STEREOSELECTIVE INCORPORATION OF BORON INTO MOLECULES VIA ADDITIONS OF ALPHA-BORYLATED ORGANOMETALLICS TO ELECTROPHILES

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ABSTRACT

MATTHEW VINCENT JOANNOU: Stereoselective Incorporation of Boron into Molecules via Additions of alpha-Borylated Organometallics to Electrophiles
(Under the direction of Simon J. Meek)

■ **Chapter 1: Enantio- and Diastereoselective Synthesis of β-Hydroxyboronates via Cu-catalyzed Addition of *gem*-Diboronate Esters to Aldehydes**. The development of an enantio- and diastereoselective addition of *gem*-diboronate esters to aryl and alkenyl aldehydes in the presence of stoichiometric LiO*t*-Am is presented. The reaction proceeds in up to 92% yield, >99:1 d.r., and 96:4 e.r. Mechanistic studies reveal the formation of a lithium *tert*-butylborate species that stereospecifically transmetallates to a copper catalyst, which then diastereoselectively adds to the aldehyde.
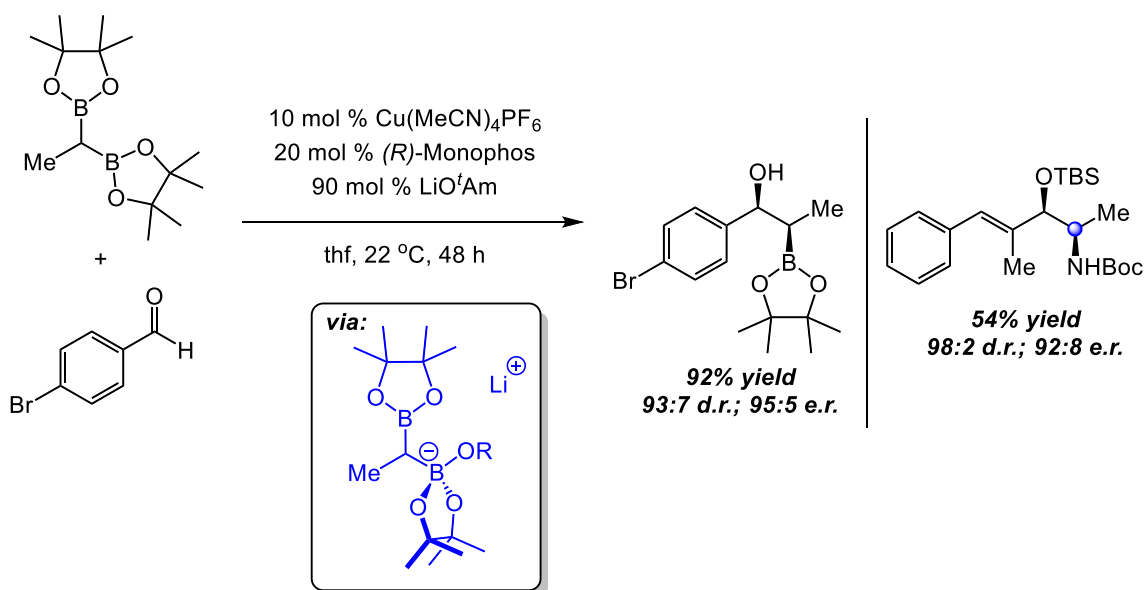

■ **Chapter 2: Ag(I)-Catalyzed Synthesis of *anti*-1,2-Hydroxyboronates through α-Boryl Alkyl Silver Additions to Aldehydes.** The Ag(I)-catalyzed, diastereoselective addition of various *gem*-diboronate esters to aryl, alkenyl, and alkyl aldehydes is discussed. The reactions proceed in the

presence of either stoichiometric KOt-Bu or n-BuLi at -25 °C in thf. Mechanistic studies indicate an α-boryl-alkyl silver species as the active nucleophile in the reaction. The hydroxyboronates are isolated in up to 77% yield and 99:1 d.r. favoring the *anti* diastereomer.
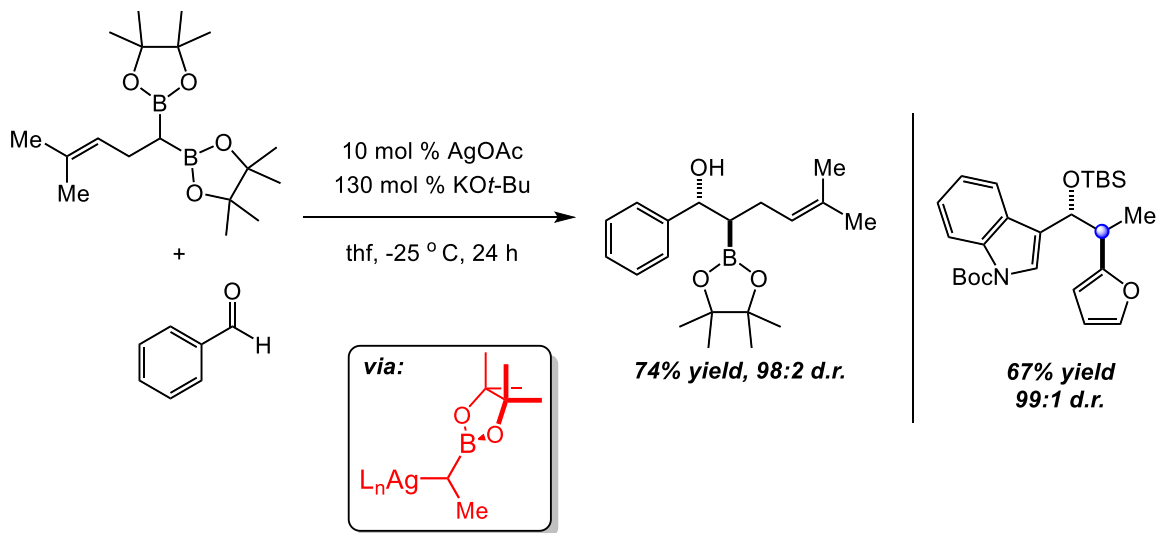
■ **Chapter 3: Enantio- and Diastereoselective Synthesis of 1-Hydroxy-2,3-Bisboronates via a Copper–Catalyzed Multicomponent Reaction.** The multicomponent coupling of vinyl boronic acid pinacol ester, $B_2(pin)_2$, and various aldehydes in the presence of a copper-bis-phosphine catalyst is discussed.   The reaction can be accomplished both diastereoselectively and enantioselectively. Mechanistic investigations reveal that nitrile ligands have a deleterious effect on the enantioselectivity of the reaction, manifested in the isolation of a copper(keteneimide) complex, which is potentially the first ever of its kind to be reported. The 1-hydroxy-2,3-bisboronate esters are isolable via silica gel chromatography in up to 84% yield, >99:1 d.r., and 97:3 e.r.
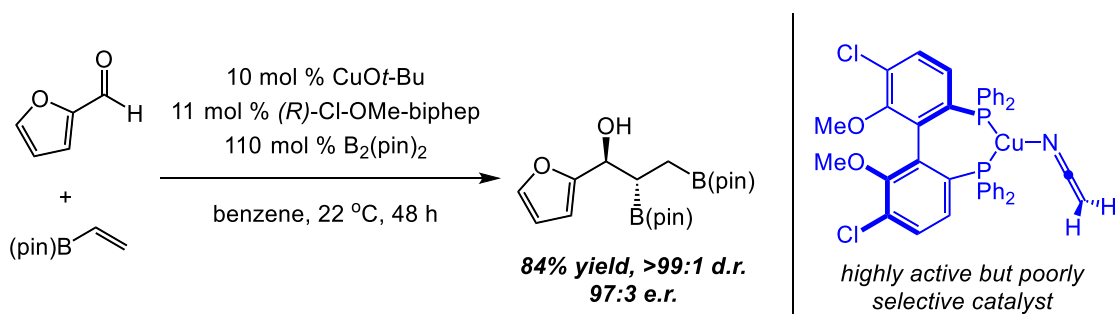
ACKNOWLEDGEMENTS

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To all the teachers I've had at UNC, thank you for enriching my mind with chemistry knowledge I didn't even know existed when I first arrived. To the friends I've made at UNC, in the department and outside, I could not have done this without your support, love, and friendship…and your abilities to get me out of lab to have fun! I don't know what I'm going to do without you all in my life, but you'll always be in my heart, regardless of where we are in the world.

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To my grandfather, a shining example of how you are never too old to learn something new or to fall in love with something cool, like particle physics or chemistry.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ILLUSTRATIONS

LIST OF ABBREVIATIONS

12-crown-4	1,4,7,10-tetraoxacyclododecane
(R)-binap	(R)-(+)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
(R)-Cl-OMe-biphep	(R)-(+)-5,5'-Dichloro-6,6'-dimethoxy-2,2'-bis(diphenylphosphino)1,1'-biphenyl
(R)-dtbm-segphos	(R)-(−)-5,5′-bis[di(3,5-di-tert-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole
(R)-Monophos	(R)-(-)-(3,5-Dioxa-4-phospha-cyclohepta[2,1-a;3,4-a']dinaphthalen-4-yl)dimethylamine
(R,R)-BOX	(+)-2,2′-Isopropylidenebis[(4R)-4-phenyl-2-oxazoline]
(R,R)-Me-duphos	(−)-1,2-bis[(2R,5R)-2,5-dimethylphospholano]benzene
(R,S)-josiphos	(R)-(-)-1-[(S)-2-(diphenylphosphino)ferrocenyl]ethyldicyclohexylphosphine
[Rh(COD)Cl]$_2$	chloro(1,5-cyclooctadiene)rhodium(I)
° C	degrees Celsius
Å	angstrom
AgBF$_4$	silver(I) tetrafluoroborate
AgCl	silver(I) chloride
AgClO$_4$	silver(I) perchlorate
AgNO$_3$	silver(I) nitrate
AgOAc	silver(I) acetate
AgOTf	silver(I) trifluoromethanesulfonate
AgOTs	silver(I) tosylate
AgSbF$_6$	silver(I) hexafluoroantimonate
Ar	generic aryl group
B$_2$H$_6$	borane
B$_2$(pin)$_2$	bis(pinacolato)diboron

BCl$_3$	borontrichloride
B(dan)	1,8-diaminonaphthyl boryl group
BF$_3$·OEt$_2$	boron trifluoride diethyl etherate
Boc	*tert*-butyl carbonate group
Boc$_2$O	di-*tert*-butyl dicarbonate
cat	catecholato group
CDI	carbodiimidazole
CH$_2$	methylene group
CH$_2$Br$_2$	dibromomethane
CH$_2$=N$_2$	diazomethane
Cu(MeCN)$_4$PF$_6$	tetrakis(acetonitrile)copper hexafluorophosphate
Cu(OAc)$_2$	copper(II) acetate
Cu(OMe)$_2$	copper(II) methoxide
Cu(OTf)$_2$	copper(II) trifluoromethanesulfonate
CuCl	copper(I) chloride
CuI	copper(I) iodide
d.r.	diastereomeric ratio
dce	1,2-dichloroethane
dme	1,2-dimethoxyethane
dmf	N,N'-dimethylformamide
dppb	1,2-diphenylphosphinobutane
e.r.	enantiomeric ratio
E$^+$	generic electrophile
ee%	enantiomeric excess
Et	ethyl group
Et$_3$N	triethylamine

Et$_2$O	diethyl ether
h	hour(s)
H$_2$	hydrogen (diatomic)
HCOOH	formic acid
H$_2$O	water
H$_2$O$_2$	hydrogen peroxide
HB(pin)	pinacolborane
HOMO	highest occupied molecular orbital
^{i}Pr	isopropyl group
KIE	Kinetic Isotope Effect
KOH	potassium hydroxide
LiOMe	lithium methoxide
LiO^{t}Am	lithium *tert*-amylate
LiO^{t}Bu	lithium *tert*-butoxide
LiTMP	lithium 2,2,6,6-tetramethylpiperidide
L$_n$	generic ligands on a metal center
LUMO	lowest unoccupied molecular orbital
M	generic metal
Me	methyl group
MeCN	acetonitrile
MeOH	methanol
MeONH$_2$	methoxyamine
Mes	mesityl group (2,4,6-trimethylphenyl)
MesLi	mesityl lithium
min	minute(s)
n-BuLi	*n*-butyllithium

NaBO$_3$·4H$_2$O	sodium perborate tetrahydrate
NaOH	sodium hydroxide
NaO^{t}Bu	sodium *tert*-butoxide
Na$_2$S$_2$O$_3$	sodium thiosulfate
NBS	N-bromosuccinamide
NMR	nuclear magnetic resonance
OR	generic alkoxy group
Pd/C	palladium supported on activated carbon
Pd$_2$(dba)$_3$	tris(dibenzylideneacetone)dipalladium
Pd(OAc)$_2$	palladium(II) acetate
Pd[P(^{t}Bu$_3$)]$_2$	bis[tri(*tert*-butyl)phosphine]palladium(0)
Ph	phenyl group
pin	pinacolato group
PCy$_3$	tricyclohexylphosphine
P(*n*-Bu)$_3$	tri(*n*-butyl)phosphine
PPh$_3$	triphenylphosphine
Pt(dba)$_3$	tris(dibenzylideneacetone)platinum(0)
Pt(PPh$_3$)$_4$	tetrakis(triphenylphosphine)platinum(0)
R	generic organic group
rac-binap	racemic 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
SiMes·HCl	1,3-bis(2,4,6-trimethylphenyl)imidazolinium chloride
TBS	*tert*-butyldimethylsilyl group
^{t}Bu	*tert*-butyl group
thf	tetrahydrofuran
thf-d_8	octadeuteriotetrahydrofuran
TIPS	triisopropylsilyl group

Chapter 1: Enantio- and Diastereoselective Synthesis of β-Hydroxyboronates via Cu-catalyzed Addition of *gem*-Diboronate Esters to Aldehydes[*]

1.1   Introduction

Enantiopure organoboron compounds are an extremely important class of molecules in chemical synthesis. They are configurationally stable and can be stereospecifically transformed into a plethora of different functional groups, making them useful synthetic intermediates (Figure 1.1).[1] Carbon-boron bonds are most commonly oxidized to the corresponding alcohols or amines, but several carbon-carbon bond forming transformations have been developed, with the field still growing. Besides being valuable building blocks in chemical synthesis, there are a number of boron-containing biologically active molecules and pharmaceutical products in use today. Most notably Bortezomib (Velcade®), which is an FDA-approved drug for the treatment of several types of blood cancers (multiple myeloma, lymphoma, etc.), contains a stereogenic organoboron moiety in the molecule.[2] Stereoselective preparation of sp^3-organoborons, therefore, is a valuable method in chemical synthesis worthy of further investigation and development.

The enantioselective preparation of sp^3-alkyl organoboron compounds has been accomplished via a number of methods, including: hydroboration[3], diboration[4], and conjugate boration[5], among several others. These approaches directly generate a carbon-boron bond through a metal-boryl intermediate. These methodologies have been showcased in the efficient synthesis of several biologically active molecules, and highlights the utility of the alkyl organoboron products formed.

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[*] A portion of this chapter appeared as a communication in the *Journal of the American Chemical Society*, the reference is as follows: Joannou, M. V.; Moyer, B. S.; Meek, S. J. *J. Am. Chem. Soc.* **2015**, *137*, 6176–6179
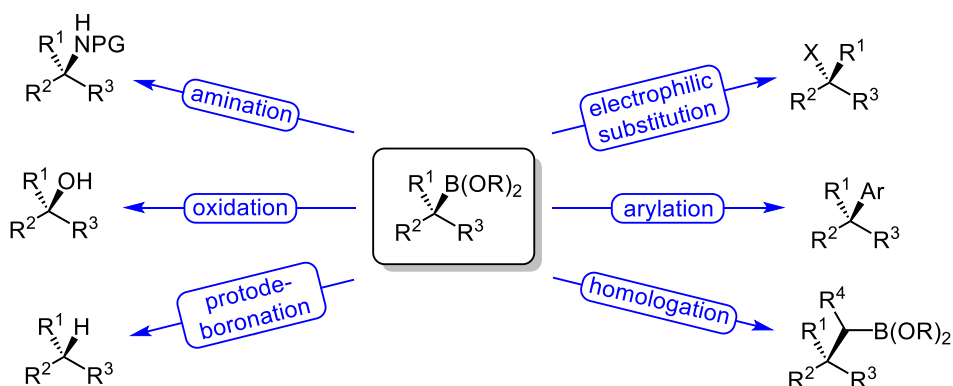
Figure 1.1 List of Stereospecific Functionalizations of Boronic Acid Esters

Over the past decade, Hoveyda and co-workers have developed a number of methodologies for the asymmetric conjugate addition of various nucleophiles to α,β-unsaturated carbonyls. In 2010, the group developed an enantioselective conjugate boration of α,β-unsaturated esters and thioesters with chiral N-heterocyclic carbene copper catalysts.[6] The tertiary boronate esters (**1.2**, **1.3**, and **1.4**) are produced in good to excellent yields, with good to excellent enantioselectivities. The authors propose a mechanism that involves a copper-boryl intermediate (**1.6**) (formed from the transmetallation of a copper-alkoxide and B$_2$(pin)$_2$) inserting across the bound α,β-unsaturated esters (an activated alkene). These organoboron products have been used by Hoveyda and co-workers as intermediates in the synthesis of several biologically active molecules, most notably crassinervic acid, a potent antifungal compound.[7] This demonstrates the utility of enantiopure organoboron compounds as synthetic intermediates to efficiently and rapidly synthesize complex, single-enantiomer molecules.

Scheme 1.1 Stereoselective Conjugate Boration of α,β-Unsaturated Esters and Thioesters with

B$_2$(pin)$_2$
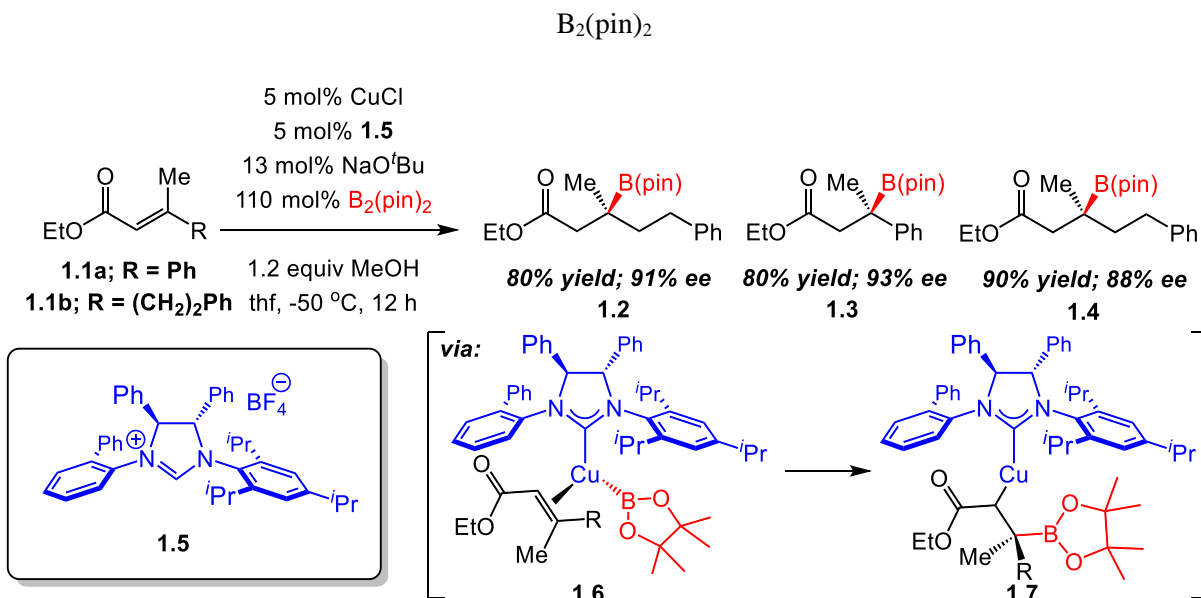
Diboration of alkenes is another useful method for installing boron into molecules which has the added advantage of incorporating two boron moieties into a molecule, which in some cases may be selectively transformed into different groups. Morken and co-workers disclosed an enantioselective diboration of terminal aryl and alkyl alkenes with bis(pinacolato)diboron, utilizing a platinum-phosphoramidite catalyst system.[4e] The 1,2-diboronate ester products are able to be isolated by silica gel column chromatography. For ease of isolation and determination of enantioselectivity, the products were oxidized to the corresponding diols. The diols are produced in good to excellent yields with varying levels of enantioselectivity; alkyl olefins produce the highest *ee*% values (90-96%), while styrenyl olefins give between 80-90% *ee.* The mechanism of the reaction was elucidated through combined KIE, kinetics analysis, and computational studies. The Pt(0) catalyst undergoes oxidative addition of B$_2$(pin)$_2$ to form the platinum bis-boryl compound (**1.11**). Boryl insertion onto the bound olefin and subsequent reductive elimination forms the 1,2-diboronate ester (**Scheme 1.2**). Morken demonstrates the value of this methodology in the total synthesis of pregabalin (Lyrica®), which is accomplished in 5 steps with a total yield of 36%, highlighting the usefulness of boron-containing molecules.[8]

Scheme 1.2 Platinum-Catalyzed Enantioselective Diboration of Terminal Olefins
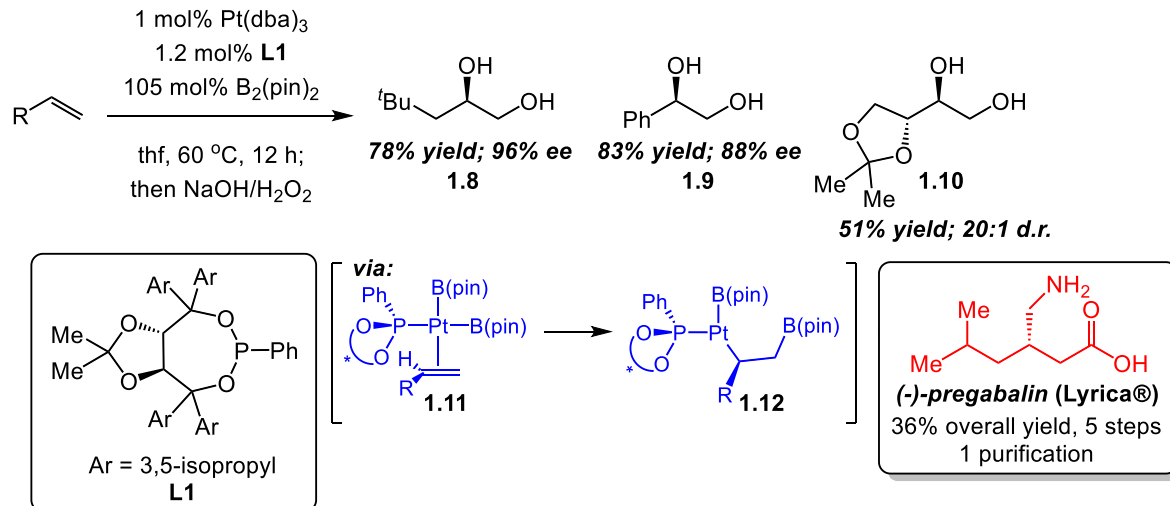
One of the oldest and most well-studied methods for incorporating boron into molecules is hydroboration. There are multiple variants with and without a transition metal catalyst, but most enantioselective hydroborations utilize a transition metal catalyst.[3a] Regioselectivity is often a problem and careful selection of both the borane and the olefin help to address these problems. Hayashi and co-workers developed a protocol for the enantioselective hydroboration of styrenes using a cationic rhodium bis-phosphine catalyst.[9] With catecholborane (**1.14**) and 2 mol% of the cationic rhodium complex, styrene can undergo hydroboration in up to 96% *ee* and 92% yield. The mechanism of the reaction is as follows: The initial Rh(I)-phosphine complex undergoes oxidative addition of catecholborane to form the cationic Rh(III) complex **1.15**. This species undergoes migratory insertion of the bound styrene with the hydride ligand to produce **1.16**. Reductive elimination of the benzyl and boryl ligands produces the carbon-boron bond and furnishes the product.

All of the methods described in the previous section are extremely powerful synthetic tools and have been demonstrated in the synthesis of a wide variety of complex, biologically active molecules. In each of these methodologies, a single boron unit is incorporated into the molecule by inserting a metal-boryl species to an unsaturated C-C bond, generating a single stereogenic center. This requires that the carbon scaffold (i.e., olefins, enones, etc.) already be in place before the addition of the boron

unit. While there are countless ways to synthesize olefins, what if there was a methodology that could combine the synthesis of C-C bonds (i.e. the carbon skeleton of a molecule) with the stereoselective incorporation of boron into a single process? One way to accomplish this is through the stereoselective synthesis and addition of alpha-borylated organometallics to carbonyl compounds.

Scheme 1.3 Enantioselective Hydroboration of Styrenyl Olefins
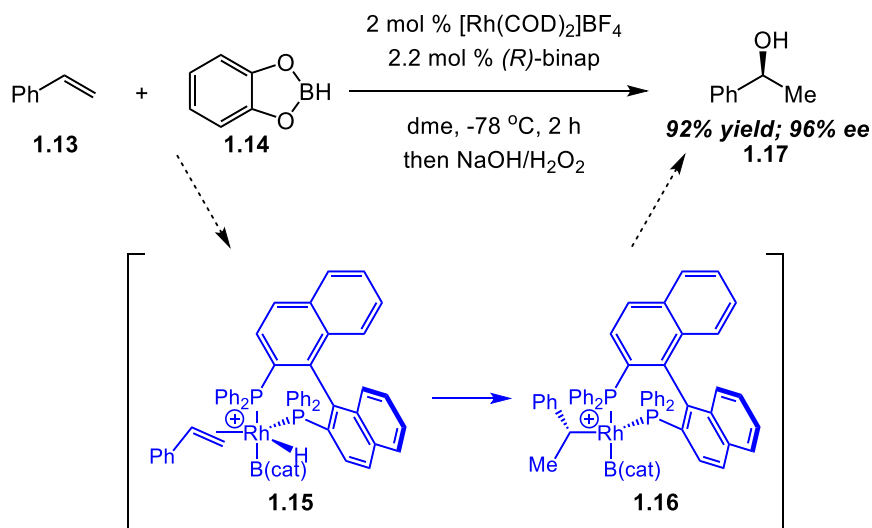
Figure 1.2 depicts a representative example of the addition of a substituted alpha-borylated organometallic species, **I**, to benzaldehyde. The transformation produces the 1,2-hydroxyboronate ester, **II** which contains a new carbon-carbon bond and two vicinal stereogenic centers. One of those stereocenters contains a boronate ester group which can be functionalized into a number of different molecules. Illustrated in the figure are three common and useful functionalizations. Cross-coupling a vinyl bromide with **II** produces the α-stereogenic alcohol **III**. These types of products are usually formed by diastereoselective addition to α-chiral aldehydes, substrates that are oftentimes laborious to synthesize. While Suzuki-Miyaura cross-couplings of secondary sp^3-organoboron groups is a difficult problem in synthetic chemistry, recently, methodologies have emerged where this carbon-carbon bond forming reaction can be carried out under relatively mild conditions.[10] Oxidation, a well-known functionalization of organoboron groups, allows the 1,2-hydroxyboronate ester to be converted into diol **IV**. This transformation yields products similar to those of the Sharpless asymmetric

dihydroxylation, but with different chemoselectivity and bond disconnections.[11] One-carbon homologation of organoboron compounds is another well-studied functionalization; first developed by Matteson and co-workers, homologation inserts a methylene unit (and other CH_2R groups) into the boron-carbon bond.[12] Oxidation of organoborons to the corresponding amine derivative has gained attention in recent years and a useful protocol for this transformation has been developed by Morken and co-workers.[13] One-carbon homologation of **II**, followed by oxidation to the amine produces the aminoalcohol **V**, a moiety which is found a number of biologically active molecules.[13] All of these transformations are stereospecific, meaning that any stereochemical purity gained in the initial formation of **II** is retained upon functionalization of the boron group.
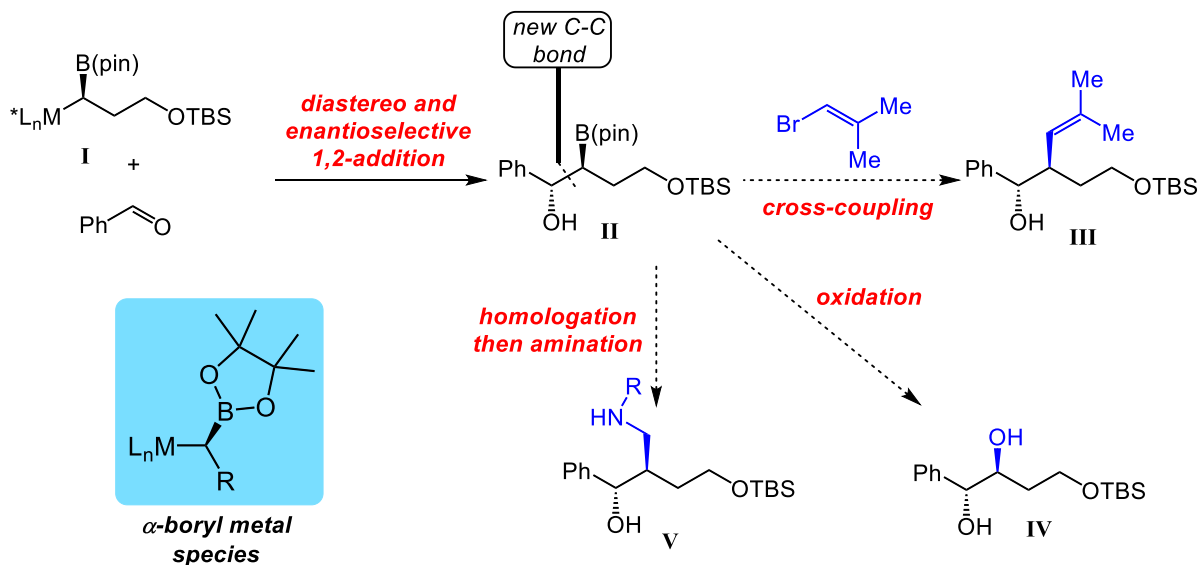
Figure 1.2 Strategy and application for the additions of α-boryl organometallic species to aldehydes: concomitant C-C bond formation and boron incorporation for further synthetic functionalizations

Figure 1.2 highlights the significance of α-boryl organometallics, and how they can be utilized to (1) stereoselectively generate carbon-carbon bonds (2) stereoselectively incorporate boron into molecules (3) generate multiple stereocenters in a single transformation. The 1,2-hydroxyboronate ester products formed are also versatile synthetic intermediates, and can be functionalized to access a number of different scaffolds relevant to the synthesis of biologically-active molecules. While the synthesis of chiral racemic α-boryl metal species has been previously reported, these methods require

air/water sensitive reagents to generate them, and have only been shown in stoichiometric reactions with electrophiles. Our strategy, depicted in Figure 1.3, involves *catalytically* generating α-boryl organometallic species from *gem*-diboronate esters. These reagents are air and water stable and can be synthesized through a number of different methods, some developed by our own lab. Utilizing a chiral transition metal catalyst, the *gem*-diboronate ester undergoes a stereoselective transmetallation to form the enantioenriched α-boryl metal species, which then reacts with an electrophile to form chiral sp^3-organoboron products and regenerate the catalyst. The combined strategies depicted in Figures 1.2 and 1.3 were applied to many of the reactions I studied throughout my graduate work and form the basis of my first two publications.
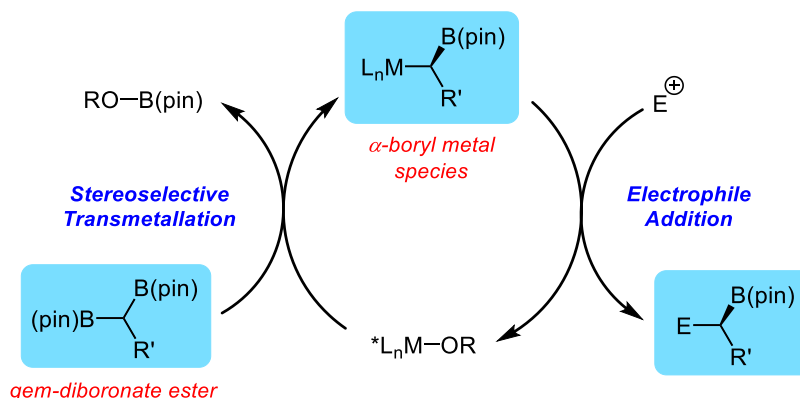
Figure 1.3 Catalytic generation and addition of α-boryl metal species through stereoselective transmetallation of *gem*-diboronate esters to transition metal catalysts

1.2   Background

Polyborylated compounds have gained much attention in recent years, as they can be utilized in the synthesis of complex, multiple functional group-containing molecules. *Gem*-diboronate esters have been shown to undergo several useful C – C bond forming reactions such as cross-coupling, alkylation, 1,2-addition, and allylic substitution both racemically and stereoselectively.[14-20] While their prevalence in organic methodologies is only a recent occurrence, the synthesis of *gem*-diboronate esters and other polyborylated alkanes has been known since the 1960's. Matteson and co-workers

7

synthesized di, tri, and tetraborylmethane utilizing a novel bis(methoxy)chloroborate species, **1.19**.[21]

Two equivalents of trimethylborate react with BCl_3 gas to form **1.19**, which then reacts with a lithiated

chloromethane to form a new boron – carbon bond (releasing LiCl as a byproduct). The lithiation and

alkylation process is then repeated m-1 times (m=number of chlorines in the starting chloromethane) to

form the desired borylated methane. While the yields are low, the synthesis is amenable to large scales

and allowed Matteson and co-workers to explore the properties and reactivity of these compounds (*vide*

infra).

Scheme 1.4 Preparation of di-, tris-, and tetraborylmethane *via* lithiation of chloromethanes and

subsequent alkylation with bis(methoxy)chloroborate
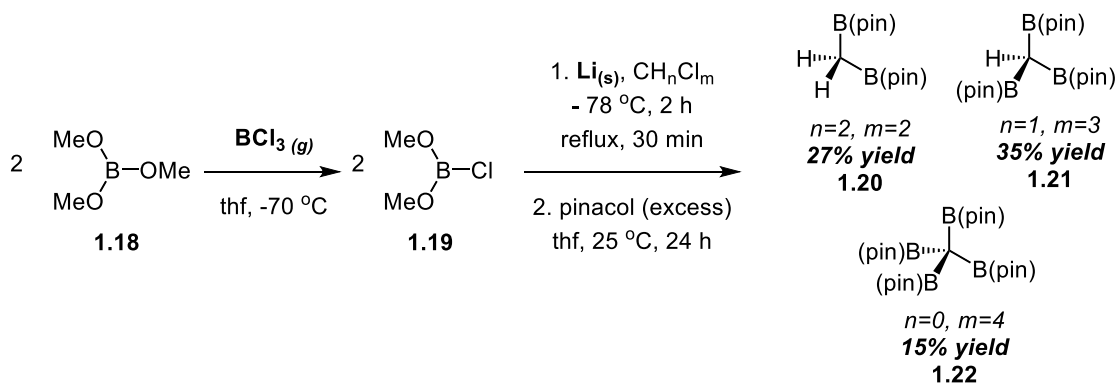
In the last decade, a number of syntheses of substituted and unsubstituted *gem*-diboronate esters

have been published (Scheme 1.5). In 2001, Srebnik and co-workers synthesized diborylmethane, **1.24**,

through a platinum catalyzed insertion of diazomethane into bis(pinacolato)diboron, **1.23**.[22] The yield

is good, but the high platinum catalyst loading and excess diazomethane (a toxic and highly explosive

reagent) prevent this reaction from being conducted on large, synthetically relevant scales (i.e. >500

mg). Shibata and co-workers developed a rhodium-catalyzed synthesis of *gem*-diboronate esters

through the regioselective dihydroboration of terminal alkynes.[23] The reaction has a broad substrate

scope, but a limitation is that the substituents on the alkyne have to be aryl or large alkyl groups (e.g.

tert-butyl, benzyl, etc.) to ensure good yields and high regioselectivity (1,1-hydroboration over 1,2-

hydroboration). Recently, the lab of James P. Morken developed a copper-catalyzed diborylation of

1,1-dibromoalkanes to generate a number of *gem*-diboronate esters.[20] The products are generated in good to excellent yields, and despite some limitations (excess **1.23** and 2 step synthesis of the dibromide starting material) it is still a useful methodology that can access a variety of *gem*-diboronate esters.

Scheme 1.5 Preparation of substituted and unsubstituted *gem*-diboronate esters

■ **Srebnik (2001)**

1.23

10 mol% Pt(PPh$_3$)$_4$
CH$_2$=N$_2$ (3 equiv)

Et$_2$O, 0 °C, 24 h

1.24
82% yield

via:

■ **Shibata (2001)**

[Rh(cod)Cl]$_2$ 5 mol%
dppb 10 mol%
HB(pin) 2.1 equiv

dce, 25 °C, 18 h

26-75% yield
R = aryl, bulky alkyl

■ **Morken (2014)**

1.23

+

10 mol % CuI
300 mol % LiOMe

dmf, 22 °C, 12 h

50-89% yield
R = H, alkyl
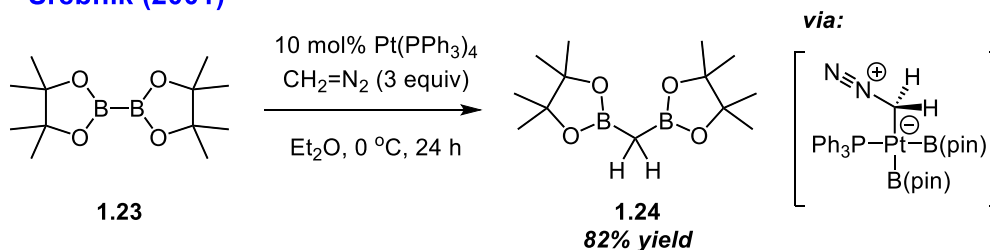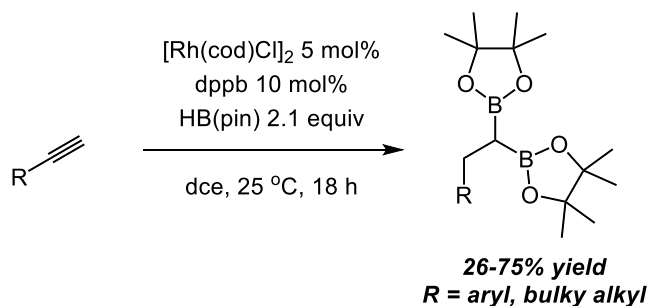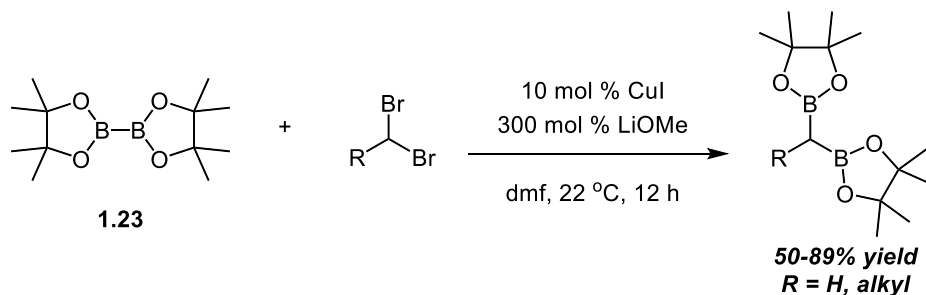
Scheme 1.6 Synthesis of diborylmethane using isopropylmagnesium chloride and B$_2$(pin)$_2$

1.25   **1.26**

thf

-78 °C, 2.5 h

1.27

B$_2$(pin)$_2$ *(1 equiv)*

-78 °C to -55 °C, 24 h

1.24
86% yield
15 g scale
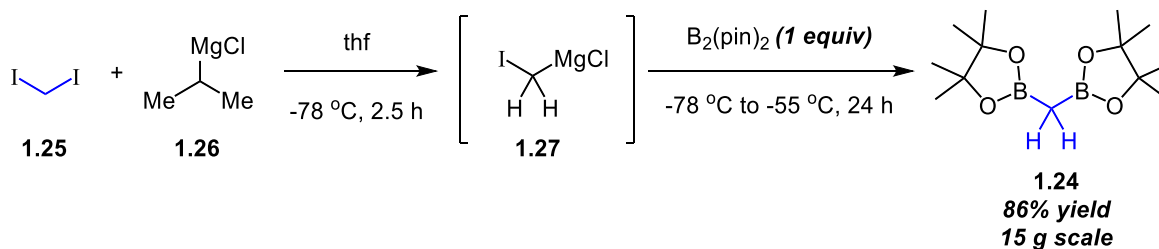
During my graduate work, I developed an efficient, cost-effective, and scalable synthesis of diborylmethane, which could be further functionalized to other substituted variants.[24] Reacting diiodomethane with isopropylmagnesium chloride at -78 °C results in magnesium-halogen exchange to form the α-iodomethyl Grignard, **1.27**. This then complexes to a boron on bis(pinacolato)diboron and enacts a 1,2 borotropic shift, releasing the iodide and generating diborylmethane. The reaction is efficient and amenable to large scale syntheses, with an 86% yield on a 15 g scale (relative to $B_2(pin)_2$ used). Diborylmethane can also be used to generate substituted *gem*-diboronate esters utilizing a deprotonation/alkylation strategy. The α-protons of diborylmethane are much more acidic than normal alkanes (pK_a ~ 30), due to the stabilizing effect of the boryl groups, and can be deprotonated using hindered lithium amides.[25] The resulting α-diboryl carbanion can be quenched with a variety of alkyl halides to produce substituted *gem*-diboronate esters in excellent yields. This methodology has good functional group tolerance, as the alkylation is tolerant of arenes (**1.29**), alkenes (**1.32**), alkynes (**1.31**), esters (**1.33**), and silylethers (**1.30**) (Scheme 1.6).[26] The reaction is limited to primary alkyl halides, as secondary alkyl bromides and iodides (e.g. cyclohexyl iodide) are formed in <25% yield.

Scheme 1.7 Synthesis of substituted *gem*-diboronate esters through alkylation of diborylmethane

1.24

1.28
88% yield
>8g scale

1.29
92% yield

1.30
96% yield

1.31
71% yield

1.32
90% yield

1.33
67% yield
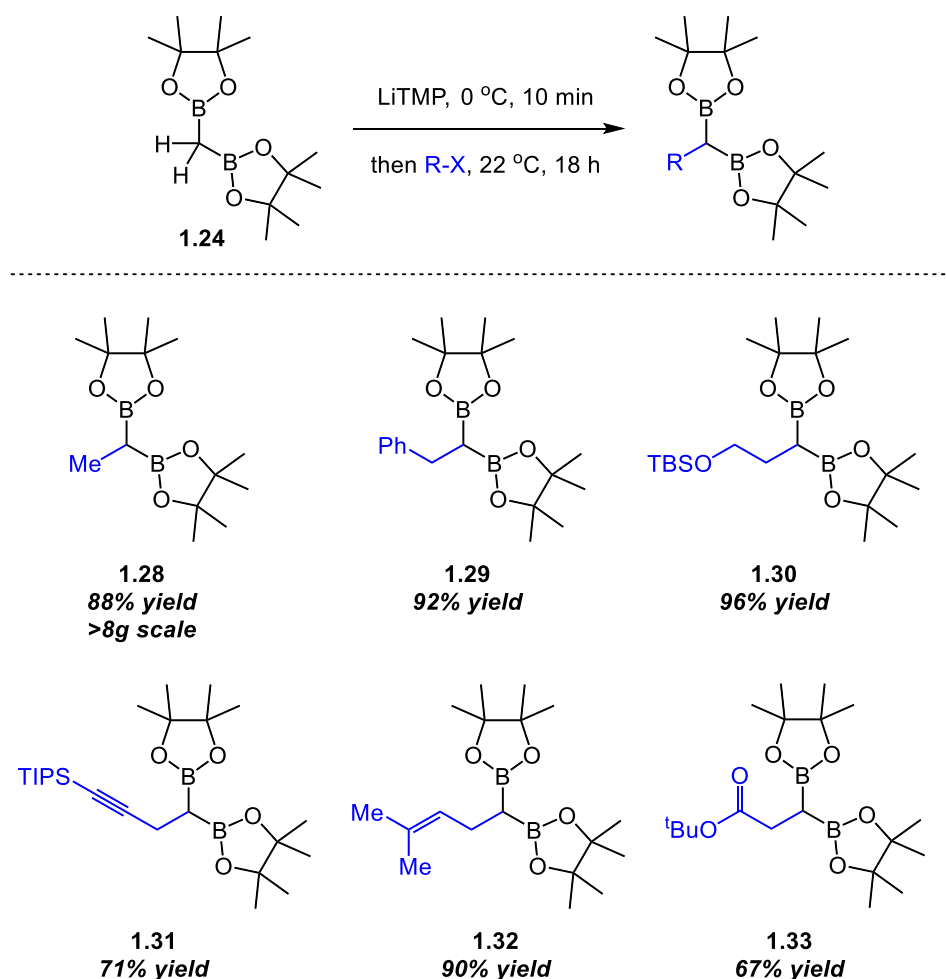
G*em*-diboronate esters are stable to both air and moisture, but are readily activated by Lewis bases. Figure 1.4 demonstrates that, when reacted with Lewis bases such as hydroxide, fluoride, and alkoxides, *gem*-diboronate esters form borate complexes, **III**, which can react with electrophiles in a deborylative fashion. Electrophiles include alkyl halides, carbonyls, epoxides, transition metals, etc. Under certain conditions, **III** has been known to deborylate in solution and form α-boryl carbanions, which can also react with electrophiles similar to **III**.[20] *Gem*-diboronate esters can also be deprotonated at the base of the two boryl groups (α-position) when large amide bases are used (e.g. LiTMP, LiNCy$_2$, LDA, etc.) which prevent complexation of the base to the boron through steric repulsion.[25] The resulting carbanion is stabilized by both boryl groups and is stable in the solid state under an inert atmosphere, or in solution at low temperatures. These carbanions can react with a similar scope of

electrophiles as borate complexes, however both boryl groups are retained in the product. This is the species that is generated during the synthesis of substituted *gem*-diboronate esters in Scheme 1.7, where the electrophile is an alkyl iodide or bromide.

Figure 1.4 Different reactivity patterns of *gem*-diboronate esters: α-deprotonation vs borate formation dependent on the Lewis base, i.e. non-coordinating vs. coordinating.
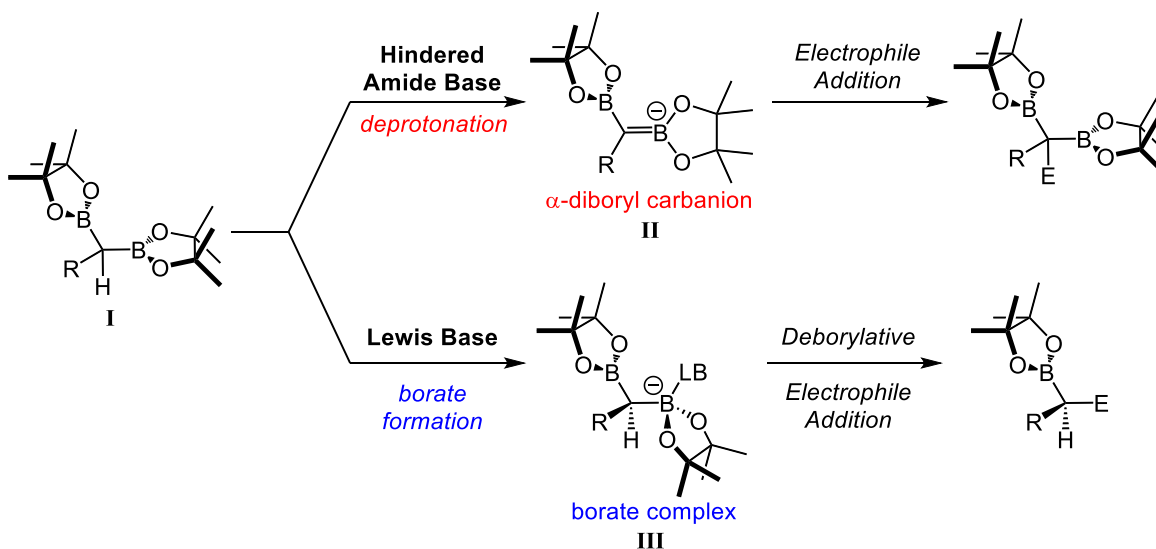
Even though *gem*-diboronate esters have been known for decades, their utilization in transition metal catalyzed processes has been a relatively recent development. The first instance of their use in a transition metal catalyzed reaction was from the labs of Takanori Shibata in 2010.[27] In their *J. Am. Chem. Soc.* communication, various substituted *gem*-diboronate esters are cross-coupled to aryl iodides using a palladium (0) catalyst and aqueous KOH as the activator (Scheme 1.8). Two aspects of the methodology are of note: 1) the reaction occurs at ambient temperature and 2) the reaction is selective for *gem*-diboronate esters over primary boronate esters. Most Suzuki-Miyaura reactions that involve the formation of sp^3-sp^2 C – C bonds (alkyl boronate esters with aryl halides) require elevated temperatures. This demonstrates that *gem*-diboronate esters have a substantially lower energy barrier for activation and transmetallation to palladium than their monoboryl counterparts. Shibata took advantage of this reactivity disparity and demonstrated that the cross-coupling of *gem*-boronate ester

1.34 with **1.35** produced **1.36** in 84% yield with >98% chemoselectivity for coupling the *gem*-diboronate ester over the alkyl boronate ester (Scheme 1.8).

Scheme 1.8 First example of *gem*-diboronate esters being used in transition metal catalysis: Pd-catalyzed Suzuki-Miyaura cross coupling.

1.34   **1.35**   **1.36**
                                84% yield
■ <2% coupling of
primary boronate ester

Reaction conditions:
5 mol % Pd[P(^{t}Bu)$_3$]$_2$
450 mol % KOH
H_2O:dioxane, 25 ^{o}C, 12 h
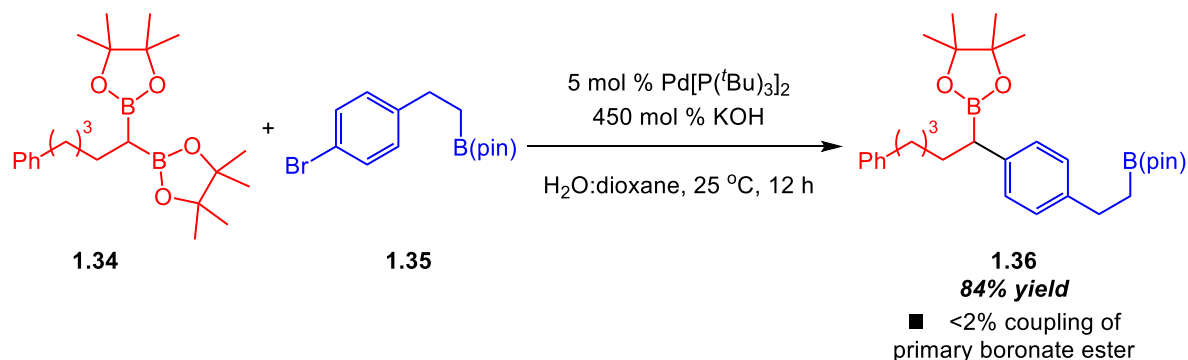
Shibata was able to shed light on why *gem*-diboronate esters are more easily activated by Lewis bases using Density Functional Theory (DFT). The optimized geometry and molecular orbitals for truncated diborylethane **I** (Figure 1.5) (where the pinacol groups are reduced to ethylene glycol groups), were generated using a B3LYP level of theory with a 6-31G** basis set. The LUMO of **I** is depicted in Figure 1.5 on the left. The LUMO is highly delocalized across each boron atom, most likely a combination of both *p* orbitals on boron. This overlap lowers the relative energy of the LUMO compared to a monoboryl compound (7.1 kcal/mol lower than 1,2-diborylethane) and assists in the formation of borate complexes via Lewis base activation.
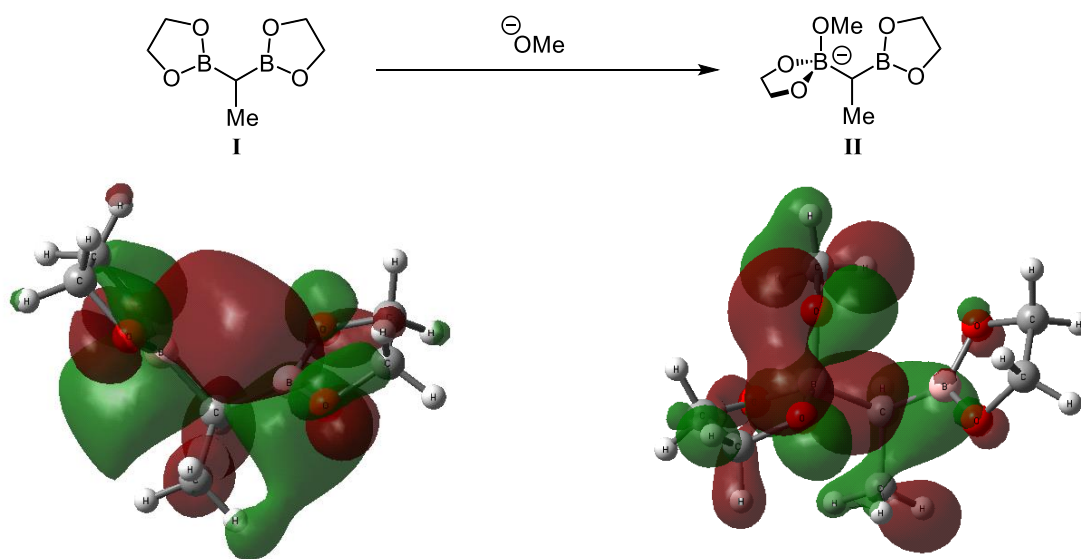
Figure 1.5 Left: LUMO of truncated diborylethane. Right: HOMO of truncated diborylethane activated with a methoxide anion. Both were generated using Gaussian09 with a B3LYP level of theory with a 6-31G** basis set for the left structure, and a 6-31++G** basis set for the right structure.

 I generated the optimized geometries and molecular orbitals for the methoxide-activated diborylethane **II** using a similar basis set: 6-31++G** (see Experimental Section for details). The "++" is a diffuse functional on heavy atoms and hydrogen and assists in calculations involving anions such as borates. The HOMO of **II** is depicted in Figure 1.5 on the right. It contains a large coefficient along the boron-carbon bond (expected for a borate, which is nucleophilic at carbon) but also has large lobes at the methoxy and ethylene glycoxy oxygens. This might indicate that transmetallation of a borate like **II** would involve initial coordination of the borate to the metal complex through an oxygen donor, followed by metal-carbon bond formation. This is the mechanism that Shibata proposes for the Suzuki-Miyaura reaction and is presented in Scheme 1.9. Complex **1.37** is formed after phosphine dissociation and oxidative addition of the aryl iodide to the palladium pre-catalyst. Borate **1.38** (which Shibata observes through ¹¹B NMR studies) binds to the palladium catalyst and undergoes transmetallation to form the α-boryl palladium alkyl species **1.39**. Subsequent reductive elimination produces the cross-coupled product and regenerates the palladium (0) catalyst.

Scheme 1.9 Activation of *gem*-diboronate ester and mechanism of transmetallation to palladium(II)

phosphine catalyst
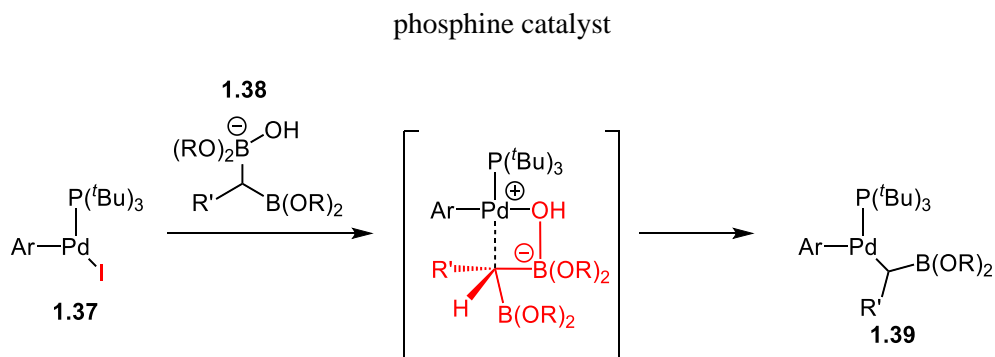
In 2014, Morken and co-workers published a stereoselective version of the reaction Shibata disclosed in 2010. Using a chiral phosphoramidite-bound palladium catalyst, Morken could cross-couple a number of different substituted *gem*-diboronate esters to aryl iodides in good to excellent yields in good enantioselectivities (Scheme 1.10)[20]. The use of 15 equivalents of KOH is essential for high yield and enantioselectivity, which Morken attributes to hydrolysis of the pinacol ester to the *gem*-diboronic acid. Boronic acids transmetallate faster and at lower temperatures than boronate esters. Dennis Hall and co-workers confirmed this hypothesis in a subsequent cross-coupling paper using similar ligands and substrates.[28]

Scheme 1.10 Enantioselective cross-coupling of *gem*-diboronate esters to aryl halides. Catalyst controlled stereoselective transmetallation of *gem*-diboronate ester.
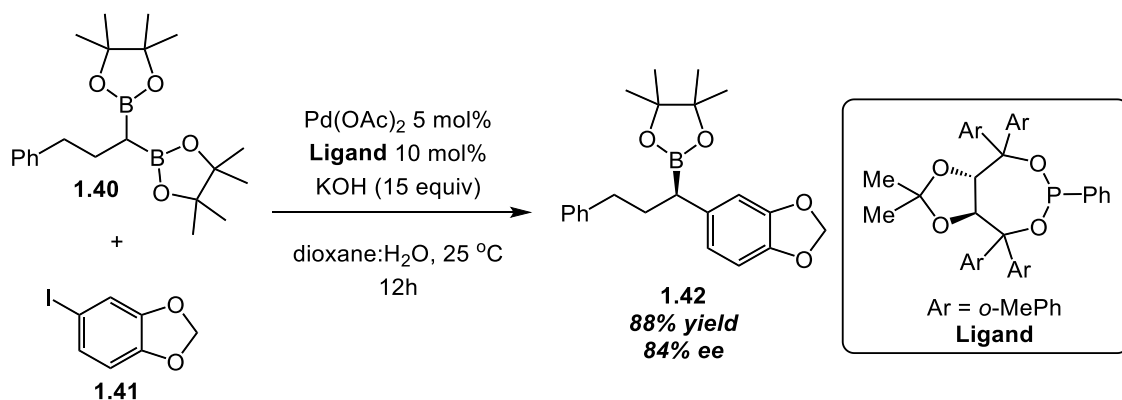
To elucidate the mechanism of the transmetallation step of the reaction in Scheme 1.10, Morken and co-workers synthesized an enantioenriched,*gem*-diboronate ester, **1.43**, where one boron was

enriched (>99%) with ^{10}B, while the other boron contains a natural abundance of both ^{10}B and ^{11}B (~1:4 ratio). Using high resolution mass spectrometry, they were able to calculate which type of boron was contained within the product, i.e. solely ^{10}B or the natural abundance of both ^{10}B and ^{11}B. Under standard reaction conditions with the *(R,R)* enantiomer of the ligand, the *(R)*-enantiomer of the product is formed (**R-1.44**) in 92:8 e.r. When the *(S,S)* enantiomer of the ligand is used, the *(S)*-enantiomer of the product is formed (**S-1.44**), also in 92:8 e.r. and with the boron containing solely the ^{10}B isotope. This shows that the catalyst controls which boron is transmetallated to the meta center and that the transmetallation occurs with inversion about the stereocenter at the base of the two boryl groups.

Scheme 1.11 Evidence for catalyst controlled, stereoinvertive transmetallation of *gem*-diboronate ester
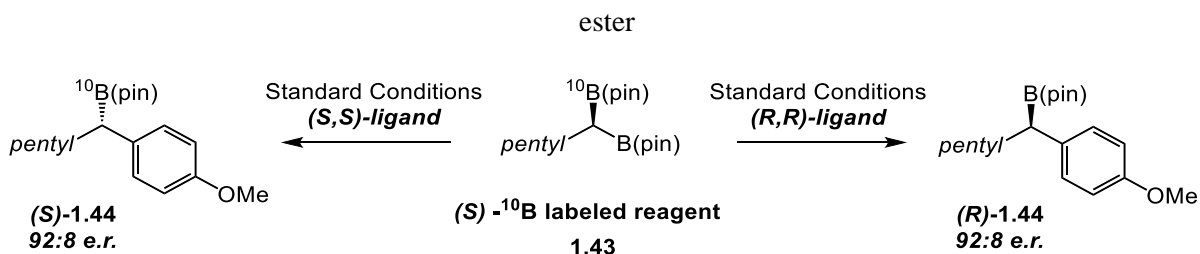
1.3 Reaction Discovery and Optimization

Based on the reaction profile depicted in Figure 1.3, I set out to develop a method for the enantio- and diastereoselective addition of *gem*-diboronate esters to aldehydes utilizing a chiral transition metal catalyst. I began my studies on the model reaction of adding diborylethane, **1.28**, to benzaldehyde in a common polar organic solvent: tetrahydrofuran. These substrates were chosen for two reasons: 1) Diborylethane is the simplest substituted *gem*-diboronate ester and should have the highest reactivity. 2) The reaction generates 1,2-hydroxyboronate **1.46** which has two vicinal stereocenters, so diastereoselectivity could also be used to probe the effect of the catalyst/activator on the reaction.

Table 1.1 Counterion effect on the background reaction of diborylethane and benzaldehyde promoted

by alkali alkoxides[a]
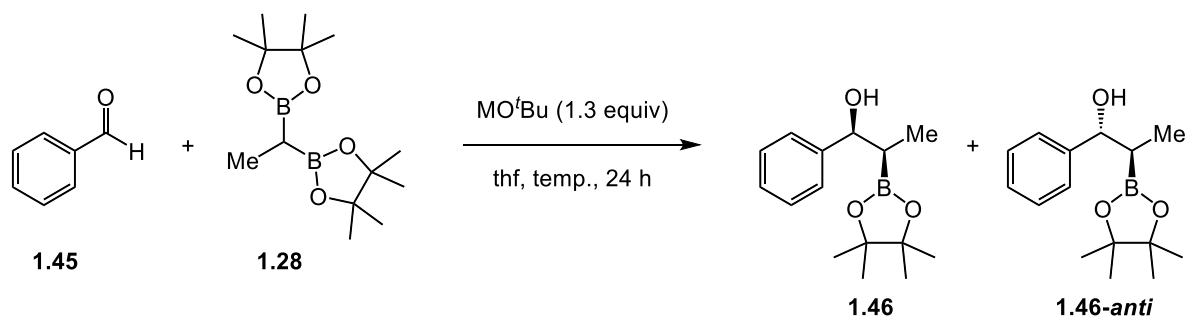
Entry	M	temp. (°C)	NMR yield (%)[b]	d.r.[c]
1	Li	22	<2	-
2	Li	60	<2	-
3	Na	22	63	50:50
4	Na	4	<2	-
5	K	22	54	52:48
6	K	-20	<2	-

[a]Reaction performed under an N_2 atmosphere; see Experimental Section for details. [b]Determined using ^{1}H NMR spectroscopy, hexamethyldisiloxane was used as an internal standard. [c]Determined using ^{1}H NMR spectroscopy

Tert-butoxide is a common base in organic chemistry that is readily soluble in a number of polar organic solvents. The lithium, sodium, and potassium salts are all commercially available and have been used in a plethora of reactions involving borylation of unsaturated compounds using bis(pinacolato)diboron. I set out to determine if there was an uncatalyzed background reaction between diborylethane and benzaldehyde in the presence of stoichiometric *tert*-butoxide activator. The results of this study are summarized in Table 1.1. Treatment of benzaldehyde and **1.28** with 1.3 equivalents of LiO[t]Bu produces no 1,2-addition product at ambient temperature or 60 °C (Entries 1 and 2). With 1.3 equivalents of NaO[t]Bu, however, a non-selective reaction occurs and **1.46** forms in 63% conversion as a 1:1 mixture of diastereomers (Entry 3). This background reaction can be suppressed if the reaction is conducted at 4 °C (Entry 4, <2% conversion). KO[t]Bu is also capable of promoting the 1,2-addition reaction, albeit in lower conversion and higher consumption of diborylethane than NaO[t]Bu (Entry 5). Due to its higher activity, -20 °C is required to completely shut down the non-selective background

reaction with KO^{t}Bu (Entry 6). With these data, lithium *tert*-butoxide was chosen as the optimal

activator for the 1,2-addition reaction. Since there is no background reaction with LiO^{t}Bu, any product

formed in a transition metal catalyzed reaction can only be derived from a catalyzed process.

        With the activator selected, I screened a number of transition metal catalysts (Groups 8, 9, 10,

11) for the 1,2 addition reaction of diborylethane with benzaldehyde. With a broad scope of ligands

and metals, I obtained <2% conversion to product in all cases. Based on previous work by Knochel

and Suzuki, copper was selected as the metal most likely promote the reaction and a more extensive

ligand screen with copper(II) triflate was conducted (Table 1.2). Chiral biaryl phosphines such as *(R)*-

binap and *(R)*-dtbm-segphos do not promote the reaction (Entries 1 and 2), nor do mixed alkyl/aryl

phosphines such as *(R,R)*-Me-duphos and *(R,S)*-josiphos (Entries 3 and 4). Bis-oxazolines are common

ligands employed in a myriad of copper-catalyzed processes[29], but *(R,R)*-**BOX** does not deliver the 1,2-

addition product (Entry 5). N-heterocyclic carbenes are another common ligand class in transition

metal catalysis, but **SIMes** fails to produce any product (Entry 6). Gratifyingly, treatment of

benzaldehyde and **1.28** with 10 mol % Cu(OTf)$_2$ and 11 mol % *(R)*-Monophos affords **1.46** in 31%

NMR yield as a 91:9 mixture of diastereomers (favoring the *syn*) and 88:12 enantiomeric ratio (for the

syn diastereomer). While the initial yield was low, it was promising to observe both high

diastereoselectivity and good enantioselectivity.

Table 1.2 Copper-catalyzed addition of diborylethane to benzaldehyde: ligand screen with LiOtBu[a]
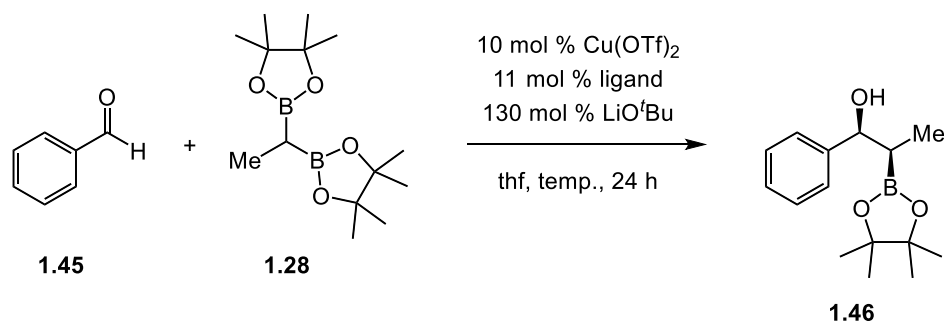
Entry	ligand	temp. (°C)	NMR yield (%)[b]	d.r.[c]	e.r.[d]
1	*(R)*-binap	45	<2	-	-
2	*(R)*-dtbm-segphos	45	<2	-	-
3	*(R,R)*-Me-duphos	45	<2	-	-
4	*(R,S)*-josiphos	45	<2	-	-
5	*(R,R)*-BOX	22	<2	-	-
6[e]	SIMes·HCl	22	<2	-	-
7	*(R)*-Monophos	45	31	91:9	88:12

[a]Reaction performed under an N$_2$ atmosphere; see Experimental Section for details. [b]Determined using ^{1}H NMR spectroscopy, hexamethyldisiloxane was used as an internal standard. [c]Determined using ^{1}H NMR spectroscopy. [d]Determined by HPLC analysis of the oxidized product (1,2-diol). [e]An extra 6 mol % LiO^{t}Bu was used deprotonate the imidazolinium salt and generate the carbene ligand.

***(R)*-binap**   ***(R)*-dtbm segphos**
Ar = 3,5-di-*tert*-butyl-
4-methoxy   ***(R,S)*-josiphos**   ***(R,R)*-Me-duphos**   ***(R,R)*-BOX**

SIMes

***(R)*-Monophos**
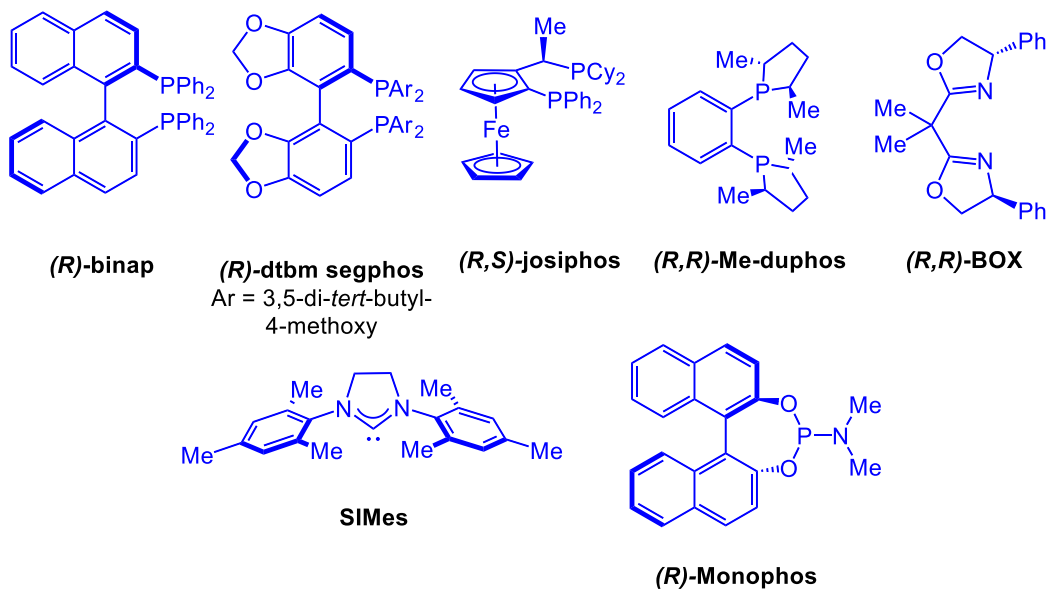
With a promising catalyst discovered, I moved on to optimizing the reaction conditions including: copper source, ligand equivalents, base equivalents, temperature, etc. (summarized in Table 1.3). Increasing the amount of ligand to 20 mol % more than doubles the amount of product formed, as **1.46** is produced in 64% NMR yield, 91:9 diastereoselectivity, and 76% *ee* (Entry 1), selectivity values identical to the 11 mol % result (Table 1.2, Entry 7). Since the alkoxide base is intimately involved in the activation and transmetallation of **1.28** to the copper catalyst, I reasoned that increasing the size of the activator would increase the enantioselectivity of the reaction. Using 90 mol % lithium *tert*-amylate as the activator, **1.46** forms in nearly identical NMR yield and diastereoselectivity to Entry 1, but with a dramatic increase in enantioselectivity to 88% *ee* (Entry 2). The drop in amount of activator from 130 mol % to 90 mol % helps to prevent decomposition of the aldehyde during the reaction. I next conducted a screen of different copper sources to determine which formed the optimal precatalyst. Employing 10 mol % CuCl in the reaction results in lower diastereo and enantioselectivities (85:15 d.r. and 62% *ee*, Entry 3) while 10 mol % CuI results in a decrease in NMR yield and enantioselectivity (20% NMR yield and 76% ee, Entry 4). Copper(II) derived precatalysts proved to be more active and selective:10 mol % $Cu(OAc)_2$ provides the product in 60% yield, 92:8 d.r., and 89% *ee* while 10 mol % $Cu(OMe)_2$ affords the product in 62% yield, 92:8 d.r., and 92% *ee*. These results, however, were not reproducible and often gave varying conversions and diastereoselectivities, most likely due to the low solubility of copper(II) salts in thf. Moving to a more soluble and stable copper(I) salt, $Cu(MeCN)_4PF_6$ provided reproducible yields and diastereoselectivities at 66% NMR yield, 92:8 d.r., and 88% *ee*. Decreasing the reaction temperature to ambient temperature (22 °C) and lengthening the reaction time to 48 hours resulted in 92% NMR yield of **1.46** in 92:8 d.r. and 88% *ee*.

Table 1.3 Copper-catalyzed addition of diborylethane to benzaldehyde: copper salt screen and lithium

alkoxide optimization[a]
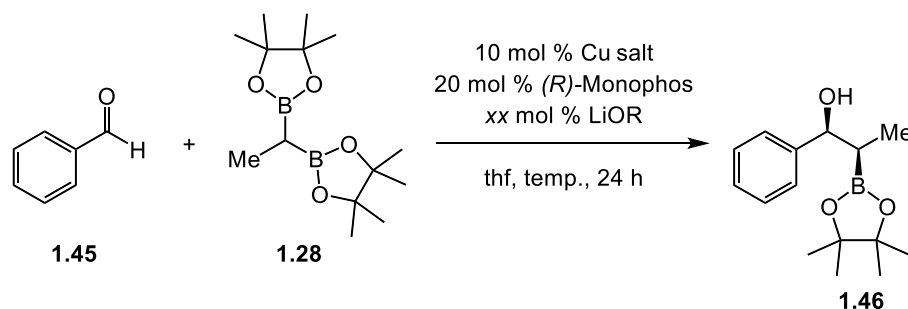
Entry	Cu salt	LiOR; mol %	temp. (°C)	NMR yield (%)[b]	d.r.[c]	ee%[d]
1	Cu(OTf)$_2$	LiO^{t}Bu; 130	45	65	91:9	*76*
2	Cu(OTf)$_2$	LiO^{t}Am; 90	45	64	91:9	*88*
3	CuCl	LiO^{t}Am; 90	45	67	85:15	*62*
4	CuI	LiO^{t}Am; 90	45	20	93:7	*76*
5	Cu(OAc)$_2$	LiO^{t}Am; 90	45	60	92:8	*89*
6[e]	Cu(OMe)$_2$	LiO^{t}Am; 90	45	62	92:8	*92*
7	Cu(MeCN)$_4$PF$_6$	LiO^{t}Am; 90	45	66	92:8	*88*
8[f]	Cu(MeCN)$_4$PF$_6$	LiO^{t}Am; 90	22	92	92:8	*88*

[a]Reaction performed under an N$_2$ atmosphere; see Experimental Section for details. [b]Determined using ^{1}H NMR spectroscopy, hexamethyldisiloxane was used as an internal standard. [c]Determined using ^{1}H NMR spectroscopy. [d]Determined by HPLC analysis of the oxidized product (1,2-diol). [e]Conversions with Cu(OMe)$_2$ were not consistent under seemingly identical conditions. [f]Reaction was run for 48 hours.

A selection of different chiral phosphoramidite ligands was screened to test if there was an effect on the enantioselectivity of the reaction. The reaction proved very sensitive to even the smallest alterations to the ligand structure as shown by the results in Scheme 1.12. With ligand **1.47**, a small change of the amino group (Me to Et) leads to a drop in yield, d.r., and *ee*% (57% conv.; 88:12 d.r.; 82% *ee*). Similarly, ligand **1.48**, which contains a morpholine group bound to phosphorus(III), affords the product in similar yield and selectivity (77% conv.; 87:13 d.r.; 82% *ee*). Introducing stereocenters and sterics to the amino group on the phosphoramidite ligand, **1.49**, leads to a drastic drop in conversion and *ee*% (30% conv.; 34% *ee*). Since altering the amino group on the ligand proved disastrous, I

proceeded to screen ligands with alterations to the binaphthyl backbone. Substituting the 3 and 3'

positions of the binaphthyl rings with either methyl groups, **1.50**, or bromine, **1.51**, completely shuts

down the reaction and no product is formed. Ligand **1.52**, which contains a partially hydrogenated

binaphthyl ring, produces the product in diminished yield and d.r., with a complete erosion of *ee*%

(46% conv.; 84:16 d.r.; 3% *ee*). Based on these data, the original *(R)*-Monophos with an NMe$_2$ group

bound to phosphorus was the most optimal ligand for copper to catalyze the reaction between

diborylethane and benzaldehyde.

Scheme 1.12 Copper-catalyzed addition of diborylethane to benzaldehyde: phosphoramidite ligand

screen (original NMe$_2$-Monophos is the optimal ligand)
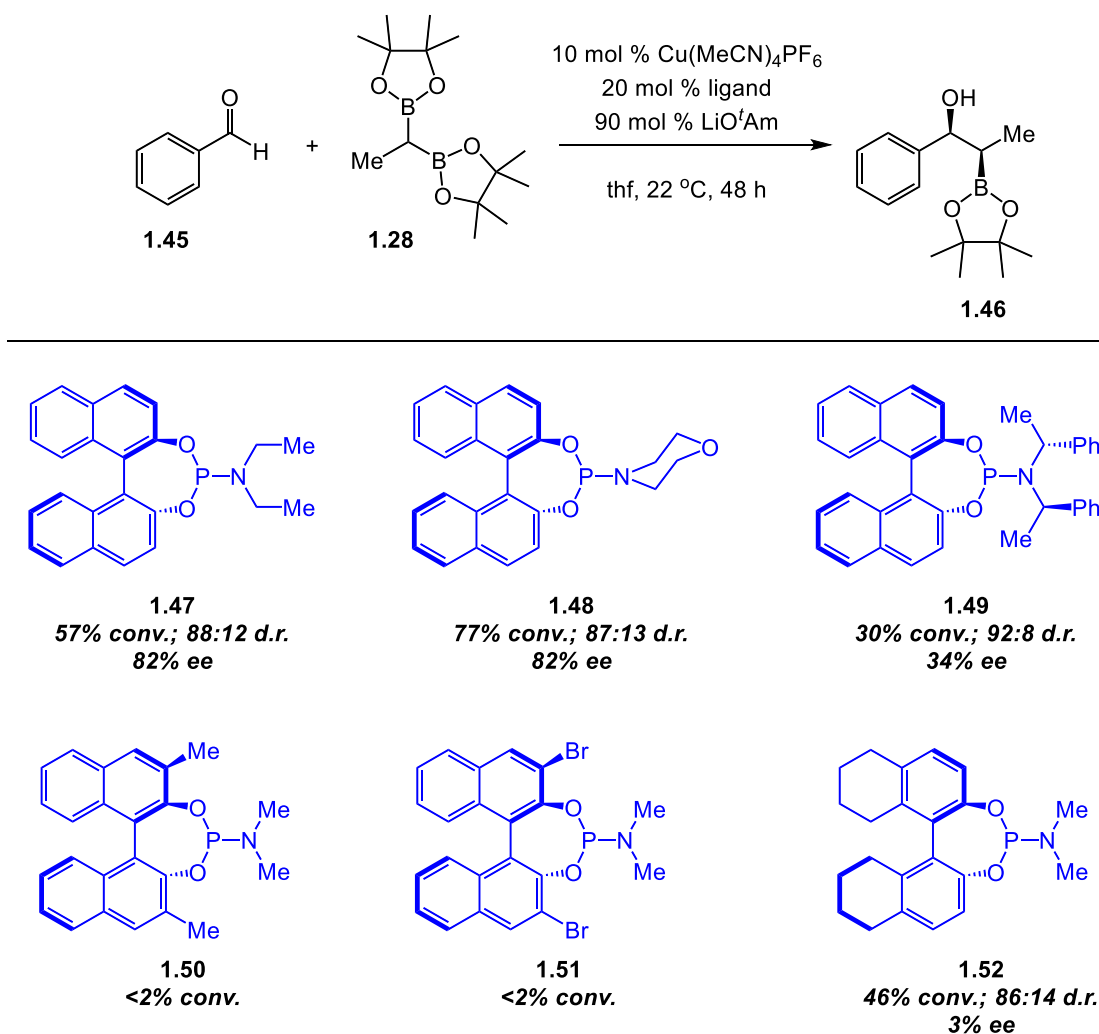
1.4   Substrate Scope

With the optimal copper salt, ligand, activator, and conditions obtained, I set out to expand the substrate scope of the 1,2-addition reaction of diborylethane to aryl aldehydes. Due to the varying stability of the 1,2-hydroxyboronate products (aside from **1.46**), all of the products were isolated and characterized after oxidation to the 1,2-diol. The list of aryl aldehyde substrates is presented in Scheme 1.13. All reactions are conducted in the presence of 10 mol % Cu(MeCN)$_4$PF$_6$, 20 mol % *(R)*-Monophos, and 90 mol % LiO^{t}Am. The reactions occur at ambient temperature for 48 hours with thf as the solvent. All oxidations are performed using excess NaBO$_3$·4H$_2$O in a 1:1 mixture of thf:H$_2$O for 2.5 hours at ambient temperature. Benzaldehyde-derived 1,2-diol **1.53** is isolated in 67% yield, 92:8 d.r., and 94:6 e.r. The reaction is tolerant of halogen substituents at the *para* position; as **1.54** and **1.55** form in 77% yield (92:8 d.r.; 94:6 e.r.) and 91% yield (93:7 d.r.; 95:5 e.r.), respectively. Electron-donating groups work well in the 1,2-addition reaction, producing *para*-methoxy containing **1.56** in 69% yield, 97:3 d.r., and 93:7 e.r. Nitro groups at the *para* and *meta* positions of the aryl ring form products **1.57** and **1.60**, respectively, but in lower yields (34% and 35% respectively) yet still with high selectivity (95:5 e.r. for both substrates). Substrates containing *m*-Me and *m*-CF$_3$ groups are also tolerated, producing 1,2-hydroxyboronates **1.58** and **1.59** in 76% yield (92:8 d.r.; 98:2 e.r.) and 59% yield (90:10 d.r.; 94:6 e.r.), respectively. Products derived from aldehydes with substituents in the *ortho* position form as a single diastereoisomer in good yields and enantioselectivities: **1.61** is afforded in 68% yield, >99:1 d.r., and 93:7 e.r. and **1.62** is afforded in 65% yield, >99:1 d.r., and 93:7 e.r. The reaction is not sensitive to nitrogen or oxygen-containing heterocycles, and 3-pyridyl and 2-furyl derived products are formed in good yields and enantioselectivities, but with slightly diminished diastereoselectivities. Pyridine-containing 1,2-hydroxyboronate **1.63** is produced in 68% yield, 83:17 d.r., and 90:10 e.r., while furan-containing 1,2-hydroxyboronate **1.64** is produced in 55% yield, 86:14 d.r., and 95:5 e.r.

23

Scheme 1.13 Substrate scope for copper-catalyzed addition of diborylethane to aryl aldehydes
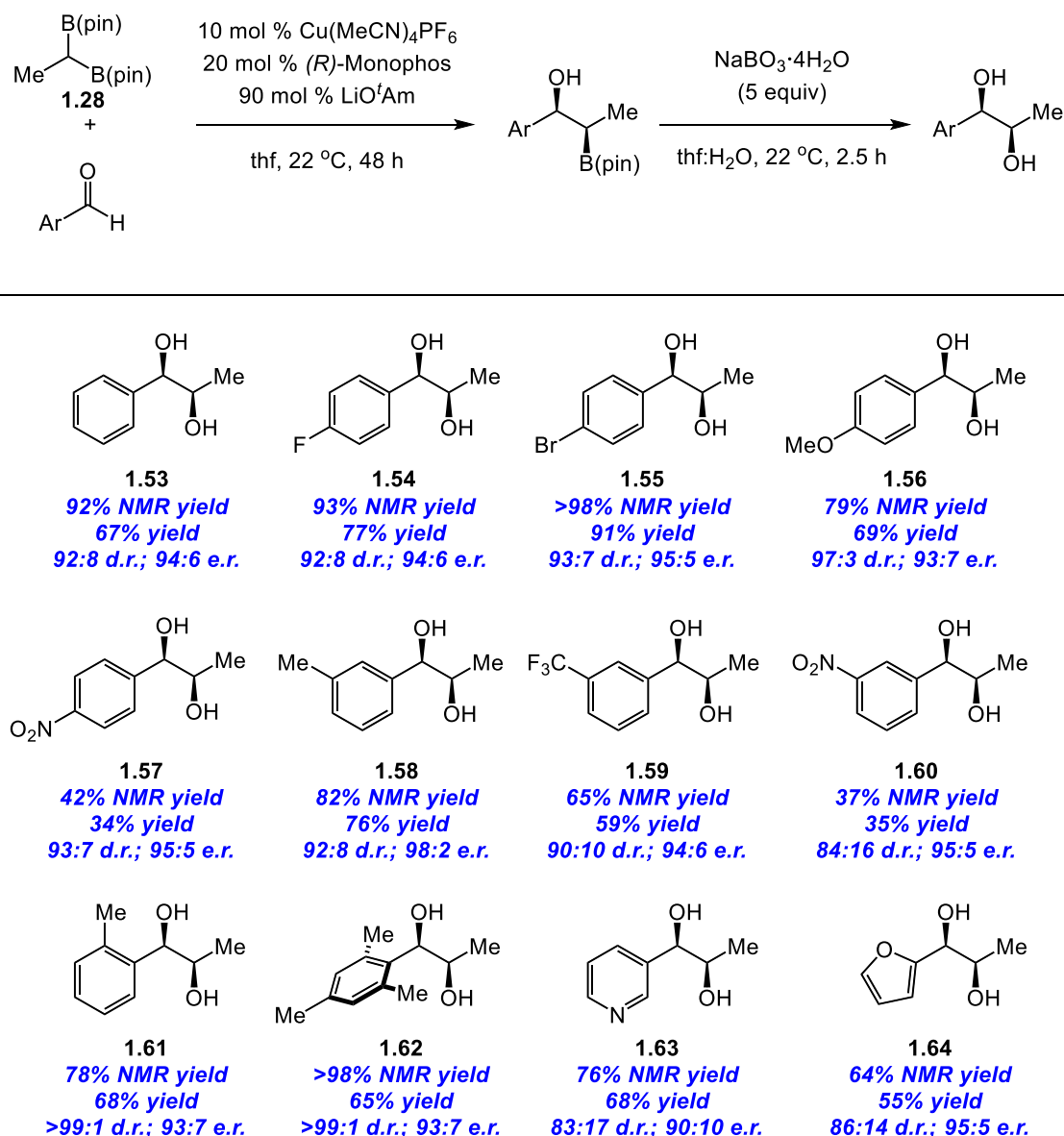
Alkenyl aldehydes may also undergo 1,2-additions with diborylethane under similar conditions as aryl aldehydes. The diastereoselectivities are lower than those of the aryl aldehyde addition products, but the enantioselectivity remains high for most substrates. The substrates form in the presence of 7.5 mol % $Cu(MeCN)_4PF_6$, 15 mol % *(R)*-Monophos, and 60-80 mol % LiO^{t}Am at ambient temperature. The 1,2-hydroxyboronates are oxidized to the 1,2-diols with an excess of $NaOH/H_2O_2$ mixture at 0 °C for 4 hours. Cinnamaldehyde derived 1,2-diol **1.65** forms in 59% yield, 54:46 d.r., and 97:3 e.r. (*syn*)/92:8 e.r. (*anti*). The reaction tolerates substituents in the *para* position of the aryl ring: *p*-Cl-

cinnamaldehyde-derived product **1.66** is afforded in 38% yield, 54:46 d.r., and 97:3 e.r. (*syn*)/94:6 e.r. (*anti*); *p*-NO$_2$-cinnamaldehyde derived product **1.67** is afforded in 46% yield, 45:55 d.r., and 95:5 e.r. (*syn* and *anti*). Installing substitution at the α-position of alkenyl aldehydes restores the diastereoselectivity of the reaction, with only a slight decrease in enantioselectivity: **1.68** forms in 54% yield, 97:3 d.r., and 80% *ee*, while **1.69** forms in only 34% yield, 96:4 d.r., and 66% *ee*.

Scheme 1.14. Substrate scope for copper-catalyzed addition of diborylethane to alkenyl aldehydes

1.65
75% NMR yield
59% yield; 54:46 d.r.
97:3 e.r. (syn); 92:8 e.r. (anti)

1.66
57% NMR yield
38% yield; 54:46 d.r.
97:3 e.r. (syn); 94:6 e.r. (anti)

1.67
50% NMR yield
46% yield; 45:55 d.r.
95:5 e.r. (syn); 95:5 e.r. (anti)

1.68
73% NMR yield
54% yield
97:3 d.r.; 90:10 e.r.

1.69
64% NMR yield
34% yield
96:4 d.r.; 83:17 e.r.
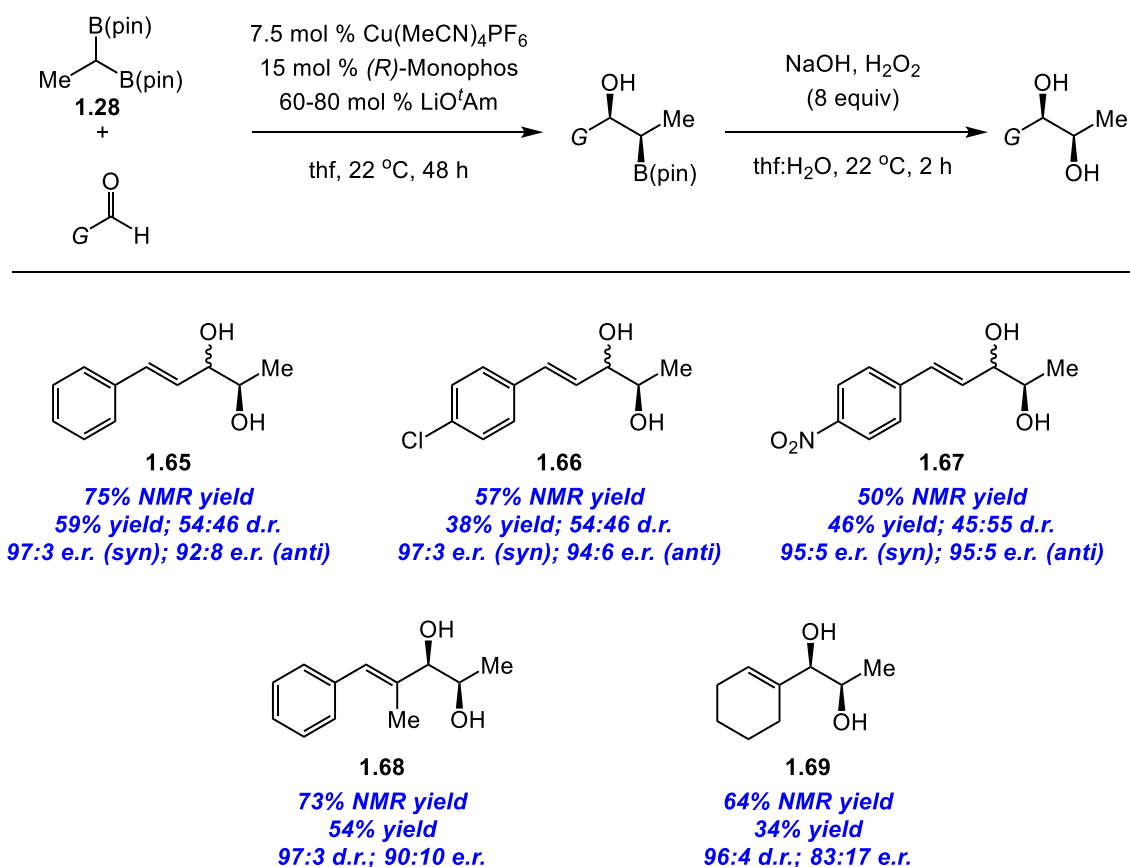
1.5   Mechanistic Investigations

Figure 1.6 depicts our proposed catalytic cycle for the 1,2-addition reaction between diborylethane and aldehydes. Initial activation of **1.28** forms a borate complex, **I**, which transmetallates to the copper precatalyst to form α-boryl alkyl copper species **II**. This complex can bind the aldehyde and undergo 1,2-addition to form the copper-bound hydroxyboronate **IV**. After product dissociation as the lithium alkoxide salt, **V** (a structure that helps to prevent olefination through the Boron-Wittig mechanism), and regeneration of the copper catalyst, another equivalent of **I** transmetallates to copper and repeats the cycle. Throughout the course of my studies on these reactions, I conducted a number of experiments that corroborate the mechanism proposed in Figure 1.6: how the *gem*-diboryl reagent is activated, the identity of the copper precatalyst, and the nature of the transmetallation of the *gem*-diboryl reagent/stereoselection of the 1,2-addition.
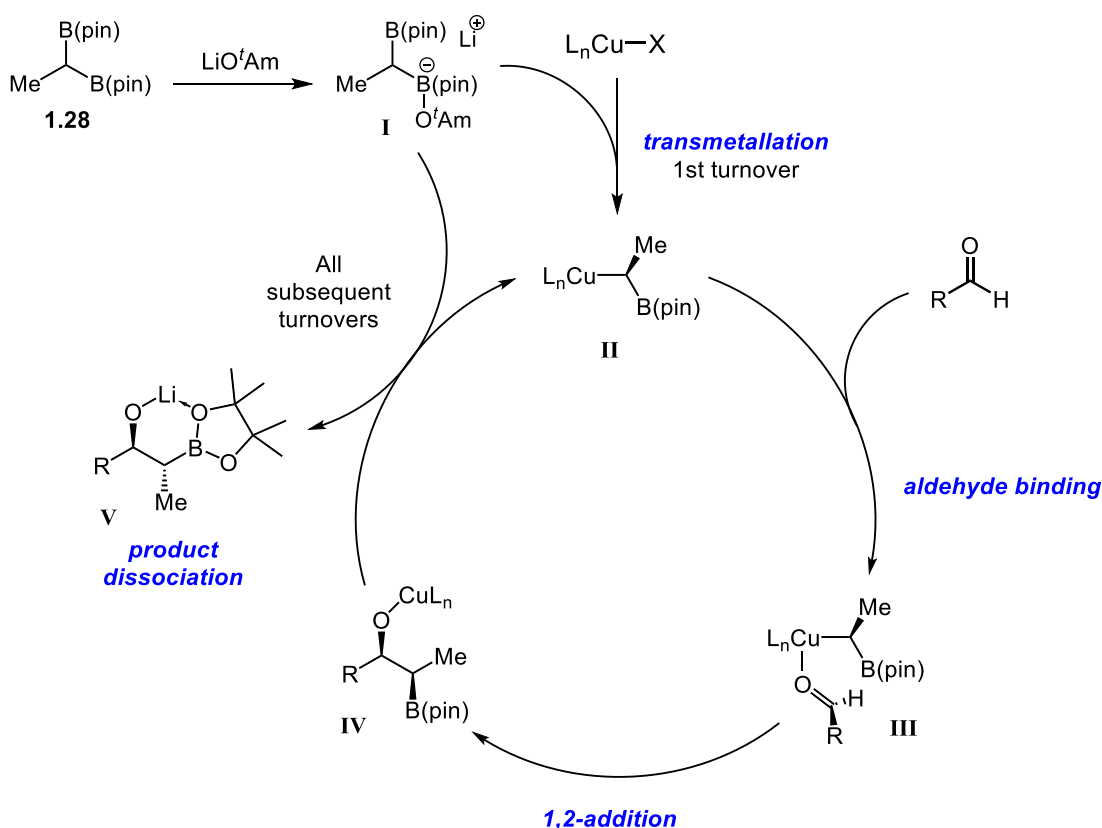
Figure 1.6 Proposed catalytic cycle for the copper-catalyzed addition of diborylethane to aldehydes

26

To gain insight into the activation of diborylethane by lithium alkoxides, I monitored a reaction between diborylethane and lithium *tert*-butoxide by ^{1}H and ^{11}B NMR spectroscopy. As depicted in Figure 1.7, treatment of **1.28** with 1.7 equivalents of lithium *tert*-butoxide in thf-d_8 at ambient temperature results in 21% conversion to the *tert*-butoxy borate **1.70** after 2.5 hours, as judged by ^{1}H and ^{11}B NMR chemical shifts. The most prominent signal is the upfield shift corresponding to the proton *geminal* to the boryl groups, from δ 0.54 for **1.28** to δ 0.06 ppm for **1.70**. This drastic shift is likely due to the increased electron density at the now negatively charged boron, which inductively increases electron density at the neighboring carbon. A new signal in the ^{11}B NMR spectrum also appears at δ 6.9 which corresponds to the four-coordinate borate boron of **1.70**. The signals for the sp^2-hybridized B(pin) groups on **1.70** and **1.28** coalesce to one broad signal at δ 32.3. Morken and co-workers have shown that *gem*-diboronate esters deborylate at room temperature in the presence of sodium *tert*-butoxide to produce boron-stabilized carbanions.[20] Boron-stabilized carbanion **1.71**, however, was not detected by either ^{1}H or ^{11}B NMR spectroscopy during the course of the reaction (even at 50 °C). This demonstrates that the counterion to the borate has a huge effect on its stability and reactivity in solution. Lithium is smaller, more electropositive, and forms stronger bonds to oxygen than sodium. This might lead to lithium chelation between oxygen atoms within **1.70**, which could stabilize the compound and prevent deborylation to **1.71**.

While the NMR experiment illustrated Figure 1.7 is informative, it does not necessarily prove that **1.71** is what transmetallates to the copper catalyst. To explore this processes and delineate what species is actually transmetallating to copper, I conducted two experiments using Cu(O^{t}Am)$_2$ as the copper source for the reaction (Scheme 1.15). In the presence of 20 mol % Cu(O^{t}Am)$_2$ and 40 mol % *(R)*-Monophos without any exogenous base, the reaction of **1.28** and benzaldehyde affords no 1,2-addition product. When the same reaction is run, but in the presence of 90 mol % LiO^{t}Am, the product is afforded in 67% NMR yield, 90:10 d.r., and 92% *ee* (values similar to reactions conducted under the conditions depicted in Table 1.3 and Scheme 1.13). This indicates that external base is required for the reaction to occur, i.e. an activated borate like **1.70** is necessary for transmetallation to copper.

Association of **1.28** to a copper alkoxide complex is not enough to form the copper-carbon bond, likely due to the high copper-oxygen bond strength, which is not nucleophilic enough to add to **1.28** and activate it for transmetallation.
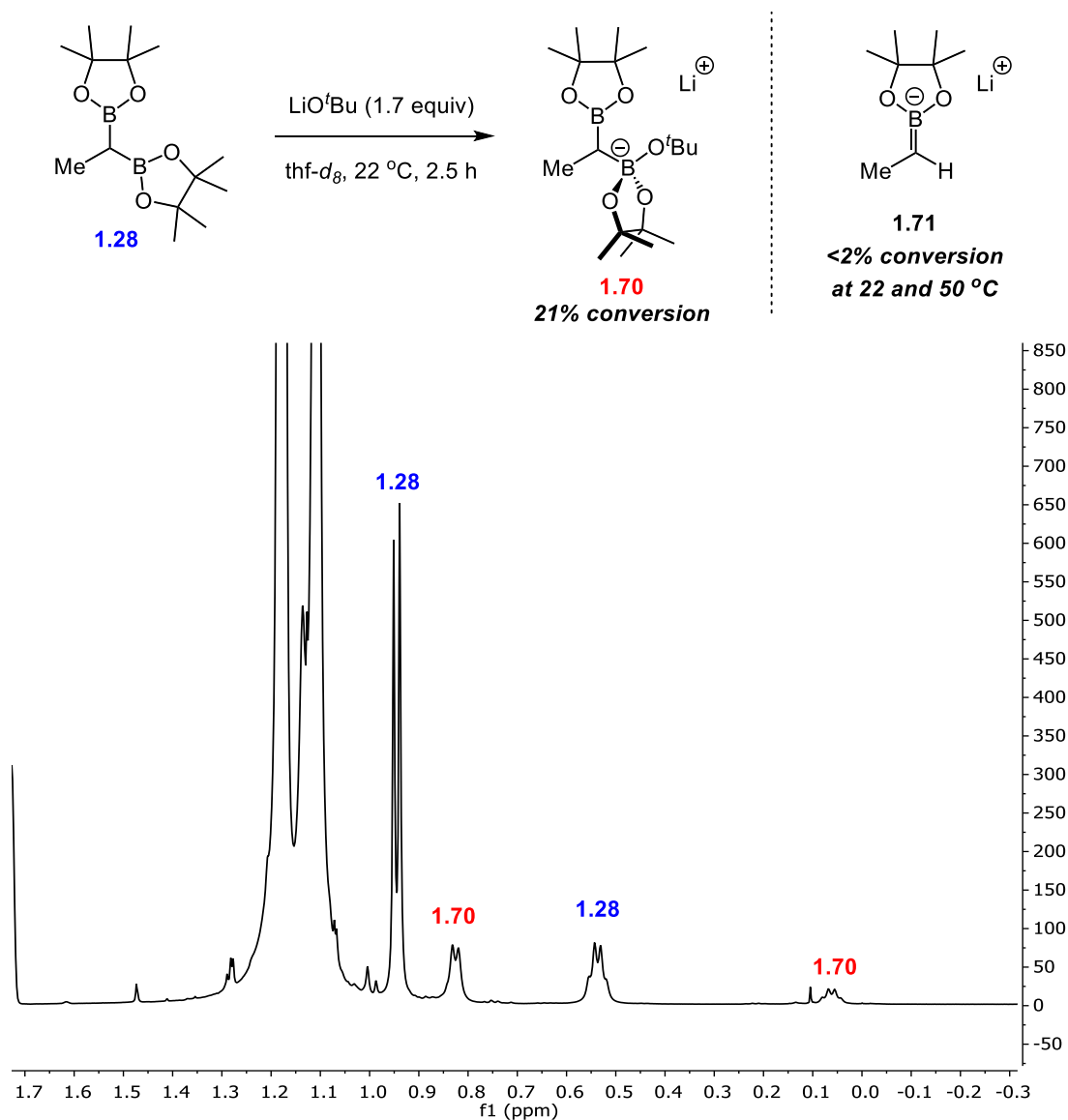
Figure 1.7 Activation of diborylethane with LiO*t*Bu monitored by ^{1}H and ^{11}B NMR spectroscopy. Pictured above is the ^{1}H NMR spectrum of the reaction after 2.5 hours. The ^{11}B NMR spectrum contains two signals: δ 32.3 ppm (*sp²*-hybridized B(pin) groups on **1.28** and **1.70**) and δ 6.9 ppm (borate B(pin) group of **1.70**).

Copper(I) (d^{10} electron count) normally forms 18 electron tetrahedral complexes, unless ligated with strongly σ-donating or sterically encumbered ligands such as N-heterocyclic carbenes or bis-phosphines. Several phosphoramidite-copper(I) complexes are known and have been characterized by X-Ray crystallography and NMR spectroscopy.[30-33] Of these complexes, most are either tetrahedral or trigonal planar, and usually contain two to three phosphoramidite ligands per copper. First, I set out to determine the number of *(R)*-Monophos ligands bound to the copper catalyst vaguely depicted in Figure 1.6. The conditions of Entry 7, Table 1.2 and Entry 1, Table 1.3 differ only in the mol % of *(R)*-Monophos used in the reaction: 11 mol % and 20 mol%, respectively. The diastereo- and enantioselectivities of **1.46** for both reactions are identical (91:9 d.r. and 76% *ee*), but the NMR yield of the 20 mol % *(R)*-Monophos reaction is 65%, while the 11 mol % reaction is only 31%. Since the selectivities are identical for both amounts of *(R)*-Monophos, it indicates that the same catalyst is being generated in both reactions and most likely has one phosphoramidite ligand bound to copper. The differences in yield are likely attributed to more of the copper-*(R)*-Monophos catalyst forming *in situ* when 20 mol % of ligand is used. The extra equivalent of *(R)*-Monophos could also help to prevent catalyst decomposition throughout the reaction by preventing dissociation of the ligand.

Scheme 1.15 Isolation of a catalytically active copper-phosphoramidite-alkoxide complex
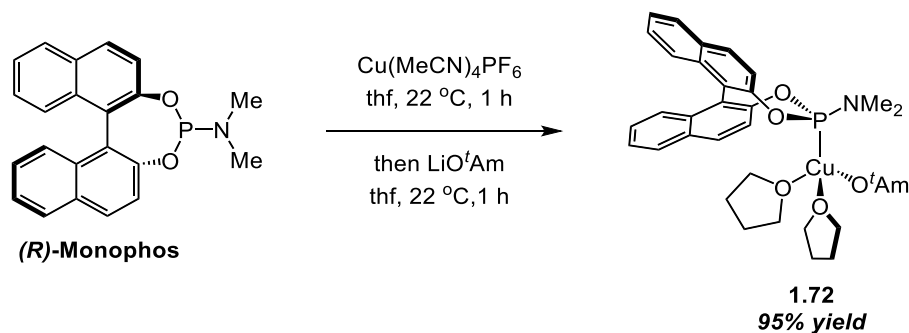
With a 1:1 ratio of copper to ligand being the probable identity of the catalyst, I set out to synthesize the copper-phosphoramidite-alkoxide complex that I generate *in situ* during the reaction. Stirring an equimolar mixture of Cu(MeCN)$_4$PF$_6$ and *(R)*-Monophos together in thf at 22 °C for 1 hour, followed by stirring for an additional hour after addition of one equivalent of LiO^{t}Am affords the copper

complex **1.72** 95% yield. The complex was characterized by ^{1}H and ^{31}P NMR spectroscopy. The ^{31}P NMR spectrum displays a single broad resonance at δ 124.6 ppm and is most likely broadened due to quadrupoloar relaxation of the $^{63/65}$Cu coupling to the ^{31}P nucleus. The ^{1}H NMR spectrum displays resonances that indicate a 1:1 ratio of phosphoramidite:*tert*-amylate ligands bound to copper. Two molecules of thf occupy the other two coordination sites at copper, as the resonances for thf are shifted downfield in reference to the residual proteo-thf in the NMR solvent. Complex **1.72** is catalytically active under the conditions depicted in Scheme 1.13 for the addition of diborylethane to benzaldehyde and **1.46** is formed in 91:9 d.r. and 88% *ee*. It is unknown whether the alkoxide ligand remains on copper after the transmetallation step. While an α-boryl alkyl cuprate complex would be more nucleophilic than a neutral organocopper variant, the negative charge on copper might disfavor aldehyde binding and result in external addition, possibly eroding diastereoselectivity. It is, however, only speculation and I have no evidence to prove either. It is also unknown whether or not the aldehyde is bound to copper during the transmetallation step, however this would explain the small variations in enantioselectivity with different aldehyde substrates (**1.58**: 92% *ee*; **1.62**: 86% *ee*) and other carbonyl electrophiles.[34]

Recalling that in the Cu-*(R)*-Monophos catalyzed addition of diborylethane to alkenyl aldehydes, products are formed with high enantioselectivity but poor diastereoselectivity (cf. Scheme 1.14). I wanted to asses which stereocenter is responsible for the poor diastereoselectivity of the product and to determine which stereocenter is being set by the copper catalyst during the transmetallation step. To address this, we removed the allylic alcohol from 1,2-allylic diol **1.65**, which exists as 52% *syn* diastereomer (90:10 e.r.) and 48% *anti* diastereomer (97:3 e.r.). The diol was reacted with carbodiimidazole to form an allylic carbonate which was then exposed to allylic reduction conditions: 1 mol % Pd$_2$(dba)$_3$, 2 mol % PPh$_3$ with NEt$_3$ and formic acid in thf from 0 to 22 °C. The resulting homoallylic alcohol (which oftentimes was isolated as a mixture with the hydrogenated product) was hydrogenated with Pd/C under an H$_2$ atmosphere in MeOH to produce the secondary alcohol **1.73** in an overall 22% yield. The alcohol was assayed by HPLC and was found to have an

enantiomeric ratio of 92:8, which is an exact average of the two enantioselectivities of the starting

diastereomers. This shows that the stereocenter of alcohol **1.73** corresponds to the secondary boronate

ester stereocenter generated in high enantioselectivity during the 1,2-addition reaction. These data

suggest that an α-boryl alkyl copper nucleophile is being generated in high stereopurity

(transmetallation) through differentiation of the two boron units of prochiral **1.28**. The low

diastereoselectivity observed for less sterically hindered alkenyl aldehydes is likely a result of poor

facial discrimination of the aldehyde by the copper catalyst during the 1,2-addition step.

Scheme 1.16 Allylic reduction of substrate **1.65**: confirmation that the stereocenter derived from the

α-boryl Cu-alkyl nucleophile is enantio-enriched
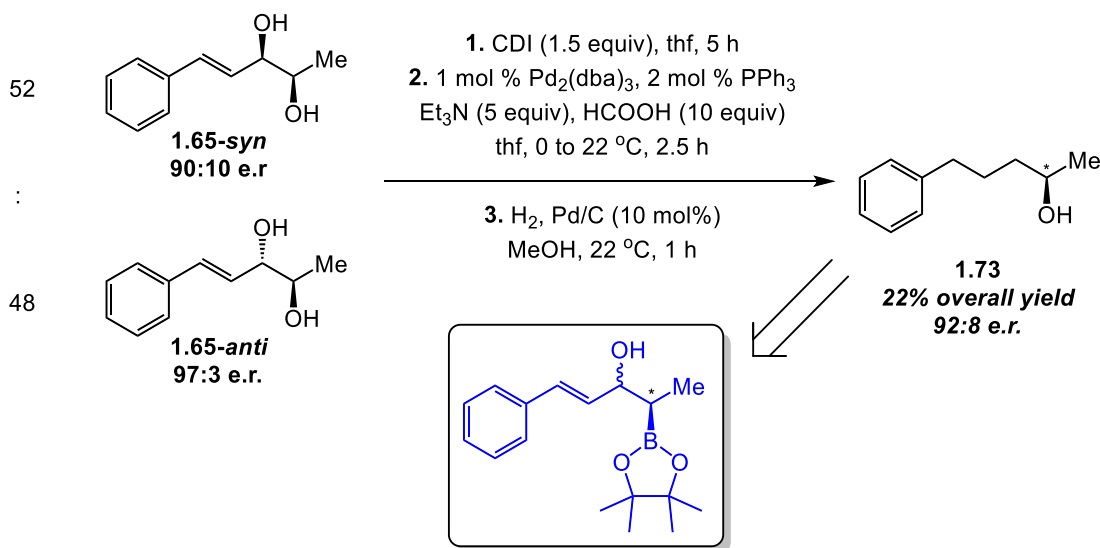
With all the mechanistic data taken together, I have proposed a stereochemical model for how

the 1,2-addition reaction of diborylethane to aldehydes occurs. Initial activation of diborylethane by

LiO^{t}Am generates a mixture of *(R)* and *(S)* borate species. Since only 21% of the borate forms with

LiO^{t}Bu at ambient temperature (cf. Figure 1.7), it is likely a reversible process and the enantiomers can

interconvert through a dissociation/re-association pathway. While both enantiomers of the borate form,

one enantiomer preferentially transmetallates to the copper catalyst over the other to generate the α-

boryl alkyl copper species in high stereopurity. Steric interactions between the α-boryl alkyl ligand

and the binaphthanol ring most likely favor one diastereomer of the catalyst forming over the other (i.e.

(R,R) diastereomer over the *(R,S)*). Since the borate can equilibrate between the *R* and *S* enantiomer through the prochiral *gem*-diboronate ester, the reaction should funnel to forming almost exclusively the *(R,R)* diastereomer of the catalyst. Binding of the aldehyde determines the diastereoselectivity of the reaction. Steric interactions between the substituent on the aldehyde and the catalyst determines how the aldehyde binds to the catalyst and whether the addition occurs at the *re* or *si* face. This interaction explains the decreases in diastereoselectivity observed for alkenyl aldehydes and smaller heteroaryl aldehydes: the R substituents on the aldehyde are not large enough for the catalyst to facial discriminate and present only one face of the aldehyde to the nucleophile, leading to lower diastereoselectivities.
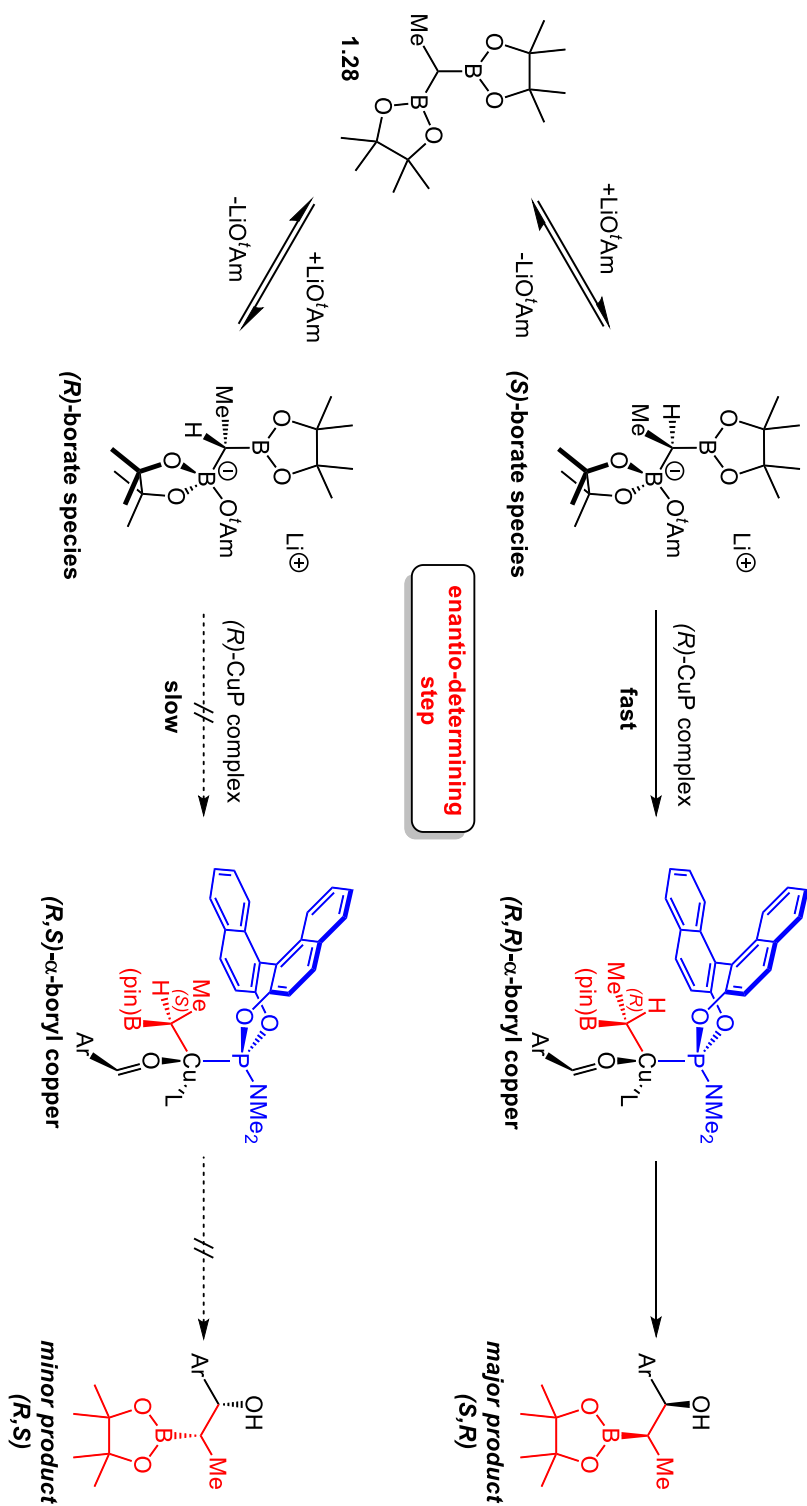
Figure 1.8 Proposed stereochemical model for the copper-catalyzed addition of diborylethane to aldehydes: catalyst-controlled enantioselective transmetallation, followed by catalyst-controlled diastereoselective addition. L = thf, ArCHO, O^{t}Am.

The 1,2-hydroxyboronate products formed in this study are amenable to transformations into useful synthetic building blocks through functionalization of the organoboron moiety. Oxidations and carbon-carbon bond formations are tolerated after protection of the hydroxyl group (Scheme 1.18). TBS-protection of **1.46** with TBSCl and imidazole furnishes the TBS-protected-1,2-hydroxyboronate **1.74** (in 76% yield), which is then homologated by one carbon with *in situ* generated bromomethyllithium at -78 °C for 2 hours. The TBS-protected 1,3-hydroxyboronate ester **1.75** is afforded in 75% yield and 91:9 diastereoselectivity. Similarly, TBS-protection of the 1,2-hydroxyboronate generated from addition to α-Me-cinnamaldehyde with TBSCl and imidazole affords **1.76** in 64% yield. Amination of **1.76** in the presence of *n*-BuLi and MeONH$_2$ produces the aminoalcohol **1.77** in 57% yield and >98:2 d.r. after quenching with di-*tert*-butyl dicarbonate.

Scheme 1.17 Functionalizations of the C-B *sp^3* bonds of the 1,2-hydroxyboronate products: one

carbon homologation and amination
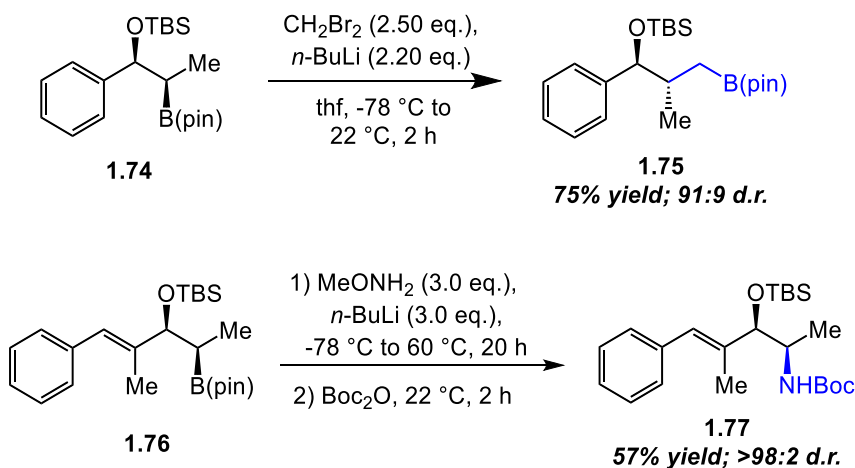
A limitation of this methodology lies in the scope of the *gem*-diboronate ester that react effectively with aldehydes under the reaction conditions. While diborylethane is effective in the transformation, adding any substituents to the β-position of the *gem*-diboronate ester reduces the reactivity drastically. For instance, under standard reaction conditions for the addition of diborylethane to benzaldehyde (10 mol % Cu(MeCN)$_4$PF$_6$, 20 mol % *(R)*-Monophos, 90 mol % LiO^{t}Am at 45 °C in thf) *gem*-diboronate ester **1.29** adds to benzaldehyde to form 1,2-hydroxyboronate **1.77** in only 30%

NMR yield but in high diastereo- and enantioselectivity (92:8 d.r.; 90% *ee*). The use of other substituted *gem*-diboronate esters lead to even lower yields, most not even forming product. For example, 1,2-hydroxyboronate **1.78** is not observed from the addition of **1.32** and benzaldehyde, while hydroxyboronate **1.79** is produced in <10% NMR yield and 95:5 d.r. (from the addition of **1.30** and benzaldehyde). While these more highly substituted reagents cannot react with aldehydes, recent data collected by other lab members suggests that these larger boron reagents do indeed transmetallate to the copper catalyst, but they simply do not add to aldehydes effectively and require more electrophilic carbonyl substrates to add to (e.g. α-ketoesters and CF$_3$-ketones).

Scheme 1.18 Additions of higher substituted *gem*-diborylalkanes to benzaldehyde: limitations to larger substituents
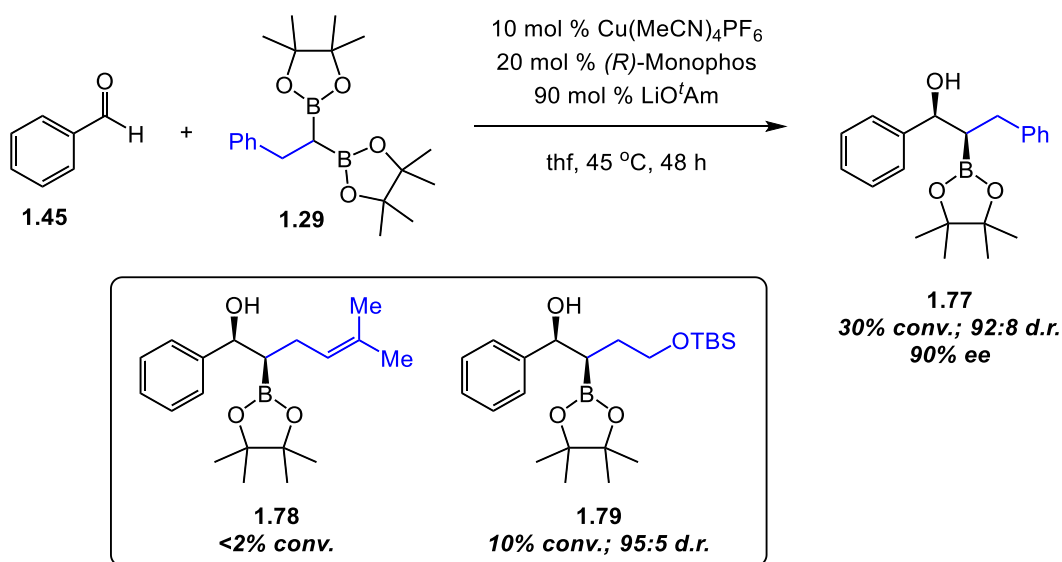
1.6 Conclusions

I have developed a highly enantio- and diastereoselective method for the addition of *gem*-diboronate esters to aryl and alkenyl aldehydes. The reaction is catalyzed by a copper-phosphoramidite catalyst in the presence of LiO^{t}Am as an activator of the boron reagent. The reaction is tolerant of a number of substitution patterns on the arene of aryl aldehydes and products are formed in up to 91% yield, >99:1 d.r., and 92% *ee*. Alkenyl aldehydes can also be used, but are formed in slightly reduced

yields and diastereoselectivities: up to 59% yield, 97:3 d.r., and 94% *ee* (for the major diastereomer). Mechanistic studies suggest that an α-boryl alkyl copper species is generated *via* stereoselective transmetallation of alkoxide-activated diborylethane. This copper alkyl species then adds to aldehydes in a diastereoselective fashion, where the facial selectivity is dictated by the steric interactions of the aldehyde and the catalyst. The hydroxyboronates generated in this methodology are also amenable to functionalization reactions of the organoboron group and can be oxidized to alcohols and amines, and homologated by one methylene unit. This reaction manifold is currently limited to only diborylethane, as other more highly substituted *gem*-diboronate esters are formed in reduced yields, but high diastereo- and enantioselectivity (up to 30% NMR yield, 95:5 d.r., and 90% *ee*).

