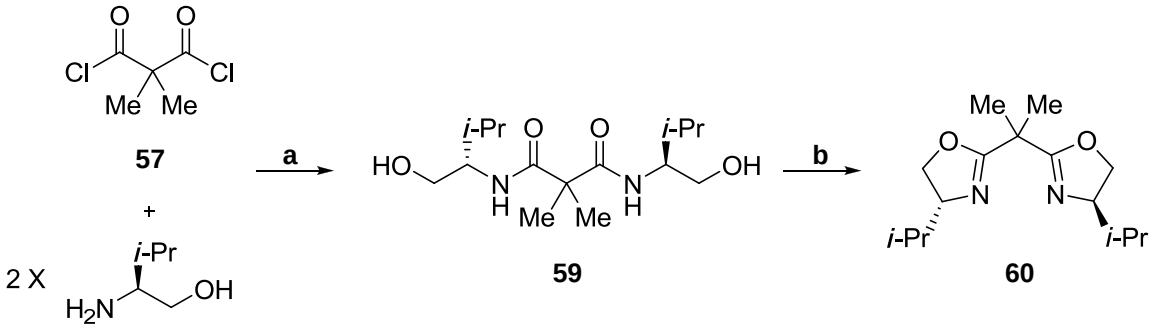
56

Reagents and Conditions: (a) $CoCl_2$ / L* (**56**) (0.1mol%), $NaBH_4$ (1 equiv.), EtOH/diglyme, 23 ˚C, >95%, 97% ee.

1.4.6 *Bis*-oxazolines

The oxazoline family of ligands are notable both because of their enantioselectivity in various asymmetric reactions and their ease of synthesis. The large majority of these ligands are derived from readily available chiral nonracemic amino alcohols in short, high-yielding synthetic sequences, such as the one displayed below which affords an isopropyl *bis*-oxazoline compound (Scheme 1.4.6.1). The ease of synthesis of these compounds has led to the development of a wide variety of oxazoline based compounds, and within this rich field some of the most highly studied ligands have been the *bis*-oxazolines.[80]

Scheme 1.4.6.1: Evans' Synthesis of (-)-(*S*,*S*)-*bis*(4-Isopropyloxazoline) (60)[81]



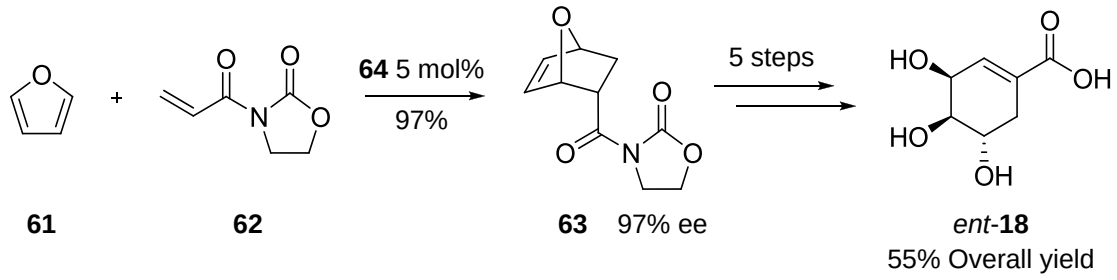
Reagents and Conditions: (a) Triethylamine (50 mol %), CH_2Cl_2, 0 ˚C, 70 min. 84%; (b) DMAP (9 mol %) CH_2Cl_2, rt, 30 min, then triethylamine (4.0 equiv.), TsCl (2 equiv.) CH_2Cl_2, rt, 27 h 83%.

The enantiocontrolling stereocentre of these ligands typically resides on the carbon atom neighbouring the coordinating nitrogen atoms of the oxazoline rings and is thus in close proximity to the metal centre. This allows the chiral group to have a direct influence on the stereochemical outcome of the reaction.[80,82,83] These C_2-symmetric ligands have been applied in a number of asymmetric carbon-carbon bond forming reactions, including cyclopropanation reaction of alkenes,[84-88] Friedel-Crafts,[89,90] [2+2]

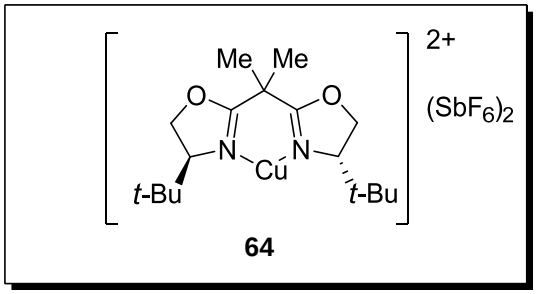
photocycloaddition,[91] Diels-Alder,[92-95] allylic substitution,[84,96] Mukaiayama aldol[97,98] and Michael addition[99] reactions.

As an example, a *bis*-oxazoline-copper(II) complex **64** was employed in the asymmetric Diels-Alder reaction of furan **61** and 3-acryloyloxazolidin-2-one **62** which was the initial step toward the synthesis of the enantiomer of shikimic acid *ent*-**18** (Scheme 1.4.6.2).[94] This is an important compound mentioned previously in this introduction (section 1.2.5, page 14).

Scheme 1.4.6.2: Evans' Synthesis of *ent*-Shikimic Acid (18) Employing Asymmetric Catalysis to Establish the Stereochemistry[94]



61 **62** **63** 97% ee *ent*-**18**
55% Overall yield

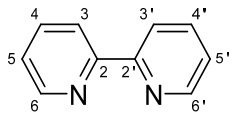


64

1.5 2,2'-Bipyridines

1.5.1 Introduction

In the pursuit of new useful ligands it is prudent to examine non-chiral compounds which have already been proven to have exceptional metal binding characteriztics. Pyridine is such a compound and is widely used in coordination chemistry. It exhibits strong σ-dative interactions which are further enhanced by opportunities for overlap between the aromatic π-system of the pyridine and the d-orbitals of the coordinated transition metal ions. Within the range of pyridine-based ligand systems, one class that has received considerable attention is that of the 2,2'-bipyridines (Figure 1.5.1.1).



65

Figure 1.5.1.1: A depiction of unfunctionalized 2,2'-bipyridine (65).

The first paper concerning a compound of a bipyridyl nature was published in 1889.[100] Since then, complexes of 2,2'-bipyridine compounds with virtually every metal found on the periodic table have been reported.[101-103] In addition to its exceptional binding properties, 2,2'-bipyridine **65** and its derivatives are generally extremely stable in air and aqueous solutions, unlike most phosphine and cyclopentadienyl compounds.[104] Their broad range of complexing partners and stability under ambient conditions makes 2,2'-bipyridyl ligands attractive targets for the development of general and robust catalyst systems.

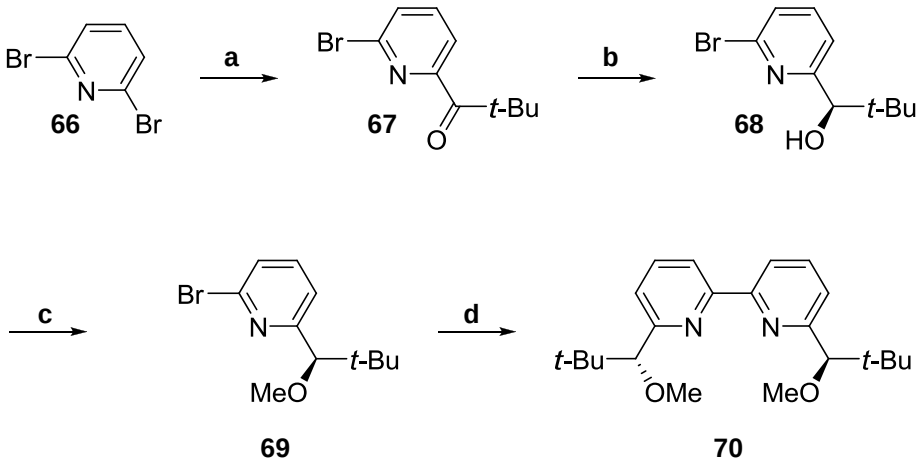
Despite the widespread interest in 2,2'-bipyridine compounds as complexing agents, it wasn't until 1984 that the first chiral nonracemic 2,2'-bipyridine was

synthesized.[105] Since that time, a wide variety of chiral nonracemic 2,2'-bipyridine compounds have been synthesized.[103,106,107] In the following subsections the syntheses of several interesting 2,2'-bipyridines are described. These syntheses incorporate chiral resolutions, chiral auxiliaries, chiral reagents and asymmetric catalysis. In addition, all three of the aforementioned forms of molecular chirality; tetrahedral, axial and planar, are incorporated into these representative compounds. The discussion of these syntheses is followed by a description of a modular synthesis of a new class of chiral 2,2'-bipyridines that was performed in our laboratory to the research project that is described in this thesis.[108]

1.5.2 Synthesis of Chiral Nonracemic 2,2'-Bipyridines

Some of the earliest chiral nonracemic 2,2'-bipyridines to be synthesized incorporated stereogenic tetrahedral carbon centres. For instance, in 1990, Bolm and co-workers reported the synthesis of the chiral nonracemic C_2-symmetric 2,2'-bipyridine **70**.[109] The synthesis of this compound began by monolithiation of 2,6-dibromopyridine **66** which was reacted with methyl 2,2-dimethypropionate to afford the ketone **67** in 80% yield. A chiral reductant, (-)-*β*-chlorodiisopinocampheylborane, was then used to asymmetrically reduce the ketone to afford the alcohol **68** in 59% yield and in high enantiomeric excess (90% ee). After alkylation of the chiral alcohol with methyl iodide, the chiral 2-bromopyridine **69** was subjected to a nickel(0)-mediated reductive-coupling reaction that afforded the desired C_2-symmetric 2,2'-bipyridine **70** in 65% yield and in high enantiomeric purity (>99% ee).

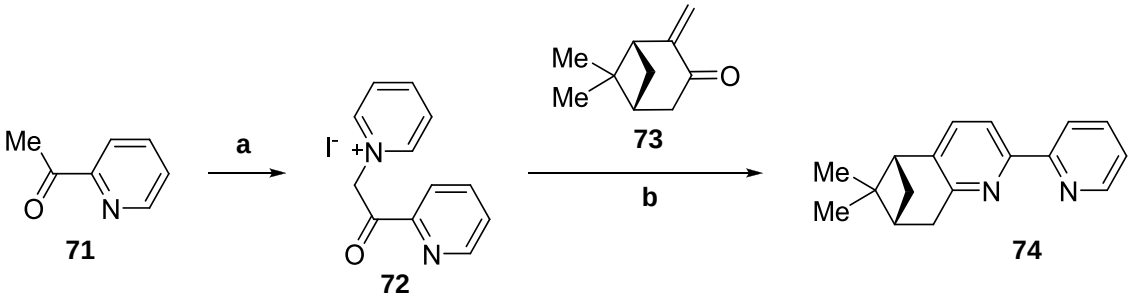
Scheme 1.5.2.1: Bolm and Co-Worker's Synthesis of the Chiral Nonracemic C_2-Symmetric 2,2'-Bipyridine (70)[109]



Reagents and Conditions: (a) *n*-BuLi, THF, -78 ˚C then *t*-BuCO_2CH_3, -78 ˚C to rt, 3 h, 80%; (b) (-)-*β*-chlorodiisopinocamphenylborane (1.2 equiv.), neat, rt, 2 days then 2,2'-iminodiethanol (3.6 equiv.), ether, 3 h, 59%, 90% ee; (c) NaH, CH_3I, THF, 0 ˚C to rt, 1.5 h, 85%; (d) $NiCl_2(H_2O)_6$ (12 equiv.), Zn dust (1.3 equiv.), PPh_3 (4.8 equiv.), DMF, 72 ˚C, 3.5 h, 65%, 99% ee.

In 1992, the synthesis of a nonracemic C_1-symmetric [5,6]-cycloalkeno-fused 2,2'-bipyridine **74** was reported by von Zelewsky and co-workers.[110] The synthesis of this compound involved a Kröhnke-type condensation reaction of the 2-acetylpyridinepyridinium iodide **72** with the terpene-derived *α,β*-unsaturated carbonyl compound (+)-pinocarvone **73** in the presence of ammonium acetate.[111] This condensation reaction afforded the chiral nonracemic 2,2'-bipyridine **74** in 55% yield.

Scheme 1.5.2.2: Von Zelewsky and Co-Worker's Synthesis of the Chiral Nonracemic [5,6]-Cycloalkeno-Fused 2,2'-Bipyridine (74)[110]

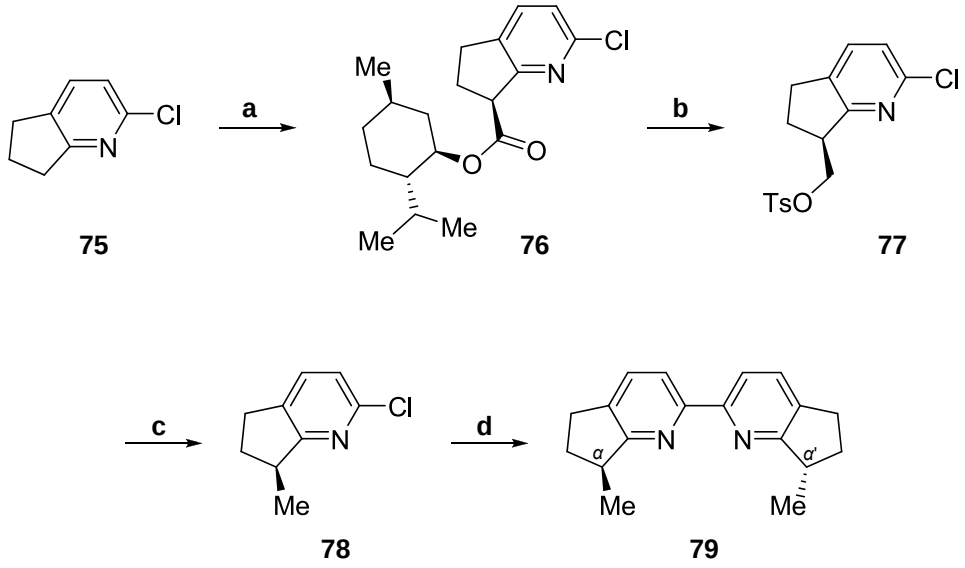


Reagents and Conditions: (a) I_2, pyridine; (b) NH_4OAc, formamide, 70 ˚C, 6 h, 75%.

Also in 1992, Katsuki and co-workers published a series of papers concerning the synthesis and evaluation of a number of chiral nonracemic C_2-symmetric 2,2'-bipyridines that contained [5,6]-cycloalkeno-fused bipyridine units with stereogenic centres at the *α,α′*-positions of the fused rings.[66,73,112] Amongst the first of these reported compounds was the *α,α′*-dimethyl substituted bipyridine **79**.[113] The synthesis of this compound began from the commercially available 2-chloropyridine **75** that was deprotonated with lithium *N,N*-diisopropylamide. The resultant anion was subsequently condensed with (-)-menthyl chloroformate to afford the carbonate **76** as a mixture of diastereoisomers that were separated by flash chromatography. The more polar diastereoisomer was found to have an (*S*)-configuration at the newly established stereogenic centre. The chiral auxiliary of this compound was then removed through reduction with alane and the

resultant alcohol was converted to its corresponding tosylate **77**. This was then reduced with lithium triethylborohydride to afford the 2-chloropyridine **78**, which was subjected to a nickel(0)-mediated reductive coupling reaction to afford the chiral nonracemic C_2-symmetric 2,2'-bipyridine **79**.

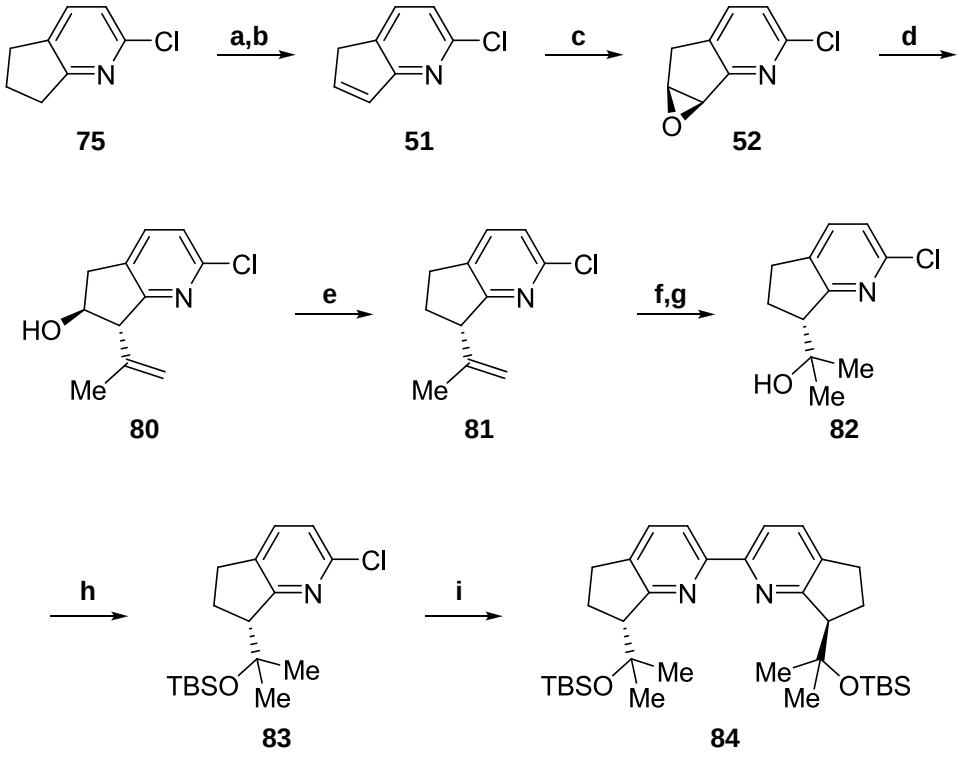
Scheme 1.5.2.3: Katsuki and Co-Workers' Synthesis of the C_2-Symmetric Chiral Nonracemic Bipyridine (79)[113]



Reagents and Conditions: (a) LDA, (-)-menthyl chloroformate, -78 ˚C, then chromatographic separation of the diastereoisomers, 43%; (b) AlH_3, THF then TsCl, NEt_3, DMAP (cat.); (c) $LiBEt_3H$, THF; (d) $NiCl_2(H_2O)_6$, Zn dust, PPh_3, DMF, 47% (over 4 steps).

Katsuki and co-workers subsequently reported the synthesis of the 2,2'-bipyridine **84** that had larger substituents at the α- and α'- positions (Scheme 1.5.2.4).[66] This compound was synthesized by a route which employed the aforementioned Mn-salen asymmetric epoxidation protocol (Scheme 1.4.4.1, section 1.4.4, page 24). This route began with the 2-chloropyridine **75**. This compound was functionalized through deprotonation with lithium *N*,*N*-diisopropylamide, followed by treatment with diphenyldiselinde. The product of this reaction was then subjected to an oxidation process with hydrogen peroxide and the subsequent selenoxide underwent elimination of phenylselenic acid to afford the desired 2-chloropyrindene **51**. This compound was then epoxidized using the chiral nonracemic manganese(III)-salen complex **53** to afford the chiral epoxides in 89% yield with an enantiomeric purity of 96% ee. This epoxide was subsequently opened upon treatment with 1-methylvinylcuprate to afford the alcohol **80**. This alcohol was then transformed to the corresponding thiocarbonate with phenyl chlorothioformate. The resultant compound was reduced using tri-*n*-butyltin hydride and triethylborane to afford the alkene **81**. This compound was then reacted with *m*-chloroperoxybenzoic acid and the resultant epoxide was opened using triethylborohydride to afford the tertiary alcohol **82**. This alcohol was then reacted with *tert*-butyldimethylsilyl triflate to afford the corresponding silyl ether **83**. This compound was then reductively-coupled using a nickel(0)-coupling reaction to afford the C_2-symmetric chiral nonracemic 2,2'-bipyridine **84** in high enantiomeric excess (99.9% ee).

Scheme 1.5.2.4: Katsuki and Co-Workers' Asymmetric Synthesis of the Chiral Nonracemic C_2-Symmetric Bipyridine (84)[66]

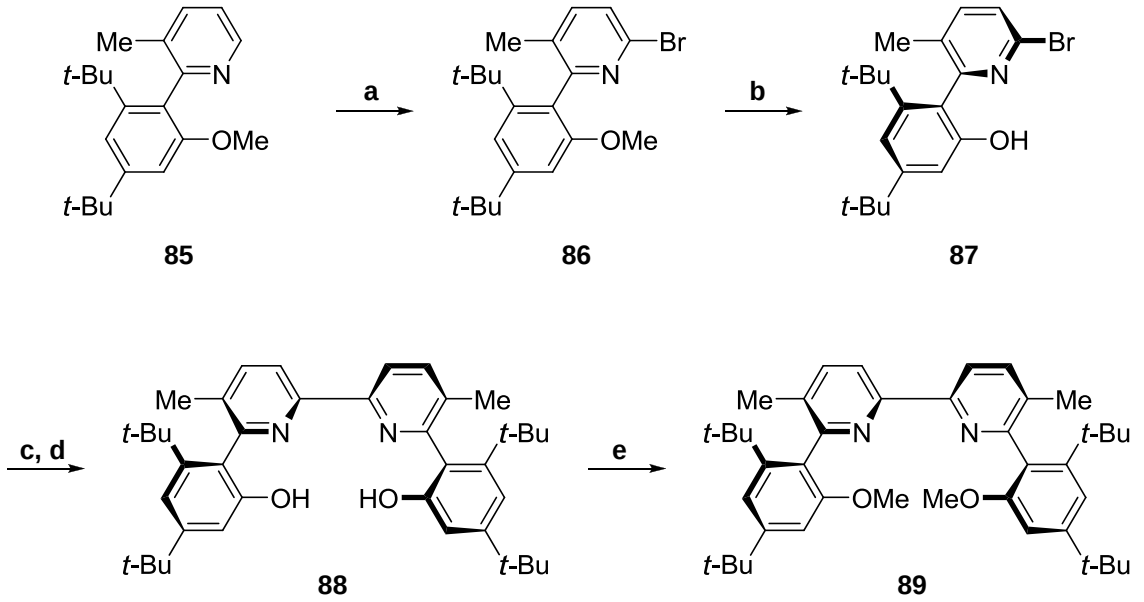


Reagents and Conditions: (a) LDA, THF, -78 ˚C to -20 ˚C, 1 h then PhSeSePh, 10 min; (b) H_2O_2, $NaHCO_3$, EtOAc/THF (2:1), 0 ˚C, 30 min, 72% (over two steps); (c) chiral nonracemic Mn-salen complex, NaClO, 4-phenylpyridine-*N*-oxide, CH_2Cl_2, 0 ˚C, 3 h, 89%; (d) *t*-BuLi, 2-bromopropene, CuCN, THF,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

Chiral 2,2'-bipyridines with axial chirality, such as compound **89**, have also been synthesized. The synthesis of this compound was reported by Chan and co-workers in 2000. The synthetic route that they developed began by deprotonation of the substituted pyridine **85** with *tert*-butyl lithium and the resultant anion was bromonated upon treatment with 1,2-dibromoethane. Demethylation of the methyl ether moiety of the 2-bromopyridine **86** then afforded the axially chiral phenol **87**, which was then separated into its atropisomers by preparative chiral HPLC. This compound was then subjected to

a nickel(0)-mediated reductive-coupling reaction to afford the 2,2'-bipyridine **88**. This compound was then reacted with dimethyl sulfate to afford the chiral nonracemic C_2-symmetric 2,2'-bipyridine **89**.

Scheme 1.5.2.5: Synthesis of the Axially Chiral 2,2'-Bipyridine (89)[114]

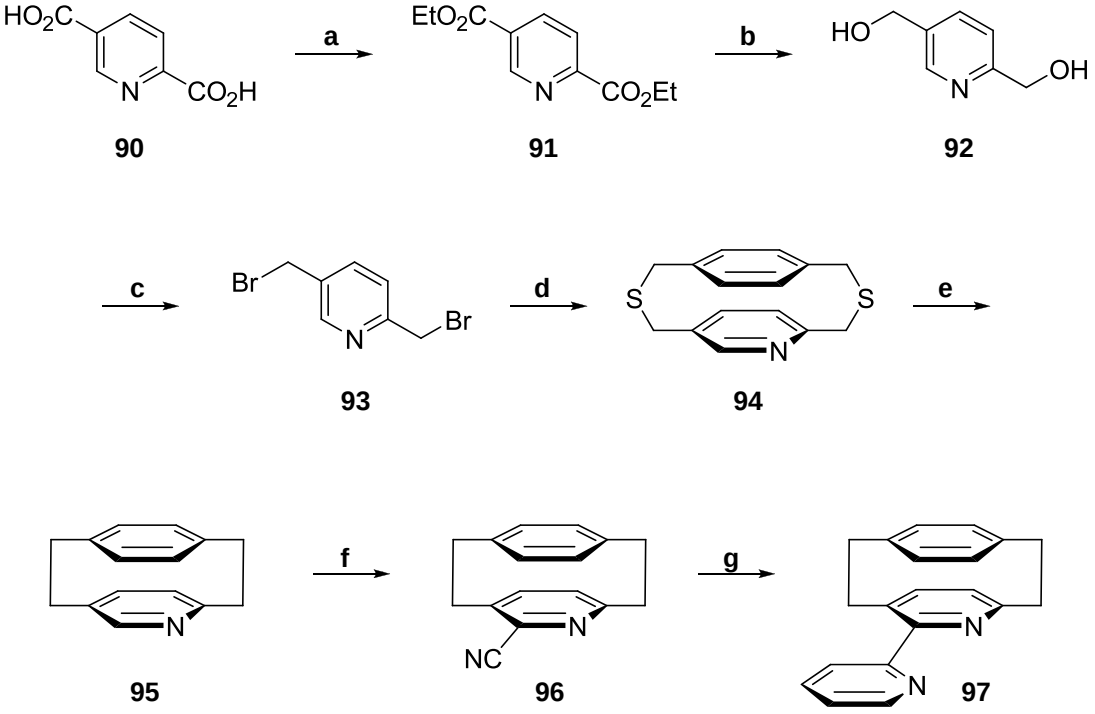


Reagents and Conditions: (a) *t*-BuLi (1.5 equiv.), THF, -78 ˚C, 1 h then 1,2-dibromoethane, -78 ˚C to rt, 4 h, 71%; (b) HBr/AcOH, 120 ˚C, 8 h, 95%; (c) HPLC resolution (Daicel Chiracel OD column); (d) $Ni(PPh_3)_2Cl_2$ (1 equiv.), Zn dust (2 equiv.), Et_4NI (1.5 equiv.), THF, 60 ˚C, 8 h, 89%; (e) NaOH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

In addition to axial chirality, chiral nonracemic 2,2'-bipyridine incorporating elements of planar chirality have also been synthesized. In 1999, Vögtle and co-workers reported the synthesis of the chiral nonracemic 2,2'-bipyridine **97** which has planar chirality, the first 2,2'-bipyridine with this type of chirality.[115] The synthesis of this compound began from 2,5-pyridinedicarboxylic acid **90**. This compound was esterified *via* the diacid chloride to give the corresponding ethyl diester **91** which was then reduced with sodium borohydride to give the diol **92**. This diol was converted to this dibromide **93** upon treatment with 30% hydrogen bromide in acetic acid. Under high dilution the

corresponding *bis*(sulfanylmethyl)benzene was coupled to the dibromide to afford the *bis*(thioether) **94**. Irradiation of this compound with UV light (Hg, 180 W) in the presence of trimethoxyphosphine afforded the cyclophane **95**. This material was then oxidized to the corresponding *N*-oxide which was then converted to the nitrile **96** upon reaction with trimethylsilyl cyanide and dimethylcarbamoyl chloride. Finally, a cobalt(I)-catalyzed [2+2+2] cyclotrimerization reaction of the nitrile with acetylene afforded the racemic compound **97**, which was resolved by preparative chiral HPLC.

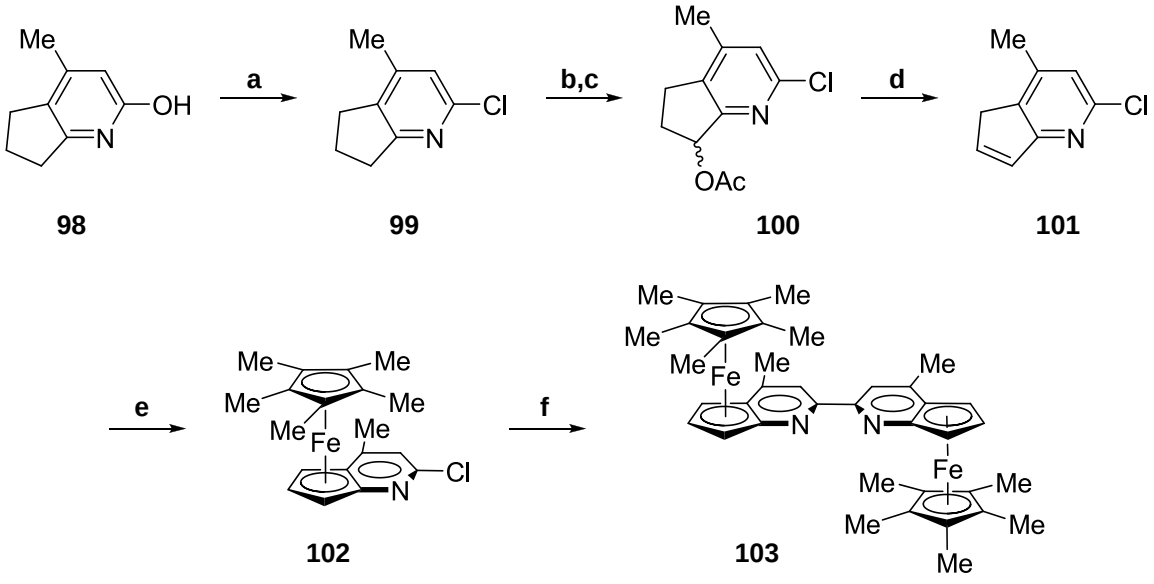
Scheme 1.5.2.6: Synthesis of the Planar Chiral 2,2'-Bipyridine (97)[115]



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, rt, 16 h, 67%; (c) HBr/AcOH, rt, 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), rt, 18 h, 84%; (f) *m*-CPBA (2 equiv.), CH_2Cl_2, rt, 20 h, then *N*,*N*-dimethylcarbamyl chloride (1.3 equiv.), TMSCN (1.3 equiv.), CH_2Cl_2, rt, 16 h, 75%; (g) cyclopentadienylcycloocta-1,5-dienecobalt (2 equiv.), C_2H_2 (1.5 bar), toluene, 120 ˚C, 20 h, 23% then resolution by chiral HPLC.

Fu and co-workers reported the synthesis of a chiral nonracemic 2,2'-bipyridine which included planar chirality derived from a ferrocene moiety.[116] The synthesis of this interesting and notable compound began with the 2-hydroxypyridine **98**. This compound was converted to the corresponding 2-chloropyridine **99** using phosphoryl chloride, which was in turn oxidized with hydrogen peroxide and the resultant *N*-oxide was converted to the acetate **100** upon heating with acetic anhydride. Elimination of the acetate with sulfuric acid afforded the pyrindine **101** as a mixture of regioisomers. This mixture of compounds was then treated with *n*-butyl lithium to afford an anion which was complexed with Cp*FeCl to afford the ferrocene derivative **102**. This compound then underwent a nickel(0)-mediated coupling reaction to afford the 2,2'-bipyridine **103** which was subsequently resolved by preparative chiral HPLC.

Scheme 1.5.2.7: Fu and Co-Workers Synthesis of the Ferrocene-derived Planar Chiral Nonracemic C_2-Symmetric 2,2'-Bipyridine (103)[116]

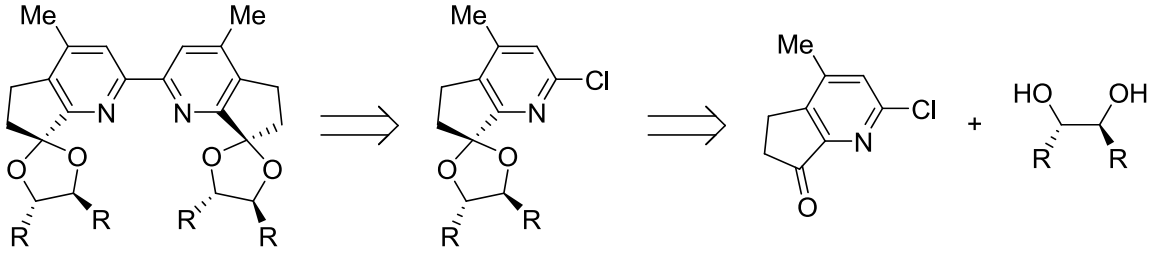


Reagents and Conditions: (a) $POCl_3$, 74%; (b) H_2O_2, AcOH, 88%; (c) Ac_2O, 58% (over two steps); (d) H_2SO_4, 79%; (e) *n*-BuLi then Cp*FeCl, 58%; (f) $Ni(PPh_3)Br_2$, Zn dust, EtNI, 58% then resolution by chiral HPLC (Regis Whelk-O column).

1.5.3 2,2'-Bipyridine Compounds that Incorporate Chiral Nonracemic Acetals

A new class of chiral nonracemic 2,2'-bipyridines was recently designed, synthesized and evaluated by our research group. The fundamental design concept was to prepare a compound that could be easily modified in a structural-sense at a late stage in synthesis. Thus, this would allow for the efficient fine-tuning of the ligand towards its effective use in any particular reaction.[1] In order to achieve this, it was envisioned that the reductive-coupling reactions of a series of chloropyridyl chiral acetals **105a-c** would lead to the series of related 2,2'-bipyridines **104a-c**. The chloropyridyl chiral acetals would be accessible from condensation of the ketone **106** with readily available chiral nonracemic 1,2 diols **107a-c** (Scheme 1.5.3.1).

Scheme 1.5.3.1: Retrosynthetic Analysis of 2,2'-Bipyridines (104a-c)

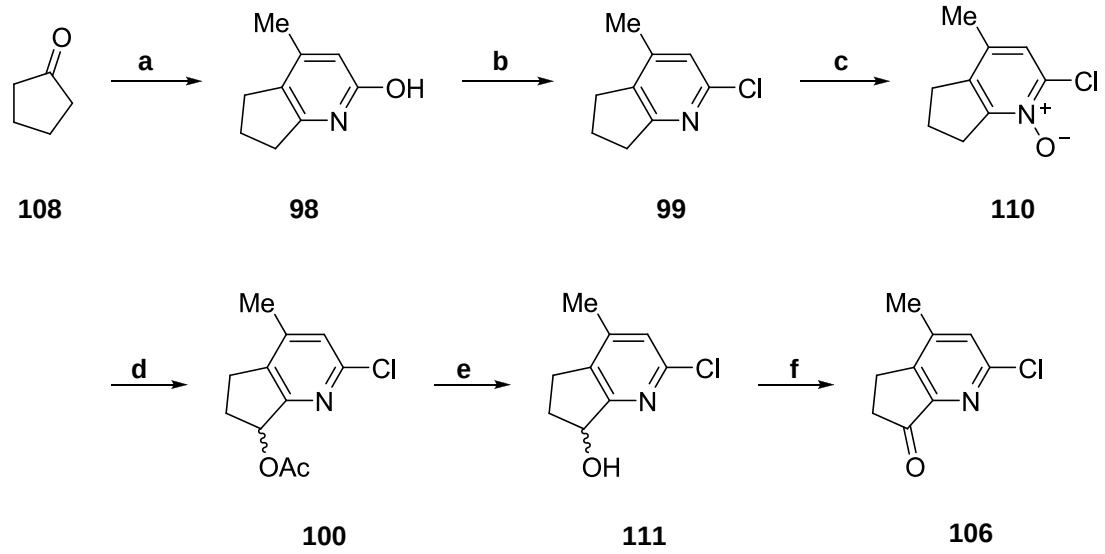


104a-c (R = Me, *i*-Pr, Ph) **105a-c** (R = Me, *i*-Pr, Ph) **106** **107a-c** (R = Me, *i*-Pr, Ph)

The synthesis of compounds **104a-c** began with the synthesis of the ketone **106**. This ketone is available in two steps from known acetate **100** which is available from cyclopentanone in four steps (Scheme 1.5.3.2). Accordingly, a three-component condensation reaction of cyclopentanone, ethyl acetoacetate and ammonium acetate afforded the 2-hydroxypyridine **98** in 23% yield. This compound was subsequently converted to the corresponding 2-chloropyridine **99** in 83% yield upon heating to 160 ˚C in phenyl phosphonic dichloride. Oxidation of the 2-chloropyridine to the pyridine *N*-

oxide **110** using hydrogen peroxide followed by an acetylation/migration reaction afforded the acetate **100** in 60% yield over two steps. This acetate was then hydrolyzed using lithium hydroxide to afford the corresponding alcohol **111** in 94% yield. This material was then oxidized under Swern conditions to afford the target ketone **106** in 90% yield. This advanced intermediate was then employed in the divergent synthesis of the 2,2'-bipyridines **104a-c**.

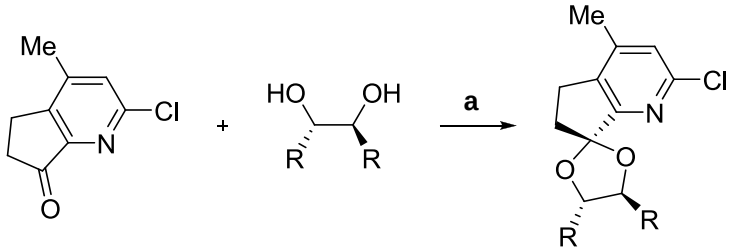
Scheme 1.5.3.2: Synthesis of the Chloropyridyl Acetate (100)



Reagents and Conditions: (a) Ethyl acetoacetate **109**, 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, rt, 1 h then 100 ˚C, 4 h, 60% (over two steps); (e) LiOH, THF, H_2O, rt, 16 h 94%; (f) $(COCl)_2$, DMSO, CH_2Cl_2, then NEt_3 -78 ˚C to rt, 90%.

The chiral acetals **105a-c** were prepared on condensation of the ketone **106** with three different optically pure chiral 1,2 diols **107a-c** on heating to reflux in benzene with a catalytic amount of *p*-toluenesulfonic acid (Scheme 1.5.3.3).

Scheme 1.5.3.3: Synthesis of Chiral Acetals (105a-c)

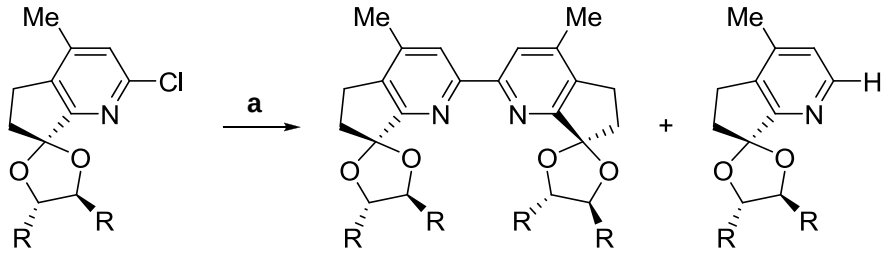


106 **107a-c** (R = Me*, *i*-Pr, Ph) **105a-c** (R = Me*, *i*-Pr, Ph)

Reagents and Conditions: (a) 1,2 diols **107a-c** (R = Me, *i*-Pr, Ph), *p*-TsOH (cat.), benzene, reflux, 16 h, 85% (**107a**), 89% (**107b**), 79% (**107c**). * The compound used in this study was the enantiomer of that indicated in the reaction scheme.

The chiral acetals **105a-c** were converted to the corresponding chiral nonracemic C_2-symmetric 2,2'-bipyridyl **104a-c** upon heating in tetrahydrofuran with dibromo*bis*(triphenylphosphine)nickel(II), tetraethylammonium iodide and zinc dust (Scheme 1.5.3.4). The formation of the reductively-dehalogenated-byproduct **112a** that occurred during the reductive-coupling of the chiral acetal **105a** was later minimized through use of the corresponding 2-bromopyridine of the chiral acetal **116a**.

Scheme 1.5.3.4: Reductive-Coupling of Chiral Acetals (105a-c) to Afford the C_2-Symmetric Chiral Nonracemic 2,2'-Bipyridines (104a-c)

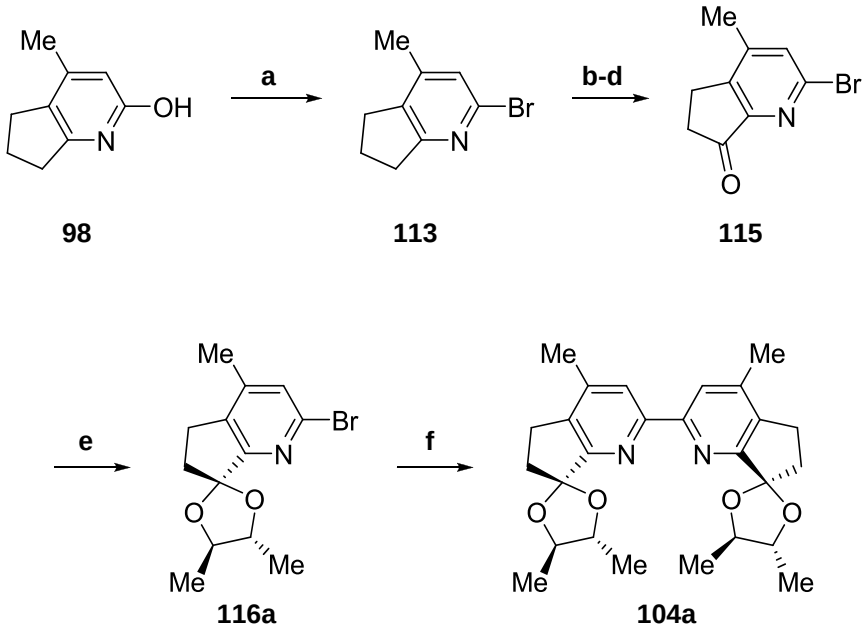


105a-c (R = Me*, *i*-Pr, Ph) **104a-c** (R =Me*, *i*-Pr, Ph) **112a** (R =Me*)

Reagents and Conditions: (a) $NiBr_2(PPh_3)_2$, Zn dust, Et_4NI, THF, 60 ˚C, 4 days, 41% (**104a**) and 35% (**112a**), 89% (**104b**), 79% (**104c**). * The compound used in this study was the enantiomer of that indicated in the reaction scheme.

However, the synthesis of the 2-bromopyridine **113** was much lower yielding than its 2-chloropyridine analogue **99** (Scheme 1.5.3.5). Thus, use of this bromo-analogue as a general as an intermediate in the synthesis of these compounds was not pursued further.

Scheme 1.5.3.5: Synthesis of the 2-Bromopyridine (116a) and its Reductive-Coupling Reaction to Afford the 2,2'-Bipyridine (104a)



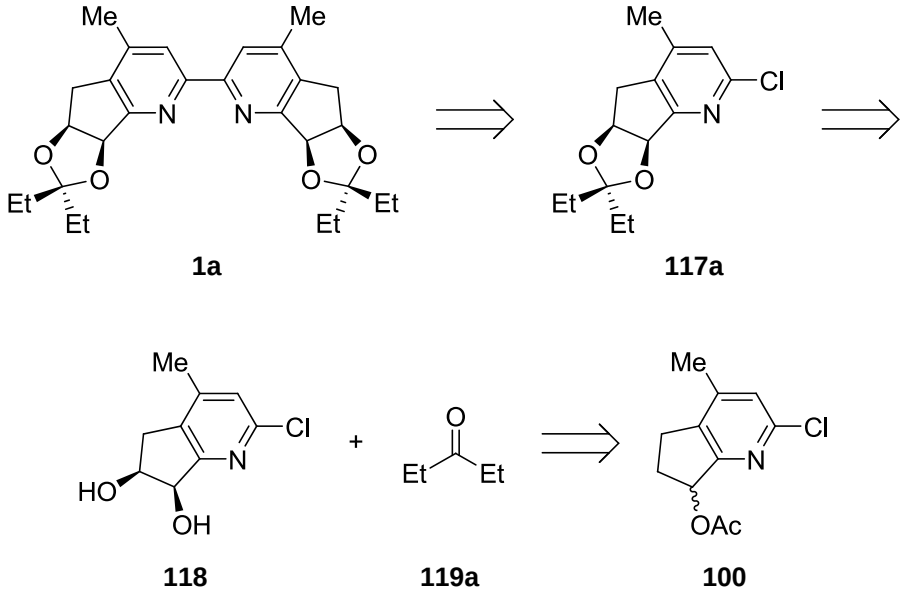
Reagents and Conditions: (a) PBr_3, reflux, 12 h, 52%; (b) H_2O_2, H_2O, ACOH, 80 ˚C 16 h; (c) Ac_2O, rt, 1 h, then 100 ˚C, 4 h, 54% (over two steps); (d) LiOH, THF, H_2O, rt, 16 h, 95%; (e) $(COCl)_2$, DMSO, CH_2Cl_2: NEt_3, -78 ˚C to rt, 90%; (f) (2*R*,3*R*)-2,3-butanediol **107a** ,*p*-TsOH (cat.), benzene, reflux, 20 h, 89% (g) $NiBr_2(PPh_3)_2$, Zn dust, Et_4NI, THF, 60 ˚C, 72 h, 83% (**104a**).

1.5.4 Synthesis of the 2,2'-Bipyridine (1a)

To further explore the utility of the divergent synthesis used to access ligands **104a-c**, a new approach towards the introduction of chirality into these systems was considered by our research group. It was conceived that the chirality of 2,2'-bipyridine could be incorporated directly onto the pyrindine moiety. Thus, the 2,2'-bipyridine **1a** was targeted for synthesis. This compound could be accessed by the reductive-coupling of the chiral acetal **117a**, which could be prepared upon condensation of the chiral diol

118 with 3-pentanone **119a** (Scheme 1.5.4.1). The chiral nonracemic diol **118**, in principle, could be prepared from an advanced intermediate, the acetate **100**, that was used in the synthesis of the previous class of 2,2'-bipyridines **104a-c**.

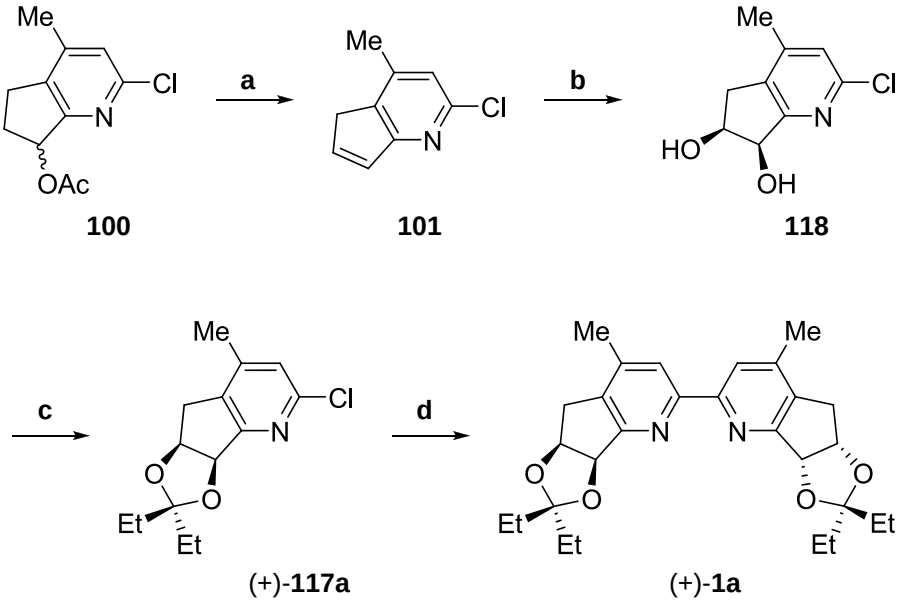
Scheme 1.5.4.1: Retrosynthetic Analysis of the 2,2'-Bipyridine (1a)



To access to the chiral acetal **117a** the alkene **101** was synthesized by elimination of the acetate moiety of compound **100** (Scheme 1.5.4.2). This alkene was subjected to a Sharpless asymmetric dihydroxylation that employed a tenfold increase in the concentration of potassium osmate dihydrate (1 mol%) and its co-catalyst $(DHQD)_2PHAL$ (5 mol%) over commercially available AD-mix (AD-mix concentrations = 0.1 mol% $KOsO_4 \bullet 2H_2O$ and 0.5 mol% $(DHQD)_2PHAL$). Condensation of the crude product mixture obtained from this dihydroxylation reaction with 3-pentanone afforded the desired chiral acetal **117a** (R = Et), in good yield (81% over two steps) and excellent enantiomeric purity, 90% ee. This chiral nonracemic acetal was then reductively-coupled using a nickel(0) catalyst that was prepared *in situ* by the reduction of nickel(II) hexahydrate with zinc dust in the presence of triphenylphosphine in *N*,*N*-

dimethylformamide. This led to the isolation of the 2,2'-bipyridine **1a** in 84% yield which had an enantiomeric purity greater than 99% ee.

Scheme 1.5.4.2: Synthesis of the Chiral Nonracemic C_2-Symmetric 2,2'-Bipyridine (1a)



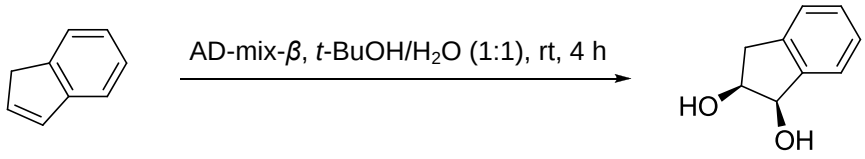
100 **101** **118**

(+)-**117a** (+)-**1a**

Reagents and Conditions: (a) H_2SO_4, 120 ˚C, 10 min, 81%; (b) 1 mol% K_2OsO_4•$2H_2O$, 5 mol% (DHQD)2PHAL, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH/H_2O (1:1), rt, 2 h; (c) PhH, *p*-TsOH (cat.), reflux, 16 h, 81% (over two steps), 90% ee; (d) $NiCl_2(H_2O)_6$, PPh_3, Zn, DMF, 60 ˚C, 4 h, 84%, >99% ee.

The stereoselectivity of the dihydroxylation of the alkene **101** was exceptional when one considers that the diols obtained from the asymmetric dihydroxylations of *cis*-alkenes typically have low enantiomeric purities.[49] Indene **120**, for example, has been reported to yield its corresponding 1,2 diol **121** in only 33-40% ee when subjected to a Sharpless asymmetric dihydroxylation reaction (Scheme 1.5.4.3).[117]

Scheme 1.5.4.3: Asymmetric Dihydroxylation of Indene (120)



120 **121** (33-40% ee)

In addition to the exceptional stereoselectivity of the asymmetric dihydroxylation reaction of the alkene **101**, the reductively-coupled derivative of the acetal **117a**, the 2,2'-bipyridine **1a**, was found to have an enantiomeric purity exceeding 99% ee. This significant enantiomeric enrichment was attributed to the conversion of the minor enantiomer (-)-**117a** into a diastereomeric *meso*-bipyridine, which was isolated in ~5% yield (Figure 1.5.4.1). The absolute stereochemistry of the chiral 2,2'-bipyridine **1a** was inferred based on the known stereoselectivity of the Sharpless asymmetric dihydroxylation.

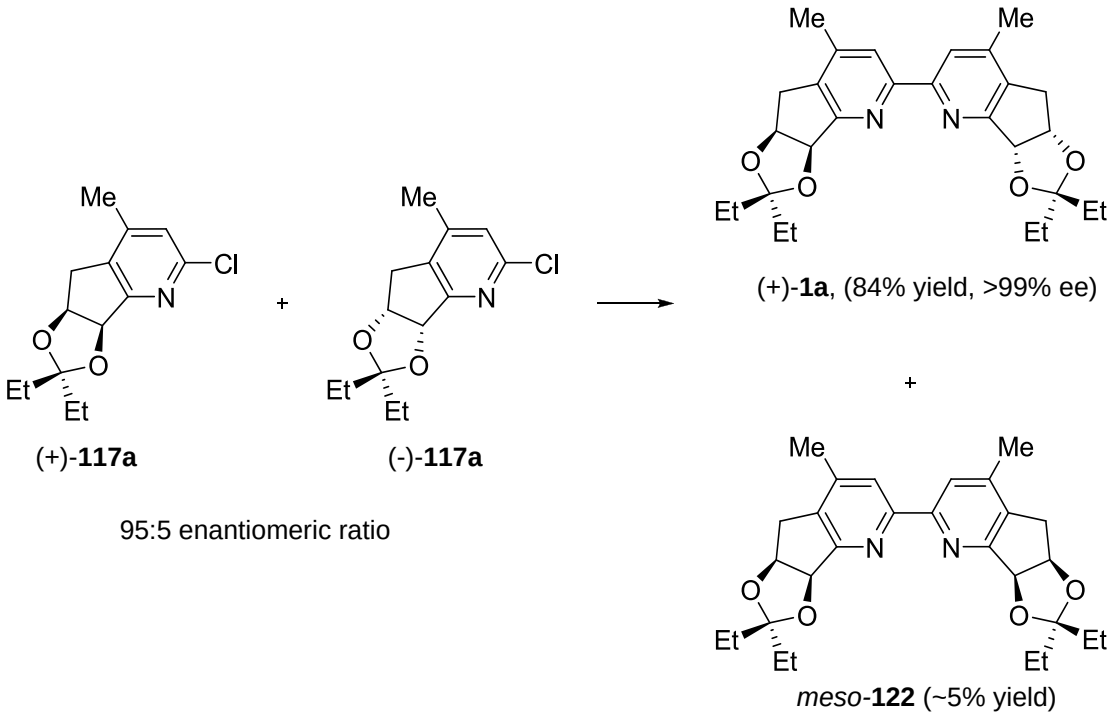


Figure 1.5.4.1: Enrichment of enantiomeric purity in the reductive-coupling reaction of the 2-chloropyridine [(+)-117a].

1.6 Catalytic Asymmetric Copper-Catalyzed Reactions with 2,2'-Bipyridines

Chiral nonracemic 2,2'-bipyridine copper complexes have been employed in a variety of asymmetrically catalyzed reactions, including the asymmetric cyclopropanation reaction of alkenes with diazoesters[118-121], the allylic oxidation of alkenes with *t*-butyl peroxybenzoate and asymmetric Friedel-Crafts reactions of indole-derivatives. The most widely studied of these reactions is the asymmetric cyclopropanation reaction of alkenes by diazoesters.

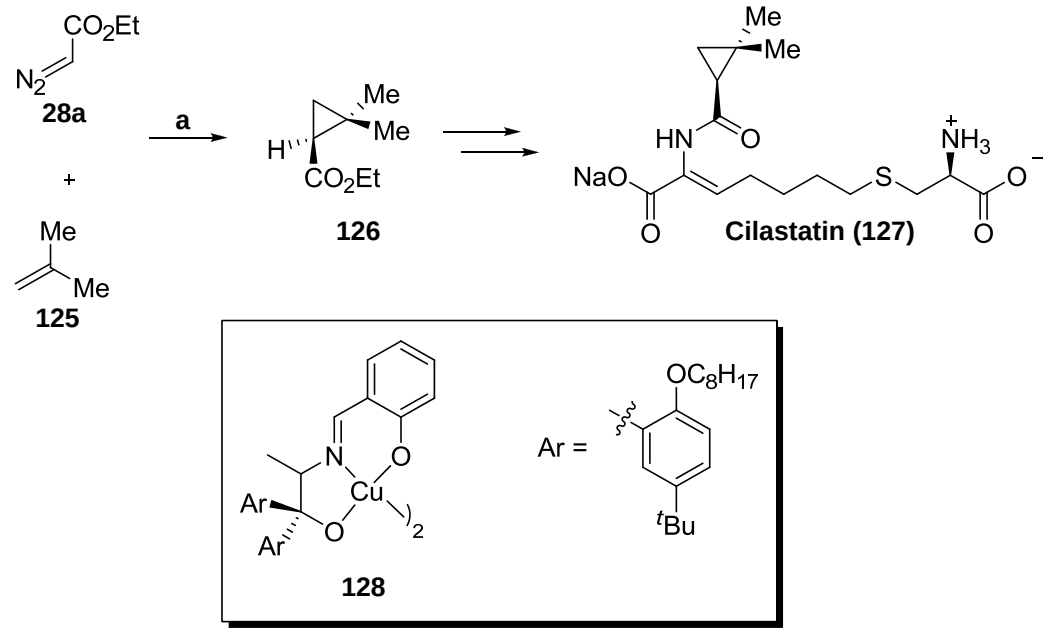
1.6.1 Introduction to Copper(I)-Catalyzed Asymmetric Cyclopropanation Reaction of Alkenes

The asymmetric cyclopropanation reactions of alkenes with diazoesters using a copper(I) catalyst to afford the corresponding *cis*- and *trans*-cyclopropane products has become the standard "benchmark" reaction by which the stereoselectivity imparted by new chiral nonracemic 2,2'-bipyridines are evaluated.[122] The reason for this is that excellent results, both in overall yield and stereoselectivity, can be obtained in this reaction using both 2,2'-bipyridines and the structurally related *bis*-oxazolines, allowing for identification of superior ligands for application in other asymmetric processes. As such it has become one of the most extensively studied reactions in the organic chemist's arsenal, and there still remains room for improvement in the process.[118-121]

In addition to being the benchmark reaction for the evaluation of asymmetric 2,2'-bipyridyl ligands, the asymmetric cyclopropanation reaction of alkenes has been employed in the industrial production of cilastatin **127**, a drug used to prolong the activity of the antibiotic imipenem, which is degraded in the kidney. In the synthesis of this

compound, the key chiral nonracemic cyclopropane unit is derived from the highly enantioselective cyclopropanation reaction of isobutene with ethyl diazoacetate.[123-125]

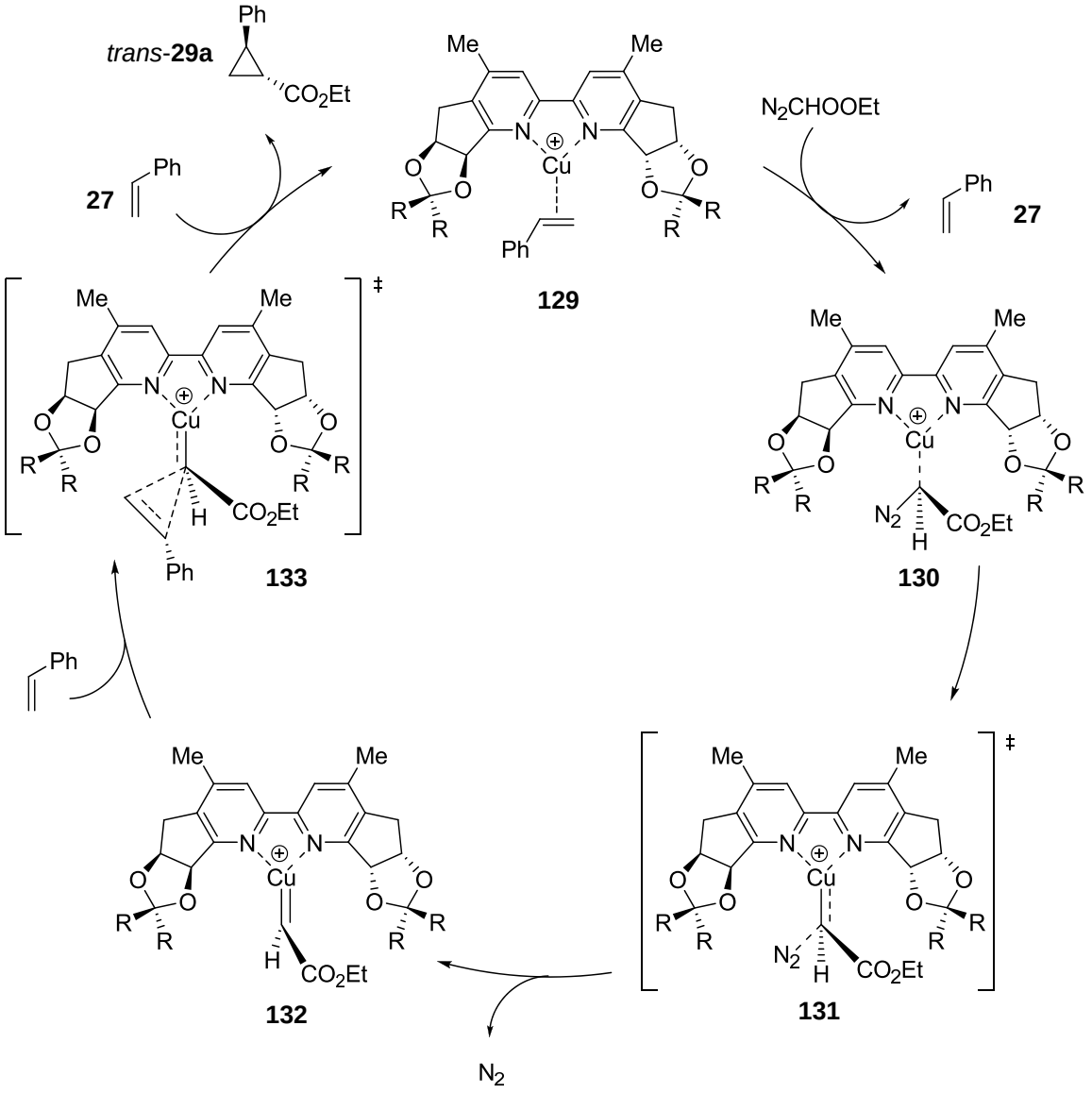
Scheme 1.6.1.1: The Industrial Synthesis of Cilastatin (127) Employing a Catalytic Asymmetric Cyclopropanation Reaction



Reagents and Conditions: (a) 1.0 mol % copper-complex **128**, CH_2Cl_2, rt, 92% ee.

The generally accepted catalytic cycle for the cyclopropanation reaction of styrene **27** (a common substrate employed in these reactions), with a diazoacetate reagent involves three steps. The first step involves the dissociation of a bound styrene molecule (which is employed in excess) and the addition of the diazoacetate to the copper catalyst **129** to afford the complex **130**. Subsequently elimination of dinitrogen (which is the rate limiting step) gives the copper-stabilized carbene **132**. The final step is the addition of styrene to afford the desired cyclopropane which is then eliminated regenerating the active copper(I) catalyst **129** on rebinding of a styrene molecule.[126]

Scheme 1.6.1.2: Catalytic Cycle of the Copper(I)-Catalyzed Cyclopropanation Reaction of Styrene with Ethyl Diazoacetate[126]



Several different methods have been used to carry out copper(I)-catalyzed cyclopropanation reactions. The most direct method involves the use of copper(I) trifluoromethanesulfonate as the copper(I) source. This method, however, requires a great deal of experimental care to ensure the integrity of this highly air- and moisture-sensitive reagent.[127] Another method uses the more stable copper(II) trifluoromethanesulfonate as the copper source, which is then reduced to the active

copper(I) species with phenyl hydrazine.[77,88] 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 species is then accessed by reduction with either phenylhydrazine or a slight excess of the diazoester.[128] In all cases, the diazoester is added to the reaction mixture, which contains an excess of alkene, over the course of several hours. This is done in order to avoid the undesired dimerization of the diazoester, which affords the corresponding fumarates.

As stated earlier, the asymmetric cyclopropanation reaction of alkenes is a benchmark reaction for the evaluation of asymmetric 2,2'-bipyridines as chiral ligands. Moreover, a wide variety of these compounds have been utilized in asymmetric cyclopropanation reaction of styrene **27** with ethyl or *t*-butyl diazoacetate **28a**,**c** (Scheme 1.6.1.3).[107] The results reported for some of these ligands are summarized below (Table 1.6.1.1, page 50). The data in this table was adapted from an extensive review article concerning the synthesis and utility of chiral 2,2'-bipyridines.[107] Included in this table are the 2,2'-bipyridines which have exhibited the highest enantioselectivities in copper(I)-catalyzed asymmetric cyclopropanation reactions of styrene, the 2,2'-bipyridines **84** and **70**. Also, included are ligands with interesting sources of chirality, 2,2'-bipyridines **103** and **97**, and some C_1-symmetric bipyridines. The stereoinduction afforded by C_1-symmetric compounds is in general quite low. It is interesting, however, to note that the *C*-symmetric ligand **124** showed somewhat lower stereoselectivity (13% ee) than its C_1-symmetric analogue **123** (20% ee). The syntheses of many of these 2,2'-bipyridines were discussed earlier (Section 1.5.2, pages 30-38).

Scheme 1.6.1.3: Asymmetric Cyclopropanation Employing Various Chiral 2,2'-Bipyridines

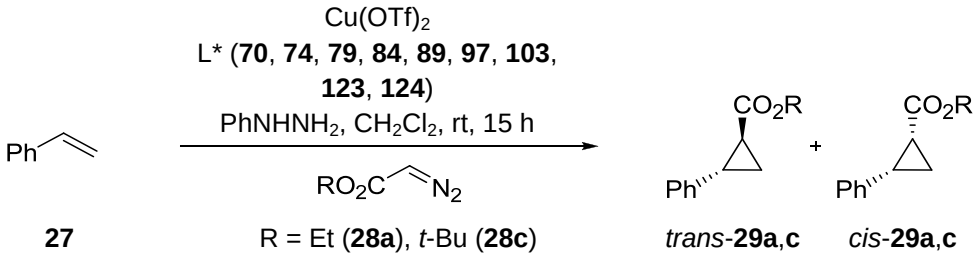
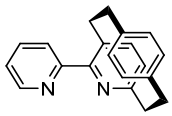
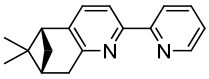
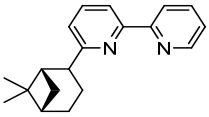
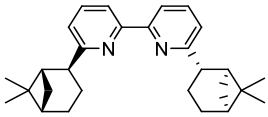
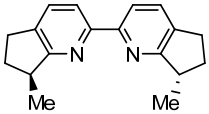
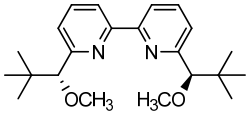
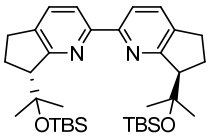
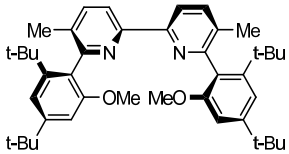
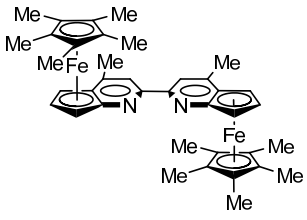


Table 1.6.1.1: Asymmetric Cyclopropanation Reactions Employing Various Chiral 2,2'-Bipyridines[107]

Ligand		R	*trans:cis* ratio	Yield (%)	% ee (*trans*)	% ee (*cis*)
	**97**[115]	Et	67:33	75	26	26
	**74**[129]	Et	70:30	74	0	20
	**123**[130]	Et	58:42	54	20	8
	**124**[130]	Et	69:31	13	13	-
	**79**[113]	Et	67:33	77	77	73
	**70**[128]	*t*-Bu	80:20	50	89	74
	**84**[112]	Et	81:19	76	94	-
	**89**[114]	*t*-Bu	86:14	89	80	-
	**103**[116]	Ar	93:7	50	87	-

Ar = 2,6-di-*tert*-butyl-4-methylphenyl

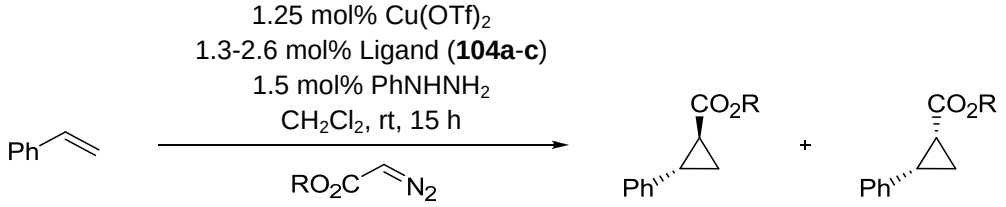
C_2-symmetric ligands in general have been shown to perform well in the asymmetric cyclopropanation reaction of styrene **27** with diazoesters, as is exemplified

by many of the C_2-symmetric bipyridines shown above (Table 1.6.1.1). Compound **70**, synthesized by Bolm and co-workers, afforded the *trans*-cyclopropane in high enantiomeric excess (up to 92% ee).[128] The ligands reported by Katsuki and co-workers also showed high enantioselectivities.[66,112,113] In these cases, the larger ligand **84** afforded higher enantioselectivity (83% ee) than the smaller analogue **79** (77% ee). Chan and co-workers found that their axially chiral bipyridine **89** afforded good stereoselectivity at room temperature (79% ee) and better enantiomeric excess at 0 ˚C when employed in the asymmetric cyclopropanation reaction of styrene with ethyl diazoacetate.[114] They also noted that in the case of *p*-substituted styrenes with electron withdrawing groups that higher degrees of stereoinduction in this reaction was obtained.

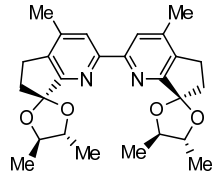
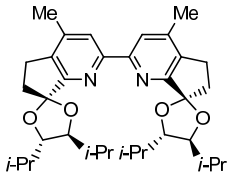
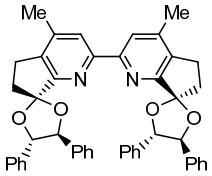
1.6.2 Application of the 2,2'-Bipyridines (104a-c) Towards the Asymmetric Cyclopropanation Reaction of Styrene (27)

The group of related bipyridines **104a-c** synthesized in our laboratory were evaluated in the asymmetric cyclopropanation reaction of styrene **27** (Table 1.6.2.1). The reactions involved the slow addition of the diazoacetates **28a,c** over the course of approximately three hours to a solution of styrene and the copper(I)-ligand complexes. These complexes were generated *in situ*, on complexation of the 2,2-bipyridyl ligands **104a-c** to copper(II) triflate, followed by reduction with phenyl hydrazine. From these experiments a maximum enantioselectivity of 44% ee (using a 2:1 ratio ligand **104b** and *t*-butyl diazoacetate) was achieved. These results were discussed in detail in a full account of this work and thus led to the synthesis and evaluation of a new ligand **1a** that is discussed in the following section.[131]

Table 1.6.2.1: Results of the Asymmetric Cyclopropanation Reactions of Styrene Employing Ethyl or *tert*-Butyl Diazoacetate and the 2,2'-Bipyridines (104a-c)

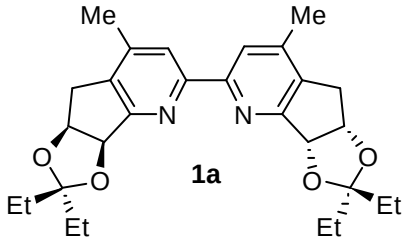


27 **28a,c** *trans*-**29a,c** *cis*-**29a**,**c**

Entry	Ligand	R	L*:Cu Ratio	Product	*trans*:*cis*	Yield (%)	% ee (*trans*)
1	 **104a**	Et	1:1	*ent*-**29a**	63:37	55	9
2		*t*-Bu	1:1	*ent*-**29b**	80:20	67	7
3		Et	2:1	*ent*-**29a**	51:49	48	24
4		*t*-Bu	2:1	*ent*-**29b**	73:27	47	38
5	 **104b**	Et	1:1	**29a**	68:32	62	25
6		*t*-Bu	1:1	**29b**	83:17	59	44
7		Et	2:1	**29a**	68:32	53	34
8		*t*-Bu	2:1	**29b**	75:25	57	42
9	 **104c**	Et	1:1	(±)-**29a**	63:37	58	0
10		Et	2:1	-	-	No reaction	-

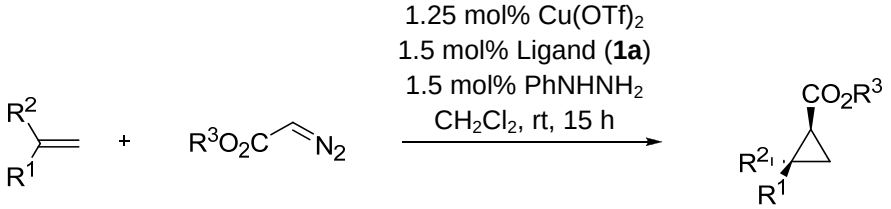
1.6.3 Evaluation of the 2,2'-Bipyridine [(+)-1a] in Copper(I)-Catalyzed Asymmetric Cyclopropanation Reactions of Alkenes

Following the encouraging results obtained from the 2,2 bipyridine series **104a-c** the new chiral nonracemic C_2-symmetric 2,2'-bipyridine **1a** was evaluated in the copper(I)-catalyzed asymmetric cyclopropanation reaction of various alkenes **27a**, **d-g** (Table 1.6.3.1). In the cyclopropanation reaction of styrene the 2,2'-bipyridine **1a** afforded exceptional enantioselectivities, up to 92% ee in the cyclopropanation of styrene **27a**. In the case of *p*-fluorostyrene **27e** the cyclopropane product had an enantiopurity of 99% ee. These results were competitive with the best chiral 2,2'-bipyridyl ligands evaluated in this reaction at that time.[107]



1a

Table 1.6.3.1: Results of the Asymmetric Cyclopropanation Reactions of Alkenes (27a, d-g) Employing the 2,2'-Bipyridine (1a)



27a, d-g **28a-c** **29a-g**

entry	R^1	R^2	R^3	Product	*trans*:*cis*	yield (%)	% ee
1	Ph	H	Et	**29a**	80:20	74	82 (*trans*)
2	Ph	H	Bn	**29b**	98:2	49	84 (*trans*)
3	Ph	H	*t*-Bu	**29c**	93:7	67	92 (*trans*)
4	*p*-$MeOC_6H_4$	H	*t*-Bu	**29d**	>95:5	69	71 (*trans*)
5	*p*-FC_6H_4	H	*t*-Bu	**29e**	92:8	73	99 (*trans*)
6	$PhCH_2CH_2$	H	*t*-Bu	**29f**	>95:5	82	83 (*trans*)
7	Ph	Ph	*t*-Bu	**29g**	-	81	72

Due to the exceptional enantioselectivity afforded by the 2,2'-bipyridine **1a** in the copper-catalyzed asymmetric cyclopropanation reaction of styrene and styryl derivatives this ligand was evaluated in other copper-catalyzed asymmetric reactions: the asymmetric allylic oxidation of cycloalkenes, asymmetric Friedel-Crafts reactions and asymmetric Michael addition reactions.

