CATALYTIC STEREOSELECTIVE INSTALLATION OF BORON *VIA* C–C BOND FORMATION and STEREOSELECTIVE SYNTHESIS OF *N*-HETEROCYCLIC SCAFFOLDS *VIA* MAIN GROUP LEWIS ACID CATALYSIS

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ABSTRACT

BRANDON S. MOYER: CATALYTIC STEREOSELECTIVE INSTALLATION OF BORON *VIA* C–C BOND FORMATION
(Under the guidance of Simon J. Meek)

Enantiomerically pure chiral boron-containing molecules provide enabling platforms for chemical synthesis in that they are configurationally stable, they function as useful synthons for various functional groups, and their transformations into those diverse functionalities are stereospecific. With consensus that chiral alkyl sp^3 C–B bond-containing compounds are desirable building blocks, and given that most enantioselective preparations to date focus on installing a stereodefined C–B bond, our group sought to develop catalytic methods to generate and use chiral α-boron-containing nucleophiles that would enable the direct formation of a new C–C bond. To this extent, we exploited the utility of alkyl 1,1-diboron reagents, which have been shown to readily undergo facile activation and transmetalation in the presence of alkoxide bases to form chiral α-boryl nucleophiles.

The result of these investigations was the development of the first catalytic enantio- and diastereoselective synthesis of *syn*-1,2-hydroxyboronates *via* addition to aldehydes (Ch. 1). The reactions are promoted by a readily available chiral monodentate phosphoramidite–Cu(I) complex in the presence of an alkyl 1,1-diboron reagent. The products contain two contiguous stereogenic centers and are obtained in up to 91% yield, >98:2 d.r., and 98:2 e.r. The reaction is tolerant of aryl and vinyl aldehydes, and the 1,2-hydroxyboronate products can be transformed into versatile derivatives. Mechanistic experiments indicate that control of absolute stereochemistry resides at the α-boryl component.

Further investigations resulted in the development of a substantially more reactive Ag(I) catalytic protocol for the diastereoselective synthesis of complementary *anti*-1,2-hydroxyboronates with up to 99:1 d.r. (Ch. 2). We found that the increased reactivity of Ag(I), in conjunction with stoichiometric KO*t*Bu, allowed for a substantial broadening of substituted 1,1-diboronates that participate in the reaction. In addition, alkyl aldehydes were found to be suitable electrophiles with *n*-BuLi as an activator.

BRANDON S. MOYER: STEREOSELECTIVE SYNTHESIS OF *N*-HETEROCYCLIC SCAFFOLDS *VIA* MAIN GROUP LEWIS ACID CATALYSIS
(Under the guidance of Michel R. Gagné)

Silylium ions (formally $[R_3Si]^+$) have long been the subject of investigations and significant debate in both theoretical and experimental chemistry, but few catalytic, synthetic applications have been reported due to the exceptionally high reactivity and Lewis acidity of these elusive species. Chapter 3 discusses the application of easily accessible silylium ion catalysts to the stereoselective synthesis of various *N*-heterocyclic pyrrolidine and piperidine scaffolds. The tested substrates are derived from the chiral pool and can be obtained in three high-yielding steps from amino alcohols; subsequent stereoselective silylium ion-catalyzed *Prins*-cyclization and trapping with R_3Si–Nu nucleophiles (*e.g.* Nu = H, allyl, azide, and enol ethers) results in novel nitrogen-containing polycyclic scaffolds with potential medicinal chemistry applications. An appendix to this chapter (A) discusses the substrate scope of the unpublished discovery that the Lewis acid $B(C_6F_5)_3$ catalyzes a stereospecific *Prins* cyclization followed by an elimination (formally a carbonyl-ene reaction) to form *trans*-tetrahydropyridine products in exceptionally high yield and diastereoselectivity.

ACKNOWLEDGEMENTS

In hindsight, the last five years have gone by so quickly; it's difficult to believe that the end of my Ph.D. is at hand and that I'll finally be moving on to greener pastures. I've doubted my ability to see it through to the end on many occasions over the past five years and sometimes graduate school felt insurmountable. During this long maturation process and through the occasional existential crisis, I've relied on many people in different ways to help me make it through and I would like to acknowledge them here.

I owe a debt of gratitude to both of my advisers, Dr. Simon J. Meek and Dr. Michel R. Gagné. I spent my first three years of graduate school in Simon's lab and appreciated the work ethic and structure that he instilled in the group. Simon is an idea-generating machine and it was often inspiring to hear his proposals. However, after those three years and two publications, I desired to better exercise the independent and creative aspects of earning a Ph.D., and so I joined Mike's group. I really appreciate the support, freedom, and trust he provided to make me stand on my own, pursue an independent project, and get it published.

I would like to thank all the former Meek lab members, Dr. Courtney C. Roberts, Dr. Matthew J. Goldfogel, and particularly Dr. Matthew V. Joannou, for teaching me useful synthetic/laboratory skills and providing valuable advice during the dark days of early graduate school. We found the simple things in life to make it through the daily grind (gorging on snacks after group meeting, Taco Tuesdays, and dubstep Saturdays).

I'm also thankful to the Gagné lab members for accepting me into the group without reservations, for being available for the occasional, spontaneous after-work drink, and in

general, just being really fun and laidback people.

I am grateful for the long-lasting core friendships that I've formed while in graduate school with (the now) Dr. Trandon Bender, Sam Bartlett, and Alex Brugh. As a private and introverted individual, I don't have many friendships, but the ones I do have I nurture and they are deep and strong. It's rare for me to find such intelligent, open-minded, and accepting individuals who can tolerate my dark and dry sense of humor, and I have greatly treasured your friendships. I hope we'll be able to maintain our friendships over the distances that will separate us. Here's to future reunions, wine nights, beach/mountain trips, and shots of Evan Williams at the movie theater.

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Finally, I can't quite express how much I appreciate (and needed) the love and support from my fiancé Katherine Henderson. Since we first started dating in November of 2014, she has centered me and dramatically increased my happiness, outlook, and quality of life. She was there for me when I was seriously considering whether I belonged in graduate school; she has always been there for me, bringing support, understanding, and communication to the relationship table. I hope to have many fun adventures and new experiences with you as we grow together in the future.

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LIST OF ABBREVIATIONS

°C	degrees Celsius
Å	angstrom
Ac	acetyl
aq.	aqueous
BCF	tris[pentafluorophenyl]borane; $B(C_6F_5)_3$
Bn	benzyl
Bz	benzoyl
Cbz	carboxybenzyl
δ	delta – chemical shift (NMR)
d	doublet (NMR)
D	dextrorotary (stereochemistry, relative to glyceraldehyde)
DCM	dichloromethane
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
eq.	equivalent
ESI	electrospray ionization
Et	ethyl
g	gram
µg	microgram
GCMS	gas chromatography – mass spectroscopy

h	hour
HR-MS	high resolution – mass spectrometry
Hz	hertz (NMR coupling constants)
i-Pr	isopropyl
L	liter
L	Levorotary (stereochemistry, relative to glyceraldehyde)
mg	milligram
mL	milliliter
μL	microliter
λ	lambda - wavelength
M	molar – 1 mol / liter (concentration)
Me	methyl
MeOH	methanol
mg	milligram
MgSO4	magnesium sulfate
MHz	megahertz
μL	microliter
min	minutes
mM	millimolar – 10^{-3} mol / liter (concentration)
mmol	millimole
mol %	mole percent (catalyst loading)
MS	molecular sieves
m/z	mass-to-charge ratio (mass spectrometry)

NMR	nuclear magnetic resonance
PG	any unspecified protecting group
PPTS	pyridinium *p*-toluenesulfonate (an acidic a resin)
Ph	phenyl
π	pi – electrons involved in multiple bonds
PPh_3	triphenylphosphine
ppm	parts per million (NMR relative difference)
^{i}Pr	*iso*-propyl
q	quartet (NMR)
R-	any unspecified carbon-containing group
RT	room temperature
σ	sigma – electrons involved in C-C single bonds
σ^*	antibonding orbital in C-C single bonds
s	singlet (NMR))
t	triplet (NMR)
t-Bu	*tert*-butyl
TES	triethylsilyl
THF	tetrahydrofuran
TMS	trimethylsilyl
trityl $BArF_{20}$	trityl tetrakis[pentafluorophenyl]borate; $[Ph_3C][B(C_6F_5)_4]$
WCA	weakly coordinating anion
wt %	weight percent

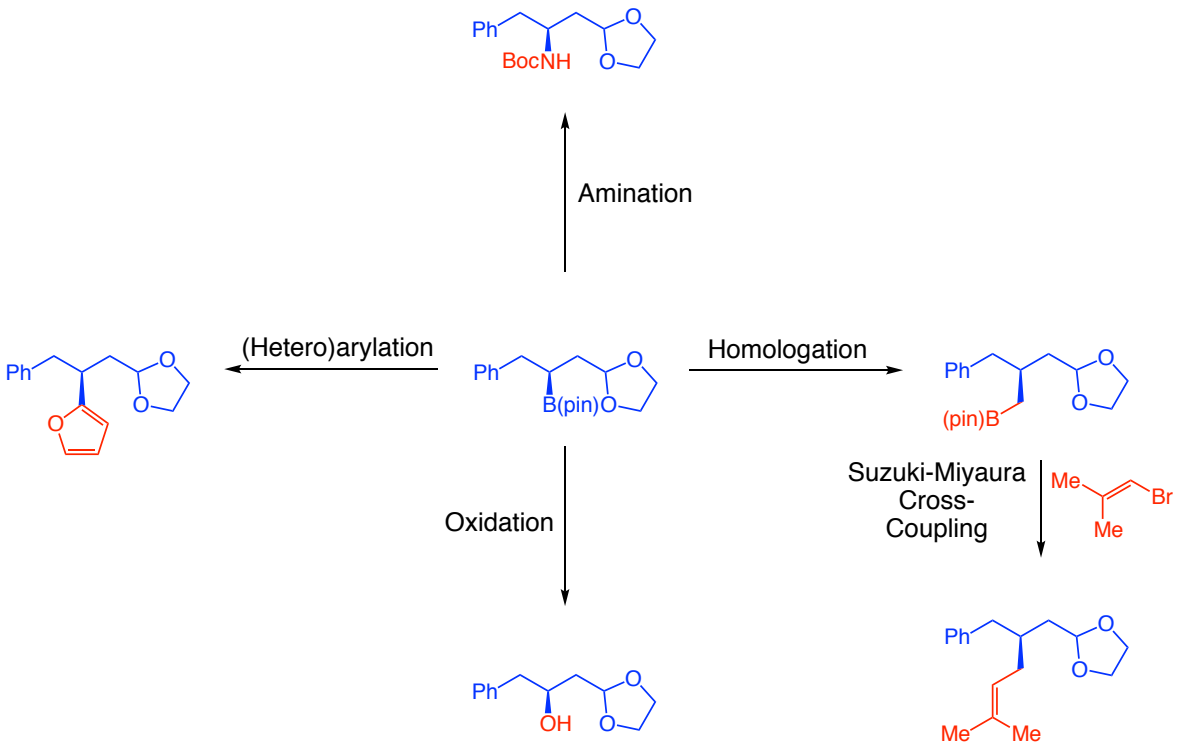
1 Chapter 1: Enantio- and Diastereoselective Synthesis of 1,2-Hydroxyboronates through Cu-Catalyzed Additions of Alkylboronates to Aldehydes

This chapter is adapted and reprinted with permission from Joannou, M. V.; Moyer, B. S.; Meek, S. J. *J. Am. Chem. Soc.* **2015**, *137*, 6176-6179. This chapter resulted from a collaboration with Dr. Matthew V. Joannou.

