ABSTRACT

The Origin of Remarkable Chromatographic Differences in Novel Azulenyl-1,5-diols and Synthesis and Use of Phosphinine and Phosphabarrelene Ligands for Asymmetric Catalysis

Dana Ann Horgen, Ph.D.

Mentor: Charles M. Garner, Ph.D.

The synthesis, characterization and analysis of novel chiral molecules advance many areas of synthetic organic chemistry, both industrially and academically. This work touches on three of the major methods for obtaining enantiomerically pure compounds.

Based on the observation of a remarkably large difference in the silica TLC mobility of a pair of azulene 1,5-diol diastereomers, a series of such azulene 1,5-diols were prepared. Every pair of diastereomers was especially well separated, and X-ray crystallography revealed a conformational explanation of the large differences in mobility. The separation of the diol enantiomers was then studied on two chiral HLPC columns. The enantiomers were well-resolved, the separation appearing to benefit from the presence of the azulene ring. In addition, the more polar diastereomers on silica TLC gave dramatically better enantiomer separations on a Chiralcel-OD-H column.

Very few chiral phosphinine and phosphabarrelene ligands have been reported in the literature but have shown promise as good ligands for asymmetric catalysis. Our group had previously synthesized a *C*₂-symmetric chiral bis-camphorphosphinine and the derived bis-camphorphosphabarrelene but neither had been tested as ligands for hydroformylation. In this work, optimization of the synthesis of these two compounds was undertaken. In addition, modifications to the structure of these molecules that incorporated electron donating (N,N-dimethylaminophenyl-) or electron withdrawing (trifluoromethyl-) substituents were made in an attempt to affect the electronic nature of the phosphorus atom. Steric modifications were also done to create a more hindered environment around the phosphorus atom.

The activity and selectivity of bis-camphorphosphinine, bis-camphorphosphabarrelene and other chiral phosphinine molecules serving as ligands in the rhodiumcatalyzed hydroformylation of styrene were compared to other phosphorus ligands recently published in the literature. All of these ligands gave complexes that have moderate activity with good regioselectivity but very little enantioselectivity. Therefore, more tuning of these ligands' properties need to be done in order to achieve the activity and selectivity of other chiral monodentate-ligands. The bis-camphorphosphabarrelene was also a successful organocatalyst of the Baylis-Hillman reaction, showing its versatility in both metal-catalyzed and metal-free catalysis. The Origin of Remarkable Chromatographic Differences in Novel Azulenyl-1,5-diols; & Synthesis and Use of Phosphinine and Phosphabarrelene Ligands for Asymmetric Catalysis

by

Dana Ann Horgen, B.A.

A Dissertation

Approved by the Department of Chemistry and Biochemistry

Patrick J. Farmer, Ph.D., Chairperson

Submitted to the Graduate Faculty of Baylor University in Partial Fulfillment of the Requirements for the Degree of

Doctor of Philosophy

Approved by the Dissertation Committee

Charles M. Garner, Ph.D., Chairperson

Kevin G. Pinney, Ph.D.

Robert R. Kane, Ph.D.

Kevin K. Klausmeyer, Ph.D.

Christopher M. Rios, Ph.D.

Accepted by the Graduate School August 2014

J. Larry Lyon, Ph.D., Dean

Page bearing signatures is kept on file in the Graduate School.

Copyright © 2014 by Dana Ann Horgen

All rights reserved

TABLE OF CONTENTS

LIST OF FIGURES	vii
LIST OF TABLES	ix
LIST OF SCHEMES	X
LIST OF ABBREVIATIONS	xii
ACKNOWLEDGMENTS	xiv
CHAPTER ONE Introduction	1
Background—Chiral Molecules	1
Azulene Project	4
Phosphabarrelene Project	10
Catalysis Project	15
CHAPTER TWO Azulene Diols	22
Introduction/Background	22
Synthesis	27
Analysis and Separation of Diastereomers	31
Analysis and Separation of Enantiomers	37
Conclusions	43
CHAPTER THREE Phosphabarrelene Synthesis Optimization and Derivatives	45
Introduction/Background	45
Synthesis of the Ligands	49
Derivatives at the Phenyl Position	56
Derivatives of the Heteroatom	60

Other Derivatives	62
CHAPTER FOUR Asymmetric Catalysis Utilizing Phosphinine and Phosphabarrelene Containing Catalysts	67
Introduction/Background	67
NMR Binding Studies	73
Catalytic Studies	75
Organocatalysis—Baylis-Hillman Reaction	80
Discussion	
CHAPTER FIVE Materials and Methods	
General Section	
Azulene Diols	84
Phosphabarrelene Derivatives	91
Asymmetric Catalysis	
APPENDICES	
APENDIX A:	
Selected NMR Spectra	
APPENDIX B	
Select Spectral Data from GC-MS, HPLC, and CD	
APPENDIX C	
Tables of X-ray Crystallographic Data	
REFERENCES	

LIST OF FIGURES

Figure 1.1 Structures of gaiazulene and azulene.	5
Figure 1.2. Structures of naphthalene, azulene with one of its resonance forms	6
Figure 1.3. Structures of bis-camphorphosphinine 6 and bis-camphorphosphabarrelene 7 .	10
Figure 1.4. Structure of (+)-camphor	11
Figure 1.5. <i>C</i> ₂ -symmetry in the bis-camphorphosphinine molecule	12
Figure 1.6. Metal-phosphorus bonding orbitals, and Tolman parameters.	13
Figure 1.7. Related aromatic derivatives and phosphabarrelene structure.	14
Figure 1.8. Structure of DABCO and, phosphabarrelene.	20
Figure 2.1. <i>d</i> , <i>l</i> -Diol and meso diol synthesized by Harmata	23
Figure 2.2. Azulene diol derivatives 5 , 9-10	26
Figure 2.3. Cycloalkyldiol diastereomers 22 - 24	31
Figure 2.4. Photograph of diastereomeric TLC separation of	32
Figure 2.5. X-ray crystal structures of diols, $5_{RS = SR}$, $9_{RR/SS}$, $10_{RR/SS}$, $10_{RR/SS}$, $10_{RS/SR}$, and $11_{RR/SS}$.	35
Figure 3.1. Various phosphinine and phosphabarrelene ligands.	46
Figure 3.2. Quantification of steric hindrance using an average of α and β for planar phosphorus to obtain θ	47
Figure 3.3. Isomers of halobenzylidene camphor (29 and 32).	52
Figure 3.4. Anisotropic effects of phosphabarrelene, 7 , observed in the ¹ H NMR spectum.	55
Figure 3.5. X-ray crystal structures on phopshinine 47	64
Figure 3.5. Camphor-alkyne, and proposed C_3 -symmetric triscamphorphosphabarrelene, 48	65

Figure 4.1. ³¹ P NMR spectrum of phosphabarrelene:rhodium in a 2:1 ratio	74
Figure 4.2 Mono-barrelene rhodium complex, 50 , and di-substituted phosphabarrelene-rhodium complex 51-trans	74
Figure 4.3. ³¹ P NMR spectrum of the phosphabarrelene-rhodium complex (2:1 ratio).	75
Figure 4.4. DABCO and a phosphabarrelene molecule	81
Figure 4.5. Structure of the oxidized phosphabarrelene, 55	82

LIST OF TABLES

Table 2.1. Summary of chromatographic and spectral differences between diastereomers.	33
Table 2.2 'Dihedral' O-C-C-O angles calculated from the X-ray structures	36
Table 2.3. Results from compounds separated on a Chiralcel OD-H chiral column	38
Table 2.4. Results from compounds separated on a Phenomenex Lux Cellulose 2 column	39
Table 2.5. Results from compounds screened by Phenomenex, Regis Technologies and Chiral Technologies	40
Table 3.1. Various Tolman type parameters for common phosphines and new phosphinines and phosphabarrelene molecules.	48
Table 4.1. Published hydroformylation results using phosphinine ligands with styrene.	71
Table 4.2. Hydroformylation results of phosphinine and phosphabarrelene ligands	78

LIST OF SCHEMES

Scheme 1.1. Synthesis of 4,6,8-trimethylazulene 3 from cyclopentadiene and trimethylpyrylium.	7
Scheme 1.2. General pathway for azulene diol synthesis	8
Scheme 1.3. [2+4] Addition of benzyne to phosphinine.	14
Scheme 1.4. Generic heterogeneous catalytic cycle.	16
Scheme 1.5. Hydroformylation pathway to each regioisomer. ⁴⁸	18
Scheme 1.6. Asymmetric hydroformylation of styrene.	19
Scheme 2.1. Electrophilic aromatic substitution of TMA with electrophile, E	24
Scheme 2.2. Synthesis of bis-trifluoroacetylated azulenes	27
Scheme 2.3. Reduction of azulene diketones to cyclized and non-cyclized azulene diols.	28
Scheme 2.4. Proposed dehydration of the methyl azulene diol occurring in the GC	29
Scheme 2.5. Syntheses of benzene diols 16 and 18.	30
Scheme 3.1. Dr. Jason Bell's published synthesis of bis-camphor phosphinine 6	50
Scheme 3.2. Unpublished synthesis of bis-camphorphosphabarrelene 7.	51
Scheme 3.3. Synthetic route to 29 and 32 using different halide sources	51
Scheme 3.4. Synthetic routes to phosphabarrelene, 7	54
Scheme 3.5. Synthetic route to new derivatives of benzoyl camphor	56
Scheme 3.6. Synthetic route to trifluoromethyl substituted derivatives.	58
Scheme 3.7. Keto-enol tautamorization of dimethylaminobenzoylcamphor, 34	59
Scheme 3.8. Synthetic route to <i>p</i> -dimethylaminophenyl derivatives.	60
Scheme 3.9. Synthetic route to bis-camphor pyridiniums, 41 and 42 and pyridine, 43	62

Scheme 3.10. Synthesis of phenyl camphor, 44.	63
Scheme 3.11. Synthesis of bis-(thiophenyl)camphorphosphinine, 47	64
Scheme 3.12. Proposed reaction between cis-bromo(trimethylstannyl)camphor 49 and phosphinine 6 forming C_3 -symmetric tris-camphorphosphabarrelene, 48	65
Scheme 4.1. Asymmetric hydroformylation of styrene.	68
Scheme 4.2 Morita-Baylis-Hillman reaction catalyzed by phosphabarrelene, 7	81

LIST OF ABBREVIATIONS

Å	angstroms
AHF	asymmetric hydroformylation
Ammi Bi	ammonium bicarbonate
cat.	catalytic
CD	hircular dichroism
DCM	dichloromethane
DEA	diethanolamine
DME	dimethoxyethane
EAS	electrophilic aromatic substitution
EDG	electron donating group
ee	enantiomeric excess
EtOAc	ethyl acetate
EWG	electron withdrawing group
GC	gas chromatography
HPLC	high pressure liquid chromatography
Hz	hertz
IPA	isopropanol
LDA	lithiumdiisopropylamine
LiETBH	lithium triethylborohydride
М	mol L ⁻¹
MS	mass spectrometry
m/z	mass to charge ratio
NAS	nucleophilic aromatic substitution
NMR	nuclear magnetic resonance
Р	phosphorus
Ph	phenyl
ppm	parts per million

Ref.	reference
TFA	trifluoroacetyl
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMA	4,6,8-trimethyl azulene
UV	ultra-violet

ACKNOWLEDGMENTS

Above all I would like to acknowledge and thank my advisor, Dr. Charles Garner. It is because of his support, guidance, motivation and inspiration that I have succeeded in my time at Baylor. His curiosity and knowledge about chemistry taught me more about the subject then reading journal articles alone could ever have. Also, he not only allowed me to take the time to cultivate my professional development as a teacher but was a constant source of encouragement for that path.

I would also like to thank the rest of my committee members, Drs. Kevin Pinney, Bob Kane, Kevin Klausmeyer and Chris Rios for their time and support during this endeavor.

For fostering my desire to be an educator and to inspire students to love chemistry, I would like to thank Dr. Brian Coppola and Dr. Laine Scales. Also, I would like to thank the students I have taught while a Baylor for both challenging me and reminding me why I want to teach. For their help with my research projects, I would like to thank Dr. Kevin Klausmeyer and his students for their work with the X-ray crystal structures reported here. Also, I would like to thank Dr. Chris Rios for giving me the opportunity to help the Graduate School begin a professional development program for STEM students.

Without the help, encouragement and camaraderie of my lab mates, mainly Dr. Nelson van der Velde, and Matthew Jackson (as well as all the undergraduates who have worked with me in the last five years.) I own so much to a group of lovely ladies for

xiv

their friendship and strength: Sara Rae, Carrie, Christine and Lindsay. Although they may have been far away at times I would also like to thank my friends Greta, Claire and Chip for their encouragement along the way.

Lastly, I would not be anywhere without the continuous and immense love and support of my family. I'm forever grateful for my mom, Cindy, who has been my rock during good times and bad. I'm thankful for my Dad, Doug, and Karin, for always pushing me to study hard and do my best. Also, I am so lucky to be surrounded by so many caring family members, including my Grandma Betty. It has been a difficult road on this journey so far from home but I am always reassured that they will have my back no matter where life takes me.

CHAPTER ONE

Introduction

Background—Chiral Molecules

The research presented in this dissertation is unified under the theme of stereochemistry, chirality, and some ways to approach non-racemic compounds. Chirality is an important aspect of synthetic organic chemistry and many of its sub-areas of research rely on the ability to obtain pure chiral materials.

Even non-scientists realize the importance of how objects are arranged in space in relation to one another, although the subtlety of spatial arrangement in molecular structures is generally only appreciated by chemists. It is easy to see this when comparing the arrangement of fingers on the left versus the right hand. This type of difference between left and right hands in chemistry is referred to as chirality. Each "hand" is a type of chiral arrangement that can either be arranged in a left configuration or a right configuration. In chemistry the right handed configuration is designated with the letter R for *Rectus*, meaning right in Latin, and the left handed configuration receives the letter S for *Sinister*, meaning left in Latin.¹ The technical name given to a molecule that exists as one of these configurations is called an enantiomer. Enantiomers are nonsuperimposable mirror images of each other. A pair of enantiomers consists of, for example, one version of a given molecule in the R configuration and one version of the same given molecule in the S configuration. Although the average person might only realize chirality in a few ways, like handedness, it is a major component in chemistry, biochemistry, molecular biology and other scientific fields.

The most common place where chirality exists in organic chemistry is when a carbon atom is bound to four different groups or substituents. Chirality is not limited to a tetrahedral carbon; it can also exist in heteroatoms such as sulfur or phosphorus, in unsymmetrical carbon-carbon double bonds in special twisted molecules and a few other places. As alluded to earlier, the human body is very rich in chirality, from the macroscopic (e.g., our hands) down to the sub-microscopic (e.g. proteins, enzymes and metabolites). The building blocks of these macromolecules (amino acids) each have a chiral center that occurs naturally in the S configuration. These chiral macromolecules are vital to many processes within the body. Chirality is especially important when considering how chiral macromolecules interact with the man-made drugs humans consume every day. The subtlety of drug design is a crucial area of synthetic organic chemistry.

Drugs are designed (or determined by trial and error) with a specific arrangement in space in order to correctly interact with a particular chiral macromolecule in the body. Each enantiomer of a chiral drug molecule will interact in some way with a given macromolecule to afford some response that through metabolic pathways will eventually manifest the effects of the drug. For example, aspirin is used as a pain reducing medication because it inhibits an enzyme, cyclooxygenase, from producing the metabolites thromboxane and prostaglandins, which are responsible for transmission of pain information to the brain.

Chiral drugs can be sold as either a mixture of the pair of enantiomers, called a racemic mixture, or as one enantiomerically pure form.² In 1996 of the 500 synthetic chiral drugs only 10% of them were sold as single enantiomers.³ In some cases, if the

drug is not completely pure, or of the wrong handedness, it can not only fail to provide the desired benefit but may also have deleterious effects due to improper interaction with the macromolecule target or interaction with a totally different macromolecule in a different pathway that will manifest different results. This was most notably seen in the thalidomide drug disaster of the 1950's. Thalidomide has one chiral center, and the configuration of that chiral center determines whether the drug helps to ease morning sickness or causes teratogenic effects.⁴ The drug was initially taken by women in a racemic mixture of the enantiomers. Unfortunately, only after many cases of babies born with defects was the problem uncovered. This was one of the major historic events that drove an increase in the study of the resolution and purification of chiral molecules.

Studying chiral molecules is still to this day a vital area of synthetic organic chemistry. This is most obvious in the synthesis of drugs, although it is also important to obtain enantiomerically pure compounds for industrial products, optical sensors and more.⁵

Chiral resolution means either the separation or purification of racemic mixtures into their enantiomerically pure form. However, synthesizing enantiomerically pure compounds directly is a more advantageous way to obtain enantiomerically pure compounds.

Three main ways to obtain enantiomerically pure substances are presently in use:

- i. The synthesis of racemic mixtures followed by the separation of the enantiomers, known as chiral resolution
- ii. The synthesis of enantiomerically pure compounds starting from available enantiomerically pure starting materials and building upon that structure, in which case the compound maintains its chirality and remains as one single mirror image

iii. Through reactions that enantioselectively favor the production of one enantiomer over the other from achiral starting materials known as asymmetric synthesis. If this process can be made to function with a chiral catalyst, it is referred to as asymmetric catalysis

The work herein has explored each of the ways listed above of obtaining enantiomerically pure compounds. In the study of azulene diols, the reactions were not enantioselective, resulting in racemic mixtures. Chiral resolution techniques were then employed to obtain enantiomerically pure compounds. In the synthesis of the chiral phosphinine and phosphabarrelene molecules, chirality was maintained from the chiral starting material. In the asymmetric catalysis reactions, enantioselectivity was desired as an outcome of the reactions.

Azulene Project

The novel synthesis and analysis of azulene diols studied the chemical properties associated with chiral separations.^{6,7} The separation of 1,5-azulene diols turned out to be much easier than expected, which led to the research described here.

Initially the premise for this project was to find a new and challenging diastereomer separation experiment to be performed in an undergraduate teaching lab. Reactions done using azulenes make for good experiments to be performed in undergraduate chemistry labs because of the intense colors and the many reaction types possible that involve a visible color change.^{8–10} The color changes for reactions that are described in Chapter two, were due to previously known transformations, as well as some new reactions, of azulenes. In order to better understand the purpose and design of this work, some background knowledge about azulene molecules is presented first. Then an

overview of the methods used to separate and study the stereoisomers will be discussed to better appreciate the significance and conclusions of this research.

Azulenes are deep blue compounds, the first of which was discovered in the 15th century by steam distillation of German chamomile.¹⁰ This first isolation was actually of guaiazulene **1**, a tri-substituted azulene derivative. The structure of azulene **2** itself was not known until 1936 when Pfau and Plattner determined it.^{10,11}



Figure 1.1 Structures of gaiazulene and azulene.

The azulene core is an unsaturated bicyclic hydrocarbon made up of fused 7membered and 5-membered aromatic rings. The aromaticity of each ring can be viewed two ways. First, using Huckel's rules for aromaticity, and secondly, when considering the most prominent resonance form. Huckel's rules for aromaticity require the molecule to be cyclic, planar and having a given number of π electrons *i* that satisfies the equation 4n+2 = i, where n is any integer. Azulene fulfills all three of these requirements, with 10 π electrons completing the equation for n = 2. Also, Figure 1.2 shows the resonance form that moves the electrons in such a way that places a positive charge on the 7-membered ring and a negative charge on the 5-membered ring. This shows how each ring can individually fulfill Huckel's rules. Theoretical calculations have proven the electron withdrawing nature associated with the 5-membered ring.¹⁰ This resonance form of azulene can also be used to explain the substantial dipole moment observed.¹² The value of the dipole moment (1.08 D)¹³ is comparable to that of HCl (1.11 D). Azulenes, like many other naturally occurring organic compounds, have some biological activity, like the ability to reduce inflammation, antiulcer capabilities and tumor specific cytotoxicity, etc.^{11,12,14} Although azulene is a structural isomer of naphthalene, the unique properties (non-alternate conjugation) in its ring system causes azulene to be a dark blue solid at room temperature, whereas naphthalene (alternate conjugation) is colorless.



Figure 1.2. Structures of naphthalene, azulene with one of its resonance forms and a general dipole moment depiction.

The first syntheses for both azulene **2** and 4,6,8-trimethylazulene (TMA) **3** were published by Hafner in 1957 and 1958 respectively.^{15,16} Azulene itself is quite expensive, with 1 gram costing \$310.50 from Sigma Aldrich (12/10/13). The synthesis is quite involved and takes several days. The TMA synthesis, on the other hand, is much quicker. Shown in Scheme 1.1. is the TMA synthesis that has been done as a two part experiment by undergraduates in a teaching laboratory. Over two lab periods, students can synthesize the 2,4,6-trimethylpyrylium salt, that subsequently reacts with sodium hydride and cyclopentadiene to afford the dark purple 4,6,8-trimethylazulene from the pyrylium tetrafluoroborate salts in modest yield. The use of the perchlorate salt provided much higher yields, (43-49%) but is dangerous (shock sensitive) and unsuited for a teaching lab.^{15,17} Various other ways of synthesizing azulenes exist starting from aromatic organic salts, cycloheptatriene containing molecules, and acetylenic compounds.¹⁰



Scheme 1.1. Synthesis of 4,6,8-trimethylazulene **3** from cyclopentadiene and trimethylpyrylium.

The partially negative charge associated with the 5-membered ring makes it very reactive in electrophilic aromatic substitution (EAS) at the 1 and 3 positions. Acyl substitution was of particular interest because of the vibrant color change from blue to red with mono-substitution and then to orange with bis-substitution of azulene.^{9,18,19} Since it is easier for students to observe the progress of the reaction and the separation of the final products when they are colored, substituted azulene molecules provide a good system to teach the principals involved with these techniques. The ability to see the compounds also eliminates the sometimes complex and time consuming analysis required for colorless materials e.g., TLC visualization, fraction analysis in flash column chromatography, etc.

Chiral azulenes can be synthesized by attaching chiral centers to the core ring structure through EAS or nucleophilic aromatic substitution (NAS) reactions. There is only one example of the synthesis of a non-racemic azulene in the literature²⁰ and only a few racemic azulenes have been synthesized and separated previously.^{21–26} More chiral azulenes have been synthesized and separated as a result of this work.^{6,7}

The synthesis of azulene diol **5** began with the known trifluoroacetylation of 2,4,6-trimethylazulene (TMA) that causes a redshift of the color from purple to red/orange.^{8,9,18,19} Mono-acylation of TMA affords a red color change while the bis-

acylation product is visibly more orange. Using an excess of trifluoroacetic anhydride (TFAA) at room temperature, acylation occurs in less than 30 minutes at both the 1 and 3 positions of the azulene ring for a variety of azulene derivatives. Once the acyl groups have been attached, the two carbonyl groups were each reduced to alcohols, changing the color from orange back to purple/pink.⁶ The reduction is not stereoselective, resulting in the production of both R and S chiral centers at both of the chiral carbons. Two chiral centers with two possible configurations generally mean that both diastereomers and enantiomers were synthesized; therefor there are a total of four different stereoisomeric products expected. An exception to this principle occurs if the molecule has a plane of symmetry. Molecules that have a plan of symmetry where one chiral center is a reflection of the other defines a type of stereoisomer called a meso isomer. The two configurations theoretically possible of a meso isomer are not enantiomers but are actually identical molecules (because of the plane of symmetry). The meso isomer is diastereomeric to the other two non-meso enantiomers.



Scheme 1.2. General pathway for azulene diol synthesis.

Upon attempting to purify the product, an interesting observation was made during the analysis of the crude mixture using thin layer chromatography (TLC). Two pinkish purple spots were seen with very different R_f values. Neither of the two spots matched with the R_f value of the purple TMA starting material. Further analysis determined that these two spots were in fact that the two diastereomers of the diol product that happened to be extremely well separated from one another on the achiral silica gel plates. Diastereomers generally have different enough properties that allow some of them to be separated using a typical silica gel column; however, the great separation (R_f difference = 0.40) of these isomers was unexpected.⁶ Silica gel columns separate compounds based on their polarity which is a function of how strongly a given compound interacts with the polar surface of the silicon dioxide stationary phase. Therefore, to observe diastereomers that exhibit such different polarities was quite unusual. Three other types of azulene 1,5-diols were then synthesized to help determine the cause of this interesting observation (structures shown in Chapter two).

These compounds were easily separated using flash chromatography into the individual diastereomers, all racemic except the meso examples.

After column chromatography was used to purify the diol diastereomers, chiral resolution was used to isolate each enantiomer of the azulene diols. The separation of the enantiomers within each diastereomer pair relies on a chirally selective technique. The best way to chromatographically separate enantiomers is to use preparative high pressure liquid chromatography (HPLC) with a column containing a chiral stationary phase. HPLC is a chromatographic technique that separates compounds based on their interaction with the solid stationary phase. This stationary phase can be achiral or chiral. Cellulose, amylose and cyclodextrins are all common molecules that are used to make chiral stationary phases. Only chiral stationary phases have the ability to separate enantiomers and even then many different types of stationary phases may have to be

tried. Chiral HPLC has recently been applied on a large scale^{27,28} and is an important process for monitoring the production and environmental fate of pharmaceuticals.^{29,30} Not all enantiomers are separable on all columns, and two types of chiral HPLC columns were used to separate the enantiomers of the azulene diols.⁷

More about the background and context as well as the synthesis, separation, analysis and conclusion of the work done with these chiral azulene 1,5-diols will be discussed fully in Chapter two.

Phosphabarrelene Project

The bis-camphorphosphinine and bis-camphorphosphabarrelene syntheses bring the second concept of obtaining enantiomerically pure compounds into this work. Enantiomerically pure compounds can be synthesized from chiral starting materials utilizing their inherent chirality to produce an enantiomerically pure final product.



Figure 1.3. Structures of bis-camphorphosphinine 6 and bis-camphorphosphabarrelene 7.

The synthesis of the chiral molecule bis-camphorphosphinine **6** begins with a chiral molecule, (+)-camphor. (+)-Camphor is a naturally occurring monoterpenoid isolated from the plant *Cinnamomum camphora*.³¹ (+)-Camphor is quite inexpensive and can be purchased from Sigma Aldrich at \$80.60 for 500 grams. (sig Aldrich 1/21/14)

Camphor comes naturally as the (+) enantiomer which means that it rotates plane polarized light in the clockwise direction known as dextrorotatory. The price and the high enantiopurity make camphor a good building block for chiral ligands.³² Shown below (Figure 1.4), the structure of (+)-camphor has two chiral centers, both in the R configuration. The ketone functionality can easily react with strong bases to form only one enolate that does not readily react with another camphor carbonyl. This characteristic allows for simple aldol reactions that do not interfere with the chiral centers of (+)-camphor. (+)-Camphor was chosen as the building block for the synthesis of a novel C_2 —symmetric phosphinine.



Figure 1.4. Structure of (+)-camphor.

The synthesis of the phosphinine utilizes a second molecule of (+)-camphor later in the process. The addition of the second (+)-camphor results in it's bridge pointing in the opposite direction of the other (+)-camphor molecule. The natural chirality of the (+)camphor remains intact throughout this synthesis, providing the desired biscamphorphosphinine molecule in its enantiomerically pure form. The two camphor rings point in opposite directions like a two-bladed fan. This type of molecule has a rotational axis of symmetry which is known as C_2 -symmetry. C_2 -symmetry means that the molecule can be rotated 180° and be superimposed upon its original structure. The figure on the left shows how the (+)-camphor molecules are oriented in the product that produces the C_2 -symmetry seen in the structure to the right. The picture below displays bis-camphorphosphinine from the plane of the phosphinine ring showing the direction of the bridging groups from camphor.



Figure 1.5. C₂-symmetry in the bis-camphorphosphinine molecule.

This phosphorus-containing molecule was designed and synthesized with the purpose of being used as a ligand for a metal catalyst. The use of this molecule as a ligand in catalytic reactions will be discussed in Chapter four; however, a brief overview of what makes a good organic ligand for an asymmetric metal catalyst will be covered here.

Most often organic ligands are attached or complexed to the metal through a noncarbon heteroatom such as phosphorus, nitrogen, or sulfur. Metals can also interact with small organic molecules through π -bonds and aromatic rings. The bond between a heteroatom and a metal is not as static as a regular carbon-carbon bond, for example. Therefore, the interaction between the metal and the ligands can vary greatly with respect to strength and type of orbital interaction. Phosphorus ligands are distinctive in that the way they interact with a metal and the environment of the complex can be tuned.^{33,34} Tolman showed that by simply changing the type and shape of the substituents attached to phosphorus ligand, the metal complex displayed a wide range of characteristics, which in turn would affect the selectivity and reactivity of the complex as a heterogeneous

catalyst.³⁴ The bonding nature between the bonding atom of the ligand (phosphorus in Figure 1.6) and a metal is typically described in terms of the ligands ability to accept electrons density from the metal into the phosphorus π orbital and donate sigma-bonding electrons to the metal. Also shown below in Figure 1.6, the depiction of Tolman's idea that both the electronic or bonding interaction as well as the steric or environmental interaction between ligands and metals should be taken into account together to paint a complete picture of the complex that results.



Figure 1.6. Metal-phosphorus bonding orbitals, and Tolman parameters.

Although there are many different classes of phosphorus ligands, this work focuses on two newer classes, phosphinines (also known as phosphabenzenes), and phosphabarrelenes (also known as phosphatriptycenes), which can be synthesized from phosphinines. Phosphinines and phosphabarrelenes were not discovered until 1966 and 1968, respectively.^{35–37} Phosphinines contain a trivalent phosphorus atom within an aromatic ring. Phosphinines were a momentous discovery at the time because they showed that other higher main group elements could participate in aromaticity.³⁷ It is believed that the aromaticity is what makes phosphinines more air stable than most other phosphorus ligands.³⁸ Phosphinines are much less basic, ($pK_a = -16$ for an unsubstituted phosphinine)³⁹, compared to their pyridine analogues ($pK_a = 5$).³⁷ Therefore the phosphinine is also less nucleophilic than pyridine (Figure 1.7).³⁹ The lower electron density around the phosphorus atom makes phosphinines good π -accepting ligands when bound to metals.⁴⁰

The traditional route of synthesis for phosphinines is substitution of the oxygen atom of a pyrylium salt with a source of phosphorus.³⁷ However, chiral pyryliums are almost non-existent in the literature.⁴¹ Most of the chiral pyrylium salts, and the only C₂-symmetric pyrylium salt, in the literature were synthesized by our research group.^{41,42}



Figure 1.7. Related aromatic derivatives and phosphabarrelene structure.

Phosphabarrelenes can be made by reacting phosphinine molecules with an electron rich dienophile, typically a benzyne, across the phosphinine ring in a Diels Alder fashion (Scheme 1.3). The first Diels Alder reaction across the diene portion of the phosphinine ring was performed by Markl in 1968. However, he first transformed the phosphinine into the pentavalent phosphinine sulfide before the addition reaction, which also showed that P=C could act as a dienophile in a Diels-Alder reaction.^{36,37}



Scheme 1.3. [2+4] Addition of benzyne to phosphinine.

The electronic properties of the phosphorus and the steric/chiral properties from the (+)-camphor make for a well-designed ligand. The optimization of the synthesis of bis-camphorphosphabarrelene and some electronically and sterically derivatized molecules will be discussed in Chapter three.

Catalysis Project

Finally, the use of the phosphinine **6** and phosphabarrelene **7** ligands in a metal catalyzed asymmetric reaction, and the phosphabarrelene molecule **7** as an organocatalyst, brings in the third approach for obtaining enantiomerically pure or enriched compounds into this work.

Direct asymmetric synthesis through catalyzed reactions is the most efficient and environmentally friendly way to obtain enantiomerically pure chiral materials, when such methods are available.^{43,44} Catalysis works in such a way that each reaction uses a very small amount chiral and non-racemic catalyst to help perform a specific reaction many times over, turning large amounts of achiral starting materials into large amounts of chiral products. Often times in catalyzed reactions every atom from the starting materials are incorporated into the desired product creating very few byproducts in the process. The measure of the efficiency of a reaction at not generating waste in this way is referred to as atom economy.⁴³ The atom economy for some catalyzed reactions, like hydroformylation, is usually quite high and the catalysts that perform these transformations can often times be recovered and reused.

Metal complexes must usually be activated prior to use in catalytic reactions. The metal centers become activated upon binding of certain types of non-metal groups (ligands). Throughout the reaction these ligands can either stay attached (complexed) to

the metal or can be released and reattached to the metal during the process. The reaction proceeds after the metal complex is activated by the binding of appropriate ligands (step a in the figure below). Next, starting materials complex to the active metal center (step b and c) where the reaction then takes place involving the complexed materials (step d). Once the reaction is complete the metal releases the finished product molecule and the catalyst can ideally continue to repeat this cycle many times (step e).



Scheme 1.4. Generic heterogeneous catalytic cycle.

Catalytic reactions can be very complex, therefore it is hard to find a single catalyst that works for a variety of reactions in a variety of conditions.⁴⁵ This is even more evident in reactions that produce chiral products, where one configuration is desired. Chiral catalysts can induce a chiral environment during the reaction favoring the synthesis of one enantiomer over the other. Chiral organic ligands are used to create the

chiral metal complex that causes the catalyzed reactions to be enantiomerically selective. Enantioselective reactions are referred to as *asymmetric* because the products are chiral and non-racemic.

Chiral catalysts must maintain high activity while being selective for the appropriate regioisomers, and where possible, stereoisomers. Given the need for large quantities of chiral molecules and the required efficiency for industrial scales of this type of reaction, the area of research that studies asymmetric metal catalysis, and more specifically the organic ligands associated with the complexes, is currently an important area of synthetic organic and inorganic chemistry.⁴⁵

The metal bound chiral ligands have bulky steric hindering effects that cause the substrate to react along a particular catalytic pathway (Scheme 1.5). If the ligand is bulky enough to induce a specific stereochemical environment, then the substrate will more greatly favor the pathway with the least steric hindrance over the other and will give mostly or only one stereoisomer of the product. When multiple structural isomers of the products are possible, the shape of the ligand is very important. Chiral ligands can not only be selective for the regioisomers, but also for the chirality of any products that have a chiral center.

The hydroformylation reaction is a very important industrial process and accounts for the production of many tons of aldehydes annually. Aldehydes produced from this process are used as plasticizers, detergents, in the production of specialty chemicals, synthesis of drugs such as the (+) form of ibuprofen called dexibuprofen and 2-aryl propionic acids which have anti-inflammatory activity. Hydroformylation is the specific addition reaction between some alkene, like styrene pictured above, with one molecule of

carbon monoxide and one molecule of hydrogen in the presence of a metal catalyst, usually rhodium. This addition reaction to styrene produces either the branched aldehyde or the linear aldehyde (the pathway to each of these are shown Scheme 1.5 below). Variations of the reaction conditions, including varying the ligands, can influence the regioselectivity. Currently there are ligands that are selective for the linear aldehyde⁴⁶ and others for the branched⁴⁷.