1.7   Experimental

■   **General:** All reactions were carried out in oven-dried (150 ˚C) or flame-dried glassware under an inert atmosphere of dried N_2 unless otherwise noted. Analytical thin-layer chromatography was performed on glass plates coated with 0.25 mm of 60 Å mesh silica gel. Plates were visualized by exposure to UV light (254 nm) and/or immersion into Seebach's or $KMnO_4$ stain followed by heating. Column chromatography was performed using silica gel P60 (mesh 230-400) supplied by Silicycle. All solvents were sparged with argon and then purified under a positive pressure of argon through an SG Water, USA Solvent Purification System. Tetrahydrofuran (OmniSolv) was passed successively through two columns of neutral alumina. 1,4-dioxane was distilled from Na/benzophenone, sparged with N_2 and stored over 4Å molecular sieves. The ambient temperature in the laboratory was approximately 22 ˚C.

■   **Instrumentation:** All ^1H NMR spectra were recorded on Bruker Spectrometers (AVANCE-600 and AVANCE-400). Chemical shifts are reported in ppm from tetramethylsilane and referenced to the residual protio solvent peak ($CDCl_3$: δ 7.26). Data are reported as follows: chemical shift, multiplicity

(s = singlet, d = doublet, t = triplet, qu = quartet, quint = quinttet, br = broad, m = multiplet, app = apparent), integration, and coupling constants are given in Hz. ^{13}C NMR spectra were recorded on Bruker Spectrometers (AVANCE-600 and AVANCE-400) with carbon and proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane and referenced to the residual protio solvent peak ($CDCl_3$: δ 77.16). All IR Spectra were recorded on a Jasco 260 Plus Fourier transform infrared spectrometer. Mass Spectrometry was performed on a Thermo Scientific LTQ-FT-ICR Mass Spectrometer. Optical rotations were determined using a Jasco P1010 polarimeter and concentrations are reported in g/100mL. Enantiomeric ratios were determined on an Agilent Technologies 1220 Infinity LC using the following columns: Diacel CHIRALPAK IA (4.6 mm x 250 mmL x 5 μm), Diacel CHIRALPAK IB (4.6 mm x 250 mmL x 5 μm), and Diacel CHIRALPAK IC (4.6 mm x 250 mmL x 5 μm). Enantiomeric ratios for compound **18** were determined on a Berger Instruments Supercritical Fluid Chromatograph using a Regis RegisPack Column (25 cm x 4.6 mm x 5 μm).

■ **Reagents:** All liquid aldehydes were distilled from CaH_2 under vacuum and then sparged with dry N_2. Solid aldehydes were purified *via* recrystallization, followed by azeotropic drying with benzene. *(R)*-Me-Monophos **(L2)**, *(R)*-Et-Monophos **(L3)**, and *(R)*-MorphPhos **(L4)** and **L5** were synthesized according to published literature procedures.[35,36] *(R)*-binap, *(R)*-dtbm segphos, and *(R,R)*-josiphos **(L1)** were purchased from Strem Chemicals and stored in an N_2 filled glovebox. Copper(II) methoxide, copper(I) chloride, copper(II) triflate, were purchased from Strem Chemicals and kept in a N_2 filled glove box. Copper(I) tetrakisacetonitrile hexafluorophosphate was purchased from Sigma-Aldrich and kept in an N_2-filled glovebox.

4-Anisaldehyde was purchased from Alfa-Aesar, vacuum distilled from CaH_2, and then sparged with dry N_2

Benzaldehyde was purchased from Alfa-Aesar, vacuum distilled from CaH_2, and then sparged with dry N_2

Benzene-d_6 was purchased from Cambridge Isotope Laboratories and distilled over Na/benzophenone, sparged with dry N_2, and kept in an N_2-filled glove box over 3Å molecular sieves

4-Bromobenzaldehyde was purchased from Alfa-Aesar, recrystallized from methanol, and then azeotropically dried with benzene three times prior to use

Dibromomethane was purchased from Alfa Aesar and passed through a short column of neutral alumina and then sparged with dry N_2 before use

Calcium hydride was purchased from Strem and used without further purification

Calcium sulfate was purchased from Fisher and used without further purification

Chloroform-d_3 was purchased from Cambridge Isotope Laboratories and used without further purification

1-Cyclohexene-1-carboxyaldehyde was purchased from Alfa-Aesar, vacuum distilled from CaH_2, and then sparged with dry N_2

4-Fluorobenzaldehyde was purchased from Alfa-Aesar, vacuum distilled from CaH_2, and then sparged with dry N_2

2-Furylaldehyde was purchased from Acros Organics, vacuum distilled from CaH_2, and then sparged with dry N_2 and kept in an amber vial

Iodomethane was purchased from Alfa-Aesar, and passed through a short column of neutral alumina and purged with dry N_2 prior to use

Imidazole was purchased from Alfa-Aesar and used as received

Lithium *tert*-butoxide were purchased from Strem and used as received

Methoxyamine was prepared according to literature procedures as a solution in tetrahydrofuran[13a]

n-Butyllithium was purchased from Strem as a 1.6M solution in hexanes and titrated with 1,10-phenanthroline/*sec*-butanol before use

Nicotinaldehyde was purchased from Alfa-Aesar, vacuum distilled from CaH_2, and then sparged with dry N_2

3-Nitrobenzaldehyde was purchased from Alfa-Aesar, and azeotropically dried with benzene prior to use

4-Nitrobenzaldehyde was purchased from Alfa-Aesar, and azeotropically dried with benzene prior to use

Potassium *tert*-butoxide was purchased from Strem and used as received

Sodium perborate tetrahydrate was purchased from Sigma Aldrich and used as received

Sodium *tert*-butoxide was purchased from Strem and used as received

***tert*-Amyl alcohol** was purchased from Alfa Aesar, refluxed over CaH_2, distilled onto 4Å molecular sieves, and then sparged with dry N_2

***tert*-butyldimethylsilyl chloride** was purchased from Sigma-Aldrich and used as received

2-Tolualdehyde was purchased from Alfa-Aesar, vacuum distilled from CaH_2, and then sparged with dry N_2

3-Tolualdehyde was purchased from Alfa-Aesar, vacuum distilled from CaH_2, and then sparged with dry N_2

***trans*-Cinnamaldehyde** was purchased from Alfa-Aesar, vacuum distilled from CaH_2, and then sparged with dry N_2

***trans*-2-Methoxycinnamaldehyde** was purchased from Alfa-Aesar, and azeotropically dried with benzene prior to use

***trans*-4-Chlorocinnamaldehyde** was purchased from Alfa-Aesar, and azeotropically dried with benzene prior to use

***trans*-4-Nitrocinnamaldehyde** was purchased from Alfa-Aesar and azeotropically dried with benzene prior to use

***trans*-α-Methylcinnamaldehyde** was purchased from Alfa-Aesar, vacuum distilled from CaH_2, and then sparged with dry N_2

■ **Synthesis of Lithium *tert*-amylate**
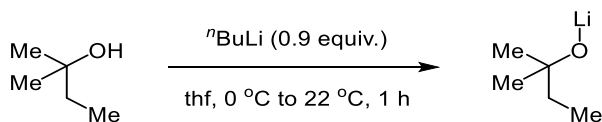
Procedure: A flame-dried round-bottom flask equipped with a magnetic stir bar was charged with anhydrous *tert*-amyl alcohol (8.7 mL, 79 mmol) and 20 mL of anhydrous thf. The reaction was allowed to cool to 0 ˚C (ice/water bath) and n-BuLi (44.6 mL of a 1.62 M solution in hexanes, 72.2 mmol) was added drop-wise. After the addition, the reaction was allowed to stir at 0 ˚C for 10 minutes and then allowed to warm up to ambient temperature with stirring for 1 h. The solvent was removed under a positive pressure of N_2 and the residue dried under vacuum. The flask was brought into an N_2-filled glove box where the residue was taken up in hexanes and filtered twice through Celite®. Concentration of the filtrate produced a fluffy, white powder in 97% yield (6.6 g). **^{1}H NMR** (C_6D_6, 400 MHz): δ 1.50 (qu, 2H, J = 7.5 Hz), 1.23 (s, 6H), 0.98 (tr, 3H, J = 5.8 Hz). **^{13}C NMR** (C_6D_6, 120 MHz): δ 68.9, 41.1, 32.1, 10.5.

■ Synthesis of Diborylmethane
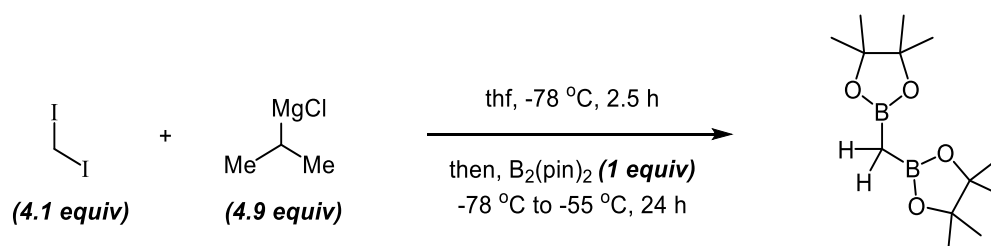
Procedure: An oven-dried 2-liter, 3-necked flask with a magnetic stir bar was fitted with an addition funnel and then allowed to cool under vacuum. After back-filling the apparatus with N_2 and evacuating it two more times, the entire apparatus was purged out with N_2 for 20 mintues. Anhydrous thf (552 mL) was added via syringe, followed by diiodomethane (15.6 mL, 193 mmol). The flask was allowed to cool to -78 ˚C (dry-ice/acetone bath) and the addition funnel was charged with iPr-MgCl (93.8 mL, 1.72 M solution in thf). The Grignard was then added to the reaction over 20 minutes (care was taken NOT to allow the Grignard solution to drip down the side of the flask). After the addition, the addition funnel was washed with 5 mL of anhydrous thf and added to the reaction. After allowing the reaction to stir at -78 ˚C for 2.5 hours (a white suspension formed), a 0.197 M solution of bis(pinacolato)diboron (10.0 g, 39.4 mmol) in thf was transferred *via* canulla to the reaction at -78 ˚C. After an additional 30 minutes of stirring, the flask was transferred to a cryobath set to -55 ˚C and the reaction was allowed to stir for 24 h. The reaction was quenched at -55 ˚C with ~200 mL of a saturated aqueous solution of NH_4Cl. After allowing the mixture to warm to ambient temperature, the biphasic mixture was extracted three times with diethyl ether (1.5 L total) and the combined organic extracts were dried over $MgSO_4$, filtered, and then concentrated *in vacuo*. The resulting orange residue was taken up in 50 mL of diethyl ether and filtered again and concentrated *in vacuo*. The crude mixture was purified by silica gel chromatography (20:1 hexanes:ethyl acetate) to afford the desired product in 80% yield (8.0 g). The spectral data of the diboronate ester matched those previously reported.[20]

■ **Synthesis of Diborylethane (1.28)**
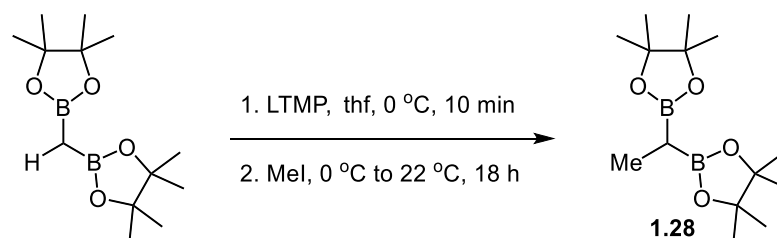
Procedure: In an N_2-filled glove box, an oven-dried round-bottom flask was charged with diboryl methane (3.00 g, 11.2 mmol) and a magnetic stir-bar, capped with a rubber septum, and sealed with electrical tape. A separate oven-dried, conical flask was charged with lithium 2,2,6,6-tetramethylpiperidide (1.73 mg, 11.8 mmol), capped with a rubber septum, and sealed with electrical tape. The two flasks were brought out of the glove box, where the diboryl methane flask was charged with 47.0 mL of dry thf and the LiTMP-containing flask was charged with 93.0 mL of thf (0.17M total). Both flasks were allowed to cool to 0 ˚C (ice/water-baths). The LiTMP solution was then cannula transferred to the diboryl methane flask with stirring. After the transfer, the reaction was allowed to stir for 10 min at 0 ˚C. Iodomethane (1.74 mL, 28.0 mmol) was then added to the reaction via a syringe and allowed to warm up to 22 ˚C over 18 hours with stirring. The reaction was quenched with 50 mL of a saturated aqueous solution of NH_4Cl. The biphasic mixture was extracted 3 times with diethyl ether (900 mL total), and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude reaction mixture was purified by silica gel column chromatography (20:1 hexanes:EtOAc; R_f=0.20) to give the desired diboryl reagent in 89% yield (2.8 g). The spectral data of the diboronate ester matched those previously reported.[37]

■ **General Procedures for Cu-Catalyzed 1,2-Addition Reaction:**
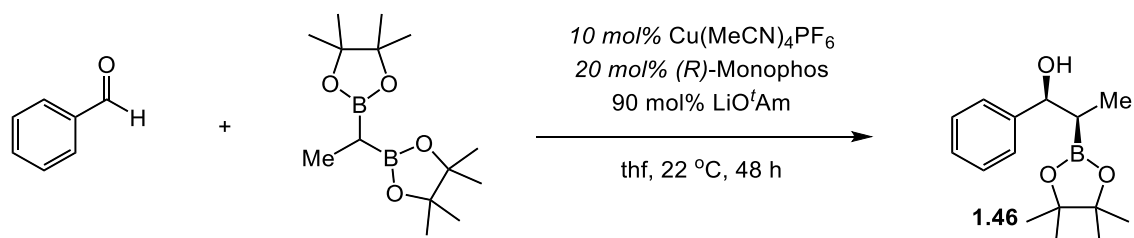
Procedure A (aryl aldehydes): In an N_2-filled glove box, an 8-mL vial equipped with a magnetic stir bar was charged with Cu(MeCN)$_4$PF$_6$ (3.7 mg, 0.010 mmol) and *(R)*-Monophos (7.2 mg, 0.020 mmol) and dissolved in 0.50 mL of thf. After allowing the reaction to stir for 5 min, LiO^{t}Am (0.90 mg, 0.010 mmol) was added to the reaction as a solution in thf (0.10 mL). After an additional 15 min of stirring, diboryl ethane (56 mg, 0.20 mmol) was added to the vial via syringe, followed by LiO^{t}Am (7.5 mg, 0.080 mmol) as a solution in thf (0.20 mL). The resulting solution was allowed to stir at ambient temperature for 5 minutes, after which time the aldehyde (0.10 mmol) was added to the reaction. The vial was capped, sealed, and then removed from the glove box and allowed to stir at ambient temperature for 48 hours. The reaction was quenched with 1.5 mL of a saturated aqueous solution of NH$_4$Cl, and the aqueous layer extracted three times with diethyl ether. The combined organic extracts were dried over MgSO$_4$, filtered, and concentrated *in vacuo*. Conversion and diastereomeric ratios were determined by ^{1}H NMR using hexamethyldisiloxane as an internal standard.
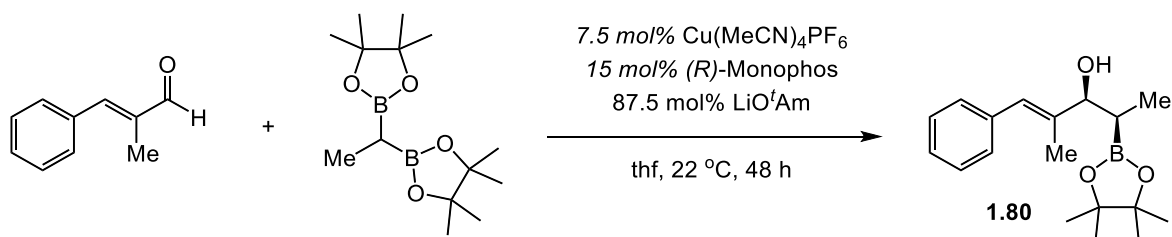
Procedure B (α-substituted vinyl aldehydes): In an N_2-filled glove box, an 8-mL vial equipped with a magnetic stir bar was charged with Cu(MeCN)$_4$PF$_6$ (2.8 mg, 7.5 μmol), *(R)*-Monophos (5.4 mg, 0.015

mmol) and LiO^{t}Am (0.7 mg, 7.5 μmol). The reaction was then dissolved in 0.56 mL of thf and allowed

to stir at ambient temperature for 30 min. Diboryl ethane (71 mg, 0.25 mmol) was added to the vial via

syringe, and this entire solution was added to a solution of LiO^{t}Am (7.5 mg, 0.080 mmol) in thf (0.27

mL). The resulting solution was allowed to stir at ambient temperature for 5 minutes, after which time

the aldehyde (0.10 mmol) was added to the reaction. The vial was capped and then removed from the

glove box and allowed to stir at 22 °C for 48 h. The reaction was quenched with 1.0 mL of a saturated

aqueous solution of NH$_4$Cl and the aqueous layer was extracted three times with diethyl ether. The

combined organic extracts were dried over MgSO$_4$, filtered, and concentrated *in vacuo*. Conversion

and diastereomeric ratios were determined by ^{1}H NMR using hexamethyldisiloxane as an internal

standard.
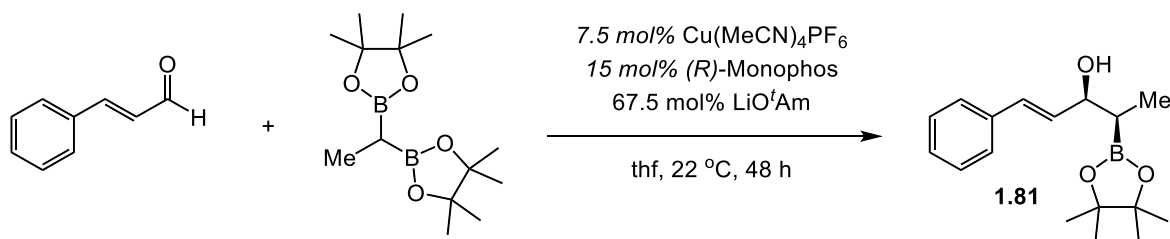
Procedure C (vinyl aldehydes): In an N$_2$-filled glove box, an 8-mL vial equipped with a magnetic stir

bar was charged with Cu(MeCN)$_4$PF$_6$ (2.8 mg, 7.5 μmol), *(R)*-Monophos (5.4 mg, 0.015 mmol) and

LiO^{t}Am (0.7 mg, 7.5 μmol). The reaction was then dissolved in 0.56 mL of thf and allowed to stir at

ambient temperature for 30 min. Diboryl ethane (141 mg, 0.50 mmol) was added to the vial via syringe,

and this entire solution was added to a solution of LiO^{t}Am (5.6 mg, 0.060 mmol) in thf (0.27 mL). The

resulting solution was allowed to stir at ambient temperature for 5 minutes, after which time the

aldehyde (0.10 mmol) was added to the reaction. The vial was capped and then removed from the glove

box and allowed to stir at 22 °C for 48 h. The reaction was quenched with 1.0 mL of a saturated aqueous

solution of NH$_4$Cl and the aqueous layer was extracted three times with diethyl ether. The combined

organic extracts were dried over MgSO$_4$, filtered, and concentrated *in vacuo*. Conversion and diastereomeric ratios were determined by ^{1}H NMR using hexamethyldisiloxane as an internal standard.

For the case of ***aryl* hydroxyboronates**, the crude reaction mixtures were oxidized to the corresponding diols using the following procedure:

The crude reaction mixture was dissolved in a 1:1 mixture of thf and H$_2$O and charged with NaBO$_3$·4H$_2$O (5 equivalents). The resulting heterogeneous mixture was allowed to stir vigorously at ambient temperature for 2.5 hours and then quenched by the addition of a saturated aqueous solution of NH$_4$Cl. The aqueous layer was extracted three times with diethyl ether and the combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Pinacol was removed by dissolving the crude oxidation mixture in 1:1 methanol:water, followed by concentration *in vacuo* on a rotary evaporator with the water bath set between 55-60 ˚C. The procedure was repeated until no pinacol was detected by TLC (usually 2-3 cycles). Purification by silica gel chromatography yielded the diol.

For the case of **α-substituted *vinyl* hydroxyboronates**, the crude reaction mixtures were oxidized to the corresponding diols using the following procedure:

The crude reaction mixture was dissolved in 1 mL of thf and then allowed to cool to 0 ˚C (ice/water bath). 400 μL of a 3 M NaOH (8 equivalents) solution was then added to the reaction, followed by 200 μL of a 30% H$_2$O$_2$ solution (12 equivalents). The reaction was allowed to warm up to ambient temperature over 4 hours. The reaction was then quenched at 0 ˚C with 1 mL of a 1M solution of Na$_2$S$_2$O$_3$. The aqueous layer was extracted three times with ethyl acetate and the combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Pinacol was removed

by dissolving the crude oxidation mixture in 1:1 methanol:water, followed by concentration *in vacuo* on a rotary evaporator with the water bath set between 55-60 ˚C. The procedure was repeated until no pinacol was detected by TLC (usually 2-3 cycles). Purification by silica gel chromatography yielded the diol. For the case of ***vinyl hydroxyboronates*** the exact procedure above was followed, except 800 μL of 3 M NaOH and 400 μL H_2O_2 were used instead.

1.53
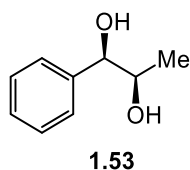
1-phenylpropane-1,2-diol (1.53). Following Procedure A, the crude oxidation mixture was purified by silica gel chromatography (1:1 hexanes:ethyl acetate) to yield diol **1.53** as a colorless oil in 67% yield (10.2 mg) and 92:8 d.r (syn:anti). The spectral data of the diol matched those previously reported.[38] $[\alpha]^{22}_D$ = +42.1˚ (c = 0.458, CH_2Cl_2, l = 100 mm).

Enantiomeric excess was determined by HPLC analysis compared to the authentic racemic material. Absolute stereochemistry was determined by the $[\alpha]_D$ value compared to those previously reported.[39,40]

Diacel CHIRALPAK IA Column; 99:1 hexanes:iPrOH; 1.0 mL/min; 210 nm

Racemic Material

File Information			#	Time	Area	Height	Width	Area%	Symmetry
LC-File	MVJ-V-261 D FL.D		1	28.921	17773.5	481.7	0.5625	24.890	0.803
File Path	C:\CHEM32\1\DATA\JOANNOU\		2	33.52	16189.8	398	0.6136	22.672	0.779
Date	06-Mar-15, 19:22:26		3	34.488	19387.9	405.7	0.7095	27.151	0.768
Sample	MVJ-V-261 D FL		4	36.595	18057.5	386.9	0.7125	25.288	0.862

Syn-diastereomer: (1*S,2S*) enantiomer: 32.8 min; (1*R,2R*) enantiomer 41.2 min: 94:6 e.r.

1.54
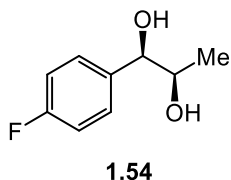
1-(4-fluorophenyl)propane-1,2-diol (1.54). Following Procedure A, the crude oxidation mixture was purified by silica gel chromatography (1:1 hexanes:ethyl acetate) to yield diol 1.**54** as a colorless oil in 77% yield (13.0 mg) and 92:8 d.r (syn:anti). ***Syn* diastereomer: ^{1}H NMR** (CDCl$_3$, 400 MHz): δ 7.36-7.31 (m, 2H), 7.08-7.03 (m, 2H), 4.37 (d, 1H, $J = 7.6$ Hz), 3.83 (quintt, 1H, $J = 6.6$ Hz), 2.73 (br s, 2H), 1.06 (d, 3H, $J = 6.4$ Hz). ^{13}**C NMR** (CDCl$_3$, 101 MHz): δ 136.8, 128.7, 128.6, 115.6, 115.4, 79.0, 72.4, 18.9. ***Anti* diastereomer**: ^{1}**H NMR** (CDCl$_3$, 400 MHz) δ 7.36-7.31 (m, 2H), 7.08-7.03 (m, 2H), 4.68 (d, 1H, $J = 4.2$ Hz), 4.01 (quintt, 1H, $J = 1.9$ Hz), 1.93 (br s, 1H), 1.64 (br s, 1H), 1.07 (d, 3H, $J = 6.3$ Hz). ^{13}**C NMR** (CDCl$_3$, 101 MHz): δ 136.8, 128.5, 128.4, 115.5, 115.2, 78.96, 72.4, 17.4. **HRMS (ESI$^+$)** calcd for C$_9$H$_{11}$O$_2$FNa$^+$ 193.0641, found: 193.0635 [M+Na]. **IR (v/cm^{-1}):** 3399 (br, s), 2980 (s), 1605 (m), 1510 (m), 1455 (m), 1373 (w), 1223 (m), 1157 (w). **[α]^{22}$_D$** = +22.4 ° ($c = 0.352$, CH$_2$Cl$_2$, l = 100 mm).

Enantiomeric excess was determined by HPLC analysis compared to the authentic racemic material.

Absolute stereochemistry was inferred from the stereochemistry obtained for compound **4**.

Diacel CHIRALPAK IC Column; 99:1 hexanes:iPrOH; 1.0 mL/min; 210 nm

Racemic Material

File Information		#	Time	Area	Height	Width	Area%	Symmetry
LC-File	MVJ-V-261 A FL_5.D	1	58.768	20990.8	294.2	1.1891	25.416	0.767
File Path	C:\CHEM32\1\DATA\JOANNOU\	2	61.319	21375.2	279.7	1.2739	25.882	0.712
Date	17-Mar-15, 10:51:34	3	71.667	20084.8	228.8	1.4629	24.319	0.752
Sample	MVJ-V-261 A FL_5	4	76.084	20137.8	214.4	1.5655	24.383	0.728

Enantio-enriched Material

File Information		#	Time	Area	Height	Width	Area%	Symmetry
LC-File	MVJ-V-231 A FL_2.D	1	87.38	90569.6	810.5	1.7316	94.048	0.523
File Path	C:\CHEM32\1\DATA\JOANNOU\	2	93.961	5731.5	47.7	1.759	5.952	0.808

Syn-diastereomer: (1*R*,2*R*) enantiomer: 87.3 min; (1*S*,2*S*) enantiomer 93.9 min: 94:6 e.r.
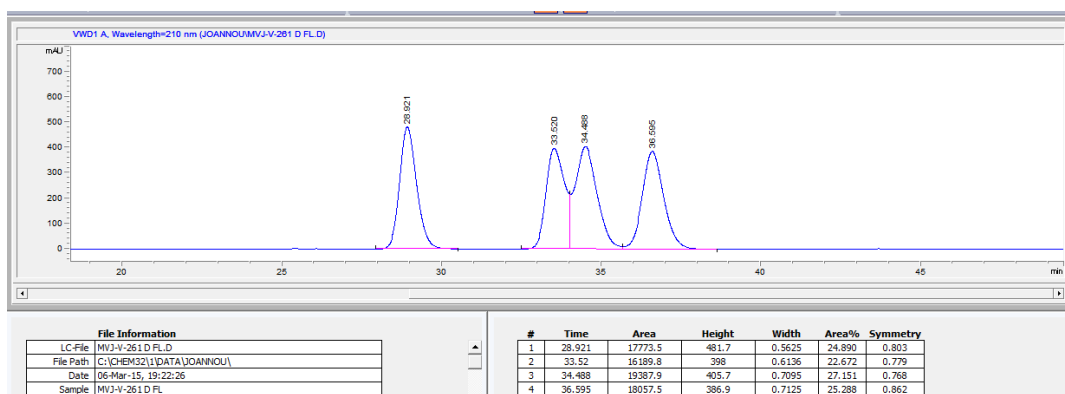
1.55

1-(4-bromophenyl)propane-1,2-diol (1.55). Following Procedure A, the crude oxidation mixture was purified by silica gel chromatography (1:1 hexanes:ethyl acetate) to yield diol **1.55** as a colorless oil in 91% yield (21.0 mg) and 93:7 d.r (syn:anti). *Syn* **diastereomer: ^{1}H NMR** (CDCl$_3$, 400 MHz): δ 7.51 – 7.44 (m, 1H), 7.25 – 7.18 (m, 1H), 4.33 (d, 1H, J = 7.3 Hz), 3.79 (quintt, 1H, J = 6.5 Hz), 2.91 (br s, 1H), 2.56 (br s, 1H), 1.05 (d, 3H, J = 6.2 Hz). ^{13}**C NMR** (CDCl$_3$, 101 MHz): δ 140.2, 131.7, 128.7, 122.1, 78.9, 75.2, 18.9. *Anti* **diastereomer: ^{1}H NMR** (CDCl$_3$, 400 MHz): δ 7.51 – 7.44 (m, 2H), 7.25 – 7.18 (m, 2H), 4.65 (d, 1H, J = 4.1 Hz), 3.98 (dd, 1H, J = 6.6, 4.4 Hz), 2.64 (br s, 1H), 1.71 (br s, 1H), 1.03 (d, 3H, J = 6.0 Hz). ^{13}**C NMR** (CDCl$_3$, 101 MHz): δ 140.2, 131.5, 128.7, 128.5, 122.1, 78.9, 71.2, 17.2. **HRMS (ESI$^+$)** calcd for C$_9$H$_{11}$O$_2$BrNa$^+$ 252.9840, found: 252.9835 [M+Na]. **IR (v/cm^{-1}):** 3391 (br, s), 2979 (s), 1488 (s), 1373 (m), 1138 (m). **[α]$^{22}_D$** = +64.3 ˚ (c = 0.457, CH$_2$Cl$_2$, l = 100 mm).
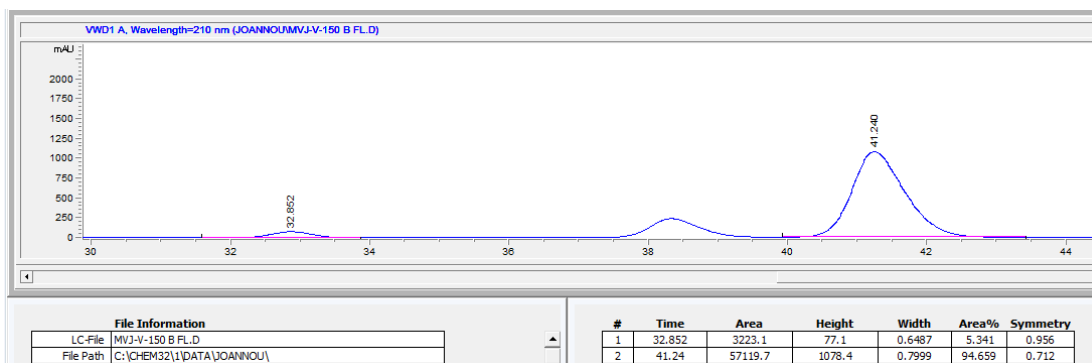
Enantiomeric excess was determined by HPLC analysis compared to the authentic racemic material. Absolute stereochemistry was inferred from the stereochemistry obtained for compound **4**.

Diacel CHIRALPAK IC Column; 99:1 hexanes:iPrOH; 1.0 mL/min; 210 nm

Racemic Material

File Information		#	Time	Area	Height	Width	Area%	Symmetry
LC-File	MVJ-V-261 B FL_3.D	1	37.278	25710.8	519.1	0.7719	25.110	0.814
File Path	C:\CHEM32\1\DATA\JOANNOU\	2	40.212	25690.5	467.9	0.8516	25.090	0.722
Date	09-Mar-15, 13:56:59	3	45.361	25373	416.8	0.9393	24.780	0.705
Sample	MVJ-V-261 B FL_3	4	48.127	25619.4	391	1.0094	25.020	0.711

Enantio-enriched Material

VWD1 A, Wavelength=210 nm (JOANNOU\MVJ-V-231 B FL_2.D)

File Information			#	Time	Area	Height	Width	Area%	Symmetry
LC-File	MVJ-V-231 B FL_2.D		1	45.816	125575.8	1910.2	1.013	94.547	0.508
File Path	C:\CHEM32\1\DATA\JOANNOU\		2	49.022	7242.7	106.2	1.0476	5.453	0.806

Syn-diastereomer: (1*R*,2*R*) enantiomer: 45.8 min; (1*S*,2*S*) enantiomer 49.0 min: 95:5 e.r.
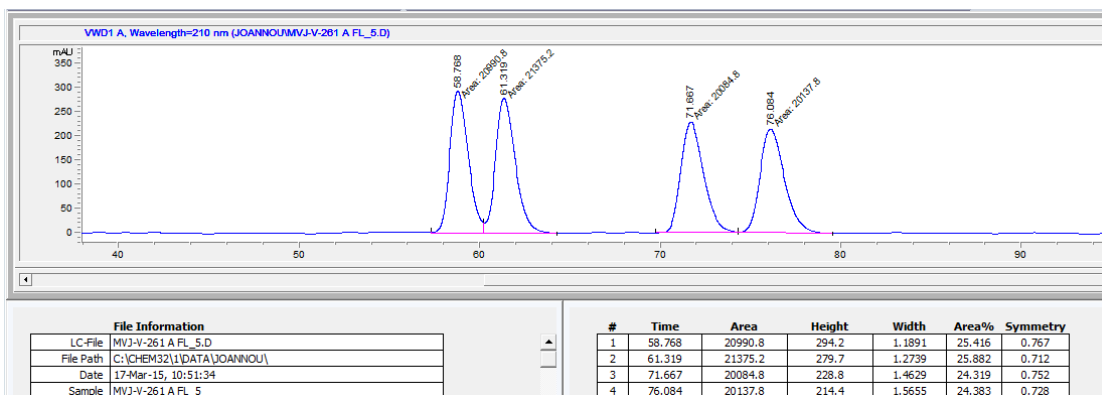

1.56

1-(4-methoxyphenyl)propane-1,2-diol (1.56). Following Procedure A, the crude oxidation mixture was purified by silica gel chromatography (1:1 hexanes:ethyl acetate) to yield diol **1.56** as a colorless oil in 69% yield (12.4 mg) and 97:3 d.r (syn:anti). *Syn diastereomer*: **^{1}H NMR** (CDCl$_3$, 600 MHz): δ 7.32 – 7.23 (m, 2H), 6.95 – 6.84 (m, 2H), 4.32 (d, 1H, *J* = 7.6 Hz), 3.84 (m, 1H), 3.81(s, 3H), 2.53 (br s, 2H), 1.04 (d, 3H, *J* = 6.3 Hz). **^{13}C NMR** (CDCl$_3$, 101 MHz): δ 159.6, 133.3, 128.1, 114.0, 79.3, 72.4, 55.4, 18.9. *Anti diastereomer:* **^{1}H NMR** (CDCl$_3$, 600 MHz): δ 7.32 – 7.23 (m, 2H), 6.95 – 6.84 (m, 2H), 4.60 (d, 1H, *J* = 4.6 Hz), 3.98 (m, 1H), 3.81 (s, 3H), 2.53 (br s, 2H), 1.10 (d, 3H, *J* = 6.3 Hz). **^{13}C NMR** (CDCl$_3$, 101 MHz): δ 159.6, 133.3, 128.0, 113.9, 79.3, 72.4, 55.4, 17.7. **HRMS (ESI$^+$)** calcd for C$_{10}$H$_{14}$O$_3$Na$^+$: 205.0841, found: 205.0835 [M+Na]. **IR (v/cm^{-1}):** 3399 (br, s), 2980 (s), 1613 (s), 1513 (m), 1457 (w), 1372 (m), 1248 (w), 1177 (w). **[α]$^{22}_D$** = +37.2 ° (c = 0.265, CH$_2$Cl$_2$, l = 100 mm).

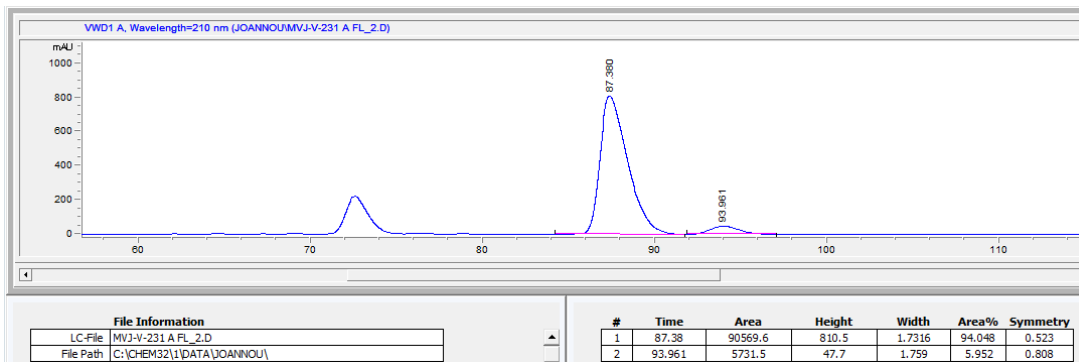Enantiomeric excess was determined by HPLC analysis compared to the authentic racemic material. Absolute stereochemistry was inferred from the stereochemistry obtained for compound **4**.

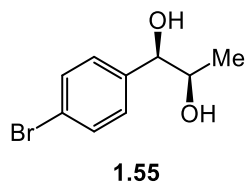*Diacel CHIRALPAK IC Column; 99:1 hexanes:iPrOH; 0.75 mL/min; 210 nm*

Racemic Material

#	Time	Area	Height	Width	Area%	Symmetry
1	132.426	17023.9	91.2	3.1113	25.413	0
2	139.569	16608.9	88.4	3.1298	24.793	0
3	147.023	16966.7	82.7	3.4175	25.327	0.635
4	156.642	16389.9	74.9	3.6484	24.466	0.556

Enantio-enriched Material

#	Time	Area	Height	Width	Area%	Symmetry
1	143.045	37572.2	193	2.4384	92.663	0.677
2	152.012	2974.9	16.7	2.1758	7.337	0.646

Syn-diastereomer: (1*R*,2*R*) enantiomer: 143.0 min; (1*S*,2*S*) enantiomer 152.0 min: 93:7 e.r.
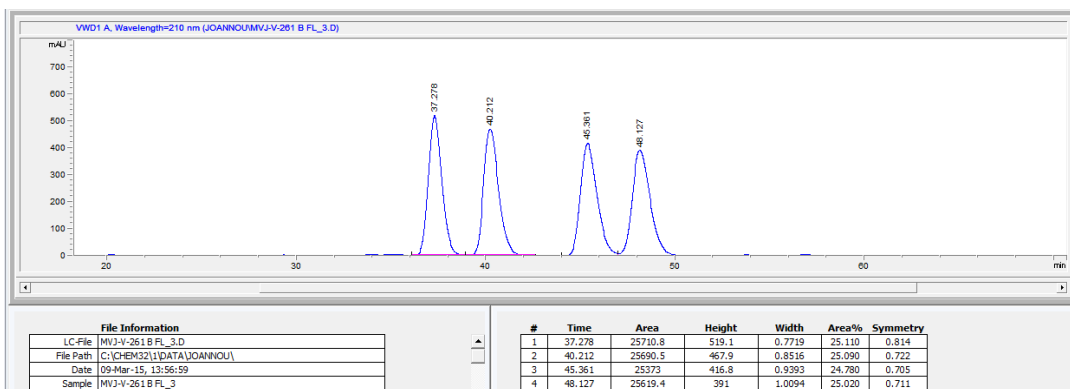

1.57

1-(4-nitrophenyl)propane-1,2-diol (1.57). Following Procedure A, the crude oxidation mixture was purified by silica gel chromatography (1:1 hexanes:ethyl acetate) to yield diol **1.57** as an orange oil in 34% yield (6.6 mg) and 96:4 d.r (syn:anti). *Syn* **diastereomer:** **^{1}H NMR** (CDCl$_3$, 600 MHz): δ 8.28 – 8.21 (m, 2H), 7.61 – 7.55 (m, 2H), 4.56 (d, 1H, *J* = 6.7 Hz), 3.88 (quint, 1H, *J* = 6.4 Hz), 2.94 (s, 2H),

1.16 (d, 1H, J = 6.3 Hz). **^{13}C NMR** (151 MHz, CDCl3): δ 148.3, 147.7, 127.7, 123.7, 78.3, 72.0, 19.1.

***Anti* diastereomer: ^{1}H NMR** (CDCl$_3$, 600 MHz): δ 8.28 – 8.21 (m, 2H), 7.61 – 7.55 (m, 2H), 4.89 (d, 1H, J = 3.9 Hz), 4.12 (qd, 1H, J = 6.4, 3.9 Hz), 2.34 (s, 2H), 1.07 (d, 3H J = 6.4 Hz). **^{13}C NMR** (151 MHz, CDCl3): δ 148.3, 147.6, 127.4, 123.5, 76.4, 71.0, 16.9. **HRMS (ESI$^+$)** calcd for $C_9H_{11}O_4NNa^+$ 220.0586, found: 220.0581 [M+Na]. **IR (v/cm^{-1}):** 3400 (br, s), 2982 (s), 1528 (s), 1381 (s), 1248 (m), 1217 (m). **[α]$^{22}_D$** = -32.1 ˚ (c = 0.572, CH$_2$Cl$_2$, l = 100 mm).

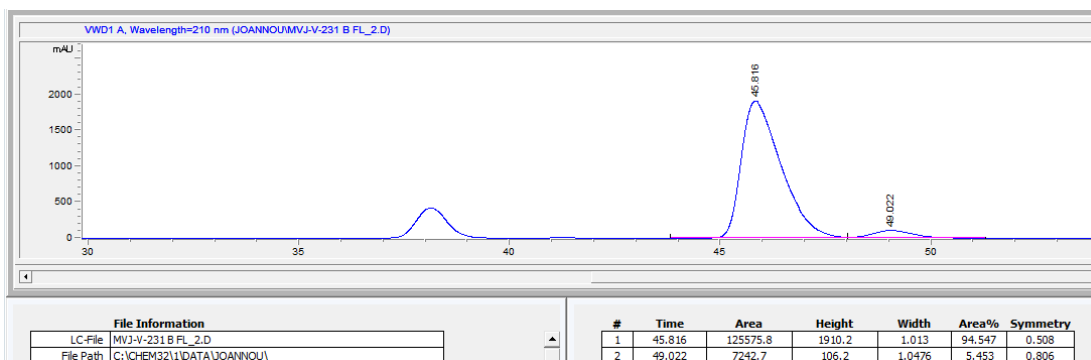Enantiomeric excess was determined by HPLC analysis compared to the authentic racemic material. Absolute stereochemistry was inferred from the stereochemistry obtained for compound **4**.

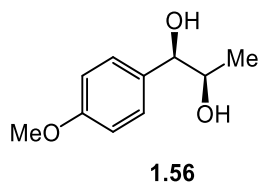*Diacel CHIRALPAK IA Column; 92:8 hexanes:ethyl acetate; 1.0 mL/min; 210 nm*

Racemic Material

#	Time	Area	Height	Width	Area%	Symmetry
1	166.599	1319.4	6.1	3.5856	3.738	0.453
2	186.305	1186.6	6.7	2.9333	3.362	0
3	190.656	16617.6	46	6.0268	47.084	0.302
4	218.093	16169.6	37.9	7.11	45.815	0.277

File Information	
LC-File	MVJ-V-243 B FL_10.D
File Path	C:\CHEM32\1\DATA\JOANNOU\
Date	01-Apr-15, 14:46:09
Sample	MVJ-V-243 B FL_10
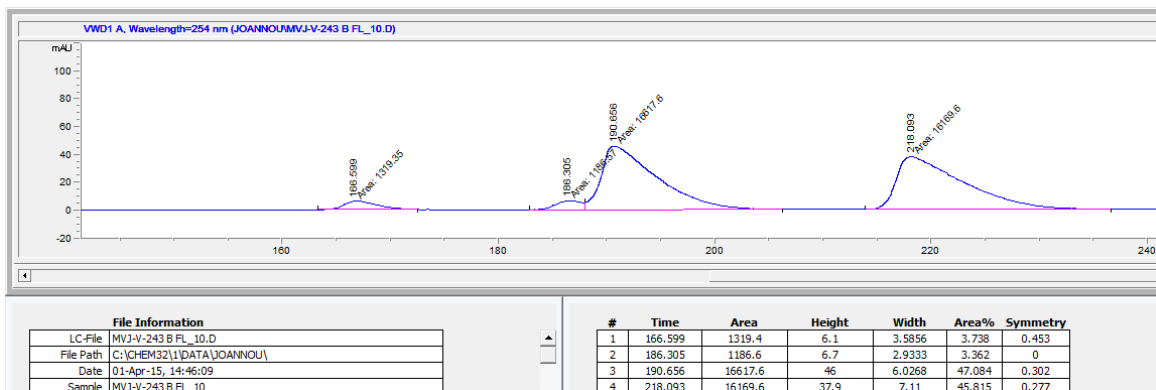
Syn-diastereomer: (1*S,2S*) enantiomer: 162.0 min; (1*R,2R*) enantiomer 175.7 min: 95:5 e.r.

1-(3-nitrophenyl)propane-1,2-diol (1.60). Following Procedure A, the crude oxidation mixture was

purified by silica gel chromatography (1:1 hexanes:ethyl acetate) to yield diol **1.60** as a yellow oil in

35% yield (6.6 mg) and 84:16 d.r (syn:anti). ***Syn* diastereoemer: ^{1}H NMR** (CDCl$_3$, 600 MHz): δ 8.25

(t, 1H, *J* = 2.0 Hz), 8.20 – 8.12 (m, 1H), 7.70 (dt, 1H, *J* = 7.7, 1.4 Hz), 7.54 (td, 1H, *J* = 7.9, 3.3 Hz),

4.53 (d, 1H, *J* = 6.8 Hz), 3.87 (quint, 1H, *J* = 6.4 Hz), 2.95 (s, 2H), 1.14 (d, 2H, *J* = 6.3 Hz). **^{13}C NMR**

(151 MHz, CDCl$_3$): δ 148.3, 143.3, 133.0, 129.4, 123.1, 121.9, 78.2, 72.0, 19.1. ***Anti* diastereoemer:**

^{1}H NMR (CDCl$_3$, 600 MHz): δ 4.84 (m, 1H), 4.10 (qd, 1H, *J* = 6.4, 3.9 Hz), 2.30 (s, 2H), 1.05 (d, 3H,

J = 6.4 Hz). **^{13}C NMR** (151 MHz, CDCl$_3$): δ 148.3, 142.4, 132.8, 129.2, 122.7, 121.7, 76.3, 71.0, 17.0.

HRMS (ESI$^+$) calcd for C$_9$H$_{11}$O$_4$NNa$^+$ 220.0586, found: 220.0581 [M+Na]. **IR (neat):** 3402 (br, s),

2987 (s), 1528 (s), 1345 (s), 1260 (m) 1220 (m). **[α]^{22}$_D$** = –45.2 ˚ (*c* = 0.657, CH$_2$Cl$_2$, l = 100 mm).
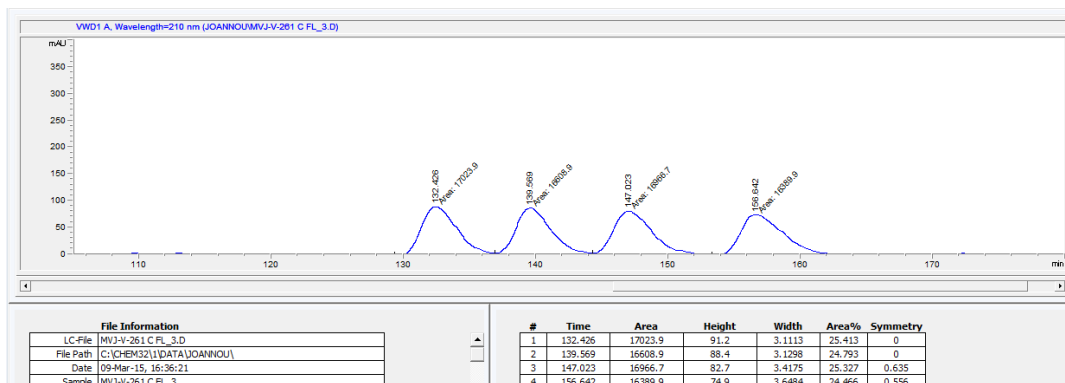
Enantiomeric excess was determined by HPLC analysis compared to the authentic racemic material.

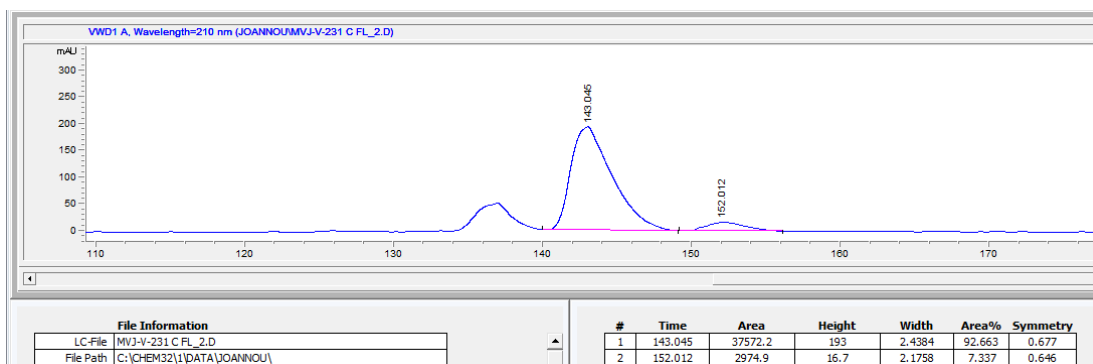Absolute stereochemistry was inferred from the stereochemistry obtained for compound **4**.

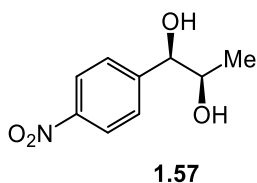*Diacel CHIRALPAK IC Column; 97:3 hexanes:iPrOH; 1.0 mL/min; 210 nm*

Racemic Material

#	Time	Area	Height	Width	Area%	Symmetry
1	73.306	4927.1	48.5	1.6919	8.490	0.762
2	79.402	24235.7	208.6	1.9362	41.763	0.569
3	91.79	23935.7	184.1	2.1668	41.246	0.64
4	120.128	4932.5	30.5	2.6969	8.500	0.75

File Information
LC-File: MVJ-V-243 A FL_4.D
File Path: C:\CHEM32\1\DATA\JOANNOU\
Date: 15-Mar-15, 17:08:39
Sample: MVJ-V-242 A FL_4
Sample Info: m-NO2Ph 1,2 diol from reaction 239 A; 97:3 hex:iPrOH; 1.0 mL/min;

Enantio-enriched Material

#	Time	Area	Height	Width	Area%	Symmetry
1	35.827	4157.6	85.9	0.7384	5.087	0.855
2	52.318	77575.9	981.5	1.1551	94.913	0.51

File Information
LC-File: MVJ-V-236 B FL.D
File Path: C:\CHEM32\1\DATA\JOANNOU\

Syn-diastereomer: (1*S*,2*S*) enantiomer: 35.8 min; (1*R*,2*R*) enantiomer 52.3 min: 95:5 e.r.

1-(3-tolyl)propane-1,2-diol (1.58). Following Procedure A, the crude oxidation mixture was purified by silica gel chromatography (1:1 hexanes:ethyl acetate) to yield diol **1.58** as a colorless oil in 76% yield (12.6 mg) and 96:4 d.r (syn:anti). ***Syn* diastereomer: ^{1}H NMR** (CDCl$_3$, 600 MHz): δ 7.26 – 7.22 (m, 1H), 7.19 – 7.10 (m, 3H), 4.34 (d, 1H *J* = 7.3 Hz), 3.90 – 3.83 (m, 1H), 2.63 (s, 1H), 2.53 (s, 1H),

1.06 (d, 3H, J = 6.3 Hz). **^{13}C NMR** (CDCl$_3$, 151 MHz): δ 141.0, 138.2, 128.9, 128.4, 127.4, 123.9, 79.5, 75.1, 21.5, 18.8. **Anti diastereomer:** **^{1}H NMR** (CDCl$_3$, 600 MHz): δ 7.26 – 7.22 (m, 1H), 7.19 – 7.10 (m, 3H), 4.66 (d, J = 4.5 Hz, 1H), 4.03 (qd, J = 6.4, 4.7 Hz, 1H), 2.63 (s, 1H), 2.53 (s, 1H), 1.13 (dd, J = 6.4, 0.8 Hz, 3H). **^{13}C NMR** (CDCl$_3$, 151 MHz): δ 140.3, 138.1, 128.6, 128.3, 127.3, 123.7, 77.6, 71.3, 21.5, 17.4. **HRMS (ESI$^+$)** calcd for C$_{10}$H$_{14}$O$_2$Na$^+$: 189.0893, found: 189.0888 (M + Na$^+$). **IR (v/cm^{-1}):** 3417 (br, s), 2917 (s), 1646 9 (s), 1456 (m), 1130 (m). **[α]$^{22}_D$** = +49.2 ° (c = 0.675, CH$_2$Cl$_2$, l = 100 mm).

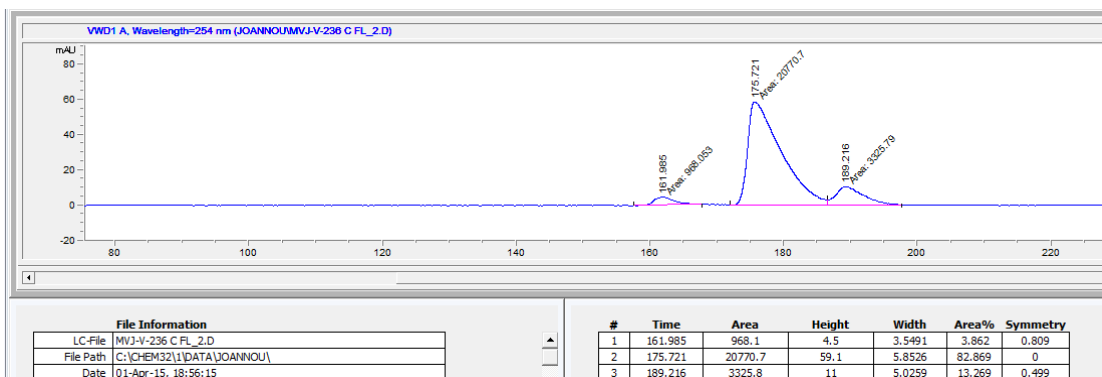Enantiomeric excess was determined by HPLC analysis compared to the authentic racemic material. Absolute stereochemistry was inferred from the stereochemistry obtained for compound **4**.

Diacel CHIRALPAK IA Column; 99:1 hexanes:iPrOH; 1.0 mL/min; 210 nm

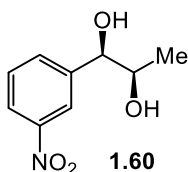*Racemic Material*

#	Time	Area	Height	Width	Area%	Symmetry
1	25.383	22190.2	673	0.5027	26.458	0.8
2	30.263	19907.4	473.9	0.6431	23.736	0.652
3	35.543	19639.7	424.6	0.7046	23.417	0.748
4	40.678	22133.3	408.7	0.8258	26.390	0.695

File Information
LC-File: MVJ-V-262 A FL.D
File Path: C:\CHEM32\1\DATA\JOANNOU\
Date: 08-Mar-15, 14:50:37
Sample: MVJ-V-262 A FL
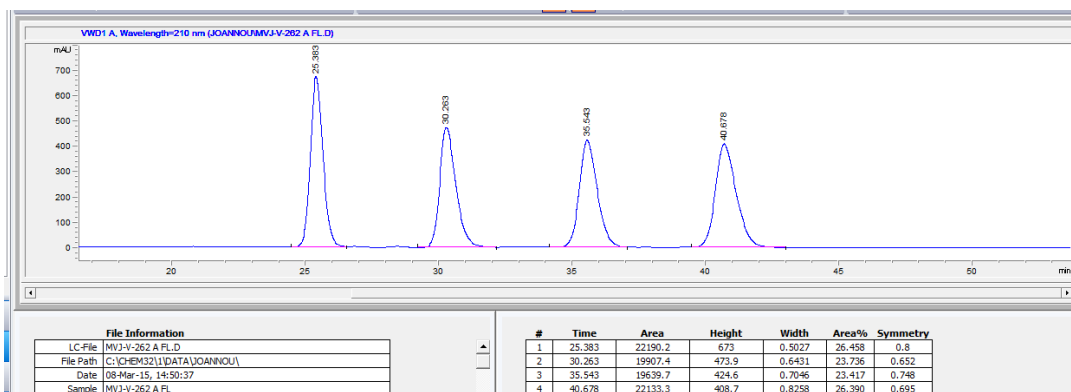
Syn-diastereomer: (1*S*,2*S*) enantiomer: 23.3 min; (1*R*,2*R*) enantiomer 40.2 min: 98:2 e.r.
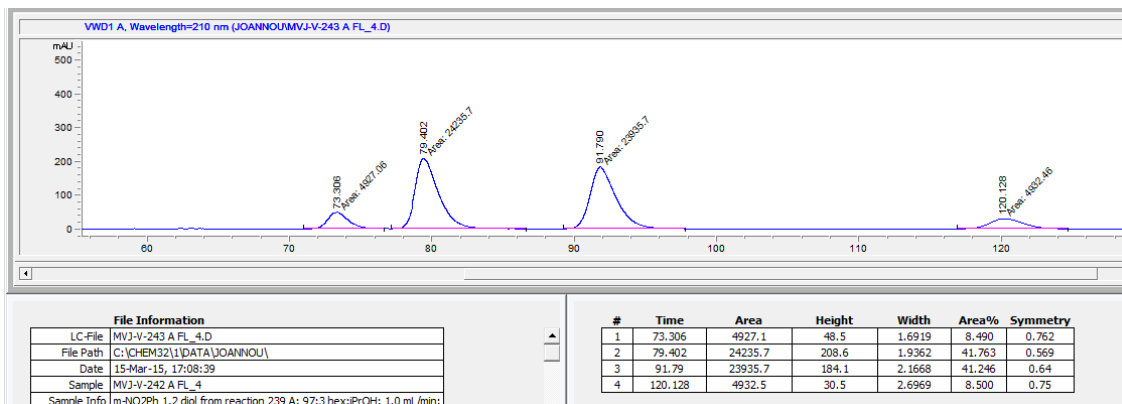

1-(3-(trifluoromethyl)phenyl)propane-1,2-diol (1.59). Following Procedure A, the crude oxidation

mixture was purified by silica gel chromatography (1:1 hexanes:ethyl acetate) to yield diol **1.59** as a

colorless oil in 59% yield (12.9 mg) and 96:4 d.r (syn:anti). *Syn* **diastereomer:** **^{1}H NMR** (CDCl$_3$, 600

MHz): δ 7.64 (s, 1H), 7.56 (dd, 2H, *J* = 16.0, 7.7 Hz), 7.48 (t, 1H, *J* = 7.7 Hz), 4.45 (d, 1H, *J* = 7.1 Hz),

3.85 (quint, 1H, *J* = 6.5 Hz), 3.44 (s, 1H), 2.89 (s, 1H), 1.10 (d, 3H, *J* = 6.3 Hz). **^{13}C NMR** (CDCl$_3$,

151 MHz): δ 142.3, 131.1, 130.9, 130.7, 130.5, 130.3, 128.9, 125.0, 124.8, 124.8, 123.7, 123.7, 123.7,

123.6, 78.7, 72.0, 18.9. *Anti* **diastereomer:** **^{1}H NMR** (CDCl$_3$, 600 MHz): δ 7.65 (s, 1H), 7.56 (dd,

2H, *J* = 16.0, 7.7 Hz), 7.48 (t, 1H, *J* = 7.7 Hz) 4.79 (d, 1H, *J* = 3.9 Hz), 4.05 (dd, 1H, *J* = 6.4, 4.0 Hz),

3.17 (s, 1H), 2.89 (s, 1H), 1.06 (d, 3H, *J* = 6.5 Hz). **^{13}C NMR** (CDCl$_3$, 151 MHz): δ 141.5, 130.7, 130.5,

130.0, 128.7, 124.5, 124.4, 123.4, 123.4, 123.2, 76.7, 71.1, 16.9. **HRMS (ESI$^+$)** calcd for

C$_{10}$H$_{11}$F$_3$O$_2$Na$^+$: 243.0609, found: 243.0604 [M+Na]. **IR (v/cm^{-1}):** 3416 (br, s), 2918 (s), 2849 (s), 1647

(m), 1454 (m), 1329 (w), 1166 (w). **[α]^{22}$_D$** = +37.5 ˚ (*c* = 0.225, CH$_2$Cl$_2$, l = 100 mm).

Enantiomeric excess was determined by HPLC analysis compared to the authentic racemic material.
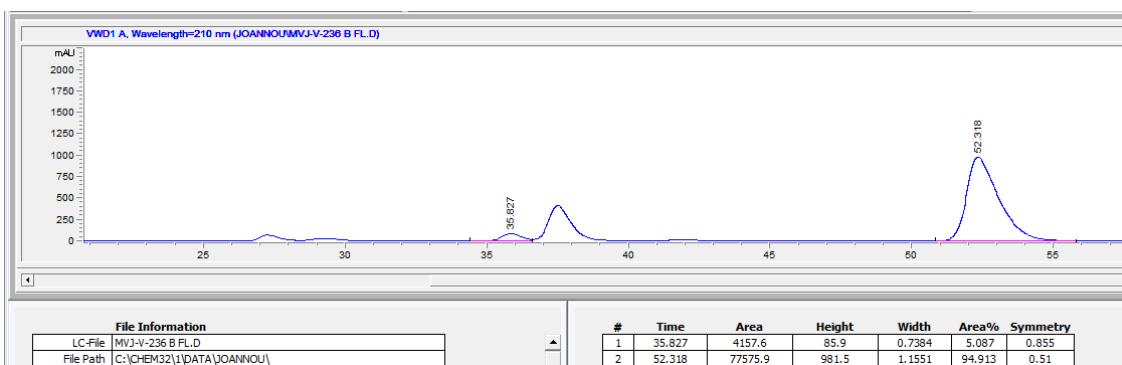
Absolute stereochemistry was inferred from the stereochemistry obtained for compound **4**.

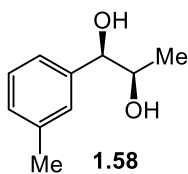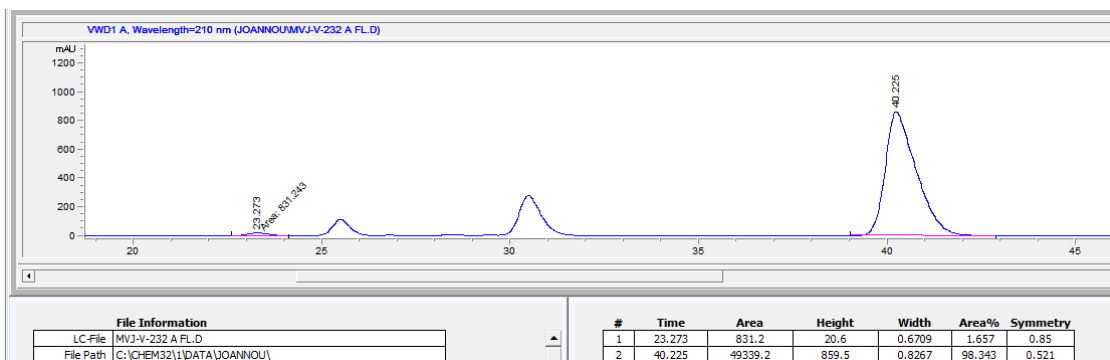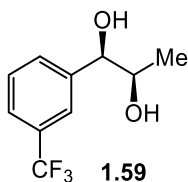*Diacel CHIRALPAK IC Column; 99:1 hexanes:iPrOH; 1.0 mL/min; 210 nm*

Racemic Material

	File Information		#	Time	Area	Height	Width	Area%	Symmetry
LC-File	MVJ-V-261 E_2 FL.D		1	10.756	8131.5	515.5	0.244	26.941	0.811
File Path	C:\CHEM32\1\DATA\JOANNOU\		2	12.269	7942.6	452.7	0.2727	26.315	0.836
Date	07-Mar-15, 14:51:12		3	12.802	7074.1	374	0.2907	23.438	0.833
Sample	MVJ-V-261 E_2 FL		4	13.531	7034.2	348.7	0.3114	23.306	0.799

Enantio-enriched Material

	File Information		#	Time	Area	Height	Width	Area%	Symmetry
LC-File	MVJ-V-232 B FL_2.D		1	12.699	44865.5	2306.2	0.303	94.474	0.68
File Path	C:\CHEM32\1\DATA\JOANNOU\		2	13.445	2624.4	128.6	0.3122	5.526	0.826

Syn-diastereomer: (1*R*,2*R*) enantiomer: 12.7 min; (1*S*,2*S*) enantiomer 13.4 min: 94:6 e.r.

1.61
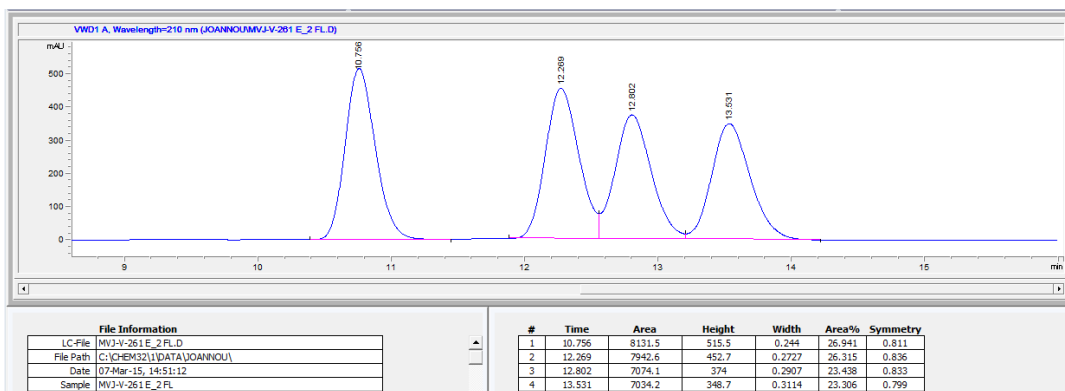
1-(2-tolyl)propane-1,2-diol (1.61). Following Procedure A, the crude oxidation mixture was purified

by silica gel chromatography (1:1 hexanes:ethyl acetate) to yield diol **1.61** as a colorless oil in 68%

yield (10.8 mg) as a single detectable diastereomer (*syn*). **^{1}H NMR** (CDCl$_3$, 600 MHz): δ 7.38 (dd, 1H,

J = 7.5, 1.5 Hz), 7.24 – 7.11 (m, 3H), 4.68 (d, 1H, J = 7.3 Hz), 3.91 (quint, 1H, J = 6.6 Hz), 2.91 (br, d, 2H), 2.36 (s, 3H), 1.06 (d, 3H, J = 6.4 Hz). **^{13}C NMR** (CDCl$_3$, 151 MHz): δ 139.4, 135.4, 130.5, 127.7, 126.4, 126.3, 75.0, 72.1, 19.6, 18.5. **HRMS (ESI$^+$)** calcd for C$_{10}$H$_{14}$O$_2$Na$^+$: 189.0893, found: 189.0888 (M + Na$^+$). **IR (v/cm^{-1}):** 3292 (br, s), 2918 (s), 2360 (s), 1645 (s), 1467 (m). **[α]^{22}$_D$** = +46.3 ° (c = 0.564, CH$_2$Cl$_2$, l = 100 mm).

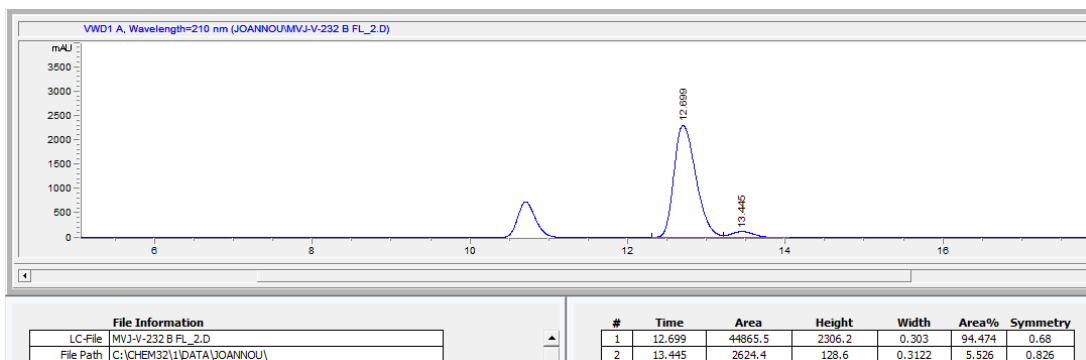Enantiomeric excess was determined by HPLC analysis compared to the authentic racemic material. Absolute stereochemistry was inferred from the stereochemistry obtained for compound **4**.

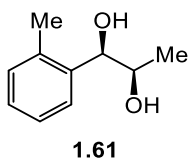*Diacel CHIRALPAK IA Column; 99:1 hexanes:iPrOH; 1.0 mL/min; 210 nm*

Racemic Material

	File Information		#	Time	Area	Height	Width	Area%	Symmetry
LC-File	MVJ-V-262 B FL.D		1	24.942	6666	211	0.4826	30.984	0.843
File Path	C:\CHEM32\1\DATA\JOANNOU\		2	26.746	8214.6	186.4	0.6981	38.182	0.861
Date	08-Mar-15, 15:45:39		3	28.331	6633.9	185.2	0.5469	30.835	0.905

Enantio-enriched Material

	File Information		#	Time	Area	Height	Width	Area%	Symmetry
LC-File	MVJ-V-232 C FL.D		1	24.77	5365.7	156.4	0.5222	7.301	0.807
File Path	C:\CHEM32\1\DATA\JOANNOU\		2	27.929	68126.7	1765.7	0.5831	92.699	0.658

Syn-diastereomer: (1*S,2S*) enantiomer: 24.8 min; (1*R,2R*) enantiomer 27.9 min: 93:7 e.r.

1.62

1-mesitylpropane-1,2-diol (1.62). Following Procedure A, the crude oxidation mixture was purified by silica gel chromatography (1:1 hexanes:ethyl acetate) to yield diol **1.62** as a colorless oil in 65% yield (12.7 mg) as a single detectable diastereomer (*syn*). **¹H NMR** 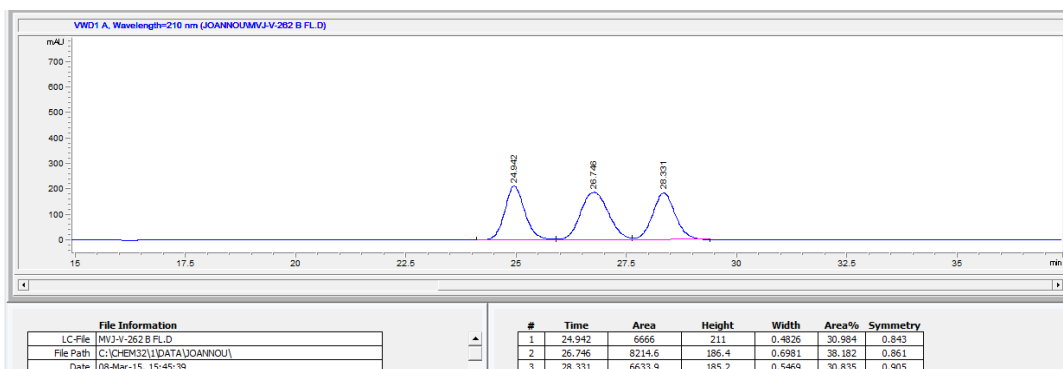(CDCl₃, 600 MHz): δ 6.9 (s, 2H), 4.92 (d, 1H, *J* = 9.1 Hz), 4.35 (dq, 1H, *J* = 9.1, 6.3 Hz), 2.45 (s, 6H), 2.38 (s, 3H), 1.06 (d, 3H, *J* = 6.6 Hz). **¹³C NMR** (CDCl₃, 151 MHz): δ 137.2, 136.9, 133.2, 130.3, 76.4, 69.8, 21.2, 20.8, 18.7. **HRMS (ESI⁺)** calcd for C₁₂H₁₈O₂Na⁺ 217.1205, found: 217.1120 [M+Na]. **IR (v/cm⁻¹):** 3293 (br, s), 2920 (s), 1644 (m), 1454 (m), 1121 (w), 1015 (m). **[α]²²_D** = +64.5 ° (*c* = 0.679, CH₂Cl₂, l = 100 mm).

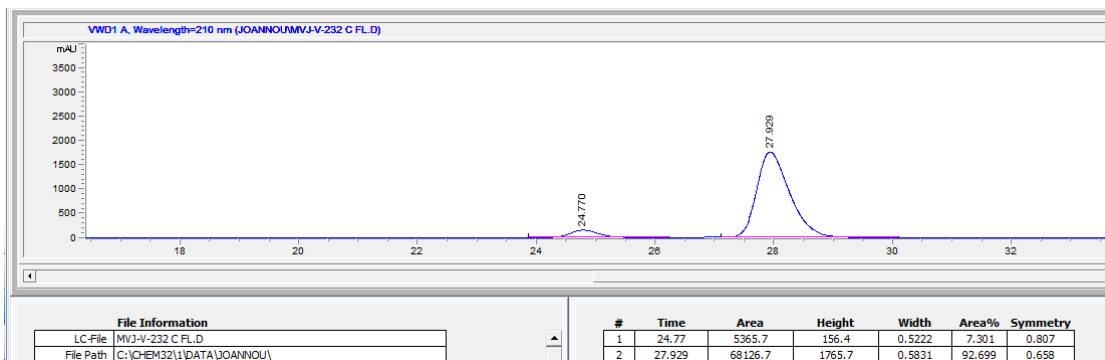Enantiomeric excess was determined by HPLC analysis compared to the authentic racemic material. Absolute stereochemistry was inferred from the stereochemistry obtained for compound **4**.

Diacel CHIRALPAK IA Column; 99:1 hexanes:iPrOH; 0.75 mL/min; 210 nm

Racemic Material

#	Time	Area	Height	Width	Area%	Symmetry
1	39.485	21348.3	425.9	0.8355	49.100	0.822
2	42.444	21454	399	0.8962	49.344	0.802
3	45.872	676.6	7.6	1.4838	1.556	0.629

File Information	
LC-File	MVJ-V-262 C FL.D
File Path	C:\CHEM32\1\DATA\JOANNOU\
Date	08-Mar-15, 16:41:45

59

Syn-diastereomer: (1*S,2S*) enantiomer: 39.7 min; (1*R,2R*) enantiomer 42.3 min: 93:7 e.r.

1.64

1-(furan-3-yl)propane-1,2-diol (1.64). Following Procedure A, the crude oxidation mixture was purified by silica gel chromatography (1:1 hexanes:ethyl acetate) to yield diol **1.64** as a colorless oil in 56% yield (7.9 mg) and 96:4 d.r (syn:anti) ***Syn* diastereomer:** **^{1}H NMR** (CDCl$_3$, 600 MHz): δ 7.42 (d, 1H, *J* = 1.0 Hz), 6.40-6.38 (m, 2H), 4.41 (m, 1H), 4.45 (d, 1H, *J* = 7.0 Hz), 4.12 (m, 1H), 2.71 (s, 2H), 1.18 (d, 3H, *J* = 6.3 Hz). **^{13}C NMR** (CDCl$_3$, 151 MHz): δ 153.9, 142.4, 110.4, 107.7, 72.6, 69.9, 18.8. ***Anti* diastereomer:** **^{1}H NMR** (CDCl$_3$, 600 MHz): δ 7.44 (d, 1H, *J* = 3.6 Hz), 6.37-6.35 (m, 2H), 4.67 (d, 1H, *J* = 4.4 Hz), 4.15 (m, 1H), 2.61 (br s, 2H), 1.21 (d, 3H, *J* = 6.0 Hz). **^{13}C NMR** (CDCl$_3$, 101 MHz): δ 153.5, 142.3, 110.4, 107.9, 71.8, 70.0, 18.3. **HRMS (ESI$^+$)** calcd for C$_7$H$_{10}$O$_3$Na$^+$ 165.0528, found: 165.05221 [M+Na]. **IR (v/cm^{-1}):** 3416 (br, s), 2980 (s), 1643 (s), 1454 (m), 1380 (m), 1011 (m). **[α]^{22}$_D$** = +15.4 ° (*c* = 0.232, CH$_2$Cl$_2$, l = 100 mm).

Enantiomeric excess was determined by HPLC analysis compared to the authentic racemic material. Absolute stereochemistry was inferred from the stereochemistry obtained for compound **4**.

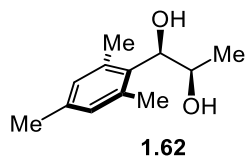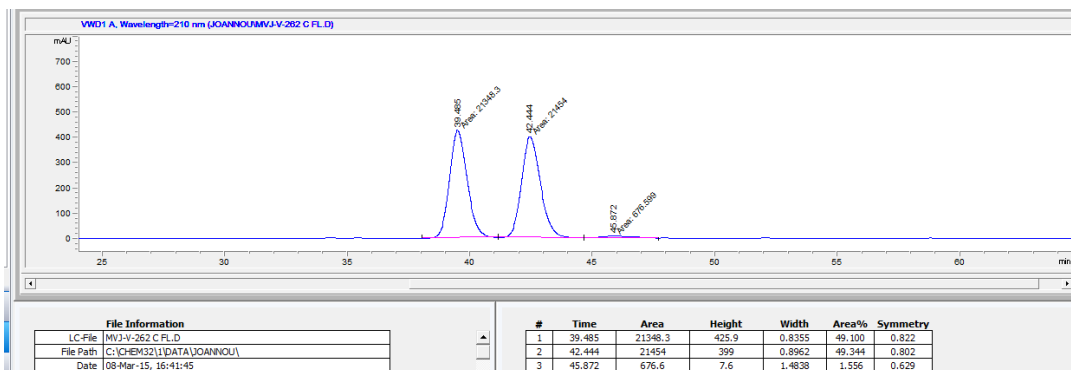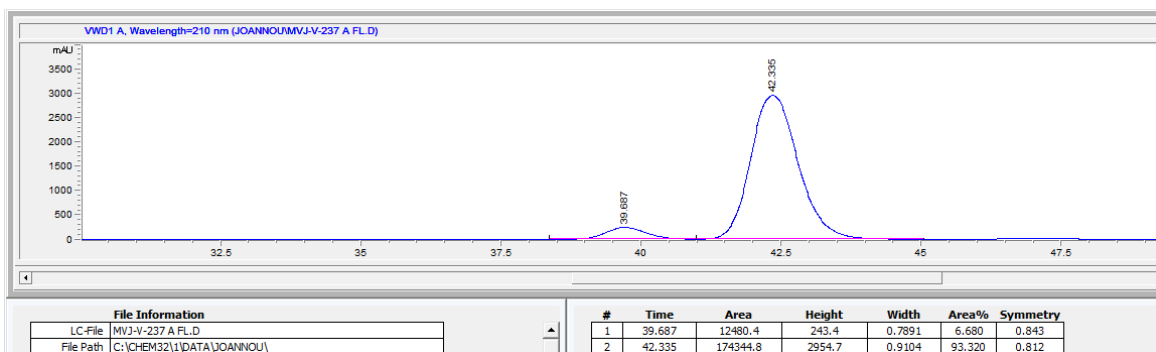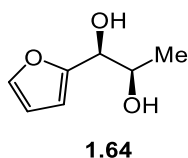*Diacel CHIRALPAK IA Column; 99:1 hexanes:iPrOH; 1.0 mL/min; 210 nm*

Racemic Material

#	Time	Area	Height	Width	Area%	Symmetry
1	31.643	2227.6	56.2	0.6609	17.997	0.924
2	34.304	2279.1	52.8	0.7197	18.413	0.974
3	37.919	3885.8	78.5	0.8253	31.393	0.767
4	41.916	3985.3	73.7	0.9017	32.197	0.843

File Information
LC-File MVJ-V-262 E FL_4.D
File Path C:\CHEM32\1\DATA\JOANNOU\
Date 09-Mar-15, 10:29:38
Sample MVJ-V-262 E FL_4

Enantio-enriched Material

#	Time	Area	Height	Width	Area%	Symmetry
1	30.407	4671.3	120.8	0.5941	5.035	0.931
2	32.782	88114.1	2049.6	0.6526	94.965	0.681

File Information
LC-File MVJ-V-237 A FL_2.D
File Path C:\CHEM32\1\DATA\JOANNOU\

Syn-diastereomer: (1*S,2S*) enantiomer: 30.4 min; (1*R,2R*) enantiomer 32.8 min: 95:5 e.r.
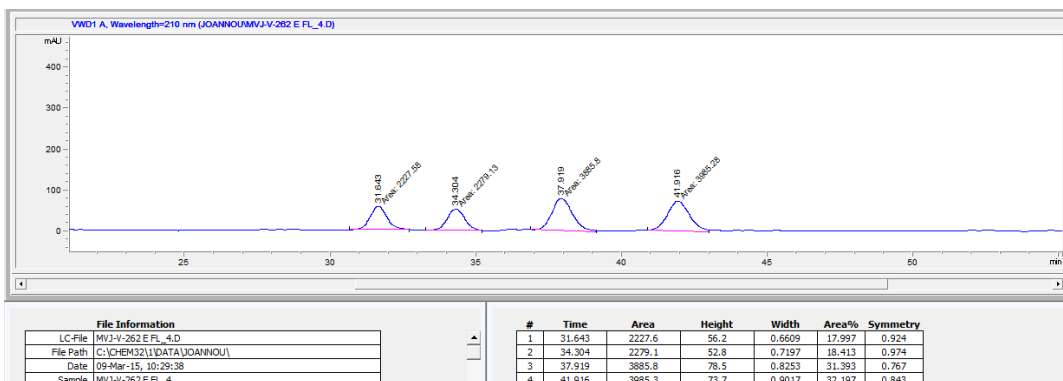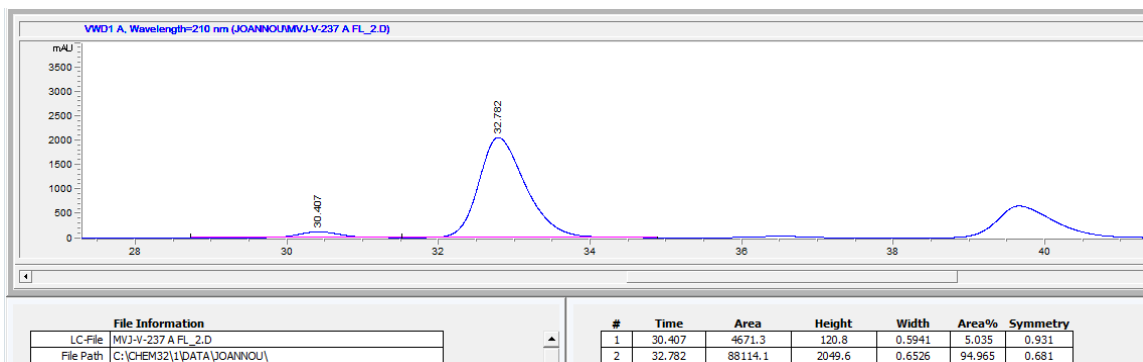

1.63

1-(pyridin-3-yl)propane-1,2-diol (1.63). Following Procedure A, the crude oxidation mixture was purified by silica gel chromatography (1:1 hexanes:ethyl acetate) to yield diol **15** as a colorless oil in 68% yield (10.4 mg) and 84:16 d.r (syn:anti). ***Syn* diastereomer: ^{1}H NMR** (CDCl$_3$, 600 MHz): δ 8.60 (br, d, 2H, *J* = 11.6 Hz), 7.77 (d, 1H, *J* = 8.0 Hz), 7.34 (m, 1H), 4.47 (d, 1H, *J* = 7.0 Hz), 3.90 (m, 1H), 1.13 (d, 3H, *J* = 4 Hz). **^{13}C NMR** (CDCl3, 151 MHz) δ 149.1, 148.3, 134.6, 123.4, 77.26, 77.1, 76.8, 75.2, 71.0, 17.2. **Anti Diastereomer: ^{1}H NMR** (CDCl$_3$, 600 MHz): δ 8.60 (br d, 2H, *J* = 11.6 Hz), 7.77 (d, 1H, *J* = 8.0 Hz), 7.34 (m, 1H), 4.78 (d, 1H, *J* = 4.0 Hz), 4.11 (m, 1H), 1.09 (d, 3H, *J* = 6.3 Hz).

¹³C NMR (CDCl3, 151 MHz) δ 149.1, 148.3, 134.6, 123.4, 77.3, 77.1, 76.8, 75.2, 71.0, 17.2. **HRMS**

(ESI⁺) calcd for $C_8H_{12}O_2N^+$ 154.168, found: 154.182 [M+H]. **IR (neat):** 3322 (br, s), 2963 (s), 1584

(s), 1470 (m), 1370 (m), 1302 (m), 1290 (m). **[α]²²_D** = +14.2 ˚ (c = 0.145, CH₂Cl₂, l = 100 mm).

Enantiomeric excess was determined by HPLC analysis compared to the authentic racemic material.

Absolute stereochemistry was inferred from the stereochemistry obtained for compound **4**.

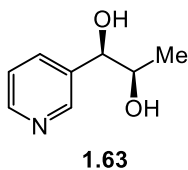*Diacel CHIRALPAK IC Column; 85:15 hexanes:iPrOH; 0.5 mL/min; 210 nm*

Racemic Material

	File Information		#	Time	Area	Height	Width	Area%	Symmetry
LC-File	MVJ-V-276 FL_15.D		1	37.756	8639.2	145	0.8919	49.114	0.548
File Path	C:\CHEM32\1\DATA\JOANNOU\		2	42.118	7781.8	117.9	0.9933	44.240	0.54
Date	31-Mar-15, 17:39:49		3	46.173	366	5.6	0.9849	2.081	0.971
Sample	MVJ-V-276 FL_15		4	49.138	803	11.2	1.0679	4.565	0.604

Enantio-enriched Material

	File Information		#	Time	Area	Height	Width	Area%	Symmetry
LC-File	MVJ-V-237 C .D		1	37.241	5418.9	80.9	1.1165	90.167	0
File Path	C:\CHEM32\1\DATA\JOANNOU\		2	39.765	591	9.9	0.9904	9.833	0.961

Syn-diastereomer: (1*R*,2*R*) enantiomer: 37.2 min; (1*S*,2*S*) enantiomer 39.8 min: 90:10 e.r.
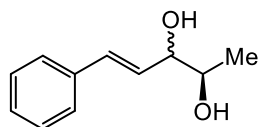
1.65

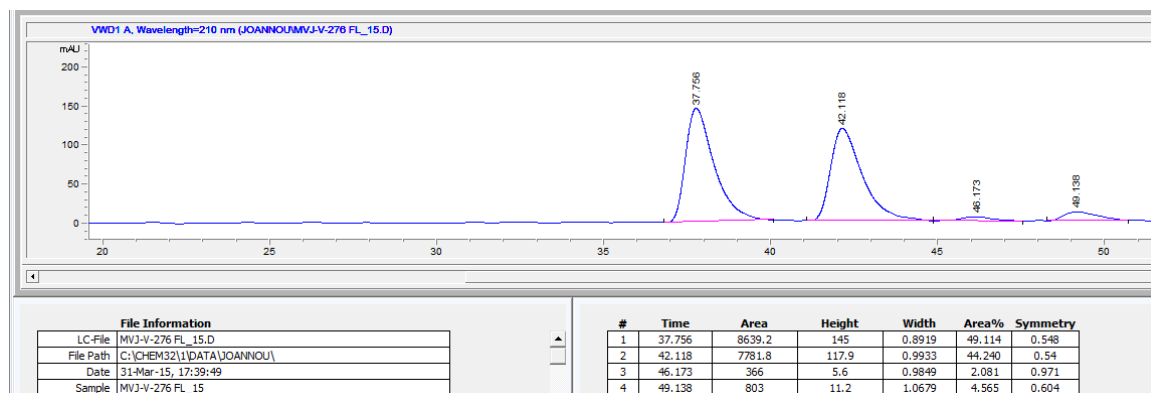**(2*R*,*E*)-5-phenylpent-4-ene-2,3-diol (1.65).** Following Procedure C, the crude oxidation mixture was purified by silica gel chromatography (2:1 to 1:1 hexanes:ethyl acetate), the product diol **1.65** was isolated as a colorless oil in 59% yield (10.5 mg) and 54:46 d.r (*anti:syn*). ***anti*-diastereomer: ¹H NMR** (CDCl₃, 600 MHz): δ 7.40 (t, 2H, *J* = 6.8 Hz), 7.33 (d, 2H, *J* = 7.2 Hz), 7.26 (t, 1H, *J* = 6.6 Hz), 6.67 (d, 1H, *J* = 12.6 Hz), 6.27 (dd, 1H, J = 16.2, 7.2 Hz), 4.26 (dd, 1H, *J* = 7.2, 1.2 Hz), 3.97 (m, 1H), 1.20 (d, 1H, *J* = 6.6 Hz); **¹³C NMR** (CDCl₃, 151 MHz): δ 136.5, 133.3, 128.8, 128.1, 127.2, 126.7, 76.7, 70.5, 17.9; ***syn*-diastereomer: ¹H NMR** (CDCl₃, 600 MHz): δ 7.40 (t, 2H, *J* = 6.8 Hz), 7.33 (d, 2H, *J* = 7.2 Hz), 7.26 (t, 1H, *J* = 6.6 Hz), 6.69 (d, 1H, *J* = 13.2 Hz), 6.19 (dd, 1H, J = 16.2, 7.2 Hz), 4.04 (td, 1H, *J* = 8.4, 1.2 Hz), 3.75 (quint, 1H, *J* = 6.0 Hz), 1.23 (d, 1H, *J* = 6.0 Hz); **¹³C NMR** (CDCl₃, 151 MHz): δ 136.5, 133.0, 128.8, 128.5, 128.1, 126.7, 77.9, 71.1, 19.2; **IR** (v/cm⁻¹): 3385 (OH, br, s), 3027 (w), 2972 (w), 2925 (m), 2870 (w), 2851 (w), 1457 (m), 1375 (w), 1070 (w), 1027 (w); **HRMS**-(ESI⁺) [M+Na]⁺ calcd for C₁₁H₁₄NaO₂⁺ 201.0892, found: 201.0887.
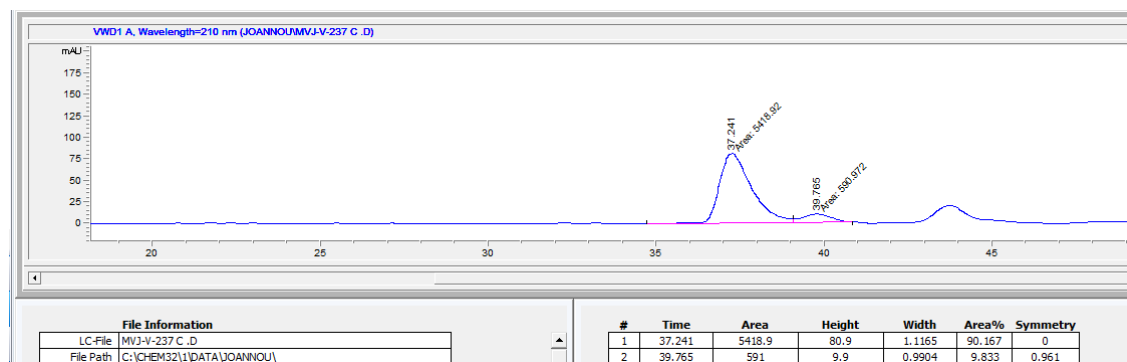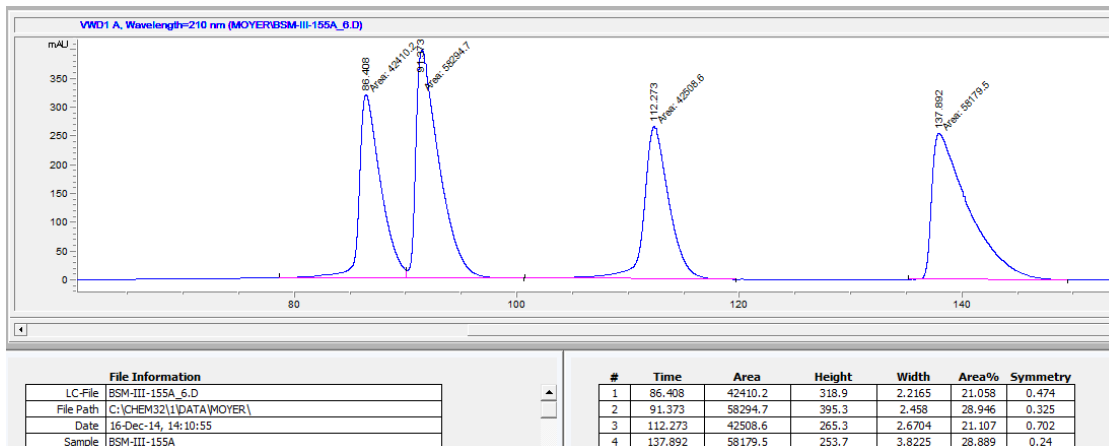
Enantiomeric purity was determined by HPLC analysis compared to the authentic racemic material. Absolute stereochemistry was inferred from the stereochemistry obtained for compound **20** and **22** (defunctionalization experiment, see S31)[41]

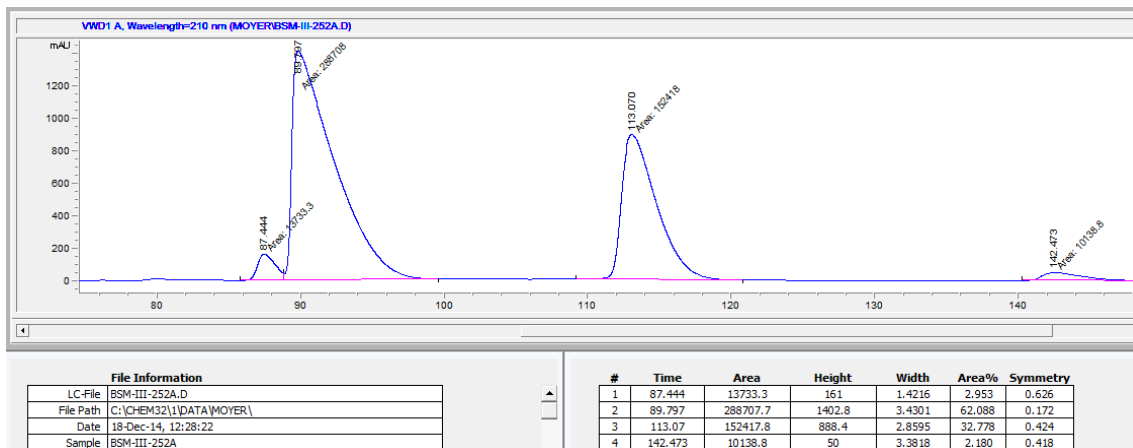*Diacel CHIRALPAK IB Column; 98:2 hexanes:iPrOH; 0.75 mL/min; 22 °C, 210 nm.*

Racemic Material

#	Time	Area	Height	Width	Area%	Symmetry
1	86.408	42410.2	318.9	2.2165	21.058	0.474
2	91.373	58294.7	395.3	2.458	28.946	0.325
3	112.273	42508.6	265.3	2.6704	21.107	0.702
4	137.892	58179.5	253.7	3.8225	28.889	0.24

*syn*-diastereomers: (2*S*,3*S*)-enantiomer: 86.4 min.; (2*R*,3*R*)-enantiomer: 112.3 min.;

anti-diastereomers: (2*R*,3*S*)-enantiomer: 91.4 min.; (2*S*,3*R*)-enantiomer: 137.9 min.

Enantio-enriched Material

#	Time	Area	Height	Width	Area%	Symmetry
1	87.444	13733.3	161	1.4216	2.953	0.626
2	89.797	288707.7	1402.8	3.4301	62.088	0.172
3	113.07	152417.8	888.4	2.8595	32.778	0.424
4	142.473	10138.8	50	3.3818	2.180	0.418

syn-diastereomers: (2*S*,3*S*)-enantiomer: 87.4 min.; (2*R*,3*R*)-enantiomer: 113.1 min.: 92:8 e.r.

anti-diastereomers: (2*R*,3*S*)-enantiomer: 89.8 min.; (2*S*,3*R*)-enantiomer: 142.5 min.: 97:3 e.r.
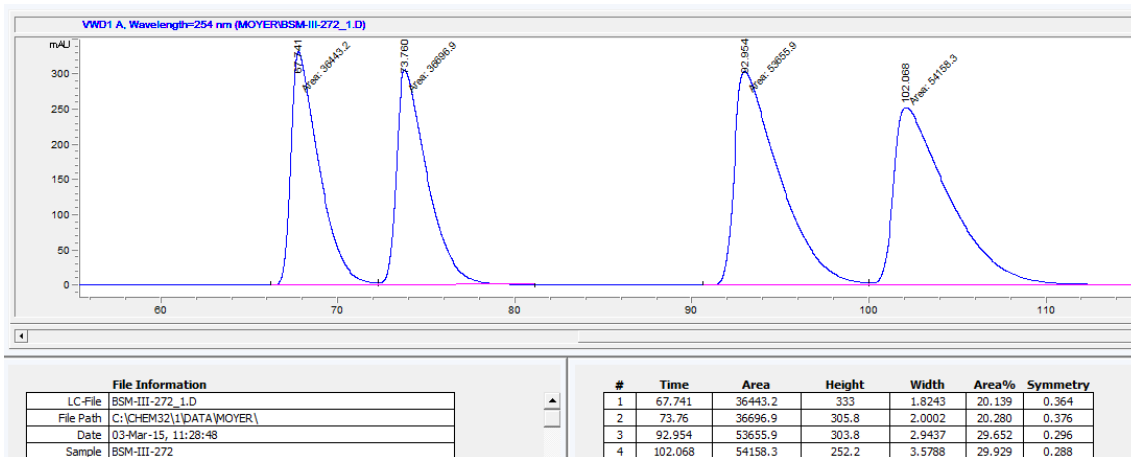
1.66
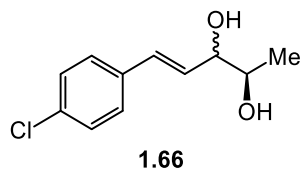
(*2R,E*)-5-(4-chlorophenyl)pent-4-ene-2,3-diol (1.66). Following Procedure C, the crude oxidation mixture was purified by silica gel chromatography (2:1 to 1:1 hexanes:ethyl acetate), the product diol **1.66** was isolated as a colorless oil in 38% yield (8.1 mg) and 54:46 d.r (*anti:syn*). **anti-diastereomer:** **¹H NMR** (600 MHz, CDCl₃): δ 7.28-7.32 (m, 4H), 6.60 (d, 1H, *J* = 15.0 Hz), 6.24 (dd, 1H, *J* = 16.2, 7.2 Hz), 4.25 (dd, 1H, *J* = 7.2, 1.2 Hz), 3.97 (m, 1H), 1.19 (d, 1H, *J* = 6.6 Hz); **syn-diastereomer: ¹H NMR** (600 MHz, CDCl₃): δ 7.28-7.32 (m, 4H), 6.64 (d, 1H, *J* = 13.8 Hz), 6.17 (dd, 1H, J = 16.2, 7.2 Hz), 4.03 (t, 1H, *J* = 6.6 Hz), 3.75 (quint, 1H, *J* = 6.0 Hz), 1.23 (d, 1H, *J* = 7.8 Hz); **mixture of syn- and anti-diastereomers: ¹³C NMR** (151 MHz, CDCl₃): δ 135.0, 135.0, 133.7, 133.7, 131.9, 131.7, 129.2, 128.9, 128.9, 127.9, 77.7, 76.5, 71.0, 70.4, 19.3, 17.9; **IR** (ν/cm⁻¹): 3384 (OH, br, s), 2973 (m), 2927 (m), 2870 (m), 1491 (m), 1472 (w), 1457 (w), 1405 (w), 1374 (w), 1135 (w), 1091 (m), 1012 (m); **HRMS**-(ESI⁺) [M+Na]⁺ calcd for C₁₁H₁₃ClNaO₂⁺ 235.0502, found: 235.0496.

Enantiomeric purity was determined by HPLC analysis compared to the authentic racemic material. Absolute stereochemistry was inferred from the stereochemistry obtained for compounds **20** and **22**.

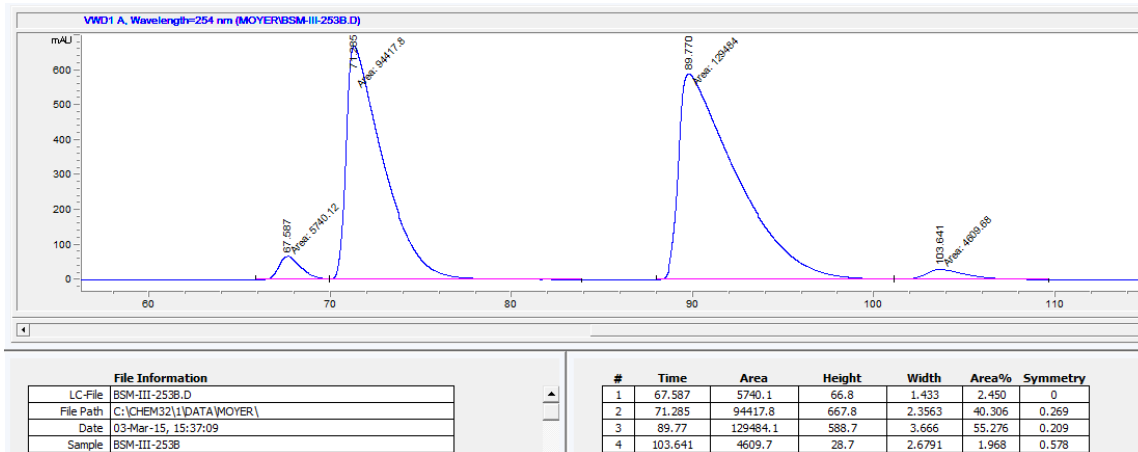*Diacel CHIRALPAK IA Column; 90:10 hexanes:EtOAc; 1.00 mL/min; 22 °C, 254 nm.*

Racemic Material

#	Time	Area	Height	Width	Area%	Symmetry
1	67.741	36443.2	333	1.3243	20.139	0.364
2	73.76	36696.9	305.8	2.0002	20.280	0.376
3	92.954	53655.9	303.8	2.9437	29.652	0.296
4	102.068	54158.3	252.2	3.5788	29.929	0.288

File Information
LC-File: BSM-III-272_1.D
File Path: C:\CHEM32\1\DATA\MOYER\
Date: 03-Mar-15, 11:28:48
Sample: BSM-III-272

syn-diastereomers: (2*S*,3*S*)-enantiomer: 67.7 min.; (2*R*,3*R*)-enantiomer: 73.8 min.;

*anti*-diastereomers: (2*R*,3*S*)-enantiomer: 93.0 min.; (2*S*,3*R*)-enantiomer: 102.1 min.

Enantio-enriched Material

#	Time	Area	Height	Width	Area%	Symmetry
1	67.587	5740.1	66.8	1.433	2.450	0
2	71.285	94417.8	667.8	2.3563	40.306	0.269
3	89.77	129484.1	588.7	3.666	55.276	0.209
4	103.641	4609.7	28.7	2.6791	1.968	0.578

File Information
LC-File: BSM-III-253B.D
File Path: C:\CHEM32\1\DATA\MOYER\
Date: 03-Mar-15, 15:37:09
Sample: BSM-III-253B

syn-diastereomers: (2*S*,3*S*)-enantiomer: 67.6 min.; (2*R*,3*R*)-enantiomer: 71.3 min.: 94:6 e.r.

anti-diastereomers: (2*R*,3*S*)-enantiomer: 89.8 min.; (2*S*,3*R*)-enantiomer: 103.6 min.; 97:3 e.r.
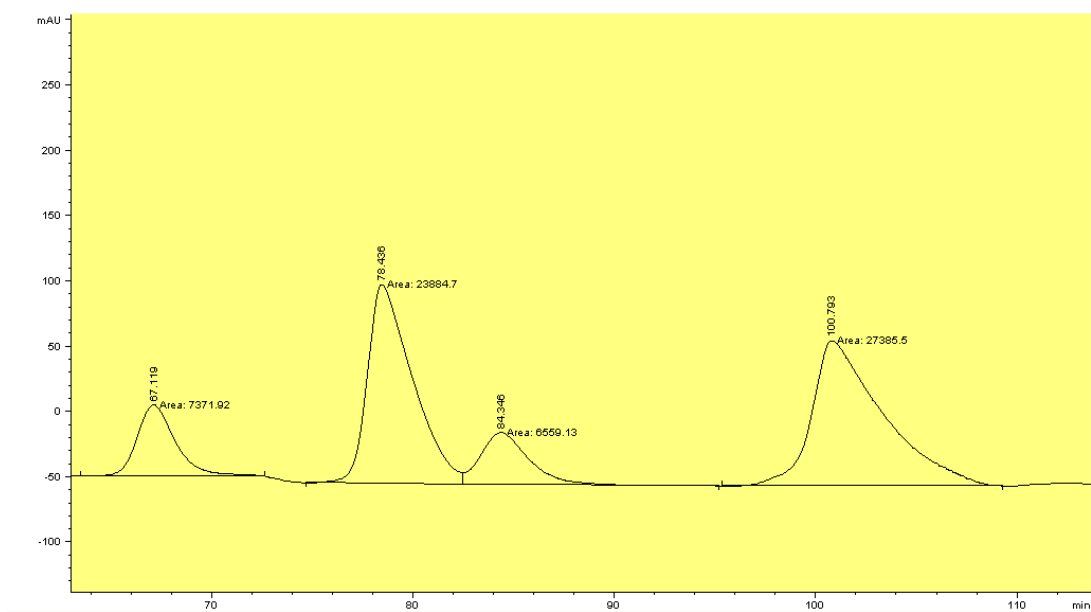
1.67
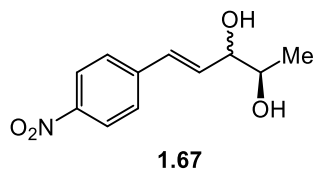
(2*R*,*E*)-5-(4-nitrophenyl)pent-4-ene-2,3-diol (1.67). Following Procedure C, the crude oxidation mixture was purified by silica gel chromatography (1:1 pentane:ethyl acetate), the product diol **1.67** was isolated as a viscous orange oil in 46% yield (10.2 mg) and 55:45 d.r (*syn:anti*). *syn*-**diastereomer:** ^{1}**H NMR** (600 MHz, CDCl$_3$): δ 8.19 (d, 2H, *J* = 8.4 Hz), 7.52 (d, 2H, *J* = 8.4 Hz), 6.78 (d, 1H, *J* = 16.8 Hz), 6.40 (dd, 1H, *J* = 16.2, 6.0 Hz), 4.11 (t, 1H, *J* = 6.6 Hz), 3.79 (quint, 1H, *J* = 6.6 Hz), 1.27 (d, 1H, *J* = 6.0 Hz); *anti*-**diastereomer:** ^{1}**H NMR** (600 MHz, CDCl$_3$): 8.19 (d, 2H, *J* = 8.4 Hz), 7.53 (d, 2H, *J* = 8.4 Hz), 6.75 (d, 1H, *J* = 16.2 Hz), 6.46 (dd, 1H, *J* = 15.6, 6.0 Hz), 4.33 (m, 1H), 4.02 (m, 1H), 1.21 (d, 1H, *J* = 6.0 Hz); **mixture of *syn*- and *anti*-diastereomers:** ^{13}**C NMR** (151 MHz, CDCl$_3$): δ 147.2, 147.2, 143.1, 143.0, 133.5, 132.3, 130.5, 130.4, 127.2, 127.2, 124.2, 76.0, 70.9, 70.4, 19.4, 17.9; **IR** (ν/cm^{-1}): 3392 (OH, br, s), 2976 (w), 2926 (w), 2855 (w), 1596 (m), 1515 (m), 1345 (m), 1110 (w), 1076 (w), 1027 (w); **HRMS**-(ESI$^+$) [M+Na]$^+$ calcd for C$_{11}$H$_{13}$NNaO$_4^+$ 246.0742, found: 246.0738.

Enantiomeric purity was determined by SFC analysis compared to the authentic racemic material. Absolute stereochemistry was inferred from the stereochemistry obtained for compounds **20** and **22**.

Regis RegisPack (RP, cat# 783104) column; 93:7 CO_2:MeOH; 1.00 mL/min; 40 °C, 210 nm (SFC).
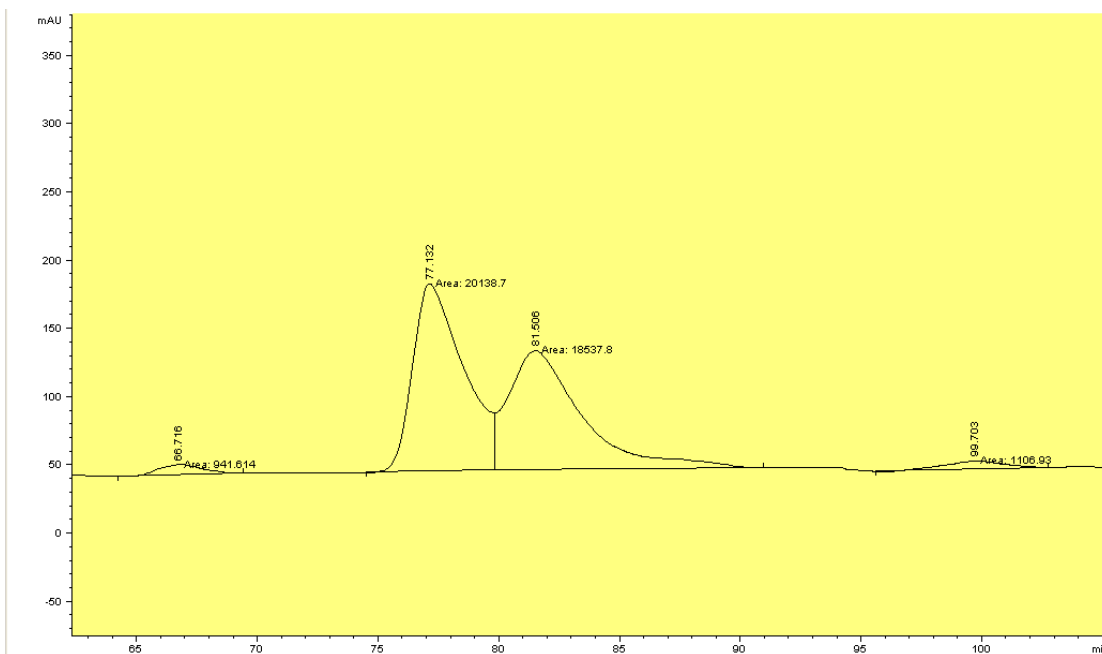
Racemic Material

syn-diastereomers: (2*S*,3*S*)-enantiomer: 67.1 min.; (2*R*,3*R*)-enantiomer: 84.4 min.;
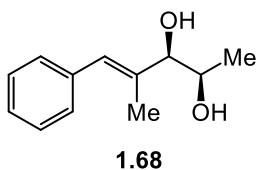
anti-diastereomers: (2*R*,3*S*)-enantiomer: 78.4 min., (2*S*,3*R*)-enantiomer: 100.8 min.

Enantio-enriched Material

syn-diastereomers: (2*S*,3*S*)-enantiomer: 66.7 min.; (2*R*,3*R*)-enantiomer: 81.5 min.: 95:5 e.r.

anti-diastereomers: (2*R*,3*S*)-enantiomer: 81.5 min.; (2*S*,3*R*)-enantiomer: 99.7 min.: 95:5 e.r.

1.68

(2R,3R,E)-4-methyl-5-phenylpent-4-ene-2,3-diol (1.68). Following Procedure B, the crude oxidation mixture was purified by silica gel chromatography (2:1 to 1:1 hexanes:ethyl acetate), the product diol **1.68** was isolated as a colorless oil in 54% yield (10.4 mg) and 97:3 d.r (*syn:anti*). **syn-diastereomer:** **¹H NMR** (CDCl₃, 600 MHz): δ 7.34 (t, 2H, *J* = 7.2), 7.28 (d, 2H, *J* = 7.8), 7.23 (t, 1H, *J* = 7.2), 6.54 (s, 1H), 3.87-3.91 (m, 2H), 1.88 (d, 3H, *J* = 1.2), 1.20 (d, 3H, *J* = 6.0); **¹³C NMR** (CDCl₃, 151 MHz): δ 137.4, 137.2, 129.1, 128.6, 128.3, 126.9, 83.2, 69.2, 19.2, 13.8; **IR** (ν/cm⁻¹): 3385 (OH, br, s), 3024 (w), 2970 (m), 2925 (m), 2862 (m), 1457 (m), 1374 (w), 1273 (w), 1127 (m), 1072 (w), 1040 (m), 1012
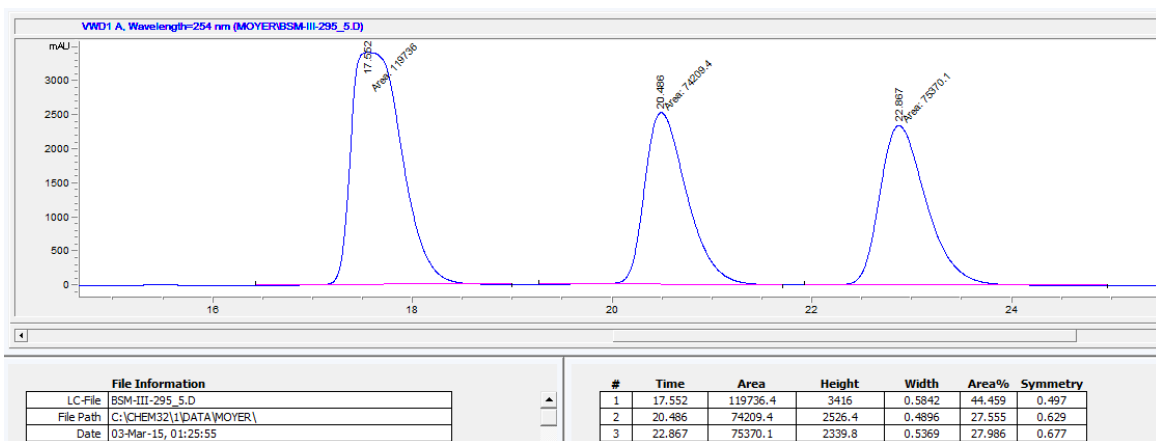
69

(m); **HRMS**-(ESI⁺) [M+Na]⁺ calcd for $C_{12}H_{16}NaO_2^+$ 215.1048, found: 215.1043; **[α]$_D^{19}$** = +50.2° (c =

0.485, CH_2Cl_2, l = 100 mm), Lit.: $[α]_D^{25}$ = +69.8° (c = 1.2, EtOH),[9] Lit.: $[α]_D^{20}$ = +76° (c = 1.0, EtOH).[10]

Enantiomeric purity was determined by HPLC analysis compared to the authentic racemic material. Absolute stereochemistry was determined by comparison of the $[α]_D$ value to those previously reported.[40,41]

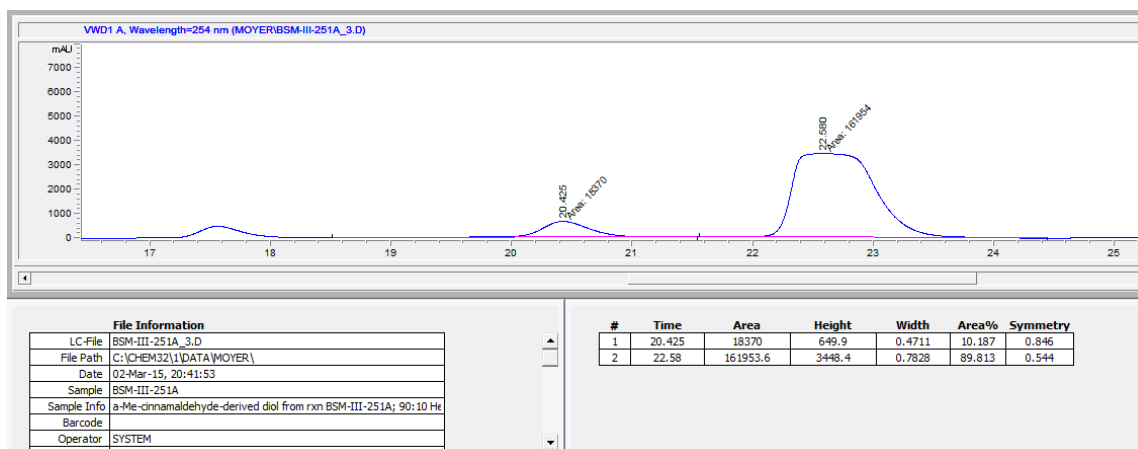*Diacel CHIRALPAK IC Column; 90:10 hexanes:EtOAc; 1.00 mL/min; 22 °C, 254 nm.*

Racemic Material

		File Information
LC-File	BSM-III-295_5.D	
File Path	C:\CHEM32\1\DATA\MOYER\	
Date	03-Mar-15, 01:25:55	

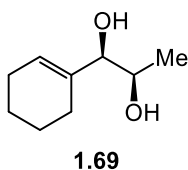| #	Time	Area	Height	Width	Area%	Symmetry
1	17.552	119736.4	3416	0.5842	44.459	0.497
2	20.486	74209.4	2526.4	0.4896	27.555	0.629
3	22.867	75370.1	2339.8	0.5369	27.986	0.677

syn-diastereomers: (2*S*,3*S*)-enantiomer: 20.5 min., (2*R*,3*R*)-enantiomer: 22.9 min.;

anti-diastereomers: Both (2*R*,3*S*)- and (2*S*,3*R*)-enantiomers: 17.6 min.

Enantio-enriched Material

VWD1 A, Wavelength=254 nm (MOYER\BSM-III-251A_3.D)

File Information	
LC-File	BSM-III-251A_3.D
File Path	C:\CHEM32\1\DATA\MOYER\
Date	02-Mar-15, 20:41:53
Sample	BSM-III-251A
Sample Info	a-Me-cinnamaldehyde-derived diol from rxn BSM-III-251A; 90:10 He
Barcode	
Operator	SYSTEM

#	Time	Area	Height	Width	Area%	Symmetry
1	20.425	18370	649.9	0.4711	10.187	0.846
2	22.58	161953.6	3448.4	0.7828	89.813	0.544

syn-diastereomers: (2*S*,3*S*)-enantiomer: 20.4 min.; (2*R*,3*R*)-enantiomer: 22.6 min.: 90:10 e.r.

1.69

(**1R,2R**)-1-(cyclohex-1-en-1-yl)propane-1,2-diol (1.69). Following Procedure B, the crude oxidation

mixture was purified by silica gel chromatography (2:1 to 1:1 hexanes:ethyl acetate), the product diol

1.69 was isolated as a colorless oil in 34% yield (5.3 mg) and 96:4 d.r (*syn:anti*). **syn-diastereomer:**

¹H NMR (600 MHz, CDCl₃): δ 5.72 (m, 1H), 3.77 (quint, 1H, *J* = 6.6 Hz), 3.67 (d, 1H, *J* = 7.2 Hz),

2.10-2.14 (m, 2H), 2.03 (m, 2H), 1.49-1.69 (m, 4H), 1.12 (d, 3H, *J* = 6.6 Hz); **¹³C NMR** (151 MHz,

CDCl₃): δ 137.3, 126.1, 81.8, 69.1, 25.2, 24.3, 22.7, 22.7, 19.1;

IR (ν/cm⁻¹): 3384 (OH, br, s), 2964 (w), 2927 (m), 2857 (w), 2836 (w), 1507 (w), 1489 (w), 1457 (w),

1437 (w), 1372 (w), 1240 (w), 1126 (w), 1064 (w), 1020 (m); **HRMS**-(ESI⁺) [M+Na]⁺ calcd for

$C_9H_{16}NaO_2^+$ 179.1048, found: 179.1044; **[α]$_D^{20}$** = +2.7° (*c* = 0.245, CH₂Cl₂, *l* = 100 mm).

Enantiomeric purity was determined by HPLC analysis compared to the authentic racemic material.