1.6.4 Evaluation of the 2,2'-Bipyridine (1a) in the Copper(I)-Catalyzed Asymmetric Allylic Oxidation of Cycloalkenes[132]

The copper-catalyzed allylic oxidation of alkenes was first reported by 1959 by Kharash and Sonovsky.[133] They showed that alkenes, such as cyclohexene, could be oxidized with a stoichiometric amount of *t*-butyl peroxybenzoate in the presence of copper(I) bromide. The mechanism for this reaction involves the complexation of *t*-butyl peroxybenzoate to a copper (I) species. The *t*-butyl peroxybenzoate then decomposes oxidizing the copper to copper(III) and generating the corresponding benzoate and *t*-butoxy species. Upon complexation of cyclohexene, the *t*-butoxy species is protonated and eliminated. The resultant complex then undergoes a rearrangement/reductive elimination process, which upon complexation of cyclohexene affords the product and regenerates the copper(I) species.[134]

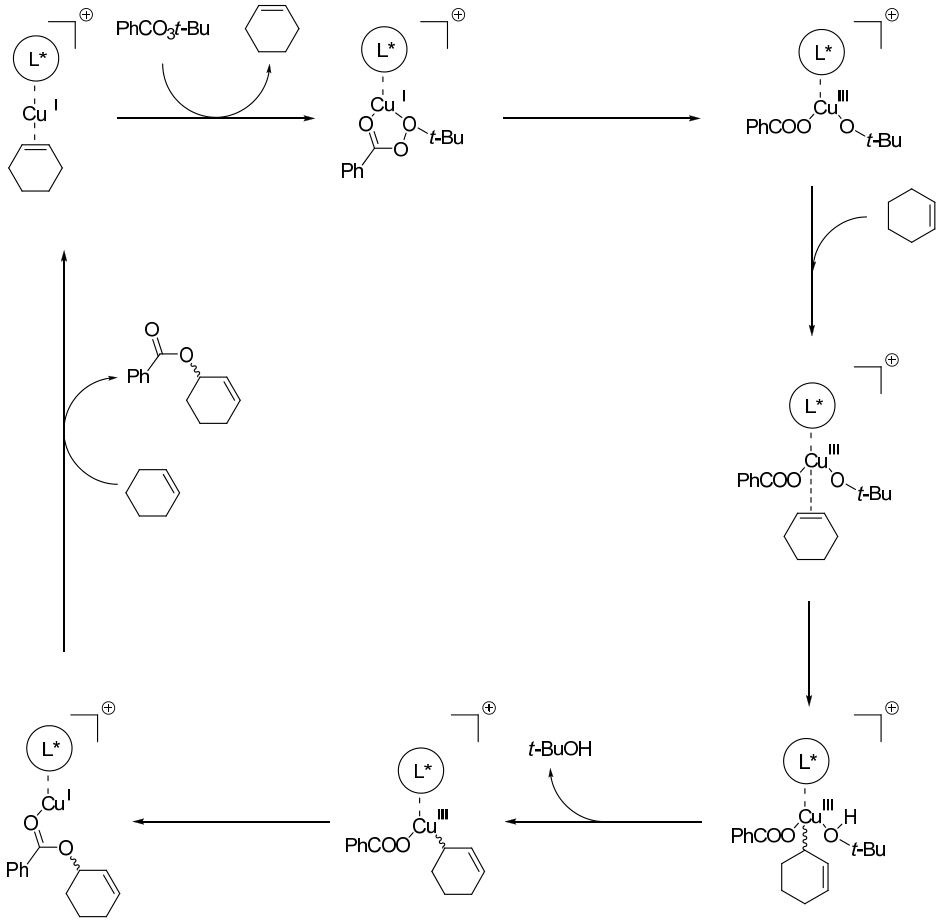


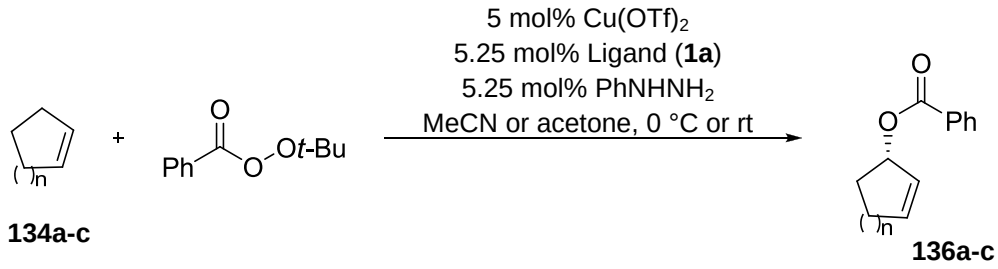
Figure 1.6.4.1: Catalytic cycle of the Kharash and Sonovsky allylic oxidation reaction.[134]

Asymmetric versions of this reaction employing chiral ligands have met with varying success.[135,136] However, some of these reactions have been shown to afford enantiomeric purities as high as 99% ee when employing a *bis*-oxazoline complex as the catalyst and cyclohexene as the reactive substrate.[137] High enantioselectivities have been achieved in this allylic oxidation, however extremely long reaction times are often required. For example, a reaction employing a semicorrin ligand system required three weeks to go to completion.[79] In light of this, it would be beneficial to identify an effective chiral nonracemic ligand that allows for relatively short reaction time, while maintaining a high level of enantioselectivity. It has been found that bipyridyl ligands

allow for relatively fast reaction times in this allylic oxidation reaction.[138] Thus the 2,2'-bipyridyl ligand **1a** was evaluated in this reaction.[131]

The copper(I)-catalyzed asymmetric allylic oxidations of cycloalkenes **134a-c** (n = 1-3) were carried out using *tert*-butylperoxy benzoate **135** as the oxidant (Table 1.6.4.1). These reactions employed a copper(I) complex that was formed *in situ* by the reduction of the complex formed between 5.25 mol% of the chiral ligand **1a** and copper(II) triflate in either acetone or acetonitrile. Results demonstrated that using acetonitrile as the reaction solvent increased enantioselectivities in every case. However, acetone afforded higher yields in most cases. An enantioselectivity of 91% ee, the highest reported value for a 2,2'-bipyridine, was obtained in a relatively short period of time when performing the reaction at 0 °C in acetonitrile and using cyclohexene as the substrate.[132]

Table 1.6.4.1: Results of Asymmetric Allylic Oxidation Reaction Employing the Chiral 2,2'-Bipyridine (1a)[132]



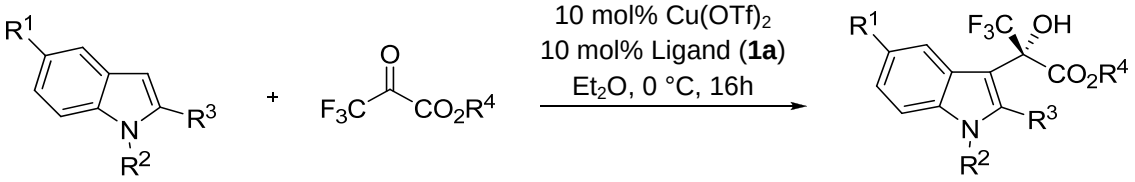
134a-c **136a-c**

entry	Cycloalkene	n	Solvent	temperature	yield (%)	% ee	Time (h)
1	**135** **134a**	1	acetone	rt	64	32	24
2	**134a**	1	MeCN	rt	69	34	16
3	**134b**	2	acetone	rt	67	65	16
4	**134b**	2	MeCN	rt	56	84	72
5	**134b**	2	acetone	0 °C	51	81	48
6	**134b**	2	MeCN	0 °C	45	91	96
7	**134c**	3	acetone	rt	72	36	16
8	**134c**	3	MeCN	rt	76	40	16

1.6.5 Asymmetric Friedel-Crafts Reactions[139]

The Friedel-Crafts reaction is possibly one of the oldest and well known Lewis acid-catalyzed reactions; thus, it is a prime target for development as a catalytic asymmetric reaction. This was first demonstrated in 2000 by Jørgesen and co-workers who used a chiral *bis*-oxazoline-copper(II) complex to catalyze the reaction of activated aromatic compounds and electron-deficient alkenes and ketones.[140] Accordingly, the 2,2'-bipyridine **1a** was employed in the asymmetric Friedel-Crafts reaction of a series of commercially available indoles **137a-f** with ethyl and methyl esters of 3,3,3-trifluoropyruvic acid **138a,b**. These reactions were carried out using a copper(II) catalyst which was generated *in situ* on complexation of 10 mol% of the 2,2'-bipyridine **1a** with 10 mol% of copper(II) triflate. The reactions were performed at 0 ˚C and went to completion in sixteen hours in all cases. The reaction of indole **137a** with methyl 3,3,3-trifluoropyruvate **138a** afforded the corresponding product in 77% yield and an enantiomeric purity of 90% ee. The use of methyl 3,3,3-trifluoropyruvate **138a** provided both superior yields and enantioselectivities than ethyl 3,3,3-trifluoropyruvate **138b** in this reaction. It was found that performing the reaction at - 10 ˚C provided an equivalent enantioselectivity, and so all subsequent reactions were performed at 0 ˚C using methyl 3,3,3-trifluoropyruvate **138a**. The Friedel-Crafts reaction of other indoles **137b-f** showed good enantioselectivities (60-86% ee) except when the nitrogen atom was substituted, in which cases the enantioselectivities were quite low.

Scheme 1.6.5.1: Asymmetric Friedel-Crafts Reaction of Substituted Indoles (137a-f) and 3,3,3-Trifluoropyruvate (138a-b)[139]



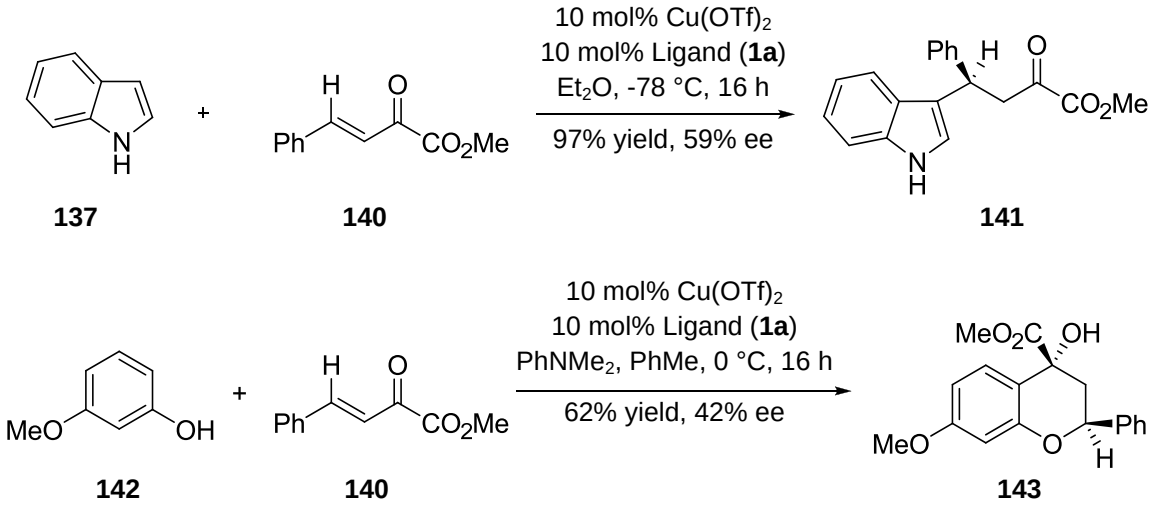
137a-f **138a-b** **139a-g**

entry	R^1	R^2	R^3	R^4	yield (%)	% ee
1	H	H	H	Et	68	74
2	H	H	H	Me	77	90
3[1]	H	H	H	Me	62	90
4	H	H	Me	Me	79	86
5	OMe	H	H	Me	69	72
6	NO_2	H	H	Me	75	60
7	H	Me	H	Me	73	18
8	H	Me	Ph	Me	65	18

The 2,2'-bipyridyl ligand **1a** was also evaluated in a related class of reactions: which involved the conjugate addition of two different activated aromatic systems to a β,γ-unsaturated α-ketoester **140**. The conjugate addition of indole **137a** to the ketoester **140** was found to afford an exceptional yield of the product **141** (97%), and provided moderate enantioselectivity (59% ee). The conjugate addition reaction of 3-methoxyphenol **142** to the same ketoester afforded the bicyclic product **143** in moderate yield (62%) and in moderate enantioselectivity (42% ee). What is notable about the latter reaction is that following the asymmetric conjugate addition reaction to the ketoester **140**, an intramolecular asymmetric Friedel Crafts-type reaction occurred forming a bicyclic product as a single diastereoisomer.

[1] The reaction was performed at -10 ˚C.

Scheme 1.6.5.2: Conjugate Addition Reactions of Indole (137) and 3-Methoxyophenol (142) to the *β,γ*-Unsaturated *α*-Ketoester (140)



137 **140** **141**

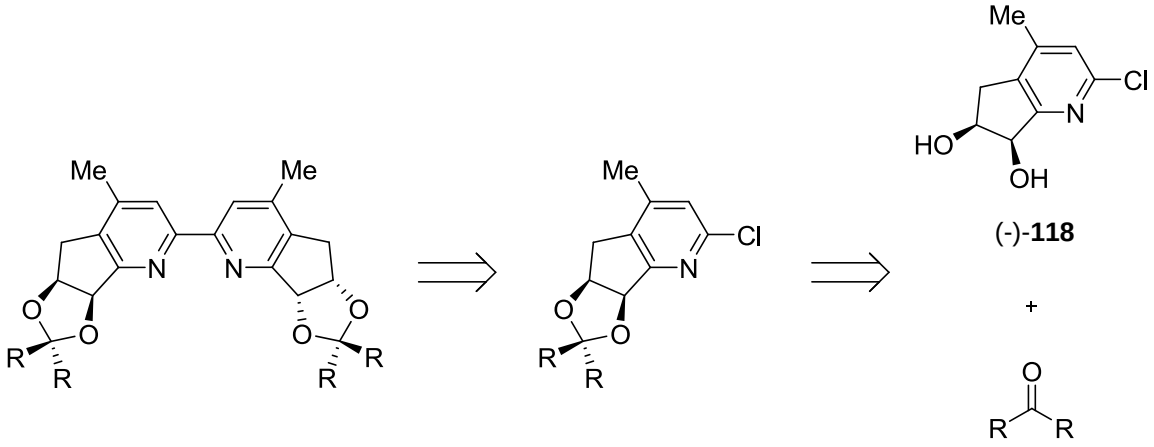
142 **140** **143**

1.7 Research Objectives and Thesis Overview

1.7.1 Research Objectives

The chiral nonracemic 2,2'-bipyridine **1a** was proven to be an effective chiral director in several asymmetric catalytic transformations. Thus, this ligand provides a good template upon which improved ligands can be designed. The objective of the research described in this thesis was to synthesize a family of ligands related to the 2,2'-bipyridine **1a**. The acetal functionality of ligand **1a** is the moiety which acts as a chiral director in asymmetric reactions. Thus, this was the aspect of the ligand targeted for investigation. The family of new ligands were to contain a variety different chiral acetal functionalities in order to probe the effect of this group in the asymmetric induction that can obtained with these the ligands in asymmetric cyclopropanation reaction of styrene. These new ligands were to be accessed by the reductive coupling of the corresponding chloropyridines, which were in turn to be synthesized from the condensation of various ketones with the known chiral nonracemic diol (-)-**118** (Scheme 1.7.1.1).

Scheme 1.7.1.1: Retrosynthetic Analysis of the Target Ligand Series



Once synthesized, the new ligands would be evaluated in the asymmetric cyclopropanation styrene **27** with ethyl diazoacetate **28c** in order to identify the superior chiral ligand in this synthetic transformation. This superior ligand would then be tested in the asymmetric allylic oxidation reaction of three different cycloalkenes **134a-c** and *t*-butyl peroxybenzoate **135** in order to evaluate its broader utility in catalytic asymmetric synthesis.

1.7.2 Thesis Overview

In *Chapter Two* the synthesis and characterization of the series of chiral nonracemic C_2 symmetric 2,2'-bipyridines **1b-g** is described.

In *Chapter Thr*ee the results obtained from the cyclopropanation reaction of reaction of styrene **27**, employing the series of chiral nonracemic 2,2'-bipyridines **1b-g** as ligands, are described. The allylic oxidation of cyclopentene **134a**, cyclohexene **134b** and cycloheptene **134c** catalyzed by ligand **1g** is also discussed.

In *Chapter 4* full experimental data and procedures are presented for all of tthe compounds synthesized are discussed in this thesis.

CHAPTER 2: RESULTS AND DISCUSSION 1

Synthesis of Chiral Nonracemic C_2-Symmetric 2'2-Bipyridines

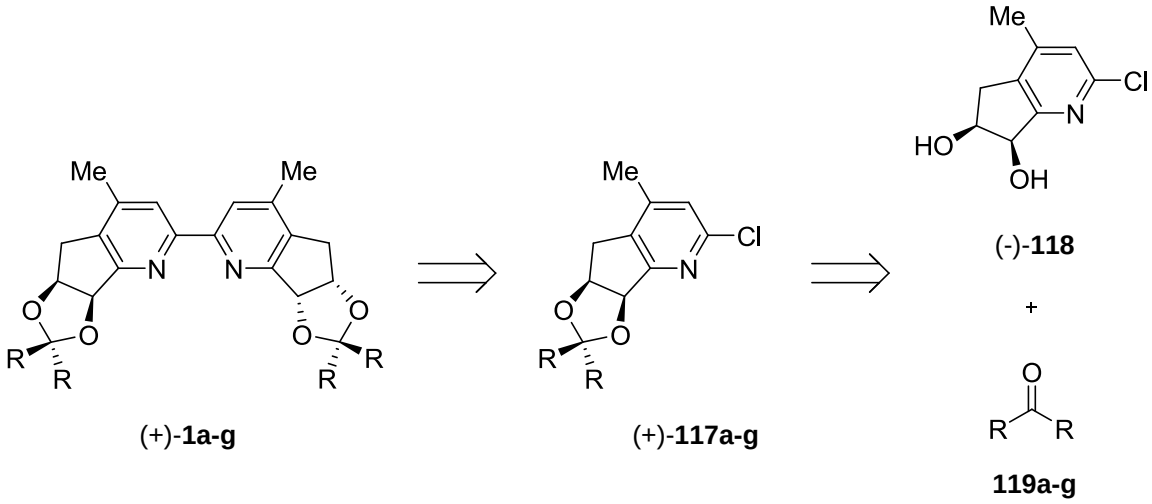
2.1 Introduction

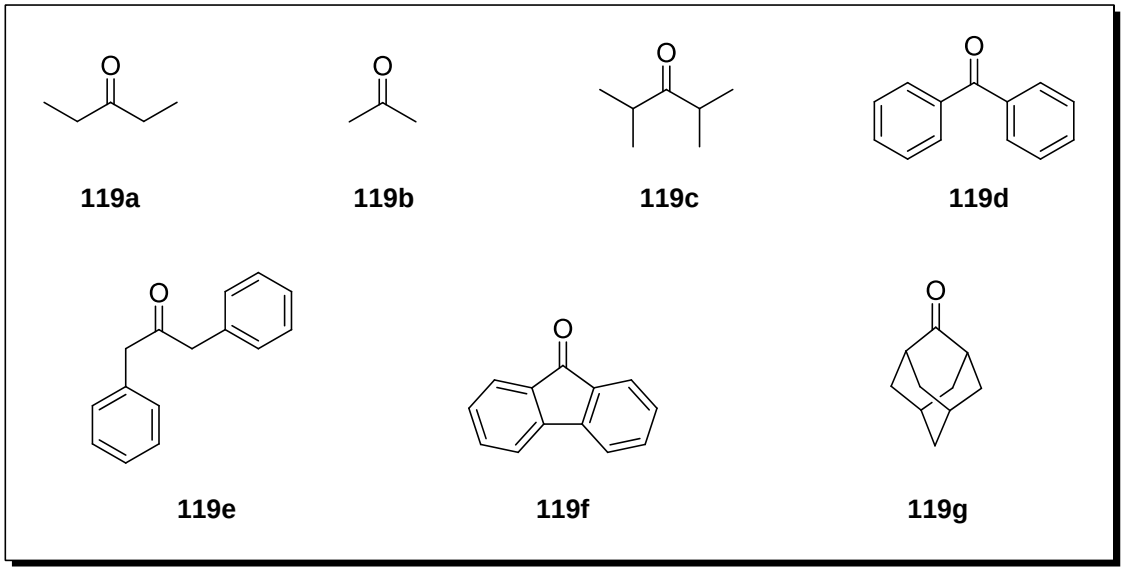
2.1.1 A Modular Synthesis of a Series of Chiral Nonracemic 2,2'-Bipyridines

In this chapter, the synthesis and characterization of a series of chiral nonracemic C_2-symmetric 2,2'-bipyridines **1a-g** are described (Scheme 2.1.1.1). These compounds, which vary structurally only in their acetal unit, were made in order to determine which features of this unit afforded the best chiral induction in various asymmetric copper-catalyzed reactions. The impetus to synthesize and evaluate these ligands in such processes was spurred by positive results obtained from employing the 2,2'-bipyridine **1a** in these classes of chemical reactions.[132,139,141]

The synthetic strategy used by our laboratory toward the discovery and synthesis of these new chiral 2,2'-bipyridines is modular in nature. This can be seen by retrosynthetic analysis of the ligand series **1a-g** (Scheme 2.1.1.1). These 2,2'-bipyridines all stem from the reductive-coupling of a series of chloropyridine acetal precursors **117a-g**. In turn, these acetals could be derived on condensation of the nonracemic diol (-)-**118** with a series of symmetric ketones **119a-g**. In this fashion, a wide variety of ligands can be created from a common precursor, facilitating the synthesis of an array of structurally-related compounds, for systematic structure-function studies.

Scheme 2.1.1.1: Retrosynthetic Analysis of the Series of Chiral Nonracemic 2,2'-Bipyridines (1a-g)





The common precursor, the known chiral nonracemic diol **(-)-118**, was synthesized using a practical multiple-gram scale series of chemical operations and obtained in high optical purity. The synthesis of this diol was optimized in the course of this study and it was then used to prepare a series of acetals **117a-g** through condensation with various symmetrical ketones, or ketone equivalents. These acetals were then reductively-coupled to obtain the target series of C_2-symmetric 2,2'-bipyridines **1a-g**.

The synthesis of an achiral 2,2'-bipyridine **161** derived from the reductive-coupling of a common precursor, the 2-chloropyridine **99**, was also accomplished (*vide infra*).

2.2 Synthesis of the Heterocyclic Chiral Nonracemic Diol [(-)-118]

2.2.1 Overview of the Synthesis of Diol [(-)-118]

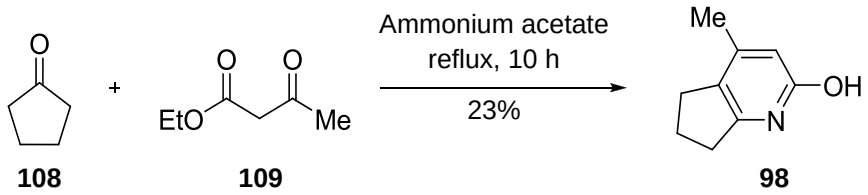
The diol (-)-**118** was the common precursor for the proposed synthesis of the series of 2,2'-bipyridines **1a-g** and the synthesis of this compound represents the foundation for the synthetic work carried out in this thesis. In the first instance, we pursued the preparation of this key compound using the successful route previously established by Lyle for the synthesis of the lead chiral 2,2'-bipyridine **1a** (See: Scheme 1.5.3.1, page 38 and Scheme 1.5.4.2, page 43).[1,141] In the following subsections the synthesis of this diol is described. Further synthetic improvements and observations are also discussed.

2.2.2 Synthesis of the 2-Hydroxypyridine (98)[1,116,141]

The 2-hydroxypyridine **98** was prepared upon heating ammonium acetate with cyclopentanone **108** and ethyl acetoacetate **109** on a molar-scale (> 1.5 mol, Scheme 2.2.2.1). The product of this reaction was isolated by simple filtration and purified by recrystallization of the precipitated product from ethanol. In one case, fifty-four grams (23% yield) of product **98** was obtained from this reaction. The low yield of the reaction is acceptable as the starting materials are inexpensive and readily available. The IR spectrum of this compound showed a broad absorption band at ~ 3100 cm^{-1} indicating that the compound was mainly present as its aromatic enol tautomer. The additional

spectrographic data* collected for this compound was also in full agreement with that previously reported in detail by Lyle.[1,141,142]

Scheme 2.2.2.1: Synthesis of 2-Hydroxypyridine (98)



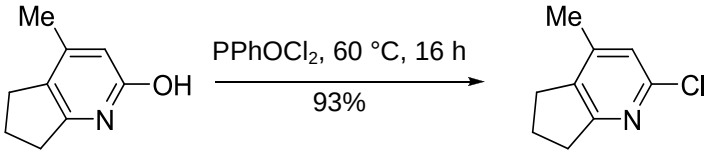
108 **109** **98**

2.2.3 Synthesis of the 2-Chloropyridine (99)[1,116,141]

The 2-hydroxypyridine **98** (26.5 g) was subsequently converted to the corresponding 2-chloropyridine **99** following treatment with phenylphosphine dichloride and on heating at 160 ˚C for sixteen hours (Scheme 2.2.3.1). The 2-chloropyridine **99** was readily purified by flash chromatography to afford twenty-six grams of product (93% yield). The IR spectrum of this compound did not show any absorbance bands corresponding to a hydroxyl group. In addition to this, the mass spectrum of the compound showed two isotopic molecular ion peaks at 168 and 170 *m*/*z* in a 3:1 ratio, indicating the incorporation of a chlorine atom. All other spectrographic data collected for this compound were in full agreement with that previously reported.[1,116,141]

* All known compounds that were synthesized during this study were characterized by ^{1}H NMR, ^{13}C NMR, IR, mass spectroscopy and optical rotation where applicable. This data is presented in the experimental section (*Chapter 4*) of this thesis.

Scheme 2.2.3.1: Synthesis of the 2-Chloropyridine (99)

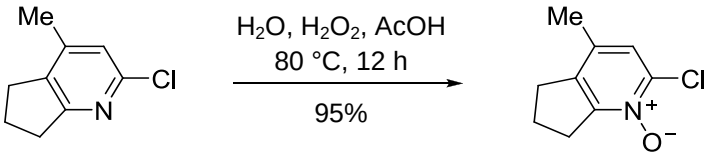


98 **99**

2.2.4 Synthesis of the Pyridine N-Oxide (110) and the Acetate (100)[1,116,141]

In order to functionalize the cyclopentyl ring of the chloropyridine **99**, this compound was converted to its corresponding pyridine *N*-oxide **110** following treatment with hydrogen peroxide in acetic acid and on subsequent heating at 80 ˚C for twelve hours (Scheme 2.2.4.1).

Scheme 2.2.4.1: Synthesis of the Pyridine *N*-Oxide (110)



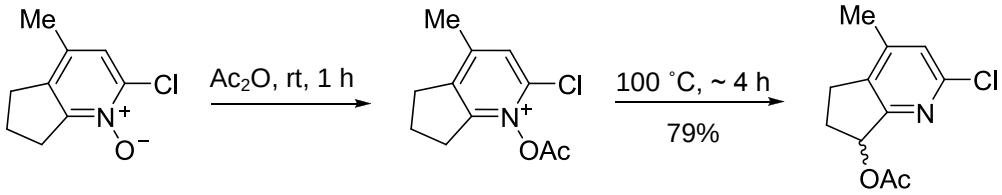
99 **110**

The crude pyridine *N*-oxide **110** was isolated as a white solid (27.6 g, ~ 95%) on concentration of the reaction mixture *in vacuo*. This material was not characterized or purified, but was employed directly in a subsequent synthetic transformation (Scheme 2.2.4.2). Thus, treatment of the crude pyridine *N*-oxide **110** with acetic anhydride at room temperature afforded the acetylated pyridine *N*-oxide **144**. Upon heating the reaction mixture slowly to 100 ˚C over the course of one hour*, followed by maintenance of this reaction temperature for an additional three hours, this intermediate was converted to the acetate **100**. Purification of the crude product by flash chromatography afforded the acetate **100** as an orange oil (26.5 g, 79%) which crystallized upon standing (m.p. 50-

* It was found necessary to slowly heat this reaction mixture in order to avoid the formation of byproducts.

51 °C[†]).[1,116,141] The IR spectrum of this compound displayed a strong absorbance band at 1737 cm^{-1} that was indicative of the acetyl carbonyl group. The ^1H NMR spectrum showed the two expected methyl singlets at δ = 2.08 and 2.26 ppm and the singlet that corresponded to the aryl hydrogen at δ = 7.05 ppm. In addition, the compound displayed five signals at δ = 2.03, 2.62, 2.76, 2.94 and 5.99 each with a complex splitting pattern and each integrated for one proton. These five signals correspond to the five hydrogen atoms of the cyclopentyl ring, four of which are diastereotopic. This confirmed that the acetate had been incorporated onto the cyclopentyl ring. Moreover, all spectrographic data collected for this compound were again in full agreement with that previously reported.[1,116,141]

Scheme 2.2.4.2: Synthesis of the Acetate (100)

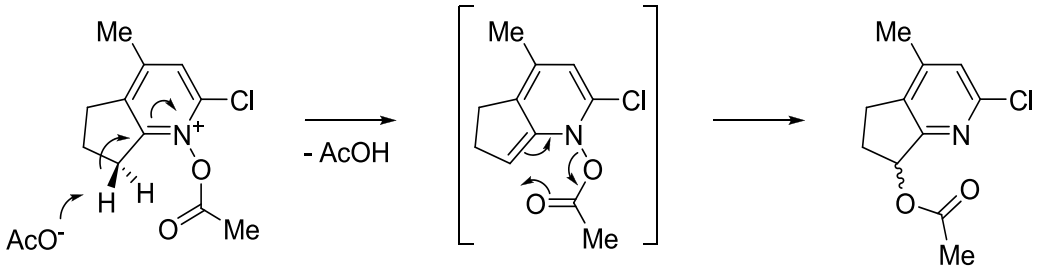


110 **144** **100**

The acetylation and migration process used to access the acetate **100** is commonly referred to as the Boekelheide reaction.[143] The mechanism of this reaction involves the deprotonation of the acetylated pyridine *N*-oxide **144** to generate the non-aromatic *N*-oxide acetate **145**. This intermediate then undergoes a formal [3.3] sigmatropic rearrangement to afford the desired acetate **100** and regenerate the aromaticity in this compound (Scheme 2.2.4.3).

[†] This data was not previously reported.

Scheme 2.2.4.3: Proposed Mechanism of the Boekelheide Reaction[144]

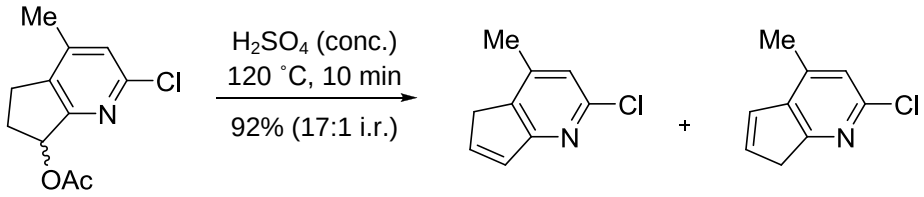


144 **145** **100**

2.2.5 Synthesis of the Alkene (101)

In order to prepare the alkene **101**, the direct precursor of the chiral diol (-)**-118**, the acetate **100** was heated in concentrated sulphuric acid at 120 ˚C for ten minutes (Scheme 2.2.5.1). This afforded the corresponding alkene **101** and its positional isomer **146** in a 17:1 isomeric ratio (i.r.). [1] This was determined by the ^{1}H NMR spectrum of the crude material.* This material was subsequently purified by flash chromatography to afford the pure alkene **101** (6.10 g, 92%) as a white solid (m.p. 41-42 ˚C) which was stable at -20 ˚C. Of note, when this material is left at room temperature for extended periods (twenty-four hours) it undergoes an isomerisation process to afford a ~ 1:1 mixture of the two alkenes **101** and **146**. This indicated a possible complication for the use of this material in subsequent reactions.

Scheme 2.2.5.1: Synthesis of the Alkene (101)



100 **101** **146**

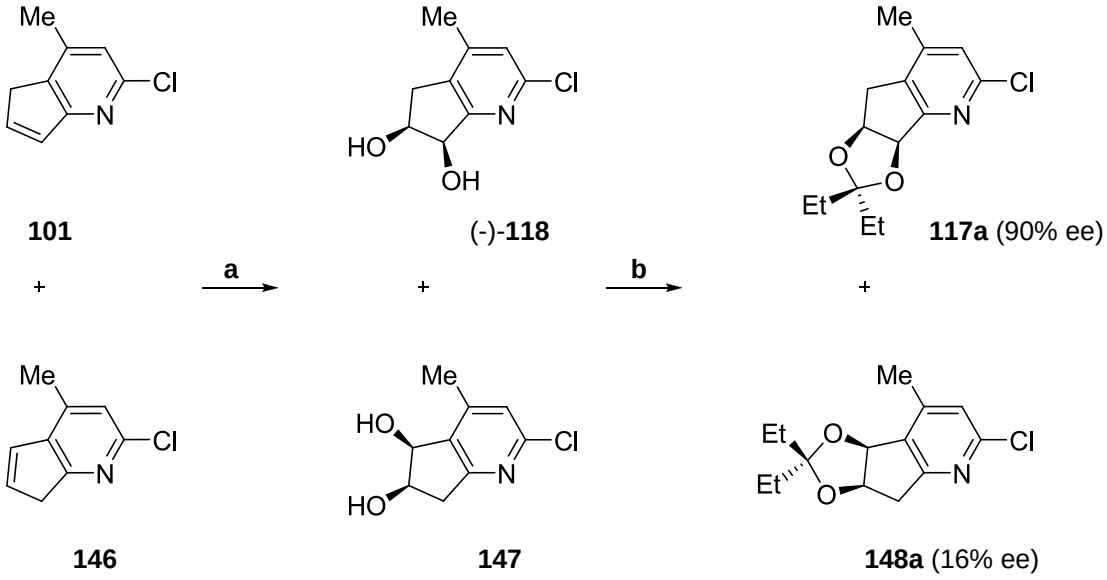
* On smaller scales (0.5-1.0 g) the crude material from this reaction had an i.r. of 26:1. (see Chapter 4.2.4, page 179).

The molecular structure of alkene **101** was confirmed on analysis of its ^{1}H-NMR spectrum. A multiplet at δ = 6.93 ppm corresponded to three protons. This resonance can be assigned to the two vinylic hydrogen atoms and the aromatic hydrogen atom of the pyridine ring. The position of the double bond was not confirmed at this stage, however its location was confirmed through the formation of a derivative that was isolated from subsequent reactions. The minor isomer **146** was not isolated in pure form but a set of resonances similar to those of the alkene **101** were observed in the ^{1}H-NMR spectrum of the ~ 1:1 mixture compounds that was formed on storage at room temperature. Moreover, a derivative of the isomer **146** was also isolated from subsequent reactions.

2.2.6 Dihydroxylation of the Alkene (101) to Form the Chiral Nonracemic Diol [(-)-118]

With the alkene **101** in hand, the synthesis of the optically active diol (-)-**118**, which is the penultimate precursor of the targeted bipyridine series **1a-g**, was pursued. In order to prepare this diol in optically active form, the alkene **101** was subjected to a modified Sharpless asymmetric dihydroxylation process that had previously been employed in our laboratory (Scheme 2.2.6.1).[1] In this previous work, the crude product of this dihydroxylation reaction was condensed with 3-pentanone **119a**. This afforded the chiral nonracemic acetal **117a** in 81% isolated yield over two steps. The enantiomeric purity of this material was determined by analytical chiral HPLC to be 90% ee.[1,141] Of note, it had been previously observed that favourable results for this asymmetric dihydroxylation reaction were obtained only when less than 200 mg of alkene **101** was used, as performing this reaction on a larger scale resulted in a precipitous drop in yield.

Scheme 2.2.6.1: Previously Reported Dihydroxylation and Subsequent Acetalization of an ~ 8:1 Mixture of Alkenes (101) and (146)[1,141]



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), rt, 2 h; (b) PhH, *p*-TsOH (cat.), reflux, 16 h, 81% **117a** (over two steps).

On repeating this reaction on 200 mg scale the diol (-)-**118** was isolated in lower yield (40-60% for only the dihydroxylation step) and in poorer enantioselectivity (70-75% ee, as determined by analytical chiral HPLC of the corresponding acetal **117a**) than had previously been observed. The isomeric ratio (2:1) of the diols (-)-**118** and **147** was also poorer in comparison to the published results. It was noted that an extended period of time was required in order for the alkene starting material to be consumed in these reactions. It was postulated that this extra time allowed for the isomerisation and decomposition of the alkenyl starting material. Thus, it was concluded that a means to increase the rate of reaction was required to improve the efficiency of this key synthetic transformation.

On consideration of the reaction process it was determined that the reaction rate depended in part on how the reaction mixture was stirred. This is principally due to the

fact that the Sharpless asymmetric dihydroxylation reaction is performed in a biphasic medium (Figure 2.2.6.1). A typical Sharpless asymmetric dihydroxylation reaction employs potassium ferricyanide as the stoichiometric oxidant. This oxidant resides in the aqueous phase of the reaction mixture and thus the aqueous phase is where the catalytic cycle begins. However, oxidation of the alkene takes place in the organic phase. The cycle operates as follows: the osmium(VI) species **151** is oxidized to the osmium(VIII) species **152** by the action of potassium ferricyanide in the aqueous phase. Subsequent loss of two hydroxyl groups from this osmium species affords osmium tetroxide **149**, which is soluble in the organic layer. Osmium tetroxide diffuses into aqueous phase where it binds to a chiral ligand [in this case $(DHQD)_2PHAL$)] providing a reactive species that is able to dihydroxylate the alkene. The resultant osmate ester **150** is then hydrolytically cleaved, releasing an optically active diol, the chiral ligand and the reduced osmium(VI) species **152** which in turn migrates to the aqueous phase, starting the catalytic cycle again.[49] It follows that in order for this catalytic cycle to function efficiently, that osmium species must migrate to and from the aqueous phase. By stirring the mixture more vigorously the phases are more intimately dispersed, which leads to a larger interface between the aqueous and organic phases. This allows for an increase in the rate of the migration of the osmium species migration and therefore an increase in the rate of reaction.

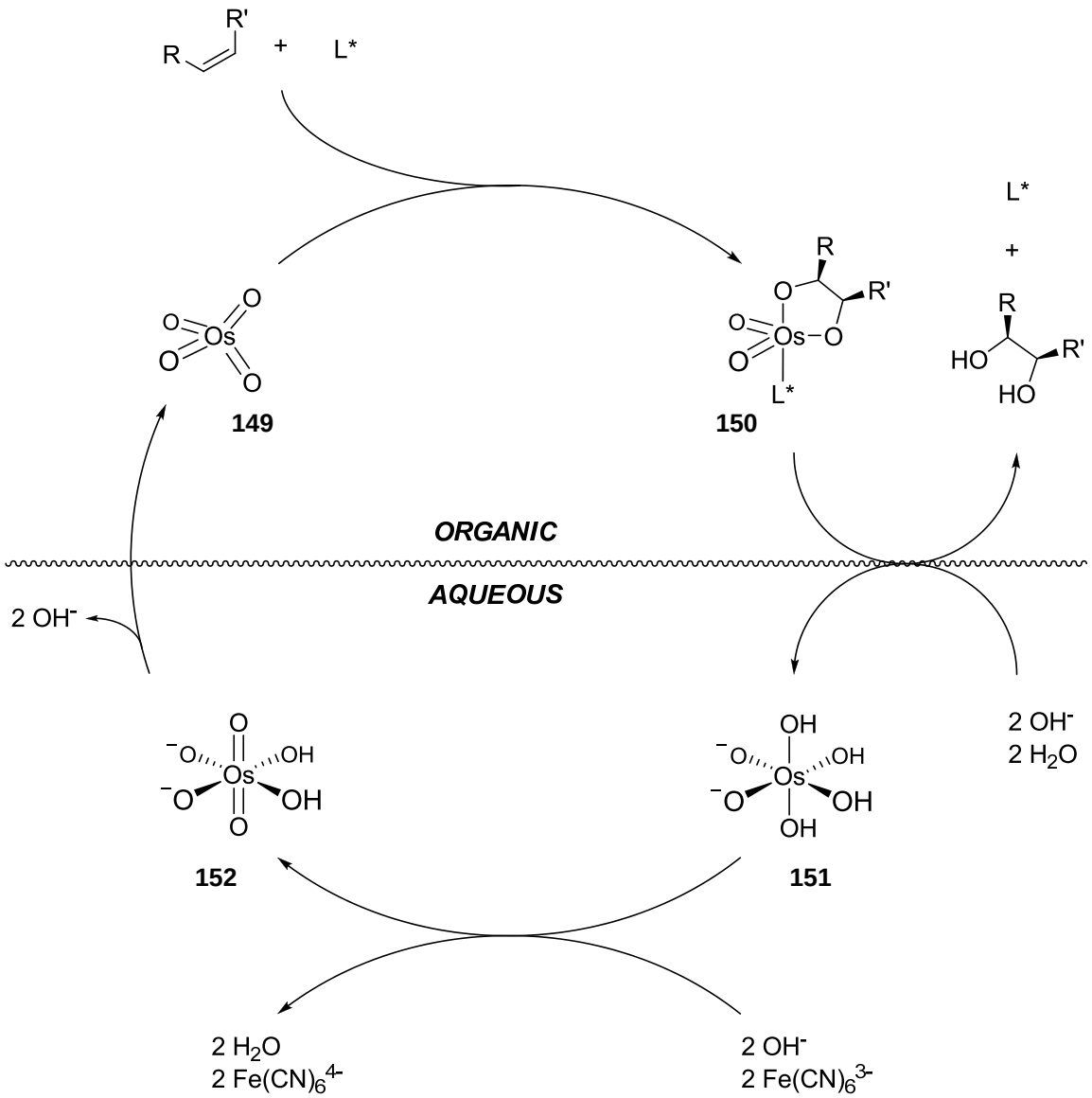
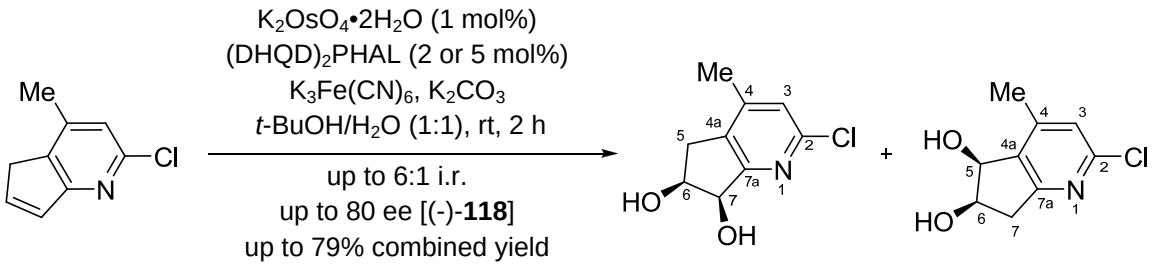


Figure 2.2.6.1: The catalytic cycle of the Sharpless asymmetric dihydroxylation reaction in a biphasic medium.[49]

It was found subsequently that through the use of vigorous stirring and a large stir bar that the time required for this reaction to proceed to completion was reduced to two hours. This decrease in reaction time increased the combined yield of positional diol isomers (-)-**118** and **147** (i.r. = 6:1) to 79% (Scheme 2.2.6.2). In addition, the enantiomeric purity of the corresponding acetal of the major isomeric diol was determined to be 80% ee. Although this was not optimal, it was deemed acceptable for

use in subsequent reactions. Furthermore, it was found through employment of vigorous stirring that the reaction could be carried out on multi-gram scale without any loss in yield or enantioselectivity.

Scheme 2.2.6.2: Dihydroxylation Reaction of the Alkene (101)



101 (-)-**118** **147**

A final investigation of this reaction revealed that lowering the $(DHQD)_2PHAL$ concentration from 5 mol% to 2 mol% had no detrimental effect on the reaction yield nor on the enantiomeric purity of the diol (-)-**118**. Thus, with this improved process it was now possible to efficiently access multi-gram quantities of the diol (-)-**118** in acceptable enantiomeric purity, using a significantly smaller quantity of the expensive chiral ligand $(DHQD)_2PHAL$.* Of final note, the two isomeric diols could not be separated by flash chromatography at this stage, but were instead separated and purified upon conversion to their corresponding acetals.

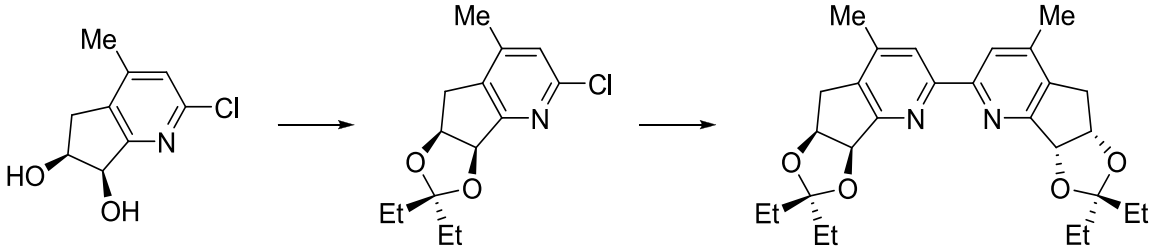
* From a commercial supplier, Aldrich, $(DHQD)_2PHAL$ costs ~ $100 per gram. Using a 5% loading of this catalyst, 2.5 grams are required to generate 10 grams of the chiral diol (-)-**118**. At 2% loading this requirement is lowered to 1 gram.

2.3 Synthesis of the Known Chiral Nonracemic C_2-Symmetric 2,2'-Bipyridine (1a)

2.3.1 Overview

In the first instance it was decided to pursue synthesis of the known chiral 2,2' bipyridine **1a** before pursuing the synthesis of the target 2,2'-bipyridines **1b-g**. Thus, the optically active diol (-)-**118** was condensed with 3-pentanone **119a** and the resultant optically active acetal was then reductively-coupled to afford the known chiral nonracemic C_2-symmetric 2,2'-bipyridine **1a** (Scheme 2.3.1.1). These synthetic transformations are described in more detail in the following subsections.

Scheme 2.3.1.1: Synthesis of the Known Chiral Nonracemic C_2-Symmetric 2,2'-Bipyridine (1a)

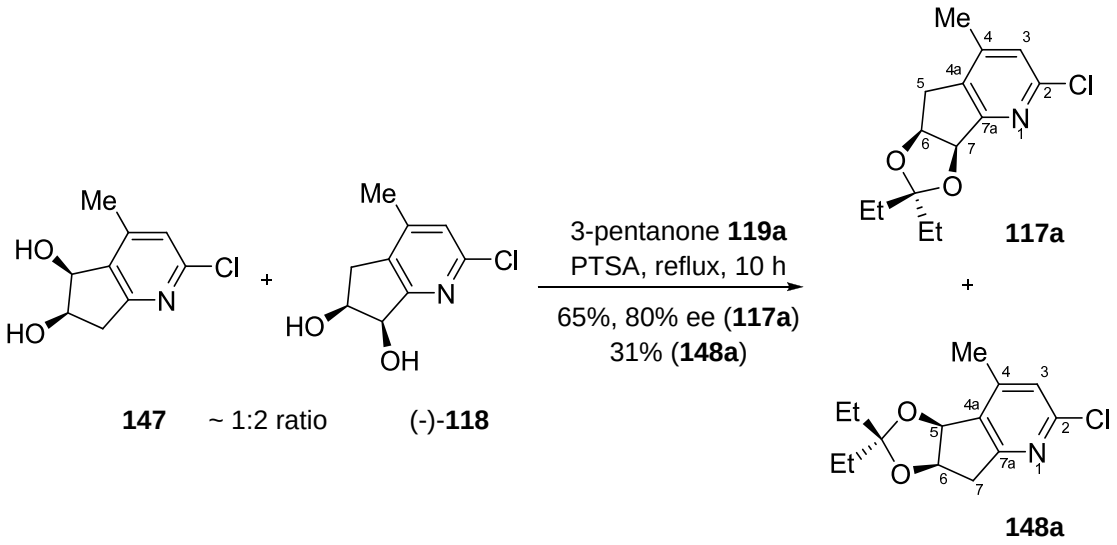


(-)-**118** **117a** **1a**

2.3.2 Synthesis of the Known Chiral Acetal (117a)

To synthesize the chiral acetal **117a**, an inseparable mixture of the optically active diol (-)-**118** and its isomer **147** (i.r. 3:1) was condensed with 3-pentanone **119a**. This acid-catalyzed process was performed in benzene using a Dean Stark trap that permitted the azeotropic removal of water (Scheme 2.3.2.1). This afforded the acetals **117a** and **148a** that were separated and purified by flash chromatography in excellent yield (65 and 31% yield, respectively).

Scheme 2.3.2.1: Formation of the Acetal (117a) and the Isomer (148a)



147 ~ 1:2 ratio (-)-**118**

The mass spectrum of the acetal **117a** displayed the expected molecular ion peaks at 268 and 270 *m/z* in a 3:1 ratio that corresponded to the two isotopic masses of the protonated compound; M[^{35}Cl] + H and M[^{37}Cl] + H. In addition, the expected resonances for two diastereotopic ethyl moieties were displayed in the ^{1}H NMR spectrum. The signals that corresponded to the methyl groups of these ethyl moieties were observed as a pair of triplets at δ = 0.58 and 0.94 ppm. The more upfield of these signals was assigned as the group on the concave face of the acetal moiety. This assignment was made due to the expected anisotropic shielding provided by the pyridine ring. The methylene units of these diastereotopic ethyl groups correspond to a pair of multiplets at δ = 1.47 and 1.68 ppm. The more upfield signal was again assigned to the group on the concave face of the acetal moiety. The singlet found at δ = 2.25 ppm corresponds to the methyl group at C-4 of the pyridine ring system. The diastereotopic hydrogen atoms at C-5 correspond to a multiplet at δ = 2.99 ppm. The hydrogen atoms at C-6 and C-7 are found at δ = 5.0 and 5.4 ppm respectively and these assignments were

made due to the fact that the more upfield singlet is a doublet of doublet of doublets, which is in agreement with the expected splitting pattern of *H*-6 which is split by three inequivalent protons (*H*-5$_\alpha$, *H*-5$_\beta$ and *H*-7$_\beta$,). * The more downfield of the two signals is a doublet and has the expected multiplicity to be assigned to *H*-7$_\beta$. The most downfield signal, found at δ = 7.06 ppm, corresponds to the only aromatic hydrogen atom present in this molecule, *H*-3. The ^{13}C NMR spectrum displayed fourteen carbon atoms, which is also in accordance with the structural assignment of this compound.

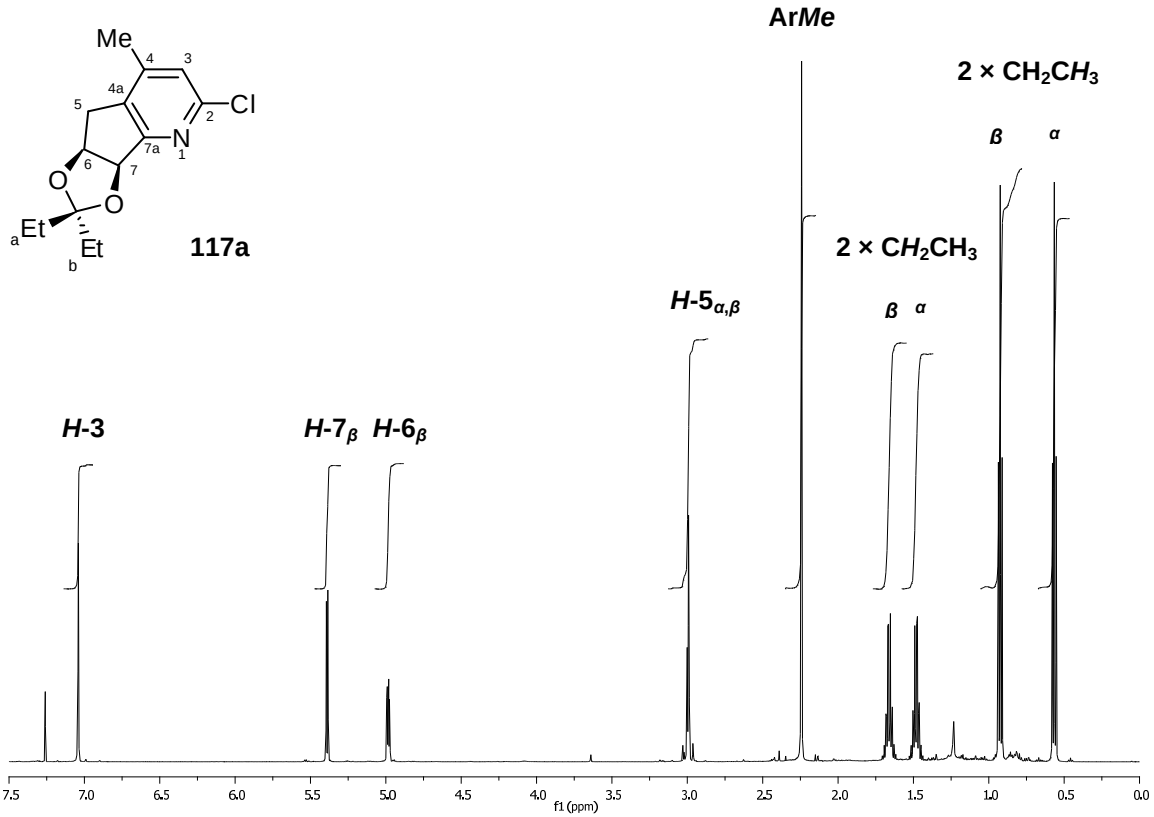
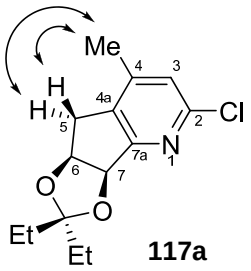


Figure 2.3.2.1: ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of the acetal (117a).

All other spectrographic data collected for this compound were in full agreement with that previously reported.[1,116,141] The assignment of the location of the acetal moiety

* Herein *α* refers to the top face and *β* refers to the bottom face of the molecule, as drawn.

(at C-6 and C-7) was further supported by a 1D nOe experiment. Here, through-space contacts between the C-4 methyl substituent and the diastereotopic hydrogen atoms of the C-5 methylene unit were observed. This reflects the close spatial arrangement of these atoms (Figure 2.3.2.2). Of note, there was no contact observed between the C-4 methylene unit and either of the more distal hydrogen atoms located at C-6 and C-7. This indicates a more distal relationship between these atoms. The enantiomeric purity of this compound varied depending on the source of the diol (-)-**118** starting material. However, using the optimized procedure for the synthesis of this compound, the enantiomeric purity of the corresponding acetal **117a** was determined to be 80% ee by chiral HPLC analysis. The sign of the optical rotation of this material was the same as that of previously reported data.[1,141] Thus, the absolute stereochemistry of this compound was confirmed as being the same as that previously reported (6*S*, 7*R*). The absolute stereochemistry of this previously reported material was determined by the known stereoselectivity of the Sharpless asymmetric dihydroxylation and on the rationalization of the outcomes of subsequent asymmetric reactions that were catalyzed by the ligand derived from this material.



117a

Figure 2.3.2.2: Diagnostic nOe contacts observed for the acetal (117a).

In previous studies conducted in our laboratory, the formation of the isomeric acetal **148a** had been observed. However, only small quantities of the compound had

been isolated which had precluded structural characterization of this compound.[1,141] Thus, in this study it was fully characterized.* The mass spectrum of this isomeric acetal displayed isotopic molecular ion peaks at 268 and 270 *m/z* in a 3:1 ratio that corresponded to M[^{35}Cl] + H and M[^{37}Cl] + H. In addition, the ^{1}H NMR spectrum displayed signals that corresponded to the two diastereotopic ethyl groups (Figure 2.3.2.3). The ^{13}C NMR spectrum, as expected, also displayed fourteen carbon atom signals.

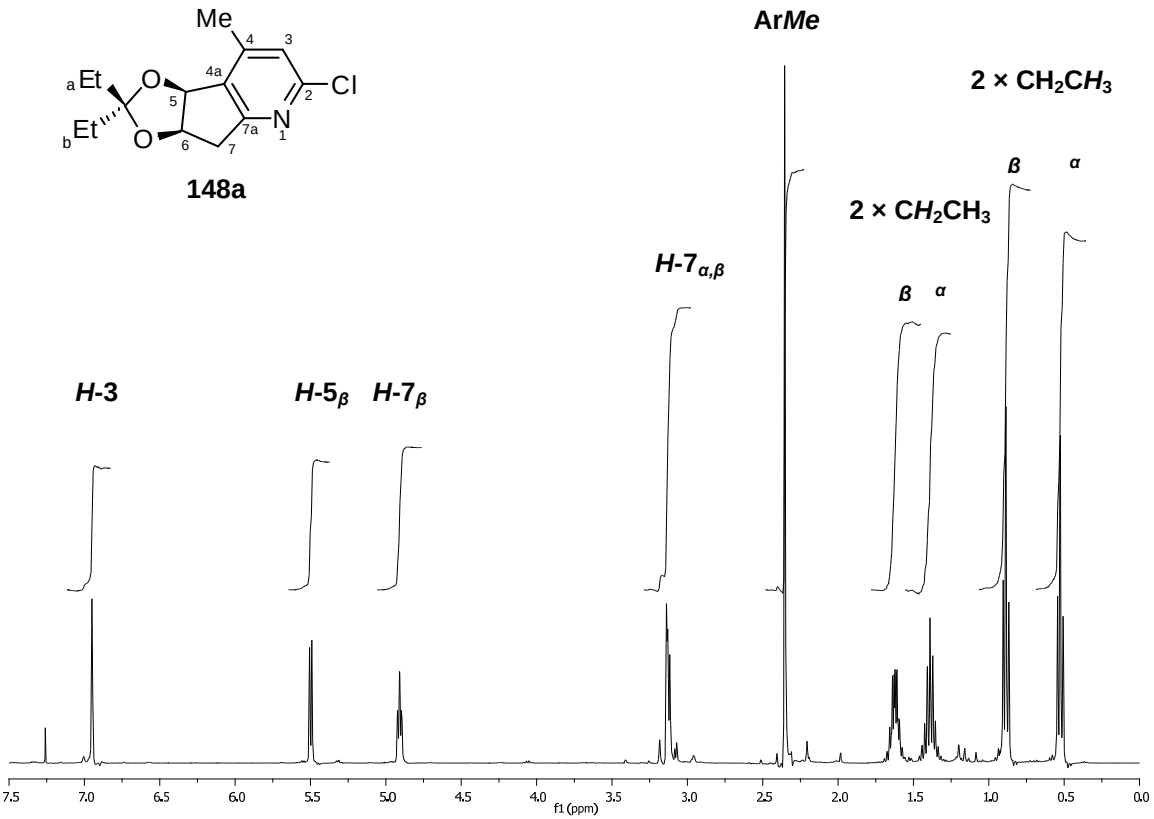
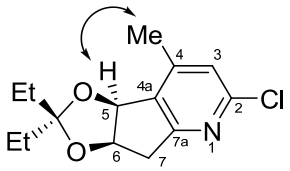


Figure 2.3.2.3: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of the isomeric acetal (148a).

* All new and previously uncharacterized compounds that were synthesized during the course of this study were analyzed by the standard methods as well as by elemental analysis or high resolution mass spectrometry.

The spectral data for this compound and its corresponding isomer were very similar. However, it was possible to assign the location of the acetal moiety (at C-5 and C-6) by a 1D nOe experiment. Here, contacts between the hydrogen atoms of the C-4 methyl substituent and the hydrogen atom at C-5 were observed that indicated a close spatial relationship between these atoms. In addition, no contact was observed between the C-4 methyl group and the diastereotopic hydrogen atoms of the C-7 methylene unit. This indicated a more distal relationship between these substituents. This compound was also subjected to chiral HPLC analysis under the same conditions as those used for the acetal **117a**. However, the enantiomers (+)-**148a** and (-)-**148a** were not resolved. As this compound was not required for our proposed studies, no further attempts were made to determine the enantiomeric purity of this material.



148a

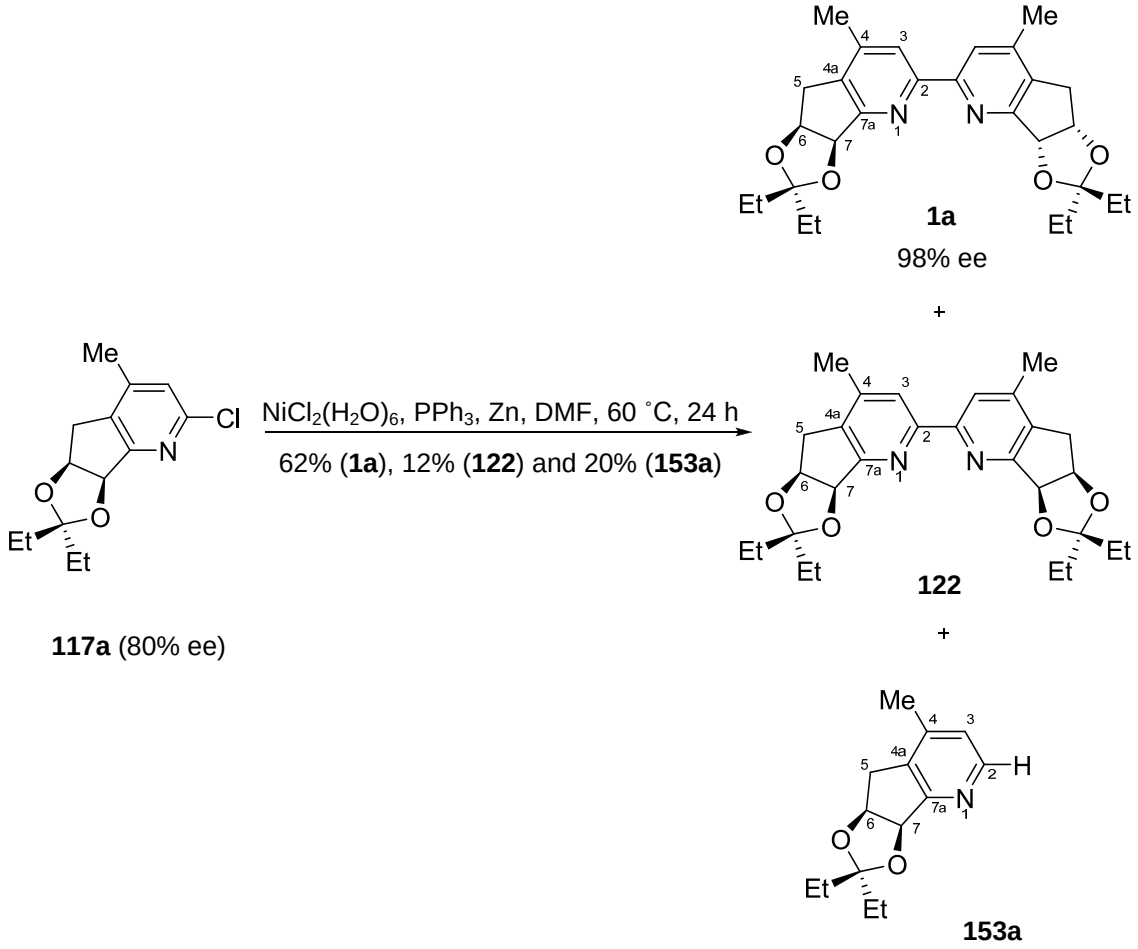
Figure 2.3.2.4: Diagnostic nOe contacts observed from acetal (148a).

2.3.3 Synthesis of the Known Chiral Nonracemic C_2-Symmetric 2,2'-Bipyridine (1a), the *Meso*-Compound (122) and the Reductively-Dehalogenated Pyridine (153a)

The synthesis of the 2,2'-bipyridine **1a** was achieved through dimerization of the chiral acetal **117a** by a reductive-coupling process. This reaction was performed by generating a nickel(0) species *in situ* on reduction of nickel(II) chloride hexahydrate with zinc dust in the presence of triphenylphosphine in *N*,*N*-dimethylformamide at 60 ˚C. Three products were isolated by flash chromatography from this reaction: the desired

2,2'-bipyridine **1a**, the *meso*-2,2'-bipyridine **122** and the reductively-dehalogenated pyridine **153a** (Scheme 2.3.3.1).

Scheme 2.3.3.1: Reductive-Coupling of the 3-Pentanone-Derived Acetal (117a)



117a (80% ee)

The known bipyridine (+)-**1a** was isolated in 62% yield and identified as a C_2-symmetric 2,2'-bipyridine by a characteriztic signal observed at δ = 8.29 ppm in the ^{1}H NMR spectrum that corresponds to the equivalent *H*-3 and *H*-3' protons. In addition, the mass spectrum of this compound displayed the expected molecular ion peak at 465 *m/z*, which corresponds to the mass of a protonated dehalogenated dimer of the acetal **117a**. The inherent symmetry of this molecule is displayed in the ^{1}H NMR and ^{13}C NMR spectra, as they contain the same number of resonances (at similar shifts) as the parent

acetal **117a**. Furthermore, the spectrographic data collected for this compound were in full agreement with that previously reported.[116,141] The enantiomeric purity of this compound was determined to be 98% ee, by analytical chiral HPLC. Moreover, from this compound was observed an optical rotation of $[\alpha]_D^{20}$ = + 157. The sign of this optical rotation was the same as that of the material previously reported in the literature, confirming the absolute configuration of our compound. [1,141] To gain further insight into this molecule, a 3D representation of the molecule was generated and compared to an X-ray crystal structure of its copper(II) complex which was previously obtained.[145] This 3D structure is in good accord with the crystal structure although it depicts the ethyl groups as roughly orthogonal to the main body of the ligand they are flexible and capable of rotating. This flexibility provides the ethyl groups the propensity to further impinge on the binding site of the molecule (Figure 2.3.3.1). Additional views of this 3D representation from various angles are also presented below (Figure 2.3.3.2: A 3D representation of the 2,2'-bipyridine [(+)-1a] viewed from three different perspectives.Figure 2.3.3.2)

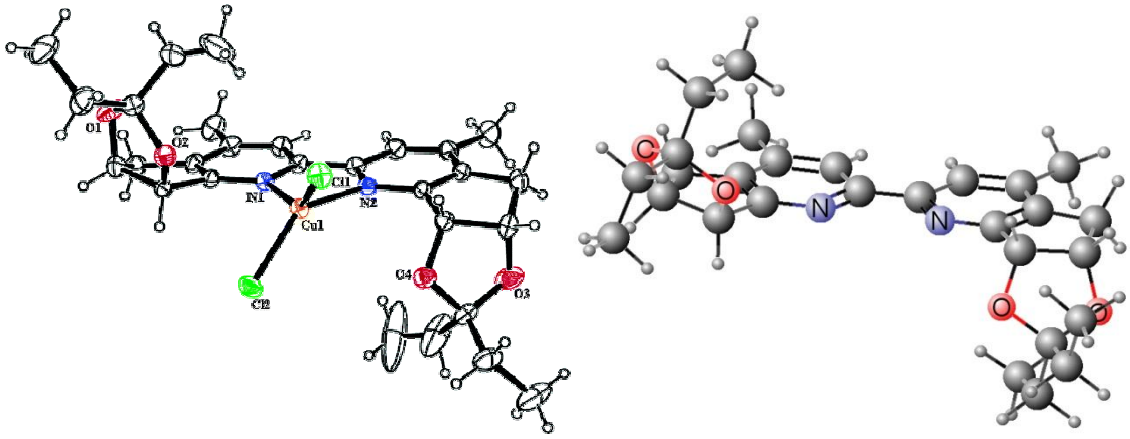


Figure 2.3.3.1: An X-Ray crystal structure of the copper(II) chloride complex of compound (1a) obtained by Lyle (left).[139] A molecular model

generated by the ChemAxon program "Marvin Sketch" (right, copper has been removed for clarity).

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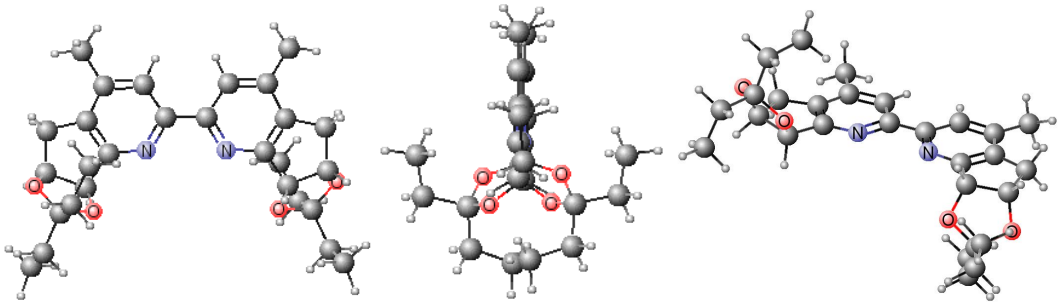


Figure 2.3.3.2: A 3D representation of the 2,2'-bipyridine [(+)-1a] viewed from three different perspectives.

Of important note, the substantial enhancement of enantiomeric purity (from 80% to 98% ee) of the chiral 2,2'-bipyridine (+)-**1a** from that of the the starting material can be explained by a statistical analysis of this dimerization reaction. There is a lower abundance of the minor enantiomer of the chloropyridine **117a**, thus, there is a lower statistical probability that two molecules of the minor enantiomers will couple and form the enantiomeric chiral bipyridine (-)-**1a**. The most probable fate for a molecule of the minor enantiomer of the chloropyridine **117a** is for it to couple with its enantiomeric counterpart to form the *meso*-compound **122**. Thus the enantiomeric excess of the chiral 2,2'-bipyridine (+)-**1a** is enhanced, as proportionally less (-)-**1a** is formed. This enhancement can be predicted using the formula (1), where ee_p is the enantiomeric excess of the product and ee_{sm} is the enantiomeric excess of the starting material.*

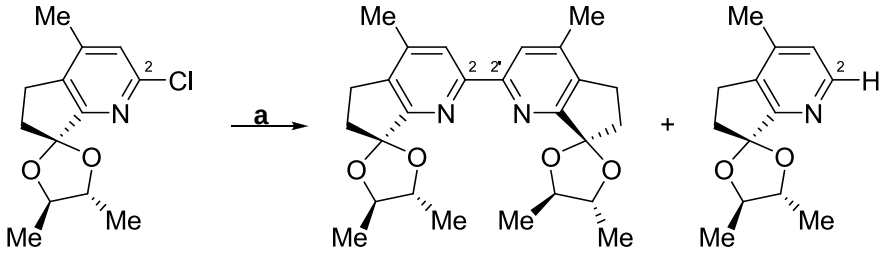
* The derivation of this formula is presented and discussed in *Appendix I* (see page 262).

$$\mathbf{ee_p} = \frac{\mathbf{2(ee_{sm})}}{\mathbf{1 + \left(\frac{ee_{sm}}{100\%}\right)^2}} \qquad (1)$$

The *meso*-compound **122** was isolated as a white solid (315-316 ˚C) in 12% yield. This compound had previously been isolated. However, at the time, insufficient quantities of material precluded the full characterization of this compound.[1,141] Thus, it was fully characterized by spectroscopic means. The compound was identified as a 2,2'-bipyridine by the characteriztic resonance in the ^{1}H NMR spectrum at δ = 8.33 ppm that corresponds to the equivalent *H*-3 and *H*-3' protons. The mass spectrum was also in accord with this assignment, as a protonated molecular ion peak at 465 *m/z*, (M + H) was observed. The spectral data for this compound was essentially identical to that of the chiral nonracemic C_2-symmetric 2,2'-bipyridine **1a**. However, this compound was shown to be optically-inactive and so was confidently assigned as the *meso*-2,2'-bipyridine **122**.

The reductively-dehalogenated-product **153a** displayed two doublets at δ = 6.98 and 8.38 ppm in its ^{1}H NMR spectrum. These signals correspond respectively to the *H*-3 and *H*-2 hydrogen atoms of the pyridine ring. The presence of an additional resonance in the aromatic region of this spectrum indicated that there was no substituent at the C-2. The remainder of the signals were similar to those found in the corresponding 2,2'-bipyridines (+)-**1a** and **122**. In addition, the mass spectrum contained a protonated molecular ion peak at 234 *m/z* (M + H) that allowed for confident assignment of the molecular structure of this compound. The formation of this byproduct was not unexpected as a reductively-dehalogenated-byproduct was also isolated, in significant yield, in previous studies toward the synthesis of the related bipyridine **104a** (Scheme 2.3.3.2).[1,131]

Scheme 2.3.3.2: Synthesis of the 2,2'-Bipyridine (104a) and Formation of the Reductively-Dehalogenated-Byproduct (112a)[1,131]

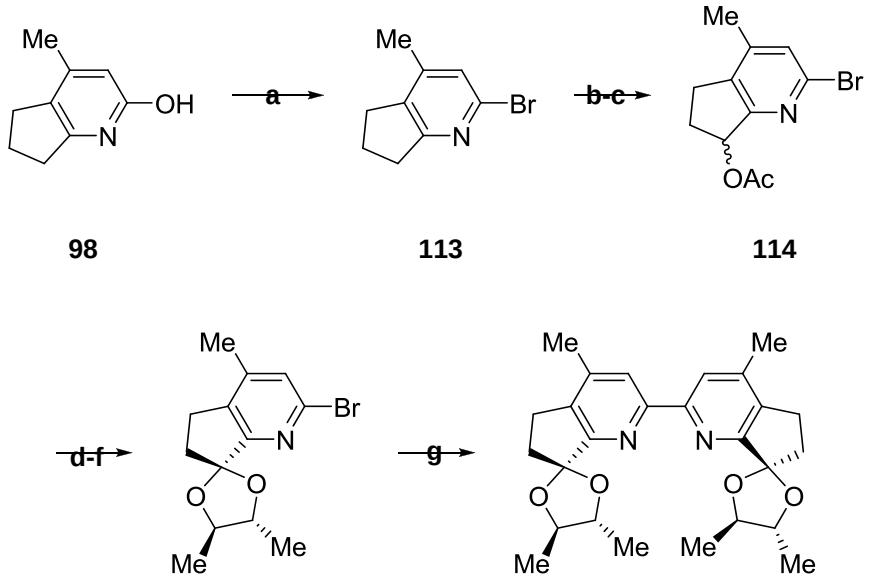


105a **104a** **112a**

Reagents and Conditions: (a) $NiBr_2(PPh_3)_2$, Zn dust, Et_4NI, THF, 60 ˚C, 4 days, 41% (**104a**) and 35% (**112a**).

In this earlier study, the formation of this byproduct was alleviated by employing the corresponding 2-bromo-derivative analogue **116a** of the acetal **105a** (Scheme 2.3.3.3). It was found that the reductive-coupling reaction of this bromopyridyl compound did not afford any of the dehalogenated-byproduct **112a**. However, the synthesis of this bromo-derivative was much lower in overall yield than that recorded for the chloro-derivative. Thus, this alternative route was not employed towards the synthesis of the 2,2'-bipyridines described in this thesis.

Scheme 2.3.3.3: Synthesis of the 2-Bromopyridine (116a) and its Reductive-Coupling Reaction to Form the 2,2'-Bipyridine (104a)



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 (**107a**), *p*-TsOH (cat.), benzene, reflux, 20 h, 89%; (g) $NiBr_2(PPh_3)_2$, Zn dust, Et_4NI, THF, 60 ˚C, 72 h, 83% (**104a**).

2.4 Synthesis of the Acetone-Derived Acetal (117b) and Access to the Highly Enantiomerically-Enriched Diol [(-)-118]

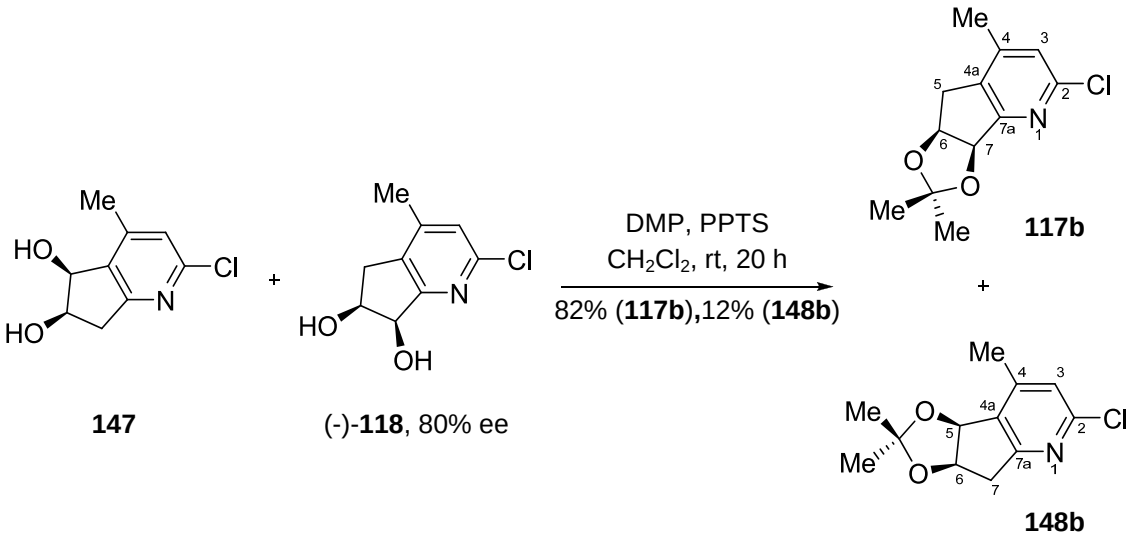
2.4.1 Overview

The synthesis of new 2,2'-bipyridines **1b-g** was initiated by the synthesis of the precursor to the 2,2'-bipyridine **1b**, the acetal **117b**. This acetal is slightly less bulky than that of the 3-pentanone-derived acetal **117a**. Acetals of smaller size are more easily formed.[146-148] Thus this compound was a good target for the synthesis of a new acetal based on the chiral diol (-)-**118**.

2.4.2 Synthesis of the Acetone-Derived Acetal (117b)

The acetal **117b** was synthesized on condensation of the diols (-)-**118** (80% ee) and **147** (~ 6:1) with 2,2-dimethoxypropane in the presence of a catalytic amount of pyridinium *p*-toluenesulfonic acid in dichloromethane (Scheme 2.4.2.1).[149] A mixture of these two diols was used, rather than pure diol (-)-**118**, as they were both formed in the previous dihydroxylation reaction and proved to be inseparable by flash chromatography (as previously stated). The desired acetal **117b** was isolated from this reaction and readily purified by flash chromatography to afford a white solid (m.p. 127-128 ˚C) in 82% yield. This compound was found to form well-defined crystals upon recrystallization from heptanes. Although the acetal **117b** failed to fully resolve on analytical chiral HPLC, the two enantiomers were separable to a degree such that the minor enantiomer was observable as a shoulder on the peak which corresponded to the major enantiomer in the HPLC trace. This shoulder peak was not present in the chiral analytical HPLC trace recorded from the recrystallized material indicating an enhancement of enantiomeric purity on recrystallization. The isomeric acetal **148b** was isolated as a clear oil, which crystallized upon standing (m.p. 61-62 ˚C), in 12% yield.

Scheme 2.4.2.1: Synthesis of the Acetal (117b) and its Isomer (148b)



The acetal **117b** was fully characterized by spectroscopic means, including elemental analysis. The ^{1}H NMR spectrum of this compound showed the expected resonances of the pyridyl-diol moiety at δ = 2.25, 2.98, 3.04, 4.99 and 5.39 and 7.06 ppm (Figure 2.4.2.1).* It is interesting to note that in the ^{1}H NMR spectrum of this compound the signals that can be assigned to the protons *H*-5$_\alpha$ and *H*-5$_\beta$ are well-resolved. The signal corresponding to the proton *H*-5$_\alpha$ is only split by *H*-5$_\beta$ which corresponds to a signal at δ = 2.98 ppm (J = 16.9 Hz). This indicates that it is approximately orthogonal to *H*-6$_\beta$ as it is not coupled to this proton.[150,151] The proton *H*-5$_\beta$ is on the same face of the cyclopentyl ring as *H*-6$_\beta$, and so these protons are approximately in the same plane, it follows that *H*-5$_\beta$ corresponds to a doublet of doublets at δ = 3.04 ppm (J = 17.5 Hz, 5.6 Hz). In addition, two upfield singlets at δ = 1.28 and 1.41 ppm that correspond to the two diastereotopic methyl groups of the acetal moiety were observed. As before, the more upfield signal of these two resonances can be assigned to the methyl group found on the

* The assignment for these resonances are depicted below (Figure 2.4.2.1), and in the experimental section. These assignments are based on the same reasoning as was used in the assignment of the ^{1}H NMR spectrum of acetal **117a** (see: *Section* 2.3.2, on page 73).

concave face of the acetal moiety as it should experience anisotropic shielding due to its position over the pyridyl ring.

