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Mechanistic Investigation, Development and Synthetic Applications of a Catalytic Enantioselective and Diastereoselective Allylboration Methodology

by

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With love and respect to Baba, Maiya and Baji

Abstract

Over the past two decades and continuing on, carbonyl allylation chemistry has been a very useful and popular tool for the stereocontrolled formation of carbon-carbon bonds in the field of organic synthesis. In the context of natural product synthesis, the efficiency and status of aldehyde allylboration method is only matched by the asymmetric and diastereoselective aldol methodology. Unfortunately, prior to the new millennium, the means to control the absolute stereoselectivity in the addition of allylic boron reagents had been restricted to stoichiometric chiral directors, appended onto the metal center. In 2002, the research groups of Hall and Miyaura reported a new Lewis acid-catalyzed allylboration reaction manifold, which raised intriguing mechanistic questions and also paved the way for a catalytic enantioselective methodology development.

Chapter 2 of this thesis details mechanistic studies related to the new Lewis acid-catalyzed allylboration. In this chapter, various control experiments and kinetic studies are presented, the results of which allowed us to propose a hypothesis involving the electrophilic boronate activation as the key factor for the observed rate enhancement.

Chapter 3 describes the initial phase of our research to develop a catalytic enantioselective allylboration methodology. We discovered that Brønsted acid catalysts derived from diol•$SnCl_4$ complexes were promising catalysts for the asymmetric addition of air and moisture stable and commercially available allylic pinacol boronates. Under this 1st generation catalyst-system, the corresponding homoallylic alcohols were obtained in moderate to good enantioselectivity and excellent diastereoselectivity.

The development of a novel chiral Brønsted acid catalyst for the highly enantio- and diastereoselective allylboration reaction methodology is the single most important result to come

from this thesis. Chapter 4 outlines the development of the 2nd generation catalyst system. A systematic study of the diol component of the catalyst system led us to arrive at a novel diol nicknamed Vivol on behalf of my contribution. The resulting Brønsted acid derived from Vivol•$SnCl_4$ now provided the corresponding homoallylic alcohol products in very good to excellent enantioselectivity. Preliminary mechanistic studies along with the X-ray diffraction structure of the catalyst system are also presented. Based on this information, an even better performaning diol (termed F-Vivol) was developed. This 3rd generation catalyst system derived from F-Vivol•$SnCl_4$ complex was shown to display consistently superior reactivity and selectivity over its 2nd generation predecessor.

Chapter 5 describes our efforts to expand the reagent scope of the Brønsted acid catalyzed allylboration methodology. Furthermore, this chapter also describes the successful application of the catalytic process towards the synthesis of simple and complex molecules. Accordingly, the preparation and application of the Brønsted acid-catalyzed addition of 2-bromoallyl boron pinacolate is described. The successful transformation of the corresponding bromo-homoallylic alcohols to a compelling class of γ-butyrolactones is also presented. The later part of the Chapter presents the synthesis of natural products (+) dodoneine and palmerolide A.

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Although this thesis carries my name, the work presented is certainly not a solo effort. I would like to convey my gratitude for the help and support of a great number of people who made this research possible.

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List of Abbreviations

AB	AB quartet
Ac	Acetyl
Anal.	Elemental Analysis
Ar	Aryl group
9BBN	9-Borabicyclononane
Binol	1,1'Bi-2-naphtol
Bn	Benzyl
br s	Broad Singlet
Bu	*n*-Butyl
*t*Bu	*tert*-Butyl
Calcd	Calculated
cat	Catalytic amount
Cy	Cyclohexyl
dd	Doublet of doublets
ddd	Doublet of doublets of doublets
DEAD	Diethyl azodicarboxylate
DIBAL-H	Diisobutylaluminum hydride
DMAP	Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulfoxide
dppf	1,1'-Bis(diphenylphosphono)ferrocene
dppp	1,3-Bis (diphenylphosphino) propane
dr	Diastereomeric ratio
dt	Doublet of triplets
ee	Enantiomeric excess
EI	Electron Impact
equiv	Equivalents
er	Enantiomeric ratio
ESI	Electrospray Ionization

Et	Ethyl
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
IR	Infrared Spectroscopy
LA	Lewis Acid
LBA	Lewis acid assisted Brønsted acid
m	Multiplet
Me	Methyl
Nu	Nucleophile
OAc	Acetoxy
ORTEP	Oak Ridge Thermal Ellipsoid Plot
OBn	Benzyloxy
OEt	Ethoxy
O*i*-Pr	*iso*-Propoxy
O*t*-Bu	*tert*-Butoxy
OMe	Methoxy
OMs	Methanesulfonate
OTf	Trifluoromethanesulfonate
Ph	Phenyl
PMA	Phosphomolybdic Acid
Pr	*n*-Propyl
i-Pr	*iso*-Propyl
*p*TSOH	*para*-Toluenesulfonic acid
PyBOX	2,6-bis(4,5-dihydro-4-phenyl-2-oxazolyl)pyridine
PMB	*para*-Methoxybenzyl
q	Quartet
qt	Quartet of triplets
R	Generic alkyl group
RT	Room temperature
t	Triplet
TBAF	Tetra-*n*-Butylammonium fluoride

TBS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-butyldimethyphenyllsilyl
TES	Triethylsilyl
THF	Tetrahydrofuran
TIPS	Triisopropylsiyl
TMEDA	*N*,*N*,*N'*,*N'*-Tetramethylethylenediamine
TMS	Trimethylsilyl
Ts	*para*-Toluenesulfonyl

Chapter 1

Introduction: Chirality, Asymmetric Synthesis, Catalytic Asymmetric Synthesis, and Allylboration Chemistry

1.1 Introduction

In Nature, the majority of biological systems recognize a pair of stereoisomers (molecules that are identical in all aspects except for the spatial orientation of their component atoms) as two different entities. In this context, a pair of enantiomers (stereoisomers that are non-superimposable complete mirror images) will also bring forth different responses. A classic example is illustrated by the distinct aroma of the lemons and oranges, a sensory response brought about by two enantiomers of limonene which are non-superimposable mirror images of each other. Along the same line, the distinct smell of Persian cumin and mint arise from two different enantiomers of carvone (Figure 1.1).

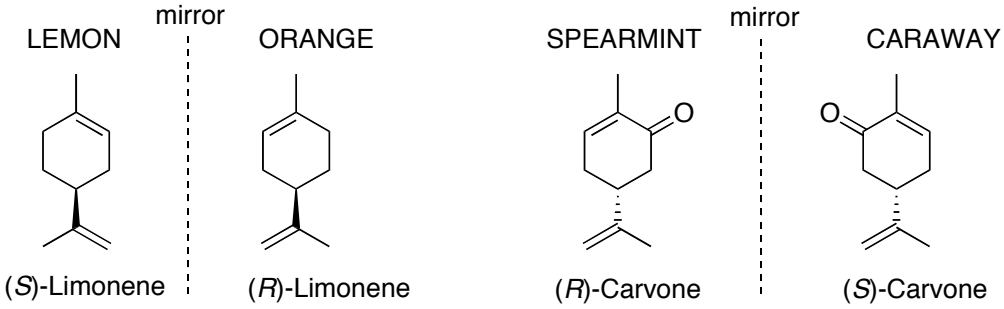


Figure 1.1. Chirality and biological response.

In terms of therapeutic relevance, one enantiomer may act as a drug while the other isomer may be extremely toxic. This statement is best realized by the example of the thalidomide disaster in the early 1960s. One isomer of the drug caused fetal birth defects by restricting the development of blood vessels in0 rapidly dividing tissues whereas the other enantiomer provided the therapeutically desired sedative effect.[1] In regard to this important issue of drug therapy, synthetic organic chemists have had to bear the responsibility to provide highly efficient and reliable methods to produce desired compounds in enantiomerically pure state. As such, the importance of asymmetric synthesis as a tool to construct enantiomerically enriched compounds has been fully acknowledged by chemists in organic, medicinal, agricultural, and pharmaceutical

professions. Indeed, at the beginning of the year 2000, the chiral drug industry represented one-third of the total drug sales worldwide and topped the US$ 100 billion mark.[2]

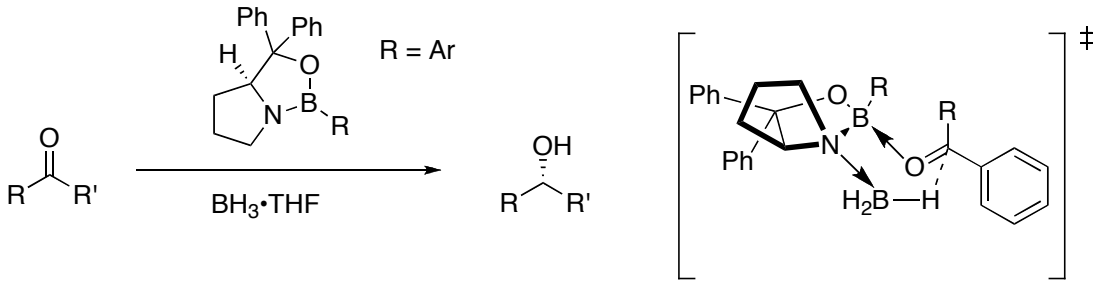
There are several ways of producing compounds as single enantiomers. One approach requires the optical resolution of naturally available racemate compounds, but this method is not readily applicable towards the synthesis of unnatural and scarce chiral compounds. To address this issue, traditional synthetic methods have employed a stoichiometric chiral director approach. In this method, the asymmetric information of the appended chiral backbone in the reacting substrate is relayed to the reaction products. However, this approach suffers from lack of atom economy and the requirement of additional steps for the attachment and removal of the chiral director. The emergent field of catalytic asymmetric synthesis has recently dealt with this issue where in, a sub-stoichiometric additive; a chiral catalyst can be used to create a vast number of chiral product molecules.[3]

1.2 Chiral acid catalysts

Modern chiral acid catalysts can be divided into chiral Lewis acids, chiral Brønsted acids and the class of combined acid catalyst system.[4]

1.2.1 Chiral Lewis acid catalysts

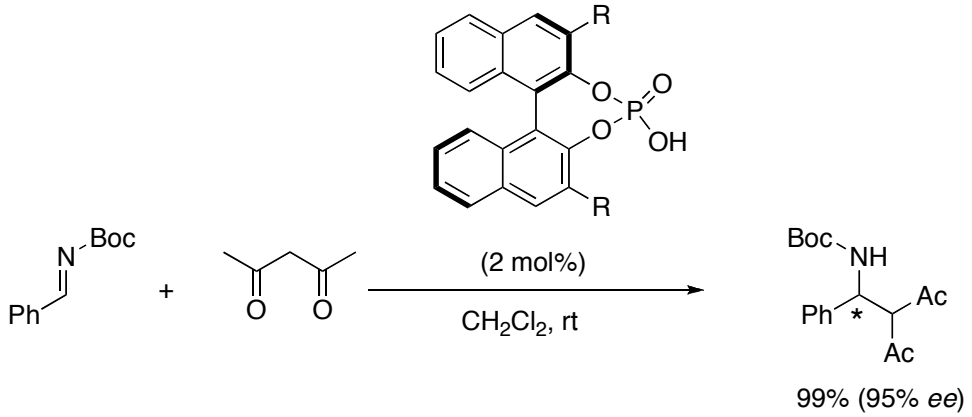
Chiral Lewis acids generally incorporate a Lewis acidic metal center that is complexed with a chiral ligand through a covalent or dative bond. This type of catalyst system has been the workhorse in the field of carbonyl activation. A widely used example of this form of activation is the asymmetric reduction of prochiral ketones catalyzed by oxazoborolidine catalysts (Equation 1.1).[5] More recently, Lewis acids derived from late transition metals have been shown to be efficient π-activators for the cyclization reactions involving en-yne substrates.[6]



Equation 1.1. Oxazaborolidine catalyzed asymmetric reduction of ketones.

1.2.2 Chiral Brønsted acid catalysts

Chiral Brønsted acids possess acidic protons held in a chiral environment and are often categorized as organocatalysts since most of these molecules are devoid of any metal counterpart. The recent emergence of imine activation by binaphthyl derived phosphoric acid catalysts, pioneered by Akiyama[7a] and Terada[7b] best illustrates the effectiveness of such catalyst systems. One excellent example of the application of Brønsted acid catalysis is the direct Mannich type reaction involving the use of diketones as nucleophiles (Equation 1.2).



Equation 1.2. Chiral Brønsted acid catalyzed asymmetric Mannich type reactions.[7a,b]

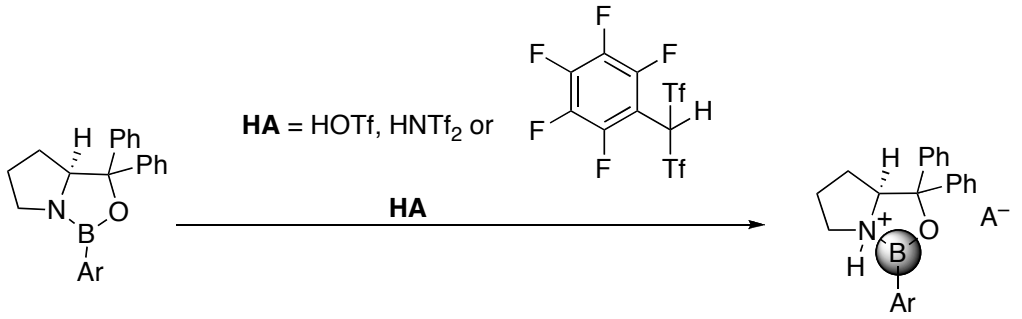
1.2.3 Combined acid catalysts

Alternatively, the incorporation of two acid entities in a single catalyst system can result in significantly enhanced acidity and organization of the activating species.[8] Such catalyst systems can be further divided into 4 subcategories.

1.2.3.1 Brønsted acid-assisted Lewis acid catalysts (BLA)

The combination of a Brønsted acid with a Lewis acidic catalyst system can lead to enhanced acidity of the Lewis acidic metal center. Such a catalyst system is best illustrated by the widespread use of protonated oxazaborolidines (Equation 1.3) to catalyze the enantioselective Diels-Alder reaction, as demonstrated by Corey[9] and Yamamoto.[10] Mechanistically speaking, the coordination of achiral Brønsted acid to the Lewis basic nitrogen atom in the oxazaborolidine

leads to significant depletion of electron density on the boron atom. This phenomenon results in enhanced Lewis acidity of the boron center and thus accelerated reaction rates.



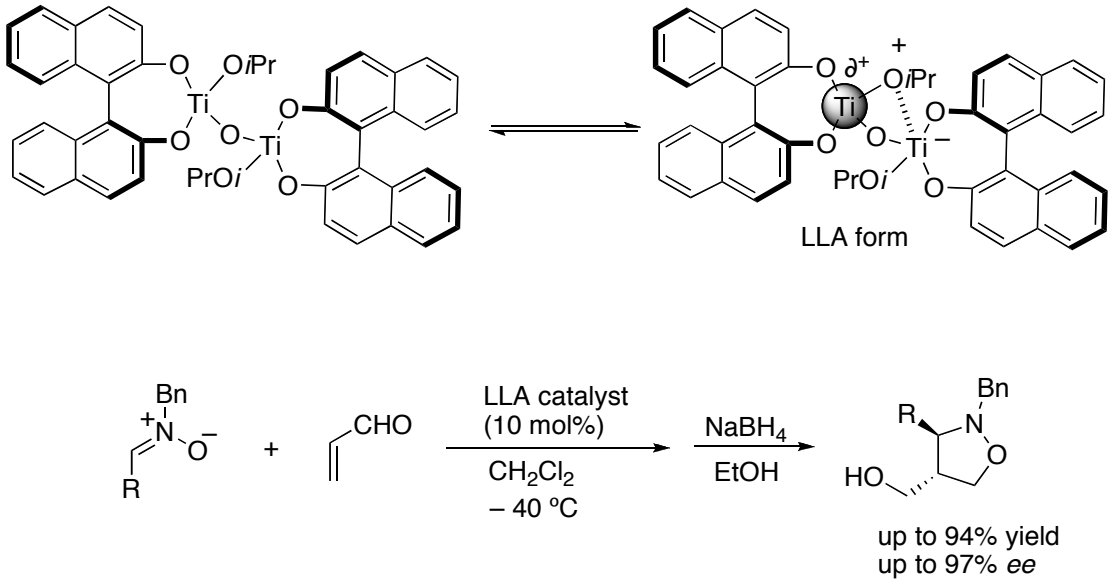
Equation 1.3. Corey and Yamamoto's protonated oxazaborolidine catalysts.[9,10]

1.2.3.2 Lewis acid-assisted Lewis acid catalysts (LLA)

The enhancement of the Lewis acidity by incorporation of another Lewis acid is well documented in the literature. Similar to BLA, the incorporation of an additional Lewis acid component results in depletion of electron density at the catalytically active Lewis acidic site (Equation 1.4).[11]

Equation 1.4. Corey and Yamamoto's Lewis acid activated oxazaborolidine catalyst.[11]

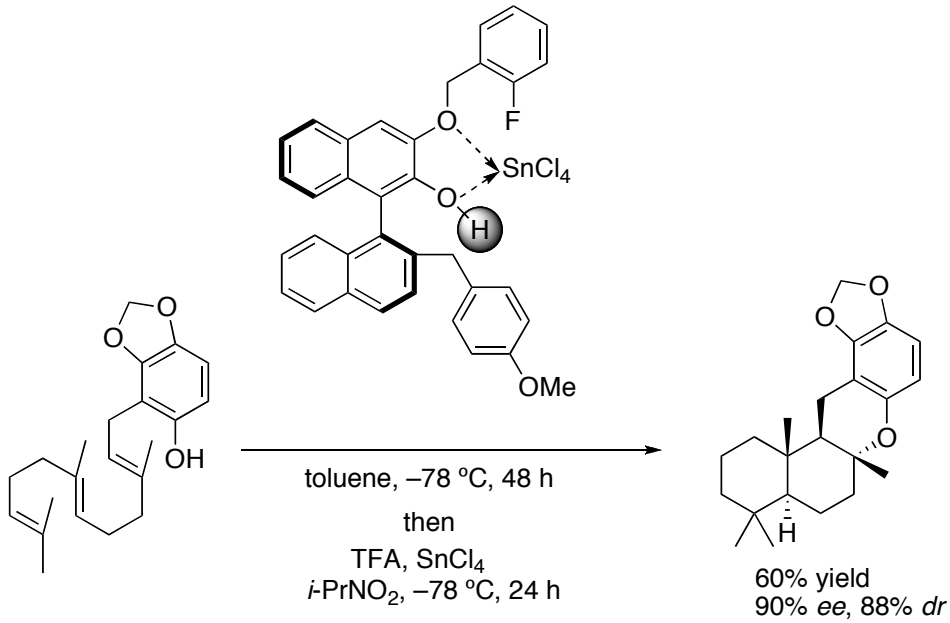
The catalyst system of Maruoka and coworkers is another excellent example of an LLA catalyst system (Equation 1.5) and provides superior selectivity for the asymmetric 1,3-dipolar cycloaddition reactions between nitrones and enals.[12a] It has been proposed that the Lewis acidity of one titanium center could be enhanced by the intramolecular coordination of the oxygen atom of the isopropoxy group to the other titanium center within the same catalyst. Such a type of activation is prevalent in many hetero-bimetallic catalysts systems that have been reported by the Shibasaki group.[12b]



Equation 1.5. 1,3-Dipolar cycloaddition catalyzed by a chiral bis(titanium)catalyst.[12a]

1.2.3.3 Lewis acid-assisted Brønsted acidity (LBA)

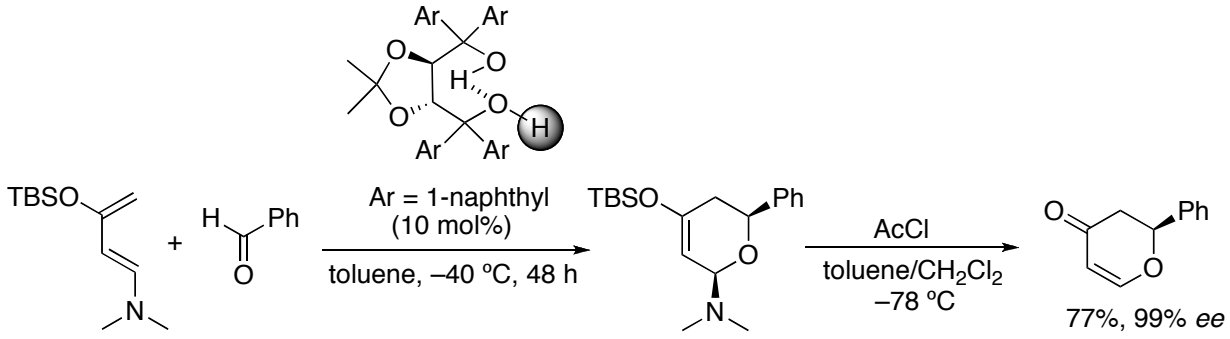
In this class of combined acidity, the combination of a Lewis acid with a Brønsted acid gives the opportunity to create a distinctive proton. In this case, the coordination of a Lewis acid to the heteroatom of the Brønsted acid can increase the acidity of the latter. If the Brønsted acid is a chiral alcohol, such complexation would result in the increased acidity of the alcoholic proton, and because the activated proton is held in a rigid environment, this strategy effectively allows for the generation of a chiral Brønsted acid. Such complexes have been shown by Yamamoto and coworkers to be remarkably effective in poly-ene cyclizations and consequently termed as artificial cyclases (Equation 1.6).[13]



Equation 1.6. $SnCl_4$-Catechol complex as LBA catalyst for enantioselective synthesis of polyprenoids.[13]

1.2.3.4 Brønsted acid assisted Brønsted Acid catalysts (BBA)

Intramolecular hydrogen bonding plays a critical role in organization of the three-dimensional structure of enzymes and is often implicated in the reaction of the active site of an enzyme. A molecular equivalent of such an organization and activation is best represented by the hydrogen bond catalysis of the Diels-Alder reaction as reported by Rawal and coworkers (Equation 1.7).[14] It has been proposed by the authors that intramolecular hydrogen bond leads to well-defined organization of the asymmetric backbone and also leads to enhanced Brønsted acidity of the other hydroxyl proton.

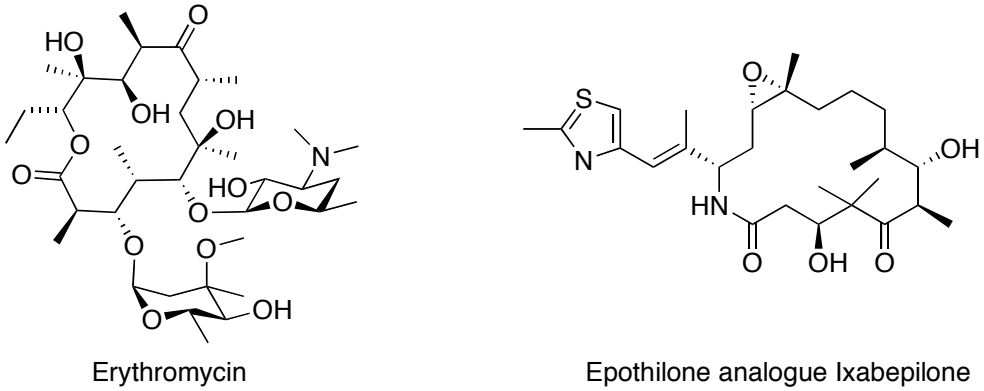


Equation 1.7. Asymmetric hetero Diels-Alder reaction catalyzed by Taddol derivative.[14]

1.3 Synthesis of polyacetate and polypropionate units

1.3.1 Introduction

Nature has provided mankind with an immense repertoire of biologically active natural products, many of which have been the starting point for drug development and are still being used since their discovery. For example, erythromycin (Figure 1.2) is a macrolide antibiotic that has found widespread use as a broad-spectrum antimicrobial antibiotic and is often given to people who are allergic to penicillins. Another class of biologically important molecules include the epothilones, which have been shown to possess potent anti-cancer properties similar to that of taxanes but come with the added benefit of superior efficacy and water solubility.[15] Moreover, the analogue ixabepilone (Figure 1.2) was approved in 2007 by the United States Food and Drug Administration for the treatment of aggressive metastatic or locally advanced breast cancer that no longer responds to currently available chemotherapies.[16]



Erythromycin

Epothilone analogue Ixabepilone

Figure 1.2. Complex natural products employed as therapeutic molecules.

A recurrent theme in the structural architecture of the above described and numerous other biologically relevant macrolides is the prevalence of polyacetate and polypropionate motifs (Figure 1.2 and Fig 1.3). Unfortunately, many therapeutically promising macrolides are scarce in nature and consequently require modern organic synthesis to address this issue. An outstanding example of such a problem was recently encountered in the large-scale synthesis[17] of (+)-discodermolide (Figure 1.3),[18] by Novartis pharmaceuticals, required for the preclinical

testing of this potent anti-cancer compound. Here again, the molecule possesses an array of polyacetate and propionate units that had to be synthesized in stereo selective manner.

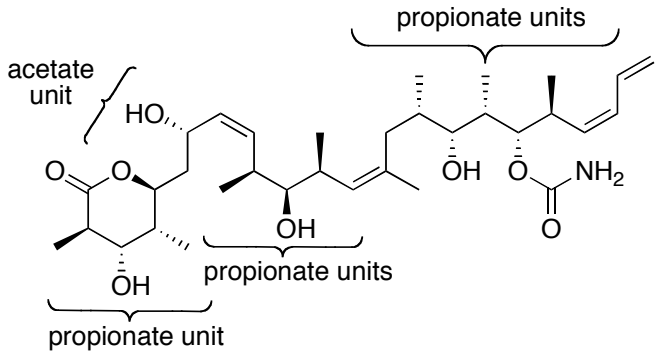


Figure 1.3. Structure of (+)-discodermolide showing propionate and acetate units.

Many well known reactions have addressed the important issue of construction of a sequence of stereocenters. These include the aldol addition, addition of allylmetals to aldehydes, epoxidation, dihydroxylation, hydroboration and stereo-controlled reductions. One key feature in these methods is the high degree of stereocontrol and a significant level of predictability, which assures success in the application towards new synthetic situations. Amongst all these processes, carbonyl allylation reactions occupy a central position.

1.3.2 Aldehyde allylation reactions

The addition of an allylmetal reagent onto an aldehyde has proven to be a very successful method for the stereo-controlled construction of contiguous stereocenters. This method has gained widespread popularity because of four key salient features: the high degree of diastereo- and enantioselectivity observed, the tremendous diversity of reagent reactivity based on the nature of the metal, the ability to access various kinds of stereodiads and triads, and the underlying functionality of the homoallylic products which makes this reaction ideal for the synthesis of complex molecules.[19] Moreover, the recent emergence of alkene-metathesis has significantly extended the usefulness of homoallylic alcohol products.[20]

The majority of aldehyde allylation reagents are based on metals and metalloids such as silicon[21], titanium[22], boron[23], chromium[24], indium[25], tin[26] and zinc.[27] In 1982 Denmark classified these allylmetal reagents based on the stereochemical mode of their reactions with 3-substituted allylic units.[28] The most common class: Type I reagents include organoboron, trihalosilicon, and

organoaluminum. Type I reagents are diastereospecific w.r.t. the allylic reagent, since the *syn*/*anti* product ratio is directly proportional to the *Z*/*E* ratio of the starting material's allylic geometry. This general observation is rationalized by invoking a compact, cyclic chair-like Zimmerman-Traxler transition structure (Figure 1.4).[29] In these reactions, the metal center provides activation of the aldehyde by the coordination to the carbonyl oxygen atom; therefore, the addition of external Lewis acids to activate the aldehyde is not required.

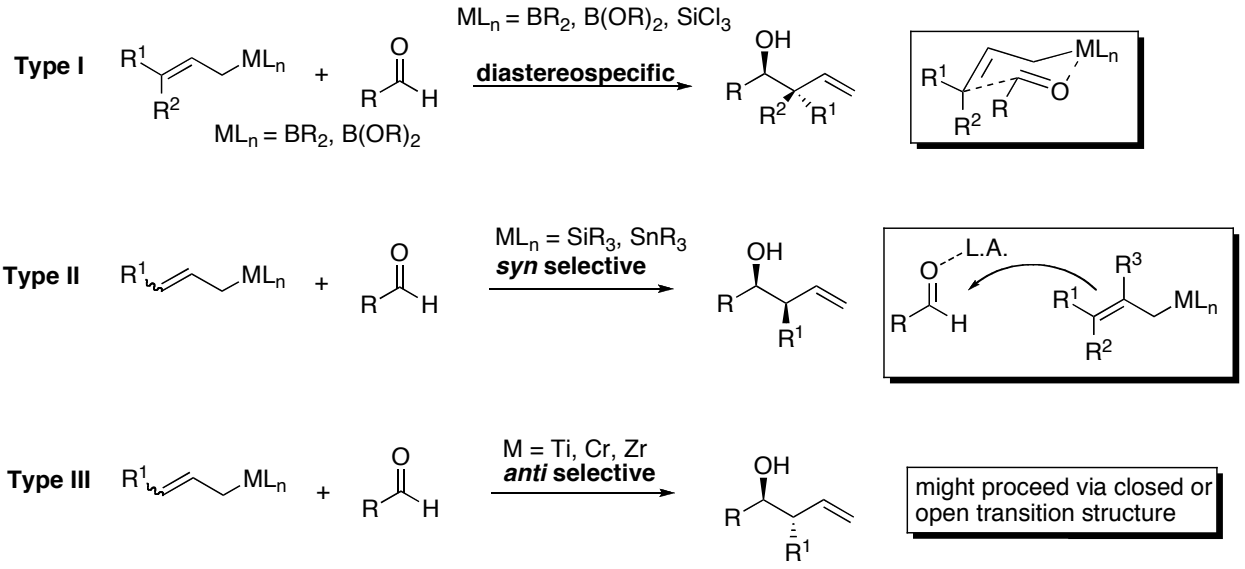


Figure 1.4. Classification of allylation reagents according to Denmark.[28]

On the other hand, Type II reagents include trialkylsilane and some trialkyltin reagents. These reagents are *syn* selective independent of the allylmetal's geometry. Moreover, these reagents require the presence of external Lewis acids to activate the aldehyde substrate and often provide low diastereoselectivity when using tri-substituted reagents since the reaction goes through a less organized, open transition state structure (Figure 1.4).

The lesser-known Type III reagents are exemplified by organotitanium, organochromium and organozirconium reagents. They are *anti* selective independent of the geometry of the allylmetal unit. Pre-equilibration of the allylmetal species to the more stable *E* isomer is rapid with these reagents. Open chain and chair-like transition structures have been invoked to rationalize the sterochemical outcome of aldehyde additions with these reagents.

As a consequence of their respective mechanism and mode of aldehyde addition, allyl transfer reactions based on Type I reagents have gained utmost importance because they are

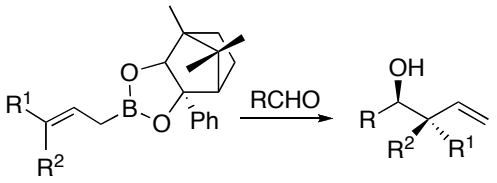
stereospecific, highly diastereoselective and predictable, with *cis* and *trans* crotyl reagents providing *syn* and *anti* propionate products respectively.

Amongst all Type I reagents, the stability, low toxicity, and ease of handling of organoboron reagents has contributed to their widespread application in organic synthesis.[31] The addition of an allylboron reagent to an unsaturated substrate is called the allylboration reaction. There are two subclasses of organoboron reagents used for allylboration: the highly reactive dialkyl allyl- and crotyl boranes (containing one allylic and two alkyl groups on the boron atom) and allylic boronic esters, also referred to as allylboronates (containing one allylic group and two alkoxy groups on the boron). The latter group provides the benefit of improved configurational stability and lower reactivity thus making them easier to handle and manipulate.

1.3.3 Allylboron reagents

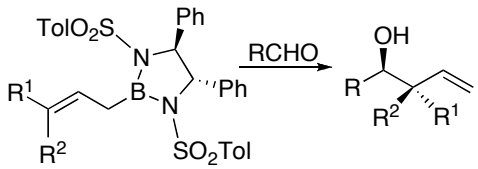
In 1964, Mikhailov and Bubnov first reported the addition of allylic organoboranes to carbonyl compounds and also showed the allylic inversion of 2-butenylboranes via a 1,3-boratropic shift.[23a] Subsequently, in late 1970's Hoffmann and coworkers pioneered the use of camphor derived allylboron reagents in the preparation of enantiomerically enriched homoallylic alcohols.[23b] After this report, the groups of Masamune, Brown, Roush and Corey designed auxiliaries for attachment into the boron center (Figure 1.5).[23] Of these reagents, Brown's terpene derived allylboranes have enjoyed widespread application in the creation of absolute stereochemistry whereas the Roush's tartrate derived reagents have found popularity in simple and double diastereocontrolled additions onto chiral aldehyde substrates. More recently, the research groups of Soderquist and Chong have also reported new chiral auxiliary systems.

Hoffmann



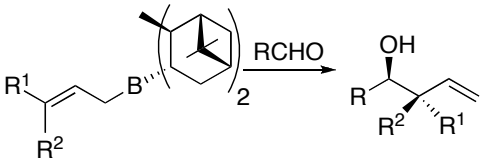
65-76% *ee*
R^1 or R^2 = Me: > 95% *dr*

Corey



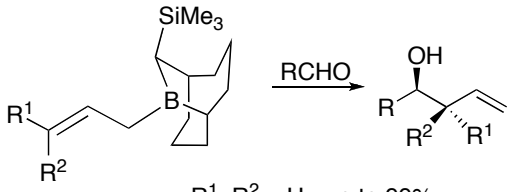
R^1, R^2 = H: > 95% *ee*
R^1 or R^2 = Me: up to 92% *ee*
and > 98% *dr*

Brown



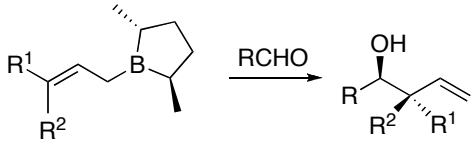
R^1, R^2 = H: up to 99% *ee*
R^1 or R^2 = Me: 88-92% *ee*
and > 98% *dr*

Soderquist



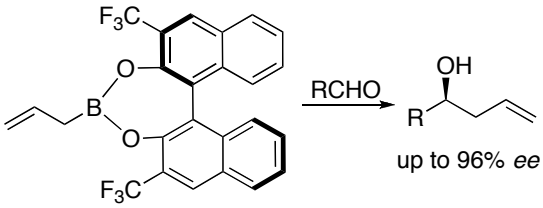
R^1, R^2 = H: up to 99% *ee*
R^1 or R^2 = Me: up to 99% *ee*
and > 98% *dr*

Masamune



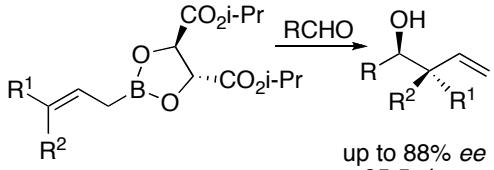
R^1 or R^2 = Me: up to 97% *ee*
and > 93:7 *dr*

Chong



up to 96% *ee*

Roush



up to 88% *ee*
> 95:5 *dr*

Figure 1.5. Chirally modified allylboron reagents and their representative stereo- and diastereoselectivities for allyl- and crotylborations of aldehydes.

1.3.4 Difficulties of attaining a catalytic allylboration method

It is noteworthy that after three decades since Hoffmann's report of asymmetric allylboration, there are no reports of a catalytic enantioselective allylboration of carbonyl substrates. Brown and coworkers have systematically studied the relative half-life of the allylation of benzaldehyde with various types of allylic boron reagents (Table 1.1).[29] From these studies, it is clear that allylic boronic acids, their acyclic ester derivatives, and the cyclic esters of catechol have significant background reaction at low temperature, and therefore the induction of asymmetry via a catalytic cycle would be hard to envision .[29] Although the cyclic esters of ethane and propane diol demonstrate the desirable negligible activity at low temperatures, these reagents are hydrolytically labile and require strictly anhydrous conditions. The presence of trace amount of adventitious moisture in allylation reaction can possibly lead to the formation of a very reactive allylic boronic acid, which can undergo a fast racemic reaction. It should also be pointed out that allylic boranes are next to impossible for application towards a catalytic enantioselective method because of their instantaneous reactivity (even at low temperatures) with aldehyde substrates.

In terms of practicality and reactivity, the hydrolytically stable and commercially available allylic boronate reagents derived from pinacol offer the best scenario for the development of a catalytic enantioselective allylboration approach.

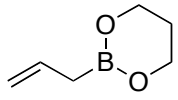
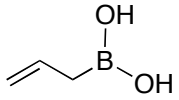
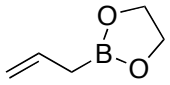
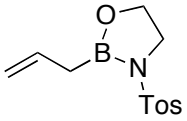
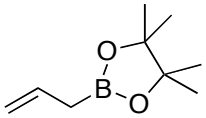
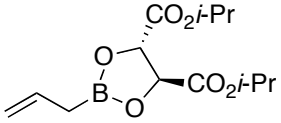
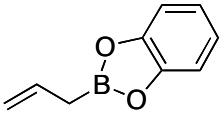
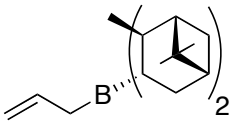
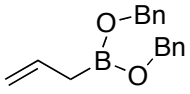
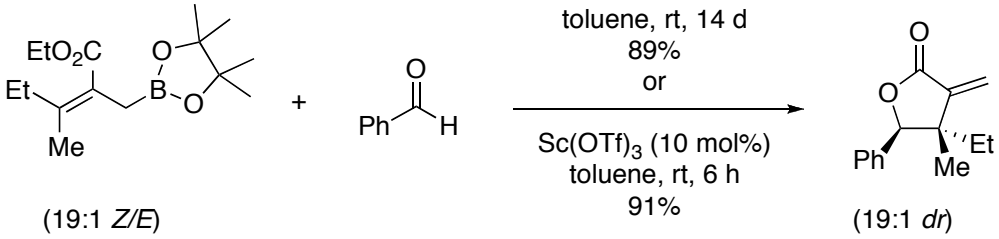
Reagent	% Reaction at low temperature	Reagent	% Reaction at low temperature
 **a**	0, 12 h, –78 ºC	 **f**	100, < 30 s, –50 ºC
 **b**	12, 6 h, –78 ºC	 **g**	100, 10 min, –78 ºC
 **c**	0, 12 h, –78 ºC	 **h**	12, 6 h, –78 ºC
 **d**	100, < 30 s, –50 ºC	 **i**	100, 15 min, –78 ºC
 **e**	50, 0.5 h, –50 ºC		

Table 1.1. Comparison of the rate of allylboration with representative allylic boron reagents with benzaldehyde.[31]

However, the main issue that prevented chemists from rendering aldehyde allylboration catalytic was the Type I mechanistic nature of the allylboron addition onto aldehydes (Figure 1.4). Since the allylboration reaction operates via self-activation of the aldehyde substrate by the boron atom of the reagent, incorporation of external Lewis acids would sequester the carbonyl lone pairs and thus change the course of the reaction to a Type II, open transition state manifold. Consequently, there could be complete loss of the desired stereospecificity that is normally observed with this reaction.

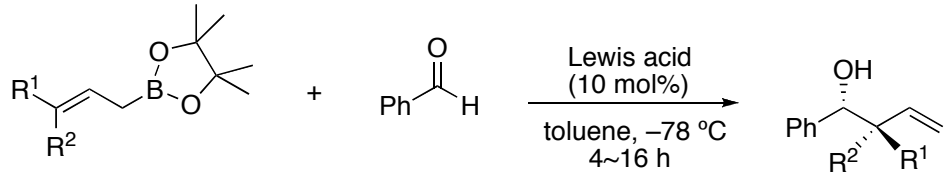
1.3.5 Lewis acid catalyzed allylboration

In 2002, the perception that carbonyl allylboration could not be catalyzed was changed by the reports of Hall and coworkers[32] and soon after by Miyaura and coworkers.[33] Hall's research group reported that metal salts like $Sc(OTf)_3$, $Cu(OTf)_2$ and $Yb(OTf)_3$ were efficient catalysts for the addition of very unreactive 2-alkoxy carbonylallylboronates onto aldehydes and provided up to 35 fold increase in rate acceleration. More importantly, they were able to show that there was complete preservation of the intrinsic diastereoselectivity of the reaction (Equation 1.8).[33]



Equation 1.8. Lewis acid-catalyzed allylboration.[32]

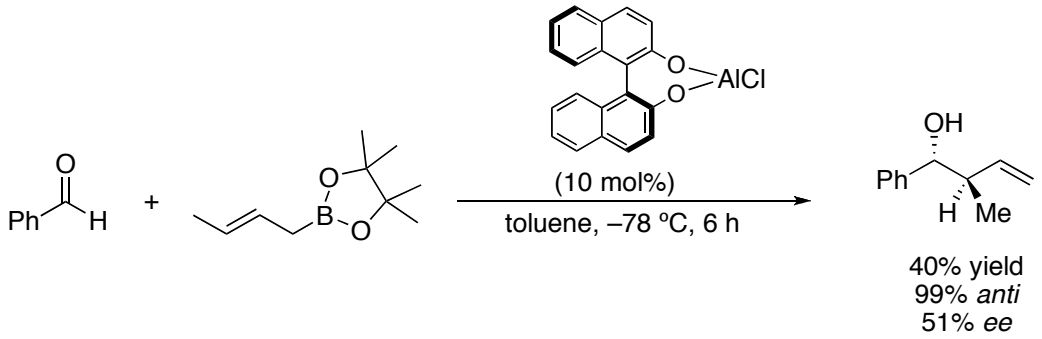
Miyaura and coworkers soon after reported significant rate differences between the catalyzed and uncatalyzed addition of simple allylic boronates to aldehydes at –78 ºC. They showed that allyl pinacolboronate was completely ineffective for the addition to benzaldehyde at –78 ºC and that addition of Lewis acids such as $AlCl_3$ and $Sc(OTf)_3$ did indeed catalyze the reaction, thus affording homoallylic alcohol products (Table 1.2).[33]



Boronate	Lewis Acid	Yield (%)	*anti*/*syn*
$R^1 = H, R^2 = H$	$AlCl_3$	88	-
$R^1 = H, R^2 = H$	$Sc(OTf)_3$	80	-
$R^1 = Me, R^2 = H$	$AlCl_3$	92	99/1
$R^1 = H, R^2 = Me$	$AlCl_3$	87	2/98

Table 1.2. Addition of allyl- and crotylboronates to benzaldehyde catalyzed by Lewis acids.[33]

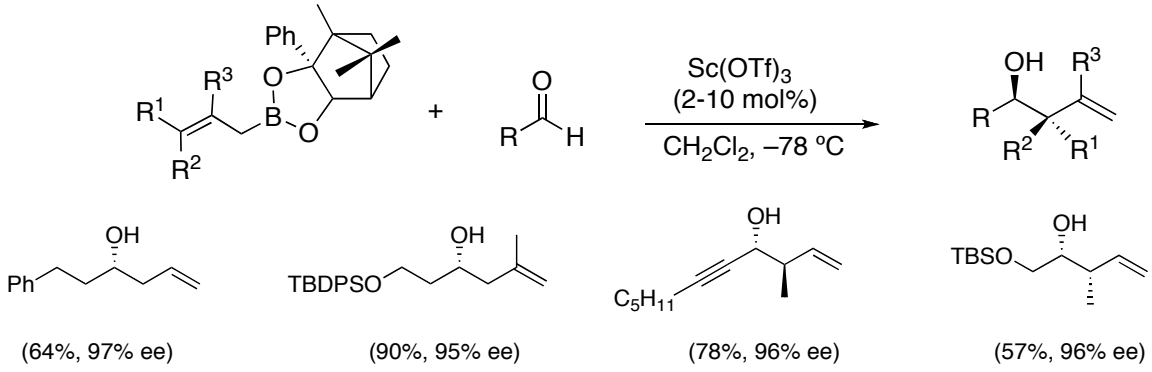
Here as well, the addition of (*E*)- or (*Z*)-2-butenylboronic esters to benzaldehyde produced the *syn* and *anti* homoallylic alcohols with high diastereoselectivities. Furthermore, they also reported the first examples of a catalytic asymmetric addition of allylboronates to benzaldehyde that was catalyzed by a chiral binol complex of aluminum Lewis acid (Equation 1.9).[33]



Equation 1.9. Chiral Lewis acid catalyzed asymmetric crotylboration of benzaldehyde as reported by Miyaura and coworkers.[33]

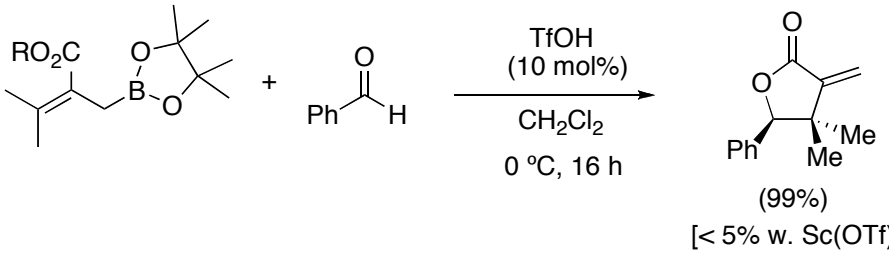
1.3.6 Applications of the acid-catalyzed allylboration of aldehydes

In 2003, Hall and coworkers exploited the rate acceleration phenomenon to develop a general and highly enantioselective additions of Hoffmann's camphor derived allylboronates onto aldehyde substrates.[34] Without a catalyst, these allylboronates are inert towards aldehydes at low temperature and give moderate selectivity at room temperature. However, under the new Lewis acid-catalyzed manifold, these reagents react with a wide variety of aldehydes at low temperature and provide the requisite homoallylic alcohol products in high enantio- and diastereocontrol (Equation 1.10).[34]



Equation 1.10. Lewis acid catalyzed enantioselective allyl-, methallyl- and crotylboration of aldehydes.[34]

In 2005, Hall and coworkers also reported the first case of Brønsted acid catalyzed allylboration of aldehydes.[35] The addition of a deactivated allylboronate onto benzaldehyde and other electron-rich aromatic aldehydes under Lewis acid catalysis provided less than 5% conversion at 0 ºC for 16 hours (Equation 1.11). However, utilization of triflic acid as a protic acid catalyst provided the requisite product as the desired lactone (after cyclization), in near quantitative yield despite the fears of reagent proto-deboronation and or cationic oligomerization.



Equation 1.11. Brønsted acid catalyzed allylboration of benzaldehyde with sterically and electronically deactivated allylboronates.[35]

1.4 Research objectives

The foundation for this thesis was overlaid by the discovery of the new Lewis acid-catalyzed allylboration of aldehydes. The next line of research called for the understanding of the mechanistic nature of this catalytic manifold as knowledge of the activation may help in the development of a catalytic enantioselective allylboration methodology.

Thus, this thesis starts with the report of mechanistic studies of the new Lewis acid catalyzed allylboration of aldehydes. In particular, Chapter 2 discusses various control experiments along with kinetic studies that lead us to hypothesize the possible mode of Lewis acid activation of allylboronates for the addition onto aldehyde substrates. Chapter 2 also describes a very recent computational study on the same reaction, which is in excellent agreement with our proposed hypothesis.

The ultimate application of the new Lewis and Brønsted acids catalyzed allylboration of aldehydes is the development of a general, catalytic enantioselective allylation and crotylation of aldehydes. Although the Brown methodology employing chiral allylic dialkylboranes has been proven to be highly reliable for more than two decades and is virtually recognized as a "cult reaction" in organic synthesis, these reagents are air and moisture sensitive and must be formed

in situ. Additionally, the oxidative workup of the reaction generates super-stoichiometric amounts of pinane derived alcohol, which in many occasions, coincidently has similar polarity to that of the homoallylic alcohol products, and thus difficult to separate. Moreover, all popular aldehyde allylation methods are stoichiometric in nature. It would thus represent a significant advantage to develop an effective and general method using stable and commercially available allyl- and crotylboronates derived from pinacol. Because these reagents have been shown to possess negligible reactivity at low temperature, this may allow for a catalytic enantioselective approach. If accomplished, such a method would be expected to have widespread application in the synthesis of polyacetates and polypropionate units.

Chapter 3 discusses my initial attempts to identify such a catalytic enantioselective system and Chapter 4 discusses an optimized catalyst system for the enantioselective allylboration of aldehyde substrates. The mechanistic studies performed on the optimized catalyst system allowed me to develop an even better performant catalyst. This work is the subject of the later part of chapter 4. Chapter 5 describes the application of this new catalytic enantioselective allylboration methodology towards the synthesis of chiral exomethylene γ-lactones and natural products (+)-dodoneine and palmerolide A.

1.5 References

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Chapter 2

Mechanistic Investigations of the New Lewis Acid Catalyzed Allylboration of Aldehydes[1]

2.1 Introduction

As mentioned in the previous chapter, allylic boron compounds are considered as Type I reagents. All known variants of allylic boron reagents likely react with aldehyde substrates through a compact, cyclic six-membered chairlike Zimmerman-Traxler transition state[2] and the dia-stereoselectivity of the reaction strongly correlates with the allylic geometry (*E* or *Z*) of the boron reagent. In this transition state, the Lewis acidic metal center of the reagent coordinates to one of the electron lone pairs of the carbonyl group and thus activates the aldehyde. This mode of self-activation is manifested in significantly enhanced B-O bonding in the transition state as depicted from the previous computational work of Fujimoto and coworkers and dominates the reaction over the incipient C-C bond formation.[3]

It was this very mechanistic understanding of allylboration that seemed to preclude the use of catalysts for the acceleration of slow thermal reactions. Moreover, there was an obvious concern that addition of an external Lewis acid might sequester the carbonyl lone pairs and render the reaction Type II, a process with reduced diastereoselectivity. The problem of slow reactivity with allylic boronates was often dealt with by the use of high temperatures and prolonged reaction times.[4]

By 2002, Hall and coworkers had developed a stereoselective route for the preparation of tertrasubstituted allylboronates such as **2.1** (Figure 2.1), with the anticipation of forming challenging quaternary carbon centers.[5] However, the reactivity of boronate **2.1** was significantly compromised by the presence of the 2-alkoxycarbonyl group as well as the presence of two alkyl substituents on C-3. Not surprisingly, the addition of **2.1** to model aldehydes took two full weeks at room temperature to go to completion. It was out of this necessity of faster reactions with reagents like **2.1** that led to the discovery of Lewis acid catalysis of aldehyde allylboration.[6] As mentioned in Chapter 1 Section 3.3, Hall and coworkers first reported that certain Lewis acids like $Sc(OTf)_3$ did indeed catalyze the addition of **2.1** onto aldehydes and provided up to 35 fold rate acceleration.[6] Shortly thereafter, Miyaura and co-workers also

disclosed similar findings and reported that Lewis acids like $Sc(OTf)_3$ and $AlCl_3$ efficiently catalyzed the low temperature addition of reagents **2.2-2.4** (Figure 2.1).[7]

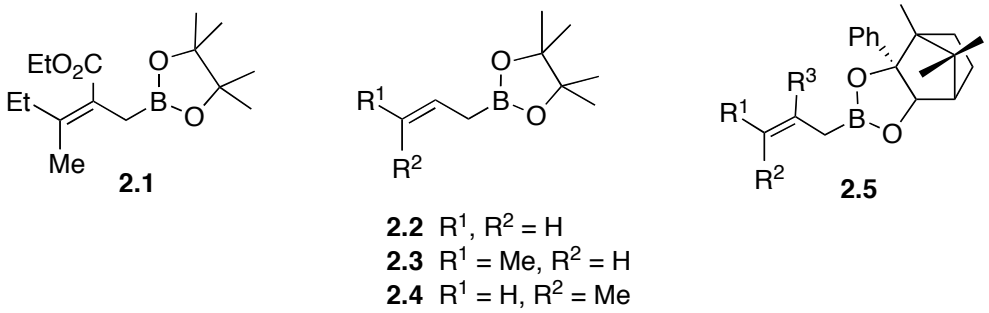


Figure 2.1. Allylic boronates implicated in the mechanistic study.[1]

Hall and coworkers later utilized this beneficial rate acceleration phenomenon for the advantage of a low temperature, advantage and subsequently disclosed the highly diastereo- and enantioselective allylboration of aldehydes by making use of Hoffmann's camphor derived allylic boronates.[8] It should be noted that boronate **2.5** (Figure 2.1) possesses negligible reactivity towards aldehydes at –78 ºC and tends to provide moderate enantioselectivity at room temperatures. However, the addition of Lewis acids provided the potential to run the reactions at much lower temperatures, which allowed the reactions to be more selective.

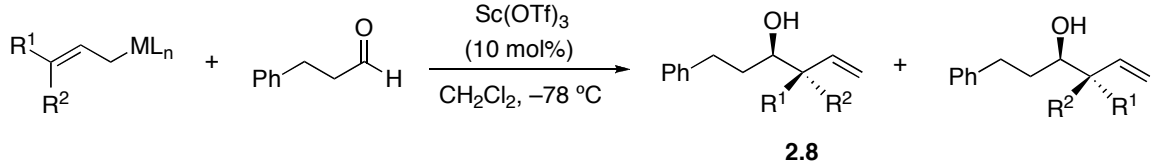
These reports begged the question about the intriguing mechanism of the novel Lewis acid catalyzed manifold to be addressed.

2.2 Type I or Type II?

The first general mechanistic question was the nature of the reaction. Did the reaction operate via a closed transition structure (Type I) or an open state (Type II). The observation that there was complete preservation of the diastereospecificity of the uncatalyzed reaction when using reagents **2.1**, **2.3** and **2.4** presented a strong indication that a Type I mechanism was at play.[4,5]

However, it was necessary to rule out the remote possibility that $Sc(OTf)_3$ could be an intrinsic promoter of a Type I stereoselectivity irrespective of the allylmetal species. The corresponding crotyl stannanes **2.6** and **2.7** (Figure 2.2) react with aldehydes in the presence of $BF_3{\bullet}OEt_2$ in a stereo-convergent fashion, a hallmark of a Type II process.[9] To address this issue, we needed to subject $Sc(OTf)_3$ as a Lewis acid catalyst to the Type II crotylstannation reaction

using reagents **2.6** and **2.7**. In order to test this hypothesis, isomerically enriched crotylstannanes **2.6** and **2.7** were prepared following literature procedures.[10] Test reactions of stannanes with hydrocinnamaldehyde were undertaken at low temperatures. In the event, it was found that $Sc(OTf)_3$ did not alter the intrinsic reactivity of **2.6** and **2.7** and the *syn* diastereomer **2.8** predominated regardless of the allylic geometry of the corresponding stannanes (Figure 2.2). These results confirmed the Type II stereochemical behavior of $Sc(OTf)_3$-catalyzed crotylstannations, which led us to conclude that a Type I mechanism was operative in the additions of allylboronates in the presence of $Sc(OTf)_3$ Lewis acid.



2.8

$ML_n = B(OR)_2$ (**2.3**), $R^1 = H$, $R^2 = Me$	**98**	:	**2**
$ML_n = B(OR)_2$ (**2.4**), $R^1 = Me$, $R^2 = H$	**2**	:	**98**
$ML_n = SnBu_3$ (**2.6**), $R^1 = H$, $R^2 = Me$	**98**	:	**2**
$ML_n = SnBu_3$ (**2.7**), $R^1 = Me$, $R^2 = H$	**98**	:	**2**

Figure 2.2. Lewis acid catalyzed crotylborations and crotylstannations.

2.3 Exact role of scandium Lewis acid

The next crucial issue concerned the exact role of the scandium in the allylboration reaction. The presence of triflate groups on the metal center necessitated precluding triflate anion from the catalysis of allylboration. To this end, test reactions with Bu_4NOTf as additive were undertaken and we did not observe any rate acceleration of the background allylation reaction at low temperature. However, the most coaxing fear was the possibility that the presence of adventitious water in the reaction medium could potentially lead to hydrolysis of the metal triflate and inadvertently form TfOH (a strong Brønsted acid) along with Sc_2O_3 (Equation 1, Figure 2.3). A similar phenomenon is well precedented from the work of Bosnich and coworkers.[11] In their mechanistic investigation on the addition of allyltrimethylsilane to aldehydes by Lewis acids such as $[Ti(Cp)_2(OTf)_2]$ **2.9**, the authors found that the reactive species is actually the trimethylsilyl cation (Equation 2 and 3, Figure 2.3). In this study, it was

conclusively shown that a trace amount of water in the reaction medium could hydrolyze the triflate containing Lewis acid to generate TfOH, a strong Brønsted acid. This Brønsted acid then reacted with allyltrimethylsilane to produce Me_3SiOTf, the actual Lewis acid catalyst for the allylmetal addition.

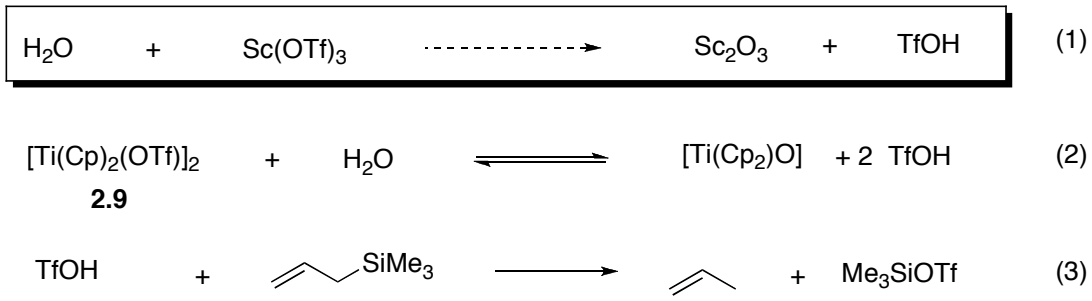
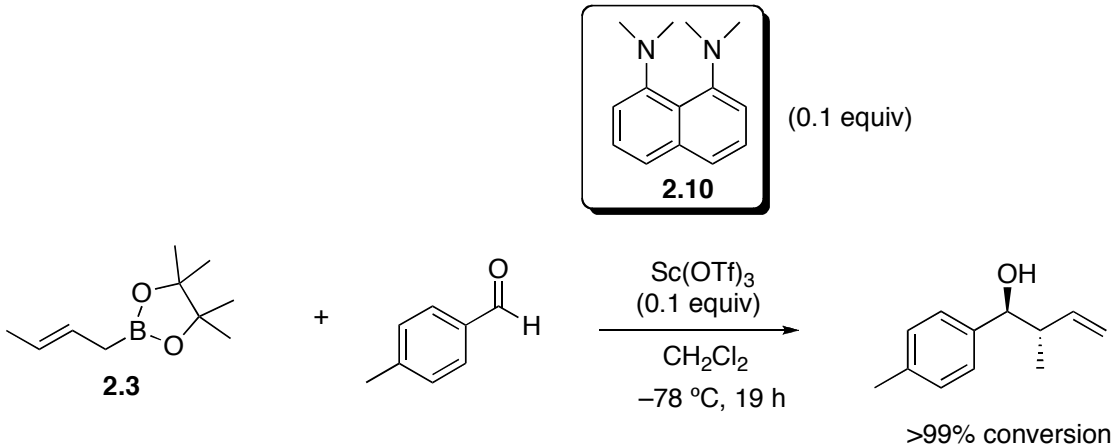


Figure 2.3. Adventitious water leading to the formation of triflic acid.[11]

Accordingly, we had to rule out the possibility that the active catalyst in the $Sc(OTf)_3$ catalyzed allylboration was TfOH. To this end, we subjected the $Sc(OTf)_3$ catalyzed reaction between **2.3** and *p*-tolualdehye in the presence of equivalent amounts of highly basic proton sponge **2.10** (pK_{BH+} = 12.1).[12] In the event, it was found that proton sponge does not shut down the catalytic effect (Equation 2.1). This experiment led us to conclude that TfOH was not a promoter of the reaction when $Sc(OTf)_3$ is employed.

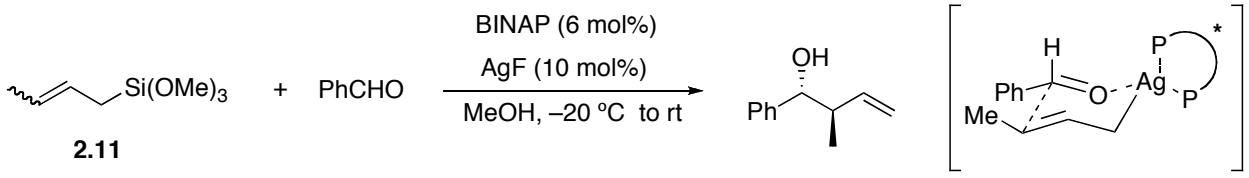
Thus, both control experiments led us to conclude that the rate acceleration for the addition of allylic boronates was due to the Lewis acidic scandium metal center.



Equation 2.1. Control reaction with proton sponge **2.10**.

2.4 Transmetalation possibilities

In catalytic reactions, transmetalation processes are a recurrent phenomenon. The best-known example is the boron to palladium transmetalation in the Suzuki reaction.[13] However, in terms of relevance to allylmetal additions, Yamamoto and coworkers described the most striking example.[14] In their study of the silver catalyzed addition of 2-butenyltrimethoxysilanes **2.11** (Type II reagents), the authors found that *anti* adducts were formed irrespective of the geometric composition of crotylsilanes in high diastereoselectivity and enantioselectivity (a Type III reaction outcome). To explain this anomaly, the authors have proposed a transmetalation mechanism followed by a fast isomerization of the 2-butenylsilver intermediate prior to aldehyde addition.



2.11 *E*/*Z*	*anti* (*er*)	*syn* (*er*)
83 : 17	92 (98 / 2)	8 (81 / 19)
1 : 99	94 (97 / 3)	6 (80 / 20)
45 : 55	93 (97 / 3)	7 (80 / 20)

Equation 2.2. Yamamoto's allylation involving a transmetalation mechanism.[14]

More recently, Shibasaki and coworkers reported a novel allylboration of ketones using allylboronate **2.2** in which the actual allylating species is postulated to be an allyl copper species.[15] In their mechanistic studies, ^{11}B-NMR of a mixture of **2.2** and CuF•PPh_3 in THF-d_8 indicated the formation of an ate complex **2.12** (^{11}B-NMR –13.4 ppm) and **2.13** (^{11}B-NMR +4.3), which implicitly suggested the formation of allylcopper species (Figure 2.4).

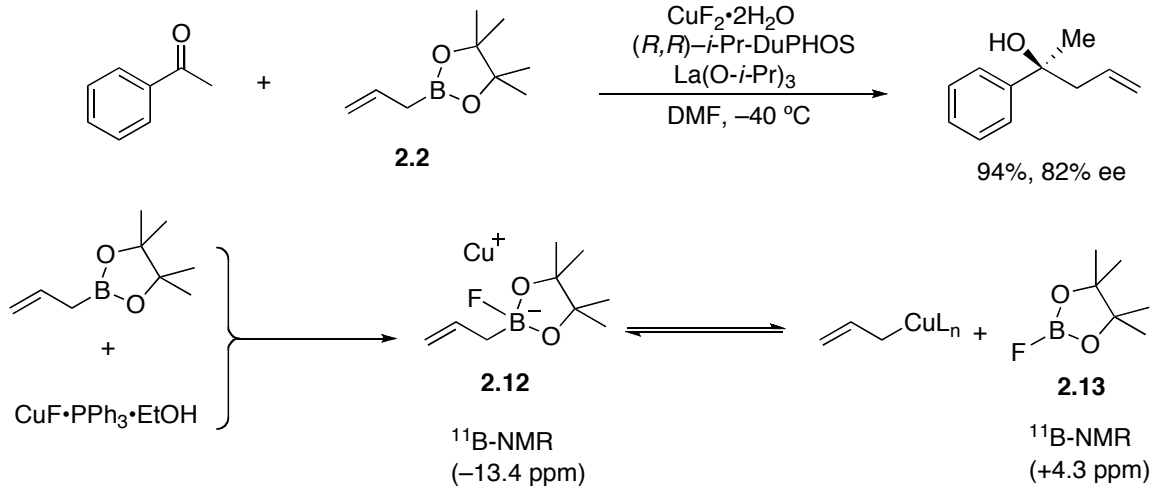
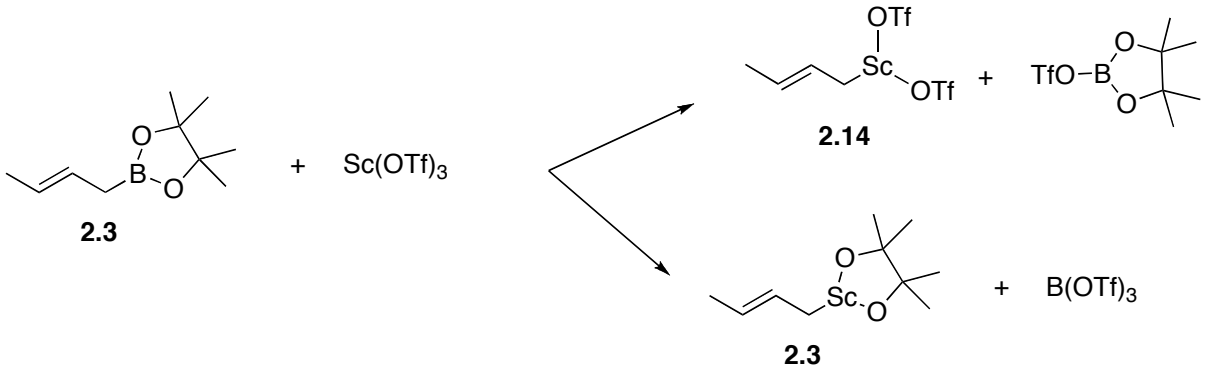


Figure 2.4. Boron-to-copper transmetalation in Shibasaki's allylboration of ketones.[15]

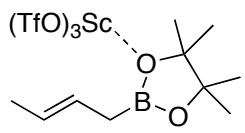
In the current setting of metal catalyzed aldehyde allylboration, transmetalation from boron to scandium would potentially lead to highly reactive allyl-scandium species **2.14** (Equation 2.2). However, we could confidently rule out the possibility of transmetallation to a highly reactive allyl-scandium species because the analogous scandium-catalyzed reactions of Hoffmann's camphor derived allylboronates **2.5** (Figure 2.1), which provide homoallylic alcohol products in >95% ee, would not be enantio- and diastereoselective (*vide infra*).[8] Transmetallation between **2.5** and $Sc(OTf)_3$ is expected to result in the formation of an achiral allylic scandium reagent **2.14** and thus, it would be difficult to rationalize the observed enantioselectivities and the Type 1 diastereoselectivity (*vide supra*). This led us to believe that the allyl transfer agent is truly a boronate.



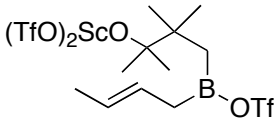
Equation 2.2. Possible transmetalation in Lewis acid catalyzed allylboration of aldehydes.

2.5 Complexation and kinetic studies

To gain insights on the nature of rate acceleration observed under Lewis acid catalysis, we ran low temperature NMR experiments in CD_2Cl_2 and many other solvents including THF-d_8 and toluene-d_3. In the event, we could not detect any complex between allylboronate **2.3** and $Sc(OTf)_3$ at –80 ºC or upon warming the mixture, by ^1H or ^{11}B-NMR. These results diminish the possibility for the formation of a stable allylboronate-$Sc(OTf)_3$ complex **2.15** (Figure 2.5) in the rate-determining step. Moreover, the probability of an activation mode involving the dioxaborolane opening and subsequent formation of a highly electrophilic boron triflate **2.16** is further undermined.



2.15



2.16

Figure 2.5. Unlikely complexes between **2.3** and $Sc(OTf)_3$.

To further negate the formation of an allylboronate–$Sc(OTf)_3$ complex, we undertook the study of the rate law governing the Lewis acid-catalyzed allylboration. For this study, we chose CD_2Cl_2, as the preferred solvent for this reaction. We chose *p*-tolualdehye **2.17** and boronate **2.3** as the model substrates. Boronate **2.3** was chosen because the $Sc(OTf)_3$ Lewis acid catalyzed addition of **2.3** onto aldehydes took 18-24 hours to undergo completion. As such, this reaction is slow enough to allow for precise kinetic studies using the method of initial rate measurements.[16]

For this study, we used freshly prepared 1.0 M solution of aldehyde and allylboronate **2.3** in CD_2Cl_2. We then performed NMR experiments at –80 ºC. First, we studied the kinetic profile of the reaction employing 1.0 equivalent of aldehyde and 1.0 equivalent of allylboronate **2.3** in the presence of 0.1 equivalent of $Sc(OTf)_3$ in order to obtain a slope for the reference reaction. We then ran experiments in which we doubled the amounts of aldehyde or allylboronate while keeping other reaction parameters constant. Unfortunately, we could not determine the relevant rate order of $Sc(OTf)_3$ because of its poor solubility in CD_2Cl_2. In the event, we determined that doubling the concentration of either aldehyde or allylboronate led to doubling of the reaction rate. As such, we concluded that the rate law governing the Lewis acid catalyzed allylboration was first order in aldehyde and allylboronate. This study further negated the formation of a

unisubstrate-scandium complex **2.15** as being rate determining (Figure 2.6). Moreover, the above study also supported a closed Type I transition structure involving both the aldehyde and allylboronate counterparts.

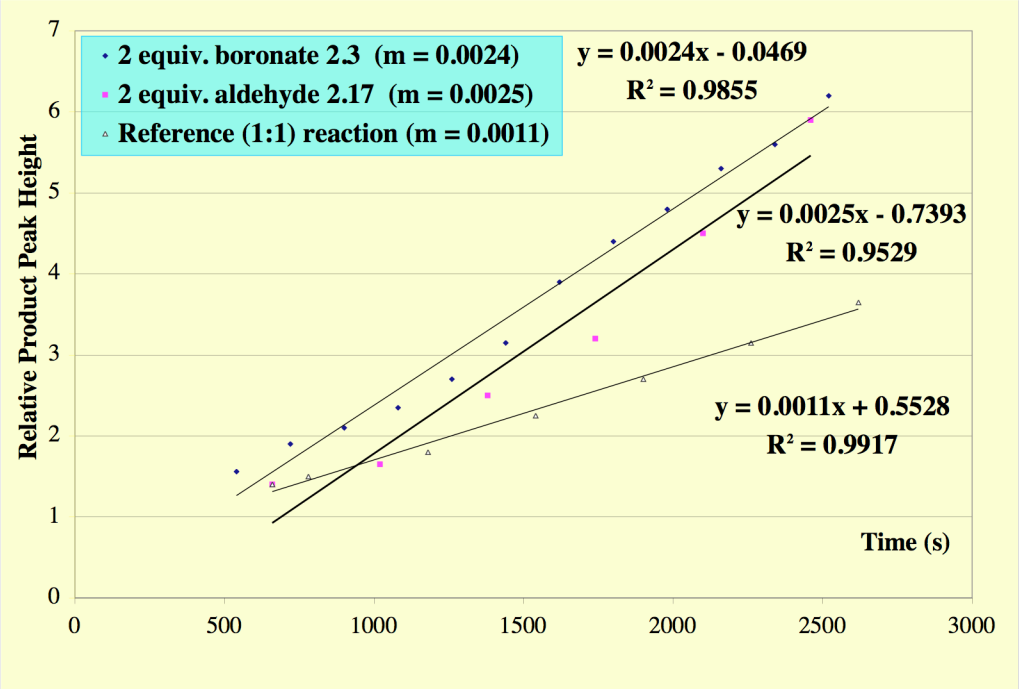


Figure 2.6. Graph of initial velocity of reaction allylboronate **2.3** and *p*-tolualdehyde.

2.6 Binding site of the metal ion in the transition state

The last but most fundamentally important question to address was the binding site of the metal ion in the putative Type I transition state structure. To address this issue, we arrived at two hypotheses for the possible mode of activation to account for the observed rate acceleration.

In the first hypothesis **A** (Figure 2.7), coordination of the Lewis acid to one of the oxygens in the dioxaborolane would suppress the n_O–p_B overlap. This interaction would lead to an increase in the acidic character of boron, which would be compensated by a stronger interaction with the aldehyde carbonyl in the transition state. This assumption is in line with Brown's experimental demonstration that electrophilicity of the boron atom parallels reactivity in the allylboration of aldehydes.[17] For example, allylic boranes have the most electrophilic boron atom as evident by the chemical shift of the boron atom (^{11}B-NMR, δ +75-85 ppm).[17] These reagents instantaneously react with aldehydes, even at –100 ºC. On the other hand, allylic

boronates, in which there is significant amount of n_O–p_B overlap, have a considerably less electrophilic boron atom (^{11}B-NMR, δ +32 ppm). This weak electrophilicity of allylboronates is manifested by their negligible reactivity with aldehydes at –78 ºC.

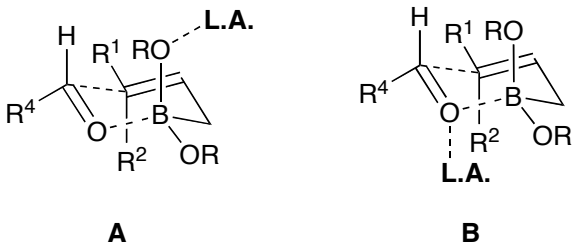


Figure 2.7. Possible closed transition structures with Lewis acid activation.

Hypothesis **A** is also supported by the previous MO calculations of Fujimoto and coworkers, in which they show that the boron-carbonyl interaction is the dominant interaction of the allylboration process and the main factor responsible for the lowering of activation energy of allylborations.[3]

Hypothesis **B** (Figure 2.7) portrays double coordination of the aldehyde, i.e.; the aldehyde being activated both by the boron center and by the external Lewis acid. This type of transition structure would result in "super-activation" of the aldehyde substrate, and thus create a significantly advanced C-C bond. However, this hypothesis seemed very unlikely because in the normal allylboration transition state, there is very little C-C bond development. According to the computational studies of Fujimoto and coworkers, the B-O bond distance of the thermal reaction between formaldehyde and allylboronic acid ethyleneglycolate has been calculated at 1.613 Å and the C-C bond at 2.206 Å.[3]

To discriminate between hypotheses **A** and **B**, we needed to test the catalytic effect of $Sc(OTf)_3$ on an allylic boron reagent that is lacking the oxygens of **2.3**, that is to say, an allylic dialkylborane. As mentioned before in this chapter, allylic dialkylboranes tend to react instantaneously with aldehydes even at –78 ºC. After surveying the literature, we found that borane **2.18**, which is doubly-substituted at the 3 position, does not react instantaneously with aldehydes at –78 ºC.[18] This attenuated reactivity is most likely the result of steric interactions during the reactant assembly and also in the allylboration transition state.

For the inference of this control experiment, if the added Lewis acid led to rate acceleration versus the background reaction, hypothesis **B** involving superactivation of aldehyde would be operative. On the contrary, if the added Lewis acid did not alter the rate of the background uncatalyzed reaction, then we could with assurance claim that the oxygens of the boronate moiety are essential for the rate acceleration (hypothesis **A**).

In the event, in this key experiment $Sc(OTf)_3$ provided no appreciable rate acceleration for the addition of allylic borane **2.18** to benzaldehyde (Figure 2.8). On the other hand, $Sc(OTf)_3$ was found to accelerate the reaction of the analogous allylboronate **2.19** and hydrocinnamaldehyde by a factor of >100 (based on $t_{1/2}$ extrapolations). The slight deceleration (10%) of the reaction of **2.18** in the presence of $Sc(OTf)_3$ could likely arise from a partial sequestration of the aldehdye lone pairs by the added Lewis acid. This explanation further supports hypothesis **A**.

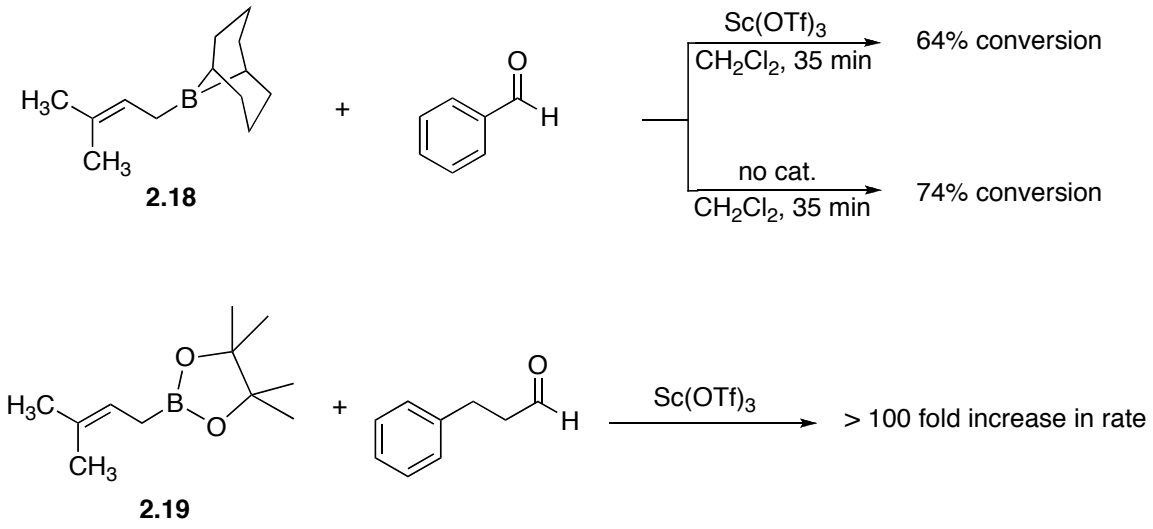


Figure 2.8. Control experiments to determine the Sc(III) binding site.

These results strongly indicate that the boronate oxygens are required for the Lewis acid activation to occur. It is doubtful that each of the two oxygens coordinates with a molecule of $Sc(OTf)_3$ as this process would be entropically disfavored. We were thus left with the question as to which of the two oxygens could the Lewis acid coordinate with. Sterically speaking, the oxygen that is oriented pseudo-equatorial is more accessible, but electronically speaking, the pseudo axial oxygen is more basic. Nevertheless, a possible explanation could be postulated for the Lewis acid catalyzed enantioselective allylboration of aldehydes.[8] From the accepted model for stereoinduction based on p_{phenyl}-$p^*_{C=O}$ attraction,[19] the proposed transition structure would

implicate the coordination of Sc(III) to the least hindered lone pair (*syn* to H) of the pseudo-equatorial oxygen (Figure 2.9). Such coordination would lead to suppression of n_O-p_B conjugation, which would accordingly result in increased boron carbonyl bonding. It is at this stage that we concluded our mechanistic studies, with the anticipation that further high-level calculations would eventually address this issue.

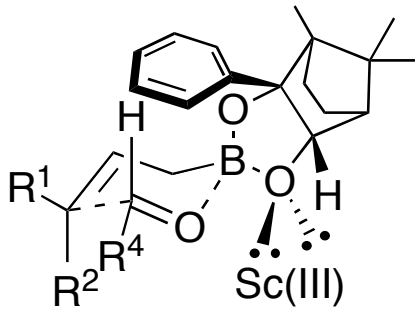


Figure 2.9. Proposed binding of metal center in the Lewis acid catalyzed allylboration of camphor derived allyic boronates.

2.7 Conclusion of experimental mechanistic studies

Through various control experiments and kinetic studies, light was shed on the mechanistic intricacies of the Lewis acid-catalyzed allylboration of aldehydes. Strong evidence was garnered that pointed to electrophilic boron activation by coordination of the metal ion to one of the oxygens of the dioxaborolane in a closed transition state.

2.8 Recent quantum chemical studies from Fujimoto and coworkers[20]

In 2008, Fujimoto and coworkers reported a detailed quantum chemical study that effectively correlated with our proposed hypothesis involving electrophilic boronate activation mechanism.[20] In their studies, they were also able to also address the last remaining question as to which of the two oxygens did the Lewis acid coordinate.

2.8.1 Background reaction

In their calculations, and as previously observed,[3] the authors found a relatively large activation barrier for the reaction of pinacol allylboronate **2.2** with benzaldehyde in the absence of the

Lewis acid. The salient features of this mode of addition included a high barrier of activation (+30.1 kcal/mol). In the transition state, the B-O bond distance between the boron atom and the carbonyl oxygen was calculated to be at 1.525 Å, and the incipient bond forming C-C bond at 2.198 Å (Figure 2.10).

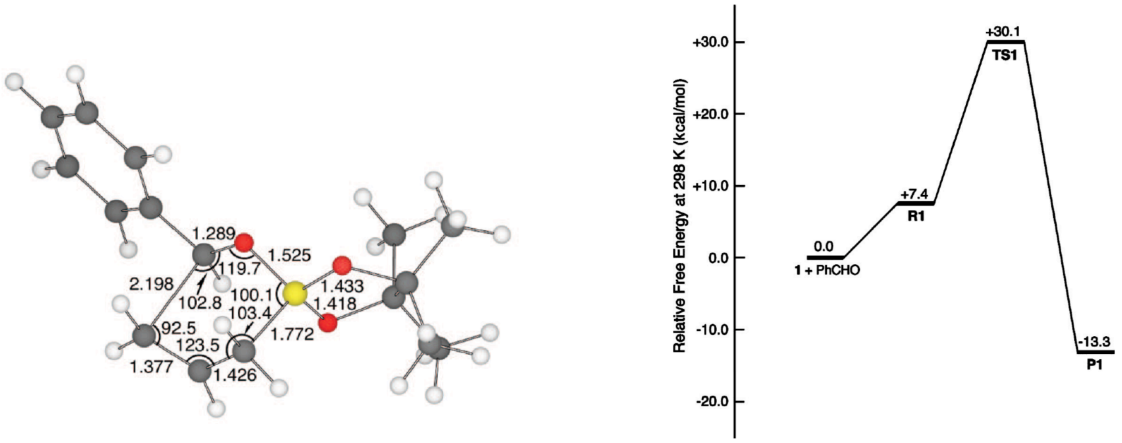


Figure 2.10. Transition state assembly and relative free energy diagram for the uncatalyzed allylboration reaction.[20]

2.8.2 Aldehyde activation

Analogous to hypothesis **B** (Section **2.6**), the authors also located a complex in which a molecule of Lewis acid ($AlCl_3$) was found to be coordinated to the carbonyl oxygen of benzaldehyde (Figure 2.11). In this pathway, the free energy corresponding to the transition state was calculated to be +23.8 Kcal/mol relative to the resting stage of reactants, but +35 Kcal/mol when compared to reaction assembly that precedes the transition state.[20] This increase in activation energy largely arises from the additional stabilization energy of 17.1 Kcal/mol gained from coordination of the Lewis acid to the carbonyl oxygen. Consequently, in the transition state, the B-O bond distance is significantly elongatedand calculated to be 2.202 Å (implying very little bonding) and the new incipient C-C bond distance is at 1.639 Å, implying advanced bonding interaction. These observations clearly negate the possibility of an aldehyde activation mechanism (hypothesis **B**) and further support our experimental mechanistic findings.

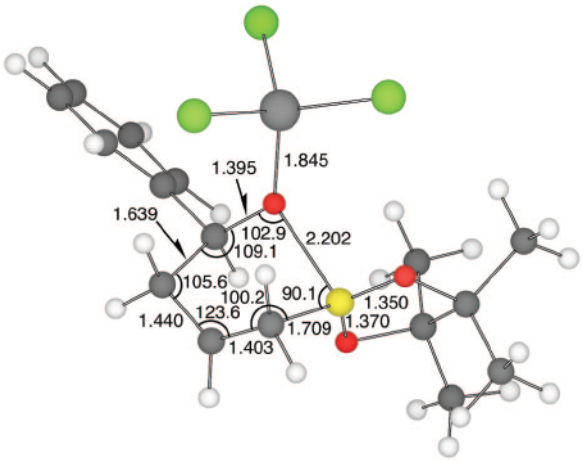


Figure 2.11. Calculated transition state in the aldehyde activation pathway.[20]

2.8.3 Boronate activation

The authors then looked into two pathways of boronate activation. One pathway **C** involved the coordination of the Lewis acid ($AlCl_3$) to the oxygen that is distal to the allyl group of allylboronate **2.2** (correlating to the equatorial oxygen in the transition state) and the other pathway **D** corresponding to coordination to the proximal oxygen (correlating to the axial oxygen in the transition state) (Figure 2.12). The authors have noted that coordination of the Lewis acid to the oxygen that is proximal to the allyl moiety (pathway **D**) creates repulsive interactions, which leads to rotation of the allyl group about the B-C^{α} bond in order to allow for minimization of steric effects. This adaptation leads to the distortion of the dioxaborolane ring from planarity. Furthermore, attachment of benzaldehyde to the already distorted boronate-Lewis acid complex creates additional deformation in the reaction complex preceding the transition state. As a result, the reactant assembly of pathway **D** lies 7.8 Kcal/mol higher in energy that that of pathway **C**.[20]

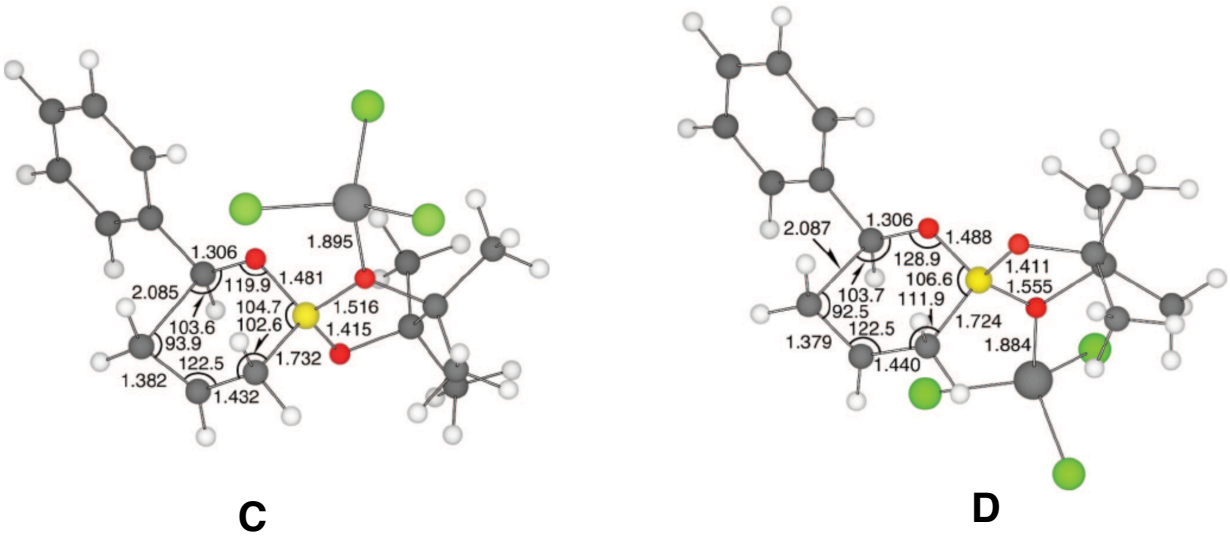


Figure 2.12. Transition state assembly of pathway **C** and **D**.[20]

In the event, the transition state of pathway **C** (Figure 2.12) reveals a very advanced B-O bonding of 1.481 Å, and the incipient C-C bond length is considerably shorter and calculated to be 2.085 Å. These results clearly validate our proposed mechanistic hypothesis that coordination of the Lewis acid to boronate oxygens would lead to suppression of n_O–p_B overlap and create a more Lewis acidic boron atom.

2.9 Final picture

Combining the results of our experimental mechanistic studies[1] along with the recent high level calculations of Fujimoto and coworkers,[20] we can now effectively conclude that Lewis acids catalyze the addition of allylboronates by coordination to the least hindered equatorial oxygen in the closed, Type I transition structure (Figure 2.13).

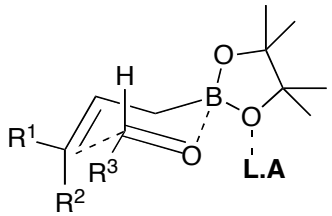


Figure 2.13. Proposed mode of Lewis acid activation based on Fujiimoto's calculation.

2.10 Experimental

2.10.1 General

Unless otherwise noted, all reactions were performed under argon atmosphere using flame-dried glassware. CH_2Cl_2 was distilled over CaH_2. THF was distilled over sodium/benzophenone ketyl. All employed aldehydes were purified by bulb-to-bulb distillation. Thin layer chromatography (TLC) was performed on Merck Silica Gel 60 F_{254} plates and visualized with UV light and 5 % phosphomolybdic acid/EtOH (PMA) or $KMnO_4$ stain. Flash chromatography was performed on Silicycle SiliaFlash® F60 ultra pure silica gel 230-400 mesh. NMR spectra were recorded on Varian INOVA-300, INOVA 400 or INOVA 500 instruments. Variable temperature spectroscopy at –80 ºC was recorded on Varian INOVA 400. The residual solvent protons (^{1}H) or the solvent carbons (^{13}C) were used as reference for chemical shifts. Boron NMR spectra are referenced to external BF_3•Et_2O. Allyl pinacolboronate **2.2**, (*E*)-crotylpinacolboronate **2.3** and (*Z*)-crotylpinacolboronate **2.4** were prepared by the reaction of their corresponding organometallics with B(O*i*-Pr)$_3$ followed by esterification with pinacol.[21] 80% (*E*)-crotylstannane **2.7** was made by the procedure of Naruta.[9a] Isomerically pure (*Z*)-crotylstanane **2.6** was prepared by following Schlosser's procedure.[9b] Prenyl-9BBN **2.18** was prepared by hydroboration of 3-methyl-1,2-butadiene.[8a] Prenyl-pinacolboronate **2.19** was prepared by homologation of iodo-methyl-pinacolboronate with 2-methyl-1-propenylmagnesium bromide.[22] All homoallylic alcohol products of this study have been previously described in the literature.[23]

2.10.2 Reaction of *Z*-crotyl stannane 2.6 (>99% cis) with hydrocinnamaldehyde in the presence of Sc(OTf)$_3$

To a sample of Sc(OTf)$_3$ (7.0 mg, 0.0150 mmol, 1.00 equiv) in a 25 mL round-bottom flask was added 0.50 mL of freshly distilled CH_2Cl_2 and this mixture was cooled to –78 ºC and maintained for 15 min. To the mixture was then added freshly distilled hydrocinnamaldehyde (19.0 µL, 0.140 mmol, 1.00 equiv) and the solution was allowed to stir for 10 min. After the elapsed time, Z-crotylstannane **2.6** (50.0 mg, 0.150 mmol, 1.00 equiv) dissolved in 0.5 mL of anhydrous CH_2Cl_2 was added and the reaction mixture was allowed to stir for 19 h at –78 ºC.

After the elapsed time, DIBAL-H (1.0 M in toluene, 0.290 mL, 0.290 mmol, 2.00 equiv) was added to quench the aldehyde. The reaction mixture was allowed to stir for 30 min after which 3.0 mL of saturated $NaHCO_3$ was added, and the reaction mixture was allowed to warm to room temperature over the course of 1 h. The crude product was extracted with (3 x 10 mL) of CH_2Cl_2 and the combined organic extracts were washed with 10 mL of brine, followed by drying over anhydrous Na_2SO_4 and filtration. The crude product was concentrated *in vacuo* (16 torr, 20 ºC). Upon ^1H NMR analysis of this crude mixture, it was established that the only detectable product was the *syn* diastereomer **2.8** and conversion was established to be only 1.5%. The *anti* adduct was not detected even after baseline expansion.

2.10.3. Reaction of (*E*)-crotyl stannane 2.7 (80% trans) with hydrocinnamaldehyde in the presence of $Sc(OTf)_3$

Following the procedure outlined in **2.10.3** except using (*E*)-crotyl stannane **2.7**, product **2.8** was the only detectable diastereomer and the conversion was established to be 33%.

2.10.4 Control experiment with Bu_4NOTf

Bu_4NOTf (7.5 mg, 0.0200 mmol, 0.100 equiv) was dissolved in 0.5 mL of freshly distilled CH_2Cl_2 and cooled to –78 ºC. To the solution was added hydrocinnamaldehyde (25.0 µL, 0.200 mmol, 1.00 equiv) and the mixture was maintained at –78 ºC for 15 min. *E*-crotyl pinacolboronate **2.3** (42.0 mg, 0.230 mmol, 1.15 equiv) dissolved in 0.50 mL of freshly distilled CH_2Cl_2 was then added and the reaction mixture was stirred for 18 h at –78 ºC, after which the aldehyde was quenched with DIBAL-H (1.0 M in toluene, 0.380 mL, 3.80 mmol, 2.00 equiv) and allowed to stir for 30 min. To the resulting mixture was added 0.76 mL of 1 *N* HCl at –78 °C and the reaction mixture was brought to room temperature over a period of 1 h. The crude product was extracted with Et_2O (3 x 10 mL) and the combined ethereal extracts were washed with brine (10 mL) and dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* (16 torr, 20 °C) and the crude product, which was analyzed for % conversion. Upon ^1H NMR analysis of the crude reaction mixture, the % conversion was established to be 2.9%.

2.10.5 Control experiment with proton sponge

A sample of $Sc(OTf)_3$ (12.0 mg, 0.0250 mmol, 0.100 equiv) was charged into a 25 mL round-bottom flask and the flask was purged with argon. Freshly distilled CH_2Cl_2 (0.75 mL) was then added and the resulting suspension was cooled to –78 ºC. Under a positive pressure of argon was then added [1,8-bis-(dimethyl amino)-naphthalene] **2.10** (5.40 mg, 0.0250 mmol, 0.100 equiv). This was followed by addition of *p*-tolualdehyde (29.0 µL, 0.250 mmol, 1.00 equiv). This mixture was maintained at –78 ºC for 15 min after which *E*-crotyl pinacolboronate **2.3** (50.0 mg, 0.270 mmol, 1.10 equiv) pre-dissolved in 1.0 mL of CH_2Cl_2 was added. The reaction mixture was allowed to stir for 19 h after which the aldehyde was quenched with DIBAL-H (1.0 M in toluene, 0.500 mL, 0.500 mmol, 2.00 equiv) and allowed to stir for 30 min. To the resulting mixture was added 1.5 mL of I *N* HCl at –78 ºC and the reaction mixture was brought to room temperature over a period of 1 h. The crude product was extracted with ether (3 x 20 mL) and the combined ethereal extracts were washed with brine (10 mL) and dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* (16 torr, 20 ˚C) to give the crude product. The analysis of the integration ratio between the carbinol hydrogen of product (doublet at 4.40 ppm) and the benzylic hydrogens of the reduced aldehyde (singlet at 4.7 ppm) indicated the % conversion to be >99%.

2.10.6 Determination of the rate orders of aldehyde and (*E*)-crotylpinacolboronate

2.10.6.1 Reference reaction

Freshly prepared (*E*)-crotylpinacolboronate **2.3** (0.180 g, 1.00 mmol) was dissolved in CD_2Cl_2 to make a 1.0 M solution. Freshly distilled *p*-tolualdehyde **2.17** (0.120 mL, 1.00 mmol) was dissolved in CD_2Cl_2 to make a 1.0 M solution. Scandium triflate (0.0170 g, 0.0350 mmol, 0.100 equiv) was added to a flame-dried NMR tube, and the tube was flushed with argon. To the catalyst in the NMR tube at –78 ºC was added 1.0 M solution of *p*-tolualdehyde **2.3 (**0.350 mL, 0.350 mmol, 1.00 equiv) and this mixture was maintained at –78 ºC for 10 min. To the resulting solution was then added 1.0 M solution of (*E*)-crotylpinacolboronate **2.3** (0.350 mL, 0.350 mmol, 1.00 equiv) and the reaction mixture was analyzed for product formation by NMR spectroscopy with the probe maintained at –80 ºC. The experiment was run in a pre-acquisition

delay mode (PAD). The change in the product composition over time was analyzed by measuring the relative peak heights of the carbinol-proton of the borate product; doublet at 4.73 ppm.

A graph of the change in peak height over time provided the slope (rate of the reaction) of this reaction. The equation of the line generated is **y = 0.0012x+ 0.5424** (with the R^2 value of 0.996). This slope of the equation was the reference for determination of rate orders of *p*-tolualdehyde and (*E*)-crotylpinacolboronate. A sample NMR spectrum is provided in the appendix.

2.10.6.2 Aldehyde = 2 x

Similar to the above protocol, the reaction involving 2.00 equivalents of aldehyde **2.17** (from a 2.0 M aldehyde solution in CD_2Cl_2), 1.00 equivalent of (*E*)-crotylpinacolboronate **2.3**, and 0.1 equivalent of $Sc(OTf)_3$ was analyzed. A graph of the change in peak height over time gave the slope (rate of the reaction) of this reaction. The equation of the line generated is **y = 0.0025x - 0.7393** (with the R^2 value of 0.9529). The ratio of the slope obtained (0.0025) to that of reference (0.0012) is 2.08, and the ratio of log 2.08 / log 2 implicates a rate order of 1.06 for the aldehyde substrate in the rate equation. A sample NMR spectrum is provided in the appendix.

2.10.6.3 (*E*)-Crotylpinacol boronate 2.3 = 2 x

Following a similar procedure as the reference reaction except using 2.0 equivalents of (*E*)-crotylpinacolboronate **2.3** (from a 2.0 M aldehyde solution in CD_2Cl_2), the kinetic profile of the reaction was analyzed. A graph of the change in peak height over time gave the slope (rate of the reaction) of this reaction. The equation of the line generated is **y = 0.0022x + 0.3186** (with the R^2 value of 0.9812). The ratio of the slope obtained (0.0022) to that of reference reaction is 1.83, and the ratio of log 1.83/log 2 (which comes from doubling the concentration of the reagent compared to the reference reaction) implies a rate order of 0.87 for the (*E*)-crotylpinacolboronate in the rate equation. A sample NMR spectrum is provided in the appendix.

For all of the above runs, the data was collected until the % conversion of the aldehyde was approximately 0-15 %. It was assumed that this initial portion of the reaction conversion would provide representative tangent of the initial rate, thereby giving a reliable reaction order. The experimental results were satisfactorily reproduced for each run. The slope values of tangents; 0.87, 1.06 ≈ 1.0 are within experimental error.

2.10.7 Comparisons of the rates of reaction between $Sc(OTf)_3$-catalyzed allylboration and the background reaction of allylboronates

2.10.7.1 Preparation of standard solutions

Prenyl pinacolboronate **2.19** (0.200 g. 1.00 mmol) was dissolved in CD_2Cl_2 to make a 1.0 M solution. Freshly distilled hydrocinnamaldehyde (0.140 mL, 1.00 mmol) was dissolved in CD_2Cl_2 to make a 1.0 M solution.

2.10.7.2 $Sc(OTf)_3$-catalyzed reaction

To a flame-dried NMR tube was added $Sc(OTf)_3$ (12.0 mg, 0.0250 mmol, 0.100 equiv) and the tube was flushed with argon and cooled to –78 ºC. To the flask was added hydrocinnamaldehyde (1.0 M in CD_2Cl_2, 0.250 mL, 0.250 mmol, 1.00 equiv) and the mixture was maintained at –78 ºC for 10 min after which prenyl pinacolboronate **2.19** (1.0 M in CD_2Cl_2, 0.250 mL, 0.250 mmol, 1.00 equiv) was added. The reaction mixture was analyzed for product formation by variable temperature NMR spectroscopy at –80 ºC. A graph of extrapolated % conversion with time gave the equation of **y = 0.0866x + 1.4133** (with R^2 = 0.9518). Sample graph is provided in the appendix.

2.10.7..3 Background reaction

To a clean dry NMR tube was added hydrocinnamaldehyde (1.0 M in CD_2Cl_2, 0.250 mL, 0.250 mmol, 1.00 equiv) and the solution was maintained at –78 ºC for 10 min after prenyl pinacolboronate **2.19** (1.0 M in CD_2Cl_2, 0.250 mL, 0.250 mmol, 1.00 equiv) was added. The reaction mixture was analyzed for product formation by NMR spectroscopy at –78 ºC. A graph of extrapolated % conversion with time gave the equation of **y = 0.0006x + 2.2868** (with R^2 =

0.9509). The ratio of the slopes of catalyzed and background reaction is 144, which implies that the velocity of the catalyzed reaction is in excess of 2 orders of magnitude faster than the uncatalyzed reaction. Sample graph is provided in the appendix.

2.10.8 Reaction of benzaldehyde with prenyl-9-BBN (2.18) in the absence of $Sc(OTf)_3$

2.10.8.1 Preparation of 2.18 and analysis of background reaction

9BBN-dimer (0.0400 g, 0.170 mmol, 1.00 equiv) was charged into a flame-dried 25 mL round bottom flask under argon atmosphere (glove bag) and dissolved in 1.0 mL of freshly distilled THF. To the flask was added 3-methyl-1,2-butadiene (0.0360 mL, 0.360 mmol, 1.10 equiv) at room temperature. The reaction mixture was allowed to stir for 2 h at room temperature after which the solvent (THF) and unreacted allene were evaporated under high vacuum (0.1 mm Hg). To thus obtained borane **2.18** was added 2.0 mL of freshly distilled CH_2Cl_2 and the solution was stirred for 15 minutes followed by evaporation of the solvent under high vacuum. This process was repeated for another cycle. The yield for this reaction was assumed to be 70% (c.a 0.23 mmol) in order to assure sufficient amount of reagent for the aldehyde addition step; which amounts to 0.23 mmol of **2.18**.

This reagent **2.18** was then dissolved in 1.0 mL of freshly distilled CH_2Cl_2 and cooled to –78 ºC. To the resulting mixture was added freshly distilled benzaldehyde (19.5 μL, 0.190 mmol, 1.00 equiv) and the solution was stirred for 20 min at –78 ºC after which the aldehyde was quenched with DIBAL-H (1.0 M in toluene, 0.380 mL, 0.380 mmol, 2.00 equiv) and the mixture was stirred for 30 min. This was followed by addition of 0.13 mL of 3.0 M NaOH (0.130 mL, 0.390 mmol, 1.20 equiv relative to **2.18**) and 0.13 mL of 30% H_2O_2 at –78 $^{\circ}$C. The reaction mixture was gradually warmed to room temperature and allowed to stir overnight under argon atmosphere. The crude product was extracted with ether (3 x 10 mL) and the combined ethereal extracts were washed with brine (10 mL) and dried over anhydrous Na_2SO_4 and filtered. The mixture was concentrated *in vacuo* (16 torr, 20 ºC) and the crude product was analyzed by ^{1}H-NMR for conversion. Upon comparison of the integral values of the benzylic alcohol protons (of the reduced aldehyde) with the olefinic protons of the homoallylic alcohol product, % conversion of the reaction was calculated to be 74%.