Absolute stereochemistry was inferred from the stereochemistry obtained for compound **20** and **22**.

Diacel CHIRALPAK IC Column; 99:1 hexanes:iPrOH; 0.75 mL/min; 22 °C, 190 nm.
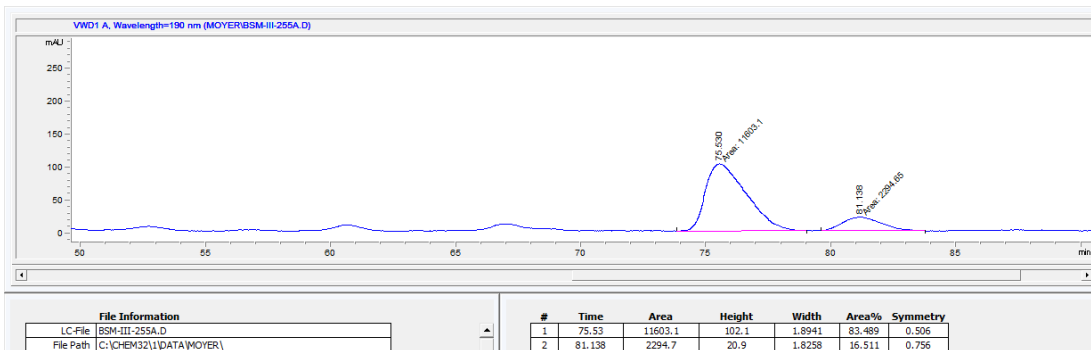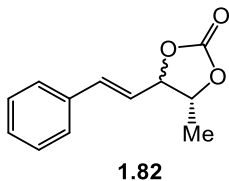
Racemic Material

#	Time	Area	Height	Width	Area%	Symmetry
1	55.702	6784	86.4	1.3084	25.874	0.56
2	59.768	6790.2	78.7	1.4375	25.897	0.58
3	75.627	6287.9	61.8	1.6947	23.981	0.609
4	80.426	6357.6	54.2	1.9548	24.247	0.507
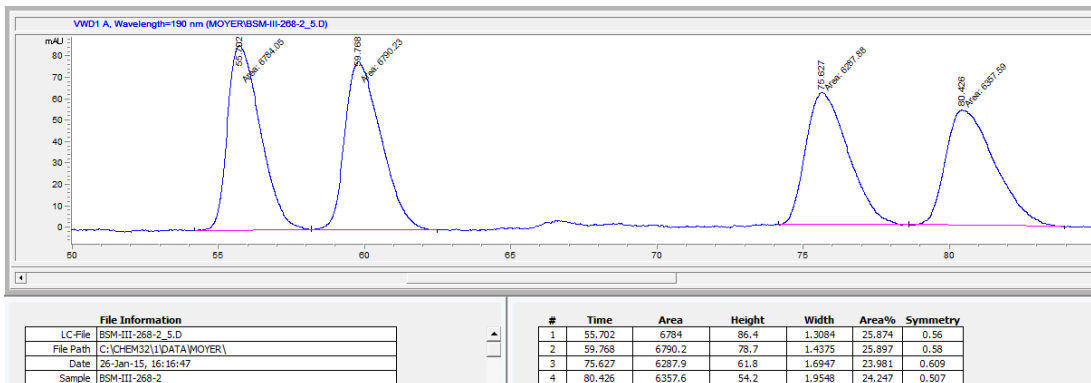
syn-diastereomers: (1*R*,2*R*)-enantiomer: 75.6 min., (1*S*,2*S*)-enantiomer: 80.4 min.;

anti-diastereomers: 55.7 min., 59.8 min.

Enantio-enriched Material

#	Time	Area	Height	Width	Area%	Symmetry
1	75.53	11603.1	102.1	1.8941	83.489	0.506
2	81.138	2294.7	20.9	1.8258	16.511	0.756

syn-diastereomers: (1*R*,2*R*)-enantiomer: 75.5 min.; (1*S*,2*S*)-enantiomer: 81.1 min.: 83:17 e.r.

1.82

(4*R*)-4-methyl-5-((*E*)-styryl)-1,3-dioxolan-2-one (1.80). Diol **1.65** was transformed to the title cyclic

carbonate **1.82** according to a modified literature procedure.[42] A flame-dried 20-mL scintillation vial

equipped with a magnetic stir bar was flushed with N_2 and charged with diol **1.65** (44.7 mg, 0.251 mmol) and 1.9 mL of anhydrous thf. Carbonyldiimidazole (61.0 mg, 0.376 mmol) was added to the stirring solution and the headspace was purged with N_2. The solution was allowed to stir for 5 h, during which time it was monitored by TLC (2:1 hexanes:ethyl acetate, UV visualization). Water was added to quench the reaction when the diol was observed to be consumed. The crude reaction mixture was purified by silica gel column chromatography (2:1 hexanes:ethyl acetate) and the 52:48 d.r. mixture of carbonate diastereomers **1.82** was isolated as a viscous oil in 60% yield (30.7 mg). **¹H NMR** (600 MHz, CDCl$_3$): δ 7.40-7.43 (m, 4H), 7.35-7.38 (m, 4H), 7.32-7.34 (m, 2H), 6.78 (d, 2H, J = 16.2 Hz), 6.16 (m, 2H), 5.28 (t, 1H, J = 5.3 Hz), 4.95 (quintt, 1H, J = 7.2 Hz), 4.77 (t, 1H, J = 7.8 Hz), 4.53 (m, 1H), 1.53 (d, 3H, J = 6 Hz), 1.40 (d, 3H, J = 6.6 Hz); **¹³C NMR** (151 MHz, CDCl$_3$): δ 154.5, 154.4, 137.1, 136.9, 135.2, 134.9, 129.3, 129.2, 129.0, 129.0, 127.1, 127.1, 121.8, 119.8, 84.7, 80.7, 78.8, 76.6, 18.2, 15.9; **IR** (v/cm^{-1}): 2979 (w), 2953 (w), 2919 (m), 2851 (w), 1798 (CO, s), 1450 (w), 1351 (w), 1186 (m), 1070 (m), 1020 (m); **HRMS**-(ESI$^+$) [M+Na]$^+$ calcd for $C_{12}H_{12}NaO_3^+$ 227.0684, found: 227.0679.

The enantiomeric purity of the diol starting material (**1.80**) for the carbonate protection/defunctionalization sequence was independently determined by HPLC analysis.
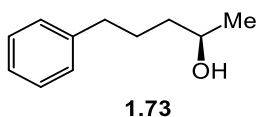
Enantio-enriched Material

#	Time	Area	Height	Width	Area%	Symmetry
1	90.425	5154.3	47.9	1.7935	4.213	0
2	94.868	67960.1	425.5	2.662	55.548	0.289
3	118.91	46782.3	295.3	2.6405	38.238	0.515
4	147.446	2448	12.9	3.171	2.001	0.562
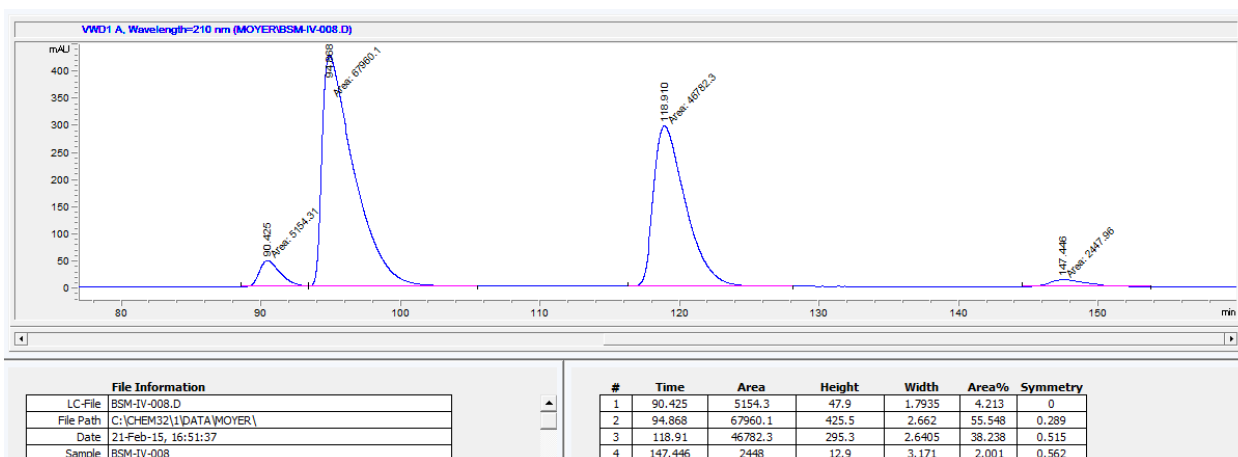
syn-diastereomers: (2*S*,3*S*)-enantiomer: 90.4 min.; (2*R*,3*R*)-enantiomer: 118.9 min.: 90:10 e.r.

anti-diastereomers: (2*R*,3*S*)-enantiomer: 94.9 min.; (2*S*,3*R*)-enantiomer: 147.5 min.: 97:3 e.r.

1.73

(***R***)-5-phenylpentan-2-ol (**1.73**). Compound **1.82** was defunctionalized and then hydrogenated to the title alcohol **22** according to a modified literature procedure.[42] In an N_2-filled glove box, an 8-mL vial equipped with a magnetic stir bar and septum cap was charged with carbonate (14.8 mg, 0.0725 mmol) and a 560 μL thf solution containing Pd_2(dba)$_3$ (0.67 mg, 0.000725 mmol) and PPh_3 (0.38 mg, 0.00145). The vial was removed from the glove box, cooled to 0 °C, and charged with Et_3N (50 μL, 0.363 mmol) and HCOOH (27 μL, 0.725 mmol). The reaction was monitored by TLC (2:1 hexanes/diethyl ether, UV visualization), and after 5 hours the solvent was removed by purging with a stream of H_2 gas. Pd/C (15 mg (5 wt %), 0.00725 mmol) was added to the vial, in addition to 1.0 mL of wet methanol. The septum cap was replaced and the headspace was purged with H_2 gas. The solution was allowed to vigorously stir at 22 °C for 1 h before being filtered through a plug of silica gel with ethyl acetate. The crude reaction mixture was purified by silica gel column chromatography (2:1 hexanes:diethyl ether)
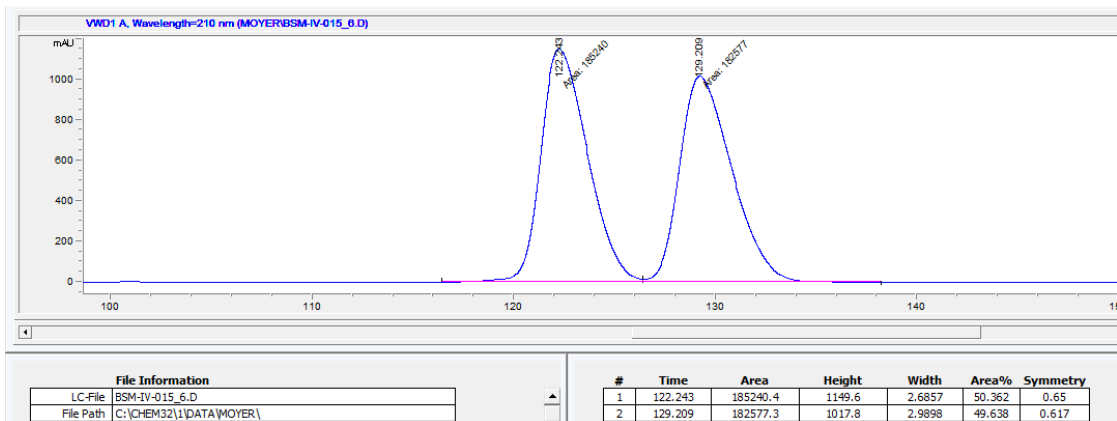
to yield the title compound as a clear, colorless oil in 50% yield (6.0 mg). The title compound was found to be identical to literature spectra.[12] HPLC analysis of compound **1.73** in comparison to a previously prepared racemic sample provided an enantiomeric ratio of 92:8 e.r., which can be compared to the average e.r. of the two diol diastereomers (52:48 (*syn:*anti); *syn*: 90:10 e.r.*; anti*: 97:3 e.r.) from which it was derived. The measured optical rotation $[\boldsymbol{\alpha}]_{\mathbf{D}}{}^{\mathbf{20}} = $ —7.4° ($c = 0.455$, CH_2Cl_2, $l = 100$ mm) matches the sign and approximate magnitude of the opposite enantiomer of that reported in the literature (lit.[12] $[\alpha]_{\mathbf{D}}{}^{\mathbf{20}} = +8.0°$ ($c = 1.0$, $CHCl_3$, 97% *ee*, (*S*)-isomer) and lit.[13] $[\alpha]_{\mathbf{D}}{}^{\mathbf{27}} = +8.47°$ ($c = 3.0$, $CHCl_3$, (*S*)-isomer)).

Enantiomeric purity was determined by HPLC analysis compared to the authentic racemic material. Absolute stereochemistry was determined by comparison with the signs of the previously reported $[\alpha]_{\mathrm{D}}$ values.[12,13]

Diacel CHIRALPAK IC Column; 99:1 hexanes:iPrOH; 0.20 mL/min; 22 °C, 210 nm.

(*R*)-enantiomer: 122.24 min., (*S*)-enantiomer: 129.21 min.

Racemic Material

	File Information		#	Time	Area	Height	Width	Area%	Symmetry
LC-File	BSM-IV-015_6.D		1	122.243	185240.4	1149.6	2.6857	50.362	0.65
File Path	C:\CHEM32\1\DATA\MOYER\		2	129.209	182577.3	1017.8	2.9898	49.638	0.617

(*R*)-enantiomer: 122.2 min.; (*S*)-enantiomer: 129.2 min.
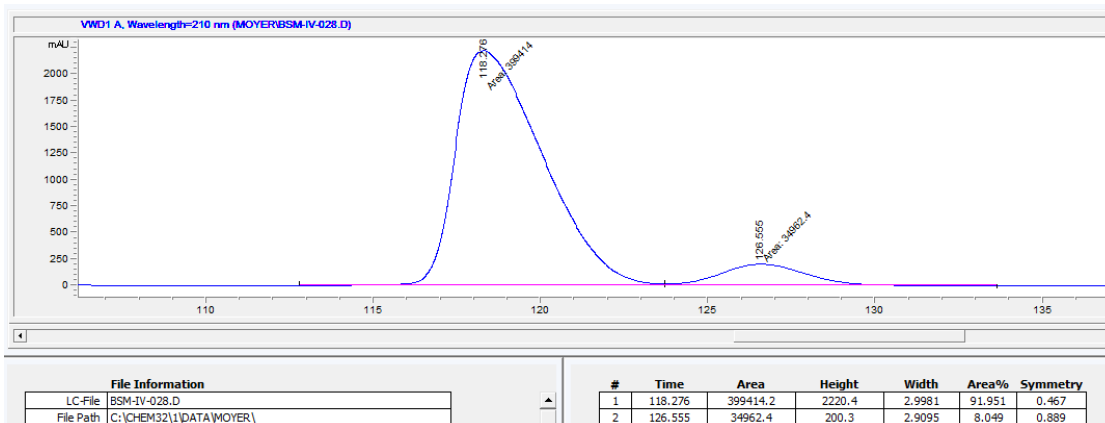
(*R*)-enantiomer: 118.3 min., (*S*)-enantiomer: 126.6 min.: 92:8 e.r.

1.74
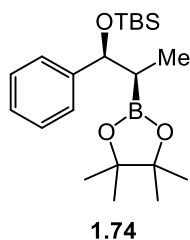
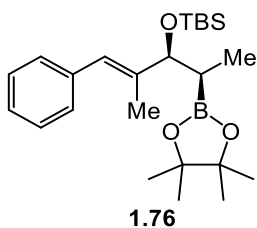**tert-butyldimethyl((1*S*,2*R*)-1-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propoxy)silane (1.74).** The title benzylic *tert*-butyldimethylsilyl ether **1.74** was prepared from hydroxyboronate **2** according to a standard literature procedure.[42] A flame-dried 8-mL vial equipped with a magnetic stir bar was charged with hydroxyboronate **1.46** (65.5 mg, 0.250 mmol) and 2.0 mL of anhydrous DMF. Imidazole (34.0 mg, 0.500 mmol) was added, followed by tert-butyldimethylsilyl chloride (56.5 mg, 0.375 mmol). The vial was capped with a screw-cap septum and purged with N_2 for 5 minutes before being allowed to stir at 22 °C for 24 h (TLC monitoring; 2:1 hexanes:diethyl ether, R_f = 0.7, UV and Seebach stain). The reaction was quenched with 1.0 mL of a saturated aqueous solution of NH_4Cl, and the aqueous layer was extracted three times with ethyl acetate. The combined organic layers were then washed twice with saturated aqueous $NaHCO_3$, followed by two washes with saturated aqueous NaCl. The resulting organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*.

76

The crude residue was purified by silica gel column chromatography (25:1 pentane:diethyl ether) and **1.74** was isolated as a colorless oil in 76% yield (71.8 mg) and 89:11 d.r. (*syn:anti*). ***syn*-diastereomer:** **¹H NMR** (CDCl₃, 600 MHz): δ 7.30 (dd, 2H, *J* = 7.8, 1.2 Hz), 7.26 (t, 2H, *J* = 7.2 Hz), 7.19 (tt, 1H, *J* = 7.2, 1.8 Hz), 4.71 (d, 1H, *J* = 7.8 Hz), 1.49 (quint, 1H, *J* = 7.8 Hz), 1.25 (s, 6H), 1.24 (s, 6H), 0.86 (s, 9H), 0.75 (d, 3H, *J* = 7.2 Hz), 0.02 (s, 3H), —0.29 (s, 3H); **¹³C NMR** (CDCl₃, 151 MHz): δ 145.2, 127.7, 127.0, 126.9, 83.1, 77.8, 26.1, 25.4, 24.8, 18.3, 11.7, —4.3, —4.6; **IR** (ν/cm⁻¹): 3086 (w), 3063 (w), 3030 (w), 2978 (m), 2957 (m), 2929 (m), 2886 (m), 2857 (m), 1493 (w), 1471 (w), 1462 (m), 1402 (w), 1380 (m), 1371 (m), 1319 (m), 1255 (m), 1211 (w), 1184 (w), 1166 (w), 1146 (m), 1110 (w), 1078 (w), 1060 (m), 1029 (w), 1006 (w); **HRMS**-(ESI⁺) [M+Na]⁺ calcd for $C_{21}H_{37}BNaO_3Si^+$ 399.2503, found: 399.2498; **[α]ᴅ¹⁷** —23.8° (*c* = 3.59, CH₂Cl₂, *l* = 100 mm).

1.75
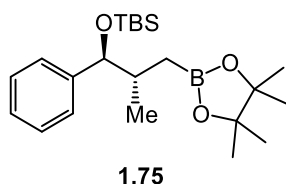
***tert*-butyldimethyl((1*S*,2*S*)-2-methyl-1-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propoxy)silane (1.75).** Homologated pinacol boronic ester **1.75** was prepared from TBS-protected **2** according to a modified literature procedure.[12] To a stirred solution of TBS-protected **2** (35.0 mg, 0.0930 mmol) and dibromomethane (16 μL, 0.233 mmol) in anhydrous thf (0.93 mL) at —78 °C in a flame-dried 8-mL vial equipped with a magnetic stir bar, was added *n*-BuLi (1.6 M in hexanes, 0.205 mmol) dropwise. The resulting mixture was stirred for 10 min. at —78 °C and then warmed to 22 °C and allowed to stir for 2 h. The reaction was quenched with 1.0 mL of a saturated aqueous solution of NH₄Cl, and the aqueous layer was diluted with 1.0 mL of deionized water and extracted three times with diethyl ether. The resulting organic layer was dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (25:1 pentane:diethyl ether; TLC in 4:1 hexanes:diethyl ether, R_f = 0.65, Seebach stain) and the title compound **1.75** was isolated

as a colorless oil in 75% yield (27.3 mg) and 91:9 d.r. (*syn:anti*). **syn-diastereomer: ^{1}H NMR** (CDCl$_3$, 600 MHz): δ 7.24-7.27 (m, 4H), 7.18-7.21 (m, 1H), 4.39 (d, 1H, *J* = 6.0 Hz), 1.97 (m, 1H), 1.23 (s, 6H), 1.23 (s, 6H), 1.03 (dd, 1H, *J* = 15.6, 4.2 Hz), 0.87 (s, 9H), 0.80 (d, 3H, *J* = 7.2 Hz), 0.62 (dd, 1H, *J* = 15.6, 10.2 Hz), 0.01 (s, 3H), —0.24 (s, 3H); **^{13}C NMR** (CDCl$_3$, 151 MHz): δ 144.2, 127.6, 127.2, 126.8, 83.0, 80.3, 38.0, 26.1, 25.1, 24.8, 18.4, 18.4, —4.5, —4.9; **IR** (v/cm^{-1}): 3087 (w), 3063 (w), 3028 (w), 2977 (m), 2957 (m), 2929 (m), 2888 (m), 2857 (m), 1493 (w), 1471 (w), 1463 (w), 1370 (m), 1318 (m), 1255 (m), 1214 (w), 1165 (w), 1146 (m), 1087 (m), 1063 (m), 1027 (w), 1006 (w); **HRMS**-(ESI$^+$) [M+Na]$^+$ calcd for C$_{22}$H$_{39}$BNaO$_3$Si$^+$ 413.2660, found: 413.2654; **[α]$_D^{22}$** —24.2° (*c* = 1.37, CH$_2$Cl$_2$, *l* = 100 mm).

1.76

***tert*-butyldimethyl(((3*S*,4*R*,*E*)-2-methyl-1-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-1-en-3-yl)oxy)silane (1.76).** The title allylic *tert*-butyldimethylsilyl ether **1.76** was prepared from **1.80** according to a literature procedure.[42] A flame-dried 8-mL vial equipped with a magnetic stir bar was charged with **1.80** (57.5 mg, 0.190 mmol) and 1.54 mL of anhydrous DMF. Imidazole (25.9 mg, 0.380 mmol) was added, followed by tert-butyldimethylsilyl chloride (43.0 mg, 0.285 mmol). The vial was capped with a screw-cap septum and purged with N$_2$ for 5 minutes before being allowed to stir at 22 °C for 20 h. The progress of the reaction was followed by TLC (2:1 hexanes:diethyl ether, R$_f$ = 0.75, UV visualization). The reaction was quenched with 1.0 mL of a saturated aqueous solution of NH$_4$Cl, and the aqueous layer was extracted three times with ethyl acetate. The combined organic layers were then washed twice with saturated aqueous NaHCO$_3$, followed by two washes with saturated aqueous NaCl. The resulting organic layer was dried over MgSO$_4$, filtered, and concentrated *in vacuo*.
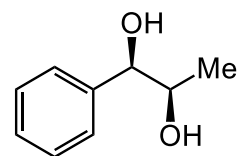
The crude residue was purified by silica gel column chromatography (25:1 pentane:diethyl ether) and the title compound **1.76** was isolated as a colorless oil in 64% yield (50.6 mg) and as a single detectable diastereomer. ***syn*-diastereomer: ^{1}H NMR** (CDCl$_3$, 400 MHz): δ 7.33 (t, 2H, J = 7.6 Hz), 7.27 (d, 2H, J = 8.4 Hz), 7.21 (t, 1H, J = 7.2 Hz), 6.40 (s, 1H), 4.19 (d, 1H, J = 9.2 Hz), 1.80 (d, 3H, J = 1.2 Hz), 1.44 (quint, 1H, J = 8.4 Hz), 1.27 (s, 6H), 1.26 (s, 6H), 0.91 (s, 9H), 0.85 (d, 3H, J = 7.6 Hz), 0.12 (s, 3H), 0.03 (s, 3H); **^{13}C NMR** (CDCl$_3$, 100 MHz): δ 140.4, 138.2, 129.0, 128.2, 126.7, 126.3, 83.0, 82.0, 26.2, 25.4, 24.8, 18.4, 12.6, 12.5, —4.1, —4.7; **IR** (v/cm^{-1}): 3082 (w), 3059 (w), 3025 (w), 2976 (m), 2955 (m), 2930 (m), 2889 (m), 2857 (m), 1462 (m), 1380 (m), 1320 (m), 1252 (m), 1146 (m), 1109 (w), 1058 (m), 1005 (m); **HRMS**-(ESI$^+$) [M+Na]$^+$ calcd for C$_{24}$H$_{41}$BNaO$_3$Si$^+$ 439.2816, found: 439.2811; **[α]$_D^{19}$** +16.2° (c = 2.53, CH$_2$Cl$_2$, l = 100 mm).

1.77
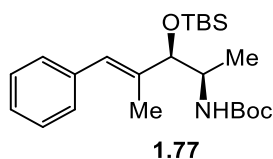
***tert*-butyl((2R,3R,E)-3-((*tert*-butyldimethylsilyl)oxy)-4-methyl-5-phenylpent-4-en-2-yl)carbamate (1.77).** Carbamate **1.77** was prepared from compound **1.76** according to literature procedure[13a]. A flame-dried 8-mL vial equipped with a magnetic stir bar was flushed with N$_2$ and charged with **1.76** (25.2 mg, 0.0605 mmol) and 500 μL of anhydrous thf. A 0.928 M solution of *O*-methylhydroxylamine (196 μL, 0.182 mmol) was added to a separate N$_2$-flushed, flame-dried 8-mL vial and then diluted with 418 μL of anhydrous thf. Both vials were cooled to —78 °C in a dry ice/acetone bath. A 1.59 M solution of *n*-butyllithium in hexanes (114 μL, 0.182 mmol) was added dropwise to the *O*-methylhydroxylamine solution and this was allowed to stir at —78 °C for 30 minutes. After this time, the *in* situ generated solution of lithium *O*-methylhydroxylamide was cannula transferred to the cooled solution of **S3**. The resulting solution was allowed to warm to room temperature and was then heated to 60 °C with stirring for 20 h. After this time, the solution was allowed to cool to 22 °C and di-*tert*-butyl dicarbonate (44.5 μL, 0.194 mmol) was added via syringe. The

solution was allowed to stir for 2 hours at 22 °C. The reaction was quenched with 3 mL of deionized water, and the aqueous layer was extracted four times with ethyl acetate. The combined organic layers were then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (10:1 pentane:diethyl ether), yielding both returned starting material (5.6 mg, 22%) and title carbamate **1.77**. The title compound was isolated as a colorless oil in 57% yield (14.0 mg). ***syn*-diastereomer: ^{1}H NMR** (CDCl$_3$, 600 MHz): δ 7.31 (t, 2H, *J* = 7.2 Hz), 7.24 (d, 2H, *J* = 7.8 Hz), 7.20 (t, 1H, *J* = 7.2 Hz), 6.49 (s, 1H), 4.65 (s, br, 1H), 3.97 (d, 1H, *J* = 3.0 Hz), 3.90 (s, br, 1H), 1.85 (d, 3H, *J* = 1.2 Hz), 1.37 (s, 9H), 1.19 (d, 3H, *J* = 6.6 Hz), 0.96 (s, 9H), 0.10 (s, 3H), 0.06 (s, 3H); **^{13}C NMR** (CDCl$_3$, 151 MHz): δ 155.8, 138.1, 137.9, 129.1, 128.1, 126.4, 126.1, 80.3, 79.0, 49.1, 28.56, 26.1, 19.5, 18.4, 15.3, —4.3, —5.0; **IR** (ν/cm^{-1}): 3449 (w), 3365 (br, w), 2972 (m), 2956 (m), 2930 (m), 2892 (w), 2885 (w), 2857 (m), 1716 (CO, s), 1496 (s), 1455 (m), 1390 (m), 1365 (m), 1253 (m), 1170 (s), 1106 (m), 1057 (m), 1007 (w); **HRMS**-(ESI$^+$) [M+Na]$^+$ calcd for C$_{23}$H$_{39}$NNaO$_3$Si$^+$ 428.2597, found: 428.2594; **[α]$_D^{19}$** —25.7° (*c* = 0.650, CH$_2$Cl$_2$, *l* = 100 mm).

1.72
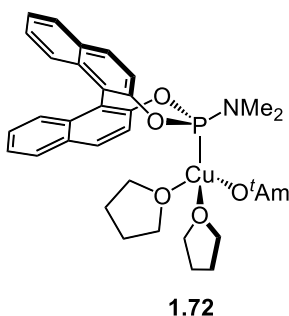
bis(tetrahydrofuran)[(*R*)-Monophos]cuprous *tert*-amylate (1.72). In an N$_2$-filled glovebox, Tetrakis(acetonitrile)copper(I) hexafluorophosphate (20.7 mg, 0.0557 mmol) and *(R)*-Monophos (20.0 mg, 0.0557 mmol) were added to an 8-mL vial equipped with a magnetic stir bar and then charged with 1.0 mL of thf (0.56 M) and allowed to stir at ambient temperature for 30 minutes. LiO^{t}Am (5.2 mg, 0.0557 mmol) dissolved in 0.5 mL of thf was then added via syringe to the reaction mixture and allowed to stir for an additional hour at ambient temperature. The reaction was filtered through a plug of

Celite™ and then concentrated *in vacuo*. Benzene was added to the residue and this slurry was filtered through Celite™ again and washed with more benzene. This residue was concentrated *in vacuo*, charged with Et$_2$O and then re-concentrated *in vacuo* to produce **1.72** as a free-flowing yellow powder (34.5 mg) in 95% yield. **^{1}H NMR** (600 MHz, thf-*d$_8$*) δ 8.21 – 7.94 (m, 4H), 7.67 (s, 1H), 7.54 (d, J = 8.8 Hz, 1H), 7.45 (t, J = 7.3 Hz, 2H), 7.37 – 7.24 (m, 4H), 3.61 (d, J = 5.3 Hz, 4H), 2.55 (s, 6H), 1.77 (d, J = 3.7 Hz, 4H), 1.40 (d, J = 7.5 Hz, 2H), 1.08 (s, 6H), 0.87 (t, J = 7.5 Hz, 3H). **^{31}P NMR** (243 MHz, thf-*d$_8$*) δ 124.6 (br s)

1.53

^{1}H NMR (600 MHz, CDCl$_3$)
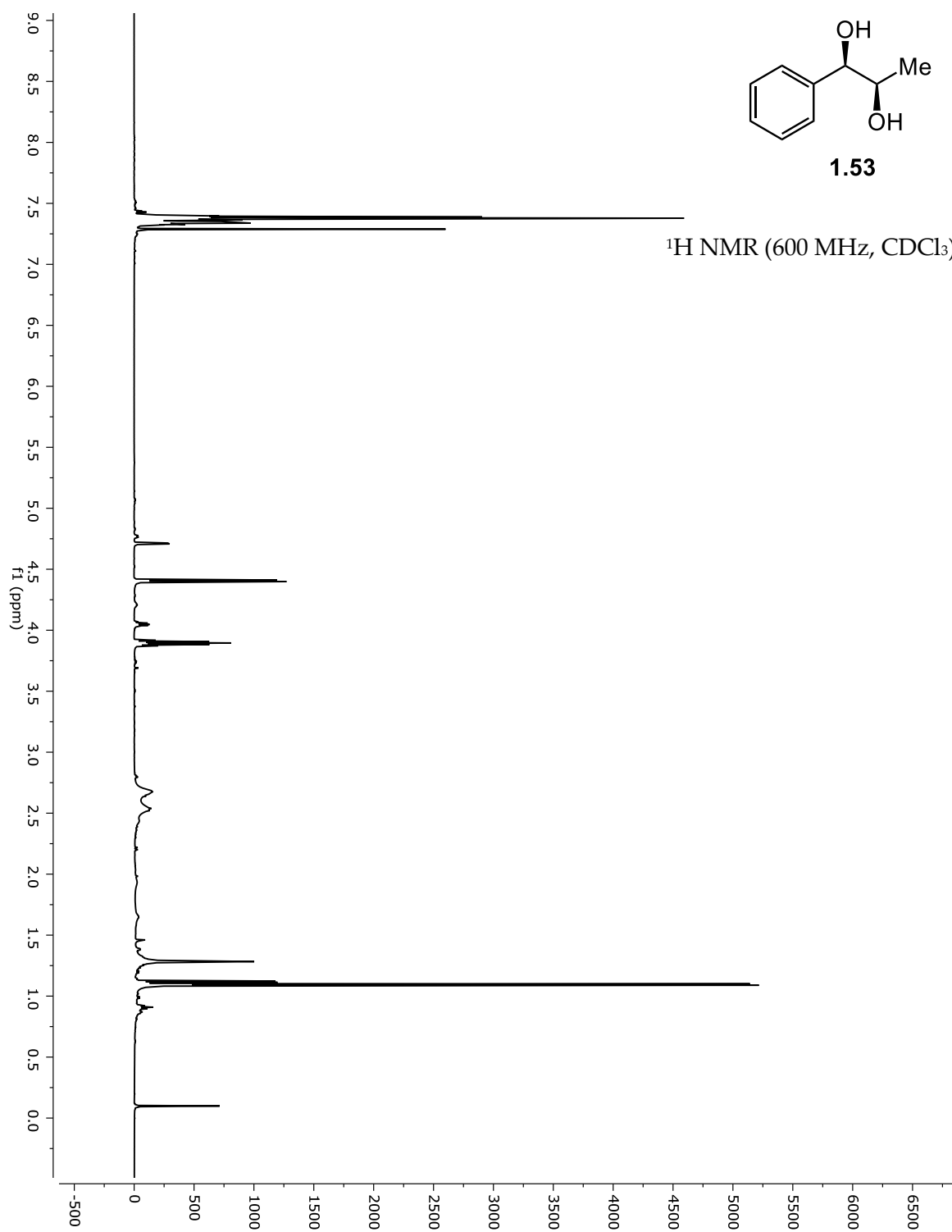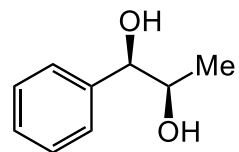
1.53

^{13}C NMR (151 MHz, CDCl$_3$)
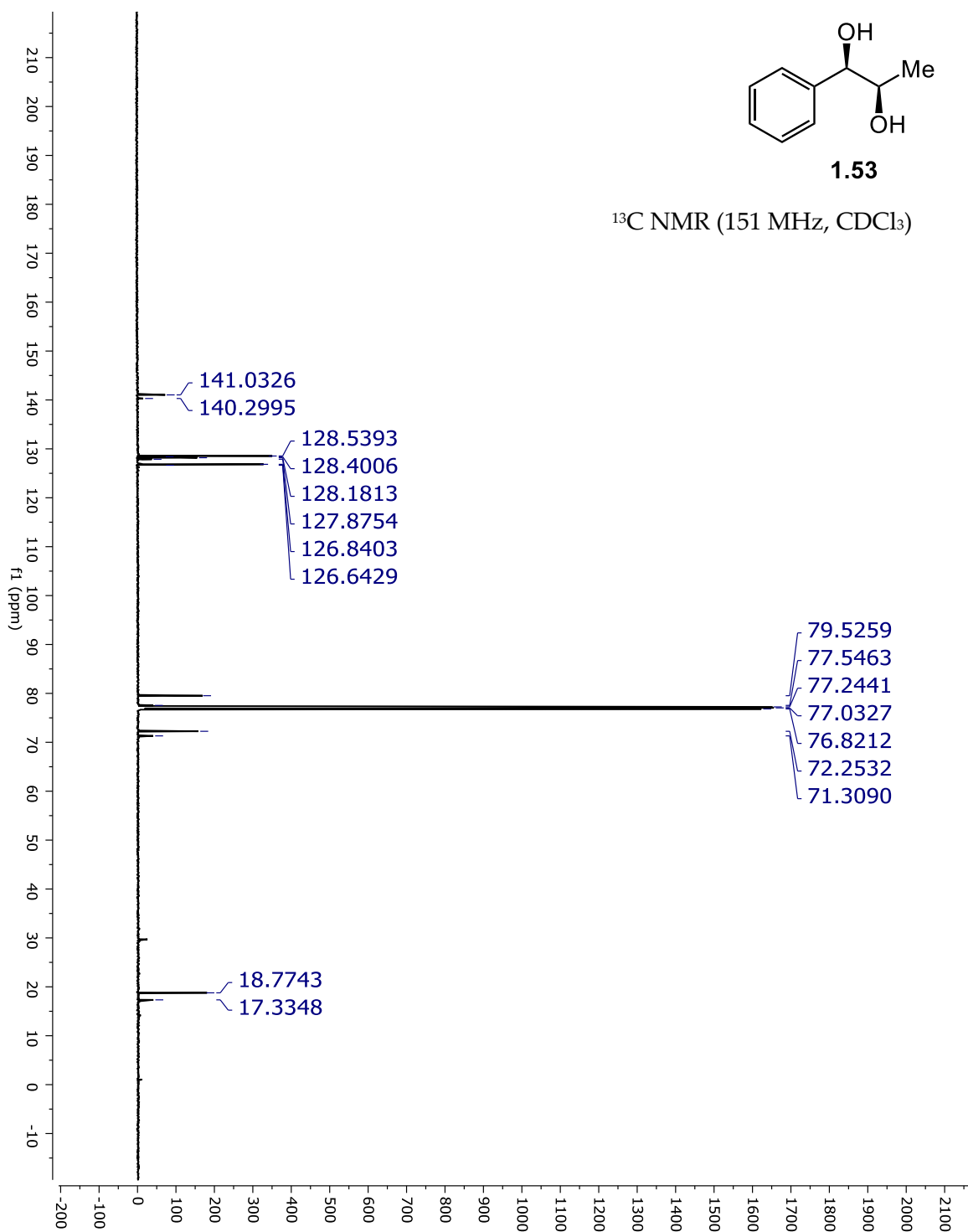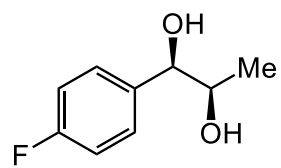
141.0326
140.2995

128.5393
128.4006
128.1813
127.8754
126.8403
126.6429

79.5259
77.5463
77.2441
77.0327
76.8212
72.2532
71.3090

18.7743
17.3348

f1 (ppm)

1.54

¹H NMR (600 MHz, CDCl₃)

84

^{13}C NMR (151 MHz, CDCl$_3$)

163.3597
163.1875
161.7285
161.5577

136.7633
128.5291
128.4763
128.3165
115.4767
115.3350
115.3018
115.1620

78.8482
77.2375
77.0262
76.8146
72.2895
71.2034

18.8156
17.2403

f1 (ppm)

1.55

^{1}H NMR (600 MHz, CDCl$_3$)

86

1.55

^{13}C NMR (151 MHz, CDCl$_3$)

140.0145
139.2578
131.6228
131.4370
128.5635
128.3414
122.0129
121.6677

78.8007
77.2478
77.0363
76.8249
76.7493
72.1194
71.1077

18.8267
17.0987
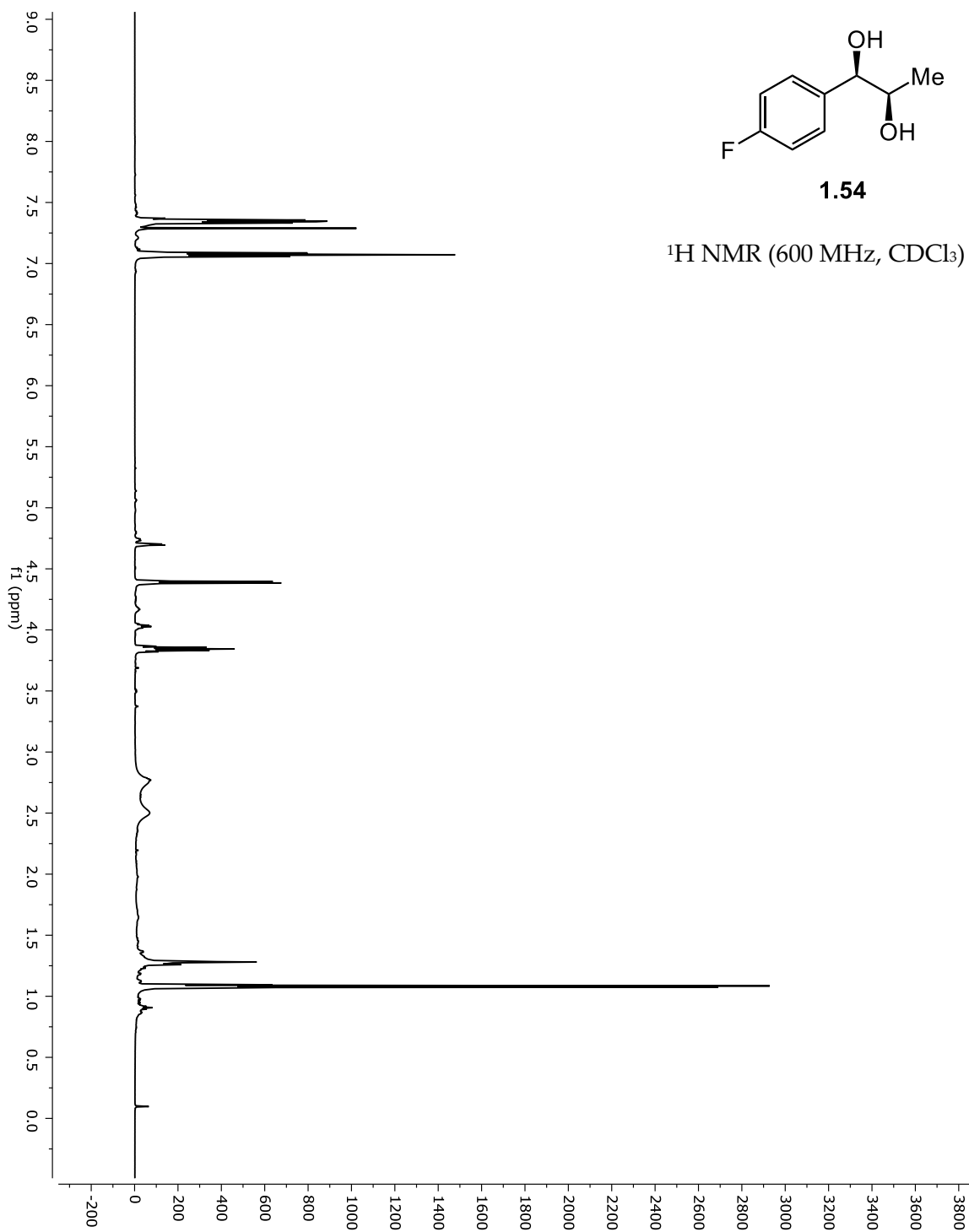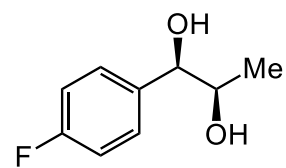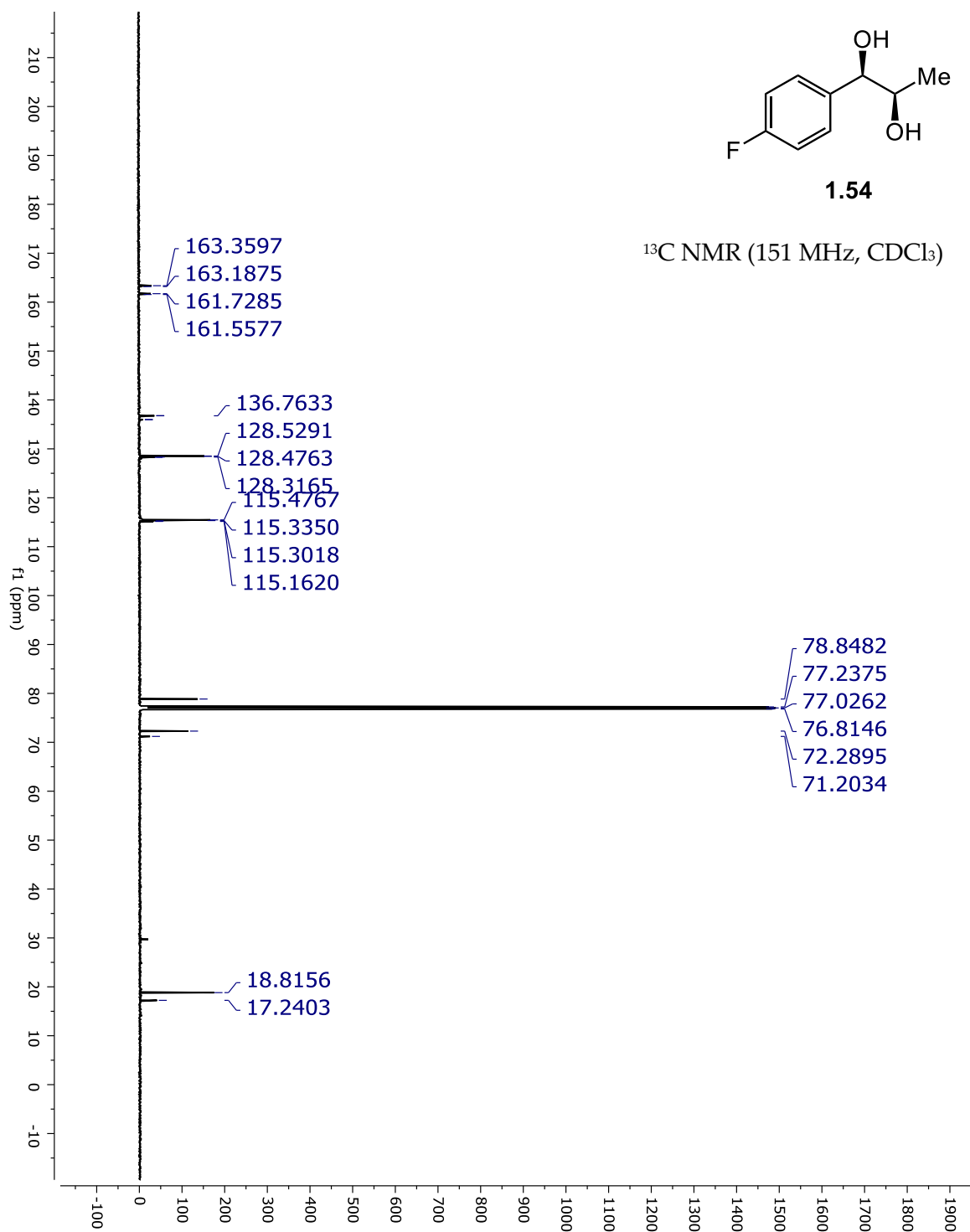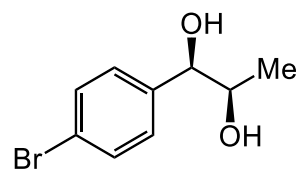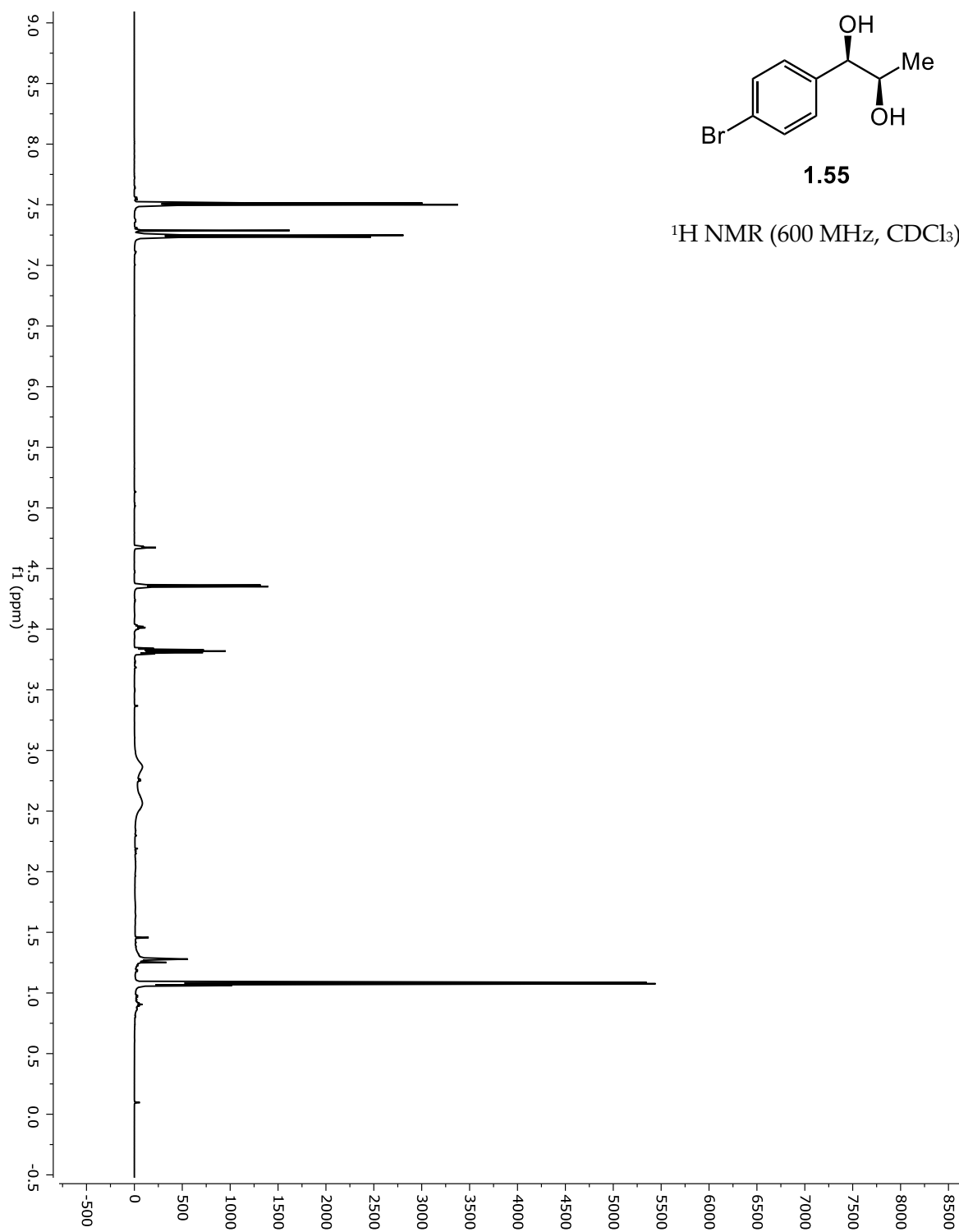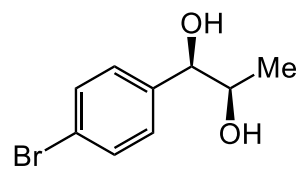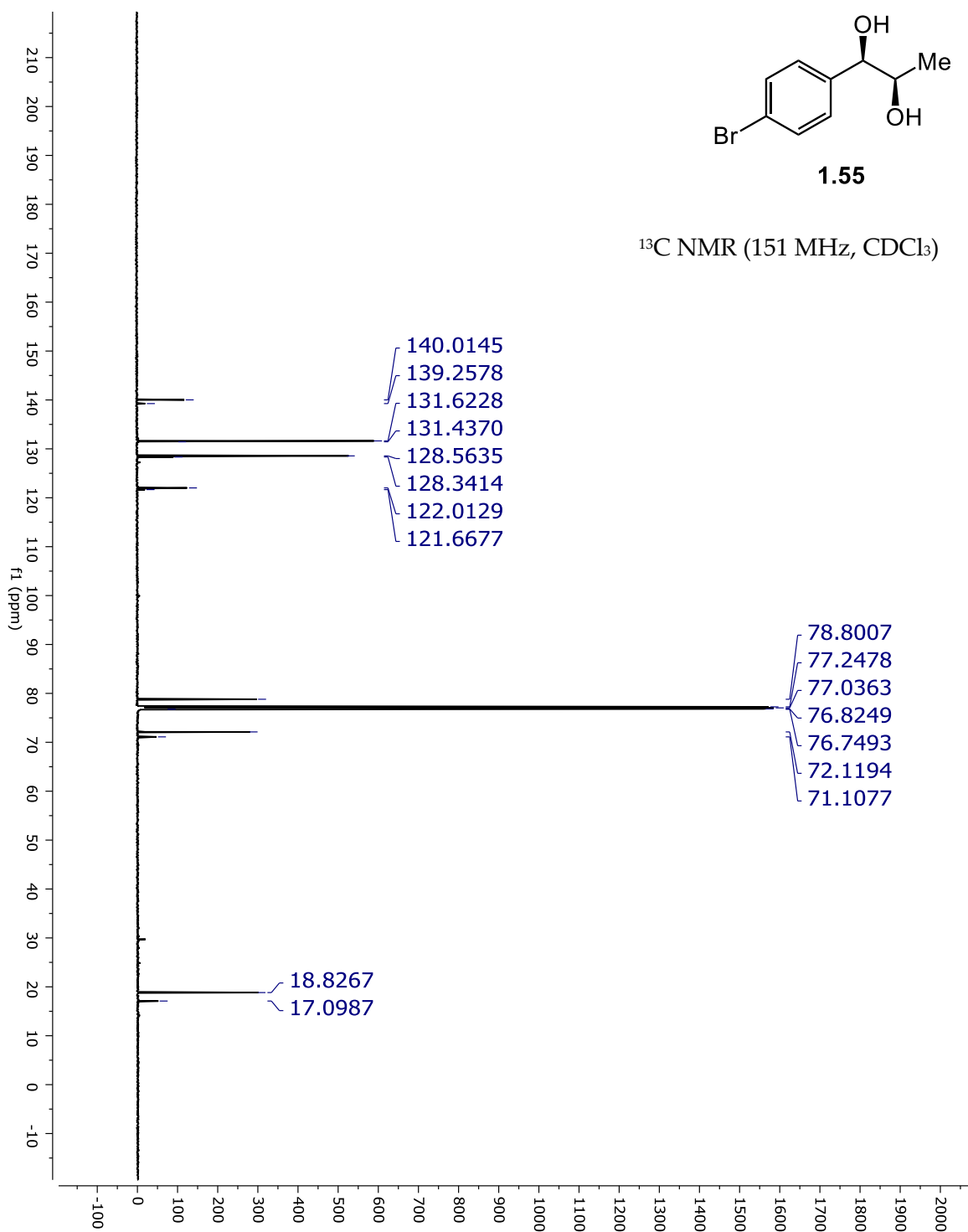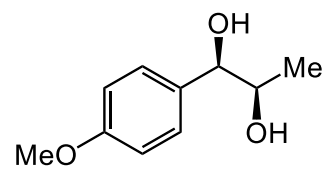
1.56

^{1}H NMR (600 MHz, CDCl$_3$)

1.56

^{13}C NMR (151 MHz, CDCl$_3$)

159.4757
159.3060

133.1578
132.3967
128.0281
127.9298

113.9159
113.8179

79.1687
77.3136
77.2404
77.0289
76.8174
72.3006
71.2762

55.2971

18.7450
17.5712

f1 (ppm)

1.57

^{1}H NMR (600 MHz, CDCl$_3$)

^{13}C NMR (151 MHz, CDCl$_3$)

148.3309
147.7248
147.5952

127.7293
127.3791
123.6644
123.4931

78.3379

76.8992

76.3545
72.0199
71.0316

19.0887
16.8896

f1 (ppm)

^{1}H NMR (600 MHz, CDCl$_3$)

92

^{13}C NMR (151 MHz, CDCl$_3$)

148.3383
143.2779
142.4428
133.0007
132.7538
129.4325
129.2112
123.0558
122.7159
121.8895
121.6594

78.2139
76.2640
72.0058
70.9729

19.0896
17.0178

f1 (ppm)

OH

Me

OH

Me   **1.58**

¹H NMR (600 MHz, CDCl₃)

13C NMR (151 MHz, CDCl₃)

140.9923
140.2861
138.2398
138.1014
128.9184
128.6446
128.4222
128.3123
127.4415
127.2919
123.9415
123.7350

79.5373
77.6488

72.2131
71.3101

21.5053
21.4612
18.7931
17.4515

^{1}H NMR (600 MHz, CDCl$_3$)

96

^{13}C NMR (151 MHz, CDCl$_3$)

142.0497
141.2889
130.9976
130.7841
130.2712
129.9929
128.9446
128.7464
124.9924
124.9666
124.9404
124.9166
124.6011
123.6820
123.6569
123.6315
123.6061
123.4054
123.3800
123.1288

78.7746
76.7395
72.1138
71.1226

18.9353
17.0238

1.61

^{1}H NMR (600 MHz, CDCl$_3$)

1.61

^{13}C NMR (151 MHz, CDCl$_3$)
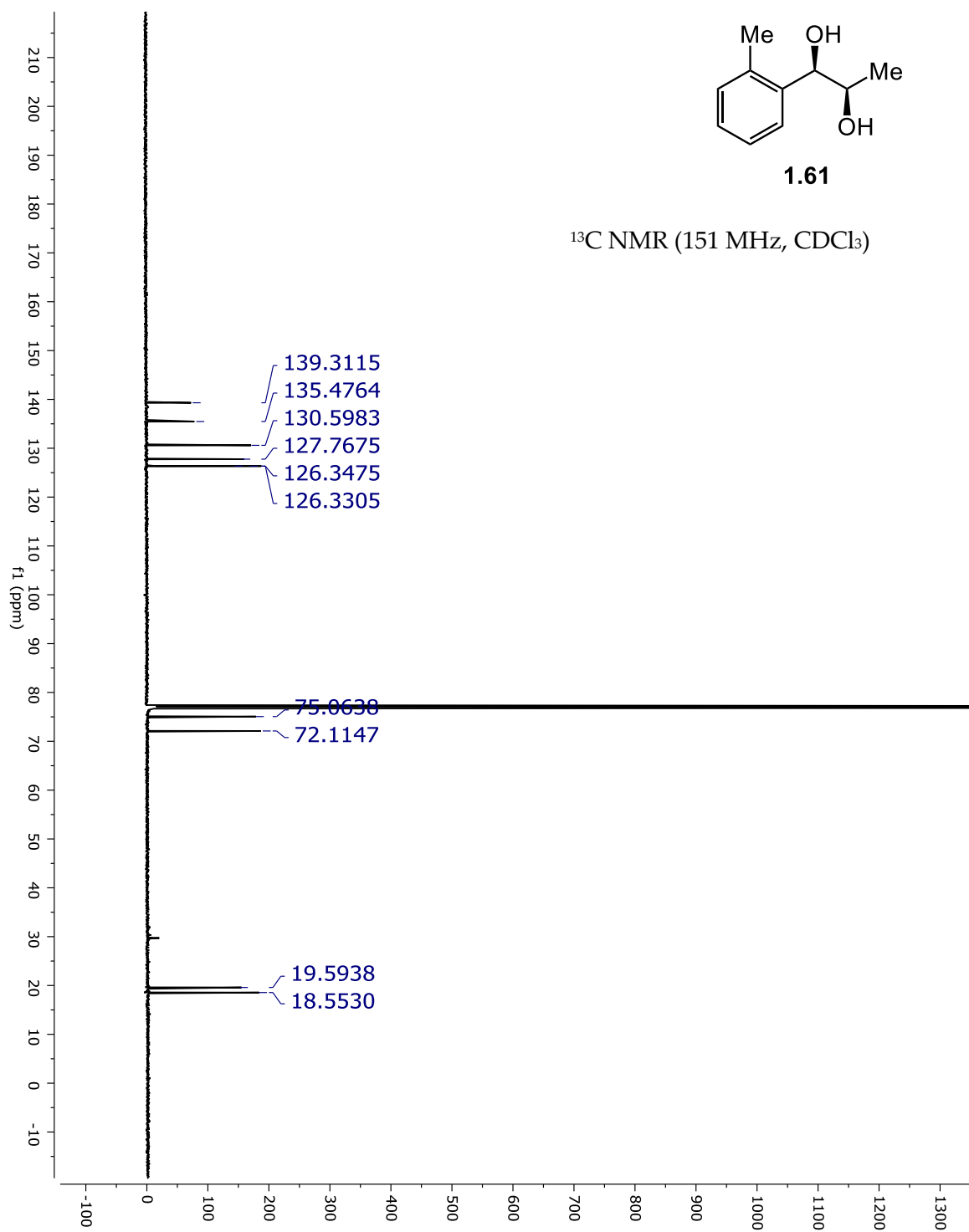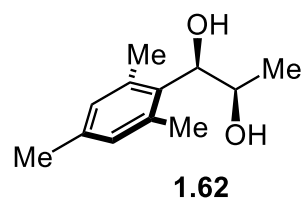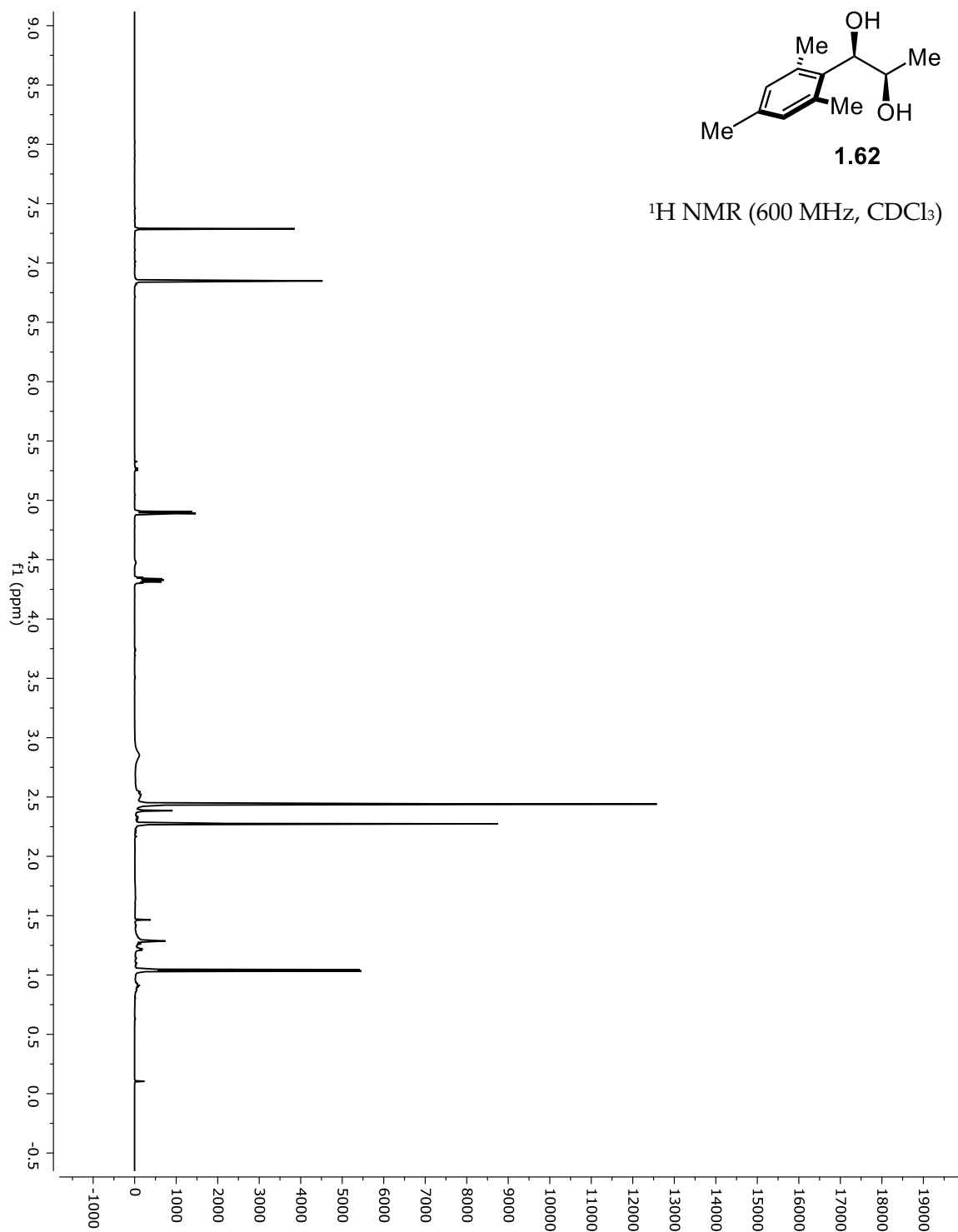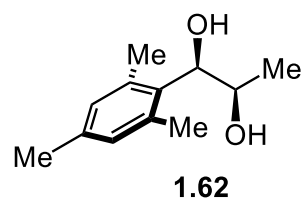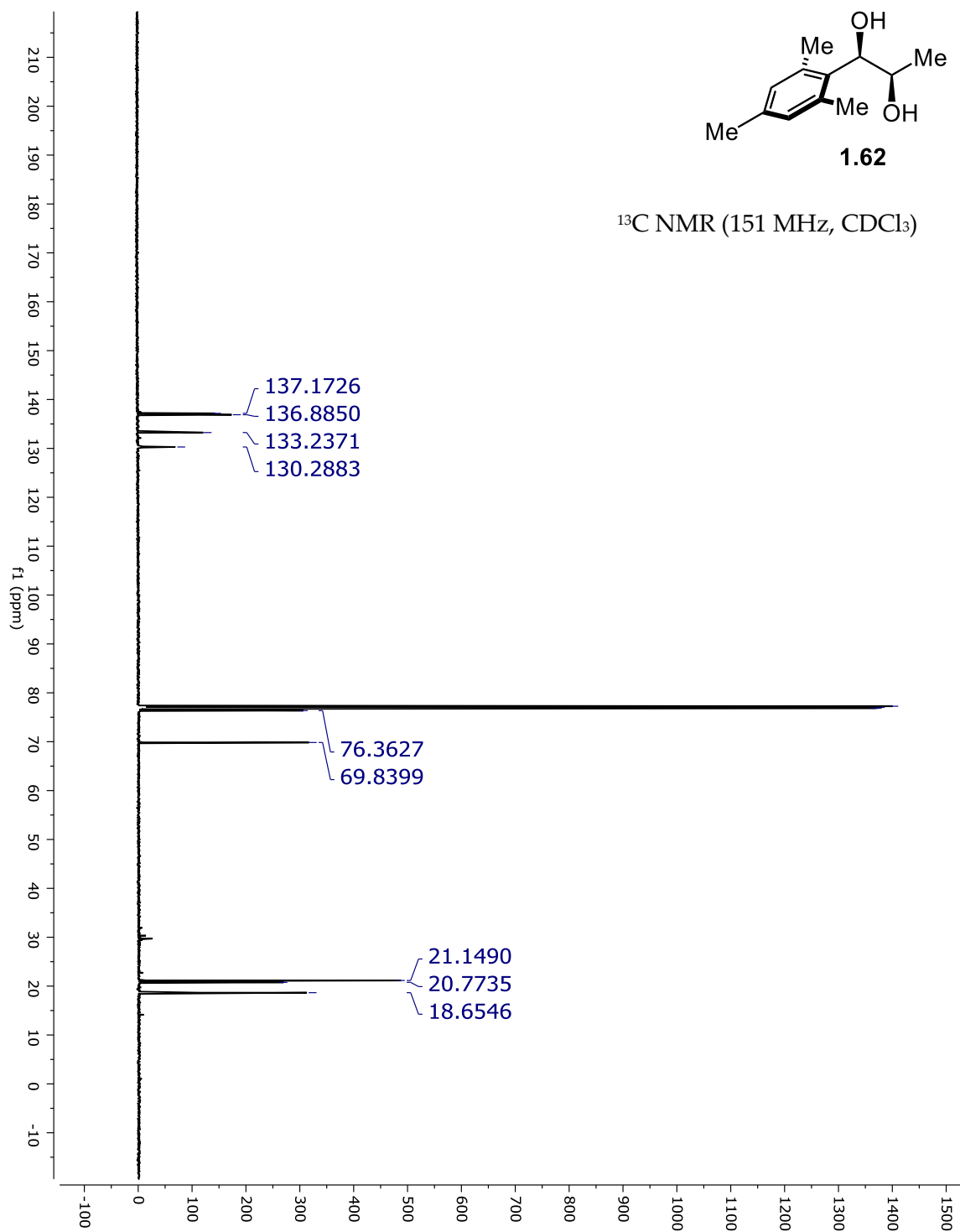
139.3115
135.4764
130.5983
127.7675
126.3475
126.3305

75.0638
72.1147

19.5938
18.5530

f1 (ppm)

1.62

^{1}H NMR (600 MHz, CDCl$_3$)

^{13}C NMR (151 MHz, CDCl$_3$)

137.1726
136.8850
133.2371
130.2883

76.3627
69.8399

21.1490
20.7735
18.6546

f1 (ppm)

1.64

¹H NMR (600 MHz, CDCl₃)

^{13}C NMR (151 MHz, CDCl$_3$)

153.8759
153.5341
142.3995
142.3427
110.3468
107.9192
107.7196
72.5954
71.8011
69.9678
69.8571
18.8084
18.2894

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

1.64

¹H NMR (600 MHz, CDCl₃)

1.63

104

1.63

^{13}C NMR (151 MHz, CDCl$_3$)

149.0911
148.3383
134.6329
123.4420
75.2125
70.9850
17.1999

f1 (ppm)
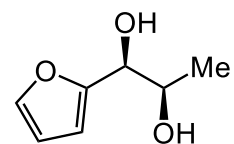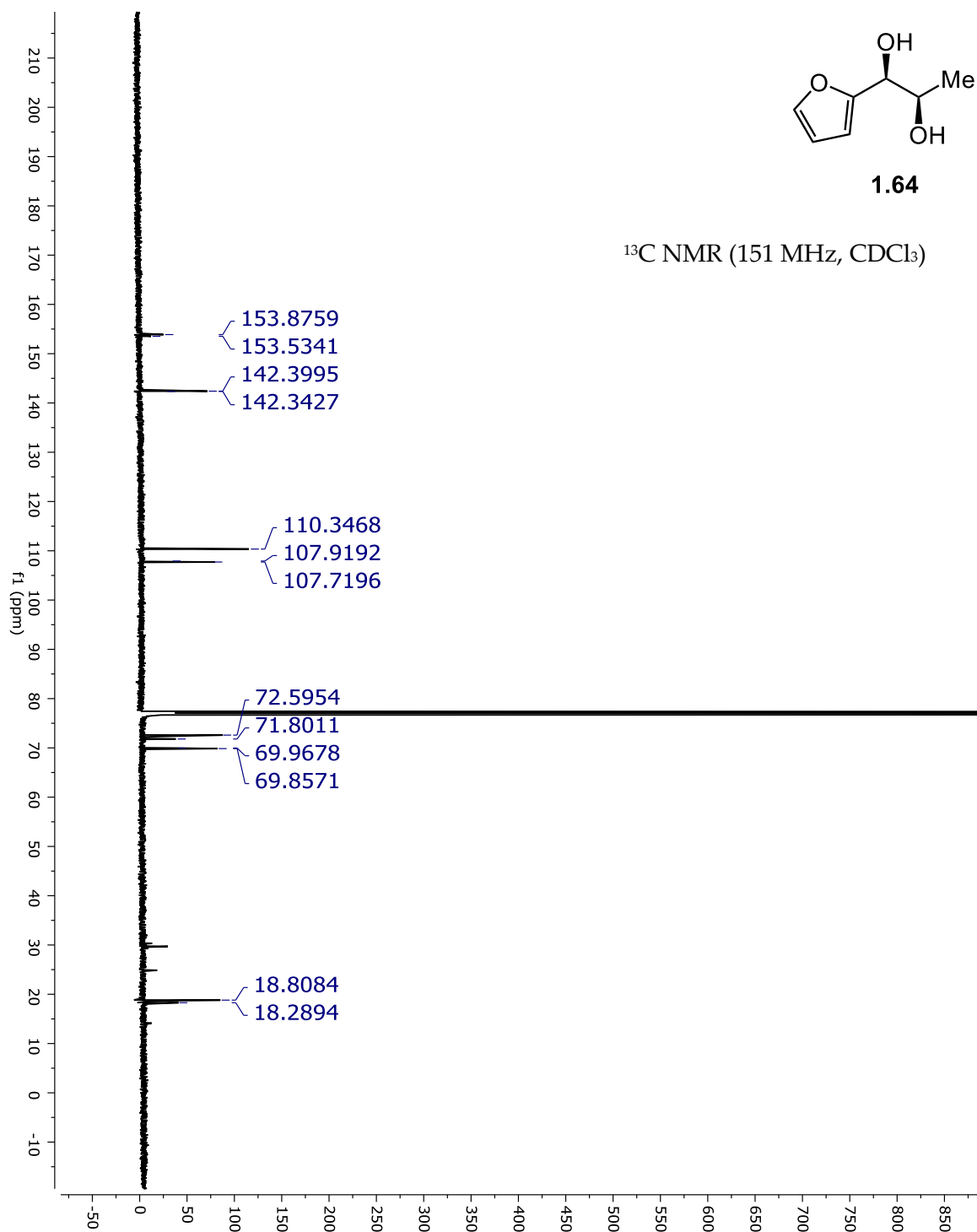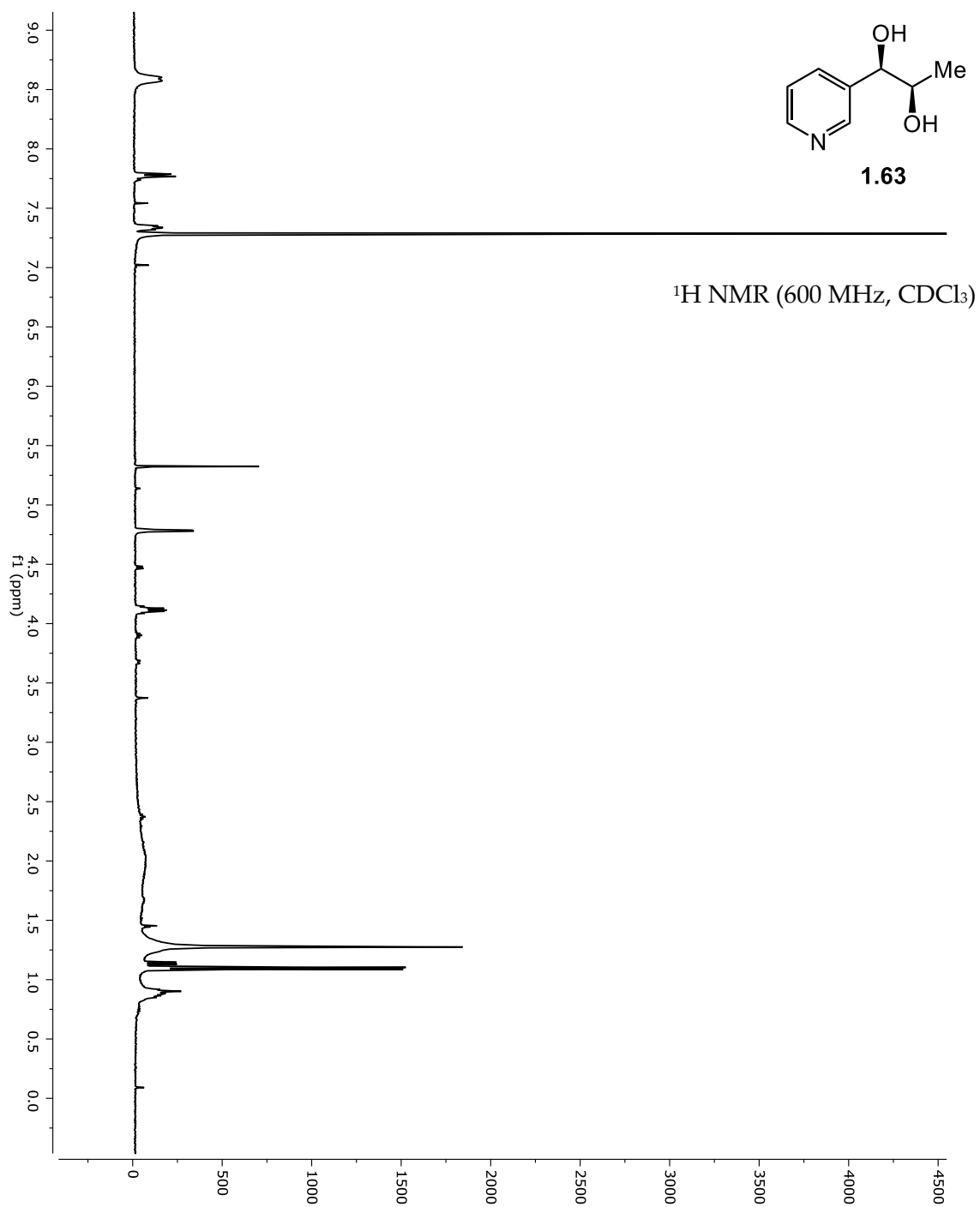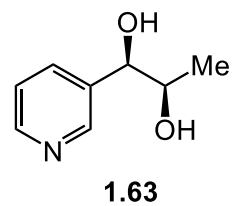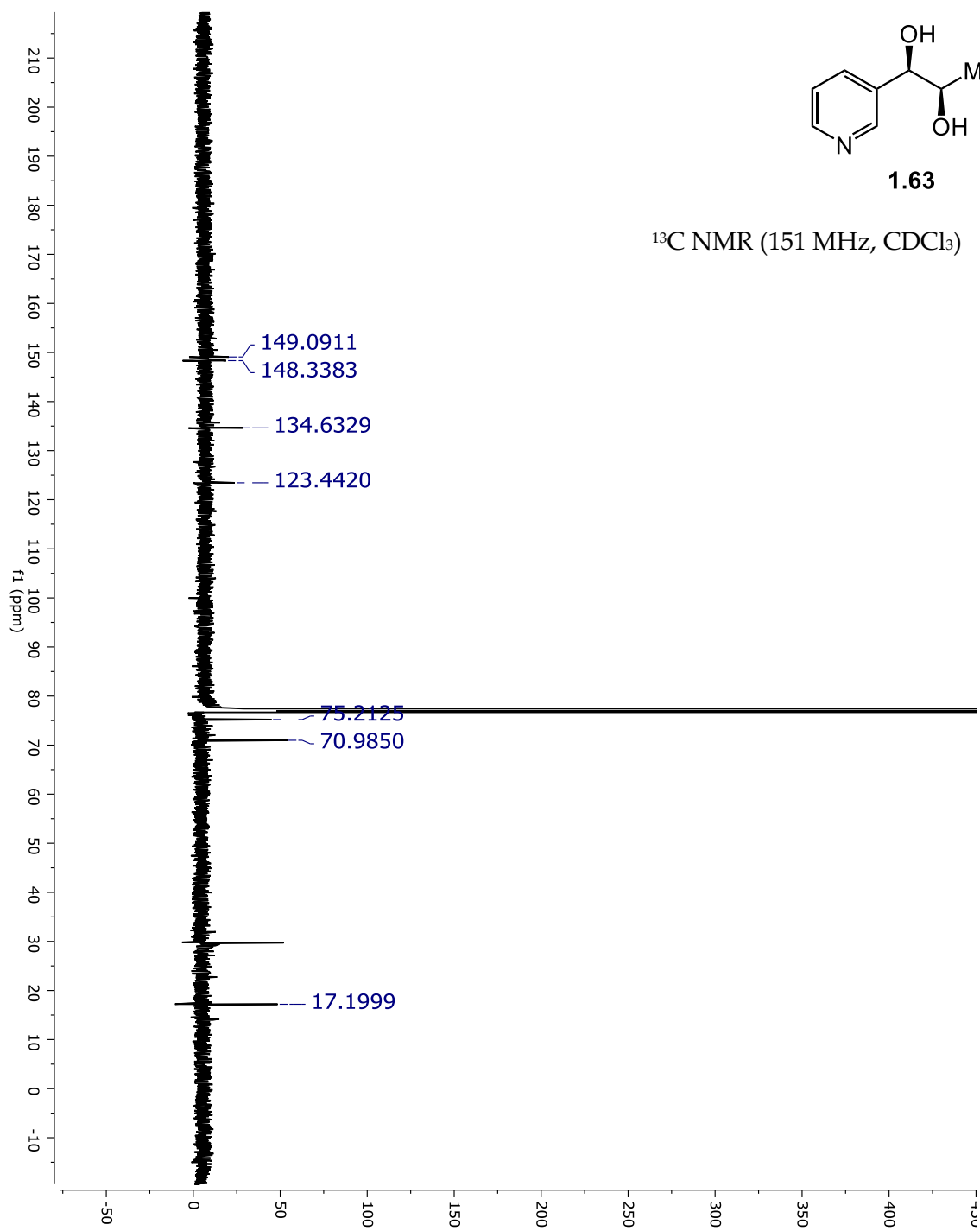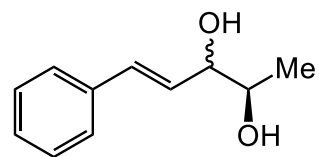
1.65
^{1}H NMR (600 MHz, CDCl$_3$)

1.65

^{13}C NMR (151 MHz, CDCl$_3$)
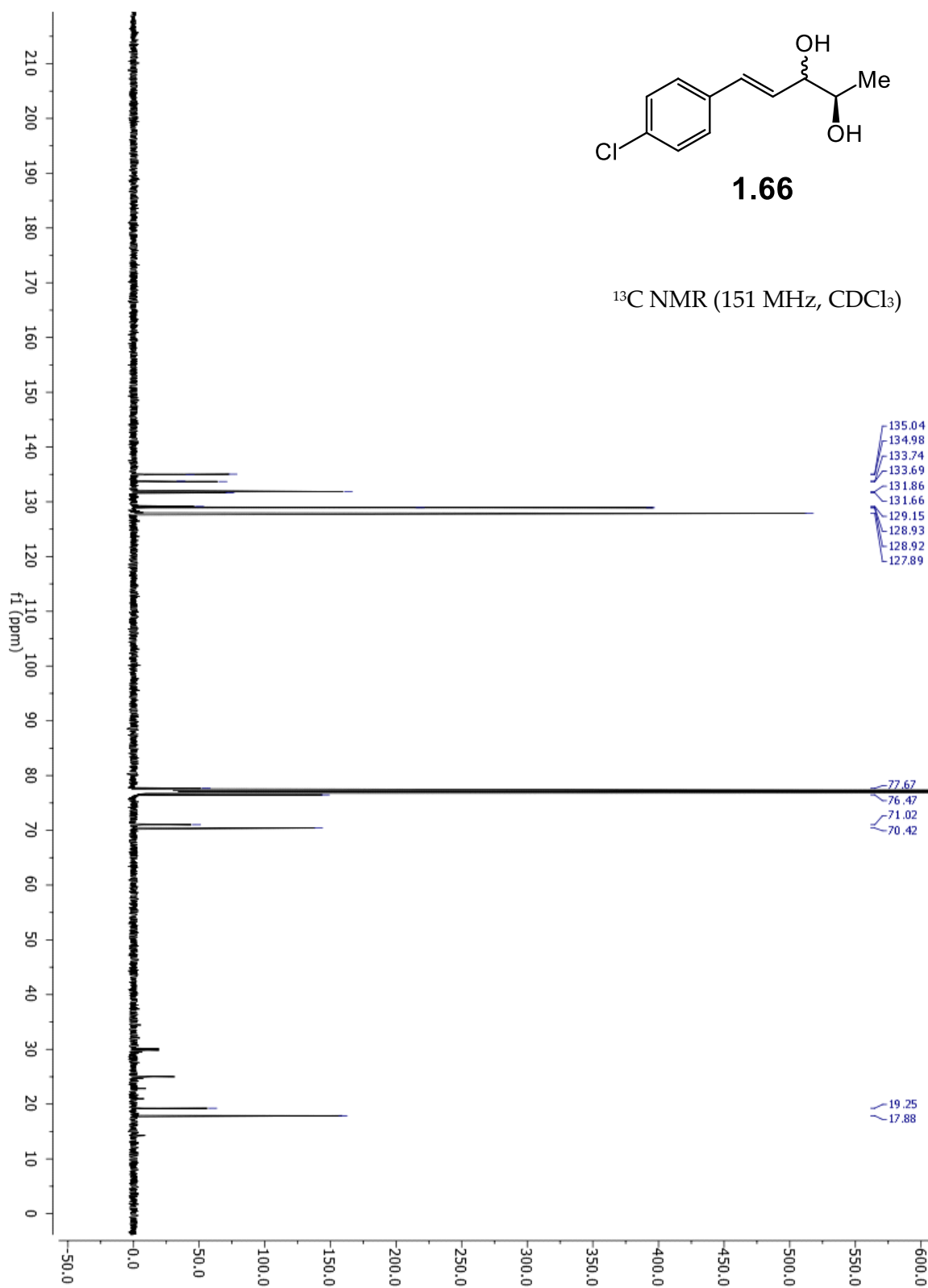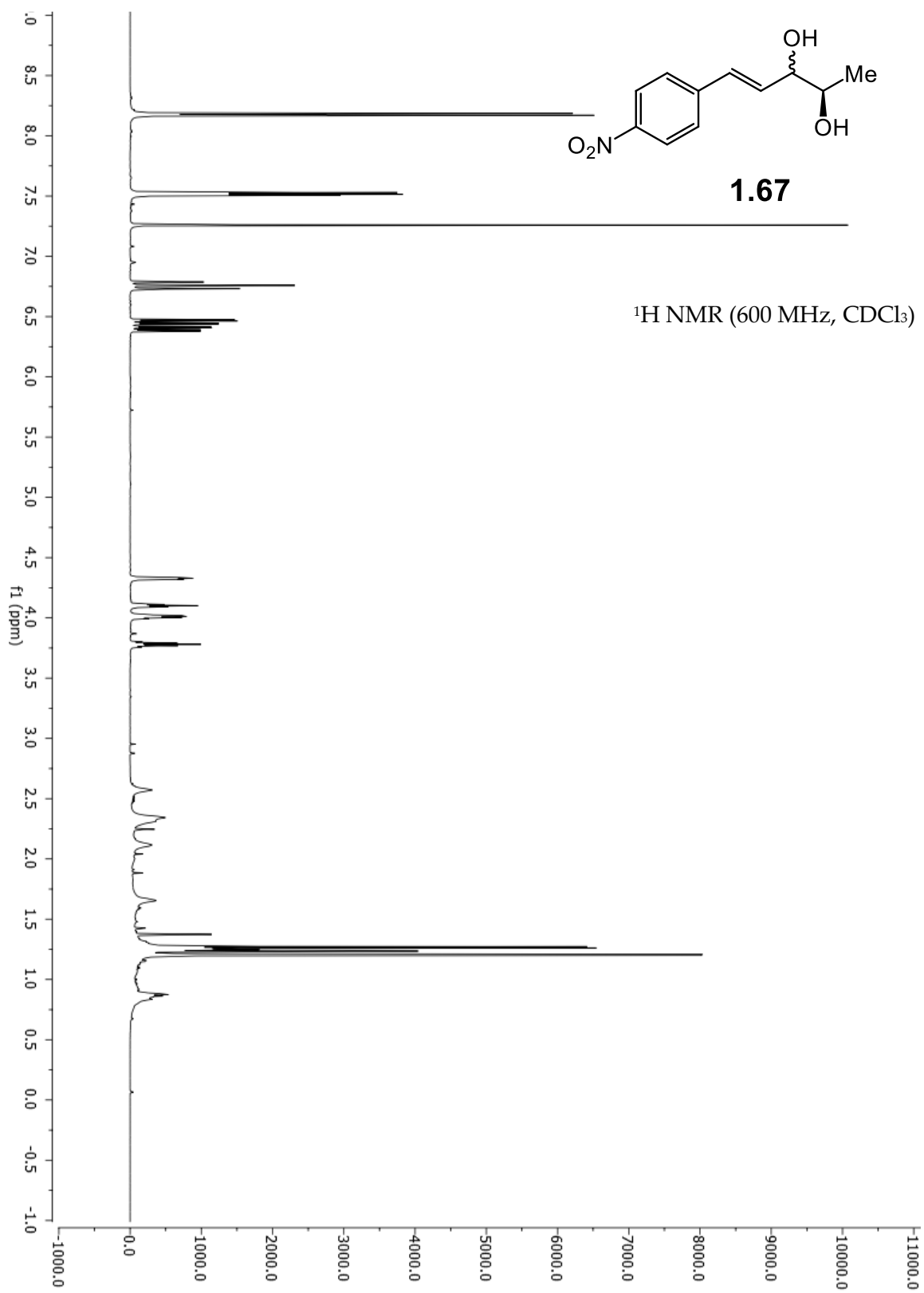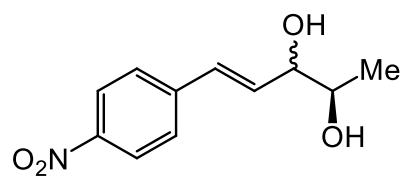
136.51
136.47
133.26
133.02
128.77
128.76
128.45
128.12
128.09
127.18
126.70
126.70

77.92
76.70
71.08
70.45

19.16
17.88

1.66

^{1}H NMR (600 MHz, CDCl$_3$)

^{13}C NMR (151 MHz, CDCl$_3$)

135.04
134.98
133.74
133.69
131.86
131.66
129.15
128.93
128.92
127.89

77.67
76.47
71.02
70.42

19.25
17.88

f1 (ppm)

^{1}H NMR (600 MHz, CDCl$_3$)

1.67

^{13}C NMR (151 MHz, CDCl$_3$)
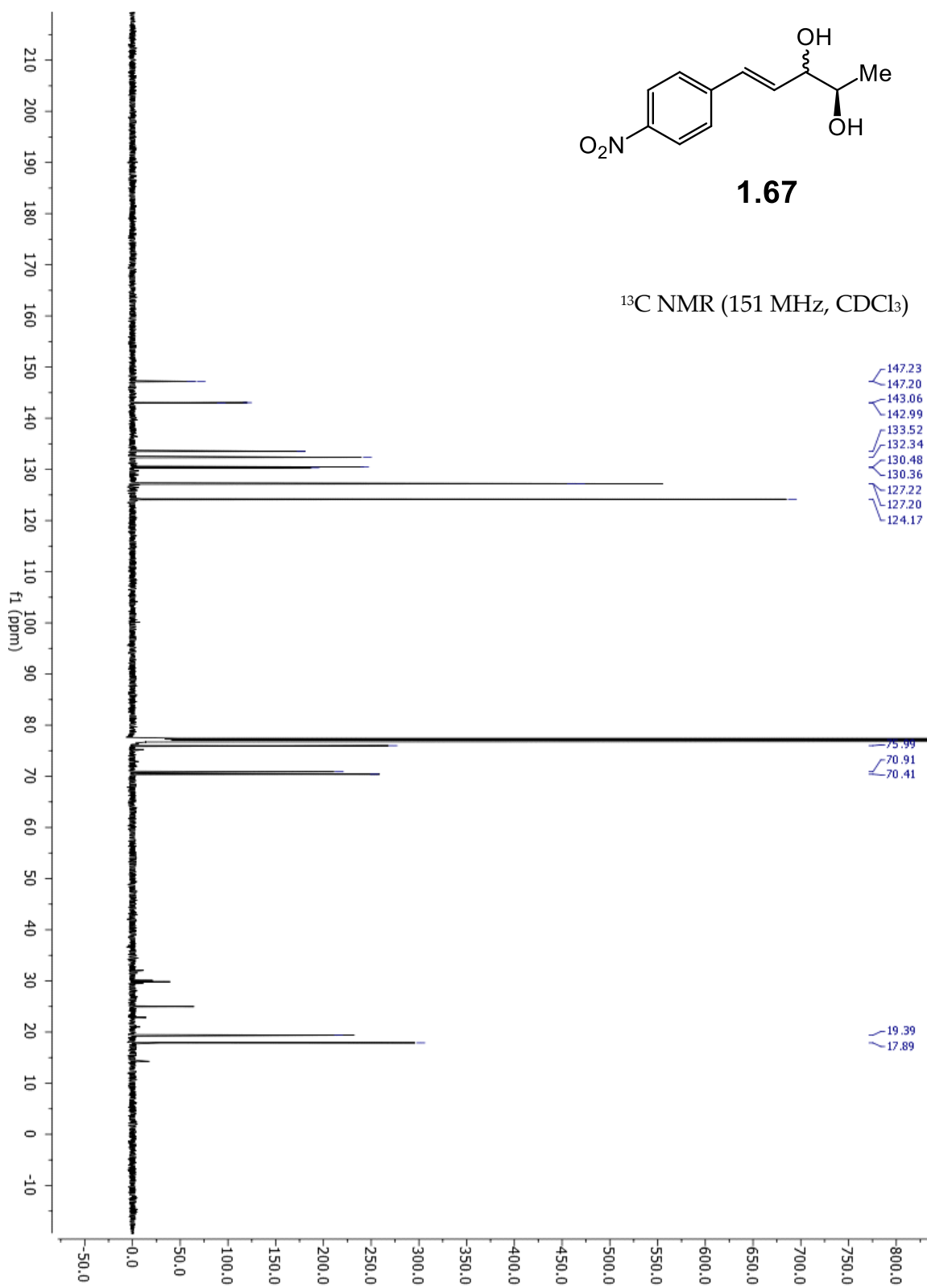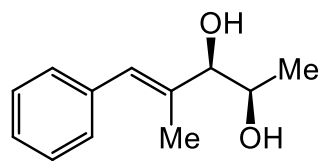
147.23
147.20
143.06
142.99
133.52
132.34
130.48
130.36
127.22
127.20
124.17

75.99
70.91
70.41

19.39
17.89

^{1}H NMR (600 MHz, CDCl$_3$)

1.68

112

1.68

^{13}C NMR (151 MHz, CDCl$_3$)

137.34
137.21
129.13
128.59
128.32
126.88
83.20
69.23
19.24
13.84

1.69

^{1}H NMR (600 MHz, CDCl$_3$)

^{13}C NMR (151 MHz, CDCl$_3$)

1.69

— 137.33

— 126.09

— 81.78

— 69.08

— 25.19
— 24.26
— 22.71
— 22.65
— 19.07

1.82
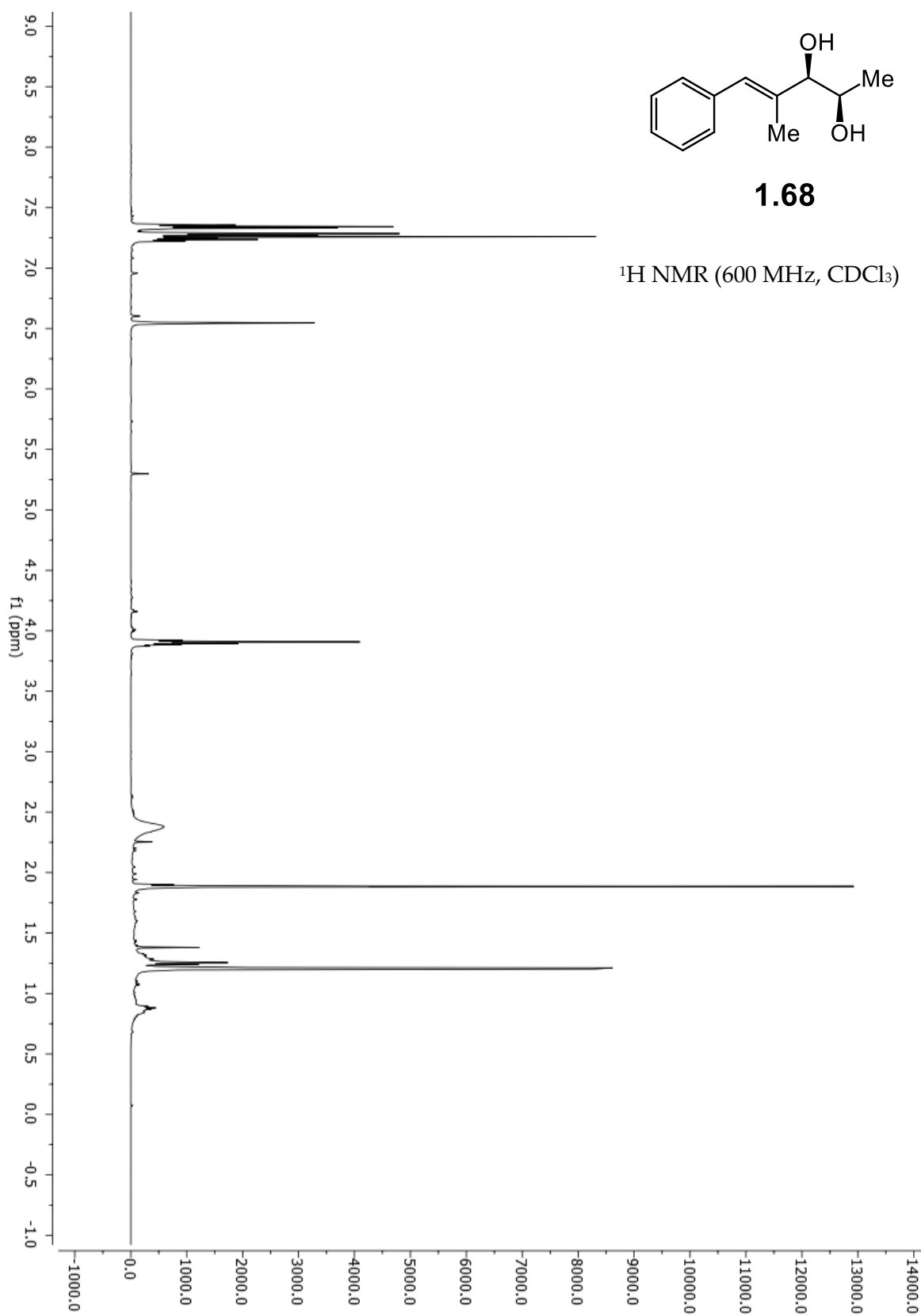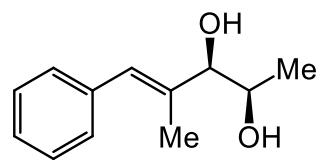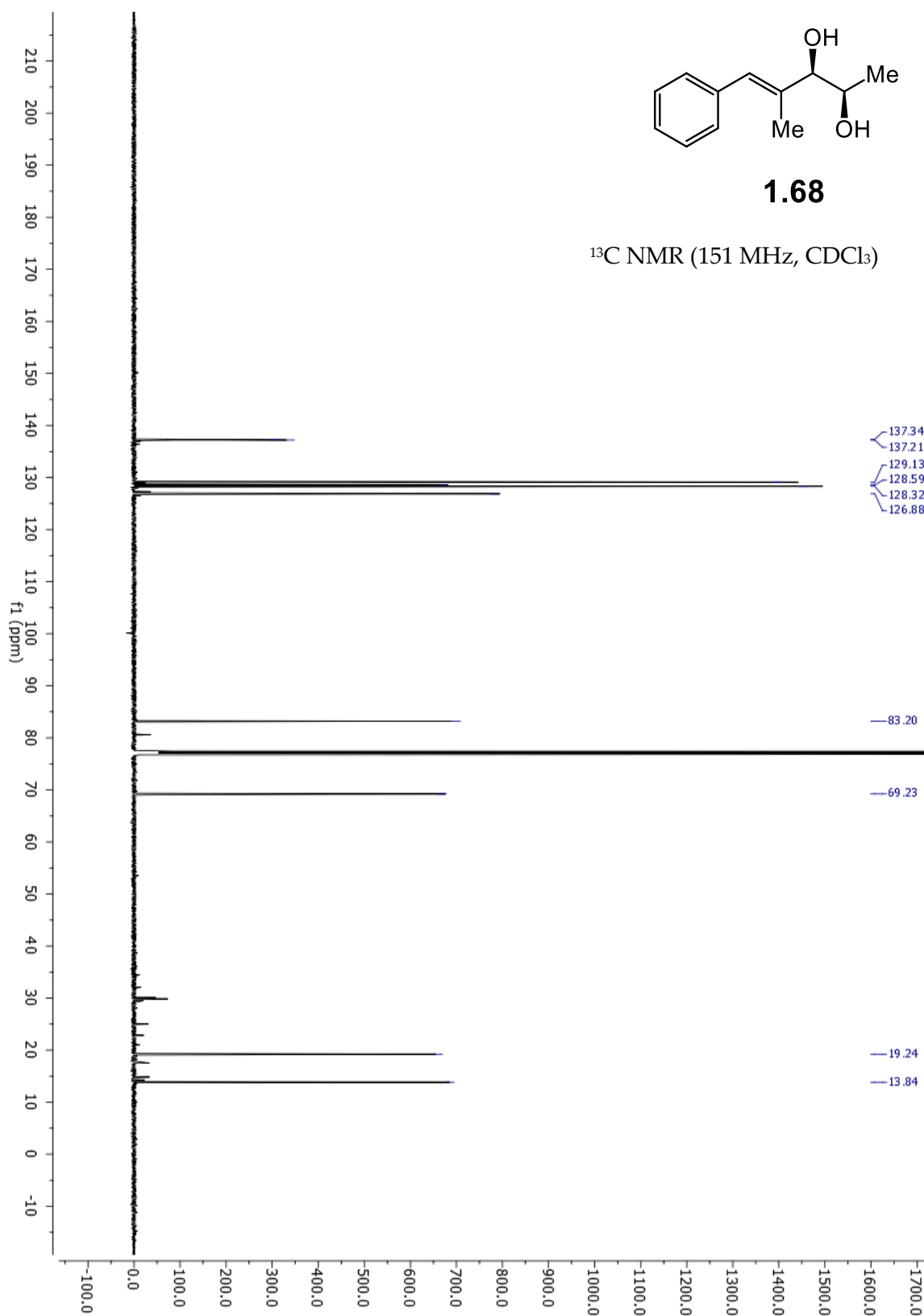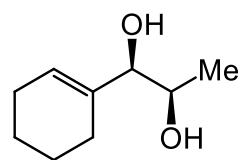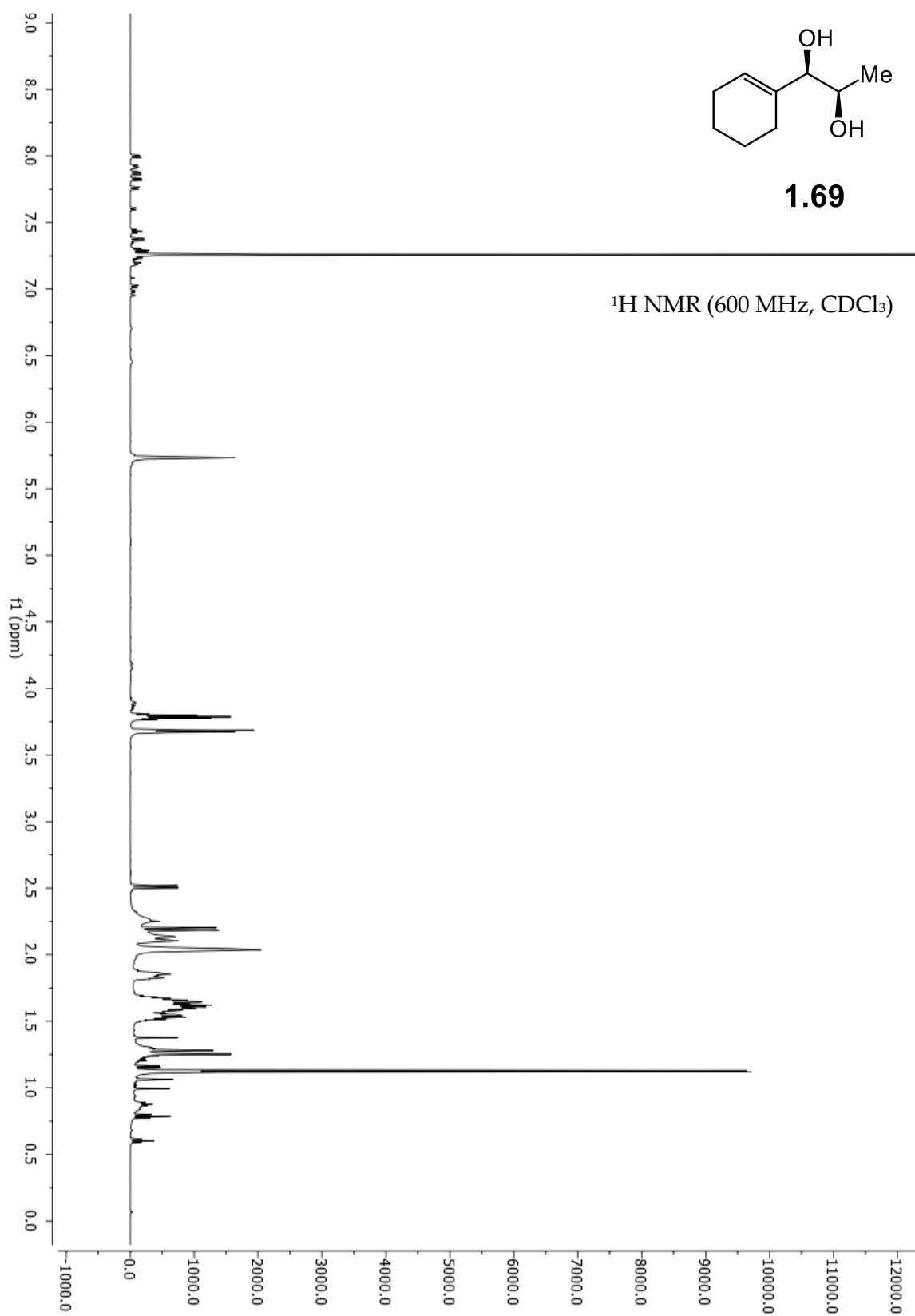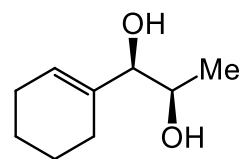
^{1}H NMR (600 MHz, CDCl$_3$)

1.82

^{13}C NMR (151 MHz, CDCl$_3$)

154.53
154.39

137.11
136.86
135.15
134.93
129.29
129.15
128.98
127.12
127.06
121.84
119.79

84.73
80.67
78.76
76.95
76.58

18.19
15.90

f1 (ppm)
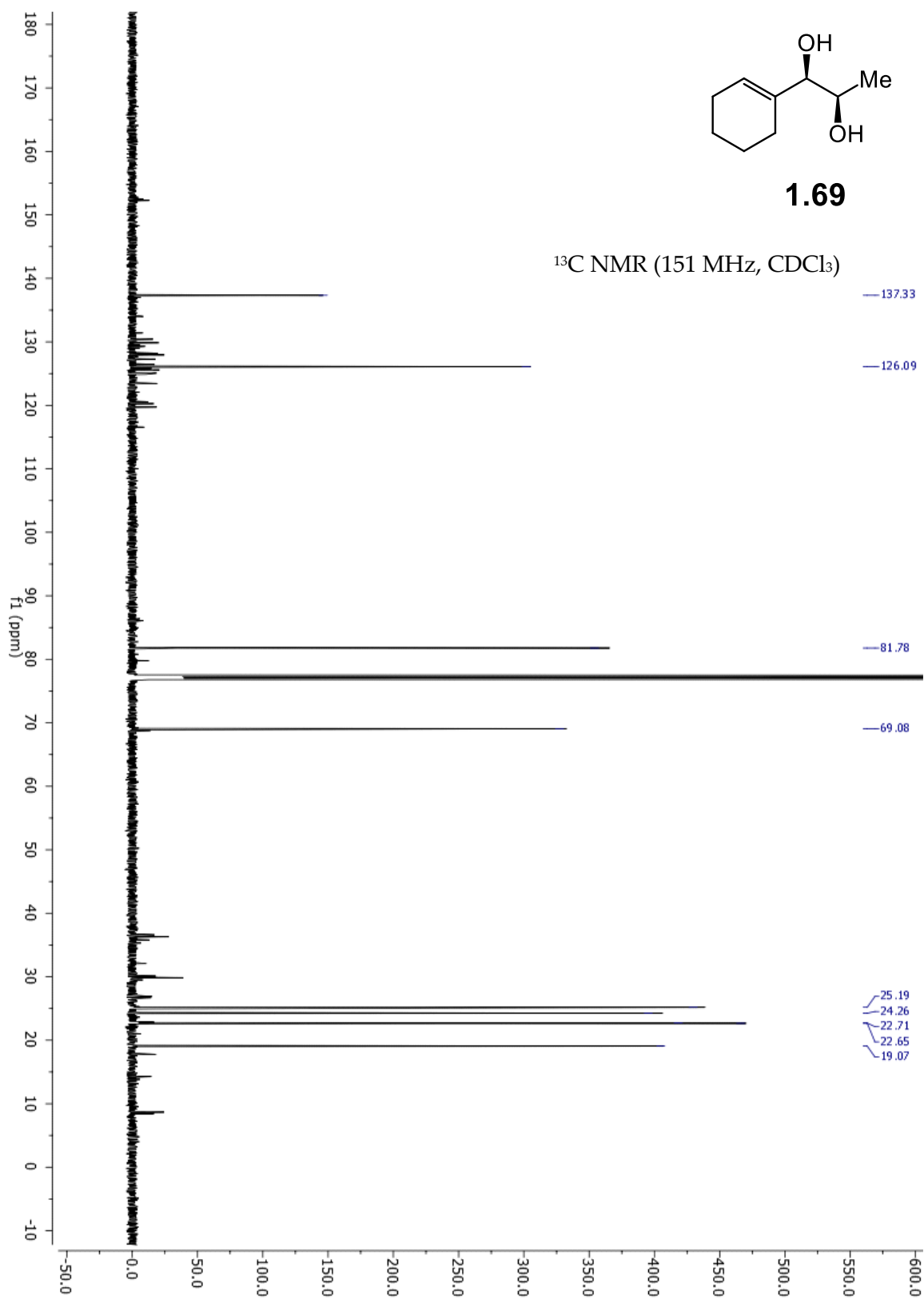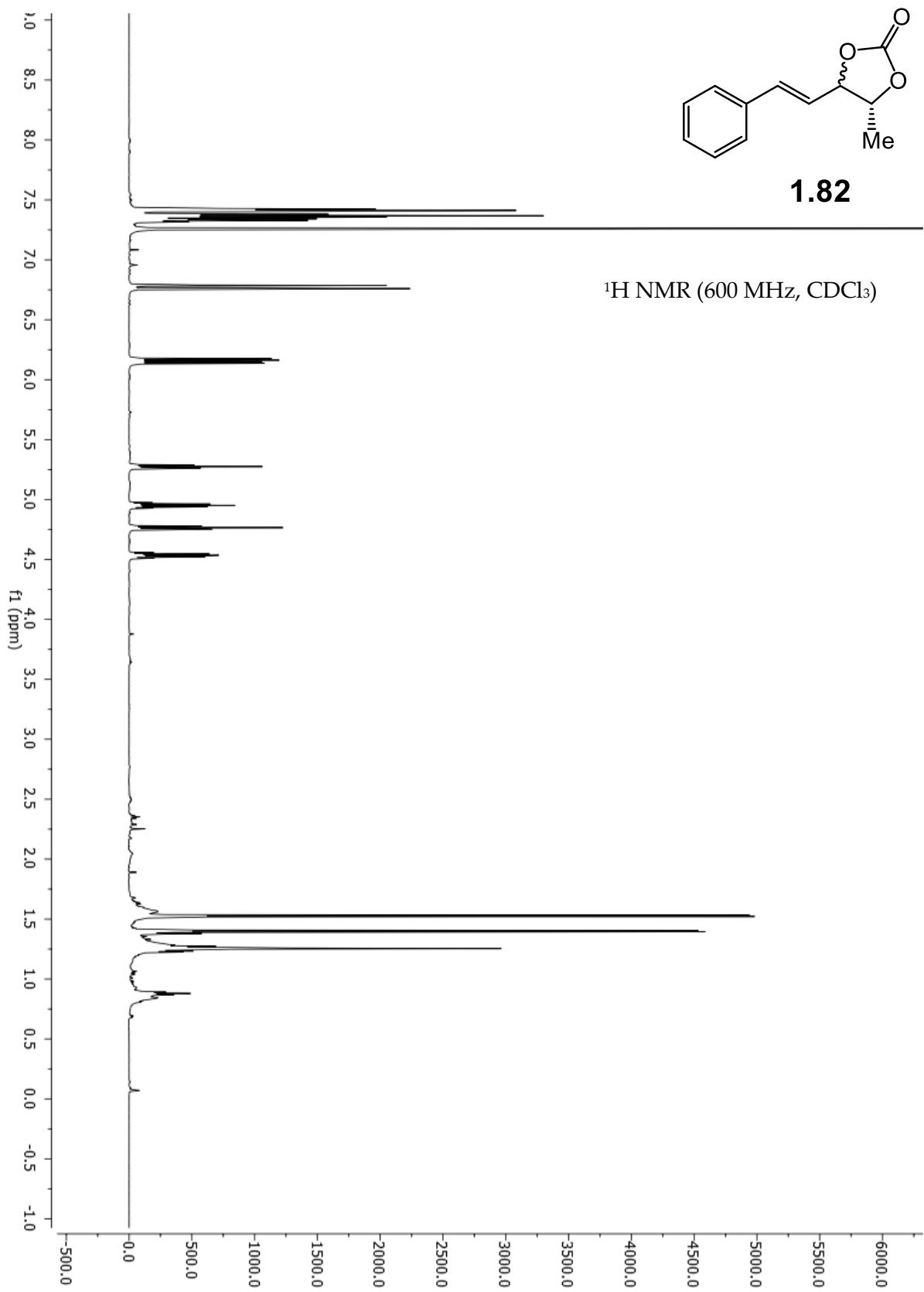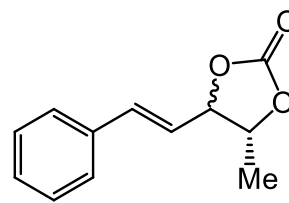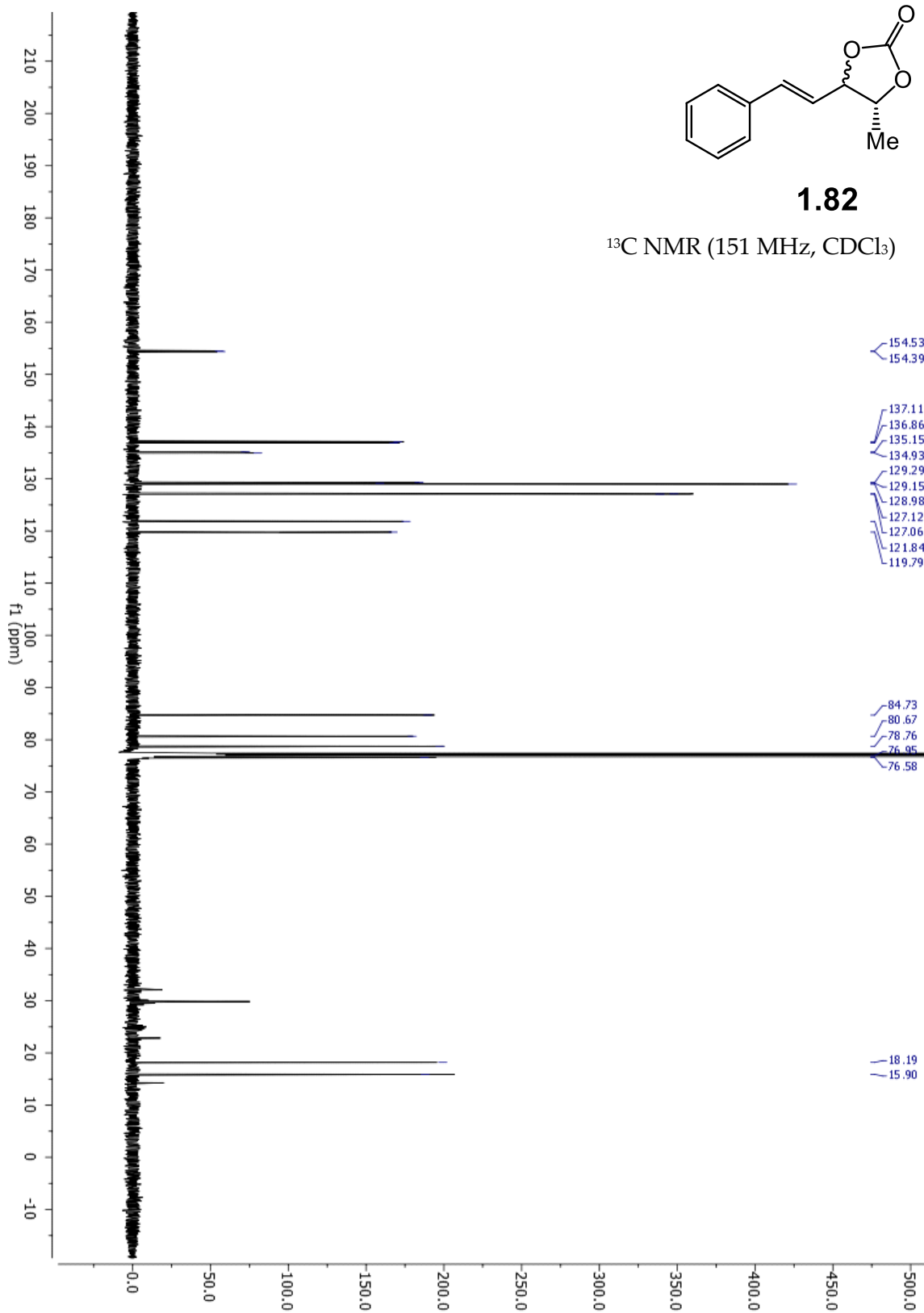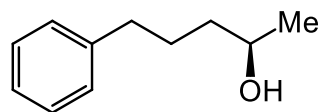
1.73

^{1}H NMR (600 MHz, CDCl$_3$)

1.73

^{13}C NMR (151 MHz, CDCl$_3$)

—142.49

128.54
128.43
125.88

—68.16

—39.00
—36.00

—27.73
—23.68

f1 (ppm)
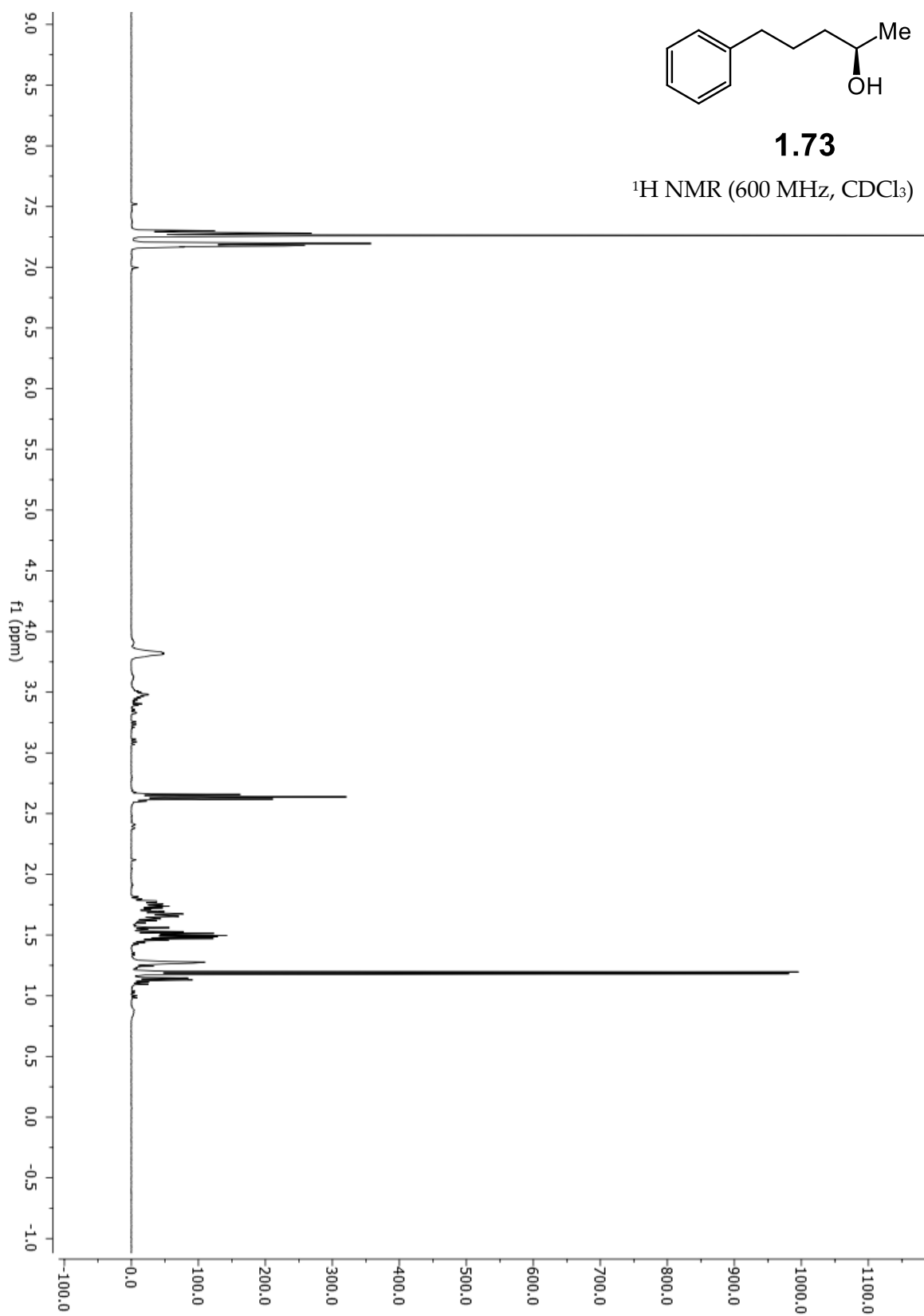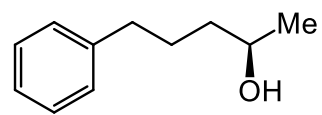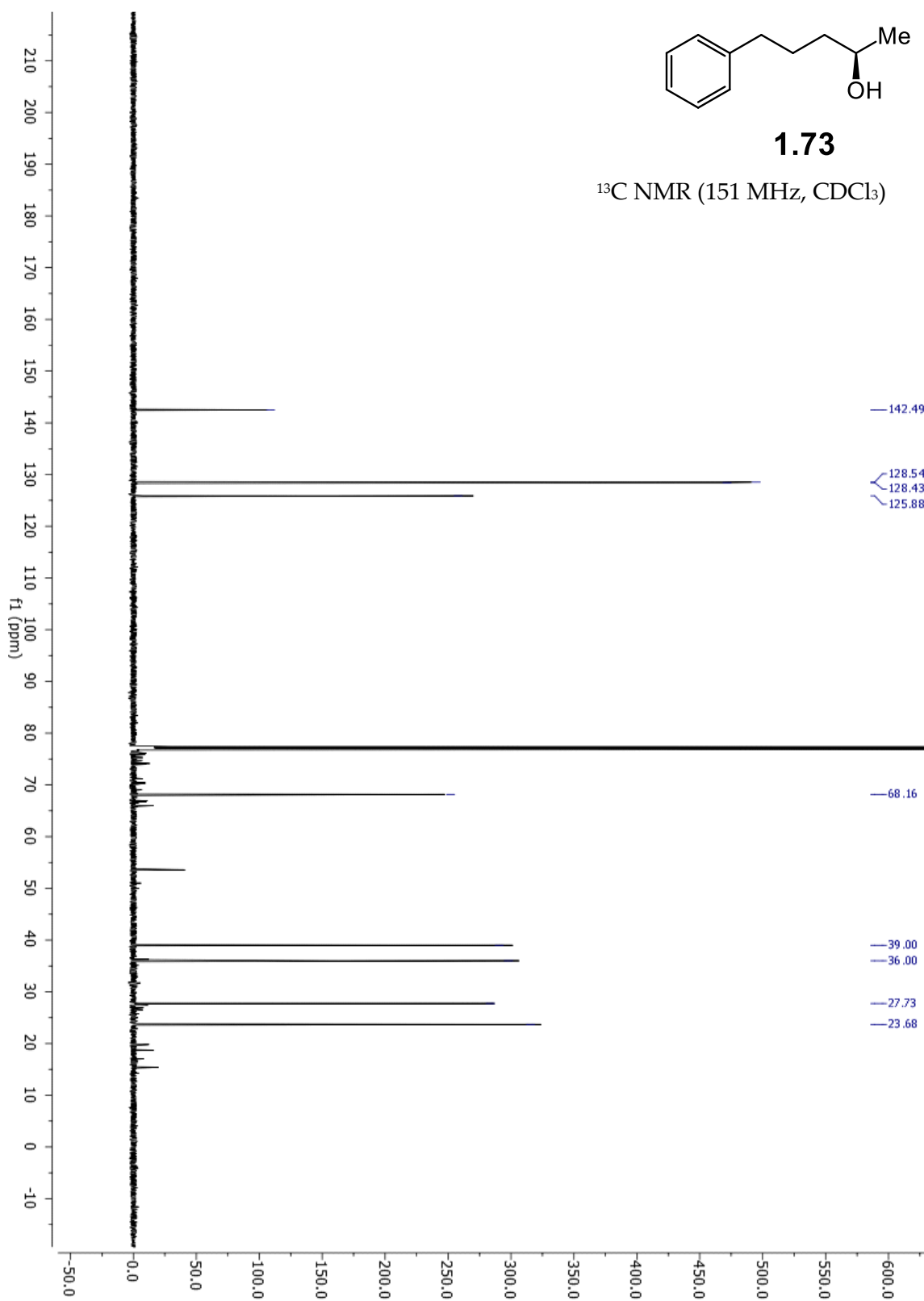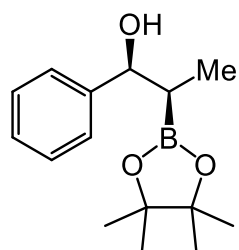
1.46