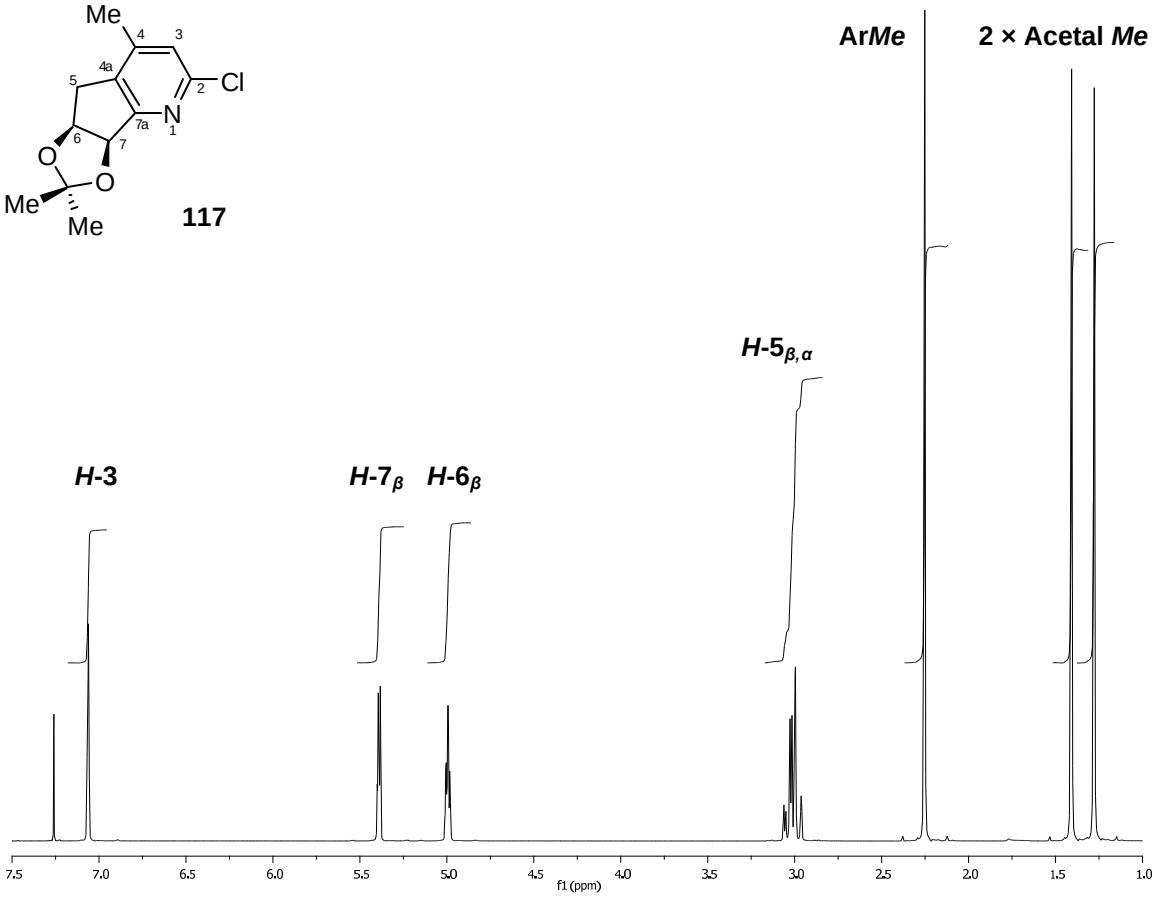


Figure 2.4.2.1: ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of the acetal (117b).[*]

Combustion analysis, for the elemental abundances of carbon, nitrogen and hydrogen of this compound were found to be within 0.35% of their calculated values. From mass spectral analysis, molecular ion peaks at 240 and 242 *m/z* in a 3:1 ratio that correspond to M[^{35}Cl] + H and M[^{37}Cl] + H were also observed. The position of the acetal moiety on the cyclopentyl ring was confirmed through a 1D nOe experiment. Here, contacts between the C-4 methyl substituent and the diastereotopic hydrogen atoms of the C-5 methylene unit were observed which indicated that these atoms were in close

[*] In this instance the *H*-5$_\beta$ is more downfield than *H*-5$_\alpha$. Thus, this pair of signals is assigned as *H*-5$_{\beta,\alpha}$ as opposed to *H*-5$_{\alpha,\beta}$.

spatial proximity (Figure 2.4.2.1). In addition, no interaction was found between the protons of the C-4 methyl group and protons *H*-6$_\beta$ and *H*-7$_\beta$. This indicated a more distal relationship between these hydrogen atoms. Finally, the ^{13}C NMR spectrum displayed twelve resonances that corresponded to the twelve unique carbon atoms present in this molecule. Thus, the combined data allowed for the conclusive assignment of the major reaction product as the acetal **117b**.

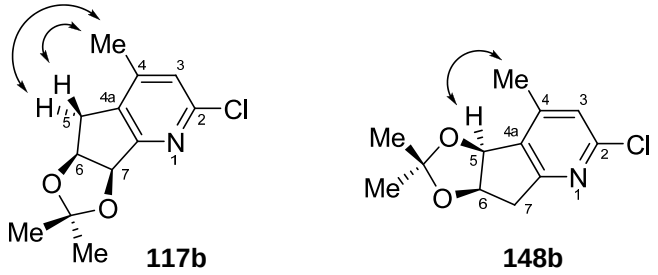


Figure 2.4.2.2: Characteriztic nOe contacts of the acetals [(+)-117b and 148b].

The positional isomer **148b** was identified by the same methods used to determine the molecular structure of the acetal (+)-**117b**. The data were similar but here an nOe contact between the C-4 methyl substituent and the hydrogen atom of C-5 was observed (Figure 2.4.2.3). This indicated a close spatial relationship between these substituents. There was no contact observed between the C-4 methyl substituent and the C-7 methylene unit, which indicated that these two moieties were more remote from each other. This latter study allowed for confident assignment of the molecular structure of this compound as the acetal **148b**.

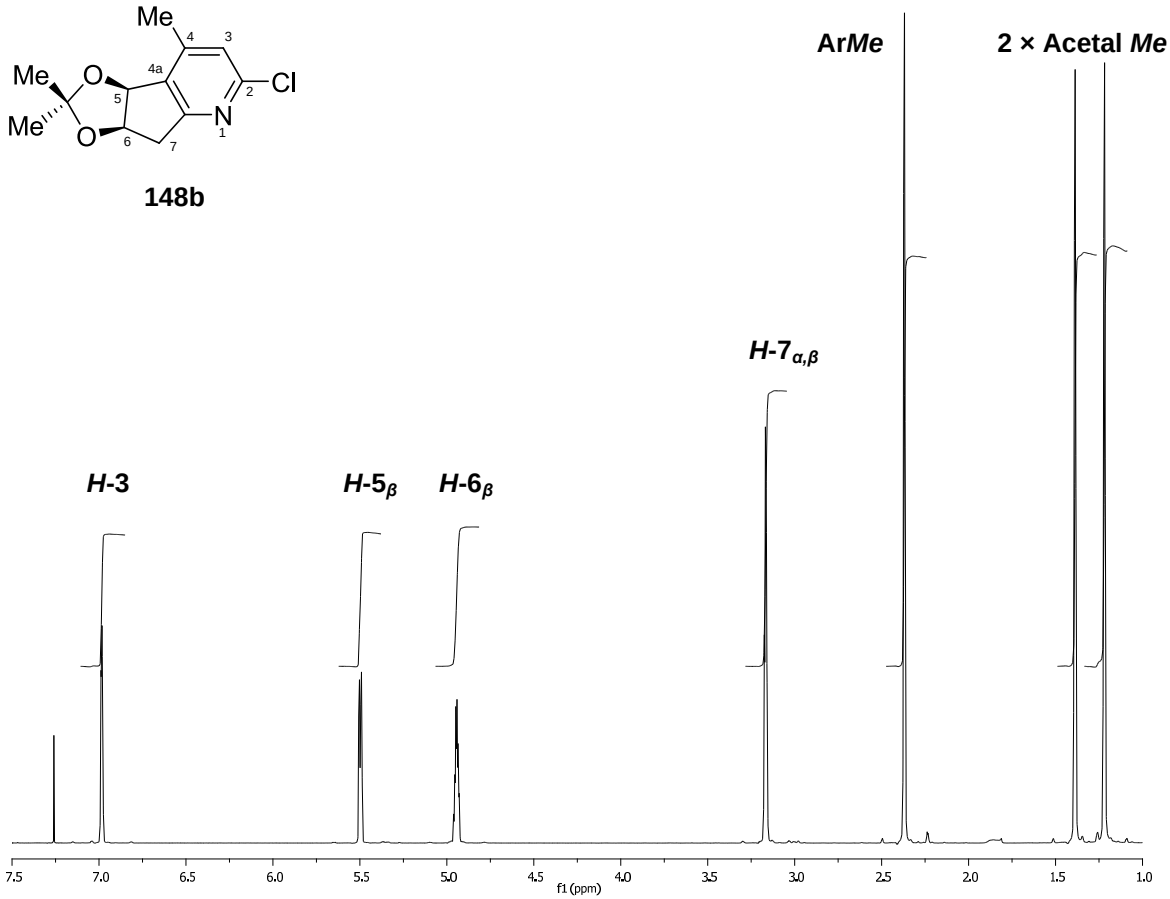


Figure 2.4.2.3: ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of the acetal (148b).*

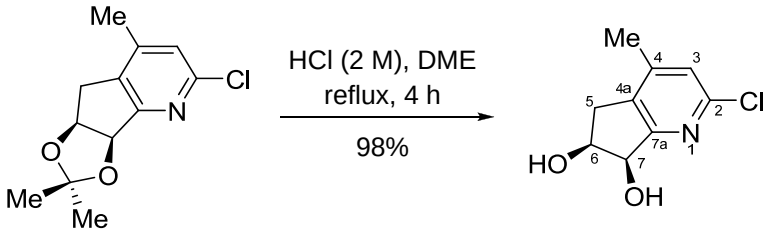
2.4.3 Deprotection of the Acetal [(+)-117b] and Preparation of the Optically-Enriched Diol [(-)-118]

Direct determination of the enantiomeric purity of the recrystallized acetal **117b** was not feasible, as its two enantiomers failed to resolve completely on an analytical chiral HPLC column (Daicel Chiracel OD column). Thus the acetonide was converted to the its 3-pentanone-acetal analogue by a two-step process. Deprotection of the acetal (+)-**117b** was achieved on heating it in 1,2-dimethoxyethane with aqueous hydrochloric acid (2M).[152] This afforded the enantiomerically enriched starting diol (-)-**118** which was isolated by flash chromatography as a white solid (m.p. 133-134 ˚C) in 98% yield

* In this instance the signals corresponding to *H*-7$_\alpha$ and *H*-7$_\beta$ are unresolved. Thus, this pair of signals is referred to as *H*-7$_{\alpha,\beta}$

(Scheme 2.4.3.1). A portion of this material was subsequently condensed with 3-pentanone and the resultant acetal was found to have an enantiomeric purity of 97% ee by chiral HPLC analysis. Thus, by inference it was determined that the acetonide (+)-**117b** had been optically enriched from 80% ee through the aforementioned recrystallization process to provide a pure product of high enantiomeric purity (97% ee).

Scheme 2.4.3.1: Deprotection of the Acetone-Derived Chiral Acetal [(+)-117b]



117b (-)-**118**, 97% ee

The improved optical purity and ease with which the acetal (+)-**117b** was separated from the positional isomer **148b** led to the use of this two-step process to provide a source of the highly optically and isomerically pure diol (-)-**118**. The use of this material would preclude the formation of isomeric byproducts in subsequent condensation reactions. Furthermore, higher yields of reductively-coupled bipyridines derived from a series of acetals of greater optical purity as less *meso*-byproduct would be formed.* In addition, the coupled bipyridines prepared from material that has an enantiomeric purity of 97% ee would be expected to form with > 99.95% ee.

The diol (-)-**118** had not been isolated in previous studies as it had been used directly in subsequent reactions. Thus, it was fully characterized at this point by spectroscopic methods and subjected to elemental analysis. The ^{1}H NMR spectrum displayed two broad doublets at δ = 4.31 and 3.12. These signals correspond to the

* See *Appendix I*, page 262.

hydrogen atoms of the two hydroxyl groups. In addition, the IR spectrum of the compound showed two broad bands at 3408 and 3343 cm^{-1} that again indicated the presence of the diol moiety. The mass spectrum for this compound displayed the expected isotopic molecular ion peaks at 200 and 202 *m/z* in a 3:1 ratio which correspond to M[^{35}Cl] + H and M[^{37}Cl] + H. This data allowed for the confident assignment of this compound as the diol (-)-**118**.

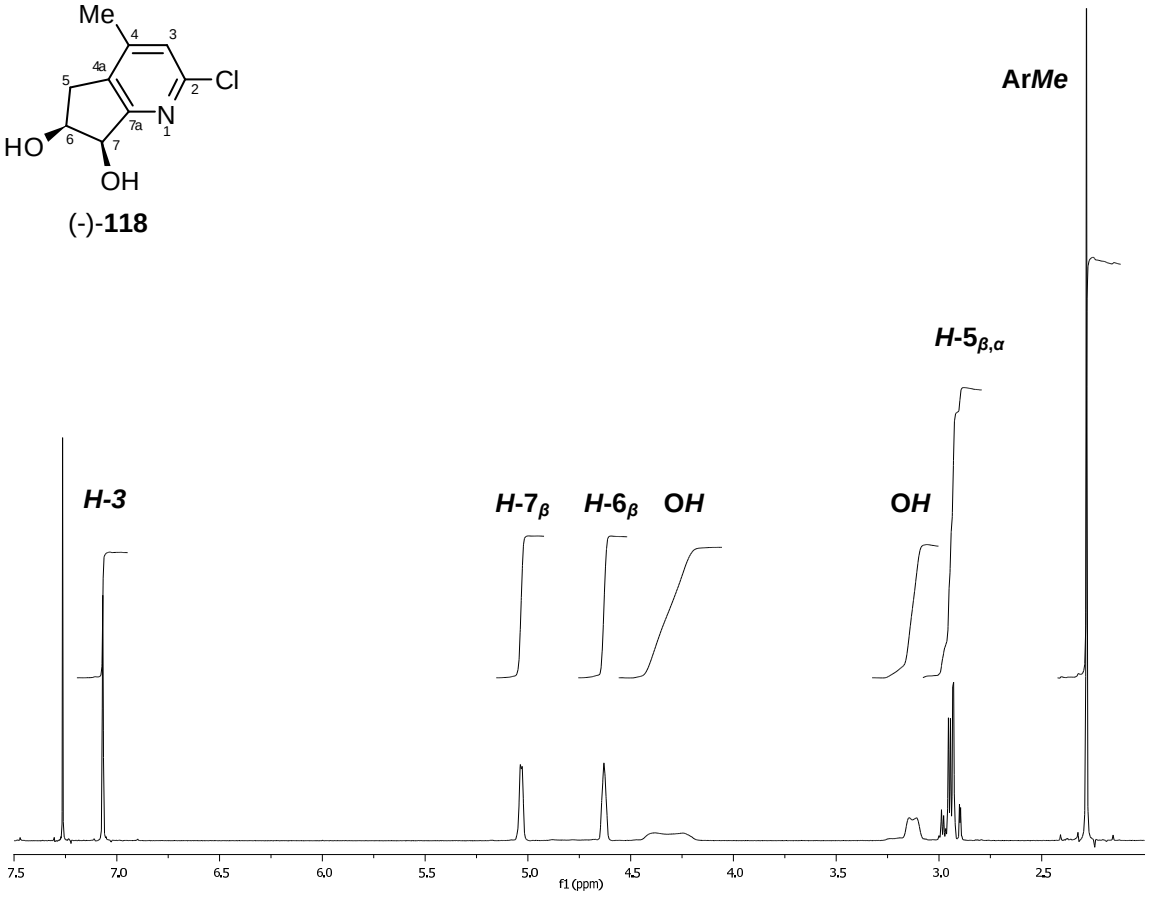


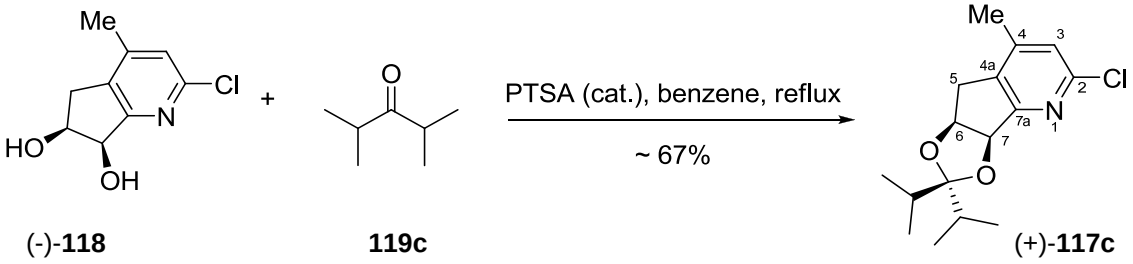
Figure 2.4.3.1: ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of the diol [(-)-118].

2.5 Synthesis of Sterically Encumbered Acetals (117c-g)

2.5.1 Condensation of Diisopropyl Ketone (119c) with the Diol [(-)-118]

It was envisioned that a more sterically encumbered analogue of the acetone-derived acetal (+)-**117b** could be accessed by condensation of diisopropyl ketone **119c** and the optically active diol (-)-**118** (Scheme 2.5.1.1). This condensation reaction was attempted by heating a mixture of this ketone and the diol in benzene at reflux, in the presence of *p*-toluenesulfonic acid monohydrate with azeotropic removal of water using a Dean-Stark trap. After twenty-four hours at reflux, the acetal **117c** was isolated in ~ 67% yield by flash chromatography. The ^{1}H NMR spectrum displayed the four expected doublets that corresponded to the four diastereotopic methyl groups of the isopropyl units, indicating that the desired product had been formed. However, closer inspection of the ^{1}H NMR spectrum of the material recovered from this reaction revealed the formation of an unidentified byproduct. Attempts were made to purify the material; however, the unidentified byproduct could not be separated by either column chromatography or recrystallization from various solvents and solvent mixtures.

Scheme 2.5.1.1: Condensation of Diisopropyl Ketone (119c) with the Diol [(-)-118] to Form Acetal [(+)-117c]

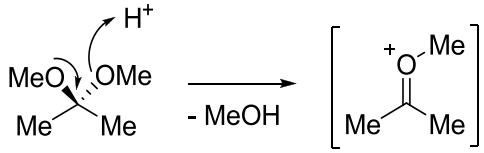


(-)-**118** **119c** (+)-**117c**

It was thus determined that an alternative method of generating this sterically encumbered acetal was required. To do this it was envisioned that a more reactive ketone equivalent was needed in order to react more readily with the diol (-)-**118**. A readily

accessible reactive ketone equivalent was used to generate an alkyl oxonium ion species had in fact been employed previously in the synthesis of the acetone-acetal (+)-**117b**. In this previous case, a dimethyl acetal (2,2'-dimethoxypropane) **154b** was subjected to acidic conditions in order to generate the methyl oxonium species **155b**. The mechanism of this reaction involves protonation and subsequent loss of one of the methoxy groups as methanol (Scheme 2.5.1.2).[153-155] The resultant reactive cation species then undergoes a condensation reaction with the diol (-)-**118** to form the desired acetal.

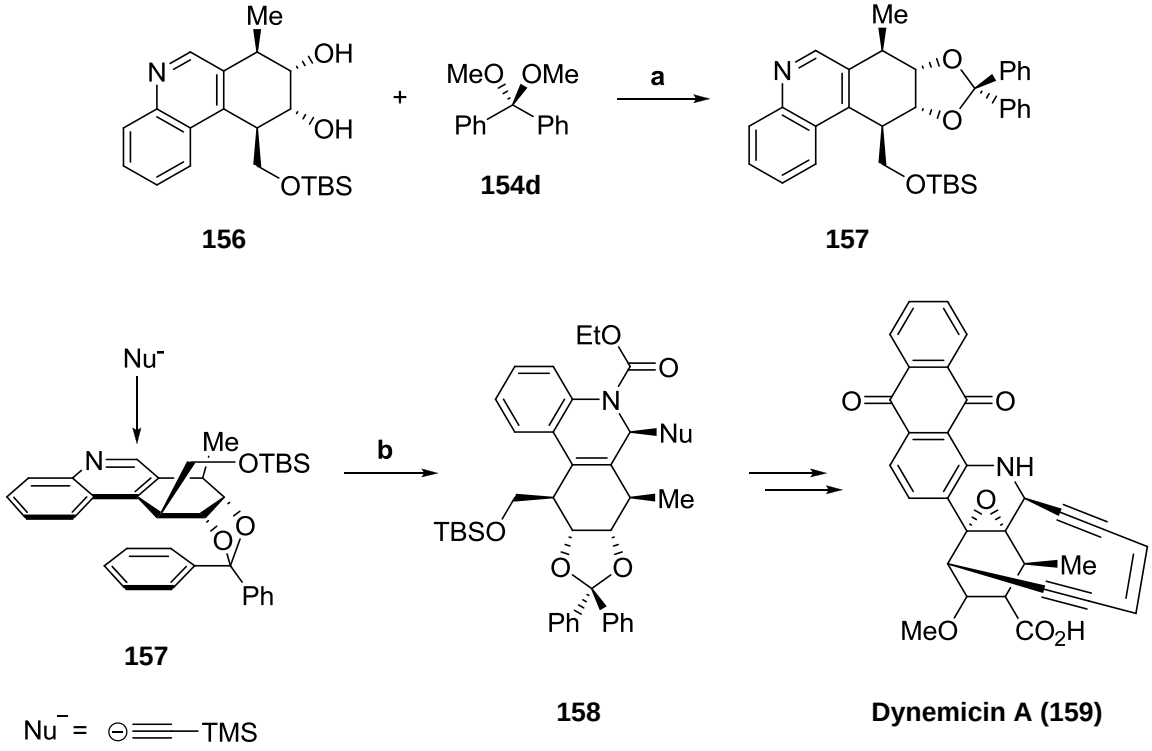
Scheme 2.5.1.2: Formation of a Reactive Oxonium Ion Species (155b) Under Acid-Catalyzed Conditions[156]



154b **155b**

The reactivity of the methyl oxonium cation was made use of by Danishefsky and co-workers in their pursuit of the total synthesis of dynemicin A **159**. As part of their synthetic strategy they had determined that a sterically large group was required to block one face of the pyridine **156** in order to effect a stereoselective ethynylation and subsequent carbamoylation reaction (Scheme 2.5.1.3). The bulky group chosen was a benzophenone acetal, which was installed by the condensation of the sterically encumbered diol **156** and benzophenone dimethyl acetal **154e** under acidic conditions in dichloromethane. This condensation reaction was found afford the acetal **157** in 90% yield, which was encouraging as diaryl ketones are the least reactive ketones towards acetal formation.[146-148] Furthermore, the bulk of this acetal was able to overcome the steric influence of the extremely cumbersome *tert*-butyldimethylsilyl group in directing the facial selectivity of a subsequent nucleophilic addition reaction.

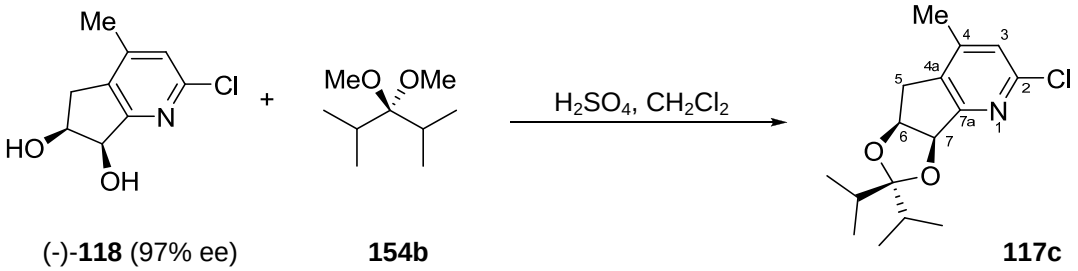
Scheme 2.5.1.3: Formation of The Benzophenone Acetal (157) and its Subsequent Transformation to the Carbamate (158)



Reagents and Conditions: (a) H_2SO_4 (1.1 equiv.), CH_2Cl_2, 40 ˚C, 2 h, 90%; (b) (triisopropylsilyl)acetylene, EtMgBr, THF, rt, 2 h; then - 78 ˚C, **157**, $ClCO_2CH_3$, - 20 ˚C, 20 h, 75%.

From consideration of the results achieved by Danishefsky, and those previously observed in the synthesis of acetal (+)-**117b**, we were confident that treatment of the dimethyl acetal **154b** with the optically active diol (-)-**118** under acid-catalyzed conditions would smoothly generate the sterically encumbered acetal **117c** (Scheme 2.5.1.4). Toward this end, the synthesis of the dimethyl acetal of diisopropyl ketone was pursued.

Scheme 2.5.1.4: Planned Synthesis of The Sterically Encumbered Acetal (117c)

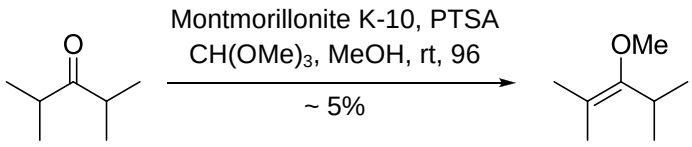


(-)-**118** (97% ee) **154b** **117c**

Recently, Regas and co-workers published a simple, high yielding and mild method for the conversion of ketones into their corresponding dimethoxy and diethoxy acetals.[146] This process involves the treatment of a ketone with trimethyl orthoformate in the presence of catalytic amount of *p*-toluenesulfonic acid monohydrate and Montmorillonite K-10 clay in methanol. Their results showed near-quantitative transformations for unreactive ketones such as benzophenone **154d**, 1,3-diphenylacetone **154e** and fluorenone **154f**. Thus, diisopropyl ketone **119c** was subjected to these reaction conditions (Scheme 2.5.1.5). After three days of reaction, analysis of the crude reaction mixture by ^{1}H NMR spectroscopy showed that a product to starting material ratio of roughly 3:1 had been established. However, upon workup and vacuum distillation, no dimethyl acetal product was isolated. What was collected was a mixture (1:5.3*) of diisopropyl ketone **119c** and its corresponding methyl enolether **160** in ~ 5% yield.

* This ratio was determined by ^{1}H NMR spectroscopy.

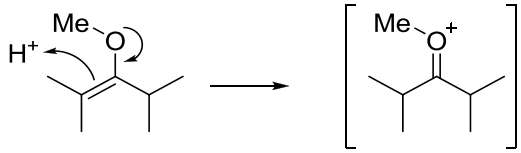
Scheme 2.5.1.5: Synthesis of the Methyl Enolether (160) of Diisopropyl Ketone (119c)



119c **160**

It was presumed that the vinyl ether **160**, *in lieu* of the corresponding dimethyl acetal, would function adequately as a condensation partner with the diol (-)-**118** under acidic conditions. This is because the methyl enolether **160** is also a synthetic equivalent of the desired reactive species: the oxonium **155c** (Scheme 2.5.1.6). The low yield of the conversion was acceptable as only a small amount of ketone equivalent was needed and that diisopropyl ketone is readily available and inexpensive.

Scheme 2.5.1.6: Formation of a Reactive Oxonium Ion Species (155c) From the Enolether (160) Under Acid-Catalyzed Conditions



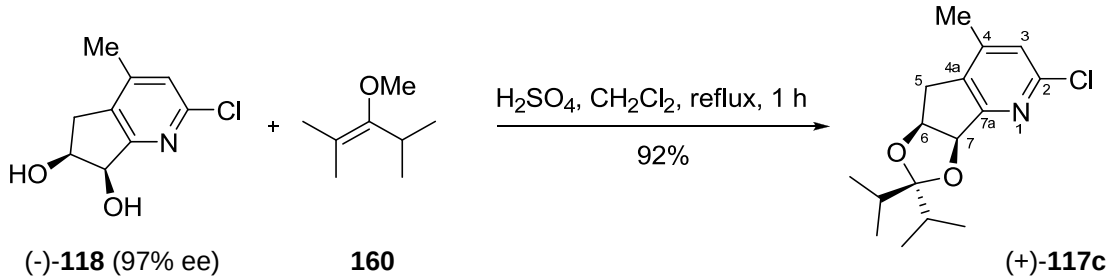
160 **155c**

In accordance to Danishefsky's condensation procedure, a stock solution of concentrated sulphuric acid in dichloromethane (1 g H_2SO_4/100 mL CH_2Cl_2) was prepared and used as the solvent for the proposed condensation reaction (Scheme 2.5.1.7).* To eleven millilitres of this stock solution was added 2.00 mmol of the optically pure diol (-)-**118**, followed by dropwise addition of a solution of ~ 2.10 mmol of the methyl enolether in one millilitre of dichloromethane, and the resultant solution heated at reflux. The product of this reaction was readily purified by column

* In a separate experiment, concentrated sulphuric acid was added directly to the reaction mixture as an acid-catalyst.. However, this yielded poor results. Thus, it was determined that this stock solution was necessary in order to obtain optimal results.

chromatography to afford the acetal (+)-**117c** as a white solid (m.p. 116-117 ˚C) in 92% yield.

Scheme 2.5.1.7: Condensation of the Methyl Enolether (160) with the Optically Active Diol [(-)-118] to Form Acetal (117c)



(-)-**118** (97% ee) **160** (+)-**117c**

The ^{1}H NMR spectrum of the major product of this reaction displayed the four expected doublets that corresponded to the four diastereotopic methyl groups of the isopropyl units (Scheme 2.5.1.1). These doublets clustered into two sets, each integrated to six protons. The two more upfield signals, observed at δ = 0.53 and 0.55 ppm and due to anisotropic shielding from the pyridyl ring, can be assigned to the two methyl groups on the concave face of the acetal moiety. The two downfield signals, observed at δ = 0.98 and 0.99 ppm, can conversely be assigned to the methyl groups on the convex face of the acetal. The ^{1}H NMR spectrum also displayed two expected multiplets at δ = 5.1 and 5.5 ppm that correspond to the protons, *H*-6$_{\beta}$ and *H*-7$_{\beta}$. The mass spectrum of this material displayed the isotopic molecular ion peaks at 296 and 298 *m/z* in a 3:1 ratio which correspond to the mass of the protonated chloropyridine **117c**, M[^{35}Cl] + H and M[^{37}Cl] + H. Moreover, elemental analysis by combustion of this compound indicated that the carbon, nitrogen and hydrogen compositions were within 0.19% of their calculated values. This combined data firmly supports the formation of the desired acetal.

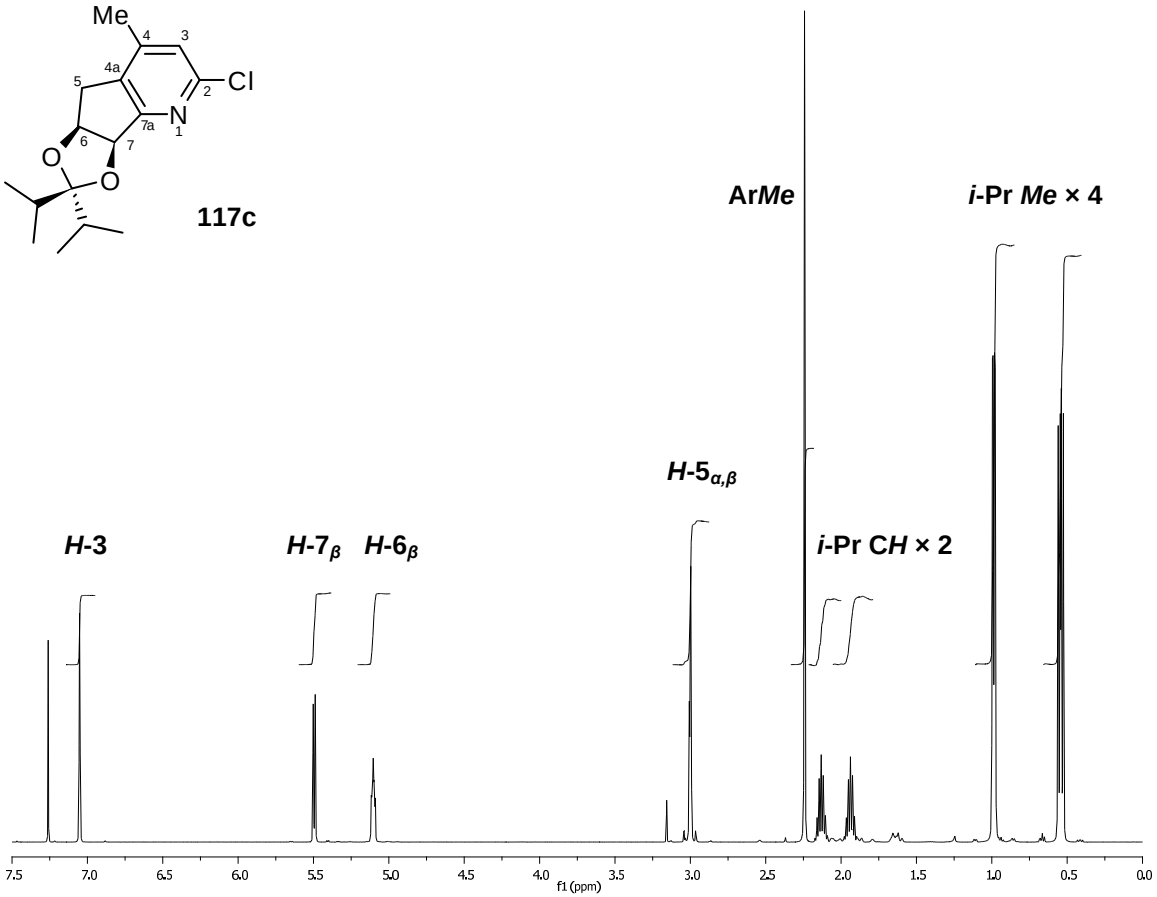


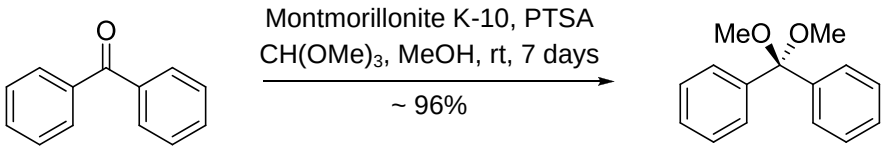
Figure 2.5.1.1: ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of the acetal (117c).

2.5.2 Synthesis of the Benzophenone Dimethyl Acetal (154d) and its Condensation Reaction with the Chiral Diol [(-)-118]

Although the conditions presented by Regas and co-workers were not effective in generating the dimethyl acetal of diisopropyl ketone, they had reported exceptional results with benzophenone **119d**.[146] Thus, benzophenone was subjected to these conditions for one week after which the corresponding dimethyl acetal **154d** was isolated on filtration of the reaction mixture to afford the crude product in ~ 96% yield (Scheme 2.5.2.1). Analysis by ^{1}H NMR spectroscopy showed the crude product to be pure dimethyl acetal **154d**. In addition, the NMR data of this compound was in agreement with that published in literature.[146] The simplicity and high yield of this dimethyl acetal

forming reaction prompted the use of this standard procedure for the synthesis of related compounds that are described in the following sections.

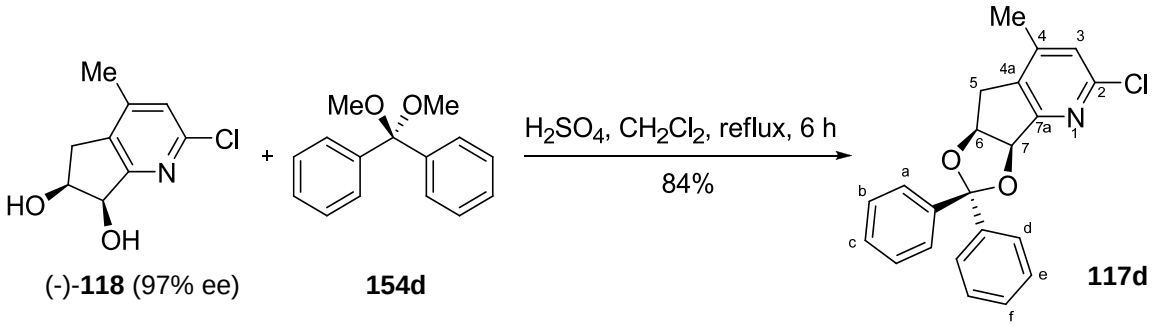
Scheme 2.5.2.1: Formation of the Benzophenone Dimethyl Acetal (154d)



119d **154d**

Following Danishefsky's procedure; a stock solution of concentrated sulphuric acid in dichloromethane (1g H_2SO_4/100 ML CH_2Cl_2) was prepared and used as the solvent for the condensation reaction of the above acetal with the diol (-)-118 (Scheme 2.5.2.2). Thus, to sixteen millilitres of this stock solution was added 1.25 mmol of the optically pure diol (-)-**118** followed by dropwise addition of a solution of ~ 1.26 mmol of the dimethyl acetal **154d** in two millilitres of dichloromethane. The product of this reaction was readily purified by column chromatography to afford the acetal **117d** as a colourless solid (m.p. 156-157 ˚C) in 84% yield (Scheme 2.6.9). The efficient formation of this acetal is notable, as benzophenone is typically unreactive towards acetal formation. Thus, the conditions employed in this condensation reaction were used as the standard acetal forming procedure for the remaining target acetals **155e-g**.

Scheme 2.5.2.2: Condensation of the Benzophenone Dimethyl Acetal (154d) and the Optically Active Diol [(-)-118] to Form Acetal (117d)



(-)-**118** (97% ee) **154d** **117d**

The acetal **117d** was fully characterized by spectroscopic methods. Characteriztic data acquired for this compound included the presence of resonances corresponding to the aromatic hydrogen atoms of phenyl moieties, observed from δ = 7.15 – 7.67 ppm, in its ^{1}H NMR spectrum (Figure 2.5.2.1). Notably, the resonances corresponding to *H*-5$_{\beta}$ and *H*-5$_{\alpha}$ were found at δ = 3.07 and 3.15 respectively. This is opposite to the position of the chemical resonances that are observed in the ^{1}H NMR spectrum of **117b** and is also counter to the position of the chemical shifts of that are assigned for other chiral acetals synthesized in during the course of this study. In the present case, this is due to anisotropic deshielding of *H*-5$_{\alpha}$ by the phenyl group on the concave face of the acetal. The mass spectrum of this compound showed molecular ion peaks at 364 and 366 *m/z* in a 3:1 ratio corresponding to M[^{35}Cl] + H and M[^{37}Cl] + H. The compound was found to be unamenable towards elemental analysis, even when using V_2O_5 as an oxidative propellant, and so it was subjected to high resolution mass spectroscopy. This found the exact mass of the protonated molecule (M[^{35}Cl] + H) was 364.1096 *m/z* which is within 2 ppm of the calculated value.

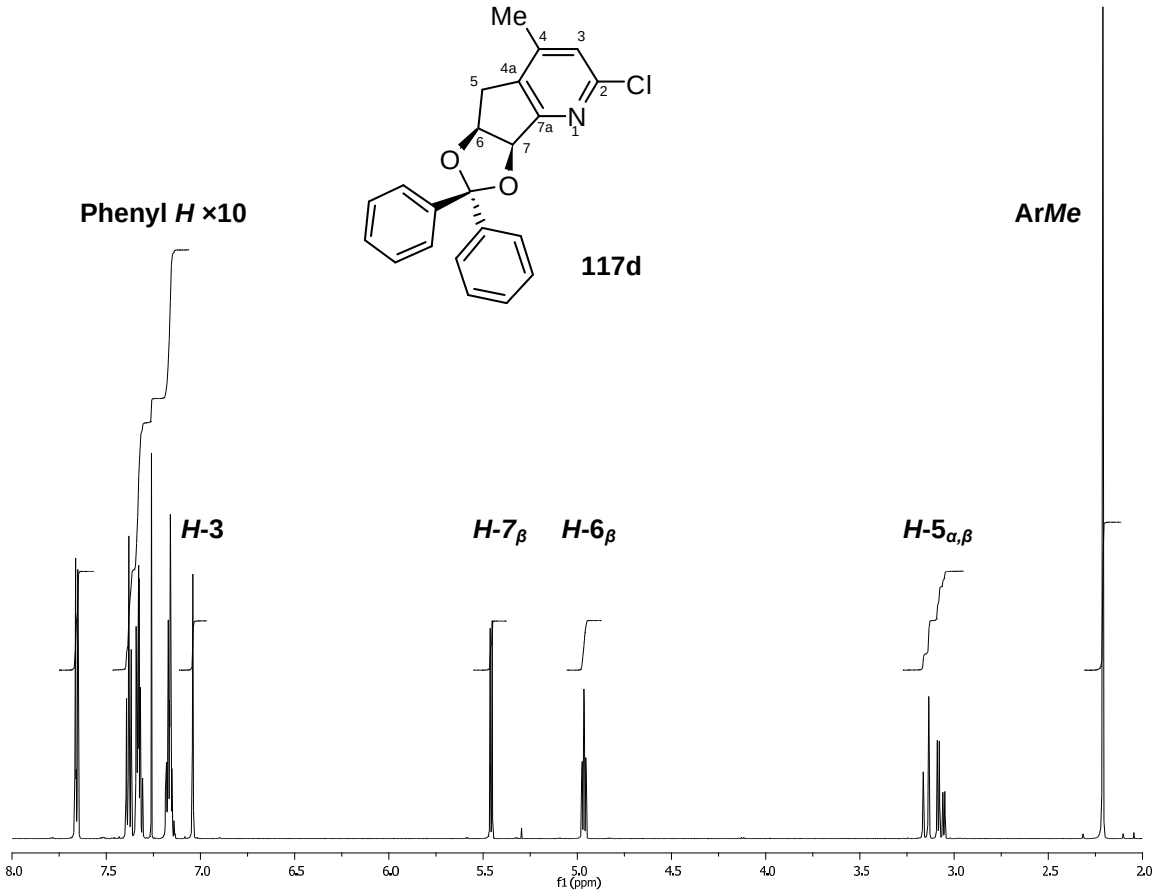
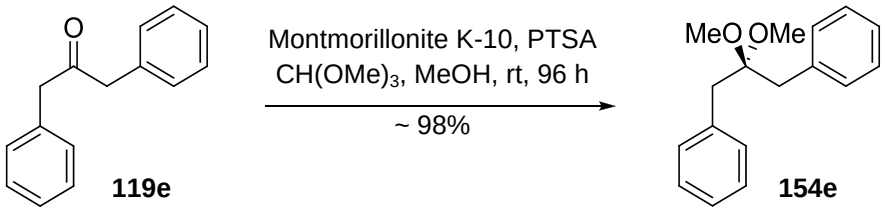


Figure 2.5.2.1: ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of the acetal (117d).

2.5.3 Synthesis of the 1,3-Diphenylacetone Dimethyl Acetal (154e) and its Condensation Reactions with the Chiral Diol [(-)-118]

The dimethyl acetal **154e** was[42,131] synthesized using the standard dimethyl acetal formation procedure (Scheme 2.5.3.1) and was isolated in 98% yield, on filtration and concentration of the reaction mixture. The material was in pure form as indicated by its ^{1}H NMR spectrum.[146]

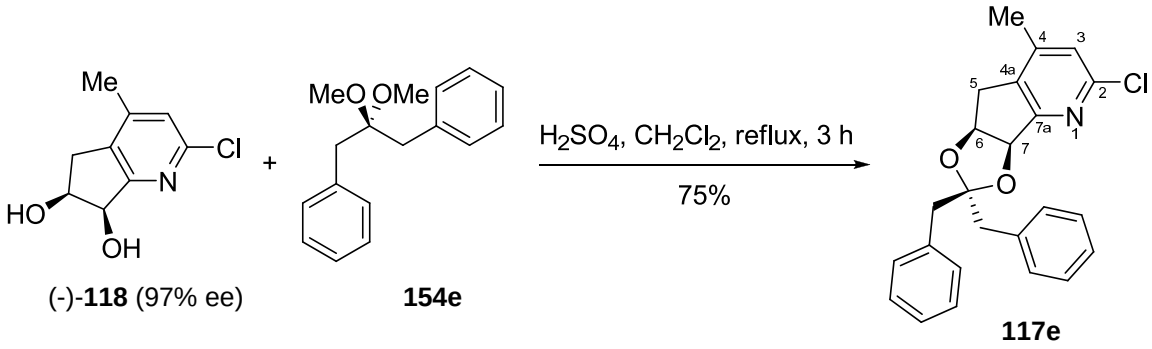
Scheme 2.5.3.1: Formation of the 1,3-Diphenylacetone Dimethyl Acetal (154e)



119e **154e**

To perform the condensation of the dimethyl acetal **154e** and the optically active diol (-)-**118**, the standard condensation conditions were employed. The product was readily purified by flash chromatography to afford the acetal **117e** as a white solid (m.p. 113-114 ˚C) in 75% yield (Scheme 2.5.3.2).

Scheme 2.5.3.2: Condensation Reaction of the 1,3-Diphenylacetone Dimethyl Acetal (154e) and the Optically Active Diol [(-)-118] to form Acetal (117e)



(-)-**118** (97% ee) **154e** **117e**

The product of the above reaction was fully characterized by spectroscopic means. Most notably, the ^{1}H NMR spectrum of this compound showed two pairs of doublets between δ = 2.8 and 3.1 ppm that corresponded to the individual protons of the diastereotopic methylene subunits of the 1,3-diphenylacetone moiety (Figure 2.5.3.1). Once again, the more upfield of these pairs of doublets can be assigned to the methylene unit of the benzyl moiety on the concave face of this molecule. In addition, the resonances that correspond to the diastereotopic protons of the methylene unit of the cyclopentyl moiety were well-resolved. Anisotropic shielding by the benzyl ring located

on the concave face of the molecule caused the proton *H*-5$_\alpha$ to be observed as a doublet at δ = 2.35. The proton, *H*-5$_\beta$, appeared as a doublet of doublets at δ = 2.52. The mass spectrum of this compound also showed the expected molecular ion peaks at 392 and 394 *m/z* in a 3:1 ratio corresponding to M[^{35}Cl] + H and M[^{37}Cl] + H.

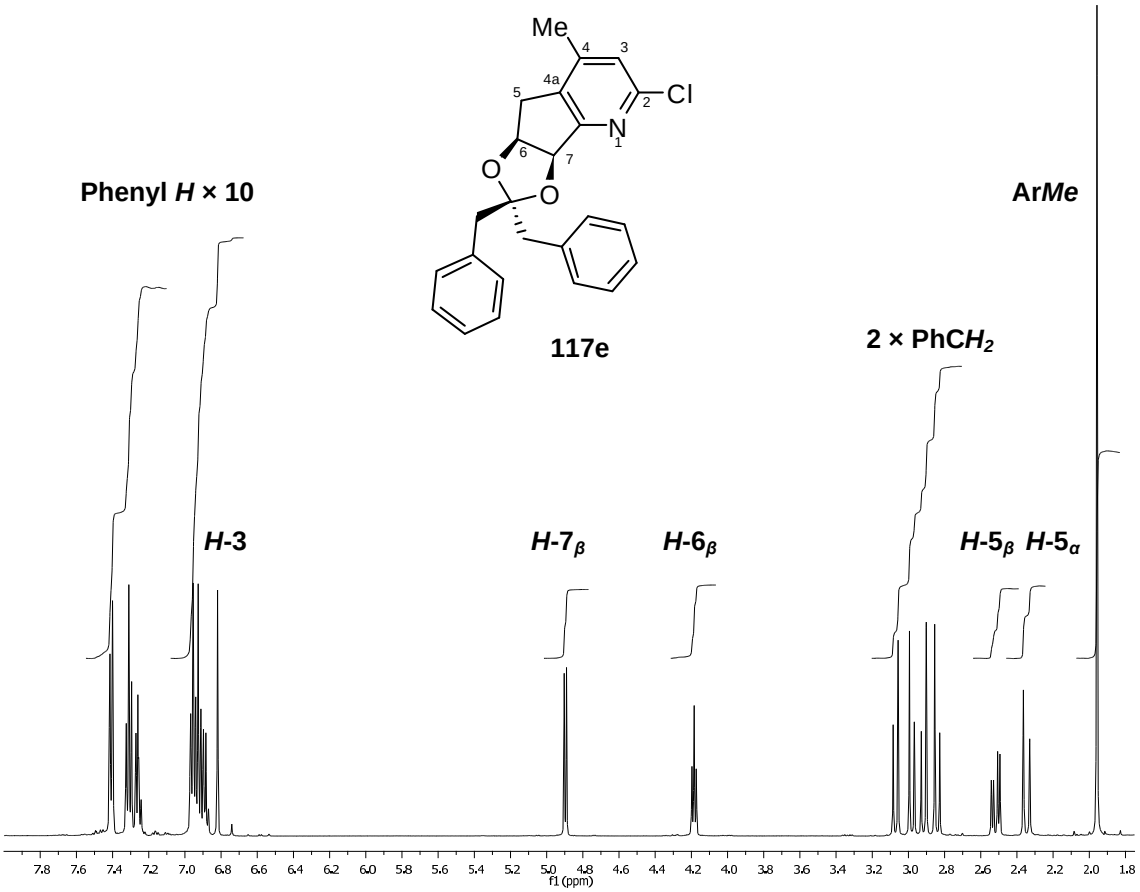
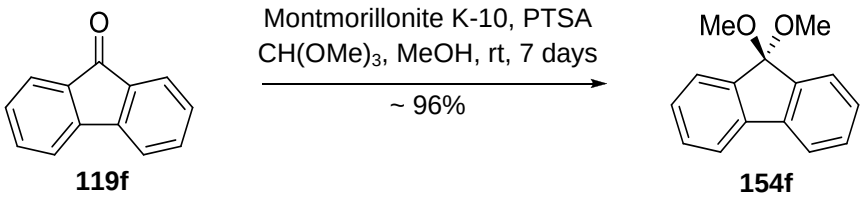


Figure 2.5.3.1: ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of the acetal (117e).

2.5.4 Synthesis of the Fluorenone Dimethyl Acetal (154f) and its Condensation Reaction with the Chiral Diol [(-)-118]

Fluorenone **119f** was converted to its corresponding dimethyl acetal **154f** using the standard dimethyl acetal formation procedure (Scheme 2.5.4.1).[146] The dimethyl acetal **154f** was isolated in 96% yield on filtration and concentration of the reaction mixture. The ^{1}H NMR spectrum of the crude product showed it to be pure, which is in agreement to that reported in the literature.[146]

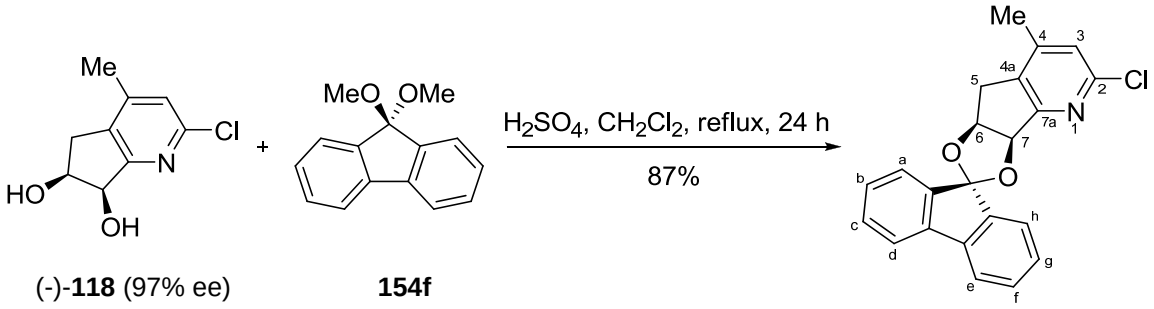
Scheme 2.5.4.1: Formation of the Fluorenone Dimethyl Acetal (154f)



119f **154f**

To perform the condensation of the dimethyl acetal **154f** and the optically active diol (-)-**118**, the standard condensation procedure was employed (Scheme 2.5.4.2). The product of this reaction was readily purified by flash chromatography to afford the acetal **117f** as a white solid (m.p. 254-255 ˚C) in 87% yield.

Scheme 2.5.4.2: Condensation Reaction of the Fluorenone Dimethyl Acetal (154f) and the Optically Active Diol [(-)-118] to Form Acetal (117f)



(-)-**118** (97% ee) **154f** (+)-**117f**

The above compound was fully characterized by spectroscopic means. Notably, the ^{1}H NMR spectrum of this compound **117f** displayed seven sets of well-resolved resonances between δ = 6.5 - 7.6 ppm corresponding to the eight aromatic hydrogen atoms present on the fluorenone moiety and the hydrogen atom of the pyridine ring (Figure 2.5.4.1). The resolution of these resonances is remarkable and can be attributed to anisotropic shielding due to the fluorene moiety being positioned over the pyridine ring. This shielding effect is most pronounced for the resonance that corresponds to H_a,

which is ~ 1 ppm upfield from H_h. In order to investigate these aryl resonances, a gCOSY experiment was performed (Figure 2.5.4.2).

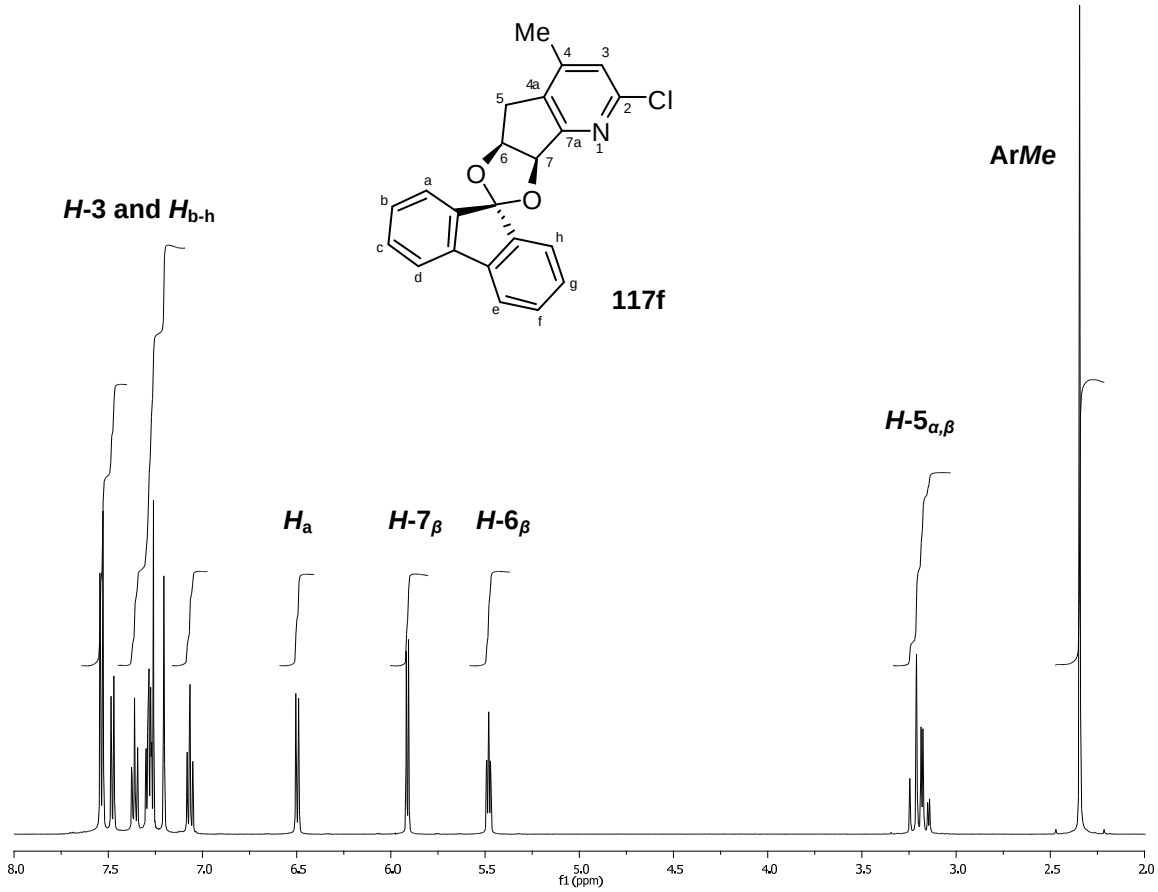


Figure 2.5.4.1: ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of the acetal [(+)-117f].

The proton, H_a, was assigned as the doublet at δ = 6.5 ppm as it was the most shielded fluorenyl signal found in the spectrum. On inspection of the molecule it can be seen that this atom is positioned over the pyridyl ring and thus experiences a large amount of anisotropic shielding. Using this assignment, resonances $H_{b\text{-}d}$ were unambiguously determined by COSY correlations (Figure 2.5.4.2). The proton H_h was assigned to the most downfield signal, a multiplet that integrated to two protons. Accordingly, the protons $H_{e\text{-}g}$ were then assigned in relation to proton H_h using COSY correlations.

In addition to the shielding effects exerted upon the fluorene moiety by the pyridyl ring, anisotropic deshielding caused by the fluorene moiety on the pyridine-diol moiety is observed. The resonances corresponding to *H*-6_β and *H*-7_β are observed one ppm downfield of where they are found in the ^{1}H NMR spectrum of the fluorenone acetal **117e**, and roughly half a ppm downfield from where they are typically seen in the ^{1}H NMR spectra of the other acetals which were synthesized from the diol (-)-**118**. In addition to these interesting anisotropic effects, the melting point of this compound was almost one hundred degrees higher than that of the benzophenone acetal **117d**, a compound which in terms of molecular mass varies from the fluorenone acetal **117e** by only two hydrogen atoms.. The mass spectrum of this compound showed molecular ion peaks at 362 and 364 *m/z* in a 3:1 ratio corresponding to M[^{35}Cl] + H and M[^{37}Cl] + H. These combined data allowed for confident assignment of the molecular structure of this compound.

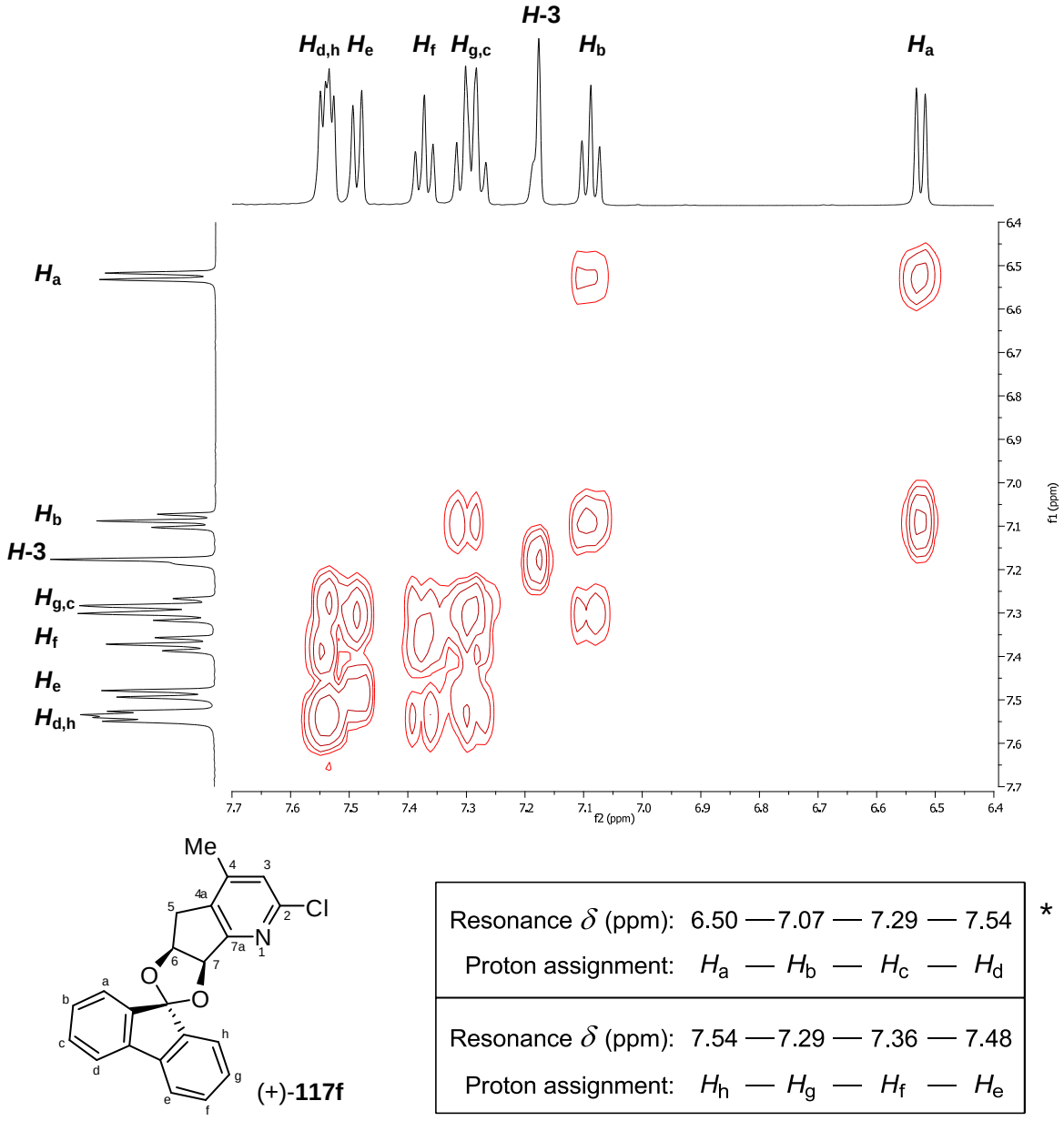


Figure 2.5.4.2: *g*COSY spectrum (500 MHz, $CDCl_3$) of the acetal [(+)-117f].

2.5.5 Synthesis of the Adamantanone Dimethyl Acetal (154g) and its Condensation Reaction with the Chiral Diol [(-)-118]

Adamantanone **119g** was converted to its corresponding dimethyl acetal **154g** using the standard dimethyl acetal formation procedure (Scheme 2.5.5.1). The dimethyl

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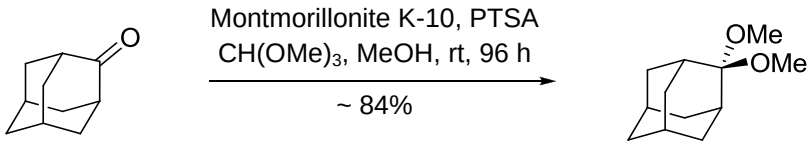
* The numbers in this figure represent the chemical shift of individual proton resonances. An interaction observed between any two proton resonances is represented by a line connecting them. Under each set of COSY interactions is a diagram depicting the assignment of individual protons.

acetal **154g** was isolated in 77% yield, on filtration and concentration of the reaction mixture. Analysis of the crude product by ^{1}H NMR spectroscopy showed it to be a mixture of the desired dimethyl acetal **154g** and adamantanone **119g** (23:2).

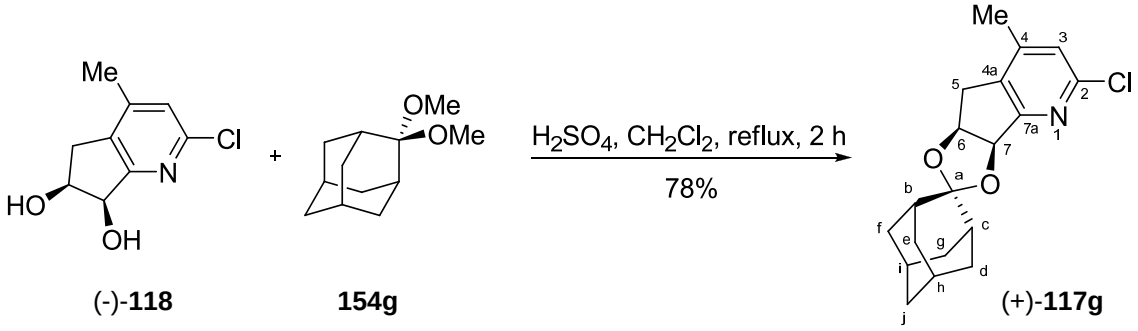
Scheme 2.5.5.1: Formation of the Adamantanone Dimethyl Acetal (154g)



119g **154g**

The acetal **117g** was synthesized using the standard conditions. Through flash chromatography the product was obtained as a mixture with adamantanone **119g**.* This mixture was recrystallized from heptanes, which afforded the acetal **117g** as granular crystals (m.p. 163-164 ˚C) in 78% yield (Scheme 2.5.5.2).

Scheme 2.5.5.2: Condensation Reaction of the Adamantanone Dimethyl Acetal (154g) and the Optically Active Diol [(-)-118] to Form Acetal (117g)



(-)-**118** **154g** (+)-**117g**

The product of this condensation reaction was identified as **117g** on analysis of a series of key resonances in the alkyl region of its ^{1}H NMR spectrum that integrated to

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* Adamantanone is UV inactive as well as resistant to staining on thin layer chromatography plates, the stains employed were $KMnO_4$ and anisaldehyde. However, adamantanone did stain to a small degree upon exposure to iodine after extended periods of time, revealing it had a close R_f to the desired product. Thus, it was difficult to separate the excess adamantanone from the desired acetal by flash chromatography.

fourteen protons (Figure 2.5.5.1). These resonances correspond to the adamantyl protons of compound **117g**, and of note it was possible to fully assign the ^{1}H NMR spectrum of the bipyridine **1g** derived from this product (Section 2.6.7, pages 134-139). The mass spectrum of this compound also showed molecular ion peaks at 332 and 334 *m/z* in a 3:1 ratio corresponding to M[^{35}Cl] + H and M[^{37}Cl] + H.

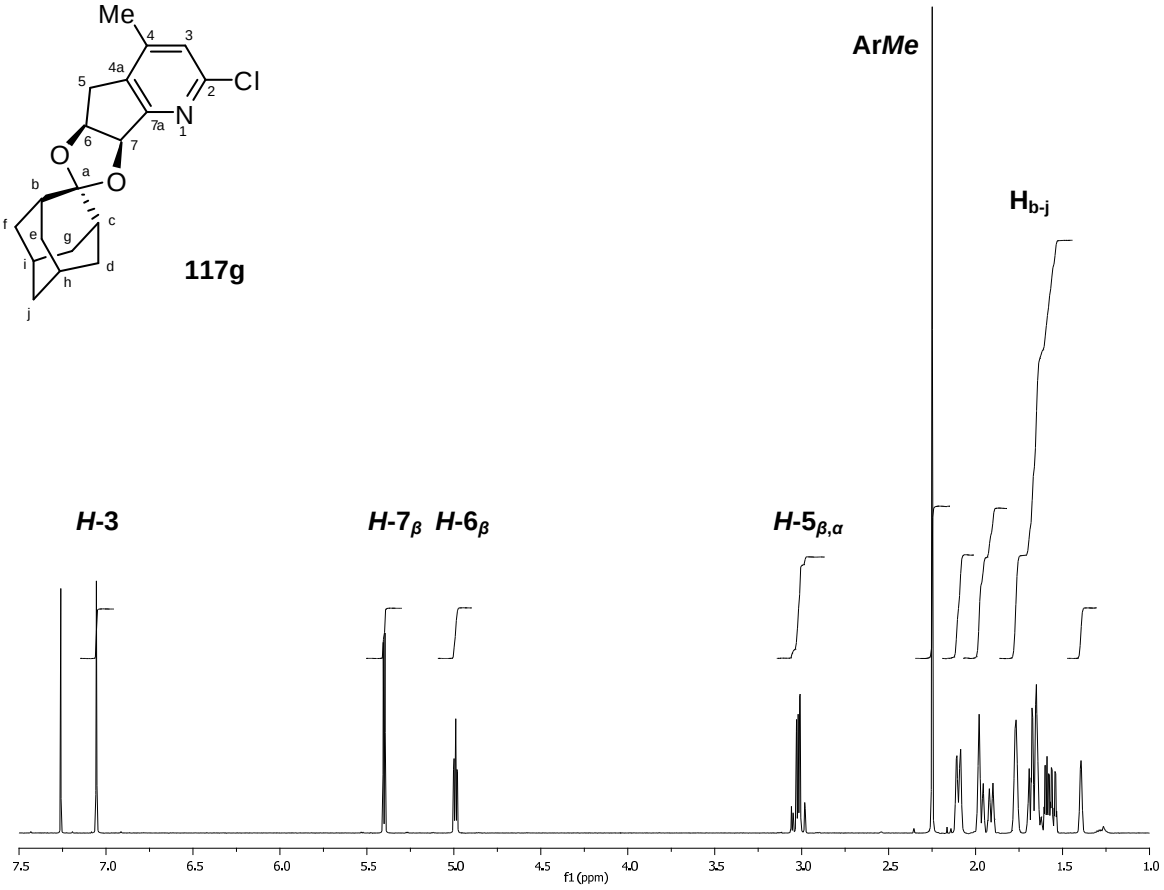


Figure 2.5.5.1: ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of the acetal [(+)-117g].

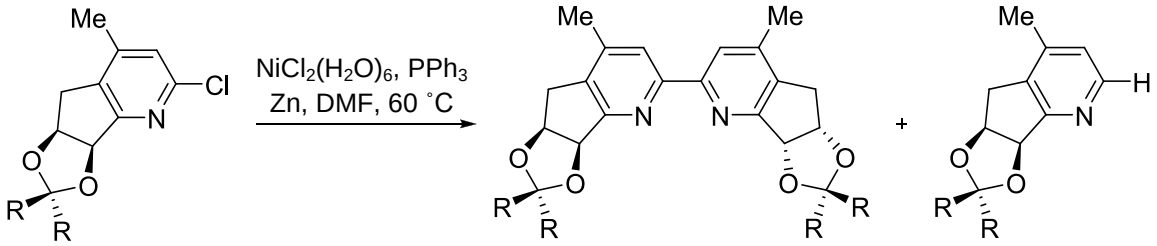
2.6 Synthesis of the 2,2'-Bipyridines (1b-g)

2.6.1 Section Overview

The series of new chiral nonracemic C_2-symmetric 2,2'-bipyridines **1b-g** was synthesized by the reductive-coupling of each of the chloropyridines **117b-g**. The coupling reactions were performed using a nickel(0) catalyst which was prepared *in situ*

on the reduction of nickel(II) hexahydrate with zinc dust in the presence of triphenylphosphine in *N*,*N*-dimethylformamide at 60 ˚C (Scheme 2.6.1.1).[141]

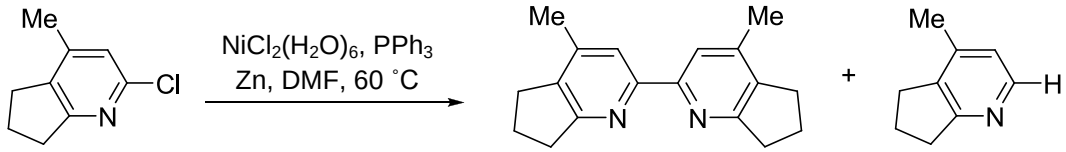
Scheme 2.6.1.1: Reductive-Coupling of the Acetals (117a-g) to Form Their Corresponding 2,2'-Bipyridines (1a-g) and the Anticipated Dehalogenated-Byproducts (153a-g)



117a-g **1a-g** **153a-g**

In addition to the chiral 2,2'-bipyridines **1b-g**, the achiral 2,2'-bipyridine **161** which contained the 2*H*-dihydropyrindene skeleton was also synthesized (Scheme 2.6.1.2). This related achiral compound could be used examine the effect of the bipyrindene motif on the diastereomeric outcome of the proposed cyclopropanation reactions that are discussed in *Chapter* 3.

Scheme 2.6.1.2: Reductive-Coupling of the Chloropyridine (99) to Form the Corresponding 2,2'-Bipyridine (161) and the anticipated Dehalogenated-Byproduct (162)



99 **161** **162**

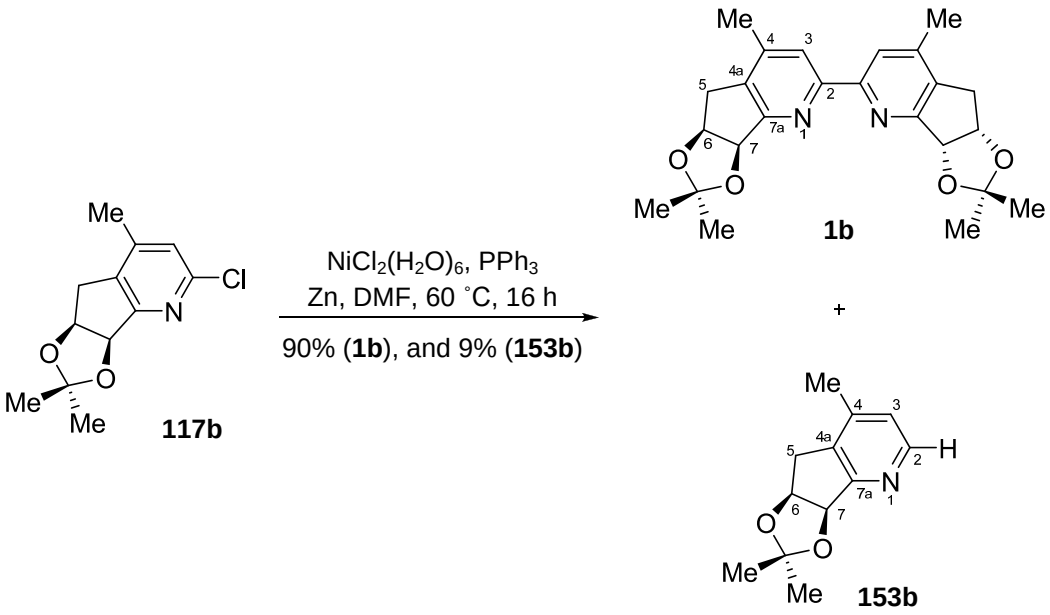
All of the coupling reactions provided both a 2,2'-bipyridine and a reductively-dehalogenated-byproduct. The high optical purity of the starting materials resulted in generation of only minimal quantities of *meso*-byproducts (which was calculated to be a maximum of 3% overall yield). Accordingly it was not possible to isolate any *meso*-compounds from coupling reactions of the chiral acetals **117a-g**. The 2,2'-bipyridine

products could be readily identified using their ^{1}H NMR spectra which all displayed a highly deshielded singlet slightly above 8 ppm. This signal corresponded to the equivalent *H*-3 and *H*-3' protons of the 2,2'-bipyridine. Reductively-dehalogenated-products of these reactions showed two doublets in the aromatic region of their ^{1}H NMR spectra corresponding to the *H*-2 and *H*-3 protons. In the following subsections, each coupling reaction and the characterization of the products is discussed in greater detail.

2.6.2 Reductive-Coupling of the Chloropyridine (117b) to Form the Corresponding 2,2'-Bipyridine (1b) and the Dehalogenated-Byproduct (153b)

When the acetone-derived chloropyridine **117b** was subjected to the standard reductive-coupling conditions, the 2,2'-bipyridine **1b** and pyridine byproduct **153b** were isolated in 90% and 9% yield, respectively, by flash chromatography (Scheme 2.6.2.1).

Scheme 2.6.2.1: Reductive-Coupling of the Chloropyridine (117b) to Form the Corresponding 2,2'-Bipyridine (1b) and the Dehalogenated-Byproduct (153b)



The 2,2'-bipyridine **1b** was fully characterized by spectroscopic methods. Notably, the presence of a downfield singlet δ = 8.35 ppm was evident in the ^{1}H NMR spectrum which corresponds to the equivalent *H*-3 and *H*-3' protons (Figure 2.6.2.1).* Two upfield diastereotopic methyl groups of the acetal moiety were observed as singlets at δ = 1.31 and 1.46 ppm. The ^{13}C NMR spectrum contained twelve peaks, this is in accordance with the twelve sets of equivalent carbon atoms in the molecule. In addition,

* Each signal in the ^{1}H NMR spectrum of this compound represents two symmetric sets of hydrogen atoms, as do all spectra of C_2 symmetric 2,2'-bipyridines in this thesis.

the mass spectrum of this compound displayed the expected protonated molecular ion peak for the expected reductively-coupled product at 409 *m/z* (M + H).

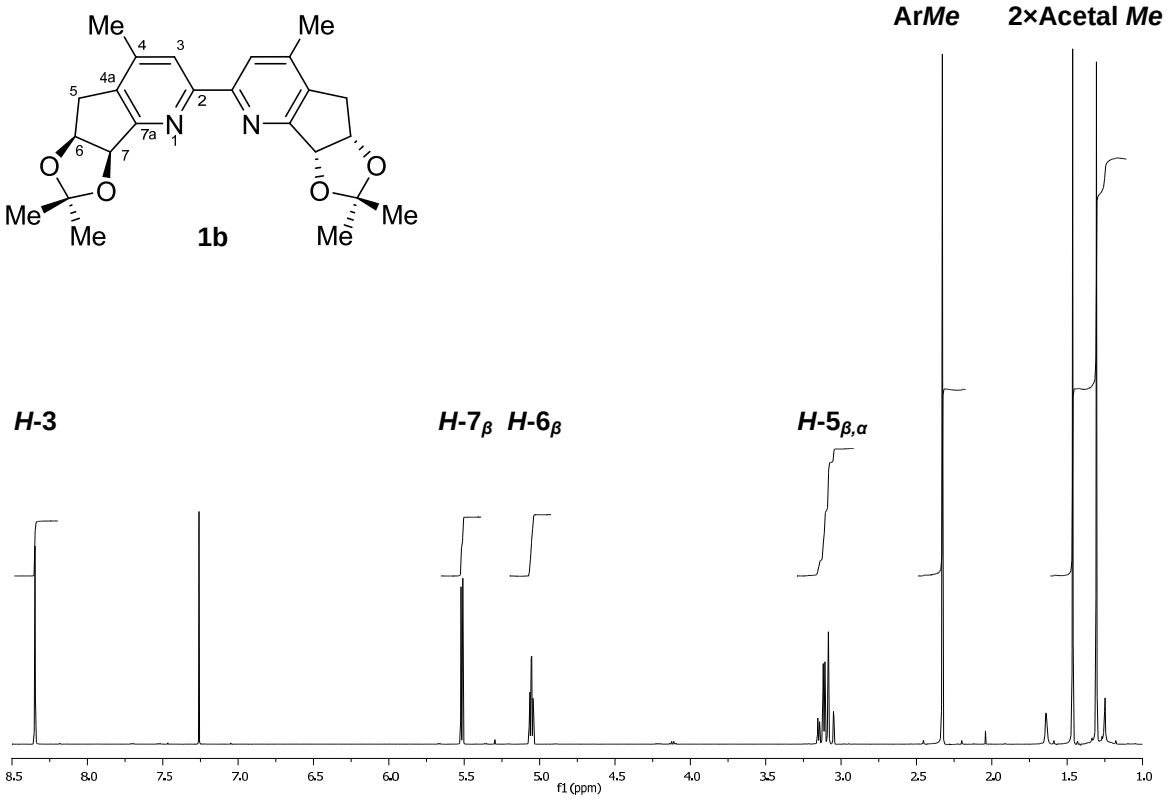


Figure 2.6.2.1: ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of the chiral nonracemic C_2-symmetric 2,2'-bipyridine (1b).