Scheme 1.5. Hydroformylation pathway to each regioisomer.⁴⁸

As described earlier, chiral catalysts are employed to enhance the enantiomeric selectivity of the chiral center in the branched products. This is the only way to induce selectivity for one enantiomer of the branched product over the other.

There still exist some challenges with the selectivity of hydroformylations catalysts at conditions that are suitable for greener large scale reaction sizes. For this reason we chose to synthesize new chiral ligands with the intention of improving activities and enantioselectivities for chiral monodentate phosphorus ligands in asymmetric hydroformylation (AHF) (example, Scheme 1.6 below).



Scheme 1.6. Asymmetric hydroformylation of styrene.

Some non-metal containing molecules also have the ability to catalyze reactions. A small organic molecule catalyst is called an organocatalyst. An organocatalyst is completely metal free and instead contains a heteroatom with the ability to bind to a substrate, perform catalytic transformations and then dissociate. Only about 1.6 organocatalysis articles exist per 100 metal catalyst articles, but publications about organocatalysts have increased 10 fold in the last 10 years. (Scifinder 3/24/2014) Organocatalysts are also extremely green because of their high atom economy and the fact that unlike metal catalysts, they don't leech into the environment.⁴⁹ Leeching can occur when a metal from a metal catalyst does not get completely separated from the products. This is undesirable because many of these products are consumed as pharmaceuticals and if there are metals present they can be detrimental to the human body.

As described in Chapter three, regarding the phosphinine and phosphabarrelene molecules, phosphorus containing organic molecules can have varying electronic properties. The phosphabarrelene phosphorus has similarities in both its electronic properties and structural appearance to a commercially available and widely used

organocatalyst called DABCO (1,4-diazabicyclo[2.2.2]octane) and may serve in the same capacity.

Figure 1.8. Structure of DABCO and, phosphabarrelene.

DABCO is most commonly used for the Baylis-Hillman reaction shown below. However, before Baylis-Hillman discovered the more popular amine catalyzed reaction in 1972⁵⁰, Morita actually discovered a similar reaction that was catalyzed by a phosphine in 1968.^{49,51,52}



Scheme 1.7. An example of the Baylis-Hillman reaction catalyzed by DABCO. The Morita version uses a nucleophilic phosphine molecule to catalyze a similar reaction.

The Morita-Baylis-Hillman (MBH) reaction occurs between an electron rich aldehyde, and an electron poor terminal alkene. DABCO catalyzes this reaction by nucleophilically attacking the terminal carbon of the alkene (conjugate addition) creating an anion that can then attack the aldehyde (aldol reaction). An intramolecular proton transfer results in a third transition state that favors the formation of the product and the release of DABCO.^{49,53}

The nitrogen of DABCO is more basic (conjugate acid $pK_a = 8.7$)⁵⁴ than some other nitrogen containing compounds (pyridine conjugate acid $pK_a = 5.4$) and can react in

a nucleophilic manner. Although some phosphorus molecules contain a basic phosphorus (PPh₃ $pK_a = 2.7$), phosphabarrelene is less basic and equally nucleophilic compared other phosphines.³⁴ The lone pair of electrons on these nucleophilic heteroatoms is shared in a similar way to the sharing of electrons by metal complexes and thus, they can catalyze reactions in a similar fashion.

Many of the substrates of the MBH reaction create at least one chiral center; therefore asymmetric organocatalysts for this reaction are being pursued. Recently a phosphine-thiourea organocatalyst has produced high enantioselectivies (85-98% ee) for the MBH reaction.⁵¹ The catalyst was less selective for regiochemistry, *syn* vs *anti* where applicable, but the yields (63-96%) were also high for all but 1 of the 34 reactions attempted. Therefor the chiral-bis-camphorphosphabarrelene **7** could potentially act as an active asymmetric organocatalyst for this reaction and open the door to a new class of catalysts for this reaction.
CHAPTER TWO

Azulene Diols

Introduction/Background

Our studies of the preparation and separation of azulene diol diastereomers (5, 9, 10, and 11) began as an idea for an undergraduate laboratory experiment. It was anticipated that the two possible diol diastereomers could be prepared by a hydride reduction of the known diketone (Scheme 2.2), and their separation by column chromatography would present a challenge suitable for an advanced laboratory experience. The colors would add a visual confirmation of the separation, or lack thereof, and enhance the learning experience. However, to our surprise the diastereomers exhibited a remarkably large separation on silica gel TLC. We proceeded to study the origin of this phenomenon, which involved preparing and analyzing a series of such diols.

It is known that diastereomers technically have different chemical and physical properties. However, diastereomers that have chiral centers that are many bonds apart do not tend to exhibit very different properties such as chromatographic mobility or NMR chemical shifts.^{6,55} Generally, distant chiral centers have little to no influence on each other. There are reports that slight differences between diastereomers with less proximate chiral centers can be seen in the NMR specta due to anisotropy that occurs near the chiral center resulting in an amplification of differences resolved in the spectrum.⁵⁶ However, these differences do not translate to chromatographic separability. Also there are some examples of molecules containing structural aspects that force two

22

chiral centers to be near one another in space even though they are actually many bonds apart.^{3,55} These molecules can often be easily separated chromatographically.

The only other example of a 5-bond separation between two chiral centers that exhibited a significant difference in polarity was published by Harmata. Harmata's work on molecule tweezers produced the diol below that showed a large chromatographic separation (Figure 2.1). He, like us, postulated that benzylic strain forces the OH groups to either be on the same side of the benzene ring or opposite side. This strain effectively doubles the polarity experienced on the face with the two OH groups compared to the diastereomer that only has one OH group on each side.⁵⁷ More on this hypothesis will be discussed below.



Figure 2.1. *d*,*l*-Diol and meso diol synthesized by Harmata.

Therefore, it is very atypical to have chiral centers four or more bonds apart that separate so readily on silica chromatography as was seen with these azulene diols.⁶ TLC is a fairly basic analytical technique used to view the separation of molecules based on how the molecules interact with the stationary phase and the mobile phase. The distance the molecule travels on the TLC plate can be compared to the movement of the mobile phase resulting in a unit-less value known as an R_f value. R_f values provide a quantitative measure of the movement of molecules that is unique to the conditions (stationary phase

and mobile phase). The larger the difference in R_f values the larger the separation between molecules. The original azulene diol **5** and the three other azulene diols all demonstrated differences in R_f values (called ΔR_f), between the diastereomers that were greater than 0.22 and as large as 0.41.⁶ Therefore we set out to understand what was causing these diastereomeric differences in mobility. In order to find trends and make comparisons, derivatives **5**, **9**, **10**, and **11** were synthesized as well as other non-azulene aromatic diols **16** and **18**, and various cycloalkane diols **20**, **22**, **23**, and **24** varying in ring size and the bond number between the chiral centers.

Prior to this work, azulene diols were entirely unknown in the literature, though some azulene mono-alcohols had been reported.²² Such azulene alcohols were prepared by additions to azulenyl ketones or aldehydes. Azulenyl ketones have been made by the Friedel-Crafts acylation of a variety of azulenes with open 1 and/or 3 positions. Electrophilic attack at these positions generates a cycloheptatrienyl subunit (Scheme 2.1), thereby retaining part of the aromaticity and greatly lowering the activation energy compared to reactions of benzenoid systems.



Scheme 2.1. Electrophilic aromatic substitution of TMA with electrophile, E.

In fact, azulenes are so reactive that a second acylation is possible at open 1/3 positions despite the presence of the strongly deactivating carbonyl group. These acylations result in dramatic color changes; the blue or purple azulene typically becomes

a red or orange color due to the additional conjugation.⁹ However, there is generally little difference in color between mono- and di-acylated azulenes.

Acetylation (both mono- and di-) has been accomplished using acetyl chloride and tin (IV) chloride, described by Anderson in 1957.¹⁸ Anderson then replaced the acyl groups with bromine or oxidized to them to esters. However, the more reactive TFAA requires no Lewis acid catalyst, accomplishing mono-acylation in seconds and, if excess TFAA is used, di-acylation in minutes or hours (shown Scheme 2.2).^{23,58} No other positions on the azulenes react even given long reaction times and excess TFAA. Thus, both mono- and bis-trifluoroacetylated derivatives of azulene and 4,6,8-trimethylazulene are known.^{18,23,58} However, only the bis-trifluoroacetyl derivative of 2,4,6,8tetramethylazulene **14** has been reported, the curious claim being that the mono-acylated compound was more reactive than the azulene starting material, resulting in a rapid second acylation.²³

By far the most available azulene is guaiazulene **1**, but this was unusable for our purposes since it can only form a mono-acyl derivative. Guaiazulene and its derivatives are less air-stable than other azulenes, probably because of the presence of a tertiary benzylic hydrogen susceptible to autoxidation.

The first step in the synthesis is acetylation of the azulene ring. Acylation causes a change in the conjugation of the system. The carbonyl group adds conjugation which accounts for the color change.^{8,18,19} The first acylation results in a color change from blue or purple to red. The second acylation changes the color from red to orange. Molecular modeling shows that the electron withdrawing nature of the CO away from the

25

ring causes the redshift.⁹ Both mono and disubstituted trifluoroacetylazulenes were shown more recently to induce apoptosis against human oral tumor cell lines.¹⁴

Reduction of the acetylated azulenes results in alcohols that are purple to pink due to the loss of the extra conjugation to the carbonyl. However, it has been noted that electron donation through induction, alcohols alone can cause a blue shift.⁹ Some alcohol substituted azulenes have been synthesized previously. The mono-alcohol from the reduced form of the mono-acetylated guaiazulene was synthesized in 1970 by Nakamura (using LiAlH₄ or CH₃MgI with 1-azulenylaldehyde).²² In 2004, Naoshima used a lipase to catalyze the synthesis of an enantiomerically pure chiral azulene mono-alcohol.²⁰ However, reduction of azulene ketones to their corresponding alcohols was not done with sodium borohydride until this work.⁶

Symmetry in chiral molecules limits the number of isomers possible. A chiral molecule that has a plane of symmetry that mirrors one of the chiral centers onto the other identical chiral center possesses only three isomers. There is one diastereomer that is made up of a pair of enantiomers and there is one (achiral) meso diastereomer.



Figure 2.2. Azulene diol derivatives 5, 9-10.

This is the case for azulene diols **5** and **9**. The plane of symmetry for these molecules runs from the 2 position to the 6 position of the azulene ring (Figure 2.2).

However, the third ring in diols **10** and **11** disrupts that plane of symmetry and thus, each of these diols has two diastereomers each with two enantiomers.

Synthesis

TMA and azulene syntheses were discussed in Chapter one. The other azulene, 2,4,6,8-tetramethylazulene was synthesized following the method of Hafner and Kaiser.^{23,59} The non-regioselective reaction between methylcyclopentadiene and trimethylpyrylium tetrafluoroborate produced a mixture of 1,4,6,8- and 2,4,6,8- tetramethylazulene that was inseparable by column chromatography so the mixture of the two was taken into the acylation reaction.

The first diol **5**, was synthesized from trimethylazulene **3** and diol **9** from azulene **2**. The synthesis of the diketone was done, usually with quite high yields (75% average), using TFAA (Scheme 2.2). The orange diketones, **4**, **13** and **14**, were purified by crystallization. The monotrifluoroacetylated 1,4,6,8-tetramethylazulene was separated from the desired diketone of 2,4,6,8-tetramethyl azulene **12** first by silica gel chromatography, then by crystallization.



Scheme 2.2. Synthesis of bis-trifluoroacetylated azulenes.

Each reduction done with sodium borohydride produced high yields of the solid purple diastereomers (Scheme 2.3). GC-MS of the crude reaction mixtures indicated that the diastereomers were not formed in equal amounts; however, no trend in the favorability of one diastereomer over the other was found. Other reducing agents that are known to reduce ketones were also explored, such as 'super hydride' (LiTEBH) and Shvo's catalyst⁶⁰ but produced low yields (less than 10%) or were unable (like sodium borohydride) to reduce other diketone derivatives, for example **14**.

Next, utilizing a known cyclization,²³ two tricyclic azulene diketones were synthesized. This cyclization requires a methyl group on the 8 position of the ring so both TMA and 2,4,6,8-tetramethylazulene were used. Both of the cyclized azulene diols, **10** and **11**, were prepared first by cyclizing with sodium hydroxide, which afforded the first alcohol group. This newly cyclized mono-alcohol mono-ketone compound, was never isolated but rather was reduced immediately. Bis-cyclization was not possible under a variety of conditions.





Based on the X-ray crystal structure, it was observed that the cyclization forces the methyl and methylene carbons on the other side of the ring to be too far apart to undergo a second cyclization. The mono-cyclization was followed by reduction of the ketone to an alcohol with sodium borohydride in good yields (Scheme 2.3.).

The attempts to synthesize a few other azulene diols were not successful. For example, none of the diacetylazulenes (as opposed to trifluoroacetylazulenes) were stable upon reduction, resulting in messy brown mixtures. GC-MS did show traces of the mass of the dehydration product, diethylene substituted azulenes (Scheme 2.4), but never any of the intended diol. Although reduction of acetylazulenes has been reported previously in the literature, instability of the resulting products was also noted.^{23,61} There is also a possibility that upon formation of the alkene shown below, polymerization occurred explaining the gooey mixtures.



Scheme 2.4. Proposed dehydration of the methyl azulene diol occurring in the GC.

Also, the reduction of 2,4,6,8-tetramethylazuelene bis-trifluoromethylketone **14** to the non-cyclized diol was entirely unsuccessful. This might have been caused by too much steric hindrance at the carbonyl carbon to allow reduction at the ketones, but no starting material was observed. The steric hindrance is less in the cyclized version of this azulene because the cyclization pulls the carbonyl carbon away from the methyl at the 2 position as it cyclizes, reducing the steric strain so that the other ketone is able to be reduced.²³

Two benzene 1,5-diols were synthesized for comparison **16** and **18** (Scheme 2.5). These were chosen because of their aromaticity, having the same number of bonds between the diol and the same substituents on the chiral centers. The trifluoromethyl containing diol **16** was synthesized via the literature procedure⁶² using TMS-CF₃ (also known as Ruppert's reagent), tertbutylammonium fluoride and isophthalaldehyde. The methyl containing derivative **18** was synthesized via the reduction of the commercially available diketone with sodium borohydride to produce the diol.⁶³



Scheme 2.5. Syntheses of benzene diols 16 and 18.

Four non-aromatic cyclic-diols **20**, **22**, **23** and **24** were synthesized as well (Scheme 2.6). Each of these differed in their ring size or the number of bonds between the chiral centers. These were used to compare whether other diols, with chiral centers separated by varying distances, would show such large differences in R_f values. These diols were synthesized via hydrogenation of a diketone with commercially available Shvo's ruthenium catalyst⁶⁰ **21**. The published procedure, however, gave very low yields (less than 4%) and had to be modified. Upon adding hydrogen in addition to the mixture already containing isopropyl alcohol, which was thought to be the sole source of hydrogen, the reaction was successful with modest yields (50% average). Borohydride

reductions of these cycloalkyl diketones gave complex mixtures and were synthetically worthless.



Scheme 2.6. Hydrogenation using Shvo's catalyst to make diol **20**. Extra H_2 gas was added to this reaction.



Figure 2.3. Cycloalkyldiol diastereomers 22 - 24.

Analysis and Separation of Diastereomers

All of the azulene diols exhibited rather large differences in mobility on silica TLC ($\Delta R_f = 0.22$ -0.46) in DCM-based mobile phases (Figure 3), and lesser separations ($\Delta R_f = 0.10$ -0.28) in 25% ethyl acetate in hexanes, as noted in Table 2.1. Diastereomeric differences in GC were more modest, and only small differences were evident in the NMR spectra. In contrast, the benzene derivatives (**16** and **18**) showed no chromatographic differences by TLC or GC, and only slight differences in the NMR spectra. Remarkably, even the series of 1,2-, 1,3- and 1,4-cycloalkane diols (**20**, **22**, **23** and **24**) showed no TLC differences, except diol **20** ($\Delta R_f \sim 0.02$), despite having more proximate chiral centers. However, the cycloalkane diols did exhibit much more substantial differences in both ¹H and ¹³C NMR spectra than the azulene or benzene diols. This was expectedly prominent in the cycloalkane diols containing chiral centers that were only 1 or 2 bonds apart.



Figure 2.4. Photograph of diastereomeric TLC separation of the pink and purple azulene diols and the colorless benzene diols, on a silica thin layer chromatography plate using 25% ethyl acetate in DCM as the eluting solvent.

The diastereomers were easily separated by silica column chromatography using 10% ethyl acetate in dichloromethane. Radial chromatography, another type of flash chromatography using a silica gel stationary phase, was also used for some of these separations. X-ray crystallography revealed a consistent stereochemical relation between all of the azulene diols and their chromatographic mobilities on silica gel.

Careful recrystallization provided X-ray quality crystals of the faster-moving diastereomers of diols **9**, **10** and **11**, and the slower-moving diastereomers of diols **5** and **10**. The other diastereomers gave fibrous crystals that were not suited for X-ray crystallography. This consistently showed the faster moving diastereomer to have the (RR)/(SS) stereochemistry, and the slower moving diastereomer to have the (RS)/(SR) configuration. For diols **5** and **9**, the slower-moving diastereomer is a meso stereoisomer.

Molecule	Compound	$\Delta R_{\rm f}$ TLC	$GC \Delta ret.$ (min)	$\Delta\delta \text{ NMR} \ (\text{ppm})^{d}$
H_3C H_3C HO CF_3 H_3C H_3C HO CF_3	5	0.10^{a} 0.40^{b}	0.37	¹ H: 0.145 (H2) 0.112 (OH) ¹⁹ F: 0.196 (CF ₃) ¹³ C: 0.092(C2)
F_{2}	9	0.14 ^a 0.22 ^b	0.05	¹ H: 0.120 (H2) 0.012 (OH) ¹⁹ F: 0.016 (CF ₃) ¹³ C: 0.176 (C5/7)
$H_{3}C \xrightarrow{HO} \overset{16}{} CF_{3}$ $H_{3}C \xrightarrow{I_{10}} OH \xrightarrow{I_{10}} OH \xrightarrow{I_{17}} CF_{3}$	10	0.28 ^a 0.46 ^b	0.15	¹ H: 0.008 (H2) 0.087 (OH10) ¹⁹ F: 0.040 (F17) 0.013 (F16) ¹³ C: 0
$H_{3}C$ HO 17 CF_{3} $H_{3}C$ CH_{3} $H_{3}C$ CH_{3} $H_{3}C$ $H_{3}C$	11	0.21 ^a 0.39 ^b	0.07	¹ H: 0.007 (H11a) 0.030 (CH ₃ 16) ¹⁹ F: 0.150 (F17) 0.103 (F18) ¹³ C: 0.117 (CH ₂)
HO GF_3 FO CF_3 CF_3	16	0.00 ^{a,b}	0	¹ H: 0.01 (OH) ¹⁹ F: 0.016 (CF ₃) ¹³ C: 0.081(C4/6)

Table 2.1. Summary of chromatographic and spectral differences between diastereomers.

	Table 2.1. continued								
Molecule	Compound	$\Delta R_{\rm f}$ TLC	$GC \Delta ret.$ (min)	$\Delta\delta \text{ NMR} \ (\text{ppm})^{d}$					
HO CH ₃ CH ₃ CH ₃ HO	18	0.00 ^{a,b}	0	¹ H: 0.01 (CH ₃) ¹³ C: 0.12 (C4/6)					
OH	20	0.02 ^c	0.13	¹ H: 0.15 (H1/3) ¹³ C: 1.42 (C2)					
ОН 2 1_ОН	22	0.00 ^c	0	¹ H: 0.42 (H1/2) ¹³ C: 5.06 (C1/2) 2.24 (C3/6)					
OH 3 1 OH	23	0.00 ^c	0.05	¹ H: 0.31 (H1/3) ¹³ C: 1.57 (C2)					
OH 4 HO 1	24	0.00 ^c	0	¹ H: 0.12 (H2) ¹³ C: 0					

TLC analyses were run in a. 25% EtOAc/hexanes, b. 10% EtOAc/DCM, c. 100% EtOAc (all v/v), d. numbered atoms in parentheses relate to atom number given in the X-ray crystal structures.

The X-ray structures also revealed that there was a correlation between the stereochemistry and support for the differences in polarity (Figure 2.5). The dihedral angle between the two C-O bonds (Table 2.2) was significantly greater (48-102°, average 72°) in the (RR)/(SS) diastereomers than in the (RS)/(SR) stereoisomers (13-41°, average 27°). Thus, in the (RS)/(SR) diastereomers both OH groups are better positioned to engage a silica surface *simultaneously*, behaving in effect as a more polar arrangement, reminiscent of a chelate effect.^{64,65} In contrast, the much larger dihedral angle in the (RR)/(SS) diastereomers make simultaneous binding much less likely. We believe these conformational preferences have both steric and electronic origins. In all of the X-ray

structures, and independent of which diastereomer, the conformationally mobile CF_3 groups exhibit a distinct tendency to be roughly perpendicular to the azulene ring (see Table 2.2).



Figure 2.5. X-ray crystal structures of diols, $5_{RS = SR}$, $9_{RR/SS}$, $10_{RS/SR}$, $10_{RS/SR}$, and $11_{RR/SS}$.

The azulene ring enforces close proximity between the 4 and/or 8 substituents (methyl in 5, 10 and 11; H in 9) and the C1 and/or C3 substituents (CF₃, OH or H). The conformation with a roughly perpendicular CF₃ group and the OH oriented away from the C4/C8 positions likely minimizes this steric interaction and avoids even a coplanar interaction with the **H**-C(OH) proton. Electronically, this arrangement also avoids alignment of the CF₃ dipole with the significant $(1.08 \text{ D})^{19}$ dipole moment of the azulene ring.

Compound	Approximate edge-on view	O-C-C-O dihedral angle	Relative silica mobility
5 _{RS=SR}	azulene CF ₃ CF ₃ OH	41 ^a	Slower
9 _{RR/SS}	azulene CF ₃ OH CF ₃	48	Faster
10 _{RR/SS}	azulene OH CF ₃ OH CF ₃	102 ^a	Faster
10 _{RS/SR}	azulene CF ₃ CF ₃ OH	13	Slower
11 _{RR/SS}	azulene OH CF ₃ OH CF ₃	67	Faster

Table 2.2 'Dihedral' O-C-C-O angles calculated from the X-ray structures (i.e., looking at azulene ring edge-on). a. average of three independent molecules in unit cell.

Calculations were attempted using the Guassian energy minimization function on ChemBioDraw 3D to prove that the X-ray structures were in fact the lowest energy confirmations and that the high rotational energy would enable the rigid structure to support our hypothesis. Although the lowest energy values did seem to offer support, the results were only preliminary and incomplete. Studies done by Nakamura to determine if there was rotational isomerism in a mono-alcohol azulene proved that although there was polymorphism noted in the crystals, no differences were seen in the IR and NMR spectra proved that there was no rotational isomermism.²² His work agrees with our results that there is indeed a high barrier for rotation about the carbon-azulene bond.

Analysis and Separation of Enantiomers

Since very little non-racemic (or even chiral) azulene chemistry has been reported in the literature, we undertook the chromatographic separation of the optical isomers using chiral High Performance Liquid Chromatography.²⁴ Chiral HPLC uses specific chiral stationary phases, generally cellulose derivatives, to separate enantiomers. Some stationary phases work better for molecules containing certain functional groups so it is common to screen racemic mixtures on a variety of columns before the optimal separation is achieved.

Separating the enantiomers brings up a naming issue. The absolute configuration of the enantiomers was never determined; therefore they could not be identified by their exact structure, so they will be referred to by the configuration of the chiral centers based on X-ray crystallography which determined that the faster moving diastereomer on TLC was always the (RR)/(SS) diastereomer, so the faster moving diastereomer (or the less polar) of **11** will be referred to as $\mathbf{11}_{RR/SS}$. Then because the enantiomer configurations could not be determined, they will be identified based on elution order from the chiral HPLC, i.e. fast or slow enantiomers.

The initial column used was a Chiralcel-OD-H (cellulose tri-(3,5-

dimethylphenyl)carbamate coated on 5 micrometer silica gel). Normal phase conditions of varying percentages of isopropanol in hexanes worked extremely well for five of the six pairs of enantiomers ($9_{RR/SS}$, both diastereomers of 10 and 11) seen in Table 2.3.⁷ However, in order to properly separate the enantiomers of compound $5_{RR/SS}$, we employed the HPLC column screening opportunity given by several chromatography companies (Table 2.5 give the results of these screenings).. Upon the recommendation of the screening services, a Lux Cellulose 2 column (cellulose tris-(3-chloro-4-methylphenylcarbamate)), was used to successfully separate the enantiomers of $5_{RR/SS}$.

compound	R _f value	Rt 1 (min)	Rt 2 (min)	$w_{1/2} \ 1$	w _{1/2} 2	Dead volume	R _s	α
5 _{RR/SS}	0.59	1.43 ^f	1.61 ^f	0.30	0.30	0.41	0.35	1.17
9 _{RR/SS}	0.39	4.70 ^e	9.80 ^e	0.41	0.90	0.38	4.61	2.18
10 _{RR/SS}	0.63	1.75 ^f	2.97^{f}	0.16	0.31	0.41	3.10	1.91
10 _{RS/SR}	0.17	1.30 ^g	8.13 ^g	0.21	0.76	0.38	8.28	8.43
11 _{RR/SS}	0.58	1.88 ^b	4.73 ^b	0.27	0.63	0.40	3.74	2.93
11 _{RS/SR}	0.18	1.87 ^c	11.15 ^c	0.39	0.97	0.38	8.05	7.25
16	0.31	6.92 ^b	7.68 ^b	0.70	1.14	0.46	0.49	1.12
18	0.10	2.78 ^a	3.82 ^a	0.16	0.30	0.80	2.65	1.53

Table 2.3. Results from compounds separated on a Chiralcel OD-H chiral columnin varying % of IPA:Hex

Solvent gradients: a. isocratic 5% IPA in hexanes. b. 5% to 10% IPA in hexanes over 22 minutes. c. 10% to 20% IPA in hexanes over 22 minutes. d. isocratic 20% IPA in hexanes. e. 7.5% to 10% IPA in hexanes over 22 minutes. f. 2.75% to 5 % IPA in hexanes over 22 minutes. g. 10% to 15% IPA in hexanes over 22 minutes.

Tables 2.3 and 2.4 include all the data for all separations including those done of benzene diol compounds **16** and **18**. All of the separated azulene enantiomers had a resolution, R_s , between 3 and 8 when separated using the Chiralcel OD-H column except

compound $\mathbf{5}_{\mathbf{RR/SS}}$ which gave an R_s of 1.2 on the Chiralcel column. However, the resolution improved greatly for $\mathbf{5}_{\mathbf{RR/SS}}$, achieving an R_s of 8.7 using the Lux column. Neither of the benzene diols (16 and 18) were well resolved on either of the columns tested (R_s less than 1.5). The azulene diol resolution is far superior to all four of the other aromatic alcohols considered.

compound	R _f value	Rt 1 (min)	Rt 2 (min)	$w_{1/2} \ 1$	$w_{1/2} \; 2$	Dead volume	R _s	α
5 _{RR/SS}	0.59	5.90 ^d	7.92 ^d	0.16	0.19	1.14	8.71	1.42
9 _{RR/SS}	0.39	3.23 ^c	3.53 ^c	0.46	0.46	1.13	0.38	1.14
10 _{RR/SS}	0.63	5.32 ^b	6.10 ^b	0.21	0.24	1.25	2.06	1.19
10 _{RS/SR}	0.17	2.28 ^c	2.85 ^c	0.55	0.55	1.15	0.61	1.50
11 _{RR/SS}	0.58	3.82 ^b	4.93 ^b	0.19	0.25	1.45	2.98	1.47
11 _{RS/SR}	0.18	6.65 ^b	7.77 ^b	0.36	0.38	1.40	1.78	1.21
16	0.31	3.75 ^b	3.98 ^b	0.12	0.24	1.27	0.76	1.09
18	0.10	9.70 ^b	10.4 ^b	0.51	0.70	1.20	0.63	1.08

Table 2.4. Results from compounds separated on a Phenomenex Lux Cellulose 2 column in varying % of IPA in hexanes.

Solvent gradients: a. isocratic 5% IPA in hexanes. b. 5% to 10% IPA in hexanes over 22 minutes. c. 10% to 20% IPA in hexanes over 22 minutes. d. isocratic 20% IPA in hexanes. e. 7.5% to 10% IPA in hexanes over 22 minutes. f. 2.75% to 5 % IPA in hexanes over 22 minutes. g. 10% to 15% IPA in hexanes over 22 minutes.

Since four of these racemic azulene diols (diastereomers of **10** and **111**) represent two sets of diastereomers (RR)/(SS) vs (RS)/(SR), we can compare the degree of resolution for diastereomeric pairs of enantiomers. On Chiralcel-OD-H, the enantiomers of the (RR)/(SS) diastereomers **10**_{RR/SS} and **11**_{RR/SS} averaged an R_s of 3.4 and α of 2.4.

Compound	Column Name	Stationary Phase	Solvent system	R _s	α
5 _{RR/SS}	Phenomenex Lux 5u Cellulose 4	Cellulose tris(4-chloro-3- methylphenylcarbamate)	60:40:0.1 AmmBi:ACN: DEA	4.40	1.23
5 _{RR/SS}	Phenomenex Lux 5u Cellulose 3	Cellulose tris(4- methylbenzoate	60:40:0.1 AmmBi:ACN: DEA	2.90	1.21
5 _{RR/SS}	Phenomenex Lux 5u Cellulose 2	Cellulose tris(3-chloro - 4-dimethylphenyl carbamate)	60:40:0.1 AmmBi:ACN: DEA	1.03	1.14
5 _{RR/SS}	Phenomenex Lux 5u Amylose 2	Amylose tris(5-chloro- 2metheylphenyl carbamate)	60:40:0.1 AmmBi:ACN: DEA	0.82	1.07
5 _{RR/SS}	Phenomenex Lux 5u Cellulose 2	Cellulose tris(3-chloro - 4-dimethylphenyl carbamate)	90:10:0.1 Hex:IPA:DEA	4.45	1.52
5 _{RR/SS}	Phenomenex Lux 5u Amylose 2	Amylose tris(5-chloro- 2metheylphenyl carbamate)	90:10:0.1 Hex:IPA:DEA	3.20	1.80
9 _{RR/SS}	(S,S)-Whelk- O 1 (Regis Tech.)	4-(3,5-dinitro benzamindo) tetrahydrophenathrene on silica	90:10 Hex:IPA	4.22	1.23
9 _{RR/SS}	RegisPack ^a	Tris(3,5-dimethylphenyl) carbamoyl amylose	90:10 Hex:MeOH	4.64	1.22
9 _{RR/SS}	RegisCell ^b	Tris(3,5-dimethylphenyl) carboamoyl cellulose	85:15 Hex:EtOH	9.51	1.78
10 _{RS/SR}	CHIRALPAK IB-3 (Chiral Tech.)	Cellulose tris(3,5- dimethylcarbamate)	80:20 Hex:EtOH	10.6 4	1.31

Table 2.5. Results from compounds screened by Phenomenex, Regis Technologies and Chiral Technologies on various columns with both reverse and normal mobile phases.

a. Same stationary phase as the ChiralPack AD. B. Same stationary phase as the Chrialcel OD.

In contrast, the (RS)/(SR) diastereomers $10_{RS/SR}$ and $11_{RS/SR}$ gave an average R_s of 8.1 and α of 7.8. In both cases, the more polar (based on normal phase TLC mobility) (RS)/(SR) diastereomers were much better resolved than the less polar (RR)/(SS)

diastereomers. This may be related to the polarities, as a rough correlation ($r^2 = 0.65$) exists between silica TLC R_f and R_s on Chiralcel OD-H. The earlier study of these compounds⁷ revealed that the (RS)/(SR) diastereomers favor a conformation in which both OH groups are oriented toward the same face of the planar azulene system, which is the origin of the higher affinity for silica. Specifically how this might influence enantioselectivity is unclear. While some enantioseparations have been reported^{66–68} for diastereomeric molecules, these studies have not attempted to correlate diastereomeric differences (e.g., polarity) with observed resolution. Thus, whether more polar diastereomers are generally better resolved than less polar ones is an open question. With the Lux cellulose 2 column, no large differences in resolution between diastereomers was evident.

Each enantiomer was collected over several runs on the analytical sized columns (150 cm x 2.1-4.6 cm ID) and concentration was determined by UV spectroscopy. Although we had noticed no instability during preparation and isolation of these diols, many of the enantiomers, once separated, decomposed to a brown solid upon evaporating to dryness. Therefore the diol containing solutions were continually being concentrated partially and then re-diluted in methanol (as methanol was the desired solvent for UV and CD studies). Some of these samples also did not last more than 24 hours before decomposing to a brown liquid. This could be due to the formation followed by concentration of peroxides formed in the isopropanol. Peroxides would react with the azulene diols causing the decomposition observed.

Circular dichroism (CD) spectroscopy is often used when traditional methods for enantiomeric excess cannot be used. These compounds did not ionize well and were thus

41

not seen on the chiral GC. Also the fact that the diols are purple and strongly absorb yellow light, polarimetry was not an option because it is traditionally done at 589 nm. CD presented none of these issues and was chosen to analyze the enantiomers. CD can be used to identify the presence of a single enantiomer and in some cases where molecules containing similar chromophores to previously elucidated configurations, the exact configuration of an unknown enantiomer can be made.⁶⁹

CD spectroscopy was run on each of the separated enantiomers, giving equal but opposite curves of molar extinction versus wavelength over the 200 nm to 800 nm range. The UV spectrum was used to determine the concentration of each sample. However according to the literature⁶⁹ the ideal concentration of a CD sample is one that has a UV absorption around 0.8. In order to achieve this absorption, the typically purple solutions were so faint the characteristic purple color was barely seen even when the sample was held up to a white background. When the concentration of the enantiomers was this low (less than 15 micromolar) the spectra that resulted gave no appreciable opposite CD curves for the enantiomers.

Upon running samples of more concentrated samples (more than 55 micromolar) the spectra did give curves that were equal and opposite, at least for the near UV portion (300 nm to 400 nm) of the total wavelength range observed (200 nm to 800 nm). Although the UV λ_{max} was around 280 nm for each diol, the range for observing the equal but opposite CD spectrum was usually at a higher wavelength.

Com	Compound		$\Delta \epsilon$	
5	fast	349.8	11.64	
⊃ _{RR/SS}	slow	349.8	-6.47	
0	fast	356.3	11.23	
9 _{RR/SS}	slow	356.3	-10.66	
10	fast	349.7	-7.45	
10 _{RR/SS}	slow	349.7	8.60	
10	fast	345.0	-2.83	
IU _{RS/SR}	slow	345.0	4.17	
11	fast	314	-3.56	
11 RR/SS	slow	314	7.12	
11	fast	339.7	-9.67	
11 _{RS/SR}	slow	339.7	10.70	

Table 2.6. CD data for each of the separated enatiomers. Each enantiomer is identified by its order of elution from the HPLC.

