Stereoselective Synthesis of β-Aminoalkylboronic Acid Derivatives Using 1,1-Diboron Compounds

by

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Abstract

As an important class of chiral alkylboron compounds, α-aminoalkylboronic acids display distinct utility in medicinal chemistry as a bioisostere of α-amino acids and α-amino aldehydes, which is highlighted by the commercialization of two anticancer drugs (bortezomib, ixazomib) and one antibiotic drug (vaborbactam). By analogy with α-aminoalkylboronic acids, β-aminoalkylboronic acids are a bioisostere of β-amino acids, thus have obvious potential in pharmaceutical drug development. In addition, β-aminoalkylboronates can act as catalysts in organic reactions and are valuable synthetic building blocks, which can be exploited to access many useful compounds, such as β-amino alcohols and 1,2-diamines. However, despite these attractive applications, the development of synthetic approaches to these valuable compounds has not received much attention until recently. Among all of the reported methods, only a small number of stereoselective methods can provide primary β-aminoalkylboronic esters, and even fewer methods are applicable to α,β-disubstituted β-aminoalkylboronic esters. This thesis describes successful efforts to develop novel and efficient approaches using 1,1-diboron compounds towards optically pure β-aminoalkylboronates, including the syn and anti diastereomers of α,β-disubstituted β-aminoalkylboronates.

Chapter 2 presents a 1,2-addition/monoprotodeboronation sequence developed to access enantioenriched α,β-disubstituted β-aminoalkylboronates. The 1,2-addition of lithiated 1,1-diborylalkanes to chiral sulfinimine derivatives delivered enantiomerically pure β-sufinimido *gem*-bis(boronates) in good yields with high levels of diastereoselectivity. A subsequent mono-protodeboronation of the resulting β-sufinimido *gem*-bis(boronates) afforded *syn*-α,β-disubstituted β-aminoalkylboronates. In addition, studies were made to investigate the

stereochemical outcome (syn-selectivity) in the monoprotodeboronation. The details of the reaction scope and synthetic applications also will be discussed.

In order to access the elusive *anti*-α,β-disubstituted β-aminoalkylboronates, a complementary variant of the abovementioned monoprotodeboronation was developed. To favor the formation of the anti diastereomer, the steps of protodeboronation and deprotection of the *N*-sulfinyl amine were inverted. Chapter 3 describes the details of the optimization of this anti-selective monoprotodeboronation using *N*-desulfinylated β-amino *gem*-bis(boronates). The substrate scope, mechanistic studies, and synthetic applications also are discussed.

Inspired by the previous work on a Cu-catalyzed asymmetric 1,2-addition of 1,1-diborylalkanes to aldehydes for the synthesis of 1,2-hydroxyboronates, it was envisioned that this 1,2-addition strategy could be applied to imines, thus providing a straightforward and catalytic approach to enantioenriched β-aminoalkylboronates. In Chapter 4, the extensive optimization of such an asymmetric 1,2-addition is presented. To enhance the enantioselectivity, a ligand high-throughput screening (HTS) approach was employed through a collaboration with a team of scientists at Pfizer and will be discussed in detail.

Preface

Chapter 2 of this thesis has been published as Li, X.; Hall, D. G. "Diastereocontrolled Monoprotodeboronationof β-Sulfinimido *gem*-Bis(boronates): A General and Stereoselective Route to α,β-Disubstituted β-Aminoalkylboronates" *Angew. Chem., Int. Ed.* **2018**, *57*, 10304 –10308. As the sole experimentalist, I was responsible for the reaction optimization, studies of substrate scope and synthetic applications, mechanistic studies, and data collection and analysis of compounds synthesized. I also wrote the manuscript with assistance from Prof. D. G. Hall, who was the supervisory author and created the concept used in project initiation.

Chapter 3 of this thesis has been submitted for publication as Li, X.; Hall, D. G. "Stereodivergent Asymmetric Synthesis of α,β-Disubstituted β-Aminoalkylboronic Acid Derivatives via Group-Selective Protodeboronation Enabling Access to the Elusive anti Isomer" I was responsible for the reaction optimization, studies of substrate scope and synthetic applications, mechanistic studies, and data collection and analysis of compounds synthesized. Prof. D. G. Hall was responsible for the molecular modeling. I wrote the manuscript with assistance from Prof. D. G. Hall, who was the supervisory author and was involved with concept formation and project initiation.

Chapter 4 of this thesis is based on non-published work initiated by Prof. D. G. Hall. I was responsible for the synthesis of starting materials, reaction optimization, and data collection and analysis of compounds synthesized. The HTS was conducted by a team of scientists at Pfizer, coordinated by Dr. Jack Lee.

Acknowledgment

Pursuing a PhD degree is a challenging journey, but I feel grateful for the help and support from many incredible individuals over the past five years, without which, this degree is not possible. First of all, I would like to express my deepest gratitude to my supervisor, Prof. Dennis G. Hall, for his guidance and support throughout my doctoral studies. He has provided me with training and challenges to help me become a qualified chemist. His great suggestions, lessons, and patience helped me improve my presentation and writing skills. I also would like to thank him for sending me to various conferences, allowing me to broaden my horizons by interacting with different chemists and keeping up with cutting-edge research topics. In addition to a research supervisor, he is a life mentor, who cares about my life and career by offering me firm support.

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I am thankful to all my lab mates, past and present. It is such a pleasure to work with these friendly, talented, and knowledgeable individuals, who have helped and guided me over the years. I am especially thankful to Dr. Taras Rybak, who mentored me when I first started my graduate research in the laboratory. Most of all, I am grateful to Dr. Burcin Akgun and Youri Kim, who became my closest friends in the department. I will definitely miss the time we spent together in and outside of the laboratory. I am thankful to those who have provided advice while I was writing my dissertation: Dr. Marco Paladino, Dr. Helen Clement, Hweeting

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Outside of the Hall group, I also would like to express my appreciation and thanks to a group of people in the ECCC church for making my life enjoyable, supporting, and praying for me when I faced difficulties. Our faith united us and brought us closer to each other, and the ECCC church is like a home to me.

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List of Schemes

List of Abbreviations

Ac	Acetyl
app d	Apparent doublet
app dt	Apparent doublet of triplets
app td	Apparent triplet of doublets
app qd	Apparent quartet of doublets
app dtd	Apparent doublet of triplet of doublet
aq	Aqueous
Ar	Aryl
BAC	Boronic acid catalysis
BDPP	(2*S*,4*S*)-2,4-Bis(diphenylphosphino)pentane
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-Bi-2-naphthol
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
B_2pin_2	Bis(pinacolato)diboron
bpy	2,2'-Bipyridine
br	Broad
n-Bu	*n*-Butyl
s-Bu	*sec*-Butyl
t-Bu	*tert*-Butyl
Bz	Benzoyl

calcd	Calculated
$CHCl_3$	Chloroform
CH_3CN	Acetonitrile
cm	Centimetre
cm^{-1}	Wavenumbers
comp m	Complex multiplet
conv.	Conversion
Cp	Cyclopentadienyl
Cy	Cyclohexyl
d	Doublet
dan	1,8-Diaminonaphthyl
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
dd	Doublet of doublets;
ddd	Doublet of doublet of doublets;
dddd	Doublet of doublet of doublet of doublets;
ddq	Doublet of doublet of quartets
CFL	Compact fluorescent lamp
DFT	Density functional theory
DIAD	Diisopropyl azodicarboxylate
DIPEA	*N*,*N*-Diisopropylethylamine
DMBQ	2,6-Dimethoxy-1,4-benzoquinone
dme	Dimethoxyethane

DMF	Dimethylformamide
DMP	Dess–Martin periodinane
DMSO	Dimethyl sulfoxide
dppbz	1,2-Bis(diphenylphosphino)benzene
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dppp	1,3-Bis(diphenylphosphino)propane
dq	Doublet of quartets
dr	Diastereomeric ratio
dtbbpy	4,4’-Di-*tert*-butyl-2,2-dipyridyl
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	Enantiomeric excess
EI	Electron ionization
eq	Equation
equiv	Equivalent
ESI	Electrospray ionization
esp	α,α,α′,α′-Tetramethyl-1,3-benzenedipropionic acid
Et	Ethyl
Et_2O	Diethyl ether
EtOAc	Ethyl Acetate
FDA	Food and Drug Administration
Fmoc	Fluorenylmethyloxycarbonyl
gem	Geminal
h	Hour

HBpin	Pinacolborane
HDMS	Bis(trimethylsilyl)amine
HOBt	Hydroxybenzotriazole
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
HTS	High-throughput screening
IR	Infrared spectroscopy
iv	Intravenous
KPC	*Klebsiella pneumoniae* carbapenemase
LC-MS	Liquid chromatography–mass spectrometry
LDA	Lithium diisopropylamide
LiTMP	Lithium tetramethylpiperidide
m	Multiplet
M	Molar concentration
Me	Methyl
MeOH	Methanol
Mes	Mesityl
MIC	Minimum inhibitory concentration
MIDA	*N*-Methyliminodiacetic acid
min	Minute
mL	Milliliter
mmol	Millimole
mol	Mole

mp	Melting point
MS	Molecular sieves
MTBE	Methyl *tert*-butyl ether
N	Equivalent concentration
NBS	*N*-Bromosuccinimide
NHC	*N*-Heterocyclic carbene
NIS	*N*-Iodosuccinimide
NMR	Nuclear magnetic resonance
Nu	Nucleophile
PG	Protecting group
Ph	Phenyl
Phth	Phthalimide
pin	Pinacolato
piv	Pivaloyl
po	Oral
PPTS	Pyridinium *p*-toluenesulfonate
ppy	2-Phenylpyridine
i-Pr	Isopropyl
q	Quartet
qd	Quartet of doublets
RBpin	Pinacol boronic ester
rt	Room temperature
s	Singlet

sep	Septet
sex	Sextet
SFC/MS	Supercritical fluid chromatography/mass spectrometry
SMC	Suzuki–Miyaura cross-coupling
t	Triplet
TADDOL	α,α,α',α'-Tetraaryl-2,2-disubstituted 1,3-dioxolane-4,5-dimethanol
TBAF	Tetrabutylammonium fluoride
TBS	*tert*-Butyldimethylsilyl
Tf	Triflyl
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
TM	Transition metal
TMP	2,2,6,6-Tetramethylpiperidine
TMS	Trimethylsilyl
Ts	Tosyl
TsOH	*p*-Toluenesulfonic acid
UV	Ultraviolet
wt.	Weight

Chapter 1

Introduction: Preparation and Applications of β-Aminoalkylboronic Acids (Derivatives)

1.1 Bioisosteres in Medicinal Chemistry

1.1.1 Concept of Bioisosterism

In 1919, Irving Langmuir first introduced the term "isosterism" to describe his observation that certain molecules, such as N_2 and CO, N_2O and CO_2, and N_3^- and NCO^-, exhibit similar physical properties.[1] He defined compounds or groups of atoms that have the same number and arrangement of electrons as isosteric compounds or isosteres. In 1925, the concept of isosteres was extended further by H. G. Grimm with Grimm's hydride displacement law.[2] As stated by this law: "Atoms anywhere up to four places in the periodic system before an inert gas change their properties by uniting with one to four hydrogen atoms, in such a manner that the resulting combinations behave like pseudoatoms, which are similar to elements in the groups one to four places respectively, to their right." Thus, by following this law, CH is isosteric with N, and CH_2 and NH are isosteric with O. In 1932, Friedrich Erlenmeyer broadened Grimm's definition of isosteres and defined isosteres as atoms, ions or molecules in which the peripheral layers of electrons can be consider identical.[3] According to his definition, all the elements in the same group of the periodic table are isosteres of each other (e.g., F, Cl, Br, and I). In 1951, Harris Friedman first introduced the term "bioisosteres", which defines atoms or molecules that fit the broadest definition for isosteres and exhibit similar biological effects.[4] Nowadays, isosteres defined by Grimm's hydride displacement law and Erlenmeyer's definition are classified as classical bioisosteres. In 1991, Friedman's definition of bioisosteres was followed by a broader definition from Alfred Burger: "Compounds or groups that possess near-equal molecular shapes and volumes, approximately the same distribution of electrons, and which exhibit similar physicochemical properties."[4] Burger's definition of bioisosteres includes not only classical bioisosteres but also non-classical bioisosteres that do not obey the steric and electronic definition of classical isosteres. For example, carboxylic acid bioisosteres, such as hydroxamic acids, phosphonic acids, sulphonic

acids, tetrazoles, and squaric acids, represent a typical class of non-classical bioisosteres (Figure 1-1).

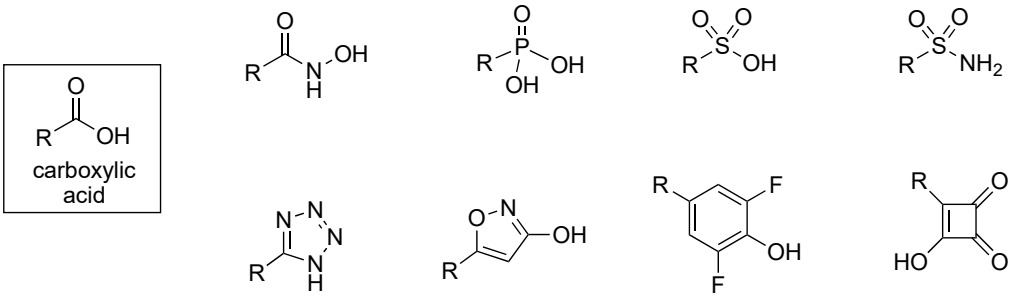


Figure 1-1. Selected examples of non-classical bioisosteres of carboxylic acids.

1.1.2 Application of Bioisosteres in Drug Design

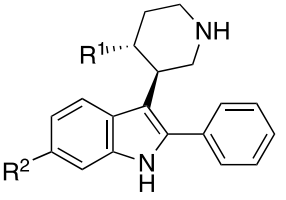
In the process of developing a drug candidate, a lead compound with a desired pharmacological activity is identified first. However, the lead compound often is associated with some undesired side effects, such as metabolic instability, poor selectivity, and toxicity. Thus, small, defined changes to the lead compound are made to overcome these shortcomings, and bioisosteric replacement serves as an efficient tool for this purpose.[5] When replacing a functional group of the lead compound with a bioisostere, many parameters play important roles and must be taken into consideration, such as size, shape, pKa, polarity, and lipophilicity. The outcome of bioisosteric replacement can be beneficial or detrimental, relying on the particular context.

A representation of the application of bioisosteric replacement in drug-discovery research is the commonly used substitution of hydrogen atoms by fluorine atoms.[6] The fluorine atom (van der Waals radius of 1.47 Å) has a similar size to the hydrogen atom (van der Waals radius of 1.2 Å), however, it is much more electronegative than the hydrogen atom. Due to the high electronegativity, fluorine substitution can result in different pharmacological properties. An example of fluorine substitution for improving pharmacological properties is the discovery of indole derivative **1-3** as an antipsychotic drug with high affinity, selectivity, and oral bioavailability for the 5-HT_{2A} receptor (Table 1-1).[7] As shown in Table 1-1, indole derivative **1-1** has poor bioavailability, and it was found that introduction of an electron-withdrawing fluorine atom onto the piperidine of **1-1** led to moderately improved

bioavailability by lowering the pKa of the basic amine group (see **1-2**). Further investigation revealed that when the metabolically labile 6-position of the indole of **1-2** was blocked by a fluorine atom, the metabolism of **1-2** was reduced, thus resulting in much better bioavailability (see **1-3**). Moreover, incorporation of two fluorine atoms in **1-1** delivers a significant improvement on the affinity at the 5-HT_{2A} receptor (**1-1** vs. **1-3**).

Besides hydrogen's bioisosteres, the bioisosteres of other functional groups, such as carboxylic acid, phenol, amide, and ester, have been studied and exploited to optimize drugs or drug candidates.[8] As a well-established concept, the development and application of bioisosteres have been adopted as a fundamental tactical approach to problem solving in drug design.[8]

Table 1-1. Effects of Fluorine Atoms on the Physicochemical Properties of 2-Phenyl-3-(3-piperidyl)indoles



Compound	R^1	R^2	pKa	5-HT_{2A}[a]	F%[b]
1-1	H	H	10.4	0.99	poor
1-2	F	H	8.5	0.43	18
1-3	F	F	–	0.06	80

[a]Affinity at human cloned 5-HT_{2A}. [b]Bioavailability calculated from dosing at 0.5–2 mg per Kg iv and po.

1.2 α-Aminoalkylboronic Acids in Drug Discovery

1.2.1 Boronic Acids as a Bioisostere of Carbonyl Compounds

Boron has atomic number 5 and is positioned in the same period of the periodic table as carbon, however, with one less electron than carbon. This characteristic of boron can lead to many structural similarities between boron-containing and carbon-containing compounds. For example, the trigonal planarity of boronic acids closely resembles that of carbonyl compounds, such as aldehydes, ketones, and carboxylic acids, thus, boronic acids are a bonafide bioisostere of these carbonyl compounds (Figure 1-2). As a bioisostere of carbonyl compounds, boronic acids recently have emerged as a novel chemotype in drug design.[9] Boron is electrophilic because of the empty *p*-orbital of the boron atom, thus can have interactions with biological nucleophiles (e.g., hydroxyl and amine groups present in enzyme residues, carbohydrates, and nucleic acids), which convert a neutral and trigonal planar sp^2 boron to an anionic tetrahedral sp^3 boron (Figure 1-2).[10] This type of interaction can result in the formation of covalent bonds to the target protein, thus makes many boron-containing compounds potent and selective enzymes inhibitors.[11]

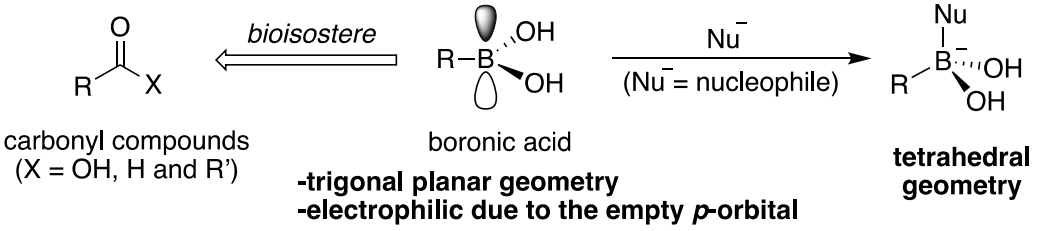


Figure 1-2. Boronic acids as a bioisostere of carbonyl compounds and their interactions with biological nucleophiles.

1.2.2 Applications of α-Aminoalkylboronic Acids in Drug Discovery

α-Aminoalkylboronic acids are bioisosteric to α-amino carbonyl compounds, especially naturally occurring α-amino acids, and have made a remarkable contribution to pharmaceutical drug development. The first successful boron-containing agent approved by the U.S. Food and Drug Administration (FDA) in 2003, bortezomib (Velcade®), is an optically pure dipeptidyl α-aminoalkylboronic acid (Figure 1-3).[12] Bortezomib is the first successful proteasome inhibitor and has been used for the treatment of multiple myeloma in over 50

countries. In the process of the development of bortezomib, initial studies started with dipeptidyl compound **1-4**, which exhibits low selectivity for 20S proteasome (K_i = 1600 nM; Figure 1-3).[13] It was found that replacing the α-amino aldehyde moiety of **1-4** with an α-aminoalkylboronic acid moiety resulted in an extremely high selectivity for the 20S proteasome (K_i = 0.62 nM; Figure 1-3), which is attributed to the good ability of the boron atom to accept the oxygen lone pair of the active site serine residue. These studies have paved the way for the success of bortezomib that encouraged further investigation on the application of α-aminoalkylboronic acids and other organoboron compounds in drug discovery.[14]

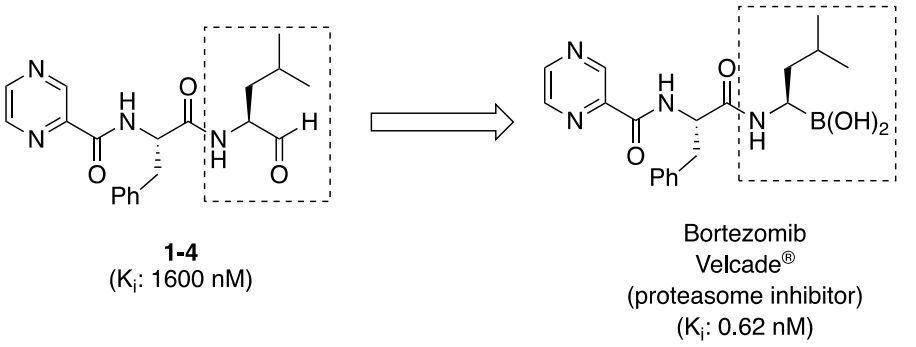


Figure 1-3. Discovery of bortezomib via bioisosteric replacement of the α-amino aldehyde moiety of dipeptidyl compound **1-4** with an α-aminoalkylboronic acid moiety.

In addition to bortezomib, one of its analogues, ixazomib (Ninlaro®), was approved by the FDA in 2015 for multiple myeloma treatment (Figure 1-4).[15] Additionally, vaborbactam is a β-lactamase inhibitor, which contains a cyclic α-aminoalkylboronic acid moiety (Figure 1-4), and has been commercialized recently with meropenem (a β-lactam antibiotic) for complicated urinary tract infections.[16] The discovery of vaborbactam was driven by the poor inhibition of *Klebsiella pneumoniae* carbapenemase (KPC) using clinically important α-amino acid-containing β-lactamase inhibitors, including clavulanic acid, sulbactam, and tazobactam.[16] Using the concept of α-aminoalkylboronic acids as a bioisostere of α-amino acids, testing of numerous peptidyl α-aminoalkylboronic acids eventually identified vaborbactam as a highly effective inhibitor for KPC. Besides three commercialized drugs outlined in Figure 1-3 and 1-4, various α-aminoalkylboronic acid-containing compounds are in Phase I, II, or III clinical trials,[17] which exemplifies the distinct utility of α-

aminoalkylboronic acids as an effective bioisostere of α-amino carbonyl compounds in drug discovery.

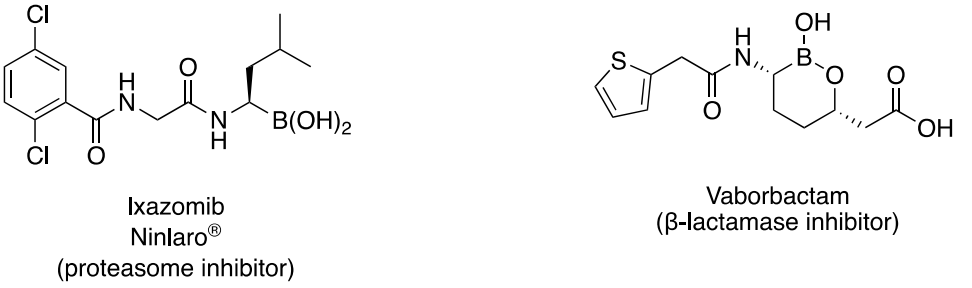


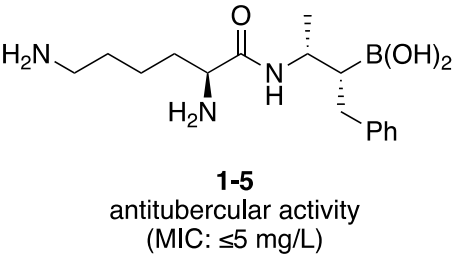
Figure 1-4. Other FDA approved α-aminoalkylboronic acid-containing drugs.

1.3 β-Aminoalkylboronic Acids in Drug Discovery

Although β-amino acids do not occur in nature as frequently as α-amino acids, it have been demonstrated that β-amino acids could modulate the conformation, dynamics, and proteolytic susceptibility of native α-peptides.[18] Thus, incorporation of β-amino acids into peptides has been successful in creating peptidomimetics that display various biological activities, including antimicrobial activity, inhibition of protein–protein interactions, and antiangiogenic activity.[19] By extension of α-aminoalkylboronic acids, β-aminoalkylboronic acids are a bioisostere of pharmaceutically important β-amino acids, thus have obvious potential in drug discovery. However, β-aminoalkylboronic acids have attracted much less attention compared to α-aminoalkylboronic acids.

The potential of β-aminoalkylboronic acids in pharmaceutical drug development has been demonstrated recently by Lejon and co-workers.[20] On the basis of the fact that peptides and β-amino acid-containing peptidomimetics tested over the years have exhibited no or poor antitubercular activity, Lejon and co-workers turned their attention to a bioisostere of β-amino acids, β-aminoalkylboronic acids. In their studies, a variety of β-substituted and α,β-disubstituted peptidyl β-aminoalkylboronic esters or acids were synthesized and subjected to in vitro testing for antitubercular activity. Among all of the β-aminoalkylboronic esters and acids tested, alkylboronic acid **1-5** was found to exhibit the highest activity with ≤5

mg/L MIC (minimum inhibitory concentration) against *Mycobacterium tuberculosis* (Figure 1-5).



1-5
antitubercular activity
(MIC: ≤5 mg/L)

Figure 1-5. An example of a peptidyl β-aminoalkylboronic acid as an antitubercular agent.

1.4 Other Applications of β-Aminoboronic Acids (Derivatives)

1.4.1 β-Aminoalkylboronic Esters in Organic Synthesis

1.4.1.1 Importance of Alkylboronic Esters in Organic Synthesis

Organoboron compounds are valuable synthetic intermediates that have made great contributions to organic synthesis; this was recognized by two Nobel prizes to Herbert C. Brown in 1979[18] and Akira Suzuki in 2010.[19] As a subclass of organoboron compounds, alkylboron compounds, when they exist in their enantiomerically pure forms, display a unique utility in asymmetric synthesis.[23] Among all of the alkylboron compounds, including alkylboronic acids (derivatives) and *N*-methyliminodiacetic acid-protected (MIDA) boronates (Figure 1-6), alkylboronic esters, especially pinacol boronic esters (RBpin), have become most popular owing to their relative good stability and reactivity, ease of handling and purification, and low cost.[24] Therefore, there have been many developments with regard to efficient methods to access enantioenriched alkylboronic esters over the past decade.[25]

With numerous methods established to synthesize chiral alkylboronic esters with high levels of stereocontrol, a number of C–B bond derivatization methodologies have been developed to convert the boryl group [$B(OR)_2$] into a wide range of functional groups, such as aryl, alcohol, amine, and halogen groups (Figure 1-7).[26] Importantly, transformations of optically pure alkylboronates generally proceed through a stereoretentive or stereoinvertive pathway, thus providing a powerful platform for asymmetric synthesis. The origin of the stereospecificity in most of these transformations is ascribed to the nature of the 1,2-metallate

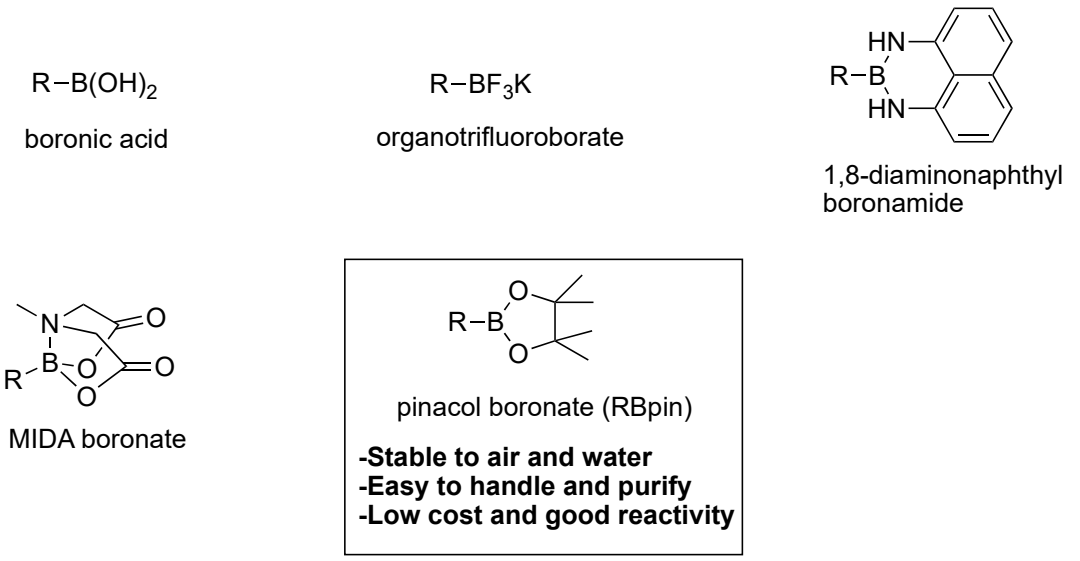


Figure 1-6. Selected examples of alkylboron compounds.

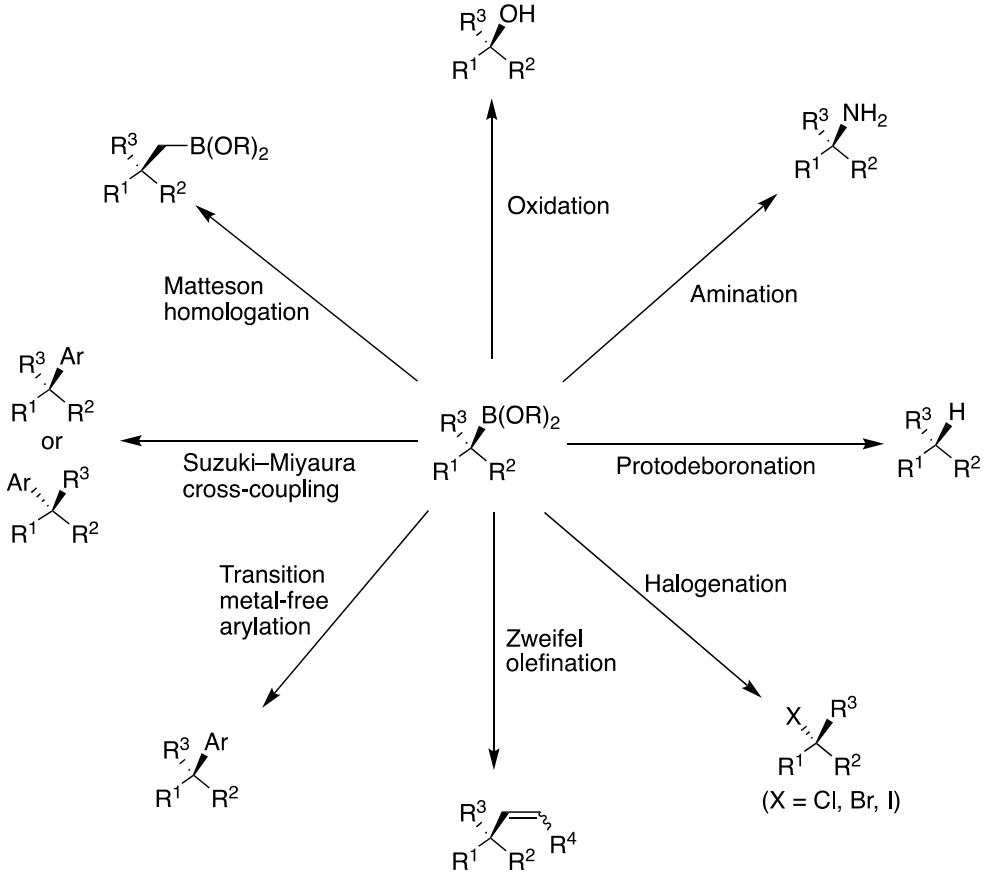
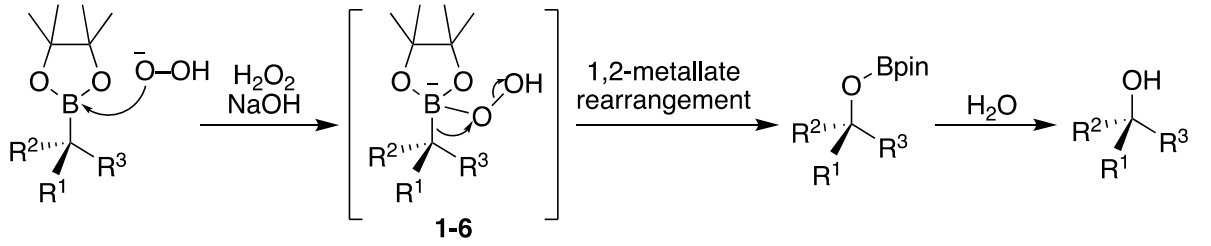


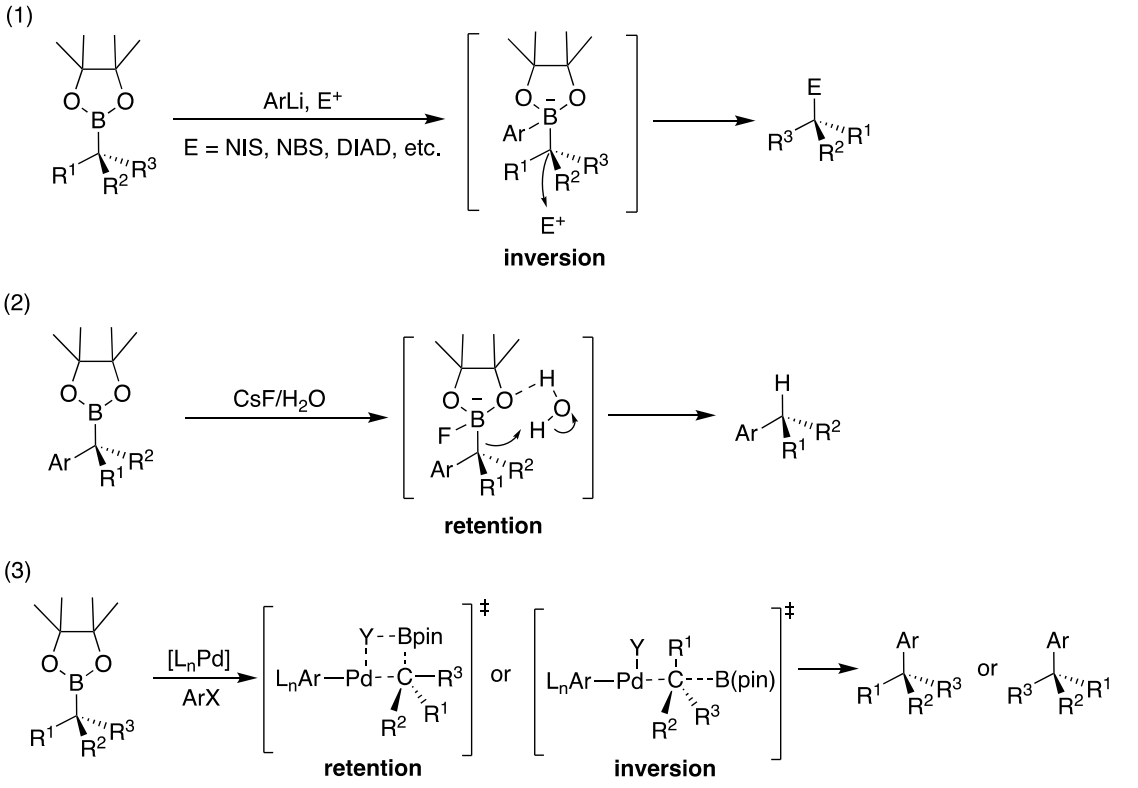
Figure 1-7. Selected stereospecific transformations of chiral alkylboronic esters.

rearrangement of borate complexes formed by a nucleophilic attack on the boryl group of alkylboronates. An example is the oxidation of chiral alkylboronates, in which borate complex **1-6** is formed first. Then, the C–B bond migrates to the adjacent oxygen atom (1,2-metallate rearrangement) with the loss of a hydroxide, followed by hydrolysis to afford the alcohol with complete retention of stereochemistry (Scheme 1-1). This type of 1,2-metallate rearrangement of borate complexes also applies to many other transformations of chiral alkylboronic esters, such as amination,[27–30] Matteson homologation,[31,32] Zweifel olefination,[31,33] and transition metal-free arylation.[34,35]



Scheme 1-1. Stereoretentive oxidation of chiral alkylboronic esters via 1,2-metallate rearrangement.

As shown in Scheme 1-2, other reactivities of chiral alkylboronates that do not involve a 1,2-metallate rearrangement also have been uncovered. It has been reported that nucleophilic borate complexes reacted with electrophiles such as *N*-iodosuccinimide (NIS), *N*-bromosuccinimide (NBS), and diisopropyl azodicarboxylate (DIAD) through a S_E2 pathway, leading to inversion of stereochemistry (eq. 1).[36,37] Moreover, alkylboronates can complex with water in protodeboronation, which ensures a stereoretentive proton delivery from the same side of the C–B bond (eq. 2).[38] In the Pd-catalyzed Suzuki–Miyaura cross-coupling (SMC), alkylboronates can undergo stereoretentive or stereoinvertive transmetalation with the palladium catalyst (eq. 3).[39] The transmetalation, stereoretentive or stereoinvertive, is controlled by the catalyst and ligand or the alkylboronate substrate.



Scheme 1-2. Other reactivities of chiral alkylboronic esters that do not involve a 1,2-metallate rearrangement: 1) stereoinvertive S_E2 reactions of borate complexes with electrophiles, 2) stereoretentive protodeboronation with water and 3) stereoretentive or stereoinvertive Pd-catalyzed SMC.

1.4.1.2 Synthetic Applications of β-Aminoalkylboronic Esters

β-Aminoalkylboronic acid derivatives are a subclass of alkylboron compounds, thus, they are amenable to various C–B bond derivatization reactions of alkylboron compounds. Specifically, when β-aminoalkylboronic esters of high optical purity are used, they can undergo many stereospecific transformations of optically pure alkylboronates, which can lead to the asymmetric synthesis of many useful building blocks. As shown in Figure 1-8, subjecting enantioenriched β-aminoalkylboronic esters to oxidation and amination conditions can deliver optically pure β-amino alcohol **1-7** and 1,2-diamine **1-8**, respectively.[40] Enantiomerically pure β-aminoalkylboronic esters also can be engaged in transition metal-free stereoretentive Zweifel olefination,[41] Matteson homologation,[42] and furanylation[43] conditions for C–C bond formation (see **1-9**–**1-11**). Furthermore, it has been demonstrated that chiral β-aminoalkylboronic esters could undergo Pd-catalyzed SMC with aryl halides (see **1-12**).[44]

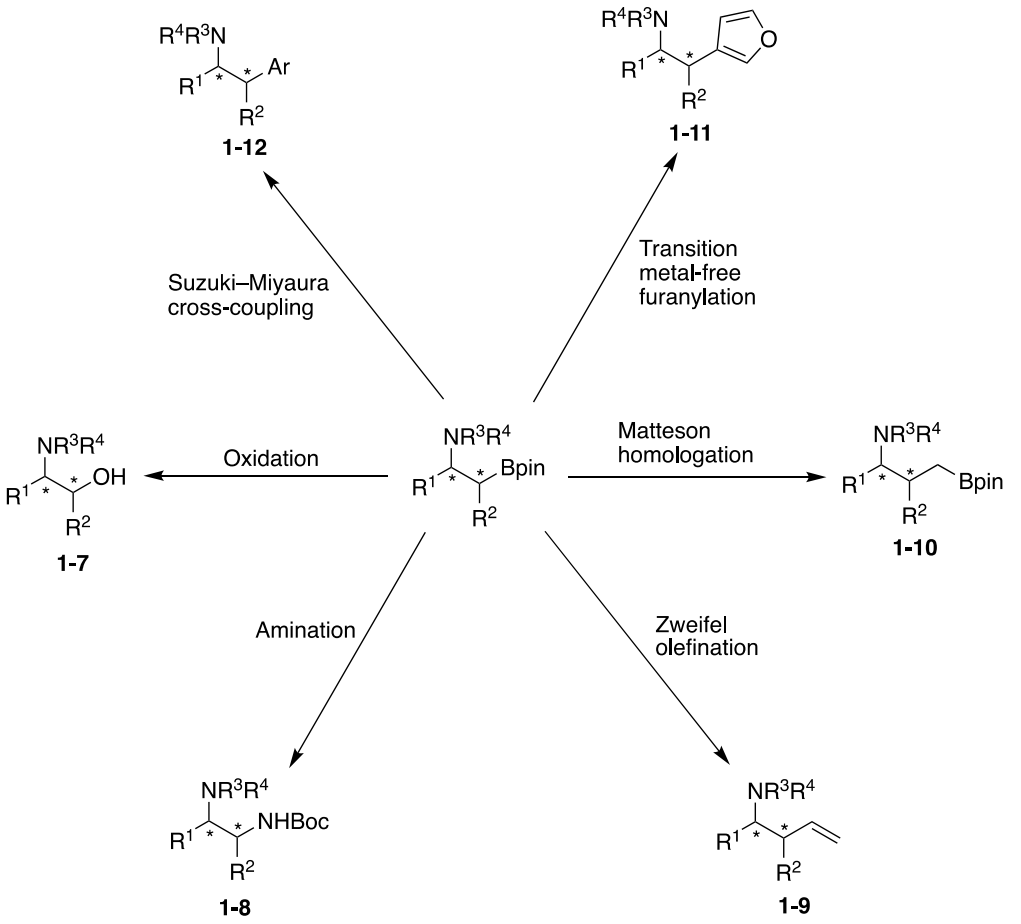
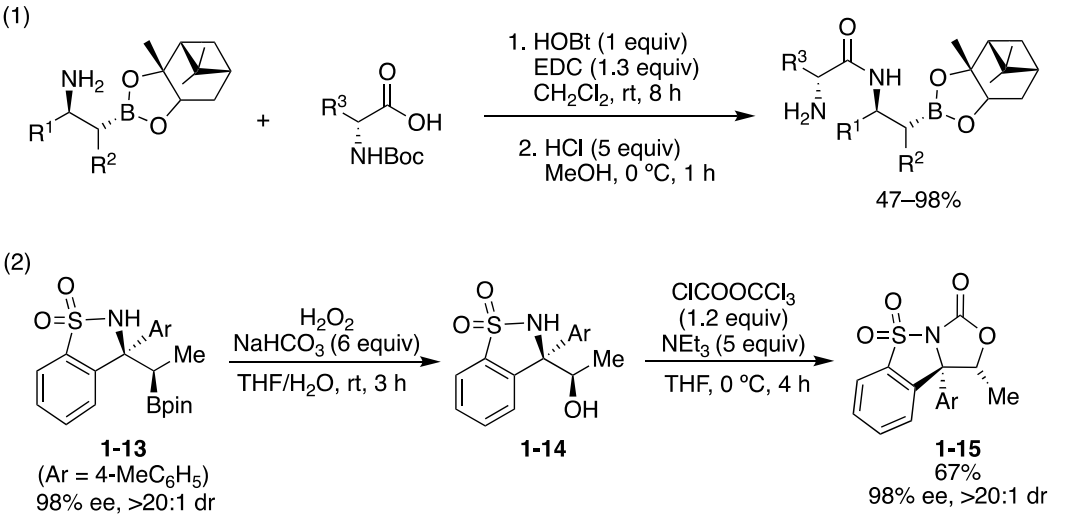


Figure 1-8. Selected examples of stereospecific C–B bond derivatizations of chiral β-aminoalkylboronates.

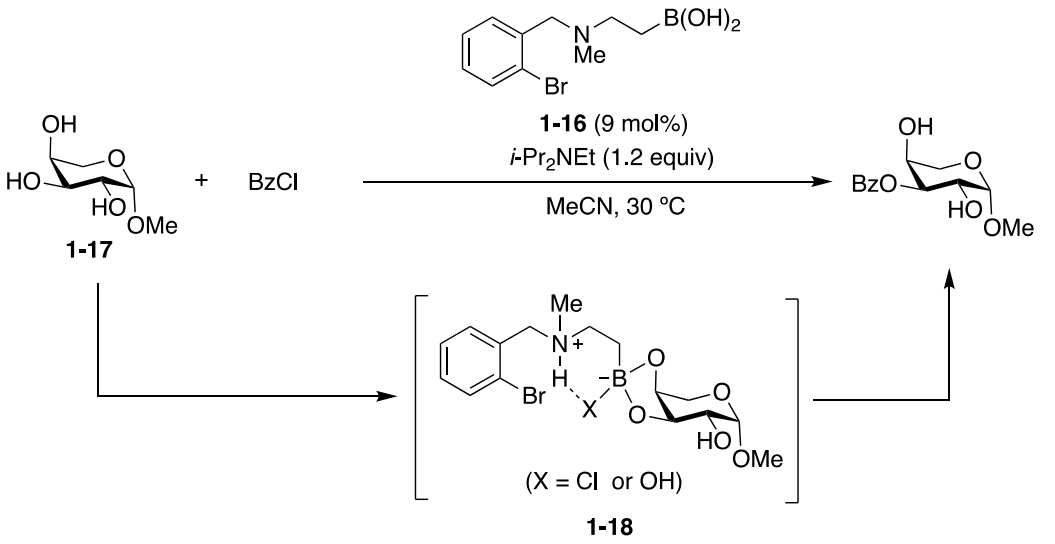
Besides C–B derivatization reactions, the nucleophilic reactivity of the amine group of β-aminoalkylboronic esters opens further synthetic utility. For example, Lejon and co-workers have employed the coupling of β-aminoalkylboronic esters and peptides to synthesize peptidyl β-aminoalkylboronic esters that are attractive scaffolds for drug design (Scheme 1-3, eq. 1).[20] Another good example that involves the nucleophilic amine group is the preparation of oxazolidinone derivatives. It has been reported that after stereoretentive oxidation of β-aminoalkylboronic ester **1-13** into β-amino alcohol **1-14**, treatment of **1-14** with trichloromethyl chloroformates furnished oxazolidinone derivative **1-15** in a good yield (Scheme 1-3, eq. 2).[45]



Scheme 1-3. Examples of transformations involving the nucleophilic reactivity of the amine group of β-aminoalkylboronates: 1) coupling with peptides and 2) synthesis of oxazolidinone derivatives.

1.4.2 β-Aminoalkylboronic Acids in Catalysis

Besides applications in organic synthesis and drug discovery, an emerging application of boronic acids is their use as reaction catalysts for activating hydroxy-containing substrates, such as carboxylic acids and alcohols.[46] However, the majority of boronic acid-catalyzed reactions focus on arylboronic acids, and alkylboronic acids rarely have been reported for this purpose. Recently, it has been reported by Yudin and Taylor that anthracene-bearing β-aminoalkylboronic acid **1-16** could catalyze a highly regioselective *O*-benzoylation of arabinopyranoside derivative **1-17** (Scheme 1-4).[47] It was proposed that the *O*-benzoylation involved the formation of tetracoordinate anionic complex **1-18** through complexation of the *cis*-diol group of the arabinopyranoside with catalyst **1-16**. Complex **1-18** behaves as an activated nucleophile favoring *O*-benzoylation at the equatorial oxygen, and the observed regioselectivity is consistent with that of the diphenylborinic acid-catalyzed *O*-benzoylation.[48] Although the yield was not reported, when monitoring the reaction using attenuated total reflection infrared spectroscopy, β-aminoalkylboronic acid **1-16** exhibited a superior reactivity to diphenylborinic acid.



Scheme 1-4. β-Aminoalkylboronic acid-catalyzed *O*-benzoylation of an arabinopyranoside derivative.

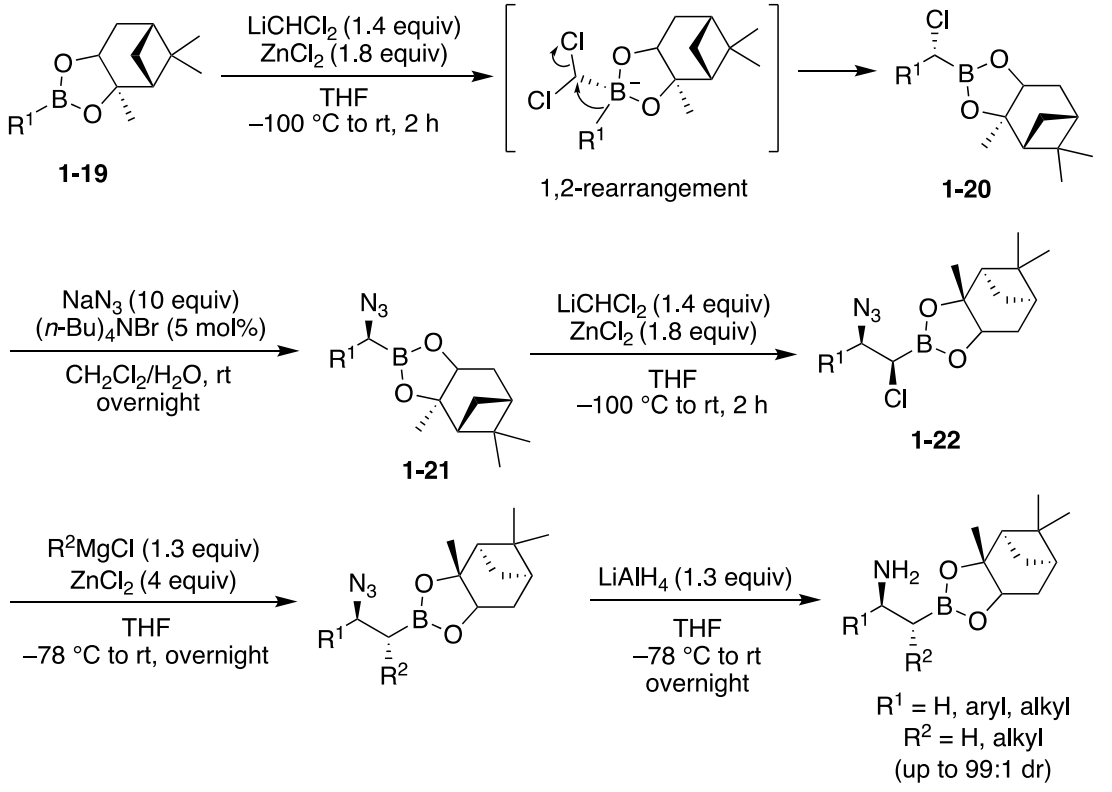
1.5 Methods for the Synthesis of β-Aminoalkylboronic Esters

The development of synthetic approaches to β-aminoalkylboronic esters has not received much attention until recently. In this section, the body of reported methods to access these compounds will be evaluated. For the ease of discussion, all the syn and anti stereochemistry described in this section represents the relative stereochemistry of the vicinal boron and nitrogen substituents of β-aminoalkylboronic esters.

1.5.1 Matteson Homologation

In 1986, Matteson and co-workers reported the first synthesis of β-aminoalkylboronic esters by employing the optically pure pinanediol alkylboronate as the starting material (Scheme 1-5).[49] The (+)- or (–)-pinanediol protecting group is used to control the stereochemistry in the synthesis. In this approach, two key steps are the one-carbon homologation of alkylboronate **1-19** and **1-21**, in which **1-19** and **1-21** undergo a 1,2-metallate rearrangement (Scheme 1-5) with the lithiated chloromethane (also called Matteson homologation) to afford enantioenriched alkylboronate **1-20** and **1-22**, respectively. In combination with some nucleophilic substitution reactions, the Matteson homologation can accomplish the synthesis of α,β-disubstituted β-aminoalkylboronic esters with high syn selectivity (up to 99:1 dr).

When Matteson and co-workers developed this methodology, only a single example had been reported. The scope of Matteson's method has been expanded recently to α- and β-substituted, and other *syn*-α,β-disubstituted β-aminoalkylboronic esters by the group of Lejon.[20,50] Nonetheless, this original Matteson approach requires multiple steps (five steps) and cryogenic conditions (–100 ºC) with harsh reagents (e.g., $LiCH_2Cl$ and R^2MgCl).



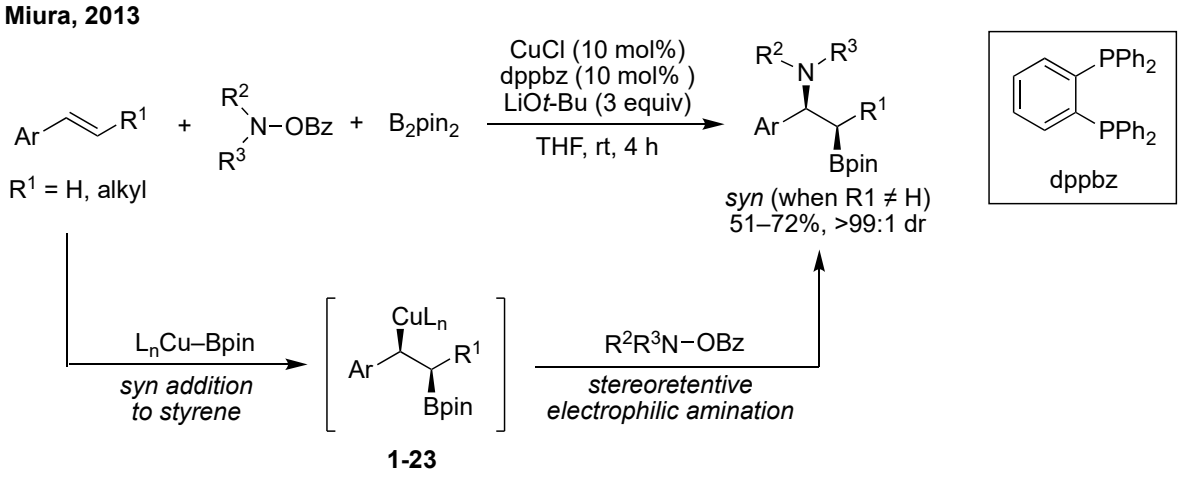
Scheme 1-5. Synthesis of optically pure β-aminoalkylboronates using the Matteson homologation.

1.5.2 Addition to Alkenes

1.5.2.1 Aminoboration of Alkenes

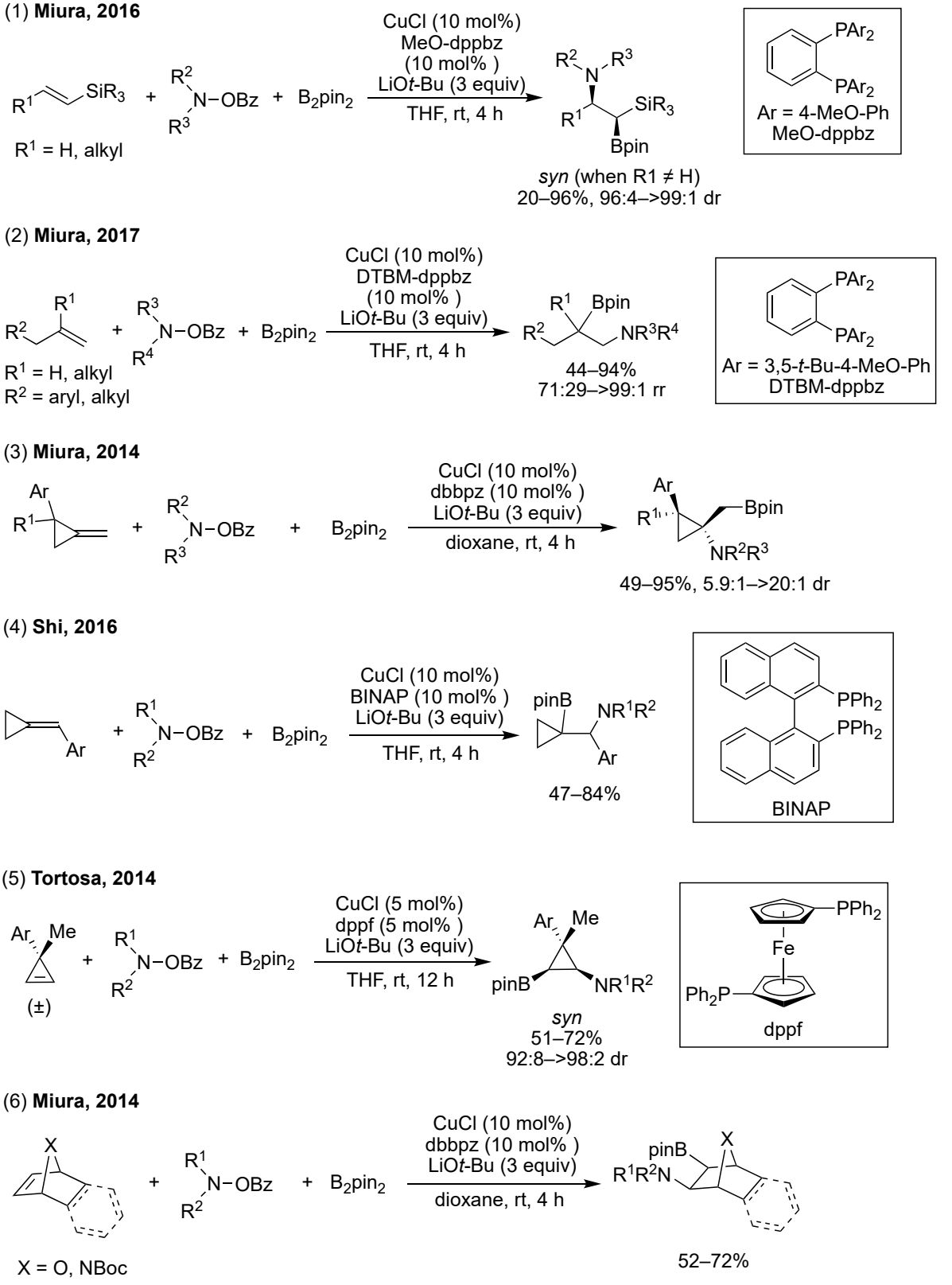
Aminoboration of alkenes provides a new, straightforward, and mild approach for the synthesis of β-aminoalkylboronic esters since both the boron and amine groups are introduced simultaneously onto the two carbons of the C=C double bonds. The majority of aminoboration reactions are promoted by Cu catalysts, allowing an efficient control of the regio- and stereoselectivity.

The first Cu-catalyzed aminoboration was reported by Miura and co-workers in 2013 using styrenes as the alkene substrate, *O*-protected hydroxyamine as the electrophilic amine source, and bis(pinacolato)diboron (B_2pin_2) as the boron source (Scheme 1-6).[40] This method allows the generation of primary or secondary β-aminoalkylboronic esters in moderate to good yields with excellent regioselectivity. In addition, the aminoboration reaction is highly diastereospecific (when $R^1/R^2 \neq H$), favoring the syn isomer when using (*E*)-styrenes, and the anti isomer when using (*Z*)-styrenes. It was proposed that the diastereospecificity stems from the syn addition mode between the Cu–Bpin species and styrenes (Scheme 1-6). Furthermore, the resulting Cu(I) intermediate **1-23** reacts with the *O*-protected hydroxyamine with retention of configuration (Scheme 1-6). Nonetheless, Miura's method is restricted to styrene substrates. Moreover, using a chiral Duphos ligand, the β-aminoalkylboronate products were obtained in 80–86% ee.



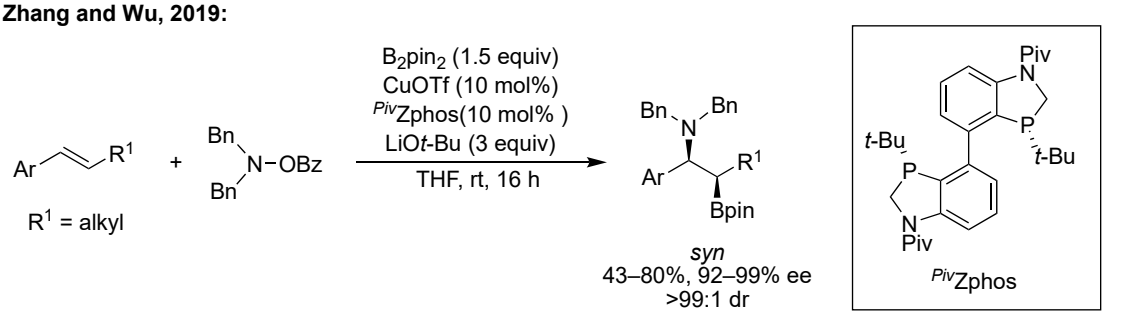
Scheme 1-6. First Cu-catalyzed aminoboration of styrenes for the synthesis of β-aminoalkylboronates.

Later, efforts were placed into expanding the scope of the alkene substrate by the Miura group and other groups. As shown in Scheme 1-7, by changing reaction parameters, such as the Cu source, ligand, and base, new catalytic systems have been developed to enable the aminoboration of alkenylsilanes (eq. 1),[53] unactivated terminal alkenes (eq. 2),[51,52] alkylidenecyclopropanes (eq. 3 and 4),[54,55] and cyclic alkenes (eq. 5 and 6),[56,57] yielding the corresponding acyclic or cyclic β-aminoalkylboronates efficiently.



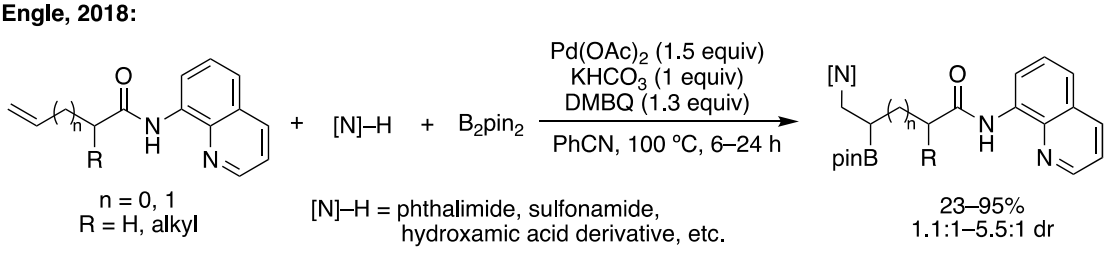
Scheme 1-7. Cu-catalyzed aminoboration of various alkenes for the synthesis of β-aminoalkylboronates.

Despite achieving high regio- and diastereoselectivity in all the above-mentioned aminoboration reactions, only moderate enantioselectivity was observed with most of the examples where chiral ligands were employed. It was only recently that Zhang and Wu identified a newly developed ^{Piv}Zphos ligand as a highly effective chiral ligand for the Cu-catalyzed aminoboration of (*E*)-styrenes (Scheme 1-8).[58] Under the optimized conditions, all β-aminoalkylboronate products were obtained in a syn diastereochemistry with ≥92% ee (up to 99% ee).



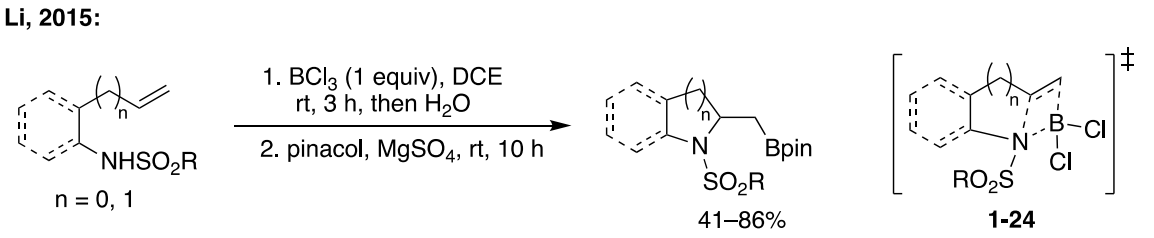
Scheme 1-8. A highly enantioselective Cu-catalyzed aminoboration of alkenes using ^{Piv}Zphos.

In addition to Cu-catalyzed aminoboration, aminoboration of terminal alkenes with B_2pin_2 has been realized with Pd catalysis, as recently demonstrated by Engle and co-workers (Scheme 1-9).[59] This Pd-catalyzed aminoboration, which proceeds with excellent regioselectivity, is controlled by the 8-aminoquinoline directing group. Moreover, it is applicable to various terminal alkenes and nitrogen nucleophiles, including phthalimides, sulfonamides, and hydroxamic acid derivatives. Unfortunately, with alkene subsrates bearing an α-substituent (R ≠ H), the reaction suffered from low diastereoselectivity (1.1:1–5:1 dr).



Scheme 1-9. A Pd-catalyzed aminoboration of terminal alkenes.

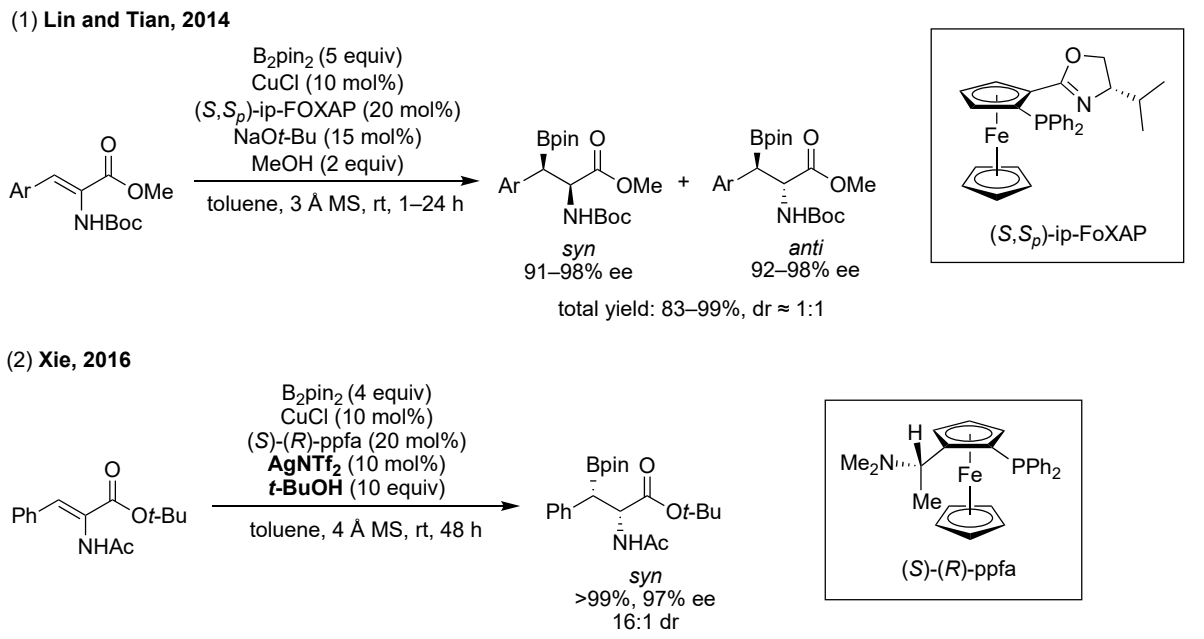
In 2015, Li and co-workers disclosed a direct and catalyst-free intramolecular aminoboration of the sulfonamide derivatives of 4-penten-1-amines, 5-hexen-1-amines, and 2-allylanilines using BCl_3 as the sole boron source (Scheme 1-10).[60] The reaction proceeds with the formation of an N–BCl_2 intermediate, followed by a fast intramolecular aminoboration through a cyclic transition state **1-24**. The resulting boronic acid products can react with pinacols readily at room temperature, providing five- and six-membered *N*-heterocyclic boronates in moderate to good yields.



Scheme 1-10. Transition metal-free intramolecular aminoboration of alkenes.

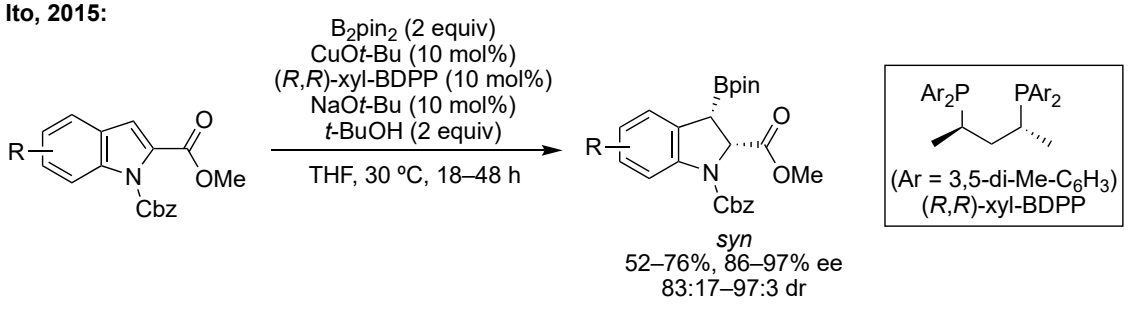
1.5.2.2 Cu-Catalyzed Borylation of Nitrogen-Containing Alkenes

Cu-catalyzed borylation of alkenes provides an alternative approach to β-aminoalkylboronates, however, nitrogen-containing alkenes are required. In 2014, the group of Lin and Tian established the Cu-catalyzed asymmetric conjugate borylation of β-substituted α-dehydroamino acid derivatives using B_2pin_2 as the boron source for the synthesis of β-aminoalkylboronates (Scheme 1-11, eq. 1).[61] This reaction is highly regio- and enantioselective but produces a separable 1:1 mixture of syn and anti isomer. It was reasoned that the use of a strong base (NaO*t*-Bu) could result in the racemization on the α-position of the carbonyl products, thus leading to low diastereoselectivity. To improve the diastereoselectivity of this type of conjugate borylation, Xie and co-workers developed milder conditions using a weaker base ($AgNTf_2$), achieving high syn selectivity (Scheme 1-11, eq. 2).[62] Further mechanistic studies revealed that besides the use of the weaker base $AgNTf_2$, the increased steric bulk and pKa of the alcohol additive (*t*-BuOH) also had an influence on the diastereoselectivity. However, in spite of achieving high diastereoselectivity, only a single example was reported in Xie's work.



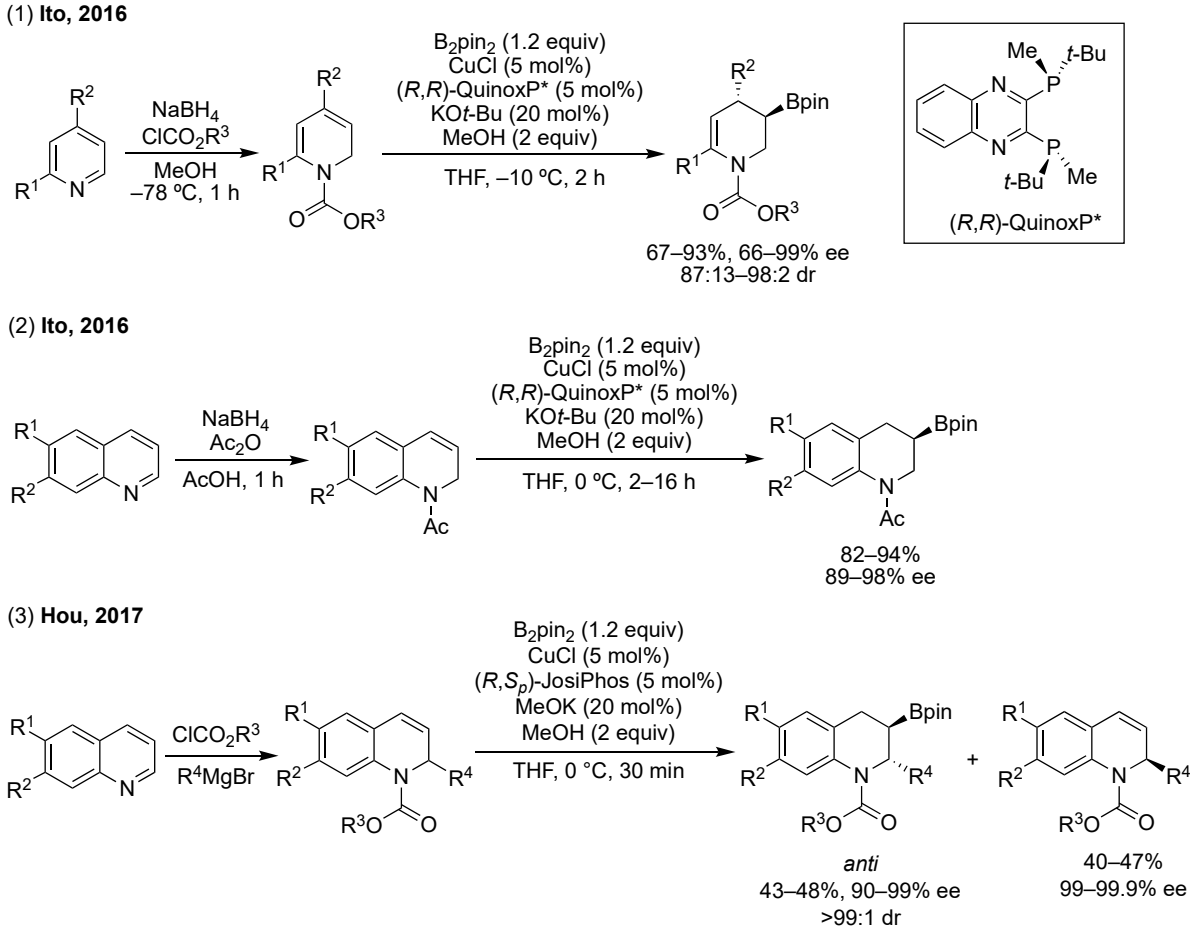
Scheme 1-11. Cu-catalyzed conjugate borylation for the synthesis of acyclic β-aminoalkylboronates.

Cu-catalyzed borylation of indole substrates has proven to be challenging due to the higher energy barrier encountered during the dearomatization process. In 2015, Ito and co-workers successfully applied the Cu-catalyzed conjugate borylation strategy to indoles bearing an ester substituent at the 2-position (Scheme 1-12).[63] With the combination of CuO*t*-Bu catalyst and (*R*,*R*)-xyl-BDPP chiral ligand, the addition of the boryl group occurs exclusively at the 3-position of indoles to yield cyclic *syn*-β-aminoalkylboronates in good yields with high enantio- and diastereoselectivity.



Scheme 1-12. Cu-catalyzed conjugate borylation of indoles for the synthesis of cyclic *syn*-β-aminoalkylboronates.

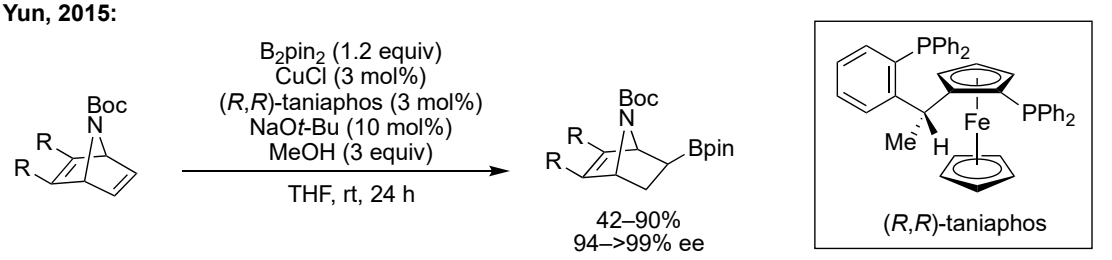
Although the direct borylation of pyridines was unsuccessful, the group of Ito discovered an alternative strategy, which first involved the partial reduction of pyridines to 1,2-dihydropyridines (Scheme 1-13, eq. 1).[42] Then, engaging the resulting 1,2-dihydropyridines in the Cu-catalyzed asymmetric borylation conditions successfully afforded the optically pure cyclic β-aminoalkylboronate products (Scheme 1-13, eq. 1). The utility of this dearomatization/borylation sequence was exemplified later with quinoline substrates, offering a facile access to the corresponding chiral β-aminoalkylboronates (3-boryl-tetrahydroquinolines) (Scheme 1-13, eq. 2).[64] Nonetheless, this two-step sequence is compatible only with quinolines bearing substituents at the 6- or 7-position. Later, Hou and co-workers expanded the scope to quinoline substrates bearing substituents at the 2-position



Scheme 1-13. Dearomatization/enantioselective Cu-catalyzed borylation of indoles or quinolines for the synthesis of cyclic β-aminoalkylboronates.

by using a similar sequence (Scheme 1-13, eq. 3).[65] In this case, however, the Cu-catalyzed asymmetric borylation step proceeds through a kinetic resolution, forming chiral 3-boryl-1,2,3,4-tetrahydroquinolines with two stereogenic centers in an anti diastereochemistry.

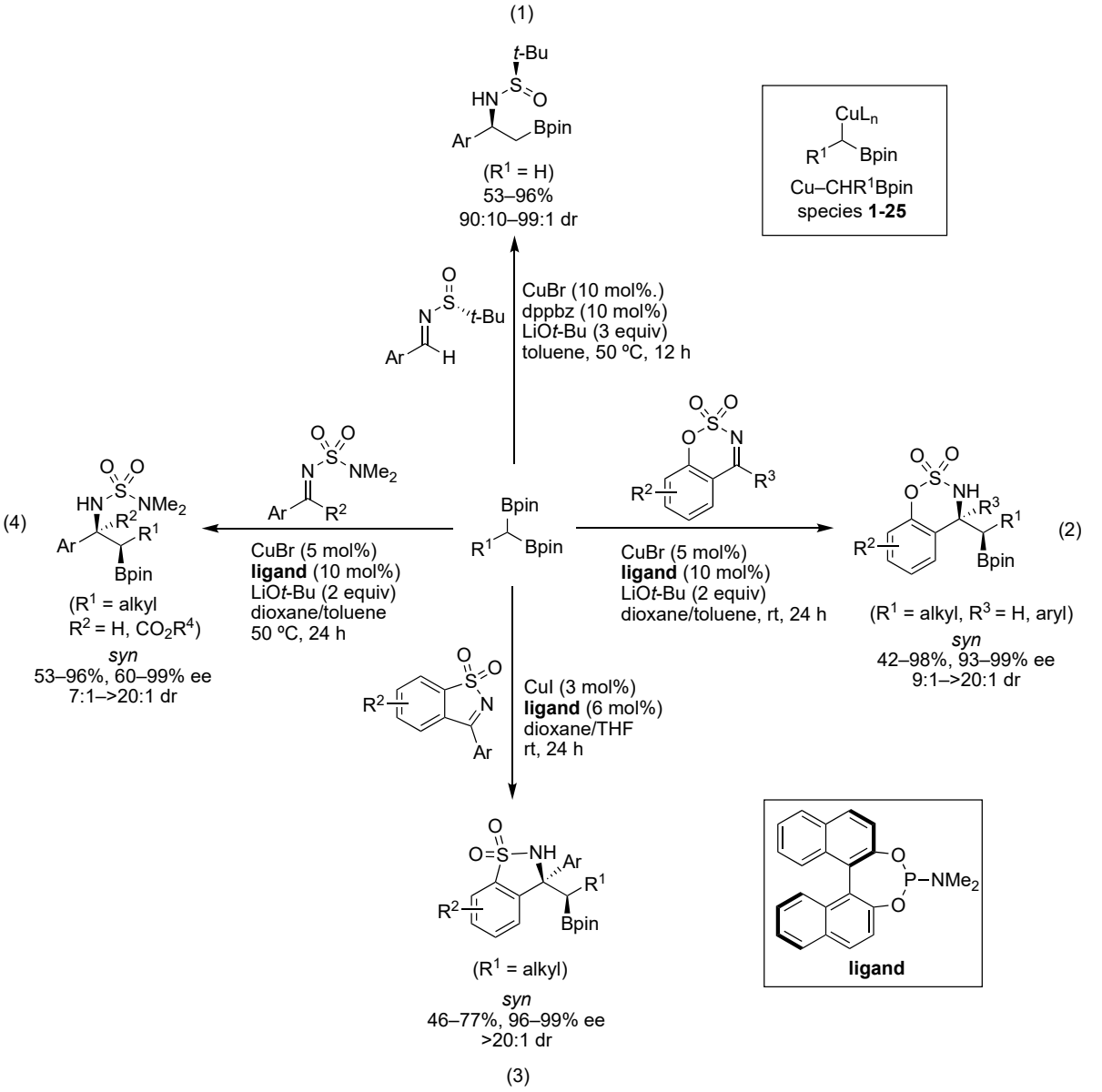
Azabicyclic alkenes also have proven to be suitable substrates for enantioselective Cu-catalyzed borylation (Scheme 1-14).[66] As demonstrated by Yun and co-workers, borylation of azabicyclic alkenes produces the corresponding bicyclic β-aminoalkylboronates with excellent enantioselectivity.



Scheme 1-14. Cu-catalyzed asymmetric borylation of bicyclic alkenes for the synthesis of bicyclic β-aminoalkylboronates.

1.5.3 Cu-Catalyzed 1,2-Addition of 1,1-Diborylalkanes to Imines

Since 1,1-diborylalkanes are capable of transmetallation with Cu catalysts to form nucleophilic species **1-25** (Scheme 1-15),[67] 1,2-addition of the nucleophilic species **1-25** to imines can provide another strategy for the synthesis of β-aminoalkylboronates. Cho and co-workers turned this concept into a reality and reported the first Cu-catalyzed 1,2-addition of 1,1-diborylmethane to optically pure sulfinyl aldimines to produce primary β-aminoalkylboronates in moderate to high yields with high diastereoselectivity (Scheme 1-15, eq. 1).[68] In this method, the aldimine substrate is restricted to aromatic substituents, and no other 1,1-diborylalkanes were reported other than 1,1-diborylmethane. As shown in Scheme 1-15, further investigation by the same group found that employing chiral Cu catalysts with re-optimized conditions expanded the scope of imines to cyclic ketimines (eq. 2 and 3)[45] and α-imino esters (eq. 4)[45] and the scope of 1,1-diborylalkanes to monosubstituted ones (eq. 2–4).[41,43,45] All of these enantioselective 1,2-additions proceed efficiently to yield α,β-disubstituted β-aminoalkylboronates with high syn selectivity (up to >20:1 dr) and enantioselectivity (up to 99% ee).



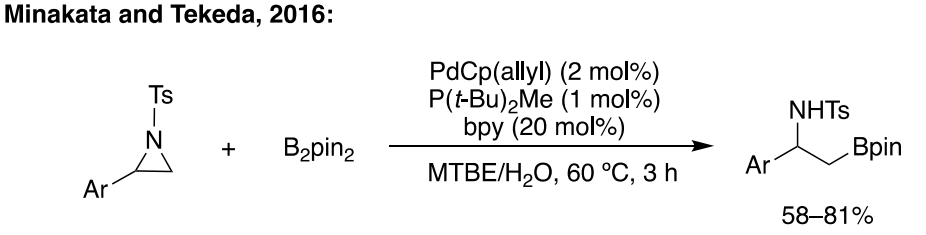
Scheme 1-15. Cu-catalyzed 1,2-addition of 1,1-diborylalkanes to imines for the synthesis of β-aminoalkylboronates.

1.5.4 Ring Opening Reactions

1.5.4.1 Pd-Catalyzed Borylative Ring Opening of Aziridines

A Pd-catalyzed borylative ring opening of aziridines with B_2pin_2 was devised to access β-aminoalkylboronates by Minakata and Tekeda in 2016 (Scheme 1-16).[44] This ring opening process proceeds through a S_N2-like mechanism, thus, no epimerization occurred when optically pure aziridines were used. With various racemic aziridine substrates, primary

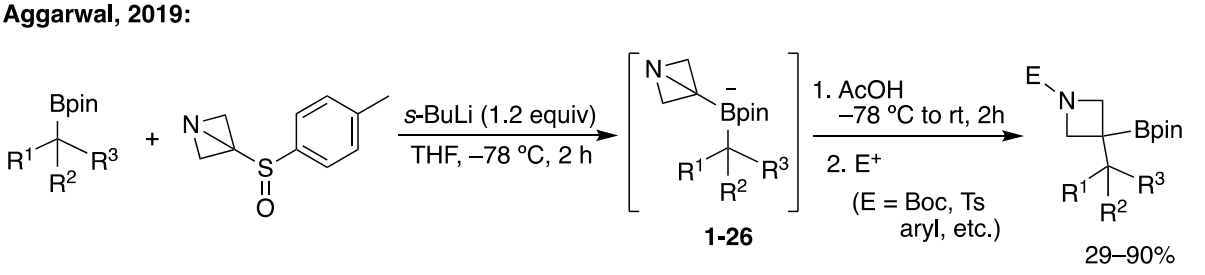
β-aminoalkylboronate products were obtained in 58–81% yield. However, this method cannot be applied to disubstituted or alkyl monosubstituted aziridines.



Scheme 1-16. Pd-catalyzed ring opening borylation of aziridines for the synthesis of β-aminoalkylboronates.

1.5.4.2 Strain-Release-Driven Ring Opening of Azetidines

The ring opening strategy also can be realized under transition metal-free conditions, however, ring strain as the driving force is required. Very recently, by taking advantage of the ring strain of azabicyclo[1.1.0]butanes, Aggarwal and co-workers developed an approach to four-membered β-aminoalkylboronates, azetidinyl boronic esters (Scheme 1-17).[69] This approach



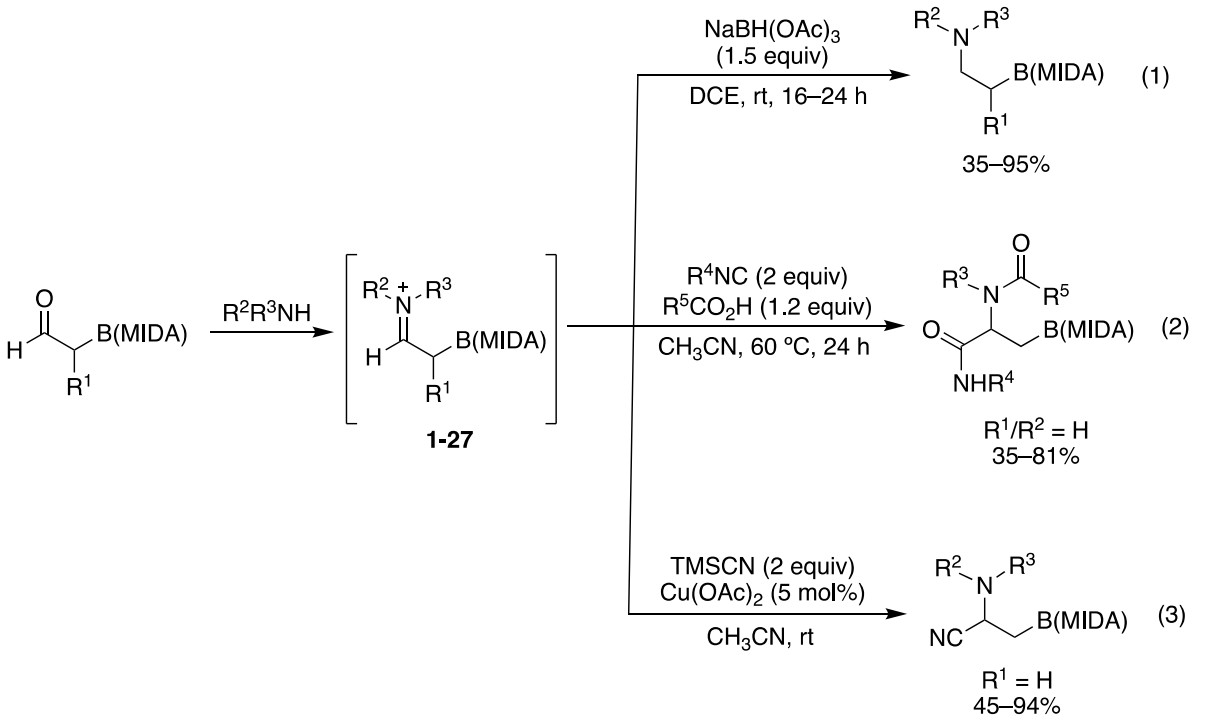
Scheme 1-17. Ring opening of azetidines with lithiated alkylboronates for the synthesis of four-membered heterocyclic β-aminoalkylboronates.

requires the generation of the lithiated azabicyclo[1.1.0]butane from azabicyclo[1.1.0]butyl sulfoxides and *s*-BuLi. The lithiated azabicyclo[1.1.0]butane can react with an alkylboronate to produce the corresponding borate complex **1-26**, which subsequently can undergo a 1,2-metallate rearrangement. The rearrangement to relieve the ring strain by the cleavage of the central C–N bond is facilitated by acetic acid, followed by protection of the amine group with electrophiles to afford racemic azetidinyl boronic esters. This method is applicable to various boronic esters, such as primary, secondary, tertiary, aryl, and alkenyl boronic esters. Moreover,

the reaction occurs with complete retention of stereochemical information when optically pure boronic esters are employed.

1.5.5 Transformations of α-Boryl Aldehydes

MIDA-protected α-boryl aldehydes are bench-stable versatile reagents that offer a means for the generation of β-amino MIDA-boronates. It has been demonstrated by Yudin and co-workers that MIDA-protected α-boryl aldehydes and amines can form iminium ion **1-27**. Then, trapping iminium ion **1-27** with $NaBH(OAc)_3$ provided reduced products (β-amino MIDA-boronates) in moderate to good yields (Scheme 1-18, eq. 1).[70]



Scheme 1-18. Transformations of MIDA-protected α-boryl aldehydes for the synthesis of various β-amino MIDA-boronates.

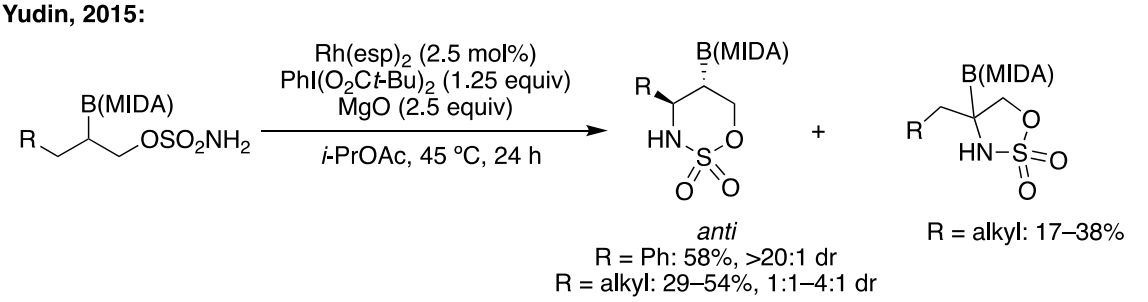
Besides reduction with $NaBH(OAc)_3$, iminium ion **1-27** could be engaged in the Ugi four-component reaction (Scheme 1-18, eq. 2)[71] or trapped by cyanide reagents (eq. 3)[72] to access β-amino MIDA-boronates. While these reaction are not stereoselective, they provide a

wide range of β-amino MIDA-boronates, including peptidomimetics, by varying the substituents (R^1–R^5) on the reactants.

1.5.6 Other Miscellaneous Methods

1.5.6.1 Rh-Catalyzed C–H Amination

Rh-Catalyzed C–H amination of boryl sulfamates, as reported by Yudin and co-workers, provides a method for the synthesis of heterocyclic β-aminoalkylboronate (Scheme 1-19).[73] In this amination reaction, when the MIDA boryl sulfamate bearing a benzyl substituent (R = Ph) is used, the amination results in a six-membered β-aminoalkylboronate product in a good yield (58%) with high anti selectivity (>20:1 dr). But a notable drawback of this C–H amination is that when alkyl-substituted (R = alkyl) MIDA boryl sulfamates are used, the amination delivers the six-membered β-aminoalkylboronate products in only low to moderate yields with poor anti selectivity (1:1–4:1 dr), accompanied with 17–38% of five-membered α-aminoalkylboronate side products.

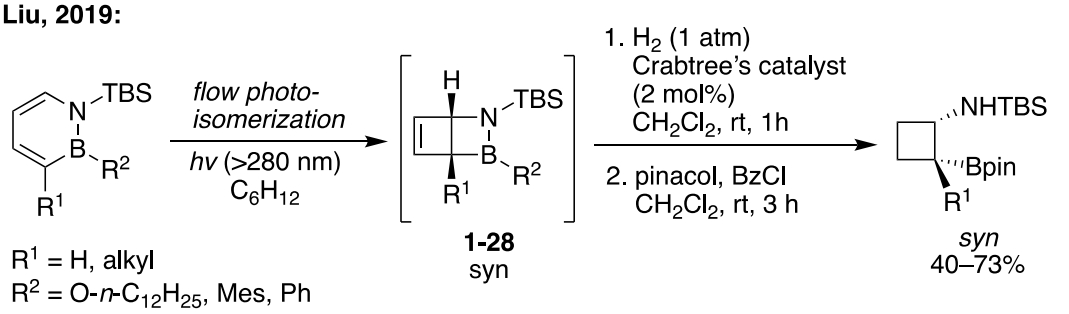


Scheme 1-19. Synthesis of cyclic *anti*-β-aminoalkylboronates via Rh-catalyzed C–H amination.

1.5.6.2 Transformations of 1,2-Azaborine

Aminoborylated cyclobutanes are four-membered β-aminoalkylboronates that cannot be accessed by all of the aforementioned methods. However, they have been synthesized recently by Liu and co-workers using the 1,2-azaborine reagents (Scheme 1-20).[74] The key step of this protocol is the photoisomerization of 1,2-azaborines, which was performed in a flow photoreactor. This photochemically induced 4-electron electrocyclic ring-closing isomerization proceeds through disrotation, thus exclusively yields the syn photoisomer **1-28**.

The photoisomer **1-28** can be transformed into the corresponding aminoborylated cyclobuanes in moderate to good yields by undergoing a hydrogenation of the C=C bond and a subsequent B–N bond cleavage. However, this method is only applicable to C3-substituted 1,2-azaborine substrates.



Scheme 1-20. Synthesis of aminoborylated cyclobutanes via transformations of 1,2-azaborines.

1.6 Thesis Objectives

α-Aminoalkylboronic acids display distinct utility in medicinal chemistry as a bioisostere of α-amino acids and α-amino aldehydes, which is validated by three commercial drugs (bortezomib, ixazomib, and vaborbactam). A variety of highly stereoselective and efficient methods to access these compounds have been reported.[75] Like α-aminoalkylboronic acids, β-aminoalkylboronates are viewed as a bioisostere of β-amino acids, thus have substantial potential in drug discovery. Moreover, β-aminoalkylboronates are valuable building blocks, which can be used to access many useful compounds, such as β-amino alcohols and 1,2-diamines. In addition, β-aminoalkylboronates can act as catalysts in organic reactions. However, despite the recent advances regarding synthetic approaches to β-aminoalkylboronates, as described in Section 1.5, there is a lack of stereoselective methods to access β-aminoalkylboronates, especially α,β-disubstituted β-aminoalkylboronates, with high enantio- and diastereoselectivity. Furthermore, most of the diastereoselective methods favor the formation of the syn isomer of α,β-disubstituted β-aminoalkylboronates, and very limited approaches have been reported to access β-aminoalkylboronates in an anti diastereochemistry. The goal of this thesis is to develop novel and efficient strategies by

employing 1,1-diboryalkanes to synthesize optically pure β-aminoalkylboronates, including the anti isomer of α,β-disubstituted β-aminoalkylboronates.

Encouraged by the recent advances on selective transformations of 1,1-diboronic esters for the synthesis of alkylboronic esters, my studies were initiated by proposing a 1,2-addition/monoprotodeboronation sequence using 1,1-diboronic esters to access optically pure α,β-disubstituted β-aminoalkylboronates. The 1,2-addition of lithiated 1,1-diborylalkanes to chiral sulfinimine derivatives delivered enantiomerically β-sufinimido *gem*-bis(boronates). A subsequent mono-protodeboronation of the resulting β-sufinimido *gem*-bis(boronate) afforded *syn*-α,β-disubstituted β-aminoalkylboronates. In Chapter 2, the development of this sequence, substrate scope, mechanistic studies, and synthetic applications will be detailed.

In order to access the elusive *anti*-α,β-disubstituted β-aminoalkylboronates, it is essential to develop a complementary variant of the abovementioned monoprotodeboronation. Examination of different conditions for the monoprotodeboronation of β-sufinimido *gem*-bis(boronates) to access the *anti*-β-aminoalkylboronates was unsuccessful. The key to the success of the anti-selective monoprotodeboronation is the use of *N*-desulfinylated β-amino *gem*-bis(boronates). The evaluation of reaction parameters was conducted to obtain excellent anti-selectivity. These studies will be discussed, and the substrate scope, mechanistic studies, and synthetic applications also will be described in Chapter 3.

Inspired by the Cu-catalyzed asymmetric 1,2-addition of 1,1-diborylalkanes to aldehydes for the synthesis of 1,2-hydroxyboronates,[67] it was envisioned that this 1,2-addition strategy could be applied to imines, thus providing a straightforward and catalytic approach to enantioenriched β-aminoalkylboronates. Chapter 4 will present the extensive optimization made towards the asymmetric 1,2-addition. To improve the enantioselectivity further, a ligand high-throughput screening (HTS) approach was used in collaboration with the Pfizer company and will be presented in this chapter.

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Chapter 2

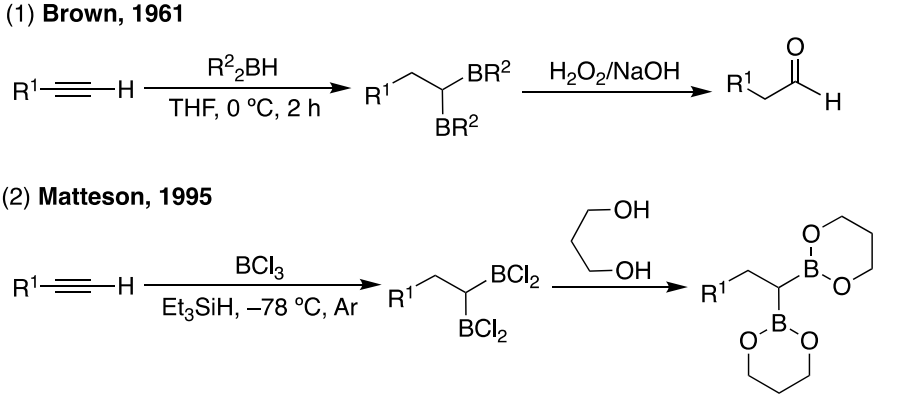
Stereoselective Synthesis of *syn*-α,β-Disubstituted β-Aminoalkylboronates via Diastereocontrolled Monoprotodeboronation of β-Sulfinimido *gem*-Bis(boronates)[†]

2.1 Introduction

2.1.1 Preparation of 1,1-Diboron Compounds

Recently, 1,1-diborylalkanes have emerged as efficient reagents for the synthesis of organoboron compounds, including chiral alkylboronates, through selective C–C bond formation.[1–3] Due to their chemical stability, operational simplicity, and extensive applications in organic synthesis, there has been a growing interest in the development of synthetic methods to access 1,1-diborylalkanes.

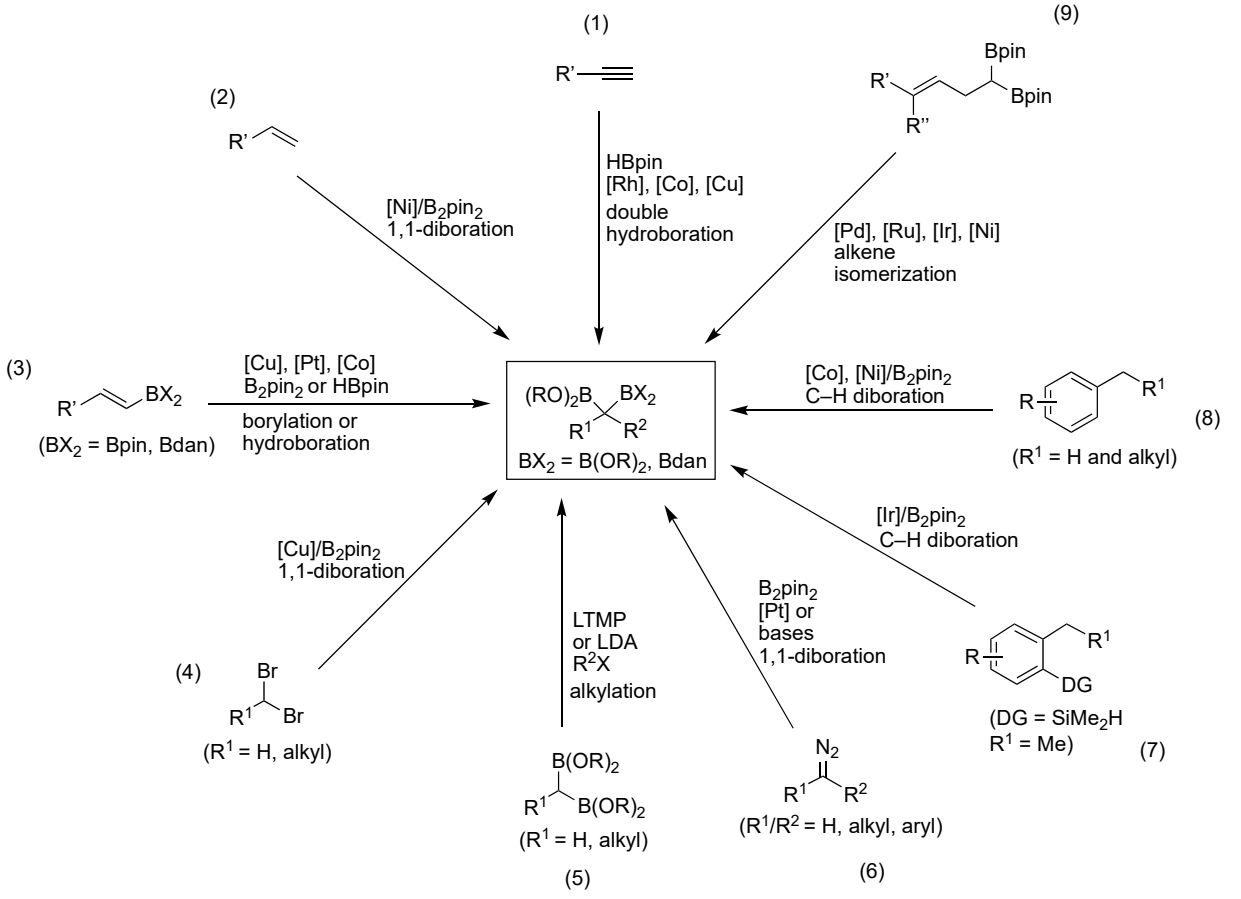
In 1961, Brown and co-workers synthesized the first 1,1-diboron compounds through double hydroboration of terminal acetylenes with dialkylboranes (Scheme 2-1, eq. 1).[4] Due to the instability of the resulting 1,1-diboranes, they subsequently were oxidized into aldehydes. Later on, Matteson and co-workers developed a method to produce and isolate 1,1-diboronic



Scheme 2-1. Pioneering work in the synthesis of 1,1-diborylalkanes.

[†]A version of this chapter has been published. Li, X.; Hall, D. G. *Angew. Chem., Int. Ed.* **2018**, *57*, 10304−10308.

esters through the double hydroboration of terminal acetylenes with a mixture of trichloroborane and triethylsilane, followed by treatment with the 1,3-propanediol (Scheme 2-1,eq. 2).[5] However, these original approaches employ air- and moisture-sensitive reagents, require multiple steps, and suffer from poor substrate scope. Modern protocols using transition metal-catalyzed (Rh, Co, and Cu) double hydroboration of readily available terminal alkynes and pinacolboranes (HBpin) provide a new and straightforward method to synthesize 1,1-diboronic esters, as demonstrated by the groups of Shibata,[6] Yun,[7] and Huang[8] (Scheme 2-2, eq. 1). The double hydroboration is generally regioselective with the two pinacolboryl groups (Bpin) added on the terminal carbon of the terminal alkyne. The addition of two boronyl moieties onto the terminal carbon of the terminal alkene is also a feasible approach to synthesize 1,1-diboronic esters. As demonstrated by Fu and co-workers,[9] the Ni-catalyzed



Scheme 2-2. Modern methods to synthesize 1,1-diborylalkanes.

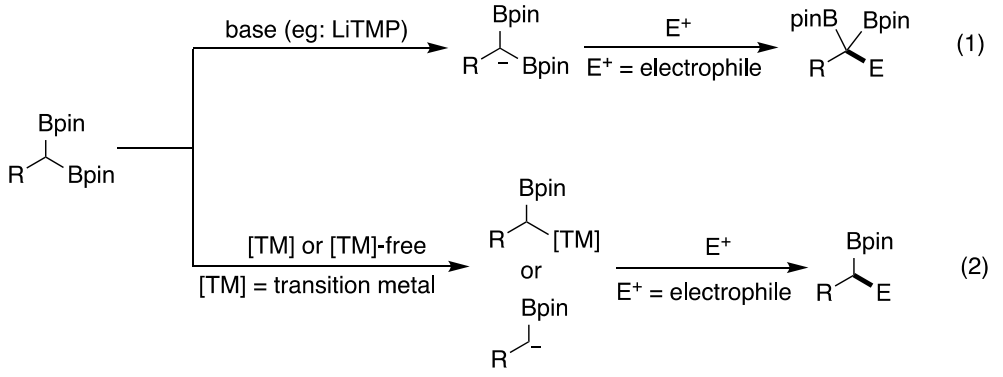
1,1-diboration of various terminal alkenes (vinylarenes and aliphatic alkenes) is highly chemo- and regioselective (Scheme 2-2, eq. 2). An alternative strategy is to employ borylalkenes as the substrates, which can undergo transition-metal catalyzed monoborylation[10] or monohydroboration[11] to produce 1,1-diborylalkanes (Scheme 2-2, eq. 3). Furthermore, the groups of Hall[12] and Yun[13] recently have demonstrated that the use of a pre-installed 1,8-naphthalenediaminatoboryl group (Bdan) on the alkene would allow the synthesis of optically pure 1,1-diboron compounds since a different Bpin moiety could be added onto the borylalkenes (Scheme 2-2, eq. 3). In addition, Cu-catalyzed 1,1-diboration of 1,1-dibromo compounds with bis(pinacolato)diboron agents (B_2pin_2) represents another efficient method for the synthesis of 1,1-diborylmethane and monosubstituted 1,1-diborylalkanes (Scheme 2-2, eq. 4).[14,15] However, the limited availability of 1,1-dibromo compounds restricts the practicability of this method. Since 1,1-diborylmethane is now commercially available, it can serve as the starting material for the synthesis of monosubstituted 1,1-diborylalkanes. Deprotonation of 1,1-diborylmethane with strong bases, such as lithium tetramethylpiperidide (LiTMP) and lithium diisopropylamide (LDA), followed by alkylation with alkyl halides, can deliver monosubstituted 1,1-diborylalkanes, and the same protocol can be employed to synthesize dialkyl substituted 1,1-diborylalkanes (Scheme 2-2, eq. 5).[16–18] Insertion of diazo compounds into the B–B bond of B_2pin_2 is also applicable to prepare 1,1-diborylalkanes. The insertion process was realized first by platinum catalysts,[19,20] but it was found later that this process also could be promoted by bases (NaOMe or NaH) under metal-free conditions[21,22] (Scheme 2-2, eq. 6).

Despite all of these significant advances in the preparation of 1,1-diborylalkanes, methods to access benzylic and allylic 1,1-diborylalkanes are still rare. Most existing methods to form benzylic 1,1-diborylalkanes involve transition metal-catalyzed C–H bond functionalization. For example, Hartwig and co-workers discovered an approach to synthesize 1,1-benzyldiboronic esters by Ir-catalyzed 1,1-diboration of benzylic C–H bonds (Scheme 2-2, eq. 7).[23] This transformation was applied to various 2-methyl hydrosilylarenes under mild conditions, but it requires a hydrosilane ($SiMe_2H$) as a traceless directing group. When using cobalt[24] or nickel catalysts[25], Chirik and co-workers developed new strategies for catalyzing non-directed 1,1-diboration of benzylic C–H bonds, albeit under a high reaction temperature and a long reaction time (Scheme 2-2, eq. 8). Recently, the groups of Murakami and Cho

independently achieved the synthesis of allylic 1,1-diborylalkanes by Pd-,[26] Ru-,[27] or Ir-catalyzed[28] alkene isomerization of homoallylic 1,1-diborylalkanes (Scheme 2-2, eq. 9). However, Murakami's and Cho's methods can generate only (*E*)-1,1-allyldiboronic esters. To enable the *Z*-selective alkene isomerization to access (*Z*)-1,1-allyldiboronic esters, new conditions are necessary using nickel catalysts, as demonstrated by Chen and co-workers.[29,30]

2.1.2 Applications of 1,1-Diboron Compounds

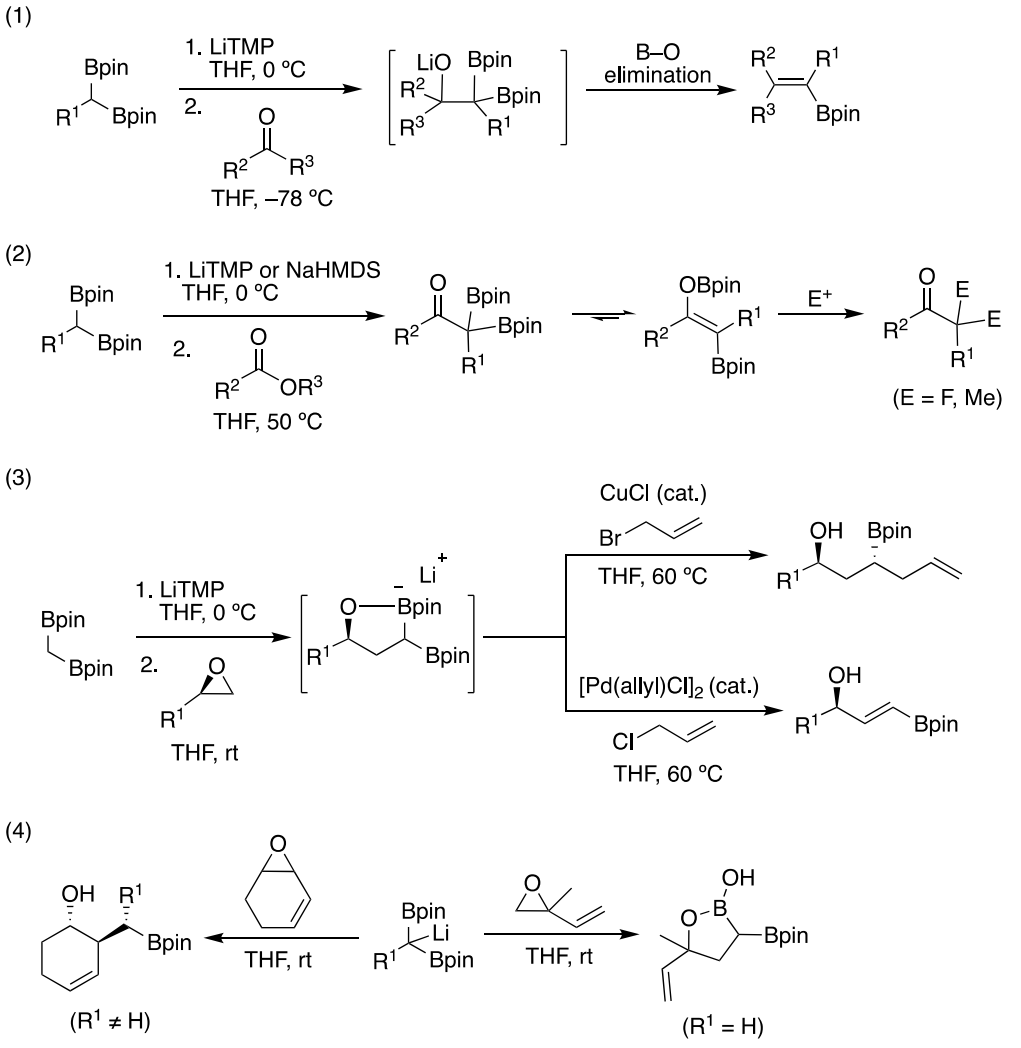
Transformations of 1,1-diborylalkanes for C–C bond formation can be classified into two main categories, based on their activation mode (Scheme 2-3). One category involves the deprotonation of 1,1-diborylalkanes with strongly hindered bases, such as LiTMP and LDA, which allows the formation of 1,1-diborylalkane carbanions (Scheme 2-3. eq. 1). The other category involves the monodeborylation of 1,1-diborylalkanes, which can be realized by base attack on the boron center to generate α-boryl carbanions or via transmetalation with a transition metal to generate α-boryl metal species (Scheme 2-3, eq. 2). In both categories, the carbanion or α-boryl metal species is stabilized by the vacant *p*-orbital of the remaining boryl unit, which allows it to be trapped by various electrophiles for generation of new C–C bonds.



Scheme 2-3. Two main categories for the use of 1,1-diborylalkanes in C–C bond formation: 1) deprotonation, followed by trapping with electrophiles and 2) monodeborylation, followed by trapping with electrophiles.

2.1.2.1 C–C Bond Formation Involving 1,1-Diborylalkane Carbanions

In addition to the alkylation reaction shown in Scheme 2-2 (eq. 5), 1,1-diborylalkane carbanions can be engaged in additions to aldehyde or ketone electrophiles to afford the alkoxide intermediate (Scheme 2-4, eq. 1). [31–35] The alkoxide intermediate cannot be isolated and immediately will undergo B–O bond elimination to generate di-, tri-, and tetra-substituted



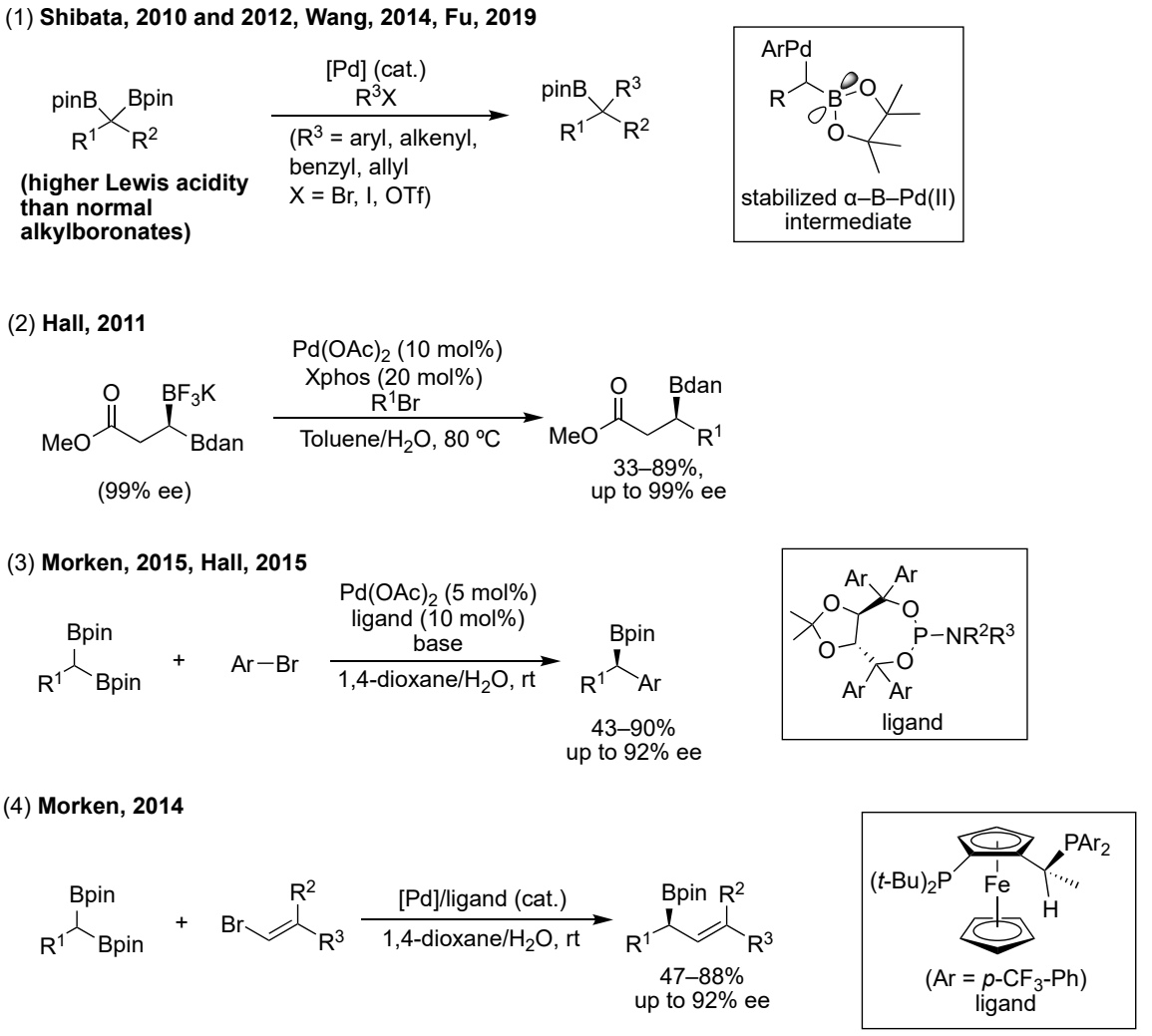
Scheme 2-4. Transformations of 1,1-diborylalkane carbanions for C–C bond formation.

alkenylboronates with high stereoselectivity. The 1,1-diborylalkane carbanion is also susceptible to react with esters, affording the α-diboryl ketone intermediate, which reacts as a α,α-bis(enolate) equivalent (Scheme 2-4, eq. 2).[36] The double electrophilic trapping of the

α-diboryl ketone intermediate with methyl halides and fluorinating agents delivers difunctionalized ketones. When employing optically pure epoxides as the electrophile, Meek and co-workers discovered that ring opening with lithiated 1,1-diborylmethane yielded cyclic borates stereospecifically (Scheme 2-4, eq. 3). Subjecting the cyclic borate to Cu-[37] and Pd-catalyzed[38] allylation afforded 1,3-hydroxyboronates and allylic alcohol-containing alkenyllboronates, respectively. Fernández and co-workers also have reported the same type of ring opening reaction, however, with a specific epoxide (vinyl epoxide) (Scheme 2-4, eq. 4).[39] The ring opening with vinyl epoxides forms the monodeborylated homoallylboronates or cyclic *gem*-diboronates, depending on the substitution patterns of the vinyl epoxide and 1,1-diborylalkane.

2.1.2.2 C–C Bond Formation Involving α-Boryl Carbanions or α-Boryl Metal Species

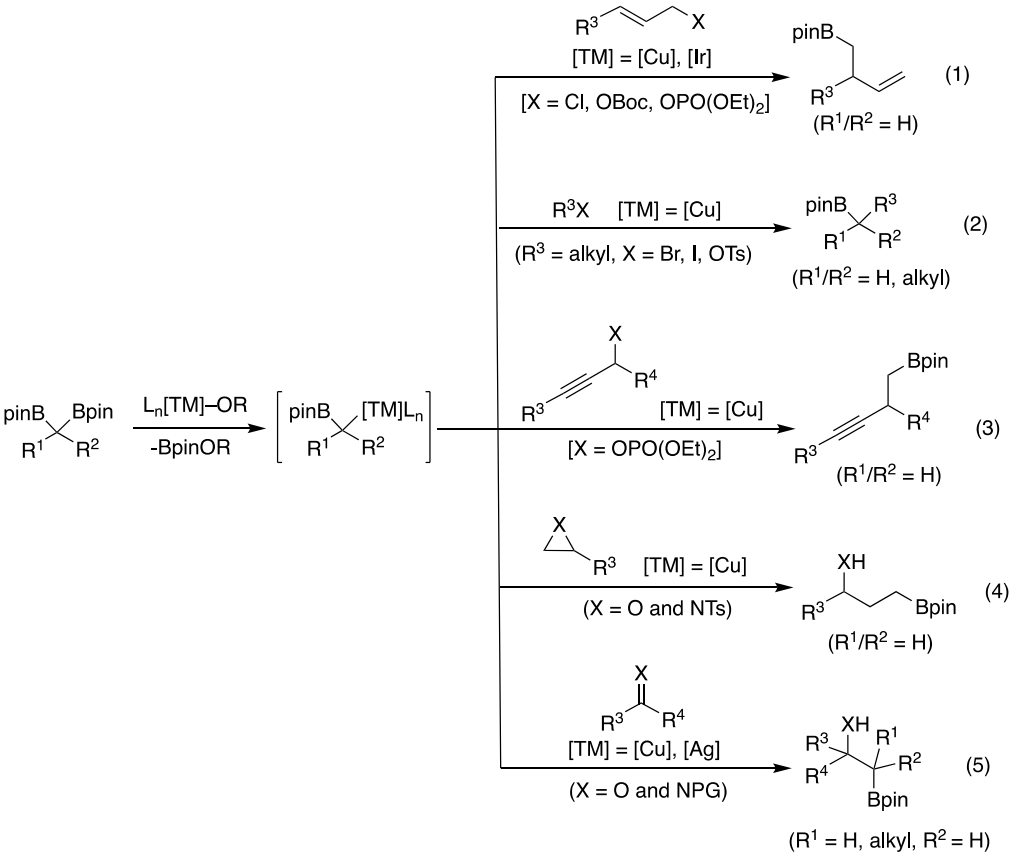
The most important and extensively studied deborylative transformation of 1,1-diborylalkanes is the Pd-catalyzed Suzuki–Miyaura cross-coupling (SMC). SMC is generally challenging with alkylboronates due to slow transmetalation, competing β-hydride elimination, and protodeboronation.[40,41] 1,1-Diborylalkanes, however, proved to be more reactive than alkylboronates and can undergo efficient Pd-catalyzed SMC with aryl, alkenyl, benzylic, and allylic halides, as demonstrated by the groups of Shibata,[42,43] Wang,[44] and Fu[45] (Scheme 2-5, eq. 1). ^{11}B NMR analysis and DFT calculations by Shibata and co-workers revealed that the adjacent boryl group not only enhances the Lewis acidity of the other boron atom significantly but also stabilizes the carbanionic α-B-Pd(II) intermediate through its empty *p*-orbital, thus dramatically improving the rate of transmetallation (Scheme 2-5, eq. 1).[43] In 2011, Hall and co-workers illustrated a chemoselective SMC of optically pure 1,1-diborylalkanes with aryl and alkenyl bromides, which occurred stereospecifically via inversion of its configuration to generate benzylic or allylic boronates (Scheme 2-5, eq. 2).[12] When employing suitable chiral ligands, SMC of prochiral 1,1-diborylalkanes and aryl and alkenyl halides can be achieved by way of enantioselective desymmetrization, producing chiral alkylboronates (Scheme 2-5, eq. 3 and 4).[46–48]



Scheme 2-5. Suzuki–Miyaura cross-coupling of 1,1-diboron compounds.