1.1 Introduction

1.1.1 Background

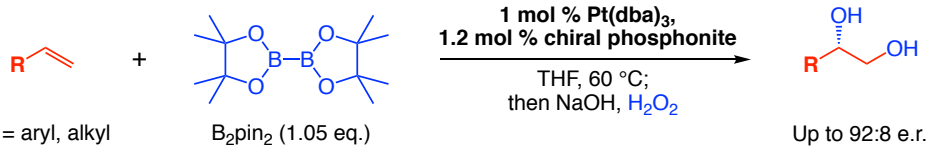
Enantiomerically pure chiral boron-containing molecules provide enabling platforms for chemical synthesis.[1] Chiral organoborons are among the most configurationally stable classes of organometallic reagents (*e.g.* organolithiums < organomagnesiums < organozincs < organocuprates < organosilanes < organostannanes < organoboranes), and are considered to be non-toxic.[2] In addition, boronic esters function as useful synthons for numerous functional groups (Scheme 1.1). Their transformations are almost universally highly stereospecific and often proceed with retention of stereochemistry. In combination, these properties establish boronic esters as excellent chiral intermediates / versatile building blocks in organic synthesis. A selection of transformations are shown below in Scheme 1.1, including amination,[3] homologation,[4] Suzuki-Miyaura cross-coupling (1° and 2° alkyl boronic esters),[5] heteroarylation,[6] and oxidation.[7]



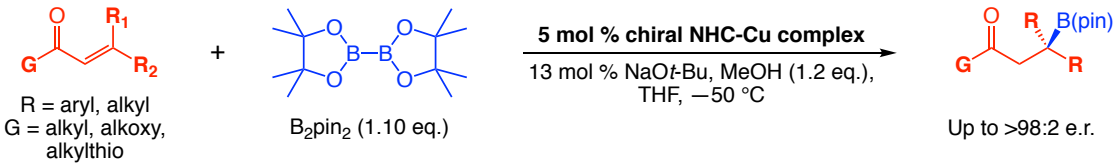
Scheme 1.1. Stereospecific transformations of chiral boronic esters.

Direct catalytic enantioselective preparation of chiral alkyl sp^3 carbon–boron-containing compounds can be achieved by a number of reported methods, for example, hydroboration,[8,9] diboration (Scheme 1.2a),[10] allylic substitution,[9,11] conjugate boron addition (Scheme 1.2b),[12] and arylborylation.[13] These methods directly generate stereodefined C–B bonds.

a) Morken (2013): Diboration of monosubstituted alkenes:



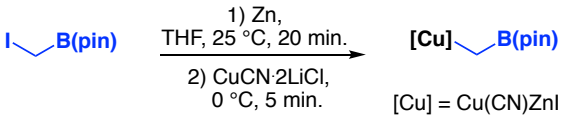
b) Hoveyda (2010): NHC-Cu-catalyzed conjugate boron addition



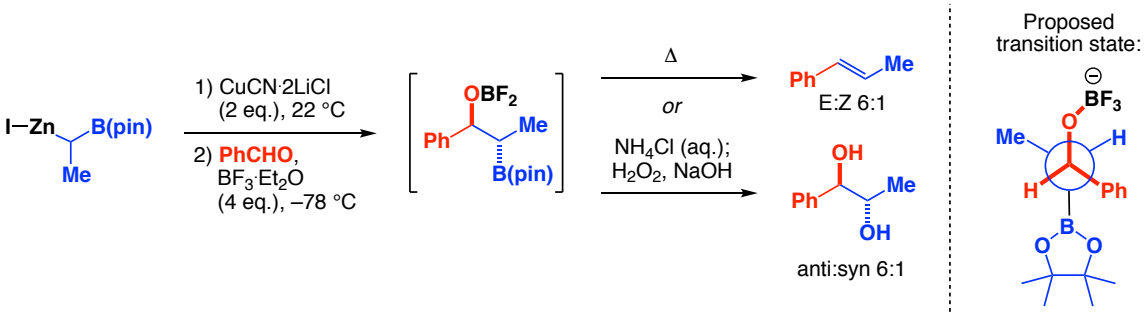
Scheme 1.2. Select examples of enantioselective diboration[10e] and conjugate boration[12g].

An alternative approach is through the use of chiral α-boron-containing nucleophiles; such reagents do not involve the direct formation of a new C–B bond but rather a C–C bond. α-Boron–carbon nucleophiles can be generated in a number of ways: (1) Through the formation of stoichiometric copper reagents, (2) deprotonation of alkyl boronates, and (3) the activation of 1,1-diboronates. α-Boron substituted alkyl cuprates, developed by Knochel and further investigated by Miyaura and coworkers, readily undergo C–C bond formation with a variety of electrophiles (particularly aldehydes), providing an effective *stoichiometric* method for the installation of alkyl α-boron units (Scheme 1.3a and b).[14] In addition, alkylation methods that employ boron-stabilized carbanions generated through deprotonation of alkyl boronate esters and boranes are limited due to the requirement of strong alkyl or amide lithium bases (Scheme 1.3c).[15] Alternatively, reactive α-boryl species can be conveniently accessed through deborylation by treatment of 1,1-diboronates with an alkoxide base (d).[10i,16]

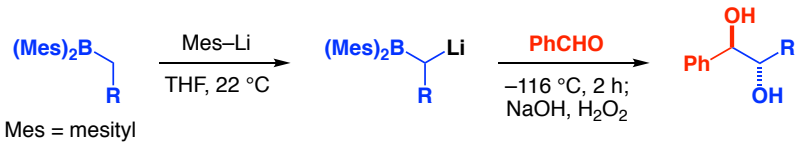
a) Knochel: Precedent for preparation of an sp³-hybridized α-boryl organometallic nucleophile:



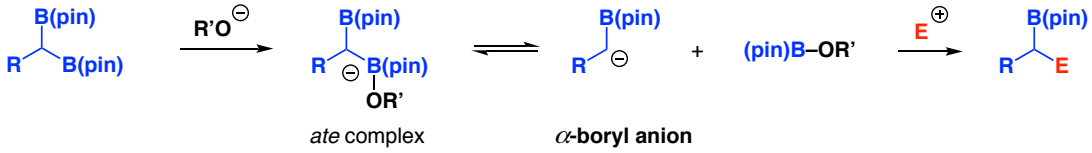
b) Miyaura: Expanded application/investigation of alkyl 1,1-Cu-B-heterobimetallics



c) Pelter: Deprotonation–alkylation (alkyl dimesitylboron-stabilized carbanions)



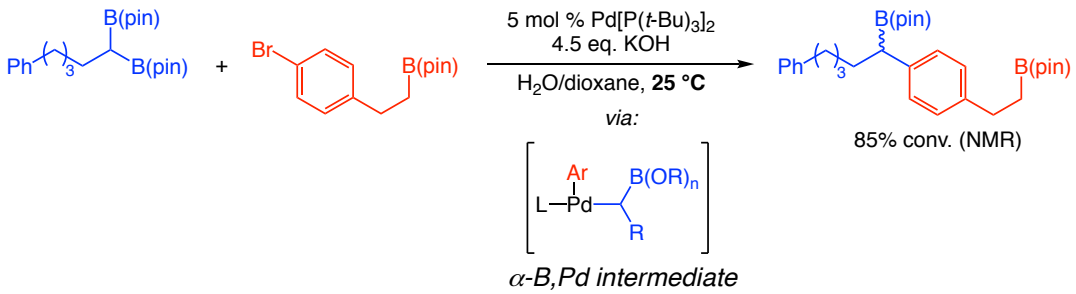
d) Morken: Deborylation–alkylation



Scheme 1.3. Methods (1-3) to generate α-boryl nucleophiles.

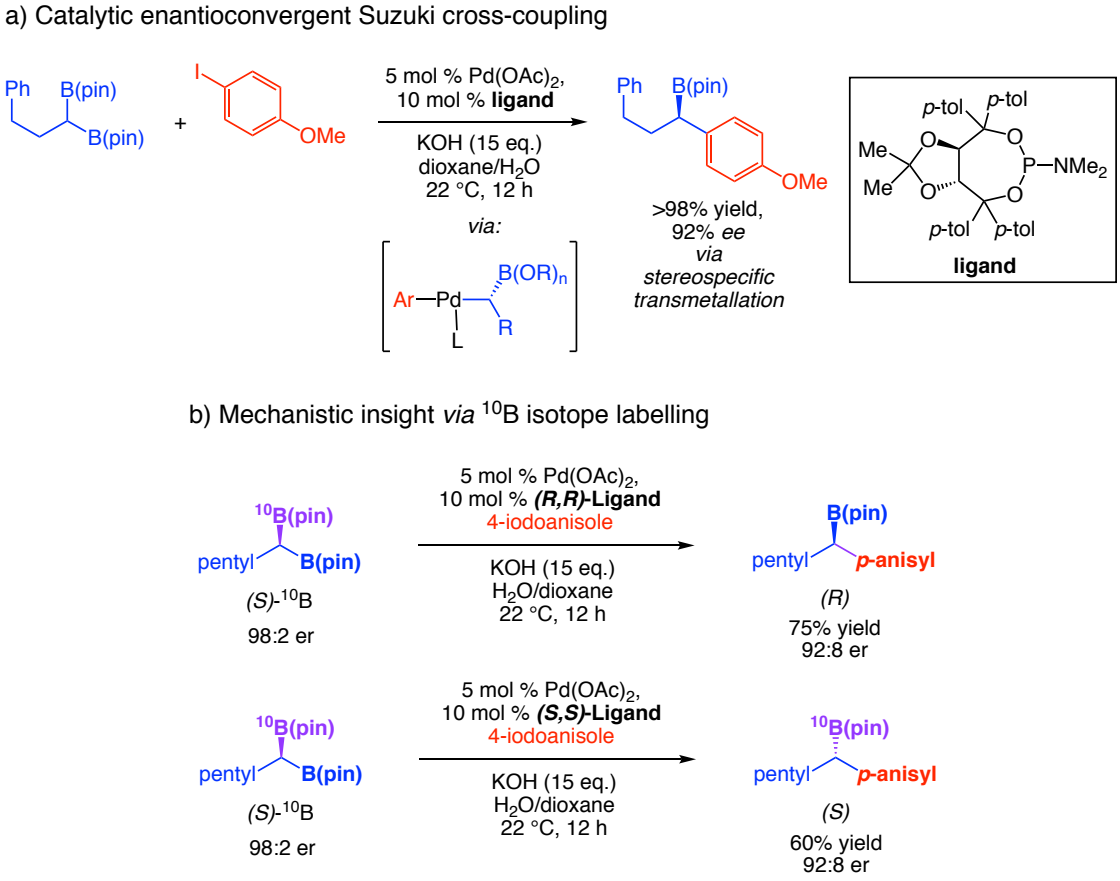
The emerging utility of alkyl 1,1-diboron reagents for chemical synthesis has recently been demonstrated in chemoselective Suzuki cross-coupling reactions by Shibata and co-workers.[17] Using the reported methodology, 1,1-diboronates undergo facile transmetalation at room temperature, allowing for chemoselectivity even in the presence of primary alkyl boronates (Scheme 1.4). The observed absence of β-hydride elimination and protodeboration in these reactions is attributed to the stabilizing effect of the α-boryl-palladium intermediate on the σ-alkyl-palladium bond. DFT calculations (B3LYP/6-31G**) performed by the group

suggest that the reason for such facile activation and transmetallation of the 1,1-diboronates is due to the presence of a large, delocalized LUMO distributed between the adjacent boron atoms.