Two CD spectra have been run for chiral azulene molecules.^{21,24} These spectra are not very conclusive because they, like us, observed the $\Delta \epsilon = 0$ at the UV max. We believe this is because the chromophore that gives the strong absorption of UV light around 280 is due to the conjugation in the azulene ring. The azulene chromophore may not be affected enough by the chiral centers displaced from the ring. The chromophore that is actually showing the difference in absorption of the circularly polarized light is from the OH or CF₃ groups on the chiral centers.⁷⁰

Conclusions

The synthesis of several azulene-containing 1,5-diol diastereomers and the remarkable ease by which these diastereomers are chromatographically separable was

first published by our group.⁶ The origin of the diastereomeric differences was attributed to conformational preferences wherein the (RR)/(SS) diastereomers have larger O-C-C-O dihedral angles than the (RS)/(SR) diastereomers. The larger angle in the (RR)/(SS) diastereomers renders both OH groups less likely to simultaneously bind a silica surface, and therefore behave as less polar than the (RS)/(SR) diastereomers.²²

The racemic mixtures were also well separated on chiral HPLC. Despite separating and analyzing each enantiomer, the exact configuration determination has yet to be accomplished. This work also lends itself to a question about the trend seen for the increased resolution on chiral HPLC of the more retained (on silica) racemic diastereomer compared to the poorer resolution for the less retained racemic diastereomer.⁷

The excellent separations observed during this project suggest that an azulenederivatized silicon oxide (for GC) or cellulose (for HPLC) might give better separation of a wide range of analytes. Matthew Jackson, a fellow graduate student in the Garner group, has begun the synthesis of azulene coated siloxane polymers for use as a GC stationary phase. Also undergraduate lab courses can benefit from the visible and exciting color changes followed by easy separations of colored diastereomers using typical methods taught in organic lab courses.

CHAPTER THREE

Phosphabarrelene Synthesis Optimization and Derivatives

Introduction/Background

Very few catalyst complexes work for many different reactions, therefore new catalysts are continually being sought to fill the gaps or lack of activity/selectivity for certain reactions. Although reactions can be catalyzed with different metals, new catalyst research mainly focuses on the ligands that surround the metal. The design and synthesis of the phosphinine and phosphabarrelene molecules described here are a part of this effort. The significance of the ligands discussed in this section will then be applied to catalytic studies in Chapter four.

The original design of the C_2 -symmetric phosphinine utilizes two camphor molecules. Natural chiral monoterpenoids like camphor are often commercially available inexpensively with high enantiomeric purity.³²

Metal catalyzed asymmetric synthesis is of particular interest because of its applications to the field of medicinal chemistry and the importance of chirality in drug targets. The alternative, separating racemic mixtures of organic compounds, is a time consuming and inefficient way to obtain enantiomerically pure substances when only one enantiomer is useful. On industrial scales, obtaining the desired products with high yields and high enantiomeric purity can save time and money by eliminating the amount of unwanted products and processes involved in removing these. Therefore asymmetric catalysis in particular is a significant aspect of catalysis research. A favorable trait for asymmetric catalysis is symmetry within the ligand(s) complexed to the metal.⁴⁵ C_2 -symmetry within a ligand helps to reduce the number of substrate-metal arrangements and generally improves enantioselectivity.^{45,71} C_2 -symmetric ligands have been made for other types of catalysis however, no C_2 -symmetric phosphinine ligands have been synthesized prior to work done in the Garner group by Dr. Jason Bell.⁴²

Phosphinine and phosphabarrelene molecules are some of the least studied phosphorus ligands.^{38,40} Since the first synthesis of a phosphinine compound in 1966 by Märkl there have been many derivatives made.^{37,40,41} However, there are currently only ten chiral phosphinines known, five of which were first synthesized by our group (examples in Figure 3.1).^{41,42}



Figure 3.1. Various phosphinine and phosphabarrelene ligands.

Märkl was also the first to synthesize the class of compounds called phosphabarrelenes from phosphinines.³⁶ Currently, there are only 30 references found on Scifinder containing the concept of phosphabarrelenes, many of which are reviews and not original research articles.^{36,37,40} There are only six chiral phosphabarrelenes currently in the literature and none with higher than C_1 -symmetry.⁷²

Phosphinines and phosphabarrelenes have dramatic differences in their electronic and steric interactions with metals. Transition metal ligands have two components to their metal binding, σ -donation and π -acceptance. Based on Tolman's study of phosphorus-containing ligands, the original way to compare their σ and π bonding characteristics was to look at the IR stretching of CO molecules on nickel complexes.^{33,34,73} Tolman developed parameters to classify phosphorus ligands based on two variables: v for electronics, and θ for sterics. Phosphinines are planar at the phosphorus and so they lack the third dimension so an average of measurements α , in the x direction, and β , in the y direction, are used to calculate the steric parameter.³⁸



Figure 3.2. Quantification of steric hindrance using an average of α and β for planar phosphorus to obtain θ (cone angle in degrees).

Preparation of these nickel complexes required the use of very toxic Ni(CO)₄, so metals such as rhodium, tungsten, iridium, cobalt and others have been used more recently, and now correlations exist to compare bonding characteristics of most ligands on many different metals. Various IR frequencies of CO molecules in phosphorus containing complexes including phosphinine and phosphabarrelene ligands are listed below.^{33,34,40,72–74} Phosphinines have similar electronic properties to phosphites, which are relatively weak σ donors and strong π acceptors.³⁸ It is because of these bonding characteristics that phosphinines are a desirable class of ligands to stabilize electron-rich metal centers for catalysis.³⁷ This is important because many selective catalysts known in the literature include phosphite ligands like BINAPHOS for metal catalyzed hydroformylation.⁷⁵

Compound	Tolman Parameter	Cone Angle	$\delta^{31}P$	$v (cm^{-1})$			
Compound	χ	θ (deg)	(ppm)	Ni(CO) ₃ L	W(CO) ₅ L	L ₂ RhCl(CO)	
PH ₃		87	-240	2083.2			
P(t-Bu) ₃	0.0	182	63.3	2056.4	1934	2013	
P(OMe) ₃	23.3^{40}	107	139.7	2076 ⁴⁰	1954	2006 ⁴⁰	
PPh ₃	12.9^{40}	145	8.0	2069 ^f	1942	1965 ⁷²	
26 ^a	24 ⁷⁴	135 ^{c,38}	(178.2) 185.1 ⁷⁴		1994.1	1999 ⁴⁰	
27 ^b		94.3 ⁷²	- 69.0 ⁷²		1942	1993 ⁷²	

Table 3.1. Various Tolman type parameters for common phosphines and new phosphinines and phosphabarrelene molecules.

a. Triphenylphosphinine = 26 b. Triphenylphosphabarrelene = 27 c. Θ is determined by averaging α and β values.

On the other hand, phosphabarrelenes are more similar to phosphines but show a greater pyramidalization than phosphines at the phosphorus. This pyramidalization means a smaller cone angle, which leads to more s character on the phosphorus atom. More s character makes the ligand a better σ donor and weaker π acceptor.⁴⁰ More s character also makes the phosphorus lone pair slightly more basic.

The few known phosphinine and phosphabarrelene ligands have been studied mostly in the context of hydrogenation^{76,77} and hydroformylation,⁷⁴ with little or no study

of other reaction types. The activity of some phosphinine rhodium complexes in hydroformylation reactions have been shown to be very similar to that the early rhodium catalysts discovered by Wilkinson that include phosphines.³⁷

To better define the usefulness of these ligands, we have pursued the C_2 symmetric class of phosphinines and their phosphabarrelene derivatives. Dr. Jason Bell of our group prepared and published the first C_2 -symmetric phosphinine and a brief study of its catalytic activity in palladium catalyzed asymmetric hydrosilylation. Herein we have attempted to modify the synthesis to prepare more C_1 - and C_2 -symmetric phosphinines, phosphabarrelenes, pyridines and pyridiniums, as well as optimize some of the synthetic steps to these products. By changing certain pieces of the already established phosphinine ligand synthesized in our group we hope to create more reactive and selective ligands.

The catalytic nature of complexes with these ligands and results of catalytic studies will be further explored in Chapter four. In this chapter the synthesis of the ligands will be discussed.

Synthesis of the Ligands

Dr. Bell's original synthesis of bis-camphorphosphinine **6** was published in 2009 (Scheme 3.1).⁴² The first step of the synthesis is benzoylation of camphor to form benzoyl camphor, **28**. Phosphorus trichloride then causes substitution of the hydroxyl for chlorine resulting in chlorobenzylidene camphor, **29**. In camphor diketones, this reaction is quite selective for the "benzoyl OH". Then camphor enolate (made from potassium hydride) attacks the chlorobenzylidene camphor to give the 1,5-diketone called enedione, **30**. This reaction must be done in hexanes; use of THF results in reduction of the

49

chloride. The enedione is then dehydrated with fluoroboric acid to form the pyrylium salt, **31**. Using the traditional route for phosphinine synthesis, tris(trimethyl)silyl phosphine is used to replace the oxygen of the pyrylium salt with phosphorus, thus completing the synthesis of the C_2 -symmetric bis-camphorphosphinine, **6**.^{42,78}



Scheme 3.1. Dr. Jason Bell's published synthesis of bis-camphor phosphinine 6.

Once the synthesis of the phosphinine is completed, the phosphabarrelene derivative, 7, can be made by a [4+2] reaction with a benzyne intermediate. It is known that phosphinines require dienophiles that are very electron rich, which is why benzyne was chosen for the completion of the phosphabarrelene structure.³⁷ However, other alkynes have been used, for example, perfluorbut-2-yne and dimethyl

acetylenedicarboxylate.^{79–81} *o*-Fluoroiodobenzene and magnesium are used to form benzyne *in situ* and reacts with two conjugated bonds in the phosphinine ring structure via a Diels-Alder mechanism to produce the bis-camphorphosphabarrelene.^{72,78}

Several optimizations were attempted to improve the overall yield from the published 12% over five steps to the phosphinine and 3.3% over six steps to the phosphabarrelene.⁷⁸ In particular, the percent yields from the Grignard—type benzyne forming reaction (Scheme 3.2) to produce the phosphabarrelene **7** is noted to be quite low, ~ 26%.⁷²



Scheme 3.2. Unpublished synthesis of bis-camphorphosphabarrelene 7.⁷⁸

The first attempt to improve yields was to use PBr₃ or SOCl₂ instead of PCl₃ in the second step of the synthesis shown in Scheme 3.3., which is one of the lowest yielding steps. Employing the readily available thionyl chloride, might decrease unwanted side reactions as both of the byproducts of this reaction, SO₂ and HCl are gases.



Scheme 3.3. Synthetic route to 29 and 32 using different halide sources.

Employing a better nucleophile, bromide instead of chloride, might help improve the yields of this reaction. Bromine is also a better leaving group than chlorine and thus if the synthesis of **32** is accomplished in good yields, the enedione formation reaction that follows might benefit as well. GC-MS showed that the PBr₃ reaction yielded more of the Z isomer whereas the PCl₃ gave more than 97% pure E isomer, confirmed by the X-ray crystal structure of the major isomer of chlorobenzylidene, **29**. However, the bromine species, **32**, had a higher overall yield, 80.5%. The SOCl₂ reaction produced more of the other structural isomer, shown below in Figure 3.3., with almost a 1:10:10 yield of the Z to E to the unwanted isomer (see Figure 4), 72.8% yield overall. GC-MS was used to determine the ratios of each isomer of the product obtained from each of the three reactions attempted.



Figure 3.3. Isomers of halobenzylidene camphor (29 and 32).

Using purified halobenzylidenes, **22** and **32**, it was found that the chlorine compound gave a higher yield of enedione in the subsequent step of the synthesis. The use of chlorobenzylidene as the starting material in the enedione **30** synthesis gave enedione in a 44% yield, while bromobenzylidine only gave enedione **30** in a 36% yield.

In an attempt to improve upon the 55% yield of the pyrylium salt, **31**, optimization was attempted by an undergraduate in our group, Eric Wallace. This reaction utilized a Dean-Stark trap in order to trap the water that is created during the

reaction. Water can cause a reverse reaction hydrolyzing the pyrylium back to the corresponding 1,5-diketone. Toluene is used as the solvent because of its high boiling point and ability to form an azeotrope with water. Some of our unsuccessful attempts to raise the yield included using molecular sieves to trap water. First the Dean-Stark trap was filled with molecular sieves to make sure the water was really trapped away from the reaction. It was believed that the distance that the solvent had to travel (i.e., insufficient reflux occurring) may have been a problem so a shorter path for water removal was considered. A tube with a glass frit at the bottom and a ground glass joint was filled with sieves and was directly attached above the reaction flask and below the condenser. This minimized the distance the toluene carrying water would travel, the sieves would trap the water and the toluene would fall directly back into the reaction. However, results were similar, most likely because the sieves were not adequately keeping the water from draining back into the reaction. The last attempt was to try benzene, which is also azeotropic with water and has a lower boiling point than toluene. None of these improved upon Dr. Bell's published yield, although the reactions were still successful with modest yields (35%).

Optimization was needed for the last step of the synthesis, from phosphinine to phosphabarrelene, because the yields consistently were never higher than 27%. Three methods were attempted to create the benzyne intermediate *in situ* to perform the Diels-Alder reaction with the bis-camphorphosphinine. Several procedures were attempted utilizing a refluxing solution of the phosphinine, benzyne forming reagents and solvent. Unnoted in the literature for other phosphabarrelene syntheses, this reaction (regardless of benzyne source) turned a bright green color while refluxing. This is noteworthy

53

because green is an unusual color for organic reactions, particularly when there are no metals present, as in the case of route b. The two new routes to the benzyne intermediate were b) anthranilic acid with isoamylnitrite⁸² and c) 2-(tristrimethylsilyl)phenyl trifluoromethanesulfonate with tetra-n-butylammonium fluoride.⁸³



Scheme 3.4. Synthetic routes to phosphabarrelene, 7.

The GC-MS of the crude reaction mixture utilizing the anthranilic acid method indicated some left over starting material. Subsequent attempts with high equivalents of anthranilic acid and isoamyl nitrite did not completely eliminate the presence of phosphinine seen in the GC-MS. Only a 5% yield of phosphabarrelene was obtained after purification by column chromatography and crystallization. The TMS triflate method, although the solution turned the same green color as the other methods upon addition of the phosphinine, yielded no desired product. The GC-MS indicated starting material was well as many other unidentifiable peaks. TBAF was used initially as the fluoride source; CsF was also attempted with no success. However, the traditional Grignard type route was found to be most successful yielding around 25% of 7. Typically Grignard reactions are done in ether; this reaction is no exception to that rule. However, where many Grignard reactions are successful using the cyclic ether THF, this reaction gave no product when THF was used instead of diethyl ether.

An interesting aspect of the phosphabarrelene 7 1 H NMR spetrum was found. There are two remarkably upfield shifts observed (+ 0.07 and – 0.19 ppm). The X-ray structure of the barrelene shows that the hydrogens that are responsible for these shifts are projected into the face of the aromatic ring. It is the anisotropy of the aromatic ring that shields the nuclei within the cones (below) causing the signals to shift upfield, as shown in Figure 3.4.



Figure 3.4. Anisotropic effects of phosphabarrelene, 7, observed in the ¹H NMR spectum.

An unfortunate problem with the phosphabarrelene ligand was that it was susceptible to air oxidation, unlike phosphinines which are entirely air-stable. This is a common problem for phosphines, particularly those without aryl groups on phosphorus; many become oxidized immediately upon contact with air and small phosphines are pyrophoric.⁷² Apparently aryl groups protect against oxidation by resonance with the phosphorus lone pair. The oxidized phosphabarrelene molecules were seen in the ³¹P NMR spectra and in the GC-MS, even after the compound had been stored for several weeks under vacuum.

Derivatives at the Phenyl Position

Derivatives at the phenyl position were sought in an to attempt to test the tunability of the electronics of the phosphorus. Changing the electronic interaction between the phosphorus of a ligand and the metal can help improve upon the activity of the catalyst. Various properties such as the chemical shift of the phosphorus would show how greatly the P is affected by the change in structure, as seen in Figure 1.6 in Chapter one. One of each, a more electron donating (EDG) substituent and a more electron withdrawing (EWG) substituent were proposed to replace the phenyl ring in the original phosphinine structure. *p*-Dimethylaminophenyl was chosen as the electron donating substituent.

Scheme 3.5. Synthetic route to new derivatives of benzoyl camphor using alternative esters.

Tuning the electronics of the phosphorus using these groups (EWD and EDG), would be expected to have an effect on the selectivity and activity of the catalysts they support. Undoubtedly one of these will perform better and the other will be worse than the standard phenyl group. It has been shown that although the addition of a $4-(p-CF_3-$

phenyl)-2,6-diphenylphosphinine gave similar yields to triphenylphosphinine, the selectivity of the catalyst made with these ligands doubled, in the hydroformylation of oct-2-ene.⁷⁴ Other benefits of EWG and EDG inclusion is the possibility for increased reactivity of the intermediates at steps during the phosphinine/phosphabarrelene synthesis. For example, the electron withdrawing nature of the trifluoromethyl group would make the ester slightly more reactive towards nucleophilic attack during the first step of the phosphabarrelene synthesis shown in Scheme 3.3. It would also decrease electron density about the phosphorus and ultimately make it a better π accepting ligand. The 4-dimethylaminobenzene is electron donating and would increase electron density at the phosphorus, but decrease reactivity towards nucleophilic attack in the first step of the synthesis in Scheme 3.1. Both starting esters were readily available and lacked functional groups that might be disturbed or directly affected by reagents used in making the phosphinine. These derivatives were made using the appropriate esters, ethyl trifluoroacetate, and methyl 4-dimethylaminobenzoate, attempts are described below.

Work on the trifluoroacetyl derivative was done with help from Julia Vickery, an undergraduate researcher in our lab. Trifluoroacetyl camphor **33** was synthesized according to the procedure used in the published synthesis described in Scheme 3.1.⁴² The desired product **33** was seen by GC-MS and confirmed to be in the enol configuration by ¹H NMR spectrum. However, the trifluoroacetyl camphor and camphor have very similar volatility and silica gel mobility, so the usual method of recovery (i.e. chromatography) of unreacted camphor could not be used. Kugelrohr distillation was attempted but the ratios of product to camphor only slightly changed, favoring camphor in the fraction that moved and the product in the fraction that stayed behind. Although

57
camphor can sublime, it resisted evaporation under vacuum. Using camphor as the limiting reagent and all other reagents in excess (greater than 3 equivalents) did not force the reaction to completion. In spite of not obtaining pure compound, the crude mixture was taken into the next reaction step with PCl_3 and the chlorinated product 35 was obtained with the same percentage of camphor and still a small amount of the unreacted enol present in the GC-MS (Scheme 3.6). Column chromatography was used with only moderate success to purify the chloride. PBr₃ was also used to successfully synthesize the bromotrifluoromethylidene camphor **36**; however, like the chlorinated version; starting materials were difficult to remove. A mixture of the halogenated and enol compounds was taken into the enedione stage successfully. Kugelrohr distillation was then able to separate the enedione from all the other compounds, because of the larger difference in boiling points, producing the oily enedione product 37, 57% yield (based on the moles of the crude mixture used) for the last step. Although more attempts (distillation, Kugelrohr, chromatography, etc) were made at purifying the compounds at each reaction step, no further improvements were made. The reaction of the enedione with HBF₄ was attempted but no product was observed in the ¹³C NMR spectrum (which gives characteristic shifts for pyryliums) nor was any starting material isolated.



Scheme 3.6. Synthetic route to trifluoromethyl substituted derivatives.

Dimethylaminobenzoylcamphor was synthesized successfully, as reported previously in the literature. However, there was an interesting discrepancy between our results and the published of the NMR spectra. An article published by Wu⁸⁴ stated that the dimethylaminobenzoyl camphor is in equilibrium between keto-enol forms shown in Scheme 3.7. There should then be evidence in the NMR spectra of both the enol hydrogen and the diketone CH hydrogen. However, the NMR spectra of the product shows the molecule is apparently entirely in the diketone form. The integration of the diketone CH hydrogen, $\delta = 4.6$ ppm, has a normalized value of 1.0 compared to the 4.0 integration for the four aromatic hydrogens.



Scheme 3.7. Keto-enol tautamorization of dimethylaminobenzoylcamphor, 34.

The authors list an incorrect chemical shift, $\delta = 2.88$ ppm, for the diketone CH with an integration of 0.8, indicating that they believe that at room temperature, the diketone accounts for 80% of the mixture. However, they fail to identify the OH peak that would account for the other 20% of the mixture. The ¹³C NMR spectrum also has conflicting assignments. The shift at 153 ppm was assigned to the carbon of the alkene of enol form and no assignment of the carbon from the diketone form was made, which, according to their ¹H NMR spectra should both be present. The shift at 153 ppm is actually, most likely, the shift of the C-N aromatic carbon. The authors lump this peak in

with the other aromatic peaks because it can be difficult to distinguish in ¹³C NMR spectrum how many carbons are responsible for each peak.

Compound **34**, was reacted with both PCl₃ and PBr₃ to yield the subsequent halogenated products **38** and **39** in 63.9 % and 80.5% yields, respectively (Scheme 3.8). These crude mixtures, containing some unreacted starting material, were taken into the enedione reaction with mild success. There was a very small peak seen on the GC-MS with the correct mass (433 m/z) corresponding to the desired product **40**; however, no pure material was isolated from purification attempts made using column chromatography. Time did not allow further attempts of this reaction.



Scheme 3.8. Synthetic route to *p*-dimethylaminophenyl derivatives.

Derivatives of the Heteroatom

A related derivative synthesized from the bis-camphorpyrylium salt **4**, was biscamphorpyridine and pyridinium (Scheme 3.9). This work was done with help from Clara Dutton, an undergraduate researcher in our group. Beginning with the biscamphorenedione **30** or pyrylium **31**, the bis-camphorpyridine can be made. Pyridines, like phosphinines, are also used as ligands for metal catalyzed synthesis.^{32,85} Pyridines and pyridiniums can easily be made from their corresponding pyrylium salts.⁸⁶ To show the versatility of camphor in cyclization reactions with other heteroatoms, Sotiroppoulos also used camphor to synthesize a number of pyridine containing molecules.⁸⁷ Although he successfully synthesized a bis-camphorpyridine molecule, the synthesis utilized a diketone, which lacked the alkene between the carbonyl groups. Kotsuki also synthesized a bis-camphorpyridine that lacked the phenyl group on the pyridine ring.⁸⁸ His studies showed that the nitrogen of this pyridine was not nucleophilic enough for catalysis. Their attempt to place a substituent in the position of the ring, opposite of the nitrogen (where pyridine **9** has the phenyl group), post synthesis of the pyridine was unsuccessful.^{32,88}

The pyridinium structure was sought as a potential aid in chiral analysis of amines. It was hoped that diastereomeric salts could be made from a chiral amine of unknown enantiomeric excess and single enantiomer of the bis-camphorpyrylium. Integrals from the ¹H NMR spectrum can be used to calculate enantiomeric purity. Initial NMR experiments using benzyl amine and cyclohexyl amine to produce the biscamphorpyridinium versions of these achiral amines were inconclusive. The desired structure resulting from the reaction between the bis-camphorpyrylium with benzyl amine did not give the expected AB pattern for the benzyl group in the ¹H NMR. The only conclusion that could be drawn from ¹³C NMR spectrum of the crude reaction mixture was that the signature downfield pyrylium peaks were diminishing and some new peaks were appearing, most strikingly in the aromatic region.



Scheme 3.9. Synthetic route to bis-camphor pyridiniums, 41 and 42 and pyridine, 43.

We were successful in the synthesis of the phenyl bis-camphorpyridine **43** from ammonium chloride with triethylamine, observed in the GC-MS (371.3 m/z). This pyridine might also be useful as a chiral ligand for asymmetric catalysis, but has not been pursued.

Other Derivatives

The poor degree of asymmetric induction in the palladium catalyzed asymmetric hydrosilylation using the phosphinine **6** was thought to result from two factors. First, the methyl groups that extended into the metal environment are almost certainly too small to enforce an effective chiral environment at the metal center. Secondly, the methyl groups only showed an 18° angle above and below the plane of the phosphinine ring.⁴² Therefore, we sought new bulkier camphor derivatives to improve the steric effect of the ligand.

It is known that bulkier phosphite ligands maintained high activity with increased selectivity.⁷⁴ To accomplish the goal of synthesizing a bulkier phosphinine, a benzyl group was chosen replace the methyl in the starting camphor molecule. A phenyl ring at this position of the target phosphinine/barrelene molecule would have a much greater effect on the metal environment compared with the significantly smaller methyl group. It

would not only reach further into the metal environment but would likely also have a greater angle above and below the plane of the phosphinine ring system. Initially, the route attempted to synthesize the phenyl containing camphor, **44**, came directly from the literature.⁸⁹ Utilizing an Fe(acac)₃ catalyst, Grignard reagents have been shown to couple with a sulfonyl chlorides, to get C-C cross coupled products. Camphor sulfonyl chloride was reacted with phenyl Grignard in the presence of the Fe(acac)₃ in THF and N-methylpyrrolidone (NMP) at 80° C (Scheme 3.10). Although this particular combination was straight from the literature, in our hands this reaction failed to yield any of the desired phenyl camphor as analyzed by GC-MS. Rather, formation of biphenyl was predominant. Another route to more sterically hindered camphor derivatives was sought.



Scheme 3.10. Synthesis of phenyl camphor, 44.

The second attempt at synthesizing a bis-camphor-type phosphinine ligand with more steric hindrance utilized a thiophenyl group added to what was the methyl group of camphor. Work on this synthesis was mostly done by Jessica Almond, an undergraduate researcher in our group. To synthesize thiophenylcamphor **46**, (-)-camphor sulfonic acid was reacted with an excess of iodine and triphenylphosphine to produce iodocamphor, **45**.⁹⁰ Iodocamphor **45** can undergo a simple nucleophilic substitution by sodiumthiophenylate, which produced thiophenylcamphor **46** which was purified by Kegulrohr distillation (Scheme 3.11).



Scheme 3.11. Synthesis of bis-(thiophenyl)camphorphosphinine, 47.

The thiophenylcamphor was then reacted along the same pathway outlined in Scheme 3.1 which resulted in bis-(thiophenyl)camphorphosphinine, **47**. X-ray crystallographic data was obtained and confimed that the enaniomerically pure bis (-)-(thiophenyl)camphorphosphinine had been formed (Figure 3.5). This ligand was tested for its activity as a ligand for the AHF which is discussed in Chapter four.



Figure 3.5. X-ray crystal structures on phopshinine 47.

The importance of symmetry in ligands for asymmetric catalysis led to the idea that the phosphabarrelene ligand would ideally possesses C_n symmetry, like biscamphorphosphinine. C_2 -symmetry has proven to be a powerful element of ligands showing high enantioselectivity.⁴⁵ The barrelene that was synthesized from the C_2 symmetric bis-camphorphosphinine lost that symmetry in the barrelene-forming reaction. Therefore a synthetic route was hypothesized that would keep the symmetrical element incorporated in the barrelene ligand. This would be done by replacing the benzyne group used to create the barrelene core with another "benzyne" synthesized from (+)-camphor (Figure 3.5). If done correctly, this would produce a C_3 -symmetrical triscamphorphosphabarrelene. This would be the first monodentate C_3 -symmetric phosphorus ligand in the literature.



Figure 3.5. Camphor-alkyne, and proposed C_3 -symmetric triscamphorphosphabarrelene, **48**.

In order to synthesize the tris-camphorphosphabarrelene the first step would be to synthesize a camphor molecule containing substituents that would allow for the formation of an endocyclic alkyne functionality *in situ*.



Scheme 3.12. Proposed reaction between cis-bromo(trimethylstannyl)camphor 49 and phosphinine 6 to form the C_3 -symmetric tris-camphorphosphabarrelene, 48.

The DeLucchi group published the synthesis for a multicyclic triscamphor compound that the author's believe is formed from the cyclization of three alkyne containing intermediates of camphor resulting from the copper catalyzed bromo-tin camphor trimerization.^{91,92}

If an alkyne-containing camphor can be synthesized *in situ* via this method, then it could react in a Diels Alder fashion similar to benzyne and produce a C_3 -symmetric chiral tris-camphorphosphabarrelene **48**, (Scheme 3.12). The synthesis of the bromo-tin camphor, **49**, is currently being pursued although at this time no novel materials have been synthesized for this project.

CHAPTER FOUR

Asymmetric Catalysis Utilizing Phosphinine and Phosphabarrelene Containing Catalysts

Introduction/Background

Asymmetric catalysis is in theory and increasingly in practice the best way to obtain enantiomerically pure or enriched compounds. Chiral non-racemic products are desirable because of their wide use in synthesis, especially of small organic molecules with medicinal properties.^{40,72} Most asymmetric catalysis is done with metal complexes in which one or more of the ligands are chiral. Chiral ligands with heteroatoms like phosphorus are commonly used to complex to the metal center. The fact that the electronic and steric effects of phosphorus ligands can be relatively easily "tuned" makes them ideal for catalysis because even small changes can greatly affect the ligand's interaction and activation of the metal complex, often making the complexes active for a variety of substrates and conditions. It is commonly known that ligands containing C_2 symmetry are often more stereoselective than nonsymmetrical versions, and many examples are known.^{45,47} Hence the recent discovery of the successful phosphinine/barrelene ligand motifs combined with the C_2 -symmetry added from the camphor moieties might provide an active and selective catalyst for the model reaction of asymmetric hydroformylation of styrene.

Since its inception in 1965, the rhodium catalyzed hydroformylation reaction has been extremely popular, now producing millions of tons of aldehyde products annually.^{93,94} Hydroformylation describes a reaction between an alkene with one equivalent of both carbon monoxide and hydrogen gas to form a new carbon-carbon bond

. The final product is an aldehyde. Shown below is the hydroformylation of styrene and the three possible isomers of the product. Small molecules containing aldehydes are produced on gigantic scales for many industrial applications. Osborn, Young and Wilkinson⁹³ reported the first use of rhodium-phosphine complexes that improved upon the older cobalt-based catalysts. Although Wilkison's original catalyst used only phosphines, many different phosphorus containing ligands have improved the percent conversion, catalyst turn over frequency (TOF), regioselectivity and, for chiral ligands, stereoselectivity. The hydroformylation of styrene has been used as the gold standard to experimentally determine how successful a catalyst is based on these four features. Once a catalyst has been determined to have high activity with styrene, more challenging substrates can be addressed.



Scheme 4.1. Asymmetric hydroformylation of styrene.

Despite the wide use of hydroformylation in industrial processes, the method still struggles with the hydroformylation of internal alkenes, which are quite unreactive. This makes the development for new catalysts an important area of research.^{40,74} Current catalysts require harsh conditions, such as high temperatures and pressures, to help improve the activity of these reactions; however, these conditions are harder to maintain

on large industrial scales.⁷⁴ Therefore, it would be beneficial to have catalysts that are active under lower temperatures and pressures and with less catalyst loading.

Phosphine ligands make for active hydroformylation catalysts because of their electronic properties. Energy calculations and molecular modeling have shown that the π -accepting nature of the ligand causes the metal complex to bind alkenes weakly allowing for the reaction to occur more easily and ultimately have higher activity.^{74,95} It is believed that the phosphinine's strong π -acceptance is what accounts for the use of this ligand. However, the phosphabarrelene, like phosphines, are slightly weaker π -acceptors and stronger σ -donors than phosphinines, have the benefit of a third dimensional steric effect on the complex. The rate determining step of catalyzed hydroformylation is still un agreed upon, the results from the most recent study on rhodium catalyzed hydroformylation of octene state that the 1,2-insertion of the hydride to the alkene is the slowest step in the catalytic cycle.⁹⁶ Therefore, ligands, like phosphinines and phosphabarrelenes that are electron rich and sterically force the hydride and the alkene to be close in proximity produce high activities for these catalysts.

Utilizing metal complexes with chiral ligands, asymmetric hydroformylation (AHF) can in principle produce enantiomerically pure products. Fernandez-Perez summarizes recent publications on AHF by stating that "asymmetric hydroformylation of alkenes remains one of the most powerful transformations for preparing enantiopure aldehydes, which are valuable precursors of active pharmaceutical ingredients (APIs) and agrochemicals."⁴⁷ For example, the chiral branched aldehyde produced from styrene can be used in the synthesis of 2-arylpropionic acids which have anti-inflammatory properties.⁹⁷

In 1993, Takava published his work on the synthesis and application of a bidentate phosphine-phosphite ligand for AHF.⁷⁵ AHF of styrene catalyzed with a rhodium-(S,R)-BINAPHOS catalyst produced 99% conversion with a 94% ee.⁷⁵ In 2005. the percent yield and %ee were slightly improved upon by the use of a novel ligand reported by the Yan group.⁹⁸ The bi-dentate phosphine-phosphoramidite ligand was made slightly more rigid than the BINAPHOS structure by substituting one of the oxygen atoms for an ethylamine. This ligand was more enantioselective towards styrene than BINAPHOS, reaching enantioselectivities up to 97% under less harsh conditions.⁹⁸ In 2007 the area of monodentate ligands began to be taken more seriously after Beller et al, produced 12 new mono-dentate ligands. Each of the catalysts made using these ligands gave good conversions, branched to linear (B:L) ratios but only modest enantioselectivities (12-48%).⁹⁹ The latest improvement of monodentate ligands for AHF was made by Alexakis in 2010 with the use of new phosphoramidite ligands.¹⁰⁰ These catalysts gave only modest conversions under the reaction conditions, but the B:L ratios were extremely high (92 to 99.9 : 1) and similar enantioselectivities (best $\sim 40\%$) to the previous catalysts. None of these catalysts have yet been commercialized. The improving results of catalytic reactions using monodentate phosphorus ligands show that it might be possible to narrow the gap between the successes of mono- and bi-dentate ligands.