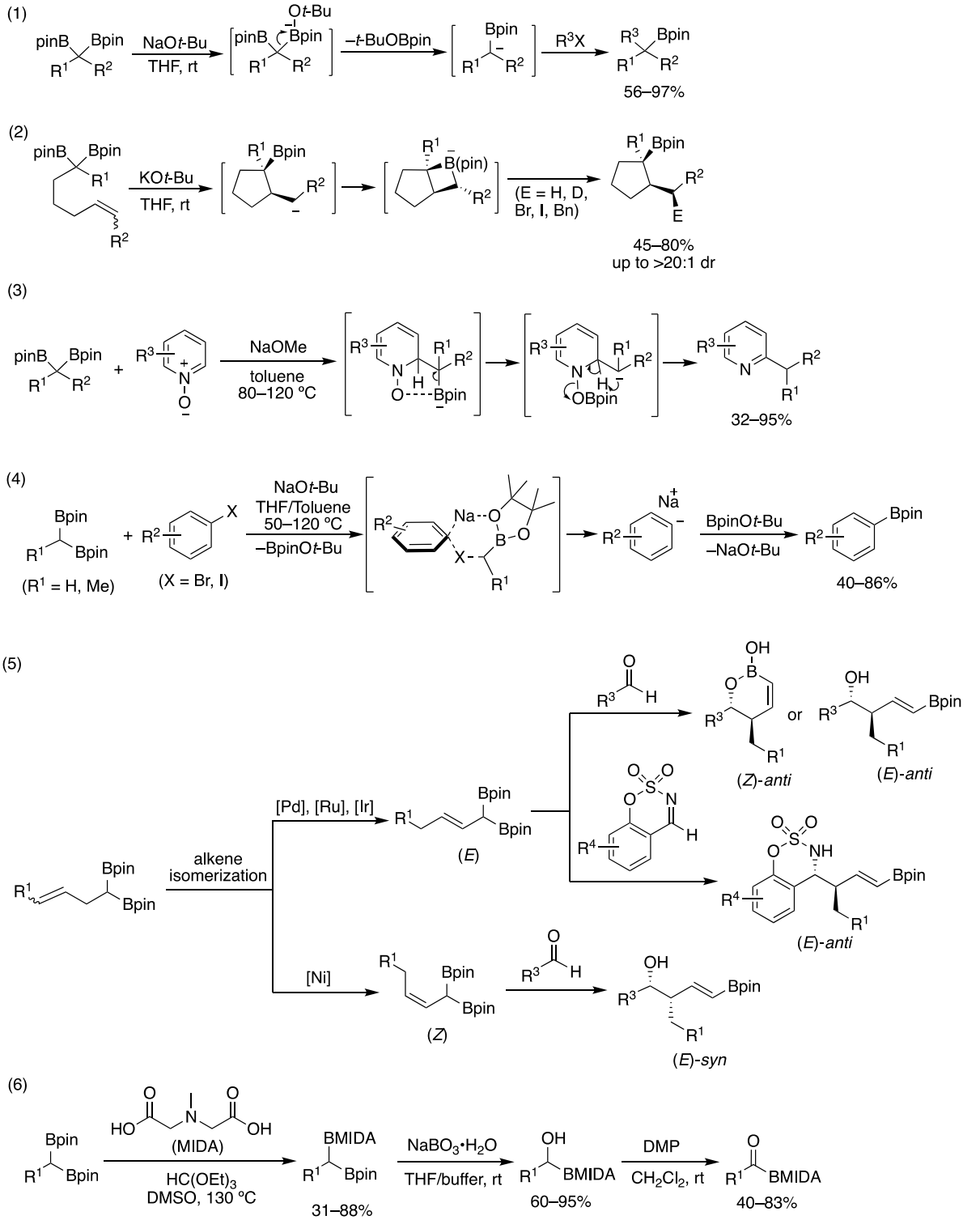
Besides Pd-catalyzed deborylative SMC, other transition metals also are susceptible for forming α-boryl metal species via alkoxide-promoted deborylation, thus enabling formation of new C–C bonds by reacting with various electrophiles (Scheme 2-6). For instance, it has been reported that α-boryl Cu species could be engaged in a S_N2'-type allylation with various allylic electrophiles to produce homoallylic boronates (Scheme 2-6, eq. 1).[49–51] By exploiting a combination of suitable chiral ligands and Cu[52] or Ir[53] catalysts, the enantioselective S_N2'-type allylation of 1,1-diborylakanes could be achieved. Propargylic[54] and alkyl[15] electrophiles also are applicable for trapping α-boryl Cu species via S_N2-type alkylations, affording propargylic and alkyl boronates, respectively (Scheme 2-6, eq. 2 and 3). The reactivity of

α-boryl Cu species also has been exemplified in its ring opening reaction with epoxides and *N*-sulfonyl aziridines for the synthesis of γ-hydroxyl and γ-amino boronates with high regioselectivity (Scheme 2-6, eq. 4).[55] In addition, Meek and co-workers established the Cu-[56,57] and Ag-catalyzed[58] deborylative 1,2-addition of 1,1-diboronates to aldehydes and α-ketoesters for generation of 1,2-hydroxyboronates (Scheme 2-6, eq. 5).[57] Later on, the Cu-catalyzed deborylative 1,2-addition strategy was applied to aldimine and ketimine electrophiles stereoselectively by employing chiral auxiliaries or chiral ligands, thus affording enantioenriched β-aminoalkylboronates (Scheme 2-6, eq. 5).[59–62]



Scheme 2-6. Other transition metal-catalyzed deborylative transformations of 1,1-diborylalkanes.

Under transition metal-free conditions, metal alkoxides, such as NaO*t*-Bu and KO*t*-Bu, can induce the monodeborylation of 1,1-diborylalkanes to form the α-boryl carbanion. Alkylation of α-boryl carbanions with alkyl halides provides a strategy for constructing alkylboronates under mild reaction conditions (Scheme 2-7, eq. 1). This type of alkylation was



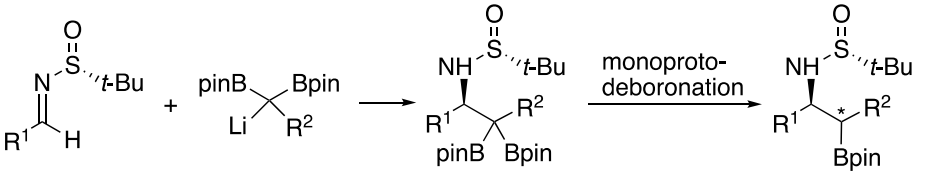
Scheme 2-7. Transition metal-free deborylative transformations of 1,1-diborylalkanes for C–C bond formation.

discovered first by the group of Matteson[18] and recently has been generalized by the group of Morken.[17] In 2017, Morken and co-workers observed an unusual addition of α-boryl carbanions to alkenes when an alkene-containing 1,1-diboronate was employed (Scheme 2-7, eq. 2).[63] The addition yields cyclized intermediates, which can be intercepted by a number of electrophiles to generate cyclic boronates with high diastereoselectivity. The α-boryl carbanion also has been proved by Cho's group to be an effective alkyl source for alkylation of pyridine *N*-oxides (Scheme 2-7, eq. 3).[64,65] The alkylation proceeds through the attack of α-boryl carbanions on pyridine *N*-oxides, followed by the migration of a boryl group, subsequent C2–H transfer, and rearomatization to afford the C2–alkylated pyridines in good yields. Cho and co-workers also developed a unique approach of utilizing 1,1-diborylalkanes as the boron source for the borylation of aryl halides (Scheme 2-7, eq. 4).[66] Under this circumstance, one of the boryl groups is transferred to aryl halides, which is facilitated by an unusual formation of a Lewis acid/base adduct between aryl halides and α-boryl carbanions. As a subclass of 1,1-diborylalkanes, the 1,1-allyldiboronic ester, which could be synthesized in situ by transition metal-catalyzed alkene isomerization (see Scheme 2-2, eq. 9), has exhibited its unique application in the chemo- and stereo-selective crotylation of aldehydes and cyclic aldimines (Scheme 2-7, eq. 5).[26–30] The crotylation reaction offers a new strategy for the synthesis of homoallylic alcohols or homoallylic amines with an alkenylboronate moiety. The stereochemistry of the product can be controlled by a proper choice of the geometry of the double bond of 1,1-allyldiboronic ester and the crotylation conditions. Very recently, monoprotection with the MIDA protecting group has been achieved with 1,1-diboronic esters by Sharma and co-workers to form unsymmetrical 1,1-diborylalkanes (Scheme 2-7, eq. 6).[67] The resulting unsymmetrical 1,1-diborylalkane is amenable to a chemoselective oxidation to access α-hydroxy MIDA alkylboronates, which can undergo further oxidation to form MIDA acylboronates.

2.2 Objectives

Chapter 1 of this thesis reviewed the state-of-the-art methods for the synthesis of β-aminoalkylboronates. Despite these advances, only a small number of stereoselective methods were developed to provide primary β-aminoalkylboronic esters, and even fewer stereoselective methods are applicable to secondary alkylboronates. Therefore, it is essential to broaden the synthetic accessibility to optically pure secondary β-aminoalkylboronic esters. It was envisioned that utilizing the reactivity of 1,1-diborylalkanes (deprotonation and monodeborylation) would provide a strategy to these compounds since 1,1-diboron compounds recently have emerged as a versatile class of reagents for the preparation of alkylboronic esters, as shown in the previous sections.

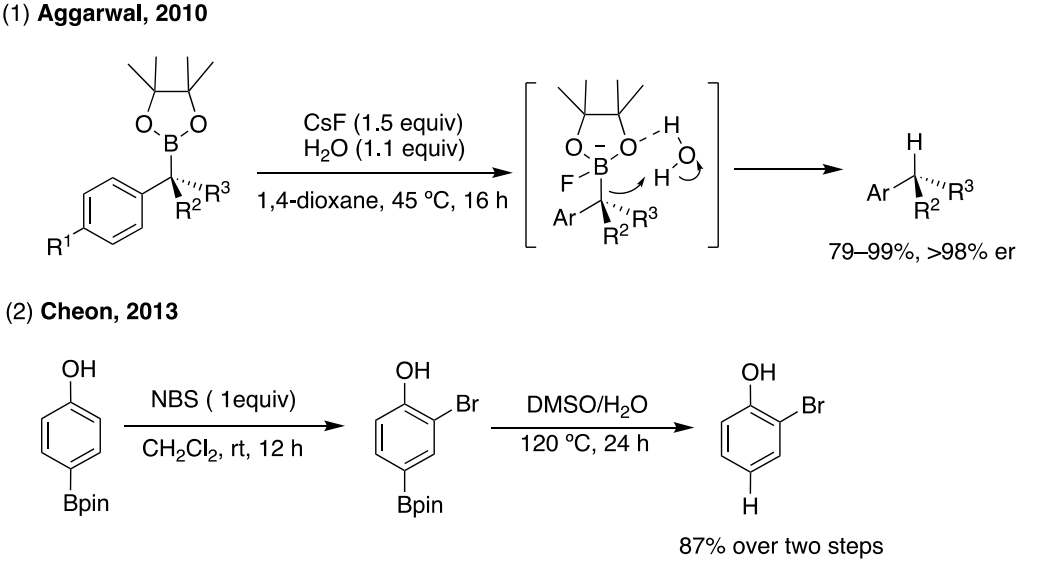
As discussed in Section 2.1.2, while 1,1-diborylalkane carbanions have been reported to react as a nucleophilic species towards aldehydes, alkyl halides, and epoxides, there is no precedent for additions onto C=N functional groups. It was surmised that the addition of lithiated 1,1-diborylalkanes onto chiral sulfinimine derivatives would produce optically pure β-sulfinimido *gem*-bis(boronates) (Scheme 2-8). A subsequent diastereotopic-group-selective monoprotodeboronation of the resulting β-sulfinimido *gem*-bis(boronates) would provide a general approach to the desired α,β-disubstituted β-aminoalkylboronates (Scheme 2-8).



Scheme 2-8. Proposal for the synthesis of optically pure α,β-disubstituted β-aminoalkylboronates via diastereocontrolled monoprotodeboronation of β-sulfinimido *gem*-bis(boronates).

Protodeboronation, as a decomposition pathway of organoboron compounds, i.e., conversion of R–B(OR')$_2$ to R–H, has been treated generally as an undesired reaction.[68–70] However, protodeboronation can be productive, as exemplified in a few instances, such as deborylative synthetic strategies (Scheme 2-9, eq. 1)[71] and removal of B(OH)$_2$ blocking groups (eq. 2).[72] Under our circumstance, diastereocontrolled monoprotodeboronation of

β-sulfinimido *gem*-bis(boronates) would provide ready access to enantioenriched α,β-disubstituted β-aminoalkylboronates.

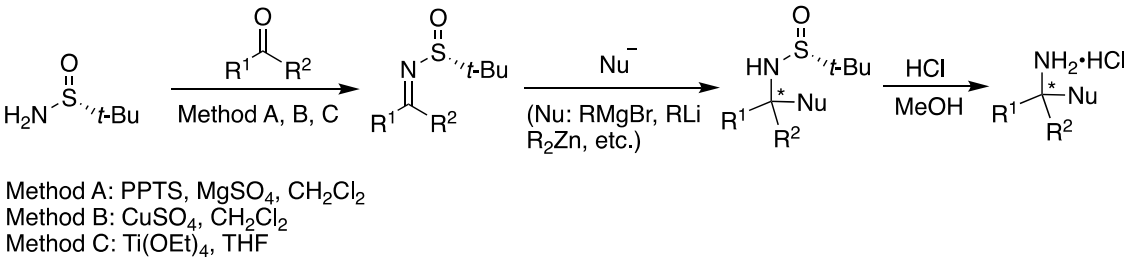


Scheme 2-9. Examples of protodeboronation as a productive pathway: 1) protodeboronation for construction of tertiary alkyl stereogenic centers and 2) protodeboronation for removal of $B(OH)_2$ blocking groups.

2.3 Synthesis of Optically Pure β-Sulfinimido *gem*-Bis(boronates) via 1,2-Addition to Chiral *N*-Sulfinyl Imines

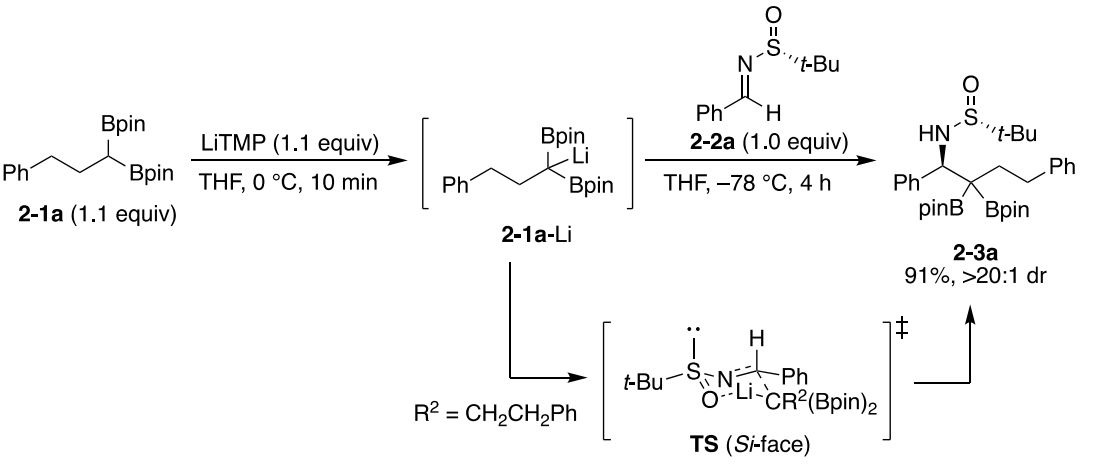
Over the past decades, numerous researchers in academia and industry have demonstrated the widespread applications of chiral *N*-*tert*-butanesulfinyl imines in the synthesis of optically pure amine-containing compounds, including drugs and natural products.[73] Several distinguishing characteristics of chiral *N*-*tert*-butanesulfinyl imines have led to their popularity in asymmetric synthesis: (1) *N*-*tert*-Butanesulfinyl imines can be synthesized in good yields by the condensation of aldehydes or ketones with the enantiomerically pure *N*-*tert*-butanesulfinamide (Method A–C, Scheme 2-10).[74] Chiral *N*-*tert*-butanesulfinamide was synthesized and isolated first by Ellman and co-workers in 1997[75] and is now an inexpensive reagent supplied by many chemical companies. (2) As a chiral auxiliary, the *tert*-butanesulfinyl group can result in high diastereoselectivity for the addition of chiral *N*-*tert*-butanesulfinyl imines with diverse nucleophiles, such as organo-magnesium, lithium, and zinc reagents (Scheme 2-10). (3) *N*-*tert*-Butanesulfinyl imines are much less hydrolytically labile

than most *N*-alkyl, aryl, acyl, or carbamoyl imines. (4) As a protecting group, the *N*-*tert*-butanesulfinyl group can tolerate various reaction conditions such as strong bases and transition metal-catalyzed process. (5) The *N*-*tert*-butanesulfinyl protecting group can be removed easily under acidic conditions to provide the amine hydrochloride products in a high yield (Scheme 2-10).



Scheme 2-10. Synthesis and synthetic applications of *N*-*tert*-butanesulfinyl imines.

It was assumed that the synthesis of the required optically pure β-sulfinimido *gem*-bis(boronate) precusors could be achieved by taking advantage of the versatility of chiral *N*-*tert*-butanesulfinyl imines in asymmetric synthesis. The synthesis began by employing the 1,2-addition between optically enriched *N*-*tert*-butanesulfinyl aldimine **2-2a** and lithiated 1,1-diborylalkane **2-1a**-Li as a model reaction. The lithiated 1,1-diborylalkane **2-1a**-Li was prepared by mixing 1,1-diborylalkane **2-1a** and LiTMP in THF at 0 ºC for 10 min (Scheme 2-11). It was found that the 1,2-addition of lithiated 1,1-diborylalkane **2-1a**-Li to *N*-*tert*-butanesulfinyl aldimine **2-2a** in THF at –78 ºC for 4 h afforded β-sulfinimido *gem*-bis(boronate) **2-3a** in 91% yield with high diastereoselectivity (>20:1 dr). The relative stereochemistry of **2-3a** was assigned as R_s,*S* (see Scheme 2-12), which can be rationalized by the lithium-chelated six-membered chairlike transition structure generally accepted for these reactions,[73] with the addition of **2-1a**-Li occurring from the *Si*-face of **2-2a** (Scheme 2-11).



Scheme 2-11. 1,2-Addition of lithiated 1,1-diborylalkane **2-1a**-Li to *N*-*tert*-butanesulfinyl aldimine **2-2a**.

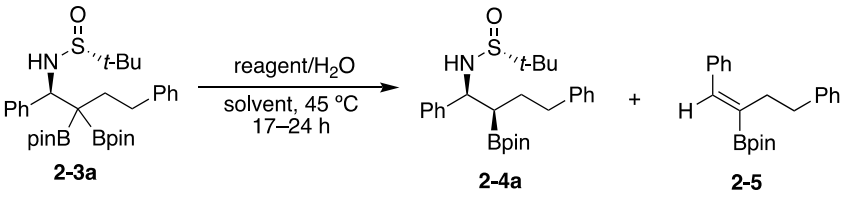
2.4 Reaction Optimization of the Monoprotodeboronation of β-Sulfinimido *gem*-Bis(boronate) 2-3a

The monoprotodeboronation of β-sulfinimido *gem*-bis(boronate) **2-3a** was examined next. Aggarwal and co-workers reported efficient methods to protodeboronate secondary and tertiary alkylboronates in the presence of fluoride-based reagents (see Scheme 2-9, eq. 1).[71,76] These protodeboronation procedures are limited to activated alkylboronates, such as benzylic and allylic boronates. However, previous studies (cf., Section 2.1.2.2), which have shown that Bpin units of 1,1-diborylalkanes can activate each other towards the formation of a stabilized α-boryl carbanion, indicate that *gem*-bis(boronate) **2-3a** can undergo a monoprotodeboronation to give the desired β-aminoalkylboronate product without over-reaction (i.e., double deboronation).

In the study of reaction optimization, the yield was determined by ^{1}H NMR analysis using dibromomethane as the internal standard, and the diastereomeric ratio (dr) was determined by peak integrations of isolated resonances in the ^{1}H NMR spectra of the crude reaction mixture. It was found that the monoprotodeboronation of **2-3a** is highly diastereoselective and affords 70% of *syn*-β-aminoalkylboronate **2-4a** (>20:1 dr), accompanied with 22% of elimination product **2-5** (Table 2-1, entry 1) when the protodeboronation conditions reported by Aggarwal and co-workers[71] were employed. As shown in Scheme 2-12, *syn*-β-aminoalkylboronate **2-4a** could be oxidized stereospecifically

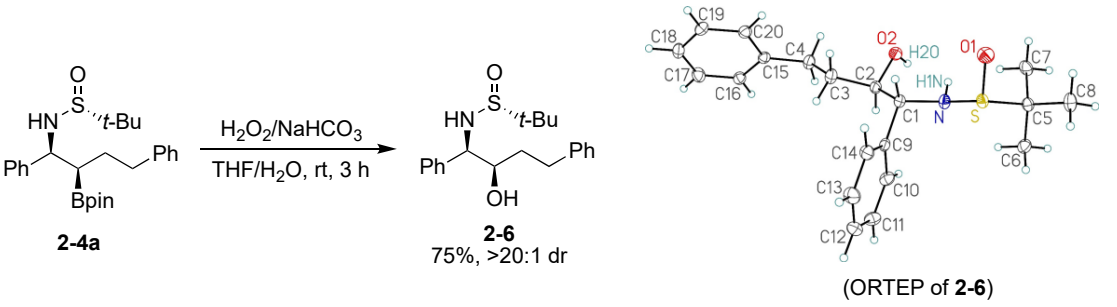
into *syn*-β-amino alcohol **2-6** in 75% yield. The X-ray crystallographic analysis of **2-6** allowed a confirmation of the relative stereochemistry of **2-4a** as (R_s,1*S*,2*R*) (Scheme 2-11).

Table 2-1. Optimization of Reaction Conditions[a]



Entry	Reagent (equiv)	Solvent	Yield of **2-4a**[b] [%]	Yield of **2-5**[b] [%]	dr[c]
1	CsF (1.5)	dioxane	70	22	>20:1
2	CsF (1.1)	dioxane	78	21	>20:1
3	CsF (1.0)	dioxane	81	18	>20:1
4	CsF (1.0)	MeOH	13	<5	4:1
5	CsF (1.0)	EtOAc	86	14	15:1
6	CsF (1.0)	acetone	82	18	13:1
7	CsF (1.0)	DMF	71	22	15:1
8	CsF (1.0)	CH_3CN	88	12	18:1
9	CsF (1.0)	toluene	66	20	>20:1
10	CsF (1.0)	THF	69	12	>20:1
11	CsF (1.0)	Et_2O	76	21	>20:1

[a] Reaction conditions: 0.10 mmol **2-3a**, 1.0–1.5 equiv of reagent and 1.1 equiv of water at 45 °C for 17–24 h. [b]Yield was determined by ^{1}H NMR using dibromomethane as the internal standard. [c]dr was determined by ^{1}H NMR of the crude reaction mixture. dioxane = 1,4-dioxane.

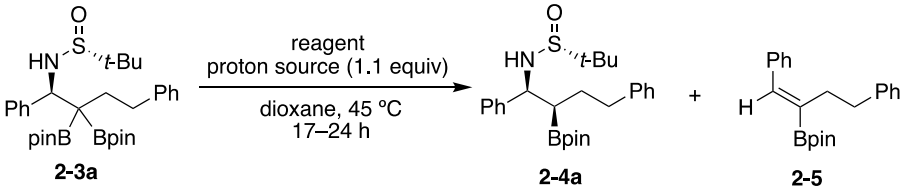


Scheme 2-12. Oxidation of *syn*-β-aminoalkylboronate **2-4a** and ORTEP representation of X-ray crystallographic structure of β-amino alcohol **2-6**.

Aiming to enhance the yield of **2-4a** further, it was found that lowering the amount of CsF to one equivalent suppressed the formation of **2-5** and increased the yield of **2-4a** to 81% (Table 2-1, entry 3). Screening of the reaction solvent revealed that switching from dioxane to more polar solvents, such as MeOH, acetone, or EtOAc, led to a lower diastereoselectivity (Table 2-1, entries 4–8). Since the NH···OB hydrogen-bonding interaction and the interaction between water and the oxygen atom of the Bpin unit are essential for the high syn-selectivity in the monoprotodeboronation, as indicated by the mechanistic studies (see Section 2.6), polar solvents can disfavor these types of interaction to afford lower diastereoselectivity. Use of toluene as a non-polar solvent gave a lower yield but with high diastereoselectivity (Table 2-1, entry 9). Other ethereal solvents were not as effective as dioxane (Table 2-1, entries 10 and 11).

Other proton sources, such as AcOH and MeOH, were evaluated and found to be much less efficient than water (Table 2-2, entries 2 and 3), which could be ascribed to the lack of a possible hydrogen-bonding interaction with the oxygen atom of the Bpin unit (see Section 2.7). Using excess water was found to be detrimental to the reaction (Table 2-2, entry 4). Attempts to increase or decrease the reaction temperature resulted in lower yields (Table 2-2, entries 5 and 6). Utilizing CsOH or K_2CO_3 in dioxane is effective but lower-yielding than CsF (Table 2-2, entries 7 and 8). Evaluation of other fluoride-based reagents and bases (Table 2-2, entries 10–13) revealed that 1.1 equivalent of RbF with 1.1 equivalent of water at 45 ºC in dioxane were the optimal conditions for the protodeboronation of **2-4a**, affording **2-4a** in 87% yield (>20:1 dr) with only 13% of side-product **2-5** (Table 2-2, entry 11). Although RbF provides only a marginal increase in product yield, its use leads to reduced formation of the elimination side product compared with CsF (entry 13 of Table 2-2 vs. entry 2 of Table 2-1). Since both CsF and RbF generally have low solubilities in organic solvents,[77] it was reasoned that the lower solubility of RbF in dioxane, compared to CsF, would give a lower concentration of fluoride anion in dioxane, thus diminished the formation of the elimination side product to afford a higher yield of product **2-4a**. Therefore, the conditions of entry 13 (Table 2-2) were deemed to be optimal in providing a high yield of the product with excellent diastereoselectivity.

Table 2-2. Further Optimization of Reaction Conditions[a]



Entry	Reagent (equiv)	Proton Source	Yield of **2-4a**[b] [%]	Yield of **2-5**[b] [%]	dr[c]
1	CsF (1.0)	H_2O	81	18	>20:1
2	CsF (1.0)	AcOH	9	0	>20:1
3	CsF (1.0)	MeOH	18	0	>20:1
4[d]	CsF (1.0)	H_2O	54	8	>20:1
5[e]	CsF (1.0)	H_2O	72	18	>20:1
6[f]	CsF (1.0)	H_2O	72	22	>20:1
7	CsOH•H_2O (1.0)	–	72	18	>20:1
8	K_2CO_3 (1.0)	H_2O	61	6	>20:1
9[g]	(*i*-Pr)$_2$NH (1.0)	H_2O	70	0	2:1
10	TBAF•3H_2O (1.0)	–	26	23	>20:1
11	KF (1.0)	H_2O	19	<5	>20:1
12	RbF (1.0)	H_2O	81	13	>20:1
13	RbF (1.1)	H_2O	87 (87)[h]	13	>20:1

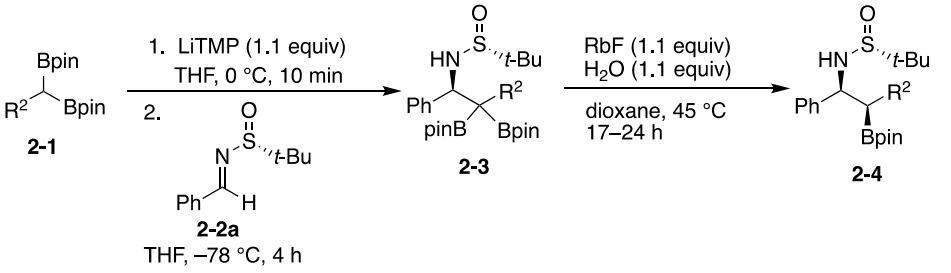
[a]Reaction conditions: 0.10 mmol **2-3a**, 1.0–1.1 equiv of reagent and 1.1 equiv of water at 45 ºC for 17–24 h. [b]Yield was determined by ^{1}H NMR using dibromomethane as the internal standard. [c]dr was determined by ^{1}H NMR of the crude reaction mixture. [d]0.10 mL of water was used. [e]Reaction was performed at room temperature. [f]Reaction was performed at 60 ºC. [g]Reaction was performed at 80 ºC and 0.50 mL of water was used. [h]Isolated yield.

2.5 Scope of 1,2-Addition and Monoprotodeboronation

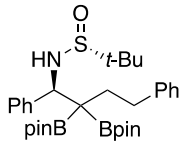
With the optimal protodeboronation conditions of Table 2-2 (entry 13), the scope of 1,1-diborylalkanes and *N*-*tert*-butanesulfinyl aldimines was investigated. β-Sulfinimido *gem*-bis(boronates) **2-2** and β-aminoalkylboronates **2-4** are stable on the silica gel column, and the indicated yields in Table 2-3 and 2-4 are based on products **2-2** and **2-4** after isolation by flash column chromatography. The relative configuration of β-sulfinimido *gem*-bis(boronates) **2-2** and β-aminoalkylboronates **2-4** was assigned based on the X-ray analysis of optically enriched **2-6** (see Scheme 2-12).

The 1,2-addition was applied successfully to a representative selection of 1,1-diborylalkanes containing aryl, silyl ether, alkenyl, and cyclohexyl functional groups, giving the desired β-sulfinimido *gem*-bis(boronates) (**2-3a**–**d**) in good to excellent yields (78–91%) with high diastereoselectivity (>20:1 dr) (Table 2-3). The subsequent monoprotodeboronation of **2-3a**, **2-3b**, and **2-3c** afforded the corresponding β-aminoalkylboronates (**2-4a**–**c**) in good yields (82–87%) and high diastereoselectivity (>20:1 dr). The protodeboronation of **2-3d** under standard conditions only gave a moderate conversion, probably due to the increased steric hindrance from the cyclohexyl group. Further optimization revealed that increasing the amount of RbF to two equivalents and elevating the reaction temperature to 90 ºC allowed the

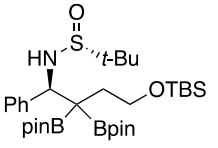
Table 2-3. Scope of 1,1-Diborylalkanes[a]



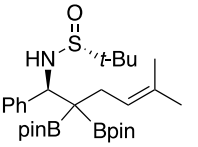
β-Sulfinimido *gem*-bis(boronates) **2-3**:



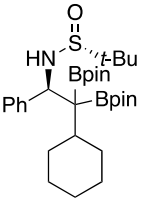
2-3a
(R^2 = CH_2CH_2Ph)
91%, >20:1 dr



2-3b
(R^2 = CH_2CH_2OTBS)
78%, >20:1 dr

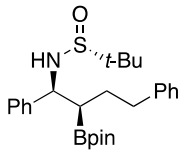


2-3c
[R^2 = $CH_2CHC(CH_3)_2$]
90%, >20:1 dr

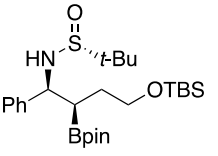


2-3d
(R^2 = cyclohexyl)
85%, >20:1 dr

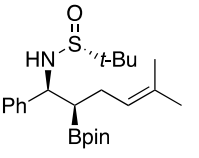
β-Aminoalkylboronates **2-4**:



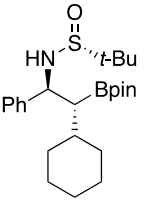
2-4a
(R^2 = CH_2CH_2Ph)
87%, >20:1 dr



2-4b
(R^2 = CH_2CH_2OTBS)
87%, >20:1 dr



2-4c
[R^2 = $CH_2CHC(CH_3)_2$]
82%, >20:1 dr

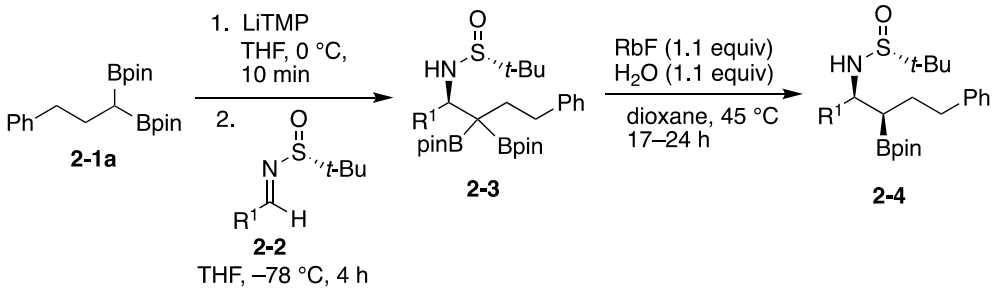


2-4d[b,c]
(R^2 = cyclohexyl)
83%, >20:1 dr

[a]Yields of isolated products are given. The dr values were determined by ^{1}H NMR analysis of the crude reaction mixture. [b]With 2.0 equiv of RbF. [c]At 90 ºC. dioxane = 1,4-dioxane.

protodeboronation of **2-3d** to produce **2-4d** in 83% yield (>20:1 dr). Of note, in all of the protodeoboronation reactions of **2-3a**-**d**, 0–15% of the elimination by-products were observed by ^{1}H NMR analysis of the crude reaction mixture. But they were separable from the desired β-aminoalkylboronate products using silica gel column chromatography.

Table 2-4. Scope of *N*-*tert*-Butanesulfinyl Aldimines[a]



Entry	R^1	Product **2-3**		Product **2-4**	
		Yield [%][a]	dr[b]	Yield [%][a]	dr[b]
1	(2-Me)C_6H_4	**2-3e** (98)	>20:1	**2-4e** (91)	>20:1
2	(3-Me)C_6H_4	**2-3f** (80)	>20:1	**2-4f**[c,f] (60)	>20:1
3	(3-MeO)C_6H_4	**2-3g** (78)	>20:1	**2-4g** (78)	>20:1
4	(4-MeO)C_6H_4	**2-3h** (96)	>20:1	**2-4h**[c,e] (94)	>20:1
5	(4-Me_2N)C_6H_4	**2-3i** (98)	>20:1	**2-4i**[c,e] (84)	>20:1
6	(4-F)C_6H_4	**2-3j** (82)	>20:1	**2-4j**[c] (87)	>20:1
7	(4-Cl)C_6H_4	**2-3k** (84)	>20:1	**2-4k** (72)	>20:1
8	(4-Br)C_6H_4	**2-3l** (91)	>20:1	**2-4l** (91)	>20:1
9	(4-Bpin)C_6H_4	**2-3m** (90)	>20:1	**2-4m** (75)	>20:1
10	(4-CN)C_6H_4	**2-3n** (N.D.)	>20:1[h]	**2-4n** (52)	5:1
11	3-pyridyl	**2-3o** (79)	10:1	**2-4o** (73)	>20:1
12	2-furyl	**2-3p** (72)	>20:1	**2-4p** (69)	>20:1
13	$CH_3(CH_2)_4C{\equiv}C$	**2-3q** (91)	>20:1	**2-4q**[c,e] (56)	>20:1
14	PhHC=CH	**2-3r** (85)	>20:1	**2-4r**[c,e] (74)	>20:1
15	Me	**2-3s** (84)	>20:1	**2-4s**[c,f] (59)	11:1
16	cyclohexyl	**2-3t** (86)	>20:1	**2-4t**[d,g] (55)	9:1
17	$PhCH_2$	**2-3u** (33)	>20:1	**2-4u**[d,f] (57)	>20:1

[a]Yields of isolated products. [b]The dr values were determined by ^{1}H NMR analysis of the crude reaction mixture. The crude products **2-4e**–**2-4r** contained 0–15% of the corresponding elimination side products (18–20% for **2-4s**–**2-4u**). [c]With 1.5 equiv of RbF. [d]With 2.0 equiv of RbF. [e]At 60 ºC. [f]At 70 ºC. [g]At 90 ºC. [h]N.D. = Not determined. NMR conversion: 100%. 1:8, dr (diboryl): >20:1; dr (monoboryl): 3:1. dioxane = 1,4-dioxane.

The 1,2-addition and protodeboronation sequence also was applied to a variety of *N*-*tert*-butanesulfinyl aldimines (Table 2-4). Aryl aldimines bearing substituents at the ortho or meta positions were found to be suitable, reacting efficiently in the 1,2-addition to give **2-3e**, **2-3f**, and **2-3g** in good to excellent yields (78–98%) with high diastereoselectivity (>20:1 dr). These *gem*-Bis(boronates), **2-3e** and **2-3g**, were mono-protodeboronated successfully to afford **2-4e** and **2-4g** in good yields (>20:1 dr). The protodeboronation of **2-3f** required a larger amount of RbF and a higher reaction temperature so as to obtain good conversion of **2-3f**, thus affording **2-4f** in 60% yield (>20:1 dr). *Para*-substituted aryl aldimines bearing methoxy, amino, fluoro, chloro, bromo, and boronyl functional groups underwent the 1,2-addition and protodeboronation reactions uneventfully, affording β-aminoalkylboronates (**2-4h**–**m**) in good to excellent yields with consistently high diastereoselectivity (>20:1 dr). The 1,2-addition of an aryl aldimine containing a cyano substituent at the para position yielded an inseparable 1:8 mixture of β-sulfinimido *gem*-bis(boronate) **2-3n** (>20:1 dr) and β-aminoalkylboronate **2-4n** (3:1 dr). It was reasoned that the formation of **2-4n** is attributed to the monoprotodeboronation of **2-3n** under the basic 1,2-addition conditions when an aqueous solution was added to quench the reaction mixture. In this case, the crude mixture was subjected directly to the protodeboronation, affording **2-4n** in 52% yield (5:1 dr) over two steps. Heteroaryl aldimines, such as pyridyl and furyl aldimines, are compatible substrates, as exemplified by the efficient formation of β-sulfinimido *gem*-bis(boronates) (**2-3o** and **2-3p**) and β-aminoalkylboronates (**2-4o** and **2-4p**).

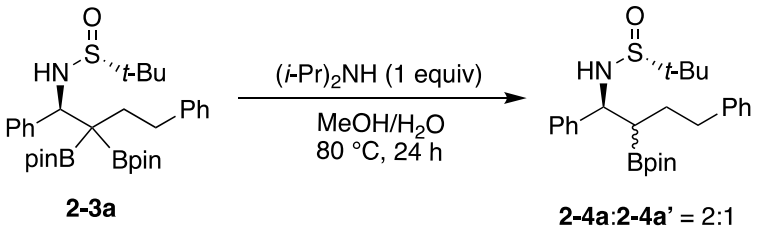
Besides aryl and heteroaryl aldimines, alkynyl and alkenyl aldimines also underwent the highly diastereoselective 1,2-addition to produce **2-3q** and **2-3r** in good yields (>20:1 dr). The protodeboronation of **2-3q** and **2-3r** subsequently yielded the corresponding β-aminoalkylboronates (**2-4q** and **2-4r**) in moderate to good yields (56–74%) with high diastereoselectivity (>20:1 dr). The 1,2-addition of alkyl aldimines containing methyl and cyclohexyl groups was successful, with the formation of **2-3s** and **2-3t** in good yields (>20:1 dr). The conversion of diboronates **2-3s** and **2-3t** was low under the standard protodeboronation conditions. By employing a larger amount of RbF and a higher reaction temperature, diboronates **2-3s** and **2-3t** could be mono-protodeboronated efficiently to afford **2-4s** in 59% yield (11:1 dr) and **2-4t** in 55% yield (9:1 dr), respectively. The 1,2-addition of benzyl aldimine to synthesize **2-3u** was low-yielding, probably due to the presence of acidic

α-hydrogens in the benzyl aldimine, which would favor the formation of the corresponding enamine, thus resulted in side reactions. The protodeboronation of **2-3u** afforded **2-4u** in 57% yield (>20:1 dr) under modified protodeboronation conditions. Although the protodeboronation of **2-2e-u** resulted in 0–20% of the elimination by-products, the desired β-aminoalkylboronates **2-3e-u** were separated easily from these by-products using silica gel column chromatography.

2.6 Mechanistic Studies for the Monoprotodeboronation of β-Sulfinimido *gem*-Bis(boronates)

2.6.1 Control Experiments

To further understand the observed syn-diastereoselectivity in the protodeboronation of β-sulfinimido *gem*-bis(boronates) **2-3**, a mixture of major syn diastereomer **2-4a** and minor anti diastereomer **2-4a'** was prepared by employing the protodeboronation conditions of Table 2-2 (entry 9) and was isolated in a ratio of 2:1 (Figure 2-1) that is much lower than the outstanding diastereoselectivity of the optimal conditions of Table 2-2 (entry 13). Treatment of this mixture in the optimal protodeboronation conditions returned the ratio of **2-4a** and **2-4a**' unchanged (Figure 2-2). This result strongly suggests that the major diastereomer **2-4a** is a kinetically favorable product and is not the thermodynamically favored isomer of an equilibrating mixture.



2-3a

2-4a:**2-4a'** = 2:1

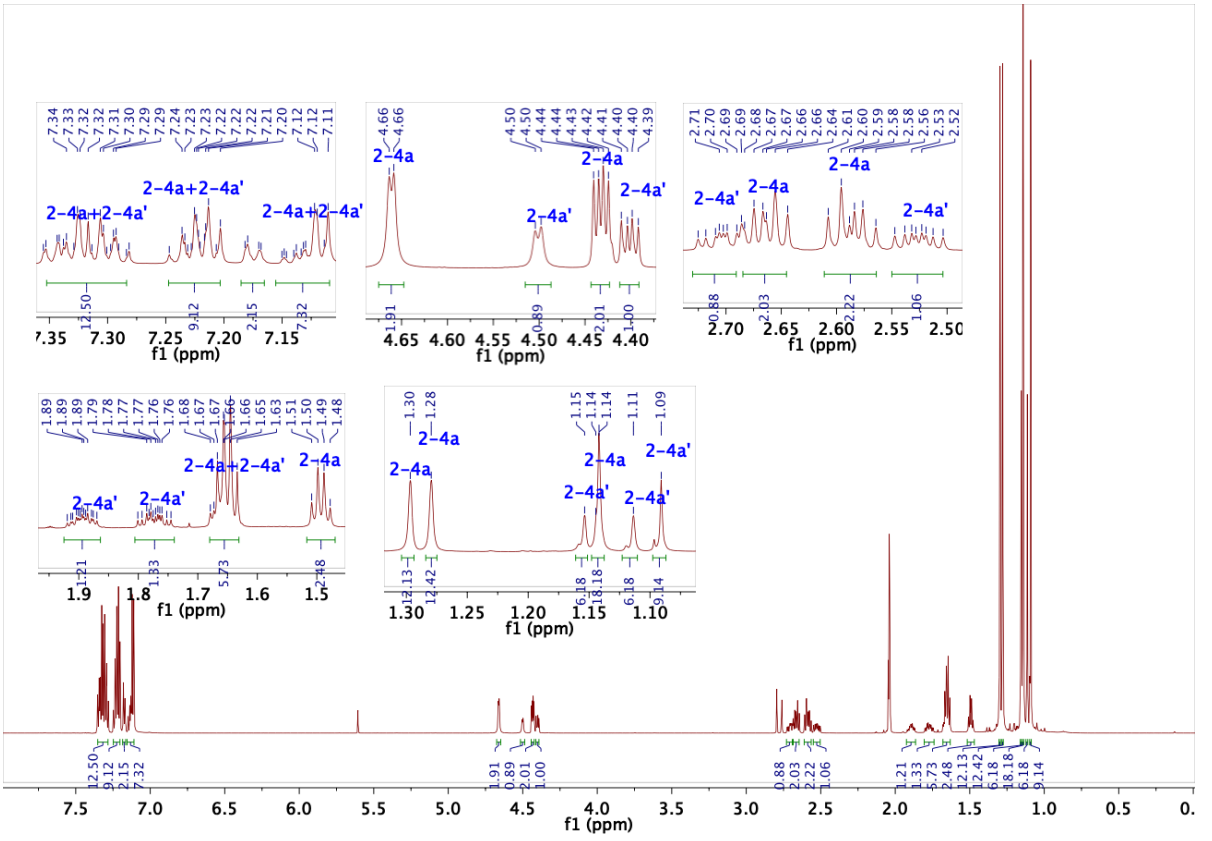


Figure 2-1. ^{1}H NMR spectrum of the mixture of **2-4a** and **2-4a'**.

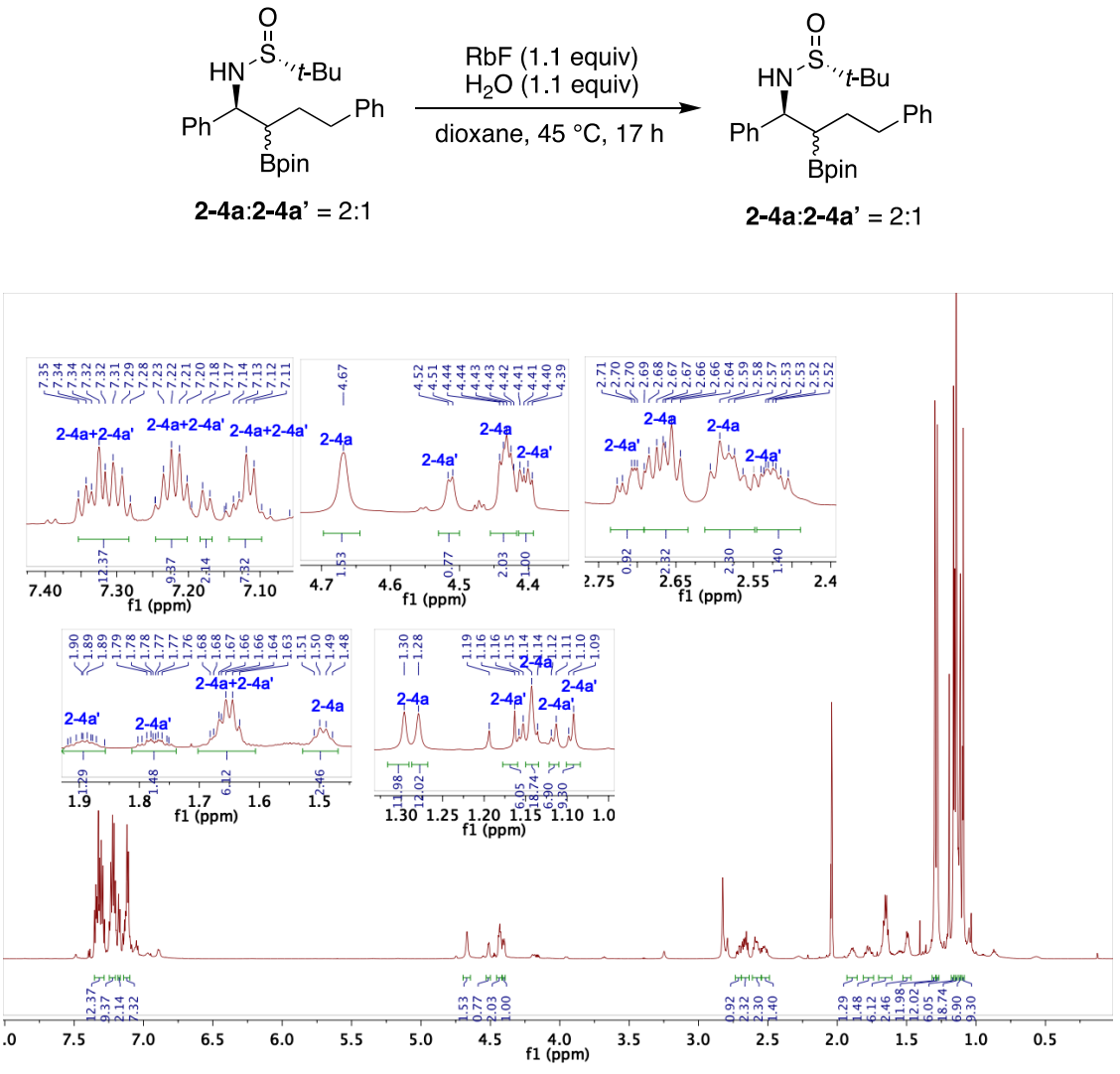
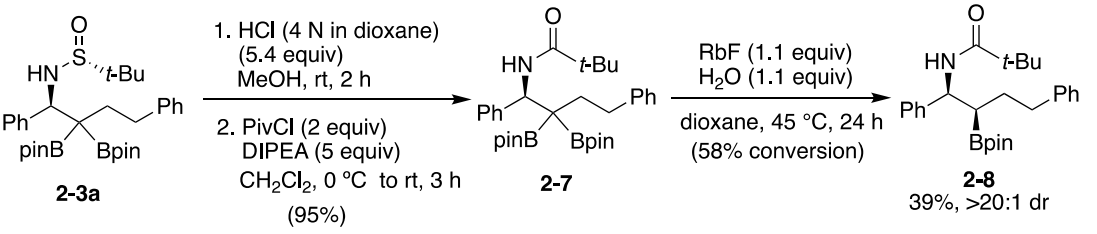


Figure 2-2. ^{1}H NMR spectrum of the crude mixture of the protodeboronation of the mixture of **2-4a** and **2-4a'**.

The effect of the chirality of the sulfinyl moiety on the diastereoselectivity by replacing it with the achiral pivaloyl group also was examined. *N*-pivaloyl-protected (*N*-Piv) β-amino *gem*-bis(boronate) **2-7** was prepared by removal of the *N*-sulfinyl group of *gem*-bis(boronate) **2-3a** followed by *N*-pivaloylation (Scheme 2-13). It was found that under the optimal protodeboronation conditions of Table 2-2 (entry 13), β-amino *gem*-bis(boronate) **2-7** afforded 39% of the corresponding β-aminoalkylboronate **2-8** (>20:1 dr) with syn stereochemistry, confirmed to be the same as that of β-aminoalkylboronates **2-4** (Scheme 2-13). Despite the low yield of **2-8**, its stereoselective formation indicates that the chirality of the sulfinyl moiety of β-aminoalkylboronates **2-4** does not play an important role in

controlling the diastereoselectivity of the monoprotodeboronation of β-sulfinimido *gem*-bis(boronates) **2-3**.



Scheme 2-13. Synthesis of *gem*-diboronate **2-7** and investigation of the effect of the chirality of the sulfinyl moiety of *gem*-bis(boronates) **2-3** on the diastereoselectivity.

As shown by the ^{11}B NMR of β-sulfinimido *gem*-bis(boronate) **2-3a** (δ = 32.4 ppm), there appears to be no dative bond between the sulfinyl unit and the boryl groups. Instead, the X-ray crystallographic structure of **2-3a** shows that the amino (NH) group of **2-3a** interacts with the oxygen atom of one Bpin unit via a hydrogen bond (Figure 2-3). Presumably, the NH···OB hydrogen-bonding interaction renders the boron atom of that Bpin unit more acidic,

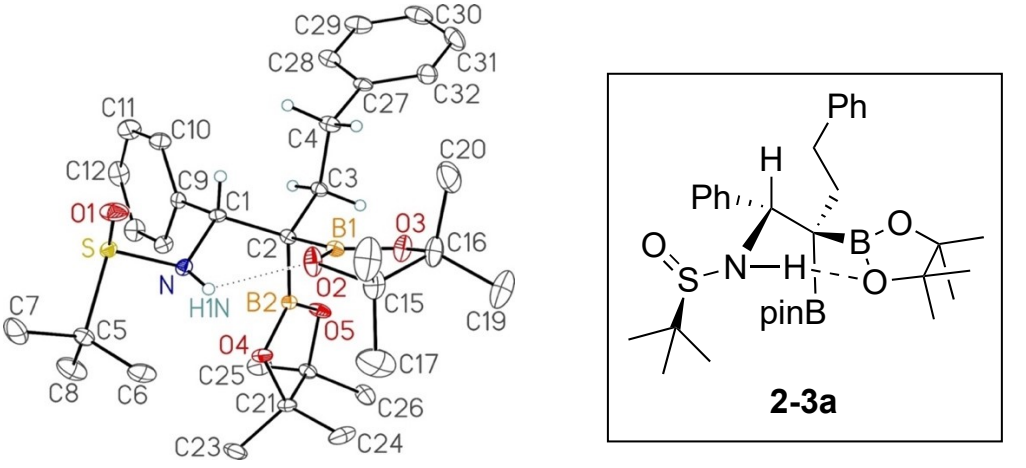
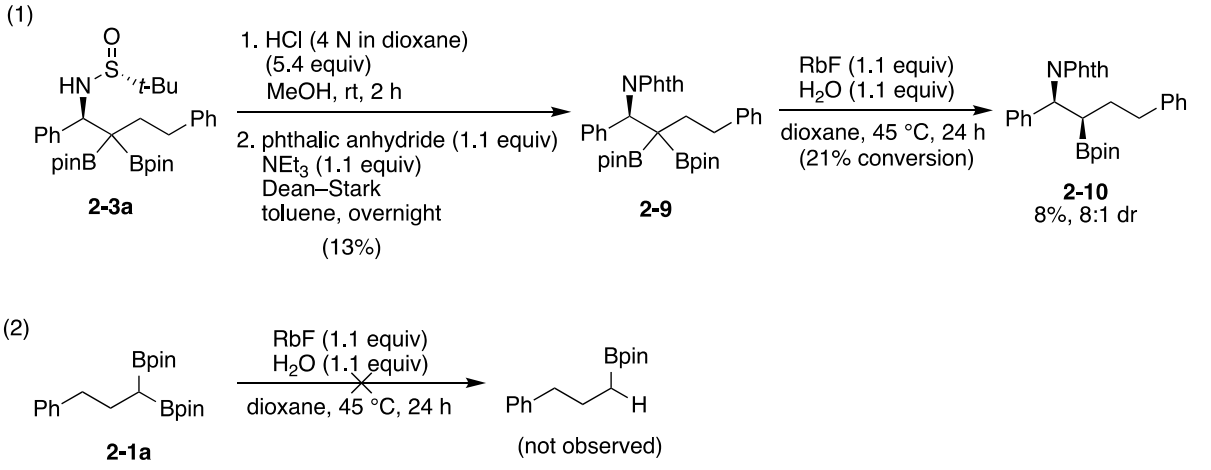


Figure 2-3. ORTEP representation of X-ray crystallographic structure of *gem*-bis(boronate) **2-3a**.

and thus more likely to coordinate anions. The poor reaction conversion of β-sulfinimido *gem*-bis(boronate) **2-3a** in MeOH (13% yield with 4:1 dr) in the protodeboronation reaction (Table 2-1, entry 4) implies the importance of this type of hydrogen bond since MeOH as a protic solvent is capable of competing with the NH···OB hydrogen-bonding interaction. To

investigate the importance of the NH unit further, *N*-phthalimide-protected (*N*-Phth) *gem*-diboronate **2-9** was synthesized by removal of the *N*-sulfinyl group of *gem*-bis(boronate) **2-3a**, followed by the amine protection with phthalic anhydride (Scheme 2-14, eq. 1). The poor reactivity of *gem*-diboronates **2-9** (Scheme 2-14, eq. 1) and **2-1a** (eq. 2) without an NH unit under the optimized protodeboronation conditions confirms that the presence of the sulfinyl NH is essential for the high reactivity and syn-selectivity in the protodeboronation.

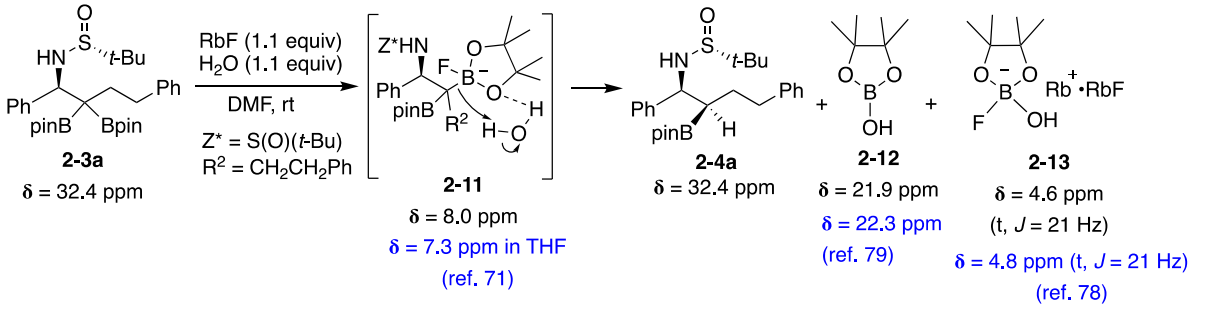


Scheme 2-14. Investigation of the role of NH unit for syn-selectivity of the protodeboronation of β-sulfinimido *gem*-bis(boronates) **2-3**: 1) synthesis and protodeboronation of *gem*-diboronate **2-9** and 2) protodeboronation of *gem*-diboronate **2-1a**.

2.6.2 ^{11}B NMR Studies

The mechanism of monoprotodeboronation of *gem*-bis(boronates) **2-3** was explored further by ^{11}B NMR spectroscopy. In this experiment, RbF, *gem*-bis(boronate) **2-3a**, water, and DMF (DMF was chosen as the solvent to maximize the solubility of RbF, and a small amount of toluene-d_8 was added to lock the NMR signal) were mixed in a quartz NMR tube. The protodeboronation process was monitored by ^{11}B NMR spectroscopy at room temperature. It was found that mixing all the reagents and solvent immediately gave rise to peaks at 32.4, 21.9, 8.0, and 4.6 ppm (Figure 2-4). The signal at 32.4 ppm can be assigned to the non-quaternized Bpin groups of **2-3a**, **2-11**, and **2-4a**. The signals at 21.9 and 4.6 ppm (a triplet) can be assigned as HOBpin (**2-12**) and RbF•Rb[Bpin(OH)F] (**2-13**), respectively, which have been identified and characterized in the literature.[78,79] It was reasoned that the signal at 8.0 ppm corresponds to the ate complex **2-10**, which is similar to the ate complex observed by

Aggarwal and co-workers.[71] As the reaction progresses, the resonance ascribed to the HOBpin by-product (**2-12**) increases in intensity, along with a small amount of RbF•Rb[Bpin(OH)F] (**2-13**) (Figure 2-5).



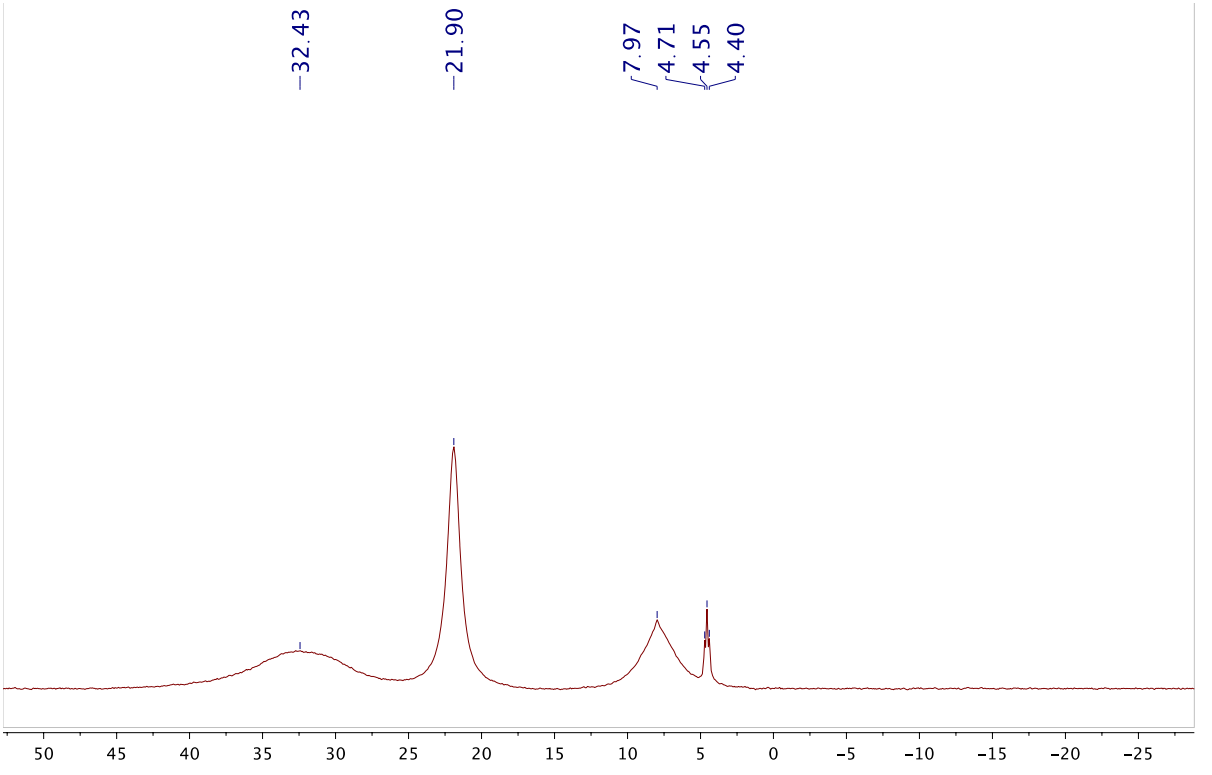


Figure 2-4. Initial ^{11}B NMR spectrum of the reaction mixture at room temperature.

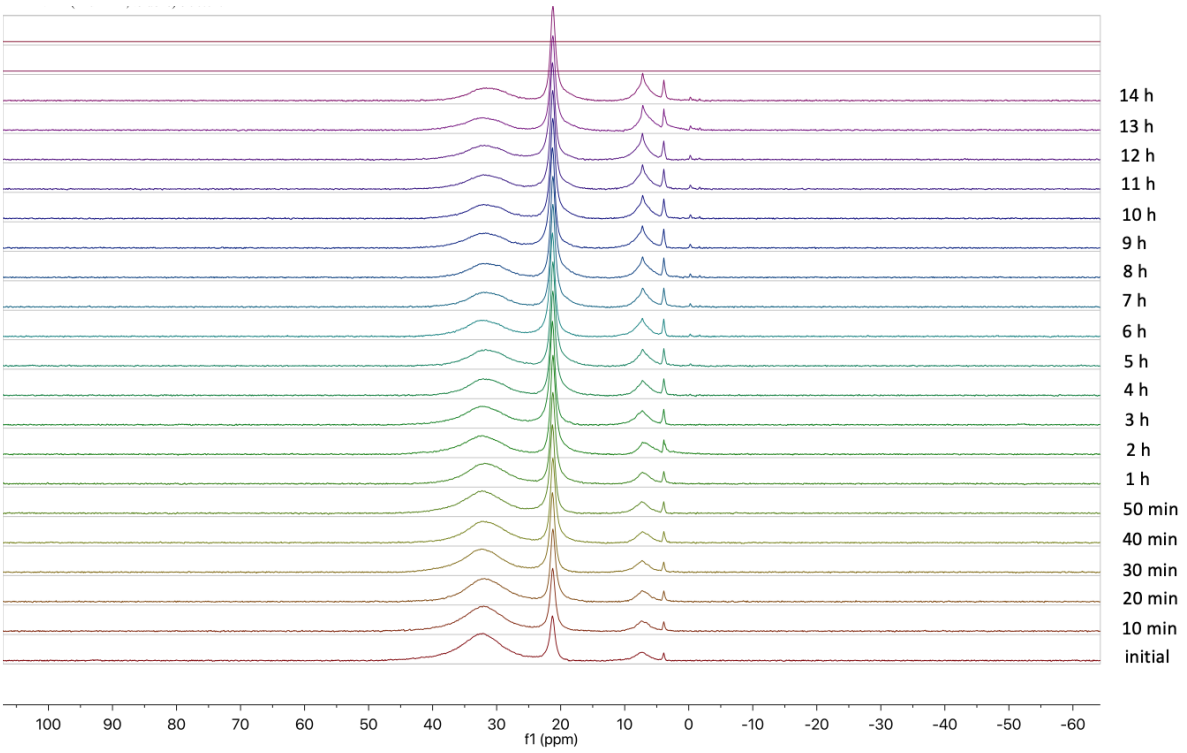
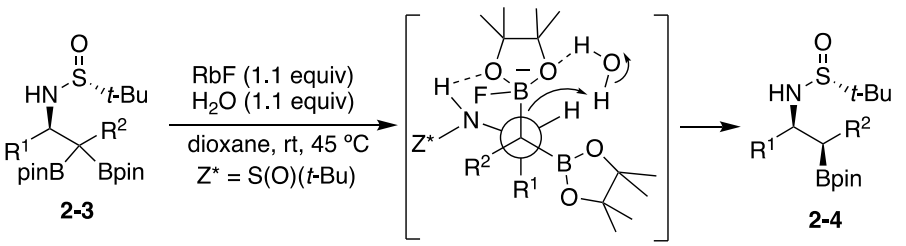


Figure 2-5. Monitoring the protodeboronation reaction at room temperature by ^{11}B NMR spectroscopy (chemical shifts for four peaks from the left to the right: 32.4, 21.9, 8.0, and 4.6 ppm).

2.7 Proposed Mechanism and Stereochemical Model

Based on the mechanistic studies discussed in Section 2.6, it is likely that the monoprotodeboronation of β-sulfinimido *gem*-bis(boronates) occurs through a mechanism similar to that proposed for monoborylated substrates.[71] Specifically, since CsOH is also an effective base for the protodeboronation (Table 2-2, entry 7), either the fluoride or hydroxide anion may coordinate the boron atom of the Bpin unit. Water interacts with one of the basic oxygen atoms of the resulting tetrahedral boronate unit, ensuring a stereospecific (retentive) proton delivery from the same side as the C–Bpin unit (Scheme 2-15). To explain the diastereotopic group selectivity, a reactive conformer that minimizes severe gauche interactions by placing the small H substituent between the two large Bpin units was proposed (Scheme 2-15). In this conformer, the requisite Bpin unit undergoes protodeboronation because it is activated toward tetrahedral adduct formation by the sulfinyl NH unit, and it involves the most nucleophilic C–B bond (i.e., the one not involved in synperiplanar $\sigma^*_{(C–N)}$-$\sigma_{(C–B)}$ hyperconjugation.[80]

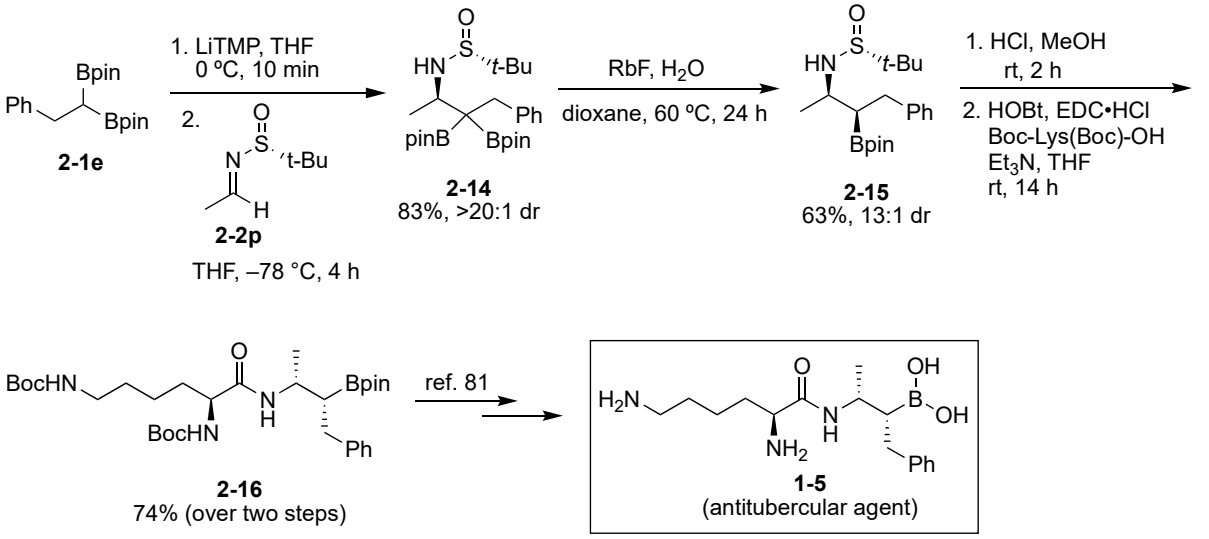


Scheme 2-15. Proposed mechanism and a possible stereochemical model for the monoprotodeboronation of β-sulfinimido *gem*-bis(boronates).

2.8 Synthetic Utility of *syn*-β-Aminoalkylboronates

2.8.1 Formal Synthesis of Antitubercular Agent 1-5

Besides the typical oxidation of β-aminoalkylboronate **2-4a** affording a synthesis of optically pure β-amino alcohol **2-6**, as shown in Scheme 2-12, the potential of this methodology also was highlighted in the formal synthesis of antitubercular agent **1-5**[81] (see structure in Figure 1-5). The 1,2-addition of lithiated 1,1-diborylalkane **2-1e** onto *N*-*tert*-butanesulfinyl aldimine **2-2p** gave *gem*-bis(boronate) **2-14** in 83% yield (>20:1 dr). Monoprotodeboronation of **2-14**



Scheme 2-16. Formal synthesis of antitubercular agent **1-5**.

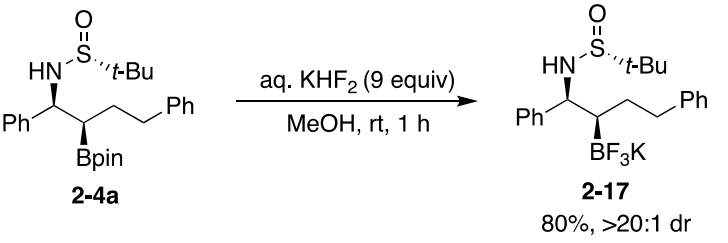
subsequently afforded β-aminoalkylboronate **2-15** in 63% yield (13:1 dr). Removal of the moiety under acidic conditions, followed by coupling with Boc-Lys(Boc)-OH, produced

peptidyl β-aminoalkylboronate **2-16** in 74% yield over two steps without any epimerization of its stereogenic centers. Aminoboronate **2-16,** which was accessed in four steps and 39% overall yield from **2-1e** (compared to 6 steps and 2% overall yield for the published synthesis[81]), can be transformed into peptide **1-5** using the literature procedure.[81]

2.8.2 Other Attempts at Expanding the Synthetic Utility of β-Aminoalkylboronates for the Formation of C–C and C–N Bonds

2.8.2.1 Suzuki–Miyaura Cross-Coupling (SMC)

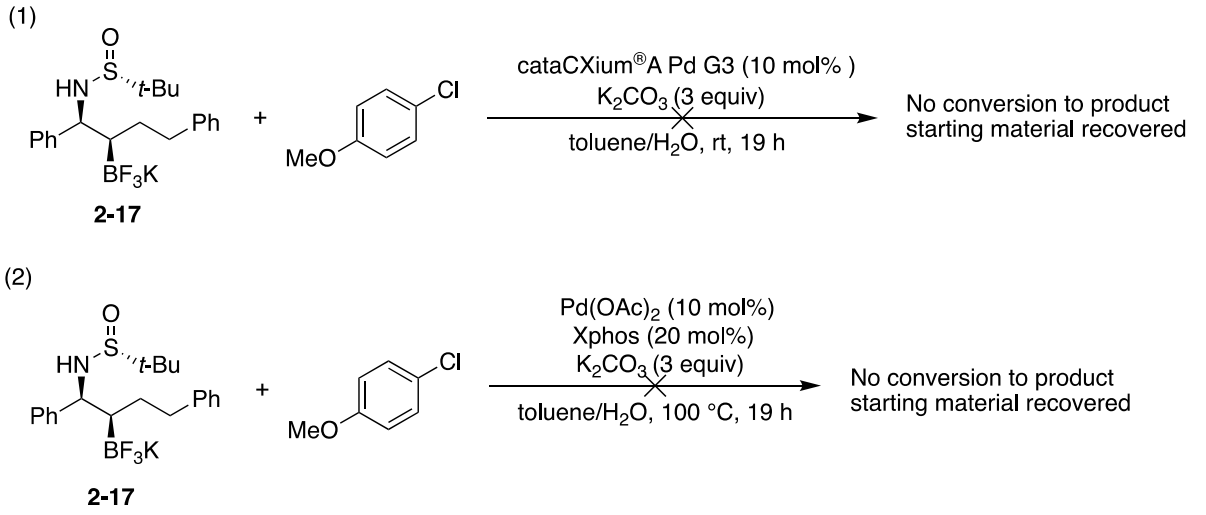
As stable and easily handled organoboron compounds, trifluoroborate salts have been used extensively in SMC due to their relative resistance to protodeboronation under cross-coupling conditions.[69] Therefore, to engage β-aminoalkylboronate **2-4a** in SMC for C–C bond formation, the corresponding enantioenriched trifluoroborate salt **2-17** was prepared first in 82% yield by following a literature procedure (Scheme 2-17).[82]



Scheme 2-17. Synthesis of the trifluoroborate salt of β-aminoalkylboronate **2-4a**.

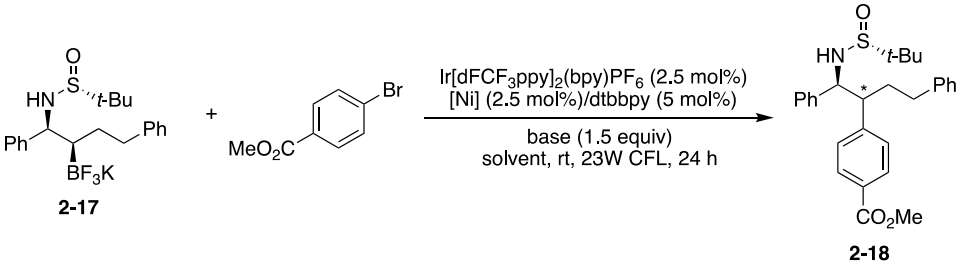
Next, Pd-catalyzed SMC of trifluoroborate salt **2-17** was attempted under conditions reported by the group of Takacs[83] (Scheme 2-18, eq. 1) and Molander[84] (eq. 2) for stereospecific cross-coupling of secondary trifluoroborate salts. However, ^{1}H NMR analysis of the crude reaction mixture indicated only little conversion of starting material **2-17**.

Molander and co-workers recently have developed the single electron transfer transmetallation chemistry via photoredox/nickel dual catalysis to offer a new and efficient strategy to cross-coupling of alkylboron compounds.[85] Under their dual catalysis conditions for secondary alkylboron cross-coupling (Table 2-5, entry 1),[86] the formation of the desired



Scheme 2-18. Attempts made at the Pd-catalyzed SMC of trifluoroborate salt **2-17**: 1) SMC using Takacs' conditions and 2) SMC using Molander's conditions.

Table 2-5. Cross-coupling of **2-17** Using Photoredox/Nickel Dual Catalysis Conditions



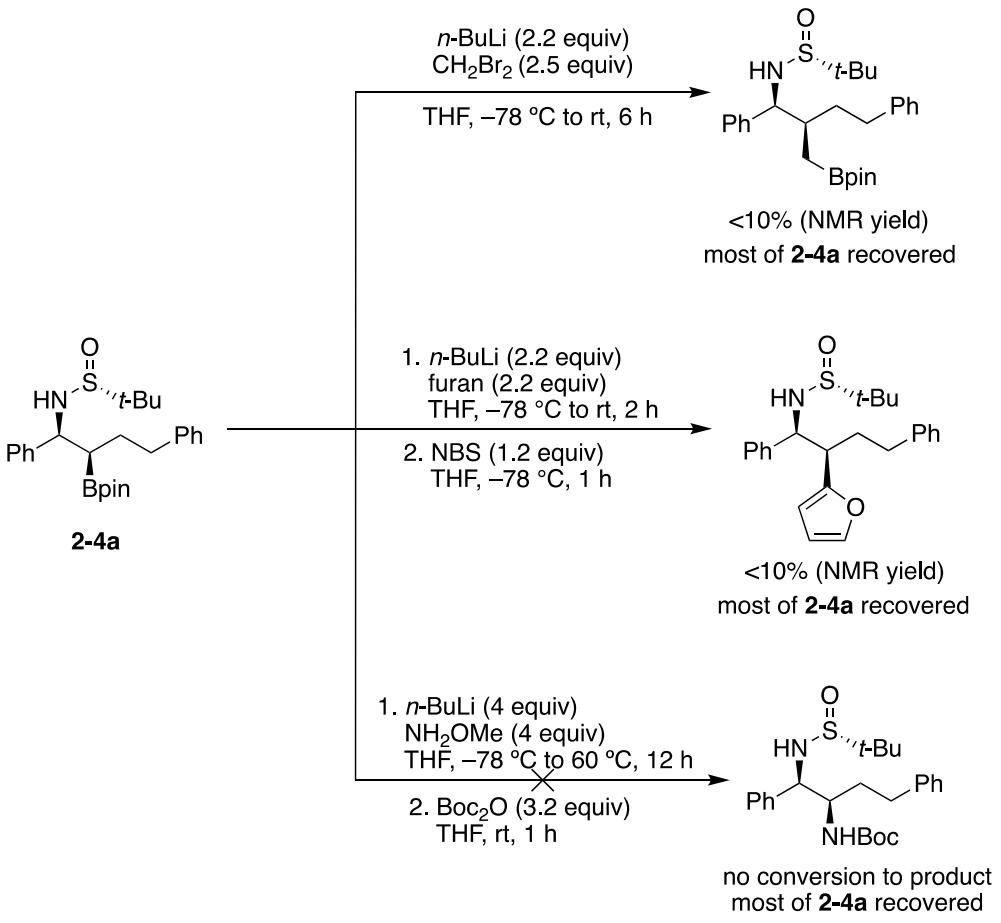
Entry	[Ni]	Base	Solvent	Yield of **2-18**[a] [%]
1	$NiCl_2$•dme	Cs_2CO_3	dioxane	<5
2	$Ni(cod)_2$	Cs_2CO_3	dioxane	N.R.
3	$Ni(acac)_2$	Cs_2CO_3	dioxane	N.R.
4	$Ni(TMHD)_2$	Cs_2CO_3	dioxane	N.R.
5	$NiCl_2$•dme	K_2HPO_4	dioxane	<5
6	$NiCl_2$•dme	K_2CO_3	dioxane	N.R.
7	$NiCl_2$•dme	Cs_2CO_3	DMF	<5
8	$NiCl_2$•dme	Cs_2CO_3	toluene	N.R.

[a]Yield was determined by ^1H NMR analysis of the crude reaction mixture using dibromomethane as the internal standard. The dr values were notdetermined. N.R. = No reaction. dioxane = 1,4-dioxane.

cross-coupled product **2-18**, which was produced from the cross-coupling of **2-17**, was observed by LC-MS and ^{1}H NMR of the crude reaction mixture, albeit with a low yield (<5% NMR yield). Efforts have been placed into the evaluation of the nickel catalyst, base, and solvent so as to increase the yield of **2-18** (Table 2-5). Unfortunately, all of these reaction conditions led to no- or low-conversion of **2-17**, along with the protodeboronation and dehalogenation side products, as indicated by ^{1}H NMR analysis of the crude reaction mixture. In fact, SMC is generally challenging with sp^3 alkylboron compounds, especially secondary and tertiary alkylboron compounds since their transmetallation with transition metals is slow due to steric hindrance.[69] Thus, subsequent protodeboronation and β-hydride elimination become competing side reactions. In the case with **2-17**, the very hindered nature of **2-17** is probably the key reason for the failure of its cross-coupling reactions.

2.8.3.2 Transition Metal-Free Transformations with β-Aminoalkylboronate 2-4a

Besides SMC, other attempts at the synthetic applications of β-aminoalkylboronate **2-4a** on the formation of C–C and C–N bonds also have been made (Scheme 2-19). Unfortunately, under the typical reaction conditions, Matteson homologation,[87] furanylation,[88] and amination[89] of **2-4a** all suffered from no- or low-conversion, which is probably ascribed to the very hindered nature of β-aminoalkylboronate **2-4a**. The fact that these transformations with **2-4a** suffered from low efficiency is indicative of a lack of substrates generality in these typical transformations of alkylboronic esters.



Scheme 2-19. Various attempts at other transition metal-free transformations of β-aminoalkylboronate **2-4a** for C–C and C–N bond formation.

2.9 Summary

In conclusion, this chapter reports an efficient method for 1,2-addition of lithiated 1,1-diborylalkanes onto chiral *N-tert*-butanesulfinyl aldimines to afford optically pure β-sulfinimido *gem*-bis(boronates) products in moderate to high yields (33–98%) with good to excellent diastereoselectivity (10:1–>20:1 dr). In a new application of protodeboronation chemistry, a highly diastereoselective mono-protodeboronation of β-sulfinimido *gem*-bis(boronates) subsequently afforded a wide range of synthetically and biologically important *syn*-α,β-disubstituted β-aminoalkylboronates in moderate to high yields (52–94%) with moderate to high diastereoselectivity (5:1–>20:1 dr). Mechanistic studies revealed that the monoprotodeboronation involves the formation of a tetrahedral borate where water interacts with one of the basic oxygen atoms to ensure a stereoretentive proton delivery from the same

side as the C–Bpin unit. Furthermore, the NH···OB hydrogen-bonding interaction between the sulfinyl NH unit and one Bpin unit of β-sulfinimido *gem*-bis(boronates) plays a key role for the high reactivity and syn-selectivity. The synthetic applications of the β-aminoalkylboronate products have been demonstrated by the synthesis of an optically enriched β-amino alcohol and a diastereocontrolled formal synthesis of the optically enriched β-aminoalkylboronate unit of a potent antitubercular agent.

2.10 Experimental

2.10.1 General Methods

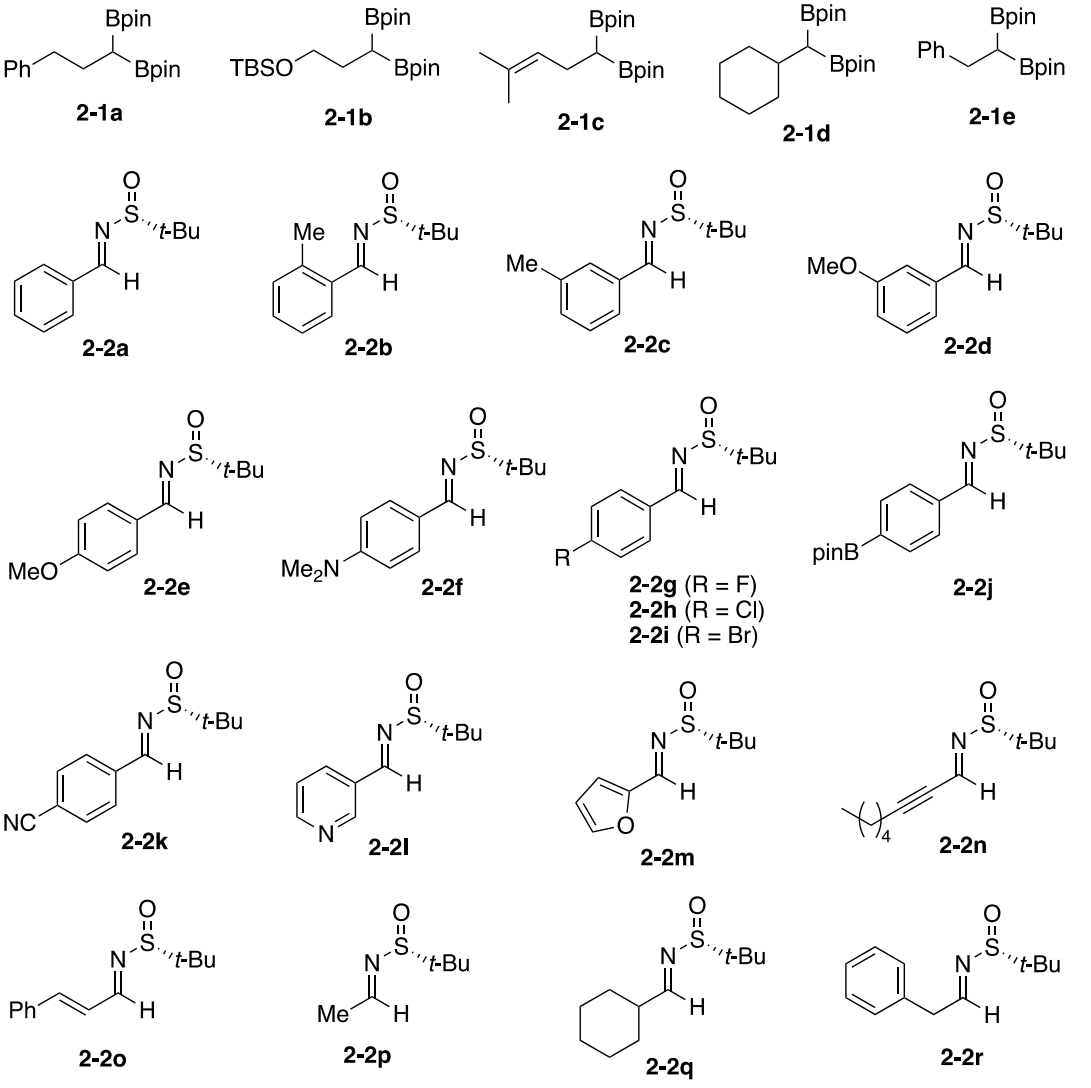
Unless otherwise stated, all reactions were performed under a nitrogen atmosphere. The elimination side products of the protodeboronation of *gem*-bis(boronate) **2-3b-u** were not isolated and characterized. Tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), and *N*,*N*-dimethylformamide (DMF) were purified using a cartridge solvent purification system prior to use. 1,4-Dioxane was distilled over sodium/benzophenone, 2,2,6,6-tetramethylpiperidine (TMP) was distilled over calcium hydride, and *n*-BuLi was titrated using 2,2-diphenylacetic acid prior to use.

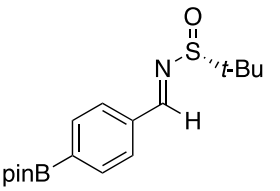
Unless otherwise noted, all other chemicals were purchased from commercial sources and used as received. Chromatographic separations were performed on silica gel 60 using ACS grade hexanes, ethyl acetate, dichloromethane, and diethyl ether as eluents. Thin layer chromatography (TLC) was performed on silica gel 60 F254 plates, which were visualized under UV light, $KMnO_4$, and *p*-anisaldehyde stains. NMR spectra were recorded on INOVA-400, INOVA-500, INOVA-600, or INOVA-700 MHz instruments. The residual solvent protons (^1H) of $CDCl_3$ (7.26 ppm), CD_3CN (1.94 ppm), C_6D_6 (7.15 ppm), acetone-d_6 (2.05 ppm), and $(CD_3)_2SO$ (2.50 ppm), and the solvent carbons (^{13}C) of $CDCl_3$ (77.06 ppm), CD_3CN (1.32 and 118.26 ppm), C_6D_6 (128.06 ppm), acetone-d_6 (29.84 and 206.26 ppm), and $(CD_3)_2SO$ (39.52 ppm) were used as internal standards. ^1H NMR data is presented as follows: chemical shift in ppm (δ) downfield from tetramethylsilane (multiplicity, coupling constant, integration). The following abbreviations are used in reporting NMR data: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet; comp m, complex multiplet; dd, doublet of doublets; qd, quartet of doublets; ddd, doublet of doublet of doublets; ddq, doublet

of doublet of quartets; app s, apparent singlet; app d, apparent doublet; app dt, apparent doublet of triplets; app td, apparent triplet of doublets; app qd, apparent quartet of doublets; app dtd, apparent doublet of triplet of doublet. The quaternary carbon bound to the boron atom often is missing due to the quadrupolar relaxation of boron. This effect was observed in each boron-containing compound. High-resolution mass spectra (HRMS) were recorded by the University of Alberta mass spectrometry services laboratory using electrospray ionization (ESI) techniques. Optical rotations were measured using a 1-mL cell with a 1-dm length on a P.E. 241 polarimeter. Melting points were determined in a capillary tube using a Gallenkamp melting point apparatus and are uncorrected.

2.10.2 Preparation and Characterization of Starting Materials

1,1-Diborylalkanes **2-1a**,[46] **2-1b**,[46] **2-1c**,[58] **2-1d**,[46] and **2-1e**[17], and *N*-*tert*-butanesulfinyl aldimines **2-2a**–**r**[74] were synthesized according to literature procedures.





(*R*,*E*)-2-Methyl-*N*-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzylidene)propane-2-sulfinamide (2-2j): To a 0.50 M solution of (*R*)-(+)-2-methyl-2-propanesulfinamide (0.97 g, 8.0 mmol, 1.0 equiv) in CH_2Cl_2 were added PPTS (0.10 g, 0.40 mmol, 0.050 equiv) and anhydrous $MgSO_4$ (4.8 g, 40 mmol, 5.0 equiv), followed by addition of 4-formylphenylboronic acid, pinacol ester (5.6 g, 24 mmol, 3.0 equiv). The mixture was stirred at room temperature for 24 h. Upon completion, the reaction mixture was filtered through a pad of Celite, and the filter cake was washed well with CH_2Cl_2. The crude mixture was purified by flash silica gel chromatography (CH_2Cl_2) to afford *N*-*tert*-butanesulfinyl aldimine **2-2j** as a white solid (1.7 g, 63%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1H), 7.92–7.88 (m, 2H), 7.86–7.81 (m, 2H), 1.36 (s, 12H), 1.27 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.9, 136.2, 135.3, 128.5, 84.2, 58.0, 25.0, 24.9, 22.7.

^{11}B NMR (128 MHz, $CDCl_3$) δ 31.2.

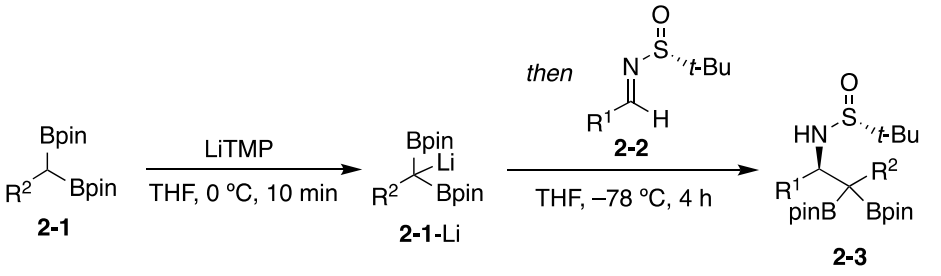
IR (cast film, cm^{-1}): 2979, 1610, 1361,1089.

HRMS (ESI-TOF) for $C_{17}H_{27}BNO_3S$ $(M + H)^+$: *calcd.*: 336.1805; *found*: 336.1799.

$[\alpha]_D^{20}$: –35.4 (*c* 0.64, $CHCl_3$).

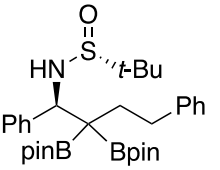
mp: 119.1–122.0 ºC.

2.10.3 General Procedure for the Synthesis of β-Sulfinimido *gem*-Bis(boronates)



A flame-dried round-bottomed flask was charged with a 1.0 M solution of TMP (1.2 equiv) in THF under N_2. The rapidly stirred solution was cooled to 0 ºC, followed by dropwise addition of *n*-BuLi (2.5 M in hexanes, 1.1 equiv). The reaction mixture was stirred at 0 ºC for 30 min, a 1.0 M solution of 1,1-diborylalkane (1.1 equiv) in THF was added via syringe, and the reaction mixture was allowed to stir at 0 ºC for 10 min. The reaction mixture was cooled to –78 ºC, a 0.50 M solution of *N*-*tert*-butanesulfinyl aldimine (1.0 equiv) in THF was added, and the reaction mixture was allowed to stir at –78 ºC for another 4 h. Upon completion, the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl or an aqueous solution of HCl (1 N) at –78 ºC. The cooling bath was removed, and the aqueous mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The diastereomeric ratio was determined by ^1H NMR analysis of the crude reaction mixture. The crude mixture was purified by flash silica gel chromatography to yield the desired β-sulfinimido *gem*-bis(boronates).

2.10.4 Full Characterization of β-Sulfinimido *gem*-Bis(boronates)



(*R*)-*N*-((*S*)-1,4-Diphenyl-2,2-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl)-2-methylpropane-2-sulfinamide (2-3a): Prepared by following the general procedure with TMP (0.42 mL, 2.4 mmol, 1.2 equiv), *n*-BuLi (2.5 M in hexanes, 0.88 mL, 1.1 equiv), 1,1-diborylalkane **2-1a** (0.82 g, 2.2 mmol, 1.1 equiv) and *N*-*tert*-butanesulfinyl aldimine **2-2a** (0.42 g, 2.0 mmol, 1.0 equiv). The reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl (10 mL). The crude mixture was purified by flash silica gel chromatography (3:1 to 2:1 hexanes/EtOAc) and isolated as a white solid (1.1 g, 91%). ^{1}H NMR analysis of the crude mixture indicated >20:1 diastereoselectivity.

^{1}H NMR (400 MHz, acetone-d_6) δ 7.51–7.46 (m, 2H), 7.35–7.30 (m, 2H), 7.27–7.23 (m, 1H), 7.23–7.18 (m, 2H), 7.13–7.06 (m, 3H), 5.08 (d, J = 2.3 Hz, 1H), 4.83 (d, J = 2.2 Hz, 1H), 2.79–2.73 (comp m, AB part of ABMX, 2H), 1.78 (comp m, M part of ABMX, 1H), 1.56 (comp m, X part of ABMX, 1H), 1.32 (s, 6H), 1.31 (app s, 12H), 1.26 (s, 6H), 1.18 (s, 9H).

^{13}C NMR (101 MHz, acetone-d_6) δ 144.5, 142.2, 130.1, 129.1, 129.0, 128.6, 128.2, 126.3, 84.6, 84.5, 60.6, 55.4, 35.7, 33.5, 25.6, 25.5, 25.14, 25.07, 23.0.

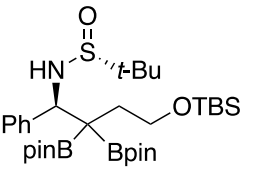
^{11}B NMR (128 MHz, acetone-d_6) δ 34.0.

IR (cast film, cm^{-1}): 3284, 3062, 2978, 1603, 1317, 1137.

HRMS (ESI-TOF) for $C_{32}H_{50}B_2NO_5S$ $(M + H)^+$: *calcd.*: 582.3590; *found*: 582.3615.

mp: 50.1–52.9 ºC.

$[\alpha]_D^{20}$: –51.6 (*c* 0.62, $CHCl_3$).



(*R*)-*N*-((*S*)-4-((*tert*-Butyldimethylsilyl)oxy)-1-phenyl-2,2-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl)-2-methylpropane-2-sulfinamide (2-3b): Prepared by following the general procedure with TMP (0.42 mL, 2.4 mmol, 1.2 equiv), *n*-BuLi (2.5 M in hexanes, 0.88 mL, 1.1 equiv), 1,1-diborylalkane **2-1b** (0.94 g, 2.2 mmol, 1.1 equiv), and *N*-*tert*-butanesulfinyl aldimine **2-2a** (0.42 g, 2.0 mmol, 1.0 equiv). The reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl (10 mL). The crude mixture was purified by flash silica gel chromatography (3:1 to 2:1 hexanes/EtOAc) and isolated as a white solid (0.99 g, 78%). ^{1}H NMR analysis of the crude mixture indicated >20:1 diastereoselectivity.

^{1}H NMR (500 MHz, CD_3CN) δ 7.38–7.35 (m, 2H), 7.34–7.30 (m, 2H), 7.30–7.26 (m, 1H), 4.84 (d, *J* = 2.0 Hz, 1H), 4.65 (d, *J* = 1.9 Hz, 1H), 3.82 (ddd, *J* = 11.7, 9.7, 5.4 Hz, 1H), 3.61 (ddd, *J* = 11.8, 9.7, 4.9 Hz, 1H), 1.64 (ddd, *J* = 13.5, 11.8, 5.4 Hz, 1H), 1.53 (ddd, *J* = 13.5, 11.7, 4.9 Hz, 1H), 1.27 (app d, *J* = 6.4 Hz, 12H), 1.24 (s, 6H), 1.16 (app s, 15H), 0.87 (s, 9H), 0.02 (app d, *J* = 3.4 Hz, 6H).

^{13}C NMR (125 MHz, CD_3CN) δ 141.3, 130.2, 128.8, 128.6, 84.9, 84.8, 63.8, 60.4, 55.6, 33.3, 26.4, 25.5, 25.4, 25.2, 25.1, 23.0, 18.9, -4.88, -4.89.

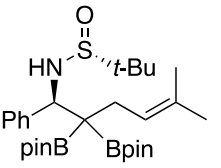
^{11}B NMR (160 MHz, CD_3CN) δ 33.2.

IR (cast film, cm^{-1}): 3279, 3031, 2978, 1495, 1472, 1321, 1138, 1073.

HRMS (ESI-TOF) for $C_{32}H_{60}B_2NO_6SSi$ $(M + H)^+$: *calcd.*: 636.4091; *found*: 636.4111.

mp: 85.6–87.2 ºC.

$[\alpha]_D^{20}$: –60.9 (*c* 0.73, $CHCl_3$).



(*R*)-2-Methyl-*N*-((*S*)-5-methyl-1-phenyl-2,2-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-4-en-1-yl)propane-2-sulfinamide (2-3c): Prepared by following the general procedure with TMP (0.42 mL, 2.4 mmol, 1.2 equiv), *n*-BuLi (2.5 M in hexanes, 0.88 mL, 1.1

equiv), 1,1-diborylalkane **2-1c** (0.82 g, 2.2 mmol, 1.1 equiv), and *N*-*tert*-butanesulfinyl aldimine **2-2a** (0.42 g, 2.0 mmol, 1.0 equiv). The reaction mixture was quenched by the addition of a saturated aqueous solution of NH_4Cl (10 mL), purified by flash silica gel chromatography (3:1 to 2:1 hexanes/EtOAc), and isolated as a white solid (0.98 g, 90%). ^{1}H NMR analysis of the crude mixture indicated >20:1 diastereoselectivity.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 6.6 Hz, 2H), 7.25–7.16 (m, 3H), 5.25 (app t, *J* = 7.1 Hz, 1H), 5.15 (d, *J* = 2.1 Hz, 1H), 4.80 (d, *J* = 2.1 Hz, 1H), 2.30 (dd, *J* = 15.6, 6.6 Hz, 1H), 1.96 (dd, *J* = 15.5, 7.4 Hz, 1H), 1.66 (s, 3H), 1.47 (s, 3H), 1.25 (d, *J* = 5.7 Hz, 18H), 1.19 (d, *J* = 2.7 Hz, 15H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.9, 131.3, 129.4, 127.6, 127.2, 124.5, 83.6, 83.4, 59.6, 55.4, 27.6, 26.2, 25.1, 25.0, 24.9, 24.7, 22.8, 18.1.

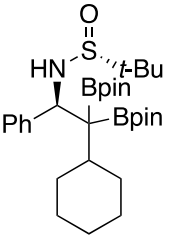
^{11}B NMR (128 MHz, $CDCl_3$) δ 33.7.

IR (cast film, cm^{-1}): 3287, 3031, 2978, 1476, 1454, 1317, 1138.

HRMS (ESI-TOF) for $C_{29}H_{50}B_2NO_5S$ $(M + H)^+$: *calcd.*: 546.3590; *found*: 546.3605.

mp: 128.3–130.0 ºC.

$[\alpha]_D^{20}$: –83.9 (*c* 0.82, $CHCl_3$).



(*R*)-*N*-((*S*)-2-Cyclohexyl-1-phenyl-2,2-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)-2-methylpropane-2-sulfinamide (2-3d): Prepared by following the general procedure with TMP (0.21 mL, 1.2 mmol, 1.2 equiv), *n*-BuLi (2.5 M in hexanes, 0.44 mL, 1.1 equiv), 1,1-diborylalkane **2-1d** (0.39 g, 1.1 mmol, 1.1 equiv), and *N*-*tert*-butanesulfinyl aldimine **2-2a** (0.21 g, 1.0 mmol, 1.0 equiv). The reaction was quenched by the addition of a saturared aqueous solution of NH_4Cl (5 mL). The crude mixture was purified by flash silica gel chromatography (3:1 to 2:1 hexanes/EtOAc) and isolated as a white solid (0.48 g, 85%). ^{1}H NMR analysis of the crude mixture indicated >20:1 diastereoselectivity.

^{1}H NMR (500 MHz, CD_3CN) δ 7.45–7.42 (m, 2H), 7.32–7.24 (m, 3H), 5.10 (d, *J* = 3.0 Hz, 1H), 4.66 (d, *J* = 3.0 Hz, 1H), 1.89–1.80 (m, 2H), 1.62–1.56 (m, 2H), 1.53–1.51 (m, 1H),

1.48–1.38 (m, 1H), 1.29 (app d, J = 3.5 Hz, 12H), 1.25 (app d, J = 3.9 Hz, 12H), 1.10 (s, 9H), 1.07–0.88 (m, 5H).

^{13}C NMR (126 MHz, CD_3CN) δ 142.4, 130.8, 128.5, 128.3, 84.4, 84.3, 60.8, 55.6, 40.9, 32.0, 31.7, 28.2, 27.9, 27.5, 25.8, 25.4, 25.3, 25.2, 23.0.

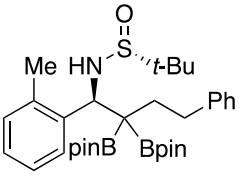
^{11}B NMR (160 MHz, CD_3CN) δ 33.6.

IR (cast film, cm^{-1}): 3278, 2978, 1495, 1453, 1372, 1137.

HRMS (ESI-TOF) for $C_{30}H_{52}B_2NO_5S$ $(M + H)^+$: *calcd.*: 560.3769; *found*: 560.3747.

mp: 143.2–145.3 ºC.

$[\alpha]_D^{20}$: –48.9 (*c* 0.57, $CHCl_3$).



(*R*)-2-Methyl-*N*-((*S*)-4-phenyl-2,2-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(o-tolyl)butyl)propane-2-sulfinamide (2-3e): Prepared by following the general procedure with TMP (0.21 mL, 1.2 mmol, 1.2 equiv), *n*-BuLi (2.5 M in hexanes, 0.44 mL, 1.1 equiv), 1,1-diborylalkane **2-1a** (0.41 g, 1.1 mmol, 1.1 equiv), and *N*-*tert*-butanesulfinyl aldimine **2-2b** (0.22 g, 1.0 mmol, 1.0 equiv). The reaction mixture was quenched by the addition of an aqueous solution of HCl (1 N, 5 mL). The crude mixture was purified by flash silica gel chromatography (3:1 to 2:1 hexanes/EtOAc) and isolated as a white solid (0.58 g, 98%). ^{1}H NMR analysis of the crude mixture indicated >20:1 diastereoselectivity.

^{1}H NMR (500 MHz, acetone-d_6) δ 7.65–7.59 (m, 1H), 7.30–7.26 (m, 2H), 7.25–7.17 (m, 4H), 7.15–7.10 (m, 2H), 5.14 (d, J = 3.6 Hz, 1H), 5.11 (d, J = 3.5 Hz, 1H), 2.74 (comp m, AB part of ABMX, 2H), 1.97 (app td, J = 13.2, 5.0 Hz, 1H), 1.75 (app td, J = 13.1, 4.7 Hz, 1H), 1.41 – 1.36 (m, 24H), 1.19 (s, 9H).

^{13}C NMR (126 MHz, acetone-d_6) δ 144.5, 141.2, 137.8, 131.0, 130.0, 129.1, 129.0, 127.8, 126.5, 126.4, 84.6, 84.3, 55.9, 55.4, 35.5, 34.4, 25.5, 25.4, 25.2, 25.0, 22.9, 20.5.

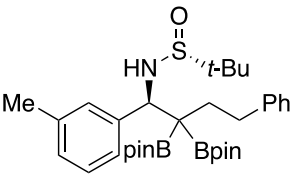
^{11}B NMR (128 MHz, acetone-d_6) δ 33.7.

IR (cast film, cm^{-1}): 3296, 3025, 2978, 1604, 1314, 1138.

HRMS (ESI-TOF) for $C_{33}H_{51}B_2NNaO_5S$ $(M + Na)^+$: *calcd.*: 618.3566; *found*: 618.3566.

mp: 128.1–130.5 ºC.

[α]$_D^{20}$: –50.0 (*c* 0.63, $CHCl_3$).



(*R*)-2-Methyl-*N*-((*S*)-4-phenyl-2,2-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(m-tolyl)butyl)propane-2-sulfinamide (2-3f): Prepared by following the general procedure with TMP (0.11 mL, 0.60 mmol, 1.2 equiv), *n*-BuLi (2.5 M in hexanes, 0.22 mL, 1.1 equiv), 1,1-diborylalkane **2-1a** (0.21 g, 0.55 mmol, 1.1 equiv), and *N*-*tert*-butanesulfinyl aldimine **2-2c** (0.11g, 0.50 mmol, 1.0 equiv). The reaction mixture was quenched by addition of an aqueous solution of HCl (1.0 N, 2.5 mL).. The crude mixture was purified by flash silica gel chromatography (3:1 to 2:1 hexanes/EtOAc) and isolated as a white solid (0.24 g, 80%). ^{1}H NMR analysis of the crude mixture indicated >20:1 diastereoselectivity.

^{1}H NMR (400 MHz, acetone-d_6) δ 7.31–7.26 (m, 2H), 7.24–7.18 (m, 3H), 7.13–7.04 (m, 4H), 5.06 (d, *J* = 2.1 Hz, 1H), 4.80 (d, *J* = 2.1 Hz, 1H), 2.76 (comp m, AB part ABMX, 2H), 2.31 (s, 3H), 1.78 (comp m, M part of ABMX, 1H), 1.56 (comp m, X part of ABMX, 1H), 1.33 (s, 6H), 1.31 (app s, 12H), 1.26 (s, 6H), 1.18 (s, 9H).

^{13}C NMR (101 MHz, acetone-d_6) δ 144.6, 142.1, 137.8, 130.6, 129.07, 128.97, 128.8, 128.5, 127.2, 126.3, 84.5, 84.4, 60.5, 55.4, 35.7, 33.5, 25.6 (×2), 25.2, 25.1, 23.0, 21.5.

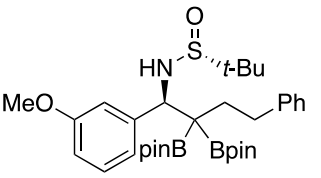
^{11}B NMR (128 MHz, acetone-d_6) δ 32.9.

IR (cast film, cm^{-1}): 3283, 3025, 2979, 1605, 1372, 1367.

HRMS (ESI-TOF) for $C_{33}H_{51}B_2NNaO_5S$ $(M + Na)^+$: *calcd.*: 618.3566; *found*: 618.3567.

mp: 52.9–55.8 ºC.

[α]$_D^{20}$: –60.0 (*c* 0.66, $CHCl_3$).



(*R*)-*N*-((*S*)-1-(3-Methoxyphenyl)-4-phenyl-2,2-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl)-2-methylpropane-2-sulfinamide (2-3g): Prepared by following the general procedure with TMP (0.11 mL, 0.60 mmol, 1.2 equiv), *n*-BuLi (2.5 M in hexanes, 0.22 mL, 1.1 equiv), 1,1-diborylalkane **2-1a** (0.21 g, 0.55 mmol, 1.1 equiv), and *N*-*tert*-butanesulfinyl aldimine **2-2d** (0.12 g, 0.50 mmol, 1.0 equiv). The reaction mixture was quenched by addition of an aqueous solution of HCl (1 N, 5 mL). The crude mixture was purified by flash silica gel chromatography (3:1 to 2:1 hexanes/EtOAc) and isolated as a white solid (0.24 g, 78%). ^{1}H NMR analysis of the crude mixture indicated >20:1 diastereoselectivity.

^{1}H NMR (400 MHz, CD_3CN) δ 7.28–7.20 (m, 3H), 7.16–7.11 (m, 1H), 7.08–7.05 (m, 2H), 7.05–6.99 (m, 2H), 6.86–6.83 (m, 1H), 4.99 (d, J = 2.0 Hz, 1H), 4.72 (d, J = 1.9 Hz, 1H), 3.76 (s, 3H), 2.71 (comp m, AB part of ABMX, 2H), 1.66 (comp m, M part of ABMX, 1H), 1.47 (comp m, X part of ABMX, 1H), 1.28 (app d, J = 1.5 Hz, 12H), 1.27 (s, 6H), 1.23 (s, 6H), 1.18 (s, 9H).

^{13}C NMR (101 MHz, CD_3CN) δ 160.5, 144.6, 143.6, 130.0, 129.4, 129.0, 126.6, 122.6, 116.0, 113.6, 84.9, 84.8, 60.5, 55.9, 55.8, 35.7, 33.7, 25.65, 25.58, 25.2, 25.0, 23.0.

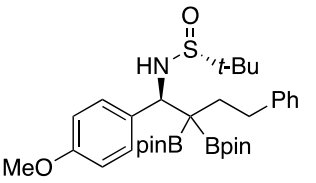
^{11}B NMR (128 MHz, CD_3CN) δ 33.0.

IR (cast film, cm^{-1}): 3282, 3025, 2978, 1601, 1488, 1456, 1315, 1137.

HRMS (ESI-TOF) for $C_{33}H_{51}B_2NNaO_6S$ $(M + Na)^+$: *calcd.*: 634.3516; *found*: 634.3515.

mp: 132.7–134.6 ºC.

$[\alpha]_D^{20}$: –63.8 (*c* 0.52, $CHCl_3$).



(*R*)-*N*-((*S*)-1-(4-Methoxyphenyl)-4-phenyl-2,2-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl)-2-methylpropane-2-sulfinamide (2-3h): Prepared by following the general procedure with TMP (0.21 mL, 1.2 mmol, 1.2 equiv), *n*-BuLi (2.5 M in hexanes, 0.44 mL, 1.1 equiv), 1,1-diborylalkane **2-1a** (0.41 g, 1.1 mmol, 1.1 equiv), and *N*-*tert*-butanesulfinyl aldimine **2-2e** (0.24 g, 1.0 mmol, 1.0 equiv). The reaction mixture was quenched by addition of a saturated aqueous solution of NH_4Cl (5 mL). The crude mixture was purified by flash silica gel chromatography (3:1 to 2:1 hexanes/EtOAc) and isolated as a white solid (0.59 g, 96%). ^{1}H NMR analysis of the crude mixture indicated >20:1 diastereoselectivity.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.31 (m, 2H), 7.23–7.18 (m, 2H), 7.14–7.10 (m, 1H), 7.10–7.06 (m, 2H), 6.85–6.77 (m, 2H), 5.12 (d, J = 2.3 Hz, 1H), 4.86 (d, J = 2.2 Hz, 1H), 3.78 (s, 3H), 2.68 (comp m, AB part of ABMX, 2H), 1.84 (comp m, M part of ABMX, 1H), 1.57 (comp m, X part of ABMX, 1H), 1.28 (app s, 18H), 1.24 (s, 6H), 1.20 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.9, 143.6, 132.9, 130.4, 128.4, 127.9, 125.5, 113.2, 83.7, 83.5, 59.1, 55.24, 55.19, 34.9, 32.0, 25.22, 25.19, 24.9, 24.8, 22.8.

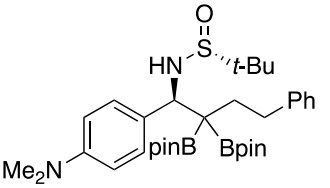
^{11}B NMR (128 MHz, $CDCl_3$) δ 32.8.

IR (cast film, cm^{-1}): 3283, 3026, 2978, 1611, 1513, 1456, 1316, 1137.

HRMS (ESI-TOF) for $C_{33}H_{51}B_2NNaO_6S$ $(M + Na)^+$: *calcd.*: 634.3528; *found*: 634.3515.

mp: 148.6–150.2 ºC;

$[\alpha]_D^{20}$: –59.0 (*c* 0.58, $CHCl_3$).



(*R*)-*N*-((*S*)-1-(4-(Dimethylamino)phenyl)-4-phenyl-2,2-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl)-2-methylpropane-2-sulfinamide (2-3i): Prepared by following the general procedure with TMP (0.11 mL, 0.60 mmol, 1.2 equiv), *n*-BuLi (2.5 M in hexanes,

0.22 mL, 1.1 equiv), 1,1-diborylalkane **2-1a** (0.21 g, 0.55 mmol, 1.1 equiv), and *N-tert*-butanesulfinyl aldimine **2-2f** (0.13 g, 0.50 mmol, 1.0 equiv). The reaction was quenched by the addition of an aqueous solution of HCl (1.0 N, 2.5 mL). and washed with saturated sodium bicarbonate solution (5 mL). The crude mixture was purified by flash silica gel chromatography (2:1 to 1:1 hexanes/EtOAc) and isolated as a white solid (0.31 g, 98%). ^{1}H NMR analysis of the crude mixture indicated >20:1 diastereoselectivity.

^{1}H NMR (500 MHz, CD_3CN) δ 7.27–7.21 (m, 4H), 7.16–7.11 (m, 1H), 7.09–7.06 (m, 2H), 6.73–6.68 (m, 2H), 4.94 (d, J = 1.9 Hz, 1H), 4.65 (d, J = 2.0 Hz, 1H), 2.91 (s, 6H), 2.71 (comp m, AB part of ABMX, 2H), 1.67 (comp m, M part of ABMX, 1H), 1.45 (comp m, X part of ABMX, 1H), 1.28 (app d, J = 3.9 Hz, 18H), 1.23 (s, 6H), 1.17 (s, 9H).

^{13}C NMR (126 MHz, CD_3CN) δ 151.3, 144.8, 130.9, 129.3, 129.0, 128.7, 126.5, 112.6, 84.8, 84.7, 59.9, 55.4, 40.7, 35.8, 33.7, 25.62, 25.56, 25.2, 25.0, 23.1.

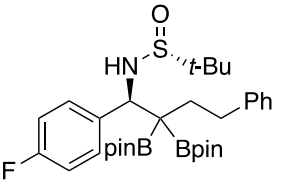
^{11}B NMR (128 MHz, CD_3CN) δ 33.4.

IR (cast film, cm^{-1}): 3284, 3026, 2978, 1615, 1523, 1318, 1137.

HRMS (ESI-TOF) for $C_{34}H_{54}B_2N_2NaO_5S$ $(M + Na)^+$: *calcd.*: 647.3831; *found*: 647.3832.

mp: 152.8–153.5 ºC.

$[\alpha]_D^{20}$: –41.9 (*c* 0.60, $CHCl_3$).



(*R*)-*N*-((*S*)-1-(4-Fluorophenyl)-4-phenyl-2,2-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl)-2-methylpropane-2-sulfinamide (2-3j): Prepared by following the general procedure with TMP (0.21 mL, 1.2 mmol, 1.2 equiv), *n*-BuLi (2.5 M in hexanes, 0.44 mL, 1.1 equiv), 1,1-diborylalkane **2-1a** (0.41 g, 1.1 mmol, 1.1 equiv), and *N-tert*-butanesulfinyl aldimine **2-2g** (0.23 g, 1.0 mmol, 1.0 equiv). The reaction mixture was quenched by the addition of a saturated aqueous solution of NH_4Cl (5 mL). The crude mixture was purified by flash silica gel chromatography (3:1 to 2:1 hexanes/EtOAc) and isolated as a white solid (0.49 g, 82%). ^{1}H NMR analysis of the crude mixture indicated >20:1 diastereoselectivity.

^{1}H NMR (500 MHz, acetone-d_6) δ 7.64–7.59 (m, 2H), 7.33–7.28 (m, 2H), 7.22–7.18 (m, 5H), 5.16 (d, J = 2.2 Hz, 1H), 4.92 (d, J = 2.1 Hz, 1H), 2.87–2.82 (comp m, AB part of ABMX,

2H), 1.88 (comp m, M part of ABMX, 1H), 1.65 (comp m, X part of ABMX, 1H), 1.41 (s, 6H), 1.40 (app s, 12H), 1.35 (s, 6H), 1.27 (s, 9H).

^{13}C NMR (126 MHz, acetone-d_6) δ 162.9 (d, J = 243.8 Hz), 144.4, 138.1 (d, J = 2.5 Hz), 131.9 (d, J = 8.8 Hz), 129.1, 129.0, 126.4, 115.2 (d, J = 20.1 Hz), 84.6, 84.5, 59.7, 55.4, 35.6, 33.4, 25.54, 25.50, 25.1, 25.0, 22.9.

^{11}B NMR (160 MHz, acetone-d_6) δ 33.1.

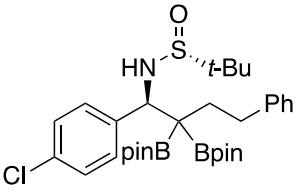
^{19}F NMR (469 MHz, acetone-*d6*) δ -116.8.

IR (cast film, cm^{-1}): 3282, 3025, 2979, 1604, 1510, 1317, 1136.

HRMS (ESI-TOF) for $C_{32}H_{48}B_2FNNaO_5S$ $(M + Na)^+$: *calcd.*: 622.3326; *found*: 622.3316.

mp: 54.5–57.5 ºC.

$[\alpha]_D^{20}$: –53.3 (*c* 0.50, $CHCl_3$).



(*R*)-*N*-((*S*)-1-(4-Chlorophenyl)-4-phenyl-2,2-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl)-2-methylpropane-2-sulfinamide (2-3k): Prepared by following the general procedure with TMP (0.11 mL, 0.60 mmol, 1.2 equiv), *n*-BuLi (2.5 M in hexanes, 0.22 mL, 1.1 equiv), 1,1-diborylalkane **2-1a** (0.21 g, 0.55 mmol, 1.1 equiv), and *N*-*tert*-butanesulfinyl aldimine **2-2h** (0.12 g, 0.50 mmol, 1.0 equiv). The reaction mixture was quenched by the addition of an aqueous solution of HCl (1.0 N, 2.5 mL). The crude mixture was purified by flash silica gel chromatography (3:1 to 2:1 hexanes/EtOAc) and isolated as a white solid (0.26 g, 84%). ^{1}H NMR analysis of the crude mixture indicated >20:1 diastereoselectivity.

^{1}H NMR (400 MHz, acetone-d_6) δ 7.53–7.49 (m, 2H), 7.40–7.35 (m, 2H), 7.24–7.19 (m, 2H), 7.14–7.08 (m, 3H), 5.09 (d, J = 2.1 Hz, 1H), 4.82 (d, J = 2.1 Hz, 1H), 2.79–2.71 (comp m, AB part of ABMX, 2H), 1.78 (comp m, M part of ABMX, 1H), 1.56 (comp m, X part of ABMX, 1H), 1.32 (s, 6H), 1.31 (app s, 12H), 1.27 (s, 6H), 1.18 (s, 9H).

^{13}C NMR (101 MHz, acetone-d_6) δ 144.4, 141.1, 133.4, 131.8, 129.1, 129.0, 128.6, 126.4, 84.7, 84.6, 59.8, 55.5, 35.6, 33.4, 25.53, 25.50, 25.2, 25.0, 22.9.

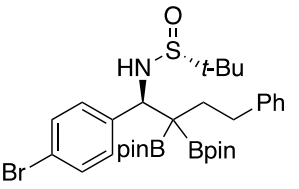
^{11}B NMR (128 MHz, acetone-d_6) δ 32.8.

IR (cast film, cm^{-1}): 3281, 3025, 2979, 1600, 1491, 1455, 1318, 1136.

HRMS (ESI-TOF) for $C_{32}H_{48}B_2ClNNaO_5S$ $(M + Na)^+$: *calcd.*: 638.3020; *found*: 645.3022.

mp: 62.0–64.3 ºC.