2.10.8.2 Experiment of the reaction of benzaldehyde with prenyl-9BBN (2.18) in the presence of $Sc(OTf)_3$

Prenylborane **2.18** was prepared as above using 9BBN-dimer (0.0480 g, 0.200 mmol, 1.00 equiv), 1.0 mL freshly distilled THF and 3,3-dimethyl-1,2-butadiene (0.0430 mL, 0.440 mmol, 1.10 equiv). These values of reagents amounted to 0.280 mmol of **2.18**.

This reagent **2.18** was then dissolved in 1.0 mL of freshly distilled CH_2Cl_2 and cooled to –78 ºC. To above under positive pressure of argon was added $Sc(OTf)_3$ (10.0 mg, 0.0230 mmol, 0.100 equiv relative to aldehyde). The resulting mixture was then maintained at –78 ºC for 10 min and then freshly distilled benzaldehyde (24.0 μL, 0.230 mmol, 1.00 equiv) was added and the solution was maintained at –78 ºC for 20 min after which the aldehyde was quenched with DIBAL-H (1.0 M in toluene, 0.460 mL, 0.460 mmol, 2.00 equiv) and the mixture was stirred for 30 min. This was followed by addition of 0.16 mL of 3.0 M NaOH (0.160 mL, 0.480 mmol, 1.2 equiv. relative to the moles of **2.18**) and 0.16 mL of 30% H_2O_2 at –78 ºC. The reaction mixture was gradually warmed to room temperature and allowed to stir overnight. The crude product was extracted with ether (3 x 10 mL) and the combined ethereal extracts were washed with brine (10 mL) and dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* (16 torr, 20 $^{\circ}$C) to give the crude product, which was analyzed by ^{1}H NMR for % conversion. Upon analysis of the integrals for the benzylic protons (of the reduced aldehyde) and the olefinic protons of the homoallylic alcohol, the % conversion was established as 68 %.

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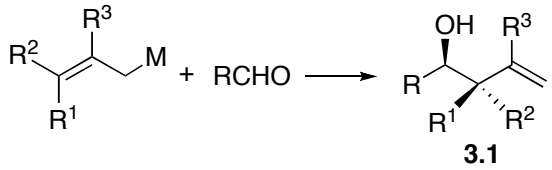
Chapter 3

Catalytic Enantioselective and Diastereoselective Allylboration of Aldehydes

3.1 Introduction

Carbonyl allylation represents an important class of carbon-carbon bond forming reactions[1a-e] and in this context, asymmetric aldehyde allylation (Equation 3-1) has served as an important surrogate for the aldol reaction.[2] During the past two decades, an extensive repertoire of allylation methods has emerged to answer the needs of the synthetic community.

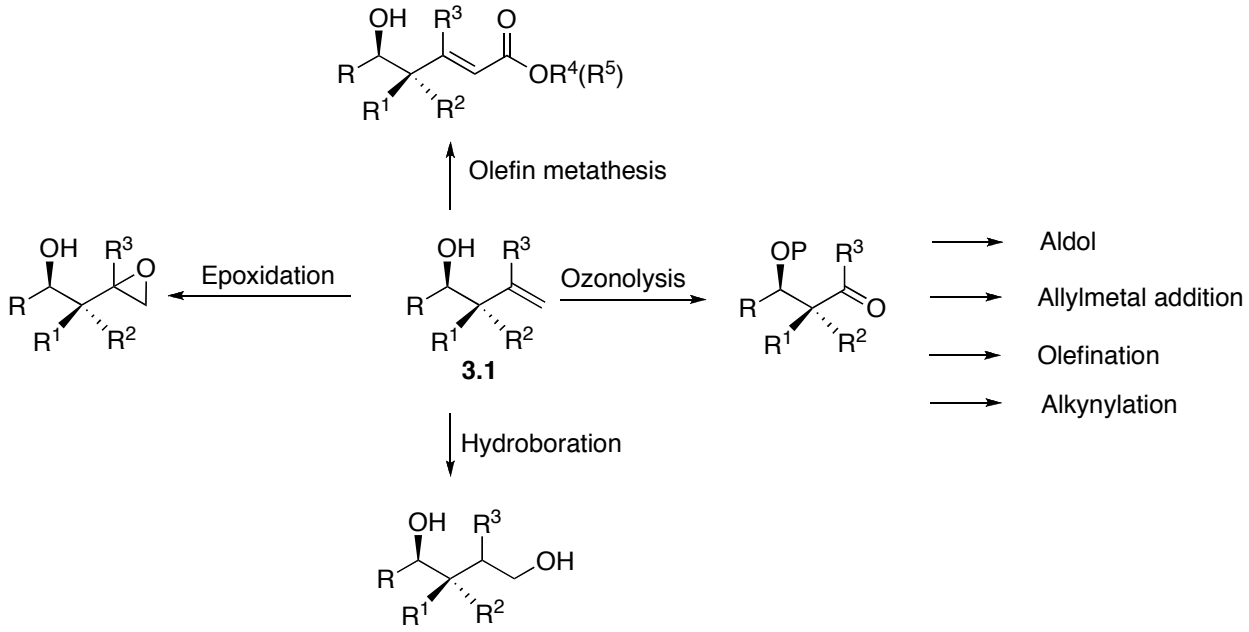


3.1

M = Si, Ti, B, Cr, In, Sn, Zn, etc.

Equation 3.1. Prototypical aldehyde allylation.

Indeed, the products of aldehyde allylation, i.e. homoallylic alcohols **3.1**, are very useful building blocks for elaboration into polyacetate and propionate units that are commonly found in numerous biologically interesting marine macrolides and natural products. As allylation products **3.1** contain terminal olefins, which contain a latent carbonyl functionality, these intermediates can be readily utilized in complexity-building reactions that utilize aldehydes as substrate (Scheme 3.1). Additionally, one can readily utilize homoallylic alcohols in the olefin cross-metathesis for the generation of enones and enoates and thus bypass oxidative manipulations.[3]



Scheme 3.1. Precedented synthetic applications of homoallylic alcohol products.

3.2 Stoichiometric chiral director approach

Many elegant stoichiometric approaches with chiral directors have been developed to address the asymmetric addition of allyl and crotyl metals onto aldehydes. These methods are largely based on boron (c.f. Chapter 1, Section 1.3.3)[4] and titanium.[5] In 1983, Brown and coworkers reported one of the most successful examples of asymmetric aldehyde allylboration using pinane derived auxiliaries as the chiral director.[4e] Soon after in 1986, Brown and coworkers reported the analogous diastereo- and enantioselective crotylboration of aldehydes, using the same terpene as the chiral modifier.[4f] These methods are commonly known as Brown allylation and Brown crotylation and research groups all around the globe utilize this protocol for the construction of acetate and propionate units in natural product synthesis. Other important asymmetric allylboration processes using stoichiometric chiral directors have been reported by the groups of Masamune,[4c,d] Corey,[4i,j] Roush,[4g,h] and Soderquist,[4k] although these methods have been less popular.

Asymmetric allylation based on chiral titanium reagents have been reported by Duthaler, Ronchi and coworkers. However, because of the requirement of multiple steps for reagent preparation, this method has only found sporadic use.[5]

3.3 Catalytic enantioselective aldehyde allylation methods

The use of a stoichiometric chiral director is undoubtedly associated with problems of waste and lack of atom economy. The solution to this issue would be to devise methods that require a sub-stoichiometric amount of catalyst, which would control the course of the reaction and the absolute stereochemistry of the resulting product when using an achiral reagent.

The field of catalytic asymmetric carbonyl allylation has developed more slowly than the related aldol reaction; however, significant progress has been made. In this field, the majority of catalytic enantioselective allylation reactions involve the use of chiral Lewis acids as catalysts and allylic silanes or stannanes as the allyl-transfer reagents (Type II reactions). In these processes, the Lewis acid serves to concurrently activate the aldehyde substrate towards nucleophillic attack and direct the course of facial selectivity.

The first examples of Type II catalytic enantioselective allylation were reported by Yamamoto and coworkers[6a] but the most widely studied chiral Lewis acid catalyzed allylation reaction has been the asymmetric addition of allylstannane **3.2**. Pioneering studies were reported by Keck[6c] and Umani-Ronchi[6b] in 1993 (Figure 3.1). Both methods make use of Lewis acid catalysts derived from Ti(IV) salts and binol **3.3**. These protocols provide homoallylic alcohol products in good to excellent yield and high enantioselectivity for non-hindered aldehydes. However, since the resulting complex is a rather weak Lewis acid, these methods require prolonged reaction times (24-48 h), which consequently lead to problems of reproducibility. To address the issues of reactivity, Maruoka and coworkers disclosed the highly active bidentate titanium complex **3.6** that performs better than **3.4** and **3.5** for asymmetric addition of allylstannane **3.2** (Figure 3.1).[6d]

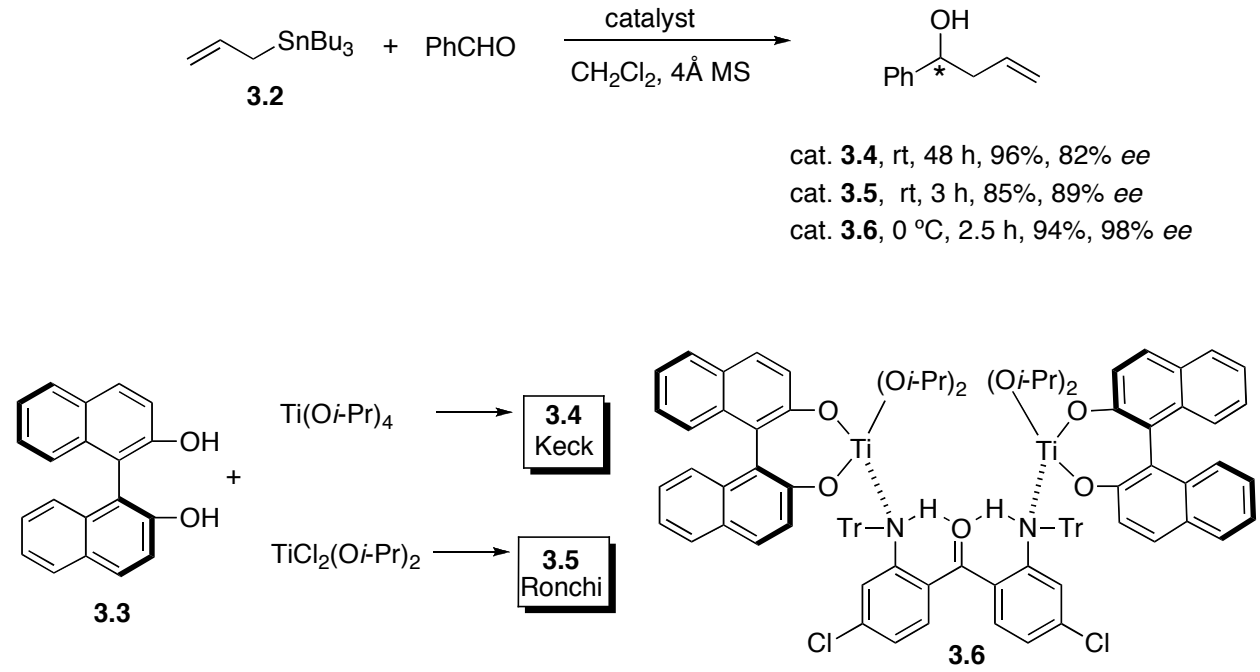


Figure 3.1. Notable catalytic enantioselective allylstannation reactions.

Catalysts **3.4**, **3.5** and **3.6**, however, fail to promote the addition of less reactive and greener allylic silanes. Carreira and coworkers have presented a solution to this issue by devising a catalyst made from binol **3.3** and the more Lewis acidic TiF_4.[6e] However, this method fails to provide homoallylic alcohol products in high enantioselectivities when compared to that of Keck and Ronchi methods.

Additionally, various chiral metal complexes based on Zr,[6f] Rh,[6g] Ag,[6h] and Si[6i] have been successfully employed for catalyzing the enantioselective addition of allylic stannanes to aldehydes. However, these Type II reagents predominantly give *syn*-diastereoselectivities with γ-substituted reagents, and thus are most useful for simple allylation reactions of aldehydes (i.e. γ-unsubstituted reagents). Moreover, the use of allylstannane **3.2** produces a stoichiometric amount of toxic organic tin residues and thus represents a significant limitation of this carbonyl allylation methodology.

In order to address issues of lack of diastereoselectivity and "greenness" in catalytic systems employing Type II allylic tin reagents, Denmark and coworkers have made use of highly electrophilic trichloroallylic silanes **3.7** (Figure 3.2). Due to the significantly enhanced Lewis acidity of the silicon center in **3.7**, these reagents can self-activate the aldehyde partner (Type I

mechanism), which ensures high diastereoselectivity. In this process, a mechanistically different mode of Lewis base activation of **3.7** (Figure 3.2) is operative.[7] Thus, the use of bidentate chiral phosphoramide **3.8** in this system results in further polarization of the metal center (there by increasing the Lewis acidity of the silicon metal center) and this outcome ensures high enantio- and diastereoselectivities for the additions of allylic silanes onto aromatic and conjugated aldehydes. Unfortunately, the very important class of aliphatic aldehydes do not participate in this reaction because of competitive formation of α-chlorosilylethers **3.9** (Figure 3.2).

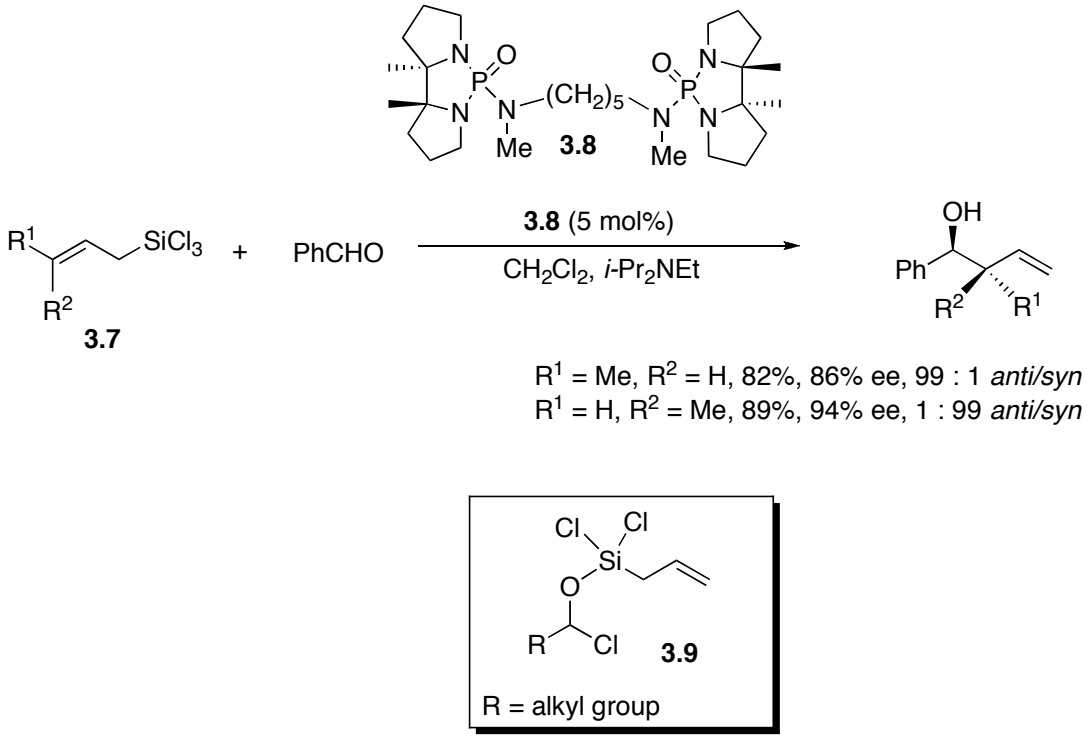


Figure 3.2 Denmark's catalytic enantioselective aldehyde allylation.[7]

Catalytic enantioselective methods that do not require the use of pre-formed allylmetal reagents are primarily based on chromium[8] and indium,[9] with the former being more popular. Reactions based on catalytic chromium metal employ stoichiometric amounts of co-reductant, and follow the general course of Type III allylmetal additions, providing *anti* adducts as major diastereomers irrespective of the allylic geometry.[8a,b] In this category, Yamamoto and coworkers have reported the most effective method (Figure 3.3). Using the newly designed chromium catalyst **3.10**, homoallylic alcohol products are obtained in consistently high enantioselectivities. The corresponding γ-substituted allylic halides provide *anti*-adducts in high enantioselectivities

and moderate diastereoselectivity. The most significant limitation with catalytic asymmetric Type III allylmetal additions is the failure to produce the *syn*-propionate adducts.

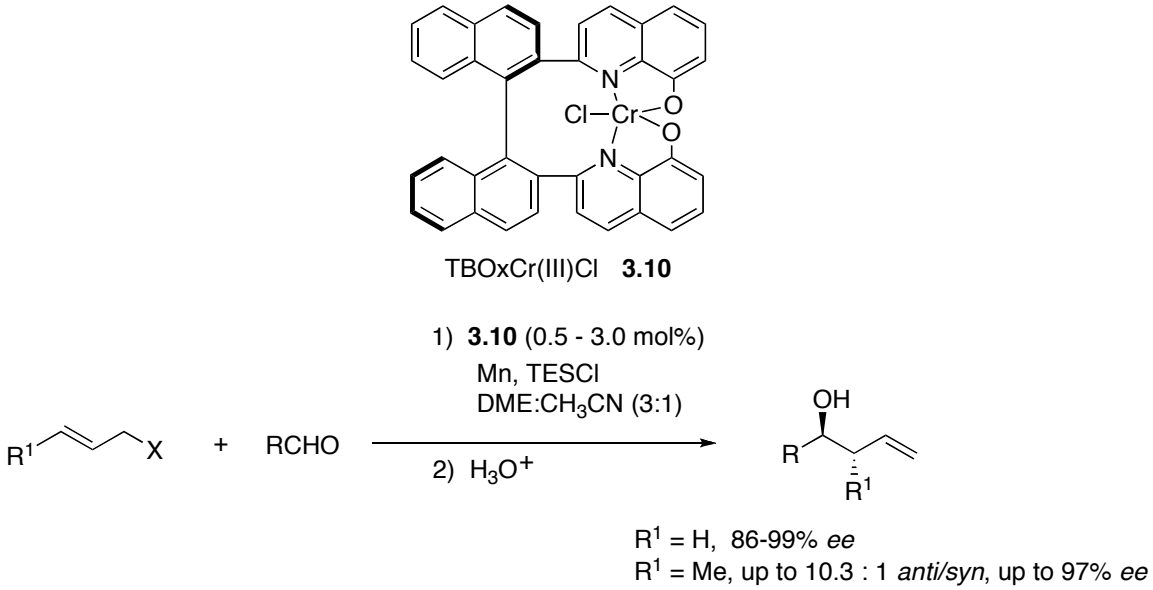
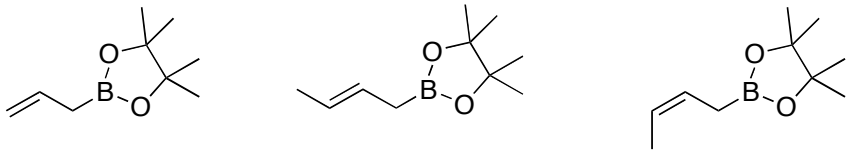


Figure 3.3. Yamamoto's catalytic asymmetric allylation of aldehydes.[8b]

Despite the success of the above mentioned stoichiometric and catalytic allylation methodologies, there is still no methodology that possesses all of the following attributes: mildness and chemoselectivity, substrate generality (both for the allyl-metal reagent and the aldehyde substrate), high levels of diastereo- and enantioselectivity, and practicality (ease of use, low cost, non-toxic and low environmental impact). One can see that most catalytic methods that make use of Type II allylic tin and Type III chromium metals suffer from a lack of diastereocontrol and toxicity issues, whereas trihaloallylic silanes provide high diastereoselectivities but fail to add onto aliphatic aldehydes, which are the more important substrates for application in natural product synthesis. Although the Brown allylation/crotylboration methodology provides high enantioselectivity and diastereoselectivity, this method makes use of chiral auxiliaries and produces super-stoichiometric amounts of wasteful by-product. It is with these underlying limitations that we sought out to discover a catalytic method based on allylic-boron pinacolate **3.11** and its crotyl derivatives **3.12** and **3.13** (Figure 3.4). Indeed, allylic boronates are non-toxic, commercially available and react with aldehydes through a closed six-membered transition state ensuring high diastereocontrol, thus allowing easy access to *syn*- and *anti*-propionate adducts with appropriate choice of **3.12** or **3.13**.

Since these reagents were shown to have negligible reactivity at low temperatures (–78 ºC), they were perfectly suited for a catalytic enantioselective allylboration protocol.[10]

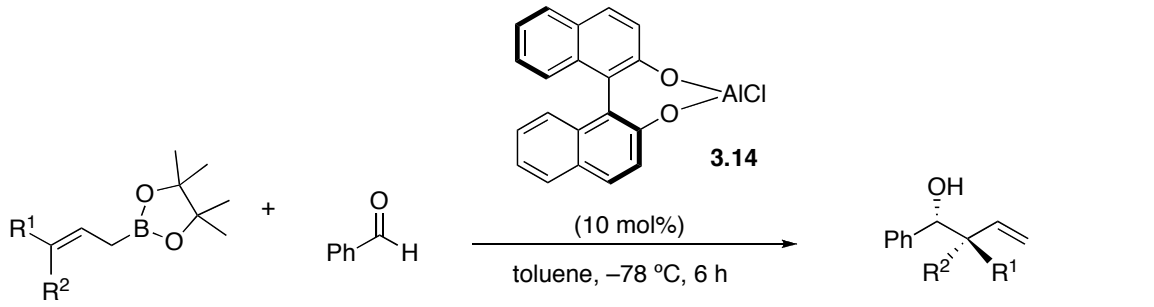


3.11 **3.12** (*E*) **3.13** (*Z*)

Figure 3.4. Commercially available allylic boron pinacolates.

3.4 First examples of catalytic enantioselective allylboration of aldehydes

As mentioned in Chapter 1, Section 3.5, soon after the discovery of Lewis acid catalysis by Hall and coworkers,[11] Miyaura and coworkers reported the first example of a catalytic enantioselective and diastereoselective addition of allylic boron pinacolates to aldehydes.[12] The authors showed that catalyst **3.14** generated from the combination of binol **3.2** and Et_2AlCl, provided moderate enantioselectivity but high diastereoselectivity for the addition of boronates **3.12** and **3.13** (Equation 3.2). It is also worth mentioning that the crotylation reactions with *trans*-crotylboronate **3.12** provided significantly higher yields and enantioselectivity when compared to *cis*-crotylboronate **3.13**.[12]

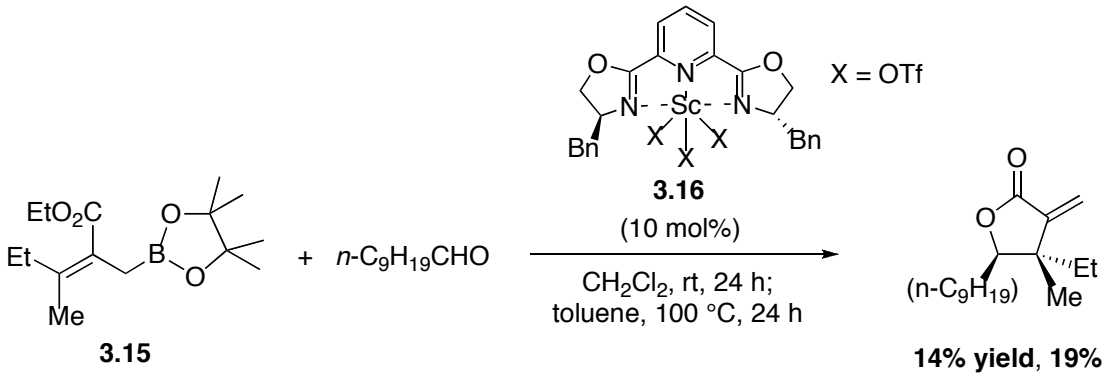


3.12 R^1 = Me, R^2 = H
3.13 R^1 = H, R^2 = Me

R^1 = Me, R^2 = H, 40%, 99% *anti,* **51% *ee***
R^1 = H, R^2 = Me, 19%, 99% *syn,* **8% *ee***

Equation 3.2. Miyaura's catalytic enantioselective allylboration of benzaldehyde.[12]

Hall and coworkers also saw the possibility for catalysis of allylboration reactions. Using the deactivated allylboronate **3.15**, and scandium pybox catalyst **3.16**, the authors were able to obtain the desired lactone product in only 19% *ee* (Equation 3.3).[13] Moreover, these reactions were extremely sluggish as evident by the minimal yield of the product.



Equation 3.3. Catalytic enantioselective allylboration of aldehyde by Hall and Kennedy.[13]

Hall and coworkers also envisioned the enantioselective addition of **3.11** under the influence of various chiral Lewis acids including aluminum catalyst **3.17**, oxazaborolidine **3.18** and its protonated derivative **3.19** (Figure 3.5). However, in all the cases, the reactions produced negligible amounts of products and more importantly in racemic form.[14]

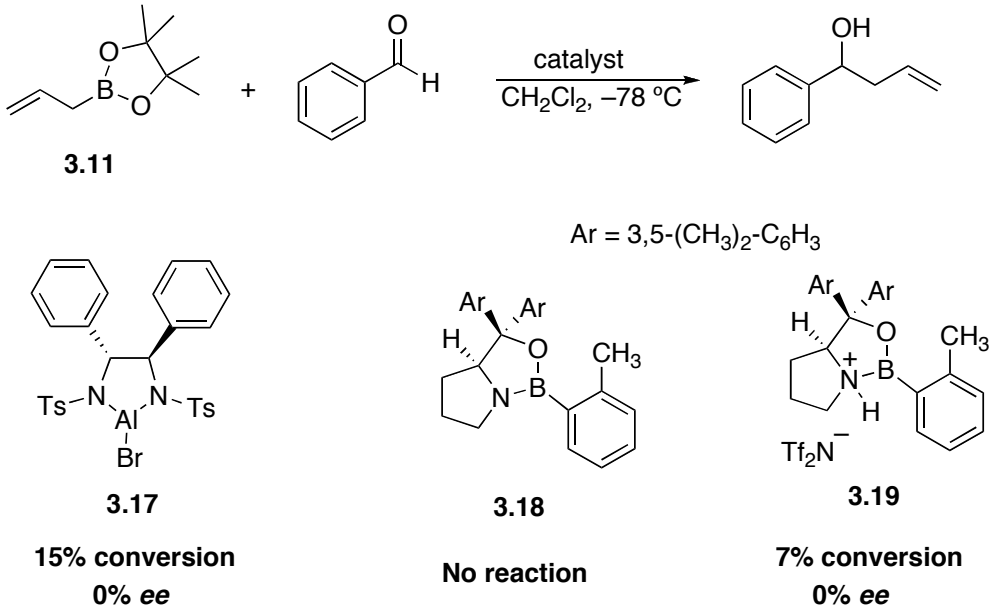


Figure 3.5. Initial attempts towards chiral Lewis acid catalyzed allylboration by Hall and coworkers.[14]

Based on the proposed mode of Lewis acid activation of allylboron pinacolate,[15] it seemed reasonable that the binding site of the Lewis acid was sterically congested due to the presence of an adjacent quaternary center (Figure 3.6), and such overcrowding would lead to inefficient

coordination of the Lewis acidic metal center with the boronate oxygen, which would consequently lead to minimal catalysis.

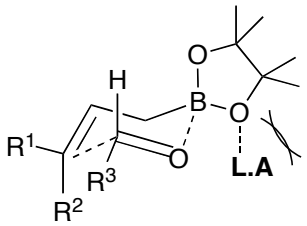
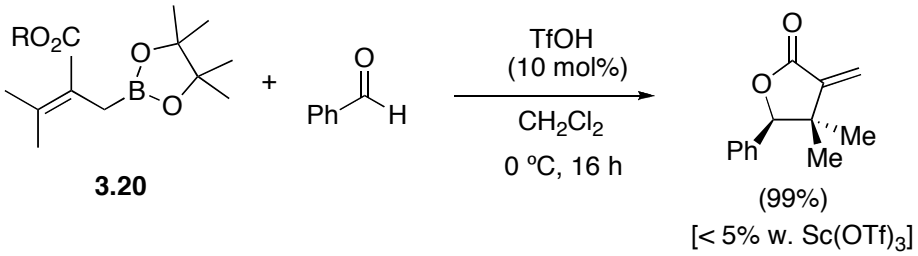


Figure 3.6. Proposed steric interaction of Lewis acid with adjacent quaternary carbon.

This hypothesis thus called for a smaller chiral inducer in the form of chiral protic acid. In line with this hypothesis was the observation by Hall and coworkers that triflic acid was a strikingly superior catalyst for the addition of disubstituted boronate **3.20** compared to $Sc(OTf)_3$ (Equation 3.4).[16]

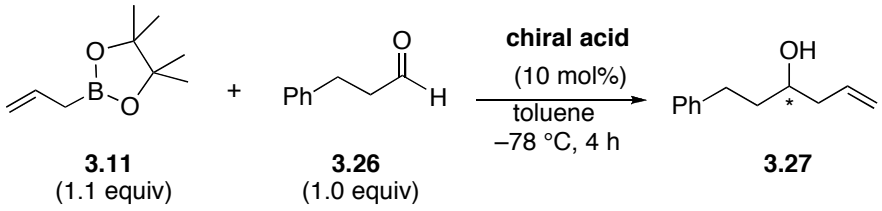


Equation 3.4. Triflic acid as a superior catalyst for the allylboration of benzaldehyde.[15]

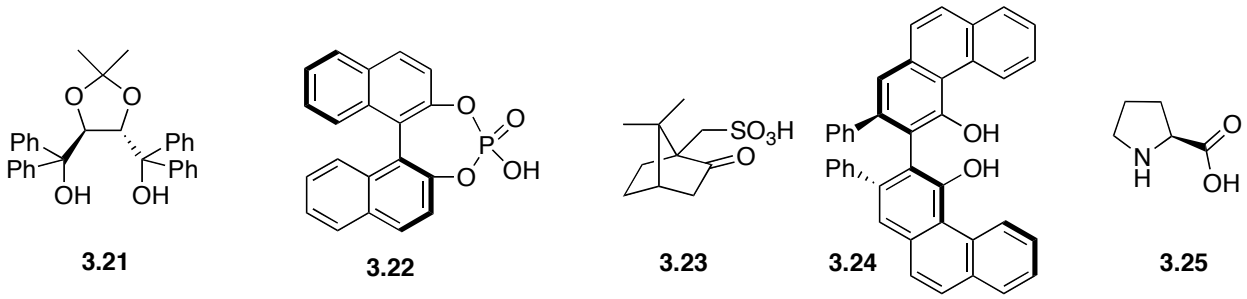
3.5 Results[17]

3.5.1 Initial screening of chiral Brønsted acids

Having realized the ability of strong Brønsted acids as superior catalysts for the addition of deactivated allylic boronates, we examined the effectiveness of select chiral Brønsted acids **3.21**-**3.25** for the enantioselective addition of allylboronate **3.11** onto hydrocinnamaldehyde (**3.26**) at –78 °C (Table 3.1). In the event, most chiral Brønsted acids were ineffective at promoting the reaction and although camphorsulfonic acid (**3.23**) provided a 100% conversion of the aldehyde into product **3.27** (entry 3), we did not observe any asymmetric induction. These early results clearly pointed to the requirement for a strong Brønsted acid in which the acidic proton is rigidly held in a chiral environment.



3.11 (1.1 equiv) **3.26** (1.0 equiv) **3.27**

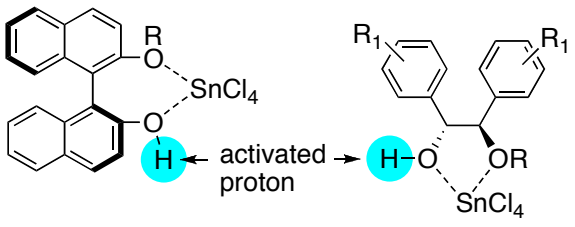


3.21 **3.22** **3.23** **3.24** **3.25**

Entry	Brønsted acid	conversion (%)	*ee* (%)
1	**3.21**	16	0
2	**3.22**	10	0
3	**3.23**	100	0
4	**3.24**	<5	n.d
5	**3.25**	9	0

Table 3.1. Preliminary screening of chiral Brønsted acids.

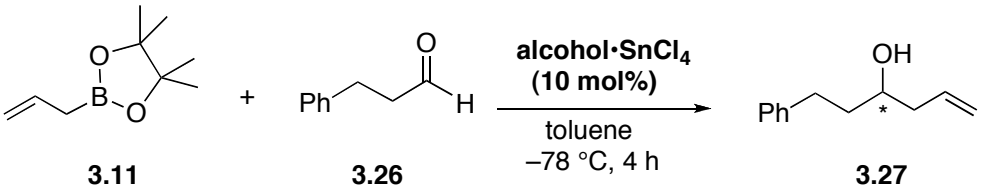
Next, we turned our attention to other sources of chiral Brønsted acids. In this context and as mentioned in Chapter 1, Section 1.2.3, Yamamoto and co-workers have designed numerous combined acid catalyst systems, including BLA and LBA concepts. In particular, their concept of Lewis acid assisted Brønsted acid catalysis (LBA) has been shown to be remarkably effective for the enantioselective protonation of prochiral silyl enol ethers and silyl ketene acetals, and also for the protonation induced enantioselective polyene cyclization.[18] In this catalyst system, coordination of $SnCl_4$ to the oxygens of chiral alcohols in complexes such as **3.28** and **3.29** restricts the directional orientation of the hydroxylic protons and simultaneously increases their acidity (Figure 3.7).

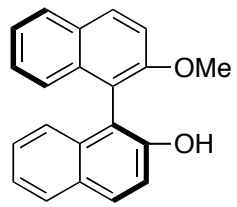


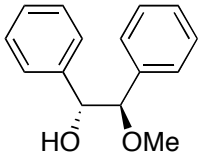
3.28 **3.29**

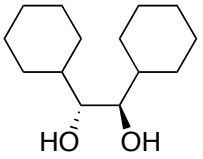
Figure 3.7. Yamamoto's Lewis acid assisted Brønsted acid catalyst system based on chiral diol•$SnCl_4$ catalyst complexes.

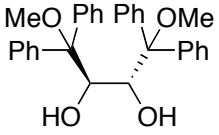
Pursuing the application of LBA catalysts, we first examined the efficiency of chiral alcohols **3.30** and **3.31** and diols **3.32-3.37** (Table 2) in conjunction with $SnCl_4$ as LBA catalysts for the enantioselective allylboration of a model aldehyde, hydrocinnamaldehyde (Table 3.2). Alcohols **3.30** and **3.31** had been successfully used by Yamamoto and coworkers for the protonation of prochiral silylenol ethers to generate chiral ketones.[18]

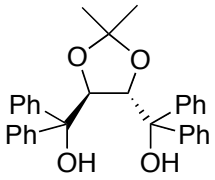


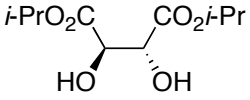


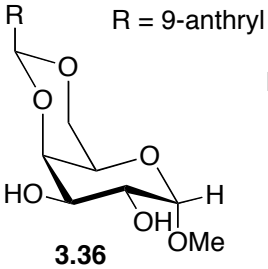


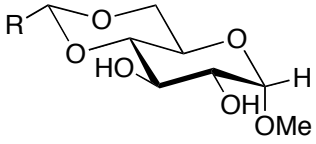












Entry	alcohol/diol	conversion (%)	*ee* (%)
1	**3.30**	78	10
2	**3.31**	100	35
3	**3.32**	100	7
4	**3.33**	100	7
5	**3.34**	100	24
6	**3.35**	100	0
7	**3.36**	85	17
8	**3.37**	100	21

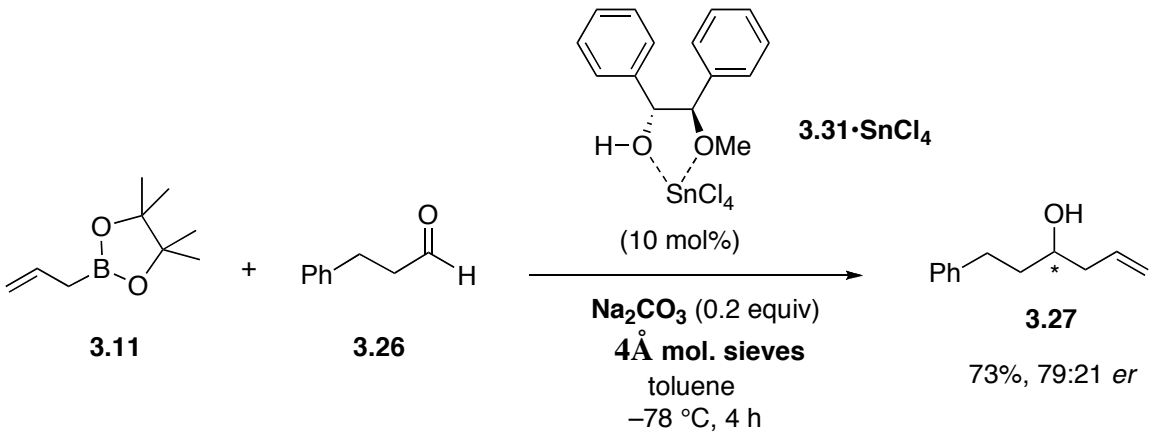
Table 3.2. Initially screened chiral alcohols and diols for use in the LBA catalyst system.
In the present system, the active catalyst was generated *in situ* by the addition of a 1.0 M CH_2Cl_2 solution of anhydrous $SnCl_4$ to a slight excess of chiral alcohol in anhydrous toluene at room temperature, and cooled to –78 ºC.[18] This slight excess of diol was chosen to sequester any free $SnCl_4$, a potentially strong Lewis acid catalyst that could promote a racemic reaction cycle (for the non-chiral reaction). This was followed by addition of a toluene solution of **3.11**, and after 15 min, a dropwise addition of hydrocinnamaldehyde (**3.26**). After 4 h, any unreacted amounts of **3.26** were quenched by addition of DIBAL-H at –78 ºC, and the borate ester of **3.27** was hydrolyzed by the addition of 1.0 *N* HCl to release the free homoallylic alcohol product **3.27**.[19] The enantioselectivity of the product was readily measured by integration of diastereomeric peaks of the corresponding Mosher esters using ^{19}F NMR.

In the event, we were very satisfied to observe complete consumption of the aldehyde starting material during the 4 h reaction time period, and particularly ecstatic to see enantiofacial selectivity under this LBA system. From this initial screening, it became apparent that diols providing higher transfer of stereochemical information were benzylic in nature. For example, hydrobenzoin derivative **3.31** (Table 3.2, entry 2) and TADDOL **3.34** (entry 5) proved to be more efficient in stereo-induction when compared to other chiral alcohols. Thus, the simple hydrobenzoin derivative **3.31** provided homoallylic alcohol **3.27** in 35% *ee* (entry 2). Gratifyingly, alcohol **3.31** presented a platform for rapid modulation of the sterics and electronics of the aryl substituents on the catalyst's chiral backbone. Although the glucopyranoside derivative **3.37** provided appreciable selectivity, it appeared difficult towards further manipulation, and as such, was not pursued any further.

From here onwards, we explored various other Lewis acidic metal salts in conjunction with the optimal chiral alcohol **3.31** for use as LBA catalyst for the same model allylboration reaction. These Lewis acids included $SnBr_4$, $TiCl_4$, TiF_4, $Cu(OTf)_2$, $Zn(OTf)_2$, $Yb(OTf)_3$, $Sc(OTf)_3$, $SnBr_4$ and others; however, they all failed in comparison to $SnCl_4$ giving dismal conversions and enantioselectivities.

3.5.2 Effect of additives on 3.31•$SnCl_4$ catalysis

Having found the optimal chiral alcohol **3.31** for the LBA catalyst system at this early stage of our studies, we explored the effect of additives to further improve the enantioselectivity of the reaction. At this stage, we had also realized that commercially available $SnCl_4$ would produce fumes of HCl gas, upon exposure to air. In the current catalyst system, we anticipated that the presence of adventitious moisture in the reaction medium could potentially lead to hydrolysis of $SnCl_4$ and the generation of HCl, a strong Brønsted acid that could potentially catalyze the unwanted racemic reaction cycle. These hypotheses led us to investigate the use of molecular sieves (to sequester adventitious water) and the use of bases (to neutralize HCl). During this phase, we also became aware that soluble organic bases could deprotonate the hydroxylic protons on the diol•$SnCl_4$ catalyst and lead to the immediate formation of tin alkoxides. This recourse would consequently destroy the active LBA catalyst system.[20] Thus, modulation of this parameter therefore called for insoluble inorganic bases, which would passively sequester free HCl in the reaction medium. In the event, we found that the incorporation of powdered anhydrous Na_2CO_3 (which is completely insoluble in the reaction media) as basic additive along with 4Å molecular sieves and led to a noticeable improvement of reaction enantioselectivity and the desired product was obtained in 58% *ee* (Equation 3.5). It was also found that freshly distilled $SnCl_4$ in the absence of dehydrating agents did provide similar enantioselectivity; however, the addition of 4Å molecular sieves assured reproducibility of the allylation reaction when using undistilled $SnCl_4$.[17]

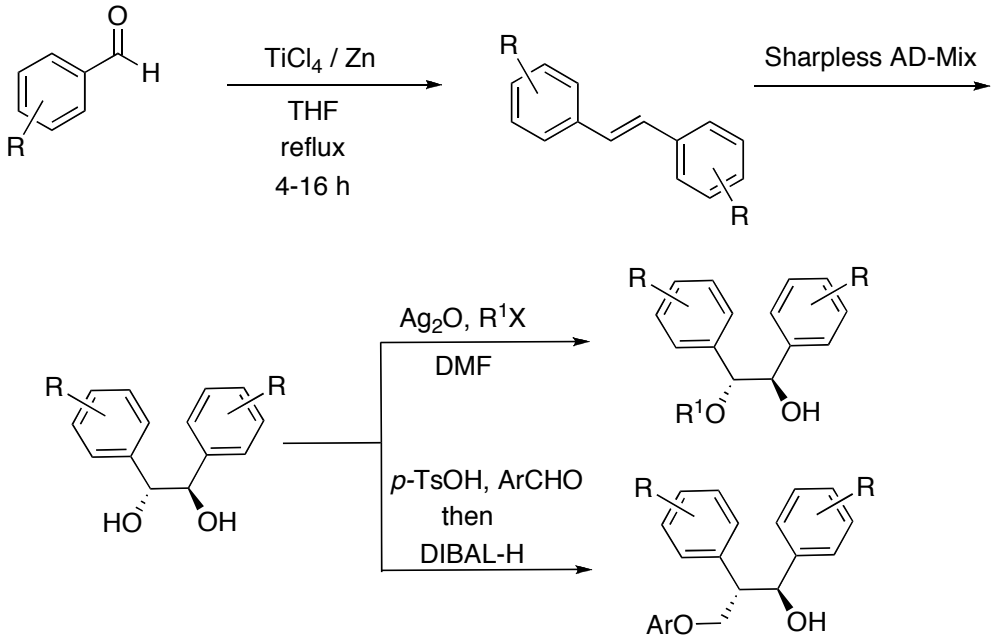


Equation 3.5. Optimal additives for the LBA catalyzed allylboration of hydrocinnamaldehyde.

3.5.3 Electronic and steric modulation of chiral alcohol/diol

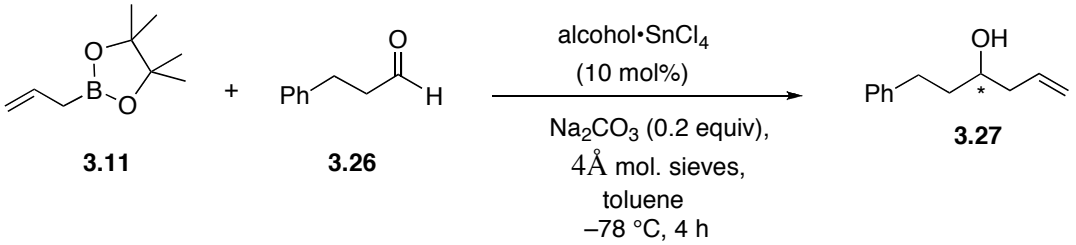
Having identified the optimal reaction conditions, we began to explore steric and electronic modification on the aryl rings that are present in alcohol **3.31**.

The most important aspect of catalyst selection at this stage was directly related to the commercial availability of the parent aldehydes that were utilized in the synthesis of diols/alcohols. As outlined in Scheme 3.2, the synthesis of modified hydrobenzoin derivatives employed a McMurry coupling of benzaldehyde derivatives to provide the requisite *trans*-stilbenes as major isomers. In most cases, a simple recrystallization from CH_2Cl_2/MeOH afforded the stilbene adducts in isomerically pure form.[21] Sharpless asymmetric dihydroxylation of the stilbenes using $(DHQD)_2PHAL$ as the chiral ligand led to the formation of hydrobenzoins, which were isolated in optically pure form by two consecutive recrystallizations from CH_2Cl_2/hexanes.[22] Mono-protection was accomplished using literature methods.[8]

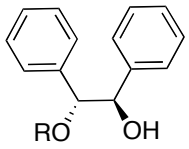


Scheme 3.2. Preparation of sterically and electronically modulated hydrobenzoin derivatives.

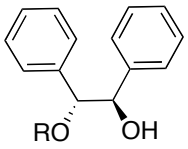
In the event, we prepared diols **3.41**-**3.47** and alcohols **3.38**-**3.40** following the sequence of Scheme 3.2. Diol **3.42** was obtained as a generous gift from Prof. Hishashi Yamamoto (University of Chicago). We then subjected these chiral alcohols in the alcohol•$SnCl_4$-catalyzed allylboration of model aldehyde **3.26** (Table 3.3).



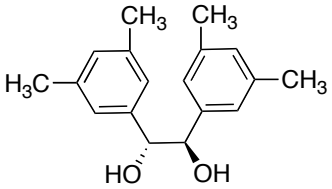
3.11 **3.26** **3.27**



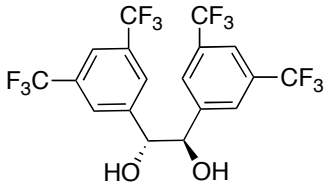
3.38 (R = H)
3.39 (R = Bn)



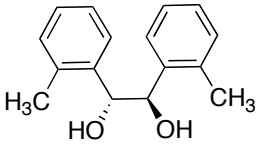
R = 9-methyl-10-anthryl
3.40



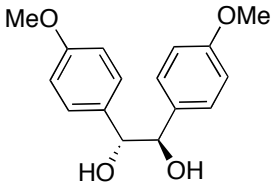
3.41



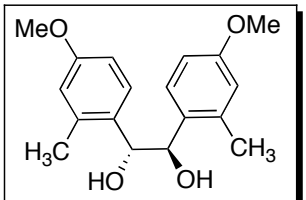
3.42



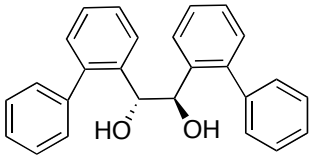
3.43



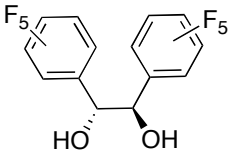
3.44



3.45



3.46



3.47

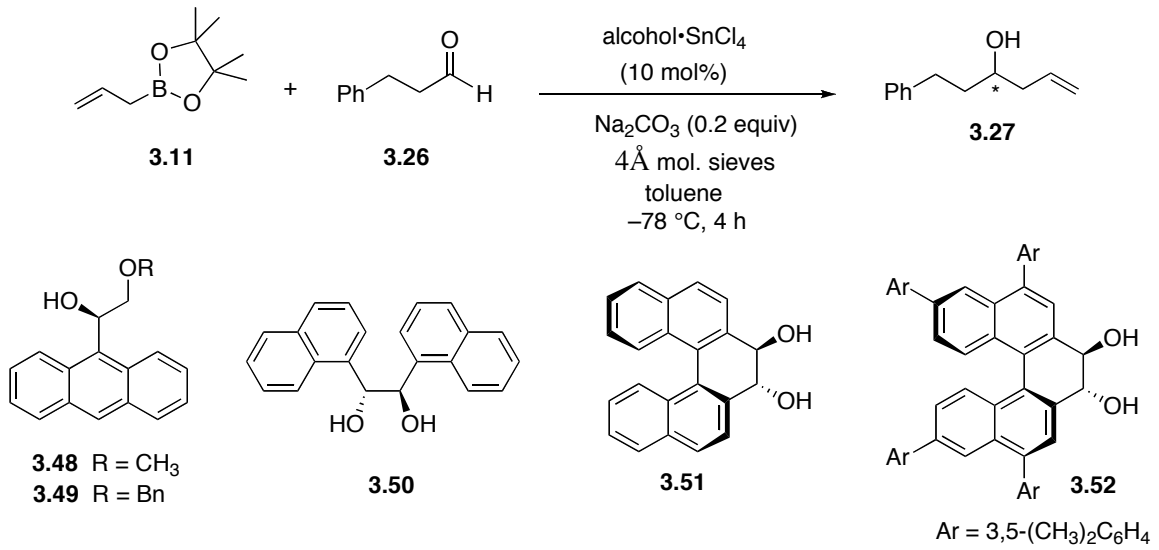
Entry	alcohol/diol	yield (%)	*ee* (%)
1	**3.38**	80	33
2	**3.39**	82	62
3	**3.40**	80	63
4	**3.41**	74	48
5	**3.42**	90	26
6	**3.43**	75	69
7	**3.44**	90	45
8	**3.45**	73	73
9	**3.46**	60	33
10	**3.47** (82% *ee*)	86	50

Table 3.3. Evaluation of chiral alcohols in the LBA catalyzed allylboration of hydrocinnamaldehyde.

At the outset, the use of free diol hydrobenzoin **3.38**, instead of mono-methyl ether **3.31** also looked promising (entry 1, 33% *ee*). This was particularly appreciated since the preparation of the catalyst component would thus be one step shorter. It was also seen that manipulation of the alkyl ether of **3.31** in the form of a benzyl group in **3.39** resulted in a noticeable increase in product enantioselectivity (entry 2); however, further modification in this direction by introduction of an anthryl group in **3.40** (entry 3) did not lead to further increase in product enantioselectivity. Additionally, electronic and steric manipulation of the para- and meta-location of the aromatic ring such as in **3.41, 3.42** and **3.44** did not provide the desired effect on enantioselectivity (entries 4,5 and 7). However, placement of substituents on the ortho- position of the aromatic ring did render dramatic effects. For example, introduction of a methyl group in the ortho- position of hydrobenzoin as in **3.43** led to a significant increase in observed enantioselectivity (compare entry 6 vs. entry 1). On the contrary, use of aryl-substituted hydrobenzoin **3.46** resulted in a significantly decreased enantioselectivity (entry 9). In the event, the prominent hydrobenzoin derivative turned out to be diol **3.45** (entry 8), which provided the desired product in 73% *ee* and 73% yield. It should also be mentioned that we had also hoped to screen the ortho-ortho-disubstituted hydrobenzoins, however, in our hands, the synthesis of these hindered hydrobenzoins was not successful due to the failure of the asymmetric dihydroxylations on the corresponding stilbenes.

Unfortunately we were not able to further optimize diol **3.45** due to the lack of commercial availability of substituted benzaldehydes. Consequently, we looked into other forms of C_2-symmetric diols, which contained the hydrobenzoin skeleton as well as the use of chiral secondary alcohols. In particular, we explored the potential use of anthracene-derived alcohols **3.48**-**3.49** and commercially available naphthaldehyde derived diol **3.50** (Table 3.4). After surveying the literature, we also came across binaphthol derived diol **3.51** which contains two elements of chirality in the form of central chirality of diol unit and axial chirality of the binaphthyl system (Table 3.4).[23] We also synthesized diol **3.52** with anticipation of increased steric discrimination.[24] From the obtained results, we were very pleased to see that commercially available diol **3.50** provided 77% *ee* of the homoallylic alcohol product (entry 3, Table 3.4).

Interestingly, diol **3.51** provided moderate enantioselectivity (55% *ee*) of the requisite product (entry 4, Table 3.4) and as anticipated its aryl-substituted analogue **3.52** gave the product with an improved 83% *ee* (entry 5).

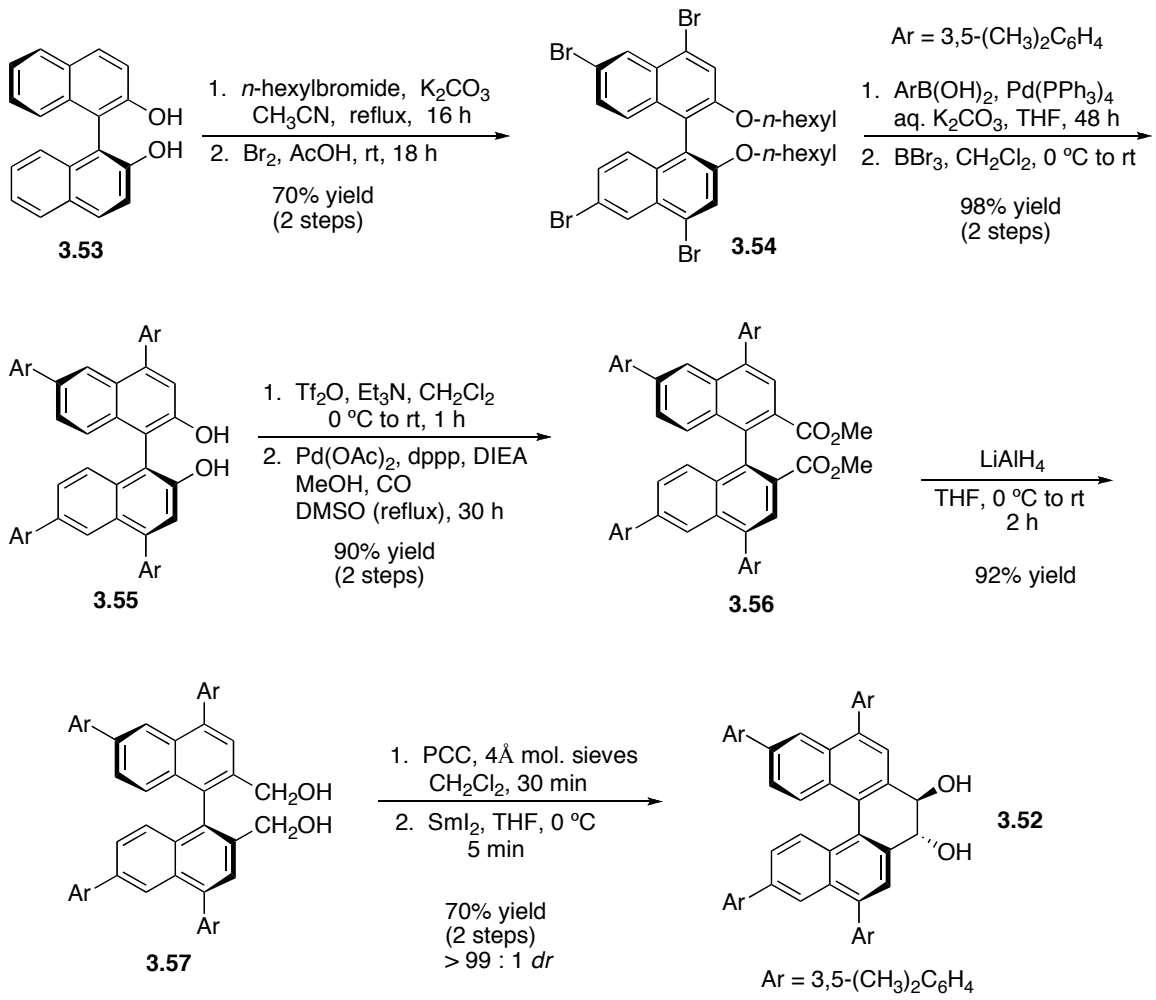


Entry	alcohol/diol	yield (%)	*ee* (%)
1	**3.48**	85	57
2	**3.49**	83	41
3	**3.50**	85	77
4	**3.51**	83	55
5	**3.52**	99	83

Table 3.4. Evaluation of non-hydrobenzoin chiral alcohols as LBA catalyst component for asymmetric allylboration of hydrocinnamaldehyde.

3.5.4 Synthesis of binaphthol derived diol

It was envisioned that diol **3.52** would be made in a similar approach to that of diol **3.51**, through a samarium mediated diastereoselective pinacol coupling. The decoration of the binaphthyl ring was thought to arise from a standard Suzuki-Miyaura cross-coupling reaction.



Scheme 3.3. Synthesis of binaphthol derived diol **3.52**.

Thus, the readily available (*S*,*S*)-1-1'-bi(2-naphthol) **3.53** was alkylated and subjected to bromination under acidic conditions to provide tetrabromide **3.54**. Tetrabromide **3.54** was subjected to a quadruple Suzuki-Miyaura cross-coupling with 3,5-dimethyl phenylboronic acid and the crude product after workup was subjected to dealkylation with BBr_3. This two step process led to a very high yield of binol-derivative **3.55**, which was activated as the corresponding bis-triflate, and subsequent carbonylative esterification with methanol under palladium catalysis led to the formation of diester **3.56**. Reduction of the diester to the corresponding benzylic diol **3.57** was accomplished using $LiAlH_4$, and oxidation to the corresponding di-aldehyde was achieved using anhydrous PCC conditions. The thus obtained crude aldehyde was immediately subjected to a diastereoselective intramolecular pinacol coupling mediated by SmI_2 which led to the formation of diol **3.52**. In line with Suzuki's report,

there is complete transfer of axial chirality from the binaphthyl ring and a single diastereomer was obtained.[23] The observed stereochemistry of the product is rationalized through a *synclinal* arrangement of dialdehyde **3.57**, which is facilitated by the bidentate coordination of the aldehyde carbonyls to the samarium metal. The corresponding antiperiplanar arrangement of the dialdehyde (leading to the *S,S*-diastereomer) is expected to experience repulsive interaction between carbonyl lone pairs and the π-system of the adjacent naphthyl ring system (Figure 3.8).

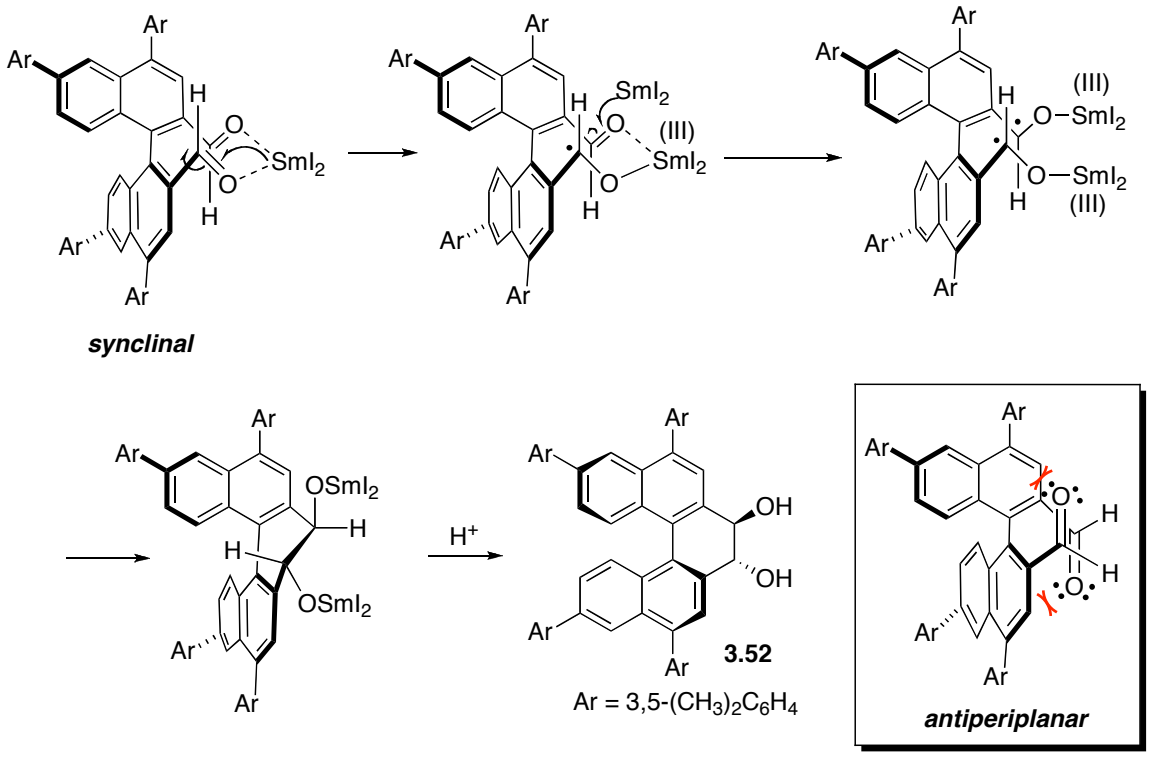
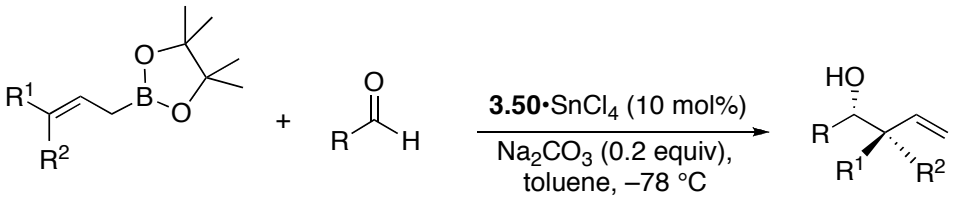


Figure 3.8. Proposed mechanism for diastereoselective pinacol coupling.

3.5.4 Substrate scope of Brønsted acid catalyzed allyl- and crotylboration of aldehydes[17]

Even though diol **3.52** provided the highest enantioselectivity (83% *ee*) for the allylboration of hydrocinnamaldehyde, its synthesis required nine linear steps. Given that diol **3.50** was commercially available and provided comparable enantioselectivity (77% *ee*), we chose to explore the substrate scope with this diol and boron reagents **3.11**, **3.12** and **3.13**. A panel of model aldehydes including aliphatic, functionalized aliphatic, conjugated and aromatic aldehyde substrates were studied (Table 3.5). In contrast with the most stereoselective catalytic allylation systems reported in the literature (Section 3.3),[7] we found that aliphatic aldehydes gave higher

enantioselectivities in this catalytic allylboration process. Whereas aromatic and unsaturated aldehydes gave modest selectivities, the enantioselectivities in the allylation and crotylation of aliphatic aldehydes approached 80% *ee*. Akin to previous reports by Miyaura and coworkers,[12] we also observed higher enantioselectivities with the *trans*-crotyl reagent **3.12** when compared to *cis*-crotyl reagent **3.13**. Moreover, the enantioselectivities for the crotylboration reactions were slightly lower than that of the simple allylboration. Importantly, the diastereoselectivities for the crotylations were very high (>98:2 *dr*) and consistent with the corresponding non-catalyzed thermal reactions of **3.12** and **3.13.**



3.11 R^1, R^2 = H
3.12 R^1 = Me, R^2 = H
3.13 R^1 = H, R^2 = Me

Entry	aldehyde (R)	boronate	product	*syn*/*anti*	yield (%)	*ee* (%)
1	**3.26** $PhCH_2CH_2$	**3.11**	**3.27**	–	95	77
2	**3.58** $CH_3(CH_2)_8$	**3.11**	**3.64**	–	76	80
3	**3.59** C_6H_{11}	**3.11**	**3.65**	–	90	70
4	**3.60**	**3.11**	**3.66**	–	90	74
5	**3.61** Ph	**3.11**	**3.67**	–	99	10
6	**3.62** PhCH=CH	**3.11**	**3.68**	–	72	20
7	**3.63** $CH_3(CH_2)_4CC$	**3.11**	**3.69**	–	99	12
8	**3.26** $PhCH_2CH_2$	**3.12**	**3.70**	*anti*	99	72
9	**3.58** $CH_3(CH_2)_8$	**3.12**	**3.71**	*anti*	70	72
10	**3.26** $PhCH_2CH_2$	**3.13**	**3.72**	*syn*	87	40
11	**3.58** $CH_3(CH_2)_8$	**3.13**	**3.73**	*syn*	70	46
12[a]	**3.26** $PhCH_2CH_2$	**3.11**	**3.74**	_	95	83

Table 3.5. Enantioselective additions of allyl- and crotylboronates.

[a] 100 mol% of **3.50**•$SnCl_4$ was used.

In order to distinguish the extent of uncatalyzed background reaction on the observed enantioselectivity, we also performed the addition of allylboronate **3.31** to hydrocinnamaldehyde

under 100 mol% of LBA catalyst **3.50**•$SnCl_4$ (entry 12, Table 3.5). In the event, stoichiometric loading of the LBA catalyst only led to a modest improvement in product enantioselectivity (83% *ee* vs. 77% *ee*). This result suggested that in the case of aliphatic aldehydes, the enantioselectivity was not limited by the competing background uncatalyzed reaction and made us realize that there was certainly room for improvement in the enantioselectivity of the catalyst.

Pleasingly, the optimized reaction conditions were found to be effective in the diastereocontrolled additions of **3.11** and **3.13** to chiral α-methyl aldehyde **3.74**, providing the very useful propionate units **3.75** and **3.76** (Figure 3.9). In the event, we observed that the LBA catalyst **3.50**•$SnCl_4$ exerted a strong influence on the diastereofacial selectivity in the simple allylation of aldehyde **3.74**. In the case of *cis*-crotylation, the catalyst system was found to significantly enhance the intrinsic preference of the $SnCl_4$-catalyzed reaction in a matched combination, providing the *anti-syn*-adduct **3.77** in 20:1 ratio over the *syn-syn*-adduct **3.78** (compared to ~2:1 with $SnCl_4$ alone as Lewis acid). Unfortunately, for unclear reasons, we observed a low conversion when using *trans*-crotylboronate **3.12** and we could not improve upon this result.

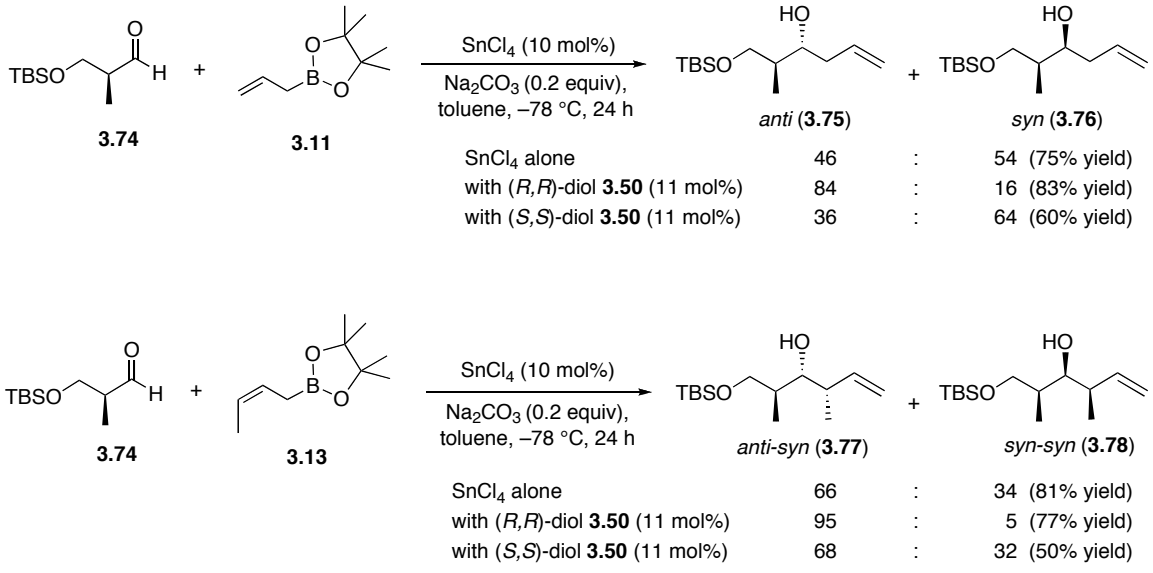
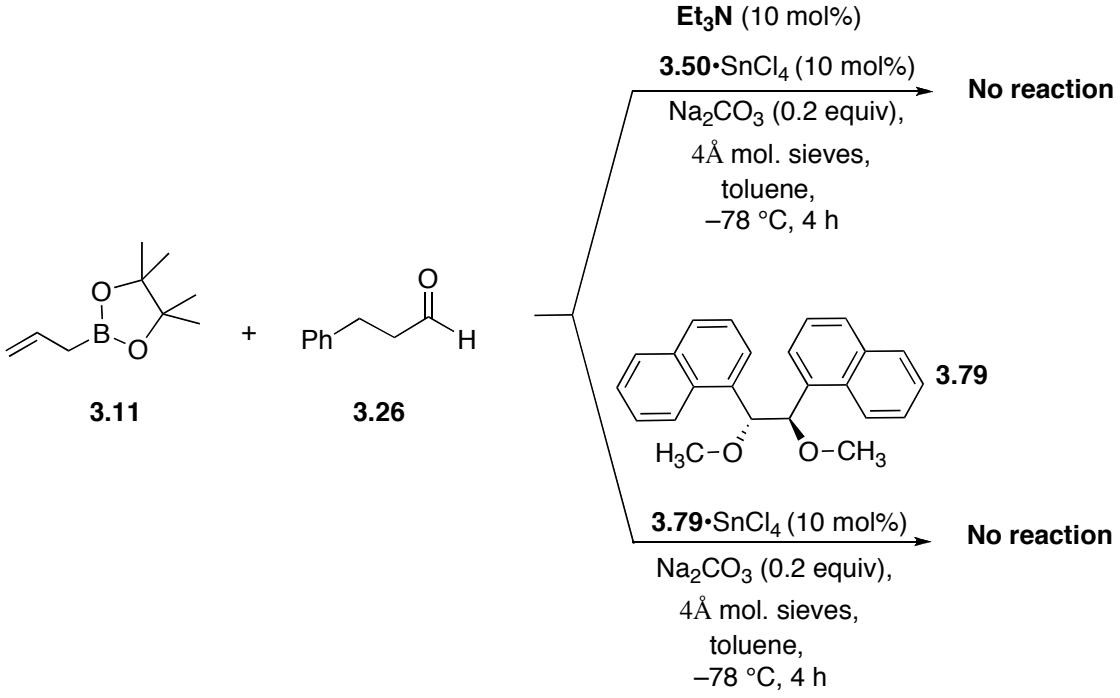


Figure 3.9. Diastereoselective additions of allyl- and *Z*-crotylboronate to a chiral aldehyde.[17]

3.5.5 Mechanistic aspects of 3.50•$SnCl_4$ catalyzed allylboration

To validate the existence of a Brønsted acid catalyst, we carried out the model allylboration reaction in the presence of Et_3N as a base. In the event, we observed no catalysis of the reaction

(Scheme 3.14).[20] This result implies that the presence of acidic hydroxylic protons is necessary for catalysis to occur. Moreover, when we substituted diol **3.50** with its bis-methylether **3.79**, we did not observe any reaction, which further emphasized the importance of hydroxylic protons over the Lewis acidity through the tin metal (Scheme 3.4). We also conducted NMR experiments to determine the nature of the active catalyst. These structural studies at –80 ºC revealed the presence of activated hydroxylic protons by ^{1}H-NMR shifts and according to the chemical shift of the tin atom (–575.6 ppm) in ^{119}Sn-NMR, the Brønsted acid catalyst system unambiguously consisted of a hexa-coordinated metal center.[25] This observation further invalidates the presence of tin (IV) alkoxides as active catalyst.



Scheme 3.4. Control experiments that highlight the importance of Brønsted acidity.

3.5.6 Conclusion–First generation catalyst system

During this stage, the novel chiral Brønsted acid-catalyzed enantioselective allylation **3.50•SnCl$_4$** constituted the most effective catalytic enantioselective allylboration. This new system represents a significant advance over the previous reports of Miyaura and coworkers[12] and highlighted the strong potential of chiral Brønsted acid-catalysis towards the development of an ideal carbonyl allylation methodology.

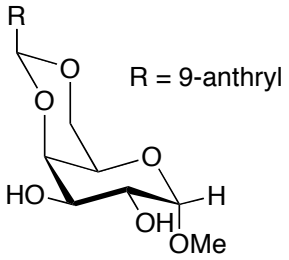
3.6 Experimental

3.6.1 General

Unless otherwise noted, all reactions were performed under an argon atmosphere using flame-dried glassware. Toluene, hexanes and CH_2Cl_2 were distilled over CaH_2. THF and Et_2O were distilled over sodium/benzophenone ketyl. All aldehydes were purified by Kugelrohr distillation, prior to use. Molecular sieves were prepared by heating under vacuum at 130 ºC (overnight) and then stored inside an oven maintained at 125 ºC. Thin layer chromatography (TLC) was performed on Merck Silica Gel 60 F254 plates and, visualized with UV light and $KMnO_4$ and 5% phosphomolybdic acid / EtOH (PMA). NMR spectra were recorded on Varian INOVA-300, INOVA-400, INOVA-500 or Unity 500 instruments. The residual solvent protons (^1H) or the solvent carbons (^{13}C) were used as internal standards. Boron NMR spectra are referenced to external $BF_3{\cdot}OEt_2$; ^{19}F spectra are referenced to external $CFCl_3$. ^1H NMR data are presented as follows: chemical shift in ppm upfield towards tetramethylsilane (multiplicity, coupling constant, integration). The following abbreviations are used in reporting NMR data: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; qt, quartet of triplets; dd, doublet of doublets; dt, doublet of triplets; AB, AB quartet; m, multiplet. High-resolution mass-spectra were recorded by the University of Alberta Mass Spectrometry Services Laboratory, using either electron impact (EI) or electrospray (ES) ionization techniques. Infrared-spectra and optical rotations were recorded by University of Alberta Spectral Services and combustion analyses were performed by the University of Alberta Micro-Analytical Lab. Allylic boronates **3.11, 3.12** and **3.13** were prepared by the procedure of Roush and coworkers.[26] Chiral Brønsted acids **3.21**-**3.25** are commercially available and were used without further purification. Diol **3.51** has been previously reported in literature.[23] Aldehyde **3.75** was prepared from the corresponding Roche ester.[27] Optical purities of homoallylic alcohol products were measured by Chiral HPLC (Diacel OD Column, 0.46 X 25 cm) or by formation of Mosher esters and subsequent ^1H or ^{19}F NMR analysis of the crude product. Specific details are indicated in the experimental section for each individual product

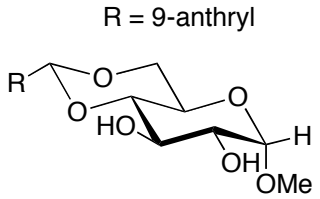
3.6.2 Preparation of carbohydrate derived diols

(2*S*,4a*R*,6*S*,7*R*,8*R*,8a*R*)-2-(anthracen-9-yl)-6-methoxyhexahydropyrano[3,2-*d*][1,3]dioxine-7,8-diol (3.36)



A mixture of α-methyl-galactopyranoside (0.670 g, 3.17 mmol, 1.00 equiv), anthracene dimethylacetal (1.00 g, 3.98 mmol, 1.30 equiv) and *p*-TsOH (14.0 mg, 0.398 mmol, 0.0100 equiv) was stirred in 20 mL of CH_3CN at room temperature for 16 h after which the reaction mixture was diluted with water and extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and evaporated *in vacuo* to provide the crude product, which was purified by flash chromatography (0-10% EtOAc/hexanes) to afford 1.25 g (100% yield) of the title compound **3.36** as a yellow solid. $[\alpha]_D^{25}$ +108.81 (*c* 1.61, $CHCl_3$); IR (cast film) 3407, 3054, 302, 2907, 1449, 1189, 1160, 1035, 979, 759 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.74 (d, *J* = 9.0 Hz, 2H), 8.49 (s, 2H), 8.00 (d, *J* = 8.0 Hz, 2H), 7.53-7.44 (m, 4H), 6.93 (s, 1H), 5.14 (d, *J* = 3.5 Hz, 1H), 4.43 (dd, *J* = 13.0, 2.0 Hz, 1H), 4.35 (d, *J* = 3.0 Hz, 1H), 4.22 (dd, *J* = 12.5 Hz, 1.5 Hz, 1H), 3.99 (ddd, *J* = 10.0, 10.0, 4.0, Hz, 1H), 3.90 (ddd, *J* = 9.5, 9.5, 3.5 Hz, 1H), 3.53 (s, 3H), 2.34 (d, *J* = 9.5 Hz, 1H), 2.26 (d, *J* = 8 Hz, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 131.5, 129.8, 129.7, 128.9, 126.1, 124.9, 124.8, 100.4, 99.5, 76.6, 70.1, 70.0, 69.9, 63.1, 55.8; HRMS (ESI) Calcd. $[M+H]^+$ $C_{22}H_{23}O_6$: 383.14891. Found: 383.14835.

(2*R*,4a*R*,6*S*,7*R*,8*R*,8a*S*)-2-(anthracen-9-yl)-6-methoxyhexahydropyrano[3,2-*d*][1,3]dioxine-7,8-diol (3.37)



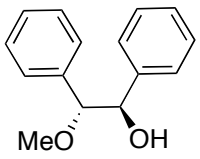
A mixture of α-methyl-glucopyranoside (0.670 g, 3.17 mmol, 1.00 equiv), anthracene dimethylacetal (1.00 g, 3.98 mmol, 1.28 equiv) and *p*-TsOH (14.0 mg, 0.317 mmol, 0.100 equiv) was stirred in 20 mL of CH_3CN at room temperature for 16 h after which the reaction mixture was diluted with water and extracted with EtOAc and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product which was purified by flash chromatography (0-10% EtOAc/hexanes) to afford 0.360 g (30% yield) of the title compound **3.37** as a yellow solid. $[\alpha]_D^{25}$ +90.69 (*c* 0.71, $CHCl_3$); IR (cast film) 3430, 2932, 2907, 1465, 1107, 1060, 757 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.63 (d, *J* = 9.0 Hz, 2H), 8.50 (s, 2H), 8.00 (dd, *J* = 8.5, 1.0 Hz, 2H), 7.56-7.53 (m, 2H), 7.48-7.45 (m, 2H), 6.92 (s, 1H), 4.81 (d, *J* = 4.0 Hz, 1H), 4.46 (dd, *J* = 10.5, 5.0 Hz, 1H), 4.15 (ddd, *J* = 10.0, 10.0, 5.0 Hz, 1H), 4.00 (ddd, *J* = 9.5, 9.5, 2.0 Hz, 1H), 3.69-3.64 (m, 2H), 3.53 (s, 3H), 2.77 (d, *J* = 1.0 Hz, 1H), 2.35 (dd, *J* = 10.0, 9.5 Hz, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 131.5, 130.0, 129.7, 129.1, 126.5, 126.2, 124.9, 124.8, 100.7, 100.0, 82.2, 72.8, 71.8, 70.0, 62.54, 55.88; HRMS (ESI) Calcd. $[M+H]^+$ $C_{22}H_{23}O_6$: 383.14891. Found: 383.14878.

3.6.3 Preparation of hydrobenzoin derived diols and their derivatives

(*R*,*R*)-1,2-Diphenyl-ethane-1,2-diol (3.38)

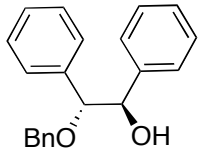
Commercially available from Aldrich.

(*R*,*R*)-2-Methoxy-1,2-diphenyl-ethanol (3.31)



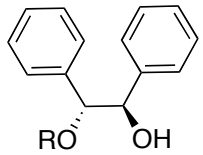
To a solution of (*R,R*)-(+)-hydrobenzoin (100 mg**,** 0.466 mmol, 1.00 equiv) in 2 mL of DMF under argon was added Ag_2O (108 mg, 0.466 mmol, 1.00 equiv) and iodomethane (32.0 μL, 0.513 mmol, 1.10 equiv) and this mixture was stirred in the dark for 24 h. This resulting solution was then filtered over a short pad of Celite and the Celite was subsequently washed with 10 mL of CH_2Cl_2. The resulting solution was evaporated *in vacuo* and purified by flash chromatography (5% EtOAc/hexanes) to give the title compound in 68% yield with analytical and spectral properties in accordance with the literature.[18]

(*R,R*)-2-Benzyloxy-1,2-diphenyl-ethanol (3.39)



To a solution of (*R,R*)-hydrobenzoin (200 mg, 0.934 mmol, 1.00 equiv) in 10 mL of reagent grade benzene was added (17.7 mg, 0.0900 mmol, 0.100 equiv) of *p*-TsOH and to this mixture was added freshly distilled benzaldehyde (114 μL, 1.12 mmol, 1.20 equiv) and the reaction mixture was refluxed for 3 h under a dean-stark trap (to remove water) after which, the reaction mixture was concentrated *in vacuo*. The resulting solid was dissolved in 2 mL of toluene and cooled to 0 ºC, after which DIBAL-H (1.0 M in toluene, 2.80 mL, 2.80 mmol, 3.00 equiv) was added and the reaction mixture was stirred at 0 ºC for 2 h. The reaction was quenched with 2 mL of MeOH and then diluted with Et_2O (25 mL), followed by the addition of 10% NaOH and then the resulting mixture was filtered through a pad of Celite and transferred to a seperatory funnel and washed with brine followed by drying over anhydrous Na_2SO_4. The resulting solution was filtered and concentrated *in vacuo* and the crude product was purified by flash chromatography (5% EtOAc/hexane) to yield 241 mg (84% yield) of the title compound as a colorless solid. The ^{1}H NMR, ^{13}C NMR, IR, HRMS properties were identical to those reported.[3]

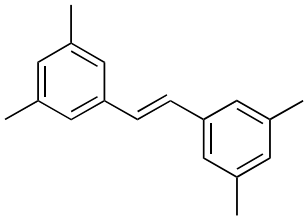
(1*R*,2*R*)-2-(10-Methylanthracen-9-yl)methoxy)-1,2-diphenylethanol (3.40)



R = 9-methyl-10-anthryl

Following the procedure for the preparation of **3.39** but using 10-methyl-9-anthracene carboxyaldehyde, the title compound was obtained in 75% yield as a faint yellow solid. $[\alpha]_D^{25}$ – 85.55 (*c* 0.84, $CHCl_3$); IR (cast Film) 3508, 3062, 3030, 2884, 1673, 1592, 1453, 1331, 1285, 1070, 748, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37-8.30 (m, 2H), 8.23-8.19 (m, 2H), 7.57-7.50 (m, 4H), 7.37-7.35 (m, 3H), 7.26-7.22 (m, 2H), 7.16-7.14 (m, 3H), 7.04 (dd, *J* = 1.6, 7.2 Hz), 5.46 (d, *J* = 11.2 Hz, 1H), 5.34 (d, *J* = 11.6 Hz, 1H), 4.70 (d, *J* = 8.4 Hz, 1H), 4.55 (d, *J* = 8.4 Hz, 1H), 3.44 (s, 1H), 3.15 (s, 3H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 139.1, 138.0, 134.1, 132.4, 130.8, 129.9, 128.3, 128.3, 128.2, 127.8, 127.6, 127.3, 127.2, 126.5, 125.9, 125.4, 124.9, 124.6, 87.6, 78.5, 63.5, 14.5; HRMS (EI) Calcd. $C_{30}H_{26}O_2$: 418.19327. Found: 418.19414.

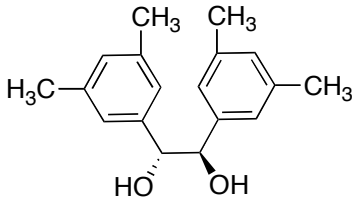
(*E*)-1,2-Di-(3,5-bis-dimethylphenyl)-ethene (3.41a)



Into a 250 mL two-neck round bottom flask equipped with a condenser and a magnetic stirrer under argon was added Zn dust (2.02 g, 45.0 mmol, 3.00 equiv) and 150 mL of freshly distilled THF. To this suspension was added drop-wise $TiCl_4$ (2.47 mL, 22.5 mmol, 1.50 equiv). This mixture was heated to 80 ºC for 1 h after which freshly distilled 3,5-dimethyl-benzaldehyde (2.02 mL, 15.0 mmol, 1.00 equiv) was added and the reaction mixture was refluxed for an additional 4 h. After the elapsed time, the reaction mixture was poured over ice cold solution of 1.0 *N* HCl and this solution was filtered through a pad of Celite and the resulting biphasic mixture was extracted with CH_2Cl_2, washed with brine and dried over Na_2SO_4, filtered and concentrated *in vacuo* and purified by flash chromatography (1-5% EtOAc/hexanes). Subsequent recrystallization from MeOH gave 65% yield of isomerically pure (*E*)-alkene as a

crystalline solid. IR (cast film) 3021, 2912, 2859, 1599, 962, 847, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.15 (s, 4H), 7.05 (s, 2H), 6.91 (s, 2H), 2.35 (s, 12H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 138.1, 137.5, 129.3, 128.5, 124.4, 21.4; HRMS (EI) Calcd. $C_{18}H_{20}$: 236.1565. Found: 236.1568.

(1*R*,2*R*)-1,2-Bis(3,5-dimethylphenyl)ethane-1,2-diol (3.41)

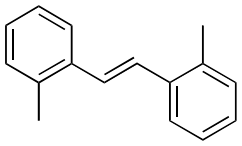


To a round bottom flask was added K_2CO_3 (3.00 equiv), $K_3Fe(CN)_6$ (3.00 equiv), $(DHDQ)_2PHAL$ (0.0100 equiv), *t*-BuOH (5 mL/mmol of stilbene), H_2O (5 mL/mmol of stilbene) and the mixture was cooled to 0 ºC to give an orange viscous mixture which was vigorously stirred. At this stage, $K_2OsO_2(OH)_4$ (0.00250 equiv), stilbene **3.41a** (1.00 equiv), and $MeSO_2NH_2$ (1.00 equiv) were added in the listed order. The reaction mixture was allowed to gradually warm to room temperature and stirred for 48 h, after which, 3.00 g of Na_2SO_3 (per mmol of stilbene) was added and the reaction mixture was stirred for additional 1 h. The reaction mixture was diluted with EtOAc and then poured into a sepratory funnel and washed with 1.0 *N* KOH followed by washing with water. The aqueous layer was back extracted with EtOAc and the combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product, which was purified by flash chromatography (5-20% EtOAc/hexanes) and the resulting product was recrystallized twice from hot CCl_4 to give the title compound in 75% yield as a white amorphous solid. $[\alpha]_D^{25}$ +66.36 (*c* 2.97, $CHCl_3$). IR (cast film) 3373, 3293, 2907, 1608, 1464, 1070, 848 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.90 (s, 2H), 6.82 (s, 4H), 4.65 (s, 1H), 2.67 (br s, 2H), 2.27 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.2, 137.6, 129.4, 124.5, 78.4, 21.3; HRMS (EI) Calcd. $[C_{18}H_{22}O_2\text{-}H_2O]^+$: 252.15142. Found: 252.15162.

(*R*,*R*)-1,2-Bis-(3,4-bis-trifluoromethyl-phenly)-ethane-1,2-diol (3.42)

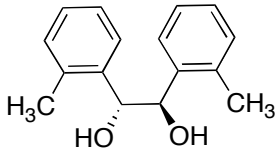
Gift from Prof. H. Yamamoto at University of Chicago.

(*E*)-1,2-Di-(2-methylphenyl)-ethene (3.43a)



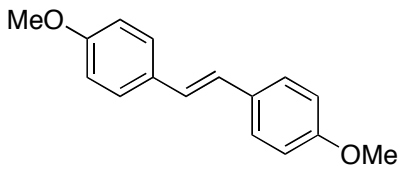
Following the procedure of McMurry coupling in the preparation of **3.41a**, the product was isolated as 1.2:1.0 mixture of *E*/*Z* alkenes as determined by ^{1}H NMR. This isomeric mixture was subjected to iodine catalyzed isomerization in refluxing xylenes for 24 h to give the requisite product as a white solid after recrystallization from methanol in 50% yield. IR (cast film) 723, 763, 978, 1492, 1954, 2860, 2946, 3015, 3062, 3094 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.65 (m, 2H), 7.33-7.26 (m, 8H), 2.51 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.9, 135.9, 130.4, 128.1, 127.6, 126.2, 125.6, 20.0; HRMS (EI) Calcd. $C_{16}H_{16}$: 208.1252. Found: 208.1251.

(1*R*,2*R*)-1,2-Di-*o*-tolylethane-1,2-diol (3.43)



Following the procedure used for the preparation of diol **3.41**, the title compound was isolated in 80% yield after recrystallization from hot CCl_4. as a white amorphous solid. $[\alpha]_D^{25}$ +63.87 (*c* 1.43, $CHCl_3$); IR (cast film) 3388, 3062, 3023, 2928, 1604, 1491, 1198, 1043, 792, 762 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.5 Hz, 2H), 7.26-7.11 (m, 4H), 6.93 (d, *J* = 7.5 Hz, 2H), 4.99 (s, 2H), 2.91 (br s, 2H), 1.68 (s, 6H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 138.0, 135.9, 130.2, 127.7, 127.2, 125.6, 74.7, 18.7; HRMS (EI) Calcd. $C_{18}H_{22}O_2$: 242.13068. Found: 242.13068.

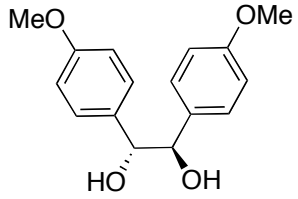
(*E*)-1,2-Di-(4-methoxyphenyl)-ethene (3.44a)



Following the procedure used for he preparation of **3.41a**, the title compound was obtained in 40% yield after recrystallization from CH_2Cl_2/MeOH. IR (cast film) 3094, 3021, 2956, 2937,

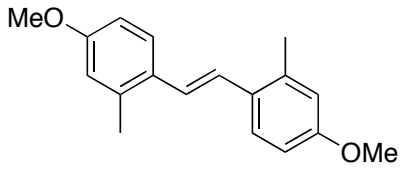
2911, 2838, 1608, 1517, 1278, 1030, 834 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.8 Hz), 6.93 (s, 2H), 6.89 (d, *J* = 8.8 Hz, 4H), 3.83 (s, 6H), 6.89 (d, *J* = 8.8 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 130.6, 127.5, 126.3, 114.2, 55; HRMS (EI) Calcd. $C_{16}H_{16}O_2$: 240.11503. Found: 240.11502.

(1*R*,2*R*)-1,2-Bis(4-methoxyphenyl)ethane-1,2-diol (3.44)



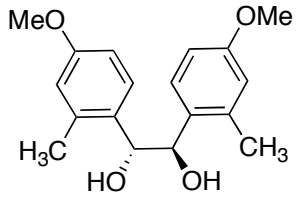
Following the procedure used for the preparation of **3.41**, the title compound was obtained in 72% yield after recrystallization from CH_2Cl_2/MeOH. $[\alpha]_D^{25}$ +101.56 (*c* 1.23, $CHCl_3$); IR (cast film) 3405, 2929, 2836, 1612, 1248, 1033, 831 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.05 (d, *J* = 8.7 Hz, 2H), 6.77 (d, *J* = 9.0 Hz, 2H), 4.64 (s, 2H), 2.75 (br s, 2H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 159.2, 132.2, 128.2, 113.5, 78.8, 55.2; HRMS (EI) Cacld. $C_{18}H_{18}O_4$: 274.12051. Found: 274.12051.

(*E*)-1,2-bis(4-methoxy-2-methylphenyl)-ethene (3.45a)



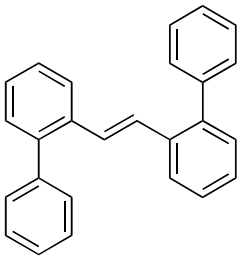
Following the procedure used for the preparation of **3.41a**, the title compound was obtained in 70% yield after recrystallization from CH_2Cl_2/MeOH as a white solid (isomerically pure *E*-alkene). IR (cast film) 3033, 2955, 2836, 1607, 1507, 1257, 1212, 1054 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.8 Hz, 2H), 7.05 (s, 2H), 6.80-6.74 (m, 4H), 3.83 (s, 6H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 158.9, 137.2, 130.0, 126.6, 125.7, 115.7, 111.8, 55.3, 20.3; HRMS (EI) Calcd. $C_{18}H_{20}O_2$: 268.14633. Found: 268.14648.

(1*R*,2*R*)-1,2-Bis(4-methoxy-2-methylphenyl)ethane-1,2-diol (3.45)



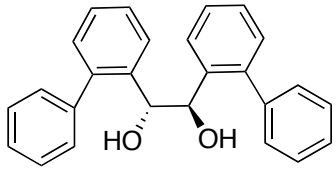
Following the procedure used for the preparation of diol **3.41**, the title compound was obtained in 77% yield after recrystallization from CH_2Cl_2/hexanes as a white solid. $[\alpha]_D^{25}$ +104.60 (*c* 0.55, $CHCl_3$); IR (cast film) 3414, 3000, 2925, 2852, 2836, 1609, 1504, 1289, 1253, 1197, 1046 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.5 Hz, 2H), 6.73 (dd, *J* = 3.0, 8.5 Hz, 2H), 6.46 (d, *J* = 2.5 Hz, 2H), 4.87 (s, 2H), 3.75 (s, 6H), 3.01 (br s, 2H), 1.69 (s, 6H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 158.8, 137.5, 130.5, 128.4, 115.4, 111.3, 74.5, 55.1, 19.1; HRMS (EI) Calcd. $[C_{18}H_{22}O_4\text{-}H_2O]^+$: 284.14214. Found: 284.14210.

(*E*)-1,2-Di-(2-phenylphenyl)-ethene (3.46a)



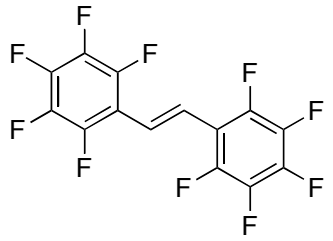
Following the procedure of the McMurry coupling reaction used for the preparation of **3.41a**, the title compound was obtained as a 5.7:1 mixture of *E*/*Z* alkenes. The isomerically impure olefin was subjected to iodine-catalyzed isomerization in refluxing xylenes for 24 h to give isomerically pure *E*-alkene, which was further purified by recrystallization from CH_2Cl_2/MeOH in 60% yield. IR (cast film) 3056, 3020, 1595, ,1498, 1479, 1073, 965, 775, 761, 742, 720, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56-7.41 (m, 12H), 7.38-7.30 (m, 6H), 7.12 (s, 2H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 141.1, 140.9, 135.7, 130.2, 129.9, 128.1, 127.5, 127.1, 125.9; HRMS (EI) Calcd. $C_{26}H_{20}$: 332.15650. Found: 332.15657.

(1*R*,2*R*)-1,2-di(biphenyl-2-yl)ethane-1,2-diol (3.46)



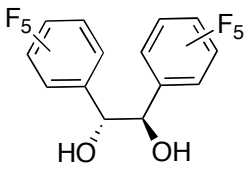
Following the procedure used for the preparation of **3.41**, the title compound was obtained in 56% yield as a white solid after recrystallization from CH_2Cl_2/hexanes. $[\alpha]_D^{25}$ +88.68 (*c* 0.98, $CHCl_3$). IR (cast film) 3468, 3349, 3025, 2977, 2930, 1597, 1437, 1190, 1075, 998, 754, 707 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33-6.99 (m, 14H), 6.77 (br s, 4H), 4.94 (s, 2H), 2.61 (br s, 2H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 142.0, 140.6, 136.6, 129.7, 127.9, 127.4, 126.7, 74.44; HRMS (EI) Calcd. $C_{26}H_{22}O_2$: 366.16198. Found: 366.16179.

(*E*)-1,2-Bis(pentafluorophenyl)ethene (3.47a)



Following the procedure used in the preparation of **3.41a**, the title compound was obtained by McMurry coupling of pentafluorobenzaldehyde in 50% yield as a white solid after recrystallization from CH_2Cl_2/MeOH. IR (cast film) 3013, 1647, 1631, 1598, 1501, 1344, 980, 973 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (s, 2H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 146.6-146.4 (m), 144.1-143.9 (m), 142.4-142.1 (m), 139.9-139.5 (m), 139.5-139.2 (m), 137.0-136.7 (m), 121.6, 111.9-111.6 (m); ^{19}F NMR (376 MHz) δ –142.43 to –142.35 (m), –154.17 (t, *J* = 21.0 Hz), –162.72 to –162.59 (m); HRMS (EI) Calcd $C_{14}H_2F_{10}$: 359.99969. Found: 360.00027.

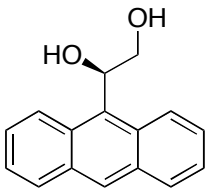
(1*R*,2*R*)-1,2-Bis(pentafluorophenyl)ethane-1,2-diol (3.47)



Following the procedure used in the preparation of **3.41**, the title compound was obtained in 50% yield as a white solid after recrystallization from toluene in 81.9% ee.[18e] $[\alpha]_D^{25}$ +48.68 (*c* 0.70, $CHCl_3$); IR (cast film) 3411, 1658, 1529, 1502, 1131, 990 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.49 (s, 2H), 3.10 (s, 2H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 146.1, 144.1, 142.5, 140.2, 138.7-138.5 (m), 136.7-136.4 (m), 112.0-111.8 (m), 68.2; ^{19}F NMR (376 MHz) δ –141.88 to –141.82 (m), –152.09 to –152.00 (m), –160.77 to –160.65 (m); HRMS (EI) Calcd. $C_{14}H_4F_{10}O_2Na$: 416.99438. Found: 416.99559.

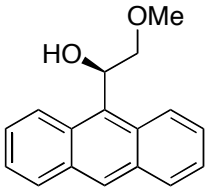
3.6.4 Preparation of anthracene derived chiral alcohols 3.48 and 3.49

(*R*)-1-(Anthracen-9-yl)ethane-1,2-diol (3.48a)



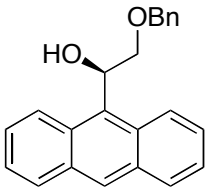
The title compound was prepared by the Sharpless asymmetric dihydroxylation of 9-vinyl-anthracene following the procedure used in the preparation of diol **3.41**, giving the title compound in 75% yield after recrystallization from CH_2Cl_2/hexane as yellow needles. $[\alpha]_D^{25}$ –16.44 (*c* 0.36, $CHCl_3$); IR (cast film) 3304, 3051, 1624, 1447, 1067, 1023, 886, 725 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.66 (d, *J* = 8.5 Hz, 2H), 8.43 (s, 2H), 8.01 (dd, *J* = 1.5, 8.0 Hz, 2H), 7.52-7.45 (m, 4H), 6.38 (dd, *J* = 4.1 Hz, 1H), 4.47 (dd, *J* = 10, 11.5 Hz, 1H), 3.93 (dd, *J* = 4, 12 Hz, 1H), 2.89 (br s, 1H), 2.50 (br s, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 131.6, 130.3, 129.9, 129.3, 128.7, 125.9, 124.9, 124.7, 72.5, 66.2; HRMS (EI) Calcd for $C_{16}H_{14}O_2Na$: 261.08860. Found: 261.08940.

(*R*)-1-(Anthracen-9-yl)-2-methoxyethanol (3.48)



Sodium hydride (60 wt%, 50.4 mg, 1.26 mmol, 1.00 equiv) was suspended in DMF (3.0 mL) and cooled to –40 ºC. To the suspension was added the diol compound **3.48a** (0.30 g, 1.26 mmol, 1.00 equiv) in three portions under positive pressure of argon. After completion of addition, the mixture was allowed to warm to –10 ºC and allowed to stir for 50 min after which iodomethane (0.0790 mL, 1.26 mmol, 1.00 equiv) was added to the reaction mixture and the reaction mixture was stirred for additional 30 min and then allowed to warm to room temperature over 1 h. The reaction was quenched by addition of water and extracted with EtOAc, and the combined organic extracts was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to give the crude product which was a mixture of dimethylated, and the two regio-isomeric monomethylated products. The desired product **3.48** (480 mg, 0.190 mmol, 15% yield) eluted second using 0-10% EtOAc/hexanes. $[\alpha]_D^{25}$ –18.76 (*c* 0.21, $CHCl_3$); IR (cast film) 3427, 3051, 2926, 1672, 1447, 1308, 1142, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.70 (d, *J* = 8.4 Hz, 2H), 8.42 (s, 1H), 8.00 (dd, *J* = 0.8, 8.4 Hz, 2H), 7.53-7.44 (m, 4H), 6.48 (dd, *J* = 3.6, 10.0 Hz, 1H), 4.28 (t, *J* = 10.0 Hz, 1H), 3.68 (dd, *J* = 3.2, 10.0 Hz, 1H), 3.52 (s, 3H), 3.05 (br s, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$) 131.6, 130.2, 129.9, 129.3, 128.6, 125.8, 124.8, 76.2, 70.6, 59.1; HRMS (EI) Calcd $C_{17}H_{16}O_2$: 252.11504. Found: 252.11500.