Phosphinine ligands were first used for hydroformylation by Breit in 1996.^{74,97} He prepared the catalysts *in situ* by combining monodentate phosphinines with Rh(CO)₂(acac) in toluene. Using styrene as the substrate, initial results were modest, with the phosphinine catalysts giving percent conversions of 51% to 80% and B:L ratios

of 24:1 compared to 31% and 26:1 B:L for triphenylphosphine under the same conditions.⁹⁷ In 1997 Breit showed that phosphinines were also more active than the previously popular π -accepting phosphite ligands in both % conversion and catalyst TOF.¹⁰¹

paper	ligand	conditions	S : L : Rh	B:L	% conv.	% ee
Breit 1997	PPh ₃	20 bar, 25°C 2.5 hr, toluene	280 : 5 : 1	24:1	8	
Breit 1997	26	20 bar, 25°C 2.5 hr, toluene	280 :5 : 1	20:1	18	
Breit 1997	2-methyl-4,6- diphenyl phosphinine	20 bar, 25°C 2.5 hr, toluene	280 : 5 : 1	20:1	29	
Breit 1996	PPh ₃	50 bar, 20°C, 22 hr, toluene	280 : 20 : 1	25.8:1	31	
Breit 1996	4-cyclohexyl phosphinine	50 bar, 20°C, 22 hr, toluene	280 : 20 : 1	0	0	
Breit 1996	2,6-diMe-4-Ph phosphinine	50 bar, 20°C, 22 hr, toluene	280 : 5 : 1	23.2:1	51	
Breit 1996	2,6-diMe-4-Ph phosphinine	50 bar, 20°C, 22 hr, toluene	280 : 2 : 1	26.6:1	80	
Takaya 1993	(S,R)-Binaphos	100 atm, 60°C, 43 hr, benzene	400 : 4 : 1	7.3:1	99	94(S)
Yan 2005	(R,S)-phosphite- phosphoramidite	10 atm, 60°C, 36 hr, benzene	1000 : 4 : 1	7.3:1	99	97(R)
Erre 2008	4,5-dihydro-3H- dinaphthol phosphepine	40 bar, 60°C, 24 hr, toluene	2000 : 8 : 1	21.5:1	95	38(R)
Mazue- la 2010	biaryl-phosphor- amidite	25 bar (CO:H ₂ , 1:2), 25 °C, 16 hr, toluene	500 : 2 : 1	99:1	16	40(S)

Table 4.1. Published hydroformylation results using phosphinine ligands with styrene, also the most successful published mono- and bi-dentate ligands.

Unlike phosphites, that can undergo hydrolysis, phosphinine molecules are quite stable to air, most likely due the aromatic nature of the ring and poor σ availability of the phosphorus lone pair.^{74,76,101}

Breit was the first one to show that phosphabarrelene molecules could be used as ligands for homogeneous catalysis.⁷² This class of ligands disproved an earlier hypothesis stating that σ -donors would not make active catalysts because they would be deactivating ligands for hydroformylation. The few phosphabarrelene ligands that have been tested for hydroformylation have not only been shown to be as active as their phosphinine precursors but have been more successful at inhibiting double bond isomerization of the substrates.^{72,94} This result was significant because isomerization sometimes leads to many unwanted regioisomers. Table 4.1 includes some of the phosphinines that have been tested as chiral ligands for asymmetric hydroformylation of styrene, as well as the current leading chiral catalysts.

Previous work by Dr. Jason Bell explored the use of the bis-camphorphosphinine ligand **6** in the Pd catalyzed asymmetric hydrosilylation reaction of alkenes.⁴² Hydrosilylation is the addition of a silicon-hydrogen bond across a carbon-carbon double bond in Markovnikov fashion. Using Tamao-Fleming oxidation conditions, the silylated product can be converted to an alcohol with retention of the configuration. Although the results were marginal, the reaction did proceed making it the first successful hydrosilylation reaction utilizing a chiral monodentate phosphinine ligand showing any enantioselectivity. Using the bis-camphorphosphinine-Pd catalyst, only a 27% ee was observed for the hydrosylilation-oxidation of styrene. Based on the X-ray structure of the complex, two deficiencies in the structure of the phosphinine are evident. (a) The methyl

groups that project into the metal environment only deviate 18° from the plane of the phosphinine ring⁴², which is only a very small deviation from the flat non-chiral plane of the rings. (b) The size of the methyl groups does not appear to sterically crowd the metal environment like more effective ligands have been shown to do. However, no hydroformylation reactions were attempted with either the bis-camphorphosphinine or bis-camphorphosphabarrelene ligands.

Asymmetric hydrogenation of dimethyliticonate was also attempted by Dr. Bell using the bis-camphorphosphinine-Pd complex with no enantioselectivity observed.

NMR Binding Studies

³¹P NMR studies were performed to better understand the how the ligands would bind in solution with the rhodium complexes. Samples were made using varying concentrations of ligand to rhodium to determine how the ratio affects complexation, and whether one or two ligands would add per metal.

Consistent with Breit's rhodium-phosphinine complexes that gave chemical shifts around 166.1-173.8 ppm in the ³¹P NMR spectrum with phosphorus-rhodium coupling of 175 Hz, the rhodium-bis-camphorphosphinine complex made from $[CIRh(CO)_2]_2$ had a doublet at 122 ppm with a 128 Hz Rh-P coupling.⁷⁸ Based on the excess of ligand added in solution, a doublet with a coupling of that size indicates that there are two equivalent phosphinines bound to the metal.

A 2:1 phosphabarrelene to rhodium solution was prepared using $[ClRh(CO)_2]_2$ as the rhodium source. The ³¹P of this solution showed free phosphabarrelene at 12.8 ppm and a doublet at -28.5 ppm with a J = 130 Hz, which is from the di-substituted phosphabarrelene-rhodium complex **51-trans** (Figure 4.1). Also, what was believed to

be mono-substituted phosphabarrelene-rhodium complex **50** appeared at -11.7 ppm with a coupling constant of 176 Hz (Figure 4.2).



Figure 4.1. ³¹P NMR spectrum of phosphabarrelene:rhodium complex (2:1 ratio).



Figure 4.2 Mono-barrelene rhodium complex, **50**, and di-substituted phosphabarrelene-rhodium complex **51-trans**.

An equilibrium study was done to figure out exactly how much phosphabarrelene was needed to fully di-substitute the rhodium. When more barrelene was added, enough to reach the 2.5:1 phosphabarrelene to rhodium, there was still some free

phosphabarrelene present (Figure 4.3). This amount successfully resulted in disubstitution, seen by the elimination of the mono-substitution peak.



Figure 4.3. ³¹P NMR spectrum of the phosphabarrelene:rhodium complex (2.5:1 ratio).

Briet's barrelene-rhodium complexes gave splitting patterns with similar coupling constants, around 140 Hz, but are shifted further downfield, likely due to the many aryl groups present.⁷² Phosphabarrelenes have been shown to coordinate two molecules per metal with both platinum and palladium when an excess of ligand is used.^{102,103}

Catalytic Studies

Although the [ClRh(CO)₂]₂ served as a good model system to show that our ligands would bind to Rh, it has been reported that the presence of chloride greatly

decreases the activity of rhodium complexes toward hydroformylation.^{48,104} The most common Rh source used in the catalytic studies is $Rh(CO)_2$ acac.

Rh(CO)₂acac was chosen, like most rhodium catalyst precursors for AHF reported in the literature, as the metal catalyst precursor because it gives high activity and good selectivity,⁴⁷ in the presence of phosphinines. Catalysts were made *in situ* by combining the metal catalyst precursor and the ligand in toluene (constant volume of 10 mL) with styrene, using decane as an internal standard for gas chromatography analysis. Rhodium was always kept at 0.002 mmol, 0.4 mol% per reaction, relative to the substrate, while the amounts of ligand were varied. Although some literature procedures highlighted the importance of generating the active catalyst before adding the substrate, our results do not indicate there was any problem with the formation of the active catalyst.⁷⁴ It is believed that inactive rhodium carbonyl clusters can form if the phosphorus ligands do not bind well.⁷⁴

Styrene was the main substrate tested because it is the most widely used substrate in the literature and allows for comparison with almost every other ligand that has shown success for AHF.^{48,105} The advantages for testing styrene are that it readily undergoes hydroformylation to give regio- and stereo-isomers that are easily resolved and quantified using GC. The enantiomers of the branched product, **8**, were baseline resolved using the Restek β DEXsa chiral column. The branched product, also sometimes called the isoproduct, is chiral and therefore a total of three possible products are formed. This allows for facile determination of whether the catalyst being tested has high activity, is regioselective and whether or not it is enantioselective regardless of the regioselectivity. Although other substrates were tested, (like α -pinene) none of these attempts gave good

results. Decane was used as an inert internal standard that would allow us to quantify the results by both chiral and achiral GC without interfering with product peaks.

To model mild conditions, the synthesis gas was held at a constant ratio of 1:1 $CO:H_2$ and at a constant pressure of 150 psi (roughly 10 bar). Internal stirring was also constant. During initial tests, temperature and time were varied from 25 °C to 60 °C and from 4 to 24 hours.

The results are given in the Table 4.2 below. The Rh catalyst with no ligand gave only conversion from styrene to the hydrogenated product, ethyl benzene. Rhodium metal is a documented hydrogenation catalyst.⁷⁶ Triphenylphosphine (PPh₃) at concentrations of 3:1 L:Rh, produced modest conversions of 36-42% at room temperature (25°) for 8 hours with a 99:1 branched to linear ratio, but gave 100% conversion at 60 °C for 4 hours and only 10:1 B:L. Thus, mild temperature (25°) was chosen in order to allow for comparisons that could either be better or worse than the standard PPh₃. Under these conditions, PPh₃, **26** gave better conversions (43-72%) but was less selective (13:1) towards the desired branched product. Also bis-camphorphosphinine **6** gave similar 10:1 B:L ratios but was less active, at most 24% conversion. Increasing the ligand:rhodium ratio decreased the regioselectivity while only increasing the yields slightly for all phosphinine ligands tested. Briet also saw this trend with phosphinine ligand concentrations used to hydroformylate 1-octene.⁷⁴

Ligand	Cond.	S:L:Rh	B:L	%conv.	%ee
No Ligand	25 °C 8 hours	234:0:1		1% ^a	
	25 °C 8 hours	228:3:1	99:1	40%	,
Ph	25 °C 8 hours	220:3:1	99:1	42%	
Ph ^{_P} _Ph	25 °C 8 hours	252:21:1	19:1	36%	
	60 °C 4 hours	277:3:1	10:1	100%	
Ph	25 °C 8 hours	235:3:1	13:1	72%	
26	25 °C 8 hours	231:3:1	13:1	43%	
Ph ^{//} P ^{//} Ph	60 °C 4 hours	242:18:1 ^b	1.3:1	100%	
27 Ph Ph Ph	25 °C 8 hours	232:2.5:1	49:1	76%	
Ph	25 °C 8 hours	247:2:1	8:1	14%	0.4%
	25 °C 8 hours	259:3:1	12:1	12%	0.4%
P	25 °C 8 hours	239:18:1	10:1	24%	2.0%
6	60 °C 4 hours	250:2.5:1	1.2:1	37%	0.4%
P Ph	25 °C 8 hours	248:4.3:1	10:1	5%	0.6%
Ph Ph S 47 S ^{-Ph}	25 °C 8 hours	231:4.2:1	100:0	9%	1.8%
Ph Ph Ph F Ph F F F F F F F F F F F F F	25 °C 8 hours	244:3:1	5:1	7%	0.0%
Ph 53 ^d	60 °C 4 hours	239:6:1	1.1:1	10%	0.8%

Table 4.2. Hydroformylation results of phosphinine and phosphabarrelene ligands.

a. Conversion to ethylbenzene was seen with a 17% yield, b. higher ratios of ligand were most likely responsible for the inflated conversion. C. $2-(1R,3R-1-methyl-3-isopropyl-cyclopentyl)-4,6-diphenylphosphinine d. <math>2-(1,2,2,3-tetramethyl-cyclopentyl)-4,6-diphenylphosphinine^{41}$

Unfortunately, although formation of the branched products was favored, the chiral column showed that the chiral ligand, **6**, was not enantioselective, giving only a marginal 0.4% ee.

Bis-(thiophenyl)camphorphosphinine **47** showed complete selectivity of the branched aldehyde over the linear, although the conversion was quite low (9%). This ligand, as expected, gave a greater enantioselectivity compared to the less bulky phosphinine **6**. However, an enantiomeric excess of 1.8% is not comparable to the %ee seen for the best chiral catalysts.

The alkyl substituted asymmetric phosphinine **52** synthesized by Dr. Nelson van der Velde⁴¹ gave similar conversion, 23%, but the 5:1 B:L ratio showed that it was less regioselective than the other phosphinines. Neither of these phosphinines showed any enantioselectivity. The results for the three phosphinines tested at 60 °C for 4 hours all gave better conversions overall but were significantly less selective for the branched product, averaging 1.2:1 B:L.

Relative to values for phosphinines presented in the literature, the phosphinines synthesized in our group were comparable. Breit's phosphinines gave the highest yield of 80% with less than 5% ee for reactions done at 50 bar for 22 hours.

Triphenylphosphabarrelene **27** produced the highest conversions under the mild conditions. This ligand also had the highest selectivity for the branched over the linear product. These results support the conclusion that phosphabarrelenes are indeed good ligands for rhodium catalyzed HF. Bis-camphorphosphabarrelene **7**, did form an active catalyst although yields and selectivity were quite low. This is most likely contributed to the less-than-desirable steric environment enforced upon the complex. More studies

could be done regarding the ability of this ligand to inhibit isomerization as well as the more difficult internal or tetra-substituted alkenes.

Organocatalysis—Baylis-Hillman Reaction

Although metal catalyzed reactions are much more common, asymmetric catalysis can also be performed using organocatalysts. Organocatalysis is included in the growing field of green chemistry. The characteristics of the phosphorus atom in the phosphabarrelene suggest that it could be an effective chiral organocatalyst (Figure 4.5). The nucleophilicity and the steric structure of phosphabarrelene is similar to the popular organocatalyst DABCO (1,4-diazabicyclo[2.2.2]octane). DABCO is used to catalyze the Baylis-Hillman reaction. Therefore we also seek to explore the possibility of phosphabarrelene **7** as a chiral organocatalyst for the asymmetric Baylis-Hillman reaction.

The Baylis-Hillman reaction, also known as the Morita-Baylis-Hillman (MBH) reaction, forms a new carbon-carbon bond between an alkene and carbon electrophile.^{49,50,52,53} Typical reagents include acrylic esters and vinyl ketones as the electron poor-alkene molecule while aldehydes are typically used as the electrophile.⁵³ The reaction is catalyzed by a nucleophilic heteroatom. The reaction traditionally uses a tertiary amine, most commonly done with DABCO.^{49,53}

Although, phosphorus compounds have been used has organocatalysts in the Baylis-Hillman reaction, there is no precedent in the literature for the use of a phosphabarrelene catalyst in this reaction.



Figure 4.4. DABCO and a phosphabarrelene molecule.

We attempted to use phosphabarrelene 7 as an asymmetric organocatalyst in the MBH reaction between 4-pyridinecarboxaldehyde and methylacrylate. The product has only one chiral center and no other structural isomers. The neat reaction mixture was stirred for an hour. GC-MS indicated that there was a very small amount of the desired product, **54**, m/z 193.1.



Scheme 4.2 Morita-Baylis-Hillman reaction catalyzed by phosphabarrelene, 7.

However, no amount of the material was able to be isolated. This original sample was tested for enantiomeric excess using chiral HPLC; however, the chromatogram gave a complex mixture of peaks and any enantiomers present were unable to be identified.

Subsequent attempts using what was believed to be pure phosphabarrelene turned out to be the oxidized phosphabarrelene **55** (Figure 4.6), which was later confirmed the mass, 480 m/z, observed in the GC-MS. Reversal of the oxidation process has been noted using trichlorosilane⁷² However, not enough of the oxidized material was recovered to attempt the reduction. These reactions appeared to turn into a viscous redbrown liquid over time. Chiral GC-MS was employed on these crude mixtures and showed only starting material.



Figure 4.5. Structure of the oxidized phosphabarrelene, 55.

Discussion

Although the phosphinine and phosphabarrelene ligands were proven to make active catalysts for hydroformylation, the lack of enantioselectivity and regioselectivity shows that they are not selective catalysts. Modifications to the original scaffold (as was presented in Chapter three) will hopefully elevate the selectiveness of this reaction. The poor yields at several steps of the ligand synthesis unfortunately make this particular scaffold less desirable. In order to be competitive and suitable for industrial use, chiral phosphorus ligands must be made more efficiently and catalyze more effectively.

CHAPTER FIVE

Materials and Methods

General Section

All reactions which used air or water sensitive materials were performed under a nitrogen atmosphere, unless otherwise noted. Reagents and solvents were generally purchased from Aldrich Chemical Company, Alfa Aesar or EMD. Hexanes, dichloromethane, ethyl acetate and THF were all distilled before using, the latter from potassium metal. Thin layer chromatography was performed on glass coated with 60 F254 silica. Column chromatography was performed using 260-400 mesh silica gel with modest air pressure. Radial chromatography was performed on Adsorbasil Plus silica coated onto a radial chromatotron plate. NMR spectra were obtained using a Varian 500 MHz NMR operating at 500 MHz for ¹H, 125 MHz for ¹³C, 470 MHz for ¹⁹F, and 202 MHz for ³¹P. NMR spectra are all referenced to TMS (0 ppm) for ¹H and the deuterated solvent for ¹³C. ¹⁹F NMR spectra were referenced to fluorobenzene (-113.26 ppm). ³¹P were referenced using an internal standard capillary tube filled with 85% H₃PO₄ (0 ppm). Gas chromatography-mass spectrometry was performed on a Thermo Scientific Focus GC with a DSQ II mass spectrometer. The GC-MS column was a DB-5MS by J&W Scientific (20 m x 0.18 mm, 0.18 micron film) with helium carrier and EI ionization. Gas Chromatography spectra were obtained from an HP 5890 Series II GC with a ZB-5HT INFERNO (20 m x 0.18 mm ID, carborane polydimethyl siloxane polymer) column and a Restek βDEXsa (2,3-di-acetoxy-6-O-tert-butyl dimethylsilyl beta cyclodextrin added into 14% cyanopropylphenyl/86% dimethyl polysiloxane), 30 m x 0.25 mm, chiral column. High Performance Liquid Chromatography (HPLC) was performed using a Beckman System Gold instrument with a Chiralcel OD-H column or Phenomenex Lux Cellulose 2. Ultraviolet (UV) spectroscopy was performed with a Shimadzu UV-2550 spectrometer. Circular Dichroism(CD) was performed using a JASCO 810 spectrometer over a wavelength range of 400 to 200 nm.

Azulene Diols

General. 4,6,8-trimethylazulene and 2,4,6,8-tetramethylazulene were synthesized according to the literature.^{15,59} Azulene was purchased from Alfa Aesar or made according to the literature.¹⁶ All commercial reagents were used as received. Shvo's catalyst⁹ was obtained from Strem Chemicals. The GC-MS temperature program unless otherwise noted: 140 °C, hold 2 minutes, then 10 °C per minute to 260 °C, hold 5 minutes. Any assignments made to numbered atoms refer to the numbering given in the X-ray crystal structures.

General procedure for HPLC separations and CD spectroscopy: Sample for HPLC was prepared by dissolving 3.8 mg of the racemic azulene diol into 1.5 mL of 10% IPA:Hex. Then 20 μ L of the solution was injected into the HPLC utilizing the 5 μ m Phenomenex Lux cellulose 2 column with the column pressure maximum at 2 atm and a flow rate of 1.0 mL/min at ambient temperature. The eluent solution gradient began at a concentration of 5% IPA:Hex and was increased to 20% IPA:Hex evenly over 20 minutes. UV spectra were gathered by taking the collected fractions and diluting them with methanol (MeOH). To obtain CD spectra the IPA:Hex was removed under vacuum and the compounds were dissolved in MeOH. First a blank of pure MeOH was run in a 1 mm quartz cuvette from 195 to 400 nm (CD parameters: sensitivity high (5 mdeg), data

pitch 0.1, scanning mode: continuous, scanning speed: 100 nm/min, response 0.25 sec, band width: 1 nm, accumulation 5, room temperature.) The Cotton Effect observed for the enantiomers was greatest between 300 nm and 400 nm.

Synthesis and separation of 1,1'-(4,6,8-trimethylazulene-1,3-divl)-bis-(2,2,2trifluoroethanol) diastereomers and enantiomers (5). Under a nitrogen atmosphere, 1,3bis-trifluoroacetyl-4,6,8-trimethylazulene (201 mg, 0.555 mmol) was dissolved in THF (2.25 mL) and ethanol (1 mL) in a round bottom flask with a stir bar. The flask was cooled to 0 °C and solid sodium borohydride (87 mg, 2.3 mmol, 4 equiv) was quickly added to the stirring solution. The solution was allowed to reach room temperature. Upon completion of reaction by TLC, brine (10 mL) was added to the mixture and the aqueous phase was extracted with ethyl acetate four times. The combined extracts were dried with MgSO₄, filtered and the solvent was removed by rotary evaporation to afford a purple solid (164 mg, 81%). GC-MS indicated only the two diastereomers: 10.30 minutes (58%) for the (RR)/(SS) diastereomer, and 10.67 minutes (42%) for the (RS = SR) diastereomer. TLC was run in two solvents: in 10% ethyl acetate in DCM, yielding spots at $R_f = 0.59$ (RR)/(SS) and 0.18 (RS = SR); and in 25% ethyl acetate in hexanes was observed $R_f = 0.22$ (RR)/(SS) and 0.13 (RS = SR). The diastereomers were separated by radial chromatography using a gradient from 6% ethyl acetate in hexanes to 20% ethyl acetate in hexanes to yield purple solids; racemic, $5_{RR/SS}$ (94 mg, 46% yield) and $5_{RS = SR}$ (60 mg, 30% yield). Recrystallization of the (RS = SR) diastereomer by vapor diffusion of diethyl ether into a DCM solution gave X-ray quality crystals of $1_{RS=SR} \cdot \frac{1}{3}$ DCM.

5_{**RR/SS**}: δ ¹H (500 MHz, d₆-acetone): 2.60 (3H, s, CH₃) 3.11 (6H, s, 2CH₃) 5.67 (2H, br s, 2 OH) 6.12 (2H, p, J = 7.0 Hz H9/10) 7.25 (2H, s, H5/7) 8.34 (1H, s, H2); δ ¹³C

(125 MHz, d₆-acetone): 27.86 (CH₃11/13) 28.98 (2 CH₃12) 68.56 (CH10/9) 123.25 (C14/15) 126.84 (2-CF₃) 131.95 (CH 5/7) 136.54 (C1/3) 137.96 (C6) 146.95 (CH2) 147.27 (C4/8); δ^{19} F (470 MHz, d₆-acetone): -74.76 (d, J_H = 7.05 Hz, CF₃); MS (EI): 366 (M⁺, 22%), 297 (100%), 165 (40%). The enantiomers were separated on a Phenomonex Lux Cellulose 2 chiral column; R_t **5**_{**RR/SS**}(fast) = 1.58, R_t **5**_{**RR/SS**}(slow) = 1.76. CD for each enantiomer: wavelength = 349.8 nm, molar absorptivity fast = 11.64, slow = -6.47

5_{RS = SR}: δ ¹H (500 MHz, d₆-acetone): 2.60 (3H, s, CH₃) 3.12 (6H, s 2CH₃) 5.55 (2H, d, J = 6.5 Hz, 2 OH) 6.14 (2H, m, J = 6.5, H9/10) 7.26 (2H, s, H5/7) 8.30 (1H, s, H2); δ ¹³C (125 MHz, d₆-acetone): 27.86 (CH₃11/13) 28.90 (2CH₃12) 68.58 (CH10/9) 123.23 (C14/15) 126.87 (2-CF₃) 132.02 (CH 5/7) 136.52 (C1/3) 137.84 (C6) 147.15 (CH2) 147.31 (C4/8); δ ¹⁹F (470 MHz, d₆-acetone): -74.57 (d, J_H = 7.1 Hz, 2CF₃); MS (EI): 366 (M⁺, 22%), 297 (100%), 165 (40%).

Synthesis and separation of 1,1'-(azulene-1,3-diyl)-bis-(2,2,2-trifluoroethanol) diastereomers and enantiomers (9). The procedure was the same as for compound 5, using 1,3-bis-trifluoroacetylazulene (162 mg, 0.506 mmol). Rotary evaporation yielded a purple solid (141 mg, 93%). GC-MS (program: 200° C hold 1 minute, at 5° C per minute to 230° C hold 1 minute) indicated two diastereomers, 7.80 minutes (48%) for the (RR)/(SS) diastereomer, and 7.85 minutes (52%) for the (R,S) diastereomer. TLC was run in 10% ethyl acetate in DCM yielding spots at $R_f = 0.39$ (RR)/(SS) and 0.17 (RS = SR), and in 25% ethyl acetate in hexanes, giving $R_f = 0.27$ (RR)/(SS) and 0.14 for the (RS = SR) diastereomers, resp. The diastereomers were separated by radial chromatography using 5% ethyl acetate in DCM to 15% ethyl acetate in DCM to yield two purple solids; **9**_{RR/SS} (72 mg, 51% yield) and **9**_{RS = SR} (69 mg, 49% yield). Recrystallization of the (RR)/(SS) diastereomer from hot 1:4 ethyl acetate:hexanes gave X-ray quality crystals.

 $9_{RR/SS}$: $\delta^{-1}H$ (500 MHz, d₆-acetone): 5.80 (2H, s, OH) 5.93 (2H, q, J = 7.00 Hz, H9/10) 7.43 (2H, dd, J = 10.0 Hz, H5/7) 7.83 (1H, t, J = 10.0 Hz, H6) 8.31 (1H, s, H2) 8.74 (2H, d, J = 10.00 Hz, H4/8); $\delta^{-13}C$ (125 MHz, d₆-acetone): 67.66 (CH9/10) 122.82 (C1/3) 125.48 (CH8/4) 126.57 (2-CF₃) 135.87 (CH7/5) 137.27 (C14/15) 139.10 (CH6) 139.88 (CH2); $\delta^{-19}F$ (470 MHz, d₆-acetone): -76.57 (d, J_H = 7.1 Hz, 2CF₃); MS (EI): 324 (M⁺, 26%), 255 (100%), 128 (92%). The enantiomers were separated on a Chiralcel OD-H chiral column; Rt $9_{RR/SS}$ (fast) = 4.7, Rt $9_{RR/SS}$ (slow) = 9.8. CD for each enantiomer: wavelength = 356.3 nm, molar absorptivity fast = 11.23, slow = -10.66

9_{**RS** = **SR**}: δ ¹H (500 MHz, d₆-acetone): 5.82 (2H, s, 2OH) 5.94 (2H, q, J =7.00 Hz, H9/10) 7.44 (2H, dd, J=10.0 Hz, H5/7) 7.85 (1H, t, J = 9.2 Hz, H6) 8.29 (1H, s, H2) 8.77 (2H, d, J = 9.8 Hz, H4/8); δ ¹³C (125 MHz, d₆-acetone): 67.66 (q, *J* = 32.2 Hz), 122.82 (s), 125.48 (s), 126.57 (q, *J* = 281.9 Hz), 135.87 (s), 137.27 (s), 139.10 (s), 139.88 (s); δ ¹⁹F (470 MHz, d₆-acetone): -75.53 (d, J_H = 6.6 Hz, 2 CF₃); MS (EI): 324 (M⁺, 28%), 255 (100%), 128 (92%).

Synthesis and separation of 5,7-dimethyl-4-(2,2,2-trifluoro-1-hydroxyethyl)-2-(trifluoromethyl)-1,2-dihydrocyclopenta[cd] azulen-2-ol) diastereomers and enantiomers (10). 1,3-bistrifluoroacetyl-4,6,8-trimethylazulene, (125 mg, 0.340 mmol) was dissolved in methanol (1 mL), treated with solid NaOH (100 mg, 2.50 mmol) and allowed to stir for 3 hours until cyclization was complete by TLC. Then a solution of 0.5 M NaBH₄ in 0.5 M NaOMe in methanol (1.5 mL, 0.75 mmol) was added and allowed to stir for 45 min until complete by TLC. Brine (10 mL) was added and the aqueous phase was extracted three times with ethyl acetate. The organic extracts were dried with MgSO₄, filtered and concentrated to yield a purple solid (115 mg, 91.8%). GC-MS indicated two diastereomers, 10.15 minutes (46%) for the (RR)/(SS) diastereomer, and 10.30 minutes (54%) for the (RS)/(SR) diastereomer. TLC was run in 10% ethyl acetate in DCM yielding spots at R_f = 0.63 (RR)/(SS) and 0.17 (RS)/(SR), and in 25% ethyl acetate in hexanes, giving R_f = 0.40 (RR)/(SS) and 0.13 for the (RS)/(SR) diastereomers, resp. The diastereomers were separated by radial chromatography, using pure DCM to 10% ethyl acetate in DCM to yield two purple solids; racemic, $10_{RR/SS}$ (43 mg, 34% yield) and $10_{RS/SR}$ (72 mg, 58% yield). Recrystallization of both diastereomers from hot 1:4 ethyl acetate:hexanes gave X-ray quality crystals of $10_{RR/SS} \cdot \frac{1}{3}$ H₂O and $10_{RS/SR} \cdot EtOAc$.

 $10_{RR/SS}$: δ^{-1} H (500 MHz, d₆-acetone): 2.67 (3H, s, CH₃) 3.01 (3H, s, CH₃) 3.80 (1H, d, J = 18.3 Hz, H11a) 4.18 (1H, d, J = 18.1 Hz, H11b) 5.62 (1H, d, J= 6.1 Hz, OH9) 5.74 (1H, s, OH10) 6.05 (1H, 5, J_F = 6.6 Hz, H9) 7.22 (2H, unresolved s, H5/7) 7.78 (1H, s, H2); δ^{-13} C (125 MHz, d₆-acetone): 26.39 (s), 29.07 (s), 51.38 (d, J = 1.0 Hz), 68.21 (q, J = 31.3 Hz), 78.65 (q, J = 30.9 Hz), 122.45 (s), 125.14 (d, J = 3.1 Hz), 126.67 (q, J = 282.2 Hz), 127.18 (q, J = 282.4 Hz), 127.25 (s), 127.31 (s), 127.75 (s), 128.01 (s), 131.12 (d, J = 7.9 Hz), 131.36 (s), 134.72 (d, J = 6.4 Hz), 146.94 (s), 149.27 (s), 151.32 (s), 151.97 (s); δ^{-19} F (470 MHz, d₆-acetone): 79.84 (3F, s, CF₃10), 75.25 (3F, d, J_H = 6.6 Hz, CF₃9) ; MS (EI): 364 (M⁺, 8%), 328 (70%), 259 (100%). The enantiomers were separated on a Chiralcel OD-H chiral column; Rt $10_{RR/SS}$ (fast) = 0.63, Rt $10_{RR/SS}$ (slow) = 1.75. CD for each enantiomer: wavelength = 349.7 nm, molar absorptivity fast = -7.45, slow = 8.60 $10_{RS/SR}$: δ^{-1} H (500 MHz, d₆-acetone): 2.67 (3H, s, CH₃) 3.01 (3H, s, CH₃) 3.80 (1H, d, J = 18.1 Hz, H11a) 4.20 (1H, d, J = 18.1 Hz, H11b) 5.63 (1H, d, J= 6.1 Hz, OH9) 5.84 (1H, s, OH10) 6.05 (1H, 5, J_F= 6.8 Hz, H9) 7.22 (2H, unresolved s, H5/7) 7.88 (1H, s, H2); δ^{-13} C (125 MHz, d₆-acetone): 26.36 (s), 29.07 (s), 51.28 (s), 68.26 (q, J = 31.2 Hz), 78.66 (q, J = 31.0 Hz), 122.44 (s), 126.71 (q, J = 317.0 Hz), 127.21 (s,), 127.40 (q, J = 282.3 Hz), 127.65 (s), 128.05 (s), 131.34 (s), 132.02 (s), 134.73 (s), 146.95 (s), 147.15 (s), 149.34 (s), 151.32 (s), 151.91 (s); δ^{-19} F (470 MHz, d₆-acetone): -79.83 (3F, s, CF₃10) -75.21 (3F, d J_H = 7.6 Hz, CF₃9) ; MS (EI): 364 (M⁺, 6%), 328 (74%), 259 (100%). The enantiomers were separated on a Chiralcel OD-H chiral column; Rt 10_{RR/SS} (fast) = 0.4, Rt 10_{RR/SS} (slow) = 1.3. CD for each enantiomer: wavelength = 345 nm, molar absorptivity fast = -2.83, slow = 4.17.

Synthesis and separation of 3,5,7-trimethyl-4-(2,2,2-trifluoro-1-hydroxyethyl)-2-(trifluoromethyl)-1,2-dihydrocyclopenta[cd] azulen-2-ol diastereomers and enantiomers (11). The procedure is the same as the procedure for compound 10, using starting material 1,3-bis-trifluoroacetyl-2,4,6,8-tetramethylazulene, (74 mg, 0.20 mmol). Rotary evaporation yielded a purple solid (73 mg, 97%). GC-MS indicated two diastereomers, 11.11 minutes (64%, 11_{RR/SS}) and 11.16 minutes (36%, 11_{RS/SR}). TLC was run using 10% ethyl acetate in DCM yielding spots at R_f = 0.58 (RR)/(SS) and 0.18 (RS)/(SR), and in 25% ethyl acetate in hexanes, giving R_f = 0.38 (RR)/(SS) and 0.17 (RS)/(SR). The diastereomers were separated by radial chromatography, using pure DCM to 30% ethyl acetate in DCM to yield purple solids; 11_{RR/SS} (37 mg, 49%) and 11_{RS/SR} (22 mg, 30%). Recrystallization of the (RR)/(SS) diastereomer from hot 1:4 ethyl acetate:hexanes gave X-ray quality crystals. **11**_{**RR/SS**}: δ¹H (500 MHz, d₆-acetone): 2.60 (3H, s, CH₃), 2.78 (3H, s, CH₃), 2.93 (3H, s, CH₃), 3.73 (1H, d, J = 17.9 Hz, H11a), 4.19 (1H, d J=17.99 Hz, H11b), 5.68 (1H, br s, H9), 5.70 (1H, s, OH10), 6.33 (1H, br s, OH9), 7.12 (1H, s, H5 or 7), 7.13 (1H, s, H5 or 7); δ¹³C (125 MHz, d₆-acetone): 15.06 (s), 27.29 (s), 28.77 (s), 52.15 (d, *J* = 1.1 Hz), 69.10 (q, *J* = 31.6 Hz), 79.83 (q, *J* = 30.9 Hz), 122.33 (s), 127.12 (q, *J* = 283.0 Hz), 127.52 (q, *J* = 283.0 Hz), 128.46 (s), 131.95 (s), 134.01 (s), 143.51 (s), 146.50 (s), 148.98 (s), 149.06 (s); δ¹⁹F (470 MHz, d₆-acetone): -78.20 (3F, s, CF₃10) -74.23 (3F, d, J_H = 6.6 Hz, CF₃9); MS (EI): 378 (M⁺, 4%), 342 (100%), 189 (68%). The enantiomers were separated on a Chiralcel OD-H chiral column; Rt **11**_{**RR/SS}(fast**) = 1.88, Rt **11**_{**RR/SS}(slow**) = 4.73. CD for each enantiomer: wavelength = 314 nm, molar absorptivity fast = -3.56, slow = 7.12</sub></sub>

11_{**RS/SR}: δ¹H (500 MHz, d₆-acetone): 2.60 (3H, s, CH₃) 2.79 (3H, s, CH₃) 2.96 (3H, s, CH₃) 3.73 (1H, d, J = 17.9 Hz, H11a) 4.21 (1H, d, J = 178.0 Hz, H11b) 5.63 (1H, s, OH10) 5.70 (1H, br s, H9) 6.32 (1H, br s, OH9) 7.13 (1H, s, H5 or 7) 7.14 (1H, s, H5 or 7); δ¹³C (125 MHz, d₆-acetone): 14.80 (s), 27.51 (s), 28.76 (s), 52.03 (d,** *J* **= 1.1 Hz), 68.91 (q,** *J* **= 31.8 Hz), 79.77 (q,** *J* **= 31.0 Hz), 122.36 (s), 124.45 (s), 127.13 (q,** *J* **= 282.9 Hz), 127.51 (q,** *J* **= 282.9 Hz), 128.76 (s), 131.95 (s), 134.04 (s), 143.18 (s), 146.47 (s), 146.65 (s), 148.98 (s), 149.03 (s); δ¹⁹F (470 MHz, d₆-acetone): -78.11 (3F, s, CF₃10) - 74.10 (3F, d, J_H = 3.9 Hz, CF₃9); MS (EI): 378 (M⁺, 6%), 342 (100%), 189 (62%). The enantiomers were separated on a Chiralcel OD-H chiral column; Rt 11**_{**RS/SR}(fast**) = 1.87, Rt **11**_{**RS/SR}(slow**) = 11.15. CD for each enantiomer: wavelength = 339.7 nm, molar absorptivity fast = -9.67, slow = 10.70</sub></sub></sub>

Phosphabarrelene Derivatives

General. All commercial reagents were used as received. Biscamphorphosphinine **6** was synthesized according to the literature.⁴² All THF was freshly distilled from molten potassium. GC-MS program unless otherwise stated: 40 °C, hold 2 minutes, at 25 °C per minute to 300 °C, hold 5 minutes.