In order to appreciate the three-dimensional nature of the series of 2,2'-bipyridines synthesized in this thesis, a computer program was used to model these compounds.[145] In the case of the acetone-derived 2,2'-bipyridine **1b**, the model shows a lack of steric congestion about the *N*,*N*'-bipyridine binding site (Figure 2.6.2.2). This is in comparison with the model of the 3-pentanone-derived 2,2'-bipyridine **1a** (Figure 2.3.3.2, page 81). In addition to the lack of relative steric congestion, the acetal moiety is rigid, unlike that of the 2,2'-bipyridine **1a**.

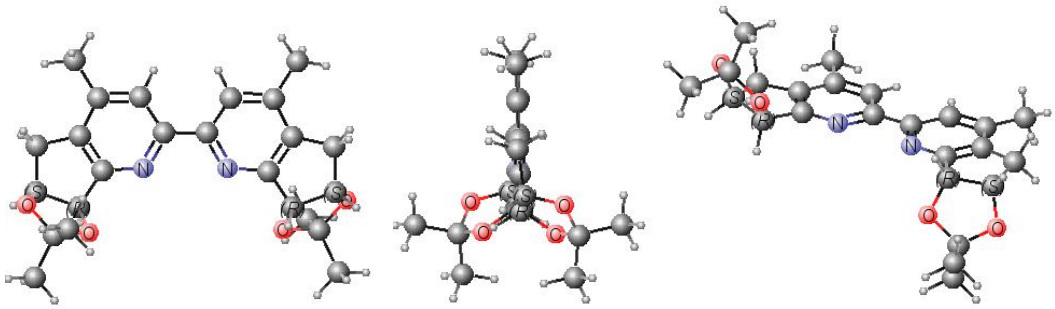


Figure 2.6.2.2: A 3D representation of the 2,2'-bipyridine (1b) viewed from three different perspectives.

The structure of the pyridine **153b**, a reductively-dehalogenated-product, was determined from the presence of two doublets in the aromatic region at δ = 7.01 and 8.40 ppm of its ^{1}H NMR spectrum (Figure 2.6.2.3). These signals correspond to the *H*-3 and *H*-2 protons, respectively, of the pyridine ring. Not surprisingly, the other spectrographic data obtained for this compound were quite similar to that of the 2,2'-bipyridine **1b**. However, the mass spectrum displayed the expected protonated molecular ion peak at 206 *m/z* (M + H).

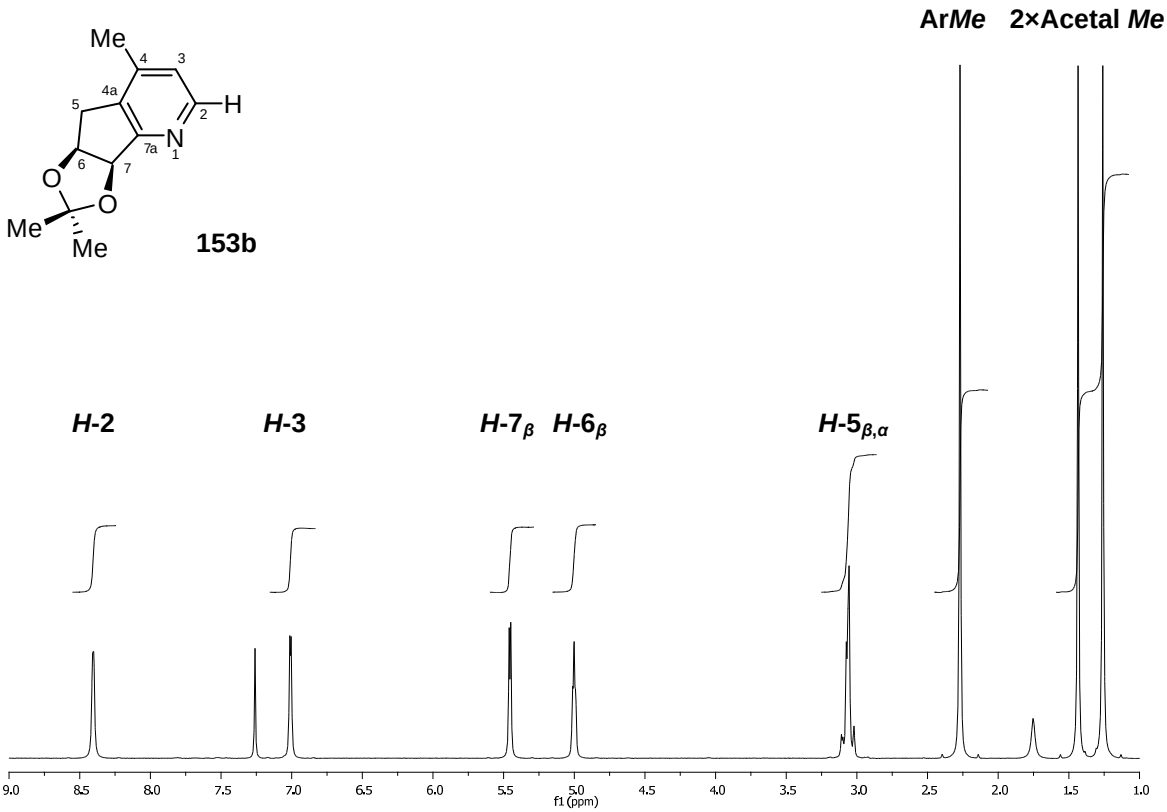
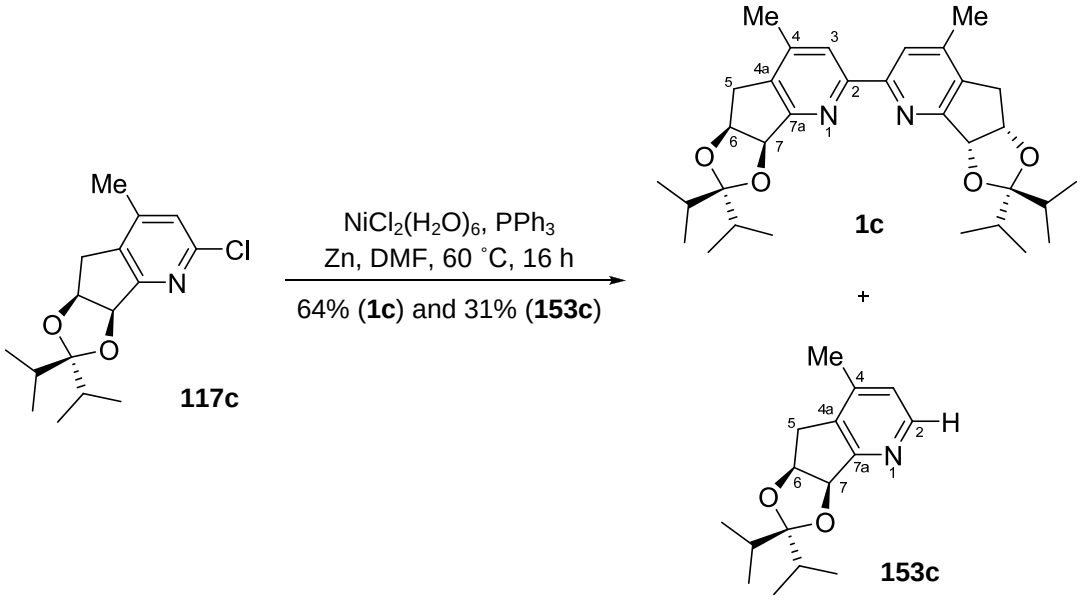


Figure 2.6.2.3: ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of the reductively-dehalogenated-byproduct (153b).

2.6.3 Reductive-Coupling of the Chloropyridine (117c) to Form the Corresponding 2,2'-Bipyridine (1c) and the Dehalogenated-Byproduct (153c)

The diisopropyl ketone-derived chloropyridine **117c** was subjected to the standard reductive-coupling conditions. Upon flash chromatography of the crude product mixture, the 2,2'-bipyridine **1c** and the pyridine **153c** were isolated in 64% and 31% yield, respectively, by flash chromatography (Scheme 2.6.3.1).

Scheme 2.6.3.1: Reductive-Coupling of the Chloropyridine (117c) to Form the Corresponding 2,2'-Bipyridine (1c) and the Dehalogenated-Byproduct (153c)



The 2,2'-bipyridine **1c** was fully-characterized by spectroscopic methods. Notably, the presence of a highly deshielded singlet was found at δ = 8.26 ppm that corresponded to the equivalent *H*-3 and *H*-3' protons in its ^{1}H NMR spectrum (Figure 2.6.3.1). The ^{13}C NMR spectrum of this compound showed only sixteen resonances despite the fact that the compound contains thirty-two carbon atoms which is in accord with the C_2-symmetry of this molecule. In order to unequivocally assign this product as the desired 2,2'-bipyridine a mass spectrum was acquired. This showed the expected

molecular ion peak at 521 *m/z* which corresponds to the mass of the protonated 2,2'-bipyridine **1c**.

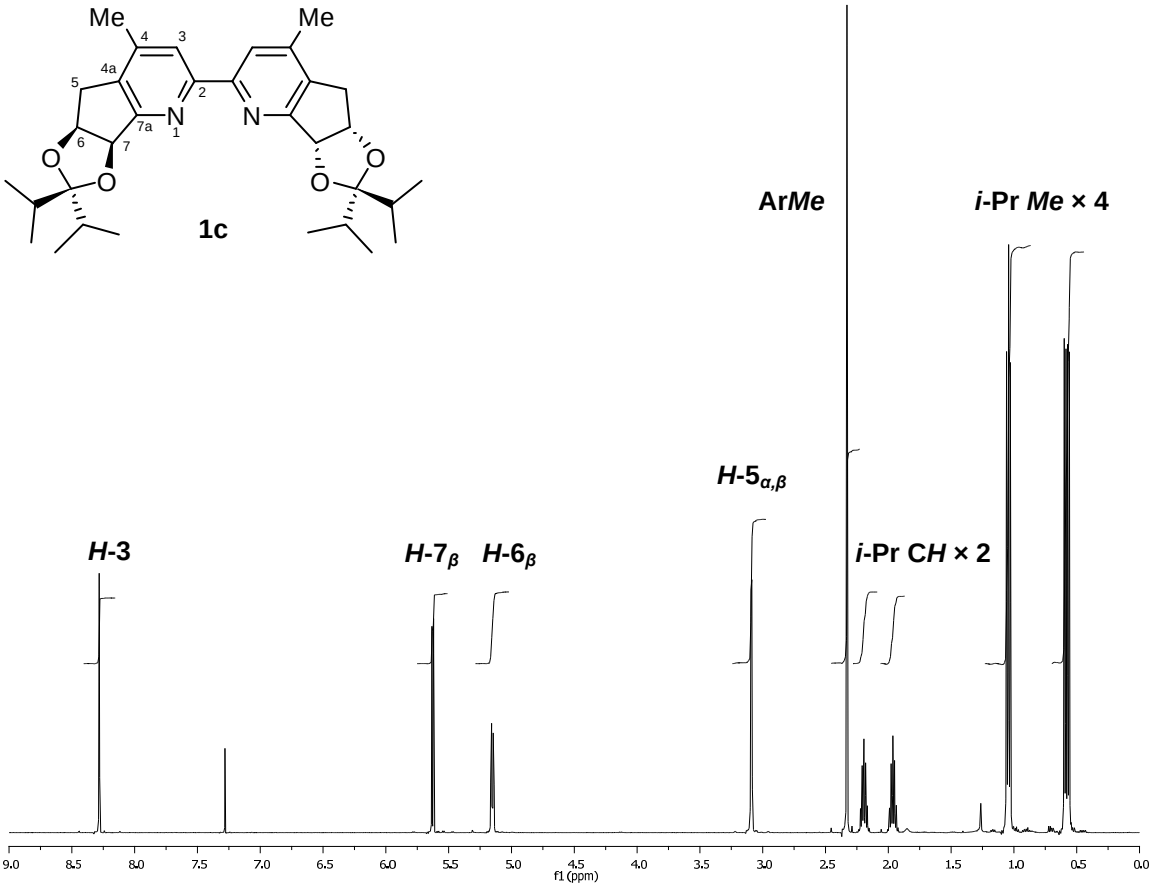


Figure 2.6.3.1: ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of the chiral nonracemic C_2-symmetric 2,2'-bipyridine (1c).

A three-dimensional model of this compound was created (Figure 2.6.3.2). This model clearly showed that the *N*,*N'*-bipyridyl binding site of this molecule was impinged upon by the acetal moiety to a larger degree than that of the original ligand, the 3-pentonone-derived 2,2'-bipyridine **1a**. This increase in steric hindrance is expected to afford greater enantioselectivity in asymmetric copper-catalyzed reactions than was afforded by the original chiral 2,2'-bipyridine, which was derived from a smaller ketone.

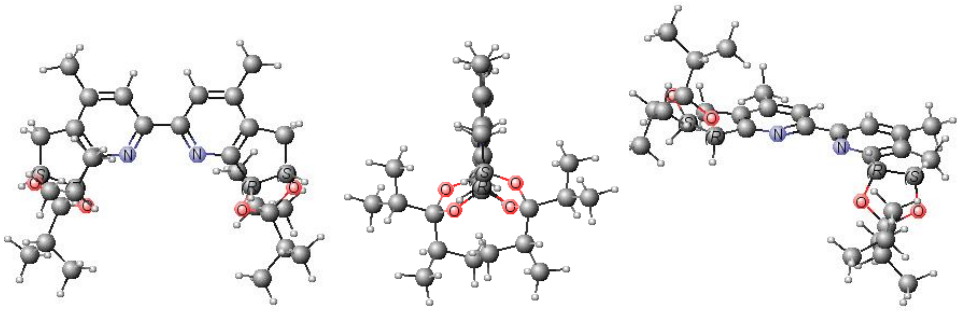


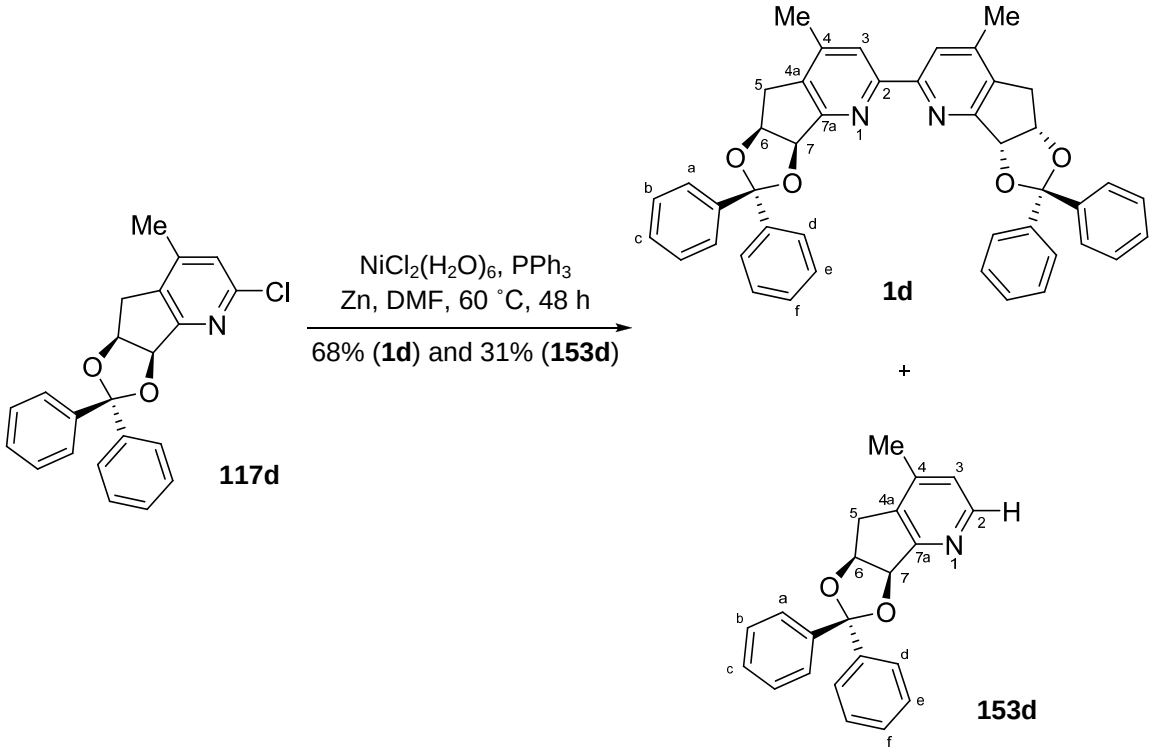
Figure 2.6.3.2: A 3D representation of the 2,2'-bipyridine (1c) viewed from three different perspectives.

The pyridine **153c**, the reductively-dehalogenated-product, was identified by the presence of two doublets in the aromatic region, at δ = 6.96 ppm and 8.38 ppm, that corresponded to the *H*-3 and *H*-2 protons in its ^{1}H NMR spectrum. In addition, the mass spectrum of this compound displayed the expected signal at 262 *m/z* which corresponds to the mass of the protonated molecular ion. This was further supported by elemental analysis from which the carbon, nitrogen and hydrogen composition content was within 0.11% of the calculated values.

2.6.4 Reductive-Coupling of the Chloropyridine (117d) to Form the Corresponding 2,2'-Bipyridine (1d) and the Dehalogenated-Byproduct (153d)

The benzophenone-derived chloropyridine **117d** was subjected to the standard reductive-coupling conditions. Upon flash chromatography of the crude product mixture, the 2,2'-bipyridine **1c** and the pyridine **153d** were isolated in 68% and 31% yield, respectively, by flash chromatography (Scheme 2.6.4.1).

Scheme 2.6.4.1: Reductive-Coupling of the Chloropyridine (117d) to Form the Corresponding 2,2'-Bipyridine (1d) and the Dehalogenated-Byproduct (153d)



The bipyridine **1d** was fully characterized by spectroscopic methods. A highly deshielded singlet observed at δ = 8.31 ppm in the ^{1}H NMR spectrum of the compound corresponds to the equivalent *H*-3 and *H*-3' protons (Figure 2.6.4.1). In this compound, the signals of *H*-5$_\beta$ and *H*-5$_\alpha$ were found at δ = 3.21 and 3.28, respectively, which is counter to the typical order of these resonances found in the other 2,2'-bipyridines

synthesized in this project. The proton *H*-5$_\alpha$ is on the concave face of the molecule and thus it will be most influenced by anisotropy due to the diphenylacetal moiety. As such, this proton is deshielded by the phenyl group on the concave face of the acetal indicating that the phenyl group is not parallel to the cyclopentyl ring, but closer to perpendicular. The signals of the phenyl protons $H_{a\text{-}f}$ of the acetal moiety are seen in the aromatic region of the spectrum and were well resolved which allowed for their assignment using COSY couplings.

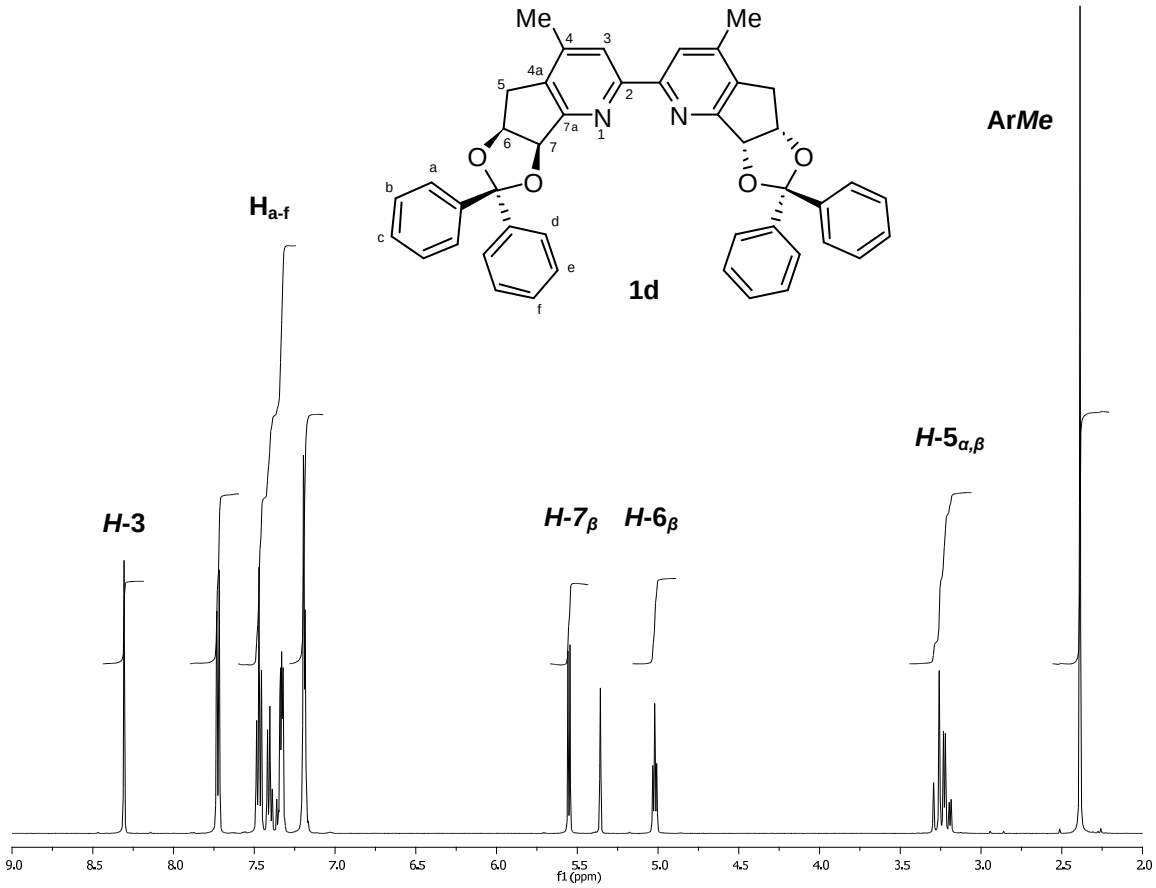


Figure 2.6.4.1: ^{1}H NMR spectrum (500 MHz, CD_2Cl_2) of the chiral nonracemic *C*$_2$-symmetric 2,2'-bipyridine (1d).

The couplings observed in the gCOSY spectrum allow for unambiguous assignment of the hydrogen atoms $H_{d\text{-}f}$, with the signal for H_d being the most deshielded signal of the group due to anisotropy (based on the inspection of molecular models,

Figure 2.6.4.2). In the series of protons $H_{a\text{-}c}$ there is overlap between two of the signals, thus the assumption was made that most upfield aromatic signal δ = 7.19, a multiplet that integrated to six protons, was attributed to the protons H_a and H_c. This is because the proton H_a is expected to experience the greatest anisotropic shielding from the pyridine ring. The ^{13}C NMR spectrum for this compound displayed eighteen unique signals which is very few considering that the compound contains forty-four carbon atoms. The simplicity of this spectrum is due in part to the symmetry of the phenyl group, and also to the C_2-symmetry of the molecule.

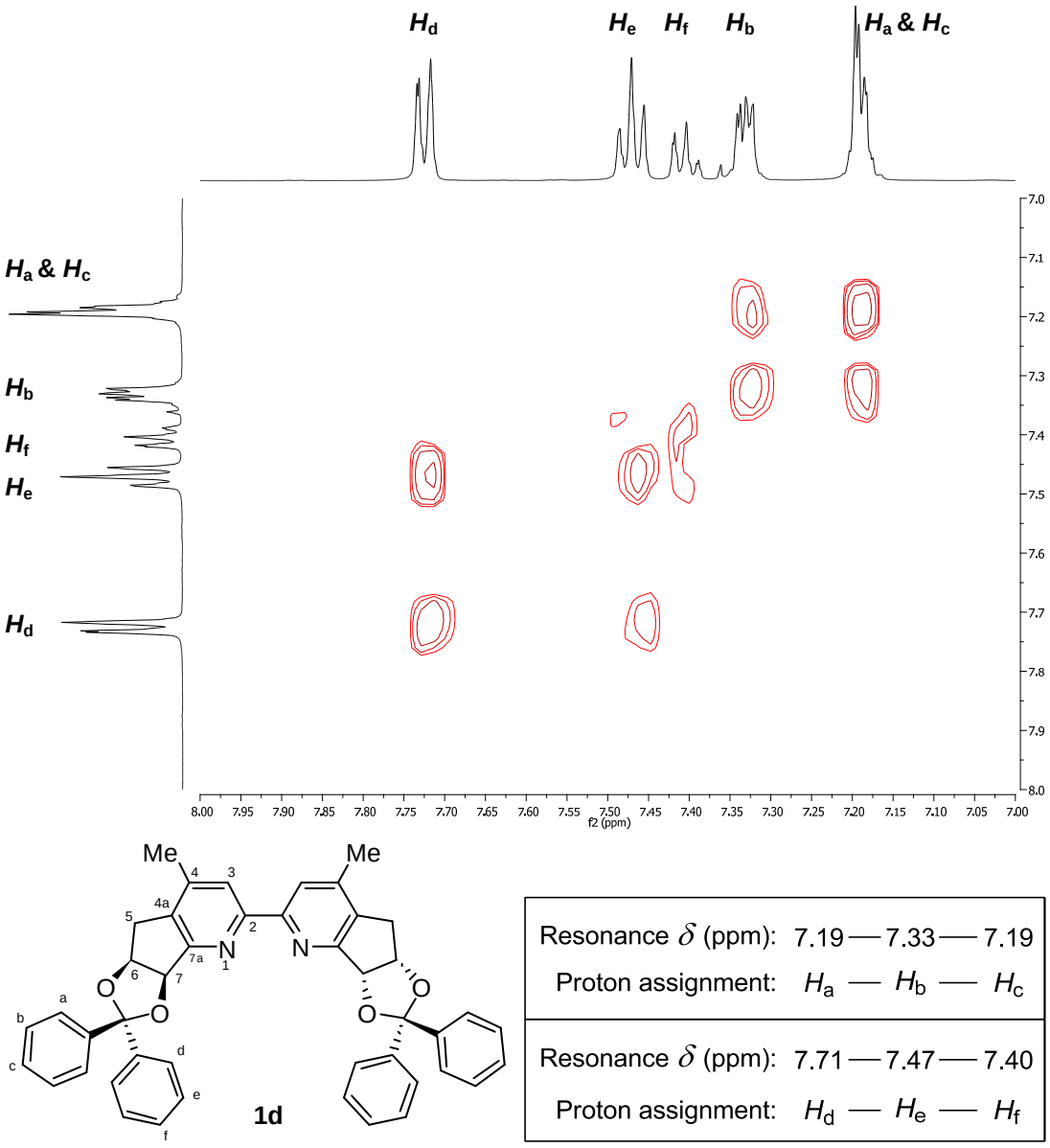


Figure 2.6.4.2: Downfield region of the gCOSY spectrum (500 MHz, CD_2Cl_2) of the 2,2'-bipyridine (1d).

The mass spectrum of this compound was recorded on a MALDI-TOF machine, and the spectrum displayed a molecular ion peak at 1376 *m/z*, which corresponds to a the mass of a dimer copper complex: 2 × M + ^{63}Cu. In addition, a protonated molecular ion

* The numbers in this figure represent the chemical shift of individual proton resonances. An interaction observed between any two proton signals is represented by a line connecting them. Under each set of COSY interactions is a diagram depicting the assignment of individual protons.

peak was observed at 657 *m/z* (M + H). The presence of the peak corresponding to a ligand-metal complex is a testament to the affinity these compounds have for metals, specifically copper. The only source of metal ion that this compound was exposed to would have been trace metals found in solvents during workup or from the matrix used in acquiring this spectrum.

A three-dimensional model of the benzophenone-derived 2,2'-bipyridine **1d** indicates that although the two phenyl groups of the acetal can rotate, the phenyl group on the concave face of the acetal moiety is most stable when it is roughly orthogonal to the main ring system (Figure 2.6.4.1). This is in fact supported by NMR data which showed that this phenyl ring causes anisotropic *de*-shielding of the protons in the cyclopentyl ring. Alternatively, if the ring systems were parallel, the phenyl ring would be expected to exert an anisotropic shielding effect on the cyclopentyl protons. The acetal ring system in the fluorenone-derived 2,2'-bipyridine **1f** is not flexible and is thus forced to be perpendicular to the pyrindine ring system (*vide infra*). The NMR data of this compound displayed the same deshielding effects as seen in the current case. This is opposite to that realized from modelling the 1,3-diphenylacetone-derived 2,2'-bipyridine **1e**, here the parallel ring systems have the effect of shielding the cyclopentyl protons. In addition to the predicted spatial arrangement of the phenyl groups of the benzophenone-derived 2,2'-bipyridine **1d**, these large substituents impinge on the *N*,*N*'-bipyridyl binding site of the molecule. Comparison of this model to that of the original 3-pentanone-derived 2,2'-bipyridine **1a** clearly shows this compound to be more sterically congested.

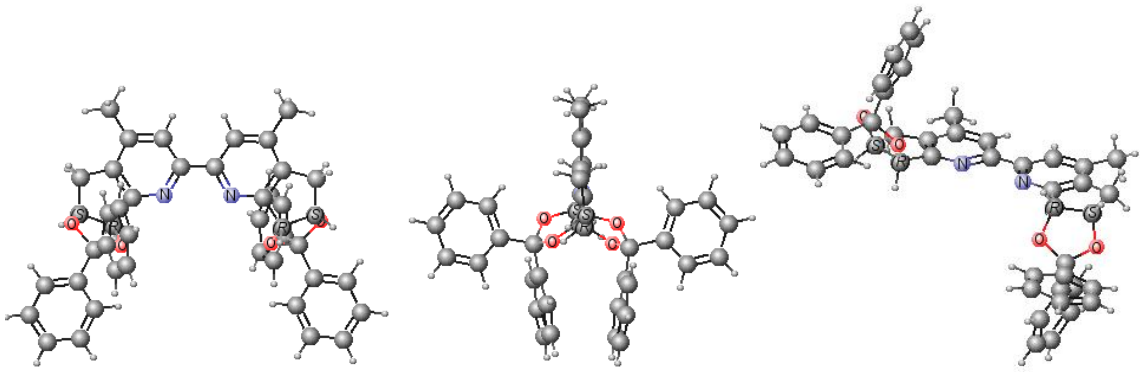


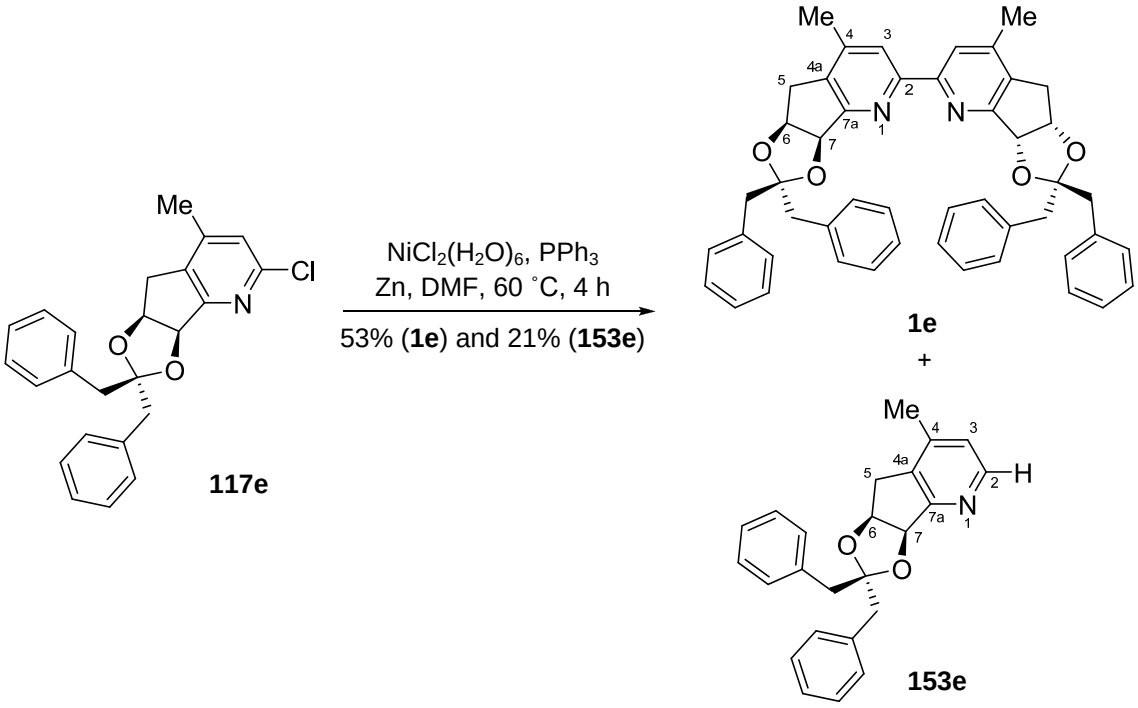
Figure 2.6.4.3: A 3D representation of the 2,2'-bipyridine (1d) observed from three different perspectives.

The reductively-dehalogenated-product, the pyridine **153d**, was identified by the presence of two doublets in the aromatic region: one at δ = 6.98 ppm and the other at 8.42 ppm, corresponding to the *H*-3 and *H*-2 protons in its ^{1}H NMR spectra. In addition, the mass spectrum of this compound displayed a protonated molecular ion peak at 330 *m/z*, (M + H).

2.6.5 Reductive-Coupling of the Chloropyridine (117e) to Form the Corresponding 2,2'-Bipyridine (1e) and the Dehalogenated-Byproduct (153e)

When the diphenylacetone-derived chloropyridine **117e** was subjected to the standard reductive-coupling conditions, the 2,2'-bipyridine **1e** and the pyridine **153e** were isolated in 53% and 21% yield, respectively, by flash chromatography (Scheme 2.6.5.1).

Scheme 2.6.5.1: Reductive-Coupling of the Chloropyridine (117e) to Form the Corresponding 2,2'-Bipyridine (1e) and the Dehalogenated-Byproduct (153e)



The bipyridine **1e** was fully characterized by spectroscopic methods. The ^{1}H NMR spectrum of this compound displayed a characteriztic highly deshielded singlet at δ = 8.21 ppm that corresponds to the equivalent *H*-3 and *H*-3' protons. The signals for the diastereotopic protons *H*-5$_{\alpha}$ and *H*-5$_{\beta}$ were found at δ = 2.53 and 2.67 ppm, respectively. The fact that the proton on the concave face of the molecule was more shielded than the one on the convex face indicates that the benzyl group on the concave face of the acetal

was exerting an anisotropic-shielding effect upon the cyclopentyl ring. This would be expected to occur if the two ring systems were parallel. Also of note was that the mass spectrum of this compound, which was recorded on a MALDI-TOF mass spectrometer, displayed a molecular ion peak at 1490 *m/z*. This corresponds to the mass of a dimer Zn complex (2 × M + ^{64}Zn). In addition, a protonated molecular ion peak was found at 657 *m/z* (M + H). Once again, the appearance of a ligand-metal complex in the mass spectrum of this compound is intriguing, especially considering that the metal bound in this case was different from that bound by the 2,2'-bipyridine **1d**.

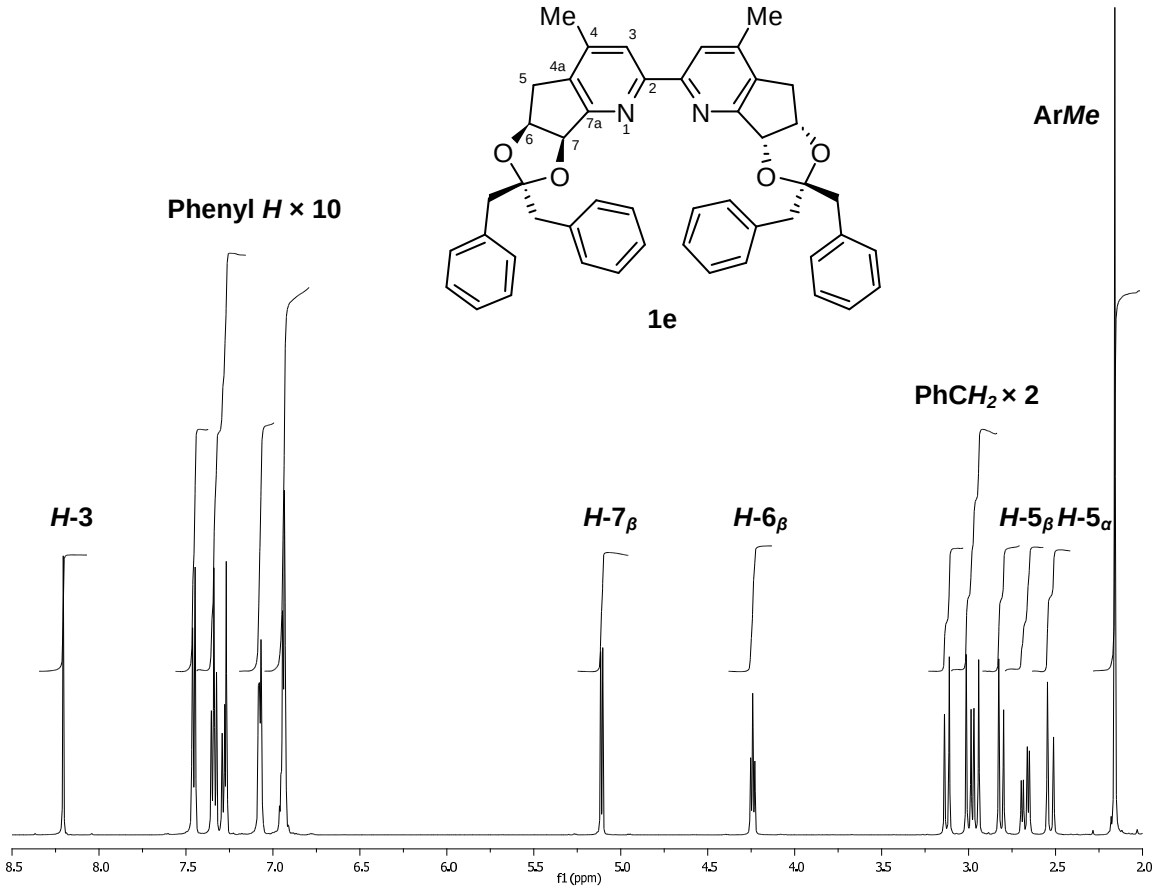


Figure 2.6.5.1: ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of the chiral nonracemic C_2-symmetric 2,2'-bipyridine (1e).

A three-dimensional model of this compound predicted that the most stable conformer of the flexible acetal unit would be where the benzyl group on the convex face

of the acetal moiety was positioned in an approximately parallel manner to the main ring system (Figure 2.6.5.2). This is in accord with the NMR data collected for this compound. In comparison to the other 2,2'-bipyridines in this series, this compound clearly contains the largest and most flexible acetal moieties. This may lead to a decrease in the yields of products derived from copper-catalyzed reactions involving this compound, as the steric bulk of this acetal may impede the reaction process.

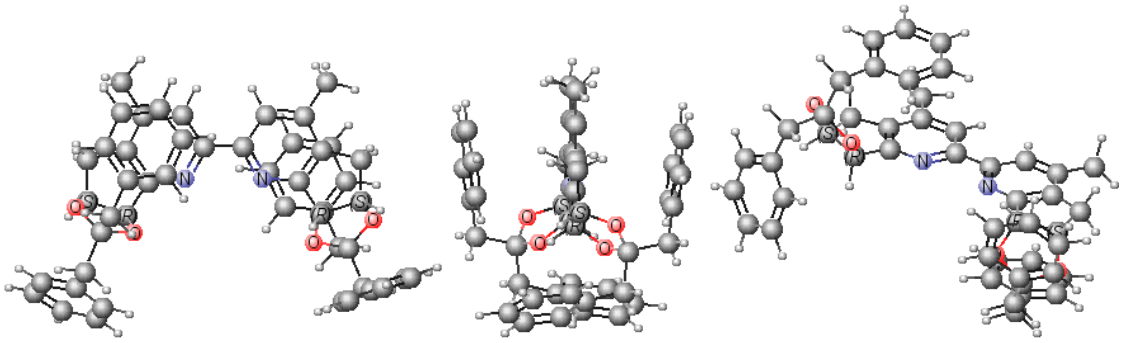


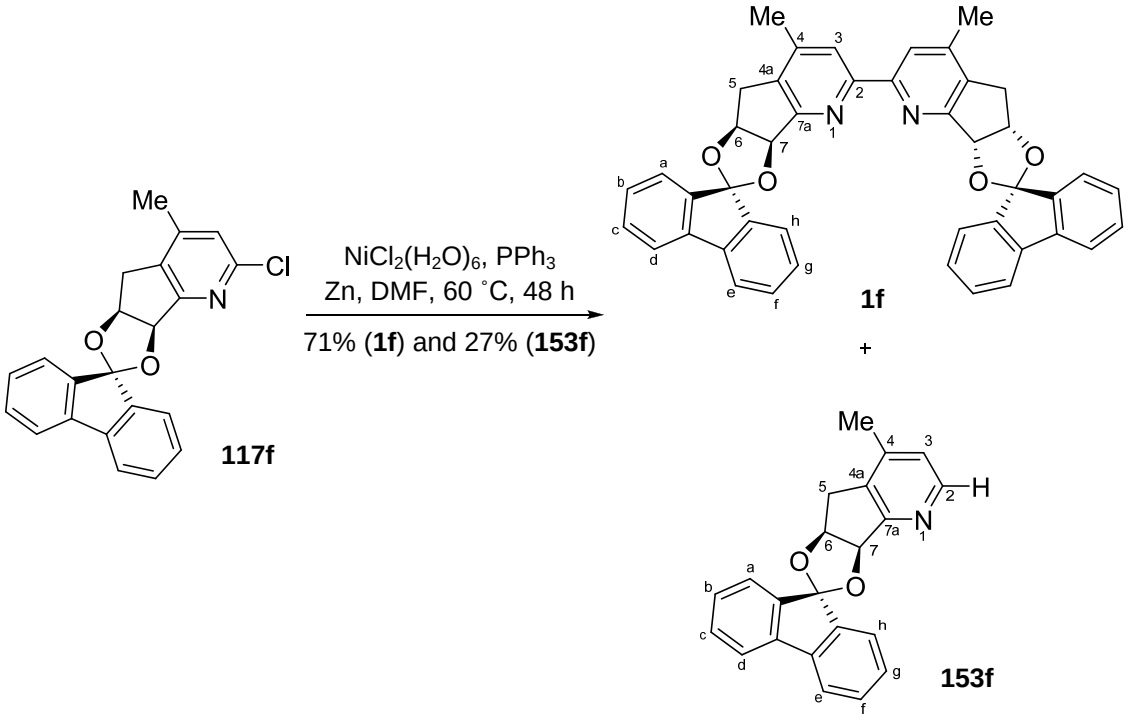
Figure 2.6.5.2: A 3D representation of the 2,2'-bipyridine (1e) observed from three different perspectives.

The pyridine **153e**, the reductively-dehalogenated-product, displayed two doublets in the aromatic region in its ^{1}H NMR spectrum at δ = 6.83 ppm and 8.28 ppm, correspond to the *H*-3 and *H*-2 protons. In addition, the mass spectrum of this compound displayed a protonated molecular ion peak at 358 *m/z* (M + H).

2.6.6 Reductive-Coupling of the Chloropyridine (117f) to Form the Corresponding 2,2'-Bipyridine (1f) and the Dehalogenated-Byproduct (153f)

The fluorenone-derived chloropyridine **117f** was subjected to the standard reductive-coupling conditions. Upon flash chromatography of the crude product mixture, the 2,2'-bipyridine **1f** and the pyridine **153f** were isolated in 71% and 27% yield, respectively, by flash chromatography (Scheme 2.6.6.1).

Scheme 2.6.6.1: Reductive-Coupling of the Chloropyridine (117f) to Form the Corresponding 2,2'-Bipyridine (1f) and the Dehalogenated-Byproduct (153f)



The bipyridine **1f** was fully characterized by spectroscopic methods. Here, the ^{1}H NMR spectrum of this compound displayed a highly deshielded singlet at δ = 8.40 ppm that corresponded to the equivalent *H*-3 and *H*-3' protons of its pyridyl rings. In addition, the fluorenyl acetal moiety exerted an anisotropic deshielding effect on the diastereotopic cyclopentyl methylene protons *H*-5$_\beta$ and *H*-5$_\alpha$ which were observed at δ = 3.23 and 3.28 ppm, respectively.

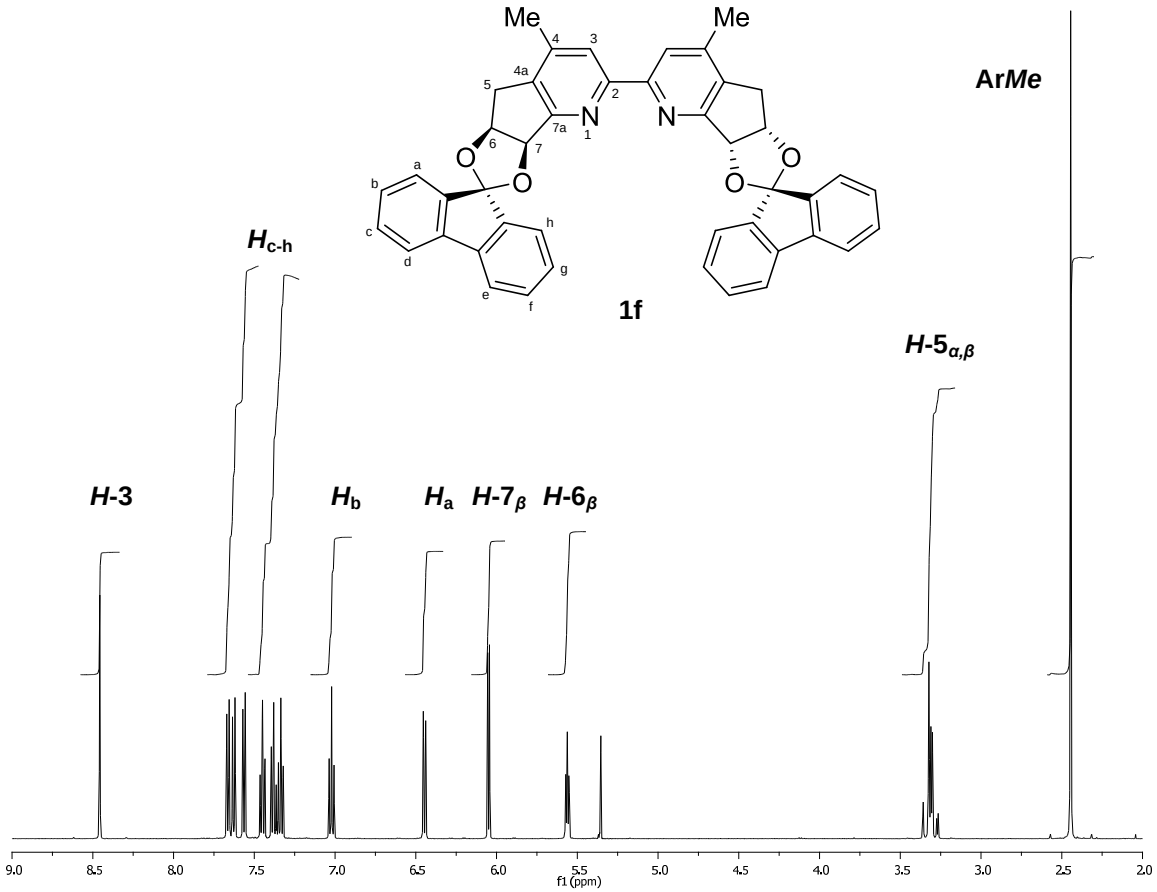
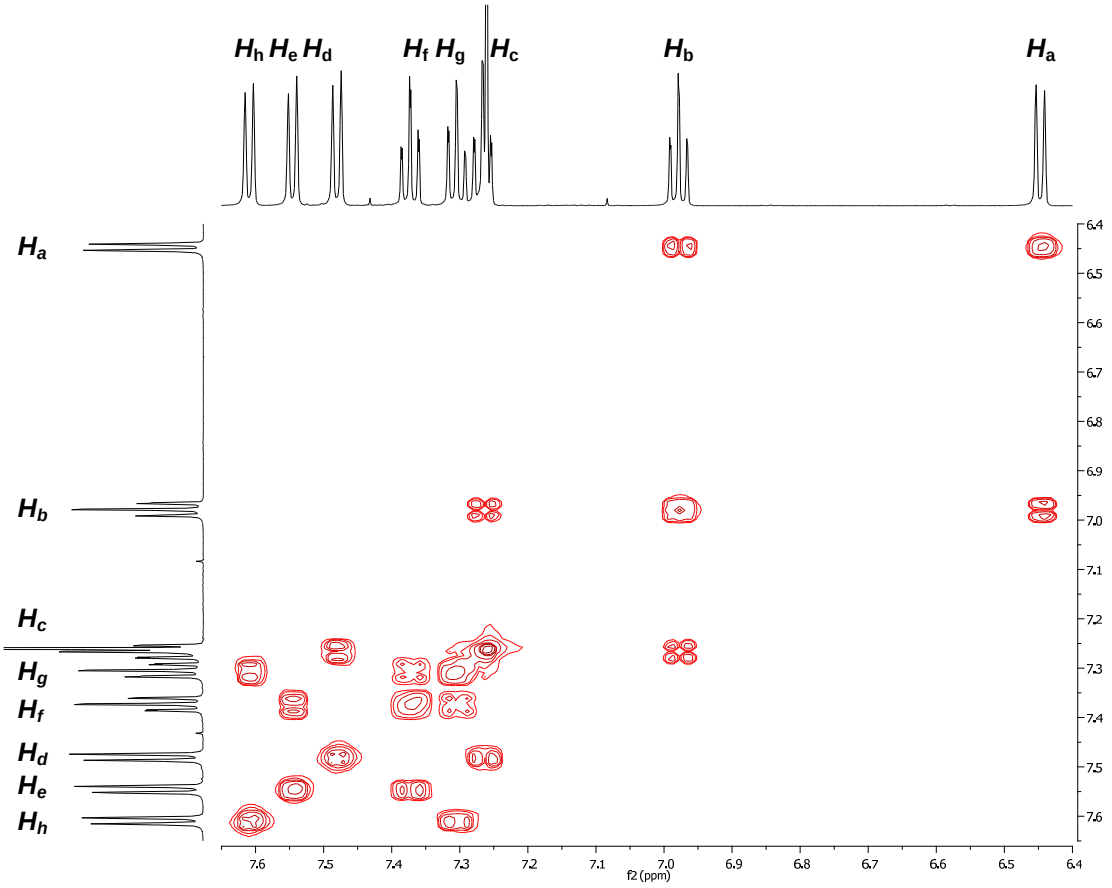
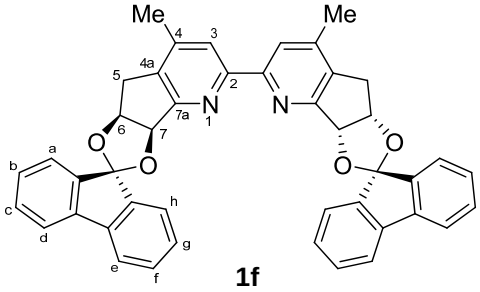


Figure 2.6.6.1: ^{1}H NMR spectrum (500 MHz, CD_2Cl_2) of the chiral nonracemic C_2-symmetric 2,2'-bipyridine (1f).

Another interesting anisotropic effect was the shielding of some of the signals corresponding to the fluorenyl protons (H_{a-h}) by the pyridine ring. From this shielding effect, the fluorenyl signals were well-resolved. Using COSY coupling correlations, these resonances were assigned to specific protons on the fluorenyl moiety of the 2,2'-bipyridine **1f** (Figure 2.6.6.2). These assignments were in accord with the aromatic resonances found and assigned in the ^{1}H NMR spectrum of the precursor chloropyridine **117f**.





1f

Resonance δ (ppm):	6.39	6.96	7.28	7.51
Proton assignment:	H_a	H_b	H_c	H_d

Resonance δ (ppm):	7.61	7.32	7.39	7.57
Proton assignment:	H_h	H_g	H_f	H_e

*

Figure 2.6.6.2: Aromatic region of the gCOSY spectrum (600 MHz, $CDCl_3$) of the 2,2'-bipyridine (1f).

It is of interest that the mass spectrum of this compound which was recorded on a MALDI-TOF mass spectrometer, displayed a molecular ion peak at 1367 *m/z*. This peak corresponds to the mass of a 2,2'-bipyridyl dimer-copper complex (2 × M + ^{63}Cu) and

---

* The numbers in this figure represent the chemical shift of individual proton resonances. An interaction observed between any two proton signals is represented by a line connecting them. Under each set of COSY interactions is a diagram depicting the assignment of individual protons.

was the base peak of the mass spectrum. Other ligand-metal complex signals included a peak at 1362 *m/z* (2 × M + ^{58}Ni) and a peak at 715 *m/z* (M + ^{63}Cu). A molecular ion peak that corresponded to the free protonated 2,2'-bipyridine **1f** was observed at 653 *m/z* (M + H). Of all the 2,2'-bipyridines subjected to MALDI-TOF mass spectral analysis in the course of this study, the fluorenone-derived the 2,2'-bipyridine **1f** showed the greatest number and most intense peaks attributable to metal-ligand complexes.

Three-dimensional models of this compound explicitly show that the aryl rings are held rigidly in an orthogonal position to the plane of the 2,2'-bipyridine (Figure 2.6.6.3). Due to the rigid and planar nature of the acetal moieties, they represent two "walls" enclosing the binding site of the ligand while not impinging on it. A enclosed binding pocket such as this could increase the stability of ligand-metal complexes formed by this compound by protecting the bound metal ion from desorption. This would explain the increased abundance of metal complexes observed in the mass spectrum of this compound in comparison to the other 2,2 bipyridines examined during the course of this study.

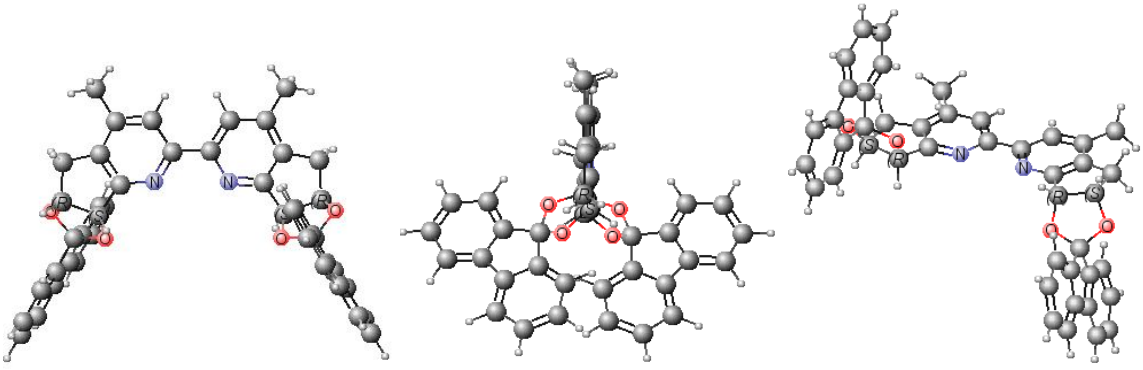


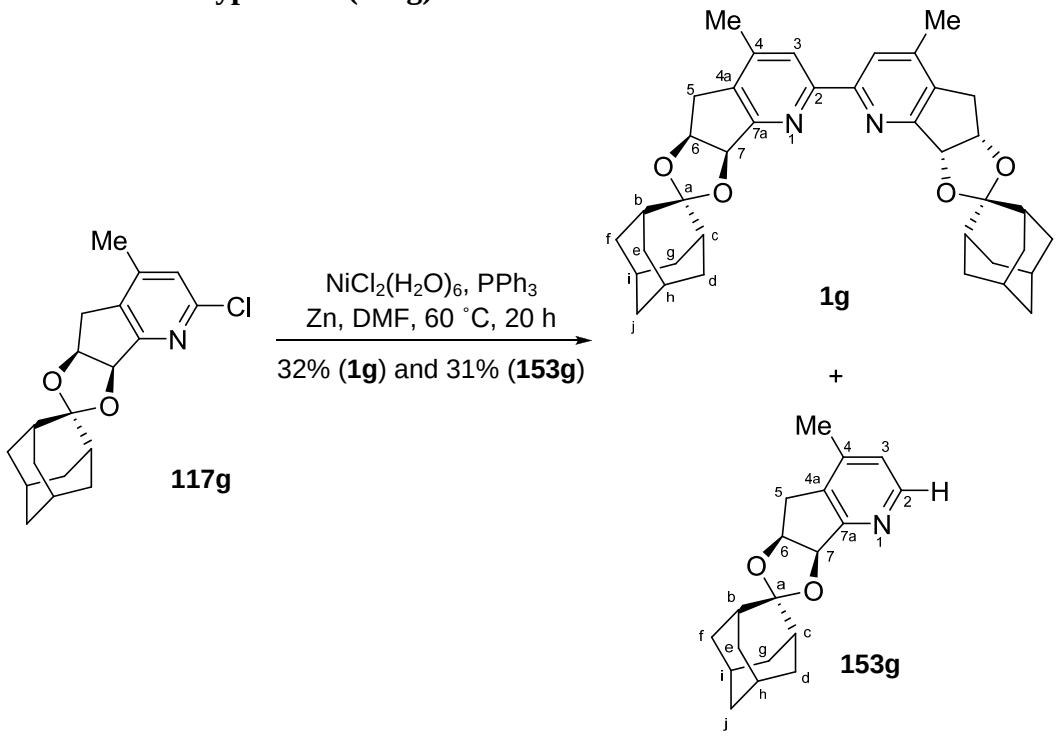
Figure 2.6.6.3: A 3D representation of the 2,2'-bipyridine (1f) observed from three different perspectives.

The pyridine **153f**, the reductively-dehalogenated-product, was identified by the presence of two doublets in the aromatic region, one at δ = 6.98 ppm and the other at 8.42 ppm, that corresponded to the *H*-3 and *H*-2 protons in its ^{1}H NMR spectrum. In addition, the mass spectrum of this compound displayed a protonated molecular ion peak at 328 *m/z* (M + H).

2.6.7 Reductive-Coupling of the Chloropyridine (117g) to Form the Corresponding 2,2'-Bipyridine (1g) and the Dehalogenated-Byproduct (153g)

The adamantanone-derived chloropyridine **117g** was subjected to the standard reductive-coupling conditions. The 2,2'-bipyridine **1g** and the pyridine **153g** were isolated in 32% and 31% yield, respectively, from flash chromatography (Scheme 2.6.7.1). The low overall yield of this reaction is attributed to difficulties encountered during flash chromatography of these products, as they have low solubility in various solvents.

Scheme 2.6.7.1: Reductive-Coupling of the Chloropyridine (117g) to Form the Corresponding 2,2'-Bipyridine (1g) and the Dehalogenated-Byproduct (153g)



The adamantanone-derived bipyridine **1g** was identified by the presence of a highly deshielded singlet found at δ = 8.23 ppm that correspond to the equivalent *H*-3 and *H*-3' protons in its ^{1}H NMR spectrum (Figure 2.6.7.1). In addition, many of the adamantyl protons ($H_{b\text{-}j}$) were well-resolved from one another in the ^{1}H NMR spectrum. In order to assign these resonances, several 1D nOe spectra were recorded as well as a gCOSY spectrum (Figure 2.6.7.4 and Figure 2.6.7.6).

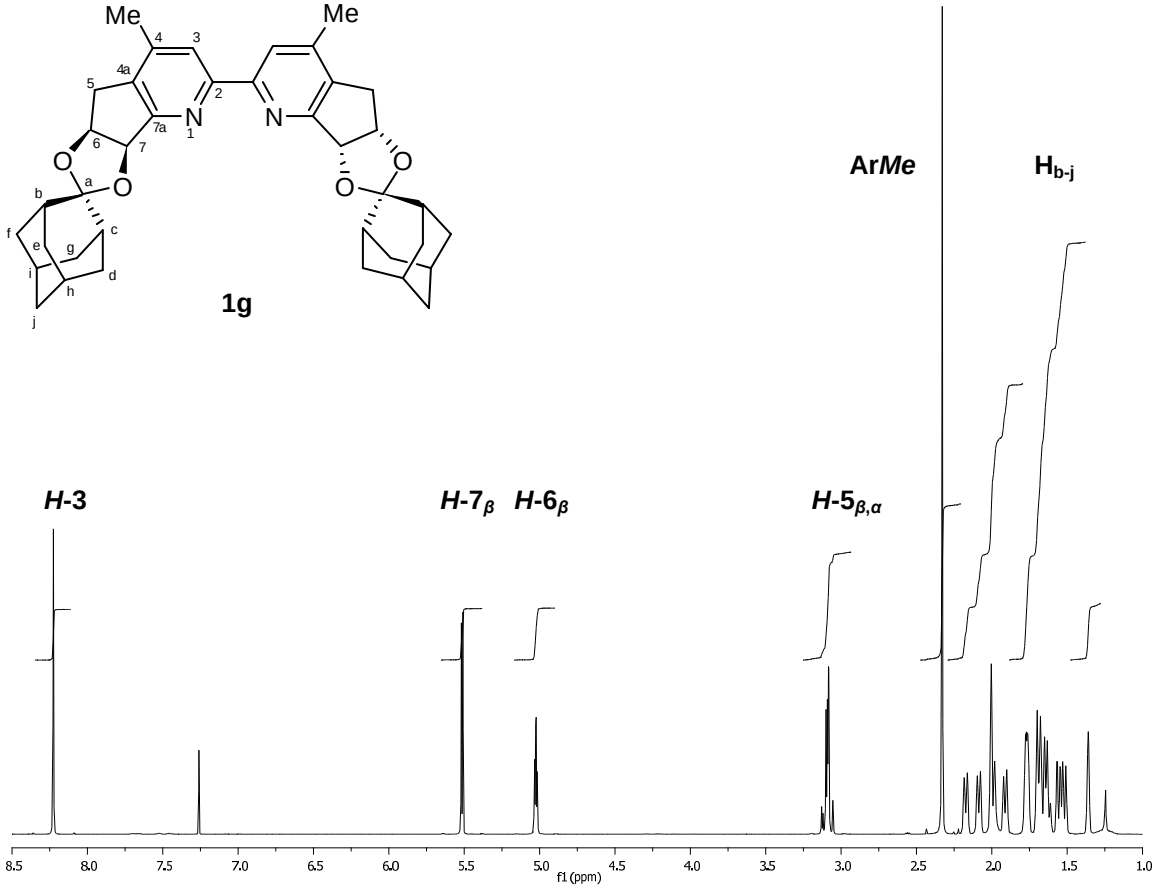


Figure 2.6.7.1: ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of the chiral nonracemic C_2-symmetric 2,2'-bipyridine (1g).

The upfield region of the ^{1}H NMR spectrum contains the resonances corresponding to the fourteen adamantyl protons (Figure 2.6.7.2). These fourteen protons are represented by twelve distinguishable signals within this region. Due to the large number of signals in this region, discussions of them can be simplified by referring to

individual signals by an arbitrary set of greek letter labels, rather than shift. These labels are displayed in Figure 2.6.7.2.

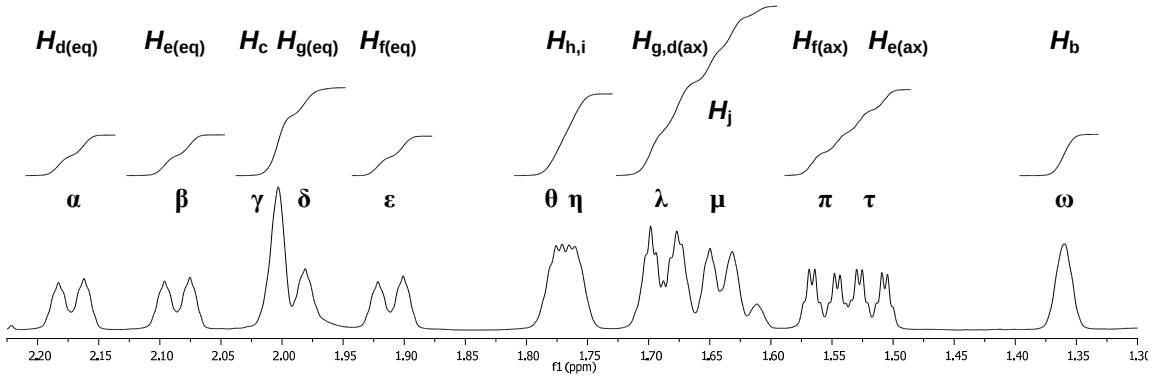


Figure 2.6.7.2: Aliphatic region of the ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of the 2,2'-bipyridine (1g).

An nOe contact was found to exist between $H_{d(ax)}$ and H-7$_\beta$, thus the signal α could be assigned to proton $H_{d(eq)}$ (Figure 2.6.7.3 and Figure 2.6.7.4). In addition, an nOe contact was observed between H_c and H-7$_\beta$ and also H-6$_\beta$. Thus, H_c was assigned as the singlet γ. Furthermore, nOe contacts were found between $H_{g(eq)}$ and the two cyclopentyl protons H-6$_\beta$ and H-7$_\beta$, allowing assignment of the resonance δ to the proton $H_{g(eq)}$. With these three signals assigned to their corresponding protons, the full assignment of this compounds in the upfield region was possible following a gCOSY experiment.

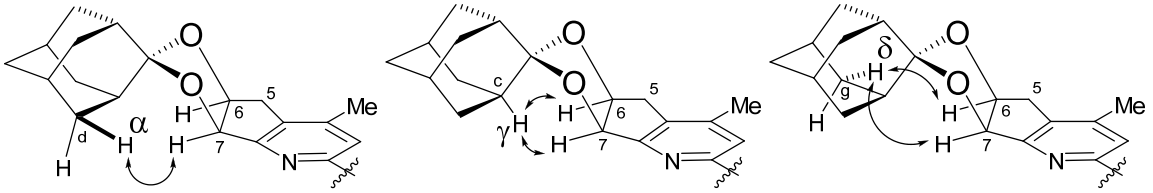


Figure 2.6.7.3: nOe interactions of various protons of the adamantyl moiety to the cyclopentyl protons of the 2,2'-bipyridine [(+)-1g].

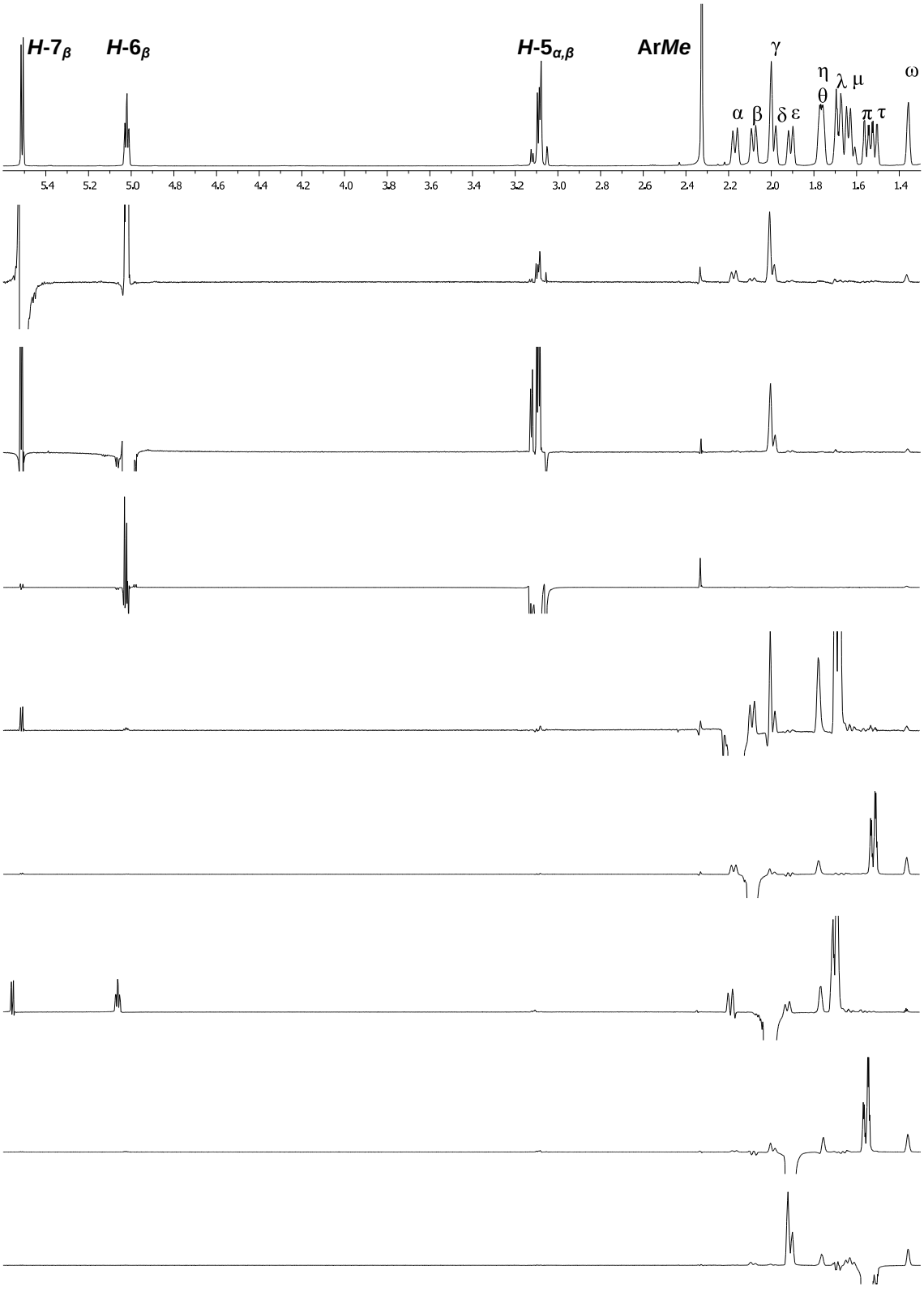

H-7β
H-6β
H-5α,β
ArMe
α β γ δ ε η θ λ μ π τ ω
5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4

Figure 2.6.7.4: The nOe data (600 MHz, $CDCl_3$) acquired from the 2,2'-bipyridine [(+)-1g] (inverted resonances correspond to the protons that were under investigation in a particular experiment).

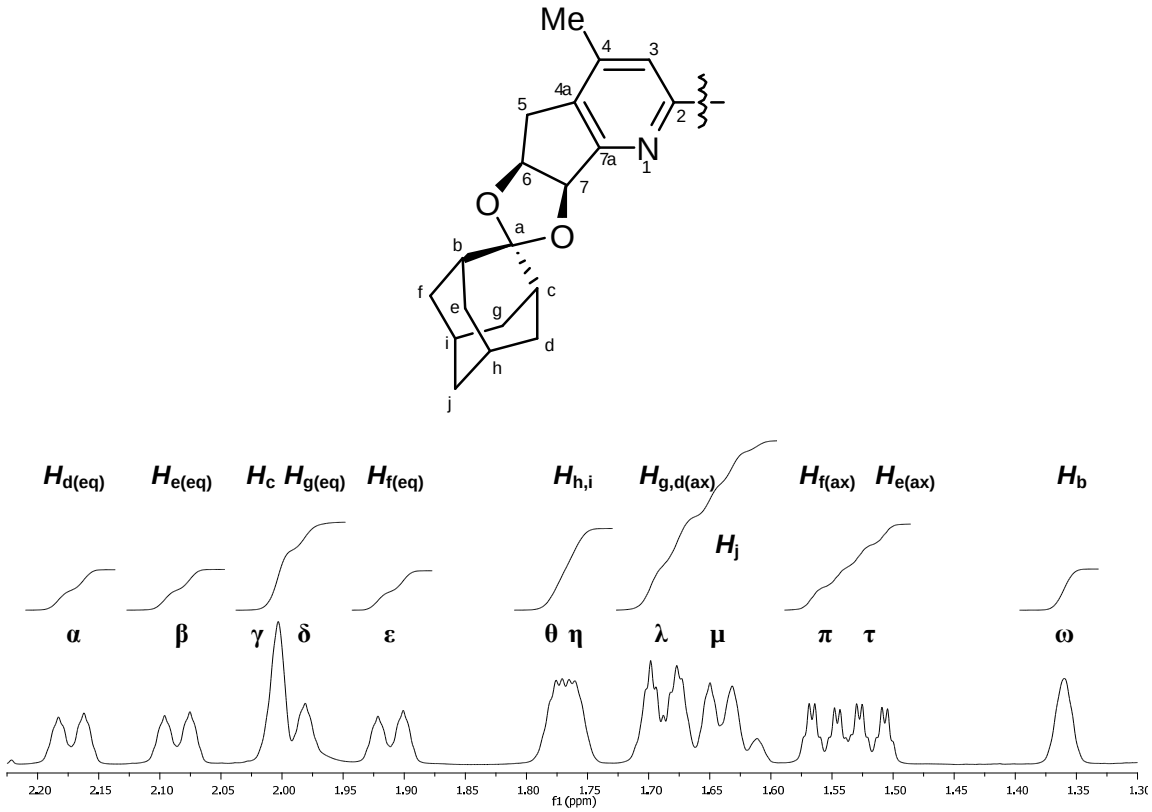


Figure 2.6.7.5: Aliphatic region of the ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of the 2,2'-bipyridine (1g).

The protons that can be expected to have the strongest COSY couplings are those which belong to the same methylene unit. Thus, signals δ and λ are both attributed to 2 × H_g. The signal corresponding to $H_{g(eq)}$ is already known, thus signal λ can be assigned as $H_{g(ax)}$. The methylene 2 × H_g couples to both H_c and H_i. Thus, the signal that corresponds to H_i is θ. The proton H_c was already assigned; however, the COSY coupling supports its assignment as corresponding to the signal γ. The proton H_i couples to two disparate methylene groups: 2 × H_j and 2 × H_f. The signals corresponding to the two diastereotopic protons $H_{f(eq)}$ and $H_{f(ax)}$ can be assigned as ε and π respectively. This is due to the fact that this methylene group will exhibit two signals. The methylene 2 ×

H_j, however, is far removed from the stereocentres of the molecules and thus is not expected to show two distinct signals, and so is assigned as signal μ. The terminal methylene 2 × H_j couples to H_h hence signal η corresponds to this proton. This proton couples to the two methylene groups H_e and H_d. The equatorial hydrogen of methylene 2 × H_d has already been assigned as signal α, and so the axial proton, $H_{d(ax)}$, is assigned as signal λ. Signals β and τ are attributed to the diastereotopic hydrogens $H_{e(eq)}$ and $H_{e(ax)}$. The methylene 2 × H_e couples with the proton H_b, thus signal ω was attributed to this proton. Finally, the proton H_b is held nearest to the aromatic pyridine ring, and so is expected to experience the greatest diastereotopic shielding, which is borne out in the shift of its ^{1}H NMR signal.

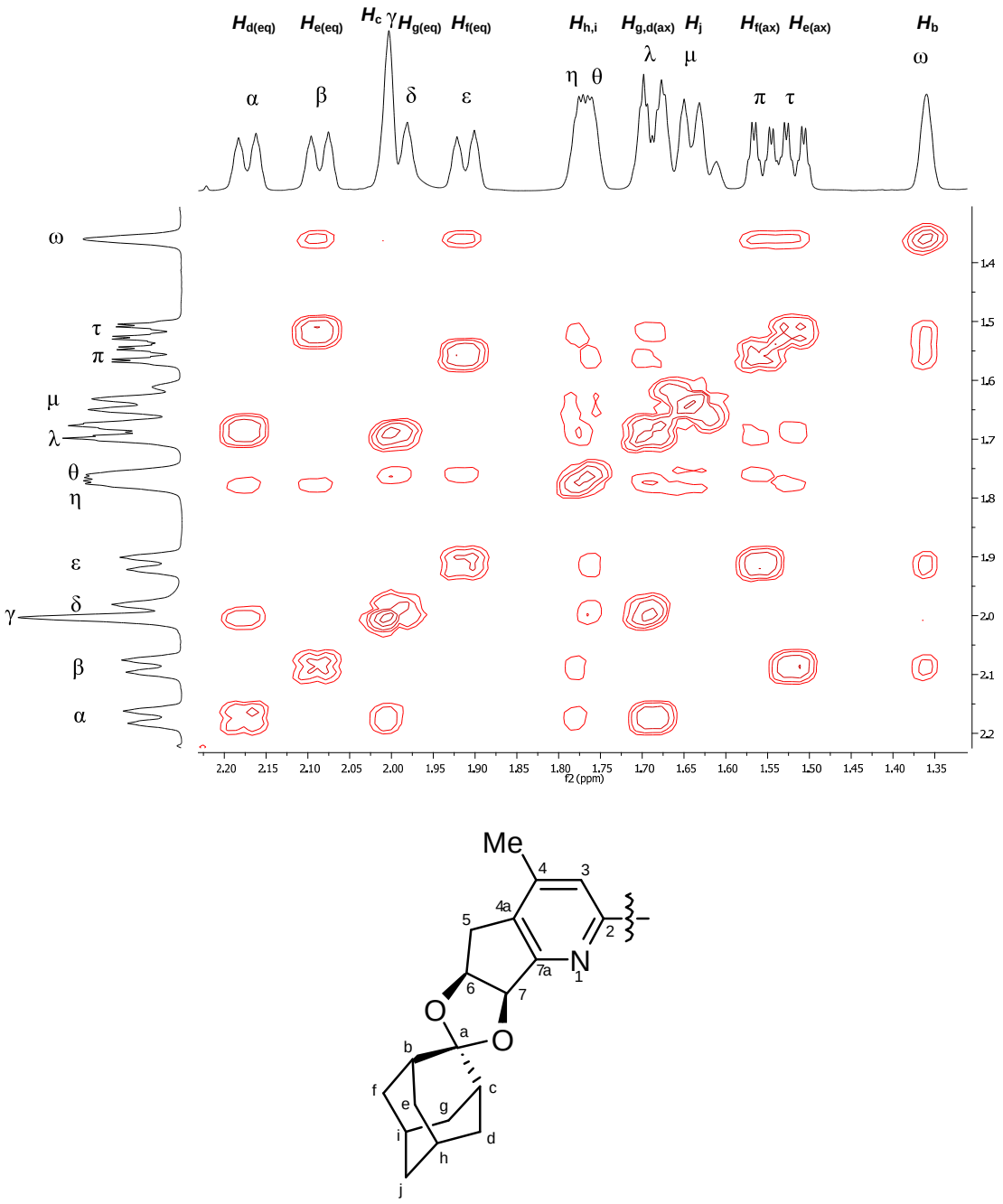


Figure 2.6.7.6: Alkyl region of the gCOSY (600 MHz, $CDCl_3$) of the 2,2'-bipyridine [(+)-1g].