(*R*)-1-(Anthracen-9-yl)-2-(benzyloxy)ethanol (3.49)



Alcohol **3.48a** was treated in a similar manner with NaH (1.00 equiv) and BnBr (1.00 equiv) to give the desired product **3.49** (35% yield) along with di-benzylether derivative and the regioisomeric benzylation product of the secondary alcohol, which could be readily separated by flash chromatography (0-5% EtOAc/hexanes). $[\alpha]_D^{25}$ –8.26 (*c* 0.96, $CHCl_3$); IR (cast film) 3437, 3053, 2861, 1673, 1453, 1285, 1099, 733, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, *J* = 8.0 Hz, 2H), 8.42 (s, 1H), 8.00 (d, *J* = 8.5 Hz, 2H), 7.51-7.44 (m, 4H), 7.40-7.31 (m, 5H), 6.50 (d, *J* = 7.0 Hz, 1H), 4.73 (d, *J* = 9.6 Hz, 1H), 4.66 (d, *J* = 11.5 Hz, 1H), 3.79 (dd, *J* = 3.5, 10.5 Hz, 1H), 3.09 (s, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$) 131.6, 130.0, 129.3, 128.6, 128.5, 128.4,

128.2, 128.1, 127.9, 127.2, 125.7, 124.8, 75.3, 73.7, 73.5; HRMS (EI) Calcd $C_{23}H_{20}O_2$: 328.14633. Found: 328.14648.

3.6.5 Preparation of non-hydrobenzoin type diols

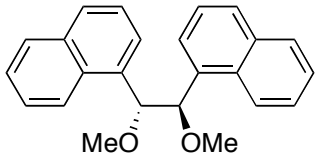
Dibenzo[c,g]phenanthrene-3,4-diol, 3,4-dihydro-, (3*R*,4*R*) (3.51)

The requisite product was prepared according to the procedure of Suzuki and coworkers.[23]

(*R*,*R*)-(+)-Di-(1-Naphthyl)-1,2-ethane-diol (3.50)

Commercially available from Aldrich.

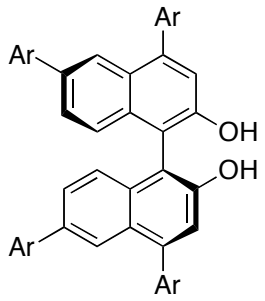
(*R*,*R*)-(+)-Di-(1-Naphthyl)-1,2-dimethoxy-ethane (3.79)



Into a flame-dried 25 mL round bottom flask was added (50.0 mg, 0.160 mmol, 1.00 equiv) of diol **3.50** and the diol was dissolved in 2 mL of freshly distilled THF and the mixture was cooled to 0 ºC. To the solution was added in portions NaH (60 wt%, 22.0 mg, 0.560 mmol, 3.50 equiv) and after 30 min iodomethane (20.3 μL, 0.330 mmol, 2.05 equiv) was added, and the reaction mixture was allowed to stirred at room temperature overnight. The reaction was quenched with addition of water and the product was extracted with Et_2O and washed with brine and dried over Na_2SO_4, filtered and concentrated *in vacuo* and purified by column chromatography (0-5% EtOAc/hexane) thus giving 55.0 mg of product (>99% yield) as a white solid. $[\alpha]_D^{25}$ +158.88 (*c* 0.11, $CHCl_3$); IR (cast film) 3046, 2926, 2820, 1596, 1509, 1447, 1228, 802, 767, 802 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (br s, 2H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.54 (d, *J* = 8.4 Hz. 2H), 7.36-7.28 (m, 4H), 7.16-7.10 (m, 4H), 5.35 (s, 2H), 3.34 (s, 6H); ^{13}C NMR (100.5.58 Hz, $CDCl_3$) δ 134.0, 133.6, 131.7, 128.5, 125.5, 124.7, 123.9, 57.3; HRMS (EI) Calcd. $C_{24}H_{22}O_2$: 342.16198. Found: 342.15982.

3.6.6 Preparation of binol derived diol 3.52[24]

(*S,S*)-4,6,4'6'-Tetrakis(3,5-dimethyl-phenyl)-[1,1']binaphthyl-2,2'-diol (3.55)

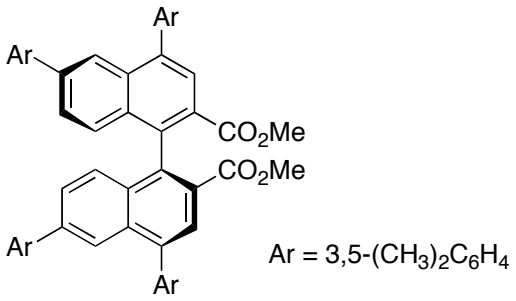


Ar = 3,5-$(CH_3)_2C_6H_4$

To a flame-dried 250 mL flask equipped with a magnetic stir bar and a reflux condenser was charged (2.35 g, 3.00 mmol, 1.00 equiv) of **3.54**,[29] (2.10 g, 13.7 mmol, 4.50 equiv) of 3,5-dimethylboronic acid, and (423 mg, 0.370 mmol, 0.120 equiv) of $Pd(PPh)_3$. To this mixture was added 60 mL of anhydrous THF. To the obtained solution was then added 2.0 M aqueous K_2CO_3 (36.5 mL, 73.0 mmol, 24.0 equiv) and the resulting mixture was degassed under vacuum and purged with argon (this cycle was repeated 3 times). The resulting solution was then stirred at reflux temperature for 48 h, then poured over water (30 mL), extracted with ethyl acetate (3 × 50 mL), washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and transferred to a flame dried 100 mL round bottom flask equipped with a stir bar. The resulting solution was concentrated and placed under high vacuum for 30 min. The crude solid was then dissolved with anhydrous CH_2Cl_2 (50 mL) and the solution was cooled to 0 ºC. To the solution was added drop-wise BBr_3 (1.0 M solution in CH_2Cl_2, 9.14 mL, 9.14 mmol, 3.00 equiv). The reaction mixture was stirred overnight and then cooled to 0 ºC, and to it was slowly added water (10 mL). The crude product was extracted with EtOAc (3 × 50 mL), and the combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered, concentrated under vacuum, and subjected to flash chromatography (10% EtOAc/hexanes) to give 2.10 g of **3.55** in 98% yield as a off white solid. $[\alpha]_D^{25}$ +87.98 (*c* 0.82, $CHCl_3$). IR (cast film): 3530, 302, 2916, 1600, 1585 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, *J* = 1.5, 2H), 7.69 (d, *J* = 1.5 Hz, 2H), 7.59 (d, *J* = 2 Hz, 2H), 7.42 (s, 4 H), 7.33 (s, 4H), 7.19 (s, 4H), 7.17 (s, 2H), 6.99 (s, 2H), 5.22 (br s, 2H), 2.49 (s, 12H), 2.37 (s, 12H); ^{13}C NMR (100.5 MHz) δ 152.4, 144.6, 141.5, 140.1, 138.5, 138.2, 137.4,

133.4, 129.6, 128.0, 128.5, 128.1, 127.4, 125.5, 125.5, 125.3, 125.1, 119.2, 113.2, 110.5, 21.7, 21.6.; HRMS Calcd. $C_{52}H_{46}O_2$: 702.3498. Found: 702.3511.

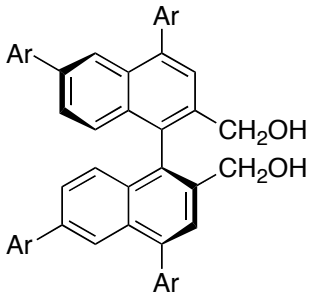
(*S*,*S*)-4,6,4'6'-Tetrakis(3,5-dimethyl-phenyl)-[1,1']binaphthyl-2,2'-dicarboxylic acid dimethyl ester (3.56)



To a flame-dried 100 mL round bottom flask equipped with a magnetic stir bar was added diol **3.55** (1.61 g, 2.30 mmol, 1.00 equiv), 20 mL of anhydrous CH_2Cl_2, and to this solution was added Et_3N (1.00 mL, 7.17 mmol, 3.00 equiv). The resulting solution was cooled to –78 ºC. To the cooled solution was added Tf_2O (0.710 mL, 4.26 mmol, 2.20 equiv) and the reaction mixture was allowed to warm to room temperature and stirred for an additional 45 min. The reaction mixture was poured onto 20 mL of (1.0 *N* HCl) and then extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to 10 mL volume. This concentrate was passed through a short plug (2" diameter, 2" length) of silica gel and then concentrated under vacuum to afford the bistriflate. The bistriflate was immediately added to a flame dried 100 mL Schlenk flask equipped with a magnetic stir bar. To the Schlenk flask was then added $Pd(OAc)_2$ (71.1 mg, 0.316 mmol, 0.150 equiv) and bis(diphenylphosphino)propane (dppp) (144 mg, 0.349 mmol, 0.165 equiv), diisopropylethylamine (1.84 mL, 10.5 mmol, 5.00 equiv), MeOH (4.30 mL, 134 mmol, 30.0 equiv), and 15 mL of anhydrous DMSO, and the flask was fitted with a reflux condenser and capped with a rubber septum (and the cap was secured with a black electrical tape). The mixture was degassed for 10 min by bubbling argon into the solution through a needle from the side arm while allowing the gas to escape from an outlet needle placed in the septum on top of the condenser. Similarly, CO gas was bubbled through the side arm into the solution and allowed to escape from the outlet needle for another 10 min after which both needles were removed and the side-arm closed. Then, CO gas at 5-psi (outlet valve pressure)

was inserted via a needle into the rubber septum on top of the reflux condenser and the reaction mixture was heated to reflux and stirred for 30 h. After the elapsed time, the reaction mixture was poured over water (50 mL) and extracted with (3 × 50 mL) of EtOAc and the combined organic extracts were washed with 30 mL of brine, dried over anhydrous Na_2SO_4, filtered, concentrated *in vacuo* and subjected to silica gel flash chromatography (0-5% EtOAc/hexanes) to give 1.55 g of **3.56** as an off-white solid, in 90% yield for two steps. $[\alpha]_D^{25}$ +59.03 (*c* 0.54, $CHCl_3$); IR (cast film): 3022, 2947, 2916, 1729, 1601, 1235 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.24 (d, *J* = 1.6 Hz, 2H), 8.19 (s, 2H), 7.50 (dd, *J* = 8.8, 1.6 Hz, 2H), 7.36 (s, 4H), 7.31 (d, *J* = 8.8 Hz), 7.17 (s, 4H), 7.15 (s, 2H), 6.98 (s, 2H), 3.58 (s, 6H), 2.48 (s, 12H), 2.35 (s, 12H); ^{13}C NMR (100.5 MHz) δ 167.3, 141.0, 140.6, 140.6, 140.2, 139.5, 138.2, 138.0, 133.6, 132.7, 129.3, 129.2, 128.3, 128.2, 127.3, 126.7, 126.4, 125.5, 124.2, 52.0, 21.5, 21.4; HRMS Calcd. $C_{56}H_{50}O_4$: 786.3709. Found: 787.3705.

(*S*,*S*)-4,6,4'6'-Tetrakis(3,5-dimethyl-phenyl)-2,2'-bis-hydroxymethyl[1,1']binaphthyl (3.57)

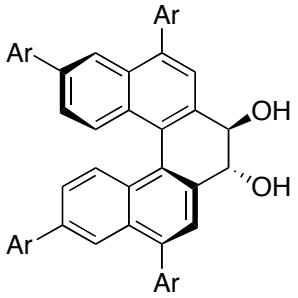


Ar = 3,5-$(CH_3)_2C_6H_4$

To a flame-dried 50 mL round bottom flask equipped with a magnetic stir bar was added diester **3.56** (1.28 g, 1.70 mmol, 1.00 equiv) and 10 mL of anhydrous THF. This solution was cooled to 0 ºC and $LiAlH_4$ (78.0 mg, 2.55 mmol, 1.50 equiv) was added in portions. The resulting mixture was brought to room temperature and stirred for an additional 1 h, after which excess $LiAlH_4$ was destroyed with slow addition of water. The resulting mixture was extracted with EtOAc (3 × 50 mL) and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude product was subjected to silica gel chromatography (20-40% EtOAc/hexanes) to afford 1.14 g of **3.57** in 92% yield as a white solid. $[\alpha]_D^{25}$ +97.74 (*c* 0.59, $CHCl_3$); IR (cast film): 3303, 3209, 2916, 1601 cm^{-1}; ^1H NMR (400

MHz, $CDCl_3$) δ 7.70 (s, 2H), 7.50 (dd, *J* = 1.6, 8.8 Hz, 2H), 7.32 (s, 4H), 7.27 (d, *J* = 9.2 Hz, 2H), 7.16 (s, 4H), 7.13 (s, 2H), 6.96 (s, 2H), 4.49 (d, 11.6 Hz, 1H), 4.30 (d, *J* = 11.6 Hz, 1H)), 2.48 (s, 12H), 2.37 (s, 12H); ^{13}C NMR (100.5 MHz) δ 141.5, 141.2, 140.4, 139.2, 138.3, 138.0, 136.7, 133.7, 132.7, 131.8, 129.2, 129.1, 129.0, 128.1, 127.3, 126.3, 125.5, 124.4, 63.5, 21.5, 21.4; HRMS Calcd. $C_{54}H_{50}O_2$: 730.3811. Found: 730.3811.

1,6,8,13-Tetrakis-(3,5-dimethyl-phenyl)-3,4-dihydro-dibenzo-phenanthrene-3,4-diol (3.52)



Ar = 3,5-$(CH_3)_2C_6H_4$

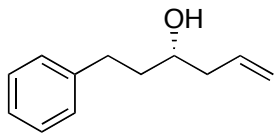
To a flame-dried 100 mL round bottom flask equipped with a magnetic stir bar was added diol **3.57** (1.09 g, 1.49 mmol, 1.00 equiv), 745 mg of 4Å molecular sieves, and to the heterogeneous mixture was added 15 mL of anhydrous CH_2Cl_2. To this mixture at room temperature was added PCC (0.970 g, 4.47 mmol, 3.00 equiv) and the mixture was stirred for 30 min, after which time it was passed through a short plug of silica (2" diameter, 2" length) and the silica was rinsed with 50% Et_2O/hexanes (50 mL). The eluents containing the dialdehyde were combined and concentrated *in vacuo* and transferred with the aid of anhydrous THF (10 mL) into a flame-dried 25 mL flask, and the THF was evaporated to give the dialdehyde, which was immediately used for the next step.

To a flame-dried 100 mL round bottom flask equipped with a magnetic stirrer was added samarium metal powder (634 mg, 4.19 mmol, 2.81 equiv). This powder was then heated under vacuum with a torch flame, then cooled to room temperature under argon, and to this flask was added 36 mL of anhydrous THF. The mixture was then cooled to 0 ºC, and CH_2I_2 (0.140 mL, 1.73 mmol, 1.17 equiv) was added and the mixture was stirred at 0 ºC for 1 h and at room temperature for another 1 h. At this point, a dark blue solution of SmI_2 was obtained, to which was slowly added a 10 mL THF solution of the above obtained dialdehyde. The mixture was stirred for 5 min at 0 ºC and then poured over ice cold 30 mL of 1.0 *N* HCl. The product was

extracted with EtOAc (3 × 50 mL) and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to give the crude diol. The crude diol was recrystallized from CH_2Cl_2/hexanes to give a light brown solid, which was filtered and dried under high vacuum to give the pure diol in 70% yield for two steps. $[\alpha]_D^{25}$ +101.80 (*c* 0.59, $CHCl_3$); IR (cast film): 3363, 3024, 2916, 1601, 775, 711 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 2H), 7.95 (s, 2H), 7.83 (d, *J* = 8.8 Hz, 2H), 7.58 (dd, *J* = 8.0, 2.0 Hz, 2H), 7.34 (s, 4H), 7.25 (s, 4H), 7.14 (s, 2H), 7.00 (s, 2H), 4.86 (s, 2H), 2.84 (br s 2H), 2.47 (s, 12H), 2.38 (s, 12H); ^{13}C NMR (100.5 MHz) δ 141.5, 141.2, 140.8, 138.3, 138.2, 138.0, 135.5, 132.1, 129.7, 129.1, 129.0, 128.2, 128.13, 127.6, 125.4, 125.0, 124.3, 122.7, 74.9, 21.5, 21.5. HRMS Calcd. $C_{54}H_{48}O_2$: 728.3654. Found: 728.3675.

3.6.7 Model procedure for catalytic enantioselective addition of allylic boronates to aldehydes

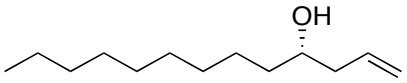
3.6.7.1 (3*S*)-1-Phenyl-hex-5-en-3-ol (3.27)



Into a flame dried 25 mL round bottom flask equipped with a magnetic stir bar was added (*R,R*) 1,2-di-naphthyl-ethanediol **3.50** (8.65 mg, 0.0250 mmol, 0.110 equiv), anhydrous Na_2CO_3 (5.60 mg, 0.0500 mmol, 0.0500 equiv) and activated 4 Å molecular sieves (50.0 mg), and to this mixture, under argon was added 0.5 mL of freshly distilled toluene. To the above solution at room temperature was added $SnCl_4$ (1.0 M solution in CH_2Cl_2, 25.0 μL, 0.0250 mmol, 0.100 equiv). The resulting mixture was stirred for 5 min and cooled to –78 ºC and maintained at this temperature for 15 min after which allyl boronic pinacol ester **3.11** (46.2 mg, 0.275 mmol, 1.10 equiv) (pre-dissolved in 0.5 mL of toluene) was added via syringe. The reaction mixture was maintained at –78 ºC for 15 min, after which freshly distilled hydrocinnamaldehyde (32.6 μL, 0.250 mmol, 1.00 equiv) was added drop-wise. The reaction mixture was stirred at –78 ºC for 12 h after which DIBAL-H (1.0 M in toluene, 0.500 mL, 0.500 mmol, 2.00 equiv) was added to quench any remaining aldehyde. After 30 min, 2 mL of 1.0 *N* HCl was added and the reaction

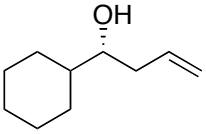
mixture was brought to room temperature and stirred for 1 h. At this point, a dark brown biphasic solution was obtained which upon extraction with Et_2O (2 x 25 mL) gave a clear organic layer, which was then washed with brine and dried over Na_2SO_4, filtered and concentrated *in vacuo*. The thus obtained crude product was purified by flash chromatography (5% EtOAc/hexanes) to give 37.4 mg of the corresponding homoallylic alcohol in 85 % yield. Analytical data of this product were in complete accordance with the literature.[30] $[\alpha]_D^{25}$ –4.54 (*c* 0.41, $CHCl_3$); HPLC (chiralcel-OD); 5% *i*-PrOH/hexane, 0.5 mL/min, λ = 254 nm, T_{major} = 26.2 min, T_{minor} = 37.6 min; 77% *ee*.

3.6.7.2 (4*S*)-Tridecen-4-ol (3.64)



Following the procedure used in the preparation of **3.27**, the title compound was obtained as a colorless oil in 76% yield. The spectral data were in agreement with the literature.[5] $[\alpha]_D^{25}$ –6.64 (*c* 0.39, $CHCl_3$). The optical purity of the product was deduced from HPLC analysis of the *p*-nitrobenzoyl ester. HPLC (chiralcel-OD); 100% hexane, 1.0 mL/min, λ = 254 nm, T_{major} = 24.8 min, T_{minor} = 28.6 min; 80% *ee*.

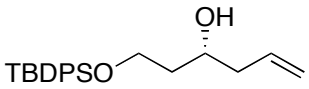
3.6.7.3 (1*R*)-1-Cyclohexyl-3-buten-1-ol (3.65)



Following the procedure used in the preparation of **3.27**, except that the product was purified by 5% Et_2O/pentane eluent system, the title compound was obtained in 90% yield. The spectroscopic data of the product are identical with those reported in the literature.[31] $[\alpha]_D^{25}$ –0.43 (*c* 0.46, $CHCl_3$). The purified product (1.0 equiv) was then placed into a 1-dram vial and this was followed by the addition of (*R*)-Moser acid chloride (1.5 equiv) and DMAP (1.0 equiv) and 0.5 mL CH_2Cl_2. To the solution was then added Et_3N (10 equiv) and the mixture was stirred for 10 min during which TLC indicated complete consumption of the starting alcohol. The crude product was then passed through a one-inch silica placed in a 9" pipette and further eluted with

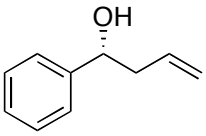
30% EtOAc/hexanes. The fraction containg the product (first 2 mL) was concentrated *under vacuo* and the product was analyzed by NMR for optical purity. The optical purity of the product was determined from the integration of the diastereomeric peaks in ^{19}F NMR of the corresponding (*R*) Mosher ester; ^{19}F NMR (376 MHz) δ 71.54 ppm (major), 71.61 ppm (minor); 70% *ee*.

3.6.7.4 (3*R*)-1–(*tert*-Butyl-diphenyl-silanoxy)-hex-5-en-3-ol (3.66)



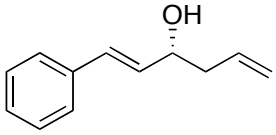
Following the procedure used in the preparation of **3.27**, the title compound was obtained as a colorless syrup in 90% yield. The spectroscopic data of this were identical with those reported in the literature.[30] $[\alpha]_D^{25}$ +1.47 (*c* 0.58, $CHCl_3$). HPLC (chiralcel OD); 2.5% *i*-PrOH/hexane, 1.0 mL/min, λ = 254 nm, T_{major} = 29.6 min, T_{minor} = 24.3 min; 66% *ee*.

3.6.7.5 (1*R*)-1-Phenyl-3-butene-1-ol (3.67)



Following the procedure used in the preparation of **3.27**, the title compound was obtained as a colorless oil, 99% yield. The spectroscopic data of this are identical with those reported in the literature.[30] $[\alpha]_D^{25}$ –4.90 (*c* 0.49, $CHCl_3$). HPLC (chiralcel OD); 5% *i*-PrOH/hexane, 0.5 mL/min, λ = 254 nm, T_{major} = 31.9 min, T_{minor} = 29.8 min; 10% *ee*.

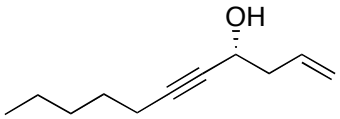
3.6.7.6 (1*E*,3*R*)-1-Phenyl-1,5-hexadien-3-ol (3.68)



Following the procedure used in the preparation of **3.27**, the title compound was obtained as a faint yellow oil in 99% yield. The spectral properties of the obtained compound were identical

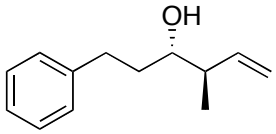
to those reported in the literature.[32] $[\alpha]_D^{25}$ –5.69 (*c* 0.13, $CHCl_3$). HPLC (chiralcel OD); 5% *i*-PrOH/hexane, 0.5 mL/min, λ = 254 nm, T_{major} = 42.6 min, T_{minor} = 75.3 min; 20% *ee*.

3.6.7.7 (4*R*)-Undec-1-en-5-yn-1-ol (3.69)



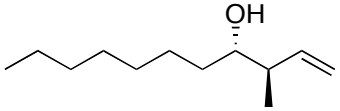
Following the procedure used in the preparation of **3.27**, the title compound was obtained as a faint yellow oil in 99% yield. The spectroscopic data of this samplae were identical with those reported in the literature.[33] $[\alpha]_D^{25}$ –4.00 (*c* 0.13, $CHCl_3$). The optical purity of the product was determined by integration of the diastereomeric peaks of the corresponding (*S*)- Mosher-ester; ^{19}F NMR (376 MHz) δ 71.96 ppm (major), 72.18 ppm (minor); 12% *ee*.

3.6.7.8 (3*R*,4*S*)-4-Methyl-1-phenyl-5-hexen-3-ol (3.70)



Following the procedure used in the preparation of **3.27** except that *(E)*-crotylboronate **3.12** and the antipode (*S*,*S*)-(–)-1,2-di(1-naphthyl)-1,2-ethane diol of **3.50** was used and that the reaction time was 24 h, the title compound was obtained as a colorless oil in 99% yield. The spectroscopic data of this sample were in accordance to those reported in literature.[26] $[\alpha]_D^{25}$ +13.20 (*c* 0.45, $CHCl_3$). HPLC (chiralcel OD); 10% *i*-PrOH/hexane, 1.0 mL/min, λ = 254 nm, T_{major} = 12.6 min, T_{minor} = 18.5 min; 72% *ee*.

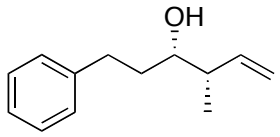
3.6.7.9 (3*S*, 4*S*)-3-Methyl-tridec-1-en-4-ol (3.71)



Following the procedure used in the preparation of **3.27** except *(E)*-crotylboronate **3.12** was used and the reaction was allowed to stir for 24 h, the title compound was obtained as a colorless oil in

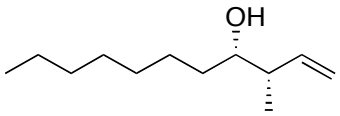
70% yield. The spectroscopic data of this sample were in accordance to those reported in the literature.[5] $[\alpha]_D^{25}$ –23.94 (*c* 0.75, $CHCl_3$). Enantiomeric excess was determined by integration of the diastereomeric peaks of the corresponding (*S*)-Mosher-ester; ^{19}F NMR (376 MHz) δ 71.47 ppm (minor), 71.53 ppm (major); 72% *ee*.

3.6.7.10 (3*S*,4*S*)-4-Methyl-1-phenyl-5-hexen-3-ol (3.72)



Following the procedure used in the preparation of **3.27** except that *(Z)*-crotyl pinacol boronate **3.13** was used and the reaction time was 24 h, the title compound was obtained as a colorless oil in 87% yield. The spectroscopic data of the title compound were in accordance to those reported in the literature.[26] $[\alpha]_D^{25}$ –20.36 (*c* 0.72, $CHCl_3$). HPLC (chiralcel OD); 10% *i*-PrOH/hexane, 1.0 mL/min, λ = 254 nm, T_{major} = 10.8 min, T_{minor} = 15.8 min; 40% *ee*.

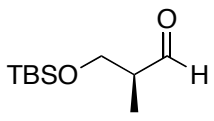
3.6.7.11 (*S*)-3-Methyl-tridec-1-en-4-ol (3.73)



Following the procedure used in the preparation of **3.73**, the title compound was obtained as a colorless oil in 70% yield. The spectroscopic data of this sample were identical with those reported in literature.[5] $[\alpha]_D^{25}$ –15.92 (*c* 0.23, $CHCl_3$). Enantiomeric excess was determined by integration of the diastereomeric peaks of the corresponding (*S*)-Mosher-ester; ^{19}F NMR (376.141 MHz) δ 71.43 ppm (minor), 71.52 ppm (major); 46% *ee*.

3.6.8 Diastereoselective reactions

(*S*)-2-Methyl-3-[(tert-butyldimethylsilyl)oxy]propionaldehyde (3.74)



Aldehyde **3.74** was prepared according to the literature procedure.[28] The crude aldehyde that was obtained (after the work-up and evaporation of the solvent) from Swern oxidation was filtered through a short plug (~10 cm, 1 inch diameter) of silica using 30% EtOAc/hexanes to free the aldehyde from any residual ammonium salt and other inorganic impurities followed by bulb-to-bulb distillation under high vacuum. Freshly prepared **3.11**, **3.12**, and **3.13** were used for the following reactions. Temperature control during reaction was provided by cryocool systems.

Procedure for the reaction of allyl (3.11) or ciscrotyl boronic pinacol ester (3.13) with aldehyde 3.74

3.75 **3.76**

Into a flame-dried 25 mL round bottom flask equipped with a stir bar was charged (*R*,*R*) diol **3.50** (17.3 mg, 0.0550 mmol, 0.110 equiv) or its (*S*,*S*) antipode, Na_2CO_3 (10.3 mg, 0.100 mmol, 0.200 equiv) and 4 Å activated molecular sieves (50.0 mg) and the flask was capped with a septa and put under argon. To this mixture was added 0.75 mL of toluene followed by $SnCl_4$ (1.0 M in CH_2Cl_2, 50.0 μL, 0.0500 mmol, 0.100 equiv) and the resulting mixture was stirred for 5 min and cooled to –78 ºC and maintained at this temperature for 15 min. Allylboronic pinacol ester **3.11** (84.0 mg, 0.550 mmol, 1.10 equiv) or freshly prepared (*Z*) crotyl boronic acid pinacol ester **3.13** (100 mg, 0.550 mmol, 1.10 equiv, pre-dissolved in 0.5 mL of toluene) were slowly added and this mixture is maintained at –78 ºC for another 15 min. After the elapsed time, freshly prepared aldehyde **3.74** (101 mg, 0.500 mmol, 1.00 equiv, pre-dissolved in 0.25 mL of toluene), was added dropwise and the reaction was stirred for 24 h. After the elapsed time, DIBAL-H (1.0 M in toluene, 1.00 mL, 2.00 equiv, 2.00 mmol) was slowly added to the reaction mixture and the mixture is stirred for 30 min after which, 2.0 mL of 1.0 *N* HCl was added in one portion, and the reaction mixture was let to warm to room temperature over 1 h. The resulting biphasic mixture was extracted with Et_2O (2 x 25 mL), washed with water (10 mL) followed by brine (10 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated *in vacuo* to give the crude mixture, which was analyzed for diastereomeric composition by ^1H NMR. The diastereomeric mixture was determined by integration of the doublet signals of the methyl group of the propionate units (See attached NMR insets).

Compound **3.75**, **3.76** were obtained in a 83% combined yield using (*R*,*R*) **3.50** in 84:16 ratio favoring of **3.75** over **3.76** (Figure 3.4). In the mismatched case using the (*S*,*S*) isomer of diol **3.50**, the products were obtained in 60% combined yield in 36:64 ratio favoring the *syn* diastereomer **3.76** (see appendix). The spectral characteristics of these products were in accordance to literature reports.[28]

3.77 **3.78**

Compounds **3.77** and **3.78** were obtained in 77% yield for the matched case using (*R*,*R*) diol **3.50** and boronate **3.11** in 95:5 ratio favoring the *anti-syn*-adduct **3.77**. In the case of (*S*,*S*) antipode of diol **3.50**, the products were obtained in 50% combined yield in 66:34 ratio favoring the *anti-syn*-adduct **3.77** over *syn-syn*-adduct **3.78**. The spectral characteristics of these mixtures were in accordance with the literature.[28]

For the $SnCl_4$ catalyzed reaction of **3.11** with aldehyde **3.74**, the procedure was analogous except that no molecular sieves, or Na_2CO_3 or the diol auxiliary was used. Diastereomers **3.75** and **3.76** were obtained in 75% combined yield and 54:46 ratio favoring the *syn* diastereomer **3.76** over *anti* **3.75.** For cis-crotylation with $SnCl_4$, a similar purification as the one described above was used to give a combined yield of 81% and a ratio of 66:34 in favor of the *anti-syn* diastereomer **3.77** over the *syn-syn* diastereomer **3.78**.

3.7 References

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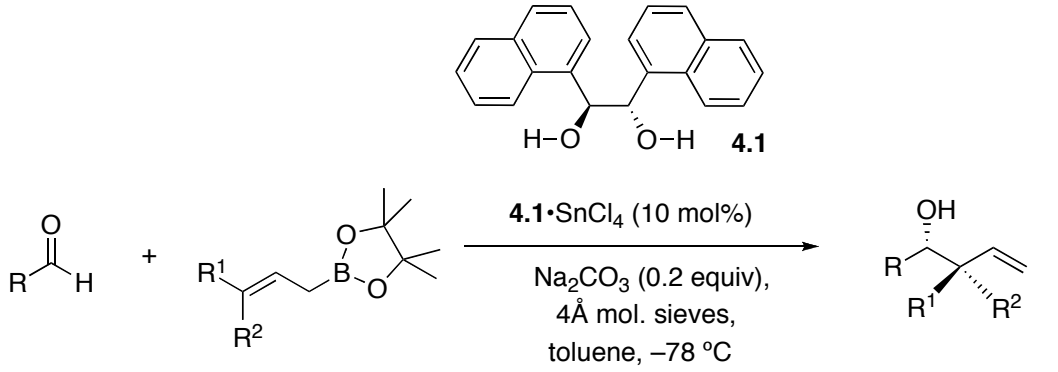
Chapter 4

A Second Generation Catalyst System for the Enantioselective Allylboration of Aldehydes

4.1 Introduction

As described in previous chapter, in 2006, we reported the first examples of a chiral Brønsted acid catalyzed addition of allylic boron pinacolates to aldehydes.[1] Utilizing Yamamoto's elegant concept of Lewis acid assisted Brønsted acidity,[2] (c.f. Chapter 1, Section 1.2.3) we showed that the complex derived from commercially available diol **4.1** and $SnCl_4$ was an efficient catalyst for the enantio- and diastereoselective addition of allylic boronates **4.2**, **4.3** and **4.4** to aliphatic aldehydes. However, the enantioselectivities were only modest (up to 80% *ee*), and thus this method could not be applied to synthesis (Equation 4.1).[1] Nevertheless, when we ran a model reaction under stoichiometric LBA catalyst, we only observed a modest increase in enantioselectivity of the reaction, namely 83% *ee*, which led us to believe that the competing background (uncatalyzed) reaction was not a major complication, and that consequently, there was undoubtedly room for catalyst improvement.



Equation 4.1. First-generation catalytic enantioselective allylboration.

4.2 Evaluation of ortho-substituted hydrobenzoin[3]

At the outset, steric and electronic manipulation of diol **4.1** appeared unappealing since the parent substituted-naphthaldehyde derivatives were not commercially available and required multi-step syntheses. Consequently, we decided to revisit the simpler hydrobenzoins, since a host of substituted benzaldehyde precursors were commercially available.

Upon analysis of the correlation between steric and electronic factors and product enantioselectivity, we noticed that ortho-subtituents had a dramatic impact (Figure 4.1). For instance, replacement of the ortho hydrogens of hydrobenzoin **4.7** with methyl groups as in **4.8** provided a considerable increase in product enantioselectivity (69% *ee* versus 34% *ee*). However, introduction of a phenyl ring (**4.9**) on the contrary led to significantly lower enantioselectivity (33% *ee*) of the homoallylic alcohol product **4.6**.[1]

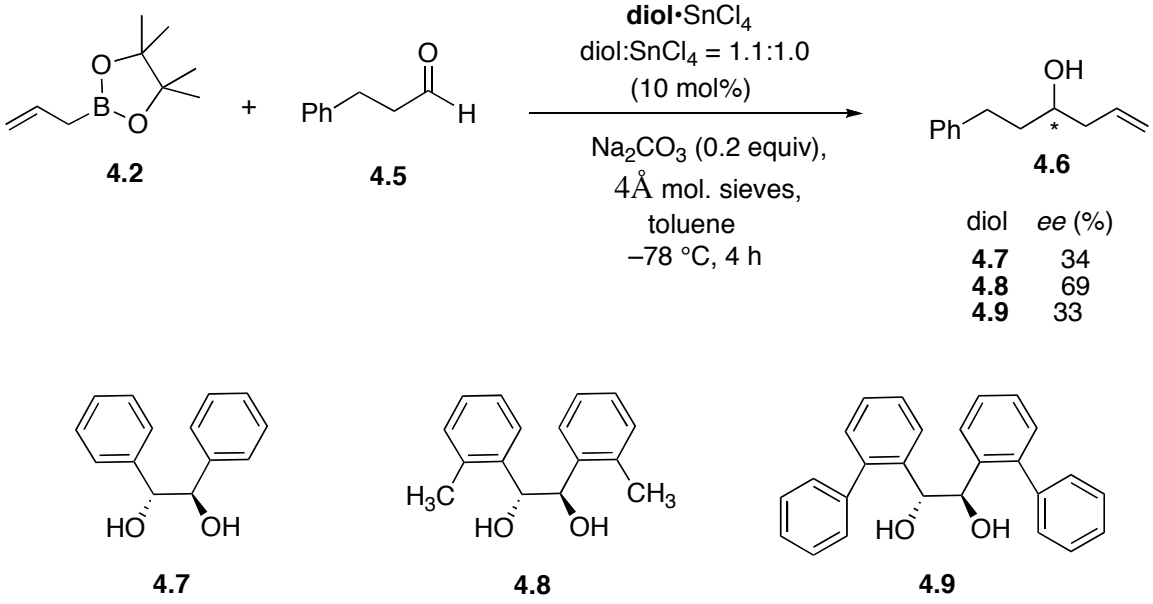
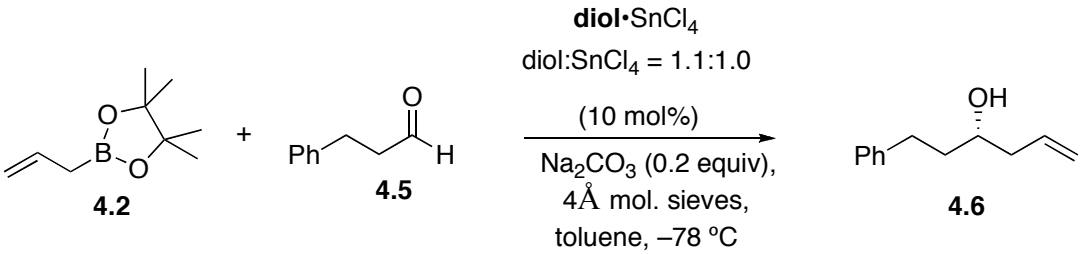
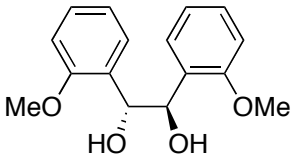


Figure 4.1. Effect of ortho-substituents on the enantioselectivity of model allylboration.

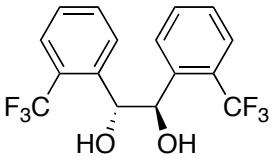
Pursuing this direction, and taking into account steric and electronic factors, a select group of ortho-substituted hydrobenzoins (namely **4.10**-**4.15**) were prepared and evaluated as components of the LBA catalyst for the model allylboration of hydrocinnamaldehyde.[3] Diols **4.10**-**4.13** were chosen to elucidate electronic effects whereas diols **4.14** and **4.15** were chosen to account for steric effects along with the nature of the carbon center that is directly attached to the aromatic ring, i.e. sp^2 and sp^3. All diols were readily prepared by a two-step McMurry-coupling[4]/Sharpless asymmetric dihydroxylation sequence.[5] Diol **4.14** required three additional

steps from diol **4.13** (acetonide formation, Suzuki-Miyaura cross-coupling, acetonide deprotection).

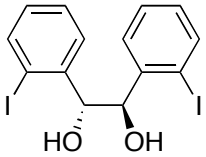




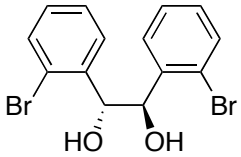
4.10



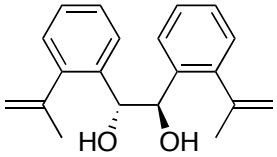
4.11



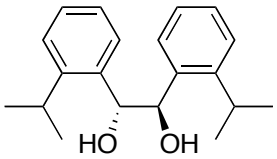
4.12



4.13



4.14



4.15

Entry	diol	yield (%)	*ee* (%)
1	**4.10**	75	69
2	**4.11**	96	12
3	**4.12**	99	59
4	**4.13**	94	77
5	**4.14**	n.d	n.d
6	**4.15**	71	80

Table 4.1. Evaluation of ortho-substituted diols for the model allylboration of hydrocinnamaldehyde.

Upon evaluation of diols **4.10**-**4.15** as diol•$SnCl_4$ catalysts for the model allylboration reaction, it appeared that large non-polar substituents had a beneficial effect on the enantioselectivity of the reaction (Table 4.1). Although diol **4.13** led to improved enantioselectivity of the product (entry 4, 77% *ee*), its iodo-counterpart, diol **4.12**, failed to provide similar results (entry 3, 59% *ee*).

Surprisingly, diol **4.14** failed to give an acceptable level of catalysis under the LBA system (entry 5). A plausible explanation for this failure may be attributed to the isopropylene π–electrons, which can potentially sequester the Brønsted acidity of the activated proton *via* an OH-π interaction, or even form a cyclic ether *via* a benzylic tertiary carbocation (a dead-end for catalysis). Gratifyingly, when we subjected diol **4.15 (** with ortho-isopropyl substituents) to the model reaction, we observed a significant improvement in the enantioselectivity (entry 6, 80% *ee*). Moreover, this result was superior to that obtained with diol **4.1** (c.f. Scheme 4.1) of our first-generation catalyst system.[1] These results led us to hypothesize that bulky non-polar alkyl substituents at the ortho-position of hydrobenzoin were essential for the efficient discrimination of the transition state structures, leading to the requisite homoallylic alcohol product in higher enantioselectivity.

The obvious line of action was to increase the steric bulk of **4.15** and replace the isopropyl groups with *tert*-butyl or trialkylsilyl groups. Pursuing this hypothesis, diols **4.16** (equipped with ortho-tert-butyl groups) and **4.17** (equipped with ortho-triethylsilyl groups) were prepared. In the event, when we utilized diols **4.16** and **4.17** as catalyst components, we were very disappointed to see significantly diminished enantioselectivities and reaction rates (Figure 4.2). We attribute the slow reaction rates to inefficient substrate activation, possibly arising from the inherent steric impediment of the **4.16**•$SnCl_4$ and **4.17**•$SnCl_4$ complexes.[3]

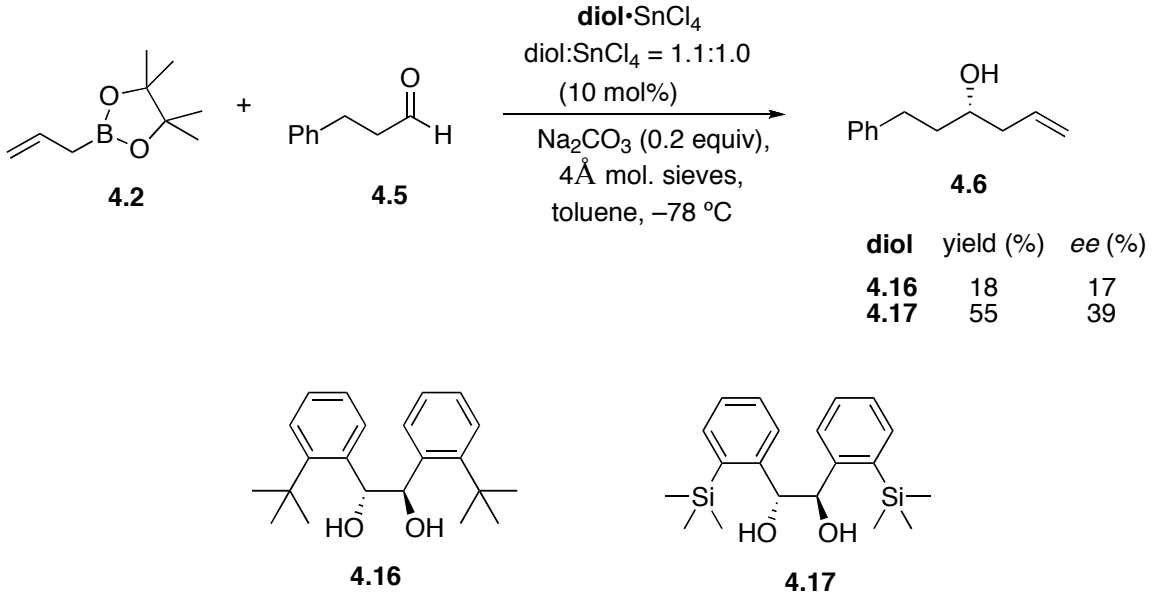


Figure 4.2. Evaluation of sterically hindered diols.

As such we concluded that there must be at least one benzylic hydrogen in the ortho-substituent of the diol unit in order to maintain a desirable level of activity in the LBA catalyst (Figure 4.3).

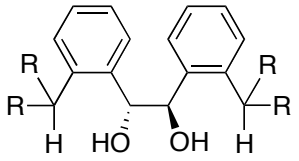
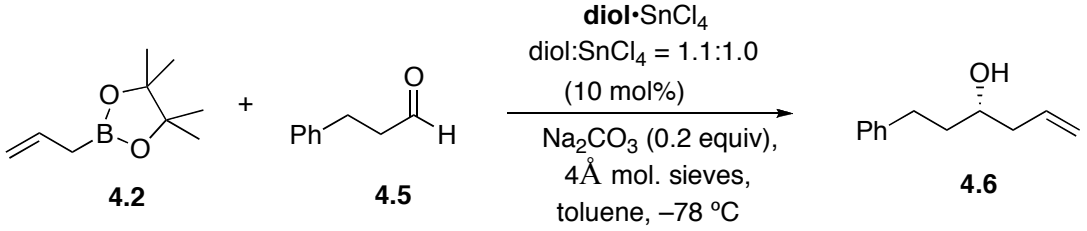
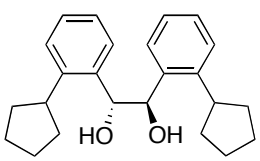


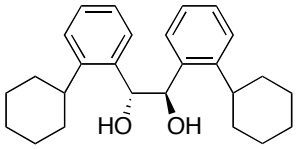
Figure 4.3. Requisite diol structure for efficient catalysis and asymmetric induction.

To this end, we decided to re-examine the optimal diol, **4.15**, and extend the isopropyl framework further in space. Subsequent design in this approach called for elaboration of the isopropyl framework through the use of cycloalkyl rings. To test this hypothesis, diols **4.18**-**4.25** (Table 4.2) were synthesized and subjected to the model allylboration of hydrocinnamaldehyde under LBA catalysis. To our great delight, we observed a gradual increase in the enantioselectivity of the reaction with increasing ring size. For example, whereas diol **4.18** containing cyclopentyl rings in the ortho-position gave 80% *ee*, diol **4.19** containing cyclohexyl rings provided 86% *ee*, diol **4.20** containing cycloheptyl rings gave 91% *ee*, and diol **4.21** equipped with cyclooctyl rings provided an optimal *ee* of 93% of the corresponding product (Table 4.2, entry 4). However, further increases in the ring size led to a gradual decrease in the enantioselectivity of the product, along with diminished reaction rates possibly arising from adverse catalyst-substrate interaction. Thus, diol **4.22** containing cyclononyl rings gave 70% conversion and 89% *ee*, diol **4.23** containing cyclodecyl rings gave 50% conversion and 83% *ee*, and finally diol **4.24** containing cyclododecyl rings gave a dismal 20% conversion and 72% *ee* of the desired product **4.6**. Interestingly, substitution within the ortho-cyclohexane rings such as in diols **4.25** and **4.26** also gave encouraging results (entries 8 and 9). However, since these diols were obtained as a mixture of diastereomers from their precursors, they were not pursued further. Surprisingly, the use of mono-methyl ether derivative **4.27** (of diol **4.21**) led to a significantly diminished reaction rate and lower enantioselectivity of the product (entry 10). Overall, the most outstanding diol appeared to be **4.21**, named Vivol, by Prof. Hall, (on behalf of my contribution to its design and inception), and as such we proceeded with this diol for the optimization of reaction parameters and exploration of substrate scope.[3]

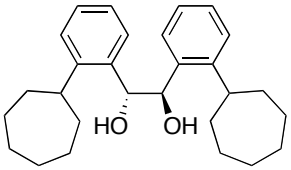




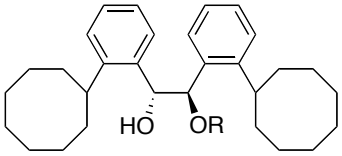
4.18



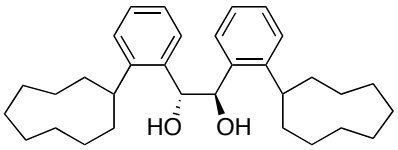
4.19



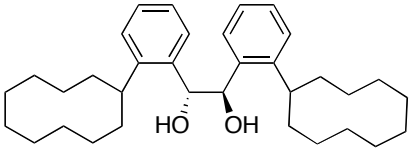
4.20



4.21 R = H
4.27 R = CH_3



4.22



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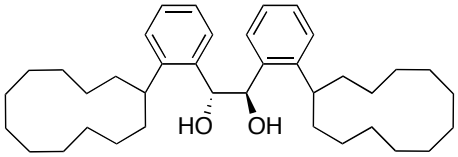
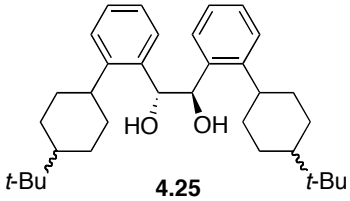
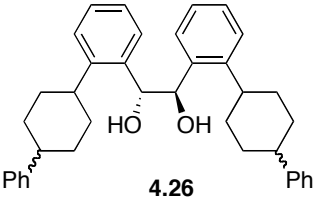


4.24



4.25



4.26

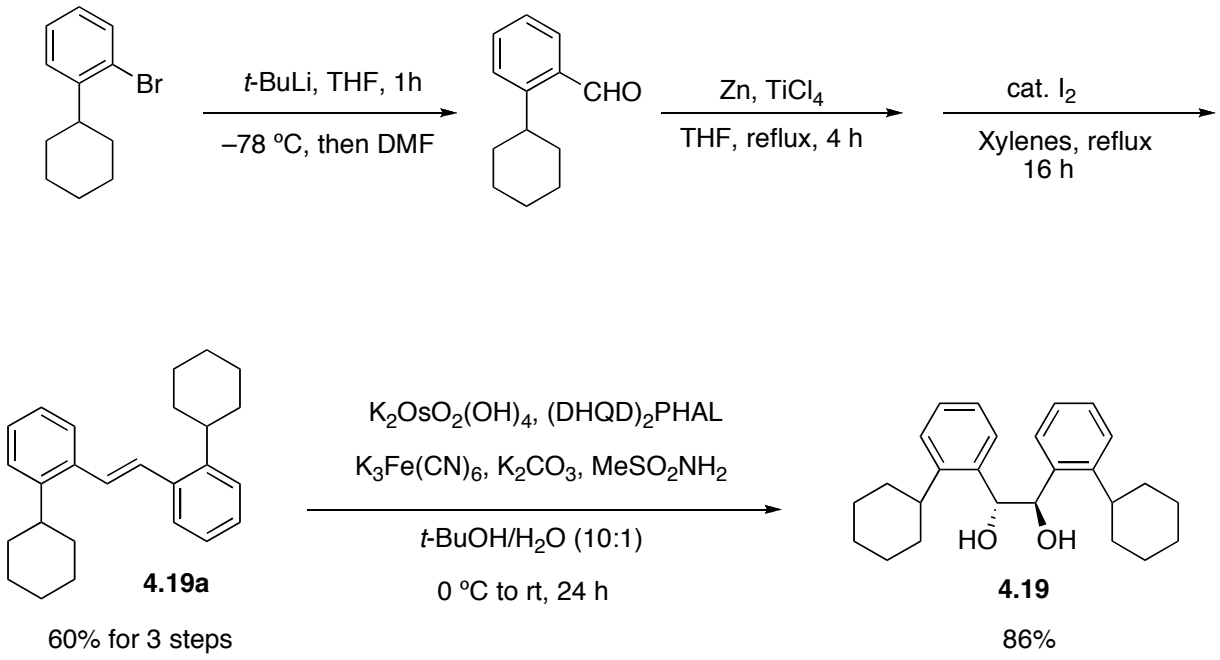
Entry	diol	% conversion	*ee* (%)
1	**4.18**	100	80
2	**4.19**	100	86
3	**4.20**	100	91
4	**4.21**	100	93
5	**4.22**	70	89
6	**4.23**	50	82
7	**4.24**	20	72
8	**4.25**	100	91
9	**4.26**	100	91
10	**4.27**	50	85

Table 4.2. Evaluation of ortho-cycloalkyl diols in the diol•$SnCl_4$ catalyzed allylboration reaction.

4.3 Synthesis of diols

4.3.1 Synthesis of 4.19 and 4.20

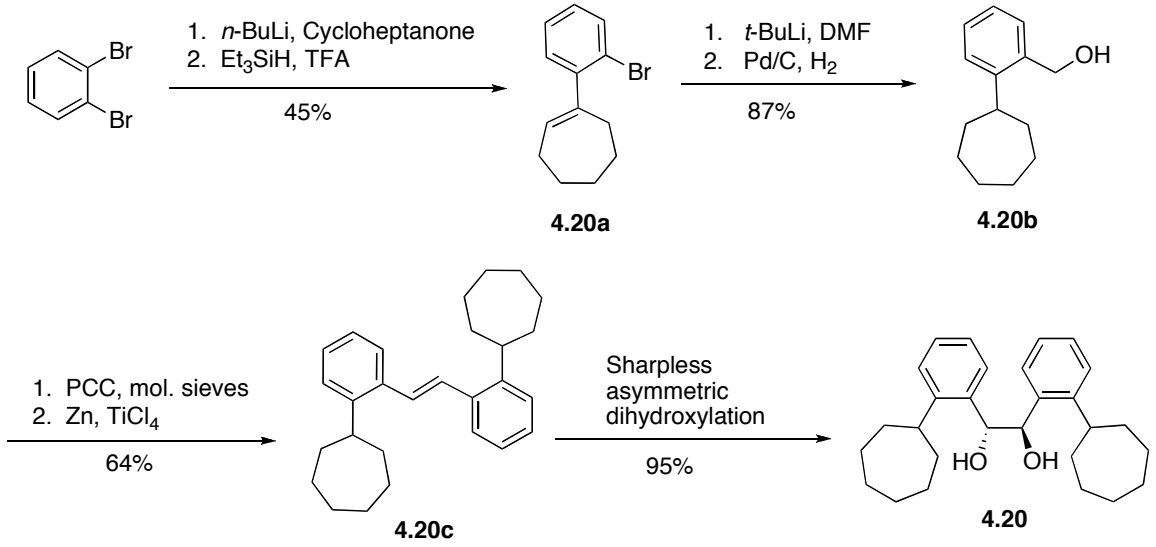
The synthesis of diols **4.19** and **4.20** was based on a McMurry coupling[4]/Sharpless asymmetric dihydroxylation approach.[5] For the synthesis of **4.19**, **c**ommercially available ortho-cyclohexyl-bromobenzene was lithiated and quenched with anhydrous DMF to provide the requisite aldehyde. Subsequent McMurry coupling, followed by isomerization of the olefin to the thermodynamic isomer led to *trans*-stilbene **4.19a** in acceptable yield. Finally, a Sharpless asymmetric dihydroxylation and subsequent recrystallization provided the optically pure diol **4.19** in good yield (Scheme 4.1).



Scheme 4.1. Synthesis of diol **4.19**.

The synthesis of diol **4.20** commenced with a low temperature addition of ortho-lithio bromobenzene to cycloheptanone (Scheme 4.2). Dehydration of the tertiary benzylic alcohol provided cycloalkene **4.20a**. Cycloalkene **4.20a** was metallated and trapped with DMF to yield the aldehyde intermediate, which was immediately subjected to reduction conditions. In the event, hydrogenation of the aldehyde led to the desired saturation of the cycloolefin, but also led to concomitant reduction of the aldehyde functionality to the corresponding benzyl alcohol **4.20b**. Nevertheless, this alcohol intermediate was oxidized using standard chromate conditions

to the requisite aldehyde, which was subjected to McMurry coupling to provide the corresponding *E*-stilbene **4.20c**. Sharpless asymmetric dihydroxylation of stilbene **4.20c** and subsequent recrystallization provided diol **4.20** in excellent yield.



Scheme 4.2. Synthesis of diol **4.20**.

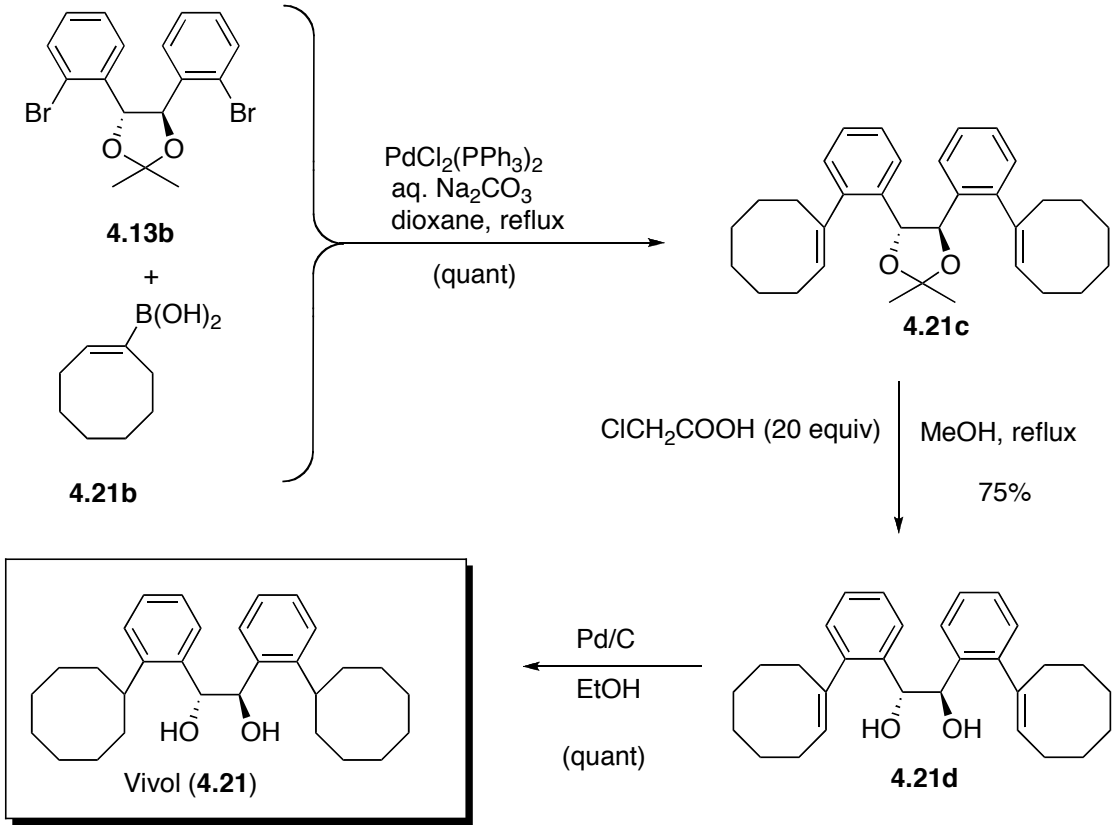
4.3.2 Convergent synthesis of ortho-cycloalkyl diols

Although diols **4.19** and **4.20** were obtained in good overall yields, the synthetic scheme was rather linear. In order to gain rapid access to other cycloalkyl-substituted diols, we envisioned a more convergent approach in which the cycloalkyl rings are installed at a later stage onto a common intermediate. A representative sequence for the synthesis of **4.21** is outlined in Scheme 4.3.

The common intermediate, dibromo-acetonide **4.13b**, is prepared in three simple operations in ~50% overall yield from commercially available 2-bromo-benzaldehyde.[6] From here onwards, a divergent bidirectional Suzuki-Miyaura cross-coupling with cyclooctyl boronic acid **4.21b** led to the formation of acetonide **4.21c**. Surprisingly, the cycloalkenyl sp^2 protons of the corresponding acetonide product **4.21c** appear misleadingly upfield (δ = 4.44 ppm) as a broad singlet and show correlation in the 2D-COSY only upon heating the sample to 60 ºC. The next step called for hydrogenation of the intermediate **4.21c** followed by deprotection of the acetal moiety to provide the requisite diol **4.21**. However, in our hands, hydrogenation failed to yield any appreciable amounts of the desired product, probably because of the sterically hindered

nature of the cycloalkene units. We tried many reduction conditions including diimide reduction, Adams' catalyst, Pearlman's catalyst, Crabtree's catalyst, Wilkinson's catalyst, and Pd/C. To overcome this hurdle, we decided to reverse the sequence. After rigorous optimization, we were able to deprotect the acetal **4.21c** in acceptable yield, thus affording intermediate **4.21d**, and prevent side-products resulting from etherification of the alkene. Hydrogenation of the unsaturated diol **4.21d** was then attempted. Surprisingly, hydrogenation of **4.21d** required a 50-wt % of Pd/C per double bond. Although we could lower the loading of Pd/C to 25-wt %, this protocol required high pressure and temperature, during which, we observed partial hydrogenolysis of the benzylic alcohol functionality.

Following the synthetic scheme outlined in Scheme 4.3, we were able to prepare multi-gram quantities of either antipode of Vivol **4.21**. Since the point of divergence was the bidirectional Suzuki-Miyaura cross-coupling of acetonide **4.13b**, we could readily prepare various ortho cycloalkyl-substituted hydrobenzoin derivatives using a similar sequence. However, this synthetic scheme was only viable if the nucleophile partners (cycloalkenyl boronic acid or esters) in the Suzuki-Miyaura cross-coupling were readily available or prepared.

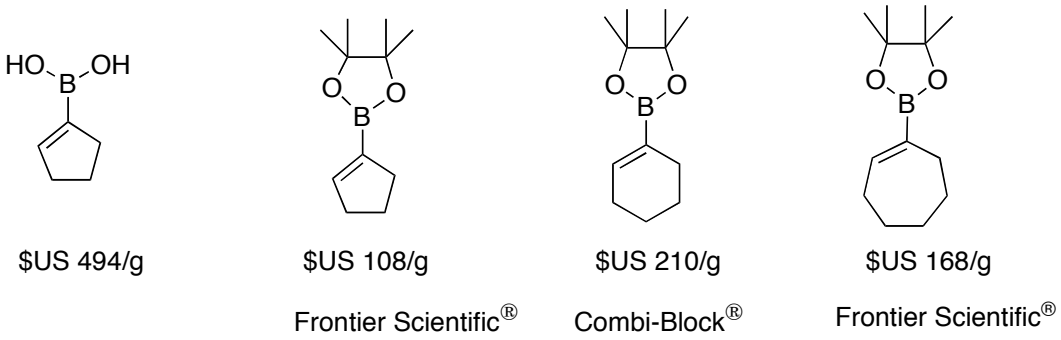


Scheme 4.3. Synthesis of Vivol **4.21**.

4.3.3 A convenient and economic preparation of cycloalkenyl boronic acid pinacol esters[7]

The synthesis of various ortho-substituted hydrobenzoins required the use of super-stoichiometric (3.0 equivalents) amounts of cycloalkenyl boronic acids in the Suzuki-Miyaura cross-coupling reaction (Scheme 4.3) Upon inspection of commercial availability, we found that boronic acid and/or their corresponding pinacol esters were forbiddingly expensive, and some higher cycloalkenyl boronic acid analogues were not commercially available.

The representative price of some of the boronic acid pinacol esters are shown in Figure 4.4. Considering the requirement of up to 3.0 equivalents of these boronic acid derivatives and their expensive price, we required an economical synthesis of these compounds and their higher cycloalkyl analogues.

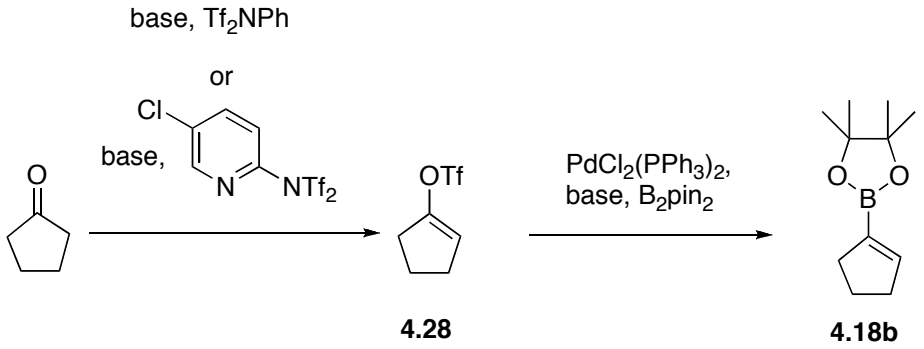


$US 494/g | $US 108/g Frontier Scientific® | $US 210/g Combi-Block® | $US 168/g Frontier Scientific®

Figure 4.4. Representative price of commercially available cycloalkenylboronic acids.

4.3.4 Literature methods for the preparation of cycloalkenyl boronic acids

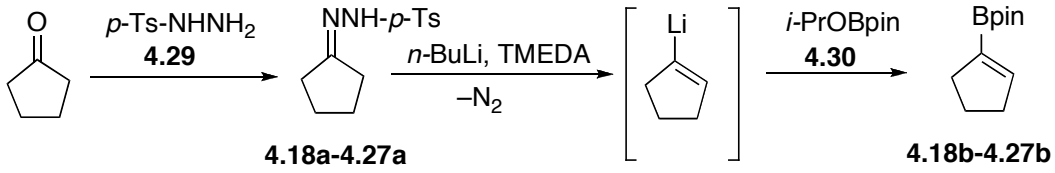
In general, literature methods for the preparation of cycloalkenyl boronic ester derivatives employ a Miyaura borylation protocol (Scheme 4.4).[8] In this procedure, the parent cycloalkanones are converted to the corresponding cycloalkenyl triflates **4.28** using expensive triflating agents. It should also be mentioned that these vinyl triflate species are very sensitive and tend to decompose during long term storage.[8] The thus obtained cycloalkenyl triflates are then coupled with expensive bispinacolatodiboron reagent, under palladium catalysis to yield the requisite cycloalkenyl boron pinacolates.



Scheme 4.4. Miyaura borylation protocol for the preparation of cycloalkenyl boronic acid pinacol esters.

4.3.5 Shapiro reaction approach for the synthesis of cycloalkenyl boronic acid derivatives[7]

In the context of economical access to diols **4.18**-**4.26**, we needed to avoid introduction of costly triflating reagents. Accordingly, alternatives to the Pd-catalyzed borylation protocol (Scheme 4.4) were sought. At this stage, a Shapiro reaction was envisaged to prepare the requisite cycloalkenyl boronates. After surveying the literature, we found one example that utilized the Shapiro reaction to generate cycloalkenyl boronic acids; however, the authors did not report on the isolation and characterization of these compounds.[10] We sought to utilize this method to generate the corresponding cycloalkenyl lithium intermediates and quench with commercially available boron electrophile **4.30** (Scheme 4.5).



Scheme 4.5. Shapiro reaction approach for the synthesis of cycloalkenyl boronic acid pinacol esters.

In the event, cycloalkylhydrazones **4.18a**-**4.27a** were readily obtained as crystalline solids in near quantitative yields by a simple addition/dehydration reaction with inexpensive hydrazide reagent **4.29**, in refluxing absolute ethanol. The majority of cycloalkyl hydrazone substrates started to precipitate out when the reaction reached completion, after which the reaction mixture

was cooled in an ice bath to allow for completion of crystallization. The thus freshly obtained cycloalkyl hydrazones were suspended in hexanes followed by addition of TMEDA (3 mL/mmol of hydrazone) and cooled to –78 ºC. This mixture was treated with four equivalents of *n*-BuLi, after which, dinitrogen was extruded at room temperature during 1-2 h. The resulting orange to red-brown solutions containing the corresponding cycloalkenyl anion equivalents were cooled to –78 ºC and treated with isopropoxypinacol borate **4.30** (Scheme 4.5), and following aqueous workup, the resulting crude products were easily purified by flash chromatography over silica gel. The resulting cycloalkenyl boronate products **4.18b**-**4.27b** are robust and can be stored on the bench top for weeks without any observable decomposition. Table 4.3 illustrates the scope of this method. The majority of the products were obtained in good to excellent yields and this chemistry appears to be general for the preparation of various ring-sizes of cycloalkenyl boronic esters.[7]

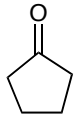
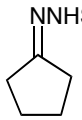
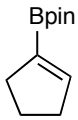
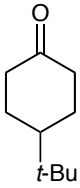
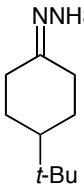
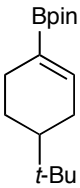
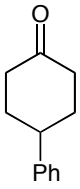
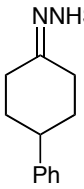
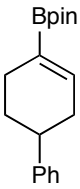
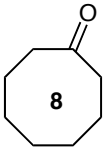
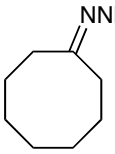
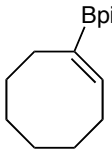
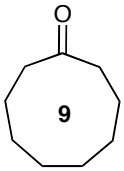
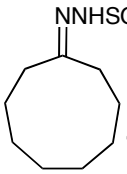
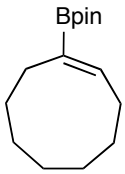
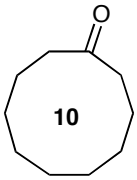
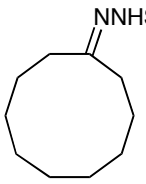
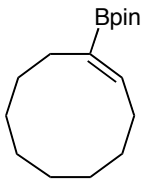
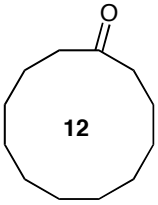
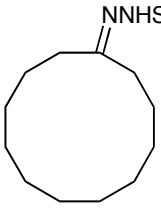
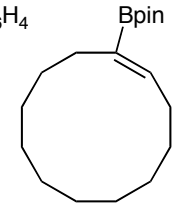
Entry	cycloalkanone	cyclohydrazone	product	Yield (%) [two steps]
1		 **4.18a**	 **4.18b**	80
2		 **4.25a**	 **4.25b**	70
3		 **4.26a**	 **4.26b**	65
4		 **4.21a**	 **4.21b**	80
5		 **4.22a**	 **4.22b**	70
6		 **4.23a**	 **4.23b**	88
7		 **4.24a**	 **4.24b**	95

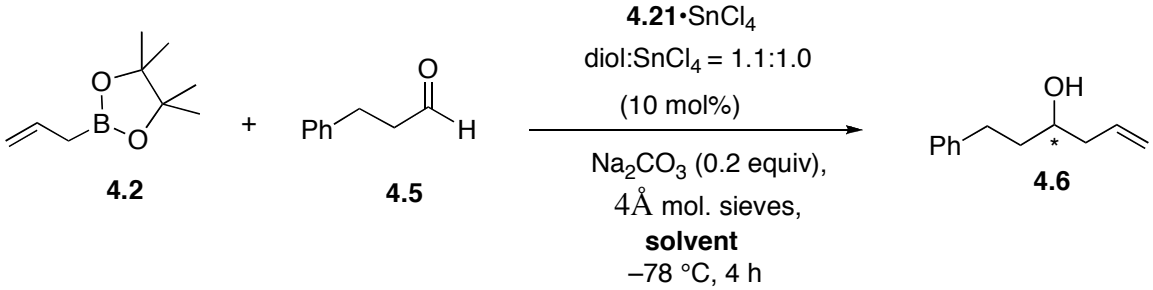
Table 4.3. Preparation of cycloalkenylboronic esters.[7]

4.4 Optimization of reaction parameters[3]

Having identified the optimal diol, Vivol **4.21**, and prepared multi-gram amounts, we turned our attention to the optimization of reaction parameters including reaction solvent, diol:$SnCl_4$ stoichiometry, and the concentration of the reaction.

4.4.1 Optimization of reaction solvent

Allylboration reactions are known to operate best in polar non-coordinating solvents.[11] Accordingly, we screened several polar non-coordinating solvents including mixed solvent systems that do not freeze at –78 ºC (Table 4.4). In the event, toluene was found to be the solvent of choice, just as in our first generation conditions.[1] It was quite surprising, however, that dichloromethane provided significantly diminished enantioselectivities (75% *ee*).



4.2 + **4.5** → **4.6**

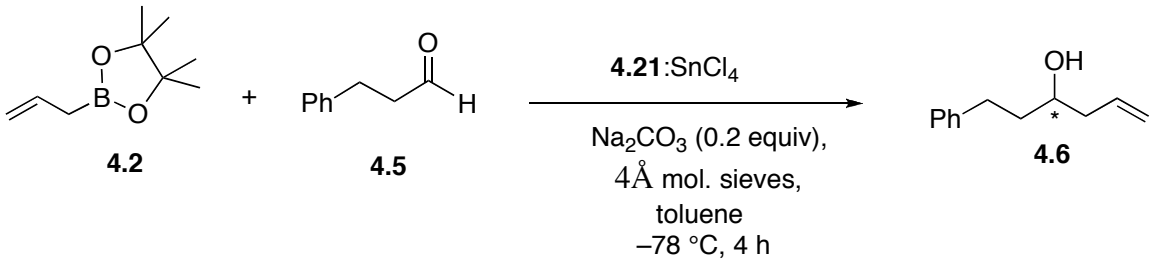
Entry	solvent	yield (%)	*ee* (%)
1	*o*-dichlorobenzene:toluene, 1:2	66	80
2	*o*-xylenes:toluene, 1:1	77	76
3	chlorobenzene:toluene, 1:3	70	87
4	benzene:toluene, 1:3	91	88
5	α-trifluorotoluene:toluene, 1:3	89	82
6	toluene	91	93
7	dichloromethane	33	75

Table 4.4. Optimization of reaction solvent.

4.4.2 Optimization of diol:$SnCl_4$ stoichiometry

With toluene as the optimal solvent, we then proceeded to optimize the stoichiometry of the catalyst components. Along this line, it was found that $SnCl_4$ alone is a strong activator of the non-enantioselective reaction. A 10-mol% loading of $SnCl_4$ provided a 70% conversion of the

model allylboration reaction after four hours at –78 ºC. As such, we had previously utilized a slight excess of diol over $SnCl_4$ (11-mol% of diol **4.1** versus 10-mol% of $SnCl_4$). Upon further optimization of the **4.21**:$SnCl_4$ ratio in this second-generation catalyst system, increased enantioselectivities were observed with a slightly higher loading of diol, which was found to be optimal at a 1.3:1.0 ratio of **4.21**:$SnCl_4$ (Table 4.5, entry 4).

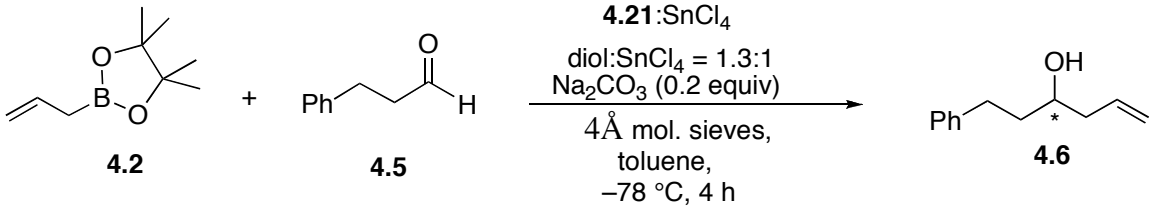


Entry	**4.21** (mol%)	$SnCl_4$ (mol%)	conversion (%)	*ee* (%)
1	10	10	100	90
2	11	10	100	94
3	12.5	10	100	94.8
4	13	10	100	95
5	20	10	90	90

Table 4.5. Optimization of diol versus $SnCl_4$ stoichiometry.

4.4.3 Optimization of reaction concentration

In our first report, we performed the catalytic reaction at 0.25 M concentration of aldehyde substrate.[1] With the new **4.21**•$SnCl_4$ complex, it was found that an increase in the operating reaction concentration led to faster reactions and a slight increase in the enantioselectivity of the product (Table 4.6). Taking advantage of increased reaction rates at higher concentrations, the loading of the catalyst could now be lowered to 5-mol% of diol **4.21** without a negative impact in the product enantioselectivity (entry 5). Remarkably, it was found possible to lower the loading of $SnCl_4$ down to 2-mol% and observe a similar enantioselectivity of the homoallylic alcohol product (entry 7).



Entry	$SnCl_4$ (mol%)	**4.5**[M]	time (h)	conversion (%)	*ee* (%)
1	10	0.25	4	100	95
2	10	1.0	4	100	95.3
3	5	0.5	4	100	95.1
4	5	1.0	4	100	95.6
5[a]	3.85	1.0	5	100	95
6	2	0.5	16	100	94
7	2	1.0	16	100	94.3

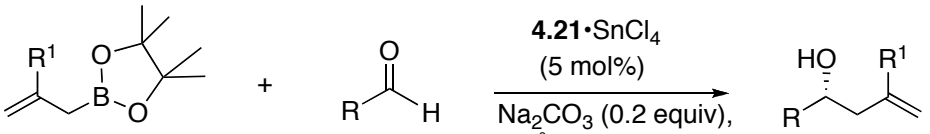
[a] 5-mol% of diol **4.21** was employed.

Table 4.6. Optimization of reaction concentration.

4.5 Substrate scope for allylation and methallylation of aldehydes

Having optimized reaction parameters with the Vivol **4.21**•$SnCl_4$ complex, we then explored the scope of the simple allylboration of aldehyde substrates (Table 4.7). Analogous to our previous report,[1] the preferred substrates for this second generation LBA catalyst system turned out to be aliphatic aldehydes. The reaction gave near quantitative yields for the majority of reactions, including aromatic substrates, and consistently high enantioselectivities for the aliphatic aldehyde substrates. Synthetically useful homoallylic alcohol products from functionalized aldehydes were obtained in excellent enantioselectivity (entries 5-7, 9-11). Straight chain aliphatic aldehydes also gave the corresponding products in high enantioselectivity (entry 16). For oxygenated aliphatic aldehydes, insulation of the coordinating group by protection with bulky silyl groups gave better enantioselectivities than when using benzyl protection (compare entries 5-7 vs. 8). Catalytic allylation of phenylacetaldehyde, however, was more efficient with **4.19** (entry 4, using 10 mol% catalyst loading) as the diol component of the LBA catalyst when compared to diols **4.21** (entry 2) or **4.20** (entry 3). For aldehydes possessing α-substituents, we had to employ a 10-mol% loading of $SnCl_4$ and employ a less hindered diol with a smaller ring size (entries 2, 12-15). For the allylation of cyclohexanecarboxaldehyde, diol **4.21** gave moderate results (74% *ee* and 50% yield) (entry 15). However, by switching to diols with smaller ring sizes, a gradual increase in the product enantioselectivity was observed, with diol **4.18** providing optimal enantioselectivity and yield (entry 12). Unfortunately, the present catalytic manifold gives comparably diminished enantioselectivity for the allylboration of protected α-hydroxy aldehydes (entries 17-18).

Compared to our first generation LBA system,[1] the products of aromatic aldehyde substrates are now obtained with much improved enantioselectivities. In particular, electron-poor aromatic aldehydes give better results than electron rich ones. We were particularly delighted to see high enantioselectivity for the allylation of 3,5-bis-trifluoromethyl benzaldehyde (entry 19). A limitation to the current methodology lies in the allylation of deactivated aromatic aldehydes (entry 21). The present catalytic manifold is also applicable to the methallylboration reaction, and provides good to excellent enantioselectivity and yields of the corresponding products (entries 25-27).



4.2 $R^1 = H$
4.31 $R^1 = CH_3$

4.6-4.49
4.50-4.52

Entry[a]	R^1	aldehyde	product	yield (%)	*ee* (%)
1	H	$Ph(CH_2)_2CHO$	**4.6**	99	95
2	H	$PhCH_2CHO$	**4.32**	99	74
3	H	$PhCH_2CHO$	**4.32**	99	82[c]
4	H	$PhCH_2CHO$	**4.32**	99	93[e]
5	H	$TBSO(CH_2)_2CHO$	**4.33**	98	95
6	H	$TIPSO(CH_2)_2CHO$	**4.34**	99	95
7	H	$TBDPSO(CH_2)_2CHO$	**4.35**	99	90[e]
8	H	$BnO(CH_2)_2CHO$	**4.36**	99	80
9	H	$TBDPSO(CH_2)_3CHO$	**4.37**	95	93
10	H	$TBSO(CH_2)_3CHO$	**4.38**	85	92
11	H	$TIPSO(CH_2)_3CHO$	**4.39**	99	92
12	H	$C_6H_{11}CHO$	**4.40**	94	91[c,e]
13	H	$C_6H_{11}CHO$	**4.40**	91	82[b,e]
14	H	$C_6H_{11}CHO$	**4.40**	90	80[d,e]
15	H	$C_6H_{11}CHO$	**4.40**	50	74[e]
16	H	$CH_3(CH_2)_3CHO$	**4.41**	90	95
17	H	$TBDPSOCH_2CHO$	**4.42**	99	77[e]
18	H	$BnOCH_2CHO$	**4.43**	99	70[e]
19	H	$3,5\text{-}(CF_3)_2C_6H_3CHO$	**4.44**	99	94
20	H	$2\text{-}F\text{-}C_6H_4CHO$	**4.45**	99	80
21	H	$4\text{-}OMe\text{-}C_6H_4CHO$	**4.46**	45	13

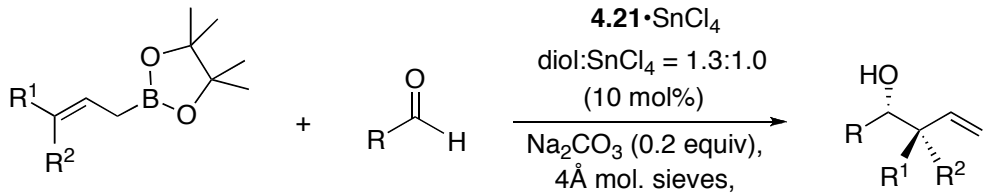
22	H	2-Br-C_6H_4CHO	**4.47**	99	60
23	H	2-CF_3-C_6H_4CHO	**4.48**	95	75
24	H	C_6H_5CHO	**4.49**	99	71
25	CH_3	TBDPSO$(CH_2)_2CHO$	**4.50**	99	92
26	CH_3	Ph$(CH_2)_2CHO$	**4.51**	99	84
27	CH_3	TBDPSO$(CH_2)_2CHO$	**4.52**	95	85

[a]Reaction conditions: Unless noted, all reactions were performed with 1.10 mmol of boronate, 1.00 mmol of aldehyde, 3.85 mol% of $SnCl_4$, 5.00 mol% of **4.21**, 0.077 mmol of Na_2CO_3, 50 mg of 4Å molecular sieves and 1.0 mL of toluene at –78 ºC for 6-8 h. The optical purity of homoallylic alcohol products was determined by chiral HPLC and or ^{19}F-NMR analysis of diastereomeric Mosher esters (error associated in *ee* measurement is ±. 2.5%). [b]Diol **4.19** was used. [c] Diol **4.18** was used. [d] Diol **4.20** was used. [e]10 mol% of catalyst was used.

Table 4.7. Substrate scope in the second-generation catalytic allyl- and methallylboration of aldehydes.[3]

4.6 Substrate scope in the crotylboration of aldehydes

The next line of research concerned the catalytic enantioselective construction of propionate units through the analogous crotylboration of aliphatic aldehydes. Freshly prepared reagents **4.3** and **4.4** of >95% isomeric purity were reacted with aliphatic aldehydes under **4.21**•$SnCl_4$ catalysis (Table 4.8). The obtained results draw a parallel with our previous report, i.e., that the *E*-crotylboronate **4.3** affords better enantioselectivity than the corresponding *Z*-crotylboronate **4.4**.[1] Enantioselectivities as high as 96% are observed, and more importantly, the *E*/*Z* geometry of the reagent is completely transferred diastereospecifically to the product. Since the reaction is significantly slower than simple allylboration, we opted to use a 10-mol% catalyst loading. Lower catalyst loading does provide the requisite product in a slightly lower yield and comparable enantioselectivity (entry 2). The corresponding *cis*-crotylboration reaction also provides improved enantioselectivities of the products when compared to the first-generation catalyst system (Table 4.8, entries 8-10). Overall, it is remarkable that the stereoselectivity of this catalytic enantioselective *trans*-crotylboration is superior to that of the most popular stoichiometric reagents.[12]



4.3 $R^1 = CH_3$, $R^2 = H$
4.4 $R^1 = H$, $R^2 = CH_3$

4.53-4.58
4.59-4.61

Entry	R	R^1	R^2	product	*syn*/*anti*	yield (%)	*ee* (%)
1	$Ph(CH_2)_2CHO$	CH_3	H	**4.53**	*anti*	93	96
2[a]	$Ph(CH_2)_2CHO$	CH_3	H	**4.53**	*anti*	80	93
3	$TBDPSO(CH_2)_2CHO$	CH_3	H	**4.54**	*anti*	94	93
4	$TBSO(CH_2)_2CHO$	CH_3	H	**4.55**	*anti*	99	91
5	$TBSO(CH_2)_3CHO$	CH_3	H	**4.56**	*anti*	93	91
6	$CH_3(CH_2)_3CHO$	CH_3	H	**4.57**	*anti*	74	95
7	$3,5\text{-}(CF_3)_2C_6H_3CHO$	CH_3	H	**4.58**	*anti*	99	90
8	$PhCH_2CH_2CHO$	H	CH_3	**4.59**	*syn*	78	84
9	$TBDPSOCH_2CH_2CHO$	H	CH_3	**4.60**	*syn*	75	80
10	$TBDPSOCH_2(CH_2)_2CHO$	H	CH_3	**4.61**	*syn*	70	88

[a]5-mol% of catalyst was used.

Table 4.8. Substrate scope in the second-generation catalytic enantioselective crotylboration of aldehydes.[3]

4.7 Mechanistic studies

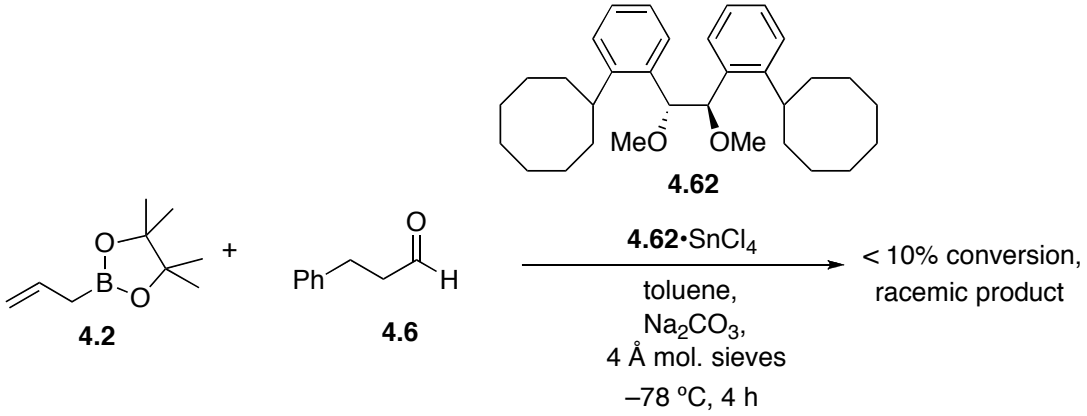
4.7.1 Extent of background uncatalyzed reaction

Mechanistic investigations can provide a better understanding of this LBA catalysts system and could help in the design of improved catalysts. The first issue to address was the extent of the absolute background (uncatalyzed) reaction between allylboronate **4.2** and model aldehydes at –78 ºC, and its impact on the enantioselectivity of the catalytic cycle. Although Brown and co-workers have reported that there is no reaction between allylboronate **4.2** and benzaldehyde at –78 ºC for 12 hours,[11] we found that this is not the case with aldehyde **4.6**. In our studies of the low temperature (–78 ºC) reactivity of **4.2** with hydrocinnamaldehyde (**4.6**), we did observe trace amounts (2%) of the borate ester precursor to the product after a 5-hour reaction time period at 0.2 M concentration of aldehyde. This result implies that during the standard 6-8 hour allylation

run at aldehyde concentrations of 1.0 M, the background reaction could possibly account for at least two percent of the opposite enantiomer. Consequently, the current LBA catalyst can only provide a maximum of approximately 96% *ee*.

4.7.2 Truly a Brønsted acid catalyst?

Given the complexity of the diol•$SnCl_4$ system, it seemed appropriate to ask whether the active catalyst is truly a Brønsted acid or a bisalkoxy-dichloro-tin species.[13] To this end, we synthesized **4.62** (the dimethoxy ether derivative of the diol **4.21**), which is devoid of hydroxylic protons. In the event, the addition of allylboronate **4.2** into hydrocinnamaldehyde under **4.62**•$SnCl_4$ catalysis led to low yields of the desired product in racemic form (Equation 4.2). Similar results were obtained when using the $SnCl_4$ complex of fully protected diol **4.1** as its dimethyl ether (see Scheme 3.4).[1] These results strongly suggest the important role of hydroxylic protons for efficient catalysis and facial selectivity of the aldehyde substrates. As indicated by the moderate activity of monomethyl ether **4.27**•$SnCl_4$ complex (entry 10, Table 4.2), a single hydroxylic proton suffices for enantioselective catalysis although it is not as efficient as two protons (compare with **4.21**, entry 4, Table 4.2).



Equation 4.2. Control reaction with fully protected diols.

A similar outcome was also observed when replacing anhydrous Na_2CO_3 with a soluble base, Et_3N, which shuts down L.A and B.A catalysis. Addition of Et_3N (2.0 equivalents vs. **4.21**) most likely leads to a bisalkoxide tin species, which is a weak Lewis acid compared to the strongly Lewis acidic $SnCl_4$, and shuts down protic acid.[13] Additionally, based on ^{119}Sn-NMR studies, the

complex of **4.1**•$SnCl_4$ in toluene-d_8, with or without added anhydrous Na_2CO_3, exhibits octahedral geometry around the tin atom. In these experiments, we observed only a single peak at –572.70 ppm, a region associated with hexa-coordinated tin complexes.[14] We also ran the model reaction under the presence of proton sponge and failed to observe any catalysis. These observations clearly point to a Brønsted acid activation manifold for the allylboration reaction with the presence of diol•$SnCl_4$ LBA catalyst.

4.7.3 Possiblility of trans-esterification?

If the kinetic barrier for trans-esterification is low enough, boronic esters can exchange with free diols.[15] We wanted to rule out the possibility that a Lewis or a Brønsted acid catalyzed trans-esterification process could lead to the chiral allylboron intermediate **4.63**, which could be responsible for the observed enantioselectivity in the product. To this end, an authentic reagent **4.63** (Figure 4.5) appended with a (*R*,*R*)-Vivol (**4.21**) scaffold was synthesized.[15] To our surprise, subjecting this chiral reagent under Lewis acid catalysis or combined acid catalysis (pinacol•$SnCl_4$) provided products in much lower enantioselectivity and with opposite absolute stereochemistry (based on HPLC retention times) (Figure 4.5). Such a low level of enantioselectivity is in line with previously reported aldehyde allylation results from Roush and co-workers when employing chiral hydrobenzoin derived auxiliaries.[16] *Indeed, it is thus truly remarkable that chiral diol* **4.21** *functions much better when acting as a component of the LBA catalyst than when used stoichiometrically as a chiral auxiliary reagent*.

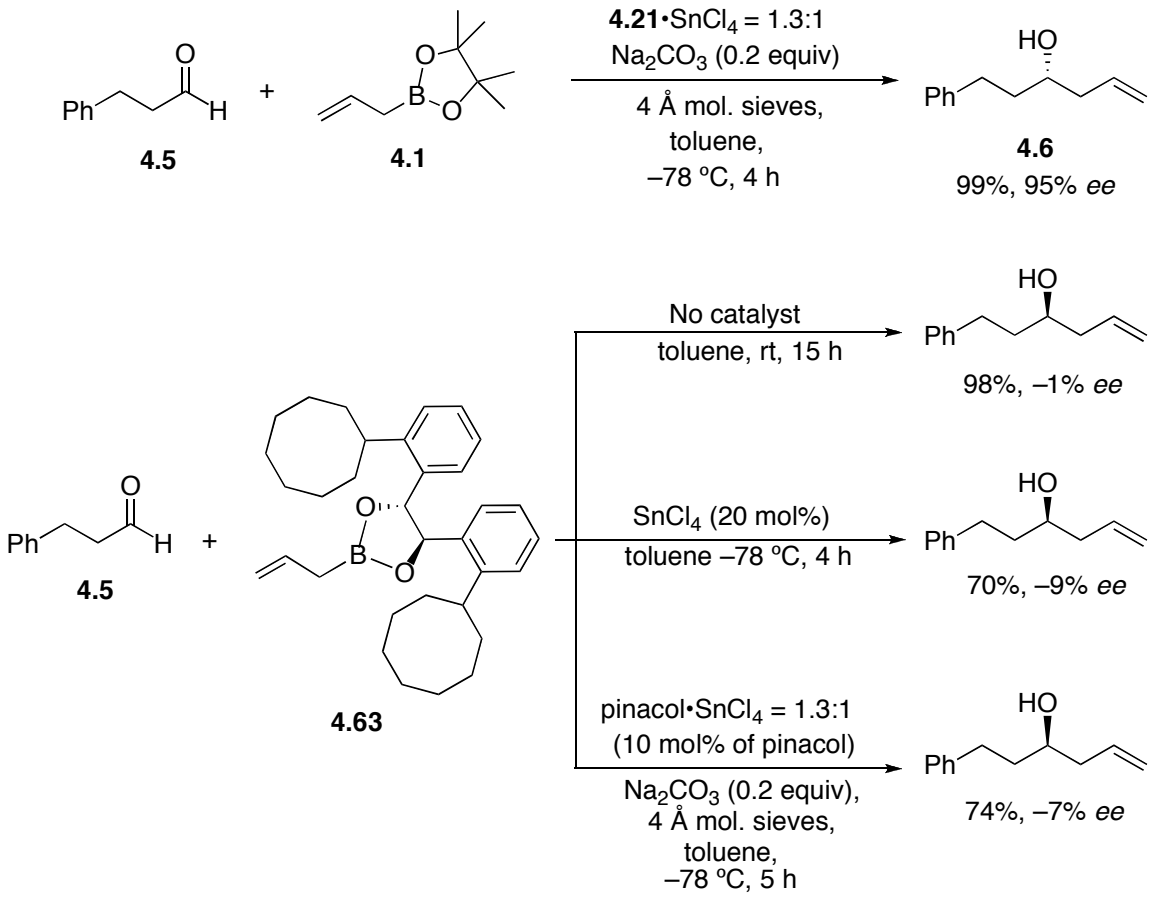


Figure 4.5. Control reactions that rule out a trans-esterification mechanism.

Further to these control experiments, the possibility of boron-to-tin transmetallation to form an allylic tin reagent is equally unlikely as it would be hard to reconcile with the lack of activity of the fully protected diol and the diastereoselectivity of the reaction would represent a Type II reaction manifold (c.f. Equation 4.2). Moreover, low-temperature (–78 °C) NMR experiments between equimolar **4.2** and **4.21**•$SnCl_4$ hint to complexation of the boronate unit, however with a negligible change of chemical shift for the methylene protons (CH_2B). Altogether, these results confirm that the role of the LBA catalyst is to accelerate by non-covalent interactions the addition of allylboronate **4.2** onto aldehydes, and at the same time provide asymmetric bias for the enantiofacial selectivity.

4.7.4 Explanation for requirement of excess diol

The optimal conditions in this second-generation catalytic system employ a slightly different diol:$SnCl_4$ stoichiometry compared to the first-generation catalyst system. Although there is not a highly significant variation of enantioselectivity in going from 1.1:1 to 1.3:1 ratio (Table 4.5), we felt the need to understand the seemingly anomalous use of up to 0.3 additional equivalents of diol in the in-situ catalyst preparation. During the course of this study, we have found that the (*R,R*)-1,2-di-naphthyl ethanediol **4.1** alone slowly catalyzes the addition of allylboronate **4.2** onto hydrocinnamaldehyde (**4.5**), giving rise to homoallylic alcohol product **4.6** in 70% conversion and –17% *ee* after 24 hours. In contrast, Vivol (**4.21**) was found to catalyze the same reaction to give the product in 60% conversion in essentially racemic form (Figure 4.6). Hence, in order to avoid aggravating any erosion of enantioselectivity, it is logical that the first-generation catalyst system functions well with a minimal excess of diol **4.1** vs $SnCl_4$. The second-generation catalyst system, however, requires a slightly higher excess of the diol, **4.21**, and indeed the product enantioselectivity gradually rose from 90% *ee* to 95% *ee* by going from 1.1 to 1.3:1 ratio of diol vs $SnCl_4$ (see Table 4.5).

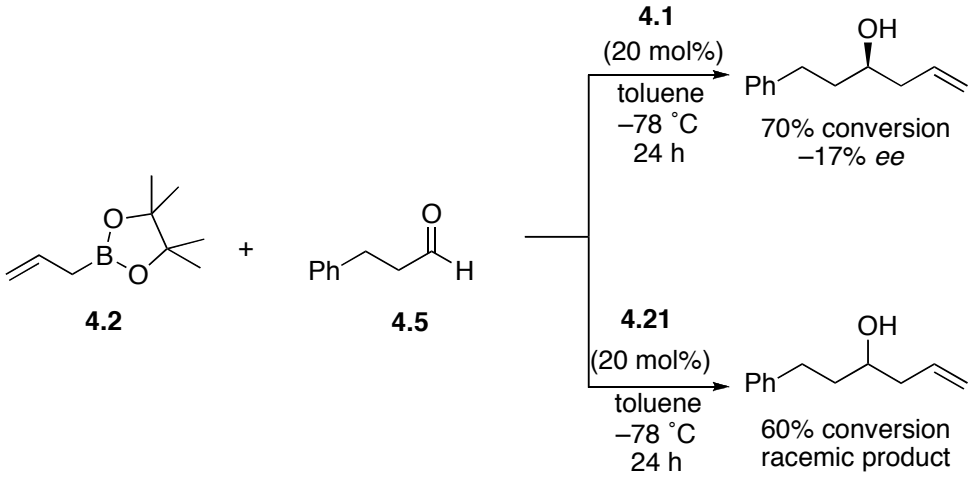


Figure 4.6. Control reactions with diol catalysis of the model allylboration reaction.

We reasoned that this slightly higher loading of diol **4.21** is required in order to sequester any uncomplexed $SnCl_4$ (which can act as a strong achiral Lewis acid catalyst for the same reaction) (c.f. Section **4.7.3**). It was hypothesized that uncomplexed $SnCl_4$ would originate from a slow and reversible dissociation of the **4.21**•$SnCl_4$ complex. To probe this assumption, we subjected a pre-formed (1:1) complex of (*R,R*)-Vivol **4.21**•$SnCl_4$ at –78 ºC with one equivalent of (*R,R*)-

hydrobenzoin. After a 3 hour time period, we could see up to 6% exchange of $SnCl_4$ from the (*R*,*R*)-Vivol **4.21**•$SnCl_4$ complex to the (*R*,*R*)-hydrobenzoin•$SnCl_4$ complex by ^{119}Sn-NMR spectroscopy. The reverse exchange experiment also provided similar results with an even larger amount of $SnCl_4$ exchange. Along the same line, Yamamoto and co-workers have mentioned the phenomenon of reversible complexation of diols with $SnCl_4$ as a reason for difficulty in obtaining diol•$SnCl_4$ crystals.[2] As such, any free-floating $SnCl_4$ in the reaction medium would be detrimental to the enantioselecivity of the reaction; hence the presence of excess diol is needed for sequestering this strong racemic activator. These observations are summarized in Figure 4.7.

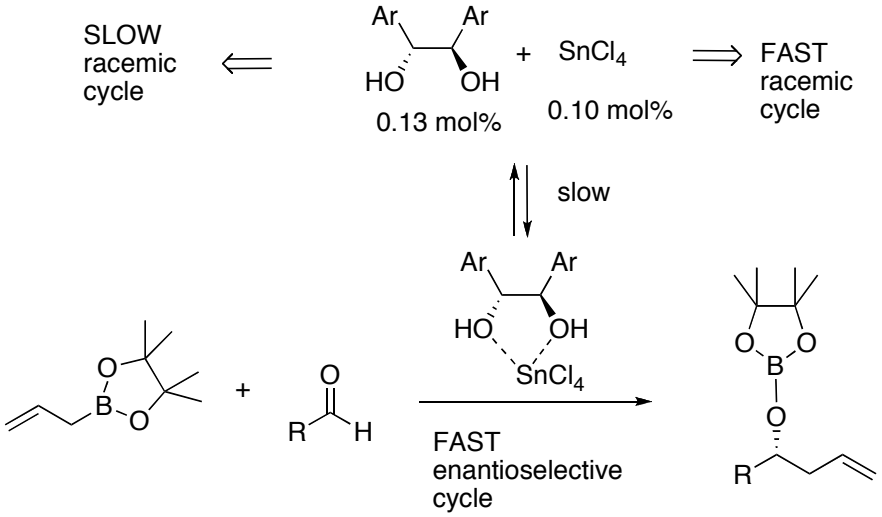


Figure 4.7. Schematic representation of diol•$SnCl_4$ exchange phenomenon and its implication in the reaction's enantioselectivity.

4.7.5 Catalyst structure and origin of enantioselectivity

To shed light into the structure of the active catalyst, crystallization of a 1:1 mixture of (*R*,*R*)-Vivol (**4.21**) and $SnCl_4$ in toluene and methylene chloride was attempted. After extensive optimization of the crystallization conditions and numerous failed attempts, I was fortunate to get clear and colorless needles from a 1:1 mixture of Vivol (**4.21**) and $SnCl_4$ during a two-month period at –15 ºC. Single crystal X-ray diffraction analysis of this LBA catalyst provided the structure shown in Figure 4.8 wherein the five-membered ring system represents the classic delta conformation. Surprisingly, the complex does not exhibit the extended conformation (**A**) that would minimize steric interactions between the two cycloalkyl substituents. Instead, it prefers a stacked structure (**B**) where the cyclooctyl group of one aryl substituent piles over the arene unit

of the other substituent, and vice versa. Although this conformation may simply result from crystal packing, it would explain the subtle effect observed with respect to the ortho substituent's ring size and the asymmetric environment of the activated protons, and provides an explanation as to why the diol **4.16** failed to provide good enantioselectivity (c.f. Figure 4.3). The ORTEP representation (**C**) shows intermolecular hydrogen-bonding interactions between the activated proton H-20 and apical Cl-3 of another complex (Figure 4.9). Similar interactions can also be seen between activated proton H-10 and co-crystallized water molecule in an extended hydrogen-bonded chain network (Figure 4.9). It is likely that H-10 is also the point of electrophilic activation of reagent **4.2** through hydrogen bonding interaction with one of the oxygens of the dioxaborolane, as proposed previously in the case of Lewis acid activation (c.f. Chapter 2, Figure 2.13).[17] Another key observation concerns the direction of the activated protons, i.e., H-10 and H-20. Both potential Brønsted acids are pointing outwards in pseudo-equatorial direction from the 5-membered chelated ring system of Vivol (**4.21**)•$SnCl_4$ (the location of the two activated protons H-20 and H-10 was confidently ascertained based on the proximity and atomic radii of the adjacent atoms in the unit cell). This phenomenon depicts the rigidness, i.e., lack of orientation flexibility of the activated H-10 and H-20 and as such, these hydroxylic protons bear chiral information of the diol scaffold. From the Spartan structure of the crystal structure (**D**), a highly dissymmetric environment is evident around both activated protons. The edge of the cyclooctyl ring along with the equatorial and apical chlorine atoms, Cl-2 and Cl-4, block several directions around both activated protons and are the most likely elements that influence the stereochemical outcome of the reaction. In this model, the plane of the aryl group may thus provide a surface for the transition state assembly, and its precise orientation, which is potentially influenced by the adjacent cyclooctyl groups, could be critical to the selectivity provided by the catalyst.