Synthesis of bromobenzylidene camphor (1R, 4S, Z)-3-(bromo(phenyl)methylene)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one **32**. 3.9 mL (40 mmol) PCl₃ was added to 2.05 g (8.02 mmol) benzoyl camphor **28**, and the solution refluxed for 12 hours. The mixture was then poured over ice and the aqueous layer was neutralized with K₂CO₃ then extracted 3 x 15 mL of ethyl acetate and washed with brine. The solvent was removed via rotary evaporation to afford a pale yellow oil, 1.79 g of bromobenzylidene camphor, 70.3% yield. GC-MS indicated product at 9.73 min (E isomer) 10.1 min (Z isomer), MS 318.1 m/z.

Synthesis of chlorobenzylidene camphor 29. 2.55 mL (35.1 mmol) SOCl₂ was added to 3.0 g (12 mmol) benzoyl camphor 28, and the solution refluxed for 24 hours. The mixture was then poured over ice and the aqueous layer was neutralized with K_2CO_3 then extracted 3 x 15 mL of ethyl acetate and washed with brine. The solvent was removed via rotary evaporation to afford a pale yellow oil, 2.24 g, of chlorobenzylidene camphor, 72.8% yield. GC-MS indicated product at 7.3 min (E isomer) 7.4 min ('other'isomer) and 7.8 min (Z isomer), MS 274.

Synthesis of Bis-camphorphosphabarrelene ((5s, 10s)-4, 13, 14, 14, 18, 18hexamethyl-10-phenyl-1, 2, 3, 4, 10, 13, 14, 15, 16, 17-decahydro-5, 10-[2]bicyclo-1, 4methanoacridophosphine).7 Route a) To an oven dried flask with 378 mg (0.972 mmole) bis-camphorphosphinine 6, and 101 mg (4.16 mmol) Mg in 8 mL of dry THF, 0.40 mL (2.7 mmol) of o-fluoro-iodobenzene was added slowly. After stirring for 4 hours the solution turned a cloudy light green color. 20 mL of water was added and the organic product was extracted 4 times with 25 mL of ethyl acetate. The organic layer was washed with brine and dried with MgSO₄. The solvent was removed with rotary evaporation. TLC in 20% EtOAc in hexanes have two spots $R_f = 0.4$ and 0.49. The product was isolated using column chromatography, run at a gradient of 10% to 40% EtOAc in hexanes. 68 mg (14.7% yield) of the solid white product was isolated. Route b) Bis-camphorphosphinine 6 (446.8 mg, 1.150 mmol) was added to isoamylnitrite (0.330 mL, 2.52 mmol) in 30 mL of dry DME. This mixture was heated to reflux. Anthranilic acid (382.8 mg, 2.79 mmol) dissolved in 15 mL of dry DME and was added via syringe over 30 minutes. The refluxing solution immediately turned a pale green upon the addition which continued to reflux for an hour. Upon cooling to room temperature the solvent was removed in vaccuo. GC-MS (150 °C hold 2 minutes, at 25 °C to 340 °C hold 5 minutes) showed product at 8.29 minutes and TLC was performed in 20% EtOAc in hexanes ($R_f = 0.41$). Flash chromatography was used to purify the product using hexanes to 20% EtOAc in hexanes to yield 0.0279 g (5.21% yield) of the white solid, bis-camphorphosphabarrelene 7.

δ¹H (500 MHz, CDCl₃): 7.66 (1H, s), 7.65 (1H, s), 7.54 (1H, m), 7.50 (2H, m), 7.38 (2H, m), 6.92 (1H, t, *J* = 7.4 Hz), 6.87 (1H, t, *J* = 7.3 Hz), 3.13 (1H, d *J* = 3.6 Hz), 1.77 (1H, d, *J* = 3.09), 1.53 (2H, m), 1.35 (2H, m), 1.27 (2H, m), 1.21 (3H, s), 1.16 (3H, s), 0.73 (3H, s), 0.71 (3H, s), 0.63 (3H, s), 0.47 (3H, s), 0.07 (1H, ddd, *J* = 11.9, 9.1, 3.1), -0.19 (1H, ddd, *J* = 11.9, 9.0, 3.1); δ¹³C (125 MHz, CDCl₃): 164.35 (d, *J* = 3.2 Hz), 162.57 (d, J = 5.9 Hz), 154.19 (d, J = 25.4 Hz), 150.86 (d, J = 4.8 Hz), 145.22 (d, J = 11.7 Hz), 138.39, 129.79 (d, J = 37.4 Hz), 126.89, 125.21, 123.97 (d, J = 1.6 Hz), 122.04 (d, J = 12.7 Hz), 121.99, 63.67, 58.25 (d, J = 3.0 Hz), 58.12 (d, J = 16.6 Hz), 57.99 (d, J = 1.6 Hz), 57.81 (d, J = 16.5 Hz), 57.29 (d, J = 3.1 Hz), 56.86 (d, J = 1.8 Hz), 33.16 (d, J = 3.5 Hz), 30.39, 25.89, 25.42, 24.46, 21.34, 20.93, 20.27 (d, J = 2.1 Hz), 20.22 (d, J = 2.1 Hz), 16.17, 15.03 (d, J = 4.3 Hz), 14.84 (d, J = 3.9 Hz); δ^{31} P (MHz, CDCl₃): 13.00 . MS (EI): 464.5 (M⁺, 80 %), 311.3 (100%), 109.1 (75%).

Synthesis of trifluoroacetylcamphor (1R,4S,Z)-1,7,7-trimethyl-3-(2,2,2-trifluoro-1-hydroxyethylidene)bicyclo[2.2.1]heptan-2-one **33**. NaH (2.60 g of 57-63% by weight suspension in mineral oil, 54.1 mmol) was refluxed with camphor (4.51 g, 29.6 mmol) in DME (50 mL) for 1 hour. Ethyl-2,2,2-trifluoroacetate (10.71 mL, 90.00 mmol) was added over 15 minutes via syringe. The mixture was allowed to reflux for 12 hours. The mixture was then poured over ice and extracted with 3 x 25 mL aliquots of DCM. The organic phase was dried with MgSO₄ and the solvent was removed by rotary evaporation. The pale orange liquid was shown by GC-MS to contain camphor, product peak at 6.04 min, 248.1 m/z. The product was purified by Kegulrohr distillation to give an oil.

Synthesis of chlorotrifluoroethylidene camphor ((1R,4S,Z)-3-(1-chloro-2,2,2trifluoroethylidene)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one, **35**. PCl₃ (15.2 mL, 0.174 mol) was added via syringe to the crude mixture of trifluoroacetylcamphor **33** (12.0 g, 48.3 mmol—if entirely pure). The solution was allowed to reflux for 18 hours. The mixture was then poured over ice and the aqueous layer was neutralized with K₂CO₃ then extracted 3 x 15 mL of ethyl acetate and washed with brine. The solvent was removed
via rotary evaporation to afford a clear orange oil. The GC-MS of the crude reaction indicated the presence of camphor and trifluoroacetylcamphor, 6.38 minutes, 266.1 m/z.

Synthesis of bromotrifluoromethylidene camphor ((1R,4S,Z)-3-(1-bromo-2,2,2trifluoroethylidene)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one, **36**. PBr₃ (5.0 mL, 53 mmol) was added via syringe to trifluoroacetylcamphor **33** (2.0 g, 8.1 mmol). The solution was allowed to reflux for 48 hours. The mixture was then poured over ice and the aqueous layer was neutralized with K_2CO_3 then extracted 3 x 25 mL of ethyl acetate and washed with brine. The solvent was removed via rotary evaporation to afford a viscous dark orange oil. The GC-MS of the crude reaction indicated the presence of camphor, trifluoroacetylcamphor and product at 7.25 min, 309.9 m/z.

Synthesis of trifluoromethyl enedione ((1R,4S,E)-1,7,7-trimethyl-3-(phenyl((1R,4R)-4,7,7-trimethyl-3-oxobicyclo[2.2.1]heptan-2-

yl)methylene)bicyclo[2.2.1]heptan-2-one) **37**. After removal, using hexanes, of mineral oil from a suspension of KH (576 mg, 33% in mineral oil, 4.75 mmol), 5 mL of hexanes and camphor (285 mg, 1.88 mmol) in 10 mL of hexanes was added via cannula. The mixture was allowed to reflux for 2 hours. To the light brown solution, chlorotrifluoromethylidene camphor **35** (50 mg, 1.9 mmol) dissolved in 10 mL hexanes was added via syringe. The solution was allowed to reflux for 24 hours. NH₄Cl was added dropwise to quench the reaction. 1 M HCl (5 mL) was used to acidify the aqueous layer to pH 1. Diethyl ether (3 x 15 mL) was used to extract the desired product. The organic layer was dried with MgSO₄ and the solvent removed via rotary evaporation. Keugelrhor distillation was done under house vacuum at 130°C to yield 239 mg of an oily

94

enedione product, 57.0% yield. However, GC-MS indicated product at 10.03 min, M⁺ 382.3 m/z.

Synthesis of dimethylaminobenzoylcamphor: ((1R,4S,Z)-3-((4-(dimethylamino)phenyl)(hydroxy)methylene)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one). **34** NaH (12.9 g 57-63% by weight suspension in mineral oil, 0.269 mol) was refluxed with camphor (9.12 g, 59.9 mmol) in DME (50 mL) for 1 hour. Ethyl-4dimethylaminobenzoate (34.47 g, 0.1784 mol) was added over 15 minutes via syringe. The mixture was allowed to reflux for 12 hours. The mixture was then poured over ice and extracted with 3x25 mL aliquots of DCM. The organic phase was dried with MgSO₄ and the solvent was removed by rotary evaporation. GC-MS of the solid showed product at 12.96 minutes, 299.2 m/z. Recrystallization done with hexanes afforded 7.92 g (44% yield) of pale yellow crystals.

δ¹H (500 MHz, CDCl₃): 7.82 (d, *J* = 9.1 Hz, 1H), 6.64 (d, *J* = 9.1 Hz, 1H), 4.16 (dd, *J* = 4.8, 1.4 Hz, 1H), 3.05 (s, 6H), 2.46 (s, 1H), 1.70 (m, 3H), 1.41 (m, 1H), 1.01 (s, 3H), 0.99, (s, 3H), 0.96 (s, 3H). δ¹³C (125 MHz, CDCl₃): 213.79, 194.90, 153.51, 130.59, 124.58, 110.61, 58.75, 58.31, 48.89, 46.27, 39.98, 29.00, 22.15, 19.70, 19.04, 9.69. MS (EI): 299.2 (M⁺, 25 %), 148.1 (100%), 121.1 (55%).

Synthesis of chloro-4-(dimethylamino)benzylidene camphor: ((1R,4S,Z)-3-(chloro(4-(dimethylamino)phenyl)methylene)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one), **38**. To dimethylaminobenzoylcamphor **34** (100 mg, 0.334 mmol), PCl₃ (0.087 mL, 1.0 mmol) was added via syringe. The solution was allowed to reflux for 18 hours. The mixture was then poured over ice and the aqueous layer was neutralized with K₂CO₃ then extracted 3 x 15 mL of ethyl acetate and washed with brine. The solvent was removed via rotary evaporation. TLC was run in 50:50 ethyl actetate:hexanes indicating unwanted material at the baseline with the product $R_f = 0.67$. GC-MS of the oil showed product at 12.57 minutes, 317.2 m/z. Radial chromatography using 30% ethyl acetate in hexanes afforded 67 mg, (63.9 % yield) of a light yellow solid.

δ ¹H (500 MHz, CDCl₃): 7.42 (d, *J* = 9.0 Hz, 1H), 6.60 (d, *J* = 9.0 Hz, 1H), 2.96 (s, 6H), 2.04 (m, 1H), 1.68 (m, 2H), 1.58 (m, 1H), 1.43 (m, 1H), 0.99 (s, 3H), 0.94 (s, 3H), 0.88 (s, 3H). (¹³C NMR spectrum assignments were difficult to determine because of the presence of both (*Z*) and (E) diastereomers, the spectrum is shown in Appendix A) MS (EI): 317.2 (M⁺, 60%), 254.2 (100%), 238.2 (20%).

Synthesis of bromo-4-(dimethylamino)benzylidene camphor: ((1R,4S,Z)-3-(bromo(4-(dimethylamino)phenyl)methylene)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one), **39**. Following the procedure for compound **38** (above) using dimethylaminobenzoylcamphor **34** (100 mg, 0.334 mmol), and PBr₃ (0.097 mL, 1.0 mmol). GC-MS of the crude reaction mixture (150 °C hold 2 minutes, at 25 °C per

minute to 340 °C hold 5 minutes) indicated product at 7.72 mins, 361 m/z. Radial

chromatography afforded 96.3 mg of a light yellow oil (80.5% yield).

 δ^{1} H (500 MHz, CDCl₃): 7.36 (d, J = 8.6 Hz, 1H), 6.63 (d, J = 8.8 Hz, 1H). 3.01 (s, 6H), 2.05-1.48 (m, 5H), 1.02-0.82 (m, 9H). (¹³C NMR spectrum assignments were difficult to determine because of the presence of both (Z) and (E) diastereomers, the spectrum is shown in Appendix A) MS (EI): 361.1 (M⁺, 20%), 282.1 (100%), 254.5 (45%).

Synthesis of dimethylaminobenzyl enedione ((1R,4S,E)-3-((4-(dimethylamino)phenyl)((1R,4R)-4,7,7-trimethyl-3-oxobicyclo[2.2.1]heptan-2- *yl)methylene)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one)* **40**. To a solution of KH (5.4 g, 30% in mineral oil, 0.041 mol) in hexanes, camphor (4.2 g, 0.026 mol) in 20 mL of hexanes was added via cannula. The mixture was allowed to reflux for 2 hours. To the light brown solution the chloro(dimethylamino)benzylidenecamphor **38** (4.2 g, 0.013 mol) was added via syringe. The solution was allowed to reflux for 24 hours. NH₄Cl was added drop wise to quench the reaction. 1 M HCl (15 mL) was used to neutralize the aqueous layer to pH 7. Diethyl ether (3 x 15 mL) was used to extract the desired product. The organic layer was dried with MgSO₄ and the solvent removed via rotary evaporation. GC-MS indicated product at 15.27 minutes, 433.3 m/z.

Synthesis of bis-camphorpyridine (1S,4R,5R,8S)-4,5,11,11,12,12-hexamethyl-9-phenyl-1,2,3,4,5,6,7,8-octahydro-1,4:5,8-dimethanoacridine, **43**. To a flask with 0.1 g (0.2 mmol) bis-camphorpyrylium **31**, 10 mL of acetonitrile, 10 mL of ethanol and 0.1 mL of aqueous ammonium chloride were added. The solution refluxed for 20 minutes after which 0.03 mL of TEA was added. The yellow solution continued to reflux for 1 hour, then cooled to room temperature before 15 mL of DI water and 15 mL DCM were added. The organic layer was separated and washed with brine, then dried with MgSO₄. Rotary evaporation was used to remove the solvent to give a clear oil. GC-MS of the oil indicated the presence of product at 15.27 min, 371.3 m/z.

Asymmetric Catalysis

General procedure for hydroformylation reactions. Rh(CO)₂acac (8.0 mg, 0.020 mmol) was weighed into a freshly dried flask followed by the addition of the phosphorus ligand, styrene (520.7 mg 5.000 mmol), decane (355.7 mg, 2.500 mmol), and 6 mL of

97

toluene. The Parr reactor was assembled and air was removed from the system using house vacuum. The reaction mixture was pulled into the reaction via cannula followed by the addition of 4 mL of toluene to insure all contents of the mixture had been washed into the reactor. The system was flushed twice with 10 bar of $1:1 \text{ H}_2/\text{CO}$, removed each time with house vacuum. Moderate mechanical stirring began and the heating mantle was set to the desired temperature. Upon arriving at the desired reaction time, the reaction was cooled, vented, and removed from the apparatus by disassembling the reactor. GC-MS (both chiral and achiral) were taken of the crude reaction mixture.

Morita-Baylis-Hillman reaction procedure (**54**).¹⁰⁶ To a 3 mL conical vial 2.7 mg (0.0050 mmol) of phosphabarrelene **7**, 12.6 mg (0.118 mmol) of freshly distilled 4pyridine carboxaldehyde was weighed and 10.0 mg (0.12 mmol) of methylacrylate were added. The reaction mixture sat for 45 minutes until the solution became a deep red viscous solution. The solution was suspended in 5 mL of DCM and the solid was isolated by filtration and recrystallized from MeOH. GC-MS indicated the presence of catalyst, 12.77 minutes, 464 m/z, and product **54** at 7.74 minutes, 193.1 m/z. APPENDICES

APENDIX A:

Selected NMR Spectra

Figure A.2.1. ¹ H NMR (500 MHz CDCl ₃ ref. to TMS) of compound $5_{RS} = \mathbf{sR}$	102
Figure A.2.2. ¹³ C NMR (125.7 MHz ref. to d_6 -acetone) of compound $5_{RS = SR}$	103
Figure A.2.3. ¹⁹ F NMR (470.27 MHz d ₆ -acetone ref. to fluorobenzene) of compound $5_{RS = SR}$	104
Figure A.2.4. ¹ H NMR (500 MHz d_6 -acetone ref. to TMS) of compound $5_{RR/SS}$	105
Figure A.2.5. ¹³ C NMR (125.7 MHz ref. to d_6 -acetone) of compound $S_{RR/SS}$	106
Figure A.2.6. ¹⁹ F NMR (470.27 MHz d ₆ -acetone ref. to fluorobenzene) of compound 5 _{RR/SS}	107
Figure A.2.7. ¹ H NMR (500 MHz d ₆ -acetone ref. to TMS) of compound $9_{RS = SR}$	108
Figure A.2.8. ¹³ C NMR (125.7 MHz ref to d_6 -acetone) of compound $9_{RS = SR}$	109
Figure A.2.9. ¹⁹ F NMR (470.27 MHz d ₆ -acetone ref. to fluorobenzene) of compound $9_{RS = SR}$.	110
Figure A.2.10. ¹ H NMR (500 MHz d ₆ -acetone ref. to TMS) of compound $9_{RR/SS}$	111
Figure A.2.11. ¹³ C NMR (125.7 MHz ref. to d_6 -acetone) of compound $9_{RR/SS}$	112
Figure A.2.12 ¹⁹ F NMR (470.27 MHz d ₆ -acetone ref externally with fluorobenzene) of compound $9_{RR/SS}$	113
Figure A.2.13. ¹ H NMR (500 MHz d_6 -acetone ref. to TMS) of compound $10_{RS/SR}$	114
Figure A.2.14. ¹³ C NMR (125.7 MHz ref to d_6 -acetone) of compound $10_{RS/SR}$	115
Figure A.2.15 ¹⁹ F NMR (470.27 MHz d_6 -acetone ref. to fluorobenzene) of compound $10_{RS/SR}$.	116
Figure A.2.16. ¹ H NMR 500 MHz d ₆ -acetone ref. to TMS) of compound $10_{RR/SS}$	117
Figure A.2.17. ¹³ C NMR (125.7 MHz ref. to d_6 -acetone) of compound $10_{RR/SS}$	118
Figure A.2.18. ¹⁹ F NMR (470.27 MHz d ₆ -acetone ref. to fluorobenzene) of compound 10 _{RR/SS}	119

Figure A.2.19. ¹ H NMR (500 MHz d_6 -acetone ref. to TMS) of compound $11_{RS/SR}$	120
Figure A.2.20. ¹³ C NMR (125.7 MHz ref. to d_6 -acetone) of compound $11_{RS/SR}$	121
Figure A.2.21. ¹⁹ F NMR (470.27 MHz d ₆ -acetone ref. to fluorobenzene) of compound 11 _{RS/SR}	122
Figure A.2.22. ¹ H NMR (500 MHz d_6 -acetone ref. to TMS) of compound $11_{RR/SS}$	123
Figure A.2.23. ¹³ C NMR (125.7 MHz ref. to d_6 -acetone) of compound $11_{RR/SS}$	124
Figure A.2.24. ¹⁹ F NMR (470.27 MHz d ₆ -acetone ref to fluorobenzene) of compound 11 _{RR/SS}	125
Figure A.3.1. ¹ H NMR (500 MHz CDCl ₃ ref to TMS) of compound 7	126
Figure A.3.2. ¹³ C NMR (125.7 MHz ref to CDCl ₃) of compound 7.	127
Figure A.3.3. ³¹ P NMR (MHz CDCl ₃ ref toH ₃ PO ₄) of compound 7.	128
Figure A.3.4. ¹ H NMR (500 MHz CDCl ₃ ref to TMS) of compound 34.	129
Figure A.3.5. ¹³ C NMR (125.7 MHz ref to CDCl ₃) of compound 34.	130
Figure A.3.6. ¹ H NMR (500 MHz CDCl ₃ ref to TMS) of compound 38.	131
Figure A.3.7. ¹³ C NMR (125.7 MHz ref to CDCl ₃) of compound 38.	132
Figure A.3.8. ¹ H NMR (500 MHz ref to CDCl ₃) of compound 39.	133
Figure A.3.9. ¹³ C NMR (125.7 MHz ref to CDCl ₃) of compound 39.	134































Figure A.2.10. $^1\mathrm{H}$ NMR (500 MHz d_6-acetone ref. to TMS) of compound $9_{\mathrm{RR/SS}}$



























Figure A.2.18. $^{19}\mathrm{F}$ NMR (470.27 MHz d₆-acetone ref. to fluorobenzene) of compound $10_{\mathrm{RR/SS}}$

















Figure A.2.23. 13 C NMR (125.7 MHz ref. to d₆-acetone) of compound $11_{\rm RR/SS}$







Figure A.3.1. ¹H NMR (500 MHz CDCl₃ ref to TMS) of compound 7.




























APPENDIX B

Select Spectral Data from GC-MS, HPLC, and CD

Figure B.2.1. Mass spectrum for diastereomer 5 _{RR/SS}	. 137
Figure B.2.2. Mass spectrum for diastereomer $5_{\mathbf{RS} = \mathbf{SR}}$. 138
Figure B.2.3. Mass spectrum for diastereomer 9 _{RR/SS}	. 139
Figure B.2.4. Mass spectrum for diastereomer 9 _{RS/SR}	. 140
Figure B.2.5. Mass spectrum for diastereomer 10 _{RR/SS}	. 141
Figure B.2.6. Mass spectrum for diastereomer 10 _{RS/SR}	. 142
Figure B.2.7. Mass spectrum for diastereomer $11_{RR/SS}$. 143
Figure B.2.8. Mass spectrum for diastereomer 11 _{RS/SR}	. 144
Figure B.3.1. Mass spectrum for phosphabarrelene 7	. 145
Figure B.3.2. Mass spectrum for trifluoroacetylcamphor, 33.	. 146
Figure B.3.3. Mass spectrum for chlorotrifluoromethylidenecamphor, 35	. 147
Figure B.3.4. Mass spectrum for bromotrifluoromethylidenecamphor, 36	. 148
Figure B.3.5. Mass spectrum for dimethylaminobenzoylcamphor, 34	. 149
Figure B.3.7. Mass spectrum for dimethylaminobromobenzylidenecamphor, 39	. 151
Figure B.3.8. Mass spectrum for oxidized phosphabarrelene, 55	. 152
Figure B.3.9. Mass spectrum for bis-camphorpyridine, 43	. 153
Figure B.4.1. GC (MS) of MBH reaction catalyzed by phosphabarrelene	. 154
Figure B.4.2. MBH product catalyzed by phosphabarrelene, 54	. 155
Figure B.2.9. HPLC for compound azulene diastereomer $9_{RS/SR}$ on the Lux column	. 156

Figure B.2.10. HPLC for compound trimethylazulene diastereomer 5 _{RS/SR} on the Lux column	156
Figure B.2.11. CD spectrum for the enantiomers of $5_{RS/SR}$	
Figure B.2.12. CD spectrum for the enantiomers of $9_{RS/SR}$	
Figure B.2.13. CD spectrum for the enantiomers of $10_{RS/SR}$	
Figure B.2.14. CD spectrum for the enantiomers of $10_{RR/SS}$	
Figure B.2.15. CD spectrum for the enantiomers of $11_{RS/SR}$	
Figure B.2.15. CD spectrum for the enantiomers of $11_{RR/SS}$	159







Figure B.2.2. Mass spectrum for diastereomer **5**_{RS = SR}.



Figure B.2.3. Mass spectrum for diastereomer 9_{RR/SS}.



Figure B.2.4. Mass spectrum for diastereomer 9_{RS/SR}.







Figure B.2.6. Mass spectrum for diastereomer 10_{RS/SR}.











Figure B.3.1. Mass spectrum for phosphabarrelene 7_{-}



























Figure B.3.8. Mass spectrum for oxidized phosphabarrelene, 55







Figure B.4.1. GC (MS) of MBH reaction catalyzed by phosphabarrelene.







Figure B.2.9. HPLC for compound azulene diastereomer $9_{RS/SR}$ on the Lux column using 10% IPA in hexanes to 20% IPA in hexanes over 22 minutes.



Figure B.2.10. HPLC for compound trimethylazulene diastereomer $5_{RS/SR}$ on the Lux column using %20 IPA in hexanes.



Figure B.2.11. CD spectrum for the enantiomers of $5_{RS/SR}$ named based on their elution time through the HPLC.



Figure B.2.12. CD spectrum for the enantiomers of $9_{RS/SR}$ named based on their elution time through the HPLC.



Figure B.2.13. CD spectrum for the enantiomers of $10_{RS/SR}$ named based on their elution time through the HPLC.



Figure B.2.14. CD spectrum for the enantiomers of $10_{RR/SS}$ named based on their elution time through the HPLC.



Figure B.2.15. CD spectrum for the enantiomers of $11_{RS/SR}$ named based on their elution time through the HPLC.



Figure B.2.15. CD spectrum for the enantiomers of $11_{RR/SS}$ named based on their elution time through the HPLC.

APPENDIX C

Tables of X-ray Crystallographic L

Table C.2.1. Summary of X-ray crystallographic data.	163
Table C.2.2. Crystal data and structure refinement for $5_{RS/SR}$	164
Table C.2.3. Atomic coordinates ($x \ 10^4$) and equivalent isotropic displacement parameters (Å ² x 10^3) for 5 _{RS/SR} .	165
Table C.2.4. Bond lengths [Å] and angles [°] for 5 _{RS/SR} .	168
Table C.2.5. Anisotropic displacement parameters ($Å^2 x \ 10^3$) for 5 _{RS/SR}	174
Table C.2.6. Hydrogen bonds for $5_{\mathbf{RS/SR}}$ [Å and °]	177
Table C.2.7. Crystal data and structure refinement for 10_{RR/SS}	178
Table C.2.8. Atomic coordinates ($x \ 10^4$) and equivalent isotropic displacement parameters (Å ² x 10 ³) for 10 _{RR/SS} .	179
Table C.2.9. Bond lengths [Å] and angles [°] for $10_{RR/SS}$.	182
Table C.2.10. Anisotropic displacement parameters $(Å^2 x \ 10^3)$ for $10_{RR/SS}$	186
Table C.2.11. Hydrogen bonds for $10_{RR/SS}$ [Å and °]	189
Table C.2.12. Crystal data and structure refinement for $9_{RR/SS}$.	190
Table C.2.13. Atomic coordinates ($x \ 10^4$) and equivalent isotropic displacement parameters (Å ² x 10 ³) for 9 _{RR/SS} .	191
Table C.2.14. Bond lengths [Å] and angles [°] for $9_{RR/SS}$	192
Table C.2.15. Anisotropic displacement parameters ($Å^2 x \ 10^3$) for 9 _{RR/SS}	193
Table C.2.16. Hydrogen bonds for 9_{RR/SS} [Å and °]	194
Table C.2.17. Crystal data and structure refinement for 10_{RS/SR}	195
Table C.2.18. Atomic coordinates ($x \ 10^4$) and equivalent isotropic displacement parameters (Å ² x 10 ³) for 10 _{RS/SR} .	196
Table C.2.19. Bond lengths [Å] and angles [°] for 10 _{RS/SR}	197

Table C.2.20.	Anisotropic displacement parameters $(Å^2 x \ 10^3)$ for $10_{RS/SR}$	199
Table C.2.21.	Hydrogen bonds for $10_{RS/SR}$ [Å and °]	200
Table C.2.22.	Crystal data and structure refinement for 11 _{RR/SS} .	201
Table C.2.23. parameter	Atomic coordinates ($x \ 10^4$) and equivalent isotropic displacement rs (Å ² x 10 ³) for 11 _{RR/SS} .	202
Table C.2.24.	Bond lengths [Å] and angles [°] for $11_{RR/SS}$	203
Table C.2.25.	Anisotropic displacement parameters ($Å^2 x \ 10^3$) for $11_{\mathbf{RR/SS}}$	205

General information: Data was collected at 110 K on a Bruker X8 Apex using Mo-K radiation ($\lambda = 0.71073$ Å). All structures were solved by direct methods after correction of the data using SADABS.^{13, 14} Details of the crystal parameters, data collection, and refinement are summarized in supplementary information. The molecular structures of the compounds are displayed in Figure 2. Summary of selected bond lengths, angles, and interatomic distances are given in supplementary information.

All the data were processed using the Bruker AXS SHELXTL software, version 6.10.¹⁵ All non-hydrogen atoms were refined anisotropically and hydrogen atoms were placed in calculated positions.

The crystal structure of compound $\mathbf{5}_{RS=SR}$ contained one CH₂Cl₂ molecule and three independent molecules in the asymmetric unit. Compound $\mathbf{10}_{RR/SS}$ contained one molecule of water and three independent molecules in the asymmetric unit, the O-H bond lengths for the water molecule were restrained to 0.90 Å. The crystal structure of $\mathbf{10}_{RS/SR}$ contained one molecule of ethyl acetate which is H-bonded to the O1 hydroxy group. Compound $\mathbf{10}_{RR/SS}$ was twinned and was refined using the TWIN protocol in SHELX resulting in a batch scale factor of 0.915.

Crystallographic data for the structures $5_{RS=SR}$, $9_{RR/SS}$, $10_{RR/SS}$, $10_{RS/SR}$ and $11_{RR/SS}$ in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 943706, 943708, 943707, 943709, and 943710, respectively. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336033 or email:deposit@ccdc.cam.ac.uk). Abbreviated crystallographic data are given below.

162

Compound	$5_{\text{RS/SR}} \cdot \frac{1}{3}$ CH ₂ Cl ₂	9 _{RR/SS} .	$10_{\rm RR/SS} \bullet \frac{1}{3}$ H ₂ O	10 _{RS/SR} • EtOAc	11 _{RR/SS} .
Formula	$C_{52}H_{50}Cl_2F_{18}O_6$	$C_{14}H_{10}F_6O_2$	C ₅₁ H ₄₄ F ₁₈ O ₇	$C_{19}H_{18}F_6O_3$	$C_{18}H_{16}F_6O_2$
Geometry	Monoclinic,	Triclinic,	Monoclinic,	Monoclinic,	Triclinic,
Geometry	Cc	P-1	Cc	C2/c	P-1
<i>a</i> (Å)	16.081(5)	8.0864(14)	11.072(3)	19.2572(16)	9.8755(7)
<i>b</i> (Å)	18.297(6)	9.1407(17)	23.071(7)	14.1615(12)	9.8911(4)
<i>c</i> (Å)	17.581(5)	9.6053(16)	19.035(4)	14.1880(11)	10.0443(4)
α	90°	71.603(4)°	90°	90°	117.467(2)°
β	95.390(17)	67.915(3)°	99.011(5)°	112.1980(10)°	94.555(3)°
γ	90°	73.695(3)°	90°	90°	110.150(3)°
V (Å ³⁾	5150(3)	613.56(19)	4802(2)	3582.4(5)	783.09(7)
Ζ	4	2	4	8	2
T (K)	110	110	110	110	110
μ (mm ⁻¹)	0.241	0.176	0.147	0.142	0.151
$\rho (Mg/m^3)$	1.527	1.755	1.536	1.514	1.604
GOF on F^2	1.004	1.029	1.000	1.074	1.070
R	0.0461	0.0277	0.0516	0.0695	0.0476
R_{w}	0.0837	0.0704	0.1208	0.1937	0.1305
I _{obs}	[I>2σ(I)]	[I>2 σ (I)]	[I>2 σ (I)]	[I>2 σ (I)]	[I>2 σ (I)]

Table C.2.1. Summary of X-ray crystallographic data.

Identification code	cg17	
Empirical formula	C52 H50 Cl2 F18 O6	
Formula weight	1183.82	
Temperature	110(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	Cc	
Unit cell dimensions	a = 16.081(5) Å	α=90°
	b = 18.297(6) Å	β=95.390(17)°.
	c = 17.581(5) Å	$\gamma = 90^{\circ}$.
Volume	5150(3) Å ³	
Ζ	4	
Density (calculated)	1.527 Mg/m ³	
Absorption coefficient	0.241 mm ⁻¹	
F(000)	2424	
Crystal size	0.32 x 0.16 x 0.15 mm ³	
Theta range for data collection	1.69 to 28.66°.	
Index ranges	-21<=h<=21, -23<=k<=24, -	
	23<=1<=22	
Reflections collected	22113	
Independent reflections	11221 [R(int) = 0.0505]	
Completeness to theta =	98.4 %	
25.00°		
Absorption correction	Semi-empirical from	
	equivalents	
Max. and min. transmission	0.9656 and 0.9265	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	11221 / 2 / 712	
Goodness-of-fit on F ²	1.004	
Final R indices [I>2sigma(I)]	R1 = 0.0461, wR2 = 0.0837	
R indices (all data)	R1 = 0.0716, wR2 = 0.0930	
Absolute structure parameter	-0.02(5)	
Largest diff. peak and hole	0.301 and -0.345 e.Å ⁻³	

Table C.2.2. Crystal data and structure refinement for $\mathbf{5}_{RS/SR}$.