^{1}H NMR (400 MHz, CDCl$_3$)

1.46

^{13}C NMR (100 MHz, CDCl$_3$)

—144.46

128.24
127.34
126.44

—83.53
—77.54

24.84
24.72

—12.47

OTBS

Me

B

O O
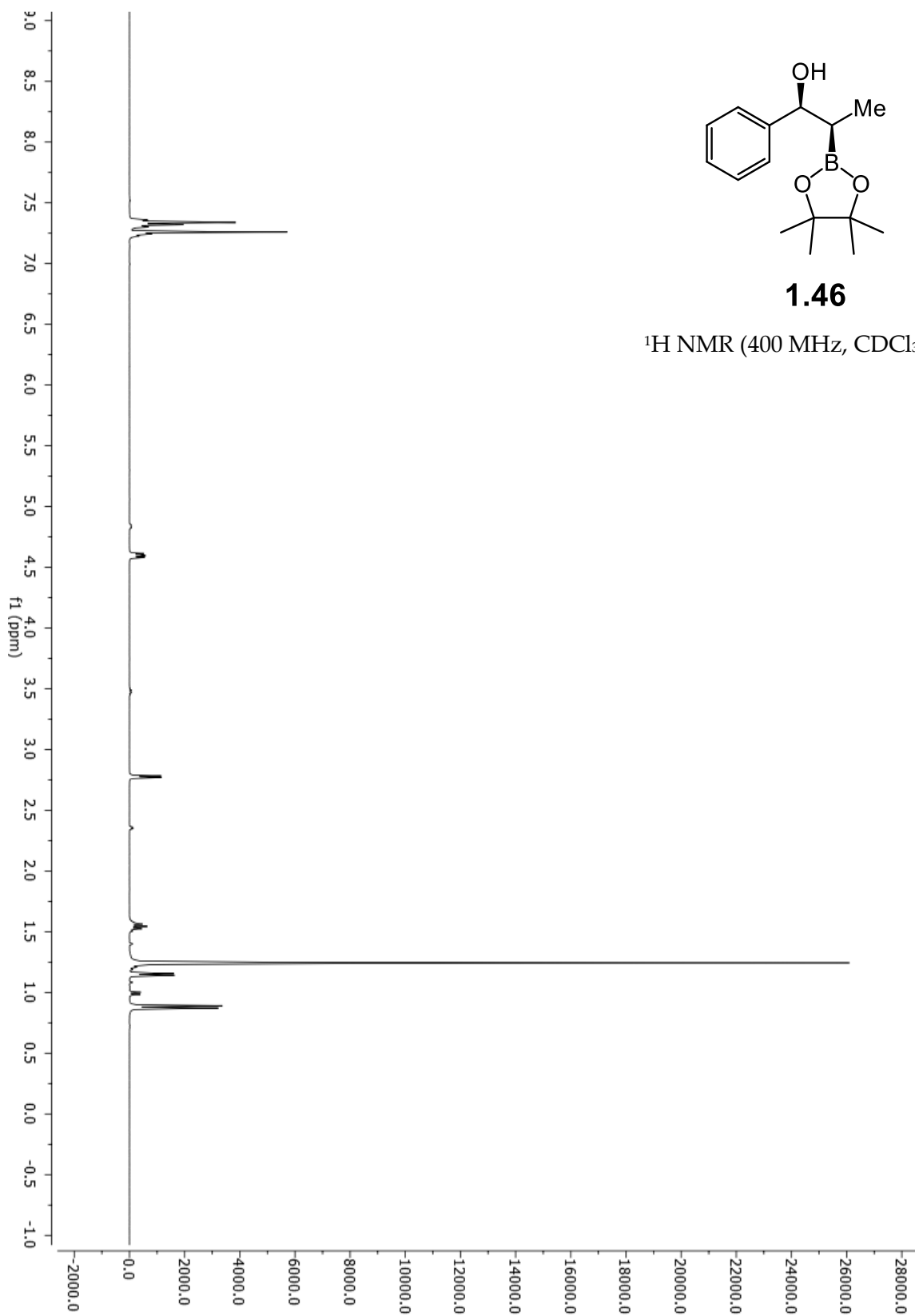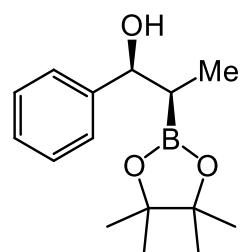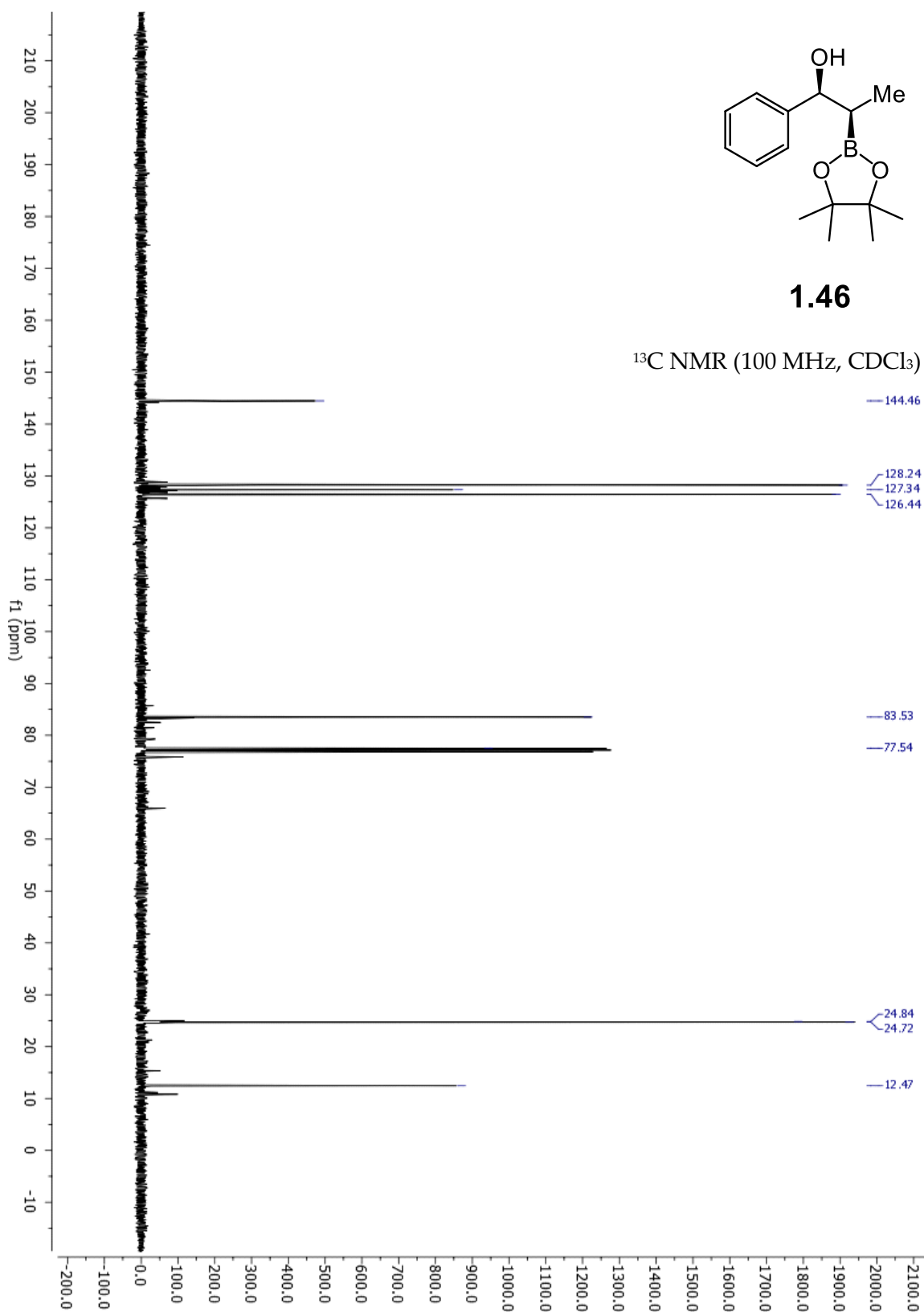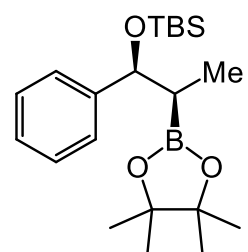
1.74

^{1}H NMR (600 MHz, CDCl$_3$)

1.74

^{13}C NMR (151 MHz, CDCl$_3$)

— 145.21

127.74
127.01
126.91

— 83.06
— 77.78

26.07
25.35
24.81

— 18.26

— 11.68

-4.34
-4.64
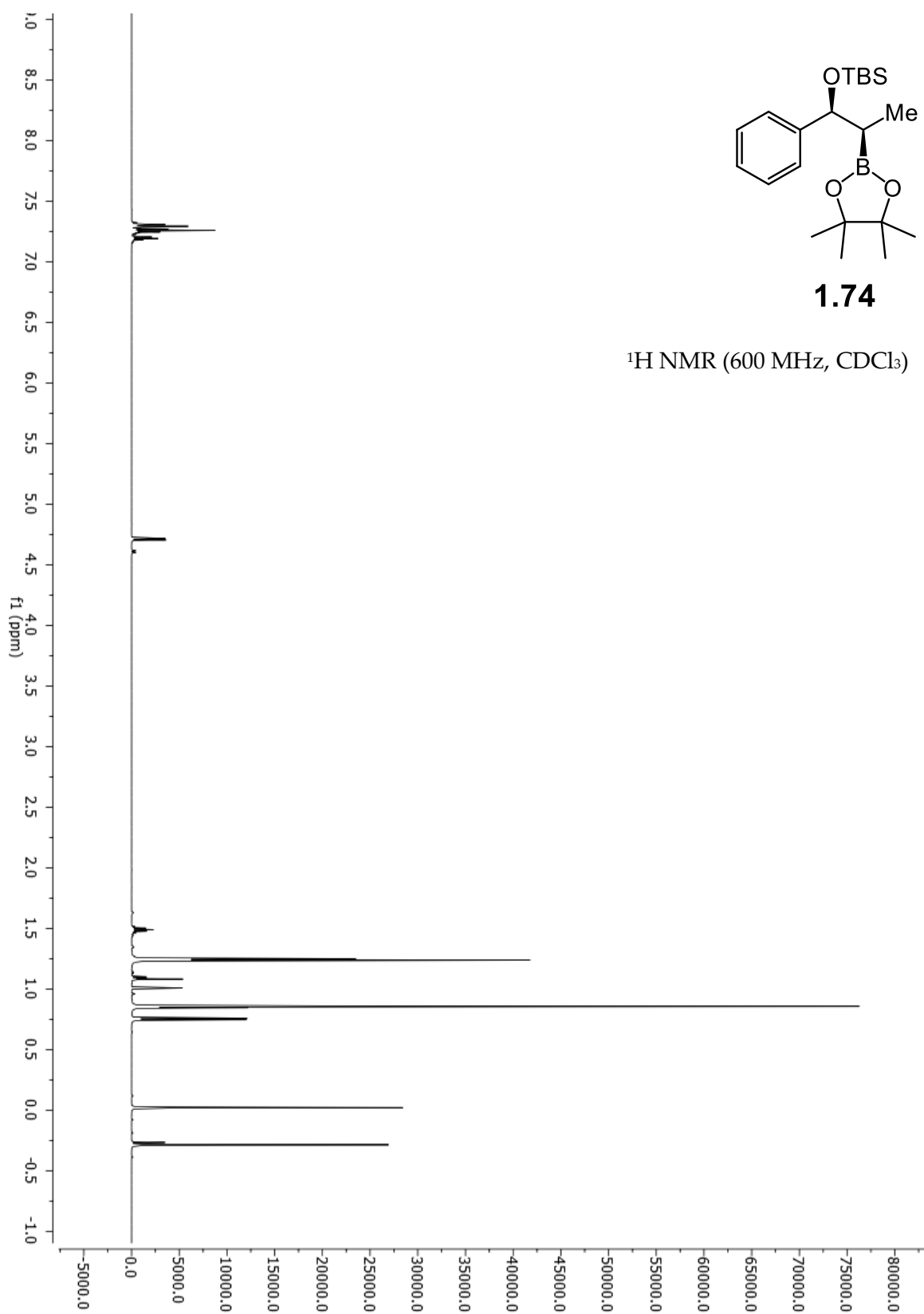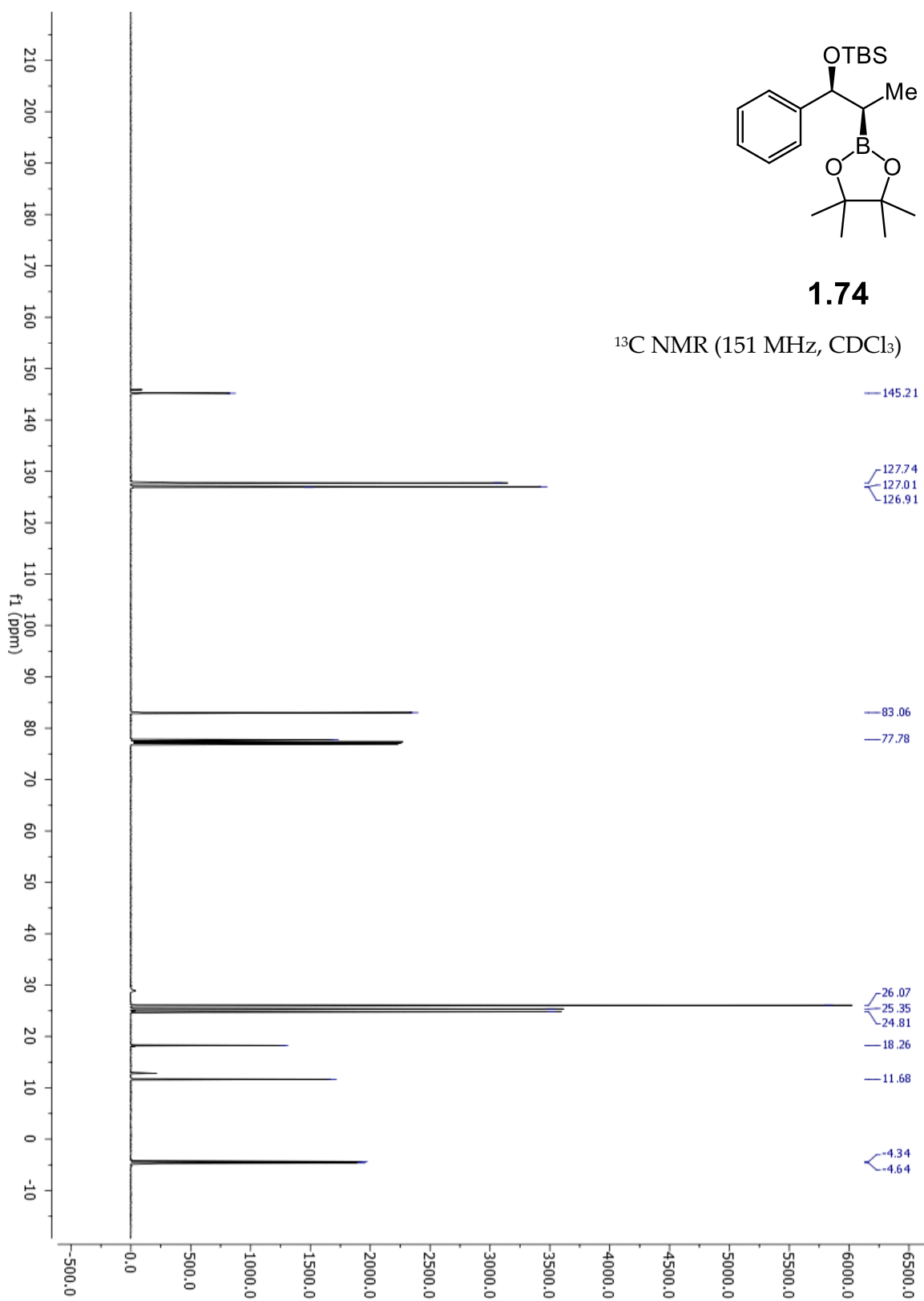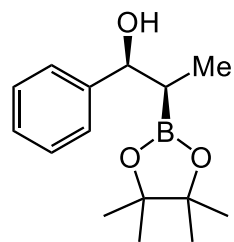
1.74

^{11}B NMR (151 MHz, CDCl$_3$)

124

1.75

^{1}H NMR (600 MHz, CDCl$_3$)

OTBS

1.75

^{13}C NMR (151 MHz, CDCl₃)

— 144.15

127.63
127.24
126.78

— 82.98
— 80.32

— 37.99

26.05
25.14
24.83
18.41
18.36

-4.48
-4.87
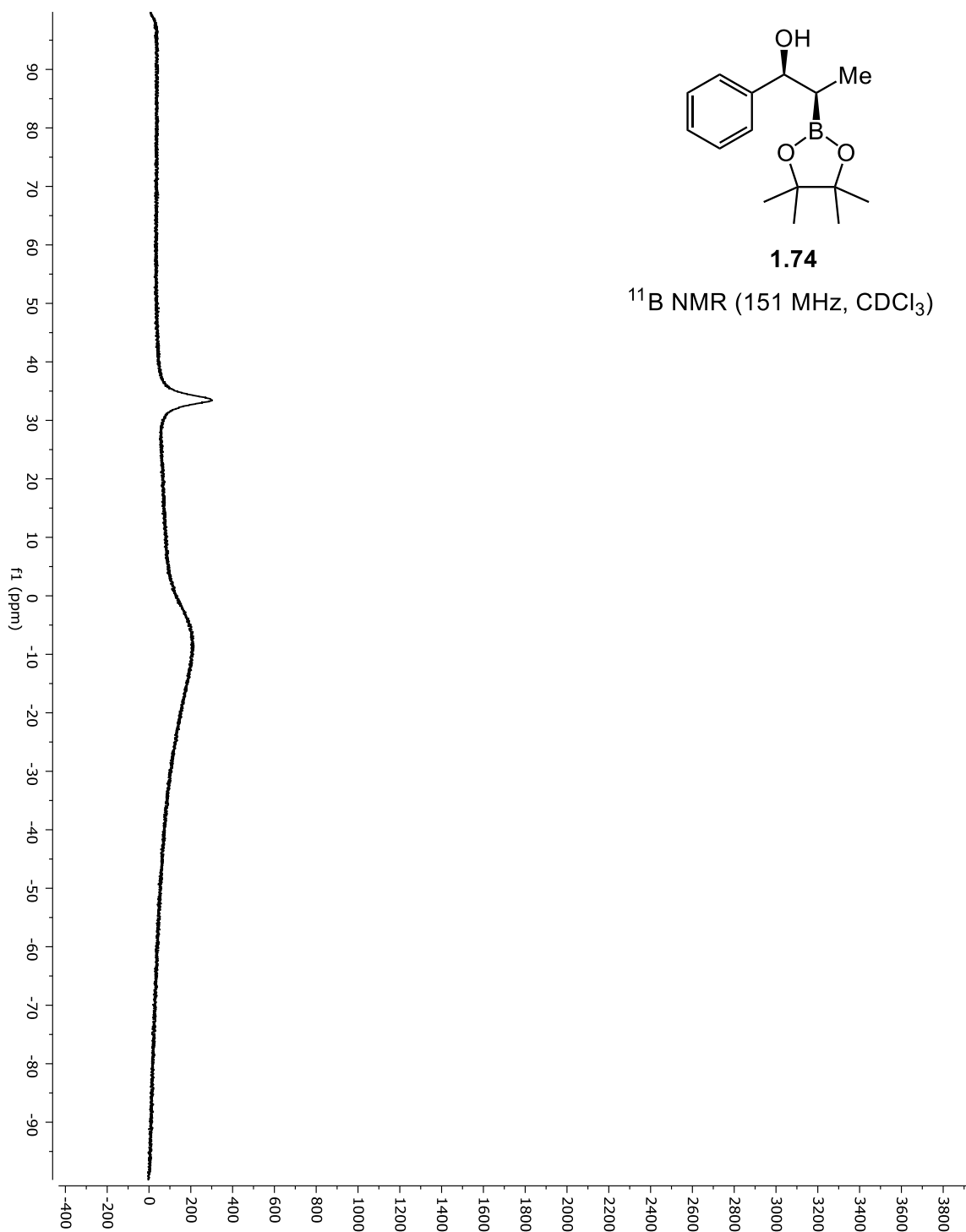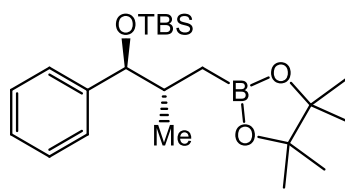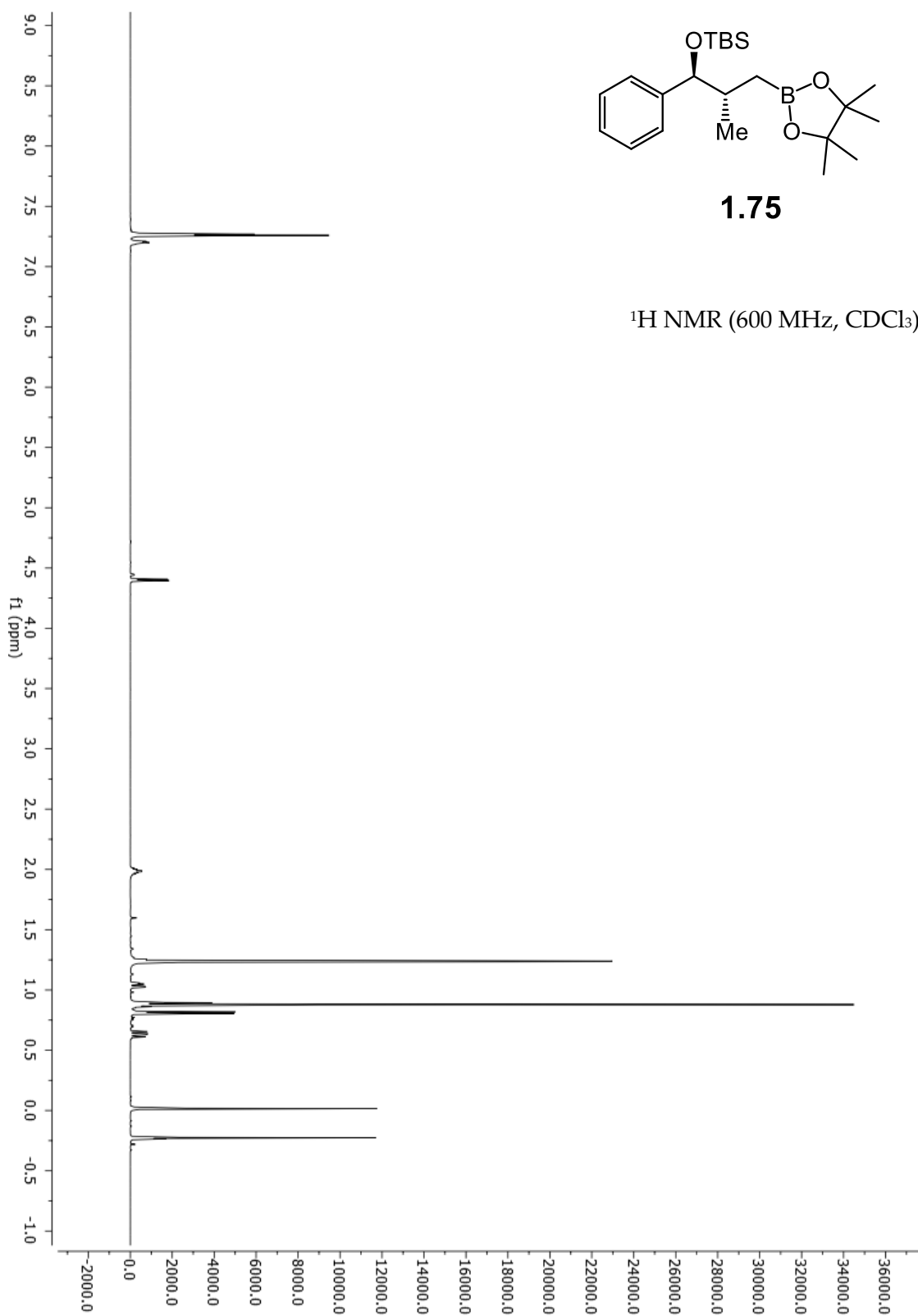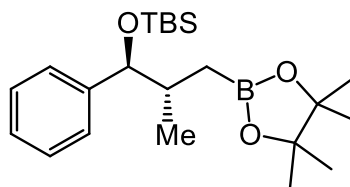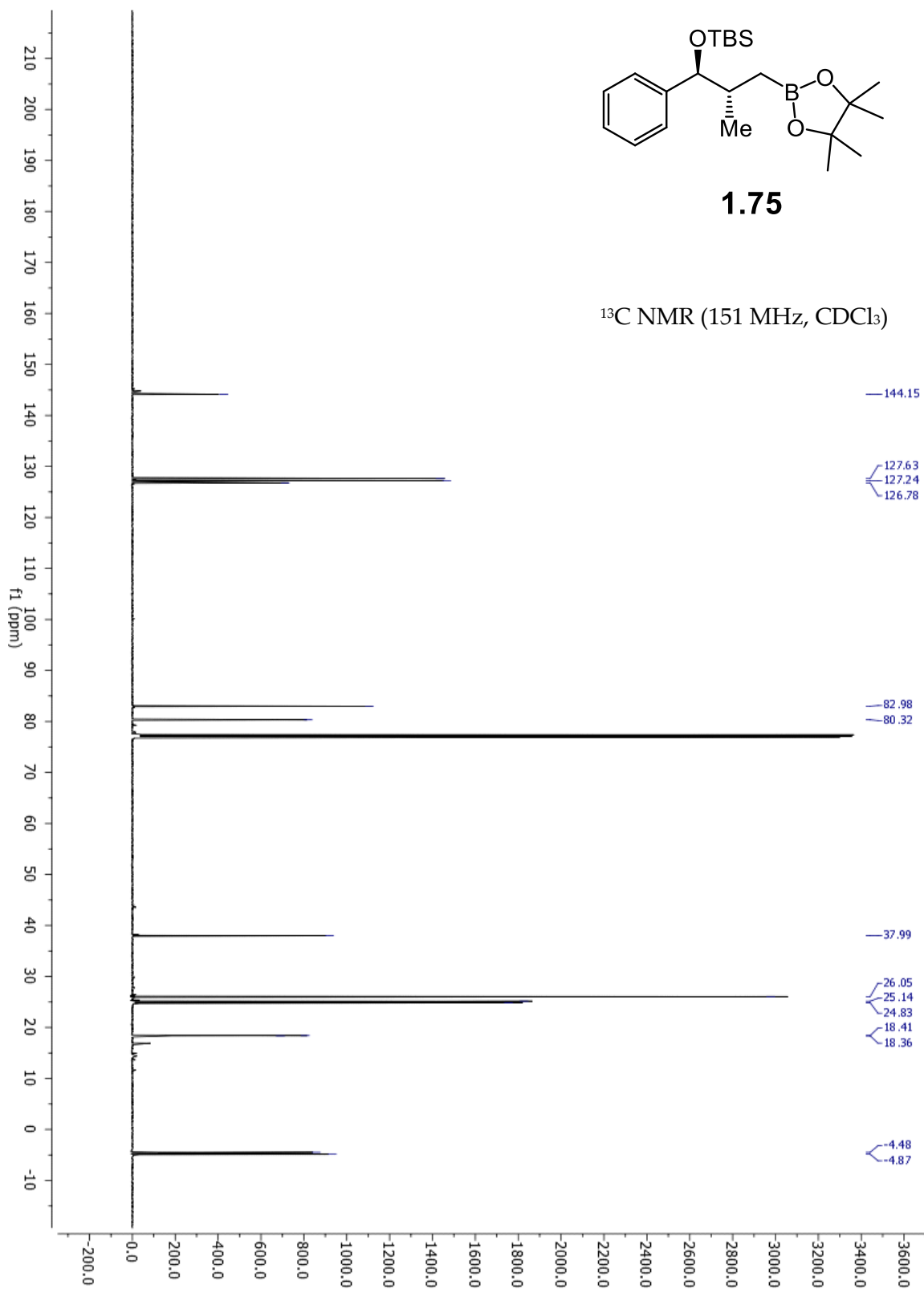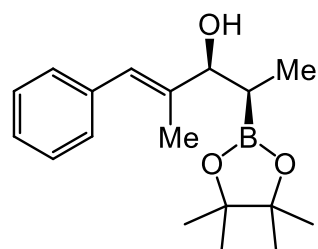
1.80

^{1}H NMR (600 MHz, CDCl$_3$)

1.80

^{13}C NMR (151 MHz, CDCl$_3$)

139.72
137.90

129.16
128.17
126.68
126.42

83.60
81.33

24.96
24.83
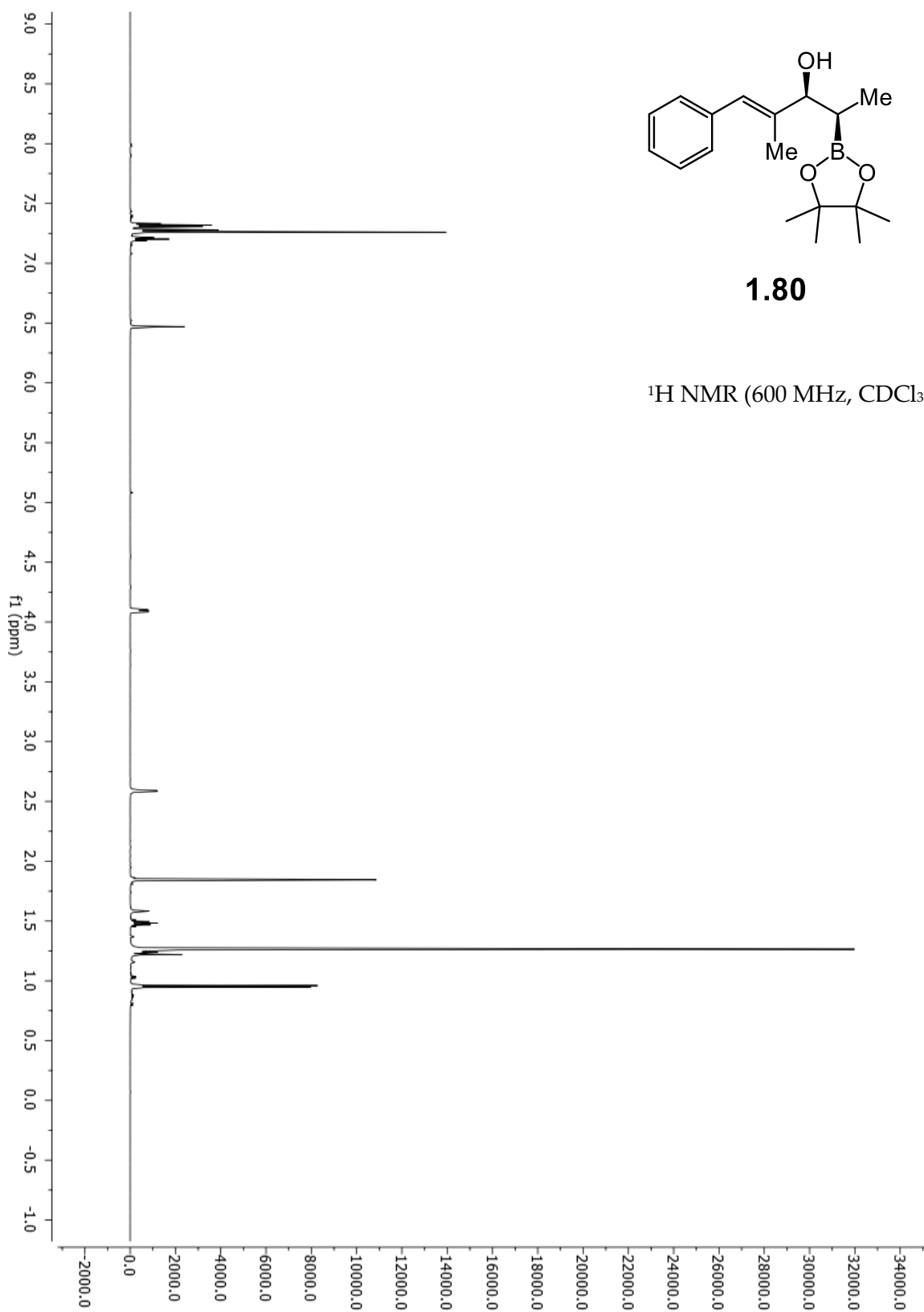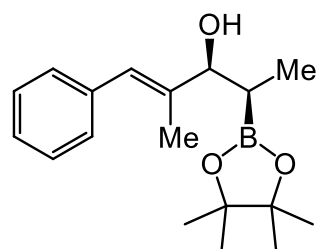
12.88
12.63
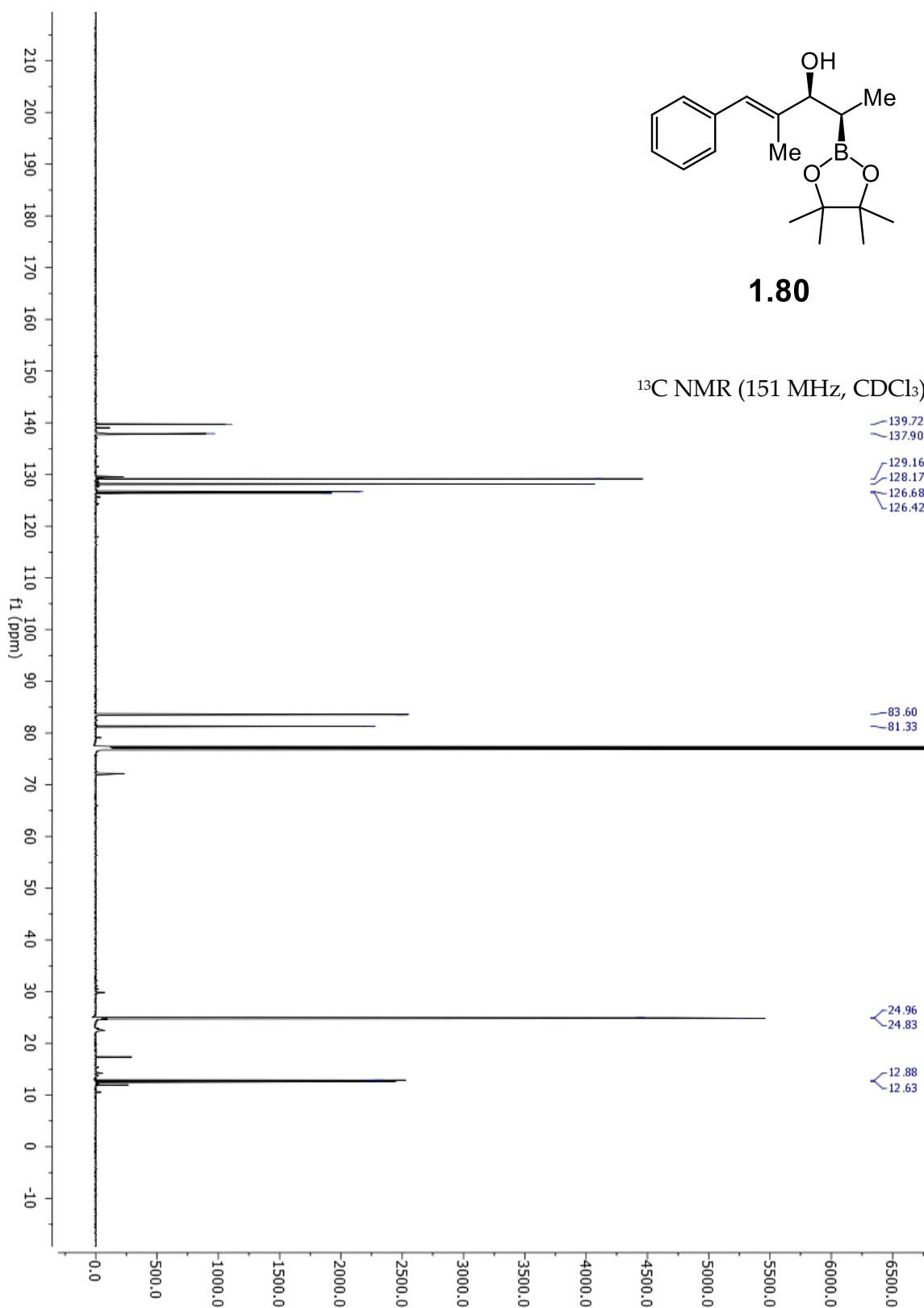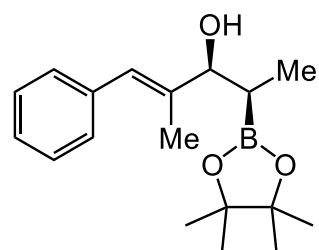
1.80

^{11}B NMR (151 MHz, CDCl$_3$)

1.76

^{1}H NMR (400 MHz, CDCl$_3$)
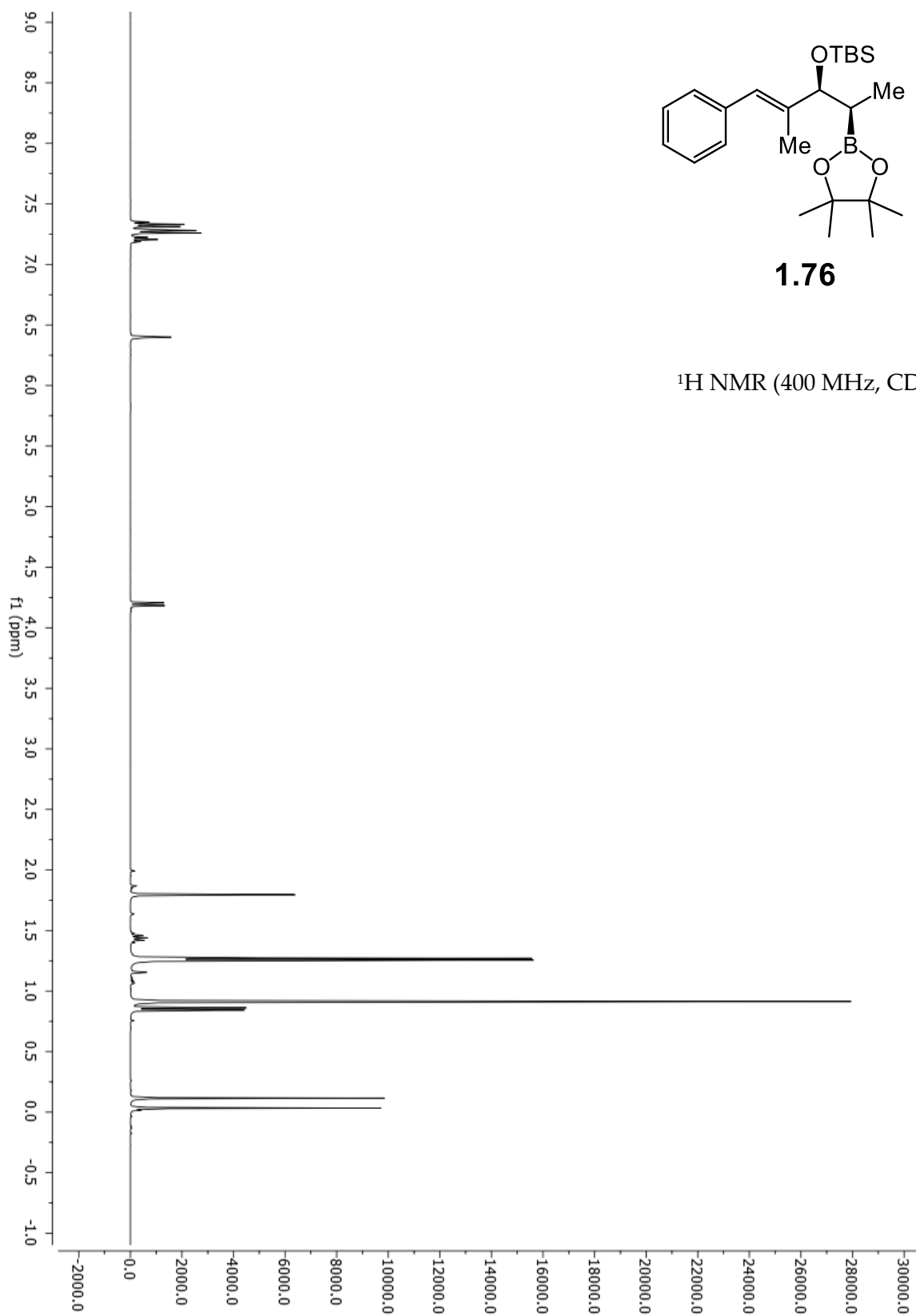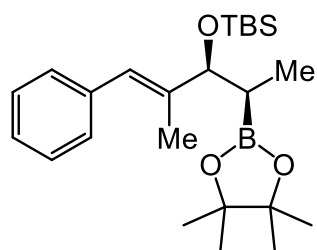
^{13}C NMR (100 MHz, CDCl$_3$)

— 140.36
— 138.20

— 129.02
— 128.18
— 126.74
— 126.27

— 83.01
— 81.99

— 26.17
— 25.41
— 24.80
— 18.36
— 12.64
— 12.52

— -4.05
— -4.65

1.77

¹H NMR (600 MHz, CDCl₃)

132

1.77

^{13}C NMR (151 MHz, CDCl$_3$)

155.81

138.07
137.90

129.12
128.13
126.39
126.13

80.30
79.01

49.10

28.56
26.08

19.54
18.43
15.32

-4.31
-4.96

f1 (ppm)

^{1}H NMR (400 MHz, C$_6$D$_6$)

¹³C NMR (121 MHz, C₆D₆)

68.9365

41.1206

32.1405

10.5249

f1 (ppm)

135
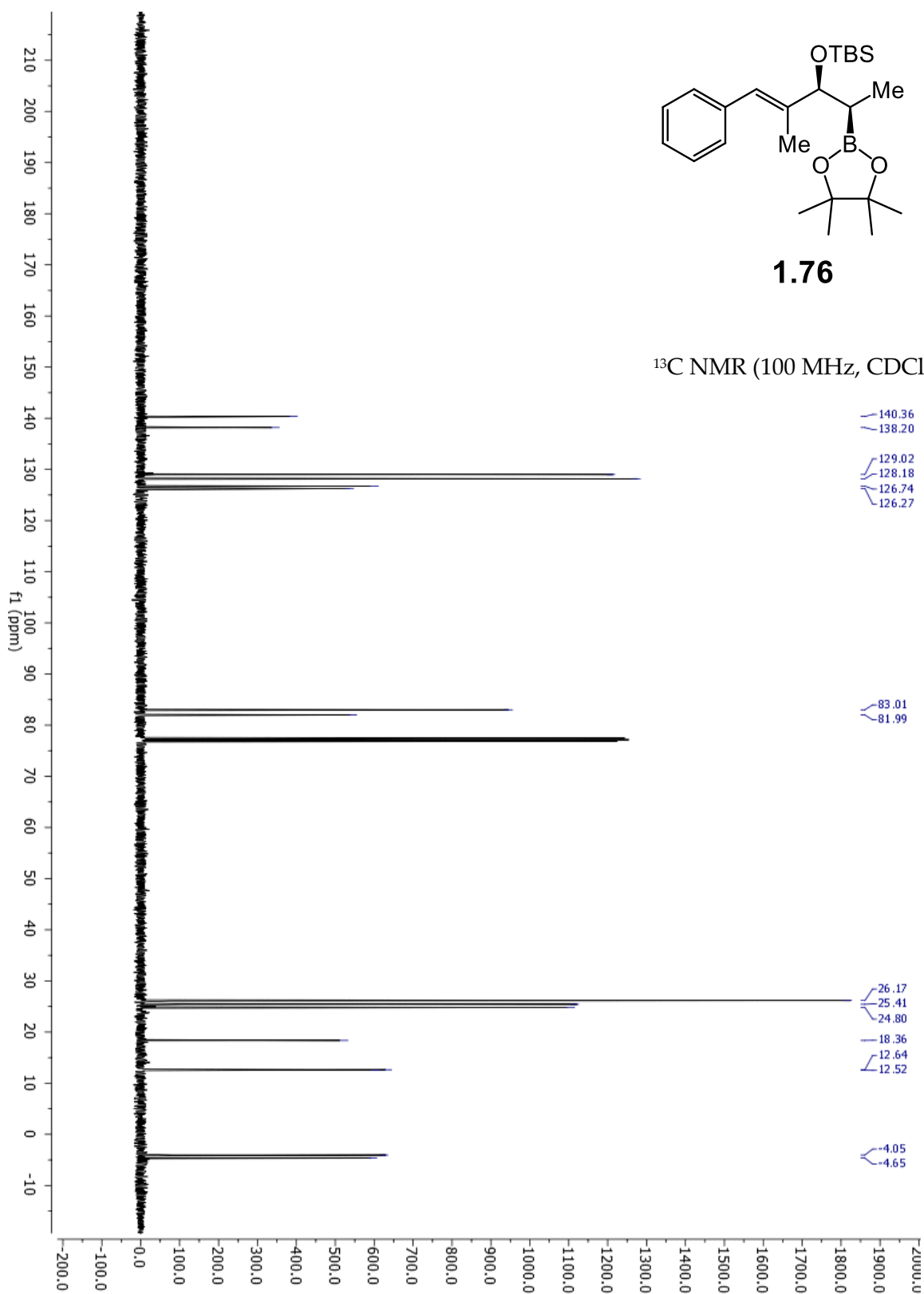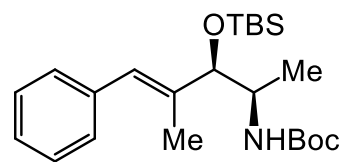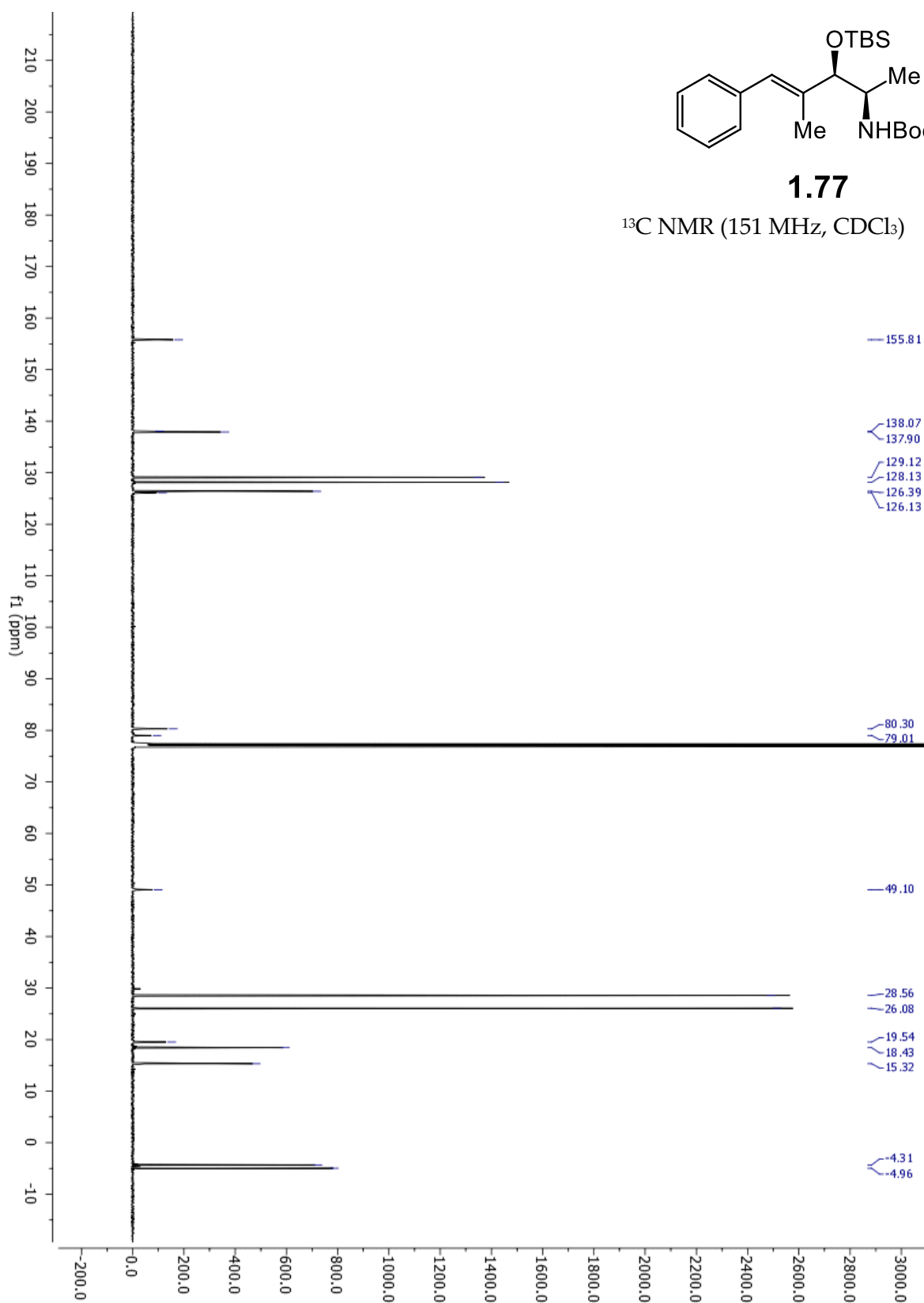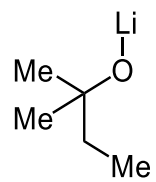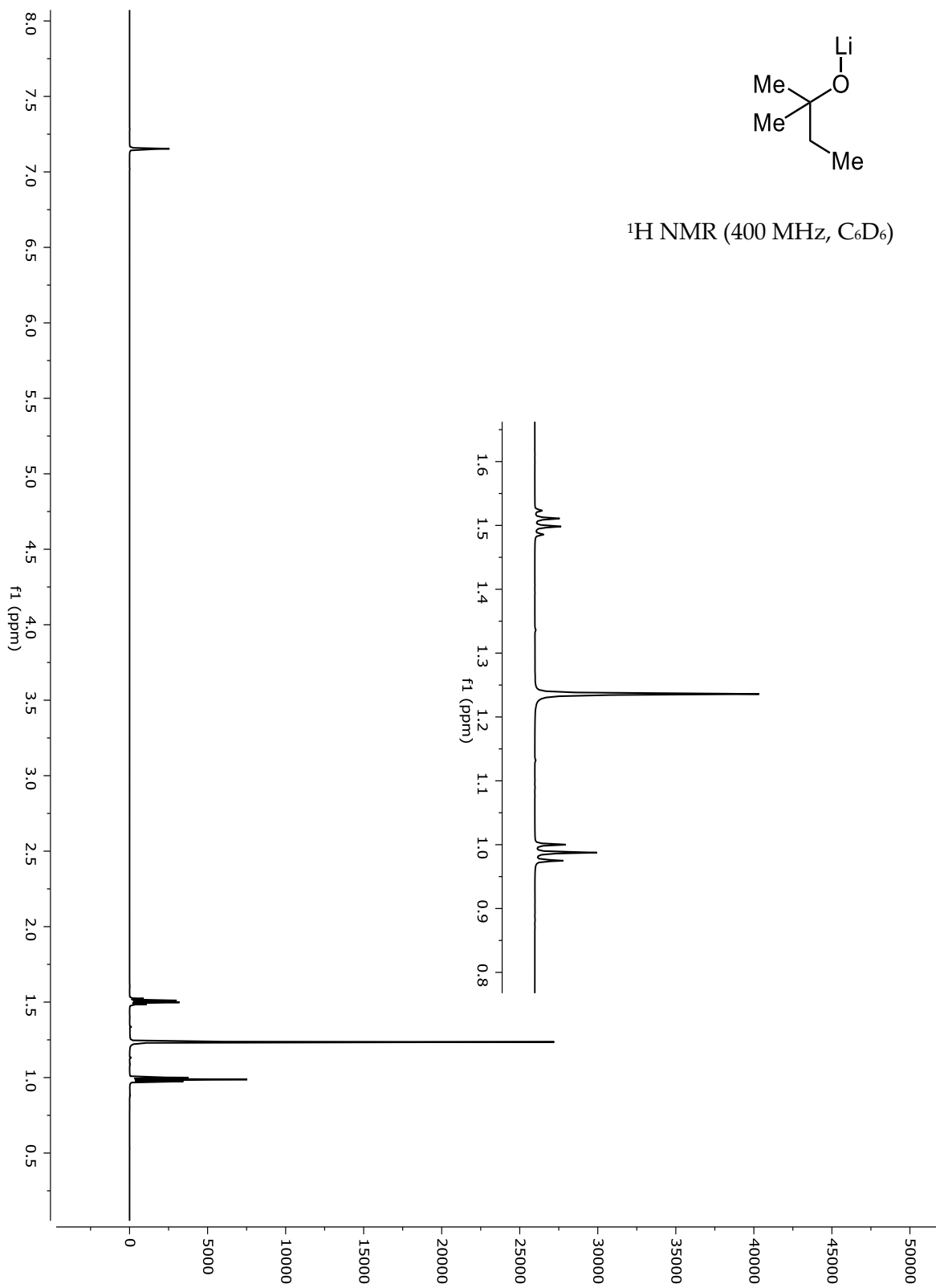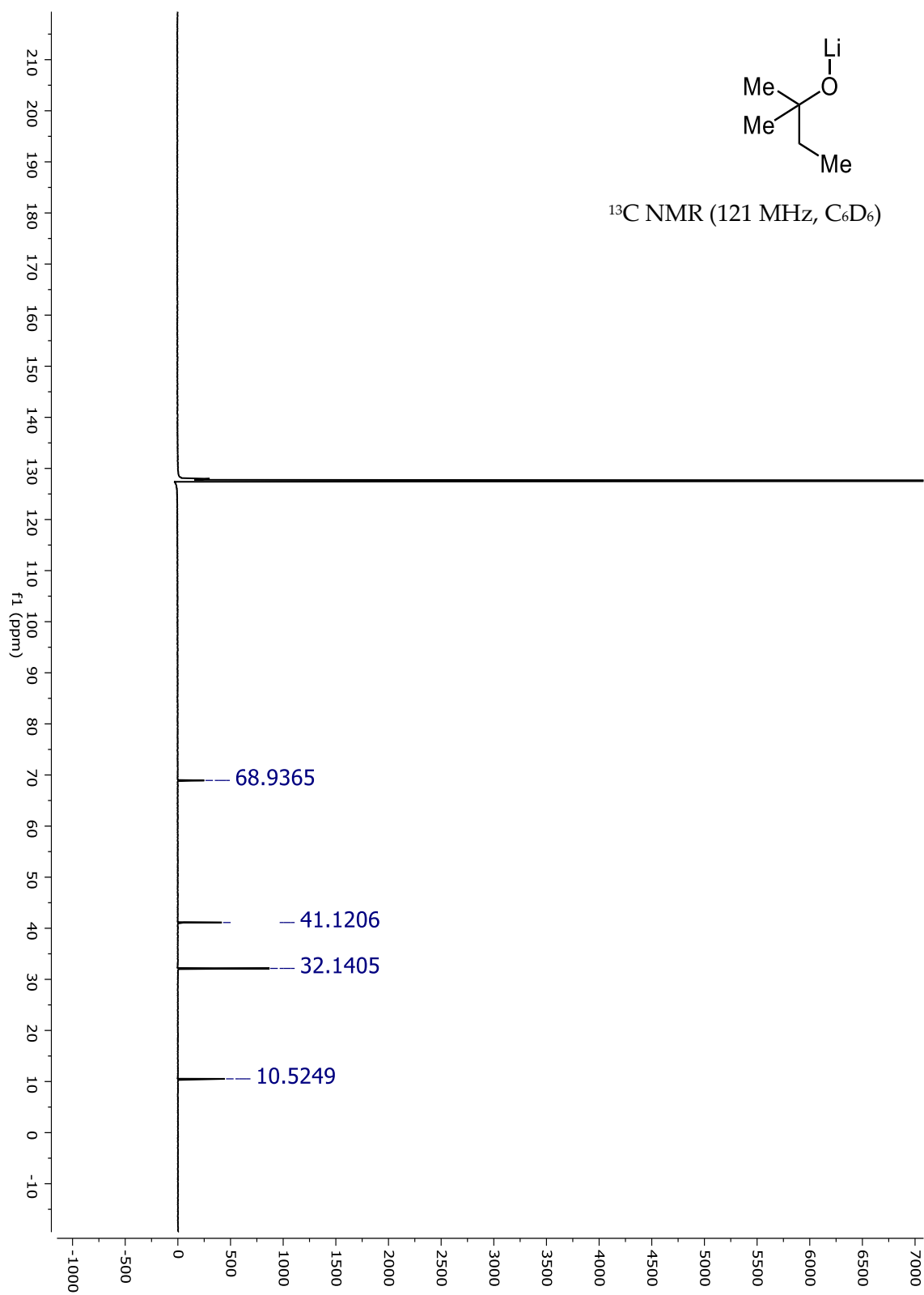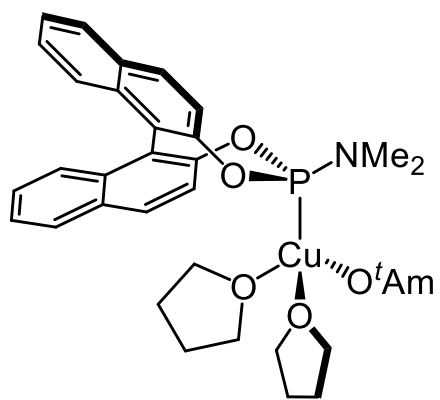
1.72

^{1}H NMR (600 MHz, thf-d_8)

1.72

— 124.63

^{31}P NMR (243 MHz, thf-d_8)

f1 (ppm)
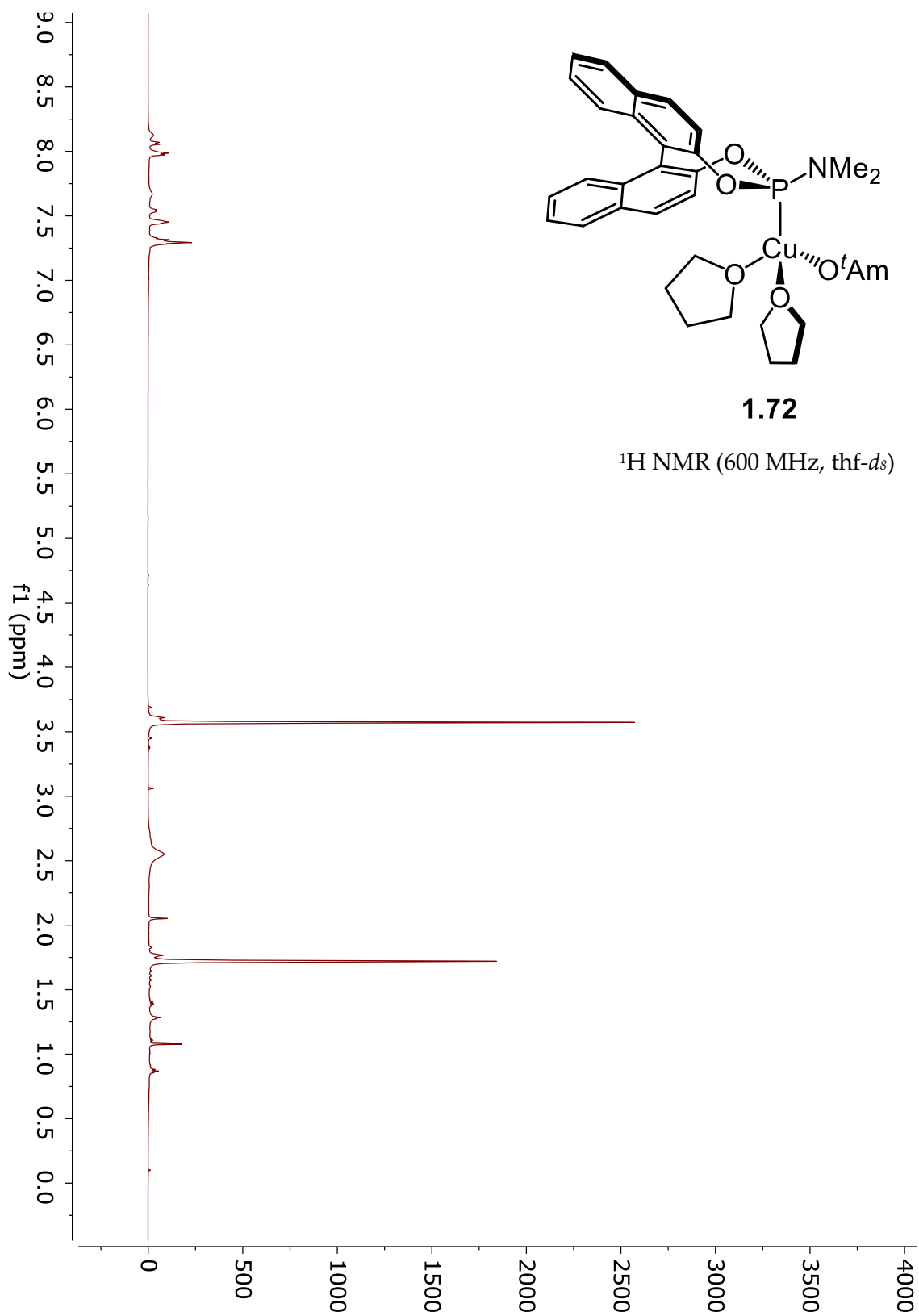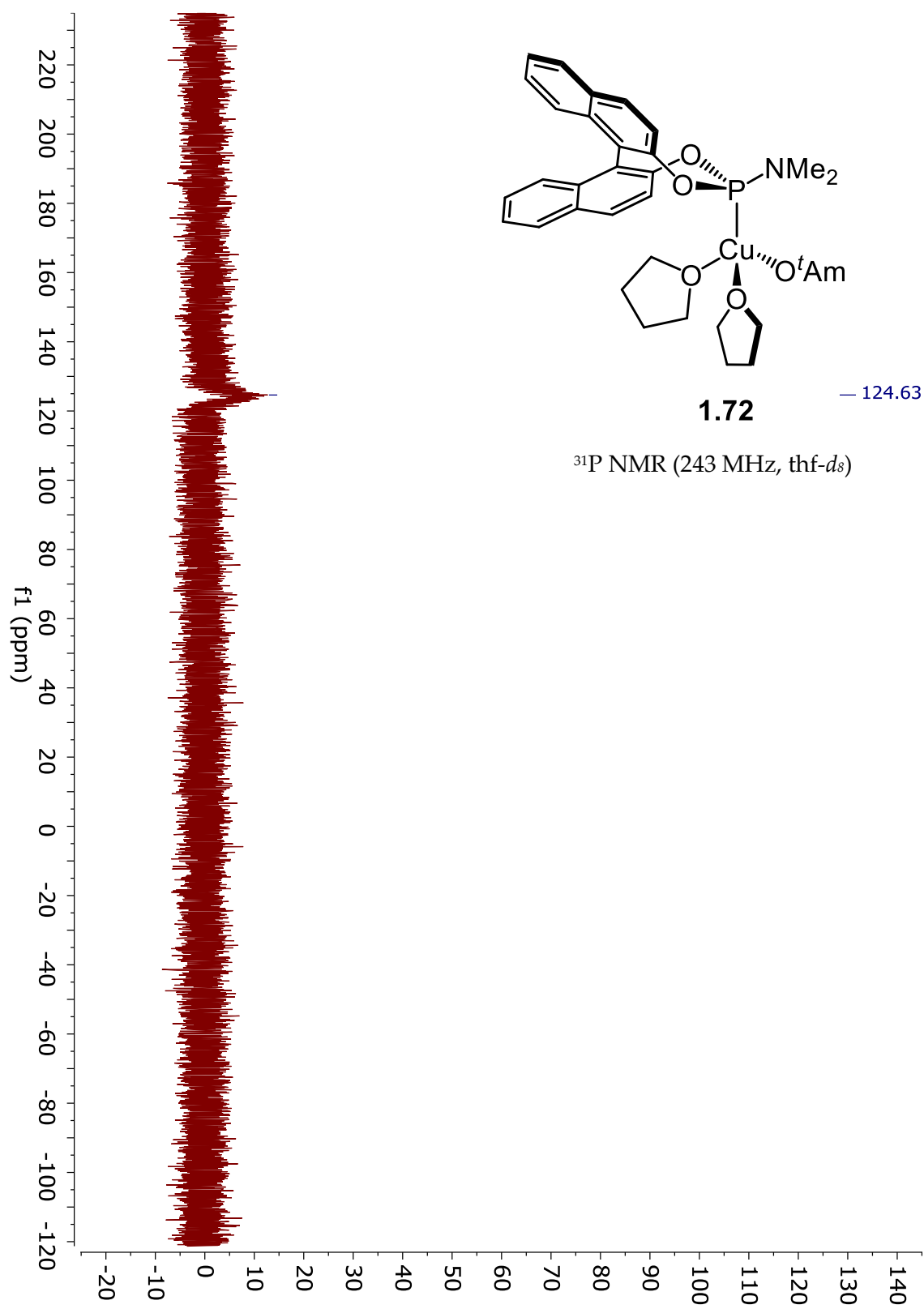
Procedure: In an N_2-filled glovebox, a screw-cap NMR tube was charged with LiO^{t}Bu (5.1 mg, .063 mmol) and diborylethane (10.5 mg, .0373 mmol) followed by tetrahydrofuran-d_8 (0.75 mL). The tube was seal with Teflon tape and removed from the glovebox and vortexed for 5 minutes. ¹H and ¹¹B NMR spectra were obtained after 2.5 hours of reacting. The NMR tube was then placed in a water bath set to 50 ˚C for 2.5 hours, after which time ¹H and ¹¹B NMR spectra were obtained.
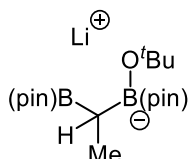
1.70

After 2.5 h at 22 ˚C: **¹H NMR** (400 MHz, thf-d_8): δ 0.83 (d, 3H, J = 4.3 Hz), 0.061 (qu, 1H, J = 5.0 Hz). **¹¹B NMR** (128 MHz, thf-d_8): δ 32.3 (s), 6.9 (s)
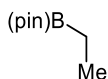
Proteodeborated **1.28**

After 2.5 h at 50 ˚C: **¹H NMR** (400 MHz, thf-d_8): δ 0.76 (tr, 3H, J = 7.6 Hz), 0.22 (qu, 1H, J = 7.6 Hz). **¹¹B NMR** (128 MHz, thf-d_8): δ 32.3 (s)
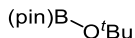
Tert-butyl pinacol borate

After 2.5 h at 50 ˚C: **¹¹B NMR** (128 MHz, thf-d_8): δ 19.4 (s)
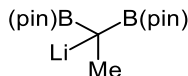
Deprotonated **1.28** (potentially)

After 2.5 h at 50 ˚C: **¹¹B NMR** (128 MHz, thf-d_8): δ 3.55 (s)

B(pin)

Me⌒B(pin)

1.28

^{1}H NMR (400 MHz, thf-d_8)

B(pin)
Me⌃B(pin)
1.28

^{11}B NMR (128 MHz, thf-d_8)

— 32.2719

f1 (ppm)

46 44 42 40 38 36 34 32 30 28 26 24 22 20 18 16 14 12 10 8 6 4 2 0 -2 -4 -6 -8

-50 0 50 100 150 200 250 300 350 400 450 500 550 600 650 700

LiO^{t}Bu
(1.7 equiv)

thf-d_8, 22 °C
2.5 h

(pin)B — B(pin)

H   Me
1.28

Li$^\oplus$
O^{t}Bu

(pin)B — B(pin)$^\ominus$

H   Me
1.70

^{1}H NMR (400 MHz, thf-d_8)

0.9512
0.9389

0.8318
0.8192

0.5552
0.5431
0.5308
0.5182

0.0810
0.0681
0.0553

f1 (ppm)

LiO^{t}Bu
(1.7 equiv)

thf-d_8, 50 °C
2.5 h

(pin)B B(pin)
H
Me
1.28

Li$^\oplus$
O^{t}Bu
(pin)B B(pin)
H $\ominus$
Me **1.70**

(pin)B H
H
Me

^{1}H NMR (400 MHz, thf-d_8)

0.8380
0.8189
0.7764
0.7566
0.7371

0.5665
0.5482
0.5299
0.5113

0.2478
0.2283
0.2088
0.1894

0.0924
0.0734
0.0541

f1 (ppm)

x-axis labels: 50, 45, 40, 35, 30, 25, 20, 15, 10, 5, 0, -5, -10, -15, -20, -25, -30, -35, -40, -45

f1 (ppm)

bottom axis: -100, 0, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300

Peak labels:
— 32.3095
— 19.4021
— 6.8481
— 3.5206

(pin)B—B(pin)
H   Me
1.28

LiO^{t}Bu
(1.7 equiv)

thf-d_8, 50 °C
2.5 h

Li$^\oplus$
O^{t}Bu
(pin)B—B(pin)
H   Me $\ominus$ **1.70**

(pin)B   H
      H
   Me

^{t}BuO—B(pin)

(pin)B—B(pin)   **?**
Li   Me

^{11}B NMR (128 MHz, thf-d_8)

■ **DFT Calculations**

DFT calculations were performed using the Gaussian 09 computer program suite.[46] All geometries were optimized using B3LYP level of theory. Trunctated structure **1.28** (which reduced the pinacolatoboryl groups to dioxaborylanyl groups) was optimized with a 6-31G** basis set, while trunctated structure **1.70** (which truncated both the pinacolato boryl groups and the *tert*-butoxy group to dioxaborylanyl and methoxy groups, respectively) was optimized with a 6-31++G** basis set. All optimized structures were checked by means of frequency calculations to ensure that all ground state geometries contained only real frequencies and were truly at a local minimum. All calculations were carried out in the gas-phase.
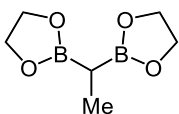
Sum of electronic and thermal free energies: -586.525124 Hartree

Zero Point Correction: 0.192906 (Hartree/particle)

Coordinates (angstroms)

Atom	X	Y	Z
C	0.007709	1.028663	0.79391
H	-0.00708	0.948691	1.890087
C	0.036949	2.513818	0.364788
H	-0.82608	3.063316	0.755672
H	0.940427	3.018551	0.721729
H	0.019577	2.607149	-0.72474
C	-2.97372	-0.3687	-1.09657
C	-3.00611	-1.20783	0.202706
H	-3.83807	0.297693	-1.18496
H	-2.91543	-0.98546	-1.99744
H	-3.96706	-1.14924	0.720752
H	-2.76871	-2.26173	0.024379
C	3.144678	-0.33631	-0.86292
C	2.803905	-1.45961	0.145503
H	3.031026	-0.65958	-1.90274
H	4.154853	0.05995	-0.72924
H	2.675889	-2.43388	-0.33399

Atom	X	Y	Z
H	3.557702	-1.55521	0.933837
B	-1.27005	0.269239	0.280979
B	1.269642	0.222502	0.311594
O	-1.97976	-0.63438	1.036363
O	-1.77936	0.430081	-0.98756
O	2.185676	0.70465	-0.59288
O	1.556511	-1.054	0.741501
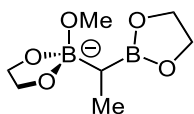
Sum of electronic and thermal free energies: -701.910273 Hartree

Zero Point Correction: 0.235809 (Hartree/particle)

Coordinates (angstroms)

Atom	X	Y	Z
B	1.491151	-0.21069	0.397072
C	0.096725	-0.26408	1.068731
H	0.096164	0.475413	1.884658
C	-0.22252	-1.649	1.672107
H	0.510043	-1.96927	2.425208
H	-1.2052	-1.64966	2.153543
H	-0.2438	-2.42279	0.898811
O	2.064513	-1.26124	-0.3111
O	-1.32473	-0.74864	-1.09954
O	-2.41498	0.267411	0.727635
O	2.345476	0.886931	0.42513
C	3.573875	0.54685	-0.23907
H	3.828524	1.331305	-0.95443
H	4.371591	0.480969	0.506916
C	3.28826	-0.80879	-0.91336
H	4.073106	-1.54683	-0.73656
H	3.135569	-0.71114	-1.99212
C	-2.66983	-1.18239	-1.07328
H	-3.08216	-1.23384	-2.08979
H	-2.74228	-2.19009	-0.63153
C	-3.39747	-0.1559	-0.19502
H	-4.25941	-0.58123	0.33371
H	-3.76035	0.687015	-0.80703
B	-1.09578	0.221476	0.013095
O	-0.79088	1.528769	-0.64034

C	-0.6517	2.664307	0.174482
H	-0.56224	3.551305	-0.46437
H	-1.52113	2.812086	0.832057
H	0.245473	2.620972	0.808264

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Chapter 2: Ag(I)-Catalyzed Synthesis of *anti*-1,2-Hydroxyboronates through α-Boryl Alkyl Silver Additions to Aldehydes[*]

2.1 Introduction

Enantiomerically pure secondary alkyl-organoboron compounds are valuable reagents in chemical synthesis and can be functionalized to access complex products useful to synthetic organic chemists.[1] Being able to efficiently and selectively construct C (sp^3) – B bonds is, therefore, an important problem to address. There are a number of current methods for generating secondary alkyl-organoboron compounds including: hydroboration[2], diboration[3], conjugate boration[4], among several others. Our group has developed a new strategy for stereoselectively incorporating boron into molecules *via* the addition of enantiomerically-enriched α-borylated organometallics to aldehydes.[5,6] This process constructs a new C(sp^3) – C(sp^3) bond with two vicinal stereocenters, one of which contains an organoboronate ester. This methodology allows for the rapid construction of complex, highly functionalized molecules from simple and achiral starting materials.

I initially developed an enantio- and diastereoselective copper-catalyzed addition of diborylethane, **2.2** to various aryl and alkenyl aldehydes in the presence of a lithium alkoxide activator with good yields, enantio-, and diastereoselectivities (Scheme 2.1: **2.3** forms in 92% yield, 93:7 d.r., 95:5 e.r.).[5] A drawback to this method, however, was the limitation of the scope of the *gem*-diboronate ester, as only diborylethane could be efficiently added to aldehydes (Scheme 2.2). Under optimal reaction conditions for diborylethane (10 mol % Cu(MeCN)$_4$PF$_6$, 20 mol % *(R)*-Monophos, and 90 mol % LiO^{t}Am), 1,2-hydroxyboronate **2.5** is only formed in 30% NMR yield, albeit in good diastereo- and

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[*]A portion of this chapter appeared in a communication in *Angewandte Chemie International Edition*, the reference is as follows: Joannou, M. V.; Moyer, B. S.; Goldfogel, M. J.; Meek, S. J. *Angew. Chem. Int. Ed.* **2015**, *54*, 14141-14145.

enantioselectivity (92:8 d.r. and 95:5 e.r.). Other substituents on the *gem*-diboronate ester are similarly

unreactive, as 1,2-hydroxyboronates **2.6** and **2.7**, which contain olefin and silyl ether groups

(respectively), form in <2% conv. and 10% conv., respectively. Two possible causes for decreased

reactivity but maintained selectivity are: 1) The α-boryl alkyl unit is too large and prevents binding of

the aldehyde to the copper catalyst, and 2) The α-boryl alkyl copper is not nucleophilic enough to add

to the aldehyde.

Scheme 2.1 Cu-catalyzed additions of diborylethane to aryl and alkenyl aldehydes

■ *Construction of new C−C bond*
■ *Two vicinal stereocenters (one with C(sp³)−B unit)*
■ *18 examples of aryl and alkenyl aldehydes*

2.3
>98% NMR yield
93:7 d.r.; 95:5 e.r.
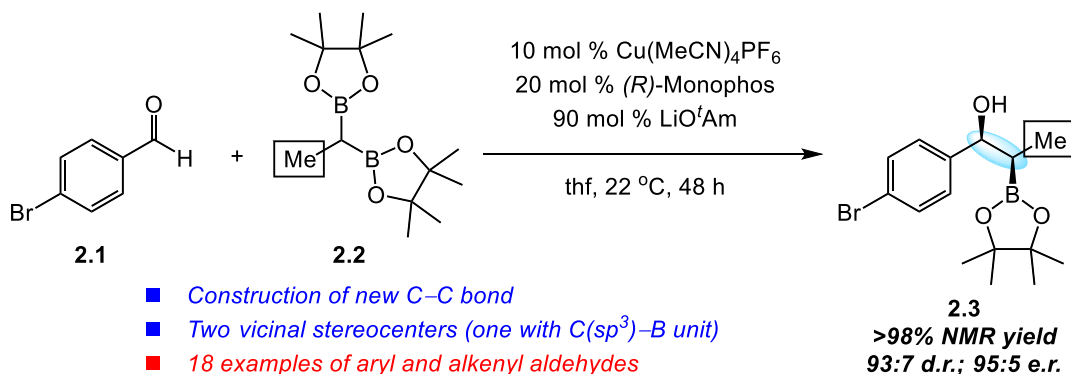
Scheme 2.2 Cu-catalyzed additions of more highly substituted *gem*-diboronate esters to benzaldehyde

2.5
30% NMR yield
92:8 d.r.; 95:5 e.r.

2.6
<2% conv.

2.7
10% conv.; 95:5 d.r.

152
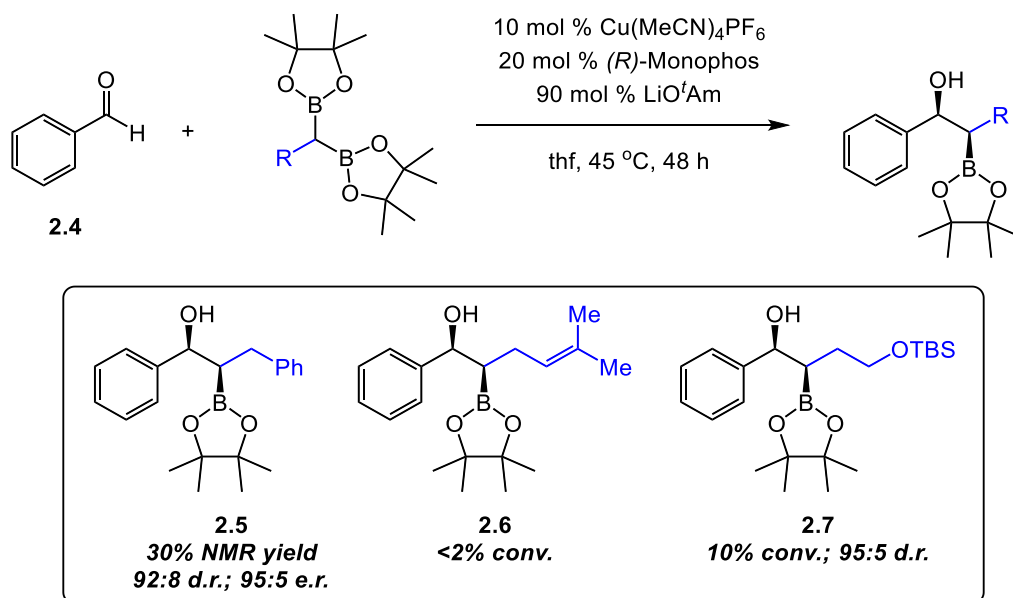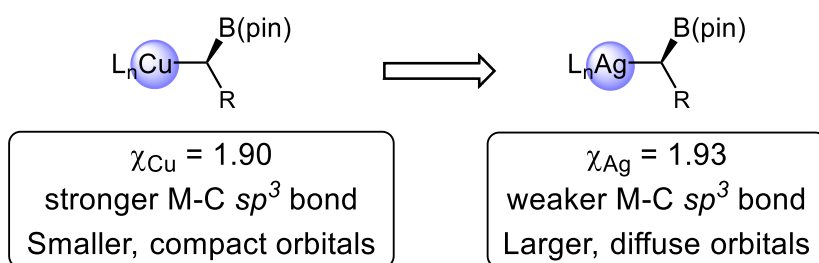
Figure 2.1 Switching from copper to silver α-boryl alkyl species to increase nucleophilicity and to

tolerate larger R groups in additions to aldehydes

To remedy poor reactivity and promote additions of larger *gem*-diboronate esters to aldehydes,

we envisioned switching from a copper to a silver-based catalyst system (Figure 2.1). As depicted in

Figure 2.1, silver has a slightly higher electronegativity, χ, and is larger and has more diffuse orbitals

involved in bonding.[7] This leads to Ag – C bonds being much weaker and more reactive than

corresponding Cu – C bonds. Several groups have used Density Functional Theory to estimate the

bond strengths of Cu – C(sp^3) and Ag – C(sp^3) bonds: on average Cu – C(sp^3) bonds are 10-20 kcal/mol

stronger than the corresponding Ag – C(sp^3) bonds.[8] This indicates that a silver-alkyl species should

be more reactive than its copper congener, and require less energy to break the Ag – C(sp^3) bond during

a reaction. In addition to being larger, silver is also more polarizable than copper and has longer Ag –

ligand bonds. For instance, the copper-phosphorus bond distance in the binap-CuCl dimer **2.9** is 2.26

Å[9], while the silver-phosphorus bond distance in the binap-AgOAc complex **2.8** is 2.51 Å[10]. Longer

bond lengths should help the silver complex accommodate the increased size of larger α-boryl alkyl

units. For these reasons, silver should be able to accommodate larger α-boryl alkyl groups, while at the

same time being nucleophilic enough to add to aldehydes.
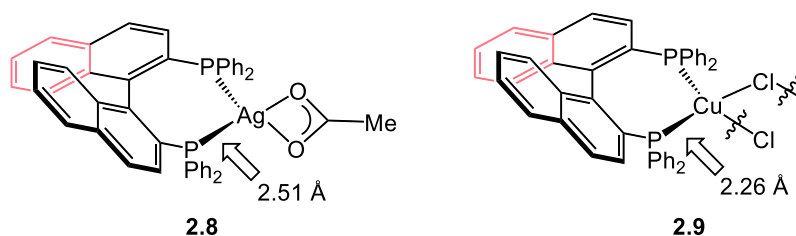
Figure 2.2 Silver and copper phosphorus bond distances in binap(M) complexes: Ag – P > Cu – P

2.2   Background

The stoichiometric addition of α-borylated organometallic nucleophiles to aldehydes has been known since the early 1990's and was pioneered by Paul Knochel. In a 1990 *JACS* communication, he disclosed the synthesis of several α-borylcyanocuprates prepared *in situ* from the corresponding α-haloboronate ester (Scheme 2.3, top).[11] For instance, iodomethyl boronic acid pinacol ester, **2.10** reacts with zinc dust at 25 °C in thf to afford the α-borylmethylzinciodide, which is then further reacted with CuCN·2LiCl to produce the α-borylcyanocuprate, **2.12**. While Knochel demonstrates that substituted α-borylcuprates add to a number of electrophiles including silyl chlorides, enones, enals, acyl chlorides, and alkyl bromides, the addition to aldehydes only occurs with the unsubstituted α-borylcuprate, **2.12**. **2.12** reacts with naphthylaldehyde to produce the 1,2-hydroxyboronate **2.13** in 93% yield after oxidation. This highlights the importance of sterics in the 1,2-addition of cuprates to less reactive electrophiles such as aldehydes.

Suzuki and co-workers published a subsequent paper in 1995 with an aldehyde substrate scope for Knochel's reaction depicted in the top of Scheme 2.3.[12]   They also disclosed several functionalizations of the resulting 1,2-hydroxyboronates such as olefination (through the boron-Wittig elimination) and oxidation using NaOH/H_2O_2. Most significant was the addition of a methyl-substituted α-borylcyanocuprate, **2.14** to benzaldehyde, the product of which Suzuki isolated in 91% yield in an 84:16 *anti*:*syn* diastereoselectivity. In the presence of a superstoichiometric amount of BF_3·OEt_2 (8 equivalents) to activate the aldehyde, larger α-borylcyanocuprates can be added efficiently to aryl aldehydes, indicating that either the electrophile needs to be activated or the cuprate's nucleophilicity needs to be increased to add larger α-boryl units.

Scheme 2.3 Knochel's α-boryl cyanocuprate in 1,2-addition reactions: only examples have limited

substitution at α position (H and methyl only)

■ Knochel (1990)
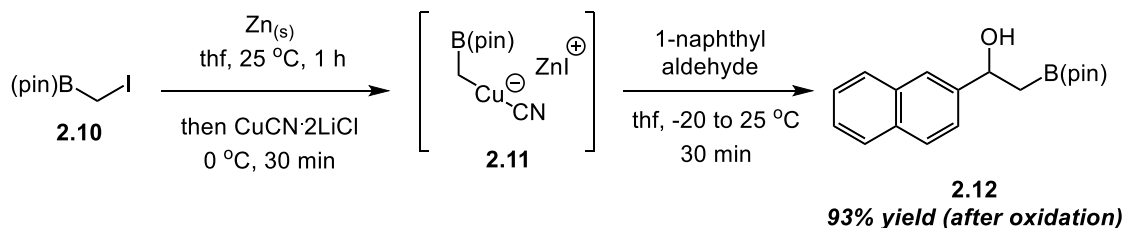
■ Suzuki (1995)
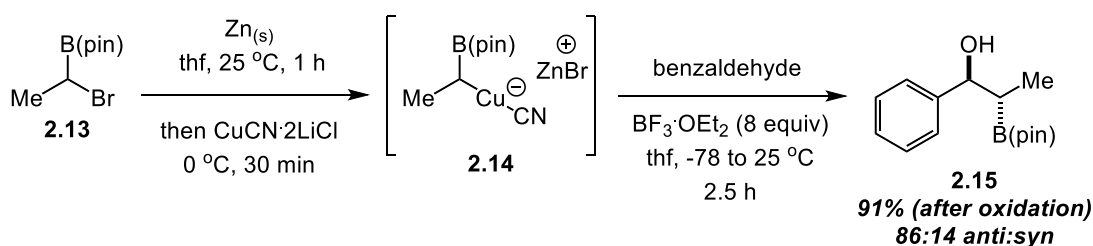
      In addition to the use of α-boryl copper species in 1,2-addition reactions, Andrew Pelter and co-workers developed a method for generating α-bis(mesityl)boron alkyllithiums and various methodologies for their subsequent additions to electrophiles including acyl chlorides, aldehydes, and ketones.[13]   As presented in Scheme 2.4, bis(mesityl)alkylborane **2.16** is deprotonated with mesityllithium at -110 °C to form *in situ* the α-bis(mesityl)boron alkyllithium, **2.17**. While maintained at -110 °C, this nucleophile is added to benzaldehyde and then quenched with an oxidative work-up to furnish the *anti*-1,2-diol **2.18** in 84% yield and 95:5 *anti* diastereoselectivity. Of significance is the fact that more highly substituted α-lithioalkylboranes can be added to aldehydes, including H, Me, heptyl, hexyl, etc. This is in contrast to reports by Knochel and Suzuki where the largest group tolerated in the α-position is methyl during a 1,2-addition reaction to aldehydes. This increased reactivity most likely stems from the nature of the carbon-lithium bond in the α-lithioalkylborane.

Scheme 2.4 In situ generation of α-boryl alkyllithiums from alkylboranes and their additions to aldehydes
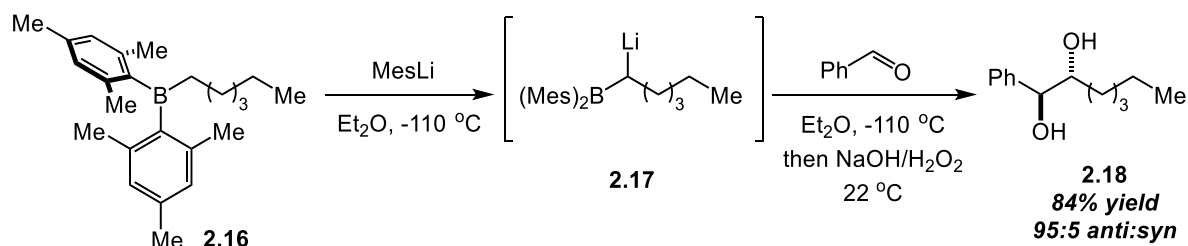
Phillip Powers and co-workers were able to isolate and characterize by NMR spectroscopy and X-Ray crystallography deprotonated bis(mesityl)borylmethane.[14] Using LiTMP, the α-lithioborylmethane **2.17** is observed in solution (^{11}B NMR) and readily converts to the α-borylcarbanion **2.18** upon exposure to 12-crown-4, a lithium cation scavenger (Figure 2.2). An X-Ray structure of **2.18** was obtained and the double bond character of the B – C bond was confirmed (B – C 1.45 Å) as well as the complete removal of lithium from the molecule (now associated with the crown ether, which was eliminated for clarity).   It is probable that these larger α-boryl groups can undergo 1,2-addition reactions with aldehydes due to their increased reactivity and transient interaction of the lithium with the α-carbon, which behaves more like a carbanion than an organometallic species. This bodes well for α-boryl silver complexes being more reactive than copper analogues due to the weaker association of silver and carbon (i.e. having more carbanion-like character).
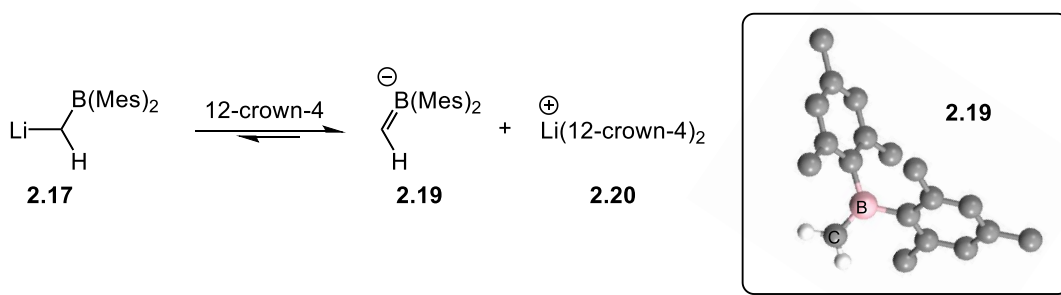
Figure 2.3 Equilibrium between α-boryl alkyllithium and boron-stabilized carbanion

2.3   Reaction Discovery and Optimization

To determine whether silver(I) salts were capable of catalyzing the addition of *gem*-diboronate esters to aldehyde, I conducted experiments using the model reaction of adding diborylethane, **2.2** to benzaldehyde, **2.4** in the presence of a catalytic amount of a silver(I) salt and a stoichiometric amount of a *tert*-butoxide activator. Depicted in Table 2.1 are the results of the reaction optimizations including temperature, *tert*-butoxide activator, and ligand. As stated in Chapter 1 of this document, the uncatalyzed background reaction of **2.2** and **2.4** is highly dependent on the counterion of the *tert*-butoxide activator. Lithium *tert*-butoxide is unable to promote the reaction at ambient (Entry 1) or elevated temperatures, which makes it an ideal base for a metal-catalyzed process. With 130 mol % LiO^{t}Bu in the presence of 10 mol % AgOAc with or without 10 mol % *rac*-binap however, no product was observed (Entries 2 and 3). Sodium *tert*-butoxide is capable of promoting an unselective (50:50 d.r.) addition of **2.2** to **2.4** (Entry 4, 63% NMR yield), but this background reaction can be completely suppressed if the reaction temperature is lowered to 0 °C (Entry 5). With no background reaction at 0 °C with NaO^{t}Bu, any product observed in the reaction must stem from a silver(I) catalyzed process.

With 10 mol % AgOAc and 130 mol % NaO^{t}Bu at 0 °C, **2.21** forms in 18% NMR yield as a 50:50 mixture of diastereomers (Entry 6). Due to the low solubility of AgOAc in thf, I opted to ligate silver with different phosphorus-based ligands to help solubilize the silver catalyst, which might improve both reactivity and potentially diastereoselectivity. With 10 mol % added PPh$_3$, the NMR yield of the reaction increased to 47%, but with only a small increase in diastereoselectivity (Entry 7, 54:46 d.r.). Using 10 mol % of a bidentate ligand, *rac*-binap, affords the product in 42% NMR yield and 84:16 d.r (Entry 8). To further improve the diastereoselectivity, the reaction temperature was lowered to -25 °C, where the product forms in 33% NMR yield and 92:8 d.r. (Entry 9). Since the counterion of the *tert*-butoxide ion has such a dramatic effect on the background reaction, I reasoned that the more dissociating potassium counterion would more strongly activate the *gem*-diboronate ester and increase the reaction yield. Gratifyingly, with 130 mol % KO^{t}Bu in the presence of 10 mol % AgOAc and 10 mol % *rac*-binap, **2.21** forms in 50% NMR yield and 93:7 d.r. (Entry 10). Interested in

157

whether ligand-denticity or temperature controlled the diastereoselectivity of the reaction, I conducted

two reactions with 10 mol % PPh$_3$ and 10 mol % PCy$_3$, both monodendate ligands, at -25 °C with 130

mol % KO^{t}Bu and 10 mol % AgOAc (Entries 11 and 12). These reactions afford hydroxyboronate **2.21**

in 47% NMR yield, 95:5 d.r. and 64% NMR yield, 93:7, respectively. From this data, it can be inferred

that the temperature of the reaction has a much greater control over diastereoselectivity than the identity

of the ligand. Surprisingly, without any ligand or additive, 10 mol % AgOAc with 130 mol % KO^{t}Bu

promotes the reaction to 84% NMR yield with a 97:3 *anti*:*syn* diastereomeric ratio, the highest yield

and selectivity observed to that point (Entry 13). No product is formed when AgOAc is excluded from

the reaction, indicating AgOAc is indeed a catalyst for the addition of diborylethane and benzaldehyde.

Other silver sources such as AgOTf, AgCl, AgBF$_4$, AgSbF$_6$, and AgClO$_4$ catalyze the reaction depicted

in Table 2.1, but in lower yields.

Table 2.1 Ag-catalyzed 1,2-addition of diborylethane to benzaldehyde: activator, ligand, and temperature optimization[a]

10 mol % AgOAc
10 mol % ligand
130 mol % activator

thf, temp. 24 h

2.4   **2.2**   **2.21**   **2.21-*syn***
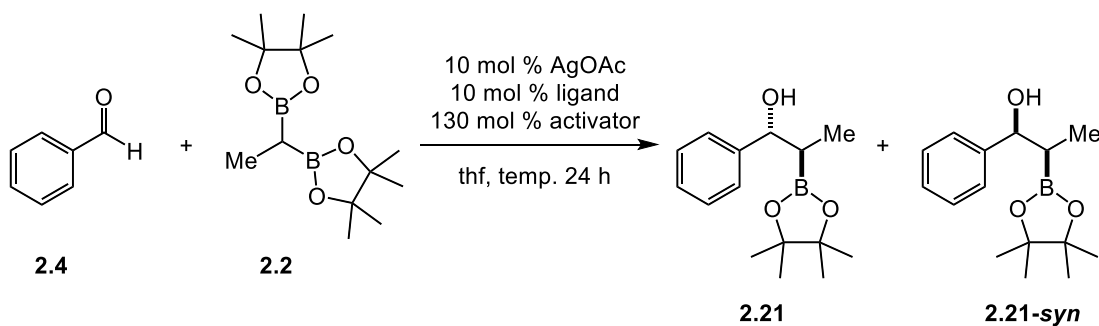
Entry	Silver salt	ligand	activator	temp. (°C)	NMR yield (%)[b]	d.r.[c]
1	-	-	LiO^{t}Bu	22	<2	-
2	AgOAc	-	LiO^{t}Bu	22	<2	-
3	AgOAc	*rac*-binap	LiO^{t}Bu	22	<2	-
4	-	-	NaO^{t}Bu	22	63	50:50
5	-	-	NaO^{t}Bu	0	<2	-
6	AgOAc	-	NaO^{t}Bu	0	18	50:50
7	AgOAc	PPh$_3$	NaO^{t}Bu	0	47	54:46
8	AgOAc	*rac*-binap	NaO^{t}Bu	0	42	84:16
9	AgOAc	*rac*-binap	NaO^{t}Bu	-25	33	92:8
10	AgOAc	*rac*-binap	KO^{t}Bu	-25	50	93:7
11	AgOAc	PPh$_3$	KO^{t}Bu	-25	47	95:5
12	AgOAc	PCy$_3$	KO^{t}Bu	-25	64	93:7
13	AgOAc	-	KO^{t}Bu	-25	84	97:3
14	-	-	KO^{t}Bu	-25	<2	-

[a]Reaction performed under an N$_2$ atmosphere; see Experimental Section for details. [b]Deteremined using ^{1}H NMR spectroscopy with hexamethyldisiloxane as an internal standard. [c]Determined using ^{1}H NMR spectroscopy.

2.4   Substrate Scope

With a set of optimal conditions for the model reaction of diborylethane to benzaldehyde, I proceeded to expand the substrate scope of aldehydes in this silver-catalyzed 1,2-addition reaction. The *anti*-1,2-hydroxyboronate products generated in these reactions are stable to isolation *via* silica gel column chromatography. To ensure high yields with all substrates, the silica gel used was deactivated with 3% NaOAc$_{(aq)}$ which led to synthetically useful yields for many of the substrates in this methodology. Using standard silica gel leads to elimination of the product to the olefin. Scheme 2.15 summarizes the results of the additions of diborylethane to different aryl and alkenyl aldehydes. With 10 mol % AgOAc and 130 mol % KO^{t}Bu at -25 °C, benzaldehyde-derived 1,2-hydroxyboronate **2.21** is isolated in 70% yield and 97:3 d.r. The reaction is tolerant of both electron-withdrawing and donating groups in the *para* position of the arene ring: *p*-F, *p*-Br, and *p*-OMe aryl aldehydes undergo 1,2-addition reactions to yield the 1,2-hydroxyboronates in 65%, 64%, and 73% yield, respectively, in up to 97:3 d.r. *Meta*-substituted aldehydes also efficiently undergo 1,2-addition with diborylethane: *m*-Me-derived hydroxyboronate **2.25** forms in 75% yield and 97:3 d.r., while *m*-NO$_2$ and *m*-CF$_3$ aryl substituted products are afforded in slightly diminished yields (53% and 52% yield, respectively) but with high diastereoselectivity (97:3 d.r.). Substituents in the *ortho* position provide products with almost complete diastereoselectivity, as 1,2-hydroxyboronate **2.28** is delivered in 69% yield and 99:1 d.r. 1,2-addition reactions to heteroaromatic substrates containing furyl (71% yield, 91:9 d.r.), pyridyl (45% yield, 96:4 d.r.), and indolyl (77% yield, 99:1 d.r.) groups are well tolerated with no significant inhibition. As with the copper-catalyzed addition methodology, alkenyl aldehydes are afforded in diminished diastereoselectivity: cinnamaldehyde, **2.32** and *p*-Cl-cinnamaldehyde, **2.33** derived products are formed in 65% yield, 88:12 d.r. and 40% yield, 86:14 d.r., respectively. When reacted with α-methyl-cinnamaldehyde, the diastereoselectivity of product **2.34** is restored to more synthetically useful values (92:8 d.r.).

160

Scheme 2.5 Substrate scope of Ag-catalyzed addition of diborylethane to aryl and alkenyl aldehydes

2.21
70% yield
97:3 d.r.

2.22
65% yield
97:3 d.r.

2.23
64% yield
97:3 d.r.

2.24
73% yield
96:4 d.r.

2.25
75% yield
97:3 d.r.

2.26
53% yield
97:3 d.r.

2.27
52% yield
97:3 d.r.

2.28
69% yield
99:1 d.r.

2.29
71% yield
91:9 d.r.

2.30
45% yield
96:4 d.r.

2.31
77% yield
99:1 d.r.

R^1=H R^1=Cl R^1=H
R^2=H R^2=H R^2=Me
2.32   **2.33**   **2.34**
65% yield *40% yield* *64% yield*
88:12 d.r. *86:14 d.r.* *92:8 d.r.*
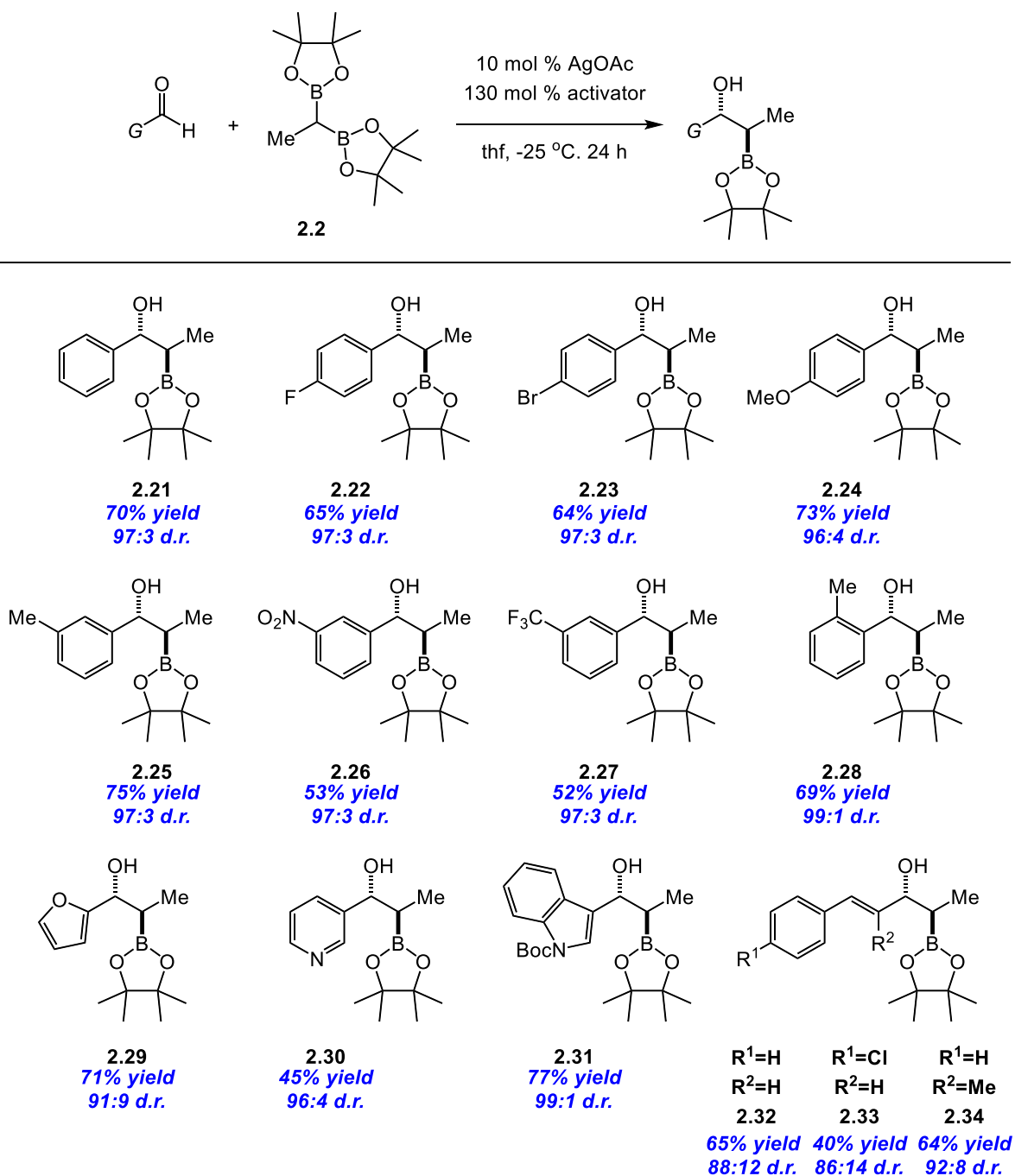
While AgOAc is an efficient catalyst for promoting the addition of diborylethane to aryl and alkenyl aldehydes, the purpose of switching to a silver catalyst was to allow for the addition of more highly substituted *gem*-diboronate esters to aldehydes. Under identical conditions to those in Scheme 2.5, 10 mol % AgOAc and 130 mol % KO^{t}Bu at -25 °C, other substituted *gem*-diboronate esters may

be added to benzaldehyde in good yields and selectivities (Scheme 2.6). *anti*-1,2-hydroxyboronates containing a phenyl ring (**2.35**), an olefin (**2.36**), a silyl ether (**2.37**), an *n*-alkyl chain (**2.38**), and a *tert*-butyl ester group (**2.39**) are all tolerated with yields up to 77% and up to 98:2 d.r. Only in the case of the *tert*-butyl ester containing *gem*-diboryl reagent is low diastereoselectivity observed (47:53 d.r.). This drop in selectivity is likely due to chelation of the carbonyl group of the ester to the adjacent B(pin) group during the 1,2-addition. β-branched secondary *gem*-diboronate esters are not capable of undergoing 1,2-additions to benzaldehyde, as **2.40** forms in <5% yield. This is most likely due to KO*t*Bu's inability to activate larger *gem*-diboronate ester (*vide infra*).

Scheme 2.6 Ag-catalyzed additions of substituted *gem*-diboronate esters to benzaldehyde
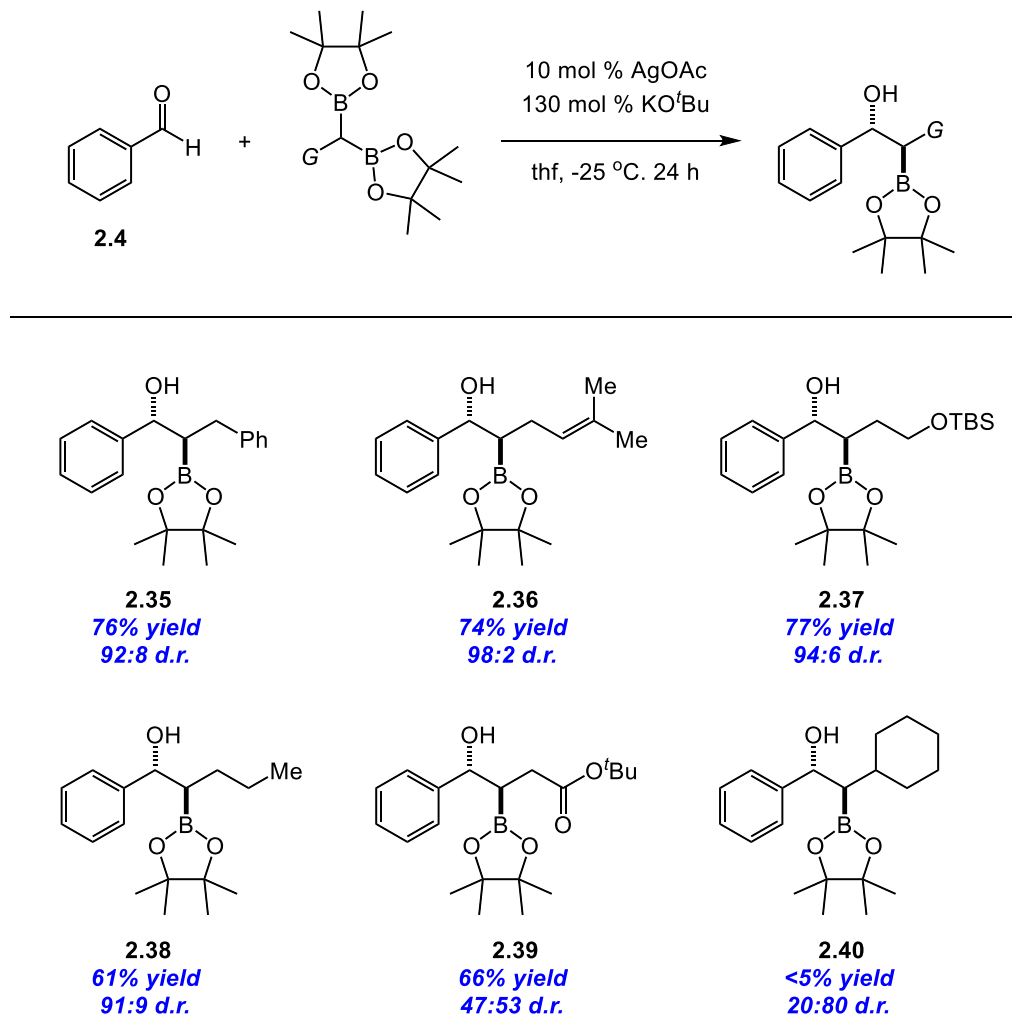
I next extended the protocol of the 1,2-addition of *gem*-diboronate esters to alkyl aldehydes, a substrate class previously unattainable in our lab. Under the standard conditions which use KO*t*Bu as a stoichiometric activator, 1,2-hydroxyboronate **2.41** is delivered in 6% yield and 79:21 d.r. I reasoned that deprotonation of the α-proton of cyclohexanecarboxaldehyde by free KO*t*Bu was responsible for the low yield of the product. I opted to switch to a stronger and irreversible activator for diborylethane, i.e. *n*-butyllithium. Alkyllithiums have been shown to irreversibly bind and activate boronate esters for nucleophilic additions[15], which would help to prevent enolization of the alkyl aldehyde substrates and to increase the yield of the reaction. Gratifyingly, with 10 mol % AgOAc and 100 mol % *n*-BuLi, **2.41** is afforded in 51% yield and 88:12 d.r. (Scheme 2.7). Without AgOAc, no 1,2-addition is observed. This manifold of activation was extended to several alkyl aldehydes with different substituted *gem*-diboronate esters. Cyclohexanecarboxaldehyde undergoes addition *gem*-diboronate esters containing an olefin (**2.42**; 61% yield, 78:22 d.r.), a benzyl group (**2.43**, 51% yield, 95:5 d.r.), and a silyl ether (**2.45**; 49% yield, 83:17 d.r.). Isobutyraldehyde is also a competent substrate and the 1,2-hydroxyboronate **2.44** is delivered in 62% yield and >99:1 d.r. With *n*-BuLi or KO*t*Bu as the activator, pivalaldehyde-derived hydroxyboronate **2.46** is afforded in up to 34% yield and 98:2 d.r. The lower diastereoselectivities for some of the substrates can be attributed to a lithium counterion being present in the reaction, which could chelate to the aldehyde and erode diastereoselectivity. With no enolizable protons on the aldehyde, either activation manifold can be used without detriment to the already fair yield of the reaction. Acetal-containing hydroxyboronate **2.47** forms in 54% yield and >99:1 d.r under *n*-BuLi activating conditions and cyclohexyl-containing hydroxyboronate **2.40** is afforded in 64% NMR yield and 80:20 d.r. favoring the *syn* diastereomer. The switch in diastereoselectivity can be derived from the larger A-value of the cyclohexyl group compared to a B(pin) group. Being able to use two different activators for *gem*-diboronate esters, one reversible and one irreversible, allows for access to a wider range of 1,2-addition substrates

Scheme 2.7 *n*-BuLi promoted, Ag-catalyzed additions of *gem*-diboronate esters to alkyl and aryl aldehydes

2.41
51% yield
88:12 d.r.

2.42
61% yield
78:22 d.r.

2.43
51% yield
95:5 d.r.

2.44
62% yield
>99:1 d.r.

2.45
49% yield
83:17 d.r.

2.46
34% yield
98:2 d.r.

2.47
54% yield
>99:1 d.r.

2.40
65% NMR yield
80:20 d.r.
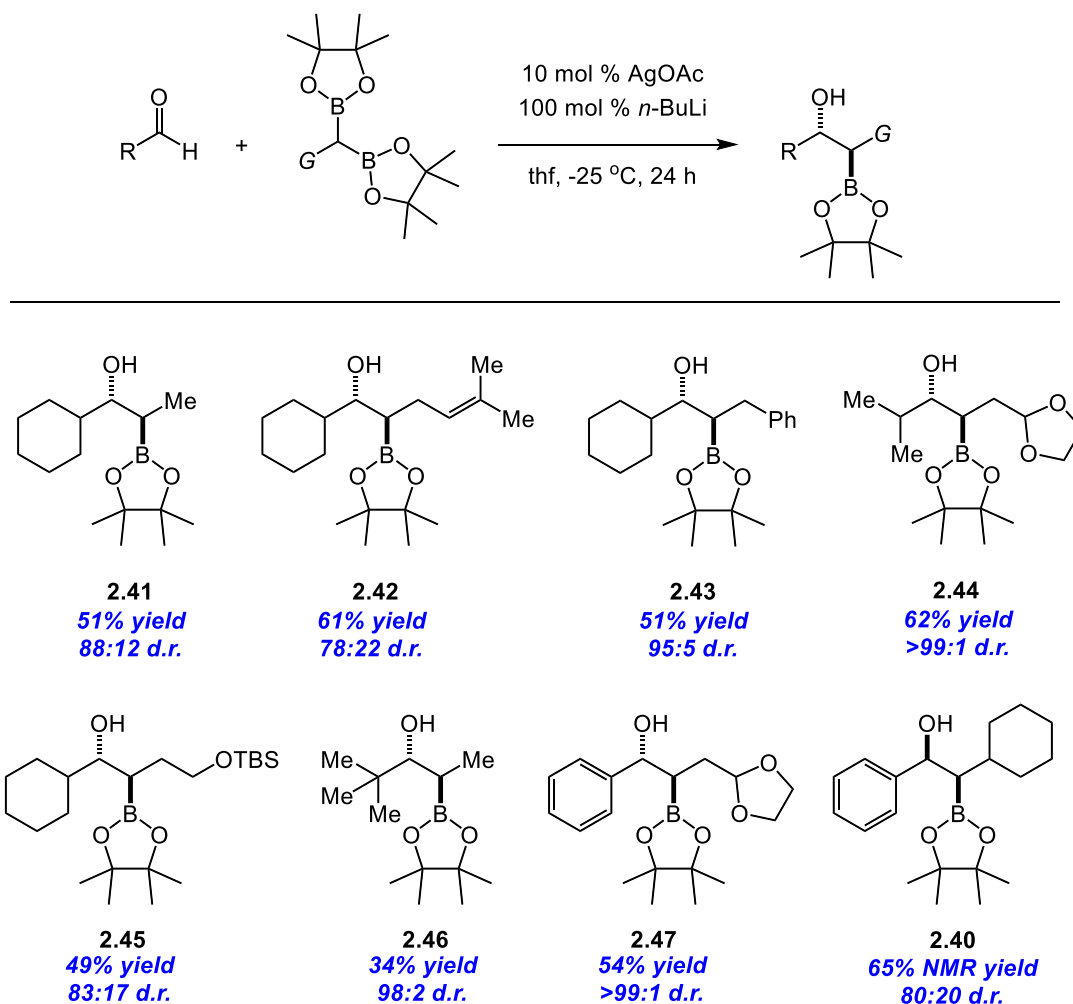
2.5   Mechanistic Investigations

To investigate the mechanism of the *anti*-selective 1,2-addition reaction, the activation of *gem*-diboronate esters with *n*-butyllithium and KO*t*Bu was probed. As shown in Scheme 2.8, reacting diborylethane with *n*-BuLi at -78 °C and allowing the reaction to warm to ambient temperature over the course of 30 minutes affords the *n*-butyl-borate complex **2.48** in 98% yield as a white solid after concentration of the reaction. The molecule was unambiguously characterized by ^{1}H and ^{11}B NMR spectroscopy and several distinct signals are of note. The proton at the base of both boryl groups has a

chemical shift at δ -0.16 ppm and appears as a quartet, while the proton resonances of the *n*-butyl

protons geminal to the borate boron appear at δ 0.12 ppm as a complex multiplet. These protons are

adjacent to a stereogenic center, which is likely the reason for the complex splitting pattern. The [11]B

NMR spectrum contains two signals: a broad singlet at δ 36.0 (corresponding to the B(pin) group) and

a sharp singlet at δ 6.1 (corresponding to the borate boron). This shows that *n*-BuLi activation of *gem*-

diboronate esters is irreversible and forms highly nucleophilic borates capable of adding highly

substituted α-boryl alkyl units to aldehydes.