$[\alpha]_D^{20}$: –61.3 (*c* 0.82, $CHCl_3$).



(*R*)-*N*-((*S*)-1-(4-Bromophenyl)-4-phenyl-2,2-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl)-2-methylpropane-2-sulfinamide (2-3l): Prepared by following the general procedure with TMP (0.11 mL, 0.60 mmol, 1.2 equiv), *n*-BuLi (2.5 M in hexanes, 0.22 mL, 1.1 equiv), 1,1-diborylalkane **2-1a** (0.21 g, 0.55 mmol, 1.1 equiv), and *N*-*tert*-butanesulfinyl aldimine **2-2i** (0.14 g, 0.50 mmol, 1.0 equiv). The reaction mixture was quenched by the addition of an aqueous solution of HCl (1.0 N, 2.5 mL). The crude mixture was purified by flash silica gel chromatography (3:1 to 2:1 hexanes/EtOAc) and isolated as a white solid (0.30 g, 91%). ^{1}H NMR analysis of the crude mixture indicated >20:1 diastereoselectivity.

^{1}H NMR (500 MHz, acetone-d_6) δ 7.56–7.52 (m, 2H), 7.48–7.44 (m, 2H), 7.24–7.21 (m, 2H), 7.15–7.10 (m, 3H), 5.10 (d, J = 2.0 Hz, 1H), 4.82 (d, J = 2.0 Hz, 1H), 2.77 (comp m, AB part of ABMX, 2H), 1.78 (comp m, M part of ABMX, 1H), 1.56 (comp m, X part of ABMX, 1H), 1.33 (s, 6H), 1.32 (app s, 12H), 1.28 (s, 6H), 1.19 (s, 9H).

^{13}C NMR (126 MHz, acetone-d_6) δ 144.4, 141.6, 132.2, 131.7, 129.1, 129.0, 126.4, 121.6, 84.7, 84.6, 59.9, 55.6, 35.7, 33.4, 25.6, 25.5, 25.2, 25.1, 22.30.

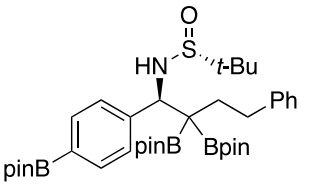
^{11}B NMR (160 MHz, acetone-d_6) δ 33.4.

IR (cast film, cm^{-1}): 3281, 3025, 2979, 1603, 1486, 1455, 1319, 1137.

HRMS (ESI-TOF) for $C_{32}H_{48}B_2BrNNaO_5S$ $(M + Na)^+$: *calcd.*: 682.2529; *found*: 682.2515.

mp: 52.2–54.9 ºC.

$[\alpha]_D^{20}$: –54.9 (*c* 0.73, $CHCl_3$).



(*R*)-2-Methyl-*N*-((*S*)-4-phenyl-2,2-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)butyl)propane-2-sulfinamide (2-3m): Prepared by following the general procedure with TMP (0.11 mL, 0.60 mmol, 1.2 equiv), *n*-BuLi (2.5 M in hexanes, 0.22 mL, 1.1 equiv), 1,1-diborylalkane **2-1a** (0.21 g, 0.55 mmol, 1.1 equiv), and *N*-*tert*-butanesulfinyl aldimine **2-2j** (0.17 g, 0.50 mmol, 1.0 equiv). The reaction was quenched by the addition of an aqueous solution of HCl (1.0 N, 2.5 mL). The crude mixture was purified by flash silica gel chromatography (3:1 to 2:1 hexanes/EtOAc) and isolated as a white solid (0.32 g, 90%). ^{1}H NMR analysis of the crude mixture indicated >20:1 diastereoselectivity.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 8.1 Hz, 2H), 7.22–7.17 (m, 2H), 7.13–7.09 (m, 1H), 7.09–7.05 (m, 2H), 5.17 (d, *J* = 2.4 Hz, 1H), 4.90 (d, *J* = 2.3 Hz, 1H), 2.69 (comp m, AB part of ABMX, 2H), 1.79 (app td, *J* = 13.7, 5.1 Hz, 1H), 1.52 (ddd, *J* = 13.9, 12.4, 5.1 Hz, 1H), 1.34 (app d, *J* = 1.5 Hz, 12H), 1.29–1.27 (m, 18H), 1.25 (s, 6H), 1.18 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.6, 143.4, 134.4, 128.5, 128.4, 128.2, 125.5, 83.8, 83.7, 83.6, 60.0, 55.4, 34.8, 32.1, 25.21, 25.17, 25.0, 24.92, 22.87 (×2), 22.8.

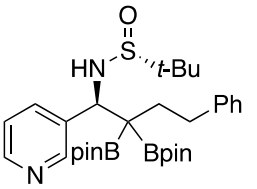
^{11}B NMR (128 MHz, $CDCl_3$) δ 34.5.

IR (cast film, cm^{-1}): 3282, 3025, 2979, 1612, 1469, 1456, 1360, 1144.

HRMS (ESI-TOF) for $C_{38}H_{60}B_3NNaO_7S$ $(M + Na)^+$: *calcd.*: 730.4262; *found*: 730.4270.

mp: 100.4–103.5 ºC.

$[\alpha]_D^{20}$: –40.7 (*c* 0.67, $CHCl_3$).



(*R*)-2-Methyl-*N*-((*S*)-4-phenyl-1-(pyridin-3-yl)-2,2-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl)propane-2-sulfinamide (2-3o): Prepared by following the general procedure with TMP (0.21 mL, 1.2 mmol, 1.2 equiv), *n*-BuLi (2.5 M in hexanes, 0.44 mL, 1.1 equiv), 1,1-diborylalkane **2-1a** (0.41 g, 1.1 mmol, 1.1 equiv), and *N*-*tert*-butanesulfinyl aldimine **2-2l** (0.21 g, 1.0 mmol, 1.0 equiv). The reaction mixture was quenched by the addition of an aqueous solution of HCl (1 N, 5 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (5 mL). The crude mixture was purified by flash silica gel chromatography (2:1 to 2:3 hexanes/EtOAc) and isolated as a light yellow solid (0.46 g, 79%). ^{1}H NMR analysis of the crude mixture indicated 10:1 diastereoselectivity.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, *J* = 1.9 Hz, 1H), 8.48 (dd, *J* = 4.8, 1.7 Hz, 1H), 7.74 (app dt, *J* = 7.9, 2.0 Hz, 1H), 7.24–7.22 (m, 3H), 7.15–7.12 (m, 1H), 7.12–7.09 (m, 2H), 5.16 (d, *J* = 2.2 Hz, 1H), 4.93 (d, *J* = 2.1 Hz, 1H), 2.70 (comp m, AB part of ABMX, 2H), 1.93–1.79 (comp m, M part of ABMX, 1H), 1.67–1.56 (comp m, X part of ABMX, 1H), 1.29–1.27 (m, 18H), 1.22 (s, 6H), 1.21 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.8, 148.7, 143.1, 136.9, 136.4, 128.3, 128.2, 125.6, 122.7, 83.9, 83.8, 57.7, 55.5, 34.9, 31.6, 25.13, 25.10, 24.8, 24.7, 22.7.

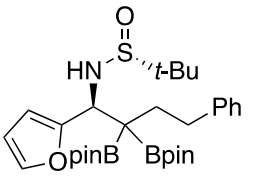
^{11}B NMR (128 MHz, $CDCl_3$) δ 34.0.

IR (cast film, cm^{-1}): 3280, 3026, 2979, 1475, 1455, 1372, 1136.

HRMS (ESI-TOF) for $C_{31}H_{49}B_2N_2O_5S$ $(M + H)^+$: *calcd.*: 583.3548; *found*: 583.3543.

mp: 165.8–167.0 ºC.

$[\alpha]_D^{20}$: –58.8 (*c* 0.64, $CHCl_3$).



(*R*)-*N*-((*S*)-1-(Furan-2-yl)-4-phenyl-2,2-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl)-2-methylpropane-2-sulfinamide (2-3p): Prepared by following the general procedure with TMP (0.11 mL, 0.60 mmol, 1.2 equiv), *n*-BuLi (2.5 M in hexanes, 0.22 mL, 1.1 equiv), 1,1-diborylalkane **2-1a** (0.21 g, 0.55 mmol, 1.1 equiv), and *N*-*tert*-butanesulfinyl aldimine **2-2m** (0.10 g, 0.50 mmol, 1.0 equiv). The reaction mixture was quenched by the addition of an aqueous solution of HCl (1.0 N, 2.5 mL). The crude mixture was purified by flash silica gel chromatography (3:1 to 2:1 hexanes/EtOAc) and isolated as a light yellow solid (0.21 g, 72%). ^{1}H NMR analysis of the crude mixture indicated >20:1 diastereoselectivity.

^{1}H NMR (400 MHz, acetone-d_6) δ 7.47 (dd, J = 1.8, 0.9 Hz, 1H), 7.23–7.18 (m, 2H), 7.14–7.05 (m, 3H), 6.39–6.38 (m, 1H), 6.36–6.35 (m, 1H), 5.14 (d, J = 4.4 Hz, 1H), 4.84 (d, J = 4.4 Hz, 1H), 2.68 (comp m, AB part of ABMX, 2H), 1.79–1.69 (comp m, M part of ABMX, 1H), 1.54–1.45 (comp m, X part of ABMX, 1H), 1.30 (app d, J = 2.8 Hz, 24H), 1.12 (s, 9H).

^{13}C NMR (101 MHz, acetone-d_6) δ 155.7, 144.5, 142.4, 129.04, 128.99, 126.3, 110.7, 109.4, 84.5, 84.3, 55.6, 55.4, 35.2, 34.4, 25.3, 25.25, 25.22, 25.0, 22.8.

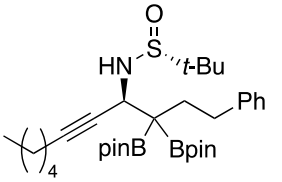
^{11}B NMR (128 MHz, acetone-d_6) δ 32.7.

IR (cast film, cm^{-1}): 3340, 3285, 3026, 2978, 1602, 1470, 1456, 1352, 1138.

HRMS (ESI-TOF) for $C_{30}H_{47}B_2NNaO_6S$ $(M + Na)^+$: *calcd.*: 594.3202; *found*: 594.3205.

mp: 138.3–139.3.

$[\alpha]_D^{20}$: –37.5 (c 0.97, $CHCl_3$).



(*R*)-2-Methyl-*N*-((*S*)-1-phenyl-3,3-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)undec-5-yn-4-yl)propane-2-sulfinamide (2-3q): Prepared by following the general procedure with TMP (0.11 mL, 0.60 mmol, 1.2 equiv), *n*-BuLi (2.5 M in hexanes, 0.22 mL, 1.1 equiv), 1,1-diborylalkane **2-1a** (0.21 g, 0.55 mmol, 1.1 equiv), and *N*-*tert*-butanesulfinyl

aldimine **2-2n** (0.11 g, 0.50 mmol, 1.0 equiv). The reaction mixture was quenched by the addition of an aqueous solution of HCl (1.0 N, 2.5 mL). The crude mixture was purified by flash silica gel chromatography (3:1 to 2:1 hexanes/EtOAc) and isolated as a yellow solid (0.27 g, 91%). ^{1}H NMR analysis of the crude mixture indicated >20:1 diastereoselectivity.

^{1}H NMR (500 MHz, CD_3CN) δ 7.27 (t, *J* = 7.5 Hz, 2H), 7.19–7.13 (m, 3H), 4.60 (d, *J* = 3.7 Hz, 1H), 4.41 (app dt, *J* = 4.2, 2.1 Hz, 1H), 2.80 (app td, *J* = 12.9, 4.9 Hz, 1H), 2.59 (app td, *J* = 12.9, 4.8 Hz, 1H), 2.21 (app td, *J* = 6.8, 2.1 Hz, 2H), 2.04 (app td, *J* = 13.3, 4.9 Hz, 1H), 1.99–1.95 (m, 1H), 1.52–1.44 (m, 2H), 1.43–1.36 (m, 2H), 1.33–1.27 (m, 2H), 1.24 (app d, *J* = 6.6 Hz, 24H), 1.19 (s, 9H), 0.86 (app t, *J* = 7.3 Hz, 3H).

^{13}C NMR (126 MHz, CD_3CN) δ 144.9, 129.3, 129.1, 126.6, 87.9, 84.8, 84.7, 79.2, 55.6, 49.8, 36.1, 33.8, 31.7, 29.2, 25.3, 25.11, 25.08, 25.0, 23.0, 22.9, 19.1, 14.3.

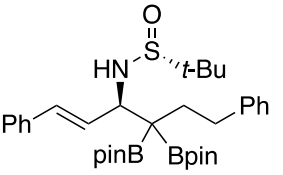
^{11}B NMR (160 MHz, CD_3CN) δ 33.1.

IR (cast film cm^{-1}): 3280, 3025, 2977, 1603, 1324, 1138.

HRMS (ESI-TOF) for $C_{33}H_{56}B_2NO_5S$ $(M + H)^+$: *calcd.*: 600.4060; *found*: 600.4064.

mp: 86.4–89.1 ºC.

$[\alpha]_D^{20}$: –43.5 (*c* 0.53, $CHCl_3$).



(*R*)-*N*-((*S*,*E*)-1,6-Diphenyl-4,4-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-1-en-3-yl)-2-methylpropane-2-sulfinamide (2-3r): Prepared by following the general procedure with TMP (0.11 mL, 0.60 mmol, 1.2 equiv), *n*-BuLi (2.5 M in hexanes, 0.22 mL, 1.1 equiv), 1,1-diborylalkane **2-1a** (0.21 g, 0.55 mmol, 1.1 equiv), and *N*-*tert*-butanesulfinyl aldimine **2-2o** (0.12 g, 0.50 mmol, 1.0 equiv). The reaction mixture was quenched by the addition of an aqueous solution of HCl (1.0 N, 2.5 mL). The crude mixture was purified by flash silica gel chromatography (3:1 to 2:1 hexanes/EtOAc) and isolated as a white solid (0.26 g, 85%). ^{1}H NMR analysis of the crude mixture indicated >20:1 diastereoselectivity.

^{1}H NMR (500 MHz, CD_3CN) δ 7.45–7.41 (m, 2H), 7.35 (t, *J* = 7.7 Hz, 2H), 7.27 (d, J = 7.3 Hz, 1H), 7.25–7.21 (m, 2H), 7.16–7.12 (m, 3H), 6.70 (d, *J* = 15.9 Hz, 1H), 6.23 (dd, *J* = 15.9, 9.3 Hz, 1H), 4.84 (d, *J* = 2.3 Hz, 1H), 4.27 (dd, *J* = 9.2, 2.3 Hz, 1H), 2.75–2.65 (comp m, AB

part of ABMX, 2H), 1.86 (comp m, M part of ABMX, 1H), 1.77 (comp m, X part of ABMX, 1H), 1.27–1.23 (m, 24H), 1.19 (s, 9H).

^{13}C NMR (126 MHz, CD_3CN) δ 144.7, 137.8, 133.8, 130.6, 129.7, 129.3, 129.1, 128.7, 127.3, 126.6, 84.7, 84.6, 59.2, 55.6, 35.5, 33.6, 25.5, 25.4, 25.09, 24.99, 23.1.

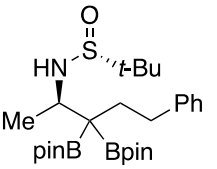
^{11}B NMR (160 MHz, CD_3CN) δ 33.4.

IR (cast film, cm^{-1}): 3283, 3028, 2978, 1601, 1357, 1138.

HRMS (ESI-TOF) for $C_{34}H_{51}B_2NNaO_5S$ $(M + Na)^+$: *calcd.*: 608.3566; *found*: 608.3570.

mp: 122.6–124.0 ºC.

$[\alpha]_D^{20}$: –73.1 (*c* 0.40, $CHCl_3$).



(*R*)-2-Methyl-*N*-((*R*)-5-phenyl-3,3-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentan-2-yl)propane-2-sulfinamide (2-3s): Prepared by following the general procedure with TMP (0.21 mL, 1.2 mmol, 1.2 equiv), *n*-BuLi (2.5 M in hexanes, 0.44 mL, 1.1 equiv), 1,1-diborylalkane **2-1a** (0.41 g, 1.1 mmol, 1.1 equiv), and *N*-*tert*-butanesulfinyl aldimine **2-2p** (0.15 g, 1.0 mmol, 1.0 equiv). The reaction mixture was quenched by the addition of a saturared aqueous solution of NH_4Cl (5 mL). The crude mixture was purified by flash silica gel chromatography (3:1 to 2:1 hexanes/EtOAc) and isolated as a white solid (0.44 g, 84%). ^{1}H NMR analysis of the crude mixture indicated >20:1 diastereoselectivity.

^{1}H NMR (400 MHz, acetone-d_6) δ 7.27–7.20 (m, 4H), 7.16–7.11 (m, 1H), 4.51 (d, J = 3.4 Hz, 1H), 3.78 (qd, J = 6.4, 3.4 Hz, 1H), 2.80–2.73 (comp m, M part of ABMX, 1H), 2.57 (app td, J = 12.4, 5.4 Hz, 1H), 1.91 (comp m, AB part of ABMX, 2H), 1.30 (d, J = 6.5 Hz, 3H), 1.27 (app s, 12H), 1.26 (app d, J = 2.4 Hz, 12H), 1.19 (s, 9H).

^{13}C NMR (101 MHz, acetone-d_6) δ 144.7, 129.13, 129.08, 126.3, 84.18, 84.15, 55.2, 51.5, 35.4, 33.1, 25.3, 25.1 (×2), 25.0, 23.0, 19.2.

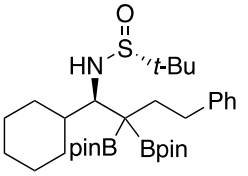
^{11}B NMR (128 MHz, acetone-d_6) δ 33.4.

IR (cast film, cm^{-1}): 3283, 3025, 2978, 1470, 1455, 1313, 1139.

HRMS (ESI-TOF) for $C_{27}H_{48}B_2NO_5S$ $(M + H)^+$: *calcd.*: 520.3440; *found*: 520.3434.

mp: 113.9–115.6 ºC.

[α]$_D^{20}$: –33.2 (*c* 0.69, $CHCl_3$).



(*R*)-*N*-((*S*)-1-Cyclohexyl-4-phenyl-2,2-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl)-2-methylpropane-2-sulfinamide (2-3t): Prepared by following the general procedure with TMP (0.11 mL, 0.60 mmol, 1.2 equiv), *n*-BuLi (2.5 M in hexanes, 0.22 mL, 1.1 equiv), 1,1-diborylalkane **2-1a** (0.21 g, 0.55 mmol, 1.1 equiv), and *N*-*tert*-butanesulfinyl aldimine **2-2q** (0.11 g, 0.50 mmol, 1.0 equiv). The reaction mixture was quenched by the addition of an aqueous solution of HCl (1.0 N, 2.5 mL). The crude mixture was purified by flash silica gel chromatography (5:1 to 4:1 hexanes/EtOAc) and isolated as a white solid (0.11 g, 86%). ^{1}H NMR analysis of the crude mixture indicated >20:1 diastereoselectivity.

^{1}H NMR (500 MHz, acetone-d_6) δ 7.28–7.23 (m, 4H), 7.15–7.12 (m, 1H), 5.00 (d, J = 6.9 Hz, 1H), 3.43 (dd, J = 6.9, 2.2 Hz, 1H), 2.93 (app td, J = 12.8, 4.9 Hz, 1H), 2.57 (app td, J = 12.8, 4.2 Hz, 1H), 1.93 (app td, J = 13.2, 4.9 Hz, 1H), 1.80 (app dd, J = 13.1, 4.3 Hz, 1H), 1.77–1.72 (m, 2H), 1.69 (app dd, J = 11.4, 2.7 Hz, 1H), 1.66–1.61 (m, 2H), 1.48–1.41 (m, 2H), 1.32–1.30 (m, 24H), 1.25 (s, 9H), 1.22–1.04 (m, 4H).

^{13}C NMR (126 MHz, acetone-d_6) δ 144.8, 129.3, 129.0, 126.3, 84.2, 83.9, 63.6, 57.0, 43.2, 35.4, 34.5, 32.8, 28.0, 27.6, 27.3, 27.0, 25.8, 25.33, 25.32, 25.2, 23.8.

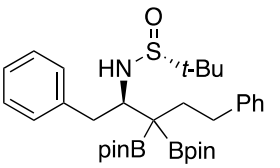
^{11}B NMR (160 MHz, acetone-d_6) δ 33.6.

IR (cast film, cm^{-1}): 3320, 3023, 2929, 1450, 1372, 1139.

HRMS (ESI-TOF) for $C_{32}H_{56}B_2NO_5S$ $(M + H)^+$: *calcd.*: 588.4068; *found*: 588.4060.

mp: 143.7–145.0 ºC.

[α]$_D^{20}$: –11.2 (*c* 0.66, $CHCl_3$).



(*R*)-*N*-((*R*)-1,5-Diphenyl-3,3-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentan-2-yl)-2-methylpropane-2-sulfinamide (2-3u): Prepared by following the general procedure with TMP (0.22 mL, 1.2 mmol, 1.2 equiv), *n*-BuLi (2.5 M in hexanes, 0.44 mL, 1.1 equiv), 1,1-diborylalkane **2-1a** (0.41 g, 1.1 mmol, 1.1 equiv), and *N*-*tert*-butanesulfinyl aldimine **2-2r** (0.22 g, 1.0 mmol, 1.0 equiv). The reaction was quenched by the addition of an aqueous solution of HCl (1 N, 5 mL). The crude mixture was purified by flash silica gel chromatography (5:1 to 4:1 hexanes/EtOAc) and isolated as a yellow solid (0.20 g, 33%). ^{1}H NMR analysis of the crude mixture indicated >20:1 diastereoselectivity.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.27 (m, 3H), 7.25–7.22 (m, 2H), 7.22–7.21 (m, 3H), 7.20–7.16 (m, 1H), 7.15–7.10 (m, 1H), 4.27 (d, *J* = 5.9 Hz, 1H), 3.97 (ddd, *J* = 9.3, 6.0, 3.1 Hz, 1H), 3.21 (dd, *J* = 14.1, 3.0 Hz, 1H). 2.89–2.79 (comp m, 2H), 2.55 (app td, *J* = 12.7, 4.5 Hz, 1H), 2.04 (comp m, AB part of ABMX, 2H), 1.30 (app d, *J* = 1.6 Hz, 12H), 1.27 (app s, 12H), 1.00 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.7, 140.9, 129.9, 128.7, 128.17, 128.16, 125.9, 125.4, 83.4 (×2), 59.2, 55.9, 42.7, 34.0, 32.8, 25.01, 25.00, 24.97, 24.9, 22.9.

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.4.

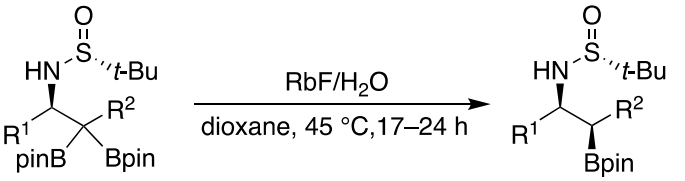
IR (cast film, cm^{-1}): 3315, 3026, 2978, 1603, 1496, 1455, 1372, 1138.

HRMS (ESI-TOF) for $C_{33}H_{51}B_2NNaO_5S$ $(M + Na)^+$: *calcd.*: 618.3566; *found*: 618.3560.

mp: 49.0–51.0 ºC.

$[\alpha]_D^{20}$: –16.0 (*c* 0.58, $CHCl_3$).

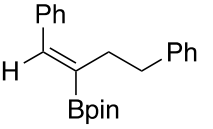
2.10.5 General Procedure for the Monoprotodeboronation of β-Sulfinimido *gem*-Bis(boronates)



2-3 **2-4**

To a reaction tube was added RbF (1.1 equiv), β-sulfinimido *gem*-bis(boronates) (1.0 equiv), water (1.1 equiv), and dioxane. The resulting reaction mixture was stirred at 45 ºC for 17–24 h. Upon completion, Et_2O (5 mL) was added, and the reaction mixture was filtered through a short pad of Celite, washed with Et_2O, and concentrated under reduced pressure. The diastereomeric ratio was determined by ^{1}H NMR analysis of the crude mixture. The crude mixture was purified by flash column chromatography to yield the desired β-amino alkylboronates **2-4**.

2.10.6 Characterization of Elimination Side Product 2-5



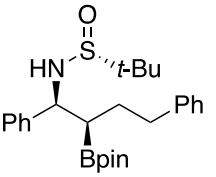
(*Z*)-2-(1,4-Diphenylbut-1-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**2-5**): Isolated as a colorless oil from the crude reaction mixture of monoprotodeboronation of β-sulfinimido *gem*-bis(boronate) **2-3a**.

^{1}H NMR (498 MHz, $CDCl_3$) δ 7.33–7.29 (m, 2H), 7.27–7.25 (m, 3H), 7.25–7.24 (m, 1H), 7.25–7.21 (m, 2H), 7.20–7.14 (m, 3H), 2.79 (dd, *J* = 9.9, 6.0 Hz, 2H), 2.69 (dd, *J* = 9.9, 6.2 Hz, 2H), 1.31 (s, 12H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 142.7, 142.5, 137.9, 128.9, 128.6, 128.25, 128.15, 127.1, 125.7, 83.5, 36.1, 31.4, 29.8, 24.9;

The spectral data is identical to the known compound.[90]

2.10.7 Full Characterization of β-Aminoalkylboronates



(*R*)-*N*-((1*S*,2*R*)-1,4-Diphenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl)-2-methylpropane-2-sulfinamide (2-4a): Prepared by following the general procedure with RbF (0.12 g, 1.1 mmol, 1.1 equiv), β-sulfinimido *gem*-bis(boronate) **2-3a** (0.58 g, 1.0 mmol, 1.0 equiv), water (20 μL, 1.1 mmol, 1.1 equiv), and dioxane (10 mL). The crude mixture was purified by flash silica gel chromatography (3:1 to 2:1 hexanes/EtOAc) and isolated as a colorless oil (0.40 g, 87%). ^{1}H NMR analysis of the crude mixture indicated >20:1 diastereoselectivity and 13% of elimination side product.

^{1}H NMR (500 MHz, CD_3CN) δ 7.33–7.28 (m, 4H), 7.27–7.22 (m, 3H), 7.17–7.13 (m, 1H), 7.12–7.09 (m, 2H), 4.60 (d, *J* = 3.8 Hz, 1H), 4.41 (dd, *J* = 7.1, 3.9 Hz, 1H), 2.68–2.62 (comp m, A part of ABMX, 1H), 2.59–2.53 (m, B part of ABMX, 1H), 1.61 (app q, *J* = 7.9 Hz, 2H), 1.45 (app q, *J* = 7.1 Hz, 1H), 1.28 (s, 6H), 1.26 (s, 6H), 1.14 (s, 9H).

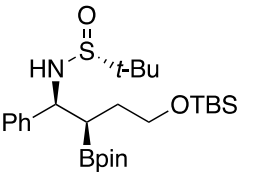
^{13}C NMR (126 MHz, CD_3CN) δ 144.3, 143.4, 129.28, 129.26, 129.2, 128.5, 128.2, 126.7, 84.9, 60.8, 55.9, 35.5, 31.5, 25.4, 25.2, 22.9.

^{11}B NMR (160 MHz, CD_3CN) δ 33.4.

IR (cast film cm^{-1}): 3282, 3026, 2978, 1603, 1381, 1168.

HRMS (ESI-TOF) for $C_{26}H_{38}BNO_3S$ $(M + H)^+$: *calcd.*: 456.2743; *found*: 456.2738.

$[\alpha]_D^{20}$: –56.6 (*c* 0.52, $CHCl_3$).



(*R*)-*N*-((1*S*,2*R*)-4-((*tert*-Butyldimethylsilyl)oxy)-1-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl)-2-methylpropane-2-sulfinamide (2-4b): Prepared by following the general procedure with RbF (58 mg, 0.55 mmol, 1.1 equiv), β-sulfinimido *gem*-

bis(boronate) **2-3b** (0.32 g, 0.50 mmol, 1.0 equiv), water (10 μL, 0.55 mmol, 1.1 equiv), and dioxane (5 mL). The crude mixture was purified by flash silica gel chromatography (3:1 to 2:1 hexanes/EtOAc) and isolated as a colorless oil (0.22 g, 87%). ^{1}H NMR analysis of the crude mixture indicated >20:1 diastereoselectivity and 10% of elimination side product.

^{1}H NMR (500 MHz, CD_3CN) δ 7.34–7.34 (m, 4H), 7.28–7.23 (m, 1H), 4.62 (d, *J* = 3.4 Hz, 1H), 4.34 (dd, *J* = 6.9, 3.5 Hz, 1H), 3.64 (ddd, *J* = 9.9, 7.6, 5.0 Hz, 1H), 3.50 (app dt, *J* = 10.0, 6.8 Hz, 1H), 1.59–1.51 (comp m, AB part of ABMXY, 2H), 1.51–1.44 (comp m, M part of ABMXY, 1H), 1.24 (app d, *J* = 5.6 Hz, 12H), 1.15 (s, 9H), 0.86 (s, 9H), -0.01 (app d, *J* = 5.6 Hz, 6H).

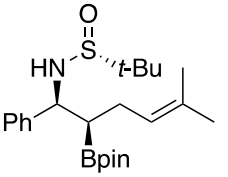
^{13}C NMR (126 MHz, CD_3CN) δ 144.1, 129.1, 128.7, 128.2, 84.8, 62.8, 60.7, 55.8, 32.3, 26.3, 25.3, 25.2, 22.9, 18.8, -5.07, -5.11.

^{11}B NMR (160 MHz, CD_3CN) δ 33.5.

IR (cast film, cm^{-1}): 3286, 3031, 2956, 1472, 1463, 1372, 1143, 1075.

HRMS (ESI-TOF) for $C_{26}H_{49}BNO_4SSi$ $(M + H)^+$: *calcd.*: 510.3239; *found*: 510.3237.

$[\alpha]_D^{20}$: –59.3 (*c* 0.56, $CHCl_3$).



(*R*)-2-Methyl-N-((1*S*,2*R*)-5-methyl-1-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-4-en-1-yl)propane-2-sulfinamide (2-4c): Prepared by following the general procedure with RbF (58 mg, 0.55 mmol, 1.1 equiv), β-sulfinimido *gem*-bis(boronates) **2-3c** (0.27 g, 0.50 mmol, 1.0 equiv), water (10 μL, 0.55 mmol, 1.1 equiv), and dioxane (5 mL). The crude mixture was purified by flash silica gel chromatography (3:1 to 2:1 hexanes/EtOAc) and isolated as a white solid (0.17 g, 82%). ^{1}H NMR analysis of the crude mixture indicated >20:1 diastereoselectivity and 14% of elimination side product.

^{1}H NMR (500 MHz, C_6D_6) δ 7.30–7.26 (m, 2H), 7.14–7.12 (m, 2H), 7.07–7.03 (m, 1H), 5.30 (m, 1H), 4.68 (br s, 1H), 4.66 (d, *J* = 2.7 Hz, 1H), 2.33 (app dt, *J* = 14.2, 8.5 Hz, 1H), 2.15 (app dt, *J* = 13.4, 6.1 Hz, 1H), 1.68 (app td, *J* = 8.8, 5.3 Hz, 1H), 1.62 (s, 3H), 1.50 (s, 3H), 1.09 (s, 9H), 1.08 (s, 6H), 1.06 (s, 6H).

^{13}C NMR (126 MHz, C_6D_6) δ 143.8, 132.3, 128.5, 128.4, 127.4, 124.2, 83.8, 60.3, 55.0, 27.7, 26.0, 25.1, 24.8, 22.7, 18.0.

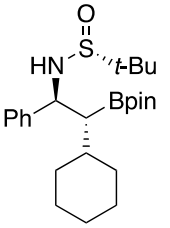
^{11}B NMR (160 MHz, C_6D_6) δ 33.5.

IR (cast film, cm^{-1}): 3284, 3031, 2977, 1603, 1380, 1142, 1074.

HRMS (ESI-TOF) for $C_{23}H_{38}BNNaO_3S$ $(M + Na)^+$: *calcd.*: 442.2558; *found*: 442.2556.

mp: 43.0–45.8 ºC.

$[\alpha]_D^{20}$: –77.7 (*c* 0.65, $CHCl_3$).



(*R*)-N-((1*S*,2*R*)-2-Cyclohexyl-1-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)-2-methylpropane-2-sulfinamide (2-4d): Prepared by following the general procedure with RbF (20 mg, 0.40 mmol, 2.0 equiv), β-sulfinimido *gem*-bis(boronate) **2-3d** (0.11 g, 0.20 mmol, 1.0 equiv), water (4.0 μL, 0.22 mmol, 1.1 equiv), and dioxane (2 mL). The reaction mixture was stirred at 90 ºC for 24 h. The crude mixture was purified by flash silica gel chromatography (3:1 to 2:1 hexanes/EtOAc) and isolated as a white solid (72 mg, 83%). ^{1}H NMR analysis of the crude mixture indicated >20:1 diastereoselectivity and 7% of elimination side product.

^{1}H NMR (500 MHz, CD_3CN) δ 7.32–7.30 (m, 4H), 7.26–7.22 (m, 1H), 4.55 (dd, *J* = 6.3, 4.5 Hz, 1H), 4.49 (d, *J* = 4.6 Hz, 1H), 1.86–1.80 (m, 1H), 1.75–1.63 (m, 4H), 1.63–1.58 (m, 1H), 1.39–1.34 (m, 1H), 1.25 (s, 6H), 1.19 (s, 6H), 1.14 (s, 9H), 1.13–1.01 (m, 5H).

^{13}C NMR (126 MHz, CD_3CN) δ 145.0, 129.1, 128.3, 127.9, 84.6, 58.9, 56.0, 37.6, 33.4, 32.8, 27.30, 27.28, 27.2, 25.53, 25.50, 22.9.

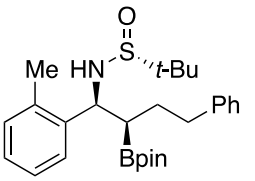
^{11}B NMR (160 MHz, CD_3CN) δ 32.9.

IR (cast film cm^{-1}): 3281, 3028, 2925, 1604, 1381, 1142.

HRMS (ESI-TOF) for $C_{24}H_{41}BNO_3S$ $(M + H)^+$: *calcd.*: 434.2895; *found*: 434.2898.

mp: 114.8–118.4 ºC.

$[\alpha]_D^{20}$: –63.5 (*c* 0.67, $CHCl_3$).



(*R*)-2-Methyl-*N*-((1*S*,2*R*)-4-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(o-tolyl)butyl)propane-2-sulfinamide (2-4e): Prepared by following the general procedure with RbF (12 mg, 0.11 mmol, 1.1 equiv), β-sulfinimido *gem*-bis(boronate) **2-3e** (60 mg, 0.10 mmol, 1.0 equiv), water (2.0 μL, 0.11 mmol, 1.1 equiv), and dioxane (1 mL). The crude mixture was purified by flash silica gel chromatography (3:1 to 2:1 hexanes/EtOAc) and isolated as a colorless oil (43 mg, 91%). ^{1}H NMR analysis of the crude mixture indicated >20:1 diastereoselectivity and 9% of elimination side product.

^{1}H NMR (500 MHz, CD_3CN) δ 7.34–7.32 (m, 1H), 7.26–7.23 (m, 2H), 7.18–7.15 (m, 2H), 7.14–7.11 (m, 4H), 4.70 (d, *J* = 5.0 Hz, 1H), 4.61 (dd, *J* = 6.4, 4.2 Hz, 1H), 2.70–2.58 (comp m, AB part of ABMNX, 2H), 2.28 (s, 3H), 1.80–1.70 (comp m, M part of ABMNX, 1H), 1.68–1.59 (comp m, N part of ABMNX, 1H), 1.46–1.41 (comp m, X part of ABMNX, 1H), 1.29 (s, 6H), 1.25 (s, 6H), 1.14 (s, 9H).

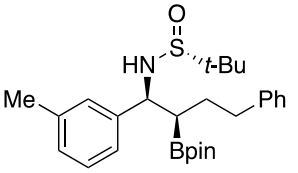
^{13}C NMR (126 MHz, CD_3CN) δ 143.4, 142.7, 136.4, 131.2, 129.3, 129.2, 128.0, 127.9, 126.9, 126.7, 84.9, 57.2, 55.9, 35.5, 31.8, 25.4, 25.2, 22.9, 19.4.

^{11}B NMR (160 MHz, CD_3CN) δ 33.4.

IR (cast film, cm^{-1}): 3283, 3026, 2978, 1604, 1373, 1141, 1072.

HRMS (ESI-TOF) for $C_{27}H_{40}BNNaO_3S$ $(M + Na)^+$: *calcd.*: 492.2714; *found*: 470.2824.

$[\alpha]_D^{20}$: –30.5 (*c* 0.52, $CHCl_3$).



(*R*)-2-Methyl-*N*-((1*S*,2*R*)-4-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(m-tolyl)butyl)propane-2-sulfinamide (2-4f): Prepared by following the general procedure with RbF (23 mg, 0.30 mmol, 1.5 equiv), β-sulfinimido *gem*-bis(boronate) **2-3f** (0.12 g, 0.20 mmol, 1.0 equiv), water (4.0 μL, 0.22 mmol, 1.1 equiv), and dioxane (2 mL). The reaction mixture was stirred at 70 ºC for 21 h. The crude mixture was purified by flash silica gel

chromatography (3:1 hexanes/EtOAc) and isolated as a colorless oil (57 mg, 60%). ^{1}H NMR analysis of the crude mixture indicated >20:1 diastereoselectivity and 13% of elimination side product.

^{1}H NMR (500 MHz, CD_3CN) δ 7.24 (t, *J* = 7.5 Hz, 2H), 7.19 (t, *J* = 7.5 Hz, 1H), 7.15 (t, *J* = 7.3 Hz, 1H), 7.11 (app d, *J* = 7.2 Hz, 3H), 7.07 (t, *J* = 7.0 Hz, 2H), 4.58 (d, *J* = 3.9 Hz, 1H), 4.36 (dd, *J* = 6.9, 3.9 Hz, 1H), 2.67–2.62 (comp m, A part of ABMNX, 1H), 2.60–2.53 (comp m, B part of ABMNX, 1H), 2.30 (s, 3H), 1.62 (comp m, MN part of ABMNX, 2H), 1.44–1.40 (app q, *J* = 7.1 Hz, 1H), 1.26 (app d, *J* = 10.0 Hz, 12H), 1.14 (s, 9H).

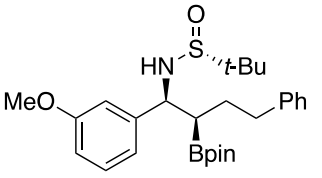
^{13}C NMR (126 MHz, CD_3CN) δ 144.3, 143.4, 138.7, 129.30, 129.26, 129.14, 129.09, 128.8, 126.7, 125.6, 84.9, 60.8, 55.9, 35.5, 31.5, 25.4, 25.2, 22.9, 21.5.

^{11}B NMR (160 MHz, CD_3CN) δ 33.9.

IR (cast film, cm^{-1}): 3284, 3026, 2978, 1606, 1496, 1455, 1380, 1142, 1073.

HRMS (ESI-TOF) for $C_{27}H_{40}BNNaO_3S$ $(M + Na)^+$: *calcd.*: 492.2719; *found*: 492.2712.

$[\alpha]_D^{20}$: –51.2 (*c* 0.61, $CHCl_3$).



(*R*)-*N*-((1*S*,2*R*)-1-(3-Methoxyphenyl)-4-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl)-2-methylpropane-2-sulfinamide (2-4g): Prepared by following the general procedure with RbF (23 mg, 0.22 mmol, 1.1 equiv), β-sulfinimido *gem*-bis(boronate) **2-3g** (0.12 g, 0.20 mmol, 1.0 equiv), water (4.0 μL, 0.11 mmol, 1.1 equiv), and dioxane (2 mL). The crude mixture was purified by flash column chromatography (2:1 hexanes/EtOAc) and isolated as a colorless oil (75 mg, 78%). ^{1}H NMR analysis of the crude mixture indicated >20:1 diastereoselectivity and 14% of elimination side product.

^{1}H NMR (500 MHz, CD_3CN) δ 7.26–7.21 (m, 3H), 7.18–7.13 (m, 1H), 7.14–7.11 (m, 2H), 6.90–6.84 (m, 2H), 6.81–6.79 (m, 1H), 4.59 (d, *J* = 3.6 Hz, 1H), 4.38 (dd, *J* = 7.4, 3.5 Hz, 1H), 3.74 (s, 3H), 2.71–2.63 (comp m, A part of ABMNX, 1H), 2.61–2.53 (comp m, B part of ABMNX, 1H), 1.62 (comp m, MN part of ABMNX, 2H), 1.46 (comp m, X part of ABMNX, 1H), 1.28 (s, 6H), 1.26 (s, 6H), 1.15 (s, 9H).

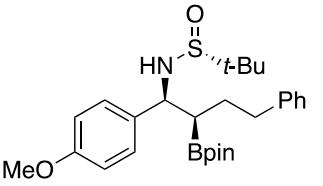
^{13}C NMR (126 MHz, CD_3CN) δ 160.7, 146.1, 143.4, 130.2, 129.30, 129.27, 126.7, 120.9, 113.8, 113.6, 84.9, 60.7, 55.9, 55.8, 35.5, 31.5, 25.4, 25.2, 23.0.

^{11}B NMR (160 MHz, CD_3CN) δ 33.8.

IR (cast film cm^{-1}): 3284, 3025, 2977, 1601, 1380, 1142, 1072.

HRMS (ESI-TOF) for $C_{27}H_{40}BNNaO_4S$ $(M + Na)^+$: *calcd.*: 508.2663; *found*: 508.2668.

$[\alpha]_D^{20}$: –43.7 (*c* 0.58, $CHCl_3$).



(*R*)-*N*-((1*S*,2*R*)-1-(4-Methoxyphenyl)-4-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl)-2-methylpropane-2-sulfinamide (2-4h): Prepared by following the general procedure with RbF (16 mg, 0.15 mmol, 1.5 equiv), β-sulfinimido *gem*-bis(boronate) **2-3h** (61 mg, 0.10 mmol, 1.0 equiv), water (2.0 μL, 0.11 mmol, 1.1 equiv), and dioxane (1 mL). The reaction mixture was stirred at 60 ºC for 18 h. The crude mixture was purified by flash silica gel chromatography (3:1 to 2:1 hexanes/EtOAc) and isolated as a colorless oil (46 mg, 94%). ^{1}H NMR analysis of the crude mixture indicated >20:1 diastereoselectivity and 5% of elimination side product.

^{1}H NMR (500 MHz, CD_3CN) δ 7.25–7.22 (m, 2H), 7.22–7.19 (m, 2H), 7.17–7.13 (m, 1H), 7.11–7.08 (m, 2H), 6.89–6.84 (m, 2H), 4.54 (d, J = 3.5 Hz, 1H), 4.34 (dd, J = 7.6, 3.5 Hz, 1H), 3.76 (s, 3H), 2.64 (comp m, A part of ABMNX, 1H), 2.55–2.49 (comp m, B part of ABMNX, 1H), 1.58 (comp m, MN part of ABMNX, 2H), 1.41 (app q, J = 7.2 Hz, 1H), 1.27 (app d, J = 6.5 Hz, 12H), 1.13 (s, 9H).

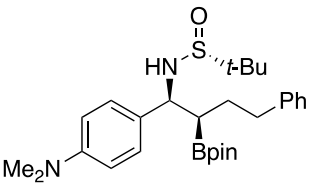
^{13}C NMR (126 MHz, CD_3CN) δ 159.9, 143.5, 135.9, 129.8, 129.3 (×2), 126.7, 114.43, 84.87, 60.06, 55.84, 55.76, 35.46, 31.41, 25.40, 25.21, 22.94.

^{11}B NMR (160 MHz, CD_3CN) δ 33.3.

IR (cast film cm^{-1}): 3284, 3026, 2978, 1612, 1513, 1373, 1142, 1071.

HRMS (ESI-TOF) for $C_{27}H_{40}BNNaO_4S$ $(M + Na)^+$: *calcd.*: 508.2663; *found*: 508.2658.

$[\alpha]_D^{20}$: –55.1 (*c* 0.54, $CHCl_3$).



(*R*)-*N*-((1*S*,2*R*)-1-(4-(Dimethylamino)phenyl)-4-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl)-2-methylpropane-2-sulfinamide (2-4i): Prepared by following the general procedure with RbF (16 mg, 0.15 mmol, 1.5 equiv), β-sulfinimido *gem*-bis(boronate) **2-3i** (62 mg, 0.10 mmol, 1.0 equiv), water (2.0 μL, 0.11 mmol, 1.1 equiv), and dioxane (1 mL). The reaction mixture was stirred at 60 ºC for 22 h. The crude mixture was purified by flash silica gel chromatography (2:1 to 1:1 hexanes/EtOAc) and isolated as a yellow solid (42 mg, 84%). ^{1}H NMR analysis of the crude mixture indicated >20:1 diastereoselectivity and 15% of elimination side product.

^{1}H NMR (500 MHz, CD_3CN) δ 7.26–7.20 (m, 2H), 7.17–7.14 (m, 1H), 7.13–7.07 (m, 4H), 6.71–6.67 (m, 2H), 4.50 (d, *J* = 3.4 Hz, 1H), 4.28 (dd, *J* = 5.0, 10.0 Hz, 1H), 2.89 (s, 6H), 2.64 (app dt, *J* = 13.5, 7.9 Hz, 1H), 2.50 (app dt, *J* = 13.4, 8.2 Hz, 1H), 1.55 (app q, *J* = 7.7 Hz, 2H), 1.40 (app q, *J* = 7.4 Hz, 1H), 1.28 (app d, 12H), 1.13 (s, 9H).

^{13}C NMR (126 MHz, CD_3CN) δ 151.1, 143.6, 131.1, 129.4, 129.2 (×2), 126.7, 113.1, 84.8, 60.1, 55.6, 40.8, 35.5, 31.4, 25.4, 25.2, 23.0.

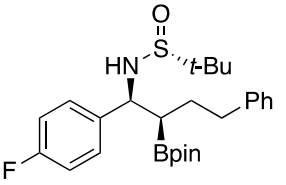
^{11}B NMR (160 MHz, CD_3CN) δ 33.9.

IR (cast film, cm^{-1}): 3283, 3025, 2978, 1614, 1523, 1373, 1141, 1068.

HRMS (ESI-TOF) for $C_{28}H_{43}BN_2NaO_3S$ $(M + Na)^+$: *calcd.*: 521.2980; *found*: 521.2978.

mp: 47.9–50.4 ºC.

$[\alpha]_D^{20}$: –46.7 (*c* 0.47, $CHCl_3$).



(*R*)-*N*-((1*S*,2*R*)-1-(4-Fluorophenyl)-4-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl)-2-methylpropane-2-sulfinamide (2-4j): Prepared by following the general procedure with RbF (16 mg, 0.15 mmol, 1.5 equiv), β-sulfinimido *gem*-bis(boronate) **2-3j** (60 mg, 0.10 mmol, 1.0 equiv), water (2.0 μL, 0.11 mmol, 1.1 equiv), and dioxane (1 mL). The

crude mixture was purified by flash silica gel chromatography (3:1 to 2:1 hexanes/EtOAc) and isolated as a colorless oil (41 mg, 87%). ^{1}H NMR analysis of the crude mixture indicated >20:1 diastereoselectivity and 12% of elimination side product.

^{1}H NMR (500 MHz, CD_3CN) δ 7.33–7.28 (m, 2H), 7.27–7.22 (m, 2H), 7.17–7.13 (m, 1H), 7.12–7.09 (m, 2H), 7.08–7.02 (m, 2H), 4.58 (d, *J* = 3.7 Hz, 1H), 4.41 (dd, *J* = 7.4, 3.7 Hz, 1H), 2.67–2.62 (comp m, A part of ABMNX, 1H), 2.58–2.51 (comp m, B part of ABMNX, 1H), 1.62–1.56 (comp m, MN part of ABMNX, 2H), 1.42 (app q, *J* = 7.5 Hz, 1H), 1.26 (app d, *J* = 8.3 Hz, 12H), 1.14 (s, 9H).

^{13}C NMR (126 MHz, CD_3CN) δ 162.8 (d, *J* = 260.2 Hz), 143.4, 140.3 (d, *J* = 3.8 Hz), 130.4 (d, *J* = 8.8 Hz), 129.3 (×2), 126.7, 115.7 (d, *J* = 21.4 Hz), 85.0, 60.0, 55.9, 35.4, 31.4, 25.4, 25.2, 22.9.

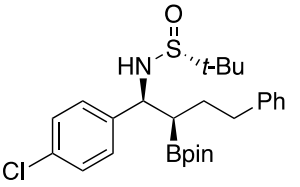
^{11}B NMR (160 MHz, CD^3CN) δ 33.4.

^{19}F NMR (469 MHz, CD_3CN) δ -117.4.

IR (cast film, cm^{-1}): 3283, 3026, 2978, 1604, 1509, 1380, 1141, 1073.

HRMS (ESI-TOF) for $C_{26}H_{37}BFNNaO_3S$ $(M + Na)^+$: *calcd.*: 494.2463; *found*: 494.2469.

$[\alpha]_D^{20}$: –48.3 (*c* 0.43, $CHCl_3$).



(*R*)-*N*-((1*S*,2*R*)-1-(4-Chlorophenyl)-4-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl)-2-methylpropane-2-sulfinamide (2-4k): Prepared by following the general procedure with RbF (23 mg, 0.22 mmol, 1.1 equiv), β-sulfinimido *gem*-bis(boronate) **2-3k** (0.12 g, 0.20 mmol, 1.0 equiv), water (4.0 μL, 0.22 mmol, 1.1 equiv), and dioxane (2 mL). The crude mixture was purified by flash silica gel chromatography (2:1 hexanes/EtOAc) and isolated as a white solid (71 mg, 72%). ^{1}H NMR analysis of the crude mixture indicated >20:1 diastereoselectivity and 11% of elimination side product.

^{1}H NMR (500 MHz, CD_3CN) δ 7.32 (d, *J* = 8.5 Hz, 2H), 7.28 (d, *J* = 8.3 Hz, 2H), 7.24 (t, *J* = 7.5 Hz, 2H), 7.15 (t, *J* = 7.3 Hz, 1H), 7.11 (d, *J* = 7.1 Hz, 2H), 4.60 (d, *J* = 3.2 Hz, 1H), 4.41 (dd, *J* = 7.3, 3.8 Hz, 1H), 2.68–2.62 (comp m, A part of ABMNX, 1H), 2.60–2.52 (comp m,

B part of ABMNX, 1H), 1.60 (comp m, MN part of ABMNX, 2H), 1.43 (app q, J = 7.2 Hz, 1H), 1.26 (app d, J = 8.3 Hz, 12H), 1.14 (s, 9H).

^{13}C NMR (126 MHz, CD_3CN) δ 143.3, 143.2, 133.30, 130.27, 129.3 (×2), 129.2, 126.8, 85.0, 60.1, 56.0, 35.4, 31.4, 25.4, 25.2, 22.9.

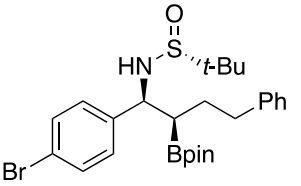
^{11}B NMR (160 MHz, CD_3CN) δ 35.1.

IR (cast film cm^{-1}): 3282, 3026, 2979, 1602, 1373, 1141.

HRMS (ESI-TOF) for $C_{26}H_{37}BClNNaO_3S$ $(M + Na)^+$: *calcd.*: 512.2168; *found*: 512.2174.

mp: 97.5–99.1 ºC.

$[\alpha]_D^{20}$: –53.5 (*c* 0.72, $CHCl_3$).



(*R*)-*N*-((1*S*,2*R*)-1-(4-Bromophenyl)-4-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl)-2-methylpropane-2-sulfinamide (2-4l): Prepared by following the general procedure with RbF (12 mg, 0.11 mmol, 1.1 equiv), β-sulfinimido *gem*-bis(boronate**) 2-3l** (66 mg, 0.10 mmol, 1.0 equiv), water (2.0 μL, 0.11 mmol, 1.1 equiv), and dioxane (1 mL). The crude mixture was purified by flash column chromatography (3:1 to 2:1 hexanes/EtOAc) and isolated as a white solid (49 mg, 91%). ^{1}H NMR analysis of the crude mixture indicated >20:1 diastereoselectivity and 7% of elimination side product.

^{1}H NMR (500 MHz, CD_3CN) δ 7.49–7.44 (m, 2H), 7.27–7.21 (m, 4H), 7.18–7.13 (m, 1H), 7.12–7.09 (m, 2H), 4.59 (d, J = 3.8 Hz, 1H), 4.39 (dd, J = 7.2, 3.8 Hz, 1H), 2.69–2.61 (comp m, A part of ABMNX, 1H), 2.59–2.52 (comp m, B part of ABMNX, 1H), 1.63–1.57 (comp m, MN part of ABMNX, 2H), 1.42 (comp m, X part of ABMNX, 1H), 1.26 (app d, J = 8.2 Hz, 12H), 1.14 (s, 9H).

^{13}C NMR (126 MHz, CD_3CN) δ 143.7, 143.3, 132.2, 130.6, 129.3 (×2), 126.7, 121.4, 85.0, 60.2, 56.0, 35.4, 31.4, 25.4, 25.2, 22.9.

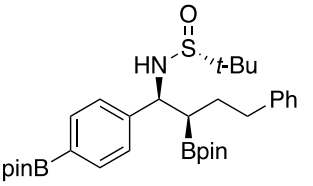
^{11}B NMR (160 MHz, CD_3CN) δ 33.4.

IR (cast film cm^{-1}): 3281, 3026, 2978, 1603, 1372, 1141.

HRMS (ESI-TOF) for $C_{26}H_{37}BBrNNaO_3S$ $(M + Na)^+$: *calcd.*: 556.1663; *found*: 556.1657.

mp: 104.6–106.7 ºC.

[α]$_D^{20}$: –48.7 (*c* 0.60, $CHCl_3$).



(*R*)-2-Methyl-N-((1*S*,2*R*)-4-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)butyl)propane-2-sulfinamide(2-4m): Prepared by following the general procedure with RbF (12 mg, 0.11 mmol, 1.1 equiv), β-sulfinimido *gem*-bis(boronate) **2-3m** (71 mg, 0.10 mmol, 1.0 equiv), water (2.0 μL, 0.11 mmol, 1.1 equiv), and dioxane (1 mL). The crude mixture was purified by flash silica gel chromatography (3:1 to 2:1 hexanes/EtOAc) and isolated as a white solid (43 mg, 75%). ^{1}H NMR analysis of the crude mixture indicated >20:1 diastereoselectivity and 14% of elimination side product.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.8 Hz, 2H), 7.27 (s, 1H), 7.25 (s, 1H), 7.22 (t, *J* = 7.5 Hz, 2H), 7.15–7.11 (m, 1H), 7.11–7.07 (m, 2H), 4.64 (d, *J* = 3.4 Hz, 1H), 4.47 (dd, *J* = 7.7, 3.3 Hz, 1H), 2.70–2.63 (comp m, A part of ABMNX, 1H), 2.60–2.51 (comp m, B part of ABMNX, 1H), 1.73–1.60 (comp m, MN part of ABMNX, 2H), 1.50–1.47 (comp m, X part of ABMNX, 1H), 1.34 (app s, 12H), 1.27 (app d, *J* = 4.4 Hz, 12H), 1.17 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 146.2, 142.1, 134.7, 128.5, 128.3, 127.1, 125.7, 83.9, 83.8, 59.9, 55.51, 35.0, 20.0, 25.1, 25.0, 24.93, 24.88, 22.8.

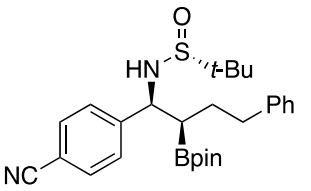
^{11}B NMR (160 MHz, $CDCl_3$) δ 31.54.

IR (cast film, cm^{-1}): 3281, 3063, 2979, 1612, 1361, 1167.

HRMS (ESI-TOF) for $C_{32}H_{49}B_2NNaO_5S$ $(M + Na)^+$: *calcd.*: 604.3410; *found*: 604.3420.

mp: 163.8–166.1 ºC.

[α]$_D^{20}$: –34.1 (*c* 0.66, $CHCl_3$).



(*R*)-*N*-((1*S*,2*R*)-1-(4-Cyanophenyl)-4-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl)-2-methylpropane-2-sulfinamide (2-4n): Prepared by following the general procedure for synthesis of β-sulfinimido *gem*-bis(boronate) with TMP (0.11 mL, 0.50 mmol, 1.2 equiv), *n*-BuLi (2.5 M in hexanes, 0.22 mL, 1.1 equiv), 1,1-diborylalkane **2-1a** (0.21 g, 0.55 mmol, 1.1 equiv), and *N*-*tert*-butanesulfinyl aldimine **2-2k** (0.12 g, 0.50 mmol, 1.0 equiv). The reaction mixture was quenched by the addition of an aqueous solution of NaOH (1.0 N, 2.5 mL) solution, and the aqueous mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. ^{1}H NMR analysis of the crude mixture indicated formation of a mixture of *gem*-bis(boronate) **2-3n** (>20:1 dr) and β-amino alkylboronate **2-4n** (3:1 dr) in a 1:8 ratio. The mixture of **2-3n** and **2-4n** was subjected directly to the standard conditions for synthesis of β-aminoalkylboronates with RbF (58 mg, 0.55 mmol, 1.1 equiv), water (10 μL, 0.55 mmol, 1.1 equiv), and dioxane (5 mL). The crude product from the protodeoboronation reaction was purified by flash silica gel chromatography (8:1 to 7:1 Et_2O/DCM) and isolated as a white solid (0.13 g, 52%). ^{1}H NMR analysis of the crude mixture indicated 5:1 diastereoselectivity and 14% of elimination side product.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.3 Hz, 2H), 7.26–7.22 (m, 2H), 7.18–7.14 (m, 1H), 7.10–7.05 (m, 2H), 4.67 (d, *J* = 3.1 Hz, 1H), 4.50 (dd, *J* = 7.7, 3.1 Hz, 1H), 2.68 (ddd, *J* = 14.5, 9.6, 5.4 Hz, 1H), 2.60–2.53 (comp m, B part of ABMNX, 1H), 1.72 (comp m, M part of ABMNX, 1H), 1.60–1.56 (comp m, N part of ABMNX, 1H), 1.44 (comp m, X part of ABMNX, 1H), 1.27 (app d, *J* = 5.2 Hz, 12H), 1.19 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.6, 141.7, 132.1, 128.48, 128.46, 128.4, 125.9, 118.9, 111.2, 84.2, 59.5, 55.7, 34.8, 29.8, 25.1, 24.9, 22.7.

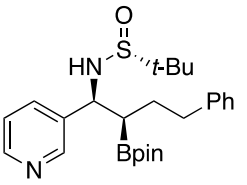
^{11}B NMR (160 MHz, $CDCl_3$) δ 28.0.

IR (cast film cm^{-1}): 3281, 3025, 2979, 2228, 1608, 1474, 1455, 1374, 1109.

HRMS (ESI-TOF) for $C_{27}H_{37}BN_2NaO_3S$ $(M + Na)^+$: *calcd.*: 503.2510; *found*: 503.2509.

mp: 35.6–38.6 ºC.

[α]D20: –50.5 (*c* 0.58, $CHCl_3$).



(*R*)-2-Methyl-*N*-((1*S*,2*R*)-4-phenyl-1-(pyridin-3-yl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl)propane-2-sulfinamide (2-4o): Prepared by following the general procedure with RbF (23 mg, 0.22 mmol, 1.1 equiv), β-sulfinimido *gem*-bis(boronate) **2-3o** (0.12 g, 0.20 mmol, 1.0 equiv), water (4.0 μL, 0.22 mmol, 1.1 equiv), and dioxane (2 mL). The crude mixture was purified by flash silica gel chromatography (1:1 to 2:3 hexanes/EtOAc) and isolated as a white solid (66 mg, 100%). ^{1}H NMR analysis of the crude mixture indicated >20:1 diastereoselectivity.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (br s, 2H), 7.53 (d, *J* = 7.7 Hz, 1H), 7.23 (t, *J* = 7.5 Hz, 3H), 7.14 (t, *J* = 7.3 Hz, 1H), 7.09 (d, *J* = 7.2 Hz, 2H), 4.66 (d, *J* = 3.2 Hz, 1H), 4.51 (dd, *J* = 7.9, 3.3 Hz, 1H), 2.71–2.65 (comp m, A part of ABMNX, 1H), 2.60–2.54 (comp m, B part of ABMNX, 1H), 1.76–1.70 (comp m, M part of ABMNX, 1H), 1.69–1.61 (comp m, N part of ABMNX, 1H), 1.47 (app td, *J* = 8.3, 5.3 Hz, 1H), 1.27 (app d, *J* = 5.3 Hz, 12H), 1.19 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 149.4, 148.5, 141.8, 135.1, 128.5 (×2), 128.4 (×2), 125.8, 84.1, 57.9, 55.7, 34.8, 29.8, 25.1, 24.9, 22.7.

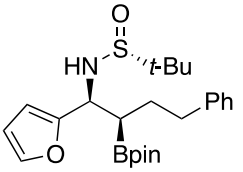
^{11}B NMR (160 MHz, $CDCl_3$) δ 28.0.

IR (cast film, cm^{-1}): 3281, 3026, 2978, 1577, 1455, 1380, 1142.

HRMS (ESI-TOF) for $C_{25}H_{37}BN_2NaO_3S$ $(M + Na)^+$: *calcd.*: 479.2510; *found*: 479.2517.

mp: 132.3–133.8 ºC.

[α]D20: –50.7 (*c* 0.85, $CHCl_3$).



(*R*)-*N*-((1*S*,2*R*)-1-(Furan-2-yl)-4-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl)-2-methylpropane-2-sulfinamide (2-4p): Prepared by following the general procedure with RbF (23 mg, 0.22 mmol, 1.1 equiv), β-sulfinimido *gem*-bis(boronate) **2-3p** (0.11 mg, 0.20 mmol, 1.0 equiv), water (4.0 μL, 0.22 mmol, 1.1 equiv), and dioxane (2 mL). The crude mixture was purified by flash column chromatography (3:1 to 2:1 hexanes/EtOAc) and isolated as a yellow oil (61 mg, 69%). ^{1}H NMR analysis of the crude mixture indicated >20:1 diastereoselectivity and 14% of elimination side product.

^{1}H NMR (500 MHz, CD_3CN) δ 7.41–7.39 (m, 1H), 7.28–7.25 (m, 2H), 7.20–7.16 (m, 3H), 6.33 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.22 (d, *J* = 3.3 Hz, 1H), 4.60 (d, *J* = 6.0 Hz, 1H), 4.48 (app t, *J* = 5.8 Hz, 1H), 2.62 (comp m, AB part of ABMNX, 2H), 1.72 (comp m, MN part of ABMNX, 2H), 1.60 (comp m, X part of ABMNX, 1H), 1.25 (app s, 12H), 1.14 (s, 9H).

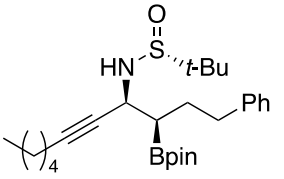
^{13}C NMR (126 MHz, CD_3CN) δ 156.9, 143.4, 142.9, 129.4, 129.3, 126.7, 111.0, 107.8, 84.8, 56.2, 55.8, 35.5, 31.2, 25.3, 25.1, 22.9.

^{11}B NMR (160 MHz, CD_3CN) δ 33.2.

IR (cast film, cm^{-1}): 3308, 3026, 2978, 1603, 1380, 1142, 1075.

HRMS (ESI-TOF) for $C_{24}H_{36}BNNaO_4S$ $(M + H)^+$: *calcd.*: 468.2342; *found*: 468.2350.

$[\alpha]_D^{20}$: –46.2 (*c* 0.58, $CHCl_3$).



(*R*)-2-Methyl-*N*-((3*R*,4*S*)-1-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)undec-5-yn-4-yl)propane-2-sulfinamide (2-4q): Prepared by following the general procedure with RbF (16 mg, 0.15 mmol, 1.5 equiv), β-sulfinimido *ge*m-bis(boronate) **2-3q** (60 mg, 0.10 mmol, 1.0 equiv), water (2.0 μL, 0.11 mmol, 1.1 equiv), and dioxane (1 mL). The reaction mixture was stirred at 60 ºC for 22 h. The crude mixture was purified by flash silica gel chromatography (3:1 to 2:1 hexanes/EtOAc) and isolated as a yellow solid (27 mg,

56%). ^{1}H NMR analysis of the crude mixture indicated >20:1 diastereoselectivity and 13% of elimination side product.

^{1}H NMR (500 MHz, CD_3CN) δ 7.29–7.25 (m, 2H), 7.22–7.16 (m, 3H), 4.23 (d, *J* = 5.5 Hz, 1H), 4.12–4.09 (m, 1H), 2.70 (ddd, *J* = 13.5, 10.1, 5.4 Hz, 1H), 2.58 (ddd, *J* = 13.5, 9.9, 6.7 Hz, 1H), 2.19–2.16 (m, 4H), 1.92–1.85 (m, 1H), 1.84–1.78 (m, 1H), 1.49–1.43 (m, 2H), 1.40–1.33 (m, 3H), 1.27 (app s, 12H), 1.16 (s, 9H), 0.88 (app t, *J* = 7.2 Hz, 3H).

^{13}C NMR (126 MHz, CD_3CN) δ 143.6, 129.4, 129.3, 126.7, 86.4, 84.7, 80.6, 56.0, 49.5, 35.5, 31.7, 30.5, 29.1, 25.3, 25.2, 22.9 (×2), 19.0, 14.3.

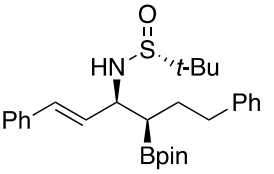
^{11}B NMR (160 MHz, CD_3CN) δ 33.3.

IR (cast film, cm^{-1}): 3279, 3026, 2956, 1604, 1380, 1143, 1075.

HRMS (ESI-TOF) for $C_{27}H_{45}BNO_3S$ $(M + H)^+$: *calcd.*: 474.3208; *found*: 474.3213.

mp: 43.7–45.4 ºC.

$[\alpha]_D^{20}$: –32.2 (*c* 0.43, $CHCl_3$).



(*R*)-*N*-((3*S*,4*R*,*E*)-1,6-Diphenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-1-en-3-yl)-2-methylpropane-2-sulfinamide (2-4r): Prepared by following the general procedure with RbF (16 mg, 0.15 mmol, 1.5 equiv), β-sulfinimido *gem*-bis(boronate) **2-3r** (61 mg, 0.10 mmol, 1.0 equiv), water (2.0 μL, 0.11 mmol, 1.1 equiv), and dioxane (1 mL). The reaction mixture was stirred at 60 ºC for 22 h. The crude mixture was purified by flash silica gel chromatography (3:1 to 2:1 hexanes/EtOAc) and isolated as a yellow oil (36 mg, 74%). ^{1}H NMR analysis of the crude mixture indicated >20:1 diastereoselectivity and 14% of elimination side product.

^{1}H NMR (500 MHz, CD_3CN) δ 7.40–7.37 (m, 2H), 7.34–7.31 (m, 2H), 7.29–7.23 (m, 3H), 7.21–7.15 (m, 3H), 6.57 (d, *J* = 15.9 Hz, 1H), 6.08 (dd, *J* = 15.9, 7.6 Hz, 1H), 4.24 (d, *J* = 7.9 Hz, 1H), 4.05–3.98 (comp m, 1H), 2.71–2.67 (comp m, A part of ABMNX, 1H), 2.64–2.58 (comp m, B part of ABMNX, 1H), 1.88–1.73 (comp m, MN part of ABMNX, 2H), 1.39–1.33 (comp m, X part of ABMNX, 1H), 1.25 (app s, 12H), 1.18 (s, 9H).

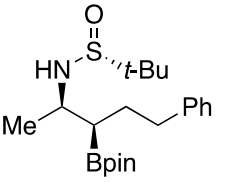
^{13}C NMR (126 MHz, CD_3CN) δ 143.6, 137.8, 132.7, 131.9, 129.6, 129.4, 129.3, 128.6, 127.2, 126.7, 84.7, 59.5, 56.0, 35.7, 30.8, 25.3, 25.2, 23.0.

^{11}B NMR (160 MHz, CD_3CN) δ 33.5.

IR (cast film cm^{-1}): 3286, 3026, 2978, 1602, 1380, 1142.

HRMS (ESI-TOF) for $C_{28}H_{40}BNNaO_3S$ $(M + Na)^+$: *calcd.*: 504.2714; *found*: 504.2714.

$[\alpha]_D^{20}$: –65.4 (*c* 0.58, $CHCl_3$).



(*R*)-2-Methyl-*N*-((2*R*,3*R*)-5-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentan-2-yl)propane-2-sulfinamide (2-4s): Prepared by following the general procedure with RbF (16 mg, 0.15 mmol, 1.5 equiv), β-sulfinimido *gem*-bis(boronate) **2-3s** (52 mg, 0.10 mmol, 1.0 equiv), water (2.0 μL, 0.11 mmol, 1.1 equiv), and dioxane (1 mL). The reaction mixture was stirred at 70 ºC for 22 h. The crude mixture was purified by flash silica gel chromatography (3:1 to 2:1 hexanes/EtOAc) and isolated as a colorless oil (23 mg, 59%). ^{1}H NMR analysis of the crude mixture indicated 11:1 diastereoselectivity and 18% of elimination side product.

^{1}H NMR (500 MHz, CD_3CN) δ 7.31–7.25 (m, 2H), 7.24–7.20 (m, 2H), 7.19–7.15 (m, 1H), 4.00 (d, *J* = 5.9 Hz, 1H), 3.45 (app q, *J* = 5.6 Hz, 1H), 2.61 (app t, *J* = 8.0 Hz, 2H), 1.86 (comp m, AB part of ABMNX, 2H), 1.26 (app s, 12H), 1.15 (app s, 10H), 1.13 (d, *J* = 6.7 Hz, 3H).

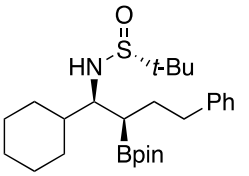
^{13}C NMR (126 MHz, CD_3CN) δ 143.8, 129.4, 129.3, 126.6, 84.5, 55.7, 53.8, 35.9, 30.9, 25.3, 25.2, 23.0, 22.9.

^{11}B NMR (160 MHz, CD3CN) δ 33.6.

IR (cast film, cm^{-1}): 3316, 3026, 2976, 1604, 1380, 1142, 1072.

HRMS (ESI-TOF) for $C_{21}H_{37}BNO_3S$ $(M + H)^+$: *calcd.*: 394.2582; *found*: 394.2577.

$[\alpha]_D^{20}$: –36.9 (*c* 0.62, $CHCl_3$).



(*R*)-N-((1*S*,2*R*)-1-Cyclohexyl-4-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl)-2-methylpropane-2-sulfinamide (2-4t): Prepared by following the general procedure with RbF (21 mg, 0.20 mmol, 2.0 equiv), β-sulfinimido *gem*-bis(boronate) **2-3t** (59 mg, 0.10 mmol, 1.0 equiv), water (2.0 μL, 0.11 mmol, 1.1 equiv), and dioxane (1 mL). The reaction mixture was stirred at 90 ºC for 24 h. The crude mixture was purified by flash silica gel chromatography (5:1 hexanes/EtOAc) and isolated as a colorless oil (25 mg, 55%). ^{1}H NMR analysis of the crude mixture indicated 9:1 diastereoselectivity and 20% of elimination side product.

^{1}H NMR (500 MHz, CD_3CN) δ 7.30–7.24 (m, 2H), 7.24–7.21 (m, 2H), 7.19–7.14 (m, 1H), 4.52 (d, *J* = 7.2 Hz, 1H), 3.06 (ddd, *J* = 7.5, 5.8, 2.3 Hz, 1H), 2.71 (ddd, *J* = 13.4, 10.0, 6.1 Hz, 1H), 2.53 (ddd, *J* = 13.4, 9.9, 5.9 Hz, 1H), 1.87–1.79 (m, 1H), 1.79–1.68 (m, 4H), 1.68–1.59 (m, 2H), 1.30–1.26 (m, 2H), 1.24 (app d, *J* = 1.9 Hz, 12H), 1.20 (s, 9H), 1.18–1.07 (m, 3H), 1.04–0.91 (m, 2H).

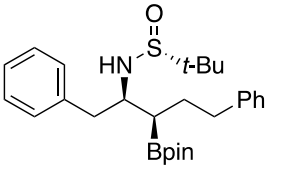
^{13}C NMR (126 MHz, CD_3CN) δ 143.7, 129.5, 129.2, 126.6, 84.5, 63.97, 56.6, 46.5, 35.7, 32.1, 30.9, 30.3, 27.2, 27.1, 27.0, 25.3, 25.0, 23.4.

^{11}B NMR (160 MHz, CD_3CN) δ 33.8.

IR (cast film, cm^{-1}): 3316, 3026, 2926, 1604, 1381, 1141, 1073.

HRMS (ESI-TOF) for $C_{26}H_{44}BNNaO_3S$ $(M + Na)^+$: *calcd.*: 484.3027; *found*: 484.3036.

$[\alpha]_D^{20}$: –37.9 (*c* 0.90, $CHCl_3$).



(*R*)-*N*-((2*R*,3*R*)-1,5-Diphenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentan-2-yl)-2-methylpropane-2-sulfinamide (2-4u): Prepared by following the general procedure with RbF (21 mg, 0.20 mmol, 2.0 equiv), β-sulfinimido *gem*-bis(boronate) **2-3u** (60 mg, 0.10 mmol, 1.0 equiv), water (2.0 μL, 0.11 mmol, 1.1 equiv), and dioxane (1 mL). The reaction

mixture was stirred at 70 ºC for 21 h. The crude mixture was purified by flash silica gel chromatography (5:1 to 4:1 hexanes/EtOAc) and isolated as a yellow oil (27 mg, 57%); ^{1}H NMR analysis of the crude mixture indicated >20:1 diastereoselectivity and 20% of elimination side product.

^{1}H NMR (500 MHz, CD_3CN) δ 7.29–7.25 (m, 2H), 7.25–7.21 (m, 2H), 7.21–7.17 (m, 3H), 7.16–7.12 (m, 3H), 4.25 (d, *J* = 7.7 Hz, 1H), 3.59 (app qd, *J* = 7.5, 2.7 Hz, 1H), 2.78 (dd, *J* = 13.6, 7.7 Hz, 1H), 2.70 (dd, *J* = 13.6, 7.1 Hz, 1H), 2.63 (ddd, *J* = 13.4, 9.8, 6.1 Hz, 1H), 2.51 (ddd, *J* = 13.4, 9.7, 6.1 Hz, 1H), 1.87–1.80 (comp m, A part of ABMNX, 1H), 1.79–1.70 (comp m, B part of ABMNX, 1H), 1.30–1.27 (m, 13H), 1.04 (s, 9H).

^{13}C NMR (126 MHz, CD_3CN) δ 143.6, 140.4, 130.5, 129.4, 129.20, 129.18, 127.1, 126.6, 84.7, 60.8, 56.1, 45.0, 35.7, 31.0, 25.3, 25.2, 23.0.

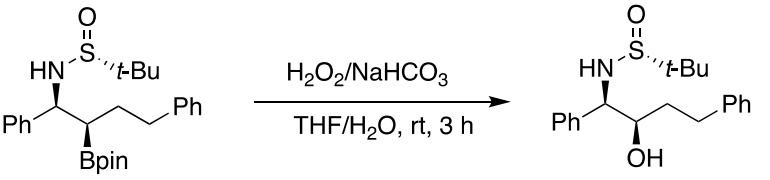
^{11}B NMR (160 MHz, CD_3CN) δ 33.4.

IR (cast film cm^{-1}): 3313, 3026, 2977, 1603, 1380, 1142, 1072.

HRMS (ESI-TOF) for $C_{27}H_{40}BNNaO_3S$ $(M + Na)^+$: *calcd.*: 492.2714; *found*: 492.2719.

$[\alpha]_D^{20}$: –23.2 (*c* 0.58, $CHCl_3$).

2.10.8 Oxidation of β-Aminoalkylboronates



2-4a **2-6**

The obtained β-amino alcohol **2-6** was prepared by following literature procedures.[49] In a 10 mL round-bottomed flask, β-aminoalkylboronate **2-4a** (0.12 g, 0.20 mmol, 1.0 equiv) and $NaHCO_3$ (0.13 g, 1.2 mmol, 6.0 equiv) were dissolved in THF:H_2O (2.5 mL, v/v 1:1). To this mixture, H_2O_2 (30 wt%, 0.67 mL) was added, and the reaction mixture was allowed to stir at room temperature for 3 h. The aqueous phase was extracted with EtOAc (4×10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture was purified by flash silica gel chromatography (1:1 hexanes/EtOAc) to afford the desired β-amino alcohol **2-6** as a white solid (65 mg, 75%).

^{1}H NMR (500 MHz, acetone-d_6) δ 7.35–7.29 (m, 4H), 7.28–7.25 (m, 1H), 7.20–7.17 (m, 2H), 7.12–7.08 (m, 1H), 7.06–7.04 (m, 2H), 4.74 (d, J = 3.7 Hz, 1H), 4.54 (d, J = 6.0 Hz, 1H), 4.16 (dd, J = 8.3, 3.7 Hz, 1H), 3.72–3.65 (comp m, X part of ABMNX, 1H), 2.81–2.77 (comp m, A part of ABMNX, 1H), 2.56 (ddd, J = 13.7, 9.9, 7.0 Hz, 1H), 1.67–1.58 (comp m, M part of ABMNX, 1H), 1.58–1.51 (comp m, N part of ABMNX, 1H), 1.14 (s, 9H).

^{13}C NMR (126 MHz, acetone-d_6) δ 143.0, 141.4, 129.18, 129.16, 129.1, 129.0, 128.4, 126.4, 75.0, 66.0, 55.5, 36.4, 32.4, 22.7.

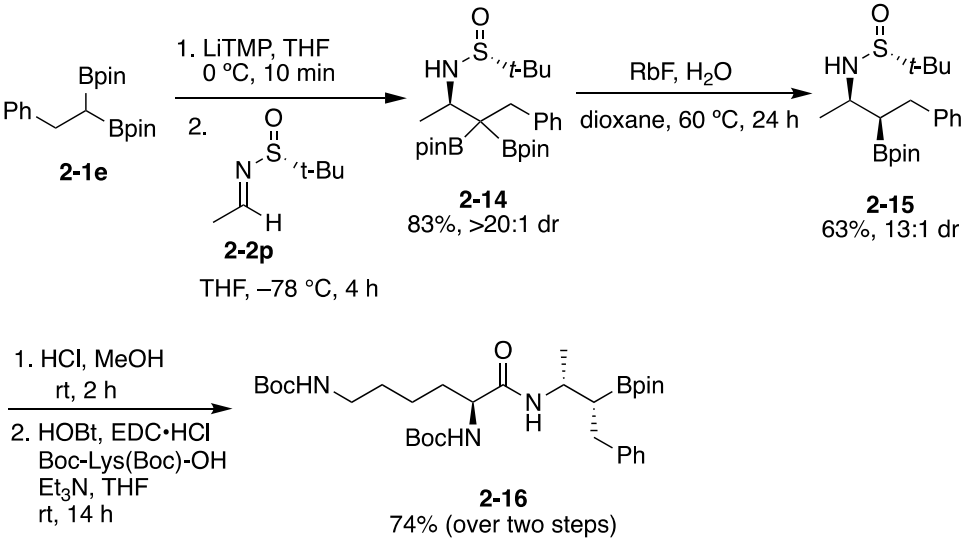
IR (cast film cm^{-1}): 3277, 3028, 2956, 1602, 1454, 1045.

HRMS (ESI-TOF) for $C_{20}H_{27}NNaO_2S$ $(M + Na)^+$: *calcd.*: 368.1656; *found*: 368.1655.

mp: 117.2-119.7 ºC.

$[\alpha]_D^{20}$: –50.4 (*c* 0.56, $CHCl_3$).

2.10.9 Formal Synthesis of Antitubercular Agent 1-5



The obtained β-sulfinimido *gem*-bis(boronate) **2-14** was prepared by following the general procedure for the synthesis of β-sulfinimido *gem*-bis(boronates) **2-1e** with TMP (0.42 mL, 2.4 mmol, 1.2 equiv), *n*-BuLi (2.5 M in hexanes, 0.88 mL, 1.1 equiv), 1,1-diborylalkane **2e** (0.79 g, 2.2 mmol, 1.1 equiv), and *N*-*tert*-butanesulfinyl aldimine **2-2p** (0.29 g, 2.0 mmol, 1.0 equiv). The reaction was quenched by the addition of an HCl solution (1.0 N, 10 ml). The crude mixture was purified by flash silica gel chromatography (3:1 to 2:1 hexanes/EtOAc) and isolated as a colorless oil (0.84 g, 83%). ^{1}H NMR analysis of the crude mixture indicated >20:1

diastereoselectivity.

^{1}H NMR (500 MHz,CD_3CN) δ 7.33 (d, *J* = 7.5 Hz, 2H), 7.23 (t, *J* = 7.6 Hz, 2H), 7.15 (t, *J* = 7.4 Hz, 1H), 4.53 (s, 1H), 3.53–3.43 (m, 1H), 2.98 (app q, *J* = 14.4 Hz, 2H), 1.25 (app d, *J* = 17.9 Hz, 15H), 1.19 (app d, *J* = 17.9 Hz, 12H), 1.11 (s, 9H).

^{13}C NMR (126 MHz, CD_3CN) δ 142.4, 130.8, 128.9, 126.8, 84.7, 84.5, 55.4, 51.1, 35.1, 25.5, 25.31, 25.27, 25.2, 23.0, 18.6.

^{11}B NMR (160 MHz, CD_3CN) δ 33.1.

IR (cast film cm^{-1}): 3288, 3028, 2978, 1603, 1313, 1138.

HRMS (ESI-TOF) for $C_{26}H_{46}B_2NO_5S$ $(M + H)^+$: *calcd.*: 506.3277; *found*: 506.3276.

$[\alpha]_D^{20}$: –48.1 (*c* 0.46, $CHCl_3$).

The obtained β-aminoalkylboronate **2-15** was prepared by following the general procedure for the synthesis of β-aminoalkylboronates **2-4** with RbF (0.16 g, 1.5 mmol, 1.5 equiv), β-sulfinimido *gem*-bis(boronate) **2-14** (0.53 g, 1.0 mmol, 1.0 equiv), water (20 μL, 1.1 mmol, 1.1 equiv), and dioxane (10 mL). The reaction mixture was stirred at 60 ºC for 21 h. The crude mixture was purified by flash silica gel chromatography (3:1 to 2:1 hexanes/EtOAc) and isolated as a colorless oil (0.24 g, 63%); ^{1}H NMR analysis of the crude mixture indicated 13:1 diastereoselectivity.

^{1}H NMR (500 MHz, CD_3CN) δ 7.29–7.24 (m, 4H), 7.16 (t, *J* = 6.5 Hz, 1H), 4.06 (d, *J* = 6.3 Hz, 1H), 3.38 (ddq, *J* = 9.9, 6.7, 3.2 Hz, 1H), 2.78 (app qd, *J* = 13.6, 8.1 Hz, 2H), 1.56 (app td, *J* = 8.3, 3.3 Hz, 1H), 1.27–1.11 (m, 24H).

^{13}C NMR (126 MHz, CD_3CN) δ 142.9, 130.0, 129.1, 126.8, 84.5, 55.8, 53.8, 34.2, 25.2, 25.1, 23.2, 22.9.

^{11}B NMR (160 MHz, CD_3CN) δ 33.2.

IR (cast film cm^{-1}): 3321, 3027, 2977, 1603, 1380, 1112.

HRMS (ESI-TOF) for $C_{20}H_{35}BNO_3S$ $(M + H)^+$: *calcd.*: 380.2430; *found*: 380.2425.

$[\alpha]_D^{20}$: –60.0 (*c* 0.49, $CHCl_3$).

The obtained peptidyl β-aminoalkylboronate **2-16** was prepared by following literature procedures[61] with slight modification. In an oven-dried 5 mL round-bottomed flask, β-amino alkylboronate **2-15** (0.24 g, 0.64 mmol, 1.0 equiv) was dissolved in MeOH (2.5 mL), followed

by dropwise addition of an HCl solution (4 N in dioxane, 0.86 mL, 5.4 equiv) at room temperature. After stirring for 2 h at room temperature, the reaction mixture was concentrated under reduced pressure. The crude mixture was used for the next step without further purification. In an oven-dried 50 mL three-neck round-bottom flask, the above obtained crude β-amino alkylboronate (*ca.* 0.64 mmol), HOBt (0.11 g, 0.83 mmol, 1.3 equiv), and EDC•HCl (0.16 g, 0.83 mmol, 1.3 equiv) was dissolved in 38 mL THF. The solution was stirred under nitrogen and triethylamine (0.26 mL, 1.9 mmol, 3.0 equiv) was added. To the heterogeneous mixture, Boc-Lys(Boc)-OH (0.32 g, 0.83 mmol, 1.3 equiv) was added. The resulting mixture was stirred at room temperature for 14 h. Upon completion, the reaction mixture was transferred to a 1-L separatory funnel containing EtOAc (70 mL) and water (70 mL), and the aqueous layer was separated and extracted with EtOAc (2×20 mL). The combined organic layers were washed with 1N HCl solution (2×50 mL), water (50 mL), saturated sodium bicarbonate solution (3×50 mL), and brine (50 mL). The solution was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude mixture was purified by flash silica gel chromatography (2:1 to 1:1 hexanes/EtOAc) to give the peptidyl β-amino alkylboronate **2-16** as a white solid (0.28 g, 74%).

^{1}H NMR (498 MHz, $CDCl_3$) δ 7.23 (t, *J* = 7.5 Hz, 2H), 7.17–7.13 (m, 3H), 6.60 (d, *J* = 8.7 Hz, 1H), 5.16 (s, 1H), 4.62 (s, 1H), 4.13–4.04 (m, 2H), 3.09 (d, *J* = 7.6 Hz, 2H), 2.70 – 2.61 (m, 2H), 1.65–1.49 (m, 5H), 1.43 (app d, *J* = 13.6 Hz, 18H), 1.17 (app d, *J* = 33.6 Hz, 14H), 1.09 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 156.0, 155.6, 141.0, 128.9, 128.3, 126.0, 83.7, 79.8, 79.0, 54.6, 46.1, 40.2, 34.8, 33.1, 29.7, 28.44, 28.38, 25.1, 24.6, 22.6, 21.8.

^{11}B NMR (160 MHz, $CDCl_3$) δ 33.4.

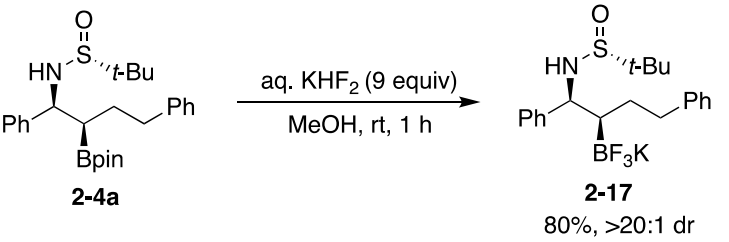
IR (cast film cm^{-1}): 3327, 3062, 2978, 1703, 1663, 1522, 1455, 1367, 1172.

HRMS (ESI-TOF) for $C_{32}H_{55}BN_3O_7$ $(M + H)^+$: *calcd.*: 604.4133; *found*: 604.4137.

mp: 43.9–45.5 ºC.

$[\alpha]_D^{20}$: +9.7 (*c* 0.62, $CHCl_3$).

2.10.10 Synthesis of Trifluoroborate Salt 2-17



(*R*)-*N*-((1*S*,2*R*)-1,4-Diphenyl-2-(trifluoro-l^4-boraneyl)butyl)-2-methylpropane-2-sulfinamide, potassium salt (**2-17**): Prepared by following the literature procedures.[82] To a 5 mL round-bottomed flask, β-aminoalkylboronate **2-4a** (0.75 g, 1.6 mmol, 1 equiv) was added, followed by addition of anhydrous methanol (1 mL). The KHF_2 (1.2 g, 15 mmol, 9 equiv) was dissolved in degassed water (1.2 mL) in a separate 10 mL round-bottomed flask. Then, the solution of **2-4a** in methanol was transferred dropwise into the aqueous solution of KHF_2. The reaction mixture was allowed to stir for 1 h, after which the solvent was removed under reduced pressure. The remaining solid was extracted with acetonitrile (3×40 mL). The combined acetonitrile washes were concentrated under reduced pressure. The resulting solid was washed with hexane to afford the desired trifluoroborate **2-17** as a white solid (0.58 g, 82%).

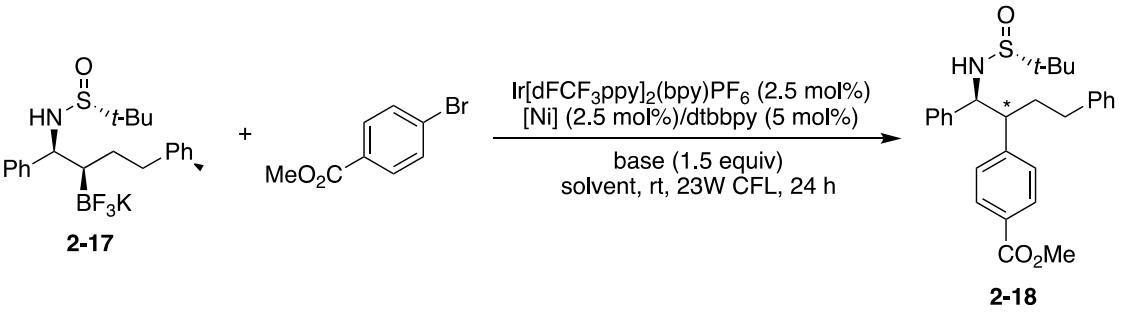
^{1}H NMR (498 MHz, DMSO-d_6) δ 7.34–7.19 (m, 4H), 7.16 (t, J = 7.1 Hz, 1H), 7.10 (t, J = 7.5 Hz, 2H), 7.01 (t, J = 7.4 Hz, 1H), 6.82 (d, J = 7.5 Hz, 2H), 5.36 (app q, J = 7.0 Hz, 1H), 4.10 (d, J = 10.2 Hz, 1H), 2.37 (app td, J = 12.4, 5.2 Hz, 1H), 2.17 (app td, J = 12.8, 12.3, 5.4 Hz, 1H), 1.25–1.08 (m, 2H), 1.03 (s, 9H), 0.61 – 0.49 (m, 1H);

^{13}C NMR (125 MHz, DMSO-d_6) δ 145.1, 144.3, 128.4, 127.85, 127.78, 127.4, 126.2, 124.8, 60.1, 53.9, 34.4, 31.0, 22.4;

^{11}B NMR (128 MHz, DMSO-d_6) δ 4.4;

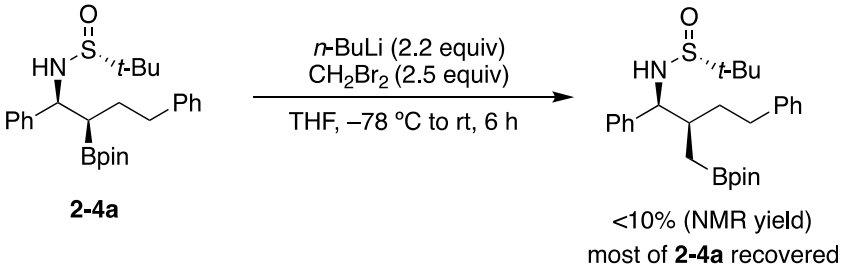
HRMS (ESI-TOF) for $C_{20}H_{26}BF_3NOS$ $[M^*]^-$: *calcd.*: 396.1786; *found*: 396.1783.

2.10.11 Attempted SMC of Compound 2-17 Using Photoredox Conditions



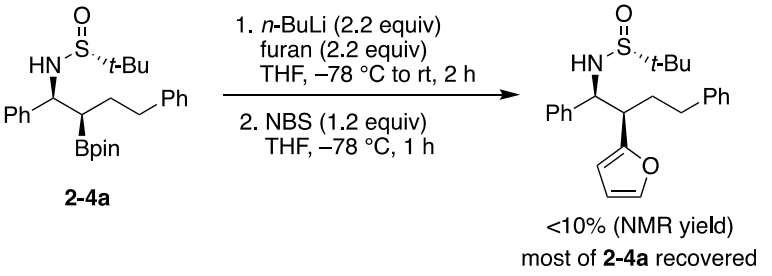
The SMC of compound **2-17** was conducted by following a literature procedure.[86] To a reaction tube equipped with a Teflon-coated magnetic stir bar were added dtbbpy (2.7 mg, 0.010 mmol, 5.0 mol%), the Ni catalyst (0.010 mmol, 5.0 mol%), and THF (0.5 mL). The resulting suspension was heated briefly with a heat gun until the Ni catalyst and ligand were solubilized fully, yielding a pale green solution. Then, the solvent was removed under reduced pressure to give a fine coating of the ligated Ni complex (pale evergreen in color). Once dry, aryl bromide (43 mg, 0.20 mmol, 1.0 equiv), trifluoroborate salt **2-17** (0.16 g, 0.30 mmol, 1.5 equiv), $Ir[dFCF_3ppy]_2(bpy)PF_6$ (5.0 mg, 0.0050 mmol, 2.5 mol%), and base (0.30 mmol, 1.5 equiv) were added in succession. The reaction tube was capped and purged and evacuated four times with N_2, followed by addition of the reaction solvent (4 mL). The reaction tube containing all the reagents was sealed further with parafilm and stirred for 24 h approximately 4 cm away from two 23W compact fluorescent lamps. A fan was blown across the reaction setup to maintain an ambient temperature around 24 °C. After 24 h, the reaction mixture was filtered through a short plug of Celite and washed with EtOAc (20 mL). The resulting solution was concentrated, and the crude mixture was analyzed by LC-MS and ^1H NMR.

2.10.12 Attempted Matteson Homologation of β-Aminoalkylboronate 2-4a



The Matteson homologation of β-aminoalkylboronate **2-4a** was conducted by following the literature procedure.[87] To a stirred solution of **2-4a** (0.12 g, 0.20 mmol, 1.0 equiv) and dibromomethane (35 μL, 0.50 mmol, 2.5 equiv) in anhydrous THF (2 mL) at –78 °C, was added *n*-BuLi (2.5 M in hexanes, 0.18 mL, 0.44 mmol, 2.2 equiv) dropwise. The resulting mixture was stirred for 10 min at –78 °C, then warmed to room temperature and stirred for 6 h. The reaction was quenched by addition of saturated aqueous NH_4Cl solution (1.0 mL) and extracted with CH_2Cl_2 (10 mL×3). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. ^1H NMR analysis of the crude reaction mixture using dibromomethane as the internal standard indicated <10% formation of the desired homologated product and recovery of most of starting material **2-4a**.

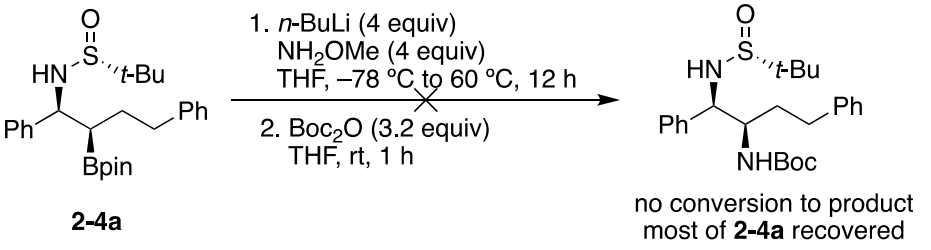
2.10.13 Attempted Furanylation of β-Aminoalkylboronate 2-4a



The furanylation of *anti* β-aminoalkylboronate **2-4a** was performed by following the literature procedure.[88] To a 5 mL round-bottomed flask equipped with a magnetic stir bar were added furan (33 μL, 0.44 mmol, 2.2 equiv) and THF (0.8 mL). The reaction was cooled to –78 ºC, followed by dropwise addition of *n*-BuLi (2.4 M in hexane, 0.18 mL, 0.44 mmol, 2.2 equiv). The cooling bath was removed, and the reaction was stirred at room temperature for 1 h. The

mixture was cooled back down to –78 ºC, and a solution of β-aminoalkylboronate **2-4a** (0.12 g, 0.20 mmol, 1.0 equiv) in THF (0.5 mL) was added dropwise. The reaction mixture was stirred for 1 h, and a solution of *N*-bromosuccinimide (43 mg, 0.24 mmol, 1.2 equiv) in THF (0.8 mL) was added. After allowing the reaction to stir for 1 h, saturated $Na_2S_2O_3$ aqueous solution (1.0 mL) was added to the reaction and stirred at room temperature for 30 min. The reaction mixture was poured into a separate funnel and extracted with Et_2O (10 mL×3). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure. ^{1}H NMR analysis of the crude reaction mixture using dibromomethane as the internal standard indicated <10% formation of the desired product and recovery of most of starting material **2-4a**.

2.10.14 Attempted Amination of β-Aminoalkylboronate 2-4a

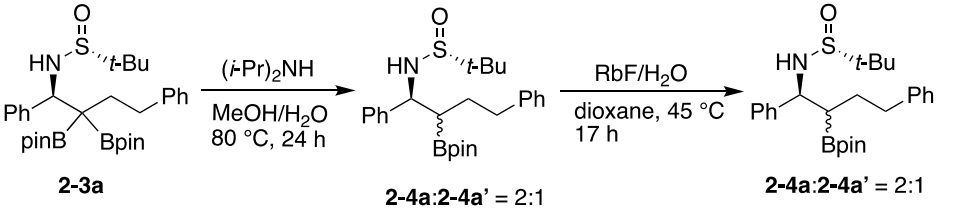


The amination of *anti* β-aminoalkylboronate **2-4a** was performed by following the literature procedure.[88] To a flame-dried round-bottomed flask equipped with a magnetic stir bar were added *O*-methylhydroxylamine solution (3.0 M in THF, 0.27 mL, 0.80 mmol, 4.0 equiv) and THF (2 mL). The reaction flask was cooled to –78 °C, a solution of *n*-BuLi (2.1 M in hexanes, 0.58 mL, 0.80 mmol, 4.0 equiv) was added dropwise, and the reaction was allowed to stir at –78 °C for 30 min. A solution of β-aminoalkylboronate **2-4a** (87 mg, 0.20 mmol, 1.0 equiv) in THF (0.5 mL) was added dropwise to the solution of deprotonated *O*-methylhydroxylamine dropwise via syringe. The reaction flask was warmed to room temperature and then heated to 60 °C. After stirring at 60 °C for 12 h, the reaction flask was cooled to room temperature, and Boc anhydride (0.14 g, 0.64 mmol, 3.2 equiv) was added. After stirring at room temperature for 1 h, the reaction was quenched with water (4 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3×10 mL). The combined organics were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford the

crude reaction mixture. ^{1}H NMR analysis of the crude reaction mixture using dibromomethane as the internal standard indicated no formation of the desired amination product and recovery of most of starting material **2-4a**.

2.10.15 Mechanistic Studies

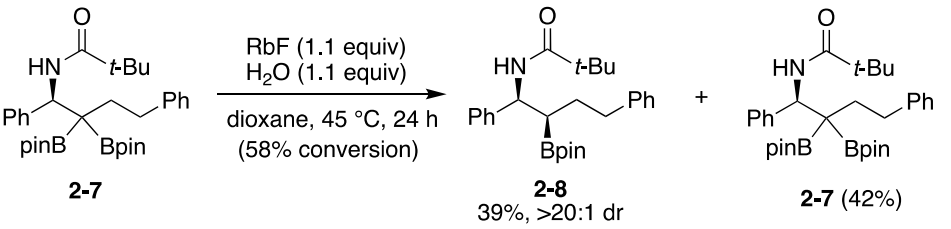
2.10.15.1 Absence of Stereoisomer Equilibration



Synthesis of the mixture of 2-4a and 2-4a': The mixture of **2-4a** and **2-4a'** was prepared by employing the protodeboronation condition in Table 2-2 (entry 9) with (*i*-Pr)$_2$NH (21 μL, 0.15 mmol, 1.0 equiv), **2-3a** (87 mg, 0.15 mmol, 1.0 equiv), H_2O (0.75 mL), and MeOH (0.75 mL). The resulting mixture was stirred at 80 ºC for 24 h. Upon completion, the reaction mixture was diluted with brine (2 mL) and extracted with EtOAc (2×2 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude mixture was purified by flash silica gel chromatography to afford a mixture of **2-4a** and **2-4a'** (48 mg, 70%). ^{1}H NMR analysis of the mixture indicated a 2:1 (**5a**:**5a'**) ratio.

The above obtained mixture of **2-4a** and **2-4a'** (*ca.* 0.10 mmol) was subjected to the standard protodeboronation conditions with RbF (11 mg, 0.11 mmol, 1.1 equiv), water (2.0 μL, 0.11 mmol, 1.1 equiv), and dioxane (1 mL). The reaction mixture was stirred at 45 ºC for 17 h. Upon completion, Et_2O (5 mL) was added. The mixture was filtered through a short pad of Celite, washed with Et_2O, and concentrated under reduced pressure. ^{1}H NMR analysis of the crude mixture indicated an unchanged 2:1 (**2-4a**:**2-4a'**) ratio.

2.10.15.2 Synthesis and Protodeboronation of *N*-Piv-Protected *gem*-Bis(boronate) 2-7



Synthesis of *N*-pivaloyl-protected *gem*-bis(boronate) 2-7: In an oven-dried 5 mL round-bottomed flask, β-sulfinimido *gem*-bis(boronate) **2-3a** (0.29 g, 0.50 mmol, 1.0 equiv) was dissolved in MeOH (2 mL), followed by dropwise addition of an HCl solution (4N in dioxane, 0.70 mL, 5.4 equiv) at room temperature. After stirring for 2 h at room temperature, the reaction mixture was concentrated under reduced pressure. The crude mixture was used for the next step without further purification. In an oven-dried 10 mL round-bottomed flask, the above obtained β-amino *gem*-bis(boronate) (*ca.* 0.50 mmol) was dissolved in DCM (4 mL). The mixture was cooled to 0 °C, and diisopropylethylamine (0.44 mL, 2.5 mmol, 5.0 equiv) was added dropwise to the flask. The resulting mixture was stirred for 5 min. Pivaloyl chloride (0.13 mL, 1.0 mmol, 2.0 equiv) was added dropwise, and the reaction mixture was allowed to warm to room temperature and stirred for 3 h. Upon completion, the flask was cooled to 0 °C, and the reaction mixture was quenched by the addition of saturated sodium bicarbonate aqueous solution (4 mL). The aqueous and organic layers were separated, and the aqueous layer was extracted with EtOAc (3×15 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude mixture was purified by flash silica gel chromatography (4:1 hexanes/EtOAc) to afford *gem*-bis(boronate) **2-7** as a white solid (0.27 g, 95%).

^{1}H NMR (500 MHz, CD_3CN) δ 7.90 (d, *J* = 8.0 Hz, 1H), 7.40–7.6 (m, 2H), 7.31–7.28 (m, 2H), 7.24–7.17 (m, 3H), 7.15–7.10 (m, 1H), 7.03–7.01 (m, 2H), 5.01 (d, *J* = 8.0 Hz, 1H), 2.72 (app td, *J* = 13.2, 4.7 Hz, 1H), 2.53 (app td, *J* = 13.1, 4.4 Hz, 1H), 1.59 (app td, *J* = 13.6, 4.4 Hz, 1H), 1.33 (s, 6H), 1.29 (s, 6H), 1.28 (s, 6H), 1.26 (s, 6H), 1.22–1.16 (m, 1H), 1.13 (s, 9H).

^{13}C NMR (126 MHz, CD_3CN) δ 176.9, 144.8, 144.3, 129.3, 128.97, 128.95, 128.4, 127.9, 126.6, 84.9, 84.7, 56.1, 39.2, 35.0, 34.2, 27.8, 25.6, 25.5, 25.3, 25.0.

^{11}B NMR (160 MHz, CD_3CN) δ 33.9.

IR (cast film cm^{-1}): 3421, 3027, 2979, 1665, 1524, 1496, 1324, 1137.

HRMS (ESI-TOF) for $C_{33}H_{50}B_2NO_5$ $(M + H)^+$: *calcd.*: 562.3870; *found*: 562.3873.

mp: 150.4–152.8 ºC.

$[\alpha]_D^{20}$: +4.6 (*c* 0.92, $CHCl_3$).

Procedure for protodeboronation of *N*-pivaloyl-protected *gem*-bis(boronate) 2-7: Protodeboronation of *gem*-bis(boronate) **2-7** was performed by following the procedure for synthesis of β-aminoalkylboronate **2-4a** with RbF (11 mg, 0.11 mmol, 1.1 equiv), β-amino *gem*-bis(boronate) **2-7** (56 mg, 0.10 mmol, 1.0 equiv), water (2.0 μL, 0.11 mmol, 1.1 equiv), and dioxane (1 mL). The crude mixture was purified by flash silica gel chromatography (5:1 hexanes/EtOAc) to afford β-aminoalkylboronate **2-8** as a white solid (17 mg, 39%), accompanied with 42% recovery of *gem*-bis(boronate) **2-7**; ^{1}H NMR analysis of the crude mixture indicated >20:1 diastereoselectivity.

^{1}H NMR (500 MHz, CD_3CN) δ 7.31–7.27 (m, 4H), 7.25–7.21 (m, 3H), 7.20–7.17 (m, 4H), 5.06 (dd, *J* = 8.5, 4.5 Hz, 1H), 2.68 (comp m, AB part of ABMNX, 2H), 1.70 (comp m, MN part of ABMNX, 2H), 1.52 (app q, *J* = 7.5 Hz, 1H), 1.20 (app d, *J* = 3.2 Hz, 15H), 1.15 (s, 6H);

^{13}C NMR (126 MHz, CD_3CN) δ 178.2, 145.2, 143.3, 129.4, 129.3, 129.2, 127.6, 126.9, 126.8, 84.7, 54.2, 39.5, 35.5, 32.5, 27.9, 25.2, 25.1;

^{11}B NMR (160 MHz, CD_3CN) δ 33.5;

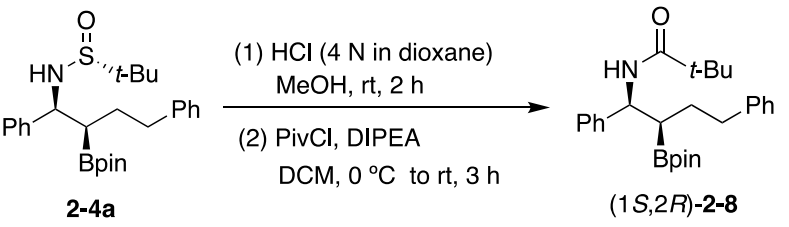
IR (cast film cm^{-1}): 3428, 3027, 2977, 1668, 1522, 1383, 1141;

HRMS (ESI-TOF) for $C_{27}H_{38}BNNaO_3$ $(M + Na)^+$: *calcd.*: 458.2837; *found*: 458.2840.

mp: 83.6–84.9 ºC.

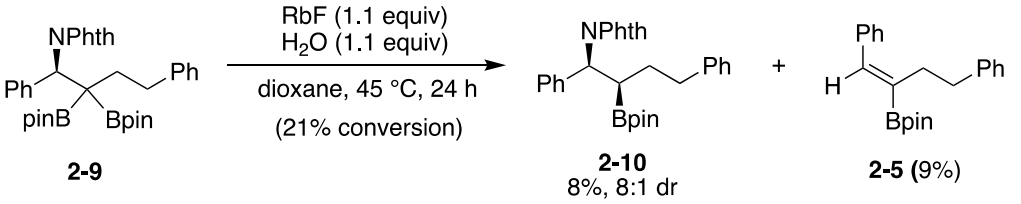
$[\alpha]_D^{20}$: –11.4 (*c* 0.65, $CHCl_3$).

Confirmation of the stereochemistry of β-aminoalkylboronate 2-8: Removal of the sulfinyl moiety of β-aminoalkylboronate **2-4a** followed by protection of the amino group (NH_2) with PivCl afforded the corresponding (1*S*,2*R*)-*N*-pivaloyl-protected alkylboronate, which is the same isomer as the above obtained β-aminoalkylboronate **2-8** by comparing their NMR spectrum.



The *N*-pivaloyl-protected β-aminoalkylboronate (1*S*,2*R*)-**2-8** was prepared by following literature procedures[61,91] with slight modification**.** In an oven-dried 5 mL round-bottomed flask, β-aminoalkylboronate **2-4a** (92 mg, 0.20 mmol, 1.0 equiv) was dissolved in MeOH (0.8 mL), followed by dropwise addition of an HCl solution (4N in dioxane, 0.27 mL, 5.4 equiv) at room temperature. After stirring for 2 h at room temperature, the reaction mixture was concentrated under reduced pressure. The crude mixture was used for the next step without further purification. In an oven-dried 5 mL round-bottomed flask, the above obtained β-amino alkylboronate (*ca.* 0.20 mmol) was dissolved in CH_2Cl_2 (1.6 mL). The mixture was cooled to 0 °C and diisopropylethylamine (0.18 mL, 1.0 mmol, 5.0 equiv) was added dropwise to the flask. The resulting mixture was stirred for 5 min. Pivaloyl chloride (52 μL, 0.40 mmol, 2.0 equiv) was added dropwise, and the reaction mixture was allowed to warm to room temperature and stirred for 3 h. Upon completion, the flask was cooled to 0 °C, and the reaction mixture was quenched by the addition of saturated sodium bicarbonate aqueous solution (2 mL). The aqueous and organic layers were separated, and the aqueous layer was extracted with EtOAc (3×5 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude mixture was purified by flash silica gel chromatography (4:1 hexanes/EtOAc) to afford the desired β-aminoalkylboronate (1*S*,2*R*)-**2-7** as a white solid (76 mg, 88%).

2.10.15.3 Synthesis and Protodeboronation of *N*-Phth-Protected *gem*-Bis(boronate) 2-9



Synthesis of phthalimide-protected *gem*-bis(boronate) 2-9: In an 10 mL round-bottomed flask, β-sulfinimido *gem*-bis(boronate) **2-3a** (0.58 g, 1.0 mmol, 1.0 equiv) was dissolved in MeOH (4 mL), followed by dropwise addition of an HCl solution (4 N in dioxane, 1.4 mL, 5.4 equiv) at room temperature. After stirring for 2 h at room temperature, the reaction mixture was concentrated under reduced pressure. The crude mixture was used for the next step without further purification. In a 50 mL round-bottomed flask, the above obtained β-amino *gem*-bis(boronate) (*ca.* 1.0 mmol) and triethylamine (1.5 mL, 1.1 mmol, 1.1 equiv) were dissolved in toluene (20 mL), followed by the addition of phthalic anhydride (0.16 g, 1.1 mmol, 1.1 equiv) . The resulting mixture was refluxed overnight using a Dean–Stark apparatus. Upon completion, 1N HCl (20 mL) and EtOAc (20 mL) were added, and the layers were separated off. The aqueous layer was extracted further with EtOAc (2×20 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude mixture was purified by flash silica gel chromatography (10:1 to 7:1 hexanes/EtOAc) to afford *gem*-bis(boronate) **2-9** as a white solid (78 mg, 13%).

^{1}H NMR (498 MHz, $CDCl_3$) δ 7.79 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.77–7.73 (m, 2H), 7.67–7.63 (m, 2H), 7.25–7.18 (m, 3H), 7.15 (t, *J* = 7.5 Hz, 2H), 7.07 (t, *J* = 7.3 Hz, 1H), 7.03–6.99 (m, 2H), 5.92 (s, 1H), 2.56 (app dtd, *J* = 30.9, 12.9, 4.9 Hz, 2H), 2.11 (app td, *J* = 13.2, 4.8 Hz, 1H), 1.97 (app td, *J* = 13.3, 5.2 Hz, 1H), 1.27 (s, 6H), 1.22 (s, 6H), 1.19 (s, 6H), 1.16 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.9, 143.5, 140.1, 133.5, 132.3, 130.2, 128.5, 128.0, 127.2, 127.0, 125.3, 123.0, 83.3, 83.2, 57.1, 34.3, 33.9, 25.13, 25.11, 25.0, 24.9.

^{11}B NMR (160 MHz, $CDCl_3$) δ 33.6.

IR (cast film cm^{-1}): 3061, 2977, 1712, 1324, 1139.

HRMS (ESI-TOF) for $C_{36}H_{44}B_2NO_6$ $(M + H)^+$: *calcd.*: 608.3349; *found*: 608.3351.

mp: 50.4–53.9 ºC.

$[\alpha]_D^{20}$: +63.9 (*c* 0.92, $CHCl_3$).

Procedure for protodeboronation of *N*-phthalimide-protected *gem*-bis(boronate) 2-9: Protodeboronation of *gem*-bis(boronate) **2-9** was performed by following the procedure for synthesis of β-amino alkylboronate **2-4a** with RbF (11 mg, 0.11 mmol, 1.1 equiv), β-amino *gem*-bis(boronate) **2-9** (61 mg, 0.10 mmol, 1.0 equiv), water (2.0 μL, 0.11 mmol, 1.1 equiv), and dioxane (1 mL). The crude mixture was purified by flash silica gel chromatography (9:1 to 8:1 hexanes/EtOAc) to afford β-aminoalkylboronate **2-10** as a white solid (4 mg, 8%), accompanied with 9% of elimination product **2-5** and 79% recovery of β-amino *gem*-bis(boronate) **2-9**; ^{1}H NMR analysis of the crude mixture indicated 8:1 diastereoselectivity.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (dd, *J* = 5.3, 3.0 Hz, 2H), 7.65 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.57 (d, *J* = 7.2 Hz, 2H), 7.29 (t, *J* = 7.5 Hz, 2H), 7.23 (app t, *J* = 7.5 Hz, 3H), 7.14 (t, *J* = 7.4 Hz, 1H), 7.07 (d, *J* = 7.3 Hz, 2H), 5.34 (d, *J* = 12.7 Hz, 1H), 2.93 (ddd, *J* = 13.3, 10.0, 3.9 Hz, 1H), 2.73 (ddd, *J* = 13.4, 11.0, 4.9 Hz, 1H), 2.52 (ddd, *J* = 13.5, 10.6, 6.4 Hz, 1H), 1.74–1.64 (comp m, A part of ABMNX, 1H), 1.64–1.56 (comp m, B part of ABMNX, 1H), 1.04 (s, 6H), 1.03 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.2, 142.4, 139.2, 133.7, 132.2, 129.0, 128.6, 128.4, 128.3, 127.8, 125.7, 123.0, 83.3, 56.4, 35.0, 31.1, 24.8, 24.6.

^{11}B NMR (160 MHz, $CDCl_3$) δ 33.8.

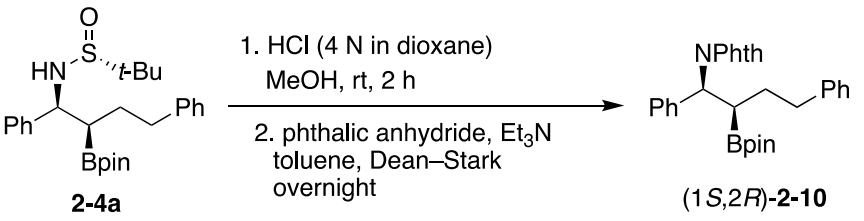
IR (cast film cm^{-1}): 3063, 2980, 1713, 1385, 1168.

HRMS (ESI-TOF) for $C_{30}H_{32}BNNaO_4$ $(M + Na)^+$: *calcd.*: 504.2317; *found*: 504.2318.

mp: 163.8–166.1 ºC.

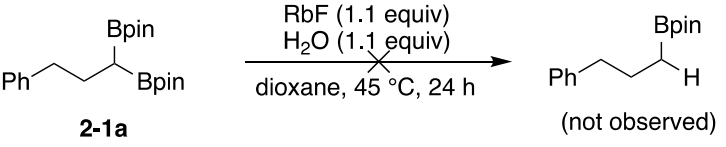
$[\alpha]_D^{20}$: +5.3 (*c* 0.71, $CHCl_3$).

Confirmation of stereochemistry of β-aminoalkylboronate 2-10: Removal of the sulfinyl moiety of β-aminoalkylboronate **2-4a**, followed by protection of the amino group (NH_2) with phthalic anhydride afforded the corresponding (1*S*,2*R*)-phthalimide-protected alkylboronate, which is the same isomer as the above obtained β-amino alkylboronate **2-10** by comparing their NMR spectrum.



The phthalimide-protected β-aminoalkylboronate (1*S*,2*R*)-**2-10** was prepared by following literature procedures[61,92] with slight modification**.** In an oven-dried 5 mL round-bottomed flask, β-aminoalkylboronate **2-4a** (0.23 g, 0.50 mmol, 1.0 equiv) was dissolved in MeOH (2 mL), followed by dropwise addition of HCl solution (4 N in dioxane, 0.68 mL, 5.4 equiv) at room temperature. After stirring for 2 h at room temperature, the reaction mixture was concentrated under reduced pressure. The crude mixture was used for the next step without further purification. In a 25 mL round-bottomed flask, the above obtained β-amino alkylboronate (*ca.* 0.50 mmol) and triethylamine (74 μL, 0.55 mmol, 1.1 equiv) were dissolved in toluene (10 mL), followed by the addition of phthalic anhydride (78 mg, 0.55 mmol, 1.1 equiv) . The resulting mixture was refluxed overnight using a Dean–Stark apparatus. Upon completion, an aqueous solution of HCl (1.0 N, 10 mL) and EtOAc (10 mL) were added and the layers were seperated. The aqueous layer was extracted further with EtOAc (2×10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude mixture was purified by flash silica gel chromatography (8:1 to 7:1 hexanes/EtOAc) to afford the desired β-amino alkylboronate (1*S*,2*R*)-**2-10** as a white solid (0.18 g, 74%);

2.10.15.4 Attempted Protodeboronation of 1,1-Diborylalkane 2-1a



Protodeboronation of *gem*-bis(boronate) **2-1a** was performed by following the procedure for synthesis of β-aminoalkylboronate **2-4a** with RbF (11 mg, 0.11 mmol, 1.1 equiv), *gem*-bis(boronate) **2-1a** (37 mg, 0.10 mmol, 1.0 equiv), water (2.0 μL, 0.11 mmol, 1.1 equiv), and dioxane (1 mL). The resulting mixture was stirred at 45 ºC for 24 h. ^{1}H NMR analysis of the

crude mixture indicated no formation of the desired product and only recovery of starting material **2-1a**.

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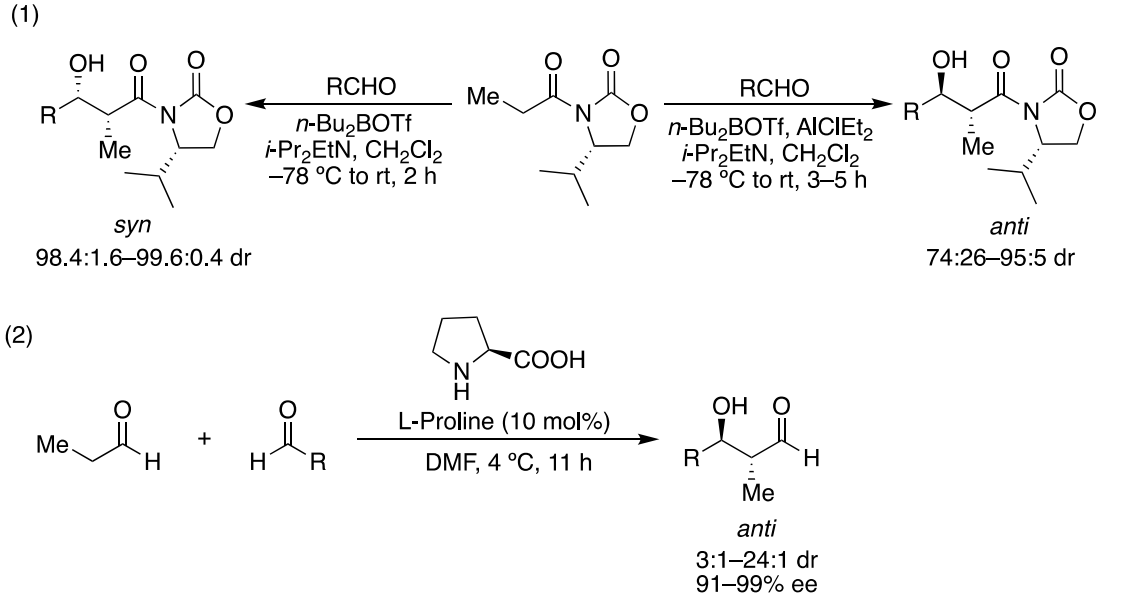
Chapter 3

Inverting the Stereoselectivity of Monoprotodeboronation of β-Amino *gem*-Bis(boronates) Towards the Elusive *anti*-α,β-Disubstituted β-Aminoalkylboronates

3.1 Introduction

3.1.1 Importance of Stereodivergent Synthesis

Controlling the absolute stereochemistry of organic molecules is a crucial endeavor in drug discovery, one that is made possible by advances in enantioselective synthetic methods achieved in the past decades.[1,2] Meanwhile, it is equally important but also challenging to control the relative configuration of a chiral molecule since chiral molecules possessing multiple stereogenic centers are very common in natural products and bioactive compounds.[3] This paradox is exemplified well by the longstanding '*anti*-aldol problem' that long plagued propionate synthesis.[4,5] In 1981, Evan and co-workers developed an extremely powerful oxazolidinone chiral auxiliary for asymmetric aldol reactions. As shown in Scheme 3-1 (eq.