Atom number	X	у	Z	U(eq)
Cl(1)	-111(1)	3043(1)	8790(1)	42(1)
Cl(2)	-403(1)	1771(1)	7798(1)	46(1)
F(1)	6776(1)	8635(1)	9221(1)	44(1)
F(2)	8099(1)	8746(1)	9452(1)	48(1)
F(3)	7582(1)	7746(1)	8986(1)	40(1)
F(4)	6554(1)	6112(1)	7346(1)	37(1)
F(5)	7697(1)	6371(1)	6849(1)	29(1)
F(6)	6809(1)	5650(1)	6259(1)	34(1)
F(7)	5511(1)	8006(1)	2466(1)	35(1)
F(8)	4458(1)	8729(1)	2364(1)	34(1)
F(9)	4288(1)	7586(1)	2106(1)	29(1)
F(10)	7690(1)	7896(1)	4056(1)	38(1)
F(11)	7535(1)	8947(1)	3512(1)	44(1)
F(12)	8534(1)	8772(1)	4392(1)	36(1)
F(13)	8513(1)	10328(1)	5769(1)	39(1)
F(14)	9736(1)	10611(1)	6274(1)	44(1)
F(15)	8747(1)	10395(1)	6993(1)	43(1)
F(16)	10617(2)	10530(1)	8915(1)	56(1)
F(17)	10827(1)	9976(1)	9995(1)	52(1)
F(18)	9748(1)	9711(1)	9232(1)	51(1)
O(1)	8384(1)	8570(1)	7978(1)	24(1)
O(2)	6823(1)	7033(1)	5578(1)	22(1)
C(1)	6906(2)	8465(2)	7570(1)	20(1)
C(2)	7062(2)	7802(2)	7228(2)	19(1)
C(3)	6395(2)	7574(1)	6726(1)	16(1)
C(4)	4982(2)	8111(2)	6283(2)	19(1)
C(5)	4319(2)	8601(2)	6342(2)	24(1)
C(6)	4232(2)	9209(2)	6789(2)	24(1)
C(7)	4847(2)	9529(2)	7287(2)	28(1)
C(8)	5679(2)	9339(2)	7494(2)	24(1)
C(9)	7570(2)	8778(2)	8151(2)	21(1)

Table C.2.3. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å²x 10^3) for **5**_{RS/SR}. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.
	14010 0.2	e: comuou		
Atom number	X	у	Z	U(eq)
C(10)	6417(2)	6888(1)	6263(1)	18(1)
C(11)	4799(2)	7540(2)	5673(2)	23(1)
C(12)	3403(2)	9600(2)	6700(2)	34(1)
C(13)	6154(2)	9906(2)	7976(2)	38(1)
C(14)	6091(2)	8695(2)	7289(2)	19(1)
C(15)	5758(2)	8118(1)	6735(1)	17(1)
C(16)	7505(2)	8476(2)	8950(2)	29(1)
C(17)	6877(2)	6260(2)	6685(2)	23(1)
O(3)	4749(1)	7184(1)	3608(1)	26(1)
O(4)	7459(1)	8480(1)	5480(1)	27(1)
O(5)	8601(1)	8984(1)	6556(1)	33(1)
O(6)	11018(1)	8647(1)	9318(1)	24(1)
C(18)	5897(2)	8308(2)	4091(2)	20(1)
C(19)	5038(2)	8435(1)	3948(2)	19(1)
C(20)	4532(2)	7920(1)	3415(2)	20(1)
C(21)	4702(2)	8054(2)	2586(2)	24(1)
C(22)	4826(2)	9072(1)	4344(2)	18(1)
C(23)	5625(2)	9328(1)	4778(1)	17(1)
C(24)	6262(2)	8835(1)	4584(2)	18(1)
C(25)	7190(2)	8869(2)	4797(2)	21(1)
C(26)	7725(2)	8613(2)	4186(2)	27(1)
C(27)	5720(2)	9916(2)	5290(2)	20(1)
C(28)	5134(2)	10464(2)	5408(2)	25(1)
C(29)	4314(2)	10561(2)	5132(2)	25(1)
C(30)	3837(2)	10055(2)	4680(2)	27(1)
C(31)	4023(2)	9395(2)	4350(2)	24(1)
C(32)	6531(2)	10018(2)	5790(2)	30(1)
C(33)	3876(2)	11239(2)	5356(2)	33(1)
C(34)	3268(2)	9020(2)	3950(2)	46(1)
C(35)	10150(2)	9469(1)	7641(2)	19(1)
C(36)	10059(2)	9191(2)	6901(2)	20(1)
C(37)	9314(2)	9382(2)	6351(2)	20(1)
C(38)	9087(2)	10182(2)	6359(2)	28(1)
C(39)	10717(2)	8694(1)	6810(1)	19(1)
C(40)	11281(2)	8735(1)	7546(2)	19(1)

Table C.2.3. continued.

Atom number	X	у	Z	U(eq)
C(41)	10876(2)	9204(1)	8044(2)	18(1)
C(42)	11085(2)	9307(2)	8895(2)	22(1)
C(43)	10558(2)	9879(2)	9255(2)	36(1)
C(44)	12077(2)	8421(2)	7694(2)	21(1)
C(45)	12443(2)	7893(2)	7257(2)	26(1)
C(46)	12158(2)	7549(2)	6582(2)	26(1)
C(47)	11430(2)	7701(2)	6122(2)	26(1)
C(48)	10797(2)	8210(2)	6194(2)	21(1)
C(49)	12643(2)	8679(2)	8373(2)	31(1)
C(50)	12692(2)	6925(2)	6320(2)	45(1)
C(51)	10113(2)	8176(2)	5538(2)	30(1)
C(52)	326(2)	2249(2)	8415(2)	33(1)

Atom Number	Å (°)	Atom Number	Å (°)
Cl(1)-C(52)	1.768(3)	C(4)-C(11)	1.505(4)
Cl(2)-C(52)	1.754(3)	C(5)-C(6)	1.377(4)
F(1)-C(16)	1.338(4)	C(5)-H(5)	0.9500
F(2)-C(16)	1.333(3)	C(6)-C(7)	1.387(4)
F(3)-C(16)	1.343(4)	C(6)-C(12)	1.509(4)
F(4)-C(17)	1.345(3)	C(7)-C(8)	1.396(4)
F(5)-C(17)	1.338(3)	C(7)-H(7)	0.9500
F(6)-C(17)	1.343(3)	C(8)-C(14)	1.415(4)
F(7)-C(21)	1.341(3)	C(8)-C(13)	1.502(4)
F(8)-C(21)	1.342(3)	C(9)-C(16)	1.522(4)
F(9)-C(21)	1.336(3)	C(9)-H(9)	1.0000
F(10)-C(26)	1.332(3)	C(10)-C(17)	1.522(4)
F(11)-C(26)	1.343(3)	C(10)-H(10)	1.0000
F(12)-C(26)	1.348(3)	C(11)-H(11A)	0.9800
F(13)-C(38)	1.349(3)	C(11)-H(11B)	0.9800
F(14)-C(38)	1.324(4)	C(11)-H(11C)	0.9800
F(15)-C(38)	1.344(4)	C(12)-H(12A)	0.9800
F(16)-C(43)	1.340(4)	C(12)-H(12B)	0.9800
F(17)-C(43)	1.342(3)	C(12)-H(12C)	0.9800
F(18)-C(43)	1.335(4)	C(13)-H(13A)	0.9800
O(1)-C(9)	1.423(3)	C(13)-H(13B)	0.9800
O(1)-H(1A)	0.8400	C(13)-H(13C)	0.9800
O(2)-C(10)	1.447(3)	C(14)-C(15)	1.501(4)
O(2)-H(2A)	0.8400	O(3)-C(20)	1.424(3)
C(1)-C(2)	1.387(4)	O(3)-H(3A)	0.8400
C(1)-C(14)	1.419(4)	O(4)-C(25)	1.427(3)
C(1)-C(9)	1.519(4)	O(4)-H(4A)	0.8400
C(2)-C(3)	1.387(4)	O(5)- $C(37)$	1.432(3)
C(2)-H(2)	0.9500	O(5)-H(5A)	0.8400
C(3)-C(15)	1.430(4)	O(6)-C(42)	1 427(3)
C(3)-C(10)	1.498(4)	O(6)-H(6A)	0.8400
C(4)-C(5)	1.404(4)	C(18)-C(24)	1 389(4)
C(4)-C(15)	1.416(4)	C(18) - C(19)	1 400(4)

Table C.2.4. Bond lengths [Å] and angles [°] for $\mathbf{5}_{\text{RS/SR}}$.

Table C.2.4. continued.

Atom Number	Å (°)	Atom Number	Å (°)
C(18)-H(18)	0.9500	C(37)-C(38)	1.509(4)
C(19)-C(22)	1.415(4)	C(37)-H(37)	1.0000
C(19)-C(20)	1.511(4)	C(39)-C(48)	1.414(4)
C(20)-C(21)	1.527(4)	C(39)-C(40)	1.511(3)
C(20)-H(20)	1.0000	C(40)-C(44)	1.404(4)
C(22)-C(31)	1.421(4)	C(40)-C(41)	1.427(4)
C(22)-C(23)	1.506(3)	C(41)-C(42)	1.515(4)
C(23)-C(27)	1.402(4)	C(42)-C(43)	1.521(4)
C(23)-C(24)	1.430(4)	C(42)-H(42)	1.0000
C(24)-C(25)	1.506(4)	C(44)-C(45)	1.398(4)
C(25)-C(26)	1.512(4)	C(44)-C(49)	1.508(4)
C(25)-H(25)	1.0000	C(45)-C(46)	1.383(4)
C(27)-C(28)	1.405(4)	C(45)-H(45)	0.9500
C(27)-C(32)	1.515(4)	C(46)-C(47)	1.386(4)
C(28)-C(29)	1.372(4)	C(46)-C(50)	1.525(4)
C(28)-H(28)	0.9500	C(47)-C(48)	1.393(4)
C(29)-C(30)	1.402(4)	C(47)-H(47)	0.9500
C(29)-C(33)	1.498(4)	C(48)-C(51)	1.519(4)
C(30)-C(31)	1.385(4)	C(49)-H(49A)	0.9800
C(30)-H(30)	0.9500	C(49)-H(49B)	0.9800
C(31)-C(34)	1.510(4)	C(49)-H(49C)	0.9800
C(32)-H(32A)	0.9800	C(50)-H(50A)	0.9800
C(32)-H(32B)	0.9800	C(50)-H(50B)	0.9800
C(32)-H(32C)	0.9800	C(50)-H(50C)	0.9800
C(33)-H(33A)	0.9800	C(51)-H(51A)	0.9800
C(33)-H(33B)	0.9800	C(51)-H(51B)	0.9800
C(33)-H(33C)	0.9800	C(51)-H(51C)	0.9800
C(34)-H(34A)	0.9800	C(52)-H(52A)	0.9900
C(34)-H(34B)	0.9800	C(52)-H(52B)	0.9900
C(34)-H(34C)	0.9800		
C(35)-C(36)	1.392(4)	C(9)-O(1)-H(1A)	109.5
C(35)-C(41)	1.395(4)	C(10)-O(2)-H(2A)	109.5
C(35)-H(35)	0.9500	C(2)-C(1)-C(14)	107.9(2)
C(36)-C(39)	1.415(4)	C(2)-C(1)-C(9)	118.4(2)
C(36)-C(37)	1.509(3)	C(14)-C(1)-C(9)	133.6(3)

Table C.2.4. continued.

Atom Number	Å (°)	Atom Number	Å (°)
C(3)-C(2)-C(1)	112.2(2)	H(11A)-C(11)-H(11B)	109.5
C(3)-C(2)-H(2)	123.9	C(4)-C(11)-H(11C)	109.5
C(1)-C(2)-H(2)	123.9	H(11A)-C(11)-H(11C)	109.5
C(2)-C(3)-C(15)	107.2(2)	H(11B)-C(11)-H(11C)	109.5
C(2)-C(3)-C(10)	122.8(2)	C(6)-C(12)-H(12A)	109.5
C(15)-C(3)-C(10)	129.9(2)	C(6)-C(12)-H(12B)	109.5
C(5)-C(4)-C(15)	126.0(3)	H(12A)-C(12)-H(12B)	109.5
C(5)-C(4)-C(11)	113.4(2)	C(6)-C(12)-H(12C)	109.5
C(15)-C(4)-C(11)	120.6(2)	H(12A)-C(12)-H(12C)	109.5
C(6)-C(5)-C(4)	132.6(3)	H(12B)-C(12)-H(12C)	109.5
C(6)-C(5)-H(5)	113.7	C(8)-C(13)-H(13A)	109.5
C(4)-C(5)-H(5)	113.7	C(8)-C(13)-H(13B)	109.5
C(5)-C(6)-C(7)	126.6(3)	H(13A)-C(13)-H(13B)	109.5
C(5)-C(6)-C(12)	117.4(3)	C(8)-C(13)-H(13C)	109.5
C(7)-C(6)-C(12)	115.8(3)	H(13A)-C(13)-H(13C)	109.5
C(6)-C(7)-C(8)	131.9(3)	H(13B)-C(13)-H(13C)	109.5
C(6)-C(7)-H(7)	114.0	C(8)-C(14)-C(1)	126.7(2)
C(8)-C(7)-H(7)	114.0	C(8)-C(14)-C(15)	127.1(2)
C(7)-C(8)-C(14)	126.9(3)	C(1)-C(14)-C(15)	106.2(2)
C(7)-C(8)-C(13)	113.5(3)	C(4)-C(15)-C(3)	125.6(2)
C(14)-C(8)-C(13)	119.5(3)	C(4)-C(15)-C(14)	127.8(2)
O(1)-C(9)-C(1)	111.0(2)	C(3)-C(15)-C(14)	106.5(2)
O(1)-C(9)-C(16)	104.1(2)	F(2)-C(16)-F(1)	106.3(2)
C(1)-C(9)-C(16)	112.3(2)	F(2)-C(16)-F(3)	106.3(2)
O(1)-C(9)-H(9)	109.7	F(1)-C(16)-F(3)	106.1(3)
C(1)-C(9)-H(9)	109.7	F(2)-C(16)-C(9)	111.7(3)
C(16)-C(9)-H(9)	109.7	F(1)-C(16)-C(9)	112.9(2)
O(2)-C(10)-C(3)	109.5(2)	F(3)-C(16)-C(9)	113.0(2)
O(2)-C(10)-C(17)	107.9(2)	F(5)-C(17)-F(6)	105.9(2)
C(3)-C(10)-C(17)	113.7(2)	F(5)-C(17)-F(4)	107.3(2)
O(2)-C(10)-H(10)	108.5	F(6)-C(17)-F(4)	107.3(2)
C(3)-C(10)-H(10)	108.5	F(5)-C(17)-C(10)	114.6(2)
C(17)-C(10)-H(10)	108.5	F(6)-C(17)-C(10)	110.2(2)
C(4)-C(11)-H(11A)	109.5	F(4)-C(17)-C(10)	111.3(2)
C(4)-C(11)-H(11B)	109.5	C(20)-O(3)-H(3A)	109.5

Table C.2.4. continued.

Atom Number	Å (°)	Atom Number	Å (°)
C(25)-O(4)-H(4A)	109.5	C(26)-C(25)-H(25)	106.7
C(37)-O(5)-H(5A)	109.5	F(10)-C(26)-F(11)	107.1(2)
C(42)-O(6)-H(6A)	109.5	F(10)-C(26)-F(12)	106.4(2)
C(24)-C(18)-C(19)	110.5(2)	F(11)-C(26)-F(12)	105.9(2)
C(24)-C(18)-H(18)	124.8	F(10)-C(26)-C(25)	114.2(2)
C(19)-C(18)-H(18)	124.8	F(11)-C(26)-C(25)	112.8(2)
C(18)-C(19)-C(22)	109.1(2)	F(12)-C(26)-C(25)	110.0(2)
C(18)-C(19)-C(20)	118.2(2)	C(23)-C(27)-C(28)	127.5(2)
C(22)-C(19)-C(20)	132.7(2)	C(23)-C(27)-C(32)	120.3(3)
O(3)-C(20)-C(19)	109.7(2)	C(28)-C(27)-C(32)	112.3(2)
O(3)-C(20)-C(21)	108.6(2)	C(29)-C(28)-C(27)	132.5(3)
C(19)-C(20)-C(21)	111.0(2)	C(29)-C(28)-H(28)	113.8
O(3)-C(20)-H(20)	109.2	C(27)-C(28)-H(28)	113.8
C(19)-C(20)-H(20)	109.2	C(28)-C(29)-C(30)	124.9(3)
C(21)-C(20)-H(20)	109.2	C(28)-C(29)-C(33)	118.3(3)
F(9)-C(21)-F(7)	106.9(2)	C(30)-C(29)-C(33)	116.7(3)
F(9)-C(21)-F(8)	106.9(2)	C(31)-C(30)-C(29)	133.2(3)
F(7)-C(21)-F(8)	106.1(2)	C(31)-C(30)-H(30)	113.4
F(9)-C(21)-C(20)	112.1(2)	C(29)-C(30)-H(30)	113.4
F(7) -C(21)-C(20)	113.8(2)	C(30)-C(31)-C(22)	126.7(3)
F(8)-C(21)-C(20)	110.6(2)	C(30)-C(31)-C(34)	113.3(3)
C(19)-C(22)-C(31)	127.3(2)	C(22)-C(31)-C(34)	120.0(3)
C(19)-C(22)-C(23)	105.8(2)	C(27)-C(32)-H(32A)	109.5
C(31)-C(22)-C(23)	126.8(2)	C(27)-C(32)-H(32B)	109.5
C(27)-C(23)-C(24)	126.8(2)	H(32A)-C(32)-H(32B)	109.5
C(27)-C(23)-C(22)	126.9(2)	C(27)-C(32)-H(32C)	109.5
C(24)-C(23)-C(22)	106.2(2)	H(32A)-C(32)-H(32C)	109.5
C(18)-C(24)-C(23)	108.4(2)	H(32B)-C(32)-H(32C)	109.5
C(18)-C(24)-C(25)	122.3(2)	C(29)-C(33)-H(33A)	109.5
C(23)-C(24)-C(25)	129.1(2)	C(29)-C(33)-H(33B)	109.5
O(4)-C(25)-C(24)	113.7(2)	H(33A)-C(33)-H(33B)	109.5
O(4)-C(25)-C(26)	107.2(2)	C(29)-C(33)-H(33C)	109.5
C(24)-C(25)-C(26)	115.4(2)	H(33A)-C(33)-H(33C)	109.5
O(4)-C(25)-H(25)	106.7	H(33B)-C(33)-H(33C)	109.5
C(24)-C(25)-H(25)	106.7	C(31)-C(34)-H(34A)	109.5

Table C.2.4. continued.

Atom Number	Å (°)	Atom Number	Å (°)
C(31)-C(34)-H(34B)	109.5	O(6)-C(42)-H(42)	107.3
H(34A)-C(34)-H(34B)	109.5	C(41)-C(42)-H(42)	107.3
C(31)-C(34)-H(34C)	109.5	C(43)-C(42)-H(42)	107.3
H(34A)-C(34)-H(34C)	109.5	F(18)-C(43)-F(16)	107.5(3)
H(34B)-C(34)-H(34C)	109.5	F(18)-C(43)-F(17)	106.5(3)
C(36)-C(35)-C(41)	110.9(2)	F(16)-C(43)-F(17)	106.6(3)
C(36)-C(35)-H(35)	124.6	F(18)-C(43)-C(42)	114.1(3)
C(41)-C(35)-H(35)	124.6	F(16)-C(43)-C(42)	111.1(3)
C(35)-C(36)-C(39)	109.1(2)	F(17)-C(43)-C(42)	110.6(2)
C(35)-C(36)-C(37)	121.4(2)	C(45)-C(44)-C(40)	127.2(3)
C(39)-C(36)-C(37)	129.3(2)	C(45)-C(44)-C(49)	113.5(2)
O(5)-C(37)-C(38)	107.0(2)	C(40)-C(44)-C(49)	119.3(3)
O(5)-C(37)-C(36)	109.1(2)	C(46)-C(45)-C(44)	131.6(3)
C(38)-C(37)-C(36)	113.4(2)	C(46)-C(45)-H(45)	114.2
O(5)-C(37)-H(37)	109.1	C(44)-C(45)-H(45)	114.2
C(38)-C(37)-H(37)	109.1	C(45)-C(46)-C(47)	127.0(3)
C(36)-C(37)-H(37)	109.1	C(45)-C(46)-C(50)	116.7(3)
F(14)-C(38)-F(15)	107.9(2)	C(47)-C(46)-C(50)	116.3(3)
F(14)-C(38)-F(13)	106.7(2)	C(46)-C(47)-C(48)	131.7(3)
F(15)-C(38)-F(13)	106.1(2)	C(46)-C(47)-H(47)	114.2
F(14)-C(38)-C(37)	112.3(2)	C(48)-C(47)-H(47)	114.2
F(15)-C(38)-C(37)	113.9(2)	C(47)-C(48)-C(39)	127.5(2)
F(13)-C(38)-C(37)	109.4(2)	C(47)-C(48)-C(51)	112.7(3)
C(48)-C(39)-C(36)	127.8(2)	C(39)-C(48)-C(51)	119.7(2)
C(48)-C(39)-C(40)	126.6(2)	C(44)-C(49)-H(49A)	109.5
C(36)-C(39)-C(40)	105.4(2)	C(44)-C(49)-H(49B)	109.5
C(44)-C(40)-C(41)	126.4(2)	H(49A)-C(49)-H(49B)	109.5
C(44)-C(40)-C(39)	127.0(2)	C(44)-C(49)-H(49C)	109.5
C(41)-C(40)-C(39)	106.4(2)	H(49A)-C(49)-H(49C)	109.5
C(35)-C(41)-C(40)	107.9(2)	H(49B)-C(49)-H(49C)	109.5
C(35)-C(41)-C(42)	123.8(2)	C(46)-C(50)-H(50A)	109.5
C(40)-C(41)-C(42)	127.6(2)	C(46)-C(50)-H(50B)	109.5
O(6)-C(42)-C(41)	112.9(2)	H(50A)-C(50)-H(50B)	109.5
O(6)-C(42)-C(43)	107.1(2)	C(46)-C(50)-H(50C)	109.5
C(41)-C(42)-C(43)	114.6(2)	H(50A)-C(50)-H(50C)	109.5

Atom Number	Å (°)	Atom Number	Å (°)
H(50B)-C(50)-H(50C)	109.5	Cl(2)-C(52)-Cl(1)	111.98(17)
C(48)-C(51)-H(51A)	109.5	Cl(2)-C(52)-H(52A)	109.2
C(48)-C(51)-H(51B)	109.5	Cl(1)-C(52)-H(52A)	109.2
H(51A)-C(51)-H(51B)	109.5	Cl(2)-C(52)-H(52B)	109.2
C(48)-C(51)-H(51C)	109.5	Cl(1)-C(52)-H(52B)	109.2
H(51A)-C(51)-H(51C)	109.5	H(52A)-C(52)-H(52B)	107.9
H(51B)-C(51)-H(51C)	109.5		

Table C.2.4. continued.

Atom Number	U11	U22	U33	U23	U13	U12
Cl(1)	47(1)	40(1)	41(1)	4(1)	9(1)	10(1)
Cl(2)	47(1)	48(1)	42(1)	1(1)	-3(1)	-10(1)
F(1)	42(1)	62(1)	28(1)	-3(1)	10(1)	9(1)
F(2)	52(1)	69(2)	21(1)	-7(1)	-11(1)	-15(1)
F(3)	58(1)	35(1)	28(1)	8(1)	3(1)	6(1)
F(4)	46(1)	31(1)	33(1)	13(1)	8(1)	6(1)
F(5)	23(1)	28(1)	33(1)	-6(1)	-10(1)	9(1)
F(6)	38(1)	17(1)	45(1)	-10(1)	-14(1)	8(1)
F(7)	31(1)	48(1)	27(1)	-8(1)	6(1)	-5(1)
F(8)	50(1)	20(1)	29(1)	6(1)	-10(1)	-4(1)
F(9)	39(1)	27(1)	21(1)	-6(1)	-6(1)	-5(1)
F(10)	30(1)	37(1)	47(1)	-16(1)	-4(1)	6(1)
F(11)	36(1)	73(2)	23(1)	14(1)	2(1)	13(1)
F(12)	18(1)	49(1)	42(1)	-2(1)	0(1)	-2(1)
F(13)	38(1)	38(1)	36(1)	7(1)	-16(1)	13(1)
F(14)	44(1)	25(1)	59(1)	12(1)	-12(1)	-6(1)
F(15)	44(1)	45(1)	39(1)	-13(1)	-9(1)	21(1)
F(16)	107(2)	22(1)	33(1)	-4(1)	-15(1)	22(1)
F(17)	86(2)	48(1)	19(1)	-10(1)	-11(1)	28(1)
F(18)	46(1)	77(2)	30(1)	-1(1)	3(1)	29(1)
O(1)	21(1)	32(1)	20(1)	1(1)	-2(1)	1(1)
O(2)	27(1)	27(1)	13(1)	-6(1)	-2(1)	-1(1)
C(1)	25(2)	19(1)	14(1)	-1(1)	-1(1)	1(1)
C(2)	22(1)	19(1)	15(1)	0(1)	1(1)	2(1)
C(3)	18(1)	16(1)	13(1)	2(1)	0(1)	2(1)
C(4)	20(1)	19(1)	18(1)	6(1)	2(1)	0(1)
C(5)	20(1)	25(2)	27(2)	8(1)	0(1)	3(1)
C(6)	25(2)	21(2)	29(2)	11(1)	8(1)	6(1)
C(7)	40(2)	19(2)	27(2)	3(1)	8(1)	10(1)
C(8)	31(2)	20(2)	21(1)	2(1)	2(1)	6(1)
C(9)	22(1)	19(1)	19(1)	-2(1)	-4(1)	2(1)

Table C.2.5. Anisotropic displacement parameters (Å²x 10³) for **5**_{RS/SR}. The anisotropic displacement factor exponent takes the form: $-2\pi^2$ [h² a*²U¹¹ + ... + 2 h k a* b* U¹²]

	Table C.2.5. continued.						
Atom Number	U11	U ²²	U33	U23	U13	U12	
C(10)	18(1)	20(1)	16(1)	-1(1)	-3(1)	4(1)	
C(11)	16(1)	28(2)	25(2)	0(1)	-6(1)	4(1)	
C(12)	28(2)	27(2)	47(2)	9(2)	10(2)	10(1)	
C(13)	47(2)	25(2)	41(2)	-12(2)	-9(2)	17(2)	
C(14)	25(2)	17(1)	14(1)	-1(1)	3(1)	1(1)	
C(15)	20(1)	17(1)	13(1)	2(1)	2(1)	3(1)	
C(16)	31(2)	34(2)	20(2)	-5(1)	-4(1)	3(1)	
C(17)	25(2)	20(2)	24(2)	-4(1)	-3(1)	5(1)	
O(3)	31(1)	13(1)	30(1)	1(1)	-15(1)	-4(1)	
O(4)	31(1)	27(1)	20(1)	6(1)	-11(1)	-9(1)	
O(5)	28(1)	47(1)	22(1)	10(1)	-10(1)	-18(1)	
O(6)	32(1)	21(1)	19(1)	4(1)	-8(1)	-3(1)	
C(18)	21(1)	18(1)	19(1)	0(1)	-1(1)	2(1)	
C(19)	23(1)	18(1)	16(1)	2(1)	-2(1)	-1(1)	
C(20)	23(1)	15(1)	21(1)	2(1)	-4(1)	1(1)	
C(21)	24(2)	21(2)	26(2)	-2(1)	-5(1)	-1(1)	
C(22)	23(1)	17(1)	13(1)	4(1)	-1(1)	0(1)	
C(23)	23(1)	16(1)	13(1)	1(1)	0(1)	-4(1)	
C(24)	21(1)	20(1)	14(1)	3(1)	-3(1)	-1(1)	
C(25)	24(1)	20(2)	18(1)	1(1)	-5(1)	-4(1)	
C(26)	22(2)	30(2)	26(2)	3(1)	-7(1)	4(1)	
C(27)	25(2)	22(2)	14(1)	0(1)	1(1)	-6(1)	
C(28)	36(2)	20(2)	19(1)	-6(1)	5(1)	-3(1)	
C(29)	35(2)	24(2)	16(1)	1(1)	5(1)	4(1)	
C(30)	27(2)	30(2)	25(2)	0(1)	-2(1)	5(1)	
C(31)	24(2)	24(2)	24(2)	-2(1)	-5(1)	2(1)	
C(32)	30(2)	37(2)	23(2)	-12(1)	-1(1)	-6(1)	
C(33)	43(2)	25(2)	31(2)	-4(1)	5(2)	4(1)	
C(34)	24(2)	37(2)	73(3)	-23(2)	-15(2)	10(1)	
C(35)	23(1)	14(1)	18(1)	-1(1)	-2(1)	2(1)	
C(36)	23(1)	18(2)	16(1)	3(1)	-3(1)	0(1)	
C(37)	24(1)	20(2)	14(1)	2(1)	-7(1)	-1(1)	
C(38)	26(2)	28(2)	27(2)	2(1)	-9(1)	4(1)	
C(39)	23(1)	20(2)	14(1)	3(1)	-3(1)	-3(1)	

Atom Number	U11	U ²²	U ³³	U ²³	U13	U12
C(40)	24(1)	16(1)	16(1)	-1(1)	-2(1)	-2(1)
C(41)	21(1)	16(1)	16(1)	1(1)	-5(1)	-2(1)
C(42)	28(2)	16(1)	20(1)	2(1)	-6(1)	2(1)
C(43)	59(2)	30(2)	18(2)	-1(1)	-7(2)	14(2)
C(44)	23(1)	22(2)	17(1)	2(1)	-2(1)	-2(1)
C(45)	20(1)	27(2)	32(2)	2(1)	-1(1)	1(1)
C(46)	25(2)	24(2)	31(2)	-4(1)	8(1)	2(1)
C(47)	34(2)	23(2)	22(2)	-6(1)	6(1)	-1(1)
C(48)	26(2)	20(2)	17(1)	1(1)	-1(1)	0(1)
C(49)	23(2)	40(2)	29(2)	0(1)	-4(1)	2(1)
C(50)	33(2)	44(2)	58(2)	-16(2)	3(2)	12(2)
C(51)	40(2)	33(2)	17(2)	-7(1)	-6(1)	3(1)
C(52)	30(2)	39(2)	30(2)	3(1)	-3(1)	5(1)

 $C \rightarrow F$ 1-1 . .1

D-HA	d(D-H)	d(HA)	d(DA)	<(DHA)
O(1)-H(1A)O(5)	0.84	1.83	2.667(3)	179.5
O(2)-H(2A)O(6)#1	0.84	1.92	2.756(3)	176.7
O(3)-H(3A)O(1)#1	0.84	1.91	2.737(3)	169.5
O(4)-H(4A)O(2)	0.84	2.02	2.849(3)	171.0
O(5)-H(5A)O(4)	0.84	1.86	2.674(3)	163.3
O(6)-H(6A)O(3)#2	0.84	1.91	2.749(3)	178.9

Table C.2.6. Hydrogen bonds for $\mathbf{5}_{RS/SR}$ [Å and °].

#1 x-1/2,-y+3/2,z-1/2 #2 x+1/2,-y+3/2,z+1/2

Identification code	cg18	
Empirical formula	C51 H44 F18 O7	
Formula weight	1110.86	
Temperature	110(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	Cc	
Unit cell dimensions	a = 11.072(3) Å	<i>α</i> = 90°.
	b = 23.071(7) Å	β= 99.011(5)°.
	c = 19.035(4) Å	$\gamma = 90^{\circ}$.
Volume	4802(2) Å ³	
Ζ	4	
Density (calculated)	1.536 Mg/m ³	
Absorption coefficient	0.147 mm ⁻¹	
F(000)	2272	
Crystal size	0.22 x 0.21 x 0.05 mm ³	
Theta range for data collection	1.77 to 26.51°.	
Index ranges	-13<=h<=13, -28<=k<=28, -	
	23<=1<=22	
Reflections collected	18766	
Independent reflections	8727 [R(int) = 0.0458]	
Completeness to $\theta = 25.00^{\circ}$	96.3 %	
Absorption correction	Semi-empirical from	
	equivalents	
Max. and min. transmission	0.9928 and 0.9680	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	8727 / 5 / 698	
Goodness-of-fit on F ²	1.000	
Final R indices [I>2sigma(I)]	R1 = 0.0516, $wR2 = 0.1208$	
R indices (all data)	R1 = 0.0947, wR2 = 0.1395	
Absolute structure parameter	0.9(6)	
Largest diff. peak and hole	0.474 and -0.329 e.Å ⁻³	

Table C.2.7. Crystal data and structure refinement for $10_{RR/SS}$.