Scheme 1.4. Chemoselective Suzuki coupling of 1,1-diboronates.

More recently, Morken and co-workers (and shortly thereafter Hall and co-workers) reported efficient enantioselective Pd-catalyzed Suzuki couplings of alkyl 1,1-diboronates with aryl (Scheme 1.5a) and vinyl halides.[18] The catalysis proceeds *via* a stereochemistry-determining transmetalation step to form a stereodefined α-boryl Pd(II)-alkyl complex ligated by a chiral, monodentate phosphoramidite ligand. Mechanistic experiments with chiral ^{10}B-enriched 1,1-diboronates suggest that the reaction occurs by a stereospecific transmetalation that occurs with inversion of configuration at carbon (Scheme 1.5b). Such a transmetalation step must occur *via* either a desymmetrization of equivalent 1,1-diboronates *or* a dynamic kinetic resolution (DKR) of racemic monoborate species. This seminal work was proof-of-concept to us that chiral α-boryl organometallics could be generated in catalytic quantities and used to form stereodefined C–C bonds in useful organic transformations.



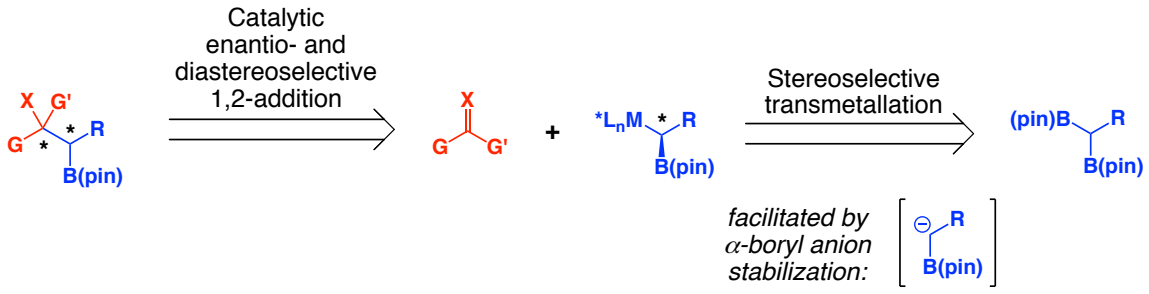
Scheme 1.5. Catalytic, enantioconvergent Suzuki reaction with aryl electrophiles.

As an addendum, since the publication of the manuscript on which this dissertation chapter is based, numerous other examples of 1,1-organodiboronate esters being developed as α-boryl carbanions for use in stereoselective deborylative C–C bond forming reactions have emerged.[19] This includes an elaboration of the methodology described here in Chapter 1 with application to enantio- and diastereoselective 1,2-additions to α-ketoesters with substituted 1,1-diboron reagents.[19a] In general, however, the development of catalytic, *enantioselective* protocols which employ *substituted* 1,1-diborylalkanes is still a challenge. One very recently published, clever workaround to this problem involves a multicomponent enantioselective borylcupration of vinyl boronates to produce a stereodefined α,β-bisboryl-alkyl-Cu, followed by a diastereoselective 1,2-addition to aldehydes. This protocol enables

the production of hydroxy bis(boronates) containing a new C–C *and* C–B bond and up to three contiguous stereocenters.[20]

1.1.2 Research objectives

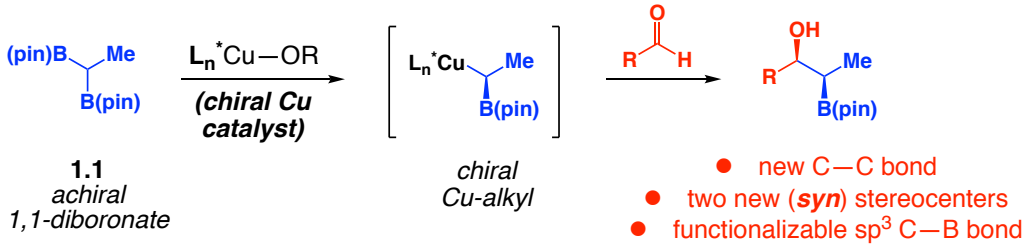
Our laboratory's research objective (highlighted in Scheme 1.6) was to develop robust methodology for the catalytic, enantio-, and diastereoselective 1,2-additions of chiral α-boryl organometallics to sp^2-hybridized (carbonyl-derived) electrophiles, namely aldehydes. While Chapters 1 and 2 in this dissertation (and the publications on which they are based) describe methodology for 1,2-additions to aldehyde substrates, much as yet unpublished work has been conducted on catalytic 1,2-additions to aryl phosphinoyl-protected imines and aryl CF_3-ketones. The foundation of all of our methodology has been the screening and development of catalytic systems that allow for stereoselective transmetalation to produce stable, α-boryl organometallic species. To this extent, we built off of the precedent and insights set by Morken and co-workers (Scheme 1.5) with Pd(II) and the stoichiometric work by Knochel and Miyaura with Cu(I) (Scheme 1.3). Chapter 1 discusses our success in developing a catalytic, stereoselective protocol based on the latter Cu(I) manifold.



Scheme 1.6. Strategy for the 1,2-addition of α-borylated organometallics to electrophiles.

1.2 Strategy for the synthesis of *syn*-1,2-hydroxyboronates

In this chapter, we discuss our published protocol for the enantio- and diastereoselective generation of 1,2-hydroxyboronates through the Cu-catalyzed addition of sp^3 1,1-diboron reagents to aryl and vinyl aldehydes (Scheme 1.7). Reactions are promoted by 7.5-10 mol % of a readily available Cu(I) salt and chiral monodentate phosphine in conjunction with an alkoxide base; products are delivered in up to 91% yield, 98:2 e.r., and >98:2 d.r., and the chiral 1,2-hydroxyboronate building blocks can be further elaborated to directly access functionalized small molecules.



Scheme 1.7. Strategy for the synthesis of 1,2-hydroxyboronates.

1.3 Optimization of the catalytic reaction

Initial studies of catalytic reaction conditions identified Cu salts in conjunction with monodentate phosphines as effective promoters for the addition of 1,1-diboryl reagents to aldehydes.[i] The data illustrated in Table 1.1 summarize the optimization of Cu-phosphine conditions. As entry 1 shows, there is no background addition of **1.1** to benzaldehyde with LiO*t*-Bu at 45 °C. Conversely, use of sodium or potassium alkoxides lead to a significant nonselective background reaction. Of note, catalytic quantities of LiO*t*-Bu were found not to be effective in promoting the reaction, while increasing the amount of base (>1.3 eq.) leads to >98% consumption of aldehyde but low conversion to product. We found bidentate

[i]Reactions of more substituted 1,1-diboron reagents result in low conversions to product; the result of these studies are reported in Joannou, M. V.; Moyer, B. S.; Goldfogel, M. J. *Angew. Chem. Int. Ed.* **2015**, *54*, 14141-14145 and form the basis for Chapter 2 of this dissertation.

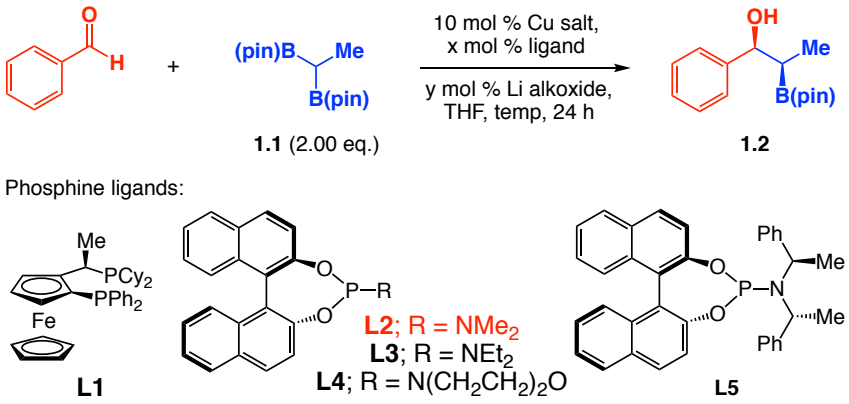
phosphine–Cu complexes to be ineffective (for example, (*R*)-binap, (*R*)-DTBM-segphos, and **L1**, entries 2-4, Table 1.1), but discovered that a monodentate phosphine–Cu complex can deliver the desired 1,2-hydroxyboronate **1.2**. Treatment of benzaldehyde and **1.1** with 10 mol % of the Cu–phosphine complex derived from $Cu(OTf)_2$ and ligand **L2** with LiO*t*-Bu at 45 ° C affords **1.2** (65% conv.) in favor of the *syn*-diastereoisomer (91:9 d.r. and 88:12 e.r.). Steric modification of the lithium alkoxide base revealed that LiO*t*-Am (entry 6) is an equally efficient (64% conv.) but more stereoselective activator (91:9 d.r. and 94:6 e.r.) for the formation of **1.2**.[ii] Catalytic 1,2-additions in the presence of various Cu(I) and Cu(II) salts (entries 7− 9) revealed $Cu(NCMe)_4PF_6$ to be the most effective promoter, delivering **1.2** in 66% conversion, 92:8 d.r., and 94:6 e.r (entry 9).[iii] The reaction efficiency was found to further improve upon conducting the reaction at 22 °C for 48 h (entry 10); **1.2** is generated in 92% conversion, 92:8 d.r., and 94:6 e.r. Further efforts to increase reaction selectivity through modification of the phosphoramidite *N*-$(alkyl)_2$ moiety (**L3-5**) result in a decrease in reaction efficiency and stereoselectivity (entries 11-13).[iv]

[ii]Application of lithium alkoxide bases containing smaller alkyl groups than *t*-Bu (*e.g.* methyl) leads to <5% conversion.