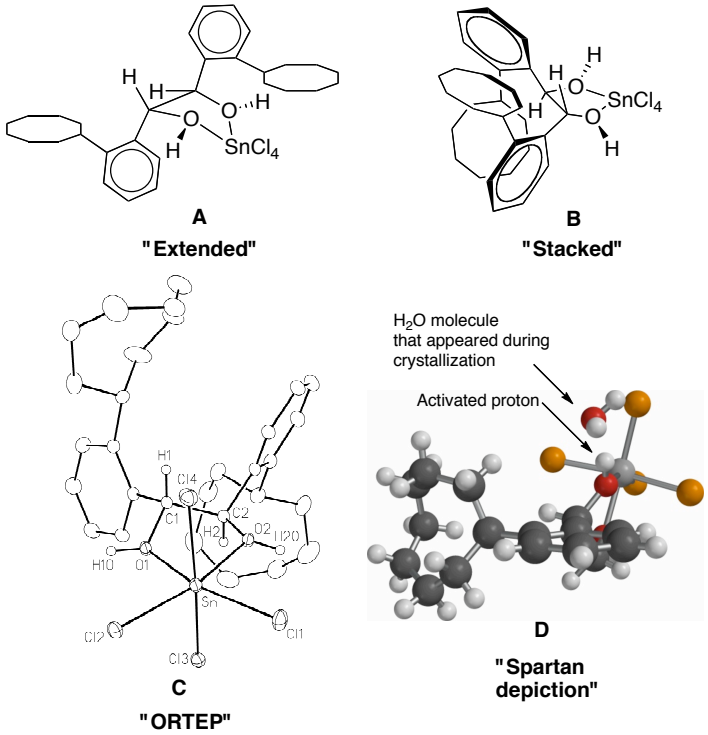


Figure 4.8. X-ray crystallographic structure of **4.21**•$SnCl_4$ and it chemdraw representations along with Spartan depiction.

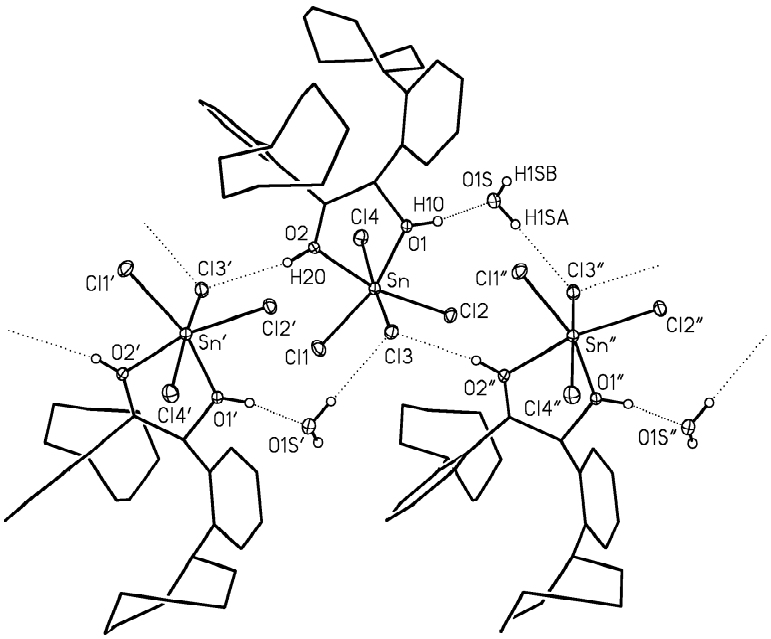


Figure 4.9. View of the extended hydrogen-bonded chain network involving adjacent molecules of **4.21**•**$SnCl_4$** and co-crystallized solvent water.

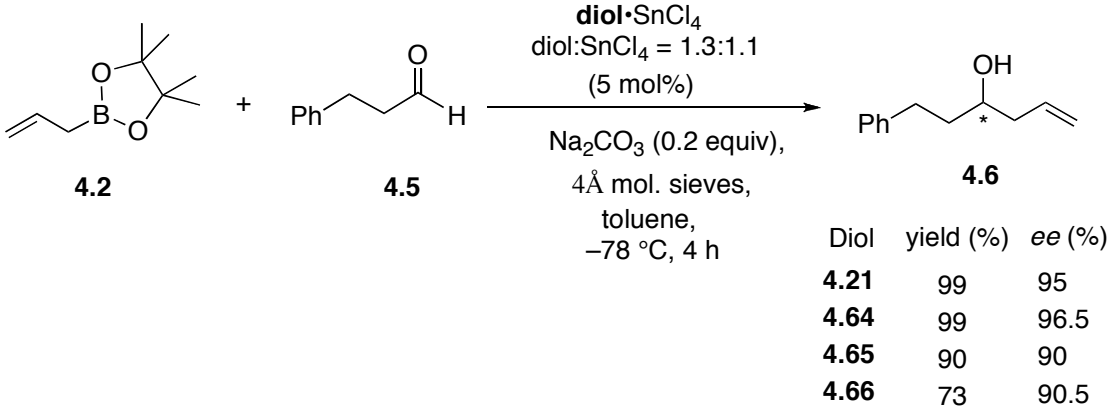
4.8 Rational design of an improved, third-generation diol for the catalytic enantioselective allylboration of aldehydes[18]

To summarize this part of research, an efficient catalyst system was developed for the enantioselective allyl- and crotylboration of aliphatic aldehydes. Homoallylic alcohols were obtained in good to excellent enantioselectivities. Remarkably, the products of *trans*-crotylboration are obtained with superior enantioselectivities than that of the well-established, stoichiometric allylboration methods. Using control reactions and X-ray crystallographic analysis of the optimal Vivol (**4.21**)•$SnCl_4$ complex, it was shown that the active catalyst in this reaction is a Brønsted acid that is rigidly held in a highly dissymmetrical environment. I also uncovered the unusual requirement for a small excess of diol in the in-situ preparation of the catalyst and its likely role as a sequestering agent for free $SnCl_4$, which may act as a racemic catalyst and would be formed in small amounts from the dynamic nature of the diol•$SnCl_4$ complex.[3] Since it was discovered that the background uncatalyzed reaction is limiting the product enantioselectivity in the simple allylation reaction, diols based on the Vivol (**4.21**) scaffold with increased acidity could be designed and provide more active diol•$SnCl_4$ complexes. In addition to the field of catalytic asymmetric allyl- and crotylboration of aldehyde, we also developed an economical route for the preparation of cycloalkylboronic acid pinacolates,[7] and this method is bound to find applications in target and diversity oriented synthesis.

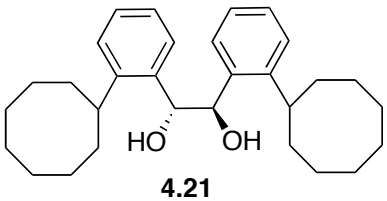
As we had previously noted a non-negligible uncatalyzed background reaction in excess of 4% at significantly lower reaction concentration (0.2 M versus 1.0 M of catalyzed reaction) (c.f. Section 4.7.1), we rationalized that a more acidic and thus more active Brønsted acid was required in order to shorten the reaction times and suppress the background uncatalyzed reaction. In this regard, it was expected that electron-withdrawing groups on the aryl ring of the diol unit could decrease the pKa of the hydroxylic protons in the diol•$SnCl_4$ complex.[3]

Looking back on the X-ray crystallographic structure of the diol•$SnCl_4$ complex, we had noticed an intimate steric relationship between the cyclooctyl unit and the aryl group of the adjacent carbons, which appear to stack with one another (c.f. Section 4.7.5). Upon inspection of the crystal structure, modulating electronic effects at the para position of the aryl groups appeared to least disrupt the catalyst's spatial arrangement.

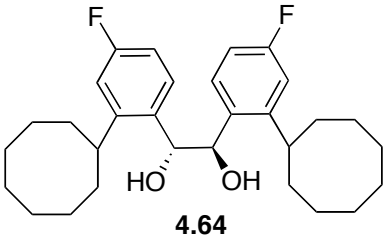
To this end, we decided to synthesize diols **4.64** and **4.65** equipped with para-fluoro and para-trifluoromethyl substituents (Figure 4.10). In order to support the hypothesis of electronic modulation of catalyst acidity, diol **4.66** was also targeted to serve as a negative control. Diols **4.64** and **4.65** were prepared as before, whereas diol **4.65** required an alternate approach, similar to that of Scheme 4.2. These diols were tested in the prototypic allylation of model hydrocinnamaldehyde. In the event, diol **4.64** provided the highest yield and enantioselectivity (Figure 4.9). Surprisingly, diol **4.65** containing the trifluoromethyl substituents only provided 90% *ee*. Although diol **4.65** is expected to have more acidic hydroxylic protons than **4.21**, the presence of sterically hindered trifluoromethyl substituents in the diol•$SnCl_4$ complex is non-negligible and could account for decreased enantioselectivity.



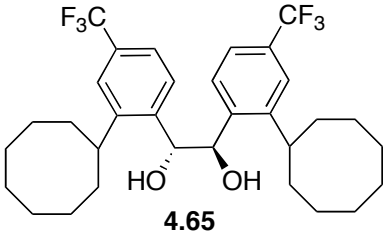
Diol	yield (%)	*ee* (%)
4.21	99	95
4.64	99	96.5
4.65	90	90
4.66	73	90.5



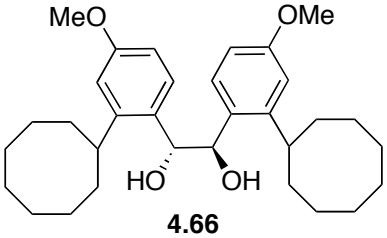
4.21
Vivol



4.64



4.65



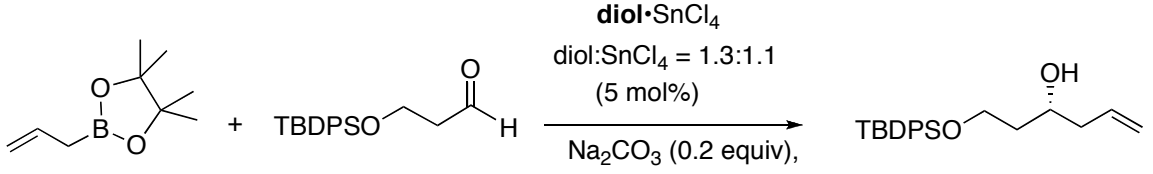
4.66

Figure 4.10. Comparison between a set of electronically modulated diols in the diol•$SnCl_4$-catalyzed model allylboration of hydrocinnamaldehyde with allylboronate **4.2**.

Although F-Vivol **4.64** provided a relatively small increase in product enantioselectivity in the simple allylation of model hydrocinnamaldehyde, its effect on other aliphatic aldehydes and substituted allylboronates is significant and thus appears to be general. In line with the previous Vivol **4.21**•$SnCl_4$ catalyzed allylborations, the optimal F-Vivol: $SnCl_4$ ratio was found to be 1.2. This observation indirectly supports our hypothesis that the diol F-Vivol possesses more acidic hydroxylic protons, which would lead to a relatively faster "free-diol"-catalyzed racemic reaction.

4.9 Efficiency of F-Vivol (4.64) in diol•$SnCl_4$ catalyzed additions of allylic boronates

We then tested this new catalyst system in reactions where Vivol•$SnCl_4$ catalyst gave moderate results. In the event, under the newly developed catalyst system, the synthetically useful beta-silyloxy aldehyde **4.35a** was allylated to give the product in substantially improved 96% *ee* (Equation 4.3).

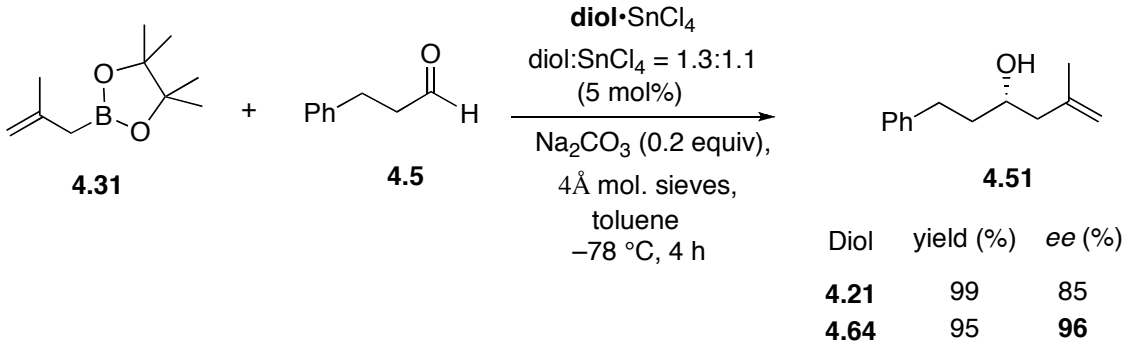


4.2 + **4.35a** → **4.35**

Diol	yield (%)	*ee* (%)
4.21	99	90
4.64	99	**96**

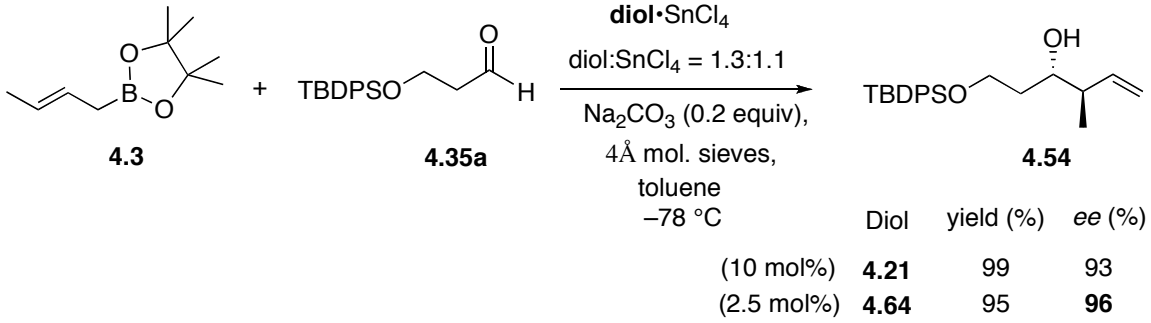
Equation 4.3. Comparison between Vivol•$SnCl_4$ and F-Vivol•$SnCl_4$-catalyzed allylboration.

The new diol **4.64** was particularly beneficial when used with more reactive methallylboronate **4.31** and provided 96% *ee* of the requisite product **4.51** (Equation 4.4).



Equation 4.4. Comparison between Vivol•$SnCl_4$ and F-Vivol•$SnCl_4$-catalyzed methallylboration.

In the crotylation example, we were now able to run the reaction at 2.5-mol% loading of the catalyst and obtain excellent yields and enantioselectivity of **4.54** (Equation 4.5). Moreover, we could readily recover the diol catalyst by flash chromatography in up to 80% yield after recrystallization.



Equation 4.5. Comparison between Vivol•$SnCl_4$ and F-Vivol•$SnCl_4$-catalyzed *trans*-crotylboration.

Unfortunately, the new catalyst system did not fare well with aromatic aldehydes: the allylation of benzaldehyde gave the product in only 60% *ee*. Nevertheless, the results of Equations 4.3, 4.4 and 4.5 clearly demonstrate the superiority of the new diol **4.64**, F-Vivol, as a component of the chiral LBA for the enantioselective allyl-, methallyl- and crotylboration of aliphatic aldehydes. While only a small panel of aldehydes was employed, all examples gathered thus far have led to an increase of enantioselectivity with **4.64**•$SnCl_4$, suggesting that its benefit is general and applicable to other aldehydes that were previously studied with **4.63**•$SnCl_4$ (see Table 4.7).

4.10 Semi-quantitative kinetic analysis of the velocity of reaction with diols 4.21, 4.64 and 4.66

In order to determine the relative rates of the diol•$SnCl_4$ catalyzed allylboration reaction with electronically modulated diols **4.21, 4.64** and **4.66**, we decided to lower the concentration of the model reaction to 0.5 M in aldehyde substrate, and terminate the reaction after exactly 1.0 hour. In the event, the model allylation reaction gave 40% conversion with **4.64**•$SnCl_4$, and 34% conversion with **4.21**•$SnCl_4$. The catalyst from the negative control, **4.66**•$SnCl_4$ only provided 17% conversion of the reaction (Figure 4.11).

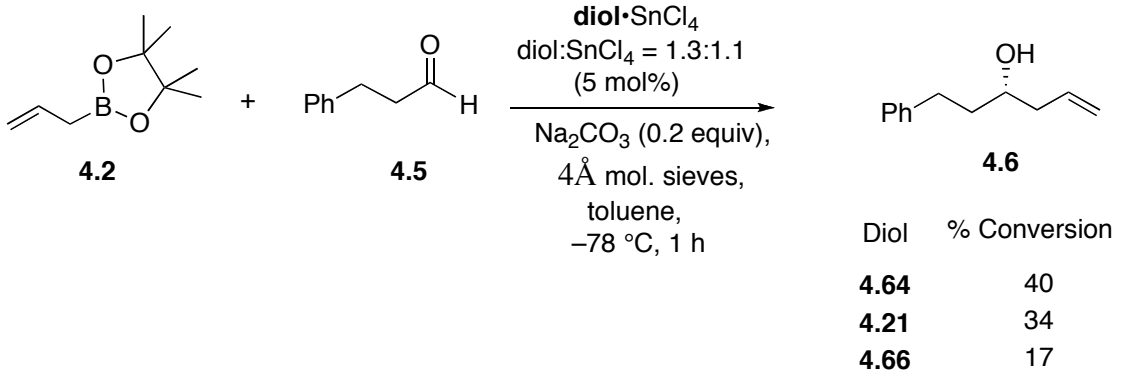


Figure 4.11. Comparison of relative rate of allylboration.

Over the course of complete conversion, it can be deduced that F-Vivol **4.64**•$SnCl_4$ would provide 15-20% increase in conversion rates over Vivol **4.21**•$SnCl_4$. It is thus conceivable that the more active catalyst **4.64**•$SnCl_4$ helps overcome the erosion of enantioselectivity by the competing background uncatalyzed reaction that is more prevalent in the reactions employing **4.21**•$SnCl_4$ as catalyst. However, a possible subtle change in the structure of the catalyst complex cannot be ruled out. Indeed, the small fluorine atoms in **4.64** are essentially isosteric to the hydrogen atoms found in **4.21**, which would avoid any significant change in the active LBA catalyst's structure. In this regard, an opposite trend might be expected in diol **4.65**, which contains *p*-trifluoromethyl substituents, in which the larger size of the trifluoromethyl group could possibly lead to a decrease in discrimination between the two competing transition states leading to the respective enantiomers of the homoallylic alcohol products.

4.11 Conclusion

Following the lead hypothesis of our mechanistic studies regarding the negative impact of the background uncatalyzed reaction on the enantioselectivity of the allylboration reaction, we were able to design an even better performant diol, *p*-F-Vivol (**4.64**). The LBA catalyst derived from **4.64**•$SnCl_4$-complex was shown to deliver acetate and propionate units in high yield and high enantio- and diastereoselectivities when compared to the parent Vivol (**4.21**)•$SnCl_4$ complex. Under this third-generation catalyst system, the homoallylic alcohol products are obtained in up to 97% *ee*. Additionally, since allylic boron pinacolates can be readily diversified, the use of **4.64**•$SnCl_4$ Brønsted acid catalyst is expected to provide novel homoallylic alcohol scaffolds in comparable enantio- and diastereoselectivities. Moreover, F-Vivol is also expected to find use in reactions that are susceptible towards LBA catalyst including polyene-cyclization and enantioselective protonation of prochiral silylenol ethers.[19]

4.12 Experimental

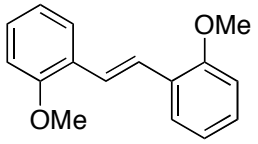
4.12.1 General

Unless otherwise noted, all reactions were performed under an argon atmosphere using flame-dried glassware. Toluene, hexanes and CH_2Cl_2 were distilled over CaH_2. THF and Et_2O were distilled over sodium/benzophenone ketyl. All aldehydes were purified by Kugelrohr distillation, prior to use. Molecular sieves were activated by heating under vacuum at 130 ºC (overnight) and then stored inside an oven maintained at 125 ºC. Thin layer chromatography (TLC) was performed on Merck Silica Gel 60 F254 plates and, visualized with UV light, $KMnO_4$ and 5% phosphomolybdic acid/EtOH (PMA). NMR spectra were recorded on Varian INOVA-300, INOVA-400, INOVA-500 or Unity 500 instruments. The residual solvent protons (^1H) or the solvent carbons (^{13}C) were used as internal standards. Boron NMR spectra are referenced to external $BF_3{\cdot}OEt_2$; ^{19}F spectra are referenced to external $CFCl_3$. ^1H NMR data are presented as follows: chemical shift in ppm upfield towards tetramethylsilane (multiplicity, coupling constant, integration). The following abbreviations are used in reporting NMR data: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; qt, quartet of triplets; dd, doublet of doublets; dt, doublet of triplets; AB, AB quartet; m, multiplet. High-resolution mass-spectra were recorded by the University of Alberta Mass Spectrometry Services Laboratory, using either electron impact (EI)

or electrospray (ES) ionization techniques. Infrared-spectra and optical rotations were recorded by University of Alberta Spectral Services. Allylic boronates **4.2**-**4.4** and **4.31** were prepared by the procedure of Roush and coworkers.[20] Optical purities of homoallylic alcohol products were determined by Chiral HPLC or by formation of Mosher esters and subsequent ^{1}H or ^{19}F NMR analysis of the crude product. Specific details are indicated in the experimental section for each individual product.

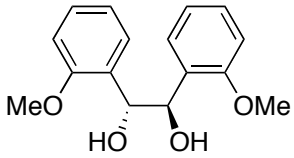
4.12.2 Sythesis of diol 4.10

4.12.2.1 (*E*)-1,2-Bis-(2-methoxyphenyl)ethene (4.10a)



The title compound was prepared following the procedure used in the preparation of **3.41a**, and gave spectral properties identical to that found in literature.[21]

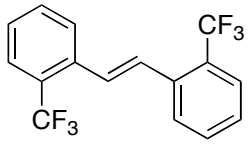
4.12.2.2 (1*R*,2*R*)-1,2-Bis(2-methoxyphenyl)ethane-1,2-diol (4.10)



The title compound was obtained in 70% yield by following the procedure used in the preparation of **3.41**. $[\alpha]_D^{25}$ +70.31 (*c* 2.78, $CHCl_3$); IR (cast film) 3462, 2956, 2836, 1601, 1492, 1463, 1247, 1049, 756 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (t, *J* = 7.2 Hz, 4H), 6.85 *(t,* J = 7.2 Hz), 6.75 (d, *J* = 8.8 Hz), 5.04 (s, 2H), 3.66 (s, 6H), 3.46 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 128.4, 128.4, 128.2, 120.4, 110.1, 74.4, 55.1; HRMS (EI) Calcd. $C_{16}H_{18}O_4$: 274.12051. Found: 274.12036.

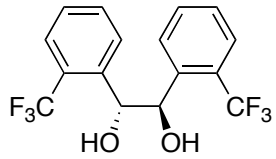
4.12.3 Synthesis of diol 4.11

4.12.3.1 (*E*)-1,2-Bis(2-(trifluoromethyl)phenyl)ethane (4.11a)



The title compound was prepared following the procedure used in the preparation of **3.41a**, using ortho-trifluoromethyl benzaldehyde, to give **4.11a** in 65% yield, as a white solid after recrystallization from CH_2Cl_2/MeOH. IR (cast film) 3084, 1604, 1578, 1493, 1314, 1103, 961, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 6 Hz, 2H), 7.69 (dd, *J* = 0.4, 6.4 Hz, 2H), 7.58 (dd, *J* = 6.0, 6.0 Hz, 2H), 7.45 (s, 2H) 7.41 (dd, *J* = 6.0, 6.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.9 (q, *J* = 1.5 Hz), 132.1 (1.0 Hz), 128.5, 127.7, 127.8 (q, *J* = 30 Hz), 125.9 (q, *J* = 5.6 Hz), 124.3 (q, *J* = 272 Hz); ^{19}F (376 MHz) δ –59.71 (s); HRMS (EI) Calcd. $C_{16}H_{10}F_6$: 316.06866. Found: 316.06837.

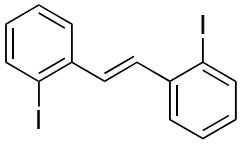
4.12.3.2 (1*R*,2*R*)-1,2-Bis(2-(trifluoromethyl)phenyl)ethane-1,2-diol (4.11)



The title compound was obtained by Sharpless asymmetric dihydroxylation of the corresponding stilbene in 80% yield after recrystallization from CH_2Cl_2/hexanes. $[\alpha]_D^{25}$ +21.06 (*c* 0.48, $CHCl_3$); IR (cast film) 3293, 1610, 1456, 1312, 1129, 766 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.0 Hz, 2H), 7.57 (t, *J* = 8.0 Hz, 4H), 7.38 (dt, *J* = 1.1, 7.7 Hz, 2H), 5.37 (s, 2H), 3.03 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8, 132.2, 129.6, 128.3, 125.8 (q, *J* = 5.7 Hz), 125.5, 122.8, 71.9; ^{19}F (376 MHz, $CDCl_3$) –58.02 (s); HRMS (ESI) Calcd. $C_{16}H_{12}O_2F_6Na_2$: 373.06337. Found: 373.06317.

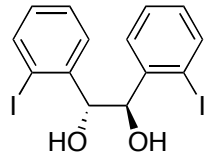
4.12.4 Synthesis of diol 4.12

4.12.4.1 (*E*)-1,2-Bis(2-iodophenyl)ethene (4.12a)



The title compound was obtained by McMurry coupling of 2-iodobenzaldehyde following the procedure used in the preparation of **3.41a** in 55% yield as a white solid, after recrystallization from CH_2Cl_2/MeOH. IR (cast film) 3046, 2917, 2849, 1581, 1469, 1433, 1007, 951, 752, 711 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 1.2, 7.6 Hz, 2H), 7.69 (dd, *J* = 1.2, 7.6 Hz, 4H), 7.39 (dt, *J* = 1.6, 7.6 Hz, 2H), 7.18 (s, 2H), 6.99 (dt, *J* = 1.2, 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.9, 139.6, 135.2, 129.4, 128.6, 126.8, 100.46; HRMS (EI) Calcd. $C_{14}H_{11}I_2$: 432.89502. Found: 432.89146.

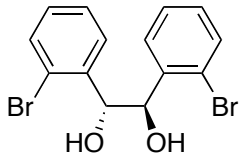
4.12.4.2 (1*R*,2*R*)-1,2-Bis(2-iodophenyl)ethane-1,2-diol (4.12)



The title compound was obtained by following the procedure used in the preparation of **3.41** as a white amorphous solid, in 75% yield, after recrystallization from hot CCl_4. $[\alpha]_D^{25}$ –34.28 (*c* 0.54, $CHCl_3$); IR (cast film) 3389, 3055, 2918, 1586, 1564, 1196, 1048, 1010, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (dd, *J* = 0.8, 7.6 Hz, 2H), 7.68 (dd, *J* = 1.2, 8 Hz, 2H), 7.36 (dt, *J* = 1.2, 8 Hz, 2H), 7.96 (dt, *J* = 1.2, 7.6 Hz, 2H), 5.12 (s, 2H), 3.16 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.7, 139.6, 129.9, 129.8, 128.4, 99.2, 79.8; HRMS (ESI) Calcd. $C_{14}H_{12}O_2I_2Na$: 488.88191. Found: 488.88224.

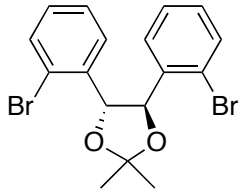
4.12.5 Synthesis of diol 4.13

4.12.5.1 (1*R*,2*R*)-1,2-Bis(2-bromophenyl)ethane-1,2-diol (4.13)



Prepared according to a literature procedure.[6]

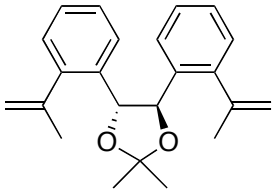
4.12.5.2 (4*R*,5*R*)-4,5-Bis(2-bromophenyl)-2,2-dimethyl-1,3-dioxolane (4.13b)



The title compound was prepared according to a literature procedure and the spectroscopic properties of the title compound were identical to those reported in the literature.[6] Literature $[\alpha]_D^{20.5}$ –11.4 (*c* 0.92, $CHCl_3$);[6] obtained $[\alpha]_D^{25}$ –9.62 (*c* 0.93, $CHCl_3$); enantiomer $[\alpha]_D^{25}$ +9.45 (*c* 0.93, $CHCl_3$).

4.12.6 Synthesis of diol 4.14

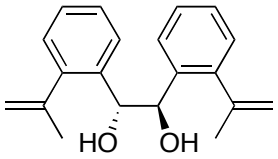
4.12.6.1 (4*R*,5*R*)-2,2-Dimethyl-4,5-bis(2-(prop-1-en-2-yl)phenyl)-1,3-dioxolane (4.14a)



Into a round bottom flask equipped with a magnetic stir bar and a reflux condenser was charged acetal **4.13b** (0.650 g, 1.58 mmol, 1.00 equiv), isoprenyl-boronic acid (0.410 g, 4.70 mmol, 3.00 equiv), $Pd(PPh_3)_4$ (183 mg, 0.158 mmol, 0.100 equiv), and 10 mL of dioxane. To the above mixture was added 4.80 mL of 2M aqueous K_2CO_3 (6.00 equiv) and the resulting mixture was degassed under a freeze-thaw cycle using argon purge. The resulting mixture was heated to

reflux for 24 h after which, the reaction mixture was poured over water and extracted with Et_2O (2 X 25 mL). The ethereal extracts were combined and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* and the crude product was purified by flash chromatography (0-5% EtOAc/hexanes) affording 520 mg (98.5% yield) of the title compound as a white solid. $[\alpha]_D^{25}$ +67.21 (*c* 0.67, $CHCl_3$); IR (cast film) 3077, 2983, 2932, 1641, 1371, 1235, 1052, 900, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 1.2, 8 Hz, 2H), 7.30 (dt, *J* = 1.2, 7.2 Hz, 2H), 7.20 (dt, *J* = 1.2, 7.6 Hz, 2H), 6.96 (dd, *J* = 1.2, 7.6 Hz, 2H), 5.15 (s, 2H), 4.81 (q, *J* = 1.2 Hz, 2H), 4.05 (d, *J* = 0.8 Hz, 2H), 1.68 (s, 6H), 1.52 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.6, 144.0, 132.7, 128.0, 127.9, 127.9, 127.4, 115.4, 108.9, 85.1, 27.6, 25.4; HRMS (ESI) Calcd. $C_{23}H_{26}O_2Na$: 357.18279. Found: 357.18250.

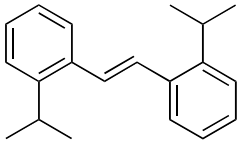
4.12.6.2 (1*R*,2*R*)-1,2-Bis(2-(prop-1-en-2-yl)phenyl)ethane-1,2-diol (4.14)



Acetal **4.14a** (500 mg) was suspended in a mixture of AcOH/H_2O/MeOH (16mL/2mL/2mL) and the suspension was heated to reflux at 100 ºC for 5 h. After the elapsed time, the mixture was poured over an ice-cold saturated solution of Na_2CO_3, and the product was extracted with EtOAc (2 X 50 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product, which was purified by flash chromatography to afford 264 mg (60% yield) of the desired product as a white solid. $[\alpha]_D^{25}$ +188.9 (*c* 1.74, $CHCl_3$); IR (cast film) 3331, 3075, 2965, 2914, 1640, 1433, 1191, 1059, 900, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.0, 7.2 Hz), 7.23 (dt, *J* = 1.2, 8.0 Hz), 7.16 (dt, *J* = 1.2, 7.6 Hz, 2H), 6.96 (dd, *J* = 1.2, 7.6 Hz, 2H), 5.16 (s, 2H), 5.05 (s, 2H), 4.46 (s, 2H), 2.96 (br s, 2H), 1.68 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3, 143.6, 136.4, 127.3, 127.7, 127.6, 127.1, 115.6, 74.2, 25.2; HRMS (ESI) Calcd. $C_{20}H_{22}O_2Na$: 317.15120. Found: 317.15057.

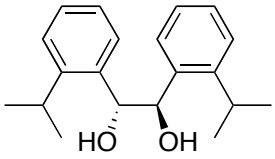
4.12.7 Synthesis of diol 4.15

4.12.7.1 (*E*)-1,2-Bis(2-isopropylphenyl)ethene (4.15a)



To a solution 2-isopropyl-bromobenze (1.87 g, 9.44 mmol, 1.00 equiv) in 8 mL THF at –78 ºC was added *t*-BuLi (17.8 mL, 29.2 mmol, 3.10 equiv) and the mixture was stirred for 30 min followed by addition of DMF (4.36 mL, 56.5 mmol, 6.00 equiv). The reaction mixture was brought to room temperature and quenched by addition of saturated solution of NH_4Cl. The mixture was diluted with ether and washed with water and brine and then dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to give the crude aldehyde (9.31 g, 99% yield). On the side, a round bottom flask equipped with a reflux condenser was charged Zn dust (1.82 g, 28.0 mmol, 3.00 equiv) and 100 mL of THF, and to the suspension was slowly added $TiCl_4$ (1.54 mL, 14.0 mmol, 1.50 equiv), and the mixture was heated to reflux at 80 ºC for 1 h. The flask was lifted from the oil bath and to the reaction mixture was added a solution of the aldehyde in 20 mL THF. The resulting mixture was refluxed for 5 h, after which it was poured over ice-cold 1 *N* HCl (40 mL), and the mixture was extracted with CH_2Cl_2 (2 X 100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude stilbene which was purified by flash chromatography (0-5% EtOAc/hexanes) to afford the title compound as a viscous oil, in a mixture of *E*:*Z* (20:1) stilbene. This mixture was subjected to isomerization using catalytic iodine in *o*-xylenes at 165 ºC for 15 h, after which, the volatiles were removed *in vacuo* and the product was purified by flash chromatography (0-5% EtOAc/hexanes) to afford isomerically pure stilbene (730 mg, 59%) as a white amorphous solid. IR (cast film) 2962, 2927, 1487, 1448, 1035, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.56 (d, J = 6.8 Hz, 2H), 7.34-7.29 (m, 6H), 7.28-7.21 (m, 2H), 3.36 (sept, J = 6.8 Hz), 1.28 (d, J = 6.8 Hz, 6H), 1.28 (d, J = 6.8 Hz, 6H); δ ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.2, 136.2, 128.8, 127.9, 126.4, 125.9, 125.0, 29.3, 23.5; HRMS (EI) Calcd. $C_{20}H_{24}$: 264.18781. Found: 264.18782.

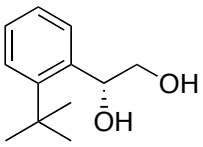
4.12.7.2 (1*R*,2*R*)-1,2-Bis(2-isopropylphenyl)ethane-1,2-diol (4.15)



Following the procedure used in the preparation of **3.41**, Sharpless asymmetric dihydroxylation of stilbene **4.15a** (0.440 g, 1.67 mmol, 1.00 equiv) under standard conditions using $K_3Fe(CN)_6$ (3.00 equiv), K_2CO_3 (3.00 equiv), $(DHDQ)_2PHAL$ (0.250 equiv) $K_2OsO_2(OH)_4$ (0.050 equiv), $MeSO_2NH_2$ (1.00 equiv) afforded 425 mg (86% yield) of the requisite product, which was recrystallized from CH_2Cl_2/hexanes to afford the title compound as a white solid. $[\alpha]_D^{25}$ –19.25 (*c* 0.48, $CHCl_3$); IR (cast film) 3339, 3054, 2967, 2929, 1488, 1445, 1028, 834, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64-7.60 (m, 2H), 7.24-7.17 (m, 4H), 7.09-7.05 (m, 2H), 5.17 (s, 2H), 2.87 (s, 2H), 2.71 (sept, *J* = 6.8 Hz, 1H), 1.06 (d, *J* = 6.8 Hz, 6H), 0.50 (d, *J* = 6.8 Hz, 6H) (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.7, 136.3, 128.1, 127.1, 125.8, 125.2, 74.1, 28.2, 24.9, 22.3; HRMS (EI) Calcd. $C_{20}H_{26}O_2$: 298.19327. Found: 298.19244.

4.12.8 Synthesis of diol 4.16

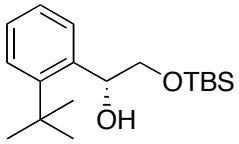
4.12.8.1 (*R*)-1-(2-*tert*-Butylphenyl)ethane-1,2-diol (4.16a)



To a 100 mL round bottom flask equipped with a stir bar was added K_2CO_3 (2.41g, 17.5 mmol, 3.00 equiv), $K_3Fe(CN)_6$ (5.75 g, 17.5 mmol, 3.00 equiv), $(DHQD)_2PHAL$ (40.5 mg, 0.0520 mmol, 0.00900 equiv), and to this mixture was added 30 mL of *t*-BuOH and 30 mL of distilled water. The mixture was stirred for 10 min at room temperature to which was added $K_2OsO_2(OH)_4$ (17.3 mg, 0.0470 mmol) followed by 1-(*t*-butyl)-2-vinylbenzene (931 mg, 5.82 mmol, 0.00800 equiv, prepared by diazotization of ortho *t*-butylaniline and quenching with KI).[22] The reaction mixture was allowed to stir for 2 days at room temperature. Sodium thiosulfate (7.60 g, 48.0 mmol, 8.24 equiv) was added to the reaction mixture and the reaction was stirred for another 1 h. After the elapsed time, the reaction was diluted with ethyl acetate and then

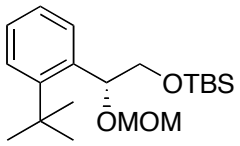
washed with 1.0 *N* potassium hydroxide followed by water. The aqueous layer was back extracted with ethyl acetate and the combined organic extracts are dried over anhydrous Na_2SO_4, filtered, concentrated *in vacuo* and purified by flash chromatography (20-45% EtOAc/hexanes) to afford 889 mg (79%) of the diol as a white solid, which was further recrystallized from EtOAc/hexanes to afford the title compound in 99% *ee*. $[\alpha]_D^{25}$ –49.5 (*c* 0.54, $CHCl_3$); IR (neat) 3316, 2957, 1049, 1024 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56-7.51 (m, 1H), 7.43-7.38 (m, 1H), 7.30-7.23 (m, 2H), 5.54 (dt, *J* = 5.2, 3.4 Hz, 1H), 3.82-3.69 (m, 1H), 2.60 (d, *J* = 2.4 Hz, 1H), 2.53 (dd, *J* = 7.6, 4.8 Hz, 1H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.4, 139.3, 128.5, 128.1, 126.5, 126.0, 71.6, 68.1, 35.7, 32.3; HRMS (EI) Calcd. $C_{12}H_{18}O_2$: 194.1307. Found: 194.1307.

4.12.8.2 (*R*)-2-(*tert*-Butyldimethylsilyloxy)-1-(2-*tert*-butylphenyl)ethanol (4.16b)



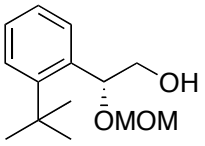
Diol **4.16a** (669 mg, 3.45 mmol, 1.00 equiv) in dry DMF (15 mL) was stirred with imidazole (469 mg, 6.90 mmol, 2.00 equiv) and TBSCl (574 mg, 3.80 mmol, 1.00 equiv) at room temperature for 12 h. Ethyl acetate (40 mL) was added and the organic phase was washed with water (3 X 15 mL), dried with anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give an oily residue. Flash chromatography (10% EtOAc/hexanes) yielded 989 mg (93%) of desired product **4.16b** as a colorless oil. $[\alpha]_D^{25}$ –36.9 (*c* 1.9, $CHCl_3$); IR (neat) 3459, 2956, 1253, 861 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61-7.58 (m, 1H), 7.42-7.37 (m, 1H), 7.29-7.20 (m, 2H), 5.45 (ddd, *J* = 9.2, 3.2, 1.2 Hz, 1H), 3.77 (dd, *J* = 10.4, 3.2 Hz, 1H), 3.66 (dd, *J* = 10.4, 9.2 Hz, 1H), 2.95 (d, *J* = 1.6 Hz, 1H), 1.46 (s, 9H), 0.95 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.5, 138.6, 128.9, 127.7, 126.2, 125.7, 71.2, 68.8, 35.6, 32.2, 25.9, –5.3; HRMS (EI) Calcd. $C_{14}H_{23}SiO_2$: 251.1467. Found: 251.1467.

4.12.8.3 (*R*)-5-(2-*tert*-Butylphenyl)-8,8,9,9-tetramethyl-2,4,7-trioxa-8-siladecane (4.16c)



To a solution of **4.16b** (785 mg, 2.55 mmol, 1.00 equiv) in *N*,*N*-diisopropylethylamine (6.0 mL) were added chloromethyl methyl ether (226 mg, 2.81 mmol, 1.10 equiv) and tetra-*n*-butyl ammonium iodide (941 mg, 2.55 mmol, 1.00 equiv), and the mixture was stirred at 70 °C for 3 h. Evaporation of the solvent *in vacuo* gave an oily residue, which was dissolved in $CHCl_3$. The solution was washed with water, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to yield an oil. Evaporation of the filtrate yielded an oil, which was subjected to flash chromatography (9% EtOAc/hexanes) to give 853 mg (95%) of the desired product **4.16c** as a colorless liquid. $[\alpha]_D^{25}$ –67.5 (*c* 0.9, $CHCl_3$); IR (neat) 2956, 1118, 1031 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63-7.57 (m, 1H), 7.41-7.37 (m, 1H), 7.24-7.17 (m, 2H), 5.43 (dd, *J* = 8.0, 2.4 Hz, 1H), 4.66 (d, *J* = 6.8 Hz, 1H), 4.56 (d, *J* = 6.8 Hz, 1H), 3.77 (dd, *J* = 11.2, 8.0 Hz, 1H), 3.66 (dd, *J* = 11.2, 2.4 Hz, 1H), 3.40 (s, 3H), 1.46 (s, 9H), 0.92 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7, 138.2, 128.8, 127.6, 126.0, 125.8, 93.7, 75.6, 68.8, 55.1, 35.7, 31.9, 25.9, 18.3, –5.2, –5.5; HRMS (EI) Calcd. $C_{16}H_{27}SiO_3$ (M^+–*t*-Bu): 295.1729. Found: 295.1730.

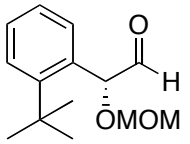
4.12.8.4 (*R*)-2-(2-*tert*-Butylphenyl)-2-(methoxymethoxy)ethanol (4.16d)



To a solution of the silyl ether **4.16c** (853 mg, 2.42 mmol, 1.00 equiv) in tetrahydrofuran (8 mL), was added TBAF (2.90 mL, 1.0 M solution in tetrahydrofuran, 2.90 mmol, 1.20 equiv) and the resulting solution was stirred for 2 h. The solvent was evaporated *in vacuo* and the crude product was purified by flash chromatography (20% EtOAc/hexanes) to give 509 mg (88%) of the primary alcohol **4.16d** as a colorless oil. $[\alpha]_D^{25}$ +174.1 (*c* 2.00, $CHCl_3$); IR (neat) 3448, 2958, 1151, 1030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52-7.48 (m, 1H), 7.43-7.38 (m, 1H), 7.26-7.20 (m, 2H), 5.45 (dd, *J* = 8.4, 2.8 Hz, 1H), 4.65 (d, *J* = 6.8 Hz, 1H), 4.62 (d, *J* = 6.8 Hz, 1H), 3.80-

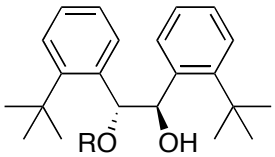
3.66 (m, 2H), 3.45 (s, 3H), 3.00 (dd, *J* = 9.6, 3.2 Hz, 1H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.8, 137.3, 128.7, 127.9, 126.1, 126.0, 94.3, 77.3, 68.0, 55.6, 35.7, 32.0; HRMS (EI) Calcd for $C_{14}H_{22}O_3$: 238.1569. Found: 238.1569.

4.12.8.5 (*R*)-2-(2-*tert*-Butylphenyl)-2-(methoxymethoxy)acetaldehyde (4.16e)



N-Methylmorpholine-*N*-oxide (510 mg, 4.36 mmol, 2.00 equiv) was added in one portion to a stirred suspension of alcohol **4.16d** (520 mg, 2.18 mmol, 1.00 equiv) and powdered 4Å molecular sieves (700 mg) in anhydrous CH_2Cl_2 (10.0 mL) under argon at rt. The suspension was stirred for 30 min and solid tetra-*n*-propylammonium perruthenate (39.0 mg, 0.110 mmol, 0.0500 equiv) was added at 0 ºC. After stirring for 50 min at 0 ºC, the reaction mixture was diluted with 15 mL of Et_2O and filtered through Celite. The filtrate was concentrated *in vacuo* and the residue was extracted with hexanes (2 x 10 mL). The organic layer was evaporated to afford 491 mg (95%) of aldehyde **4.16e** as colorless oil, which was used for the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.68 (d, *J* = 1.6 Hz, 1H), 7.58-7.40 (m, 2H), 7.30-7.24 (m, 2H), 5.89 (d, *J* = 1.6 Hz, 1H), 4.76 (d, *J* = 6.8 Hz, 1H), 4.72 (d, *J* = 6.8 Hz, 1H), 3.42 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.4, 149.1, 132.8, 130.4, 128.8, 126.6, 126.5, 94.6, 79.0, 56.0, 35.6, 32.2; HRMS (EI) Calcd. $C_{14}H_{20}O_3Na$: 259.1305. Found: 259.1306.

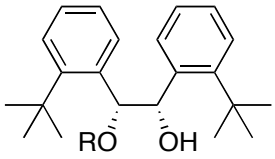
4.12.8.6 (1*S*,2*R*)-1,2-Bis(2-*tert*-butylphenyl)-2-(methoxymethoxy)ethanol (4.16f)



t-BuLi (1.7 M in pentane, 3.33 mL, 8.32 mmol, 4.30 equiv) was added to a solution of 1-(*tert*-butyl)-2-bromobenzene (886 mg, 4.16 mmol, 2.20 equiv) in anhydrous THF (8 mL) at –78 ºC. After 1 h at this temperature, a solution of aldehyde **4.16e** (491 mg, 1.92 mmol, 1.00 equiv) in THF (6 mL) was added. The reaction mixture was allowed to warm to –20 ºC and stirred for 24

h. The reaction mixture was quenched by addition of 10 mL of saturated aqueous NH_4Cl, and the aqueous layer was extracted with ether (2 × 10 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (10% EtOAc/hexanes) to afford 256 mg (33 %) of alcohol **4.16f** as a white solid and after further elution, 394 mg (51%) of diastereomer **4.16g** as a colorless oil. $[\alpha]_D^{25}$ –84.6 (*c* 0.66, $CHCl_3$); IR (neat) 3522, 2957, 1483, 1151, 1048 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.73 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.49 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.42 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.36-7.21 (m, 4H), 5.87 (d, *J* = 8.4 Hz, 1H), 5.67 (dd, *J* = 8.4, 3.2 Hz, 1H), 4.39 (d, *J* = 7.2 Hz, 1H), 4.17 (d, *J* = 7.2 Hz, 1H), 3.48 (d, *J* = 5.6 Hz, 1H), 2.73 (s, 3H), 1.59 (s, 9H), 1.53 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.3, 148.9, 140.9, 139.0, 129.4, 128.7, 128.2, 127.7, 126.7, 126.5, 126.5, 126.0, 92.6, 74.2, 55.0, 36.2, 35.8, 32.9, 32.7; HRMS (EI) Calcd. $C_{13}H_{19}O_2$ (M^+–*t*-Bu-C_6H_4-CHOH): 207.1385. Found: 207.1395.

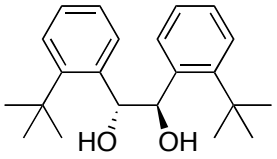
4.12.8.6 (1*R*,2*R*)-1,2-Bis(2-*tert*-butylphenyl)-2-(methoxymethoxy)ethanol (4.16g)



R = MOM

$[\alpha]_D^{25}$ –49.8 (*c* 0.50, $CHCl_3$); IR (neat) 3526, 2957, 1151, 1023 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.87 (d, *J* = 7.6 Hz, 1H), 7.36 (dt, *J* = 8.8, 1.2 Hz, 2H), 7.33-7.20 (m, 5H), 5.85 (d, *J* = 4.0 Hz, 1H), 5.47 (dd, *J* = 5.2, 4.0 Hz, 1H), 4.70 (d, *J* = 6.8 Hz, 1H), 4.66 (d, *J* = 6.8 Hz, 1H), 3.80 (d, *J* = 5.6 Hz, 1H), 3.55 (s, 3H), 1.23 (s, 9H), 1.19 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 141.5, 139.3, 130.3, 129.7, 127.7, 127.7, 126.5, 126.4, 126.3, 126.2, 93.6, 75.8, 73.6, 56.4, 35.7, 35.7, 32.5, 32.4; HRMS (EI) Calcd. $C_{13}H_{19}O_2$ (M^+–*t*-Bu-C_6H_4-CHOH): 207.1385. Found: 207.1386.

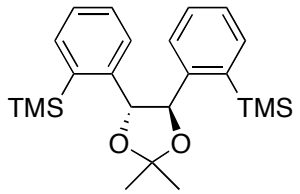
4.12.8.7 (1*R*,2*R*)-1,2-Bis(2-*tert*-butylphenyl)ethane-1,2-diol (4.16)



Concentrated HCl (2.0 mL) was added to a solution of **4.16g** (201 mg, 0.540 mmol) in methanol (15.0 mL) and the mixture was stirred at 60 ºC for 3 h. The volatiles were removed *in vacuo* and the residue was diluted in dichloromethane and washed with saturated aqueous $NaHCO_3$. The organic phase was separated, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to afford an oil, which was purified by flash chromatography (20% EtOAc/hexanes) to afford 142 mg (80%) of diol **4.16** as a white solid. After recrystallization from methanol, 99% *ee* pure product was obtained. $[\alpha]_D^{25}$ +32.9 (*c* 0.33, $CHCl_3$); IR (neat) 3401, 2966, 1482, 1054, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, *J* = 7.6, 1.2 Hz, 2H), 7.37 (dd, *J* = 7.6, 1.2 Hz, 2H), 7.33 (td, *J* = 11.2, 1.2 Hz, 2H), 7.28-7.23 (m, 2H), 5.67 (d, *J* = 6.0 Hz, 2H), 2.99 (d, *J* = 6.0 Hz, 2H), 1.30 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.4, 143.3, 128.9, 128.0, 127.3, 126.1, 72.1, 35.6, 32.6; HRMS (ESI) Calcd. $C_{22}H_{30}O_2Na$: 349.2138. Found: 349.2136. HPLC (Chiralcel OD) 5:95 *i*-PrOH/hexane, 0.5 mL/min, λ = 230 nm, T_{major} = 20.1 min, T_{min} = 25.1 min, 99.1 % ee.

4.12.9 Synthesis of diol 4.17

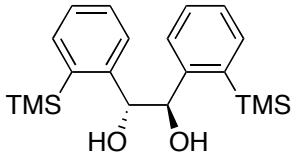
4.12.9.1 (2,2'-(4*R*,5*R*)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl)-bis(2,1phenylene)-bis(trimethylsilane) (4.17a)



Dibromoacetal **4.13b** (0.200 g, 0.485 mmol, 1.00 equiv) was dissolved in freshly distilled THF (5 mL) and cooled to –78 ºC. To this solution was added *t*-BuLi (1.7 M in pentane, 1.70 mL, 2.91 mmol, 6.00 equiv) and the reaction mixture was allowed to stir for 1 h at this temperature. After the elapsed time, TMSCl (0.740 mL, 5.82 mmol, 12.0 equiv) was added to the reaction, and the mixture was brought to room temperature and stirred for 2 h. The reaction was quenched with saturated aqueous NH_4Cl and extracted with ether. The combined organic extracts were

washed with brine and dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography (0-5% EtOAc/hexanes) to afford 190 mg (98% yield) of the desired product **4.17a** as a colorless solid. $[\alpha]_D^{25}$ +44.73 (*c* 1.24, $CHCl_3$); IR (cast film) 3058, 2983, 2953, 1591, 1370, 1250, 1051, 839, 764 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (dd, *J* = 7.6, 0.8 Hz, 2H), 7.49-7.45 (m, 4H), 7.28-7.23 (dt, *J* = 7.2, 0.8 Hz, 2H), 5.34 (s, 2H), 1.73 (s, 6H), 0.10 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.9, 140.2, 134.7, 129.4, 128.2, 127.8, 109.1, 84.1, 27.8, 0.7; (EI) Calcd. $C_{23}H_{34}O_2Si_2$: 398.2. Found: 398.2.

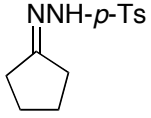
4.12.9.2 (1*R*,2*R*)-1,2-Bis(2-(trimethylsilyl)phenyl)ethane-1,2-diol (4.17)



Acetal **4.17a** (0.210 g, 0.485 mmol) from above was suspended in AcOH/H_2O (5mL/1 mL) and heated to reflux at 100 ºC for 4 h. After the elapsed time, the reaction mixture was poured over ice-cold saturated Na_2CO_3. The resulting mixture was extracted with EtOAc (2 X 50 mL) and the combined organic extract was dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified by flash chromatography to give 150 mg (86% yield) of the desired product **4.17** as a white solid. $[\alpha]_D^{25}$ +43.91 (*c* 0.49, $CHCl_3$); IR (cast film) 3367, 3056, 2953, 2899, 1736, 1252, 840, 756, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 1.5, 6.0 Hz, 2H), 7.26 (dd, *J* = 1.5, 7.5 Hz, 2H), 7.18 (dt, *J* = 1.5, 7.0 Hz, 2H), 7.13 (dt, *J* = 1.5, 6.0 Hz, 2H); 5.13 (s, 2H), 2.67 (br s, 2H), 0.21 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.3, 139.1, 135.3, 129.3, 127.4, 127.2, 76.5, 1.2; HRMS (ESI) Calcd. $C_{20}H_{30}O_2Na_2Si_2$: 381.16766. Found: 381.16744.

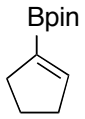
4.12.10 Synthesis of diol 4.18

4.12.10.1 *N*'-Cyclopentylidene-4-methylbenzenesulfonohydrazide (4.18a)



The following procedure is representative for the preparation of cycloalkylhydrazones. Into a 250 mL flask equipped with a magnetic stir-bar was added *p*-tolylsulfonylhydrazine (90.0 g, 0.480 mol, 1.00 equiv) and the solid was suspended in 60 mL of absolute EtOH. To the suspension was added cyclopentanone (40.7 g, 0.480 mol, 1.00 equiv) and the reaction mixture was heated to reflux at 100 ºC. After heating for 20 min, the mixture dissolved and after another 20 min, white solid of the hydrazone started to precipitate. Further heating for 1 h, the reaction mixture was cooled using an ice-water bath to precipitate the majority of the hydrazone. The resulting solid was collected by filtration and was washed thoroughly with ice-cold EtOH (50 mL). Air-drying under reduced pressure for 1 h afforded 114 g of the required hydrazone **4.18a** in near quantitative yield as a white solid with identical spectral and analytical properties in accordance with the literature.[23]

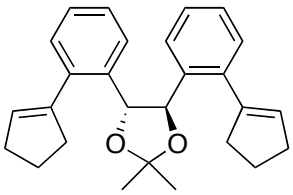
4.12.10.2 2-Cyclopentenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.18b)



The following procedure is representative for the preparation of all cycloalkenyl boronic esters. Into a flame dried 500 mL round bottom flask equipped with a magnetic stir-bar and rubber septum was added cyclopentanone *p*-tolylsulfonylhydrazone **4.18a** (6.48 g, 27.2 mmol, 1.10 equiv) followed by 80 mL of anhydrous hexane. To this mixture was added anhydrous TMEDA (80 mL, ~3mL/mmol of hydrazone) and the reaction mixture was cooled to –78 ºC and maintained at this temperature for 15 min, after which *n*-BuLi (2.5 M in hexane, 43.0 mL, 108 mmol, 4.00 equiv) was added over 15 min. The reaction mixture was stirred for 1 h at –78 ºC and then brought to room temperature and stirred for 1.5 h. Nitrogen slowly evolved from the reaction, and at the end of that period, the reaction mixture was brought to –78 ºC and maintained for another 15 min. Pinacol isopropyl borate (20.1 g, 109 mmol, 4.00 equiv) was added over 15 min. The reaction mixture was stirred for 1 h and subsequently brought to room temperature and stirred for 3 h. The reaction was quenched by addition of saturated NH_4Cl and extracted with Et_2O (2 X 250 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was subjected to flash chromatography (2% EtOAc/hexanes) to afford 4.19 g (80%) of **4.18b** as a light yellow oil. IR (neat) 2979, 1615,

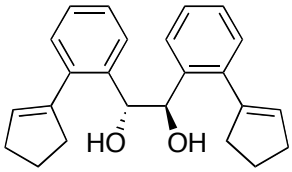
1374, 1318, 1146 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.54 (t, *J* = 2.0 Hz, 1H), 2.48-2.31 (m, 4H), 1.88-1.74 (m, 2H), 1.27 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.5, 83.0, 34.8, 34.5, 24.8, 23.9; HRMS (EI) Calcd. $C_{11}H_{19}O_2B$: 194.1478. Found: 194.1482.

4.12.10.3 (4*R*,5*R*)-4,5-Bis(2-cyclopentenylphenyl)-2,2-dimethyl-1,3-dioxolane (4.18c)



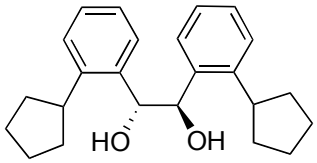
Into a 250 mL round bottom flask equipped with a stir bar was charged cyclopentenylboronate **4.18b** (3.20 g, 16.5 mmol, 3.00 equiv), dibromo-dioxalane **4.13b** (2.27 g, 5.51 mmol, 1.00 equiv), $Pd(OAc)_2$ (126 mg, 0.550 mmol, 0.100 equiv), PPh_3 (720 mg, 2.75 mmol, 0.500 equiv), and K_3PO_4 (7.00 g, 33.0 mmol, 6.00 equiv). To this mixture was added 60 mL of anhydrous dioxane and 6 mL of degassed distilled water. The round bottom flask was then equipped with a condenser and then subjected to three freeze thaw cycle (to remove any dissolved oxygen) and heated at 111 ºC for 2 d. The reaction mixture was brought to room temperature and poured into a 250 mL sepratory funnel and the residue in the flask was further rinsed with Et_2O (100 mL), and transferred into a sepratory funnel. The combined organic layer was then washed with saturated aqueous NH_4Cl (30 mL), separated, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The dark oily residue was purified by flash chromatography (2% EtOAc/hexanes) to afford 2.12 g (100%) of **4.18c** as a light yellow oil. $[\alpha]_D^{25}$ +40.14 (*c* 2.33, $CHCl_3$); IR (neat) 2932, 1234, 1050, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 8.0, 1.2 Hz, 2H), 7.29 (dt, *J* = 7.6, 1.6 Hz, 2H), 7.19 (dt, *J* = 7.6, 1.6 Hz, 2H), 6.99 (ddd, *J* = 7.6, 1.6, 0.4 Hz, 2H), 5.10 (s, 2H), 4.65 (t, *J* = 2.0 Hz, 1H), 2.38-2.27 (m, 2H), 2.27-2.12 (m, 4H), 1.90-1.64 (m, 6H), 1.68 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5, 139.6, 133.5, 129.5, 128.0, 127.5, 127.2, 126.9, 108.6, 82.0, 37.9, 33.5, 27.4, 23.6; HRMS (EI) Calcd. $C_{27}H_{30}O_2$: 386.2246. Found: 386.2251.

4.12.10.4 (1*R*,2*R*)-1,2-Bis(2-cyclopentenylphenyl)ethane-1,2-diol (4.18d)



To a 100 mL round bottom flask equipped with a stir bar was added **4.18c** (2.12 g, 5.49 mmol), chloroacetic acid (6.40 g, 82.3 mmol, 15.0 equiv) and anhydrous MeOH (35 mL). The flask was equipped with a reflux condenser and heated at 95 ºC for 2 d. The solvent was concentrated *in vacuo* and 60 mL of hexanes was added. The organic layer was washed with a 3 M aqueous NaOH solution (2 X 10 mL), brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The yellow residue was purified by flash chromatography (5-15% EtOAc/hexanes) to afford 1.25 g (66%) of diol **4.18d** as a light yellow oil, which was recrystallized from hot hexanes to afford the title compound as a white solid. $[\alpha]_D^{25}$ +141.95 (*c* 1.45, $CHCl_3$); IR (neat) 3340, 2950, 1443, 1038, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (dd, *J* = 8.0, 1.6 Hz, 2H), 7.21 (dt, *J* = 7.6, 1.2 Hz, 2H), 7.14 (dt, *J* = 7.6, 1.6 Hz, 2H), 6.94 (dd, *J* = 8.0, 1.6 Hz, 2H), 5.15 (t, *J* = 2.0 Hz, 1H), 5.13 (s, 2H), 2.87 (s, 2H), 2.52-2.36 (m, 6H), 1.96-1.76 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.2, 139.1, 137.3, 129.5, 128.0, 127.5, 127.4, 126.8, 74.6, 37.7, 33.6, 23.7; HRMS (ESI) Calcd. $C_{24}H_{26}O_2Na$: 369.1825. Found: 369.1827.

4.12.10.5 (1*R*,2*R*)-1,2-Bis(2-cyclopentylphenyl)ethane-1,2-diol (4.18)

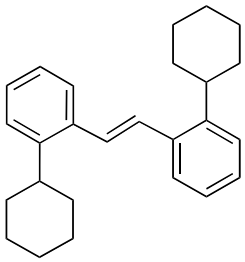


Into a round bottom flask was charged 1.00 g of diol **4.18d**, and absolute EtOH (50 mL). The resulting solution was degassed and purged with argon. At this point, Pd/C (10 wt%, 1.00 g) was carefully added to the reaction flask. (**Caution!! Since this is a high loading of flammable palladium, the addition should take place strictly under argon**). After the completion of addition of Pd/C, the sidewalls of the flask was washed with EtOH (2.0 mL) and the reaction mixture was degassed and purged with hydrogen. This cycle was repeated twice, after which the reaction was let to stir for 10 h at rt. After the elapsed time, the reaction was tested for

completion using ^{1}H NMR of a small aliquot. Once the reaction is judged complete, the reaction mixture was filtered through a pad of Celite and concentrated *in vacuo* and the crude product was purified by flash chromatography (10-20% EtOAc/hexanes) and to give the title compound **4.18** in quantitative yield. $[\alpha]_D^{25}$ +11.70 (*c* 0.53, $CHCl_3$); IR (neat) 3402, 2953, 1448, 1039, 755 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62-7.56 (m, 2H), 7.24-7.16 (m, 4H), 7.16-7.07 (m, 2H), 5.18 (s, 2H), 2.88 (s, 2H), 2.76-2.64 (m, 2H), 2.00-1.89 (m, 2H), 1.79-1.45 (m, 6H), 1.43-1.22 (m, 4H), 1.20-1.06 (m, 2H), 0.92-0.77 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7, 137.5, 128.1, 127.0, 126.1, 125.6, 74.4, 40.5, 36.0, 34.4, 25.9, 25.7; HRMS (ESI) Calcd. $C_{24}H_{30}O_2Na$: 373.2138. Found: 373.2135.

4.12.11 Synthesis of diol 4.19

4.12.11.1 (*E*)-1,2-Bis(2-cyclohexylphenyl)ethene (4.19a)

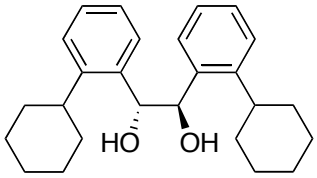


2-Cyclohexyl bromobenzene (2.02 g, 8.40 mmol, 1.00 equiv) was dissolved in THF (10 mL) and cooled to –78 ºC. To the solution was added *t*-BuLi (15.4 mL, 26.2 mmol, 3.0 equiv, 1.7 M in pentane) and the reaction mixture was stirred for 45 min, after which DMF (3.90 mL, 50.7 mmol, 6.0 equiv) was added. The reaction mixture was stirred for 15 min at –78 ºC and then warmed to room temperature and quenched by addition of saturated aqueous NH_4Cl, and extracted with Et_2O (2 X 50 mL). The combined organic extracts were washed with H_2O, brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude aldehyde, which was filtered through a 5 cm length of silica using 10% Et_2O/hexanes as the eluent. The fractions containing the product were combined and the solvent was evaporated *in vacuo* and then high vacuum for 10 min to furnish 2-cyclohexyl-benzaldehyde (in quantitative yield), which was immediately dissolved in THF (20 mL).

Into a round bottom flask equipped with a stir bar and a reflux condenser was added zinc dust (1.73 g, 26.4 mmol, 4.00 equiv) and THF (120 mL). To the suspension was added dropwise

$TiCl_4$ (1.45 mL, 13.2 mmol, 1.50 equiv). The resulting mixture was heated to reflux at 80 ºC for 1 h, after which the flask was lifted from the oil bath. To the reaction mixture was slowly added the THF solution of aldehyde from above. The resulting mixture was heated to reflux for 5 h. After the elapsed time, the mixture was poured into ice-cold 1.0 *N* HCl (50 mL). The product was extracted with CH_2Cl_2 and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product. This residue was dissolved in a minimal amount of CH_2Cl_2 and recrystallized by addition of ice-cold MeOH to furnish 870 mg (60% yield) of the desired product **4.19a** as a white solid. IR (cast film) 3052, 3022, 2926, 2852, 1597, 1449, 967, 757, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (m, 2H), 7.36-7.29 (m, 6H), 7.28-7.26 (m, 2H), 2.99-2.94 (m, 2H), 1.93-1.90 (m, 8H), 1.86-1.81 (m, 2H), 1.51-1.43 (m, 2H), 1.37-1.30 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.4, 136.3, 128.8, 127.8, 126.5, 125.9, 125.7, 40.1, 34.0, 27.1, 26.3; HRMS (EI) Calcd. $C_{26}H_{32}$: 344.25040. Found: 344.25061.

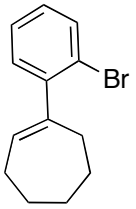
4.12.11.2 (1*R*,2*R*)-1,2-Bis(2-cyclohexylphenyl)ethane-1,2-diol (4.19)



Sharpless asymmetric dihydroxylation of the above stilbene (0.490 g, 1.44 mmol, 1.00 equiv) was carried out under standard conditions using $K_3Fe(CN)_6$ (3.00 equiv), K_2CO_3 (3.00 equiv), $(DHDQ)_2PHAL$ (0.100 equiv) $K_2OsO_2(OH)_4$ (0.0200 equiv), $MeSO_2NH_2$ (1.00 equiv) and afforded 425 mg (86% yield) of the requisite product which was recrystallized from CH_2Cl_2/hexanes to afford 380 mg of the title compound **4.19** as a white solid. $[\alpha]_D^{25}$ +0.64 (*c* 0.75, $CHCl_3$); IR (cast film) 3420, 3055, 3006, 2929, 2852, 1445, 1214, 1030, 761 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 1.6, 8.0 Hz, 2H), 7.24 (dt, *J* = 1.6, 8 Hz, 2H), 7.16 (dt, *J* = 1.6, 7.6 Hz, 2H), 7.00 (dd, *J* = 1.2, 8.0 Hz, 2H), 5.14 (s, 2H), 2.96 (s, 2H), 2.15-2.07 (m, 2H), 1.73-1.60 (m, 6H), 1.49-1.46 (m, 2H), 1.29-0.87 (m, 10H), 0.86-0.18 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.7, 136.6, 129.9, 127.9, 127.1, 125.9, 74.2, 38.8, 35.6, 32.3, 27.1, 26.9, 26.1; HRMS (ESI) Calcd. $C_{26}H_{34}O_2Na$: 401.24516. Found: 401.24510.

4.12.12 Synthesis of diol 4.20

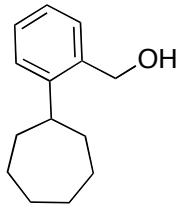
4.12.12.1 1-(2-Bromophenyl)cyclohept-1-ene (4.20a)



Ortho-dibromobenzene (4.82 mL, 40.0 mmol, 1.00 equiv) was dissolved in THF (120 mL) and 120 mL of Et_2O (120 mL). The resulting solution was cooled to –110 ºC, after which *n*BuLi (24.0 mL, 38.5 mmol, 0.960 equiv) was added over 45 min while maintaining the internal temperature below –100 ºC. The resulting solution was stirred for 1 h, after which a solution of cycloheptanone (4.80 g, 38.0 mmol, 0.950 equiv) dissolved in THF (20 mL) was added to the reaction mixture. The reaction mixture was stirred for 1 h at –110 ºC, after whichit was allowed to warm to rt and let to stir overnight. The reaction was quenched by addition of saturated NH_4Cl and extracted with Et_2O (2 X 100 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford the crude tertiary alcohol. At this stage, the product was contaminated with unreacted ortho-dibromobenzene and cycloheptanone, which have a similar polarity. This crude product was passed through a 20 cm silica plug (10% Et_2O/hexanes) and the fractions containing the products were combined and evaporated *in vacuo* (1.0 mm Hg) at 80 ºC. The residue (5.54 g) containing the tertiary alcohol was transferred into a round bottom flask and diluted with anhydrous CH_2Cl_2 (20 mL). To the solution was added TFA (3.16 mL, 41.0 mmol, 1.02 equiv) and Et_3SiH (4.06 mL, 25.4 mmol, 0.635 equiv) and the mixture was stirred for 30 min at room temperature, after which the reaction was quenched by slow addition of solid Na_2CO_3, and then 50 mL of water. The product was extracted with ether and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography (0-2% EtOAc/hexanes) to furnish 4.70 g (45% yield for 2 steps) of the desired product **4.20a** as a colorless oil. IR (cast film) 3052, 2921, 2848, 1465, 1433, 1023, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 1.2, 7.6 Hz, 1H), 7.23 (dt, *J* = 1.2, 7.2 Hz, 1H), 7.16 (dd, *J* = 2, 7.6 Hz, 1H), 7.07 (ddd, *J* = 1.6, 7.2, 9.6 Hz, 1H), 5.81 (t, *J* = 6.4 Hz, 1H), 2.50-2.47 (m, 2H), 2.31-2.27 (m, 2H), 1.86-1.73 (m, 2H), 1.72-1.65 (m, 2H), 1.65-1.60 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$)

δ 147.4, 145.8, 132.6, 132.5, 130.3, 127.8, 127.1, 122.2, 34.6, 32.5, 29.1, 27.1, 27.0; HRMS (EI) Calcd. $C_{13}H_{15}Br$: 252.03366. Found: 252.03464.

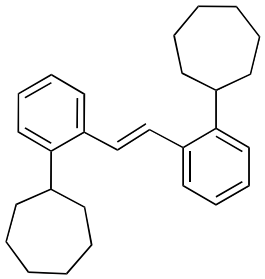
4.12.12.2 (2-Cycloheptylphenyl)methanol (4.20b)



A sample of cycloalkene **4.20a** (1.69 g, 6.76 mmol, 1.00 equiv) from above was dissolved in THF (10 mL) and cooled to –78 ºC. To the solution was added *t*BuLi (11.6 mL, 19.8 mmol, 3.00 equiv, 1.7 M in pentane) and the reaction mixture was allowed to stir for 45 min after which DMF (2.90 mL, 38.3 mmol, 6.00 equiv) was added in one portion. The reaction mixture was stirred for 15 min, after which it was allowed to warm to room temperature. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl, washed with water and the product was extracted with Et_2O (2 X 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The resulting aldehyde was passed through a 10 cm plug of silica using 10% Et_2O/hexanes as the eluent. The fractions containing the product were combined and concentrated *in vacuo* to give 1.30 g (95%) of aldehyde, which was immediately dissolved in absolute EtOH (20 mL).

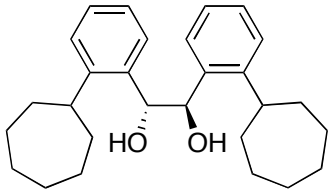
The solution was degassed and purged with argon using a freeze-thaw cycle. To the above solution was carefully added 260 mg Pd/C (10 wt%). The reaction mixture was stirred for 5 h after which, ^{1}H-NMR of the aliquot showed complete conversion to the desired product. Accordingly, the reaction mixture was then filtered through Celite (4 cm) and the Celite was rinsed with CH_2Cl_2 (50 mL). The filtrate was concentrated *in vacuo* and the residue was purified by flash chromatography (0-20% EtOAc/hexanes) to give 1.10 g (87% yield for 2 steps) of the desired product **4.20b** as a viscous oil. IR (cast film) 3307, 3062, 2924, 2854, 1488, 1451, 1007, 753 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.33 (m, 1H), 7.30-7.28 (m, 2H), 7.20-7.16 (m, 1H), 7.45 (s, 2H), 3.04-2.97 (m, 1H), 1.93-1.56 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 136.7, 128.4, 128.3, 126.5, 125.6, 63.4, 41.2, 36.8, 27.9, 27.7; HRMS (EI) Calcd. $C_{17}H_{20}O$: 204.15141. Found: 204.15196.

4.12.12.3 (*E*)-1,2-Bis(2-cycloheptylphenyl)ethane (4.20c)



A sample of alcohol **4.20b** (0.630 g, 3.09 mmol, 1.00 equiv) was dissolved in CH_2Cl_2 (10 mL) and to the solution was added 1.55 g of 4Å molecular sieves. To the reaction was added pyridinium chlorochromate (1.00 g, 4.60 mmol, 1.50 equiv) and the reaction mixture was stirred for 30 min after which TLC indicated complete conversion to the aldehyde. The reaction mixture was passed through 5 cm of silica gel (placed in a sintered glass funnel) and the silica was washed with additional CH_2Cl_2 (20 mL). The combined CH_2Cl_2 solution was then concentrated to 5 mL volume and passed through 20 cm silica gel and the product was eluted with 10% Et_2O/hexanes. The fractions containing the product were combined and concentrated *in vacuo* to give 590 mg (95% yield) of the desired product which was dissolved in THF (10 mL) and slowly added to a Zn/Ti couple derived from $TiCl_4$ (0.460 mL, 4.10 mmol, 1.5 equiv) and zinc dust (779 mg, 8.20 mmol, 4.0 equiv) in 30 mL of THF. The resulting mixture was heated to reflux at 80 ºC for 5 h and then poured over ice-cold 1.0 *N* HCl (20 mL), and the product was extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was recrystallized from CH_2Cl_2/MeOH to furnish 380 mg of the stilbene product, which was dissolved in 25 mL of xylenes. To the solution was added a small crystal of iodine and the reaction mixture was heated to reflux (160 ºC) for 15 h after which, the reaction mixture was brought to room temperature followed by evaporation of the solvent was evaporated *in vacuo*. The product was purified by recrystallization from CH_2Cl_2/MeOH to furnish 350 mg (64% yield) of the desired stilbene **4.20c** as a white solid. IR (cast film) 3060, 2924, 2854, 1597, 1485, 1458, 975, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.58-7.56 (dd, J = 1.2, 7.2 Hz), 7.31-7.29 (m, 4H), 7.29 (s, 2H), 7.26-7.22 (m, 2H); 3.14-3.09 (m, 2H), 2.20-1.95 (m, 4H), 1.89-1.83 (m, 4H), 1.75-1.58 (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.5, 135.7, 129.0, 127.8, 126.5, 126.1, 125.7, 42.0, 36.2, 28.0, 27.6; HRMS (EI) Calcd. $C_{28}H_{36}$: 372.28171. Found: 372.28133.

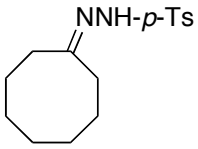
4.12.12.4 (1*R*,2*R*)-1,2-Bis(2-cycloheptylphenyl)ethane-1,2-diol (4.20)



Sharpless asymmetric dihydroxylation of the above stilbene (0.600 g, 1.61 mmol, 1.00 equiv) under standard conditions using $K_3Fe(CN)_6$ (3.00 equiv), K_2CO_3 (3.00 equiv), $(DHDQ)_2PHAL$ (0.125 equiv) $K_2OsO_2(OH)_4$ (0.0250 equiv), $MeSO_2NH_2$ (1.00 equiv) afforded 623 mg (95% yield) of the requisite product, which was further recrystallized from CCl_4 to afford the title compound as a white solid. $[\alpha]_D^{25}$ –7.65 (*c* 0.52, $CHCl_3$); IR (cast film) 3539, 3339, 3058, 2923, 2853, 1487, 1458, 1034, 759, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (dd, *J* = 1.2, 7.6 Hz, 2H), 7.22 (dt, *J* = 1.6, 7.6 Hz, 2H), 7.16 (dt, *J* = 1.6, 7.6 Hz, 2H), 7.01 (dd, *J* = 1.2, 7.6 Hz, 2H), 5.13 (s, 2H), 3.00 (br s, 2H), 2.34-2.28 (m, 2H), 1.73-1.33 (m, 20H), 1.27-1.21 (m, 2H), 1.05-0.95 (m, 2H), 0.52-0.48 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 1470.8, 135.9, 128.0, 127.0, 126.1, 125.8, 74.3, 40.7, 38.3, 34.7, 27.6, 27.5, 27.3, 27.2; HRMS (EI) Calcd. $C_{28}H_{38}O_2$: 406.28717. Found: 406.28703.

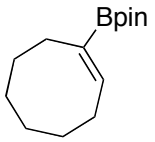
4.12.13 Synthesis of diol 4.21 (Vivol)

4.12.13.1 *N*'-Cyclooctylidene-4-methylbenzenesulfonohydrazide (4.21a)



Following the general procedure used in the preparation of **4.18a**, the product was isolated in quantitative yield as a white solid. IR (neat) 3214, 2926, 1330, 1160 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.4 Hz, 2H), 7.88-7.56 (s, 1H), 7.28 (d, *J* = 8.4 Hz, 2H), 2.40 (s, 3H), 2.28 (t, *J* = 6.4 Hz, 2H), 2.22 (t, *J* = 6.4 Hz, 2H), 1.70-1.60 (m, 4H), 1.42-1.31 (m, 4H), 1.21-1.12 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 143.9, 135.9, 129.4, 127.9, 35.5, 30.5, 28.3, 27.6, 27.5, 24.5, 23.5, 22.9, 21.5; HRMS (EI) Calcd. $C_{15}H_{23}N_2O_2S$: 295.1475. Found: 295.1475.

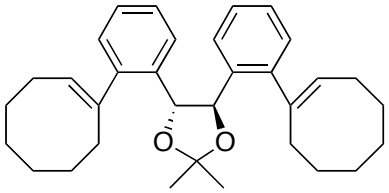
4.12.13.2 2-Cyclopentenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 4.20a



For large-scale reactions, i.e. >50 mmol scale, the cyclooctenyl boronic acid was prepared following the procedure below.

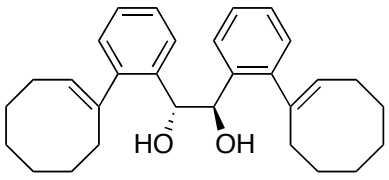
Into a flame dried 1 L round bottom flask equipped with a stir bar and rubber septum was added hydrazone **4.20a** (22.0 g, 74.7 mmol, 1.00 equiv) and added 200 mL of anhydrous hexane under argon. To this mixture was added anhydrous TMEDA (200 mL, ~ 3mL/mmol of hydrazone) and the reaction mixture was cooled to –78 ºC and maintained at this temperature for 15 min, after which *n*-BuLi (2.5 M, 120 mL, 300 mmol, 4.00 equiv) was added over 20 min. The reaction mixture was stirred for 1 h at –78 ºC and then brought to room temperature and stirred for another 1 h. Nitrogen was evolved and at the end of the 1 h time period, the reaction mixture was cooled to –78 ºC and maintained for another 15 min. Triisopropyl borate (51.5 mL, 224 mmol, 3.00 equiv) was added. The reaction mixture was stirred for another h at –78 ºC and then brought to room temperature, and stirred for 2h. The reaction was carefully poured over ice cold 6 *N* HCl (350 mL) and acidified to PH = 4. The organic layer was separated and concentrated to a volume of about 200 mL and transferred to a sepratory funnel and extracted with aqueous NaOH (4 M, 2 X 40 mL). The combined aqueous layer was acidified to pH = 4 by adding concentrated HCl at 0 ºC and the mixture was extracted with hexanes (3 X 80 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated to about 100 mL *in vacuo*. The flask was stored at room temperature for 14 h and filtered. The filtrate was evaporated *in vacuo* to afford 8.13 g (71%) of the desired product as a light yellow solid in > 95% purity. The product was characterized as its corresponding pinacol ester. IR (cast film) 2925, 1630, 1381, 1148 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.58 (t, *J* = 8.0 Hz, 1H), 2.32-2.28 (m, 2H), 2.28-2.19 (m, 2H), 1.56-1.41 (m, 8H), 1.26 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.1, 114.3, 82.9, 29.6, 28.8, 26.4, 26.2, 25.9, 24.7; HRMS (EI) Calcd. $C_{14}H_{25}O_2B$: 236.1948. Found: 236.1946.

4.12.13.3 (4*R*,5*R*)-4,5-Bis(2-(*E*)-cyclooctenylphenyl)-2,2-dimethyl-1,3-dioxolane (4.21c)



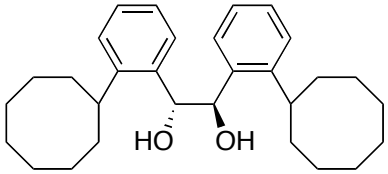
Into a 250 mL round bottom flask equipped with a stir bar was charged the crude cyclooctenylboronic acid **4.21b** (9.01 g, 58.5 mmol, 2.50 equiv), dioxolane **4.13b** (9.64 g, 23.4 mmol, 1.00 equiv), $Pd(PPh_3)_2Cl_2$ (821 mg, 1.17 mmol, 0.0500 equiv), PPh_3 (613 mg, 2.75 mmol, 0.100 equiv), and degassed 4.0 M aqueous K_2CO_3 (17.0 mL, 68.0 mmol, 3.00 equiv). To this mixture was added anhydrous dioxane (170 mL). The round bottom flask was equipped with a condenser and then subjected to a three freeze-thaw cycle (to remove any dissolved oxygen) and heated at 111 ºC for 30 h. The reaction mixture was brought to room temperature and poured into a 500 mL sepratory funnel. The residue in the flask was further washed with Et_2O (150 mL), and transferred into the seperatory funnel. The combined organic layer were washed with saturated aqueous NH_4Cl (60 mL), and then dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The dark residue was purified by flash chromatography (2% EtOAc/hexanes) to afford 10.7 g (97%) of **4.21c** as a light yellow oil, which was recrystallized from hot methanol. $[\alpha]_D^{25}$ +82.65 (*c* 0.65, $CHCl_3$); IR (neat) 2924, 1233, 1047, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 6.4, 1.2 Hz, 2H), 7.26 (dt, *J* = 6.0, 1.2 Hz, 2H), 7.14 (dt, *J* = 6.0, 1.2 Hz, 2H), 6.90 (dd, *J* = 6.0, 1.2 Hz, 2H), 5.03 (s, 2H), 4.51 (s, 2H), 2.18-1.98 (m, 4H), 1.96-1.86 (m, 2H), 1.81-1.72 (m, 2H), 1.66 (s, 6H), 1.54-1.42 (m, 10H), 1.44-1.33 (m, 4H), 1.32-1.23 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.3, 139.1, 133.1, 130.0, 128.7, 127.4, 127.3, 126.7, 108.6, 82.2, 31.16, 29.9, 27.8, 27.5, 27.1, 26.7, 26.4; HRMS (EI) Calcd. $C_{33}H_{42}O_2$: 470.3185. Found: 470.3181.

4.12.13.4 (1*R*,2*R*)-1,2-Bis(2-(*E*)-cyclooctenylphenyl)ethane-1,2-diol (4.21d)



Into a 250 mL round bottom flask equipped with a stir bar was added acetal **4.21c** (5.00 g, 10.6 mmol, 1.00 equiv), chloroacetic acid (20.0 g, 212 mmol, 20.0 equiv) and of anhydrous MeOH (70 mL). The flask was then equipped with a reflux condenser and then heated at 95 ºC for 4 d. The solvent was evaporated *in vacuo* and hexanes (120 mL) was added. The organic layer was washed with 3 M aqueous NaOH solution (2 X 15 mL), brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The yellow residue was purified by flash chromatography (5-12% EtOAc/hexanes) to afford 3.36 g (74%) of diol **4.21d** as light yellow oil, which was further recrystallized from hot hexanes to afford the title compound as a white amorphous solid. $[\alpha]_D^{25}$ +138.6 (*c* 0.58, $CHCl_3$); IR (neat) 3400, 2924, 1446, 1046, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 8.0, 1.2 Hz, 2H), 7.19 (dt, *J* = 7.6, 1.2 Hz, 2H), 7.10 (dt, *J* = 7.6, 1.2 Hz, 2H), 6.86 (dd, *J* = 7.6, 1.2 Hz, 2H), 4.97 (s, 2H), 4.74 (t, *J* = 8.0 Hz, 1H), 2.80 (s, 2H), 2.38-2.22 (m, 2H), 2.20-2.05 (m, 4H), 2.04-1.95 (m, 2H), 1.62-1.31 (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9, 139.8, 136.7, 129.9, 128.8, 127.8, 127.3, 126.6, 74.8, 31.3, 29.9, 28.1, 26.9, 26.6, 26.4; HRMS (EI) Calcd. for $C_{30}H_{38}O_2$: 430.2872. Found: 430.2864. Anal. Calcd for $C_{30}H_{38}O_2$: C, 83.72; H, 8.89. Found: C, 83.41; H, 9.20.

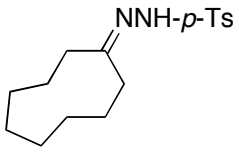
4.12.13.5 (1*R*,2*R*)-1,2-Bis(2-cyclooctylphenyl)ethane-1,2-diol (4.21)



Following the procedure used in the preparation of **4.18**, the title compound was obtained as a white amorphous solid in >99% yield after flash chromatography. $[\alpha]_D^{25}$ –7.48 (*c* 0.46, $CHCl_3$); IR (neat) 3378, 2921, 1446, 1033, 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 7.6, 1.6 Hz, 2H), 7.21 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.19 (d, *J* = 2.0 Hz, 1H), 7.18 (d, *J* = 1.6 Hz, 1H), 7.15 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.01 (dd, *J* = 7.6, 1.6 Hz, 2H), 5.16 (s, 2H), 3.23-2.60 (br s, 2H), 2.50-2.38 (m, 2H), 1.72-1.24 (m, 24H), 1.18-0.95 (m, 2H), 0.56-0.45 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 135.9, 128.0, 127.1, 126.5, 125.9, 74.3, 38.9, 35.5, 33.1, 27.2, 26.7, 26.1, 25.8, 25.6; HRMS (EI) Calcd. $C_{30}H_{42}O_2$: 434.3185. Found: 434.3171.

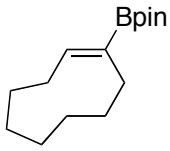
4.12.14 Synthesis of diol 4.22

4.12.14.1 *N*'-Cyclononylidene-4-methylbenzenesulfonohydrazide (4.22a)



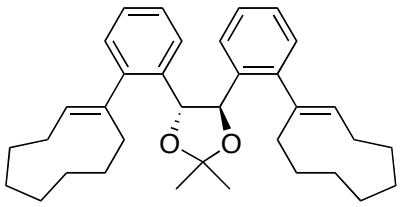
Following the procedure used in the preparation of **4.18a**, the title compound was obtained as a white crystalline solid in quantitative yield. IR (cast film) 3224, 2924, 2865, 1338, 1185, 1167 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.4 Hz, 2H), 2.41 (s, 3H), 2.31-2.28 (m, 2H), 2.23-2.20 (m, 2H), 1.72-1.60 (m, 4H), 1.55-1.49 (m, 2H), 1.47-1.41 (m, 2H), 1.29 (d, *J* = 8 Hz, 2H), 1.22-1.16 (m, 2H), 1.08-1.03 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 143.9, 135.9, 129.4, 127.9, 35.5, 30.5, 28.3, 27.6, 27.5, 24.5, 23.5, 22.9, 21.5; HRMS (EI) Calcd. $C_{16}H_{24}N_2O_2S$: 308.15585. Found: 308.15596.

4.12.14.2 2-Cyclononenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.22b)



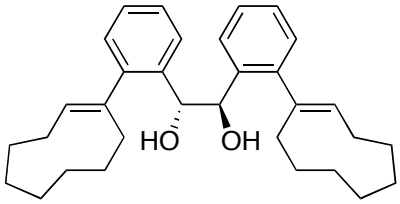
Following the procedure used in the preparation of **4.18b**, the product was obtained in 70% yield as a colorless oil. IR (cast film) 2977, 2928, 2857, 1629, 1379, 1146 1167 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.48 (t, *J* = 8.4 Hz, 1H), 2.29-2.20 (m, 4H), 1.49-1.43 (m, 10H), 1.25 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.9, 82.9, 27.4, 26.9, 26.5, 25.8, 25.6, 25.4, 24.8, 24.7, 24.6; HRMS (EI) Calcd. $C_{15}H_{27}O_2B$: 250.21041. Found: 250.11952.

4.12.14.3 (4*R*,5*R*)-4,5-Bis(2-(*E*)-cyclononenylphenyl)-2,2-dimethyl-1,3-dioxolane (4.22c)



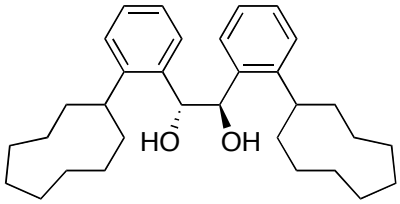
Following the procedure used in the preparation of **4.18c**, the title compound was obtained in quantitative yield as a viscous oil. $[\alpha]_D^{25}$ +74.43 (*c* 0.3, $CHCl_3$); IR (cast film) 3061, 2928, 2852, 1477, 1445, 1378, 1233, 1046, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 6.0 Hz, 2H), 7.26 (dt, *J* = 5.2, 0.8 Hz, 2H), 7.15 (dt, *J* = 6.0, 0.8 Hz, 2H), 6.94 (dd, *J* = 6.0, 1.2 Hz, 2H), 5.06 (s, 2H), 4.48 (br s, 2H), 2.11-2.05 (m, 4H), 1.99-1.93 (m, 2H), 1.79-1.72 (m, 2H), 1.66 (s, 6H), 1.56-1.46 (m, 14H), 1.41-1.34 (m, 4H), 1.26-1.20 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.5, 138.7, 133.1, 131.0, 128.8, 127.4, 127.3, 126.7, 108.6, 82.1, 31.6, 27.4, 26.8, 26.0, 25.8, 25.4, 24.9, 24.4; HRMS (EI) Calcd. $C_{35}H_{46}O_2$: 498.34978. Found: 498.35083.

4.12.14.4 (1*R*,2*R*)-1,2-Bis(2-(*E*)-cyclononenylphenyl)ethane-1,2-diol (4.22d)



Acetal **4.22c** was suspended in a 8:1:1 mixture of AcOH, MeOH and H_2O. The mixture was then heated to 100 ºC for 5 h, and the resulting mixture was slowly poured over ice-cold saturated solution of Na_2CO_3. The resulting mixture was extracted with EtOAc (3 x 50 mL) and washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (1-10% EtOAc/hexanes) afforded the title compound as a white solid. $[\alpha]_D^{25}$ +108.85 (*c* 0.87, $CHCl_3$); IR (cast film) 3375, 3061, 2927, 2852, 1474, 1445, 1046, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 8.0, 1.6 Hz, 2H), 7.18 (dt, *J* = 7.6, 2.0 Hz, 2H), 7.10 (dt, *J* = 7.6, 2.0 Hz, 2H), 6.91 (dd, *J* = 7.6, 1.2 Hz, 2H), 4.99 (s, 2H), 4.68 (br s, 2H), 2.80 (br s, 2H), 2.35-2.26 (m, 2H), 2.20-2.17 (m, 4H), 2.05-2.00 (m, 2H), 1.67-1.36 (m, 18H), 1.31-1.21 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.1, 139.4, 136.7, 131.1, 129.0, 127.8, 127.3, 126.5, 74.6, 32.1, 26.8, 26.1, 26.3, 25.1, 24.6; (ESI) Calcd. $C_{32}H_{42}O_2Na$: 481.30770. Found: 481.30884.

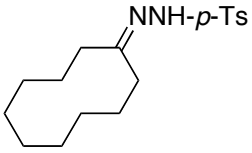
4.12.14.5 (*R*, *R*)-1,2-Bis-(2-cyclononenyl-phenyl)-ethane-1,2-diol (4.22)



Following the procedure used in the preparation of **4.18**, the title compound was obtained in 95% yield as a white amorphous solid. $[\alpha]_D^{25}$ –5.55 (*c* 0.24, $CHCl_3$); IR (cast film) 3513, 3329, 2926, 2849, 1479, 1445, 1035, 1005, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 6.8, 2.0 Hz, 2H), 7.19 (m, 4H), 7.04 (dd, *J* = 8.4, 1.6 Hz, 2H), 5.30 (s, 2H), 2.93 (s, 2H), 2.62-2.61 (m, 2H), 1.64-1.42 (m, 28 H), 1.27-1.09 (m, 2H), 0.76-0.70 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.0, 136.2, 127.9, 127.0, 126.9, 125.9, 74.2, 37.1, 33.6, 32.2, 26.4, 26.1, 25.7, 24.8, 24.6, 24.4; HRMS (EI) Calcd. $[M-H_2O]^+$: 444.33920. Found: 444.33923.

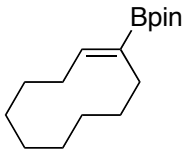
4.12.15 Synthesis of diol 4.23

4.12.15.1 *N*'-Cyclodecylidene-4-methylbenzenesulfonohydrazide (4.23a)



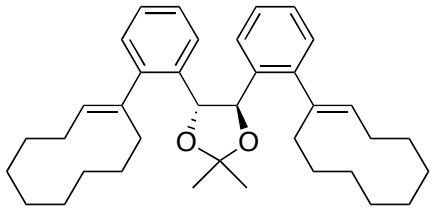
Following the procedure used in the preparation of **4.18a**, the product was isolated in quantitative yield as a white crystalline solid. IR (cast film) 3219, 2927, 2869, 1598, 1335, 1167 cm^1; ^1H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.4 Hz, 2H), 7.46 (br s, 1H), 7.30 (d, *J* = 8.4 Hz, 2H), 2.41 (s, 3H), 2.34 (app t, *J* = 6.3 Hz, 2H), 2.21 (app t, *J* = 6.6 Hz, 2H), 1.70-1.62 (m, 4H), 1.32-1.08 (m, 8H), 1.03-1.01 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 143.8, 135.7, 129.4, 128.2, 42.0, 35.0, 30.1, 25.5, 25.2, 24.0, 23.8, 23.3, 22.8, 22.6; HRMS (EI) Calcd. $C_{17}H_{27}N_2O_2S$: 323.17878. Found: 323.17850.

4.12.15.2 2-Cyclodecenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.23b)



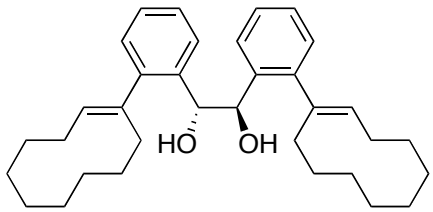
Following the procedure used in the preparation of **4.18b**, the product was isolated in 90% yield as a colorless oil. IR (cast film) 2978, 2926, 2852, 1626, 1475, 1380, 1348, 1302, 1146 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.33 (t, *J* = 8.8 Hz), 2.35-2.31 (m, 4H), 1.60-1.57 (m, 4H), 1.40-1.37 (m, 8H), 1.25 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.9, 82.8, 27.0, 26.9, 26.8, 26.4, 25.6, 24.8, 24.7, 21.4, 20.8; HRMS (EI) Calcd. $C_{16}H_{29}O_2B$: 264.22606. Found: 264.22591.

4.12.15.3 (4*R*,5*R*)-4,5-Bis(2-(*E*)-cyclodecenylphenyl)-2,2-dimethyl-1,3-dioxolane (4.23c)



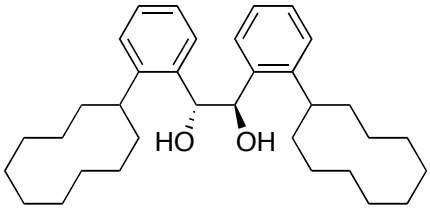
Following the procedure used in the preparation of **4.18c**, the product was isolated in 95% yield. $[\alpha]_D^{25}$ +100.69 (*c* 0.3, $CHCl_3$); IR (cast film) 3060, 2985, 2924, 2850, 1475, 1441, 1370, 1234, 1046, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 0.9, 7.8 Hz, 2H), 7.26 (dt, *J* = 8.4, 1.5 Hz, 2H), 7.14 (dt, *J* = 7.5, 1.5 Hz, 2H), 6.97 (dd, *J* = 7.8, 1.5 Hz, 2H), 5.11 (s, 2H), 4.33 (br s, 2H), 2.21-2.12 (m, 4H), 1.86 (br s, 2H), 1.65 (s, 6H), 1.53-1.09 (m, 24H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.6, 137.9, 133.3, 131.7, 128.9, 127.7, 127.3, 126.8, 108.6, 81.9, 29.2, 27.7, 27.6, 27.5, 27.1, 24.9, 24.5, 21.2, 21.2; HRMS (EI) Calcd. $C_{37}H_{50}O_2$: 526.38108. Found: 526.38089.

4.12.15.4 (1*R*,2*R*)-1,2-Bis(2-(*E*)-cyclodecenylphenyl)ethane-1,2-diol (4.23d)



Acetal **4.23c** was suspended in 8:1:1 mixture of AcOH, MeOH and H_2O. The mixture was then heated at 100 ºC for 5 h, and the resulting mixture was slowly poured over ice-cold Na_2CO_3. The resulting mixture was extracted with EtOAc (3 × 50 mL), washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification by flash chromatography (1-10% EtOAc/Hexanes) afforded the title compound as a white solid in 65% yield. $[\alpha]_D^{25}$ +117.40 (*c* 0.50, $CHCl_3$); IR (cast film) 3429, 3061, 2920, 2849, 1475, 1440, 1215, 996, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 10.4, 1.6 Hz, 2H), 7.38 (dt, *J* = 9.6, 2.0 Hz, 2H), 7.11 (dt, *J* = 10.0, 2.0 Hz, 2H), 6.95 (dd, *J* = 10, 1.6 Hz, 2H), 5.03 (s, 2H), 4.55 (br s, 2H), 2.80 (s, 2H), 2.47-2.46 (m, 3H), 2.22-2.04 (m, 4H), 1.57-1.22 (m, 25H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.1, 138.5, 137.0, 132.1, 129.3, 127.8, 127.3, 126.5, 74.4, 29.1, 28.1, 27.9, 27.3, 24.6, 24.3, 21.2, 21.1; (EI) Calcd. $[C_{34}H_{46}O_2\text{-}H_2O]^+$: 465.34705. Found: 469.34946.

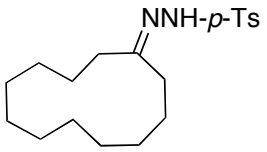
4.12.15.5 (1*R*,2*R*)-1,2-Bis(2-cyclodecylphenyl)ethane-1,2-diol (4.23)



Following the general procedure used in the preparation of **4.18**, the title compound was obtained in quantitative yield a white amorphous soild. $[\alpha]_D^{25}$ –14.13 (*c* 0.39, $CHCl_3$); IR (cast film) 3848, 3317, 2929, 2861, 1477, 1446, 1027, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (dd, *J* = 2.0, 8.0 Hz, 2H), 7.23-7.15 (m, 4H), 7.06 (dd, *J* = 1.2, 7.2 Hz, 2H), 5.10 (s, 2H), 2.86 (br s, 2H), 2.07-2.65 (m, 2H), 1.71-1.17 (m, 34H), 0.65-0.59 (m, 2H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 146.9, 136.6, 130.5, 127.8, 126.9, 126.0, 74.1, 36.9, 32.2, 31.4, 26.0, 25.1, 25.0, 24.9, 24.7, 24.0, 23.8; HRMS (EI) Calcd. $C_{34}H_{50}O_2$: 490.38107. Found: 490.38099.

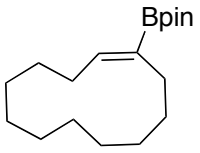
4.12.16 Synthesis of diol 4.24

4.12.16.1 *N*'-Cyclododecylidene-4-methylbenzenesulfonohydrazide (4.24a)



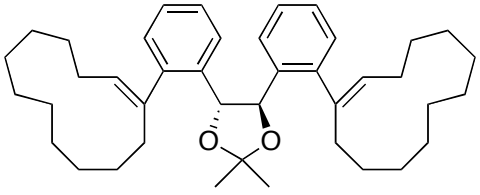
Following the procedure used in the preparation of **4.18a**, the title compound was isolated in quantitative yield as a crystalline white solid. IR (cast film) 2978, 2929, 2860, 1625, 1468, 1409, 1147 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.8 Hz, 2H), 7.47 (br s, 1H), 7.28 (d, *J* = 8.8 Hz, 2H), 2.40 (s, 3H), 2.21 (app t, *J* = 8 Hz, 2H), 2.12 (app t, *J* = 8.8 Hz, 2H), 1.65-1.57 (m, 2H), 1.49-1.41 (m, 2H), 1.15-1.08 (m, 8H), 0.95-0.80 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 143.8, 135.7, 129.5, 128.2, 31.3, 28.8, 25.9, 25.9, 23.7, 23.2, 23.0, 22.7, 22.6, 21.9, 21.6, 21.5; HRMS (EI) Calcd. $C_{19}H_{30}N_2O_2S$: 350.20280. Found: 350.20289.