Scheme 2.8 Activation of diborylethane with *n*-butyllithium: isolation of stable n-butylborate

compound

2.2

2.48
98% yield
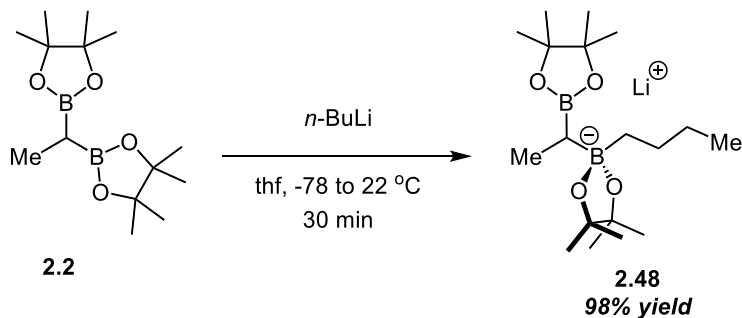
To investigate how potassium alkoxide bases activate *gem*-diboronate esters, reaction of **2.2**

with KO*t*Bu was monitored by ^{1}H and ^{11}B NMR in thf-*d₈* at 22 °C, depicted in Figure 2.3. After 15

minutes at 22 °C, >98% of **2.2** had been consumed and the *tert*-butoxyborate complex **2.49** had formed

in 86% NMR yield. The protodeboronated product, ethylboronic acid pinacol ester, **2.50** had also

formed in 14% NMR yield. While standing at ambient temperature, **2.49** undergoes further

protodeboronation, reaching 75% conversion over 18 hours. The stacked ^{1}H NMR spectra at the bottom

of Figure 2.3 show conversion of **2.49** to **2.50** over the course of 18 hours. Morken has shown that di-

alkylsubstituted borates similar to **2.49** undergo deborylation at room temperature to form α-boryl-

stabilized carbanions[16], but I was unable to confirm the presence of such a compound in >5% conv.

with either ^{1}H or ^{11}B NMR spectroscopy. The ^{11}B NMR spectrum remains mostly unchanged

throughout the reaction and contains three very distinct signals: a broad singlet at δ 36.1 ppm (*sp²*-

hybridized B(pin) groups of **2.49** and **2.50**); a sharp singlet at δ 7.8 ppm (borate B(pin) group of **2.49**); and another sharp singlet at δ 4.9 ppm, which corresponds to bis(tert-butoxy)pinacolborate. Protodeboronation of **2.49** yields *tert*-butylpinacolborate, which is immediately quenched with the excess KO^{t}Bu in the reaction to generate bis(tert-butoxy)pinacolborate. Since bis(tert-butoxy)pinacolborate is highly symmetric, tetrahedral, and an all-oxygen substituted borate, its ^{11}B NMR signal has a narrow line width and high peak intensity.[17] The oxygen atoms bound to boron also aid in spin-spin relaxation of the boron nucleus, which also increase peak intensity and line width. Since **2.49** begins to deborylate at room temperature after only 15 minutes, it was necessary to take this into consideration when optimizing the reaction conditions. Allowing the activator and diboryl reagent to stir for only 5 minutes at ambient temperature ensured complete activation of the *gem*-diboronate ester with minimal decomposition.
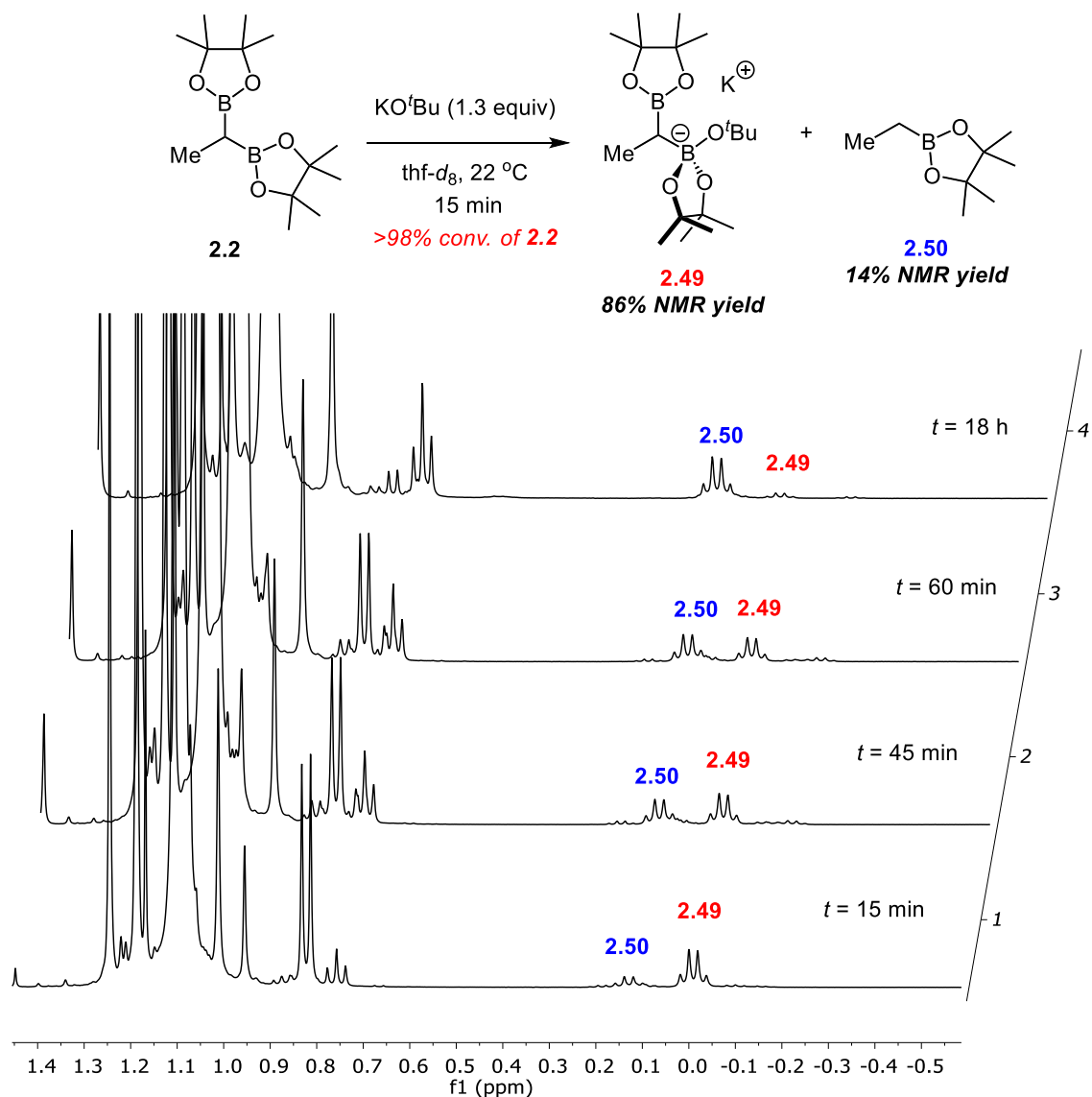
Figure 2.4 Activation of diborylethane with KO*t*Bu monitored by ^{1}H and ^{11}B NMR spectroscopy. Pictured above are ^{1}H NMR spectra of the reaction at 15, 45, 60 min, and 18 h. The ^{11}B NMR spectra contains 3 signals: δ 36.1 (*sp²*-hybridized B(pin) groups of **2.49** and **2.50**); δ 7.8 (borate B(pin) group of **2.49**); and δ 4.9 (bis(tert-butoxy)pinacolborate)

Since there was such a large difference in reactivity between diborylethane and other substituted *gem*-diboronate esters in copper-catalyzed 1,2-addition reactions, I thought it prudent to monitor the activation of a more highly substituted *gem*-diboronate ester by KO*t*Bu. I monitored the reaction of **2.51** and KO*t*Bu at 22 °C by ^{1}H and ^{11}B NMR spectroscopy, which is depicted in Scheme

2.9. After 15 minutes, 95% of the starting material had been consumed and the *tert*-butoxyborate **2.52** had formed in 79% NMR yield. Accompanying the borate was the protodeboronated product **2.53** in 16% NMR yield. Similar to the reaction in Scheme 2.8, **2.52** undergoes protodeboronation over time, leading to **2.53** in 78% NMR yield after 14 hours. The ^{11}B NMR spectrum of the reaction is identical to the reaction of **2.2** and KO*t*Bu (3 signals, all with nearly identical chemical shifts). This data suggests that in the case of potassium *tert*-butoxide, it activates diborylethane and other substituted *gem*-diboronate esters in a similar manner, which corresponds with the high isolated yields for substrates in Schemes 2.5 and 2.6.

Scheme 2.9 Activation of diborylbutane with KO*t*Bu: near quantitative conversion at 22 °C
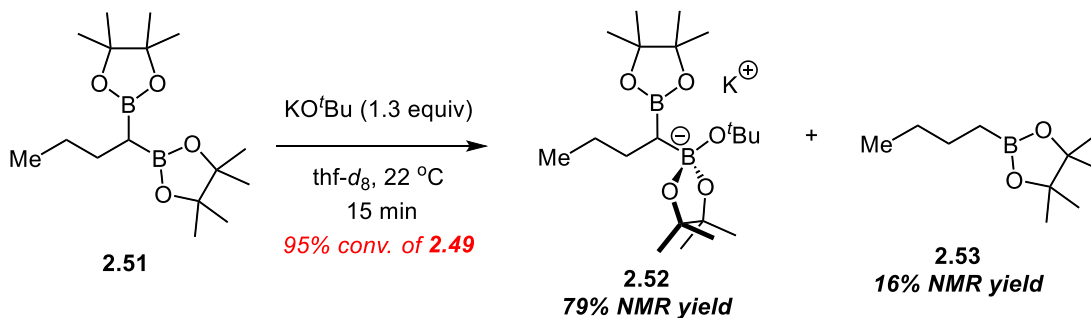
To understand the role of AgOAc in the 1,2-addition reaction, I monitored the activation of **2.2** with KO*t*Bu in the presence of one equivalent of AgOAc, by ^{1}H and ^{11}B NMR spectroscopy (Scheme 2.10). After addition of solvent, the reaction immediately turned dark grey with silver mirror forming around the NMR tube as the reaction progressed. As in Figure 2.3, complete consumption of **2.2** and *tert*-butoxyborate formation was observed, along with protodeboronated-product **2.50**. A new species, however, formed after 5 minutes of reacting, reaching 11% NMR yield after 15 minutes. This species was assigned as the homocoupled product **2.54**, and independently synthesized, isolated, and characterized by ^{1}H, ^{13}C NMR spectroscopy, mass spectrometry, and IR spectroscopy to confirm its identity (see Experimental Section for details). The identifiable ^{1}H NMR resonances are doublet of doublets at δ 1.37 ppm corresponding to the methyl groups of the compound, and a multiplet at δ 0.45 ppm which corresponds to the diastereotopic protons at the base of the boryl group. This product may

be derived from the reductive dimerization of an α-boryl alkyl silver species generated during the reaction.

Scheme 2.10 Activation of diborylethane with KO*t*Bu in the presence of AgOAc: observation of a homocoupled α-boryl alkyl unit

| 2.2 | >98% conv. of 2.2 | 2.49 76% NMR yield | 2.50 13% NMR yield | 2.54 11% NMR yield |
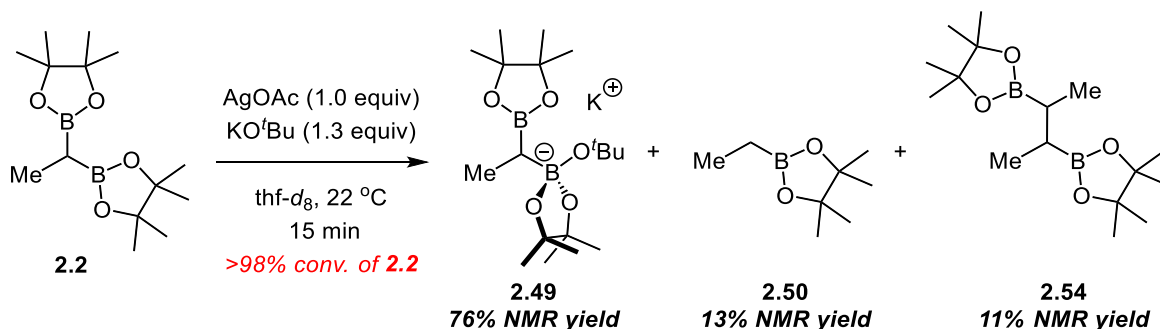
Homocoupling of Grignards and organoboron compounds has been shown to be promoted by silver(I) salts (Scheme 2.11). In 1973, Whitesides and co-workers synthesized a number of alkyl-silver-phosphine complexes and analyzed their decomposition products. [18] Tri(*n*-butyl)phopshinebutylsilver **2.55**, generated by reacting the corresponding silver iodide complex with *n*-butyllithium at -78 °C, was allowed to warm to ambient temperature over 5 minutes in Et$_2$O. Whitesides observed almost complete selectivity (93:7) for the homocoupled product, octane, with only a small amount of butane and 1-butene forming. An almost stoichiometric amount (92% yield) of silver metal was also recovered, further supporting the idea that *n*-butylsilver complexes undergo reductive dimerization to yield reduced silver and *n*-octane through a radical mechanism. Murphy and co-workers published a methodology where α,ω-dienes could be cyclized to the corresponding cycloalkanes through a hydroboration then silver promoted cyclization.[19] Hydroboration of 1,6-heptadiene, **2.56** with borane yields the 1,6-bisborylalkane which, in the presence of AgNO$_3$ and KOH in MeOH:H$_2$O yields cycloheptane in 67% yield. They proposed, based on Whitesides previous work, that the boranes are activated by KOH/MeOH to form borates, which readily transmetallate to silver and allow for the reductive dimerization to occur. Hayashi and co-workers demonstrated that alkyl Grignards could be homocoupled in the presence of catalytic AgOTs with a stoichiometric amount of 1,2-dibromoethane

169

to regenerate the silver catalyst.[20] Grignard **2.59** was dimerized to **2.60** in 80% yield with 10 mol %

AgOTs and 1 equivalent of 1,2-dibromoethane. These previous reports demonstrate that 1)

organoboron compounds can be transmetallated to silver and 2) alkyl silver species are very unstable

at ambient temperature and will rapidly undergo reductive dimerization to form homocoupled products.

The presence of **2.54** in the reaction depicted in Scheme 2.10 thus demonstrates that an α-boryl alkyl

silver species forms during the reaction, but reductively dimerizes too quickly to be observed at room

temperature.

Scheme 2.11 Examples of homocoupling reactions promoted or catalyzed by Ag(I)

■ **Whitesides (1973)**
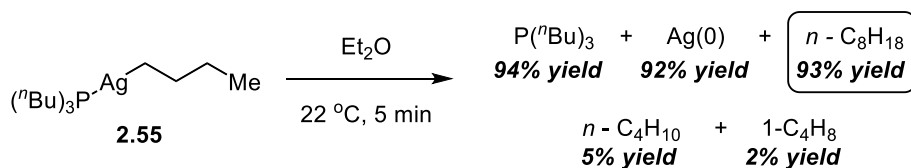
■ **Murphy (1976)**
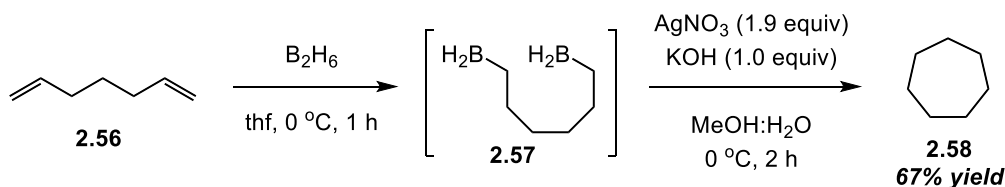
■ **Hayashi (2005)**
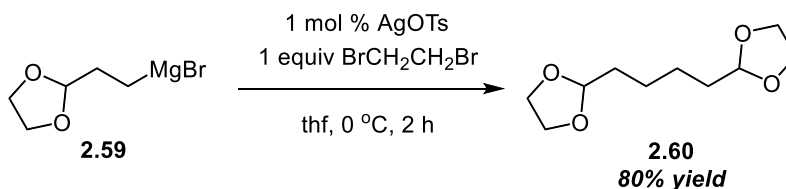
To confirm the existence of an alkyl-silver intermediate under the 1,2-addition reaction

conditions, I conducted a low-temperature NMR study, where n-butyl activated diborylethane **2.48** was

reacted with 1 equivalent of AgOAc in thf-d_8 at -80 °C and monitored by ^{1}H and ^{11}B NMR spectroscopy

as the reaction warmed to -20 °C. The spectra of **2.48** (bottom) and the reaction at -20 °C (top) are

presented in Figure 2.4. A new signal at δ -0.44 ppm in the ^{1}H NMR spectrum began to grow in as the

reaction warmed, reaching a maximum conversion of 13% at -20 °C. This signal is tentatively assigned

as geminal α-boryl proton of an α-boryl silver alkyl species. This is further confirmed by the fact that the homocoupled product, **2.54** is also formed during the reaction (growing in after -40 °C). An α-boryl stabilized carbanion was not detected during the reaction, which is not unexpected, as Morken and co-workers have shown that these compounds only form after several hours at ambient temperature.[16]
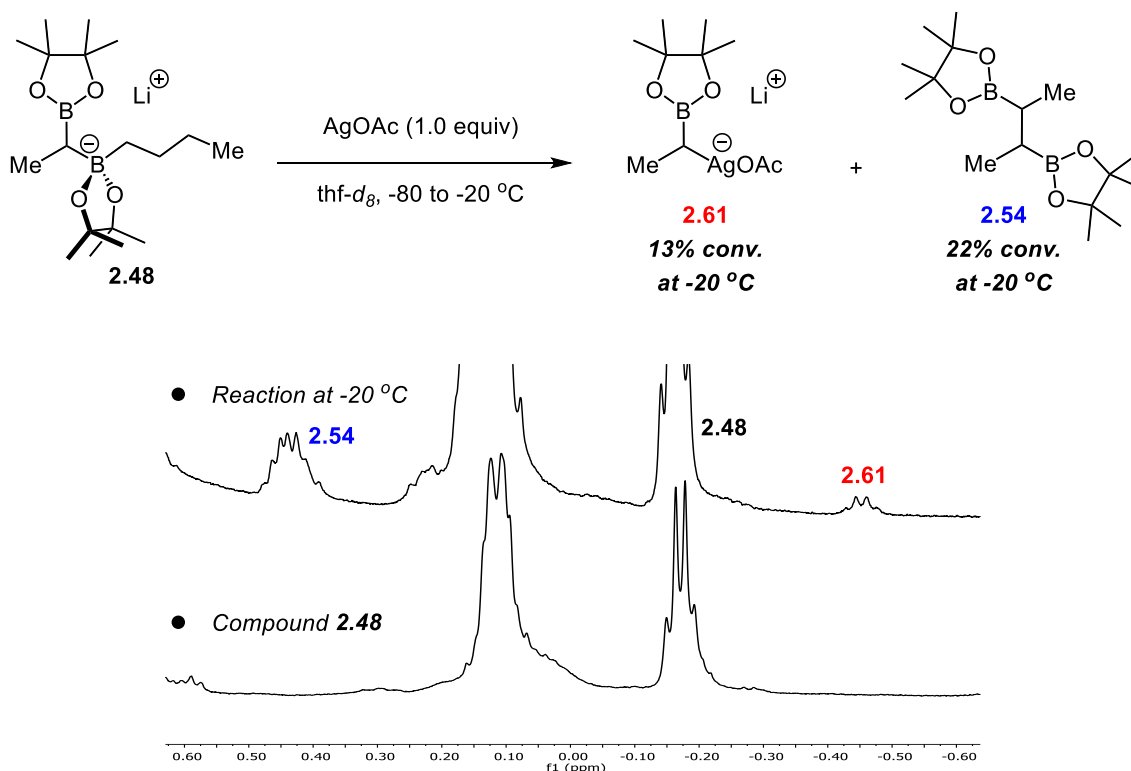
Figure 2.5 Reaction of **2.48** with AgOAc monitored by ^{1}H and ^{11}B NMR spectroscopy from -80 to -20 °C. Pictured above are ^{1}H NMR spectra of **2.48** and the reaction at -20 °C. The ^{11}B NMR spectra contains 2 signals: δ 35.5 (sp^2-hybridized B(pin) groups of **2.48** and **2.61**?) and δ 6.1 (borate B(pin) group of **2.48**)

  With these data combined, we have proposed a mechanism for the silver-catalyzed 1,2-addition of *gem*-diboronate esters to aldehydes, which is presented in Figure 2.5. Activation of diborylethane with either KO^{t}Bu or *n*-BuLi forms the borate species **I**, which undergoes transmetallation with the silver catalyst to generate the α-boryl alkyl silver species **II**. This species enacts a 1,2-addition reaction with the aldehyde to form the 1,2-hydroxyboronate anion, **III** associated with silver. A salt metathesis

releases the product as the potassium or lithium salt (depending on the activator used) and regenerates the silver catalyst. The rate of homocoupling of **II** is likely reduced under the reaction conditions as only catalytic AgOAc is used (**II** is only formed in 13% conversion with stoichiometric AgOAc; Figure 2.4). Catalytic quantities of an α-boryl alkyl silver intermediate would react faster with a large excess of aldehyde, rather than dimerizing to form **2.54**.
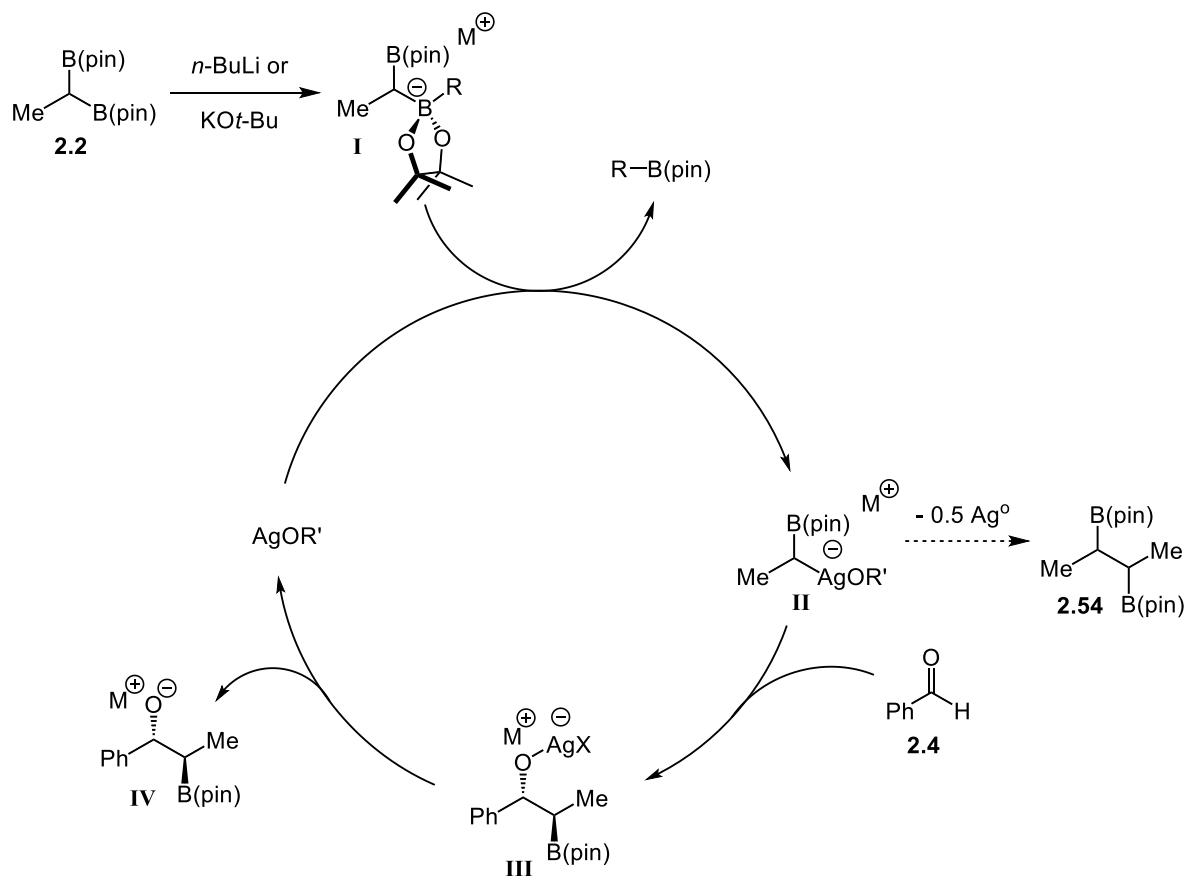
Figure 2.6 Proposed catalytic cycle for the silver-catalyzed addition of *gem*-diboronate esters to aldehydes. R' = O^{t}Bu or OAc

While it cannot be completely discounted that AgOAc is not acting as a Lewis acid during the reaction, I conducted two experiments to probe this question. A reaction between equimolar equivalents of AgOAc and benzaldehyde was monitored by ^{1}H and ^{13}C NMR in thf-d_8. No change to the chemical shifts of the aldehyde resonances were observed. Since AgOAc is only sparingly soluble in thf, I conducted a similar experiment with the thf-soluble binapAgOAc, **2.8** and benzaldehyde but

again, observed no changes to the aldehyde chemical shifts by ^{1}H or ^{13}C NMR. The ^{31}P NMR spectrum of binapAgOAc, which contains a set of doublets centered at δ 12.1 ppm ($J_{P\text{-}107Ag}$ = 343.4 Hz; $J_{P\text{-}109Ag}$ = 395.3 Hz), was unaltered upon addition of benzaldehyde and no new resonances appeared. These experiments indicate that there is unlikely to be a significant interaction between silver and an aldehyde at -25 °C.

Scheme 2.12 No observed interaction between AgOAc or binapAgOAc with benzaldehyde observed at 22 °C
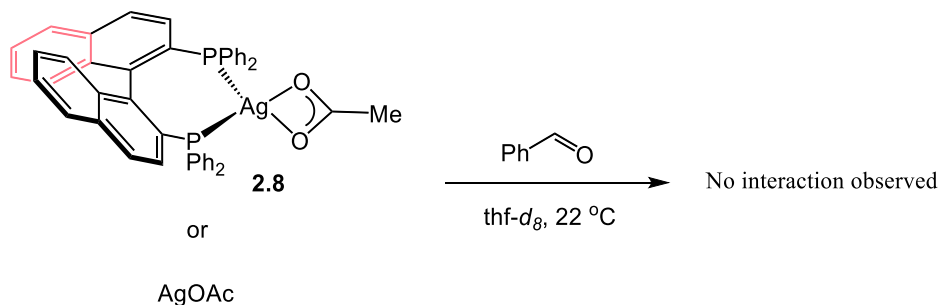
The *anti* selectivity observed in the silver-catalyzed 1,2-addition reaction is the same as that observed by Suzuki and Pelter in additions of α-borylcyanocuprates and α-lithioalkylboranes to aldehydes, respectively. The selectivity can be rationalized by an anticlinal transition state, depicted in Figure 2.6, and situates the phenyl and methyl groups *anti* to each other, with the carbonyl oxygen and the B(pin) group also *anti*. To further investigate the mechanism of the reaction, I generated optimized geometries for a truncated α-borylargenate complex, **I** using a LANL2DZ basis set for silver and 6-31++G** basis set for all other atoms. The HOMO of **I** is illustrated on the left of Figure 2.6 and is clearly the Ag – C(sp^3) bond. There is a large coefficient around the silver-carbon bond extending far around the silver atom, but there is also a lobe extending out from the carbon atom. This would allow for approach of an electrophile from the backside of the argenate, as illustrated on the right side of Figure 2.6 and support the anticlinal transition state as well as mechanisms proposed by Pelter.[13] While the association of the aldehyde with the silver center of the argenate cannot be completely discounted (*vide supra*), it is unlikely as the HOMO of the complex is centered around silver, which would disfavor aldehyde binding due to electron – electron repulsion.
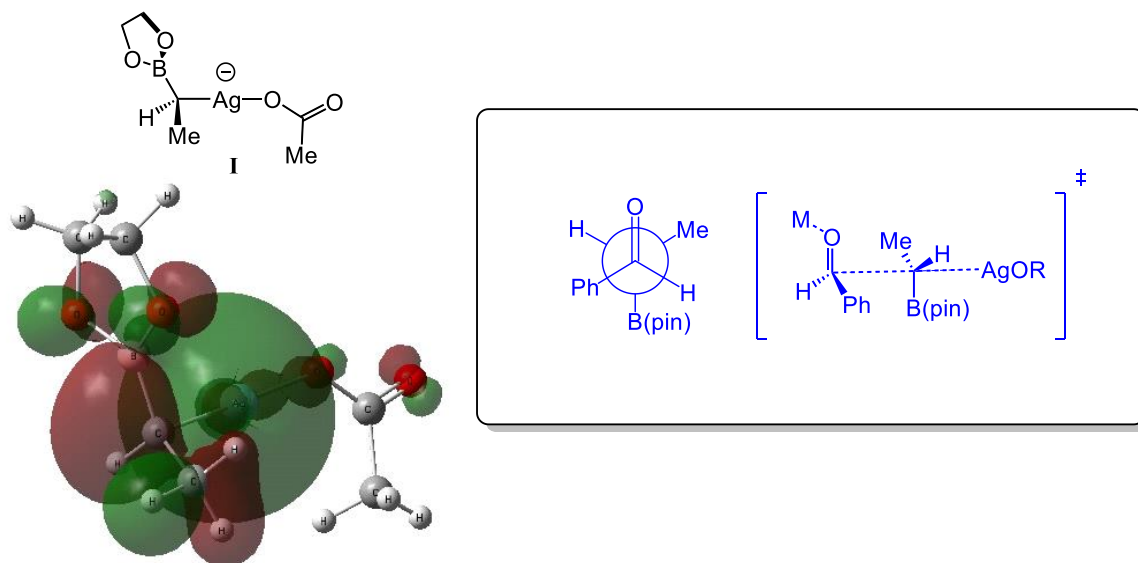
Figure 2.7 Left: HOMO of truncated α-borylethylargenate acetate. The orbitals were generated using Gaussian09 with a B3LYP level of theory, with a LANL2DZ basis set for Ag and 6-31++G** basis set for all other atoms. Right: Proposed mechanism/stereochemical model for the addition of α-boryl alkyl silver to aldehydes

2.6   Functionalization Reactions

To showcase the synthetic utility of the 1,2-hydroxyboronates formed in this methodology (aside from oxidation and homologation, which were previously reported), TBS-protected hydroxyboronate **2.62** was subjected to stereospecific arylation conditions.[21]   At -78 °C, **2.62** was treated with 2-lithiofuran, followed by NBS which was then quenched with $Na_2S_2O_3$ to furnish the 1,2-diarylated product **2.63** in 67% yield and 99:1 d.r.   After purification, 25% of the remaining starting material was able to be recovered in >98% purity.

Scheme 2.13 Arylation of TBS-protected 1,2-hydroxyboronate

2.62

2.63
67% yield
99:1 d.r.
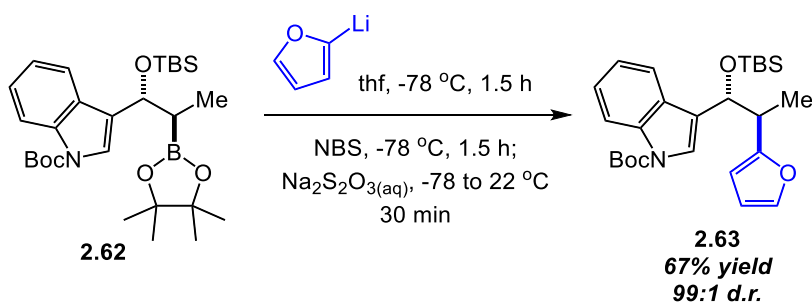
2.7   Enantioselective Ag-Catalyzed 1,2-Addition Reactions

Throughout my graduate career, I made several attempts to develop an enantioselective variant of the Ag-catalyzed 1,2-addition of *gem*-diboronate esters to aldehydes. Chiral phosphines are a ubiquitous class of ligands in stereoselective catalysis, with many being commercially available. I opted to first investigate chiral silver-phosphine based catalysts to promote enantioselective 1,2-additions, the results of which are summarized in Scheme 2.14 and Scheme 2.15. With 10 mol % AgOAc, 10 mol % *(R)*-binap, and 130 mol % KO*t*Bu, 1,2-hydroxyboronate **2.21** is formed in 54% conv., 93:7 d.r., but with 0% *ee*. I screened several different bidentate phosphines including difluorphos, dtbm-segphos, and Me-duphos, which all gave varying yields and diastereoselectivities (from 29 – 53% yield, and from 78:22 to 96:4 d.r.) and 0% *ee*. Altering the catalyst structure to a binol-phosphoric acid-derived silver salt produced the product in detectable, but still low enantioselectivity, 2% *ee*. I next switched to ferrocenyl-based phosphines, and while josiphos (**2.69**) did not impart any enantioselectivity to the reaction, enantioselectivity was observed with Walphos-based ligands. Utilizing ligand **2.70** affords **2.21** in 6% *ee*, and altering the dicyclohexylphosphine group to a diphenylphosphine group, ligand **2.71** increases the enantioselectivity to 34% at -25 °C (38% conv., 95:5 d.r.). Lowering the reaction temperature to -40 °C increased the enantioselectivity further to 55% *ee*, but with a large drop in conversion to 11%. Due to low conversion and less than optimal *ee*%, chiral bis-phosphine ligands were abandoned for promoting enantioselective catalysis.

Scheme 2.14 Ag-catalyzed enantioselective 1,2-addition of diborylethane to benzaldehyde

2.4 + **2.2**

10 mol % AgOAc
10 mol % ligand
130 mol % KO^{t}Bu

thf, -25 ^{o}C, 24 h

2.21

2.64
54% conv.
93:7 d.r.
0% ee

2.65
45% conv.
78:22 d.r.
0% ee

2.66
Ar=3,5-^{t}Bu-4-OMe
29% conv.
86:14 d.r.
0% ee

2.68
53% conv.
96:4 d.r.
0% ee

2.67
42% conv.
96:4 d.r.
2% ee

2.69
22% conv.
93:7 d.r.
0% ee

2.70
Ar=3,5-CF$_3$
52% conv.
95:5 d.r.
6% ee

2.71
Ar=3,5-CF$_3$
38% conv.
95:5 d.r.
34% ee

2.71
Ar=3,5-CF$_3$
11% conv.
95:5 d.r.
55% ee
@ -40 ^{o}C
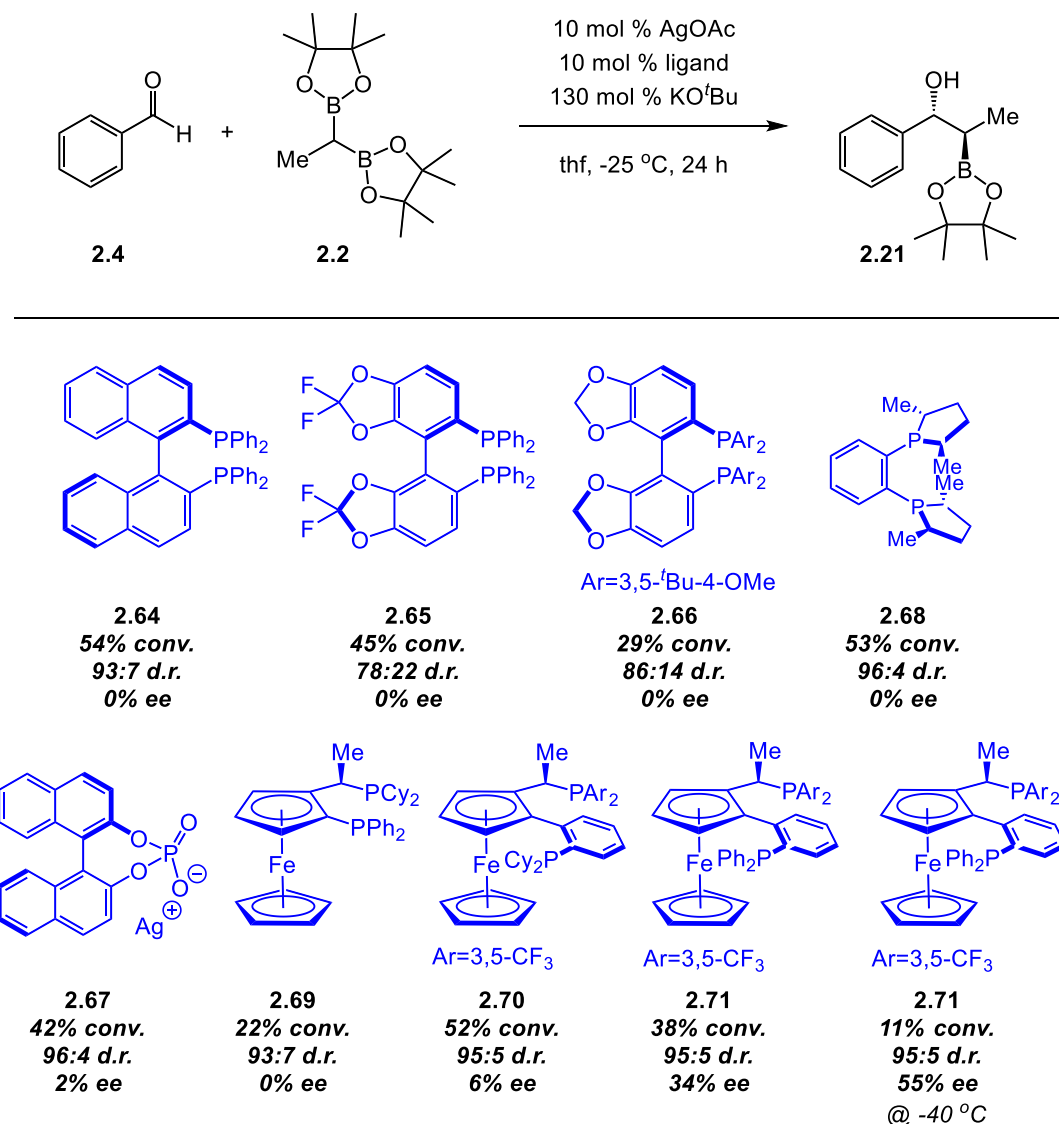
With the success of phosphoramidite ligands in enantioselective copper-catalyzed additions of *gem*-diboronate esters to aldehydes, I investigated silver-phosphoramidite complexes for promoting stereoinduction in 1,2-addition reactions. With 10 mol % AgOAc and 20 mol % *(R)*-Monophos (**2.72**), hydroxyboronate is produced in 61% conv., 90:10 d.r., and 21% *ee*. Using the partially hydrogenated binaphthyl Monophos affords the product in 14% *ee* with similar conversion and higher d.r. (58% conv., 97:3 d.r.). Exchanging the N-dimethyl group for N-diethyl (**2.74**) and N-morpholinyl (**2.75**) leads to a significant drop in enantioselectivity, 3% and 5% respectively. Using phosphoramidite with chiral

amines bound to phosphorus was also attempted: diastereomers **2.76** and **2.77** were used in the silver-catalyzed addition reaction, but both gave 0% enantioselectivity. In all of the above experiments, a 2:1 ratio of ligand to silver was used, which seemed to be essential for even poor enantioselectivity. If a 1:1 ligand to silver ratio was used with ligand **2.72**, only 3% *ee* is observed (with similar conversion and d.r. to the 20 mol % reaction). This indicated that the silver-phosphoramidite complexes are either highly fluxional in solution, or require two ligands bound to silver during the transmetallation step. Regardless of this information, silver-phosphoramidite catalysts were similarly abandoned for enantioselective 1,2-addition reactions.

Scheme 2.15 Ag-catalyzed enantioselective 1,2-addition of diborylethane to benzaldehyde:

phosphoramidite ligand screen

2.72	**2.73**	**2.74**
61% conv.	*58% conv.*	*67% conv.*
90:10 d.r.	*97:3 d.r.*	*95:5 d.r.*
21% ee	*14% ee*	*3% ee*
2.75	**2.76**	**2.77**
34% conv.	*63% conv.*	*38% conv.*
88:12 d.r.	*97:3 d.r.*	*93:7 d.r.*
5% ee	*0% ee*	*0% ee*
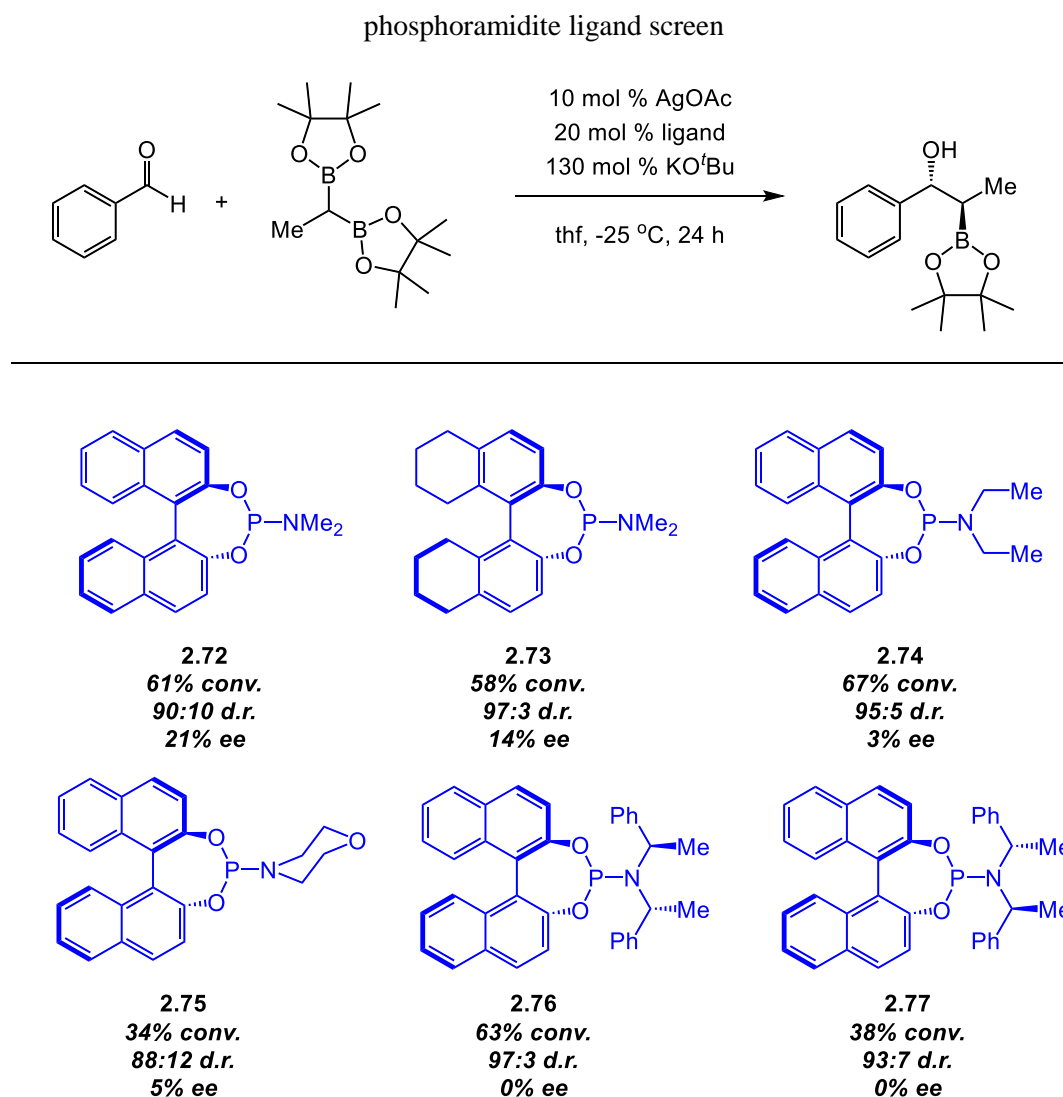
Since all attempts to develop a highly enantioselective, silver-catalyzed 1,2-addition reaction of *gem*-diboronate esters to aldehydes were unsuccessful, I wanted to understand why silver-phosphine and silver-phosphoramidite complexes were so poor at these enantioselective transformations. Yamagishi and co-workers have done a number of studies on the nature of silver-bis-phosphine complexes in solution and in the solid state.[10] While they were concerned with silver catalysts for the Mukiyama Aldol, their data of the solution and solid-state behavior of silver-phosphine complexes is applicable at this juncture. The solid state structure of binap(AgOAc) is monomeric and tetrahedral at silver, with the acetate ligand binding in a κ^2 coordination mode. In solution, however, binap(AgOAc) is much less well defined, and using ^{31}P NMR spectroscopy, they were able to study this dynamic behavior. They observed at -50 °C (to improve resolution of the rapidly equilibrating silver species), that a mixture of binap and AgOAc gave rise to three different compounds. Using the different ^{31}P chemical shifts and $^{107/109}$Ag-^{31}P coupling values, they were able to assign the three different species as the bis(binap)Ag cation complex **2.78**, the monomeric binap(AgOAc) complex, and the bis(silver acetate)binap complex **2.79**. The silver counterion has a huge effect on the product distribution, as AgOTf forms almost exclusively the **2.78** analogue. This demonstrates that silver-phosphine complexes are extremely dynamic in solution and this constantly changing structure could be the source of poor enantioselectivity for the 1,2-addition reaction.

Scheme 2.16 Solution-state behavior of silver-binap complexes. Ratios were determined using [31]P

NMR

(R)-binap + AgOAc

CDCl₃
-50 °C

2.78
10%

+

2.8
85%

+

2.79
5%
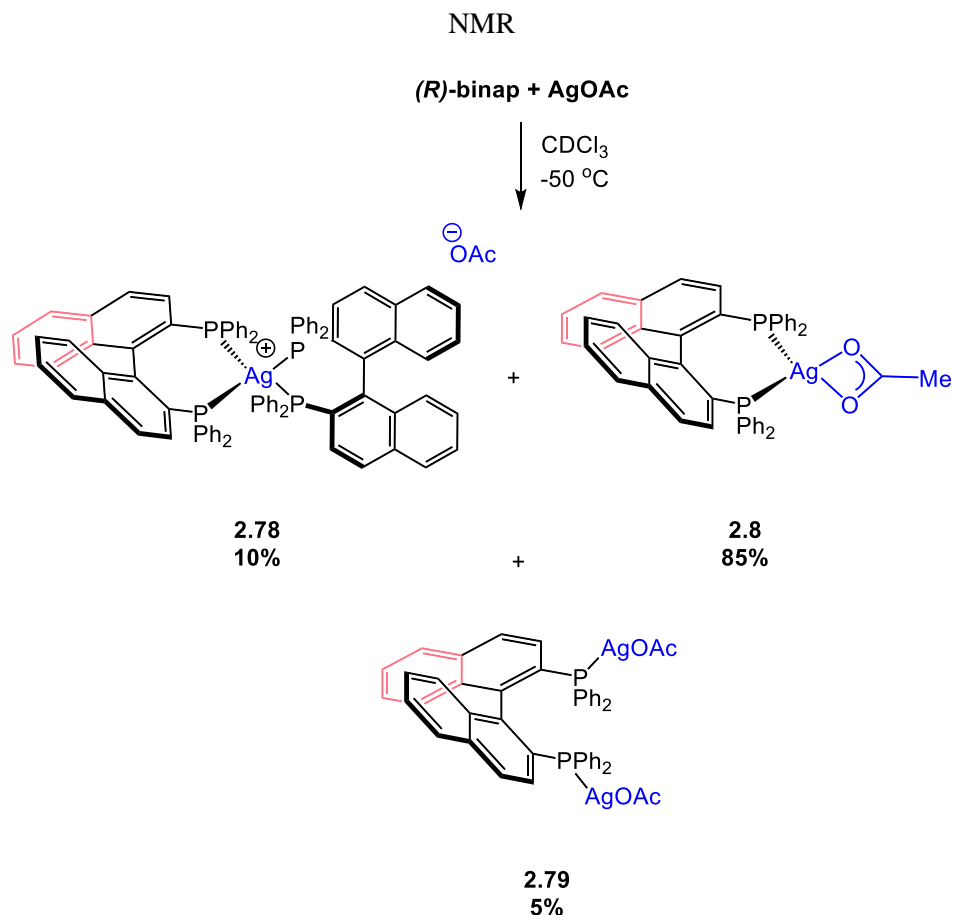
2.8   Conclusions

I have developed a highly diastereoselective method for the addition various substituted *gem*-diboronate esters to aryl, alkenyl, and alkyl aldehydes. The reaction is catalyzed by unligated AgOAc in the presence of KO*t*Bu or *n*-BuLi as a stoichiometric activator. The reaction is tolerant of a number of substitution patterns on the aldehyde, as well as on the *gem*-diboronate ester and the products are formed in up to 77% yield and 99:1 diastereoselectivity, favoring the *anti* diastereomer. Mechanistic studies reveal a putative α-boryl alkyl silver species as the reactive nucleophile in the reaction, which is generated from transmetallation of a *tert*-butoxy or *n*-butylborate species to AgOAc. Presence of the homocoupled nucleophile, **2.54** supports the claim of an α-boryl alkyl silver intermediate. The 1,2-hydroxyboronate products produced in this methodology are amenable to further manipulations of the

organoboron moiety through oxidation, amination, and stereospecific arylation. Enantioselective variants of this reaction were not extremely successful, as the highest enantioselectivity observed was for hydroxyboronate **2.21**, which forms in 11% conv., 95:5 d.r., and 55% *ee* with 10 mol % AgOAc and 10 mol % **2.71**.

2.9   Experimental

■ **General:** All reactions were carried out in oven-dried (150 ˚C) or flame-dried glassware under an inert atmosphere of dried N_2 unless otherwise noted. Analytical thin-layer chromatography was performed on glass plates coated with 0.25 mm of 60 Å mesh silica gel. Plates were visualized by exposure to UV light (254 nm) and/or immersion into Seebach's or $KMnO_4$ stain followed by heating. Column chromatography was performed using silica gel P60 (mesh 230-400) supplied by Silicycle. Deactivated silica gel was prepared by stirring a slurry of the aforementioned silica gel in a 3% NaOAc aqueous solution for 15 minutes. The deactivated silica gel was collected by filtration and then dried in a 150 ˚C oven for 3 days. All solvents were sparged with argon and then purified under a positive pressure of argon through an SG Water, USA Solvent Purification System.   Tetrahydrofuran (OmniSolv) was passed successively through two columns of neutral alumina.   The ambient temperature in the laboratory was approximately 22 ˚C.

■ **Instrumentation:** All ^1H NMR spectra were recorded on Bruker Spectrometers (AVANCE-600, AVANCE-500 and AVANCE-400). Chemical shifts are reported in ppm from tetramethylsilane and referenced to the residual protio solvent peak (CDCl$_3$: δ 7.26, thf-d_8: δ 1.72). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, qu = quartet, quint = quintet, br = broad, m = multiplet, app = apparent), integration, and coupling constants are given in Hz. ^{13}C NMR spectra were recorded on Bruker Spectrometers (AVANCE-600 and AVANCE-400) with carbon and proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane and referenced to the residual protio solvent peak (CDCl$_3$: δ 77.16). All IR spectra were recorded on a Jasco 260 Plus

Fourier transform infrared spectrometer. Mass Spectrometry samples were analyzed with a hybrid LTQ FT (ICR 7T) (ThermoFisher, Bremen, Germany) mass spectrometer. Samples were introduced *via* a micro-electrospray source at a flow rate of 10 µL/min (solvent composition 10:1 MeOH:H_2O). Xcalibur (ThermoFisher, Breman, Germany) was used to analyze the data. Molecular formula assignments were determined with Molecular Formula Calculator (v 1.2.3). Low-resolution mass spectrometry (linear ion trap) provided independent verification of molecular weight distributions. All observed species were singly charged, as verified by unit *m/z* separation between mass spectral peaks corresponding to the ^{12}C and $^{13}C^{12}C_{c-1}$ isotope for each elemental composition.

■ **Reagents:** All liquid aldehydes were distilled from CaH_2 or $CaSO_4$ under vacuum and then sparged with dry N_2. Solid aldehydes were purified *via* recrystallization, followed by azeotropic drying with benzene. Silver acetate was purchased from Strem Chemicals and kept in an N_2 filled glove box. Diboryl methane was synthesized by previous methods.[5]

4-Anisaldehyde was purchased from Alfa-Aesar, vacuum distilled from CaH_2, and then sparged with dry N_2

Benzaldehyde was purchased from Alfa-Aesar, vacuum distilled from CaH_2, and then sparged with dry N_2

Benzene-*d₆* was purchased from Cambridge Isotope Laboratories and distilled over Na/benzophenone, sparged with dry N_2, and kept in an N_2-filled glove box over 3 angstrom molecular sieves

Benzyl bromide was purchased from Aldrich, passed through a plug of neutral alumina and then used without further purification

(2-Bromoethoxy)(tert-butyl)dimethylsilane was synthesized according to a published literature procedure[22]

2-bromomethyl-1,3-dioxolane was purchased from Alfa Aesar and passed through plug of neutral alumina before use

Calcium hydride was purchased from Strem and used without further purification

Calcium sulfate was purchased from Fischer and used without further purification

Chloroform-*d₃* was purchased from Cambridge Isotope Laboratories and used without further purification

Cyclohexanecarboxyaldehyde was purchased from Alfa-Aesar, vacuum distilled from CaH_2, and then sparged with dry N_2

4-Fluorobenzaldehyde was purchased from Alfa-Aesar, vacuum distilled from CaH_2, and then sparged with dry N_2

Furan was purchased from Alfa-Aesar, vacuum distilled from sodium, and then sparged with dry N_2

2-Furylaldehyde was purchased from Acros Organics, vacuum distilled from CaH_2, and then sparged with dry N_2 and kept in an amber vial

Iodomethane was purchased from Alfa-Aesar, and passed through a short column of neutral alumina and purged with dry N_2 prior to use

1-Iodopropane was purchased from Alfa-Aesar and passed through a short column of neutral alumina and purged with dry N_2 prior to use

Lithium 2,2,6,6-tetramethylpiperidide was purchased from Sigma-Aldrich and kept in an N_2 filled glovebox

N-Boc-3-indolecarboxaldehyde was synthesized according to a published literature procedure.[24]

N-bromosuccinamide was purchased from Sigma Aldrich and azeotropically dried with benzene prior to use

n-Butyllithium was purchased from Strem Chemicals as a solution in hexanes and titrated before use with phenanthroline/*sec*-BuOH

Nicotinaldehyde was purchased from Alfa-Aesar, vacuum distilled from CaH_2, and then sparged with dry N_2

3-Nitrobenzaldehyde was purchased from Alfa-Aesar, and azeotropically dried with benzene prior to use

Pivaldehyde was purchased from Alfa-Aeasr and vacuum distilled from CaH_2, and then sparged with dry N_2

Prenyl bromide was purchased from Alfa-Aesar, passed through a plug of neutral alumina and then used without further purification

Potassium *tert*-butoxide were purchased from Strem and used as received

Sodium *tert*-butoxide was purchased from Strem and used as received

Tetrahydrofuran-*d$_8$* was purchased from Cambridge Isotopes and used as received

***tert*-Butyldimethylsilyl chloride** was purchased from Sigma-Aldrich and used as received

***tert*-Butyl-2-bromoacetate** was purchased from Alfa-Aesar, vacuum distilled from CaH_2, and then sparged with dry N_2

tert-butyl (S)-(1-oxopropan-2-yl)carbamate was synthesized according to a literature procedure[23]

2-Tolualdehyde was purchased from Alfa-Aesar, vacuum distilled from CaH_2, and then sparged with dry N_2

3-Tolualdehyde was purchased from Alfa-Aesar, vacuum distilled from CaH_2, and then sparged with dry N_2

***trans*-Cinnamaldehyde** was purchased from Alfa-Aesar, vacuum distilled from CaH_2, and then sparged with dry N_2

***trans*-4-Chlorocinnamaldehyde** was purchased from Alfa-Aesar, and azeotropically dried with benzene prior to use

***trans*-α-Methylcinnamaldehyde** was purchased from Alfa-Aesar, vacuum distilled from CaH_2, and then sparged with dry N_2

■ Representative Synthesis of Substituted Diboryl Reagents
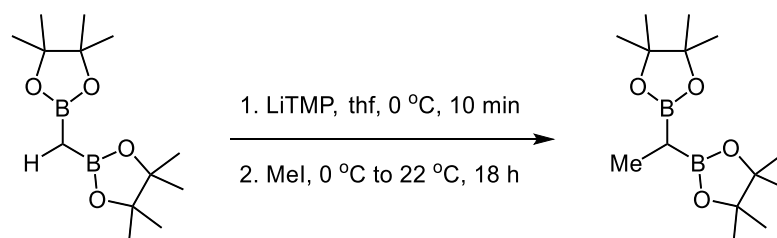
Procedure: In an N_2-filled glove box, an oven-dried round-bottom flask was charged with diboryl methane (3.00 g, 11.2 mmol) and a magnetic stir-bar, capped with a rubber septum, and sealed with electrical tape. A separate oven-dried, conical shaped flask was charged with lithium 2,2,6,6-tetramethylpiperidine (1.73 mg, 11.8 mmol), capped with a rubber septum, and sealed with electrical tape. The two flasks were brought out of the glove box, where the diboryl methane flask was charged with 47.0 mL of dry thf and the LiTMP-containing flask was charged with 93.0 mL of thf (.17M total). Both flasks were allowed to cool to 0 ˚C (ice/water-baths). The LiTMP solution was then cannula transferred to the diboryl methane flask with stirring. After the transfer, the reaction was allowed to stir for 10 min at 0 ˚C. Iodomethane (1.74 mL, 28.0 mmol) was then added to the reaction *via* a syringe and the reaction was allowed to warm up to 22 ˚C over 18 hours with stirring. The reaction was quenched with 50 mL of a saturated aqueous solution of NH_4Cl. The biphasic mixture was extracted 3 times with diethyl ether (900 mL total), and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude reaction mixture was purified by silica gel column chromatography (20:1 hexanes:EtOAc; R_f=0.20) to give the desired diboryl reagent in 89% yield (2.8 g). The spectral data of the diboronate ester matched those previously reported.[5]

2.80
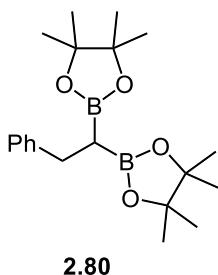
2,2'-(2-phenylethane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (2.80). Following the representative procedure, diboryl methane was alkylated with benzyl bromide and the crude reaction mixture was purified *via* silica gel chromatography in 20:1 hexanes:EtOAc to yield the product in 90% yield (1.2 g). **^{1}H NMR** (600 MHz, CDCl$_3$) δ 7.28 – 7.21 (m, 4H), 7.17 – 7.11 (m, 1H), 2.90 (d, *J* = 8.4 Hz, 2H), 1.21 (s, 7H), 1.20 (s, 6H). **^{13}C NMR** (151 MHz, CDCl$_3$) δ 144.6, 128.5, 128.1, 125.5, 83.2, 31.4, 24.9, 24.7. **IR** (v/cm^{-1}): 2978 (m), 2930 (w), 2866 (w), 1453 (w), 1381 (w), 1360 (m), 1320 (s), 1268 (w), 1241 (w), 1215 (w), 1140 (s). **HRMS** (ESI+) [M+Na]$^+$ calcd for C$_{20}$H$_{32}$B$_2$NaO$_4^+$ 381.2385, found: 381.2380.

2.81
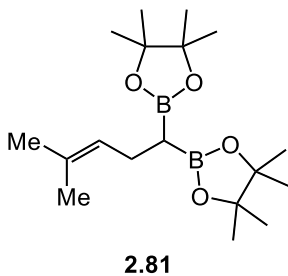
2,2'-(4-methylpent-3-ene-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (2.81). Following the representative procedure, diboryl methane was alkylated with prenyl bromide. The crude reaction mixture was purified via silica gel chromatography in 20:1 hexanes:EtOAc to yield the product in 90% yield (1.1 g). **^{1}H NMR** (CDCl$_3$, 600 MHz): δ 5.09 (t, 1H, *J* = 7.02 Hz), 2.21 (t, 2H, *J* = 7.8 Hz), 1.63 (s, 3H), 1.60 (s, 3H), 1.22 (s, 12H), 1.21 (s, 12H), 0.75 (t, 1H, *J* = 8.4 Hz). **^{13}C NMR** (CDCl$_3$, 151 MHz): δ 130.3, 127.1, 83.1, 25.9, 25.0, 24.6, 24.2, 18.0. **IR** (v/cm^{-1}): 2978 (s), 2928 (m), 2862 (w),

1446 (w), 1370 (m), 1357 (m), 1319 (m), 1270 (w), 1246 (w), 1215 (w), 1141 (s). **HRMS** (ESI+) [M+Na]$^+$ calcd for C$_{18}$H$_{34}$B$_2$NaO$_4$$^+$ 359.2541, found: 359.2539.

2.82

(3,3-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propoxy)(tert-butyl)dimethylsilane   (2.82).

Following the representative procedure, diboryl methane was alkylated with (2-bromoethoxy)(tert-butyl)dimethylsilane. The crude reaction mixture was purified via silica gel chromatography in 20:1 hexanes:EtOAc to yield the product in 92% yield (1.4 g). **^{1}H NMR** (CDCl$_3$, 400 MHz): δ 3.54 (t, 2H, J = 7.2 Hz), 1.76 (qu, 2H, J = 7.6 Hz), 1.22 (s, 12H), 1.21 (s, 12H), 0.87 (s, 9H), 0.77 (t, 1H J = 7.6 Hz), 0.03 (s, 6H). **^{13}C NMR** (CDCl$_3$, 100 MHz): δ 83.1, 65.2, 28.9, 26.2, 25.1, 24.6, 18.6, —5.1. **IR** (ν/cm^{-1}): 2978 (m), 2956 (m), 2930 (m), 2886 (w), 2857 (m), 1471 (w), 1379 (m), 1362 (m), 1318 (m), 1270 (w), 1255 (w), 1215 (w), 1165 (w), 1141 (m), 1099 (m), 1037 (w), 1006 (w). **HRMS** (ESI+) [M+Na]$^+$ calcd for C$_{21}$H$_{44}$B$_2$NaO$_5$Si$^+$ 449.3042, found: 449.3040.

2.83

tert-butyl 3,3-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoate (2.83).   Following the representative procedure, diboryl methane was alkylated with *tert*-butyl-2-bromoacetate. The crude

reaction mixture was purified via silica gel chromatography in 20:1 hexanes:EtOAc to yield the product in 68% yield (485 mg). **^{1}H NMR** (500 MHz, CDCl$_3$) δ 2.52 (d, J = 8.5 Hz, 2H), 1.43 (s, 9H), 1.25 (s, 12H), 1.23 (s, 12H), 1.07 (t, *J* = 8.5 Hz, 1H). **^{13}C NMR** (126 MHz, CDCl3) δ 174.2, 83.1, 79.6, 31.7, 28.1, 24.9, 24.5. **IR** (v/cm^{-1}): 2977 (s), 2894 (m), 2094 (w), 1729 (s), 1643 (s), 1468 (m), 1314 (w), 1268 (m), 1213 (m), 1140 (w). **HRMS** (ESI$^+$) [2M+Na]$^+$ calcd for C$_{38}$H$_{72}$B$_4$NaO$_{12}$$^+$ 787.5294, found: 787.5314.
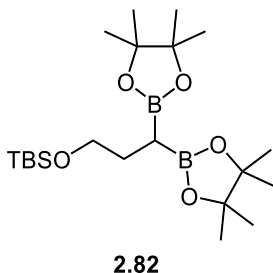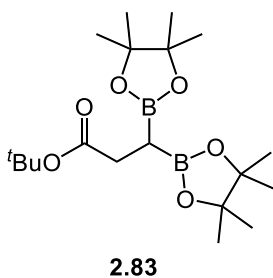

2.84

2,2'-(2-(1,3-dioxolan-2-yl)ethane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane)   (2.84). Following the representative procedure, diboryl methane was alkylated with 2-bromomethyl-1,3-dioxolane. The crude reaction mixture was purified *via* silica gel chromatography in 20:1 hexanes:EtOAc to yield the product in 44% yield (440 mg). **^{1}H NMR** (CDCl$_3$, 600 MHz): δ 4.94 (t, 1H, *J* = 3.9 Hz), 3.91-3.96 (m, 2H), 3.79-3.84 (m, 2H), 1.93 (dd, 2H, *J* = 7.6, 4.0 Hz), 1.22 (s, 12H), 1.22 (s, 12H), 0.84 (t, 1H, *J* = 7.6 Hz). **^{13}C NMR** (CDCl$_3$, 151 MHz): δ 128.5, 105.1, 83.1, 65.1, 30.1, 24.9, 24.7. **IR** (v/cm^{-1}): 2978 (s), 2930 (m), 2886 (m), 1469 (w), 1440 (w), 1369 (m), 1321 (s), 1270 (w), 1245 (w), 1215 (w), 1140 (s), 1085 (w), 1034 (w). **HRMS** (ESI+) [2M+NH$_4$]$^+$ calcd for C$_{34}$H$_{68}$B$_4$NaO$_{12}$$^+$ 726.5113, found: 726.5150.

2.85

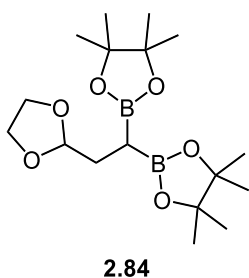**2,2'-(cyclohexylmethylene)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane)** **(2.85).** Following the representative procedure, diboryl methane was alkylated with bromocyclohexane. The crude reaction mixture was purified *via* silica gel chromatography in 20:1 hexanes:EtOAc to yield the product in 20% yield (190 mg). **^{1}H NMR** (400 MHz, CDCl$_3$) δ 1.85 – 1.55 (m, 8H), 1.26 (s, 12H), 1.24 (s, 12H), 1.17 – 1.04 (m, 1H), 1.03 – 0.85 (m, 2H), 0.66 (d, J = 10.4 Hz, 1H). **^{13}C NMR** (101 MHz, CDCl$_3$) δ 82.9, 36.1, 36.1, 26.9, 26.4, 25.0, 24.7. **IR** (v/cm^{-1}): 2978 (s), 2922 (m), 2851 (m), 2082 (m), 1639 (s), 1447 (m), 1315 (w), 1266 (m), 1140 (w). **HRMS** (ESI+) [2M+Na]$^+$ calcd for C$_{38}$H$_{72}$B$_4$NaO$_8$$^+$ 723.5630, found: 723.5603.

2.51
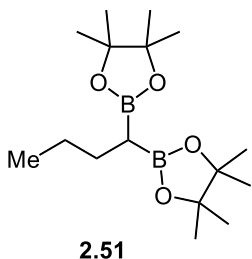
2,2'-(butane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) **(2.51).** Following the representative procedure, diboryl m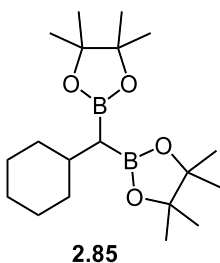ethane was alkylated with 1-iodopropane. The crude reaction mixture was purified *via* silica gel chromatography in 20:1 hexanes:EtOAc to yield the product in 78% yield (442 mg). **^{1}H NMR** (600 MHz, CDCl$_3$) δ 1.59 – 1.51 (m, 2H), 1.37 – 1.28 (m, 2H), 1.26 (s, 12H), 1.24 (s, 12H), 0.89 (t, *J* = 7.3 Hz, 3H), 0.76 (t, *J* = 7.9 Hz, 1H). **^{13}C NMR** (151 MHz, CDCl$_3$) δ 82.9, 27.9, 25.6, 24.9, 24.5, 14.2. **IR** (v/cm^{-1}): 2976 (s), 2840 (m), 1646 (m), 1314 (m), 1141 (m). **HRMS** (ESI+) [2M+Na]$^+$ calcd for C$_{32}$H$_{64}$B$_4$NaO$_8$$^+$ 643.4883, found: 643.4870.

■ **Synthesis of *n*-BuLi activated diborylethane, 2.48**

2.2   **2.48**

Procedure: In an N_2-filled glove box, an 8-mL vial was equipped with a magnetic stir bar and charged

with diborylethane, **2.2**, (100 mg, 0.355 mmol) and dissolved in 930 μL of anhydrous thf (0.33 M).

The vial was sealed with a septa-lined cap and removed from the glove box. The reaction was allowed

to cool to -78 ˚C (dry ice/acetone) and *n*-butyllithium was added to the solution under nitrogen (530

μL, 0.355 mmol, 0.67 M solution in hexanes). The reaction solidified instantaneously and the cooling

bath was removed to allow the reaction to stir at ambient temperature for 30 minutes. The reaction was

then brought back into the glove box where it was concentrated *in vacuo*, taken up in hexanes, and

filtered through a plug of Celite. After concentrating the filtrate *in vacuo*, 1 mL of diethyl ether was

added to the residue and removed *in vacuo* to yield a glassy solid. This solid was then scrapped from

the sides of the vial to yield a crystalline off-white powder in 98% yield (113 mg). **^{1}H NMR** (500

MHz, thf-d_8): δ 1.34 – 1.13 (m, 13H), 1.07 – 0.94 (m, 12H), 0.94 – 0.75 (m, 9H), 0.22 – 0.04 (m, 2H),

-0.16 (qu, *J* = 7.2 Hz, 1H). **^{11}B NMR** (500 MHz, thf-d_8): 35.9 (s), 6.1 (s).

■ General Procedures for Ag-Catalyzed 1,2-Addition Reactions:

Procedure A (aryl and vinyl aldehydes with 2.2): In an N_2-filled glove box, an 8-mL vial equipped

with a magnetic stir bar was charged with AgOAc (1.7 mg, 0.010 mmol) and KO^{t}Bu (14.6 mg, 0.13

mmol) and then shaken to evenly mix the solids. Diborylethane was then added as a solution in thf

down the side of the vial (29.7μL, 0.1 mmol in 0.8 mL of thf). The vial was sealed with a septa-lined

cap and removed from the glove box and allowed to stir at 22 ˚C for 5 min. The reaction was then

placed in a freezer set to -25 ˚C and allowed to stir for 30 more minutes. The aldehyde (0.1 mmol) was

then added to the reaction *via* syringe under argon and allowed to stir for 24 hours. The reaction was

quenched at -25 ˚C with 1.0 mL of a saturated aqueous solution of NH_4Cl, and the aqueous layer

extracted three times with diethyl ether. The combined organic extracts were dried over $MgSO_4$,

filtered, and concentrated *in vacuo*. Conversion and diastereomeric ratios were determined by ^1H NMR

using hexamethyldisiloxane as an internal standard.

Procedure B (aryl aldehydes with 2.80-2.85, 2.51): In an N_2-filled glove box, an 8-mL vial equipped

with a magnetic stir bar was charged with AgOAc (1.7 mg, 0.010 mmol) and KO^{t}Bu (14.6 mg, 0.13

mmol) and then shaken to evenly mix the solids. The diboryl reagent was then added as a solution in

thf down the side of the vial (0.1 mmol in 0.8 mL of thf). The vial was sealed with a septa-lined cap

and removed from the glove box and allowed to stir at 22 ˚C for 30 min. The reaction was then placed

in a freezer set to -25 ˚C and allowed to stir for 10 minutes. The aldehyde (0.1 mmol) was then added

to the reaction *via* syringe under argon and allowed to stir for 24 hours. The reaction was quenched at

-25 ˚C with 1.0 mL of a saturated aqueous solution of NH_4Cl, and the aqueous layer extracted three

times with diethyl ether. The combined organic extracts were dried over $MgSO_4$, filtered, and

concentrated *in vacuo*. Conversion and diastereomeric ratios were determined by ^1H NMR using

hexamethyldisiloxane as an internal standard.

Procedure C (alkyl aldehydes with all diboryl reagents): In an N_2-filled glove box, an 8-mL vial

equipped with a magnetic stir bar was charged with AgOAc (1.7 mg, 0.010 mmol) and diborylethane

(29.7 µL, 0.1 mmol), followed by 0.80 mL of anhydrous thf. The vial was sealed with a septa-lined

cap and removed from the glove box and allowed to cool to -78 ˚C (dry-ice/acetone). *n*-butyllithium

was then added at this temperature (69 µL, 0.10 mmol, 1.42 M solution in hexanes) and allowed to stir

for 20 minutes. The reaction was transferred to a freezer set to -25 ˚C and allowed to stir for 10 minutes.

The aldehyde (0.2 mmol) was then added to the reaction *via* syringe under argon and allowed to stir at

-25 ˚C for 24 hours. The reaction was quenched at -25 ˚C with 1.0 mL of a saturated aqueous solution

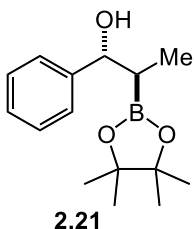of NH_4Cl, and the aqueous layer extracted three times with diethyl ether. The combined organic

extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Conversion and diastereomeric

ratios were determined by ^1H NMR using hexamethyldisiloxane as an internal standard.
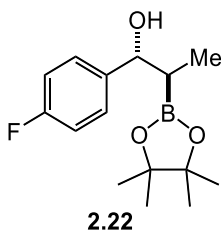
2.21

1-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-ol (2.21). Following general procedure A, the crude reaction mixture was purified by silica gel chromatography (NaOAc deactivated silica gel, 10:1 to 2:1 pentane:diethyl ether, Seebach Stain) to yield the hydroxyboronate as a colorless oil in 70% yield (18.3 mg) in 99:1 anti:syn diastereomeric ratio. **^{1}H NMR** (600 MHz, CDCl$_3$) δ 7.35 (d, J = 7.3 Hz, 2H), 7.31 (t, J = 7.6 Hz, 2H), 7.23 (m, 1H), 4.84 (dd, J = 6.5, 4.1 Hz, 1H), 2.35 (d, J = 4.1 Hz, 1H), 1.58 (m, 1H), 1.16 (s, 6H), 1.15 (s, 6H), 0.99 (d, J = 7.4 Hz, 3H). **^{13}C NMR** (151 MHz, CDCl$_3$) δ 144.1, 128.2, 127.2, 126.4, 83.4, 75.9, 24.7, 10.8. **IR** (ν/cm^{-1}): 3481 (s, br), 3085 (w), 3062 (w), 3030 (w), 2978 (s), 2932 (m), 2876 (m), 1494 (w), 1458 (m), 1381 (m), 1320 (m), 1275 (w), 1247 (w), 1215 (w), 1167 (w), 1145 (m), 1111 (w), 1073 (w), 1059 (w), 1009 (w). **HRMS (ESI+)** [M+Na]$^+$ calcd for C$_{15}$H$_{23}$BNaO$_3$$^+$ 285.1638, found: 285.1634
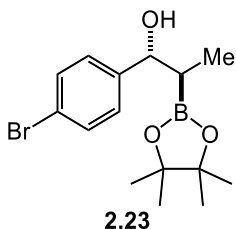

2.22

1-(4-fluorophenyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-ol (2.22). Following general procedure A, the crude reaction mixture was purified by silica gel chromatography (NaOAc deactivated silica gel, 10:1 to 2:1 pentane:diethyl ether, Seebach Stain) to yield the hydroxyboronate as a colorless oil in 65% yield (18.2 mg) in 99:1 anti:syn diastereomeric ratio. **^{1}H NMR** (600 MHz, CDCl$_3$) δ 7.40 – 7.28 (m, 2H), 7.08 – 6.92 (m, 2H), 4.81 (d, J = 6.7 Hz, 1H), 2.41 (s, 1H), 1.53 (qu, J

192

= 7.3 Hz, 1H), 1.15 (s, 6H), 1.14 (s, 6H), 0.98 (d, J = 7.4 Hz, 3H). ^{13}**C NMR** (151 MHz, CDCl$_3$) δ

162.9, 161.2, 139.9, 139.9, 128.0, 128.0, 115.0, 114.8, 83.5, 75.2, 24.7, 24.7, 10.7. **IR** (v/cm^{-1}): 3496

(s, br), 2979 (m), 2930 (w), 2877 (w), 1508 (s), 1457 (w), 1381 (s), 1320 (m), 1223 (m), 1144 (m),

1011 (m). **HRMS** (ESI$^+$) [M+Na]$^+$ calcd for C$_{15}$H$_{22}$BFO$_3$Na$^+$ 303.1544, found: 303.1537.
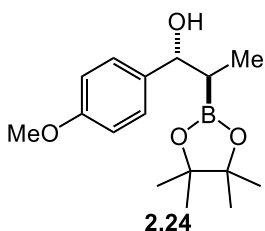

2.23

1-(4-bromophenyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-ol (2.23). Following

general procedure A, the crude reaction mixture was purified by silica gel (NaOAc deactivated silica

gel, 10:1 to 2:1 pentane:diethyl ether, Seebach Stain) to yield the hydroxyboronate as a white crystalline

solid in 65% yield (22.2 mg) in >99:1 anti:syn diastereomeric ratio. ^{1}**H NMR** (600 MHz, CDCl$_3$) δ

7.47 – 7.38 (m, 2H), 7.25 – 7.18 (m, 2H), 4.82 (d, J = 6.1 Hz, 1H), 2.48 (s, 1H), 1.56 – 1.46 (m, 1H),

1.18 (s, 6H), 1.17 (s, 6H), 0.94 (d, J = 7.4 Hz, 3H). ^{13}**C NMR** (151 MHz, CDCl$_3$) δ 143.1, 131.2, 128.1,

120.9, 83.6, 75.0, 24.8, 24.7, 10.3. **IR** (v/cm^{-1}): 3467 (s, br), 2978 (s), 2931 (w), 2876 (w), 1653 (w),

1457 (w), 1374 (s), 1320 (s), 1144 (s), 1010 (m). **HRMS** (ESI$^+$) [M+Na]$^+$ calcd for C$_{15}$H$_{22}$BBrO$_3$Na$^+$
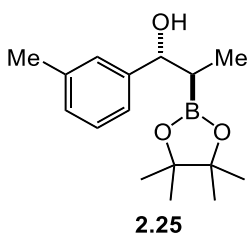
365.0743, found: 365.0716.

2.24

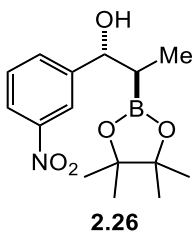**1-(4-methoxyphenyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-ol** **(2.24).**

Following general procedure A, the crude reaction mixture was purified by silica gel chromatography

(NaOAc deactivated silica gel, 10:1 to 2:1 pentane:diethyl ether, Seebach Stain) to yield the

hydroxyboronate as a colorless oil in 73% yield (21.3 mg) in 99:1 anti:syn diastereomeric ratio. **^{1}H**

NMR (600 MHz, CDCl$_3$) δ 7.29 – 7.26 (m, 2H), 6.86 – 6.82 (m, 2H), 4.76 (d, J = 7.1 Hz, 1H), 3.79 (s,

1H), 2.29 (s, 1H), 1.55 (qu, J = 7.3 Hz, 1H), 1.14 (s, 6H), 1.13 (s, 6H), 1.01 (d, J = 7.2 Hz, 3H). **^{13}C**

NMR (151 MHz, CDCl$_3$) δ 158.8, 136.5, 127.6, 113.5, 83.3, 75.7, 55.4, 24.7, 24.7, 11.1. **IR** (v/cm^{-1}):

3495 (s, br), 2978 (s), 2932 (w), 2873 (w), 1615 (m), 1514 (s), 1457 (m), 1374 (s), 1319 (m), 1248 (s),

1173 (m), 1144 (m). **HRMS** (ESI$^+$) [M+Na]$^+$ calcd for C$_{16}$H$_{25}$BO$_4$Na$^+$ 315.1744, found: 315.1737.

2.25

2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(m-tolyl)propan-1-ol (2.25). Following general

procedure A, the crude reaction mixture was purified by silica gel (NaOAc deactivated silica gel, 10:1

to 2:1 pentane:diethyl ether, Seebach Stain) to yield the hydroxyboronate as a colorless oil in 75% yield

(20.7 mg) in 97:3 anti:syn diastereomeric ratio. **^{1}H NMR** (600 MHz, CDCl$_3$) δ 7.20 (t, J = 7.5 Hz, 1H),

7.17 (s, 1H), 7.15 – 7.12 (m, 1H), 7.04 (d, J = 7.3 Hz, 1H), 4.79 (d, J = 6.7 Hz, 1H), 2.35 (s, 1H), 2.33

(s, 3H), 1.56 (quint, J = 7.3 Hz, 1H), 1.16 (s, 6H), 1.14 (s, 6H), 1.00 (d, J = 7.4 Hz, 3H). **^{13}C NMR**

(151 MHz, CDCl$_3$) δ 144.1, 137.6, 128.1, 127.9, 127.1, 123.5, 83.4, 76.0, 24.7, 21.6, 10.9. **IR** (v/cm^{-}

^{1}): 3487 (s, br), 2978(s), 2929 (m), 2874 (w), 1457 (m), 1380 (s), 1319 (m), 1145 (s), 1006 (m). **HRMS**

(ESI$^+$) [M+Na]$^+$ calcd for C$_{16}$H$_{25}$BO$_3$Na$^+$ 299.1795, found: 299.1788.

2.26

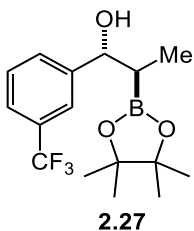**1-(3-nitrophenyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-ol (2.26).**   Following

general procedure A, the crude reaction mixture was purified by silica gel chromatography (NaOAc

deactivated silica gel, 10:1 to 2:1 pentane:diethyl ether, Seebach Stain) to yield the hydroxyboronate as

a colorless oil in 36% yield (11.1 mg) in 99:1 anti:syn diastereomeric ratio. **^{1}H NMR** (600 MHz,

CDCl$_3$) δ 8.28 (t, J = 2.0 Hz, 1H), 8.13 (ddd, J = 8.2, 2.3, 1.0 Hz, 1H), 7.75 – 7.68 (m, 1H), 7.51 (t, J =

7.9 Hz, 1H), 5.02 (d, J = 5.6 Hz, 1H), 2.77 (s, 1H), 1.60 (qd, J = 7.5, 5.6 Hz, 1H), 1.23 (s, 12H), 0.95

(d, J = 7.5 Hz, 3H). **^{13}C NMR** (151 MHz, CDCl$_3$) δ 148.2, 146.3, 132.6, 129.0, 122.1, 121.4, 83.8,

74.6, 24.8, 24.8, 10.0. **IR** (v/cm^{-1}): 3567 (br, s), 2979 (s), 2930 (m), 2877 (w), 1698 (m), 1558 (m),

1540 (s), 1457 (m), 1351 (s), 1318 (m), 1142 (m), 1018 (w). **HRMS** (ESI$^+$) [M+H]$^+$ calcd for

C$_{15}$H$_{22}$BNO$_5$$^+$ 306.1513, found: 306.1519.

2.27

2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(3-(trifluoromethyl)phenyl)propan-1-ol (2.27).

Following general procedure A, the crude reaction mixture was purified by silica gel chromatography (NaOAc deactivated silica gel, 10:1 to 2:1 pentane:diethyl ether, Seebach Stain) to yield the hydroxyboronate as a colorless oil in 52% yield (17.2 mg) in 98:2 anti:syn diastereomeric ratio. **¹H NMR** (400 MHz, CDCl₃) δ 7.66 (s, 1H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.52 (d, *J* = 7.7 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 1H), 4.93 (d, *J* = 6.3 Hz, 1H), 2.61 (s, 1H), 1.59 (quint, *J* = 7.1 Hz, 1H), 1.20 (s, 6H), 1.19 (s, 6H), 0.99 (d, *J* = 7.4 Hz, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ 145.0, 130.5, 130.1, 129.7, 128.5, 125.6, 123.9, 123.9, 123.2, 123.2, 122.9, 83.5, 75.1, 24.6, 10.4. **IR** (v/cm⁻¹): 3459 (br, s), 2980 (s), 2934 (w), 2879 (w), 1451 (m), 1382 (m), 1329 (s), 1165 (s), 1144 (m), 1126 (s), 1073 (m), 1019 (m). **HRMS** (ESI⁺) [M+Na]⁺ calcd for C₁₆H₂₂BF₃O₃Na⁺ 353.1512, found: 353.1509.
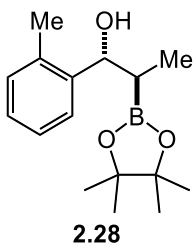

2.28

2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(o-tolyl)propan-1-ol (2.28). Following general procedure A, the crude reaction mixture was purified by silica gel chromatography (NaOAc deactivated silica gel, 10:1 to 2:1 pentane:diethyl ether, Seebach Stain) to yield the hydroxyboronate as a colorless oil in 69% yield (19.0 mg) in >99:1 anti:syn diastereomeric ratio. **¹H NMR** (600 MHz, CDCl₃) δ 7.47 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.21 (td, *J* = 7.4, 1.6 Hz, 1H), 7.16 (td, *J* = 7.3, 1.4 Hz, 1H), 7.14 – 7.11 (m,

1H), 5.08 (d, J = 6.8 Hz, 1H), 2.40 (s, 3H), 1.67 – 1.60 (m, 1H), 1.15 (s, 6H), 1.13 (s, 6H), 1.06 (d, J = 7.3 Hz, 3H). **^{13}C NMR** (151 MHz, CDCl$_3$) δ 142.0, 134.9, 130.4, 127.1, 126.4, 125.9, 83.3, 72.0, 24.7, 24.6, 19.4, 10.9. **IR** (v/cm^{-1}): 3482 (br, s), 2978 (s), 2931 (m), 2874 (w), 1459 (m), 1380 (s), 1319 (s), 1145 (s), 1008 (m). **HRMS** (ESI$^+$) [M+Na]$^+$ calcd for C$_{16}$H$_{25}$BO$_3$Na$^+$ 299.1795, found: 299.1788.

2.29

1-(furan-2-yl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-ol (2.29).   Following general procedure A, the crude reaction mixture was purified by silica gel (NaOAc deactivated silica gel, 10:1 to 2:1 pentane:diethyl ether, Seebach Stain) to yield the hydroxyboronate as a yellow oil in 71% yield (17.8 mg) in 94:6 anti:syn diastereomeric ratio. **^{1}H NMR** (600 MHz, CDCl$_3$) δ 7.35 (dd, J = 1.9, 0.8 Hz, 1H), 6.32 (dd, J = 3.3, 1.8 Hz, 1H), 6.25 (dt, J = 3.2, 0.7 Hz, 1H), 4.73 (d, J = 7.1 Hz, 1H), 2.82 (s, 1H), 1.70 (quint, J = 7.4 Hz, 1H), 1.25 (s, 6H), 1.24 (s, 6H), 1.01 (d, J = 7.5 Hz, 3H). **^{13}C NMR** (151 MHz, CDCl$_3$) δ 156.6, 141.4, 110.0, 106.4, 83.5, 70.1, 24.7, 24.6, 11.3. **IR** (v/cm^{-1}): 3469 (s, br), 2979 (s), 2932 (m), 2878 (w), 1458 (m), 1381 (s), 1322 (m), 1145 (s), 1009 (m). **HRMS** (ESI$^+$) [M+Na]$^+$ calcd for C$_{13}$H$_{21}$BO$_4$Na$^+$ 275.1431, found: 275.1427.

2.30

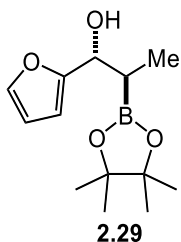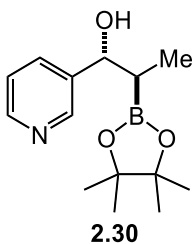**1-(pyridin-3-yl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-ol (2.30).** Following general procedure A, the crude reaction mixture was purified by silica gel chromatography (NaOAc deactivated silica gel, 10:1 to 2:1 pentane:diethyl ether, Seebach Stain) to yield the hydroxyboronate as a colorless oil in 45% yield (11.8 mg) in 99:1 anti:syn diastereomeric ratio. **^{1}H NMR** (600 MHz, CDCl$_3$) δ 8.59 (d, J = 2.2 Hz, 1H), 8.50 (dd, J = 4.8, 1.7 Hz, 1H), 7.73 (dt, J = 7.9, 2.0 Hz, 1H), 7.27 (dd, J = 4.8, 0.8 Hz,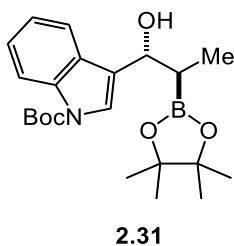 1H), 4.93 (d, J = 6.3 Hz, 1H), 2.74 (s, 1H), 1.67 – 1.53 (m, 1H), 1.20 (s, 6H), 1.19 (s, 6H), 1.00 (d, J = 7.4 Hz, 3H). **^{13}C NMR** (151 MHz, CDCl$_3$) δ 148.5, 148.2, 139.3, 134.1, 123.2, 83.7, 73.5, 24.8, 24.7, 10.4. **IR** (v/cm^{-1}): 3433 (s), 2359 (s), 2085 (w), 1643 (m), 1378 (w), 1320 (w), 1142 (m). **HRMS** (ESI)$^+$ [M+H]$^+$ calcd for C$_{14}$H$_{23}$BNO$_3^+$ 264.1772, found: 264.1761.

2.31

Synthesis of tert-butyl tert-butyl 3-(*anti*-1-hydroxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl)-1H-indole-1-carboxylate (2.31). Following general procedure A, the crude reaction mixture was purified by silica gel chromatography (NaOAc deactivated silica gel, 10:1 to 2:1 pentane:diethyl ether, Seebach Stain) to yield the hydroxyboronate as a colorless oil in 77% yield (30.9 mg) in >99:1 anti:syn diastereomeric ratio. **^{1}H NMR** (600 MHz, CDCl$_3$) δ 8.25 – 8.09 (m, 1H), 7.68 (dt, J = 7.8, 0.9 Hz, 1H), 7.58 (s, 1H), 7.33 (ddd, J = 8.4, 7.2, 1.2 Hz, 1H), 7.24 (ddd, J = 8.0, 7.3, 1.0

Hz, 1H), 5.17 (dd, J = 6.4, 2.3 Hz, 1H), 2.46 (d, J = 4.5 Hz, 1H), 1.85 – 1.75 (m, 1H), 1.68 (s, 9H), 1.21 (s, 6H), 1.21 (s, 6H), 1.08 (d, J = 7.5 Hz, 3H). ^{13}C NMR (151 MHz, CDCl$_3$) δ 149.8, 135.8, 129.1, 125.6, 124.4, 123.7, 122.8, 122.5, 120.0, 115.3, 83.5, 69.4, 28.3, 24.8, 24.7, 10.8. IR (v/cm^{-1}): 3502 (s, br), 2978 (s), 2932 (m), 2877 (w), 1733 (s), 1455 (s), 1372 (s), 1321 (m), 1255 (m), 1159 (s), 1081 (m), 1011 (m). HRMS (ESI$^+$) [M+Na]$^+$ calcd for C$_{22}$H$_{32}$BNO$_5$Na$^+$ 424.2271, found: 424.2272.
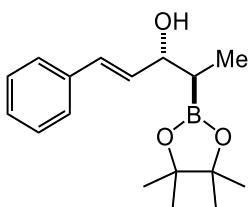

2.32

(E)-1-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-1-en-3-ol   **(2.32).**   Following general procedure A, the crude reaction mixture was purified by silica gel chromatography (NaOAc deactivated silica gel, 10:1 to 2:1 pentane:diethyl ether, Seebach Stain) to yield the hydroxyboronate as a yellow oil in 65% yield (18.7 mg) in 88:12 anti:syn diastereomeric ratio. a**nti-diastereomer:** ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.42 – 7.37 (m, 2H), 7.35 – 7.31 (m, 2H), 7.27 – 7.22 (m, 1H), 6.61 (dd, J = 15.9, 1.2 Hz, 1H), 6.28 (dd, J = 15.9, 6.5 Hz, 1H), 4.41 – 4.33 (m, 1H), 2.39 (s, 1H), 1.53 – 1.46 (m, 1H), 1.25 (s, 12H), 1.07 (d, J = 7.5 Hz, 3H). ^{13}C NMR (151 MHz, CDCl$_3$) δ 137.0, 131.7, 130.3, 128.5 127.4, 126.4, 83.4, 75.0, 24.8, 24.7, 11.0. s**yn-diastereomer:** ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.43 – 7.36 (m, 2H), 7.36 – 7.30 (m, 2H), 7.27 – 7.22 (m, 1H), 6.59 (dd, J = 15.0, 1.2 Hz, 1H), 6.25 (dd, J = 17.2, 6.5 Hz, 1H), 4.27 (m, 1H), 2.55 (s, 1H), 1.41 (quint, J = 7.4 Hz, 1H), 1.28 (s, 6H), 1.27 (s, 6H), 1.07 (d, J = 8.0 Hz, 3H). ^{13}C NMR (151 MHz, CDCl$_3$) δ 137.0, 132.5, 131.7, 130.2, 127.4, 126.4, 83.5, 75.8, 24.9, 24.7, 12.1. IR (v/cm^{-1}): 3446 (s, br), 3026 (w), 2978 (s), 2931 (m), 2875 (w), 1457 (m), 1380 (s), 1320 (m), 1144 (s), 1006 (m). HRMS (ESI$^+$) [M+Na]$^+$ calcd for C$_{17}$H$_{25}$BO$_3$Na$^+$ 311.1795, found: 311.1788.

2.33

(*E*)-1-(4-chlorophenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-1-en-3-ol **(2.33).**

Following general procedure A, the crude reaction mixture was purified by silica gel chromatography

(NaOAc deactivated silica gel, 10:1 to 2:1 pentane:diethyl ether, Seebach Stain) to yield the

hydroxyboronate as a colorless oil in 40% yield (12.9 mg) in 88:12 anti:syn diastereomeric ratio. ***anti***

diastereomer: **^{1}H NMR** (600 MHz, CDCl$_3$) δ 7.31 – 7.25 (m, 5H), 6.54 (dd, *J* = 15.9, 1.3 Hz, 1H),

6.23 (dd, *J* = 15.8, 6.4 Hz, 1H), 4.39 – 4.28 (m, 1H), 2.36 (s, 1H), 1.48 – 1.43 (m, 1H), 1.22 (s, 6H),

1.22 (s, 6H), 1.04 (d, *J* = 7.5 Hz, 3H). **^{13}C NMR** (151 MHz, CDCl$_3$) δ 135.5, 133.0, 132.4, 129.0,

128.7, 127.6, 83.5, 74.8, 24.8, 24.7, 11.0. ***syn*-diastereomer:** **^{1}H NMR** (600 MHz, CDCl$_3$) δ 7.34 –

7.27 (m, 5H), 6.56 – 6.51 (m, 1H), 6.25 – 6.20 (m, 1H), 4.25 (t, *J* = 6.5 Hz, 1H), 2.57 (s, 1H), 1.43 –

1.36 (m, 1H), 1.27 (s, 6H), 1.26 (s, 6H), 1.06 (d, *J* = 7.5 Hz, 3H). **^{13}C NMR** (151 MHz, CDCl$_3$) δ

133.2, 129.2, 128.8, 128.8, 127.6, 125.5, 83.5, 75.7, 24.8, 24.7, 12.1. **IR** (v/cm^{-1}): 3433 (s), 2385 (m),

2083 (s), 1642 (m), 1490 (w), 1378 (m), 1320 (m), 1140 (w). **HRMS** (ESI$^+$) [M+Na]$^+$ calcd for

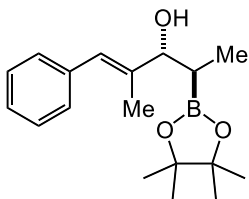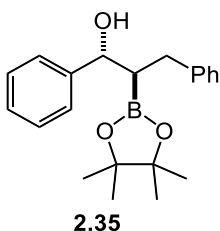C$_{17}$H$_{24}$BClO$_3$Na 345.1405, found: 345.1394.

2.34

(*E*)-1-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-1-en-3-ol **(2.34).** Following

general procedure A, the crude reaction mixture was purified by silica gel chromatography (NaOAc

deactivated silica gel, 10:1 to 2:1 pentane:diethyl ether, Seebach Stain) to yield the hydroxyboronate as a colorless oil in 64% yield (18.5 mg) in 93:7 anti:syn diastereomeric ratio. **¹H NMR** (600 MHz, CDCl₃) δ 7.38 – 7.32 (m, 2H), 7.29 (d, J = 8.8 Hz, 2H), 7.23 (td, J = 7.2, 1.5 Hz, 1H), 6.55 (s, 1H), 4.32 (d, J = 7.0 Hz, 1H), 2.14 (s, 1H), 1.88 (s, 3H), 1.55 (m, 1H), 1.24 (s, 12H), 1.05 (d, J = 7.4 Hz, 3H). **¹³C NMR** (151 MHz, CDCl₃) δ 139.8, 137.9, 129.1, 128.1, 126.3, 125.6, 83.4, 79.1, 24.9, 24.8, 14.2, 10.5. **IR** (ν/cm⁻¹): 3429 (s), 2568 (m), 2082 (m), 1643 (s), 1143 (m). **HRMS** (ESI⁺) [M+Na]⁺ calcd for $C_{18}H_{27}BO_3Na^+$ 325.1943, found: 325.1940.

2.35

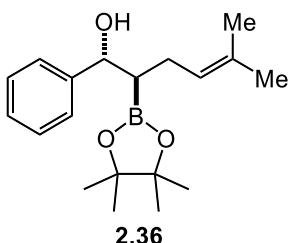**1,3-diphenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-ol (2.35).** Following general procedure B, the crude reaction mixture was purified by silica gel chromatography (NaOAc deactivated silica gel, 10:1 to 5:1 pentane:diethyl ether, Seebach Stain) to yield the hydroxyboronate as a colorless oil in 76% yield (25.7 mg) in 92:8 anti:syn diastereomeric ratio. a***nti* diastereomer**: **¹H NMR** (600 MHz, CDCl₃) δ 7.43 – 7.38 (m, 1H), 7.35 (m, 1H), 7.34 – 7.29 (m, 2H), 7.27 – 7.17 (m, 5H), 7.17 – 7.10 (m, 1H), 4.83 (dd, J = 8.1, 3.6 Hz, 1H), 3.06 (dd, J = 13.6, 5.6 Hz, 1H), 2.81 – 2.68 (m, 1H), 2.24 (d, J = 3.7 Hz, 1H), 2.02 (ddd, J = 11.1, 8.0, 5.7 Hz, 1H), 0.90 (s, 6H), 0.89 (s, 6H). **¹³C NMR** (151 MHz, CDCl₃) δ 143.9, 141.7, 129.1, 128.4, 128.3, 126.8, 126.0, 125.9, 83.4, 76.0, 34.5, 24.7, 24.7. ***syn*-diastereomer**: **¹H NMR** (600 MHz, CDCl₃) δ 7.43 – 7.38 (m, 1H), 7.35 (m, 1H), 7.34 – 7.29 (m, 2H), 7.27 – 7.17 (m, 5H), 7.17 – 7.10 (m, 1H), 4.70 (t, J = 6.7 Hz, 1H), 2.81 – 2.68 (m, 2H), 2.62 (d, J = 7.2 Hz, 1H), 1.99 – 1.91 (m, 1H), 1.08 (s, 6H), 1.07 (s, 6H). **¹³C NMR** (151 MHz, CDCl₃) δ 144.9, 141.3, 129.0, 128.4, 128.3, 127.8, 127.3, 126.0, 83.6, 75.1, 34.5, 24.9. 24.7. **IR** (ν/cm⁻¹): 3467

(s, br), 3061 (w), 3028 (m), 2979 (s), 2927 (m), 2865 (w), 1455 (m), 1380 (s), 1325 (m), 1247 (m), 1143 (s). **HRMS** (ES$^+$) [M+Na]$^+$ calcd for $C_{21}H_{27}BO_3Na^+$ 361.1951, found: 361.1949.

2.36

5-methyl-1-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-4-en-1-ol **(2.36).**

Following general procedure B, the crude reaction mixture was purified by silica gel chromatography (NaOAc deactivated silica gel, 10:1 to 5:1 pentane:diethyl ether, Seebach Stain) to yield the hydroxyboronate as a colorless oil in 74% yield (23.4 mg) in 98:2 anti:syn diastereomeric ratio. ***anti*-diastereomer: ^{1}H NMR** (CDCl$_3$, 600 MHz): δ 7.37 (d, J = 6.6 Hz, 2H), 7.30 (t, J = 7.8 Hz, 2H), 7.22 (tt, J = 7.2, 1.8 Hz, 1H), 5.17 (t, J = 7.5 Hz, 1H), 4.77 (d, J = 9.0 Hz, 1H), 2.33 (d, J = 4.2 Hz, 1H), 2.28-2.31 (m, 1H), 2.23-2.26 (m, 1H), 1.66 (s, 3H), 1.63-1.64 (m, 1H), 1.60 (s, 3H), 1.05 (s, 6H), 1.02 (s, 6H). **^{13}C NMR** (CDCl$_3$, 151 MHz): δ 144.1, 132.2, 128.3, 127.6, 126.8, 124.0, 83.3, 75.8, 26.5, 26.0, 24.7, 24.6, 18.0. ***syn*-diastereomer: ^{1}H NMR** (CDCl$_3$, 600 MHz): δ 7.34 (d, J = 7.2 Hz, 2H), 7.30 (t, J = 7.8 Hz, 2H), 7.22 (tt, J = 7.2, 1.8 Hz, 1H), 5.11 (t, J = 7.2 Hz, 1H), 4.70 (t, J = 6.6 Hz, 1H), 2.65 (d, J = 6.0 Hz, 1H), 2.11-2.16 (m, 1H), 2.00-2.04 (m, 1H), 1.65 (s, 3H), 1.58-1.59 (m, 1H), 1.55 (s, 3H), 1.19 (s, 12H). **^{13}C NMR** (CDCl$_3$, 151 MHz): δ 144.9, 132.3, 127.3, 126.2, 123.5, 83.5, 75.7, 27.1, 25.9, 25.0, 24.6, 18.0. **IR** (v/cm^{-1}): 3478 (s, br, OH), 3061 (w), 3030 (w), 2978 (m), 2925 (m), 2857 (m), 1453 (w), 1410 (w), 1379 (s), 1323 (m), 1245 (m), 1213 (w), 1166 (w), 1144 (s), 1108 (w), 1052 (w), 1008 (w). **HRMS (ESI+)** [2M+Na]$^+$ calcd for $C_{38}H_{58}B_2NaO_6^+$ 655.4318, found: 655.4309.

2.37

4-((*tert*-butyldimethylsilyl)oxy)-1-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-1-ol (2.37). Following general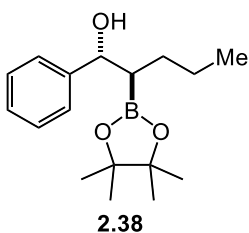 procedure B, the crude reaction mixture was purified by silica gel chromatography (NaOAc deactivated silica gel, 10:1 to 5:1 pentane:diethyl ether, Seebach Stain) to yield the hydroxyboronate as a colorless oil in 77% yield (31.3 mg) in 94:6 anti:syn diastereomeric ratio. ***anti*-diastereomer: ^{1}H NMR** (CDCl$_3$, 600 MHz): δ 3.77 (dt, J = 10.2, 6.0 Hz, 1H), 3.57-3.61 (m, 1H), 3.48 (qu, J = 5.4 Hz, 1H), 2.77 (d, J = 6.6 Hz, 1H), 1.90 (m, 1H), 1.68-1.78 (m, 4H), 1.56-1.64 (m, 2H), 1.32-1.43 (m, 2H), 1.24 (s, 9H), 1.08-1.22 (m, 3H), 0.94-1.06 (m, 2H), 0.89 (s, 6H), 0.88 (s, 6H), 0.06 (s, 6H). **^{13}C NMR** (CDCl$_3$, 151 MHz): δ 83.3, 76.8, 63.5, 42.2, 33.2, 30.1, 29.3, 27.9, 26.6, 26.4, 26.3, 26.1, 24.9, 24.9, 18.5, —5.2. ***syn*-diastereomer: ^{1}H NMR** (CDCl$_3$, 600 MHz): δ 3.67 (ddd, J = 10.0, 7.5, 6.1 Hz, 1H), 3.56-3.61 (m, 1H), 3.34 (qu, J = 7.2 Hz, 1H), 2.25 (d, J = 8.4 Hz, 1H), 1.95 (m, 1H), 1.68-1.78 (m, 4H), 1.56-1.64 (m, 2H), 1.32- 1.43 (m, 2H), 1.24 (s, 9H), 1.08-1.22 (m, 3H), 0.94-1.06 (m, 2H), 0.89 (s, 6H), 0.88 (s, 6H), 0.04 (s, 6H). **^{13}C NMR** (CDCl$_3$, 151 MHz): δ 83.4, 77.9, 62.9, 43.7, 36.5, 31.8, 30.0, 28.6, 26.7, 26.6, 26.3, 26.1, 25.0, 24.9, 18.5, —5.1, —5.1. **IR** (v/cm^{-1}): 3474 (s, br, OH), 2978 (m), 2954 (m), 2929 (m), 2885 (m), 2857 (m), 1471 (w), 1372 (m), 1321 (m), 1254 (m), 1214 (w), 1167 (w), 1144 (m), 1096 (m), 1025 (w). **HRMS (ESI+)** [M+Na]$^+$ calcd for C$_{22}$H$_{39}$BNaO$_4$Si$^+$ 429.2609, found: 429.2607.

2.38

1-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentan-1-ol (2.38). Following general procedure B, the crude reaction mixture was purified by silica gel chromatography (NaOAc, deactivated silica gel, 5:1 pentane:diethyl ether to 2:1 pentane diethyl ether, Seebach Stain) to yield the hydroxyboronate as a colorless oil in 60% yield (17.4 mg) in 94:6 anti:syn diastereomeric ratio. **^{1}H NMR** (600 MHz, CDCl$_3$) δ 7.41 – 7.37 (m, 2H), 7.33 (dd, J = 8.4, 6.8 Hz, 2H), 7.28 – 7.23 (m, 1H), 4.78 (d, J = 7.6 Hz, 1H), 2.26 (s, 1H), 1.62 (ddt, J = 12.5, 10.1, 4.5 Hz, 2H), 1.58 – 1.50 (m, 2H), 1.43 – 1.36 (m, 2H), 1.35 – 1.22 (m, 2H), 1.12 (s, 6H), 1.07 (s, 6H), 0.92 (t, J = 7.3 Hz, 3H). **^{13}C NMR** (151 MHz, CDCl$_3$) δ 144.3, 128.3, 127.5, 126.7, 83.3, 75.8, 30.0, 24.8, 24.7, 22.7, 14.6. **IR** (v/cm^{-1}): 3432 (s), 2090 (s), 1642 (m), 1454 (m), 1379 (m), 1320 (w), 1247 (m), 1143 (w). **HRMS** (ESI)$^+$ [2M+Na]$^+$ calcd for C$_{34}$H$_{54}$B$_2$O$_6$Na$^+$ 603.4004, found: 603.3987.

2.39
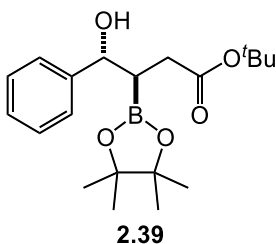
tert-butyl-4-hydroxy-4-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoate (2.39). Following general procedure B, the crude reaction mixture was purified by silica gel chromatography (NaOAc deactivated silica gel, 10:1 to 5:1 pentane:diethyl ether, Seebach Stain) to yield the hydroxyboronate as a colorless oil in 66% yield (23.9 mg) in a 47:53 anti:syn diastereomeric ratio. a*nti*-diastereomer: **^{1}H NMR** (600 MHz, CDCl$_3$) δ 7.46 – 7.29 (m, 4H), 7.28 – 7.23 (m, 1H), 4.95 (d,

J = 6.1 Hz, 1H), 3.11 (s, 1H), 2.54 – 2.17 (m, 2H), 1.87 (dt, J = 8.3, 6.1 Hz, 1H), 1.46 (s, 9H), 1.26 (s, 12H). **^{13}C NMR** (151 MHz, CDCl$_3$) δ 174.1, 143.7, 128.2, 127.2, 126.2, 83.1, 79.8, 74.3, 33.9, 32.7, 30.0, 28.1, 24.9, 24.8, 24.8. s**yn-diastereomer: ^{1}H NMR** (600 MHz, CDCl$_3$) δ 7.46 – 7.29 (m, 4H), 7.28 – 7.23 (m, 1H), 4.81 (d, J = 8.2 Hz, 1H), 2.92 (s, 1H), 2.54 – 2.17 (m, 9H), 1.80 – 1.73 (m, 1H), 1.44 (s, 9H), 1.28 (s, 6H), 1.27 (s, 6H). **^{13}C NMR** (151 MHz, CDCl$_3$) δ 173.1, 143.7, 128.3, 127.4, 126.3, 83.7, 83.5, 80.5, 80.4, 75.0, 32.7, 30.3, 28.1, 28.1, 24.8, 24.7, 24.5, 24.5. **IR** (v/cm^{-1}): 3429 (s), 2359 (s), 2341 (s), 2094 (w), 1643 (m), 1139 (m). **HRMS** (ESI)$^+$ [2M+Na]$^+$ calcd for C$_{40}$H$_{62}$B$_2$O$_{10}$Na$^+$ 747.4428, found: 747.4407.
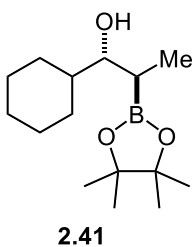

2.41

1-cyclohexyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-ol (2.41). Following general procedure C, the crude reaction mixture was purified by silica gel chromatography (NaOAc deactivated silica gel, 20:1 pentane:ethyl acetate to 5:1 pentane:diethyl ether, Seebach Stain) to yield the hydroxyboronate as a crystalline white solid in 38% yield (10.3 mg) and 88:12 anti:syn diastereomeric ratio. *anti*-**diastereomer: ^{1}H NMR** (CDCl$_3$, 600 MHz): δ 3.46 (m, 1H), 1.92-1.95 (m, 2H), 1.71-1.77 (m, 2H), 1.62-1.65 (m, 2H), 1.56-1.59 (m, 1H), 1.32-1.40 (m, 2H), 1.09-1.24 (m, 3H), 0.98-1.02 (m, 1H), 1.24 (s, 12H), 0.96 (d, J = 7.8 Hz, 3H). **^{13}C NMR** (CDCl$_3$, 151 MHz): δ 83.4, 77.4, 41.1, 29.7, 28.6, 26.6, 26.5, 26.3, 24.9, 24.8, 9.2. **IR** (v/cm^{-1}): 3522 (s, br, OH), 2977 (m), 2925 (s), 2851 (m), 1450 (m), 1379 (s), 1317 (m), 1273 (w), 1214 (w), 1166 (w), 1145 (m), 1008 (w). **HRMS** (ESI+) [2M+Na]$^+$ calcd for C$_{30}$H$_{58}$B$_2$NaO$_6^+$ 559.4318, found: 559.4314.

2.42

1-cyclohexyl-5-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-4-en-1-ol **(2.42).**

Following general procedure C, the crude reaction mixture was purified by silica gel chromatography (NaOAc deactivated silica gel, 20:1 pentane:ethyl acetate to 5:1 pentane:diethyl ether, Seebach Stain) to yield the hydroxyboronate as a colorless, crystalline white solid in 61% yield (19.5 mg) and 78:22 anti:syn diastereomeric ratio. ***anti*-diastereomer: ¹H NMR** (CDCl₃, 600 MHz): δ 5.15 (t, J = 7.2 Hz, 1H), 3.48 (t, J = 6.6 Hz, 1H), 2.17-2.26 (m, 2H), 1.86-1.92 (m, 2H), 1.72-1.77 (m 2H), 1.66 (s, 3H), 1.62 (s, 3H), 1.57-1.60 (m, 1H), 1.32-1.39 (m, 2H), 1.22 (s, 6H), 1.22 (s, 6H), 1.08-1.21 (m, 4H), 0.95-1.06 (m, 1H). **¹³C NMR** (CDCl₃, 151 MHz): δ 131.9, 124.5, 83.3, 42.4, 30.3, 27.4, 26.7, 26.6, 26.4, 26.0, 25.3, 24.9, 24.8, 18.0. ***syn*-diastereomer: ¹H NMR** (CDCl₃, 600 MHz): δ 5.11 (t, J = 7.2 Hz, 1H), 3.32 (qu, J = 7.2 Hz, 1H), 2.10-2.16 (m, 2H), 2.04 (d, 1H, J = 9.0 Hz), 1.86-1.92 (m, 2H), 1.72-1.77 (m 2H), 1.66 (s, 3H), 1.62 (s, 3H), 1.57-1.60 (m, 1H), 1.32-1.39 (m, 2H), 1.23 (s, 12H), 1.08-1.21 (m, 4H), 0.95-1.06 (m, 1H). **¹³C NMR** (CDCl₃, 151 MHz): δ 132.0, 124.1, 83.4, 78.2, 44.1, 30.0, 28.5, 27.7, 26.7, 26.6, 25.9, 25.0, 24.7, 18.0. **IR** (v/cm⁻¹): 3517 (s, br, OH), 2928 (m), 2925 (s), 2852 (m), 1449 (m), 1378 (s), 1320 (m), 1245 (w), 1213 (w), 1165 (w), 1144 (s), 1110 (w), 1044 (w). **HRMS** (ESI+) [2M+Na]⁺ calcd for $C_{38}H_{70}B_2NaO_6^+$ 667.5257, found: 667.5249.
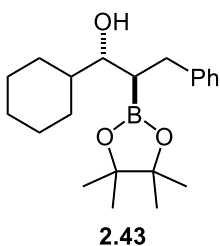
2.43

1-cyclohexyl-3-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-ol **(2.43).**

Following general procedure C, the crude reaction mixture was purified by silica gel chromatography

(NaOAc deactivated silica gel, 20:1 pentane:ethyl acetate to 5:1 pentane:diethyl ether, Seebach Stain)

to yield the hydroxyboronate as a colorless, crystalline white solid in 49% yield (17.0 mg) and 95:5

anti:syn diastereomeric ratio. ***anti*-diastereomer:** **^{1}H NMR** (CDCl$_3$, 600 MHz): δ 7.23 (m, 2H), 7.23

(m, 2H), 7.13 (m, 1H), 3.53 (t, *J* = 6.0 Hz, 1H), 2.98 (dd, *J* = 13.8 Hz, 6.0 Hz, 1H), 2.70 (dd, *J* = 13.2,

11.4 Hz, 1H), 1.93-1.96 (m, 1H), 1.87 (s, 1H), 1.73-1.80 (m, 3H), 1.63-1.67 (m, 2H), 1.39-1.46 (m,

1H), 1.12-1.27 (m, 5H), 1.11 (s, 6H), 1.05 (s, 6H). **^{13}C NMR** (CDCl$_3$, 151 MHz): δ 142.2, 129.1,

128.2, 125.8, 83.4, 77.3, 42.4, 32.7, 30.3, 27.4, 26.7, 26.6, 26.3, 24.9, 24.8. **IR** (ν/cm^{-1}): 3511 (s, br,

OH), 3061 (w), 3027 (w), 2978 (m), 2925 (s), 2852 (w), 1496 (w), 1450 (m), 1372 (s), 1323 (m), 1249

(w), 1211 (w), 1166 (w), 1143 (m), 1100 (w), 1084 (w), 1072 (w), 1040 (w). **HRMS** (ESI+) [2M+Na]$^+$

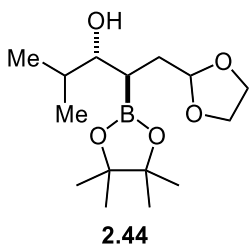calcd for C$_{42}$H$_{66}$B$_2$NaO$_6$$^+$ 711.4943, found: 711.4936.

2.44

1-(1,3-dioxolan-2-yl)-4-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentan-3-ol (2.44).

Following general procedure C, the crude reaction mixture was purified by silica gel chromatography

(NaOAc deactivated silica gel, 20:1 pentane:ethyl acetate to 5:1 pentane:diethyl ether, Seebach Stain)

to yield the hydroxyboronate as a colorless oil in 62% yield (18.6 mg) and >98:2 anti:syn diastereomeric ratio. **anti-diastereomer: ^{1}H NMR** (CDCl$_3$, 600 MHz): 4.99 (t, 1H, J = 4.2 Hz), 3.94-3.98 (m, 2H), 3.80-3.85 (m, 2H), 3.43 (t, 1H, J = 6.1 Hz), 2.32 (s, 1H), 1.88-1.95 (m, 2H), 1.67-1.73 (m, 1H), 1.40-1.44 (m, 1H), 1.24 (s, 12H), 0.92 (dd, J = 13.8, 6.7 Hz, 6H). **^{13}C NMR** (CDCl$_3$, 151 MHz): δ 104.4, 83.4, 77.1, 65.0, 65.0, 32.2, 30.5, 24.9, 24.9, 20.1, 17.1. **IR** (v/cm^{-1}): 3495 (s, br), 2976 (m), 2931 (m), 2875 (m), 1470 (w), 1373 (s), 1318 (m), 1249 (w), 1213 (w), 1144 (s), 1095 (w). **HRMS** (ESI+) [2M+H]$^+$ calcd for C$_{30}$H$_{59}$B$_2$O$_{10}$$^+$ 601.4294, found: 601.4317.

2.45

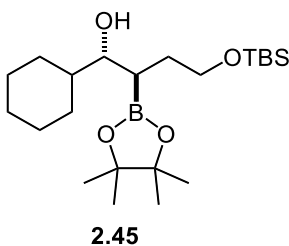**4-((*tert*-butyldimethylsilyl)oxy)-1-cyclohexyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-1-ol (2.45).** Following general procedure C, the crude reaction mixture was purified by silica gel chromatography (NaOAc deactivated silica gel, 20:1 pentane:ethyl acetate to 5:1 pentane:diethyl ether, Seebach Stain) to yield the hydroxyboronate as a colorless, crystalline white solid in 49% yield (20.3 mg) and 90:10 anti:syn diastereomeric ratio. **anti-diastereomer: ^{1}H NMR** (CDCl$_3$, 600 MHz): δ 3.77 (dt, J = 10.2, 6.0 Hz, 1H), 3.57-3.61 (m, 1H), 3.48 (qu, J = 5.4 Hz, 1H,), 2.77 (d, J = 6.6 Hz, 1H), 1.90 (m, 1H), 1.68-1.78 (m, 4H), 1.56-1.64 (m, 2H), 1.32- 1.43 (m, 2H), 1.24 (s, 9H), 1.08-1.22 (m, 3H), 0.94-1.06 (m, 2H), 0.89 (s, 6H), 0.88 (s, 6H), 0.06 (s, 6H). **^{13}C NMR** (CDCl$_3$, 151 MHz): δ 83.3, 76.8, 63.5, 42.2, 33.2, 30.1, 29.3, 27.9, 26.6, 26.4, 26.3, 26.1, 24.9, 24.9, 18.5, —5.2. **syn-diastereomer: ^{1}H NMR** (CDCl$_3$, 600 MHz): δ 3.67 (ddd, J = 10.0, 7.5, 6.1 Hz, 1H), 3.56-3.61 (m, 1H), 3.34 (qu, J = 7.2 Hz, 1H), 2.25 (d, J = 8.4 Hz, 1H), 1.95 (m, 1H), 1.68-1.78 (m, 4H), 1.56-1.64 (m, 2H), 1.32- 1.43 (m, 2H), 1.24 (s, 9H), 1.08-1.22 (m, 3H), 0.94-1.06 (m, 2H), 0.89 (s, 6H), 0.88 (s, 6H), 0.04 (s, 6H). **^{13}C NMR** (CDCl$_3$, 151 MHz): δ 83.4, 77.9, 62.9, 43.7, 36.5, 31.8, 30.0, 28.6, 26.7, 26.6, 26.3,

26.1, 25.0, 24.9, 18.5, —5.1, —5.1. **IR** (ν/cm^{-1}): 3464 (s, br, OH), 2977 (m), 2927 (s), 2854 (m), 1471 (m), 1449 (m), 1372 (m), 1317 (m), 1254 (m), 1214 (w), 1166 (w), 1145 (m), 1094 (m), 1007 (w). **HRMS** (ESI+) [M+Na]$^+$ calcd for $C_{22}H_{45}BNaO_4Si^+$ 435.3078, found: 435.3077.

2.46

2,2-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentan-3-ol (2.46). Following general procedure B, the crude reaction mixture was purified by silica gel chromatography (NaOAc deactivated silica gel, 20:1 pentane:ethyl acetate to 5:1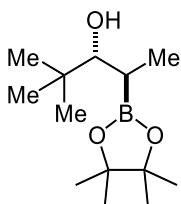 pentane:diethyl ether, Seebach Stain) to yield the hydroxyboronate as a colorless, crystalline white solid in 33% yield (7.9 mg) and >98:2 anti:syn diastereomeric ratio. **^{1}H NMR** (CDCl$_3$, 600 MHz): δ 3.44 (d, 1H, J = 7.8 Hz), 1.60 (s, 1H), 1.29 (quint, 1H, J = 7.8 Hz), 1.23 (s, 12H), 1.04 (d, 3H, J = 7.2 Hz), 0.92 (s, 9H). **^{13}C NMR** (CDCl$_3$, 151 MHz): δ 83.2, 79.9, 36.1, 26.7, 24.8, 24.8, 12.0. **IR** (ν/cm^{-1}): 3539 (s, br, OH), 2978 (m), 2953 (m), 2871 (w), 1481 (w), 1458 (w), 1379 (m), 1334 (w), 1314 (m), 1166 (w), 1145 (m), 1106 (w), 1039 (w). **HRMS** (ESI+) [2M+Na]$^+$ calcd for $C_{26}H_{54}B_2NaO_6^+$ 507.4004, found: 507.3998.

2.47

3-(1,3-dioxolan-2-yl)-1-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-ol (2.47).