[iii]$Cu(OMe)_2$ results in inconsistent conversion.

[iv]Reactions performed with 10 mol % $Cu(NCMe)_4PF_6$ and 10 mol % **L2** result in decreased conversion to product.

Table 1.1. Cu catalyst optimization.



Entry	Cu salt	ligand; mol %	Li alkoxide; mol %	temp (°C)	NMR conv (%)[b]	d.r.[b]	e.r.[c]
1	–	–	LiO*t*-Bu; 130	45	<2	–	–
2	$Cu(OTf)_2$	(*R*)-binap; 10	LiO*t*-Bu; 130	45	<2	–	–
3	$Cu(OTf)_2$	(*R*)-segphos; 10	LiO*t*-Bu; 130	45	<2	–	–
4	$Cu(OTf)_2$	**L1**; 10	LiO*t*-Bu; 130	45	<2	–	–
5	$Cu(OTf)_2$	**L2**; 20	LiO*t*-Bu; 130	45	65	91:9	88:12
6	$Cu(OTf)_2$	**L2**; 20	LiO*t*-Am; 90	45	64	91:9	94:6
7	$Cu(OMe)_2$	**L2**; 20	LiO*t*-Am; 90	45	62	92:8	96:4
8	CuCl	**L2**; 20	LiO*t*-Am; 90	45	67	85:15	81:19
9	$Cu(NCMe)_4PF_6$	**L2**; 20	LiO*t*-Am; 90	45	66	92:8	94:6
10[d]	**$Cu(NCMe)_4PF_6$**	**L2; 20**	**LiO*t*-Am; 90**	**22**	**92**	**92:8**	**94:6**
11[d]	$Cu(NCMe)_4PF_6$	**L3**; 20	LiO*t*-Am; 90	22	57	88:12	91:9
12[d]	$Cu(NCMe)_4PF_6$	**L4**; 20	LiO*t*-Am; 90	22	77	87:13	91:9
13[d]	$Cu(NCMe)_4PF_6$	**L5**; 20	LiO*t*-Am; 90	22	30	92:8	67:33

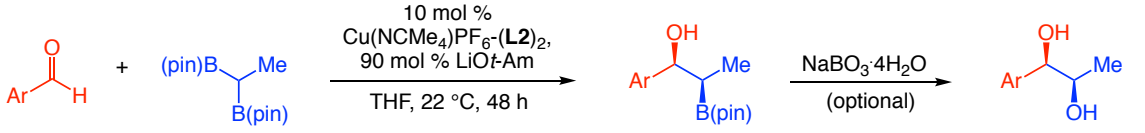
[a]Reactions performed under a N_2 atmosphere. [b]Conversion to **1.2**, values determined by analysis of 400 or 600 MHz ^{1}H NMR spectra of unpurified mixtures with HMDS as internal standard. [c]Determined by $NaBO_3$ oxidation to diol and HPLC analysis; see Experimental Section (below) for details. [d]48 h reaction.

1.4 Cu(I)-catalyzed 1,2-additions of diboryl ethane to *aryl* aldehydes

The monodentate phosphine-Cu-catalyzed 1,2-addition can be used for the enantio- and diastereoselective preparation of synthetically valuable sp^3 organoboron molecules in good yield; representative examples are illustrated in Table 1.2. Transformations proceed in the presence of 10 mol % Cu catalyst at 22 °C within 48 h. The resulting 1,2-hydroxyboronate products (**1.3**) demonstrate variable stability toward elimination during column chromatography. For ease of isolation and enantiomeric ratio determination, the

products were oxidized to the corresponding diols. For utilization and functionalization of 1,2-hydroxyboronate products, see section 1.7. Benzaldehyde derived *syn*-diol **1.4** is isolated in 67% yield (92:8 d.r.) and in 94:6 e.r. after oxidation ($NaBO_3$–$4H_2O$). Aryl aldehydes incorporating halogens may be used; 10 mol % Cu complex delivers **1.5** (77% yield, 94:6 e.r.) and **1.6** (91% yield, 95:5 e.r.) in 48 h at 22 °C after oxidation. Cu-catalyzed 1,2-additions to aryl aldehydes containing an electron-donating *p*-MeO group work effectively, generating **1.7** in 69% yield (97:3 d.r. and 93:7 e.r.). Conversely, the presence of electron-withdrawing *p*-NO_2 or *m*-NO_2 substituents delivers **1.8** and **1.9** in lower conversion (42% and 37%) but with high enantioselectivity (95:5 e.r. **1.8**, and 95:5 e.r. **1.9**). Aldehydes containing *m*-methyl and *m*-trifluoromethyl substituents are also tolerated; diols **1.10** and **1.11** are delivered in yields of 76% (92:8: d.r., 98:2 e.r.) and 59% (90:10 d.r., 94:6 e.r.), respectively. Sterically hindered aryl aldehydes participate to afford the desired 1,2-hydroxyboronates with complete diastereocontrol; for example, both **1.12** (68% yield) and **1.13** (65% yield) are formed in >99:1 d.r. and 93:7 e.r. The reaction protocol is not sensitive to N- and O-containing heteroaryl aldehydes. However, products are formed in diminished diastereoselectivity; treatment with 10 mol % Cu and **L2** furnish **1.14** in 55% yield (86:14 d.r., 95:5 e.r.) and **1.15** in 68% yield (83:17 d.r., 90:10 e.r.).

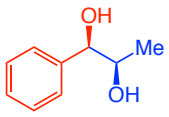
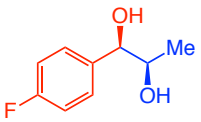
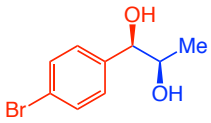
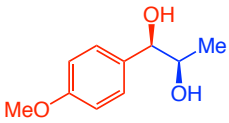
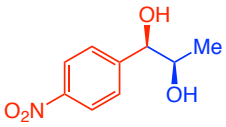
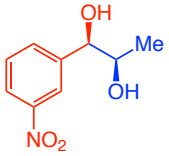
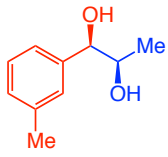
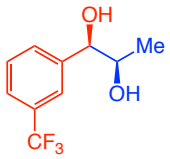
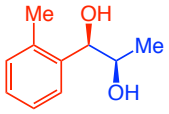
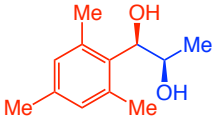
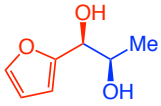
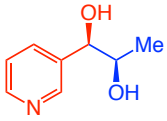
Table 1.2. Cu(I)-catalyzed 1,2-additions of diboryl ethane to aryl aldehydes.



1.1 (2.00 eq.)

1.3
(NMR conv., d.r.)[b]

1.4-1.15
(yield of diol; e.r.)[c,d]

 **1.4** 92% conv, 67% yield 92:8 d.r. (syn:anti) 94:6 e.r.	 **1.5** 93% conv, 77% yield 92:8 d.r. (syn:anti), 94:6 e.r.	 **1.6** >98% conv, 91% yield 93:7 d.r. (syn:anti), 95:5 e.r.	 **1.7** 79% conv, 69% yield 97:3 d.r. (syn:anti) 93:7 e.r.
 **1.8** 42% conv, 34% yield 93:7 d.r. (syn:anti) 95:5 e.r.	 **1.9** 37% conv, 35% yield 84:16 d.r. (syn:anti) 95:5 e.r.	 **1.10** 82% conv, 76% yield 92:8 d.r. (syn:anti) 98:2 e.r.	 **1.11** 65% conv, 59% yield 90:10 d.r. (syn:anti) 94:6 e.r.
 **1.12** 78% conv, 68% yield >99:1 d.r. (syn:anti) 93:7 e.r.	 **1.13** >98% conv, 65% yield >99:1 d.r. (syn:anti) 93:7 e.r.	 **1.14** 64% conv, 55% yield 86:14 d.r. (syn:anti) 95:5 e.r.	 **1.15** 76% conv, 68% yield 83:17 d.r. (syn:anti) 90:10 e.r.

[a]Reactions performed under a N_2 atmosphere; see Experimental Section (below) for details. [b]Conversion to 1,2-hydroxyboronate; values determined by analysis of 400 or 600 MHz ^{1}H NMR spectra of unpurified mixtures with HMDS as internal standard. [c]Yields of the corresponding purified diol. [d]e.r. determined by HPLC analysis of the diol.

1.5 Cu(I)-catalyzed 1,2-additions of diboryl ethane to *alkenyl* aldehydes

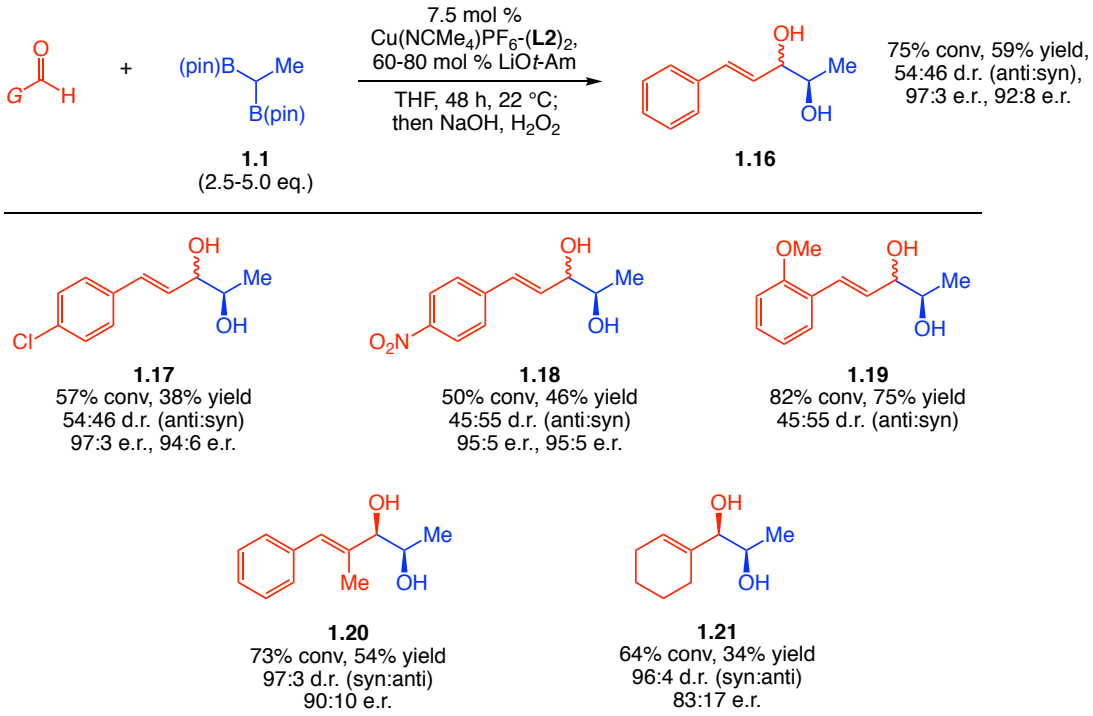
α,β-Unsaturated aldehydes react in the presence of 7.5 mol % phosphine–Cu complex with 60−80 mol % LiO*t*-Am[v] to afford functional organoboron compounds bearing allylic alcohols (Scheme 1.8).[vi] Cu-catalyzed addition to sterically unhindered cinnamaldehyde affords diol **1.16** (59% yield) in low diastereoselectivity (54:46 d.r., *anti:syn*) in slight favor of the *anti*-diastereoisomer; however, both isomers are formed in high enantioselectivity

[v]The base:boron ratio is important; vinyl aldehydes, especially those lacking an α-substituent, require larger loadings of diboryl ethane (2.5-5.0 eq.).