4.12.16.2 2-Cyclododecenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.24b)



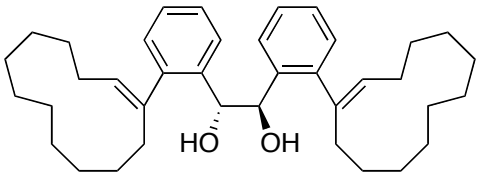
Following the procedure used in the preparation of **4.18b**, the title compound was isolated in 95% yield as a colorless oil. IR (cast film) 2977, 2928, 2859, 1625, 1468, 1408, 1379, 1344, 1301, 1147 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.28 (t, *J* = 6 Hz, 1H), 2.22-2.16 (m, 4H), 1.54-1.47 (m, 4H), 1.41-1.34 (m, 8H), 1.30-1.29 (m, 4H), 1.26 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.7, 132.6, 82.9, 34.6, 31.7, 27.4, 26.5, 25.5, 24.9, 24.2, 22.7, 22.5, 14.0, 11.0; HRMS (EI) Calcd. $C_{18}H_{33}O_2B$: 292.25736. Found: 292.25804.

4.12.16.3 (4*R*,5*R*)-4,5-Bis(2-(*E*)-cyclododecenylphenyl)-2,2-dimethyl-1,3-dioxolane (4.24c)



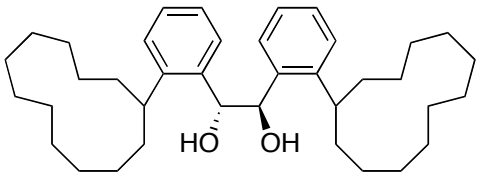
Following the general procedure used in the preparation of **4.18c**, the title compound was obtained in quantitative yield as a colorless viscous oil, which was recrystallized from methanol to give the title product as a white solid. $[\alpha]_D^{25}$ +118.99 (*c* 0.26, $CHCl_3$); IR (cast film) 3060, 2981, 2928, 2857, 1485, 1468, 1378, 1233, 1043, 899, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 8.0 Hz, 2H), 7.25 (dt, *J* = 8.0, 1.2 Hz, 2H), 7.14 (dt, *J* = 7.6, 1.2 Hz, 2H), 6.91 (dd, *J* = 7.6, 1.6 Hz, 2H), 5.15 (s, 2H), 4.49 (br s, 2H), 2.16-2.05 (m, 6H), 1.82-1.81 (m, 4H), 1.65 (s, 6H), 1.44-1.07 (m, 32H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9, 138.9, 133.6, 131.5, 129.5, 127.8, 127.2, 126.8, 108.6, 81.8, 28.9, 27.69, 27.2, 25.4, 25.3, 25.3, 25.2, 25.1, 24.9, 23.0, 22.9 ; HRMS (EI) Calcd. $C_{41}H_{59}O_2$: 582.44368. Found: 582.44402.

4.12.16.4 (1*R*,2*R*)-1,2-Bis(2-(*E*)-cyclododecenylphenyl)ethane-1,2-diol (4.24d)



Following the general procedure used in the preparation of **4.18d**, the title compound was obtained in 60% yield. $[\alpha]_D^{25}$ +102.25 (*c* 0.64, $CHCl_3$); IR (neat) 3353, 2926, 2856, 1727, 1467, 1444, 1049, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 7.5, 1.6 Hz, 2H), 7.19 (dt, *J* = 10, 2.0 Hz, 2H), 7.11 (dt, *J* = 10, 2.0 Hz, 2H), 6.86 (dd, *J* = 10, 1.6 Hz, 2H), 5.02 (s, 2H), 4.56 (br s, 2H), 2.79 (s, 2H), 2.43-1.93 (m, 8H), 1.53-1.21 (m, 32H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.2, 139.8, 137.7, 132.0, 130.0, 127.7, 127.2, 126.6, 74.4, 28.9, 27.2, 25.5, 25.2, 25.2, 25.1, 25.0, 24.6, 23.0, 22.7; HRMS (EI) Calcd. $C_{39}H_{54}O_2$: 542.41235. Found**:** 542.41193.

4.12.16.5 (*R*, *R*)-1,2-Bis-(2-cyclododecyl-phenyl)-ethane-1,2-diol (4.24)

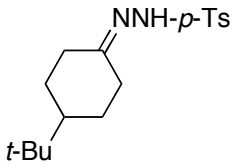


Following the procedure used in the preparation of **4.18**, the title compound was obtained in quantitative yield as a white solid. $[\alpha]_D^{25}$ –5.73 (*c* 0.45, $CHCl_3$); IR (cast film) 3382, 2936, 2861, 1470, 1445, 1040, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 8.0, 2.5 Hz, 2H), 7.19

(dt, *J* = 7.0, 1.5 Hz, 2H), 7.16 (dt, *J* = 7.5, 2.0 Hz, 2H), 7.06 (dd, *J* = 7.5, 1.5 Hz, 2H), 5.20 (s, 2H), 2.89 (s, 2H), 2.68-2.63 (m, 2H), 1.58-1.04 (m, 42H), 0.84-0.79 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2, 137.5, 127.7, 126.9, 126.8, 126.0, 73.6, 35.1, 30.9, 29.3, 24.9, 24.6, 24.5, 23.6, 23.5, 23.2, 23.0, 22.6, 21.3; HRMS (EI) Calcd. $[C_{38}H_{58}O_2–H_2O]^+$: 528.43311. Found: 528.43336.

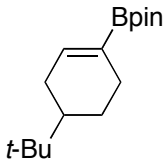
4.12.17 Synthesis of diol 4.25

4.12.17.1 *N*'-(4-*tert*-Butylcyclohexylidene)-4-methylbenzenesulfonohydrazide (4.25a)



Following the procedure used in the preparation of **4.18a**, the product was obtained in 90% yield as a white solid. IR (cast film) 3221, 2955, 2868, 1643, 1598, 1395, 1327, 1164 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.4 Hz, 2H), 7.36 (br s, 1H), 7.31 (d, *J* = 8.4 Hz, 2H), 2.72-2.68 (m, 1H), 2.49-2.44 (m, 1H), 2.43 (s, 3H), 2.06 (ddd, *J* = 4.8, 12.4, 12.4 Hz, 1H), 1.92-1.87 (m, 2H), 1.75 (ddd, *J* = 5.2, 13.6, 13.6, 1H), 1.23-1.03 (m, 3H), 0.84 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 145.2, 143.9, 135.4, 129.5, 128.5, 128.1, 126.6, 126.4, 43.1, 35.0, 33.9, 32.8, 26.7, 21.6; HRMS (EI) Calcd. $C_{17}H_{27}N_2O_2S$: 323.17878. Found: 323.17876.

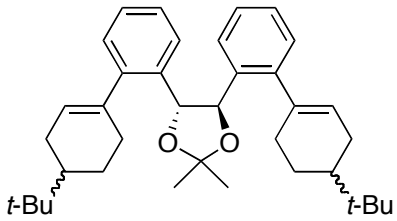
4.12.17.2 2-(4-*tert*-Butylcyclohex-1-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.25b)



Following the procedure used in the preparation of **4.18b**, the title compound was obtained in 75% yield as a pale yellow solid. IR (cast film) 3026, 2978, 2924, 1633, 1387, 1340, 1314, 1146, cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.19 (m, 5H), 6.72-6.70 (m, 1H), 2.85-2.77 (m, 1H), 2.48-2.37 (m, 2H), 2.34-2.21 (m, 2H), 2.01-1.97 (m, 1H), 1.83-1.68 (m, 1H), 1.31 (s, 12H);

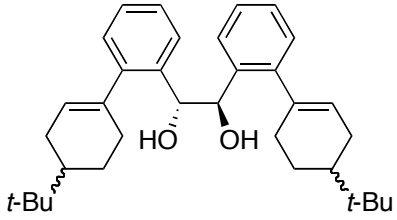
^{13}C NMR (100 MHz, $CDCl_3$) δ 147.2, 146.3, 128.4, 126.9, 126.0, 83.1, 39.8, 34.9, 29.8, 27.1, 24.9, 24.9; HRMS (EI) Calcd. $C_{19}H_{25}O_2B$: 284.19476. Found: 284.19481.

4.12.17.3 (4*R*,5*R*)-4,5-Bis(2-(4-*tert*-butylcyclohex-1-enyl)phenyl)-2,2-dimethyl-1,3-dioxolane (4.25c)



Following the procedure used in the preparation of **4.18c**, the title compound was obtained in 90% yield as a mixture of diastereomers (based on the racemic nature of the carbon in the cyclohexane ring that contains the *tert*-butyl group). $[\alpha]_D^{25}$ +50.95 (*c* 0.17, $CHCl_3$); IR (cast film) 3058, 2960, 2869, 1366, 1233, 1048, 759 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60-7.57 (m, 2H), 7.31-7.25 (m, 2H), 7.20-7.15 (m, 2H), 6.93-6.90 (m, 2H), 5.04 (dd, *J* = 16 Hz, 17 Hz, 2H), 4.66-4.62 (m, 2H), 2.05-1.08 (m, 16H), 0.88 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) (Note: peaks arising due to all diastereomers are included) δ 144.9, 144.7, 144.7, 136.5, 136.4, 133.6, 133.4, 133.3, 128.4, 127.6, 127.5, 127.5, 127.4, 127.3, 127.1, 127.0, 126.9, 126.6, 108.6, 108.6, 94.5, 82.4, 82.3, 82.2, 43.6, 43.5, 32.7, 32.5, 32.2, 27.5, 27.3, 27.0, 26.9, 24.6, 24.4, HRMS (EI) Calcd. $C_{37}H_{50}O_2$: 526.38108. Found: 526.38098.

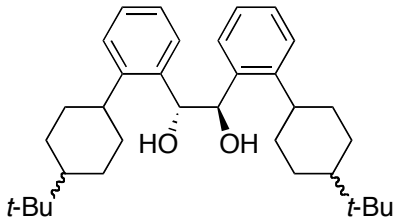
4.12.17.4 (1*R*,2*R*)-1,2-Bis(2-(4-*tert*-butylcyclohex-1-enyl)phenyl)ethane-1,2-diol (4.25d)



Following the procedure used in the preparation of **4.18d,** the title compound was obtained as a mixture of diastereomers (based on the racemic nature of the carbon in the cyclohexane ring that contains the *tert*-butyl group) through deprotection of the corresponding acetal using AcOH/H_2O/MeOH (8:1:1) under reflux for 8 h in 40% yield. $[\alpha]_D^{25}$ +84.95 (*c* 0.33, $CHCl_3$); IR

(cast film) 3410, 3055, 2959, 1480, 1365, 1023, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46-7.52 (m, 2H), 7.27-7.19 (m, 2H), 7.12 (dd, *J* = 1.2, 7.6 Hz, 2H), 6.86 (dt, *J* = 1.6, 7.6 Hz, 2H), 5.12-5.00 (m, 2H), 4.91 (br d, *J* = 16Hz, 1H), 4.82 (br d, 7.6 Hz, 1H), 2.77 (br s, 2H), 2.16-2.01 (m, 4H), 1.84-1.70 (m, 4H), 1.48-1.44 (m, 2H), 1.31-1.10 (m, 4H), 0.92 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) (Note: peaks due to all diastereomers are included) δ 144.5, 144.4, 144.3, 144.2, 137.3, 137.1, 137.0, 136.9, 136.7, 128.6, 128.2, 128.1, 128.0, 127.9, 127.6, 127.5, 127.4, 127.4, 127.3, 126.9, 126.8, 126.7, 126.6, 126.5, 126.5, 126.5, 74.9, 74.9, 74.8, 74.8, 43.7, 43.7, 43.6, 43.6, 32.5, 32.3, 32.3, 32.2, 32.1, 27.3, 27.1, 27.0, 24.6, 24.5; HRMS (EI) Calcd. $C_{34}H_{46}O_2$: 486.34979. Found: 486.35051.

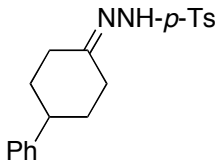
4.12.17.5 (1*R*,2*R*)-1,2-Bis(2-(4-*tert*-butylcyclohexyl)phenyl)ethane-1,2-diol (4.25)



Following the procedure used in the preparation of **4.18**, the title compound was obtained as a mixture of diastereomers in quantitative yield. $[\alpha]_D^{25}$ –32.3 (*c* 0.33, $CHCl_3$); IR (cast film) 3417, 3060, 2940, 2856, 1479, 1448, 1392, 1364, 1038, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (Note: peaks and integrations due to all possible diastereomers are included) δ 7.65-7.12 (m, 2H), 7.27-7.16 (m, 5H), 7.04-7.00 (dd, *J* = 10.0, 1.6 Hz, 1H), 5.12-5.07 (m, 2H), 2.94 (br s, 2H), 2.40-0.30 (m, 20H), 0.85 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (Note: peaks and integrations due to all possible diastereomers are included) 145.9, 145.6, 145.4, 137.4, 137.0, 137.0, 136.9, 127.9, 127.9, 127.7, 127.4, 127.3, 127.2, 127.1, 126.7, 126.7, 125.8, 125.8, 125.8, 125.8, 125.7, 74.4, 74.4, 74.3, 47.7, 44.5, 44.5, 38.9, 38.8, 35.9, 35.9, 32.9, 32.9, 32.9, 32.7, 32.6, 32.4, 32.4, 32.1, 32.1, 28.4, 28.0, 27.9, 27.9, 27.6, 27.6, 27.5, 24.2, 23.0; HRMS (EI) Calcd. $C_{34}H_{50}O_2$: 490.38107. Found: 490.38095.

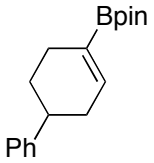
4.12.18 Synthesis of diol 4.26

4.12.18.1 4-Methyl-*N*'-(4-phenylcyclohexylidene)benzenesulfonohydrazide (4.26a)



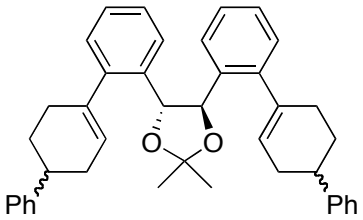
Following the procedure used in the preparation of **4.18a**, the title compound was obtained in 95% yield as a white solid. IR (cast film) 3219, 3061, 2930, 1325, 1185, 1164 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.4 Hz, 2H), 7.53 (br s, 1H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.31-7.14 (m, 5H), 2.85-2.80 (m, 1H), 2.76 (dddd, *J* = 4.0, 4.0, 12.4, 12.4 Hz, 1H), 2.60-2.55 (m, 1H), 2.45 (s, 3H), 2.26 (ddd, *J* = 4.8, 14, 14 Hz, 1H), 2.07-2.03 (m, 2H), 1.98 (ddd, *J* = 5.6, 14.8, 14.8 Hz, 1H), 1.68 (dq, *J* = 4.0, 13.2 Hz, 1H), 1.58 (dq, *J* = 4.4, 13 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 143.9, 135.6, 129.5, 128.1, 47.1, 34.9, 32.5, 27.5, 27.4, 26.7, 26.4, 21.6; HRMS (EI) Calcd. $C_{19}H_{23}N_2O_2S$: 343.14748. Found: 343.14738.

4.12.18.2 4,4,5,5-Tetramethyl-2-(4-phenylcyclohex-1-enyl)-1,3,2-dioxaborolane (4.26b)



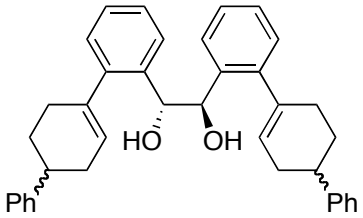
Following the procedure used in the preparation of **4.18b**, the title compound was obtained in 72% yield as a light yellow oil, which crystallized upon standing. IR (cast film) 2962, 2916, 2870, 1636, 1388, 1331, 1145 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.59 (t, *J* = 2.0 Hz, 1H), 2.36-2.26 (m, 1H), 2.14-1.97 (m, 2H), 1.90-1.77 (m, 2H), 1.24 (s, 12H), 1.15-1.03 (m, 1H), 0.92-0.83 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 83.0, 43.8, 32.3, 28.5, 27.9, 27.1, 24.9, 24.8, 24.0; HRMS (EI) Calcd. $C_{16}H_{29}O_2B$: 264.21126. Found: 264.22607.

4.12.18.3 (4*R*,5*R*)-2,2-Dimethyl-4,5-bis(2-(4-phenylcyclohex-1-enyl)phenyl)-1,3-dioxolane (4.26c)



Following the procedure used in the preparation of **4.18c**, the title compound was isolated in quantitative yield as a mixture of diastereomers (based on the racemic nature of the carbon in the cyclohexane ring that contains the phenyl group) in 95% yield. $[\alpha]_D^{25}$–16.81 (*c* 0.60, $CHCl_3$); IR (cast film) 3060, 3025, 2916, 2835, 1601, 1493, 1453, 1379, 1232, 1050, 786 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (Note: peaks and integrations due to all possible diastereomers are included) δ 7.75-7.69 (m, 2H), 7.43-7.34 (m, 6H), 7.31-7.29 (m, 4H), 7.26-7.19 (m, 4H), 7.02-7.00 (d, *J* = 7.2 Hz, 2H), 5.18-5.14 (m, 2H), 4.76 (br s, 2H), 2.75-2.68 (m, 2H), 2.21-2.17 (m, 2H), 2.07-2.06 (m, 3H), 2.07-1.78 (m, 6H), 1.78 (s, 6H), 1.68-1.57 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) (Note: peaks arising due to all diastereomers are included) δ 147.1, 145.0, 144.6, 144.5, 144.5, 144.4, 136.6, 136.6, 133.5, 133.5, 133.4, 128.6, 128.5, 128.5, 127.8, 127.7, 127.5, 127.4, 127.2, 127.2, 127.1, 126.9, 126.9, 126.3, 126.1, 109.1, 108.8, 96.1, 82.5, 82.4, 82.4, 39.5, 39.46, 33.6, 31.8, 31.6, 30.4, 30.2, 27.6; HRMS (EI) Calcd. $[M\text{-}C_3H_6O]^+$**:** 508.37947. Found: 508.37941.

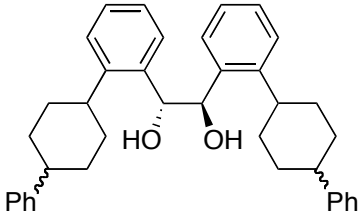
4.12.18.4 (1*R*,2*R*)-1,2-Bis(2-(4-phenylcyclohex-1-enyl)phenyl)ethane-1,2-diol (4.26d)



Following the procedure used in the preparation of **4.18d**, the title compound was obtained as a mixture of diastereomers (based on the racemic nature of the carbon in the cyclohexane ring that contains the *tert*-butyl group) in 35% yield. $[\alpha]_D^{25}$ +39.16 (*c* 0.30, $CHCl_3$); IR (cast film) 3413, 3025, 2922, 1722, 1600, 1492, 1452, 1217, 1029, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (Note: peaks and integrations due to all possible diastereomers are included) 7.65-7.58 (m, 2H), 7.39-7.24 (m, 12H), 7.18-7.14 (m, 2H), 6.94-6.92 (m, 2H), 5.18-5.09 (m, 2H), 5.00-4.88 (m, 2H), 2.99

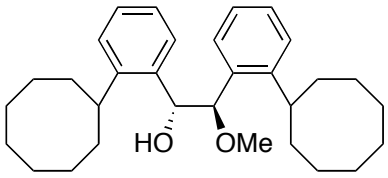
(br s, 2H), 2.81-2.79 (m, 2H), 2.63-0.85 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) (note: peaks due to all possible diastereomers are included) δ 147.0, 144.2, 137.1, 137.1, 128.6, 128.5, 128.0, 127.7, 127.6, 126.9, 126.9, 126.2, 126.1, 126.0, 96.0, 74.8, 39.6, 33.7, 33.5, 31.6, 30.3; HRMS (EI) Calcd. $[C_{38}H_{38}O_2\text{-}H_2O]^+$: 508.27661. Found: 508.27688.

4.12.18.5 (1*R*,2*R*)-1,2-Bis(2-(4-phenylcyclohexyl)phenyl)ethane-1,2-diol (4.26)



Following the procedure used in the preparation of **4.18**, the title compound was obtained as a mixture of diastereomers in 99% yield. $[\alpha]_D^{25}$ –38.43 (*c* 0.60, $CHCl_3$); IR (neat) 3411, 3059, 3026, 2926, 2854, 1601, 1491, 1448, 1034, 755, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (Note: peaks and integrations due to all possible diastereomers are included) 7.80-7.75 (m, 2H), 7.52-7.20 (m, 14H), 7.12-7.08 (m, 2H), 5.30-5.18 (m, 2H), 3.09-3.02 (m, 2H), 2.62-0.94 (m, 18H), 0.48-0.11 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (Note: peaks and integrations due to all possible diastereomers are included) 147.4, 145.5, 145.2, 144.7, 144.6, 136.9, 136.7, 128.7, 128.5, 128.4, 128.2, 128.0, 128.0, 127.9, 127.8, 127.6, 127.3, 127.2, 126.8, 126.3, 126.1, 126.0, 125.96, 125.9, 125.3, 96.0, 96.0, 84.9, 83.4, 74.4, 44.0, 38.5, 38.3, 36.1, 35.5, 34.7, 34.5, 32.5, 30.6, 30.2, 27.4; HRMS (EI) Calcd. $C_{38}H_{40}O_2$: 512.30792. Found: 512.30576.

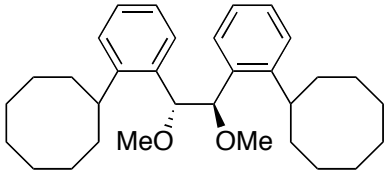
4.12.19 1*R*,2*R*)-1,2-Bis(2-cyclooctylphenyl)-2-methoxyethanol (4.27)



To a mixture of (*R*,*R*)-Vivol **4.21** (434 mg, 1.14 mmol, 1.00 equiv) and Ag_2O (264 mg, 1.00 mmol, 1.00 equiv) in 3.5 mL of anhydrous DMF was added CH_3I (0.0780 mL, 1.10 mmol, 1.10 equiv), and the mixture was stirred in the dark for 15 h, after which time, the reaction mixture was filtered through a 0.5 inch column of Celite to afford the crude product, and the Celite was

rinsed with an additional 20 mL of ether. The filtrate was concentrated *in vacuo* to give the crude product, which was purified by flash chromatography (0-5% EtOAc/hexanes) to afford 440 mg (86% yield) of the desired mono-methylated product as a colorless glassy solid. $[\alpha]_D^{25}$ – 18.30 (*c* 1.18, $CHCl_3$); IR (cast film) 3552, 3059, 2920, 2851, 1624, 1466, 1447, 1095, 753 cm^{-1}; 1H NMR (400 MHz, $CDCl_3$) δ 7.69 (dd, *J* = 1.6, 7.6 Hz, 1H), 7.53 (dd, *J* = 1.6, 7.6 Hz, 1H), 7.21-7.11 (m, 4H), 7.02-6.97 (m, 2H), 5.14 (d, *J* = 9.2 Hz, 1H), 4.63 (d, *J* = 9.2 Hz, 1H), 3.79 (s, 1H), 3.26 (s, 3H), 2.45-2.37 (m, 2H), 1.63-1.24 (m, 24H), 1.05-0.93 (m, 2H), 0.47-0.39 (m, 2H); ^{13}C NMR (100.5 MHz, $CDCl_3$) 149.8, 148.5, 135.1, 133.3, 127.9, 127.7, 127.6, 127.0, 126.3, 126.2, 125.8, 125.7, 84.0, 73.5, 56.5, 38.8, 38.3, 35.6, 35.3, 33.0, 32.8, 27.2, 27.2, 26.6, 28.5, 26.3, 26.1, 25.8, 25.7, 25.6, 25.5, 33.8; HRMS (ESI) Calcd. $C_{31}H_{44}O_2Na$: 471.32335. Found: 471.32413.

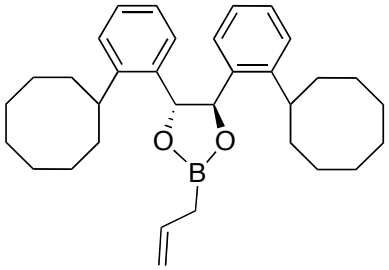
4.12.20 (1*R*,2*R*)-1,2-Bis(2-cyclooctylphenyl)-1,2-dimethoxyethane (4.62)



A sample of NaH (60 wt%, 80.0 mg, 2 mmol, 2.00 equiv) was suspended in THF (4.0 mL)and cooled to 0 ºC. To this suspension was added (*R*,*R*)-Vivol (**4.21**) (434 mg, 1.00 mmol, 1.00 equiv) in portions and the resulting mixture was brought to room temperature and stirred for 1 h. The resulting mixture was cooled to 0 ºC and to it was added CH_3I (0.160 mL, 2.50 mmol, 2.50 equiv) and the reaction mixture was allowed to warm up to room temperature and stirred for addition 1 h. Subsequently, the reaction mixture was quenched by the addition of water and extracted with ether and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography (0-5% EtOAc/hexanes) to give the desired product in 85% yield as a colorless glassy solid. $[\alpha]_D^{25}$ – 32.83 (*c* 1.33, $CHCl_3$); IR (cast film) 3059, 2920, 2852, 1602, 1465, 1446, 1114, 1095, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ δ 7.54 (d, *J* = 7.0 Hz, 2H), 7.15 (dt, *J* = 1.5, 8.0 Hz, 2H), 7.11 (dt, *J* = 1.5, 7.5 Hz, 2H), 6.95 (dd, *J* = 1.5, 7.5 Hz, 2H), 4.85 (s, 2H), 3.20 (s, 6H), 2.55 (s, 2H), 1.70-1.39 (m, 19H), 1.32-1.14 (m, 6H), 0.89-0.84 (m, 1H), 0.36 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$)

149.7, 133.7, 127.7, 127.4, 126.1, 125.7, 82.3, 56.5, 38.3, 35.4, 33.0, 29.7, 27.3, 26.4, 26.3, 25.7, 25.7; HRMS (ESI) Calcd. $C_{32}H_{46}O_2Na$: 485.33900. Found: 485.33859.

4.12.21 (4*R*,5*R*)-2-Allyl-4,5-bis(2-cyclooctylphenyl)-1,3,2-dioxaborolane (4.63)



Into a 25 mL 3-neck round bottom flask equipped with a reflux condenser and a magnetic stir bar and under argon was charged Vivol **4.21** (0.100 g, 0.230 mmol, 1.00 equiv) and THF (2.0 mL). To the solution was added freshly prepared triallylborane[24] (123 mg, 0.917 mmol, 4.00 equiv) and Et_3N (1 drop, catalytic amount). The reaction mixture was heated to reflux at 75 ºC for 2 h after which the volatiles were removed under high vacuum (0.1 mm/Hg) at the same temperature (75 ºC) for 30 min. The condenser was removed and the product was placed under high vacuum for an additional 30 min to afford the title product (moisture and acid sensitive) in quantitative yield. $[\alpha]_D^{25}$ –2.86 (*c* 0.56, $CHCl_3$); IR (cast film) 3064, 2920, 2852, 1638, 1489, 1345, 995, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$ {dried over anhydrous K_2CO_3}) δ 7.46-7.42 (m, 2H), 7.30-7.20 (m, 4H), 7.20-7.13 (m, 2H), 6.11-5.98 (m, 1H), 5.15 (dt, *J* = 17.2, 1.6 Hz, 1H), 5.04 (dd, *J* = 10, 1.2 Hz, 1H), 2.50 (t, *J* = 10 Hz, 2H), 2.04 (dd, *J* = 7.2, 1.2 Hz, 2H), 1.78-1.19 (m, 26H), 0.98-0.82 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 148.7, 135.3, 133.8, 128.6, 126.8, 126.3, 126.1, 115.4, 83.7, 38.4, 36.0, 34.5, 26.4, 26.3, 26.1, 26.0; HRMS (EI) Calcd. $C_{33}H_{45}O_2B$: 484.35126. Found: 484.35050.

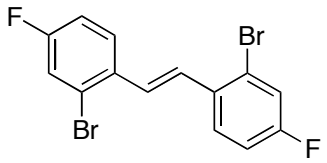
4.12.22 Preparation of single crystal of 4.21•$SnCl_4$ complex

Into a flame dried NMR tube was added **4.21** (30.0 mg, 0.0690 mmol, 1.00 equiv) and the tube was capped with a septum and sealed. Under argon, freshly distilled CH_2Cl_2 (0.70 mL) was added to the NMR tube to yield a colorless solution. To the solution at rt was added $SnCl_4$ (1.0 M in CH_2Cl_2, 69.0 μL, 0.0690 mmol, 1.00 equiv). The NMR tube was then kept at 4 ºC for 7

days after which 0.500 mL of freshly distilled toluene (0.50 mL) was added without disturbing the CH_2Cl_2 layer. After the addition, the NMR tube was placed at –15 ºC (without disturbing) for 50 days during which colorless crystals were seen deposited at the glass-liquid interface. The NMR tube was rapidly inverted, freeing the crystals from contact with solution (in previous runs, agitation had led to dissolution of the crystals upon elongated exposure of the sample to room temperature) and a suitable single crystal was analyzed by X-ray diffraction. The results are provided in the Appendix.

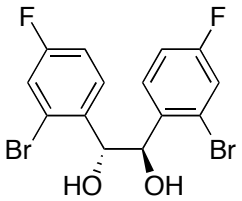
4.12.23 Synthesis of diol 4.64

4.12.23.1 (*E*)-1,2-Di-(3-fluoro-2-bromo-bisdimethylphenyl)-ethene (4.64a)



Following the procedure used in the synthesis of **3.41a**, the stilbene was obtained in 76% yield as a crystalline solid. IR (cast film) 3089, 1570, 1488, 1253, 957, 901, 859, 815 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 (dd, *J* = 6.0, 8.8 Hz, 2H), 7.35 (dd, *J* = 2.6, 8.2 Hz, 2H), 7.25 (s, 2H), 7.07 (ddd, *J* = 2.6, 8.0, 8.4 Hz, 2H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 161.9 (d, *J* = 253.5 Hz), 133.1 (d, *J* = 3.7 Hz), 128.8 (dd, *J* = 1.4, 2.2 Hz), 124.1 (d, *J* = 9.5 Hz), 120.2 (d, *J* = 24.6 Hz), 115.2 (d, *J* = 21.3 Hz); HRMS (EI) Calcd. $C_{14}H_8Br_2F_2$: 375.89200. Found: 375.89241.

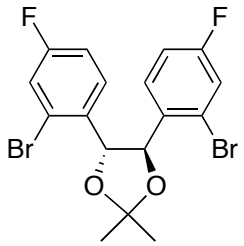
4.12.23.2 (*R*,*R*)-1,2-Bis-(2-bromo-4-fluoro-phenyl)-ethane-1,2-diol (4.64b)



Following the procedure used in the synthesis of **3.41**, the product was obtained in 85% yield as a white solid. $[\alpha]_D^{25}$ –1.48 (*c* 0.97, $CHCl_3$); IR (cast film) 3396, 1600, 1488, 1227, 1030, 882, 860 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 6.2, 8.8 Hz, 2H), 7.16 (dd, *J* = 2.6, 8.2 Hz, 2H), 7.05 (ddd, *J* = 2.6, 8.1, 8.1 Hz, 2H), 5.17 (s, 2H), 3.08 (br s, 2H); ^{13}C NMR (125.7 MHz,

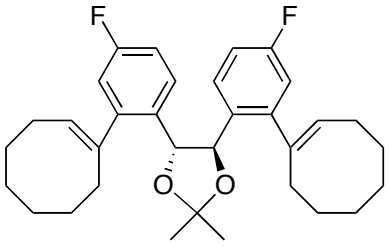
$CDCl_3$) δ 161.9 (d, *J* = 251.5 Hz), 134.4 (d, *J* = 3.5 Hz), 130.9 (d, *J* = 8.6 Hz), 122.9 (d, *J* = 9.5 Hz), 119.7 (d, *J* = 24.5 Hz), 114.8 (d, *J* = 21.2 Hz); HRMS (ESI) Calcd. $C_{14}H_{10}O_2F_2Br_2Na$: 428.89078. Found: 428.89058. HPLC (chiralcel OD) 10:90 *i*-PrOH/hexane, 0.5 mL/min, λ = 250 nm; T_{major} = 16.5 min, T_{minor} = 1.5 min, >99.5% *ee*.

4.12.23.3 (*R,R*)-4,5-Bis-(2-bromo-4-fluoro-phenyl)-2,2-dimethyl-[1,3]dioxolane (4.64c)



Following the procedure for the synthesis of acetal **4.13b**, the product was obtained in quantitative yield as a crystalline solid. $[\alpha]_D^{25}$ –10.86 (*c* 3.74, $CHCl_3$); IR (cast film) 2986, 1602, 1490, 1381, 1278, 1232, 1072, 902, 821 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 6.1, 8.7 Hz, 2H), 7.20 (dd, *J* = 2.6, 8.3 Hz, 2H), 7.12 (ddd, *J* = 2.6, 8.2, 8.7 Hz, 2H), 5.12 (s, 2H), 1.72 (s, 6H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 162.1 (d, *J* = 251.5 Hz), 131.4 (d, *J* = 3.5 Hz), 123.1 (d, *J* = 9.5 Hz), 119.9 (d, *J* = 24.5 Hz), 115.1 (d, *J* = 21.2 Hz), 109.5, 82.7 (d, *J* = 1.2 Hz), 27.2; HRMS (EI) Calcd. $C_{17}H_{14}F_2O_2{}^{79}Br^{81}Br$: 447.93082. Found: 447.93146.

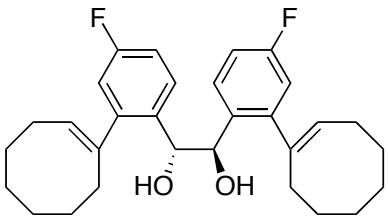
4.12.23.4 (*R,R*)-4,5-Bis-(2-cyclooct-1-enyl-4-fluoro-phenyl)-2,2-dimethyl-[1,3]dioxolane (4.64d)



Following the procedure used in the preparation of dioxolane **4.18c**, the title compound was obtained in 95% yield after recrystallization from MeOH. $[\alpha]_D^{25}$ +83.97 (*c* 2.31, $CHCl_3$); IR (cast film) 2925, 2852, 1610, 1584, 1496, 1219, 1052, 820 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.50 (dd, *J* = 5.9, 8.7 Hz, 2H), 6.96 (ddd, *J* = 2.6, 8.2 Hz, 2H), 6.62 (dd, *J* = 2.8, 9.5 Hz, 2H), 4.91 (s,

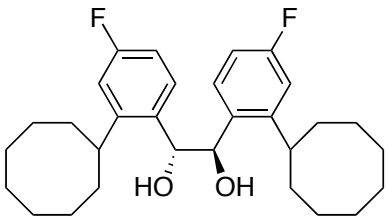
2H), 4.60 (br s, 2H), 2.05-2.09 (m, 4H), 1.96-1.90 (m, 2H), 1.81-1.76 (m, 2H), 1.64 (s, 6H), 1.55-1.38 (m, 10H), 1.33-1.25 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.8 (d, *J* = 246.9 Hz), 147.2 (d, *J* = 7.7 Hz), 138.3, 130.5, 129.1 (d, *J* = 8.8 Hz), 128.8, 115.2 (d, *J* = 20.6 Hz), 113.7 (d, *J* = 21.7 Hz), 108.7, 81.7, 30.9, 29.7, 27.7, 27.3, 26.9, 26.5, 26.3 ; HRMS (EI) Calcd. $C_{33}H_{40}F_2O_2$: 506.29965. Found: 506.29970.

4.12.23.5 (*R,R*)-1,2-Bis-(2-cyclooct-1-enyl-4-fluoro-phenyl)-ethane-1,2-diol (4.64e)



Following the procedure used in the preparation of diol **4.18d**, the title compound was obtained in 75% yield after recrystallization from CH_2Cl_2/hexanes. $[\alpha]_D^{25}$ +157.29 (*c* 0.94, $CHCl_3$); IR (cast film) 3400, 2925, 2851, 1609, 1583, 1495, 1217, 1005, 759 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 6.0, 8.7 Hz, 2H), 6.86 (ddd, *J* = 2.9, 8.6, 8.6 Hz, 2H), 6.56 (dd, *J* = 2.8, 9.5 Hz, 2H), 4.85 (s, 2H), 4.75-4.72 (m, 2H), 2.87 (m, 2H), 2.36-2.25 (m, 2H), 2.15-2.06 (m, 4H), 2.02-1.93 (m, 2H), 1.81-1.76 (m, 2H), 1.64 (s, 6H), 1.55-1.38 (m, 10H), 1.64-1.28 (m, 16H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.7 (d, *J* = 247.3 Hz), 146.9 (d, *J* = 7.2 Hz), 138.8 (d, *J* = 1.0 Hz); 132.5 (d, *J* = 3.1 Hz), 130.5, 129.6 (d, *J* = 8.8 Hz), 115.3 (d, *J* = 20.1 Hz), 113.3 (d, *J* = 21.2 Hz), 74.5, 31.1, 29.7, 28.1, 26.9, 26.6, 26.3. HRMS (ESI) Calcd. $C_{30}H_{36}F_2O_2Na$: 489.25756. Found: 489.25789.

4.12.23.6 (*R,R*)-1,2-Bis-(2-cyclooctyl-4-fluoro-phenyl)-ethane-1,2-diol (4.64)

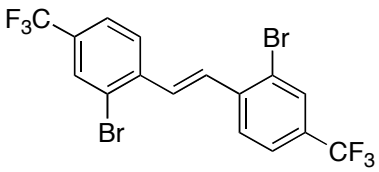


Following the procedure used in the preparation of diol **4.18**, the title compound was obtained in quantitative yield and recrystallized from CH_2Cl_2/MeOH to afford **4.64** as white solid. $[\alpha]_D^{25}$ –

4.52 (*c* 0.21, $CHCl_3$); IR (cast film) 3334, 2927, 2855, 1613, 1588, 1499, 1262, 1036, 821 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 6.2, 10.9 Hz, 2H), 6.90 (ddd, *J* = 2.8, 8.8, 8.8 Hz, 2H), 6.71 (dd, *J* = 2.6, 9.5 Hz, 2H), 5.03 (s, 2H), 2.97 (s, 2H), 2.38-2.36 (m, 2H), 1.71-1.36 (m, 22H), 1.34-1.25 (m, 2H), 1.16-1.10 (m, 2H), 0.60-0.52 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.5 (d, *J* = 245.9 Hz), 151.0 (d, *J* = 6.7 Hz), 131.5 (d, *J* = 2.6 Hz), 129.1 (d, *J* = 8.8 Hz), 113.0 (d, *J* = 12.4 Hz), 113.9 (d, *J* = 11.9 Hz), 74.1, 39.1, 35.3, 32.9, 27.0, 26.6, 25.9, 25.6, 25.4; HRMS (ESI) Calcd. $C_{30}H_{40}F_2O_2Na$: 493.2886. Found: 493.28879.

4.12.24 Synthesis of diol 4.65

4.12.24.1 (*E*)-1,2-Di-(2-bromo-4-trifluoromethyl-phenyl)-ethene (4.65a)

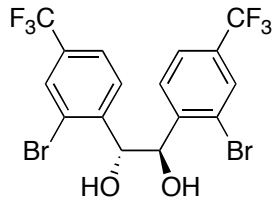


A sample of 3-bromo-4-iodobenzotrifluoride (2.35 g, 6.69 mmol, 1.00 equiv) was charged into a flame-dried round bottom flask equipped with a magnetic stir bar. To the flask was then added Et_2O (10 mL) and THF (10 mL). The solution was then cooled to –78 ºC and maintained at this temperature for another 15 min. After the elapsed time *i*-PrMgCl (2.0 M in THF, 3.38 mL, 6.76 mmol, 1.00 equiv) was added drop-wise and the reaction mixture was stirred for 2 h, after which, anhydrous DMF (1.55 mL, 13.5 mmol, 2.00 equiv) was added to the reaction. The mixture was warmed to room temperature over 30 min and quenched by the addition of saturated aqueous $NaHCO_3$ and the product was extracted with Et_2O (2 x 50 mL). The combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4, filtered, concentrated *in vacuo* to yield an oily residue which was immediately dissolved in THF (10 ml) and used for the next step without any further purification.

The crude product was treated following the procedure for the synthesis of **3.41a**, and the desired stilbene **4.65a** was obtained as a white solid in 67% yield. IR (cast film) 3064, 2925, 1929, 1776, 1609, 1399, 1323, 1168, 1132, 1040, 832 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, *J* = 1.0 Hz, 2H), 7.85 (d, *J* = 8.0 Hz, 2H), 7.64 (dd, *J* = 1.0, 8.0 Hz, 2H), 7.50 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.8 (q, *J* = 0.8 Hz), 131.5 (q, *J* = 33.3 Hz), 131.1, 130.3 (q, *J* =

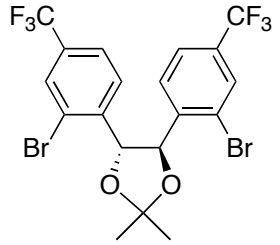
4.0 Hz), 127.6, 124.6 (q, *J* = 3.7 Hz), 124.3, 126.2 (q, *J* = 272.6 Hz); HRMS (EI) Calcd. $C_{16}H_8F_6Br_2$: 475.88559. Found: 475.88486.

4.12.24.2 (*R,R*)-1,2-Bis-(2-bromo-4-trifluoromethyl-phenyl)-ethane-1,2-diol (4.65b)



Following the procedure used in the preparation of **3.41**, the title compound was obtained in 70% yield as a white solid. $[\alpha]_D^{25}$ –3.64 (*c* 0.55, $CHCl_3$); IR (cast film) 3391, 3081, 2931, 1614, 1570, 1398, 1323, 1173, 1134, 1082, 840 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8 Hz, 2H), 7.74 (d, *J* = 1.0 Hz, 2H), 7.63 (dd, *J* = 1.0, 8.0 Hz, 2H), 5.31 (m, 2H), 1.98-2.92 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.6 (q, *J* = 1.2 Hz), 132.0 (q, *J* = 33.8 Hz), 130.3 (q, *J* = 1.2 Hz), 129.8 (q, *J* = 4.0 Hz), 124.4 (d, *J* = 3.7 Hz), 123.0 (q, *J* = 272.7 Hz), 122.7, 74.6; HRMS (ESI) Calcd. $C_{16}H_{10}O_2F_6Br_2Na$: 528.88439. Found: 528.88456. HPLC (chiralcel OD) 10:90 *i*-PrOH/hexane, 0.5 mL/min, λ = 230 nm; T_{major} = 16.8 min, T_{minor} = 16.0 min, >99.5% *ee*.

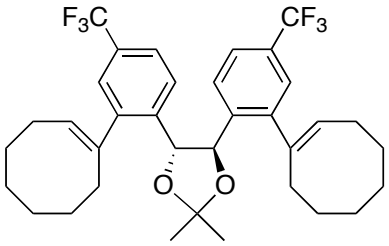
4.12.24.3 (*R,R*)-4,5-Bis-(2-bromo-4-trifluoromethyl-phenyl)-2,2-dimethyl-[1,3]dioxolane (4.65c)



Following the procedure used in the preparation of acetal **4.13b**, the title compound was obtained in quantitative yield as a white solid. $[\alpha]_D^{25}$ –12.09 (*c* 0.43, $CHCl_3$); IR (cast film) 2989, 2936, 1614, 1401, 1376, 1322, 1171, 1132, 1079, 1041, 891 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8 Hz, 2H), 7.71 (s, 2H), 7.66 (d, *J* = 8.0 Hz, 2H), 5.21 (s, 2H), 1.75 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.6 (q, *J* = 1.2 Hz), 132.1 (q, *J* = 33.0 Hz), 129.9 (q, *J* = 3.9 Hz), 124.7

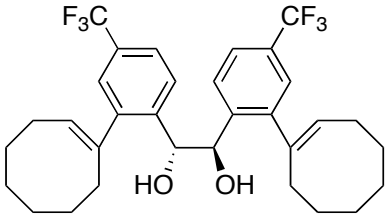
(q, *J* = 3.6 Hz), 123.2, 123.1 (q, *J* = 272.8 Hz), 110.4, 82.9, 27.2; HRMS (EI)Calcd. $C_{18}H_{11}O_2F_6{}^{81}Br_2$: 534.89893. Found: 534.89881.

4.12.24.4 (*R,R*)-4,5-Bis-(2-cyclooct-1-enyl-4-trifluoromethyl-phenyl)-2,2-dimethyl-[1,3]dioxolane (4.65d)



Following the procedure for the preparation of acetal **4.18c**, the title compound was obtained in 85% yield after recrystallization from CH_2Cl_2/MeOH. $[\alpha]_D^{25}$ +71.19 (*c* 1.26, $CHCl_3$); IR (cast film) 2926, 2853, 1467, 1335, 1235, 1166, 1125, 1056, 836 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.2 Hz, 2H), 7.54 (dd, *J* = 1.5, 8.3 Hz, 2H), 7.15 (d, *J* = 2.0 Hz, 2H)), 4.99 (s, 2H), 4.48 (br s, 2H), 2.28-2.11 (m, 2H), 2.10-2.03 (m, 2H), 1.90-1.84 (m, 2H), 1.73-1.65 (m, 2H), 1.69 (s, 2H), 1.52-1.36 (m, 14H), 1.27-1.25 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.6, 138.2, 137.0 (q, *J* = 1.3 Hz), 131.3, 129.9 (q, *J* = 32.2 Hz), 127.9, 125.6 (q, *J* = 2.1 Hz), 124.1 (q, *J* = 272.3 Hz), 123.6 (q, *J* = 3.7 Hz), 109.7, 81.98, 31.1, 29.6, 27.7, 27.3, 26.8, 26.5, 26.3; HRMS (ESI) Calcd. $C_{35}H_{40}O_2F_6Na$: 629.28247. Found. 629.28275.

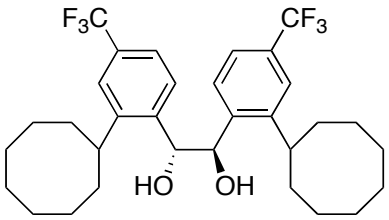
4.12.24.5 (*R,R*)-1,2-Bis-(2-cyclooct-1-enyl-4-trifluoromethyl-phenyl)-ethane-1,2-diol(4.65e)



Following the preparation of diol **4.18d**, except that the reaction time was 16 h, the title compound was obtained in 57% yield as a white solid after recrystallization from CH_2Cl_2/MeOH. $[\alpha]_D^{25}$ +131.86 (*c* 1.02, $CHCl_3$); IR (cast film) 3390, 2927, 2854, 1615, 1466, 1416, 1336, 1166, 1128, 1052, 761 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.0 Hz, 2H), 7.46 (d, *J* = 7.5

Hz, 2H), 7.07 (s, 2H), 4.91 (s, 2H), 4.52 (br s, 2H) 3.12 (br s, 2H), 2.34-2.30 (m, 2H), 2.08-2.04 (m, 4H), 1.91-1.88 (m, 2H), 1.61-1.37 (m, 14H), 1.30-1.27 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.3, 140.4 (q, J = 0.64 Hz), 138.6, 131.1, 129.7 (q, J = 32.1 Hz), 128.7, 125.6 (q, J = 3.7 Hz), 124.0 (q, J = 272.3 Hz), 123.4 (q, J = 2.2 Hz), 74.6, 31.2, 29.6, 28.0, 26.8, 26.5, 26.3, 26.2; HRMS (ESI) Calcd. $C_{32}H_{36}O_2F_6Na$: 589.25117. Found: 589.25151.

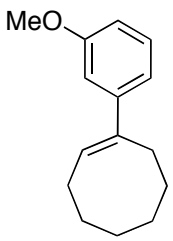
4.12.24.6 (*R*,*R*)-1,2-Bis-(2-cyclooctyl-4-trifluoromethyl-phenyl)-ethane-1,2-diol (4.65)



Diol **4.65** was prepared according to the procedure used in the preparation of diol **4.18**, except that the reaction time was 24 h. The desired product was obtained in quantitative yield as a white solid, which was further recrystallized from CH_2Cl_2/hexanes to provide analytically pure product. $[\alpha]_D^{25}$ –9.64 (*c* 0.50, $CHCl_3$); IR (cast film) 3556, 3376, 2927, 2856, 1619, 1469, 1447, 1417, 1330, 1158, 1125, 1036, 906, 837 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, J =8.0 Hz, 2H), 7.49 (d, J = 8.0 Hz, 2H), 7.27 (s, 2H), 5.15 (s, 2H), 3.16 (s, 2H), 2.38-2.33 (m, 2H), 1.70-1.33 (m, 24H), 0.99-0.83 (m, 2H), 0.46-0.42 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.1, 139.4, 130.4 (q, J = 26.3 Hz), 128.0, 124.1 (q, J = 272.3 Hz), 23.5(q, J = 3.9 Hz), 122.7 (q, J = 4.0 Hz), 73.9, 39.1, 39.6, 32.8, 26.8, 26.5, 25.9, 25.4; HRMS (ESI) Calcd. $C_{32}H_{40}O_2F_6Na$: 593.28247. Found: 593.28264.

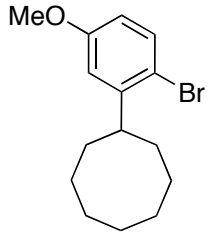
4.12.25 Synthesis of diol 4.66

4.12.25.1 1-(3-Methoxy-phenyl)-cyclooctene (4.66a)



A sample of 3-iodoanisole (3.29 g, 14.0 mmol, 1.00 equiv) was dissolved in THF (20 mL)and cooled to –78 ºC and maintained for 20 min, after which was added dropwise *n*-BuLi (1.6 M in hexane, 9.64 mL, 15.4 mmol, 1.10 equiv). The resulting mixture was stirred for 1 h after and cyclooctanone (2.12 g, 16.8 mmol, 1.20 equiv) dissolved in THF (10 mL) was added. The resulting mixture was stirred for 1 h and subsequently allowed to warm to room temperature over 1 h. The reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$ and extracted with ether. The combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4, filtered, concentrated *in vacuo*. The crude mixture was passed through a short plug of silica using 20% Et_2O/hexanes as the eluent and the resulting product was placed under high vacuum for 1 h. The resulting product was dissolved in CH_2Cl_2 (10 mL) and to the solution was added Et_3SiH (2.91 mL, 18.2 mmol, 1.30 equiv) followed by TFA (2.27 mL, 29.5 mmol, 2.10 equiv). The reaction mixture was stirred for 15 min and quenched by addition of solid Na_2CO_3 and then with H_2O. The mixture was extracted with Et_2O (2 X 50 mL) and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (0-5% Et_2O/hexanes) to afford 1.73 g of the title compound as colorless oil. IR (cast film) 2924, 2850, 1604, 1577, 1487, 1468, 1290, 1227, 1053, 772 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (t, *J* = 7.8 Hz, 1H), 7.05 (ddd, *J* = 0.8, 1.6, 7.8, Hz, 1H), 7.00 (t, *J* = 1.6 Hz, 1H), 6.81 (ddd, *J* = 0.9, 2.5, 8.2 Hz, 1H), 6.07 (t, *J* = 8.4 Hz, 1H), 3.85 (s, 3H), 2.68-2.65 (m, 2H), 2.68-2.31 (m, 2H), 1.70-1.27 (m, 8H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 159.6, 144.8, 140.1, 129.1, 128.2, 118.4, 111.8, 111.6, 55.2, 30.0, 29.5, 28.5, 27.4, 26.9, 26.2; HRMS (EI) Calcd. $C_{15}H_{20}O$: 216.15141. Found: 216.15152.

4.12.25.2 (2-Bromo-5-methoxy-phenyl)-cyclooctane (4.66b)

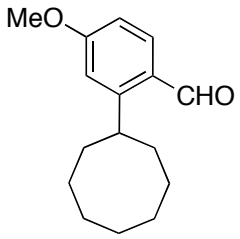


A 1.36 g sample of alkene **4.66a** was dissolved in 6.0 mL of MeOH. The resulting solution was purged with argon and under a positive pressure of argon was added Pd/C (10 wt%, 0.83 g) and the reaction mixture was stirred for 4 h and filtered through a short pad of silica eluting with

Et_2O to provide the desired cycloalkane in quantitative yield, which was carried forward to the next step.

The crude cycloalkane was dissolved in CH_3CN (30 mL) and under argon was added *N*-bromo-succinimide (1.22 g, 6.86 mmol, 1.10 equiv). The resulting mixture was heated at reflux for 16 h, after which the solvent was evaporated *in vacuo* and the residue was purified by flash chromatography (0-5% Et_2O/hexanes) to afford 1.62 g of the title compound **4.66b** along with bis-brominated impurity in a 10:1 ratio. IR (cast film) 2999, 2921, 2849, 1592, 1571, 1467, 1284, 1239, 1015, 798 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.04 (d, *J* = 8.8 Hz, 1H), 6.81 (d, *J* = 3.2 Hz, 1H), 6.60 (dd, *J* = 3.2, 8.8 Hz, 1H), 3.80 (s, 3H), 3.30-3.24 (m, 1H), 1.85-1.79 (m, 4H), 1.85-1.62 (m, 10H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 159.1, 150.1, 133.0, 114.6, 114.1, 112.2, 55.4, 42.5, 33.9, 26.8, 26.7, 26.1; HRMS (EI) Calcd. $C_{15}H_{21}O^{81}Br$: 298.07553. Found: 298.07555.

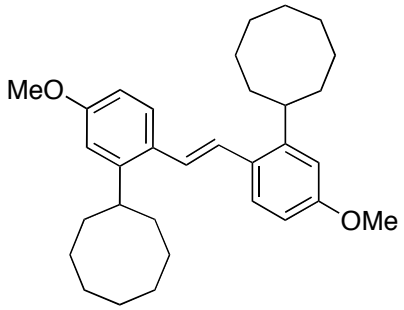
4.12.25.3 2-Cyclooctyl-4-methoxy-benzaldehyde (4.66c)



A sample of **4.66b** (1.62 g. 6.23 mmol, 1.00 equiv) was dissolved in 20 mL of THF and cooled to –78 ºfor 15 min, after which *t*-BuLi (1.7 M in pentane, 11.4 mL, 19.3 mmol, 3.10 equiv) was added dropwise and the reaction mixture was stirred for an additional 45 min. After the elapsed time, to the thick yellowish orange reaction mixture was added DMF (2.90 mL, 37.4 mmol, 6.00 equiv) and the reaction mixture was stirred for another 15 min and subsequently allowed to warm to room temperature over 30 min. The reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ and extracted with Et_2O (2 X 50 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated *in vacuo*. The crude aldehyde product was purified by flash chromatography (10% Et_2O/hexanes) to provide the title compound as a faint yellow oil in quantitative yield. IR (cast film) 2921, 2851, 2721, 1688, 1600, 1565, 1464, 1289, 1242, 1037, 812 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.21 (s, 1H), 7.79 (d, *J* = 8.7 Hz 1H), 6.86 (d, *J* = 2.4 Hz, 1H), 6.80 (dd, *J* = 2.4, 8.7 Hz, 1H), 3.90-3.85

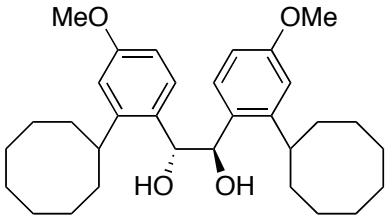
(m, 1H), 3.87 (s, 3H), 1.87-1.60 (m, 14H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 190.7, 163.9, 155.9, 134.2, 126.2, 113.3, 110.7, 55.3, 34.9, 26.6, 26.5, 26.1; HRMS (EI) Calcd. $C_{16}H_{22}O_2$: 246.16199. Found: 246.16181.

4.12.25.4 (*E*)-1,2-Di-(2-cyclooctyl-4-methoxy-phenyl)-ethene (4.66d)



Following the procedure used in the preparation of stilbene **3.41a**, the title compound was obtained in 49% yield as a crystalline white solid. IR (cast film) 2926, 2851, 2695, 1607, 1569, 1493, 1465, 1282, 1238, 1157, 1044, 964, 803 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.5 Hz, 2H), 7.10 (s, 2H), 6.81 (d, *J* = 2.5 Hz, 2H), 6.77 (dd, *J* = 2.5, 8.5 Hz, 2H), 3.84 (s, 6H), 3.21-3.16 (m, 2H), 1.90-1.58 (m, 28H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 159.1, 149.4, 128.8, 127.4, 126.9, 112.5, 110.7, 55.2, 34.1, 26.9, 26.6, 26.3; HRMS (EI) Calcd. $C_{32}H_{44}O_2$: 460.33414. Found: 460.33586.

4.12.25.5 (*R*,*R*)-1,2-Bis-(2-cyclooctyl-4-methoxy-phenyl)-ethane-1,2-diol (4.66)



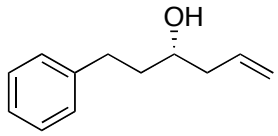
Following the procedure used in the preparation of **3.41**, the title compound was obtained in 17% yield. The major by-product in this reaction results from the instability of the diol **4.66** under oxidative conditions and was ascribed to the formation of **4.66c**. $[\alpha]_D^{25}$ +25.93 (*c* 0.29, $CHCl_3$); IR (cast film) 3449, 2921, 2851, 1608, 1577, 1503, 1465, 1282, 1236, 1041, 820, 758 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.5 Hz, 2H), 6.79 (dd, *J* = 2.0, 8.5 Hz, 2H), 6.57 (d, *J* =

2.5 Hz, 2H), 5.07 (s, 2H), 3.78 (s, 6H), 2.90 (br s, 2H), 2.49-2.42 (m, 2H), 1.70-1.29 (m, 24H), 1.12-1.09 (m, 2H), 0.68-0.64 (m, 2H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 159.0, 150.0, 128.5, 128.3, 112.1, 111.0, 55.1, 38.9, 35.4, 33.1, 27.1, 26.6, 26.0, 25.8, 25.6; HRMS (ESI) Calcd. $C_{32}H_{46}O_4Na$: 517.32883. Found: 517.32858. HPLC (chiralcel OD) 2.5:97.5 *i*-PrOH/hexane, column temperature = 10 ºC, 0.5 mL/min, λ = 230 nm; T_{major} = 59.8 min, T_{minor} = 66.6 min, >99.5% *ee*.

4.12.26 General procedure for the allyl- and crotylboration of aldehydes

The following procedure is representative for the allyl- and crotylboration of aldehydes

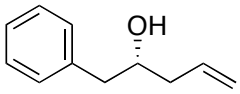
4.12.26.1 (*S*)-1-Phenylhex-5-en-3-ol (4.6)



Into a flame dried 25 mL round bottom flask equipped with a stir bar was added *R,R*-Vivol **4.21** (21.7 mg, 0.050 mmol, 0.0500 equiv), anhydrous Na_2CO_3 (8.20 mg, 0.0770 mmol, 0.0770 equiv) and 4Å-molecular sieves (50.0 mg, previously dried under high vacuum at 100 ºC and stored in an oven). The flask was capped with rubber septum and added freshly distilled toluene (1.0 mL) was added. The mixture was stirred for 2 min and $SnCl_4$ (1.0 M in CH_2Cl_2, 38.5 μL, 0.0385 mmol, 0.0385 equiv) was added. The resulting mixture was stirred at rt for 5 min and cooled to –78 ºC and maintained at this temperature for 15 min. After the elapsed time, allylboronic acid pinacol ester **4.2** (206 μL, 1.10 mmol, 1.10 equiv) was added dropwise and after 30 min, hydrocinnamaldehyde (132 μL, 1.00 mmol, 1.00 equiv) was added dropwise. The reaction was stirred for 5 h at –78 ºC after which of DIBAL-H (1.0 M in toluene, 2.00 mL, 2.00 mmol, 2.00 equiv) was added to quench unreacted aldehyde. The reaction mixture was stirred for additional 15 min at –78 ºC, after which, 1 *N* HCl (4.0 mL) was added and the reaction mixture was allowed to warm to room temperature and stirred for 30 min. The biphasic mixture was extracted with Et_2O (3 X 15 mL), and the combined organic extract were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product, which was purified by flash chromatography (5% EtOAc/hexanes), to afford 174 mg (99% yield)

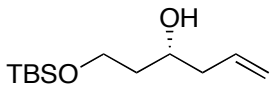
of the desired product, with spectral properties in accordance with the literature.[25] $[\alpha]_D^{25}$ –25.66 (*c* 0.24, $CHCl_3$); IR (cast film) 3369, 2928, 1641, 1496, 1453, 1047, 916, 699 cm^{-1}. HPLC (chiralcel OD), 10:90 *i*-PrOH/hexane, 0.5 mL/min, λ = 254 nm, T_{major} = 12.5 min, T_{minor} = 18.0 min, 95% *ee*.

4.12.26.2 (*R*)-1-Phenylpent-4-en-2-ol (4.32)



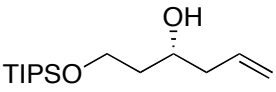
Following the procedure used in the preparation of **4.6**, however, using 6-membered ring diol **4.19** as the diol catalyst, the title compound was obtained in 99% yield and displayed spectral properties in accordance with those reported literature.[26] $[\alpha]_D^{25}$ –14.24 (*c* 0.65, $CHCl_3$); IR (cast film) 3398, 3064, 3028, 2927, 1641, 1496, 1079, 915, 746, 700 cm^{-1}. HPLC (chiralcel OD) 3:97 *i*-PrOH/hexane, 0.5 mL/min, λ = 210 nm; column temperature = 10 ºC, T_{major} = 24.8 min, T_{minor} = 17.6 min, 92% *ee*.

4.12.26.3 (*S*)-1-(*tert*-Butyldimethylsilyloxy)hex-5-en-3-ol (4.33)



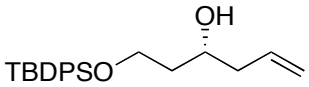
Following the procedure used in the preparation of **4.6**, the title compound was obtained in 98% yield with spectral properties in accordance with those reported in the literature.[27] $[\alpha]_D^{25}$ +6.21 (*c* 1.12, $CHCl_3$); IR (cast film) 3438, 2955, 2930, 2858, 1472, 1256, 1094, 836, 777 cm^{-1}. The enantiomeric excess of the product was determined from the para-nitrobenzoate derivative of the title compound. HPLC (chiralcel OD) 1.2:98.8 *i*-PrOH/hexane, 0.5 mL/min, λ = 254 nm; column temperature = 1.8 ºC, T_{major} = 11.6 min, T_{minor} = 10.8 min, 94% *ee*.

4.12. 26.4 (*S*)-1-(Triisopropylsilyloxy)hex-5-en-3-ol (4.34)



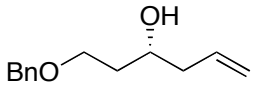
Following the procedure used in the preparation of **4.6**, the title compound was obtained in 99% yield with spectral properties in accordance with those reported in the literature.[28] $[\alpha]_D^{25}$ +6.58 (*c* 0.55, $CHCl_3$); IR (cast film) 3446, 2943, 2867, 1463, 1045, 883, 681 cm^{-1}. The enantiomeric excess of the product was determined from the para-nitrobenzoate derivative of the title compound. HPLC (chiralcel OD) 1.2:98.8 *i*-PrOH/hexane, 0.5 mL/min, λ = 254 nm; column temperature = 1.8 ºC, T_{major} = 11.0 min, T_{minor} = 10.3 min, 94% *ee*.

4.12. 26.5 (*S*)-1-(*tert*-Butyldiphenylsilyloxy)hex-5-en-3-ol (4.35)



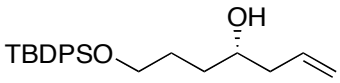
Following general procedure for the preparation of **4.6**, the title compound was obtained in 99% yield with spectral properties in accordance with those reported in the literature.[29] $[\alpha]_D^{25}$ +3.46 (*c* 0.63, $CHCl_3$); IR (cast film) 3444, 3072, 2931, 2858, 1641, 1590, 1428, 1112, 1084, 738, 702 cm^{-1}. HPLC (chiralcel OD) 1.5:98.5 *i*-PrOH/hexane, 0.5 mL/min, λ = 230 nm; column temperature = 5 ºC, T_{major} = 16.9 min, T_{minor} = 19.2 min, 90% *ee*. ($[\alpha]_D^{25}$+3.83 (*c* 0.71, $CHCl_3$, for 95.3% *ee* for the compound obtained with diol **4.64** as LBA catalyst)

4.12.26.6 (*S*)-1-(Benzyloxy)hex-5-en-3-ol (4.36)



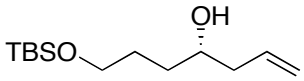
Following the procedure used in the preparation of **4.6**, the title compound was obtained in 99% yield with spectral properties in accordance with those reported in the literature.[30] $[\alpha]_D^{25}$ –3.33 (*c* 0.57, $CHCl_3$); IR (cast film) 3407, 3067, 2922, 2865, 1719, 1641, 1454, 1276, 1098, 1027, 698 cm^{-1}. HPLC (chiralcel OD) 1:99 *i*-PrOH/hexane, 0.5 mL/min, λ = 230 nm; column temperature = 10 ºC, T_{major} = 35.2 min, T_{minor} = 31.9 min, 80% *ee*.

4.12. 26.7 (*S*)-7-(*tert*-Butyldiphenylsilyloxy)hept-1-en-4-ol (4.37)



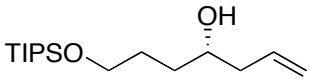
Following the procedure used in the preparation of **4.6**, except that the aldehyde was dissolved in 0.2 mL of toluene and added to the reaction mixture over 15 min. The title compound was obtained in 95% yield with spectral properties in accordance with those reported in the literature.[31] $[\alpha]_D^{25}$ –3.96 (*c* 0.56, $CHCl_3$); IR (cast film) 3474, 3072, 2931, 2858, 1641, 1590, 1428, 1112, 702 cm^{-1}. HPLC (chiralcel OD) 1.5:98.5 *i*-PrOH/hexane, 0.5 mL/min, λ = 230 nm; column temperature = 5 ºC, T_{major} = 16.9 min, T_{minor} = 19.2 min, 90% *ee*.

4.12.26.8 (*S*)-7-(*tert*-Butyldimethylsilyloxy)hept-1-en-4-ol (4.38)



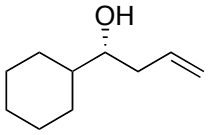
Following general procedure for the preparation of **4.6,** the title compound was obtained in 85% yield with spectral properties in accordance with those reported in the literature.[29] $[\alpha]_D^{25}$ –5.25 (*c* 0.56, $CHCl_3$); IR (cast film) 3364, 3077, 2930, 2858, 1642, 1472, 1256, 1099, 836, 776 cm^{-1}. The enantiomeric ratio of the compound was determined by formation of diastereomeric esters with (*S*)-Mosher acid chloride (1.50 equiv), DMAP (1.00 equiv), Et_3N (5.00 equiv) and **4.36** (1.0 equiv). To the crude reaction (when judged complete, ca~ 2 min), was added diisopropylamine (0.2 mL) and the mixture was passed through a 1" silica column (in a 9" pipette eluting with 30% EtOAc/hexane). ^{1}H-NMR analysis of the mixture indicated 94% *ee* of the title compound.

4.12.26.9 (*S*)-1-(Triisopropylsilyloxy)hex-5-en-3-ol (4.39)



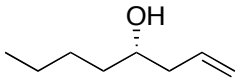
Following the procedure used the preparation of **4.6**, the title compound was obtained in 99% yield with spectral properties in accordance with those reported in the literature.[28] $[\alpha]_D^{25}$ +6.58 (*c* 0.55, $CHCl_3$); IR (cast film) 3446, 2943, 2867, 1463, 1045, 883, 681 cm^{-1}. The enantiomeric excess of the product was determined from the para-nitrobenzoate derivative of the title compound. HPLC (chiralcel OD) 1.2:98.8 *i*-PrOH/hexane, 0.5 mL/min, λ = 254 nm; column temperature = 1.8 ºC, T_{major} = 11.0 min, T_{minor} = 10.3 min, 94% *ee*.

4.12.26.10 (*R*)-1-Cyclohexylbut-3-en-1-ol (4.40)



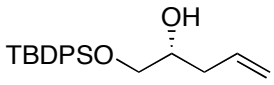
Following the procedure used in the preparation of **4.6**, however using a 10% loading of $SnCl_4$ and 13% loading of diol **4.18**, the title compound was obtained in 94% yield with spectral properties in accordance with those reported in the literature.[32] $[\alpha]_D^{25}$ –1.00 (*c* 0.57, $CHCl_3$); IR (cast film) 3377, 3076, 2925, 2853, 1641, 1450, 986, 910 cm^{-1}. The enantiomeric ratio of the product was determined by formation of para-nitro-benzoate ester of the title compound. HPLC (chiralcel OD) 1.2:98.8 *i*-PrOH/hexane, 0.5 mL/min, λ = 230 nm; column temperature = 1.8 ºC, T_{major} = 31.4 min, T_{minor} = 34.1 min, 91% *ee*.

4.12.26.11 (*S*)-Oct-1-en-4-ol (4.41)



Following general procedure for the preparation of **4.6**, the title compound was obtained in 90% yield with spectral properties in accordance with literature.[33] $[\alpha]_D^{25}$ –9.98 (*c* 1.01, $CHCl_3$); IR (cast film) 3357, 2958, 2931, 2873, 1641, 1026, 995, 912.3 cm^{-1}. The enantiomeric ratio of the compound was determined by formation of diastereomeric esters from (*S*)-Mosher acid chloride, following the procedure used in **4.38**, and judging from integration of the internal olefin peak, the optical purity was established to be 95% *ee*.

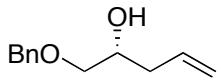
4.11.26.12 (*R*)-1-(*tert*-Butyldiphenylsilyloxy)pent-4-en-2-ol (4.42)



Following the general procedure used in the preparation of **4.6**, the title compound was obtained in 99% yield with spectral properties in accordance with those reported in the literature.[25] $[\alpha]_D^{25}$ +1.97 (*c* 0.81, $CHCl_3$); IR (cast film) 3442, 3072, 2931, 2858, 1463, 1428, 1113, 701 cm^{-1}. The enantiomeric ratio of the title compound was measured from the ^{19}F-NMR of diastereomeric

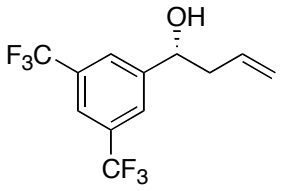
esters derived from condensation with (*S*)-Mosher acid chloride. ^{19}F NMR (376 MHz) δ major = –71.99 ppm, minor = –71.85 ppm, 77% *ee*.

4.12.26.13 (*R*)-1-(Benzyloxy)pent-4-en-2-ol (4.43)



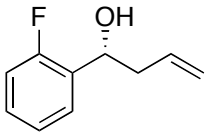
Following the procedure used in the preparation of **4.6**, but using a 10% loading of $SnCl_4$ and 13% loading of **4.21**, the title compound was obtained in 99% yield with spectral properties in accordance with those reported in the literature.[34] $[\alpha]_D^{25}$ –3.75 (*c* 0.87, $CHCl_3$); IR (cast film) 3419, 3067, 2919, 2862, 1642, 1453, 1097, 749, 698 cm^{-1}. HPLC (chiralcel OD) 10:90 *i*-PrOH/hexane, 0.5 mL/min, λ = 210 nm; column temperature = 10 ºC, T_{major} = 20.2 min, T_{minor} = 18.7 min, 70% *ee*.

4.12.26.14 (*R*)-1-(3,5-Bis(trifluoromethyl)phenyl)but-3-en-1-ol (4.44)



Following the procedure used in the preparation of **4.6**, the title compound was obtained in 99% yield with spectral properties in accordance with those reported in the literature.[35] $[\alpha]_D^{25}$ +32.31 (*c* 1.08, $CHCl_3$); IR (cast film) 3385, 3085, 2917, 1643, 1625, 1380, 1281, 1174, 1136, 898, 708, 683 cm^{-1}. HPLC (chiralcel OD) 2:98 *i*-PrOH/hexane, 0.75 mL/min, λ = 254 nm; T_{major} = 11.4 min, T_{minor} = 9.9 min, 95% *ee*.

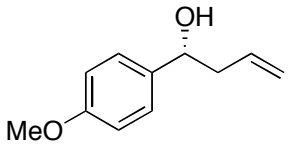
4.12.26.15 (*R*)-1-(2-Fluorophenyl)but-3-en-1-ol (4.45)



Following the procedure used in the preparation of **4.6**, the title compound was obtained in 99% yield with spectral properties in accordance with those reported in the literature.[35] $[\alpha]_D^{25}$ +48.67

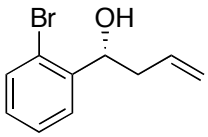
(*c* 1.17, $CHCl_3$); IR (cast film) 3368, 3078, 2922, 1642, 1617, 1586, 1489, 1455, 1224, 757 cm^{-1}. HPLC (chiralcel OD) 5:95 *i*-PrOH/hexane, 0.5 mL/min, λ = 210 nm; T_{major} = 24.6 min, T_{minor} = 26.6 min, 80% *ee*.

4.12.26.16 (*R*)-1-(4-Methoxyphenyl)but-3-en-1-ol (4.46)



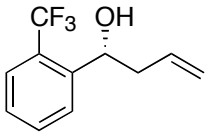
Following the procedure used in the preparation of **4.6**, the title compound was obtained in 45% yield with spectral properties in accordance with those reported in the literature.[36] $[\alpha]_D^{25}$ +1.82 (*c* 0.33, $CHCl_3$); IR (cast film) 3402, 3705, 2934, 1612, 1248, 1175, 1037, 832 cm^{-1}. HPLC (chiralcel OD) 7.5:92.5 *i*-PrOH/hexane, 0.5 mL/min, λ = 210 nm; T_{major} = 15.9 min, T_{minor} = 17.5 min, 14% *ee*.

4.12.26.17 (*R*)-1-(2-Bromophenyl)but-3-en-1-ol (4.47)



Following the procedure used in the preparation of **4.6**, the title compound was obtained in 99% yield with spectral properties in accordance with those reported in the literature.[37] $[\alpha]_D^{25}$ +50.71 (*c* 1.61, $CHCl_3$); IR (cast film) 3379, 3073, 2913, 1641, 1568, 1467, 1440, 1045, 1023, 918, 755 cm^{-1}. HPLC (chiralcel OD) 1:99 *i*-PrOH/hexane, 0.5 mL/min, column temperature = 10 ºC, λ = 254 nm; T_{major} = 36.5 min, T_{minor} = 39.9 min, 60% *ee*.

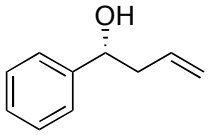
4.12.26.18 (*R*)-1-(2-(Trifluoromethyl)phenyl)but-3-en-1-ol (4.48)



Following the procedure used in the preparation of **4.6**, the title compound was obtained in 95% yield with spectral properties in accordance with those reported in the literature.[37] $[\alpha]_D^{25}$ +53.85 (*c* 0.74, $CHCl_3$); IR (cast film) 3395, 3080, 2921, 1642, 1314, 1163, 1121, 1035, 769 cm^{-1}. The

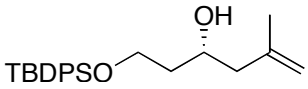
enantiomeric excess of the title compound was determined by ^{1}H NMR of the diastereomers obtained by condensation with (*S*)-Mosher acid chloride and judged to be 75% *ee*.

4.12.26.19 (*R*)-1-Phenylbut-3-en-1-ol (4.49)



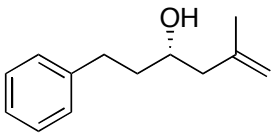
Following the procedure used in the preparation of **4.6**, the title compound was obtained in 99% yield with spectral properties in accordance with those reported in the literature.[25] $[\alpha]_D^{25}$ +34.90 (*c* 0.18, $CHCl_3$); IR (cast film) 3377, 3065, 2926, 1641, 1493, 1454, 1047, 915, 757, 700 cm^{-1}. HPLC (chiralcel OD) 5:95 *i*-PrOH/hexane, 0.5 mL/min, λ = 210 nm; T_{major} = 17.1 min, T_{minor} = 18.9 min, 71% *ee*.

4.12.26.20 (*S*)-1-(*tert*-Butyldiphenylsilyloxy)-5-methylhex-5-en-3-ol (4.50)



Following the procedure used in the preparation of **4.6** except using reagent **4.31**, the title compound was obtained in 99% yield with spectral properties in accordance with those reported in the literature.[25] $[\alpha]_D^{25}$ –0.97 (*c* 0.58, $CHCl_3$); IR (cast film) 3458, 3072, 2932, 2858, 1472, 1428, 1112, 737 cm^{-1}. HPLC (chiralcel OD) 1:99 *i*-PrOH/hexane, column temperature = 5 ºC, 0.5 mL/min, λ = 230 nm; T_{major} = 16.3 min, T_{minor} = 15.0 min, 92% *ee*.

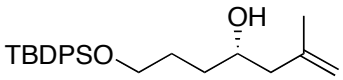
4.12.26.21 (*S*)-5-Methyl-1-phenylhex-5-en-3-ol (4.51)



Following the procedure used in the preparation of **4.6** except using reagent **4.31**, the title compound was obtained in 99% yield with spectral properties in accordance with those reported in the literature.[25] $[\alpha]_D^{25}$ –18.12 (*c* 0.63, $CHCl_3$); IR (cast film) 3405, 3074, 2933, 2860, 1645, 1603, 1495, 1454, 1056, 890, 699 cm^{-1}. HPLC (chiralcel OD) 5:95 *i*-PrOH/Hexane, 0.5 mL/min,

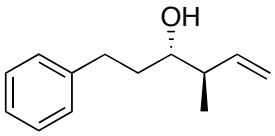
λ = 250 nm; T_{major} = 15.3 min, T_{minor} = 23.4 min, 84% *ee*. ($[\alpha]_D^{25}$ –15.00 (*c* 0.28, $CHCl_3$) for the title compound obtained with diol **4.64** as LBA catalyst, 95.5% *ee*).

4.12.26.22 (*S*)-7-(*tert*-Butyldiphenylsilyloxy)-2-methylhept-1-en-4-ol (4.52)



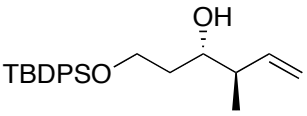
Following general procedure for the preparation of **4.6** except using reagent **4.31**, the title the title compound was obtained in 99% yield with spectral properties in accordance with those reported in the literature.[38] $[\alpha]_D^{25}$ –4.05 (*c* 0.12, $CHCl_3$); IR (cast film) 3415, 3072, 2930, 2858, 1648, 1589, 1446, 1112, 701 cm^{-1}. HPLC (chiralcel OD) 5:95 *i*-PrOH/hexane, 0.5 mL/min, λ = 230 nm; T_{major} = 15.3 min, T_{minor} = 23.4 min, 85% *ee*.

4.12.26.23 (3*S*,4*R*)-4-Methyl-1-phenylhex-5-en-3-ol (4.53)



Following the general procedure used in the preparation of **4.6**, except using reagent **4.3** and the reaction time was 16 h, the title compound was obtained in 93% yield with spectral properties in accordance with those reported in the literature.[39] $[\alpha]_D^{25}$ –15.50 (*c* 0.81, $CHCl_3$); IR (cast film) 3398, 3027, 2963, 2930, 1639, 1604, 1496, 1454, 914, 748, 700 cm^{-1}. HPLC (chiralcel OD) 5:95 *i*-PrOH/hexane, 0.5 mL/min, λ = 210 nm, T_{major} = 14.7 min, T_{minor} = 24.1 min, 96% *ee*.

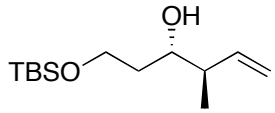
4.12.26.24 (3*S*,4*R*)-1-(*tert*-Butyldiphenylsilyloxy)-4-methylhex-5-en-3-ol (4.54)



Following the procedure used in the preparation of **4.6** except using reagent **4.3** and the reaction time was 16 h, the title compound was obtained in 94% yield with spectral properties in accordance with those reported in the literature.[40] $[\alpha]_D^{25}$ +2.52 (*c* 0.80, $CHCl_3$); IR (cast film) 3518, 3072, 2960, 2931, 2852, 1640, 1472, 1112, 1082, 702 cm^{-1}. HPLC (chiralcel OD) 5:95 *i*-

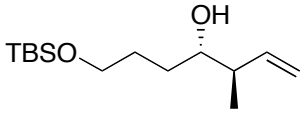
PrOH/hexane, 0.5 mL/min, λ = 210 nm, column temperature = 10 ºC; T_{major} = 12.9 min, T_{minor} = 10.9 min, 93% *ee*. ($[\alpha]_D^{25}$ +3.52 (*c* 0.71, $CHCl_3$) for the compound obtained with diol **4.64** as LBA catalyst, 96 % *ee*).

4.12.26.25 (3*S*,4*R*)-1-(*tert*-Butyldimethylsilyloxy)-4-methylhex-5-en-3-ol (4.55)



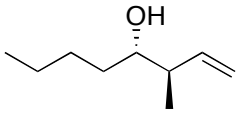
Following the procedure used in the preparation of **4.6**, except using reagent **4.3** and the reaction time was 16 h, the title compound was obtained in 99% yield with spectral properties in accordance with those reported in the literature.[41] $[\alpha]_D^{25}$ +1.42 (*c* 0.52, $CHCl_3$); IR (cast film) 3518, 3076, 2957, 2930, 2858, 1640, 1472, 1256, 1092, 837, 777 cm^{-1}. The enantiomeric excess of the title compound was determined by formation of diastereomeric esters by condensation with (*S*)-Mosher acid chloride. ^{19}F NMR (376 MHz) δ major = –71.55 ppm, minor = 71.58 ppm, 91% *ee*.

4.12.26.26 (3*R*,4*S*)-7-(*tert*-Butyldimethylsilyloxy)-3-methylhept-1-en-4-ol (4.56)



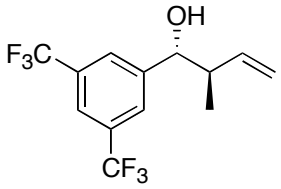
Following the procedure used in the preparation of **4.6**, except using reagent **4.3** and the reaction time was 16 h, the title compound was obtained in 93% yield with spectral properties in accordance with those reported in the literature.[42] $[\alpha]_D^{25}$ –3.12 (*c* 0.69, $CHCl_3$); IR (cast film) 3427, 2956, 2930, 2853, 1472, 1463, 1256, 1099, 836 776 cm^{-1}. The enantiomeric excess of the title compound was determined by formation of diastereomeric esters by condensation with (*S*)-Mosher acid chloride. ^{19}F NMR (376 MHz) δ major = –71.55 ppm, minor = 71.59 ppm, 91% *ee*.

4.12.26.27 (3*R*,4*S*)-3-Methyloct-1-en-4-ol (4.57)



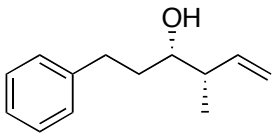
Following the general procedure used in the preparation of **4.6**, except using reagent **4.3** and the reaction time was 16 h, the title compound was obtained in 74% yield with spectral properties in accordance with those reported in the literature.[27] $[\alpha]_D^{25}$ –8.18 (*c* 0.11, $CHCl_3$); IR (cast film) 3071, 2957, 2924, 2856, 1729, 1446, 1396, 1332, 997, 752 cm^{-1}. The enantiomeric excess of the title compound was determined by formation of diastereomeric esters upon condensation with (*S*)-Mosher acid chloride, and judged to be 95% *ee*.

4.12.26.28 (1*R*,2*R*)-1-(3,5-Bis(trifluoromethyl)phenyl)-2-methylbut-3-en-1-ol (4.58)



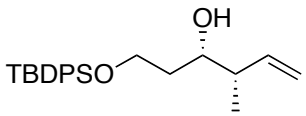
Following the procedure used in the preparation of **4.6**, except using reagent **4.3** and the reaction time was 16 h, the title compound was obtained in 99% yield. $[\alpha]_D^{25}$ +45.42 (*c* 0.80, $CHCl_3$); IR (cast film) 3431, 3085, 2979, 2936, 1641, 1624, 1379, 1281, 1174, 1136, 902, 709, 683 cm^{-1}; ^1H NMR (400 MHz) δ 7.80 (s, 3H), 5.71-5.70 (m, 1H), 5.25-5.17 (m, 2H), 4.53 (d, *J* = 7.2 Hz, 1H), 2.50-2.45 (m, 2H), 0.95 (d, *J* = 6.8 Hz); ^{13}C NMR (100 MHz) δ 145.0, 138.8, 130.9-131.9 (m), 127.4, 124.7, 122.0, 121.5-121.5 (m), 119.3, 118.1, 116.8, 46.3, 16.2; ^{19}F NMR (376 MHz) δ –63.3 (s). HPLC (chiralcel OD) 0.7:99.3 *i*-PrOH/hexane, 1.0 mL/min, λ = 224 nm, column temperature = 2 ºC; T_{major} = 29.4 min, T_{minor} = 15.8 min, 90% *ee*.

4.12.26.29 (3*S*,4*S*)-4-Methyl-1-phenylhex-5-en-3-ol (4.59)



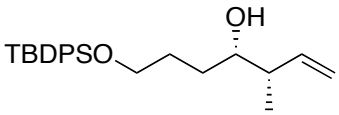
Following the procedure used in the preparation of **4.6** except using reagent **4.4** and the reaction time was 16 h, the title compound was obtained in 78% yield with spectral properties in accordance with those reported in the literature.[27] $[\alpha]_D^{25}$ –23.43 (*c* 0.53, $CHCl_3$); IR (cast film) 3390, 3064, 2928, 2868, 1496, 1454, 1039, 914, 748, 699 cm^{-1}. HPLC (chiralcel OD) 5:95 *i*-PrOH/hexane, 0.5 mL/min, λ = 254 nm, T_{major} = 15.8 min, T_{minor} = 26.2 min, 84% *ee*.

4.12.26.30 (3*S*,4*S*)-1-(*tert*-Butyldiphenylsilyloxy)-4-methylhex-5-en-3-ol (4.60)



Following the procedure used in the preparation of **4.6** except using reagent **4.4** and the reaction time was 16 h, the title compound was obtained in 80% yield with spectral properties in accordance with those reported in the literature.[43] $[\alpha]_D^{25}$ –3.16 (*c* 0.57, $CHCl_3$); IR (cast film) 3513, 3071, 2959, 2931, 2858, 1640, 1590, 1427, 1112. 1077, 702 cm^{-1}; HPLC (chiralcel OD) 5:95 *i*-PrOH/hexane, 0.5 mL/min, λ = 254 nm, column temperature = 10 ºC, T_{major} = 12.5 min, T_{minor} = 10.9 min, 80% *ee*.

4.12.26.31 (3*S*,4*S*)-1-(*tert*-Butyldiphenylsilyloxy)-4-methylhex-5-en-3-ol (4.61)



Following the procedure used in the preparation of **4.6** except using reagent **4.4** and reaction time being 16 h, the title compound was obtained in 71% yield. $[\alpha]_D^{25}$ –11.0 (*c* 0.18, $CHCl_3$); IR (cast film) 3417, 2958, 2858, 1463, 1428, 1112, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.71-7.69 (m, 4H), 7.46-7.39 (m, 6H), 5.85-5.76 (m, 1H), 5.09-5.04 (m, 2H), 3.95-3.82 (m, 2H), 3.79-3.75 (m, 1H), 3.20 (br s, 1H), 2.35-2.26 (m, 1H), 1.73-1.66 (m, 2H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1, 135.6, 133.1, 133.0, 129.8, 127.8, 114.9, 74.9, 63.7, 43.9, 35.5, 26.8, 19.0, 15.2; HRMS (EI) Calcd. $[M\text{-}C_4H_9]^+$: 325.16328. Found 325.16220. The enantiomeric excess of the title compound was determined by formation of diastereomeric esters upon condensation with (*S*)-Mosher acid chloride and established to be 88% *ee*.

4.13 References

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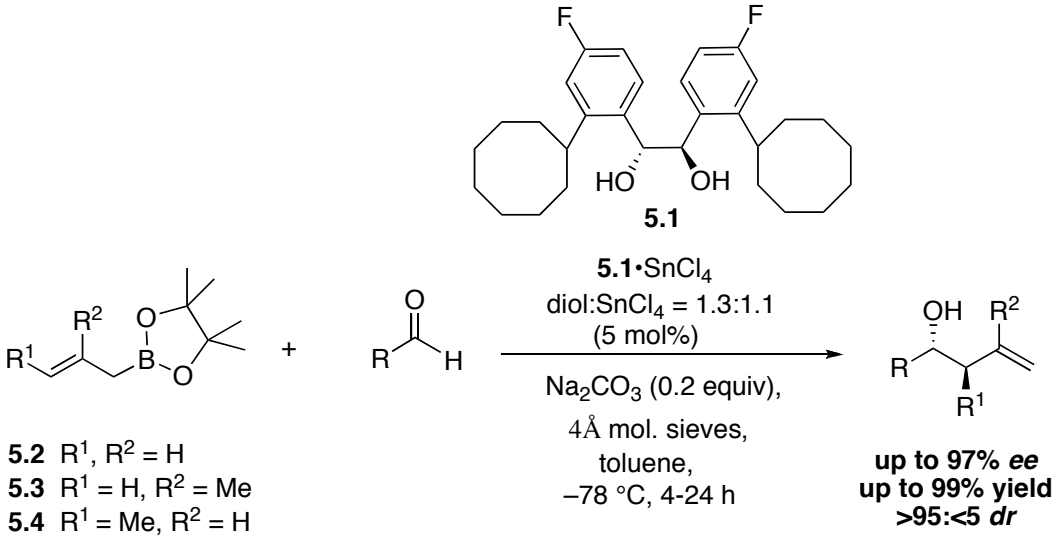
Chapter 5

Applications of Chiral Brønsted Acid Catalyzed Allylboration

5.1 Introduction

As documented in Chapter 4, a novel chiral Brønsted acid catalyst system was developed for the enantio- and diastereoselective allyl- and crotylboration of aldehydes.[1,2] The third-generation catalyst system [F-Vivol(**5.1**)]•$SnCl_4$ was shown to be remarkably efficient for the addition of various allyl- (**5.2**), methallyl- (**5.3**) and *E*-crotylboronate (**5.4**) to aldehydes, providing the desired homoallylic alcohol products in excellent yields and consistently high enantio- and diastereoselectivities (Equation 5.1). The next line of research called for the successful application of chiral Brønsted acid catalyst in the asymmetric addition of other variants of allylic boronates and also towards the synthesis of natural products containing acetate and propionate units.



Equation 5.1. Third-generation diol•$SnCl_4$ catalyst for the enantioselective addition of allylic boronates to aldehydes.[2]

5.2 Enantioselective addition of 2-substituted allylic boronates[2]

5.2.1 Introduction

Since we had observed desirable results in the addition of methallyl boronate **5.3** (c.f. Chapter 4, Section 4.9), we decided to explore the potential application of the [F-Vivol(**5.1**)]•$SnCl_4$ catalyst

system in the enantioselective addition of structurally similar allylic boron reagents. In this context, we anticipated that 2-bromoallylboron pinacolate **5.5**[2] and 2-alkoxycarbonyl allylboronate **5.6** would serve as a good extension for reagent evaluation.[3] The addition of reagent **5.5** onto aldehyde substrates was expected to provide synthetically versatile homoallylic alcohol product **5.7**, which is equipped with a handle for various transition metal-catalyzed cross-coupling reactions. Alternatively, **5.7** can also be directly utilized for the metal mediated carbonylative lactonization process, which would afford the compelling exo-methylene γ-butyrolactones **5.9**.[4] On the contrary, the acid catalyzed addition of 2-alkoxycarbonyl boronate **5.6** onto aldehydes offered the possibility to produce lactones **5.9**, potentially in a one-pot operation.[3]

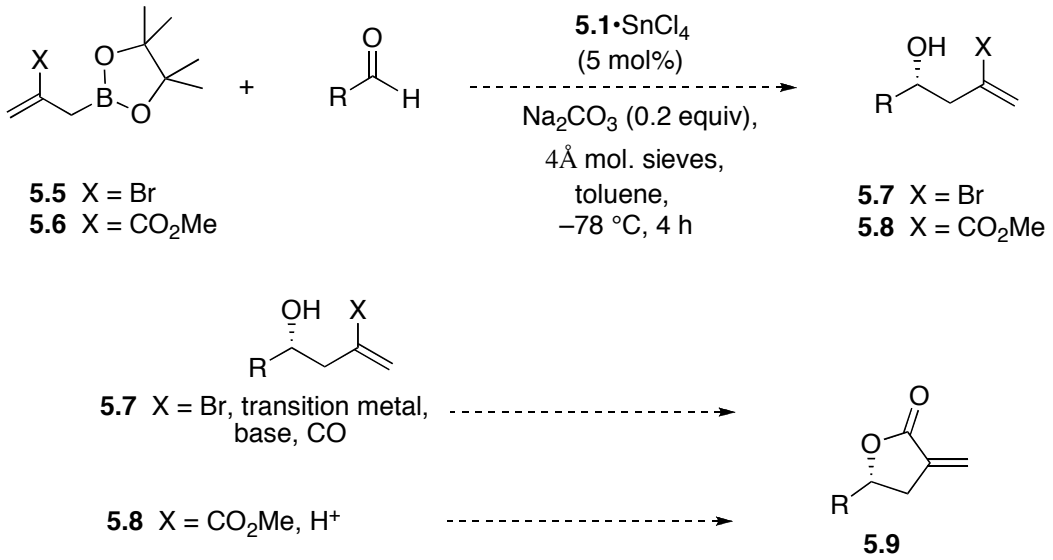
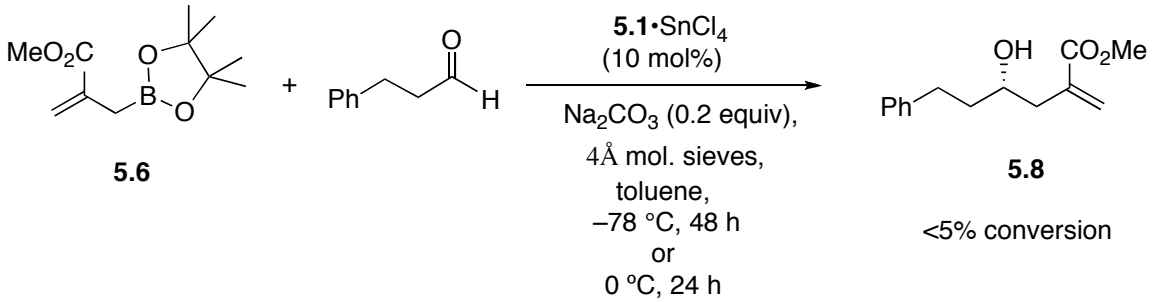


Figure 5.1. Targeted applications of diol•$SnCl_4$ catalyst system.

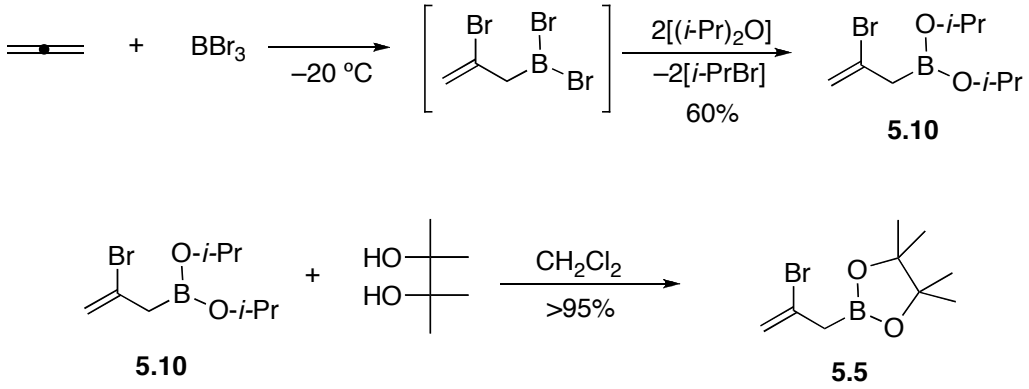
At the outset, we evaluated the asymmetric addition of allylic boronate **5.6** under the influence of the newly developed LBA catalyst **5.1**•$SnCl_4$ (Equation 5.2). In the event, we did not observe appreciable amount of product formation after 24 hours at –78 ºC. The same was also true when we ran the reaction at 0 ºC. In all cases, we observed complete recovery of the starting materials. This failure is probably a result of electronic deactivation of reagent **5.6** as well as the presence of the Brønsted basic alkoxy-carbonyl group in the 2-postion of the reagent. Consequently, we turned our attention towards the utility of 2-bromoallyl boron pinacolate **5.5**.



Equation 5.2. Attempted addition of allylic boronate **5.6** under LBA catalysis.

5.2.2 Preparation of 2-bromoallylboron pinacolate 5.5

After surveying the literature, we were very surprised to see that reagent **5.5** had no precedence in literature. A close acyclic analogue of reagent **5.5** in the form of the corresponding diisopropyl ester **5.10** had been previously reported by Suzuki and coworkers.[5] In their report, the authors performed the bromoboration of gaseous allene using BBr_3, which furnishes a very unstable dibromo-2-bromoallylborane intermediate. The authors then treated this intermediate with diisopropyl ether and the subsequent disproportionation reaction led to the requisite 2-bromoallyl diispropoxyboronate product **5.10** (Scheme 5.1). We decided to follow the exact procedure to generate allylic boronate **5.10** and later condense the adduct with pinacol to afford the requisite boronate **5.5**. In the event, we were very pleased to see a smooth condensation of pinacol with **5.10** and the desired product was obtained in near quantitative yield after a simple distillation under high vacuum.



Scheme 5.1. Preparation of 2-bromoallylboron pinacolate reagent **5.5**.

5.2.3 Enantioselective addition of 2-bromoallylboronate reagent to aldehydes catalyzed by LBA catalyst 5.1•$SnCl_4$[2]

We set out to explore the utility of the LBA catalyst **5.1**•$SnCl_4$ in the enantioselective addition of allylic boronate **5.5** to a select panel of aldehydes. Using hydrocinnamaldehyde as a model, we were able to observe up to 50% conversion with 10% diol loading after 8 hours at –78 ºC, and upon extending the reaction time to 24 hours at –78 ºC, we observed quantitative conversion of the starting aldehyde to the homoallylic alcohol product **5.11**. More importantly, the desired alcohol **5.11** was obtained in 93% *ee*. The above optimal conditions were then applied to other aldehyde substrates, and in all cases, the requisite homoallylic alcohol products were obtained in excellent yields and high enantioselectivities (Figure 5.2).