Following general procedure C, the crude reaction mixture was purified by silica gel chromatography

(NaOAc-deactivated silica gel; 2:1 pentane:diethyl ether to 1:1 pentane:diethyl ether, Seebach stain) to

yield the hydroxyboronate as a colorless, crystalline white solid in 54% yield (18.0 mg) and >98:2

anti:syn diastereomeric ratio. **^{1}H NMR** (CDCl$_3$, 600 MHz): δ 7.38 (d, J = 7.2 Hz, 2H), 7.30 (t, J = 7.8

Hz, 2H), 7.22 (t, J = 7.2 Hz, 1H), 4.99 (t, J = 4.1 Hz, 1H), 4.75 (d, 1H, J = 8.0 Hz), 3.94-3.99 (m, 2H),

3.81-3.86 (m, 2H), 2.72 (s, 1H), 2.03 (dt, J = 14.2, 4.2 Hz, 1H), 1.95 (ddd, J = 14.1, 9.7, 4.3 Hz, 1H),

1.73 (ddd, J = 9.7, 8.1, 4.6 Hz, 1H), 1.10 (s, 6H), 1.01 (s, 6H). **^{13}C NMR** (CDCl$_3$, 151 MHz): δ 143.9,
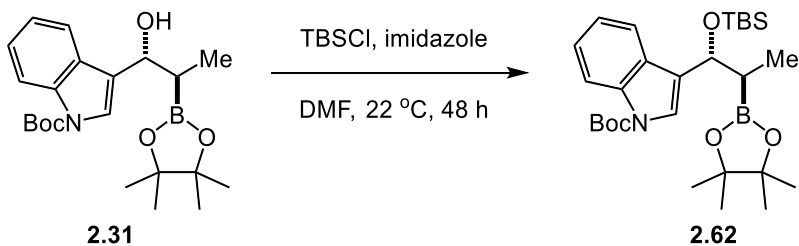
128.3, 127.6, 126.9, 104.2, 83.3, 75.2, 65.1, 65.0, 31.8, 24.9, 24.7. **IR** (ν/cm^{-1}): 3468 (s, br), 2977 (m),

2926 (m), 2887 (m), 1455 (w), 1378 (s), 1321 (m), 1249 (w), 1212 (w), 1144 (s), 1032 (m). **HRMS**

(ESI+) [2M+Na]$^+$ calcd for C$_{36}$H$_{54}$B$_2$NaO$_{10}$$^+$ 691.3801, found: 691.3827.
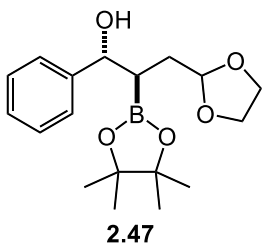
■ **Synthesis of TBS-Protected Hydroxyboronate, 2.62**

Procedure: An 8-mL vial containing hydroxyboronate **2.31** (21.6 mg, 0.0538 mmol) was charged with

imidazole (9.9 mg, 0.145 mmol) and *tert*-butyldimethylchlorosilane (16.3 mg, 0.108 mmol) and then

sealed with a septa-lined cap. Anhydrous DMF (0.360 mL) was added under N$_2$ and the reaction was

purged for 10 minutes and allowed to stir at ambient temperature for 48 hours. The reaction was quenched by the addition of 1.5 mL of a saturated aqueous solution of NH$_4$Cl and the aqueous layer extracted three times with ethyl acetate. The combined organic extracts were washed twice with a saturated aqueous solution of NaHCO$_3$ and once with brine. The organic extract was dried over MgSO$_4$ and concentrated *in vacuo*. The crude reaction mixture was purified by silica gel chromatography (NaOAc deactivated silica gel; 25:1 pentane:diethyl ether, Seebach Stain) to yield the TBS-protected hydroxyboronate in 77% yield (21.3 mg) as a colorless oil in 99:1 *anti*:*syn* diastereoselectivity. **^{1}H NMR** (600 MHz, CDCl$_3$) δ 8.09 (s, 1H), 7.76 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.42 (s, 1H), 7.31 – 7.23 (m, 1H), 7.18 (ddd, *J* = 8.0, 7.2, 1.1 Hz, 1H), 4.91 (d, *J* = 9.3 Hz, 1H), 1.73 (dq, *J* = 9.3, 7.2 Hz, 1H), 4.94 (d, *J* = 9.3 Hz, 1H), 1.65 (s, 9H), 1.11 (d, *J* = 7.3 Hz, 3H), 1.08 (s, 6H), 1.01 (s, 6H), 0.86 (s, 9H), 0.05 (s, 3H), -0.24 (s, 3H). **^{13}C NMR** (151 MHz, CDCl$_3$) δ 149.9, 135.8, 129.0, 125.4, 124.1, 122.4, 122.2, 121.6, 114.9, 83.23, 82.9, 71.1, 28.3, 26.0, 24.7, 24.5, 18.4, 12.6, -4.4, -4.9. **IR** (v/cm^{-1}): 2990 (s), 2922 (m), 2879 (w), 1734 (s), 1446 (s), 1318 (m), 1255 (m), 1159 (s), 1145 (m), 1081 (m), 1011 (m). **HRMS** (ESI$^+$): [M+Na]$^+$ calcd for C$_{28}$H$_{46}$BNO$_5$SiNa$^+$ 538.3137, found: 538.3139.

■ **Arylation of 2.62 with lithiated furan**

2.62 **2.63**
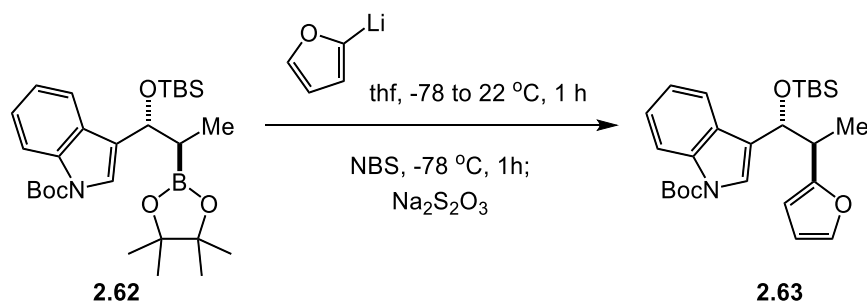
Procedure: 2.62 was prepared according to a literature procedure.[21] A flame-dried 8-mL vial was charged with furan (2.60 μL, 0.0363 mmol) and anhydrous thf (0.120 mL). The reaction was allowed to cool to -78 ˚C (dry-ice/acetone) and then charged with *n*-butyllithium (21.7 μL, 0.0363 mmol, 1.67

M solution in hexanes). The cooling bath was removed and the reaction was allowed to stir at ambient

temperature for 1 hour. The mixture was allowed to cool back down to -78 °C (dry-ice/acetone) and

then charged with **2.62** as a 0.4 M solution in thf (15.6 mg, 0.0303 mmol) and allowed to stir at that

temperature for 1.5 hour. NBS (6.50 mg, 0.0363 mmol) was then added to the reaction as a 0.3 M

solution in thf. After allowing the reaction to stir for 1.5 hours, 1 mL of a saturated aqueous solution
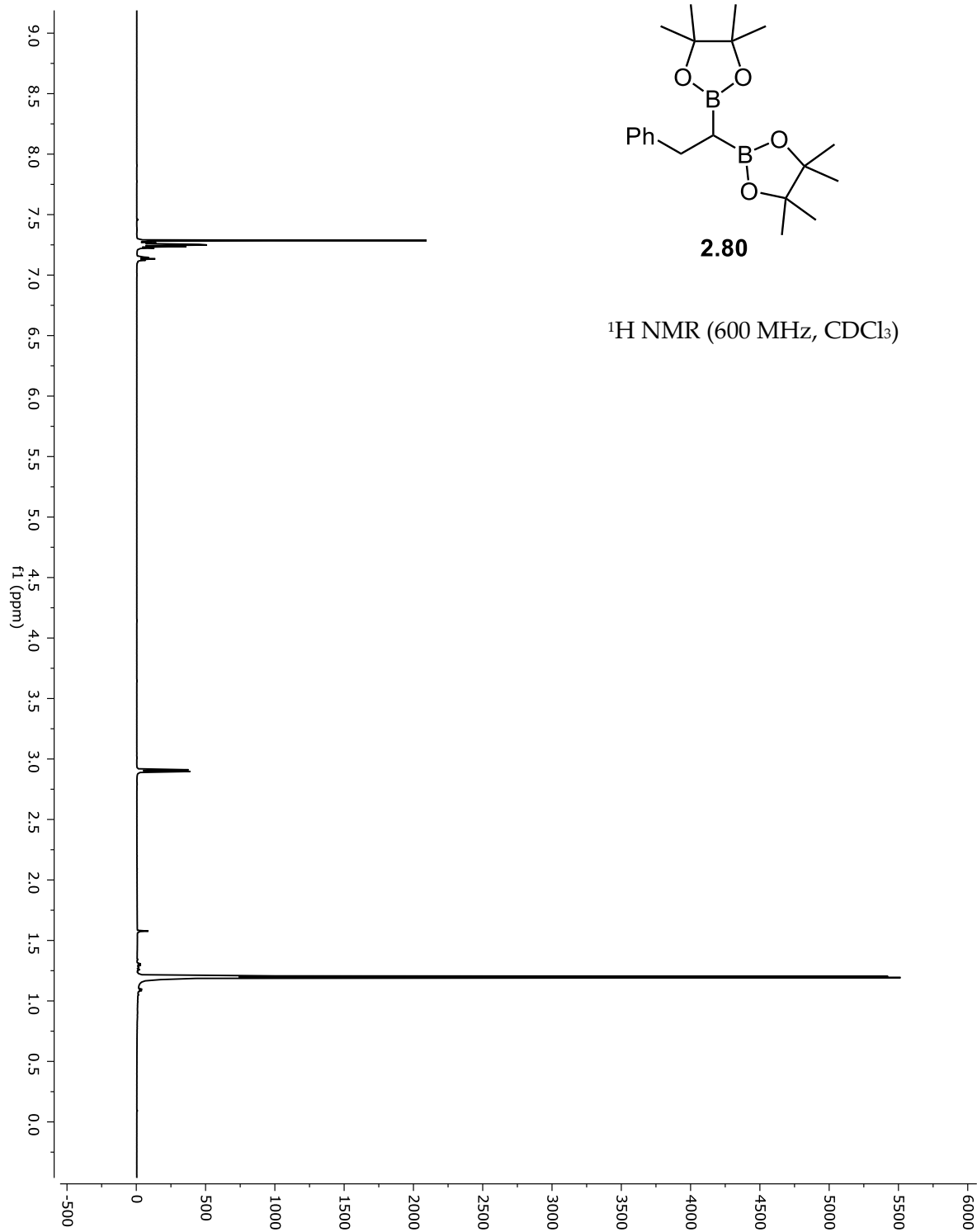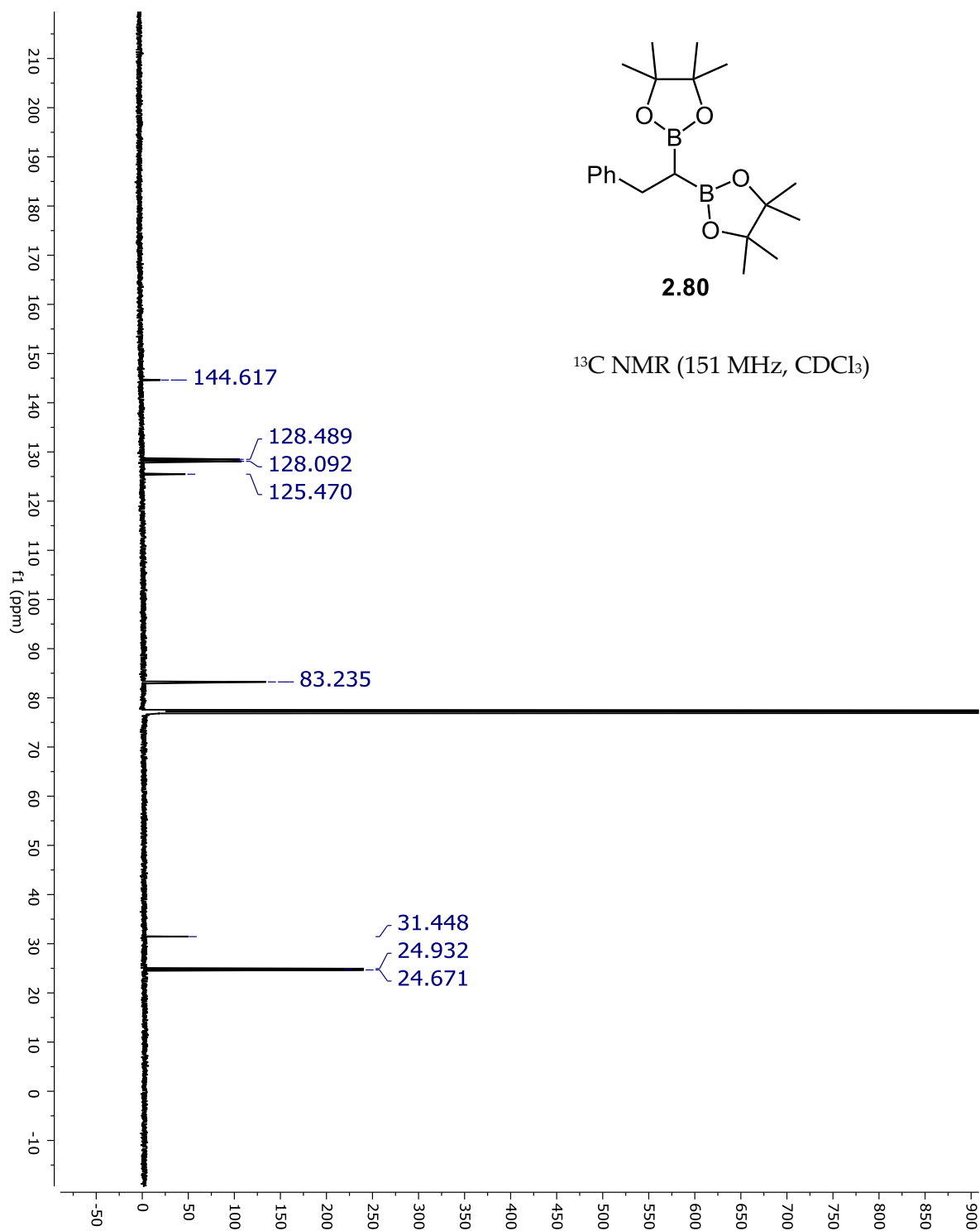
of $Na_2S_2O_3$ was added to the reaction and allowed to stir at ambient temperature for 30 minutes. The

layers were separated and extracted three times with diethyl ether. The combined organic extracts were

dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude reaction mixture was purified by

silica gel chromatography (40:1 pentane:diethyl ether, Seebach stain) to give the product **2.63** as a

colorless oil in 67% yield (9.0 mg) and >99:1 *anti*:*syn* diastereoselectivity as a mixture rotamers

(85:15). 25% of the starting material **2.62** was recovered from the reaction. (^{13}C NMR shows signals

for only one diastereomer, indicating that the ^{1}H NMR contains rotamers). Rotamer 1: **^{1}H NMR** (600

MHz, CDCl$_3$) δ 8.15 (s, 1H), 7.64 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.47 (s, 1H), 7.36 (dd, *J* = 1.9, 0.8 Hz, 1H),

7.33 (ddd, *J* = 8.4, 7.2, 1.2 Hz, 1H), 7.25 (ddd, *J* = 8.1, 7.2, 1.1 Hz, 1H), 6.29 (dd, *J* = 3.2, 1.8 Hz, 1H),

6.03 (dt, *J* = 3.2, 0.9 Hz, 1H), 5.33 (dd, *J* = 3.7, 1.1 Hz, 1H), 3.28 (td, *J* = 7.1, 3.8 Hz, 1H), 1.69 (s, 9H),

1.24 (d, *J* = 7.0 Hz, 3H), 0.88 (s, 9H), -0.20 (s, 3H), -0.20 (s, 3H). Rotamer 2: **^{1}H NMR** (600 MHz,

CDCl$_3$) δ 8.15 (s, 1H), 7.64 – 7.61 (m, 1H), 7.46 (d, *J* = 5.1 Hz, 1H), 7.36 (dd, *J* = 1.9, 0.8 Hz, 1H),

7.33 (ddd, *J* = 8.4, 7.2, 1.2 Hz, 1H), 7.27 – 7.22 (m, 1H), 6.19 (d, *J* = 3.2 Hz, 1H), 5.99 (dd, *J* = 3.3, 1.0

Hz, 1H), 5.31 (dd, *J* = 3.8, 1.2 Hz, 1H), 3.25 (m, 1H), 1.69 (s, 9H), 1.21 (d, *J* = 7.0 Hz, 3H), 0.89 (s,

9H), -0.15 (s, 3H), -0.17 (s, 3H). **^{13}C NMR** (151 MHz, CDCl$_3$) δ 157.8, 140.6, 124.1, 123.6, 123.3,

122.3, 119.9, 115.2, 110.2, 105.9, 100.0, 70.9, 65.9, 40.1, 34.1, 28.2, 25.8, 22.4, 18.2, 15.3, 14.1, 11.5,

-5.0, -5.8. **IR** (v/cm^{-1}): 2990 (s), 2901 (m), 2864 (w), 2525 (s), 2050 (m), 1736 (s), 1439 (s), 1324 (m),

1260 (m), 1148 (s), 1141 (m), 1082 (m), 1011 (m). **HRMS** (ESI$^+$): [M+Na]$^+$ cald for $C_{26}H_{37}NO_4SiNa^+$

478.2384, found: 478.2389.

2.80

^{1}H NMR (600 MHz, CDCl$_3$)

2.80

^{13}C NMR (151 MHz, CDCl$_3$)

144.617

128.489
128.092
125.470

83.235

31.448
24.932
24.671

2.81

^{1}H NMR (600 MHz, CDCl$_3$)

215

2.81

^{13}C NMR (151 MHz, CDCl$_3$)

130.25
128.47
127.12

83.06

25.92
24.97
24.63
24.19
17.97

2.82

^{1}H NMR (600 MHz, CDCl$_3$)

2.82

^{13}C NMR (151 MHz, CDCl$_3$)

83.109

65.199

28.836
26.200
25.055
24.632
18.573

-5.061

2.83

^{1}H NMR (500 MHz, CDCl$_3$)

2.83

^{13}C NMR (101 MHz, CDCl$_3$)

174.285

83.209
79.703

31.864
28.241
24.991
24.595

f1 (ppm)

2.84

¹H NMR (600 MHz, CDCl₃)

221

2.84

^{13}C NMR (151 MHz, CDCl$_3$)

128.473

105.102

83.092

65.115

30.117
24.944
24.720

f1 (ppm)

2.85

^{1}H NMR (400 MHz, CDCl$_3$)

2.85

^{13}C NMR (151 MHz, CDCl$_3$)

82.821

36.009
35.942
26.782
26.339
24.895
24.588

f1 (ppm)

2.51

^{1}H NMR (600 MHz, CDCl$_3$)

2.51

^{13}C NMR (151 MHz, CDCl$_3$)

82.858

27.944
25.615
24.848
24.538
14.210

2.21

^{1}H NMR (600 MHz, CDCl$_3$)

^{13}C NMR (151 MHz, CDCl$_3$)

144.1235

128.1688
127.2341
126.4015

83.4010
75.8836

24.7153

10.7460

2.22

^{1}H NMR (600 MHz, CDCl$_3$)

OH

Me

F

B

O O

2.22

^{13}C NMR (151 MHz, CDCl$_3$)

162.854
161.235

139.915
139.894

128.030
127.976

114.979
114.839

83.470

75.245

24.733
24.697

10.741

f1 (ppm)

2.23

^{1}H NMR (600 MHz, CDCl$_3$)

^{13}C NMR (151 MHz, CDCl$_3$)

2.23

143.085

131.181
128.130
120.856

83.572
74.982

24.778
24.731

10.294

¹H NMR (600 MHz, CDCl₃)

233

^{13}C NMR (151 MHz, CDCl$_3$)

158.819

136.498
127.609

113.514

83.328
75.650

55.378

24.717
24.692

11.086

f1 (ppm)

2.24

2.25

^{1}H NMR (600 MHz, CDCl$_3$)

2.25

^{13}C NMR (151 MHz, CDCl$_3$)

144.106
137.643
128.080
127.934
127.091
123.461

83.358
75.983

24.711
21.585
10.897

2.26

^{1}H NMR (600 MHz, CDCl$_3$)

^{13}C NMR (151 MHz, CDCl$_3$)

148.195
146.252
132.559
129.030
122.132
121.414
83.843
74.552
24.844
24.754
10.010

f1 (ppm)

^{1}H NMR (600 MHz, CDCl$_3$)

2.27

OH
Me
B
O   O
CF₃

2.27

¹³C NMR (151 MHz, CDCl₃)

145.009

129.699
128.481
123.898
123.860
123.217
123.179

83.536
75.109

24.611

10.352

240

Me OH
Me

B
O O

2.28

^{1}H NMR (600 MHz, CDCl$_3$)

241

2.28

^{13}C NMR (151 MHz, CDCl$_3$)

141.962
134.867
130.355
127.117
126.403
125.928

83.325

71.998

24.671
24.560
19.442
10.941

f1 (ppm)

^{1}H NMR (600 MHz, CDCl$_3$)

2.29

243

13C NMR (151 MHz, CDCl₃)

2.29

156.629
141.437
110.033
106.405
83.457
70.142
24.685
24.640
11.330

2.30

^{1}H NMR (600 MHz, CDCl$_3$)

2.30

^{13}C NMR (151 MHz, CDCl$_3$)

148.540
148.253
139.354
134.093
123.236

83.673

73.472

24.781
24.701

10.354

f1 (ppm)

2.31

^{1}H NMR (600 MHz, CDCl$_3$)

2.31

^{13}C NMR (151 MHz, CDCl$_3$)
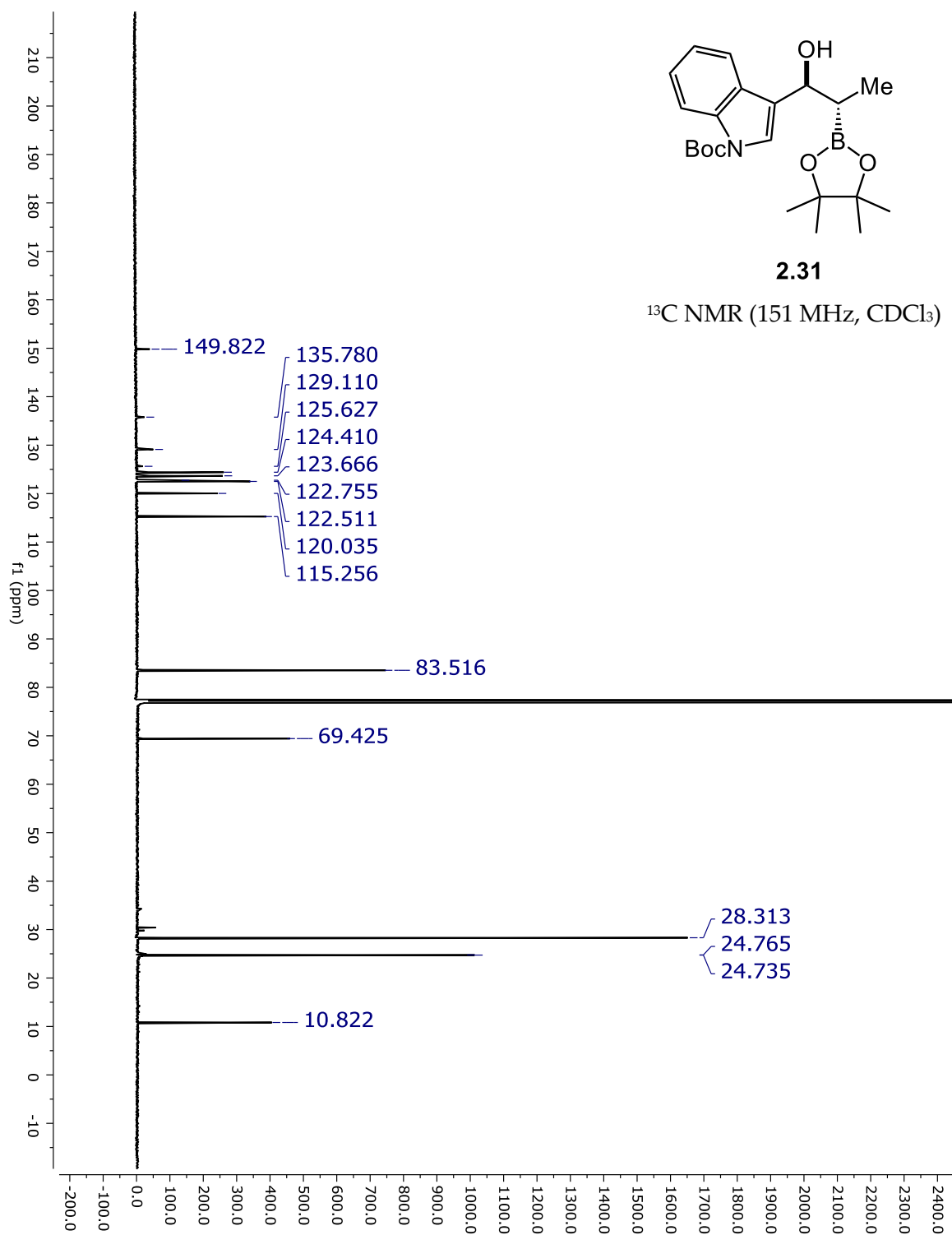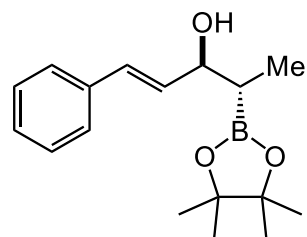
149.822

135.780
129.110
125.627
124.410
123.666
122.755
122.511
120.035
115.256

83.516

69.425

28.313
24.765
24.735

10.822

f1 (ppm)

2.32

^{1}H NMR (600 MHz, CDCl$_3$)

249

2.32

¹³C NMR (151 MHz, CDCl₃)

136.993
136.964
132.527
131.681
130.266
130.157
128.517
127.409
126.451
126.425

83.479
83.427
75.845
74.984

30.325
29.730
24.852
24.827
24.746
24.663
24.630

12.067
11.039

2.33

¹H NMR (600 MHz, CDCl₃)

2.33

^{13}C NMR (151 MHz, CDCl$_3$)

- 135.495
- 133.209
- 132.975
- 132.357
- 128.966
- 128.835
- 128.765
- 128.685
- 127.638
- 127.605
- 125.543

- 83.529
- 83.469
- 75.647
- 74.765

- 24.855
- 24.819
- 24.742
- 24.650

- 12.088
- 10.985
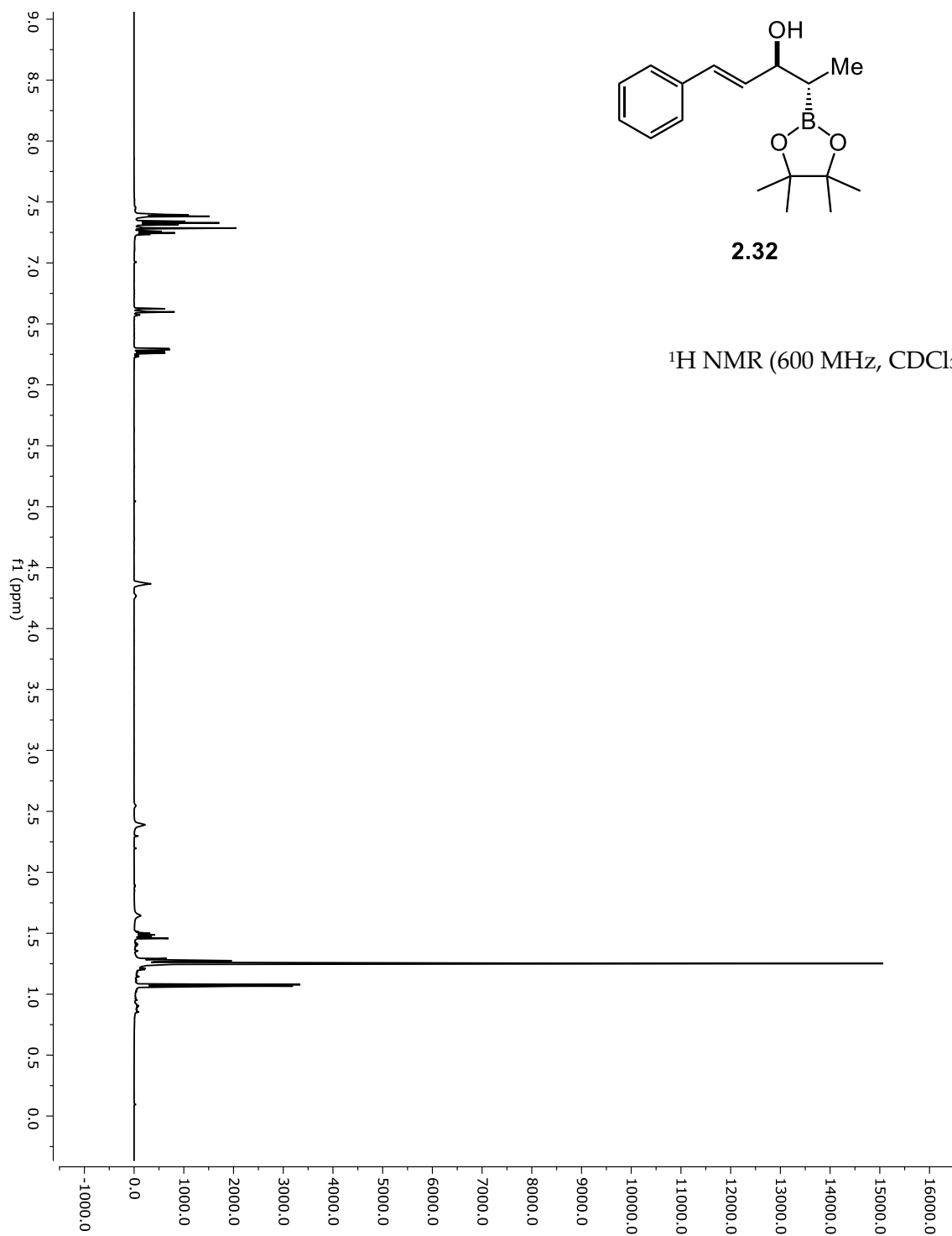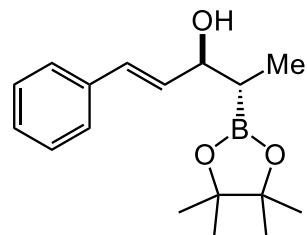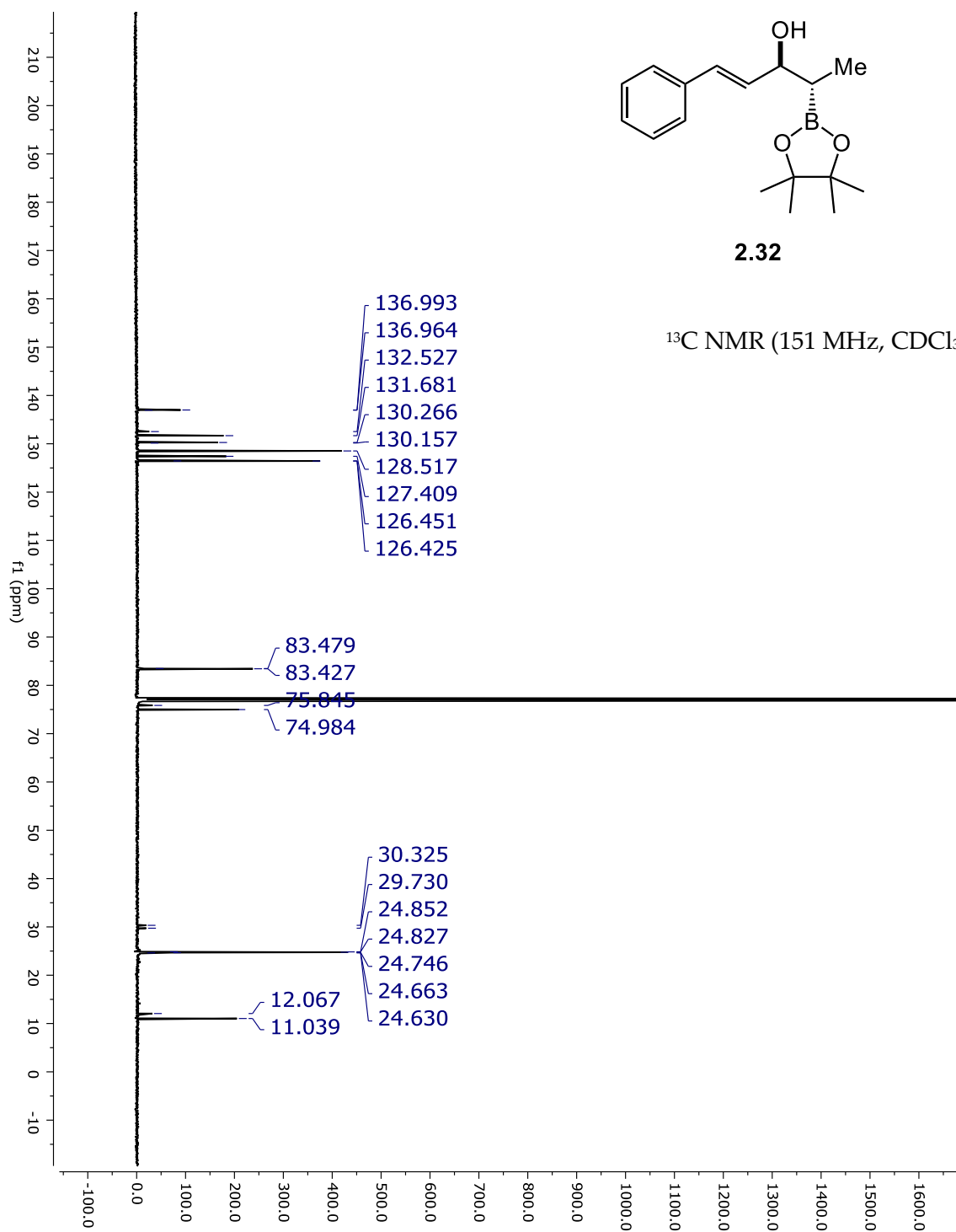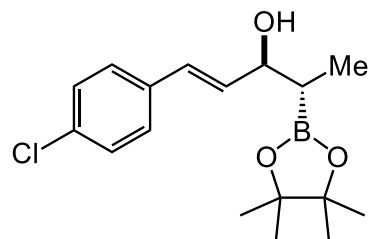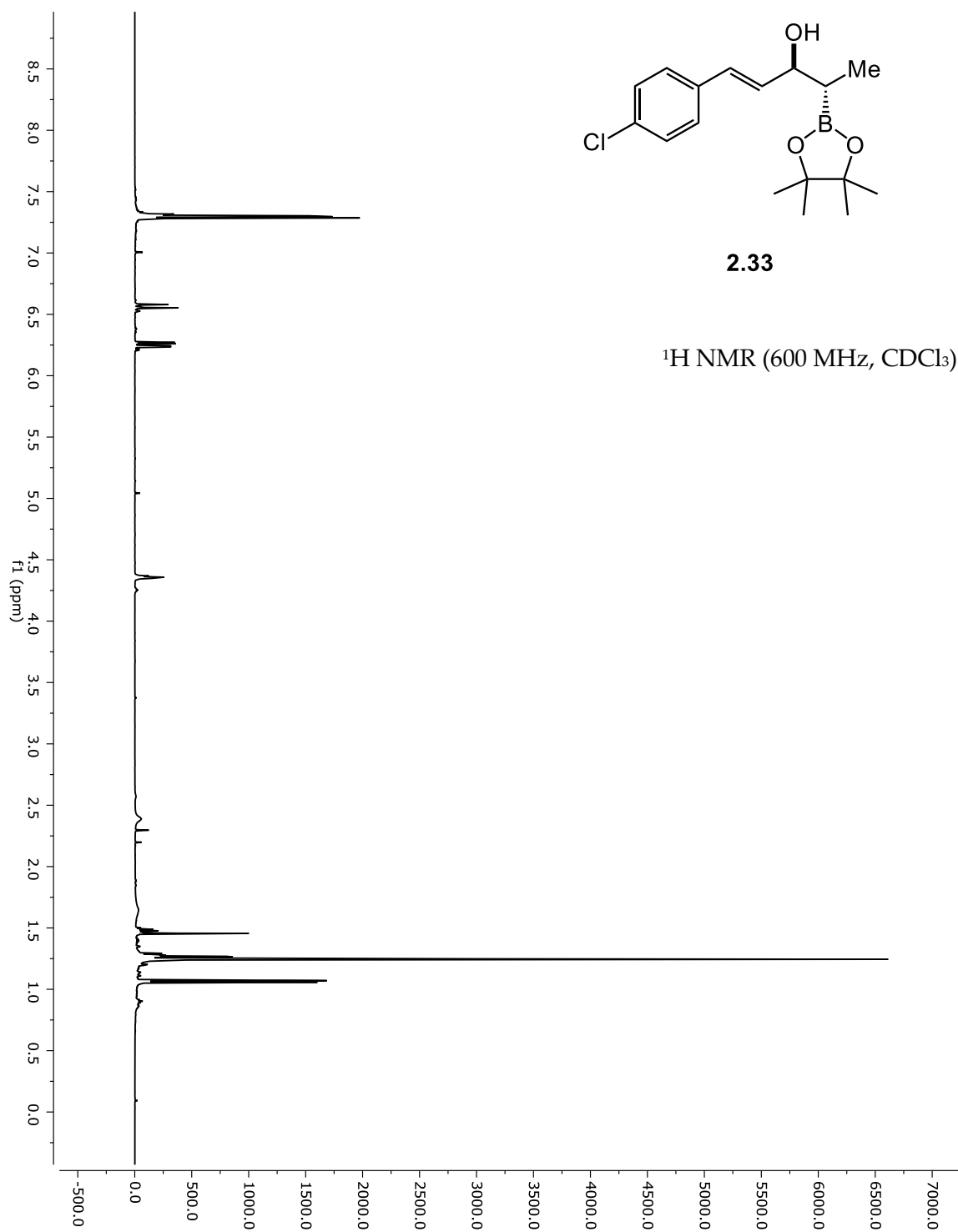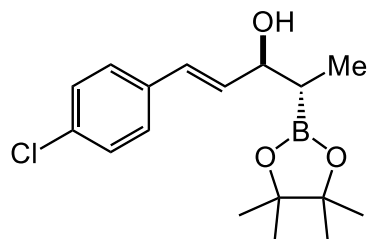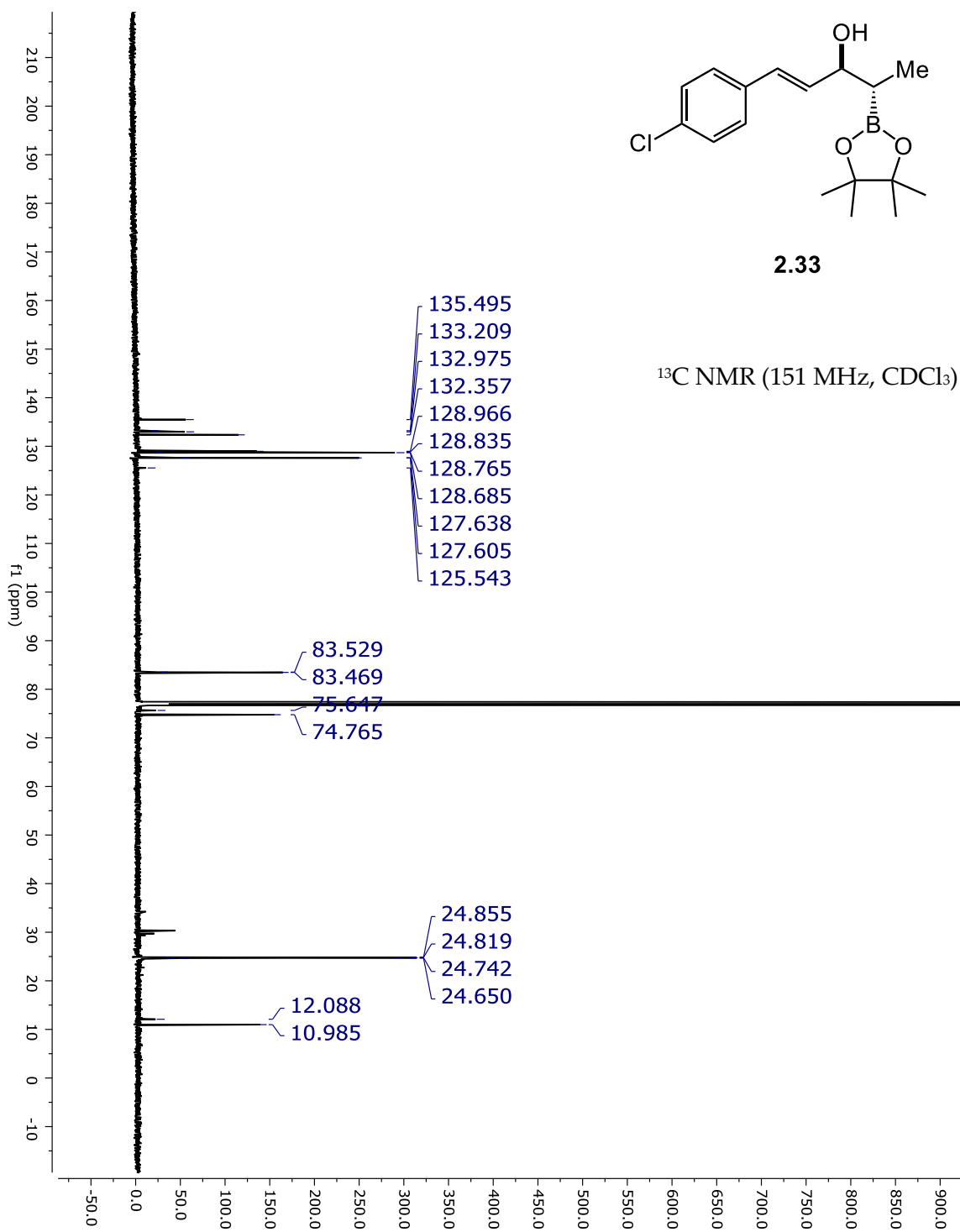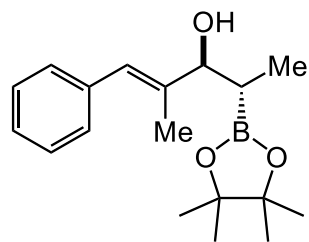
2.34

^{1}H NMR (600 MHz, CDCl$_3$)

2.34

^{13}C NMR (151 MHz, CDCl$_3$)

139.757
137.929
129.140
128.134
126.329
125.622

83.430
79.063

24.884
24.844
14.177
10.539

f1 (ppm)

OH

Ph

B

O   O

2.35

¹H NMR (600 MHz, CDCl₃)

2.35

^{13}C NMR (151 MHz, CDCl$_3$)

144.747
143.763
141.554
141.114

128.950
128.305
128.146
126.672
125.892

83.501
83.230
75.052
75.009

34.372
33.886
24.775
24.582
24.542

OH   Me

Me

B

O   O

2.36

¹H NMR (600 MHz, CDCl₃)

^{13}C NMR (151 MHz, CDCl$_3$)

144.792
144.018

132.19
132.09
128.186
128.174
127.448
127.163
126.656
126.067
123.866
123.349

83.430
83.164
75.709
75.555

27.018
26.426
25.848
25.814
24.863
24.629
24.534
24.503
17.892
17.858

f1 (ppm)

2.37

^{1}H NMR (600 MHz, CDCl$_3$)

¹³C NMR (151 MHz, CDCl₃)

144.299
128.163
128.102
127.226
126.788
126.176
83.144
75.435
63.663
31.064
26.007
25.979
24.651
24.480
18.377
-5.347
-5.360

2.38

^{1}H NMR (600 MHz, CDCl$_3$)

^{13}C NMR (151 MHz, CDCl$_3$)

144.284

128.287
127.519
126.738

83.285
75.805

29.963
24.797
24.688
22.687
14.623

f1 (ppm)

2.39

¹H NMR (600 MHz, CDCl₃)

^{13}C NMR (151 MHz, CDCl$_3$)

174.055
173.060

143.661

128.301
128.185
127.449
126.336
126.209

83.715
83.529
80.452
80.372
74.965
74.272

33.919
32.688
30.322
29.955
28.113
28.086
28.067
24.877
24.800
24.783
24.723
24.594

2.39

f1 (ppm)

2.41

^{1}H NMR (600 MHz, CDCl$_3$)

2.41

^{13}C NMR (151 MHz, CDCl$_3$)

83.364

41.125

29.678
28.610
26.585
26.524
26.276
24.846
24.825
24.725

9.161

2.42

^{1}H NMR (600 MHz, CDCl$_3$)

2.42

^{13}C NMR (151 MHz, CDCl$_3$)

132.038
131.875
124.467
124.112

83.404
83.317
78.173

44.099
42.442

30.305
29.948
28.457
27.651
27.364
26.715
26.664
26.641
26.588
26.405
25.956
25.938
25.913
25.318
25.026
24.931
24.803
24.742
18.009
17.990

f1 (ppm)

2.43

¹H NMR (600 MHz, CDCl₃)

2.43

^{13}C NMR (151 MHz, CDCl$_3$)

142.036

128.941
128.110
125.706

83.246

42.272
32.604
30.141
27.302
26.554
26.463
26.204
24.728
24.674

f1 (ppm)

270

2.44

^{1}H NMR (600 MHz, CDCl$_3$)

2.44

^{13}C NMR (151 MHz, CDCl$_3$)

104.385

83.346

65.041
65.001

32.196
30.527
24.931
24.894
24.855
20.119
17.129

272

2.45

^{1}H NMR (600 MHz, CDCl$_3$)

2.45

^{13}C NMR (151 MHz, CDCl$_3$)

43.686
42.225
33.235
31.776
30.071
29.989
29.279
28.635
27.934
26.665
26.637
26.564
26.413
26.359
26.329
26.249
26.124
26.098
24.962
24.944
24.863
24.847
18.491
18.477

83.413
83.282

63.490
62.874

-5.066
-5.106
-5.132
-5.205

2.46

^{1}H NMR (600 MHz, CDCl$_3$)

^{13}C NMR (151 MHz, CDCl$_3$)

2.46

83.096
79.826
35.953
26.576
24.725
24.688
11.902

2.47

^{1}H NMR (600 MHz, CDCl$_3$)

^{13}C NMR (151 MHz, CDCl$_3$)

143.770

128.189
127.435
126.742

104.051

83.169
75.082

64.948
64.874

31.631
24.733
24.565

2.62

^{1}H NMR (400 MHz, CDCl$_3$)

2.62

^{13}C NMR (101 MHz, CDCl$_3$)

149.930

129.000
125.405
124.119
122.417
122.254
121.549
114.937

82.926

71.101

28.307
25.986
24.708
24.514
18.373
12.580

-4.391
-4.894

2.63

^{13}C NMR (151 MHz, CDCl$_3$)

157.9028

140.7410

124.2431
123.7190
123.4091
122.4266
119.9854
115.3023
110.2537
105.9523

71.0092

65.9960

40.2116
34.2400
30.4183
28.3158
25.8742
22.4671
18.2983
15.4020
14.1985
11.6258

-4.9536
-5.7190

f1 (ppm)

282

2.48

^{1}H NMR (500 MHz, thf-d_8)

1.719

1.190
1.052
1.033
0.999
0.975
0.966
0.880
0.870
0.865
0.855
0.817
0.803
0.789

0.178
0.175
0.165
0.154
0.147
0.133
0.126
0.121
0.113
0.105
-0.144
-0.159
-0.173

2.48

^{11}B NMR (161 MHz, thf-d_8)

35.98

6.07

f1 (ppm)

■ ¹H and ¹¹B NMR Experiments
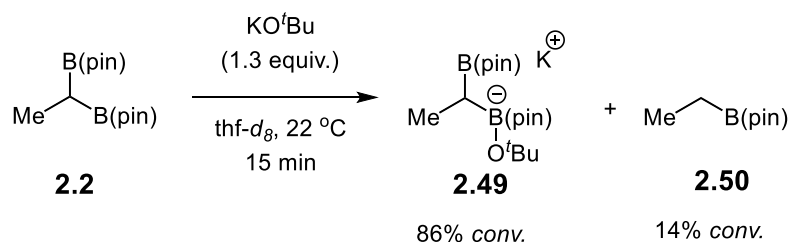
Procedure: In an N_2-filled glove box, a screw-cap NMR tube was charged with KO*t*-Bu (7.3 mg, 0.065 mmol) and diborylethane, **2.2** (14.8 µL, 0.0500 mmol), followed by 0.8 mL of tetrahydrofuran-d_8. The tube was capped and sealed with Teflon tape and removed from the glove box. ¹H and ¹¹B NMR spectra were obtained after 15 minutes of reacting at ambient temperature and at 45 min, 60 min, and 18 hour time points.

Amount of protodeboronation over time at 22 °C

Time (min)	Conv. (%) 18:19
15	86:14
45	70:30
60	63:37
1080	24:76

2.49
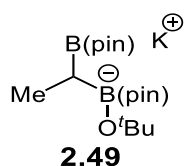
After 15 minutes: **¹H NMR** (400 MHz, thf-d_8): δ 1.18 (s, 9H), 1.11 (s, 12H), 1.08 (s, 12H), 0.83 (d, J = 7.5 Hz, 3H), -0.01 (qu, J = 7.5 Hz, 1H). **¹¹B NMR** (151 MHz, thf-d_8): δ 36.2 (s), 7.8 (s).

Me⌃B(pin)
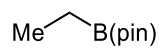
2.50

After 15 minutes: ^{1}**H NMR** (400 MHz, thf-d_8): δ 1.01 (s, 12H), 0.77 (t, J = 7.8 Hz, 3H), 0.13 (qu, J = 7.8 Hz, 2H). ^{11}**B NMR** (151 MHz, thf-d_8): δ 36.2 (s).
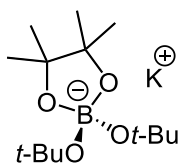
2.86

After 15 minutes: ^{11}**B NMR** (151 MHz, thf-d_8): δ 4.9[17]
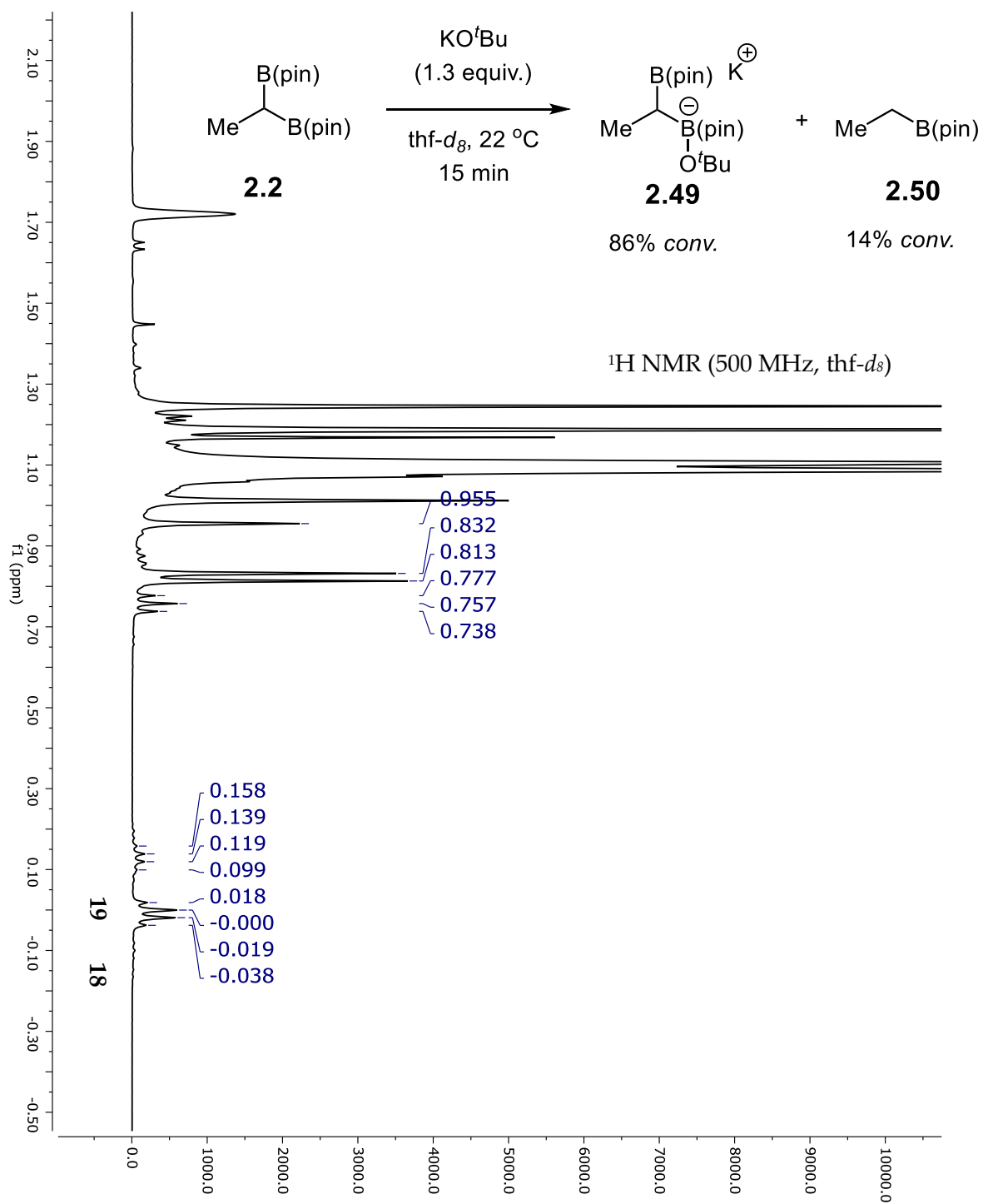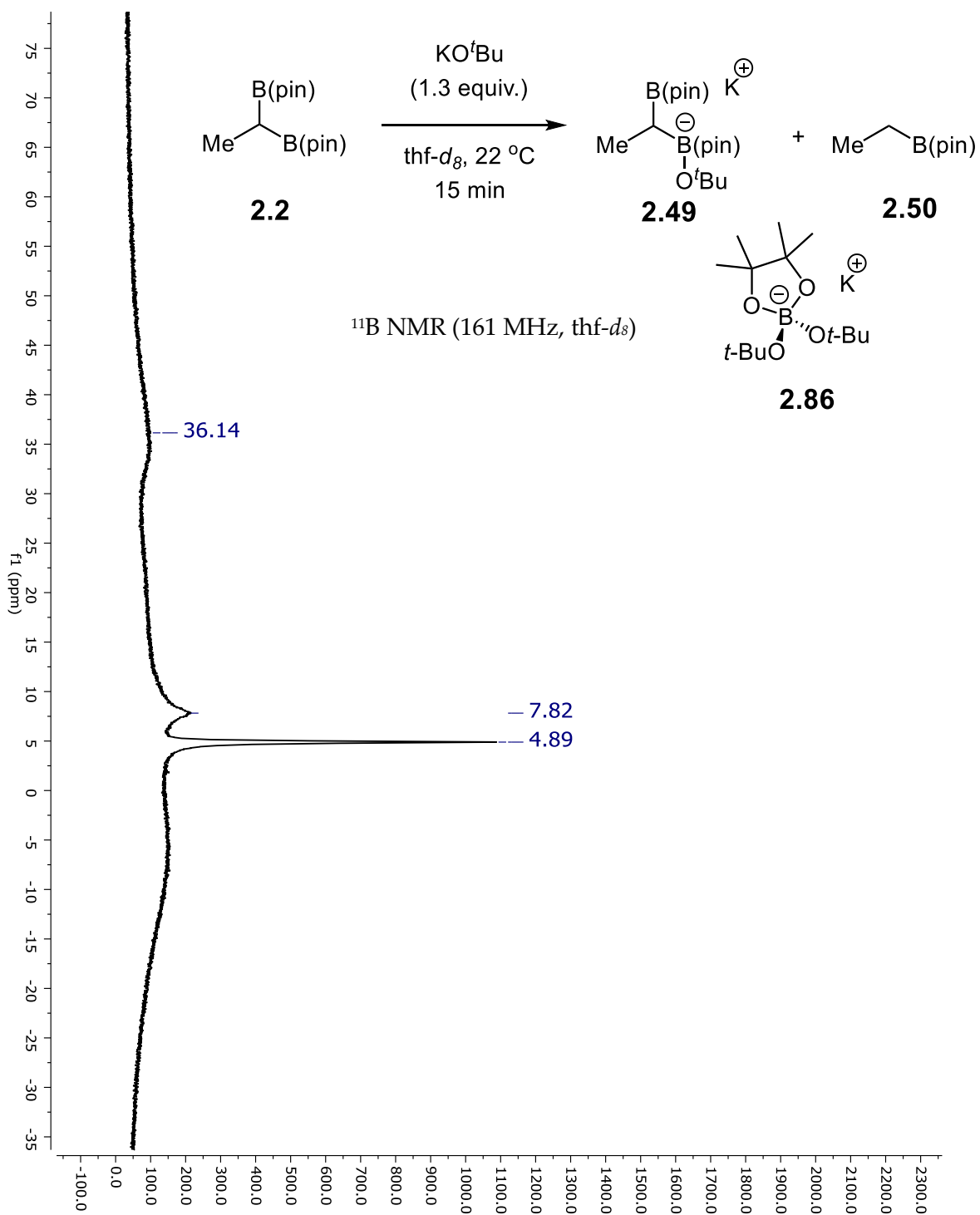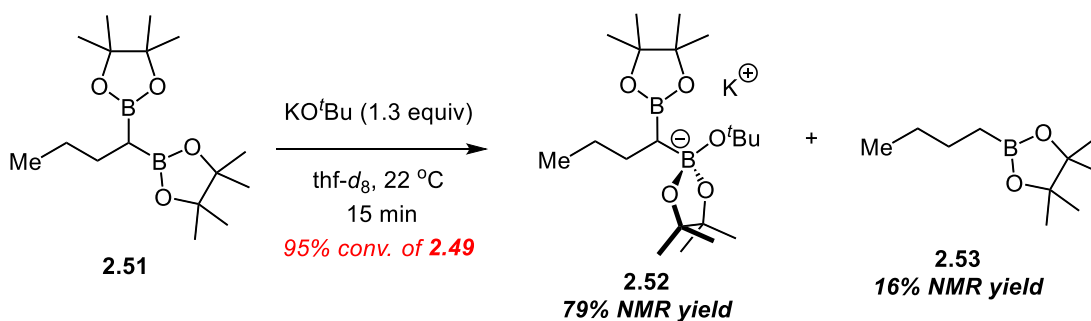
286

KO^{t}Bu
(1.3 equiv.)

thf-d_8, 22 °C
15 min

B(pin)

Me   B(pin)

2.2

B(pin) K$^{\oplus}$

Me   B(pin)$^{\ominus}$
         O^{t}Bu

2.49

86% *conv.*

+

Me   B(pin)

2.50

14% *conv.*

^{1}H NMR (500 MHz, thf-d_8)

0.955
0.832
0.813
0.777
0.757
0.738

0.158
0.139
0.119
0.099
0.018
-0.000
-0.019
-0.038

19

18

2.10
1.90
1.70
1.50
1.30
1.10
0.90
0.70
0.50
0.30
0.10
-0.10
-0.30
-0.50

f1 (ppm)

0.0
1000.0
2000.0
3000.0
4000.0
5000.0
6000.0
7000.0
8000.0
9000.0
10000.0

Procedure: In an N_2-filled glove box, a screw-cap NMR tube was charged with KOt-Bu (7.3 mg, 0.065 mmol) and diborylbutane, **2.51** (15.5 mg, 0.0500 mmol), followed by 0.8 mL of tetrahydrofuran-d_8. The tube was capped and sealed with Teflon tape and removed from the glove box. ^{1}H and ^{11}B NMR spectra were obtained after 15 minutes of reacting at ambient temperature and at 45 min, 60 min, and 14 hour time points.

2.52
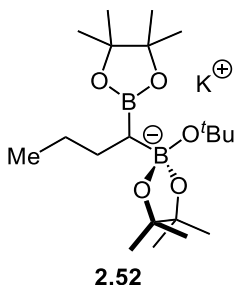
After 15 minutes: ^{1}**H NMR** (500 MHz, thf-d_8): δ -0.02 (t, J = 7.6 Hz, 1H). ^{11}**B NMR** (161 MHz, thf-d_8): δ 36.76 (s), δ 7.66 (s)

2.53
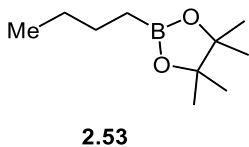
After 15 minutes: ^{1}**H NMR** (500 MHz, thf-d_8) δ 0.19 – 0.13 (m, 2H). ^{11}**B NMR** (161 MHz, thf-d_8): δ 36.76 (s)

KO^{t}Bu (1.3 equiv)

thf-d_8, 22 °C
15 min
95% conv. of 2.49

^{1}H NMR (500 MHz, thf-d_8)

2.51

2.52

+

2.53

1.44
1.42
1.41
1.28
1.28
1.24
1.24
1.22
1.19
1.19
1.17
1.16
1.14
1.13
1.12
1.10
1.09
1.08
1.08
1.07
1.05
1.05
1.03
0.96
0.96
0.86
0.85
0.84
0.84
0.83
0.82
0.81
0.80
0.79
0.79
0.78
0.77
0.18
0.17
0.16
0.15
-0.01
-0.02
-0.04

KO^{t}Bu (1.3 equiv)

thf-d_8, 22 °C
15 min
95% conv. of 2.49

2.51

2.52

+

2.53

^{11}B NMR (161 MHz, thf-d_8)
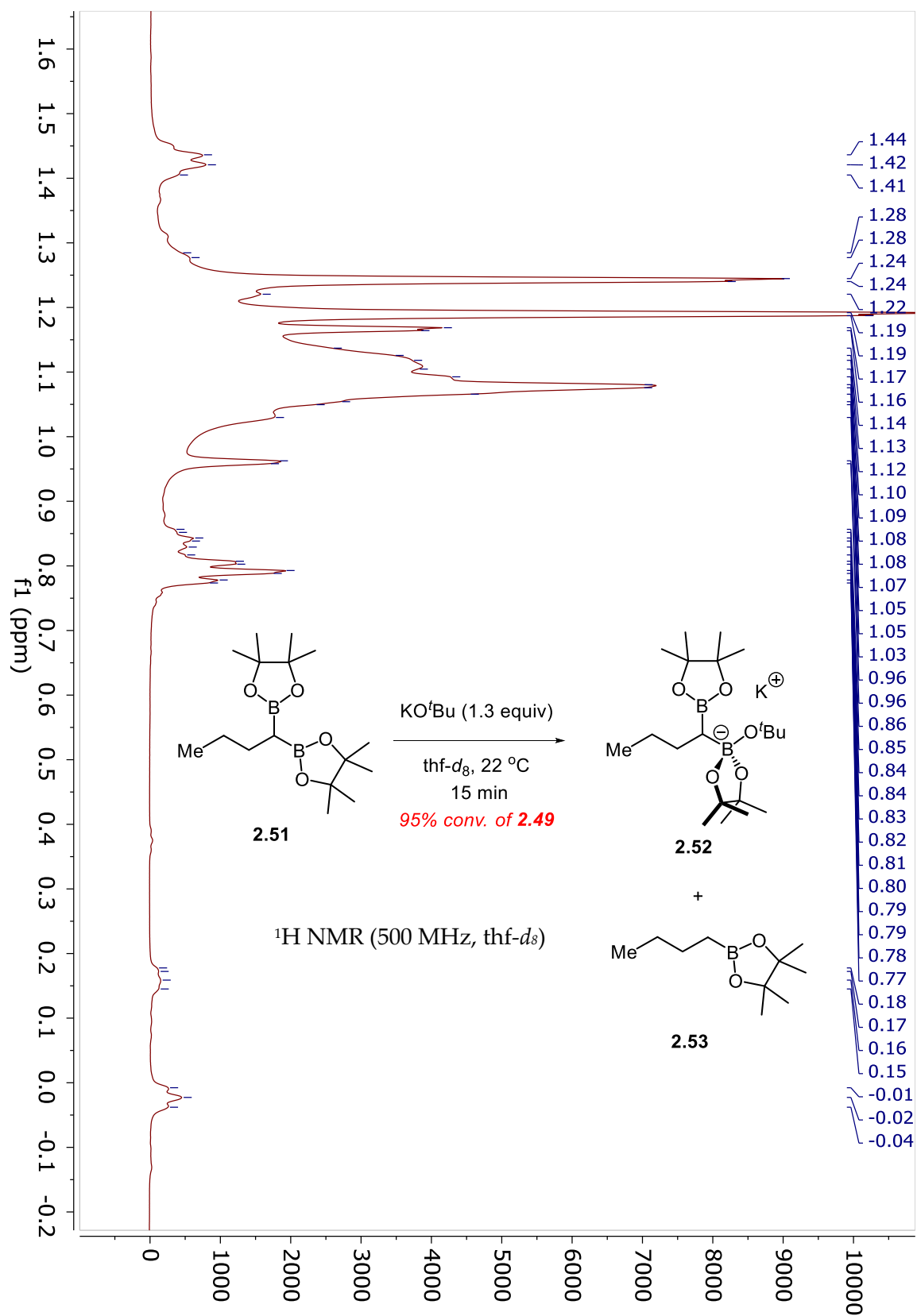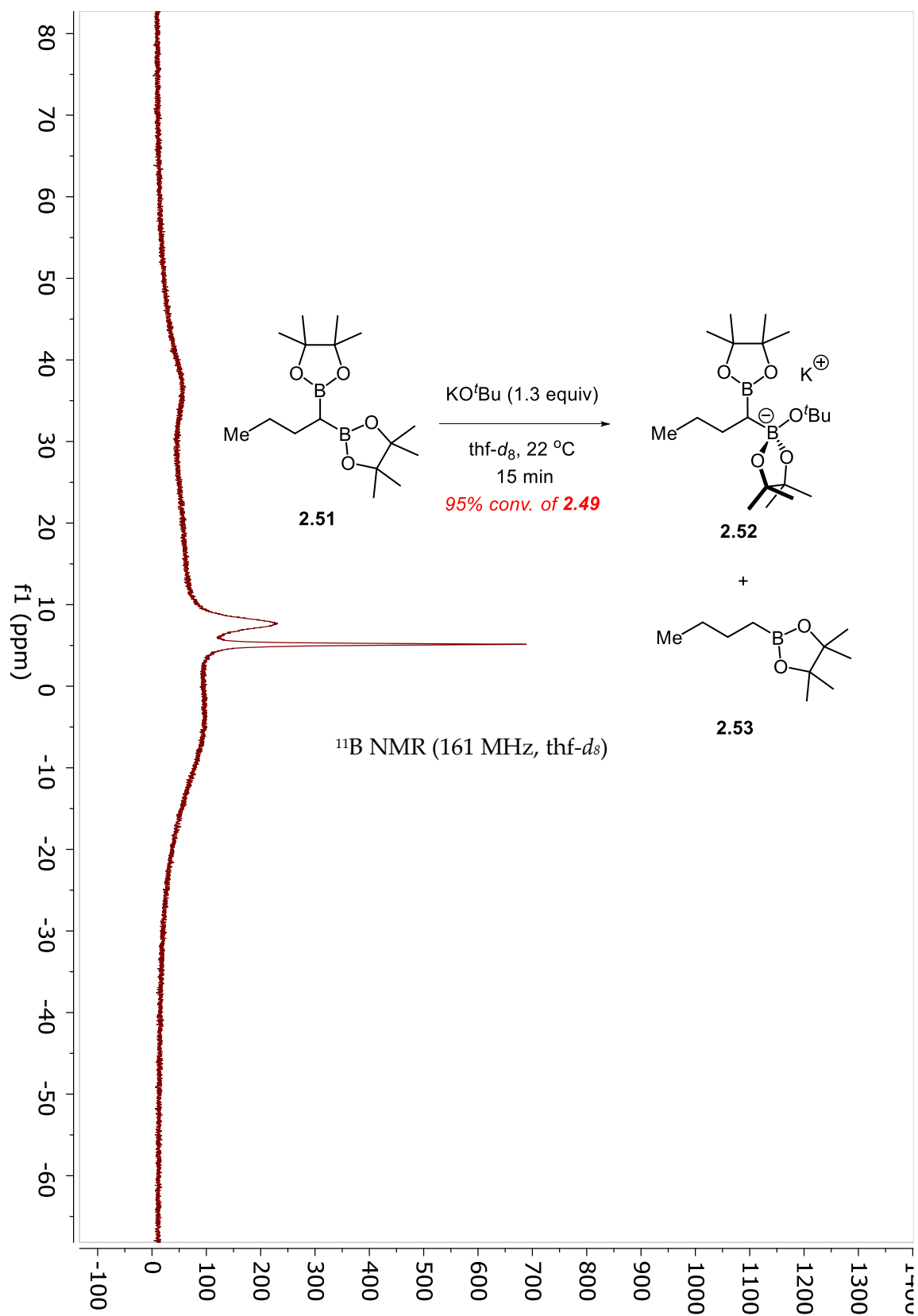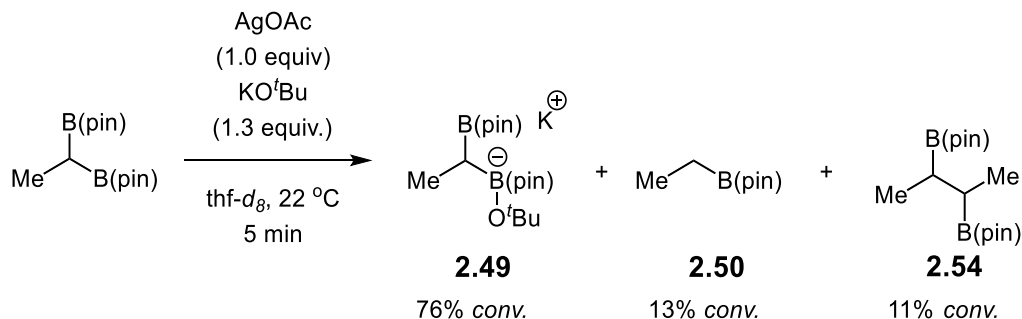
Procedure: In an N_2-filled glove box, a screw-cap NMR tube was charged with KO*t*-Bu (14.6 mg, 0.130 mmol) and AgOAc (16.7 mg, 0.100 mmol), followed by diborylethane, **2.2** (29.7 µL, 0.100 mmol) dissolved in 0.8 mL of tetrahydrofuran-d_8. The tube was capped and sealed with Teflon tape and removed from the glove box. ^{1}H and ^{11}B NMR spectra were obtained after 5 minutes of reacting at ambient temperature and at 15 and 35 min time points.

Amount of protodeboronation and homocoupling over time at 22 ⁰C

Time (min)	Conv. (%) 18:19:20
5	76:13:11
15	69:13:18
35	67:16:17

20
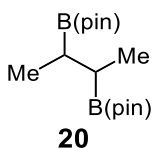
After 5 minutes: **^{1}H NMR** (500 MHz, thf-d_8): δ 1.37 (app tr, *J* = 7.0 Hz, 6H), 1.12 (app s, 24H), 0.45 (m, 2H). **^{11}B NMR** (151 MHz, thf-d_8): δ 36.2 (s).

Me

AgOAc
(1.0 equiv)
KO^{t}Bu
(1.3 equiv.)

thf-d_8, 22 °C
5 min

B(pin)

Me   B(pin)

B(pin)

Me   Me

B(pin)
2.54

B(pin) K$^{\oplus}$

Me   B(pin)$^{\ominus}$

O^{t}Bu

2.49

Me   B(pin)

2.50

^{1}H NMR (500 MHz, thf-d_8)

1.386
1.372
1.358

1.166

0.954

0.825
0.810
0.775
0.759
0.744

0.484
0.470
0.457
0.445
0.432
0.418

0.146
0.131
0.116
0.100

0.008
-0.007
-0.022
-0.037

293

AgOAc
(1.0 equiv)
KO^{t}Bu
(1.3 equiv.)

thf-d_8, 22 °C
5 min

B(pin)

Me — B(pin)

B(pin)

Me

Me

B(pin)

2.54

B(pin) K$^{\oplus}$

Me

B(pin)$^{\ominus}$

O^{t}Bu

2.49

Me — B(pin)

2.50

^{11}B NMR (161 MHz, thf-d_8)

— 36.16

— 7.81

— 4.91

f1 (ppm)

2.48   **2.54**   **2.61**

22 % conv.   *13 % conv.*
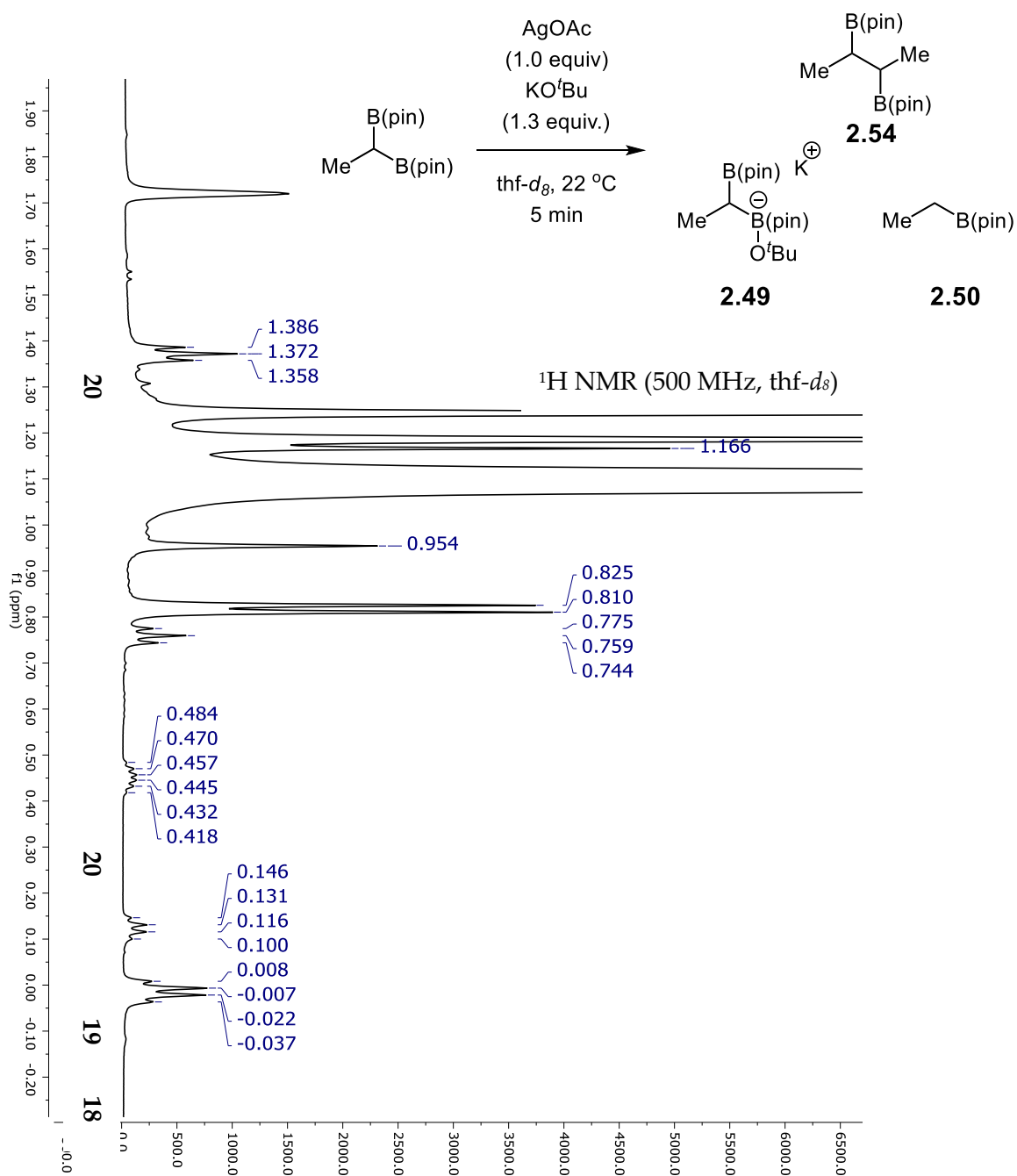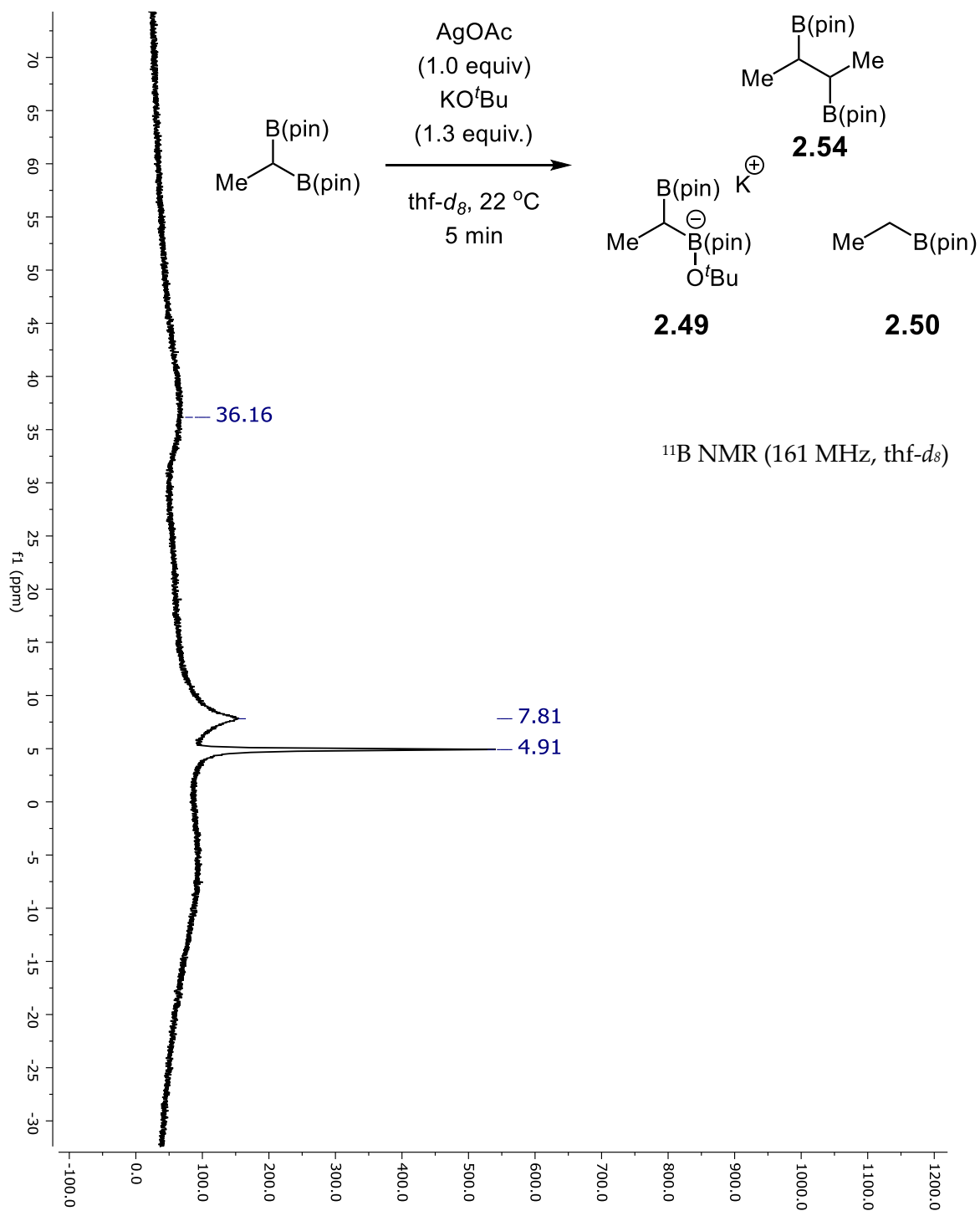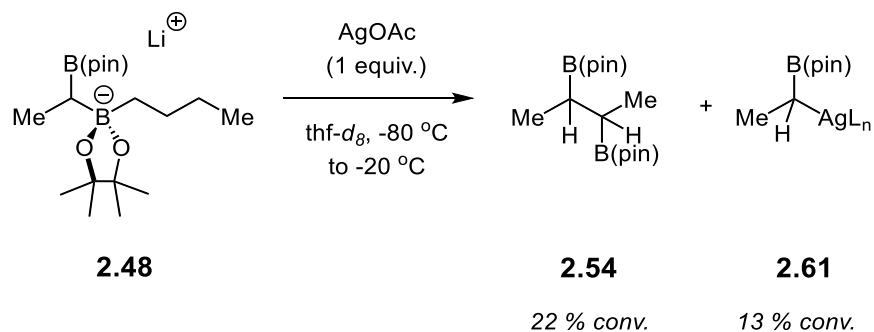
Procedure: In an N$_2$-filled glove box, a screw-cap NMR tube was charged with borate **2.48** (17.3 mg, 0.0500 mmol) and AgOAc (8.3 mg, 0.050 mmol). The tube was capped and sealed with Teflon tape and removed from the glove box. The tube was allowed to cool to -78 ˚C and a cold solution of tetrahydrofuran-d_8 was syringed into the NMR tube under N$_2$. The tube was inverted twice and ^{1}H and ^{11}B NMR spectra were recorded from -80 ˚C to -20 ˚C in 10 degree intervals. (conversions in the reaction scheme were calculated at -20 ˚C).
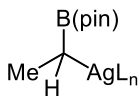
At -20 ˚C: **^{1}H NMR** (500 MHz, thf-d_8): δ -0.45 (q, J = 8.0 Hz, 1H)

^{1}H NMR (500 MHz, thf-d_8)

^{11}B NMR (161 MHz, thf-d_8)
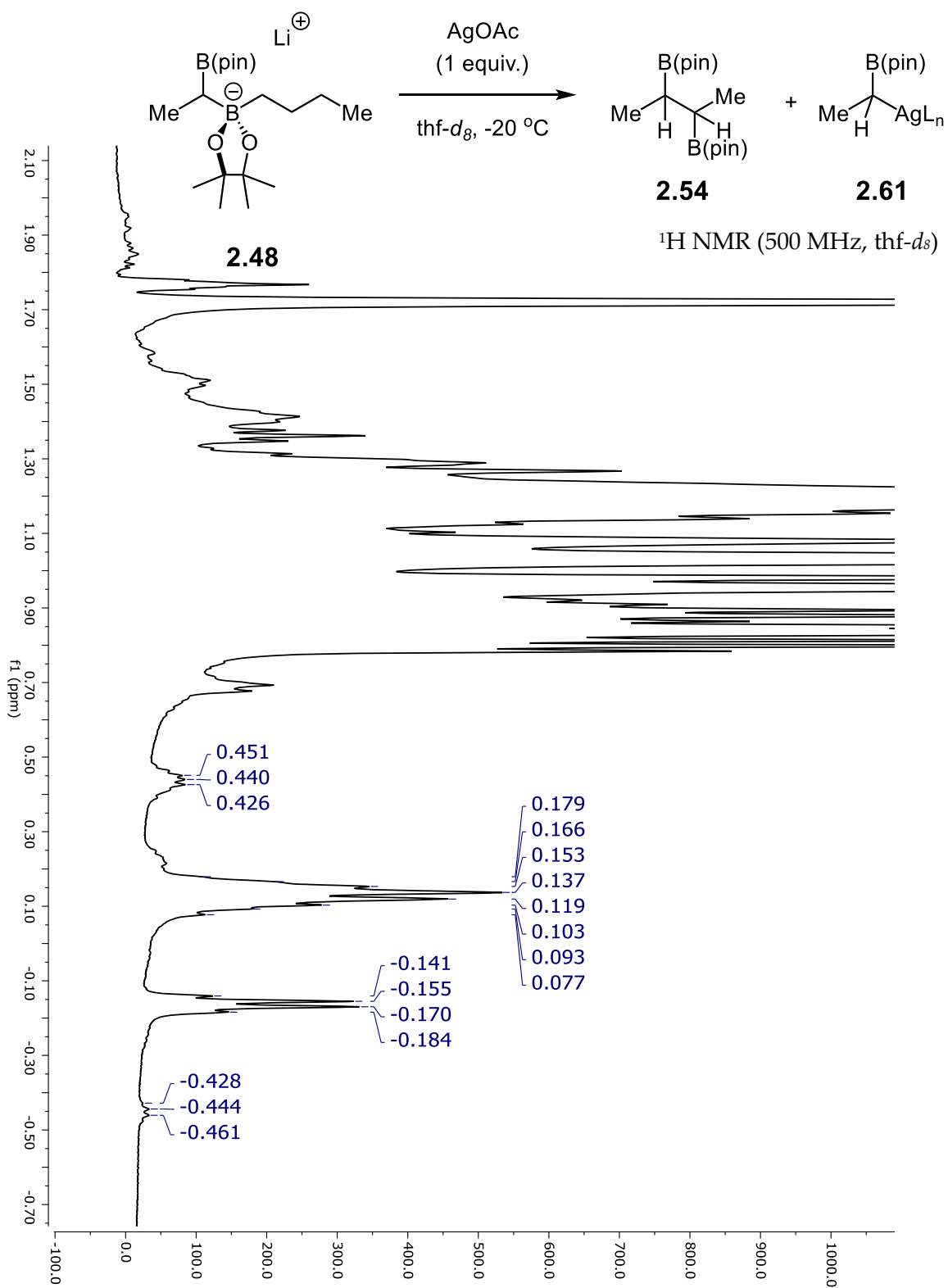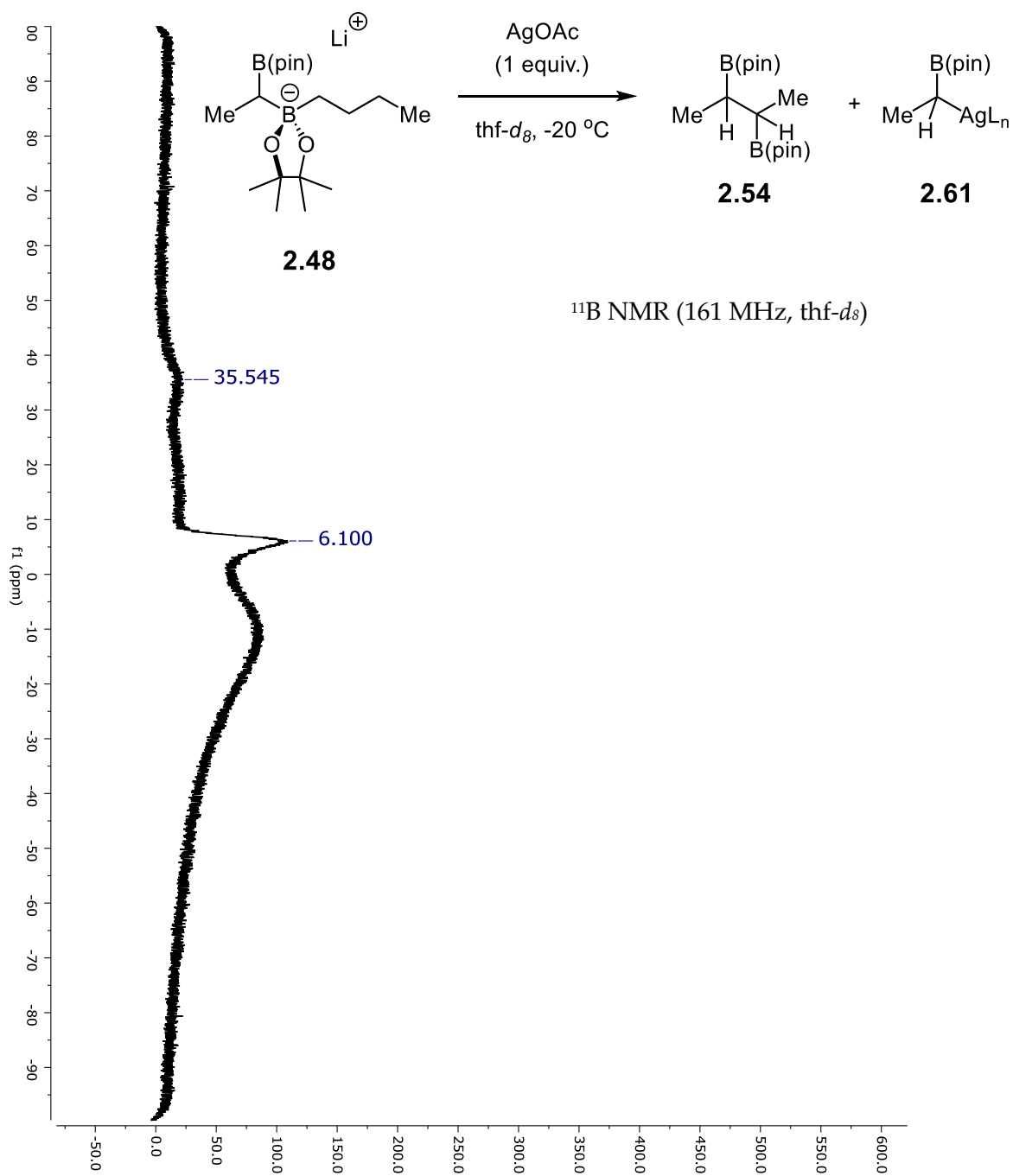
2.54

Procedure: In an N_2-filled glovebox, an 8-mL vial equipped with a magnetic stirbar was charged with

KO*t*-Bu (49.1 mg, 0.438 mmol) and AgOAc (56.2 mg, 0.337 mmol). Diborylethane (100 μL, 0.337

mmol) was then added to the vial as a solution in thf (2.70 mL). The reaction was allowed to stir in the

dark at ambient temperature for 18 hours. The reaction was quenched by addition of 1 mL of a saturated

aqueous solution of NH_4Cl and the aqueous layer was extracted three times with diethyl ether. The

combined organic extracts were dried over $MgSO_4$, filtered, and then concentrated *in vacuo*. NMR

yield of the product (with hexamethyldisiloxane as the internal standard) was determined to be 32%.

The crude mixture was purified *via* silica gel chromatography (5:1 pentane:diethyl ether, gravity,

Seebach Stain) to yield **2.54** as a colorless oil in 15% yield (15.6 mg). Isolation of the product was

problematic as the R_f of **2.54** is very similar to the other products of the reaction, namely diborylethane

and protodeboronated diborylethane. **^{1}H NMR** (600 MHz, CDCl$_3$) δ 1.25 (s, 24H), 1.21 – 1.13 (m,

2H), 1.02 – 0.96 (m, 6H). **^{13}C NMR** (151 MHz, CDCl$_3$): δ 82.9, 82.9, 25.0, 25.0, 24.9, 24.8, 14.3, 13.9.

IR (v/cm^{-1}): 2840 (s), 1699 (m), 1332 (m), 1251 (m), 1145 (w). **HRMS** (ESI$^+$) [M+Na]$^+$ calcd for

$C_{16}H_{32}B_2O_4Na^+$ 333.2385, found: 333.2377.
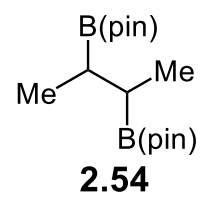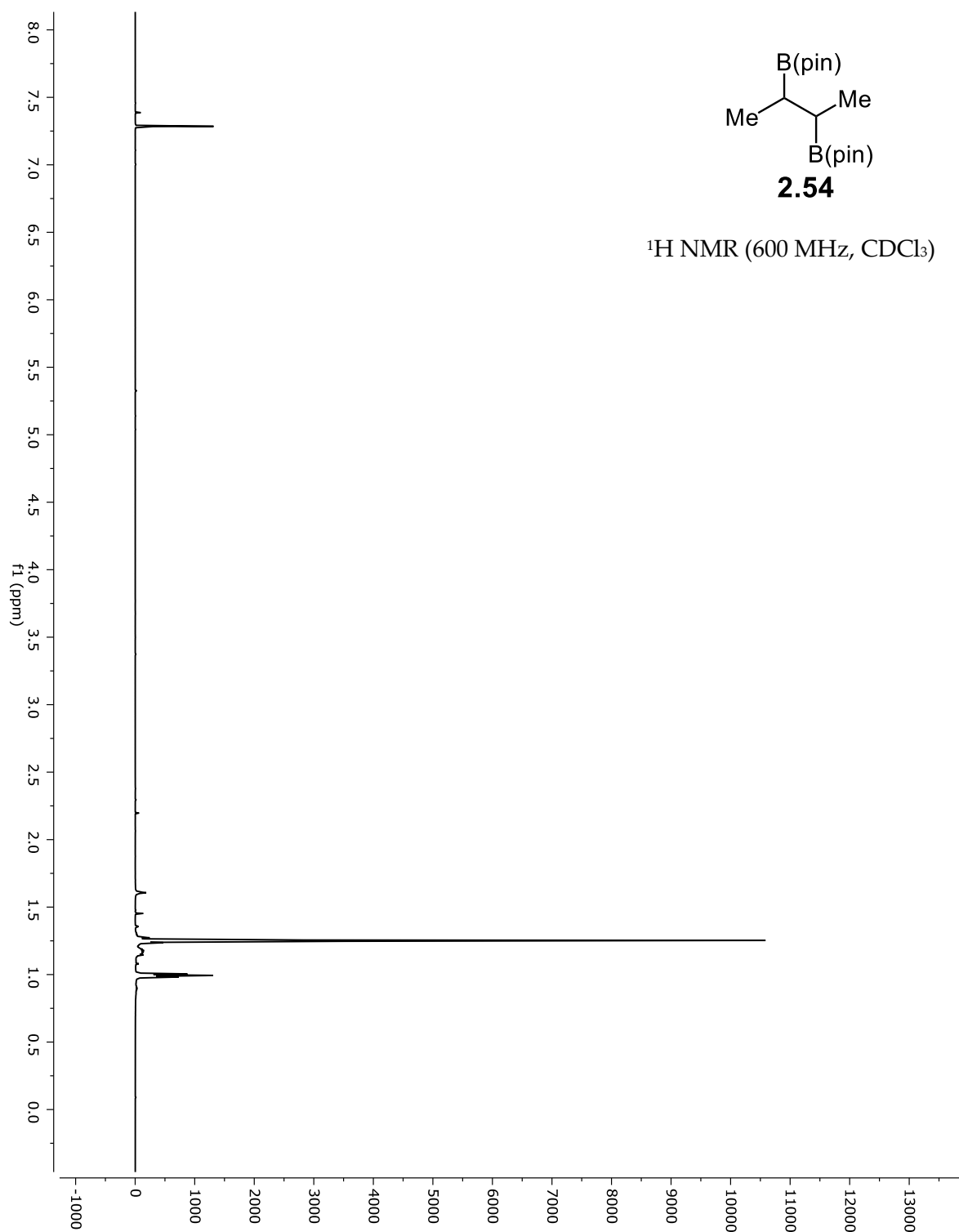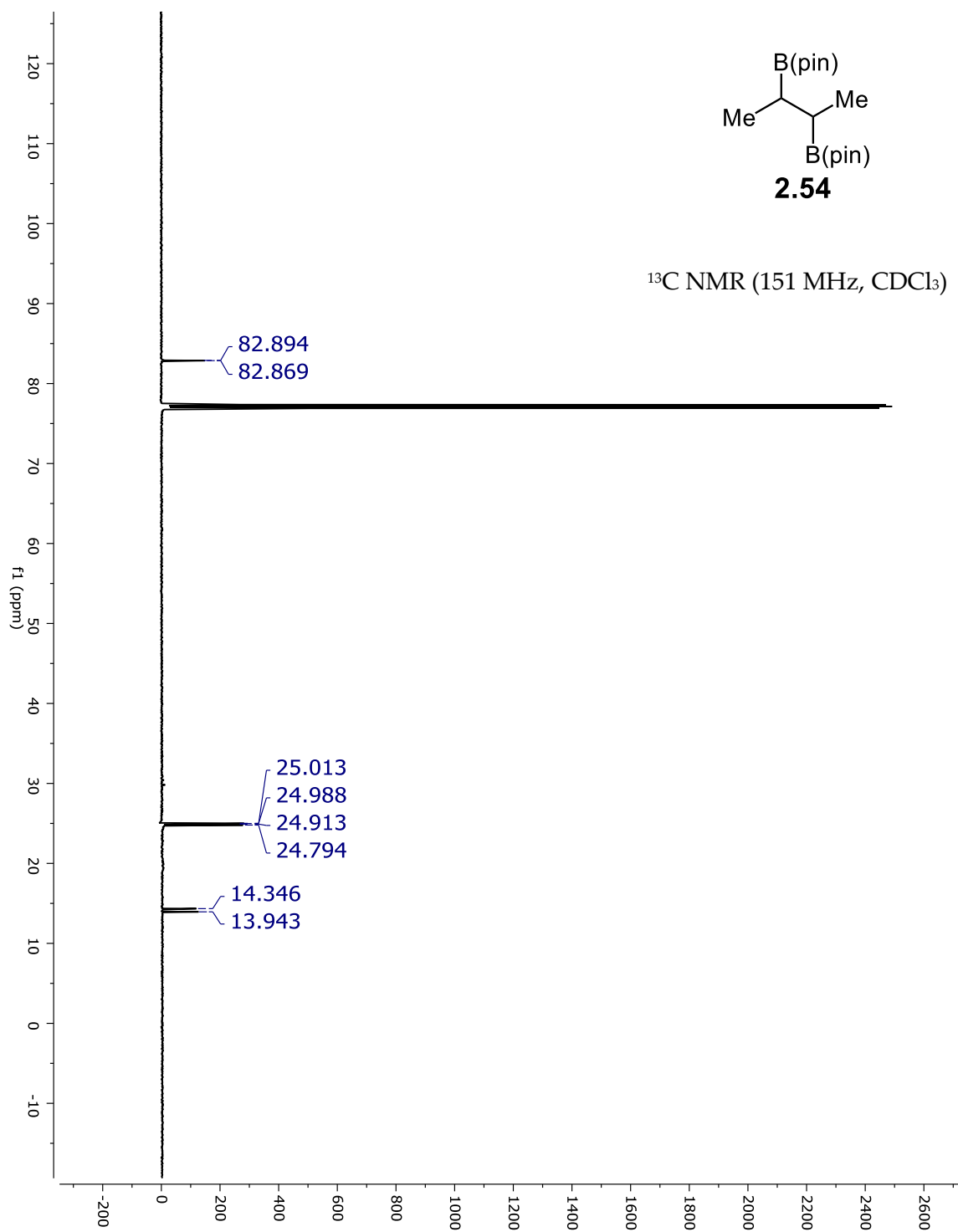
B(pin)

Me

Me

B(pin)

2.54

^{1}H NMR (600 MHz, CDCl$_3$)

B(pin)

Me ▲ Me

B(pin)

2.54

^{13}C NMR (151 MHz, CDCl$_3$)

82.894
82.869

25.013
24.988
24.913
24.794

14.346
13.943

f1 (ppm)

■ DFT Calculations

DFT calculations were performed using the Gaussian 09 computer program suite.[25] All geometries were optimized using B3LYP level of theory. Trunctated structure **I** (which reduced the pinacolatoboryl groups to dioxaborylanyl groups) was optimized with a LANL2DZ basis set for the silver atom and a 6-31++G** basis set for all other atoms. All optimized structures were checked by means of frequency calculations to ensure that all ground state geometries contained only real frequencies and were truly at a local minimum. All calculations were carried out in the gas-phase.
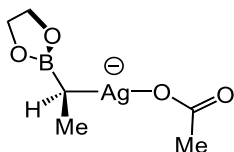
Sum of electronic and thermal free energies: -706.783304 Hartree

Zero Point Correction: 0.173946 Hartree/particle

Coordinates (angstroms)

Atom	X	Y	Z
Ag	-0.53732	0.194006	-0.1819
C	1.277402	1.382088	-0.49185
H	1.197136	1.612506	-1.56337
C	1.277855	2.645822	0.395747
H	1.341287	2.375564	1.457972
H	2.142286	3.301463	0.177577
H	0.370107	3.252612	0.261577
C	3.530037	-1.70206	-0.42782
C	3.80601	-1.09463	0.981854
H	2.908331	-2.60624	-0.36926
H	4.44788	-1.93064	-0.98187
H	3.57899	-1.79491	1.794407
H	4.842478	-0.74427	1.086791
B	2.284633	0.295676	-0.19568
O	2.90642	0.056993	1.073371
O	2.786198	-0.66074	-1.13904
O	-2.29918	-0.99442	0.108221
C	-3.58645	-0.71098	0.193775
C	-3.96632	0.782561	0.058055

H	-3.4573	1.367444	0.836175
H	-3.62863	1.163754	-0.91536
H	-5.04978	0.90983	0.148945
O	-4.50508	-1.56691	0.3744

2.10 REFERENCES

(1)   Boronic Acids; Hall, D. G., Ed.; Wiley-VCH: Weinheim, Germany, 2000.

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Chapter 3: Enantio- and Diastereoselective Synthesis of 1-Hydroxy-2,3-Bisboronates via a Copper–Catalyzed Multicomponent Reaction

3.1 Introduction

Multicomponent reactions (MCR's) are useful manifolds in chemical synthesis that react three or more starting materials to selectively form products that contain "essentially all of the atoms of the educts" (Figure 3.1).[1,2] The reagents are usually added collectively at the outset of the reaction and MCR's are generally one-pot syntheses. Stereoselective MCR's allow for the simultaneous synthesis of multiple bonds and stereocenters in an expeditious method that obviates the need for several separate reactions and minimizes waste.[3] The stereoselective synthesis of $C(sp^3)$ – B bonds is an important method in organic synthesis, as organoboron groups are useful synthetic intermediates that can be functionalized into a plethora of different molecules.[4] A multicomponent reaction involving the stereoselective incorporation of boron, the synthesis of a $C(sp^3)$ – $C(sp^3)$ bond with vicinal stereocenters, and the formation of chiral alcohols would provide a highly efficient and rapid process for constructing high-value, complex, and enantiopure synthetic building-blocks in a single transformation.
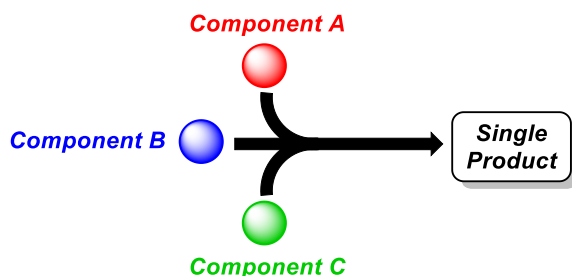
Figure 3.1 General schematic of a multicomponent reaction (MCR)

Previously, I developed an enantio- and diastereoselective copper-catalyzed methodology for the addition of diborylethane, **3.1** to aryl and alkenyl aldehydes (Figure 3.2, left). This process used a stoichiometric lithium alkoxide activator to generate an enantioenriched α-boryl alkyl copper

nucleophile.[5] The reaction was limited to non-enolizable aldehydes (due to stoichiometric alkoxide) and diborylethane, the simplest substituted *gem*-diboronate ester. We investigated other methods for generating α-boryl alkyl copper species that would allow us to surmount these restrictions and discovered that copper-boryl compounds undergo borylcupration of alkenyl boronate **3.2** to stereoselectively generate α,β-bisboryl copper alkyl species (Figure 3.2, right). This process does not require stoichiometric amounts of an alkoxide activator (*vide infra*) which allows for additions to enolizable substrates. The reaction also incorporates a second organoboron unit into the product which can be selectively functionalized, making the products more diversifiable and useful.
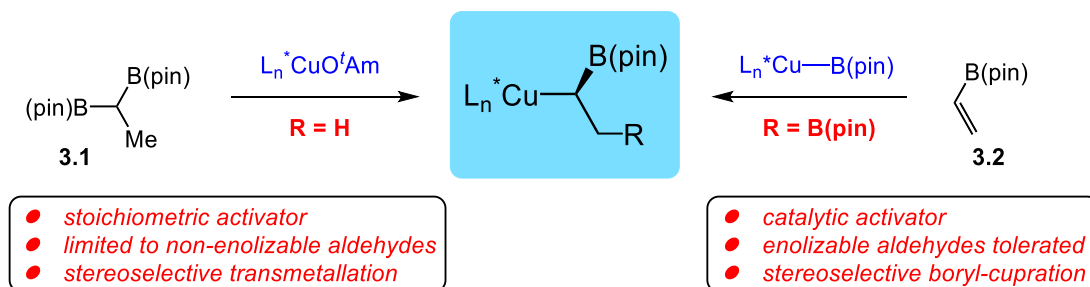
Figure 3.2 Previous and current methods for stereoselectively generating α-boryl copper alkyls

Presented in Figure 3.3 is a general mechanism for the multicomponent borylcupration/1,2-addition reaction. The initial copper-boryl compound, **I** (generated from $B_2(pin)_2$ and a copper-alkoxide) undergoes a migratory insertion of the boryl ligand onto the alkenyl boronate ester **3.2**. The transition state of the reaction is depicted at the center of the catalytic cycle and illustrates how the chiral ligands on copper select which face the *syn* boryl-cupration occurs.[6] Boryl-cupration generates α,β-bisboryl alkyl copper species **II**, which undergoes a 1,2-addition with an aldehyde **3.3** to produce the copper 1-hydroxy-2,3-bisboronate ester **III**. This copper alkoxide activates another equivalent of $B_2(pin)_2$, **3.4** and releases the product with the alcohol protected as the borate ester and regenerates the copper-boryl catalyst. This multicomponent reaction requires only catalytic base to form the initial copper-boryl catalyst, **I**; the alkoxide product generated in the reaction allows for turnover by activating $B_2(pin)_2$. This was not possible in previous 1,2-addition methodologies, as *gem*-diboronate esters are much more difficult to activate than diboron compounds (i.e. B – C bond is stronger than a B – B bond).
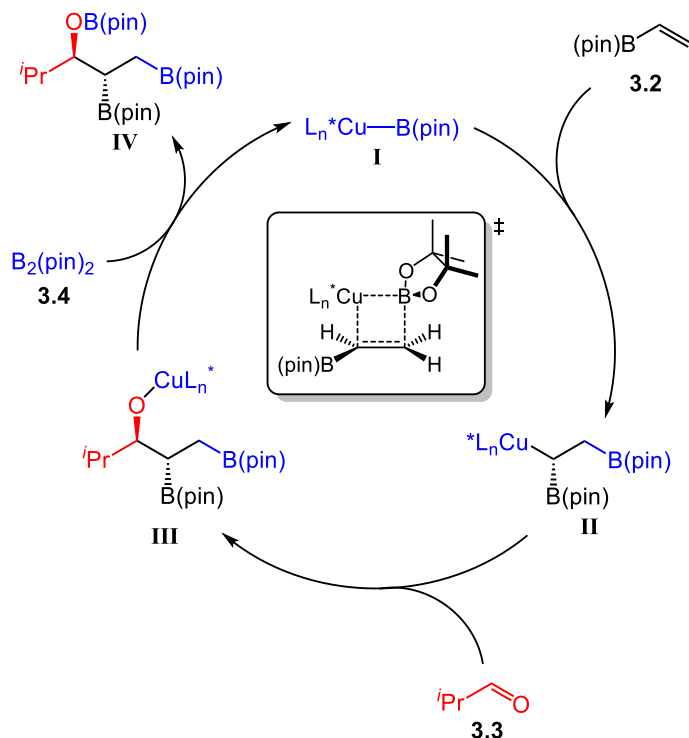
Figure 3.3 Mechanism of Cu-catalyzed multicomponent reaction: boryl-cupration followed by

diastereoselective 1,2-addition

The cornerstone of efficient multicomponent reactions is that they generate a single product even though there is a possibility for the reactants to combine in a multitude of other ways. It is necessary to highlight in this copper-catalyzed multicomponent reaction the number of side products capable of forming. As depicted in Figure 3.4, vinyl boronic acid pinacol ester, an aldehyde, and **3.4** react to form a single product **A**, however, there are a number of other products that can form under the reaction conditions. 1-hydroxy-3,3-bisboronate ester **B** can form if the regioselectivity of the boryl-cupration step is reversed, while allylic alcohol **C** can be produced if the copper-alkoxide catalyst activates **3.2** over **3.4** for nucleophilic addition to the aldehyde. α-hydroxyboronate ester **D** could arise from direct borylation of the aldehyde, where the alkenyl boronate ester is untouched by the copper catalyst. Lastly, boron-containing polymer **E** can form if the α,β-bisboryl copper alkyl species inserts into another molecule of **3.2** rather than addition to an aldehyde. It is a testament to the selectivity of the reaction that, out of all of the possible products, only one forms (*vide infra*).

307

Figure 3.4 Potential side-products from Cu-catalyzed multicomponent reaction: vinyl or boryl

addition, polymerization, or different regioselectivity

3.2   Background

There have been a number of reports in recent years on the generation of α-boryl copper species

via cuprations of alkenyl boronate esters. In 2006, Sadighi and co-workers disclosed the synthesis and

isolation of an α-boryl copper alkyl N-heterocyclic carbene (NHC) complex (Scheme 3.1).[7]   The

bridging copper-hydride dimer **3.5** (previously prepared by their group[8]) undergoes insertion of alkenyl

boronate **3.6** at ambient temperature in one hour to generate the α-boryl copper alkyl NHC complex **3.7**

in 91% yield. The high regioselectivity of the hydride insertion is significant, as the alkenyl boronate

ester contains a phenyl group at the other terminus of the olefin. Benzyl groups are known to stabilize

copper species and usually favor their formation during a cupration reaction.[9]   The insertion, however,

proceeds to form exclusively the α-boryl alkyl copper species, indicating the greater stabilizing effect

of the boryl group on copper. This stabilization potentially manifests itself via an association of the

boron empty *p*-orbital and a filled metal *d*-orbital on copper. In the X-ray crystal structure of **3.7**, the

Cu – B distance is 2.6 Å, which is within the van der Waals radii of the atoms. The boron atom,

however, is still *sp²*-hybridized and displays a ^{11}B NMR spectroscopy signal consistent with a

tricoordinate boron, which indicates that any interaction between copper and boron is weak. Despite

308

this, Sadighi's work demonstrates that insertions of copper hydrides onto alkenyl boronates occurs regioselectively to produce the α-boryl copper species.

Scheme 3.1 Hydrocupration of alkenyl boronates: isolation of an α-boryl alkyl copper NHC complex
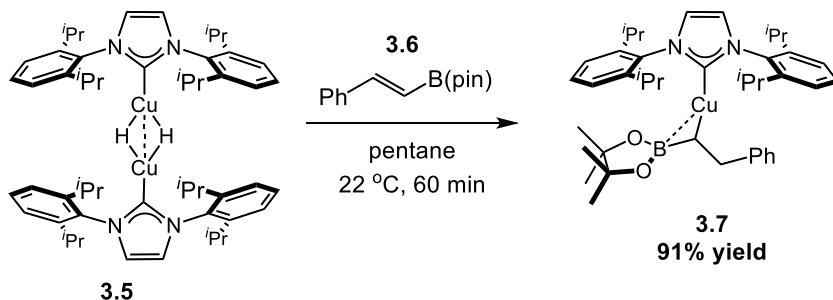
Yun *et. al.* disclosed a method for functionalizing α-boryl copper alkyl species through hydroboration. Using a chiral copper bis-phosphine catalyst, 1,8-diaminonaphthyl protected 1,2-substituted alkenyl boronate esters were hydroborated using pinacolborane, **3.9** and catalytic NaO*t*-Bu.[10] The 1,8-diaminonaphthyl group on boron was used to improve regioselectivity of the hydrocupration step, which sterically and electronically favors forming the α-boryl alkyl copper intermediate. As presented in Scheme 3.2, alkenyl boronate ester **3.8** was hydroborated with **3.9** in the presence of 3 mol % CuCl, 3 mol % *(R)*-dtbm-segphos, and 6 mol % NaO*t*-Bu to produce the substituted *gem*-diboronate ester **3.10** in 89% yield and 96% *ee*. The reaction is tolerant of a wide variety of substituents at the 2-position of the alkenyl boronate ester including substituted arenes, alkyl chains, and cycloalkanes. Yun and co-workers propose a mechanism for the enantioselective hydroboration reaction (bottom of Scheme 3.2) that begins with the generation of a copper-hydride complex, **II** via activation of pinacolborane with copper-*tert*-butoxide. The copper hydride regioselectively inserts into the alkenyl boronate to form an α-boryl copper alkyl species, **I** that rapidly undergoes a σ-bond metathesis reaction with another molecule of pinacolborane, turning over the catalyst and releasing the *gem*-diboronate ester.   This report not only demonstrates that cupration of alkenyl boronate esters can be rendered enantioselective, but that it can be accomplished with a variety of copper-phosphine complexes, not just with copper-NHC complexes.

Scheme 3.2 Cu-catalyzed enantioselective hydroboration of alkenyl boronate esters with

pinacolborane
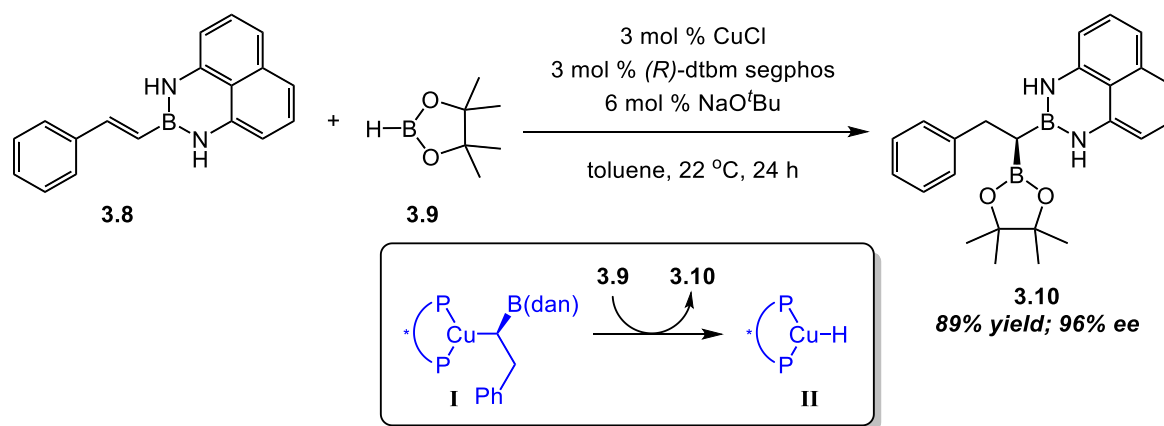
In 2009, Hoveyda and co-workers reported a net-hydroboration of styrenyl olefins via a copper-borylation, protonation manifold.[11] Scheme 3.3 depicts a representative example of an enantioselective borylation/protonation reaction: with 7.5 mol % CuCl, 7.5 mol % imidazolinium salt **3.12**, 30 mol % KOt-Bu, and two equivalents of methanol, olefin **3.11** was borylated with B$_2$(pin)$_2$ and then protonated with methanol and produced the boronate ester **3.13** in 75% yield and 96% *ee*., with >98% regioselectivity for borylating the homobenzylic position. They proposed the formation of a benzyl copper species **3.14** which forms after a copper-boryl intermediate inserts across the olefin. This was corroborated with a reaction conducted in the presence of deuterated methanol, which afforded the hydroborated product **3.13-*d*** with >98% deuterium incorporation and >98:2 diastereoselectivity for the *syn* isomer (in relation to the deuterium and B(pin) groups).   While the temperature of the reaction is not ideal (-50 °C for 48 hours), this methodology nonetheless demonstrates that boryl-cupration of olefins can generate copper alkyl species in high regio- and enantioselectivity.

Scheme 3.3 Cu-catalyzed enantioselective borylation/protonation of styrenyl olefins: net

hydroboration reaction
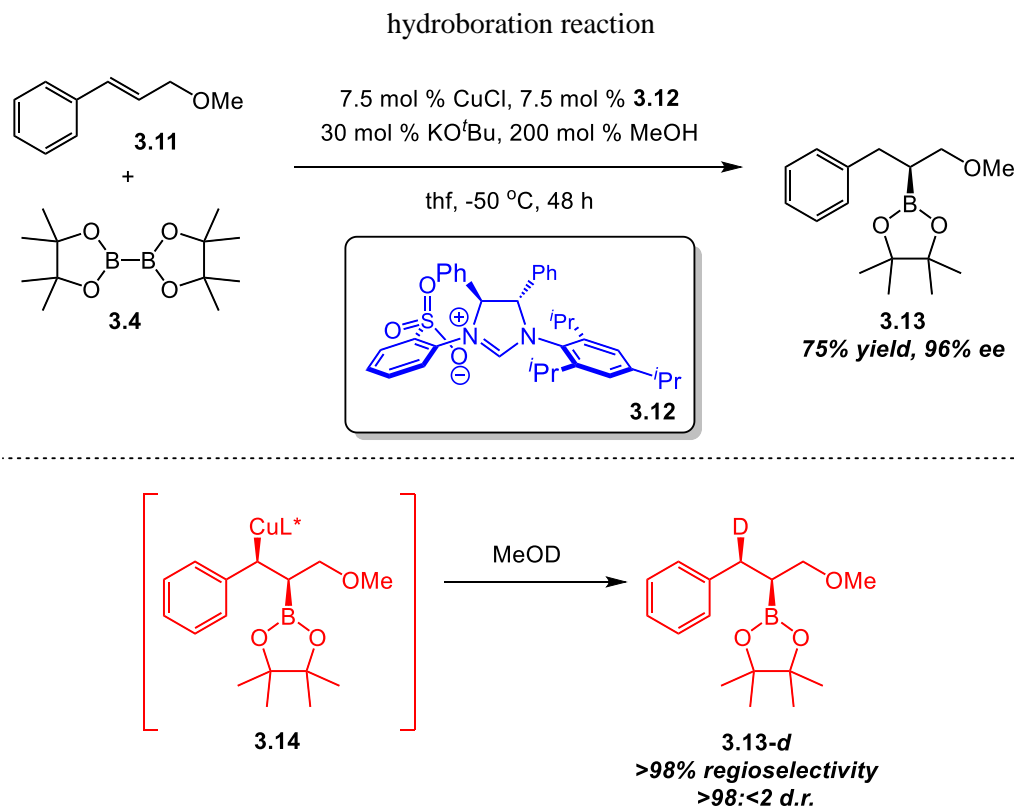
3.3 Diastereoselective Cu-Catalyzed Multicomponent Reaction

I began my investigations into the multicomponent coupling of **3.2**, **3.4**, and an aldehyde by initially attempting a non-enantioselective version of the reaction. This would simplify the analysis of the products and establish a baseline for reactivity, regio- and diastereoselectivity. As disclosed in Scheme 3.4, with 5 mol % Cu(MeCN)$_4$PF$_6$, 6 mol % *rac*-binap, 5 mol % KO*t*-Bu, and 110 mol % B$_2$(pin)$_2$, **3.2** and benzaldehyde react to produce 1-hydroxy-2,3-bisboronate ester **3.15** in >98% NMR yield, 77% isolated yield, and 90:10 d.r favoring the *anti* diastereomer. The reaction is tolerant of substitution patterns on the arene ring, as *m*-methyl containing substrate **3.16** forms in 90% NMR yield, 85% isolated yield, and 91:9 d.r. Heteroaromatic rings react well under these conditions, as the N-Boc protected indolyl substrate **3.17** is afforded in >98% NMR yield, 80% isolated yield, and 92:8 d.r. Cyclohexanecarboxaldehyde-derived product **3.18** is produced in 61% NMR yield, 40% isolated yield

in 67:33 d.r. Only the favored *anti* diastereomer was isolated from the reaction mixture, which accounts for the decrease in isolated yield. Alkenyl aldehyde substrates react in high diastereoselectivity, **3.18** forms in 75% NMR yield and 70% isolated yield as a single detectable diastereomer. The crude NMR spectra of the aforementioned substrates contain signals relating only to the starting materials and the 1-hydroxy-2,3-bisboronate product, indicating that the reaction is highly selective and none of the products pictured in Figure 3.4 were observed.

Scheme 3.4 Diastereoselective Cu-catalyzed multicomponent addition of α,β-bisboryl alkyl copper species to aldehydes
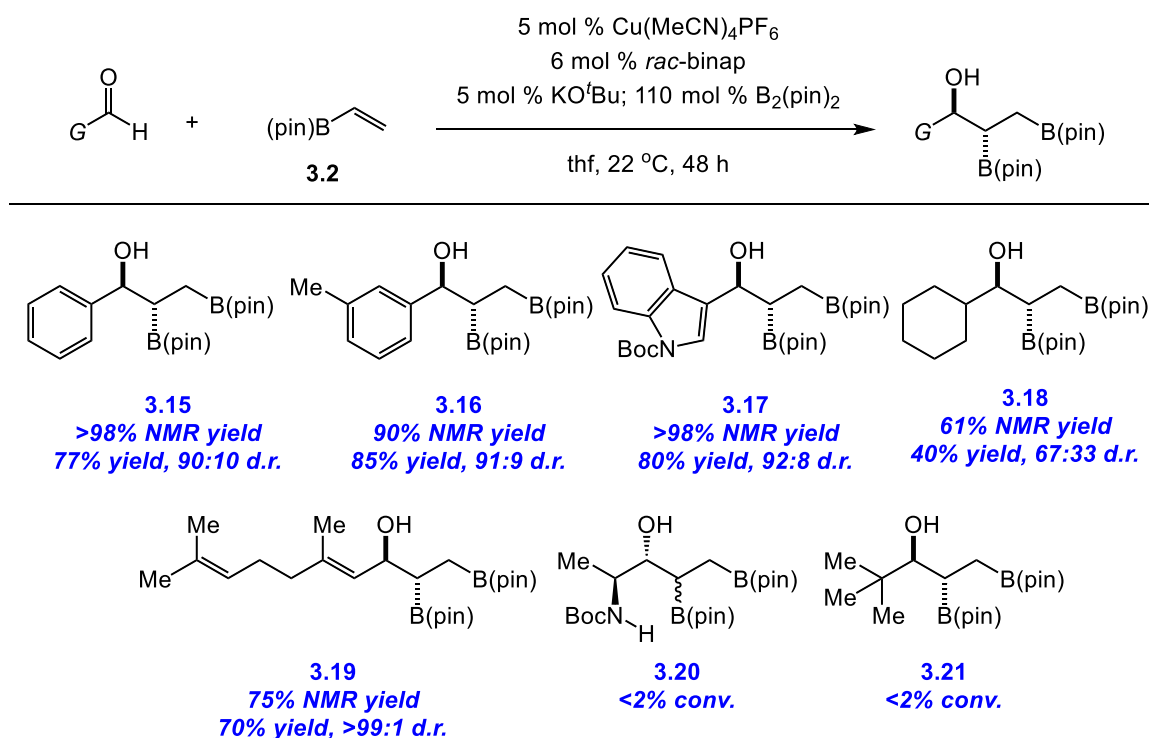
L-N-Boc-alaninal, an α-stereogenic aldehyde, was subjected to the reaction conditions, however no product was formed and 75% of the starting material was returned. This was likely due to deprotonation of the acidic amide proton on the aldehyde by the *in situ* generated α,β-bisboryl copper alkyl species, as 1,2-diborylethane was observed in the crude NMR spectrum at 25% NMR yield, indicating direct protodemetallation of the copper alkyl species had occurred. Pivalaldehyde does not

undergo 1,2-addition reaction, as **3.21** is formed in <2% NMR yield, which is likely due to the increased sterics of the *tert*-butyl group and its inability to bind to the copper catalyst.