[vi]The allylic alcohol products demonstrate variable stability to purification, particularly when electron-donating substituents are present on the aryl ring.

(97:3 e.r. *anti*, and 92:8 *syn*). Electron-withdrawing groups are tolerated: *p*-Cl and *p*-NO_2 cinnamaldehyde-derived diols **1.17** and **1.18** are generated in low diastereoselectivity (54:46 and 45:55 d.r. *anti:syn*), but the diastereoisomers are formed in high enantioselectivity (97:3−95:5 e.r. *anti*, and 94:6−95:5 e.r. *syn*). Aryl groups bearing electron-donating *ortho*-substituents are compatible as demonstrated by the formation of **1.19** in 75% yield, 45:55 d.r.[vii] α-Substituted vinyl aldehydes lead to restoration of *syn*-diastereoselectivity without significant loss in enantioselectivity; **1.20** is delivered in 73% conversion (54% yield) and 97:3 d.r. and 90:10 e.r. Cyclohexene-derived vinyl aldehydes undergo smooth diastereoselective 1,2-addition (96:4 *syn:anti*) to afford **1.21** in 64% conversion but in 83:17 enantiomeric ratio.

[vii] *p*-OMe cinnamaldehyde is converted to the corresponding 1,2-hydroxyboronate in 75% yield; however, the corresponding 1,2-diol product is unstable to purification.



[a]Reactions performed under a N_2 atmosphere; see Experimental Section for details. [b]Conversion to 1,2-hydroxyboronate; values determined by analysis of 400 or 600 MHz ^{1}H NMR spectra of unpurified mixtures with HMDS as internal standard. [c]Yields of the corresponding purified diol. [d]e.r. determined by HPLC analysis of the diol. [e]1,2-Diol **1.19** slowly decomposes precluding HPLC analysis.

Scheme 1.8. Cu(I)-catalyzed 1,2-additions of diboryl ethane to alkenyl aldehydes

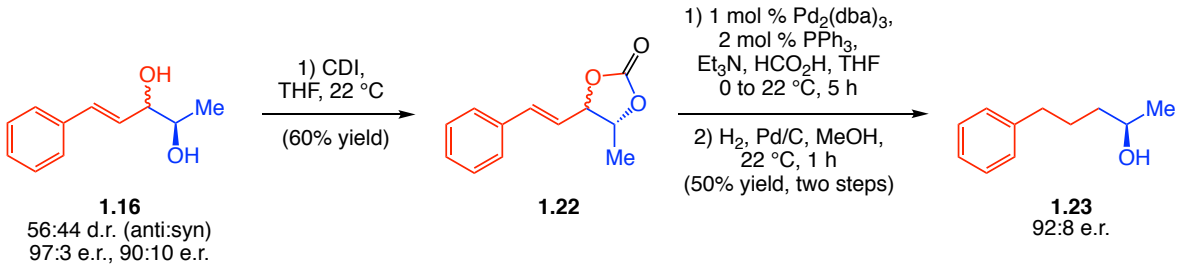
1.6 Mechanism:

1.6.1 Control of C–B stereogenic center

To address which stereogenic center is set in high enantioselectivity (allylic versus homoallylic) in the cases of low diastereoselectivity observed with vinyl aldehydes, the allylic secondary alcohol in diol **1.16** was removed. As shown in Scheme 1.9, diol **1.16** was first converted to the allylic carbonate **1.22** with CDI (60% yield), followed by 2 mol % Pd-catalyzed allylic reduction (Et_3N, HCO_2H),[21] and subsequent hydrogenation to the corresponding secondary alcohol **1.23** (50% two steps).[viii] The enantiomeric purity of **1.23** was determined to be 92:8 e.r., corresponding to the secondary boronate stereogenic center

[viii]Pd-catalyzed allylic reduction affords mixtures that contained the over-reduced product **1.23** that could not be separated.

being formed in high enantioselectivity in both *anti*- and *syn*-diastereoisomers. These data suggest a mechanism where the α-boryl nucleophile is formed with high stereopurity through catalyst controlled stereodifferentiation of the two B(pin) groups in achiral diboron **1.1**. The low diastereoselectivity observed for sterically unhindered alkenyl aldehydes is therefore likely a result of poor facial discrimination of the C=O by the Cu catalyst.



1.16
56:44 d.r. (anti:syn)
97:3 e.r., 90:10 e.r.

1.22

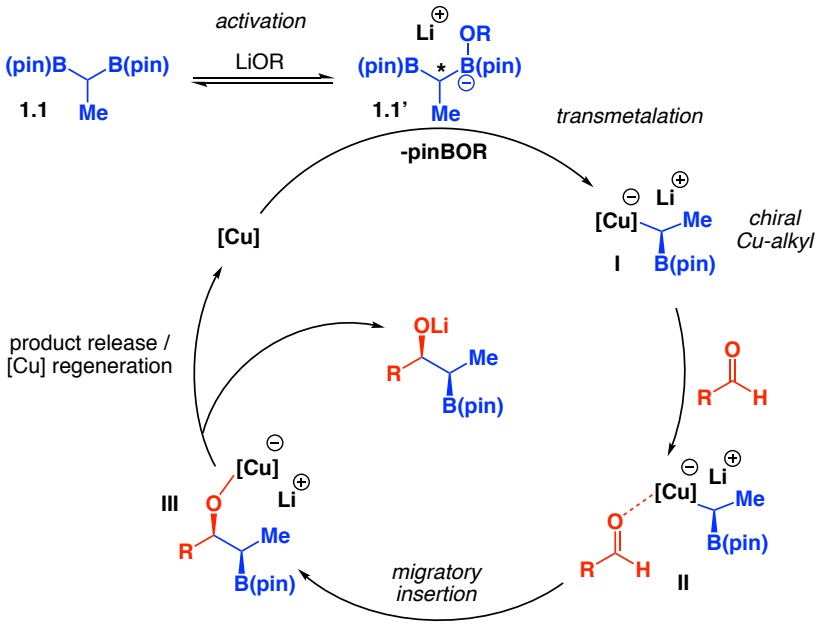
1.23
92:8 e.r.

Scheme 1.9. Control of C–B stereogenic center.

1.6.2 Catalytic cycle

Having established that control of absolute stereochemistry resides at the α-boryl component, we postulated a catalytic cycle involving transmetallation to form a stereodefined α-boryl alkyl Cu(I) complex (Scheme 1.10). The first step towards entering the catalytic cycle involves activation of diboryl ethane (**1.1**) by a lithium alkoxide to generate borate **1.1'**, a reaction which we have shown to be in an equilibrium that favors **1.1**. Borate **1.1'** then enters the catalytic cycle by undergoing a transmetalation reaction with an appropriately ligated Cu(I) species (**[Cu]**; potentially **L2**CuO*t*-Bu) to form sterodefined α-boryl alkyl Cu(I) species **I**.[ix] Upon ligation of an aldehyde to form **II**, a migratory insertion reaction occurs to form the Cu(I)-ligated product 1,2-hydroxyboronate **III**. Release of the product *via* Cu(I) to Li salt metathesis regenerates the catalyst (**[Cu]**).

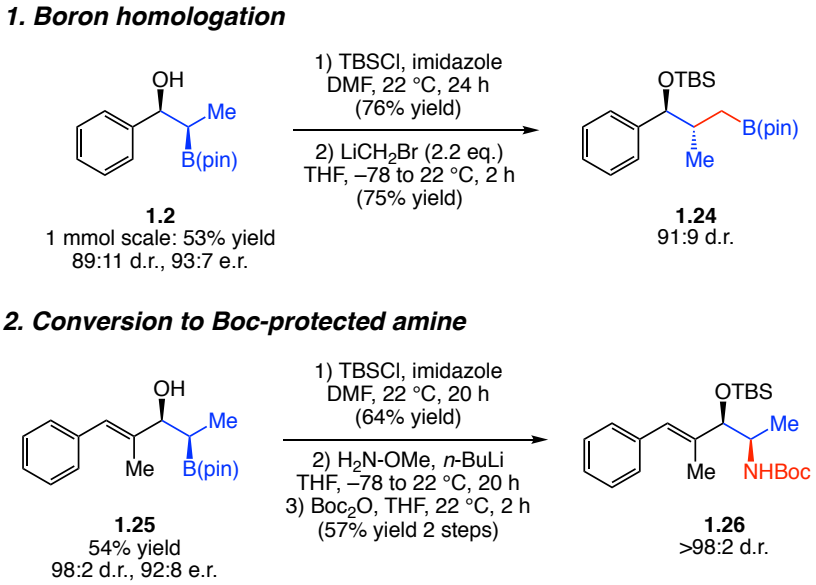
[ix]Transmetalation to form stereodefined α-boryl alkyl Cu(I) **I** could proceed *via* two possible paths: 1) stereoselective transmetalation by dynamic kinetic resolution (or desymmetrization), as is precedented for Pd(II);[18] or 2) Isomerization of the Cu(I) alkyl.



Scheme 1.10. Cu(I) catalytic cycle

1.7 Functionalizations of 1,2-hydroxyboronates

The 1,2-hydroxyboronates synthesized through this Cu-catalyzed manifold can be elaborated to generate useful functional molecules (Scheme 1.11). In addition to oxidation, 1,2-hydroxyboronate **1.2** (isolated in 53% yield on 1 mmol scale; 89:11 d.r. and 93:7 e.r.) can be converted to the TBS ether (76% yield) followed by homologation to afford alkyl organoboron **1.24** in 75% yield and 91:9 d.r. In a similar manner, allylic 1,2-hydroxyboronate **1.25** (isolated in 54% yield; 98:2 d.r. and 92:8 e.r.) can be protected as the silyl ether (64% yield), and then treated with lithiated methoxyamine[3] to cause stereospecific C−B to C−N conversion to deliver amino alcohol **1.26** (57% yield) after Boc protection.



Scheme 1.11. Functionalizations of 1,2-hydroxyboronates.