In addition to the detailed ^{1}H-NMR data recorded for the adamantanone-derived 2,2'-bipyridine **1g**, the mass spectrum was recorded on a MALDI-TOF mass spectrometer and displayed a molecular ion peak at 1249 *m/z*. This peak corresponds to the mass of a

ligand-dimer copper complex (2 × M + ^{63}Cu). Also, a protonated molecular ion peak was found at 593 *m/z* (M + H).

A three-dimensional model of this compound showed that this compound has very large and rigid acetal moieties in comparison to the original 3-pentanone derived 2,2'-bipyridine **1a**.

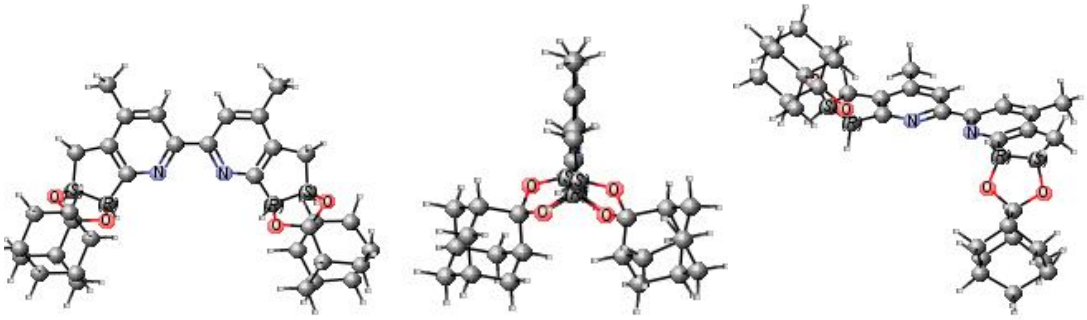


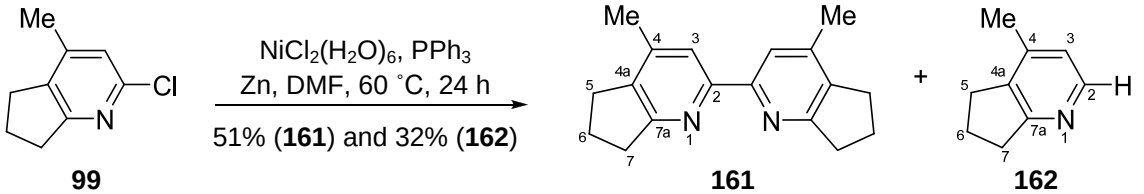
Figure 2.6.7.7: A 3D representation of the 2,2'-bipyridine (1g) observed from three different perspectives.

The reductively-dehalogenated-product, the pyridine **153g**, was identified by the presence of two doublets in the aromatic region of its ^{1}H NMR spectra found at δ = 6.97 ppm and 8.37 ppm, corresponding to the *H*-3 and *H*-2 protons. In addition, the mass spectrum of this compound displayed a molecular ion peak at 298 *m/z* (M + H).

2.6.8 Reductive-Coupling of the Achiral Chloropyridine (99) to Form the Corresponding 2,2'-Bipyridine (161) and the Dehalogenated-Byproduct (162)

The chloropyridine **99**, which was synthesized earlier in this thesis, was subjected to the standard reductive-coupling conditions. Upon flash chromatography of the crude product mixture, the 2,2'-bipyridine **161**, and the known pyridine **162** were isolated in 51% and 32% yield, respectively, by flash chromatography (Scheme 2.6.8.1).

Scheme 2.6.8.1: Reductive-Coupling the Chloropyridine (99) to Form its Corresponding 2,2'-Bipyridine (161) and the Dehalogenated-Byproduct (162)



99 **161** **162**

The bipyridine **99** was identified by the presence of a deshielded singlet found at δ = 7.93 ppm in its ^{1}H NMR spectrum, corresponding to the equivalent *H*-3 and *H*-3' protons. In addition, the mass spectrum of this compound displayed a protonated molecular ion peak at 264 *m/z* (M + H).

The known pyridine **153c**,[157] the reductively-dehalogenated-product, was identified by the presence of two doublets in the aromatic region of its ^{1}H NMR spectrum, at δ = 6.83 ppm and 8.20 ppm, corresponding to the *H*-3 and *H*-2 protons. In addition, the mass spectrum of this compound displayed a protonated molecular ion peak at 134 *m/z* (M + H). The additional data recorded for this compound were also in accord with that reported in literature.[157]

2.7 Chapter Summary

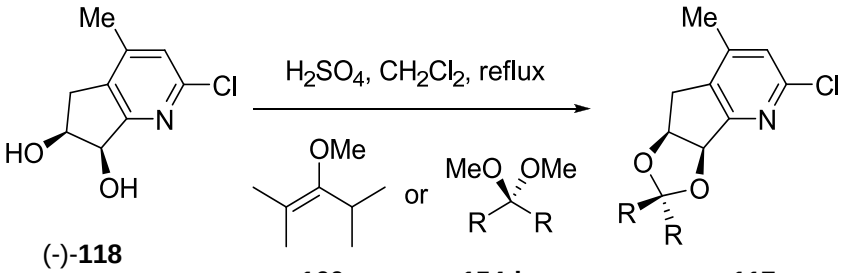
In this chapter the synthesis of six new chiral C_2-symmetric nonracemic 2,2'-bipyridines **1b**-**g**, the known 2,2'-bipyridine **1a**, and an achiral 2,2'-bipyridine were described. These compounds were prepared in order to determine the appropriate structural characteriztics that most influence the stereochemical outcome of asymmetric copper-catalyzed reactions on employing these compounds as ligands in these processes.

Access to large quantities of nearly optically pure diol (-)-**118**, was accomplished through further investigation of a previously described asymmetric dihydroxylation

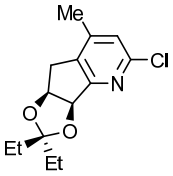
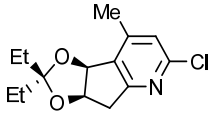
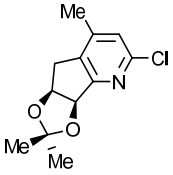
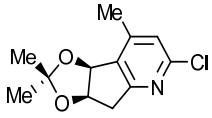
reaction. In addition to this large scale synthesis, purification and optical resolution (up to 97% ee) of this key compound was afforded through the recrystallization and deprotection of its corresponding acetone-derived acetal **117b**. The diol (-)-**118** was prepared in nine steps from inexpensive commercially available materials. It is important to note that the synthesis of these six new compounds is modular and this allowed for access to a series of chiral nonracemic 2,2'-bipyridines from an advanced synthetic precursor, following two subsequent synthetic steps [acetal formation and nickel(0) mediated coupling].

It was of great importance in this work that a general method for the synthesis of sterically encumbered acetals was successfully demonstrated. Here, good to excellent yields were recorded in all cases (Table 2.6.8.1). The reductive-coupling reactions of the acetals **117a-g** to afford the ligands **1a**-**g** were executed in moderate to good yields in most cases (Table 2.6.8.2). Unfortunately these reactions suffered a drawback whereby some of the chloropyridine (typically ~ 30%) was converted through a reductive-dehalogenation process to its corresponding pyridine. Despite this, the chiral nonracemic C_2-symmetric 2,2'-bipyridines **1a**-**g** were synthesized in optically pure form and in large enough quantities to be evaluated in copper-catalyzed reactions. The results of these studies are reported in the following chapter.

Table 2.6.8.1: Formation of Acetals (117c-g)



(-)-**118** **160c** **154d-g** **117c-g**

Ketone Equivalent	2-Chloropyridine Product(s)	Yield (%)
	 **117a**  **148a**	**96* (combined)**
	 **117b**  **148b**	**94† (combined)**

* These compounds were synthesized under acid-catalyzed conditions (PTSA) in benzene at 80 ˚C.

† These compounds were synthesized under acid-catalyzed conditions (PPTS) in dichloromethane at room temperature.

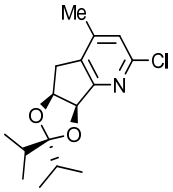
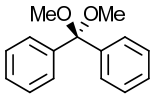
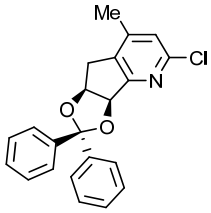
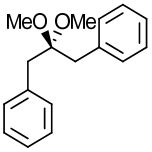
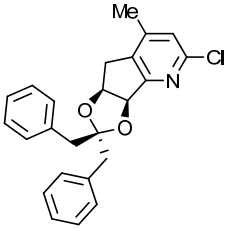
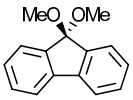
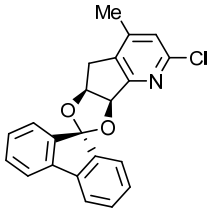
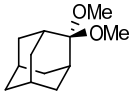
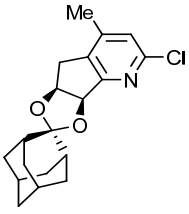
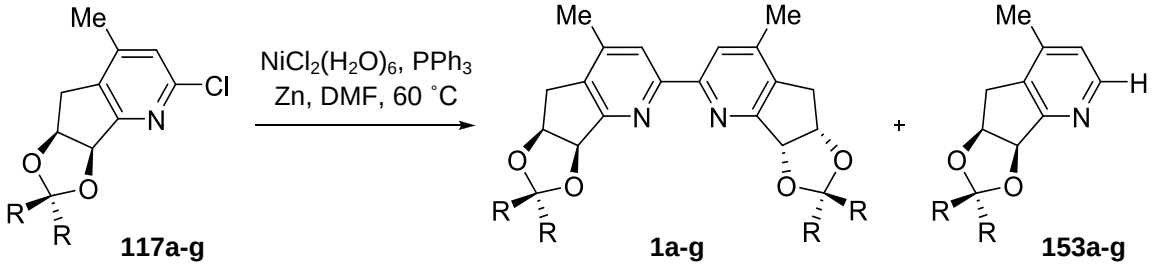
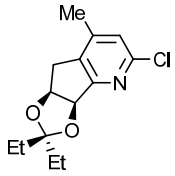
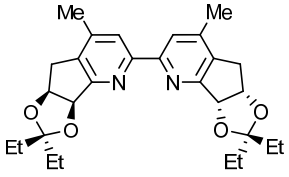
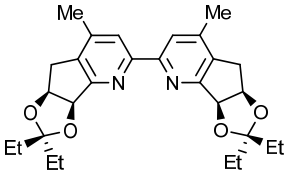
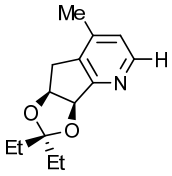
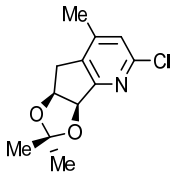
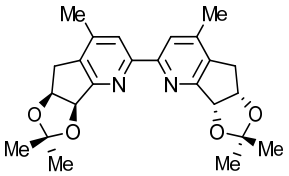
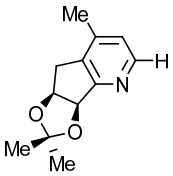
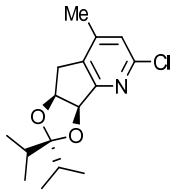
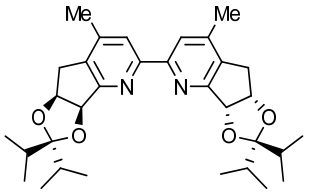
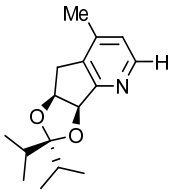
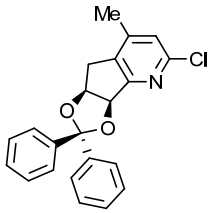
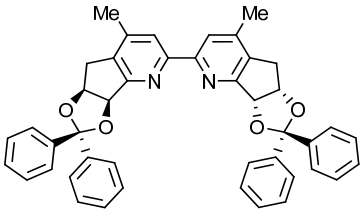
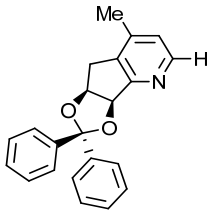
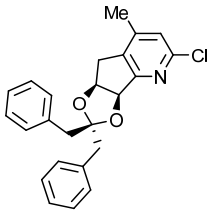
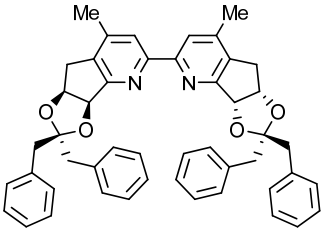
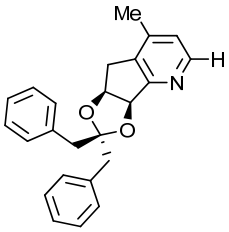
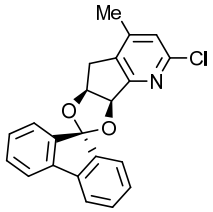
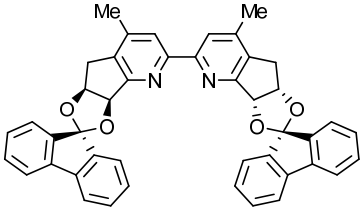
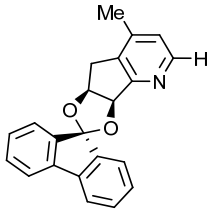
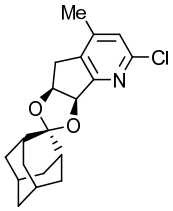
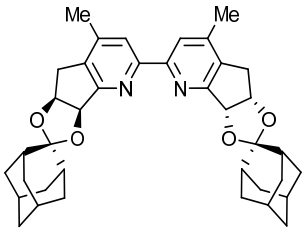
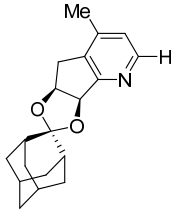
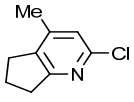
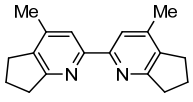
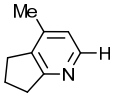
Ketone Equivalent	2-Chloropyridine Product(s)	Yield (%)
 **160**	 **117c**	**92**
 **154d**	 **117d**	**84**
 **154e**	 **117e**	**75**
 **154f**	 **117f**	**87**
 **154g**	 **117g**	**78 (84 brsm)**

Table 2.6.8.2: Results of Reductive-Coupling Reactions Concerning the Chloropyridines (117a-g) and (99)



117a-g **1a-g** **153a-g**

2-Chloropyridine	Coupled Product	Yield (%)	Reductively-Dehalogenated-product	Yield (%)
 **117a**	 **1a**  **122**	**62** **12**	 **153a**	**20**
 **117b**	 **1b**	**90**	 **153b**	**9**
 **117c**	 **1c**	**64**	 **153c**	**31**

2-Chloropyridine	Coupled Product	Yield (%)	Reductively-Dehalogenated-product	Yield (%)
 **117d**	 **1d**	**68**	 **153d**	**31**
 **117e**	 **1e**	**53**	 **153e**	**21**
 **117f**	 **1f**	**71**	 **153f**	**27**
 **117g**	 **1g**	**32**	 **153g**	**31**
 **99**	 **161**	**51**	 **162**	**32**

CHAPTER 3: RESULTS AND DISCUSSION 2

Evaluation of the Chiral Nonracemic 2,2'-Bipyridines in the Asymmetric Copper(I)-Catalyzed Cyclopropanation Reaction of Styrene and the Allylic Oxidation Reaction of Cycloalkenes

3.1 Evaluation of the Chiral Nonracemic C_2-Symmetric 2,2'-Bipyridines (1a-g)

3.1.1 Overview

In the previous chapter the syntheses and characterization of the known chiral nonracemic 2,2'-bipyridine **1a** and six new chiral nonracemic 2,2'-bipyridines **1b-g** were described. The modular and divergent synthetic strategy employed in these syntheses allowed for the efficient synthesis of this family of chiral 2,2'-bipyridines. The known chiral 2,2'-bipyridine **1a** had been proven to be effective and a notable chiral ligand in the copper(I)-catalyzed asymmetric cyclopropanation reaction of various derivatives of styrene and in the allylic oxidation of cycloalkenes. The new 2,2'-bipyridines were made in order to improve upon the original ligand's performance in such reactions.

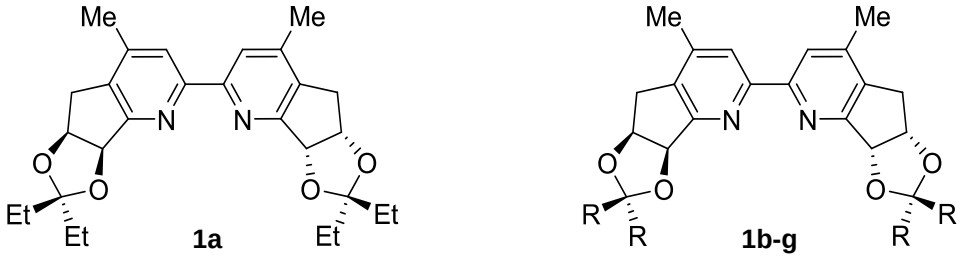


Figure 3.1.1.1: Chiral nonracemic C_2-symmetric 2,2'-bipyridines (1a-g).

With the chiral nonracemic C_2 symmetric 2,2'-bipyridines **1b-g** in hand, their evaluation as chiral nonracemic ligands in the copper(I)-catalyzed asymmetric cyclopropanation reaction of styrene with ethyldiazoacetate **28a** was undertaken (Figure 3.1.1.2). These tests led to the identification of a superior asymmetric 2,2'-bipyridyl ligand that was then evaluated in the copper(I)-catalyzed allylic oxidation reactions of cyclopentene, cyclohexene and cycloheptene with *tert*-butyl peroxybenzoate in order to examine its broader utility.

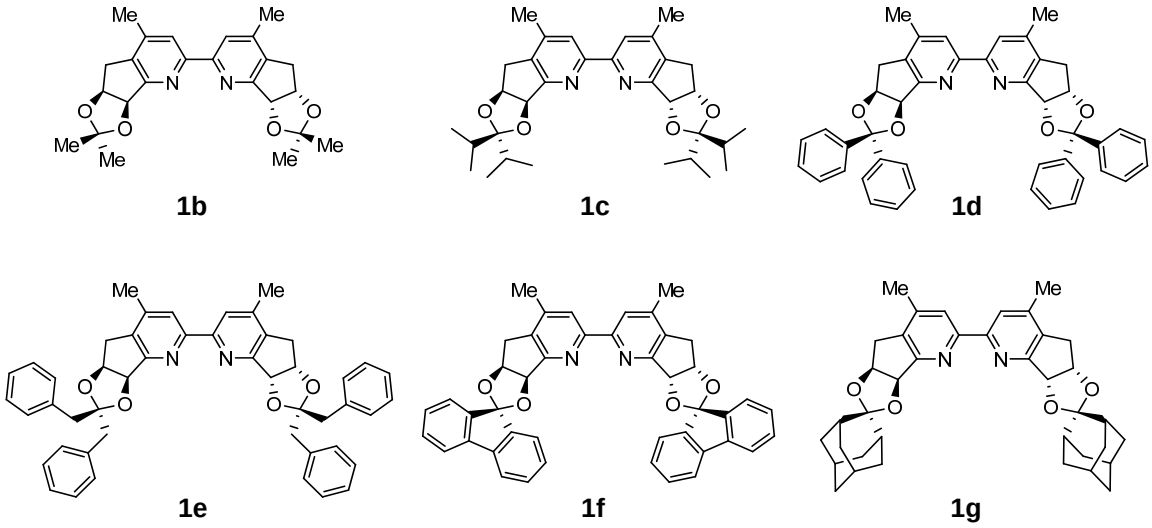


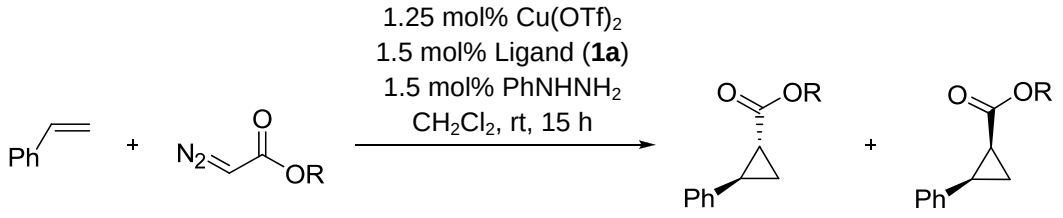
Figure 3.1.1.2: New chiral nonracemic C_2-symmetric 2,2'-bipyridines (1b-g).

3.1.2 Asymmetric Cyclopropanation Reactions

As mentioned previously in the introduction (See: Section 1.6, page 45), it was found that the 3-pentanone-derived 2,2'-bipyridyl ligand **1a** afforded good yield, enantioselectivity and diastereoselectivity of the *trans*-cyclopropane product derived from the cyclopropanation reaction of styrene and diethyl diazoacetate (74% yield, 60% de, 82% ee).[1,141] When *tert*-butyl diazoacetate was employed, even higher stereoselectivity was afforded (86% de, 92% ee). However, the yield of this reaction was somewhat compromised (Table 3.1.2.1). These results were in line with the best results

afforded by other 2,2'-bipyridines employed in this reaction. Only Katsuki's exceptional 2,2'-bipyridine **84** has enabled a higher enantioselectivity to be achieved in this benchmark reaction (Table 1.6.1.1 page 50).[112] Thus, it was hoped that through systematic modification of the original 2,2'-bipyridine **1a** that a more effective 2,2'-bipyridine for this reaction could be identified.

Table 3.1.2.1: Results of the Asymmetric Cyclopropanation Reactions of Alkenes (253a-e) Employing the 2,2'-Bipyridine (1a)[1,141]



27a-e **28a-c** *trans*-**29a,c** *cis*-**29a,c**

entry	R	product	*trans*:*cis*	yield (%)	ee (*trans*, %)
1	Et	**29a**	80:20	74	82
2	*t*-Bu	**29c**	93:7	67	92

The results obtained with the 2,2'-bipyridine **1a** in this benchmark reaction were rationalized based on a hindered approach model.[1,141] In this model, four modes of approach of styrene to the chiral copper carbene intermediate **163** were considered and are depicted looking up at the *N*,*N*'-binding site (Figure 3.1.2.1). In this model, the energetically favoured approaches of styrene to the carbene are those in which the phenyl substituent of the styrene and the large acetal moieties are on opposite faces of the complex account for the major stereoisomers isolated from this reaction. The less favoured approaches, where the phenyl group is on the same side of the complex as the acetal moieties, suffer from large steric interactions (as depicted by curly arrows) and thus led to the minor stereoisomeric products.

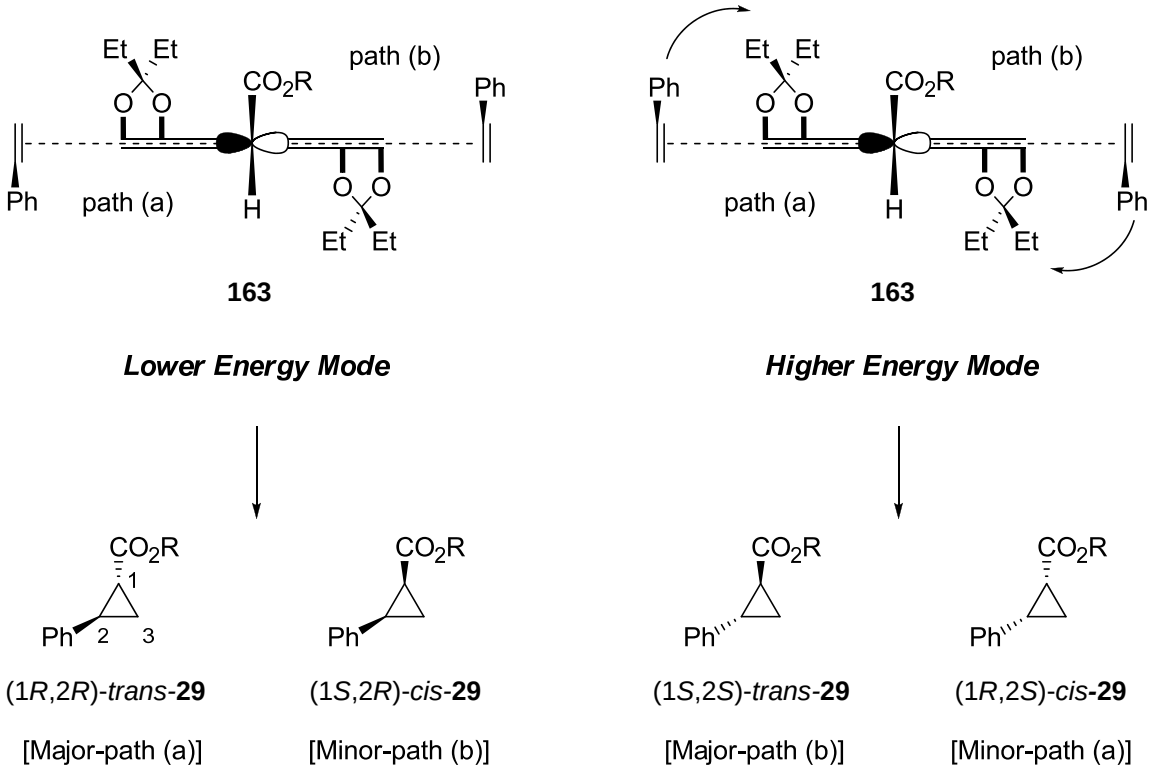


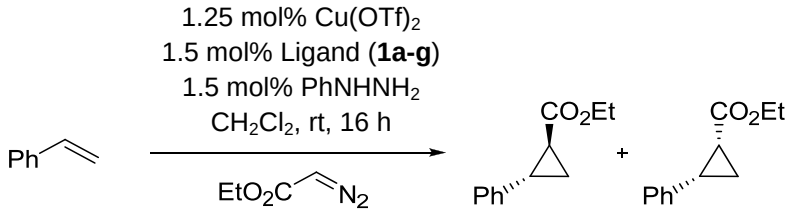
Figure 3.1.2.1: Rationalization of the stereochemical outcome of the asymmetric cyclopropanation reaction of styrene based on the minimization of steric interactions between the catalyst and the reacting species.[1,141]

These approaches can be further differentiated by the observation that when the styrene and ester moiety are on opposite faces of the ligand there is a further reduction in steric interactions. These approaches can be seen to generate the *trans*-cyclopropane products, whereas the more hindered approach yields the minor *cis*-cyclopropane products. This predicts that the main contributing factor to the diastereomeric outcome of the reaction is based mainly on the size of the diazoester moiety. This model was supported by the fact that when *t*-butyl diazoacetate was employed in this reaction higher stereoselectivities and diastereoselectivities were obtained, as compared to when ethyl diazoacetate was employed. Based on this model, it was anticipated that increased steric demand of the acetal moiety of the ligand would also increase stereoselectivity and thus, prove to be a superior ligand.

3.1.3 Evaluation of the Chiral Nonracemic C_2-Symmetric 2,2'-Bipyridines (1a-g) in the Copper(I)-Catalyzed Cyclopropanation Reaction of Styrene (27) and Ethyl Diazoacetate (28a)

The 2,2'-bipyridines **1a-g** were evaluated in the catalytic cyclopropanation reaction of styrene **27** using ethyl diazoacetate **28a** and copper(II) triflate (Figure 3.1.3.1). Although higher enantioselectivities had been observed through use of *tert*-butyl diazoacetate in this reaction, it is relevant to optimize the ligand with respect to ethyl diazoacetate, as this reagent is far more common and inexpensive. In addition, due to the lower enantioselectivities observed in cyclopropanation reactions involving ethyl diazoacetate larger improvements in the reaction's efficiency were expected. This would facilitate comparisons of the series of ligands. All cyclopropanation reactions were performed under the standard set of conditions employed in the preliminary evaluation of the original ligand **1a**.[1,141]

Figure 3.1.3.1: Asymmetric Cyclopropanation Reaction of Styrene (27) Employing Ethyl Diazoacetate and the Chiral Nonracemic 2,2'-Bipyridines (1a-g) and the Achiral 2,2'-Bipyridine (161).



27 **28a** *trans*-**29a** *cis*-**29a**

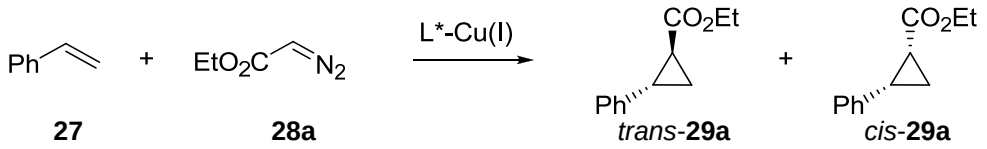
The active copper catalyst in these reactions was formed *in situ* by reduction of the complex formed between 1.25 mol % of copper(II) triflate and 1.5 mol% of the chiral nonracemic 2,2'-bipyridines **1a-g** and the achiral 2,2'-bipyridine **161** with phenylhydrazine. The colour of the solutions of these copper(II) complexes was typically of a green or reddish hue; however, upon addition of phenylhydrazine all solutions turned

a deep vibrant red colour, indicating that the copper(II) complex had been reduced to the catalytically active copper(I) species.

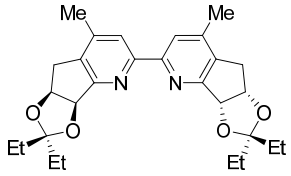
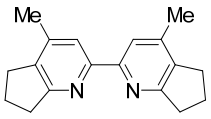
The cyclopropanation reactions were carried out at room temperature and involved the slow addition (over ~ twelve hours) of ethyl diazoacetate to a solution of 2.2 equivalents of styrene and 1.25 mol% of the preformed catalyst. The diastereoselectivity of the reaction was determined by analysis of the ^{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*-cyclopropane products. The enantiomeric purity of the *trans*-cyclopropane products were determined by analytical chiral HPLC (Daicel Chiracel OD column) of the alcohol formed upon reduction of the ester by lithium aluminum hydride. The *cis*-cyclopropanes failed to separate on the analytical Daicel Chiralcel OD chiral HPLC column. Thus, the enantiomeric purities of these compounds were determined by comparison of their optical rotations with literature values.[158] Of note, the enantiomeric purity of the minor *cis*-diastereoisomers had not been determined in the previous studies by Lyle, which concerned the original 2,2'-bipyridine **1a** (R = Et), as these compounds had not been the product of interest at that time and they were isolated on a small-scale.[1,141]

The results obtained using the 2,2'-bipyridine **1a** (R = Et) were in strong accord with those previously published using the same compound,[1,141] which indicated the reproducibility of this reaction (Table 3.1.3.1). The absolute configuration of the *trans*-cyclopropane product was determined by comparison of its optical rotation with that of literature values, and it had an optical purity of 83% *ee*.[159] Optical rotational analysis of the *cis*-cyclopropane product indicated that it had been formed with an enantiomeric purity of 20% ee.[158] Interestingly the absolute configuration from this measurement indicated that the (1*R*, 2*S*) enantiomer had formed,[160,161] which is opposite to the results predicted by the earlier rationalization.

Table 3.1.3.1: Results of the Asymmetric Cyclopropanation Reaction of Styrene (27) with Ethyl Diazoacetate (28a) and 2,2'-Bipyridines (1a) and (161)



27 **28a** *trans*-**29a** *cis*-**29a**

Ligand (L*)	*trans*:*cis*	Yield (combined, %)	ee (*trans*, %)	ee (*cis*, %)
 **1a**	79:21	72	83	20
	80:20[*141]	74[*141]	82[*141]	N/A[†]
 **161**	69:31	74	N/A	N/A

At this point the achiral 2,2'-bipyridine **161** was employed in this reaction. This was done to study the effect of employing the least sterically encumbered 2,2'-bipyridine

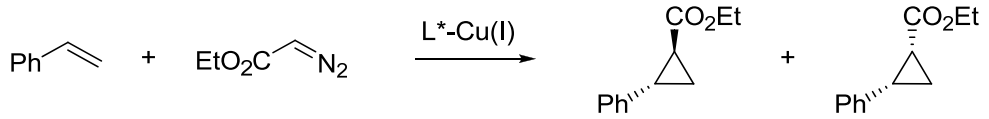
* Previously published results.

† Not determined previously.

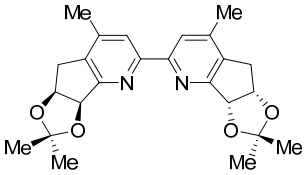
on the yield and diastereoselectivity of this reaction. In addition, the use of this achiral ligand provided racemic material which was used to confirm that the *cis*-cyclopropane ester product and its reduced alcohol analogue were irresolvable on HPLC using a Daicel Chiracel OD column. Interestingly, the reaction employing this achiral ligand afforded the same yield (74%) of the cyclopropane products as the chiral 2,2'-bipyridyl ligand **1a**. This indicates that chiral acetal functionality of the chiral ligand **1a** (R = Et) does not inhibit the reaction. The diastereoselectivity (38%) obtained through use of the achiral ligand showed that this reaction tends to afford *trans*-diastereoisomer as the major product and is independent of the chiral functionality. This supports the idea that the main contributing factor to the diastereoselectivity of this reaction is the size of the diazoester moiety.

The smallest chiral 2,2'-bipyridyl ligand (R = Me) employed in this reaction afforded the highest combined yield (76%) of cyclopropane products (Table 3.1.3.2). It also afforded the lowest diastereoselectivity (34% de) of all the chiral ligands evaluated and was similar to the results obtained through use of the achiral 2,2'-bipyridine **161**. The enantiomeric purity of the *trans*-cyclopropane product (58% ee *trans*-**29a**) isolated from this reaction was modest and significantly lower than the enantioselectivity afforded by the next largest ligand in the series, ligand **1a** (R = Et) which led to the major product in 83% ee (*trans*-**29a**). The low selectivity obtained with this ligand in comparison to the bulkier ligand was expected and supports the theory that a larger acetal would increase the stereoselectivity of this reaction.

Table 3.1.3.2: Results of the Asymmetric Cyclopropanation Reaction of Styrene (27) with Ethyl Diazoacetate (28a) and the 2,2'-Bipyridine (1b)

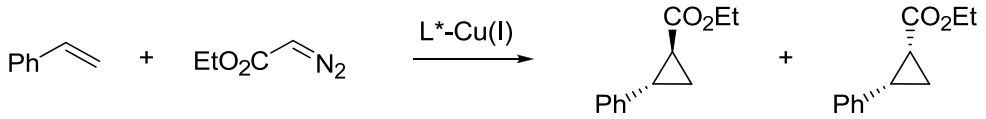


27 **28a** *trans*-**29a** *cis*-**29a**

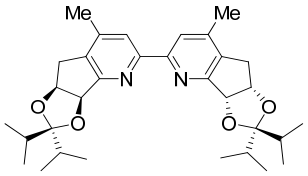
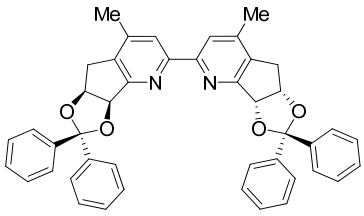
Ligand (L*)	*trans*:*cis*	Yield (combined, %)	ee (*trans*, %)	ee (*cis*, %)
 **1b**	67:33	76	58	10

The results obtained with the ligands **1c** (R = *i*-Pr) and **1d** (R = Ph) were almost identical and showed a modest increase in the enantiopurity of the *trans*-cyclopropane product (89 and 90% ee respectively, Table 3.1.3.3). The diastereoselectivity of these reactions (64% de) was slightly higher than that afforded by the original ligand **1a** (R = Et, 60% de). The isopropyl groups of the 2,2'-bipyridine **1c** (R = *i*-Pr) are larger than the analogous 2,2'-bipyridine **1a**. Thus, the increase in stereoselectivity was expected on these grounds. The similarities between the results of the two 2,2'-bipyridines **1c** and **1d** indicate that the phenyl moieties likely fill the same effective volume as the isopropyl groups.

Table 3.1.3.3: Results of the Asymmetric Cyclopropanation Reaction of Styrene (27) with Ethyl Diazoacetate (28a) and the 2,2'-Bipyridines (1c) and (1d)

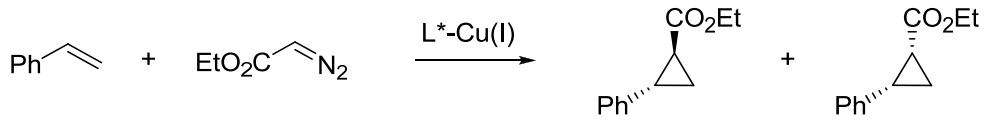


27 **28a** *trans*-**29a** *cis*-**29a**

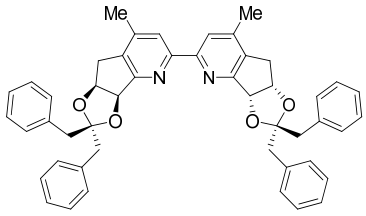
Ligand (L*)	*trans*:*cis*	Yield (combined, %)	ee (*trans*, %)	ee (*cis*, %)
 **1c**	82:18	62	89	24
 **1d**	82:18	62	90	25

In regard to the 2,2'-bipyridine **1e** (R = Bn) with the largest and most flexible acetal functionality, the enantioselectivities obtained were further improved only in the case of the *cis*-cyclopropane product (Table 3.1.3.4). In addition, the diastereoselectivity observed when employing this ligand was the highest overall (80% de). However, the overall yield of this reaction was compromised, presumably due to the increased size of the acetal functionality of the ligand.

Table 3.1.3.4: Results of the Asymmetric Cyclopropanation Reaction of Styrene (27) with Ethyl Diazoacetate (28a) and the 2,2'-Bipyridine (1e)



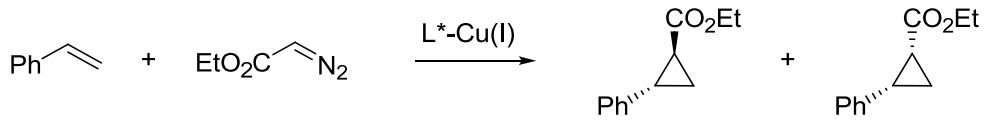
27 **28a** *trans*-**29a** *cis*-**29a**

Ligand (L*)	*trans*:*cis*	Yield (combined, %)	ee (*trans*, %)	ee (*cis*, %)
 **1e**	90:10	52	90	37

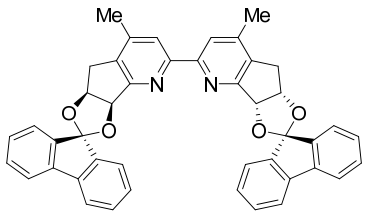
The use of the sterically encumbered and rigid ligand **1f** (R = fluorenone) led to the production of a *trans*-cyclopropane product with a very low enantiomeric purity (11% ee). This is, by far the lowest enantioselectivity obtained from this family of ligands (Table 3.1.3.5). The diastereoselectivity of this reaction was also extremely low (10% de *cis*) and was biased towards the *cis*-cyclopropane isomer. This reversal of diastereoselectivity is especially interesting considering that even the achiral 2,2-bipyridine **161** showed moderated diastereoselectivity towards the *trans*-cyclopropane product (38% de *trans*). Despite the poor selectivity of this ligand, the combined yields

of products was in line with the least bulky 2,2'-bipyridines evaluated in this study, as well as the achiral bipyridine **161**. This indicates that the overall catalytic activity of this ligand was not hampered by its interesting acetal functionalities.

Table 3.1.3.5: Results of the Asymmetric Cyclopropanation Reaction of Styrene (27) with Ethyl Diazoacetate (28a) and the 2,2'-Bipyridine (1f)



27 **28a** *trans*-**29a** *cis*-**29a**

Ligand (L*)	*trans*:*cis*	Yield (combined, %)	ee (*trans*, %)	ee (*cis*, %)
 **1f**	45:55	72	11	21

The lack of stereoselectivity afforded by the 2,2'-bipyrine **1f** in the asymmetric cyclopropanation reaction of styrene is underscored by its deviation from the results obtained by the benzophenone analogue **1d** (R = Ph), a compound that differs in a structural sense only to a small degree. The major difference between these compounds is not their steric volume but rather their rigidity. The phenyl groups of the benzophenone analogue are free to rotate and thus can interact with the binding site of the ligand whereas the acetal derived from fluorenone is completely rigid, which would cause the binding site to be relatively open (Figure 3.1.3.2).

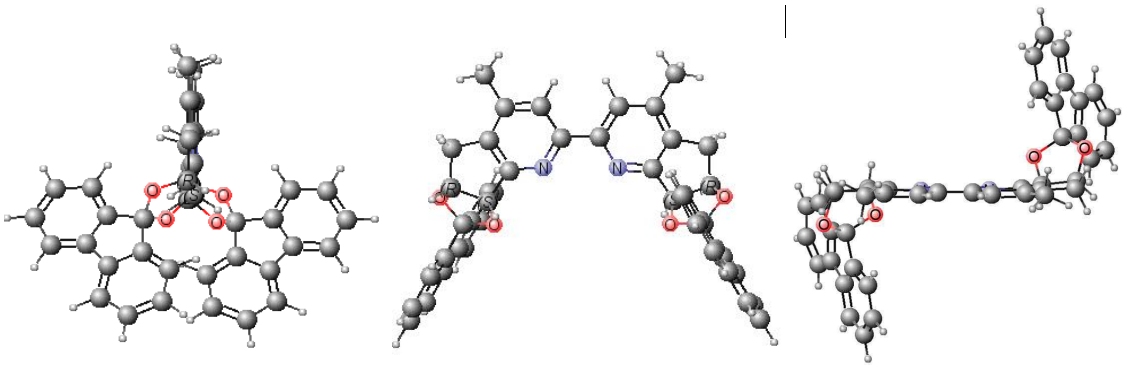


Figure 3.1.3.2: Three different perspectives of the 2,2'-bipyridine (1f).

The fluorenone acetal is held roughly orthogonal to the body of the 2,2'-bipyridine and is flat. From a *side on* view, these acetals appear extremely bulky, and seem as though they would easily to prevent the approach of styrene on the reaction centre. A *front on* view reveals their lack of encroachment on the binding centre (Figure 3.1.3.2). From this, the conclusion is made that the styrene molecule does not necessarily approach directly from the side of the ligand as was proposed earlier, but rather that a transition state involving the formation of the cyclopropane ring (Figure 3.1.3.3) is what governs the stereo-outcome of the reaction. This is discussed in more detail later in this chapter (See: Section 3.1.4, page 163).

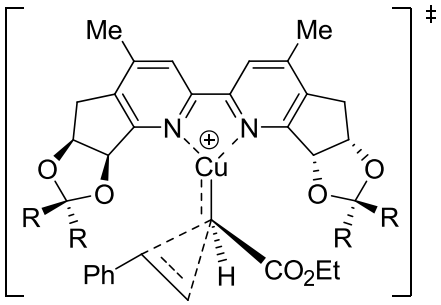


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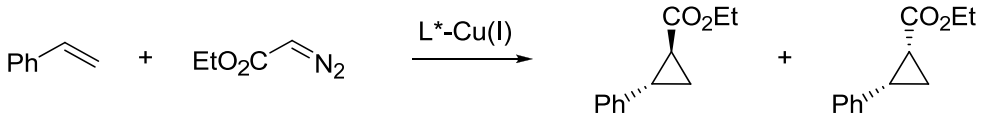
Figure 3.1.3.3: A presumed transition state involving the formation of a cyclopropyl ring from styrene and a stabilized carbene.[126]

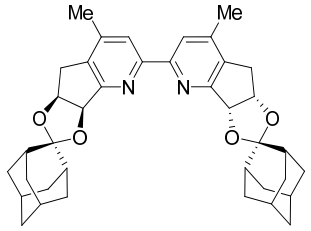
The highest enantioselectivity in the asymmetric cyclopropanation reaction of styrene was obtained using the 2,2'-bipyridine ligand **1g** (R = adamantanone). The *trans*-

cyclopropane product obtained from this reaction had an enantiomeric purity of 94% ee. The *cis*-cyclopropane product had an enantiomeric purity of 46% ee (Table 3.1.3.6). These stereoselectivities represent a marked increase from the results obtained with the original ligand **1a** (R = Et), and a similar overall yield (74%) of cyclopropane product was obtained.

Table 3.1.3.6: Results of the Asymmetric Cyclopropanation Reaction of Styrene (27) with Ethyl Diazoacetate (28a) and the 2,2'-Bipyridine (1g)



27 **28a** *trans*-**29a** *cis*-**29a**

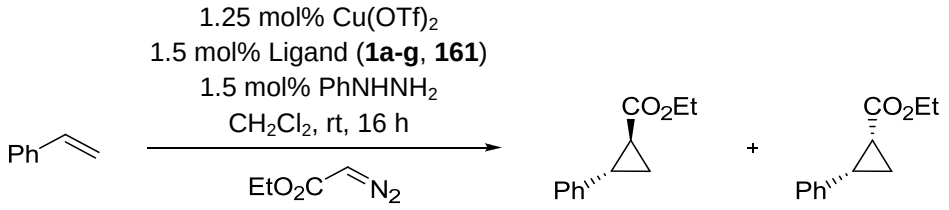
Ligand (L*)	*trans*:*cis*	Yield (combined, %)	ee (*trans*, %)	ee (*cis*, %)
	85:15	74	94	46

1g

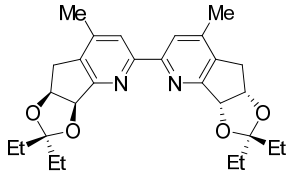
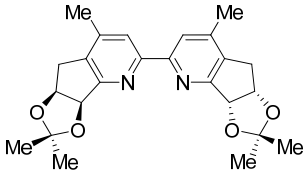
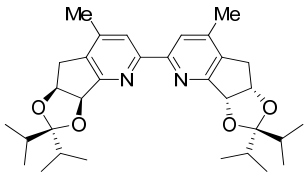
The acetal functionality of the adamantanone-derived 2,2'-bipyridine **1g** has the most spherical shape of all ligands evaluated in this asymmetric cyclopropanation reaction of styrene. In addition, with the exception of the fluorenone-derived ligand **1f**, it is also more rigid than the other chiral 2,2'-bipyridines. Due to the rigid spherical shape of this acetal it will always occupy some of the space near the catalytic centre regardless of what steric forces act upon it. This is in contrast to the flexible ligands which might be displaced from where they can influence the catalytic centre. This indicates that the enantioselectivity of the reaction may be dependent upon the continual impingement of the acetal on the active site of the catalyst.

The results obtained in these studies illustrate that there is a delicate balance between high yield and enantioselectivity in this benchmark reaction. However, through a survey of various structural motifs it was possible to satisfy both of these important criteria. These results are summarized below (Table 3.1.3.7). Thus, a superior ligand has been identified that afforded results which were equivalent to the best 2,2'-bipyridyl ligand employed to date in this reaction (See Table 1.6.1.1 on page 50).[107]

Table 3.1.3.7: Results of the Asymmetric Cyclopropanation reaction of Styrene (27) with Ethyl Diazoacetate (28a) and the 2,2'-Bipyridines (1a-g) and (161)

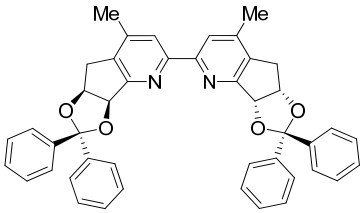
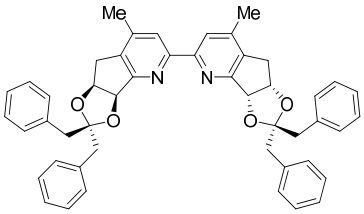
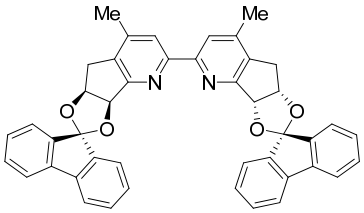
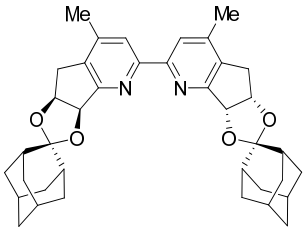
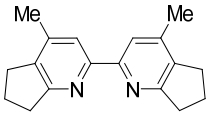


27 **28a** *trans*-**29a** *cis*-**29a**

Ligand (L*)	*trans*:*cis*	Yield (combined, %)	ee (*trans*, %)	ee (*cis*, %)
 **1a**	79:21	72	83	20
	80:20[*141]	74[*141]	82[*141]	N/A[†]
 **1b**	67:33	76	58	10
 **1c**	82:18	62	89	24

* Previously published results.

† Not previously determined.

Ligand (L*)	*trans*:*cis*	Yield (combined, %)	ee (*trans*, %)	ee (*cis*, %)
 **1d**	82:18	62	90	25
 **1e**	90:10	52	90	37
 **1f**	45:55	72	11	21
 **1g**	85:15	74	94	46
 **161**	69:31	74	N/A	N/A

3.1.4 Alternative Rationalization of the Stereochemical Outcomes of the Asymmetric Cyclopropanation Reactions of Styrene (27) with Ethyl Diazoacetate (28a) and the Chiral Nonracemic 2,2'-Bipyridines (1a-g)

Due to the interesting results obtained with the fluorenone-derived 2,2'-bipyridyl ligand **1f**, as well as the unexpected absolute stereochemistry of *cis*-cyclopropane products isolated from all the cyclopropanation reactions of styrene, it is apparent that the initial rationalization of the stereochemical outcome should be readdressed. Recent computational studies regarding the mechanism of copper(I) catalyzed cyclopropanation reactions of related systems provide support for an improved rationalization of the results reported. These computational studies investigated the direct interaction of the chiral substituents on the transition state associated with the formation of the cyclopropane ring.[126]

Using computational methods, the study gave accurate quantitative predictions of the stereoselectivity associated with a chiral ruthenium complex for the cyclopropanation reaction of styrene with methyl diazoacetate. The same computational methods could not be directly applied to the *bis*-oxazoline-copper-carbene complex **165** (Figure 3.1.4.1). This stems from a failure of the calculations to converge on transition state structures when copper complexes are considered in the cyclopropanation reaction of styrene, a problem which is routinely encountered in studies on these types of systems.

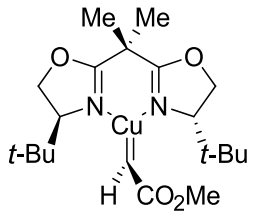


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Figure 3.1.4.1: An active ligand-copper-carbene complex that participates in the cyclopropanation reaction of styrene.

To overcome this problem, the lowest energy transition state structures of the cyclopropanation reaction of ethylene were determined. The structures derived from these calculations were then extended to styrene. From this, the following transition state structures calculated for the cyclopropanation reaction of styrene by methyl diazoacetate were determined (Figure 3.1.4.2).[126] The stereoselectivities predicted from these transition states did not quantitatively represent experimentally-derived values. However, the absolute configurations of the major products were accurately predicted. Thus, the authors concluded that these calculations were acceptable for the qualitative prediction of the stereochemical outcome of such reactions.

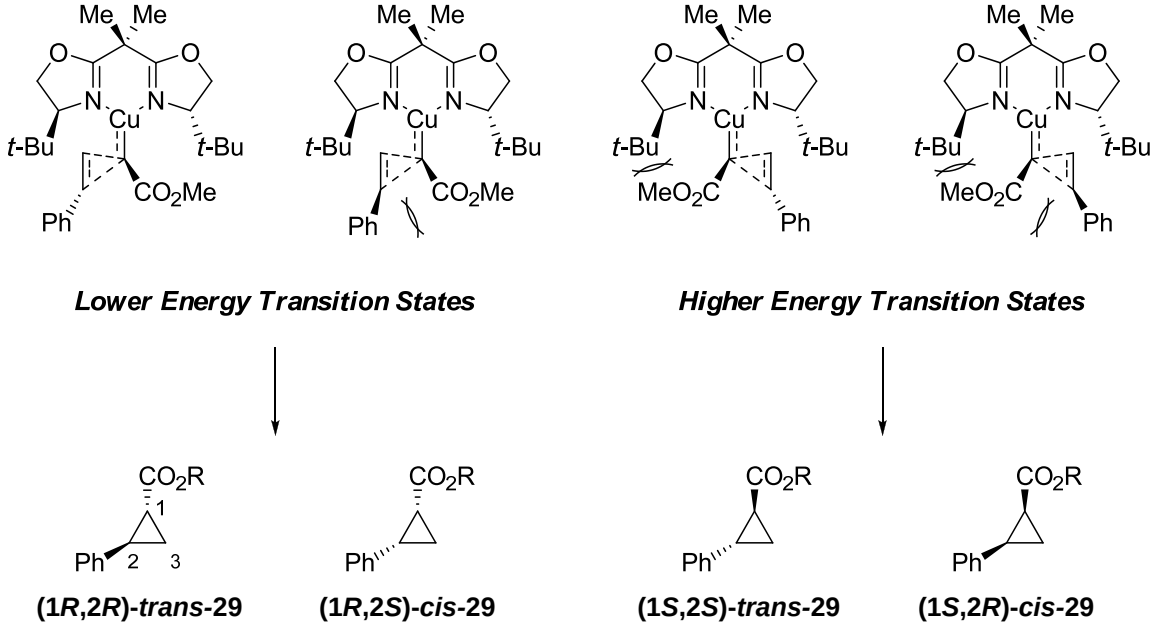


Figure 3.1.4.2: The transition states of the asymmetric cyclopropanation reaction of styrene with methyl diazoacetate using a copper-*bis*-oxazoline catalyst.[126]

The transition state structures which were predicted by computation show the alkene moiety of styrene to be roughly parallel to the copper-carbene bond. It was presumed that steric interactions between the *tert*-butyl groups of the *bis*-oxazoline and

the ester moiety of the forming cyclopropyl group inhibit the formation of the transition state on the *Si*-face of the carbene.[162,163] Application of these transition state structures to the ligand series **1a-g** accurately predicts the overall stereochemical outcome of the cyclopropanation reactions performed in this thesis project. In addition, the low enantioselectivities obtained using the fluorenone-derived ligand **1f** can be explained using these models, as the acetal moiety does not occupy the space in which the cyclopropane product forms, and thus does not influence the stereochemical outcome of the reaction to a large degree.

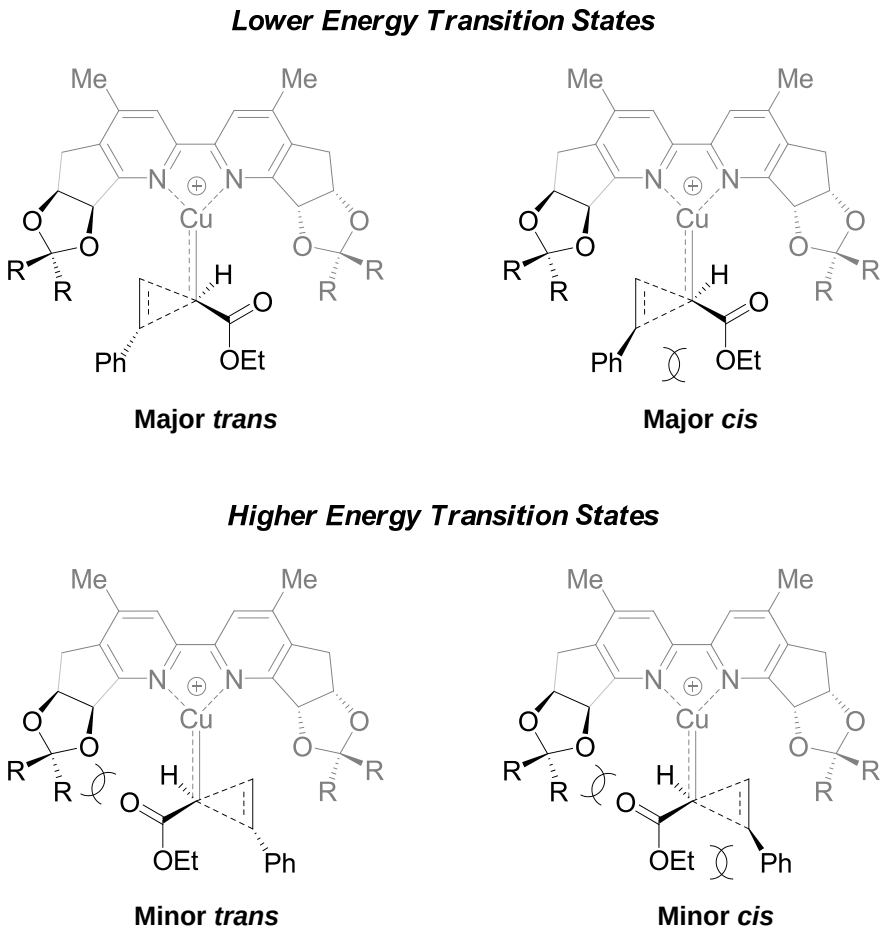


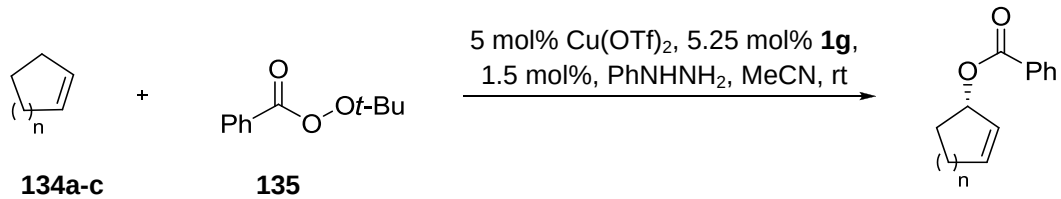
Figure 3.1.4.3: Proposed transition states of the asymmetric cyclopropanation reaction of styrene with ethyl diazoacetate leading to the four stereoisomeric cyclopropane products with the 2,2'-bipyridyl ligands (1a-g).

3.2 Copper(I)-Catalyzed Allylic Oxidation of Cycloalkenes by *tert*-Butylperoxy Benzoate using the Optimal Ligand (1g)

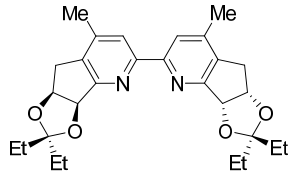
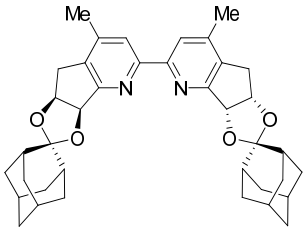
The asymmetric allylic oxidation of cycloalkenes with *tert*-butylperoxy benzoate using chiral nonracemic copper(I)-ligand complexes as a catalyst has recently attracted attention in literature.[135-138] In addition, the original ligand **1a** had been previously evaluated in this reaction.[132] Thus, due to the very positive results achieved from the use of the adamantanone-derived ligand **1g** in an asymmetric cyclopropanation reaction, it was subsequently evaluated in the asymmetric oxidation of cyclic alkenes (Table 3.1.4.1). This was done in order to determine its broader applicability in asymmetric reactions in comparison to the original ligand **1a**. These reactions were carried out at room temperature using a copper(I) complex that was formed *in situ* by the reduction of the complex formed between 5.25 mol% of the chiral nonracemic ligand **1g** and copper(II) triflate in acetonitrile. To this active catalyst system was added the requisite cycloalkene **136a-c** and *tert*-butylperoxy benzoate **135**. In comparison to the original ligand **1a**, these reactions were slower, and only the reaction involving cyclopentene went to completion.

The yields reported for these reactions are of the chromatographically purified allylic esters. The enantiomeric purities of these products were determined by analytical Chiral HPLC (Daicel Chiracel OD column) and were supported by comparison of optical rotation measurements with literature values.

Table 3.1.4.1: Asymmetric Allylic Oxidation of Cycloalkenes (134a-c) with *tert*-Butyl Peroxybenzoate (135) and the 2,2'-Bipyridine (1g)



134a-c **135** **136a-c**

Ligand	n	Yield (%)	ee (%)	Time (h)
 **1a**	1 (**134a**)	69[*132]	34	16
	2 (**134b**)	56[*132]	84	16
	3 (**134c**)	76[*132]	40	16
 **1g**	1 (**134a**)	70	36	72
	2 (**134b**)	58 (70 brsm)	84	72
	3 (**134c**)	32 (52 brsm)	91	72

The cycloalkene starting materials recovered from the reactions involving cyclohexene and cycloheptene indicated that the reaction was made more sluggish as the size of the cycloalkene was increased. These long reaction times are most likely due to the increased steric size of the adamantyl moieties of ligand **1g**, making the reaction less efficient than had been obtained with the original 3-pentanone-derived ligand **1a**.

The yield (70%) and enantioselectivity (36% ee) of the product obtained from the asymmetric allylic oxidation of cyclopentene employing the 2,2'-bipyridyl ligand **1g** was similar to the results obtained using the original 3-pentanone-derived ligand **1a**. This

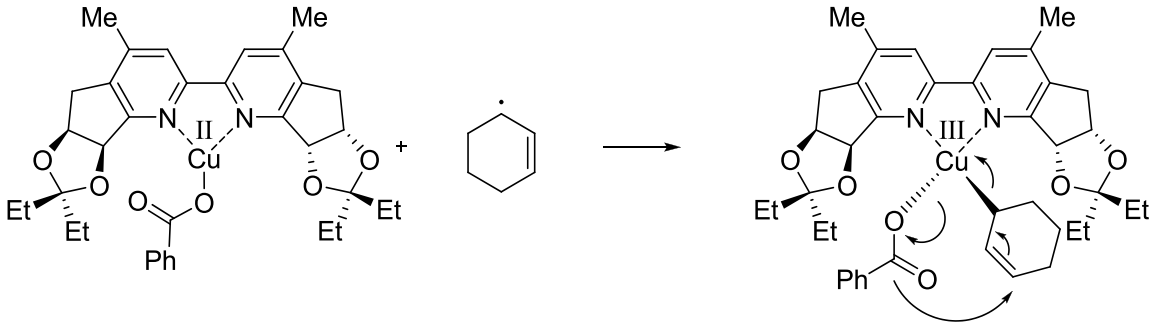
* Previously published results.

lack of improvement may indicate that even bulkier ligands may be required to afford acceptable stereoselectivity when employing cyclopentene as a substrate in this reaction.

The results obtained when employing the 2,2'-bipyridyl ligand **1g** in the allylic oxidation of cyclohexene were again similar to those reported when employing the 2,2'-bipyridine **1a**. However, the enantioselectivity of the asymmetric oxidation of cycloheptene was greatly improved, from 40% ee to 90% ee. To the best of our knowledge, this the highest reported enantioselectivity for an allylic oxidation reaction of cycloheptene involving a 2,2'-bipyridyl ligand.

The stereochemical outcome of this asymmetric reaction can be explained by considering the approach of the allylic radical to one of the less hindered quadrants of the C_2-symmetric copper(II) complex benzoate that would lead to a copper(III) species (Scheme 3.1.4.1).[1,132] This intermediate can then undergo a pericyclic rearrangement (or direct reductive elimination process) to afford the product and regenerate the active catalytic copper(I) complex.

Scheme 3.1.4.1: The Proposed Mechanism for the Asymmetric Allylic Oxidation of Cycloalkenes



3.3 General Conclusions

The newly synthesized chiral nonracemic 2,2'-bipyridine series (**1a-g**) and an achiral derivative were evaluated in the asymmetric cyclopropanation reaction of styrene with ethyl diazoacetate. All of these ligands afforded excellent catalytic systems for this reaction and four of them elicited enantioselectivities near or above 90% ee. The results indicated a trend that linked the steric size of the acetal moiety to an increase in the stereoselectivity of the reaction. The adamantanone-derived chiral nonracemic 2,2'-bipyridine **1g** was found to be the superior ligand for this reaction. It is also evident that it is not only the size of the acetal moiety that influences the stereochemical outcome of the reaction but also where this bulk of acetal moiety is located in relative to the carbene moiety of the reaction intermediate. This assertion is supported by the lack of stereoinduction obtained with the relatively open fluorenone-derived ligand **1f**. The studies also indicated that flexibility of the chiral moiety of the ligand also influences the reaction. This is observed in the asymmetric cyclopropanation reaction that employed the diphenylacetone-derived ligand **1e**. Although this ligand is clearly more sterically demanding than its benzophenone analogue **1d** it did not exhibit a marked increase in the enantiomeric purity of the *trans*-cyclopropane product. These stereochemical outcomes also shed light on the mechanism of this asymmetric reaction, and have led to a revised mechanistic interpretation. This model involves examination of the calculated lowest energy transition state and accurately predicts the qualitative stereochemical outcomes of these reactions. It is hoped that this rationalization will facilitate the design of even more effective ligands in the future. It may prove worthwhile to subject this series of ligands to the same computational procedures used to predict the transition states of the *bis*-

oxazoline complex **165** in these reactions. These computational studies help to determine if the models used were accurate enough to predict superior ligands, and thus presumably aid future studies in rational ligand design.

Due to the exceptional results obtained though employment of the adamantanone-based 2,2'-bipyridine **1g** in the asymmetric cyclopropanation reaction of styrene, this ligand was also employed in the copper(I)-catalyzed asymmetric allylic oxidation reaction of three different cycloalkenes. In the case of cycloheptene, the enantioselectivity of the catalytic allylic oxidation was more than doubled from 40% to 90%, when compared to the original ligand **1a**. This increase in enantioselectivity was not observed when either cyclopentene or cyclohexene were used as a substrate in this reaction. In these cases, the outcome of the reactions remained similar to those afforded by the original ligand **1a**. The reaction times for all these reactions were longer, presumably due to the increased size of the acetal moiety of the ligand that inhibits the rate of these processes. These reaction times could potentially be improved by changing the electronic nature of the ligand, such as by the addition of electron withdrawing substituents on the pyridine ring. This would have the effect of increasing the Lewis acidity of the metal complex which may in turn increase the rate of the reaction.

Overall, the goals set out at the beginning of this study were achieved. A series of structurally related, chiral nonracemic C_2-symmetric 2,2'-bipyridines were synthesized and fully characterized. In addition, these compounds were all found to be crystalline and were recrystallized to afford exceptionally pure material. The evaluation of these ligands in the asymmetric cyclopropanation reaction of styrene proved that this modular and divergent systematic approach for the preparation and identification of effective

ligands was valid. Moreover, these studies led to a more accurate rationalization for the stereochemical outcomes for such cyclopropanation reactions, which will hopefully aid future ligand design. The potential versatility of these 2,2'-bipyridine ligands was demonstrated in the allylic oxidation reaction of cycloheptene. In this reaction, a considerable increase in the stereoselectivity was observed when the adamantanone-derived 2,2'-bipyridine **1g** was employed instead of the less sterically demanding 3-pentanone analogue **1a**.

CHAPTER 4: EXPERIMENTAL SECTION

Experimental Procedures and Characterization Data

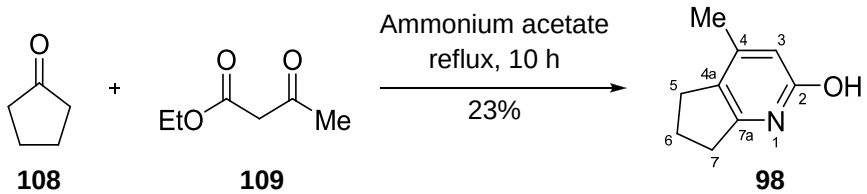
4.1 General Experimental Details

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) was dried over sodium/benzophenone ketyl and distilled under an atmosphere of dry nitrogen immediately prior to use. Benzene and dichloromethane 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.[164] 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) and Silicycle SiliaFlash® F60 (230-400 mesh).[165] Melting points (**M.p.**) were measured on a Gallenkamp capillary melting point apparatus and are uncorrected. Optical rotations ($[\alpha]_D$) were measured using a Perkin-Elemer 341 digital polarimeter. All proton and carbon nuclear magnetic resonance spectra (**^{1}H NMR** and **^{13}C NMR**, respectively) were recorded using a Bruker 400 FT spectrometer (operating frequencies: 1H, 400.13 MHz; 13C, 100.61 MHz), a Varian 500 FT spectrometer (operating frequencies: ^{1}H, 499.77 MHz; ^{13}C, 125.68 MHz) and a Bruker 600 FT spectrometer (operating frequencies: ^{1}H, 600.13 MHz; ^{13}C, 150.90 MHz) at ambient temperature. 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 77.00 ppm for ^1H and ^{13}C NMR spectra, respectively. The reference values used for deuterated dichloromethane (CD_2Cl_2) were 5.32 and 54.00 ppm for ^1H and ^{13}C NMR spectra, respectively. Infrared spectra (**IR**) were recorded as either KBr pellets (KBr) or as films (neat) using a Perkin Elmer 599B IR spectrophotometer. Low-resolution mass spectra (**MS**) were recorded on a Varian 4000 GC/MS/MS. The mode of ionization used was chemical ionization (CI) with methanol as the ionization gas. 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 electrospray ionization mass spectra (**HREIMS**) were obtained on Agilent Technologies 6210 Time-of-Flight LC/MS (Simon Fraser University). Microanalyses were performed on a Carlo Erba Model 1106 CHN analyzer (Simon Fraser University). Analytical chiral high performance liquid chromatography (**HPLC**) was performed using a Waters 1515 Isocratic HPLC pump and a Waters 2487 Dual λ absorbance detector. All separations were performed on a Daicel Chiracel OD column.

4.2 Experimental Procedures and Characterization Data Concerning *Chapter 2*

4.2.1 *4-Methyl-6,7-dihydro-5*H*-[1]pyrindine-2-ol* (98)[141]

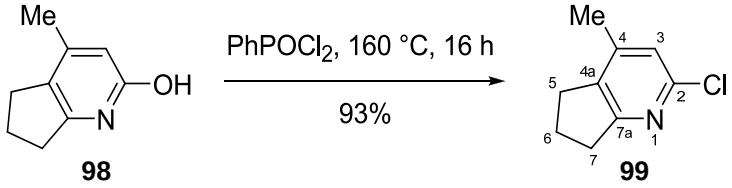


108 **109** **98**

A mixture of cyclopentanone **108** (140 mL, 1.58 mol), ethyl acetoacetate **109** (220 mL, 1.74 mol) and ammonium acetate (200 g, 2.60 mol) were stirred at reflux for ten hours. The resultant mixture was allowed to cool to room temperature and was then diluted with ether (150 mL) and filtered. The filter-cake was washed with ether (100 mL) and then recrystallized from ethanol (~ 200 mL) to afford the *title compound* **98** (54.4 g, 23%) as a pale yellow crystalline solid. $\mathbf{R_f}$ = 0.35, dichloromethane:methanol (19:1); **M.p.** 243-244 ˚C, ethanol (lit.[166] 243-244 ˚C, ethanol); **^{1}H NMR**[*] (500 MHz, $CDCl_3$) δ 2.05-2.15 (m, 5H, $ArCH_2CH_2$ and $ArCH_3$), 2.66 (t, J = 7.0 Hz, 2H, $ArCH_2$), 2.92 (t, J = 7.0 Hz, 2H, $ArCH_2$), 6.22 (s, 1H, Ar*H*); **^{13}C NMR**[*] (126 MHz, $CDCl_3$) δ 19.7, 22.3, 28.3, 30.9, 115.0, 120.5, 148.5, 150.9, 166.3; **IR** (KBr) 2978, 2967, 2921 (broad), 2878, 1719, 1660, 1588, 1570, 1474, 1439, 1422, 1382, 1313, 1267, 1208, 1193, 1118, 1100, 1086, 1024, 943, 923 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 150 (M + H, 100).

[*] The NMR spectrum is shown on page 224.

4.2.2 *2-Chloro-4-methyl-6,7-dihydro-5*H*-[1]pyrindine* (99)[141]

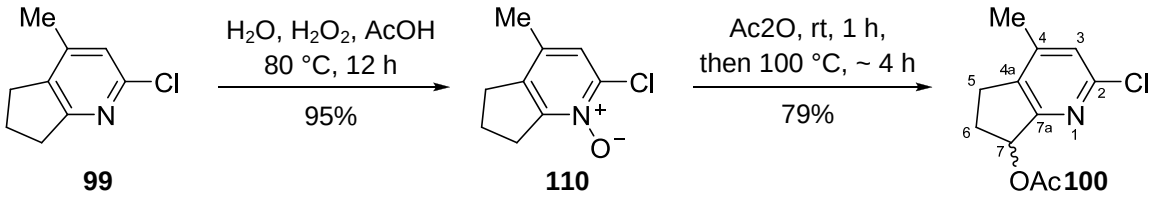


98 **99**

To phenylphosphonic dichloride (53.0 mL, 373 mmol) was added the pyridine-2-ol **98** (26.5 g, 178 mmol) and the resultant mixture was stirred at 160 ˚C for sixteen hours. The resultant mixture was allowed to cool to room temperature and then immersed in an ice bath. Water (250 mL) was cautiously added to the reaction mixture with vigorous stirring. The resultant mixture was neutralized by the careful addition of potassium carbonate (~ 50 g) and extracted with dichloromethane (3 × 200 mL). The combined organic extracts were washed with water (2 × 50 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo* to afford the crude product as a dark red oil. This material was purified by flash chromatography using chloroform as the eluant to afford the *title compound* **99** (26.4 g, 93%) as a white crystalline solid. $\mathbf{R_f}$ = 0.29, chloroform; **M.p.** 41-42 ˚C, chloroform (lit.[141] 41-42 ˚C, chloroform); **^{1}H NMR**[*] (500 MHz, $CDCl_3$) δ 2.10 (apparent p, J = 7.6 Hz, 2H, $ArCH_2CH_2$), 2.21 (s, 3H, $ArCH_3$), 2.80 (t, J = 7.5 Hz, 2H, $ArCH_2$), 2.96 (t, J = 7.8 Hz, 2H, $ArCH_2$), 6.88 (s, 1H, Ar*H*); **^{13}C NMR**[*] (126 MHz, $CDCl_3$) δ 18.7, 22.3, 28.6, 34.0, 121.7, 135.1, 145.8, 149.1, 165.4; **IR** (KBr) 3056, 2972, 2958, 2919, 2846, 1735, 1587, 1563, 1433, 1424, 1376, 1309, 1265, 1189, 1099, 1043, 1003, 884, 527 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 170 (M[^{37}Cl] + H, 31), 168 (M[^{35}Cl] + H, 100).

[*] The NMR spectrum is shown on page 225.

4.2.3 *(7*RS*)-7-Acetoxy-2-chloro-4-methyl-6,7-dihydro-5*H*-[1]pyrindine* (100)[141]



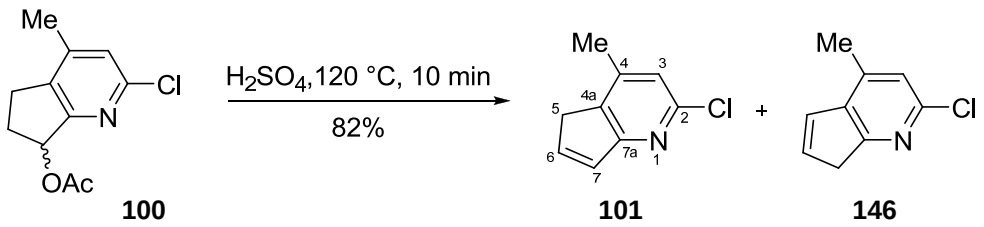
99 **110** **100**

To a stirred solution of the 2-chloropyrindine **99** (26.4 g, 157 mmol) in glacial acetic acid (220 mL) was added aqueous hydrogen peroxide (76.0 mL, 30% w/w, 790 mmol). The resultant mixture was stirred at 80 ˚C for twelve hours and then concentrated *in vacuo*. The resultant residue was diluted with water (300 mL) and then potassium carbonate (~ 80 g) was added. This mixture was extracted with dichloromethane (4 × 200 mL) and the combined organic extracts were washed with water (3 × 100 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo* to afford the corresponding pyridine *N*-oxide **110** (27.6 g, ~ 95%) as a pale brown crystalline solid. This material was dissolved in acetic anhydride (220 mL) and stirred at room temperature for one hour, followed by gradual heating to 100 ˚C over the course of one hour and then stirred at 100 ˚C for an additional three hours. The reaction mixture was then concentrated *in vacuo* to afford the crude product as a dark brown oil. This material was purified by flash chromatography using hexanes:ether (2:1) as the eluant to afford the *title compound* **100** (26.5 g, 79%) as an orange oil which crystallized upon standing. $\mathbf{R_f}$ = 0.21, hexanes:ether (2:1); **M.p.** 50-51 ˚C, chloroform; **^{1}H NMR**[*] (500 MHz, $CDCl_3$) δ 2.03-2.08 (m, 4H, $ArCH_2CHH$ and $ArCH_3$), 2.26 (s, 3H, $COCH_3$), 2.59-2.65 (m, 1H, $ArCH_2CHH$), 2.76 (ddd, J = 16.4, 8.8, 5.0 Hz, 1H, $ArCHH$), 2.94 (ddd, J = 15.6, 8.9, 5.3 Hz, 1H, $ArCHH$),

[*] The NMR spectrum is shown on page 226.

5.99 (dd, J = 7.5, 4.3 Hz, 1H, C*H*OAc), 7.05 (s, 1H, Ar*H*); **^{13}C NMR*** (126 MHz, $CDCl_3$) δ 18.2, 20.8, 25.7, 30.1, 76.4, 124.0, 135.8, 146.7, 150.3, 159.6, 170.2; **IR** (KBr) 2956, 1737, 1592, 1569, 1445, 1369, 1339, 1235, 1194, 1107, 1046, 938, 894, 886 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 228 (M[^{37}Cl] + H, 33), 226 (M[^{35}Cl] + H, 100).