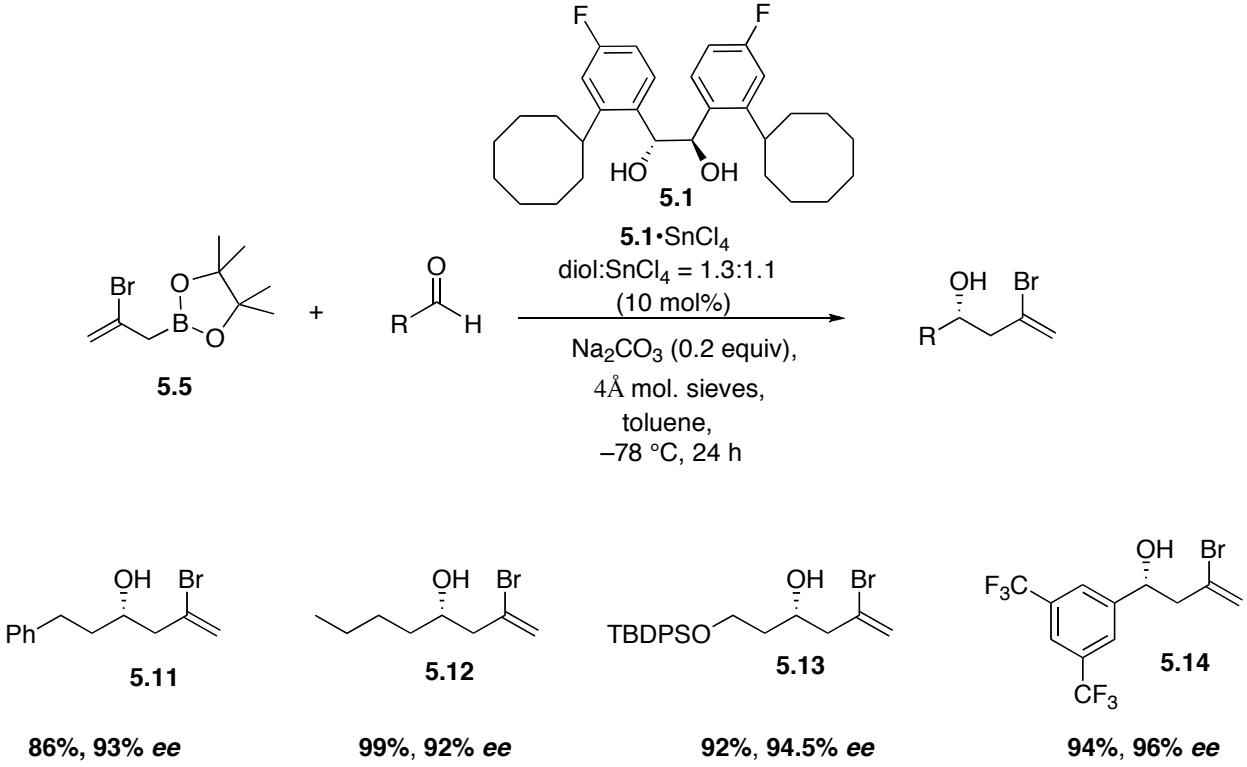


Figure 5.2. Third-generation LBA-catalyzed bromoallylboration of aldehydes.[2]

5.2.4 Preparation of α-exo-methylene γ-butyrolactones

The α-exo-methylene γ-butyrolactone motif is a key structural element in many natural products including the sesquiterpene lactones. These natural products have been shown to possess a

plethora of biological effects including anti-inflammatory, phytotoxic, and anti-microbial activities.[6]

Having established a novel enantioselective method for the generation of optically enriched homoallylic alcohol products **5.11**-**5.14**, we sought the utility of transition metal catalyzed carbonylative lactonization for the generation of the important α-exo-methylene γ-butyrolactone motif. To this end, the most straightforward method appeared to be that of a nickel mediated intramolecular carbonylative cyclization as reported by Brickner and coworkers.[4]

In my hands, subjecting homoallylic alcohol products **5.11**-**5.14** under an equimolar amount of $Ni(CO)_2(PPh_3)_2$ and triethylamine as base in refluxing THF led to the rapid formation of the exo-methylene lactone products in less than 15 minutes (Figure 5.3). The requisite lactones were obtained in good to excellent yields. Importantly, we did not notice any erosion of optical purity of the starting material, which is often observed in the acid catalyzed lactonization of benzylic alcohol containing products (see Figure 5.1) that contain cation-stabilizing aromatic rings.[7]

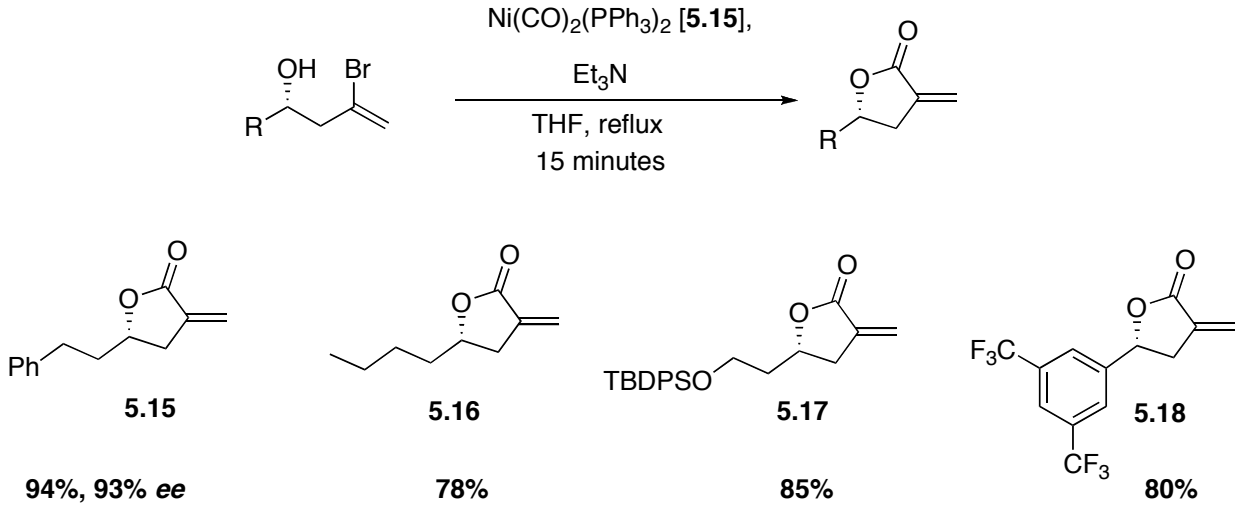


Figure 5.3. Carbonylative lactonization of brominated homoallylic alcohols.[2]

5.3 Total synthesis of (+)-dodoneine[2]

5.3.1 Introduction

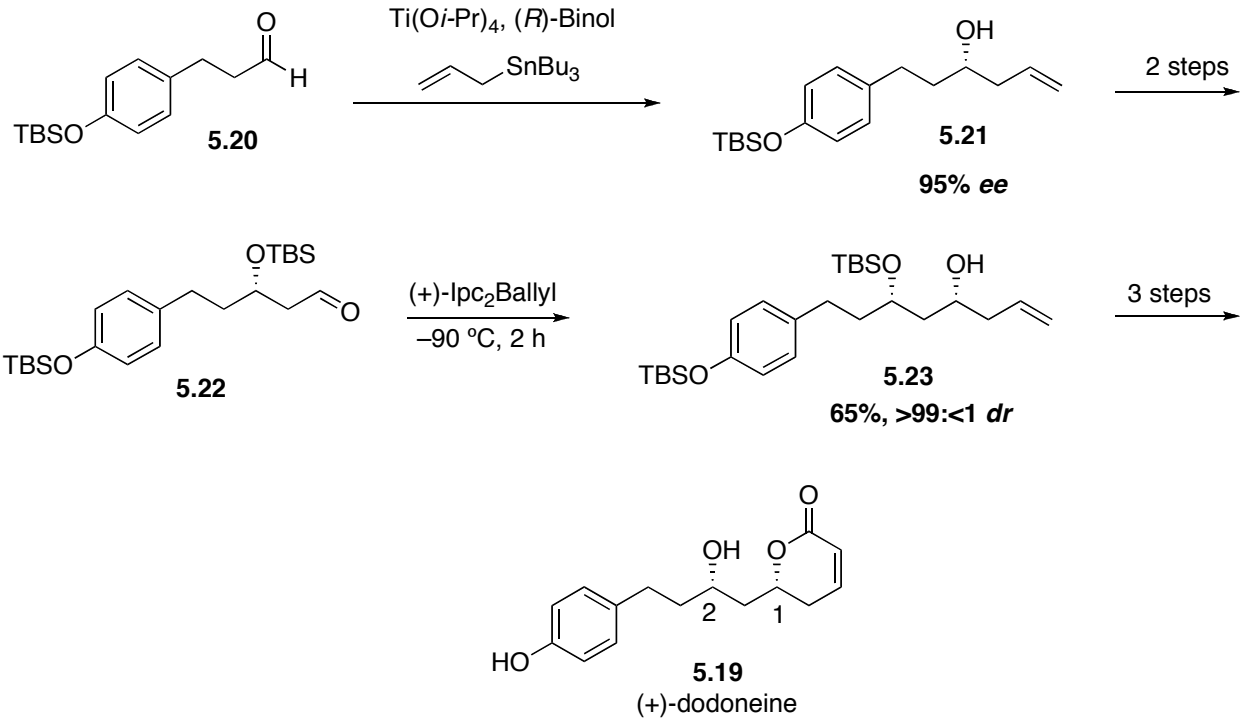
The target oriented syntheses of natural products or pharmaceutical drugs constitutes a recognized way of validating new synthetic methods. To measure up the efficiency of our new allylboration methodology under LBA catalysis, we chose (+)-dodoneine (**5.19**, Scheme 5.2) as a target. (+)-Dodoneine is a natural substance belonging to the ample group of naturally occurring 5,6-dihydropyran-2-ones, a compound class whose members exhibit many different biological activities. They have been shown, for example, to be cytotoxic, HIV protease inhibitors, apoptosis inductors, and anti-leukemic agents.[8] Some of these pharmacological effects have been related to the Michael acceptor properties of the conjugated double bond. (+)-Dodoneine was very recently isolated from *Tapinanthus dodoneifolius*, a parasitic plant that grows on the sheanut tree in Burkina Faso (West Africa), and was found to exhibit a vasorelaxant effect on preconstricted rat aortic rings. Its structure was assigned as **5.19** (Figure 5.4) on the basis of spectroscopic analyses combined with an X-ray diffraction analysis of a crystalline derivative.[8]

This target contains two stereogenic centers that would retrosynthetically arise from the LBA **5.1**•$SnCl_4$-catalyzed addition of allylboron pinacolate onto the requisite aldehyde substrates, and thus, provide a measuring ground (against previous syntheses that applied well established aldehyde allylation methods) for the efficiency of the new Brønsted acid catalyzed allylboration method.

5.3.2 Previously reported syntheses

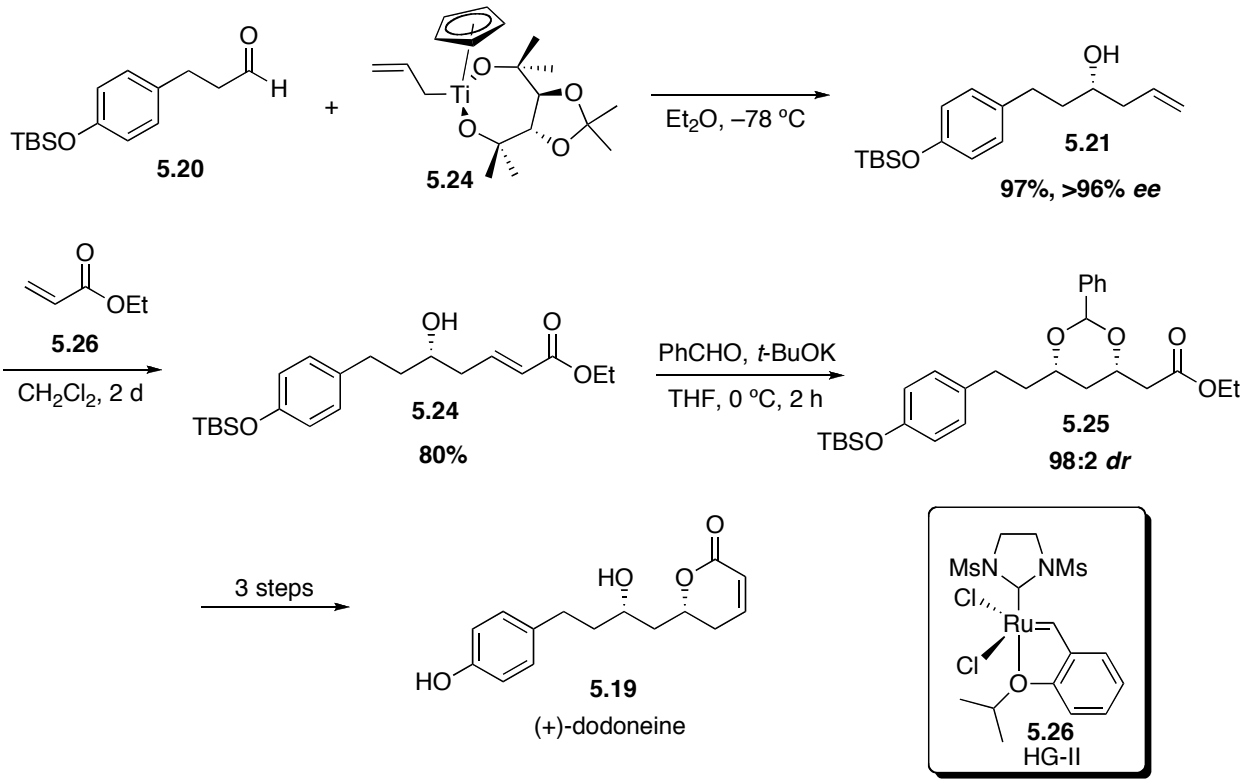
In 2008, the groups of Marco,[9] Cossy[10] and Srihari[11] independently reported the synthesis of (+)-dodoneine **5.19**. The common scheme for the synthesis of dodoneine involves the use of common aldehyde intermediate **5.20** (Scheme 5.2). In their approach to (+)-dodoneine, Marco and coworkers utilized two allylation reactions to install the stereochemistry at the carbinol centers. The authors used a Keck allylation[12] to establish the absolute stereochemistry at the C-2 carbon present in **5.21**, and a diastereoselective Brown allylation for the stereochemistry at the C-1 carbon of the dihydropyran ring in a moderate yield of 65%.[13] The same authors also explored the use of Brown allylation to establish the C-2 stereocenter, however, this method proved to be

inferior to the Keck allylation, providing the requisite product in 90% *ee* vs 95% *ee* (Scheme 5.2).



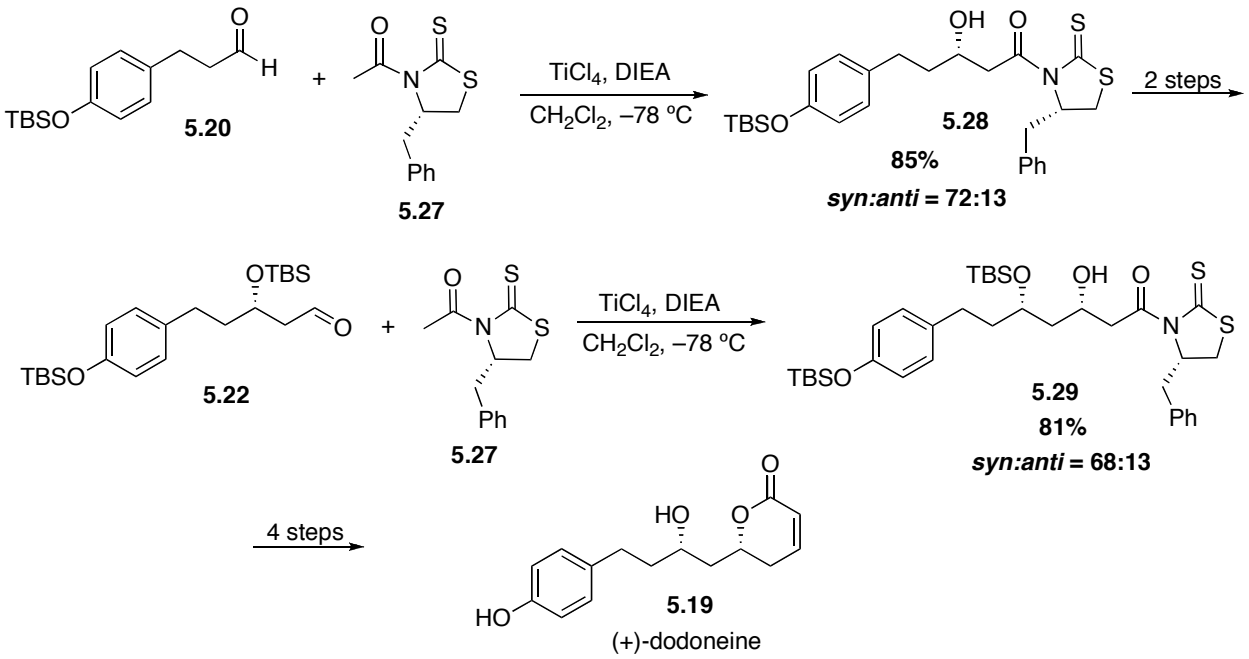
Scheme 5.2. Key steps in the approach of Marco and coworkers to (+)-dodoneine.[9]

Cossy and coworkers utilized a stoichiometric allyltitanation for the installation of the C-2 stereocenter and obtained the product **5.21** in 97% yield and >96% *ee*.[10,14] Subsequent cross-methathesis with ethylacrylate under the influence of Hoveyda-Grubs 2nd generation catalyst **5.26** led to the formation of the Michael acceptor **5.24**. Thereafter, a 1,4-addition of the oxyanion (generated from the addition of the alkoxide onto benzaldehyde) led to the formation the requisite stereocenter at C-1 in the form of acetal **5.25**.[15]



Scheme 5.3. Key steps in the synthesis of (+)-dodoneine by Cossy and coworkers.[10]

Srihari and coworkers utilized the asymmetric Crimmins aldol reaction[16] to install the C-2 and C-1 stereochemistries, in moderate to good diastereoselectivity.[11]

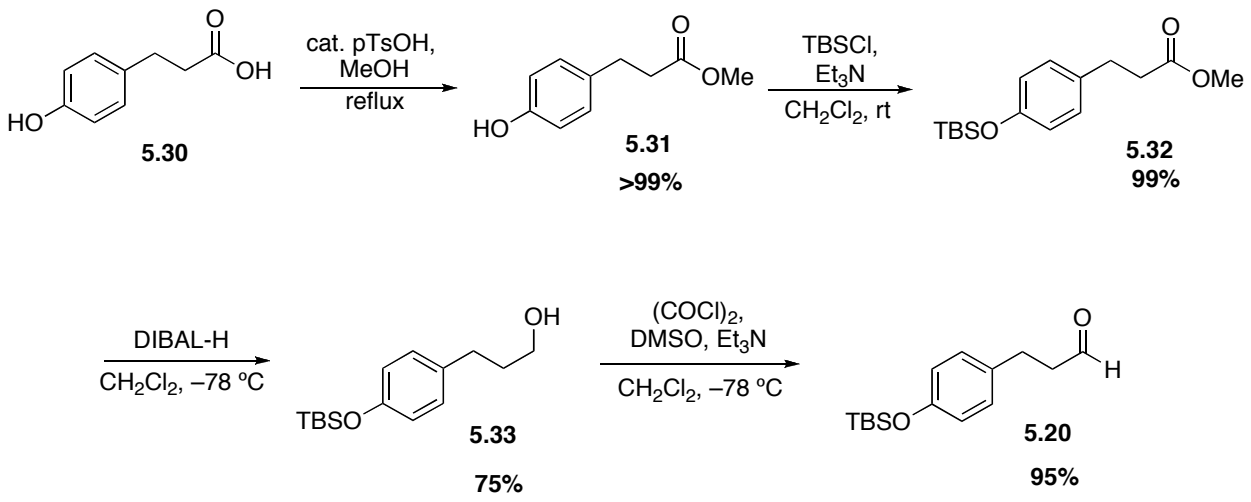


Scheme 5.4. Key steps in the synthesis of (+)-dodoneine by Srihari and coworkers.[11]

5.3.3. Application of newly developed LBA catalyst 5.1•$SnCl_4$ in the enantio- and stereoselective synthesis of (+)-dodoneine[2]

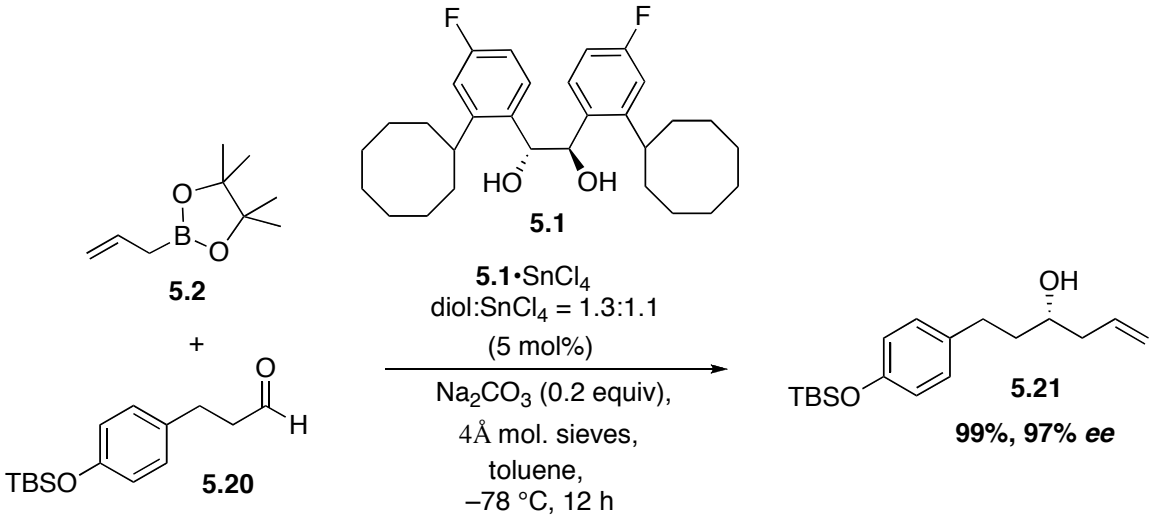
In order to measure the efficiency of the newly developed catalytic allylboration process, we decided to explore Marco's route to the natural product,[9] where it was expected that the catalyst would not only control the absolute stereochemistry at the C-2 stereocenter but also allow for a diastereoselective addition of allylboronate **5.2** onto chiral aldehyde **5.22** and afford the requisite stereochemistry at the C-1 carbon of the dihydropyranone skeleton.

The synthesis of (+)-dodoneine commenced with an acid catalyzed esterification of commercially available 4-hydroxyhydrocinnamic acid **5.30**. The phenol moiety was protected as the silyl ether and reduction of the ester to the corresponding alcohol **5.31** was accomplished with DIBAL-H. A Swern oxidation of alcohol **5.31** led to the formation of aldehyde **5.20**, which was purified by a sequence involving filtration through a short plug of silica followed by distillation.



Scheme 5.5. Preparation of aldehyde **5.20**.[2]

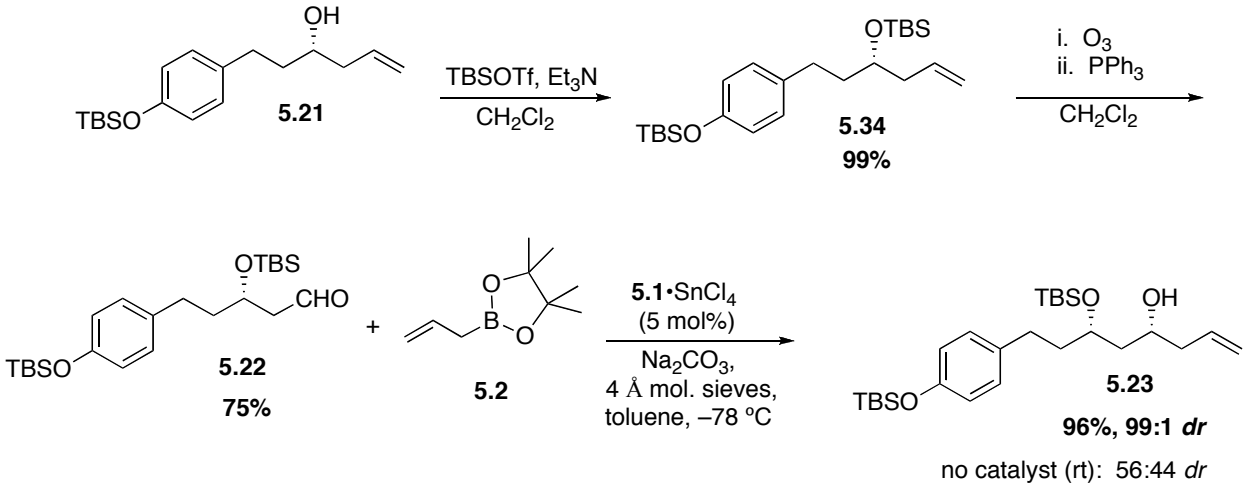
The thus obtained aldehyde **5.20** was subjected to the LBA **5.1**•$SnCl_4$ catalyzed allylboration using allylboron pinacolate **5.2** as the allyl-transfer reagent (Equation 5.3). In the event, the desired homoallylic product **5.21** was obtained in quantitative yield and 97% *ee*. The resulting enantioselectivity compares favorably with that obtained by the Keck allylation (as used by Marco and coworkers) and is superior to that obtained by the well-established Brown allylation. Moreover, the yield of the reaction is superior to both approaches.



Equation 5.3. LBA catalyzed enantioselective preparation of key intermediate **5.21**.[2]

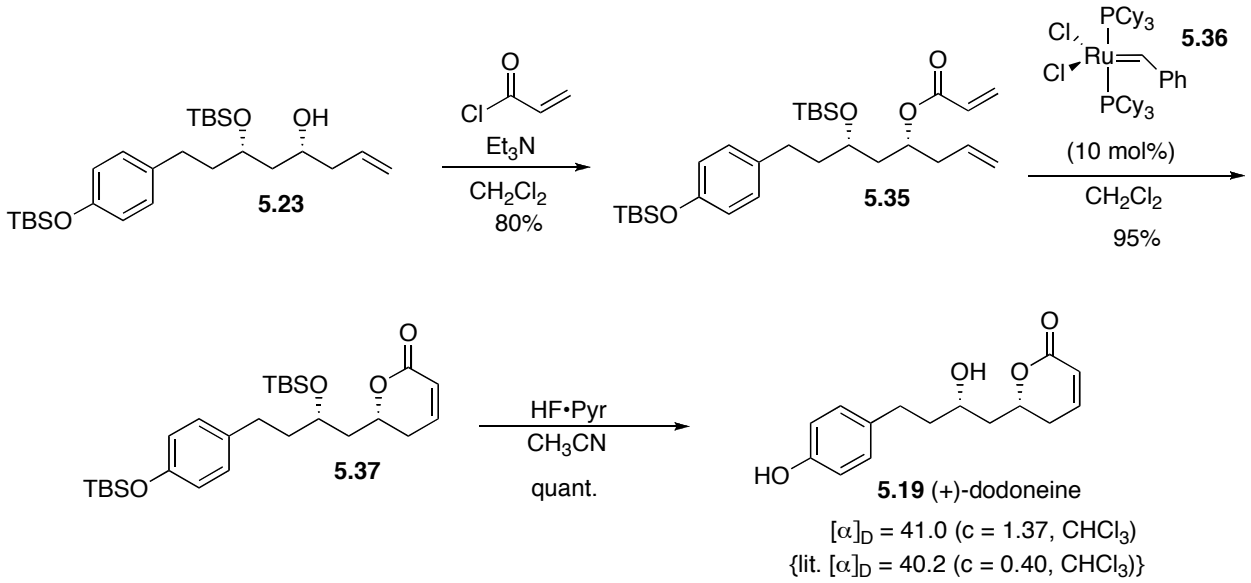
Following the approach of Marco and coworkers, the secondary alcohol of allylation product **5.21** was protected as the silyl ether, **5.34,** and the terminal double bond was cleaved under

oxidative conditions to reveal the requisite aldehyde **5.22**, the substrate for a second allylboration reaction.[9] In order to test the substrate's intrinsic diastereofacial selectivity, we first subjected the aldehyde to allylboron pinacolate under thermal conditions. In the event, we observed a 56:44 ratio favoring the desired *syn*-diastereomer (Scheme 5.6). As such, the catalytic allylboration protocol would be operating under a matched case scenario, but only slightly so favorably. We then performed the reaction between chiral aldehyde **5.22** and allylboron pinacolate **5.2** under the influence of LBA catalyst **5.1**•$SnCl_4$. Upon reaction, the desired product **5.23** was obtained in 96% yield and very high diastereoselectivity (99:1) favoring the desired *syn*-diastereomer (Scheme 5.6). The level of catalyst-controlled diastereoselectivity is truly remarkable considering that the uncatalyzed reaction gave a nearly equal diastereoselectivity. It can thus be inferred that the LBA-catalyzed diastereoselective allylboration is an effective method to access 1,3 *syn* diols in a catalyst-controlled strategy.



Scheme 5.6. Catalyst-controlled diastereoselective addition of allylboronate **5.1** onto aldehyde **5.22**.[2]

Moving along Marco and coworker's synthetic route, alcohol **5.23** was esterified with acryloyl chloride to provide ester **5.35**, setting the stage for a ring closing olefin metathesis (Scheme 5.7). Using Grubbs' 1st generation catalyst **5.36**, the desired dihydropyranone product **5.37** was obtained in 95% yield.[17] Finally, global silyl deprotection afforded the natural product (+)-dodoneine **5.19**, which showed spectral properties consisted to the natural material reported in the literature, including optical rotation.[8-11]



Scheme 5.7. Completion of the synthesis of (+)-dodoneine **5.19**.[2]

Having successfully applied the newly developed Brønsted acid-catalyzed allylboration methodology in the synthesis of a relatively simple natural product (+)-dodoneine **5.19**, the stage was set for an application towards a more complex target; palmerolide A **5.38**.

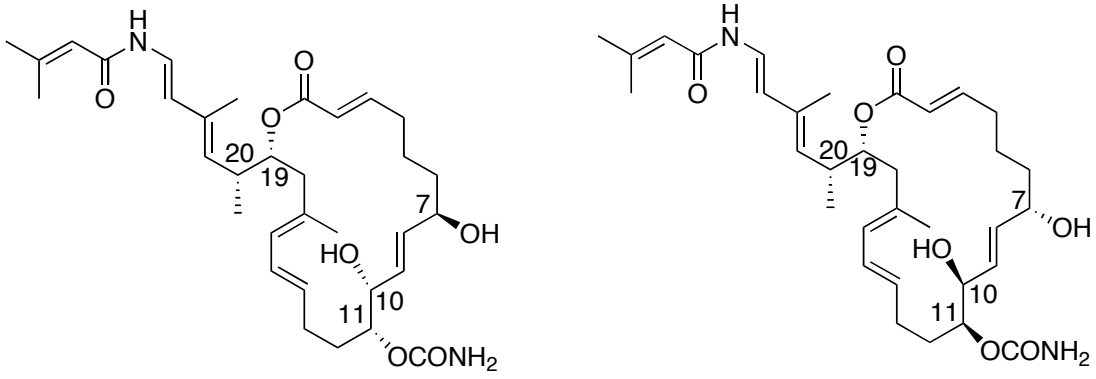
5.4 Total synthesis of palmerolide A[18]

5.4.1 Introduction

Baker and coworkers recently disclosed Palmerolide A **5.38** (see Figure 5.4), a polyketide secondary metabolite with an impressive molecular architecture and a remarkable biological profile.[19] This marine natural product was isolated from *Synoicum Adareanum*, a sac-shaped marine chordate animal, found in the shallow waters around Anvers Island on the Antarctic Peninsula. This molecule exhibited unusual selectivity against a number of cell lines in the 60-cell panel of the National Cancer Institute. More specifically, palmerolide A was found to display potent activity against the melanoma cell line UACC-62 (LC_{50} = 18 nM), and modest cytotoxicity against colon cancer cell line HCC2998 (LC_{50} = 6.5 μm) and renal cancer cell line RXF 393 (LC_{50} = 6.5 μm), and more importantly, no activity against other cell lines, thus demonstrating a selectivity index of 10^3 among the cell lines tested.[19] Interestingly, the mode of

action of this marine natural product is ascribed to the inhibition of vacuolar ATPase, with an IC_{50} value of 2 nM.[20]

Structurally, palmerolide A embeds five stereogenic centers and seven unsaturations, which include a sensitive dienamide functionality and a 1,3-diene unit. In the original disclosure of Baker and coworkers, the structure of palmerolide A was incorrectly assigned as **5.39**, wherein the absolute stereochemistry at the C-11, C-10 and C-7 centers were inverted relative to the correct structure. In their efforts to synthesize the correct structure of palmeroilde A, **5.39** (Figure 5.4), De Brabander and coworkers disclosed the synthesis of *ent*-**5.38** and soon after, Nicolaou and coworkers reported on the synthesis of several isomers of **5.38** including the natural product itself.



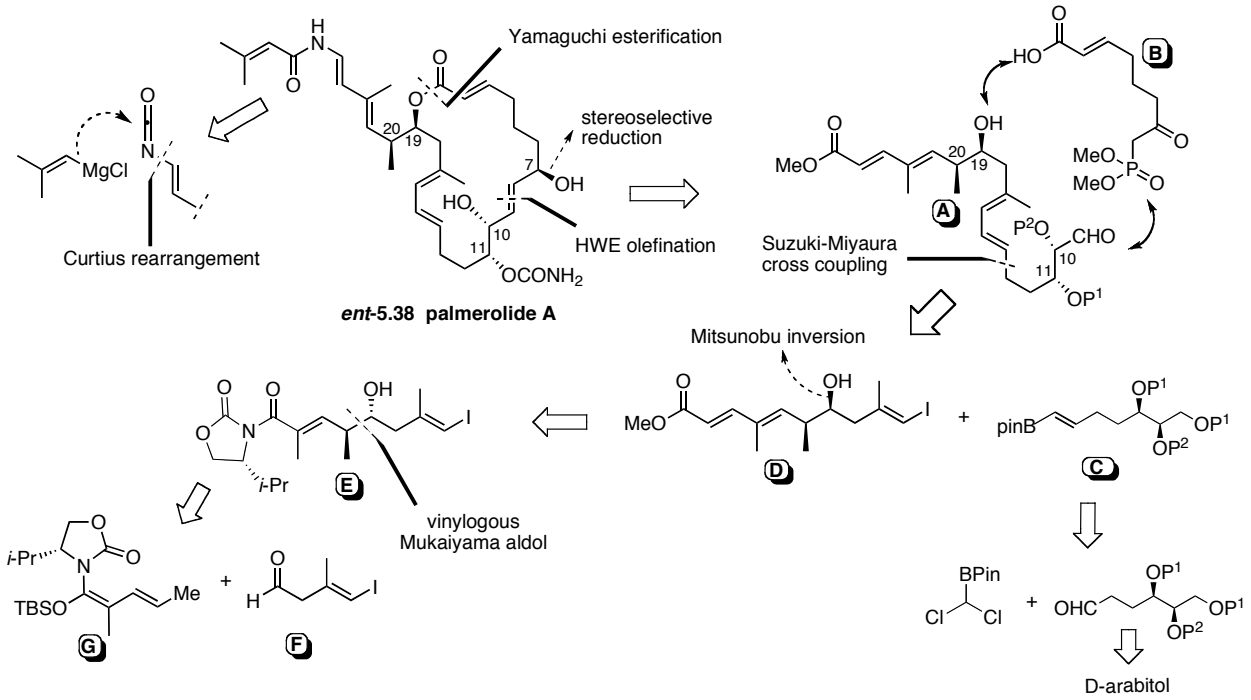
5.39 originally proposed structure **5.38** revised structure (palmerolide A)

Figure 5.4. Originally proposed (**5.39**) and revised (**5.38**) structures of palmerolide A.

5.4.2. Total synthesis of palmerolide A by De Brabander and coworkers[21]

As depicted in Scheme 5.8, De Brabander and coworkers disconnected palmerolide A into building blocks **A** and **B**. The sensitive dienamide moiety was installed post macrolactonization via a Curtius rearrangement, followed by trapping of the transient isocyanate with isoprenylmagnesium bromide.[23] The macrolactone was disconnected through a Horner-Wadsworth-Emmons olefination[24] to reveal aldehyde containing fragment **A** and enoic acid **B**. Fragment **A** was accessed through a traditional sp^2-sp^2 Suzuki-Miyaura cross-coupling reaction between alkenyl iodide **D** and alkenylboronate **C** (in which the relative stereochemistry at the carbinol center was affixed through a Mitsunobu inversion process). Fragment **C** was synthesized from D-arabitol in eight steps, with a borono-Takai olefination serving to install the

alkenylboronate moiety.[25] Fragment **D** was obtained following a Mitsunobu inversion reaction from precusor **E**. Fragment **E** was obtained through a auxiliary controlled diastereoselective vinylogous Mukaiyama aldol reaction between β,γ-unsaturated aldehyde **F** and vinylketene silyl *N*,*O*-acetal **G**.[26]

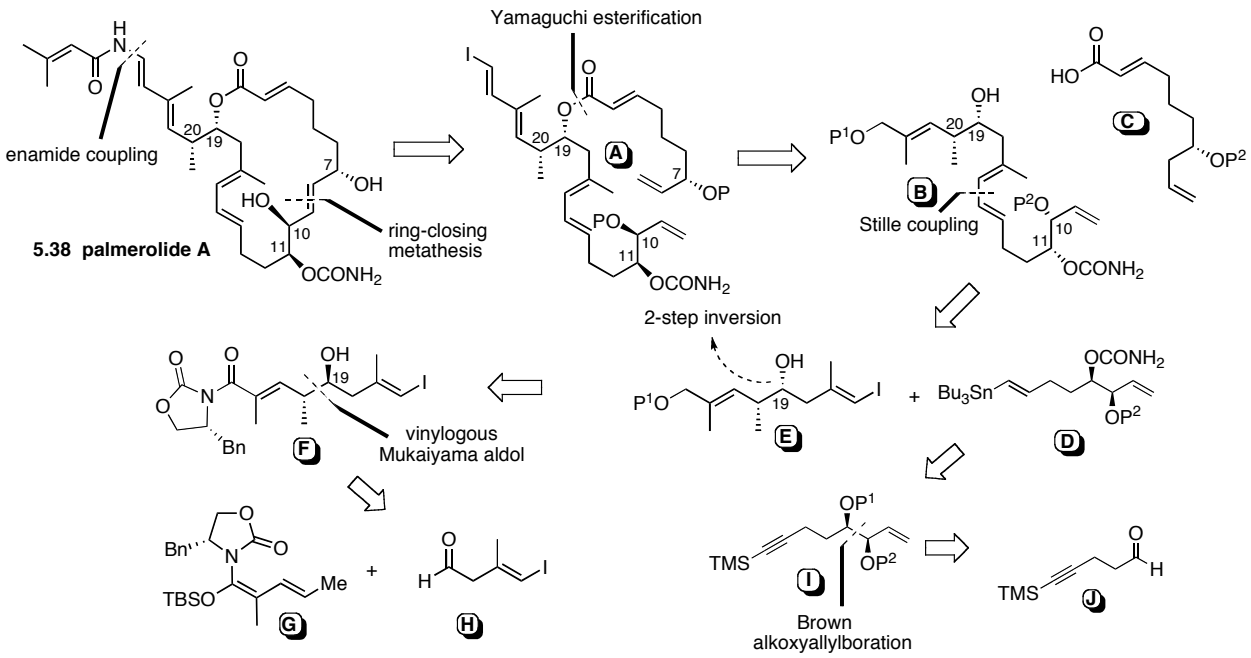


Scheme 5.8. De Brabander's retrosynthetic scheme for the synthesis of *ent*-**5.38**.[21]

5.4.3. Total synthesis of palmerolide A by Nicolaou and coworkers[22]

The synthesis of palmerolide A by Nicolaou and coworkers involved a late stage Buchwald's copper mediated enamide coupling protocol (Scheme 5.9).[27] The macrolactone was assembled through a late stage ring closing metathesis of intermediate **A**. Akin to De Brabander's approach, intermediate **A** was assembled through a Yamaguchi esterification process between alcohol **B** and enoic acid **C**. Alcohol **B** was assembled though a Stille coupling between alkenyl iodide **E** and stannane **D**. Stannane **D** was accessed through a palladium catalyzed hydrostannylation reaction from desilylated **I**, in which the absolute and the relative stereochemistry was set using the Brown alkoxyallylboration reaction of aldehyde **J**.[28] Similar to De Brabander's approach, Fragment **E** was assembled through a vinylogous Mukaiyama aldol reaction between vinylketene silyl *N*,*O*-acetal **G** and aldehyde **H**.[26] In this case, however, a two-

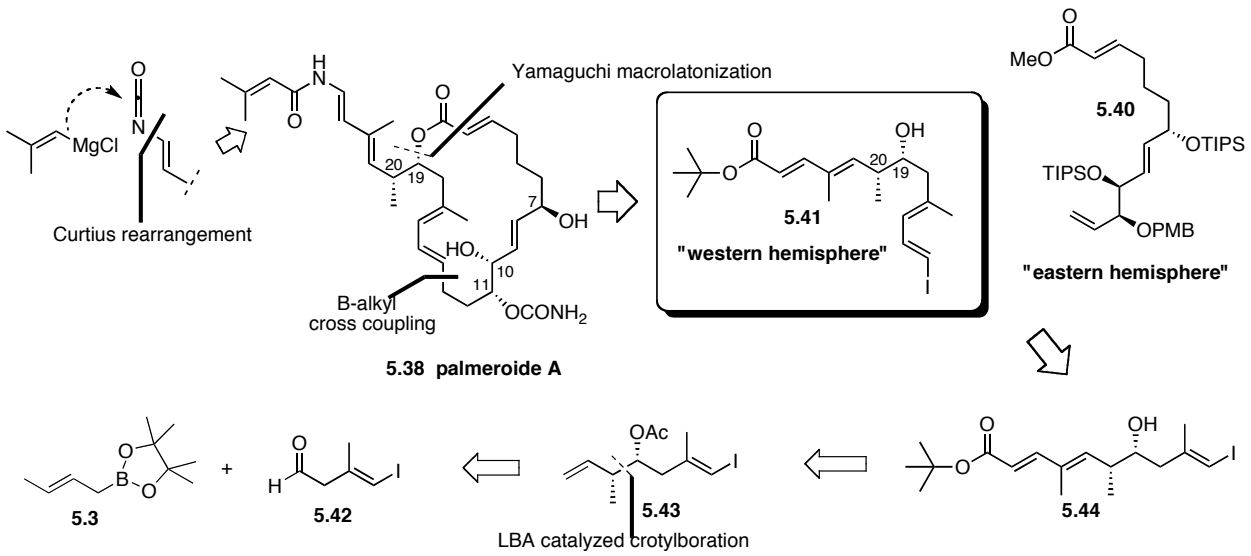
step oxidation and a stereoselective reduction process was used to correct the stereochemistry at C-19.



Scheme 5.9. Nicolaou's retosynthetic approach to palmerolide A **5.38**.[22]

5.4.4. Retrosynthesis of Hall and coworkers[18]

Taking into account the published work of De Brabander[21] and Nicolaou,[22] we envisioned a retro synthesis of palmerolide A wherein the macrolactone would be assembled using a Yamaguchi macrolactonization and preceded by a provocative Sp^2-Sp^3 cross-coupling between the borane derived from hydroboration of alkene **5.40** (eastern hemisphere) and vinyl iodide **5.41** (western hemisphere), thus establishing the C-14 and C-15 connection of the natural product (Scheme 5.10). The choice of representative carboxyl-protecting groups in the eastern and western fragments ensued from the requirement of selective methyl ester hydrolysis over the tert-butyl ester, in order to perform the desired Yamaguchi macrolactonization reaction. Vinyl iodide **5.41** was envisioned to arrive through a three-step homologation of precursor **5.44**. Lastly, the propionate unit in **5.44** was thought to arrive from the LBA **5.1**•$SnCl_4$-catalyzed crotylboration of aldehyde **5.42**.[1,2]



Scheme 5.10. Hall and coworkers retrosynthesis of palmerolide A.

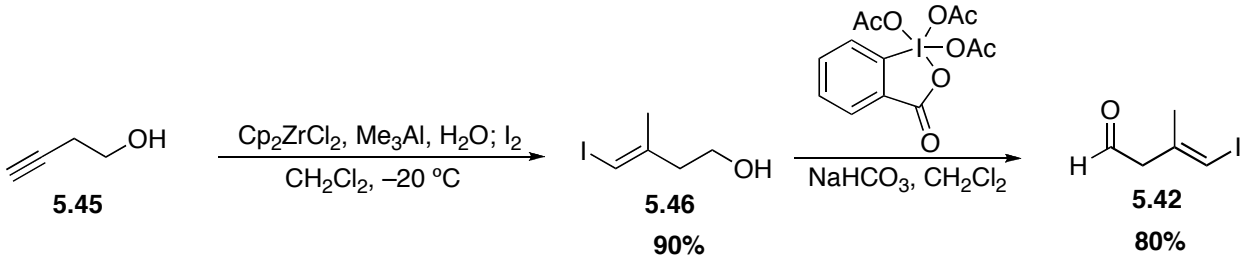
The construction of the "eastern hemisphere" **5.40** was realized by my colleague Marlin Penner. He utilized a catalytic enantioselective hetero Diels-Alder-allylboration sequence and a Claisen-Ireland rearrangement with an alkenylboronate as a precursor as the key steps to install the C7, C10 and C11 stereocenters.[31] The hydrolysis of the pyran acetal (generated from the hetero Diels-Alder reaction) and further functional group manipulation gave rise to **5.40**.

5.4.5. Synthesis of the "western hemisphere" 5.41

5.4.5.1. Synthesis of aldehyde vinyl iodide 5.42

Following a literature procedure, the synthesis of aldehyde **5.42** required the Wipf modification[32] of Negishi carboalumination.[33] Accordingly, 3-butynol **5.45** was subjected to carboalumination procedure as reported by Wipf, and the resulting organoaluminum species was quenched with iodine to afford the corresponding vinylic iodide **5.46** in excellent yield (Scheme 5.11). The necessary aldehyde **5.42** was then attained through Dess-Martin periodinane oxidation of the alcohol functionality in **5.46**.[34] It was anticipated that the β,γ-unsaturated aldehyde **5.42** would be a sensitive compound. In fact, literature reports concerning the use of aldehyde **5.42** recommended the immediate usage of the crude material that is obtained after the work-up and evaporation of the oxidation reaction. This approach was bound to leave non-negligible amounts of protic residues including water, which would potentially interfere with the LBA catalyzed

crotylboration reaction, (especially in large-scale reactions). After careful optimization, a procedure involving multiple extractions with water followed by neutralization with aqueous sodium bicarbonate and then distillation under high vacuum (80 ºC, 0.13 torr) provided the requisite aldehyde in essentially pure form and good yield as a faint yellow oil. Indeed, the usage of crude aldehyde **5.42** in the key crotylation reaction gave the resulting product in diminished yield and enantioselectivity.



5.45 → **5.46** (90%) → **5.42** (80%)

Scheme 5.11. Preparation of aldehyde **5.42**.

5.4.5.2. LBA catalyzed (*E*)-crotylboration of aldehyde 5.42

The stage was set for the application of the LBA **5.1**•$SnCl_4$-catalyzed (*E*)-crotylboration of aldehyde **5.42** (Figure 5.5). At the onset, the reaction was optimized with Vivol **5.47** as the diol. In the event, the desired product was obtained in 96% yield and 84% *ee.* It had been observed in previous studies that the ring size on the diol in the LBA catalyst was a crucial element to obtain high enantioselectivities for sterically hindered substrates.[1] Accordingly, diol **5.48** equipped with cycloheptyl substituents and **5.49** containing the cyclohexyl rings were screened for the LBA catalyzed crotylboration reaction. In the event, we observed optimal results with diol **5.48**, and the desired homoallylic alcohol product was obtained in 90% yield and 89% *ee*. Finally, switching on to the difluorinated analogue of diol **5.48**, i.e. diol **5.50**, the desired product was obtained in near quantitative yield and in 90% *ee* (Figure 5.5). As a consequence of the Type I nature of the crotylboration reaction, the *syn* diastereomer was not observed. Having identified the optimal diol for the LBA catalyst, we explored lowering the catalyst loading to 5-mol% for large-scale applications. Gratifyingly, similar results were obtained by running the reaction over 60 hours at –78 ºC.

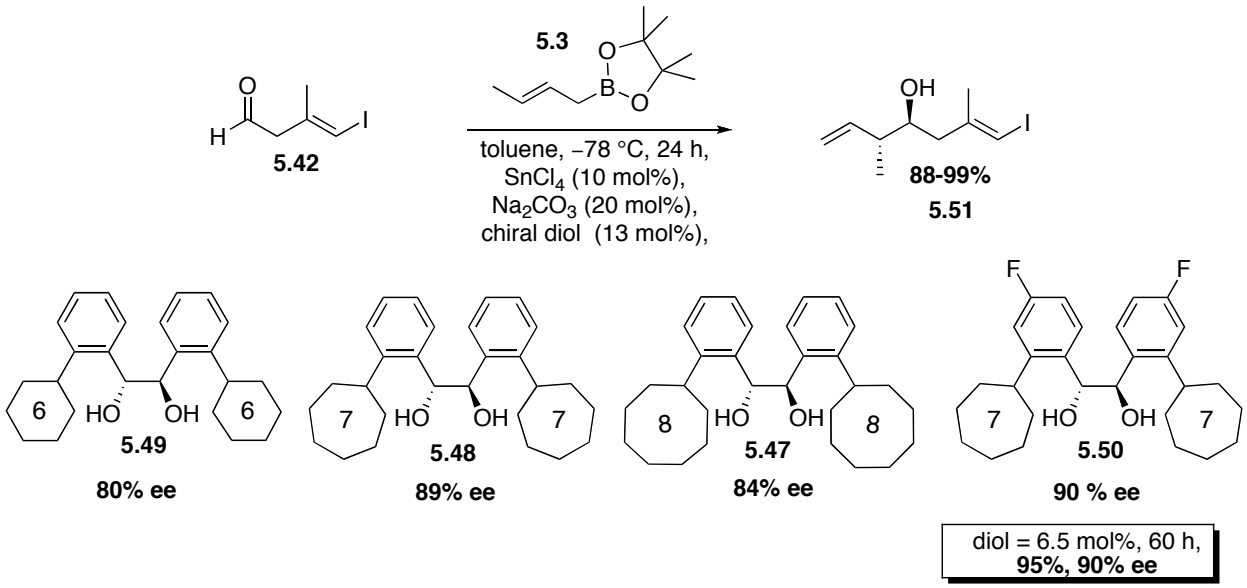
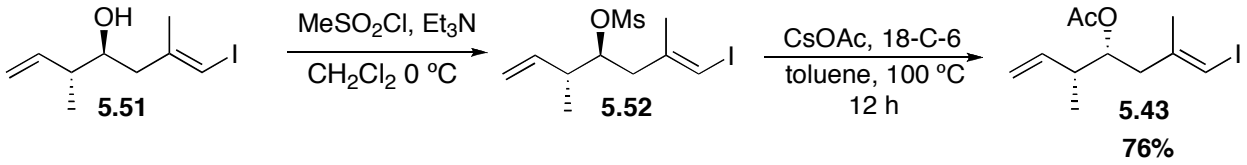


Figure 5.5. Optimization of (*E*)-crotylboration reaction with aldehyde **5.42**.[18]

5.4.5.3. Inversion of alcohol stereochemistry

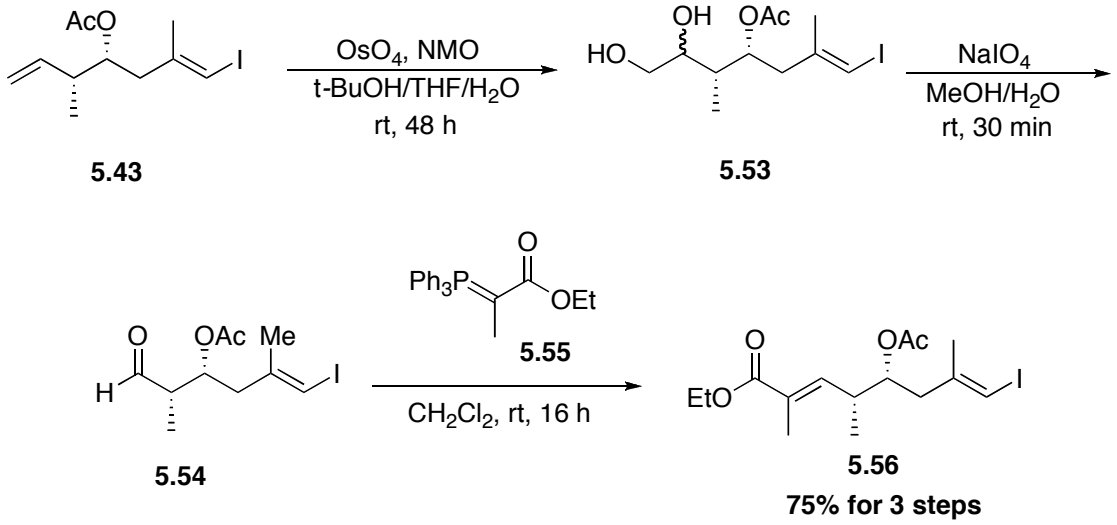
The next step in the synthesis called for an inversion of the stereochemistry at the alcohol center. Although De Brabander had reported a Mitsunobu inversion of a similar secondary alcohol,[35] this reaction only gave a moderate yield of 30% in our hands. We thus explored other possible methods for the inversion of stereochemistry at the secondary alcohol in **5.51**. To this end, Ikegami's two-step procedure involving the activation of the alcohol as the corresponding mesylate **5.52** and displacement of the mesylate with acetate anion was explored (Scheme 5.12).[36] Delightfully, under the original reaction conditions, the desired *syn*-diastereomer **5.43** was obtained in a significantly improved yield of 76%, with no evidence of the formation of the corresponding elimination product. Additionally, this reaction was consistently reproducible on large scale.



Scheme 5.12. Inversion of stereochemistry at the carbinol center of **5.51**.

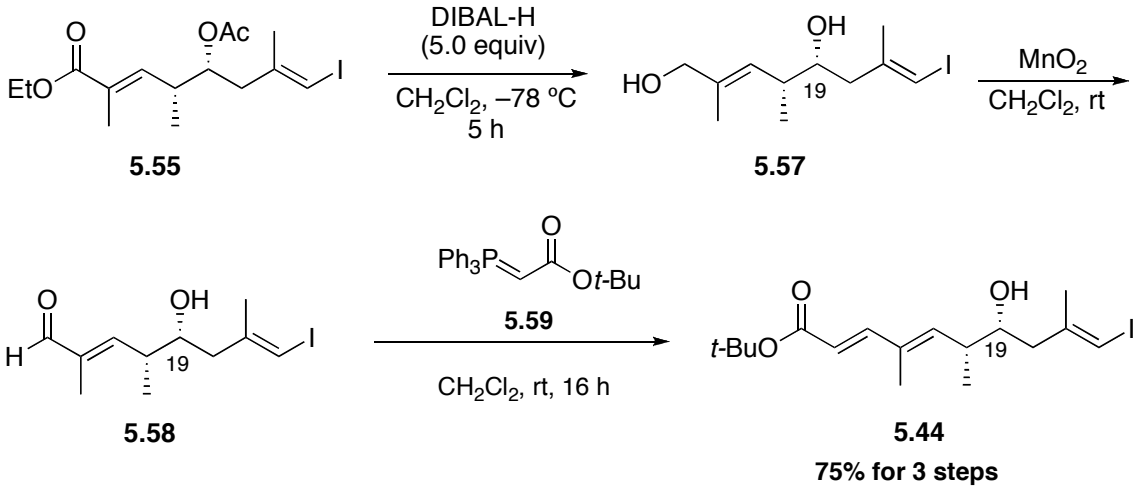
5.4.5.4. Preparation of *tert*-butyl ester 5.44

Elaboration of acetate **5.43** into advanced fragment **5.44** required the selective oxidative cleavage of the terminal double bond followed by a Wittig olefination (Scheme 5.13). After surveying the literature, it was ascertained that the trisubstituted olefin containing the alkenyl iodide moiety would not participate in the dihydroxylation reaction. In the event, following literature conditions, subjecting acetate **5.43** to catalytic osmium tetroxide and NMO as the co-oxidant in a mixture of THF, *t*-BuOH and water led to clean and selective dihydroxylation of the mono-substituted olefin thus providing the diol intermediate **5.53**, in an inconsequential 7:1 diastereoisomeric ratio.[37] After quick filtration through a pad of silica, the thus obtained diol **5.53** was subjected to oxidative cleavage to afford the requisite aldehyde **5.54** in excellent yield. This aldehyde was subjected to a high yielding Wittig reaction with phosphorane **5.55**, and the desired enoate **5.56** was obtained as a single isomer (Scheme 5.13).



Scheme 5.13. Preparation of the ester **5.55**.

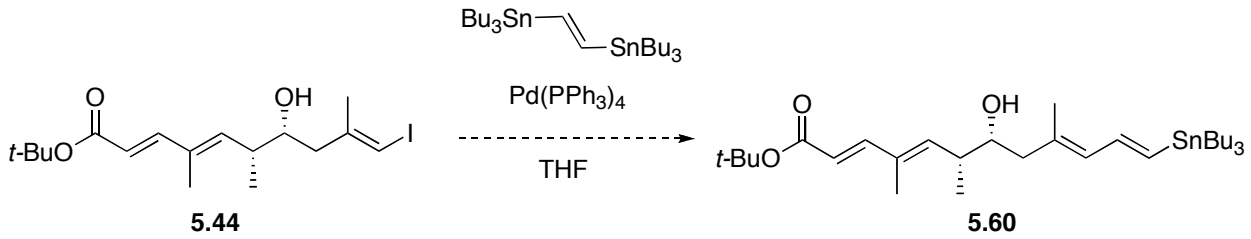
Ethyl ester **5.56** was then transformed into the desired dienoate-ester **5.44** through a reduction, oxidation and Wittig reaction process (Scheme 5.14). Firstly, the ester **5.56** was reduced with DIBAL-H to the corresponding diol **5.57**. Selective allylic oxidation of the allylic alcohol was accomplished using MnO_2 to give the corresponding aldehyde **5.58**, and finally, a Wittig reaction with *tert*-butyl phosphorane **5.59** provided the advanced fragment **5.44**. The overall yield for this three-step operation was a remarkable 90%.



Scheme 5.14. Synthesis of *tert*-butylester **5.44**.

5.4.4.5. Completion of "western hemisphere" fragment 5.41 of palmerolide A

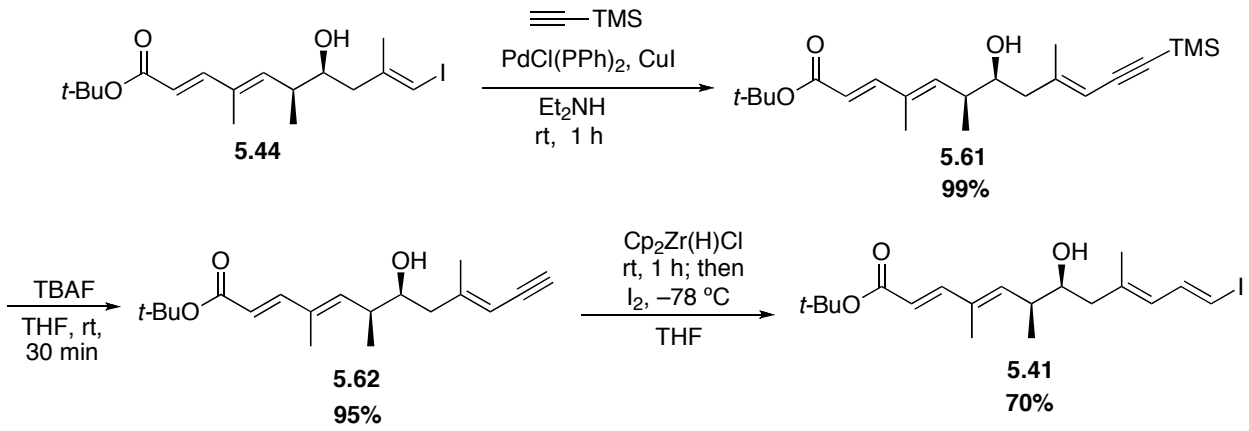
The next line of reactions involved the homologation of the alkenyl iodide **5.44** into butadienyl iodide **5.41**. At the onset, a Stille cross-coupling with bis-stannyl ethane, followed by a metal halogen exchange with iodine was envisaged.[38] However, in our hands, the first step of this reaction was unfruitful. The outcome was a mixture of products with a minimal amount of the desired product (Equation 5.4). One possible explanation for this result might be a competitive reaction of the in situ-generated stannane product **5.60** with the starting alkenyl iodide **5.44**. However, a slow addition of iodide **5.44** also failed to furnish the desired stannane **5.60**. Consequently, it was decided to abandon this approach and seek alternative methods.



Equation 5.4. Attempted preparation of stannane **5.60** via Stille coupling.

We therefore envisaged installing the (*E*)-iodo-diene through a hydrometallation reaction of the parent alkyne (Scheme 5.15). Consequently, **5.44** was subjected to a Sonagashira coupling

reaction with trimethylsilyl acetylene to afford the desired silylated alkyne **5.61** in quantitative yield. Next, the silyl group was removed under fluoride conditions to afford the desired terminal alkyne **5.62** in 95% yield. At this stage, we explored alkyne hydrozirconation followed by trapping with iodine to install the alkenyl iodide moiety of the western hemisphere.[39] The optimal conditions for this reaction required 2.05 equivalent of Schwartz's reagent and 2.1 equivalents of iodine. The extra equivalent of the zirconium reagent was required likely due to an acid base reaction between the free alcohol and the hydride of the Schwartz's reagent. In the event, the desired product **5.41** was obtained in 70% yield after purification by flash chromatography with neutralized silica gel.



Scheme 5.15. Final stages in the preparation of the "western hemisphere" of palmerolide A.

The stage was now set for the pivotal sp^3-sp^2 cross coupling.

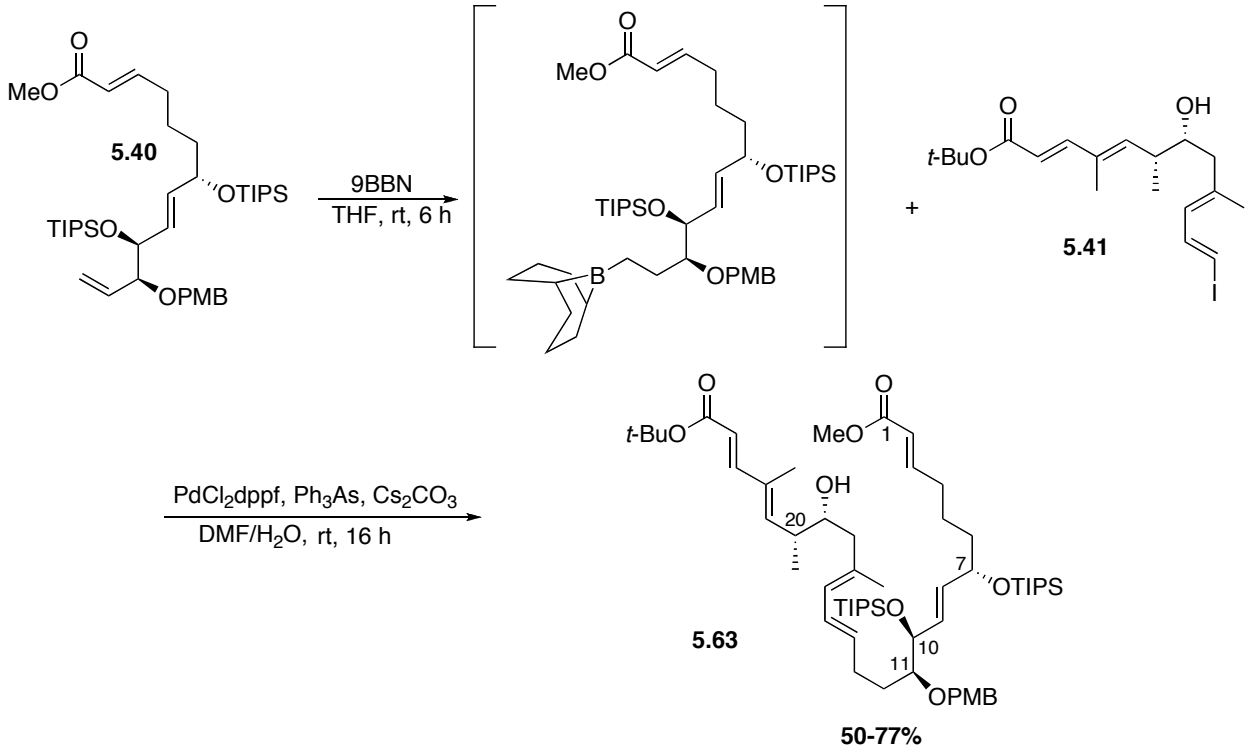
5.4.6 Late stages in the synthesis of palmerolide A

5.4.6.1 B-Alkyl Suzuki-Miyaura cross-coupling: union of advanced fragments 5.41 and 5.40

Having access to both building blocks of palmerolide A, we planned the union of two fragments **5.41** and **5.40** through a B-alkyl cross-coupling reaction. Fragment **5.40,** prepared by my colleague Marlin Penner, contained the requisite terminal olefin for the hydroboration reaction to generate the required alkylborane.[31] It was envisioned that the steric hindrance around the internal disubstituted bond due to adjacent bulky silyl groups would prevent this undesired hydroboration. For the actual cross-coupling we explored literature conditions for similar late stage B-alkyl cross-coupling reactions. After a survey of the literature, we became aware that

the Johnson modification[43] of the original procedure of Miyaura and coworkers[44] had been employed in the synthesis of several natural products with good success, partly because of the mildness of the reaction conditions.

Consequently, we decided to apply this method for the crucial union of the two building blocks **5.40** and **5.41**. In this reaction, we used 9-borabicyclo[3.3.1]nonane as the sterically hindered hydroborating reagent, and $PdCl_2$dppf as the precatalyst, triphenylarsine as the ligand, cesium carbonate in water as the requisite base and DMF as the solvent for the cross-coupling reaction. In the event, we obtained the desired cross-coupled product **5.63** in a very satisfying 77% yield in small-scale reaction (Scheme 5.16). The same conditions provided a non-optimized yield of 50% on larger scales. Moreover, the free C-17 alcohol was left untouched, and thus the construction of the macrolactone seco-acid only required the selective hydrolysis of the C-1 methyl ester belonging to the eastern hemisphere.



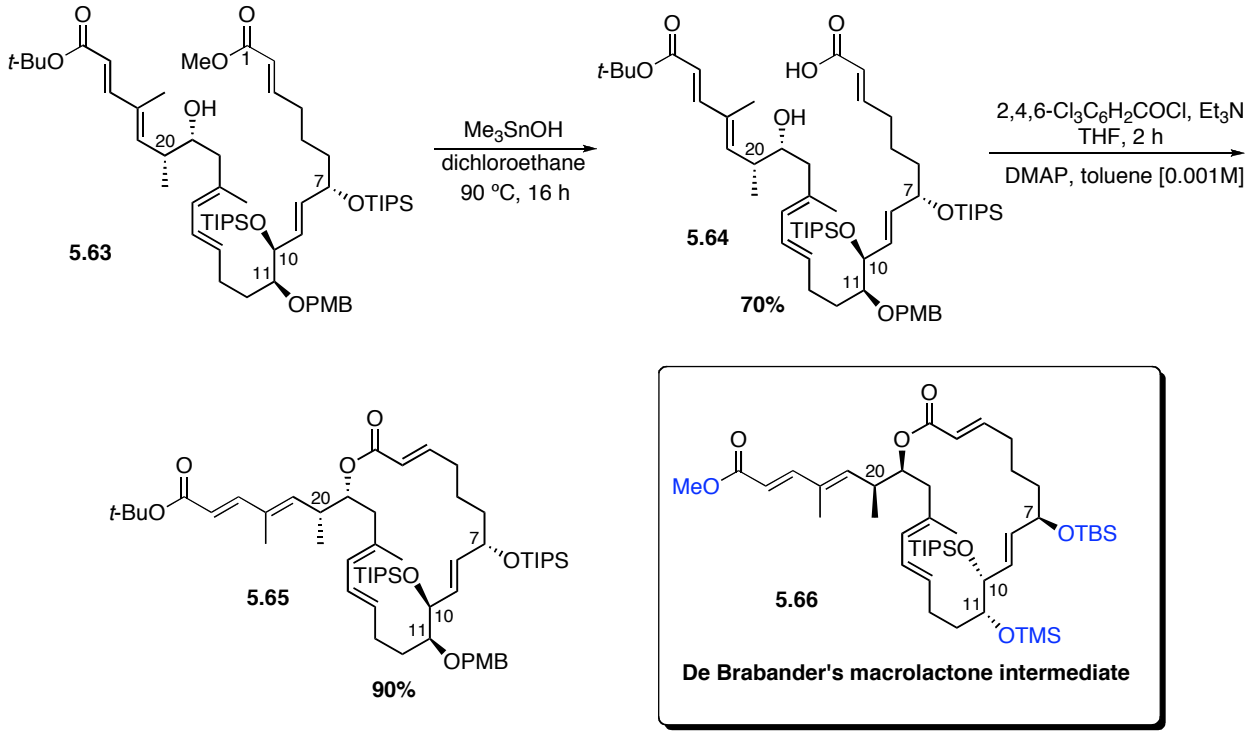
Scheme 5.16. Key B-alkyl cross-coupling en route to palmerolide A.

5.4.6.2 Construction of the macrolactone

The construction of the desired macrolactone required a mild and selective hydrolysis of the methyl ester over the *tert*-butyl ester. While surveying the literature, we came across a mild hydrolysis of methyl esters in the presence of trimethyltin-hydroxide as reported by Nicolaou and coworkers.[45] Gratifyingly, subjecting **5.63** to hydrolysis under Nicolaou's original conditions gave the desired seco-acid **5.64** in 70% yield, and thus setting the stage for the Yamaguchi macrolactonization reaction (Scheme 5.17).

In the event, the seco-acid **5.64** was transformed into the corresponding mixed anhydride and then slowly transferred into a 0.001 M toluene solution of DMAP. The desired macrolactone **5.65** was obtained with ease in 90% yield (Scheme 5.17).

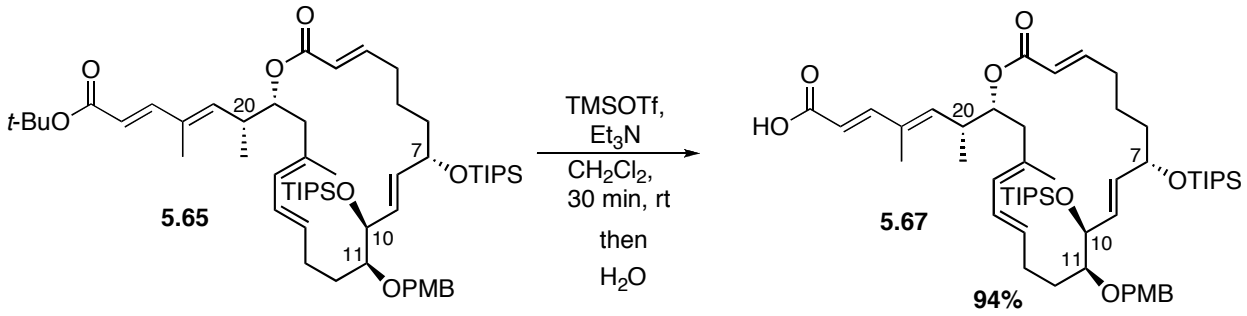
The key variations between macrolactone **5.65** and that of De Brabander's macrolactone **5.66**[21] included the presence of a *tert*-butyl ester over a methyl ester on the dienoate side chain, the presence of the para-methoxybenzyl ether over the trimethylsilyl ether at C-11 and the silyl protecting group at the C-7 carbinol.



Scheme 5.17. Construction of macrolactone **5.65**.

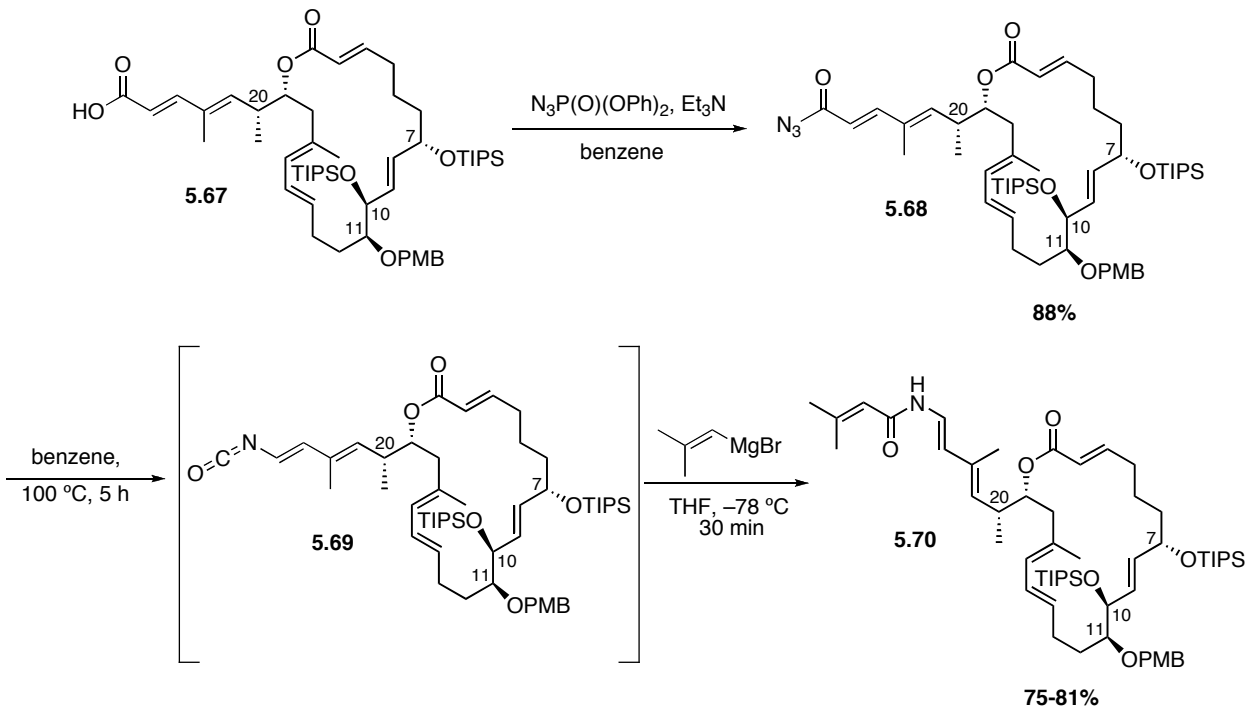
5.4.6.3 Installation of the dienamide side chain

From here onwards, our synthesis of palmerolide A followed steps similar to the reported synthesis of De Brabander and coworkers, albeit, requiring different conditions for the hydrolysis of the *tert*-butyl ester.[21] To this end, it was realized that the molecule was very sensitive to either acid or strong base. As such, we explored neutral conditions for the hydrolysis of the *tert*-butyl ester. After surveying the literature, the conditions reported originally by Bannwarth and coworkers, involving the use of trimethylsilyl triflate as a Lewis acid to trigger the loss of isobutylene, appeared most promising.[44] Gratifyingly, subjecting the tert-butyl ester **5.65** under these conditions provided a clean trans-esterification to the corresponding trimethylsilyl ester, which was hydrolyzed by washing the reaction mixture with water (Equation 5.5). Using this process, the desired acid **5.67** was obtained in 94% yield.



Equation 5.5. Mild hydrolysis of *tert*-butyl ester **5.65**.

From here onwards, the exact procedure of De Brabander was followed to install the sensitive dienamide moiety. Accordingly, the carboxylic acid was transformed into the corresponding acyl azide **5.68** in 88% yield, setting the stage for a Curtius rearrangement.[21] The requisite azide **5.68** was heated in benzene to trigger the rearrangement into the corresponding isocyanate **5.69** (not isolated). This isocyanate **5.69** was then trapped with 2-methylpropenyl magnesium bromide to the corresponding dienamide **5.70** (Scheme 5.18).

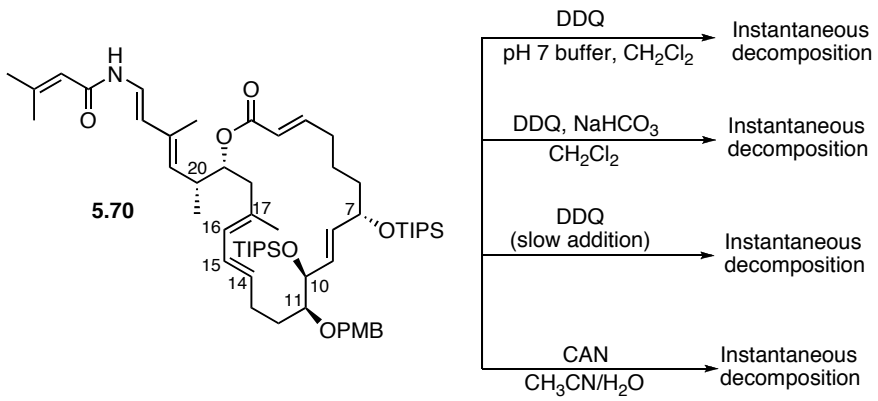


Scheme 5.18. Synthesis of the dienamide **5.70**.

5.4.6.4 Completion of the total synthesis of palmerolide A

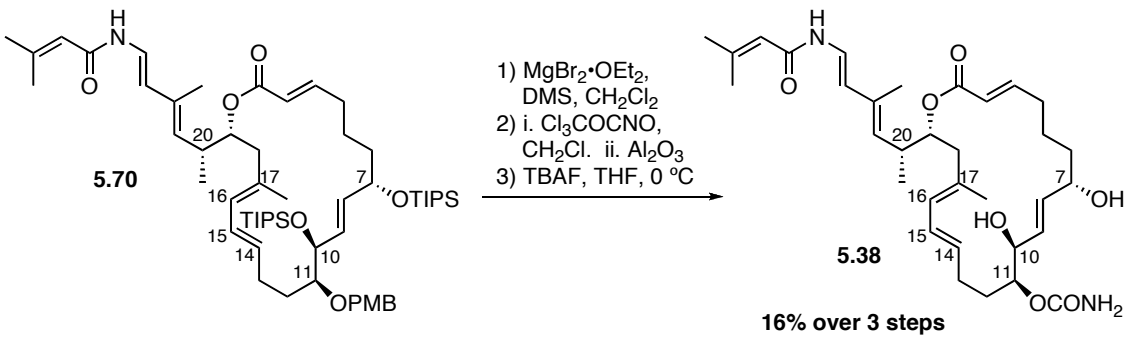
Having made the dienamide intermediate **5.70**, the remaining sequence of steps to accomplish the total synthesis of the palmerolide A involved the deprotection of the PMB ether at C-11 and transformation of the resultant free alcohol into the corresponding carbamate, followed by global silyl deprotection.

Accordingly, we subjected dienamide **5.70** to standard conditions for PMB ether cleavage to afford the secondary alcohol. Surprisingly, the molecule underwent instantaneous decomposition with oxidative conditions. Similar results were also obtained when we performed the ether cleavage under the presence of pH 7 buffer or excess $NaHCO_3$ (to quench the diphenol by-product) (Scheme 5.19). The same was also true when DDQ was slowly added to the reaction mixture. Moreover, a comparable decomposition pattern was also observed when we utilized ceric ammonium nitrate (CAN) as the oxidative reagent (Scheme 5.19).



Scheme 5.19. Unsuccessful attempts towards the deprotection of the C-11 PMB ether.

At this stage, we rationalized that the electron rich character of the dienamide moiety and the butadiene functionality between C-14 and C-17, drastically and irreversibly interfered with the electron sink of DDQ and related oxidative reagents, probably through formation of allylic radicals derived from the C-14–C17 diene framework. Consequently, we resorted to methods involving non-oxidative Lewis acid conditions. After surveying a host of Lewis acidic and neutral methods used in the cleavage of PMB ethers, we eventually arrived at condition employing the $MgBr_2 \bullet OEt_2$ and dimethylsulfide, which gave the desired free alcohol product in 30-50% isolated yield, the rest being side products arising from the decomposition of the starting material.[45] In our hands, other methods either lead to unidentified side-product or complete decompostion of the dienamide starting material. At this stage, the synthesis would once again merge with that of De Brabander and coworkers. Accordingly, the free alcohol at C-11 was transformed into the corresponding carbamate, and global desilylation under the presence of TBAF at 0 ºC afforded palmerolide A **5.38**. Synthetic palmerolide A possessed spectral properties in accordance with the literature (See experimental section).[19,20,22]



Scheme 5.20. Final stages in the total synthesis of palmerolide A.

5.5. Conclusion

In conclusion, I was able to successfully expand the reagent scope of the LBA **5.1**•$SnCl_4$-catalyzed aldehyde allylboration to include a novel reagent, 2-bromoallylboronate **5.5**, the product of which can be readily transformed into the important exo-methylene lactones. Through the enantioselective synthesis of a small natural product (+)-dodoneine, we showed that the LBA **5.1**•$SnCl_4$-catalyzed allylboration, compared favorably with that of well-established methods of Brown and Keck. Moreover, the LBA catalyzed addition of allylboronate **5.1** onto chiral aldehydes showed remarkable selectivity in the matched case, and the desired product was obtained in very high diastereoselectivity. Finally, the LBA catalyzed crotylboration methodology was put to test with a very sensitive aldehyde, **5.42**, and the desired product was obtained in very good enantio- and diastereoselectivity and excellent yield. This product **5.51**, of the LBA catalyzed crotylboration was successfully transformed into the western hemisphere **5.41** of the natural product palmerolide A. Additionally, using boron based B-alkyl Suzuki-Miyaura cross coupling, I was able to successfully connect the two advanced fragments and complete the total synthesis of palmerolide A.

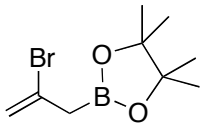
5.6 Experimental

5.6.1 General

Unless otherwise noted, all reactions were performed under an argon atmosphere using flame-dried glassware. Toluene, hexanes and CH_2Cl_2 were distilled from CaH_2. THF and Et_2O were distilled over sodium/benzophenone ketyl. All aldehydes were purified by Kugelrohr distillation, prior to use. Molecular sieves were prepared by heating under vacuum at 130 ºC (overnight) and then stored inside an oven maintained at 125 ºC. Thin layer chromatography (TLC) was performed on Merck Silica Gel 60 F254 plates and, visualized with UV light, $KMnO_4$ and 5% phosphomolybdic acid/EtOH (PMA). NMR spectra were recorded on Varian INOVA-300, INOVA-400, INOVA-500 or Unity 500 instruments. The residual solvent protons (^1H) or the solvent carbons (^{13}C) were used as internal standards. Boron NMR spectra are referenced to

external $BF_3 \cdot OEt_2$; ^{19}F spectra are referenced to external $CFCl_3$. ^1H NMR data are presented as follows: chemical shift in ppm upfield towards tetramethylsilane (multiplicity, coupling constant, integration). The following abbreviations are used in reporting NMR data: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; qt, quartet of triplets; dd, doublet of doublets; dt, doublet of triplets; AB, AB quartet; m, multiplet. High-resolution mass-spectra were recorded by the University of Alberta Mass Spectrometry Services Laboratory, using either electron impact (EI) or electrospray (ES) ionization techniques. Infrared spectra and optical rotations were recorded by University of Alberta Spectral Services. Optical purities of homoallylic alcohol products were measured by chiral HPLC (chiralcel OD column) or by formation of Mosher esters and subsequent ^1H or ^{19}F NMR analysis of the crude product.

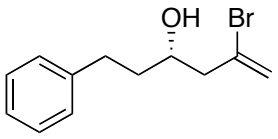
5.6.2 2-(2-Bromo-allyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (5.5)



2-Bromoallyl diisopropoxyboronate[5] (4.99 g, 19.5 mmol, 1.00 equiv) was dissolved in CH_2Cl_2 (20 mL). Pinacol (2.31 g, 19.5 mmol, 1.00 equiv) was added and the mixture was stirred for 30 min and concentrated *in vacuo*. The residue was purified by bulb-to-bulb distillation (75 ºC, 0.6 mm Hg) to provide 4.70 g of the desired product **5.5** as a colorless oil in >95% yield. Boronate **5.10** was stored under argon at –20 ºC for long-term storage and redistilled prior to use. IR (cast film) 2980, 2933, 1630, 1381, 137, 1352, 1167, 875, 846 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.57 (d, J = 1.3 Hz, 1H), 5.36 (d, J = 1.3 Hz, 1H), 2.31 (s, 2H), 1.29 (s, 12H); ^{13}C NMR (125.6 MHz, $CDCl_3$) δ 116.8, 83.9, 24.7 (peak of carbon bearing the boron atom did not appear due to quadrupolar broadening); ^{11}B NMR δ 32.2 ppm; HRMS (EI) Calcd. $C_9H_{16}O_2BrB$: 245.04631. Found: 245.04675.

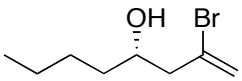
5.6.3 Catalytic enantioselective bromoallylboration of aldehydes

5.6.3.1 (*S*)-5-Bromo-1-phenyl-hex-5-en-3-ol (5.11)



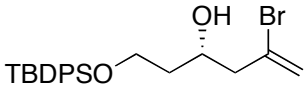
Into a flame-dried 25 mL round bottom flask equipped with a stir bar was added F-Vivol **5.1** (47.0 mg, 0.10 mmol, 0.0100 equiv), anhydrous Na_2CO_3 (16.1 mg, 0.152 mmol, 0.150 equiv) and 4Å molecular sieves (50.0 mg, previously dried under high vacuum at 100 ºC and stored in an oven). The flask was capped with a rubber septum and placed under argon followed by the addition of freshly distilled toluene (1.0 mL). Thus obtained mixture was stirred for 2 min followed by the addition of $SnCl_4$ (1.0 M in CH_2Cl_2, 76.0 μL, 0.0760 mmol, 0.0760 equiv). The catalyst solution was stirred at room temperature for 5 min and cooled to –78 ºC and maintained at this temperature for 15 min. This was followed by addition of 2-bromoallylboronic acid pinacol ester **5.5** (280 mg, 1.10 mmol, 1.10 equiv) and after 30 min, hydrocinnamaldehyde (132 μL, 1.00 mmol, 1.00 equiv) was added drop-wise. The reaction mixture was let to stir for 24 h at to –78 ºC, upon which DIBAL-H (1.0 M in toluene, 2.00 mL, 2.00 mmol, 2.00 equiv) was added to quench any unreacted aldehyde. The reaction mixture was stirred for an additional 15 min and 1.0 *N* HCl (4.0 mL) was added. The resulting mixture was allowed to warm to room temperature and let to stir for 30 min. The mixture was extracted with Et_2O (3 x 15 mL) and the combined organic extracts were washed with brine (15 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give an oily residue, which was purified by flash chromatography (5% EtOAc/hexanes) to provide 151 mg of the requisite homoallylic alcohol product **5.11** in 86% yield with spectral properties in accordance with the literature. $[\alpha]_D^{25}$ – 14.91 (*c* 0.96, $CHCl_3$); IR (cast film) 3387, 3026, 2923, 2860, 1631, 1496, 1454, 1120, 1078, 1057, 891, 748, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.29 (m, 2H), 7.25-7.19 (m, 3H), 5.72-5.71 (m, 1H), 5.56 (apparent d, *J* = 2.0 Hz, 1H), 4.04-3.96 (m, 1H), 2.91-2.84 (m, 1H), 2.78-2.66 (m, 1H), 2.61-2.58 (m, 2H), 2.01 (br s, 1H), 1.88-1.78 (m, 2H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 141.8, 130.5, 128.5, 128.4, 125.9, 119.8, 68.6, 49.4, 38.1, 32.0; HRMS (EI) Calcd. $C_{12}H_{15}OBr$: 256.02859. Found: 256.02841. HPLC (Chiralcel OD) 5:95 *i*-PrOH/hexane, 0.5 mL/min, λ = 210 nm, T_{major} = 21.2 min, T_{minor} = 32.2 min, 91% *ee*.

5.6.3.2 (*S*)-2-Bromo-oct-1-en-4-ol (5.12)



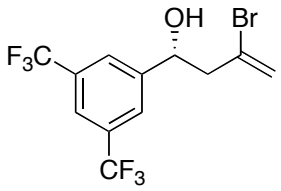
Following the procedure used in the preparation of **5.11**, the title compound was obtained in quantitative yield. The optical purity of the product was determined through HPLC analysis of the corresponding *p*-NO_2-benzoylester derivative. $[\alpha]_D^{25}$ –5.58 (*c* 0.19, $CHCl_3$); IR (cast film) 3363, 2957, 2932, 2860, 1631, 1467, 1125, 1032, 888 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.69-5.68 (m, 1H), 5.52 (d, *J* = 1.4 Hz, 1H), 3.95-3.89 (m, 1H), 2.59-2.47 (m, 2H), 1.82 (br s, 1H), 1.52-1.40 (m, 6H), 0.91 (t, *J*= 7.2 Hz, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 130.9, 119.5, 69.0, 36.1, 27.7, 22.6, 14.0; HRMS (EI) Calcd. $C_8H_{10}O$: 127.11229. Found: 127.11234. HPLC (Chiralcel OD) 2:98 *i*-PrOH/hexane, 0.5 mL/mL, λ = 250 nm, T_{major} = 15.3 min, T_{minor} = 16.9 min, 92% *ee*.

5.6.3.3 (*S*)-5-Bromo-1-(*tert*-butyl-diphenyl-silanyloxy)-hex-5-en-3-ol (5.13)



Following the procedure used in the preparation of **5.11**, the title compound was obtained in 92 % yield. The optical purity of the title compound was determined to be 94.5% *ee* by derivatization with (S)-Mosher acid chloride and subsequent ^1H NMR analysis. $[\alpha]_D^{25}$ +4.40 (*c* 0.43, $CHCl_3$); IR (cast film) 3439, 2999, 2931, 2856, 1631, 1427, 1112, 1084, 737, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72-7.70 (m, 4H), 7.48-7.41 (m, 6H), 5.70 (s, H), 5.53 (d, *J* = 0.8 Hz, 1H), 4.30-4.26 (m, 1H), 3.95-3.87 (m, 2H), 3.20 (br s, 1H), 2.68 (dd, *J* = 6.2, 11.4 Hz, 1H), 2.55 (dd, *J* = 3.8, 11.4 Hz, 1H), 1.77-1.74 (m, 5H), 1.09 (s, 9H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 135.6, 133.0, 130.7, 127.8, 119.2, 68.9, 62.9, 49.2, 37.5, 26.9, 19.1; HRMS (ESI) Calcd. $C_{22}H_{29}O_2SiBrNa$: 455.10124. Found: 455.10122.

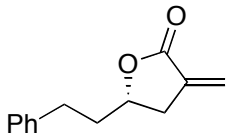
5.6.6.4 (*R*)-1-(3,5-Bis-trifluoromethyl-phenyl)-3-bromo-but-3-en-1-ol (5.14)



Following the procedure used in the preparation of **5.11**, the title compound was obtained in 94% yield. The optical purity of the title compound was determined to be 96% *ee* through condensation with (S)-Mosher acid chloride and subsequent analysis by ^{1}H NMR. $[\alpha]_D^{25}$ +6.78 (*c* 0.18, $CHCl_3$); IR (cast film) 3425, 2944, 1719, 1632, 1376, 1279, 1174, 1135, 897, 708 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (s, 2H), 7.82 (s, 1H), 5.73-5.72 (m, 1H), 5.61 (d, *J* = 1.5 Hz, 1H), 5.20-5.17 (m, 1H), 2.85-2.77 (m, 2H), 2.45 (d, *J* = 2.5 Hz, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 145.2, 131.8 (q, *J* = 33.3 Hz), 128.6, 126.0, 123.2 (q, *J* = 272.4 Hz), 121.7 (m), 121.2, 70.4, 51.5; HRMS (EI) Calcd. $C_9H_3F_6O$: 241.00880. Found: 241.00877.

5.6.4 Carbonylative lactonization of bromo-homoallylic alcohols

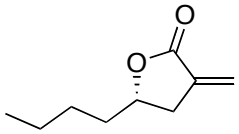
5.6.4.1 (*S*)-3-Methylene-5-phenethyl-dihydro-furan-2-one (5.15)



Alcohol **5.11** (52.9 mg, 0.207 mmol, 1.00 equiv) was dissolved in THF (6.0 mL). The solution was degassed and purged with argon. $Ni(CO)_2(PPh_3)_2$ (51.2 mg, 0.236 mmol, 1.14 equiv) was added in one portion, followed by the addition of Et_3N (59.0 μL, 0.420 mmol, 2.02 equiv) and the reaction mixture was heated to reflux at 80 ºC. After 15 min, the color changed from greenish yellow to dark green at which time TLC indicated complete conversion of the starting material. The reaction mixture was cooled to room temperature and diluted with Et_2O (25 mL) and washed with 1.0 *N* HCl (5.0 mL). The organic layer was separated and washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give an oily residue, which was purified by flash chromatography (0-10% EtOAc / hexanes) to provide 41.8 mg of the lactone **14a** in 94% yield. $[\alpha]_D^{25}$ –31.45 (*c* 0.22, $CHCl_3$); IR (cast film) 3027, 2930, 2863, 1769, 1496, 1455, 1198, 1029, 75, 701; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.28 (m, 2H), 7.23-7.19

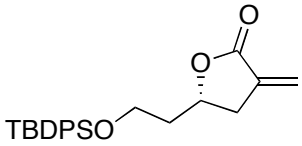
(m, 3H), 6.24 (t, *J* = 3.0 Hz, 1H), 5.63 (t, *J* = 2.7 Hz, 1H), 4.55-4.46 (m, 1H), 3.05 (ddt, *J* = 2.4, 7.7, 17.1 Hz, 1H), 2.90-2.70 (m, 2H), 2.59 (ddt, *J* = 3.0, 6.2, 18.6 Hz, 1H), 2.11-2.01 (m, 1H), 1.99-1.89 (m, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 170.2, 140.6, 134.5, 128.5, 128.4, 126.2, 122.2, 38.1, 33.5, 31.3; HRMS (E) Calcd. $C_{13}H_{14}O_2$: 202.09938. Found: 202.09857. HPLC (chiralcel OD) 10:90 *i*-PrOH/hexane, 0.5 mL/mL, λ = 210 nm, T_{major} = 23.8 min, T_{minor} = 25.4 min, 93% *ee*.

5.6.4.2 (*S*)-5-Butyl-3-methylene-dihydro-furan-2-one (5.16)



Following the procedure used in the preparation of **5.15**, except that flash chromatography was performed using 0-10% pentane/Et_2O gradient. The title compound was obtained in 78% yield. $[\alpha]_D^{25}$ –38.49 (*c* 0.13, $CHCl_3$); IR (cast film) 2958, 2933, 2862, 1764, 1277, 1118, 1004; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.21 (t, *J* = 2.5 Hz, 1H), 5.63 (t, *J* = 2.5 Hz, 1H), 4.53-4.48 (m, 1H), 3.04 (ddt, *J* = 2.6, 7.7, 17.0 Hz, 1H), 2.57 (ddt *J* = 3.0, 6.0, 17.0 Hz, 1H), 1.77-1.70 (m, 1H), 1.64-1.57 (m, 1H), 1.49-1.41 (m, 1H), 0.91 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 121.8, 76.8, 36.0, 33.6, 27.0, 22.4, 13.9; HRMS (EI) Calcd. $C_9H_{14}O_2$: 154.09938. Found. 154.09911.

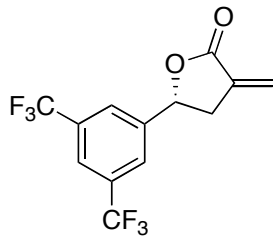
5.6.4.3 (*S*)-5-[2-(*tert*-Butyl-diphenyl-silanyloxy)-ethyl]-3-methylene-dihydro-furan-2-one (5.17)



Following the procedure used in the preparation of **5.15,** the title compound was obtained in 85% yield. $[\alpha]_D^{25}$ –25.09 (*c* 0.64, $CHCl_3$); IR (cast film) 3071, 2957, 2931, 2858, 1767, 1428, 1112, 823, 739, 703; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68-7.65 (m, 4H), 7.46-7.38 (m, 6H), 6.23 (t, *J* = 2.8 Hz, 1H), 5.62 (t, *J* = 2.3 Hz, 1H), 4.79 (m, 1H), 3.87 (ddd, *J* = 4.8, 7.9, 10.5 Hz, 1H), 3.79 (dd, *J* = 5.5, 10.8 Hz, 1H), 3.06 (ddt, *J* = 2.5, 7.7, 17.0 Hz, 1H), 2.64 (ddt, *J* = 2.9, 6.1, 17.0 Hz,

1H), 2.00-1.94 (m, 1H), 1.89-1.82 (m, 1H), 1.07 (s, 9H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 170.2, 135.5, 134.6, 133.3, 129.8, 127.7, 122.0, 74.8, 59.8, 39.0, 33.6, 26.9, 19.2; HRMS (ESI) Calcd. $C_{23}H_{28}O_3SiNa$: 403.16999. Found: 403.16997.

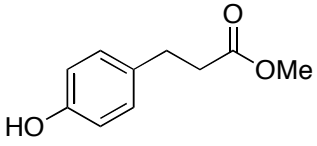
5.6.4.4 (*R*)-5-(3,5-Bis-trifluoromethyl-phenyl)-3-methylene-dihydro-furan-2-one (5.18)



Following the procedure used in the preparation of **5.14,** the title compound was obtained in 80% yield. $[\alpha]_D^{25}$ +4.86 (*c* 0.65, $CHCl_3$); IR (cast film) 3100, 2935, 1776, 1668, 1627, 1388, 1353, 1283, 1180, 11.4, 898, 706; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.80 (s, 1H), 6.38 (t, *J* = 2.8 Hz, 1H), 5.77 (t, *J* = 2.3 Hz, 1H), 5.63 (t, *J* = 7.5 Hz, 1H), 3.54 (ddt, *J* = 2.4, 8.1, 17 Hz, 1H), 2.90 (ddt, *J* = 2.9, 7.0, 17 Hz, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 169.1, 142.5, 132.7, 132.4 (q, *J* = 33.6 Hz), 125.5, 123.0 (q, *J* = 272.8 Hz), 122.4 (q, *J* = 3.6 Hz), 76.1, 36.0; HRMS (EI) Calcd. $C_{13}H_8O_2F_6$: 310.04285. Found: 310.04275.

5.6.5 Total synthesis of (+)-dodoneine

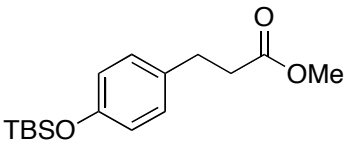
5.6.5.1 3-(4-Hydroxy-phenyl)-propionic acid methyl ester (5.31)



4-Hydroxyhydrocinnamic acid (15.0 g, 90.4 mmol, 1.00 equiv) was dissolved in MeOH (150 mL). Concentrated H_2SO_4 (0.890 mL, 0.0100 equiv) was then added and the reaction mixture was heated to reflux for 2 h. After the elapsed time, the reaction mixture was concentrated *in vacuo* and the residue was dissolved in EtOAc (120 mL) and washed with saturated aqueous $NaHCO_3$, brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* providing the

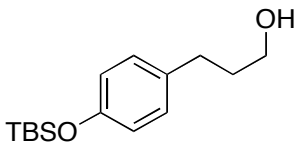
desired methylester **5.31** in quantitative yield. IR (cast film) 3395, 3023, 2954, 1713, 1614, 1516, 1441, 1223, 1103, 831 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (br s, 1H), 7.03 (d, *J* = 8.4 Hz, 2H), 6.80 (d, *J* = 8.4 Hz, 2H), 3.68 (s, 3H), 2.88 (t, *J* = 7.6 Hz, 2H), 2.62 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 174.6, 154.5, 132.0, 129.3, 115.5, 51.9, 36.1, 30.1; HRMS (EI) Calcd. $C_{10}H_{12}O_3$: 180.07864. Found: 180.07867.

5.6.5.2 3-[4-(*tert*-Butyl-dimethyl-silanyloxy)-phenyl]-propionic acid methyl ester (5.32)



Phenol **5.31** (8.00 g, 44.4 mmol, 1.00 equiv) was charged into a flame-dried round bottom flask followed by the addition of CH_2Cl_2 (150 mL). Under argon was then added TBSCl (7.40 g, 48.9 mmol, 1.10 equiv) followed by imidazole (4.50 g, 66.7 mmol, 1.50 equiv). The reaction mixture was stirred at ambient temperature overnight. Water (100 mL) was added and the mixture was extracted with Et_2O (2 x 200 mL) and the combined organic extract were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude product which was purified by flash chromatography (0-10% EtOAc / hexanes) to provide 12.9 g of the title compound in 99% yield. IR (cast film) 2955, 2931, 2859, 1743, 1611, 1512, 1473, 1258, 1170, 917, 840, 781 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.05 (d, *J* = 8.4 Hz, 2H), 6.76 (d, *J* = 8.4 Hz, 2H), 3.66 (s, 3H), 2.89 (t, *J* = 7.6 Hz, 2H), 2.60 (d, *J* = 7.6 Hz, 2H), 0.99 (s, 9H), 0.20 (s, 6H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 173.3, 154.0, 133.2, 129.1, 112.0, 51.5, 36.0, 30.2, 25.7, 18.2, –4.4; HRMS (EI) Calcd. $C_{16}H_{26}O_3Si$: 294.16513. Found: 294.16497.

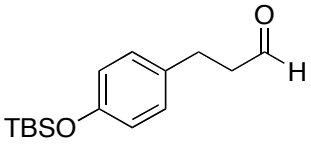
5.6.5.3 3-[4-(*tert*-Butyl-dimethyl-silanyloxy)-phenyl]-propionic acid methyl ester (5.33)



Methyl ester **5.32** (5.32 g, 18.0 mmol, 1.00 equiv) was charged into a flame dried 250 mL round-bottom flask. CH_2Cl_2 (100 mL) was added to the ester and the mixture was cooled to –78 ºC. DIBAL-H (1.5 M in toluene, 30.0 mL, 45.0 mmol, 2.50 equiv) was added dropwise and the

reaction mixture was stirred for 4 h. After the elapsed time, the reaction mixture was quenched with MeOH (3.0 mL) and brought to 0 ºC over 30 min, after which, dilute Na-K-tartarate (100 mL) was added. This mixture was stirred for 1 h to give a white precipitate, which was filtered through a pad of Celite. The pad of Celite was washed with CH_2Cl_2 (50 mL) and the filtrate was extracted with CH_2Cl_2 (2 x 250 mL), and the combined organic extract were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude product which was purified by flash chromatography (0-20% EtOAc/hexanes) to provide 3.59 g of the title compound in 75% yield. IR (cast film) 3339, 2931, 2859, 1610, 1512, 1472, 1390, 1261, 919, 840, 781 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.05 (d, *J* = 8.4 Hz, 2H), 6.76 (d, *J* = 8.4 Hz, 2H), 3.65 (t, *J* = 6.4 Hz, 3H), 2.64 (t, *J* = 7.6 Hz, 2H), 1.86 (tt, *J* = 6.4, 7.6 Hz, 2H), 1.66 (brs, 1H), 0.99 (s, 9H), 0.20 (s, 6H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 153.7, 134.4, 129.2, 119.9, 62.2, 34.4, 31.2, 25.7, 18.2, –4.4; HRMS (EI) Calcd. $C_{15}H_{26}O_2Si$: 266.17020. Found: 266.16983.