In conclusion, Chapter 1 has summarized our studies into the development of the first catalytic protocol for the enantio- and diastereoselective synthesis of 1,2-hydroxyboronates. The efficiency of the transformation is demonstrated by the concomitant generation of a new C−C bond and two vicinal stereogenic centers, while retaining a versatile C−B bond. The method is applicable to aryl and alkenyl aldehyde substrates. Mechanistic experiments indicate control of absolute stereochemistry at the α-boryl component even in cases of low aldehyde facial selectivity. A key aspect of the sp^3 B-containing secondary alcohols is the stereospecific transformations (*e.g.*, homologation and amination) made available by the alkyl B(pin) unit of the corresponding silyl protected hydroxyboronate products. The development of a complementary Ag-based catalytic protocol, which enables the diastereoselective addition of substituted alkyl 1,1-diboron reagents to aryl, alkenyl, and *alkyl* aldehydes to produce *anti*-1,2-hydroxyboronates, is discussed in Chapter 2.

1.8 Experimental Section

1.8.1 General Methods

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

1.8.1.1 Instrumentation

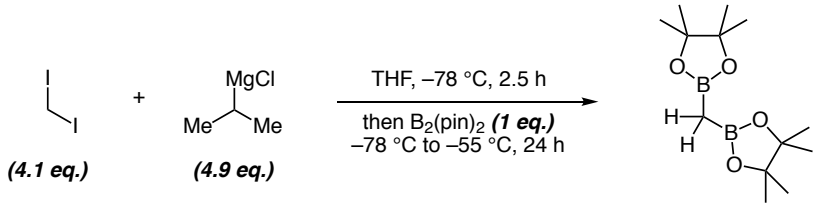
All ^1H NMR spectra were recorded on Bruker Spectrometers (AVANCE-600 and AVANCE-400). Chemical shifts are reported in ppm from tetramethylsilane and referenced to the residual protio solvent peak ($CDCl_3$: δ 7.26). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, qu = quartet, quint = quinttet, br = broad, m = multiplet, app = apparent), integration, and coupling constants are given in Hz. ^{13}C NMR spectra were recorded on Bruker Spectrometers (AVANCE-600 and AVANCE-400) with carbon and proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane and referenced to the residual protio solvent peak ($CDCl_3$: δ 77.16). All IR Spectra were recorded on a Jasco 260 Plus Fourier transform infrared spectrometer. Mass

Spectrometry was performed on a Thermo Scientific LTQ-FT-ICR Mass Spectrometer. Optical rotations were determined using a Jasco P1010 polarimeter and concentrations are reported in g/100mL. Enantiomeric ratios were determined on an Agilent Technologies 1220 Infinity LC using the following columns: Diacel CHIRALPAK IA (4.6 mm x 250 mmL x 5 μm), Diacel CHIRALPAK IB (4.6 mm x 250 mmL x 5 μm), and Diacel CHIRALPAK IC (4.6 mm x 250 mmL x 5 μm). Enantiomeric ratios for compound **1.18** were determined on a Berger Instruments Supercritical Fluid Chromatograph using a Regis RegisPack Column (25 cm x 4.6 mm x 5 μm).

1.8.1.2 Reagents

All liquid aldehydes were distilled from CaH_2 under vacuum and then sparged with dry N_2. Solid aldehydes were purified *via* recrystallization, followed by azeotropic drying with benzene. *(R)*-Me-Monophos **(L2)**, *(R)*-Et-Monophos **(L3)**, and *(R)*-MorphPhos **(L4)** and **L5** were synthesized according to published literature procedures.[22] *(R)*-binap, *(R)*-dtbm segphos, and *(R,R)*-josiphos **(L1)** were purchased from Strem Chemicals and stored in an N_2 filled glovebox. Copper(II) methoxide, copper(I) chloride, and copper(II) triflate were purchased from Strem Chemicals and kept in an N_2 filled glove box. Copper(I) tetrakisacetonitrile hexafluorophosphate was purchased from Sigma-Aldrich and kept in an N_2-filled glovebox. Methoxyamine was prepared according to literature procedures as a solution in tetrahydrofuran.[3a]

1.8.1.3 Synthesis of diboryl methane

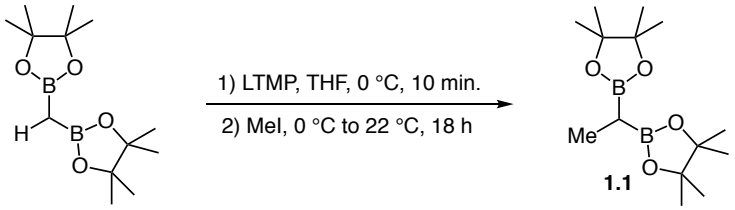


Scheme 1.12. Synthesis of diboryl methane.

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

gel chromatography (20:1 hexanes:ethyl acetate) to afford the desired product in 80% yield (8.0 g). The spectral data of the diboronate ester matched those previously reported.[18a]

1.8.1.4 Synthesis of diboryl ethane (**1.1**)

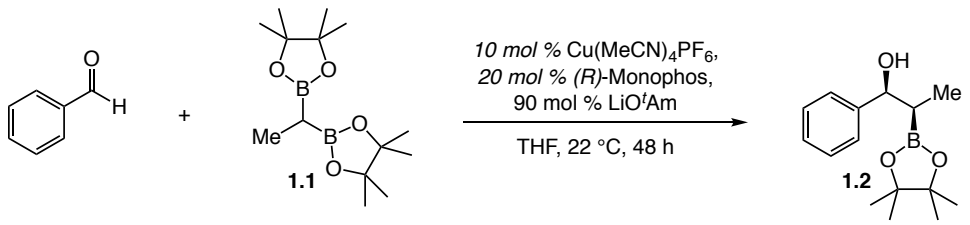


Scheme 1.13. Synthesis of diboryl ethane (1.1).

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

in 89% yield (2.8 g). The spectral data of the diboronate ester matched those previously reported.[23]

1.8.1.5 General procedures for the Cu-catalyzed 1,2-addition reaction

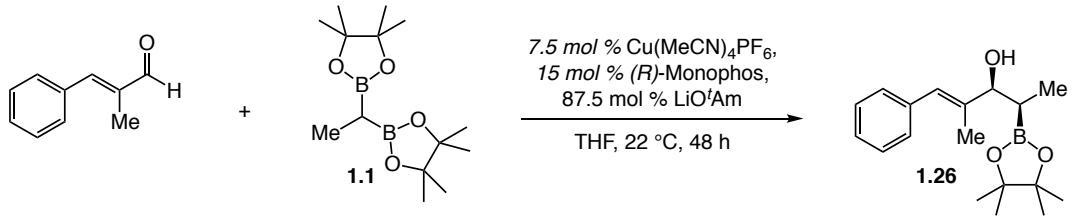


Scheme 1.14. General Procedure A (aryl aldehydes).

Procedure A (aryl aldehydes): In an N_2-filled glove box, an 8-mL vial equipped with a magnetic stir bar was charged with $Cu(MeCN)_4PF_6$ (3.7 mg, 0.010 mmol) and *(R)*-Monophos (7.2 mg, 0.020 mmol) and dissolved in 0.50 mL of THF. After allowing the reaction to stir for 5 min, LiO^tAm (0.90 mg, 0.010 mmol) was added to the reaction as a solution in THF (0.10 mL). After an additional 15 min of stirring, diboryl ethane (56 mg, 0.20 mmol) was added to the vial via syringe, followed by LiO^tAm (7.5 mg, 0.080 mmol) as a solution in THF (0.20 mL). The resulting solution was allowed to stir at ambient temperature for 5 minutes, after which time the aldehyde (0.10 mmol) was added to the reaction. The vial was capped, sealed, and then removed from the glove box and allowed to stir at ambient temperature for 48 hours. The reaction was quenched with 1.5 mL of a saturated aqueous solution of NH_4Cl, and the aqueous layer extracted three times with diethyl ether. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Conversion and diastereomeric ratios were determined by ^1H NMR using hexamethyldisiloxane as an internal standard.

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

reaction mixture was dissolved in a 1:1 mixture of THF and H_2O and charged with $NaBO_3 \cdot 4H_2O$ (5 equivalents). The resulting heterogeneous mixture was allowed to stir vigorously at ambient temperature for 2.5 hours and then quenched by the addition of a saturated aqueous solution of NH_4Cl. The aqueous layer was extracted three times with diethyl ether and the combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Pinacol was removed by dissolving the crude oxidation mixture in 1:1 methanol:water, followed by concentration *in vacuo* on a rotary evaporator with the water bath set between 55-60 ˚C. The procedure was repeated until no pinacol was detected by TLC (usually 2-3 cycles). Purification by silica gel chromatography yielded the diol.

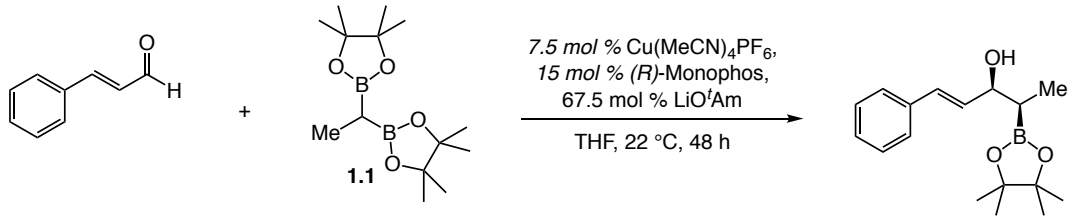


Scheme 1.15. General Procedure B (α-substituted vinyl aldehydes).

Procedure B (α-substituted vinyl aldehydes): In an N_2-filled glove box, an 8-mL vial equipped with a magnetic stir bar was charged with $Cu(MeCN)_4PF_6$ (2.8 mg, 7.5 μmol), *(R)*-Monophos (5.4 mg, 0.015 mmol), and LiO^tAm (0.7 mg, 7.5 μmol). The reaction was then dissolved in 0.56 mL of THF and allowed to stir at ambient temperature for 30 min. Diboryl ethane (71 mg, 0.25 mmol) was added to the vial *via* syringe, and this entire solution was added to a solution of LiO^tAm (7.5 mg, 0.080 mmol) in THF (0.27 mL). The resulting solution was allowed to stir at ambient temperature for 5 minutes, after which time the aldehyde (0.10 mmol) was added to the reaction. The vial was capped and then removed from the glove box and allowed to stir at 22 °C for 48 h. The reaction was quenched with 1.0

mL of a saturated aqueous solution of NH_4Cl and the aqueous layer was extracted three times with diethyl ether. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Conversion and diastereomeric ratios were determined by ^1H NMR using hexamethyldisiloxane as an internal standard.

Oxidation procedure: For the case of *α-substituted vinyl* hydroxyboronates, the crude reaction mixtures were oxidized to the corresponding diols using the following procedure: The crude reaction mixture was dissolved in 1 mL of THF and then allowed to cool to 0 ˚C (ice/water bath). 400 μL of a 3 M NaOH (8 equivalents) solution was then added to the reaction, followed by 200 μL of a 30% H_2O_2 solution (12 equivalents). The reaction was allowed to warm up to ambient temperature over 4 hours. The reaction was then quenched at 0 ˚C with 1 mL of a 1M solution of $Na_2S_2O_3$. The aqueous layer was extracted three times with ethyl acetate and the combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Pinacol was removed by dissolving the crude oxidation mixture in 1:1 methanol:water, followed by concentration *in vacuo* on a rotary evaporator with the water bath set between 55-60 ˚C. The procedure was repeated until no pinacol was detected by TLC (usually 2-3 cycles). Purification by silica gel chromatography yielded the diol.