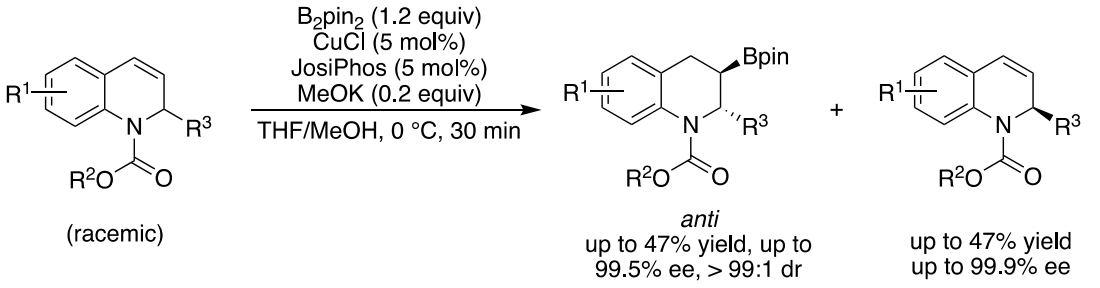
Scheme 3-1. *anti*-Aldol problem: 1) aldol reactions using the oxazolidinone chiral auxiliary and 2) aldol reactions using L-proline as the organocatalyst.

1), the aldol reaction using this chiral auxiliary provides 1,2-*syn*-propionate products with very high levels of stereoselectivity.[6] With the extra addition of a Lewis acid ($AlClEt_2$), the stereochemical outcome of the aldol reaction can be switched to afford the anti products (eq. 2), however, the level of stereoselectivity is significantly inferior to that of *syn*-aldols.[4] In addition, the more recent development of organocatalysis also exhibits major issues regarding diastereocontrol. For example, MacMillan and co-workers documented a proline-catalyzed asymmetric aldol reaction in 2002 (Scheme 3-1, eq. 2).[5] Despite achieving the 1,2-*anti*-aldol product with excellent enantioselectivity, the anti-selectivity of many examples is only low to moderate. In this regard, methods that can supply all stereoisomers of a compound independently from the same precursor constitute an ideal that is achieved rarely. This concept, stereodivergence, is particularly useful in drug discovery since drug candidates and their isomers can have distinct or even adverse bioactivities, and their effects also need to be evaluated well.[7–9]

3.1.2 Importance of Stereodivergent Synthesis of α,β-Disubstituted β-Aminoalkylboronates

As described in Chapter 1 (see Section 1.3), like their lower α homologs, β-amino-alkylboronates are viewed as a bioisostere of the corresponding β-amino acids. Bioisosterism of naturally occurring α-amino acids and α-amino aldehydes has inspired the rich chemistry of α-aminoalkylboronic acids and a variety of preparative methods to access these compounds,[10] which culminated in the commercialization of the anticancer drugs bortezomib and ixazomib and the antibiotic vaborbactam (cf., Section 1-2). Though less studied, interest in β-aminoalkylboronic acids is surging owing to their potential applications as synthetic intermediates, in catalysis, and drug discovery (cf., Section 1-3 and 1-4). Deplorably, further progress is hampered by the scarcity of selective methods to prepare both syn and anti diastereomers of optically enriched α,β-disubstituted β-aminoalkylboronates. Efficient methods exist to prepare the syn isomer in high enantioselectivity (cf., Section 1-5). In contrast, only a single efficient method was reported to access the anti diastereomer, a kinetic resolution restricted to a niche class of tetrahydroquinolines (Scheme 3-2).[11] Therefore, to expand the applications of β-aminoalkylboronic acids fully, it is essential to develop stereodivergent

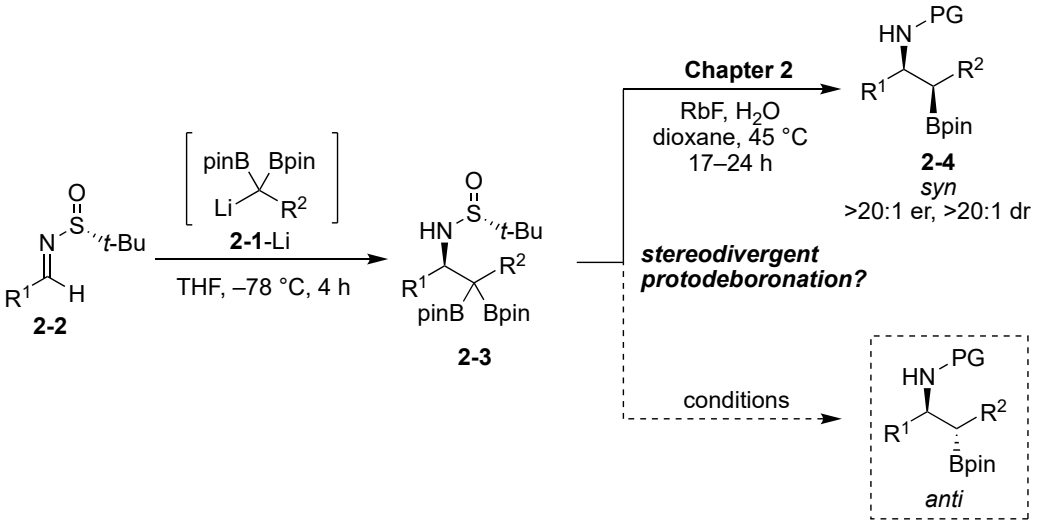
methods to access both the syn and anti diastereomers of α,β-disubstituted β-aminoalkylboronic esters.



Scheme 3-2. Synthesis of cyclic *anti*-β-aminoalkylboronates by kinetic resolution of racemic 2-substituted-1,2-dihydroquinolines.

3.2 Objective

Chapter 2 described a new and efficient strategy to prepare acyclic α,β-disubstituted β-aminoalkylboronates based on the highly stereoselective addition of lithiated *gem*-diborylalkanes onto chiral sulfinylimines. The resulting β-sulfinimido *gem*-diboronates can be monoprotodeboronated to form the *syn*-β-aminoalkylboronates in high yield and excellent diastereoselectivity for a wide scope of substituents (Scheme 3-3). To make this deboronation



Scheme 3-3. Stereodivergent synthesis of β-aminoalkylboronates via diastereospecific monoprotodeboronation of β-sulfinimido *gem*-bis(boronates).

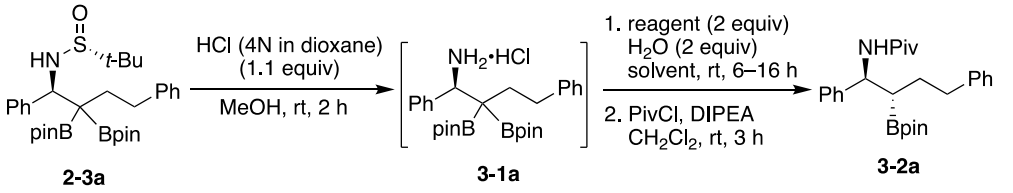
strategy truly general and versatile, it is essential to develop a complementary variant to prepare the anti diastereomers (Scheme 3-3).

3.3 Optimization of the Monoprotodeboronation of β-Amino *gem*-Bis(boronates) for the Synthesis of *anti*-α,β-Disubstituted β-Aminoalkylboronates

In the course of the previous optimization of the monoprotodeboronation of β-sulfinimido *gem*-bis(boronates) **2-3** to access *syn*-β-aminoalkylboronates **2-4**, no conditions were identified to favor the formation of the anti diastereomer (cf., Table 2-1 and 2-2). Thus, to design a complementary method favoring the *anti*-β-aminoalkylboronate, it was reasoned the steps of protodeboronation and deprotection of the *N*-sulfinyl amine could be inverted. To this end, the initial study employed *N*-*tert*-butanesulfinyl β-amino *gem*-bis(boronate) **2-3a**, which was desulfinylated first using anhydrous HCl to provide, after simple evaporation, the amine salt **3-1a** as the model substrate (Table 3-1). In this study, the amine of the first-formed deboronated product was transformed into a pivaloyl amide (**3-2a**) for ease of isolation. Thus, when employing the protodeboronation conditions previously optimized to provide the syn diastereomer (cf., Table 2-2, entry 13), **3-1a** afforded a low yield of product **3-2a** favoring the anti isomer in a 5:1 ratio (Table 3-1, entry 1).

In order to improve the yield and diastereomeric ratio, my first efforts were made towards examination of inorganic bases, fluoride-based reagents, and reaction solvents (Table 3-1). In this study of reaction optimization, the yield was determined by ^{1}H NMR analysis using dibromomethane as the internal standard, and the diastereomeric ratio was determined by comparing peak heights of isolated resonances in the ^{1}H NMR spectra of the crude reaction mixture. Screening of some fluoride-based reagents (entries 2–3), inorganic bases (entries 4–5), and reaction solvents (entries 6–8) revealed that use of RbF as the reagent with CH_2Cl_2 as the solvent increased the diastereoselectivity to 9:1, albeit, with a low yield (entry 8). It was found that switching the reagent from RbF to TBAF led to a much higher yield (81%) with slightly higher diastereoselectivity (10:1 dr; entry 9). Further evaluation of reaction solvents (entries 10–13) with TBAF led to both a lower yield and diastereoselectivity, thus confirming that CH_2Cl_2 is the optimal reaction solvent.

Table 3-1. Initial Evaluation of Reaction Conditions[a]



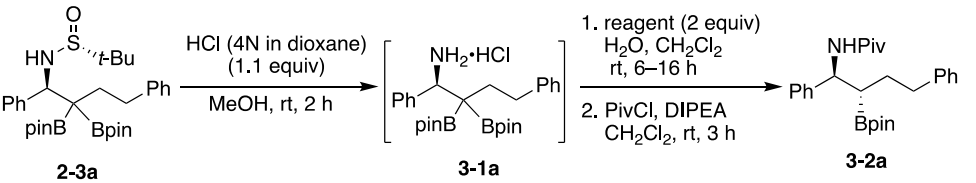
Entry	Reagent	Solvent	Yield of **3-2a** [%][b] (*anti*+*syn*)	dr[c] (*anti*:*syn*)
1	RbF	dioxane	25	5:1
2	CsF	dioxane	32	3:1
3	KHF_2	dioxane	<5	N.D.
4	K_2CO_3	dioxane	13	6:1
5	NaOH	dioxane	20	4:1
6	RbF	*n*-hexane	32	3:1
7	RbF	MeOH	33	1:1
8	RbF	CH_2Cl_2	24	9:1
9	TBAF•3H_2O	CH_2Cl_2	81	10:1
10	TBAF•3H_2O	CH_3CN	32	2:1
11	TBAF•3H_2O	THF	40	5.6:1
12	TBAF•3H_2O	toluene	59	6.1:1
13	TBAF•3H_2O	dioxane	44	6.6:1

[a]Reactions performed on a 0.1 mmol scale under N_2 atm. [b]Yield determined by ^{1}H NMR analysis using dibromomethane as the internal standard. [c]dr determined by peak heights of isolated resonances by ^{1}HNMR of the crude reaction mixture. TBA = tetrabutylammonium, dioxane = 1,4-dioxane, N.D. = not determined.

To investigate if the nature of the counteranion of the tetrabutylammonium reagent has an impact on the diastereoselectivity, numerous tetrabutylammonium reagents were examined (Table 3-2). Tetrabutylammonium reagents, such as tetrabutylammonium nitrate, hydroxide, and hydrogensulfate, were found to be less effective than TBAF (entries 2–7). Gratifyingly, the use of tetrabutylammonium acetate increased the diastereoselectivity (13:1) with a good yield (66%; entry 8). However, employing other tetrabutylammonium aliphatic carboxylates with increased steric bulk, like tetrabutylammonium isobutyrate (entry 9), trimethylacetate (entry 10), and cyclohexanecarboxylate (entry 11), resulted in a similar diastereoselectivity to that of tetrabutylammonium acetate. Surprisingly, tetrabutylammonium phenylacetate (entry 12) and diphenylacetate (entry 13) delivered an excellent diastereoselectivity (>20:1 dr). Moreover, tetrabutylammonium phenylacetate afforded **3-2a** in a slightly higher yield than

tetrabutylammonium diphenylacetate (entry 12 vs entry 13). The reason for the excellent diastereoselectivity with these two reagents is unclear. It is likely that some sort of π-stacking interactions between the phenyl groups of **3-1a** and tetrabutylammonium phenylacetate or diphenylacetate may play a role.

Table 3-2. Evaluation of Tetrabutylammonium Reagents[a]



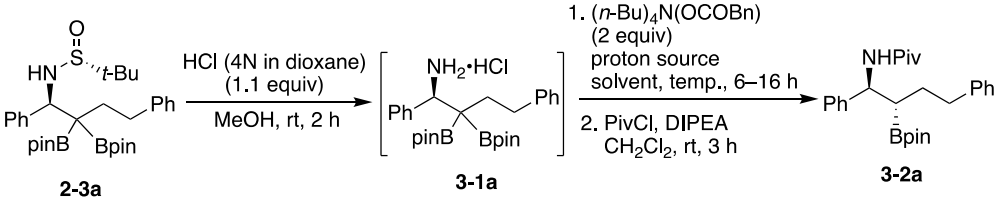
Entry	Reagent	Water (equiv)	Yield of **3-2a** [%][b] (*anti*+*syn*)	dr[c] (*anti*:*syn*)
1	TBAF•3H_2O	–	81	10:1
2	(*n*-Bu)$_4$N(OC_6H_4*p*-NO_2)	6	75	10:1
3	(*n*-Bu)$_4$NNO_3	6	N.R.	–
4	(*n*-Bu)$_4$NOH	6	76	4.2:1
5	(*n*-Bu)$_4$NHSO_4	6	<5	N.D.
6	(*n*-Bu)$_4$N(OSO_2CF_3)	6	N.R.	–
7	(*n*-Bu)$_4$N(OCOPh)	6	70	10:1
8	(*n*-Bu)$_4$N(OCOMe)	6	66	13:1
9	(*n*-Bu)$_4$N(OCO*i*-Pr)	6	70	12:1
10	(*n*-Bu)$_4$N(OCO*t*-Bu)	6	78	13:1
11	(*n*-Bu)$_4$N(OCOC_6H_{11})	6	78	12:1
12	(*n*-Bu)$_4$N(OCOBn)	6	63	>20:1
13	(*n*-Bu)$_4$N[OCOCH$(Ph)_2$]	6	61	>20:1

[a]Reactions performed on a 0.1 mmol scale under N_2 atm. [b]Yield determined by ^{1}H NMR analysis using dibromomethane as the internal standard. [c]dr determined by peak heights of isolated resonances by ^{1}HNMR of the crude reaction mixture. TBA = tetrabutylammonium, N.D. = not determined, N.R. = no reaction.

Starting with tetrabutylammonium phenylacetate, evaluation of reaction parameters, such as the proton source, solvent, and reaction temperature, was performed in order to improve the yield of monoprotodeboronation (Table 3-3). When lowering the amount of tetrabutylammonium phenylacetate, both the yield and diastereoselectivity were decreased

(entry 2). Other proton sources, such as HCl (entry 3) and TsOH (entry 4), were found to be much less effective than water. These results highlighted the importance of water as the proton source, which also was proved by the poor result of monoprotodeboronation in the absence of water (entry 5). It was found that six equivalents of water were optimal since both lowering (entry 6) or increasing (entry 7) the amount of water led to a slightly lower yield. Attempting the reaction at a lower (entry 8) or higher (entry 9) temperature also led to a lower yield. Other solvents (entries 10–13) were evaluated and were less efficient than CH_2Cl_2.

Table 3-3. Optimization of Reaction Conditions with Tetrabutylammonium Phenylacetate[a]

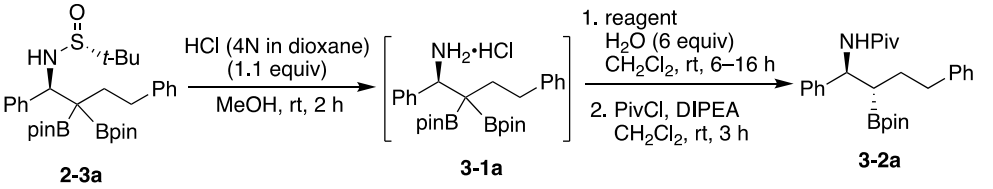


Entry	Proton Source (equiv)	Solvent	Temp. (ºC)	Yield of **3-2a** [%][b] (*anti*+*syn*)	dr[c] (*anti*:*syn*)
1	H_2O (6)	CH_2Cl_2	rt	63	>20:1
2[d]	H_2O (6)	CH_2Cl_2	rt	47	11:1
3	HCl_{aq} (1 N, 6)	CH_2Cl_2	rt	<10	N.D.
4	TsOH•H_2O (6)	CH_2Cl_2	rt	N.R.	–
5	H_2O (0)	CH_2Cl_2	rt	<5	–
6	H_2O (2)	CH_2Cl_2	rt	58	>20:1
7	H_2O (0.1 mL)	CH_2Cl_2	rt	61	>20:1
8	H_2O (6)	CH_2Cl_2	0	8	>20:1
9	H_2O (6)	CH_2Cl_2	40	48	>20:1
10	H_2O (6)	toluene	rt	30	13:1
11	H_2O (6)	dioxane	rt	31	11:1
12	H_2O (6)	$CHCl_3$	rt	44	>20:1
13	H_2O (6)	DCE	rt	51	>20:1

[a]Reactions performed on a 0.1 mmol scale under N_2 atm. [b]Yield determined by ^{1}H NMR analysis using dibromomethane as the internal standard. [c]dr determined by peak heights of isolated resonances by ^{1}HNMR of the crude reaction mixture. [d]With 0.5 equiv of $(n\text{-Bu})_4N(OCOBn)$. N.D. = not determined, N.R. = no reaction, dioxane = 1,4-dioxane, DCE = 1,2-dichloroethane.

Failing to enhance the yield through the optimization with tetrabutylammonium phenylacetate, attention was turned to the evaluation of tetrabutylammonium phosphate reagents. Since the phosphate anion is a weaker nucleophile and base than the carboxylate anion, it was reasoned that the use of tetrabutylammonium phosphates could provide milder protodeboronation conditions, thus leading to a higher yield of the product and less side products, including the elimination side product observed in the syn-selective monoprotodeboronation (cf., Table 2-1 and 2-2). As shown in Table 3-4, all of the tested tetrabutylammonium phosphates (entries 2–4) afforded an improved yield compared to tetrabutylammonium phenylacetate, and tetrabutylammonium dibenzylphosphate (entry 4) delivered the highest diastereoselectivity (>20:1). Increasing the amount of tetrabutylammonium dibenzylphosphate to 2.5 equivalents eventually led to the highest yield (82%) with excellent diastereoselectivity (>20:1 dr; entry 12), which was deemed to be satisfactory optimal conditions.

Table 3-4. Evaluation of Tetrabutylammonium Phosphates[a]



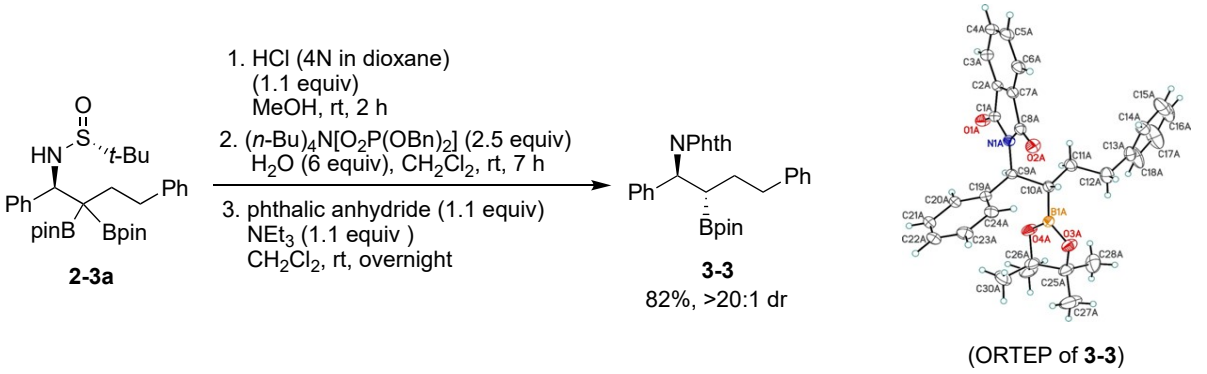
2-3a **3-1a** **3-2a**

Entry	Reagent (equiv)	Yield of **3-2a** [%][b] (*anti*+*syn*)	dr[c] (*anti*:*syn*)
1	(*n*-Bu)$_4$N(OCOBn) (2.0)	63	>20:1
2	(*n*-Bu)$_4$N[O$_2$P(OH)$_2$] (2.0)	64	9.3:1
3	(*n*-Bu)$_4$N[O$_2$P(O*t*-Bu)$_2$] (2.0)	74	15:1
4	(*n*-Bu)$_4$N[O$_2$P(OBn)$_2$] (2.0)	75	>20:1
5	(*n*-Bu)$_4$N[O$_2$P(OBn)$_2$] (2.5)	82(77)[d]	>20:1

[a]Reactions performed on a 0.1 mmol scale under N_2 atm. [b]Yield determined by ^{1}H NMR analysis using dibromomethane as the internal standard. [c]dr determined by peak heights of isolated resonances by ^{1}HNMR of the crude reaction mixture. N.R. = no reaction, N.D. = not determined. [d]Isolated yield of the anti isomer.

3.4 Proof of Stereochemistry of *anti*-α,β-Disubstituted β-Aminoalkylboronates

Besides *N*-pivaloylation, the amine of the first-formed deboronated β-aminoalkylboronate product also could undergo a *N*-phthalimide (*N*-Phth) protection, producing *N*-Phth-protected β-aminoalkylboronate **3-3** in 82% yield with excellent diastereoselectivity (>20:1 dr; Scheme 3-4). β-Aminoalkylboronate **3-3** was recrystallized to afford high-quality crystals, and the X-ray crystallographic analysis confirmed the anti stereochemistry of β-aminoalkylboronate **3-2a** (ORTEP view in Scheme 3-4); all other compounds in this study were assigned by analogy to **3-3**.

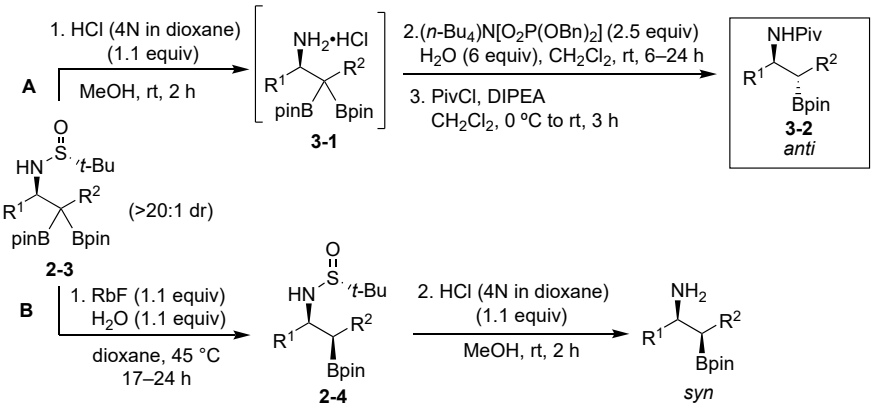


Scheme 3-4. Synthesis of *N*-Phth-protected *anti*-β-aminoalkylboronates **3-3** and ORTEP representation of X-ray crystallographic structure of **3-3** as the proof of anti stereochemistry.

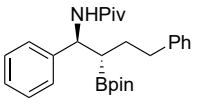
3.5 Scope of the Diastereodivergent Synthesis of α,β-Disubstituted β-Aminoalkylboronates

With the optimized protodeboronation conditions of Table 3-4 (entry 5), the substrate scope of the reaction was examined by engaging a large selection of α,β-disubstituted β-sulfinimido *gem*-bis(boronates) described in Chapter 2. *anti*-β-Aminoalkylboronates **3-2** are stable on the silica gel column, and the indicated yields in Table 3-5 are based on the product **3-2** after isolation by flash column chromatography. The diastereomeric ratio was determined by comparing peak heights of isolated resonances in the ^{1}H NMR spectra of the crude reaction mixture. Remarkably, together with the previous protodeboronation conditions to access the syn isomers (see conditions in Chapter 2), protodeboronation of β-amino *gem*-bis(boronates)

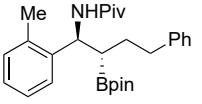
Table 3-5. Scope of the Diastereodivergent Synthesis of α,β-Disubstituted β-Aminoalkylboronates



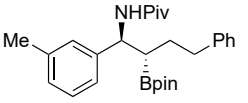
Scope of R^1(Aryl), R^2 = CH_2CH_2Ph



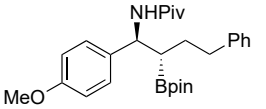
3-2a
A: 77%, >20:1 dr
[B: 87%, <1:20 dr]



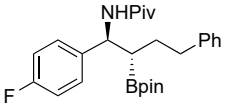
3-2b
A: 88%, >20:1 dr
[B: 91%, <1:20 dr]



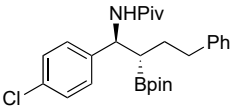
3-2c
A: 74%, >20:1 dr
[B: 60%, <1:20 dr]



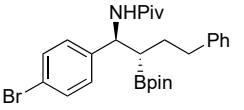
3-2d
A: 82%, >20:1 dr
[B: 78%, <1:20 dr]



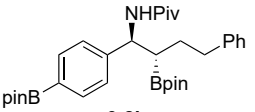
3-2e
A: 70%, >20:1 dr
[B: 87%, <1:20 dr]



3-2f
A: 50%, >20:1[b]
[B: 72%, <1:20 dr]

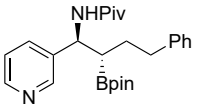


3-2g
A: 60%, 16:1 dr
[B: 91%, <1:20 dr]

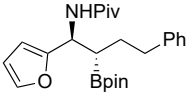


3-2h
A: 75%, 12:1 dr
[B: 75%, <1:20 dr]

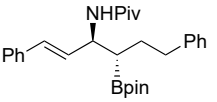
Scope of R^1 (heteroaryl, alkynyl, alkenyl, alkyl), R^2 = CH_2CH_2Ph



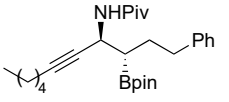
3-2i
A: 65%, 9.4:1 dr[e]
[B: 73%, <1:20 dr]



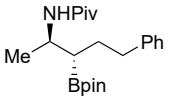
3-2j
A: 53%, 12:1 dr[c]
[B: 69%, <1:20 dr]



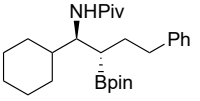
3-2k
A: 65%, 15:1 dr
[B: 74%, <1:20 dr]



3-2l
A: 39%, 5:1 dr[d,f]
[B: 56%, <1:20 dr]

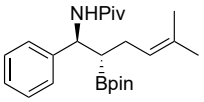


3-2m
A: 61%, 4:1 dr[e,f]
[B: 59%, 1:11 dr]

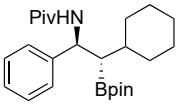


3-2n
A: 62%, 8.5:1 dr[b]
[B: 55%, 1:9 dr]

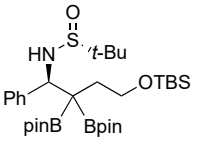
Scope of R^2, R^1 = Ph



3-2o
A: 72%, >20:1 dr
[B: 90%, <1:20 dr]



3-2p
A: 81%, >20:1 dr
[B: 85%, <1:20 dr]



2-3b
unsuccessful substrate

[a]Reactions performed on a 0.3 mmol scale under N_2 atm. Yields of isolated products are given. For conditions B (see Chapter 2), the indicated dr is *anti*:*syn*. [b]With 3 equiv of $(n\text{-Bu})_4N[O_2P(OBn)_2]$. [c]With 3.5 equiv of $(n\text{-Bu})_4N[O_2P(OBn)_2]$. [d]With 4 equiv of $(n\text{-Bu})_4N[O_2P(OBn)_2]$. [e]With 5 equiv of $(n\text{-Bu})_4N[O_2P(OBn)_2]$. [f]At 60 ºC. $CHCl_3$ used as the solvent.

3-1 allows the stereodivergent synthesis of both diastereomers of α,β-disubstituted β-aminoalkylboronates (Table 3-5).

Using sequence **A**, the simple three-step transformation of β-sulfinimido *gem*-bis(boronates) containing various aryl (R^1) substituted groups at the ortho, meta or para positions was found to be effective, producing the corresponding *anti*-β-aminoalkylboronates (**3-2b**–**h**) in good to high yields (50–88%) with good to excellent diastereoselectivity (12:1–>20:1 dr). Under the standard protodeboronation conditions, the monoprotodeboronation of heteroaryl substituted (R^1) β-amino *gem*-bis(boronates) **3-1i** and **3-1j** gave only moderate conversions. It was discovered that by employing a larger amount of $(n\text{-Bu})_4N[O_2P(OBn)_2]$, **3-1i** and **3-1j** were monoprotodeboronated efficiently to yield β-aminoalkylboronates **3-2i** and **3-2j**. *gem*-Bis(boronate) bearing an alkenyl group as the R^1 substituent also was found to be a suitable substrate and underwent the sequence **A** to deliver β-aminoalkylboronates **3-2k** in a 65% yield with high diastereoselectivity. Alkynyl- and alkyl-containing (R^1) *gem*-bis(boronates) (**3-1l**–**n**) are challenging substrates in protodeboronation, requiring a higher reaction temperature and/or a larger amount of $(n\text{-Bu})_4N[O_2P(OBn)_2]$ for full conversions. Moreover, alkynyl and alkyl substituents affect the diastereoselectivity, affording the *anti*-β-aminoalkylboronates (**3-2l**–**n**) with only low to moderate diastereoselectivity (4:1–8.5:1 dr). Attempts at improving the diastereoselectivity for these substrates were made by testing other tetrabutylammonium reagents, such as TBAF, $(n\text{-Bu})_4N(OCOBn)$, $(n\text{-Bu})_4N(OCOPh)$, and $(n\text{-Bu})_4N(OCOMe)$. Unfortunately, all of these reagents showed an inferior reactivity to $(n\text{-Bu})_4N[O_2P(OBn)_2]$. The reason for the much lower diastereoselectivity of β-aminoalkylboronates **3-2l**–**n** compared to that of aryl-containing (R^1) β-aminoalkylboronates **3-2a**–**h** is unclear. However, it can be suggested that π-stacking interactions between the aryl group (R^1) and the phenyl group of $(n\text{-Bu})_4N[O_2P(OBn)_2]$ may be essential for the excellent diastereoselectivity of β-aminoalkylboronates **3-2a**–**h**. Thus, the lack of these interactions in β-aminoalkylboronates **3-2l**–**n** can lead to lower diastereoselectivity. Of note, the monoprotodeboronation of **3-1l** and **3-1m** resulted in an inseparable mixture of syn and anti diastereomers, albeit favoring the formation of anti diastereomers.

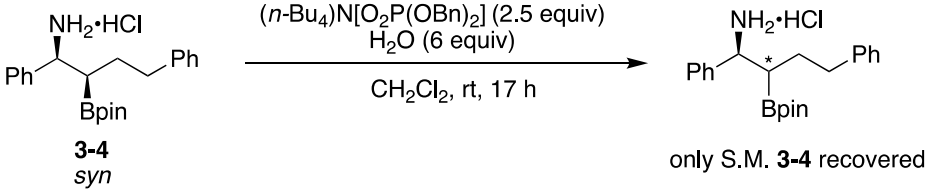
Variation at the R^2 substituents also were evaluated briefly. It was found that the sequence is compatible with R^2 substituents containing aryl, alkenyl, and cyclohexyl

functional groups, forming the expected *anti*-β-aminoalkylboronates (**3-2a**, **3-2o** and **3-2p**) in high yields with excellent diastereoselectivity (>20:1 dr). Unfortunately, a silyl ether-containing substrate (**2-3b**) failed to provide any desired β-aminoalkylboronate product, likely due to the instability of the silyl ether group under the acidic desulfinylation conditions.

3.6 Mechanistic Studies for the anti-Selective Mono-protodeboronation of β-Amino *gem*-Bis(boronates)

3.6.1 Control Experiments

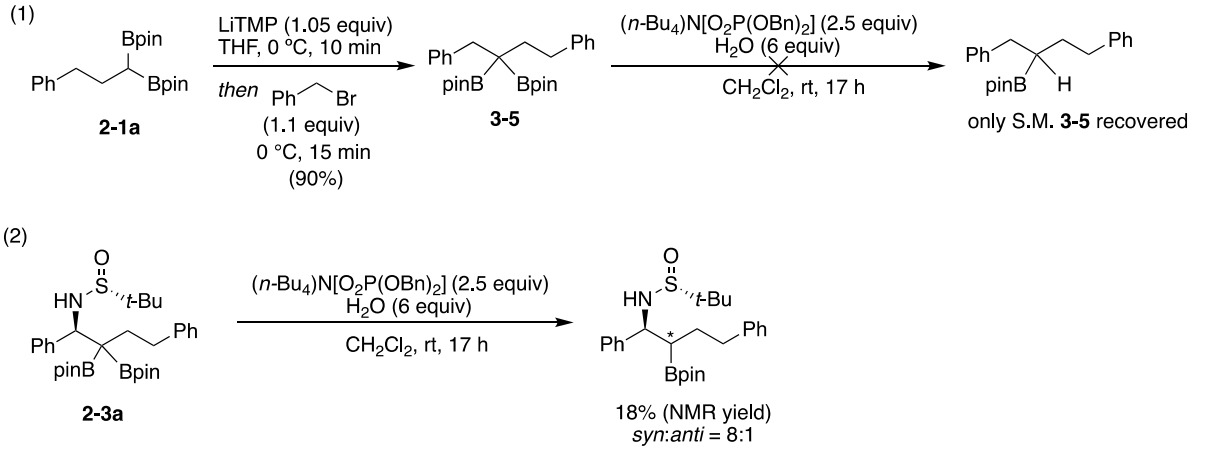
To understand the observed anti-diastereoselectivity in the protodeboronation step, a *syn*-β-aminoalkylboronate **3-4** with a primary ammonium unit was prepared using sequence **B** shown in Table 3-5. In the event, subjecting **3-4** to the optimal anti-selective protodeboronation conditions (Table 3-4, entry 5) returned it intact without any epimerization of its stereogenic centers (Scheme 3-5). This result implies that there is no equilibration, and the *anti*-β-aminoalkylboronate **3-2a** is a kinetically favored product.



Scheme 3-5. Control experiment: investigation of the epimerization of *syn*-β-aminoalkylboronate **3-4**.

The role of the primary ammonium units of β-amino *gem*-bis(boronates) **3-1** also was investigated. *gem*-Bis(boronate) **3-5** was synthesized through the benzylation of *gem*-bis(boronate) **2-1a** following a literature procedure[12] (Scheme 3-6, eq. 1). Under the optimal anti-selective monoprotodeboronation conditions (Table 3-4, entry 5), the protodeboronation of **3-5** returned only **3-5** and did not afford any protodeboronated product. This result suggests that the primary ammonium unit is essential for the high reactivity and anti-selectivity in the protodeboronation of β-amino *gem*-bis(boronates) **3-1**, which also was confirmed by the poor reactivity of sulfinimide **2-3a** under the optimal anti-selective protodeboronation conditions

(Scheme 3-6, eq. 2). This observation is consistent with the previous study of the syn-selective protodeboronation, where sulfinyl NH···OB hydrogen bonding was determined to be important for the reactivity and syn-selectivity (cf., Scheme 2-14 and Figure 2-3). Thus, in this anti-selective protodeboronation variant, it is reasonable that the same type of NH···OB hydrogen-bonding interaction occurs with both Bpin units since there are three available ammonium N–H bonds in *gem*-bis(boronates) **3-1**.



Scheme 3-6. Investigation of the role of the primary ammonium units of β-amino *gem*-bis(boronates) **2-3**: 1) synthesis and protodeboronation of 1,1-diborylalkane **3-5** and 2) protodeoboronation of **2-3a**.

3.6.2 Molecular Modeling

To support the notion that both Bpin units of *gem*-bis(boronates) **3-1** are involved in the NH···OB hydrogen-bonding interaction, molecular modeling was performed using density functional theory (DFT) with Spartan 18.[13,14] To this end, a simple representative compound was chosen to avoid long computation times. Thus, the pinacolate esters were replaced with ethylene glycol esters, and simple phenyl and methyl groups were employed. The equilibrium conformation of all three rotamers, as ammonium cations, was minimized first using PM3 (gas phase). The resulting structures were utilized as input structures for DFT (B3LYP 6-31G*) minimization [equilibrium geometry, nonpolar solvent state (THF), +1 charge]. Finally, the energy of all three rotamers were computed more accurately by DFT [ωB97X-V 6-311+G(2df,2p) nonpolar solvent state, +1 charge].

As shown in Figure 3-1, rotamer **I** with two NH···OB bonds (1.95, 2.00 Å lengths) indeed was found to be favored largely compared to rotamers **II** and **III** with only one

NH···OB bond. Moreover, rotamer **II** is more favorable than rotamer **III** since severe gauche interactions are minimized in rotamer **II** by placing the small H substituent between the two large boryl groups (Figure 3-1). The results of molecular modeling indicate that the most stable rotamer **I** could be the reactive conformer in the monoprotodeboronation of β-amino *gem*-bis(boronates) **3-1**. Nonetheless, according to the Curtin-Hammett principle, the most stable conformer does not always react quickly to produce the major product. Therefore, some transition state analysis will be required in the future to confirm that rotamer **I** can lead to the low-energy transition state for the formation of the *anti*-β-aminoalkylboronate products.

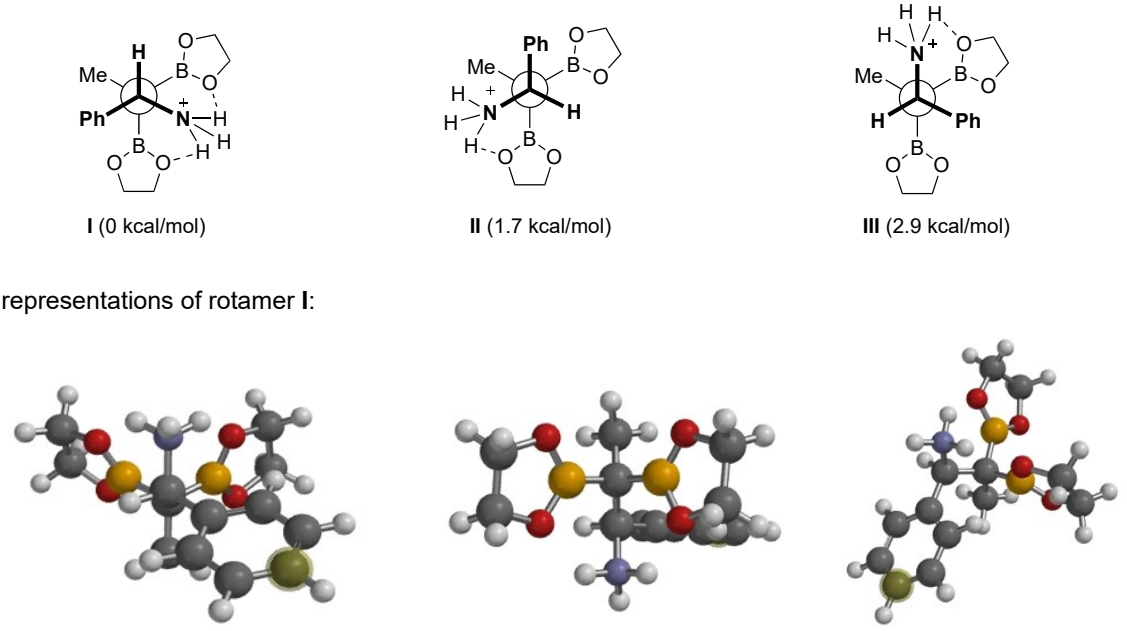
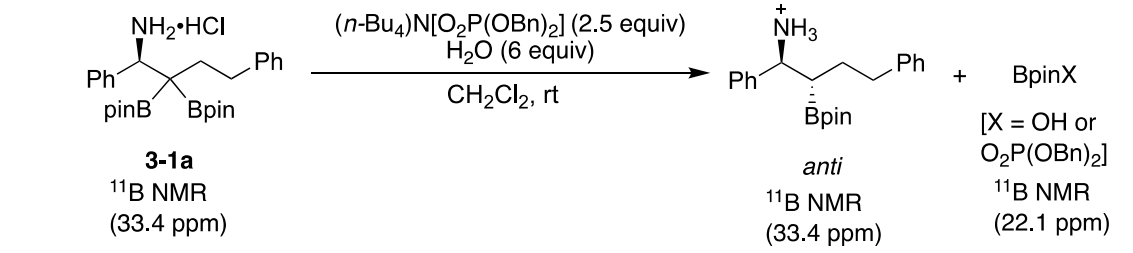


Figure 3-1. Energy of DFT minimized rotamers of a model α,β-disubstituted β-amino *gem*-bis(boronate).

3.6.3 ^{11}B NMR Studies

The mechanism of monoprotodeboronation of *gem*-bis(boronates) **3-1** was explored further using ^{11}B NMR spectroscopy. In this experiment, β-amino *gem*-bis(boronate) **3-1a** was added to a quartz NMR tube under N_2, followed by addition of a solution of tetrabutylammonium dibenzylphosphate in $CDCl_3$ and water (H_2O). The resulting mixture was shaken, and the protodeboronation process was monitored by ^{11}B NMR spectroscopy at room temperature. Mixing all the reagents and solvent together gave rise immediately to a signal at 33.4 ppm

(Figure 3-2). The signal at 33.4 ppm can be assigned to the non-quaternized Bpin groups of **3-1a**. As the reaction proceeded, a new signal at 22.1 ppm, which could be ascribed to the BpinOH or Bpin[$O_2P(OBn)_2$] by-product, was formed and increased in intensity (Figure 3-3). Contrasting with my previous study (cf., Section 2.6.2) and Aggarwal's work[15] on protodeboronation, no tetrahedral boron intermediate was observed in the reaction monitoring process. The results of ^{11}B NMR studies suggest that *gem*-bis(boronates) **3-1** undergo protodeboronation through a concerted trimolecular process that circumvents the formation of a discrete Lewis acid–base boronate complex.



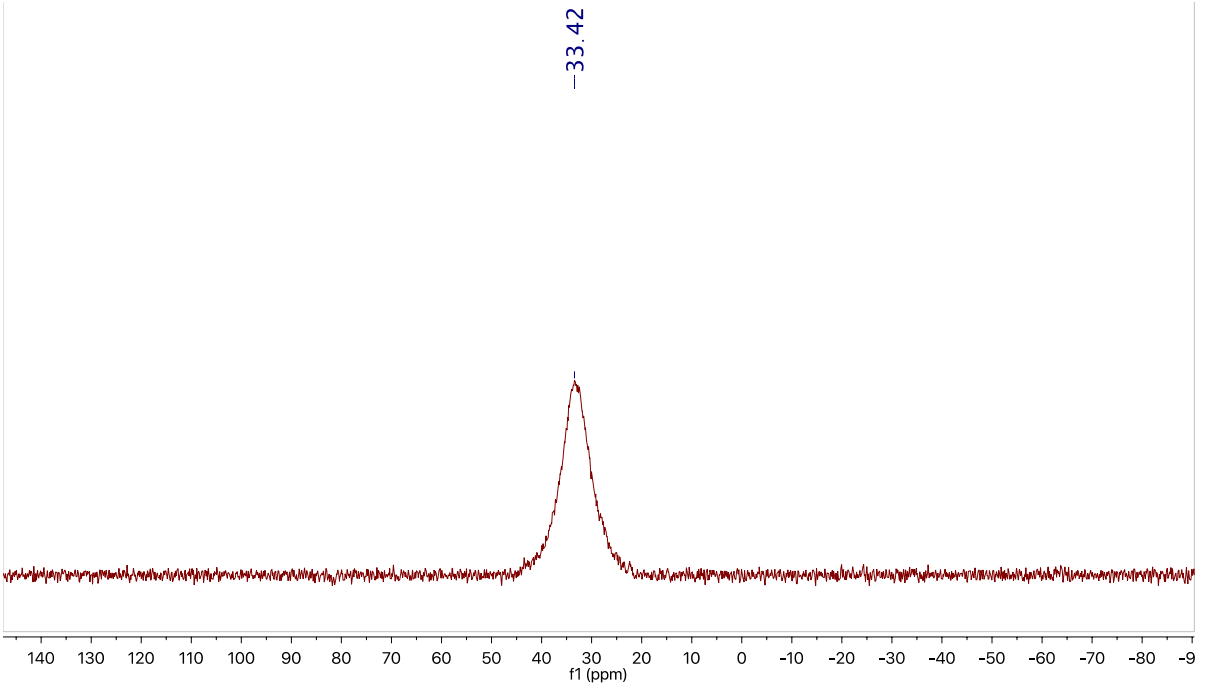


Figure 3-2. Initial ^{11}B NMR spectrum of the reaction mixture at room temperature.

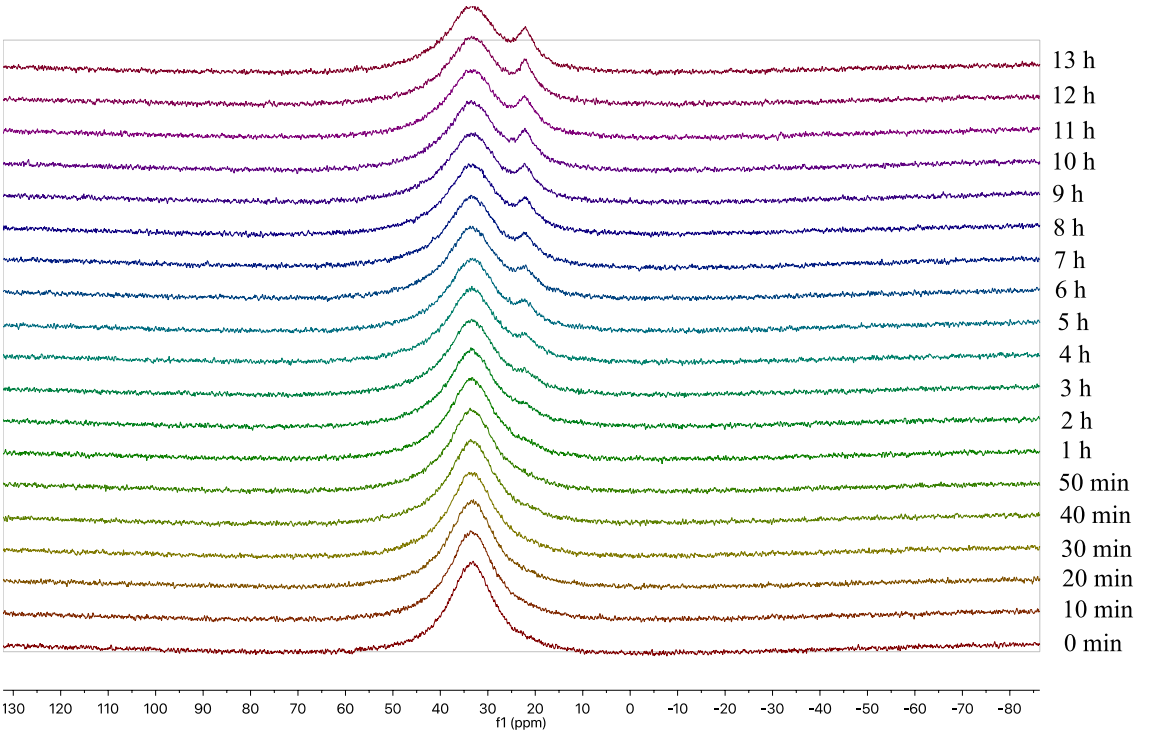
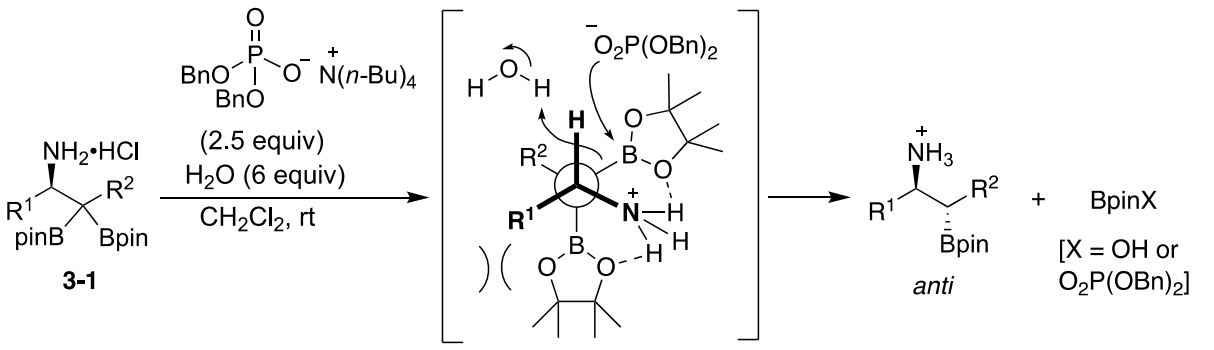


Figure 3-3. Monitoring the protodeboronation reaction at room temperature by ^{11}B NMR spectroscopy (chemical shifts for two peaks from the left to the right: 33.4, 22.1 ppm).

3.7 Proposed Mechanism and Stereochemical Model for the anti-Selective Monoprotodeboronation

Based on ^{11}B NMR studies, it is likely the monoprotodeboronation of β-amino *gem*-bis(boronates) **3-1** occurs through a concerted trimolecular pathway (Scheme 3-7). A reactive conformer similar to rotamer **I** (cf., Figure 3-1), which is rigidified by two ammonium NH···OB hydrogen bonds activating both Bpin units, was proposed to explain the anti-selectivity (Scheme 3-7). In this rotamer, the least sterically hindered boryl group is approachable from both faces, enabling an attack of the bulky dibenzylphosphate anion onto the boron atom with concomitant protonolysis of the C–B bond by water. Despite the absence of evidence for an interaction between water and the oxygen atom of the Bpin unit that was observed in the syn-selective protodeboronation (cf., Section 2.6.2), it was assumed that the proton delivery of water would still occur with stereoretention to ensure the high anti-selectivity.

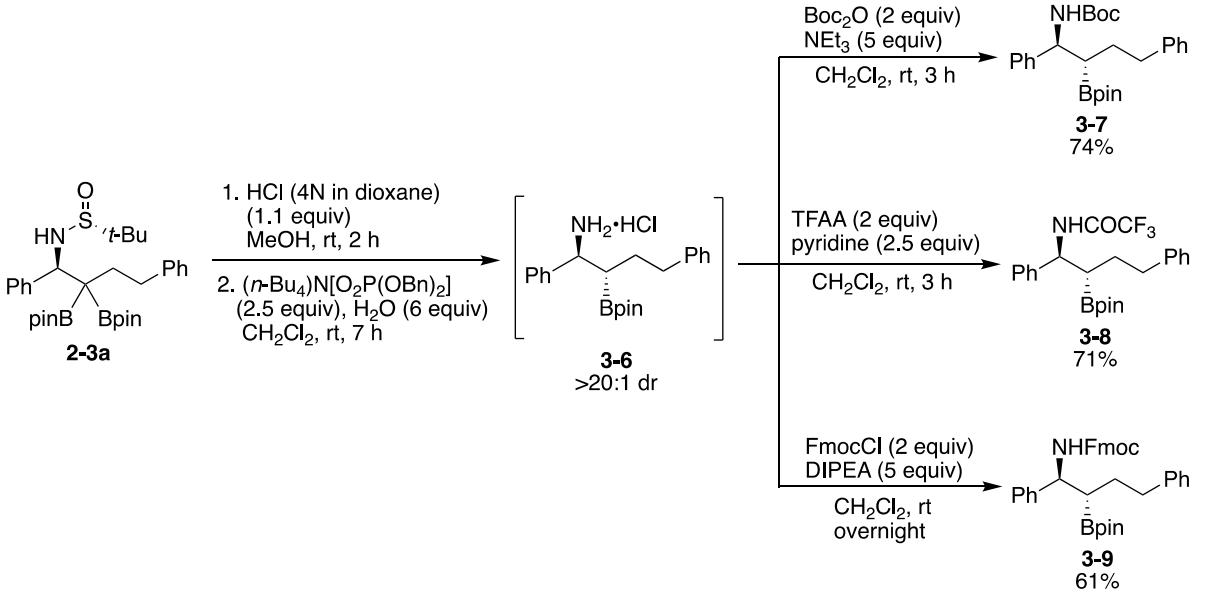


Scheme 3-7. Proposed mechanism and a possible stereochemical model for the monoprotodeboronation of β-amino *gem*-bis(boronates) **3-1**.

3.8 Applications of α,β-Disubstituted β-Aminoalkylboronates

3.8.1 Functionalization of Amine Groups of *anti*-β-Aminoalkylboronates

As shown in Scheme 3-8, besides the *N*-pivaloyl (Table 3-5) and *N*-Phth protections (Scheme 3-5), the amino group of β-aminoalkylboronate intermediate **3-6** also can be protected in good yields into Boc (**3-7**), CF_3CO (**3-8**), and Fmoc (**3-9**) derivatives.

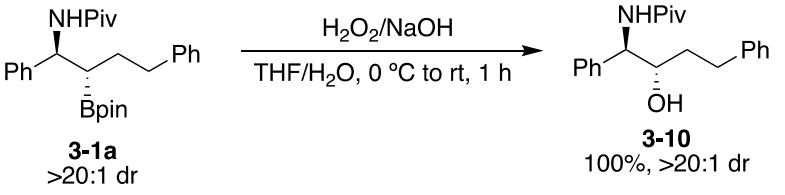


Scheme 3-8. Functionalization of the amine group of β-aminoalkylboronate intermediate **3-6**.

3.8.2 Transformations of *anti*- and *syn*-β-Aminoalkylboronates for C–O and C–C Bond Formation

3.8.2.1 Oxidation for C–O Bond Formation

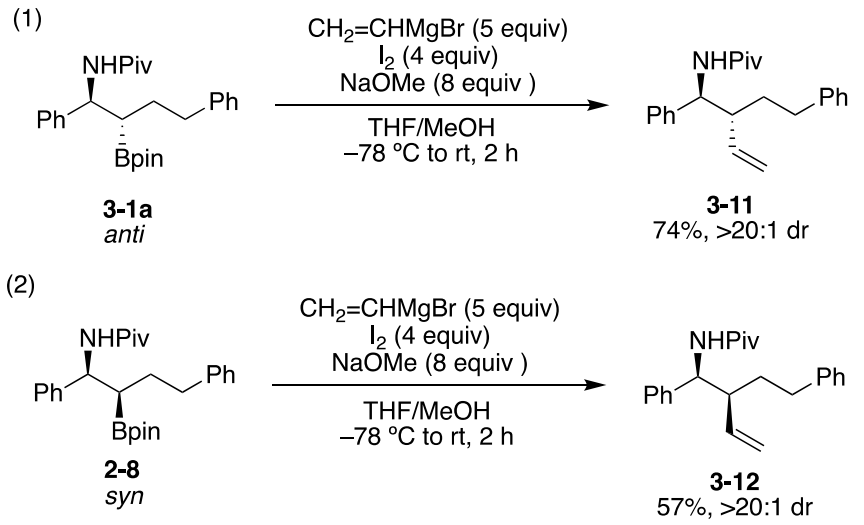
Both β-aminoalkylboronate diastereomers are amenable to C–O bond forming reactions by way of stereospecific C–B bond oxidation. The *syn*-β-aminoalkylboronate was shown to undergo stereoretentive oxidation to form *syn*-β-amino alcohol in the previous chapter (cf., Scheme 2-12). As shown in Scheme 3-9, oxidation of *anti*-β-aminoalkylboronate **3-1a** with H_2O_2/NaOH furnished *anti*-β-amino alcohol **3-10** in a quantitative yield.



Scheme 3-9. Oxidation of *anti*-β-aminoalkylboronate **3-1a** for the synthesis of *anti*-β-amino alcohol.

3.8.2.2 Zweifel Olefination for C–C Bond Formation

Both β-aminoalkylboronate diastereomers also can be engaged in C–C bond forming reactions, exemplified by the Zweifel olefination reaction. As shown in Scheme 3-10, using modified Zweifel olefination conditions,[16] both *N*-pivaloyl-protected β-aminoalkylboronate isomers (**3-1a** and **2-8**) underwent stereoretentive vinylation to afford the respective *anti*- and *syn*-homoallylic amines **3-11** and **3-12** in good yields.



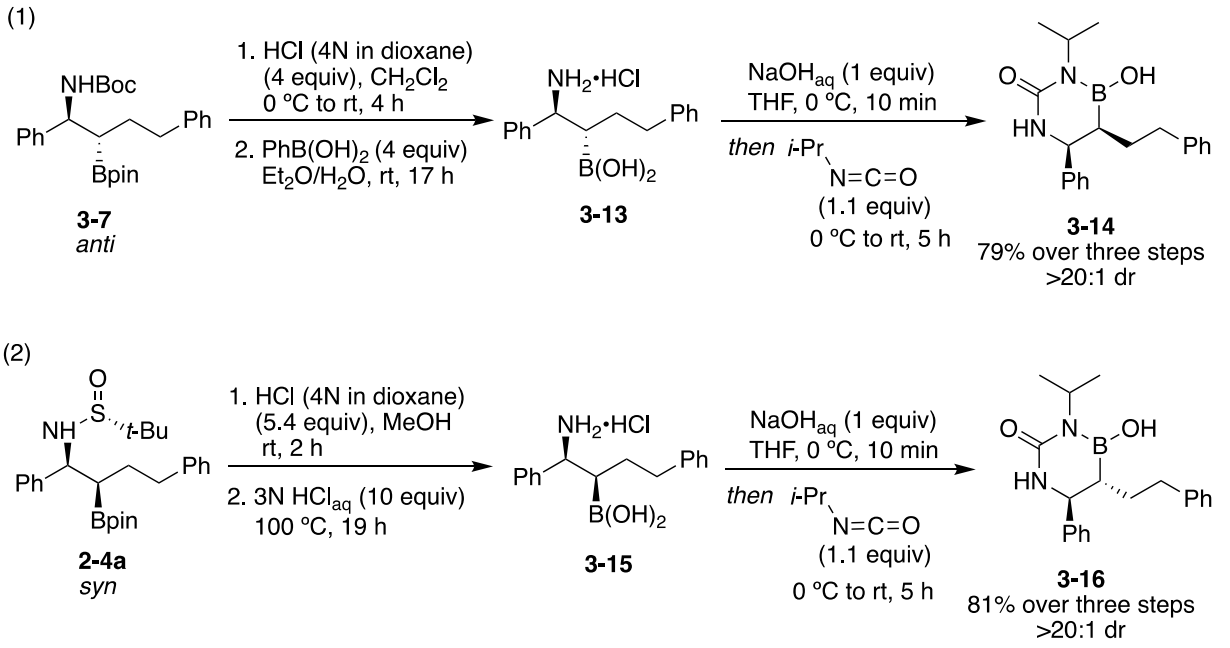
Scheme 3-10. Zweifel olefination of *anti*- and *syn*-β-aminoalkylboronates for C–C bond formation.

3.8.3 Synthesis of Boron Heterocycles

The potential utility of the β-aminoalkylboronates also was highlighted in the synthesis of boron heterocycles.[17] Starting with *anti*-β-aminoalkylboronate **3-7**, removal of the Boc moiety of **3-7** was conducted under acidic conditions without any epimerization of the stereogenic centers (Scheme 3-11, eq. 1). After the *N*-Boc deprotection, the deprotection of the Bpin unit using a biphasic transesterification method that involves phenylboronic acid afforded *anti*-β-aminoboronic acid **3-13**. Finally, addition of **3-13** to isopropyl isocyanate produced the six-membered hemiboronic heterocycle (**3-14**) in 79% yield over three steps.

This developed three-step sequence also was applied to *syn*-β-aminoalkylboronate **2-4a** to synthesize the corresponding hemiboronic heterocycle **3-16** (Scheme 3-11, eq. 2). β-Aminoalkylboronate **2-4a** underwent the desulfinylation successfully under acidic conditions. However, the aforementioned biphasic transesterification method was not suitable for the deprotection of the Bpin unit of the *syn*-*N*-desulfinylated β-aminoalkylboronate, resulting in many side products besides the desired β-aminoboronic acid product (**3-15**). The low efficiency probably is ascribed to the low solubility of the *syn*-*N*-desulfinylated β-aminoalkylboronate in the organic phase (Et_2O) since good solubilities of the reactants in the organic phase is of great importance in this biphasic transesterification. Gratifyingly, it was found that the deprotection method using an aqueous solution of HCl at 100 ºC worked well for the *syn*-*N*-desulfinylated β-aminoalkylboronate to generate of β-aminoboronic acid **3-15**.

Lastly, addition of **3-15** to isopropyl isocyanate furnished hemiboronic heterocycle **3-16** in 81% yield over three steps. The importance of saturated boron heterocycles of this sort is highlighted by the recent approval of the antibiotic vaborbactam (see structure in Figure 1-4).

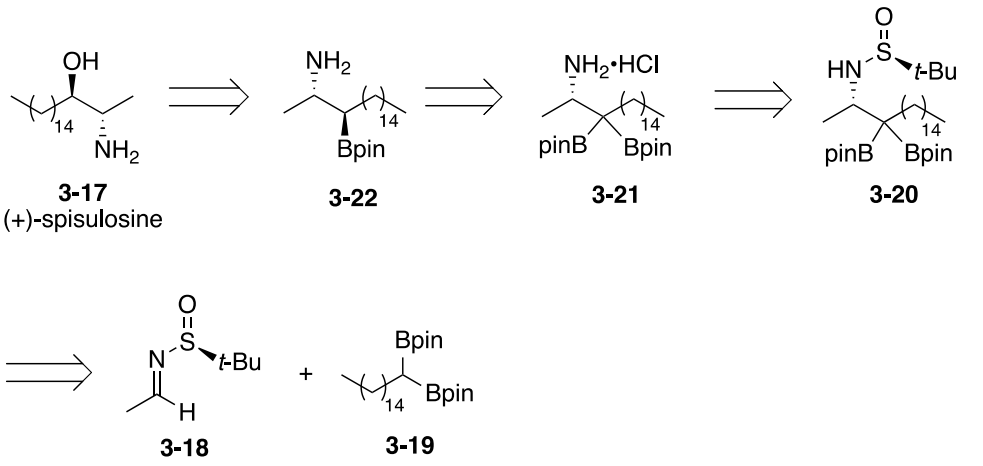


Scheme 3-11. Synthesis of boron heterocycles with *anti*- and *syn*-β-aminoalkylboronates: 1) synthesis of boron heterocycle **3-14** with *anti*-β-aminoalkylboronate **3-7** and 2) synthesis of boron heterocycle **3-16** with *syn*-β-aminoalkylboronate **2-4a**.

3.8.4 Other Attempts at Expanding the Synthetic Applications of *anti*-β-Aminoalkylboronates

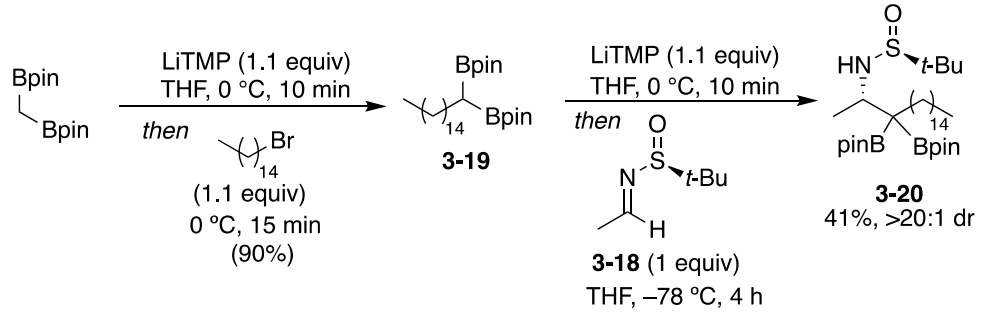
3.8.4.1 Attempts at the Synthesis of (+)-Spisulosine

(+)-Spisulosine **3-17** is an *anti*-β-amino alcohol, which was isolated from North Arctic clam *Spisula polynyma*, has been shown to exhibit significant cytotoxic activity and morphological alteration against L1210 leukemia cells.[18] There are some reported asymmetric syntheses of (+)-spisulosine, however, all of these methods require at least six steps.[19–23] It was envisioned that starting with 1,1-diborylalkane **3-19** and chiral sulfinyl aldimine **3-18**, (+)-spisulosine **3-17** could be prepared within five steps using the 1,2-addition, monoprotodeboronation and oxidation reactions (Scheme 3-12).



Scheme 3-12. Retrosynthetic analysis of (+)-spisulosine.

Efforts were placed first into the synthesis of 1,1-diborylalkane **3-19** through alkylation of 1,1-diborylmethane with 1-bromopentadecane by following the literature procedure[12] (Scheme 3-13). Diboryl reagent **3-19** was obtained in 90% yield and subjected to a subsequent 1,2-addition with sulfinyl aldimine **3-18** for the synthesis of β-sulfinimido *gem*-bis(boronate) **3-20**. The latter was isolated in a moderate yield (41%) with excellent diastereoselectivity (>20:1 dr; Scheme 3-13).

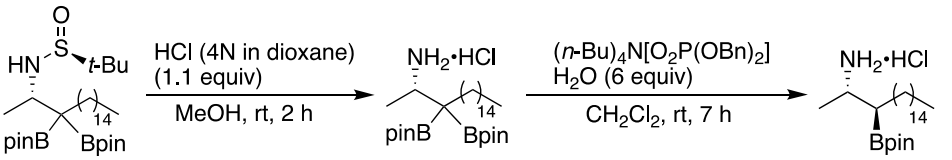


Scheme 3-13. Synthesis of *gem*-bis(boronates) **3-19** and **3-20**.

Next, the obtained *gem*-bis(boronate) **3-20** was used to synthesize *anti*-β-aminoalkylboronate **3-22** by using the deprotection/monoprotodeboronation sequence. As shown in Table 3-6, under the optimal anti-selective monoprotodeboronation conditions, *N*-desulfinylated *gem*-bis(boronate) **3-21** from **3-20** was monoprotodeboronated to produce

3-22 in 32% yield with low conversion and diastereoselectivity (2.5:1 dr; entry 1). Increasing the amount of $(n\text{-Bu})_4NOP(O)(OBn)_2$ to 3.5 (entry 2) or 4 (entry 3) equivalents only resulted in slightly higher yield and diastereoselectivity. Considering the low efficiency of the monoprotodeboronation step with substrate **3-21**, the synthesis of (+)-spisulosine **3-17** was discontinued.

Table 3-6. Evaluation of the Monoprotodeboronation of *gem*-Bis(boronate) **3-21**[a]



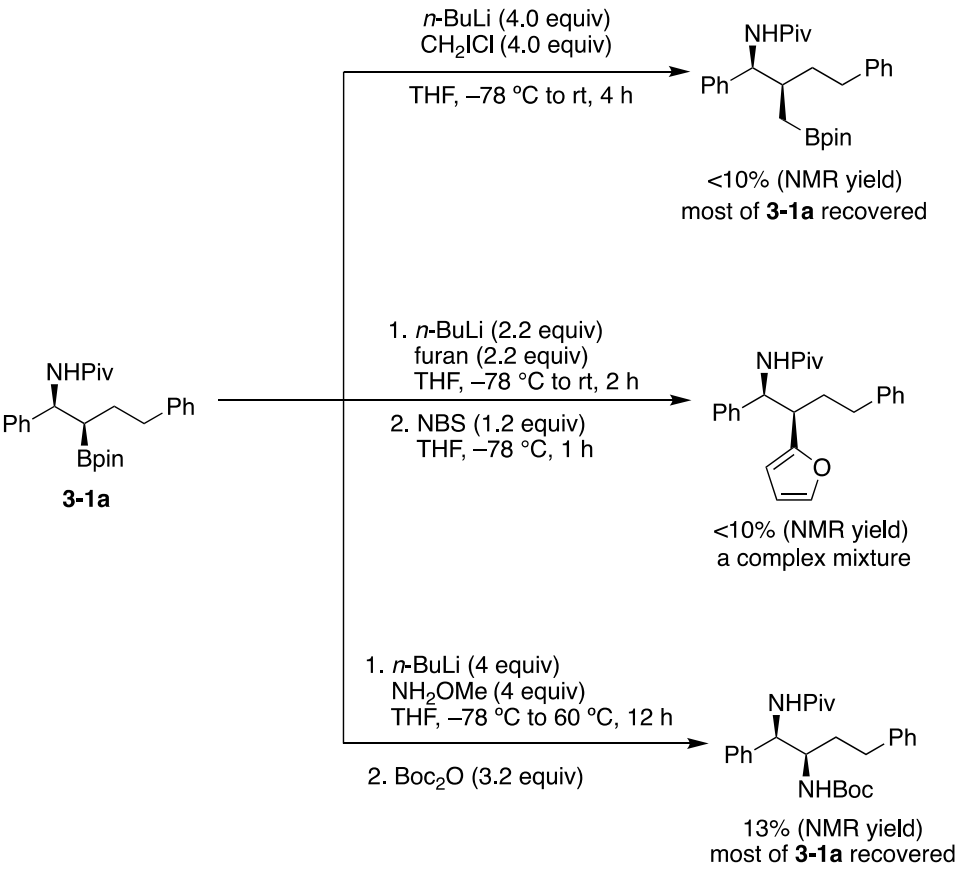
3-20 **3-21** **3-22**

Entry	$(n\text{-Bu})_4N[O_2P(OBn)_2]$ (equiv)	Yield of **3-22** [%][b] (*anti*+*syn*)	dr[c] (*anti*:*syn*)
1	2.5	32	2.5:1
2	3.5	50	4:1
3	4	54	4:1

[a]Reactions performed on a 0.1 mmol scale under N_2 atm. [b]Yield determined by ^{1}H NMR analysis using dibromomethane as the internal standard. [c]dr determined by peak heights of isolated resonances by ^{1}HNMR of the crude reaction mixture.

3.8.4.2 Attempts at Other Transformations of *anti*-β-Aminoalkylboronate 3-1a for C–C and C–N Bond Formation

As shown in Scheme 3-14, other attempts at typical C–C and C–N bond forming reactions of alkylboronates were made with *anti*-β-aminoalkylboronate **3-1a**. Unfortunately, under the typical reaction conditions, Matteson homologation,[24] furanylation,[25] and amination[26] of **3-1a** suffered from either low conversion or efficiency, which is similar to what was observed in these typical reactions of *syn*-β-aminoalkylboronate (cf., Scheme 2-19). Although other variants of these reactions[16,27,28] have been tested, no or only slight improvement was obtained. The low conversion of these transformations probably is attributed to the very hindered nature of β-aminoalkylboronate **3-1a**, which also is indicative of a lack of substrate generality in these typical transformations of alkylboronic esters.



Scheme 3-14. Various attempts at other transformations of *anti*-β-aminoalkylboronate **3-1a** for C–C and C–N bond formation.

3.9 Summary

In summary, this chapter, together with Chapter 2, recounts that using the diastereotopic group-selective mono-protodeboronation strategy, a stereodivergent set of practical reaction conditions were established to access both *syn*- and *anti*- α,β-disubstituted β-aminoalkylboronates from β-amino *gem*-bis(boronates). Theoretically, by using the antipode of the chiral sulfinyl group of β-sulfinimido *gem*-bis(boronates), all four stereoisomers of α,β-disubstituted β-aminoalkylboronates can be prepared independently in high (>95:5) selectivity. A series of mechanistic studies found that the anti-selective monoprotodeboronation proceeds through a trimolecular mechanism involving the phosphate and water, and the NH···OB hydrogen-bonding interaction with both Bpin units of *N*-desulfinylated β-amino *gem*-bis(boronates) plays a key role for the high reactivity and anti-

selectivity. The general accessibility of both diastereomers of these β-aminoalkylboronates will benefit not only their potential application in drug discovery, typically as free boronic acids or hemiboronic heterocycles, but also in organic synthesis where the versatility of the C–B bond can be exploited in stereoselective transformations.

3.10 Experimental

3.10.1 General Methods

Unless otherwise stated, all reactions were performed under a nitrogen atmosphere. Tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), and toluene were purified using a cartridge solvent purification system prior to use. Diethyl ether and 1,4-dioxane were distilled over sodium/benzophenone, and methanol was distilled over calcium hydride. *n*-BuLi was titrated using 2,2-diphenylacetic acid prior to use.

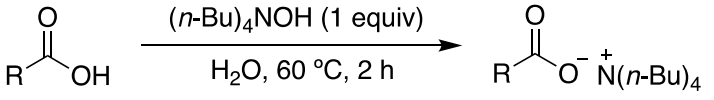
Unless otherwise noted, all other chemicals were purchased from commercial sources and used as received. Chromatographic separations were performed on silica gel 60 using ACS grade hexanes, ethyl acetate, dichloromethane, and diethyl ether as eluents. Thin layer chromatography (TLC) was performed on silica gel 60 F254 plates, which were visualized under UV light, $KMnO_4$, and *p*-anisaldehyde stains. NMR spectra were recorded on INOVA-400, INOVA-500, INOVA-600, or INOVA-700 MHz instruments. The residual solvent protons (^1H) of $CDCl_3$ (7.26 ppm), CD_3CN (1.94 ppm), CD_3OD (3.31 ppm), acetone-d_6 (2.05 ppm), and toluene-d_8 (2.08, 6.97, 7.01 and 7.09 ppm), and the solvent carbons (^{13}C) of $CDCl_3$ (77.06 ppm), CD_3CN (1.32 and 118.26 ppm), CD_3OD (49.00 ppm), acetone-d_6 (29.84 and 206.26 ppm), and toluene-d_8 (137.48, 128.87, 127.96, 125.13 and 20.43 ppm) were used as internal standards. ^1H NMR data is presented as follows: chemical shift in ppm (δ) downfield from tetramethylsilane (multiplicity, coupling constant, integration). The following abbreviations are used in reporting NMR data: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet; sep, septet; sex, sextet; comp m, complex multiplet; dd, doublet of doublets; dq, doublet of quartets; ddd, doublet of doublet of doublets; dddd, doublet of doublet of doublet of doublets; app d, apparent doublet; app dt, apparent doublet of triplets; app td, apparent triplet of doublets; app dtd, apparent doublet of triplet of doublet. The quaternary carbon bound to the boron atom often is missing due to the quadrupolar relaxation

of boron. This effect was observed in each boron-containing compound. High-resolution mass spectra (HRMS) were recorded by the University of Alberta mass spectrometry services laboratory using electrospray ionization (ESI) or electrospray ionization (EI) techniques. Optical rotations were measured using a 1 mL cell with a 1 dm length on a P.E. 241 polarimeter. Melting points were determined in a capillary tube using a Gallenkamp melting point apparatus and are uncorrected. The diastereomeric ratio for *anti*-β-aminoalkylboronates was determined using ^{1} HNMR analysis and further confirmed using liquid chromatography–mass spectrometry (LC-MS) with UV detection.

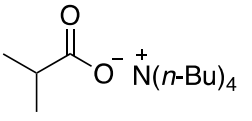
3.10.2 Preparation and Characterization of Starting Materials and Tetrabutylammonium Reagents

β-Sulfinimido *gem*-bis(boronates) were prepared using the procedure of 1,2-addition described in Chapter 2, and (n-Bu)$_4$N[O$_2$P(On-Bu)$_2$] were synthesized by following the literature procedure.[29]

3.10.2.1 Synthesis and Characterization of Tetrabutylammonium Carboxylates



Tetrabutylammonium carboxylates were prepared by following the literature procedure with slight modification.[30] An aqueous solution of tetrabutylammonium hydroxide (40 wt.% in H$_2$O, 1 equiv) was added to an aqueous suspension of carboxylic acids (1 equiv) in water (1 M). The resulting reaction mixture was stirred at 60 ºC for 2 h. Upon completion, the reaction mixture was cooled down to room temperature and lyophilized to afford the desired tetrabutylammonium carboxylates.



Tetrabutylammonium isobutyrate was synthesized by following the general procedure with tetrabutylammonium hydroxide (40 wt.% in H$_2$O, 0.65 mL, 1.0 mmol, 1.0 equiv) and 2-methyl

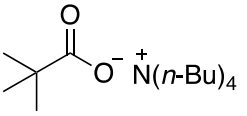
propanoic acid (88 mg, 1.0 mmol, 1.0 equiv). The desired tetrabutylammonium isobutyrate was isolated as a colorless oil (0.32 g, 98%).

^{1}H NMR (498 MHz, $CDCl_3$) δ 3.35–3.29 (m, 8H), 2.30 (sep, J = 6.9 Hz, 1H), 1.65–1.57 (m, 8H), 1.39 (sex, J = 7.4 Hz, 8H), 1.07 (d, J = 6.9 Hz, 6H), 0.95 (t, J = 7.3 Hz, 12H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 182.7, 58.8, 37.7, 24.1, 21.0, 19.8, 13.7.

IR (cast film, cm^{-1}): 2960, 2875, 1579.

HRMS (ESI-TOF) for $C_4H_7O_2$ $[M^*]^-$: *calcd.:* 87.0452; *found:* 87.0452.



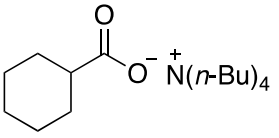
Tetrabutylammonium trimethylacetate was synthesized by following the general procedure with tetrabutylammonium hydroxide (40 wt.% in H_2O, 0.65 mL, 1.0 mmol, 1.0 equiv) and pivalic acid (0.10 g, 1.0 mmol, 1.0 equiv). The desired tetrabutylammonium trimethylacetate was isolated as a white solid (0.34 g, 100%).

^{1}H NMR (498 MHz, $CDCl_3$) δ 3.30–3.26 (m, 8H), 1.63–1.57 (m, 8H), 1.39 (sex, J = 7.4 Hz, 8H), 1.10 (s, 9H), 0.95 (t, J = 7.3 Hz, 12H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 183.8, 58.7, 39.7, 29.0, 24.0, 19.7, 13.6.

IR (cast film, cm^{-1}): 2963, 1636, 1566, 1394.

HRMS (EI) for $C_5H_{10}O_2$ $[M^*+H]$: *calcd.:* 102.0681; *found:* 102.0681.



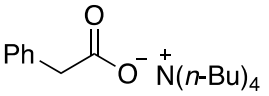
Tetrabutylammonium cyclohexanecarboxylate was synthesized by following the general procedure with tetrabutylammonium hydroxide (40 wt.% in H_2O, 0.65 mL, 1.0 mmol, 1.0 equiv) and cyclohexanecarboxylic acid (0.13 g, 1.0 mmol, 1.0 equiv). The desired tetrabutylammonium cyclohexanecarboxylate was isolated as a colorless oil (0.37 g, 100%).

^{1}H NMR (498 MHz, $CDCl_3$) δ 3.32–3.28 (m, 8H), 2.02 (tt, J = 11.6, 3.5 Hz, 1H), 1.90–1.87 (m, 2H), 1.67–1.53 (m, 11H), 1.43–1.33 (m, 10H), 1.24–1.12 (m, 3H), 0.95 (t, J = 7.3 Hz, 12H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 182.0, 58.8, 47.9, 31.0, 26.6, 24.1, 19.7, 13.6 (×2).

IR (cast film, cm^{-1}): 2960, 2929, 1573, 1382.

HRMS (EI) for $C_7H_{12}O_2$ [M^*+H]: *calcd.:* 128.0837; *found:* 128.0836.



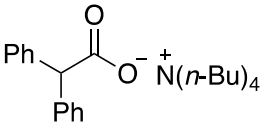
Tetrabutylammonium 2-phenylacetate was synthesized by following the general procedure with tetrabutylammonium hydroxide (40 wt.% in H_2O, 0.65 mL, 1.0 mmol, 1.0 equiv) and phenylacetic acid (0.14 g, 1.0 mmol, 1.0 equiv). The desired tetrabutylammonium 2-phenylacetate was isolated as a white solid (0.37 g, 99%).

^{1}H NMR (498 MHz, $CDCl_3$) δ 7.37 (d, *J* = 7.2 Hz, 2H), 7.16 (t, *J* = 7.6 Hz, 2H), 7.06 (d, *J* = 7.4 Hz, 1H), 3.50 (s, 2H), 3.22–3.18 (m, 8H), 1.56–1.49 (m, 8H), 1.34 (sex, *J* = 7.4 Hz, 9H), 0.93 (t, *J* = 7.3 Hz, 12H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 175.7, 141.0, 129.6, 127.61, 124.7, 58.6, 47.2, 24.1, 19.7, 13.7.

IR (cast film, cm^{-1}): 3024, 2960, 2874, 1598, 1493, 1467.

HRMS (ESI-TOF) for $C_8H_7O_2$ [M^*]$^-$: *calcd.:* 135.0452; *found:* 135.0451.



Tetrabutylammonium diphenylacetate was synthesized by following the general procedure with tetrabutylammonium hydroxide (40 wt.% in H_2O, 0.65 mL, 1.0 mmol, 1.0 equiv) and diphenylacetic acid (0.21 g, 1.0 mmol, 1.0 equiv). The desired tetrabutylammonium diphenylacetate was isolated as a white solid (0.45 g, 99%).

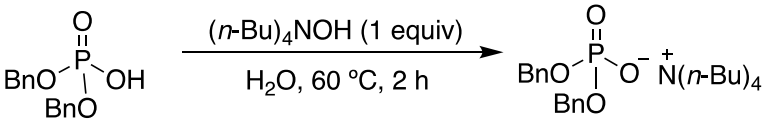
^{1}H NMR (498 MHz, $CDCl_3$) δ 7.48–7.43 (m, 4H), 7.22–7.17 (m, 4H), 7.11–7.06 (m, 2H), 4.93 (s, 1H), 3.19–3.15 (m, 8H), 1.55–1.48 (m, 8H), 1.34 (sex, *J* = 7.4 Hz, 8H), 0.94 (t, *J* = 7.3 Hz, 12H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 175.6, 144.2, 129.3, 127.6, 125.1, 62.9, 58.4, 23.9, 19.6, 13.6.

IR (cast film, cm^{-1}): 3022, 2960, 1606, 1346.

HRMS (EI) for $C_{14}H_{12}O_2$ [M^*+H]: *calcd.:* 212.0837; *found:* 212.0837.

3.10.2.2 Synthesis and Characterization of Tetrabutylammonium Phosphates



Tetrabutylammonium dibenzylphosphate was synthsized by following the literature procedure with slight modification.[30] An aqueous solution of tetrabutylammonium hydroxide (40 wt.% in H_2O, 0.65 mL, 1.0 mmol, 1 equiv) was added to an aqueous suspension of dibenzyl phosphate (0.28 g, 1.0 mmol, 1 equiv) in water (1 M, 1 mL). The resulting reaction mixture was stirred at 60 ºC for 2 h. Upon completion, the reaction mixture was cooled down to room temperature and lyophilized to afford tetrabutylammonium dibenzylphosphate as a white solid (0.51 g, 99%).

^{1}H NMR (498 MHz, CD_3OD) δ 7.35 (d, *J* = 7.5 Hz, 4H), 7.30 (t, *J* = 7.4 Hz, 4H), 7.26 (d, *J* = 7.2 Hz, 2H), 4.88 (d, *J* = 6.6 Hz, 4H), 3.25–3.20 (m, 8H), 1.73–1.59 (m, 8H), 1.41 (sex, *J* = 7.4 Hz, 8H), 1.02 (t, *J* = 7.4 Hz, 12H).

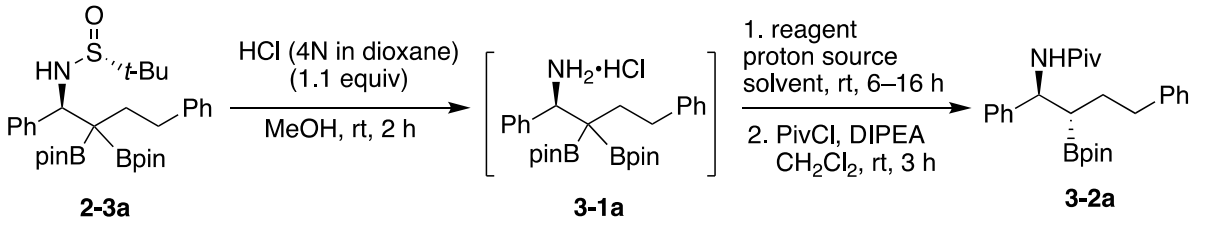
^{13}C NMR (125 MHz, CD_3OD) δ 139.62 (d, *J* = 8.1 Hz), 129.3, 128.6, 128.5, 68.42 (d, *J* = 5.4 Hz), 59.5, 24.8, 20.7, 13.9.

^{31}P NMR (202 MHz, CD_3OD) δ 0.39.

IR (cast film, cm^{-1}): 3029, 2960, 2874, 1494, 1454, 1265, 1098, 1080, 1056, 1025.

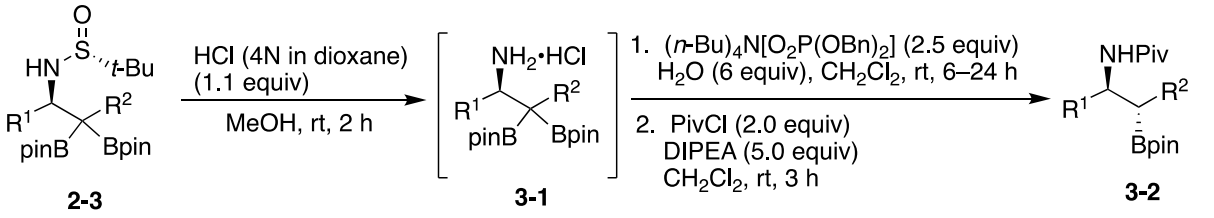
HRMS (ESI-TOF) for $C_{14}H_{14}O_4P$ $[M^*]^-$: *calcd.:* 277.0635; *found:* 277.0633.

3.10.3 General Procedure for the Optimization of the Mono-protodeboronation of β-Amino *gem*-Bis(boronate) 3-1a



In an oven-dried 5 mL round-bottomed flask, β-sulfinimido *gem*-bis(boronate) **2-3a** (58 mg, 0.10 mmol, 1.0 equiv) was dissolved in MeOH (0.40 mL, 0.26 M), followed by dropwise addition of an HCl solution (4 N in dioxane, 28 μL, 0.11 mmol, 1.1 equiv) at room temperature. After stirring at room temperature for 2 h, the reaction mixture was concentrated under reduced pressure to afford β-amino *gem*-bis(boronate) **3-1a**. To a 5 mL round-bottomed flask containing **3-1a** were added reagent, CH_2Cl_2 (1.0 mL, 0.10 M), and water. The resulting mixture was stirred at room temperature for 6–16 h. Upon completion, the reaction mixture was filtered through a short pad of Celite, washed with CH_2Cl_2, and concentrated under reduced pressure to afford the crude desulfinylated β-aminoalkylboronate product. The crude desulfinylated β-aminoalkylboronate product was dissolved in CH_2Cl_2 (1.0 mL, 0.10 M) and cooled to 0 °C, followed by dropwise addition of diisopropylethylamine (88 μL, 0.50 mmol, 5.0 equiv). The resulting reaction mixture was stirred at 0 ºC for 5 min. Next, pivaloyl chloride (24 μL, 1.0 mmol, 2.0 equiv) was added dropwise, and the reaction mixture was allowed to warm to room temperature and stirred for 3 h. The solvent was removed under reduced pressure to afford the crude product. Yield was determined by ^{1}H NMR analysis using dibromomethane as the internal standard, and the diastereomeric ratio was determined by comparing peak heights of isolated resonances in the ^{1}H NMR spectra of the crude reaction mixture.

3.10.4 General Procedure for the Synthesis of *anti*-α,β-Disubstituted β-Aminoalkylboronates

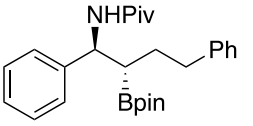


In an oven-dried 10 mL round-bottomed flask, β-sulfinimido *gem*-bis(boronates) **2-3** (0.30 mmol, 1.0 equiv) was dissolved in MeOH (1.2 mL, 0.26 M), followed by dropwise addition of an HCl solution (4 N in dioxane, 82 μL, 0.33 mmol, 1.1 equiv) at room temperature. After stirring at room temperature for 2 h, the reaction mixture was concentrated under reduced pressure to afford β-amino *gem*-bis(boronates) **3-1**. The obtained **3-1** was dissolved in CH_2Cl_2 (3.0 mL, 0.10 M) and added to another 10 mL round-bottomed flask containing tetrabutylammonium dibenzylphosphate (0.39 g, 0.75 mmol, 2.5 equiv), followed by addition of water (32 μL, 1.8 mmol, 6.0 equiv). The resulting reaction mixture was stirred at room temperature for 6–24 h. Upon completion, the reaction mixture was filtered through a short pad of Celite, washed with CH_2Cl_2, and concentrated under reduced pressure to afford the crude β-aminoalkylboronate product. The crude β-aminoalkylboronate product was dissolved in CH_2Cl_2 (3.0 mL, 0.10 M) and cooled to 0 °C, followed by dropwise addition of diisopropylethylamine (0.26 mL, 1.5 mmol, 5.0 equiv). The resulting reaction mixture was stirred at 0 ºC for 5 min. Next, pivaloyl chloride (72 μL, 0.60 mmol, 2.0 equiv) was added dropwise, and the reaction mixture was allowed to warm to room temperature and stirred for 3 h. The flask was then cooled to 0 °C, and the reaction was quenched by the addition of a saturated solution of aqueous sodium bicarbonate (3 mL). The aqueous and organic layers were separated, and the aqueous layer was extracted with EtOAc (3×5 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The diastereomeric ratio was determined by peak heights of isolated resonances by ^{1}H NMR of the crude reaction mixture (for >20:1 diastereomeric ratio, less than 5% of the minor isomer was observed). The crude mixture was purified by flash column chromatography to afford the desired *N*-pivaloyl-protected β-aminoalkylboronate **3-2**.

An important point to note for performing the protodeboronation reaction:

- Tetrabutylammonium dibenzylphosphate is a moisture-sensitive reagent. Weighing it under air can cause its decomposition. To ensure the efficiency of the protodeboronation, the exact amount of tetrabutylammonium dibenzylphosphate, based on the scale of the protodeboronation reaction, should be prepared, stored under N_2, and used immediately for the reaction. Otherwise, this reagent could be stored in a glove box and weighed out as needed.

3.10.5 Full Characterization of *anti*-β-Aminoalkylboronates



***N*-((1*S*,2*S*)-1,4-Diphenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-butyl)pivalamide** (**3-2a**): Synthesized by following the general procedure with β-sulfinimido *gem*-bis(boronate) **2-3a** (0.27 g, 0.30 mmol, 1.0 equiv). The protodeboronation reaction was performed at room temperature for 7 h. The crude product was purified by flash column chromatography (7:1 to 6:1, hexanes/EtOAc) to afford β-aminoalkylboronates **3-2a** as a colorless oil (0.10 g, 77%); ^{1}H NMR analysis of the crude mixture indicated >20:1 diastereoselectivity.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.27 (m, 3H), 7.26–7.24 (m, 3H), 7.22–7.19 (m, 1H), 7.18–7.16 (m, 3H), 6.75 (d, J = 8.5 Hz, 1H), 5.14 (app t, J = 7.9 Hz, 1H), 2.76–2.68 (comp m, A part of ABMNX, 1H), 2.67–2.59 (comp m, B part of ABMNX, 1H), 1.78–1.75 (comp m, M part of ABMNX, 1H), 1.64–1.60 (comp m, N part of ABMNX, 1H), 1.55–1.51 (comp m, X part of ABMNX, 1H), 1.20 (s, 6H), 1.18 (s, 6H), 1.18 (s, 9H).

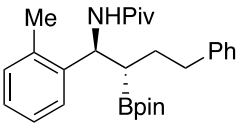
^{13}C NMR (101 MHz, $CDCl_3$) δ 177.1, 142.5, 142.4, 128.5, 128.31, 128.27, 127.1, 127.0, 125.7, 83.6, 53.9, 38.7, 35.2, 30.1, 27.6, 25.0, 24.9.

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.6.

IR (cast film, cm^{-1}): 3360, 3028, 2977, 2930, 1639, 1380, 1143.

HRMS (ESI-TOF) for $C_{27}H_{39}BNO_3$ $(M + H)^+$: *calcd.*: 436.3028; *found*: 436.3031.

$[\alpha]_D^{20}$: –28.4 (*c* 0.73, $CHCl_3$).



***N*-((1*S*,2*S*)-4-Phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(o-tolyl)-butyl)pivalamide (3-2b):** Synthesized by following the general procedure with β-sulfinimido *gem*-bis(boronate) **2-3e** (0.18 g, 0.30 mmol, 1.0 equiv). The protodeboronation reaction was performed at room temperature for 7 h. The crude product was purified by flash column chromatography (7:1, hexanes/EtOAc) to afford β-aminoalkylboronates **3-2b** as a colorless oil (0.12 g, 88%). ^{1}H NMR analysis of the crude mixture indicated >20:1 diastereoselectivity.

^{1}H NMR (498 MHz, $CDCl_3$) δ 7.27–7.24 (m, 2H), δ 7.21–7.13 (m, 4H), 7.12–7.06 (m, 3H), 6.05 (d, *J* = 8.6 Hz, 1H), 5.33 (app t, *J* = 8.1 Hz, 1H), 2.74 (ddd, *J* = 14.4, 10.0, 5.0 Hz, 1H), 2.53 (ddd, *J* = 13.5, 9.7, 7.0 Hz, 1H), 2.48 (s, 3H), 1.87–1.81 (m, 1H), 1.76–1.71 (m, 1H), 1.55 (app td, *J* = 9.7, 4.5 Hz, 1H), 1.14 (s, 9H), 1.09 (s, 6H), 1.06 (s, 6H).

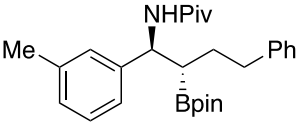
^{13}C NMR (126 MHz, $CDCl_3$) δ 177.2, 142.5, 141.0, 136.8, 130.6, 128.5, 128.3, 126.9, 125.9, 125.75, 125.74, 83.4, 49.9, 38.6, 35.4, 30.4, 27.6, 24.8, 24.5, 19.8.

^{11}B NMR (160 MHz, $CDCl_3$) δ 33.2.

IR (cast film, cm^{-1}): 3370, 3026, 2977, 2931, 1648, 1144.

HRMS (ESI-TOF) for $C_{28}H_{40}BNNaO_3$ $(M + Na)^+$: *calcd.*: 472.2993; *found*: 472.2992.

$[\alpha]_D^{20}$: –60.8 (*c* 0.78, $CHCl_3$)



***N*-((1*S*,2*S*)-4-Phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(m-tolyl)-butyl)pivalamide (3-2c):** Synthesized by following the general procedure with β-sulfinimido *gem*-bis(boronate) **2-3f** (0.18 g, 0.30 mmol, 1.0 equiv). The protodeboronation reaction was performed at room temperature for 7 h. The crude product was purified by flash column chromatography (7:1 to 6:1, hexanes/EtOAc) to afford β-aminoalkylboronates **3-2c** as a colorless oil (0.10 g, 74%); ^{1}H NMR analysis of the crude mixture indicated >20:1 diastereoselectivity.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.25 (m, 1H), 7.24–7.23 (m,1H), 7.19–7.11 (m, 4H), 7.11–7.05 (m, 2H), 7.00 (d, *J* = 7.4 Hz, 1H), 6.76 (d, *J* = 8.5 Hz, 1H), 5.14–5.06 (app t, *J* =

8.0 Hz, 1H), 2.73–2.67 (comp m, A part of ABMNX, 1H), 2.65–2.59 (comp m, B part of ABMNX, 1H), 2.30 (s, 3H), 1.77–1.73 (comp m, M part of ABMNX, 1H), 1.65–1.57 (comp m, N part of ABMNX,, 1H), 1.57–1.46 (comp m, X part of ABMNX, 1H), 1.20 (s, 6H), 1.18 (s, 6H), 1.17 (s, 9H).

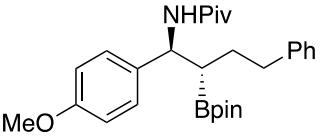
^{13}C NMR (101 MHz, $CDCl_3$) δ 177.1, 142.6, 142.3, 137.7, 128.5, 128.3, 128.2, 127.9, 127.8, 125.7, 124.1, 83.6, 53.8, 38.7, 35.2, 30.2, 27.6, 25.0, 24.9, 21.5.

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.5.

IR (cast film, cm^{-1}): 3284, 3026, 2978, 1606, 1496, 1455, 1380, 1142, 1073.

HRMS (ESI-TOF) for $C_{28}H_{41}BNO_3$ $(M + H)^+$: *calcd.*: 450.3174; *found*: 450.3174.

$[\alpha]_D^{20}$: –34.5 (*c* 0.81, $CHCl_3$).



***N*-((1*S*,2*S*)-1-(4-Methoxyphenyl)-4-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl)pivalamide (3-2d):** Synthesized by following the general procedure with β-sulfinimido *gem*-bis(boronate) **2-3g** (0.18 g, 0.30 mmol, 1.0 equiv). The protodeboronation reaction was performed at room temperature for 7 h. The crude product was purified by flash column chromatography (6:1 to 5:1, hexanes/EtOAc) to afford β-aminoalkylboronates **3-2d** as a pale yellow solid (0.12 g, 82%). ^{1}H NMR analysis of the crude mixture indicated >20:1 diastereoselectivity.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.18 (m, 4H), 7.14 (d, *J* = 7.8 Hz, 3H), 6.80 (d, *J* = 8.2 Hz, 2H), 6.71 (d, *J* = 8.5 Hz, 1H), 5.09 (app t, *J* = 7.8 Hz, 1H), 3.77 (s, 3H), 2.75–2.66 (comp m, A part of ABMNX, 1H), 2.65–2.59 (comp m, B part of ABMNX, 1H), 1.80–1.74 (comp m, M part of ABMNX, 1H), 1.64–1.58 (comp m, N part of ABMNX, 1H), 1.53–1.47 (comp m, X part of ABMNX, 1H), 1.20 (s, 6H), 1.19 (s, 6H), 1.17 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 177.0, 158.6, 142.6, 134.7, 128.5, 128.3, 128.2, 125.7, 113.7, 83.58, 55.28, 53.28, 38.68, 35.2, 30.2, 27.6, 25.0, 24.9.

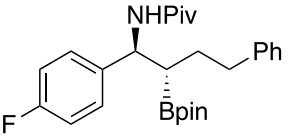
^{11}B NMR (128 MHz, $CDCl_3$) δ 33.1.

IR (cast film, cm^{-1}): 3363, 3027, 2977, 2933, 1640, 1513, 1144.

HRMS (ESI-TOF) for $C_{28}H_{41}BNO_4$ $(M + H)^+$: *calcd.*: 466.3123; *found*: 466.3123.

mp: 58.0–60.6 ºC.

$[\alpha]_D^{20}$: –40.4 (*c* 1.3, $CHCl_3$).



***N*-((1*S*,2*S*)-1-(4-Fluorophenyl)-4-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl)pivalamide (3-2e):** Synthesized by following the general procedure with β-sulfinimido *gem*-bis(boronate) **2-3j** (0.18 g, 0.30 mmol, 1.0 equiv). The protodeboronation reaction was performed at room temperature for 7 h. The crude product was purified by flash column chromatography (7:1 to 6:1, hexanes/EtOAc) to afford β-aminoalkylboronates **3-2e** as a white solid (95 mg, 70%). ^{1}H NMR analysis of the crude mixture indicated >20:1 diastereoselectivity.

^{1}H NMR (498 MHz, $CDCl_3$) δ 7.27–7.25 (m, 2H), 7.25–7.24 (m, 2H), 7.20–7.16 (m, 1H), 7.16–7.12 (m, 2H), 6.97–6.93 (m, 2H), 6.72 (d, *J* = 8.3 Hz, 1H), 5.09 (app t, *J* = 7.8 Hz, 1H), 2.74–2.69 (comp m, A part of ABMNX, 1H), 2.64–2.58 (comp m, B part of ABMNX, 1H), 1.78–1.74 (comp m, X part of ABMNX, 1H), 1.62–1.58 (comp m, M part of ABMNX, 1H), 1.53–1.47 (comp m, N part of ABMNX, 1H), 1.20 (s, 6H), 1.18 (s, 6H), 1.16 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 177.2, δ 161.9 (d, *J* = 244.9 Hz), 142.3, 138.3 (d, *J* = 3.2 Hz), 128.7, 128.6, 128.4 (d, *J* = 12.0 Hz), 125.8, 115.1 (d, *J* = 21.2 Hz), 83.7, 53.3, 38.7, 35.2, 30.2, 27.5, 25.0, 24.9.

^{11}B NMR (160 MHz, $CDCl_3$) δ 34.2.

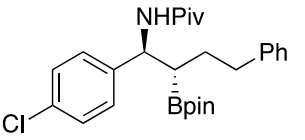
^{19}F NMR (469 MHz, $CDCl_3$) δ -116.0.

IR (cast film, cm^{-1}): 3358, 3026, 2976, 2933, 1629, 1144.

HRMS (ESI-TOF) for $C_{27}H_{37}BFNNaO_3$ $(M + Na)^+$: *calcd.*: 476.2743; *found*: 476.275.

mp: 134.7–135.8 ºC.

$[\alpha]_D^{20}$: –32.8 (*c* 1.2, $CHCl_3$).



***N*-((1*S*,2*S*)-1-(4-Chlorophenyl)-4-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl)pivalamide (3-2f):** Synthesized by following the general procedure with β-sulfinimido *gem*-bis(boronate) **2-3k** (0.19 g, 0.30 mmol, 1.0 equiv) and tetrabutylammonium dibenzylphosphate (0.47, 0.90 mmol, 3.0 equiv). The protodeboronation reaction was performed at room temperature for 7 h. The crude product was purified by flash column chromatography (6:1 to 5:1, hexanes/EtOAc) to afford β-aminoalkylboronates **3-2f** as a white solid (70 mg, 50%). ^{1}H NMR analysis of the crude mixture indicated >20:1 diastereoselectivity.

^{1}H NMR (498 MHz, $CDCl_3$) δ 7.29–7.26 (m, 2H), 7.24–7.22 (m, 4H), 7.20–7.17 (d, *J* = 7.3 Hz, 1H), 7.15 (d, *J* = 7.5 Hz, 2H), 6.79 (d, *J* = 8.2 Hz, 1H), 5.09 (app t, *J* = 7.7 Hz, 1H), 2.76–2.70 (comp m, A part of ABMNX, 1H), 2.66–2.59 (comp m, B part of ABMNX, 1H), 1.78–1.74 (comp m, X part of ABMNX, 1H), 1.65–1.55 (comp m, M part of ABMNX, 1H), 1.55–1.47 (comp m, N part of ABMNX, 1H), 1.23 (s, 6H), 1.21 (s, 6H), 1.18 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 177.3, 142.3, 141.1, 132.7, 128.50, 128.46, 128.41, 128.38, 125.8, 83.8, 53.4, 38.7, 35.2, 30.1, 27.5, 25.0, 24.9.

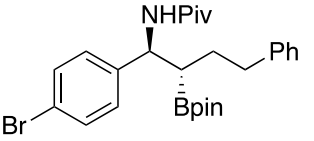
^{11}B NMR (160 MHz, $CDCl_3$) δ 33.2.

IR (cast film, cm^{-1}): 3360, 3026, 2977, 2931, 1630, 1143.

HRMS (ESI-TOF) for $C_{27}H_{28}BClNNaO_3$ $(M + Na)^+$: *calcd.*: 492.2477; *found*: 492.2457.

mp: 134.4–136.3 ºC.

$[\alpha]_D^{20}$: –35.2 (*c* 0.51, $CHCl_3$).



***N*-((1*S*,2*S*)-1-(4-Bromophenyl)-4-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl)pivalamide (3-2g):** Synthesized by following the general procedure with β-sulfinimido *gem*-bis(boronate) **2-3l** (0.20 g, 0.30 mmol, 1.0 equiv). The protodeboronation reaction was performed at room temperature for 7 h. The crude product was purified by flash

column chromatography (6:1 to 5:1, hexanes/EtOAc) to afford β-aminoalkylboronates **3-2g** as a white solid (92 mg, 60%). ^{1}H NMR analysis of the crude mixture indicated 16:1 diastereoselectivity.

^{1}H NMR (498 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.4 Hz, 2H), 7.27 (s, 1H), 7.24 (s, 1H), 7.16 (d, *J* = 8.4 Hz, 3H), 7.13 (d, *J* = 7.3 Hz, 2H), 6.78 (d, *J* = 8.2 Hz, 1H), 5.05 (app t, *J* = 7.6 Hz, 1H), 2.74–2.68 (comp m, A part of ABMNX, 1H), 2.64–2.58 (comp m, B part of ABMNX, 1H), 1.78–1.72 (comp m, X part of ABMNX, 1H), 1.60–1.53 (comp m, M part of ABMNX, 1H), 1.53–1.46 (comp m, N part of ABMNX, 1H), 1.21 (s, 6H), 1.20 (s, 6H), 1.16 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 177.3, 142.2, 141.6, 131.2, 128.9, 128.5, 128.4, 125.8, 120.9, 83.8, 53.5, 38.7, 35.2, 30.0, 27.5, 25.0, 24.9.

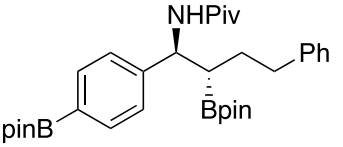
^{11}B NMR (160 MHz, $CDCl_3$) δ 33.6.

IR (cast film, cm^{-1}): 3358, 3026, 2977, 2932, 1645, 1143.

HRMS (ESI-TOF) for $C_{27}H_{38}BBrNO_3$ $(M + H)^+$: *calcd.*: 514.2123; *found*: 514.2122.

mp: 133.4–135.0 ºC.

$[\alpha]_D^{20}$: –30.2 (*c* 1.3, $CHCl_3$).



***N*-((1*S*,2*S*)-4-Phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)butyl)pivalamide (3-2h):** Synthesized by following the general procedure with β-sulfinimido *gem*-bis(boronate) **2-3m** (0.21 g, 0.30 mmol, 1.0 equiv). The protodeboronation reaction was performed at room temperature for 7 h. The crude product was purified by flash column chromatography (6:1 to 5:1, hexanes/EtOAc) to afford β-aminoalkylboronates **3-2h** as a colorless oil (0.13 g, 75%). ^{1}H NMR analysis of the crude mixture indicated 12:1 diastereoselectivity.

^{1}H NMR (498 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 7.6 Hz, 2H), 7.18–7.14 (m, 1H), 7.14–7.11 (m, 2H), 6.92 (d, *J* = 8.5 Hz, 1H), 5.15 (dd, *J* = 8.4, 6.4 Hz, 1H), 2.67 (comp m, AB part of ABMNX, 2H), 1.77–1.68 (comp m, X part of ABMNX, 1H), 1.60–1.49 (comp m, MN part of ABMNX, 2H), 1.33 (app s, 12H), 1.23 (s, 6H), 1.21 (s, 6H), 1.16 (s, 9H).

^{13}C NMR (125 MHz, CDCl3) δ 177.2, 145.8, 142.7, 135.0, 128.7, 128.5, 126.73, 125.9, 83.92, 83.88, 54.1, 38.9, 35.4, 30.2, 27.7 (×2), 25.3, 25.1 (×2).

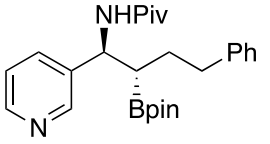
^{11}B NMR (160 MHz, $CDCl_3$) δ 31.5.

IR (cast film, cm^{-1}): 3366, 3026, 2978, 2932, 1652, 1162.

HRMS (ESI-TOF) for $C_{33}H_{50}B_2NO_5$ $(M + H)^+$: *calcd.*: 562.387; *found*: 562.3873.

mp: 125.3–128.0 ºC.

$[\alpha]_D^{20}$: –36.4 (*c* 1.2, $CHCl_3$).



***N*-((1*S*,2*S*)-4-Phenyl-1-(pyridin-3-yl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl)pivalamide (3-2i):** Synthesized by following the general procedure with HCl solution (4 N in dioxane, 0.16 mL, 0.66 mmol, 2.2 equiv), β-sulfinimido *gem*-bis(boronate) **2-3o** (0.17 g, 0.30 mmol, 1.0 equiv), and tetrabutylammonium dibenzylphosphate (0.78 g, 1.5 mmol, 5.0 equiv). The protodeboronation reaction was performed at room temperature for 24 h. The crude product was purified by flash column chromatography (1:1 to 1:2, hexanes/EtOAc) to afford β-aminoalkylboronates **3-2i** as a white solid (85 mg, 65%). ^{1}H NMR analysis of the crude mixture indicated 9.4:1 diastereoselectivity.

^{1}H NMR (498 MHz, $CDCl_3$) δ 8.57 (s, 1H), 8.46 (d, *J* = 4.8 Hz, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.23–7.15 (m, 3H), 7.14 (d, *J* = 7.5 Hz, 2H), 6.86 (d, *J* = 8.2 Hz, 1H), 5.12 (app t, *J* = 7.5 Hz, 1H), 2.76–2.70 (comp m, A part of ABMNX, 1H), 2.66–2.60 (comp m, B part of ABMNX, 1H), 1.81–1.74 (comp m, X part of ABMNX, 1H), 1.63–1.54 (comp m, MN part of ABMNX, 2H), 1.22 (s, 6H), 1.19 (s, 6H), 1.17 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 177.4, 148.6, 148.5, 142.1, 137.9, 135.0, 128.5, 128.4, 125.9, 123.1, 83.9, 52.2, 38.7, 35.1, 30.1, 27.5, 25.0, 24.9.

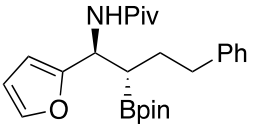
^{11}B NMR (160 MHz, $CDCl_3$) δ 33.8.

IR (cast film, cm^{-1}): 3362, 3027, 2977, 2932, 1641, 1143.

HRMS (ESI-TOF) for $C_{26}H_{37}BN_2NaO_3$ $(M + Na)^+$: *calcd.*: 459.2789; *found*: 459.2792.

mp: 101.5–103.8 ºC.

$[\alpha]_D^{20}$: –30.1 (*c* 0.63, $CHCl_3$).



***N*-((1*S*,2*S*)-1-(Furan-2-yl)-4-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl)pivalamide (3-2j):** Synthesized by following the general procedure with β-sulfinimido *gem*-bis(boronate) **2-3p** (0.17 g, 0.30 mmol, 1.0 equiv) and tetrabutylammonium dibenzylphosphate (0.55 g, 1.0 mmol, 3.5 equiv). The protodeboronation reaction was performed at room temperature for 16 h. The crude product was purified by flash column chromatography (8:1 to 7:1, hexanes/EtOAc) to afford β-aminoalkylboronate **3-2j** as a red oil (68 mg, 53%). ^{1}H NMR analysis of the crude mixture indicated 12:1 diastereoselectivity.

^{1}H NMR (498 MHz, $CDCl_3$) δ 7.26–7.23 (m, 3H), 7.16–7.13 (m, *J* = 6.5 Hz, 3H), 7.06 (d, *J* = 9.4 Hz, 1H), 6.26 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.20 (d, *J* = 3.2 Hz, 1H), 5.28 (dd, *J* = 8.9, 6.2 Hz, 1H), 2.67 (app t, *J* = 8.0 Hz, 2H), 1.79–1.72 (m, 1H), 1.51–1.40 (m, 2H), 1.28 (s, 6H), 1.27 (s, 6H), 1.17 (s, 9H).

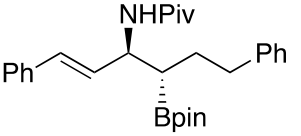
^{13}C NMR (125 MHz, $CDCl_3$) δ 177.1, 154.5, 142.6, 141.2, 128.5, 128.3, 125.7, 110.2, 107.0, 83.6, 47.6, 38.8, 35.0, 30.0, 27.5, 25.1, 24.8.

^{11}B NMR (160 MHz, $CDCl_3$) δ 33.7.

IR (cast film, cm^{-1}): 3420, 3026, 2976, 2932, 1666, 1143.

HRMS (ESI-TOF) for $C_{25}H_{36}BNNaO_4$ $(M + Na)^+$: *calcd.*: 448.263; *found*: 448.2629.

$[\alpha]_D^{20}$: –58.7 (*c* 0.50, $CHCl_3$).



***N*-((3*S*,4*S*,*E*)-1,6-Diphenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-1-en-3-yl)pivalamide (3-2k):** Synthesized by following the general procedure with β-sulfinimido *gem*-bis(boronate) **2-3r** (0.18 g, 0.30 mmol, 1.0 equiv). The protodeboronation reaction was performed at room temperature for 8 h. The crude product was purified by flash column chromatography (8:1 to 7:1, hexanes/EtOAc) to afford β-aminoalkylboronate **3-2k** as a white solid (90 mg, 65%). ^{1}H NMR analysis of the crude mixture indicated 15:1 diastereoselectivity.

^{1}H NMR (498 MHz, $CDCl_3$) δ 7.30–7.26 (m, 3H), 7.24–7.20 (m, 3H), 7.19–7.13 (m, 4H), 6.65 (d, *J* = 8.8 Hz, 1H), 6.49 (d, *J* = 15.8 Hz, 1H), 6.06 (dd, *J* = 15.8, 6.9 Hz, 1H), 4.77 (app q, *J* = 7.3 Hz, 1H), 2.75–2.63 (comp m, AB part of ABMNX, 2H), 1.89–1.83 (comp m, M part of ABMNX 1H), 1.69–1.64 (comp m, N part of ABMNX, 1H), 1.36–1.31 (comp m, X part of ABMNX, 1H), 1.24 (s, 12H), 1.20 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 177.1, 142.6, 137.1, 131.0, 129.0, 128.54, 128.49, 128.3, 127.4, 126.4, 125.7, 83.64, 51.7, 38.8, 35.2, 30.3, 27.6, 25.2, 24.8.

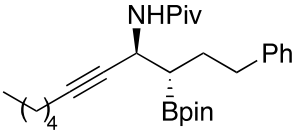
^{11}B NMR (160 MHz, $CDCl_3$) δ 33.7.

IR (cast film, cm^{-1}): 3357, 3026, 2977, 2933, 1645, 1380, 1143.

HRMS (ESI-TOF) for $C_{29}H_{41}BNO_3$ $(M + H)^+$: *calcd.*: 462.3174; *found*: 462.3172.

mp: 86.2–88.5 ºC.

$[\alpha]_D^{20}$: –25.0 (*c* 1.3, $CHCl_3$).



***N*-((3*S*,4*S*)-1-Phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)undec-5-yn-4-yl)pivalamide (3-2l):** Synthesized by following the general procedure with β-sulfinimido *gem*-bis(boronate) **2-3q** (0.18 g, 0.30 mmol, 1.0 equiv) and tetrabutylammonium dibenzylphosphate (0.62 g, 1.2 mmol, 4.0 equiv). The protodeboronation reaction was performed in $CHCl_3$ at 60 ºC for 22 h. The crude product was purified by flash column chromatography (8:1 to 7:1, hexanes/EtOAc) to afford a mixture of *anti*- and *syn*-β-aminoalkylboronates **3-2l** as a yellow oil (53 mg, 39%). ^{1}H NMR analysis of the crude mixture indicated 5:1 diastereoselectivity (*anti*:*syn*).

^{1}H NMR (498 MHz, $CDCl_3$) δ 7.28–7.27 (m, 1H-major & 1H-minor), 7.26–7.22 (m, 1H-major & 1H-minor), 7.22–7.17 (m, 2H-major & 2H-minor), 7.17–7.13 (m, 1H-major & 1H-minor), 6.80 (d, *J* = 9.0 Hz, 1H-major), δ 6.72 (d, *J* = 9.2 Hz, 1H-minor). 4.94–4.91 (m, 1H-minor), 4.91–4.86 (m, 1H-major), 2.74–2.65 (m, 2H-major), 2.60–2.54 (m, 2H-minor), 2.13 (app td, *J* = 7.0, 2.2 Hz, 2H-major & 2H-minor), 1.97–1.87 (m, 1H-major), 1.83–1.72 (m, 1H-major), 1.68–1.64 (m, 1H-minor), 1.62–1.57 (m, 1H-major), 1.56–1.52 (m, 2H-minor), 1.49–1.43 (m, 2H-major & 2H-minor), 1.36–1.29 (m, 4H-major & 4H-minor), 1.29 (app s, 12H-

minor), 1.27 (app s, 12H-major), 1.21 (s, 9H-minor), 1.19 (s, 9H-major), 0.88 (app t, J = 10.0, 3H-major & 3H-minor).

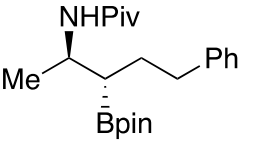
^{13}C NMR (125 MHz, $CDCl_3$) δ 177.3 (minor), 176.8 (major), 142.8 (major), 142.3 (minor), 128.6 (major), 128.5 (minor), 128.3 (minor), 128.3 (major), 125.8 (minor), 125.6 (major), 83.64 (minor), 83.55 (major), 83.0 (major), 82.2 (minor), 80.7 (minor), 79.4 (major), 41.9 (major), 41.0 (minor), 38.8 (minor), 38.6 (major), 35.1 (minor), 34.8 (major), 31.2 (minor), 31.1 (major), 30.3 (major), 30.2 (minor), 28.5 (major), 28.4 (minor), 27.5 (minor), 27.4 (major), 25.2 (major), 25.1 (minor), 24.8 (major), 24.7 (minor), 22.3 (minor), 22.2 (major), 18.8 (minor), 18.7 (major), 14.1 (minor), 14.0 (major).

^{11}B NMR (160 MHz, $CDCl_3$) δ 33.2.

IR (cast film, cm^{-1}): 3430, 3362, 3026, 2959, 2932, 1669, 1142.

HRMS (ESI-TOF) for $C_{28}H_{45}BNO_3$ $(M + H)^+$: *calcd.*: 454.3487; *found*: 454.3485.

$[\alpha]_D^{20}$: –29.7 (*c* 1.2, $CHCl_3$).



***N*-((2*R*,3*S*)-5-Phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentan-2-yl)pivalamide (3-2m):** Synthesized by following the general procedure with β-sulfinimido *gem*-bis(boronate) **2-3s** (0.16 g, 0.30 mmol, 1.0 equiv) and tetrabutylammonium dibenzylphosphate (0.78 g, 1.5 mmol, 5.0 equiv). The protodeboronation reaction was performed in $CHCl_3$ at 60 ºC for 18 h. The crude product was purified by flash column chromatography (6:1 to 5:1, hexanes/EtOAc) to afford a mixture of *anti*- and *syn*-β-aminoalkylboronates **3-2m** as a colorless oil (68 mg, 61%) ^{1}H NMR analysis of the crude mixture indicated 4:1 diastereoselectivity (*anti*:*syn*).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28–7.26 (m, 1H-major & 1H-minor), 7.26–7.24 (m, 1H-major & 1H-minor), 7.19–7.15 (m, 3H-major & 3H-minor), 6.60 (d, J = 9.3 Hz, 1H-minor), 6.47 (d, J = 8.8 Hz, 1H-major), 4.23–4.19 (m, 1H-minor), 4.18–4.12 (m, 1H-major), 2.74–2.68 (m, 1H-major & 1H minor), 2.65–2.59 (m, 1H-major), 2.59–2.54 (m, 1H-minor), 1.87–1.81 (m, 1H-major), 1.75–1.62 (m, 2H-minor), 1.62–1.57 (m, 1H-major), 1.29 (s, 12H-minor),

1.28 (s, 12H-major), 1.24–1.20 (m, 1H-major & 1H-minor), 1.19 (s, 9H-minor), 1.18 (s, 9H-major), 1.10 (d, J = 6.6 Hz, 3H-minor), 1.07 (d, J = 6.6 Hz, 3H-major).