3.4   Optimization of Enantio- and Diastereoselective Variant

Since copper-phosphine complexes appeared to be extremely efficient catalysts for this multicomponent reaction, I endeavored to develop an enantioselective variant, using an enantiomerically pure phosphine-copper complex. Table 3.1 summarizes the optimization of the reaction, including variances in the chiral phosphine ligand, temperature, and solvent of the reaction. All reactions occur with 5 mol % Cu(MeCN)$_4$PF$_6$, 5 mol % ligand, and 5 mol % KO*t*-Bu to form the precatalyst. In thf with 5 mol % **3.23,** *(R)*-binap, the product is afforded in 87% NMR yield, 87:13 d.r., and 77:23 e.r (Entry 1). Switching to toluene, an aromatic and less coordinating solvent, the NMR yield increases to >98% with 82:18 d.r., and 82:18 e.r (Entry 2). Observing an increase in both yield and enantioselectivity, I proceeded to screen a number of different chiral phosphine ligands with toluene as the reaction solvent. Using 5 mol % **3.24**, which has 3,5-Me substituted aryl groups on each phosphine, the product is formed in 98% NMR yield, 63:37 d.r., and 92:8 e.r (Entry 3). Even though **3.24** increased the enantioselectivity drastically, there was a significant drop in diastereoselectivity. Switching to 5 mol % of monodentate phosphine **3.25** did not afford any borylation/1,2-addition product (Entry 4). Using 5 mol % of a ferrocene-based bis-phosphine ligand, **3.26** produces the product in 88% NMR yield, 50:50 diastereoselectivity, and 95:5 e.r. (Entry 5). With ligands **3.27** and **3.29** no product was observed (Entries 6 and 8), and with ligand **3.28**, the product forms in only 12% NMR yield (Entry 7). Using 5 mol % **3.30**, however, affords the product **3.15** in >98% NMR yield, 76:24 d.r., and 95:5 e.r. (Entry 9), the highest d.r. and e.r. combination observed up to that point. In an attempt to improve the diastereoselectivity further, but at the same time maintaining high enantioselectivity, the reaction solvent was changed to fluorobenzene and **3.15** forms in 96% NMR yield, 83:17 d.r., and 97:3 e.r. (Entry 10). Lowering the reaction temperature to 4 °C affords the product in 97% NMR yield, 88:12 d.r., and 95:5 e.r. (Entry 11), which is only slightly lower e.r. than Entry 10.

313

Table 3.1 Optimization of multicomponent reaction: phosphine ligand, solvent, and temperature

<div align="center">

5 mol % Cu(MeCN)$_4$PF$_6$
6 mol % ligand
5 mol % KOt-Bu; 110 mol % B$_2$(pin)$_2$

Ph—CHO (O, H)   **3.22**   +   (pin)B—CH=CH$_2$ **3.2**

→ solvent, temp., 48 h →

OH
Ph —(OH)— B(pin)
B(pin)
3.15

</div>
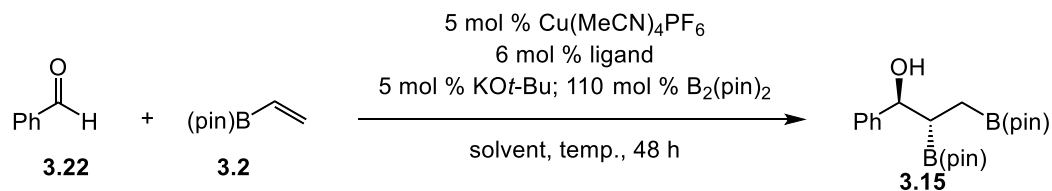
entry	ligand	solvent	temp. (°C)	NMR yield (%)[b]	d.r.[c]	e.r.[d]
1	**3.23**	thf	22	87	87:13	77:23
2	**3.23**	toluene	22	>98	82:18	82:18
3	**3.24**	toluene	22	98	63:37	92:8
4	**3.25**	toluene	22	<2	-	-
5	**3.26**	toluene	22	88	50:50	95:5
6	**3.27**	toluene	22	<2	-	-
7	**3.28**	toluene	22	12	92:8	-
8	**3.29**	toluene	22	<2	-	-
9	**3.30**	toluene	22	>98	76:24	95:5
10	**3.30**	fluorobenzene	22	96	83:17	97:3
11	**3.30**	fluorobenzene	4	97	88:12	95:5
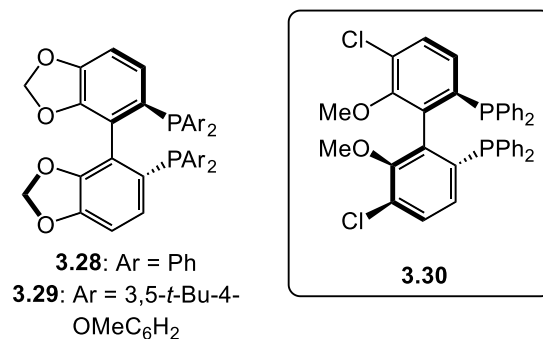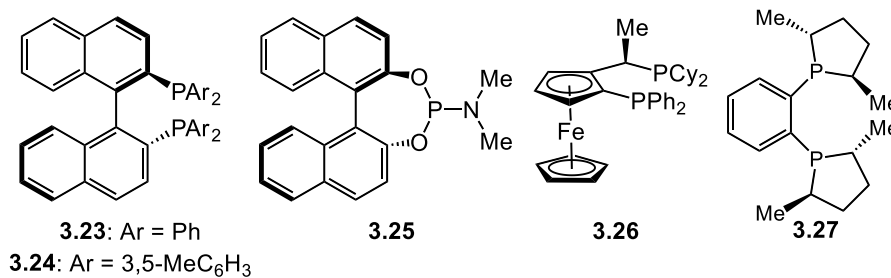
3.23: Ar = Ph
3.24: Ar = 3,5-MeC$_6$H$_3$

3.25

3.26

3.27

3.28: Ar = Ph
3.29: Ar = 3,5-t-Bu-4-OMeC$_6$H$_2$

3.30

[a]Reaction performed under an N$_2$ atmosphere; see Experimental Section for details. [b]Determined using ^{1}H NMR spectroscopy, hexamethyldisiloxane was used as an internal standard. [c]Determined using ^{1}H NMR spectroscopy. [d]Determined by HPLC analysis

3.5   Substrate Scope and Limitations of Cu(MeCN)₄PF₆ as Copper Source

With optimized conditions for the formation of hydroxy-bisboronate **3.15** (Table 3.1, Entry 11), I proceeded to develop the substrate scope for the aldehyde component of the multicomponent reaction. In the presence of 5 mol % Cu(MeCN)₄PF₆, 6 mol % **3.30**, and 5 mol % KO*t*-Bu, vinyl boronic acid pinacol ester, B₂(pin)₂, and benzaldehyde combine to produce **3.15** in >98% NMR yield, 73% isolated yield, 88:12 d.r., and 95:5 e.r. The reaction conditions are tolerant of halogen substitutions at the *para* position of the aryl aldehyde, as fluorine-containing substrate **3.31** is afforded in 93% NMR yield, 71% isolated yield, 80:20 d.r., and 95:5 e.r. The *p*-Br substrate **3.32** is produced in 93% NMR yield, 75% isolated yield, 75:25 d.r., and 96:4 e.r. While the yields and diastereoselectivities for other substrates are good to excellent (up to 80% yield and >99:1 d.r.), the enantioselectivities of other substrates are significantly lower than 95:5 e.r., making the above-mentioned conditions not optimal for all aryl aldehydes. Electron-donating groups in the *para* position causes a significant decrease in enantioselectivity, as hydroxy-bisboronate **3.33** is afforded in only 77:23 e.r. Substituents in the *meta* position similarly lead to less optimal enantioselectivities, as *m*-Me substrate **3.16** forms with 84:16 e.r. Mesitaldehyde-derived substrate **3.37** is produced in 80:20 e.r., and N-Boc indolyl substrate **3.17** is produced in 82:18 e.r. Since the reaction conditions depicted in Table 3.1 only tolerate a limited aldehyde substrate scope, I set out to determine conditions that would be more applicable to a wider range of aldehydes (i.e. enantioselectivites greater than or equal to 95:5).

Scheme 3.5 Substrate scope of enantio- and diastereoselective multicomponent coupling of **3.2**, B₂(pin)₂, and aryl/alkenyl aldehydes: limitations of enantioselectivity in fluorobenzene

3.15
>98% conv.; 73% yield
88:12 d.r.; 95:5 e.r.

3.31
94% conv.; 71% yield
80:20 d.r.; 95:5 e.r.

3.32
93% conv.; 75% yield
75:25 d.r.; 96:4 e.r.

3.33
76% conv.; 70% yield
88:12 d.r.; 77:23 e.r.

3.16
80% conv.; 68% yield
90:10 d.r.; 84:16 e.r.

3.34
83% conv.; 75% yield
>99:1 d.r.; 94:6 e.r.

3.35
51% conv.; 47% yield
>99:1 d.r.; 81:29 e.r.

3.36
43% conv.; 40% yield
>99:1 d.r.; 92:8 e.r.

3.37
69% conv.; 60% yield
>99:1 d.r.; 80:20 e.r.

3.17
98% conv.; 74% yield
73:27 d.r.; 82:18 e.r.

3.38
90% conv.; 80% yield
>99:1 d.r.; 76:24 e.r.

3.39
57% conv.; 50% yield
76:24 d.r.; 61:39 e.r.

3.19
75% conv.; 74% yield
98:2 d.r.; 80:20 e.r.

3.40
47% conv.; 40% yield
77:23 d.r.; 87:13 e.r.

3.41
86% conv.; 54% yield
61:39 d.r.; 81:19 e.r.

To re-optimize the multicomponent reaction conditions to be more tolerant of a broader range of aldehydes, I chose two substrates to examine: **3.16** and **3.33**. These substrates are formed in good yields and diastereoselectivities, but with significantly reduced enantioselectivities (77:23 and 84:16 e.r., respectively) from **3.15** (95:5 e.r.). I investigated two aspects of the reaction: the time allotted for catalyst formation (the stir time with Cu(MeCN)₄PF₆ and **3.30**), and the catalyst loading. The results

of these optimizations are presented in Table 3.2. With 5 mol % $Cu(MeCN)_4PF_6$, 6 mol % **3.30**, and 5 mol % KO*t*-Bu in toluene at 22 °C, **3.2**, **3.4**, and the aldehyde combine to produce **3.16** in 56% NMR yield, 79:21 d.r., and 95.5:4.5 e.r (Entry 1). Under identical conditions, **3.33** is produced in 38% NMR yield, 72:28 d.r., and 97.5:3.5 e.r (Entry 2). While the enantioselectivities were much improved from the results in fluorobenzene at 4 °C, the yields were significantly lower. Hypothesizing that not enough of the catalyst was forming during the catalyst formation step (stirring the copper source and ligand together in toluene before addition of the other reagents), I extended the catalyst formation time from 30 to 60 minutes. With a longer catalyst formation time, **3.16** is formed in 83% NMR yield, 76:24 d.r., and 89:11 e.r (Entry 3). **3.33** suffers a similar drop in enantioselectivity, as it is produced in 46% NMR yield, 74:26 d.r., and 87:13 e.r (Entry 4). Increasing the catalyst loading from 5 to 10 mol % further decreases the enantioselectivity to 82:18 e.r. for **3.16** and 75:25 e.r. for **3.33** (Entries 5 and 6, respectively). It should be noted that $Cu(MeCN)_4PF_6$ alone does not catalyze the multicomponent reaction.

I reasoned that with longer catalyst formation times, more of the active copper-phosphine complex was forming and releasing more acetonitrile into solution. Coordinating solvents like thf were shown to have a deleterious effect on the enantioselectivity of the reaction (*vide supra*), so acetonitrile could have a similar effect, even at low concentrations. For higher catalyst loadings, 40 mol % instead of 20 mol % acetonitrile is released into the reaction ($Cu(MeCN)_4PF_6$ theoretically can release 4 equivalents of MeCN) which would account for the further drop in enantioselectivity (89:11 to 82:18 e.r. for **3.16**).

Table 3.2 Investigation catalyst formation time and catalyst loading on the yield and e.r. of the

reaction[a]
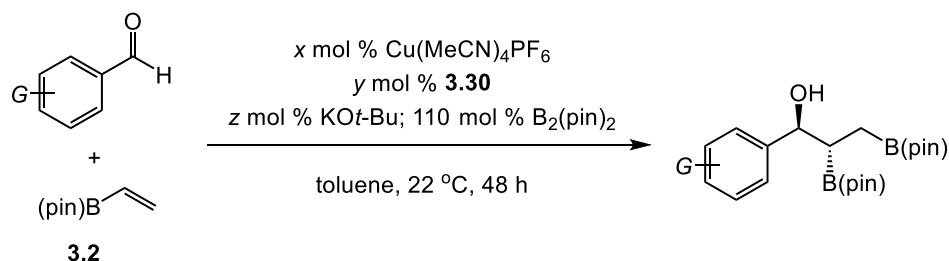
entry	G	x;y;z (mol %)	catalyst formation (min)	NMR yield (%)[b]	d.r.[c]	e.r.[d]
1	3-Me	5;6;5	30	56	79:21	95.5:4.5
2	4-OMe	5;6;5	30	38	72:28	97.5:2.5
3	3-Me	5;6;5	60	83	76:24	89:11
4	4-OMe	5;6;5	60	46	74:26	87:13
5	3-Me	10;11;10	60	>98	77:23	82:18
6	4-OMe	10;11;10	60	>98	73:27	75:25

[a]Reaction performed under an N_2 atmosphere; see Experimental Section for details. [b]Determined using ^{1}H NMR spectroscopy, hexamethyldisiloxane was used as an internal standard. [c]Determined using ^{1}H NMR spectroscopy. [d]Determined by HPLC analysis

3.6   Isolation of Copper-Phosphine Complexes/Effect of Nitrile Ligands on Multicomponent Reaction

To gain further insight into the structure of the copper complexes being formed during the reaction, I isolated a number of copper-Cl-OMe-biphep complexes that I was forming *in situ*. Reacting equimolar amounts of Cu(MeCN)$_4$PF$_6$ and **3.30** in benzene at 22 °C for 2 hours furnishes the tricoordinate, cationic Cl-OMe-biphep-copper(acetonitrile) complex **3.42** in >98% isolated yield (Scheme 3.6). The ^{31}P NMR spectrum contains two signals in roughly a 1:1 intensity: δ -2.16 (s) corresponding to the aryl phosphines bound to copper, and δ -142.9 (septet) corresponding to the signal for hexafluorophosphate. The number of acetonitrile ligands on copper was determined by ^{1}H NMR spectroscopy, specifically the integration ratios of the methyl proton signals on (δ 1.37, s, 3H) to the

methoxy protons on the Cl-OMe-biphep ligand. It is important to note that this signal is significantly

shifted from free acetonitrile in C_6D_6 (δ 0.58 ppm), which indicates that the nitrile ligand is strongly

activated by cationic copper and likely causes a significant drop in the pK_a of the methyl protons. [13]C

NMR spectroscopy was also used to confirm the presence of an acetonitrile ligand, as the resonances

for the *sp* and *sp*[3] carbons on acetonitrile were assigned at δ 121.8 and δ 1.1, respectively. Isolation of

this complex demonstrates that three equivalents of acetonitrile per copper are released into the reaction

during *in situ* catalyst generation, which potentially accounts for the drop in enantioselectivity for both

longer catalyst formation times and higher catalyst loadings.

Scheme 3.6 Isolation of Cl-OMe-biphep-copper acetonitrile complex

3.42
>98% yield
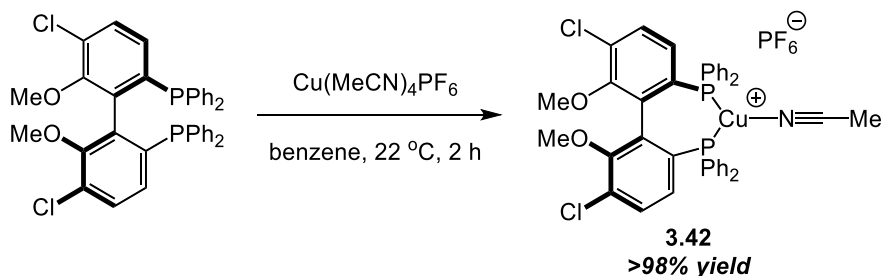
To determine how KO*t*-Bu interacts with copper(acetonitrile) complexes, I isolated the product

of reacting **3.42** (generated *in situ*) with KO*t*-Bu. Reacting Cu(MeCN)$_4$PF$_6$ and **3.30** in benzene at 22

°C for 2 hours, followed by addition of KO*t*-Bu and reacting for an additional hour affords the Cl-OMe-

biphep-copper(keteneimide) complex **3.43** in 97% yield. Expecting a ligand substitution of the nitrile

ligand for *tert*-butoxide (as observed for copper-phosphoramidite complexes, see Chapter 1), KO*t*-Bu

in fact deprotonates the ligated nitrile ligand. The presence of residual *tert*-butanol in the ^{1}H NMR

spectrum of the concentrated reaction mixture supports this claim. The ^{31}P NMR spectrum of **3.43**

contains a single resonance at δ -15.0 ppm, which is significantly upfield from the ^{31}P NMR signal in

3.42 (δ -2.16). This shift is not unexpected, as **3.43** is now a neutral complex with an electron-donating,

X-type ligand which should make copper and the phosphines more electron rich. The proton resonances

of the keteneimide ligand on **3.43** cannot be directly observed by ^{1}H NMR spectroscopy, as they fall

underneath the aryl resonances of the Cl-OMe-biphep ligand (δ 7.06-6.98, m, 18H) which should only

319

have an integration of 16 protons. ^{13}C NMR spectroscopy is ambiguous, as the resonance for the α

carbon cannot be observed (likely due to significantly high T_1 relaxation times since the carbon is *sp*

hybridized). A weak signal at δ 128.2 ppm, however, grows in after several hundred scans, which

potentially corresponds to the β-carbon (terminal carbon) of the ligand.[12] This may be the first example

of an isolated N-bound copper cyanocarbanion (keteneimide), as most examples involve late transition

metals or are C-bound cyanocarbanions.[13] Based on evidence from Miller and Guan, this complex is

likely not a C-bound cyanocarbanion, as the chemical shifts do not match. The methylene protons for

a C-bound acetonitrile ligand are below 0 ppm, as is the ^{13}C signal for that carbon.

Scheme 3.7 Isolation of Cl-OMe-biphep-copper keteneimide complex from deprotonation of **3.42**

3.43
97% yield
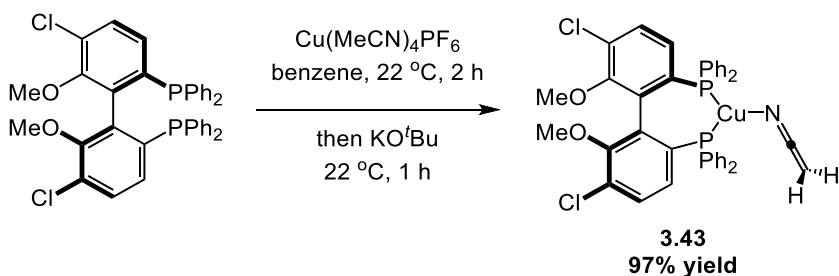
To ensure that **3.43** was not the copper *tert*-butoxide complex, outright synthesis of **3.44** was

conducted. Stirring equimolar amounts of CuO*t*-Bu and **3.30** affords the (Cl-OMe-biphep)CuO*t*-Bu

complex in >98% yield as a yellow solid. The ^{31}P NMR spectrum of the CuO*t*-Bu complex is identical

to **3.43** with a singlet at δ -15.03 ppm (which is not unexpected, as an amide and alkoxide should have

similar donor properties when bound to copper). The ^{1}H NMR spectrum contains a new broad singlet

at δ 1.29 ppm, which is not present in **3.43** and corresponds to the nine methyl protons of the *tert*-butyl

group. The ^{13}C NMR spectrum also contains two new resonances at δ 65.6 and 35.4 ppm, again,

corresponding to the *tert*-butoxy group bound to copper. This confirms that reacting KO*t*-Bu with **3.42**

forms the copper(keteneimide) complex and not a copper(*tert*-butoxide) complex. Reacting **3.44** with

ten equivalents of acetonitrile in C_6D_6 produces the copper(keteneimide) complex and *tert*-butanol after

3 hours at 22 °C.

Scheme 3.8 Isolation of Cl-OMe-biphep-copper tert-butoxide complex

3.44
>98% yield
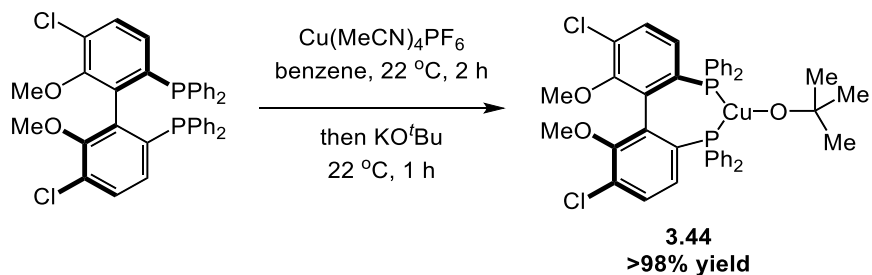
With isolated copper(acetonitrile) and copper(keteneimide) complexes in hand, I proceeded to assess their reactivity and selectivity in the multicomponent reaction of **3.2**, **3.4**, and aldehydes (presented in Table 3.3). I reasoned that, since **3.42** and **3.43** would not release any MeCN under the reaction conditions (acetonitrile bound to **3.42** would be deprotonated by KO*t*-Bu), the enantioselectivity of the products would be high. Unfortunately, with 10 mol % **3.42** and 10 mol KO*t*-Bu, **3.16** forms in >98% NMR yield, 78:22 d.r., and 85:15 e.r. (Entry 1) and **3.33** forms in >98% NMR yield, 76:24 d.r., and 77.5:22.5 e.r. (Entry 2). Interestingly, 10 mol % **3.43** affords product **3.16** in 73.5:26.5 e.r. (Entry 3), which is significantly lower enantioselectivity than with the *in situ* generated copper(keteneimide) complex from Entry 1.

Table 3.3 Effect of using isolated Cu complexes in multicomponent reaction: significant drop in

enantioselectivity[a]
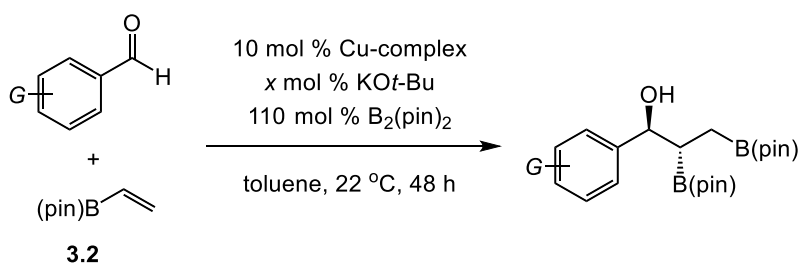
entry	G	complex;*x* (mol %)	NMR yield (%)[b]	d.r.[c]	e.r.[d]
1	3-Me	**3.42**;10	>98	78:22	85:15
2	4-OMe	**3.42**;10	>98	76:24	77.5:22.5
3	3-Me	**3.43**; 0	>98	78:22	73.5:26.5

[a]Reaction performed under an N_2 atmosphere; see Experimental Section for details. [b]Determined using ^{1}H NMR spectroscopy, hexamethyldisiloxane was used as an internal standard. [c]Determined using ^{1}H NMR spectroscopy. [d]Determined by HPLC analysis

An explanation for these differences in enantioselectivity is depicted in Figure 3.5. Reaction of copper(acetonitrile) complex **3.42** with KO*t*-Bu potentially forms both the copper(*tert*-butoxide) complex **3.44**, and copper(keteneimide) complex **3.43**. As the reaction progresses, however, **3.44** can convert into **3.42** (*vida supra*), which has been implicated as a potential mechanism in cyanomethylation reactions involving nickel. Reaction of **3.44** with $B_2(pin)_2$ produces the copper-boryl complex **I**, releasing *tert*-butoxyborate pinacol ester as the byproduct. When **3.43** reacts with $B_2(pin)_2$, however, it releases borylated acetonitrile, **3.45**, which would have similar donor properties to acetonitrile but is sterically more encumbered. This indicates that using **3.43** as a catalyst releases exactly one equivalent of a nitrile ligand (**3.45**) per copper, while using **3.42** as a precatalyst generates a mixture of copper-*tert*-butoxide and **3.43**. **3.44** and **3.43** can both activate $B_2(pin)_2$, but the top pathway (copper-*tert*-butoxide) is a more enantioselective pathway than the bottom pathway (copper-keteneimide) due to the different byproducts formed during the activation step: borate pinacol ester vs borylated acetonitrile, respectively. The exact interaction of **3.45** with the copper catalyst is unknown

322

at this time, but competitive binding of it versus the vinyl boron could potentially erode enantioselectivity.
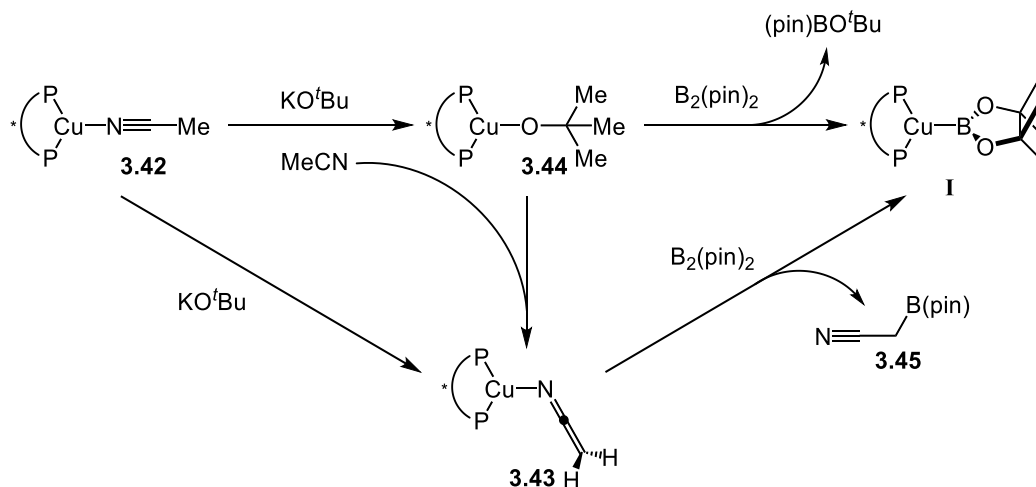
Figure 3.5 Explanation for enantioselectivity variances when using isolated acetonitrile or keteneimide copper complexes

3.7   Copper-tert-butoxide as Copper Source

Since the presence of nitrile ligands in the multicomponent reaction is deleterious to enantioselectivity, I opted to explore other copper sources for the reaction. Using other copper(I) salts such as Cu(OAc), CuCl, and CuI afforded products with substantially decreased yield and selectivities. Switching to copper(II) alkoxide salts, which do not require KO*t*-Bu to activate the catalyst, gave inconsistent conversions (from 21-98% NMR yield for **3.15**) and less than optimal enantioselectivities (<94:6 e.r.), which is likely due to Cu(OMe)$_2$ and Cu(O^{t}Am)$_2$ being extremely insoluble in aromatic solvents. The reduction from Cu(II) to Cu(I) is also a potential source of decreased yield and selectivity. Instead of trying to *in situ* generate copper-*tert*-butoxide complexes during my reaction, which is clearly not straightforward and generates a number of compounds in solution, I decided to synthesize copper(I) *tert*-butoxide.

Addition of a KO*t*-Bu solution in thf to a suspension of copper(I) iodide in thf at -20 °C, with subsequent magnetic stirring at 22 °C for 18 hours furnishes cuprous *tert*-butoxide, **3.45** as a light

yellow solid after filtration and concentration *in vacuo*. This procedure was adapted from a previous method which required sublimation of the compound to obtain pure product.[14] The solid is soluble in benzene and displays one signal in the ^{1}H NMR spectrum in C_6D_6 at δ 1.31 (s, 9H). The ^{13}C spectrum contains two signals, δ 72.3 ppm and δ 35.5 ppm, the former requiring a pulse delay time of 4.0 seconds between each scan to account for increased T_1 relaxation time of the quaternary carbon. **3.45** is extremely unstable to air and moisture, even decomposing over time in an N_2-filled glovebox when not stored sealed at -20 °C (decomposition is evidenced by the solid turning a dark brown color, indicating oxidation to copper(II)).

Scheme 3.9 Synthesis of cuprous *tert*-butoxide
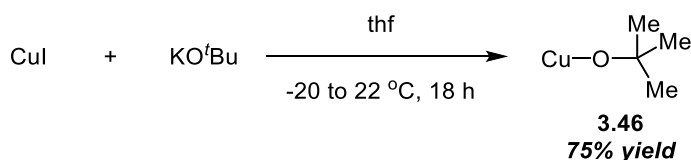
I initially screened the multicomponent reaction with CuO*t*-Bu as the copper source several different aromatic solvents, results are presented in Table 3.4. With 10 mol % CuO*t*-Bu, 11 mol % **3.30** at 22 °C at 0.10 M in benzene, **3.16** is produced in 64% NMR yield, 80:20 d.r., and 97:3 e.r. (Entry 1). Using toluene as the solvent leads to **3.16** being produced in 89% NMR yield, 78:22 d.r., and 95:5 e.r. (Entry 2). Chlorobenzene affords the product in 90% NMR yield, 86:14 d.r. (Entry 3), and 94:6 e.r, while fluorobenzene affords **3.16** in 98% NMR yield, 86:14 d.r., and 93:7 e.r (Entry 4). Benzene as the solvent produces **3.16** with the highest enantioselectivity, albeit in modest yield.
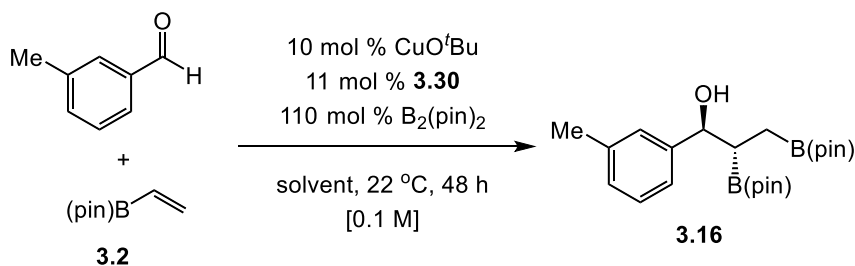
| entry	solvent	NMR yield (%)[b]	d.r.[c]	e.r.[d]
1	benzene	64	80:20	97:3
2	toluene	89	78:22	95:5
3	chlorobenzene	90	86:14	94:6
4	fluorobenzene	>98	86:14	93:7

[a]Reaction performed under an N_2 atmosphere; see Experimental Section for details. [b]Determined using ^{1}H NMR spectroscopy, hexamethyldisiloxane was used as an internal standard. [c]Determined using ^{1}H NMR spectroscopy. [d]Determined by HPLC analysis

To improve the yield of the reaction, I optimized the concentration and catalyst loading of the multicomponent coupling. With similar conditions to Table 3.4, Entries 1-4 demonstrate how increasing the concentration of benzene to 0.25 M increases the NMR yields of several different substrates (**3.16**: 98%, **3.33**: 95%, **3.16**: 96%, **3.37**: 72%) but at the same time causes the enantioselectivities to decrease (**3.16**: 95:5 e.r., **3.33**: 94.5:5.5 e.r., **3.16**: 94:6 e.r., **3.37**: 92:8 e.r.). Interestingly, when the catalyst loading is dropped from 10 to 5 mol % (Entries 5-8), the enantioselectivities increase dramatically, as **3.16** and **3.33** are formed in >98% and 60% NMR yield, respectively, both in 96:4 e.r, while **3.16** is produced in 90% NMR yield in 95.5:4.5 e.r. **3.37** only forms in 12% NMR yield. In order to strike a balance between high yield and high enantioselectivity for a broad scope of aldehydes, 10 mol % catalyst loading was used with benzene at 0.17 M (Entries 9-12). Gratifyingly, in the presence of 10 mol % CuO*t*-Bu and 11 mol % **3.30** at 0.17 M in benzene, **3.15** is afforded in >98% NMR yield, 78:22 d.r., and 95.5:4.5 e.r. **3.33** is produced in 88% NMR yield, 77:23 d.r., and 95:5 e.r., while **3.16** forms in >98% NMR yield, 81:19 d.r., and 95:5 e.r. Mesityl

containing substrate **3.37** is afforded in 47% NMR yield, >99:1 d.r., and 95:5 e.r. Decreasing the

concentration further to 0.063 M in benzene leads to significant drops in yield (Entries 13-16: from 14-

55% NMR yield). These data demonstrate the sensitivity of the multicomponent reaction to both the

concentration of the reaction and the ratio of the catalyst to the reagents. In earlier optimizations of the

reaction, excess **3.2** lead to increased enantioselectivities (from 1.0 to 2.0 equivalents), indicating that

the interaction and ratio of **3.2** and the copper catalyst has a huge effect on the enantioselectivity of the

reaction.

Table 3.5 Optimization of concentration and catalyst loading[a]
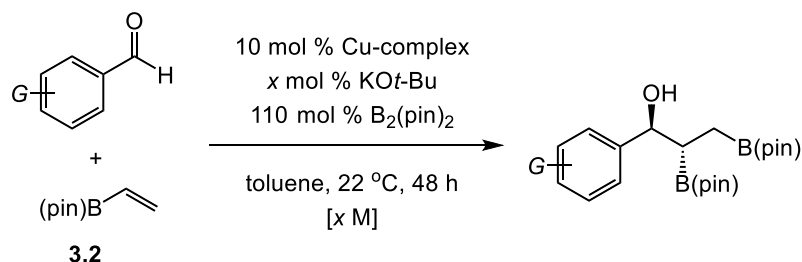
entry	G	x;y (mol %)	concentration (M)	NMR yield (%)[b]	d.r.[c]	e.r.[d]
1	H	10;11	0.25	98	78:22	95:5
2	4-OMe	10;11	0.25	95	76:24	94.5:5.5
3	3-Me	10;11	0.25	96	80:20	94:6
4	2,4,6-Me	10;11	0.25	72	>99:1	92:8
5	H	5;6	0.25	>98	78:22	96:4
6	4-OMe	5;6	0.25	60	77:23	96:4
7	3-Me	5;6	0.25	90	81:19	95.5:4.5
8	2,4,6-Me	5;6	0.25	12	>99:1	-
9	H	10;11	0.17	>98	78:22	95.5:4.5
10	4-OMe	10;11	0.17	88	77:23	95:5
11	3-Me	10;11	0.17	>98	81:29	95:5
12	2,4,6-Me	10;11	0.17	47	>99:1	95:5
13	H	10;11	0.063	55	79:21	-
14	4-OMe	10;11	0.063	46	77:23	-
15	3-Me	10;11	0.063	66	80:20	-
16	2,4,6-Me	10;11	0.063	14	>99:1	-

[a]Reaction performed under an N_2 atmosphere; see Experimental Section for details. [b]Determined using ^{1}H NMR spectroscopy, hexamethyldisiloxane was used as an internal standard. [c]Determined using ^{1}H NMR spectroscopy. [d]Determined by HPLC analysis

With reproducible conditions for the multicomponent coupling of **3.2**, B$_2$pin$_2$, and aldehydes, I proceeded to explore the substrate scope of the reaction further with different aldehydes. Repeating Scheme 3.5 with CuO*t*-Bu conditions affords the 1-hydroxy-2,3-bisboronate products in up to 84% yield, >99:1 d.r., and 97:3 e.r (substrate **3.38**). The lowest enantioselectivities are 93:7 and the lowest diastereoselectivities are 61:39 (e.g. substrate **3.41**). All d.r. values are of the crude reaction mixtures

327

and, aside from products **3.17** and **3.41**, all products were isolated in ≥98:2 d.r (likely due to the instability of the *syn* diastereomer on silica gel). This demonstrates that, even if the diastereoselectivity of the crude reaction is not optimal, only one compound is isolated, making this methodology highly selective and useful.

Scheme 3.10 Substrate scope of enantio- and diastereoselective multicomponent coupling of **3.2**, B₂(pin)₂, and aryl/alkenyl aldehydes: consistent yields and enantioselectivities
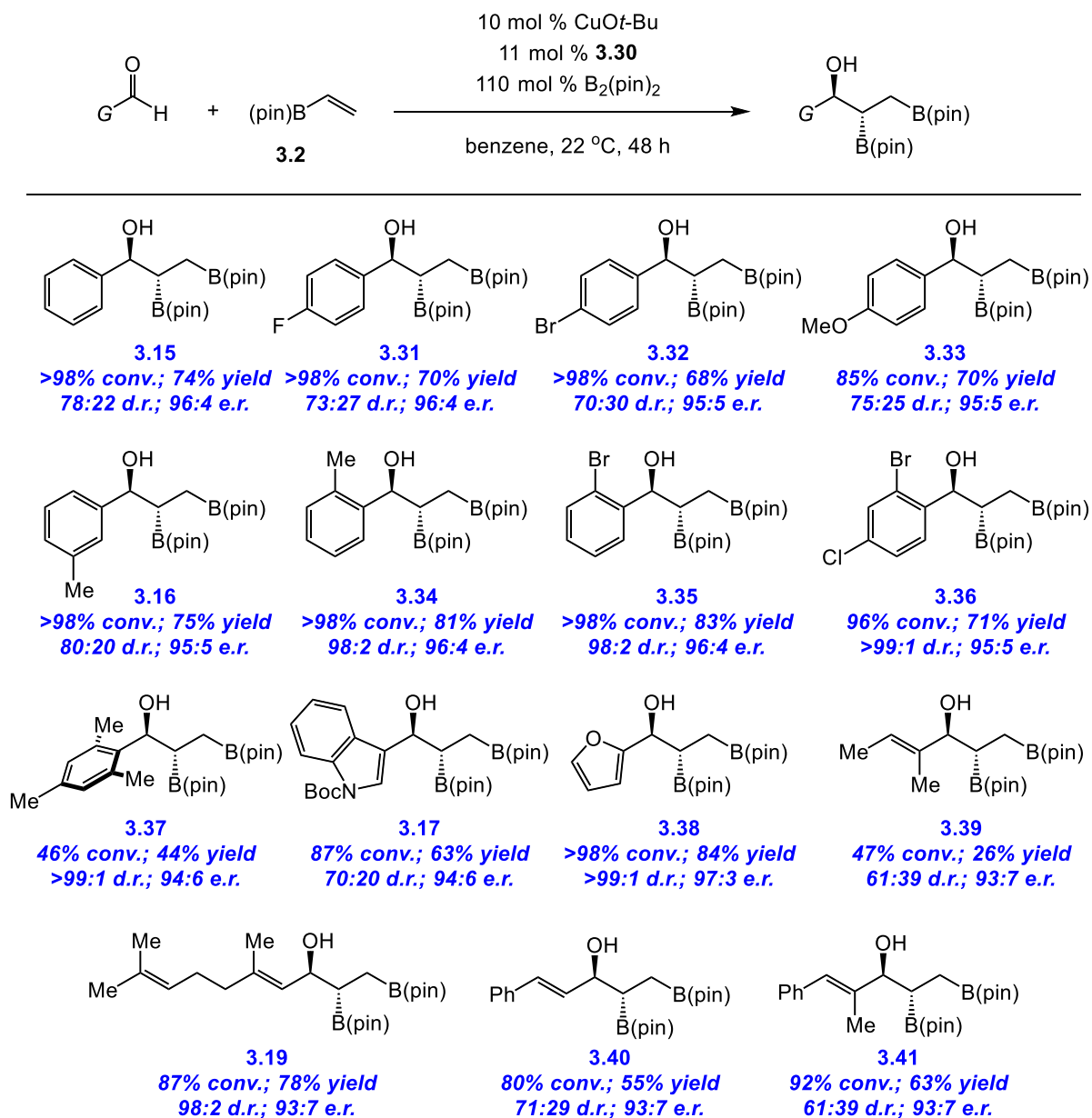
3.8 Cu-Catalyzed Borylation/1,2-Addition of Alkyl Aldehydes

Alkyl aldehydes are well tolerated under the reaction conditions depicted in Scheme 3.10. With 10 mol % CuO*t*-Bu, 11 mol % Cl-OMe-biphep, and 110 mol % $B_2(pin)_2$, substrate **3.47** is isolated in 48% yield as a single diastereomer in 93:7 e.r. The NMR yield of the reaction is >98%, indicating complete decomposition of the *syn* diastereomer during purification. Isovaleraldehyde undergoes multicomponent borylation/1,2-addition well and affords the product in 52% yield, 78:22 d.r., and 95:5 e.r. Aldehydes containing long alkyl chains are not effective substrates, as **3.49** is formed in 23% NMR yield, 67:33 d.r. Dihydrocinnamyl substrate **3.50**, however, is afforded in 67% yield, 73:27 d.r., and 90:10 e.r. 1-hydroxy-2,3-bisboronate product **3.18** is produced in 63% yield, 85:15 d.r., and 94:6 e.r. When racemic 2-phenylpropionaldehyde, an α-stereogenic aldehyde, is subjected to racemic reaction conditions, only two products are observed by ^{1}H NMR spectroscopy, and they appear to only differ by one stereocenter.

Scheme 3.11 Cu-catalyzed multicomponent addition to alky aldehydes
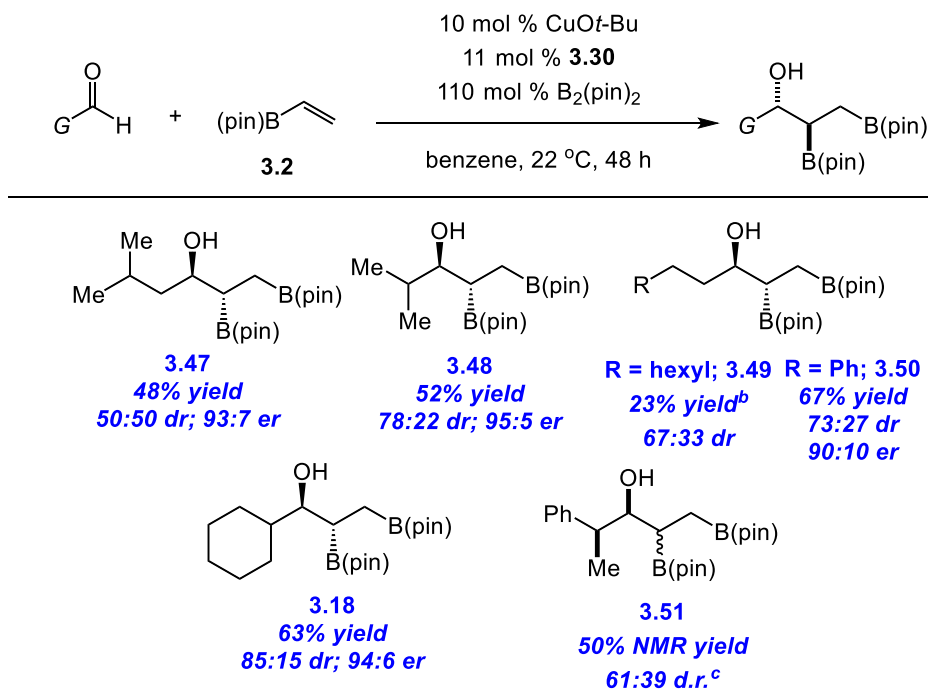
^{a}Refer to Table 3.5 footnotes about the reaction conditions and diastereo- and enantioselectivity measurements. ^{b}NMR yield. ^{c}Reaction performed with *rac*-binap

Depicted in Figure 3.6 are all the possible stereoisomers for **3.51** that can form during the reaction. The Felkin-Anh model for stereocontrol predicts that the largest substituent on the α-position of the aldehyde situates itself perpendicular to the aldehyde, which leaves the smallest substituent (in this case, a hydrogen) to be located just below the aldehyde, over which the nucleophile adds at the Burgi-Dunitz angle (~107 °) (top of Figure 3.6).[15] Chelation of the nucleophile and the aldehyde through a metal usually increases the selectivity of the reaction, which is present in this Cu-catalyzed reaction. The boxed in molecules indicate the products that form with Felkin-Anh control. Note that **II/III** and **VI/VII** are enantiomers of each other, meaning they are indistinguishable by ^{1}H NMR spectroscopy. If the reaction to form **3.51** proceeded with complete Felkin-Anh control, it would form **II/III** and **VI/VII**, which would appear as only two compounds in a ^{1}H NMR spectrum. An enantioselective variant of these reactions is presently being developed.
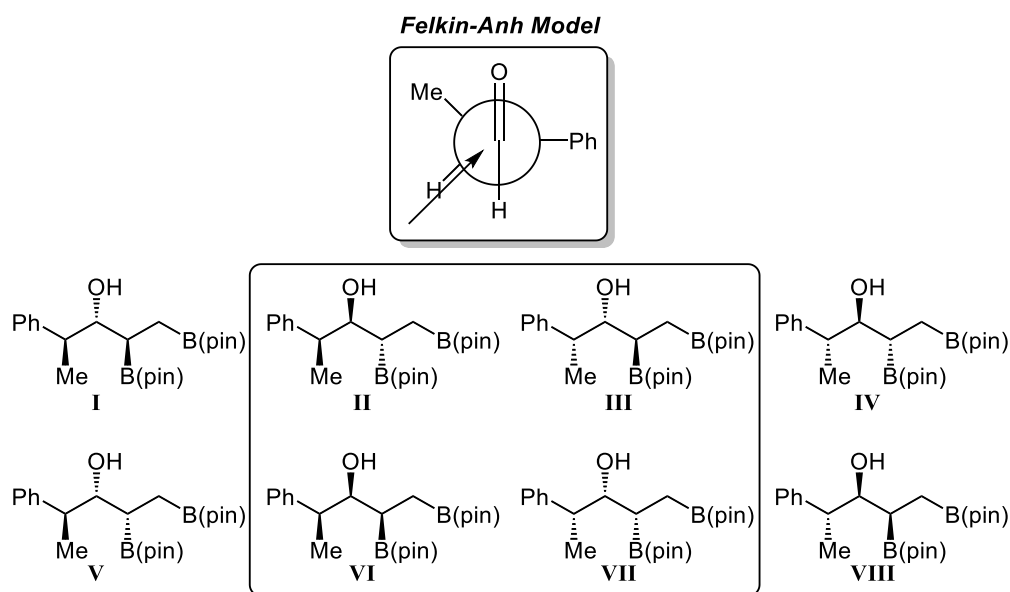
Figure 3.6 All possible stereoisomers of **3.51**, the boxed in molecules are those favored by the

Felkin-Anh model of stereocontrol

330

3.9   Functionalization Reactions

The organoboron moieties of the 1-hydroxy-2,3-bisboronate ester products produced through this methodology are capable of being selectively functionalized into several different groups. As depicted in Scheme 3.12: oxidation of geranial-derived 1-hydroxy-2,3-bisboronate ester **3.19** with basic H_2O_2 produces the 1,2,3-triol in 93% yield with retained diastereopurity. Silyl-protected hydroxy-bisboronate ester **3.53** (isolated in 62% yield from the hydroxyl-bisboronate in 84:16 d.r.) undergoes efficient Pd-catalyzed cross coupling of the primary boronate ester with vinyl bromides. In the presence of 5 mol% Pd(OAc)$_2$, 5 mol % RuPhos, and 300 mol% KOH, **3.53** is coupled to vinyl bromide **3.54** at the terminal boron group to afford 1,2-hydroxyboronate ester **3.55** in 51% yield as a single diastereomer. This shows that one or both boronate ester group of these products can be selectively functionalized and highlights the utility of these products as versatile synthetic intermediates.

Scheme 3.12 Functionalizations of 1-Hydroxy-2,3-Bisboronate Esters
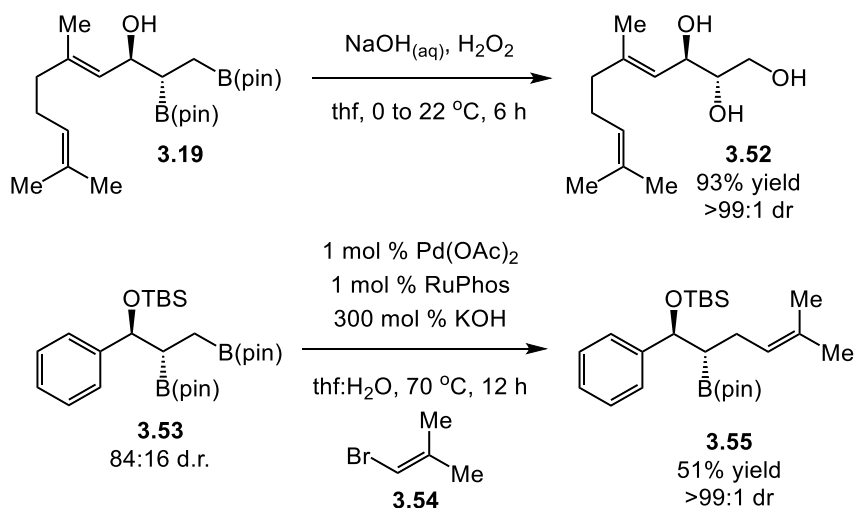
3.10   Conclusions

I have developed a highly enantio- and diastereoselective, multicomponent reaction that reacts vinyl boronic acid pinacol ester, B$_2$(pin)$_2$, and aldehydes together to form 1-hydroxy-2,3-bisboronate esters. The optimal reaction conditions involve 10 mol % CuO*t*-Bu and 11 mol % *(R)*-Cl-OMe-biphep in benzene at 22 °C. The reaction is tolerant of a number of aryl, alkenyl, and alkyl aldehydes. It was

discovered that the presence of Lewis bases like thf or nitriles significantly erodes the enantioselectivity of the reaction. During the course of these studies, it was discovered that cationic copper(acetonitrile)phosphine complexes can be deprotonated with KO*t*-Bu to yield a copper(keteneimide), examples of which are quite rare.

3.11   Experimental

■   **General:** All reactions were carried out in oven-dried (150 ˚C) or flame-dried glassware under an inert atmosphere of dried N_2 unless otherwise noted. Analytical thin-layer chromatography was performed on glass plates coated with 0.25 mm of 60 Å mesh silica gel. Plates were visualized by exposure to UV light (254 nm) and/or immersion into Seebach's or Seebach Stain stain followed by heating. Column chromatography was performed using silica gel P60 (mesh 230-400) supplied by Silicycle. Deactivated silica gel was prepared by stirring a slurry of the aforementioned silica gel in a 4.5% NaOAc aqueous solution for 15 minutes. The deactivated silica gel was collected by filtration and then dried in a 150 ˚C oven for 3 days. All solvents were sparged with argon and then purified under a positive pressure of argon through an SG Water, USA Solvent Purification System. Tetrahydrofuran, toluene, and benzene (OmniSolv) were passed successively through two columns of neutral alumina. Chlorobenzene, 2,4,6-trichlorobenzene, and fluorobenzene were dried over CaH_2 for 18 hours, distilled under reduced pressure, sparged with dry N_2, and then kept in an N_2-filled glovebox. The ambient temperature in the laboratory was approximately 22 ˚C.

■   **Instrumentation:** All ^{1}H NMR spectra were recorded on Bruker Spectrometers (AVANCE-600, AVANCE-500 and AVANCE-400). Chemical shifts are reported in ppm from tetramethylsilane and referenced to the residual protio solvent peak ($CDCl_3$: δ 7.26, C_6D_6: δ 7.16). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, qu = quartet, quint = quintet, br = broad, m = multiplet, app = apparent), integration, and coupling constants are given in Hz. ^{13}C NMR spectra were recorded on Bruker Spectrometers (AVANCE-600 and AVANCE-400) with carbon

and proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane and referenced to the residual protio solvent peak (CDCl$_3$: δ 77.16, C$_6$D$_6$: δ 128.06). All IR spectra were recorded on a Jasco 260 Plus Fourier transform infrared spectrometer. Optical rotations were determined using a Jasco P1010 polarimeter and concentrations are reported in g/100mL. Enantiomeric ratios were determined on an Agilent Technologies 1220 Infinity LC using the following columns: Diacel CHIRALPAK IA (4.6 mm x 250 mmL x 5 μm), Diacel CHIRALPAK IB (4.6 mm x 250 mmL x 5 μm), and Diacel CHIRALPAK IC (4.6 mm x 250 mmL x 5 μm). Mass Spectrometry samples were analyzed with a hybrid LTQ FT (ICR 7T) (ThermoFisher, Bremen, Germany) mass spectrometer. Samples were introduced *via* a micro-electrospray source at a flow rate of 10 µL/min (solvent composition 10:1 MeOH:H$_2$O or pure acetonitrile for copper complexes). Xcalibur (ThermoFisher, Breman, Germany) was used to analyze the data. Molecular formula assignments were determined with Molecular Formula Calculator (v 1.2.3). Low-resolution mass spectrometry (linear ion trap) provided independent verification of molecular weight distributions. All observed species were singly charged, as verified by unit *m/z* separation between mass spectral peaks corresponding to the ^{12}C and ^{13}C^{12}C$_{c-1}$ isotope for each elemental composition.

■ **Reagents:** All liquid aldehydes were distilled from CaH$_2$ or CaSO$_4$ under reduced pressure and then sparged with dry N$_2$. Solid aldehydes were purified *via* recrystallization, followed by azeotropic drying with benzene. Tetrakis(acetonitrile)copper hexafluorophosphate was purchased from Sigma Aldrich and kept in an N$_2$-filled glove box. All chiral phosphine ligands used were purchased from Strem Chemicals Inc. and used as received.

4-Anisaldehyde was purchased from Alfa-Aesar, dried over CaH$_2$, distilled under reduced pressure, and then sparged with dry N$_2$

Bis(pinacolato)diboron was purchased from Frontier Scientific, recrystallized from boiling hexanes, azeotropically dried with benzene three times, and kept in an N$_2$-filled glovebox

Benzaldehyde was purchased from Alfa-Aesar, vacuum distilled from CaH_2, and then sparged with dry N_2

Benzene-*d₆* was purchased from Cambridge Isotope Laboratories and distilled over Na/benzophenone, sparged with dry N_2, and kept in an N_2-filled glove box over 4 Å molecular sieves

Benzoic Anhydride was purchased from Acros and used as received.

2-Bromobenzaldehyde was purchased from Alfa-Aesar, dried over CaH_2, distilled under reduced pressure, and then sparged with dry N_2

4-Bromobenzaldehyde was purchased from Alfa-Aesar, recrystallized from methanol, azeotropically dried with benzene three times, and then stored in an N_2-filled glovebox

Calcium hydride was purchased from Strem and used without further purification

Chloroform-*d₃* was purchased from Cambridge Isotope Laboratories and used without further purification

Cyclohexanecarboxyaldehyde was purchased from Alfa-Aesar, dried over CaH_2, distilled under reduced pressure, and then sparged with dry N_2

1-Cyclohex-1-enecarboxyaldehyde was purchased from Alfa-Aesar, dried over CaH_2, distilled under reduced pressure, and then sparged with dry N_2

Dihydrocinnamaldehyde was purchased from Alfa-Aesar, dried over CaH_2, distilled under reduced pressure, sparged with dry N_2, and stored at -20 °C

4-Dimethylaminopyridine was purchased from Sigma Aldrich and used as received.

4-Fluorobenzaldehyde was purchased from Alfa-Aesar, dried over CaH_2, distilled under reduced pressure, and then sparged with dry N_2

2-Furylaldehyde was purchased from Acros Organics, dried over CaH_2, distilled under reduced pressure, and then sparged with dry N_2

Geranial was synthesized according to a published literature procedure[16]

Hydrogen Peroxide was purchased as a 30% solution in water and stored at -20 °C

Isobutyraldehyde was purchased from Alfa-Aesar, dried over CaH_2, distilled under reduced pressure, sparged with dry N_2, and stored at -20 °C

Isovaleraldehyde was purchased from Alfa-Aesar, dried over CaH_2, distilled under reduced pressure, sparged with dry N_2, and stored at -20 °C.

Methoxyamine was prepared according to a literature procedure[17]

***n*-Butyllithium** was purchased from Strem and titrated with phenanthroline/*sec*-butanol

N-Boc-3-indolecarboxaldehyde was synthesized according to a published literature procedure[18]

Nicotinaldehyde was purchased from Alfa-Aesar, dried over CaH_2, distilled under reduced pressure, and then sparged with dry N_2

Nonanal was purchased from Alfa-Aesar, dried over CaH_2, distilled under reduced pressure, and then sparged with dry N_2

Palladium(II) Acetate was purchased from Strem Chemicals and used as received

Pivalaldehyde was purchased from Alfa-Aesar, dried over CaH_2, distilled under reduced pressure, sparged with dry N_2, and stored at -20 °C

Potassium *tert*-butoxide were purchased from Strem and used as received

RuPhos was purchased from Sigma Aldrich and used as received

Sodium Hydroxide was purchased from Fisher Scientific and used as received

***tert*-Butyldimethylsilyl chloride** was purchased from Sigma-Aldrich and used as received

Tiglic aldehyde was purchased from Alfa-Aesar, dried over CaH_2, distilled under reduced pressure, and then sparged with dry N_2

2-Tolualdehyde was purchased from Alfa-Aesar, dried over CaH_2, distilled under reduced pressure, and then sparged with dry N_2

Triethylamine was purchased from Sigma Aldrich, dried over CaH_2, and distilled under N_2.

3-Tolualdehyde was purchased from Alfa-Aesar, dried over CaH_2, distilled under reduced pressure, and then sparged with dry N_2

trans-**Cinnamaldehyde** was purchased from Alfa-Aesar, dried over CaH_2, distilled under reduced pressure, and then sparged with dry N_2

trans-**α-Methylcinnamaldehyde** was purchased from Alfa-Aesar, dried over CaH_2, distilled under reduced pressure, and then sparged with dry N_2

Vinyl boronic acid pinacol ester was purchased from Sigma Aldrich, dried over CaH_2, distilled under reduced pressure, sparged with dry N_2, and stored at -20 °C in an N_2-filled glovebox

- **Synthesis of Copper *tert*-butoxide (3.46)**
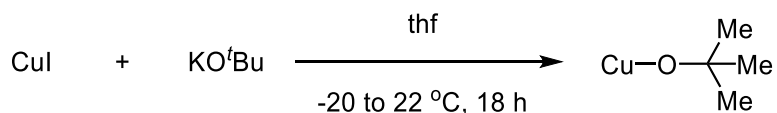
Procedure: In an N_2-filled glovebox, a -20 °C solution of KO*t*-Bu (295.6 mg, 2.625 mmol) in thf (3.35 mL) was added to a -20 °C suspension of CuI (500.0 mg, 2.625 mmol) in thf (3.35 mL) in a 20 mL scintillation vial. The vial was agitated and allowed to stand at -20 °C for 30 minutes. The reaction was then allowed to stir at ambient temperature for 18 hours. The heterogeneous reaction was allowed to settle and the supernatant was removed and filtered over Celite®. The filtrate was concentrated to afford CuO*t*-Bu as a tan/yellow powder in 75% yield (269 mg). **^{1}H NMR** (600 MHz, C_6D_6): δ 1.31 (s, 9H). **^{13}C NMR** (151 MHz, C_6D_6): δ 72.3, 35.5.
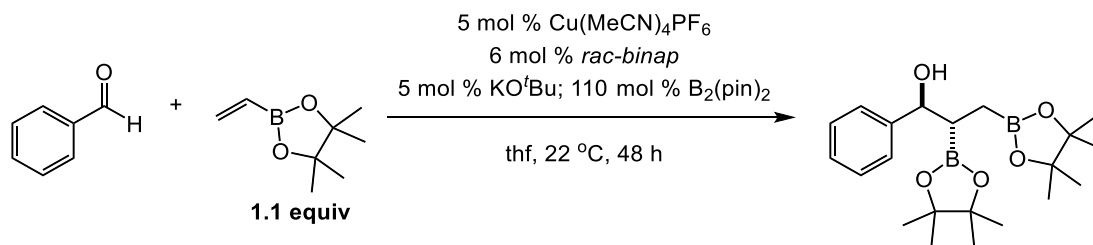
Procedure: In an N_2-filled glovebox, an 8-mL vial equipped with a magnetic stir bar was charged with Cu(MeCN)$_4$PF$_6$ (1.9 mg, 0.0050 mmol) and *rac*-binap (3.7 mg, 0.0060 mmol) and dissolved in 400 µL of thf. The reaction was allowed to stir at ambient temperature for 60 minutes, after which time the solution was transferred to an 8-mL vial containing KO^{t}Bu (0.6 mg, 0.005 mmol), the original vial was washed with 200 µL of thf and the reaction mixture allowed to stir at ambient temperature for 30 minutes. Bis(pinacolato)diboron (27.9 mg, 0.110 mmol) was added to the vial as a solution in thf (200 µL). Vinyl boronic acid pinacol ester (18.7 µL, 0.110 mmol) and the aldehyde (0.1 mmol) were added sequentially via syringe. The reaction was capped with a Teflon-lined lid, sealed with electrical tape, removed from the glovebox, and allowed to stir at ambient temperature for 48 hours. The reaction was quenched with 2 mL of a saturated aqueous solution of NH$_4$Cl and allowed to stir vigorously at 22 °C for 30 minutes. The aqueous layer was extracted three times with diethyl ether, and the combined organic extracts were dried over MgSO$_4$, filtered, and concentrated *in vacuo*. Conversions and diastereomeric ratios were determined by ^{1}H NMR, using hexamethyldisiloxane as an internal standard.

General Procedure (II) for the Enantio- and Diastereoselective Borylation/1,2-Addition Multicomponent Reaction
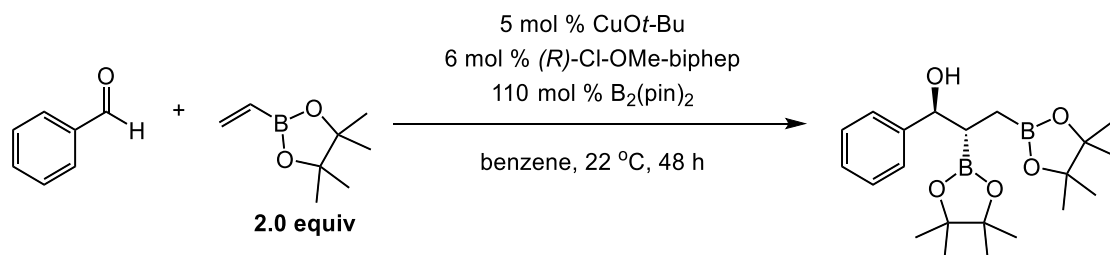
Procedure: In an N_2-filled glovebox, an 8-mL vial equipped with a magnetic stir bar was charged with CuO*t*-Bu (1.4 mg, 0.010 mmol) and *(R)*-Cl-OMe-biphep (7.2 mg, 0.011 mmol) and dissolved in 400 µL of benzene. The reaction was allowed to stir at ambient temperature for 60 minutes. Bis(pinacolato)diboron (27.9 mg, 0.110 mmol) was added to the vial as a solution in benzene (200 µL), followed by vinyl boronic acid pinacol ester (18.7 µL, 0.110 mmol), and the aldehyde (0.1 mmol) neat via syringe. The reaction was capped with a Teflon-lined lid, sealed with electrical tape, removed from the glovebox, and allowed to stir at ambient temperature for 48 hours. The reaction was quenched with 2 mL of a saturated aqueous solution of NH_4Cl and allowed to stir vigorously at 22 °C for 30 minutes. The aqueous layer was extracted three times with diethyl ether, and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Conversions and diastereomeric ratios were determined by ^{1}H NMR, using hexamethyldisiloxane as an internal standard.

For determination of the enantioselectivity of alkyl aldehyde addition products without a UV absorbing group (aryl ring, alkene, etc.), the 1-hydroxy-2,3-bisboroantes were oxidized to the triol and then benzoylated to afford the 1,2,3-tris-benzoate products, which were assayed via HPLC.

■ **General Procedure for Oxidation/Benzoylation of Alkyl Aldehyde Addition Products**
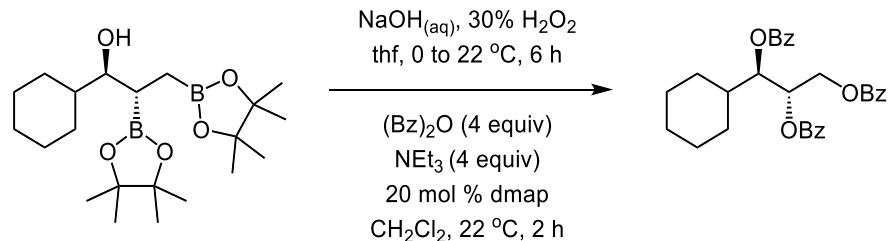
Procedure: A vial containing **2e** (0.1 mmol) was charged with thf (200 µL) and allowed to cool to 0 °C (ice/water bath). The reaction was charged with 3M NaOH (100 µL, 0.6 mmol) and then 30% H_2O_2 (100 µL, 2.0 mmol) dropwise. The reaction was allowed to slowly warm up to ambient temperature over 2 hours, followed by 4 hours of additional stirring at that temperature. The reaction was allowed to cool to 0 °C and quenched by dropwise addition of 1M $Na_2S_2O_3$. The reaction was diluted with water and then extracted 6X with EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered, and then concentrated *in vacuo*. The crude oxidation mixture was taken up in 1:1 hexanes:EtOAc and passed through a column of silica gel (to remove pinacol) and then flushed thoroughly with pure EtOAc to isolate the product. The purified triol (xx.x mg, x.xxx mmol), benzoic anhydride (xx.x mg, x.xxx mmol), and dmap (x.xx mg, x.xxx mmol) were added to an 8 mL vial equipped with a stir bar and then dried *in vacuo* for 10 minutes. The vial was purged with N_2 for 10 minutes and then charged with CH_2Cl_2 (300 µL) followed by NEt_3 (30 µL, 0.400 mmol). The reaction was allowed to stir at ambient temperature for 2 hours and then quenched with a saturated aqueous solution of NH_4Cl. The biphasic mixture was extracted 3X with diethyl ether, dried over $MgSO_4$, filtered, and then concentrated *in vacuo*. The product was purified via silica gel chromatography (5:1 pentane:Et$_2$O) to afford the product.

3.15
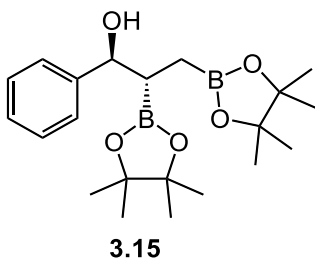
1-phenyl-2,3-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-ol (**3.15**). Following General Procedure II, the crude reaction mixture was purified *via* silica gel column chromatography (NaOAc deactivated silica gel, 5:1 to 2:1 pentane:Et$_2$O, Seebach Stain visualization) to yield the 1-hydroxy-2,3-bisboronate ester as a colorless oil in 74**%** yield (28.7 mg) and 98:2 anti:syn diastereomeric ratio. **^{1}H NMR** (600 MHz, CDCl3) δ 7.39 – 7.35 (m, 2H), 7.32 (t, J = 7.6 Hz, 2H), 7.26 – 7.22 (m, 1H), 4.72 (dd, J = 7.6, 3.7 Hz, 1H), 3.11 (d, J = 4.7 Hz, 1H), 1.66 (ddd, J = 8.9, 7.5, 5.7 Hz, 1H), 1.25 (d, J = 2.2 Hz, 24H), 0.88 – 0.74 (m, 2H). **^{13}C NMR** (151 MHz, CDCl$_3$) δ 144.3, 128.1, 127.1, 126.4, 83.5, 83.1, 28.4, 24.9, 24.8, 24.8, 24.8, 9.6. **IR** (υ/cm^{-1}): 3481 (s, br), 3080 (w), 2976 (s), 2941 (m), 2875 (m), 1489 (w), 1465 (m), 1330 (m), 1249 (w), 1230 (w), 1113 (w), 1111 (w). **HRMS** (ESI$^+$) calcd for C$_{21}$H$_{34}$B$_2$O$_5$Na$^+$ 411.2490, found: [M+Na$^+$] 411.2485. **[α]$_D^{22}$** = —20.6° (*c* = 5.45, CH$_2$Cl$_2$, *l* = 100 mm).

The absolute stereochemistry and diastereoselectivity of the product was determined by [α]$_D$ analysis of the oxidized product (1,2,3-triol) which has been previously characterized (found **[α]$_D^{22}$** = —71.67° (*c* = 2.95, CH$_2$Cl$_2$, *l* = 100 mm), lit: **[α]$_D^{21}$** = —89.73° (*c* = 0.66, CHCl$_3$).[19]

For all 1-hydroxy-2,3-bisboronate products, the ^{13}C NMR signals for the carbons bound to each boronate ester are highly broadened and sometimes absent, likely due to quadrupolar relaxation of the $^{10/11}$B nucleus coupled to ^{13}C nucleus.

Diacel CHIRALPAK IC Column; 98:2 hexanes:iPrOH; 0.3 mL/min; 210 nm

Racemic Material

VWD1 A, Wavelength=210 nm (JOANNOU\MVJ-VI-068 A FL_7.D)

File Information	
LC-File	MVJ-VI-068 A FL_7.D
File Path	C:\CHEM32\1\DATA\JOANNOU\
Date	04-Aug-15, 11:16:25
Sample	MVJ-VI-068 A FL_7
Sample Info	1-hydroxy-2,3-bisboronate ester; Column IC; 98:2 Hex:iPrOH; 0.30

#	Time	Area	Height	Width	Area%	Symmetry
1	43.252	19245.5	355.8	0.838	48.411	0.75
2	45.533	20509	348.2	0.9141	51.589	0.734

Enantio-Enriched Material

VWD1 A, Wavelength=210 nm (JOANNOU\MVJ-VII-038 A FL.D)

File Information	
LC-File	MVJ-VII-038 A FL.D
File Path	C:\CHEM32\1\DATA\JOANNOU\
Date	01-Jun-16, 00:58:44
Sample	MVJ-VII-038 A FL
Sample Info	1-Ph-1-hydroxybisboronate; 98:2 hexanes:iPrOH; 0.3 mL/min; IC C

#	Time	Area	Height	Width	Area%	Symmetry
1	43.49	3769.7	73.2	0.7979	4.412	0.86
2	45.293	81674.7	1311.8	0.9614	95.588	0.517

Anti **diastereomer:** (1*R*,2*R*) enantiomer**:** 43.4 min; (1*S*,2*S*) enantiomer: 45.3 min: 96:4 e.r.

3.31
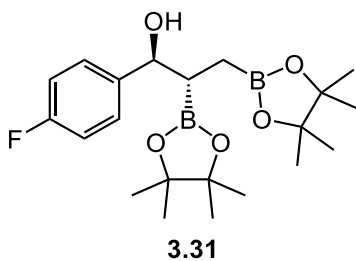
1-(4-fluorophenyl)-2,3-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-ol **(3.31)**.

Following General Procedure II, the crude reaction mixture was purified *via* silica gel column

chromatography (NaOAc deactivated silica gel, 5:1 to 2:1 pentane:Et$_2$O, Seebach Stain visualization) to yield the 1-hydroxy-2,3-bisboronate ester as a colorless oil in 70**%** yield (28.4 mg) and 98:2 anti:syn diastereomeric ratio. **¹H NMR** (600 MHz, Chloroform-d) δ 7.36 – 7.31 (m, 2H), 7.00 (t, J = 8.7 Hz, 2H), 4.70 (dd, J = 7.7, 2.9 Hz, 1H), 3.18 (d, J = 4.6 Hz, 1H), 1.65 – 1.57 (m, 1H), 1.25 (d, J = 1.5 Hz, 24H), 0.78 (qd, J = 16.1, 7.2 Hz, 2H). **¹³C NMR** (151 MHz, CDCl$_3$) δ 162.8, 161.1, 140.1, 140.0, 128.0, 128.0, 114.9, 114.7, 83.6, 83.2, 76.6, 28.5, 24.9, 24.8, 24.8, 24.8, 9.5. **IR** (υ/cm^{-1}): 3506 (s, br), 3080 (w), 2890 (m), 1510 (w), 1499 (m), 1340 (m), 1199 (w). **HRMS** (ESI$^+$) calcd for C$_{21}$H$_{33}$O$_5$B$_2$FNa$^+$ 429.2396, found: [M+Na] 429.2391. **[α]$_D$^{22}** = —39.4° (c = 5.40, CH$_2$Cl$_2$, l = 100 mm).

Enantiomeric excess was determined by HPLC analysis compared to the authentic racemic material. Absolute stereochemistry was inferred from the stereochemistry obtained for compound **3.15**.

Diacel CHIRALPAK IA Column; 98.8:1.2 hexanes:iPrOH; 0.3 mL/min; 210 nm

Racemic Material

#	Time	Area	Height	Width	Area%	Symmetry
1	42.098	41263.1	751.9	0.8473	50.668	0.6
2	44.466	40175.1	653.3	0.9465	49.332	0.591

File Information	
LC-File	MVJ-VI-262 C FL_5.D
File Path	C:\CHEM32\1\DATA\JOANNOU\
Date	18-Mar-16, 15:11:41
Sample	MVJ-VI-262 C FL_5
Sample Info	4-FPh-1-hydroxy-2,3-bisboronate ester racemic; 98.8:1.2 iPrOH:he

#	Time	Area	Height	Width	Area%	Symmetry
1	42.455	31406.2	567.6	0.8556	95.583	0.65
2	44.13	1451.4	28.9	0.7566	4.417	0.479

Anti **diastereomer:** (1*S*,2*S*) enantiomer**:** 42.5 min; (1*R*,2*R*) enantiomer: 44.1 min: <u>96:4 e.r.</u>

3.32

1-(4-bromophenyl)-2,3-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-ol **(3.32)**.

Following General Procedure II, the crude reaction mixture was purified *via* silica gel column

chromatography (NaOAc deactivated silica gel, 5:1 to 2:1 pentane:Et$_2$O, Seebach Stain visualization)

to yield the 1-hydroxy-2,3-bisboronate ester as a colorless oil in **68%** yield (31.8 mg) and 98:2 anti:syn

diastereomeric ratio. **^{1}H NMR** (400 MHz, CDCl3) δ 7.47 – 7.40 (m, 2H), 7.26 – 7.22 (m, 2H), 4.68

(d, J = 7.3 Hz, 1H), 3.22 (s, 1H), 1.63 – 1.56 (m, 1H), 1.25 (s, 24H), 0.80 (ddd, J = 14.9, 7.5, 5.7 Hz,

2H). **^{13}C NMR** (151 MHz, CDCl$_3$) δ 143.4, 131.1, 128.2, 120.8, 83.6, 83.2, 76.7, 28.3, 24.9, 24.8, 24.8,

24.8, 9.6. **IR** (υ/cm^{-1}): 3400 (s, br), 2988 (w), 2850 (m), 1599 (w), 1511 (m), 1329 (m). **HRMS** (ESI$^+$)

calcd for C$_{21}$H$_{33}$O$_5$B$_2$BrNa$^+$ 489.1595, found: [M+Na] 489.1593. **[α]$_D^{22}$** = —19.3° (*c* = 6.05, CH$_2$Cl$_2$, *l*

= 100 mm).

Enantiomeric excess was determined by HPLC analysis compared to the authentic racemic material.

Absolute stereochemistry was inferred from the stereochemistry obtained for compound **3.15**.

Diacel CHIRALPAK IC Column; 98:2 hexanes:iPrOH; 0.3 mL/min; 210 nm

Racemic Material

VWD1 A, Wavelength=210 nm (JOANNOU\MVJ-VI-185 C FL.D)

File Information	
LC-File	MVJ-VI-185 C FL.D
File Path	C:\CHEM32\1\DATA\JOANNOU\
Date	02-Jun-16, 00:14:05
Sample	MVJ-VI-185 C FL
Sample Info	1-4-BrPh-1-hydroxy-2,3-bisboronate rac; 98:2 hexanes:iPrOH; 0.3

#	Time	Area	Height	Width	Area%	Symmetry
1	29.065	21349	568	0.6264	51.893	0.801
2	33.289	19791.4	464.5	0.7102	48.107	0.781

Enantio-Enriched Material

VWD1 A, Wavelength=210 nm (JOANNOU\MVJ-VII-038 C FL.D)

File Information	
LC-File	MVJ-VII-038 C FL.D
File Path	C:\CHEM32\1\DATA\JOANNOU\
Date	01-Jun-16, 03:00:19
Sample	MVJ-VII-038 C FL
Sample Info	1-4-BrPh-1-hydroxybisboronate; 98:2 hexanes:iPrOH; 0.3 mL/min;

#	Time	Area	Height	Width	Area%	Symmetry
1	28.72	52694.8	1417.3	0.5728	95.236	0.681
2	33.012	2636.2	61.9	0.6537	4.764	0.882

Anti **diastereomer:** (1*S*,2*S*) enantiomer**:** 28.7 min; (1*R*,2*R*) enantiomer: 33.0 min: 95:5 e.r.
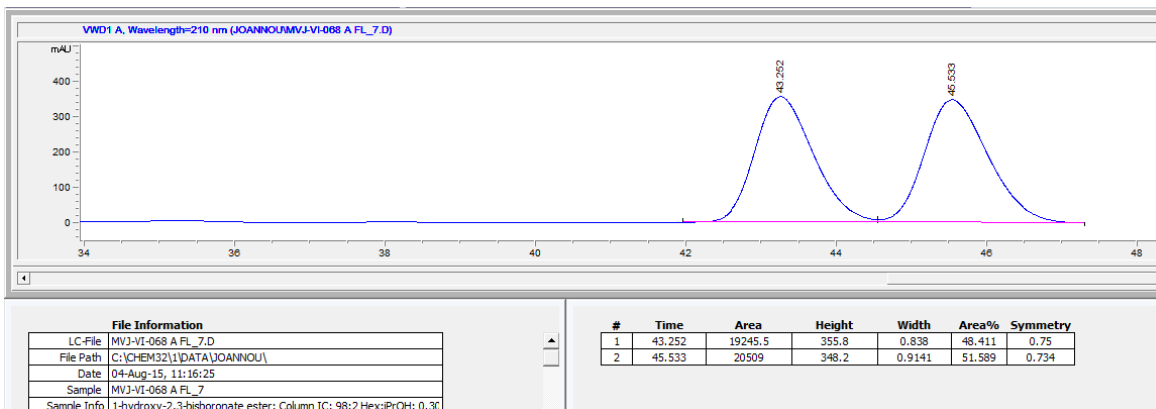
3.33

1-(4-methoxyphenyl)-2,3-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-ol **(3.33)**.

Following General Procedure II, the crude reaction mixture was purified *via* silica gel column chromatography (NaOAc deactivated silica gel, 5:1 to 2:1 pentane:Et$_2$O, Seebach Stain visualization)

344

to yield the 1-hydroxy-2,3-bisboronate ester as a colorless oil in 70**%** yield (29.3 mg) and 98:2 anti:syn

diastereomeric ratio. **¹H NMR** (600 MHz, CDCl3) δ 7.31 – 7.26 (m, 2H), 6.88 – 6.84 (m, 2H), 4.66

(dd, J = 7.9, 2.7 Hz, 1H), 3.80 (s, 3H), 3.04 (d, J = 4.3 Hz, 1H), 1.62 (ddd, J = 9.0, 7.9, 5.7 Hz, 1H),

1.26 (s, 12H), 1.23 (s, 12H), 0.81 – 0.70 (m, 2H). **¹³C NMR** (151 MHz, CDCl$_3$) δ 158.7, 136.5, 127.6,

113.4, 83.5, 83.1, 76.9, 55.3, 28.4, 24.9, 24.9, 24.8, 24.8, 9.6. **IR** (υ/cm^{-1}): 3489 (s, br), 2921 (m), 1567

(m), 1482 (w), 1289 (m). **HRMS** (ESI$^+$) calcd for C$_{22}$H$_{36}$O$_6$B$_2$Na$^+$ 441.2596, found: [M+Na] 441.2590.

[α]$_D^{22}$ = —27.8° (c = 5.56, CH$_2$Cl$_2$, l = 100 mm).

Enantiomeric excess was determined by HPLC analysis compared to the authentic racemic material.

Absolute stereochemistry was inferred from the stereochemistry obtained for compound **3.15**.

Diacel CHIRALPAK IC Column; 98:2 hexanes:iPrOH; 0.3 mL/min; 210 nm

Racemic Material

	File Information
LC-File	MVJ-VI-186 A FL.D
File Path	C:\CHEM32\1\DATA\JOANNOU\
Date	21-Mar-16, 15:39:30
Sample	MVJ-VI-186 A FL
Sample Info	4-OMePh-1-hydroxy-2,3-bisboronate ester racemic; 98:2 hexanes:i

#	Time	Area	Height	Width	Area%	Symmetry
1	103.109	51926.5	364.4	2.3747	54.178	0.459
2	111	43917.4	270.7	2.7043	45.822	0.495

Enantio-Enriched Material

Anti **diastereomer:** (1*S*,2*S*) enantiomer**:** 104.0 min; (1*R*,2*R*) enantiomer: 112.0 min: 95:5 e.r.

3.16
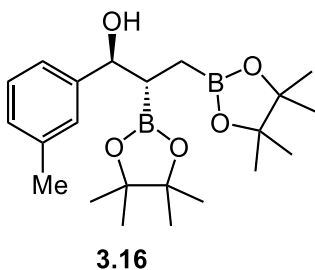
2,3-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(3-tolyl)propan-1-ol (3.16). Following General Procedure II, the crude reaction mixture was purified *via* silica gel column chromatography (NaOAc deactivated silica gel, 5:1 to 2:1 pentane:Et$_2$O, Seebach Stain visualization) to yield the 1-hydroxy-2,3-bisboronate ester as a colorless oil in **75%** yield (30.2 mg) and 98:2 anti:syn diastereomeric ratio. **^{1}H NMR** (600 MHz, CDCl3) δ 7.22 – 7.18 (m, 3H), 7.16 – 7.13 (m, 1H), 7.05 (dd, J = 7.9, 1.1 Hz, 1H), 4.68 (d, J = 7.5 Hz, 1H), 3.09 (s, 1H), 2.34 (s, 3H), 1.67 – 1.61 (m, 1H), 1.25 (d, J = 5.3 Hz, 24H), 0.87 – 0.74 (m, 2H). **^{13}C NMR** (151 MHz, CDCl$_3$) δ 144.3, 137.5, 127.9, 127.8, 127.1, 123.6, 83.5, 83.1, 77.3, 28.4, 24.9, 24.9, 24.8, 24.8, 21.5, 9.7. **IR** (υ/cm^{-1}): 3356 (s, br), 2879 (m), 1603 (m), 1594 (w), 1392 (m), 1303 (w). **HRMS** (ESI$^+$) calcd for C$_{22}$H$_{36}$O$_5$B$_2$Na$^+$ 425.2647, found: [M+Na] 425.2642. **[α]$_D^{22}$** = —30.2° (*c* = 5.73, CH$_2$Cl$_2$, *l* = 100 mm).

Enantiomeric excess was determined by HPLC analysis compared to the authentic racemic material. Absolute stereochemistry was inferred from the stereochemistry obtained for compound **3.15**.

Diacel CHIRALPAK IC Column; 98:2 hexanes:iPrOH; 0.3 mL/min; 210 nm

Racemic Material

#	Time	Area	Height	Width	Area%	Symmetry
1	42.456	21966.2	416.6	0.8152	48.208	0.75
2	45.337	23599.3	409.7	0.8941	51.792	0.722

File Information
LC-File: MVJ-VI-186 B FL.D
File Path: C:\CHEM32\1\DATA\JOANNOU\
Date: 16-Mar-16, 13:51:23
Sample: MVJ-VI-186 B FL
Sample Info: 3-MePh-1-hydroxy-2,3-bisboronate; 98:2 hexanes:iPrOH; 0.3 mL/m

Enantio-Enriched Material

#	Time	Area	Height	Width	Area%	Symmetry
1	43.357	4391.6	85	0.8613	5.379	0.863
2	45.954	77246.3	1219.9	1.0554	94.621	0.541

File Information
LC-File: MVJ-VII-039 A FL.D
File Path: C:\CHEM32\1\DATA\JOANNOU\
Date: 01-Jun-16, 06:01:57
Sample: MVJ-VII-039 A FL
Sample Info: 1-3-MePh-1-hydroxybisboronate; 98:2 hexanes:iPrOH; 0.3 mL/min;

Anti **diastereomer:** (1*R*,2*R*) enantiomer**:** 43.4 min; (1*S*,2*S*) enantiomer: 46.0 min: 95:5 e.r.

3.34
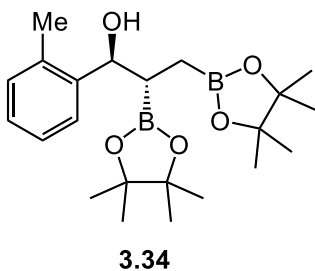
2,3-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(2-tolyl)propan-1-ol **(3.34)**. Following

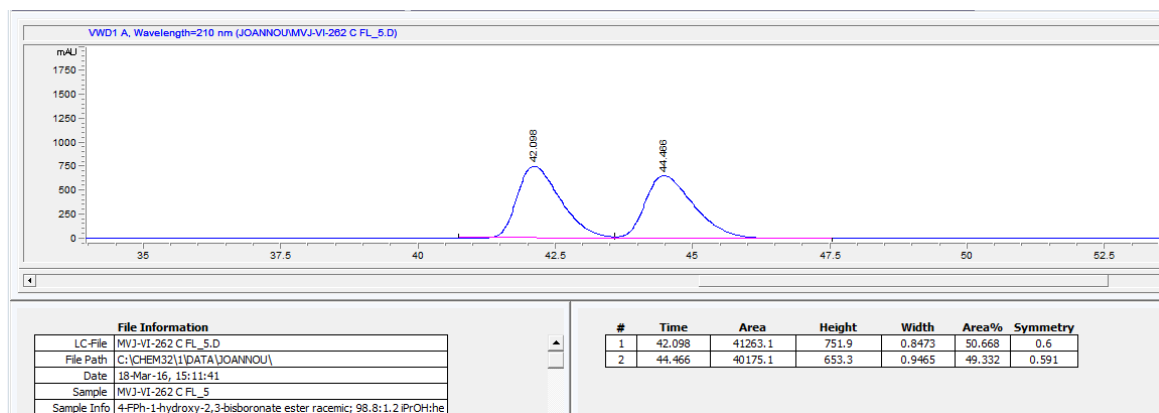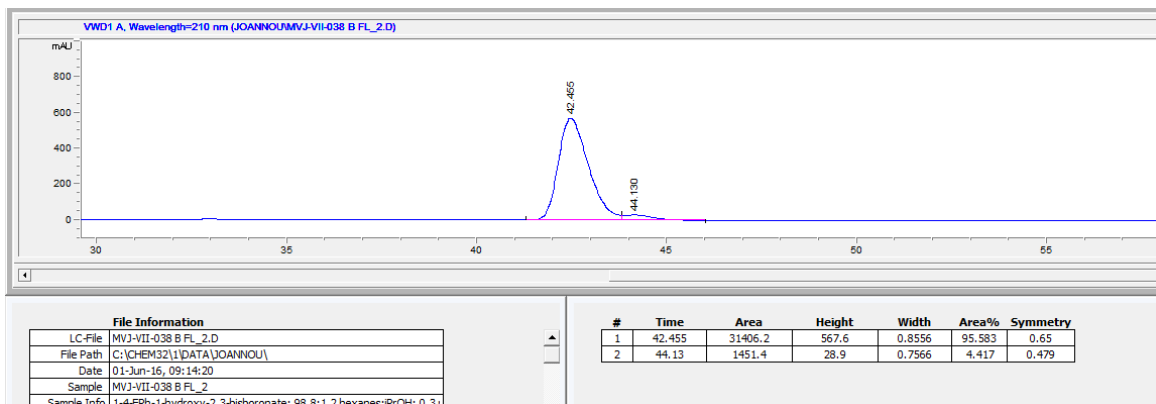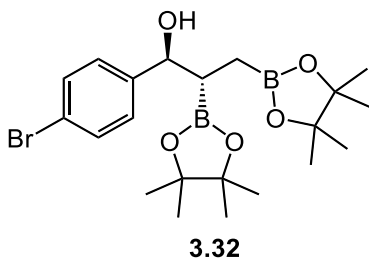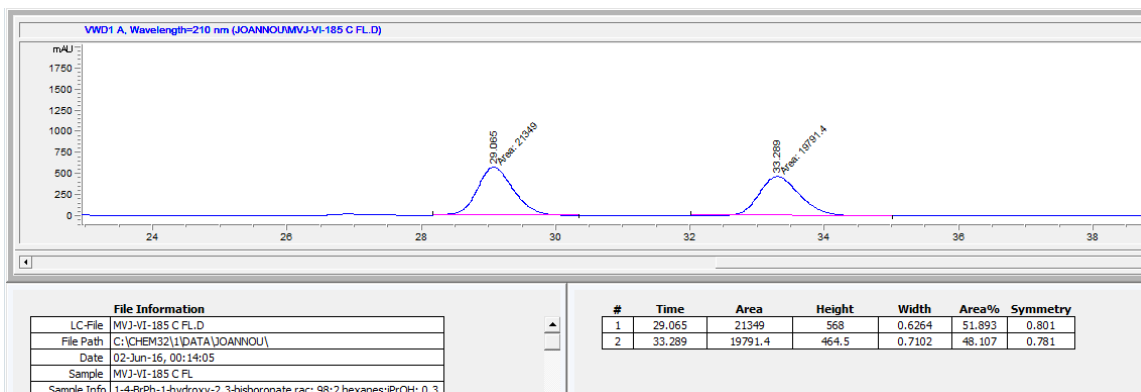General Procedure II, the crude reaction mixture was purified *via* silica gel column chromatography

(NaOAc deactivated silica gel, 5:1 to 2:1 pentane:Et$_2$O, Seebach Stain visualization) to yield the 1-

hydroxy-2,3-bisboronate ester as a colorless oil in 81% yield (32.6 mg) and 98:2 anti:syn diastereomeric ratio. ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.48 (dd, J = 7.7, 1.4 Hz, 1H), 7.20 (td, J = 7.4, 1.6 Hz, 1H), 7.16 – 7.08 (m, 2H), 4.91 (d, J = 6.8 Hz, 1H), 3.21 (s, 1H), 2.37 (s, 3H), 1.67 (dt, J = 8.7, 6.5 Hz, 1H), 1.26 (m, 12H), 1.25 (s, 12H), 0.92 – 0.81 (m, 2H). ^{13}C NMR (151 MHz, CDCl$_3$) δ 142.7, 135.3, 130.1, 126.8, 125.9, 125.6, 83.5, 83.1, 74.0, 24.9, 24.9, 24.8, 19.5, 10.2. IR (υ/cm^{-1}): 3892 (s, br), 2899 (m), 2657 (m), 1455 (w), 1515 (w) 1301 (m). HRMS (ESI$^+$) calcd for C$_{22}$H$_{36}$O$_5$B$_2$Na$^+$ 425.2647, found: [M+Na] 425.2643. $[α]_D^{22}$ = —39.2° (c = 6.19, CH$_2$Cl$_2$, l = 100 mm).

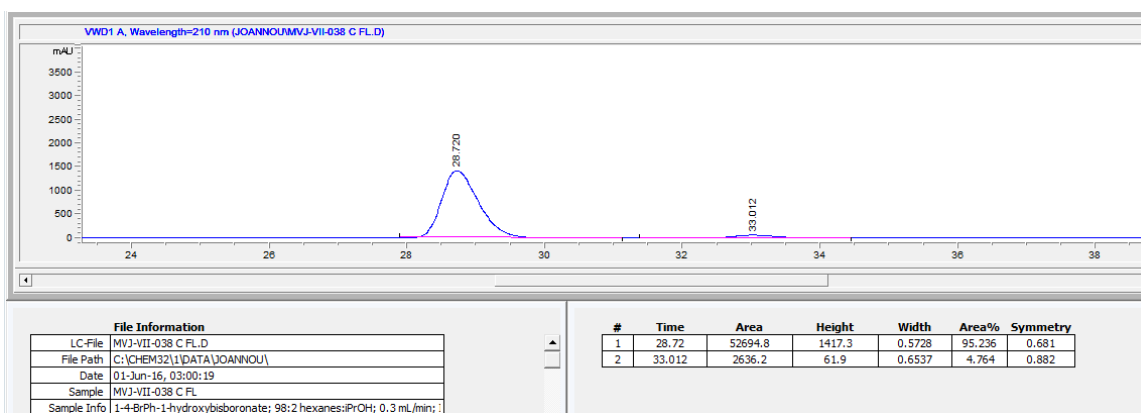Enantiomeric excess was determined by HPLC analysis compared to the authentic racemic material. Absolute stereochemistry was inferred from the stereochemistry obtained for compound 3.15.

Diacel CHIRALPAK IC Column; 98:2 hexanes:iPrOH; 0.3 mL/min; 210 nm

Racemic Material

	File Information
LC-File	MVJ-VI-192 A FL.D
File Path	C:\CHEM32\1\DATA\JOANNOU\
Date	16-Mar-16, 17:52:06
Sample	MVJ-VI-192 A FL
Sample Info	2-MePh-1-hydroxy-2,3-bisboronate racemic; 98:2 hexanes:iPrOH; (

#	Time	Area	Height	Width	Area%	Symmetry
1	38.279	17802.7	374.1	0.7352	48.412	0.769
2	53.808	18970.5	275.9	1.061	51.588	0.659

#	Time	Area	Height	Width	Area%	Symmetry
1	39.444	3709.8	74.8	0.7643	4.059	0.815
2	55.191	87681	1007.2	1.2906	95.941	0.368

Anti **diastereomer:** (1*R*,2*R*) enantiomer**:** 39.4 min; (1*S*,2*S*) enantiomer: 55.2 min: 96:4 e.r.

The peak at 42 min is the major enantiomer of the minor diastereomer, which was not present in the racemic product. It fluoresces more intensely than the *anti* diastereomer.
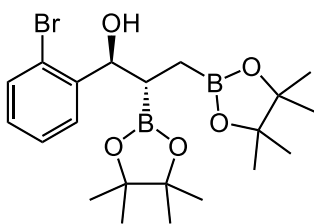
3.35

1-(2-bromophenyl)-2,3-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-ol **(3.35).** Following General Procedure II, the crude reaction mixture was purified *via* silica gel column chromatography (NaOAc deactivated silica gel, 5:1 to 2:1 pentane:Et$_2$O, Seebach Stain visualization) to yield the 1-hydroxy-2,3-bisboronate ester as a colorless oil in 83**%** yield (38.8 mg) and 98:2 anti:syn diastereomeric ratio. **^{1}H NMR** (600 MHz, CDCl3) δ 7.58 (dd, J = 7.8, 1.7 Hz, 1H), 7.50 (dd, J = 8.0, 1.2 Hz, 1H), 7.33 – 7.29 (m, 1H), 7.09 (ddd, J = 7.9, 7.3, 1.7 Hz, 1H), 5.03 (dd, J = 6.5, 3.2 Hz, 1H), 3.65 (d, J = 4.8 Hz, 1H), 1.76 (dt, J = 9.4, 5.4 Hz, 1H), 1.27 (d, J = 3.9 Hz, 24), 1.05 (dd, J = 15.9, 9.2 Hz, 1H), 0.90 (dd, J = 16.0, 5.0 Hz, 1H). **^{13}C NMR** (151 MHz, CDCl$_3$) δ 143.6, 132.4, 128.4, 127.9, 127.2, 123.0, 83.5, 83.2, 76.6, 27.5, 25.0, 24.9, 24.9, 24.8, 10.7. **IR** (υ/cm^{-1}): 3545 (s, br), 2923 (m),

1525 (m), 1359 (m), 1189 (w). **HRMS** (ESI$^+$) calcd for $C_{21}H_{33}O_5B_2BrNa^+$ 489.1595, found: [M+Na]

489.1590. $[\alpha]_D^{22}$ = —41.1° (c = 7.38, CH_2Cl_2, l = 100 mm).

Enantiomeric excess was determined by HPLC analysis compared to the authentic racemic material.

Absolute stereochemistry was inferred from the stereochemistry obtained for compound **3.15**.

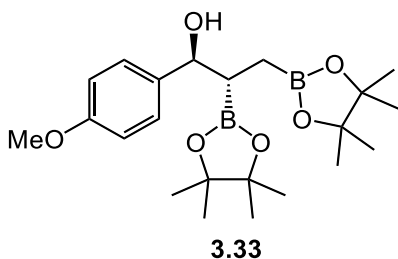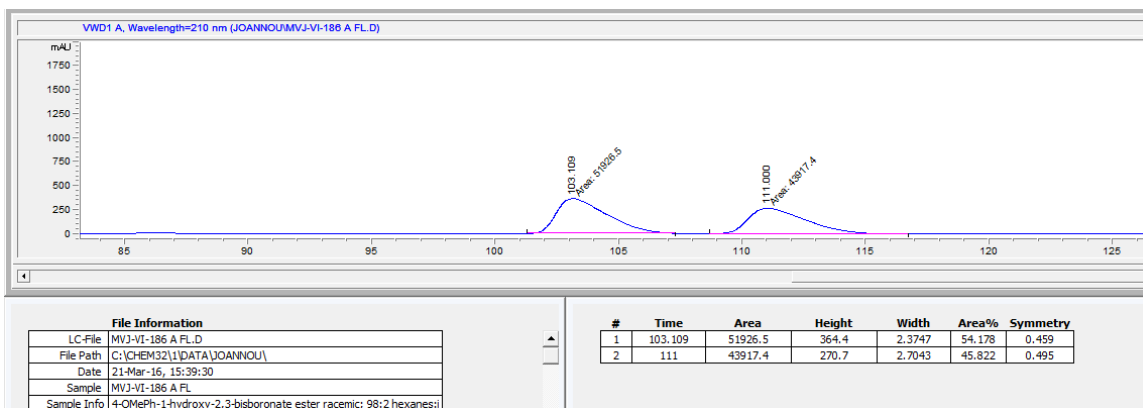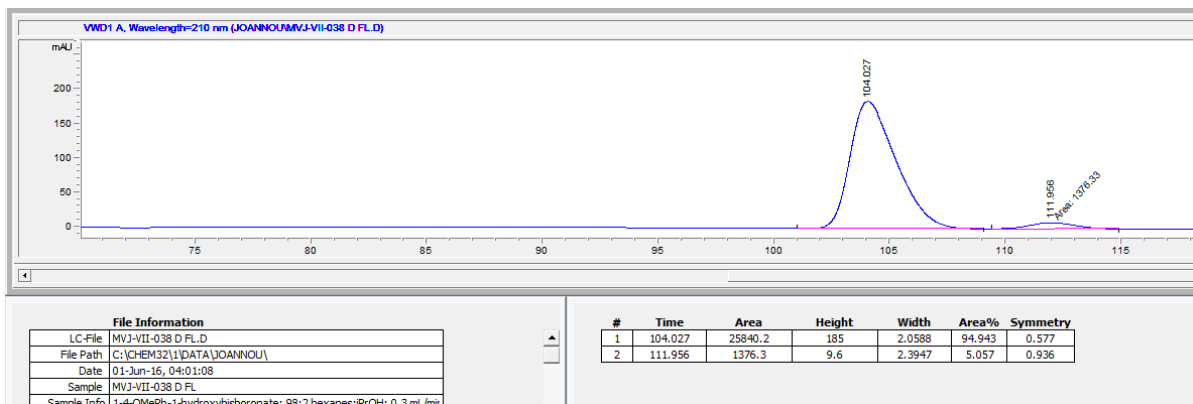*Diacel CHIRALPAK IC Column; 98:2 hexanes:iPrOH; 0.3 mL/min; 210 nm*

Racemic Material

	#	Time	Area	Height	Width	Area%	Symmetry
	1	28.427	92608.5	2427	0.5912	49.536	0.633
	2	43.445	94343.3	1478.8	0.9653	50.464	0.455

File Information
LC-File MVJ-VI-205 A FL.D
File Path C:\CHEM32\1\DATA\JOANNOU\
Date 22-Mar-16, 13:30:12
Sample MVJ-VI-205 A FL
Sample Info 2-BrPh-1-hydroxy-2,3-bisboronate ester racemic; 98:2 hexanes:iPr

Enantio-Enriched Material

	#	Time	Area	Height	Width	Area%	Symmetry
	1	28.845	5936.2	160.3	0.571	4.494	0.795
	2	44.426	126162.2	1842.6	1.0378	95.506	0.397

File Information
LC-File MVJ-VII-039 C FL.D
File Path C:\CHEM32\1\DATA\JOANNOU\
Date 01-Jun-16, 08:13:35
Sample MVJ-VII-039 C FL
Sample Info 1-2-BrPh-1-hydroxybisboronate; 98:2 hexanes:iPrOH; 0.3 mL/min;
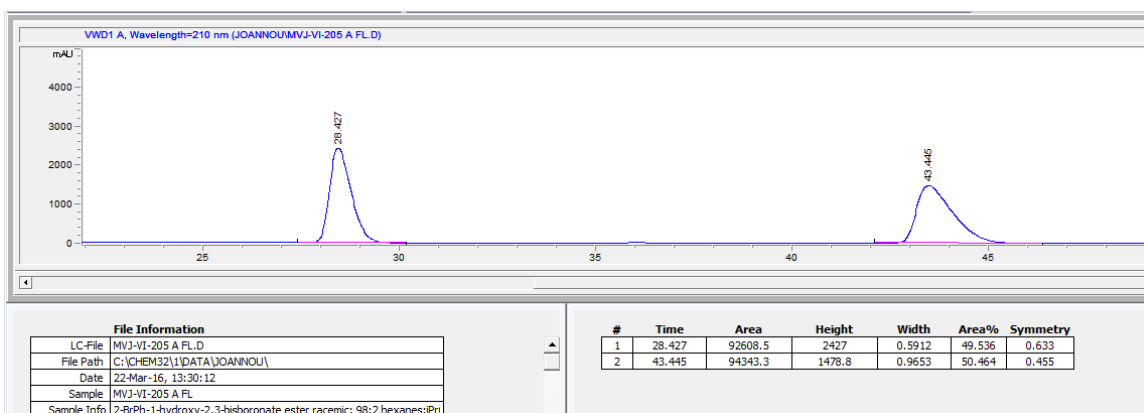
Anti **diastereomer:** (1R,2R) enantiomer**:** 28.8 min; (1S,2S) enantiomer: 44.4 min: 96:4 e.r.

The peak at 36 min is the major enantiomer of the minor diastereomer, which was not present in the

racemic product. It fluoresces more intensely than the *anti* diastereomer.
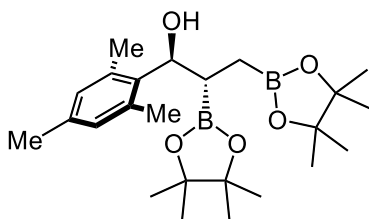
3.37

1-mesityl-2,3-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-ol **(3.37)**. Following General Procedure II, the crude reaction mixture was purified *via* silica gel column chromatography (NaOAc deactivated silica gel, 5:1 to 2:1 pentane:Et$_2$O, Seebach Stain visualization) to yield the 1-hydroxy-2,3-bisboronate ester as a colorless oil in 44**%** yield (18.9 mg) and >99:1 anti:syn diastereomeric ratio. **^{1}H NMR** (600 MHz, CDCl$_3$) δ 6.80 (s, 2H), 5.11 (d, J = 11.2 Hz, 1H), 2.65 (s, 1H), 2.44 (s, 6H), 2.25 (s, 3H), 2.00 (td, J = 11.5, 4.3 Hz, 1H), 1.33 (s, 12H), 1.20 (d, J = 1.8 Hz, 12H), 0.78 – 0.71 (m, 1H), 0.50 (dd, J = 15.8, 4.3 Hz, 1H). **^{13}C NMR** (151 MHz, CDCl$_3$) δ 137.1, 136.2, 135.8, 83.5, 83.4, 83.0, 73.9, 25.0, 24.9, 24.9, 24.9, 21.1, 20.8. **IR** (υ/cm^{-1}): 3901 (s, br), 2877 (m), 2513 (m), 1493 (w) 1300 (m). **HRMS** (ESI$^+$) calcd for C$_{24}$H$_{40}$O$_5$B$_2$Na$^+$ 453.2960, found: [M+Na] 453.2955. **[α]$_D^{22}$** = —29.9° (*c* = 3.59, CH$_2$Cl$_2$, *l* = 100 mm).
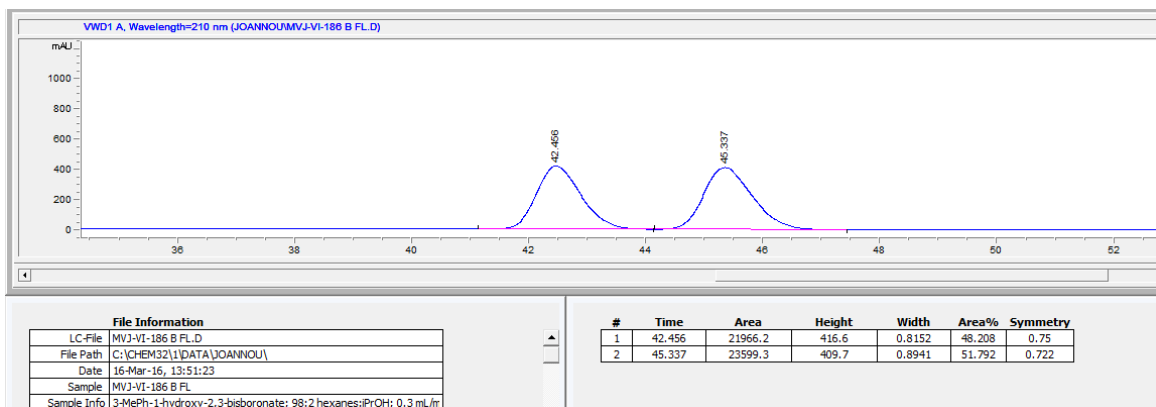
Enantiomeric excess was determined by HPLC analysis compared to the authentic racemic material. Absolute stereochemistry was inferred from the stereochemistry obtained for compound **3.15**.
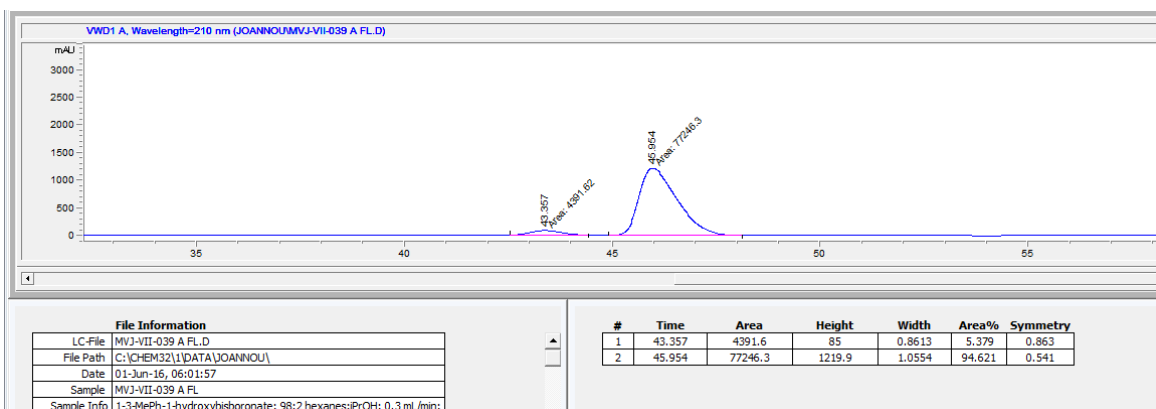
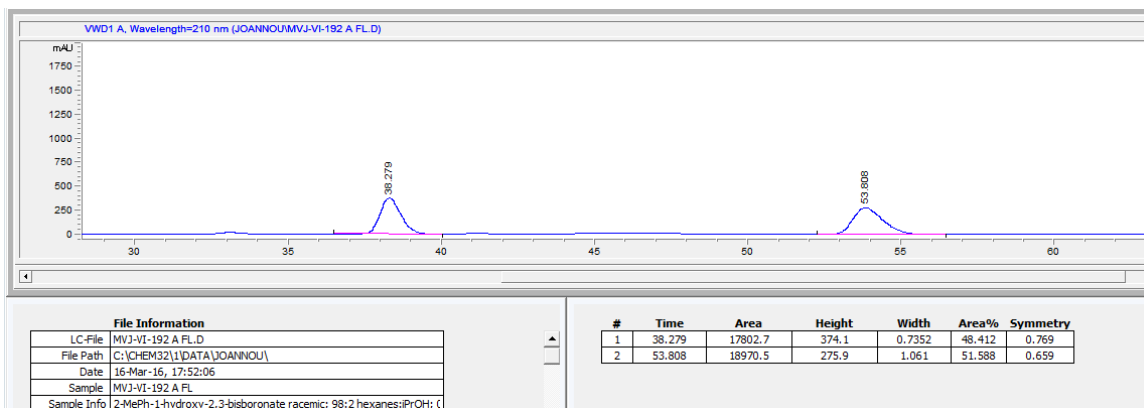*Diacel CHIRALPAK IC Column; 98:2 hexanes:iPrOH; 0.3 mL/min; 210 nm*

Racemic Material

#	Time	Area	Height	Width	Area%	Symmetry
1	29.873	67567.5	1582.9	0.658	48.843	0.598
2	49.362	70769	925.9	1.1617	51.157	0.464

File Information

LC-File	MVJ-VI-197 A FL.D
File Path	C:\CHEM32\1\DATA\JOANNOU\
Date	16-Mar-16, 20:15:05
Sample	MVJ-VI-197 A FL
Sample Info	mesityl-1-hydroxy-2,3-bisboronate racemic; 98:2 hexanes:iPrOH; 0

#	Time	Area	Height	Width	Area%	Symmetry
1	30.836	78101.1	1702.9	0.7644	94.301	0.574
2	52.627	4719.5	70.4	1.1178	5.699	0.818
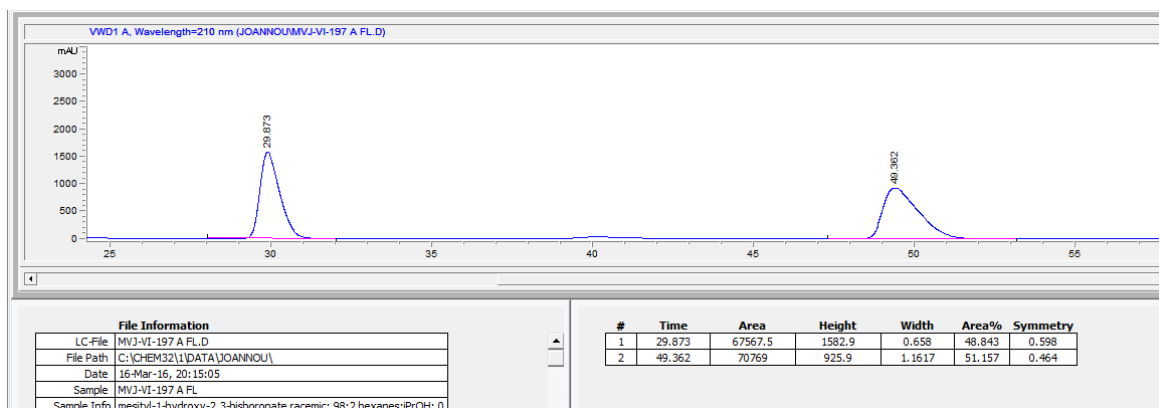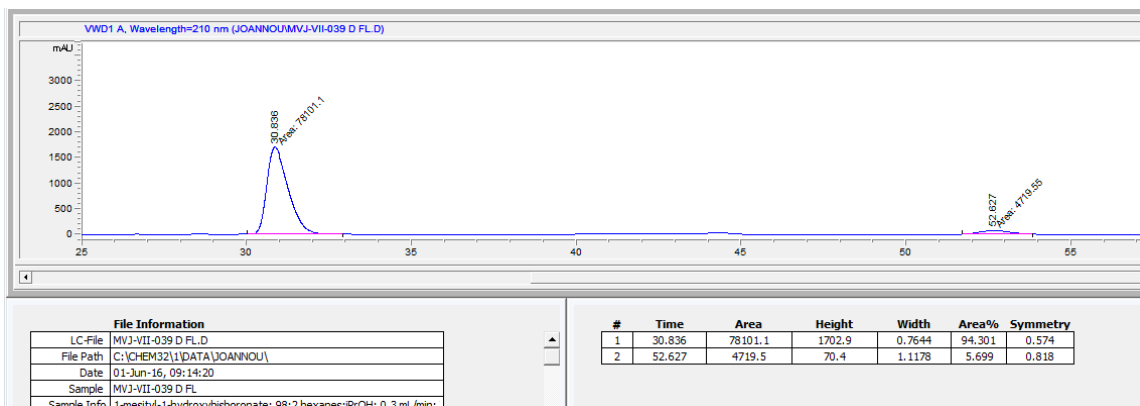
Anti **diastereomer:** (1*S*,2*S*) enantiomer**:** 30.8 min; (1*R*,2*R*) enantiomer: 52.6 min: 94:6 e.r.

3.17
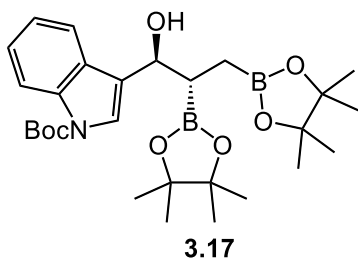
tert-butyl 3-(1-hydroxy-2,3-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl)-1H-indole-1-

carboxylate (3.17). Following General Procedure II, the crude reaction mixture was purified *via* silica

gel column chromatography (NaOAc deactivated silica gel, 5:1 to 2:1 pentane:Et$_2$O, Seebach Stain

visualization) to yield the 1-hydroxy-2,3-bisboronate ester as a colorless oil in **63%** yield (33.2 mg)

and 75:25 *anti*:*syn* diastereomeric ratio. *Anti* **diastereomer**: **^{1}H NMR** (600 MHz, CDCl$_3$) δ 8.15 (s,

1H), 7.79 (dt, J = 7.9, 1.0 Hz, 1H), 7.52 (s, 1H), 7.34 – 7.29 (m, 1H), 7.22 (ddd, J = 8.1, 7.2, 1.1 Hz,

1H), 4.99 (t, J = 5.9 Hz, 1H), 3.20 (s, 1H), 1.90 (dt, J = 8.3, 6.5 Hz, 1H), 1.66 (s, 9H), 1.27 (d, J = 3.6

Hz, 12H), 1.26 – 1.25 (m, 12H), 1.00 (dd, J = 16.2, 6.2 Hz, 1H), 0.91 (dd, J = 16.2, 8.3 Hz, 1H). *Syn*

diastereomer: **^{1}H NMR** (600 MHz, CDCl$_3$) δ 8.15 (s, 1H), 7.79 (dt, J = 7.9, 1.0 Hz, 1H), 7.52 (s, 1H),

7.34 – 7.29 (m, 1H), 7.22 (ddd, J = 8.1, 7.2, 1.1 Hz, 1H), 5.18 (d, *J* = 6.5 Hz, 1H), 1.96 – 1.91 (m, 1H)

1.21 (s, 12H), 1.20 (s, 12H). **^{13}C NMR** (151 MHz, CDCl$_3$) δ 149.7, 129.1, 129.0, 124.2, 124.1, 123.8,

122.7, 122.4, 120.5, 120.0, 115.1, 83.5, 83.4, 83.3, 83.2, 75.0, 71.2, 69.7, 28.2, 26.7, 25.0, 24.9, 24.9,

24.9, 24.8, 24.8, 24.7, 24.7, 10.0. **IR** (v/cm^{-1})**:** 3499 (s, br), 2998 (s), 2867 (w), 1732 (s), 1480 (s), 1354 (s), 1319 (m), 1267 (m).   **HRMS** (ESI$^+$) calcd for C$_{28}$H$_{43}$O$_7$NB$_2$Na$^+$ 550.3123, found: [M+Na] 550.3118. **[α]$_D$^{22}** = —9.7° (c = 5.80, CH$_2$Cl$_2$, l = 100 mm).
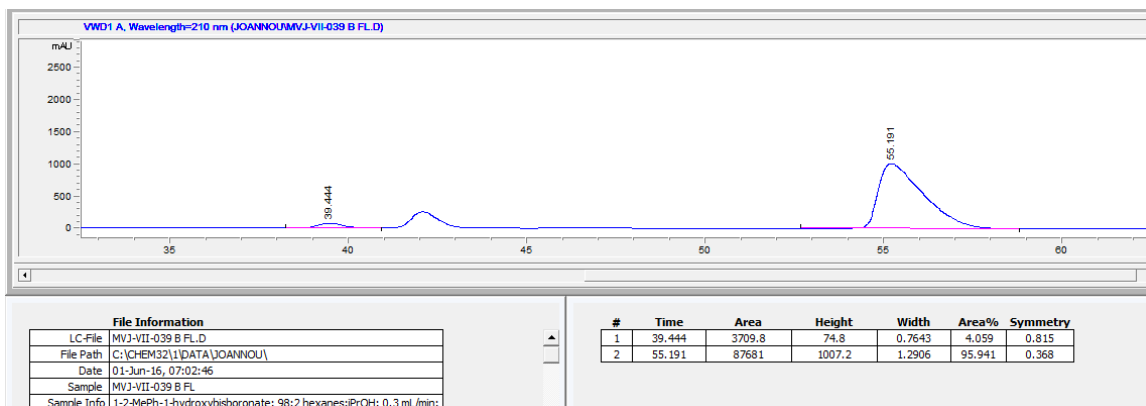
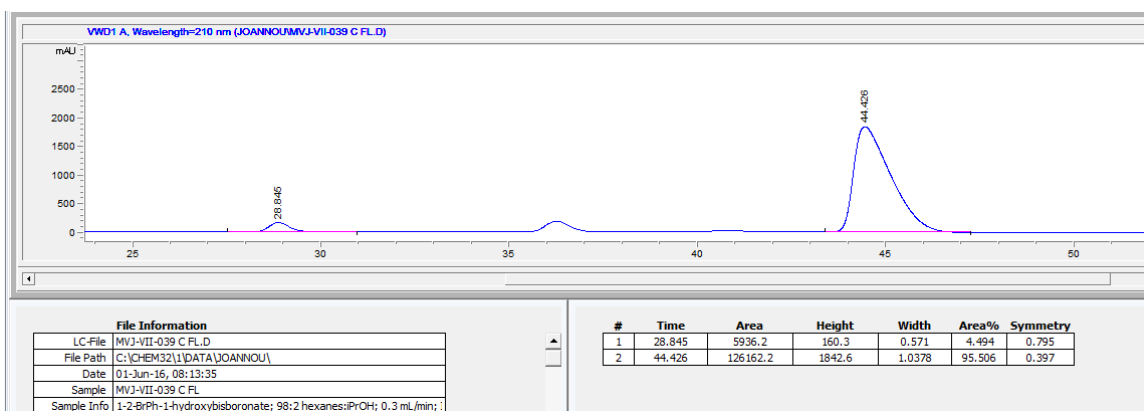Enantiomeric excess was determined by HPLC analysis compared to the authentic racemic material. Absolute stereochemistry was inferred from the stereochemistry obtained for compound **3.15**.