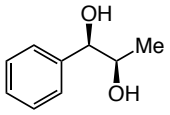
Scheme 1.16. General Procedure C (vinyl aldehydes).

Procedure C (vinyl aldehydes): In an N_2-filled glove box, an 8-mL vial equipped with a magnetic stir bar was charged with $Cu(MeCN)_4PF_6$ (2.8 mg, 7.5 μmol), *(R)*-Monophos

(5.4 mg, 0.015 mmol), and LiO^tAm (0.7 mg, 7.5 μmol). The reaction was then dissolved in 0.56 mL of THF and allowed to stir at ambient temperature for 30 min. Diboryl ethane (141 mg, 0.50 mmol) was added to the vial via syringe, and this entire solution was added to a solution of LiO^tAm (5.6 mg, 0.060 mmol) in THF (0.27 mL). The resulting solution was allowed to stir at ambient temperature for 5 minutes, after which time the aldehyde (0.10 mmol) was added to the reaction. The vial was capped and then removed from the glove box and allowed to stir at 22 °C for 48 h. The reaction was quenched with 1.0 mL of a saturated aqueous solution of NH_4Cl and the aqueous layer was extracted three times with diethyl ether. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Conversion and diastereomeric ratios were determined by ^{1}H NMR using hexamethyldisiloxane as an internal standard.

Oxidation procedure: For the case of *unsubstituted vinyl* hydroxyboronates, the exact procedure above for *α-substituted vinyl* hydroxyboronates was followed, except 800 μL of 3 M NaOH and 400 μL H_2O_2 were used instead.

1.8.2 Preparation of aryl 1,2-diols



1.4

1-phenylpropane-1,2-diol (1.4). Following Procedure A, the crude oxidation mixture was purified by silica gel chromatography (1:1 hexanes:ethyl acetate) to yield diol **1.4** as a colorless oil in 67% yield (10.2 mg) and 92:8 d.r. (syn:anti). The spectral data of the diol matched those previously reported.[24] $[\alpha]^{22}_{D}$ = +42.1° (*c* = 0.458, CH_2Cl_2, *l* = 100 mm). Enantiomeric excess was determined by HPLC analysis compared to the authentic racemic material: *Diacel CHIRALPAK IA Column; 99:1 hexanes:iPrOH; 1.0 mL/min; 210 nm. Syn-*

diastereomer: (1*S,2S*) enantiomer: 32.8 min; (1*R,2R*) enantiomer 41.2 min: 94:6 e.r. Absolute stereochemistry was determined by the $[\alpha]_D$ value compared to those previously reported.[24,25]

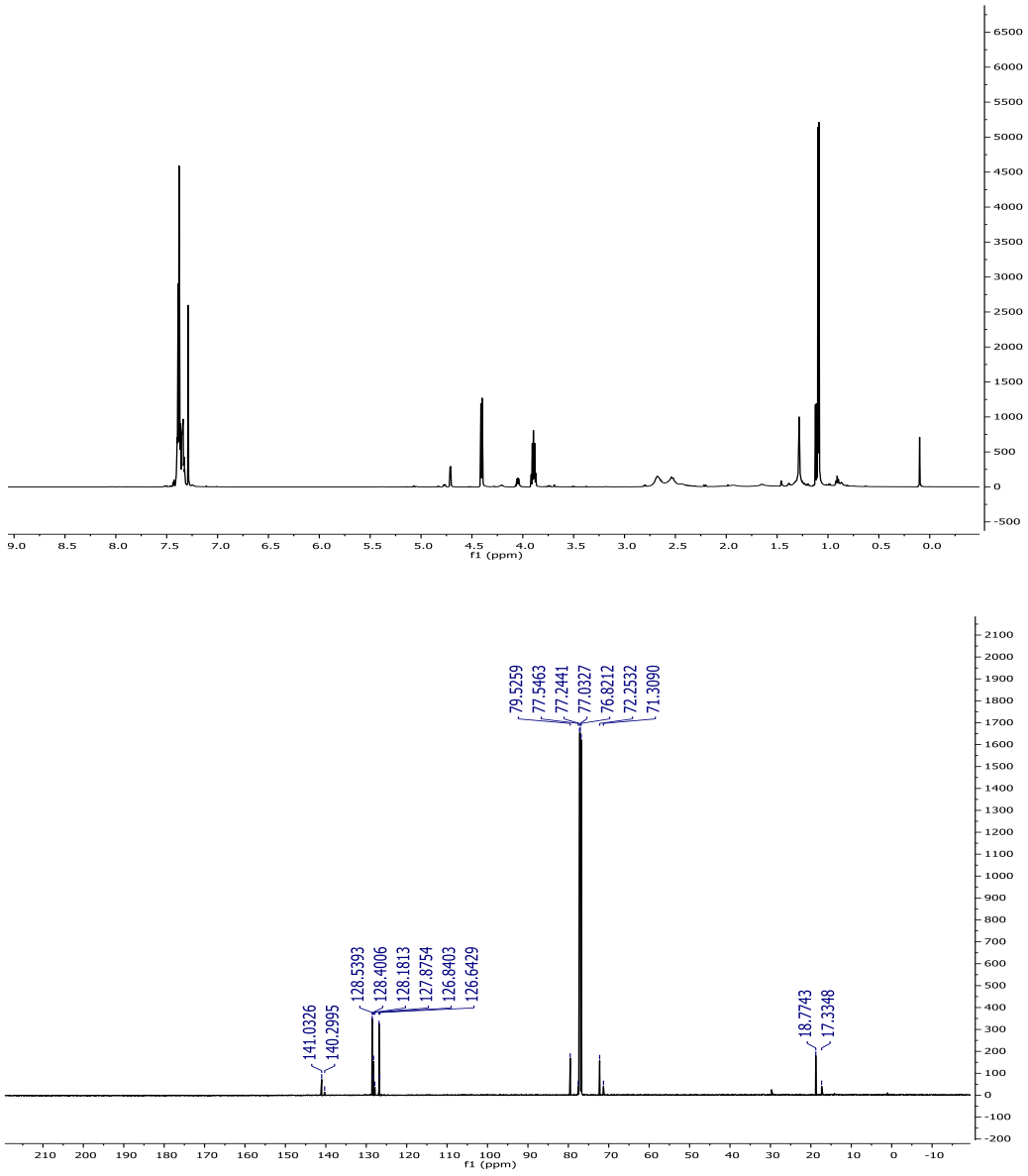
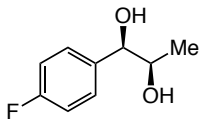


Figure 1.1. ^{1}H and ^{13}C{^{1}H} NMR spectra of 1.4.



1.5

1-(4-fluorophenyl)propane-1,2-diol (1.5). Following Procedure A, the crude oxidation mixture was purified by silica gel chromatography (1:1 hexanes:ethyl acetate) to yield diol **1.5** as a colorless oil in 77% yield (13.0 mg) and 92:8 d.r (syn:anti). ***Syn* diastereomer: ^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.36-7.31 (m, 2H), 7.08-7.03 (m, 2H), 4.37 (d, 1H, *J* = 7.6 Hz), 3.83 (quintt, 1H, *J* = 6.6 Hz), 2.73 (br s, 2H), 1.06 (d, 3H, *J* = 6.4 Hz). **^{13}C NMR** ($CDCl_3$, 101 MHz): δ 136.78, 128.65, 128.57, 115.62, 115.41, 78.96, 72.40, 18.93. ***Anti* diastereomer**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.36-7.31 (m, 2H), 7.08-7.03 (m, 2H), 4.68 (d, 1H, *J* = 4.2 Hz), 4.01 (quintt, 1H, *J* = 1.9 Hz), 1.93 (br s, 1H), 1.64 (br s, 1H), 1.07 (d, 3H, *J* = 6.3 Hz). **^{13}C NMR** ($CDCl_3$, 101 MHz): δ 136.75, 128.45, 128.36, 115.45, 115.23, 78.96, 72.40, 17.37. **HRMS (ESI^{+})** calcd for $C_9H_{11}O_2FNa^{+}$ 193.0641, found: 193.0635 [M+Na]. **IR (v/cm^{-1}):** 3399 (br, s), 2980 (s), 1605 (m), 1510 (m), 1455 (m), 1373 (w), 1223 (m), 1157 (w), 1040 (w), 950 (w), 832 (m), 544 (w). **$[\alpha]^{22}_{D}$** = +22.4 ° (*c* = 0.352, CH_2Cl_2, l = 100 mm). Enantiomeric excess was determined by HPLC analysis compared to the authentic racemic material. Absolute stereochemistry was inferred from the stereochemistry obtained for compound **1.4**. *Diacel CHIRALPAK IC Column; 99:1 hexanes:iPrOH; 1.0 mL/min; 210 nm. Syn*-diastereomer: (1*R,2R*) enantiomer: 87.3 min; (1*S,2S*) enantiomer 93.9 min: 94:6 e.r.