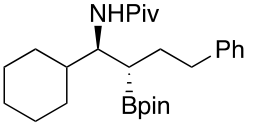
^{13}C NMR (125 MHz, $CDCl_3$) δ 177.8 (minor), 177.2 (major), 142.7 (major), 142.5 (minor), 128.53 (minor), 128.49 (major), 128.3 (major & minor), 125.72 (minor), 125.69 (major), 83.6 (minor), 83.5 (major), 45.6 (major), 45.4 (minor), 38.8 (minor), 38.6 (major), 35.32 (major), 35.28 (minor), 31.3 (minor), 30.6 (major), 27.7 (minor), 27.6 (major), 25.2 (major), 25.1 (minor), 24.83 (major), 24.76 (minor), 22.3 (minor), 18.9 (major).

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.7.

IR (cast film, cm^{-1}): 3427, 3354, 3026, 2976, 2932, 1647, 1142.

HRMS (ESI-TOF) for $C_{22}H_{36}BNNaO_3$ $(M + Na)^+$: *calcd.*: 396.268; *found*: 396.2683.

$[\alpha]_D^{20}$: +16.5 (*c* 0.55, $CHCl_3$).



***N*-((1*S*,2*S*)-1-Cyclohexyl-4-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl)pivalamide (3-2n):** Synthesized by following the general procedure with β-sulfinimido *gem*-bis(boronate) **2-3t** (0.18 g, 0.30 mmol, 1.0 equiv) and tetrabutylammonium dibenzylphosphate (0.47 g, 0.90 mmol, 3.0 equiv). The protodeboronation reaction was performed at room temperature for 23 h. The crude product was purified by flash column chromatography (7:1 to 6:1, hexanes/EtOAc) to afford β-aminoalkylboronates **3-2n** as a white solid (82 mg, 62%). ^{1}H NMR analysis of the crude mixture indicated 8.5:1 diastereoselectivity.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24–7.28 (m, 1H), 7.17 (d, J = 7.2 Hz, 3H), 5.94 (d, J = 9.9 Hz, 1H), 4.08 (app td, J = 10.5, 9.1, 4.2 Hz, 1H), 2.68–2.75 (m, 1H), 2.48–2.55 (m, 1H), 1.84–1.71 (m, 2H), 1.68–1.54 (m, 5H), 1.50–1.38 (m, 1H), 1.28 (s, 12H), 1.19 (s, 9H), 1.16–0.93 (m, 5H), 0.91–0.80 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 177.6, 142.8, 128.5, 128.3, 125.7, 83.4, 53.5, 41.4, 38.9, 35.6, 31.1, 30.2, 27.8, 27.3, 26.5, 25.2, 24.8.

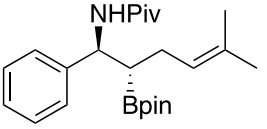
^{11}B NMR (128 MHz, $CDCl_3$) δ 31.8.

IR (cast film, cm^{-1}): 3363, 3026, 2977, 2926, 1634, 1144.

HRMS (ESI-TOF) for $C_{27}H_{45}BNO_3$ $(M + H)^+$: *calcd.*: 442.3487; *found*: 442.3484.

mp: 109.7–111.9 ºC.

$[\alpha]_D^{20}$: +7.32 (*c* 0.65, $CHCl_3$).



***N*-((1*S*,2*S*)-5-Methyl-1-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-4-en-1-yl)pivalamide (3-2o):** Synthesized by following the general procedure with β-sulfinimido *gem*-bis(boronate) **2-3c** (0.16 g, 0.30 mmol, 1.0 equiv). The protodeboronation reaction was performed at room temperature for 6 h. The crude product was purified by flash silica gel chromatography (8:1 to 7:1, hexanes/EtOAc) to afford β-aminoalkylboronates **3-2o** as a white solid (86 mg, 72%). ^{1}H NMR analysis of the crude mixture indicated >20:1 diastereoselectivity.

^{1}H NMR (498 MHz, $CDCl_3$) δ 7.27–7.26 (m, 2H), 7.23–7.18 (m, 2H), 7.18–7.16 (m, 1H), 6.68 (d, *J* = 8.4 Hz, 1H), 5.16 (app t, *J* = 7.1 Hz, 1H), 5.12–5.04 (m, 1H), 2.18–2.12 (m, 1H), 2.01–1.95 (m, 1H), 1.67 (s, 3H), 1.56–1.52 (m, 1H), 1.51 (s, 3H), 1.18 (s, 9H), 1.14 (s, 6H), 1.13 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 177.1, 142.5, 132.3, 128.2, 127.2, 127.0, 124.0, 83.5, 53.8, 38.7, 27.6, 26.5, 25.9, 24.83, 24.81, 18.0.

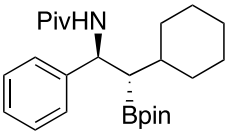
^{11}B NMR (160 MHz, $CDCl_3$) δ 33.0.

IR (cast film, cm^{-1}): 3357, 3029, 2978, 2930, 1626, 1379, 1165.

HRMS (ESI-TOF) for $C_{24}H_{39}BNO_3$ $(M + H)^+$: *calcd.*: 400.3018; *found*: 400.3016.

mp: 120.3–122.9 ºC.

$[\alpha]_D^{20}$: –34.4 (*c* 1.2, $CHCl_3$).



***N*-((1*S*,2*S*)-2-Cyclohexyl-1-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)pivalamide (3-2p):** Synthesized by following the general procedure with β-sulfinimido *gem*-bis(boronate) **2-3d** (0.17 g, 0.30 mmol, 1.0 equiv). The protodeboronation

reaction was performed at room temperature for 6 h. The crude product was purified by flash column chromatography (8:1 to 7:1, hexanes/EtOAc) to afford β-aminoalkylboronates **3-2p** as a white solid (0.10 g, 81%). ^{1}H NMR analysis of the crude mixture indicated >20:1 diastereoselectivity.

^{1}H NMR (498 MHz, $CDCl_3$) δ 7.32 (d, *J* = 7.1 Hz, 2H), 7.24 (t, *J* = 7.5 Hz, 2H), 7.17 (t, *J* = 7.3 Hz, 1H), δ 5.95 (d, *J* = 10.7 Hz, 1H), 5.19 (app t, *J* = 10.8 Hz, 1H), 1.91 (app d, *J* = 12.2 Hz, 1H), 1.72 (app d, *J* = 12.8 Hz, 3H), 1.64 (app d, *J* = 10.5 Hz, 1H), 1.50–1.46 (m, 2H), 1.31–1.16 (m, 2H), 1.15 (s, 9H), 1.13–1.02 (m, 3H), 1.00 (s, 6H), 0.98 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.9, 143.4, 128.2, 127.5, 127.0, 83.2, 51.6, 38.7, 37.4, 34.0, 30.7, 27.6, 27.2, 26.84, 26.77, 24.9, 24.6.

^{11}B NMR (160 MHz, $CDCl_3$) δ 32.6.

IR (cast film, cm^{-1}): 3379, 3063, 2979, 2929, 1626, 1164.

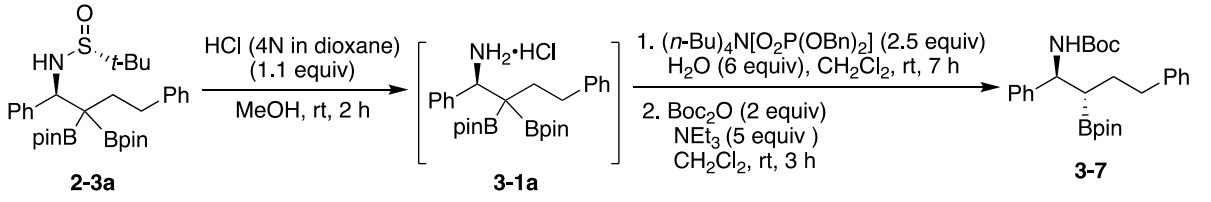
HRMS (ESI-TOF) for $C_{25}H_{40}BNNaO_3$ $(M + Na)^+$: *calcd.*: 436.2993; *found*: 436.2995.

mp: 192.4–193.7 ºC.

$[\alpha]_D^{20}$: –67.4 (*c* 0.68, $CHCl_3$).

3.10.6 Functionalization of the Amino Group of *anti*-α,β-Disubstituted β-Aminoalkylboronates

3.10.6.1 *N*-Boc Protection



***tert*-Butyl((1*S*,2*S*)-1,4-diphenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl)carbamate** (**3-7**): The desulfinylation reaction of **2-3a** and protodeboronation reaction of **3-1a** were conducted by following the general procedure for the synthesis of *anti*-β-aminoalkylboronates **3-2**, and the *N*-Boc protection reaction was performed by following the literature procedures.[31] In an oven-dried 10 mL round-bottomed flask, **2-3a** (0.17 g, 0.30 mmol, 1.0 equiv) was dissolved in MeOH (1.2 mL), followed by dropwise addition of HCl

solution (4 N in dioxane, 82 μL, 0.33 mmol, 1.1 equiv) at room temperature. After stirring for 2 h at room temperature, the reaction mixture was concentrated under reduced pressure to afford β-amino *gem*-bis(boronate) **3-1a**. The obtained **3-1a** was dissolved in CH_2Cl_2 (3 mL) and added to a 10 mL round-bottomed flask containing tetrabutylammonium dibenzylphosphate (0.39 g, 0.75 mmol, 2.5 equiv), followed by addition of water (82 μL, 1.8 mmol, 6.0 equiv). The resulting reaction mixture was stirred at room temperature for 7 h. Upon completion, the reaction mixture was filtered through a short pad of Celite, washed with CH_2Cl_2, and concentrated under reduced pressure to yield the crude β-aminoalkylboronate product. The obtained β-aminoalkylboronate was dissolved in CH_2Cl_2 (9 mL). Triethylamine (0.17 mL, 1.2 mmol, 4.0 equiv) was added, followed by addition of di-*tert*-butyl dicarbonate (0.13 g, 0.60 mmol, 2.0 equiv). The resulting reaction mixture was stirred for 3 h. Upon completion, the reaction mixture was concentrated under reduced pressure and purified by flash column chromatography (10:1, EtOAc/hexanes) to afford the desired β-aminoalkylboronate product **3-7** as a colorless oil (0.10 g, 74%). ^{1}H NMR analysis of the crude mixture indicated >20:1 diastereoselectivity.

^{1}H NMR (498 MHz, toluene-d_8) δ 7.21 (d, J = 7.3 Hz, 2H), 7.14–7.12 (m, 4H), 7.09–7.02 (m, 3H), 7.02–6.98 (m, 1H), 5.13 (app t, J = 8.3 Hz, 1H), 4.92 (d, J = 9.2 Hz, 1H), 2.88–2.73 (m, 1H), 2.59 (ddd, J = 13.5, 10.0, 6.9 Hz, 1H), 1.95–1.89 (m, 1H), 1.84 (app dtd, J = 12.9, 6.6, 3.3 Hz, 1H), 1.55–1.50 (m, 1H), 1.40 (s, 9H), 0.89 (s, 6H), 0.88 (s, 6H).

^{13}C NMR (125 MHz, toluene-d_8) δ 154.5, 143.4, 142.4, 128.6, 128.0, 127.7, 126.5, 125.4, 124.8, 82.6, 77.9, 55.4, 35.1, 30.1, 28.0, 24.2, 24.0.

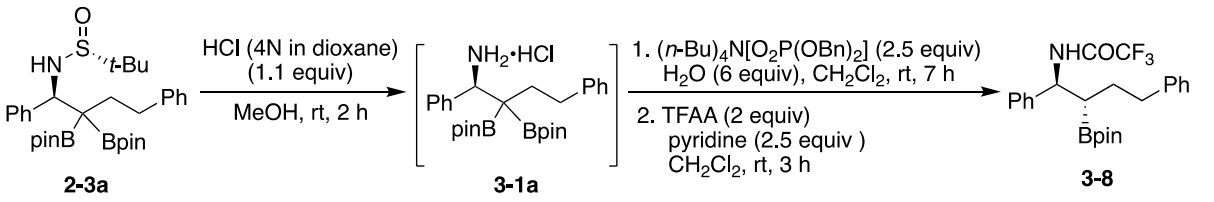
^{11}B NMR (160 MHz, toluene-d_8) δ 33.2.

IR (cast film, cm^{-1}): 3354, 3028, 2978, 2931, 1699, 1144.

HRMS (ESI-TOF) for $C_{27}H_{38}BNNaO_4$ $(M + Na)^+$: *calcd.*: 474.2786; *found*: 474.2785.

$[\alpha]_D^{20}$: –25.0 (*c* 0.57, $CHCl_3$).

3.10.6.2 *N*-CF_3CO Protection



***N*-((1*S*,2*S*)-1,4-Diphenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl)-2,2,2-trifluoroacetamide (3-8):** The desulfinylation reaction of **2-3a** and protodeboronation reaction of **3-1a** were conducted by following the general procedure for the synthesis of *anti*-β-aminoalkylboronates **3-2**, and the *N*-Fmoc protection step was carried out by following the literature procedures.[32] In an oven-dried 10 mL round-bottomed flask, **2-3a** (0.17 g, 0.30 mmol, 1.0 equiv) was dissolved in MeOH (1.2 mL), followed by dropwise addition of an HCl solution (4 N in dioxane, 82 μL, 0.33 mmol, 1.1 equiv) at room temperature. After stirring for 2 h at room temperature, the reaction mixture was concentrated under reduced pressure to afford β-amino *gem*-bis(boronate) **3-1a**. The obtained **3-1a** was dissolved in CH_2Cl_2 (3 mL) and added to a 10 mL round-bottomed flask containing tetrabutylammonium dibenzylphosphate (0.39 g, 0.75 mmol, 2.5 equiv), followed by addition of water (82 μL, 1.8 mmol, 6.0 equiv). The resulting reaction mixture was stirred at room temperature for 7 h. Upon completion, the reaction mixture was filtered through a short pad of Celite, washed with CH_2Cl_2, and concentrated under reduced pressure to yield the crude β-aminoalkylboronate product. The crude β-aminoalkylboronate product was dissolved in CH_2Cl_2 (4.5 mL) and cooled to 0 °C. Next, pyridine (60 μL, 0.75 mmol, 2.5 equiv) was added, followed by dropwise addition of trifluoroacetic anhydride (83 μL, 0.60 mmol, 2.0 equiv). The resulting mixture was allowed to warm to room temperature and stirred for 3 h. The reaction mixture was poured into an aqueous solution of HCl (1 N, 3 mL) and vigorously stirred for 5 min. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with HCl (1 N, 3 mL), H_2O (2×4 mL), and a saturated aqueous solution of $NaHCO_3$ (5 mL). The organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (12:1 to 10:1, hexanes/EtOAc) to yield the desired β-aminoalkylboronate **3-**

8 as a colorless oil (95 mg, 71%). ^{1}H NMR analysis of the crude mixture indicated >20:1 diastereoselectivity.

^{1}H NMR (498 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.8 Hz, 1H), 7.32 (d, *J* = 4.3 Hz, 4H), 7.30–7.26 (m, 3H), 7.18 (t, *J* = 7.3 Hz, 1H), 7.15 (d, *J* = 7.2 Hz, 2H), 5.18 (app t, *J* = 8.1 Hz, 1H), 2.73 (ddd, *J* = 14.5, 9.5, 5.5 Hz, 1H), 2.64 (ddd, *J* = 13.6, 9.9, 6.4 Hz, 1H), 1.85–1.76 (m, 1H), 1.67–1.58 (m, 2H), 1.20 (s, 6H), 1.18 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 156.1 (q, *J* = 36.3 Hz), 141.9, 140.0, 128.7, 128.45, 128.44, 128.0, 127.3, 126.0, 118.4 (q, *J* = 288.1 Hz), 84.0, 54.9, 35.0, 30.0, 24.83, 24.81.

^{11}B NMR (160 MHz, $CDCl_3$) δ 33.7.

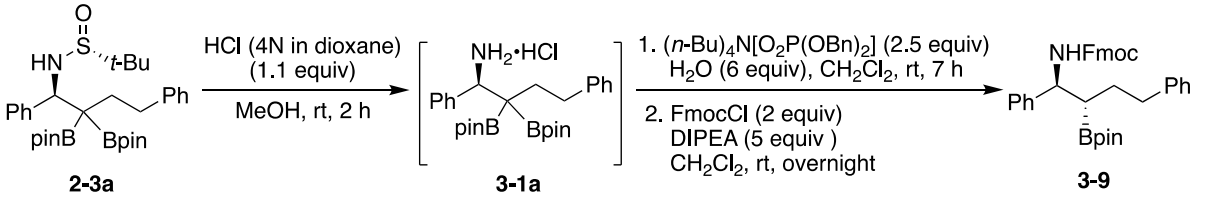
^{19}F NMR (469 MHz, $CDCl_3$) δ -76.1.

IR (cast film, cm^{-1}): 3301, 3029, 2980, 2931, 1697, 1143.

HRMS (ESI-TOF) for $C_{24}H_{29}BF_3NNaO_3$ $(M + Na)^+$: *calcd.*: 470.2085; *found*: 470.2085.

$[\alpha]_D^{20}$: –50.2 (*c* 0.53, $CHCl_3$).

3.10.6.3 *N*-Fmoc Protection



(9H-Fluoren-9-yl)methyl((1*S*,2*S*)-1,4-diphenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl)carbamate (3-9): The desulfinylation step of **2-3a** and protodeboronation reaction of **3-1a** were conducted by following the general procedure for the synthesis of *anti*-β-aminoalkylboronates **3-2**, and the *N*-Fmoc protection reaction was performed by following the literature procedures.[32] In an oven-dried 10 mL round-bottomed flask, **2-3a** (0.17 g, 0.30 mmol, 1.0 equiv) was dissolved in MeOH (1.2 mL), followed by dropwise addition of an HCl solution (4 N in dioxane, 82 μL, 0.33 mmol, 1.1 equiv) at room temperature. After stirring for 2 h at room temperature, the reaction mixture was concentrated under reduced pressure to afford β-amino *gem*-bis(boronate) **3-1a**. The obtained **3-1a** was dissolved in CH_2Cl_2 (3 mL) and added to a 10 mL round-bottomed flask containing tetrabutylammonium dibenzylphosphate (0.39 g, 0.75 mmol, 2.5 equiv), followed by addition

of water (82 μL, 1.8 mmol, 6.0 equiv). The resulting reaction mixture was stirred at room temperature for 7 h. Upon completion, the reaction mixture was filtered through a short pad of Celite, washed with CH_2Cl_2, and concentrated under reduced pressure to yield the crude β-aminoalkylboronate product. The crude β-aminoalkylboronate product was dissolved in CH_2Cl_2 (2 mL), followed by addition of diisopropylethylamine (0.26 mL, 1.5 mmol, 5.0 equiv) and the addition of a solution of Fmoc chloride (0.16 g, 0.60 mmol, 2.0 equiv) in CH_2Cl_2 (0.5 mL). After stirring overnight at room temperature, the reaction mixture was washed with an aqueous solution of HCl (1 N, 3×3 mL), a saturated solution of aqueous $NaHCO_3$ (3 mL), water (3 mL), and brine (3 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated. The crude product was purified by flash column chromatography (5:1:2, hexanes/Et_2O/CH_2Cl_2) to yield the desired β-aminoalkylboronate **3-9** as a white solid (0.10 g, 61%). ^{1}H NMR analysis of the crude mixture indicated >20:1 diastereoselectivity.

^{1}H NMR (498 MHz, $CDCl_3$), rotamers are present: δ 7.80–7.68 (m, 2H), 7.55 (t, *J* = 6.4 Hz, 1H), 7.40–7.35 (m, 2H), 7.34–7.26 (m, 7H), 7.26–7.07 (m, 6H), 5.40 & 5.29 (d, *J* = 9.0 Hz, 1H), 4.86 & 4.64 (app t, *J* = 9.0 Hz, 1H), 4.40 (dd, *J* = 10.7, 7.0 Hz, 1H), 4.31 (dd, *J* = 10.7, 6.9 Hz, 1H), 4.19 (app t, *J* = 7.0 Hz, 1H), 2.79–2.63 (m, 1H), 2.63–2.49 (m, 1H), 1.88–1.72 (m, 2H), 1.64–1.54 (m, 1H), 1.12 (s, 6H), 1.10 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.7, 144.1, 142.5, 142.3, 141.3, 128.5 (×2), 128.4 (×2), 127.6, 127.3, 127.1, 127.0, 125.8, 125.1, 125.1, 119.9, 83.5, 66.5, 56.5, 47.4, 35.3, 30.3, 24.8, 24.7.

^{11}B NMR (160 MHz, $CDCl_3$) δ 33.8.

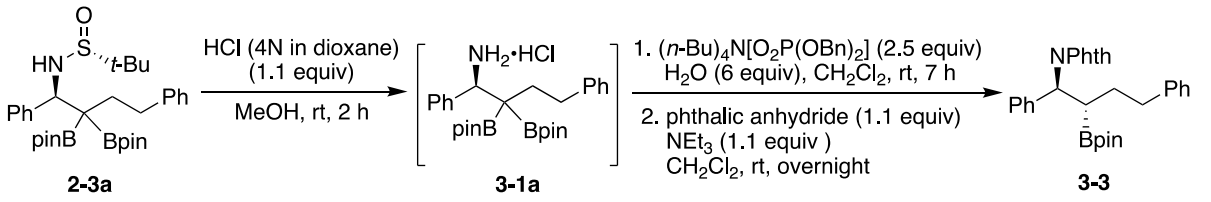
IR (cast film, cm^{-1}): 3318, 3027, 2972, 2931, 1631, 1607, 1555.

HRMS (ESI-TOF) for $C_{37}H_{40}BNNaO_4$ $(M + Na)^+$: *calcd.*: 596.2943; *found*: 596.295.

mp: 56.7–59.4 ºC.

$[\alpha]_D^{20}$: –64.8 (*c* 1.22, $CHCl_3$).

3.10.6.4 *N*-Phth Protection



2-((1*S*,2*S*)-1,4-Diphenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-butyl)-isoindoline-1,3-dione (3-3): The desulfinylation reaction of **2-3a** and protodeboronation reaction of **3-1a** were conducted by following the general procedure for the synthesis of *anti*-β-aminoalkylboronates **3-2**, and the *N*-Phth protection reaction was performed by following the procedure in Chapter 2. In an oven-dried 25 mL round-bottomed flask, β-sulfinimido *gem*-bis(boronate) **2-3a** (1.2 g, 2.0 mmol, 1.0 equiv) was dissolved in MeOH (7.7 mL), followed by dropwise addition of an HCl solution (4 N in dioxane, 0.55 mL, 2.2 mmol, 1.1 equiv) at room temperature. After stirring for 2 h at room temperature, the reaction mixture was concentrated under reduced pressure to afford β-amino *gem*-bis(boronate) **3-1a**. The obtained **3-1a** was dissolved in CH_2Cl_2 (20 mL) and added to a 100 mL round-bottomed flask containing tetrabutylammonium dibenzylphosphate (2.6 g, 5.0 mmol, 2.5 equiv), followed by addition of water (0.22 mL, 12 mmol, 6.0 equiv). The resulting reaction mixture was stirred at room temperature for 7 h. Upon completion, the reaction mixture was filtered through a short pad of Celite, washed with CH_2Cl_2, and concentrated under reduced pressure to yield the crude β-aminoalkylboronate product. The obtained β-aminoalkylboronate product and triethylamine (0.31 mL, 2.2 mmol, 1.1 equiv) were dissolved in toluene (10 mL), followed by addition of phthalic anhydride (0.33 g, 2.2 mmol, 1.1 equiv). The resulting mixture was refluxed overnight using a Dean–Stark apparatus. The reaction mixture was cooled to room temperature, followed by addition of an aqueous solution of HCl (1 N, 40 mL) and EtOAc (40 mL). The phases were separated, and the aqueous layer was extracted further with EtOAc (2×40 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (10:1, hexanes/EtOAc) to afford the desired β-aminoalkylboronate product **3-3** as a white solid (0.79 g, 82%). ^{1}H NMR analysis of the crude mixture indicated >20:1 diastereoselectivity.

^{1}H NMR (498 MHz, $CDCl_3$) δ 7.78–7.73 (m, 2H), 7.68–7.65 (m, 2H), 7.63 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.30–7.27 (m, 2H), 7.24–7.19 (m, 3H), 7.15–7.09 (m, 3H), 5.45 (d, *J* = 12.9 Hz, 1H), 3.02 (ddd, *J* = 12.9, 10.4, 4.3 Hz, 1H), 2.71 (app td, *J* = 12.8, 12.4, 5.0 Hz, 1H), 2.61 (ddd, *J* = 13.7, 11.6, 5.7 Hz, 1H), 1.86–1.76 (m, 1H), 1.76–1.66 (m, 1H), 1.00 (s, 6H), 0.97 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 142.4, 139.9, 133.8, 131.9, 129.4, 128.31 (×2), 128.29, 128.0, 125.8, 123.1, 83.4, 57.1, 35.2, 31.6, 24.5, 24.5.

^{11}B NMR (160 MHz, $CDCl_3$) δ 33.2.

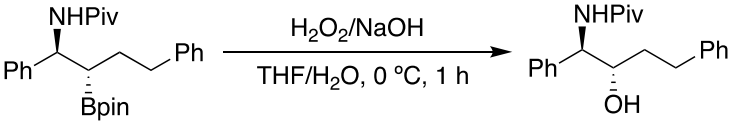
IR (cast film, cm^{-1}): 3029, 2978, 1711, 1143.

HRMS (ESI-TOF) for $C_{30}H_{32}BNNaO_4$ $(M + Na)^+$: *calcd.*: 504.2317; *found*: 504.2319.

mp: 149.9–151.8 ºC.

$[\alpha]_D^{20}$: –74.0 (*c* 0.77, $CHCl_3$).

3.10.7 Oxidation of *anti*-β-Aminoalkylboronate 3-2a



3-2a **3-10**

***N*-((1*R*,2*S*)-2-Hydroxy-1,4-diphenylbutyl)pivalamide (3-10):** Prepared by following literature procedures with slight modifications.[33] Boronic ester **3-2a** (0.12 g, 0.27 mmol) was placed in a 10 mL round-bottomed flask and dissolved in THF (2.7mL). The solution was cooled down to 0 °C, and a 2:1 mixture of NaOH (2 N)/H_2O_2 (33% aq.) (2.7 mL) was added dropwise. The reaction mixture was stirred 10 min at 0 °C, followed by 1 h at room temperature. Upon completion, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with a saturated aqueous solution of NH_4Cl (5 mL). The aqueous phase was extracted with CH_2Cl_2 (2×10 mL). The combined organic phase was dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford the crude alcohol product, which was purified by flash column chromatography (4:1 to 3:1, hexanes/EtOAc) to afford the desired alcohol **3-10** as a white solid (88 mg, 100%). ^{1}H NMR analysis of the crude mixture indicated >20:1 diastereoselectivity.

^{1}H NMR (498 MHz, $CDCl_3$) δ 7.35–7.32 (m, 2H), 7.30–7.28 (m, 3H), 7.25–7.21 (m, 2H), 7.19–7.16 (m, 1H), 7.13 (d, *J* = 7.5 Hz, 2H), 6.53 (d, *J* = 7.7 Hz, 1H), 4.96 (dd, *J* = 7.8, 3.6

Hz, 1H), 3.92–3.87 (m, 1H), 2.83–2.78 (comp m, A part of ABMX, 1H), 2.72–2.59 (comp m, B part of ABMX, 1H), 2.03 (d, J = 7.6 Hz, 1H), 1.82–1.70 (comp m, M part of ABMX, 1H), 1.50–1.43 (comp m, X part of ABMX, 1H), 1.20 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 178.1, 141.6, 138.1, 128.7, 128.5, 128.4, 127.8, 127.7, 126.0, 73.8, 57.8, 38.8, 35.8, 32.2, 27.6.

IR (cast film, cm^{-1}): 3427, 3028, 2958, 2932, 1640, 1511, 1497.

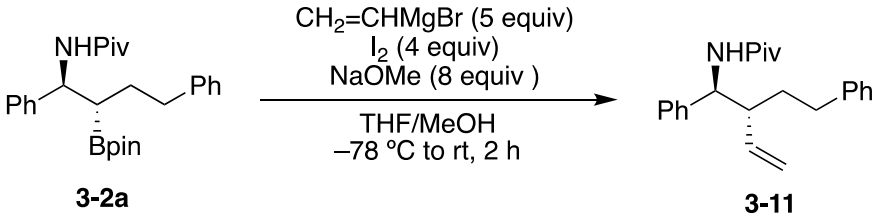
HRMS (ESI-TOF) for $C_{21}H_{27}NNaO_2$ $(M + Na)^+$: *calcd.*: 348.1934; *found*: 348.1932.

mp: 144.9–146.0 ºC.

$[\alpha]_D^{20}$: –16.8 (*c* 0.66, $CHCl_3$).

3.10.8 Zweifel Olefination of α,β-Disubstituted β-Aminoalkylboronates

3.10.8.1 Olefination of *anti*-β-Aminoalkylboronate 3-2a



The Zweifel olefination reaction of β-aminoalkylboronate **3-2a** was conducted by following the literature procedures with slight modification.[16] To a solution of **3-2a** (0.13 g, 0.30 mmol, 1.0 equiv) in anhydrous THF (3.0 mL, 0.10 M) at room temperature was added vinylmagnesium bromide (1.0 M in THF, 1.5 mmol, 5.0 equiv) dropwise. The resulting mixture was stirred at room temperature for 30 min and cooled down to –78 °C. A solution of iodine (0.31 g, 1.2 mmol, 4.0 equiv) in MeOH (4 mL) was added dropwise to the reaction mixture via cannula, followed 30 min later by a solution of NaOMe (25 wt.% in MeOH, 0.55 mL, 2.4 mmol, 8.0 equiv) diluted in MeOH (4.5 mL). Next, the reaction mixture was allowed to warm to room temperature and stirred for an additional 1 h, diluted with etheyl acetate (20 mL), and washed with a saturated aqueous solution of $Na_2S_2O_3$ (5 mL) and water (10 mL). The phases were separated, and the aqueous layer was extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine (10 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash

column chromatography (8:1 to 7:1, hexanes/EtOAc) to yield the desired product **3-11** as a yellow solid (74 mg, 74%). ^{1}H NMR analysis of the crude mixture indicated >20:1 diastereoselectivity.

^{1}H NMR (498 MHz, $CDCl_3$) δ 7.32–7.26 (m, 3H), 7.25–7.21 (m, 2H), 7.20–7.17 (m, 1H), 7.17–7.13 (m, 2H), 7.11 (d, *J* = 7.2 Hz, 2H), 6.23 (d, *J* = 8.4 Hz, 1H), 5.55 (app dt, *J* = 17.1, 10.0 Hz, 1H), 5.25 (dd, *J* = 10.2, 2.0 Hz, 1H), 5.15 (dd, *J* = 17.1, 2.0 Hz, 1H), 4.97 (dd, *J* = 8.4, 5.2 Hz, 1H), 2.63 (ddd, *J* = 14.6, 10.0, 5.0 Hz, 1H), 2.55–2.42 (m, 2H), 1.80 (dddd, *J* = 13.6, 10.4, 7.0, 3.7 Hz, 1H), 1.42–1.34 (m, 1H), 1.18 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 177.0, 142.0, 139.6, 138.4, 128.5, 128.4, 128.2, 127.5, 127.3, 125.9, 118.5, 55.5, 48.8, 38.8, 33.5, 33.3, 27.6.

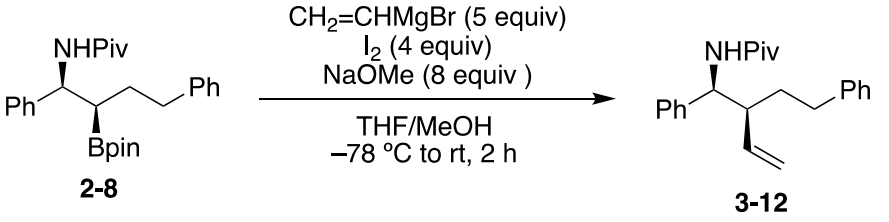
IR (cast film, cm^{-1}): 3365, 3028, 2960, 1646, 1514, 1497.

HRMS (ESI-TOF) for $C_{23}H_{30}NNaO$ $(M + Na)^+$: *calcd.*: 358.2141; *found*: 358.214.

mp: 82.7–84.0 ºC.

[α]$_D^{20}$: –48.1 (*c* 0.46, $CHCl_3$).

3.10.8.2 Olefination of *syn*-β-Aminoalkylboronate 2-8



The *syn*-*N*-Piv-protected β-aminoalkylboronate **2-8** was prepared by following the literature procedures.[16] The Zweifel olefination reaction was performed by following the literature procedures with slight modification.[8] To a solution of *syn*-*N*-Piv-protected β-aminoalkylboronate **2-8** (87 mg, 0.20 mmol, 1.0 equiv) in anhydrous THF (2.0 mL, 0.10 M) at room temperature was added vinylmagnesium bromide (1.0 M in THF, 1.0 mmol, 5.0 equiv) dropwise. The resulting mixture was stirred at room temperature for 30 min and cooled down to –78 °C. A solution of iodine (0.20 g, 0.80 mmol, 4.0 equiv) in MeOH (2.7 mL) was added dropwise to the reaction mixture via cannula, followed 30 min later by a solution of NaOMe (25 wt.% in MeOH, 0.37 mL, 1.6 mmol, 8.0 equiv) diluted in MeOH (3 mL). Next, the reaction mixture was allowed to warm to room temperature and stirred for an additional 1 h. Upon

completion, the reaction was diluted with ethyl acetate (20 mL), washed with a saturated aqueous solution of $Na_2S_2O_3$ (5 mL), and water (10 mL). The phases were separated, and the aqueous layer was extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine (10 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (8:1 to 7:1, hexanes/EtOAc) to yield the desired product **3-12** as a yellow solid (38 mg, 57%). ^{1}H NMR analysis of the crude mixture indicated >20:1 diastereoselectivity.

^{1}H NMR (498 MHz, $CDCl_3$) δ 7.31–7.28 (m, 2H), 7.25–7.21 (m, 3H), 7.17 (d, *J* = 7.1 Hz, 3H), 7.05 (d, *J* = 7.0 Hz, 2H), 5.94 (d, *J* = 8.0 Hz, 1H), 5.66 (ddd, *J* = 17.2, 10.4, 8.4 Hz, 1H), 5.23 (dd, *J* = 10.4, 1.7 Hz, 1H), 5.12 (app d, *J* = 16.9 Hz, 1H), 4.91 (app t, *J* = 7.9 Hz, 1H), 2.68 (ddd, *J* = 14.4, 9.4, 5.4 Hz, 1H), 2.52 (app dt, *J* = 13.9, 7.9 Hz, 1H), 2.47–2.39 (m, 1H), 1.72–1.55 (m, 2H), 1.16 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 177.4, 141.8, 141.5, 138.8, 128.50, 128.46, 128.3, 127.2, 126.9, 125.8, 117.8, 55.2, 48.9, 38.8, 33.1, 32.2, 27.6.

IR (cast film, cm^{-1}): 3396, 3026, 2913, 1643, 1528.

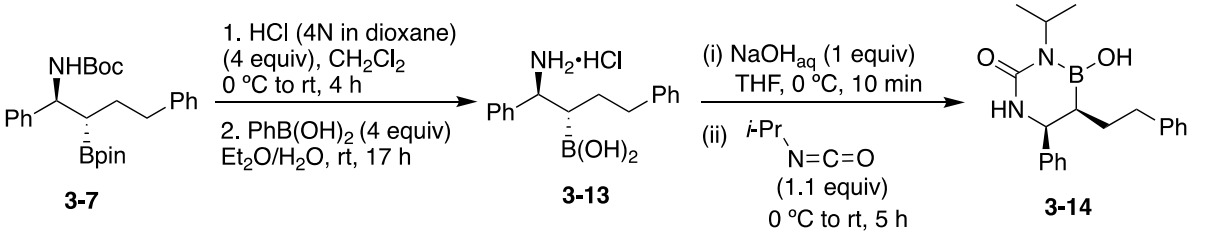
HRMS (ESI-TOF) for $C_{23}H_{29}NNaO$ $(M + Na)^+$: *calcd.*: 358.2141; *found*: 358.2141.

mp: 122.3–124.9 ºC.

$[\alpha]_D^{20}$: –37.0 (*c* 0.39, $CHCl_3$).

3.10.9 Synthesis of Boron Heterocycles

3.10.9.1 Synthesis of the Boron Heterocycle with *anti*-β-Aminoalkylboronate 3-7



(3*S*,4*S*)-2-Hydroxy-1-isopropyl-3-phenethyl-4-phenyl-1,5,2-diazaborinan-6-one (3-14): Synthesized by following the literature procedures.[17,34,35] In an oven-dried 5 mL round-bottomed flask, *anti*-*N*-Boc-protected β-aminoalkylboronate **3-7** (67 mg, 0.20 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (0.4 mL) and cooled to 0 ºC. A solution of HCl (4 N in dioxane,

0.40 mL, 1.6 mmol, 5.4 equiv) was added dropwise. The resulting reaction solution was warmed up to room temperature and stirred for 4 h. The reaction mixture was concentrated under reduced pressure to afford the deprotected β-aminoalkylboronate product. The deprotected β-aminoalkylboronate product was dissolved in 6 mL diethyl ether/water (1:1, v/v), followed by addition of phenylboronic acid (0.49 g, 0.80 mmol, 4.0 equiv). After stirring at room temperature for 17 h, the aqueous layer was separated, washed with diethyl ether (3×3 mL), and lyophilized to afford the corresponding β-aminoalkylboronic acid **3-13** as a white solid. The obtained boronic acid **3-13** was dissolved in 2 mL THF and cooled to 0 ºC, followed by dropwise addition of an aqueous solution of NaOH (5 N, 40 μL, 0.20 mmol, 1.0 equiv). The resulting reaction mixture was stirred at 0 ºC for 10 min, followed by dropwise addition of isopropyl isocyanate (21 μL, 0.22 mmol, 1.1 equiv). The reaction mixture was warmed up to room temperature and stirred for 5 h. Upon completion, the solvent was removed under reduced pressure to afford the crude product. The crude product was dissolved in CH_2Cl_2 and filtered. The filtrate was concentrated under reduced pressure and precipitated with CH_2Cl_2 (1 mL) and hexane (15 mL). The precipitate was washed with 11 mL CH_2Cl_2/hexane (1:10, v/v), and the solvent was removed under reduced pressure to afford the boron heterocycle **3-14** as a white solid (53 mg, 79%);

^{1}H NMR (500 MHz, acetone-d_6) δ 7.36 (d, J = 7.5 Hz, 2H), 7.25 (t, J = 7.5 Hz, 2H), 7.20 (d, J = 7.2 Hz, 3H), 7.13 (d, J = 7.2 Hz, 1H), 7.07 (d, J = 7.5 Hz, 2H), 6.51 (d, J = 6.3 Hz, 1H), 6.03 (bs, 1H), 5.13 (app t, J = 6.3 Hz, 1H), 3.87 (dq, J = 10.0, 12.5 Hz, 1H), 2.70 (app td, J = 12.3, 11.1 Hz, 1H), 2.42 (app td, J = 12.1, 6.1 Hz, 1H), 1.75 (app dtd, J = 13.8, 9.7, 5.2 Hz, 1H), 1.58–1.51 (m, 1H), 1.25–1.21 (m, 1H), 1.12 (d, J = 6.6 Hz, 3H), 1.09 (d, J = 6.4 Hz, 3H).

^{13}C NMR (126 MHz, acetone-d_6) δ 158.8, 145.2, 144.7, 129.4, 129.04, 128.97, 128.0, 127.4, 126.2, 57.5, 42.9, 36.8, 30.8, 23.6, 23.6.

^{11}B NMR (160 MHz, acetone-d_6) δ 22.3.

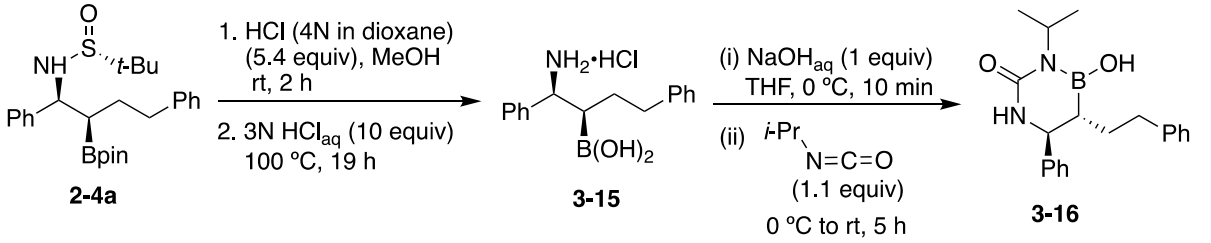
IR (cast film, cm^{-1}): 3310, 3026, 2970, 2927, 1630, 1607, 1585.

HRMS (ESI-TOF) for $C_{20}H_{26}BN_2O_2$ $(M + H)^+$: *calcd.*: 337.2082; *found*: 337.2088.

mp: 120.4–123.8 ºC.

$[\alpha]_D^{20}$: +22.3 (*c* 1.1, $CHCl_3$).

3.10.9.2 Synthesis of Boron Heterocycles with *syn*-β-Aminoalkylboronate 2-4a



(3*R*,4*S*)-2-Hydroxy-1-isopropyl-3-phenethyl-4-phenyl-1,5,2-diazaborinan-6-one (3-16): Synthesized by following the literature procedures.[17,35,36] In an oven-dried 5 mL round-bottomed flask, *syn*-*N*-sulfinyl-protected β-aminoalkylboronate **2-4a** (0.14 g, 0.30 mmol, 1.0 equiv) was dissolved in MeOH (1.2 mL), followed by dropwise addition of an HCl solution (4 N in dioxane, 0.40 mL, 1.6 mmol, 5.4 equiv) at room temperature. After stirring for 2 h at room temperature, the reaction mixture was concentrated under reduced pressure to afford the desulfinylated β-aminoalkylboronate. The desulfinylated β-aminoalkylboronate was stirred at 100°C in an aqueous solution of HCl (3 N, 1.0 mL, 10 equiv) for 19 h. The reaction mixture was cooled to room temperature and washed with Et_2O (3×3 mL). The aqueous layer was lyophilized to afford the desulfinylated β-aminoalkylboronic acid **3-15** as a white solid. The obtained boronic acid **3-15** was dissolved in 3 mL THF and cooled to 0 ºC, followed by dropwise addition of an aqueous solution of NaOH (5N, 60 μL, 0.30 mmol, 1.0 equiv). The resulting reaction mixture was stirred at 0 ºC for 10 min, followed by dropwise addition of isopropyl isocyanate (32 μL, 0.33 mmol, 1.1 equiv). The reaction mixture was warmed up to room temperature and stirred for 5 h. Upon completion, the solvent was removed under reduced pressure to afford the crude product. The crude product was dissolved in CH_2Cl_2 and filtered. The filtrate was concentrated under reduced pressure and precipitated with CH_2Cl_2 (1 mL) and hexane (15 mL). The precipitate was washed with 11 mL CH_2Cl_2/hexane (1:10, v/v), and the solvent was removed under reduced pressure to afford the boron heterocycle **3-16** as a white solid (82 mg, 81%);

^{1}H NMR (498 MHz, CD_3CN) δ 7.30 (d, *J* = 7.3 Hz, 2H), 7.25 (t, *J* = 7.5 Hz, 2H), 7.18–7.15 (m, 3H), 7.11 (t, *J* = 7.2 Hz, 1H), 6.96 (d, *J* = 7.4 Hz, 2H), 6.08 (d, *J* = 6.1 Hz, 1H), 5.68 (d, *J* = 7.5 Hz, 1H), 4.70 (app t, *J* = 10.0 Hz, 1H), 3.65 (dq, *J* = 13.3, 7.4, 6.7 Hz, 1H), 2.53 (app td, *J* = 12.3, 11.2, 5.5 Hz, 1H), 2.40 (app td, *J* = 13.1, 11.9, 5.7 Hz, 1H), 1.59–1.51 (m, 1H), 1.37–

1.29 (m, 1H), 1.18 (app q, J = 8.0 Hz, 1H), 0.97 (d, J = 6.5 Hz, 3H), 0.93 (d, J = 6.5 Hz, 3H).

^{13}C NMR (126 MHz, CD_3CN) δ 158.8, 145.6, 144.3, 129.3, 129.2, 129.1, 127.9, 127.7, 126.4, 57.7, 43.0, 36.0, 32.3, 23.4, 23.3.

^{11}B NMR (160 MHz, CD_3CN) δ 22.5.

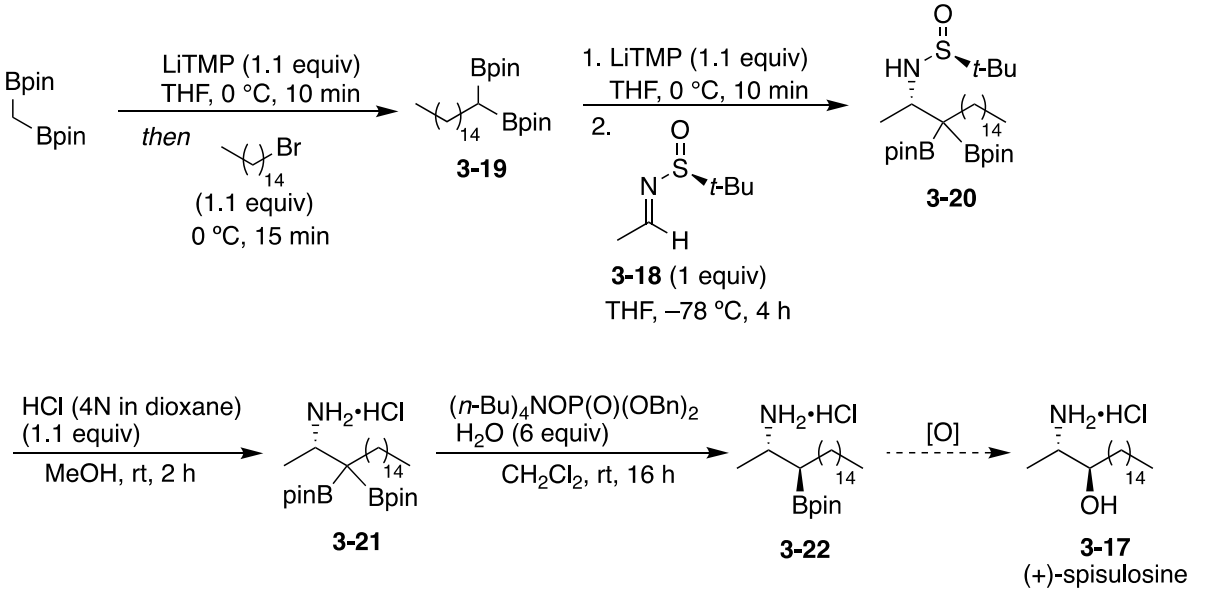
IR (cast film, cm^{-1}): 3324, 3028, 2978, 2931, 1695, 1142.

HRMS (ESI-TOF) for $C_{30}H_{32}BNNaO_4$ $(M + H)^+$: *calcd.*: 337.2082; *found*: 337.2083.

mp: 118.4–121.9 ºC.

$[\alpha]_D^{20}$: –8.1 (*c* 0.30, $CHCl_3$).

3.10.10 Attempted Synthesis of (+)-Spisulosine



1,1-Diborylalkane **3-19** was synthesized by following the literature procedures with slight modifications.[12] A flame-dried 100 mL round-bottomed flask was charged with a solution of TMP (0.960 mL, 5.50 mmol, 1.22 equiv) in THF (5.5 mL) under N_2. The rapidly stirred solution was cooled to 0 ºC, followed by dropwise addition of *n*-BuLi (2.50 M in hexanes, 2.10 mL, 5.25 mmol, 1.17 equiv). The reaction mixture was stirred at 0 ºC for 30 min. Next, THF (14 mL) was added, followed by addition of a 1.0 M solution of 1,1-diborylmethane (1.30 g, 5.00 mmol, 1.11 equiv) in THF. The reaction mixture was allowed to stir at 0 ºC for 10 min. 1-Bromopentadecane (1.30 g, 4.50 mmol, 1.00 equiv) was added dropwise, and the reaction was allowed to stir at 0 ºC for 15 min. Upon completion, the reaction mixture was

warmed to room temperature, filtered through a silica gel plug, rinsed with diethyl ether, and concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (15:1, hexanes/diethyl ether) to afford the desired 1,1-diborylalkane **3-19** as a white solid (1.9 g, 75%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52 (q, *J* = 7.3 Hz, 2H), 1.25–1.21 (m, 50H), 0.87 (t, *J* = 6.7 Hz, 3H), 0.70 (t, *J* = 7.9 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 82.9, 32.6, 32.0, 29.74 (×2), 29.72, 29.70, 29.66, 29.6, 29.4, 25.7, 24.9 (×2), 24.6 (×2), 22.7, 14.1.

^{11}B NMR (128 MHz, $CDCl_3$) δ 34.2.

HRMS (ESI-TOF) for $C_{28}H_{56}B_2NaO_4$ (M + H)+: calcd.: 501.4257; found: 501.4264.

IR (cast film, cm-1): 2924, 1370, 1142.

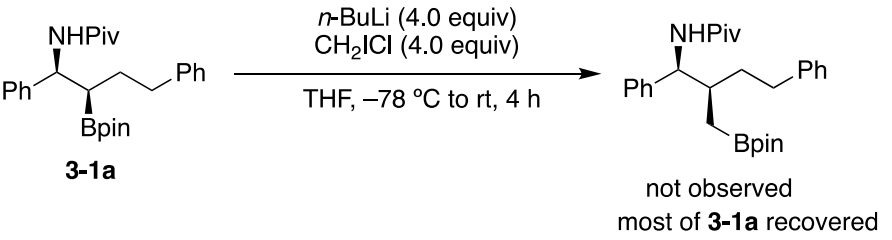
β-Sulfinimido *gem*-bis(boronate) **3-20** was synthesized by following the procedure described in Chapter 2. A flame-dried round-bottomed flask was charged with a 1.0 M solution of TMP (0.42 mL, 2.4 mmol, 1.2 equiv) in THF. The rapidly stirred solution was cooled to 0 ºC, followed by dropwise addition of *n*-BuLi (2.5 M in hexanes, 0.88 mL, 2.2 mmol, 1.1 equiv). The reaction mixture was stirred at 0 ºC for 30 min, a 1.0 M solution of 1,1-diborylalkane (0.96 g, 2.0 mmol, 1.0 equiv) in THF was added via syringe, and the reaction mixture was allowed to stir at 0 ºC for 10 min. The reaction mixture was cooled to –78 ºC, a 0.50 M solution of *N*-*tert*-butanesulfinyl aldimine (0.44 g, 3.0 mmol, 1.5 equiv) in THF was added, and the reaction mixture was allowed to stir at –78 ºC for another 4 h. Upon completion, the reaction was quenched by addition of an aqueous solution of HCl (1N, 10 mL) at –78 ºC. The cooling bath was removed, and the aqueous mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (4:1 to 3:1, hexanes/EtOAc) to afford the desired *gem*-bis(boronate) **3-20** as a colorless oil (0.52 g, 41%). ^{1}H NMR analysis of the crude reaction mixture indicated >20:1 diastereoselectivity.

^{1}H NMR (500 MHz, CDCl3) δ 4.73 (d, J = 2.8 Hz, 1H), 3.79 (dq, J = 9.3, 4.5 Hz, 1H), 1.67–1.58 (m, 2H), 1.28–1.19 (m, 62H), 0.87 (t, J = 6.8 Hz, 3H).

^{13}C NMR (126 MHz, CDCl3) δ 83.27, 83.11, 55.04, 50.36, 31.97, 30.65, 29.75 (×2), 29.71 (×2), 29.67, 29.61, 29.41, 29.02, 28.27, 25.04, 24.83 (×2), 24.76 (×2), 24.65, 22.94 (×2), 22.74, 17.72, 14.16.
^{11}B NMR (160 MHz, CDCl3) δ 34.2.

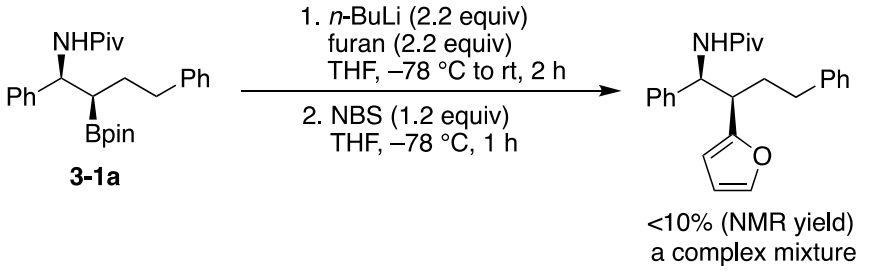
Investigation of the monoprotodeboronation of *gem*-bis(boronate) **3-21**: In an oven-dried 5 mL round-bottomed flask, β-sulfinimido *gem*-bis(boronates) **3-20** (62 mg, 0.10 mmol, 1.0 equiv) was dissolved in MeOH (0.40 mL, 0.26 M), followed by dropwise addition of an HCl solution (4 N in dioxane, 28 μL, 0.11 mmol, 1.1 equiv) at room temperature. After stirring at room temperature for 2 h, the reaction mixture was concentrated under reduced pressure to afford β-amino *gem*-bis(boronate) **3-21**. To a 5 mL round-bottomed flask containing **3-21** were added tetrabutylammonium dibenzylphosphate, water (11 μL, 0.60 mmol, 6.0 equiv), and CH_2Cl_2 (1.0 mL, 0.10 M). The resulting mixture was stirred at room temperature for 16 h. Upon completion, the reaction mixture was filtered through a short pad of Celite, washed with CH_2Cl_2 and concentrated under reduced pressure to afford the crude desulfinylated β-aminoalkylboronate product. The crude desulfinylated β-aminoalkylboronate product was dissolved in CH_2Cl_2 (1.0 mL, 0.10 M) and cooled to 0 °C, followed by dropwise addition of diisopropylethylamine (88 μL, 0.50 mmol, 5.0 equiv). The resulting reaction mixture was stirred at 0 ºC for 5 min, followed by dropwise addition of pivaloyl chloride (24 μL, 1.0 mmol, 2.0 equiv). The reaction mixture was allowed to warm to room temperature and stirred for 3 h. The solvent was removed under reduced pressure to afford the crude product. Yield was determined by ^{1}H NMR analysis using dibromomethane as the internal standard, and the diastereomeric ratio was determined by comparing peak heights of isolated resonances in the ^{1}H NMR spectra of the crude reaction mixture.

3.10.11 Matteson homologation of *anti*-β-Aminoalkylboronate 3-1a



Matteson homologation of *anti*-β-aminoalkylboronate **3-1a** was performed by following the literature procedure.[24] To a 5 mL round-bottomed flask equipped with a magnetic stir bar were added β-aminoalkylboronate **3-1a** (87 mg, 0.20 mmol, 1.0 equiv), chloroiodomethane (58 μL, 0.80 mmol, 4.0 equiv), and THF (2.0 mL). The reaction mixture was cooled to –78 ºC, and a solution of *n*-BuLi (2.4 M in hexane, 0.33 mL, 0.80 mmol, 4.0 equiv) was added slowly at the same temperature. After stirring for 4 h, the reaction was quenched by addition of a saturated aqueous solution of NH_4Cl (1.0 mL) and extracted with CH_2Cl_2 (10 mL×3). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure.^{1}H NMR analysis of the crude reaction mixture using dibromomethane as the internal standard indicated no formation of the desired homologated product and recovery of most of starting material **3-1a**.

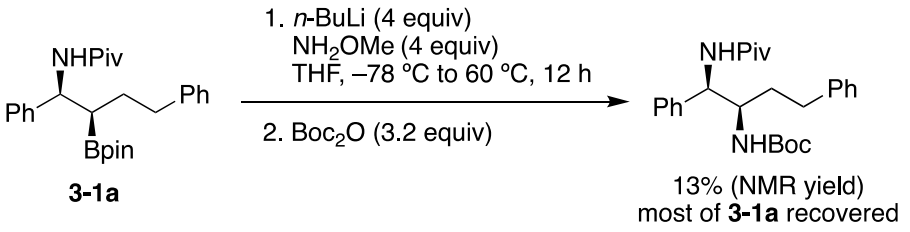
3.10.12 Furanylation of *anti*-β-Aminoalkylboronate 3-1a



The furanylation of *anti*-β-aminoalkylboronate **3-1a** was performed by following the literature procedure.[24] To a 5 mL round-bottomed flask equipped with a magnetic stir bar were added furan (33 μL, 0.44 mmol, 2.2 equiv) and THF (0.8 mL). The reaction was cooled to –78 ºC, followed by dropwise addition of *n*-BuLi (2.4 M in hexane, 0.18 mL, 0.44 mmol, 2.2 equiv). The cooling bath was removed, and the reaction was stirred at room temperature for 1 h. The

mixture was cooled back down to –78 ºC, and a solution of β-aminoalkylboronate **3-1a** (87 mg, 0.20 mmol, 1.0 equiv) in THF (0.5 mL) was added dropwise. The reaction mixture was stirred for 1 h, and a solution of *N*-bromosuccinimide (43 mg, 0.24 mmol, 1.2 equiv) in THF (0.8 mL) was added. After allowing the reaction to stir for 1 h, a saturated aqueous solution of $Na_2S_2O_3$ (1.0 mL) was added to the reaction and stirred at room temperature for 30 min. The reaction mixture was poured into a separate funnel and extracted with Et_2O (10 mL×3). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure. ^{1}H NMR analysis of the crude reaction mixture using dibromomethane as the internal standard indicated a complex mixture containing <10% of the desired product.

3.10.13 Amination of *anti*-β-Aminoalkylboronate 3-1a

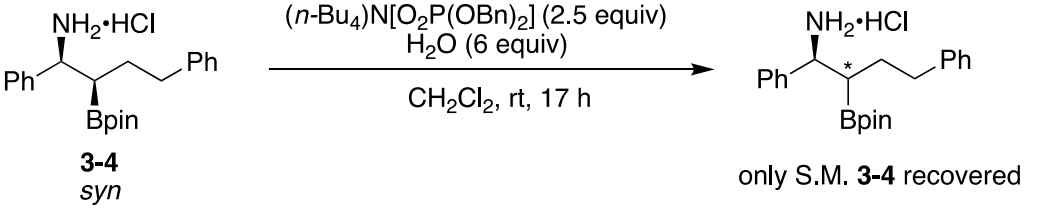


The amination of *anti*-β-aminoalkylboronate **3-1a** was performed by following the literature procedure.[26] To a flame-dried round-bottomed flask equipped with a magnetic stir bar were added *O*-methylhydroxylamine solution (3.0 M in THF, 0.27 mL, 0.80 mmol, 4 equiv) and THF (2 mL). The reaction flask was cooled to –78 °C, a solution of *n*-BuLi (2.1 M in hexanes, 0.58 mL, 0.80 mmol, 4 equiv) was added dropwise, and the reaction was allowed to stir for 30 min at –78 °C. A solution of β-aminoalkylboronate **3-1a** (87 mg, 0.20 mmol, 1.0 equiv) in THF (0.5 mL) was added dropwise to the solution of deprotonated *O*-methylhydroxylamine dropwise via syringe. The reaction flask was warmed to room temperature and then heated to 60 °C. After stirring at 60 °C for 12 h, the reaction flask was cooled to room temperature, and Boc anhydride (0.14 g, 0.64 mmol, 3.2 equiv) was added. After stirring at room temperature for 1 h, the reaction was quenched with water (4 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3×10 mL). The combined organics were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford the

crude reaction mixture. ^{1}H NMR analysis of the crude reaction mixture using dibromomethane as the internal standard indicated formation of 13% of the desired amination product and recovery of most of the starting material **3-1a**.

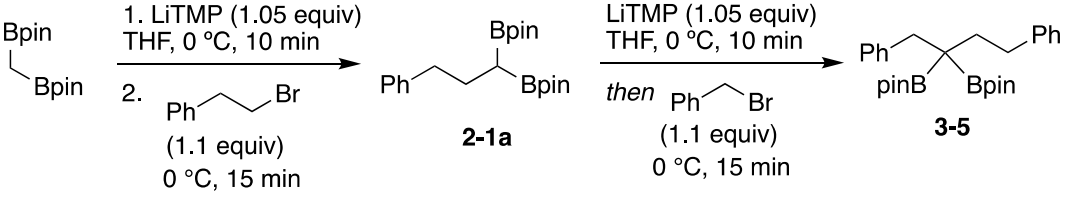
3.10.14 Mechanistic Studies

3.10.14.1 Attempted Protodeboronation of β-Aminoalkylboronate 3-4



β-Aminoalkylboronate **3-4** was synthesized by following the procedures described in Chapter 2. Protodeboronation of 1,1-diborylalkane **3-4** was performed by following the general procedure for protodebornoation of β-amino *gem*-bis(boronates) **3-1** with **3-4** (39 mg, 0.10 mmol, 1.0 equiv), tetrabutylammonium dibenzylphosphate (0.13 g, 0.25 mmol, 2.5 equiv), and water (11 μL, 0.60 mmol, 6.0 equiv). After stirring at room temperature for 17 h, the reaction mixture was filtered through a short pad of Celite, washed with CH_2Cl_2, and concentrated under reduced pressure. ^{1}H NMR analysis of the crude mixture indicated only recovery of starting material **3-4** and no formation of the anti isomer.

3.10.14.2 Attempted Protodeboronation of 1,1-Diborylalkane 3-5



β-Aminoalkylboronate **3-5** was synthesized by following the literature procedures with slight modifications.[12] A flame-dried 100 mL round-bottomede flask was charged with a solution of TMP (0.960 mL, 5.50 mmol, 1.10 equiv) in THF (5.5 mL) under N_2. The rapidly stirred solution was cooled to 0 °C, followed by dropwise addition of *n*-BuLi (2.02 M in hexanes,

2.60 mL, 5.25 mmol, 1.05 equiv). After stirring at 0 ºC for 30 min, THF (14 mL) was added, followed by addition of a 1.0 M solution of 1,1-diborylmethane (1.30 g, 5.00 mmol, 1.00 equiv) in THF. The reaction mixture was allowed to stir at 0 ºC for 10 min. (2-Bromoethyl)benzene (0.760 mL, 5.50 mmol, 1.10 equiv) was added dropwise, and the reaction was allowed to stir at 0 ºC for 15 min. Upon completion, the reaction mixture was warmed to room temperature, filtered through a silica gel plug, rinsed with diethyl ether, and concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (9:1, hexanes/diethyl ether) to afford the corresponding 1,1-diborylalkane **2-1a** as a white solid (1.4 g, 75%).

A flame-dried 25 mL round-bottomed flask was charged with a solution of TMP (0.190 mL, 1.10 mmol, 1.10 equiv) in THF (1.1 mL). The rapidly stirred solution was cooled to 0 ºC, followed by dropwise addition of *n*-BuLi (2.02 M in hexanes, 0.520 mL, 1.05 mmol, 1.05 equiv). The reaction mixture was stirred at 0 ºC for 30 minutes. Next, THF (3 mL) was added, followed by addition of a 1.0 M solution of the above obtained 1,1-diborylalkane **2-1a** (0.370 g, 1.00 mmo, 1.00 equiv) in THF. The reaction mixture was allowed to stir at 0 ºC for 10 minutes. Benzyl bromide (0.130 mL, 1.10 mmol, 1.10 equiv) was added dropwise, and the reaction was allowed to stir at 0 ºC for 15 min. Upon completion, the reaction mixture was warmed to room temperature, filtered through a silica gel plug, rinsed with diethyl ether, and concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (20:1 to 15:1, hexanes/diethyl ether) to afford 1,1-diborylalkane **3-5** as a white solid (0.41 g, 90%).

^{1}H NMR (498 MHz, $CDCl_3$) δ 7.33 (d, *J* = 7.2 Hz, 2H), 7.25–7.18 (m, 4H), 7.17–7.09 (m, 4H), 3.09 (s, 2H), 2.70–2.60 (m, 2H), 1.87–1.76 (m, 2H), 1.27 (s, 12H), 1.24 (s, 12H).

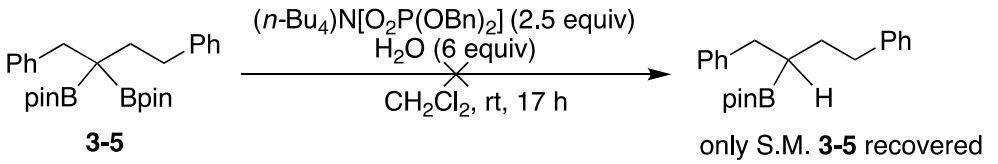
^{13}C NMR (125 MHz, $CDCl_3$) δ 143.5, 141.7, 129.8, 128.5, 128.1, 127.8, 125.6, 125.4, 83.3, 34.9, 33.9, 31.7, 25.1, 24.7.

^{11}B NMR (160 MHz, $CDCl_3$) δ 33.8.

IR (cast film, cm^{-1}): 3024, 2978, 2929, 1142.

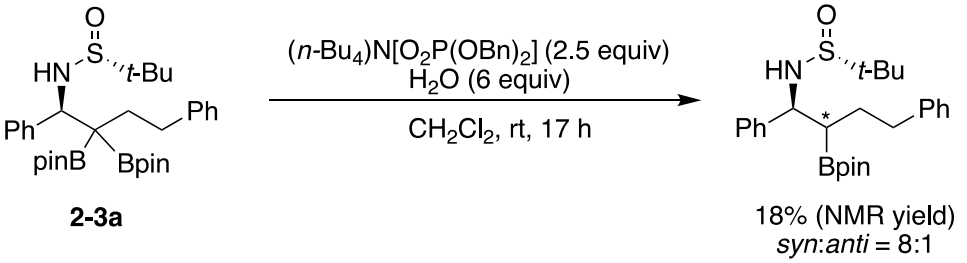
HRMS (ESI-TOF) for $C_{28}H_{40}B_2NaO_4$ $(M + Na)^+$: *calcd.*: 485.3005; *found*: 485.3008.

mp: 143.2–144.1 ºC.



Protodeboronation of 1,1-diborylalkane **3-5** was performed by following the general procedure for protodebornoation of β-amino *gem*-bis(boronates) **3-1** with **3-5** (48 mg, 0.10 mmol, 1.0 equiv), tetrabutylammonium dibenzylphosphate (0.13 g, 0.25 mmol, 2.5 equiv), and water (11 μL, 0.60 mmol, 6.0 equiv). The reaction mixture was stirred at room temperature for 18 h. The reaction mixture was filtered through a short pad of Celite, washed with CH_2Cl_2, and concentrated under reduced pressure. ^{1}H NMR analysis of the crude mixture indicated only recovery of starting material **3-5** and no formation of the prodeboronation product.

3.10.14.3 Attempted Protodeboronation of *gem*-Bis(boronate) 2-3a



Protodeboronation of 1,1-diborylalkane **2-3a** was performed by following the general procedure for protodebornoation of β-amino *gem*-bis(boronates) **3-1** with **2-3a** (58 mg, 0.10 mmol, 1.0 equiv), tetrabutylammonium dibenzylphosphate (0.13 g, 0.25 mmol, 2.5 equiv), and water (11 μL, 0.60 mmol, 6.0 equiv). The reaction mixture was stirred at room temperature for 17 h. The reaction mixture was filtered through a short pad of Celite, washed with CH_2Cl_2, and concentrated under reduced pressure. ^{1}H NMR analysis of the crude mixture indicated the formation of a mixture of *syn*- and *anti*-β-aminoalkylboronate products (*syn*:*anti* = 8:1) in a total 18% yield using dibromomethane as the internal standard.

3.10.15 Molecular Modeling

Molecular modeling was performed using Spartan 18. A simple representative compound was chosen to avoid long computation times. Thus, the pinacolate esters were replaced with

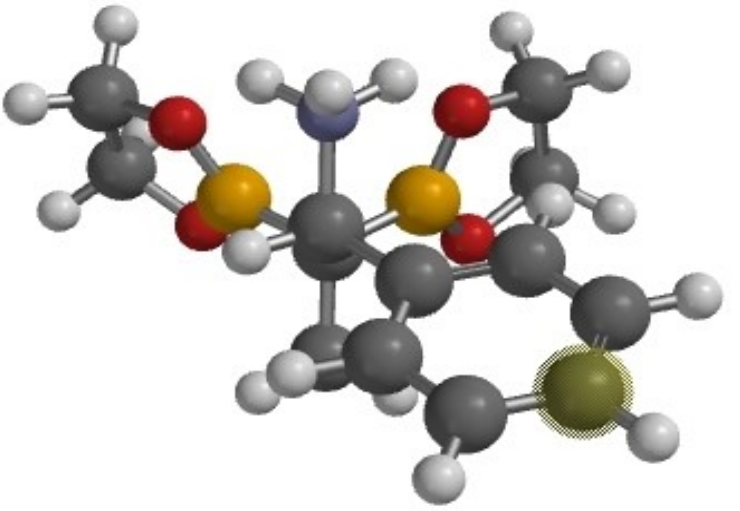
ethylene glycol esters. The equilibrium conformation of all three rotamers, as ammonium cations, was minimized first using PM3 (gas phase). The resulting structures were utilized as input structures for DFT (B3LYP 6-31G*) minimization [equilibrium geometry, nonpolar solvent state (THF), +1 charge]. Finally, the energy of all three rotamers were computed more accurately by DFT [ωB97X-V 6-311+G(2df,2p), nonpolar solvent state, +1 charge]. Energy values found are:

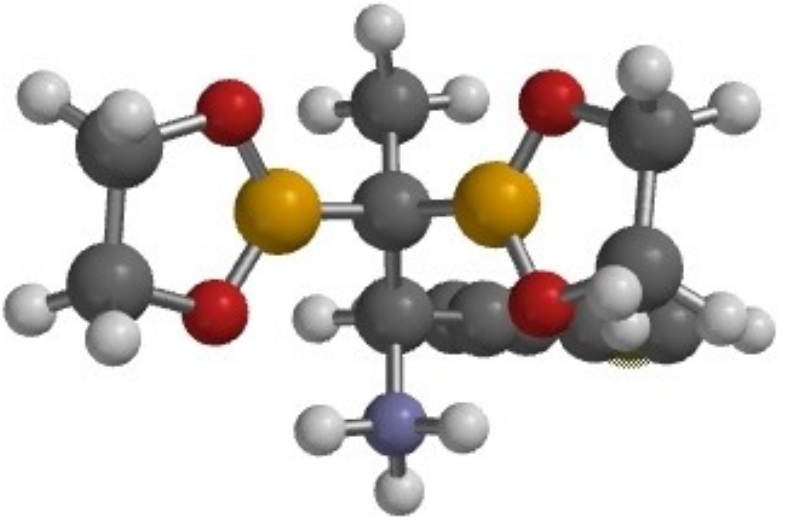
I: –912.888708 hartrees (lowest energy, 0.0 kcal/mol)

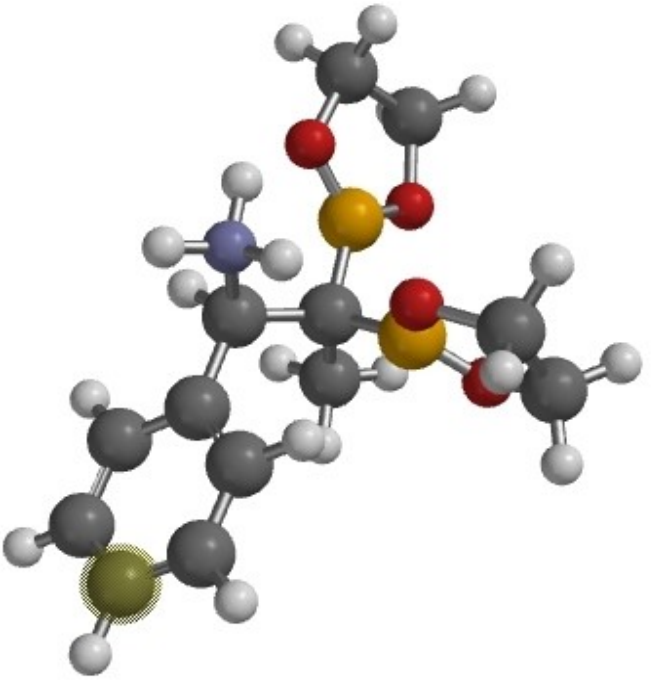
II: –912.886013 hartrees (1.7 kcal/mol)

III: –912.884097 hartrees (2.9 kcal/mol)

Selected representations of rotamer **I**:







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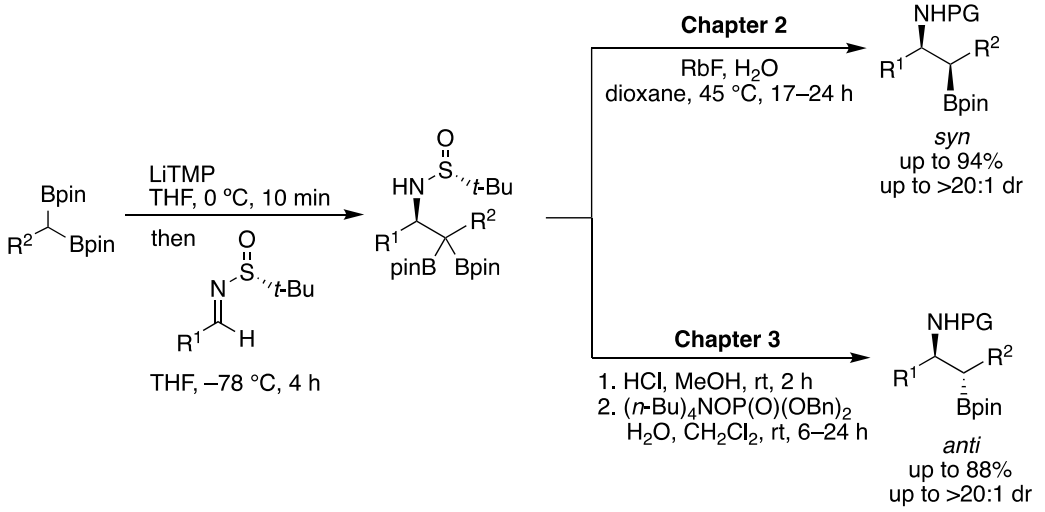
Chapter 4

Cu-Catalyzed Asymmetric 1,2-Addition of 1,1-Diboryl-alkanes to *N*-Phosphinyl Imines for the Synthesis of β-Aminoalkylboronates

4.1 Introduction

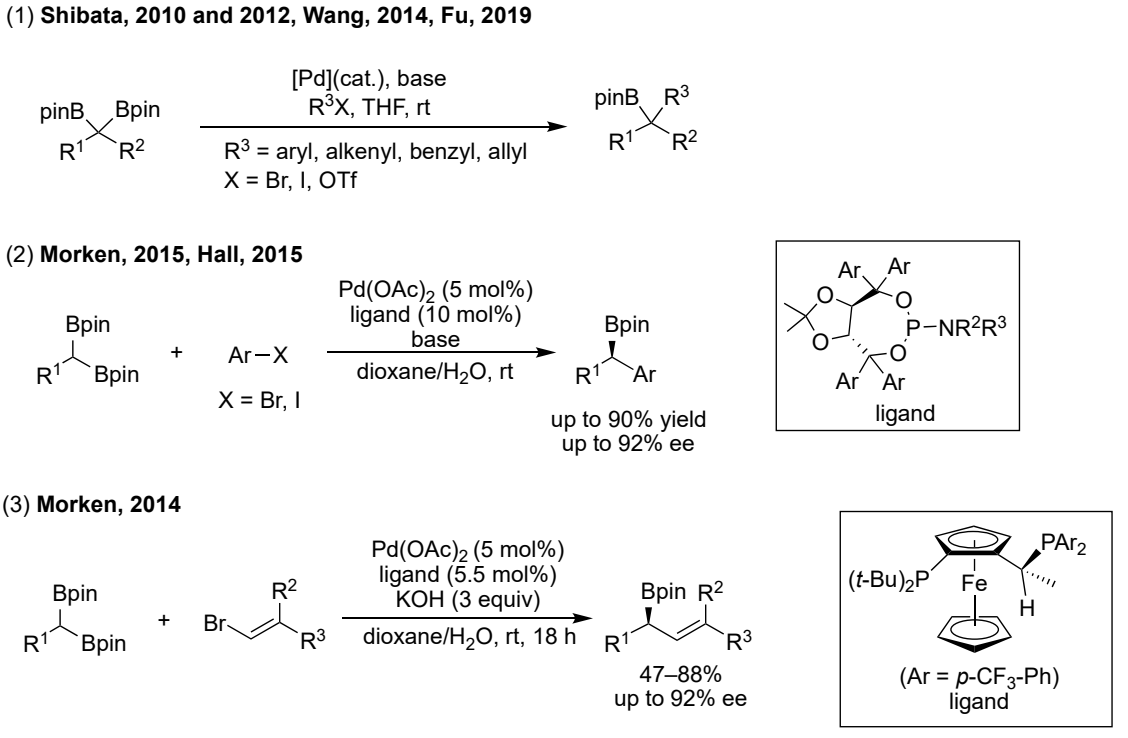
As presented in Chapter 1, β-aminoalkylboronic esters generate growing interest as versatile synthetic building blocks in asymmetric synthesis, bioisosteres of β-amino acids in drug discovery, and catalysts in organic reactions. However, interest in developing synthetic approaches to these valuable compounds has not received much attention until recently. Given the lack of stereoselective methods for the synthesis of β-aminoalkylboronic esters, a 1,2-addition/monoprotodeboronation sequence using 1,1-diboron compounds recently has been developed to access both the syn and anti isomers of α,β-disubstituted β-aminoalkylboronates as a part of my doctoral studies (see Chapter 2 and 3). Despite achieving good yields and high diastereoselectivity with a wide range of substituents, this sequence requires 2–3 steps, and the 1,2-addition step requires the use of a strong base, LiTMP (Scheme 4-1). Therefore, it



Scheme 4-1. The 1,2-addition/monoprotodeboronation sequence for the stereodivergent synthesis of α,β-disubstituted β-aminoalkylboronates.

would be advantageous to develop direct and complementary strategies to chiral β-aminoalkylboronates. Transition metal catalysis serves as a powerful tool for this purpose since it is well-known that transition metal-catalyzed reactions can construct complex molecules directly from simple starting materials.[1,2] Moreover, transition metal-catalyzed reactions often offer great generality and high levels of chemo-, regio-, and enantioselectivity.

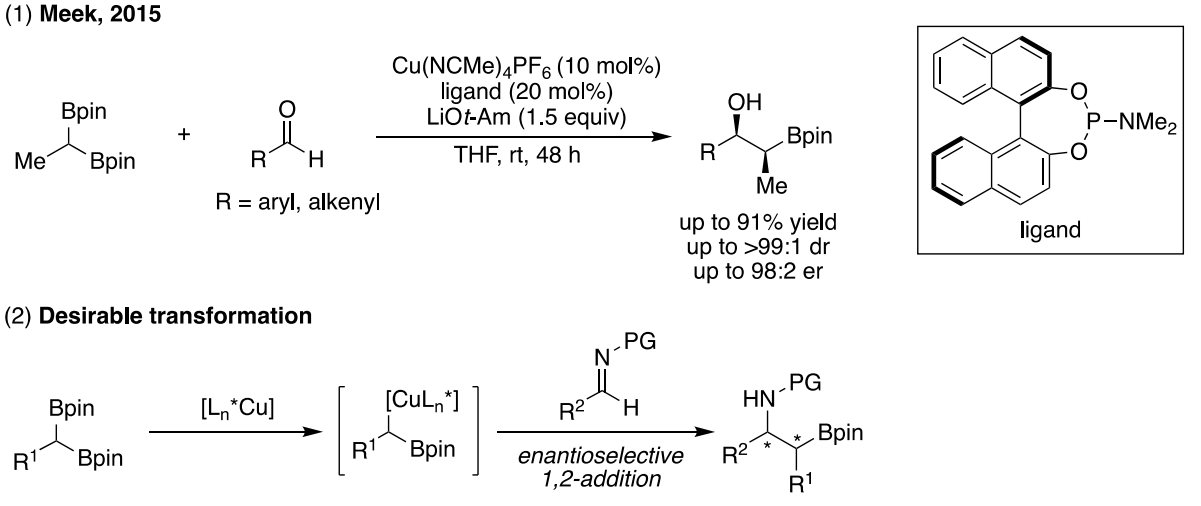
As shown in Section 2.1.2 of Chapter 2, 1,1-diboron compounds recently have been used as versatile reagents for the synthesis of alkylboron compounds in two ways: 1) deprotonation with a strong base to form the 1,1-diboryl carbanion that can react with various electrophiles and 2) mono-deborylation with a strong base or transition metal to form the nucleophilic α-boryl carbanion or alkylmetal species, which can be trapped by a variety of electrophiles. Using a strong base for the deprotonation or deborylation of 1,1-diborylalkanes often results in poor functional group compatibility. In contrast, transition metal-promoted deborylation of 1,1-diboron compounds has demonstrated its high efficiency for providing alkylboron compounds under mild conditions. For example, as shown in Scheme 4-2, 1,1-diboronates can undergo Pd-catalyzed Suzuki–Miyaura cross-coupling (SMC) with aryl,



Scheme 4-2. Pd-catalyzed Suzuki–Miyaura cross-coupling of 1,1-diboron compounds.

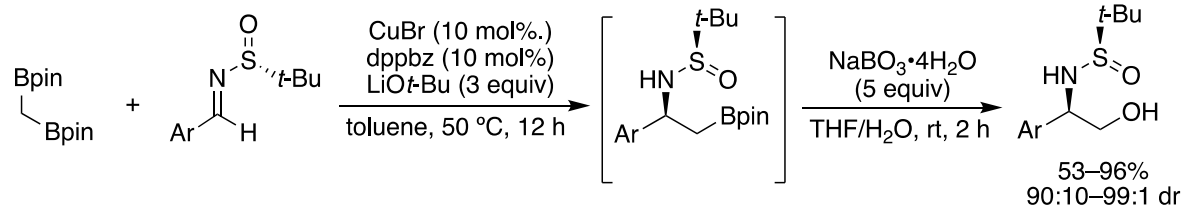
alkenyl, benzylic, and allylic halides or triflates (eq. 1).[3–6] These SMC reactions proceed at room temperature to produce a wide range of alkylboronic esters. Furthermore, when employing suitable chiral ligands, SMC of prochiral 1,1-diborylalkanes with aryl (eq. 2)[7,8] and alkenyl (eq. 3)[9] bromides can be achieved by way of enantioselective desymmetrization to deliver enantiomerically pure alkylboronates, as demonstrated by the groups of Morken and Hall. In addition to SMC, in 2015, Meek and co-workers reported a Cu-catalyzed 1,2-addition of 1,1-diborylethane to aldehydes (Scheme 4-3, eq. 1).[10] With the use of a chiral phosphoramidite ligand, the 1,2-addition affords various 1,2-hydroxyalkylboronic esters in good yields with high enantio- and diastereoselectivity.

Inspired by Meek's work, it was reasoned that Cu-catalyzed 1,2-addition of 1,1-diborylalkanes to imines would provide a straightforward and mild approach to optically pure β-aminoalkylboronates (Scheme 4-3, eq. 2). In 2016, at the time when I started this project, Cho and co-workers realized the Cu-catalyzed 1,2-addition with chiral *N*-*tert*-butanesulfinyl aldimines for the generation of enantioenriched β-aminoalkylboronates (Scheme 4-4).[11] Nonetheless, this reaction requires the use of a stoichiometric amount of a sulfinyl chiral auxiliary. Moreover, the aldimine and 1,1-diborylalkane substrates are restricted to aryl substituents and 1,1-diborylmethane, respectively. To address these drawbacks, it was envisioned that the use of prochiral imines with a chiral Cu catalyst would constitute the most attractive strategy in this project.



Scheme 4-3. 1,2-Addition of 1,1-diborylethane to aldehydes and proposed synthesis of optically pure β-aminoalkylboronates through Cu-catalyzed asymmetric 1,2-addition of 1,1-diborylalkanes to imines.

Cho, 2016:



Scheme 4-4. Cu-catalyzed 1,2-addition of 1,1-diborylmethane to *N*-*tert*-butanesulfinyl aldimines.

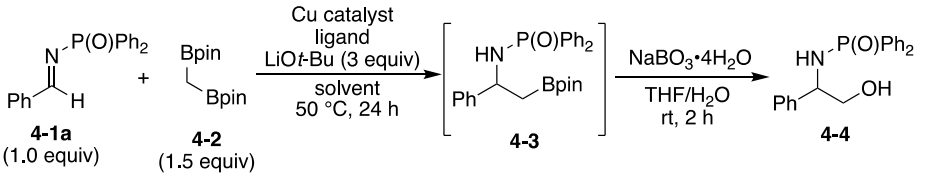
4.2 Development of Reaction Conditions for the Racemic Cu-Catalyzed 1,2-Addition of 1,1-Diborylmethane to *N*-Phosphinyl Aldimines

Efforts began by developing suitable conditions for the racemic Cu-catalyzed 1,2-addition. The diphenylphosphinyl aldimine **4-1a** and commercially available 1,1-diborylmethane **4-2** were chosen as the model substrates (Table 4-1). The diphenylphosphinyl aldimines can be constructed easily by the condensation of aldehydes and diphenylphosphinamides and obtained as a single (presumably *E*) isomer. Importantly, the diphenylphosphinyl moiety can be removed readily to the desired amines under acidic conditions without racemization or epimerization of the newly formed product. In this study, the first-formed β-aminoalkylboronates **4-3** was not isolated, instead, it was oxidized directly with $NaBO_3$ to the corresponding β-amino alcohol **4-4** for ease of isolation and determination of enantiomeric ratio using chiral HPLC. The reaction's yield was determined by ^{1}H NMR analysis of the crude reaction mixture using dibromomethane as the internal standard.

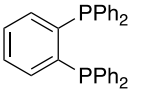
Gratifyingly, by employing the optimal conditions developed by the group of Cho[11] (Scheme 4-4), the 1,2-addition of 1,1-diborylmethane **4-2** to aldimine **4-1a**, followed by an oxidation, afforded product **4-4** in 80% yield (Table 4-1, entry 1). As shown in Table 4-1, a brief examination of the reaction parameters (entries 2–4), including the amount of CuBr and 1,2-bis(diphenylphosphino)benzene (dppbz), the reaction solvent, and the ligand, demonstrated that 10 mol% of CuBr and 1,2-bis(diphenylphosphino)benzene (dppbz) in toluene at 50 ºC represented the optimal conditions. Of note, without the presence of CuBr and dppbz, the 1,2-addition still gave product **4-4** in 29% yield. The impact of this uncatalyzed

background reaction on the enantioselectivity of the asymmetric 1,2-addition needs to be taken into consideration; this was investigated and will be discussed in a later section.

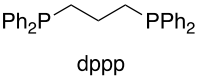
Table 4-1. Optimization of Reaction Conditions for the Racemic 1,2-Addition[a]



Entry	Catalyst (mol%)	Ligand (mol%)	Solvent	Yield of **4-4** [%][b]
1	CuBr (10)	dppbz (10)	toluene	80 (78)[c]
2	CuBr (5)	dppbz (5)	toluene	59
3	CuBr (10)	dppbz (10)	THF	56
4	CuBr (10)	dppp (10)	toluene	30
5	–	–	toluene	29



dppbz



dppp

[a]Reactions were performed on a 0.2 mmol scale under Ar atm. [b]NMR yield. [c]Isolated yield.

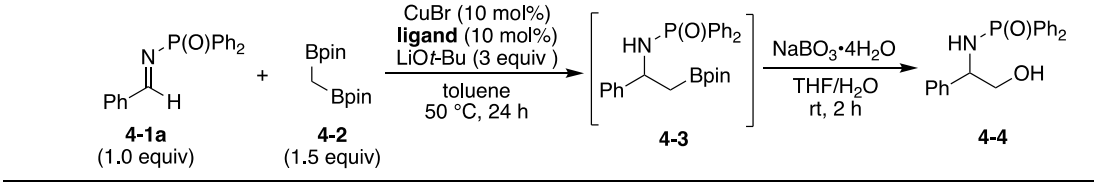
4.3 Development of the Cu-Catalyzed Asymmetric 1,2-Addition

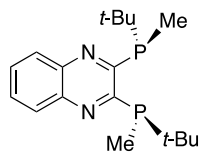
4.3.1 Evaluation of Chiral Ligands

With the optimal racemic conditions in hand (Table 4-1, entry 1), my first effort was to examine various chiral bidentate ligands for the development of an asymmetric system (Table 4-2). Three chiral bidentate ligands, QuinoxP* (**L1**) and Duphos (**L2** and **L3**) that have a similar backbone to dppbz ligand used in the racemic 1,2-addition, were tested first. While **L2** gave a low yield (20%) with low enantioselectivity (20% ee), **L1** and **L3** were found to afford product **4-4** in moderate to good yields with moderate enantioselectivity (up to 44% ee). Other bidentate ligands, including Duanphos (**L4**), TolBINAP (**L5**), Tunephos (**L6**), and BDPP (**L7**), all resulted in poor selectivity. Evaluation of ferrocenyl-based ligands like Mandyphos (**L8**),

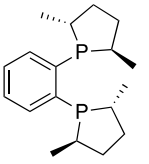
Walphos (**L9**), and Taniaphos (**L10**) was in vain, producing **4-4** with low enantioselectivity. In contrast, a Josiphos-type ligand (**L11**) was promising, affording **4-4** in 72% yield with 58% ee. In addition to bidentate phosphine ligands, a pyridine-oxazoline ligand (**L12**) was attempted, however, it gave no enantioselectivity.

Table 4-2. Evaluation of Chiral Bidentate Ligands[a]

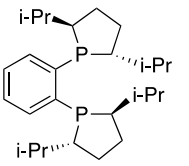




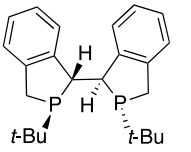
L1
yield: 69%
ee: 44%



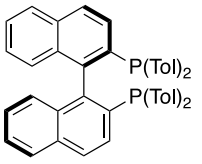
L2
yield: 20%
ee: 20%



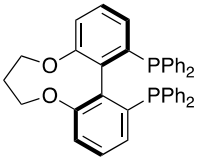
L3
yield: 42%
ee: –42%



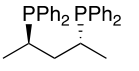
L4
yield: 46%
ee: –23%



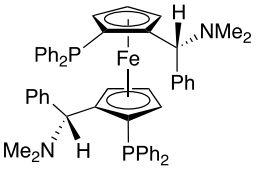
L5
yield: 33%
ee: 19%



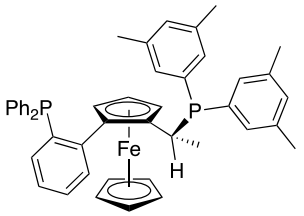
L6
yield: 31%
ee: 17%



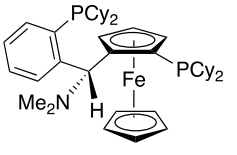
L7
yield: 41%
ee: 2%



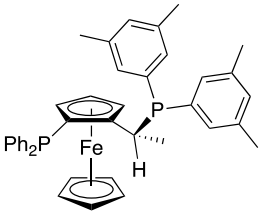
L8
yield: 54%
ee: 13%



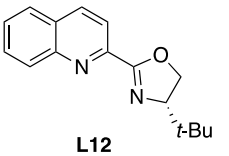
L9
yield: 35%
ee: 1%



L10
yield: 21%
ee: 3%



L11
yield: 72%
ee: 58%



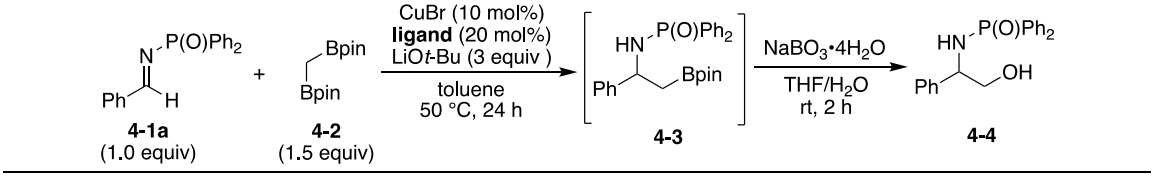
L12
yield: 35%
ee: 0%

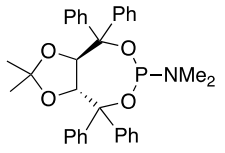
[a]Reactions were performed on a 0.2 mmol scale under Ar atm. Yields of isolated product **4-4** are given. The enantiomeric excess (ee) was determined by chiral HPLC.

Next, efforts were devoted towards the evaluation of chiral monodentate ligands, as shown in Table 4-3. TADDOL-derived ligand **L13** led to 45% yield with only 19% ee.

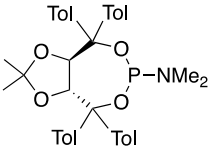
BINOL-derived phosphoramidite **L15**, which had been demonstrated by Meek and co-workers to be effective in the asymmetric 1,2-addition with aldehydes (see Scheme 4-3, eq. 1), was found to give low enantioselectivity (11% ee). Attempts at improving the enantioselectivity by examining other TADDOL-derived (**L14**) and BINOL-derived (**L16**–**19**) phosphoramidite ligands were unfruitful. At this stage, it became necessary to look into less conventional classes of ligands. In this regard, *N*-heterocyclic carbene (NHC) ligated Cu complexes have been proven to be efficient catalysts for a range of reactions, including boron-related reactions.[12] Unfortunately, the use of NHC ligand **L20** furnished product **4-4** in a low yield with no enantioselectivity. Therefore, the initial examination of bidentate and monodentate ligands determined that Josiphos ligand **L11** was the best ligand for further optimization.

Table 4-3. Evaluation of Chiral Monodentate Ligands[a]

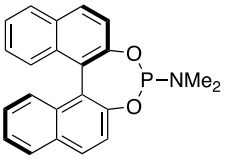




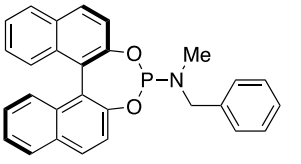
L13
yield: 45%
ee: –19%



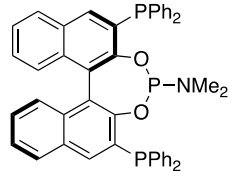
L14
yield: 33%
ee: 0%



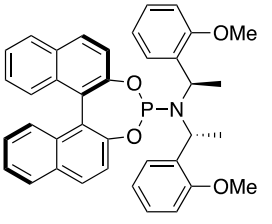
L15
yield: 57%
ee: –11%



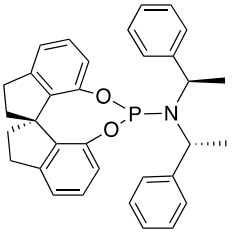
L16
yield: 58%
ee: –16%



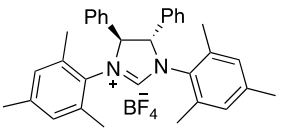
L17
yield: 37%
ee: 0%



L18
yield: 33%
ee: –4%



L19
yield: 43%
ee: 0%

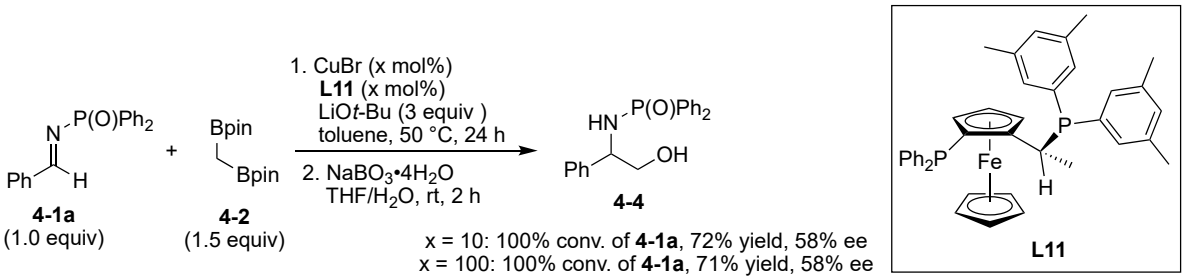


L20
yield: 24%
ee: 0%

[a]Reactions were performed on a 0.2 mmol scale under Ar atm. Yields of isolated product **4-4** are given. The enantiomeric excess (ee) was determined by chiral HPLC.

4.3.2 Study of the Background Reaction in the Asymmetric 1,2-Addition

Since a substantial background reaction was observed in the racemic 1,2-addition (see entry 5, Table 4-1), it is essential to assess whether an uncatalyzed background reaction also occurs in the asymmetric 1,2-addition and has an influence on the enantioselectivity. To address this question, a stoichiometric amount of the catalyst (CuBr) and the best ligand (**L11**) were employed to perform the 1,2-addition reaction (Scheme 4-5). Surprisingly, the reaction delivered product **4-4** in 71% yield with 58% ee and 100% conversion of aldimine **4-1a**, which is closely similar to that of the corresponding catalytic reaction (Scheme 5). This result suggests that the background reaction is probably slower under the enantioselective Cu-catalyzed conditions and does not affect the enantiomeric ratio.



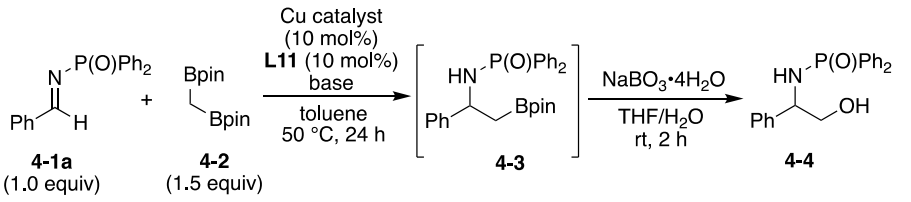
Scheme 4-5. Study of the background reaction in the enantioselective 1,2-addition by using a stoichiometric amount of CuBr and ligand **L11**.

4.3.3 Optimization of Other Reaction Parameters

With the best ligand **L11** in hand (Table 4-2), attempts at improving the enantioselectivity were made by examining other reaction parameters, such as the Cu catalyst, base, solvent, and reaction temperature. As shown in Table 4-4, other Cu catalysts, including Cu(I) (entries 2–6) and Cu(II) (entry 7) salts, were found to be less effective than CuBr. The use of other alkali *tert*-butoxides, such as KO*t*-Bu (entry 8) and NaO*t*-Bu (entry 9), only gave little selectivity albeit, with a higher yield compared to LiO*t*-Bu. It was reasoned that the low enantioselectivity can be ascribed to the severe background reaction, due to the favorable formation of α-boryl carbanion in the presence of KO*t*-Bu or NaO*t*-Bu.[13] The importance of LiO*t*-Bu was determined by the lack of conversion in the absence of LiO*t*-Bu (entry 12) or low conversion with the use of other lithium alkoxides (entries 10 and 11). The stoichiometry of LiO*t*-Bu was studied by increasing (entry 13) or lowering (entry 14) its amount. Despite obtaining similar

enantioselectivity to 3 equivalents of LiO*t*-Bu, the yields were decreased. In addition, it was found that the use of 1.1 equivalents of 1,1-diborylmethane **4-2** (entry 15) was as effective as 1.5 equivalents of **4-2**, therefore, it was selected for the following optimization studies.

Table 4-4. Evaluation of the Cu Catalyst and Base[a]



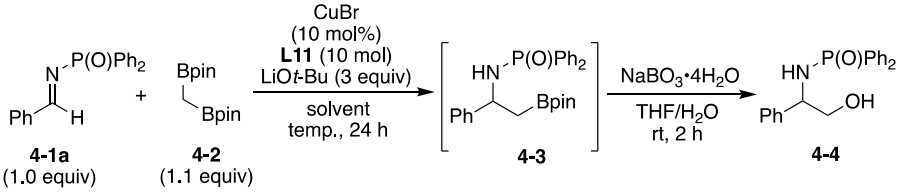
Entry	Cu Catalyst	Base (equiv)	Yield of **4-4** [%][b]	ee [%][c]
1	CuBr	LiO*t*-Bu (3.0)	72	58
2	CuI	LiO*t*-Bu (3.0)	61	54
3	CuCl	LiO*t*-Bu (3.0)	50	46
4	CuOAc	LiO*t*-Bu (3.0)	35	11
5	CuCN	LiO*t*-Bu (3.0)	45	34
6	$Cu(MeCN)_4PF_6$	LiO*t*-Bu (3.0)	10	2
7	$Cu(OTf)_2$	LiO*t*-Bu (3.0)	28	16
8	CuBr	KO*t*-Bu (3.0)	75	2
9	CuBr	NaO*t*-Bu (3.0)	79	5
10	CuBr	LiOMe (3.0)	4	N.D.
11	CuBr	LiO*i*-Pr (3.0)	7	36
12	CuBr	–	N.R.	–
13	CuBr	LiO*t*-Bu (4.0)	59	58
14	CuBr	LiO*t*-Bu (1.6)	43	52
15[d]	CuBr	LiO*t*-Bu (3.0)	72	58

[a]Reactions were performed on a 0.2 mmol scale under Ar atm. [b]Yields of isolated product **4-4** are given. [c]The enantiomeric excess (ee) was determined by chiral HPLC. [d]With 1.1 equiv of **4-2.**

Evaluation of the solvent, reaction temperature, and concentration also were conducted (Table 4-5). Other solvents (entries 2–5) were examined and found to be not as effective as toluene. When decreasing the reaction temperature from 50 ºC to 40 ºC, slightly higher enantioselectivity (62% ee) was obtained, but the yield was decreased to 58% (entry 6).

Increasing the temperature to 60 ºC also led to a drop in yield (entry 7). The use of a higher (entry 8) or lower (entry 9) reaction concentration had little impact on the yield and selectivity.

Table 4-5. Evaluation of the Solvent, Reaction Temperature, and Concentration[a]



Entry	Solvent	Temp. (°C)	Conc. (M)	Yield of **4-4** [%][b]	ee [%][c]
1	Toluene	50	0.20	72	58
2	CH_2Cl_2	50	0.20	15	18
3	Et_2O	50	0.20	59	62
4	THF	50	0.20	22	56
5	DME	50	0.20	21	63
6	Toluene	40	0.20	58	62
7	Toluene	60	0.20	65	57
8	Toluene	50	0.40	71	58
9	Toluene	50	0.10	67	59

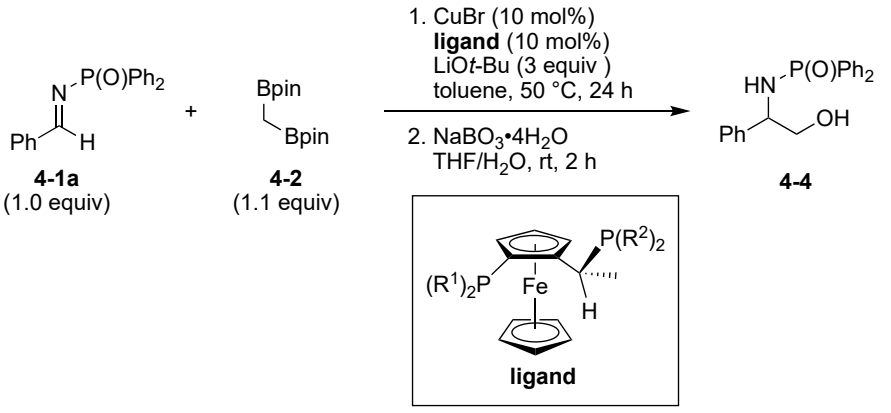
[a]Reactions were performed on a 0.2 mmol scale under Ar atm. [b]Yields of isolated product **4-4** are given.
[c]The enantiomeric excess (ee) was determined by chiral HPLC.

4.3.4 Further Evaluation of Chiral Ligands–Josiphos Derivatives

Encouraged by the good yield (72%) and promising enantioselectivity (58% ee) provided by Josiphos ligand **L11**, it was envisioned that the steric and electronic tuning of Josiphos-type ligands by varying the substituents (R^1 and R^2; Table 4-6) could enhance the enantioselectivity. Starting from ligand **L11**, the study was initiated using commercially available Josiphos derivatives (Table 4-6). It was found that alkyl-substituted (ie., R^2 = *t*-Bu or cyclohexyl) Josiphos-type ligands (**L21** and **L22**) gave inferior yields and enantioselectivity (entries 2 and 3). Then, attention was turned to varying the R^1 substituent. Josiphos derivatives containing a 2-furyl (**L23**) substituent resulted in both a drop in yield and enantioselectivity (entry 4). Increasing the size of the $P(R^1)_2$ group by using a naphthyl substituent (**L24**) led to no change

of enantioselectivity with a diminished yield (entry 5). Replacing the phenyl group (R^1) of **L11** with a more electron withdrawing 3,5-trifluoromethylphenyl group (**L25**) furnished **4-4** in a 74% yield with a lower enantioselectivity (42% ee; entry 6). It was satisfying that a more electronically rich Josiphos ligand containing the 3,5-methoxy-4-methylphenyl group (**L26**) gave an improved enantioselectivity (68% ee) with a good yield (71%). In addition, two other

Table 4-6. Evaluation of Josiphos Derivatives[a]



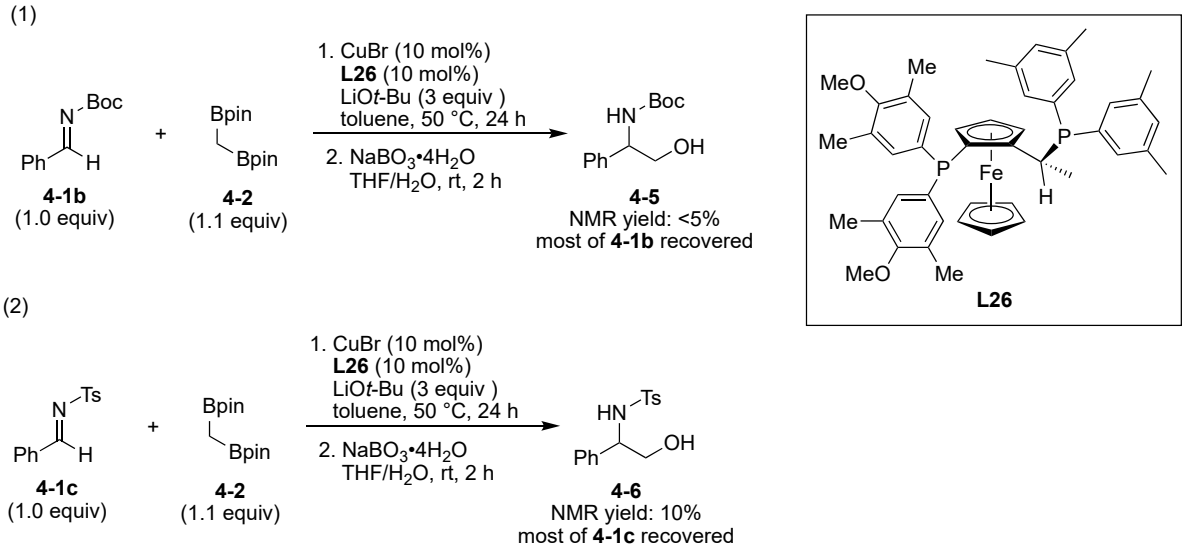
Entry	Ligand	R^1	R^2	Yield of **4-4** [%][b]	ee [%][c]
1	**L11**	Ph	3,5-methyl-Ph	72	58
2	**L21**	Ph	*t*-Bu	40	2
3	**L22**	Ph	Cy	53	44
4	**L23**	2-furyl	3,5-methyl-Ph	60	25
5	**L24**	1-naphthyl	3,5-methyl-Ph	53	58
6	**L25**	3,5-CF_3-Ph	3,5-methyl-Ph	74	42
7	**L26**	3,5-methoxy-4-methyl-Ph	3,5-methyl-Ph	71	68
8	**L27**	Cy	Cy	37	0
9	**L28**	Cy	Ph	40	9

[a]Reactions were performed on a 0.2 mmol scale under Ar atm. [b]Yields of isolated product **4-4** are given. [c]The enantiomeric excess (ee) was determined by chiral HPLC.

Josiphos-type ligands (**L27** and **L28**) were tested, affording none or little selectivity (entries 8 and 9). The examination of commercially available Josiphos derivatives demonstrated a notable influence of the R^1 and R^2 substituents on the enantioselectivity. According to the obtained results, electron rich aryl substituents on both phosphines $P(R^1)_2$ and $P(R^1)_2$ could lead to relatively good yields and enantioselectivity (see entries 1 and 7). In contrast, alkyl substituents are detrimental to the enantioselectivity (see entries 2, 3, 8 and 9). Among all of the Josiphos-type ligands examined, **L26** was deemed to be the optimal ligand (entry 7).

4.3.5 Evaluation of the Effect of the *N*-Protecting Group of the Aldimine

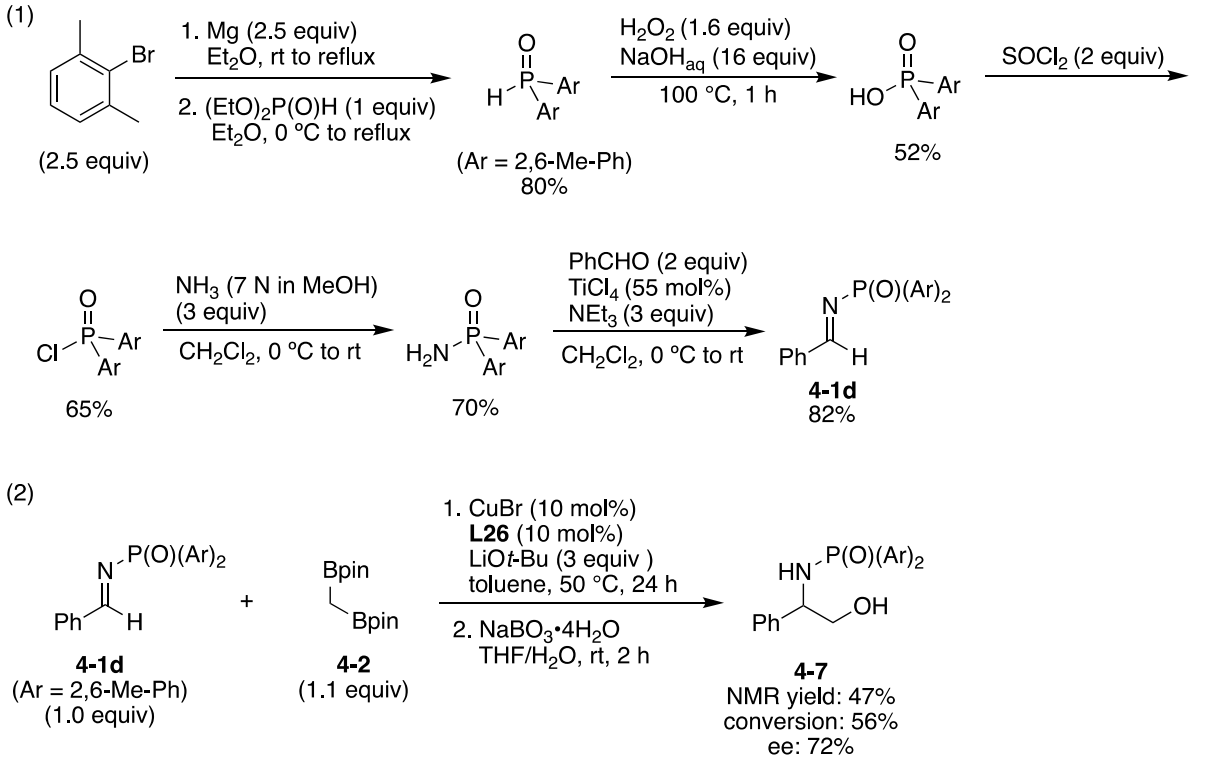
In an attempt to improve the enantioselectivity further, the effect of the *N*-protecting group of the aldimine substrate was investigated. As shown in Scheme 4-6, *N*-Boc-protected (**4-1b**) and *N*-Ts-protected (**4-1c**) aldimines were subjected to the optimal conditions (Table 4-6, entry 7). In the event, the reaction was low-yielding, with most of the aldimine starting material recovered.



Scheme 4-6. Examination of the effect of the *N*-protecting group: 1) 1,2-addition with *N*-Boc-protected aldimine **4-1b** and 2) 1,2-addition with *N*-Ts-protected aldimine **4-1c**.

A 2,6-methyldiphosphinyl analogue (**4-1d**) of the diphenylphosphinyl group on the nitrogen of aldimine **4-1a** was synthesized by following literature procedures (Scheme 4-7, eq. 1).[14] Starting from 2-bromo-1,3-dimethylbenzene and diethylphosphite, the synthesis of

aldimine **4-1d** was achieved in six steps with good yields. Under the optimal conditions (Table 4-6, entry 7), the 1,2-addition with aldimine **4-1d** gave a slightly higher enantioselectivity (72% ee), but suffered from a lower yield (47%; Scheme 4-7, eq. 2). The diminished yield probably can be ascribed to the increased steric hindrance of the 2,6-methyldiphosphinyl moiety of aldimine **4-1d**. Given the lengthy synthetic route required to access the analogue of the diphenylphosphinyl group and the slight improvement of enantioselectivity, efforts at further examining other analogues of the diphenylphosphinyl group were discontinued.



Scheme 4-7. Synthesis of analogue **4-1d** of aldimine **4-1a** and the 1,2-addition of aldimine **4-1d**.

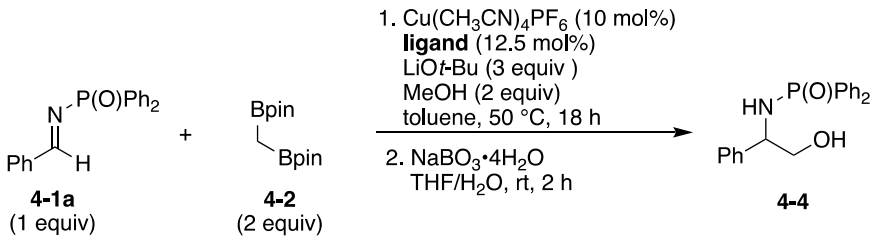
4.3.6 Ligand High-Throughput Screening (HTS)

The asymmetric 1,2-addition of 1,1-diborylmethane **4-2** and *N*-phosphinyl aldimine **4-1a** proved to be challenging, as demonstrated by the extensive optimization described in previous sections. To surmount this challenge, attention was turned to the concept of ligand high-throughput screening (HTS).[15] Our group recently has demonstrated the efficiency of the HTS approach in the enantioselective conjugate borylation of cyclobutenones, achieving tertiary cyclobutylboronates with high levels of enantioselectivity.[16]

In collaboration with a team of scientists at Pfizer, coordinated by Dr. Jack Lee, HTS of a library of 118 chiral ligands was undertaken under modified conditions from the optimal racemic conditions (Table 4-1, entry 1) using $Cu(CH_3CN)_4PF_6$ as the catalyst, LiO*t*-Bu as the base, and an extra amount of MeOH; $Cu(CH_3CN)_4PF_6$ was employed as the catalyst since it can serve as an efficient precursor to form the reactive ligated Cu complex owing to its good solubility in organic solvents and weakly coordinating acetonitrile ligands. Each reaction was set up in a glove box with <20 ppm O_2 and <20 ppm H_2, and run at a 0.002 mmol scale and 0.02 M concentration in toluene at 50 ºC for 18h. All of the 118 ligands are presented in Table 4-7, with a summary of the results in Figure 4-1, in which the product yield is shown as the mass ion count, and the enantiomeric ratio was determined by chiral HPLC.

As shown in Figure 4-1, most of the ligands gave low enantioselectivity (<20% ee), an outcome similar to that observed in the ligand screening described in the previous sections. Only two chiral ligands, a Josiphos-type ligand (SL-J004-1) and (*S*,*S*)-f-Binaphane, were found to deliver promising selectivity, ~72% ee and ~52% ee, respectively. Despite achieving the highest enantioselectivity (~72% ee), the 1,2-addition using a Josiphos-type ligand (SL-J004-1) was low-yielding. Interestingly, this Josiphos-type ligand also was tested in Section 4.3.4 but gave only 9% ee (see **L28** in entry 9 of Table 4-6). Furthermore, the best Josiphos-type ligand (**L26**) found in Section 4.3.4 (Table 4-6, entry 7) led to <30% ee in the HTS. This large discrepancy in the enantioselectivity probably is attributed to the different conditions employed in the previous section and the HTS (see Table 4-6 and 4-7). Regardless of this large discrepancy, the optimization described in the previous sections and the HTS consistently indicate that Josiphos derivatives are a type of ligand for achieving promising enantioselectivity in this asymmetric 1,2-addition. Moreover, the HTS, together with all of the aforementioned optimizations, clearly highlights the notorious challenge this asymmetric 1,2-addition offers.