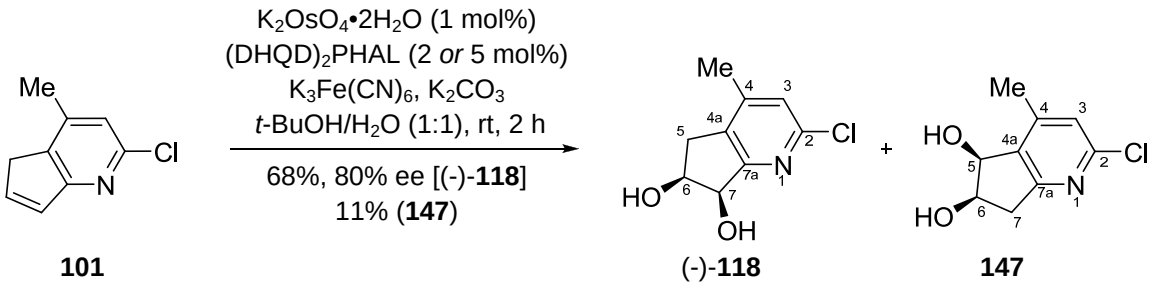
4.2.4 *2-Chloro-4-methyl-5*H*-[1]pyrindine* (101)[141]



100 **101** **146**

To a flask containing the acetate **100** (400 mg, 1.77 mmol) was added concentrated sulphuric acid (0.70 mL, 13.1 mmol). The flask was immediately immersed in an oil bath which was preheated to 120 ˚C. The reaction mixture was stirred for ten minutes and then removed from the oil bath. Crushed ice (10 g) was then added to the reaction mixture which was then poured into a cold aqueous solution of potassium hydroxide (40% w/v, 2.7 mL, 19 mmol). The resultant solution was extracted with dichloromethane (3 × 20 mL). The combined extracts were then washed with water (10 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo* to afford the crude product as a pale brown oil. This material was purified by flash chromatography using a short pad of silica with hexanes:ether (1:1) as the eluant to afford a mixture (36:1, as determined by ^{1}H NMR spectroscopy) of the *title compound* **101** and the isomer **146** (240 mg, 82%) as an oil which crystallized upon standing. $\mathbf{R_f}$ = 0.36, (1:1) hexanes:ether; **M.p.** 41-42 ˚C, chloroform; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 2.36 (s, 3H, ArC*H*$_3$), 3.32 (d, *J* = 1.7 Hz, 2H, *H*-5), 6.85-7.01 (m, 3H, *H*-6, *H*-7 and Ar*H*); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 18.0, 35.3, 120.0, 132.9, 134.4, 139.8, 144.0, 149.5, 163.8; **IR** (KBr) 3067, 2920, 2852, 1596, 1576, 1550, 1430, 1375, 1333, 1261, 1179, 1116, 892 cm^{-1}; **MS** 168 (M[^{37}Cl] + H, 31), 166 (M[^{35}Cl] + H, 100).

4.2.5 *(6S,7R)-2-Chloro-6,7-dihydro-4-methyl-5H-[1]pyrindine-6,7-diol* [(-)-118][141]



101 (-)-**118** **147**

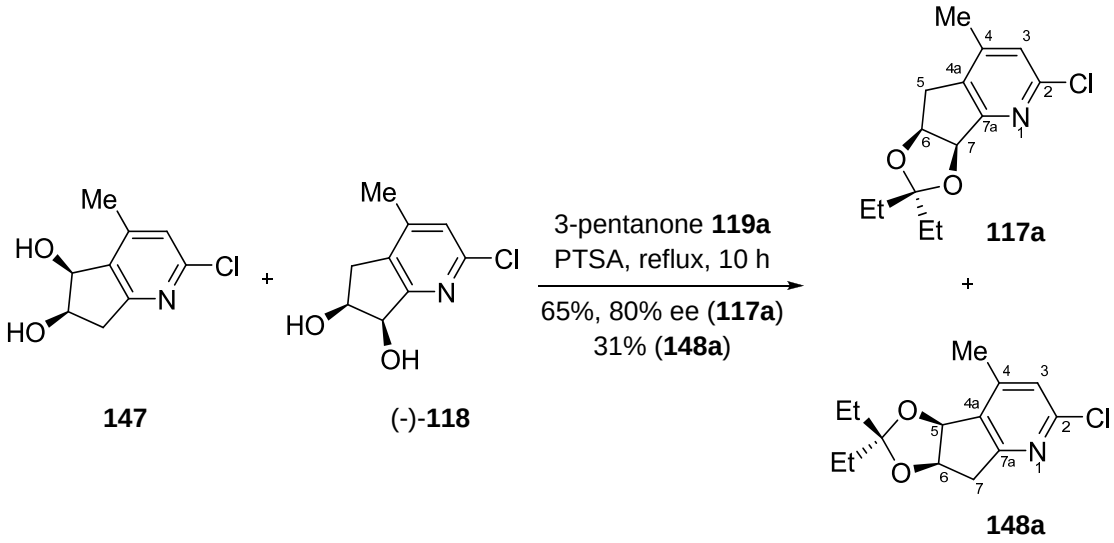
Method A:[141] To a suspension of potassium osmate dihydrate (42 mg, 120 μmol, 1 mol%) and $(DHQD)_2PHAL$ (449 mg, 577 μmol, 5 mol%) in a mixture of water (46 mL) and *t*-butanol (35 mL) were added potassium ferricyanide (11.4 g, 34.6 mmol) and potassium carbonate (4.78 g, 34.6 mmol). This suspension was stirred vigorously for thirty minutes at room temperature and then a solution of the alkenes **101** and **146** (36:1, 1.91 g, 11.5 mmol) in *t*-butanol (11 mL) was added. The resultant mixture was stirred vigorously for two hours at room temperature and then sodium sulfite (4.57 g, 36.3 mmol) was added. The solution was stirred for an additional thirty minutes and then concentrated *in vacuo*. The resultant residue was diluted with brine (150 mL) and extracted with dichloromethane (3 × 70 mL). The combined organic extracts were washed with brine (2 × 10 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo* to afford the crude product as a black tar. This material was purified by flash chromatography using ethyl acetate as the eluant to afford a mixture (6:1, determined by ^{1}H NMR) of the *title compounds* (-)-**118** and **147** (1.82 g, 79%) as a black foam. These two compounds were not separated or characterized at this stage.* The enantiomeric purity of diol (-)-**118** the corresponding acetal **117a** of the major product (-)-**118**, which was prepared on condensation of the above diol product mixture with 3-pentanone **119a**,

* For characterization of the diol (-)-**118** see page 189.

was determined to be 80% ee by analytical chiral HPLC using a Chiracel OD column [hexanes:isopropanol (96:4), flow rate 0.5 mL/min, detection at λ = 220 nm; t_{MAJOR} = 19.00 min, t_{MINOR} = 23.10 min).

Method B: To a suspension of potassium osmate dihydrate (22 mg, 60 μmol, 1 mol%) and $(DHQD)_2PHAL$ (94 mg, 121 μmol, 2 mol%) in a mixture of water (24 mL) and *t*-butanol (12 mL) were added potassium ferricyanide (5.96 g, 18.1 mmol) and potassium carbonate (2.50 g, 18.1 mmol). This suspension was stirred vigorously for thirty minutes at room temperature and then a solution of the alkenes **101** and **146** (36:1, 1.00 g, 6.03 mmol) in *t*-butanol (12 mL) was added. The resultant mixture was stirred vigorously for two hours at room temperature and then sodium sulfite (2.40 g, 190 mmol) was added. The solution was stirred for an additional thirty minutes and then concentrated *in vacuo*. The resultant residue was diluted with brine (30 mL) and extracted with dichloromethane (3 × 30 mL). The combined organic extracts were washed with brine (2 × 10 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo* to afford the crude product as a black tar. This material was purified by flash chromatography using ethyl acetate as the eluant to afford a mixture (6:1, determined by ^{1}H NMR) of the *title compounds* (-)-**118** and **147** (926 mg, 77%) as a dark foam. These two compounds were not separated or characterized at this stage. The enantiomeric purity of the corresponding acetal **117a** of the major product (-)-**118**, which was prepared on condensation of the above diol product mixture with 3-pentanone **119a**, was determined to be 80% ee by analytical chiral HPLC using a Chiracel OD column [hexanes:isopropanol (96:4), flow rate 0.5 mL/min, detection at λ = 220 nm; t_{MAJOR} = 19.00 min, t_{MINOR} = 23.10 min).

4.2.6 *(6S,7R)-2-Chloro-6,7-dihydro-4-methyl-5H-[1]pyrindine-6,7-diol 3-Pentanone Acetal* (117a) and *(5S,6R)-2-Chloro-6,7-dihydro-4-methyl-5H-[1]pyrindine-5,6-diol 3-Pentanone Acetal* (148a)[141]



To a mixture of the diol (-)-**118** and the isomer **147** (~ 2:1, 200 mg, 1.00 mmol) in benzene (15 mL) was added *p*-toluenesulfonic acid monohydrate (18 mg, 95 μmol) and 3-pentanone **119a** (0.40 mL, 3.8 mmol). The resultant solution was stirred at reflux for ten hours in a Dean-Stark apparatus and then concentrated *in vacuo* to afford the crude product as a black tar. This material was purified by flash chromatography using hexanes:ether (4:1) as the eluant to afford the *title compound* **117a** (174 mg, 65%) as a colourless oil which crystallized upon standing and the isomer **148a** (83 mg, 31%) as a colourless oil. The enantiomeric purity of the acetal **117a** was determined to be 80% ee by analytical chiral HPLC using a Chiracel OD column [hexanes:isopropanol (96:4), flow rate 0.5 mL/min, detection at λ = 220 nm; t_{MAJOR} = 19.00 min, t_{MINOR} = 23.10 min).

Title Compound **117a**: $\mathbf{R}_f$ = 0.55, hexanes:ethyl acetate (3:1); **M.p.** 42-43 ˚C, chloroform (lit.[141] 43-44 ˚C, chloroform); $[\boldsymbol{\alpha}]_D^{20}$ = + 80 (*c* 0.80, chloroform) [lit.[141] $[\boldsymbol{\alpha}]_D^{20}$

= + 80 (*c* 0.50, chloroform)], > 82% ee); **^{1}H NMR**[*] (500 MHz, $CDCl_3$) δ 0.58 (apparent t, *J* = 7.4 Hz, 3H, CH_2CH_3), 0.94 (apparent t, *J* = 7.5 Hz, 3H, CH_2CH_3), 1.45-1.51 (m, 2H, CH_2CH_3), 1.63-1.69 (m, 2H, CH_2CH_3), 2.25 (s, 3H, $ArCH_3$), 2.95-3.03 (m, 2H, *H*-5_α and *H*-5_β), 5.00 (ddd, *J* = 6.6, 4.0, 1.7 Hz, 1H, *H*-6_β), 5.40 (d, *J* = 5.9 Hz, 1H, *H*-7_β), 7.06 (s, 1H, *H*-3); **Observed nOe contacts** $ArCH_3$ to CH_2CH_3, $ArCH_3$ to CH_2CH_3, $ArCH_3$ to CH_2CH_3, $ArCH_3$ to CH_2CH_3, $ArCH_3$ to *H*-5_α, $ArCH_3$ to *H*-5_β, $ArCH_3$ to *H*-3; **^{13}C NMR**[*] (126 MHz, $CDCl_3$) δ 7.3, 8.4, 18.5, 29.2, 29.8, 39.9, 77.3, 82.9, 115.4, 124.3, 132.6, 147.6, 151.2, 160.6; **IR** (KBr) 3070, 2973, 2939, 2881, 1731, 1589, 1573, 1463, 1443, 1315, 1286, 1268, 1191, 1169, 1104, 1085, 916 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 270 (M[^{37}Cl] + H, 33), 268 (M[^{35}Cl] + H, 100), 224 (3), 182 (5).

Title compound **148a**: $\mathbf{R_f}$ = 0.67, hexanes:ethyl acetate (3:1); **^{1}H NMR**[†] (400 MHz, $CDCl_3$) δ 0.53 (apparent t, *J* = 7.4, 1.0 Hz, 3H, CH_2CH_3), 0.89 (apparent t, *J* = 7.4, 0.9 Hz, 3H, CH_2CH_3), 1.33-1.44 (m, 2H, CH_2CH_3), 1.57-1.69 (m, 2H, CH_2CH_3), 2.35 (s, 3H, $ArCH_3$), 3.10 (dd, *J* = 18.3, 5.1 Hz, 1H, *H*-7_β), 3.16 (d, *J* = 18.1 Hz, 1H, *H*-7_α), 4.89-4.92 (m, 1H, *H*-6_β), 5.50 (d, *J* = 5.8 Hz, 1H, *H*-5_β), 6.95 (s, 1H, *H*-3); **Observed nOe contacts** $ArCH_3$ to CH_2CH_3, $ArCH_3$ to CH_2CH_3, $ArCH_3$ to CH_2CH_3, $ArCH_3$ to CH_2CH_3, $ArCH_3$ to *H*-5_β, $ArCH_3$ to *H*-3; **^{13}C NMR**[†] (101 MHz, $CDCl_3$) δ 7.4, 8.3, 17.8, 29.6, 29.9, 39.5, 77.4, 81.0, 114.8, 123.1, 132.8, 148.9, 151.9, 161.70; **IR** (neat) 2975, 2936, 2884, 1719, 1590, 1564, 1436, 1268, 1075, 1017, 914, 734 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 270 (M[^{37}Cl] + H, 32), 268 (M[^{35}Cl] + H, 100); **Anal.** Calcd. for $C_{14}H_{17}ClNO_2$: C, 62.80; H, 6.78; N, 5.23. Found: C, 62.58; H, 6.89; N, 5.30.

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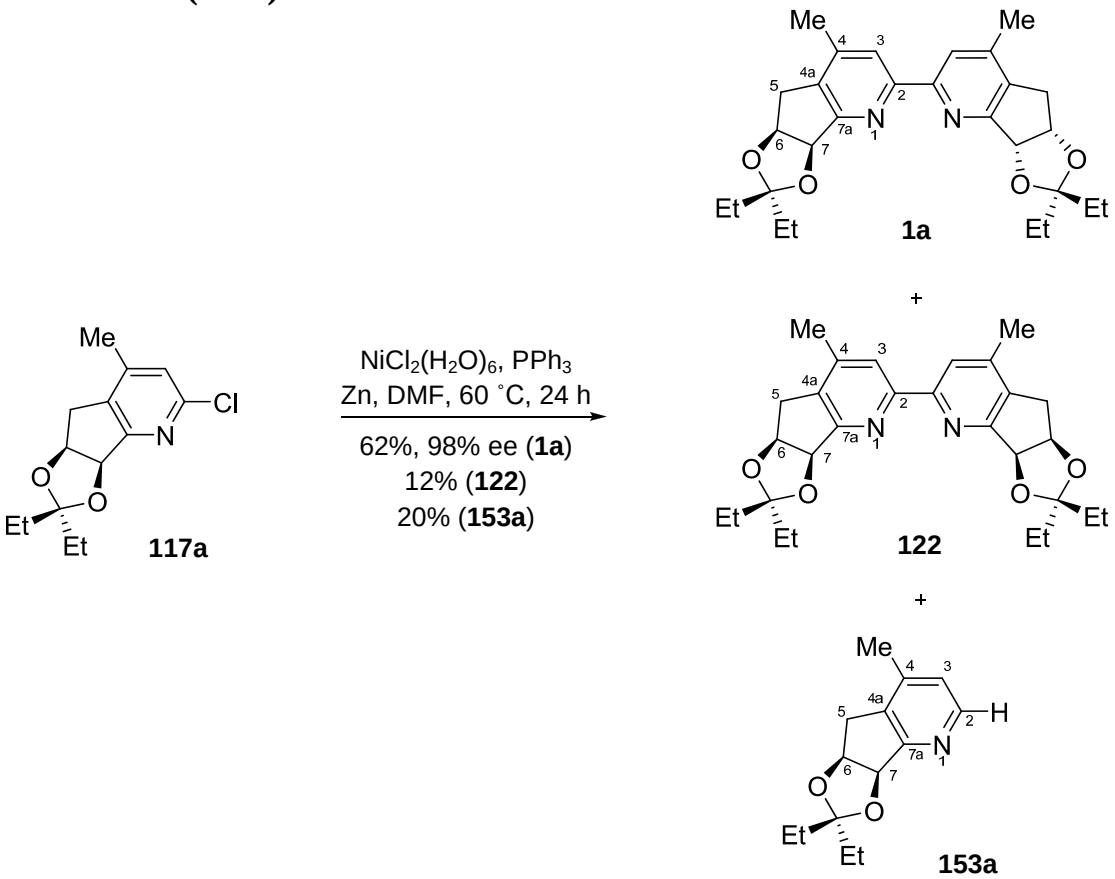
[*] The NMR spectrum is shown on page 230.

[†] The NMR spectrum is shown on page 231.

4.2.7 *(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′-tetrol 3-Pentanone* bis-*Acetal* (1a), *(6S,6′R,7R,7′S)-4,4′-Dimethyl-6,6′,7,7′-tetrahydro-5H,5′H-2,2′-bi([1]pyrindinyl)-6,6′,7,7′-tetrol 3-Pentanone* bis-*Acetal* (122) and *(6S,7R)-6,7-Dihydro-4-methyl-5H-[1]pyrindine-6,7-diol 3-Pentanone Acetal* (153a)[141]



To a stirred solution of nickel(II) chloride hexahydrate (272 mg, 1.14 mmol) and triphenylphosphine (1.19 g, 4.54 mmol) in dry degassed *N*,*N*-dimethylformamide (4 mL) was added zinc dust (<10 microns, 95 mg, 1.5 mmol). This mixture was stirred at 60 ˚C for one hour and then a solution of the acetal **117a** (2.20 g, 5.65 mmol, 80% ee) in dry degassed *N*,*N*-dimethylformamide (4 mL) was added *via* a cannula. The reaction mixture was stirred at 60 ˚C for twenty-four hours and then allowed to cool to room temperature. The resultant mixture was poured into an aqueous solution of ammonium hydroxide (10% w/w, 100 mL) and extracted with dichloromethane (3 × 50 mL). The combined

organic extracts were washed with brine (40 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford the crude product as a suspension in *N*,*N*-dimethylformamide. The *N*,*N*-dimethylformamide was removed under high vacuum (~ 5 mmHg) to afford the crude product as a beige solid. This material was purified by flash chromatography using dichloromethane as the eluant, followed by hexanes:ethyl acetate (2:1) to afford the C_2-symmetric bipyridine **1a** (162 mg, 62%) as a colourless crystalline solid, the *meso*-bipyridine **122** (31 mg, 12%) as a colourless solid and the pyridine **153a** (52 mg, 20%) as a colourless oil. The bipyridine **1a** was further purified by recrystallization on slow evaporation from a mixture of chloroform and heptanes (1:1) to afford colourless prismatic crystals. The enantiomeric purity of this compound was found to be 98% 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_{MAJOR} 23.66, t_{MINOR} = 19.54 min].

Title compound **1a**: $\mathbf{R_f}$ = 0.23, hexanes:ethyl acetate (2:1); **M.p.** 221-222 ˚C, chloroform/heptanes (lit.[141] 220-221 ˚C, hexanes/ethyl acetate); $[\boldsymbol{\alpha}]_D^{20}$ = + 157 (*c* 0.56, chloroform), [lit.[141] $[\boldsymbol{\alpha}]_D^{20}$ = + 154 (*c* 0.50, chloroform), > 99% ee)]; **^{1}H NMR**[*] (500 MHz, $CDCl_3$) 0.57 (apparent t, *J* = 7.4 Hz, 6H, 2 × CH_2CH_3), 0.97 (apparent t, *J* = 7.5 Hz, 6H, 2 × CH_2CH_3), 1.48-1.52 (m, 4H, 2 × CH_2CH_3), 1.72 (apparent q, *J* = 7.4 Hz, 4H, 2 × CH_2CH_3), 2.31 (s, 6H, 2 × ArCH_3), 3.04-3.08 (m, 4H, 2 × *H*-5_α and 2 × *H*-5_β), 5.03 (ddd, *J* = 6.2, 4.6, 2.8 Hz, 2H, 2 × *H*-6_β), 5.51 (d, *J* = 6.0 Hz, 2H, 2 × *H*-7_β), 8.29 (s, 2H, 2 × *H*-3); **^{13}C NMR**[*] (126 MHz, $CDCl_3$) δ 7.4, 8.4, 18.6, 29.5, 30.1, 34.5, 77.6, 83.6, 115.3, 122.2, 133.7, 145.0, 156.6, 159.6; **IR** (KBr) 2972, 2936, 2880, 1790, 1718, 1593,

[*] The NMR spectrum is shown on page 237.

1575, 1463, 1434, 1422, 1203, 1168, 1158, 1135, 1079, 1061, 934 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 465 (M + H, 100).

Title compound **122**: $\mathbf{R_f}$ = 0.31, hexanes:ethyl acetate (2:1); **M.p.** 315-316 ˚C, chloroform; $[\boldsymbol{\alpha}]_D^{20}$ = 0 (*c* 1.01, chloroform); **^{1}H NMR**[*] (400 MHz, $CDCl_3$) δ 0.55 (apparent t, *J* = 7.4 Hz, 6H, 2 × CH_2CH_3), 0.98 (apparent t, *J* = 7.5 Hz, 6H, 2 × CH_2CH_3), 1.48-1.53 (m, 4H, 2 × CH_2CH_3), 1.73 (apparent dq, *J* = 7.5, 1.3 Hz, 4H, 2 × CH_2CH_3), 2.33 (s, 6H, 2 × $ArCH_3$), 3.08-3.11 (m, 4H, 2 × *H*-5_α and 2 × *H*-5_β), 5.05 (ddd, *J* = 6.1, 4.2, 3.0 Hz, 2H, 2 × *H*-6_β), 5.54 (d, *J* = 6.0 Hz, 2H, 2 × *H*-7_β), 8.33 (s, 2H, 2 × *H*-3); **^{13}C NMR**[*] (101 MHz, $CDCl_3$) δ 7.4, 8.5, 18.6, 29.6, 30.2, 34.5, 77.7, 83.7, 115.3, 122.1, 133.8, 145.1, 156.6, 159.7; **IR** (neat) 2981, 2923, 1661, 1590, 1429, 1088, 908, 727 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 465 (M + H, 100), 380 (12); **Anal.** Calcd. for $C_{28}H_{36}N_2O_2$: C, 72.39; H, 7.81; N, 6.03. Found: C, 72.10; H, 7.79; N, 5.76.

Title compound **153a**: $\mathbf{R_f}$ = 0.40, hexanes:ethyl acetate (1:4); $[\boldsymbol{\alpha}]_D^{20}$ = + 10 (*c* 0.79, chloroform); **^{1}H NMR**[†] (500 MHz, $CDCl_3$) 0.55 (apparent t, *J* = 7.4 Hz, 3H, CH_2CH_3), 0.94 (apparent t, *J* = 7.5 Hz, 3H, CH_2CH_3), 1.46 (apparent dq, *J* = 7.3, 3.7 Hz, 2H, CH_2CH_3), 1.68 (apparent dq, *J* = 7.4, 0.9 Hz, 2H, CH_2CH_3), 2.25 (s, 3H, $ArCH_3$), 3.04 (d, *J* = 3.4 Hz, 2H, *H*-5_α and *H*-5_β), 4.98 (apparent td, *J* = 6.0, 3.5 Hz, 1H, *H*-6_β), 5.45 (d, *J* = 5.9 Hz, 1H, *H*-7_β), 6.98 (d, *J* = 5.0 Hz, 1H, *H*-3), 8.38 (d, *J* = 4.9 Hz, 1H, *H*-2); **^{13}C NMR**[†] (101 MHz, $CDCl_3$) δ 7.3, 8.5, 18.6, 29.3, 29.9, 34.4, 77.2, 83.4, 115.2, 124.2, 133.5, 144.5, 149.5, 160.3; **IR** (neat) 2975, 2936, 1719, 1661, 1597, 1461, 1081, 927 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 234 (M + H, 100), 148 (14), **HREIMS** Calcd. for $C_{14}H_{20}NO_2$: 234.1494. Found: 234.1490.

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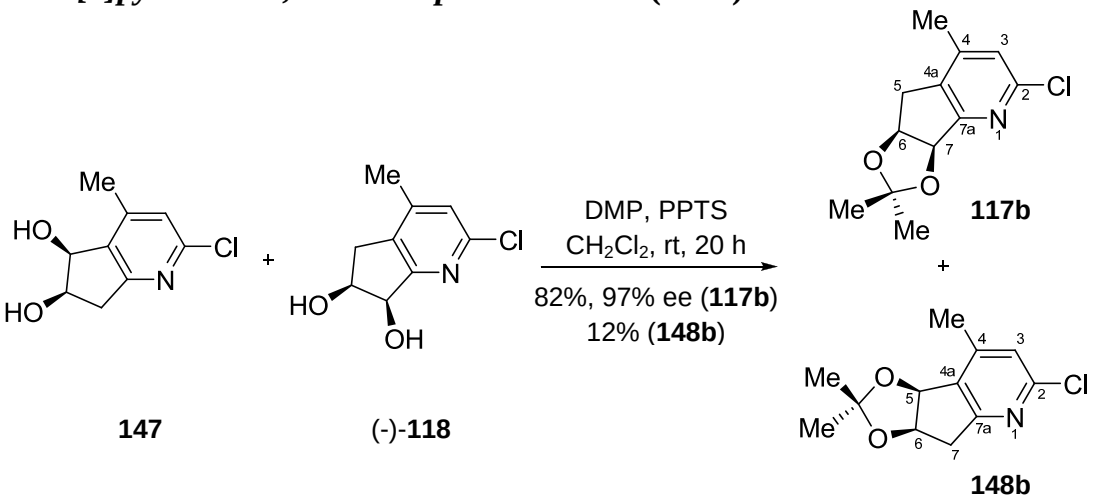
[*] The NMR spectrum is shown on page 238.

[†] The NMR spectrum is shown on page 239.

4.2.8 *(6S,7R)-2-Chloro-6,7-dihydro-4-methyl-5H-[1]pyrindine-6,7-diol Propanone Acetal* (117b) and *(5S,6R)-2-Chloro-6,7-dihydro-4-methyl-5H-[1]pyrindine-5,6-diol Propanone Acetal* (148b)



To a mixture of the diol (-)-**118** and the isomer **148b** (5:1, 1.40 g, 7.01 mmol, enantiomeric purity of (-)-**118** = 80% ee) in dichloromethane (40 mL) was added 2,2-dimethoxypropane (1.0 mL, 14 mmol) and pyridinium *p*-toluenesulfonate (106 mg, 422 *μ*mol). The resultant solution was stirred at room temperature for fourteen hours and then an additional portion of 2,2-dimethoxypropane (1.0 mL, 14 mmol) was added. This solution was stirred for six hours and then potassium carbonate (~ 300 mg) was added. The resultant mixture was filtered and the filter-cake was washed with dichloromethane (2 × 10 mL). The filtrate was then concentrated *in vacuo* to afford the crude product as a brown solid. This material was purified by flash chromatography using hexanes:ethyl acetate (4:1) as the eluant to afford the acetal **117b** (1.38 g, 82%) as a white solid and the isomer **148b** (273 mg, 16%) as a colourless oil which crystallized upon standing. The acetal **117b** was then recrystallized from heptanes to afford colourless needles. A small portion of this material was transformed to the requisite 3-pentanone acetal over two-steps (For step one See: page 188 ; For step two see; page 181) and determined to be 97%

ee by analytical chiral HPLC using a Chiracel OD column [hexanes:isopropanol (96:4), flow rate 0.5 mL/min, detection at λ = 220 nm; t_{MAJOR} = 19.00 min, t_{MINOR} = 23.10 min).

Title compound **117b**: $\mathbf{R_f}$ = 0.52, hexanes:ethyl acetate (2:1); **M.p.** 127-128 ˚C, heptanes; $[\alpha]_D^{20}$ = + 146 (*c* 1.00, chloroform); **^{1}H NMR**[*] (500 MHz, $CDCl_3$) δ 1.28 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 2.25 (s, 3H, ArCH_3), 2.98 (d, *J* = 16.9 Hz, 1H, *H*-5$_\alpha$), 3.04 (dd, *J* = 17.5, 5.6 Hz, 1H, *H*-5$_\beta$), 4.99 (apparent dt, *J* = 5.8, 1.4 Hz, 1H, *H*-6$_\beta$), 5.39 (d, *J* = 5.9 Hz, 1H, *H*-7$_\beta$), 7.06 (s, 1H, *H*-3); **Observed nOe contacts** ArCH_3 to CH_3, ArCH_3 to CH_3, ArCH_3 to *H*-5$_\alpha$, ArCH_3 to *H*-5$_\beta$, ArCH_3 to *H*-3; **^{13}C NMR**[*] (126 MHz, $CDCl_3$) δ 18.9, 25.6, 27.5, 34.2, 77.3, 83.0, 111.5, 124.8, 132.9, 148.0, 151.6, 160.7; **IR** (KBr) 3004, 2989, 2979, 2956, 2940, 2927, 1725, 1588, 1441, 1379, 1373, 1314, 1270, 1228, 1208, 1195, 1154, 1104, 1068, 1044, 1011, 892, 861 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 242 (M[^{37}Cl] + H, 33), 240 (M[^{35}Cl] + H, 100), 224 (3), 182 (5); **Anal.** Calcd. for $C_{12}H_{14}ClNO_2$: C, 60.13; H, 5.89; N, 5.84. Found: C, 60.48; H, 5.82; N, 5.79.

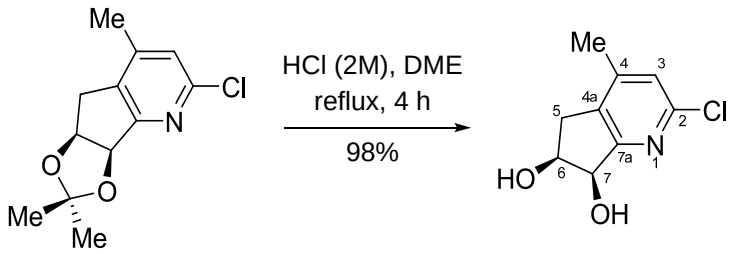
Title compound **148b**: $\mathbf{R_f}$ = 0.66, hexanes:ethyl acetate (2:1); **M.p.** 61-62 ˚C, chloroform; **^{1}H NMR**[†] (500 MHz, $CDCl_3$) δ 1.25 (s, 3H, CH_3CO$_2$), 1.42 (s, 3H, CH_3CO$_2$), 2.40 (s, 3H, ArCH_3), 3.20 (apparent d, *J* = 3.4 Hz, 2H, *H*-7$_\alpha$ and *H*-7$_\beta$), 4.95-4.99 (m, 1H, *H*-6$_\beta$), 5.52 (d, *J* = 5.8 Hz, 1H, *H*-5$_\beta$), 7.02 (s, 1H, *H*-3); **Observed nOe contacts** ArCH_3 to CH_3, ArCH_3 to CH_3, ArCH_3 to *H*-5$_\beta$, ArCH_3 to *H*-3; **^{13}C NMR**[†] (126 MHz, $CDCl_3$) δ 17.8, 25.5, 27.2, 39.4, 77.1, 80.7, 110.6, 123.1, 132.7, 148.8, 152.0, 161.7; **IR** (KBr) 3073, 2981, 2929, 1730, 1592, 1572, 1435, 1418, 1379, 1370, 1273, 1243, 1226, 1207, 1154, 1104, 1069, 1049, 1015, 892, 863, 835 cm^{-1}; **MS** (CI) *m/z* (rel.

[*] The NMR spectrum is shown on page 240.

[†] The NMR spectrum is shown on page 241.

intensity) 242 (M[^{37}Cl] + H, 33), 240 (M[^{35}Cl] + H, 100), 182 (7); **Anal.** Calcd. for $C_{12}H_{14}ClNO_2$: C, 60.13; H, 5.89; N, 5.84. Found: C, 59.87; H, 5.74; N, 5.88.

4.2.9 *(6S,7R)-2-Chloro-6,7-dihydro-4-methyl-5H-[1]pyrindine-6,7-diol* [(-)-118]



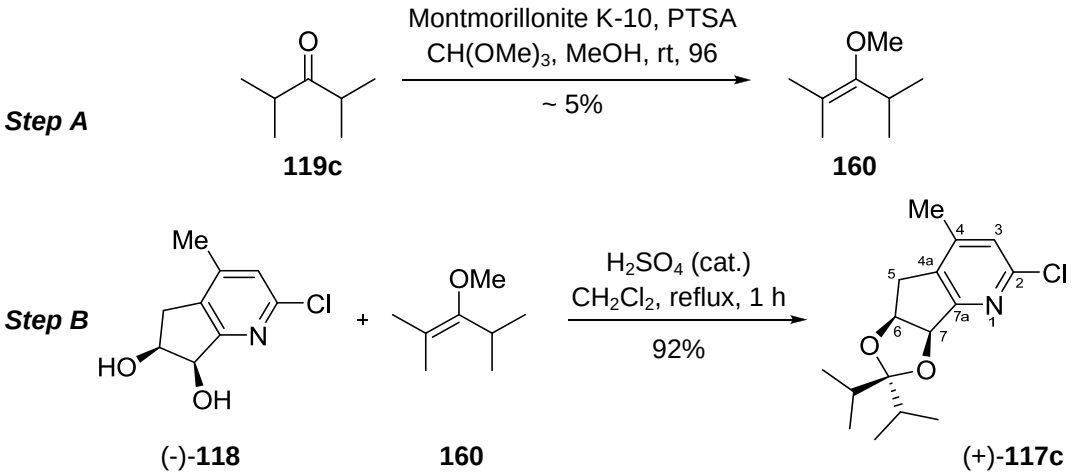
117b (-)-**118**

To a stirred solution of the acetal **117b** (3.67 g, 15.3 mmol, 97% ee) in 1,2-dimethoxyethane (570 mL) was added aqueous hydrochloric acid (2.0 M, 29 mL). The reaction mixture was stirred at reflux for 4 h, allowed to cool to room temperature, and then concentrated *in vacuo*. The resultant residue was diluted with water (50 mL), and potassium carbonate (~ 5 g) was added. This mixture was then extracted with dichloromethane (3 × 100 mL). The combined organic extracts were dried over anhydrous sodium sulfate and then concentrated *in vacuo* to afford the crude product as a beige solid. This material was purified by flash chromatography using ethyl acetate as the eluant to afford the *title compound* (-)-**118** (2.99 g, 98%) as a white solid. $\mathbf{R_f}$ = 0.31, ethyl acetate; **M.p.** 133-134 ˚C, chloroform; $[\alpha]_D^{20}$ = - 8.2 (*c* 1.05, chloroform); **^{1}H NMR**[*] (500 MHz, $CDCl_3$) δ 2.28 (s, 3H, ArC*H*$_3$), 2.91 (apparent dd, *J* = 16.6, 2.5 Hz, 1H, *H*-5$_\alpha$), 2.96 (apparent dd, *J* = 16.7, 5.0 Hz, 1H, *H*-5$_\beta$), 3.12 (broad m, 1H, O*H*), 4.31 (broad m, 1H, O*H*), 4.61-4.65 (m, 1H, *H*-6$_\beta$), 5.03 (d, *J* = 4.2 Hz, 1H, *H*-7$_\beta$), 7.06 (s, 1H, *H*-3); **^{13}C NMR**[*] (126 MHz, $CDCl_3$) δ 18.8, 34.8, 71.4, 74.7, 124.5, 132.8, 148.4, 150.4,

[*] The NMR spectrum is shown on page 227.

162.2; **IR** (KBr) 3482, 3408 (broad), 3344 (broad), 3069, 3011, 2981, 2940, 2905, 2870, 2722, 1595, 1573, 1440, 1424, 1369, 1335, 1301, 1281, 1189, 1173, 1139, 1114, 1059, 988, 923, 884, 815 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 202 (M[^{37}Cl] + H, 32), 200 (M[^{35}Cl] + H, 100), 182 (32); **Anal.** Calcd. for $C_9H_{10}ClNO_2$: C, 54.15; H, 5.05; N, 7.02. Found: C, 54.17; H, 4.93; N, 6.82.

4.2.10 *(6S,7R)-2-Chloro-6,7-dihydro-4-methyl-5H-[1]pyrindine-6,7-diol Diisopropyl Ketone Acetal* [(+)-117c]

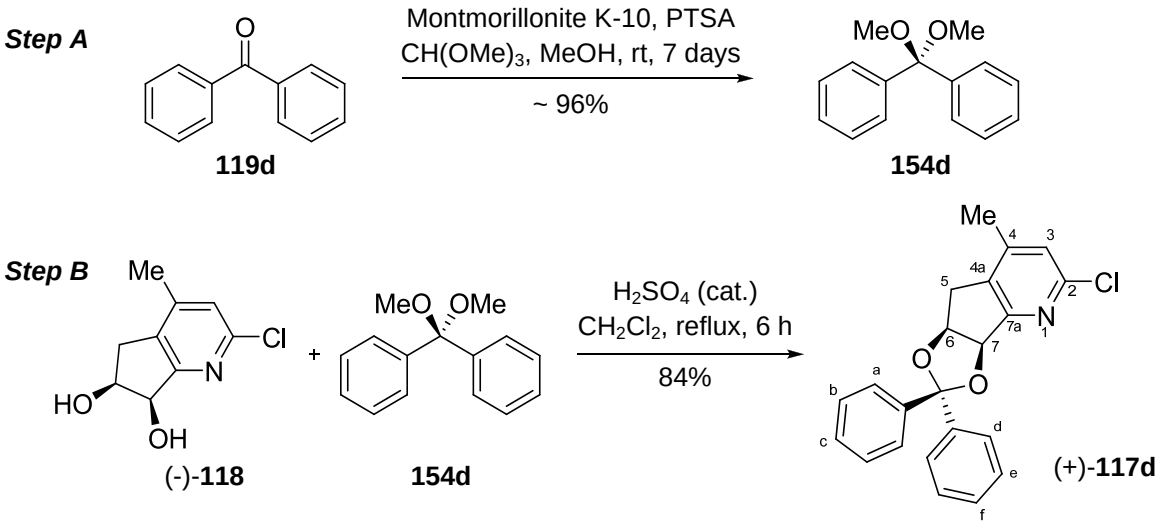


To a suspension of Montmorillonite K-10 clay (7.60 g) and trimethyl orthoformate (120 mL) in methanol (160 mL) was added *p*-toluenesulfonic acid monohydrate (1.2 g, 6.3 mmol) and diisopropyl ketone **119c** (50 mL, 350 mmol). The resultant mixture was stirred for four days at room temperature and then filtered. The filtrate was then distilled under reduced pressure to afford a mixture of the starting ketone **119c** and the corresponding methoxy-compound **160** [5.3:1, bp 40-44 ˚C, 42 mmHg, 2.72 g, 5% (**160**)] as a colourless oil. A portion of this material (164 mg, ~ 2.10 mmol of compound **160**), in dichloromethane (1 mL), was added dropwise to a stirred solution of the diol (-)-**118** (400 mg, 2.00 mmol, 97% ee) in a mixture of concentrated sulphuric acid and dichloromethane (1% w/v, 11 mL). The reaction mixture was stirred at reflux for

one hour and then allowed to cool to room temperature. The resultant mixture was washed with a saturated aqueous solution of potassium carbonate (10 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford the crude product as a yellow oil. This material was purified by flash chromatography using hexanes:ethyl acetate (4:1) as the eluant to afford the *title compound* (+)-**117c** (543 mg, 92%) as a white solid. The product was further purified by recrystallization on slow evaporation from hexanes:isopropanol (95:5) to afford colourless needles. $\mathbf{R_f}$ = 0.33, dichloromethane; **M.p.** 116-117 ˚C, hexanes/isopropanol; $[\alpha]_D^{20}$ = + 76 (*c* 0.88, chloroform); **^{1}H NMR**[*] (500 MHz, $CDCl_3$) δ 0.53 (d, *J* = 6.7 Hz, 3H, CHC*H*$_3$), 0.55 (d, *J* = 6.9 Hz, 3H, CHC*H*$_3$), 0.98 (d, *J* = 6.7 Hz, 3H, CHC*H*$_3$), 0.99 (d, *J* = 6.9 Hz, 3H, CHC*H*$_3$), 1.94 (apparent septet, *J* = 6.8 Hz, 1H, C*H*CH_3), 2.13 (apparent septet, *J* = 6.8 Hz, 1H, C*H*CH_3), 2.24 (s, 3H, ArC*H*$_3$), 2.96-3.04 (m, 2H, *H*-5$_\alpha$ and *H*-5$_\beta$), 5.08-5.12 (m, 1H, *H*-6$_\beta$), 5.49 (d, *J* = 6.4 Hz, 1H, *H*-7$_\beta$), 7.05 (s, 1H, 3-*H*); **^{13}C NMR**[*] (126 MHz, $CDCl_3$) δ 16.6, 16.7, 17.1, 17.4, 18.3, 31.7, 34.4, 35.0, 78.7, 84.3, 119.4, 124.0, 132.7, 147.1, 150.7, 160.1; **IR** (KBr) 2978, 2967, 2921, 2878, 1719, 1660, 1588, 1570, 1474, 1439, 1422, 1382, 1313, 1267, 1208, 1193, 1118, 1100, 1086, 1024, 943, 923 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 298 (M[^{37}Cl] + H, 32), 296 (M[^{35}Cl] + H, 100); **Anal.** Calcd. for $C_{16}H_{22}ClNO_2$: C, 64.97; H, 7.50; N, 4.74. Found: C, 65.16; H, 7.53; N, 4.83.

[*] The NMR spectrum is shown on page 232.

4.2.11 *(6*S*,7*R*)-2-Chloro-6,7-dihydro-4-methyl-5*H*-[1]pyrindine-6,7-diol Benzophenone Acetal* [(+)-117d][146]

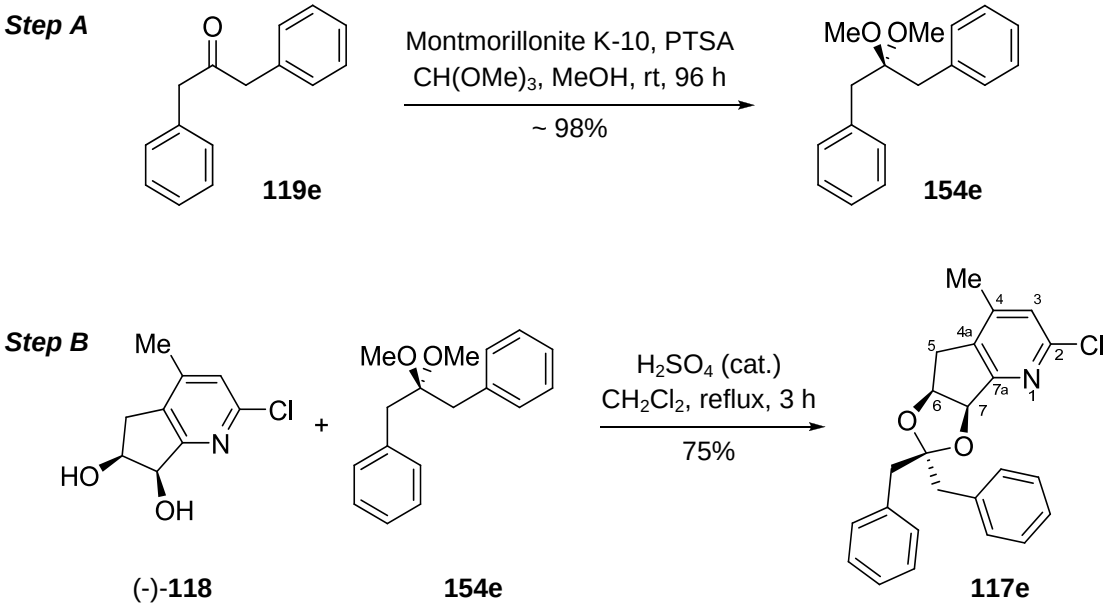


To a suspension of Montmorillonite K-10 clay (190 mg) and trimethyl orthoformate (3 mL) in methanol (4 mL) was added *p*-toluenesulfonic acid monohydrate (10 mg, 53 *μ*mol) and benzophenone **119d** (1.00 g, 5.49 mmol). The resultant mixture was stirred for seven days at room temperature and then filtered, the filter-cake was washed with dichloromethane (2 × 10 mL). The filtrate was poured into a saturated aqueous solution of sodium bicarbonate (15 mL) and extracted with dichloromethane (3 × 30 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate and then concentrated *in vacuo* to afford the crude dimethyl acetal **154d** (1.20 g, ~ 96%) as a white crystalline solid. A portion of this material (289 mg, ~ 1.26 mmol) in dichloromethane (2.0 mL) was added dropwise to a stirred solution of the diol (-)-**118** (250 mg, 1.25 mmol, 97% ee) in a mixture of concentrated sulphuric acid and dichloromethane (1% w/v, 16 mL). The reaction mixture was stirred at reflux for six hours and then allowed to cool to room temperature. The resultant mixture was then washed with a saturated aqueous solution of potassium carbonate (10 mL), dried

over anhydrous magnesium sulfate and concentrated *in vacuo* to afford the crude product as a brown oil. This material was purified by flash chromatography using dichloromethane as the eluant to afford the *title compound* **117d** (384 mg, 84%) as a white solid. This material was further purified on slow evaporation from dichloromethane to afford colourless granular crystals. $\mathbf{R_f}$ = 0.40, dichloromethane; **M.p.** 156-157 ˚C, dichloromethane; $[\boldsymbol{\alpha}]_D^{20}$ = + 68.0 (*c* 1.16, chloroform); **^{1}H NMR**[*] (600 MHz, $CDCl_3$) δ 2.21 (s, 3H, ArCH_3), 3.07 (dd, *J* = 17.6, 6.3 Hz, 1H, *H*-5$_\beta$), 3.15 (d, *J* = 17.6 Hz, 1H, *H*-5$_\alpha$), 4.96 (apparent dt, *J* = 6.4, 1.3 Hz, 1H, *H*-6$_\beta$), 5.46 (d, *J* = 6.3 Hz, 1H, *H*-7$_\beta$), 7.04 (s, 1H, *H*-3), 7.15-7.19 (m, 3H, H_a and H_c), 7.32-7.34 (m, 3H, H_b and H_f), 7.36-7.39 (m, 2H, H_e), 7.65-7.66 (m, 2H, H_d); **^{13}C NMR**[*] (151 MHz, $CDCl_3$) δ 18.6, 33.9, 77.6, 83.2, 111.5, 124.7, 126.3, 126.4, 127.7, 128.1, 128.2, 128.3, 133.3, 141.3, 141.9, 147.7, 151.3, 159.4; **IR** (KBr) 3067, 2950, 2915, 1955, 1893, 1810, 1587, 1566, 1490, 1452, 1441, 1316, 1274, 1208, 1080, 1004, 919, 750 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 366 (M[^{37}Cl] + H, 30), 364 (M[^{35}Cl] + H, 100), 286 (3), 182 (18); **HREIMS** Calcd. for $C_{22}H_{19}ClNO_2$: 364.1104. Found: 364.1098.

[*] The NMR spectrum is shown on page 233.

4.2.12 *(6S,7R)-2-Chloro-6,7-dihydro-4-methyl-5H-[1]pyrindine-6,7-diol 1,3-Diphenylacetone Acetal* [(+)117e][146]

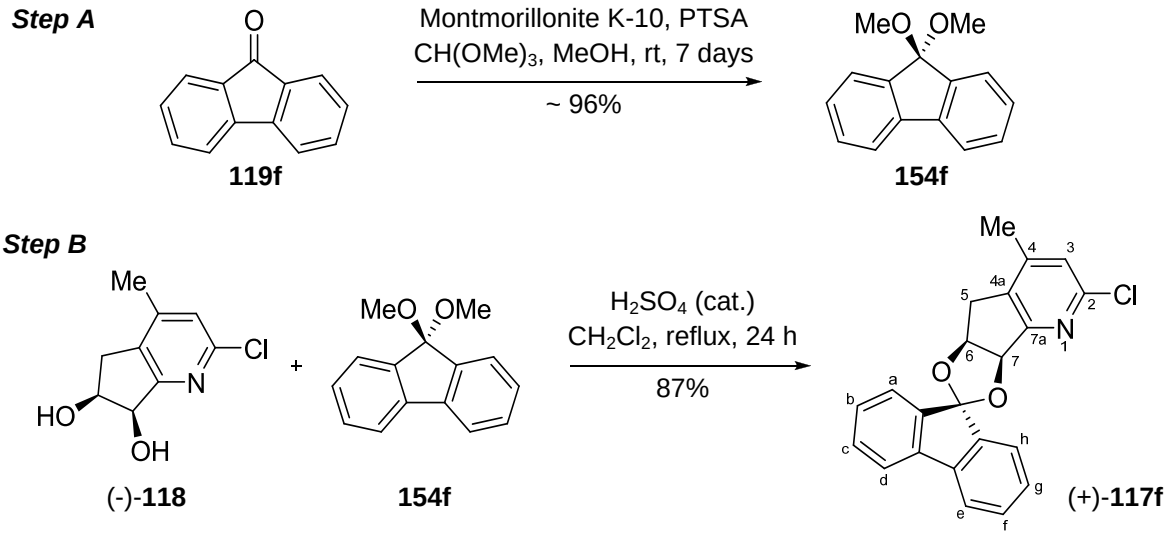


To a suspension of Montmorillonite K-10 clay (190 mg) and trimethyl orthoformate (3 mL) in methanol (4 mL) was added *p*-toluenesulfonic acid monohydrate (10 mg, 53 μmol) and 1,3-diphenylacetone **119e** (1.00 g, 4.75 mmol). The resultant mixture was stirred for four days at room temperature and then filtered, the filter-cake was washed with dichloromethane (2 × 10 mL). The filtrate was poured into a saturated aqueous solution of sodium bicarbonate (15 mL) and extracted with dichloromethane (3 × 30 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate and then concentrated *in vacuo* to afford the crude dimethyl acetal **154e** (1.19 g, ~ 98%) as a white solid. A portion of this material (1.03 g, ~ 4 mmol) was added to a stirred solution of the diol (-)-**118** (200 mg, 1.00 mmol, 97% ee) in a mixture of concentrated sulphuric acid and dichloromethane (1% w/v, 12 mL). The reaction mixture was stirred at reflux for three hours and then allowed to cool to room temperature. The resultant mixture was washed with a saturated aqueous solution of

potassium carbonate (10 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford the crude product as a beige solid. This material was purified by flash chromatography using dichloromethane:ethyl acetate (4:1) as the eluant to afford the *title compound* **117e** (294 mg, 75%) as a white solid. The product was further purified by recrystallization from heptanes to afford colourless needles. $\mathbf{R_f}$ = 0.30, hexanes:ether (4:1); **M.p.** 113-114 ˚C, heptanes; $[\alpha]_D^{20}$ = + 32 (*c* 1.65, chloroform); **^{1}H NMR**[*] (500 MHz, $CDCl_3$) δ 1.96 (s, 3H, ArC*H*$_3$), 2.35 (d, *J* = 17.4 Hz, 1H, *H*-5$_\alpha$), 2.52 (dd, *J* = 17.4, 6.2 Hz, 1H, *H*-5$_\beta$), 2.84 (d, *J* = 13.9 Hz, 1H, ArC*H*H), 2.91 (d, *J* = 13.9 Hz, 1H, ArCH*H*), 2.98 (d, *J* = 13.6 Hz, 1H, ArC*H*H), 3.07 (d, *J* = 13.6 Hz, 1H, ArCH*H*), 4.18 (apparent t, *J* = 6.0 Hz, 1H, *H*-6$_\beta$), 4.90 (d, *J* = 6.2 Hz, 1H, *H*-7$_\beta$), 6.82 (s, 1H, *H*-3), 6.87-6.97 (m, 5H, Ar*H*), 7.24-7.26 (m, 1H, Ar*H*), 7.29-7.32 (m, 2H, Ar*H*), 7.41 (apparent d, *J* = 7.1 Hz, 2H, Ar*H*); **^{13}C NMR**[*] (126 MHz, $CDCl_3$) δ 18.1, 34.0, 44.7, 46.2, 78.4, 83.9, 115.1, 124.1, 125.8, 126.4, 126.5, 128.0, 130.9, 131.0, 132.2, 135.2, 136.4, 147.1, 150.6, 159.3; **IR** (KBr) 3065, 3033, 2917, 2846, 1951, 1874, 1809, 1732, 1590, 1494, 1455, 1313, 1178, 1094, 747 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 394 (M[^{37}Cl] + H, 30), 392 (M[^{35}Cl] + H, 100), 182 (11); **Anal.** Calcd. for $C_{24}H_{22}ClNO_2$: C, 73.56; H, 5.66; N, 3.51. Found: C, 73.51; H, 5.78; N, 3.67.

[*] The NMR spectrum is shown on page 234.

4.2.13 *(6S,7R)-2-Chloro-6,7-dihydro-4-methyl-5H-[1]pyrindine-6,7-diol Fluorenone Acetal* [(+)-117f][146]

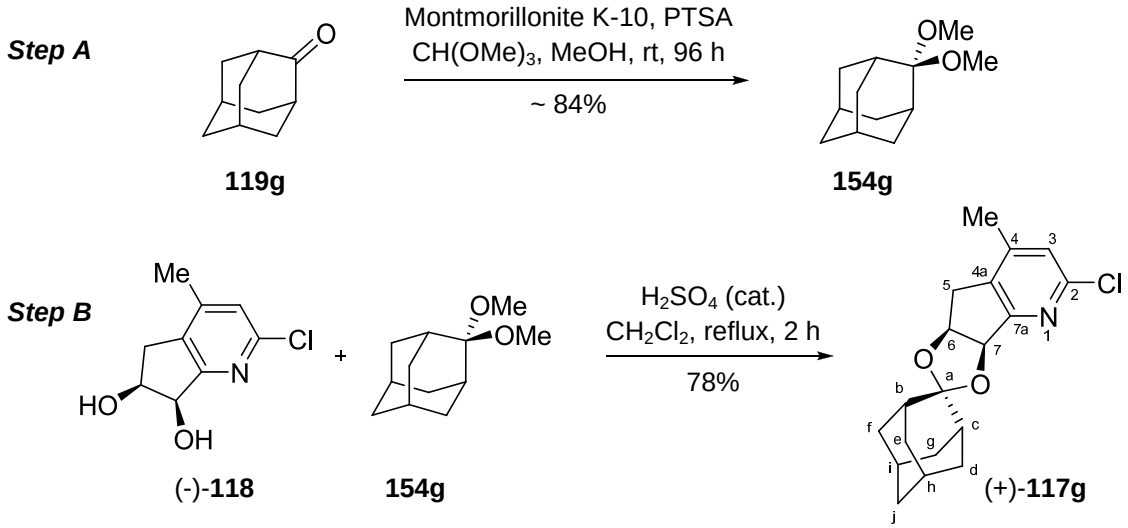


To a suspension of Montmorillonite K-10 clay (190 mg) and trimethyl orthoformate (3 mL) in methanol (4 mL) was added *p*-toluenesulfonic acid monohydrate (10 mg, 53 μmol) and fluorenone **119f** (1.00 g, 5.56 mmol). The resultant mixture was stirred for seven days at room temperature and then filtered, the filter-cake was washed with dichloromethane (2 × 10 mL). The filtrate was poured into a saturated aqueous solution of sodium bicarbonate (15 mL) and then extracted with dichloromethane (3 × 30 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate and then concentrated *in vacuo* to afford the crude dimethyl acetal **154f** (1.20 g, ~ 96%) as a pale yellow solid. A portion of this material (280 mg, ~ 1.26 mmol) in dichloromethane (2 mL) was added dropwise to a stirred solution of the diol (-)-**118** (250 mg, 1.25 mmol, 97% ee) in a mixture of concentrated sulphuric acid and dichloromethane (1% w/v, 16 mL). The reaction mixture was then stirred at reflux for sixteen hours. An additional portion of dimethyl acetal **154f** (150 mg, ~ 662 μmol) was then added and the resultant solution was heated at reflux for a further eight hours. The

reaction mixture was then allowed to cool to room temperature, was washed with a saturated aqueous solution of potassium carbonate (10 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford the crude product as a pale yellow oil. This material was purified by flash chromatography using chloroform as the eluant to afford the *title compound* (+)-**117f** (395 mg, 87%) as a colourless solid. This material was further purified by recrystallization from chloroform and heptanes, via slow diffusion, to afford small colourless prismatic crystals. $\mathbf{R}_f$ = 0.37 dichloromethane; **M.p.** 254-255 ˚C, chloroform/heptanes; $[\alpha]_D^{20}$ = + 106 (*c* 0.78, chloroform); **^{1}H NMR**[*] (500 MHz, $CDCl_3$) δ 2.34 (s, 3H, ArCH_3), 3.16 (dd, *J* = 17.6, 5.1 Hz, 1H, *H*-5$_\beta$), 3.23 (d, *J* = 17.5 Hz, 1H, *H*-5$_\alpha$), 5.48 (apparent dt, *J* = 5.4, 0.8 Hz, 1H, *H*-6$_\beta$), 5.91 (d, *J* = 5.7 Hz, 1H, *H*-7$_\beta$), 6.50 (d, *J* = 7.4 Hz, 1H, H_a), 7.07 (apparent t, *J* = 7.4, 0.7 Hz, 1H, H_b), 7.20 (s, 1H, *H*-3), 7.27-7.30 (m, 2H, H_c and H_g), 7.36 (apparent dt, *J* = 7.5, 1.0 Hz, 1H, H_f), 7.48 (d, *J* = 7.4 Hz, 1H, H_e), 7.54 (apparent d, *J* = 7.3, 1.0 Hz, 2H, H_d and H_h); **^{13}C NMR**[*] (126 MHz, $CDCl_3$) δ 18.5, 33.4, 78.6, 83.8, 114.6, 119.6, 120.0, 123.0, 124.0, 124.8, 128.1, 128.2, 129.9, 130.4, 132.8, 138.9, 139.8, 141.9, 144.6, 148.1, 151.3, 159.6; **IR** (KBr) 3068, 3043, 2931, 1923, 1817, 1611, 1588, 1487, 1450, 1439, 1255, 1226, 1210, 1189, 1118 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 364 (M[^{37}Cl] + H, 25), 362 (M[^{35}Cl] + H, 81), 279 (24), 181 (100); **Anal.** Calcd. for $C_{22}H_{16}ClNO_2$: C, 73.03; H, 4.46; N, 3.87. Found: C, 72.67; H, 4.54; N, 3.90.

[*] The NMR spectrum is shown on page 235.

4.2.14 *(6S,7R)-2-Chloro-6,7-dihydro-4-methyl-5H-[1]pyrindine-6,7-diol Adamantanone Acetal* [(+)-117g]

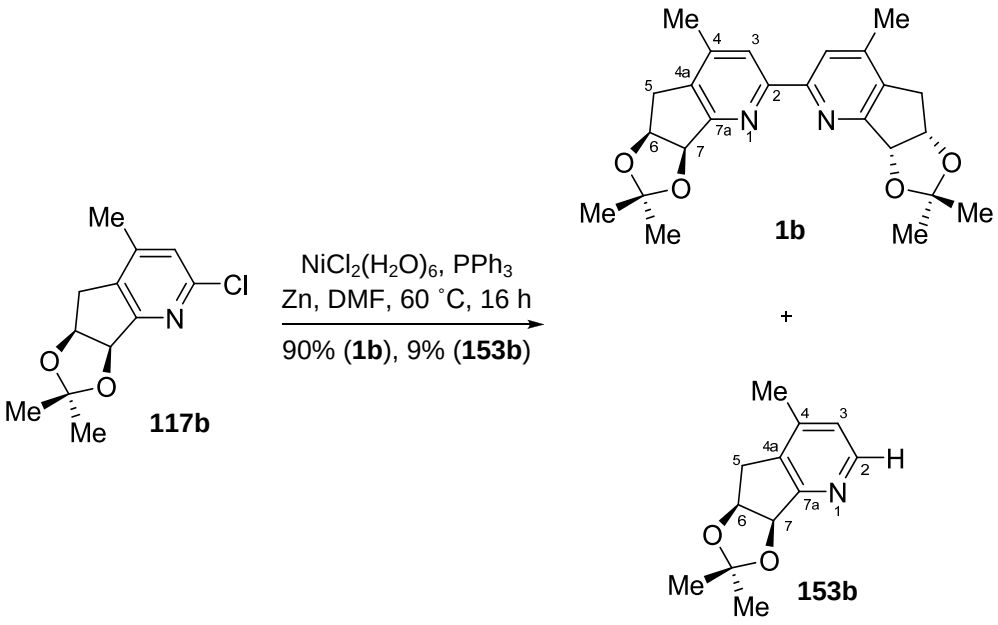


To a suspension of Montmorillonite K-10 clay (3.0 g) and trimethyl orthoformate (9 mL) in methanol (12 mL) was added *p*-toluenesulfonic acid monohydrate (90 mg, 0.47 mmol) and adamantanone **119g** (3.00 g, 20.0 mmol). The resultant mixture was stirred for four days at room temperature and then filtered, the filter-cake was washed with dichloromethane (2 × 10 mL). The filtrate was poured into a saturated aqueous solution of sodium bicarbonate (15 mL) and extracted with dichloromethane (3 × 50 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate and then concentrated *in vacuo* to afford a mixture of adamantanone **119g** and the corresponding dimethyl acetal **154g** [2:23, 3.28 g, 77% (**154g**)] as a colourless oil. A portion of this material (2.41 g, ~ 11.2 mmol of the dimethyl acetal **154g**) in dichloromethane (9 mL) was added dropwise to a stirred solution of the diol (-)-**118** (2.22 g, 11.1 mmol, 97% ee) in a mixture of concentrated sulphuric acid and dichloromethane (1% w/v, 120 mL). The reaction mixture was stirred at reflux for two hours and then allowed to cool to room temperature. The resultant mixture was washed with a saturated

aqueous solution of potassium carbonate (40 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford the crude product as a beige solid. This material was purified by flash chromatography using ethyl acetate as the eluant to afford the unreacted starting material (-)-**118** (156 mg, 7%) as a white solid and a mixture of the acetal (+)-**117g** and excess adamantanone **119g** (3.4 g) as a white solid. Recrystallization of this material from heptanes afforded the *title compound* (+)-**117g** [2.45 g, 78%, (84% brsm)] as large granular crystals. $\mathbf{R}_f$ = 0.64, hexanes:ether (1:1); **M.p.** 163-164 ˚C, heptanes; $[\alpha]_D^{20}$ = + 92 (*c* 1.18, chloroform); **^{1}H NMR**[*] (600 MHz, $CDCl_3$) δ 1.40 (s, 1H, H_b), 1.55 (apparent dq, *J* = 12.5, 2.9 Hz, 1H, $H_{f(ax)}$), 1.59 (apparent dq, *J* = 12.7, 3.0 Hz, 1H, $H_{e(ax)}$), 1.62-1.70 (m, 4H, $H_{d(ax)}$, $H_{g(ax)}$ and H_j), 1.767 (apparent s, 1H, H_h), 1.772 (apparent s, 1H, H_i), 1.89-1.93 (m, 1H, $H_{e(eq)}$), 1.95-1.97 (m, 1H, $H_{d(eq)}$), 1.98 (apparent s, 1H, H_c), 2.08-2.12 (m, 2H, $H_{f(eq)}$ and $H_{g(eq)}$), 2.25 (s, 3H, CH_3), 3.00 (dd, *J* = 17.4, 1.6 Hz, 1H, *H*-5$_\alpha$), 3.04 (dd, *J* = 17.5, 5.6 Hz, 1H, *H*-5$_\beta$), 4.99 (apparent dt, *J* = 5.8, 1.9 Hz, 1H, *H*-6$_\beta$), 5.40 (d, *J* = 6.0 Hz, 1H, *H*-7$_\beta$), 7.06 (s, 1H, *H*-3); **^{13}C NMR**[*] (151 MHz, $CDCl_3$) δ 18.5, 26.9, 27.0, 34.4, 34.6, 34.8, 34.9, 35.1, 36.0, 37.2, 38.4, 76.6, 82.3, 114.6, 124.5, 132.9, 147.7, 151.2, 160.8; **IR** (KBr) 2930, 2892, 2857, 1586, 1570, 1444, 1428, 1394, 1384, 1313, 1222, 1191, 1116, 1093, 1041, 1017, 1007, 919, 857 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 334 (M[^{37}Cl] + H, 32), 332 (M[^{35}Cl] + H, 100), 182 (12), 151 (21); **Anal.** Calcd. for $C_{19}H_{22}ClNO_2$: C, 68.77; H, 6.68; N, 4.22. Found: C, 68.49; H, 6.99; N, 3.85.

[*] The NMR spectrum is shown on page 236.

4.2.15 *(6*S*,6'*S*,7*R*,7'*R*)-4,4'-Dimethyl-6,6',7,7'-tetrahydro-5*H*,5'*H*-2,2'-bi([1]pyrindinyl)-6,6',7,7'-tetrol Propanone* bis-*Acetal* (1b) and *(6*S*,7*R*)-6,7-Dihydro-4-methyl-5*H*-[1]pyrindine-6,7-diol Propanone Acetal* (153b)



To a stirred solution of nickel(II) chloride hexahydrate (305 mg, 1.28 mmol) and triphenylphosphine (133 mg, 5.09 mmol) in dry degassed *N*,*N*-dimethylformamide (4 mL) was added zinc dust (<10 microns, 107 mg, 1.63 mmol). This mixture was stirred at 60 ˚C for one hour and then a solution of the acetal **117b** (301 mg, 1.63 mmol, 97% ee) in dry degassed *N*,*N*-dimethylformamide (5.5 mL) was added *via* a cannula. The reaction mixture was stirred at 60 ˚C for sixteen hours and then allowed to cool to room temperature. The resultant mixture was poured into an aqueous solution of ammonium hydroxide (10% w/w, 100 mL) and extracted with dichloromethane (3 × 50 mL). The combined organic extracts were washed with brine (30 mL), then dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford the crude product as a suspension in *N*,*N*-dimethylformamide. The *N*,*N*-dimethylformamide was removed under high vacuum (~ 5 mmHg) to afford the crude product as a beige solid. This material was

purified by flash chromatography using dichloromethane as the eluant, followed by dichloromethane:ethyl acetate (4:1) and then followed by dichloromethane:acetone (6:1) to afford the bipyridine **1b** (230 mg, 90%) as a colourless solid and the pyridine **153b** (23 mg, 9%) as a colourless solid. The bipyridine **1b** was further purified by recrystallization from chloroform and heptanes, *via* slow diffusion, to afford colourless needles.

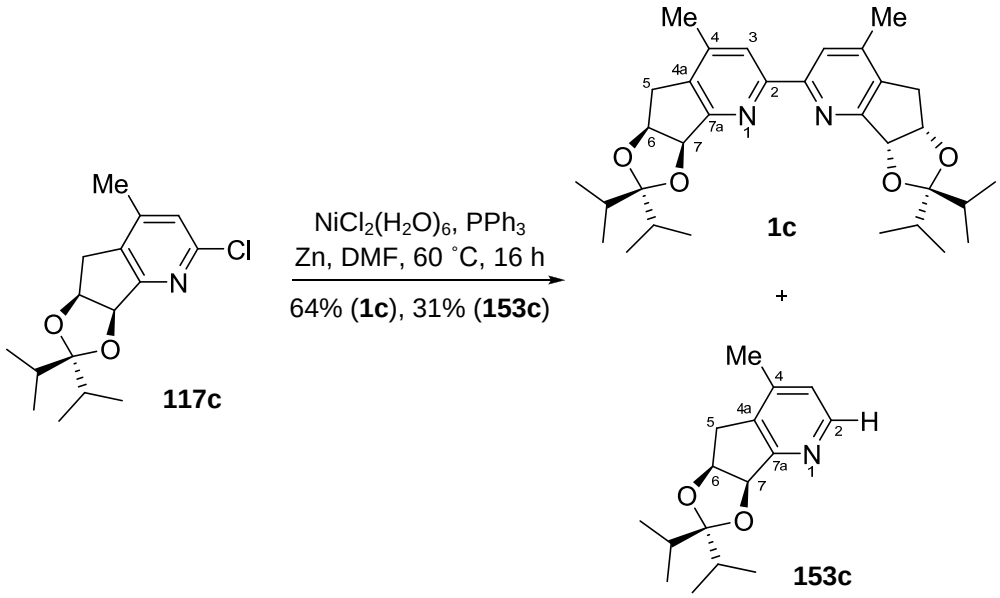
Title compound **1b:** $\mathbf{R_f}$ = 0.48, dichloromethane:ethyl acetate (4:1); **M.p.** > 200 ˚C, dec., chloroform/heptanes; $[\boldsymbol{\alpha}]_D^{20}$ = + 229 (*c* 1.33, chloroform); **^{1}H NMR**[*] (500 MHz, $CDCl_3$) δ 1.31 (s, 6H, 2 × CH_3), 1.46 (s, 6H, 2 × CH_3), 2.33 (s, 6H, 2 × ArCH_3), 3.07 (apparent d, J = 17.0 Hz, 2H, 2 × H-5$_\alpha$), 3.13 (dd, J = 17.6, 5.8 Hz, 2H, 2 × H-5$_\beta$), 5.05 (apparent dt, J = 5.9, 1.6 Hz, 2H, 2 × H-6$_\beta$), 5.52 (d, J = 6.0 Hz, 1H, 2 × H-7$_\beta$), 8.35 (s, 1H, 2 × H-3); **^{13}C NMR**[*] (126 MHz, $CDCl_3$) δ 18.6, 25.3, 27.3, 34.5, 77.2, 83.3, 111.1, 122.2, 133.8, 145.3, 156.5, 159.4; **IR** (KBr) 3060, 2988, 2975, 2925, 2854, 1731, 1706, 1643, 1593, 1576, 1436, 1380, 1370, 1268, 1205, 1189, 1156, 1071, 1039, 1010, 872, 859, 843 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 409 (M + H, 100), 393 (1), 351 (7); **HREIMS** Calcd. for $C_{24}H_{29}N_2O_4$: 409.2127. Found: 409.2120.

Title compound **153b**: $\mathbf{R_f}$ = 0.38, dichloromethane:acetone (6:1); **M.p.** 79-80 ˚C, chloroform; $[\boldsymbol{\alpha}]_D^{20}$ = + 71.1 (*c* 1.00, chloroform); **^{1}H NMR**[†] (500 MHz, $CDCl_3$) δ 1.26 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 2.27 (s, 3H, ArCH_3), 3.04 (apparent d, J = 17.1 Hz, 1H, H-5$_\alpha$), 3.09 (dd, J = 17.6, 5.3 Hz, 1H, H-5$_\beta$), 5.00 (apparent dt, J = 5.8, 1.3 Hz, 1H, H-6$_\beta$), 5.45 (d, J = 5.9 Hz, 1H, H-7$_\beta$), 7.01 (d, J = 4.8 Hz, 1H, H-3), 8.40 (d, J = 4.7 Hz, 1H, H-2); **^{13}C NMR**[†] (126 MHz, $CDCl_3$) δ 18.5, 25.4, 27.2, 34.3, 77.0, 83.2, 110.9, 124.3,

[*] The NMR spectrum is shown on page 240.
[†] The NMR spectrum is shown on page 241.

133.5, 144.7, 149.6, 160.2; **IR** (KBr) 3042, 3014, 2995, 2985, 2968, 2960, 2939, 2859, 2762, 1909, 1599, 1462, 1440, 1431, 1405, 1380, 1371, 1332, 1264, 1240, 1202, 1158, 1066, 1053, 1040, 1011 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 206 (M + H, 100), 190 (2), 148 (15); **Anal.** Calcd. for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.18; H, 7.27; N, 6.65.

4.2.16 *(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'-tetrol Diisopropyl Ketone* bis-*Acetal* (1c) and *(6S,7R)-6,7-Dihydro-4-methyl-5H-[1]pyrindine-6,7-diol Diisopropyl Ketone Acetal* (153c)



To a stirred solution of nickel(II) chloride hexahydrate (369 mg, 1.55 mmol) and triphenylphosphine (162 mg, 6.16 mmol) in dry degassed *N*,*N*-dimethylformamide (5.5 mL) was added zinc dust (<10 microns, 129 mg, 198 mmol). This mixture was stirred at 60 ˚C for one hour and then a solution of the acetal **117c** (450 mg, 1.98 mmol) in dry degassed *N*,*N*-dimethylformamide (5.5 mL) was added *via* a cannula. The reaction mixture was stirred at 60 ˚C for sixteen hours and then allowed to cool to room temperature. The resultant mixture was poured into an aqueous solution of ammonium

hydroxide (10% w/w, 135 mL) and extracted with dichloromethane (3 × 50 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford the crude product as a suspension in *N*,*N*-dimethylformamide. The *N*,*N*-dimethylformamide was removed under high vacuum (~ 5 mmHg) to afford the crude product as a beige solid. This material was purified by flash chromatography using dichloromethane as the eluant, followed by chloroform:ethyl acetate (19:1), to afford the bipyridine **1c** (254 mg, 64%) as a colourless solid and the pyridine **153c** (122 mg, 31%) as a beige solid. The bipyridine **1c** was further purified by recrystallization from heptanes to afford colourless prismatic needles. In addition, the pyridine byproduct **153c** was further purified by recrystallization from heptanes to afford colourless fibrous crystals.

Title compound **1c:** $\mathbf{R}_f$ = 0.39, chloroform:ethyl acetate (19:1); **M.p.** 245-246 ˚C, heptanes; $[\boldsymbol{\alpha}]_D^{20}$ = + 176 (*c* 1.22, chloroform); **^{1}H NMR**[*] (500 MHz, $CDCl_3$) δ 0.54 (d, *J* = 6.8 Hz, 6H, 2 × CHCH_3), 0.57 (d, *J* = 6.8 Hz, 6H, 2 × CHCH_3), 1.01 (d, *J* = 7.1 Hz, 6H, 2 × CHCH_3), 1.03 (d, *J* = 7.2 Hz, 6H, 2 × CHCH_3), 1.94 (septet, *J* = 6.8 Hz, 2H, 2 × C*H*CH_3), 2.17 (septet, *J* = 6.8 Hz, 2H, 2 × C*H*CH_3), 2.31 (s, 6H, 2 × ArCH_3), 3.07 (apparent d, *J* = 3.6 Hz, 4H, 2 × *H*-5$_\alpha$ and 2 × *H*-5$_\beta$), 5.13 (apparent td, *J* = 6.5, 3.7 Hz, 2H, 2 × *H*-6$_\beta$), 5.61 (d, *J* = 6.4 Hz, 2H, 2 × *H*-7$_\beta$), 8.26 (s, 2H, 2 × *H*-3); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 17.0, 17.1, 17.5, 17.8, 18.6, 32.2, 35.2, 35.4, 79.3, 85.4, 119.8, 122.3, 134.0, 144.7, 156.8, 159.5; **IR** (KBr) 2967, 2935, 2877, 1593, 1573, 1474, 1464, 1433, 1380, 1359, 1312, 1290, 1262, 1234, 1207, 1187, 1156, 1119, 1083, 1034, 1019, 946,

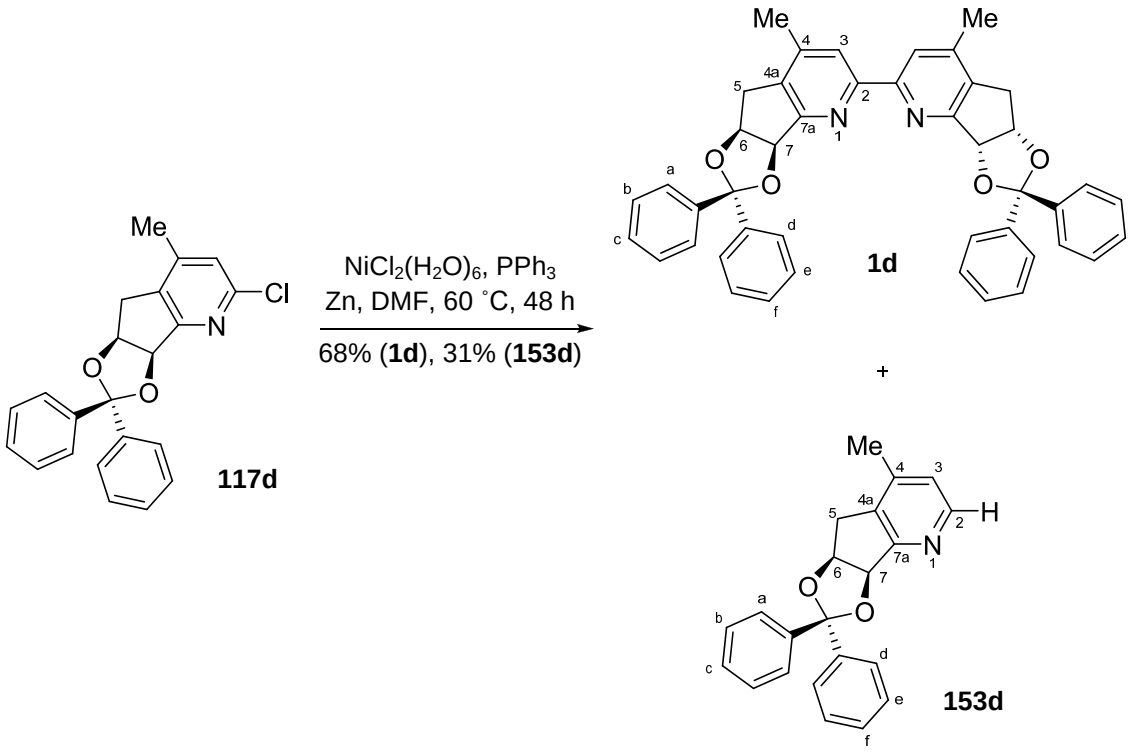
[*] The NMR spectrum is shown on page 242.

967, 917, 888, 843, 740 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 521 (M + H, 100), 477 (1), 407 (14), 115 (3); **HREIMS** Calcd. for $C_{32}H_{45}N_2O_4$: 521.3379. Found: 521.3374.

Title compound **153c**: $\mathbf{R_f}$ = 0.28, dichloromethane:acetone (49:1); **M.p.** 62-64 ˚C, chloroform; $[\boldsymbol{\alpha}]_D^{20}$ = + 29 (*c* 1.04, chloroform); **^{1}H NMR**[*] (500 MHz, $CDCl_3$) δ 0.48 (d, *J* = 6.4 Hz, 3H, CHCH_3), 0.50 (d, *J* = 6.5 Hz, 3H, CHCH_3), 0.98 (d, *J* = 3.4 Hz, 3H, CHCH_3), 0.99 (d, *J* = 3.5 Hz, 3H, CHCH_3), 1.90 (septet, *J* = 6.8 Hz, 1H, C*H*CH_3), 2.12 (septet, *J* = 6.8 Hz, 1H, C*H*CH_3), 2.23 (s, 3H, ArCH_3), 3.03 (d, *J* = 3.4 Hz, 2H, *H*-5_α and *H*-5_β), 5.08 (apparent td, *J* = 6.3, 3.7 Hz, 1H, *H*-6_β), 5.53 (d, *J* = 6.5 Hz, 1H, *H*-7_β), 6.96 (d, *J* = 4.9 Hz, 1H, *H*-3), 8.38 (d, *J* = 4.9 Hz, 1H, *H*-2); **^{13}C NMR**[*] (126 MHz, $CDCl_3$) δ 16.8, 16.9, 17.4, 17.7, 18.50, 32.0, 35.2, 35.3, 78.9, 85.2, 119.5, 124.1, 133.8, 144.2, 149.5, 160.2; **IR** (KBr) 3012, 2973, 2926, 2878, 1949, 1597, 1475, 1465, 1443, 1430, 1406, 1380, 1359, 1331, 1317, 1262, 1221, 1204, 1192, 1174, 1117, 1100, 965 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 262 (M + H, 100), 218 (5), 148 (8); **Anal.** Calcd. for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.47; H, 8.78; N, 5.47.