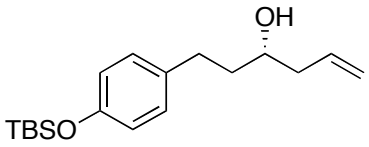
5.6.5.4 3-[4-(*tert*-Butyl-dimethyl-silanyloxy)-phenyl]-propionaldehyde (5.20)



To a flame-dried 250 mL round-bottom flask was added CH_2Cl_2 (40 mL) and $(COCl)_2$ (1.11 mL, 12.8 mmol, 1.20 equiv). This solution was cooled to –78 ºC and DMSO (1.82 mL, 25.6 mmol, 2.40 equiv) was added dropwise. After the evolution of gas had ceased (ca. 5 min), a solution of alcohol **5.33** (2.82 g, 10.6 mmol, 1.00 equiv) in CH_2Cl_2 (10 mL) was slowly added. The reaction was stirred for 45 min, after which, Et_3N (7.70 mL, 53.3 mmol, 5.00 equiv) was added. The reaction mixture was stirred for additional 15 min at –78 ºC and then warmed to room temperature and stirred for 30 min. Saturated aqueous $NaHCO_3$ (20 mL) was added to quench the reaction. The reaction mixture was then diluted with ether (100 mL) and the organic extract was washed with H_2O (50 mL), brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude aldehyde which was passed through a short plug of silica using 20% Et_2O/hexanes, and then purified by distillation (150 ºC, 0.5 mm Hg) to afford 2.67 g of aldehyde **5.20** in 95% yield. IR (cast film) 3030, 2956, 2931, 2857, 2716, 1726, 1610, 1512, 1263, 1170, 917, 840, 781 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.81 (t, *J* = 1.2 Hz, 1H),

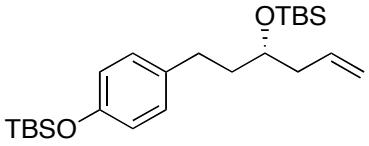
7.10 (d, *J* = 10.8 Hz, 2H), 6.81 (d, *J* = 11.2 Hz, 2H), 2.95 (t, *J* = 9.6 Hz, 2H), 2.79 (t, *J* = 8.0 Hz, 2H), 1.03 (s, 9H), 0.24 (s, 6H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 201.8, 154.0, 132.9, 129.1, 120.1, 45.5, 27.4, 18.2, –4.4; HRMS (EI) Calcd. $C_{15}H_{24}O_2Si$: 264.15457. Found: 264.15467.

5.6.5.5 (*S*)-1-[4-(*tert*-Butyl-dimethyl-silanyloxy)-phenyl]-pentan-3-ol (5.21)



Following the procedure used in the preparation of **5.11**, except that the reaction concentration was 1.3 M relative to aldehyde **5.20**, the desired product was isolated in quantitative yield. The enantiomeric ratio of the product was determined by formation of diastereomeric esters by condensation with (*S*)-Mosher acid chloride and based on ^{1}H NMR analysis, judged to be 97%. $[\alpha]_D^{25}$ –11.96 (*c* 1.02, $CHCl_3$); IR (neat) 3367, 2956, 2930, 2859, 1610, 1472, 1259, 917, 84, 780 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (d, *J* = 8.0 Hz, 2H), 6.76 (d, *J* = 8.4 Hz, 2H), 5.88-5.77 (m, 1H), 5.17-.5.12 (m, 2H), 3.64 (tt, *J* = 4.4, 7.6 Hz, 1H), 2.78-2.70 (m, 1H), 2.66-2.59 (m, 1H), 2.35-2.29 (m, 1H), 2.22-2.15 (m, 1H), 1.79-1.73 (m, 2H), 1.65 (s, 1H), 0.99 (s, 9H), 0.19 (s, 6H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 153.7, 134.7, 134.6, 129.42, 119.9, 118.2, 70.0, 42.0, 38.6, 31.2, 25.7, 18.2, –4.4; HRMS (EI) Calcd. $C_{18}H_{30}O_2Si$: 306.20151. Found: 306.20148.

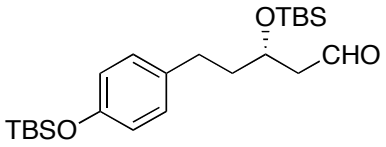
5.6.5.6 (*S*)-1-(*tert*-Butyl-dimethyl-silanyloxy)-4-[3-(*tert*-butyl-dimethyl-silanyloxy)-hex-5-enyl]-benzene (5.34)



Alcohol **5.21** (2.74 g, 8.95 mmol, 1.00 equiv) was dissolved in CH_2Cl_2 (100 mL) and cooled to 0 ºC. To the solution was then added 2,6-lutidine (1.56 mL, 13.43 mmol, 1.50 equiv) followed by TBSOTf (2.57 mL, 11.2 mmol, 1.25 equiv) and the reaction mixture was brought to room temperature and stirred for 2.5 h. Water (25 mL) was then added and the mixture was extracted with CH_2Cl_2 (2 x 100 mL) and the combined organic extract were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude product which was

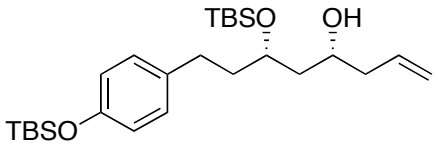
purified by flash chromatography (0-5% Et_2O/hexanes) to afford 3.76 g of the title compound in 99% yield. $[\alpha]_D^{25}$ –5.29 (*c* 0.85, $CHCl_3$); IR (cast film) 2956, 2930, 2896, 2858, 1611, 1511, 1472, 1256, 1072, 916, 837, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.04 (d, *J* = 8.4 Hz, 2H), 6.77 (d, *J* = 8.8 Hz, 2H), 5.81-5.80 (m, 1H), 5.11-5.05 (m, 2H), 3.74 (q, *J* = 5.6 Hz, 1H), 2.70-2.63 (m, 2H), 2.59-2.52 (m, 2H), 2.31-2.28 (m, 2H), 1.83-1.70 (m, 2H), 1.01 (s, 9H), 0.95 (s, 9H), 0.21 (s, 6H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.5, 135.2, 135.2, 129.1, 119.8, 116.8, 71.6, 41.9, 38.8, 30.9, 25.9, 25.7, 18.2, 18.1, –4.3, –4.4; HRMS (EI) Calcd. $C_{24}H_{44}O_2Si_2$: 420.28799. Found: 420.28787.

5.6.5.7 (*S*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-5-[4-(*tert*-butyl-dimethyl-silanyloxy)-phenyl]-pentanal (5.22)



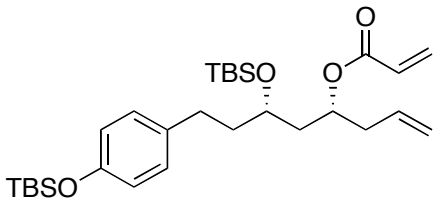
Alkene **5.34** (1.62 g, 4.00 mmol, 1.00 equiv) was dissolved in CH_2Cl_2 (100 mL) and cooled to –78 ºC. Ozone was bubbled into the solution until a deep blue color persisted (ca. 15 min). Oxygen was then purged through the reaction for 15 min and PPh_3 (2.10 g, 8.00 mmol, 2.00 equiv) was added and the mixture was stirred for 1 h while bringing the reaction to room temperature. The organic layer of the reaction mixture was separated, washed with water (20 mL), brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude product which was purified by flash chromatography (0-5% Et_2O/hexanes) to afford 1.27 g of aldehyde **5.22** in 75% yield. $[\alpha]_D^{25}$ +5.57 (*c* 2.1, $CHCl_3$); IR (cast film) 2956, 2930, 2858, 2712, 1713, 1610, 1511, 1257, 1100, 917, 838, 778 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.83 (t, *J* = 2.4 Hz, 1H), 7.03 (d, *J* = 8.4 Hz, 2H), 6.77 (d, *J* = 8.4 Hz, 2H), 4.25 (q, *J* = 5.6 Hz, 1H), 2.64-2.58 (m, 4H), 1.88-1.83 (m, 2H), 1.00 (s, 9H), 0.92 (s, 9H), 0.20 (s, 6H), 0.10 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 202.0, 153.7, 134.3, 129.1, 120.0, 67.7, 50.8, 39.7, 30.6, 25.8, 18.2, 18.0, –4.4, –4.7; HRMS (EI) Calcd. $C_{23}H_{42}O_2Si_2$: 422.26724. Found: 422.26685.

5.6.5.8 (4*R*,6*S*)-6-(*tert*-Butyl-dimethyl-silanyloxy)-8-[4-(*tert*-butyl-dimethyl-silanyloxy)-phenyl]-oct-1-en-4-ol (5.23)



Following the procedure used in the preparation of **5.11**, the requisite product was isolated in 96% yield. $[\alpha]_D^{25}$ +21.29 (*c* 0.51, $CHCl_3$); IR (cast film) 3453, 2955, 2930, 2858, 1641, 1511, 1257, 1075, 916, 838, 779 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, *J* = 8.4 Hz, 2H), 6.76 (d, *J* = 8.4 Hz, 2H), 5.90-5.78 (m, 1H), 5.16-5.11 (m, 2H), 3.99-3.93 (m, 1H), 3.83-3.80 (m, 1H), 3.01 (br s, 1H), 2.65-2.50 (m, 2H), 2.24 (t, *J* = 6.4 Hz, 2H), 1.86-1.44 (m, 4H), 0.99 (s, 9H), 0.92 (s, 9H), 0.19 (s, 6H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.7, 134.8, 134.7, 129.1, 120.0, 117.6, 72.2, 70.0, 42.3, 42.2, 39.8, 30.3, 25.9, 25.7, 18.2, 17.9, –4.0, –4.4, –4.6 ; HRMS (ESI) Calcd. $C_{26}H_{48}O_3Si_2Na$: 487.30342. Found: 487.30338. The diastereomeric ratio of the product was determined by comparison with the thermal uncatalyzed reaction, which gave a 54:46 ratio favoring diastereomer **5.23**, as determined by HPLC. Column SB-C18, 150 x 4.6 mm, 5μm; column temperature 40 ºC, mobile phase A: 0.05% formic acid in H_2O (22.5%), mobile phase B: 0.05% formic acid in CH_3CN (77.5%); UV 220 nm; T_{major} 62.9 min, T_{minor} 66.3 min.

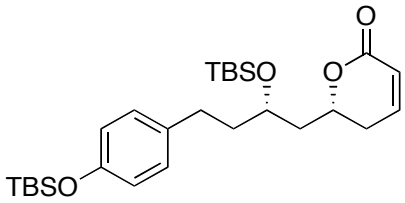
5.6.5.9 (4*R,6S*)-6-(*tert*-Butyldimethylsilyloxy)-8-[4-*tert*-butyldimethylsilyloxy) phenyl]oct-1-en-4-yl- acrylate (5.35)



Alcohol **5.23** (0.180 g, 0.390 mmol, 1.00 equiv) was dissolved in CH_2Cl_2 (3.0 mL) and cooled to 0 ºC. Acroloyl chloride (64.0 μL, 0.780 mmol, 2.00 equiv) was then added. This was followed by addition of Et_3N (225 μL, 1.55 mmol, 4.00 equiv) and the reaction mixture was stirred for 1 h after which water (1 mL) was added. The reaction mixture was then diluted with Et_2O (50 mL) and washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude product which was purified by flash chromatography (0-5%

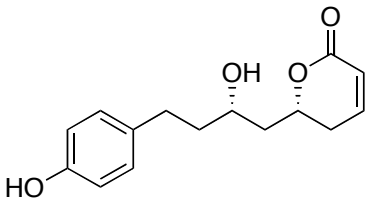
Et_2O/hexanes) to afford 195 mg of the desired ester **5.35** in 82% yield. $[\alpha]_D^{25}$ –19.42 (*c* 0.31, $CHCl_3$); IR (cast film) 2956, 2930, 2858, 1726, 1511, 1257, 1194, 1074, 916, 837, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.02 (d, *J* = 8.4 Hz, 2H), 6.75 (d, *J* = 8.4 Hz, 2H), 6.38 (dd, *J* = 1.6, 17.6 Hz, 1H), 6.1 (dd, *J* = 10.4, 17.2 Hz, 1H), 5.81 (dd, *J* = 1.6, 10.8 Hz, 1H), 5.81-5.71 (m, 1H), 5.15-5.06 (m, 2H), 3.76 (m, 1H), 2.67-2.50 (m, 2H), 2.44-2.30 (m, 2H), 1.91-1.66 (m, 4H), 0.99 (s, 9H), 0.93 (s, 9H), 0.19 (s, 6H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 165.6, 153.5, 134.9, 133.3, 130.4, 129.1, 128.7, 119.9, 118.0, 70.9, 68.8, 41.0, 39.0, 38.6, 30.7, 25.9, 25.7, 18.2, 18.1, –4.4; HRMS (ESI) Calcd. $C_{29}H_{50}O_4Si_2Na$: 541.31399. Found: 541.31402.

5.6.5.10 (*6R*)-{(S)-(*tert*-Butyldimethylsilyloxy)-4-[4-(*tert*-butyldimethylsilyloxy) phenyl]butyl}-5,6-dihydropyran-2-one (5.37)



Ester **5.35** (124 mg, 0.250 mmol, 1.00 equiv) was dissolved in degassed CH_2Cl_2 (25 mL). Grubb's 1st generation catalyst (20.3 mg, 0.0250 mmol, 0.100 equiv) dissolved in degassed CH_2Cl_2 (0.5 mL) was added to the above solution and the mixture was refluxed for 4 h after which TLC showed complete consumption of starting material. The solution was then evaporated *in vacuo* and the product was purified by flash chromatography (0-30% EtOAc/hexanes) to afford 116 mg of pyranone **5.37** in 95% yield. $[\alpha]_D^{25}$ +31.13 (*c* 0.37, $CHCl_3$); IR (cast film) 2954, 2930, 2887, 2858, 1731, 1511, 1390, 1255, 1077, 917, 838, 778 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, *J* = 8.4 Hz, 2H), 6.89-6.83 (m, 1H), 6.75 (d, *J* = 8.4 Hz, 2H), 6.02 (apparent d, *J* = 9.7 Hz, 1H), 4.63-4.54 (m, 1H), 3.96 (apparent q, *J* = 5.7 Hz), 2.68-2.52 (m, 2H), 2.37-2.31 (m, 2H), 2.14-2.05 (m, 1H), 1.91-1.69 (m, 3H), 0.98 (s, 9H), 0.90 (s, 9H), 0.18 (s, 6H), 0.08 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 164.3, 153.7, 144.9, 134.7, 129.1, 121.5, 119.9, 75.2, 68.2, 41.8, 38.6, 30.8, 29.8, 25.8, 25.7, 18.2, 18.0, –4.3, –4.4, –4.5; HRMS (ESI) Calcd. $C_{27}H_{46}O_4Si_2Na$: 513.28269. Found: 513.28262.

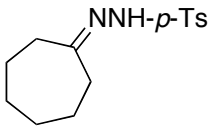
5.6.5.11 (6*R*)-[(*S*)-2-Hydroxy-4-(hydroxyphenyl)butyl]-5,6-dihydropyran-2-one (5.19)



Pyranone (59.5 mg, 0.121 mmol, 1.00 equiv) was dissolved in CH_3CN (3.0 mL). Under argon was added HF•Pyr (104 μL, 3.63 mmol, 30 equiv) and the reaction mixture was stirred for 12 h at room temperature after which EtOAc (25 mL) was added. Thus obtained mixture was washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product, which was purified by flash chromatography (0-50% EtOAc/hexanes) affording 31.5 mg of **5.19** (+)-dodoneine in quantitative yield. $[\alpha]_D^{25}$ +41.03 (*c* 1.37, $CHCl_3$); IR (cast film) 3360, 3018, 2926, 2858, 1703, 1614, 1515, 1393, 1264, 1061, 1037, 815, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.04 (d, *J* = 8.5 Hz, 2H), 6.89 (dt, *J* = 4.4, 9.7 Hz, 1H), 6.76 (d, *J* = 8.5 Hz, 2H), 6.02 (dt, *J* = 1.7, 9.9, 1H), 5.64 (br s, 1H), 4.65 (dq, *J* = 5.4, 7.8 Hz, 1H), 3.88 (tt, *J* = 4.7, 7.8, 1H), 2.742.61 (m, 2H), 2.40-2.37 (m, 2H), 2.34 (br s, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 164.3, 154.0, 145.5, 133.4, 129.5, 121.1, 115.4, 68.6, 42.0, 39.3, 30.9, 29.5 ; HRMS (EI) Calcd. $C_{25}H_{18}O_4$: 262.12051. Found: 262.12010.

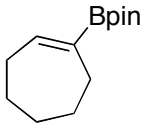
5.6.6 Synthesis of F-Vivol[7] 5.50

5.6.6.1 *N*'-Cycloheptylidene-4-methylbenzenesulfonohydrazide (5.50a)



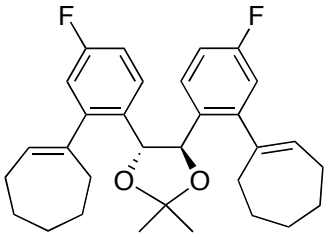
Following the procedure used the preparation of hydrazone **4.18a**, the title compound was obtained in quantitative yield as a white solid. IR (cast film) 3239, 2919, 2851, 1660, 1627, 1457, 1182 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.86 (br s, 1H), 7.81 (d, *J* = 8.2 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 2.37 (s, 3H), 2.36-2.33 (m, 2H), 2.26-2.23 (m, 2H), 1.61-1.56 (m, 2H), 1.52-1.42 (m, 6H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 164.3, 143.6, 135.6, 129.3, 127.8, 36.8, 30.4, 30.1, 29.9, 27.1, 24.2, 21.4; HRMS (ESI) Calcd. $C_{14}H_{20}N_2O_2SNa$: 303.11377. Found: 303.11390.

5.6.6.2 2-Cyclohelptenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5.50b)



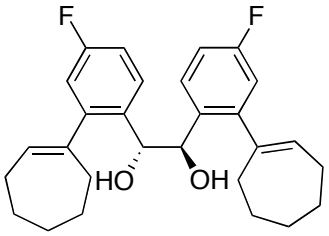
Following the procedure used in the preparation of boronate **4.18b**, the title compound was isolated in 78% yield as faint yellow oil. IR (cast film) 2978, 2920, 2850, 1630, 1387, 1329, 1146 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.77 (d, *J* = 6.4 Hz, 1H), 2.28-2.22 (m, 4H), 1.78-1.72 (m, 2H), 1.51-1.44 (m, 4H), 1.26 (s, 12H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 148.5, 83.2, 32.7, 30.5, 29.5, 27.3, 26.5, 24.8; HRMS (EI) Calcd. $C_{13}H_{23}O_2B$: 22.17911. Found 222.17906.

5.6.6.3 (*4R*,*5R*)4,5-Bis(2-(*E*)-cycloheptenyl)-2,2-dimethyl-1,3-dioxolane (5.50c)



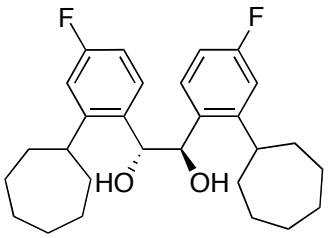
Following the procedure used in the preparation of **4.18c**, the title compound was obtained in 92% yield after recrystallization from hexanes. $[\alpha]_D^{25}$ +74.24 (*c* 1.07, $CHCl_3$); IR (cast film) 2983, 2922, 2850, 1611, 1584, 1234, 1053 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 6.0, 8.7 Hz, 2H), 6.97 (ddd, *J* = 2.7, 8.4, 8.4 Hz, 2H), 6.63 (dd, *J* = 2.7, 9.6 Hz, 2H), 4.94 (s, 2H), 4.77 (br s, 2H), 2.23-1.79 (m, 7H), 1.76-1.67 (m, 4H), 1.65 (s, 6H), 1.53-1.39 (m, 9H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 161.9 (d, *J* = 247.1 Hz), 148.8 (d, *J* = 7.5 Hz), 142.0, 132.5, 129.1 (d, *J* = 8.8 Hz), 128.2 (d, *J* = 2.8 Hz), 114.7 (d, *J* = 20.0 Hz), 113.6 (d, *J* = 21.2 Hz), 108.6, 81.8, 35.2, 32.0, 28.8, 27.4, 26.8, 26.7; HRMS (ESI) Calcd. $C_{31}H_{36}F_2O_2Na$: 501.25756. Found: 501.25724.

5.6.6.4 (*R,R*)-1,2-Bis-(2-cyclohept-1-enyl-4-fluoro-phenyl)-ethane-1,2-diol (5.50d)



Following the procedure used in the preparation of diol **4.18d**, the title compound was obtained in 78% yield after recrystallization from CH_2Cl_2/hexanes. $[\alpha]_D^{25}$ +128.34 (*c* 0.48, $CHCl_3$); IR (cast film) 3316, 2924, 2849, 1608, 1582, 1485, 1284, 1036, 856 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (dd, *J* = 5.9, 8.7 Hz, 2H), 6.87 (ddd, *J* = 2.7, 8.4, 8.4 Hz, 2H), 6.57 (dd, *J* = 2.8, 9.7 Hz, 2H), 4.98 (br s, 2H), 4.87 (s, 2H), 2.86 (br s, 2H), 2.32-2.17 (m, 2H), 2.12-2.02 (m, 6H), 1.80-1.74 (m, 4H), 1.64-1.46 (m, 8H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 162.0 (d, *J* = 247.4 Hz), 148.8 (d, *J* = 7.8 Hz), 143.0, 132.6, 132.2 (d, *J* = 3.1 Hz), 130.5, 129.6 (d, *J* = 8.7 Hz), 115.1 (d, *J* = 21.0 Hz), 113.5 (d, *J* = 21.7 Hz), 74.9, 35.4, 32.3, 29.1, 27.2, 26.9; HRMS (ESI) Calcd. $C_{28}H_{32}F_2O_2Na$: 461.22626. Found: 461.22625.

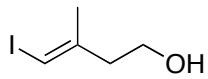
5.6.6.5 (*R,R*)-1,2-Bis-(2-cyclooctyl-4-fluoro-phenyl)-ethane-1,2-diol (5.50)



Following the procedure used in the preparation of diol **4.18**, the title compound was obtained in quantitative yield and further recrystallized from CH_2Cl_2/hexanes to afford the title compound **4.64** as white solid. $[\alpha]_D^{25}$ –6.59 (*c* 0.31, $CHCl_3$); IR (cast film) 3551, 3355, 2923, 2853, 1611, 1588, 1498, 1226, 1034, 823 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.63 (dd, *J* = 6.1, 8.8 Hz, 2H), 6.91 (ddd, *J* = 2.6, 8.8, 8.8 Hz, 2H), 6.70 (dd, *J* = 2.7, 10.8 Hz, 2H), 5.03 (s, 2H), 2.96 (s, 2H), 2.28-2.21 (m, 2H), 1.75-1.15 (m, 20H), 1.09-0.92 (m, 2H), 0.61-0.52 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.6 (d, *J* = 245.2 Hz), 150.4 (d, *J* = 6.3 Hz), 131.5, 129.0 (d, *J* = 8.4 Hz), 112.9 (d, *J* = 21.1Hz), 112.5 (d, *J* = 21.0 Hz), 74.1, 40.9, 38.2, 34.6, 27.4, 27.3, 27.1, 26.9; HRMS (ESI) Calcd. $C_{28}H_{36}F_2O_2Na$: 465.25756. Found: 465.25786.

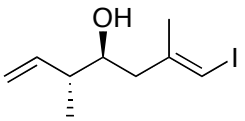
5.6.7 Total synthesis of palmerolide A

5.6.7.1 (*E*)-4-Iodo-3-methylbut-3-en-1-ol (5.46)



To a stirred solution of zirconocene dichloride (3.86 g, 13.2 mmol, 0.22 equiv) in anhydrous CH_2Cl_2 (260 mL) at –23 °C was added trimethylaluminum (2.39 M in hexanes, 78.0 mL, 186 mmol, 3.10 equiv) dropwise. After stirring the resulting yellow mixture for 10 min at –25 °C, water (1.68 mL, 93.0 mmol, 1.55 equiv) was cautiously added dropwise (**Caution: exothermic reaction**!). After an additional 10 min stirring, commercially available 3-butyn-1-ol (4.21 g, 60.0 mmol, 1.0 equiv), pretreated with trimethyl aluminum (2.39 M in hexanes, 7.80 mL, 18.6 mmol, 0.310 equiv) in anhydrous CH_2Cl_2 (50 mL) at 0 °C, was added drop-wise *via* cannula. The reaction mixture was allowed to warm to ambient temperature and the resulting yellow thick slurry was stirred overnight. The reaction mixture was then cooled to –25 °C and a solution of I_2 (22.8 g, 90.0 mmol, 1.50 equiv) in anhydrous Et_2O (100 mL) was added dropwise *via* cannula. The mixture was allowed to warm to ambient temperature and was stirred for an additional 2 h. The reaction mixture was slowly quenched with a saturated aqueous solution of potassium tartrate (50 mL). The aqueous phase was extracted with Et_2O (3 × 200 mL) and washed with $Na_2S_2O_3$ and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (pentane/Et_2O 1:1) provided the desired vinyliodide (11.5 g, 90%) as a yellow oil. Physical and spectral data of the title compound were in accordance with the literature.[35]

5.6.7.2 (*E*)-(4*S*, 5*R*)-1-Iodo-2,5-dimethyl-hepta-1,6-dien-4-ol (5.51)



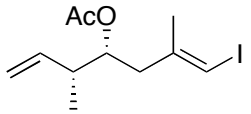
To a stirred solution of (*E*)-4-Iodo-3-methylbut-3-en-1-ol **5.46** (4.94 g, 23.3 mmol, 1.00 equiv) in freshly distilled CH_2Cl_2 (55 mL) at 0 °C was added $NaHCO_3$ (9.78 g, 117 mmol, 5.00 equiv) and Dess-Martin periodinane (11.9 g, 28.0 mmol, 1.20 equiv). The solution was allowed to warm to

rt and stirred for 1.5 h. The reaction mixture was then quenched with saturated aqueous solutions of $NaHCO_3$ (100 mL) and $Na_2S_2O_3$ (100 mL) and diluted with Et_2O (200 mL). The aqueous phase was extracted with Et_2O (2 × 100 mL). The combined organic layers were washed with water (3 × 100 mL), $NaHCO_3$ (100 mL), brine (100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was transferred into a flame dried 50 mL round bottom flask (base washed and flame-dried) and the product was purified by bulb-to-bulb distillation (0.13 *torr*, 80 ºC) to provide the requisite aldehyde **5.46** as a faint yellow oil, which was immediately used for the next step.

To a flame dried round bottom flask equipped with stir bar was added (*R,R*)-F-Vivol **5.50** (550 mg, 1.24 mmol, 0.0650 equiv), anhydrous Na_2CO_3 (207 mg, 1.95 mmol, 0.100 equiv) 4Å molecular sieves (500 mg, previously dried under high vacuum at 100 ºC and stored in an oven). The flask was capped with rubber septum and freshly distilled toluene (12.5 mL) was added. The mixture was stirred for 2 min followed by addition of $SnCl_4$ (1.0 M solution in CH_2Cl_2, 0.956 mL, 0.956 mmol, 0.0500 equiv). Thus obtained mixture was stirred at ambient temperature for 5 min, cooled to −78 ºC and maintained at this temperature for 30 min. This was followed by addition of *E*-crotylboronic acid pinacol ester **5.4** (4.71 g, 25.85 mmol, 1.18 equiv). This mixture was stirred for additional 30 min, after which, (*E*)-4-iodo-3-methylbut-3-enal (4.20 g, 21.0 mmol, 1.00 equiv) was added dropwise to the reaction mixture. The reaction was stirred for 60 h at −78 ºC, and after the elapsed time DIBAL-H (1.50 M solution in toluene, 13.3 mL, 20.0 mmol, 1.00 equiv) was added to quench unreacted aldehyde. The reaction mixture was allowed stir for additional 30 min at −78 ºC and subsequently poured over ice-cold HCl aqueous (1.0 *N*, 50 mL). The reaction mixture was then allowed to warm to ambient temperature and allowed to stir for 30 min. Thus obtained biphasic mixture is extracted with Et_2O (3 × 200 mL) and the combined organic extracts washed with brine (15 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the product, which was purified by flash chromatography on silica gel (Pentane/Et_2O 20/1), to give 5.10 g (96% yield) of the desired product. $[\alpha]_D^{25}$ −19.44 (*c* 0.79, $CHCl_3$); IR (cast film) 3441, 3073, 2965, 2928, 1377, 1273, 1144, 1000, 917, 764 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.02 (m, 1H), 5.77 (ddd, *J* = 17.2, 10.6, 8.1 Hz, 1H), 5.15-5.09 (m, 2H) 3.62-3.57 (m, 1H), 2.39 (dd, *J* = 14.3, 3.7 Hz, 1H), 2.30 (dd, *J* = 14.3, 9.9 Hz, 1H), 2.27-2.21 (m, 1H), 1.89-1.88 (m, 3H), 1.59 (d, *J* = 3.7 Hz, 1H), 1.07 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 145.2, 139.5, 116.5, 77.0, 72.0, 44.5, 43.6, 24.1, 16.2; HRMS (ESI)

Calcd. $C_9H_{15}OINa$: 289.0060. Found: 289.0061. HPLC (chiralcel OD), 10:90 *i*-PrOH/hexane, 0.5 mL/min, $\lambda = 254$ nm, $T_{major} = 12.5$ min, $T_{minor} = 18.0$ min, 90% *ee*.

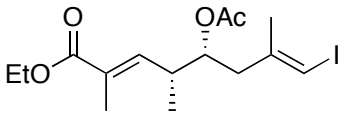
5.6.7.3 (*E*)-(1*R*, 1'*R*)-Acetic acid-4-iodo-3-methyl-1-(1-methylallyl)-but-3-enyl ester (5.43)



To a stirred solution of alcohol **5.51** (4.80 g, 18.27 mmol, 1.00 equiv) in freshly distilled CH_2Cl_2 (36 mL) at 0 °C was added triethylamine (3.82 mL, 27.4 mmol, 1.50 equiv). Mesyl chloride (1.56 mL, 20.1 mmol, 1.10 equiv) was then added dropwise. The solution was allowed to warm to rt and let to for 1 h. The reaction mixture was diluted with Et_2O (100 mL) and a saturated aqueous solution of NH_4Cl (50 mL) was added. The aqueous phase was extracted with Et_2O (2 × 60 mL). The combined organic layers were washed with brine (60 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude mesylate **5.52** was obtained as a yellow oil and was used in the next step without further purification.

Into a 100 mL round bottom flask were charged the crude mesylate, CsOAc (14.0 g, 73.1 mmol, 3.00 equiv), 18-crown-6 (4.83 g, 18.3 mmol, 1.00 equiv) and freshly distilled toluene (35 mL). The resulting mixture was stirred for 16 h at 110 ºC and subsequently cooled to ambient temperature and diluted with Et_2O (100 mL). H_2O was added and the aqueous phase was extracted with Et_2O (2 × 60 mL). The combined organic layers were washed with brine (60 mL), dried over Na_2SO_4, filtered, concentrated *in vacuo* and purified by flash chromatography on silica gel (pentane:Et_2O 50:1) to give the desired acetate **5.43** (4.11 g, 73%) as a colorless liquid. $[\alpha]_D^{25}$ +23.67 (*c* 0.37, $CHCl_3$); IR (cast film) 3078, 2975, 2926, 1742, 1375, 1277, 1237, 1025, 919 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.95-5.94 (m, 1H), 5.73 (ddd, *J* = 17.5, 10.0, 7.5 Hz, 1H), 5.09-5.04 (m, 2H), 4.96 (ddd, *J* = 10.5, 6.5, 4.0 Hz, 1H), 2.45-2.34 (m, 3H), 2.02 (s, 3H), 1.84 (d, *J* = 0.8 Hz, 3H), 1.02 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 170.4, 144.3, 139.4, 115.8, 77.1, 73.7, 41.8, 41.5, 23.9, 21.0, 15.4; HRMS (ESI) Calcd. $C_{15}H_{23}O_2INa$: 331.0166. Found: 331.0166.

5.6.7.4 Ethyl (2*E*,4*R*,5*R*,7*E*)-5-(acetyloxy)-8-iodo-2,4,7-trimethylocta-2,7-dienoate (5.55)

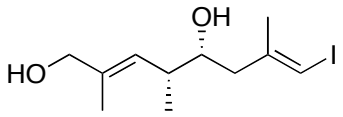


To a stirred solution of acetate **5.43** (4.13 g, 13.4 mmol, 1.00 equiv) in a mixture of *t*-BuOH/THF/H_2O (5:5:1, 30 mL/30 mL/6 mL) at 0 ºC were added OsO_4 (4 wt % in H_2O, 850 μL, 0.134 mmol, 0.0100 equiv) and NMO (50 wt% in H_2O, 4.40 mL, 18.8 mmol, 1.40 equiv). The resulting solution was allowed to warm to ambient temperature and stirred for 48 h. The reaction mixture was diluted with EtOAc (100 mL) and a saturated aqueous solution of $Na_2S_2O_3$ (50 mL) was added. The aqueous phase was extracted with EtOAc (2 × 60 mL). The combined organic layers were washed with brine (60 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Filtration of this residue through a 5-inch plug of silica using Et_2O as eluent, provided the crude diol **5.53**, which was taken to the next step.

Diol **5.53** from above was dissolved in MeOH/H_2O (60 mL/30 mL). This was followed by the addition of $NaIO_4$ (17.2 g, 80.4 mmol, 6.00 equiv) and the reaction mixture was stirred for 30 min at rt. The reaction mixture was quenched by the addition of H_2O (100 mL) and the organic product was extracted with CH_2Cl_2 (3 × 250 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford the crude aldehyde **5.54**, which was taken to the next step.

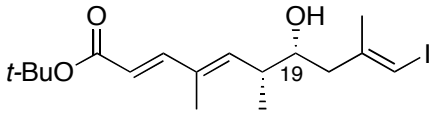
The aldehyde from above was dissolved in CH_2Cl_2 (50 mL) and to the solution was added Wittig reagent **5.55** (5.82 g, 16.1 mmol, 1.20 equiv) and the mixture was stirred for16 h. The solvent was evaporated *in vacuo* and the crude product was purified by flash chromatography (0-20% Et_2O/hexanes) to afford the desired enoic ester **5.56** (3.96 g, 10.1 mmol) in 75% yield as a faint yellow oil. $[\alpha]_D^{25}$ –32.59 (*c* 0.30, $CHCl_3$); IR (cast film) 2977, 2931, 1741, 1712, 1369, 1233, 1038 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.53 (dd, *J* = 1.5, 10.5 Hz, 1H), 5.94-5.93 (m, 1H), 4.95 (q, *J* = 6.8 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 2.76-2.68 (m, 1H), 2.37 (d, *J* = 6.5 Hz, 2H), 2.03 (s, 3H), 1.84 (m, 3H), 1.27 (t, *J* = 7.0 Hz, 3H), 1.01 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 170.3, 167.8, 143.8, 141.5, 128.9, 77.6, 60.7, 42.1, 37.1, 24.0, 20.98, 15.9, 14.3, 12.8; HRMS (ESI) Calcd. $C_{15}H_{23}O_4INa$: 417.0533. Found: 417.0536.

5.6.7.5 (2*E*,4*R*,5*R*,7*E*)-8-Iodo-2,4,7-trimethylocta-2,7-diene-1,5-diol (5.57)



Diester **5.56** (3.23 g, 8.19 mmol, 1.00 equiv) was dissolved in CH_2Cl_2 (60 mL) and cooled to –78 ºC. To the solution was then added DIBAL-H (1.5 M in toluene, 27.3 mL, 40.9 mmol, 5.00 equiv) and the reaction mixture was stirred for 5 h. After the elapsed time, MeOH (2.6 mL) was slowly added and the reaction was brought to 0 ºC and K-tartarate (50 mL) was added. The thus resultant biphasic mixture was stirred for 2 h after which the organic layer was separated. The reaction flask containing the white solid was further washed with CH_2Cl_2 (100 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Thus obtained crude product was purified by flash chromatography (10-50% EtOAc/hexanes) to afford 2.52 g of the desired diol product **5.57** in 99% yield. $[\alpha]_D^{25}$ –11.79 (*c* 0.39, $CHCl_3$); IR (cast film) 3334, 2960, 2914, 2870, 1616, 1449, 1377, 1273, 1047, 1008, 762 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.98 (s, 1H), 5.27 (dq, *J* = 1.2, 9.6 Hz, 1H), 3.99 (s, 2H), 3.55 (ddd, *J* = 3.2, 6.4, 9.6 Hz, 1H), 2.53-2.43 (m, 1H), 2.40 (dd, *J* = 2.4, 13.6 Hz, 1H), 2.24 (dd, *J* = 10.0, 14.0 Hz, 1H), 1.96 (br s, 1H), 1.85 (s, 3H), 1.67 (s, 3H), 1.01 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 145.3, 135.6, 127.6, 77.0, 72.9, 68.5, 44.7, 38.0, 24.1, 16.2, 14.1; HRMS (ESI) Calcd. $C_{11}H_{19}IO_4Na$: 333.03219. Found: 333.03222.

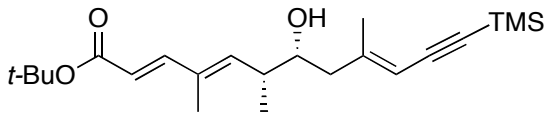
5.6.7.6 *tert*-Butyl (2*E*,4*E*,6*R*,7*R*,9*E*)-7-hydroxy-10-iodo-4,6,9-trimethyldeca-2,4,9-trienoate (5.44)



Diol **5.57** (2.52 g, 8.14 mmol, 1.00 equiv) was dissolved in CH_2Cl_2 (40 mL) and MnO_2 (12.2, 141 mmol, 17.4 equiv) was added. The reaction mixture was let to stir for 30 min after which TLC indicated complete consumption of the starting material. The reaction mixture was filtered through a pad of Celite and concentrated *in vacuo*. The crude aldehyde was carried over to the next step without any further purification.

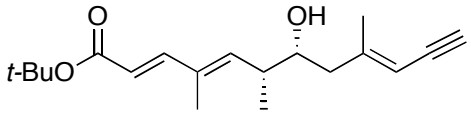
The aldehyde from above was dissolved in benzene (50 mL) and to the solution was added Wittig reagent **5.59** (6.12 g, 16.3 mmol, 2.00 equiv) and the mixture was refluxed for 3 h. Benzene was then evaporated *in vacuo* and the crude product was purified by flash chromatography (5-10% Et_2O/hexanes) to afford 2.90 g of the desired product **5.44** in 86% yield for two steps. $[\alpha]_D^{25}$ +43.12 (*c* 0.32, $CHCl_3$); IR (cast film) 3448, 2977, 2930, 1705, 1685, 1622, 1317, 1152, 981 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.20 (d, *J* =15.5 Hz, 1H), 6.00 (s, 1H), 5.75 (d, *J* = 16.0 Hz, 1H), 5.68 (d, *J* = 10.0 Hz, 1H), 3.56 (dddd, *J* = 2.5, 4.0, 7.0, 7.0 Hz), 2.62-2.55 (m, 1H), 2.38 (dd, *J* = 1.0, 13.5 Hz, 1H), 2.23 (dd, *J* = 10.0, 14.0 Hz), 1.85 (d, *J* = 0.5 Hz, 3H), 1.78 (d, *J* = 1.5 Hz, 3H), 1.77 (d, *J* = 4.0 Hz, 1H), 1.49 (s, 9H), 1.07 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 166.7, 148.1, 145.0, 133.1, 118.6, 80.2, 77.3, 76.8, 72.6, 45.3, 39.3, 28.2, 24.0, 16.2, 12.7; HRMS (ESI) Calcd. $C_{17}H_{27}IO_3Na$: 429.08971. Found: 429.08948.

5.6.7.7 *tert*-Butyl (2*E*,4*E*,6*R*,7*R*,9*E*)-7-hydroxy-4,6,9-trimethyl-12-(trimethylsilyl)dodeca-2,4,9-trien-11-ynoate (5.58)



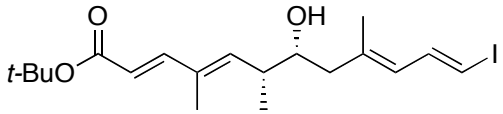
Into a round bottom flask equipped with a stir bar was added vinyliodide **5.44** (2.90 g, 7.15 mmol, 1.00 equiv), $PdCl_2(PPh_3)_2$ (502 mg, 0.715 mmol, 0.100 equiv), CuI (136 mg, 0.715 mmol, 0.100 equiv) and degassed Et_2NH (50 mL). This was followed by the addition of trimethylsilyl acetylene (2.02 mL, 14.3 mmol, 2.00 equiv) and the reaction mixture was stirred for 2 h at rt. The reaction mixture was concentrated *in vacuo* and the crude product was purified by flash chromatography (0-20% Et_2O/hexanes) to afford 2.61 g of the desired alkyne **5.61** in 97% yield. $[\alpha]_D^{25}$ +40.52 (*c* 0.19, $CHCl_3$); IR (cast film) 3438, 2962, 2932, 2215, 2134, 1752, 1707, 1684, 1629, 1249, 1152, 844 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.20 (d, *J* =16.0 Hz, 1H), 5.75 (d, *J* = 16.0 Hz, 1H), 5.68 (d, *J* = 10.5 Hz, 1H), 5.37 (s, 1H), 3.56 (m, 1H), 2.62-2.54 (m, 1H), 2.05 (d, *J* = 10.0 Hz, 1H), 2.03 (dd, *J* = 10.0, 14.0 Hz, 1H), 1.92 (s, 3H), 1.78 (d, *J* = 1.0 Hz, 3H), 1.70 (d, *J* = 4.0 Hz, 1H), 1.48 (s, 9H), 1.06 (d, *J* = 6.5 Hz, 3H), 0.18 (s, 6H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 166.7, 150.2, 148.2, 142.5, 133.1, 118.5, 108.2, 102.7, 97.5, 80.1, 72.8, 44.6, 39.5, 28.2, 19.5, 16.1, 12.7, 0.0; HRMS (ESI) Calcd. $C_{22}H_{36}NaO_3Si$: 399.23259. Found: 399.23292.

5.6.7.8 *tert*-Butyl (2*E*,4*E*,6*R*,7*R*,9*E*)-7-hydroxy-4,6,9-trimethyldodeca-2,4,9-trien-11-ynoate (5.62)



Silyl acetylene **5.61** (2.20 g, 5.86 mmol, 1.00 equiv) was dissolved in THF (30 mL). To the solution at 0 ºC was added TBAF (1.0 M in THF, 8.80 mL, 8.80 mmol, 1.50 equiv) and the reaction mixture was stirred for 15 min. After the elapsed time, the reaction mixture was diluted with water (20 mL) and the crude product was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with brine (40 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude product which was purified by flash chromatography (10% Et_2O/hexanes) to afford 1.78 g of the desired product **5.62** in quantitative yield. $[\alpha]_D^{25}$ +32.49 (*c* 0.19, $CHCl_3$); IR (cast film) 3443, 3308, 2978, 2931, 2097, 1705, 1623, 1456, 1392, 1317, 1153, 982, 850 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.20 (d, *J* =16.0 Hz, 1H), 5.75 (d, *J* = 16.0 Hz, 1H), 5.68 (d, *J* = 10.0 Hz, 1H), 5.33 (s, 1H), 3.59-3.56 (m, 1H), 3.04 (d, *J* = 2.0 Hz, 1H), 2.61-2.57 (m, 1H), 2.29 (d, *J* = 13.5 Hz, 1H), 2.07 (dd, *J* = 10.0, 14.0 Hz, 1H), 1.93 (s, 3H), 1.78 (d, *J* = 1.0 Hz, 3H), 1.72 (br s, 1H), 1.49 (s, 9H), 1.07 (d, *J* = 7.0 Hz, 3H), 0.18 (s, 6H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 166.7, 150.7, 148.2, 142.4, 133.1, 118.5, 107.0, 81.1, 80.3, 80.1, 72.8, 44.5, 39.5, 28.2, 19.4, 16.1, 12.7; HRMS (ESI) Calcd. $C_{19}H_{28}NaO_3$: 327.19307. Found: 327.19294.

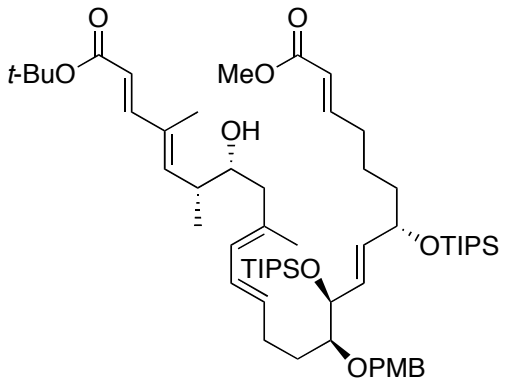
5.6.7.9 *tert*-Butyl(2*E*,4*E*,6*R*,7*R*,9*E*,11*E*)-7-hydroxy-12-iodo-4,6,9-trimethyldodeca-2,4,9,11-tetraenoate (5.41)



$Cp_2Zr(H)Cl$ (1.49 g, 5.80 mmol, 2.05 equiv) was suspended in THF (15 mL). To the suspension at 0 ºC was added alkyne **5.62** (859 mg, 2.82 mmol, 1.00 equiv) dissolved in THF (10 mL) and the reaction mixture was let to warm to rt and then stir for additional 45 min. After the elapsed time, the reaction mixture was cooled to –78 ºC and iodine (1.47 g, 5.80 mmol, 2.05 equiv, dissolved in 6 mL THF) was added, and the dark brown mixture was stirred for 10 min.

Saturated aqueous $NaHCO_3$ (10 mL) was added and the mixture was diluted with Et_2O (50 mL) and immediately poured into a sepratory funnel. The organic layer was separated and washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude product which was purified by flash chromatography (10% Et_2O/hexanes containing 1% Et_3N) to afford 961 mg of the desired product **5.41** in 75% yield. $[\alpha]_D^{25}$ +67.61 (*c* 0.32, $CHCl_3$); IR (cast film) 3443, 2976, 2929, 2871, 1705, 1622, 1367, 1316, 1152, 981, 849 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.22 (dd, *J* =11.5, 14.5 Hz, 1H), 7.19 (dd, *J* = 0.5, 15.5 Hz, 1H), 6.21 (d, *J* = 14.5 Hz, 1H), 5.83 (d, *J* = 11.5 Hz, 1H) 5.74 (dd, *J* = 0.5, 15.5 Hz, 1H), 5.68 (dd, *J* = 0.5, 10.0 Hz, 1H), 3.57-3.54 (m, 1H), 2.63-2.54 (m, 1H), 2.21 (dd, *J* = 1.5, 13.5 Hz, 1H), 1.97 (dd, *J* = 10.0, 14.0 Hz, 1H), 1.77 (d, *J* = 1.5 Hz, 1H), 1.77 (d, *J* = 1.0 Hz, 3H), 1.73 (d, *J* = 1.0 Hz, 3H), 1.48 (s, 9H), 1.06 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 166.8, 148.2, 142.7, 141.4, 136.7, 133.0, 127.9, 118.4, 80.1, 78.2, 72.6, 45.6, 39.5, 28.2, 17.1, 16.2, 12.7; HRMS (ESI) Calcd. $C_{19}H_{29}NaIO_3$: 455.10537. Found: 455.10539.

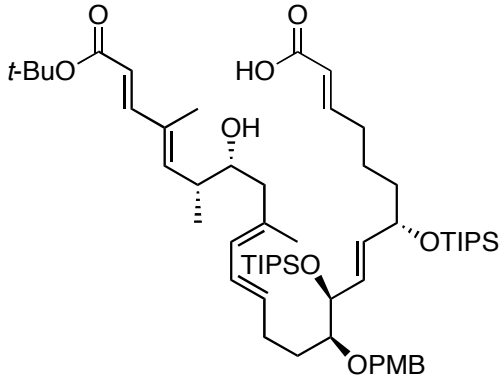
5.6.7.10 1-*tert*-Butyl 25-methyl (2*E*,4*E*,6*R*,7*R*,9*E*,11*E*,15*S*,16*S*,17*E*,19*S*,23*E*)-7-hydroxy-15-[(4-methoxybenzyl)oxy]-4,6,9-trimethyl-16,19-bis[(tripropan-2-ylsilyl)oxy]pentacosa-2,4,9,11,17,23-hexaenedioate (5.60)



Alkene **5.40** (104 mg, 0.148 mmol, 1.30 equiv) was dissolved in anhydrous THF (0.5 mL). This was followed by the addition of 9BBN-H (0.5 M in THF, 0.364 mL, 0.182 mmol, 1.60 equiv) and the resulting mixture was stirred at rt for 6 h. The solvent was reduced *in vacuo* to approximately half of the original volume (ca. 0.4 mL). Degassed H_2O (65.0 μL, 3.58 mmol, 31.5 equiv) was added and thus obtained mixture was cannulated to a round bottom flask

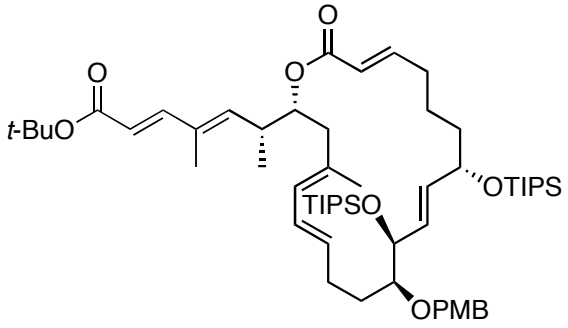
containing vinyl iodide **5.41** (49.2 mg, 0.114 mmol, 1.00 equiv), $PdCl_2$dppf (4.20 mg, 0.00573 mmol, 0.050 equiv), Ph_3As (3.50 mg, 0.0114 mmol, 0.100 equiv), Cs_2CO_3 (93.0 mg, 0.285 mmol, 2.50 equiv) and DMF (0.5 mL). The heterogeneous mixture was degassed and let to stir for 16 h at rt. After the elapsed time, brine (2 mL) was added, and the mixture was diluted with Et_2O (25 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (2 × 25 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude product which was purified by flash chromatography (0-10% Et_2O/hexanes containing 1% Et_3N) to afford 83.0 mg of the desired product **5.63** in 77% yield. $[\alpha]_D^{25}$ +12.0 (*c* 0.06, $CHCl_3$); IR (cast film) 3504, 2943, 2866, 1726, 1711, 1619, 1514, 1464, 1385, 1316, 1248, 1152, 1090, 883, 681 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.0, 2H), 7.23 (d, *J* = 15 Hz, 1H), 7.02 (dt, *J* = 7.0, 15.5 Hz, 1H), 6.86 (d, *J* = 9 Hz, 2H), 6.17 (dd, *J* = 11, 15 Hz, 1H), 5.83 (d, *J* = 11.0 Hz, 1H), 5.79 (d, *J* = 17.5 Hz, 1H), 5.77 (d, *J* = 16.0 Hz, 1H), 5.72 (d, *J* = 10 Hz, 1H), 5.68-5.67 (m, 2H), 5.54 (ddd, *J* = 7.0, 7.0, 14.5 Hz, 1H), 4.57 (d, *J* = 11.5 Hz, 1H), 4.48 (d, *J* = 11.5 Hz, 1H), 4.46-4.45 (m, 1H), 4.34-4.29 (m, 1H), 3.80 (s, 3H), 3.72 (s, 3H), 3.54 (ddd, *J* = 2.5, 7.5, 9.5 Hz, 1H), 3.39 (ddd, *J* = 2.5, 4.5, 9.5 Hz, 1H), 2.63-2.56 (m, 1H), 2.25 (d, *J* = 12.0 Hz, 2H), 2.16 (q, *J* = 7.0 Hz, 2H), 2.07 (dddd, *J* = 9.4, 9.4, 11.3, 7.5 Hz, 1H), 1.98 (dd, *J* = 10.0, 13.5 Hz, 1H), 1.79 (d, *J* = 1.5 Hz, 3H), 1.76 (d, *J* = 1.0 Hz, 1H), 1.72 (s, 3H), 1.58-1.56 (m, 5H), 1.50 (s, 9H), 1.08 (d, *J* = 7.0 Hz, 3H), 1.07-1.00 (m, 42H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 167.1, 166.8, 159.1, 149.5, 148.4, 143.1, 134.1, 134.0, 132.7, 132.1, 131.1, 129.2, 128.8, 128.4, 126.3, 120.9, 118.2, 113.7, 81.5, 80.1, 77.2, 72.8, 72.4, 72.2, 71.9, 55.2, 51.3, 45.8, 39.4, 38.1, 32.3, 29.5, 29.1, 28.2, 24.7, 22.9, 18.1, 16.5, 16.2, 12.6, 12.4; HRMS (ESI) Calcd. $C_{59}H_{100}O_9Si_2Na$: 1031.67981. Found: 1031.67996.

5.6.7.11 (2*E*,7*S*,8*E*,10*S*,11*S*,14*E*,16*E*,19*R*,20*R*,21*E*,23*E*)-25-*tert*-Butoxy-19-hydroxy-11-[(4-methoxybenzyl)oxy]-17,20,22-trimethyl-25-oxo-7,10-bis[(tripropan-2-ylsilyl)oxy]pentacosa-2,8,14,16,21,23-hexaenoic acid (5.64)



Methylester **5.63** (190 mg, 0.198 mmol, 1.00 equiv) was dissolved in dichloroethane (4 mL) and transferred into a 15 mL pressure tube. To the solution under argon was added Me_3SnOH (360 mg, 1.98 mmol, 10.0 equiv) and the vessel was capped and the mixture was heated to 90 ºC for 15 h. After the elapsed time, the solvent was evaporated *in vacuo* and the crude product was purified by flash chromatography (10-40 % EtOAc/hexanes) to afford 127 mg of the desired seco-acid **5.64** in 68% yield. $[\alpha]_D^{25}$ +4.86 (*c* 0.32, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.5, 2H), 7.23 (dd, *J* = 1.0, 15.5 Hz, 1H), 6.93 (dt, *J* = 7.0, 15.5 Hz, 1H), 6.86 (d, *J* = 8.5 Hz, 2H), 6.17 (dd, *J* = 10.5, 15 Hz, 1H), 5.83 (d, *J* = 11.0 Hz, 1H), 5.79 (dt, *J* = 1.5, 15.5 Hz, 1H), 5.75 (d, *J* = 15.5 Hz, 1H), 5.73 (d, *J* = 11 Hz, 1H), 5.68-5.66 (m, 2H), 5.56 (ddd, *J* = 7.0, 7.0, 14.5 Hz, 1H), 4.57 (d, *J* = 11.0 Hz, 1H), 4.47 (d, *J* = 11.5 Hz, 1H), 4.46-4.45 (m, 1H), 4.33-4.30 (m, 1H), 3.80 (s, 3H), 3.56 (app t, *J* = 7.5 Hz, 1H), 3.39 (ddd, *J* = 2.0, 4.0, 9.5 Hz, 1H), 2.63-2.56 (m, 1H), 2.32-2.23 (m, 1H), 2.24 (d, *J* = 13.0 Hz, 2H), 2.16 (q, *J* = 7.0 Hz, 2H), 2.07 (dddd, *J* = 9.7.6, 7.6, 7.5, 7.5 Hz, 1H), 1.97 (dd, *J* = 10.0, 13.5 Hz, 1H), 1.79 (s, 3H), 1.72 (s, 3H), 1.69-1.66 (m, 1H), 1.60-1.50 (m, 4H), 1.50 (s, 9H), 1.40-1.32 (m, 1H), 1.08 (d, *J* = 7.0 Hz, 3H), 1.06-1.00 (m, 42H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 171.0, 166.8, 159.1, 151.7, 148.4, 143.0, 134.0, 133.9, 132.8, 131.9, 131.0, 129.2, 129.0, 128.5, 126.3, 120.8, 118.2, 113.7, 81.7, 80.1, 72.9, 72.6, 72.0, 71.9, 55.2, 45.7, 39.5, 38.1, 32.4, 29.7, 29.2, 28.2, 21.9, 18.1, 16.4, 16.2, 12.6, 12.4.

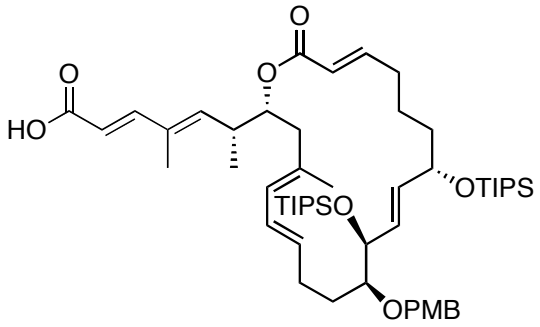
5.6.7.12 *tert*-Butyl(2*E*,4*E*,6*R*)-6-{(2*R*,4*E*,6*E*,10*S*,11*S*,12*E*,14*S*,18*E*)-10-[(4-methoxybenzyl)oxy]-4-methyl-20-oxo-11,14-bis[(tripropan-2-ylsilyl)oxy]oxacycloicosa-4,6,12,18-tetraen-2-yl}-4-methylhepta-2,4-dienoate



Secoacid **5.64** (127 mg, 0.124 mmol, 1.00 equiv) was dissolved in THF (10 mL). To the solution was added Et_3N (347 μL, 2.48 mmol, 20.0 equiv) and 2,4,6-trichlorobenzoyl chloride (289 μL, 1.86 mmol, 15.0 equiv) and the mixture was stirred for 2 h at rt. The reaction mixture was filtered through a pad of celite and concentrated *in vacuo* to afford the mixed anhydride, which was dissolved in toluene (12 mL) and added over 4 h to a solution of DMAP (556 mg, 4.96 mmol, 40.0 equiv) in toluene (104 mL). The reaction mixture was let to stir overnight. The next morning, saturated aqueous $NaHCO_3$ (50 mL) was added. The organic layer was separated and the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude product, which was purified by flash chromatography (0-20% Et_2O/hexanes containing 1% Et_3N) to afford the desired macrolactone **5.65** in 90% yield. $[\alpha]_D^{25}$ –91.58 (*c* 0.05, $CHCl_3$); IR (cast film) 3175, 2943, 2866, 1717, 1654, 1577, 1540, 1464, 1255, 1152, 1090, 1049, 979, 883, 682 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, *J* = 9.0, 2H), 7.21 (dd, *J* = 1.0, 15.5 Hz, 1H), 6.89 (d, *J* = 8.5 Hz, 2H), 6.79 (ddd, *J* = 5.5, 9.0, 15.0 Hz, 1H), 6.10 (dd, *J* = 11.5, 15 Hz, 1H), 5.76 (d, *J* = 16.0 Hz, 1H), 5.72 (dt, *J* = 1.5, 16.0 Hz, 1H), 5.66 (dd, *J* = 1.0, 14.0 Hz, 1H), 5.63-5.61 (m, 3H), 5.40 (ddd, *J* = 4.0, 10.5, 14.5 Hz, 1H), 4.96 (ddd, *J* = 2.0, 8.0, 11.5 Hz, 1H), 4.55 (d, *J* = 3.0 Hz, 1H), 4.52-4.49 (m, 2H), 4.14-4.10 (m, 1H), 3.81 (s, 3H), 3.34 (ddd, *J* = 1.5, 4.5, 6.0 Hz, 1H), 2.78-2.73 (m, 1H), 2.25-2.07 (m, 5H), 2.02 (dd, *J* = 11.5, 13.5 Hz, 1H), 1.90-1.86 (m, 1H), 1.78 (d, *J* = 1.0 Hz, 3H), 1.68 (s, 3H), 1.70-1.50 (m, 3H), 1.50 (s, 9H), 1.07-1.03 (m, 42H), 1.01 (d, 6.5 Hz, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 166.7, 166.1, 159.3, 149.3, 148.1, 141.7, 133.3, 133.0, 132.7, 131.4, 130.8, 129.5, 129.4, 128.5, 126.6, 120.6, 118.6, 113.8, 82.5, 80.1, 74.8, 73.7, 72.4, 70.5, 55.3,

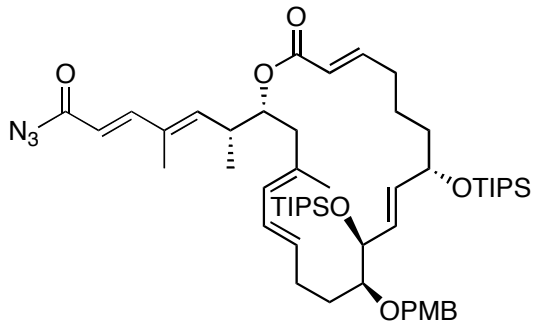
43.9, 39.4, 37.9, 33.4, 30.9, 30.8, 30.3, 28.2, 25.0, 18.1, 16.8, 16.5, 12.7, 12.5, 12.3; HRMS (ESI) Calcd. $C_{58}H_{96}O_8Si_2Na$: 999.65360. Found: 999.65314.

5.6.7.13 (2*E*,4*E*,6*R*)-6-{(2*R*,4*E*,6*E*,10*S*,11*S*,12*E*,14*S*,18*E*)-10-[(4-Methoxybenzyl)oxy]-4-methyl-20-oxo-11,14-bis[(tripropan-2-ylsilyl)oxy]oxacycloicosa-4,6,12,18-tetraen-2-yl}-4-methylhepta-2,4-dienoic acid (5.67)



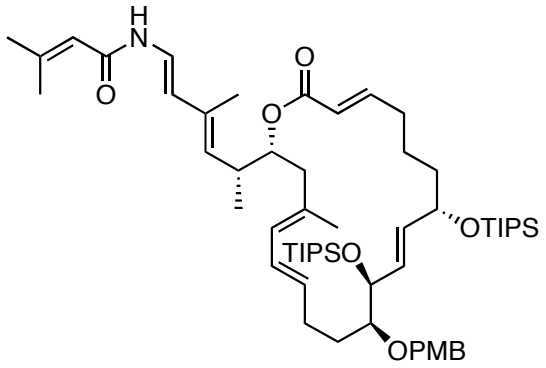
Macrolatone **5.65** (62.9 mg, 0.0541 mmol, 1.00 equiv) was dissolved in CH_2Cl_2 (2 mL) and cooled to 0 ºC. To the solution was added Et_3N (42.3 μL, 0.325 mmol, 6.00 equiv) and TMSOTf (29.7 μL, 0.162 mmol, 3.00 equiv). The reaction mixture was stirred for 30 min after which saturated aqueous $NaHCO_3$ (2 mL) was added. The mixture was extracted with Et_2O (2 × 25 mL), washed with H_2O (2 × 10 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude product which was purified by flash chromatography (40% EtOAc/hexanes) to afford 47.2 mg of the desired product **5.67** in 94% yield. $[\alpha]_D^{25}$ –58.21 (*c* 0.045, $CHCl_3$); IR (cast film) 2942, 2866, 1720, 1688, 1618, 1513, 1463, 1250, 1124, 1088, 981, 883, 682 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 16.0 Hz, 1H), 7.27 (d, *J* = 8.5 Hz, 1H), 6.89 (d, *J* = 8.5 Hz, 2H), 6.80 (ddd, *J* = 6.0, 9.0, 15.5 Hz, 1H), 6.11 (dd, *J* = 11.0, 14 Hz, 1H), 5.84 (d, *J* = 15.5 Hz, 1H), 5.77 (d, *J* = 10.0 Hz, 1H), 5.72 (d, *J* = 15.5 Hz, 1H), 5.68-5.62 (m, 3H), 5.43 (ddd, *J* = 4.5, 10.5, 15.0 Hz, 1H), 4.99 (app t, *J* = 9.5 Hz, 1H), 4.58 -4.51 (m, 2H), 4.13-4.10 (m, 1H), 3.81 (s, 3H), 3.36 (m, 1H), 2.80-2.76 (m, 1H), 2.28-2.05 (m, 6H), 1.83 (s, 3H), 1.68 (s, 3H), 1.70-1.16 (m, 6H), 1.06-1.00 (m, 45H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 172.4, 166.1, 159.3, 151.5, 149.4, 143.7, 133.3, 133.0, 132.8, 131.2, 130.8, 129.5, 128.5, 125.5, 126.6, 120.6, 115.8, 113.8, 82.5, 74.8, 73.5, 72.5, 70.5, 55.3, 43.9, 39.4, 37.8, 33.5, 30.9, 30.8, 30.3, 25.0, 18.2, 18.1, 16.6, 16.5, 12.6, 12.5, 12.4; HRMS (ESI) Calcd. $[C_{54}H_{87}O_8Si_2–H]^-$: 919.5945. Found: 919.59445.

5.6.7.14 (2*E*,4*E*,6*R*)-6-{(2*R*,4*E*,6*E*,10*S*,11*S*,12*E*,14*S*,18*E*)-10-[(4-Methoxybenzyl)oxy]-4-methyl-20-oxo-11,14-bis[(tripropan-2-ylsilyl)oxy]oxacycloicosa-4,6,12,18-tetraen-2-yl}-4-methylhepta-2,4-dienoyl azide (5.68)



Acid **5.67** (97.0 mg, 0.105 mmol, 1.00 equiv) was dissolved in benzene (10 mL). To the solution was added Et_3N (288 μL, 2.06 mmol, 19.6 equiv) and DPPA (95.2 μL, 0.442 mmol, 4.20 equiv) and the mixture was stirred at rt for 5 h. After the elapsed time, the volatiles were evaporated *in vacuo* and the crude product was purified by flash chromatography (0-20% Et_2O/hexanes containing 1% Et_3N) to afford 87.5 mg of the desired azide **5.68** in 88% yield. $[\alpha]_D^{25}$ –48.79 (*c* 0.05, $CHCl_3$); IR (cast film) 2943, 2866, 2169, 2139, 1720, 1687, 1612, 1513, 1464, 1250, 1209, 1181, 1090, 977, 883, 684 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 15.6 Hz, 1H), 7.28 (d, *J* = 8.4 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 2H), 6.80 (ddd, *J* = 6.0, 8.8, 14.8 Hz, 1H), 6.10 (dd, *J* = 10.8, 14.8 Hz, 1H), 5.82 (d, *J* = 15.6 Hz, 1H), 5.81 (d, *J* = 10.0 Hz, 1H), 5.72 (d, *J* = 15.6 Hz, 1H), 5.64-5.61 (m, 3H), 5.43 (ddd, *J* = 4.0, 10.4, 14.8 Hz, 1H), 4.99 (ddd, *J* = 2.4, 7.6, 10.8 Hz, 1H), 4.55 (d, *J* = 3.2, 2H), 4.15 (d, *J* = 0.4 Hz, 1H), 3.81 (s, 3H), 3.34 (ddd, *J* = 1.2, 4.4, 5.6 Hz, 1H), 2.83-2.73 (m, 1H), 2.28-2.01 (m, 5H), 1.93-1.80 (m, 1H), 1.80 (d, *J* = 1.2 Hz, 3H), 1.69 (s, 3H), 1.65-1.15 (m, 6H), 1.06-1.00 (m, 45H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 172.3, 166.0, 159.3, 151.3, 149.5, 145.2, 133.4, 133.0, 132.9, 131.1, 130.8, 130.0, 129.5, 128.6, 126.5, 126.1, 120.5, 113.8; 82.5, 74.8, 73.3, 72.5, 70.5, 50.3, 43.9, 39.4, 38.1, 33.5, 30.9, 30.8, 25.0, 18.2, 18.1, 16.5, 16.4, 12.6, 12.5, 12.4; HRMS (ESI) Calcd. $C_{54}H_{87}N_3O_7Si_2Na$: 968.59748. Found: 968.59646.

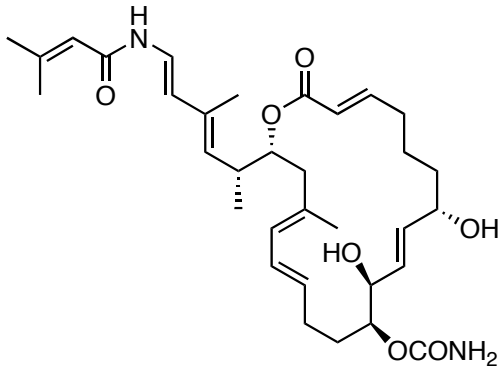
5.6.7.15 *N*-[(1*E*,3*E*,5*R*)-5-{(2*R*,4*E*,6*E*,10*S*,11*S*,12*E*,14*S*,18*E*)-10-[(4-Methoxybenzyl)oxy]-4-methyl-20-oxo-11,14-bis[(tripropan-2-ylsilyl)oxy]oxacycloicosa-4,6,12,18-tetraen-2-yl}-3-methylhexa-1,3-dien-1-yl]-3-methylbut-2-enamide (5.70)



Azide **5.68** (87.5 mg, 0.0925 mmol, 1.00 equiv) was dissolved in benzene (10 mL) and the mixture was heated to reflux at 100 ºC for 5 h to provide the putative isocyante **5.69**. After the elapsed time, the solvent was evaporated under a stream of argon and the crude isocyante **5.69** was dissolved in THF (8 mL) and over the course of 30 min, added to a –78 ºC-cooled solution of isoprenylmagnesium bromide (0.5 M in THF, 1.68 mL, 0.841 mmol, 9.10 equiv) in THF (2 mL). The reaction mixture was stirred for 30 min and Et_2O (50 mL) chilled to –78 ºC was added in one portion, followed by the addition of saturated NH_4Cl (4.0 mL). The reaction mixture was immediately poured into a seperatory funnel and the organic layer was separated. The aqueous layer was extracted with Et_2O (15 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude product, which was purified by flash chromatography (0-30% Et_2O/hexanes) to afford 68.8 mg of the desired dienamide **5.70** in 76% yield. $[\alpha]_D^{25}$ –21.25 (*c* 0.08, $CHCl_3$); IR (cast film) 3280, 2943, 2893, 2866, 1718, 1674, 1641, 1514, 1463, 1248 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.40 (dd, *J* = 14.4, 10.9, 1H), 7.30-7.25 (m, 2H), 6.99 (dt, *J* = 15.3, 7.6, 1H), 6.83-6.78 (m, 2H), 6.64 (d, *J* = 10.9, 1H), 6.39 (dd, *J* = 15.2, 11.2, 1H), 6.02-5.75 (m, 4H), 5.82 (d, *J* = 15.6, 1H), 5.68-5.62 (m, 1H), 5.61 (d, *J* = 14.5, 1H), 5.28 (ddd, *J* = 11.2, 8.1, 2.1, 1H), 5.20 (d, *J* = 9.9, 1H), 5.17-5.11 (m, 1H), 4.77 (d, *J* = 4.4, 1H), 4.57 (s, 1H), 4.16-4.11 (m, 1H), 3.57-3.55 (m, 1H), 3.30 (s, 3H), 2.72-2.58 (m, 2H), 2.3-1.4 (m, 11H) 2.23 (s, 3H), 1.78 (s, 3H), 1.60 (d, *J* = 1.0, 3H), 1.51 (s, 3H), 1.22-1.10 (m, 42H), 1.08 (d, *J* = 6.7, 3H); ^{13}C NMR (125 MHz; C_6D_6) δ 166.3, 163.1, 160.0, 153.2, 149.3, 133.64, 133.59, 132.9, 132.3, 131.3, 130.7, 130.3, 129.88, 129.79, 129.1, 128.6, 128.34, 128.15, 127.95, 127.4, 122.5, 121.5, 118.3, 117.1, 114.2, 83.0, 75.4, 74.5, 73.0, 71.4, 54.8, 53.3, 44.9, 40.1, 37.9, 33.6,

31.70, 31.61, 27.1, 25.4, 18.53, 18.50, 18.49, 18.46, 18.43, 17.6, 13.03, 12.94, 12.83, 12.80; HRMS (ESI) Calcd. $C_{58}H_{95}NO_7Si_2Na$: 996.65478. Found: 996.65393.

5.6.7.16 {(2*R*,4*E*,6*E*,10*S*,11*S*,12*E*,14*S*,18*E*)-11,14-Dihydroxy-4-methyl-2-{(2*R*,3*E*,5*E*)-4-methyl-6-[(3-methylbut-2-enoyl)amino]hexa-3,5-dien-2-yl}-20-oxooxacycloicosa-4,6,12,18-tetraen-10-yl carbamate (palmerolide A)} (5.38)



Enamide **5.70** (6.90 mg, 0.00710 mmol, 1.00 equiv) was combined with magnesium bromide diethyl etherate (44.0 mg, 0.170 mmol, 24.0 equiv) in a vial and dissolved in CH_2Cl_2 (0.3 mL). To this mixture was added dimethyl sulfide (19 μL, 340 μmol, 48 equiv). The reaction mixture was stirred for 15 min at room temperature and quenched by addition of aqueous saturated solution of sodium bicarbonate (0.5 mL). The biphasic solution was diluted with Et_2O (10 mL) and the organic layer was separated, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The organic residue was purified by silica gel chromatography (EtOAc/hexanes 10% to 30%; ~1% Et_3N) to afford 3.0 mg of white solid. Yield: 50%. The deprotected alcohol (5.00 mg, 0.00590 mmol, 1.00 equiv) was dissolved in CH_2Cl_2 (1.0 mL) and cooled to 0 ºC. To thus obtained solution was added trichloroacetyl isocyanate (3.00 μL, 25.0 μmol, 4.30 equiv) and the reaction mixture was stirred for 30 min at 0 °C. The reaction mixture was applied to a 1-inch pad of Brockmann II basic alumina and allowed to stand for 2 h at room temperature under argon. The pad was then rinsed with EtOAc (40 mL) and the crude reaction mixture was concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (EtOAc/hexane 20% to 40%; 1% Et_3N)) to afford 2.1 mg of white solid. Yield: 40%. The carbamate (2.10 mg, 2.30 μmol, 1.00 equiv) was dissolved in THF (1.0 mL) and cooled to 0 °C. To this was added 1.0 M tetrabutylammonium fluoride (70.0 μL, 70.0 μmol,

30.0 equiv) and the reaction mixture was stirred for 24 h at 0 °C. After the elapsed time, the mixture was diluted with EtOAc, washed with water, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography. First the silica was washed with 0.5% Et_3N/ CH_2Cl_2. The sample was loaded with CH_2Cl_2 and eluted with a gradient of MeOH/ CH_2Cl_2 (1% to 10%). To remove co-eluted silica the sample was dissolved in CH_2Cl_2 and centrifuged. Evaporation of the supernatant yielded 1.50 mg of off-white solid. Yield: quantitative.

^{1}H NMR spectrum (chemical shift and coupling constant correlation) of the product was consistent with those reported in the literature, except for the presence of foreign peaks in the aliphatic region (presumably grease), and hydrated DMSO (see appendix). The sign of the optical rotation was also in agreement with literature. $[\alpha]_D^{25}$ –37.91 (*c* 0.048, Methanol). Literature: **Original isolation paper** $[\alpha]_D^{24}$ –1.6 (*c* 0.5, Methanol),[19] **re-measured** $[\alpha]_D^{25}$ –99.0 (*c* 0.24, Methanol),[22] **synthetic** $[\alpha]_D^{25}$ –95.0 (*c* 0.12, Methanol).

^{1}H NMR (800 MHz; DMSO-d_6): δ 9.89 (d, *J* = 10.3, 1H), 6.85 (dd, *J* = 14.6, 10.3, 1H), 6.71 (ddd, *J* = 15.3, 10.1, 5.0, 1H), 6.60-6.38 (bd, 2H), 6.04 (dd, *J* = 14.3, 10.9, 1H), 5.85 (d, *J* = 14.4, 1H), 5.77 (d, *J* = 15.5, 1H), 5.70 (s, 1H), 5.60 (d, *J* = 11.0, 1H), 5.55 (ddd, *J* = 15.4, 8.3, 1.8, 1H), 5.48 (dd, *J* = 15.5, 3.0, 1H), 5.41 (ddd, *J* = 14.7, 10.2, 4.5, 1H), 5.17 (d, *J* = 4.9, 1H), 5.13 (d, *J* = 9.8, 1H), 4.84 (ddd, *J* = 11.3, 7.9, 2.0, 1H), 4.68 (d, *J* = 4.2, 1H), 4.48 (ddd, *J* = 10.9, 5.1, 1.7, 1H), 4.14-4.13 (m, 1H), 3.83-3.80 (m, 1H), 2.70-2.67 (m, 1H), 2.19-2.15 (m, 1H), 2.12 (s, 3H), 2.02-1.90 (m, 5H), 1.83 (s, 3H), 1.71 (s, 3H), 1.61 (s, 3H), 1.60-1.58 (m, 1H), 1.50-1.46 (m, 1H), 1.32-1.29 (m, 2H), 1.07-1.03 (m, 1H), 1.00-0.96 (m, 1H), 0.90 (d, *J* = 6.6, 3H); ^{13}C NMR (126 MHz; DMSO-d_6): δ 166.0, 163.8, 157.3, 152.5, 150.0, 134.3, 133.3, 132.6, 132.3, 130.5, 129.6, 128.4, 127.1, 122.9, 121.3, 118.8, 117.1, 75.8, 74.5, 73.2, 69.9, 63.2, 43.9, 38.5, 37.3, 33.1, 30.1, 27.7, 25.7, 20.3, 18.6, 17.8, 16.9, 13.4HRMS (ESI) Calcd. $C_{33}H_{48}N_2O_7Na$: 607.3354. Found: 607.3349.

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Chapter 6

Thesis Conclusions

The studies described in this thesis have been aimed towards the understanding of the mechanism of catalytic allylboration methodology and the development of an enantioselective variant for the stereoselective construction of the ever-important poly acetate and propionate units, which are prevalent in numerous molecules of biological interest, including marine macrolides.

Based on kinetic studies and an assortment of control experiments, I was able to shed light on the mechanistic intricacies of the novel Lewis acid catalyzed allylboration of aldehydes. More specifically, contrary to traditional carbonyl Lewis acid activation, I presented compelling evidence that pointed towards electrophilic boronate activation as the key factor for catalytic rate acceleration. This type of boronate activation was proposed to result in the enhanced electrophilicity of the boron center, which would consequently lead to increased boron-carbonyl bonding, the most crucial event in the allylboration reaction transition state. Furthermore, this mechanistic hypothesis was recently validated by the high-level calculations of Fujimoto and Sakata.

Armed with the mechanistic model of the new Lewis acid catalyzed allylboration reaction, I sought out to develop a catalytic enantioselective allylboration, in which the catalyst would be responsible for boronate activation and provide the facial selectivity in aldehyde addition reactions. Subsequently, I discovered that Yamamoto's Lewis acid assisted Brønsted acids derived from chiral diol•$SnCl_4$ complexes were promising catalysts for the enantioselective allyl- and crotylboration of aldehyde substrates. Exhaustive optimization of the diol structure led us to arrive at a novel class of ortho-cycloalkyl substituted hydrobenzoins, as the most effective diols for the diol•$SnCl_4$ catalyzed allylboration reaction. In particular, the diol termed Vivol (containing the cyclooctyl rings on the ortho-position of parent hydrobenzoin) was found to be remarkably effective for the enantioselective allylboration of aliphatic aldehydes, and the corresponding homoallylic alcohols were obtained in up to 95% *ee*. The LBA catalyst derived from Vivol•$SnCl_4$ complex also displayed remarkable selectivity for the enantioselective *E*-crotylboration of aldehydes and provided the corresponding products in excellent enantio- and diastereoselectivities. Moreover, I was able to obtain a single crystal X-ray diffraction structure

of Vivol•$SnCl_4$ complex, which clearly shows the dissymmetric environment around the activated Brønsted acidic protons (the proposed source of boronate activation). Although the Vivol•$SnCl_4$ catalyst system was efficient for aldehyde allylboration reaction, I could still observe non-negligible amounts of the racemic uncatalyzed background-reaction. Based on the hypothesis that electron poor diols based on Vivol scaffold (a design based on the X-ray crystal structure analysis of Vivol•$SnCl_4$) would provide an even more efficient Brønsted acid, I arrived at a new diol termed F-Vivol, which displayed consistently superior reactivity and selectivity over its predecessor. In my efforts to demonstrate the utility of F-Vivol•$SnCl_4$, I effectively expanded the allylic boron reagent to include 2-bromoallylboron pinacolate. The corresponding bromide-substituted homoallylic alcohol products were readily transformed into chiral α-methylene-γ-lactones.

Thereafter, I effectively utilized the F-Vivol•$SnCl_4$-catalyst system for the enantio- and stereoselective synthesis of the natural product (+)-dodoneine. During the course of synthesis of this natural product, I was able to demonstrate that the F-Vivol•$SnCl_4$ catalyzed allylboration manifold compared favorably and outperformed the well established Brown and Keck allylation reactions. Finally, the LBA catalyst derived from the F-vivol analogue (containing the seven membered ring) was successfully utilized in the multi-gram synthesis of the western hemisphere of the complex anti-melanoma natural product palmerolide A. Additionally, the need for large-scale preparation of Vivol and F-Vivol and other ring analogues required a convenient and economical access to cycloalkenylboronic acid and esters. In the event, the classic Shapiro protocol was successfully utilized to prepare all requisite ring sizes of the corresponding cycloalkeneboronic acids, in very good to excellent yields.

To summarize, I was able to shed light on the unique mode of Lewis acid activation of allylic boronates and design the first catalyst system for the highly enantioselective, diastereoselective allylboration of aldehydes. This outstanding method was successfully applied towards the total synthesis of (+)-dodoneine and palmerolide A.

Appendix

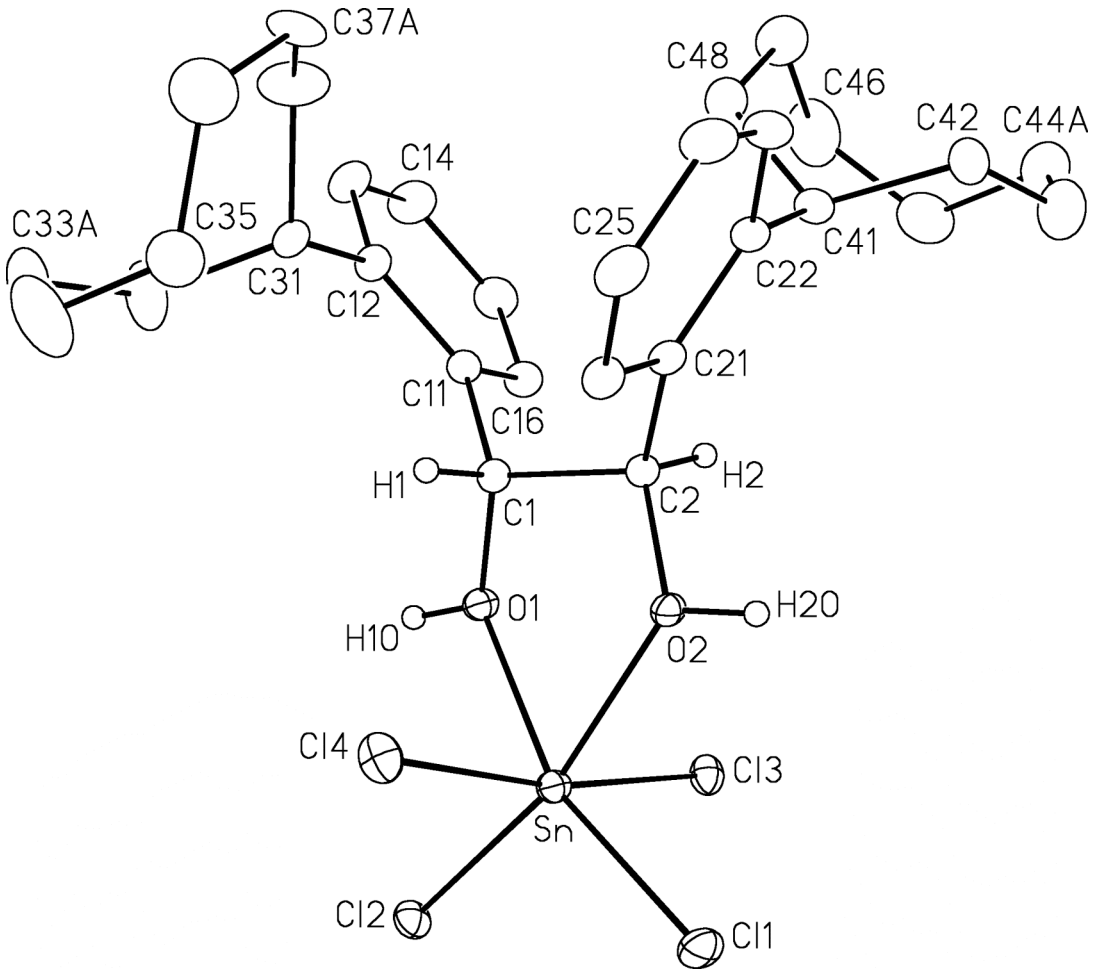
X-Ray Crystallography Report of Vivol (4.21)•$SnCl_4$

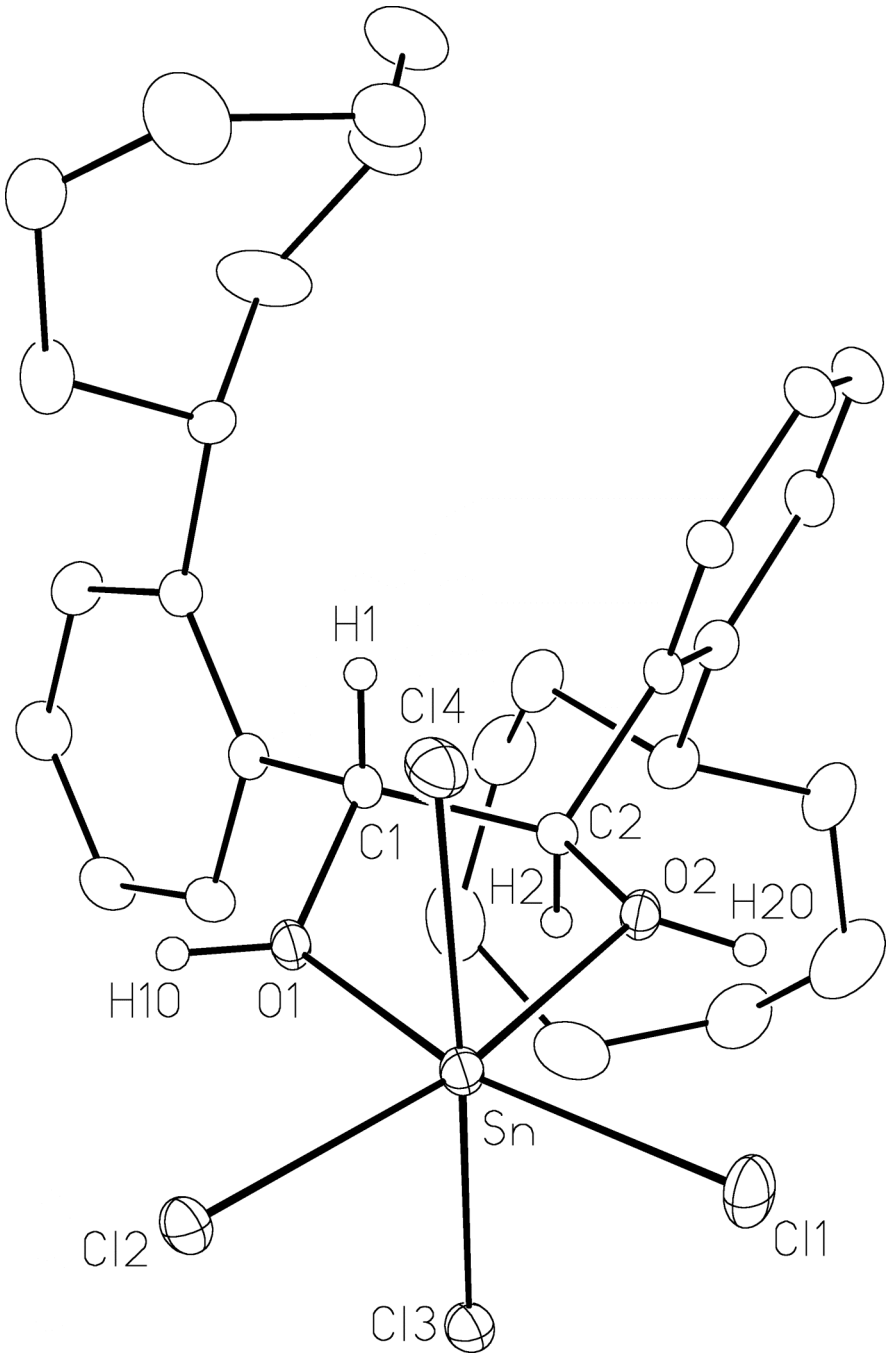
XCL Code: DGH0807 **Date:** 8 February 2008

Compound: [{1,2-bis(2-cyclooctylphenyl)ethane-1,2-diol}$SnCl_4$]•H_2O•PhMe

Formula: $C_{37}H_{56}Cl_4O_3Sn$ ($C_{30}H_{46}Cl_4O_2Sn$•H_2O•C_7H_8)

Supervisor: D. G. Hall Crystallographer: R. McDonald

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C2
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O2
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H10
O1
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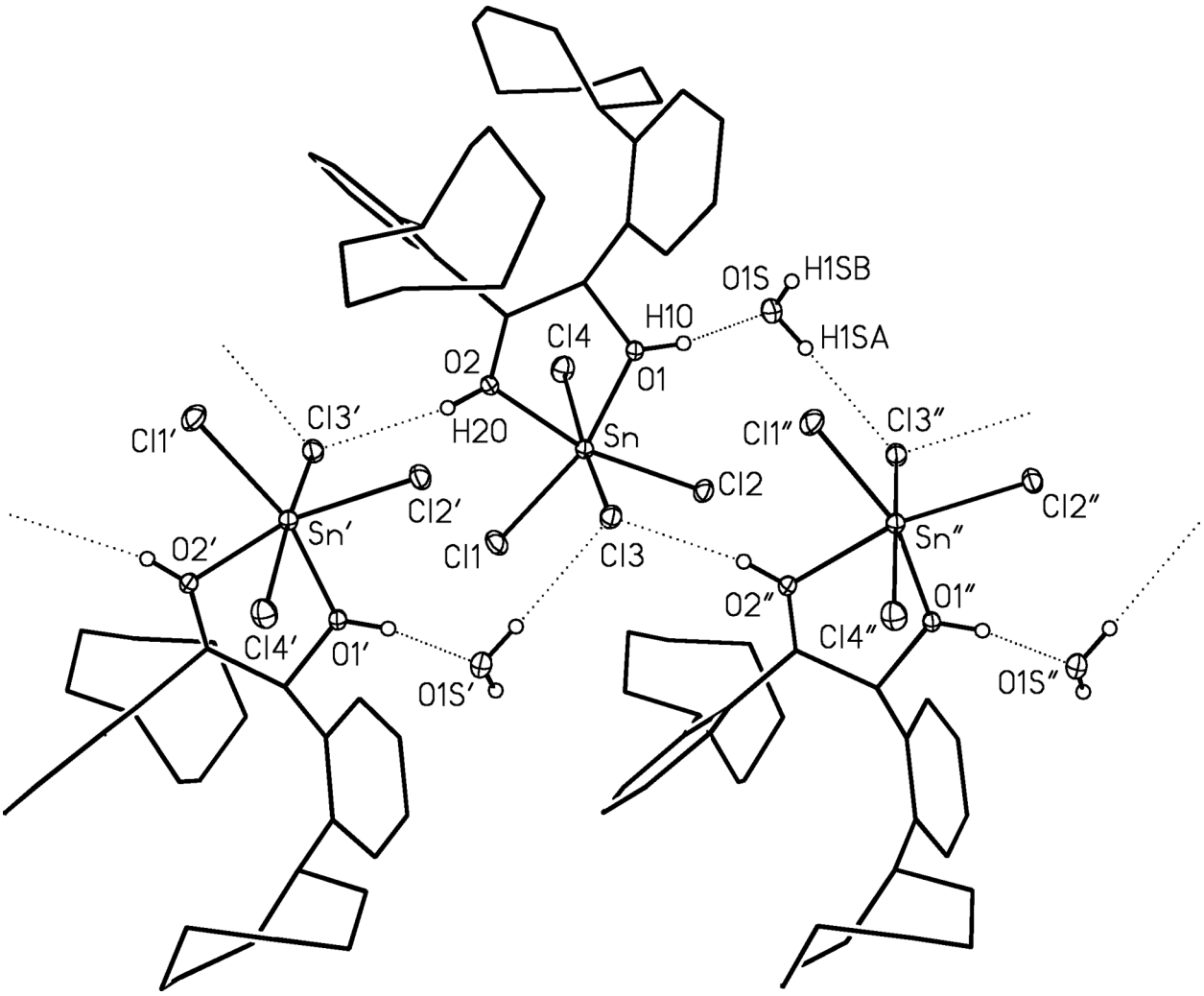
Cl2
Cl1
Cl3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Sn″
Cl2′
Sn′
O2′
Cl1
Cl3
O2″
O1″
Cl4″
Cl4′
O1′
O1S′
O1S″

Table 1. Crystallographic Experimental Details

A. Crystal Data

formula	$C_{37}H_{56}Cl_4O_3Sn$
formula weight	809.31
crystal dimensions (mm)	0.64 × 0.15 × 0.10
crystal system	orthorhombic
space group	$P2_12_12_1$ (No. 19)
unit cell parameters[a]	
a (Å)	9.9594 (7)
b (Å)	12.2807 (8)
c (Å)	31.266 (2)
V (Å^3)	3824.1 (4)
Z	4
ρ_{calcd} (g cm^{-3})	1.406
μ (mm^{-1})	0.981

B. Data Collection and Refinement Conditions

diffractometer	Bruker PLATFORM/SMART 1000 CCD[b]
radiation (λ [Å])	graphite-monochromated Mo Kα (0.71073)
temperature (°C)	–80
scan type	ω scans (0.3°) (15 s exposures)
data collection 2θ limit (deg)	54.90
total data collected	33714 ($-12 \le h \le 12$, $-15 \le k \le 15$, $-40 \le l \le 40$)
independent reflections	8736 (R_{int} = 0.0318)
number of observed reflections (*NO*)	8210 [$F_o^2 \ge 2\sigma(F_o^2)$]
structure solution method	Patterson search/structure expansion (*DIRDIF–99*[c])
refinement method	full-matrix least-squares on F^2 (*SHELXL–97*[d])
absorption correction method	multi-scan (*SADABS*)
range of transmission factors	0.9083–0.5724
data/restraints/parameters	8736 [$F_o^2 \ge -3\sigma(F_o^2)$] / 15[e] / 400
Flack absolute structure parameter[f]	-0.011(17)

goodness-of-fit (S)[g]	1.092 [$F_o^2 \geq -3\sigma(F_o^2)$]
final R indices[h]	
R_1 [$F_o^2 \geq 2\sigma(F_o^2)$]	0.0316
wR_2 [$F_o^2 \geq -3\sigma(F_o^2)$]	0.0827
largest difference peak and hole	0.910 and –0.640 e Å^{-3}

[a]Obtained from least-squares refinement of 6722 reflections with $4.30° < 2\theta < 52.68°$.

[b]Programs for diffractometer operation, data collection, data reduction and absorption correction were those supplied by Bruker.

(continued)

Table 1. Crystallographic Experimental Details (continued)

[c]Beurskens, P. T.; Beurskens, G.; de Gelder, R.; Garcia-Granda, S.; Israel, R.; Gould, R. O.; Smits, J. M. M. (1999). The *DIRDIF-99* program system. Crystallography Laboratory, University of Nijmegen, The Netherlands.

[d]Sheldrick, G. M. *Acta Crystallogr*. **2008**, *A64*, 112–122.

[e]O–H distances were given fixed idealized distances during refinement: d(O1–H1O) = d(O2–H2O) = d(O1S–H1SA) = d(O1S–H1SB) = 0.86 Å. Distances within a disordered region of one of the cyclooctyl groups were given fixed idealized values: d(C43–C44B) = d(C44B–C45A) = d(C45B–C46) = 1.54 Å; d(C43···C45B) = d(C44B···C46) = 2.56 Å. Distances involving the methyl carbon positions of the disordered solvent toluene molecule were given fixed idealized values: d(C10S–C11S) = d(C20S–C21S) = 1.50 Å; d(C10S···C12S) = d(C10S···C16S) = d(C20S···C22S) = d(C20S···C26S) = 2.50 Å. The phenyl rings of the disordered solvent toluene molecule were treated as idealized hexagons with a C–C bond length of 1.39 Å.

[f]Flack, H. D. *Acta Crystallogr*. **1983**, *A39*, 876–881; Flack, H. D.; Bernardinelli, G. *Acta Crystallogr*. **1999**, *A55*, 908–915; Flack, H. D.; Bernardinelli, G. *J. Appl. Cryst*. **2000**, *33*, 1143–1148. The Flack parameter will refine to a value near zero if the structure is in the correct configuration and will refine to a value near one for the inverted configuration.

[g]$S = [\Sigma w(F_o^2 - F_c^2)^2/(n - p)]^{1/2}$ (n = number of data; p = number of parameters varied; $w = [\sigma^2(F_o^2) + (0.0468P)^2 + 1.4331P]^{-1}$ where $P = [\mathrm{Max}(F_o^2, 0) + 2F_c^2]/3$).

[h]$R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^4)]^{1/2}$.

Table 2. Atomic Coordinates and Equivalent Isotropic Displacement Parameters

(a) atoms of [{1,2-bis(2-cyclooctylphenyl)ethane-1,2-diol}$SnCl_4$]

Atom	*x*	*y*	*z*	U_{eq}, Å^2
Sn	0.168381(19)	0.135675(17)	0.523556(6)	0.02675(6)*
Cl1	0.01856(9)	0.19942(8)	0.57549(3)	0.0451(2)*
Cl2	0.38284(7)	0.14414(7)	0.55527(3)	0.03525(16)*
Cl3	0.20144(7)	0.31738(6)	0.49498(3)	0.03500(17)*
Cl4	0.13831(9)	-0.05130(7)	0.53967(3)	0.0431(2)*
O1	0.2472(2)	0.08732(19)	0.46315(7)	0.0294(5)*
O2	0.00053(19)	0.11764(17)	0.47894(7)	0.0294(4)*
C1	0.1586(3)	0.0291(2)	0.43410(9)	0.0256(6)*
C2	0.0262(3)	0.0932(3)	0.43389(10)	0.0253(6)*
C11	0.2253(3)	0.0237(3)	0.39033(10)	0.0279(6)*
C12	0.2383(3)	-0.0741(3)	0.36771(10)	0.0309(7)*
C13	0.3096(4)	-0.0718(3)	0.32937(11)	0.0430(8)*
C14	0.3645(4)	0.0243(4)	0.31382(13)	0.0495(10)*
C15	0.3504(4)	0.1202(3)	0.33616(12)	0.0443(8)*
C16	0.2802(3)	0.1194(3)	0.37423(11)	0.0347(7)*
C21	-0.0902(3)	0.0266(3)	0.41680(10)	0.0288(6)*
C22	-0.1565(3)	0.0496(3)	0.37777(10)	0.0351(7)*
C23	-0.2627(4)	-0.0187(3)	0.36663(13)	0.0457(9)*
C24	-0.3054(4)	-0.1031(4)	0.39101(14)	0.0527(11)*
C25	-0.2405(4)	-0.1252(3)	0.42911(13)	0.0448(8)*
C26	-0.1334(3)	-0.0603(3)	0.44159(11)	0.0340(7)*
C31	0.1846(3)	-0.1827(2)	0.38366(10)	0.0313(6)*
C32	0.2985(4)	-0.2477(4)	0.40289(19)	0.0678(14)*
C33A[a]	0.2739(13)	-0.3617(11)	0.4198(5)	0.067(3)*
C33B[a]	0.2803(13)	-0.3190(11)	0.4399(4)	0.067(3)*
C34	0.1624(6)	-0.3915(5)	0.4478(2)	0.092(2)*
C35	0.0194(5)	-0.3586(4)	0.43847(14)	0.0566(10)*
C36	-0.0264(6)	-0.3824(4)	0.39440(16)	0.0756(15)*

C37A[a]	-0.0067(13)	-0.3061(10)	0.3563(3)	0.047(3)*
C37B[a]	0.0364(17)	-0.3450(10)	0.3599(5)	0.066(4)*
C38	0.1075(6)	-0.2435(4)	0.34903(15)	0.0746(16)*
C41	-0.1167(4)	0.1413(3)	0.34727(10)	0.0400(7)*
C42	-0.2436(5)	0.2070(4)	0.33354(13)	0.0550(11)*
C43	-0.2308(7)	0.3276(5)	0.32774(18)	0.0876(19)*
C44A[b]	-0.1466(7)	0.3775(6)	0.2941(2)	0.0746(18)*
C45A[b]	0.0039(8)	0.3607(6)	0.2995(3)	0.084(2)*
C44B[c]	-0.0978(12)	0.3864(12)	0.3181(8)	0.090
C45B[c]	-0.0401(16)	0.3573(14)	0.2739(6)	0.090
C46	0.0653(6)	0.2656(6)	0.2762(2)	0.0871(19)*

Table 2. Atomic Coordinates and Displacement Parameters (continued)

Atom	*x*	*y*	*z*	U_{eq}, Å^2
C47	-0.0149(6)	0.1611(4)	0.26977(14)	0.0693(14)*
C48	-0.0407(4)	0.0900(4)	0.30942(12)	0.0510(10)*

(b) solvent water and toluene atoms

Atom	*x*	*y*	*z*	U_{eq}, Å^2
O1S	0.4859(3)	0.0199(2)	0.45899(9)	0.0473(6)*
C10S[d]	0.6093(9)	-0.0338(6)	0.1762(3)	0.0728(8)
C11S[d]	0.5343(7)	0.0649(5)	0.1910(2)	0.0728(8)
C12S[d]	0.4142(7)	0.0938(5)	0.1713(2)	0.0728(8)
C13S[d]	0.3465(6)	0.1872(6)	0.1842(2)	0.0728(8)
C14S[d]	0.3988(7)	0.2516(5)	0.2168(2)	0.0728(8)
C15S[d]	0.5188(8)	0.2227(6)	0.2364(2)	0.0728(8)
C16S[d]	0.5866(7)	0.1293(6)	0.2235(2)	0.0728(8)
C20S[d]	0.6560(9)	-0.0643(6)	0.1754(3)	0.0728(8)
C21S[d]	0.5702(7)	0.0327(5)	0.1852(2)	0.0728(8)
C22S[d]	0.4600(7)	0.0565(6)	0.1595(2)	0.0728(8)
C23S[d]	0.3806(6)	0.1467(6)	0.1686(2)	0.0728(8)
C24S[d]	0.4114(7)	0.2131(5)	0.2032(2)	0.0728(8)

C25S[d]	0.5216(8)	0.1892(6)	0.2289(2)	0.0728(8)
C26S[d]	0.6010(7)	0.0990(6)	0.2198(2)	0.0728(8)

Anisotropically-refined atoms are marked with an asterisk (*). The form of the anisotropic displacement parameter is: $\exp[-2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + l^2c^{*2}U_{33} + 2klb^*c^*U_{23} + 2hla^*c^*U_{13} + 2hka^*b^*U_{12})]$. [a]Refined with an occupancy factor of 0.5. [b]Refined with an occupancy factor of 0.8. [c]Refined with an occupancy factor of 0.2 and a fixed isotropic displacement parameter. [d]Refined with an occupancy factor of 0.5 and a common isotropic displacement parameter.