Table 4-7. 118 Ligands Evaluated in the Ligand High-Throughput Screening (HTS)



4-1a (1 equiv) + **4-2** (2 equiv) → **4-4**

(*S*)-Me-f-KetalPhos	*t*-BuDPPPO	Naud SL-N011-2	(*R*)-DIFLUORPHOS
(*R*,*R*)-DACH-naphthyl Trost	(+)-TsCYDN	(*R*)-(+)-MeO-BIPHEP	CTH-(*R*)-3,5-xylyl-
(*R*,*R*)-*i*-Pr-DUPHOS	Box Ligand 15	(*R*)-SDP	2,2BNDMDiE
(*R*,*R*)-Me-BPE	(*S*,*S*)-Me-BPF	SL-J452-2	Walphos SL-W022-2
Box Ligand 1	Buwen Ligand	TCI2	(*R*)-Xyl-SDP
(*S*,*S*,*R*,*R*)-TangPhos	*N*,*N*-DTsCHN	SL-J004-1 (**L28**)	SL-J007-1
(R_a,*S*)-DTB-Bn-SIPHOX	(*R*,*R*)-Chiraphos	(*R*)-C3-Tunephos	Taniaphos SL-T002-1
Groton BINOL Ligand 1	(*S*,*S*)-BDPP	Naud SL-N008-2	(*R*)-DM-SEGPHOS
(*S*,*S*)-N-Ms-1,2-DPEN	PPM	*R*-Josiphos SL-J003-1	SL-J425-2
Box Ligand 2	(*R*,*R*)-DIPAMP	(1)_(*S*)SEGPHOS	(*S*)-BINAPINE
Box Ligand 3	Box Ligand 16	(*S*)-Methyl BoPhoz	(*R*)-(+)-XylBINAP
Box Ligand 4	(*R*,*R*)-NORPHOS	catASium T1	TCI1
Box Ligand 5	Nauds-*i*Pr Ligand	SL-J015-1	Josiphos SL-J404-2
(*R*,*R*)-Me-DuPhos	JoSPOphos 1	(*R*)-BINAP	ChenPhos
Box Ligand 6	Naud SL-N004-1	Salen	SL-J418-1 (**L26**)
(*S*,*S*)-DACH-pyridyl TROST	(*S*,*S*)-DIOP	SL-J005-2	(*R*)-Xylyl-P-Phos
Box Ligand 8	JoSPOphos 2	(*R*)-SYNPHOS	(*S*)-BINOL
Box Ligand 9	Naud SL-N012-2	*R*-Josiphos SL-J001-1	*cis*-Aindanol
Box Ligand 10	SL-J212-1	SL-J216-2	(*S*,*S*)-f-Binaphane
(*R*,*R*)-QuinoxP*	R-Monophos	CTH-(*S*)-P-Phos	Mandyphos SL-M002-1
Box Ligand 11	(2)_Xanthphos	(*R*)-Tol-SDP	*R*-Josiphos SL-J006-1
Box Ligand 12	Naud SL-N013-1	(*R*,*R*)-Et-DUPHOS	SL-J008-1
catASium MNXylF(*R*)	P(Ph_3)Chiral	(*R*)-Binam-P	Trifer
Box Ligand 13	SL-J502-1	SaxS,S-BOBPHOS	Mandyphos SL-M009-1
(*R*)-(+)-Cl-MeO-BIPHEP	(*S*,*S*)-TsDPEN	Walphos SL-W002-1	Walphos SL-W008-1
R-Josiphos SL-J009-1	SL-M003-2	SL-J013-2	Walphos SL-W005-2
Box Ligand 14	(2*R*)-iPr-BPE	CTH-(*R*)-BINAM	(*R*)-DTBM-SEGPHOS
(R_a,*S*)-Ph-Bn-SIPHOX	SL-J505-1	Pfizer Ligand	Josiphos SL-J011-1
R-Josiphos SL-J002-1	(*S*)-Phanephos	Walphos SL-W003-1R-	
(*R*,*R*,*S*,*S*)-DUANPHOS	SL-J014-1	(*R*)-(+)-TolBINAP	

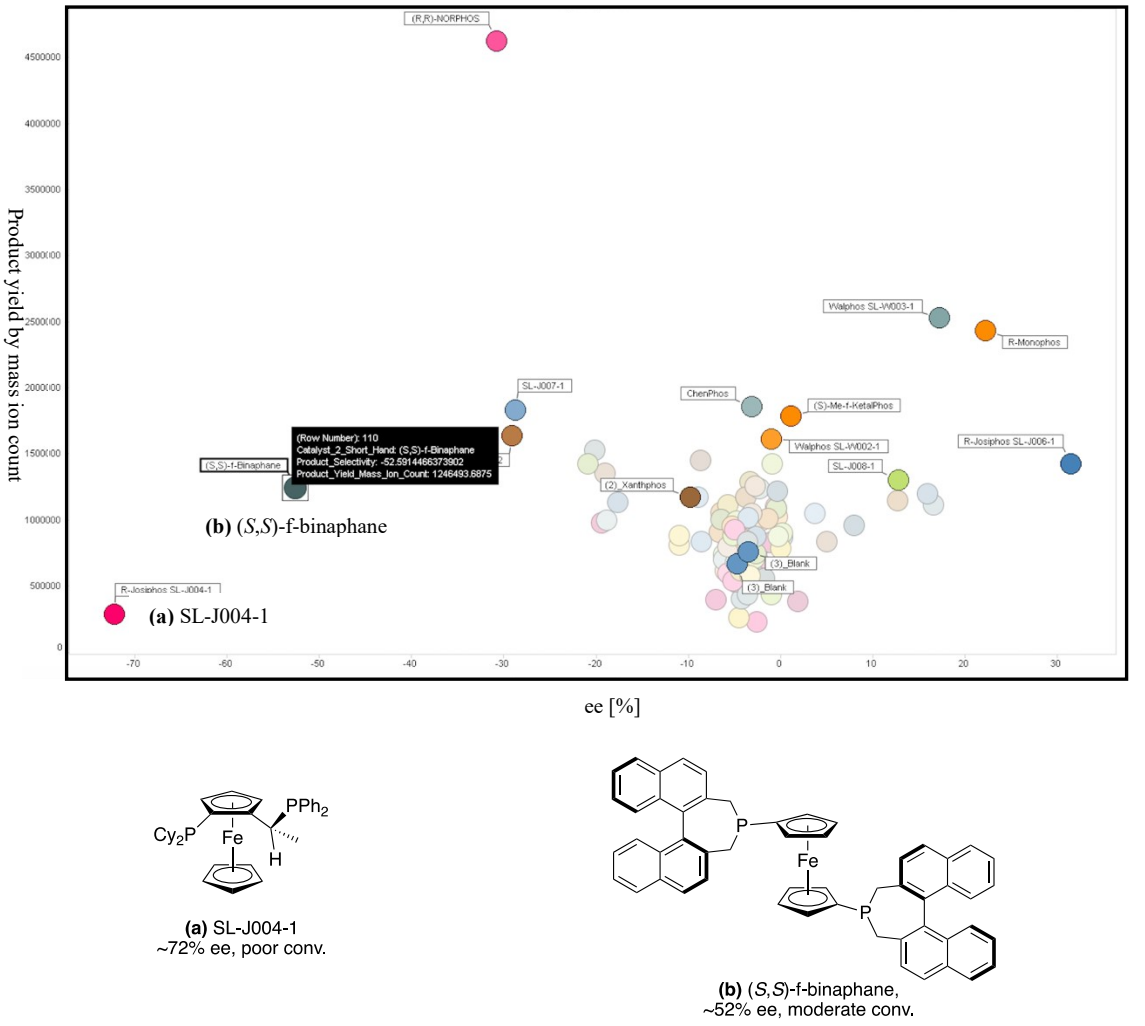
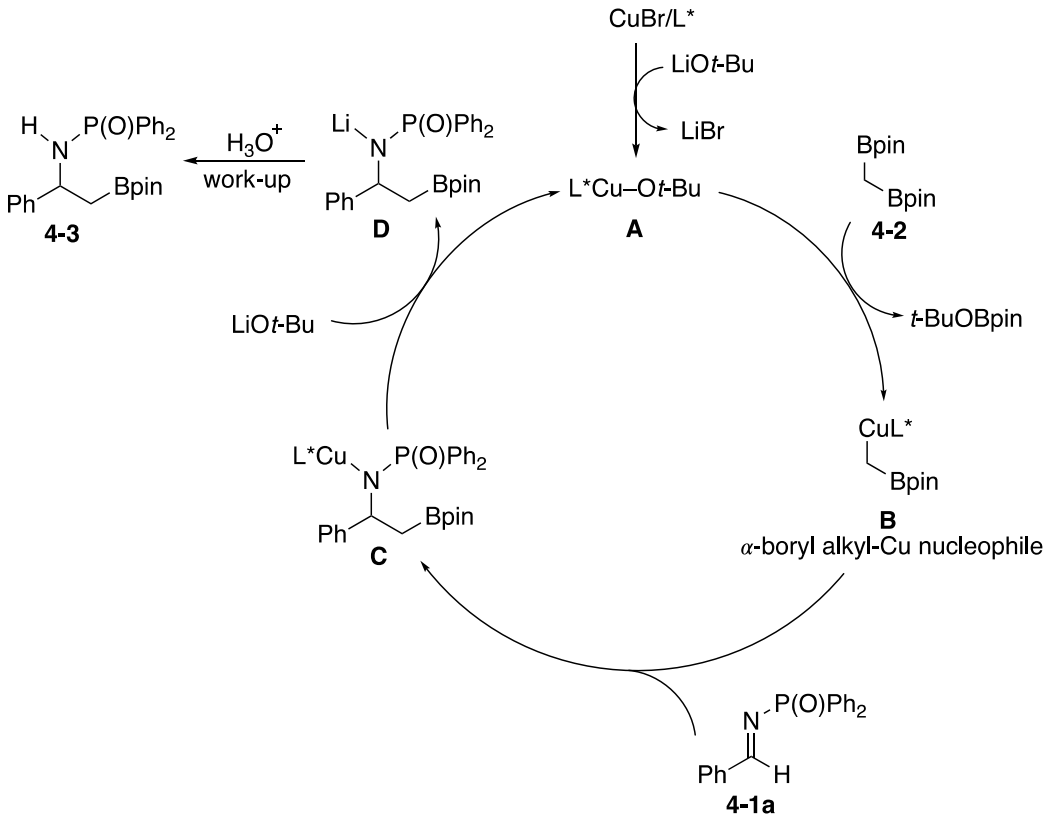


Figure 4-1. Summary of HTS results for ligand optimization. Spotfire presents product by mass ion count (vertical axis, all enantiomers added), selectivity (horizontal axis, +ve value show first eluting peak is major), metal (trellis), ligand (color and label).

4.4 Proposed Mechanism

Based on the mechanism of the 1,2-addition of 1,1-diborylalkanes to aldehydes proposed by Meek and co-workers,[10] a possible mechanism can be hypothesized for the 1,2-addition with *N*-phosphinyl aldimine **4-1a** (Scheme 4-8). First, CuBr reacts with LiO*t*-Bu to form reactive Cu(I) species **A**. The transmetalation between species **A** and 1,1-diborylmethane **4-2** generates nucleophilic α-boryl alkyl-Cu(I) intermediate **B**. A subsequent 1,2-addition of intermediate **B** to *N*-phosphinyl aldimine **4-1a** forms Cu(I) species **C**, in which the enantioselectivity could be attributed to the facial selectivity controlled by the chiral ligated Cu(I) complex. Finally,

the reaction of **C** and LiO*t*-Bu leads to intermediate **D** while regenerating reactive species **A**. In the acidic work-up, intermediate **D** was transformed into the desired product **4-3**.



Scheme 4-8. Proposed mechanism for the 1,2-addition of 1,1-diborylmethane **4-2** to *N*-phosphinyl imine **4-1a**.

4.5 Summary

In summary, this chapter reports the development of a Cu-catalyzed asymmetric 1,2-addition of 1,1-diborylmethane to *N*-diphenylphosphinyl aldimines. This 1,2-addition reaction provides a direct and mild method for the synthesis of optically enriched β-aminoalkylboronates. In this study, the racemic conditions were developed successfully and used for the examination of the asymmetric 1,2-addition. Exploration of numerous chiral ligands in our lab and in collaboration with Pfizer revealed that most of the chiral ligands result in poor enantioselectivity, and only some Josiphos-type ligands gave promising yields and enantioselectivity. Furthermore, investigation of Josiphos-type ligands bearing different substituents showed that the substituent exerted a significant impact on the enantioselectivity,

and a Josiphos derivative (**L26**) delivered the highest enantioselectivity (68% ee) with a 71% yield. However, screening of other reaction parameters, including the Cu catalyst, base, and solvent, exhibited no improvement of the enantioselectivity. Therefore, to achieve higher enantioselectivity (i.e., >90% ee), future studies should focus on the design and synthesis of new Josiphos derivatives with different electron rich aryl substituents since electron rich aryl substituents were found to give relatively good yields and enantioselectivity.

4.6 Experimental

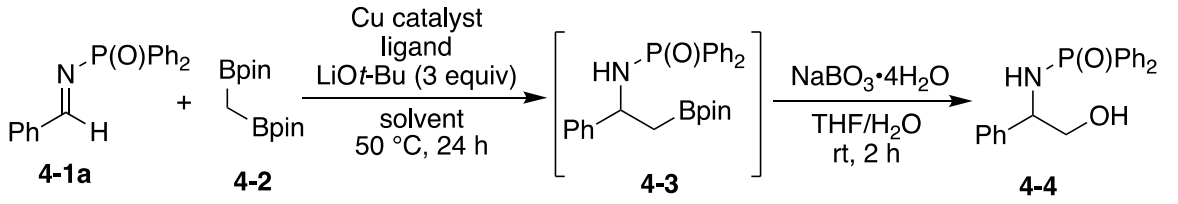
4.6.1 General methods

Unless otherwise stated, all reactions were performed under a nitrogen or argon atmosphere. Tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), and toluene were purified using a cartridge solvent purification system prior to use. 1,4-Dioxane and diethyl ether (Et_2O) were distilled over sodium/benzophenone. Ligands **L13**–**L14**,[8] **L15**–**L18**,[17] and **L20**,[18] 1,1-diborylmethane **4-2**,[19] and aldimine **4-1a**,[20] **4-1b**,[21] **4-1c**,[20] and **4-1d**[14] were synthesized by following the cited literature procedures. Unless otherwise noted, all other chemicals were purchased from commercial sources and used as received.

Chromatographic separations were performed on silica gel 60 using ACS grade hexanes, ethyl acetate, dichloromethane, and diethyl ether as eluents. Thin layer chromatography (TLC) was performed on silica gel 60 F254 plates, which were visualized under UV light, $KMnO_4$, and *p*-anisaldehyde stains. NMR spectra were recorded on INOVA-400 MHz instruments. The residual solvent protons (^1H) of $CDCl_3$ (7.26 ppm) and the solvent carbons (^{13}C) of $CDCl_3$ (77.06 ppm) were used as internal standards. ^1H NMR data is presented as follows: chemical shift in ppm (δ) downfield from tetramethylsilane (multiplicity, coupling constant, integration). The following abbreviations are used in reporting NMR data: s, singlet; br s, broad singlet; d, doublet; m, multiplet; dd, doublet of doublets; app qd, apparent quartet of doublets; app dq, apparent doublet of quartet. The quaternary carbon bound to the boron atom often is missing due to the quadrupolar relaxation of boron. This effect was observed in each boron-containing compound. High-resolution mass spectra were recorded by the University of Alberta mass spectrometry services laboratory using electrospray ionization (ESI) techniques. Optical rotations were measured using a 1 mL cell with a 1 dm length on a P.E. 241 polarimeter. The enantiomeric excesses for chiral compounds were determined using a HPLC Agilent

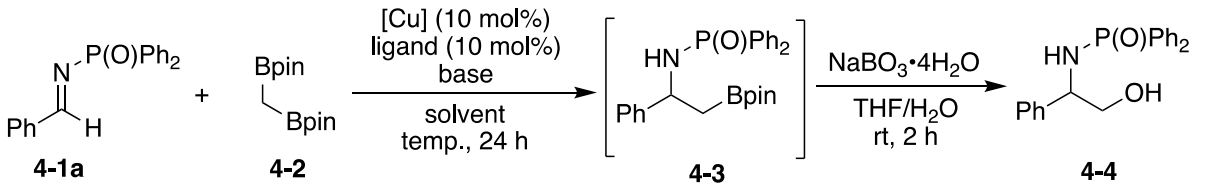
instrument with Chiralcel OD or Chiralpak IB columns with UV detection.

4.6.2 General Procedure for the Optimization of the Racemic 1,2-Addition



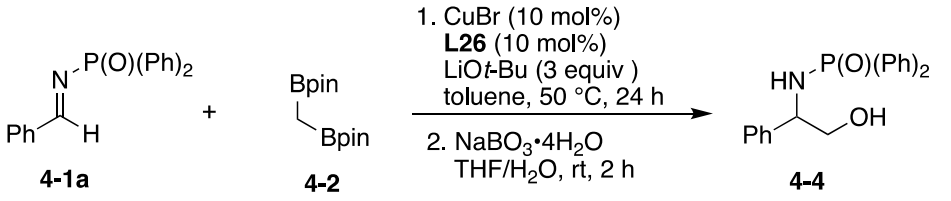
To a reaction tube were added the Cu catalyst, ligand, LiO*t*-Bu (48 mg, 0.60 mmol, 3.0 equiv), *N*-diphenylphosphinyl aldimine **4-1a** (62 mg, 0.20 mmol, 1.0 equiv), diborylmethane **4-2** (80 mg, 0.30 mmol, 1.5 equiv), and toluene (1 mL). The resulting mixture was stirred at 50 ºC for 24 h. Upon completion, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (10 mL) and extracted with CH_2Cl_2 (10 mL×3). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford the crude β-aminoalkylboronate **4-3**. In a 25 mL round-bottomed flask, β-aminoalkylboronate **4-3** and $NaBO_3$•$4H_2O$ (0.15 g, 1.0 mmol, 5 equiv) were dissolved in THF/H_2O (6 mL, 1:1). After stirring at room temperature for 2 h, the reaction mixture was extracted with CH_2Cl_2 (10 mL×4). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The yield was determined by ^1H NMR analysis of the crude mixture using dibromomethane as the internal standard.

4.6.3 General Procedure for the Optimization of the Asymmetric 1,2-Addition



To a reaction tube were added the Cu catalyst (0.020 mmol, 0.010 equiv), chiral ligand, base, *N*-diphenylphosphinyl aldimine **4-1a** (62 mg, 0.20 mmol, 1.0 equiv), diborylmethane **4-2**, and solvent. After stirring for 24 h, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (10 mL) and extracted with CH_2Cl_2 (10 mL×3). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford the crude β-aminoalkylboronate **4-3**. In a 25 mL round-bottomed flask, β-aminoalkylboronate **4-3** and $NaBO_3$•$4H_2O$ (0.15 g, 1.0 mmol, 5 equiv) were dissolved in THF/H_2O (6 mL, 1:1). After stirring at room temperature for 2 h, the reaction mixture was extracted with CH_2Cl_2 (10 mL×4). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The product was purified by flash column chromatography (98:2 to 97:3, CH_2Cl_2/MeOH) to yield β-amino alcohol **4-4** as a white solid, and the enantiomeric ratio was determined by chiral HPLC.

4.6.4 Procedure for the Synthesis of β-Amino Alcohol 4-4 Using the Optimal Conditions



To a reaction tube was added the CuBr (2.9 mg, 0.020 mmol, 0.010 equiv), Josiphos-type ligand **L26** (15 mg, 0.020 mmol, 0.010 equiv), LiO*t*-Bu (48 mg, 0.60 mmol, 3.0 equiv), *N*-diphenylphosphinyl aldimine **4-1a** (62 mg, 0.20 mmol, 1.0 equiv), diborylmethane **4-2** (59 mg, 0.22 mmol, 1.1 equiv), and toluene (1 mL). After stirring at 50 ºC for 24 h, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (10 mL) and extracted with CH_2Cl_2 (10 mL×3). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford the crude β-aminoalkylboronate **4-3**. In a 25 mL round-bottomed flask, β-aminoalkylboronate **4-3** and $NaBO_3$•$4H_2O$ (0.15 g, 1.0 mmol, 5 equiv) were dissolved in THF/H_2O (6 mL, 1:1). After stirring at room temperature for 2 h, the reaction mixture was extracted with CH_2Cl_2 (10 mL×4). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The product was purified by flash column chromatography (98:2 to 97:3, CH_2Cl_2/MeOH) to yield β-amino alcohol **4-4** as a white solid (48 mg, 71%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93–7.83 (m, 4H), 7.53–7.49 (m, 2H), 7.46–7.40 (m, 4H), 7.40–7.27 (m, 3H), 7.26–7.24 (m, 2H), 4.91 (d, J = 9.2 Hz, 1H), 4.26 (app qd, J = 8.0, 3.1 Hz, 1H), 3.86–3.74 (m, 2H), 3.50 (dd, J = 10.3, 5.3 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.4, 132.9, 132.8, 132.24, 132.18, 131.8, 131.7, 128.82, 128.75, 128.6, 127.7, 126.4, 68.3, 59.0.

^{31}P NMR (162 MHz, $CDCl_3$) δ 26.8.

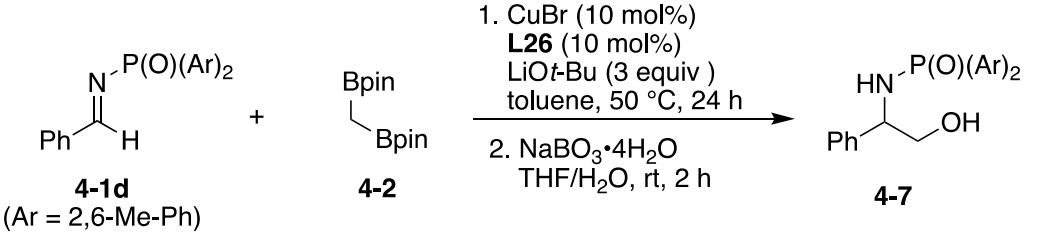
HRMS (ESI-TOF) for $C_{20}H_{21}NO_2P$ $(M + H)^+$: *calcd.*: 338.1304; *found*: 338.1309.

IR (cast film, cm^{-1}): 3288, 3078, 2937, 1439, 1175.

$[\alpha]_D^{20}$: +24.2 (*c* 0.45, $CHCl_3$).

HPLC (Chiralcel OD) 12:88 *i*-PrOH/Hexanes, 0.5 mL/min, λ = 210 nm, T_{major} = 16.2 min, T_{minor} = 22.1 min, ee = 68%.

4.6.5 Procedure for the Synthesis of β-Amino Alcohol 4-7 Using the Optimal Conditions



To a reaction tube was added the CuBr (2.9 mg, 0.020 mmol, 0.010 equiv), Josiphos-type ligand **L26** (0.020 mmol, 0.010 equiv), LiO*t*-Bu (48 mg, 0.60 mmol, 3.0 equiv), *N*-diphenylphosphinyl aldimine **4-1d** (72 mg, 0.20 mmol, 1.0 equiv), diborylmethane **4-2** (59 mg, 0.22 mmol, 1.1 equiv), and toluene (1 mL). After stirring at 50 ºC for 24 h, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (10 mL) and extracted with CH_2Cl_2 (10 mL×3). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford the crude β-aminoalkylboronate product. In a 25 mL round-bottomed flask, the β-aminoalkylboronate product and $NaBO_3$•$4H_2O$ (0.15 g, 1.0 mmol, 5.0 equiv) were dissolved in THF/H_2O (6 mL, 1:1). After stirring at room temperature for 2 h, the reaction mixture was extracted with CH_2Cl_2 (10 mL×4). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The product was purified by flash column chromatography (99:1 to 98:2, CH_2Cl_2/MeOH) to yield β-amino alcohol **4-7** as a white solid (37 mg, 47%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.26 (m, 2H), 7.25–7.19 (m, 3H), 7.14–7.08 (m, 2H), 7.03–6.97 (m, 4H), 5.49 (bs, 1H), 4.24 (app dq, *J* = 8.2, 3.8 Hz, 1H), 3.75–3.70 (m, J = 7.7 Hz, 3H), 2.43 (bs, 6H), 2.34 (bs, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.6, 141.1, 141.0, 131.2, 131.0, 130.5, 130.4, 130.3, 130.2, 128.7, 127.6, 126.4, 69.1, 60.2, 23.3, 23.2, 23.0, 22.9.

^{31}P NMR (162 MHz, $CDCl_3$) δ 28.0.

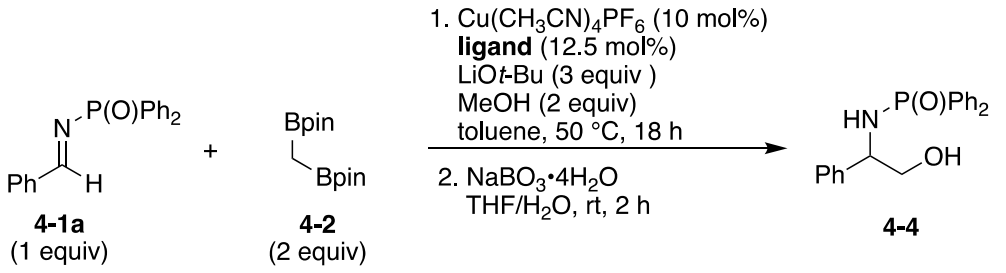
HRMS (ESI-TOF) for $C_{24}H_{28}NNaO_2P$ $(M + Na)^+$: *calcd.*: 416.175; *found*: 416.1745.

IR (cast film, cm^{-1}): 3296, 3059, 2931, 1454, 1163.

$[\alpha]_D^{20}$: –8.8 (*c* 0.36, $CHCl_3$).

HPLC (Chiralpak IB) 25:75 *i*-PrOH/Hexanes, 0.5 mL/min, λ = 210 nm, T_{major} = 8.8 min, T_{minor} = 22.1 min, ee = 72%.

4.6.6 Procedure for the Ligand High-Throughput Screening (HTS)



$Cu(CH_3CN)_4PF_6$ (5.00 μL, 0.100 equiv, 0.0400 M solution in CH_3CN) was dispensed first in an N_2-filled glove box with <20 ppm O_2 and <20 ppm H_2O before evaporation to dryness. To the resulting residue were added (*S*,*S*)-f-Binaphane (5.00 μL, 0.125 equiv, 0.0500 M solution in toluene) and THF (50.0 μL, 0.0800 M). The reaction was stirred for 1 h before the THF was evaporated to dryness. To the resulting residue was added 1,1-diborylmethane **4-2** (100 μL, 2.00 equiv, 0.0400 M solution in toluene). The reaction was stirred for 15 min before LiO*t*-Bu (6.00 μL, 3.00 equiv, 1.00 M solution in hexanes) was added. After a further 15 min, the aldimine **4-1a** (5.00 μL, 0.00200 mmol, 1.00 equiv, 0.400 M solution in THF) was added, followed by MeOH (100 μL, 2.00 equiv, 0.0400 M solution in THF). The reaction vial was crimp sealed to the glove-box environment before being stirred overnight at 50 ºC. After 18 h, the vials were diluted with $NaOB_3$•$4H_2O$ (100 μL, 5.00 equiv, 0.100 M solution in THF/H_2O 1:1), followed by DMF (200 μL), then mixed and centrifuged before being analyzed directly by SFC/MS.

4.7 References

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Chapter 5

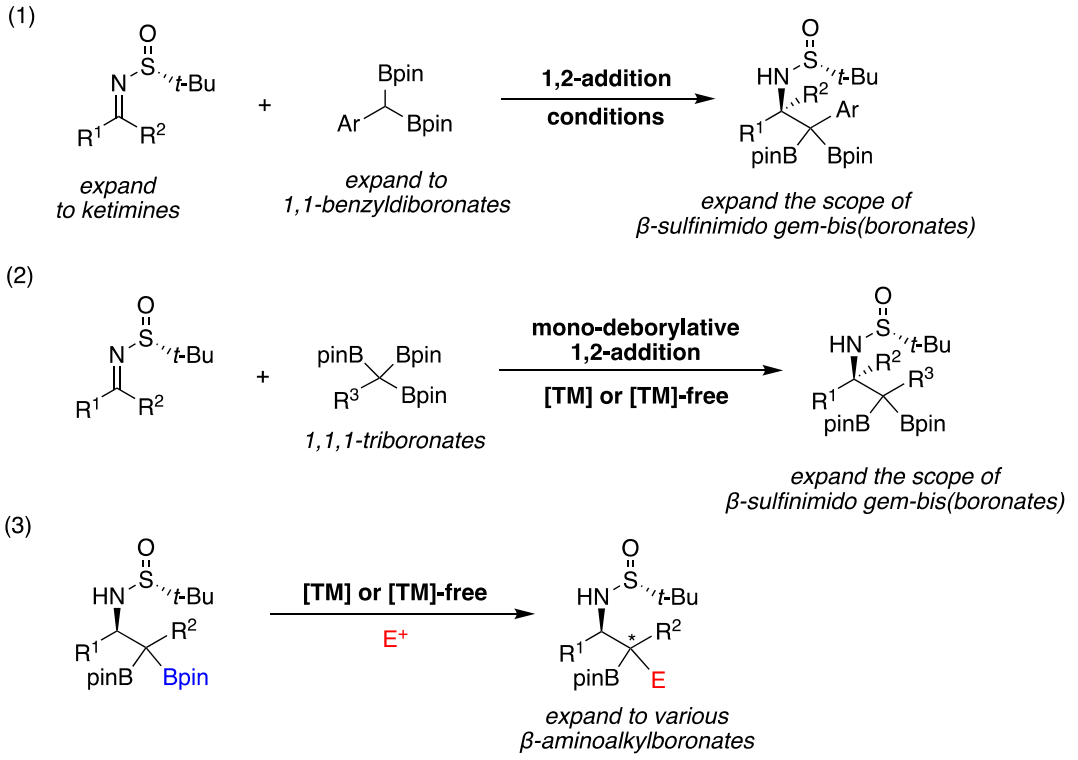
Conclusions and Future Perspectives

5.1 Conclusions and Future Perspectives

It is well-known that chiral alkylboronic esters constitute a valuable class of building blocks in asymmetric synthesis.[1] In contrast, incorporation of boron into molecules for drug discovery has not gained much attention until the approval of the first α-aminoalkylboronic acid-containing drug (bortezomib) by the U.S. FDA.[2] The success of bortezomib is attributed to the concept of α-aminoalkylboronic acids as a bioisostere of naturally occurring α-amino acids and α-amino aldehydes (see Section 1.2.2). Besides bortezomib, bioisosteric replacement using α-aminoalkylboronic acids has led to the commercialization of two other α-aminoalkylboronic acid-containing drugs, ixazomib and vaborbactam (see Figure 1-4). By extension of α-aminoalkylboronic acids, β-aminoalkylboronic acids are viewed as a bioisostere of β-amino acids. Therefore, β-aminoalkylboronic acids have substantial potential in medicinal chemistry, which is exemplified by one recent example; the antitubercular peptidyl β-aminoalkylboronic acid **1-5** (see Figure 1-5). In addition, β-aminoalkylboronic acids display their utility in asymmetric synthesis and catalysis (see Section 1.4). However, despite these attractive applications, the accessibility to enantioenriched β-aminoalkylboronic esters, especially α,β-disubstituted β-aminoalkylboronates, is limited (see Section 1.5). The general objective of this thesis is to develop novel and efficient stereoselective approaches to enantiomerically pure β-aminoalkylboronic esters using 1,1-diboron compounds since these compounds recently have emerged as a versatile class of reagent for the preparation of alkylboronic esters (see Section 2.1.2).

To access both the syn and anti diastereomers of α,β-disubstituted β-aminoalkylboronates, a 1,2-addition/monoprotodeboronation sequence using 1,1-diborylalkanes was developed (Chapter 2 and 3). The 1,2-addition of lithiated 1,1-diborylalkanes to a wide range of chiral *N*-sulfinyl aldimines afforded β-sufinimido *gem*-bis(boronates) in good yields with high levels of diastereoselectivity (Chapter 2). The resulting β-sufinimido *gem*-bis(boronates) underwent a subsequent monoprotodeboronation to deliver

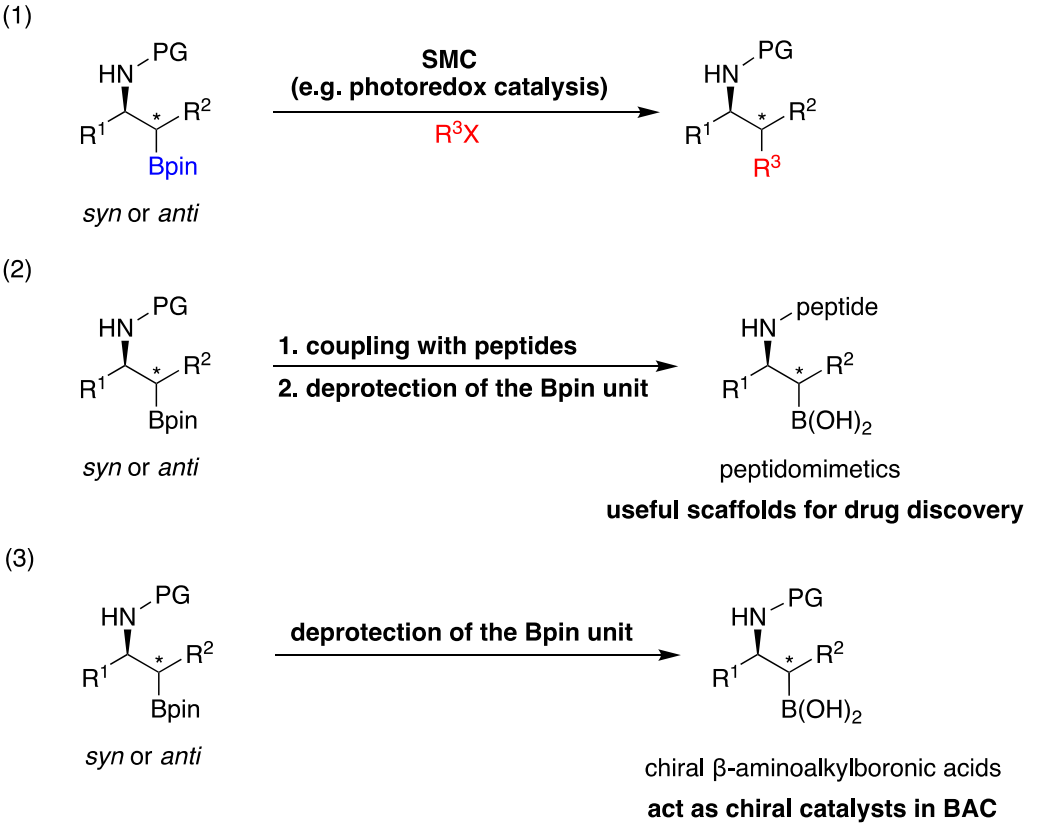
syn-α,β-disubstituted β-aminoalkylboronates under mild conditions. Chapter 3 presented a complementary variant of the monoprotodeboronation to produce the elusive anti isomer of α,β-disubstituted β-aminoalkylboronates. The key to the success of this anti-selective monoprotodeboroantion is the use of *N*-desulfinylated β-amino *gem*-bis(boronates) that can be prepared readily by desulfinylation of β-sufinimido *gem*-bis(boronates) under acidic conditions. Despite achieving good yields and excellent diastereoselectivity, there still are some areas for improvement and new opportunities in this 1,2-addition/monoprotodeboronation sequence. Although the 1,2-addition can be applied to a wide range of aldimine substrates, it is not applicable to ketimines, probably due to the presence of enolizable α-hydrogen or poorer electrophilicity of ketimines. In addition to the imine substrate, efforts could be made to expand the scope of 1,1-diborylalkanes to 1,1-benzyldiboronates.[3] In this regard, reaction conditions for a broader scope of imine and 1,1-diborylalkane substrates require further development (Scheme 5-1, eq. 1). Alternatively, with



Scheme 5-1. (1) Extension of the 1,2-addition to a broader scope of imines and 1,1-diborylalkanes, (2) mono-deborylative 1,2-addition of 1,1,1-triborylalkanes to imines for a broader scope of β-sulfinimido *gem*-bis(boronates), and 3) new transformations of β-sulfinimido *gem*-bis(boronates) for a broader scope of β-aminoalkylboronates.

recent report of methods for the synthesis of 1,1,1-triborylalkanes,[3,4] these compounds can be prepared and exploited in the 1,2-addition. Under transition metal-free or -catalyzed conditions, mono-deborylative 1,2-addition of these compounds to chiral *N*-sulfinyl imines might deliver a broader scope of the β-sufinimido *gem*-bis(boronate) products (Scheme 5-1, eq. 2). Beside monoprotodeboronation, β-sufinimido *gem*-bis(boronates) as a useful precursor can offer new opportunities to provide various β-aminoalkylboronic esters. For example, a number of transformations of 1,1-diborylalkanes (see Section 2.1.2) can be considered and investigated with β-sufinimido *gem*-bis(boronates) (Scheme 5-1, eq. 3).

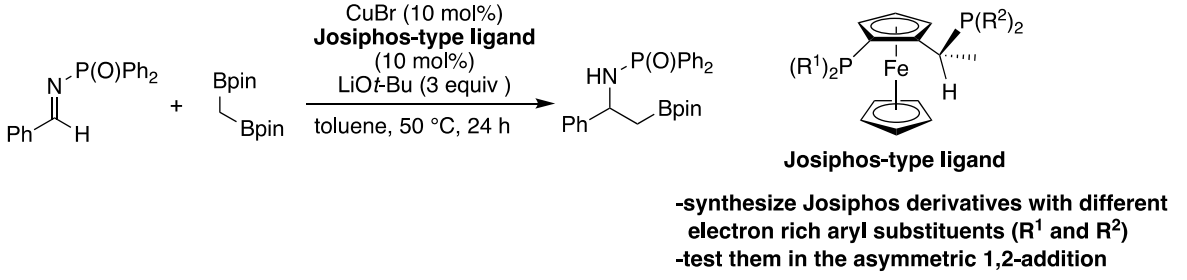
The synthetic utility of the obtained α,β-disubstituted β-aminoalkylboronates have been demonstrated in some C–O and C–C bond forming reactions (Chapter 2 and 3). However, SMC with these compounds is still a challenge but is useful in organic synthesis. More efforts should be made using newly developed SMC conditions (Scheme 5-2, eq 1).[5] Moreover, the



Scheme 5-2. Expanding the applications of α,β-disubstituted β-aminoalkylboronates: 1) SMC with β-aminoalkylboronates, 2) synthesis of peptidomimetics for drug discovery, and 3) synthesis of β-aminoalkylboronic acids for enantioselective BAC.

biological activity of the *syn*- and *anti*-β-aminoalkylboronates should be evaluated for pharmaceutical drug development. Of note, no study on the biological activity of the anti isomer of α,β-disubstituted β-aminoalkylboronates has been conducted yet. Furthermore, these β-aminoalkylboronates can be converted into a variety of pharmaceutically useful peptidomimetics (peptidyl β-aminoalkylboronic acids) by coupling with peptides and deprotection of the Bpin unit (Scheme 5-2, eq. 2). Despite significant advances achieved in boronic acid catalysis (BAC) in the past decade, enantioselective BAC rarely has been achieved.[6] It was envisioned that chiral β-aminoalkylboronic acids as chiral catalysts could provide a means to achieve enantioselective BAC and could be worthwhile to explore (Scheme 5-2, eq. 3).

Aiming to develop a direct and catalytic method for the synthesis of optically pure β-aminoalkylboronates, Chapter 4 described the development of a Cu-catalyzed 1,2-addition of 1,1-diborylmethane and a *N*-phosphinyl aldimine. Evaluation of numerous chiral ligands and other reaction parameters revealed that this 1,2-addition offers a notorious challenge, and the best result obtained so far is 71% yield with 68% ee using a Josiphos-type ligand. As discussed in Chapter 4, future studies should focus on the design and synthesis of new Josiphos derivatives[7,8] with different electron rich aryl substituents since electron rich aryl substituents were found to give relatively good yields and enantioselectivity (Scheme 5-3).



Scheme 5-3. Future evaluation of Josiphos derivatives for the improvement of the enantioselectivity in the asymmetric 1,2-addition of 1,1-diborylmethane to a *N*-phosphinyl aldimine.

The research presented in this thesis represents the most versatile approach to β-aminoalkylboronates, however, constitutes only a small fraction of this research area.[9] The author believes that continued research efforts into this area of study surely will expose more

new synthetic strategies towards β-aminoalkylboronates, thus benefit their applications in organic synthesis, drug discovery, and catalysis.

5.2 References

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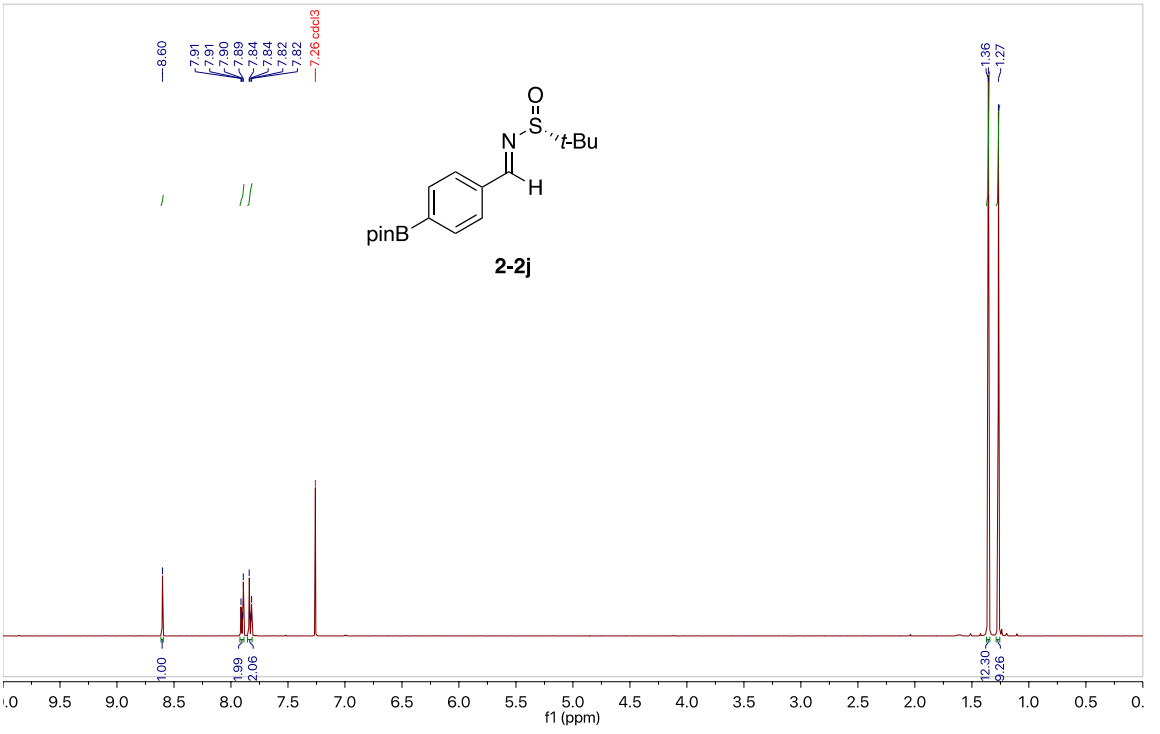
Appendices

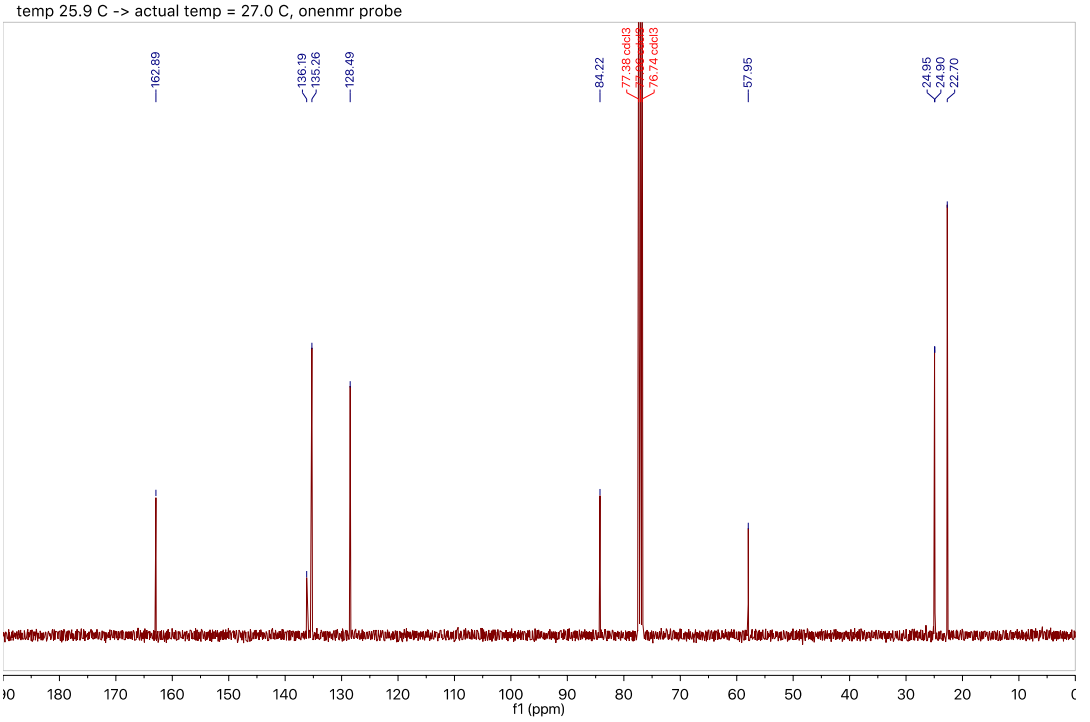
Appendix 1: Selected Copies of NMR Spectra

^{1}H NMR and ^{13}C NMR of *N-tert*-butanesulfinyl aldimine 2-2j:

2018.03.05.mr4_XLH-09-61_H1_1D; 399.978 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 25.9 C -> actual temp = 27.0 C, onenmr probe

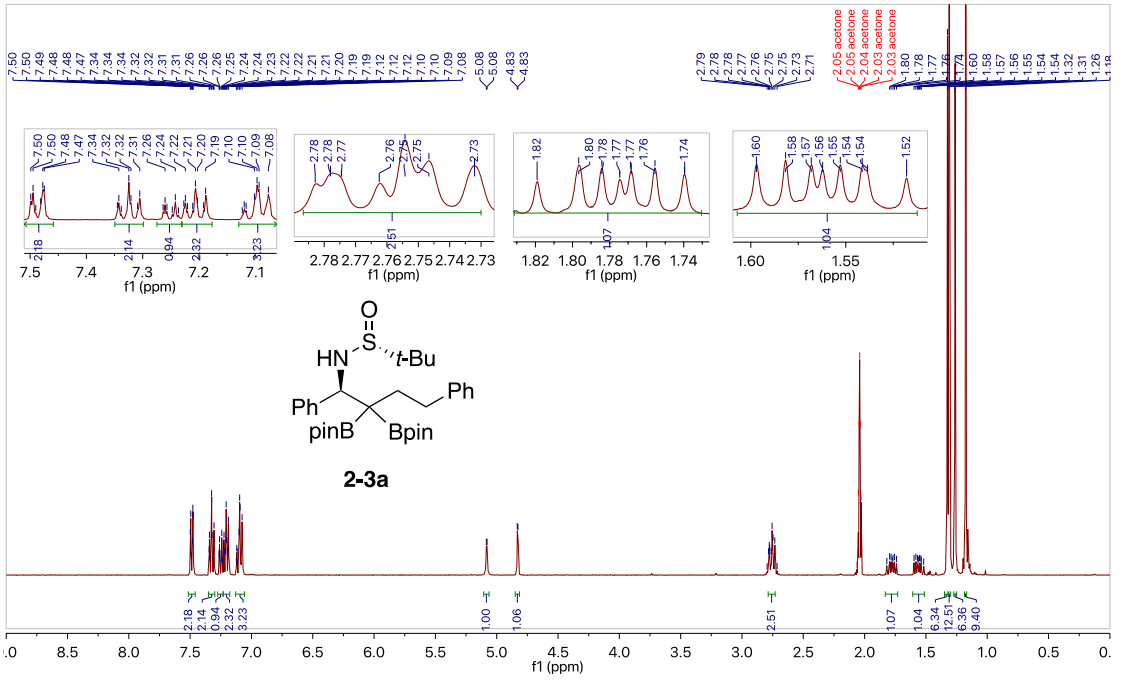


2018.03.05.mr4_XLH-09-61_C13_1D; 100.586 MHz C13{H1} 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 25.9 C -> actual temp = 27.0 C, onenmr probe

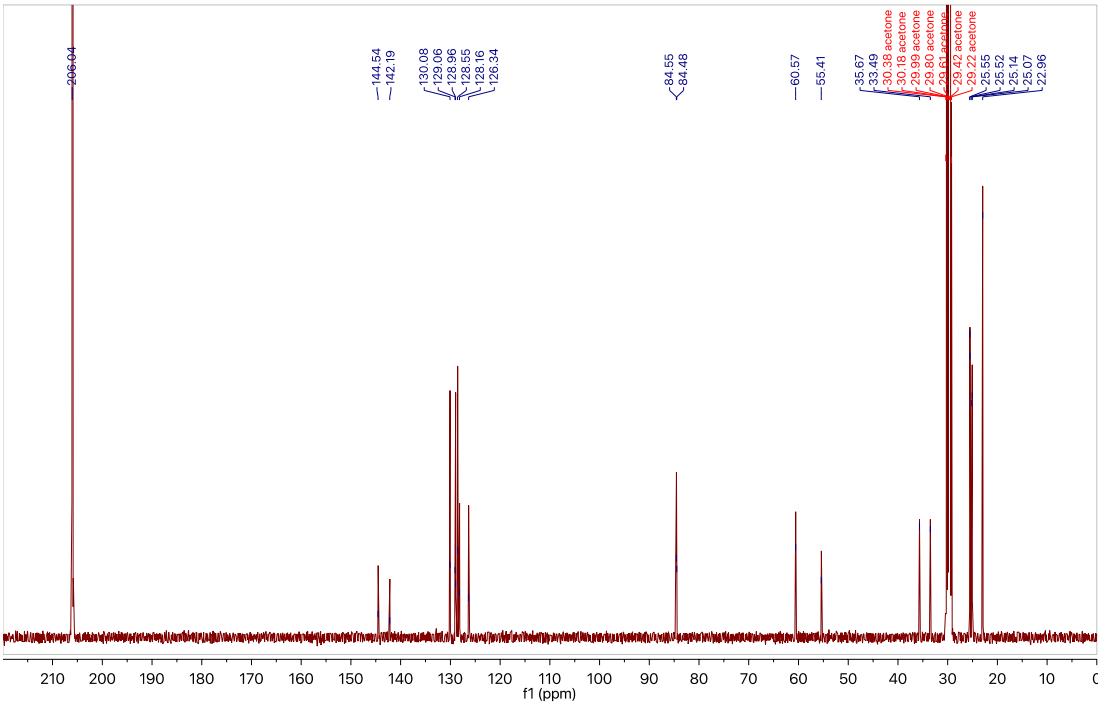


^{1}H NMR and ^{13}C NMR of β-sulfinimido *gem*-bis(boronate) 2-3a:

XLH-VII-169-acetone_H1_1D; 399.980 MHz H1 1D in acetone (ref. to acetone @ 2.04 ppm)
temp 25.9 C -> actual temp = 27.0 C, onenmr probe

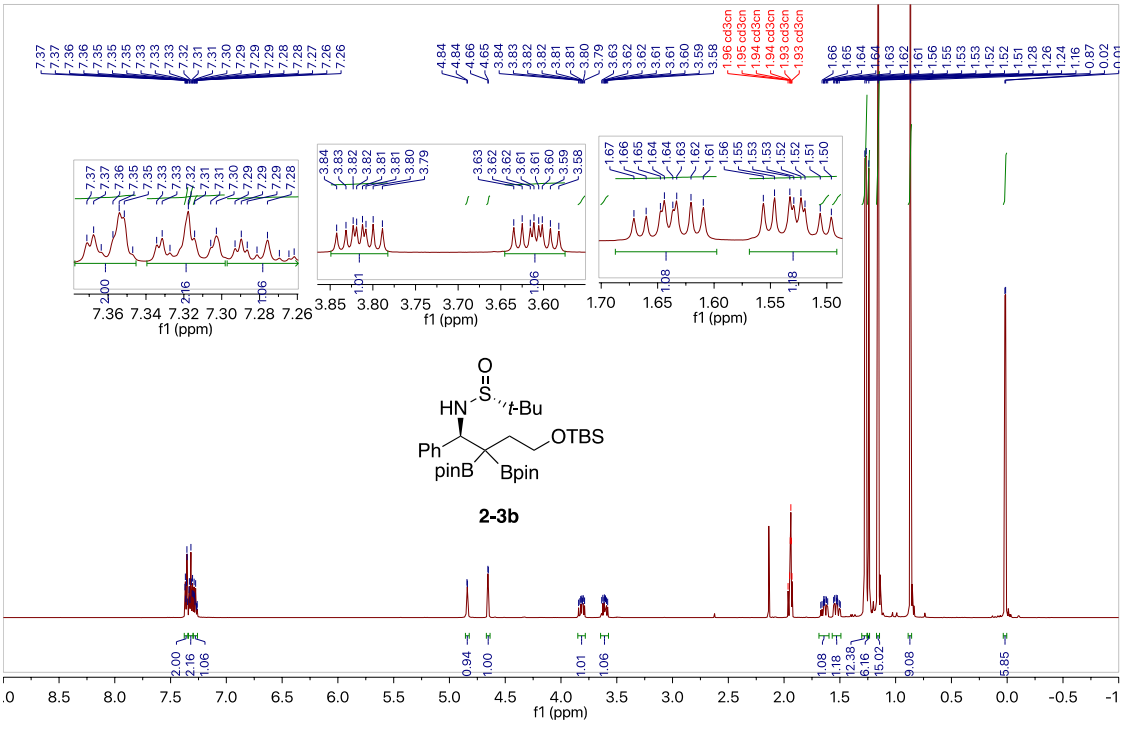


XLH-VII-169-acetone_12.30_C13_1D; 100.586 MHz C13{H1} 1D in acetone (ref. to acetone @ 29.8 ppm)
temp 25.9 C -> actual temp = 27.0 C, onenmr probe

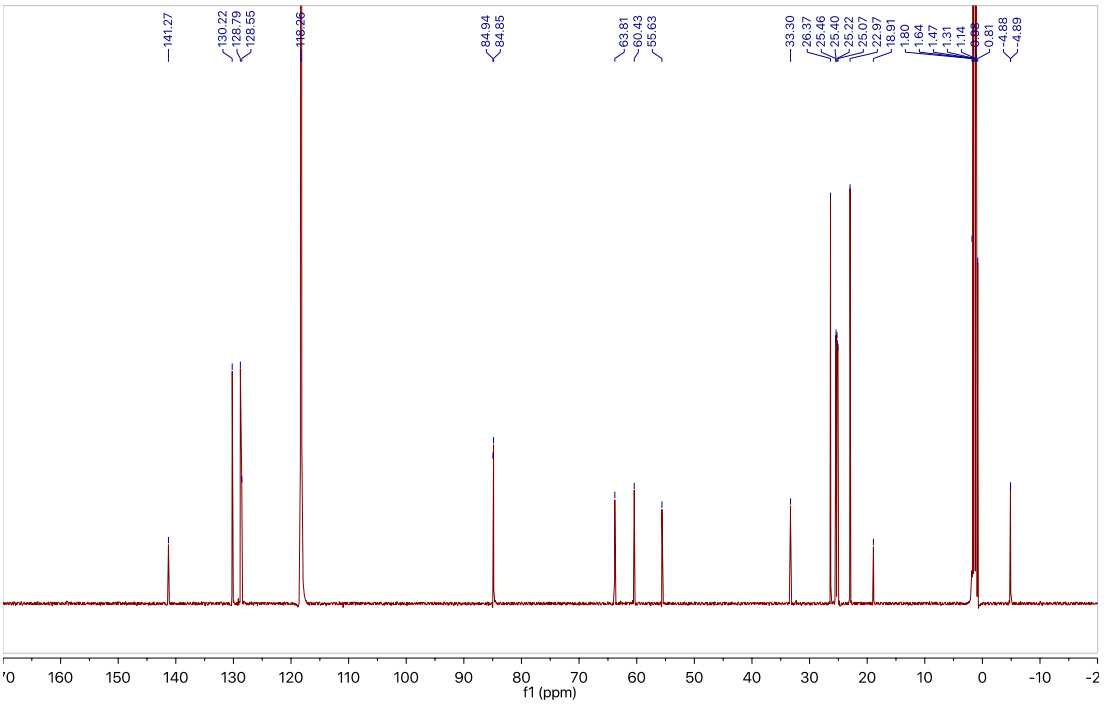


^{1}H NMR and ^{13}C NMR of β-sulfinimido *gem*-bis(boronate) 2-3b:

2018.04.09.u5_XLH-VII-131_loc9_16.26_H1_1D; XLH-VII-131; 499.800 MHz H1 1D in cd3cn
temp 27.7 C -> actual temp = 27.0 C, colddual probe

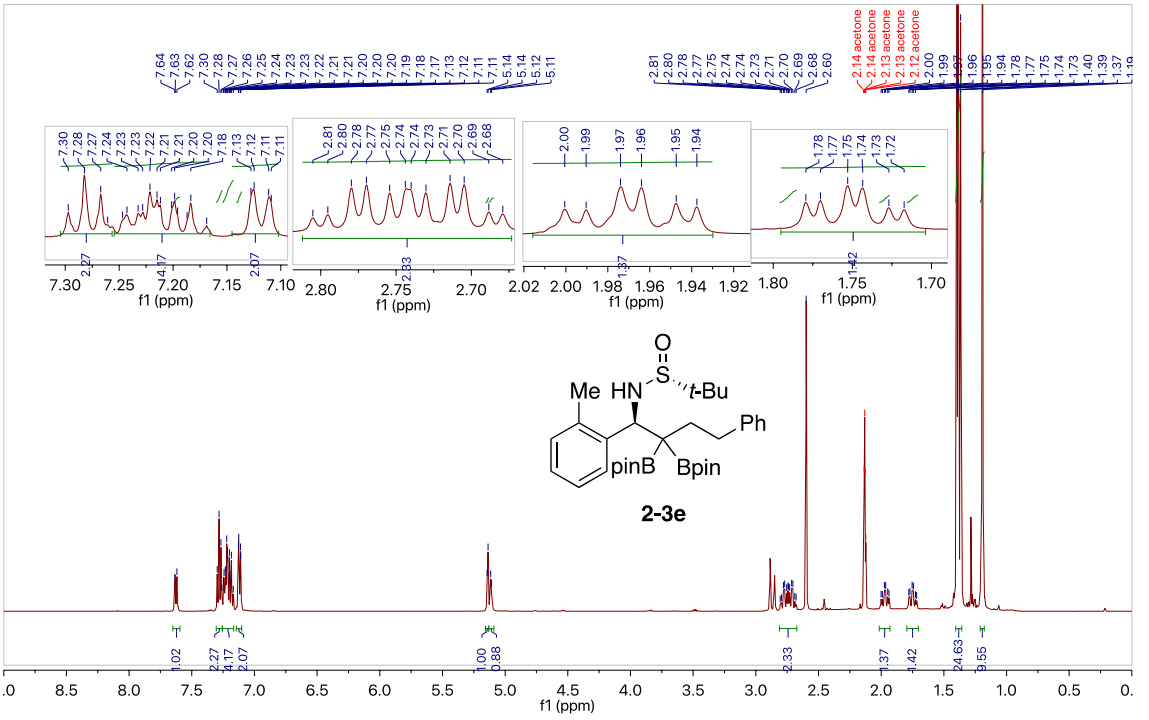


2018.04.09.u5_XLH-VII-131_loc9_16.27_C13_1D; XLH-VII-131; 125.688 MHz C13{H1} 1D in cd3cn
temp 27.7 C -> actual temp = 27.0 C, colddual probe

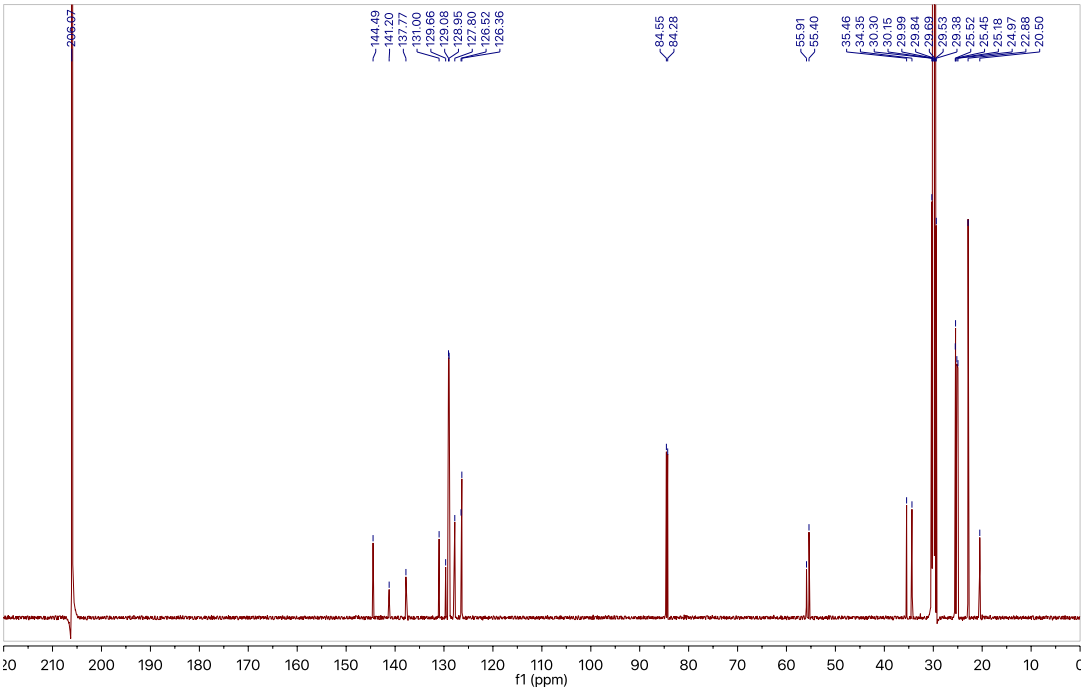


^{1}H NMR and ^{13}C NMR of β-sulfinimido *gem*-bis(boronate) 2-3e:

2018.03.21.u5_XLH-VIII-81_loc4_18.29_H1_1D; 499.800 MHz H1 1D in acetone (ref. to acetone @ 2.04 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe

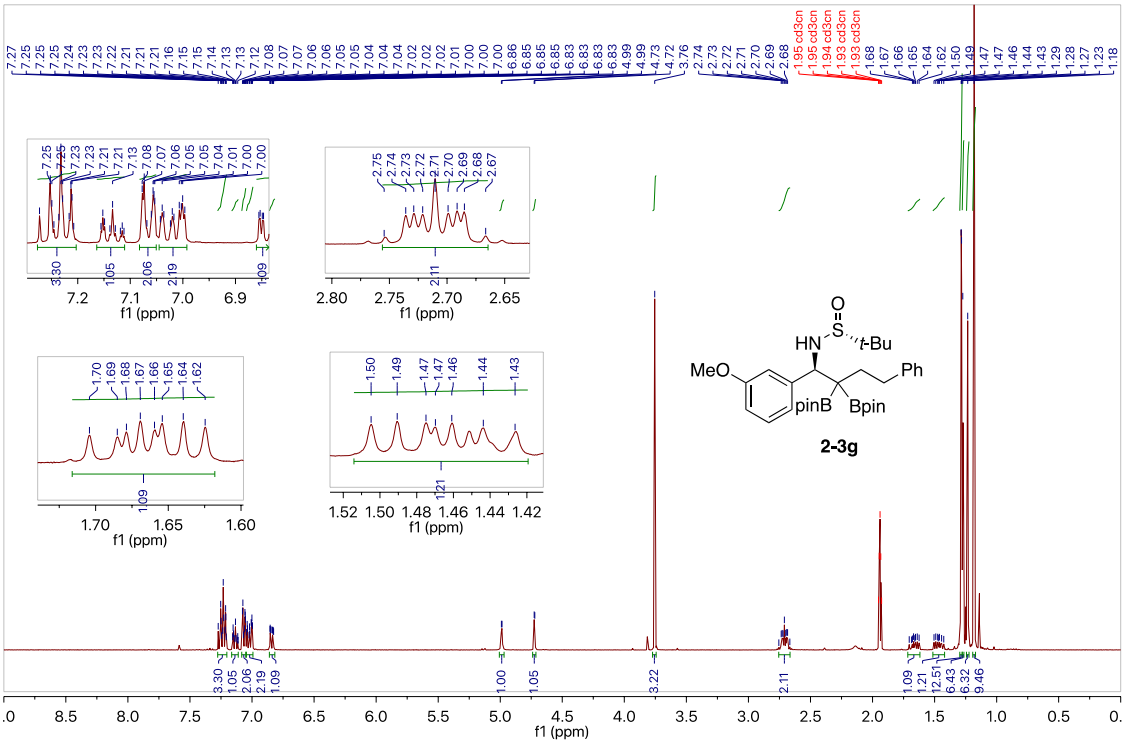


2018.03.21.u5_XLH-VIII-81_loc4_18.30_C13_1D; XLH-VIII-81; 125.689 MHz C13{H1} 1D in acetone (ref. to acetone @ 29.8 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe

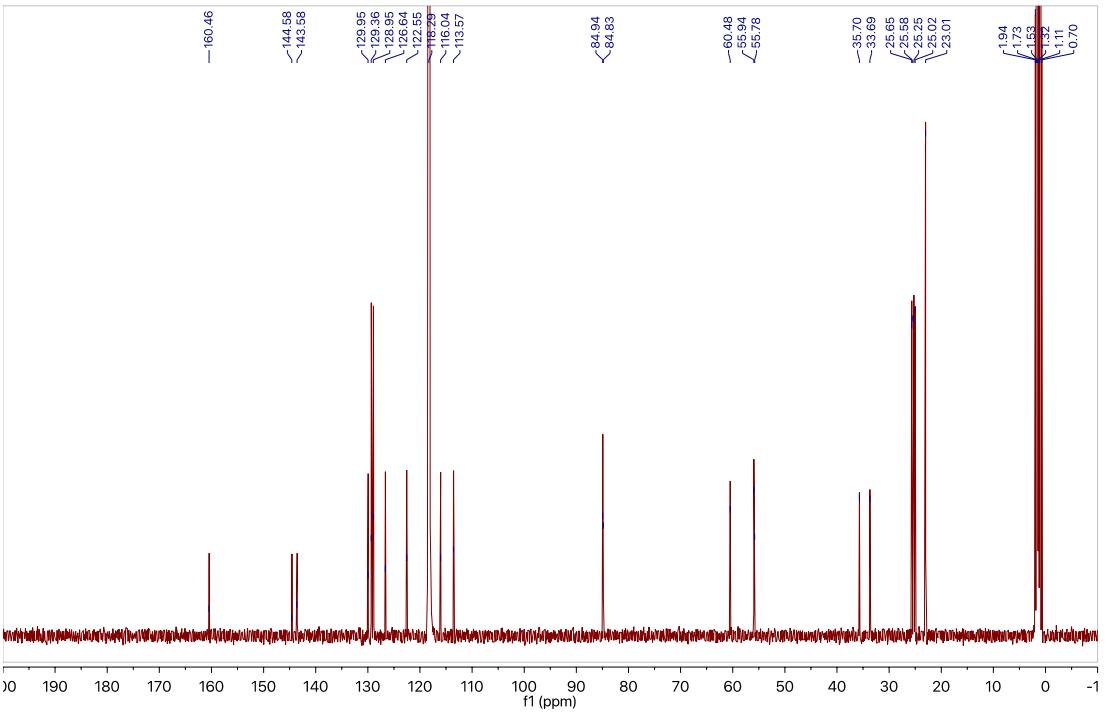


^{1}H NMR and ^{13}C NMR of β-sulfinimido *gem*-bis(boronate) 2-3g:

XLH-VIII-141-CD3CN; 399.980 MHz H1 1D in cd3cn recorded on mr400

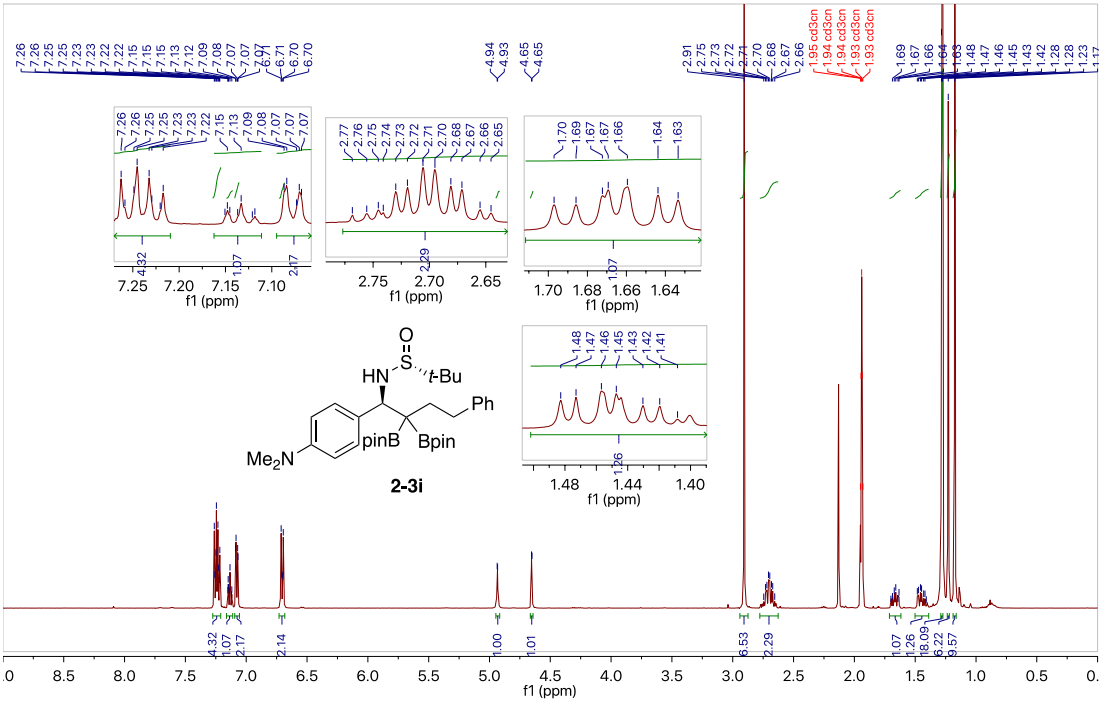


XLH-VIII-141-CD3CN_14.24_C13_1D; 100.584 MHz C13{H1} 1D in cd3cn
temp 25.9 C -> actual temp = 27.0 C, onenmr probe

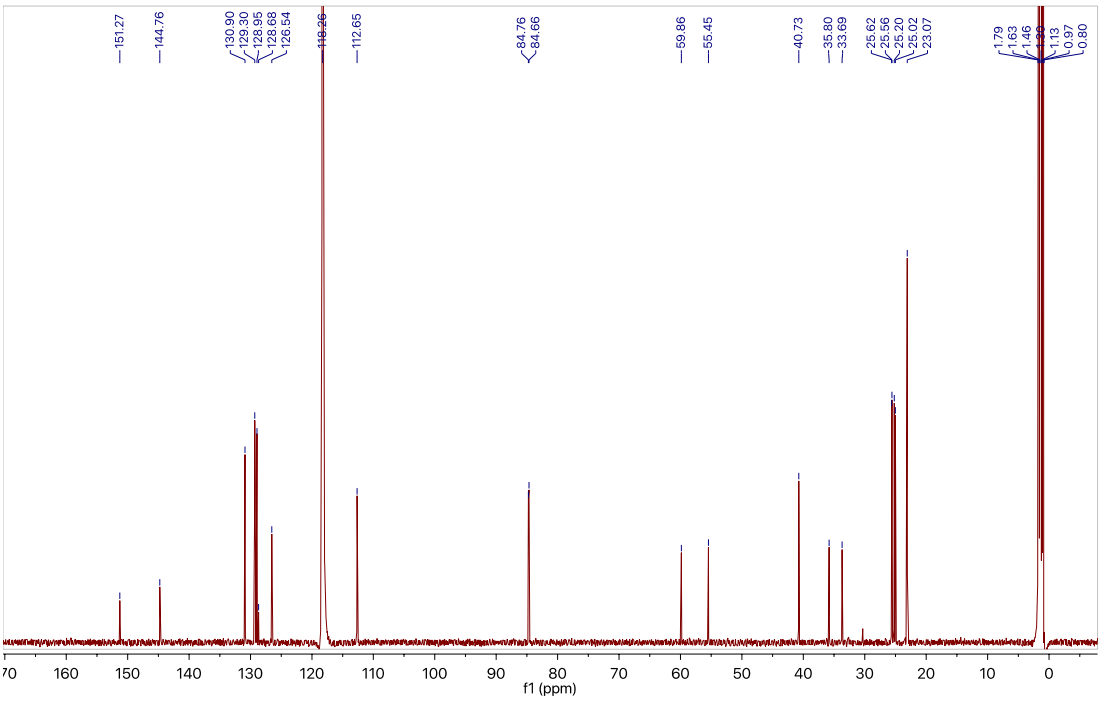


^{1}H NMR and ^{13}C NMR of β-sulfinimido *gem*-bis(boronate) 2-3i:

2018.04.01.u5_XLH-VIII-157_loc1_17.18_H1_1D; XLH-VIII-157; 499.800 MHz H1 1D in cd3cn
temp 27.7 C -> actual temp = 27.0 C, colddual probe

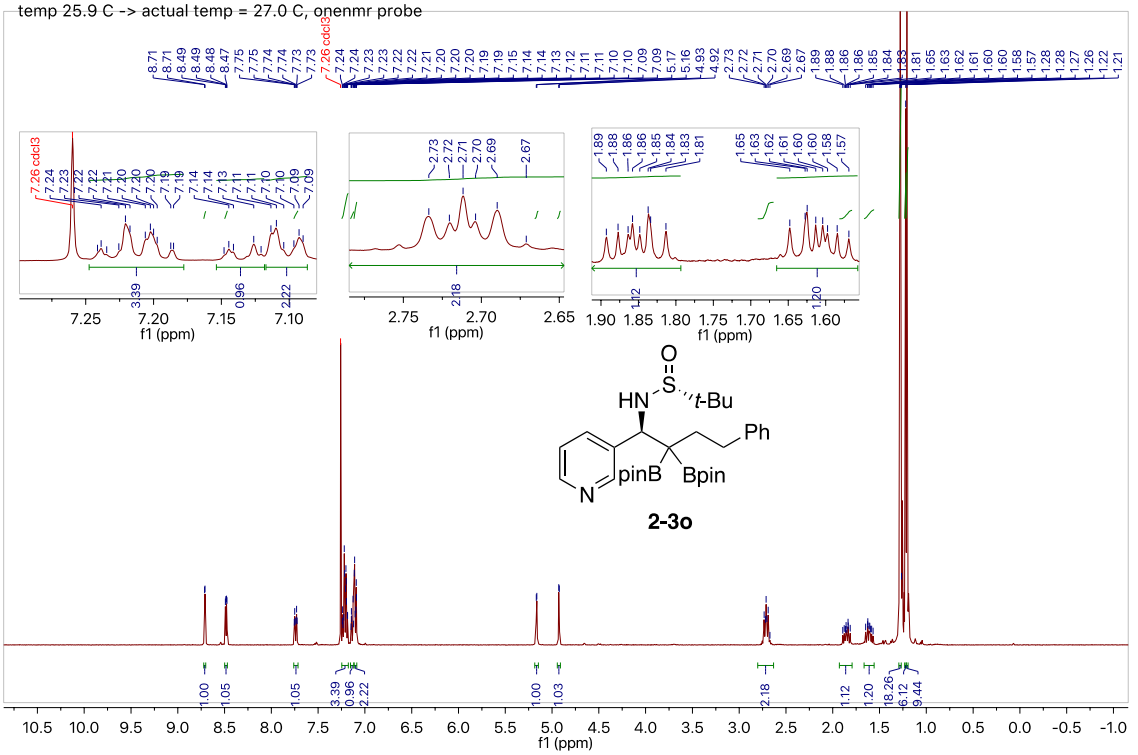


2018.04.01.u5_XLH-VIII-157_loc1_17.19_C13_1D; XLH-VIII-157; 125.688 MHz C13{H1} 1D in cd3cn
temp 27.7 C -> actual temp = 27.0 C, colddual probe

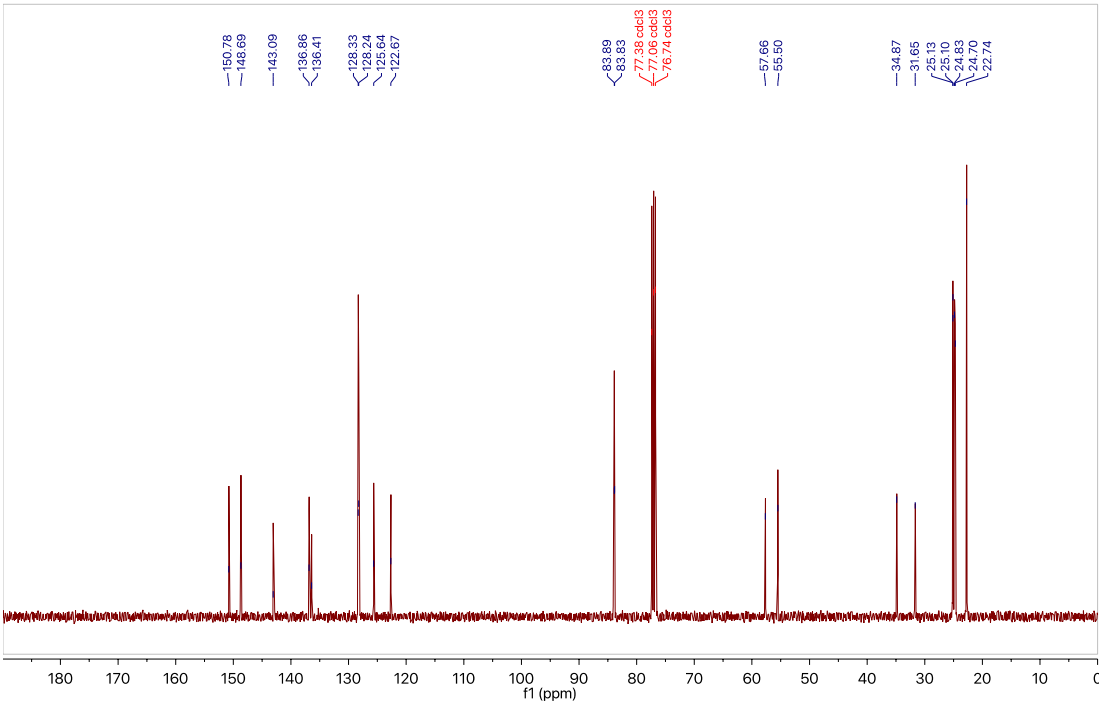


^{1}H NMR and ^{13}C NMR of β-sulfinimido *gem*-bis(boronate) 2-3o:

XLH-VIII-109_H1_1D; 399.978 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 25.9 C -> actual temp = 27.0 C, onenmr probe

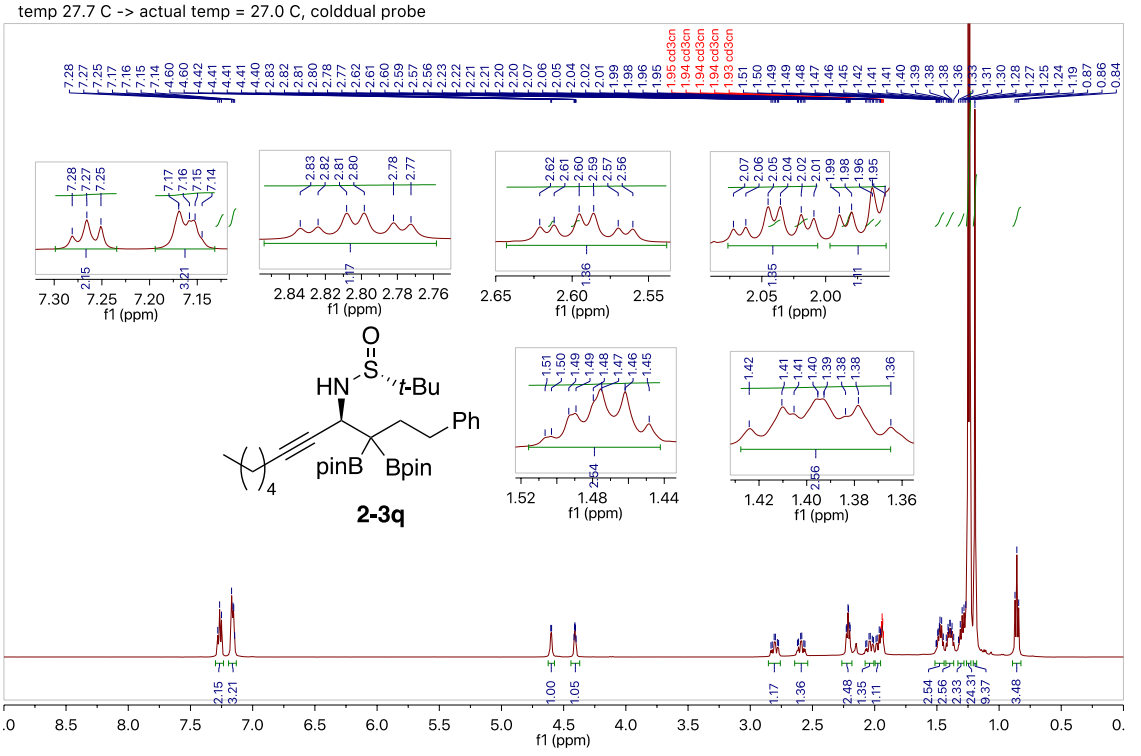


XLH-VIII-109-CDCl3_C13_1D; 100.539 MHz C13{H1} 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 26.5 C -> actual temp = 27.0 C, autoxdb probe

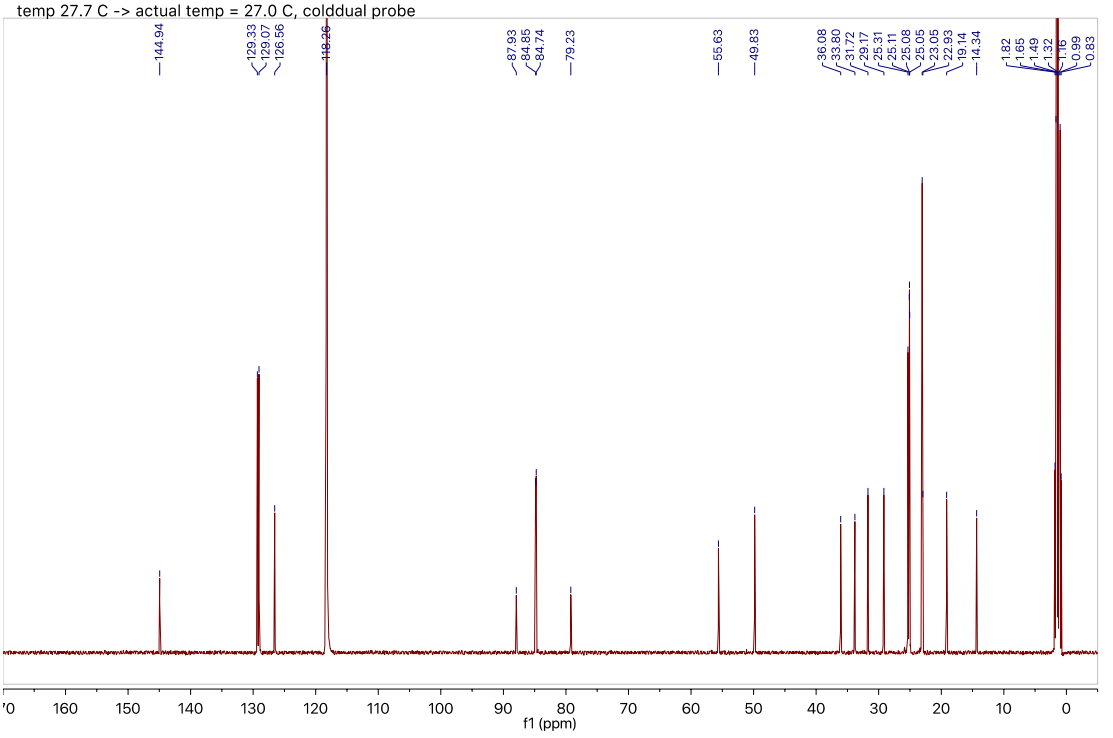


^{1}H NMR and ^{13}C NMR of β-sulfinimido *gem*-bis(boronate) 2-3q:

2018.03.27.u5_XLH-VIII-173_loc8_16.26_H1_1D; XLH-VIII-173; 499.800 MHz H1 1D in cd3cn
temp 27.7 C -> actual temp = 27.0 C, colddual probe

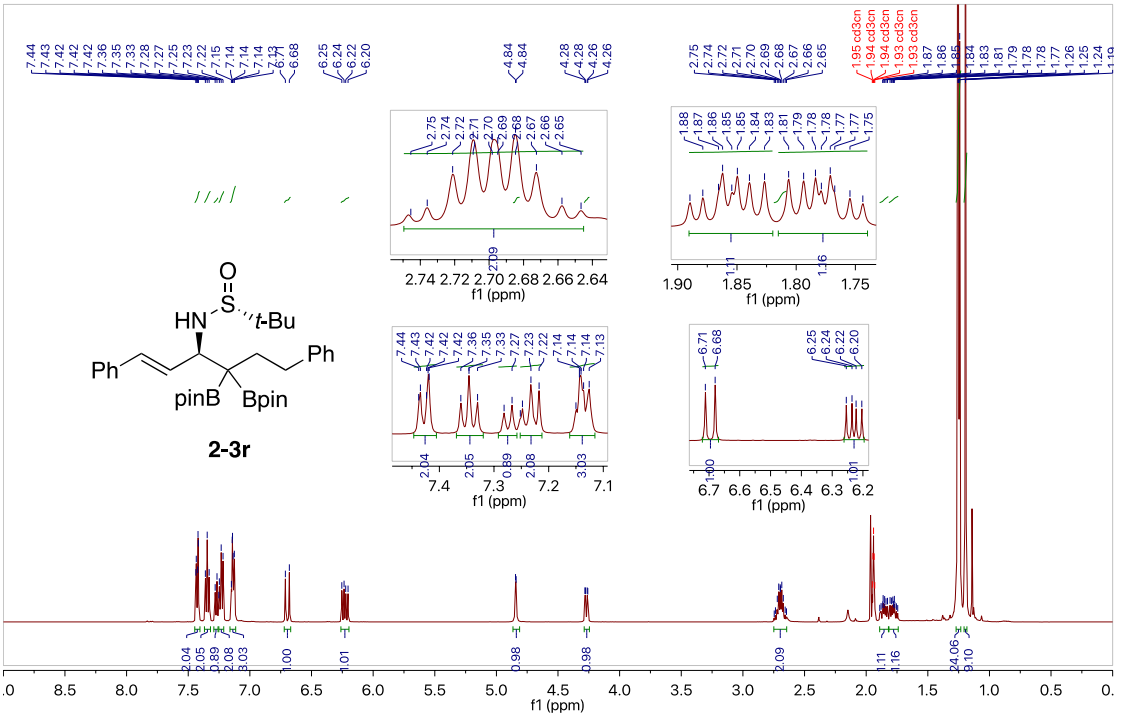


2018.03.27.u5_XLH-VIII-173_loc8_16.27_C13_1D; XLH-VIII-173; 125.688 MHz C13{H1} 1D in cd3cn
temp 27.7 C -> actual temp = 27.0 C, colddual probe

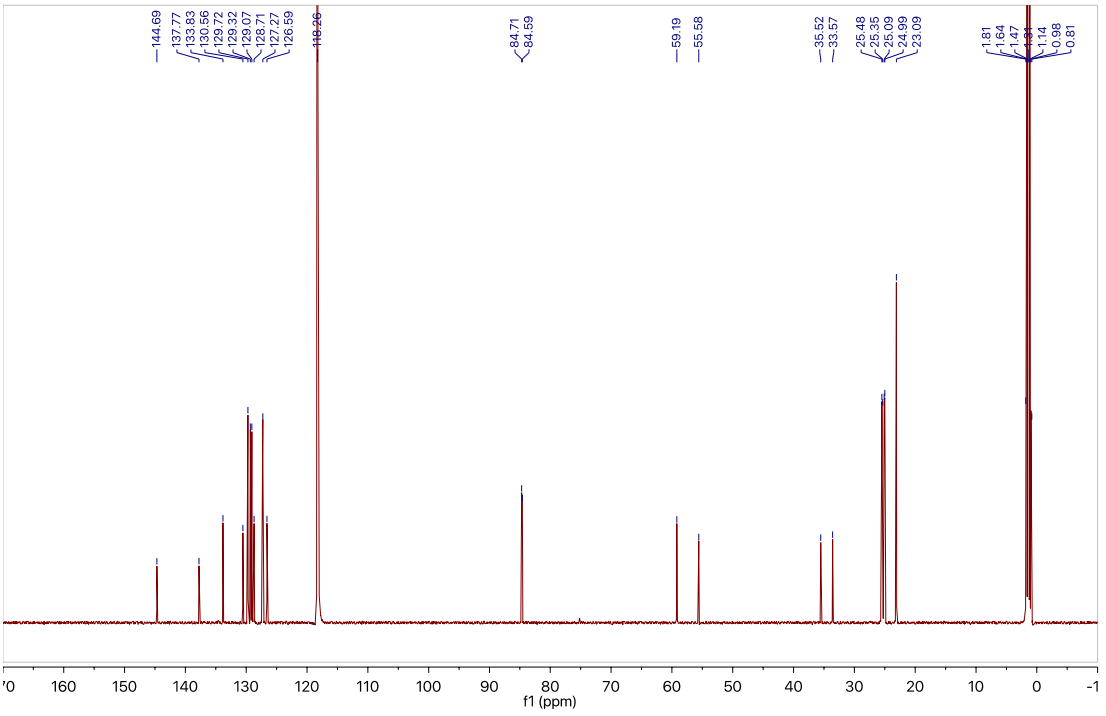


^{1}H NMR and ^{13}C NMR of β-sulfinimido *gem*-bis(boronate) 2-3r:

2018.03.27.u5_XLH-VIII-165_loc11_11.44_H1_1D; XLH-VIII-165; 499.800 MHz H1 1D in cd3cn
temp 27.7 C -> actual temp = 27.0 C, colddual probe

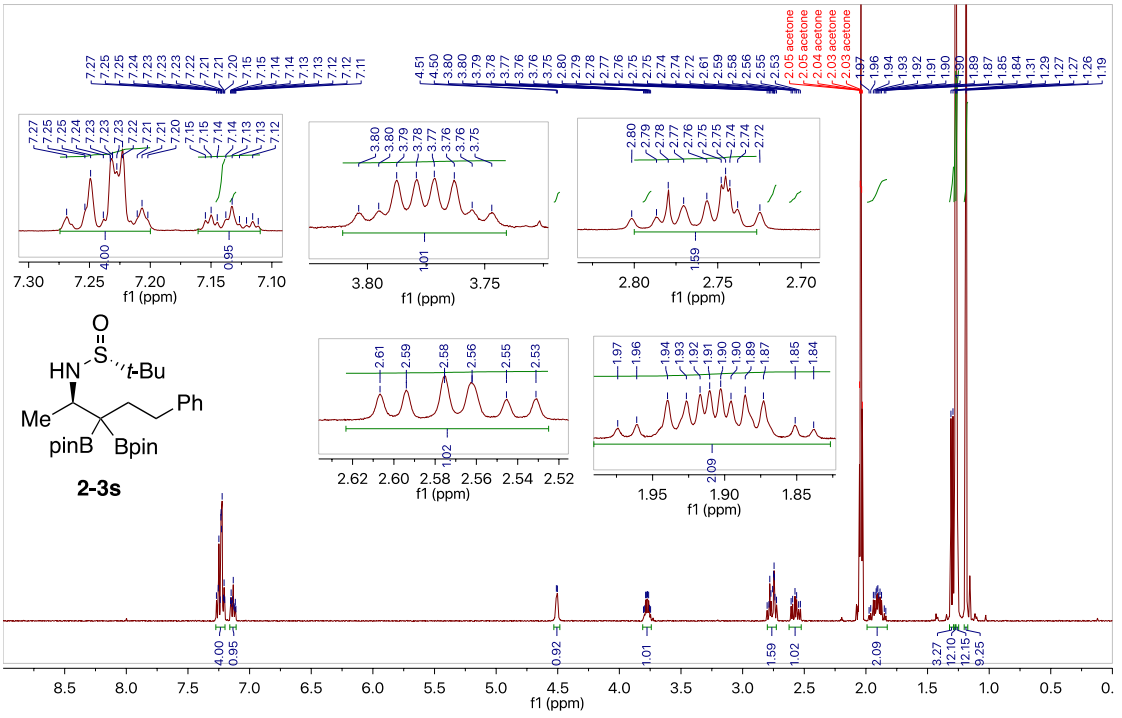


2018.03.27.u5_XLH-VIII-165_loc11_11.45_C13_1D; XLH-VIII-165; 125.688 MHz C13{H1} 1D in cd3cn
temp 27.7 C -> actual temp = 27.0 C, colddual probe

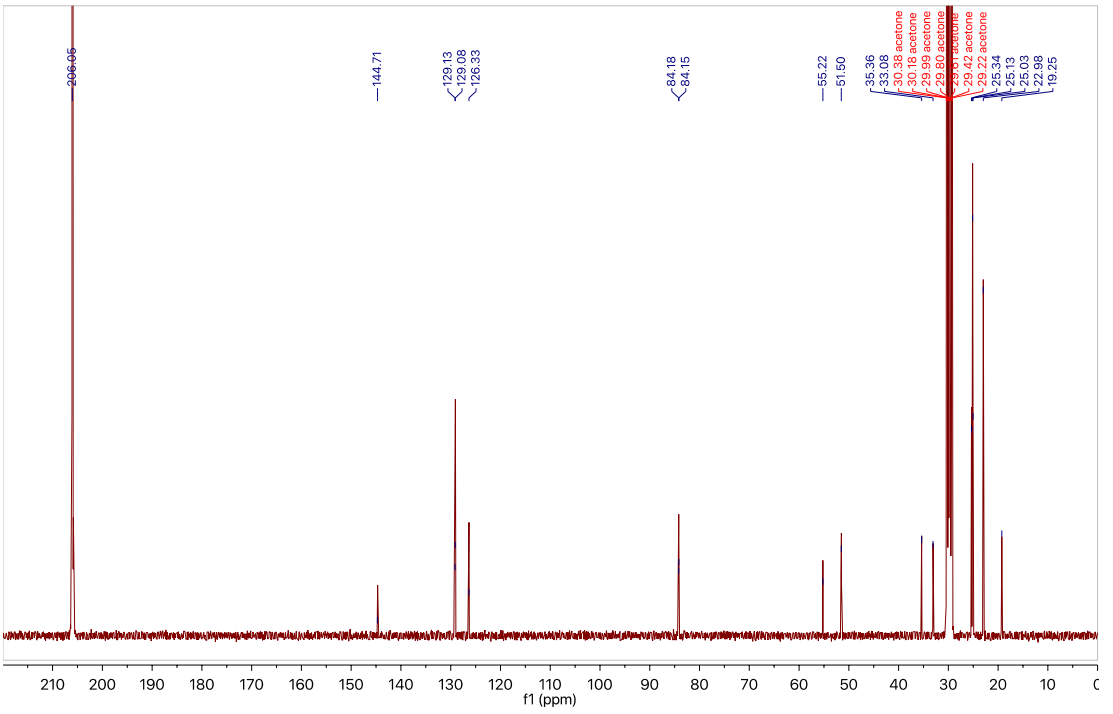


^{1}H NMR and ^{13}C NMR of β-sulfinimido *gem*-bis(boronate) 2-3s:

XLH-VII-185-acetone_H1_1D; 399.980 MHz H1 1D in acetone (ref. to acetone @ 2.04 ppm)
temp 25.9 C -> actual temp = 27.0 C, onenmr probe

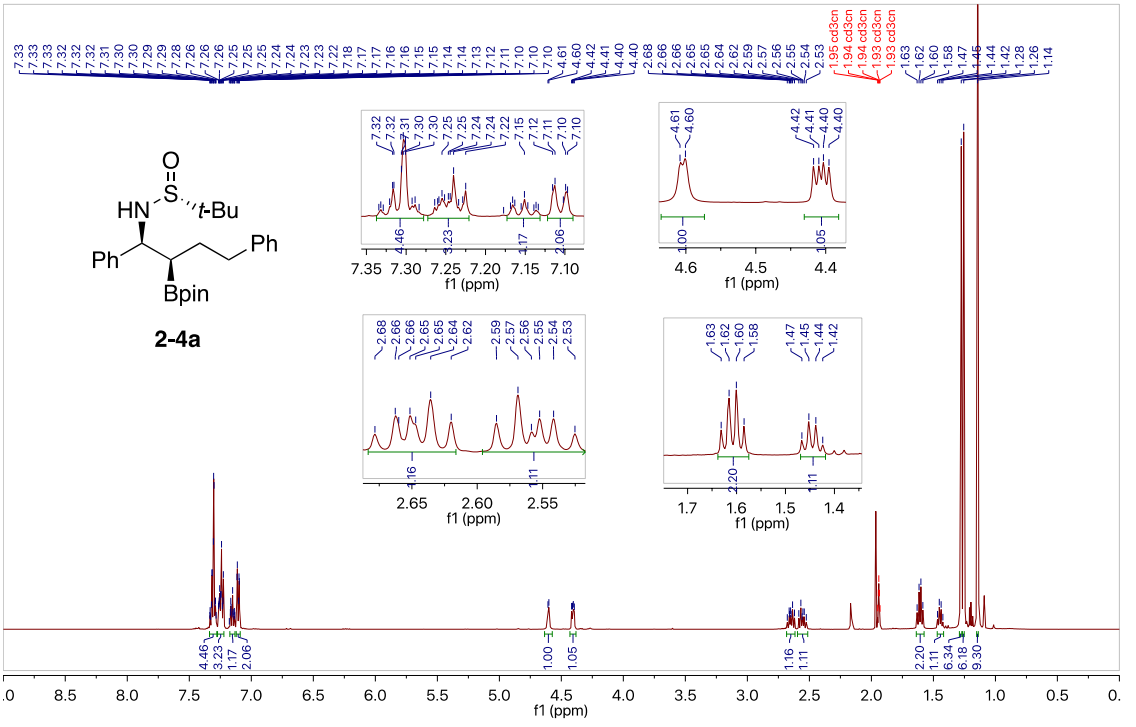


XLH-VII-185-acetone_18.51_C13_1D; 100.586 MHz C13{H1} 1D in acetone (ref. to acetone @ 29.8 ppm)
temp 25.9 C -> actual temp = 27.0 C, onenmr probe

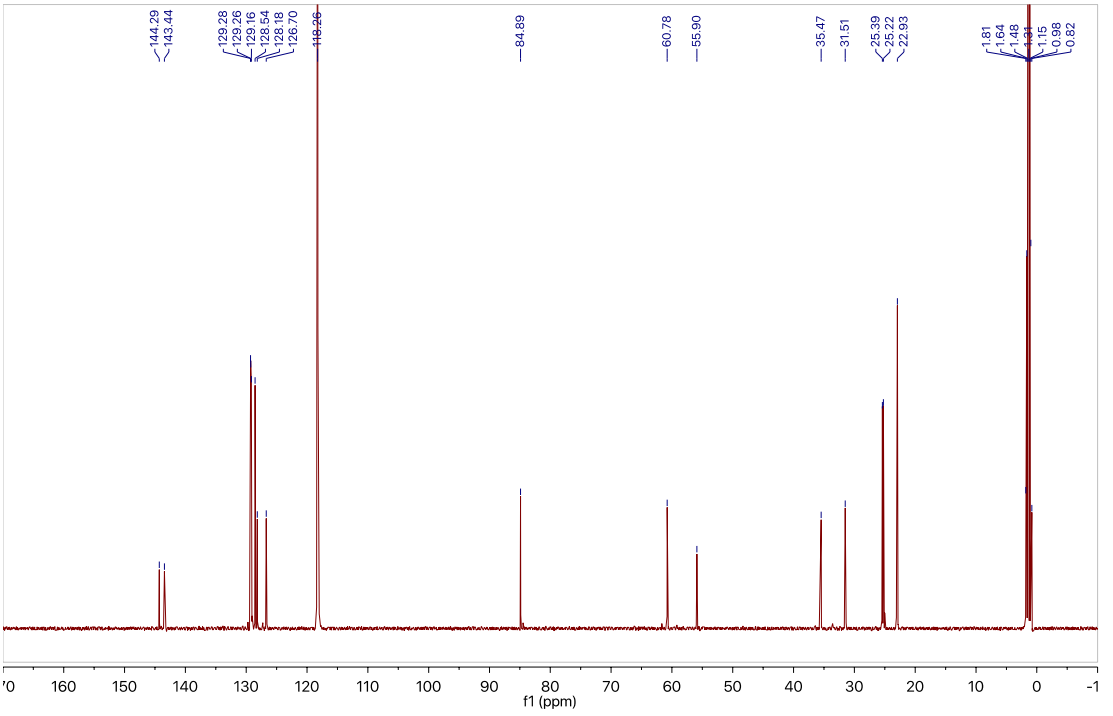


^{1}H NMR and ^{13}C NMR of β-amino alkylboronate 2-4a:

2018.03.27.u5_XLH-09-59_loc9_23.09_H1_1D; XLH-09-59; 499.800 MHz H1 1D in cd3cn
temp 27.7 C -> actual temp = 27.0 C, colddual probe

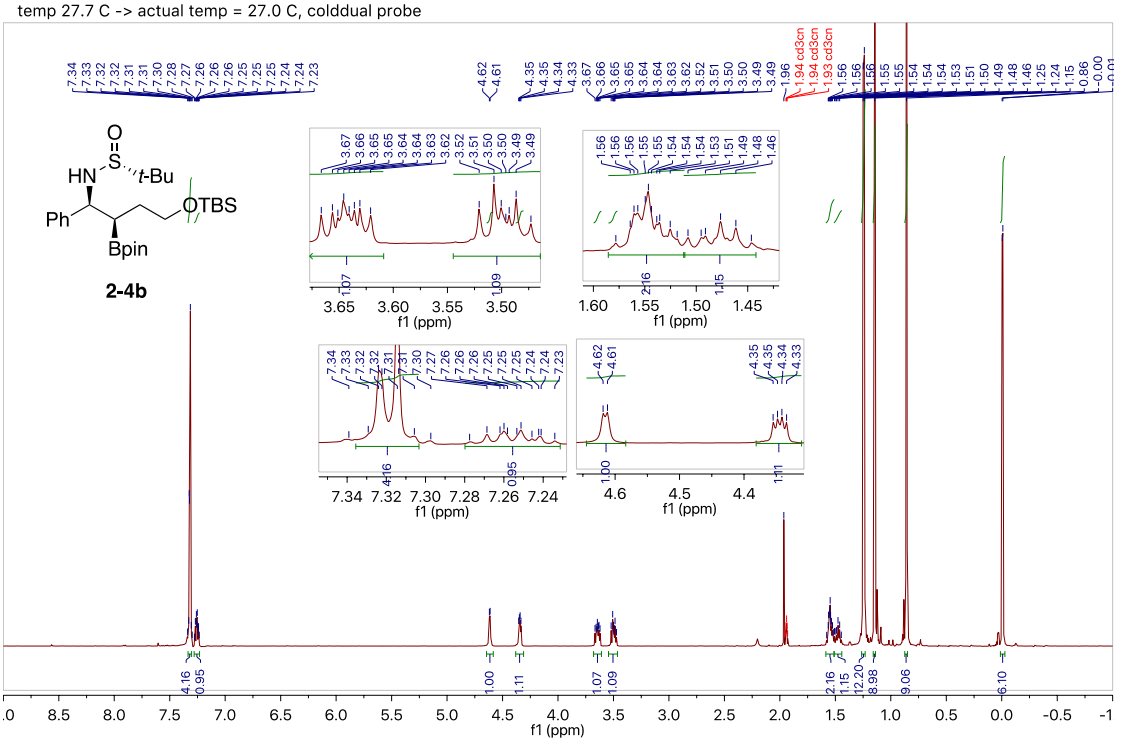


2018.03.27.u5_XLH-09-59_loc9_23.10_C13_1D; XLH-09-59; 125.688 MHz C13{H1} 1D in cd3cn
temp 27.7 C -> actual temp = 27.0 C, colddual probe

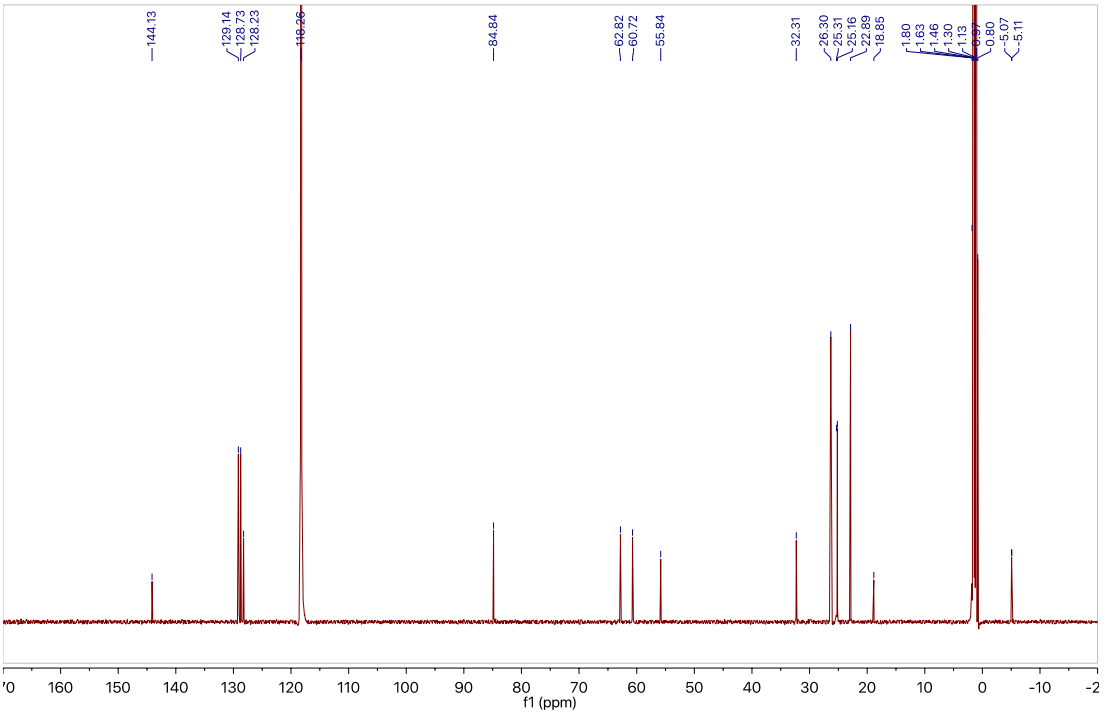


^{1}H NMR and ^{13}C NMR of β-amino alkylboronate 2-4b:

2018.03.29.u5_XLH-VII-141_loc1_07.39_H1_1D; XLH-VII-141； 499.800 MHz H1 1D in cd3cn
temp 27.7 C -> actual temp = 27.0 C, colddual probe

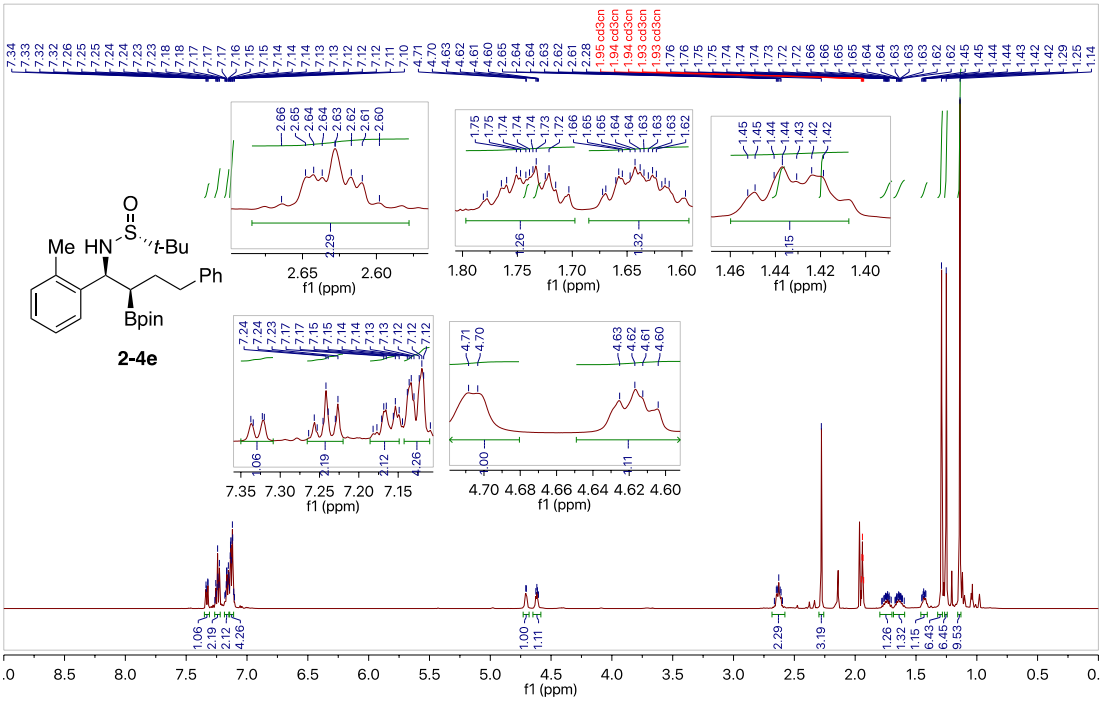


2018.04.09.u5_XLH-VII-141_loc10_16.43_C13_1D; XLH-VII-141; 125.688 MHz C13{H1} 1D in cd3cn
temp 27.7 C -> actual temp = 27.0 C, colddual probe

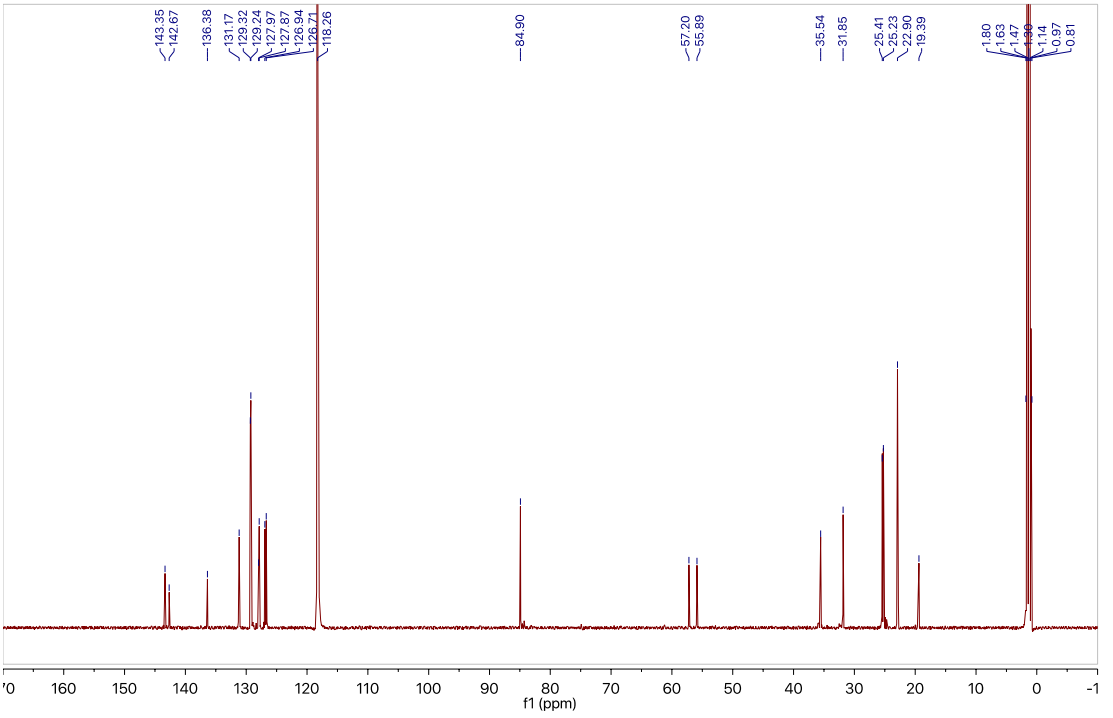


^{1}H NMR and ^{13}C NMR of β-amino alkylboronate 2-4e:

2018.03.28.u5_XLH-VIII-91_loc8_14.34_H1_1D; XLH-VIII-91; 499.800 MHz H1 1D in cd3cn
temp 27.7 C -> actual temp = 27.0 C, colddual probe

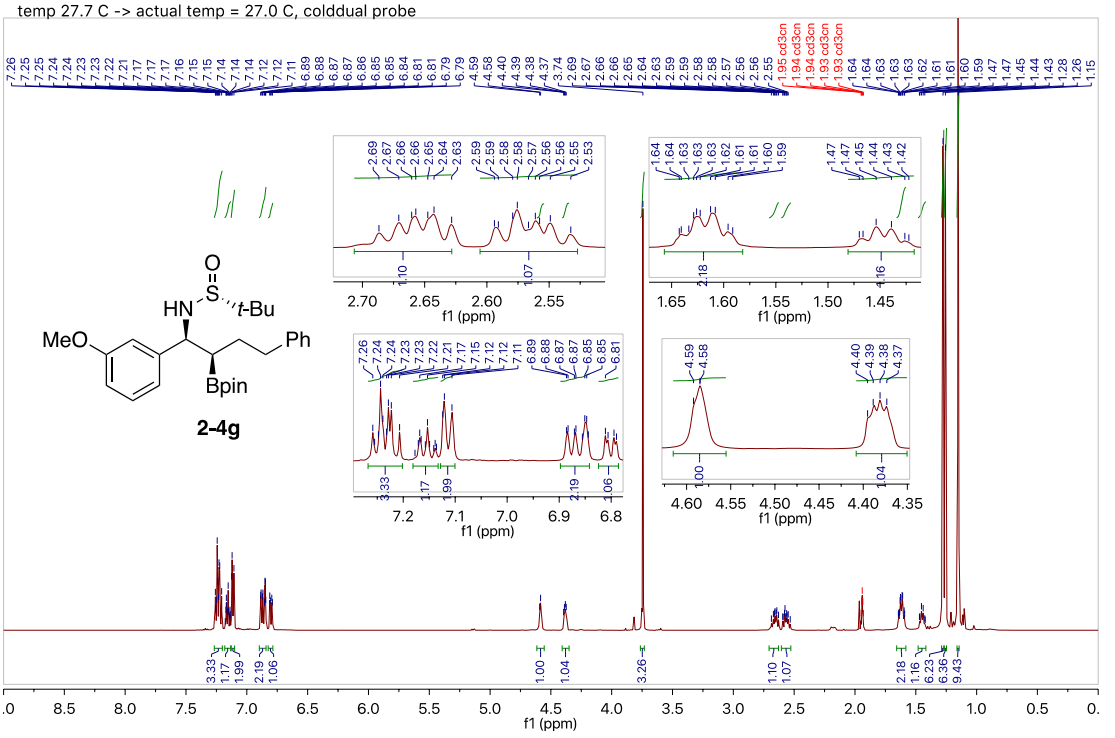


2018.03.28.u5_XLH-VIII-91_loc8_14.35_C13_1D; XLH-VIII-91; 125.688 MHz C13{H1} 1D in cd3cn
temp 27.7 C -> actual temp = 27.0 C, colddual probe

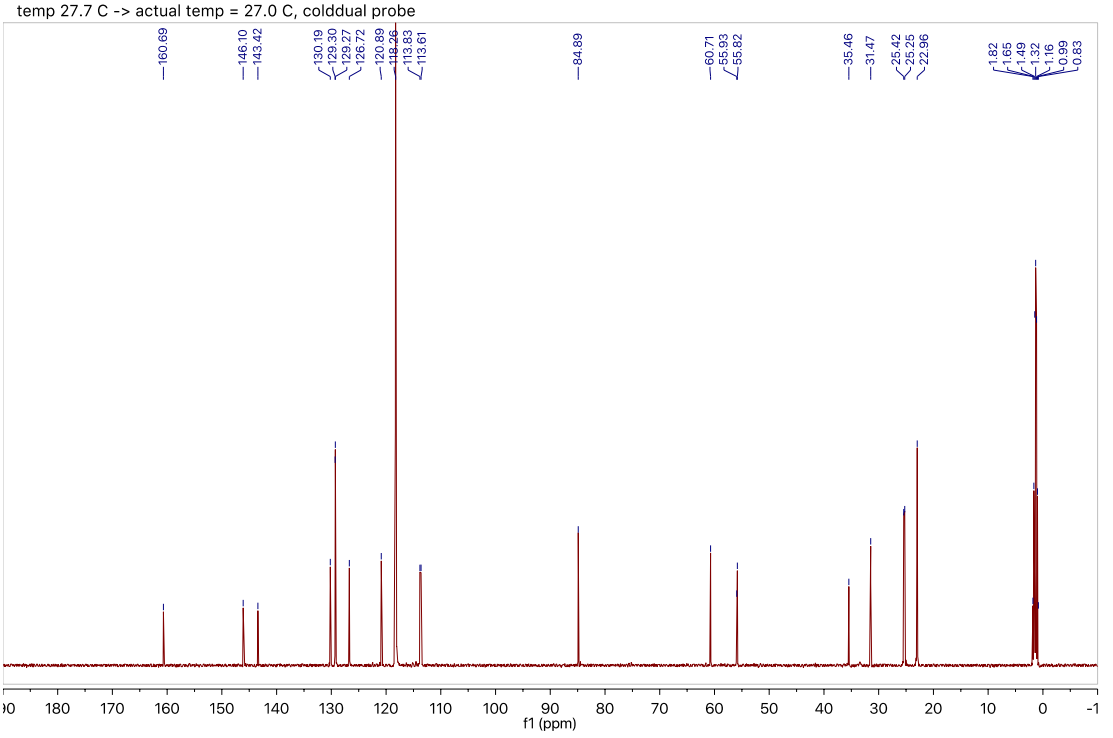


^{1}H NMR and ^{13}C NMR of β-amino alkylboronate 2-4g:

2018.03.27.u5_XLH-VIII-161_loc4_22.37_H1_1D; XLH-VIII-161; 499.800 MHz H1 1D in cd3cn
temp 27.7 C -> actual temp = 27.0 C, colddual probe

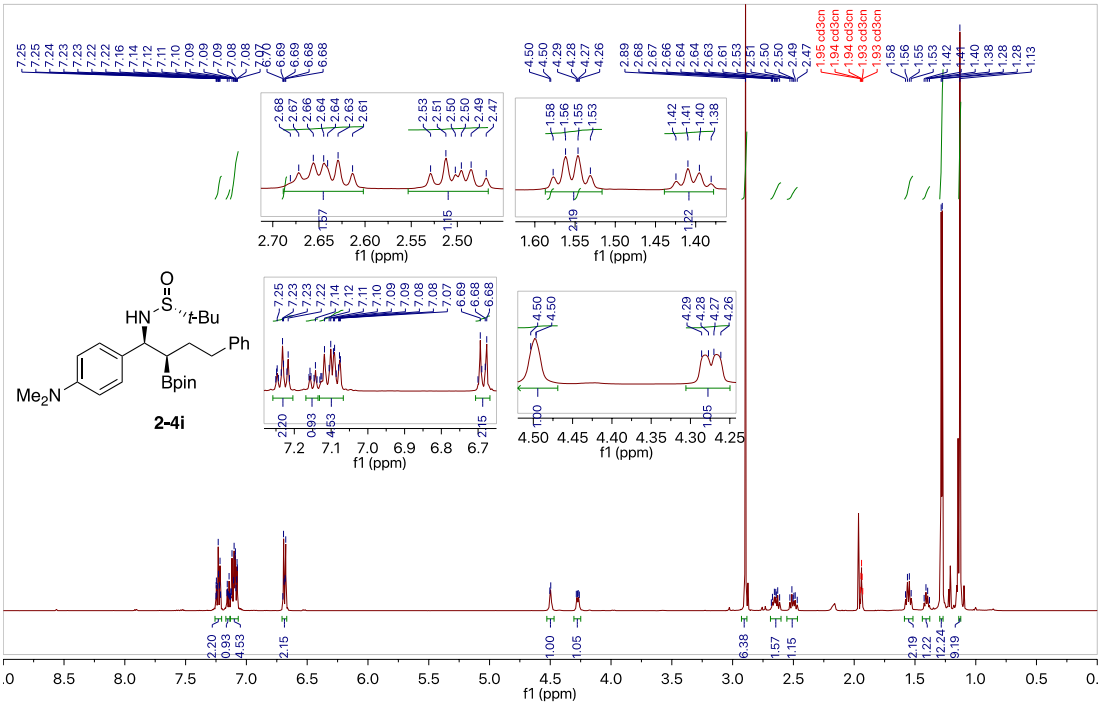


2018.03.27.u5_XLH-VIII-161_loc4_22.38_C13_1D; XLH-VIII-161; 125.688 MHz C13{H1} 1D in cd3cn
temp 27.7 C -> actual temp = 27.0 C, colddual probe

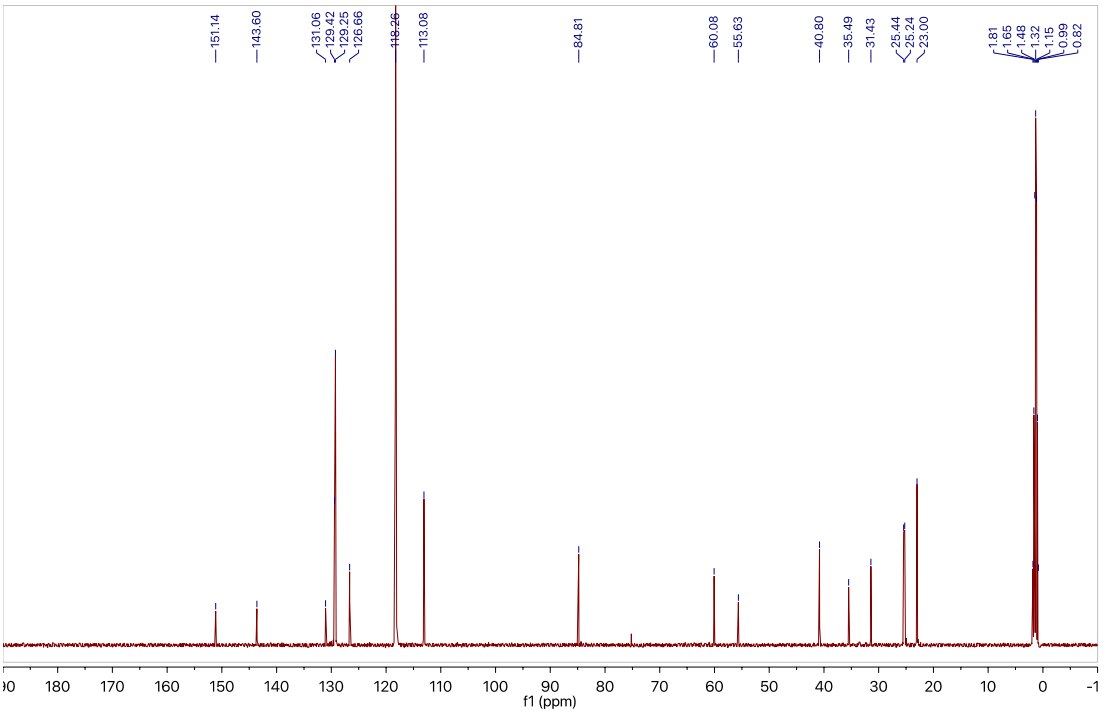


^{1}H NMR and ^{13}C NMR of β-amino alkylboronate 2-4i:

2018.03.29.u5_XLH-VIII-199 loc8_08.10_H1_1D; 499.800 MHz H1 1D in cd3cn
temp 27.7 C -> actual temp = 27.0 C, colddual probe

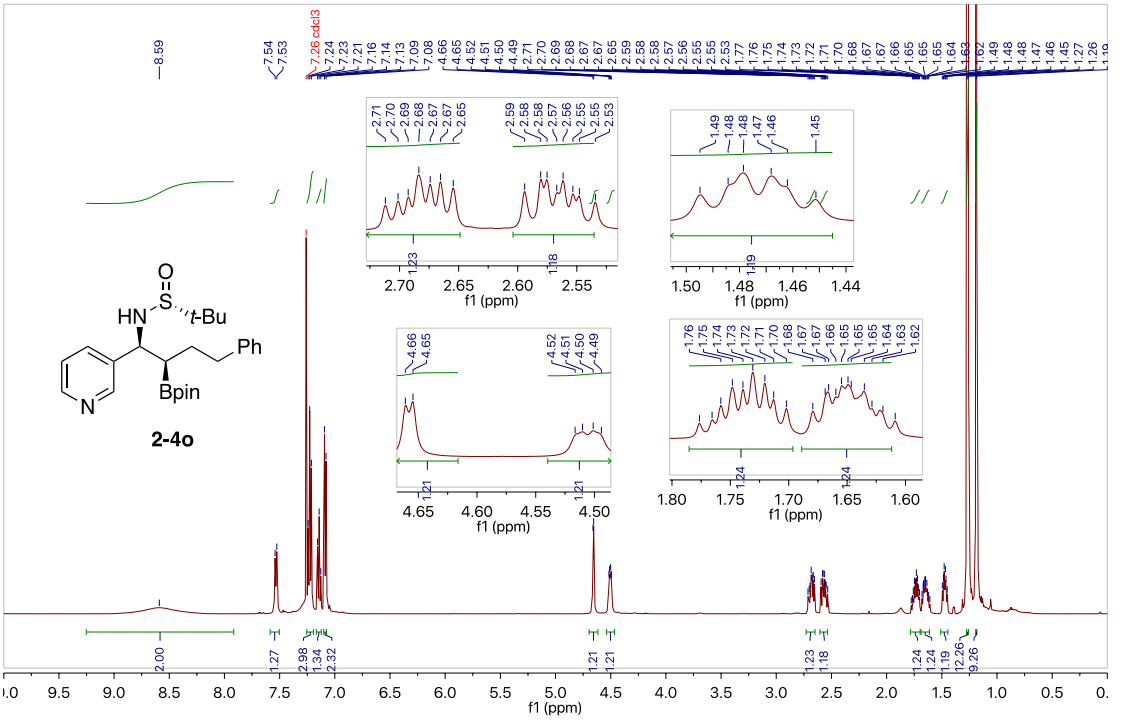


2018.03.29.u5_XLH-VIII-199_loc8_08.11_C13_1D; 125.688 MHz C13{H1} 1D in cd3cn
temp 27.7 C -> actual temp = 27.0 C, colddual probe

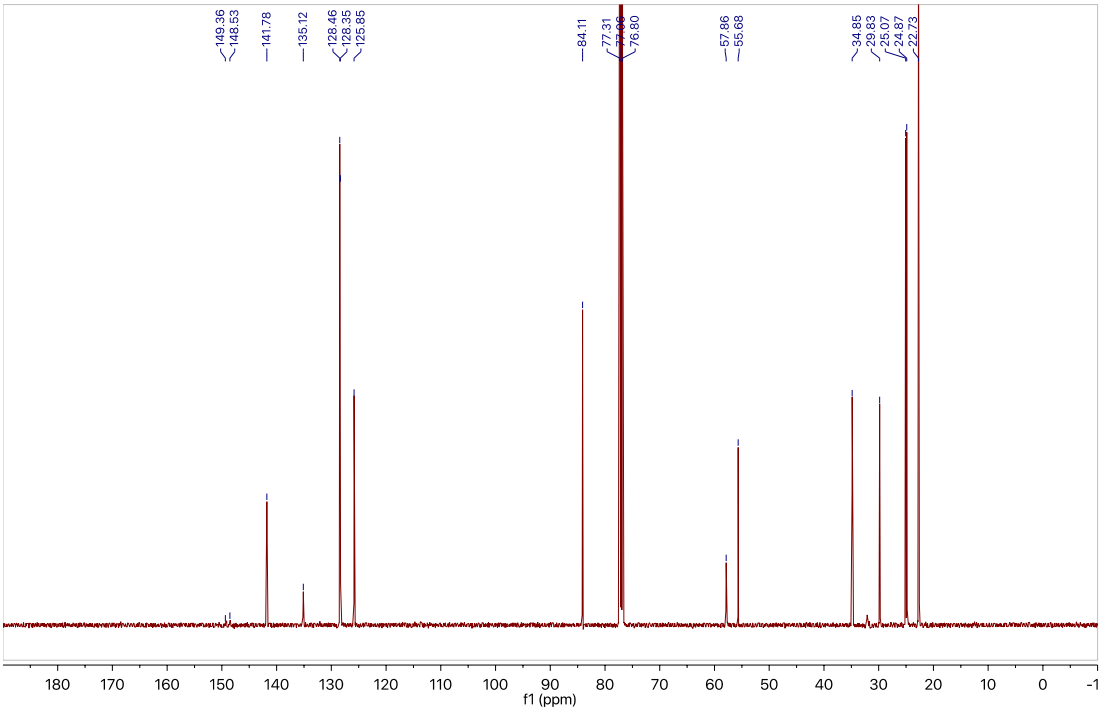


^{1}H NMR and ^{13}C NMR of β-amino alkylboronate 2-4o:

2018.03.29.u5_XLH-VIII-125_loc2_20.03_H1_1D; XLH-VIII-125; 499.797 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe

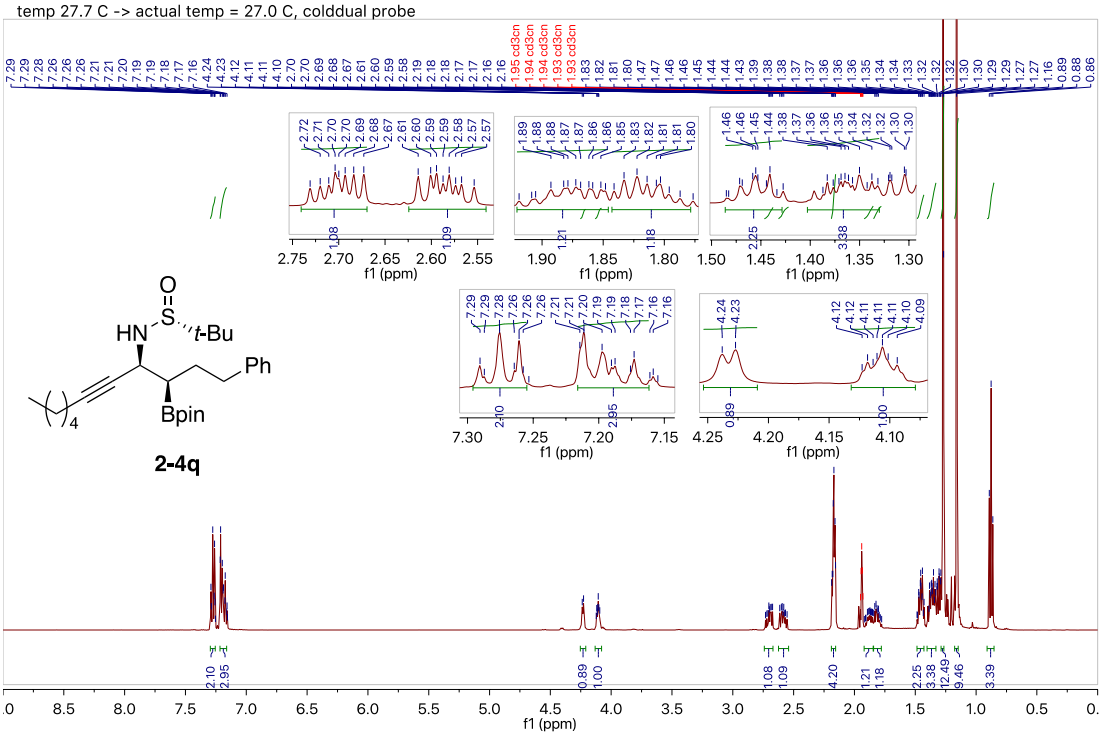


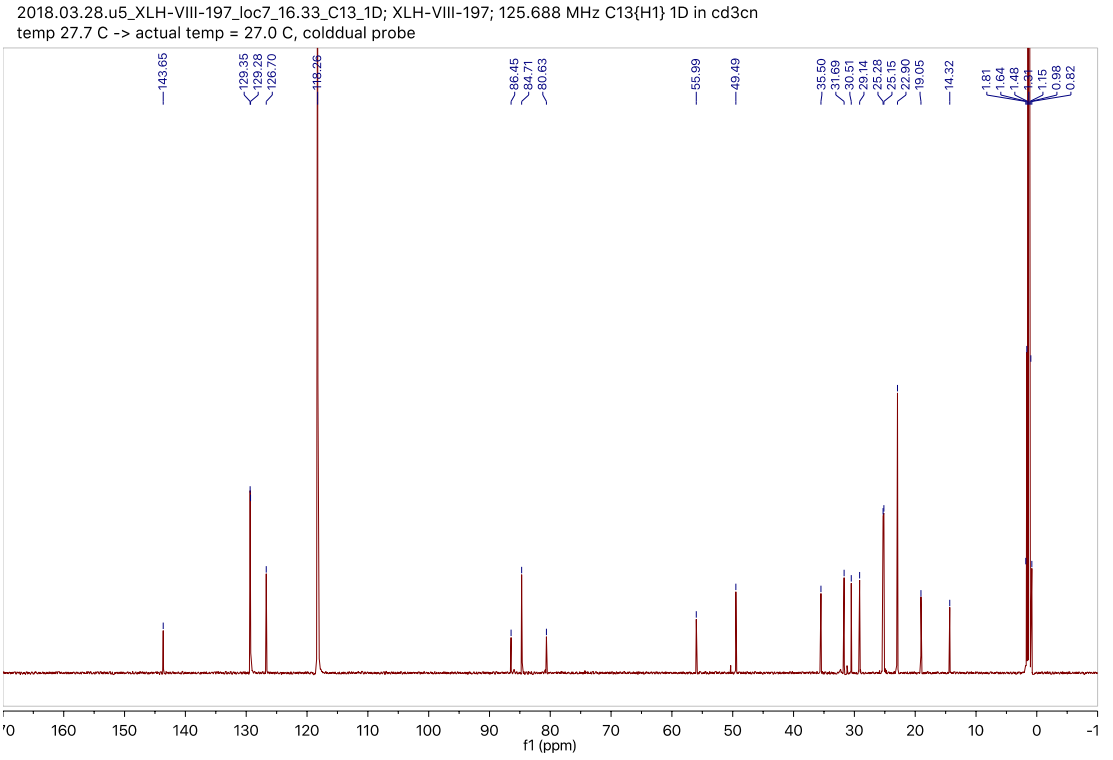
2018.03.30.i5_XLH-VIII-125_09.30_C13_1D; 125.266 MHz C13{H1} 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 26.9 C -> actual temp = 27.0 C, autoxdb probe



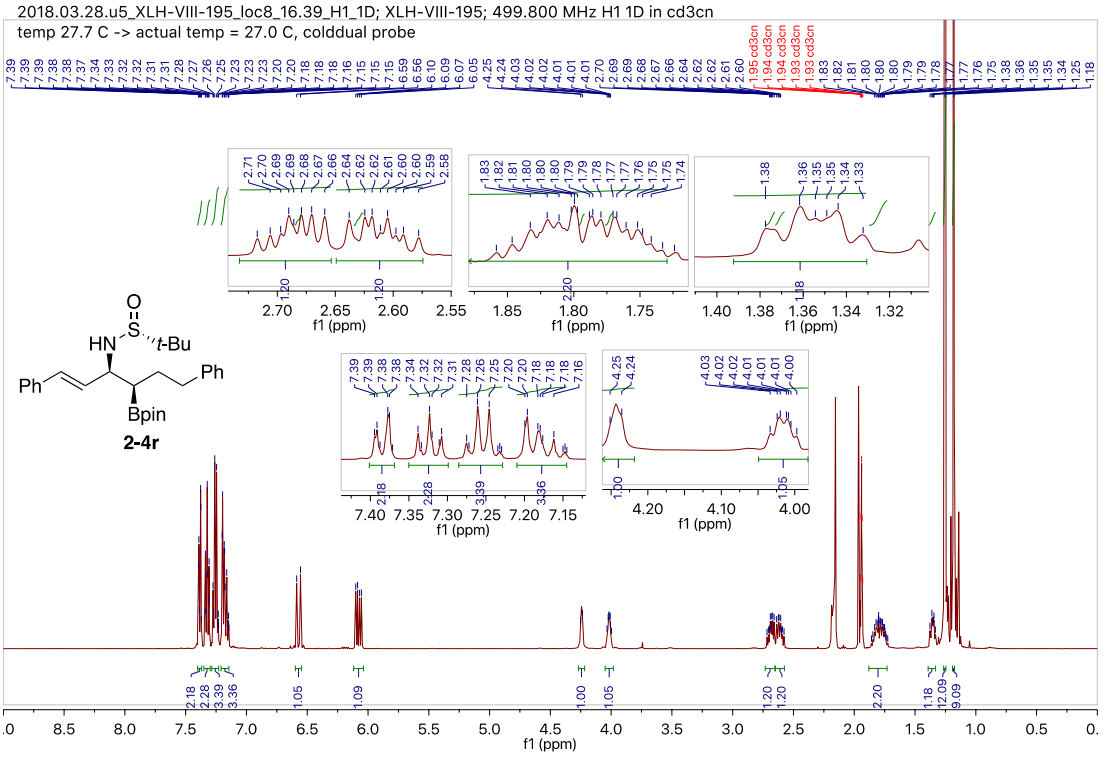
^{1}H NMR and ^{13}C NMR of β-amino alkylboronate 2-4q:

2018.03.28.u5_XLH-VIII-197_loc7_16.31_H1_1D; XLH-VIII-197; 499.800 MHz H1 1D in cd3cn
temp 27.7 C -> actual temp = 27.0 C, colddual probe

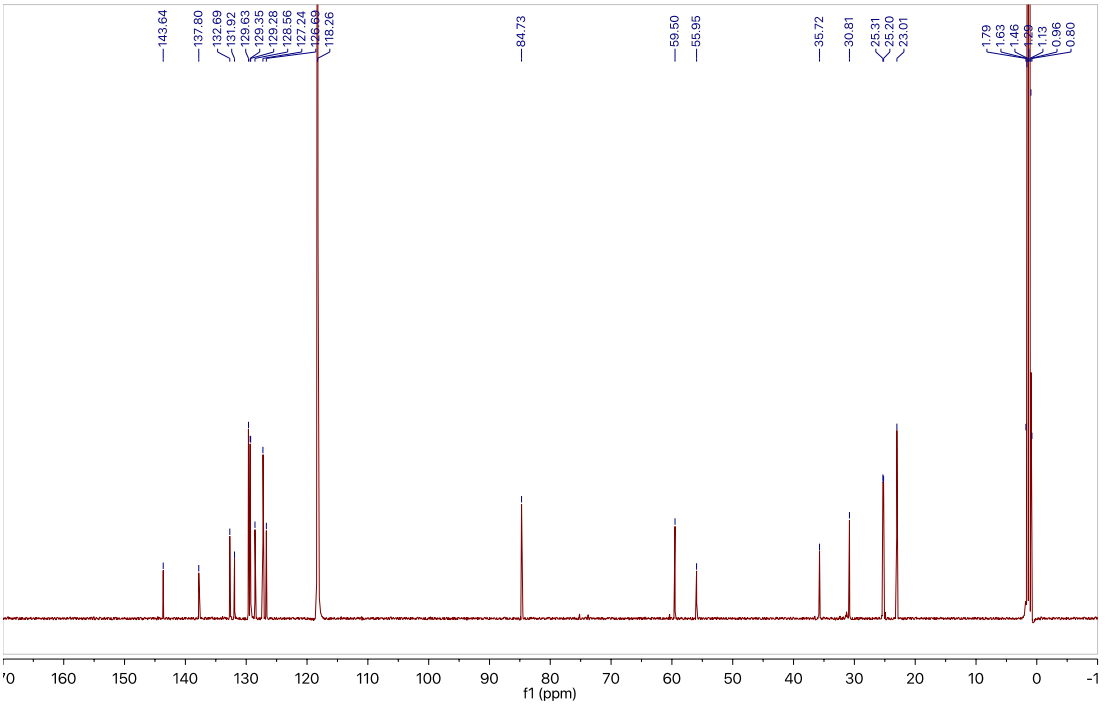




^{1}H NMR and ^{13}C NMR of β-amino alkylboronate 2-4r:

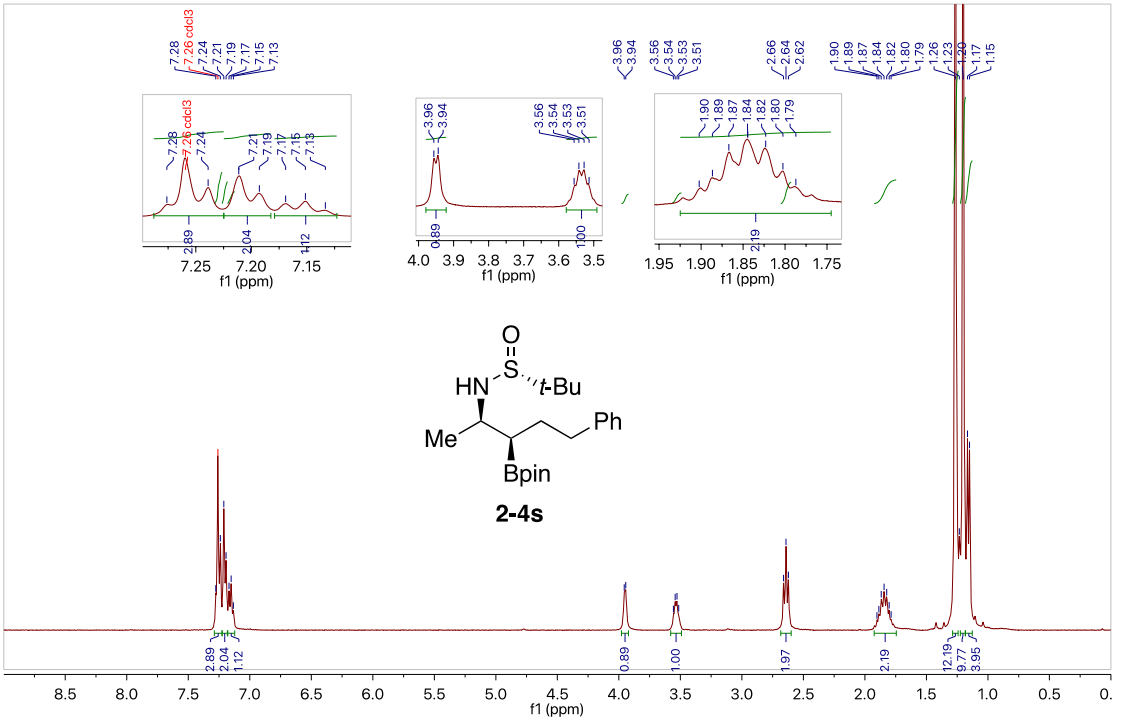


2018.03.28.u5_XLH-VIII-195_loc8_16.40_C13_1D; XLH-VIII-195; 125.688 MHz C13{H1} 1D in cd3cn
temp 27.7 C -> actual temp = 27.0 C, colddual probe

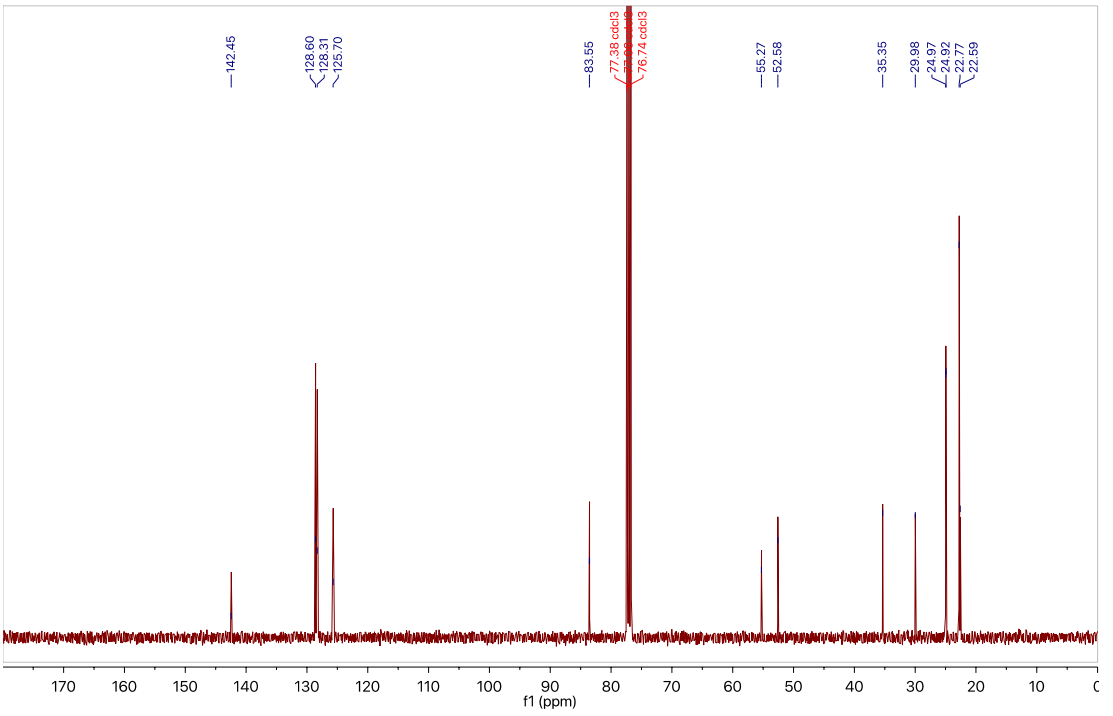


^{1}H NMR and ^{13}C NMR of β-amino alkylboronate 2-4s:

XLH-VIII-107_H1_1D; 399.978 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 25.9 C -> actual temp = 27.0 C, onenmr probe

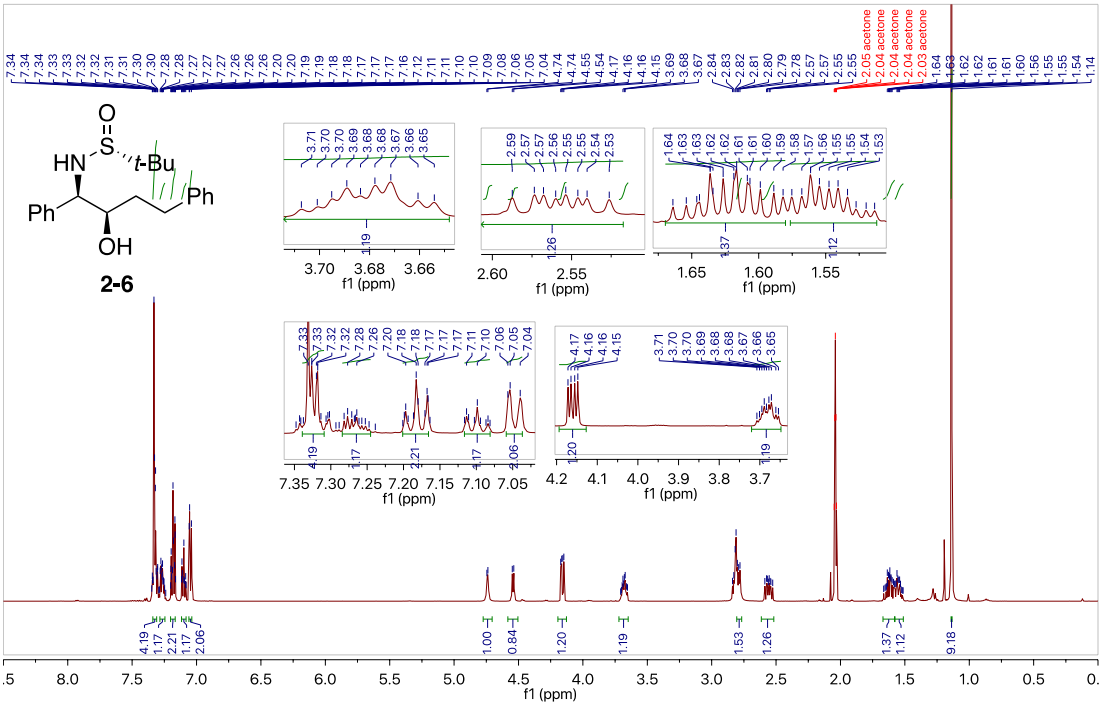


XLH-VIII-107_14.38_C13_1D; 100.586 MHz C13{H1} 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 25.9 C -> actual temp = 27.0 C, onenmr probe

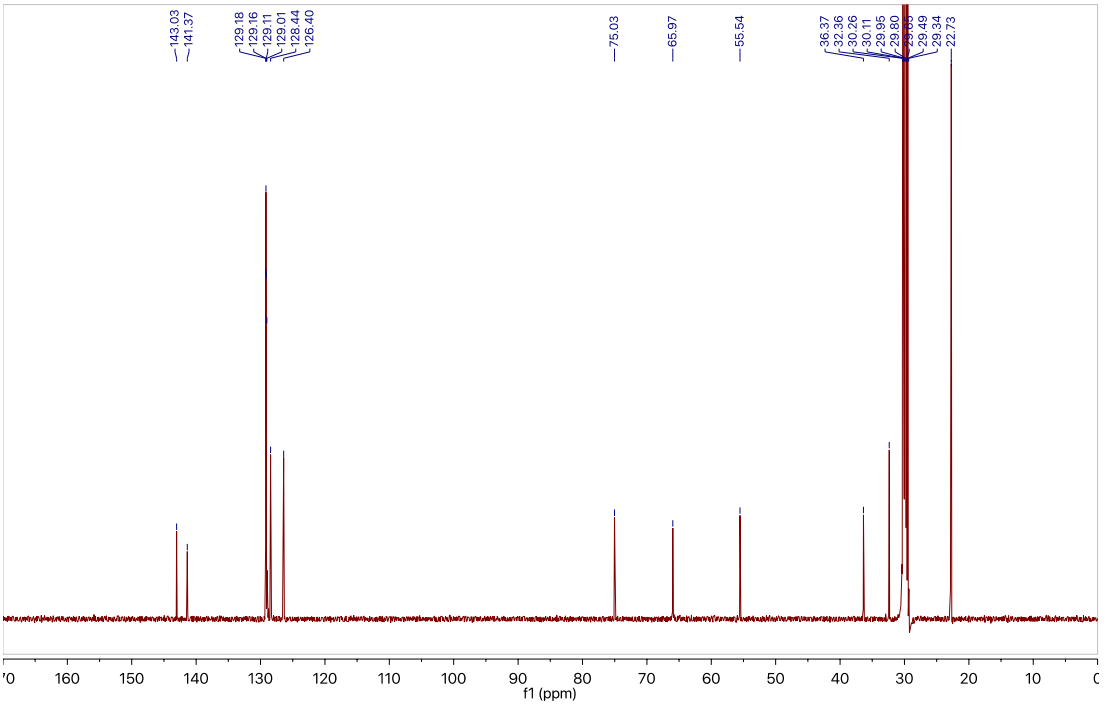


^{1}H NMR and ^{13}C NMR of β-amino alcohol 2-6:

2018.03.23.u5_XLH-VII-179_loc4_11.59_H1_1D; XLH-VII-179; 499.800 MHz H1 1D in acetone (ref. to acetone @ 2.04 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe

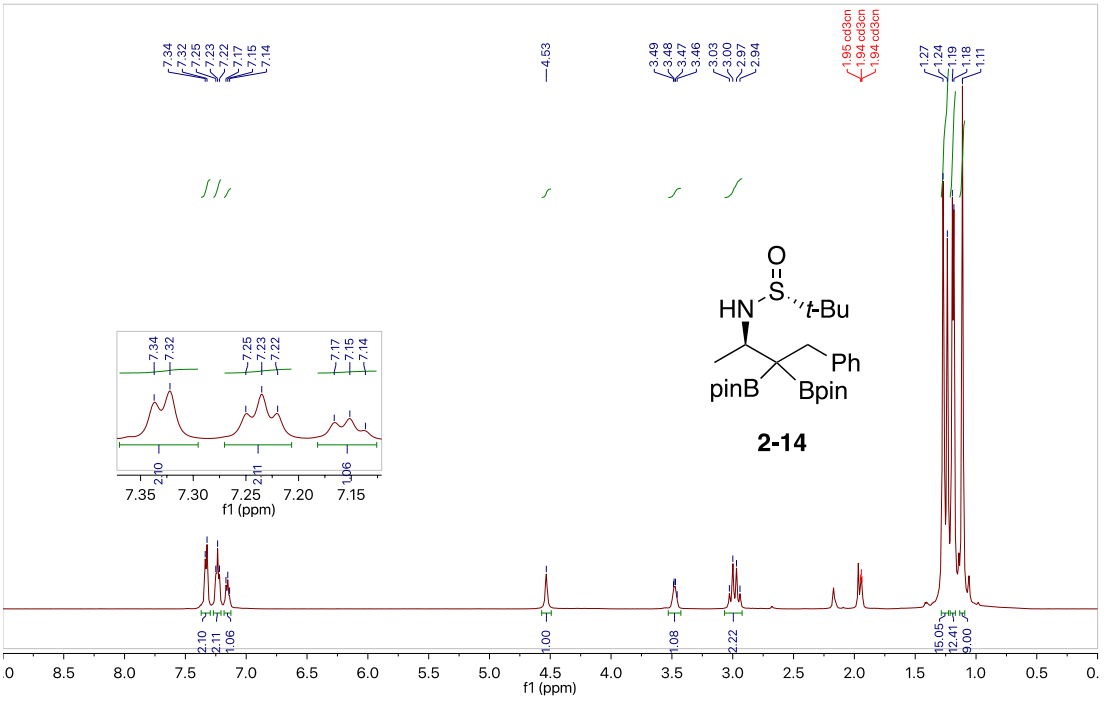


2018.03.23.u5_XLH-VII-179_loc4_10.19_C13_1D; XLH-VII-179; 125.689 MHz C13{H1} 1D in acetone (ref. to acetone @ 29.8 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe

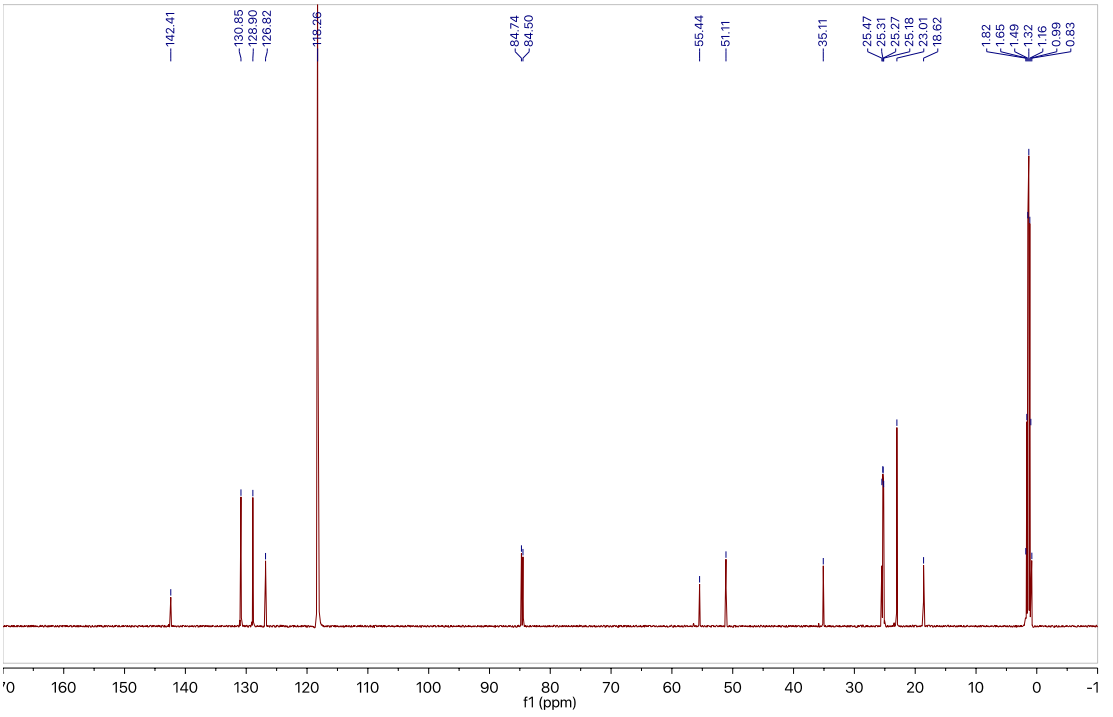


^{1}H NMR and ^{13}C NMR of β-sulfinimido *gem*-bis(boronate) 2-14:

2018.03.27.u5_XLH-09-11_loc6_16.05_H1_1D; XLH-09-11; 499.800 MHz H1 1D in cd3cn
temp 27.7 C -> actual temp = 27.0 C, colddual probe

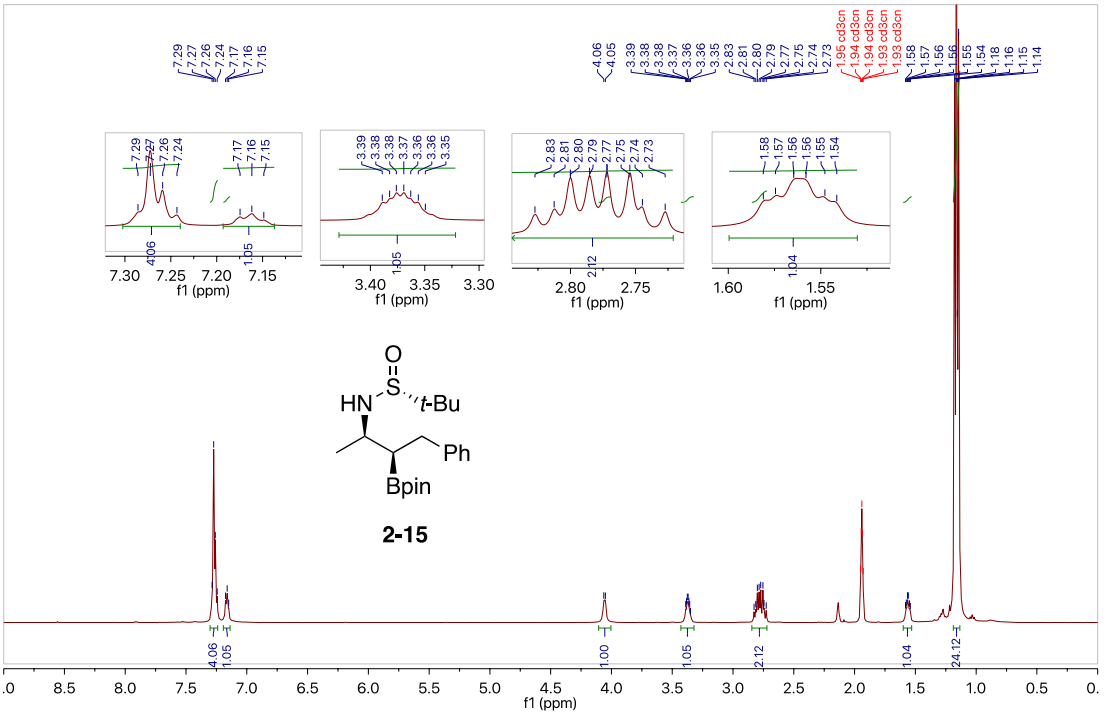


2018.03.27.u5_XLH-09-11_loc6_16.07_C13_1D; XLH-09-11; 125.688 MHz C13{H1} 1D in cd3cn
temp 27.7 C -> actual temp = 27.0 C, colddual probe

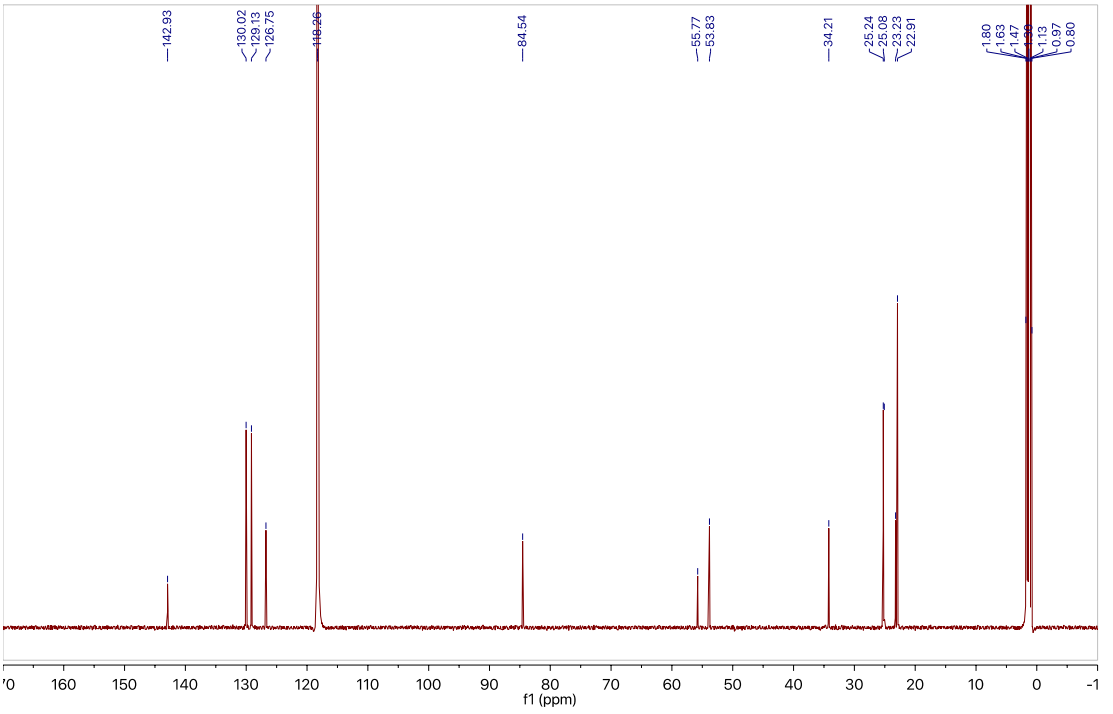


^{1}H NMR and ^{13}C NMR of β-amino alkylboronate 2-15:

2018.03.27.u5_XLH-09-19_loc9_16.34_H1_1D; XLH-09-19; 499.800 MHz H1 1D in cd3cn
temp 27.7 C -> actual temp = 27.0 C, colddual probe

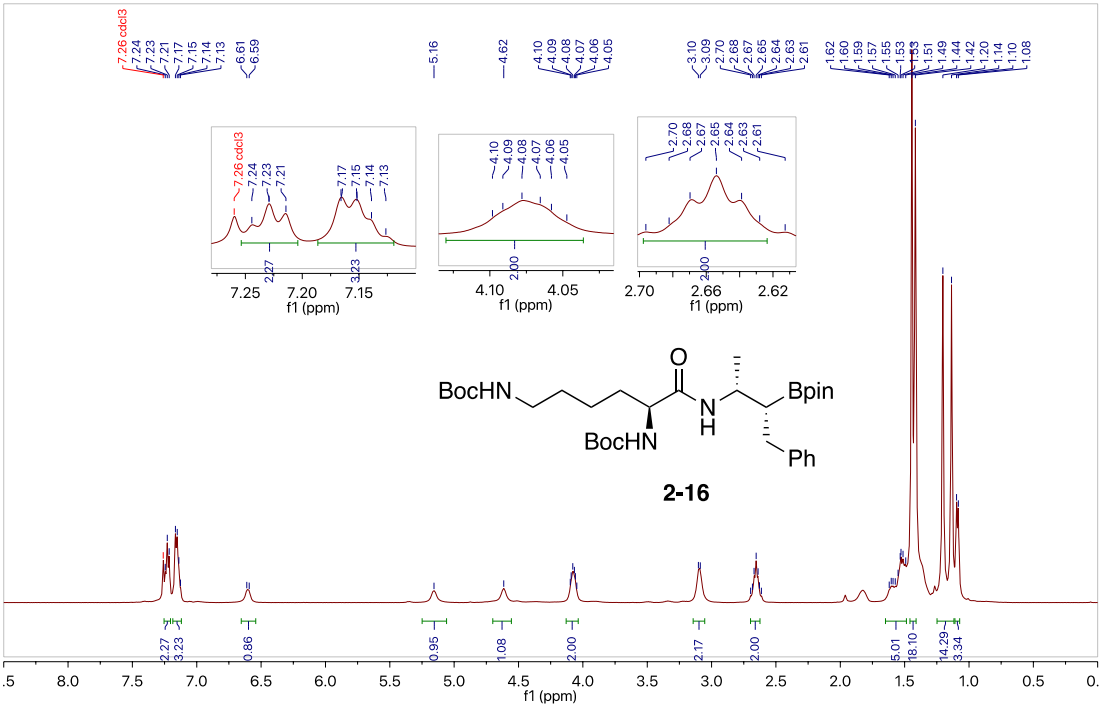


2018.03.27.u5_XLH-09-19_loc9_16.35_C13_1D; XLH-09-19; 125.688 MHz C13{H1} 1D in cd3cn
temp 27.7 C -> actual temp = 27.0 C, colddual probe

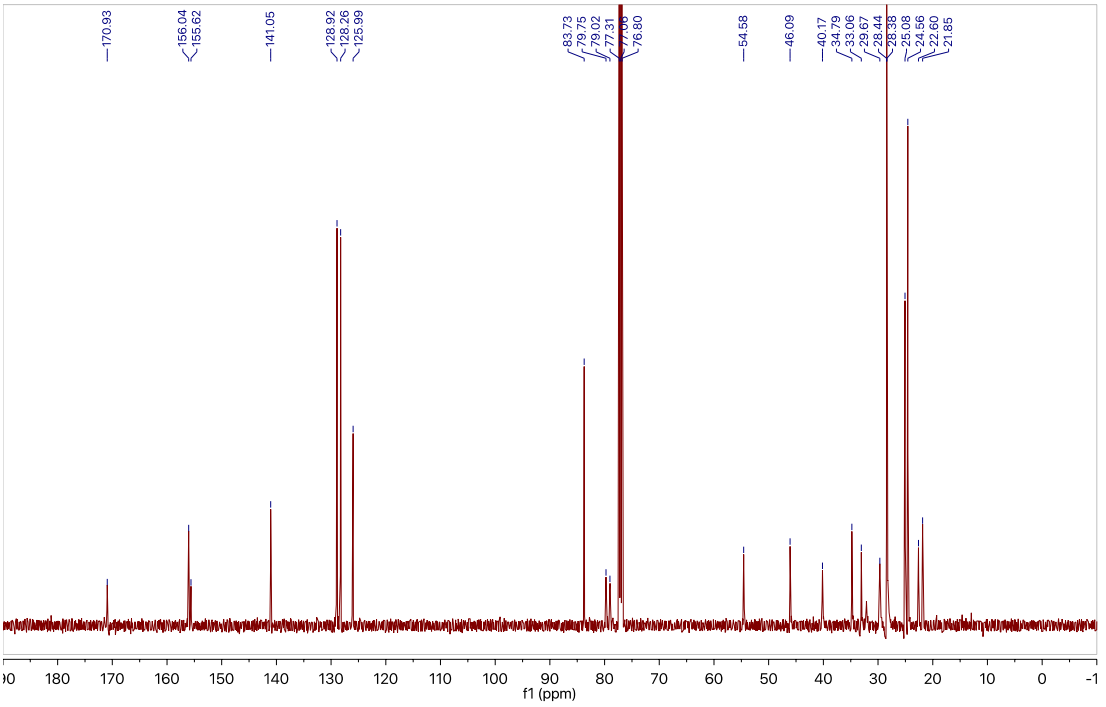


^{1}H NMR and ^{13}C NMR of β-amino alkylboronate 2-16:

2018.03.17.i5_XLH-09-119_H1_1D; 498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 26.9 C -> actual temp = 27.0 C, autoxdb probe

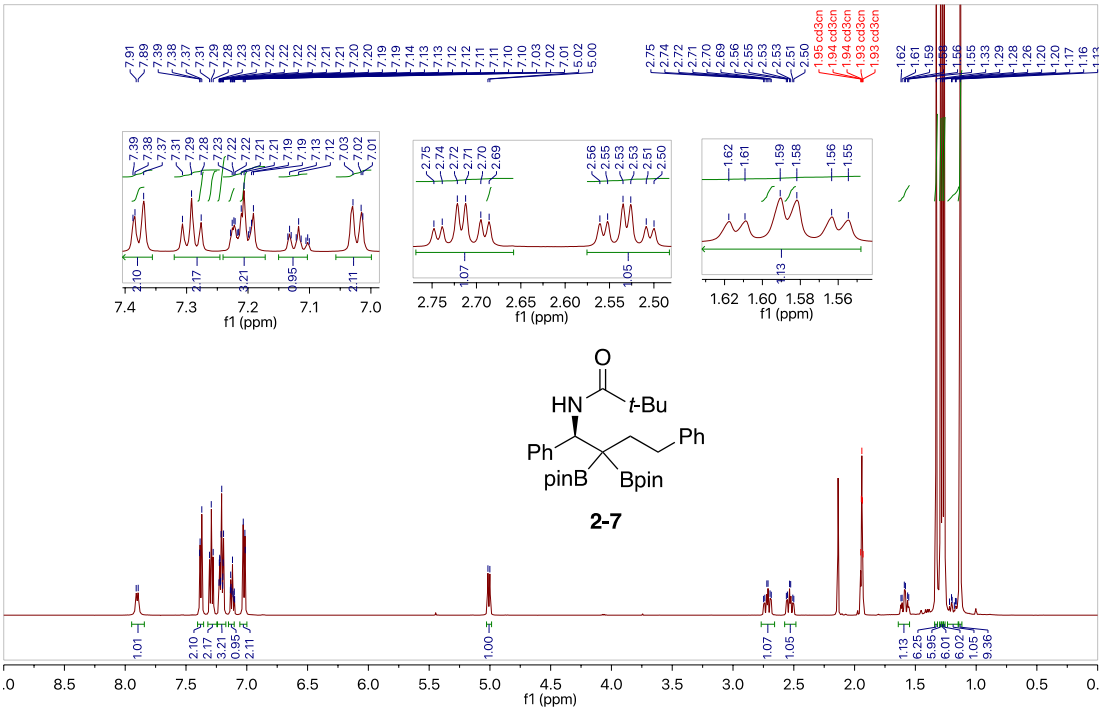


2018.03.17.i5_XLH-09-119_C13_1D; 125.266 MHz C13{H1} 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 26.9 C -> actual temp = 27.0 C, autoxdb probe

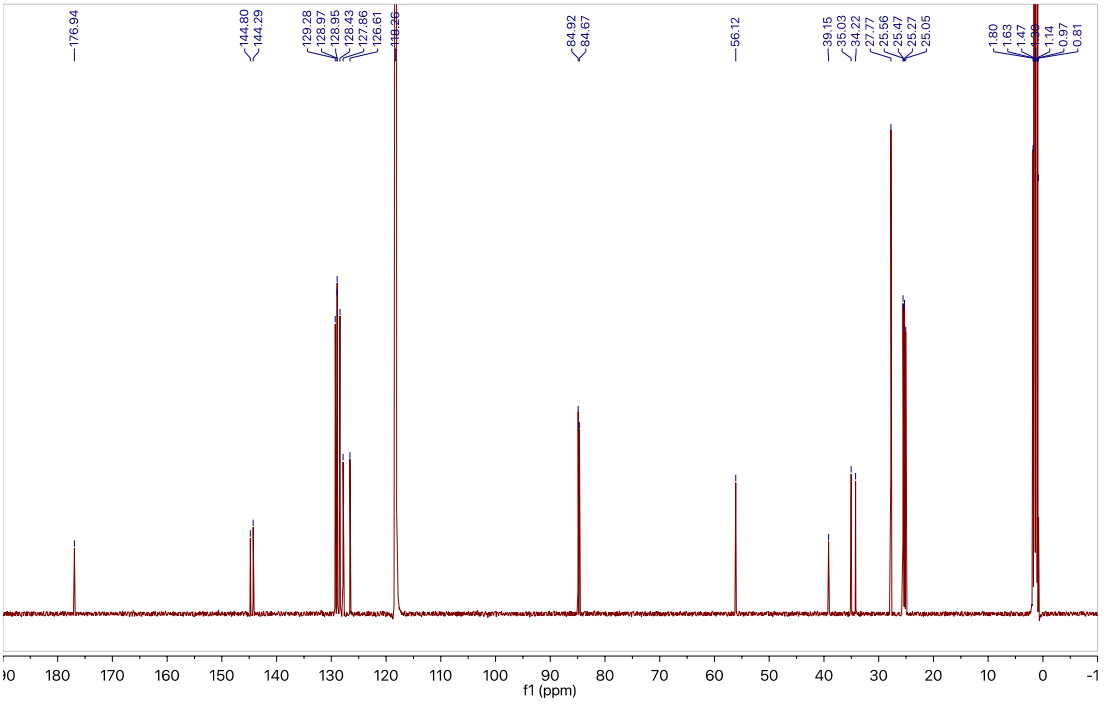


^{1}H NMR and ^{13}C NMR of β-amino *gem*-bis(boronate) 2-7:

2018.03.26.u5_XLH-09-141_loc4_16.54_H1_1D; XLH-09-141; 499.800 MHz H1 1D in cd3cn
temp 27.7 C -> actual temp = 27.0 C, colddual probe

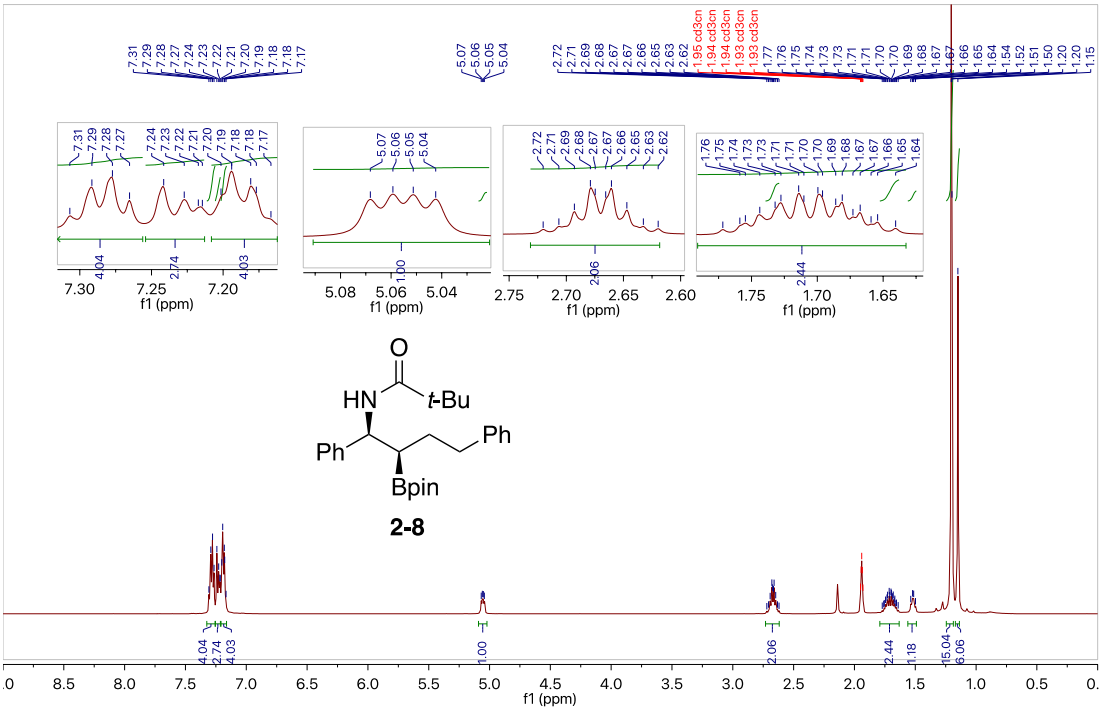


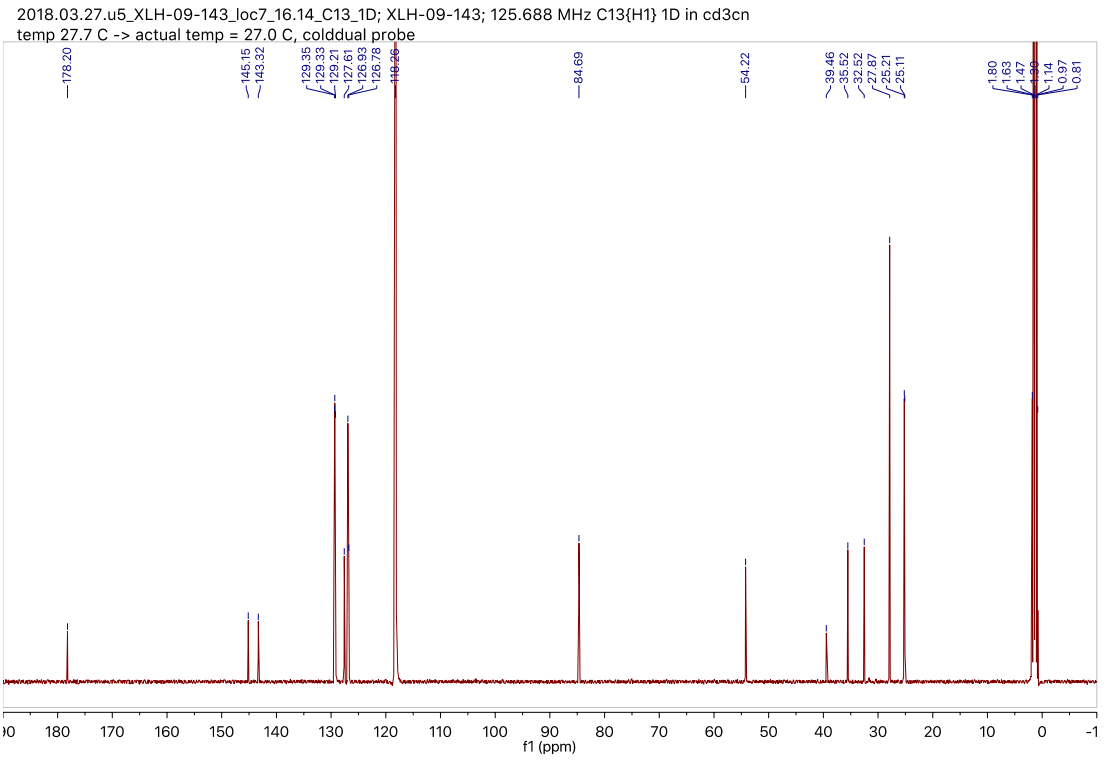
2018.03.26.u5_XLH-09-141_loc4_16.55_C13_1D; XLH-09-141; 125.688 MHz C13{H1} 1D in cd3cn
temp 27.7 C -> actual temp = 27.0 C, colddual probe



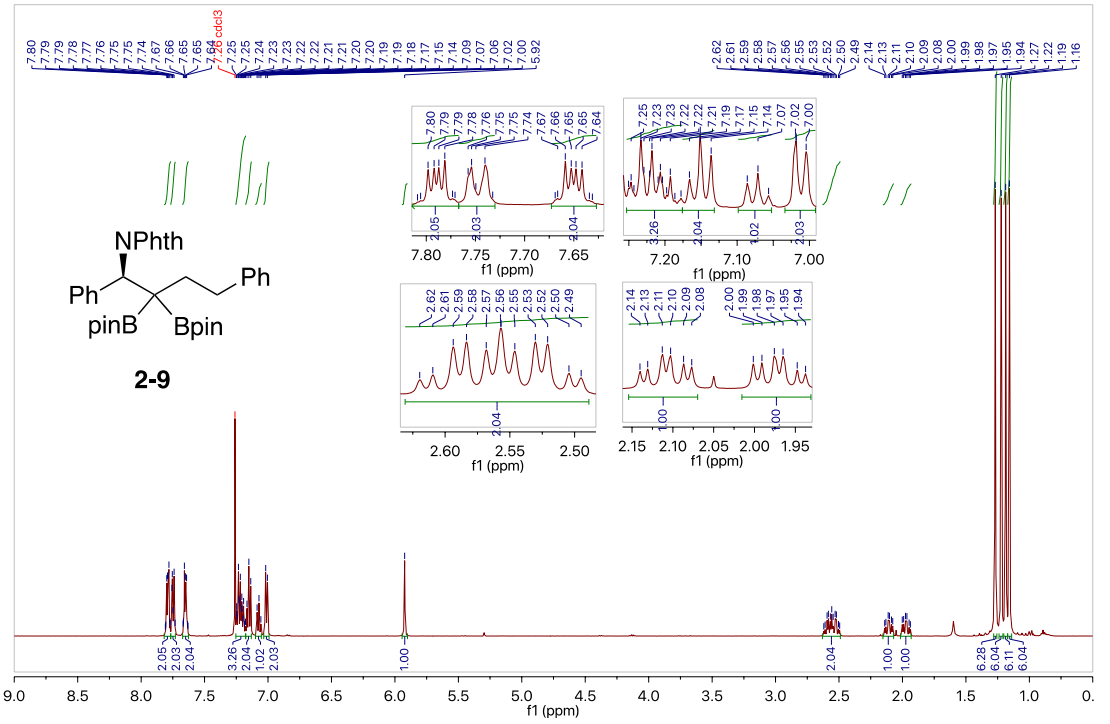
^{1}H NMR and ^{13}C NMR of β-amino alkylboronate 2-8:

2018.03.27.u5_XLH-09-143_loc7_16.13_H1_1D; XLH-09-143; 499.800 MHz H1 1D in cd3cn
temp 27.7 C -> actual temp = 27.0 C, colddual probe

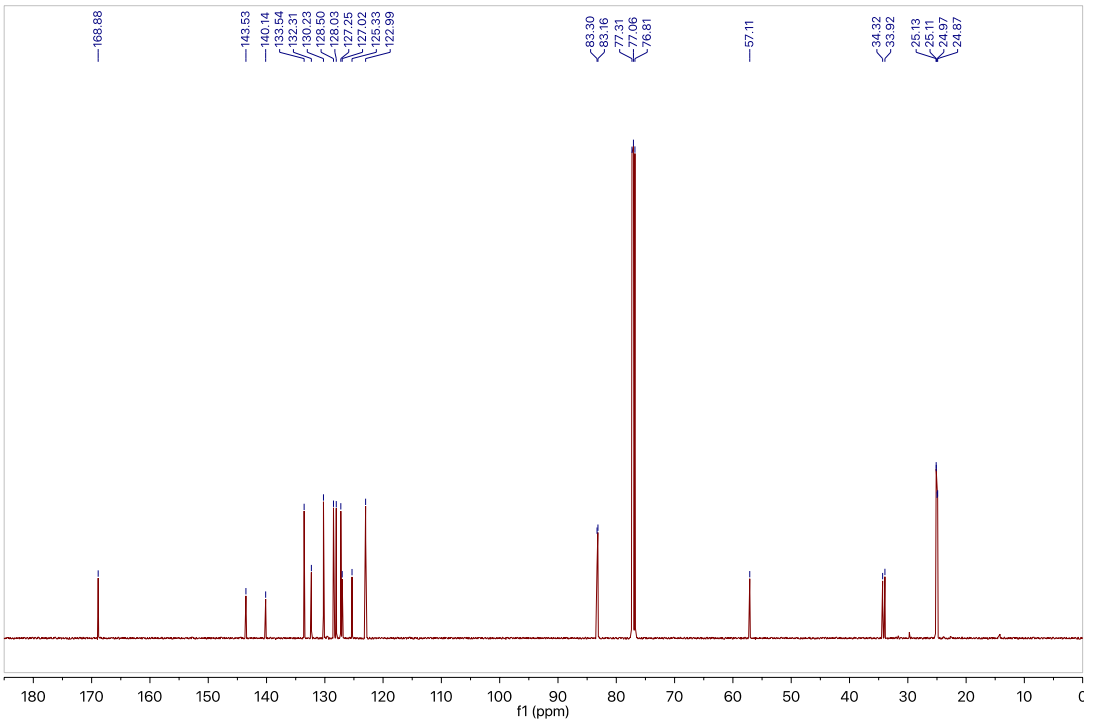




^{1}H NMR and ^{13}C NMR of β-amino *gem*-bis(boronate) 2-9:

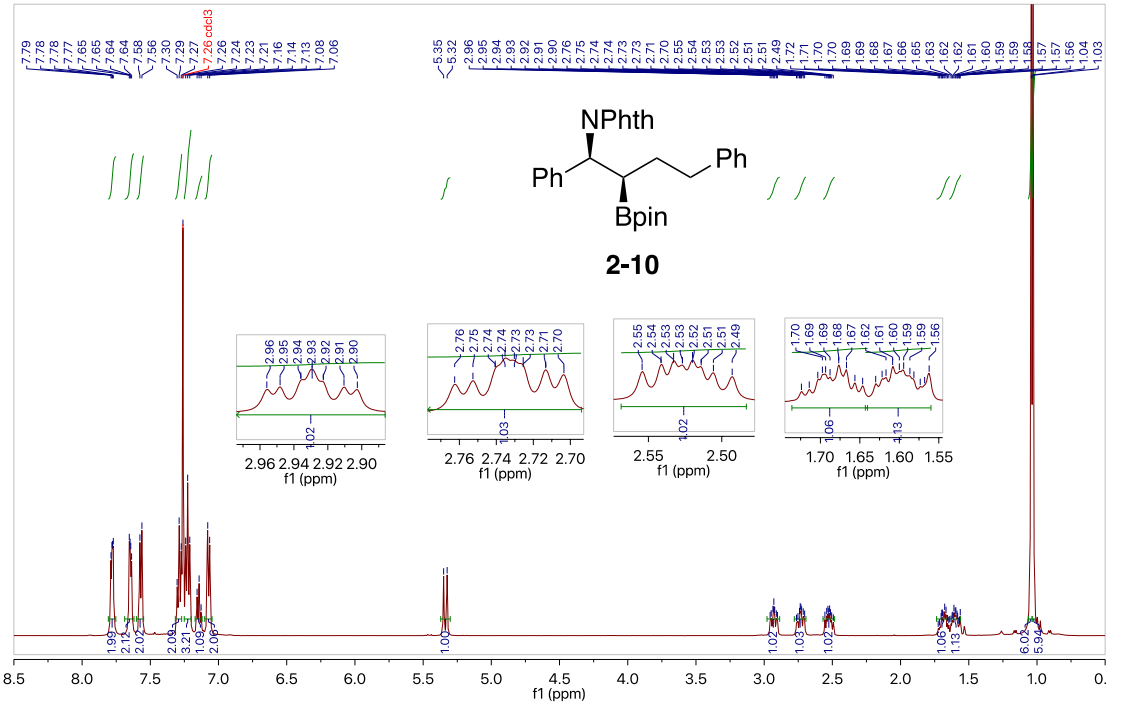


2018.06.04.u5_XLH-09-197_loc8_15.39_C13_1D; 125.688 MHz C13{H1} 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm)

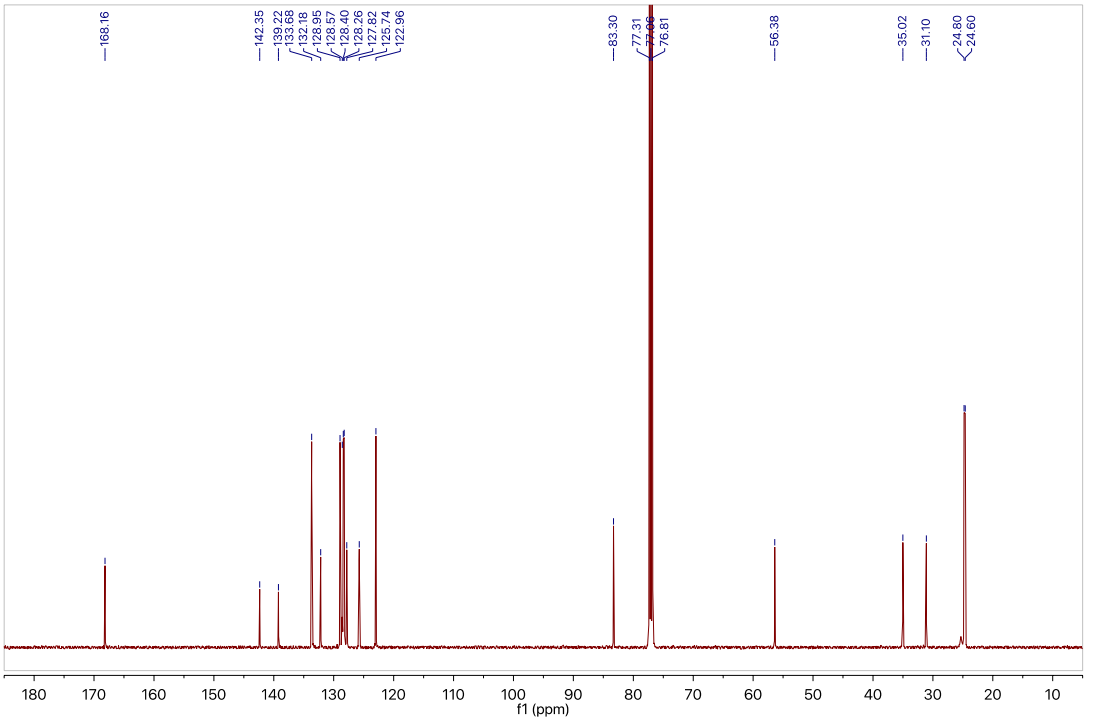


^{1}H NMR and ^{13}C NMR of β-amino alkylboronate 2-10:

2018.06.04.u5_XLH-10-25_loc8_16.54_H1_1D; 499.797 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe

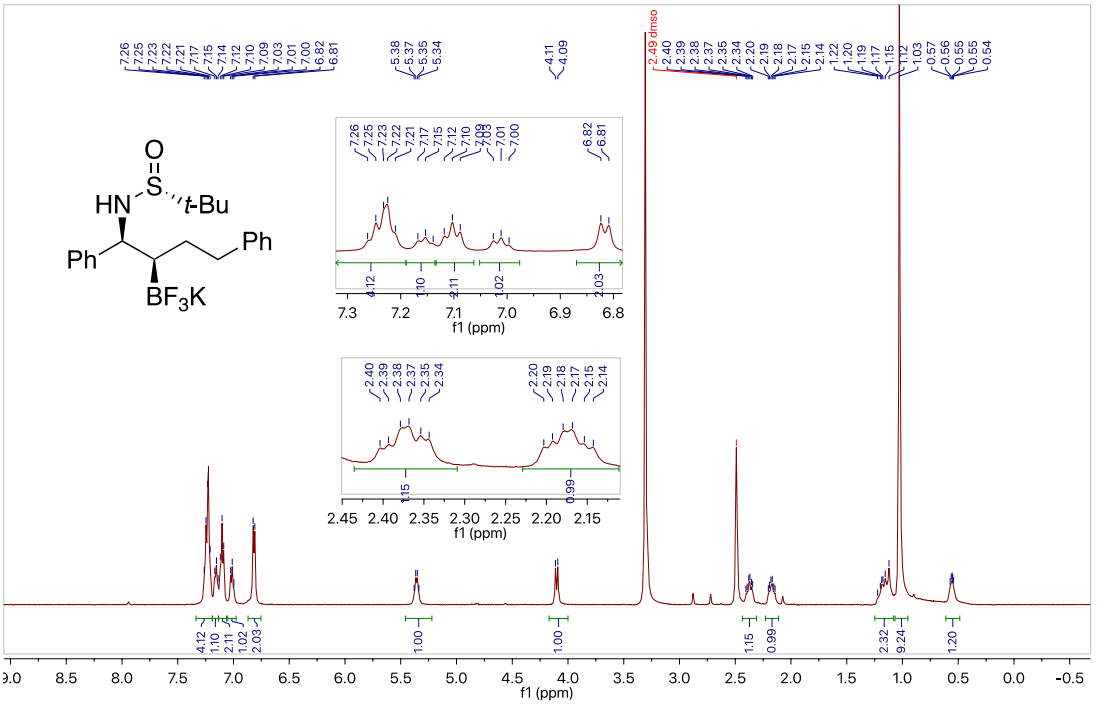


2018.06.04.u5_XLH-10-25_loc3_15.17_C13_1D; 125.688 MHz C13{H1} 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm)

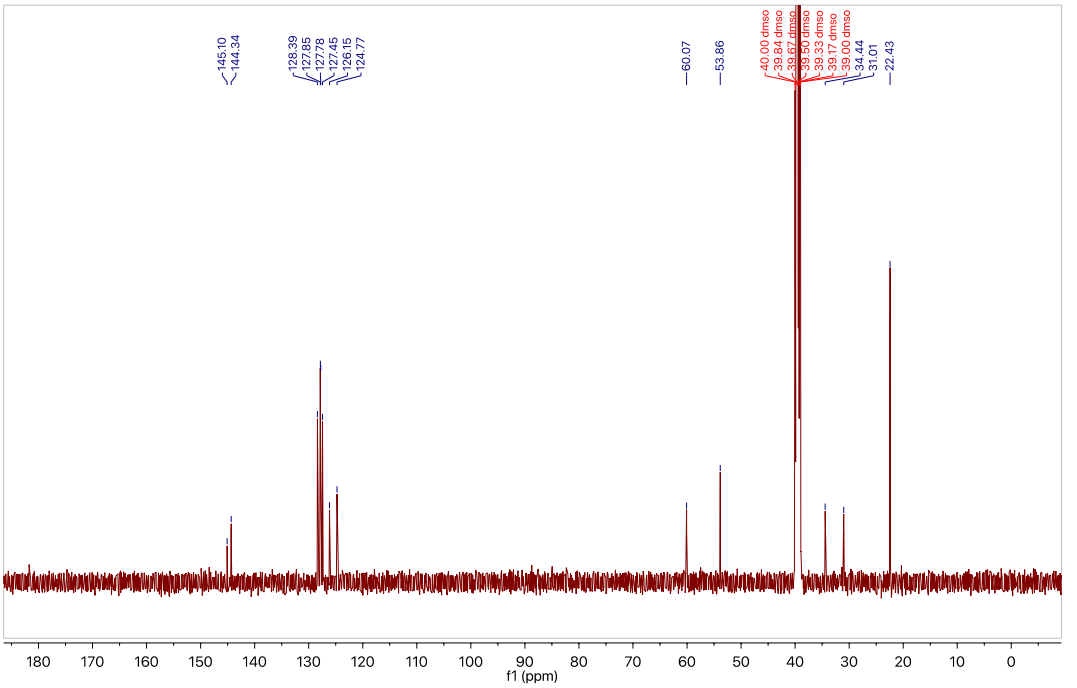


^{1}H NMR and ^{13}C NMR of β-amino alkylboronate 2-10:

2019.11.21.i5_XLH-VII-107_H1_PRESAT; 498.120 MHz H1 1D in dmso (ref. to DMSO @ 2.49 ppm)
temp 26.9 C -> actual temp = 27.0 C, autoxdb probe

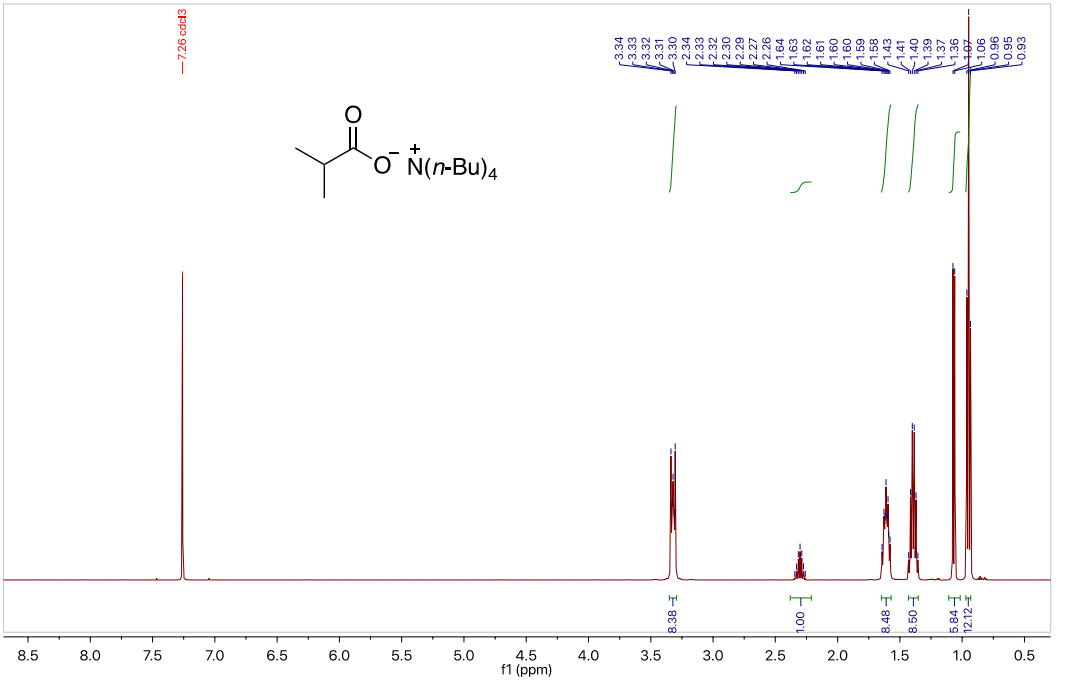


2019.11.21.i5_XLH-VII-107_13.43_C13_1D; 125.266 MHz C13{H1} 1D in dmso (ref. to DMSO @ 39.5 ppm)
temp 26.9 C -> actual temp = 27.0 C, autoxdb probe

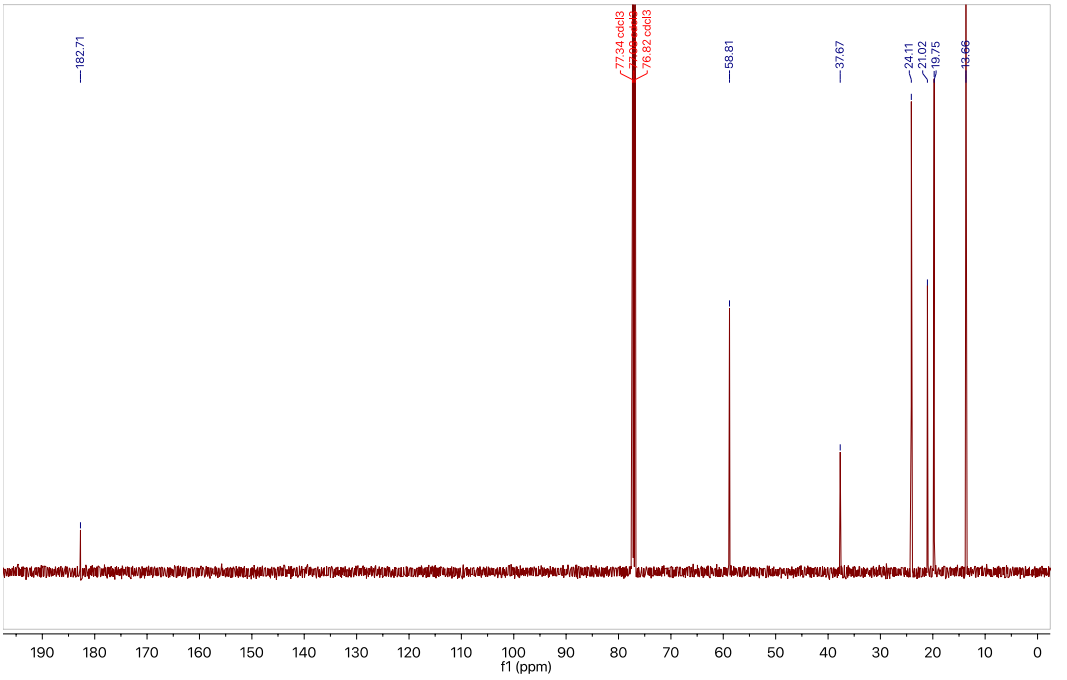


^{1}H and ^{13}C NMR of tetrabutylammonium isobutyrate

2018.11.21.i5_XLH-11-199_H1_1D; 498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 26.9 C -> actual temp = 27.0 C, autoxdb probe

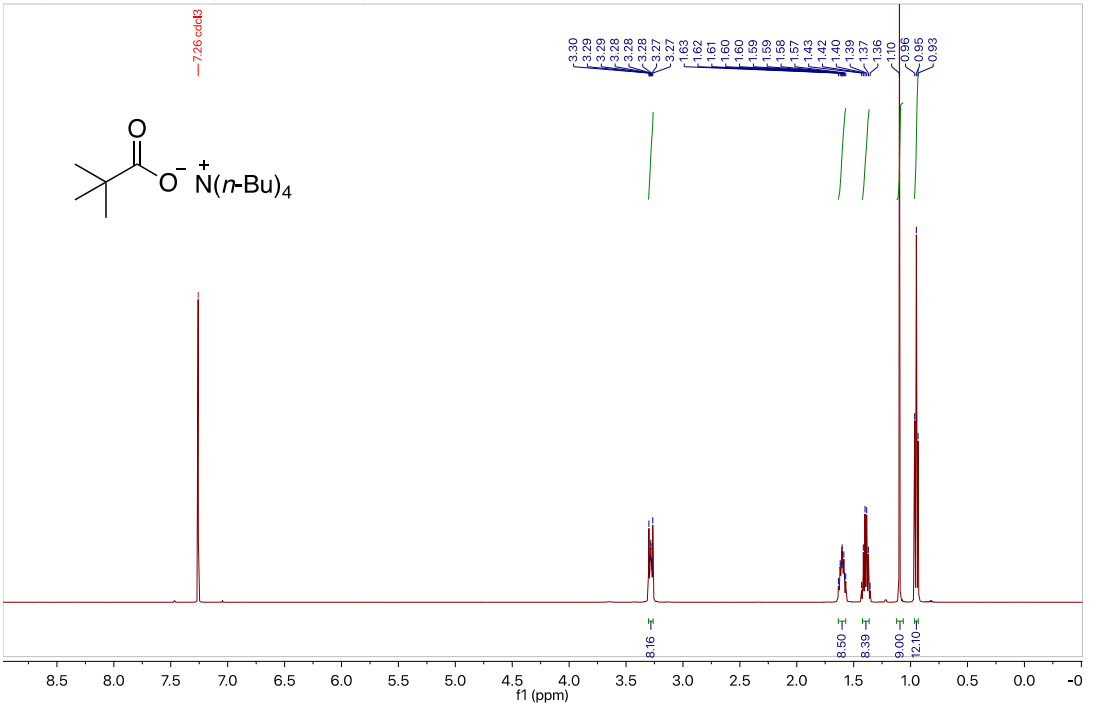


2018.11.21.i5_XLH-11-199_C13_1D; 125.266 MHz C13{H1} 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 26.9 C -> actual temp = 27.0 C, autoxdb probe

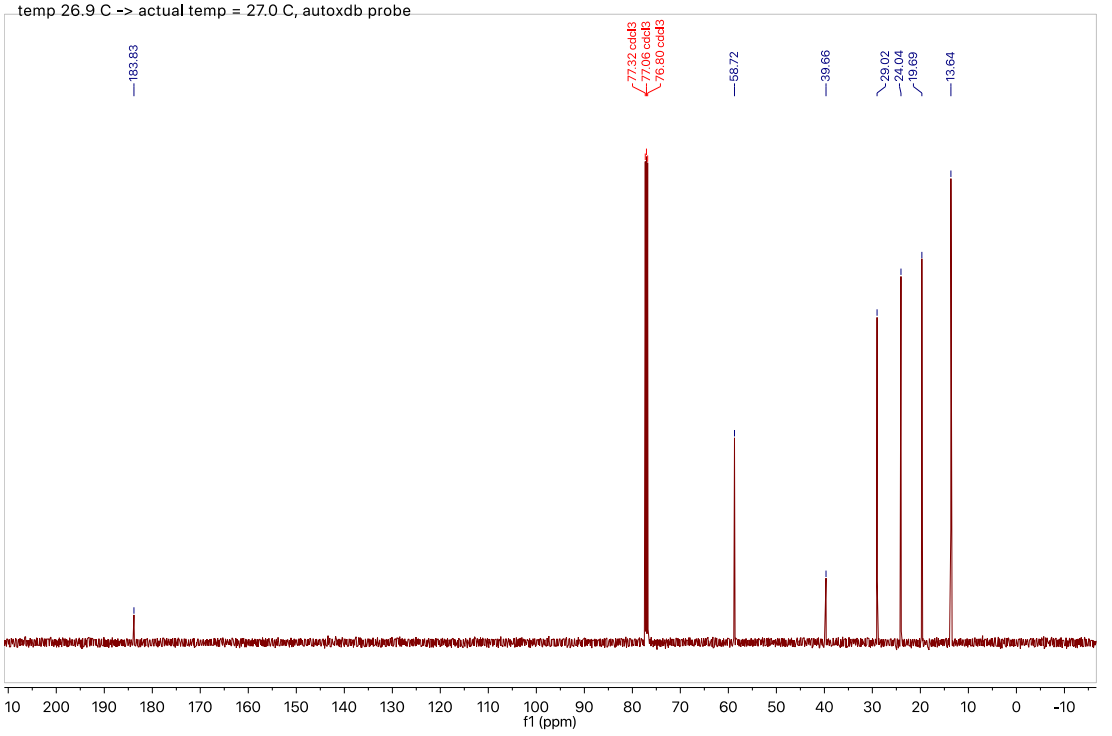


^{1}H and ^{13}C NMR of tetrabutylammonium trimethylacetate

2018.11.16.i5_XLH-11-181_H1_1D; 498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 26.9 C -> actual temp = 27.0 C, autoxdb probe

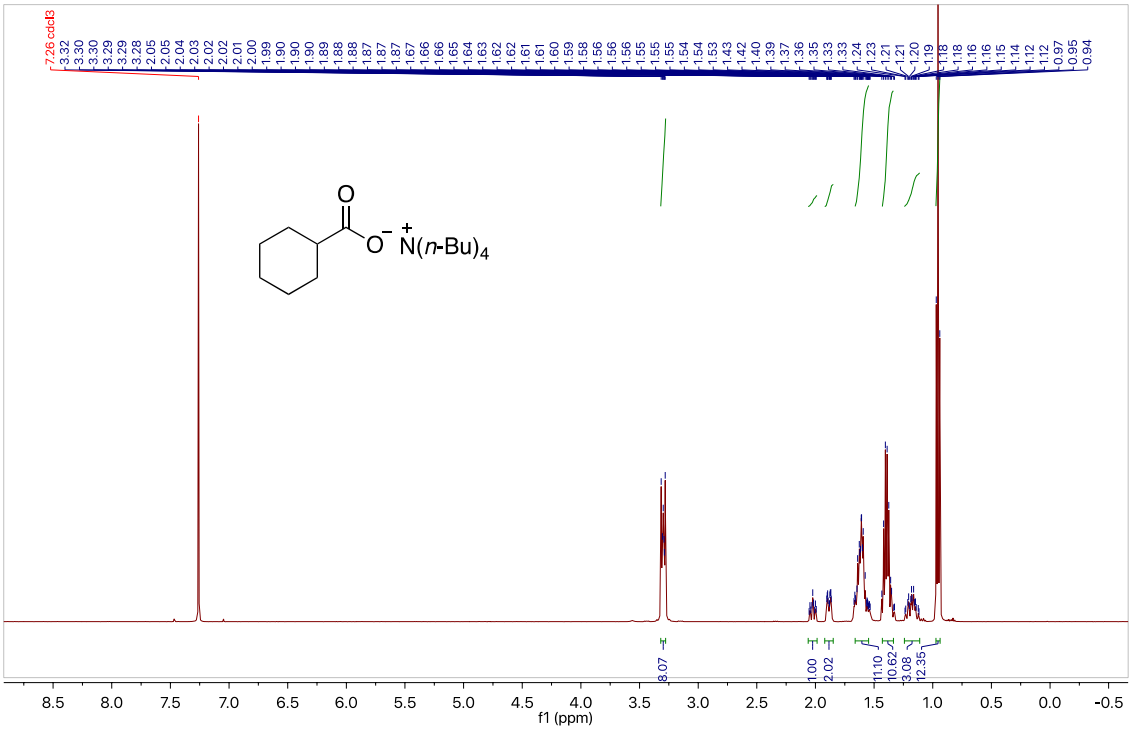


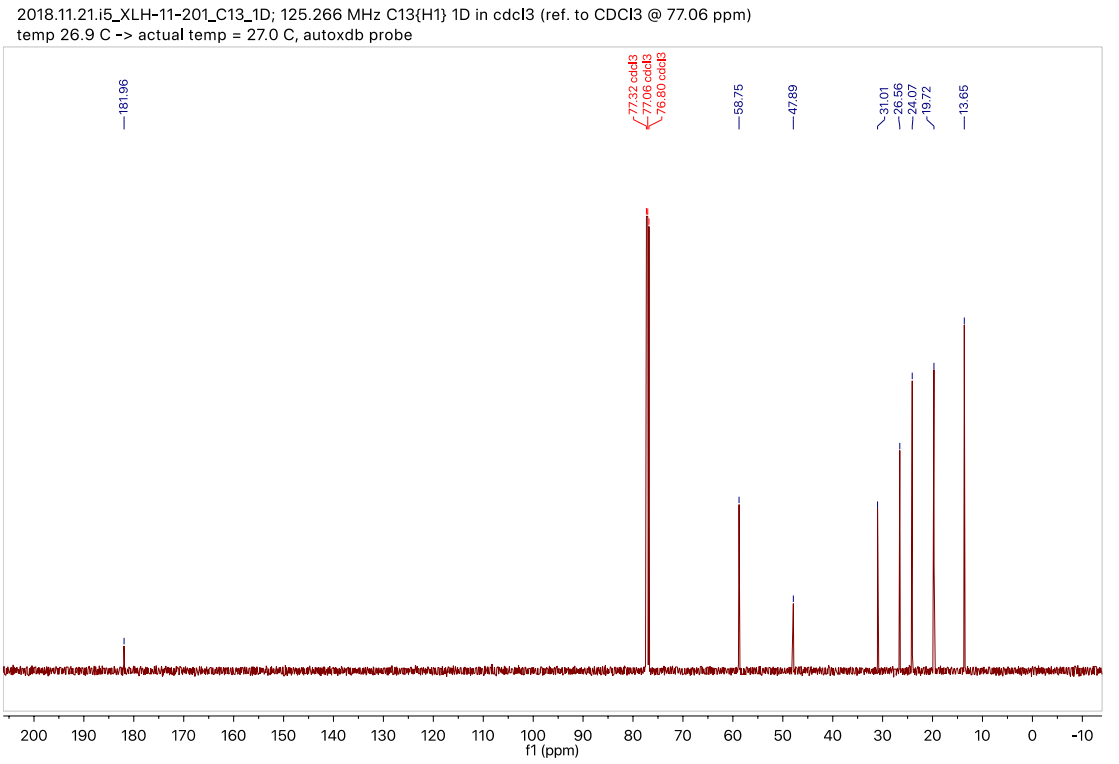
2018.11.16.i5_XLH-11-181_C13_1D; 125.266 MHz C13{H1} 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 26.9 C -> actual temp = 27.0 C, autoxdb probe



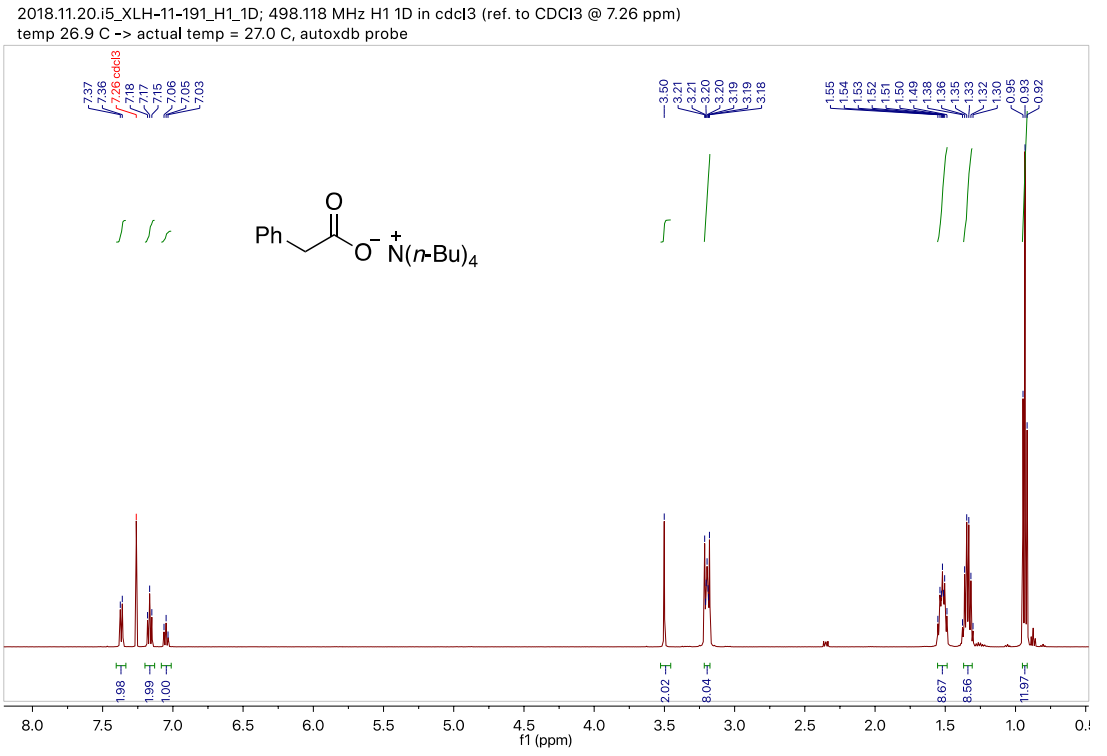
^{1}H and ^{13}C NMR of tetrabutylammonium cyclohexanecarboxylate

2018.11.21.i5_XLH-11-201_H1_1D; 498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 26.9 C -> actual temp = 27.0 C, autoxdb probe

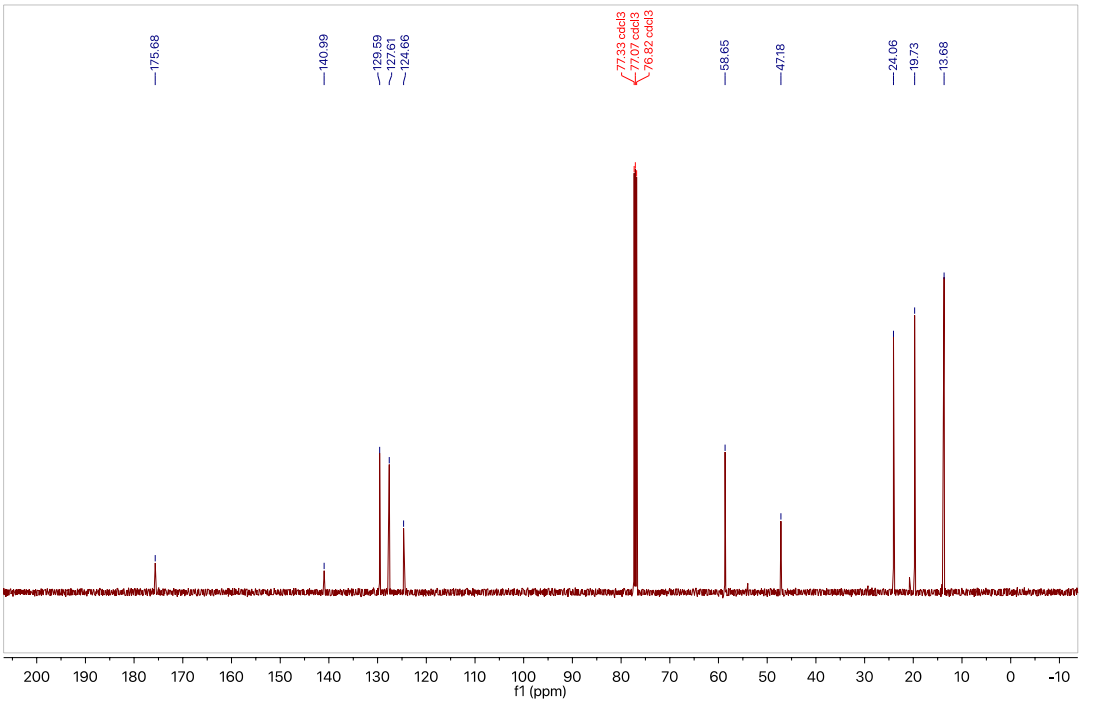




^{1}H and ^{13}C NMR of tetrabutylammonium 2-phenylacetate

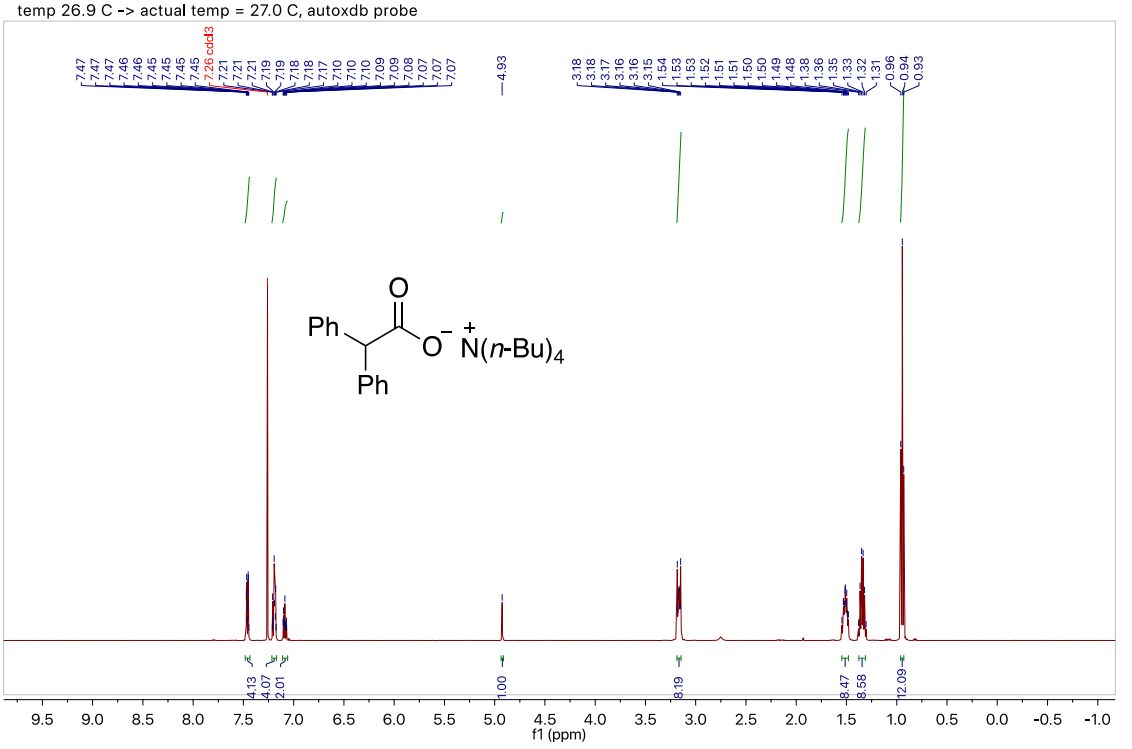


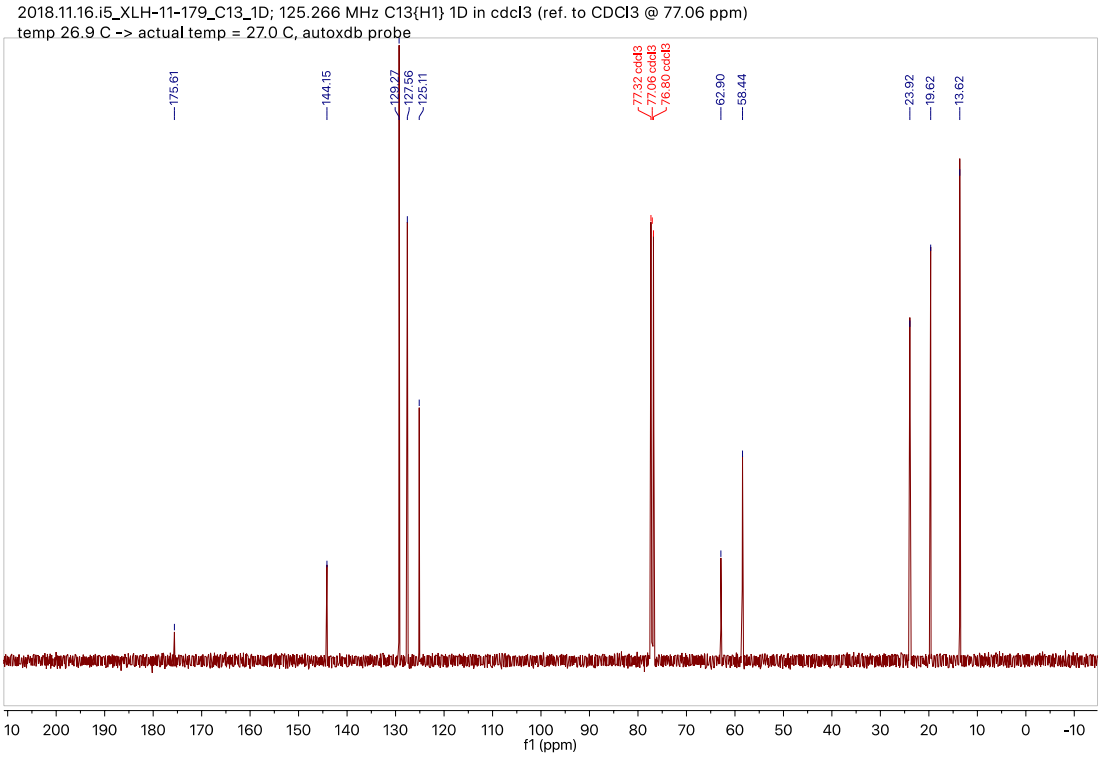
2018.11.20.i5_XLH-11-191_C13_1D; 125.266 MHz C13{H1} 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 26.9 C -> actual temp = 27.0 C, autoxdb probe



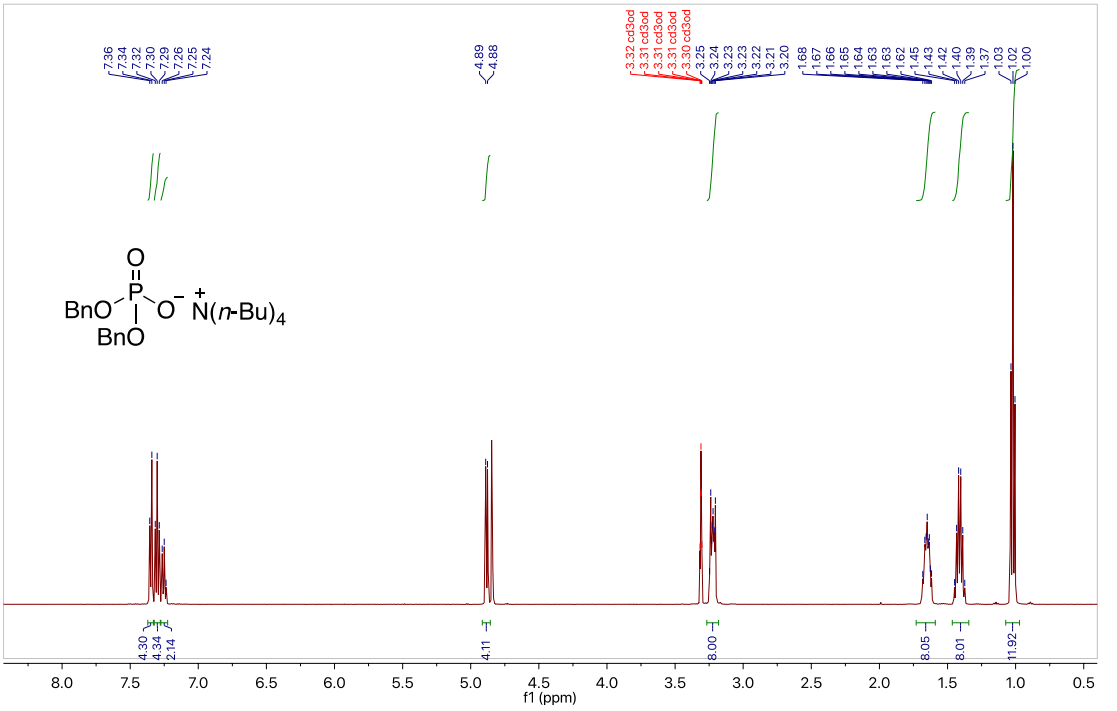
^{1}H and ^{13}C NMR of tetrabutylammonium diphenylacetate

2019.12.16.i5_XLH-11-179_H1_PRESAT; 498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 26.9 C -> actual temp = 27.0 C, autoxdb probe

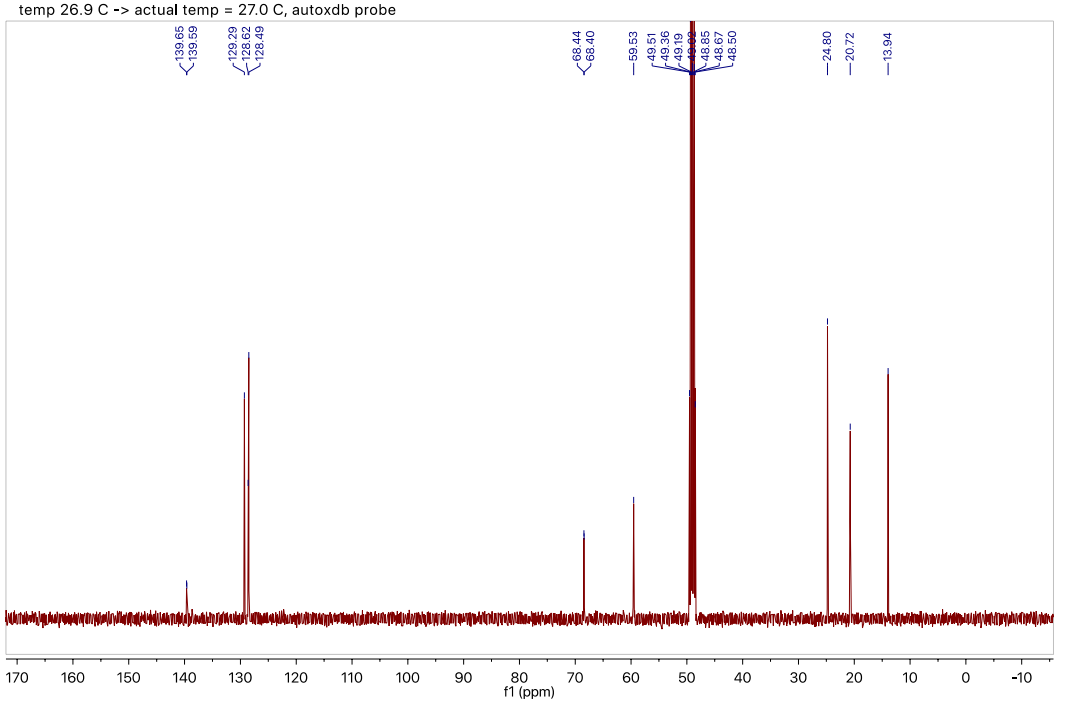




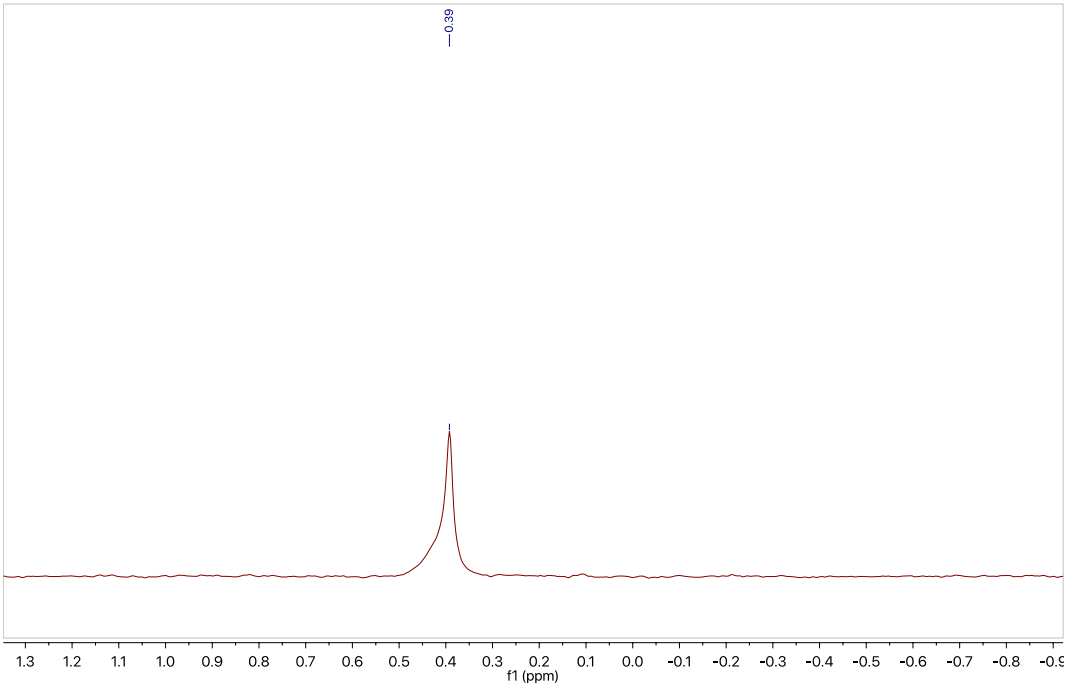
^{1}H, ^{13}C and ^{31}P NMR of tetrabutylammonium dibenzylphosphate



2019.04.11.i5_XLH-13-139_CD3OD__14.21_C13_1D; 125.266 MHz C13{H1} 1D in cd3od (ref. to CD3OD @ 49.0 ppm)
temp 26.9 C -> actual temp = 27.0 C, autoxdb probe

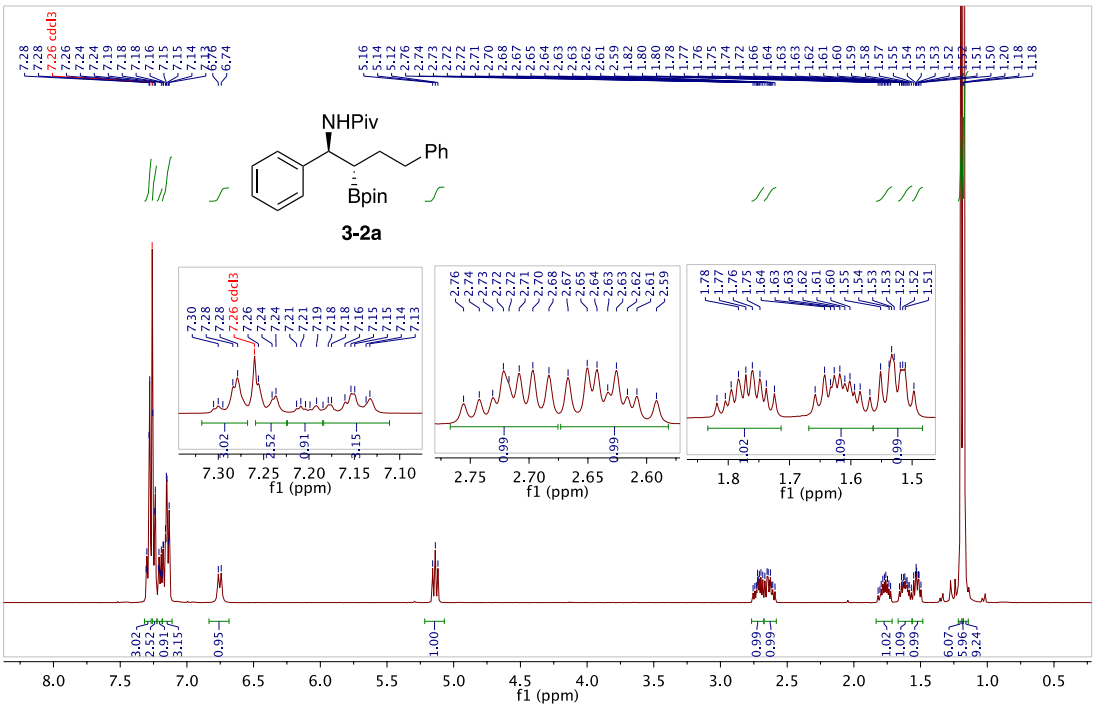


2019.04.11.i5_XLH-13-139_CD3OD__P31_1D; 201.642 MHz P31{H1} 1D in cd3od
temp 26.9 C -> actual temp = 27.0 C, autoxdb probe

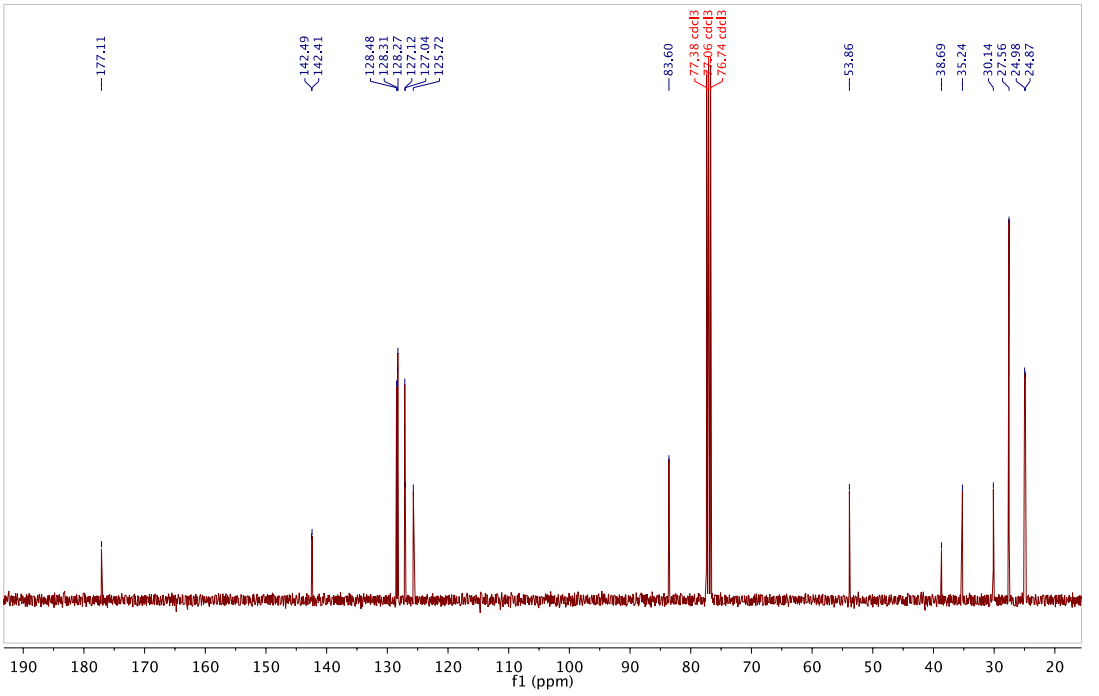


^{1}H and ^{13}C NMR of β-aminoalkylboronate 3-2a

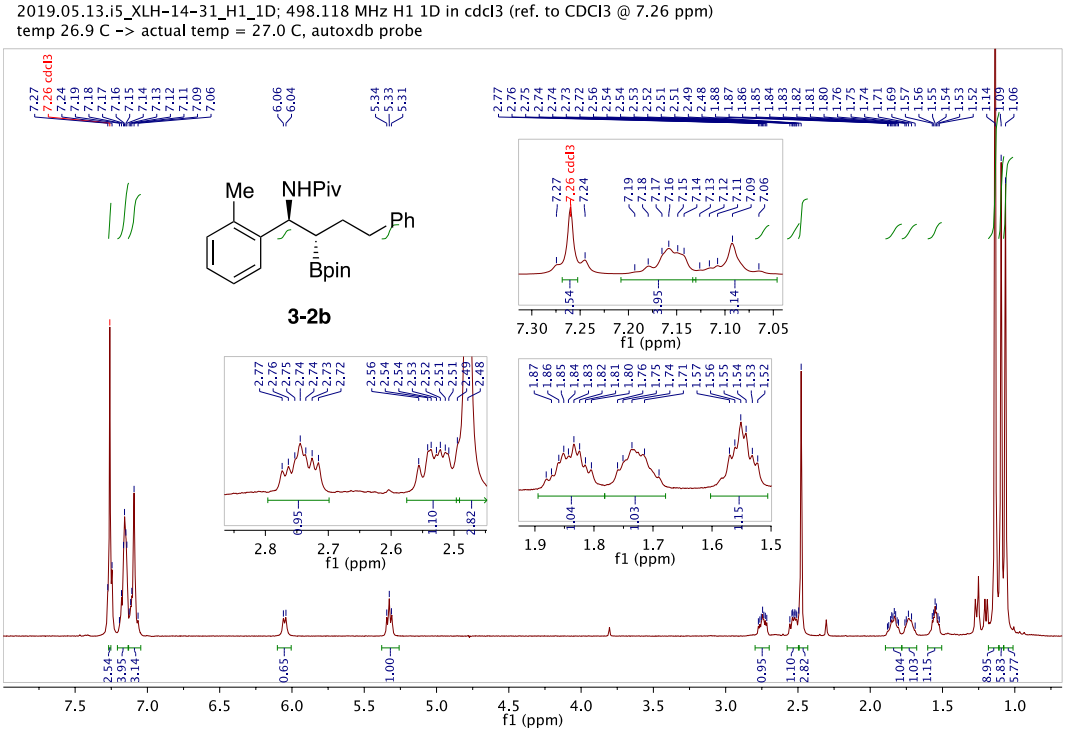
2019.04.25.mr4_XLH-13-175-2_H1_1D; 399.978 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 25.9 C -> actual temp = 27.0 C, onenmr probe

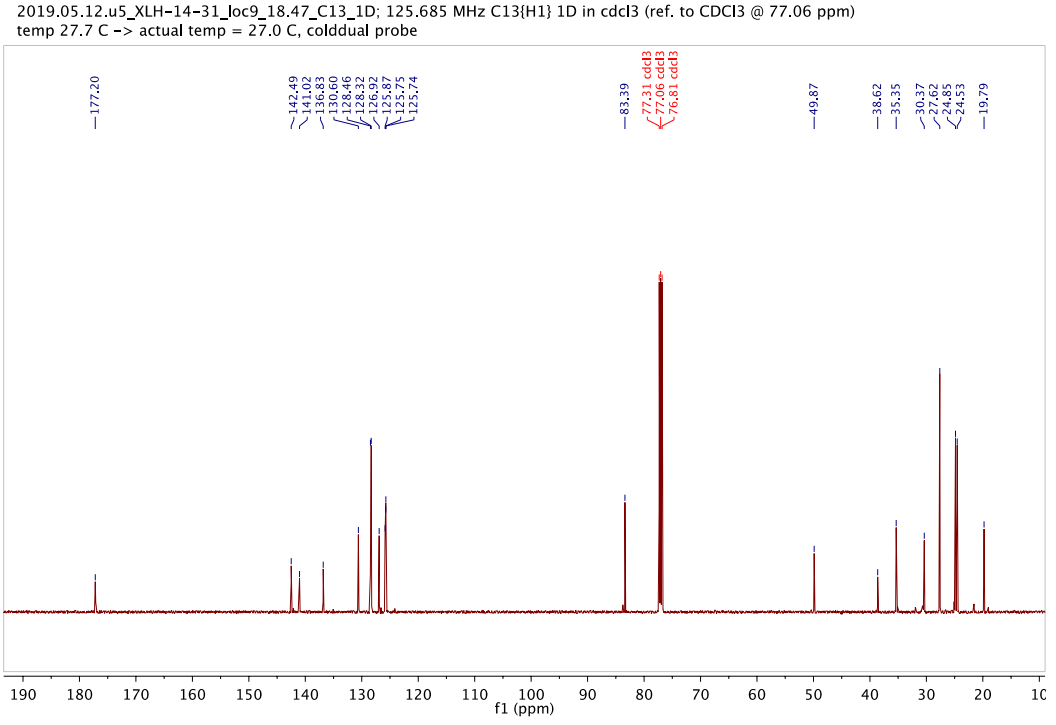


2019.04.25.mr4_XLH-13-175-2_C13_1D; 100.586 MHz C13{H1} 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 25.9 C -> actual temp = 27.0 C, onenmr probe

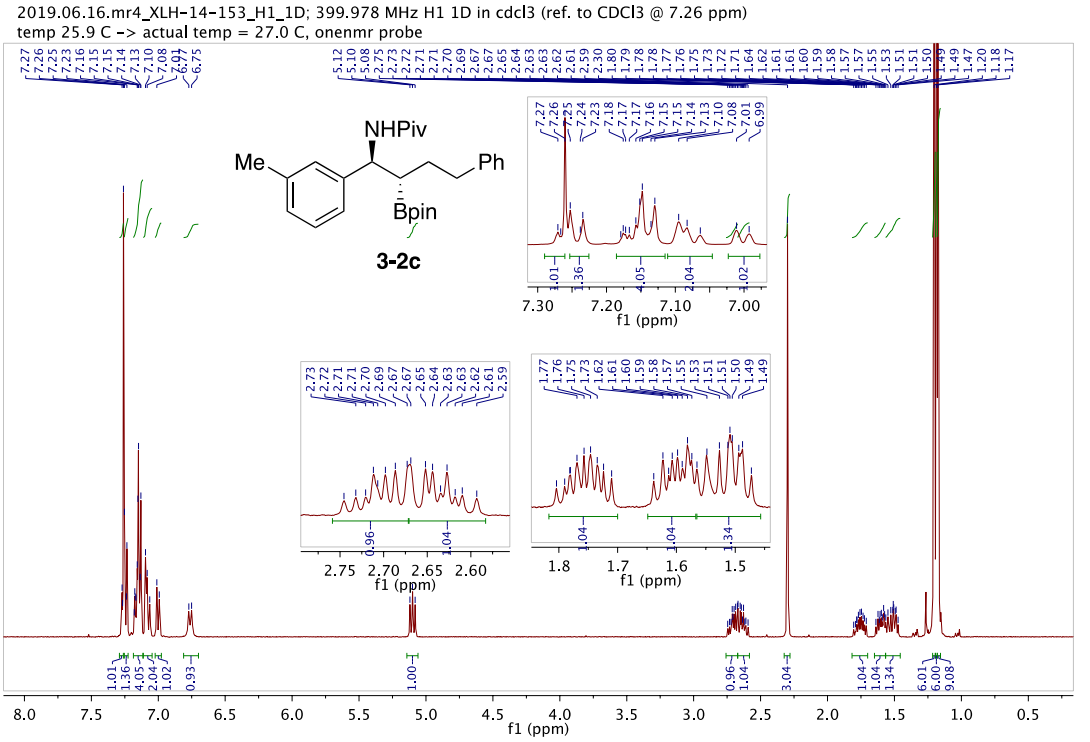


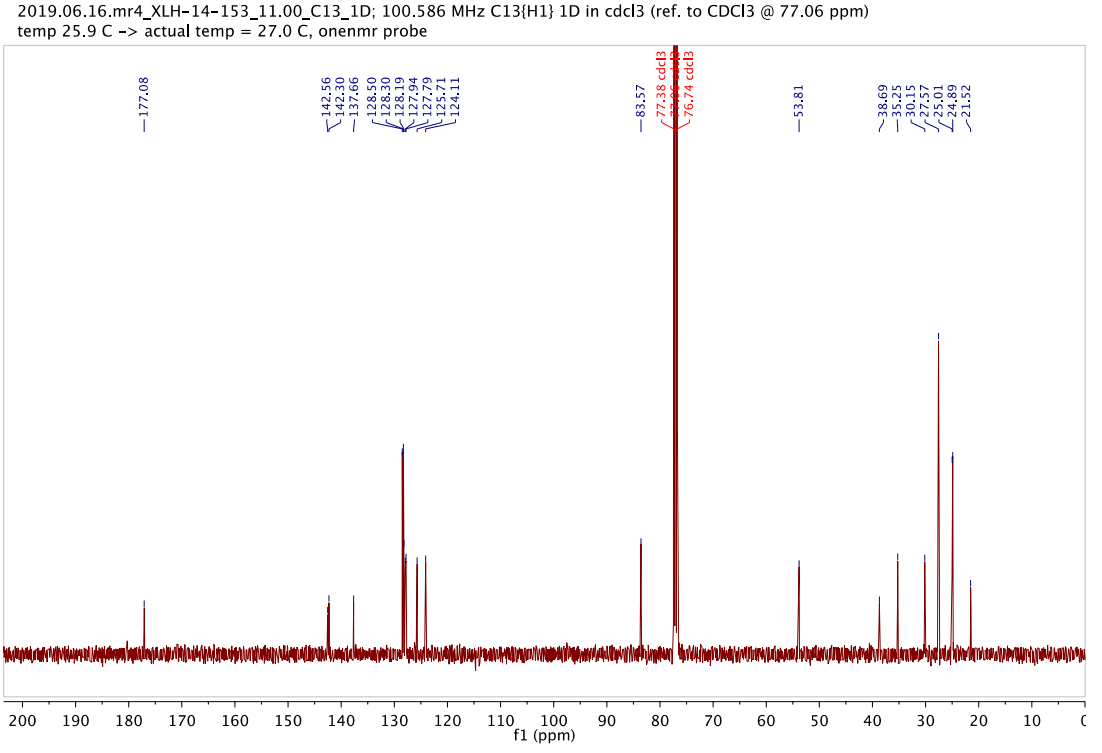
^{1}H and ^{13}C NMR of β-aminoalkylboronate 3-2b