[*] The NMR spectrum is shown on page 243.

4.2.17 *(6*S*,6'*S*,7*R*,7'*R*)-4,4'-Dimethyl-6,6',7,7'-tetrahydro-5*H*,5'*H*-2,2'-bi([1]pyrindinyl)-6,6',7,7'-tetrol Benzophenone* bis-*Acetal* (1d) and *(6*S*,7*R*)-6,7-Dihydro-4-methyl-5*H*-[1]pyrindine-6,7-diol Benzophenone Acetal* (153d)



To a stirred solution of nickel(II) chloride hexahydrate (227 mg, 0.95 mmol) and triphenylphosphine (933 mg, 3.78 mmol) in dry degassed *N*,*N*-dimethylformamide (4 mL) was added zinc dust (<10 microns, 79 mg, 1.2 mmol). This mixture was stirred at 60 ˚C for one hour and then a solution of the acetal **117d** (340 mg, 0.93 mmol) in dry degassed *N*,*N*-dimethylformamide (3 mL) was added *via* a cannula. The reaction mixture was stirred at 60 ˚C for forty-eight hours and then allowed to cool to room temperature. The resultant mixture was poured into an aqueous solution of ammonium hydroxide (10% w/w, 100 mL) and extracted with dichloromethane (3 × 50 mL). The combined organic extracts were washed with brine (20 mL), then dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford the crude product as a suspension in *N*,*N*-

dimethylformamide. The *N*,*N*-dimethylformamide was removed under high vacuum (~ 5 mmHg) to afford the crude product as a beige solid. This material was purified by flash chromatography using dichloromethane as the eluant, followed by chloroform:acetonitrile (19:1), to afford the bipyridine **1d** (210 mg, 68%) as a colourless solid and the pyridine **153d** (96 mg, 31%) as a beige solid. The bipyridine **1d** was further purified by recrystallization on slow evaporation from dichloromethane to afford fibrous colourless crystals. The pyridine byproduct **153d** was also further purified by recrystallization from heptanes to afford fine colourless needles.

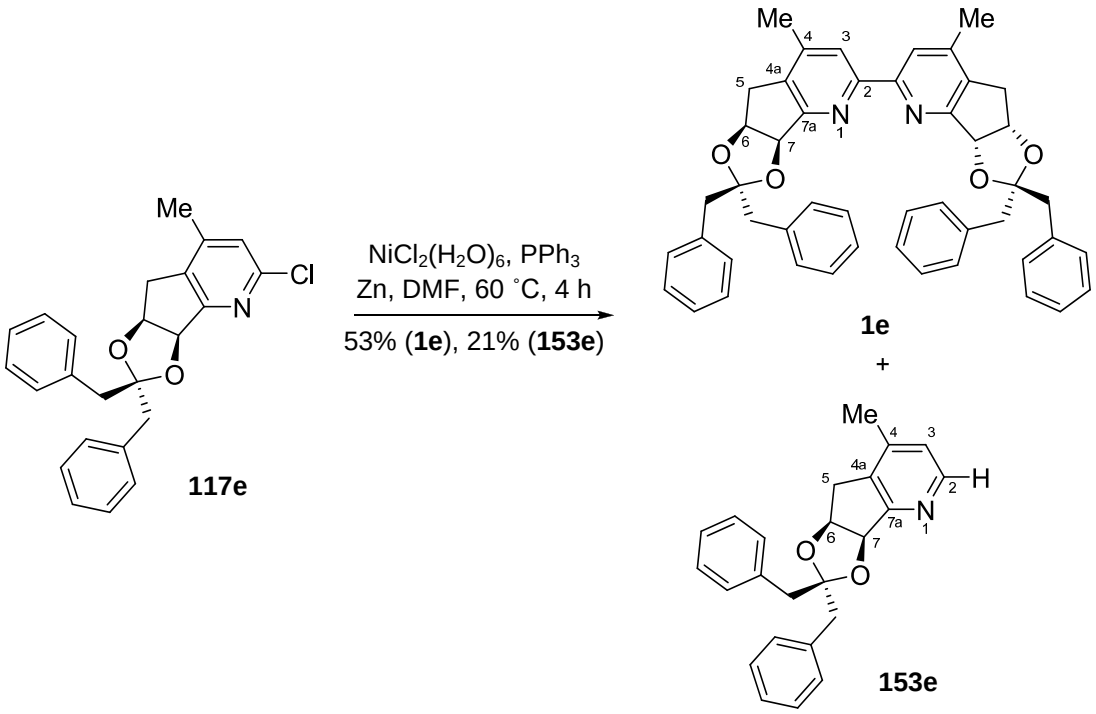
Title compound **1d**: $\mathbf{R_f}$ = 0.55, chloroform:acetonitrile (19:1); **M.p.** 340-342 ˚C, dichloromethane; $[\boldsymbol{\alpha}]_D^{20}$ = + 143 (*c* 0.83, chloroform); **^{1}H* NMR** (500 MHz, CD_2Cl_2) δ 2.39 (s, 6H, 2 × ArCH_3), 3.21 (dd, *J* = 17.8, 6.1 Hz, 2H, 2 × *H*-5$_\beta$), 3.28 (d, *J* = 17.7 Hz, 2H, 2 × *H*-5$_\alpha$), 5.02 (apparent dt, *J* = 6.2, 1.1 Hz, 2H, 2 × *H*-6$_\beta$), 5.55 (d, *J* = 6.2 Hz, 2H, 2 × *H*-7$_\beta$), 7.19 (apparent dd, *J* = 5.0, 1.5 Hz, 6H, 2 × H_a and 2 × H_c), 7.33 (apparent dd, *J* = 6.5, 3.1 Hz, 4H, 2 × H_b), 7.40 (apparent t, *J* = 7.3 Hz, 2H, 2 × H_f), 7.47 (apparent t, *J* = 7.4 Hz, 4H, 2 × H_e), 7.71 (apparent t, *J* = 10.0 Hz, 4H, 2 × H_d), 8.31 (s, 2H, 2 × *H*-3); **^{13}C NMR*** (126 MHz, CD_2Cl_2) δ 18.6, 34.2, 78.1, 83.9, 111.3, 122.0, 126.4, 126.5, 127.8, 128.17, 128.20, 128.4, 134.6, 141.7, 142.2, 145.7, 156.6, 158.8; **IR** (KBr) 3067, 3042, 3021, 2934, 1597, 1568, 1449, 1400, 1301, 1270, 1182, 1116, 1074, 996, 749, 698, 619 cm^{-1}; **MS** (MALDI-TOF) *m/z* (rel. intensity) 1376 (2 × M + ^{63}Cu, 19), 696 (M + K, 12), 679 (M + Na, 24), 657 (M + H, 100); **HREIMS** Calcd. for $C_{44}H_{37}N_2O_4$: 657.2750. Found: 657.2743.

* The NMR spectrum is shown on page 244.

Title compound **153d**: $\mathbf{R_f}$ = 0.40, chloroform:acetonitrile (19:1); **M.p.** 147-148 ˚C, heptanes; $[\alpha]_D^{20}$ = + 30 (*c* 1.02, chloroform); **^{1}H NMR**[*] (500 MHz, $CDCl_3$) δ 2.22 (s, 3H, ArCH_3), 3.10 (dd, *J* = 17.6, 6.4 Hz, 1H, *H*-5$_\beta$), 3.20 (d, *J* = 17.6 Hz, 1H, *H*-5$_\alpha$), 4.95 (apparent t, *J* = 6.1 Hz, 1H, *H*-6$_\beta$), 5.51 (d, *J* = 6.3 Hz, 1H, *H*-7$_\beta$), 6.98 (d, *J* = 4.9 Hz, 1H, *H*-3), 7.13-7.17 (m, 3H, H_a and H_c), 7.30-7.35 (m, 3H, H_b and H_f), 7.39 (apparent t, *J* = 7.5 Hz, 2H, H_e), 7.70 (apparent d, *J* = 7.6 Hz, 2H, H_d), 8.42 (d, *J* = 4.9 Hz, 1H, *H*-2); **^{13}C NMR**[*] (126 MHz, $CDCl_3$) δ 18.5, 34.2, 77.3, 83.6, 111.2, 124.4, 126.25, 126.33, 127.6, 127.9, 128.0, 128.2, 134.0, 141.3, 142.0, 144.6, 149.5, 159.1; **IR** (KBr) 3059, 3020, 2956, 1961, 1598, 1485, 1449, 1333, 1286, 1198, 1076, 1054, 1042, 1016, 992 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 330 (M + H, 100), 183 (25), 148 (38); **Anal.** Calcd. for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25. Found: C, 80.15; H, 5.75; N, 4.30.

[*] The NMR spectrum is shown on page 245.

4.2.18 *(6*S*,6'*S*,7*R*,7'*R*)-4,4'-Dimethyl-6,6',7,7'-tetrahydro-5*H*,5'*H*-2,2'-bi([1]pyrindinyl)-6,6',7,7'-tetrol 1,3-Diphenylacetone* bis-*Acetal* (1e) and *(6S,7R)-6,7-Dihydro-4-methyl-5*H*-[1]pyrindine-6,7-diol 1,3-Diphenylacetone Acetal* (153e)



To a stirred solution of nickel(II) chloride hexahydrate (158 mg, 0.67 mmol) and triphenylphosphine (694 mg, 2.65 mmol) in dry degassed *N*,*N*-dimethylformamide (2.3 mL) was added zinc dust (<10 microns, 55 mg, 0.85 mmol). This mixture was stirred at 60 ˚C for one hour and then a solution of the acetal **117e** (256 mg, 6.53 mmol) in dry degassed *N*,*N*-dimethylformamide (2.3 mL) was added *via* a cannula. The reaction mixture was stirred at 60 ˚C for four hours and then allowed to cool to room temperature. The resultant mixture was poured into an aqueous solution of ammonium hydroxide (10% w/w, 100 mL) and extracted with dichloromethane (3 × 50 mL). The combined organic extracts were washed with brine (20 mL), then dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford the crude product as a suspension in *N*,*N*-dimethylformamide. The *N*,*N*-dimethylformamide was removed under high vacuum (~ 5

mmHg) to afford the crude product as a beige solid. This material was purified by flash chromatography using dichloromethane as the eluant, followed by dichloromethane:ether (9:1), to afford the bipyridine **1e** (124 mg, 53%) as a colourless solid and the pyridine **153e** (50 mg, 21%), as a colourless oil. The bipyridine **1e** was further purified by recrystallization from chloroform and heptanes, *via* slow diffusion, to afford large colourless granular crystals.

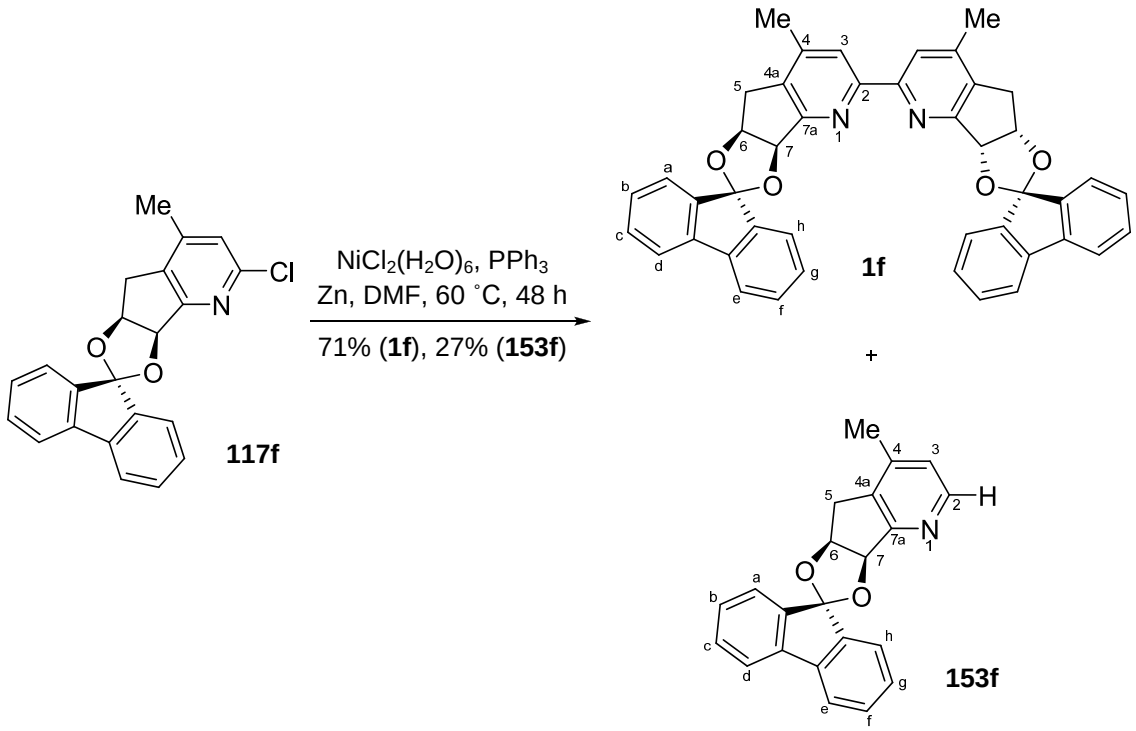
Title compound **1e:** $\mathbf{R}_f$ = 0.8, dichloromethane:ether (9:1); **M.p.** 245-246 ˚C, dichloromethane; $[\alpha]_D^{20}$ = - 0.5 (*c* 1.20, chloroform); **^{1}H NMR**[*] (500 MHz, CD_2Cl_2) δ 2.16 (s, 6H, 2 × ArC*H*$_3$), 2.53 (d, *J* = 17.5 Hz, 2H, 2 × *H*-5$_\alpha$), 2.67 (dd, *J* = 17.5, 6.1 Hz, 2H, 2 × *H*-5$_\beta$), 2.81 (d, *J* = 13.9 Hz, 2H, 2 × ArC*H*H), 2.96 (d, *J* = 13.9 Hz, 2H, 2 × ArCH*H*), 3.00 (d, *J* = 13.7 Hz, 2H, 2 × ArC*H*H), 3.12 (d, *J* = 13.7 Hz, 2H, 2 × ArCH*H*), 4.24 (t, *J* = 6.0 Hz, 2H, 2 × *H*-6$_\beta$), 5.11 (d, *J* = 6.1 Hz, 2H, 2 × *H*-7$_\beta$), 6.92-6.96 (m, 6H, 2 × Ar*H*), 7.06-7.08 (m, 4H, 2 × Ar*H*), 7.28 (apparent t, *J* = 7.0 Hz, 2H, 2 × Ar*H*), 7.34 (apparent t, *J* = 7.4 Hz, 4H, 2 × Ar*H*), 7.45 (apparent d, *J* = 7.3 Hz, 4H, 2 × Ar*H*), 8.21 (s, 2H, 2 × *H*-3); **^{13}C NMR**[*] (126 MHz, CD_2Cl_2) δ 18.4, 34.4, 45.5, 45.7, 78.8, 84.6, 114.8, 121.9, 125.9, 126.5, 126.8, 128.0, 130.8, 131.0, 133.6, 135.6, 136.6, 144.9, 156.3, 158.8; **IR** (KBr) 3085, 3062, 3028, 2924, 1727, 1595, 1576, 1495, 1453, 1435, 1422, 1375, 1340, 1318, 1304, 1236, 1126, 1181, 1085, 1069, 1057, 1031, 1021, 1006, 844, 752, 698, 660 cm^{-1}; **MS** (MALDI-TOF) *m/z* (rel. intensity) 1490 (2 × M + ^{64}Zn, 21), 1264 (13), 775 (M + ^{63}Cu, 13), 751 (M + K, 15), 735 (M + Na, 85), 713 (M + H, 100); **Anal.** Calcd. for $C_{48}H_{44}N_2O_2$: C, 80.87; H, 6.22; N, 3.93. Found: C, 80.74; H, 6.09; N, 4.12.

[*] The NMR spectrum is shown on page 246.

Title compound **153e**: $\mathbf{R_f}$ = 0.37, dichloromethane:ether (9:1); $[\alpha]_D^{20}$ = - 3.6 (*c* 0.77, chloroform); **^{1}H NMR**[*] (500 MHz, $CDCl_3$) δ 2.01 (s, 3H, ArC*H*$_3$), 2.41 (d, *J* = 17.4 Hz, 1H, *H*-5$_\alpha$), 2.62 (dd, *J* = 15.4, 6.0 Hz, 1H, *H*-5$_\beta$), 2.79 (d, *J* = 13.9 Hz, 1H, ArC*H*H), 2.85 (d, *J* = 13.9 Hz, 1H, ArCH*H*), 2.96 (d, *J* = 13.6 Hz, 1H, ArC*H*H), 3.04 (d, *J* = 13.6 Hz, 1H, ArCH*H*), 4.27 (t, *J* = 6.3 Hz, 1H, *H*-6$_\beta$), 5.00 (d, *J* = 6.2 Hz, 1H, *H*-7$_\beta$), 6.83 (d, *J* = 4.8 Hz, 1H, *H*-3), 6.91-6.94 (m, 3H, Ar*H*), 6.96-7.00 (m, 2H, Ar*H*), 7.25 (apparent t, *J* = 7.9 Hz, 1H, Ar*H*), 7.31 (apparent t, *J* = 7.4 Hz, 2H, Ar*H*), 7.41 (apparent d, *J* = 7.2 Hz, 2H, Ar*H*), 8.28 (d, *J* = 4.9 Hz, 1H, *H*-2); **^{13}C NMR**[*] (126 MHz, $CDCl_3$) δ 18.2, 34.7, 45.2, 45.8, 78.4, 84.5, 114.9, 124.1, 125.7, 126.4, 126.8, 128.0, 130.8, 131.0, 133.5, 135.6, 136.6, 144.2, 149.1, 159.2; **IR** (KBr) 3085, 3060, 3029, 2923, 2850, 1947, 1880, 1808, 1725, 1659, 1598, 1495, 1454, 1436, 1403, 1378, 1320, 1298, 1262, 1245, 1212, 1183, 1126, 1107, 1084, 1070, 1031, 1007, 838 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 358 (M + H, 100), 266 (5), 211 (4), 148 (15); **HREIMS** Calcd. for $C_{24}H_{24}NO_2$: 358.1807. Found: 358.1807.

[*] The NMR spectrum is shown on page 247.

4.2.19 *(6*S*,6'*S*,7*R*,7'*R*)-4,4'-Dimethyl-6,6',7,7'-tetrahydro-5*H*,5'*H*-2,2'-bi([1]pyrindinyl)-6,6',7,7'-tetrol Fluorenone* bis-*Acetal* (1f) and *(6*S*,7*R*)-6,7-Dihydro-4-methyl-5*H*-[1]pyrindine-6,7-diol Fluorenone Acetal* (153f)



To a stirred solution of nickel(II) chloride hexahydrate (256 mg, 116 mmol) and triphenylphosphine (1.16 g, 4.43 mmol) in dry degassed *N*,*N*-dimethylformamide (4.0 mL) was added zinc dust (<10 microns, 93 mg, 1.4 mmol). This mixture was stirred at 60 ˚C for one hour and then a solution of the acetal **117f** (396 mg, 1.09 mmol) in dry degassed *N*,*N*-dimethylformamide (3 mL) was added *via* a cannula. The resultant solution was stirred at 60 ˚C for forty-eight hours and then allowed to cool to room temperature. The resultant mixture was poured into an aqueous solution of ammonium hydroxide (10% w/w, 100 mL) and extracted with dichloromethane (3 × 50 mL). The combined organic extracts were washed with brine (20 mL), then dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford the crude product as a suspension

in *N*,*N*-dimethylformamide. The *N*,*N*-dimethylformamide was removed under high vacuum (~ 5 mmHg) to afford the crude product as a beige solid. This material was purified by flash chromatography using dichloromethane as the eluant, followed by chloroform:acetonitrile (19:1) to afford the bipyridine **1f** (255 mg, 71%) as a colourless solid and the pyridine **153f** (98 mg, 27%) as a colourless foam. The bipyridine **1f** was further purified by recrystallization on slow evaporation from chloroform to afford large colourless prismatic crystals. The pyridine byproduct **153f** was also further purified by recrystallization from heptanes to afford colourless fibrous crystals.

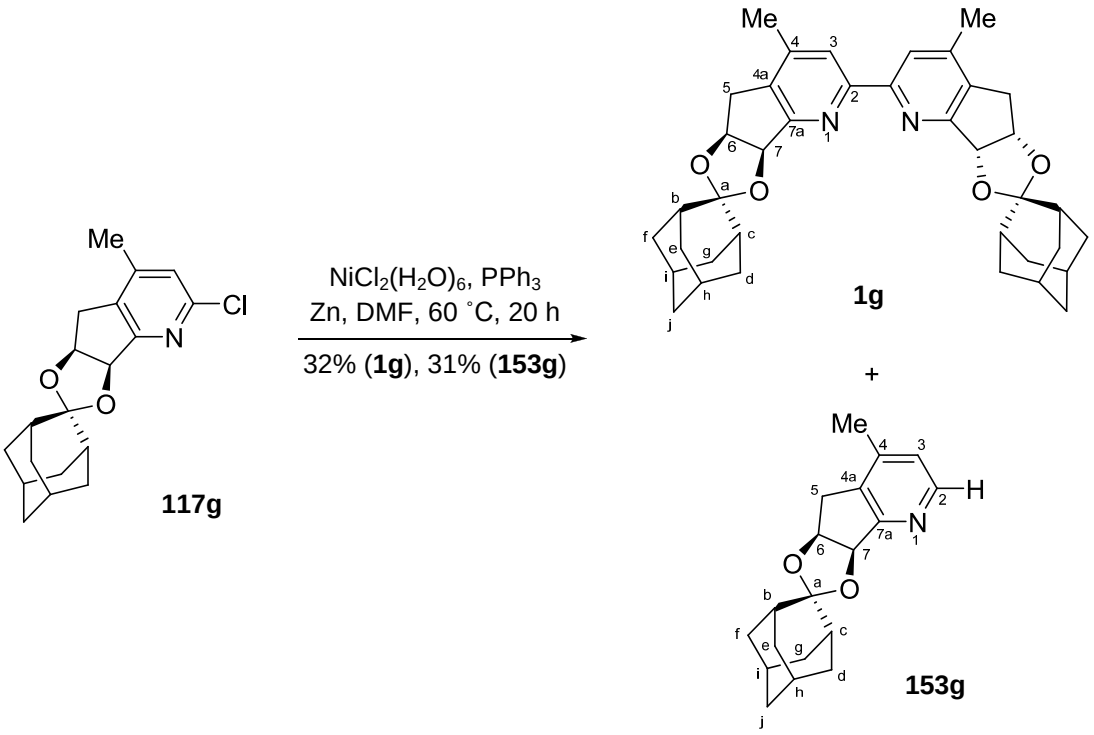
Title compound **1f**: $\mathbf{R_f}$ = 0.43, dichloromethane:ether (9:1); **M.p.** 356-357 ˚C, dichloromethane; $[\boldsymbol{\alpha}]_D^{20}$ = + 214 (*c* 0.44, chloroform); **^{1}H NMR**[*] (500 MHz, CD_2Cl_2) δ 2.39 (s, 6H, 2 × ArCH_3), 3.23 (dd, *J* = 17.8, 4.8 Hz, 2H, 2 × *H*-5$_\beta$), 3.28 (d, *J* = 17.5 Hz, 2H, 2 × *H*-5$_\alpha$), 5.51 (apparent t, *J* = 4.8 Hz, 2H, 2 × *H*-6$_\beta$), 5.99 (d, *J* = 5.7 Hz, 2H, 2 × *H*-7$_\beta$), 6.39 (d, *J* = 7.7 Hz, 2H, 2 × H_a), 6.96 (t, *J* = 7.5 Hz, 2H, 2 × H_b), 7.28 (t, *J* = 7.5 Hz, 2H, 2 × H_c), 7.32 (t, *J* = 7.5 Hz, 2H, 2 × H_g), 7.39 (t, *J* = 7.5 Hz, 2H, 2 × H_f), 7.51 (d, *J* = 7.6 Hz, 2H, 2 × H_d), 7.57 (d, *J* = 7.5 Hz, 2H, 2 × H_e), 7.61 (d, *J* = 7.3 Hz, 2H, 2 × H_h), 8.40 (s, 2H, 2 × *H*-3); **^{13}C NMR**[*] (126 MHz, $CDCl_3$) δ 18.7, 34.2, 79.1, 84.6, 114.9, 119.6, 120.0, 122.7, 123.2, 124.3, 128.2, 130.0, 130.4, 134.1, 139.2, 140.0, 142.4, 144.8, 145.9, 156.7, 159.2; **IR** (KBr) 3063, 3044, 2994, 2937, 2919, 1609, 1591, 1450, 1307, 1297, 1283, 1254, 1230, 1211, 1117, 1075, 1023, 991, 924, 769 cm^{-1}; **MS** (MALDI-TOF) *m/z* (rel. intensity) 1367 (2 × M + ^{63}Cu, 100), 1362 (2 × M + ^{58}Ni, 99), 863 (60), 715 (M + ^{63}Cu, 37), 710 (M + Ni, 15), 691 (M + K, 88), 675 (M + Na, 88), 653 (M + H, 67); **HREIMS** Calcd. for $C_{44}H_{33}N_2O_4$: 653.2440. Found: 653.2425.

[*] The NMR spectrum is shown on page 248.

Title compound **153f**: $\mathbf{R_f}$ = 0.33, dichloromethane:ether (9:1); **M.p.** 98-99 ˚C, chloroform; $[\boldsymbol{\alpha}]_D^{20}$ = + 79 (*c* 1.40, chloroform); **^{1}H NMR**[*] (500 MHz, $CDCl_3$) δ 2.30 (s, 3H, ArCH_3), 3.12 (dd, *J* = 17.5, 5.1 Hz, 1H, *H*-5$_\beta$), 3.22 (d, *J* = 17.5 Hz, 1H, *H*-5$_\alpha$), 5.42 (apparent t, *J* = 5.3 Hz, 1H, *H*-6$_\beta$), 5.93 (d, *J* = 5.6 Hz, 1H, *H*-7$_\beta$), 6.34 (d, *J* = 7.5 Hz, 1H, H_a), 7.00 (t, *J* = 7.4 Hz, 1H, H_b), 7.11 (d, *J* = 4.9 Hz, 1H, *H*-3), 7.24 (t, *J* = 7.4 Hz, 1H, H_c), 7.27 (t, *J* = 6.1 Hz, 1H, H_g), 7.34 (t, *J* = 7.5 Hz, 1H, H_f), 7.45 (d, *J* = 7.5 Hz, 1H, H_d), 7.51 (d, *J* = 7.5 Hz, 1H, H_e), 7.56 (d, *J* = 7.4 Hz, 1H, H_h), 8.51 (d, *J* = 4.3 Hz, 1H, *H*-2); **^{13}C NMR**[*] (126 MHz, $CDCl_3$) δ 18.4, 33.7, 78.6, 84.4, 114.5, 119.4, 119.9, 123.1, 123.96, 124.01, 124.6, 128.1, 129.8, 130.1, 133.6, 139.0, 139.8, 142.4, 144.8, 144.9, 149.7, 159.8; **IR** (KBr) 3067, 3041, 3021, 2934, 1597, 1451, 1401, 1301, 1252, 1209, 1182, 1116, 1071, 998, 767, 741, 730, 648, 618 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 328 (M + H, 100), 181 (71), 148 (68); **Anal.** Calcd. for $C_{22}H_{17}NO_2$: C, 80.71; H, 5.23; N, 4.28. Found: C, 80.91; H, 5.61; N, 4.22.

[*] The NMR spectrum is shown on page 249.

4.2.20 *(6*S*,6'*S*,7*R*,7'*R*)-4,4'-Dimethyl-6,6',7,7'-tetrahydro-5*H*,5'*H*-2,2'-bi([1]pyrindinyl)-6,6',7,7'-tetrol Adamantanone* bis-*Acetal* (1g) and *(6*S*,7*R*)-6,7-Dihydro-4-methyl-5*H*-[1]pyrindine-6,7-diol Adamantanone Acetal* (153g)



To a stirred solution of nickel(II) chloride hexahydrate (1.61 g, 6.76 mmol) and triphenylphosphine (7.04 g, 26.9 mmol) in dry degassed *N*,*N*-dimethylformamide (24 mL) was added zinc dust (<10 microns, 563 mg, 8.62 mmol). This mixture was stirred at 60 ˚C for one hour and then a solution of the acetal **117g** (2.20 g, 5.65 mmol) in dry degassed *N*,*N*-dimethylformamide (24 mL) was added *via* a cannula. The reaction mixture was stirred at 60 ˚C for twenty hours and then allowed to cool to room temperature. The resultant mixture was poured into an aqueous solution of ammonium hydroxide (10% w/w, 600 mL) and extracted with chloroform (3 × 100 mL). The combined organic extracts were washed with brine (40 mL), then dried over anhydrous sodium sulfate and concentrated *in vacuo* to afford the crude product as a suspension in *N*,*N*-dimethylformamide. The *N*,*N*-dimethylformamide was removed under high vacuum

(~ 5 mmHg) to afford the crude product as a beige solid. This material was purified by flash chromatography using dichloromethane as the eluant, followed by chloroform:ethyl acetate (19:1), to afford the bipyridine **1g** (631 mg, 32%) as a colourless solid and the pyridine **153g** (612 mg, 31%) as a beige solid. The bipyridine **1g** was further purified by recrystallization from chloroform and heptanes, *via* slow diffusion, to afford colourless granular crystals.

Title compound **1g**: $\mathbf{R_f}$ = 0.10 chloroform:ethyl acetate (19:1); **M.p.** ~ 200 ˚C dec., chloroform; $[\boldsymbol{\alpha}]_D^{20}$ = + 123 (*c* 1.01, chloroform); **^{1}H NMR**[*] (600 MHz, $CDCl_3$) δ 1.36 (apparent s, 2H, 2 × H_b), 1.52 (apparent ddd, J = 12.4, 5.3, 2.7 Hz, 2H, 2 × $H_{f(ax)}$), 1.56 (apparent ddd, J = 12.4, 5.4, 2.0 Hz, 2H, 2 × $H_{e(ax)}$), 1.64 (apparent dd, J = 23.2, 12.2 Hz, 4H, 2 × H_j), 1.67-1.71 (m, 4H, $H_{d(ax)}$ and 2 × $H_{g(ax)}$), 1.76 (apparent d, J = 2.9 Hz, 2H, 2 × H_h), 1.77 (apparent d, J = 3.0 Hz, 2H, 2 × H_i), 1.91 (apparent d, J = 12.4 Hz, 2H, 2 × $H_{e(eq)}$), 1.99 (apparent d, J = 13.3 Hz, 2H, 2 × $H_{d(eq)}$), 2.00 (apparent s, 2H, 2 × H_c), 2.09 (apparent d, J = 12.4 Hz, 2H, 2 × $H_{f(eq)}$), 2.17 (apparent d, J = 12.5 Hz, 2H, 2 × $H_{g(eq)}$), 2.33 (s, 6H, 2 × CH_3), 3.08 (dd, J = 17.2, 1.2 Hz, 2H, 2 × H-5$_\alpha$), 3.11 (dd, J = 17.5, 5.5 Hz, 2H, 2 × H-5$_\beta$), 5.02 (apparent dt, J = 5.7, 1.9 Hz, 2H, 2 × H-6$_\beta$), 5.51 (d, J = 5.9 Hz, 2H, 2 × H-7$_\beta$), 8.23 (s, 2H, 2 × H-3); **Observed nOe contacts** H-7$_\beta$ to H-6$_\beta$, H-7$_\beta$ to H-5$_\alpha$, H-7$_\beta$ to H-5$_\beta$, H-7$_\beta$ to CH_3Ar, H-7$_\beta$ to $H_{g(eq)}$, H-7$_\beta$ to $H_{d(eq)}$, H-7$_\beta$ to H_c, H-6$_\beta$ to H-7$_\beta$, H-6$_\beta$ to H-5$_\alpha$, H-6$_\beta$ to H-5$_\beta$, H-6$_\beta$ to CH_3Ar, H-6$_\beta$ to $H_{g(eq)}$, H-6$_\beta$ to H_c, $H_{g(eq)}$ to H-7$_\beta$, $H_{g(eq)}$ to $H_{b(eq)}$, $H_{g(eq)}$ to $H_{d(eq)}$, $H_{g(eq)}$ to $H_{d(eq)}$, $H_{g(eq)}$ to H_i, $H_{g(eq)}$ to $H_{g(ax)}$, $H_{g(eq)}$ to Hc, $H_{d(eq)}$ to H-7$_\beta$, $H_{d(eq)}$ to H-6$_\beta$, $H_{d(eq)}$ to $H_{g(eq)}$, $H_{d(eq)}$ to H_h and $H_{g(eq)}$ to $H_{d(ax)}$; **^{13}C NMR**[*] (151 MHz, $CDCl_3$) δ 18.7, 26.9, 34.5, 34.8, 34.91, 34.92, 36.3, 37.2, 38.4, 76.8, 83.0, 114.4, 122.4,

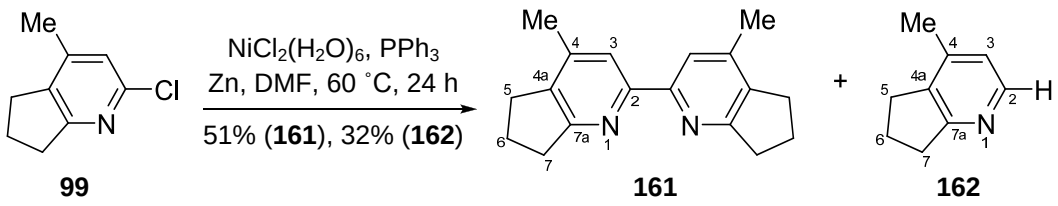
[*] The NMR spectrum is shown on page 250.

134.0, 145.1, 156.7, 159.9; **IR** (KBr) 2904, 2855, 1592, 1452, 1426, 1383, 1362, 1310, 1258, 1218, 1179, 1121, 1090, 1066, 1013, 926, 899, 856, 838, 762 cm^{-1}; **MS** (MALDI-TOF) *m/z* (rel. intensity) 1249 (2 × M + ^{63}Cu, 35), 656 (M + ^{63}Cu, 4), 616 (M + Na, 4), 593 (M + H, 100); **Anal.** Calcd. for $C_{38}H_{44}N_2O_4$: C, 77.00; H, 7.48; N, 4.73. Found: C, 76.65; H, 7.68; N, 4.61.

Title compound **153g**: $\mathbf{R_f}$ = 0.33, chloroform:ethyl acetate (19:1); **M.p.** 118-119 ˚C, chloroform; $[\alpha]_D^{20}$ = + 33.8 (*c* 1.08, chloroform); **^{1}H NMR**[*] (500 MHz, $CDCl_3$) δ 1.34 (apparent dd, J = 5.1, 3.1 Hz, 1H, H_b), 1.51 (apparent ddd, J = 12.4, 5.7, 2.9 Hz, 1H, $H_{f(ax)}$), 1.55 (apparent ddd, J = 12.7, 5.7, 2.9 Hz, 1H, $H_{e(ax)}$), 1.61-1.63 (m, 2H, H_j), 1.64-1.68 (m, 2H, $H_{d(ax)}$ and $H_{g(ax)}$), 1.74 (apparent dd, J = 5.5, 2.6 Hz, 2H, H_h and H_i), 1.89 (apparent d, J = 12.4 Hz, 1H, $H_{e(eq)}$), 1.96 (d, J = 12.4 Hz, 1H, $H_{d(eq)}$), 1.99 (apparent d, J = 2.2 Hz, 1H, H_c), 2.07 (apparent d, J = 13.2 Hz, 1H, $H_{f(eq)}$), 2.10 (apparent d, J = 12.7 Hz, 1H, $H_{g(eq)}$), 2.24 (s, 3H, CH_3), 3.02 (dd, J = 18.1, 2.3 Hz, 1H, H-5$_\alpha$), 3.07 (dd, J = 18.2, 6.0 Hz, 1H, H-5$_\beta$), 4.97 (apparent dt, J = 5.7, 2.1 Hz, 1H, H-6$_\beta$), 5.44 (d, J = 6.0 Hz, 1H, H-7$_\beta$), 6.97 (d, J = 5.0 Hz, 1H, H-3), 8.37 (d, J = 4.9 Hz, 1H, H-2); **^{13}C NMR**[*] (126 MHz, $CDCl_3$) δ 18.5, 26.9, 34.4, 34.70, 34.8, 34.9, 35.1, 35.9, 37.1, 38.3, 76.3, 82.8, 114.2, 124.2, 133.7, 144.6, 149.4, 160.4; **IR** (KBr) 3042, 3014, 2932, 2900, 2850, 1596, 1453, 1397, 1388, 1328, 1317, 1219, 1179, 1122, 1065, 1005, 928, 824 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 298 (M + H, 100), 148 (20); **Anal.** Calcd. for $C_{19}H_{23}NO_2$: C, 76.73; H, 7.80; N, 4.71. Found: C, 76.81; H, 7.87; N, 4.70.

[*] The NMR spectrum is shown on page 251.

4.2.21 *4,4'-Methyl-6,6',7,7'-dihydro-5*H*,5'*H*-2,2'bi([1]pyrindine)* (161) and *4-Methyl-6,7-dihydro-5*H*-[1]pyrindine* (162)



99 **161** **162**

To a stirred solution of nickel(II) chloride hexahydrate (1.45 g, 6.09 mmol) and triphenylphosphine (6.34 g, 24.2 mmol) in dry degassed *N*,*N*-dimethylformamide (21.5 mL) was added zinc dust (<10 microns, 507 mg, 7.76 mmol). This mixture was stirred at 60 ˚C for 1 h, and then a solution of the pyridine **99** (1.00 g, 5.97 mmol) in dry degassed *N*,*N*-dimethylformamide (25 mL) was added *via* a cannula. The reaction mixture was stirred at 60 ˚C for twenty-four hours and then allowed to cool to room temperature. The resultant mixture was poured into an aqueous solution of ammonium hydroxide (10% w/w, 600 mL) and extracted with dichloromethane (3 × 100 mL). The combined organic extracts were washed with brine (60 mL), then dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford the crude product as a suspension in *N*,*N*-dimethylformamide. The *N*,*N*-dimethylformamide was removed under high vacuum (~ 5 mmHg) to afford the crude product as a beige solid. This material was purified by flash chromatography using dichloromethane as the eluant, followed by dichloromethane:ether (19:1) to afford the bipyridine **161** (406 mg, 51%) as a colourless solid and the pyridine **162** (300 mg, 31%) as a colourless oil. The bipyridine **161** was further purified by recrystallization, on slow evaporation from dichloromethane, to afford colourless needles.

Title compound **161**: **M.p.** 250-251 ˚C, dichloromethane; **^{1}H NMR**[*] (500 MHz, CD_2Cl_2) δ 2.15 (p, J = 7.6 Hz, 4H, 2 × $ArCH_2CH_2$), 2.31 (s, 6H, 2 × CH_3), 2.89 (t, J = 7.4 Hz, 4H, 2 × $ArCH_2$), 3.08 (t, J = 7.7 Hz, 4H, 2 × $ArCH_2$), 7.93 (s, 2H, 2 × *H*-3); **^{13}C NMR**[*] (126 MHz, $CDCl_3$) δ 18.9, 22.6, 29.1, 34.4, 119.7, 136.0, 143.5, 155.1, 164.6; **IR** (KBr) 2962, 2910, 2844, 1779, 1719, 1586, 1434, 1414, 1367, 1313, 1300, 1260, 1239, 1180, 1081, 1042, 1018, 880, 844 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 265 (M + H, 100); **Anal.** Calcd. for $C_{18}H_{20}N_2$: C, 81.78; H, 7.63; N, 10.60. Found: C, 81.41; H, 7.81; N, 10.33.

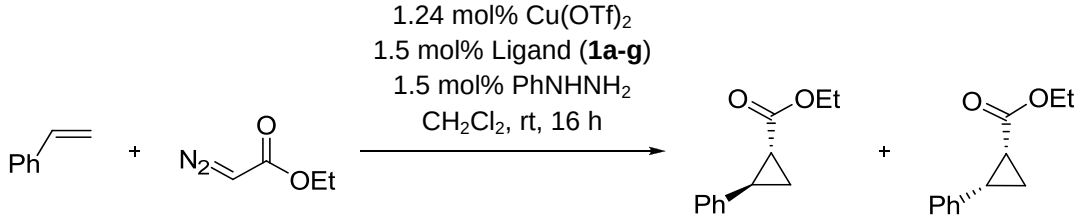
Title compound **162**:[157] **^{1}H NMR**[†] (500 MHz, $CDCl_3$) δ 2.10 (p, J = 7.8 Hz, 2H, $ArCH_2CH_2$), 2.23 (s, 3H, $ArCH_3$), 2.86 (t, J = 7.5 Hz, 2H, $ArCH_2$), 3.00 (t, J = 7.8 Hz, 2H, $ArCH_2$), 6.83 (d, J = 5.1 Hz, 1H, *H*-3), 8.20 (d, J = 5.0 Hz, 1H, *H*-2); **^{13}C NMR**[†] (126 MHz, $CDCl_3$) δ 18.1, 22.3, 29.1, 34.3, 122.1, 136.0, 142.8, 147.4, 164.9; **IR** (neat) 3400 (broad), 3053, 3010, 2952, 2918, 2848, 1599, 1575, 1461, 1436, 1396, 1318, 1287, 1256, 1222, 1181, 1130, 1083, 1042, 823 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 134 (M + H, 100).

[*] The NMR spectrum is shown on page 252.

[†] The NMR spectrum is shown on page 253.

4.3 Experimental Procedures and Characterization Data Concerning *Chapter 3*

4.3.1 General Procedure for Copper(I)-Catalyzed Asymmetric Cyclopropanation Reaction of Styrene with Ethyl Diazoacetate: Asymmetric Synthesis of *(1*R,*2*R*)*-trans-*2-Phenyl-cyclopropane-1-carboxylic Acid Ethyl Ester* (*trans*-29a) and *(1*R,*2*S*)*-cis-*2-Phenyl-cyclopropane-1-carboxylic Acid Ethyl Ester* (*cis*-29a)[141]



2 **28a** *trans*-**29a** *cis*-**29a**

To a stirred solution of copper(II) trifluoromethanesulfonate (9.0 mg, 25 μmol) in freshly distilled dichloromethane (3 mL) was added the appropriate chiral nonracemic 2,2'-bipyridine (**1a-g**, 30 μmol) or the achiral 2,2'-bipyridine (**161**, 30 μmol) and the resultant solution was stirred at room temperature for thirty minutes. Phenylhydrazine (3.0 μL, 30 μmol) and styrene **27** (500 μL, 4.37 mmol) were then added in succession to the reaction mixture. A solution of ethyl diazoacetate **28a** (210 μL, 2.00 mol) in dichloromethane (3 mL) was then added over the course of twelve hours *via* a syringe pump and the reaction mixture was stirred for an additional four hours. The resultant solution was concentrated *in vacuo* to afford the crude product as an oil. This material was purified by column chromatography using petroleum ether:ethyl acetate (96:4) as the eluant to afford the *title compound trans*-**29a** as a colourless oil and the *title compound cis*-**29a** as a colourless oil.

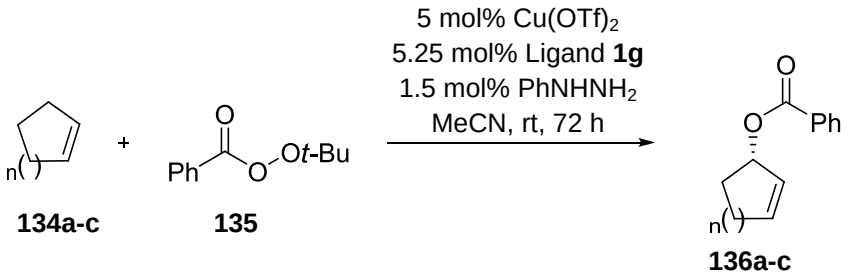
Title compound trans-**29a:** $\mathbf{R}_f$ = 0.48, petroleum ether:ethyl acetate (25:1); $[\boldsymbol{\alpha}]_D^{20}$ -233 (*c* 0.94, chloroform), 83% ee (**1a**, R = Et), ([lit.[141] (1*R*,2*R*) $[\boldsymbol{\alpha}]_D^{20}$ = - 231 (*c* 0.94,

chloroform), 82% ee][*]; **^{1}H NMR** (600 MHz, CDCl3) δ 1.29-1.37 (m, 4H, CH_2CH_3, C*H*H), 1.63 (ddd, *J* = 9.2, 5.3, 4.6 Hz, 1H, CH*H*), 1.93 (ddd, *J* = 8.4, 5.3, 4.2 Hz, 1H, C*H*CO_2), 2.55 (ddd, *J* = 9.3, 6.5, 4.2 Hz, 1H, ArC*H*), 4.20 (apparent q, *J* = 7.1 Hz, 2H, 2H, CH_2CH_3), 7.10-7.16 (m, 2H, Ar*H*), 7.21-7.26 (m, 1H, Ar*H*), 7.27-7.33 (m, 2H, Ar*H*); **^{13}C NMR** (151 MHz, $CDCl_3$) *δ* 14.3, 17.1, 24.2, 26.2, 60.7, 126.3, 128.5, 140.2, 173.5; **IR** (neat) 3087, 3065, 3030, 2982, 1956, 1872, 1780, 1720, 1385, 1337, 1189, 1040, 761 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 191 (M + H, 100), 145 (23).

Title compound cis-**29a**: $\mathbf{R_f}$ = 0.35, petroleum ether:ethyl acetate (25:1); $[\boldsymbol{\alpha}]_D^{20}$ + 9.7 (**1a**, R = Et), + 4.8 (**1b**, R = Me), + 11.6 (**1c**, R = *i*-Pr), + 12.1 (**1d**, R = Ph), + 17.9 (**1e**, R = Bn), + 10.2 (**1a**, R = fluorenyl), + 22.3 (**1a**, R = adamantyl) [lit.[158] $[\boldsymbol{\alpha}]_D^{23}$ = + 48 (*c* 1.84, chloroform), 99% ee]; **^{1}H NMR** (500 MHz, $CDCl_3$) *δ* 1.01 (apparent dt, *J* = 7.2, 1.8 Hz, 3H, CH_2CH_3), 1.35 (apparent dt, *J* = 8.3, 5.0 Hz, 1H, C*H*H), 1.73-1.77 (m, 1H, CH*H*), 2.09-2.14 (m, 1H, C*H*CO_2), 2.61 (apparent dd, *J* = 17.0, 8.5 Hz, 1H, ArC*H*), 3.91 (apparent dq, *J* = 7.1, 1.9 Hz, 2H, CH_2CH_3), 7.20-7.25 (m, 1H, Ar*H*), 7.27-7.32 (m, 4H, Ar*H*); **^{13}C NMR** (126 MHz, $CDCl_3$) *δ* 11.4, 14.3, 22.1, 25.7, 126.9, 128.1, 129.6, 138.8, 171.2; **IR** (neat) 3087, 3061, 3029, 2982, 2936, 2905, 2873, 1949, 1879, 1804, 1727, 1605, 1499, 1449, 1400, 1382, 1274, 1180, 1083, 1034, 962, 867, 793, 752 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 191 (M + H, 100), 145 (23).

[*] The optical rotations of the *trans*-cyclopropane products recovered from reactions employing other ligands were not recorded the enantiomeric purity of these products was determined by HPLC.

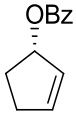
4.3.2 General Procedure for Copper(I)-Catalyzed Asymmetric Allylic Oxidation Reactions of Cyclopentene [134a (n = 1)], Cyclohexene [134b (n = 2)] and Cycloheptene [134c (n = 3)] with *tert*-Butyl Peroxybenzoate: Asymmetric Synthesis of *(1S)-cyclopent-2-enyl Benzoate* [(*S*)-136a (n = 1)], *(1S)-Cyclohex-2-enyl Benzoate* [(*S*)-136b (n = 2)] and *(1S)-Cyclohept-2-enyl Benzoate* [(*S*)-136c (n = 3)][132]



134a-c **135** **136a-c**

To a screw-cap vial was added copper(II) trifluoromethanesulfonate (6.3 mg, 17 μmol), the chiral 2,2'-bipyridine **1g** (10.9 mg, 18.3 μmol) and acetonitrile (2.5 mL). The resultant solution was stirred at room temperature for one hour. Phenylhydrazine (2.0 μL, 20 μmol) was then added and the reaction mixture was stirred for an additional five minutes. The appropriate cycloalkene was then added [cyclopentene **134a** (n = 1, 150 μL, 1.7 mmol), *or* cyclohexene **134b** (n = 2, 180 μL, 1.8 mmol) *or* cycloheptene **134c** (n = 3, 200 μL, 1.8 mmol)] followed by *t*-butyl peroxybenzoate **135** (67 μL, 350 μmol) and the vial was tightly capped. The reaction mixture was stirred for seventy-two hours at room temperature and concentrated *in vacuo* to afford the crude product. This material was purified by flash chromatography using hexanes:ether (5:1) as the eluant to afford the *title compounds* (S)-**136a-c** as colourless oils.

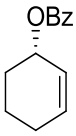
4.3.3 *(1S)-Cyclopent-2-enyl Benzoate* [(*S*)-136a]



136a

Title compound (*S*)-**136a**: $\mathbf{R_f}$ = 0.68, hexanes:ether (4:1); $[\alpha]_D^{20}$ = - 68.1 (*c* 0.75, chloroform) [lit.[167] $[\alpha]_D^{25}$ = - 116.8 (*c* 7.5, chloroform), 60% ee)] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.95-2.00 (m, 1H, CH*H*), 2.35-2.44 (m, 2H, CH_2), 2.57-2.63 (m, 1H, C*H*H), 5.93-5.97 (m, 2H, C*H*OBn and C*H*), 6.16 (apparent dt, *J* = 4.4, 2.1 Hz, 1H, C*H*), 7.42 (apparent t, *J* = 7.8, 2H, Ar*H*), 7.54 (apparent tt, *J* = 7.5, 1.2 Hz, 1H, Ar*H*), 8.03 (apparent td, *J* = 8.5, 1.6 Hz, 2H, Ar*H*); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 29.9, 31.2, 81.1, 128.2, 129.3, 129.5, 130.6, 132.7, 137.7, 166.5; **IR** (KBr) 3062, 2971, 2933, 2855, 1714, 1602, 1451, 1366, 1339, 1314, 1272, 1114, 1070, 1027, 711 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 244 (6), 188 (M, 2), 187 (M – H, 2), 133 (8), 123 (20), 105 (19), 79 (3), 67 (100).

4.3.4 *(1S)-Cyclohex-2-enyl Benzoate* [(*S*)-136b]

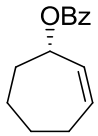


136b

Title compound (*S*)-**136b**: $\mathbf{R_f}$ = 0.73, hexanes:ether (4:1); $[\alpha]_D^{20}$ = - 151.9 (*c* 1.37, chloroform) [lit.[167] $[\alpha]_D^{25}$ = - 157.0 (*c* 2.80, chloroform), 88% ee)]; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.69-1.77 (m, 1H, C*H*H), 1.83-1.91 (m, 2H, CH_2), 2.01-2.09 (m, 2H, CH_2), 2.13-2.20 (m, 1H, CH*H*), 5.54 (apparent ddt, *J* = 5.2, 3.6, 1.7 Hz, 1H, C*H*OBn), 5.84-5.88 (m, 1H, C*H*), 6.03 (apparent dtd, *J* = 9.6, 3.9, 0.9 Hz, 1H, C*H*), 7.45 (apparent t, *J* = 7.6 Hz, 2H, Ar*H*), 7.57 (apparent t, *J* = 7.4 Hz, 1H, Ar*H*), 8.08 (apparent dd, *J* = 8.2,

1.0 Hz, 2H, Ar*H*); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 18.9, 24.9, 28.4, 68.5, 125.7, 128.2, 129.5, 130.7, 132.7, 132.8, 166.1; **IR** (neat) 3089, 3063, 3033, 2939, 2867, 2836, 1965, 1912, 1714, 1602, 1585, 1396, 1451, 1346, 1336, 1314, 1270, 1176, 1112, 1070, 1026, 917, 711 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 201 (M - H, 2), 161 (10), 123 (13), 105 (10), 95 (6), 81 (100).

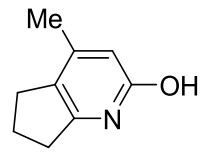
4.3.5 *(1S)-Cyclohept-2-enyl Benzoate* [(*S*)-136c]



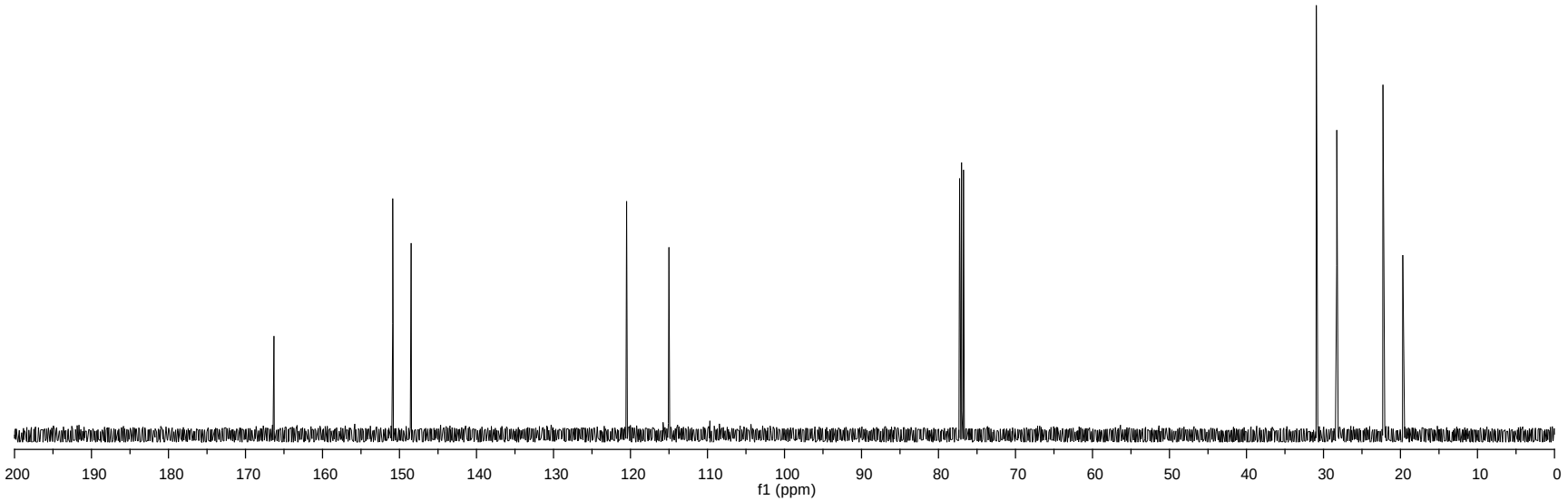
136c

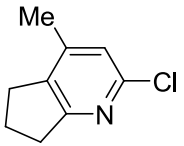
Title compound (*S*)-**136c**: $\mathbf{R}_f$ = 0.65, hexanes:ether (4:1); $[\alpha]_D^{20}$ = - 43.4 (*c* 0.97, chloroform) [lit.[167] $[\alpha]_D^{25}$ = - 38.2 (*c* 1.00, chloroform), 82% ee)]; **^{1}H NMR** (500 MHz, $CDCl_3$) 1.47-1.54 (m, 1H, C*H*H), 1.71-1.80 (m, 2H, CH_2), 1.81-1.89 (m, 1H, CH*H*), 1.97-2.05 (m, 2H, CH_2), 2.13-2.20 (m, 1H, C*H*H), 2.24-2.31 (m, 1H, CH*H*), 5.66 (d, *J* = 9.8 Hz, 1H, C*H*OBn), 5.88-5.93 (m, 1H, C*H*), 5.89 (apparent dddd, *J* = 11.9, 6.9, 5.1, 1.9 Hz, 1H, C*H*), 7.44 (apparent t, *J* = 7.7 Hz, 2H, Ar*H*), 7.55 (apparent t, *J* = 7.4 Hz, 1H, Ar*H*), 8.06 (apparent d, *J* = 7.4 Hz, 2H, Ar*H*); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 26.8, 27.0, 28.8, 33.1, 75.0, 128.6, 129.8, 131.0, 132.2, 133.1, 133.7, 166.1; **IR** (neat) 3089, 3064, 3032, 2928, 2857, 2687, 1965, 1911, 1819, 1717, 1602, 1584, 1451, 1316, 1273, 1176, 1114, 1070, 1026, 981, 712 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 217 (M + H, 3), 189 (9), 123 (7), 105 (9), 95 (100).

4.4 Selected ^{1}H and ^{13}C NMR Spectra



98

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Cl
N

99

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6.5
6.0
5.5
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3.5
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2.5
2.0
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1.0
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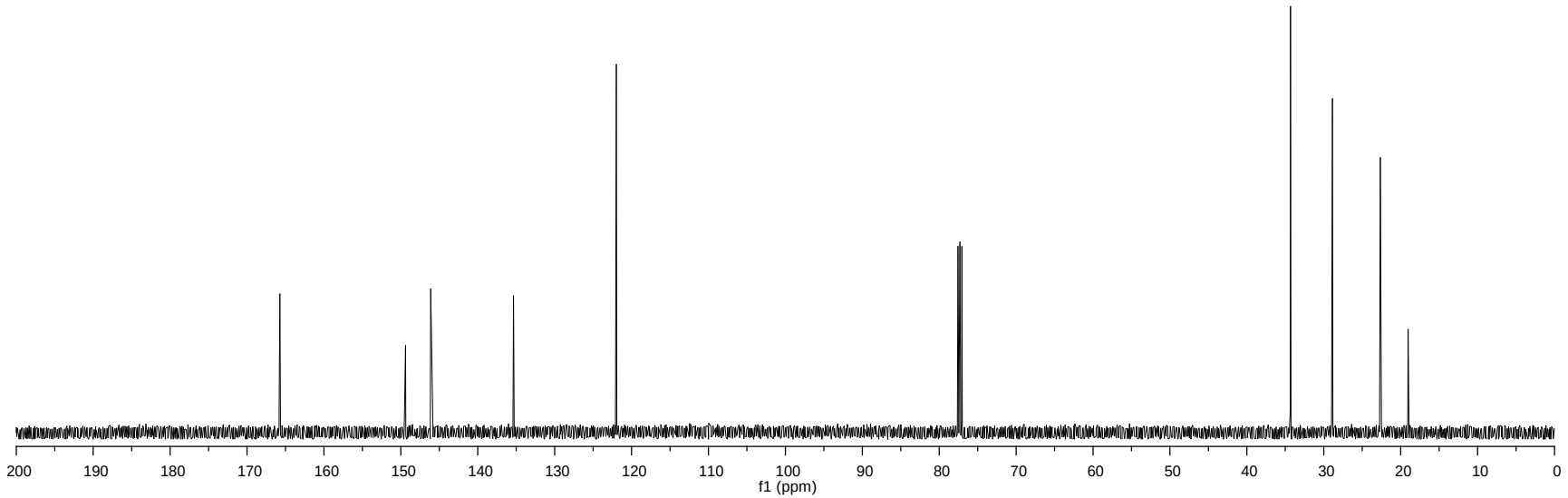
f1 (ppm)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190
180
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40
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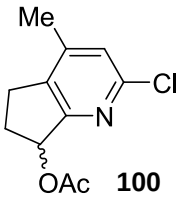
10
0
f1 (ppm)


Me
Cl
N
OAc

100

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6.0
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2.0
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1.0
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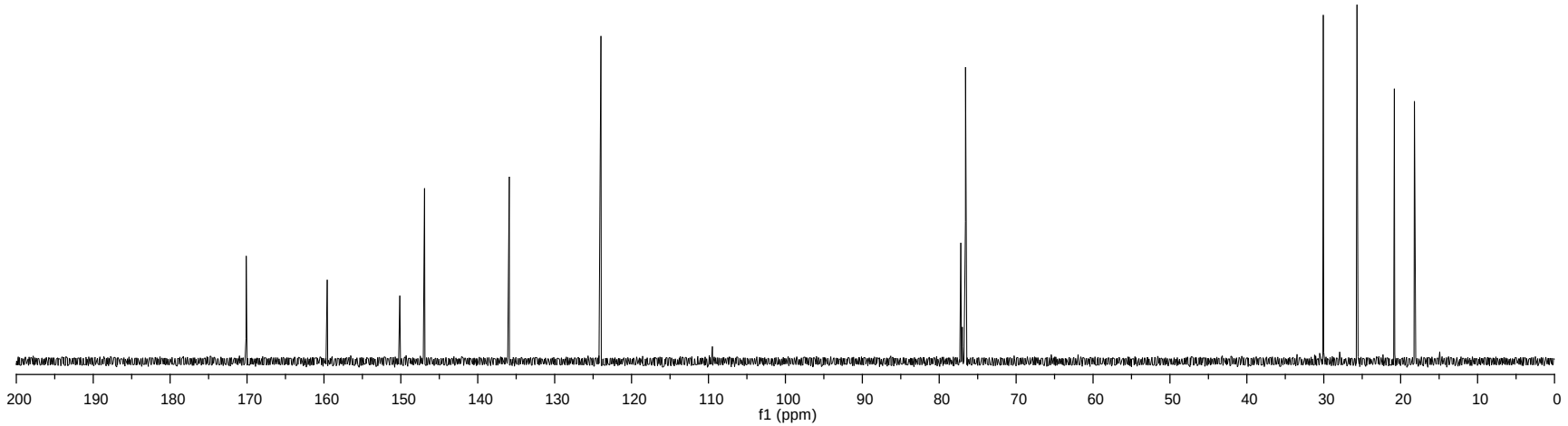
0.0
f1 (ppm)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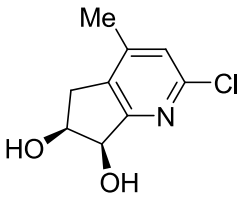
f1 (ppm)


Me
Cl
N
HO
OH

(-)-**118**

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5.5
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2.5
2.0
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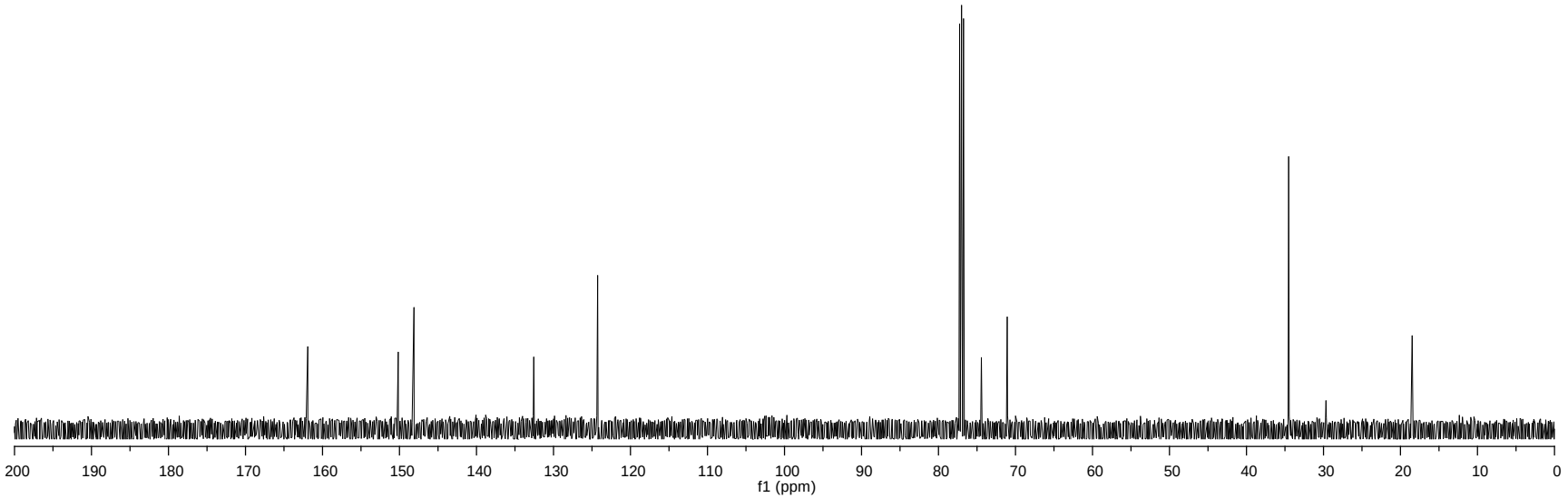
1.0
0.5
0.0
f1 (ppm)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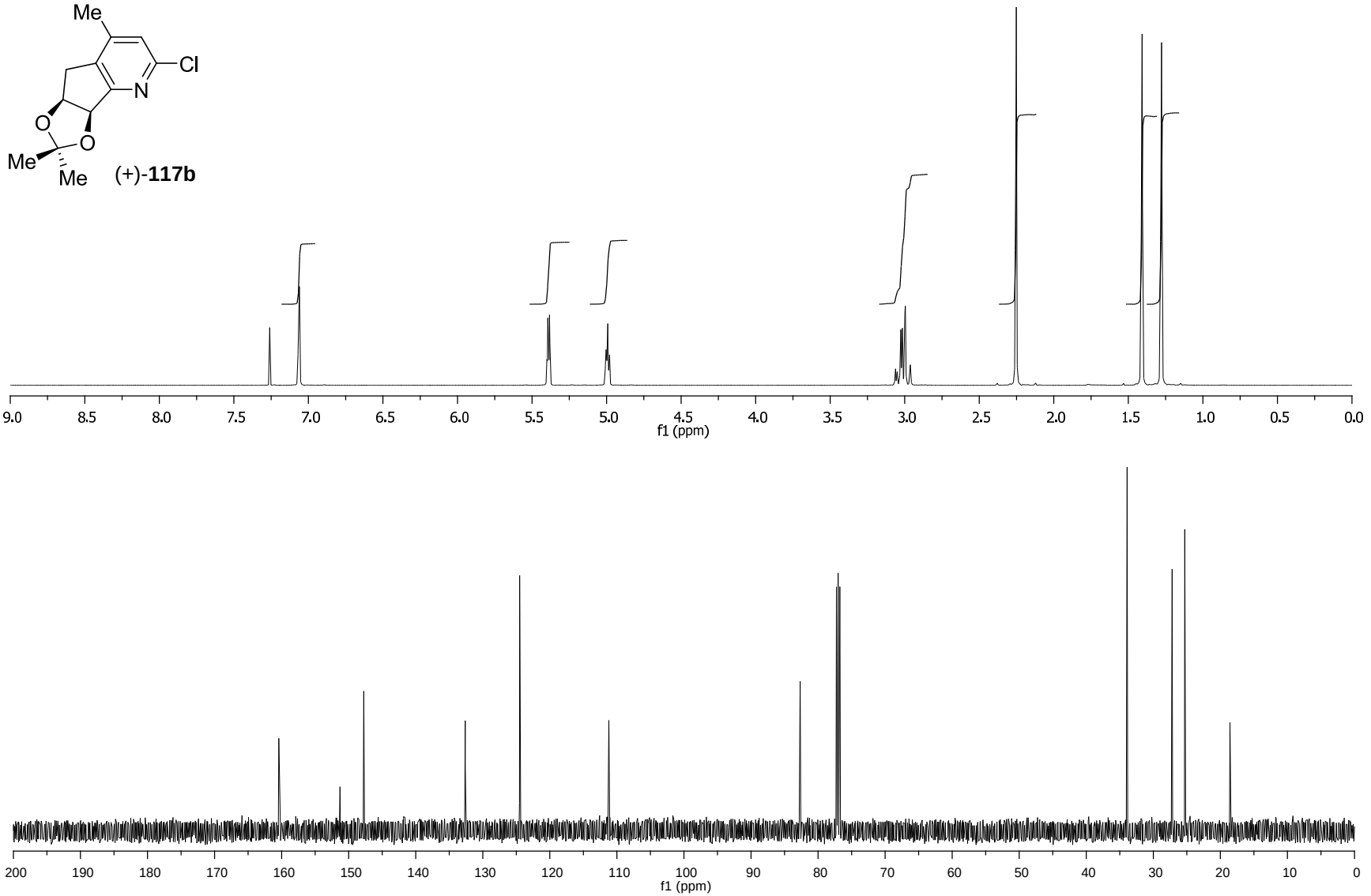
f1 (ppm)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O
O
Me
Me
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5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
200
190
180
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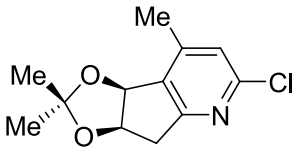
50
40
30
20
10
0
f1 (ppm)


Me
Me
O
Cl
Me
O
N

148b

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6.5
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5.5
5.0
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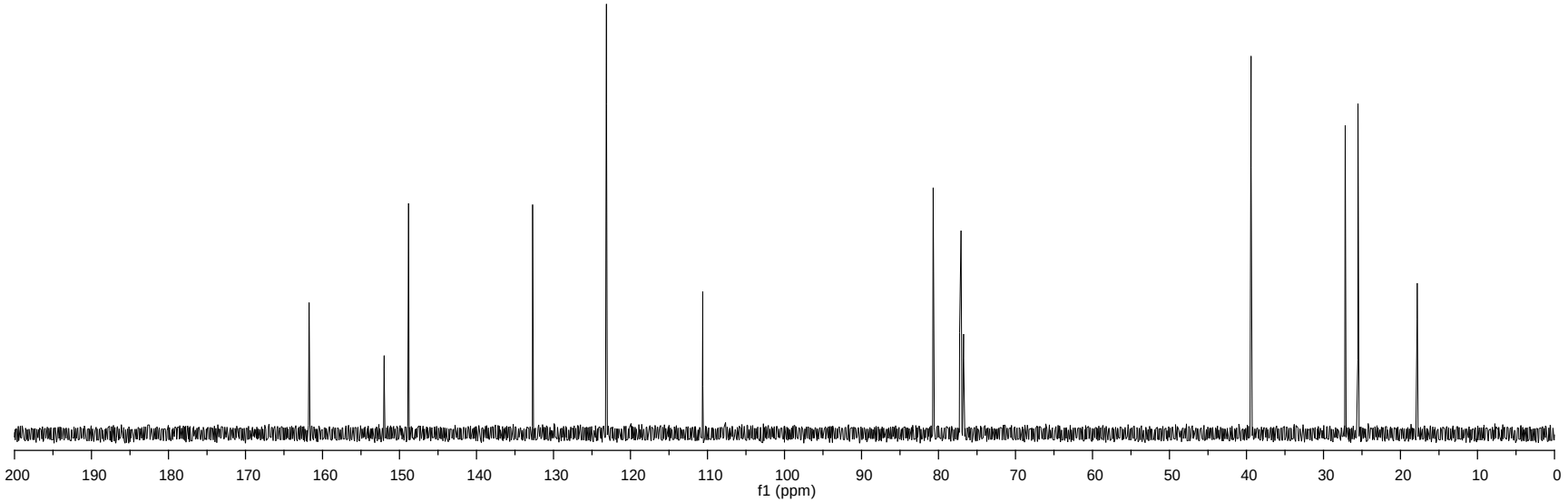
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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40
30
20
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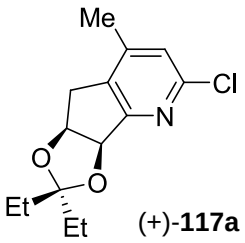
f1 (ppm)


Me
Cl
N
O
O
Et
Et

(+)-**117a**

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8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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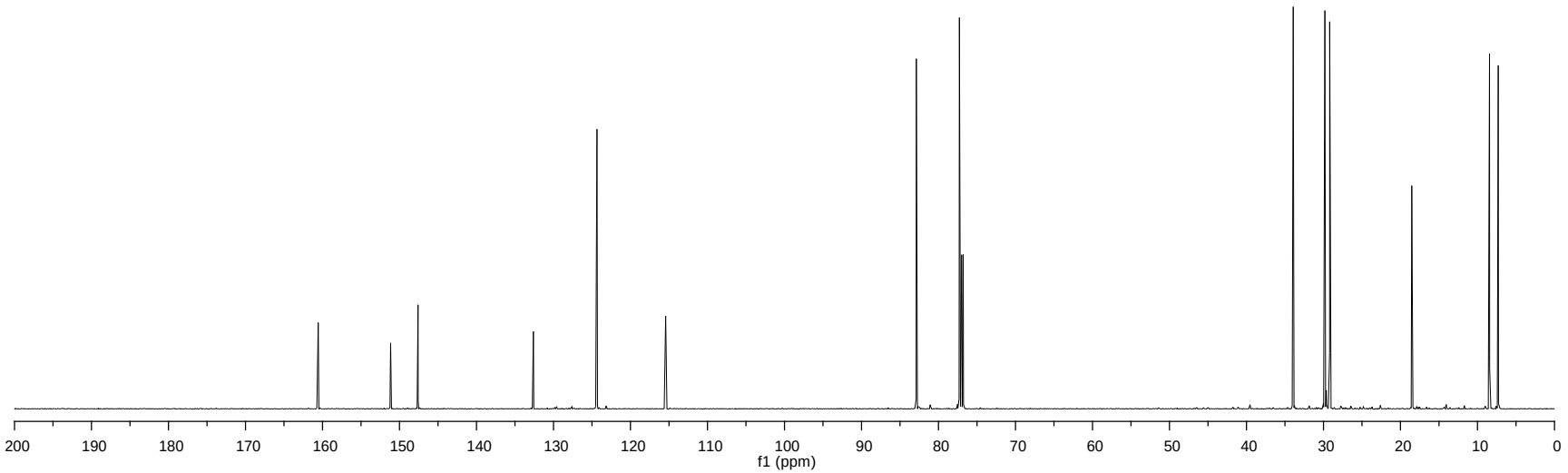
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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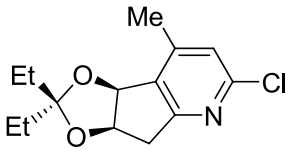
f1 (ppm)


Me
Et
O
Cl
Et
O
N

148a

9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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2.5
2.0
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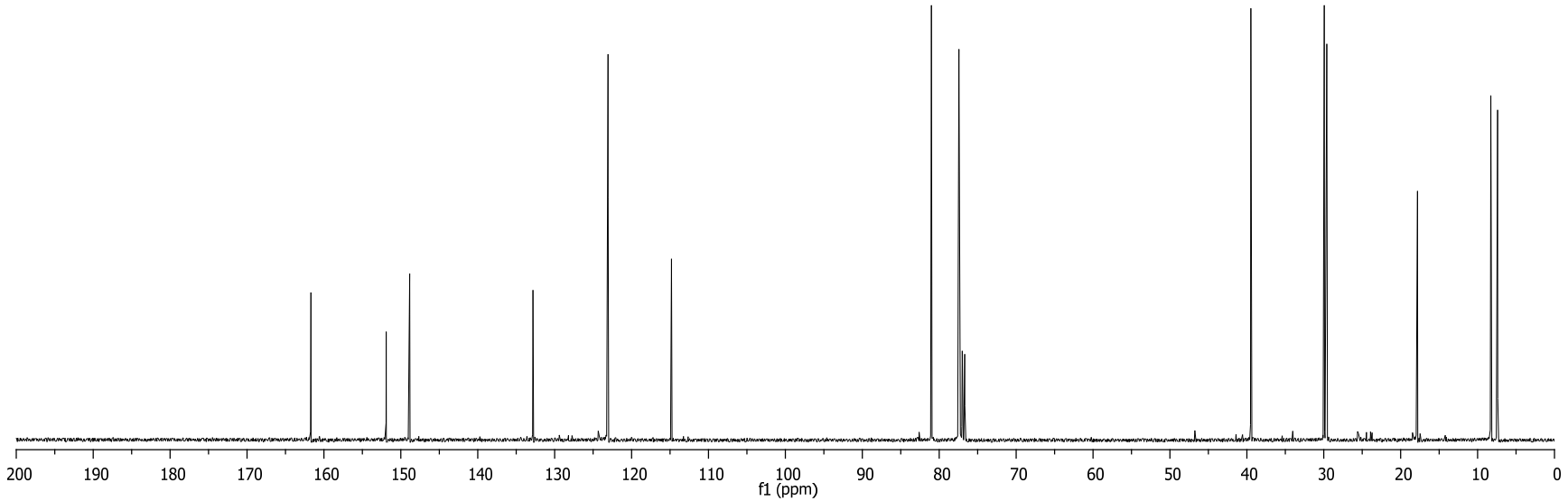
1.0
0.5
0.0
f1 (ppm)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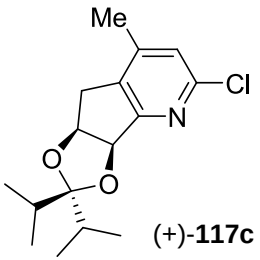
Me
Cl
N
O
O