Table 3. Selected Interatomic Distances (Å)

(a) within [{1,2-bis(2-cyclooctylphenyl)ethane-1,2-diol}$SnCl_4$]

Atom1	Atom2	Distance	Atom1	Atom2	Distance
Sn	Cl1	2.3401(8)	C25	C26	1.387(5)
Sn	Cl2	2.3571(8)	C31	C32	1.512(5)
Sn	Cl3	2.4262(8)	C31	C38	1.523(5)
Sn	Cl4	2.3698(9)	C32	C33A	1.517(15)
Sn	O1	2.130(2)	C32	C33B	1.462(14)
Sn	O2	2.188(2)	C33A	C34	1.462(15)
O1	C1	1.454(3)	C33B	C34	1.495(14)
O2	C2	1.463(4)	C34	C35	1.509(7)
C1	C2	1.535(4)	C35	C36	1.481(7)
C1	C11	1.523(4)	C36	C37A	1.529(11)
C2	C21	1.516(4)	C36	C37B	1.329(17)
C11	C12	1.400(4)	C37A	C38	1.391(13)
C11	C16	1.390(5)	C37B	C38	1.473(14)
C12	C13	1.394(5)	C41	C42	1.560(5)
C12	C31	1.521(4)	C41	C48	1.539(5)
C13	C14	1.389(5)	C42	C43	1.498(7)
C14	C15	1.376(6)	C43	C44A	1.478(9)
C15	C16	1.381(5)	C43	C44B	1.538(3)[a]
C21	C22	1.416(5)	C44A	C45A	1.522(10)
C21	C26	1.387(5)	C45A	C46	1.504(10)
C22	C23	1.394(5)	C44B	C45B	1.539(3)[a]
C22	C41	1.528(5)	C45B	C46	1.540(3)[a]
C23	C24	1.355(6)	C46	C47	1.526(8)
C24	C25	1.382(6)	C47	C48	1.537(6)

[a]Distance restrained to be 1.54(1) Å during refinement.

(b) within the disordered solvent toluene molecule

Atom1	Atom2	Distance	Atom1	Atom2	Distance
C10S	C11S	1.50[b]	C11S	C12S	1.39[b]

C11S	C16S	1.39[b]	C21S	C22S	1.39[b]
C12S	C13S	1.39[b]	C21S	C26S	1.39[b]
C13S	C14S	1.39[b]	C22S	C23S	1.39[b]
C14S	C15S	1.39[b]	C23S	C24S	1.39[b]
C15S	C16S	1.39[b]	C24S	C25S	1.39[b]
C20S	C21S	1.50[b]	C25S	C26S	1.39[b]

[b]Distance fixed during refinement.

Table 4. Selected Interatomic Angles (deg)

(a) within [{1,2-bis(2-cyclooctylphenyl)ethane-1,2-diol}$SnCl_4$]

Atom1	Atom2	Atom3	Angle	Atom1	Atom2	Atom3	Angle
Cl1	Sn	Cl2	105.73(3)	C13	C12	C31	118.6(3)
Cl1	Sn	Cl3	91.97(3)	C12	C13	C14	121.3(3)
Cl1	Sn	Cl4	95.51(4)	C13	C14	C15	120.6(3)
Cl1	Sn	O1	160.67(6)	C14	C15	C16	118.9(3)
Cl1	Sn	O2	89.37(6)	C11	C16	C15	121.1(3)
Cl2	Sn	Cl3	89.51(3)	C2	C21	C22	123.6(3)
Cl2	Sn	Cl4	93.89(3)	C2	C21	C26	117.1(3)
Cl2	Sn	O1	92.95(6)	C22	C21	C26	119.4(3)
Cl2	Sn	O2	164.74(6)	C21	C22	C23	116.7(3)
Cl3	Sn	Cl4	170.62(3)	C21	C22	C41	124.3(3)
Cl3	Sn	O1	83.10(7)	C23	C22	C41	119.0(3)
Cl3	Sn	O2	87.82(6)	C22	C23	C24	123.9(4)
Cl4	Sn	O1	87.99(7)	C23	C24	C25	119.2(3)
Cl4	Sn	O2	86.61(6)	C24	C25	C26	119.3(4)
O1	Sn	O2	71.82(7)	C21	C26	C25	121.5(3)
Sn	O1	C1	117.87(16)	C12	C31	C32	109.2(3)
Sn	O2	C2	120.07(16)	C12	C31	C38	112.0(3)
O1	C1	C2	105.8(2)	C32	C31	C38	113.7(4)
O1	C1	C11	108.6(2)	C31	C32	C33A	120.3(6)
C2	C1	C11	113.1(2)	C31	C32	C33B	122.5(6)
O2	C2	C1	104.5(2)	C32	C33A	C34	124.2(9)
O2	C2	C21	108.5(2)	C32	C33B	C34	125.9(9)
C1	C2	C21	112.5(2)	C33A	C34	C35	122.2(6)
C1	C11	C12	122.1(3)	C33B	C34	C35	123.3(6)
C1	C11	C16	117.4(3)	C34	C35	C36	114.7(5)
C12	C11	C16	120.4(3)	C35	C36	C37A	124.4(6)
C11	C12	C13	117.7(3)	C35	C36	C37B	122.8(8)
C11	C12	C31	123.7(3)	C36	C37A	C38	124.8(8)

C36	C37B	C38	135.0(13)	C43	C44A	C45A	115.1(6)
C31	C38	C37A	124.5(6)	C44A	C45A	C46	116.9(6)
C31	C38	C37B	119.5(7)	C43	C44B	C45B	112.8(3)[a]
C22	C41	C42	110.0(3)	C44B	C45B	C46	112.4(3)[a]
C22	C41	C48	107.8(3)	C45A	C46	C47	120.3(5)
C42	C41	C48	113.5(3)	C45B	C46	C47	104.6(10)[a]
C41	C42	C43	118.4(5)	C46	C47	C48	117.3(4)
C42	C43	C44A	123.0(5)	C41	C48	C47	118.0(4)
C42	C43	C44B	124.1(8)[a]				

[a]Distance restraints applied during refinement: d(C43–C44B) = d(C44B–C45A) = d(C45B–C46) = 1.54 Å; d(C43···C45B) = d(C44B···C46) = 2.56 Å.

Table 4. Selected Interatomic Angles (continued)

(b) within the disordered solvent toluene molecule

Atom1	Atom2	Atom3	Angle	Atom1	Atom2	Atom3	Angle
C10S	C11S	C12S	120.0[b]	C20S	C21S	C22S	120.0[b]
C10S	C11S	C16S	120.0[b]	C20S	C21S	C26S	120.0[b]
C12S	C11S	C16S	120.0[b]	C22S	C21S	C26S	120.0[b]
C11S	C12S	C13S	120.0[b]	C21S	C22S	C23S	120.0[b]
C12S	C13S	C14S	120.0[b]	C22S	C23S	C24S	120.0[b]
C13S	C14S	C15S	120.0[b]	C23S	C24S	C25S	120.0[b]
C14S	C15S	C16S	120.0[b]	C24S	C25S	C26S	120.0[b]
C11S	C16S	C15S	120.0[b]	C21S	C26S	C25S	120.0[b]

[b]Angle fixed during refinement.

Table 5. Hydrogen-Bonded Interactions

D–H···A	D–H (Å)	H···A (Å)	D···A (Å)	∠D–H···A (deg)	Note
O1–H1O···O1S	0.86	1.67	2.521(3)	168.9	
O2–H2O···Cl3[a]	0.86	2.42	3.190(2)	149.2	[a]At $^{-1}/_{2}+x$, $^{1}/_{2}-y$, $1-z$.
O1S–H1SA···Cl3[b]	0.86	2.41	3.267(3)	176.9	[b]At $^{1}/_{2}+x$, $^{1}/_{2}-y$, $1-z$.

Table 6. Torsional Angles (deg)

Atom1	Atom2	Atom3	Atom4	Angle	Atom1	Atom2	Atom3	Atom4	Angle
Cl1	Sn	O1	C1	-38.2(3)	C16	C11	C12	C31	178.3(3)
Cl2	Sn	O1	C1	156.60(19)	C1	C11	C16	C15	175.5(3)
Cl3	Sn	O1	C1	-114.25(19)	C12	C11	C16	C15	-1.2(5)
Cl4	Sn	O1	C1	62.81(19)	C11	C12	C13	C14	-0.8(5)
O2	Sn	O1	C1	-24.29(19)	C31	C12	C13	C14	-178.1(4)
Cl1	Sn	O2	C2	170.64(19)	C11	C12	C31	C32	-100.2(4)
Cl2	Sn	O2	C2	-1.4(4)	C11	C12	C31	C38	133.0(4)
Cl3	Sn	O2	C2	78.64(19)	C13	C12	C31	C32	76.9(4)
Cl4	Sn	O2	C2	-93.80(19)	C13	C12	C31	C38	-50.0(5)
O1	Sn	O2	C2	-4.81(19)	C12	C13	C14	C15	0.4(6)
Sn	O1	C1	C2	46.8(3)	C13	C14	C15	C16	-0.4(6)
Sn	O1	C1	C11	168.49(18)	C14	C15	C16	C11	0.7(6)
Sn	O2	C2	C1	29.0(3)	C2	C21	C22	C23	-179.4(3)
Sn	O2	C2	C21	149.15(19)	C2	C21	C22	C41	2.2(5)
O1	C1	C2	O2	-44.5(3)	C26	C21	C22	C23	-0.3(5)
O1	C1	C2	C21	-161.9(2)	C26	C21	C22	C41	-178.7(3)
C11	C1	C2	O2	-163.2(2)	C2	C21	C26	C25	179.0(3)
C11	C1	C2	C21	79.3(3)	C22	C21	C26	C25	-0.2(5)
O1	C1	C11	C12	129.6(3)	C21	C22	C23	C24	0.8(5)
O1	C1	C11	C16	-47.0(4)	C41	C22	C23	C24	179.2(4)
C2	C1	C11	C12	-113.2(3)	C21	C22	C41	C42	-132.6(3)
C2	C1	C11	C16	70.1(3)	C21	C22	C41	C48	103.2(4)
O2	C2	C21	C22	132.3(3)	C23	C22	C41	C42	49.1(4)
O2	C2	C21	C26	-46.8(4)	C23	C22	C41	C48	-75.2(4)
C1	C2	C21	C22	-112.5(3)	C22	C23	C24	C25	-0.8(6)
C1	C2	C21	C26	68.3(3)	C23	C24	C25	C26	0.2(6)
C1	C11	C12	C13	-175.4(3)	C24	C25	C26	C21	0.3(5)
C1	C11	C12	C31	1.7(5)	C12	C31	C32	C33A	-177.6(7)
C16	C11	C12	C13	1.2(5)	C12	C31	C32	C33B	144.9(8)

C38	C31	C32	C33A	-51.7(9)
C38	C31	C32	C33B	-89.3(9)
C12	C31	C38	C37A	-143.4(7)
C12	C31	C38	C37B	-173.7(9)
C32	C31	C38	C37A	92.2(9)
C32	C31	C38	C37B	61.9(10)
C31	C32	C33A	C34	-47.4(14)
C31	C32	C33B	C34	39.9(16)
C32	C33A	C34	C35	48.6(15)
C32	C33B	C34	C35	-40.0(17)
C33A	C34	C35	C36	49.6(10)
C33B	C34	C35	C36	88.1(10)
C34	C35	C36	C37A	-86.8(9)
C34	C35	C36	C37B	-56.6(10)
C35	C36	C37A	C38	38.3(15)
C35	C36	C37B	C38	-36(2)
C36	C37A	C38	C31	-40.7(15)
C36	C37B	C38	C31	33(2)
C22	C41	C42	C43	143.4(4)
C48	C41	C42	C43	-95.7(5)
C22	C41	C48	C47	167.6(4)
C42	C41	C48	C47	45.5(6)

Table 6. Torsional Angles (continued)

Atom1	Atom2	Atom3	Atom4	Angle	Atom1	Atom2	Atom3	Atom4	Angle
C41	C42	C43	C44A	65.3(7)	C43	C44B	C45B	C46	-95.9(10)
C41	C42	C43	C44B	23.3(12)	C44B	C45B	C46	C47	91.5(13)
C42	C43	C44A	C45A	-67.2(9)	C45A	C46	C47	C48	-71.2(7)
C42	C43	C44B	C45B	66.3(18)	C45B	C46	C47	C48	-105.1(8)
C43	C44A	C45A	C46	94.3(8)	C46	C47	C48	C41	59.0(6)
C44A	C45A	C46	C47	-33.3(9)					

Table 7. Anisotropic Displacement Parameters (U_{ij}, Å^2)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Sn	0.02253(9)	0.03143(10)	0.02629(9)	-0.00359(8)	0.00007(8)	-0.00028(8)
Cl1	0.0359(4)	0.0649(6)	0.0347(4)	-0.0101(4)	0.0072(3)	0.0084(4)
Cl2	0.0278(3)	0.0391(4)	0.0389(4)	-0.0007(4)	-0.0074(3)	-0.0005(3)
Cl3	0.0293(4)	0.0305(3)	0.0452(4)	0.0006(3)	-0.0038(3)	-0.0002(3)
Cl4	0.0402(5)	0.0378(4)	0.0513(5)	0.0089(4)	-0.0013(4)	-0.0052(3)
O1	0.0202(10)	0.0384(12)	0.0295(11)	-0.0081(9)	-0.0005(8)	0.0003(9)
O2	0.0219(9)	0.0371(12)	0.0291(10)	-0.0092(9)	-0.0004(9)	0.0038(8)
C1	0.0205(13)	0.0280(13)	0.0283(14)	-0.0023(11)	0.0016(12)	-0.0009(12)
C2	0.0230(13)	0.0265(14)	0.0263(14)	-0.0028(11)	0.0000(11)	-0.0012(11)
C11	0.0229(13)	0.0329(16)	0.0281(15)	-0.0018(12)	0.0014(11)	0.0000(12)
C12	0.0288(15)	0.0322(16)	0.0317(16)	-0.0014(13)	0.0051(12)	-0.0006(12)
C13	0.046(2)	0.0443(19)	0.0390(18)	-0.0062(15)	0.0157(16)	0.0019(16)
C14	0.050(2)	0.060(2)	0.0383(19)	0.0002(17)	0.0207(16)	-0.0077(18)
C15	0.044(2)	0.045(2)	0.0434(18)	0.0094(16)	0.0051(15)	-0.0117(17)
C16	0.0343(15)	0.0330(18)	0.0367(16)	-0.0007(13)	-0.0001(13)	-0.0062(13)
C21	0.0228(14)	0.0330(16)	0.0305(16)	-0.0085(12)	0.0022(12)	-0.0006(12)

C22	0.0314(16)	0.0417(17)	0.0322(15)	-0.0098(13)	-0.0019(14)	0.0037(15)
C23	0.0326(18)	0.060(2)	0.045(2)	-0.0168(18)	-0.0063(15)	-0.0031(17)
C24	0.0326(19)	0.063(3)	0.063(2)	-0.026(2)	-0.0001(17)	-0.0126(17)
C25	0.0373(17)	0.042(2)	0.055(2)	-0.0109(18)	0.0129(16)	-0.0102(16)
C26	0.0290(16)	0.0335(17)	0.0393(18)	-0.0047(14)	0.0038(13)	-0.0034(12)
C31	0.0351(17)	0.0266(14)	0.0323(15)	-0.0037(12)	0.0053(13)	-0.0002(13)
C32	0.042(2)	0.062(3)	0.099(4)	0.027(3)	0.005(2)	0.010(2)
C33A	0.048(5)	0.056(7)	0.097(10)	0.015(7)	-0.013(6)	0.010(6)
C33B	0.049(5)	0.067(8)	0.084(9)	0.029(6)	-0.008(6)	0.011(6)
C34	0.082(4)	0.093(4)	0.102(4)	0.061(3)	-0.015(3)	-0.007(3)
C35	0.063(3)	0.053(2)	0.054(2)	0.011(2)	0.0016(19)	-0.011(2)
C36	0.080(3)	0.064(3)	0.083(4)	0.017(3)	-0.003(3)	-0.027(3)
C37A	0.064(7)	0.054(8)	0.022(4)	0.011(4)	-0.014(4)	-0.022(5)
C37B	0.093(11)	0.048(8)	0.057(6)	0.022(6)	-0.026(7)	-0.024(6)
C38	0.118(5)	0.062(3)	0.043(2)	0.006(2)	-0.008(3)	-0.040(3)
C41	0.0447(18)	0.0466(19)	0.0286(15)	-0.0032(16)	-0.0054(13)	0.0069(18)
C42	0.058(3)	0.068(3)	0.039(2)	0.0002(19)	-0.0020(18)	0.024(2)
C43	0.120(5)	0.078(4)	0.065(3)	0.013(3)	-0.002(3)	0.043(4)
C44A	0.089(5)	0.065(4)	0.070(4)	0.004(3)	0.003(3)	0.013(4)
C45A	0.087(5)	0.070(4)	0.094(5)	0.000(4)	-0.025(4)	-0.017(4)
C46	0.067(3)	0.099(5)	0.095(4)	0.034(4)	0.024(3)	0.002(3)
C47	0.085(3)	0.082(4)	0.041(2)	0.001(2)	0.014(2)	0.012(3)
C48	0.054(2)	0.060(2)	0.039(2)	0.0012(18)	0.0067(17)	0.014(2)

O1S	0.0291(12)	0.0587(17)	0.0540(16)	-0.0147(13)	-0.0018(12)
	0.0056(11)				

The form of the anisotropic displacement parameter is:

$\exp[-2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + l^2c^{*2}U_{33} + 2klb^*c^*U_{23} + 2hla^*c^*U_{13} + 2hka^*b^*U_{12})]$

Table 8. Derived Atomic Coordinates and Displacement Parameters for Hydrogen Atoms

Atom	*x*	*y*	*z*	U_{eq}, Å^2
H1O	0.3312	0.0714	0.4637	0.044
H2O	-0.0708	0.1570	0.4799	0.044
H1	0.1425	-0.0462	0.4451	0.031
H2	0.0363	0.1620	0.4171	0.030
H13	0.3209	-0.1373	0.3136	0.052
H14	0.4121	0.0239	0.2875	0.059
H15	0.3885	0.1858	0.3256	0.053
H16	0.2691	0.1854	0.3897	0.042
H23	-0.3079	-0.0053	0.3404	0.055
H24	-0.3791	-0.1465	0.3820	0.063
H25	-0.2689	-0.1841	0.4466	0.054
H26	-0.0886	-0.0758	0.4677	0.041
H31	0.1197	-0.1666	0.4072	0.038
H32A[a]	0.3358	-0.2042	0.4268	0.081
H32B[a]	0.3697	-0.2530	0.3809	0.081
H32C[a]	0.3349	-0.2939	0.3797	0.081
H32D[a]	0.3700	-0.1951	0.4105	0.081
H33A[a]	0.2670	-0.4096	0.3944	0.080
H33B[a]	0.3569	-0.3834	0.4349	0.080
H33C[a]	0.2873	-0.2713	0.4653	0.080
H33D[a]	0.3602	-0.3670	0.4405	0.080
H34A[a]	0.1842	-0.3628	0.4766	0.111
H34B[a]	0.1631	-0.4719	0.4502	0.111
H34C[a]	0.1659	-0.4124	0.4784	0.111
H34D[a]	0.1790	-0.4588	0.4312	0.111
H35A	-0.0406	-0.3966	0.4588	0.068
H35B	0.0102	-0.2794	0.4437	0.068

H36A[a]	-0.1241	-0.3963	0.3963	0.091
H36B[a]	0.0156	-0.4525	0.3863	0.091
H36C[a]	-0.0292	-0.4628	0.3918	0.091
H36D[a]	-0.1206	-0.3570	0.3927	0.091
H37A[a]	-0.0190	-0.3514	0.3304	0.056
H37B[a]	-0.0830	-0.2545	0.3569	0.056
H37C[a]	-0.0321	-0.3514	0.3371	0.079
H37D[a]	0.1033	-0.4024	0.3536	0.079
H38A[a]	0.0819	-0.1883	0.3274	0.089
H38B[a]	0.1732	-0.2923	0.3350	0.089
H38C[a]	0.0415	-0.1921	0.3367	0.089
H38D[a]	0.1727	-0.2606	0.3261	0.089
H41	-0.0542	0.1916	0.3627	0.048

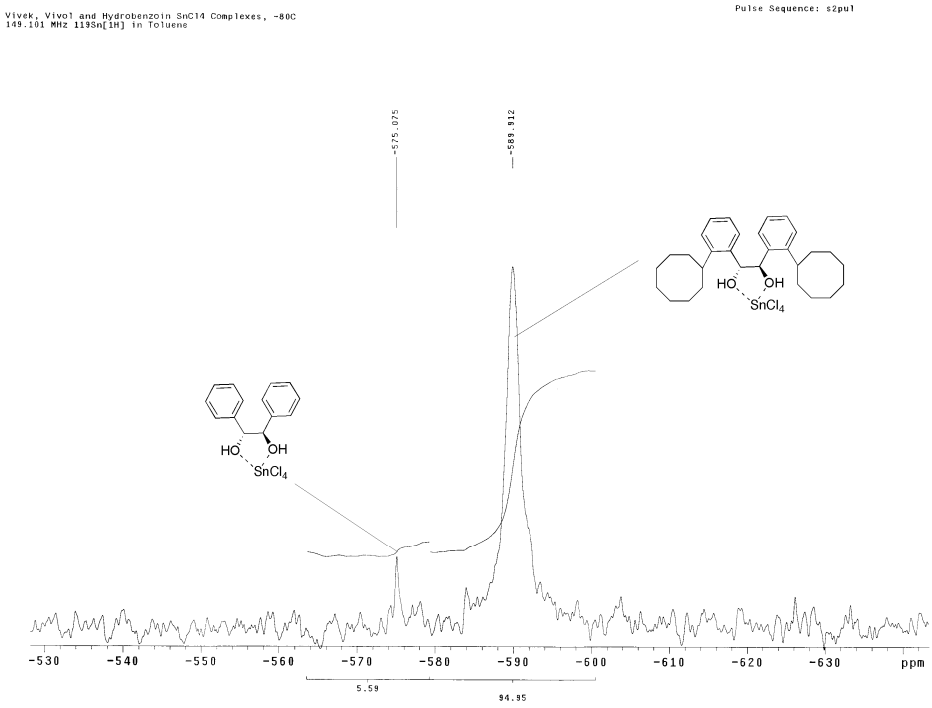
Table 8. Derived Parameters for Hydrogen Atoms (continued)

Atom	*x*	*y*	*z*	U_{eq}, Å^2
H42A	-0.2762	0.1760	0.3062	0.066
H42B	-0.3143	0.1939	0.3552	0.066
H43A[b]	-0.3229	0.3560	0.3235	0.105
H43B[b]	-0.1987	0.3573	0.3554	0.105
H43C[c]	-0.2662	0.3613	0.3542	0.105
H43D[c]	-0.2937	0.3477	0.3045	0.105
H44A[b]	-0.1649	0.4567	0.2935	0.090
H44B[b]	-0.1740	0.3472	0.2661	0.090
H45A[b]	0.0500	0.4277	0.2898	0.100
H45B[b]	0.0229	0.3521	0.3304	0.100
H44C[c]	-0.0313	0.3670	0.3404	0.108
H44D[c]	-0.1126	0.4660	0.3196	0.108
H45C[c]	0.0017	0.4229	0.2612	0.108
H45D[c]	-0.1143	0.3341	0.2549	0.108
H46A[b]	0.1486	0.2458	0.2916	0.105
H46B[b]	0.0925	0.2918	0.2476	0.105
H46C[c]	0.1333	0.2739	0.2534	0.105
H46D[c]	0.1112	0.2657	0.3043	0.105
H47A	0.0327	0.1160	0.2483	0.083
H47B	-0.1030	0.1809	0.2573	0.083
H48A	0.0474	0.0644	0.3201	0.061
H48B	-0.0914	0.0249	0.3001	0.061
H1SA	0.544	0.063	0.4701	0.071
H1SB	0.512	0.026	0.4329	0.071
H10A[a]	0.5839	-0.0507	0.1466	0.087
H10B[a]	0.5872	-0.0957	0.1947	0.087
H10C[a]	0.7061	-0.0196	0.1775	0.087
H12S[a]	0.3785	0.0498	0.1491	0.087

H13S[a]	0.2644	0.2069	0.1708	0.087
H14S[a]	0.3525	0.3154	0.2256	0.087
H15S[a]	0.5546	0.2667	0.2586	0.087
H16S[a]	0.6686	0.1096	0.2369	0.087
H20A[a]	0.6970	-0.0912	0.2018	0.087
H20B[a]	0.7267	-0.0434	0.1552	0.087
H20C[a]	0.6005	-0.1217	0.1627	0.087
H22S[a]	0.4390	0.0112	0.1359	0.087
H23S[a]	0.3053	0.1631	0.1511	0.087
H24S[a]	0.3572	0.2747	0.2094	0.087
H25S[a]	0.5426	0.2345	0.2526	0.087
H26S[a]	0.6763	0.0827	0.2374	0.087

[a]Included with an occupancy factor of 0.5. [b]Included with an occupancy factor of 0.8. [c]Included with an occupancy factor of 0.2.

^{119}Sn NMR spectrum of diol exchange studies

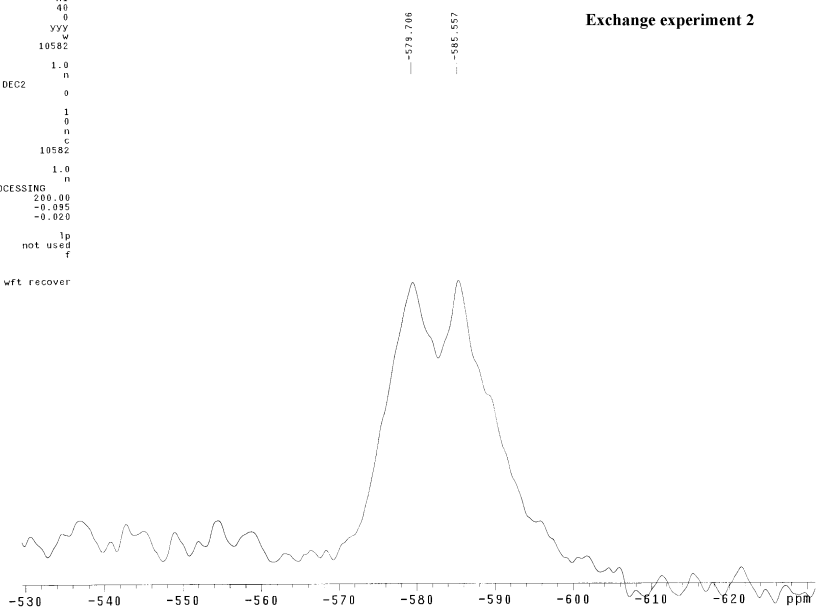


VRH-7-22_hydrobenzoin_SnCl4_VIVOL_-80C
149.101 MHz 119Sn{1H} in Toluene

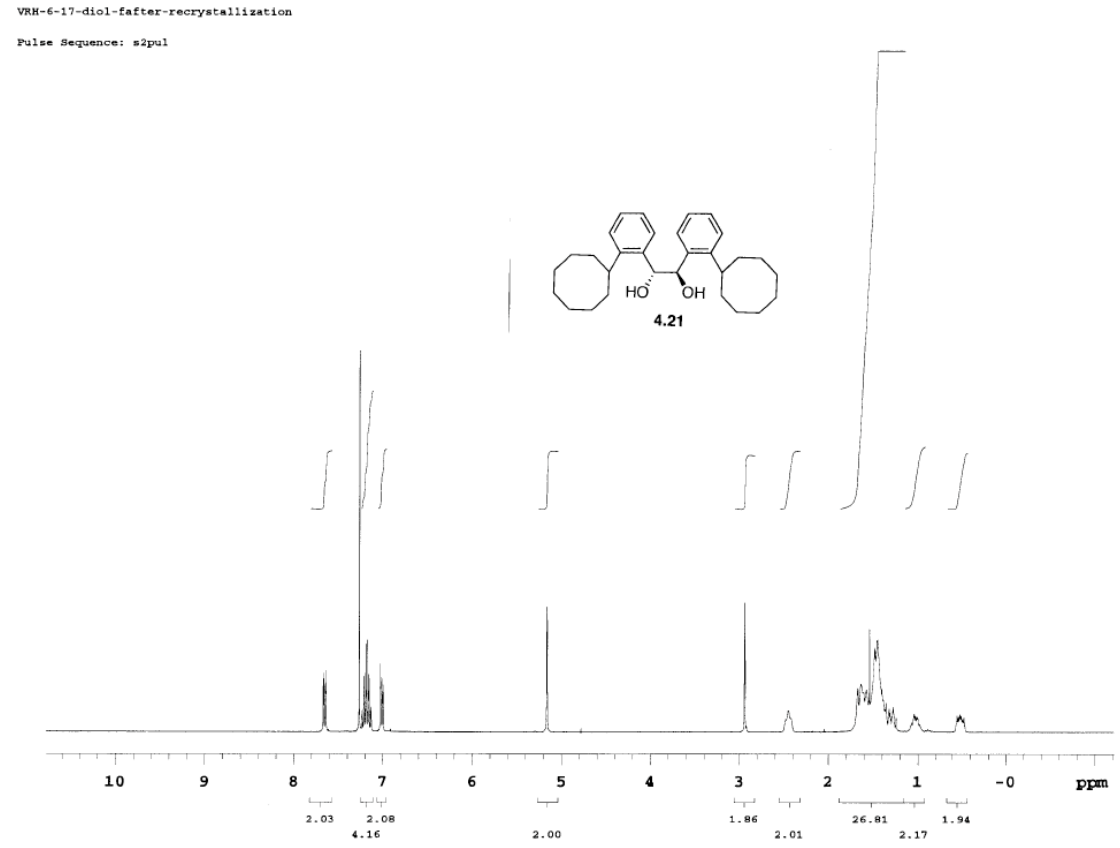
exp13 s2pul

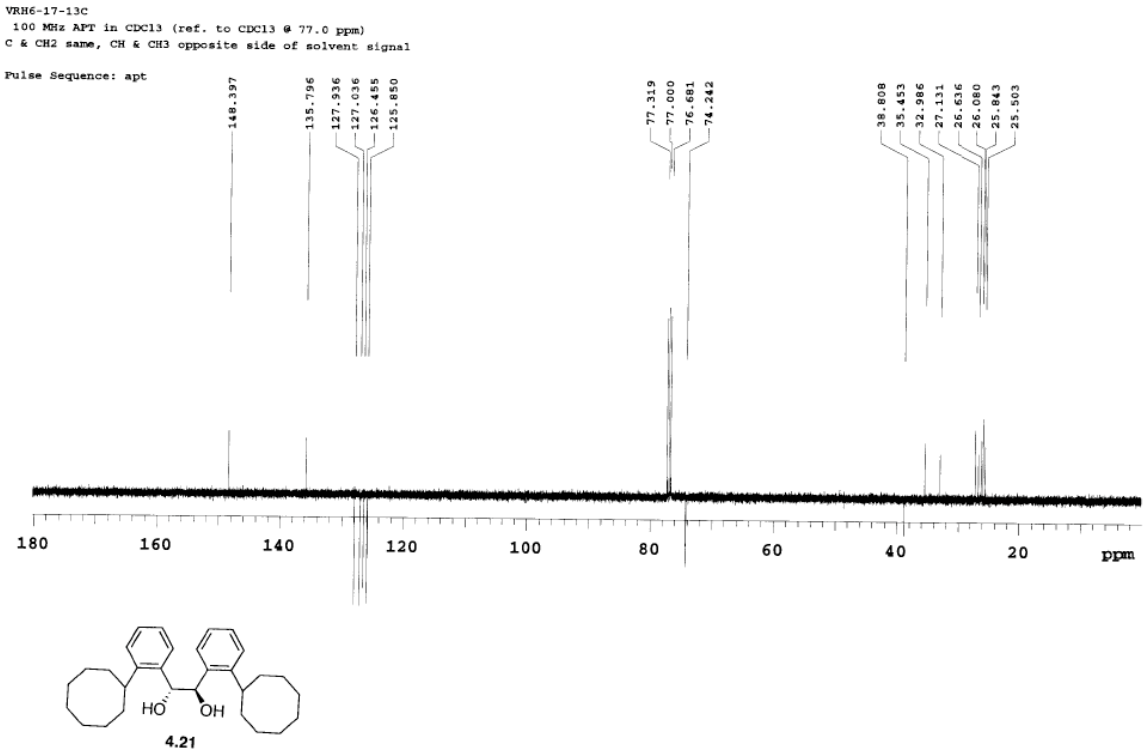
SAMPLE		DEC. & VT	
date	Feb 6 2008	dfrq	399.953
solvent	Toluene	dn	H1
file	/mnt/d600/hom~	dpwr	40
e12/gennmr/nmrdata~		dof	0
/HALL/VIVEK/2008.0~		dm	yyy
2/2008.02.06.s4_VR~		dmm	w
H-7-22_hydrobenzoi~		dmf	10582
n_SnCl4_VIVOL_-80C~		dseq	
_Sn119_1D.fid		dres	1.0
ACQUISITION		homo	n
sfrq	149.099	DEC2	
tn	Sn119	dfrq2	0
at	1.758	dn2	
np	420868	dpwr2	1
sw	119581.5	dof2	0
fb	not used	dm2	n
bs	4	dmm2	c
tpwr	55	dmf2	10582
pw	3.0	dseq2	
d1	0	dres2	1.0
tof	-45489.1	homo2	n
nt	1e+06	PROCESSING	
ct	3812	lb	200.00
alock	n	sb	-0.095
gain	20	sbs	-0.020
FLAGS		wtfile	
il	n	proc	lp
in	n	fn	not used
dp	y	math	f
hs	nn	werr	
DISPLAY		wexp	wft recover
sp	-94122.9	wbs	
wp	15139.3	wnt	
vs	98		
sc	0		
wc	200		
hzmm	75.70		
is	500.00		
rfl	104534.0		
rfp	0		
th	12		
ins	100.000		
nm no ph			

Exchange experiment 2



^{1}H and ^{13}C NMR spectra of important compounds and intermediates





Vivek, VRH-7-41C
499.823 MHz 1H in CDCl3

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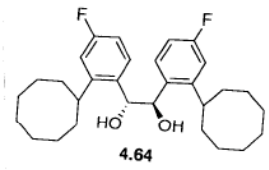
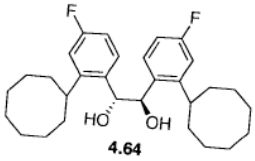


4.64

Vivek, VRH-7-41C
125 MHz APT in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 26.1 C -> actual temp = 27.0 C, autoxdb probe
C & CH2 same, CH & CH3 opposite side of solvent signal

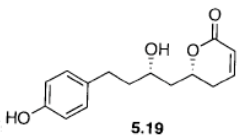
Pulse Sequence: apt



4.64

499.821 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.1 C -> actual temp = 27.0 C, autoxdb probe

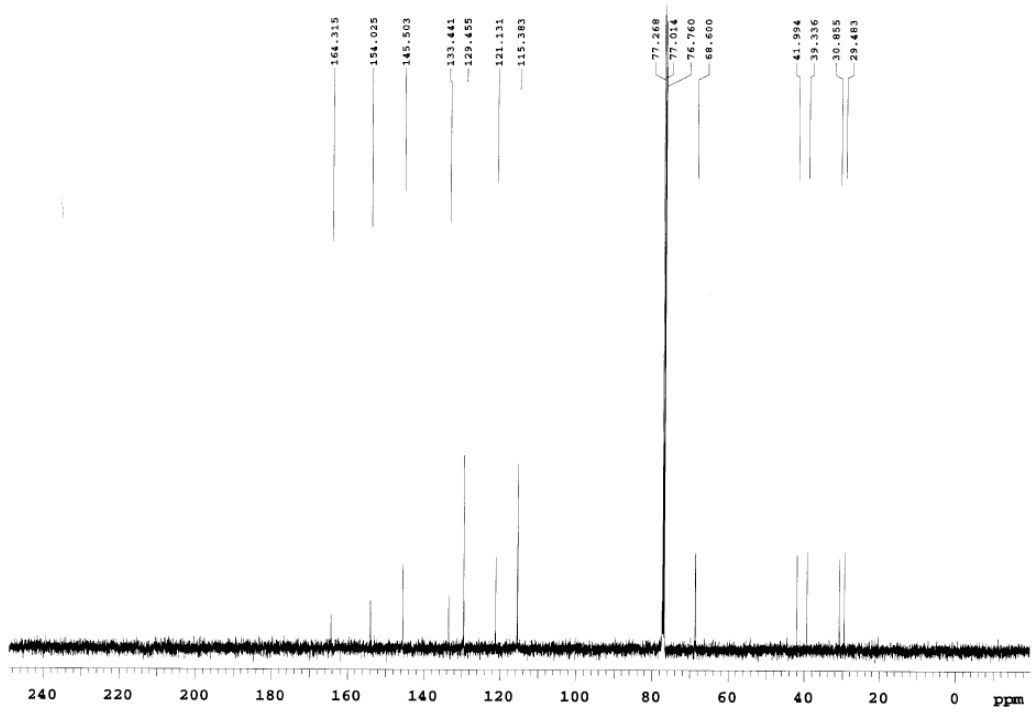
Pulse Sequence: s2pul



5.19

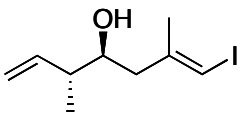
VRH-7-150-13C

Pulse Sequence: s2pul



299.971 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.5 C -> actual temp = 27.0 C, id300 probe
VRH-8-131B

Pulse Sequence: s2pul



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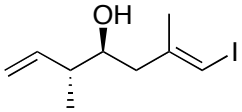
VRH-8-131B

Pulse Sequence: s2pul



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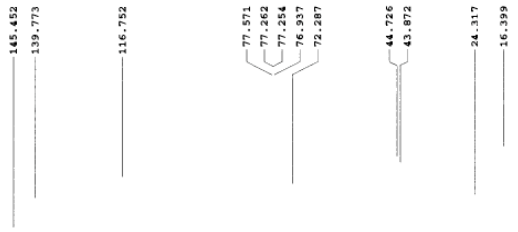
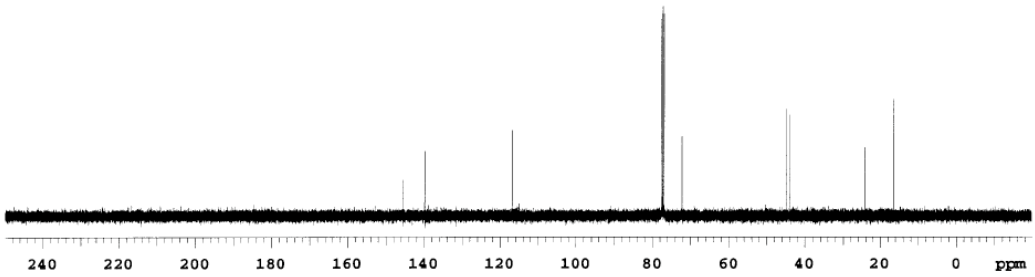
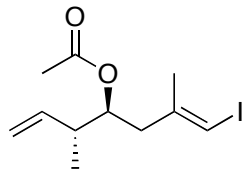




299.971 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.5 C -> actual temp = 27.0 C, id300 probe
VRH-8-132B

Pulse Sequence: s2pul



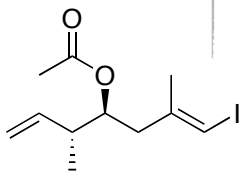
5.43

VRH-8-132B

100.579 MHz C13{H1} 1D in cdcl3

File: LKH-B024-13C-acetate

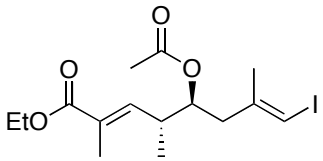
Pulse Sequence: s2pul



5.43

VRH-8-89A
499.821 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.1 C -> actual temp = 27.0 C, autoxdb probe

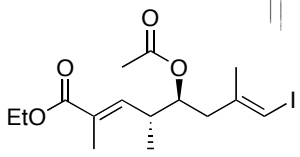
Pulse Sequence: s2pul



5.56

VRH-8-89A
125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.1 C -> actual temp = 27.0 C, autoxdb probe

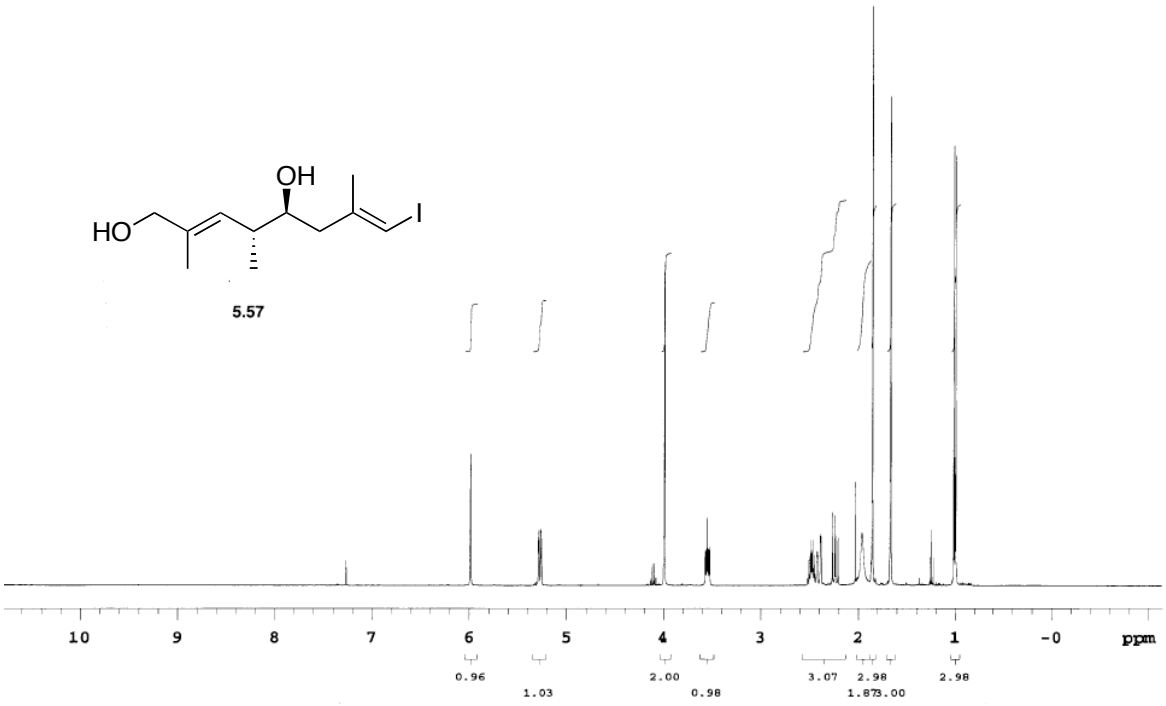
Pulse Sequence: s2pul



5.56

VRH-8-89B-diol

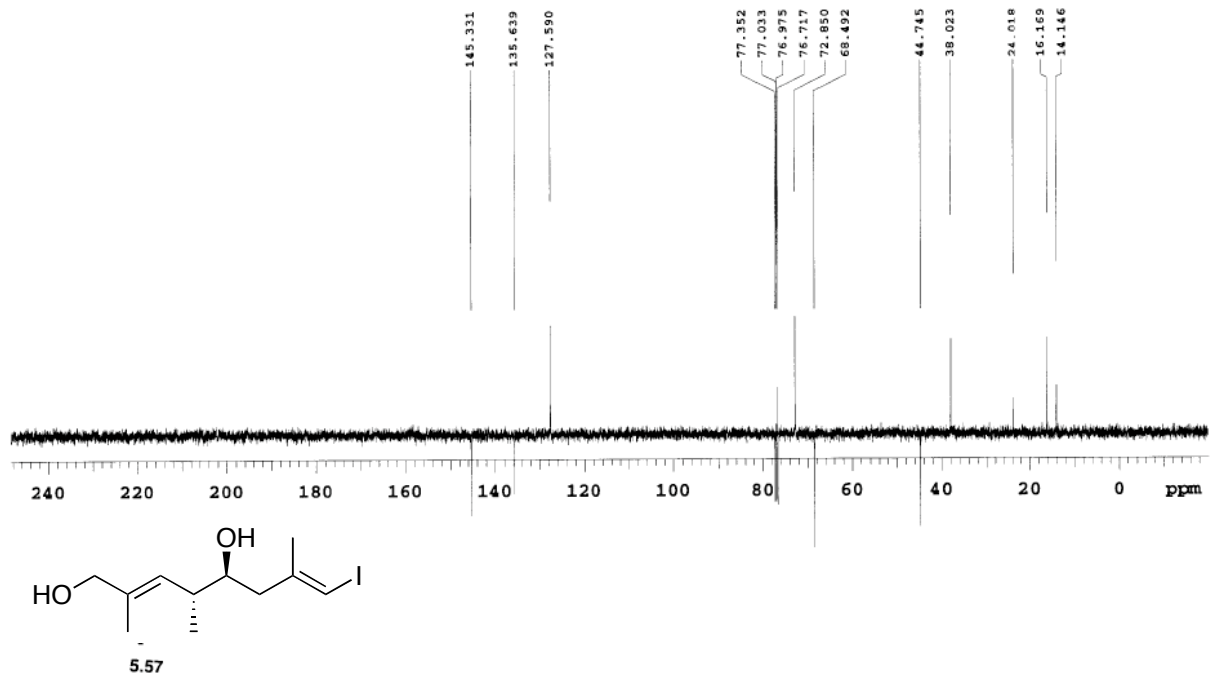
Pulse Sequence: s2pul



5.57

VRH-8-89B

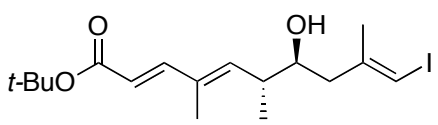
Pulse Sequence: apt



5.57

VRH-8-72

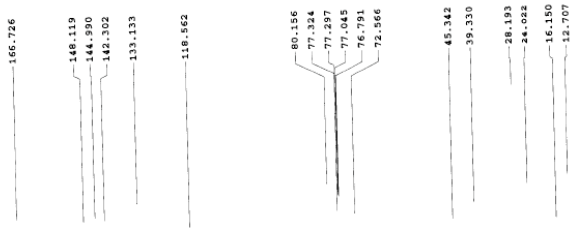
Pulse Sequence: s2pul

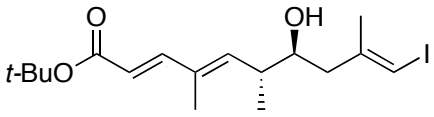


5.44

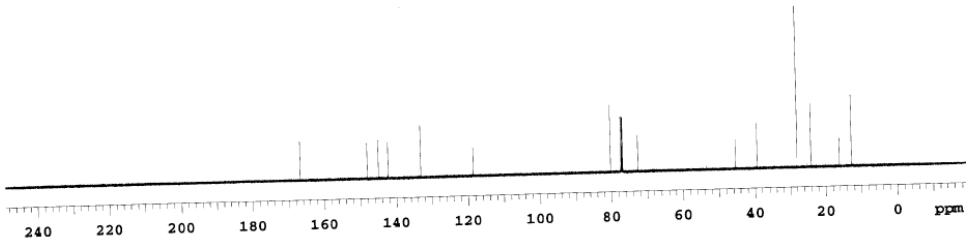
VRH-8-72-13C-tert-butyl-ester

Pulse Sequence: s2pul



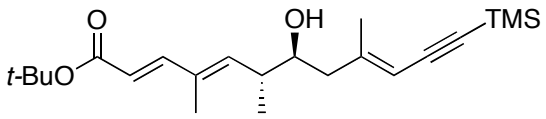


5.44



VRH-8-106-TMS-acetylene

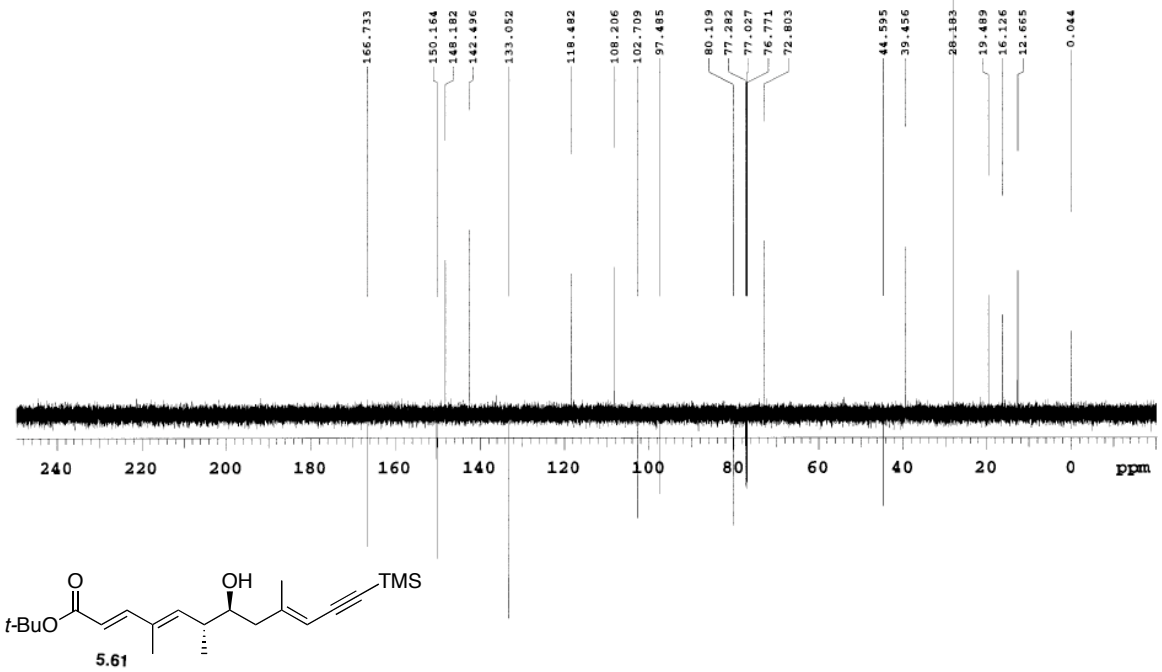
Pulse Sequence: s2pul



5.61

VRH-8-106-13C

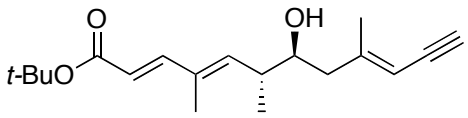
Pulse Sequence: apt



5.61

VRH-8-107-ene-yne

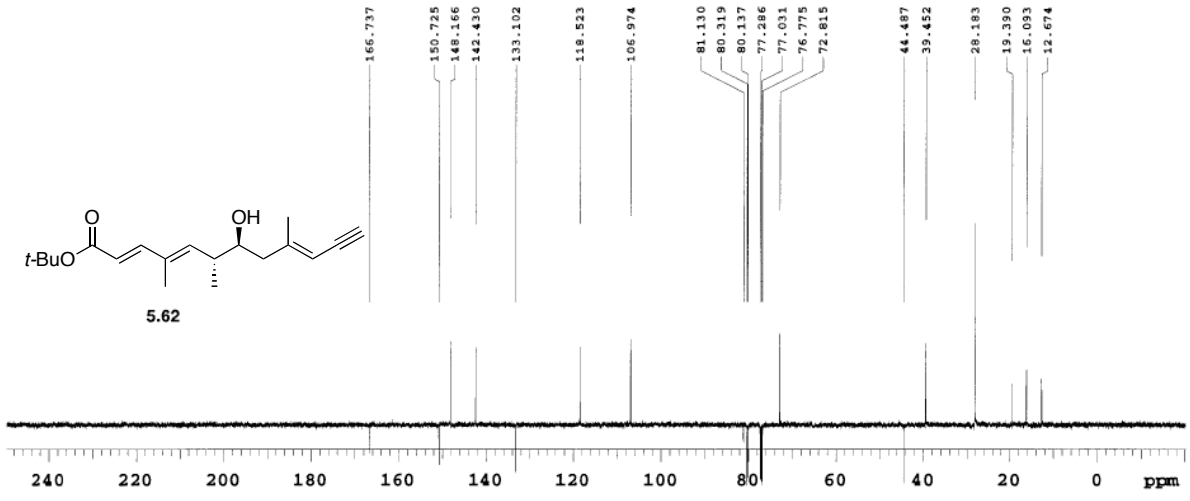
Pulse Sequence: s2pul



5.62

VRH-8-107

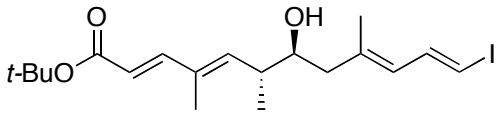
Pulse Sequence: apt



5.62

VRH-8-108-western-hemisphere

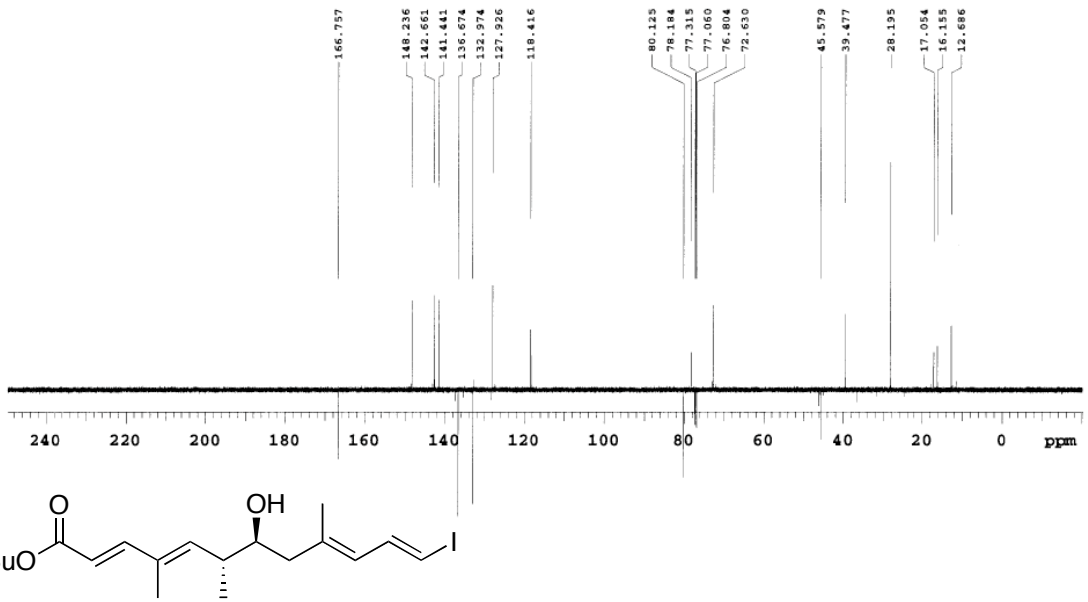
Pulse Sequence: s2pul



5.41

VRH-8-108-western-hemisphere

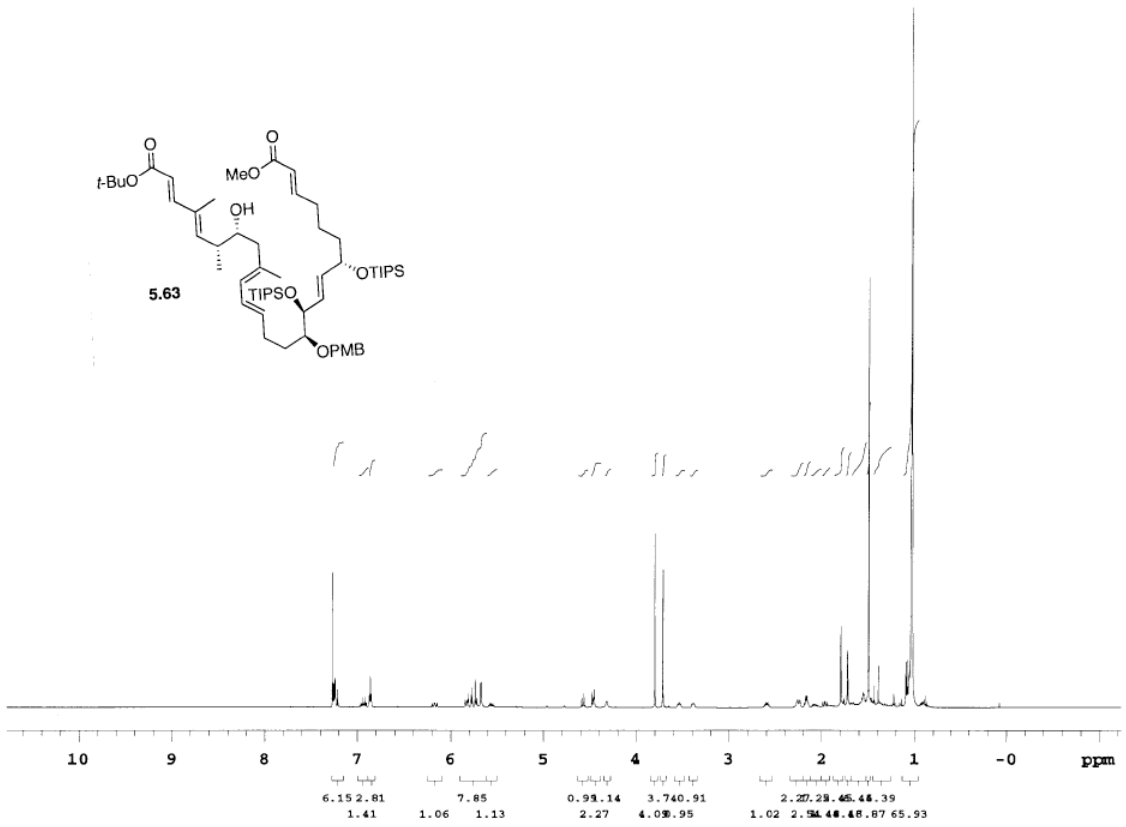
Pulse Sequence: apt

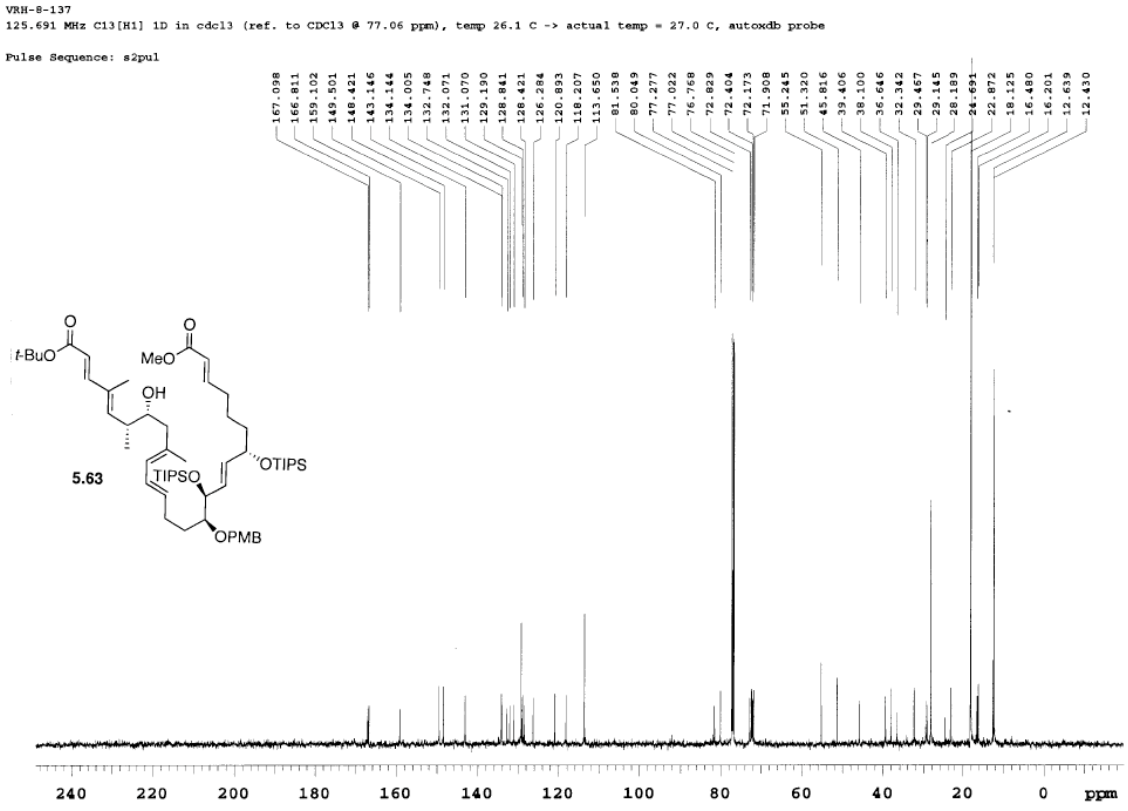


5.41

VRH-8-111-B

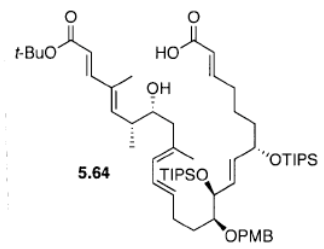
Pulse Sequence: s2pul




VRH-8-137
125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.1 C -> actual temp = 27.0 C, autoxdb probe
Pulse Sequence: s2pul
167.098
166.811
159.102
149.501
140.421
143.146
134.144
134.005
132.748
132.071
131.070
129.190
128.841
128.421
126.284
120.893
118.207
113.650
81.538
80.049
77.277
77.022
76.768
72.829
72.404
72.173
71.908
55.245
51.320
45.816
39.406
38.100
36.646
32.342
29.467
29.145
28.189
24.691
22.872
18.125
16.480
16.201
12.639
12.430
t-BuO
MeO
OH
TIPSO
OTIPS
OPMB
5.63
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

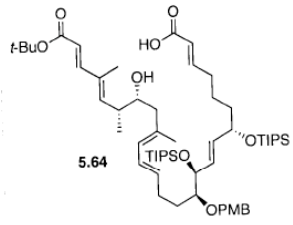
VRH-8-138

Pulse Sequence: s2pul



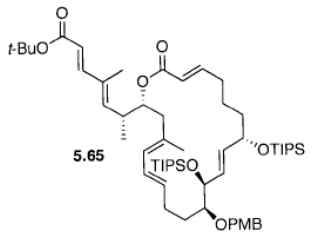
seco-acid

Pulse Sequence: s2pul



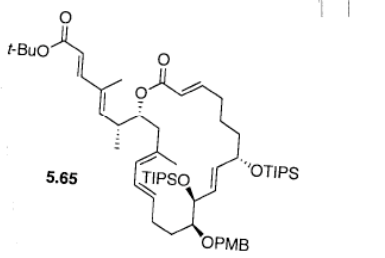
VRH-8-138B

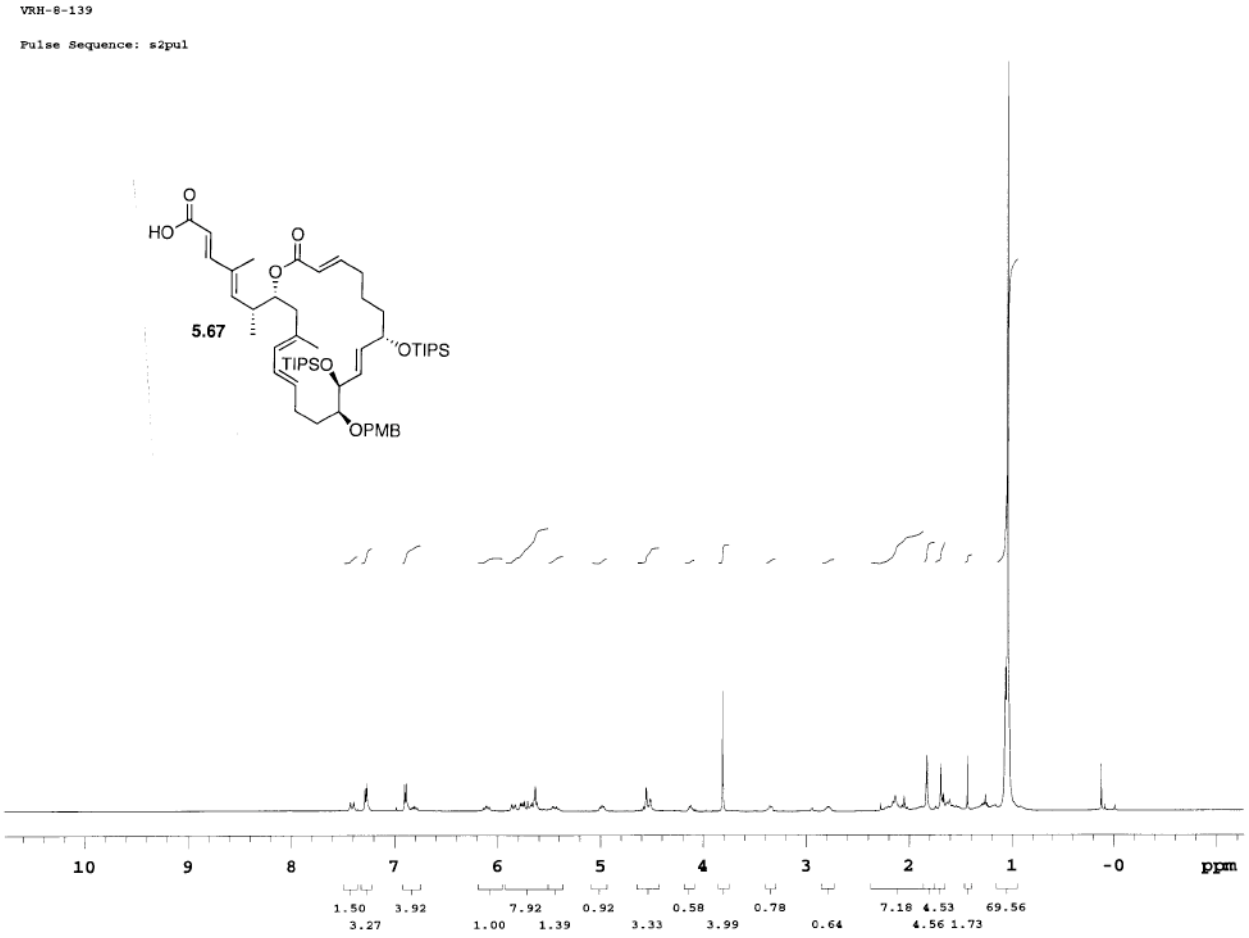
Pulse Sequence: s2pul

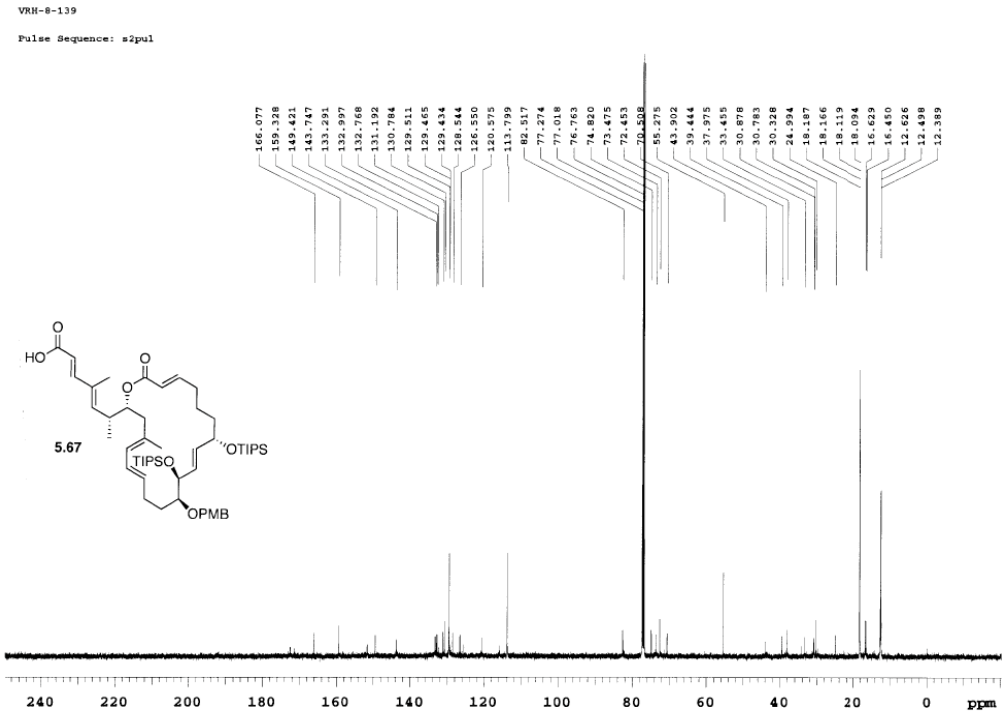


VRH-8-138-macrolactone

Pulse Sequence: s2pul

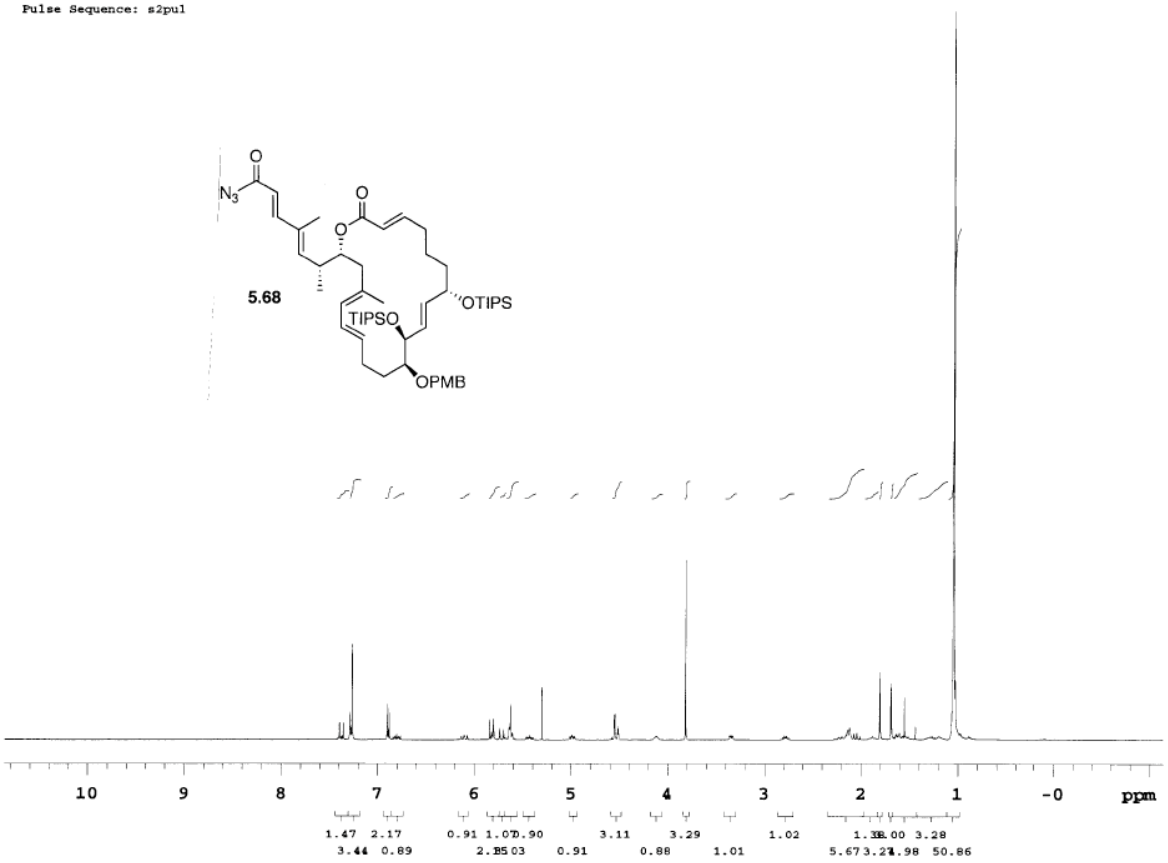



VRH-8-139
Pulse Sequence: s2pul
HO
O
O
O
5.67
TIPSO
OTIPS
OPMB
10
9
8
7
6
5
4
3
2
1
-0
ppm
1.50
3.92
7.92
0.92
0.58
0.78
7.18
4.53
69.56
3.27
1.00
1.39
3.33
3.99
0.64
4.56
1.73


VRH-8-139
Pulse Sequence: s2pul
166.077
159.328
149.421
143.747
133.291
132.997
132.768
131.192
130.784
129.511
129.465
129.434
128.544
126.550
120.575
113.799
82.517
77.274
77.018
76.763
74.820
73.475
72.453
70.508
55.275
43.902
39.444
37.975
33.455
30.878
30.783
30.328
24.994
18.187
18.166
18.119
18.094
16.629
16.450
12.626
12.498
12.389
HO
O
O
O
5.67
TIPSO
OTIPS
OPMB
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

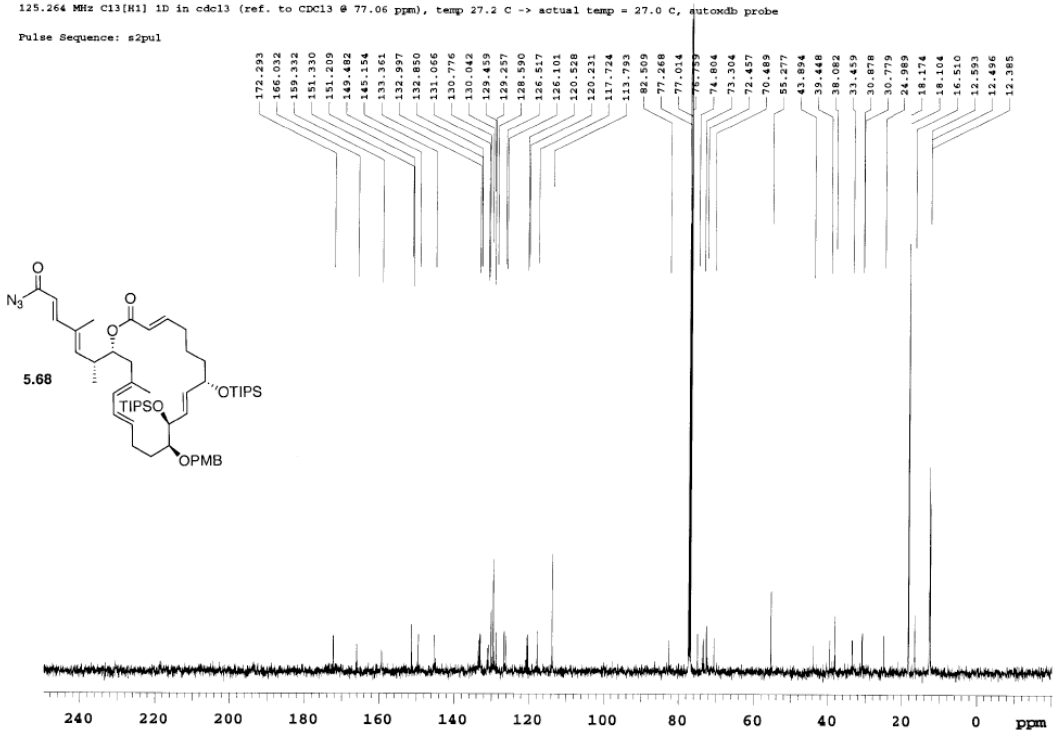
399.794 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.5 C -> actual temp = 27.0 C, autoxdb probe

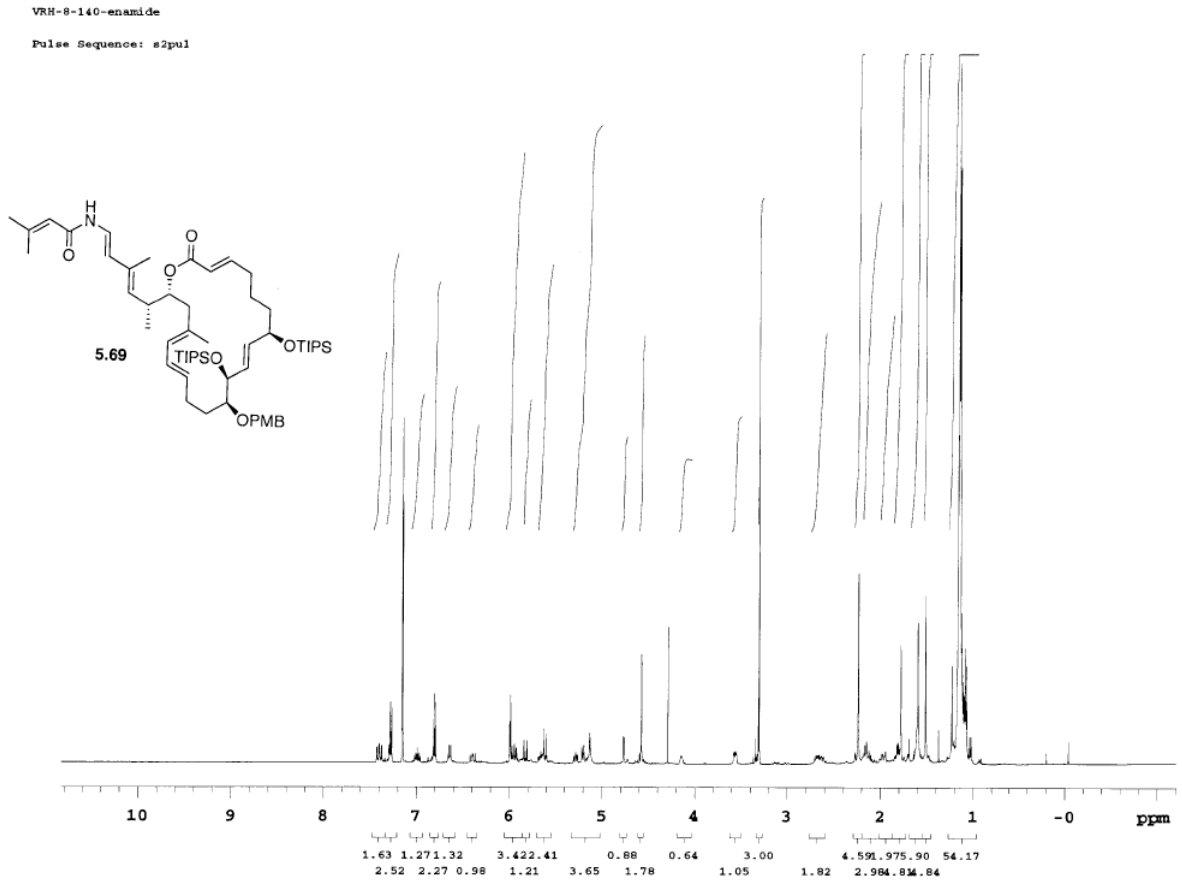
Pulse Sequence: s2pul

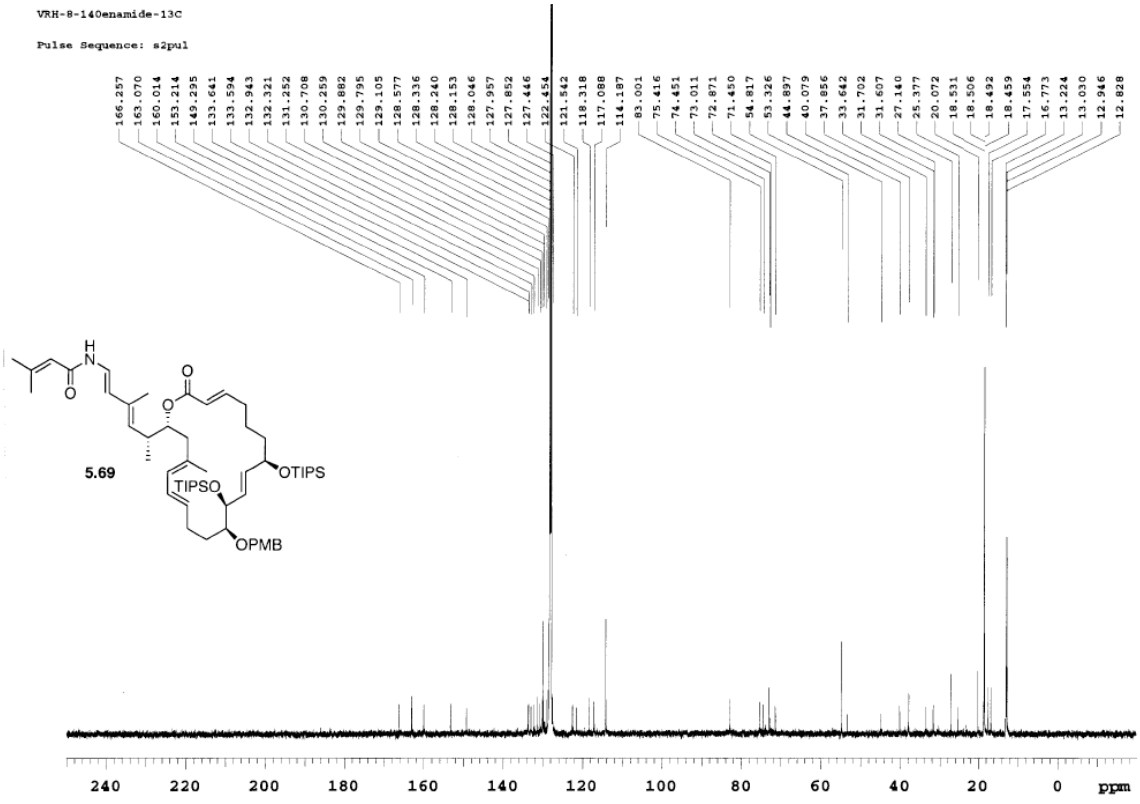


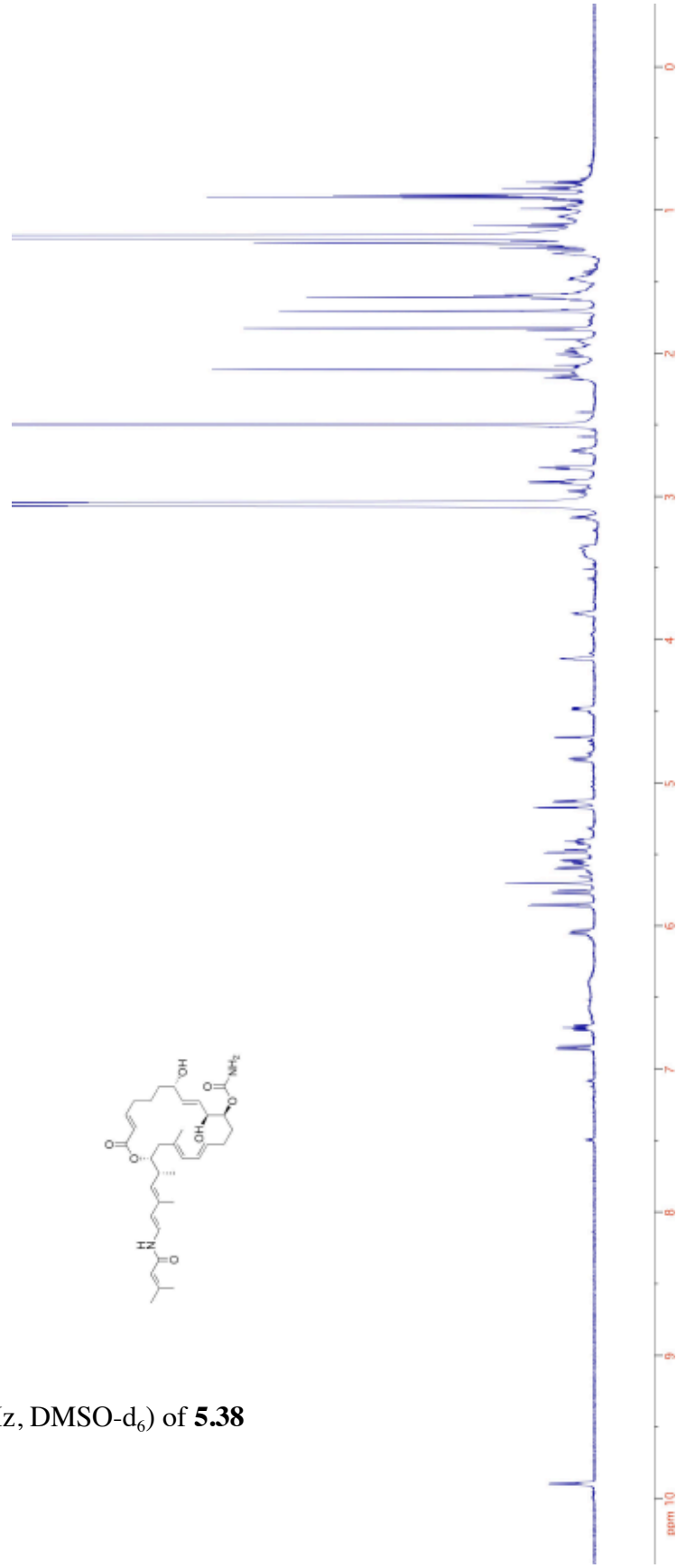
125.264 MHz C13{H1} 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.2 C -> actual temp = 27.0 C, autoxdb probe

Pulse Sequence: s2pul




VRH-8-140-enamide
Pulse Sequence: s2pul
5.69
OTIPS
TIPSO
OPMB
10 9 8 7 6 5 4 3 2 1 -0 ppm
1.63 1.27 1.32 3.42 2.41 0.88 0.64 3.00 4.59 1.97 5.90 54.17
2.52 2.27 0.98 1.21 3.65 1.78 1.05 1.82 2.98 4.81 4.84

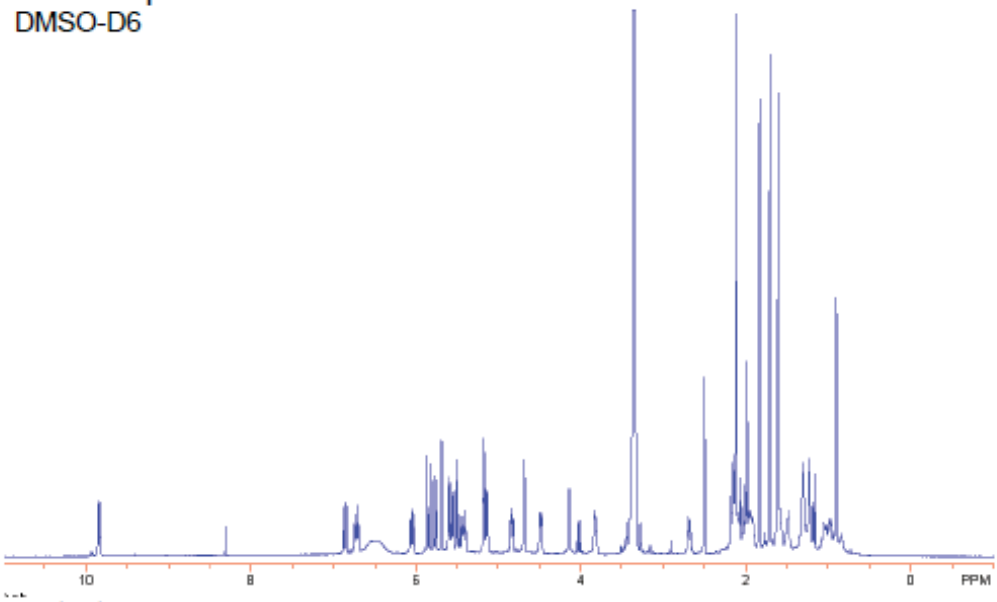

VRH-8-140enamide-13C
Pulse Sequence: s2pul
166.257
163.070
160.014
153.214
149.295
133.641
133.594
132.943
132.321
131.252
130.708
130.259
129.882
129.795
129.105
128.577
128.336
128.240
128.153
128.046
127.957
127.852
127.446
122.454
121.542
118.318
117.088
114.187
83.001
75.416
74.451
73.011
72.871
71.450
54.817
53.326
44.897
40.079
37.856
33.642
31.702
31.607
27.140
25.377
20.072
18.531
18.506
18.492
18.459
17.554
16.773
13.224
13.030
12.946
12.828
5.69
OTIPS
TIPSO
OPMB
240 220 200 180 160 140 120 100 80 60 40 20 0 ppm



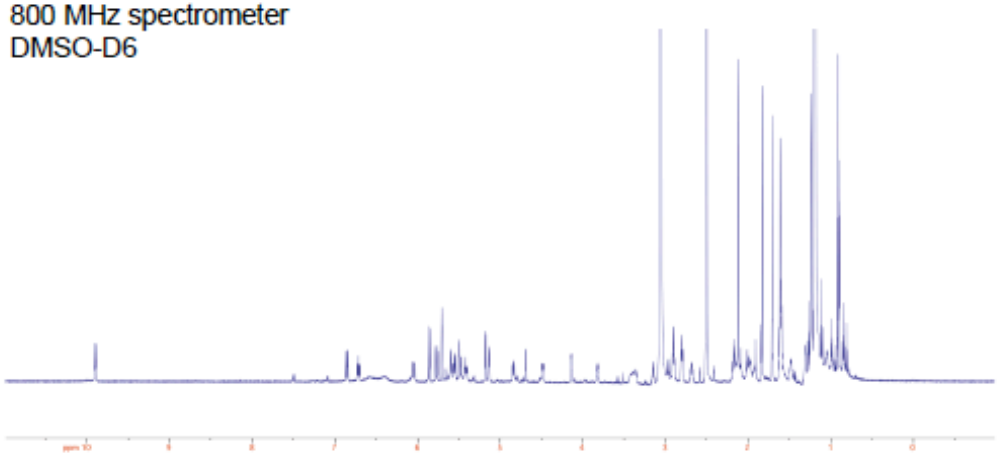
^{1}H NMR (800 MHz, DMSO-d_6) of **5.38**

(**Palmerolide A**)

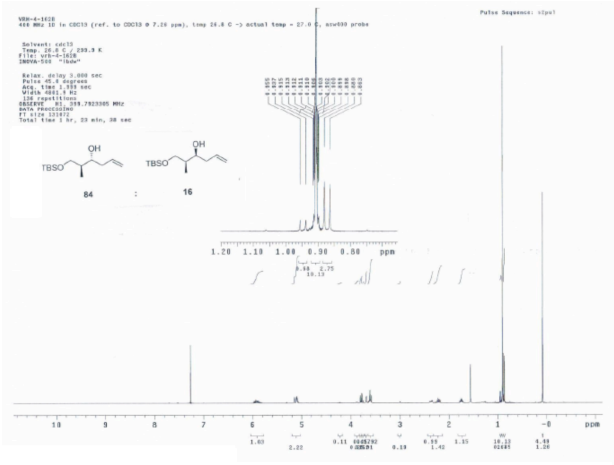
Natural Palmerolide A
500 MHz spectrometer
DMSO-D6



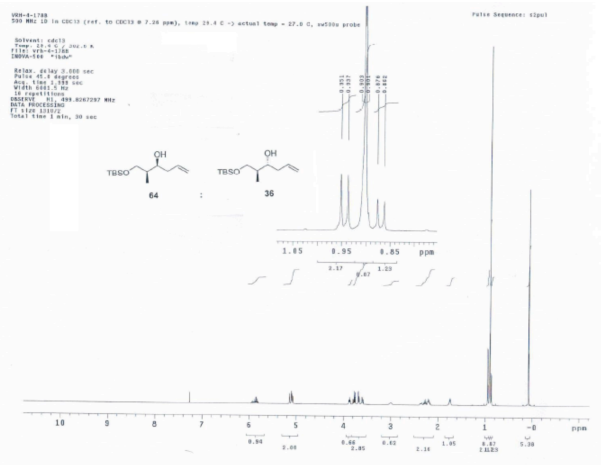
Synthetic Palmerolide A
800 MHz spectrometer
DMSO-D6



Catalyst controlled diastereoselective allylboration

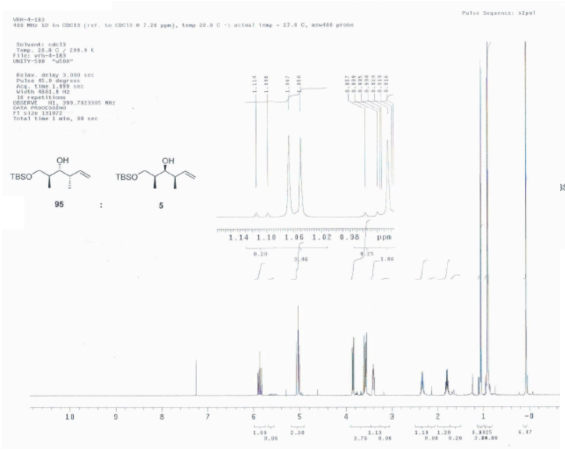


Matched allylboration

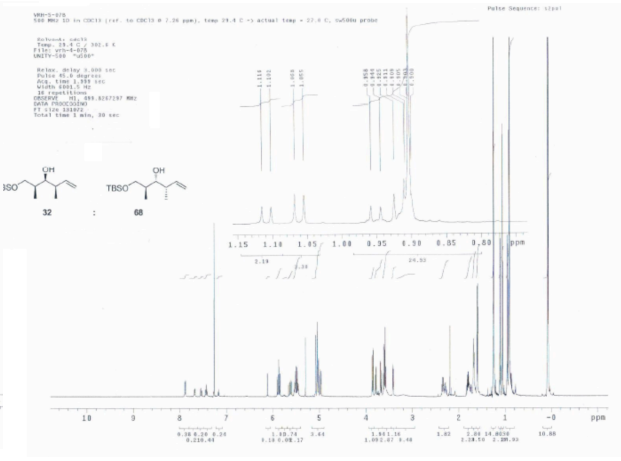


Mismatched allylboration

Diastereoselective *cis*-crotylboration

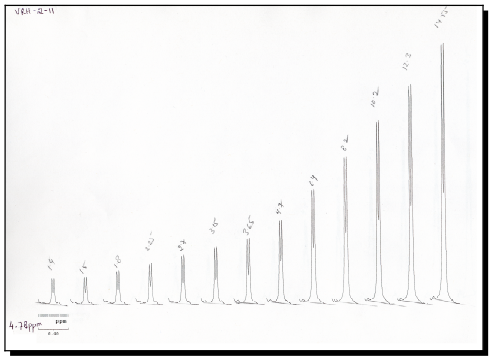


Matched case

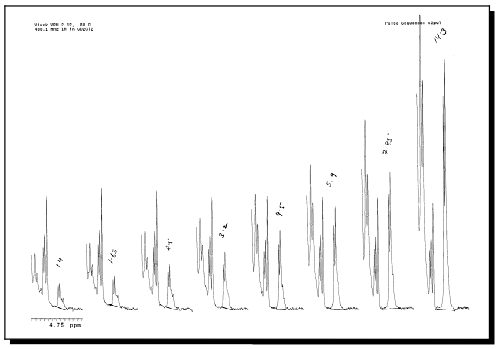


Mismatched case

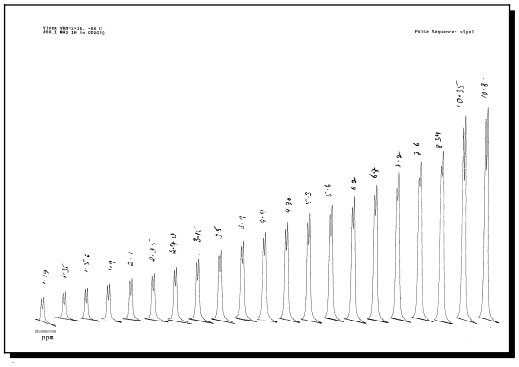
Sample NMR spectra of kinetic studies



^{1}H-NMR of reference reaction c.f., **section 2.10.6.1** [(delay between each spectrum) = 0, 60, 300, 300, 300, 300, 300, 900, 900, 900, 900, 900 s]. Actual time for spectrum at delay of 0 = 10 min from starting point of reaction.

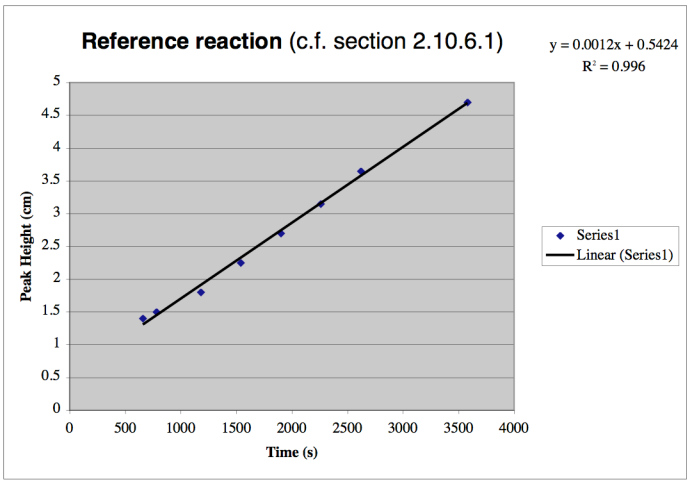


^{1}H-NMR of reaction c.f., **section 2.10.6.2** [(sequential delay between each spectrum) = 0, 300, 300, 300, 300, 300, 300, 900 s]. Actual time for spectrum at delay of 0 = 10 min from starting point of reaction.

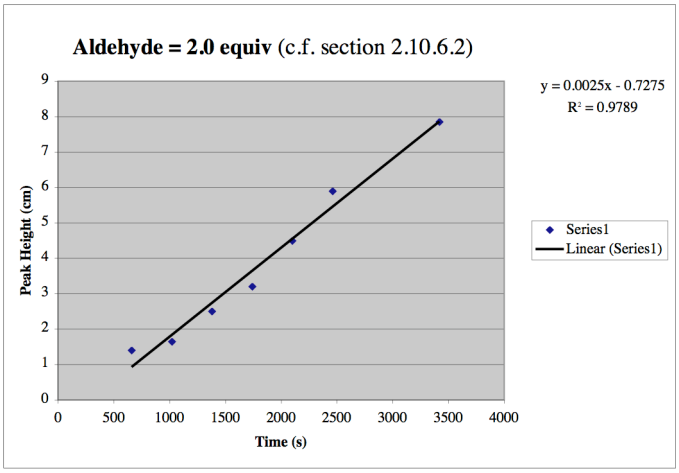


^{1}H-NMR of reaction c.f., section 2.10.6.3 [(sequential delay between each spectrum) = 0, 120, 120, 120, 120, 120, 120, 120, 120, 120, 120, 120, 120, 120, 120, 300, 300, 300, 300, 300, 300, 300, 300 s]. Actual time for spectrum at delay of 0 = 3 min from starting point of reaction.

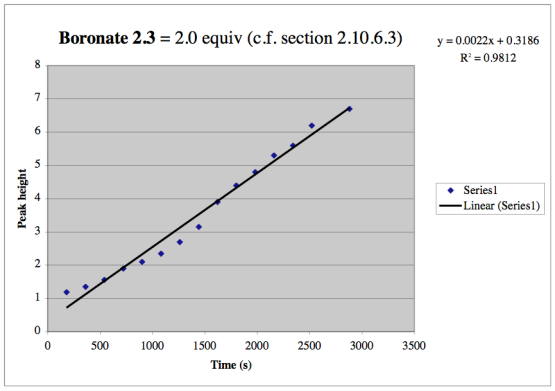
Sample graphs to determine the velocities of the reaction



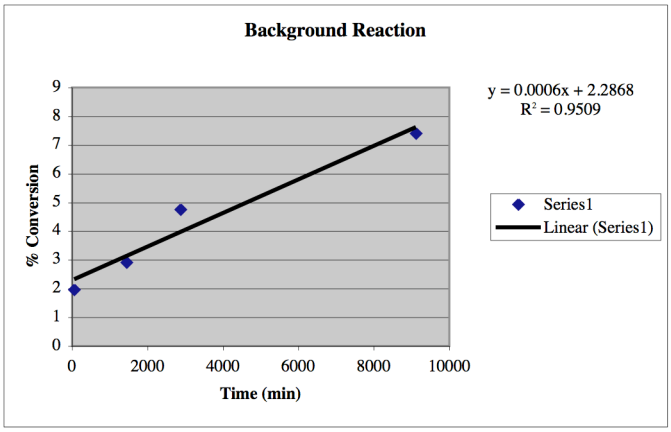
Graph for reference reaction, c.f., **Section 2.10.6.1**.



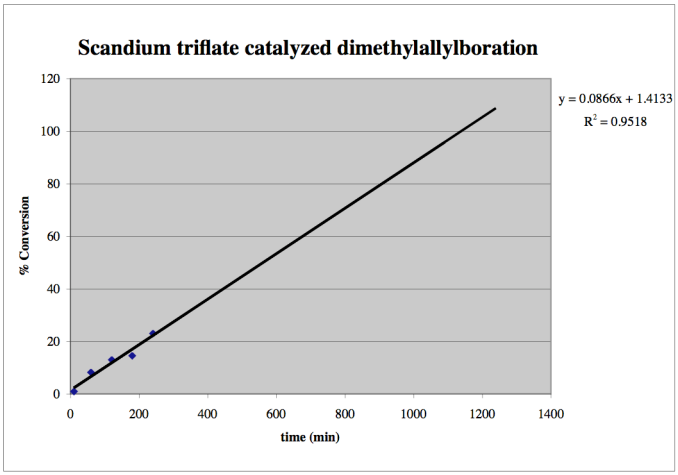
Graphical depiction of the rate of the reaction, c.f., **Section 2.10.6.2**.



Graphical depiction of the rate of the reaction, c.f., **Section 2.10.6.3**.



Graphical depiction of the uncatalyzed reaction of boronate **2.19** c.f., **Section 2.11.2**.



Graphical depiction of $Sc(OTf)_3$-catalyzed reaction of boronate **2.19** (with extrapolation), c.f.; **Section 2.11.3**.