*Diacel CHIRALPAK IC Column; 98:2 hexanes:iPrOH; 0.3 mL/min; 210 nm*

Racemic Material (anti)

#	Time	Area	Height	Width	Area%	Symmetry
1	59.114	111116.2	1192.1	1.3944	47.880	0.437
2	62.337	120955.9	1052.2	1.7322	52.120	0.453

File Information
LC-File: MVJ-VI-192 B FL.D
File Path: C:\CHEM32\1\DATA\JOANNOU\
Date: 21-Mar-16, 19:55:26
Sample: MVJ-VI-192 B FL
Sample Info: 3-N-Boc-indole1-hydroxy-2,3-bisboronate ester racemic; 98:2 hexa

Enantio-Enriched Material (anti)

#	Time	Area	Height	Width	Area%	Symmetry
1	57.853	7117.6	93.5	1.2689	6.467	0.811
2	61.054	102946.4	1060.4	1.4347	93.533	0.441

File Information
LC-File: MVJ-VII-040 A FL.D
File Path: C:\CHEM32\1\DATA\JOANNOU\
Date: 01-Jun-16, 15:43:59
Sample: MVJ-VII-040 A FL
Sample Info: 1-(N-Boc-3-indolyl)-1-hydroxybisboronate; 98:2 hexanes:iPrOH; 0.:
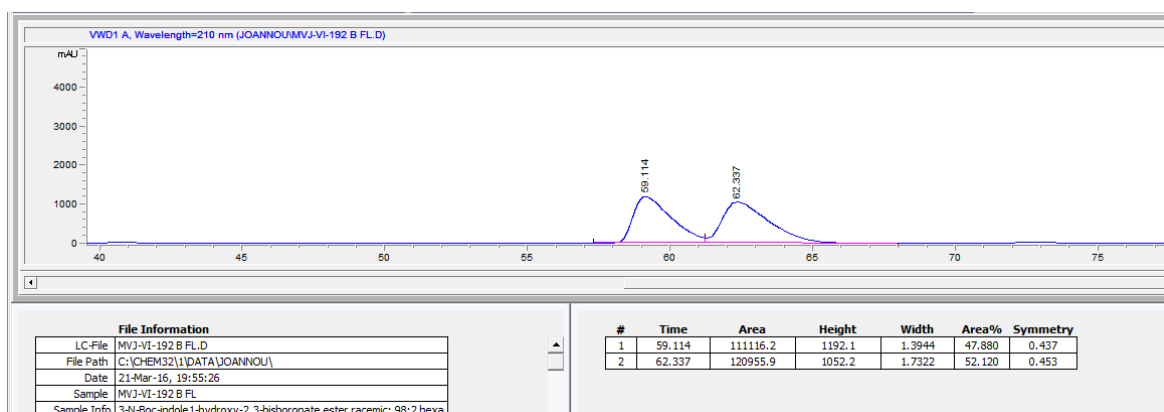
<u>***Anti* diastereomer:**</u> (1*R*,2*R*) enantiomer**:** 58.9 min; (1*S*,2*S*) enantiomer: 61.1 min: <u>94:6 e.r.</u>

Racemic Material (syn)

#	Time	Area	Height	Width	Area%	Symmetry
1	18.602	1795.6	50.5	0.593	48.157	0.864
2	19.862	1933.1	39.5	0.8163	51.843	0.809

File Information
LC-File: MVJ-VI-192 B FL.D
File Path: C:\CHEM32\1\DATA\JOANNOU\
Date: 21-Mar-16, 19:55:26
Sample: MVJ-VI-192 B FL
Sample Info: 3-N-Boc-indole 1-hydroxy-2,3-bisboronate ester racemic; 98:2 hexa

Enantio-Enriched Material (syn)

#	Time	Area	Height	Width	Area%	Symmetry
1	19.807	1565.4	46.9	0.5147	4.235	1.059
2	20.977	35393.1	752.8	0.7275	95.765	0.809

File Information
LC-File: MVJ-VII-040 A FL.D
File Path: C:\CHEM32\1\DATA\JOANNOU\
Date: 01-Jun-16, 15:43:59
Sample: MVJ-VII-040 A FL
Sample Info: 1-(N-Boc-3-indolyl)-1-hydroxybisboronate; 98:2 hexanes:iPrOH; 0..

<u>*Syn* diastereomer:</u> (1*S*,2*R*) enantiomer: 19.8 min; (1*R*,2*S*) enantiomer: 21.0 min: <u>96:4 e.r.</u>

3.38

1-(furan-2-yl)-2,3-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-ol (3.38). Following

General Procedure II, the crude reaction mixture was purified *via* silica gel column chromatography

(NaOAc deactivated silica gel, 5:1 to 2:1 pentane:Et$_2$O, Seebach Stain visualization) to yield the 1-

hydroxy-2,3-bisboronate ester as a colorless oil in **84%** yield (31.8 mg) and >99:1 anti:syn

diasteromeric ratio. **¹H NMR** (600 MHz, CDCl3) δ 7.35 (dd, J = 1.8, 0.9 Hz, 1H), 6.30 (dd, J = 3.2, 1.8 Hz, 1H), 6.23 (dt, J = 3.2, 0.8 Hz, 1H), 4.76 (t, J = 6.0 Hz, 1H), 3.18 (d, J = 6.8 Hz, 1H), 1.81 (dt, J = 8.7, 6.1 Hz, 1H), 1.27 – 1.24 (m, 24H), 0.94 – 0.83 (m, 2H). **¹³C NMR** (151 MHz, CDCl$_3$) δ 156.8, 141.5, 109.9, 106.1, 83.5, 83.2, 71.1, 25.5, 24.9, 24.8, 24.7, 9.34. **IR** (ν/cm^{-1}): 3546 (s, br), 2984 (s), 2916 (m), 1458 (m), 1381 (s), 1312 (m), 1182 (s). **HRMS** (ESI$^+$) calcd for C$_{19}$H$_{32}$O$_6$B$_2$Na$^+$ 401.2283, found: [M+Na] 401.2279. **[α]$_D^{22}$** = —16.7° (c = 6.04 CH$_2$Cl$_2$, l = 100 mm).
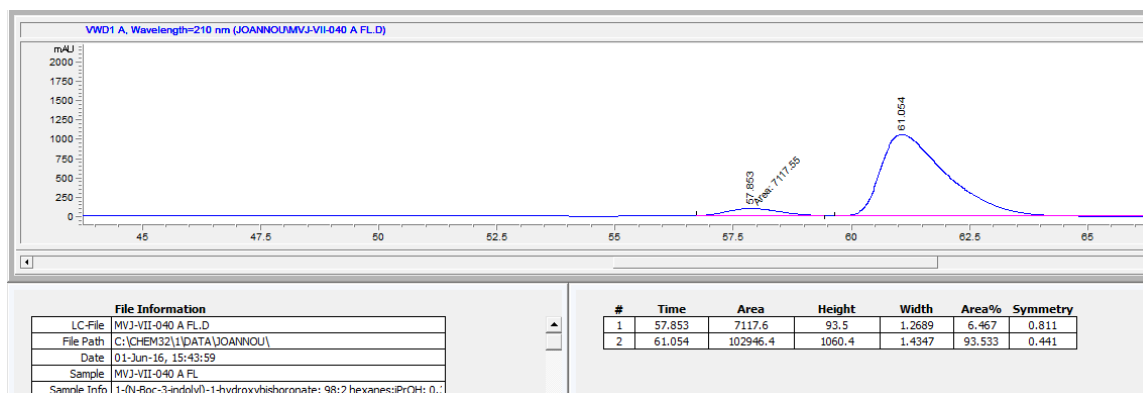
Enantiomeric excess was determined by HPLC analysis compared to the authentic racemic material. Absolute stereochemistry was inferred from the stereochemistry obtained for compound **3.15**.

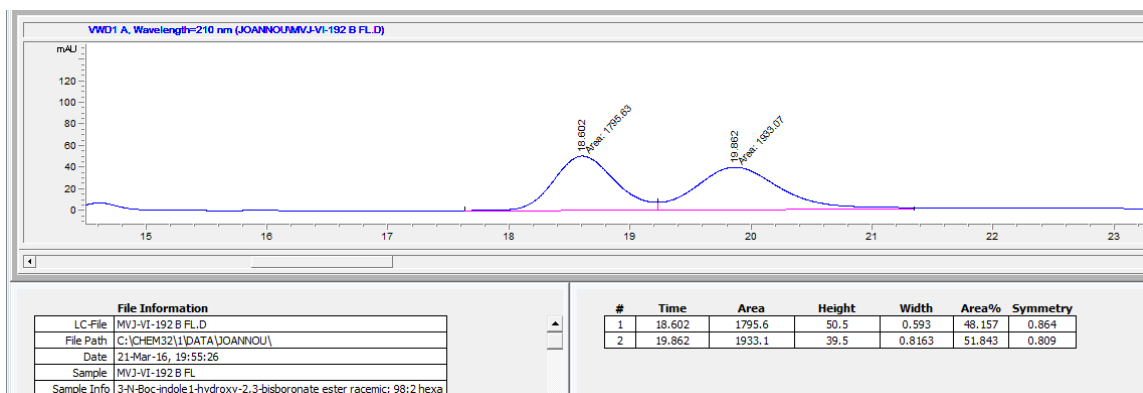*Diacel CHIRALPAK IC Column; 98:2 hexanes:iPrOH; 0.3 mL/min; 210 nm*

Racemic Material

File Information		#	Time	Area	Height	Width	Area%	Symmetry
LC-File	MVJ-VI-197C0001.D	1	74.465	9867.1	107.8	1.525	49.527	0.8
File Path	C:\CHEM32\1\DATA\JOANNOU\	2	79.077	10055.5	100	1.6765	50.473	0.772
Date	22-Mar-16, 00:08:19							
Sample	MVJ-VI-197 C FL							
Sample Info	2-furyl-1-hydroxy-2,3-bisboronate ester racemic; 98:2 hexanes:iPr							

Enantio-Enriched Material

File Information		#	Time	Area	Height	Width	Area%	Symmetry
LC-File	MVJ-VII-040 B FL.D	1	76.241	4680.9	61.3	1.2724	3.441	1.025
File Path	C:\CHEM32\1\DATA\JOANNOU\	2	78.772	131361.1	1040.4	1.8161	96.559	0.302
Date	01-Jun-16, 17:14:42							
Sample	MVJ-VII-040 B FL							
Sample Info	1-(2-furyl)-1-hydroxybisboronate; 98:2 hexanes:iPrOH; 0.3 mL/min							

***Anti* diastereomer:** (1*R*,2*R*) enantiomer**:** 76.2 min; (1*S*,2*S*) enantiomer: 78.8 min: <u>97:3 e.r.</u>
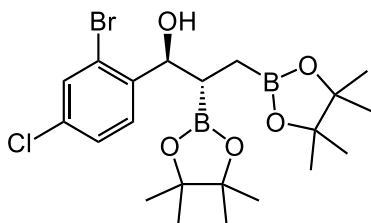
3.36

1-(2-bromo-4-chlorophenyl)-2,3-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-ol

(3.36). Following General Procedure II, the crude reaction mixture was purified *via* silica gel column chromatography (NaOAc deactivated silica gel, 5:1 to 2:1 pentane:Et$_2$O, Seebach Stain visualization) to yield the 1-hydroxy-2,3-bisboronate ester as a colorless oil in 71**%** yield (35.5 mg) and >99:1 anti:syn diastereomeric ratio. **^{1}H NMR** (600 MHz, CDCl3) δ 7.57 – 7.49 (m, 2H), 7.31 – 7.28 (m, 1H), 4.98 (dd, J = 5.7, 2.1 Hz, 1H), 3.81 (d, J = 4.2 Hz, 1H), 1.71 (dt, J = 8.9, 5.2 Hz, 1H), 1.28 – 1.25 (m, 24H), 1.10 – 0.98 (m, 1H), 0.91 (dd, J = 15.9, 5.2 Hz, 1H). **^{13}C NMR** (151 MHz, CDCl$_3$) δ 142.3, 133.1, 131.8, 128.9, 127.4, 123.1, 83.6, 83.3, 76.2, 27.7, 24.9, 24.9, 24.9, 24.81, 11.0. **IR** (v/cm^{-1}): 3589 (s, br), 2834 (s), 2865 (w), 1564 (m), 1355 (s), 1314 (s), 1147 (s). **HRMS** (ESI$^+$) calcd for C$_{21}$H$_{32}$O$_5$B$_2$BrClNa$^+$ 523.1205, found: [M+Na] 523.1203. **[α]$_D^{22}$** = +10.1° (*c* = 5.80, CH$_2$Cl$_2$, *l* = 100 mm).

Enantiomeric excess was determined by HPLC analysis compared to the authentic racemic material. Absolute stereochemistry was inferred from the stereochemistry obtained for compound **3.15**.

Diacel CHIRALPAK IC Column; 98:2 hexanes:iPrOH; 0.3 mL/min; 210 nm
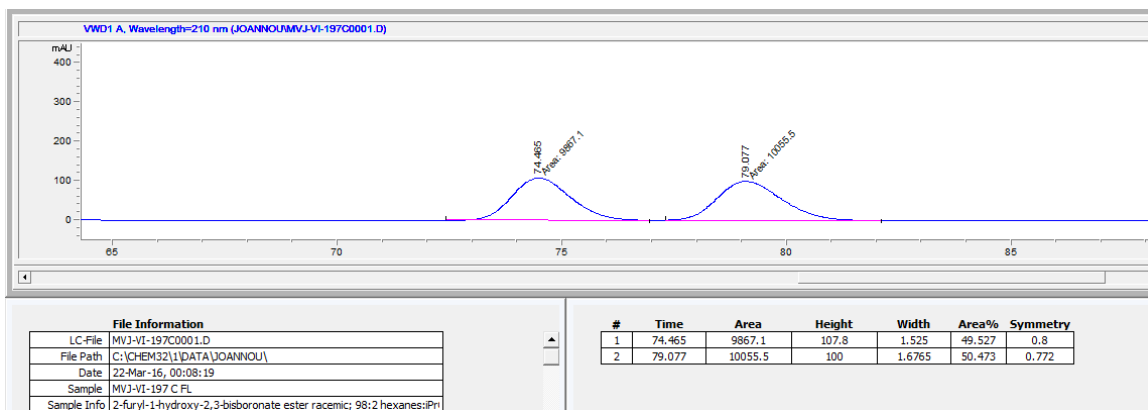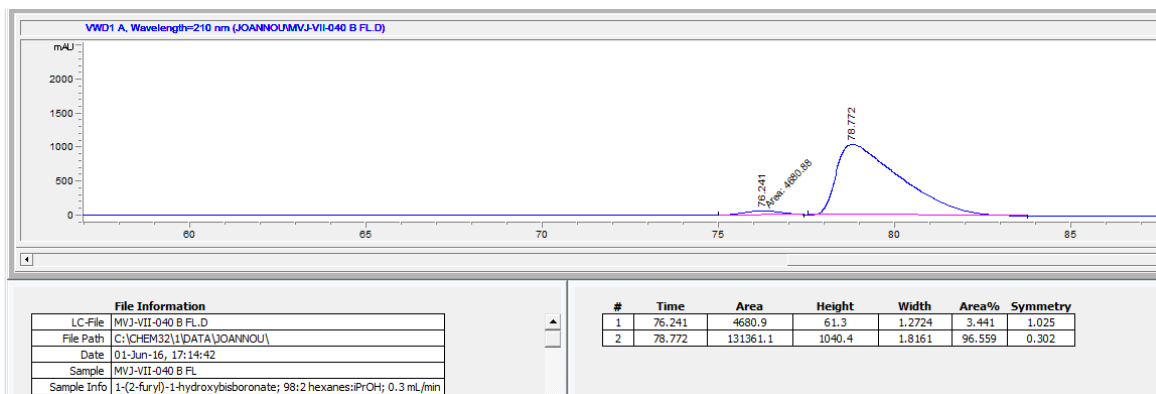
Racemic Material

	File Information
LC-File	MVJ-VI-205 B FL.D
File Path	C:\CHEM32\1\DATA\JOANNOU\
Date	22-Mar-16, 16:00:38
Sample	MVJ-VI-205 B FL
Sample Info	2-Br-4-ClPh-1-hydroxy-2,3-bisboronate ester racemic; 98:2 hexane

#	Time	Area	Height	Width	Area%	Symmetry
1	19.064	27585.2	1082.8	0.3882	50.261	0.868
2	19.939	27299.2	1038.7	0.4026	49.739	0.762

Enantio-Enriched Material

	File Information
LC-File	MVJ-VII-040 C FL.D
File Path	C:\CHEM32\1\DATA\JOANNOU\
Date	01-Jun-16, 18:45:35
Sample	MVJ-VII-040 C FL
Sample Info	1-(2-Br-4-Cl)-1-hydroxybisboronate; 98:2 hexanes:iPrOH; 0.3 mL/m

#	Time	Area	Height	Width	Area%	Symmetry
1	19.784	7469.1	332.8	0.374	5.422	0.862
2	20.731	130288.4	3466.6	0.6264	94.578	0.681

Anti **diastereomer:** (1*R*,2*R*) enantiomer**:** 19.8 min; (1*S*,2*S*) enantiomer: 20.7 min: 95:5 e.r.

3.40

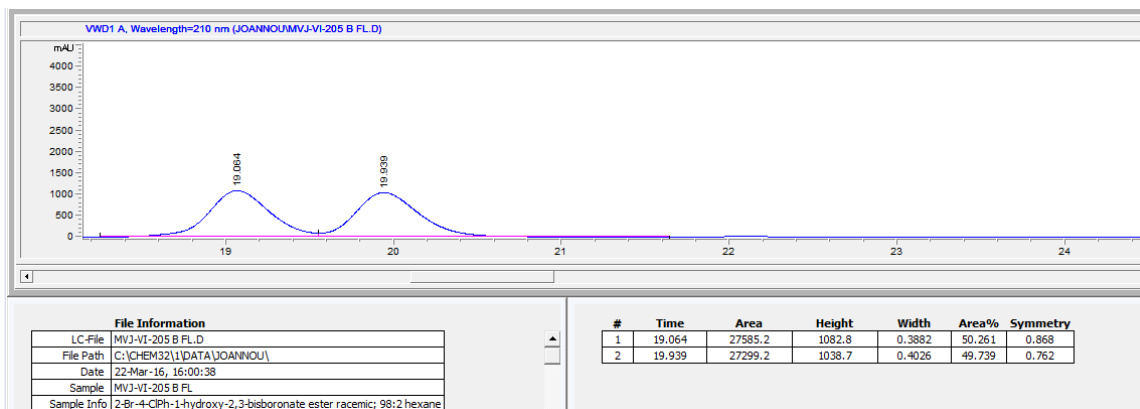**E-1-phenyl-4,5-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-1-en-3-ol (3.40).** Following

General Procedure II, the crude reaction mixture was purified *via* silica gel column chromatography

(NaOAc deactivated silica gel, 5:1 to 2:1 pentane:Et₂O, Seebach Stain visualization) to yield the 1-

hydroxy-2,3-bisboronate ester as a colorless oil in **55%** yield (22.8 mg) and 90:10 anti:syn diastereomeric ratio. **¹H NMR** (600 MHz, CDCl3) δ 7.40 – 7.36 (m, 2H), 7.33 – 7.29 (m, 2H), 7.25 – 7.20 (m, 1H), 6.61 – 6.54 (m, 1H), 6.25 (dd, J = 15.9, 6.4 Hz, 1H), 4.34 (d, J = 4.6 Hz, 1H), 2.82 (d, J = 5.3 Hz, 1H), 1.52 (dt, J = 8.8, 6.1 Hz, 1H), 1.27 (s, 6H), 1.26 (s, 6H), 1.26 (s, 6H), 1.25 (s, 6H), 1.02 – 0.92 (m, 2H). **¹³C NMR** (151 MHz, CDCl$_3$) δ 137.1, 132.5, 130.1, 128.4, 127.3, 126.5, 126.5, 126.4, 83.5, 83.1, 75.9, 26.8, 24.9, 24.9, 24.9, 24.8, 9.3. **IR** (ν/cm^{-1}): 3430 (s, br), 3019 (w), 2987 (s), 2907 (m), 2845 (w), 1398 (m), 1365 (s), 1286 (m). **HRMS** (ESI$^+$) calcd for C$_{23}$H$_{36}$O$_5$B$_2$Na$^+$ 437.2647, found: [M+Na] 437.2642. **[α]$_D^{22}$** = − 25.4° (c = 4.33, CH$_2$Cl$_2$, l = 100 mm).

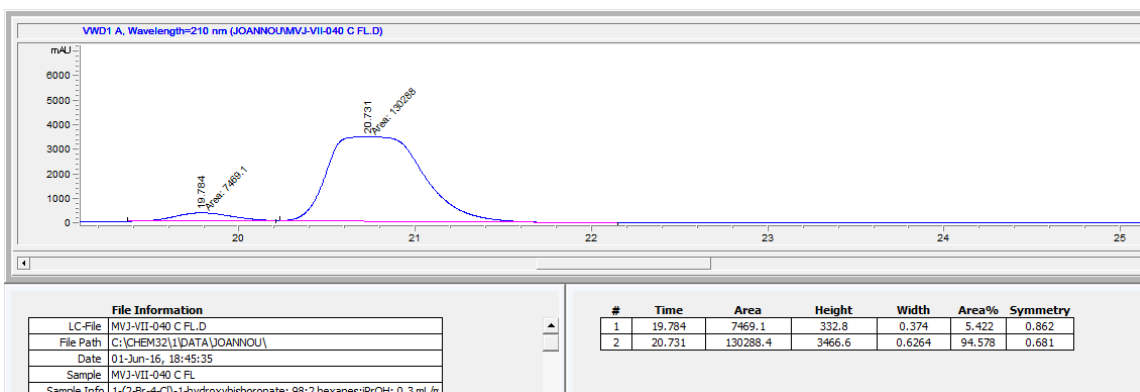Enantiomeric excess was determined by HPLC analysis compared to the authentic racemic material. Absolute stereochemistry was inferred from the stereochemistry obtained for compound **3.15**.

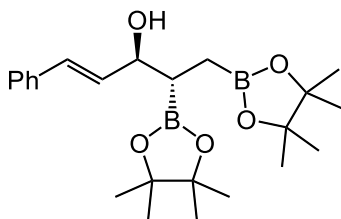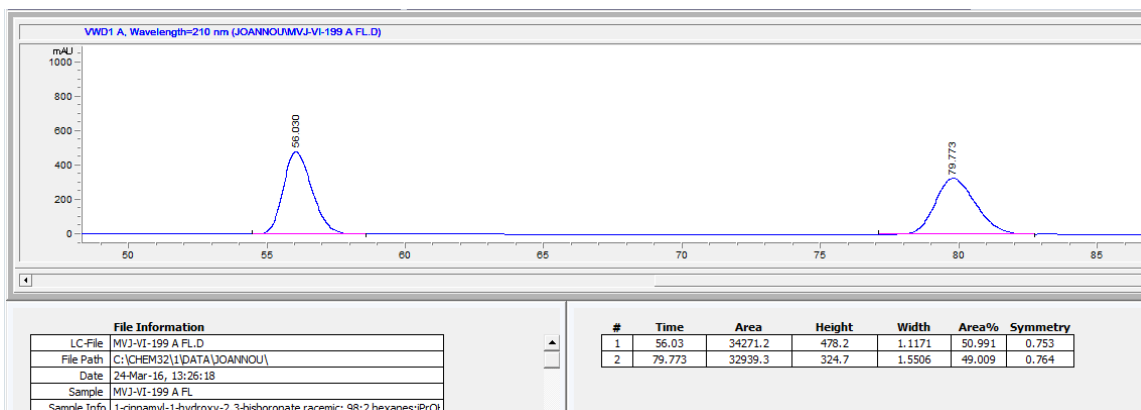*Diacel CHIRALPAK IC Column; 98:2 hexanes:iPrOH; 0.3 mL/min; 210 nm*

Racemic Material

File Information		#	Time	Area	Height	Width	Area%	Symmetry
LC-File	MVJ-VI-199 A FL.D	1	56.03	34271.2	478.2	1.1171	50.991	0.753
File Path	C:\CHEM32\1\DATA\JOANNOU\	2	79.773	32939.3	324.7	1.5506	49.009	0.764
Date	24-Mar-16, 13:26:18							
Sample	MVJ-VI-199 A FL							
Sample Info	1-cinnamyl-1-hydroxy-2,3-bisboronate racemic; 98:2 hexanes:iPrOl							

#	Time	Area	Height	Width	Area%	Symmetry
1	38.271	5355.3	119.7	0.7459	7.162	0.837
2	57.526	69416.3	924.7	1.2511	92.838	0.679

File Information

LC-File	MVJ-VII-040 D FL.D
File Path	C:\CHEM32\1\DATA\JOANNOU\
Date	01-Jun-16, 19:31:25
Sample	MVJ-VII-040 D FL
Sample Info	1-(cinnamyl)-1-hydroxybisboronate; 98:2 hexanes:iPrOH; 0.3 mL/m

<u>*Anti* **diastereomer:**</u> (1*R*,2*R*) enantiomer**:** 38.3 min; (1*S*,2*S*) enantiomer: 57.5 min: <u>93:7 e.r.</u>
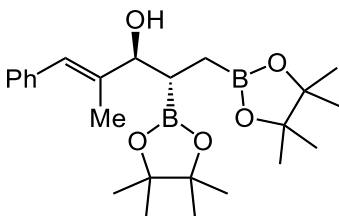
3.41

*E***-2-methyl-1-phenyl-4,5-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-1-en-3-ol (3.41).**

Following General Procedure II, the crude reaction mixture was purified *via* silica gel column chromatography (NaOAc deactivated silica gel, 5:1 to 2:1 pentane:Et$_2$O, Seebach Stain visualization) to yield the 1-hydroxy-2,3-bisboronate ester as a colorless oil in 53**%** yield (27.0 mg) and 90:10 anti:syn diastereomeric ratio. **^{1}H NMR** (600 MHz, CDCl3) δ 7.33 (dd, J = 8.1, 7.1 Hz, 2H), 7.30 (d, J = 1.6 Hz, 2H), 7.24 – 7.17 (m, 1H), 6.49 (s, 1H), 4.20 (d, J = 8.0 Hz, 1H), 2.96 (s, 3H), 1.86 (d, J = 1.4 Hz, 3H), 1.59 (ddd, J = 9.2, 8.0, 5.3 Hz, 1H), 1.28 (s, 12H), 1.25 (d, J = 2.7 Hz, 12H), 0.89 (qd, J = 16.2, 7.3 Hz, 2H). **^{13}C NMR** (151 MHz, CDCl$_3$) δ 139.6, 137.9, 129.1, 128.0, 126.5, 126.2, 83.5, 83.1, 80.9, 24.9, 24.9, 24.9, 23.9, 13.0, 9.8. **IR** (ν/cm^{-1}): 3399 (s), 2576 (m), 2102 (m), 1625 (s), 1201 (m). **HRMS** (ESI$^+$) calcd for C$_{24}$H$_{38}$O$_5$B$_2$Na$^+$ 451.2803, found: [M+Na] 451.2798. **[α]$_D^{22}$** = − 25.4° (*c* = 4.33, CH$_2$Cl$_2$, *l* = 100 mm).
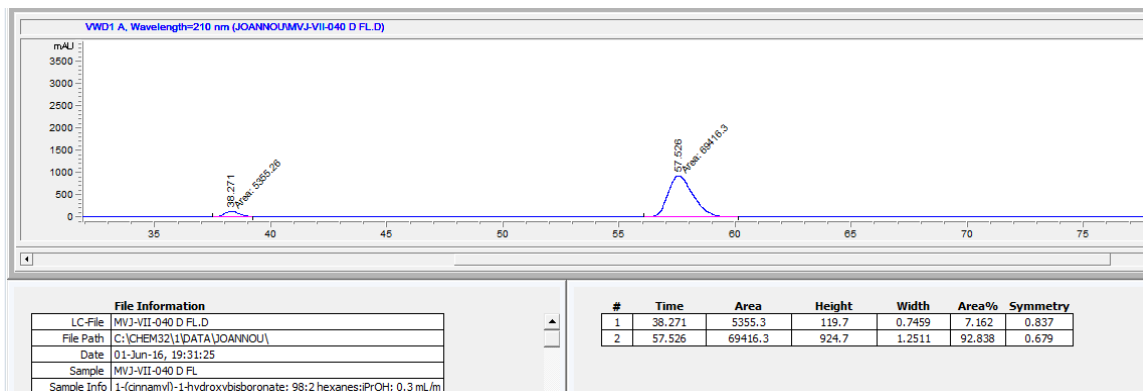
Enantiomeric excess was determined by HPLC analysis compared to the authentic racemic material.

Absolute stereochemistry was inferred from the stereochemistry obtained for compound **3.15**.

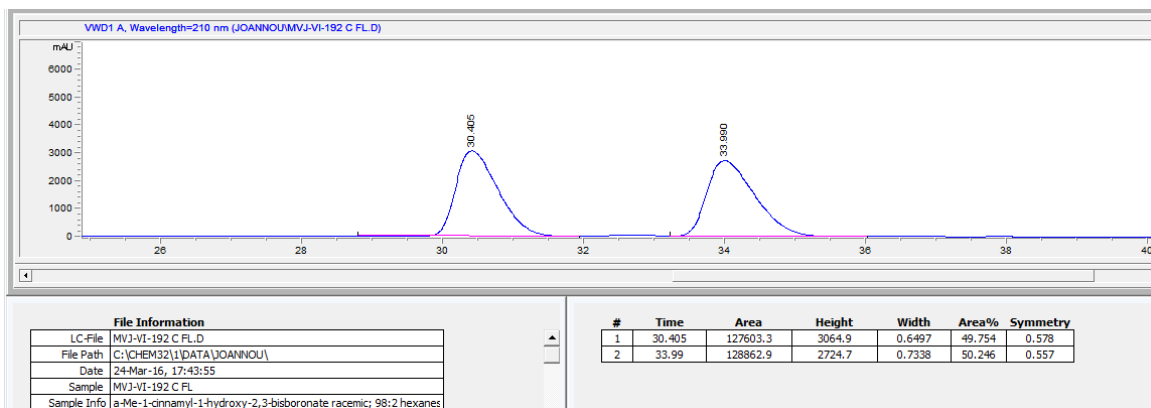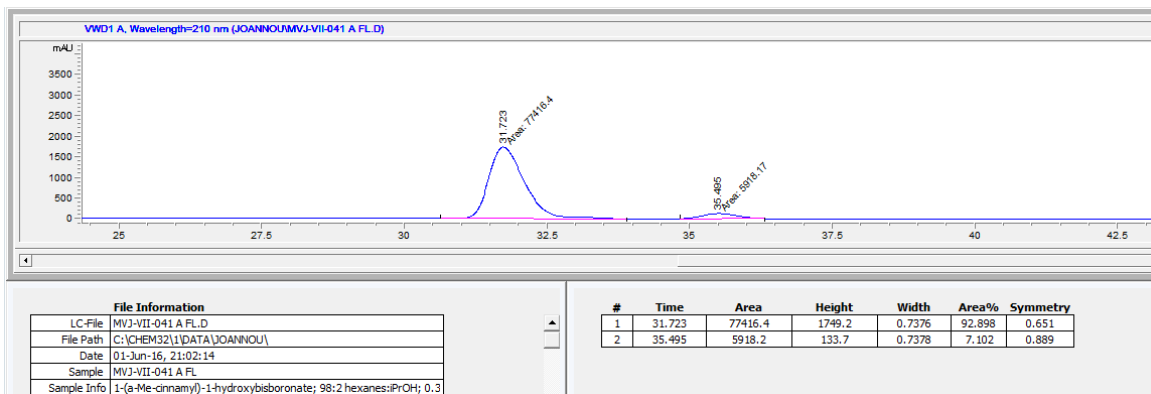*Diacel CHIRALPAK IC Column; 98:2 hexanes:iPrOH; 0.3 mL/min; 210 nm*

Racemic Material

#	Time	Area	Height	Width	Area%	Symmetry
1	30.405	127603.3	3064.9	0.6497	49.754	0.578
2	33.99	128862.9	2724.7	0.7338	50.246	0.557

File Information
LC-File: MVI-VI-192 C FL.D
File Path: C:\CHEM32\1\DATA\JOANNOU\
Date: 24-Mar-16, 17:43:55
Sample: MVJ-VI-192 C FL
Sample Info: a-Me-1-cinnamyl-1-hydroxy-2,3-bisboronate racemic; 98:2 hexanes

Enantio-Enriched Material

#	Time	Area	Height	Width	Area%	Symmetry
1	31.723	77416.4	1749.2	0.7376	92.898	0.651
2	35.495	5918.2	133.7	0.7378	7.102	0.889

File Information
LC-File: MVJ-VII-041 A FL.D
File Path: C:\CHEM32\1\DATA\JOANNOU\
Date: 01-Jun-16, 21:02:14
Sample: MVJ-VII-041 A FL
Sample Info: 1-(a-Me-cinnamyl)-1-hydroxybisboronate; 98:2 hexanes:iPrOH; 0.3

<u>***Anti* diastereomer:**</u> (1*S*,2*S*) enantiomer**:** 31.7 min; (1*R*,2*R*) enantiomer: 35.5 min: <u>93:7 e.r.</u>
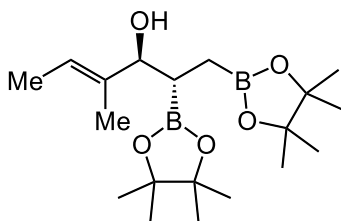
3.39

***E*-4-methyl-1,2-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-4-en-3-ol (3.39).** Following General Procedure II, the crude reaction mixture was purified *via* silica gel column chromatography (NaOAc deactivated silica gel, 5:1 to 2:1 pentane:Et₂O, Seebach Stain visualization) to yield the 1-hydroxy-2,3-bisboronate ester as a colorless oil in **26%** yield (9.5 mg) and 98:2 anti:syn diastereomeric ratio. **¹H NMR** (400 MHz, CDCl3) δ 5.44 (q, J = 6.7 Hz, 1H), 4.06 – 3.95 (m, 1H), 2.72 (d, J = 3.8 Hz, 1H), 1.64 – 1.56 (m, 6H), 1.48 – 1.39 (m, 1H), 1.27 (s, 12H), 1.24 (s, 12H), 0.84 – 0.64 (m, 2H). **¹³C NMR** (151 MHz, CDCl₃) δ 136.8, 121.7, 83.4, 83.0, 80.8, 25.0, 24.9, 24.9, 24.8, 24.8, 24.8, 23.6, 13.1, 10.5, 9.5. **IR** (v/cm⁻¹): 3530 (s, br), 3001 (w), 2896 (m), 2845 (w), 1377 (s), 1244 (m). **HRMS** (ESI⁺) calcd for C₁₉H₃₆O₅B₂Na⁺ 389.2647, found: [M+Na] 389.2645. **[α]ᴅ²²** = − 11.6° (c = 1.80, CH₂Cl₂, l = 100 mm).

Enantiomeric excess was determined by HPLC analysis compared to the authentic racemic material. Absolute stereochemistry was inferred from the stereochemistry obtained for compound **3.15**.
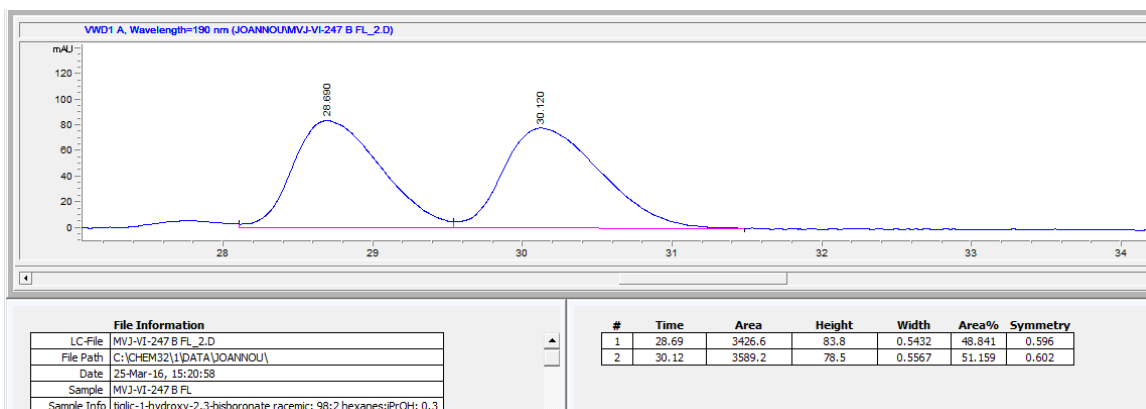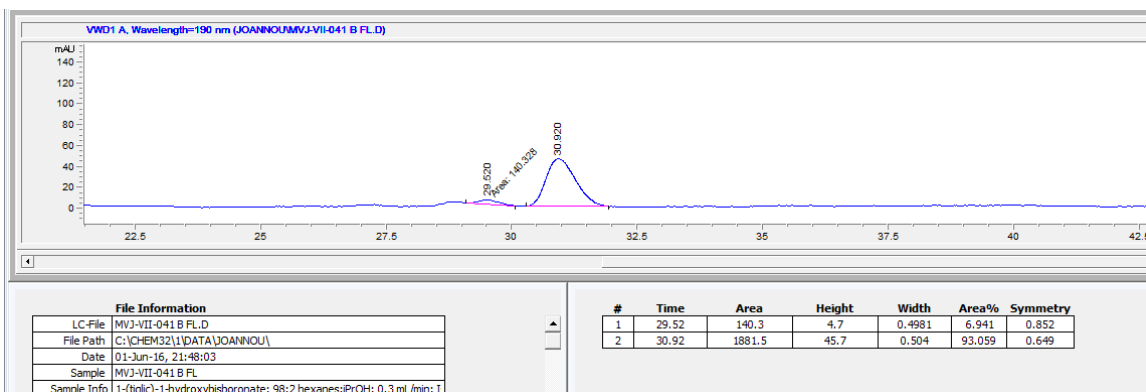
Racemic Material

#	Time	Area	Height	Width	Area%	Symmetry
1	28.69	3426.6	83.8	0.5432	48.841	0.596
2	30.12	3589.2	78.5	0.5567	51.159	0.602

File Information	
LC-File	MVJ-VI-247 B FL_2.D
File Path	C:\CHEM32\1\DATA\JOANNOU\
Date	25-Mar-16, 15:20:58
Sample	MVJ-VI-247 B FL
Sample Info	tiglic-1-hydroxy-2,3-bisboronate racemic; 98:2 hexanes:iPrOH; 0.3

Enantio-Enriched Material

#	Time	Area	Height	Width	Area%	Symmetry
1	29.52	140.3	4.7	0.4981	6.941	0.852
2	30.92	1881.5	45.7	0.504	93.059	0.649

File Information	
LC-File	MVJ-VII-041 B FL.D
File Path	C:\CHEM32\1\DATA\JOANNOU\
Date	01-Jun-16, 21:48:03
Sample	MVJ-VII-041 B FL
Sample Info	1-(tiglic)-1-hydroxybisboronate; 98:2 hexanes:iPrOH; 0.3 mL/min; I

Anti diastereomer: (1*R*,2*R*) enantiomer**:** 29.5 min; (1*S*,2*S*) enantiomer: 30.9 min: <u>93:7 e.r.</u>
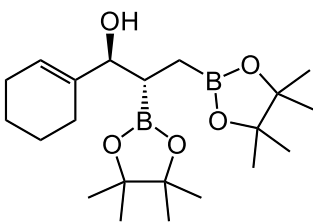
3.56

1-(cyclohex-1-en-1-yl)-2,3-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-ol   (3.56).

Following General Procedure II, the crude reaction mixture was purified *via* silica gel column

chromatography (NaOAc deactivated silica gel, 5:1 to 2:1 pentane:Et$_2$O, Seebach Stain visualization)
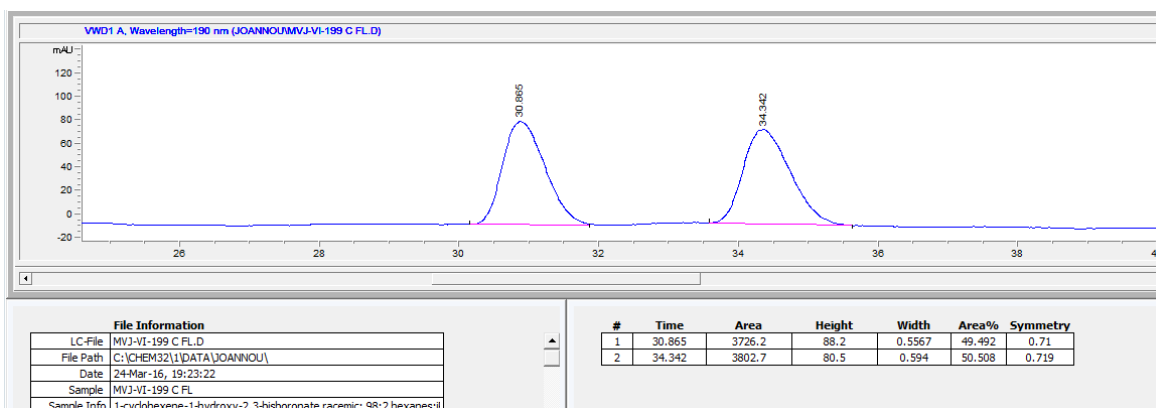
to yield the 1-hydroxy-2,3-bisboronate ester as a colorless oil in 48**%** yield (18.8 mg) and 74:26 anti:syn diastereomeric ratio. *Anti* **diastereomer:** **^{1}H NMR** (600 MHz, CDCl$_3$) δ 5.72 – 5.54 (m, 2H), 3.98 (d, J = 8.0 Hz, 1H), 2.70 (s, 1H), 2.18 – 1.82 (m, 5H), 1.70 – 1.51 (m, 4H), 1.28 (s, 12H), 1.27 (s, 12H), 0.93 – 0.75 (m, 2H). *Syn* **diastereomer:** **^{1}H NMR** (600 MHz, CDCl$_3$) δ 5.72 – 5.54 (m, 2H), 4.03 (d, J = 8.1 Hz, 1H), 2.70 (s, 1H), 2.18 – 1.82 (m, 5H), 1.70 – 1.51 (m, 4H), 1.28 (s, 12H), 1.27 (s, 12H), 0.93 – 0.75 (m, 2H).   **^{13}C NMR** (151 MHz, CDCl$_3$) δ 139.6, 138.9, 123.6, 122.6, 83.5, 83.3, 83.1, 83.0, 79.4, 29.7, 25.0, 25.0, 24.9, 24.9, 24.8, 24.8, 24.8, 24.7, 23.1, 22.7, 22.7. **IR** (v/cm^{-1}): 3589 (s, br), 2998 (w), 2954 (m), 1401 (s), 1289 (m). **HRMS** (ESI$^+$) calcd for C$_{21}$H$_{38}$O$_5$B$_2$Na$^+$ 415.2803, found: [M+Na] 415.2800. **[α]$_D^{22}$** = − 24.3° (c = 2.83, CH$_2$Cl$_2$, l = 100 mm).
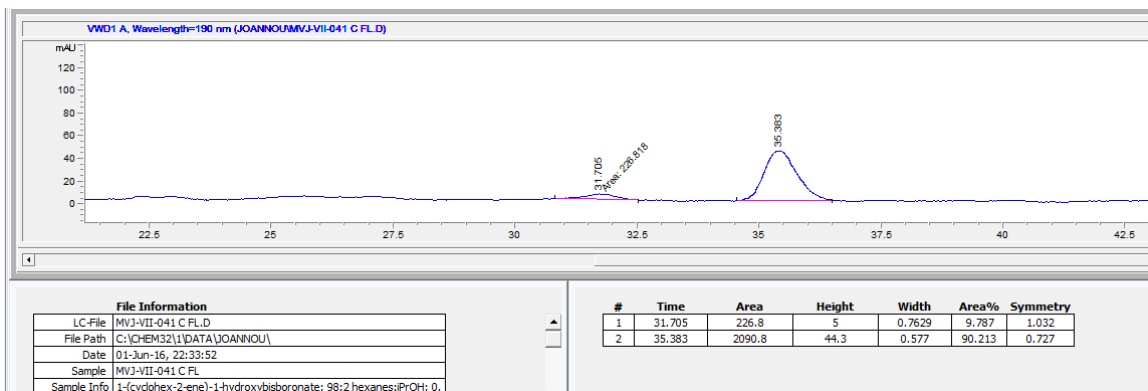
Enantiomeric excess was determined by HPLC analysis compared to the authentic racemic material. Absolute stereochemistry was inferred from the stereochemistry obtained for compound **3.15**.

Diacel CHIRALPAK IC Column; 98:2 hexanes:iPrOH; 0.3 mL/min; 190 nm

Racemic Material (anti)

	File Information
LC-File	MVJ-VI-199 C FL.D
File Path	C:\CHEM32\1\DATA\JOANNOU\
Date	24-Mar-16, 19:23:22
Sample	MVJ-VI-199 C FL
Sample Info	1-cyclohexene-1-hydroxy-2,3-bisboronate racemic; 98:2 hexanes:i

#	Time	Area	Height	Width	Area%	Symmetry
1	30.865	3726.2	88.2	0.5567	49.492	0.71
2	34.342	3802.7	80.5	0.594	50.508	0.719

Enantio-Enriched Material (anti)
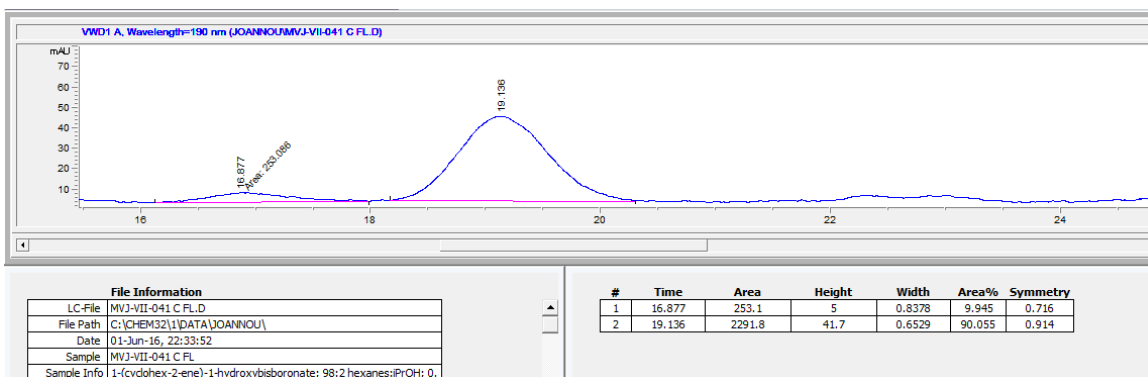

Anti diastereomer: (1*R*,2*R*) enantiomer**:** 31.7 min; (1*S*,2*S*) enantiomer: 35.3 min: <u>90:10 e.r.</u>
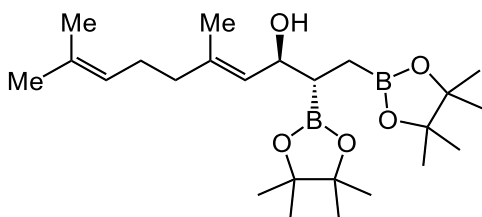
Racemic Material (syn)
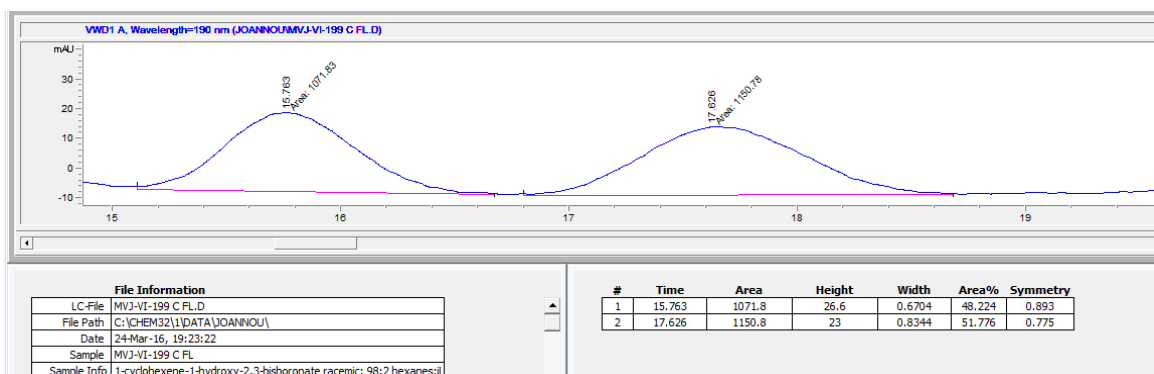
Enantio-Enriched Material (syn)

Syn diastereomer: (1*S*,2*R*) enantiomer**:** 16.9 min; (1*R*,2*S*) enantiomer: 19.1 min: <u>90:10 e.r.</u>
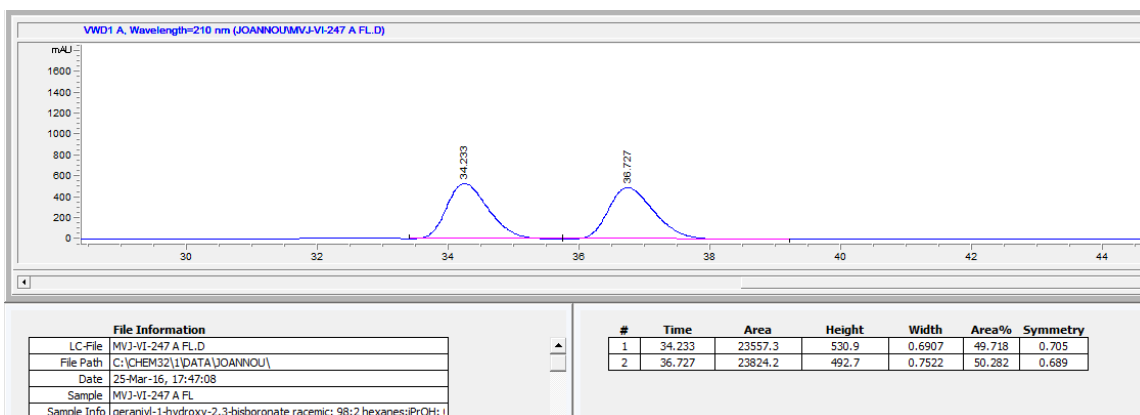
3.19

***E*-5,9-dimethyl-1,2-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)deca-4,8-dien-3-ol**   **(3.19).**
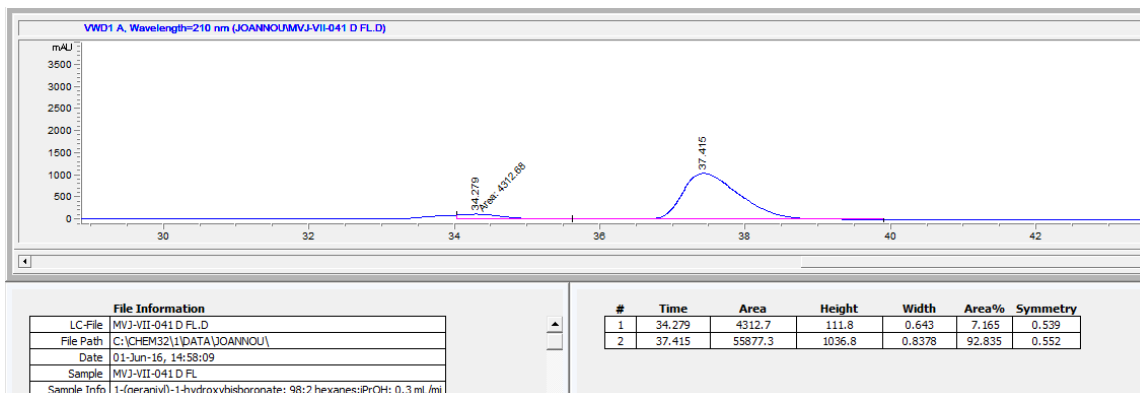
Following General Procedure II, the crude reaction mixture was purified *via* silica gel column chromatography (NaOAc deactivated silica gel, 5:1 to 2:1 pentane:Et$_2$O, Seebach Stain visualization) to yield the 1-hydroxy-2,3-bisboronate ester as a colorless oil in 78**%** yield (33.9 mg) and 98:2 anti:syn diastereomeric ratio. **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 5.19 (dq, *J* = 8.9, 1.3 Hz, 1H), 5.13 – 5.08 (m, 1H), 4.38 (dd, *J* = 8.9, 7.3 Hz, 1H), 2.54 (s, 1H), 2.10 (td, *J* = 8.7, 7.9, 4.7 Hz, 2H), 2.04 – 1.98 (m, 2H), 1.69 (dd, *J* = 4.5, 1.4 Hz, 6H), 1.61 (d, *J* = 1.3 Hz, 3H), 1.27 (s, 12H), 1.25 (s, 12H), 0.91 (dd, *J* = 16.1, 5.5 Hz, 1H), 0.83 (dd, *J* = 16.0, 9.5 Hz, 1H). **^{13}C NMR** (151 MHz, CDCl$_3$) δ 138.1, 131.5, 127.8, 124.2, 83.3, 83.0, 71.6, 39.7, 26.4, 25.7, 25.0, 24.9, 24.9, 24.8, 17.7, 16.8, 9.0. **IR** (v/cm^{-1}): 3600 (s), 2967 (m), 2897 (m), 2092 (m), 1567 (s), 1345 (m), 1274 (w), 1201 (m). **HRMS** (ESI$^+$) calcd for C$_{24}$H$_{44}$O$_5$B$_2$Na$^+$ 457.3273, found: [M+Na] 457.3268. **[α]$_D^{22}$** = − 41.6° (*c* = 6.44, CH$_2$Cl$_2$, *l* = 100 mm). Enantiomeric excess was determined by HPLC analysis compared to the authentic racemic material. Absolute stereochemistry was inferred from the stereochemistry obtained for compound **3.15**.

*Diacel CHIRALPAK IC Column; 98:2 hexanes:iPrOH; 0.3 mL/min; 190 nm*

Racemic Material

	File Information
LC-File	MVJ-VI-247 A FL.D
File Path	C:\CHEM32\1\DATA\JOANNOU\
Date	25-Mar-16, 17:47:08
Sample	MVJ-VI-247 A FL
Sample Info	geraniyl-1-hydroxy-2,3-bisboronate racemic; 98:2 hexanes:iPrOH; l

#	Time	Area	Height	Width	Area%	Symmetry
1	34.233	23557.3	530.9	0.6907	49.718	0.705
2	36.727	23824.2	492.7	0.7522	50.282	0.689

#	Time	Area	Height	Width	Area%	Symmetry
1	34.279	4312.7	111.8	0.643	7.165	0.539
2	37.415	55877.3	1036.8	0.8378	92.835	0.552

File Information
LC-File	MVJ-VII-041 D FL.D
File Path	C:\CHEM32\1\DATA\JOANNOU\
Date	01-Jun-16, 14:58:09
Sample	MVJ-VII-041 D FL
Sample Info	1-(geraniyl)-1-hydroxybisboronate; 98:2 hexanes:iPrOH; 0.3 mL/mi

<u>***Anti* diastereomer:**</u> (1*R*,2*R*) enantiomer**:** 34.3 min; (1*S*,2*S*) enantiomer: 37.4 min: <u>93:7 e.r.</u>

The peak at 34.0 min is the major enantiomer of the minor diastereomer, which was not present in the racemic product. It fluoresces more intensely than the *anti* diastereomer.
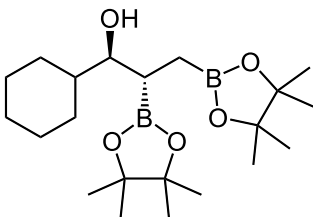
3.18

1-cyclohexyl-2,3-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-ol (2e). Following General Procedure II, the crude reaction mixture was purified *via* silica gel column chromatography (NaOAc deactivated silica gel, 5:1 to 2:1 pentane:Et$_2$O, Seebach Stain visualization) to yield the 1-hydroxy-2,3-bisboronate ester as a colorless oil in 63**%** yield (24.8 mg) and 98:2 anti:syn diastereomeric ratio. **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 3.33 (dd, *J* = 6.3, 4.8 Hz, 1H), 1.92 (dt, *J* = 12.7, 1.9 Hz, 1H), 1.80 – 1.70 (m, 3H), 1.68 – 1.61 (m, 3H), 1.49 (d, *J* = 4.9 Hz, 6H), 1.28 (s, 6H), 1.27 (s, 6H), 1.25 (s, 6H), 1.14 – 0.96 (m, 4H), 0.96 – 0.93 (m, 2H). **^{13}C NMR** (151 MHz, CDCl$_3$) δ 83.5, 83.3, 79.8, 42.8, 30.0, 28.0, 26.6, 26.5, 26.3, 25.0, 24.9, 24.9, 24.8, 24.78. **IR** (ν/cm^{-1}): 3501 (s, br), 2978 (m), 2967 (s), 1445 (m), 1379 (s), 1344 (m), 1273 (w), 1199 (w), 1161 (w). **HRMS** (ESI^{+}):

calcd for $C_{21}H_{40}O_5B_2Na$ 417.2960, found [M+Na$^+$] 417.2955. **[α]$_D^{22}$** = − 18.5° (*c* = 5.82, CH$_2$Cl$_2$, *l* = 100 mm).

Representative Example of tribenzoate:
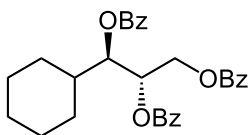
3.57

1-cyclohexylpropane-1,2,3-triyl tribenzoate (3.57). Following the General Oxidation/Benzoylation Procedure, the tribenzoate was purified *via* silica gel chromatography (10:1 to 5:1 pentane:Et$_2$O, KMnO$_4$ visualization) and isolated as a colorless oil in 90% yield (23.6 mg) in 92:8 d.r. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.24 – 7.95 (m, 5H), 7.74 – 7.37 (m, 10H), 5.88 (tq, *J* = 4.6, 2.1 Hz, 1H), 5.56 (t, *J* = 6.0 Hz, 1H), 4.89 (dt, *J* = 12.2, 2.3 Hz, 1H), 4.60 (dd, *J* = 12.1, 7.4 Hz, 1H), 2.02 – 1.55 (m, 6H), 1.26 (dt, *J* = 36.5, 8.4 Hz, 5H). **^{13}C NMR** (151 MHz, CDCl$_3$) δ 166.4, 165.8, 165.7, 162.4, 134.6, 133.3, 133.2, 133.2, 130.6, 129.8, 129.8, 129.7, 128.9, 128.8, 128.6, 128.4, 128.4, 76.3, 71.0, 62.9, 39.0, 29.4, 28.2, 26.1, 25.9, 25.7. **IR** (ν/cm^{-1}): 3350 (m), 2895 (m), 2870 (m), 1650 (s), 1625 (s), 1546 (m), 1201 (m). **HRMS** (ESI$^+$): calcd for $C_{30}H_{30}O_6Na^+$ 509.1940, found [M+ Na$^+$] 509.1935. **[α]$_D^{22}$** = − 95.2° (*c* = 2.86, CH$_2$Cl$_2$, *l* = 100 mm).
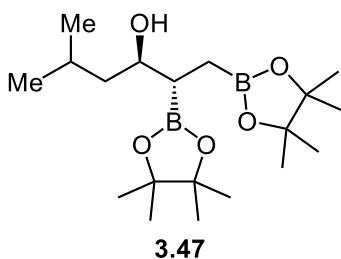
Enantiomeric excess was determined by HPLC analysis compared to the authentic racemic material. Absolute stereochemistry was inferred from the stereochemistry obtained for compound **3.15**.

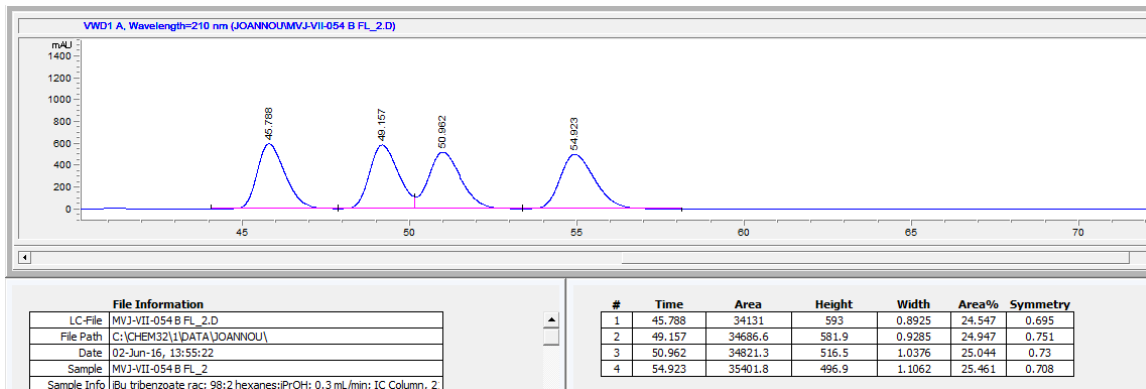*Racemic Material*

Enantio-Enriched Material

3.47
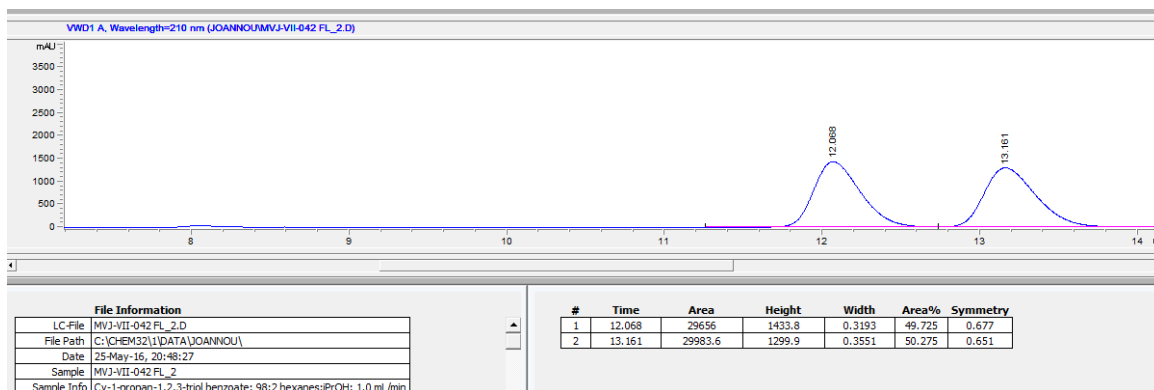
5-methyl-1,2-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexan-3-ol (3.47). Following General Procedure II, the crude reaction mixture was purified *via* silica gel column chromatography (NaOAc deactivated silica gel, 5:1 to 2:1 pentane:Et$_2$O, Seebach Stain visualization) to yield the 1-hydroxy-2,3-bisboronate ester as a colorless oil in 48**%** yield (17.7 mg) and 98:2 anti:syn diastereomeric ratio. **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 3.70 (ddd, *J* = 8.9, 4.8, 3.8 Hz, 1H), 1.82 (dqd, *J* = 9.0, 6.7, 5.0 Hz, 1H), 1.42 (ddd, *J* = 14.1, 9.3, 5.0 Hz, 1H), 1.37 – 1.29 (m, 1H), 1.26 (s, 12H), 1.25 (s, 12H), 0.96 – 0.94 (m, 2H), 0.91 (dd, *J* = 10.7, 6.7 Hz, 6H). **^{13}C NMR** (151 MHz, CDCl$_3$) δ 83.3, 83.1, 73.2, 46.2, 24.9, 24.8, 24.8, 24.7, 23.7, 22.0. **IR** (v/cm^{-1}): 3605 (s, br), 3001 (m), 1515 (m), 1410 (s), 1279 (w), 1210 (w). **HRMS** (ESI$^+$): calcd for C$_{19}$H$_{38}$O$_5$B$_2$Na$^+$ 391.2803, found [M+Na$^+$] 391.2798. **[α]$_D^{22}$** = − 27.6° (*c* = 3.23, CH$_2$Cl$_2$, *l* = 100 mm).

Enantiomeric excess was determined by HPLC analysis compared to the authentic racemic material.
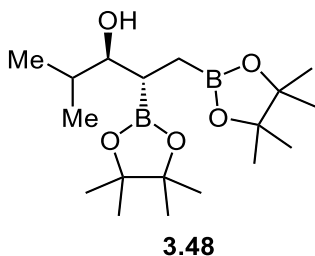
Absolute stereochemistry was inferred from the stereochemistry obtained for compound **3.15**.

Diacel CHIRALPAK IC Column; 98:2 hexanes:iPrOH; 0.3 mL/min; 210 nm

Racemic Material

#	Time	Area	Height	Width	Area%	Symmetry
1	45.788	34131	593	0.8925	24.547	0.695
2	49.157	34686.6	581.9	0.9285	24.947	0.751
3	50.962	34821.3	516.5	1.0376	25.044	0.73
4	54.923	35401.8	496.9	1.1062	25.461	0.708

File Information
LC-File MVJ-VII-054 B FL_2.D
File Path C:\CHEM32\1\DATA\JOANNOU\
Date 02-Jun-16, 13:55:22
Sample MVJ-VII-054 B FL_2
Sample Info iBu tribenzoate rac; 98:2 hexanes:iPrOH; 0.3 mL/min; IC Column, 2

Enantio-Enriched Material

3.48

4-methyl-1,2-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentan-3-ol (3.48). Following General Procedure II, the crude reaction mixture was purified *via* silica gel column chromatography (NaOAc deactivated silica gel, 5:1 to 2:1 pentane:Et$_2$O, Seebach Stain visualization) to yield the 1-hydroxy-2,3-bisboronate ester as a colorless oil in 52**%** yield (18.4 mg) and 98:2 anti:syn diastereomeric ratio. **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 3.32 (t, *J* = 5.6 Hz, 1H), 2.49 (s, 1H), 1.72 (dq, *J* = 13.3, 6.6 Hz, 1H), 1.48 (td, *J* = 7.2, 5.3 Hz, 1H), 1.28 (s, 6H), 1.27 (s, 6H), 1.25 (s, 12H), 0.94 (m, 8H). **^{13}C NMR** (151 MHz, CDCl$_3$) δ 83.3, 83.1, 80.5, 32.5, 24.9, 24.9, 24.8, 24.8, 20.0, 17.4. **IR**
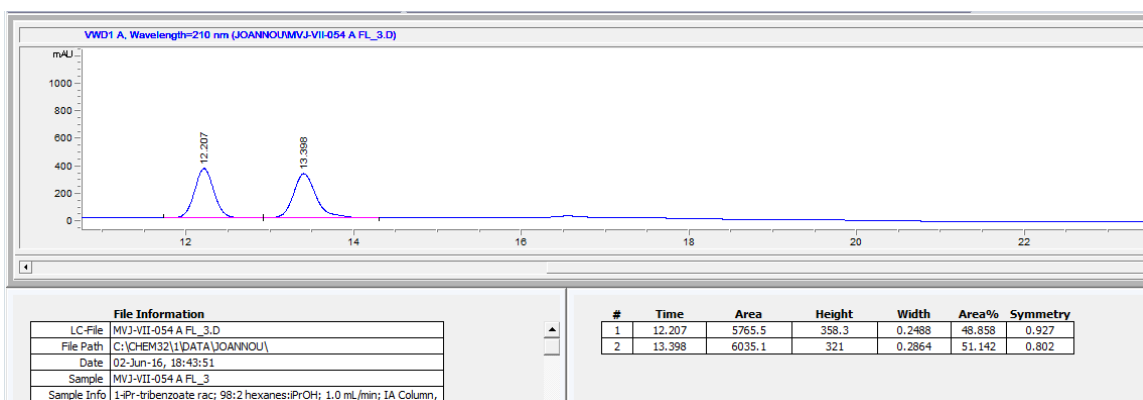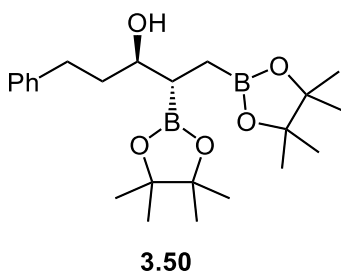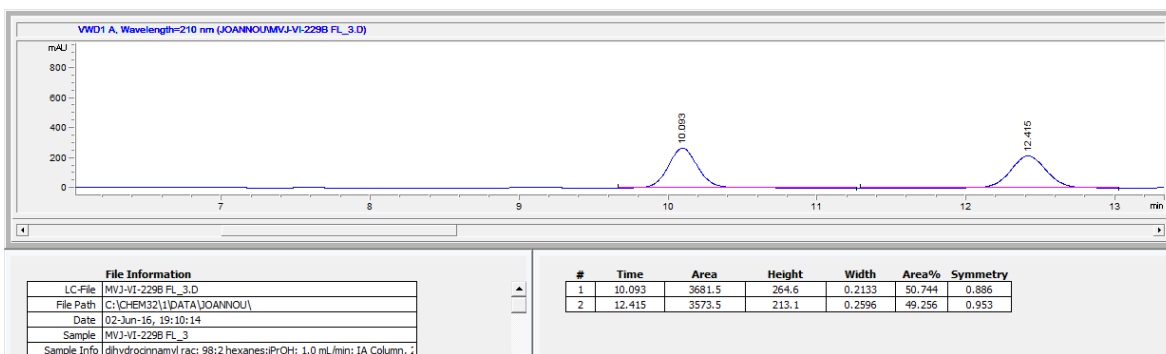
(v/cm⁻¹): 3595 (s, br), 2985 (m), 1499 (m), 1398 (s), 1253 (w). **HRMS** (ESI⁺): calcd for $C_{18}H_{36}O_5B_2Na^+$ 377.2647, found [M+Na⁺] 377.2642. **[α]$_D^{22}$** = − 19.9° (*c* = 4.22, CH₂Cl₂, *l* = 100 mm).
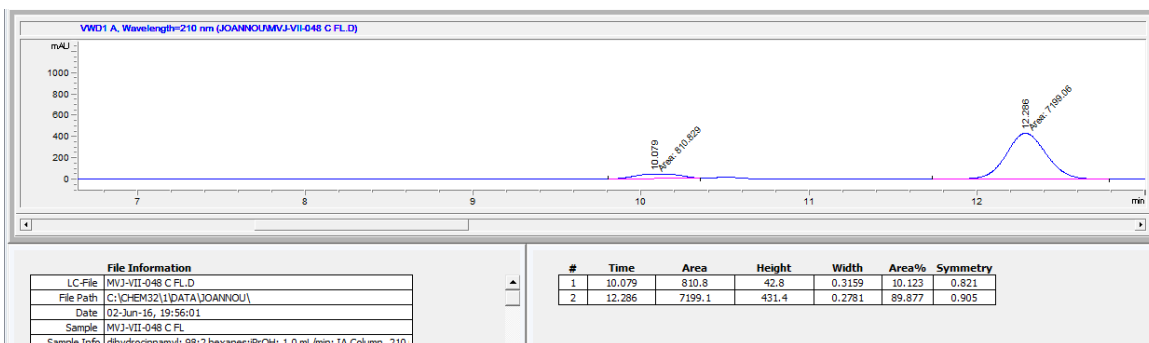
Enantiomeric excess was determined by HPLC analysis compared to the authentic racemic material.

Absolute stereochemistry was inferred from the stereochemistry obtained for compound **3.15**.

Diacel CHIRALPAK IA Column; 98:2 hexanes:iPrOH; 1.0 mL/min; 210 nm

Racemic Material

File Information		#	Time	Area	Height	Width	Area%	Symmetry
LC-File	MVJ-VII-054 A FL_3.D	1	12.207	5765.5	358.3	0.2488	48.858	0.927
File Path	C:\CHEM32\1\DATA\JOANNOU\	2	13.398	6035.1	321	0.2864	51.142	0.802
Date	02-Jun-16, 18:43:51							
Sample	MVJ-VII-054 A FL_3							
Sample Info	1-iPr-tribenzoate rac; 98:2 hexanes:iPrOH; 1.0 mL/min; IA Column,							

Enantio-Enriched Material

3.50

5-phenyl-1,2-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentan-3-ol (3.50). Following General Procedure II, the crude reaction mixture was purified *via* silica gel column chromatography (NaOAc deactivated silica gel, 5:1 to 2:1 pentane:Et₂O, Seebach Stain visualization) to yield the 1-hydroxy-2,3-bisboronate ester as a colorless oil in 67**%** yield (27.9 mg) and 75:25 anti:syn

diasteromeric ratio. ***Anti* diastereomer:** **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 3.65 (dt, *J* = 8.8, 4.5 Hz, 1H), 2.86 (ddd, *J* = 13.6, 9.6, 5.5 Hz, 1H), 2.71 – 2.64 (m, 1H), 1.81 (dtd, *J* = 9.8, 8.3, 7.7, 4.7 Hz, 2H), 1.42 – 1.36 (m, 1H), 1.26 (d, *J* = 0.7 Hz, 12H), 1.24 (d, *J* = 2.1 Hz, 14H), 0.95 (dd, *J* = 7.1, 3.6 Hz, 2H). ***Syn* diastereomer:** **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 3.71 (t, *J* = 6.5 Hz, 1H), 3.02 – 2.90 (m, 1H), 2.79 – 2.72 (m, 1H), 1.97 – 1.87 (m, 2H), 1.41 – 1.36 (m, 1H), 1.28 (s, 24H), 1.03 (dd, *J* = 18.9, 7.5 Hz, 1H), 0.88 – 0.83 (m, 1H). **^{13}C NMR** (151 MHz, CDCl$_3$) δ 142.7, 128.5, 128.5, 128.44, 128.4, 128.3, 125.5, 83.5, 83.4, 83.1, 75.1, 74.7, 38.5, 32.5, 30.3, 29.7, 25.0, 24.9, 24.8, 24.8, 24.8, 24.7, 24.7. **HRMS** (ESI$^+$): calcd for C$_{23}$H$_{38}$O$_5$B$_2$Na$^+$ 439.2803, found [M+Na$^+$] 439.2802. **[α]$_D^{22}$** = −15.6° (*c* =5.66, CH$_2$Cl$_2$, *l* = 100 mm).

Enantiomeric excess was determined by HPLC analysis compared to the authentic racemic material. Absolute stereochemistry was inferred from the stereochemistry obtained for compound **3.15**.

Diacel CHIRALPAK IA Column; 98:2 hexanes:iPrOH; 1.0 mL/min; 210 nm
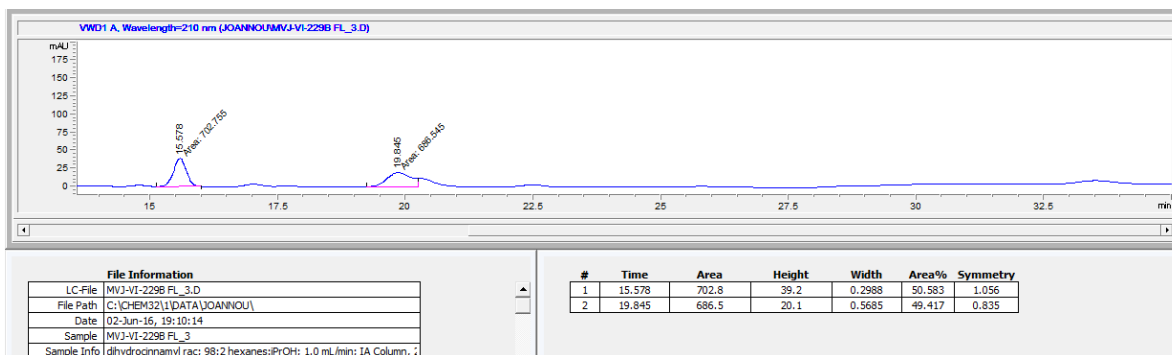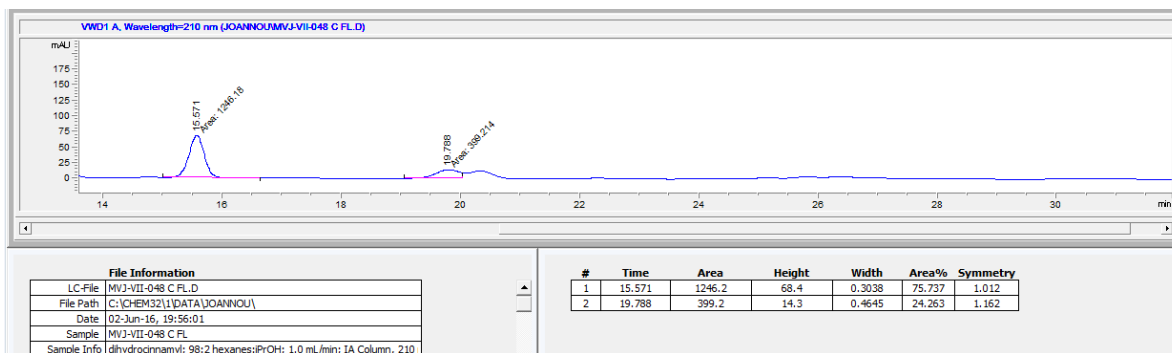
Racemic Material (anti)

File Information	
LC-File	MVJ-VI-229B FL_3.D
File Path	C:\CHEM32\1\DATA\JOANNOU\
Date	02-Jun-16, 19:10:14
Sample	MVJ-VI-229B FL_3
Sample Info	dihydrocinnamyl rac; 98:2 hexanes:iPrOH; 1.0 mL/min; IA Column,

#	Time	Area	Height	Width	Area%	Symmetry
1	10.093	3681.5	264.6	0.2133	50.744	0.886
2	12.415	3573.5	213.1	0.2596	49.256	0.953

Enantio-Enriched Material (anti)

VWD1 A, Wavelength=210 nm (JOANNOU\MVJ-VII-048 C FL.D)

File Information	
LC-File	MVJ-VII-048 C FL.D
File Path	C:\CHEM32\1\DATA\JOANNOU\
Date	02-Jun-16, 19:56:01
Sample	MVJ-VII-048 C FL
Sample Info	dihydrocinnamyl; 98:2 hexanes:iPrOH; 1.0 mL/min; IA Column, 210

#	Time	Area	Height	Width	Area%	Symmetry
1	10.079	810.8	42.8	0.3159	10.123	0.821
2	12.286	7199.1	431.4	0.2781	89.877	0.905

Anti diastereomer: (1*R*,2*R*) enantiomer**:** 10.1 min; (1*S*,2*S*) enantiomer: 12.9 min: <u>90:10 e.r.</u>

Racemic Material (syn)

VWD1 A, Wavelength=210 nm (JOANNOU\MVJ-VI-229B FL_3.D)

File Information	
LC-File	MVJ-VI-229B FL_3.D
File Path	C:\CHEM32\1\DATA\JOANNOU\
Date	02-Jun-16, 19:10:14
Sample	MVJ-VI-229B FL_3
Sample Info	dihydrocinnamyl rac; 98:2 hexanes:iPrOH; 1.0 mL/min; IA Column, 2

#	Time	Area	Height	Width	Area%	Symmetry
1	15.578	702.8	39.2	0.2988	50.583	1.056
2	19.845	686.5	20.1	0.5685	49.417	0.835

Enantio-Enriched Material (syn)

VWD1 A, Wavelength=210 nm (JOANNOU\MVJ-VII-048 C FL.D)

File Information	
LC-File	MVJ-VII-048 C FL.D
File Path	C:\CHEM32\1\DATA\JOANNOU\
Date	02-Jun-16, 19:56:01
Sample	MVJ-VII-048 C FL
Sample Info	dihydrocinnamyl; 98:2 hexanes:iPrOH; 1.0 mL/min; IA Column, 210

#	Time	Area	Height	Width	Area%	Symmetry
1	15.571	1246.2	68.4	0.3038	75.737	1.012
2	19.788	399.2	14.3	0.4645	24.263	1.162

Syn diastereomer: (1*R*,2*S*) enantiomer**:** 15.6 min; (1*S*,2*R*) enantiomer: 19.8 min: <u>76:24 e.r.</u>

3.42

(R)-(+)-5,5'-Dichloro-6,6'-dimethoxy-2,2'-bis(diphenylphosphino)-1,1'-

biphenylcopper(acetonitrile) hexafluorophosphate (3.42). Cu(MeCN)$_4$PF6 (11.0 mg, 0.030 mmol)

and *(R)*-Cl-OMe-biphep (19.2 mg, 0.030 mmol) were added to an 8-mL vial equipped with a magnetic

stir bar in an N$_2$-filled glovebox. The reaction was charged with 1.5 mL of benzene and allowed to stir

at ambient temperature for 2 hours. The reaction was filtered through a cotton plug to remove

particulates and the filtrate was concentrated *in vacuo* to leave a white, fluffy powder in >98% yield

(28 mg). **^{1}H NMR** (600 MHz, C$_6$D$_6$): δ 7.9 (m, 4 H), 7.53 (m, 4H), 7.34 (m, 4H), 7.10-6.97 (m, 8H),

6.72 (m, 2H), 6.67 (m, 2H), 3.26 (s, 6H), 1.37 (s, 3H). **^{13}C NMR** (151 MHz, C$_6$D$_6$): δ 154.6, 134.9,

134.3, 133.7, 131.1, 130.8, 129.5, 128.4, 128.2, 126.9, 121.8, 60.5, 1.1. **^{31}P NMR** (262 MHz, C$_6$D$_6$): δ

-2.16 (s), -142.88 (sep). **^{19}F NMR** (375 MHz, C$_6$D$_6$): δ -71.05 (d, J = 714 Hz). **HRMS** (ESI$^+$): calcd

for C$_{40}$H$_{33}$O$_2$NCl$_2$P$_2$$^+$ 754.0654, found: [M$^+$] 754.0648.

3.43
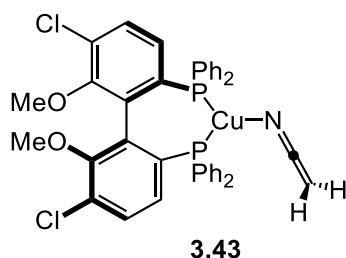
(R)-(+)-5,5'-Dichloro-6,6'-dimethoxy-2,2'-bis(diphenylphosphino)-1,1'-biphenyl

copper(keteneimide) (3.43). Cu(MeCN)$_4$PF6 (11.0 mg, 0.030 mmol) and *(R)*-Cl-OMe-biphep (19.2

mg, 0.030 mmol) were added to an 8-mL vial equipped with a magnetic stir bar in an N$_2$-filled glovebox,

charged with 1.5 mL of benzene, and allowed to stir vigorously at ambient temperature. The reaction

mixture was then transferred to an 8-mL vial containing KO*t*-Bu (3.3 mg, 0.030 mmol) and the original

vial washed with 500 μL of benzene. The now golden yellow reaction was allowed to stir at ambient temperature for 1 hour. The reaction was then allowed to stand and a white precipitate flocculated to the bottom of the vial. The reaction was slowly filtered over a plug of Celite® and then concentrated *in vacuo*. The resulting orange-gold semi-solid was charged with 1 mL of diethyl ether and then re-concentrated *in vacuo* to produce a free-flowing orange powder in 97% yield (21.6 mg). **^{1}H NMR** (600 MHz, C$_6$D$_6$): δ 7.44-7.42 (m, 8H), 7.06-6.98 (m, 18H), 3.26 (s, 6H). The spectrum also contained residual *tert*-butanol and hexanes. **^{13}C NMR** (151 MHz, C$_6$D$_6$): δ 154.8 (tr), 138.7, 138.7, 138.6 (m), 138.4 (m), 136.2 (m), 134.7 (tr), 133.0 (tr), 130.8, 130.5 128.8, 128.5, 128.4, 128.3, 128.2 (β-carbon of keteneimide), 60.0. **^{31}P NMR** (262 Hz, C$_6$D$_6$): δ -15.03 (s). **HRMS** (ESI$^+$): calcd for C$_{40}$H$_{32}$O$_2$NCl$_2$P$_2$ 753.0581 found: [M+H$^+$] 754.0650.

3.44
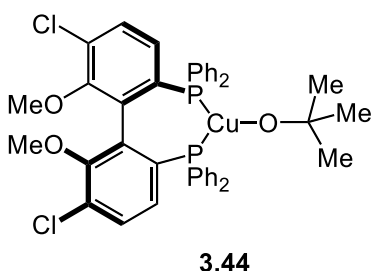
***(R)*-(+)-5,5'-Dichloro-6,6'-dimethoxy-2,2'-bis(diphenylphosphino)-1,1'-biphenyl copper(*tert*-butoxide) (3.44)**. CuO*t*-Bu (4.1 mg, 0.030 mmol) and *(R)*-Cl-OMe-biphep (19.5 mg, 0.030 mmol) were added to an 8-mL vial equipped with a magnetic stir bar in an N$_2$-filled glovebox. The reaction was charged with 1.5 mL of benzene and allowed to stir at ambient temperature for 2 hours. The reaction was filtered through a cotton plug to remove particulates and the filtrate was concentrated *in vacuo* to leave a light yellow powder, fluffy powder in >98% yield (24 mg). **^{1}H NMR** (600 MHz, C$_6$D$_6$) δ 7.43 (ddq, *J* = 6.3, 3.0, 1.5 Hz, 4H), 7.38 (dtd, *J* = 7.6, 3.8, 1.7 Hz, 4H), 7.07 – 6.96 (m, 16H), 3.26 (s, 6H), 1.29 (s, 9H). **^{13}C NMR** (151 MHz, C$_6$D$_6$) δ 154.8, 138.7, 138.6, 138.4, 136.12, 134.7, 133.0, 130.8, 130.5, 128.8, 128.5, 128.3, 128.3, 128.3, 65.6, 60.0, 35.4. **^{31}P NMR** (243 MHz, C$_6$D$_6$) δ -15.03. **HRMS** (ESI$^+$): calcd for C$_{42}$H$_{39}$O$_3$Cl$_2$P$_2$ 786.1047, found: [M - (O*t*-Bu) + (MeCN)$^+$] 754.0652. This

complex was synthesized to confirm that ligand substitution had not occurred upon reaction of **9** with KO*t*-Bu (Scheme 4, second reaction). *Addition of 10 equivalents of MeCN to **S4** produces **10** and *tert*-butanol.*

For all copper complexes, hexanes was unable to be removed from the compounds. NMR spectra of hexanes kept in the N_2 glovebox where these compounds were synthesized is provided and cross-referenced with each compound to ensure correct peak assignment in the 2.0-0.8 ppm region.

Me   OH

Me   Me

3.52
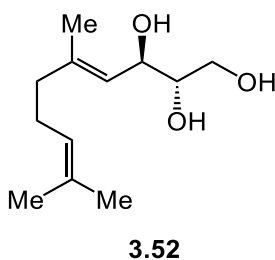
***E*-5,9-dimethyldeca-4,8-diene-1,2,3-triol (3.52).** A vial containing **3.19** (17.3 mg, 0.0398 mmol) was charged with thf (159 µL) and allowed to cool to 0 °C (ice/water bath). The reaction was charged with 3M NaOH (80 µL, 0.24 mmol) and then 30% H_2O_2 (80 µL, 0.80 mmol) dropwise. The reaction was allowed to slowly warm up to ambient temperature over 2 hours, followed by 4 hours of additional stirring at that temperature. The reaction was allowed to cool to 0 °C and quenched by dropwise addition of 1M $Na_2S_2O_3$. The reaction was diluted with water and then extracted 6X with EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered, and then dried *in vacuo*. The crude reaction mixture was purified *via* silica gel chromatography (1:1 EtOAc:hexanes to pure EtOAc) to yield the triol in 93% yield (7.9 mg) as a colorless oil. **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 5.22 (dq, *J* = 9.0, 1.3 Hz, 1H), 5.08 (tq, *J* = 5.5, 1.4 Hz, 1H), 4.42 – 4.36 (m, 1H), 3.76 – 3.68 (m, 1H), 3.60 – 3.53 (m, 2H), 3.13 (s, 1H), 2.33 (s, 2H), 2.12 (q, *J* = 7.4 Hz, 2H), 2.09 – 2.03 (m, 2H), 1.73 (d, *J* = 1.4 Hz, 3H), 1.70 (d, *J* = 1.4 Hz, 3H),, 1.62 (d, *J* = 1.3 Hz, 3H). **^{13}C NMR** (151 MHz, CDCl₃) δ 142.1, 132.0, 123.7, 123.1, 75.0, 69.5, 65.9, 39.7, 26.3, 25.7, 24.9, 17.7, 16.9. **IR** (ν/cm^{-1}): 3745 (s), 2968 (m),

2888 (m), 1314 (w), 1225 (m). **HRMS** (ESI⁺): calcd for $C_{12}H_{22}O_3Na$ 237.1467, found: [M+Na⁺] 237.1462. **[α]$_D^{22}$** = —92.1° (c = 3.95, CH_2Cl_2, l = 100 mm).
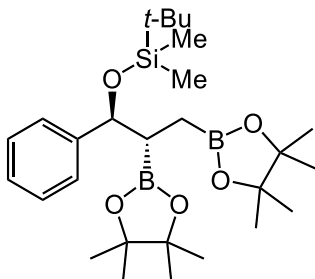
3.53

tert-butyldimethyl(1-phenyl-2,3-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propoxy)silane

(3.53). A crude reaction mixture of **3.15** (0.5 mmol scale, >98% NMR yield) was charged with imidazole (126.3 mg, 1.855 mmol) and a magnetic stir bar and dried under vacuum for 20 minutes. TBSCl (209.7 mg, 1.391 mmol) was then added to the vial and purged with N_2 for 5 minutes. Anhydrous dmf (3.1 mL) was then added via syringe under N_2 and the reaction was purged for an additional 5 minutes and then allowed to stir at ambient temperature for 48 hours. The reaction was quenched by addition of 3 mL of a saturated aqueous solution of NH_4Cl. The mixture was extracted 3X with diethyl ether and the combined organic extracts were washed with a saturated aqueous solution of $NaHCO_3$, followed by brine. The washed organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude reaction mixture was purified *via* silica gel chromatography (25:1 pentane:Et₂O, Seebach Stain visualization) to yield the product in 62% yield in 84:16 d.r. (155.6 mg). *Anti* **diastereomer**: ¹H NMR (600 MHz, Chloroform-*d*) δ 7.34 – 7.30 (m, 2H), 7.25 (dd, *J* = 8.3, 6.8 Hz, 2H), 7.20 – 7.16 (m, 1H), 4.78 (d, *J* = 6.5 Hz, 1H), 1.63 – 1.58 (m, 1H), 1.25 (s, 6H), 1.23 (s, 6H), 1.21 (s, 6H), 1.21 (s, 6H), 0.88 (s, 9H), 0.78 – 0.74 (m, 2H), 0.03 (s, 3H), -0.27 (s, 3H). *Syn* **diastereomer:** ¹H NMR (600 MHz, Chloroform-*d*) δ 7.34 – 7.31 (m, 2H), 7.25 (t, *J* = 7.6 Hz, 2H), 7.20 – 7.16 (m, 1H), 4.62 (d, *J* = 8.7 Hz, 1H), 1.54 (ddd, *J* = 12.4, 8.7, 3.6 Hz, 1H), 1.25 (s, 6H), 1.23 (s, 6H), 1.21 (s, 6H), 1.21 (s, 6H), 0.84 (s, 9H), 0.78 – 0.74 (m, 2H), 0.02 (s, 3H), -0.27 (s, 3H). **¹³C**

NMR (151 MHz, CDCl$_3$) δ 145.5, 145.1, 127.6, 127.5, 127.2, 127.0, 126.8, 126.6, 82.9, 82.9, 82.8, 82.8, 78.0, 77.9, 30.1, 26.0, 25.9, 25.2, 25.0, 25.0, 25.0, 24.9, 24.8, 24.8, 24.7, 18.2, 8.9, -4.5, -4.7. **IR** (ν/cm^{-1}): 2985 (m), 2945 (m), 2879 (m), 2843 (m), 1416 (m), 1402 (w), 1379 (m), 1371 (m). **HRMS** (ESI$^+$): calcd for C$_{27}$H$_{48}$O$_5$B$_2$SiNa$^+$ 525.3355, found [M+Na$^+$] 525.3350. **[α]$_D^{22}$** = —37.2° (c = 7.92, CH$_2$Cl$_2$, l = 100 mm).
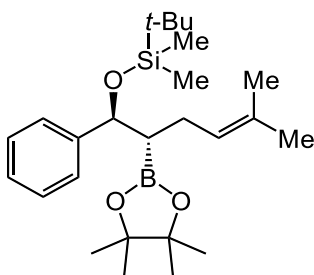
3.55

tert-butyldimethyl((-5-methyl-1-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-4-en-1-yl)oxy)silane (3.55). Following a modified literature procedure[5], **3.53** (20.0 mg, 0.0398 mmol) was charged with a thf solution (362 µL) of Pd(OAc)$_2$ (0.4 mg, 0.00199 mmol) and RuPhos (0.9 mg, 0.00119 mmol) that was allowed to stir at ambient temperature for 10 minutes under N$_2$. This was followed by vinyl bromide **3.54** (5.3 µL, 0.052 mmol) under N$_2$, and a solution of KOH (6.7 mg, 0.12 mmol) in H$_2$O (35.8 µL) that had been sparged with N$_2$ for 2.5 hours. The reaction was sealed and allowed to stir at 70 °C for 12 hours. The reaction was allowed to cool to ambient temperature, then quenched by addition of methylene chloride and water. The layers were separated and the aqueous layer was extracted 3X with methylene chloride. The combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated *in vacuo*. The crude reaction was purified *via* silica gel chromatography (25:1 pentane:Et$_2$O, Seebach Stain visualization) to afford the product in 51% yield (8.8 mg) as a single diastereomer. **^{1}H NMR** (600 MHz, CDCl$_3$) δ 7.34 – 7.26 (m, 4H), 7.25 – 7.17 (m, 1H), 5.05 (ddq, J = 7.6, 6.1, 1.4 Hz, 1H), 4.71 (d, J = 8.2 Hz, 1H), 1.99 (ddd, J = 14.1, 10.8, 8.2 Hz, 1H), 1.78 – 1.70 (m, 1H), 1.63 (d, J = 1.5 Hz, 3H), 1.50 (s, 4H), 1.25 (s, 6H), 1.25 (s, 6H), 0.87 (s, 9H), 0.02 (s, 3H), -0.34

(s, 3H). **^{13}C NMR** (151 MHz, CDCl$_3$) δ 145.4, 131.4, 127.7, 126.9, 126.8, 123.9, 83.0, 26.9, 25.9, 25.7, 25.3, 25.0, 18.1, 17.8, -4.3, -4.7. **IR** (ν/cm^{-1}): 2935 (m), 2921 (s), 2838 (m), 1328 (m), 1427 (w), 1338(m), 1376 (m). **HRMS** (ESI$^+$): calcd for C$_{25}$H$_{43}$O$_3$BSiNa$^+$ 453.2972, found: [M+Na$^+$] 453.2968.
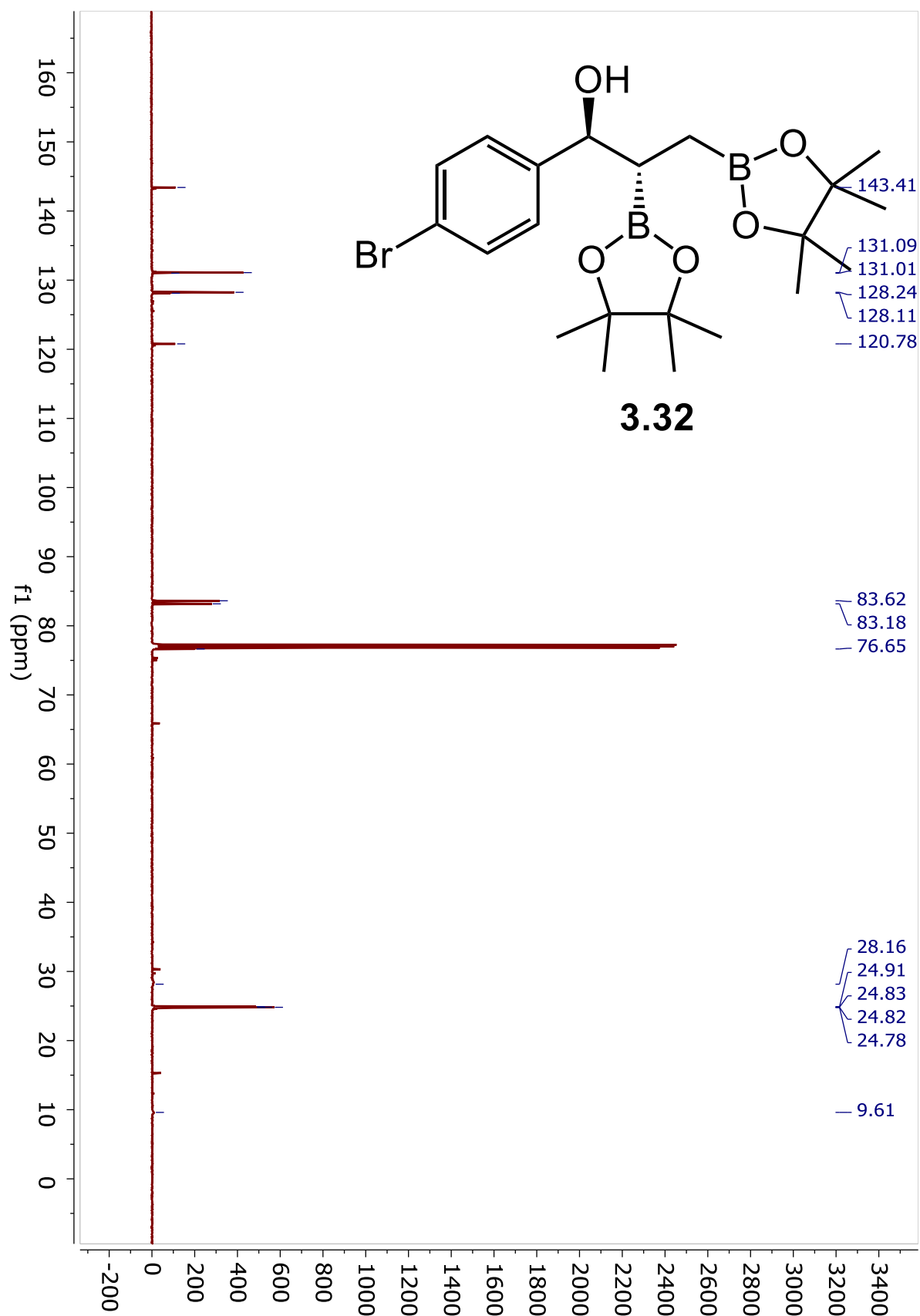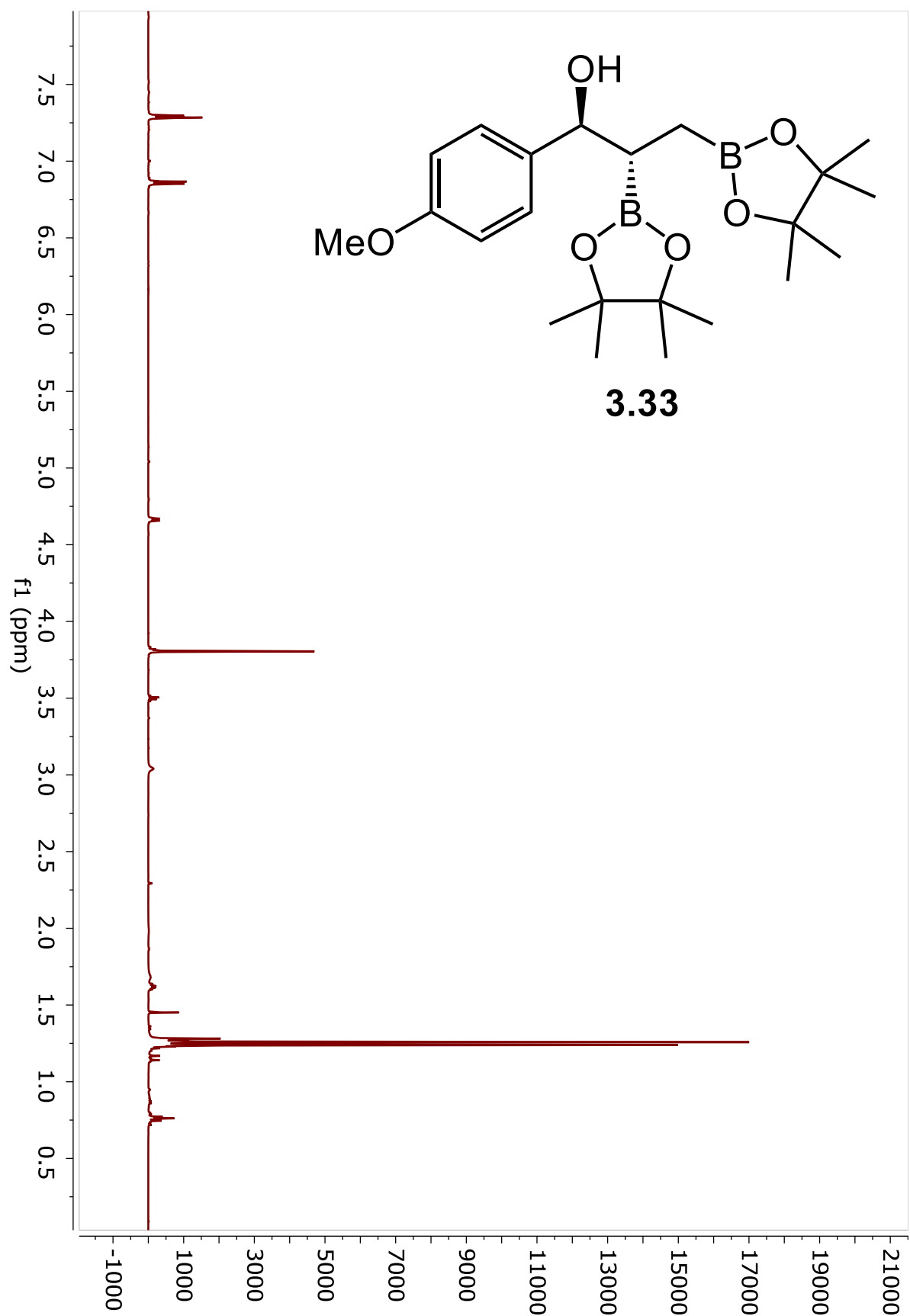
3.15

3.31

3.31

162.75
161.13

140.08
140.06
128.03
128.00
127.98
127.94
114.86
114.72
114.65

83.57
83.15
76.61

28.48
24.91
24.82
24.81
24.79

9.50

f1 (ppm)

3.32

3.32

143.41
131.09
131.01
128.24
128.11
120.78

83.62
83.18
76.65

28.16
24.91
24.83
24.82
24.78

9.61

f1 (ppm)

3.33

3.33

— 158.65

— 136.54
— 127.62

— 113.43

⟨ 83.46
⟨ 83.06
⟍ 76.92

— 55.26

⟨ 28.38
⟨ 24.91
⟨ 24.87
⟨ 24.83
⟨ 24.80

— 9.53

f1 (ppm)

3.16

— 144.27
— 137.50
127.92
127.79
127.10
123.57
83.46
83.07
77.34
28.39
24.90
24.86
24.83
24.80
21.52
— 9.73

3.16

f1 (ppm)

388

3.34

389

3.34

142.72
135.25
130.13
126.76
125.87
125.63

83.48
83.13

74.00

27.34
24.93
24.87
24.84
19.46
10.24

f1 (ppm)

3.35

391

3.35

143.55

132.40
128.39
127.89
127.24
123.02

83.53
83.23
76.64

27.56
24.95
24.92
24.88
24.82

10.80

3.37

3.37

137.08
136.17
135.78

83.53
83.41
82.96
73.87

25.04
24.91
24.89
24.86
21.13
20.76
9.63

f1 (ppm)

3.17

3.17

— 149.74

— 124.20
— 124.13
— 123.83
— 122.69
— 122.36
— 120.46
— 119.97
— 115.10

— 83.52
— 83.39
— 83.25
— 83.15
— 75.03
— 71.24

— 30.32
— 28.22
— 26.50
— 25.04
— 24.92
— 24.87
— 24.86
— 24.81
— 24.76
— 24.74
— 24.68
— 9.98

f1 (ppm)

3.38

f1 (ppm)

397

3.38

— 156.79

— 141.51

— 109.89
— 106.14

83.54
83.15

— 71.06

25.43
24.89
24.79
24.70

— 9.41

f1 (ppm)

398

3.36

3.36

3.40

401

3.40

137.12
132.54
130.12
128.43
127.26
126.46
126.45
126.42

83.47
83.14

75.89

24.89
24.87
24.85
24.79

f1 (ppm)

3.41

139.62
137.91
129.06
127.96
126.45
126.15

83.49
83.29
83.10
80.87

24.91
24.88
24.86
24.82
23.98

13.04
9.80

3.41

f1 (ppm)

3.39

405

3.39

136.81
121.67

83.35
82.99
80.78

24.89
24.85
24.83
24.81
23.61
13.09
10.48
9.51

f1 (ppm)

3.56

139.59
138.92

123.64
122.60

83.53
83.33
83.08
83.01
79.40
78.66

29.73
25.72
25.04
25.03
24.97
24.89
24.85
24.83
24.80
24.78
24.74
23.12
22.72
22.66

3.56

f1 (ppm)

3.19

Me

Me

Me

OH

3.19

138.10
131.48
127.76
124.20

83.31
83.00

71.55

39.68
26.43
25.73
25.04
24.90
24.86
24.81
24.78

17.71
16.79

f1 (ppm)

150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

-100 0 100 200 300 400 500 600 700 800 900 1000 1100 1200 1300

3.18

3.18

83.25
83.04
79.82

42.76

30.32
30.04
28.01
26.57
26.50
26.26
24.88
24.85
24.78
24.75
15.31

f1 (ppm)

412

3.57

134.59
133.27
133.22
133.16
130.60
129.80
129.72
128.91
128.83
128.57
128.43
128.40

76.32
75.87
70.99
70.37
63.69
62.90

39.04
38.66
29.74
29.43
29.38
28.16
28.06
26.09
25.87
25.75
25.71

3.57

f1 (ppm)

3.47

415

3.47

83.26
83.07

73.19

46.21

26.86
24.86
24.79
24.74
23.68
22.01

9.74

f1 (ppm)

416

3.48

95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
-5
-10
-15
-20

f1 (ppm)

-50
0
50
100
150
200
250
300
350
400
450
500
550

83.26
83.06
80.50

32.45

24.86
24.85
24.79
24.75
19.95
17.41

OH
Me
Me
B
O
O
B
O
O

3.48

3.50

3.50

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

— 142.72

⌐ 128.52
⌐ 128.25
⌐ 125.54

⌐ 83.36
⌐ 83.13
— 74.66

⌐ 38.50
⌐ 32.49
⌐ 25.04
⌐ 24.87
⌐ 24.82
⌐ 24.81

420

3.42

154.67
134.88
134.29
133.71
131.06
130.81
129.53
128.43
127.53
126.97
126.91
121.83

60.54

1.13

3.42

422

3.42

— -2.16

-137.01
-139.94
-142.87
-145.80
-148.74

f1 (ppm)

423

3.43

154.84
154.81
154.77
138.80
138.67
138.53
138.42
138.37
138.32
136.26
136.22
134.78
134.71
134.64
133.07
133.01
132.94
130.81
130.53
128.83
128.47
128.31
128.29
128.27
128.22

59.96

3.43

f1 (ppm)

425

3.43

— -15.03

f1 (ppm)

3.44

154.81
138.67
138.55
138.38
134.78
134.71
134.63
133.08
133.01
132.94
130.81
130.53
128.83
128.47
128.31
128.29
128.26

65.57
59.96

35.42

3.44

— -15.03

3.44

f1 (ppm)

3.52

3.52

— 142.07

— 132.01
⌐ 123.67
∟ 123.09

⌐ 75.04
⌐ 69.50
⌐ 65.90
∟ 63.50

— 39.67

⌐ 26.26
⌐ 25.73
∟ 24.86
⌐ 17.74
⌐ 16.91
∟ 15.30

f1 (ppm)

431

3.53

3.55

3.55

— 145.36

131.38
127.74
126.90
126.81
123.94

— 82.96

26.85
25.94
25.74
25.25
24.95
18.13
17.84

-4.31
-4.73

f1 (ppm)

435

hexanes in C$_6$D$_6$

436

hexanes in C$_6$D$_6$

41.27
36.02
34.61
34.53
31.62
29.07
27.66
25.27
22.71
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22.44
20.53
20.49
18.59
14.20
14.01
11.32

f1 (ppm)

437

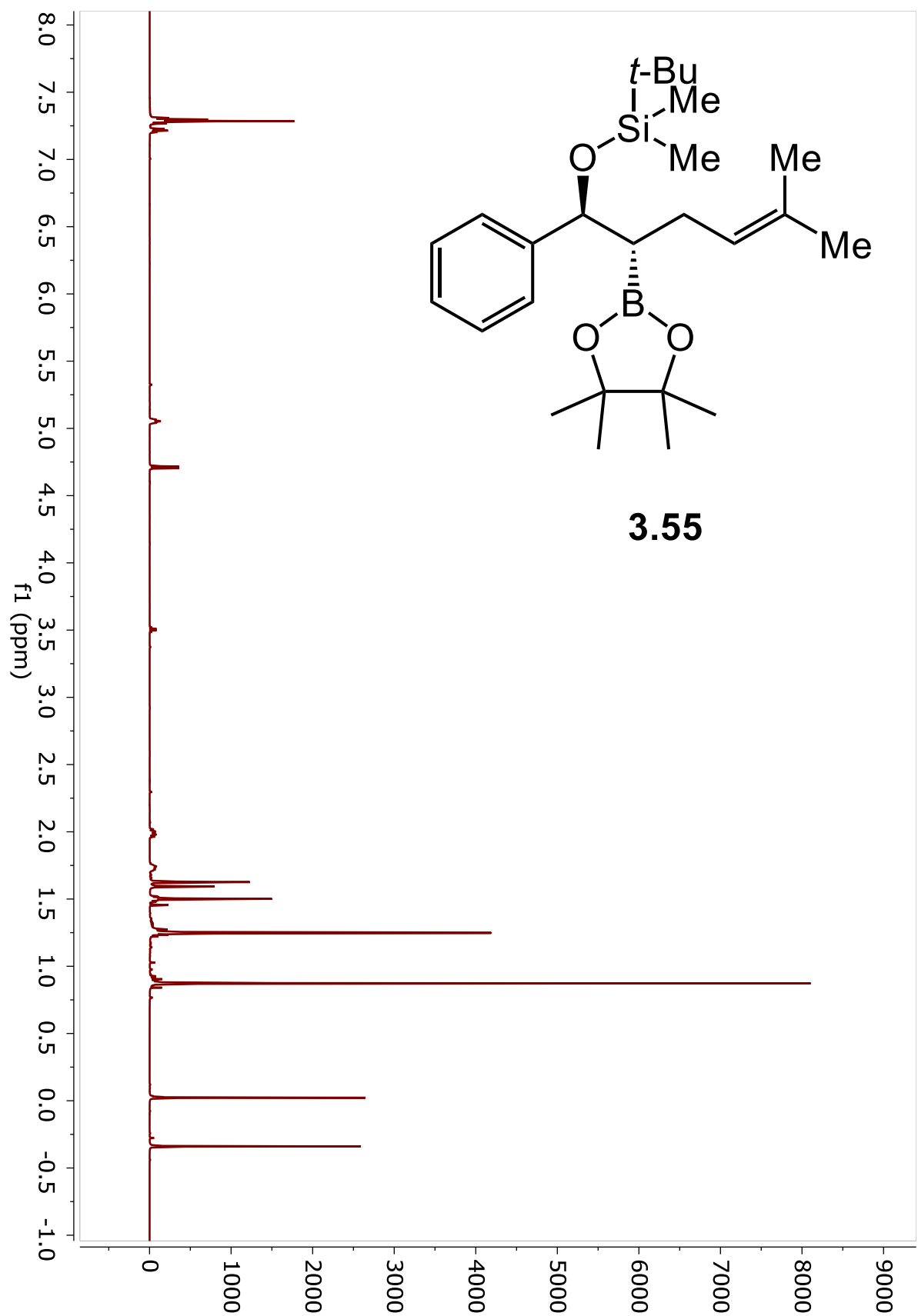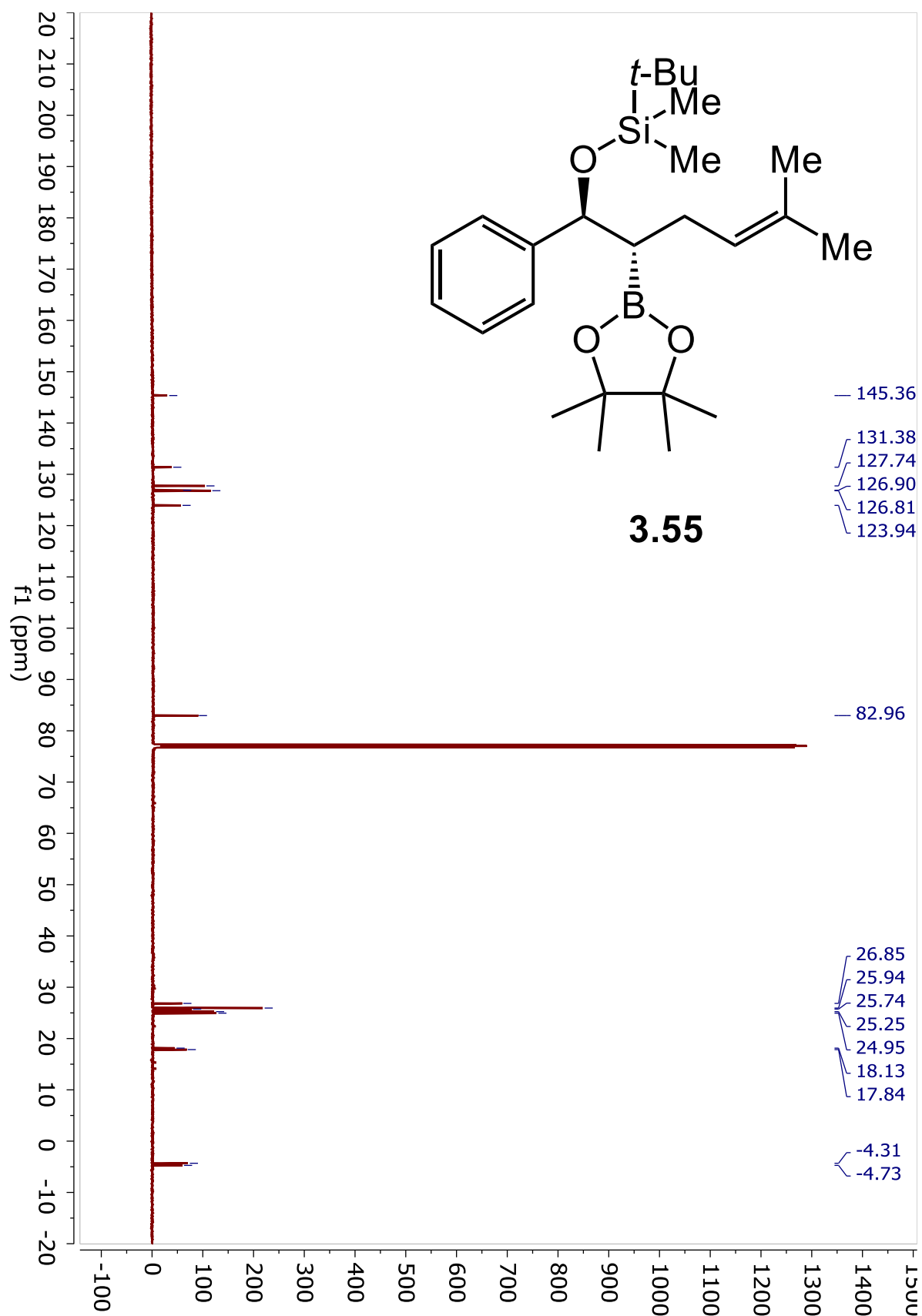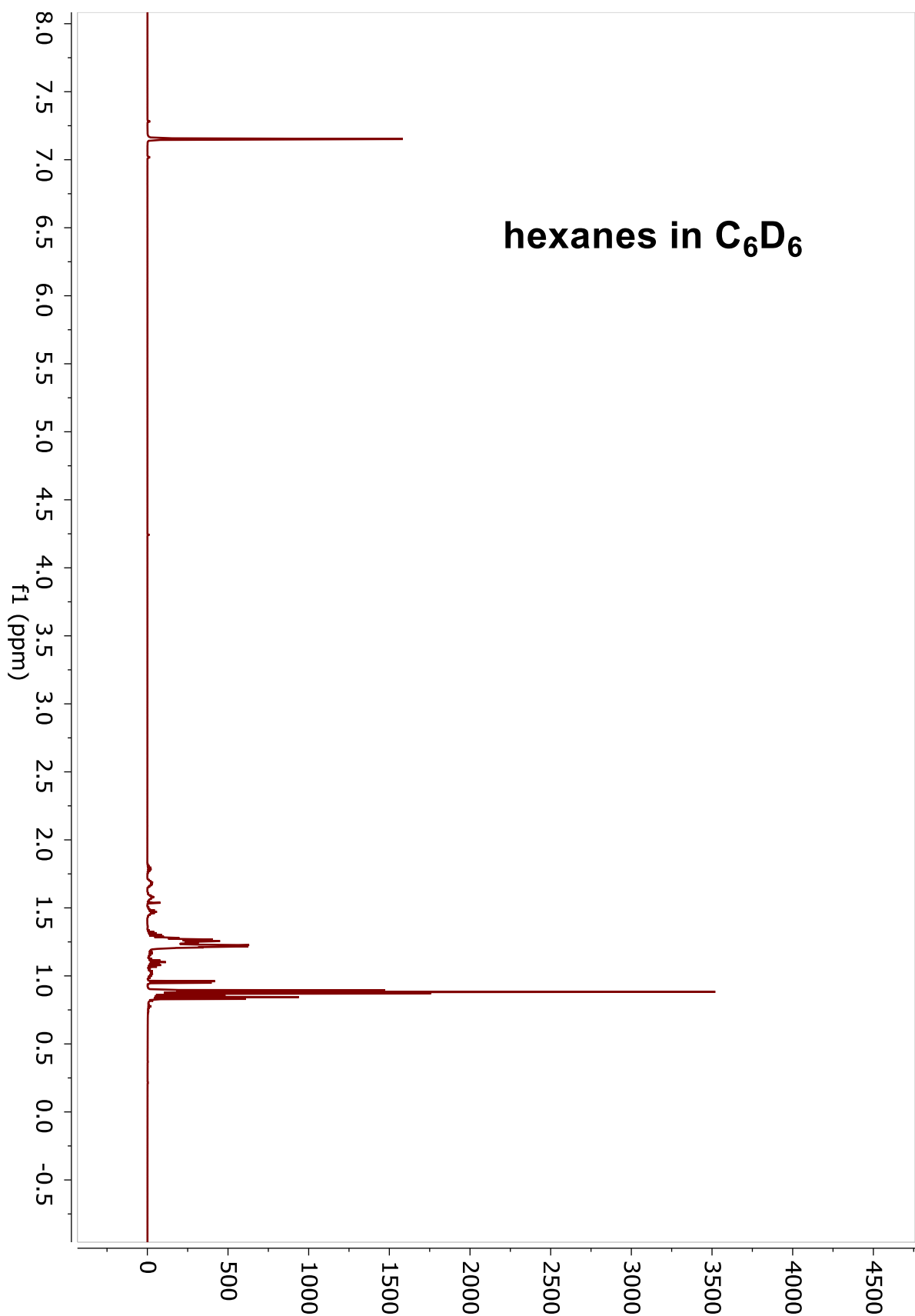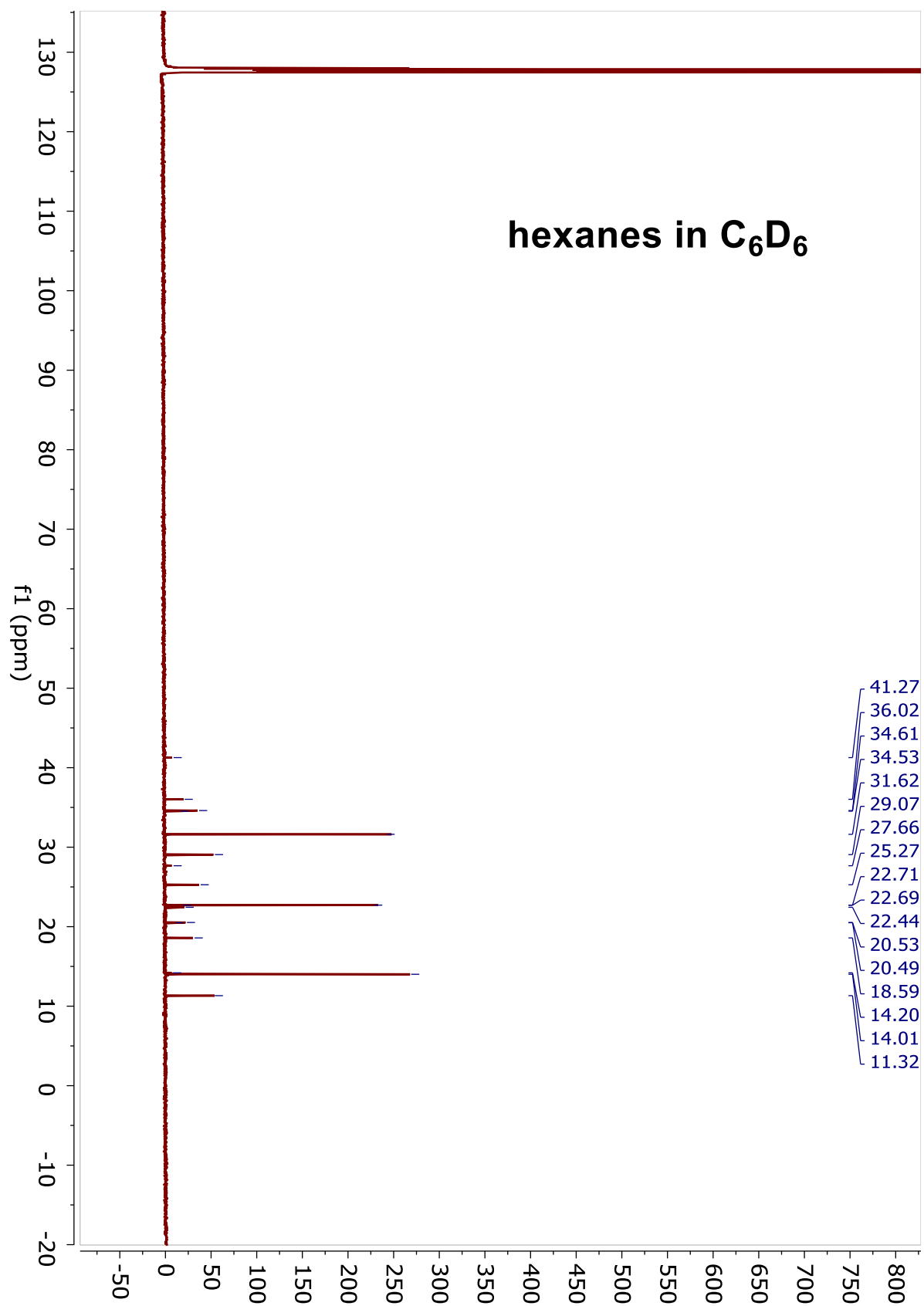## 3.12 REFERENCES

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