(+)-**117c**

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2.0
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1.0
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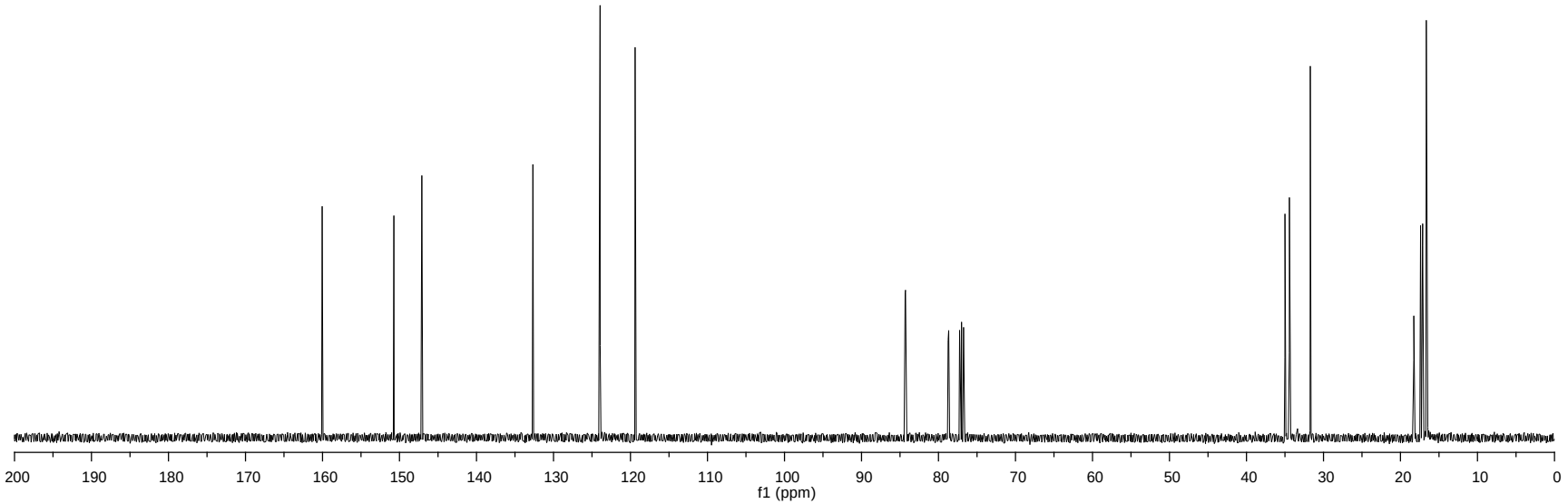
0.0
f1 (ppm)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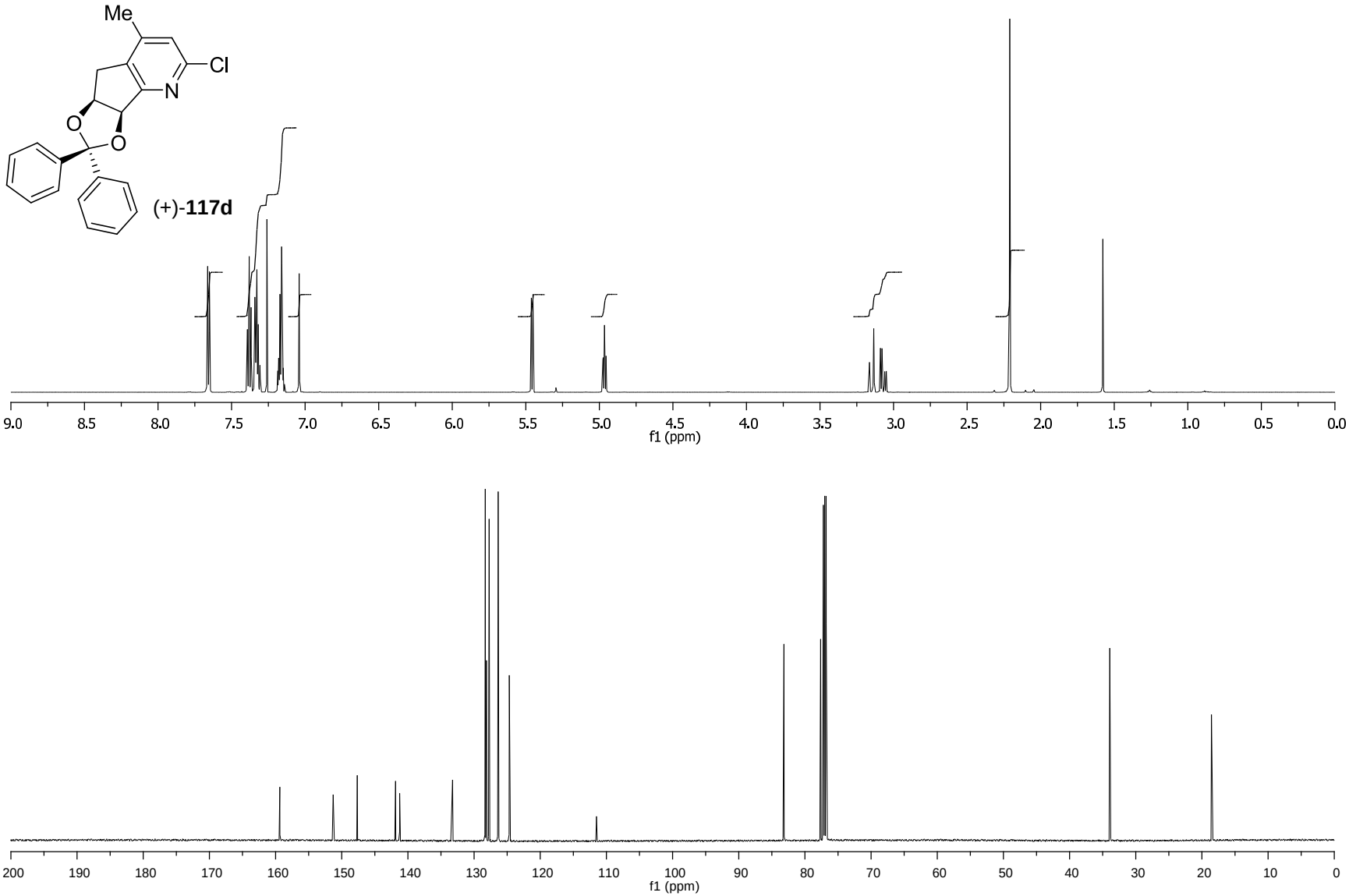
f1 (ppm)


Me
Cl
N
O
O
(+)-117d
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8.0
7.5
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6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
200
190
180
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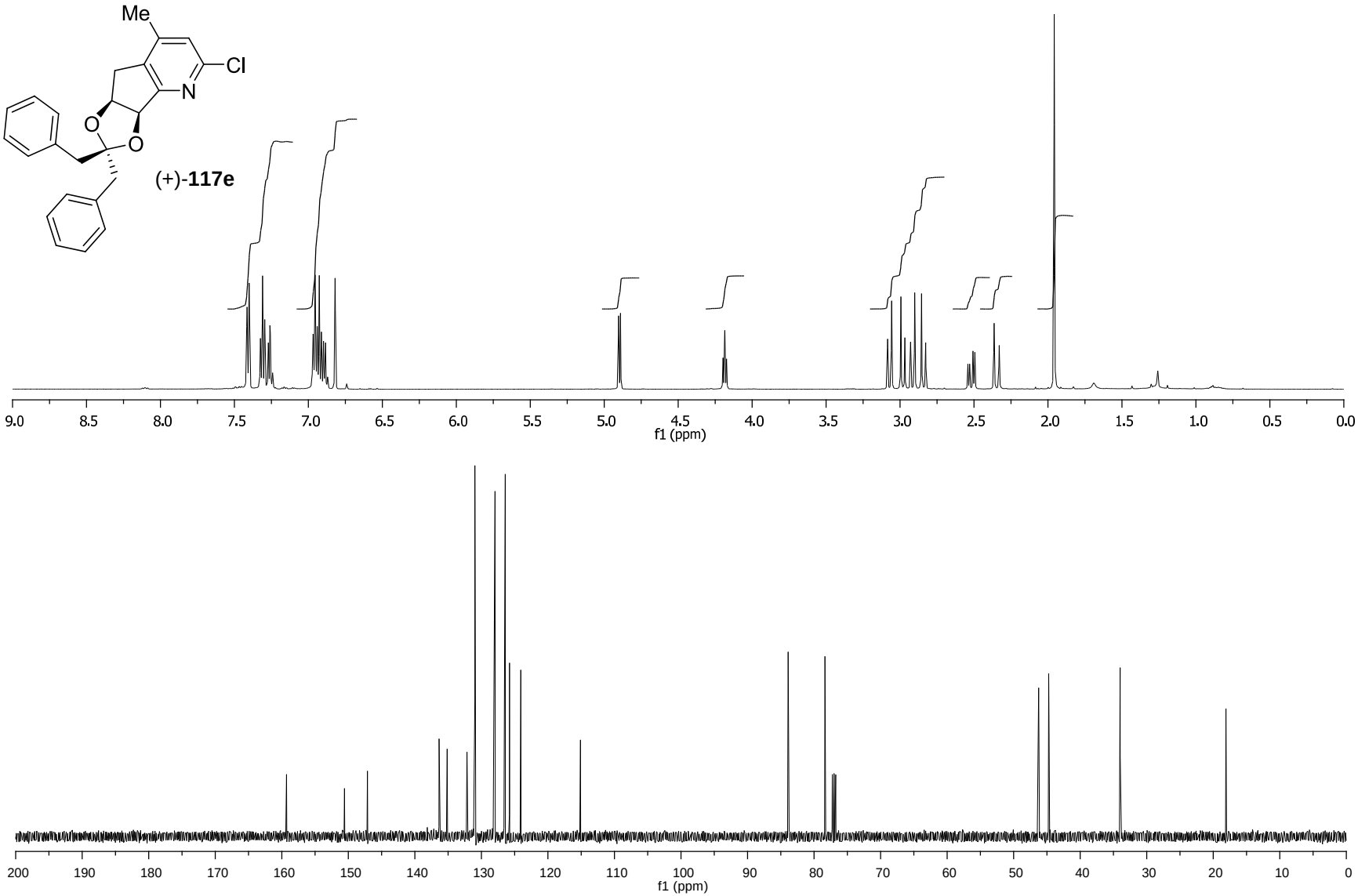
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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Cl
N
O
O
(+)-117e
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4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
200
190
180
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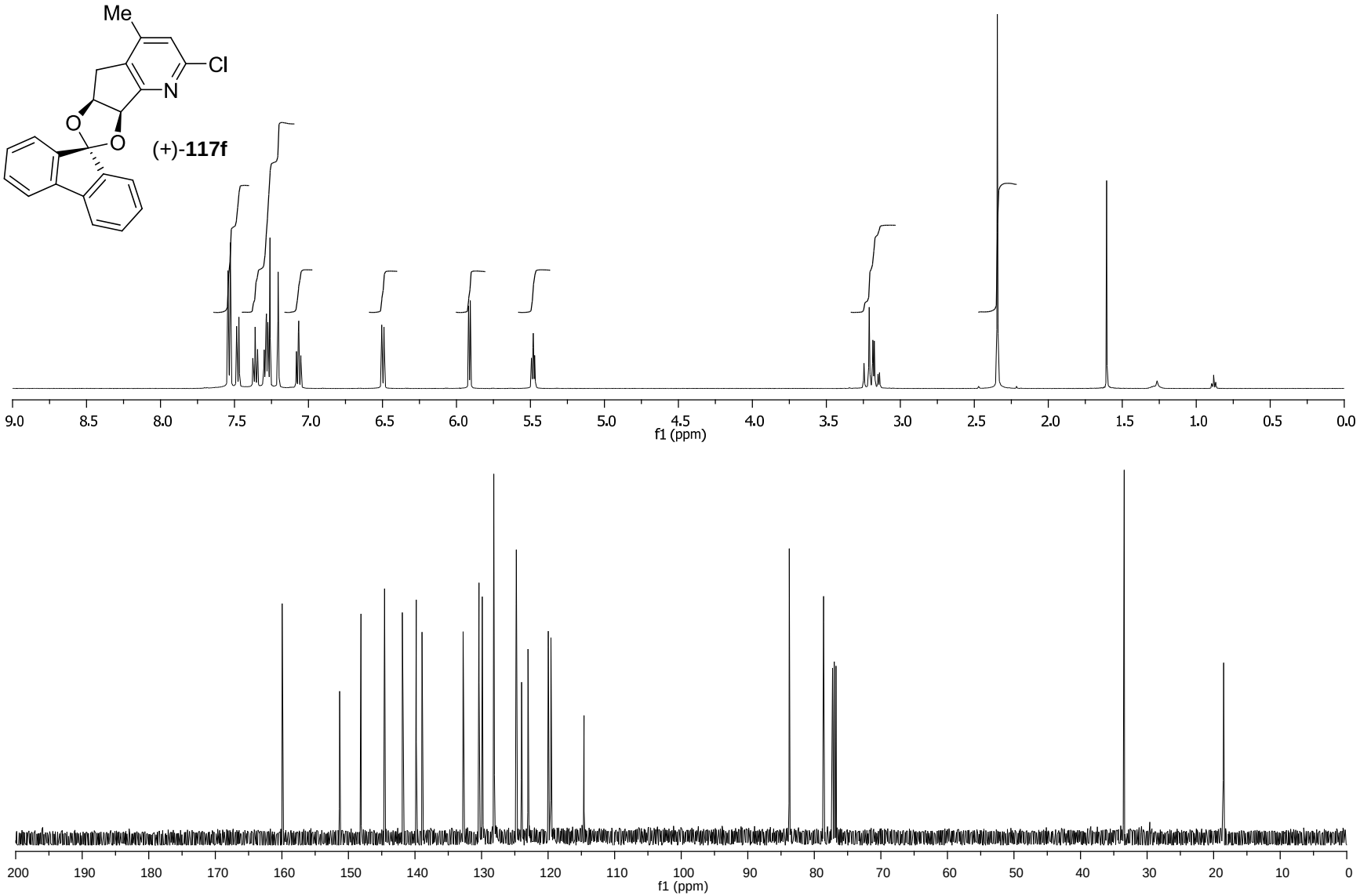
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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Cl
N
O
O
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5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
200
190
180
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140
130
120
110
100
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80
70
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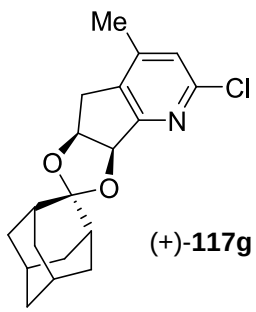
50
40
30
20
10
0
f1 (ppm)


Me
Cl
N
O
O

(+)-**117g**

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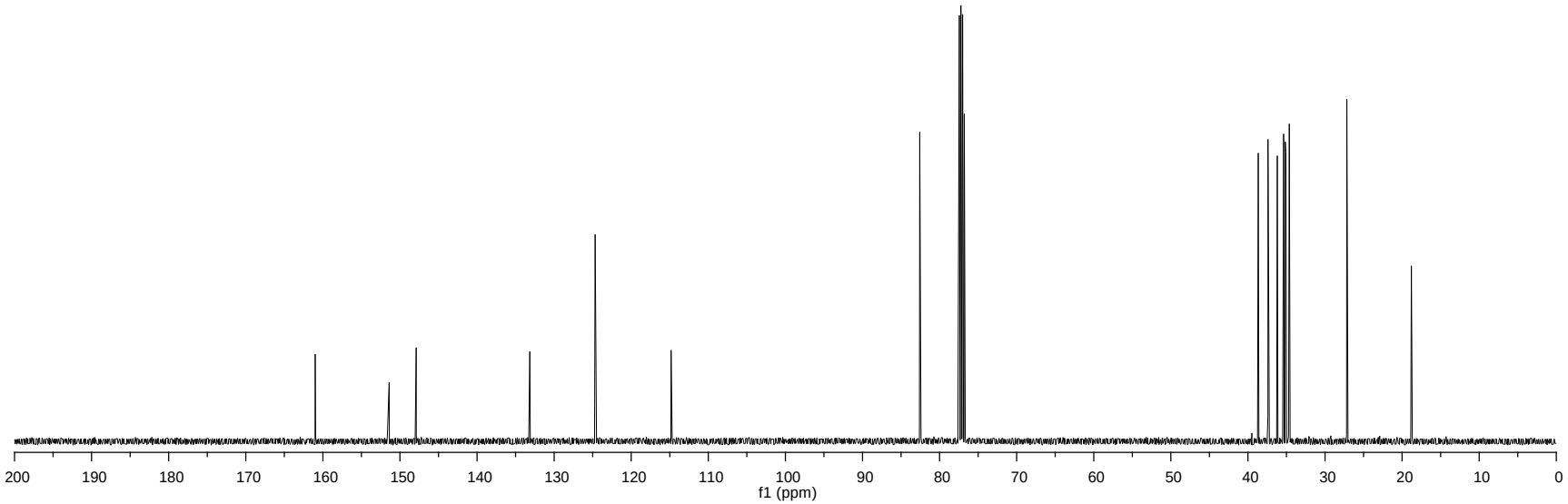
f1 (ppm)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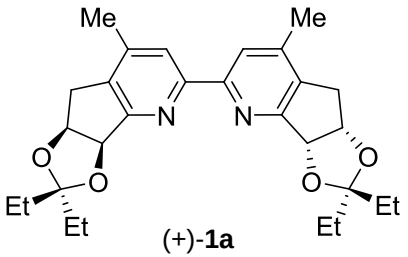
f1 (ppm)


Me
Me
N
N
O
O
O
O
Et
Et
Et
Et

(+)-**1a**

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7.0
6.5
6.0
5.5
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3.0
2.5
2.0
1.5
1.0
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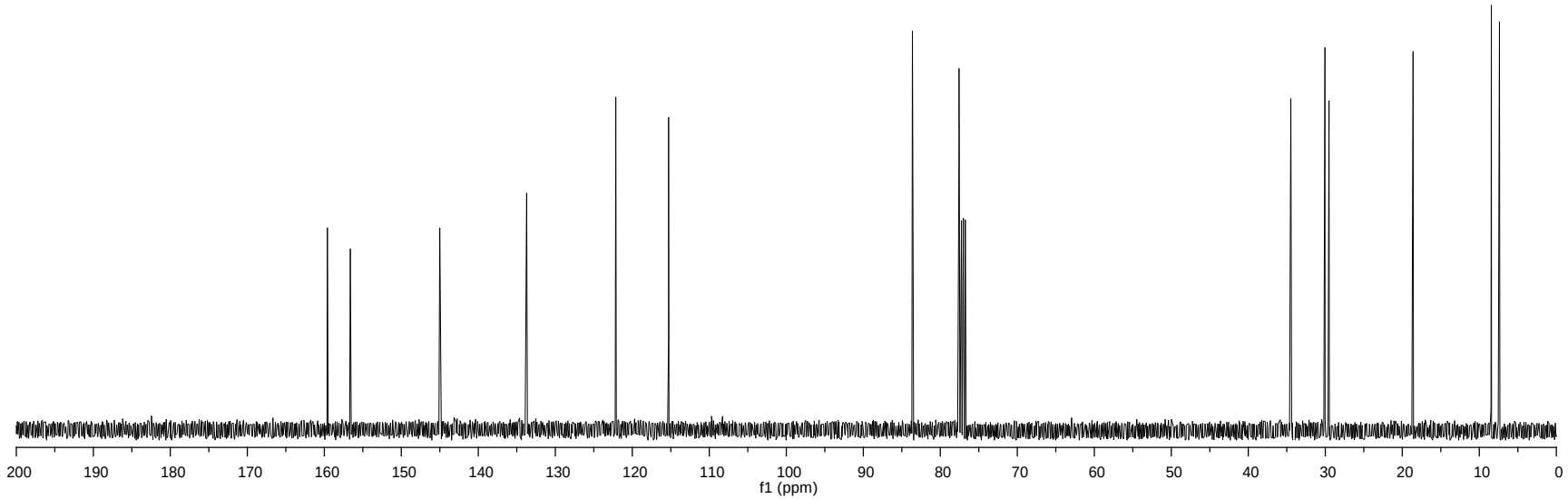
0.0
f1 (ppm)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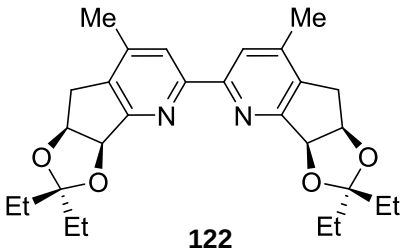
0
f1 (ppm)


Me
Me
N
N
O
O
O
O
Et
Et
Et
Et

122

9.0
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7.5
7.0
6.5
6.0
5.5
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3.0
2.5
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1.5
1.0
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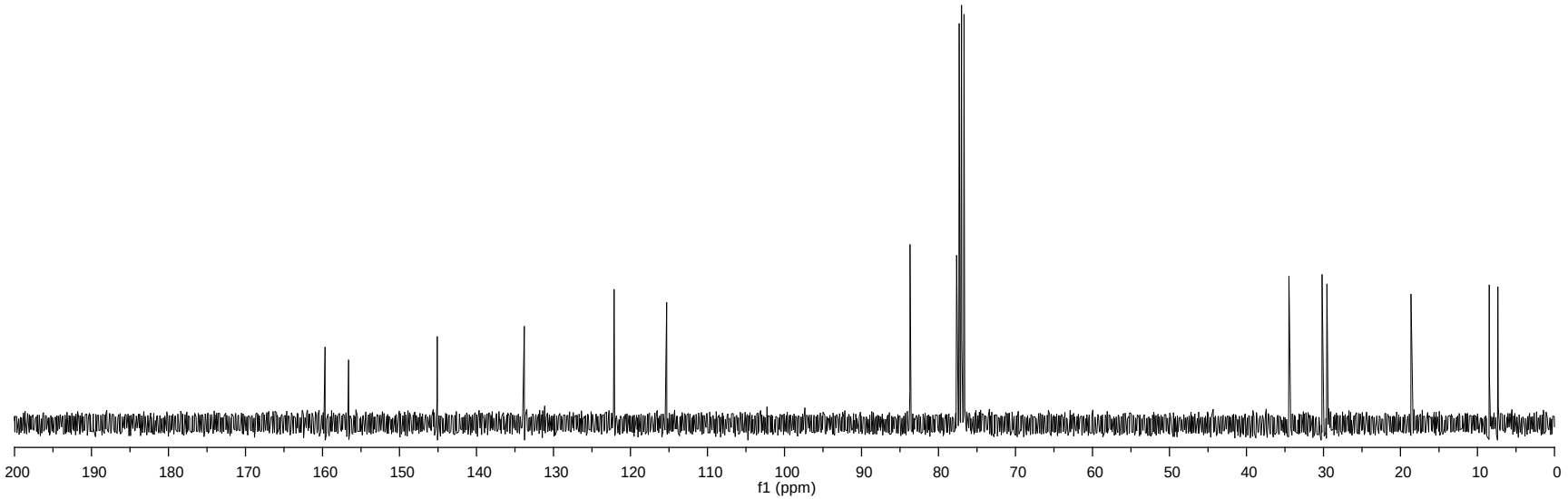
0.0
f1 (ppm)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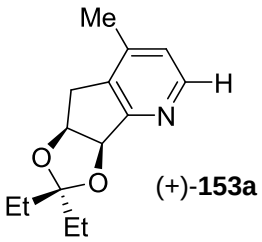
20
10
0
f1 (ppm)


Me
H
N
O
O
Et
Et

(+)-**153a**

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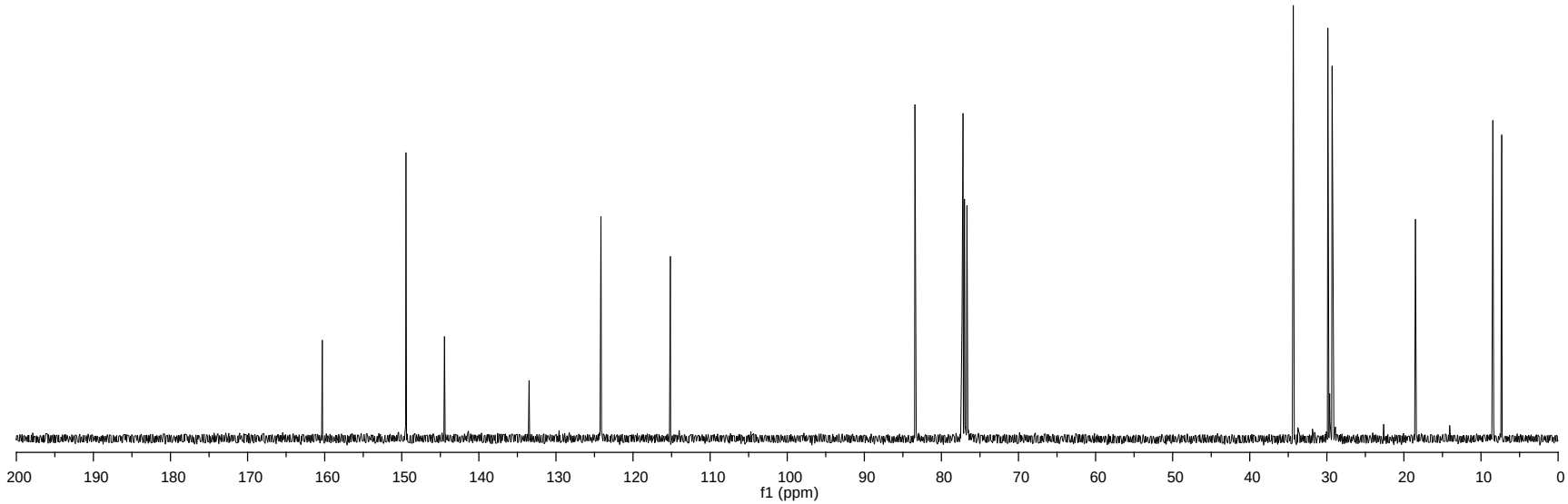
f1 (ppm)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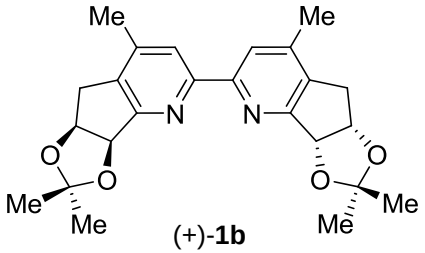
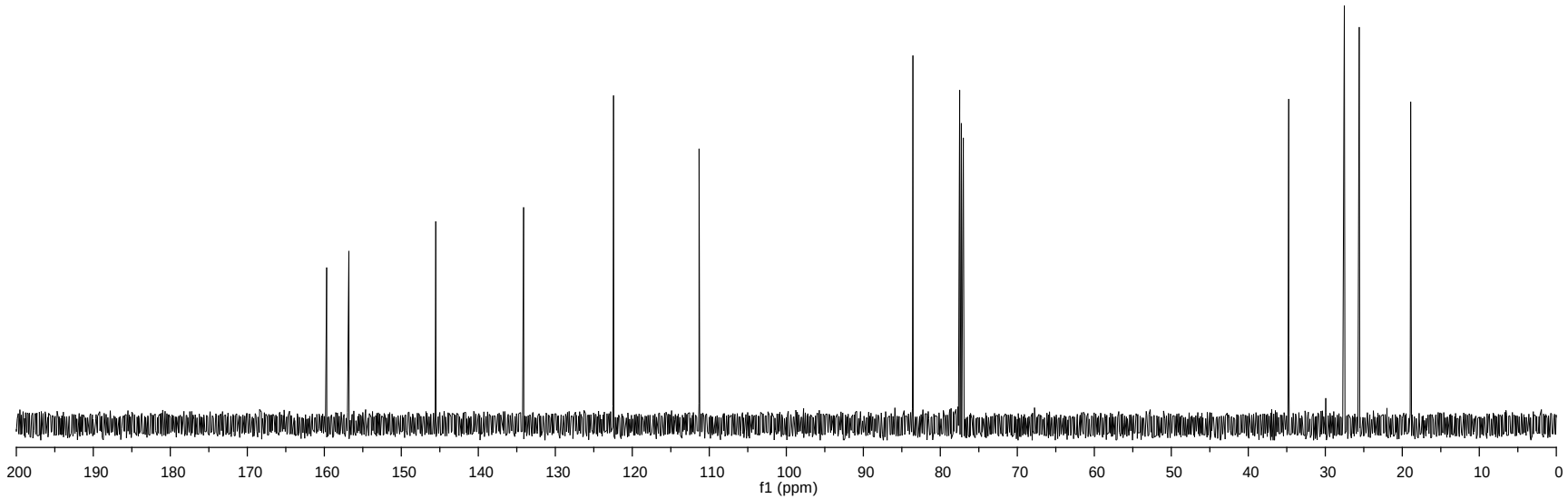
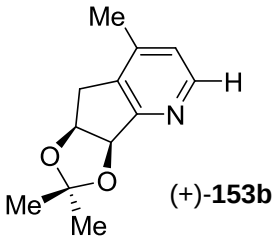
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Me
Me
N
N
O
O
O
O
Me
Me
Me
Me

(+)-**1b**

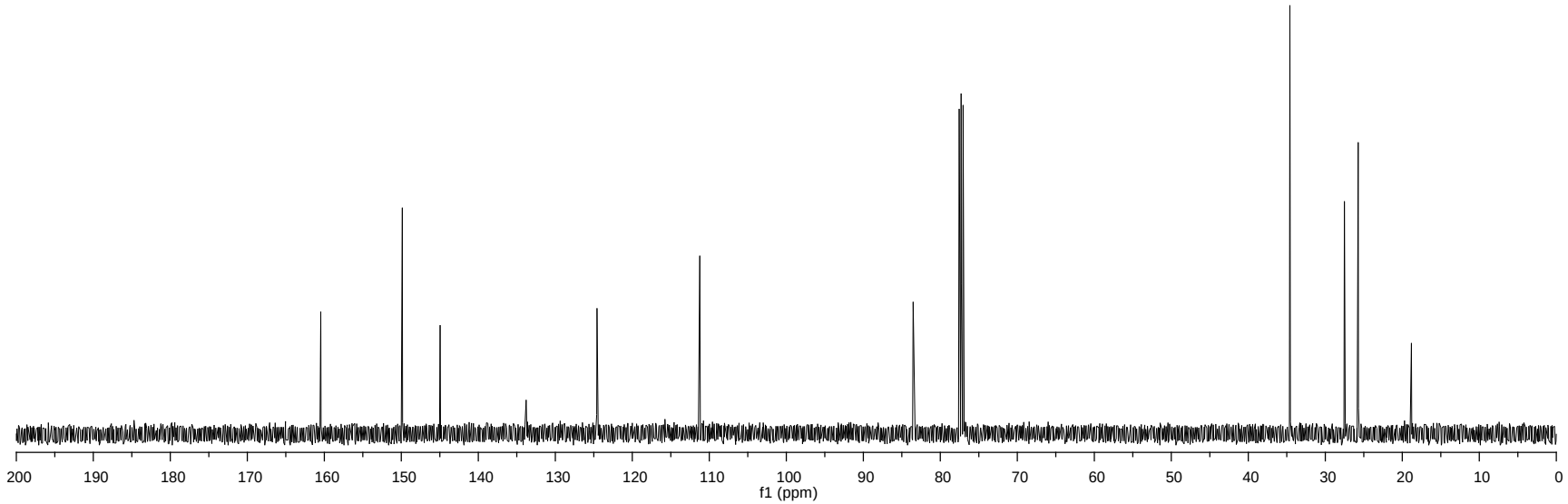
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

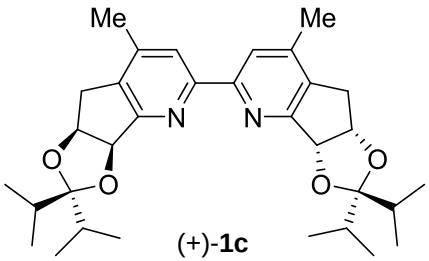

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Me
H
N
O
O
Me
Me

(+)-**153b**

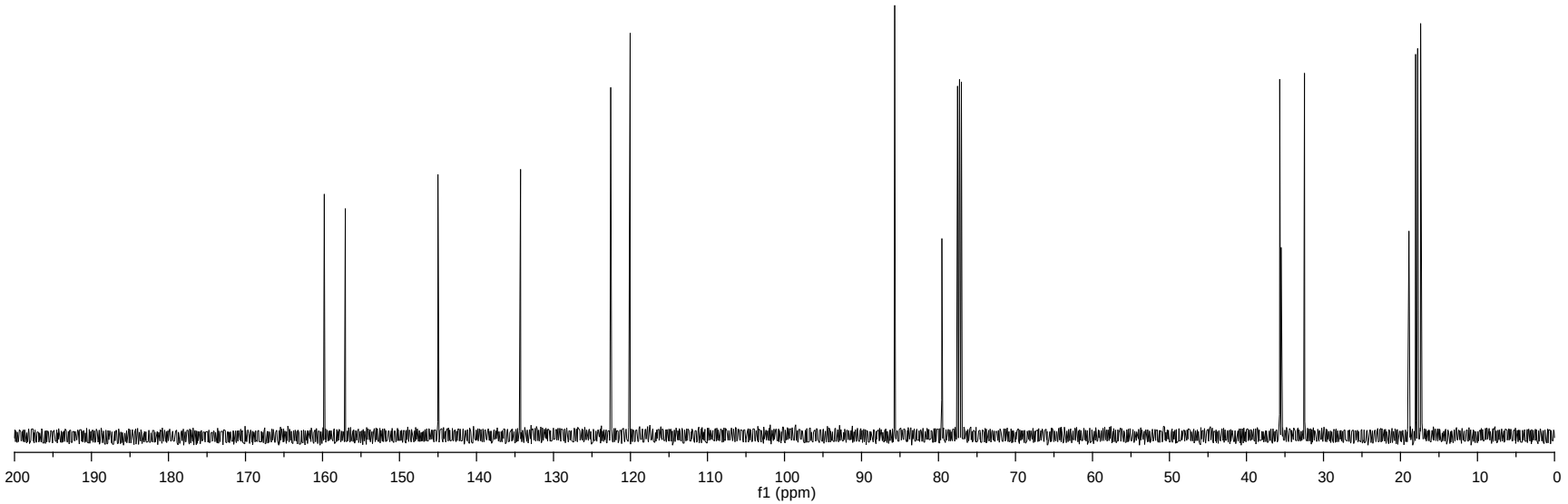
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

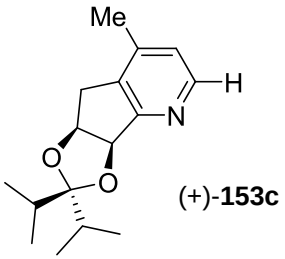

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Me
Me
N
N
O
O
O
O

(+)-**1c**

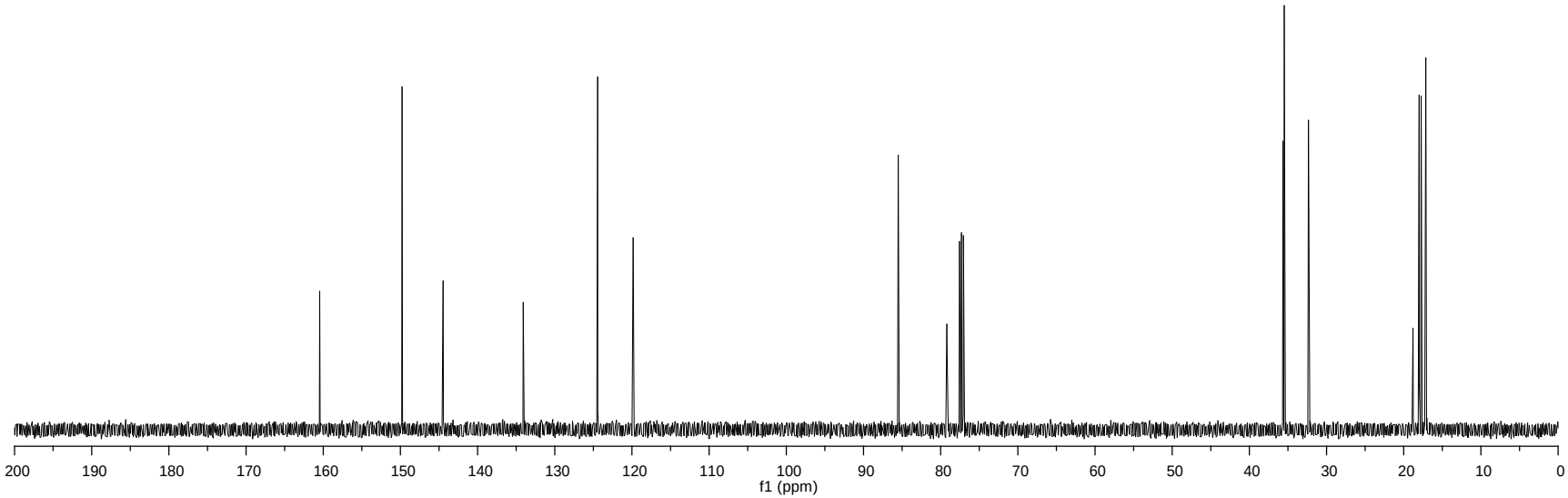
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

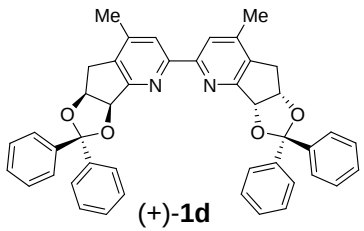

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Me
H
N
O
O

(+)-**153c**

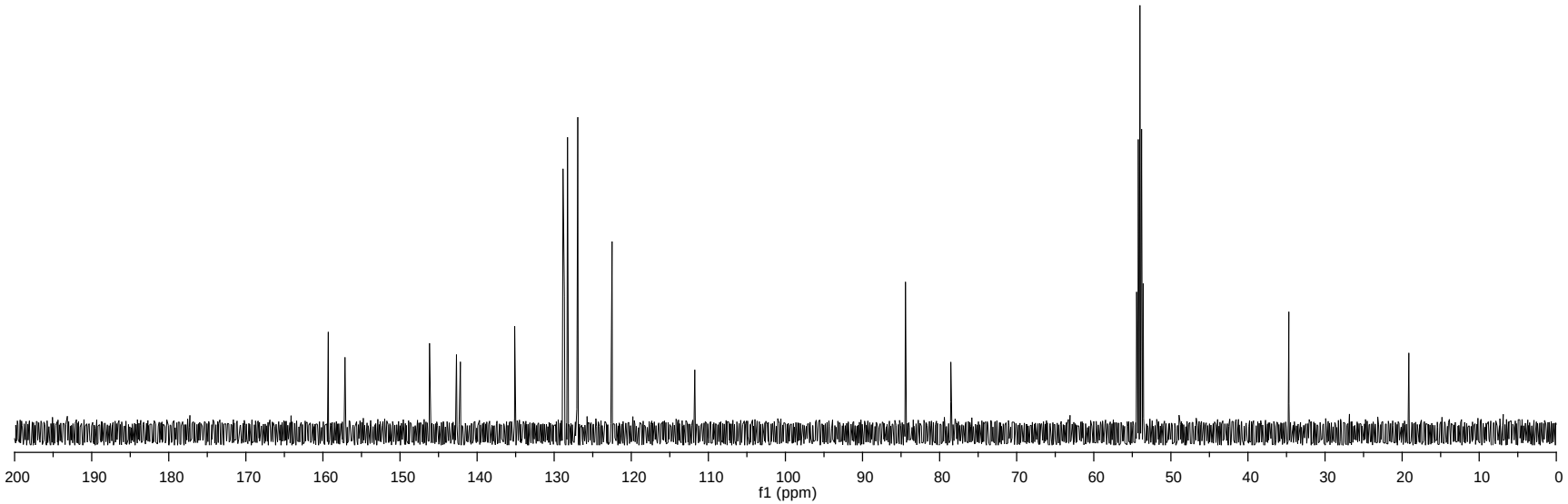
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

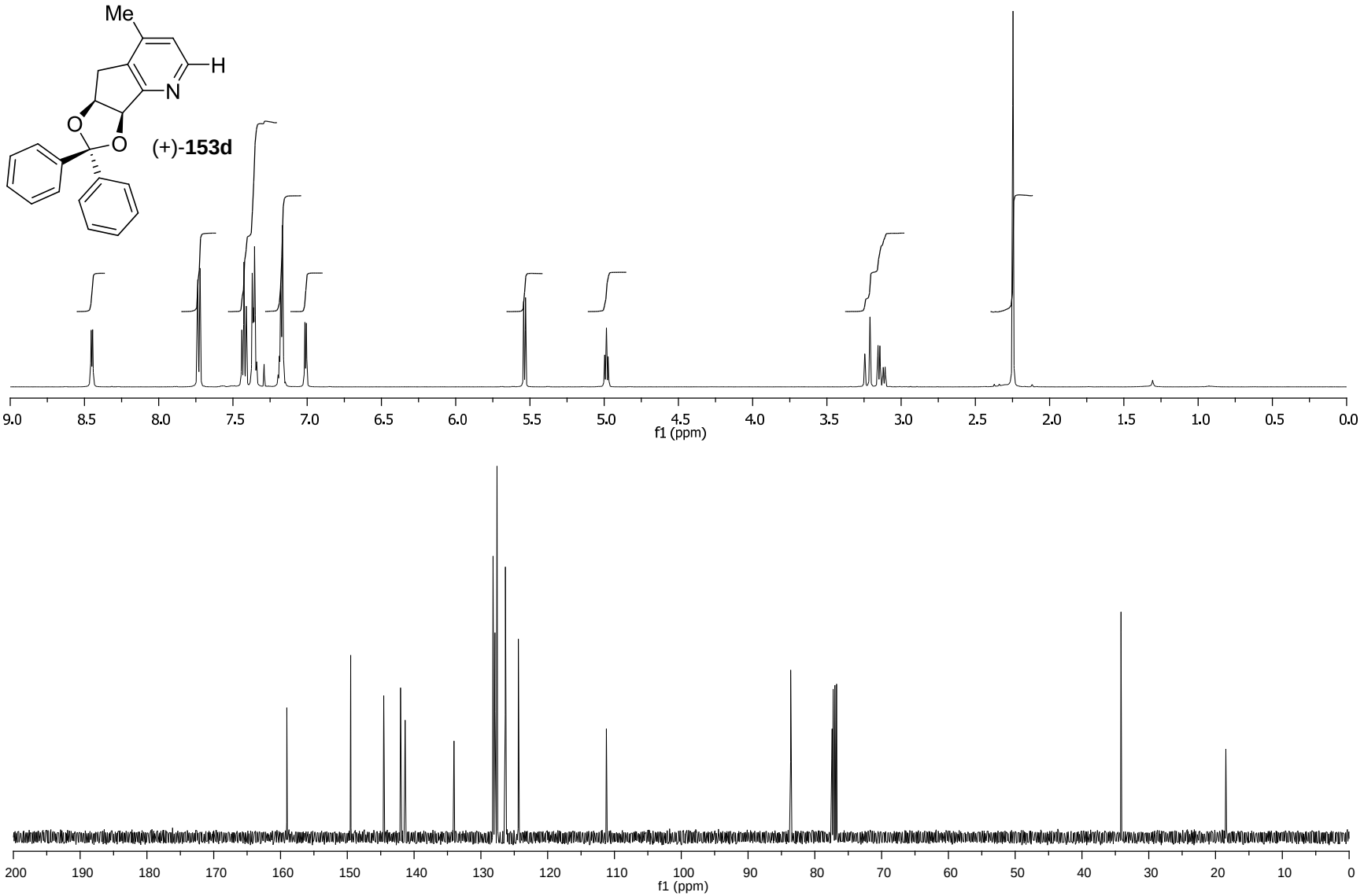

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

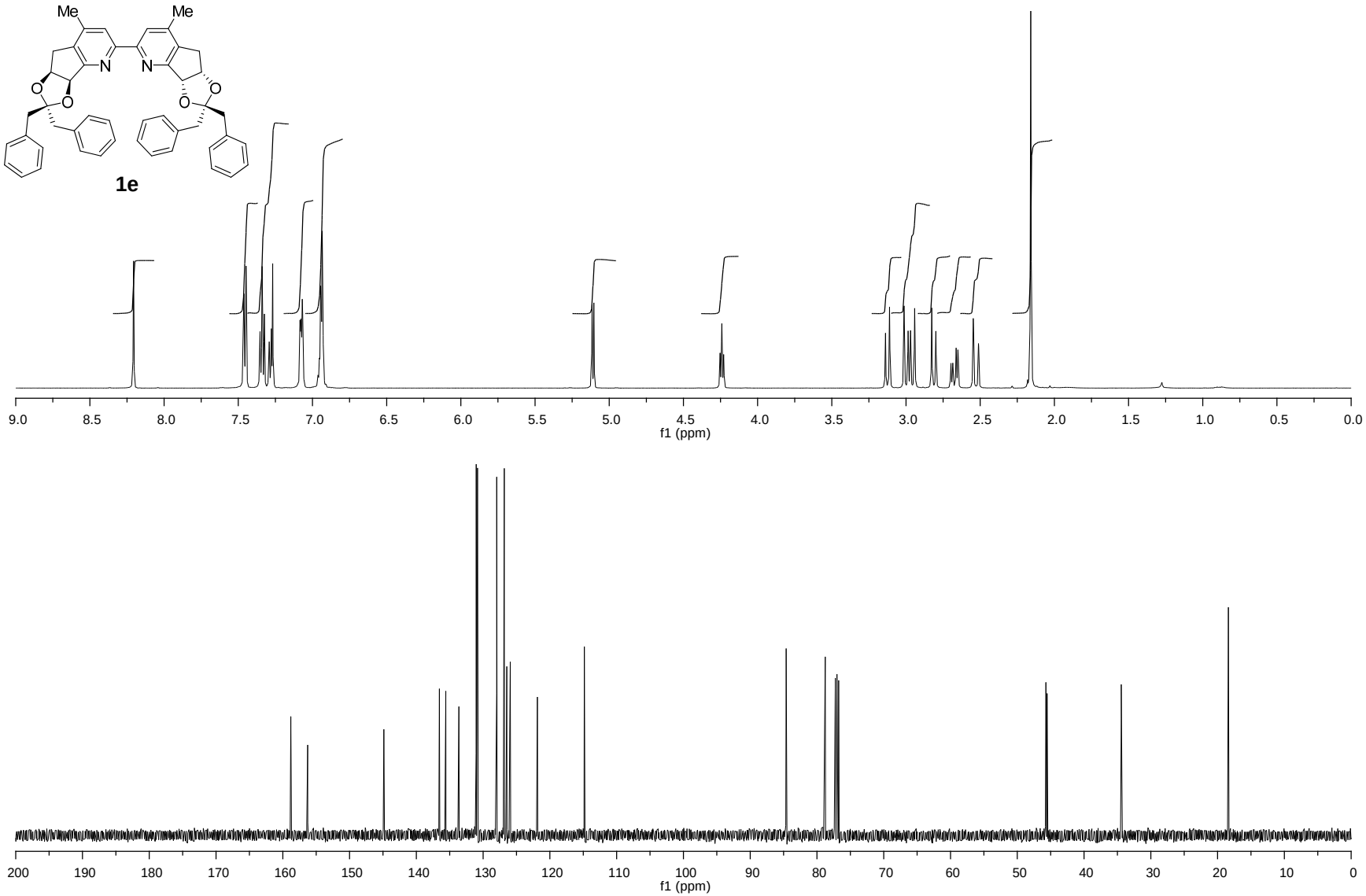

Me
Me
N
N
O
O
O
O

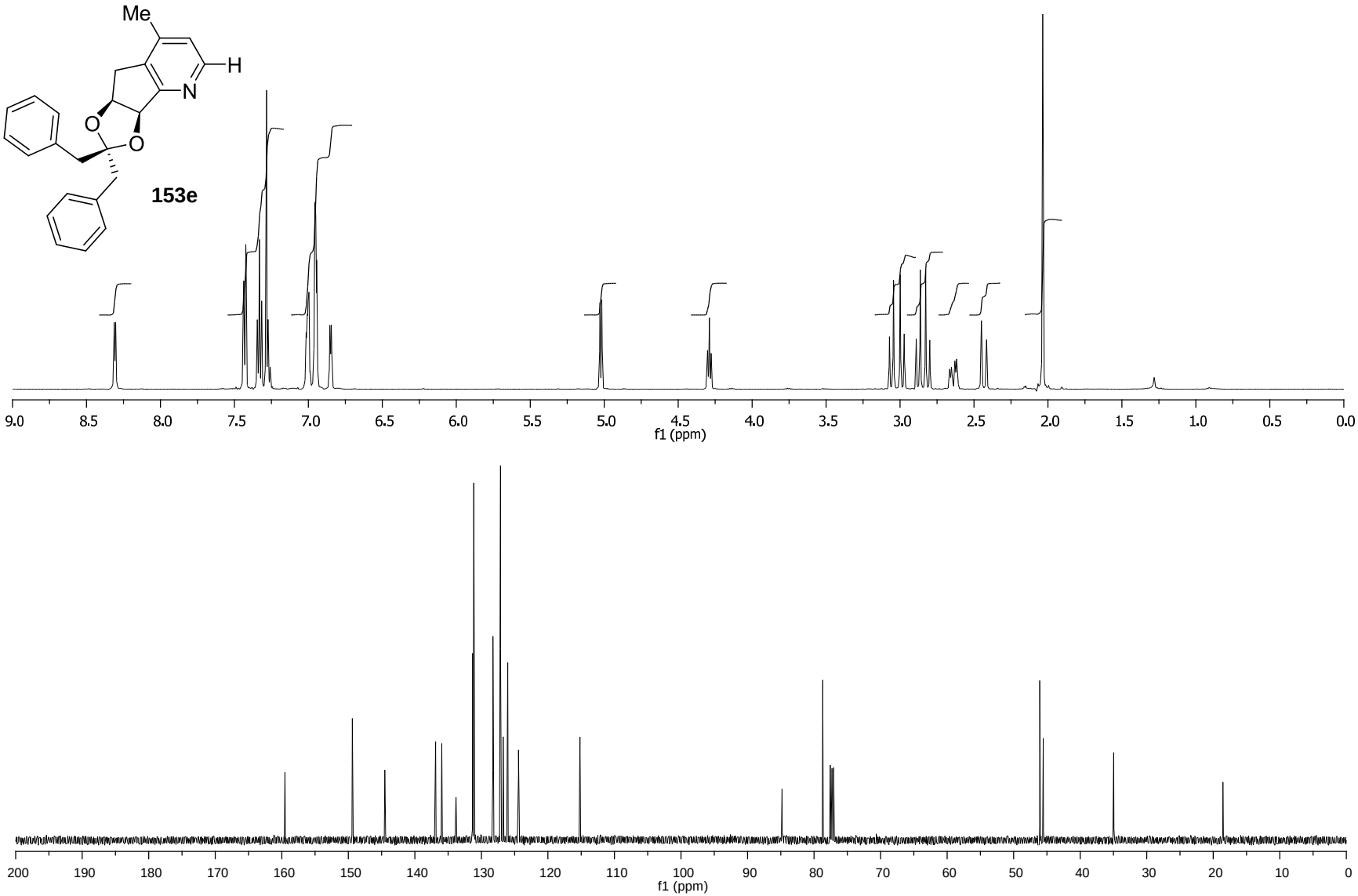
(+)-**1d**

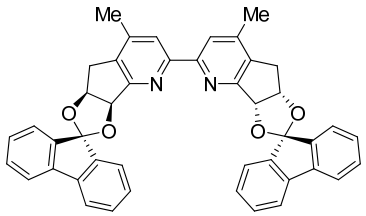
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Me
H
N
O
O
(+)-153d
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

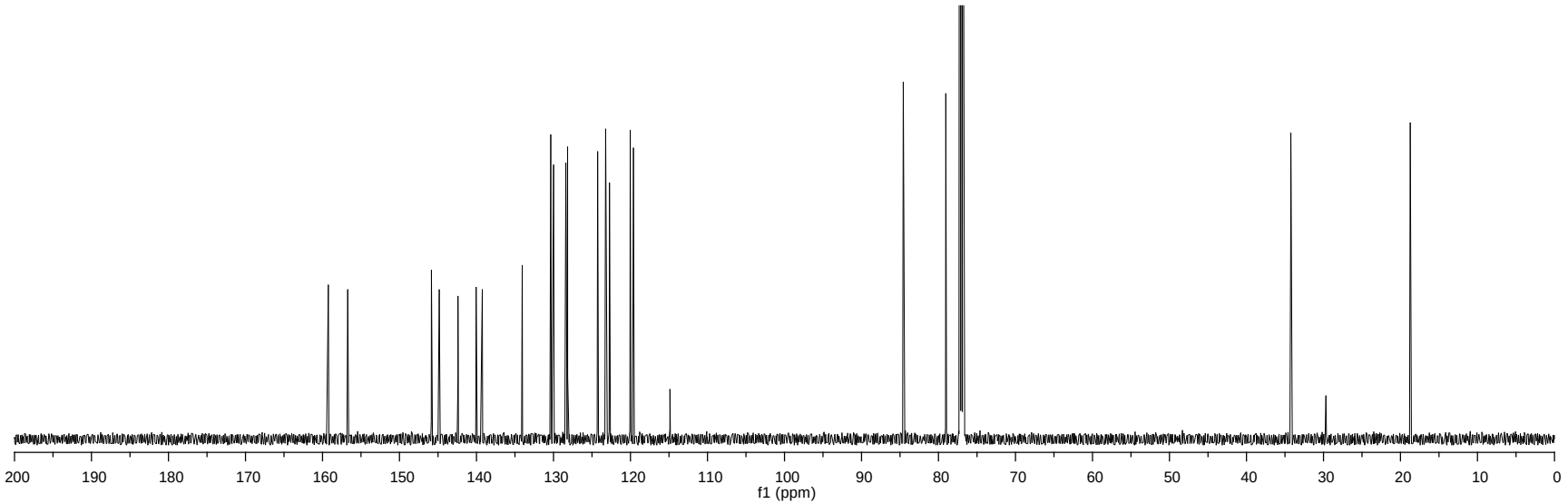

Me
Me
N
N
O
O
O
O
1e
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

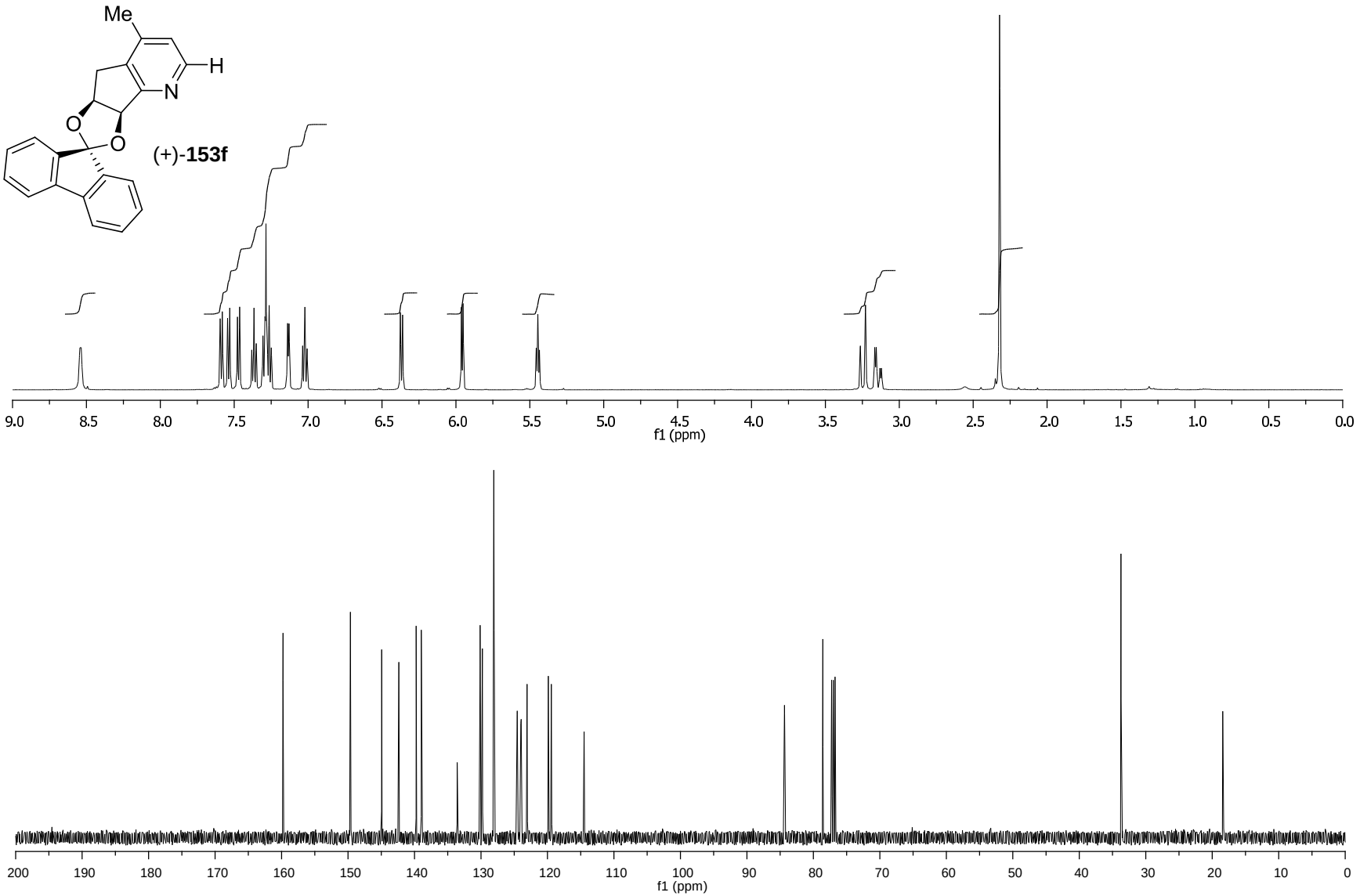

Me
H
N
O
O
153e
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

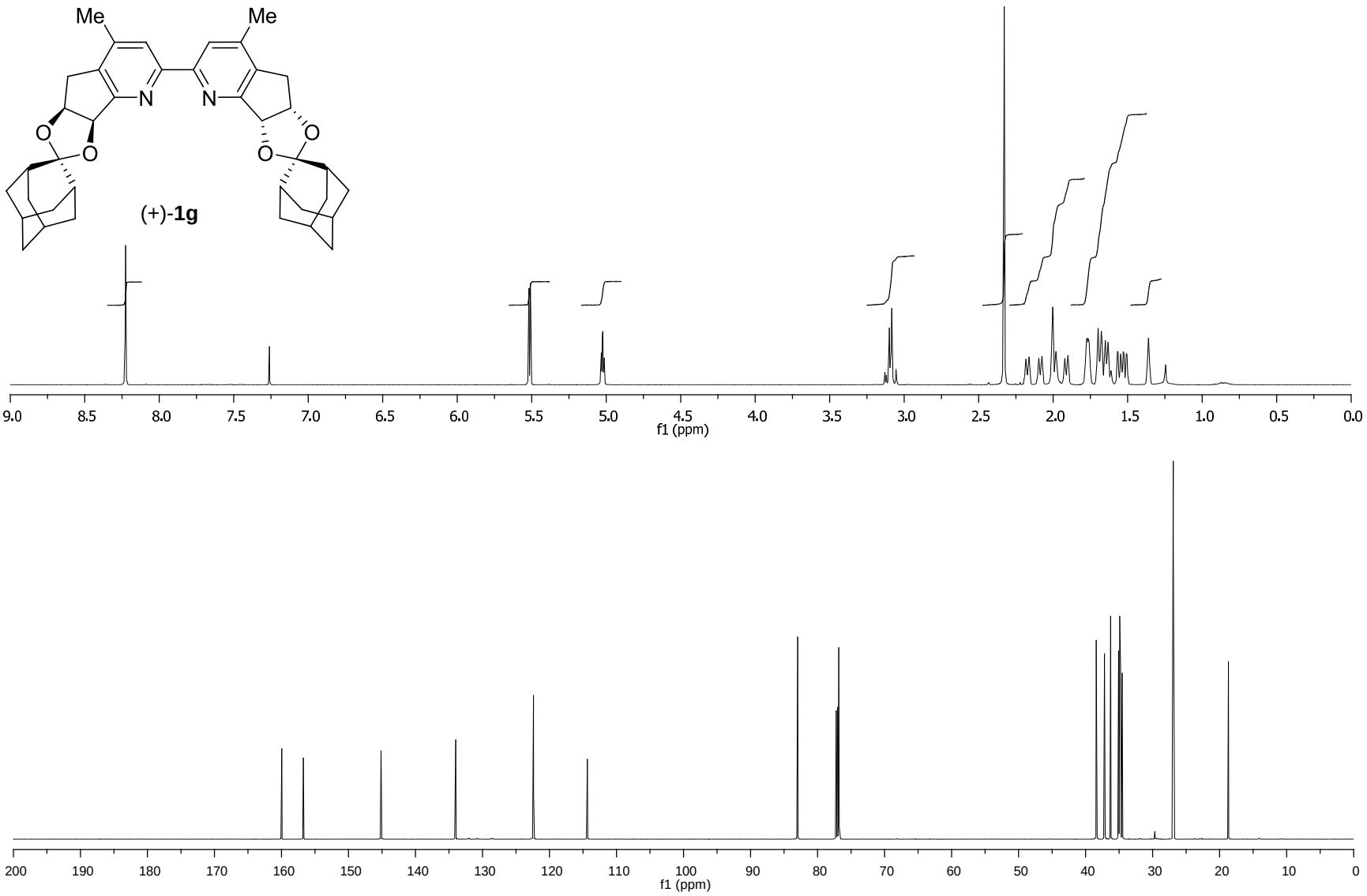

Me
Me
N
N
O
O
O
O

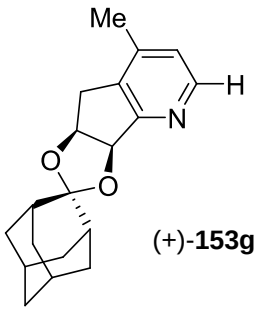
(+)-**1f**

9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

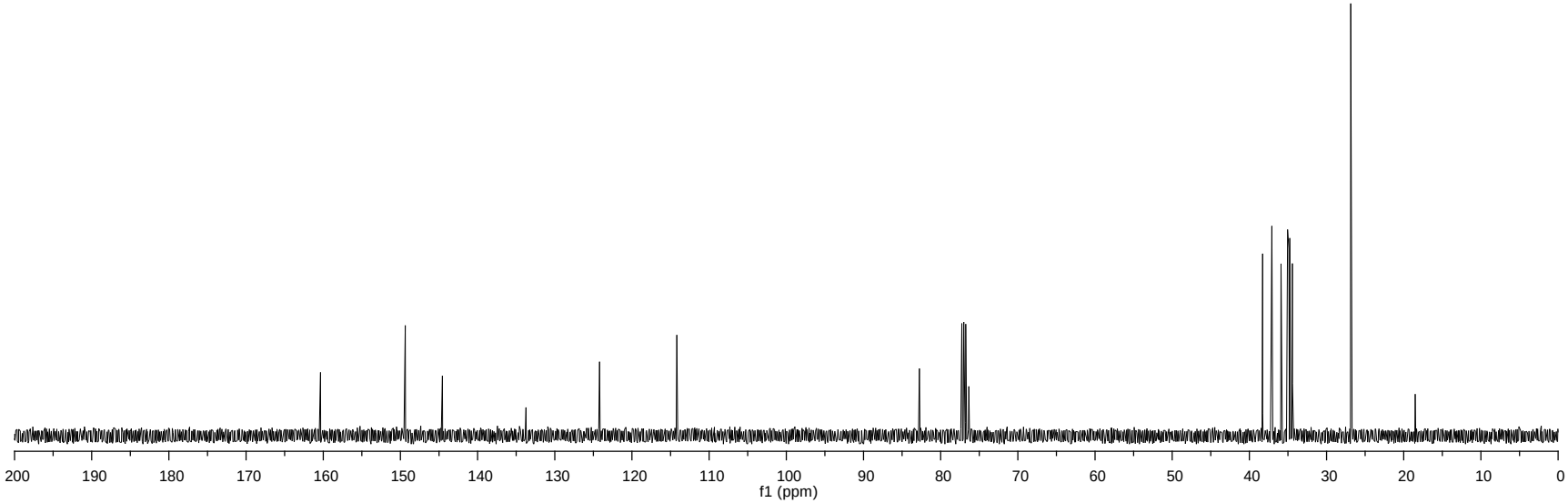

Me
H
N
O
O
(+)-153f
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

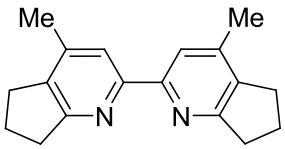

Me
Me
N
N
O
O
O
O
(+)-1g
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Me
H
N
O
O

(+)-**153g**

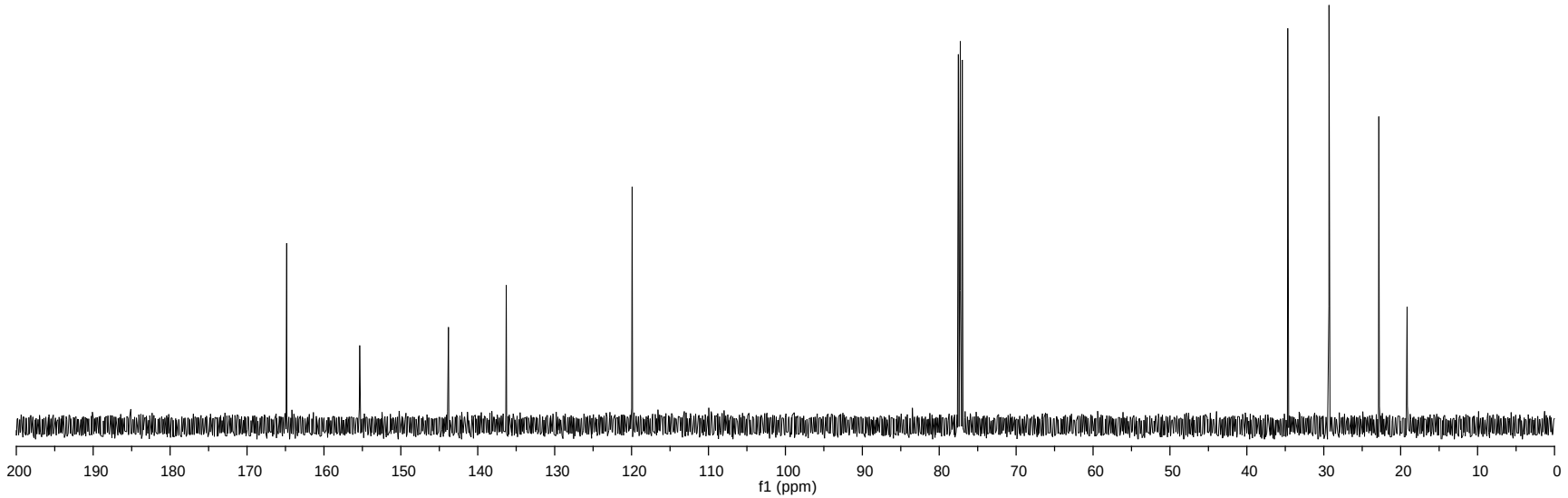
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

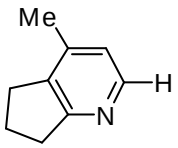

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Me
Me
N
N

161

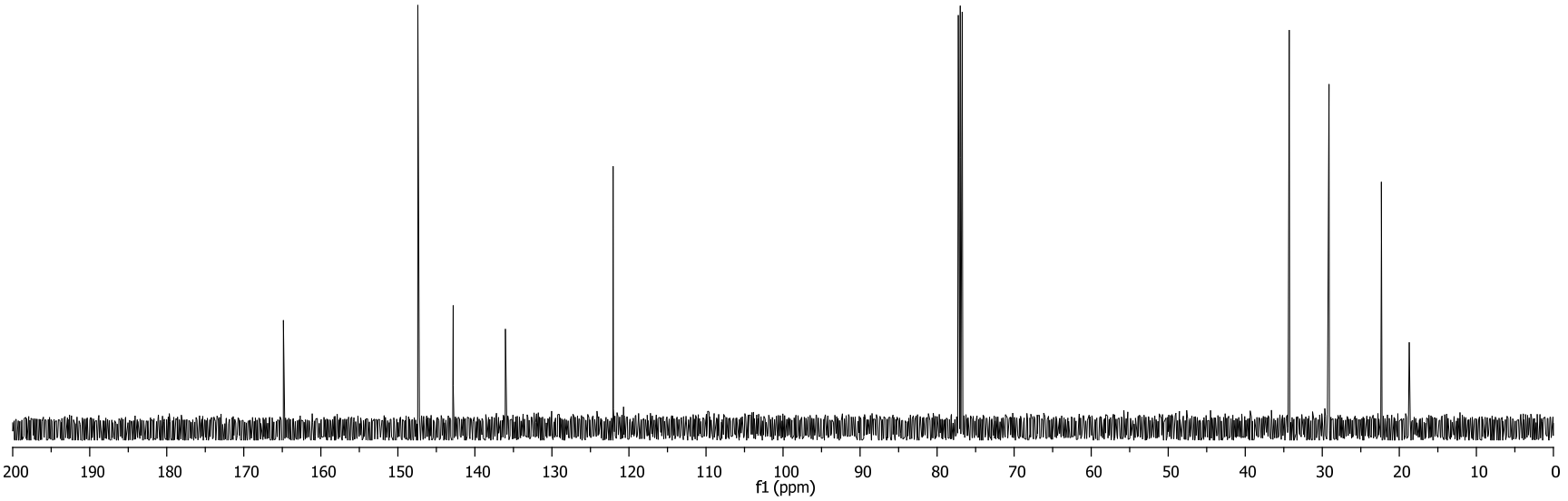
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Me
H
N

162

9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

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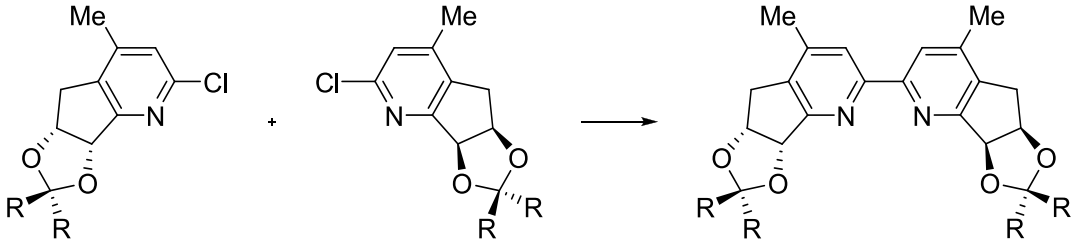
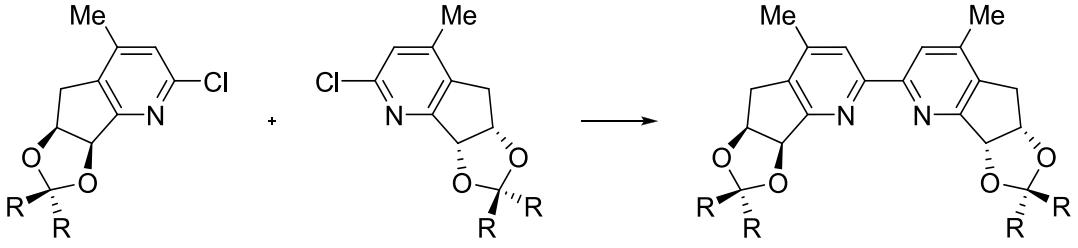
APPENDIX I

*Calculation of the Enantiomeric Enrichment of the Known Bipyridine (**1a**) and Formation of the* Meso-*Compound (**122**)*

In the reductive coupling of the enantiomeric chloropyridines (+)-**117a** and (-)-**117a** two *homo*- and two *hetero*-coupling pathways are possible. The *homo* coupling pathways lead to the two enantiomeric chiral 2,2'-bipyridines (+)-**1a** and (-)-**1a** (Scheme 4.3.5.1).

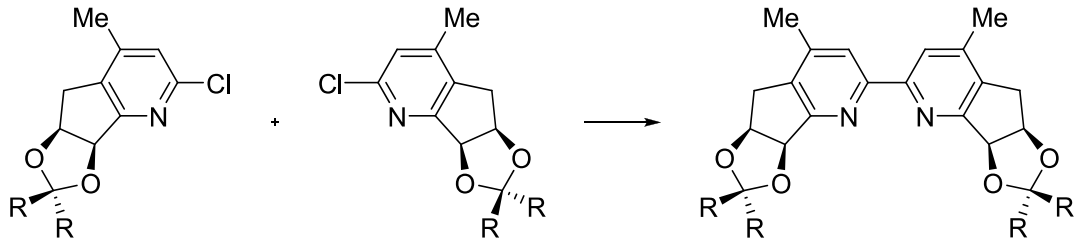
Scheme 4.3.5.1: *Homo*-Coupling of Chiral Acetal to Afford Chiral Products



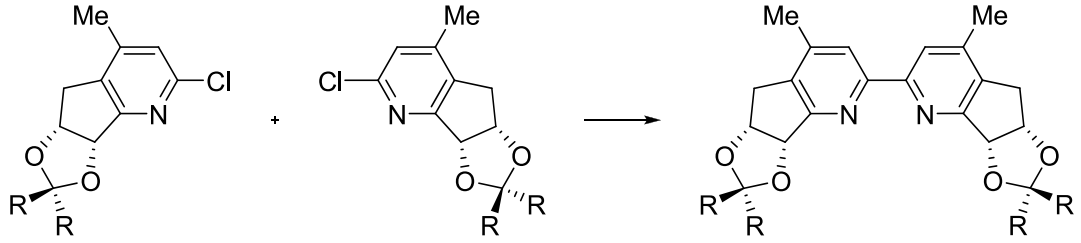


The two remaining pathways lead to the formation of the *meso*-product **122** (Scheme 4.3.5.2).

Scheme 4.3.5.2: *Homo*-Coupling of Chiral Acetal to Afford Chiral Products



(+)-**117a** (+)-**117a** **122**



(-)-**117a** (-)-**117a** **122**

In the following equations ***x*** will refer to the percentage of the major enantiomer, and ***y*** will refer to the percentage of the minor enantiomer.

$$\mathbf{x} = \%_{\boldsymbol{MAJOR}} \qquad (2)$$

$$\mathbf{y} = \%_{\boldsymbol{MINOR}} \qquad (3)$$

Under the reasonable assumption that the rate constant for the coupling of two identical molecules is similar to that of coupling two enantiomers, the statistical probability of each coupling reaction occurring is found by multiplying the abundance of the first coupling partner with that of the second. This assumption can be made as the two enantiomers have identical electronic properties; also, the chiral centre distinguishing

them from one another is remote from the coupling centre and will not likely influence the reaction.

The normalized abundance of each enantiomer of starting material is given as its percentage divided by 100%. Thus, by squaring the abundance of the major enantiomer of starting material, we obtain the normalized abundance of the major enantiomer of chiral product (+)-**1a** (represented by "***u***").

$$\left(\frac{\mathbf{x}}{\mathbf{100\%}}\right)^{\mathbf{2}} = \mathbf{u} \qquad (4)$$

The abundance of the minor enantiomer of chiral product (-)-**1a** (represented by "v") is found by squaring the abundance of the minor enantiomer of starting material.

$$\left(\frac{\mathbf{y}}{\mathbf{100\%}}\right)^{\mathbf{2}} = \mathbf{v} \qquad (5)$$

The overall enantiomeric purity of this chiral product (represented by ee_p) is given as the difference in abundance of its two enantiomers divided by its overall abundance, thus:

$$\frac{\mathbf{u - v}}{\mathbf{u + v}} = \frac{\mathbf{ee_p}}{\mathbf{100\%}} \qquad (6)$$

Substituting (4) and (5) into (6) and simplifying we get

$$\frac{\mathbf{x^2 - y^2}}{\mathbf{x^2 + y^2}} = \frac{\mathbf{ee_p}}{\mathbf{100\%}} \qquad (7)$$

Enantiomeric excess of the starting material (ee_{sm}) is defined as the difference in the percentage of the major enantiomer and the minor enantiomer of any enantiomeric mixture.

$$\mathbf{x - y = ee_{sm}} \tag{8}$$

Also, the sum of the percentages of the enantiomers is 100%:

$$\mathbf{x + y = 100\%} \tag{9}$$

Thus, the proportion of the major enantiomer in any enantiomeric mixture is:

$$\frac{\mathbf{100\% + ee_{sm}}}{\mathbf{2}} = \mathbf{x} \tag{10}$$

It follows that the proportion of minor enantiomer in any enantiomeric mixture is:

$$\frac{\mathbf{100\% - ee_{sm}}}{\mathbf{2}} = \mathbf{y} \tag{11}$$

Substituting equation (10) and (11) into (7) we get

$$\frac{\left(\frac{\mathbf{100\% + ee_{sm}}}{\mathbf{2}}\right)^2 - \left(\frac{\mathbf{100\% - ee_{sm}}}{\mathbf{2}}\right)^2}{\left(\frac{\mathbf{100\% + ee_{sm}}}{\mathbf{2}}\right)^2 + \left(\frac{\mathbf{100\% - ee_{sm}}}{\mathbf{2}}\right)^2} = \frac{\mathbf{ee_p}}{\mathbf{100\%}} \tag{12}$$

Equation (12) is rather cumbersome, but fortunately it simplifies to equation (1) which is presented in the body of this thesis. From this expression it is calculated that

when starting with racemic material the resulting product will also be racemic. Also, when starting with enantiopure material the product obtained will be enantiopure.

$$\mathbf{ee_p} = \frac{\mathbf{2(ee_{sm})}}{\mathbf{1} + \left(\frac{\mathbf{ee_{sm}}}{\mathbf{100\%}}\right)^{\mathbf{2}}} \qquad (1)$$

It follows that the percentage of the coupled product which is formed as the *meso*-compound **122** (this percentage is represented as "***w***") is the sum of the probabilities of the two redundant *meso* forming events thus:

$$\mathbf{2}\left(\frac{\mathbf{x}}{\mathbf{100\%}}\right)\left(\frac{\mathbf{y}}{\mathbf{100\%}}\right) = \frac{\mathbf{w}}{\mathbf{100\%}} \qquad (13)$$

Substituting equations (10) and (11) into equation (13) and simplifying affords equation (14):

$$\mathbf{50\%} - \frac{\mathbf{ee_{sm}}^{\mathbf{2}}}{\mathbf{200\%}} = \mathbf{w} \qquad (14)$$

From equation (14) it is calculated that when starting with racemic material fifty percent of the final coupled product would be formed as the *meso*-compound. By starting with enantiopure material no *meso*-product will be formed.

According to equation (1) the reductive-coupling reaction of the chloroacetal **117a** (80% ee) is calculated to yield a C_2-symmetric 2,2'-bipyridine (+)-**1a** with an optical purity of ~ 98% ee. The calculated proportion of coupled product which forms as the *meso*-compound from the same coupling reaction, using equation (14), is 18%. Indeed, experimental results were in agreement with these calculations.