Atom Number	Х	у	Z	U(eq)
F(1)	7554(3)	6622(1)	8210(2)	64(1)
F(2)	7092(3)	5951(2)	8879(2)	101(2)
F(3)	7607(3)	5756(2)	7833(2)	76(1)
F(4)	3125(2)	7526(1)	5402(2)	49(1)
F(5)	3822(3)	8139(1)	6218(2)	46(1)
F(6)	3974(3)	8317(1)	5127(2)	47(1)
O(1)	5018(3)	6525(1)	8302(2)	51(1)
O(2)	6192(3)	8016(1)	5891(2)	33(1)
C(1)	5489(4)	6408(2)	7124(3)	41(1)
C(2)	5360(4)	7003(2)	6985(3)	38(1)
C(3)	5341(4)	7102(2)	6254(2)	30(1)
C(4)	5506(4)	6597(2)	5226(3)	42(1)
C(5)	5602(4)	6164(2)	4753(3)	51(1)
C(6)	5633(5)	5581(2)	4937(4)	56(2)
C(7)	5631(4)	5300(2)	5596(4)	51(2)
C(8)	5585(4)	5504(2)	6290(3)	50(1)
C(9)	5623(4)	6164(2)	7870(3)	47(1)
C(10)	5272(4)	7583(2)	5725(2)	31(1)
C(11)	5448(4)	7245(2)	5028(3)	40(1)
C(12)	5643(6)	5147(3)	4310(4)	78(2)
C(13)	5579(5)	5044(2)	6841(4)	68(2)
C(14)	5535(4)	6109(2)	6485(3)	38(1)
C(15)	5453(4)	6564(2)	5941(2)	29(1)
C(16)	7002(6)	6128(3)	8196(3)	58(2)
C(17)	4038(4)	7894(2)	5610(2)	34(1)
F(7)	10496(2)	1761(1)	-9(1)	43(1)
F(8)	10962(2)	2251(1)	959(2)	48(1)
F(9)	10127(2)	1413(1)	984(2)	50(1)
F(10)	6879(3)	3669(1)	-1938(2)	56(1)
F(11)	7998(3)	3030(1)	-2348(1)	52(1)
F(12)	8051(3)	3916(1)	-2692(2)	48(1)

Table C.2.8. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å²x 10^3) for **10**_{RR/SS}. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Table C.2.8. continued.							
Atom Number	Х	у	Z	U(eq)			
O(3)	8050(2)	1780(1)	118(2)	27(1)			
O(4)	10112(3)	3610(1)	-1787(2)	37(1)			
C(18)	10113(4)	1907(2)	608(2)	34(1)			
C(19)	8875(4)	2195(2)	495(2)	24(1)			
C(20)	8875(3)	2755(2)	96(2)	24(1)			
C(21)	8865(4)	2765(2)	-651(2)	26(1)			
C(22)	8891(4)	3342(2)	-867(2)	26(1)			
C(23)	8994(4)	3695(2)	-1518(2)	31(1)			
C(24)	8930(5)	4330(2)	-1238(2)	36(1)			
C(25)	8939(4)	4274(2)	-433(2)	32(1)			
C(26)	8902(4)	3691(2)	-276(2)	24(1)			
C(27)	8876(4)	3336(2)	351(2)	24(1)			
C(28)	8874(4)	3579(2)	1032(2)	27(1)			
C(29)	8897(4)	4181(2)	1167(3)	36(1)			
C(30)	8920(4)	4682(2)	756(3)	37(1)			
C(31)	8948(4)	4736(2)	35(3)	36(1)			
C(32)	7981(4)	3577(2)	-2123(2)	37(1)			
C(33)	8802(4)	3192(2)	1665(2)	35(1)			
C(34)	8907(5)	5252(2)	1164(3)	55(2)			
F(13)	5047(3)	1014(2)	8353(2)	80(1)			
F(14)	5915(3)	451(1)	9164(2)	67(1)			
F(15)	5904(3)	1362(1)	9344(2)	62(1)			
F(16)	9400(3)	-1008(1)	7562(2)	64(1)			
F(17)	8388(3)	-1772(1)	7169(2)	56(1)			
F(18)	8084(3)	-1370(1)	8154(2)	52(1)			
O(5)	8202(3)	957(1)	9068(2)	48(1)			
O(6)	6217(3)	-1211(1)	7026(2)	35(1)			
C(35)	6004(4)	960(2)	8845(3)	39(1)			
C(36)	7173(4)	1022(2)	8538(2)	33(1)			
C(37)	7234(4)	591(2)	7961(2)	30(1)			
C(38)	7272(4)	-19(2)	8066(2)	32(1)			
C(39)	7278(4)	-294(2)	7416(2)	29(1)			
C(40)	7317(4)	-886(2)	7098(2)	36(1)			
C(41)	7527(5)	-723(2)	6313(3)	43(1)			

	Table C.2.8. continued.							
Atom Number	Х	У	Z	U(eq)				
C(42)	7370(4)	-66(2)	6227(2)	32(1)				
C(43)	7268(4)	138(2)	6894(2)	29(1)				
C(44)	7239(4)	703(2)	7228(2)	26(1)				
C(45)	7210(4)	1232(2)	6834(3)	32(1)				
C(46)	7197(4)	1256(2)	6089(3)	40(1)				
C(47)	7279(4)	835(2)	5559(3)	43(1)				
C(48)	7397(4)	251(2)	5627(3)	40(1)				
C(49)	8297(5)	-1249(2)	7488(3)	41(1)				
C(50)	7206(5)	1818(2)	7183(3)	44(1)				
C(51)	7257(6)	1084(2)	4811(3)	58(2)				
O(7)	6336(5)	7643(2)	8704(3)	91(2)				

Table C.2.8. continued.

Atom Number	Å (°)	Atom Number	Å (°)
F(1)-C(16)	1.293(6)	F(12)-C(32)	1.348(5)
F(2)-C(16)	1.353(7)	O(3)-C(19)	1.434(5)
F(3)-C(16)	1.343(7)	O(4)-C(23)	1.425(5)
F(4)-C(17)	1.333(5)	C(18)-C(19)	1.508(6)
F(5)-C(17)	1.343(5)	C(19)-C(20)	1.499(6)
F(6)-C(17)	1.335(5)	C(20)-C(21)	1.420(6)
O(1)-C(9)	1.410(6)	C(20)-C(27)	1.425(5)
O(2)-C(10)	1.428(5)	C(21)-C(22)	1.395(6)
C(1)-C(2)	1.401(7)	C(22)-C(26)	1.382(6)
C(1)-C(14)	1.407(7)	C(22)-C(23)	1.502(6)
C(1)-C(9)	1.512(7)	C(23)-C(32)	1.500(7)
C(2)-C(3)	1.406(6)	C(23)-C(24)	1.565(6)
C(3)-C(15)	1.390(6)	C(24)-C(25)	1.536(6)
C(3)-C(10)	1.494(6)	C(25)-C(26)	1.379(6)
C(4)-C(5)	1.360(7)	C(25)-C(31)	1.389(6)
C(4)-C(15)	1.374(7)	C(26)-C(27)	1.452(6)
C(4)-C(11)	1.539(7)	C(27)-C(28)	1.413(6)
C(5)-C(6)	1.390(7)	C(28)-C(29)	1.412(6)
C(6)-C(7)	1.412(8)	C(28)-C(33)	1.511(6)
C(6)-C(12)	1.559(8)	C(29)-C(30)	1.398(6)
C(7)-C(8)	1.409(8)	C(30)-C(31)	1.385(7)
C(8)-C(14)	1.448(7)	C(30)-C(34)	1.528(6)
C(8)-C(13)	1.492(8)	F(13)-C(35)	1.306(6)
C(9)-C(16)	1.557(8)	F(14)-C(35)	1.332(6)
C(10)-C(17)	1.528(6)	F(15)-C(35)	1.345(5)
C(10)-C(11)	1.577(6)	F(16)-C(49)	1.329(5)
C(14)-C(15)	1.468(6)	F(17)-C(49)	1.361(5)
F(7)-C(18)	1.352(5)	F(18)-C(49)	1.356(5)
F(8)-C(18)	1.327(5)	O(5)-C(36)	1.407(6)
F(9)-C(18)	1.345(5)	O(6)-C(40)	1.418(5)
F(10)-C(32)	1.339(5)	C(35)-C(36)	1.509(6)
F(11)-C(32)	1.334(5)	C(36)-C(37)	1.490(6)

Table C.2.9. Bond lengths [Å] and angles [°] for $10_{RR/SS}$.

Table C.2.9. continued.

Atom Number	Å (°)	Atom Number	Å (°)
C(37)-C(44)	1.419(6)	C(7)-C(8)-C(13)	115.3(5)
C(37)-C(38)	1.422(6)	C(14)-C(8)-C(13)	120.0(5)
C(38)-C(39)	1.392(6)	O(1)-C(9)-C(1)	110.1(4)
C(39)-C(43)	1.408(6)	O(1)-C(9)-C(16)	109.0(5)
C(39)-C(40)	1.496(6)	C(1)-C(9)-C(16)	109.8(4)
C(40)-C(49)	1.476(7)	O(2)-C(10)-C(3)	114.3(4)
C(40)-C(41)	1.593(6)	O(2)-C(10)-C(17)	107.1(3)
C(41)-C(42)	1.530(6)	C(3)-C(10)-C(17)	113.3(3)
C(42)-C(48)	1.361(6)	O(2)-C(10)-C(11)	110.8(3)
C(42)-C(43)	1.377(6)	C(3)-C(10)-C(11)	101.5(3)
C(43)-C(44)	1.451(6)	C(17)-C(10)-C(11)	109.8(4)
C(44)-C(45)	1.431(6)	C(4)-C(11)-C(10)	106.3(4)
C(45)-C(46)	1.416(7)	C(1)-C(14)-C(8)	134.7(5)
C(45)-C(50)	1.508(6)	C(1)-C(14)-C(15)	104.7(4)
C(46)-C(47)	1.414(7)	C(8)-C(14)-C(15)	120.6(5)
C(47)-C(48)	1.358(7)	C(4)-C(15)-C(3)	113.3(4)
C(47)-C(51)	1.532(7)	C(4)-C(15)-C(14)	137.0(4)
		C(3)-C(15)-C(14)	109.6(4)
C(2)-C(1)-C(14)	109.4(4)	F(1)-C(16)-F(3)	107.6(5)
C(2)-C(1)-C(9)	122.3(5)	F(1)-C(16)-F(2)	106.5(5)
C(14)-C(1)-C(9)	128.2(4)	F(3)-C(16)-F(2)	109.5(5)
C(1)-C(2)-C(3)	109.4(4)	F(1)-C(16)-C(9)	113.0(4)
C(15)-C(3)-C(2)	106.9(4)	F(3)-C(16)-C(9)	111.5(5)
C(15)-C(3)-C(10)	111.9(4)	F(2)-C(16)-C(9)	108.6(5)
C(2)-C(3)-C(10)	141.2(4)	F(4)-C(17)-F(6)	107.8(4)
C(5)-C(4)-C(15)	129.4(5)	F(4)-C(17)-F(5)	107.2(4)
C(5)-C(4)-C(11)	123.7(5)	F(6)-C(17)-F(5)	106.9(3)
C(15)-C(4)-C(11)	106.8(4)	F(4)-C(17)-C(10)	111.2(3)
C(4)-C(5)-C(6)	123.1(6)	F(6)-C(17)-C(10)	113.0(3)
C(5)-C(6)-C(7)	131.6(5)	F(5)-C(17)-C(10)	110.5(4)
C(5)-C(6)-C(12)	115.5(6)	F(8)-C(18)-F(9)	106.9(4)
C(7)-C(6)-C(12)	112.8(5)	F(8)-C(18)-F(7)	107.0(3)
C(8)-C(7)-C(6)	133.3(4)	F(9)-C(18)-F(7)	105.7(3)
C(7)-C(8)-C(14)	124.7(5)	F(8)-C(18)-C(19)	111.5(4)

Table C.2.9. continued.

Atom Number	Å (°)	_	Atom Number	Å (°)
F(9)-C(18)-C(19)	112.5(3)		C(29)-C(30)-C(34)	115.2(4)
F(7)-C(18)-C(19)	112.8(4)		C(30)-C(31)-C(25)	124.5(4)
O(3)-C(19)-C(20)	111.8(3)		F(11)-C(32)-F(10)	107.1(4)
O(3)-C(19)-C(18)	105.8(3)		F(11)-C(32)-F(12)	106.5(4)
C(20)-C(19)-C(18)	112.3(3)		F(10)-C(32)-F(12)	106.8(4)
C(21)-C(20)-C(27)	109.0(4)		F(11)-C(32)-C(23)	111.9(4)
C(21)-C(20)-C(19)	121.4(3)		F(10)-C(32)-C(23)	111.8(4)
C(27)-C(20)-C(19)	129.6(4)		F(12)-C(32)-C(23)	112.4(3)
C(22)-C(21)-C(20)	108.3(4)		F(13)-C(35)-F(14)	107.5(4)
C(26)-C(22)-C(21)	108.3(4)		F(13)-C(35)-F(15)	107.1(4)
C(26)-C(22)-C(23)	111.4(3)		F(14)-C(35)-F(15)	105.6(4)
C(21)-C(22)-C(23)	140.1(4)		F(13)-C(35)-C(36)	111.2(4)
O(4)-C(23)-C(32)	106.7(4)		F(14)-C(35)-C(36)	112.8(4)
O(4)-C(23)-C(22)	113.9(4)		F(15)-C(35)-C(36)	112.3(4)
C(32)-C(23)-C(22)	113.0(3)		O(5)-C(36)-C(37)	109.4(3)
O(4)-C(23)-C(24)	109.8(3)		O(5)-C(36)-C(35)	111.1(4)
C(32)-C(23)-C(24)	111.3(4)		C(37)-C(36)-C(35)	111.4(3)
C(22)-C(23)-C(24)	102.3(3)		C(44)-C(37)-C(38)	108.3(4)
C(25)-C(24)-C(23)	105.5(3)		C(44)-C(37)-C(36)	127.6(4)
C(26)-C(25)-C(31)	127.4(4)		C(38)-C(37)-C(36)	124.1(4)
C(26)-C(25)-C(24)	107.7(4)		C(39)-C(38)-C(37)	109.3(4)
C(31)-C(25)-C(24)	124.9(4)		C(38)-C(39)-C(43)	107.7(4)
C(25)-C(26)-C(22)	112.8(4)		C(38)-C(39)-C(40)	141.3(4)
C(25)-C(26)-C(27)	137.2(4)		C(43)-C(39)-C(40)	111.0(4)
C(22)-C(26)-C(27)	110.0(3)		O(6)-C(40)-C(49)	107.5(4)
C(28)-C(27)-C(20)	133.4(4)		O(6)-C(40)-C(39)	116.2(4)
C(28)-C(27)-C(26)	122.2(3)		C(49)-C(40)-C(39)	112.4(4)
C(20)-C(27)-C(26)	104.5(3)		O(6)-C(40)-C(41)	106.4(4)
C(29)-C(28)-C(27)	123.7(4)		C(49)-C(40)-C(41)	113.7(4)
C(29)-C(28)-C(33)	116.0(4)		C(39)-C(40)-C(41)	100.5(3)
C(27)-C(28)-C(33)	120.3(3)		C(42)-C(41)-C(40)	107.7(3)
C(30)-C(29)-C(28)	135.5(4)		C(48)-C(42)-C(43)	127.3(4)
C(31)-C(30)-C(29)	129.4(4)		C(48)-C(42)-C(41)	127.3(4)
C(31)-C(30)-C(34)	115.4(4)	_	C(43)-C(42)-C(41)	105.3(4)

Atom Number	Å (°)	Atom Number	Å (°)
C(42)-C(43)-C(39)	114.5(4)	F(18)-C(49)-F(17)	105.7(4)
C(42)-C(43)-C(44)	136.3(4)	F(16)-C(49)-C(40)	114.0(4)
C(39)-C(43)-C(44)	109.0(4)	F(18)-C(49)-C(40)	111.4(4)
C(37)-C(44)-C(45)	131.9(4)	F(17)-C(49)-C(40)	112.4(4)
C(37)-C(44)-C(43)	105.8(3)	F(1)-C(16)	1.293(6)
C(45)-C(44)-C(43)	122.4(4)	F(2)-C(16)	1.353(7)
C(46)-C(45)-C(44)	123.7(4)	F(3)-C(16)	1.343(7)
C(46)-C(45)-C(50)	113.9(4)	F(4)-C(17)	1.333(5)
C(44)-C(45)-C(50)	122.4(4)	F(5)-C(17)	1.343(5)
C(47)-C(46)-C(45)	134.0(4)	F(6)-C(17)	1.335(5)
C(48)-C(47)-C(46)	129.1(4)	O(1)-C(9)	1.410(6)
C(48)-C(47)-C(51)	116.5(5)	O(2)-C(10)	1.428(5)
C(46)-C(47)-C(51)	114.4(4)	C(1)-C(2)	1.401(7)
C(47)-C(48)-C(42)	126.8(4)	C(1)-C(14)	1.407(7)
F(16)-C(49)-F(18)	106.2(4)	C(1)-C(9)	1.512(7)
F(16)-C(49)-F(17)	106.7(4)	C(2)-C(3)	1.406(6)

Table C.2.9. continued.

Atom Number	U11	U22	U33	U23	U13	U12
F(1)	48(2)	75(2)	65(2)	23(2)	-5(2)	-19(2)
F(2)	60(2)	155(4)	82(3)	76(3)	-8(2)	-24(2)
F(3)	46(2)	79(2)	105(3)	18(2)	16(2)	17(2)
F(4)	29(2)	48(2)	71(2)	4(1)	11(1)	-4(1)
F(5)	58(2)	41(2)	48(2)	0(1)	32(1)	12(1)
F(6)	48(2)	41(2)	56(2)	15(1)	21(2)	3(1)
O(1)	69(3)	41(2)	48(2)	7(2)	24(2)	-1(2)
O(2)	34(2)	39(2)	30(2)	-2(1)	19(1)	-11(1)
C(1)	28(3)	46(3)	49(3)	11(2)	10(2)	-5(2)
C(2)	29(3)	50(3)	39(3)	-12(2)	16(2)	-6(2)
C(3)	19(2)	26(2)	46(3)	-3(2)	11(2)	2(2)
C(4)	21(2)	48(3)	57(3)	-16(2)	11(2)	-9(2)
C(5)	33(3)	48(3)	72(4)	-21(3)	14(3)	-6(2)
C(6)	29(3)	42(3)	100(5)	-20(3)	22(3)	-3(2)
C(7)	35(3)	26(2)	96(5)	-10(3)	27(3)	1(2)
C(8)	22(3)	37(3)	92(4)	-2(3)	16(3)	-2(2)
C(9)	28(3)	58(3)	60(4)	17(3)	17(2)	-5(2)
C(10)	32(2)	26(2)	39(3)	-10(2)	17(2)	-5(2)
C(11)	34(3)	43(3)	44(3)	-9(2)	9(2)	-6(2)
C(12)	55(4)	60(4)	119(6)	-48(4)	12(4)	-5(3)
C(13)	54(4)	38(3)	115(6)	12(3)	25(4)	3(3)
C(14)	19(2)	32(2)	64(4)	8(2)	12(2)	1(2)
C(15)	22(2)	28(2)	39(3)	-2(2)	8(2)	-6(2)
C(16)	61(4)	62(4)	50(4)	22(3)	4(3)	3(3)
C(17)	39(3)	27(2)	39(3)	-1(2)	16(2)	-1(2)
F(7)	39(2)	49(2)	44(2)	2(1)	18(1)	10(1)
F(8)	28(1)	57(2)	58(2)	-6(1)	2(1)	-8(1)
F(9)	40(2)	48(2)	61(2)	25(1)	5(1)	5(1)
F(10)	38(2)	72(2)	59(2)	13(2)	12(1)	-1(1)
F(11)	80(2)	38(2)	34(2)	-1(1)	0(1)	-12(1)
F(12)	60(2)	47(2)	37(2)	15(1)	11(1)	0(1)

Table C.2.10. Anisotropic displacement parameters (Å²x 10³) for **10**_{RR/SS}. The anisotropic displacement factor exponent takes the form: $-2\pi^2$ [h² a*²U¹¹ + ... + 2 h k a* b* U¹²]

_	Table C.2.10. continued.						
	Atom Number	U ¹¹	U ²²	U33	U ²³	U13	U12
	O(3)	30(2)	23(1)	28(2)	-7(1)	10(1)	-5(1)
	O(4)	40(2)	36(2)	39(2)	10(1)	23(2)	4(1)
	C(18)	35(3)	32(2)	35(3)	6(2)	6(2)	-10(2)
	C(19)	23(2)	23(2)	28(2)	-5(2)	9(2)	-8(2)
	C(20)	21(2)	30(2)	22(2)	-4(2)	7(2)	-6(2)
	C(21)	27(2)	24(2)	28(2)	-3(2)	10(2)	-4(2)
	C(22)	23(2)	27(2)	30(2)	2(2)	12(2)	0(2)
	C(23)	32(3)	25(2)	39(3)	-3(2)	19(2)	-4(2)
	C(24)	47(3)	27(2)	36(3)	-1(2)	14(2)	-7(2)
	C(25)	26(2)	29(2)	44(3)	-4(2)	15(2)	-6(2)
	C(26)	20(2)	23(2)	32(2)	-4(2)	13(2)	-5(2)
	C(27)	21(2)	23(2)	30(2)	-4(2)	9(2)	-7(2)
	C(28)	18(2)	34(2)	28(2)	-7(2)	6(2)	-1(2)
	C(29)	28(2)	41(3)	42(3)	-21(2)	15(2)	-3(2)
	C(30)	29(3)	32(2)	54(3)	-14(2)	20(2)	-8(2)
	C(31)	39(3)	23(2)	51(3)	-5(2)	22(2)	-5(2)
	C(32)	46(3)	30(3)	37(3)	8(2)	10(2)	-5(2)
	C(33)	39(3)	41(3)	25(3)	-7(2)	4(2)	2(2)
	C(34)	65(4)	37(3)	66(4)	-25(3)	20(3)	-4(3)
	F(13)	26(2)	137(3)	71(3)	-35(2)	-11(2)	18(2)
	F(14)	84(2)	58(2)	72(2)	-10(2)	54(2)	-19(2)
	F(15)	35(2)	73(2)	82(2)	-48(2)	17(2)	-6(1)
	F(16)	40(2)	51(2)	104(3)	-18(2)	19(2)	0(1)
	F(17)	69(2)	35(2)	68(2)	-14(1)	24(2)	8(1)
	F(18)	59(2)	38(1)	56(2)	-3(1)	1(2)	12(1)
	O(5)	30(2)	61(2)	50(2)	-35(2)	-2(2)	7(2)
	O(6)	41(2)	40(2)	27(2)	-10(1)	15(1)	-18(1)
	C(35)	28(3)	41(3)	47(3)	-25(2)	6(2)	-6(2)
	C(36)	34(3)	25(2)	40(3)	-4(2)	7(2)	-5(2)
	C(37)	34(3)	34(2)	23(2)	-6(2)	4(2)	-7(2)
	C(38)	40(3)	32(2)	23(2)	1(2)	7(2)	-9(2)
	C(39)	34(2)	28(2)	26(2)	4(2)	9(2)	-4(2)
	C(40)	47(3)	35(2)	30(3)	-5(2)	17(2)	-8(2)
-	C(41)	57(3)	35(3)	43(3)	-7(2)	24(3)	-2(2)

Table C 2 10 continued

	Table C.2.10. continued.							
Atom Number	U ¹¹	U ²²	U33	U23	U13	U12		
C(42)	31(3)	29(2)	39(3)	-11(2)	14(2)	-10(2)		
C(43)	28(2)	34(2)	23(2)	2(2)	3(2)	-6(2)		
C(44)	19(2)	31(2)	29(2)	-3(2)	6(2)	-8(2)		
C(45)	19(2)	28(2)	49(3)	-10(2)	1(2)	-2(2)		
C(46)	24(2)	41(3)	53(4)	25(2)	1(2)	-3(2)		
C(47)	36(3)	56(3)	35(3)	3(2)	3(2)	-20(2)		
C(48)	46(3)	46(3)	27(3)	2(2)	7(2)	-14(2)		
C(49)	52(3)	33(3)	44(3)	-13(2)	22(3)	-10(2)		
C(50)	51(3)	32(3)	47(3)	5(2)	0(2)	4(2)		
C(51)	69(4)	67(4)	39(3)	16(3)	5(3)	-16(3)		
O(7)	94(4)	60(3)	130(5)	7(3)	50(3)	10(2)		

D-HA	d(D-H)	d(HA)	d(DA)	<(DHA)
O(1)-H(1)O(5)#1	0.84	2.13	2.966(5)	170.1
O(2)-H(2)O(3)#2	0.84	1.95	2.750(4)	158.3
O(6)-H(6)O(4)#3	0.84	1.94	2.764(4)	166.5
O(7)-H(7B)F(1)	0.927(10)	2.09(4)	2.940(6)	151(6)
O(7)-H(7B)O(1)	0.927(10)	2.35(6)	3.005(6)	127(6)

Table C.2.11. Hydrogen bonds for $10_{RR/SS}\,$ [Å and °].

#1 x-1/2,y+1/2,z #2 x,-y+1,z+1/2 #3 x-1/2,y-1/2,z+1

Identification code	cg30	
Empirical formula	C14 H10 F6 O2	
Formula weight	324.22	
Temperature	110(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 8.0864(14) Å	α= 71.603(4)°.
	b = 9.1407(17) Å	$\beta = 67.915(3)^{\circ}$.
	c = 9.6053(16) Å	$\gamma = 73.695(3)^{\circ}$.
Volume	613.56(19) Å ³	
Ζ	2	
Density (calculated)	1.755 Mg/m ³	
Absorption coefficient	0.176 mm ⁻¹	
F(000)	328	
Crystal size	0.27 x 0.24 x 0.17 mm ³	
Theta range for data collection	2.35 to 26.00°.	
Index ranges	-9<=h<=9, -11<=k<=11, -	
	11<=1<=11	
Reflections collected	16320	
Independent reflections	2384 [R(int) = 0.0279]	
Completeness to theta = 26.00°	99.2 %	
Absorption correction	Semi-empirical from	
	equivalents	
Max. and min. transmission	0.9708 and 0.9539	
Refinement method	Full-matrix least-squares on	
	F ²	
Data / restraints / parameters	2384 / 0 / 212	
Goodness-of-fit on F ²	1.029	
Final R indices [I>2sigma(I)]	R1 = 0.0277, wR2 = 0.0704	
R indices (all data)	R1 = 0.0298, wR2 = 0.0723	
Largest diff. peak and hole	0.334 and -0.311 e.Å ⁻³	

Table C.2.12. Crystal data and structure refinement for $9_{RR/SS}$.

Atom Number	Х	у	Z	U(eq)
F(1)	1496(1)	8372(1)	5640(1)	30(1)
F(2)	4212(1)	8132(1)	4043(1)	29(1)
F(3)	3147(1)	6070(1)	5568(1)	28(1)
F(4)	579(1)	8705(1)	12670(1)	26(1)
F(5)	-1651(1)	7730(1)	14485(1)	31(1)
F(6)	919(1)	6227(1)	13719(1)	28(1)
O(1)	-1996(1)	8607(1)	11534(1)	23(1)
O(2)	4014(1)	9216(1)	6476(1)	23(1)
C(1)	2836(2)	6931(1)	8309(1)	17(1)
C(2)	1347(2)	7750(1)	9275(1)	18(1)
C(3)	686(2)	6719(1)	10702(1)	17(1)
C(4)	1472(2)	3856(2)	11840(1)	20(1)
C(5)	2477(2)	2341(2)	11896(1)	22(1)
C(6)	4036(2)	1802(2)	10788(1)	22(1)
C(7)	4961(2)	2606(2)	9322(1)	21(1)
C(8)	4553(2)	4172(2)	8573(1)	19(1)
C(9)	3936(2)	7630(1)	6691(1)	17(1)
C(10)	-882(2)	7187(2)	12043(1)	20(1)
C(11)	3178(2)	7560(2)	5490(1)	21(1)
C(12)	-244(2)	7465(2)	13225(1)	21(1)
C(14)	3151(2)	5352(1)	9109(1)	17(1)
C(15)	1732(2)	5211(1)	10663(1)	17(1)

Table C.2.13. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å²x 10^3) for **9**_{RR/SS}. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	Number	Å (°)	Atom Number	Å (°)
F(1)-	·C(11)	1.3325(15)	C(4)-C(5)-C(6)	128.45(12)
F(2)-	·C(11)	1.3483(14)	C(5)-C(6)-C(7)	129.72(12)
F(3)-	·C(11)	1.3467(15)	C(8)-C(7)-C(6)	128.94(11)
F(4)-	·C(12)	1.3375(15)	C(14)-C(8)-C(7)	129.08(11)
F(5)-	·C(12)	1.3464(14)	O(2)-C(9)-C(1)	112.62(10)
F(6)-	-C(12)	1.3378(14)	O(2)-C(9)-C(11)	107.50(10)
O(1)-	-C(10)	1.4175(16)	C(1)-C(9)-C(11)	111.81(10)
O(2)	-C(9)	1.4138(15)	O(1)-C(10)-C(3)	110.77(10)
C(1)	-C(2)	1.4013(17)	O(1)-C(10)-C(12)	106.69(10)
C(1)-	-C(14)	1.4072(17)	C(3)-C(10)-C(12)	111.91(10)
C(1)	-C(9)	1.5055(15)	F(1)-C(11)-F(3)	107.36(10)
C(2)	-C(3)	1.4028(16)	F(1)-C(11)-F(2)	106.82(10)
C(3)-	-C(15)	1.4041(17)	F(3)-C(11)-F(2)	106.44(9)
C(3)-	-C(10)	1.5050(16)	F(1)-C(11)-C(9)	113.28(10)
C(4)	-C(5)	1.3909(18)	F(3)-C(11)-C(9)	111.15(10)
C(4)-	-C(15)	1.3925(17)	F(2)-C(11)-C(9)	111.41(10)
C(5)	-C(6)	1.3920(18)	F(4)-C(12)-F(6)	107.27(10)
C(6)	-C(7)	1.3947(18)	F(4)-C(12)-F(5)	106.85(10)
C(7)	-C(8)	1.3925(18)	F(6)-C(12)-F(5)	106.61(9)
C(8)-	-C(14)	1.3918(17)	F(4)-C(12)-C(10)	112.59(10)
C(9)-	-C(11)	1.5202(16)	F(6)-C(12)-C(10)	112.11(10)
C(10)	-C(12)	1.5217(17)	F(5)-C(12)-C(10)	111.08(10)
C(14)	-C(15)	1.4952(15)	C(8)-C(14)-C(1)	126.47(11)
			C(8)-C(14)-C(15)	127.00(11)
C(2)-C((1)-C(14)	108.70(10)	C(1)-C(14)-C(15)	106.49(10)
C(2)-C	(1)-C(9)	125.68(11)	C(4)-C(15)-C(3)	126.39(11)
C(14)-C	C(1)-C(9)	125.61(11)	C(4)-C(15)-C(14)	127.23(11)
C(1)-C	(2)-C(3)	109.54(11)	C(3)-C(15)-C(14)	106.37(10)
C(2)-C((3)-C(15)	108.88(10)	F(1)-C(11)	1.3325(15)
C(2)-C((3)-C(10)	124.65(11)	F(2)-C(11)	1.3483(14)
C(15)-C	(3)-C(10)	126.46(11)	F(3)-C(11)	1.3467(15)
C(5)-C((4)-C(15)	129.43(11)	F(4)-C(12)	1.3375(15)

Table C.2.14. Bond lengths [Å] and angles [°] for $9_{RR/SS}$.

Atom Number	Å (°)	Atom Number	Å (°)
F(5)-C(12)	1.3464(14)	C(1)-C(2)	1.4013(17)
F(6)-C(12)	1.3378(14)	C(1)-C(14)	1.4072(17)
O(1)-C(10)	1.4175(16)	C(1)-C(9)	1.5055(15)
O(2)-C(9)	1.4138(15)	C(2)-C(3)	1.4028(16)

Table C.2.14. continued.

Table C.2.15. Anisotropic displacement parameters (Å²x 10³) for **9**_{RR/SS}. The anisotropic displacement factor exponent takes the form: $-2\pi^2$ [h² a*²U¹¹ + ... + 2 h k a* b* U¹²]

Atom Number	U ¹¹	U22	U33	U23	U13	U12
F(1)	25(1)	41(1)	24(1)	-6(1)	-9(1)	-7(1)
F(2)	38(1)	40(1)	10(1)	-4(1)	1(1)	-21(1)
F(3)	39(1)	30(1)	21(1)	-9(1)	-4(1)	-17(1)
F(4)	28(1)	30(1)	25(1)	-10(1)	-10(1)	-7(1)
F(5)	26(1)	48(1)	13(1)	-13(1)	0(1)	0(1)
F(6)	31(1)	32(1)	19(1)	-7(1)	-12(1)	5(1)
O(1)	17(1)	31(1)	22(1)	-14(1)	-5(1)	1(1)
O(2)	29(1)	20(1)	18(1)	-8(1)	-1(1)	-9(1)
C(1)	18(1)	22(1)	12(1)	-5(1)	-2(1)	-9(1)
C(2)	19(1)	21(1)	14(1)	-4(1)	-2(1)	-8(1)
C(3)	18(1)	23(1)	12(1)	-4(1)	-2(1)	-9(1)
C(4)	21(1)	26(1)	13(1)	-4(1)	-2(1)	-10(1)
C(5)	28(1)	24(1)	15(1)	-1(1)	-6(1)	-10(1)
C(6)	27(1)	21(1)	21(1)	-5(1)	-10(1)	-6(1)
C(7)	20(1)	24(1)	20(1)	-10(1)	-4(1)	-4(1)
C(8)	20(1)	26(1)	14(1)	-7(1)	-2(1)	-9(1)
C(9)	18(1)	18(1)	13(1)	-4(1)	0(1)	-7(1)
C(10)	18(1)	25(1)	14(1)	-5(1)	0(1)	-7(1)
C(11)	23(1)	25(1)	13(1)	-4(1)	1(1)	-11(1)
C(12)	18(1)	26(1)	14(1)	-6(1)	-2(1)	0(1)
C(14)	18(1)	24(1)	12(1)	-5(1)	-2(1)	-10(1)
C(15)	18(1)	24(1)	12(1)	-5(1)	-2(1)	-9(1)

D-HA	d(D-H)	d(HA)	d(DA)	<(DHA)
O(2)-H(2A)O(1)#1	0.81(4)	2.13(4)	2.9171(15)	166(3)
O(2)-H(2B)O(2)#2	0.75(4)	2.08(4)	2.820(2)	169(4)
O(1)-H(1A)O(2)#1	0.82(4)	2.11(4)	2.9171(16)	169(3)
O(1)-H(1A)F(5)	0.82(4)	2.49(3)	2.7912(13)	103(3)

Table C.2.16. Hydrogen bonds for $9_{RR/SS}$ [Å and °].

#1 -x,-y+2,-z+2 #2 -x+1,-y+2,-z+1

Identification code	cg31	
Empirical formula	C19 H18 F6 O3	
Formula weight	408.33	
Temperature	110(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C2/c	
Unit cell dimensions	a = 19.2572(16) Å	<i>α</i> = 90°.
	b = 14.1615(12) Å	β=112.1980(10)°.
	c = 14.1880(11) Å	$\gamma = 90^{\circ}$.
Volume	3582.4(5) Å ³	
Ζ	8	
Density (calculated)	1.514 Mg/m ³	
Absorption coefficient	0.142 mm ⁻¹	
F(000)	1680	
Crystal size	0.31 x 0.21 x 0.20 mm ³	
Theta range for data collection	1.84 to 28.28°.	
Index ranges	-25<=h<=25, -18<=k<=18, -	
	16<=1<=18	
Reflections collected	12758	
Independent reflections	4424 [R(int) = 0.0243]	
Completeness to theta = 28.28°	99.5 %	
Absorption correction	Semi-empirical from	
	equivalents	
Max. and min. transmission	0.9717 and 0.9573	
Refinement method	Full-matrix least-squares on	
	F ²	
Data / restraints / parameters	4424 / 0 / 276	
Goodness-of-fit on F ²	1.074	
Final R indices [I>2sigma(I)]	R1 = 0.0695, wR2 = 0.1937	
R indices (all data)	R1 = 0.0963, $wR2 = 0.2107$	
Largest diff. peak and hole	0.781 and -0.375 e.Å ⁻³	

Table C.2.17. Crystal data and structure refinement for $10_{RS/SR}$.