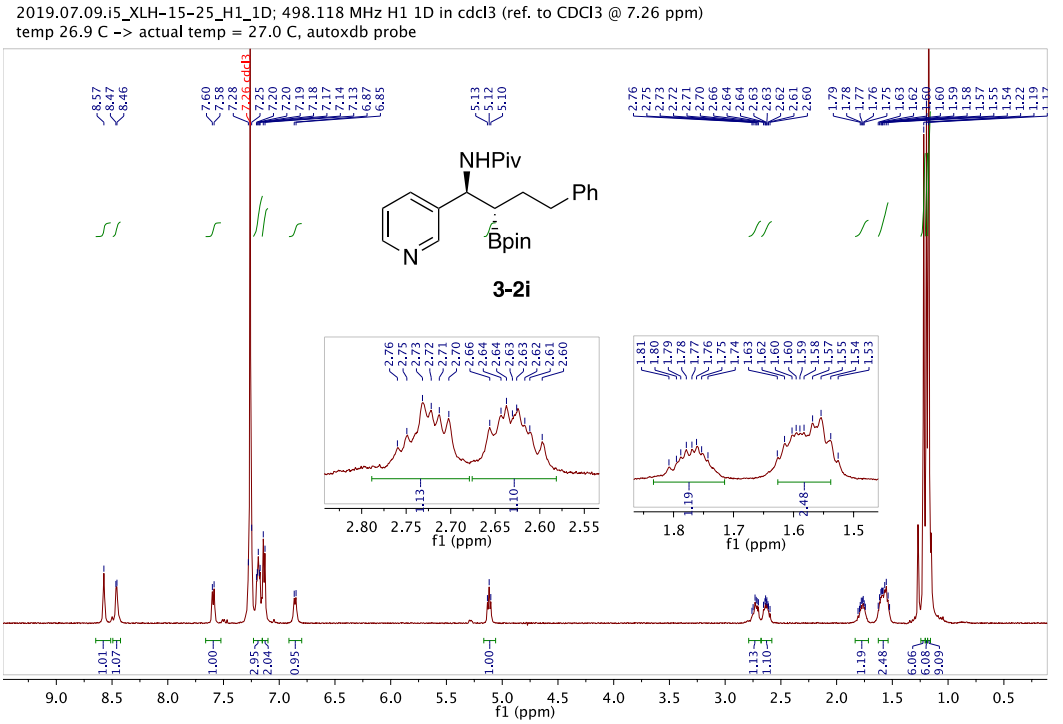


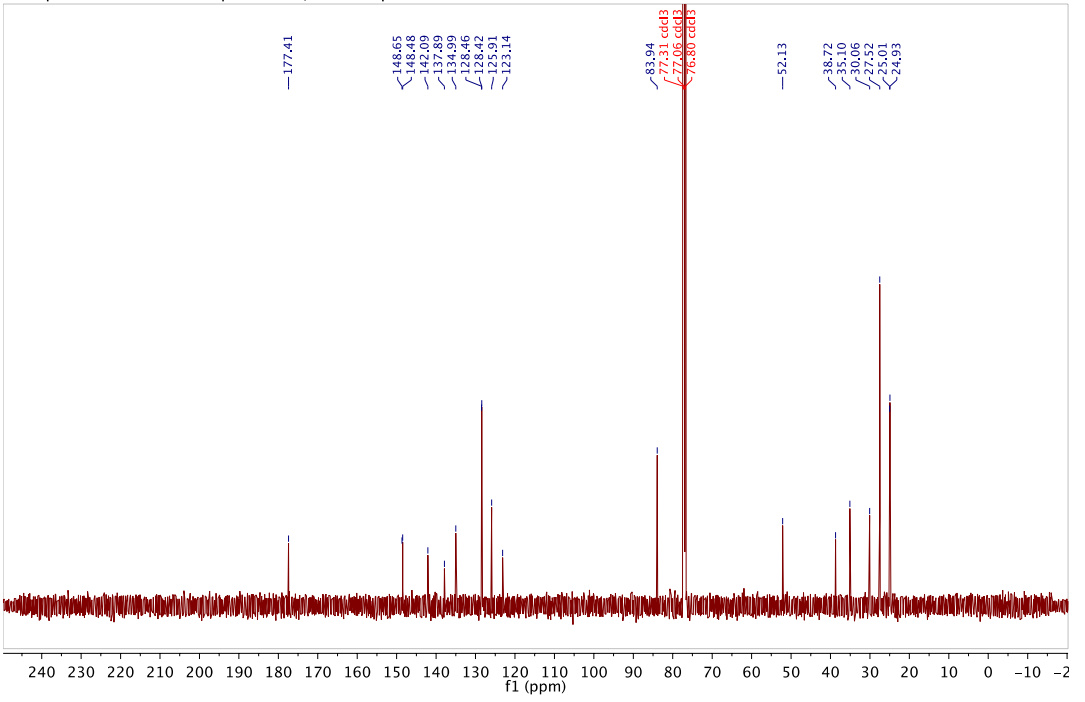
^{1}H and ^{13}C NMR of β-aminoalkylboronate 3-2c



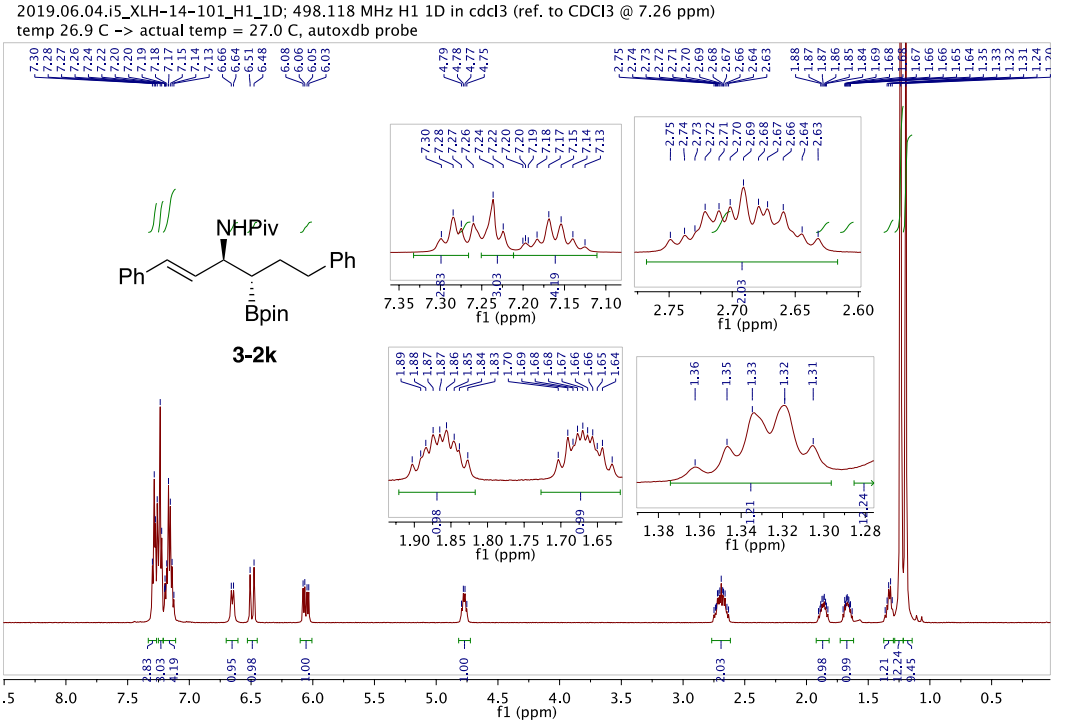


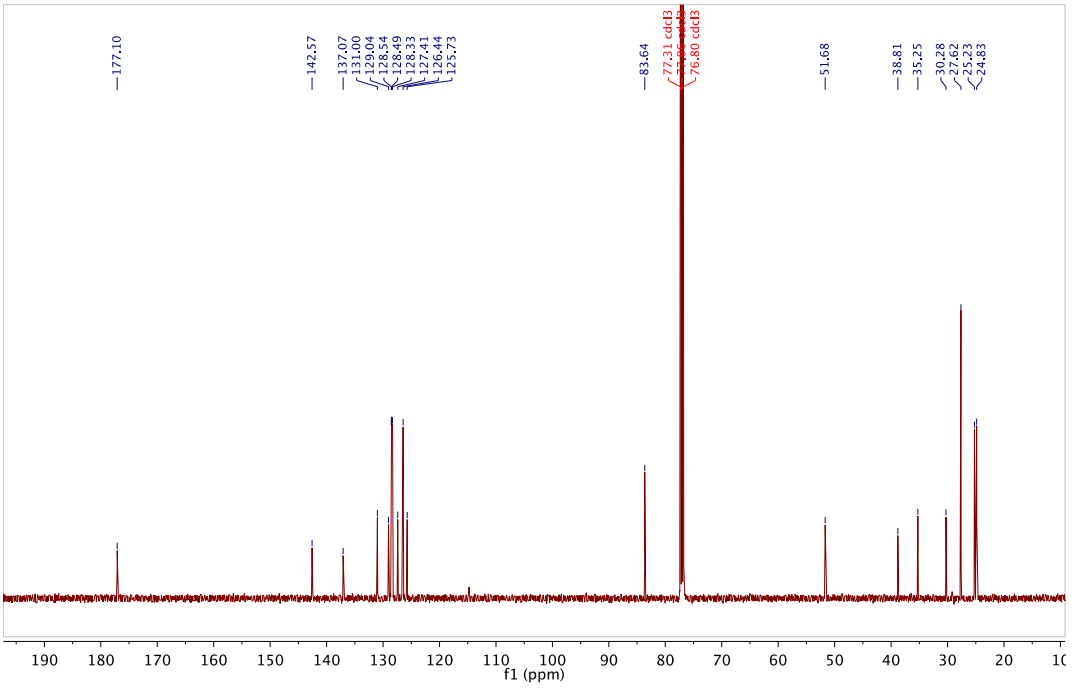
^{1}H and ^{13}C NMR of β-aminoalkylboronate 3-2i



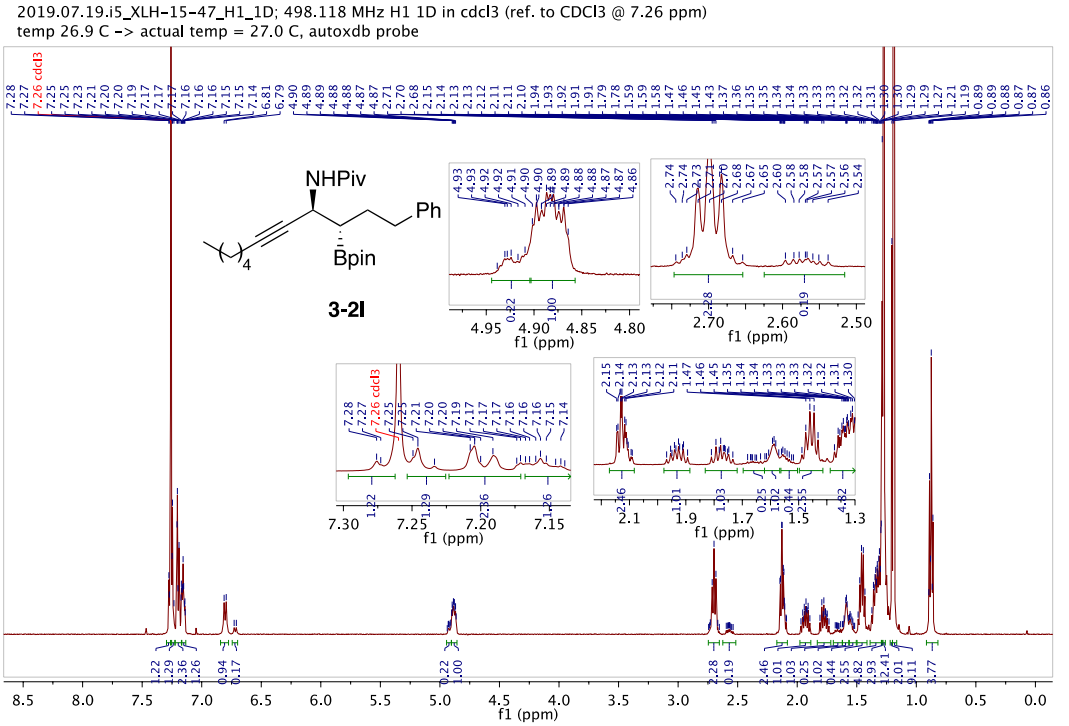


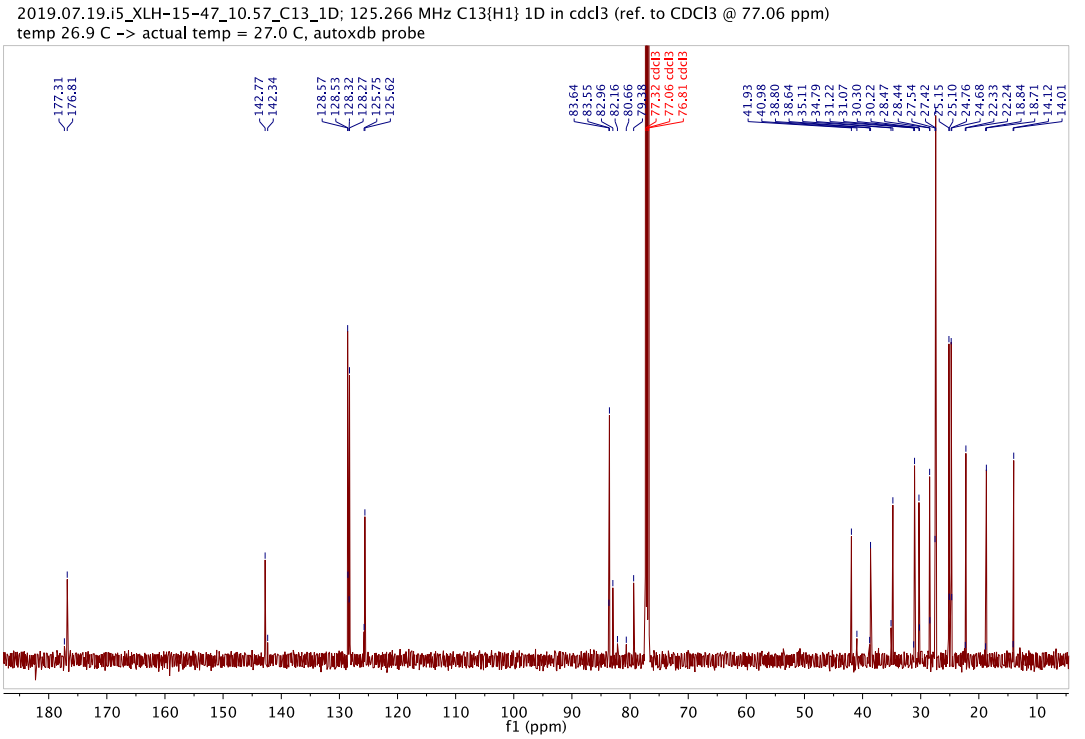
^{1}H and ^{13}C NMR of β-aminoalkylboronate 3-2k





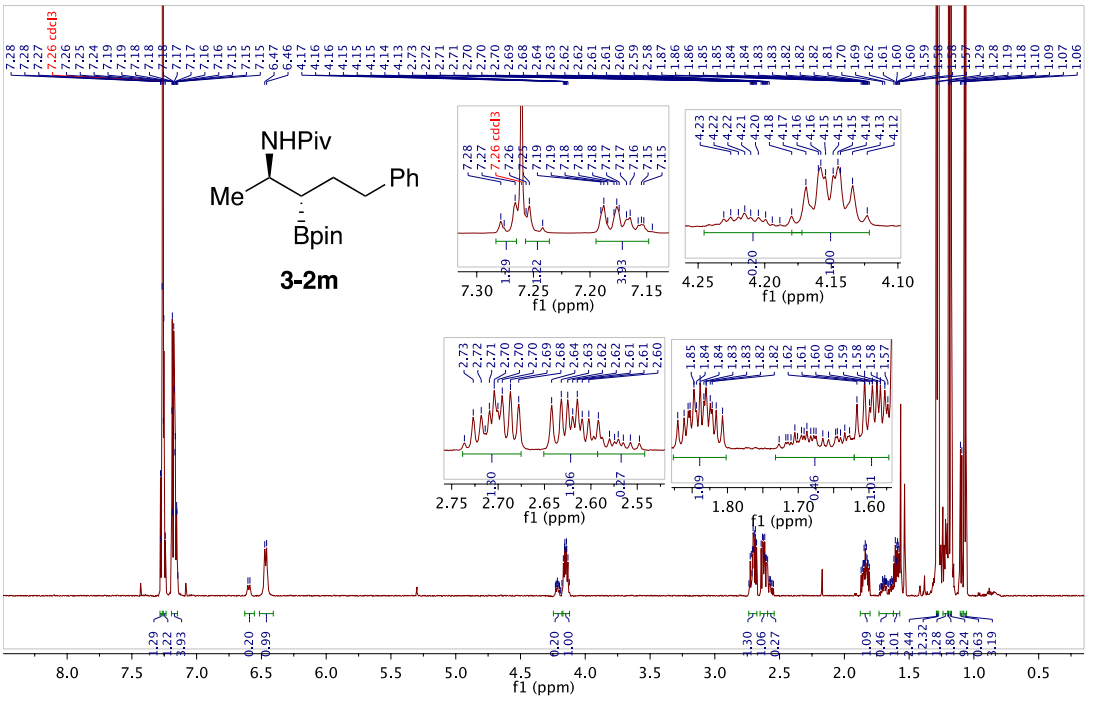
^{1}H and ^{13}C NMR of β-aminoalkylboronate 3-2l



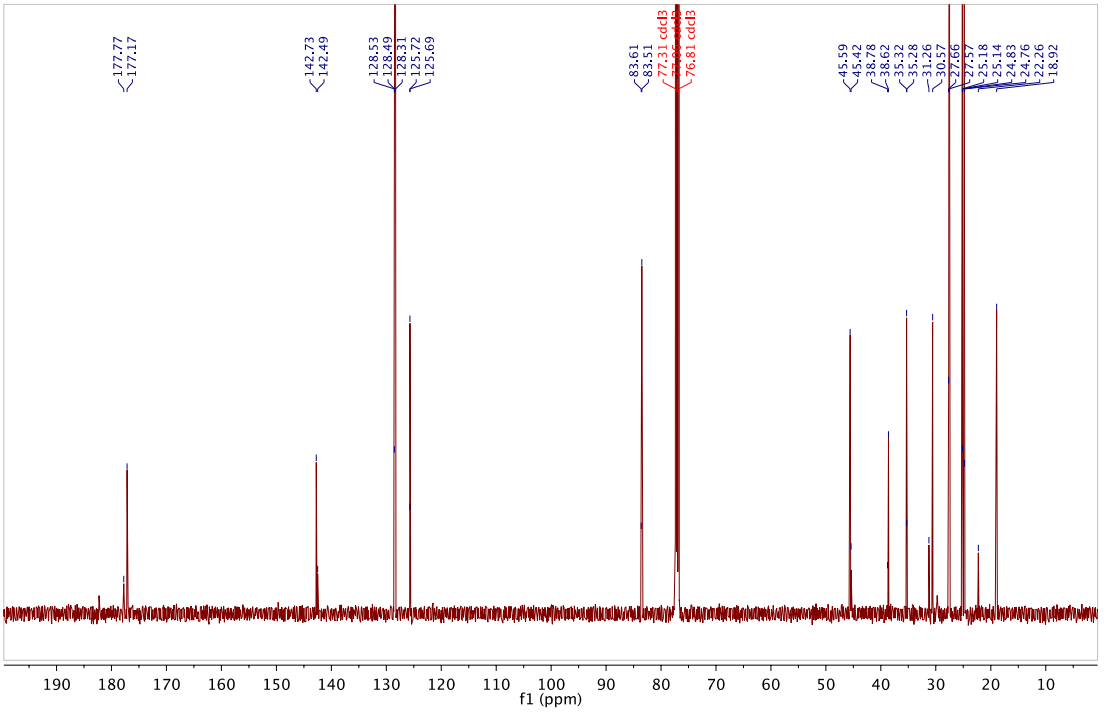


^{1}H and ^{13}C NMR of β-aminoalkylboronate 3-2m

2019.10.03.i6_XLH-15-75_H1_PRESAT; 599.926 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 26.2 C -> actual temp = 27.0 C, autoxid probe

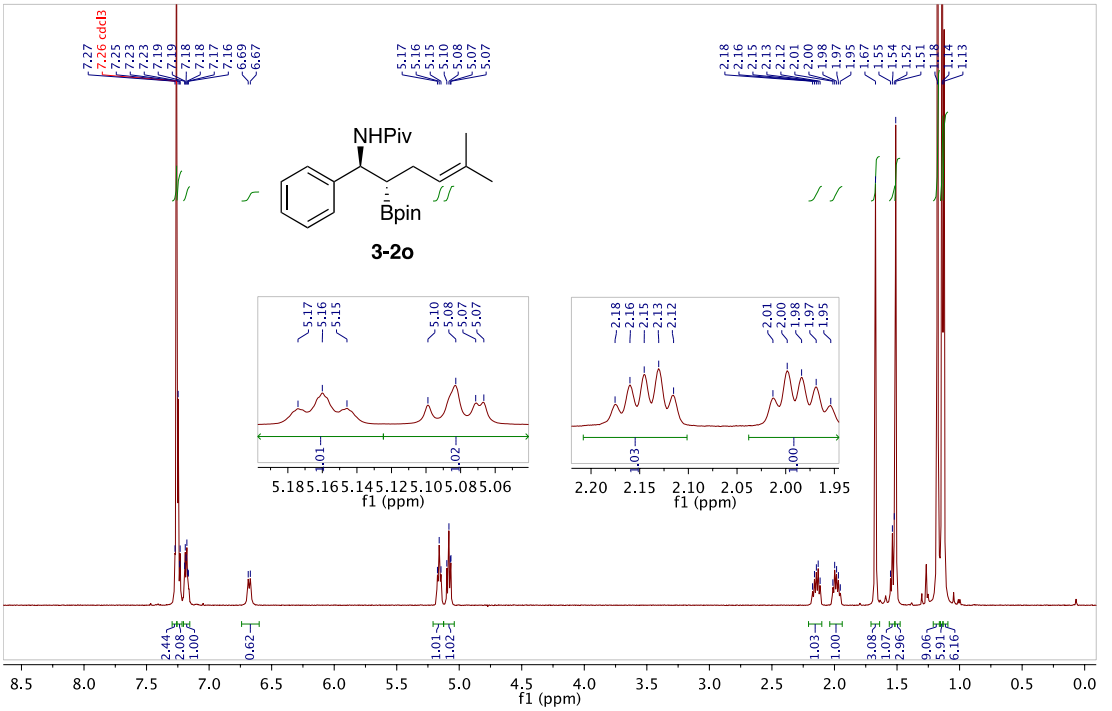


2019.07.30.i5_XLH-15-75_08.55_C13_1D; 125.266 MHz C13{H1} 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 26.9 C -> actual temp = 27.0 C, autoxdb probe

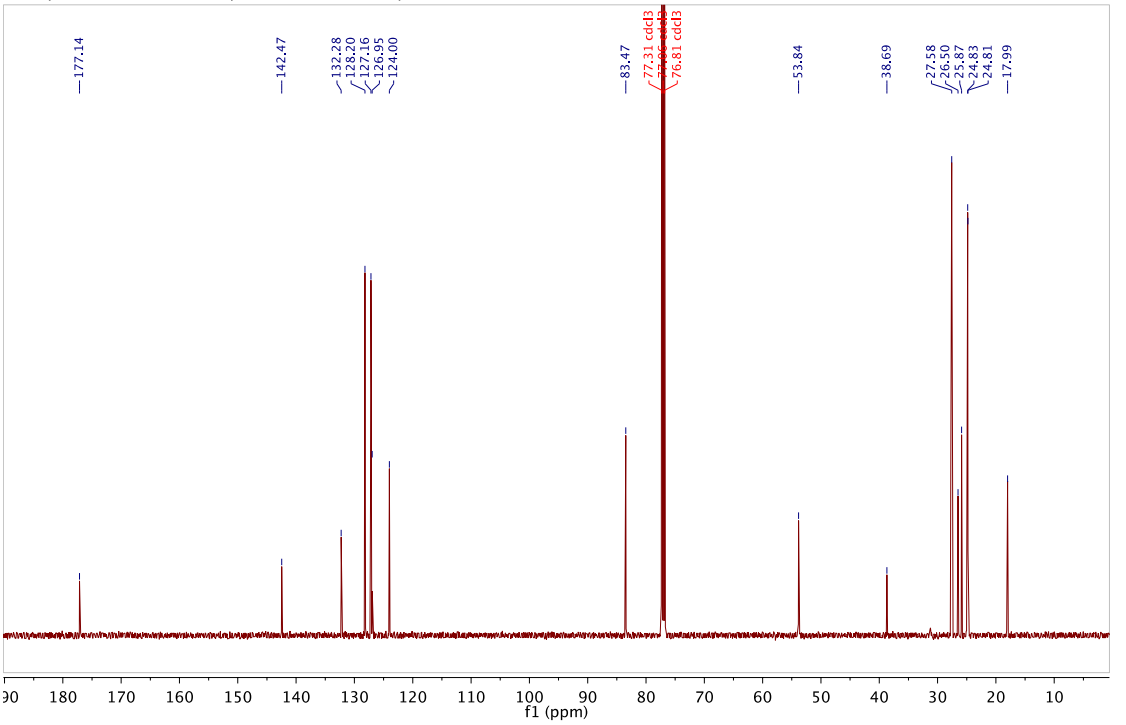


^{1}H and ^{13}C NMR of β-aminoalkylboronate 3-2o

2019.05.09.i5_XLH-14-11_H1_1D; 498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 26.9 C -> actual temp = 27.0 C, autoxdb probe

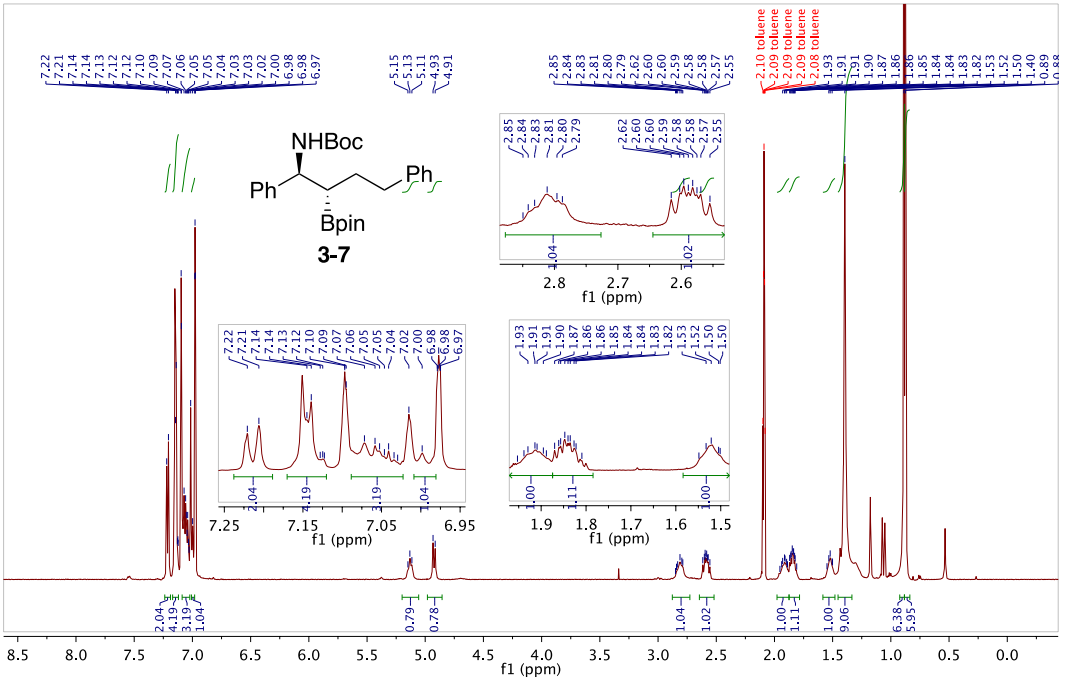


2019.05.09.u5_XLH-14-11_loc11_14.01_C13_1D; 125.685 MHz C13{H1} 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe

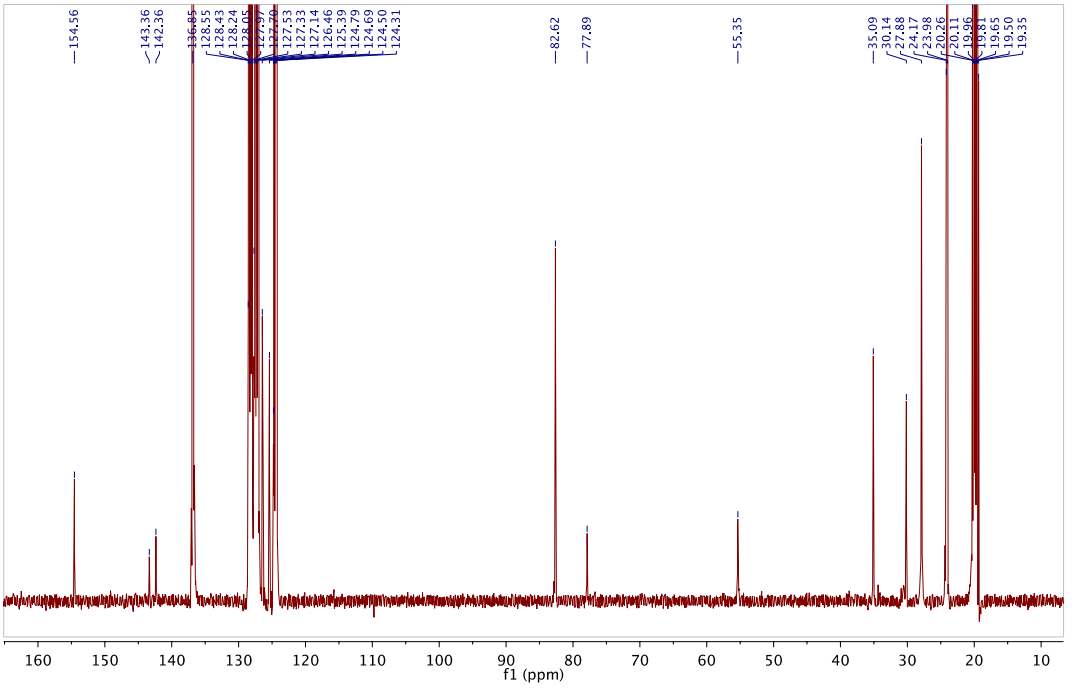


^{1}H and ^{13}C NMR of *N*-Boc-protected β-aminoalkylboronate 3-7

2019.09.25.i5_XLH-15-197_H1_1D; 498.120 MHz H1 1D in toluene
temp 26.9 C -> actual temp = 27.0 C, autoxdb probe

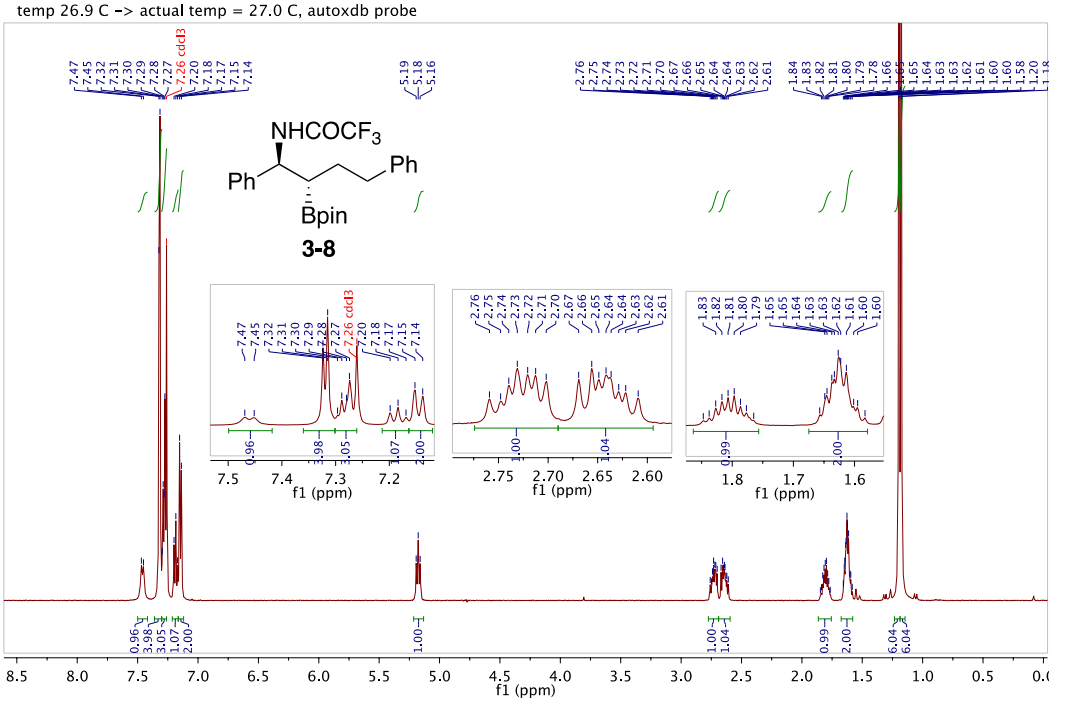


2019.09.25.u5_XLH-15-197_loc9_10.15_C13_1D; 125.685 MHz C13{H1} 1D in toluene
temp 27.7 C -> actual temp = 27.0 C, colddual probe

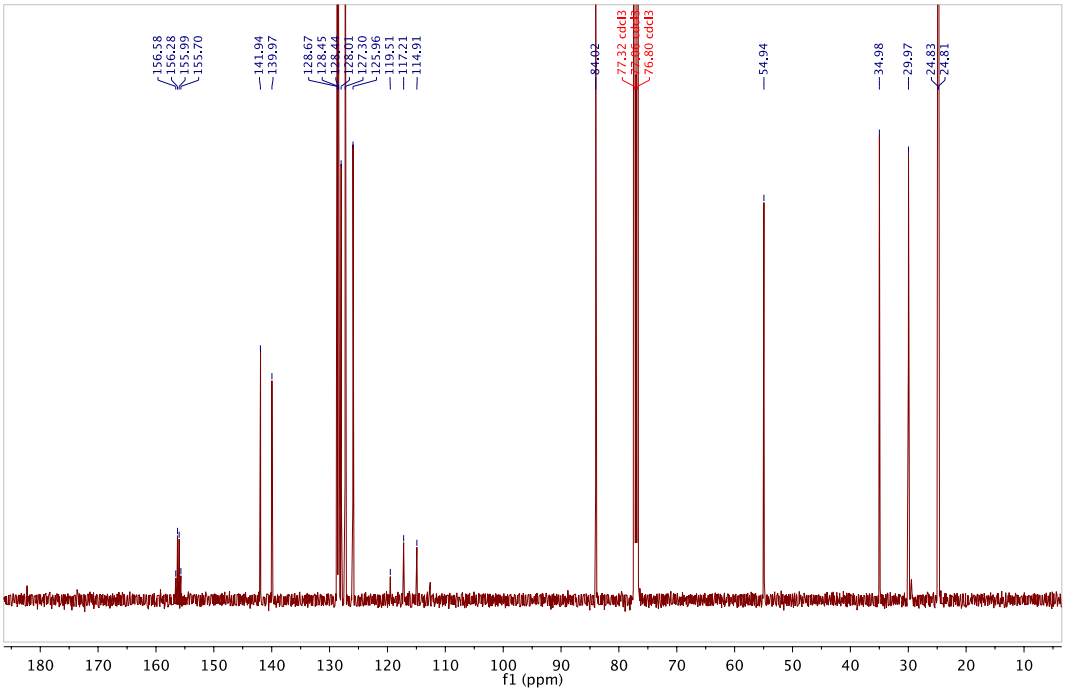


^{1}H and ^{13}C NMR of *N*-CF_3CO-protected β-aminoalkylboronate 3-8

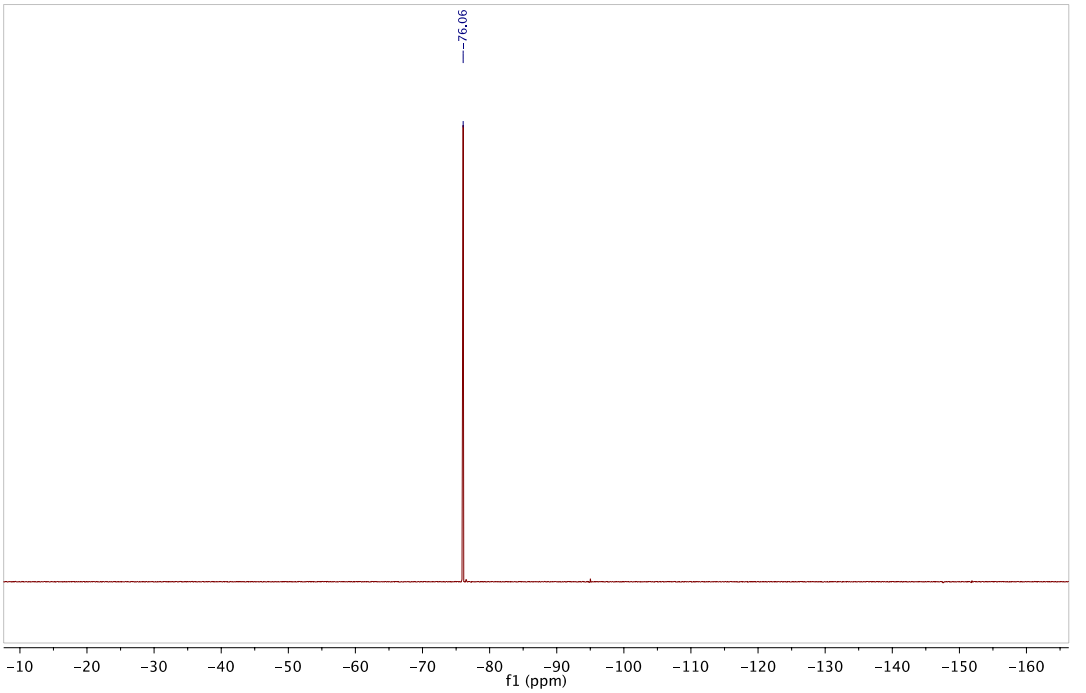
2019.04.25.i5_XLH-13-169-2_H1_1D; 498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 26.9 C -> actual temp = 27.0 C, autoxdb probe



2019.04.25.i5_XLH-13-169-2_09.47_C13_1D; 125.266 MHz C13{H1} 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 26.9 C -> actual temp = 27.0 C, autoxdb probe

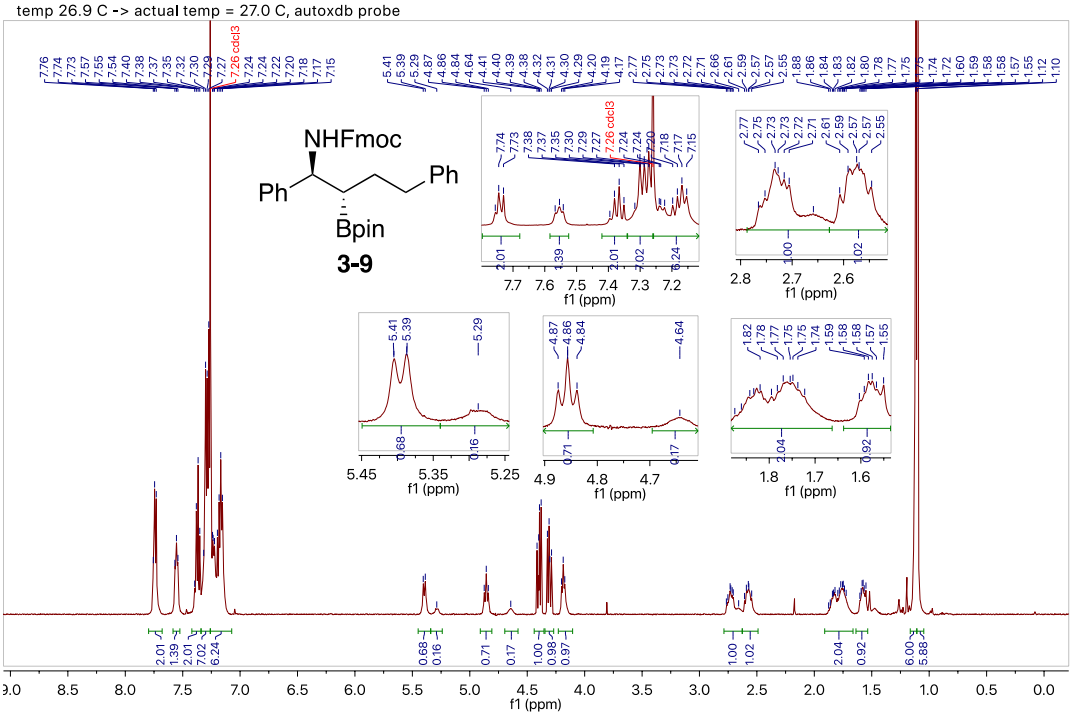


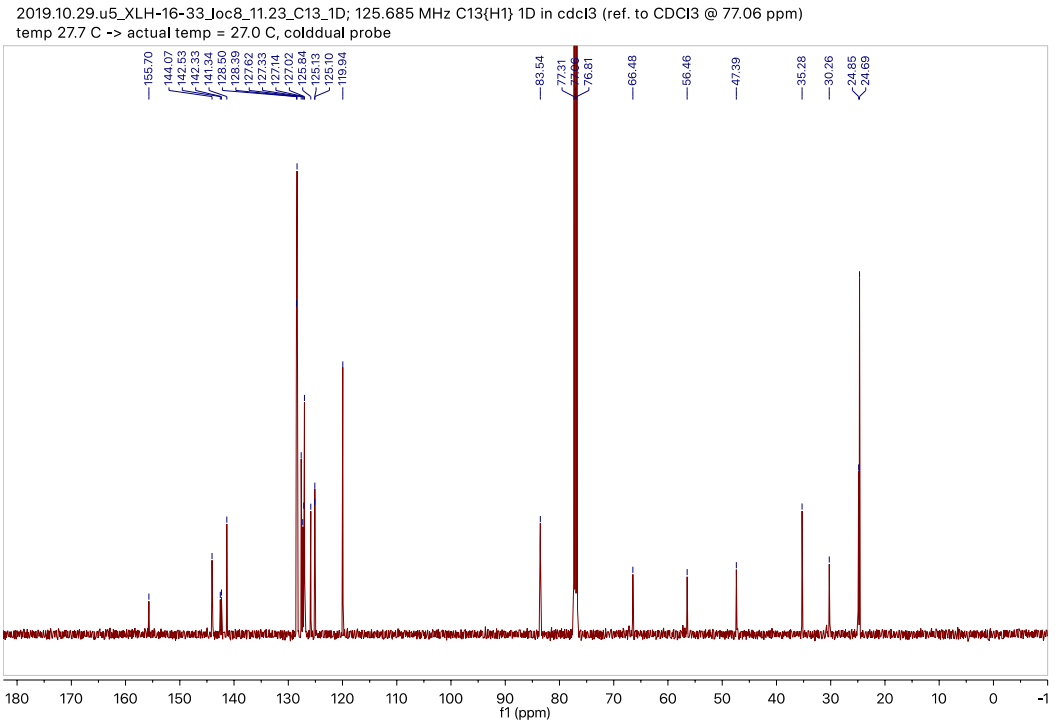
2019.04.25.i5_XLH-13-169-2_F19_1D; 468.652 MHz F19 1D in cdcl3
temp 26.9 C -> actual temp = 27.0 C, autoxdb probe



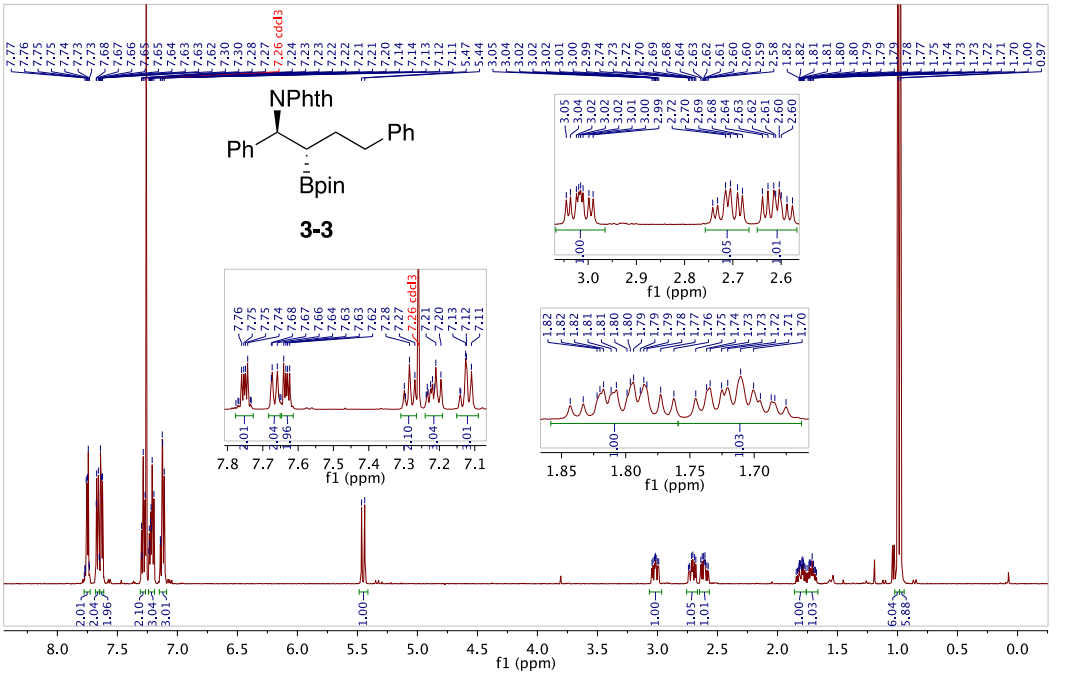
^{1}H and ^{13}C NMR of *N*-Fmoc-protected β-aminoalkylboronate 3-9

2019.10.29.i5_XLH-16-33_H1_PRESAT; 498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 26.9 C -> actual temp = 27.0 C, autoxdb probe

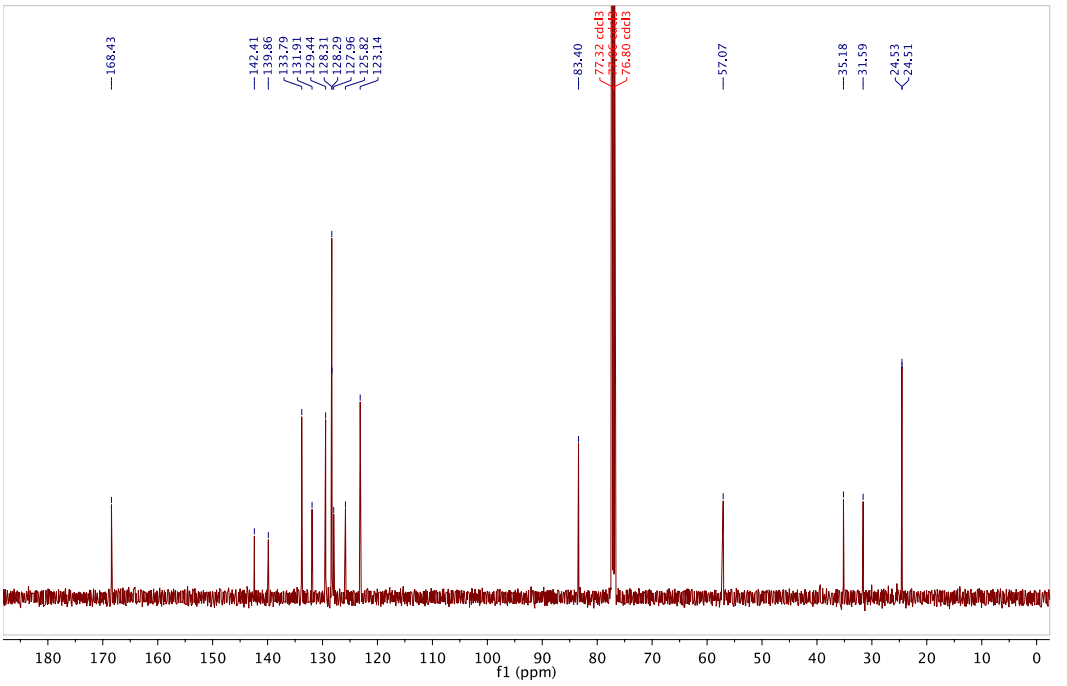




^{1}H and ^{13}C NMR of *N*-Phth-protected β-aminoalkylboronate 3-3

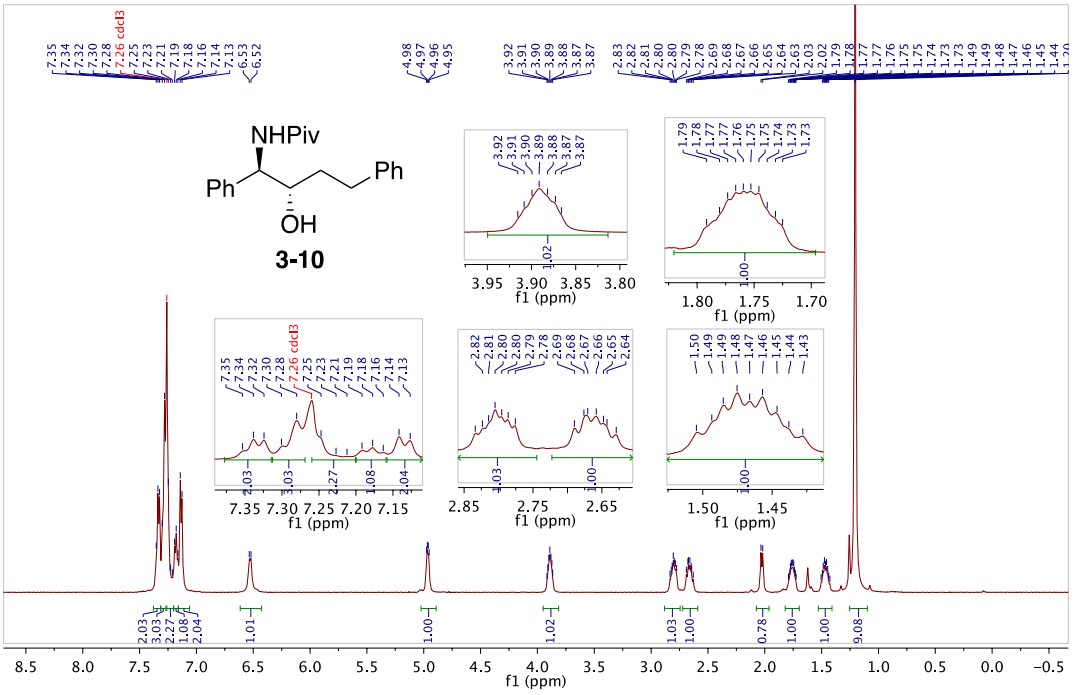


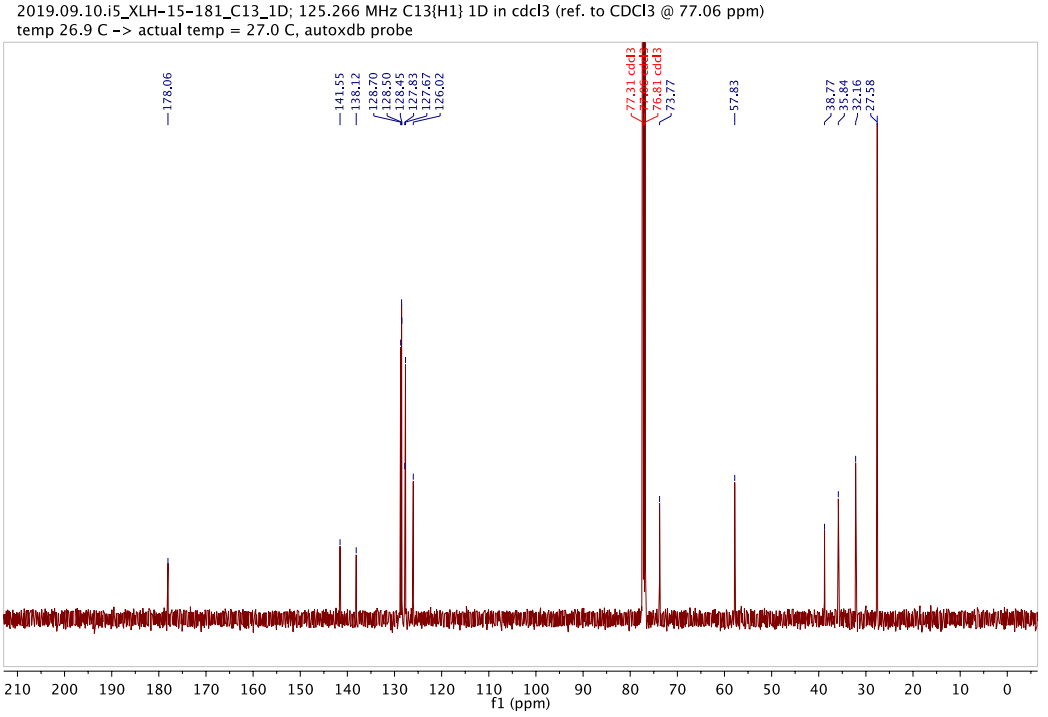
2019.08.29.i5_XLH-15-157_C13_1D; 125.266 MHz C13{H1} 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 26.9 C -> actual temp = 27.0 C, autoxdb probe



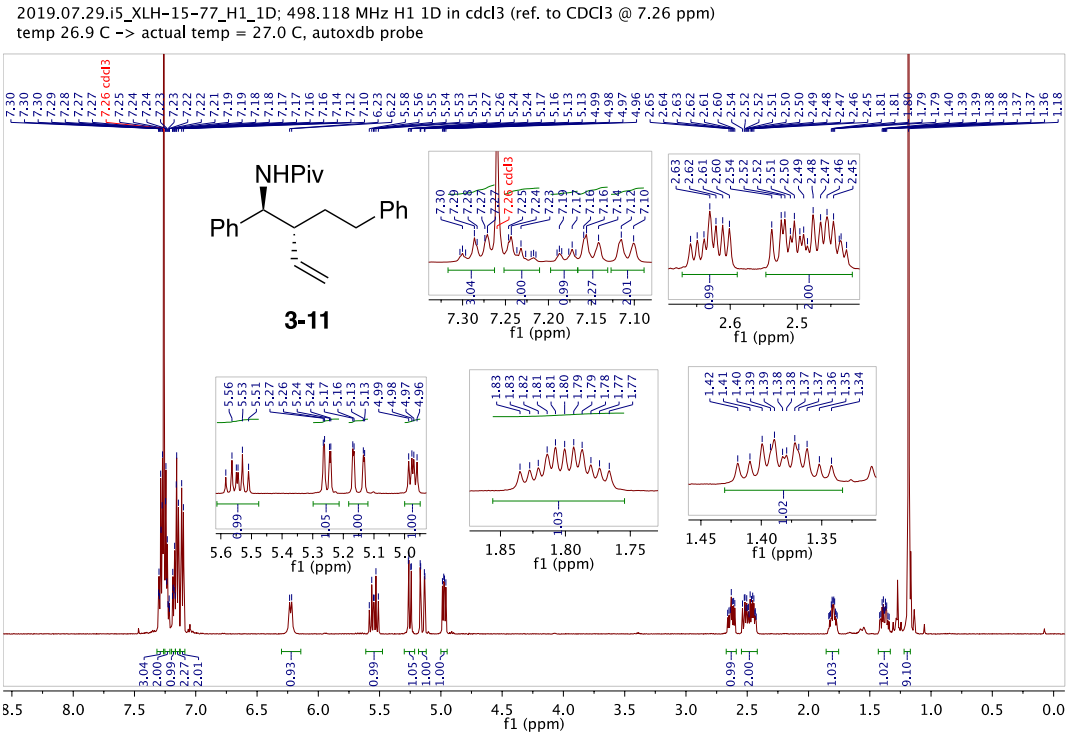
^{1}H and ^{13}C NMR of β-amino alcohol 3-10

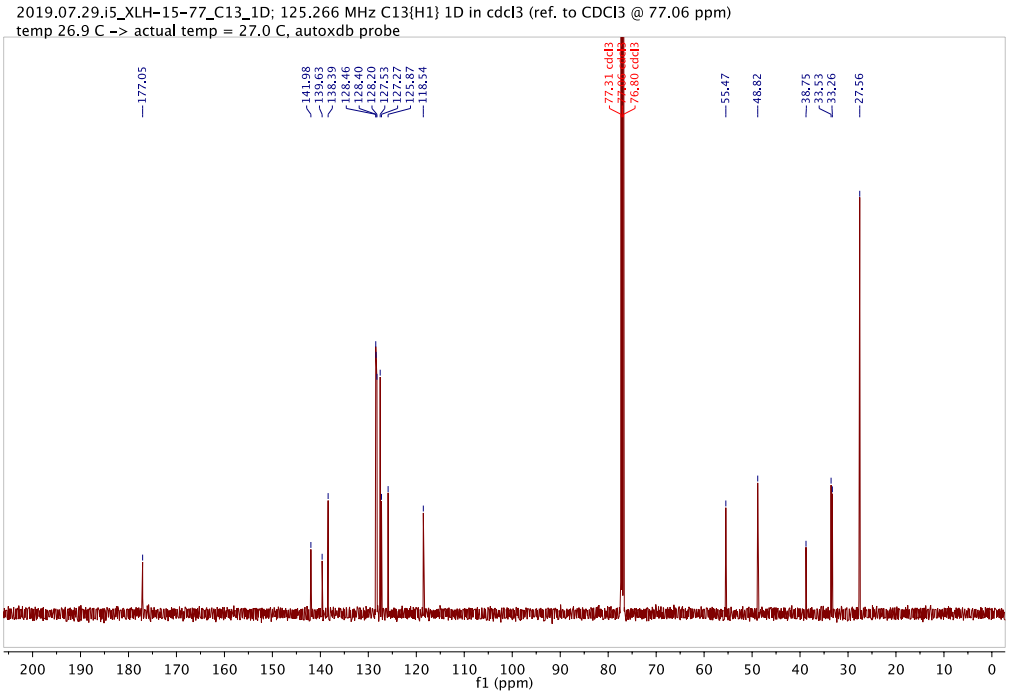
2019.09.10.i5_XLH-15-181_H1_1D; 498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 26.9 C -> actual temp = 27.0 C, autoxdb probe



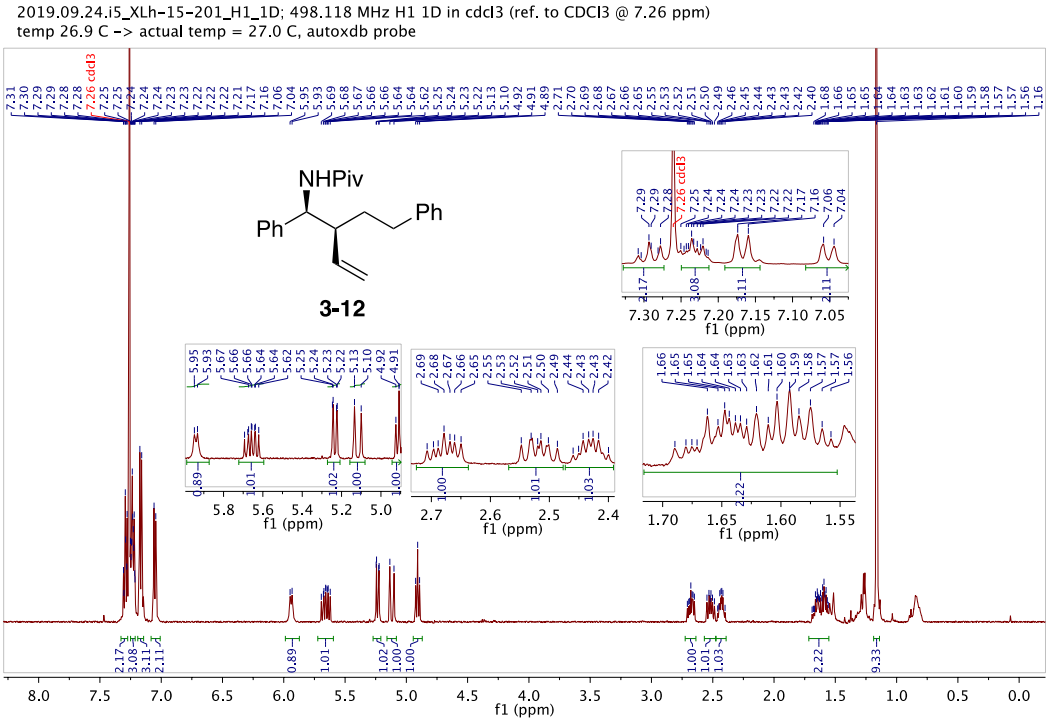


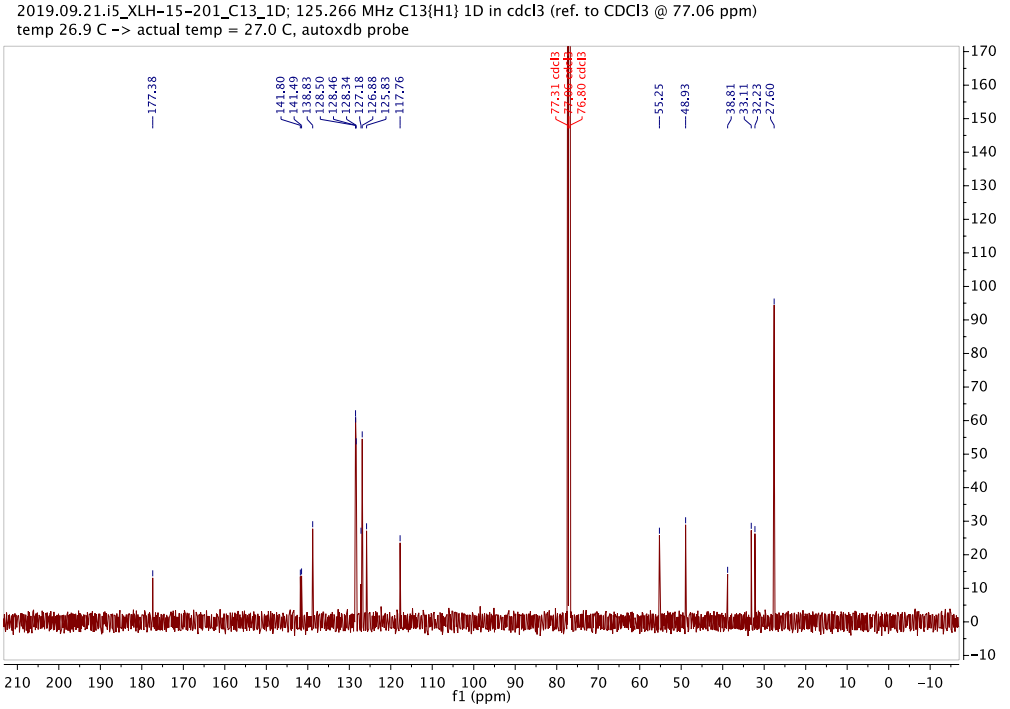
^{1}H and ^{13}C NMR of compound 3-11



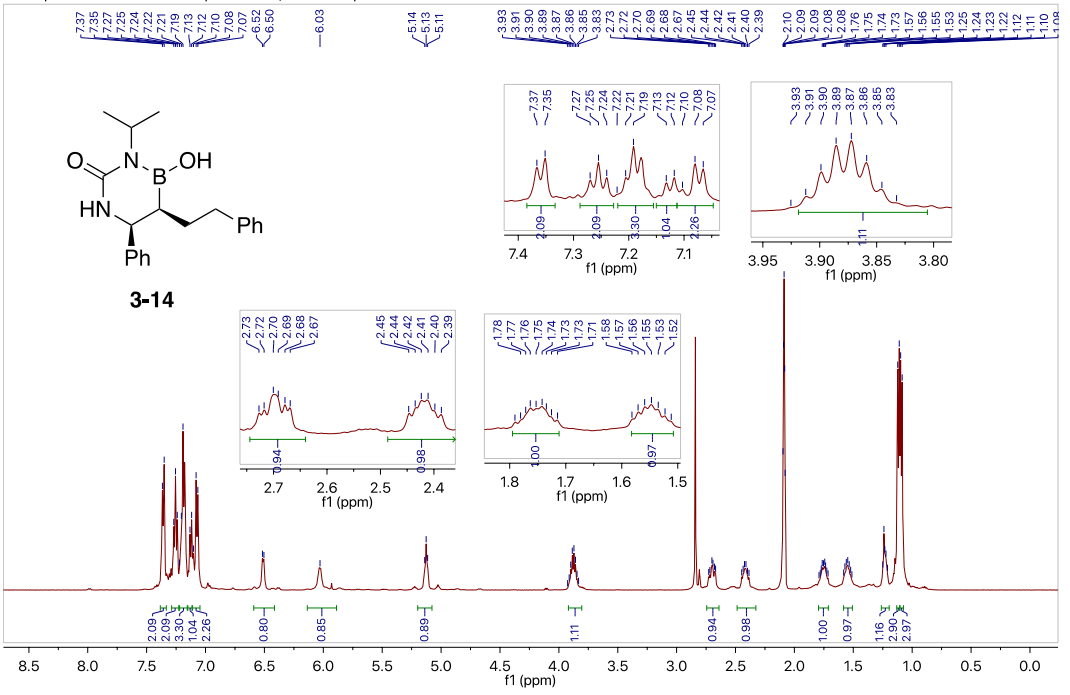


^{1}H and ^{13}C NMR of compound 3-12

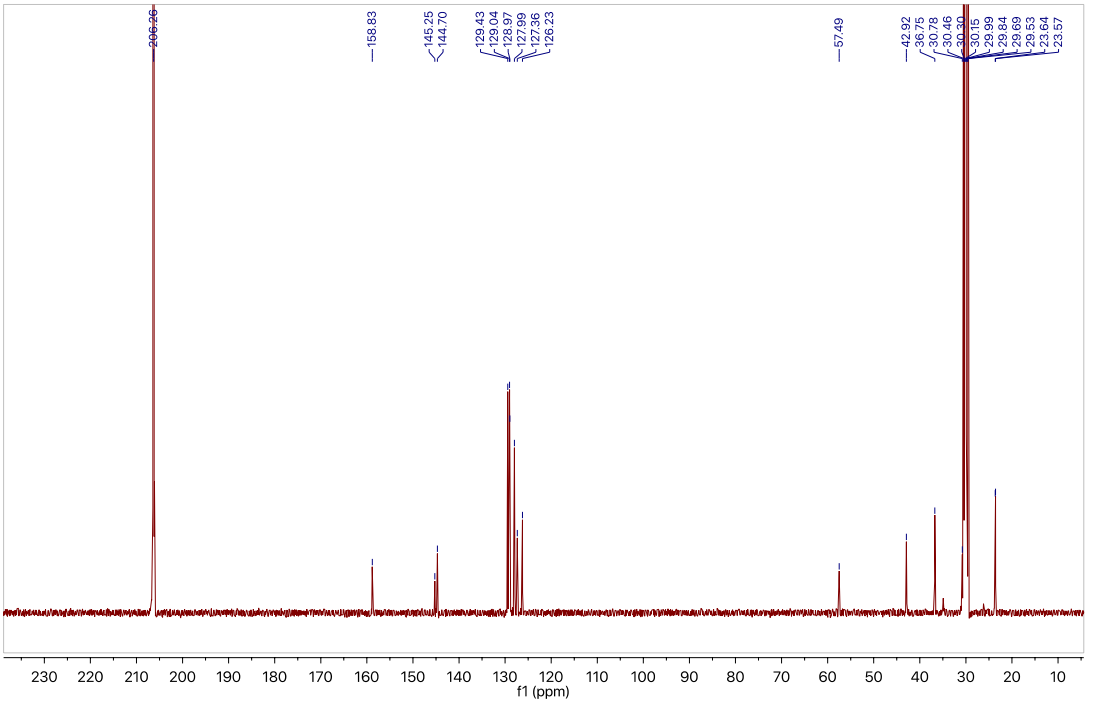




^{1}H and ^{13}C NMR of hemiboronic heterocycle 3-14

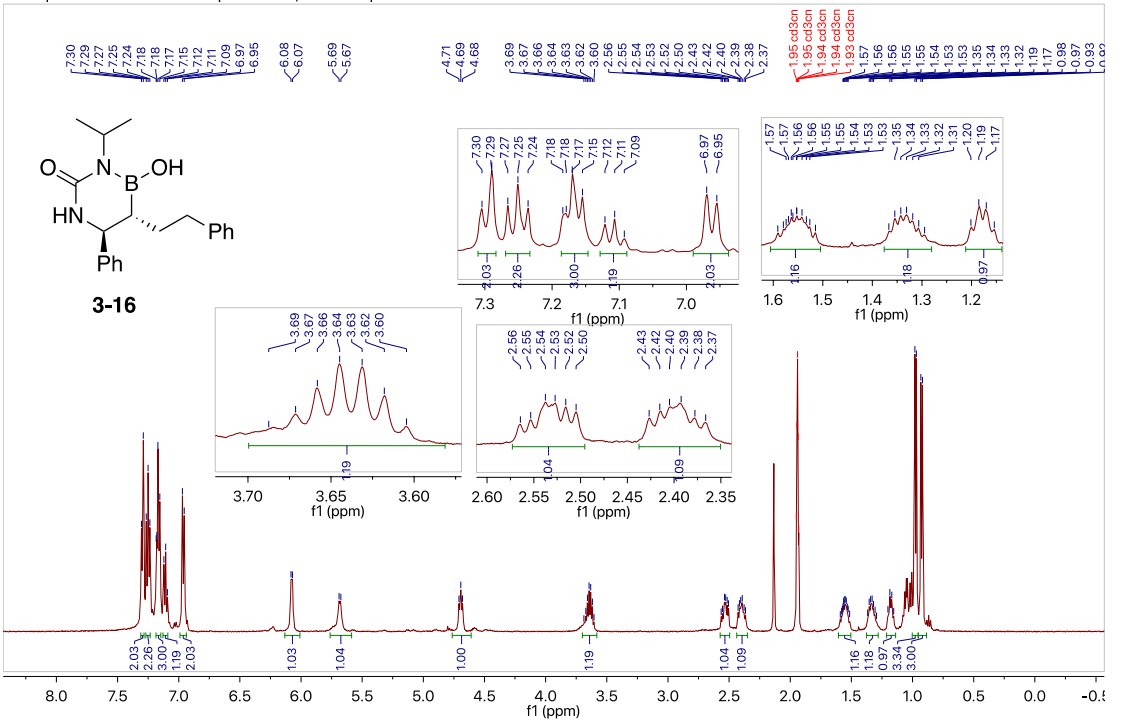


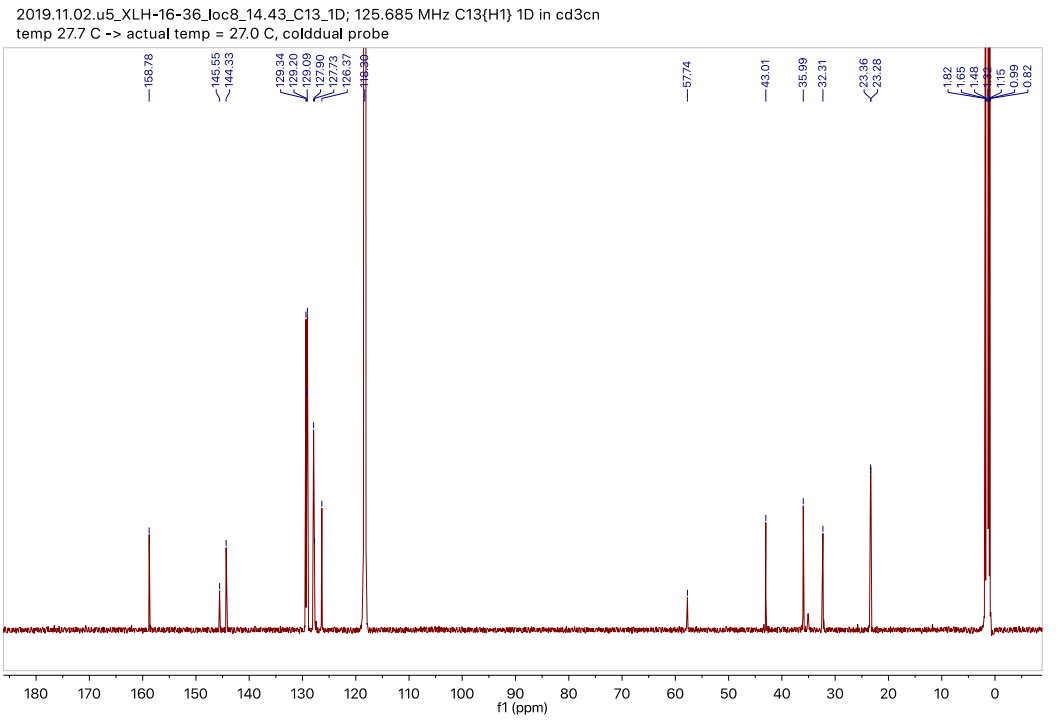
2019.10.01.u5_XLH-16-13acetone_loc11_17.12_C13_1D; 125.686 MHz C13{H1} 1D in acetone (ref. to acetone @ 29.8 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe



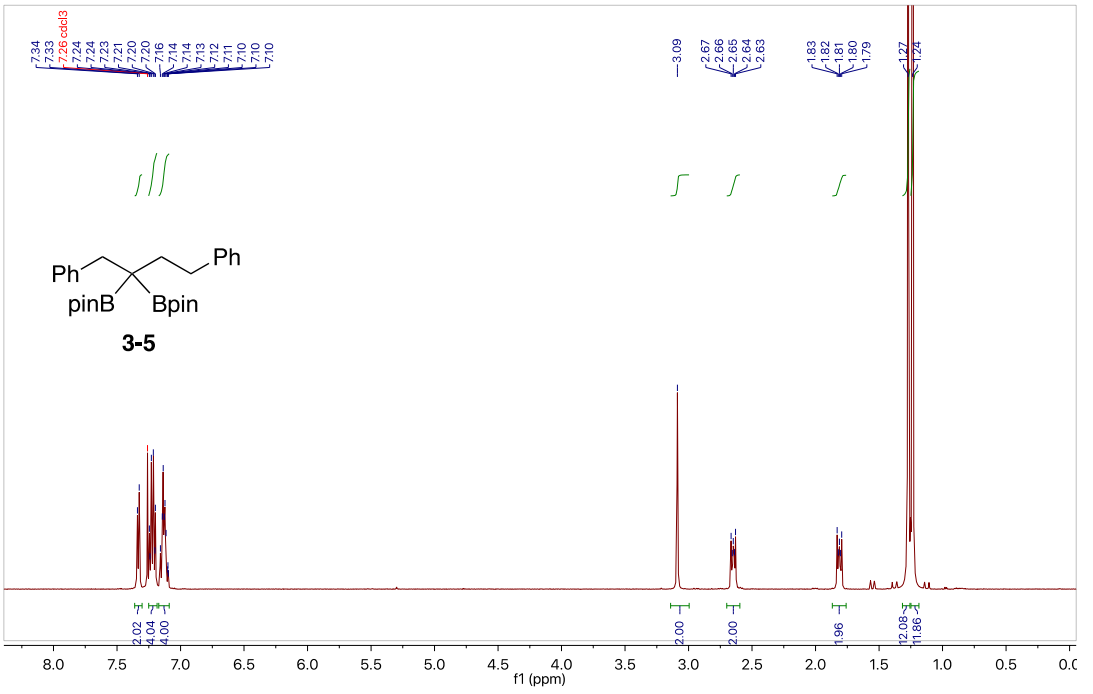
^{1}H and ^{13}C NMR of hemiboronic heterocycle 3-16

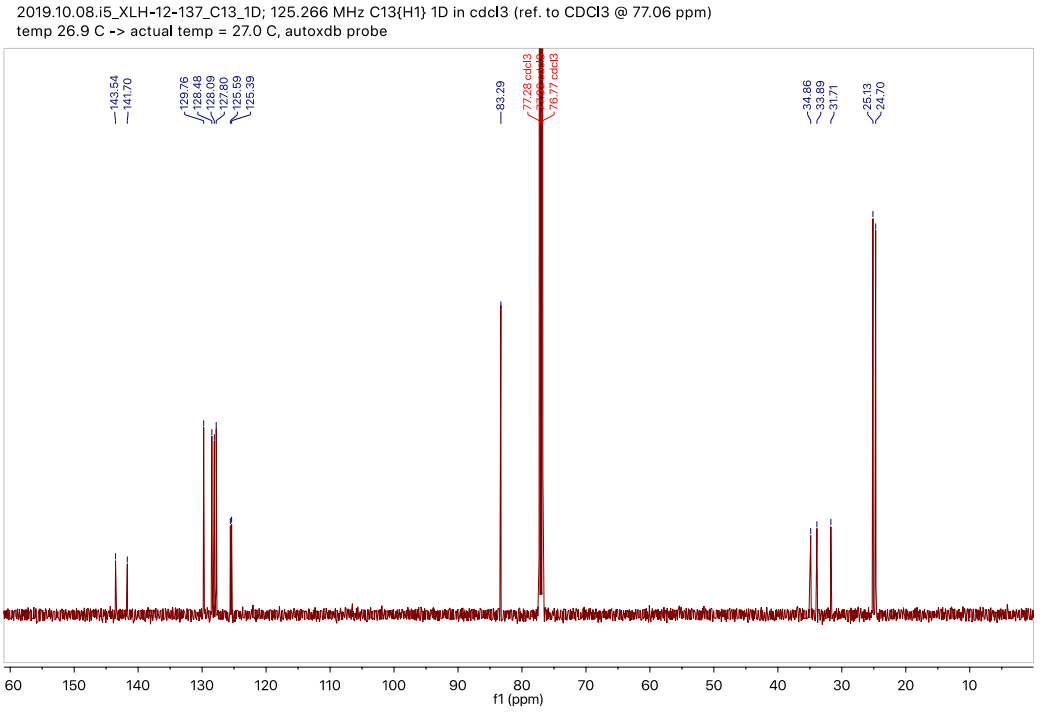
2019.11.02.i5_XLH-16-36-2_H1_PRESAT; 498.120 MHz H1 1D in cd3cn
temp 26.9 C -> actual temp = 27.0 C, autoxdb probe



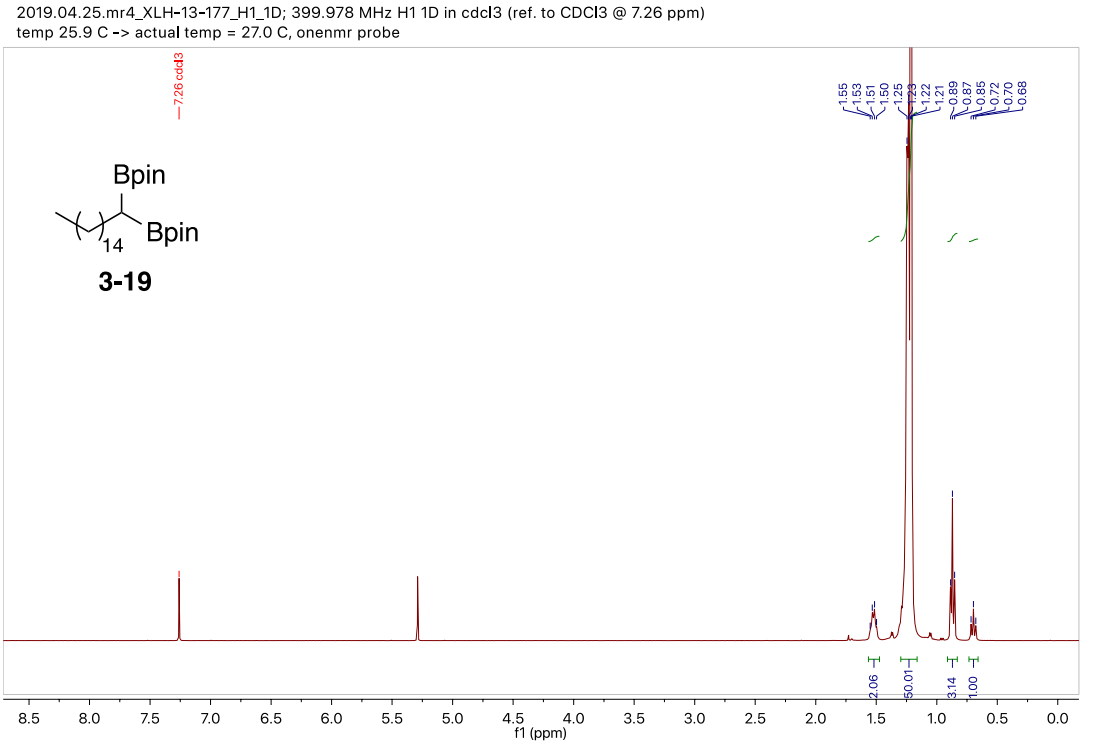


^{1}H and ^{13}C NMR of 1,1-diborylalkane 3-5

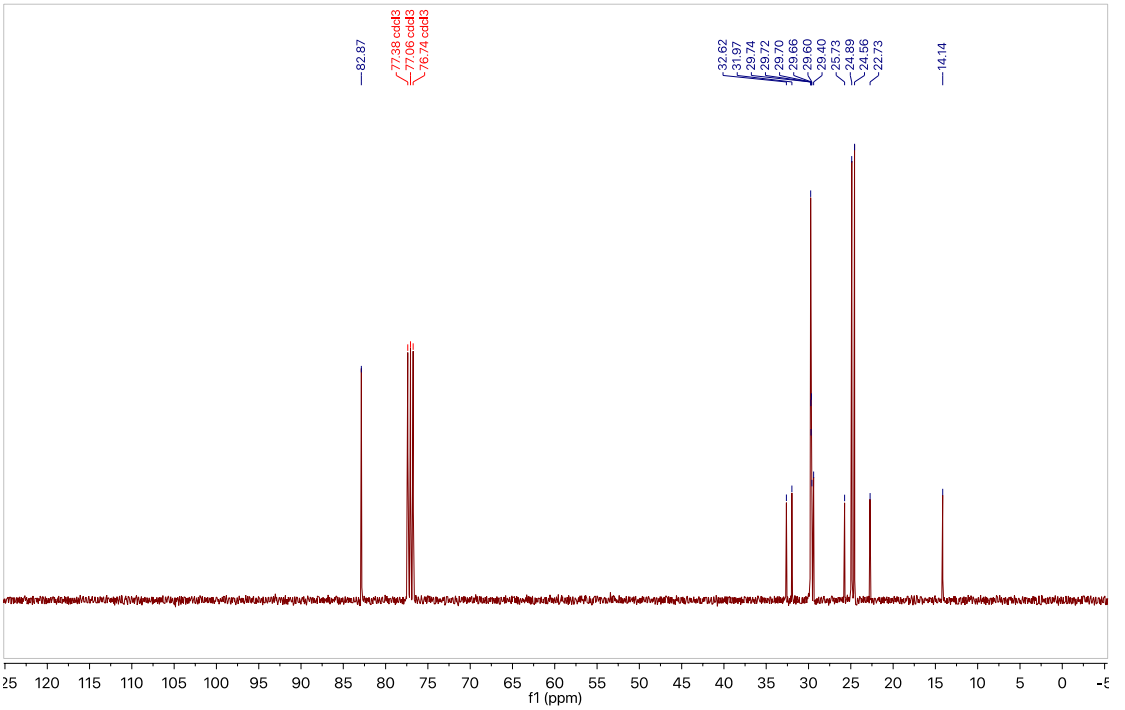




^{1}H and ^{13}C NMR of 1,1-diborylalkane 3-19

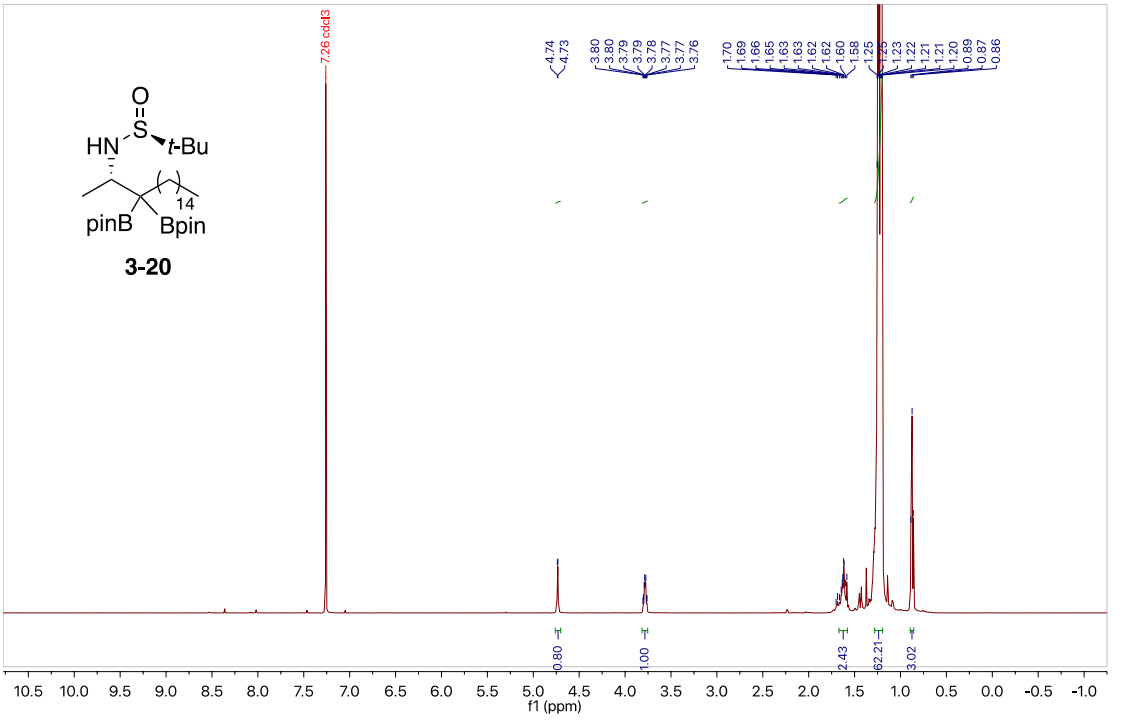


2019.04.25.mr4_XLH-13-177_C13_1D; 100.586 MHz C13{H1} 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 25.9 C -> actual temp = 27.0 C, onenmr probe



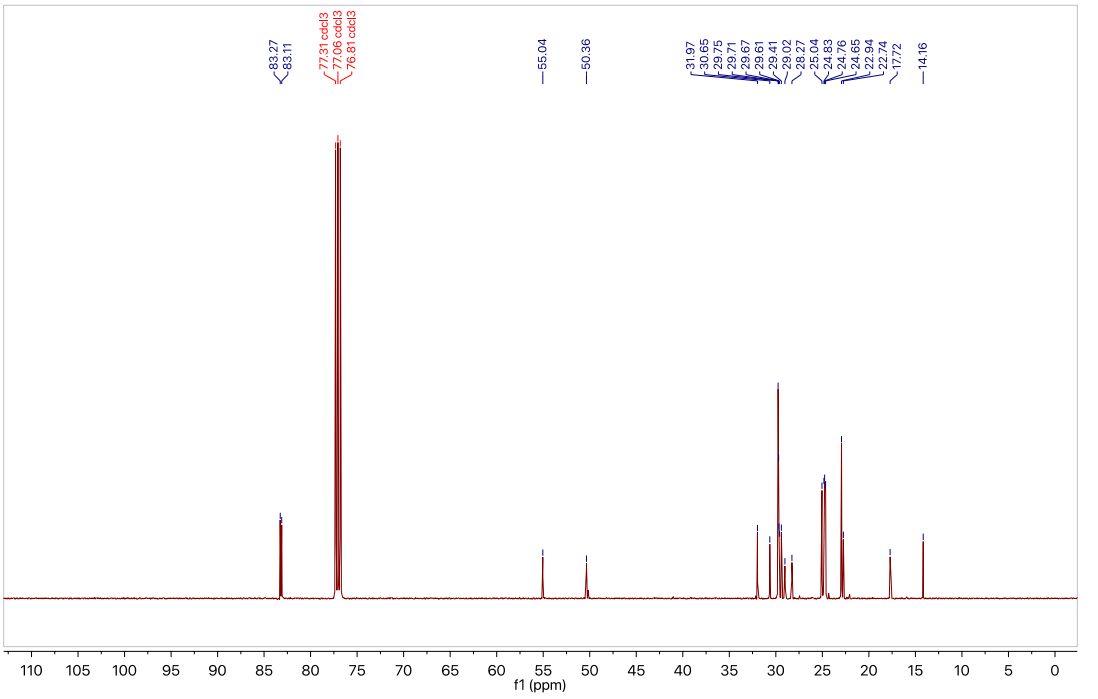
^{1}H and ^{13}C NMR of β-sufinimido *gem*-bis(boronate) 3-20

2019.05.11.u5_XLH-14-27_loc9_16.33_H1_1D; 499.787 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe



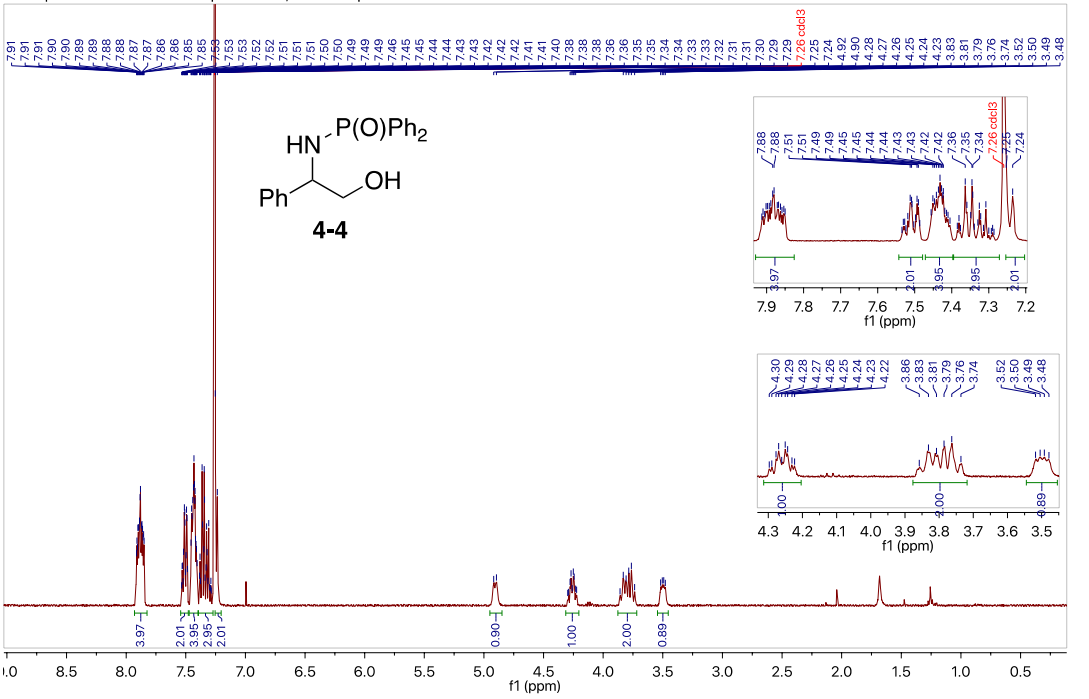
3-20

2019.05.11.u5_XLH-14-27_Ioc9_16.34_C13_1D; 125.685 MHz C13{H1} 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe

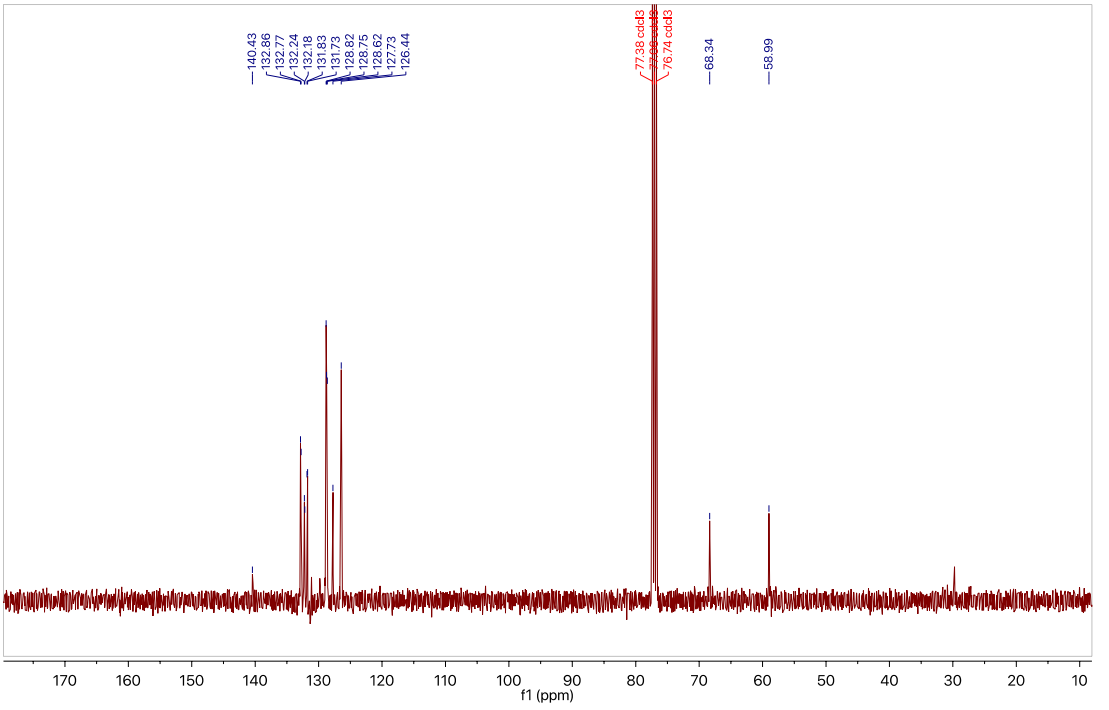


^{1}H, ^{13}C and ^{31}P NMR of β-amino alcohol 4-4:

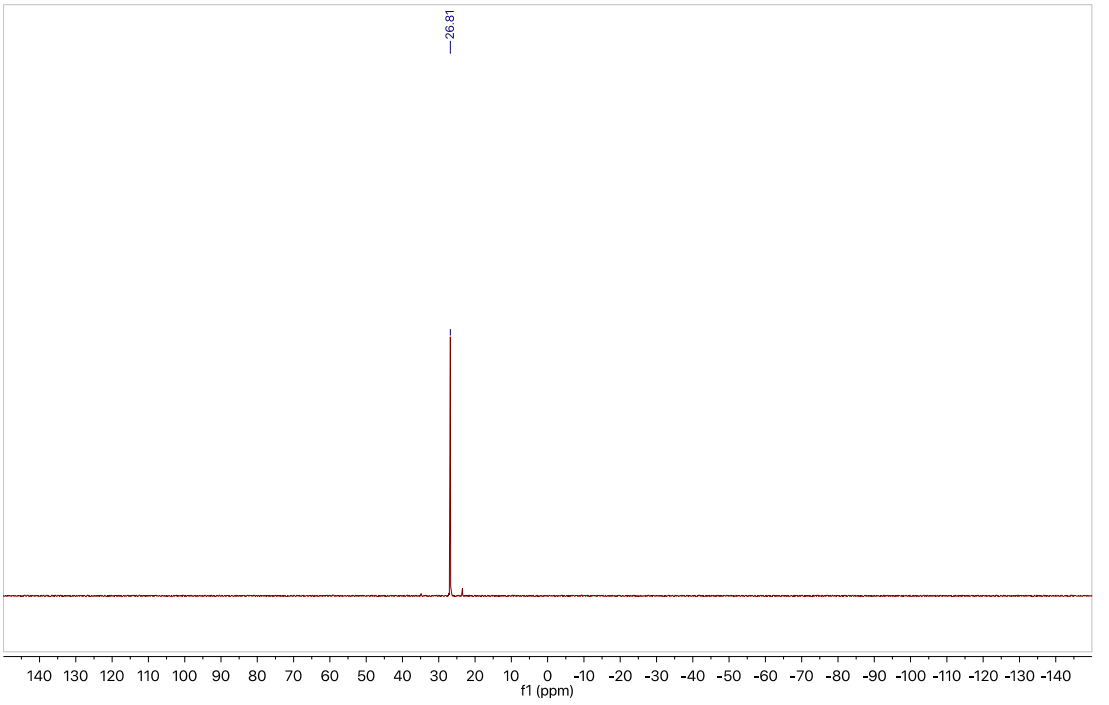
2016.08.18.i4_XLH-III-178_H1_1D; 399.794 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm),
temp 26.5 C -> actual temp = 27.0 C, autoxdb probe



2016.07.08.i4_XLH-III-70_C13_1D; 100.539 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm),
temp 26.5 C -> actual temp = 27.0 C, autoxdb probe

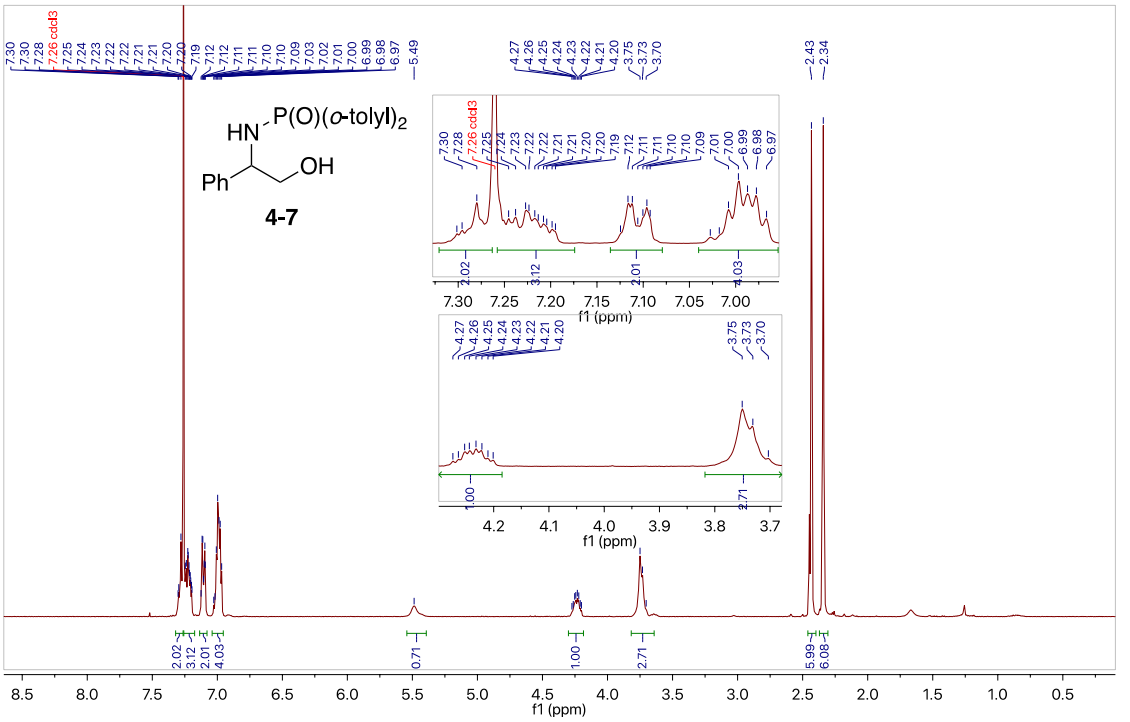


2016.06.29.i4_XLH-III-70product_P31_1D; 161.839 MHz P31[H1] 1D in cdcl3, temp 26.5 C -> actual temp = 27.0 C, autoxdb probe

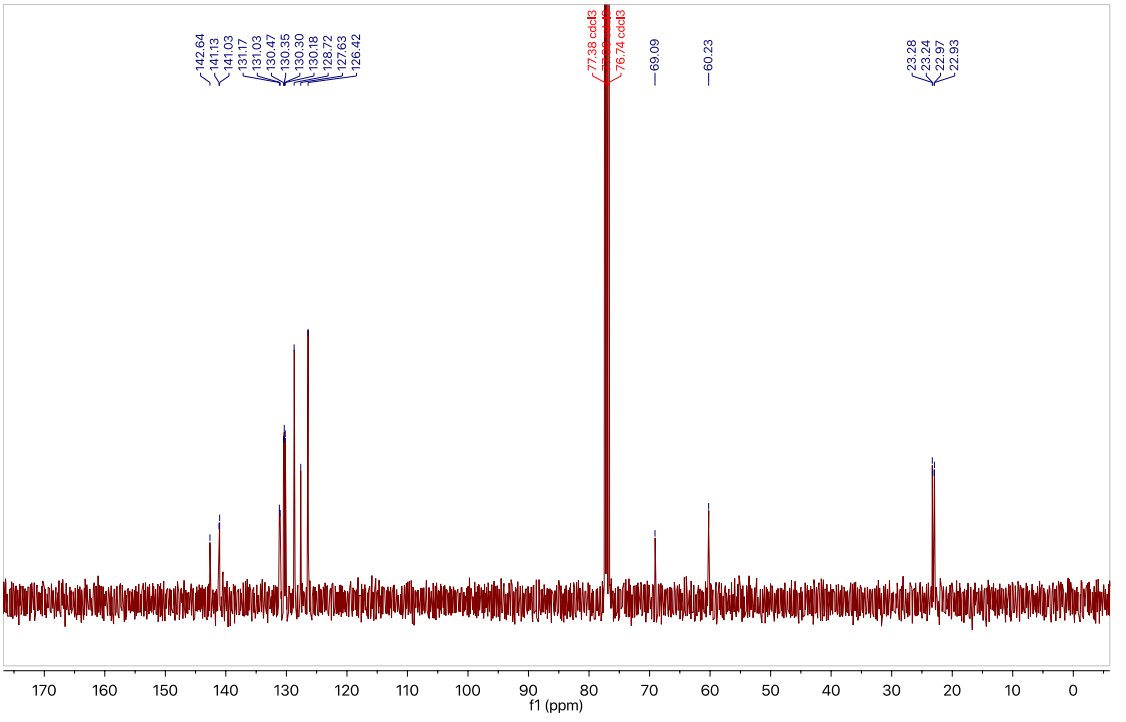


^{1}H, ^{13}C and ^{31}P NMR of β-amino alcohol 4-7

2019.12.23.i4_XLH-VII-96_Ioc19_11.04_H1_1D; 399.794 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 26.5 C -> actual temp = 27.0 C, autoxdb probe

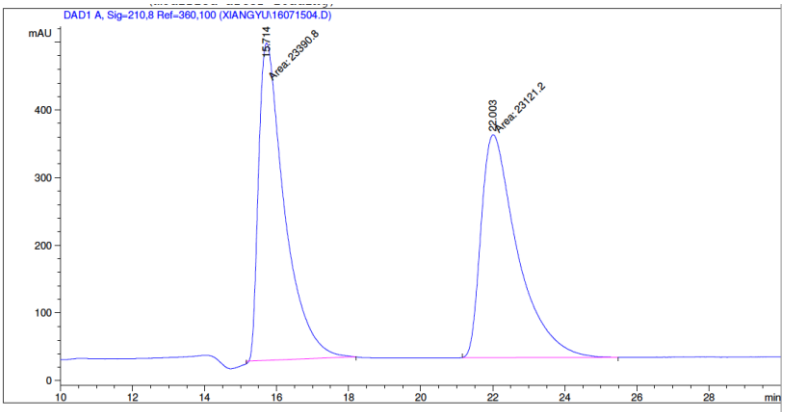


2019.12.23.i4_XLH-VII-96_Ioc19_11.09_C13_1D; 100.539 MHz C13{H1} 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 26.5 C -> actual temp = 27.0 C, autoxdb probe

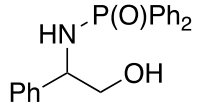


Appendix 2: Chromatograms for Enantiomeric Excess Measurement (Selected)

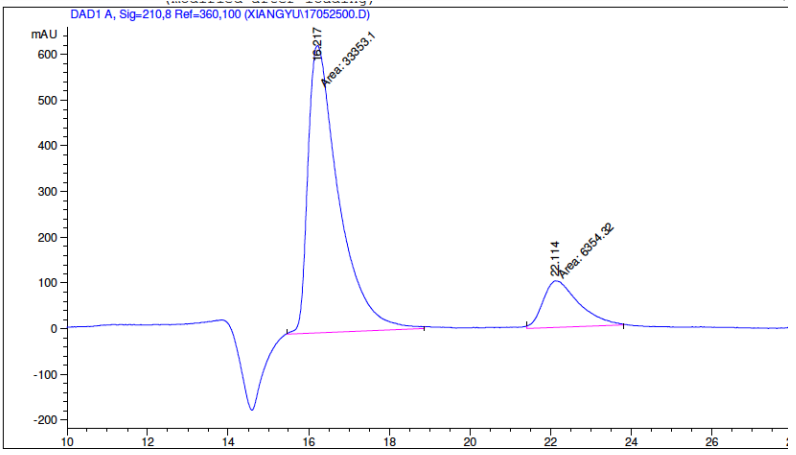
Racemic (top) and optically enriched (bottom) 4-4




```
================================================================
                    Area Percent Report
================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=210,8 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|-------|
   1  15.714 MM T  0.8314 2.33908e4   468.89609  50.2898
   2  22.003 MM T  1.1700 2.31212e4   329.36563  49.7102

Totals :                  4.65120e4   798.26172
```

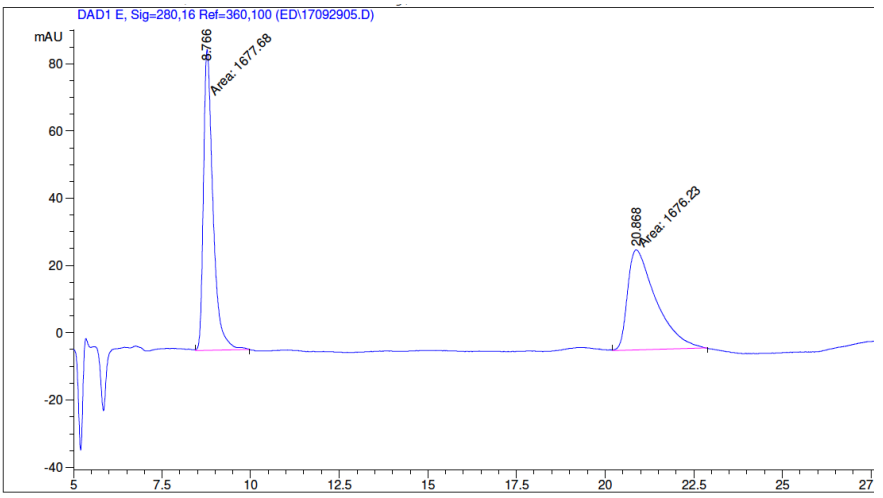


4-4

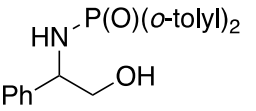



```
================================================================
                    Area Percent Report
================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=210,8 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|-------|
   1  16.217 MM T  0.8837 3.33531e4   629.03357  83.9971
   2  22.114 MM T  1.0344 6354.31689   102.38631  16.0029

Totals :                  3.97074e4   731.41988
```

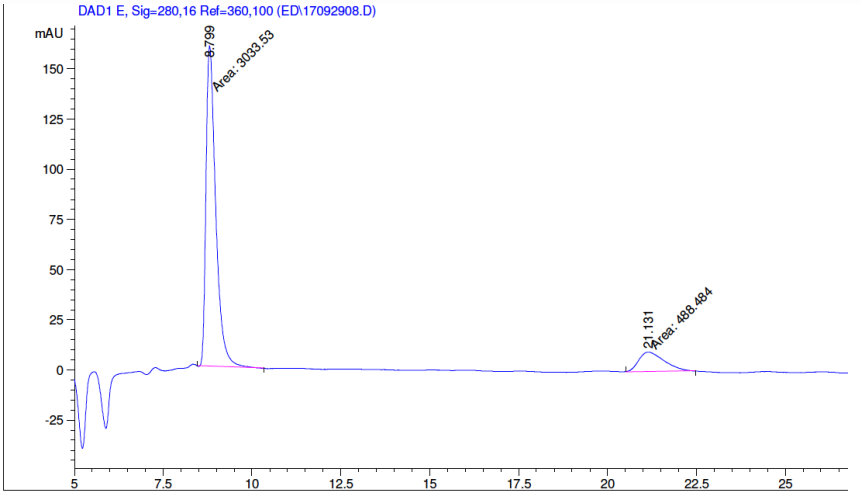
Racemic (top) and optically enriched (bottom) 4-7




```
================================================================================
                          Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 E, Sig=280,16 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   8.766 MM T  0.3120 1677.68274   89.61155  50.0216
   2  20.868 MM T  0.9356 1676.23181   29.86138  49.9784
```



4-7




```
================================================================================
                          Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 E, Sig=280,16 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   8.799 MM T  0.3564 3033.53174  159.73628  86.1305
   2  21.131 MM T  0.8387  488.48428    9.70741  13.8695
```

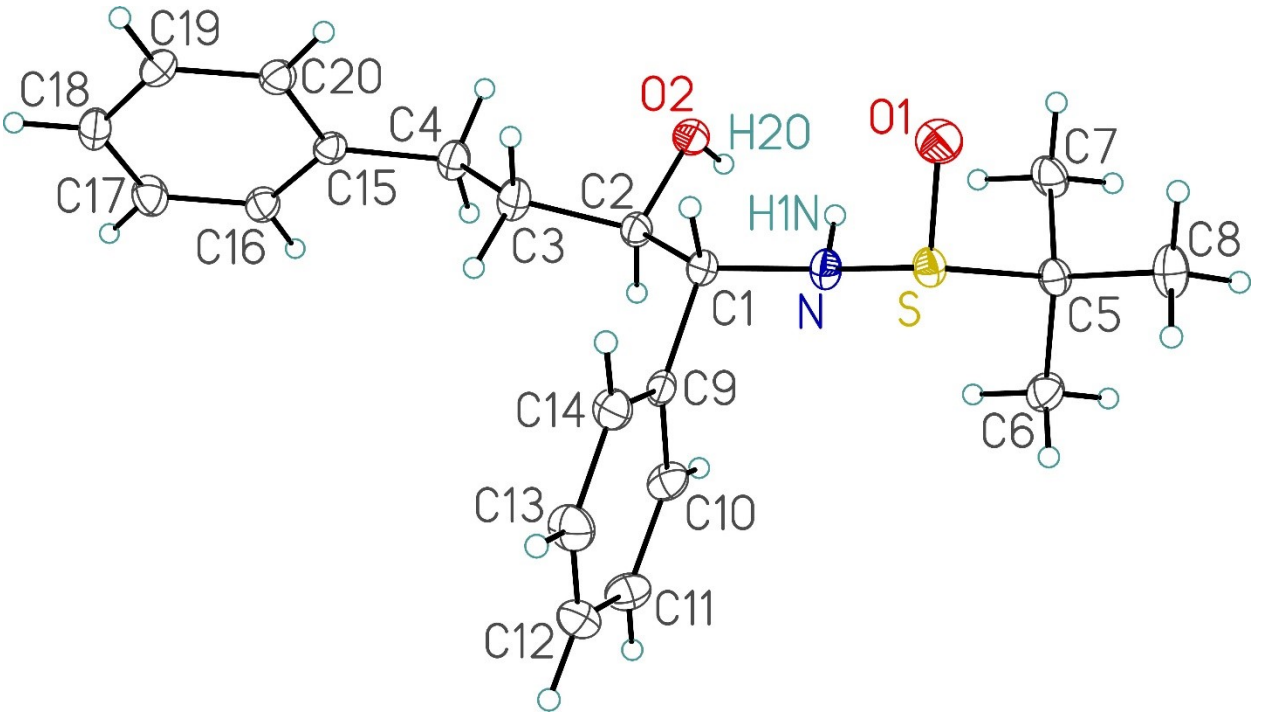
Appendix 3: Crystal Structure Report

X-ray Crystallographic data for compound 2-6

XCL Code: DGH1704 **Date:** 27 October 2017

Compound: *N*-(2-Hydroxy-1,4-diphenylbutyl)-2-methylpropane-2-sulfinamide
Formula: $C_{20}H_{27}NO_2S$

Supervisor: D. G. Hall **Crystallographer:** R. McDonald



For further information regarding this X-ray, please contact the X-ray crystallography laboratory at the University of Alberta:
Dr. Robert McDonald E-Mail: Bob.McDonald@ualberta.ca
Dr. Michael J. Ferguson E-Mail: Michael.Ferguson@ualberta.ca **Lab:** E3-09; **Office:** E3-13 Gunning/Lemieux Chemistry Centre
Phone: +1 780 492 2485; **Fax:** +1 780 492 8231

X-Ray Crystallography Laboratory, Department of Chemistry, University of Alberta, Edmonton, Alberta, T6G 2G2, Canada

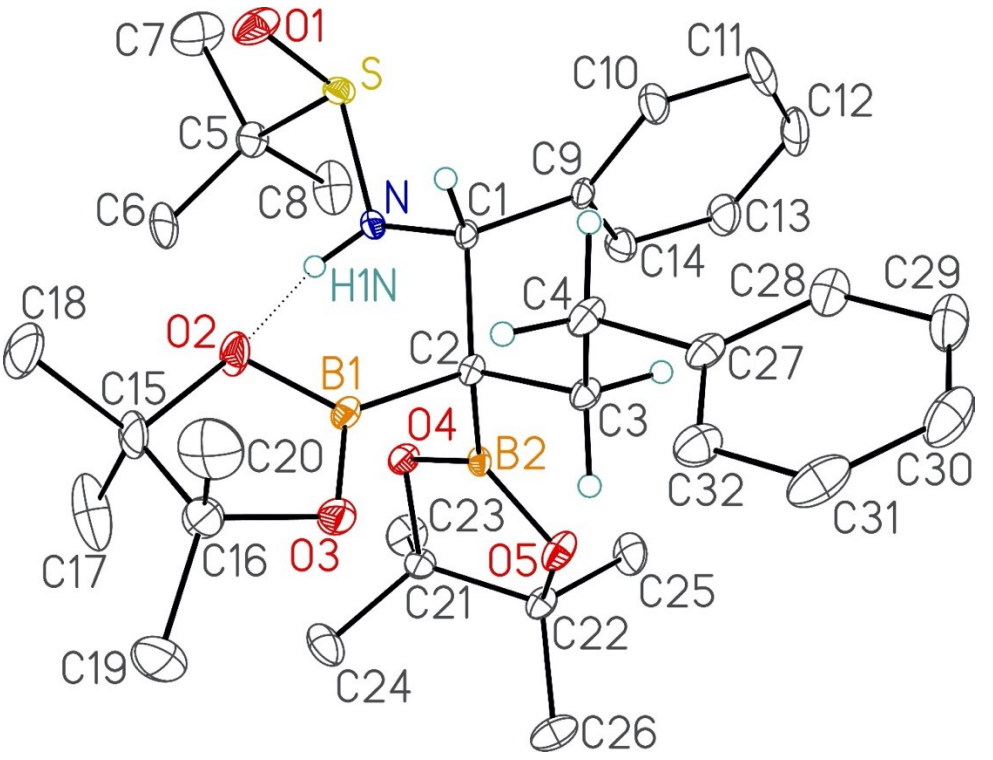
X-ray Crystallographic data for compound 2-3a

XCL Code: DGH1705 **Date:** 6 November 2017

Compound: *N*-{1,4-Diphenyl-2,2-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl}-2-methylpropane-2-sulfinamide

Formula: $C_{32}H_{49}B_2NO_5S$

Supervisor: D. G. Hall **Crystallographer:** R. McDonald



For further information regarding this X-ray, please contact the X-ray crystallography laboratory at the University of Alberta:
Dr. Robert McDonald E-Mail: Bob.McDonald@ualberta.ca
Dr. Michael J. Ferguson E-Mail: Michael.Ferguson@ualberta.ca **Lab:** E3-09; **Office:** E3-13 Gunning/Lemieux Chemistry Centre
Phone: +1 780 492 2485; **Fax:** +1 780 492 8231

X-Ray Crystallography Laboratory, Department of Chemistry, University of Alberta, Edmonton, Alberta, T6G 2G2, Canada

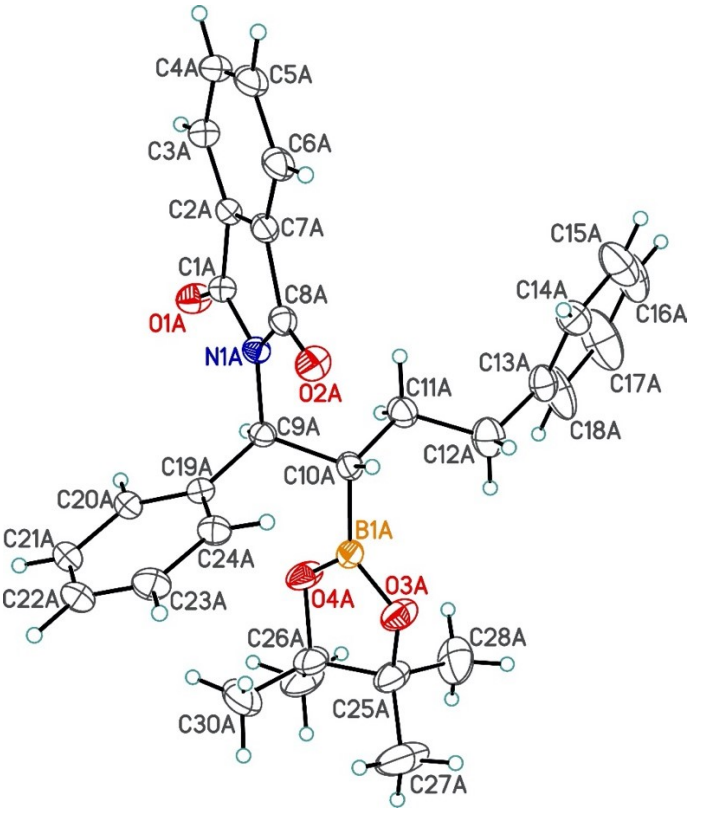
X-ray Crystallographic data for compound 3-3

XCL Code: DGH1917 **Date:** 18 November 2019

Compound: 2-[(1*S*,2*S*)-1,4-diphenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl]-1*H*-isoindole-1,3(2*H*)-dione

Formula: $C_{30}H_{32}BNO_4$

Supervisor: D. G. Hall **Crystallographer:** M. J. Ferguson



For further information regarding this X-ray, please contact the X-ray crystallography laboratory at the University of Alberta:
Dr. Robert McDonald E-Mail: Bob.McDonald@ualberta.ca
Dr. Michael J. Ferguson E-Mail: Michael.Ferguson@ualberta.ca **Lab:** E3-09; **Office:** E3-13 Gunning/Lemieux Chemistry Centre
Phone: +1 780 492 2485; **Fax:** +1 780 492 8231

X-Ray Crystallography Laboratory, Department of Chemistry, University of Alberta, Edmonton, Alberta, T6G 2G2, Canada