Atom Number	x	V	Z	U(ea)
F(1)	2827(2)	2194(2)	-695(2)	102(1)
F(2)	2027(2) 2998(1)	3629(2)	-991(2)	89(1)
F(3)	1969(1)	2959(2)	-1883(2)	61(1)
F(4)	6809(1)	2939(2) 3828(2)	852(1)	62(1)
F(5)	5970(1)	3039(2)	1171(1)	61(1)
F(6)	5770(1) 5671(1)	3037(2)	318(1)	56(1)
O(1)	6129(1)	3507(1)	-1100(1)	36(1)
O(1)	2840(1)	337(1) 3174(2)	-1190(1) 2052(2)	50(1)
O(2)	2040(1) 5014(2)	31/4(2)	-2933(2)	30(1) 22(1)
C(1)	5914(2)	3009(2)	-329(2)	33(1)
C(2)	6339(2)	2042(2)	-356(2)	40(1)
C(3)	5/41(2)	1260(2)	-/64(2)	34(1)
C(4)	5063(2)	1706(2)	-1084(2)	31(1)
C(5)	5112(2)	2685(2)	-966(2)	36(1)
C(6)	4393(2)	3057(2)	-1337(2)	35(1)
C(7)	3872(2)	2305(2)	-1692(2)	32(1)
C(8)	3044(2)	2479(2)	-2185(2)	35(1)
C(9)	2712(2)	2823(3)	-1437(2)	58(1)
C(10)	4278(1)	1435(2)	-1532(2)	28(1)
C(11)	4042(1)	487(2)	-1677(2)	31(1)
C(12)	3226(2)	223(2)	-2056(3)	47(1)
C(13)	4534(2)	-293(2)	-1474(2)	35(1)
C(14)	5326(2)	-383(2)	-1111(2)	39(1)
C(15)	5597(2)	-1396(2)	-1050(2)	47(1)
C(16)	5869(2)	316(2)	-791(2)	38(1)
C(17)	6090(2)	3554(2)	458(2)	44(1)
O(3)	5000	4785(2)	-2500	51(1)
O(4)	5210(2)	6314(3)	-2166(3)	39(1)
C(18)	4781(3)	5630(4)	-2704(4)	32(1)
C(19)	4098(11)	6017(12)	-3665(10)	46(5)
C(20)	5814(11)	6020(10)	-1347(13)	47(5)
C(21)	6497(3)	5755(5)	-1565(5)	47(2)

Table C.2.18. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å²x 10^3) for **10**_{RS/SR}. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom Number	Å (°)	Atom Number	Å (°)
F(1)-C(9)	1.334(4)	C(20)-C(21)	1.51(2)
F(2)-C(9)	1.320(5)		
F(3)-C(9)	1.342(4)	O(1)-C(1)-C(5)	114.5(2)
F(4)-C(17)	1.340(4)	O(1)-C(1)-C(17)	106.8(2)
F(5)-C(17)	1.336(4)	C(5)-C(1)-C(17)	111.8(2)
F(6)-C(17)	1.341(4)	O(1)-C(1)-C(2)	110.5(2)
O(1)-C(1)	1.427(3)	C(5)-C(1)-C(2)	101.1(2)
O(2)-C(8)	1.409(3)	C(17)-C(1)-C(2)	112.2(2)
C(1)-C(5)	1.502(4)	C(3)-C(2)-C(1)	107.3(2)
C(1)-C(17)	1.521(4)	C(16)-C(3)-C(4)	127.3(3)
C(1)-C(2)	1.565(4)	C(16)-C(3)-C(2)	126.7(3)
C(2)-C(3)	1.544(4)	C(4)-C(3)-C(2)	106.1(2)
C(3)-C(16)	1.363(4)	C(3)-C(4)-C(5)	114.0(3)
C(3)-C(4)	1.364(4)	C(3)-C(4)-C(10)	136.9(3)
C(4)-C(5)	1.395(4)	C(5)-C(4)-C(10)	109.1(2)
C(4)-C(10)	1.453(4)	C(6)-C(5)-C(4)	108.6(2)
C(5)-C(6)	1.386(4)	C(6)-C(5)-C(1)	139.9(3)
C(6)-C(7)	1.418(4)	C(4)-C(5)-C(1)	111.4(2)
C(7)-C(10)	1.431(3)	C(5)-C(6)-C(7)	108.7(2)
C(7)-C(8)	1.501(4)	C(6)-C(7)-C(10)	108.6(2)
C(8)-C(9)	1.510(4)	C(6)-C(7)-C(8)	121.8(2)
C(10)-C(11)	1.407(4)	C(10)-C(7)-C(8)	129.5(2)
C(11)-C(13)	1.413(4)	O(2)-C(8)-C(7)	114.3(2)
C(11)-C(12)	1.505(4)	O(2)-C(8)-C(9)	104.5(2)
C(13)-C(14)	1.419(4)	C(7)-C(8)-C(9)	112.5(2)
C(14)-C(16)	1.385(5)	F(2)-C(9)-F(1)	106.5(3)
C(14)-C(15)	1.518(4)	F(2)-C(9)-F(3)	106.2(3)
O(3)-C(18)#1	1.265(6)	F(1)-C(9)-F(3)	107.2(3)
O(3)-C(18)	1.265(6)	F(2)-C(9)-C(8)	113.9(3)
O(4)-C(18)	1.314(6)	F(1)-C(9)-C(8)	110.6(3)
O(4)-C(20)	1.362(17)	F(3)-C(9)-C(8)	111.9(3)
C(18)-C(19)	1.592(15)	C(11)-C(10)-C(7)	132.2(2)

Table C.2.19. Bond lengths [Å] and angles [°] for $10_{RS/SR}$.

Atom Number	Å (°)	Atom Number	Å (°)			
C(11)-C(10)-C(4)	122.8(2)	F(5)-C(17)-F(6)	107.2(3)			
C(7)-C(10)-C(4)	105.0(2)	F(4)-C(17)-F(6)	107.0(3)			
C(10)-C(11)-C(13)	124.2(2)	F(5)-C(17)-C(1)	112.2(3)			
C(10)-C(11)-C(12)	121.7(2)	F(4)-C(17)-C(1)	111.5(3)			
C(13)-C(11)-C(12)	114.1(2)	F(6)-C(17)-C(1)	111.7(2)			
C(11)-C(13)-C(14)	133.6(3)	C(18)#1-O(3)-C(18)	38.0(4)			
C(16)-C(14)-C(13)	129.0(2)	C(18)-O(4)-C(20)	114.7(7)			
C(16)-C(14)-C(15)	117.1(3)	O(3)-C(18)-O(4)	118.8(4)			
C(13)-C(14)-C(15)	113.8(3)	O(3)-C(18)-C(19)	128.1(7)			
C(3)-C(16)-C(14)	126.0(3)	O(4)-C(18)-C(19)	112.3(7)			
F(5)-C(17)-F(4)	106.8(2)	O(4)-C(20)-C(21)	115.4(14)			

Table C.2.19. continued.

#1 -x+1,y,-z-1/2

Atom Number	U11	U22	U33	U23	U13	U12
F(1)	86(2)	179(3)	59(1)	53(2)	47(1)	72(2)
F(2)	55(1)	119(2)	74(2)	-57(2)	2(1)	27(1)
F(3)	43(1)	87(2)	53(1)	4(1)	18(1)	23(1)
F(4)	43(1)	82(2)	39(1)	-11(1)	-11(1)	-7(1)
F(5)	67(1)	85(2)	25(1)	1(1)	9(1)	3(1)
F(6)	54(1)	53(1)	45(1)	-21(1)	2(1)	7(1)
O(1)	36(1)	34(1)	29(1)	5(1)	1(1)	2(1)
O(2)	33(1)	68(2)	41(1)	15(1)	6(1)	10(1)
C(1)	35(1)	34(1)	24(1)	4(1)	3(1)	8(1)
C(2)	34(2)	43(2)	35(1)	6(1)	5(1)	7(1)
C(3)	31(1)	50(2)	19(1)	5(1)	6(1)	1(1)
C(4)	41(2)	32(1)	18(1)	1(1)	10(1)	2(1)
C(5)	45(2)	33(1)	24(1)	-3(1)	7(1)	-4(1)
C(6)	42(2)	30(1)	27(1)	0(1)	7(1)	7(1)
C(7)	41(2)	31(1)	23(1)	0(1)	10(1)	7(1)
C(8)	37(2)	34(1)	31(1)	-3(1)	10(1)	5(1)
C(9)	48(2)	83(3)	36(2)	-1(2)	10(1)	26(2)
C(10)	33(1)	33(1)	16(1)	0(1)	7(1)	8(1)
C(11)	28(1)	42(1)	19(1)	1(1)	4(1)	2(1)
C(12)	38(2)	36(2)	57(2)	0(1)	5(1)	-2(1)
C(13)	52(2)	31(1)	23(1)	0(1)	14(1)	2(1)
C(14)	60(2)	42(2)	20(1)	10(1)	20(1)	27(1)
C(15)	63(2)	43(2)	35(1)	6(1)	20(1)	25(2)
C(16)	33(1)	59(2)	23(1)	10(1)	11(1)	18(1)
C(17)	35(2)	55(2)	30(1)	-4(1)	-3(1)	5(1)
O(3)	79(2)	26(1)	32(1)	0	4(2)	0
O(4)	41(3)	29(2)	39(2)	0(2)	7(2)	4(2)
C(18)	25(3)	33(3)	35(3)	-4(2)	9(2)	-1(2)
C(19)	32(6)	47(8)	33(6)	-7(5)	-17(4)	13(5)
C(20)	39(7)	17(6)	82(11)	-12(5)	20(7)	2(4)
C(21)	31(3)	45(3)	58(4)	12(3)	9(3)	-3(3)

Table C.2.20. Anisotropic displacement parameters (Å²x 10³) for **10**_{RS/SR}. The anisotropic displacement factor exponent takes the form: $-2\pi^2$ [h² a^{*2}U¹¹ + ... + 2 h k a^{*} b^{*} U¹²]

D-HA	d(D-H)	d(HA)	d(DA)	<(DHA)
O(1)-H(1A)O(3)	0.84	1.99	2.821(2)	170.3
O(2)-H(2C)O(1)#1	0.84	1.93	2.758(3)	169.0

Table C.2.21. Hydrogen bonds for $10_{RS/SR}$ [Å and °].

#1 -x+1,y,-z-1/2

Identification code	cg32	
Empirical formula	C18 H16 F6 O2	
Formula weight	378.31	
Temperature	110(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 9.8755(7) Å	α=117.467(2)°.
	b = 9.8911(4) Å	β=94.555(3)°.
	c = 10.0443(4) Å	$\gamma = 110.150(3)^{\circ}$.
Volume	783.09(7) Å ³	
Z	2	
Density (calculated)	1.604 Mg/m ³	
Absorption coefficient	0.151 mm ⁻¹	
F(000)	388	
Crystal size	0.30 x 0.20 x 0.11 mm ³	
Theta range for data collection	2.29 to 28.29°.	
Index ranges	-13<=h<=13, -13<=k<=13,	
	-12<=l<=13	
Reflections collected	8936	
Independent reflections	3813 [R(int) = 0.0248]	
Completeness to theta = 25.00°	98.9 %	
Absorption correction	Semi-empirical from	
	equivalents	
Max. and min. transmission	0.9842 and 0.9557	
Refinement method	Full-matrix least-squares on	
	F ²	
Data / restraints / parameters	3813 / 0 / 238	
Goodness-of-fit on F ²	1.070	
Final R indices [I>2sigma(I)]	R1 = 0.0476, wR2 = 0.1305	
R indices (all data)	R1 = 0.0601, wR2 = 0.1381	
Largest diff. peak and hole	0.603 and -0.331 e.Å ⁻³	

Table C.2.22. Crystal data and structure refinement for $11_{RR/SS}$.
Atom Number	Х	У	Z	U(eq)
F(1)	3005(1)	5191(1)	8789(1)	25(1)
F(2)	3796(1)	7821(2)	9570(1)	31(1)
F(3)	5229(1)	6982(2)	10379(1)	39(1)
F(4)	2721(1)	5462(1)	1744(1)	24(1)
F(5)	1448(1)	6746(2)	1468(1)	28(1)
F(6)	3461(1)	8120(1)	3387(1)	24(1)
O(1)	864(2)	7526(2)	4230(2)	23(1)
O(2)	6158(2)	7764(2)	8254(2)	28(1)
C(1)	3673(2)	5720(2)	6300(2)	16(1)
C(2)	3394(2)	6904(2)	5999(2)	17(1)
C(3)	2197(2)	5965(2)	4637(2)	16(1)
C(4)	418(2)	3229(2)	2835(2)	17(1)
C(5)	-363(2)	1490(2)	2060(2)	20(1)
C(6)	30(2)	442(2)	2416(2)	20(1)
C(7)	1256(2)	900(2)	3616(2)	19(1)
C(8)	2413(2)	2433(2)	4831(2)	16(1)
C(9)	4851(2)	6248(2)	7728(2)	21(1)
C(10)	1312(2)	6200(2)	3541(2)	17(1)
C(11)	-16(2)	4392(2)	2485(2)	19(1)
C(12)	-977(2)	-1434(2)	1398(2)	28(1)
C(13)	3481(2)	2230(2)	5811(2)	25(1)
C(14)	2636(2)	4045(2)	5124(2)	16(1)
C(15)	1691(2)	4250(2)	4106(2)	15(1)
C(16)	4176(2)	8794(2)	6962(2)	23(1)
C(17)	4217(2)	6568(3)	9123(2)	23(1)
C(18)	2241(2)	6642(2)	2535(2)	18(1)

Table C.2.23. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å²x 10^3) for **11**_{RR/SS}. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom Number	Å (°)	Atom Number	Å (°)
F(1)-C(17)	1.338(2)	C(3)-C(2)-C(1)	107.13(15)
F(2)-C(17)	1.335(2)	C(3)-C(2)-C(16)	124.85(16)
F(3)-C(17)	1.341(2)	C(1)-C(2)-C(16)	127.99(16)
F(4)-C(18)	1.343(2)	C(2)-C(3)-C(15)	109.24(15)
F(5)-C(18)	1.3406(19)	C(2)-C(3)-C(10)	140.46(16)
F(6)-C(18)	1.338(2)	C(15)-C(3)-C(10)	110.27(15)
O(1)-C(10)	1.415(2)	C(15)-C(4)-C(5)	127.19(16)
O(2)-C(9)	1.421(2)	C(15)-C(4)-C(11)	106.80(15)
C(1)-C(14)	1.423(2)	C(5)-C(4)-C(11)	125.96(15)
C(1)-C(2)	1.439(2)	C(4)-C(5)-C(6)	125.33(16)
C(1)-C(9)	1.520(2)	C(5)-C(6)-C(7)	128.51(16)
C(2)-C(3)	1.395(2)	C(5)-C(6)-C(12)	116.44(16)
C(2)-C(16)	1.499(2)	C(7)-C(6)-C(12)	115.05(16)
C(3)-C(15)	1.396(2)	C(8)-C(7)-C(6)	134.91(16)
C(3)-C(10)	1.501(2)	C(7)-C(8)-C(14)	124.91(16)
C(4)-C(15)	1.383(2)	C(7)-C(8)-C(13)	113.96(15)
C(4)-C(5)	1.384(2)	C(14)-C(8)-C(13)	121.10(16)
C(4)-C(11)	1.524(2)	O(2)-C(9)-C(1)	114.48(14)
C(5)-C(6)	1.396(3)	O(2)-C(9)-C(17)	105.36(15)
C(6)-C(7)	1.418(3)	C(1)-C(9)-C(17)	110.89(14)
C(6)-C(12)	1.515(2)	O(1)-C(10)-C(3)	116.91(14)
C(7)-C(8)	1.404(2)	O(1)-C(10)-C(18)	103.19(13)
C(8)-C(14)	1.411(2)	C(3)-C(10)-C(18)	110.71(14)
C(8)-C(13)	1.512(2)	O(1)-C(10)-C(11)	114.84(14)
C(9)-C(17)	1.525(2)	C(3)-C(10)-C(11)	101.83(13)
C(10)-C(18)	1.527(2)	C(18)-C(10)-C(11)	109.44(14)
C(10)-C(11)	1.567(2)	C(4)-C(11)-C(10)	106.21(14)
C(14)-C(15)	1.459(2)	C(8)-C(14)-C(1)	133.74(16)
		C(8)-C(14)-C(15)	121.63(15)
C(14)-C(1)-C(2)	109.65(15)	C(1)-C(14)-C(15)	104.63(14)
C(14)-C(1)-C(9)	126.86(16)	C(4)-C(15)-C(3)	113.30(15)
C(2)-C(1)-C(9)	123.41(15)	_C(4)-C(15)-C(14)	137.31(16)

Table C.2.24. Bond lengths [Å] and angles [°] for $11_{RR/SS}$.

Atom Number	Å (°)		Atom Number	Å (°)
C(3)-C(15)-C(14)	109.31(15)		F(6)-C(18)-F(5)	106.88(14)
F(2)-C(17)-F(1)	106.92(15)		F(6)-C(18)-F(4)	107.14(14)
F(2)-C(17)-F(3)	106.51(16)		F(5)-C(18)-F(4)	106.77(14)
F(1)-C(17)-F(3)	107.45(15)		F(6)-C(18)-C(10)	112.43(14)
F(2)-C(17)-C(9)	113.03(15)		F(5)-C(18)-C(10)	112.20(14)
F(1)-C(17)-C(9)	111.00(16)	-	F(4)-C(18)-C(10)	111.10(14)
F(3)-C(17)-C(9)	111.61(15)			

Table C.2.24. continued.

Atom Number	U11	U ²²	U33	U ²³	U13	U12
F(1)	24(1)	28(1)	22(1)	16(1)	9(1)	6(1)
F(2)	37(1)	24(1)	20(1)	7(1)	10(1)	8(1)
F(3)	27(1)	63(1)	22(1)	26(1)	1(1)	10(1)
F(4)	30(1)	27(1)	20(1)	13(1)	14(1)	15(1)
F(5)	30(1)	45(1)	26(1)	28(1)	12(1)	19(1)
F(6)	23(1)	21(1)	29(1)	17(1)	10(1)	5(1)
O(1)	30(1)	27(1)	26(1)	17(1)	16(1)	18(1)
O(2)	17(1)	34(1)	23(1)	15(1)	2(1)	0(1)
C(1)	17(1)	19(1)	14(1)	10(1)	6(1)	6(1)
C(2)	18(1)	16(1)	14(1)	8(1)	6(1)	4(1)
C(3)	19(1)	15(1)	15(1)	9(1)	7(1)	6(1)
C(4)	17(1)	23(1)	15(1)	12(1)	8(1)	9(1)
C(5)	14(1)	22(1)	16(1)	8(1)	2(1)	4(1)
C(6)	16(1)	16(1)	20(1)	6(1)	7(1)	3(1)
C(7)	21(1)	15(1)	23(1)	10(1)	9(1)	8(1)
C(8)	16(1)	20(1)	15(1)	11(1)	6(1)	8(1)
C(9)	18(1)	26(1)	17(1)	12(1)	5(1)	7(1)
C(10)	18(1)	19(1)	15(1)	10(1)	6(1)	8(1)
C(11)	18(1)	21(1)	19(1)	11(1)	3(1)	6(1)
C(12)	27(1)	17(1)	28(1)	8(1)	3(1)	3(1)
C(13)	27(1)	26(1)	25(1)	14(1)	4(1)	14(1)
C(14)	16(1)	18(1)	14(1)	10(1)	7(1)	7(1)
C(15)	17(1)	16(1)	14(1)	9(1)	7(1)	7(1)
C(16)	27(1)	16(1)	18(1)	8(1)	2(1)	4(1)
C(17) C(18)	18(1) 20(1)	31(1) 20(1)	16(1) 18(1)	13(1) 12(1)	2(1) 7(1)	5(1) 9(1)

Table C.2.25. Anisotropic displacement parameters (Å²x 10³) for **11**_{RR/SS}. The anisotropic displacement factor exponent takes the form: -2 π^2 [h² a*²U¹¹ + ... + 2 h k a* b* U¹²]

REFERENCES

- (1) Eliel, E. L. In Organic Chemistry; Springer, 1982; pp. 1–76.
- (2) Joesten, M. D.; Hogg, J. L.; Castellion, M. E. *The World of Chemistry: Essentials: Essentials*; Cengage Learning, 2006.
- (3) Wu, R.; Silks, L. A.; Odom, J. D.; Dunlap, R. B. Spectroscopy 1996, 11, 37–42.
- (4) Rehman, W.; Arfons, L. M.; Lazarus, H. M. *Ther. Adv. Hematol.* **2011**, *2*, 291–308.
- (5) Rouhi, A. M. *C&E News*. June 14, 2004, pp. 47–62.
- (6) Horgen, D. A.; Klausmeyer, K. K.; Carson, C.; Shen, H.; Garner, C. M. *Tetrahedron Lett.*
- (7) Horgen, D.; Garner, C. *Chromatography* **2014**, *1*, 65–74.
- (8) Garner, C. M. J. Chem. Educ. 2005, 82, 1686.
- (9) Liu, R. S. H. J. Chem. Educ. 2002, 79, 183.
- (10) Mochalin, V. B.; Porshnev, Y. N. Russ. Chem. Rev. 1977, 46, 1002–1040.
- (11) Zhang, L.-Y.; Yang, F.; Shi, W.-Q.; Zhang, P.; Li, Y.; Yin, S.-F. Bioorg. Med. Chem. Lett. 2011, 21, 5722–5725.
- (12) Kurihara, T.; Noguchi, M.; Noguchi, T.; Wakabayashi, H.; Motohashi, N.; Sakagami, H. *In Vivo* 2006, 20, 385–389.
- (13) Blice-Baum, A.; Van Dyke, A.; Sigmon, I.; Salter, E. A.; Wierzbicki, A.; Pocker, Y.; Spyridis, G. T. Int. J. Quantum Chem. 2006, 106, 2331–2338.
- (14) Akatsu, Y.; Ohshima, N.; Yamagishi, Y.; Nishishiro, M.; Wakabayashi, H.;
 Kurihara, T.; Kikuchi, H.; Katayama, T.; Motohashi, N.; Shoji, Y. *Anticancer Res.* 2006, 26, 1917–1923.
- (15) Hafner, K.; Kaiser, H. Org. Synth. 1964, 94–94.
- (16) Hafner, K.; Kaiser, H. Org. Synth. 1984, 62, 134.
- (17) Garner, C. M. *Techniques and Experiments for Advanced Organic Laboratory*; Instructor's Edition.; John Wiley & Sons, 1997.

- (18) Anderson, A. G.; Scotoni, R.; Cowles, E. J.; Fritz, C. G. J. Org. Chem. 1957, 22, 1193–1196.
- (19) Anderson, A. G.; Steckler, B. M. J. Am. Chem. Soc. 1959, 4941–4946.
- (20) Naoshima, Y.; Kimura, T.; Mori, Y.; Kamezawa, M.; Tachibana, H.; Kohara, K.; Ohtani, T. *Recent Res Devel Org Bioorg Chem* **2004**, *6*, 1–9.
- (21) Redl, F. X.; Köthe, O.; Röckl, K.; Bauer, W.; Daub, J. *Macromol. Chem. Phys.* 2000, 201, 2091–2100.
- (22) Oki, M.; Nakamura, N. Bull. Chem. Soc. Jpn. 1971, 44, 1880–1885.
- (23) Anderson Jr, A. G.; Anderson, R. G.; Hollander, G. T. J. Org. Chem. 1965, 30, 131–138.
- (24) Chen, A.; Yen, H.; Kuo, Y.; Chen, W. Synth. Commun. 2007, 37, 2975–2987.
- (25) Okano, K. Tetrahedron 2011, 67, 2483–2512.
- (26) Loidl, G.; Hans-Jurgen, M.; Budisa, N.; Huber, R.; Poirot, S.; Fourmy, D.; Moroder, L. J. Pept. Sci. 2000, 6, 139–144.
- (27) Gubitz, G.; Schmid, M. G. In *Methods in Molecular Biology*; Humana Press: Totowa NJ, 2004; Vol. 243, pp. 1–424.
- (28) Gawley, R. A.; Aube, J. In *Principles of Asymmetric Synthesis*; Elsevier: Oxford UK, 2012; pp. 76–79.
- (29) Dou, L.; Zeng, J.-N.; Gerochi, D. D.; Duda, M. P.; Stuting, H. H. J. Chromatogr. A 1994, 679, 367–374.
- (30) Ribeiro, A. R.; Castro, P. M. L.; Tiritan, M. E. Environ. Chem. Lett. 2012, 10, 239–253.
- (31) Hamidpour, R.; Hamidpour, S.; Hamidpour, M.; Shahlari, M. Int. J. Case Rep. Images 2013, 4, 86–87.
- (32) Chelucci, G. Chem. Soc. Rev. 2006, 35, 1230.
- (33) Tolman, C. A. J. Am. Chem. Soc. 1970, 92, 2953–2956.
- (34) Tolman, C. A. Chem. Rev. 1977, 77, 313–348.
- (35) Maerkl, G. Angew. Chem. 1966, 78, 907.
- (36) Maerkl, G. Tetrahedron Lett. 1968, 41, 4379.
- (37) Mathey, F.; Le Floch, P. Sci. Synth. 2005, 15, 1097–1155.

- (38) DiMauro, E. F.; Kozlowski, M. C. J. Chem. Soc. [Perkin 1] 2002, 439–444.
- (39) Pham-Tran, N.-N.; Bouchoux, G.; Delaere, D.; Nguyen, M. T. J. Phys. Chem. A 2005, 109, 2957–2963.
- (40) Muller, C.; Vogt, D. In Catalysis by Metal Complexes; pp. 151–181.
- (41) Van der Velde, N. A.; Korbitz, H. T.; Garner, C. M. *Tetrahedron Lett.* **2012**, *53*, 5742–5744.
- (42) Bell, J. R.; Franken, A.; Garner, C. M. *Tetrahedron* **2009**, *65*, 9368–9372.
- (43) Li, C.-J.; Trost, B. M. Proc. Natl. Acad. Sci. 2008, 105, 13197–13202.
- (44) Webb, P. B.; Kunene, T. E.; Cole-Hamilton, D. J. Green Chem. 2005, 7, 373.
- (45) Pfaltz, A.; Drury, W. J. Proc. Natl. Acad. Sci. 2004, 101, 5723–5726.
- (46) Broussard, M.; Juma, B.; Train, S. G.; Peng, W.-J.; Laneman, S. A.; Stanley, G. G. Science 1993, 260, 1784–1788.
- (47) Fern ndez-P rez, H.; Etayo, P.; Panossian, A.; ida 1-Ferran, A. Chem. Rev. 2011, 111, 2119–2176.
- (48) Robbins, D. Rhodium-Catalysed Stereselective Hydroformylation, 2008.
- (49) Wei, Y.; Shi, M. Chem. Rev. 2013, 113, 6659–6690.
- (50) Baylis, A.; Hillmann, M. Acrylic compounds. DE 2155113 A 19720510, 1972.
- (51) Yang, Y.-L.; Pei, C.-K.; Shi, M. Org. Biomol. Chem. 2011, 9, 3349.
- (52) Morita, K.; Suzuki, Z.; Hirose, H. Bull. Chem. Soc. Jpn. 1968, 41, 2815–2815.
- (53) Li, J. J. Name reactions: a collection of detailed mechanisms and synthetic applications; 4th expanded ed.; Springer-Verlag: Berlin, 2009.
- (54) Aggarwal, V. K.; Emme, I.; Fulford, S. Y. J. Org. Chem. 2003, 68, 692–700.
- (55) Ohrui, H. Anal. Sci. 2008, 24, 31–38.
- (56) Suárez-Castillo, O. R.; Meléndez-Rodríguez, M.; Castelán-Duarte, L. E.; Sánchez-Zavala, M.; Rivera-Becerril, E.; Morales-Ríos, M. S.; Joseph-Nathan, P. *Tetrahedron Asymmetry* 2009, 20, 2374–2389.
- (57) Harmata, M. Acc. Chem. Res. 2004, 37, 862–873.
- (58) Mathias, L. J.; Overberger, C. G. J. Org. Chem. 1980, 45, 1701–1703.

- (59) Hafner, K.; Kaiser, H. Justus Liebigs Ann. Chem. 1958, 618, 140-152.
- (60) Leijondahl, K.; Fransson, A.-B. L.; Bäckvall, J.-E. J. Org. Chem. 2006, 71, 8622– 8625.
- (61) Miyazaki, M. Chem. Pharm. Bull. (Tokyo) 1960, 8, 146–149.
- (62) Prakash, G. K. S.; Krishnamurti, R.; Olah, G. A. J. Am. Chem. Soc. 1989, 111, 393–395.
- (63) Johnston, H. W.; Williams, J. L. R. J. Am. Chem. Soc. 1947, 69, 2065–2065.
- (64) Breslow, R.; Belvedere, S.; Gershell, L.; Leung, D. *Pure Appl. Chem.* **2000**, *72*, 333–342.
- (65) Martell, A. E. Adavnces Chem. Ser. 1967, 62, 272–294.
- (66) Yang, S.; Li, C.; Wang, S.; Zhao, L.; Hou, Z.; Lou, H.; Ren, D. J. Chromatogr. A 2013, 1311, 134–139.
- (67) Tabata, H.; Yoneda, T.; Oshitari, T.; Takahashi, H.; Natsugari, H. J. Org. Chem. 2013, 78, 6264–6270.
- (68) Christov, P. P.; Hawkins, E. K.; Kett, N. R.; Rizzo, C. J. Tetrahedron Lett. 2013, 54, 4289–4291.
- (69) Berova, N.; Bari, L. D.; Pescitelli, G. Chem. Soc. Rev. 2007, 36, 914.
- (70) Frelek, J.; Klimek, A.; Ruśkowska, P. *Tetrahedron Asymmetry* 2002, 13, 2461– 2469.
- (71) Yoon, T. P.; Jacobsen, E. Science 2003, 299, 1691–1693.
- (72) Fuchs, E.; Keller, M.; Breit, B. Chem. Eur. J. 2006, 12, 6930-6939.
- (73) Wallis, C.; Edwards, P. G.; Hanton, M.; Newman, P. D.; Stasch, A.; Jones, C.; Tooze, R. P. *Dalton Trans.* 2009, 2170.
- (74) Breit, B.; Winde, R.; Mackewitz, T.; Paciello, R.; Harms, K. *Chem. Weinh. Bergstr. Ger.* **2001**, *7*, 3106–3121.
- (75) Sakai, N.; Mano, S.; Nozaki, K.; Takaya, H. J. Am. Chem. Soc. 1993, 115, 7033– 7034.
- (76) Müller, C.; Vogt, D. Dalton Trans. 2007, 5505.
- (77) Breit, B.; Fuchs, E. ChemInform 2006, 37.

- (78) Bell, J. R. Synthesis and Application of C2 Asymmetric Phosphinines via Their Pyrylium Salt Precursors. Dissertation, Baylor University, 2009.
- (79) Märkl, G.; Lieb, F. Angew. Chem. **1968**, 80, 702–703.
- (80) Ashe, A. J.; Gordon, M. D. J. Am. Chem. Soc. 1972, 94, 7596-7597.
- (81) Piechaczyk, O.; Doux, M.; Ricard, L.; le Floch, P. *Organometallics* **2005**, *24*, 1204–1213.
- (82) Cambie, R. C.; Higgs, P. I.; Rutledge, P. S.; Woodgate, P. D. Aust J Chem 1994, 47, 1815–1831.
- (83) Okuma, K.; Nojima, A.; Matsunaga, N.; Shioji, K. Org. Lett. 2009, 11, 169–171.
- (84) Wu, T.; You, X. J. Phys. Chem. A 2012, 116, 8959–8964.
- (85) Nishiyama, H.; Sakaguchi, H.; Nakamura, T.; Horihata, M.; Kondo, M.; Itoh, K. Organometallics 1989, 8, 846–848.
- (86) Katritzky, A. R.; Leahy, D. E. J. Chem. Soc. Perkin Trans. 2 Phys. Org. Chem. 1985, 171–174.
- (87) Roques, R.; Sotiropoulos, J.; Declercq, J. P.; Germain, G. Acta Crystallogr. B 1979, 35, 2948–2952.
- (88) Kotsuki, H.; Sakai, H.; Jun, J.-G.; Shiro, M. Heterocycles 2000, 52, 661.
- (89) Rao Volla, C. M.; Vogel, P. Angew. Chem. Int. Ed. 2008, 47, 1305–1307.
- (90) Lewis, F. W.; Egron, G.; Grayson, D. H. *Tetrahedron Asymmetry* **2009**, *20*, 1531–1535.
- (91) Fabris, F.; De Martin, A.; De Lucchi, O. Tetrahedron Lett. 1999, 40, 9121–9124.
- (92) Fabris, F.; Zambrini, L.; Rosso, E.; De Lucchi, O. *Eur. J. Org. Chem.* **2004**, *2004*, 3313–3322.
- (93) Osborn, J. A.; Wilkinson, G.; Young, J. F. Chem. Commun. Lond. 1965, 17.
- (94) Breit, B. J. Mol. Catal. Chem. 1999, 143, 143-154.
- (95) Aguado-Ullate, S.; Guasch, L.; Urbano-Cuadrado, M.; Bo, C.; Carbó, J. J. Catal. Sci. Technol. 2012, 2, 1694.
- (96) Zuidema, E.; Escorihuela, L.; Eichelsheim, T.; Carbó, J. J.; Bo, C.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Chem. - Eur. J.* **2008**, *14*, 1843–1853.
- (97) Breit, B. Chem. Commun. 1996, 2071–2072.

- (98) Yan, Y.; Zhang, X. J. Am. Chem. Soc. 2006, 128, 7198–7202.
- (99) Erre, G.; Enthaler, S.; Junge, K.; Gladiali, S.; Beller, M. J. Mol. Catal. Chem. 2008, 280, 148–155.
- (100) Mazuela, J.; Pàmies, O.; Diéguez, M.; Palais, L.; Rosset, S.; Alexakis, A. *Tetrahedron Asymmetry* 2010, 21, 2153–2157.
- (101) Breit, B.; Winde, R.; Harms, K. J. Chem. Soc. [Perkin 1] 1997, 2681–2682.
- (102) Blug, M.; Le Goff, X.-F.; M z ailles, .; Le Floch, P. Organometallics 2009, 28, 2360–2362.
- (103) Blug, M.; Guibert, C.; Le Goff, X.-F.; Mézailles, N.; Le Floch, P. Chem. Commun. 2009, 201.
- (104) Huang, I.-D.; Jermansen, T. G.; Oswald, A. A.; Westner, A. A. Hydroformylation catalysis by branched alkyl diaryl phosphine rhodium complexes; Google Patents, 1986.
- (105) Clark, T. P.; Landis, C. R.; Freed, S. L.; Klosin, J.; Abboud, K. A. J. Am. Chem. Soc. 2005, 127, 5040–5042.
- (106) Crouch, R. D.; Nelson, T. D. J. Chem. Educ. 1995, 72, A6.