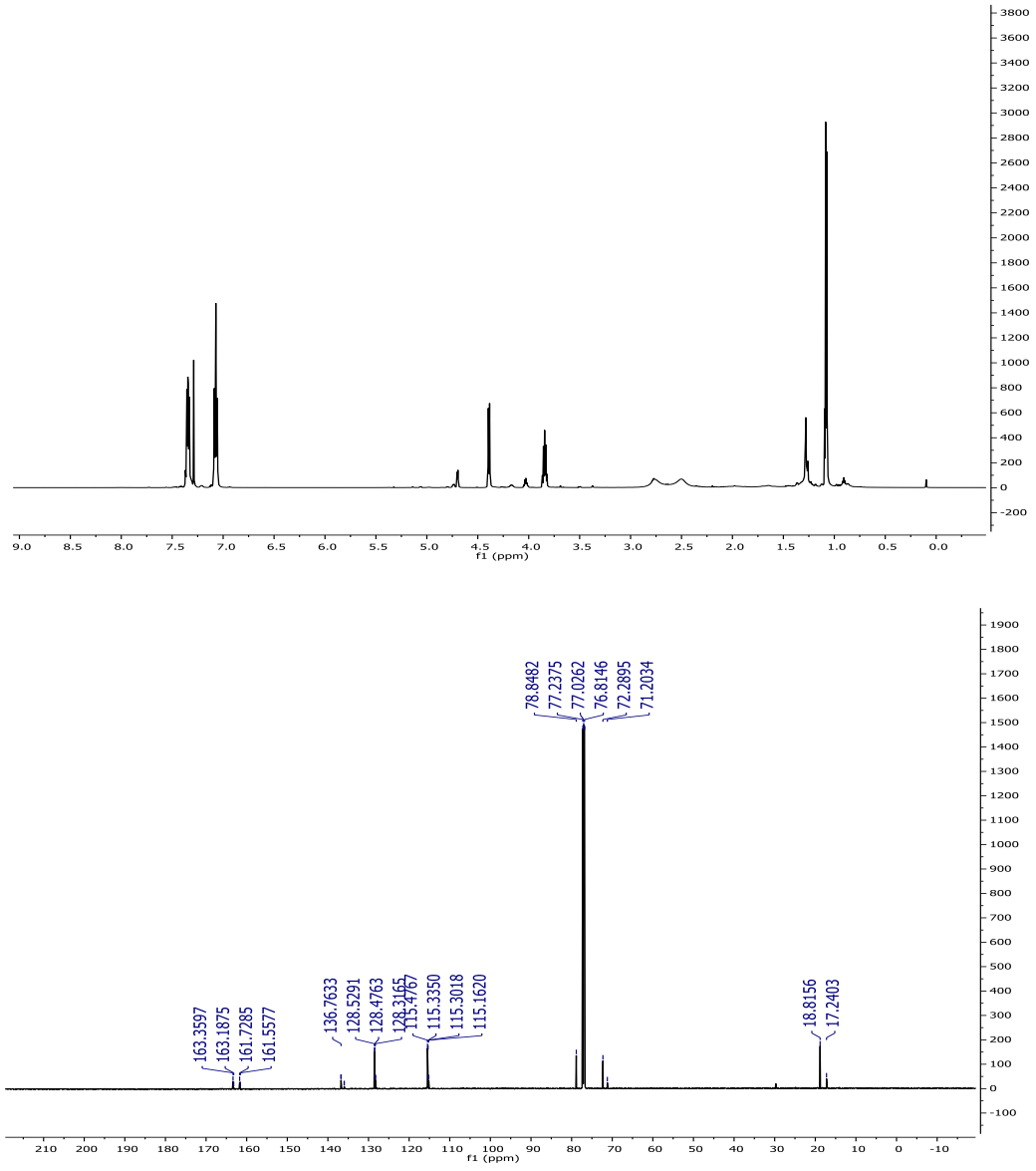
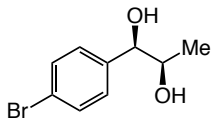


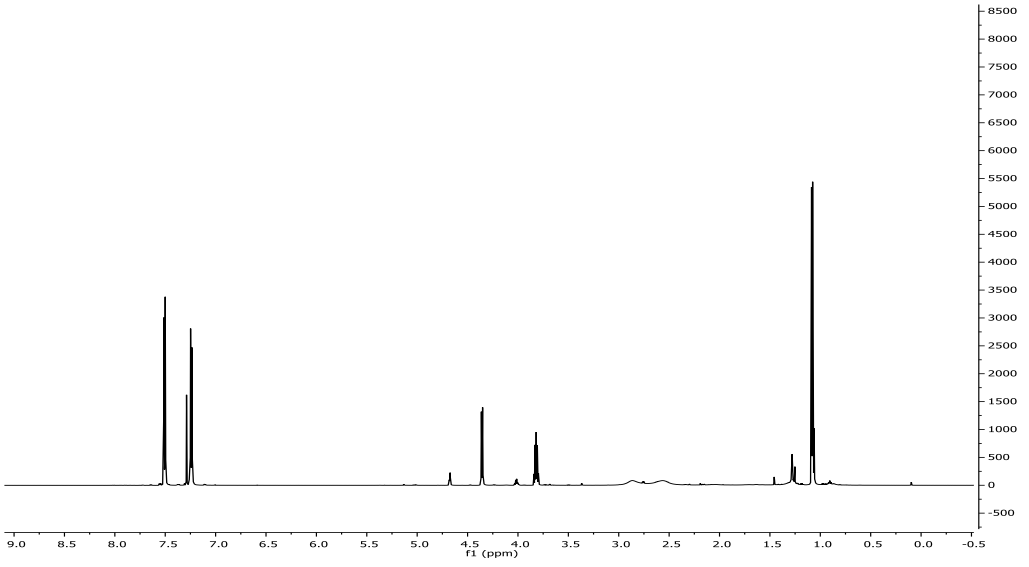
Figure 1.2. ^{1}H and ^{13}C{^{1}H} NMR spectra of 1.5.



1.6

1-(4-bromophenyl)propane-1,2-diol (1.6). Following Procedure A, the crude oxidation mixture was purified by silica gel chromatography (1:1 hexanes:ethyl acetate) to yield diol **1.6** as a colorless oil in 91% yield (21.0 mg) and 93:7 d.r (syn:anti). ***Syn* diastereomer: ^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.51 – 7.44 (m, 1H), 7.25 – 7.18 (m, 1H),

4.33 (d, 1H, J = 7.3 Hz), 3.79 (quintt, 1H, J = 6.5 Hz), 2.91 (br s, 1H), 2.56 (br s, 1H), 1.05 (d, 3H, J = 6.2 Hz). **^{13}C NMR** ($CDCl_3$, 101 MHz): δ 140.17, 131.71, 128.67, 122.09, 78.89, 75.20, 18.93. ***Anti* diastereomer: ^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.51 – 7.44 (m, 2H), 7.25 – 7.18 (m, 2H), 4.65 (d, 1H, J = 4.1 Hz), 3.98 (dd, 1H, J = 6.6, 4.4 Hz), 2.64 (br s, 1H), 1.71 (br s, 1H), 1.03 (d, 3H, J = 6.0 Hz). **^{13}C NMR** ($CDCl_3$, 101 MHz): δ 140.17, 131.53, 128.66, 128.45, 122.09, 78.89, 71.21, 17.21. **HRMS (ESI$^+$)** calcd for $C_9H_{11}O_2BrNa^+$ 252.9840, found: 252.9835 [M+Na]. **IR (v/cm^{-1}):** 3391 (br, s), 2979 (s), 1488 (s), 1373 (m), 1138 (m), 1071 (w), 1010 9 (w), 951 (w), 820 (m), 526 (w). **$[\alpha]^{22}_{D}$** = +64.3 ˚ (c = 0.457, CH_2Cl_2, l = 100 mm). Enantiomeric excess was determined by HPLC analysis compared to the authentic racemic material. Absolute stereochemistry was inferred from the stereochemistry obtained for compound **1.4**. *Diacel CHIRALPAK IC Column; 99:1 hexanes:iPrOH; 1.0 mL/min; 210 nm. Syn*-diastereomer: (1*R,2R*) enantiomer: 45.8 min; (1*S,2S*) enantiomer 49.0 min: 95:5 e.r.



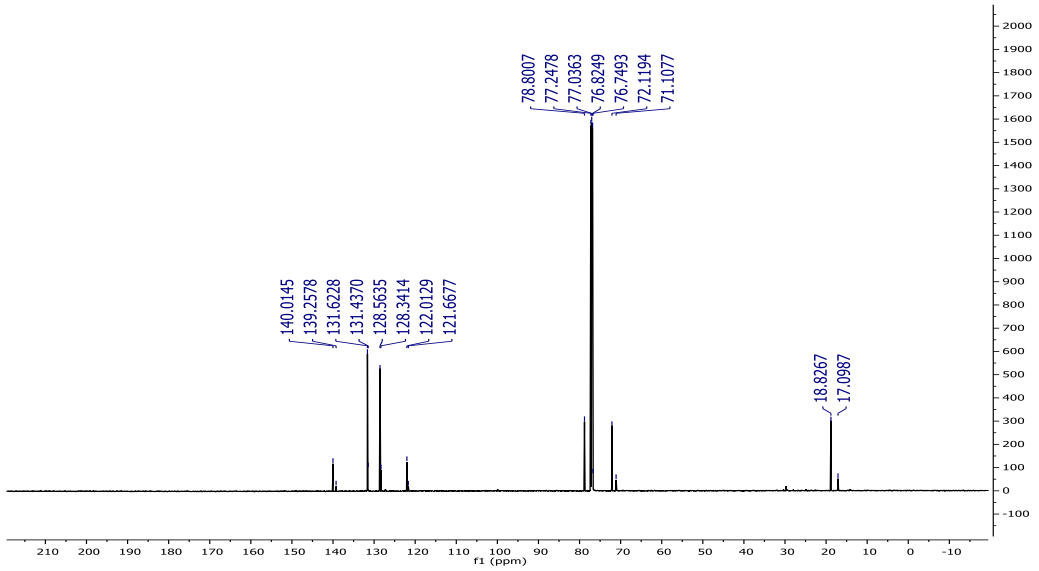
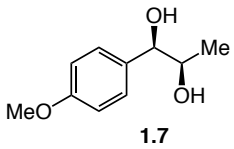


Figure 1.3. ^{1}H and ^{13}C{^{1}H} NMR spectra of 1.6.



1.7

1-(4-methoxyphenyl)propane-1,2-diol (1.7). Following Procedure A, the crude oxidation mixture was purified by silica gel chromatography (1:1 hexanes:ethyl acetate) to yield diol **1.7** as a colorless oil in 69% yield (12.4 mg) and 97:3 d.r (syn:anti). ***Syn* diastereomer**: **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 7.32 – 7.23 (m, 2H), 6.95 – 6.84 (m, 2H), 4.32 (d, 1H, J = 7.6 Hz), 3.84 (m, 1H), 3.81(s, 3H), 2.53 (br s, 2H), 1.04 (d, 3H, J = 6.3 Hz). **^{13}C NMR** ($CDCl_3$, 101 MHz): δ 159.60, 133.27, 128.13, 114.03, 79.28, 72.40, 55.40, 18.85. ***Anti* diastereomer: ^{1}H NMR** ($CDCl_3$, 600 MHz): δ 7.32 – 7.23 (m, 2H), 6.95 – 6.84 (m, 2H), 4.60 (d, 1H, J = 4.6 Hz), 3.98 (m, 1H), 3.81 (s, 3H), 2.53 (br s, 2H), 1.10 (d, 3H, J = 6.3 Hz). **^{13}C NMR** ($CDCl_3$, 101 MHz): δ 159.60, 133.27, 128.04, 113.94, 79.28, 72.40, 55.40, 17.67. **HRMS (ESI^{+})** calcd for $C_{10}H_{14}O_3Na^{+}$: 205.0841, found: 205.0835 [M+Na]. **IR (ν/cm^{-1}):** 3399 (br, s), 2980 (s), 1613 (s), 1513 (m), 1457 (w), 1372 (m), 1248 (w), 1177 (w), 1034 (w), 951 (m), 830 (w). **$[\alpha]^{22}_{D}$** = +37.2 ° (c = 0.265, CH_2Cl_2, l = 100 mm). Enantiomeric

excess was determined by HPLC analysis compared to the authentic racemic material. Absolute stereochemistry was inferred from the stereochemistry obtained for compound **1.4**. *Diacel CHIRALPAK IC Column; 99:1 hexanes:iPrOH; 0.75 mL/min; 210 nm. Syn*-diastereomer: (1*R,2R*) enantiomer: 143.0 min; (1*S,2S*) enantiomer 152.0 min: 93:7 e.r.

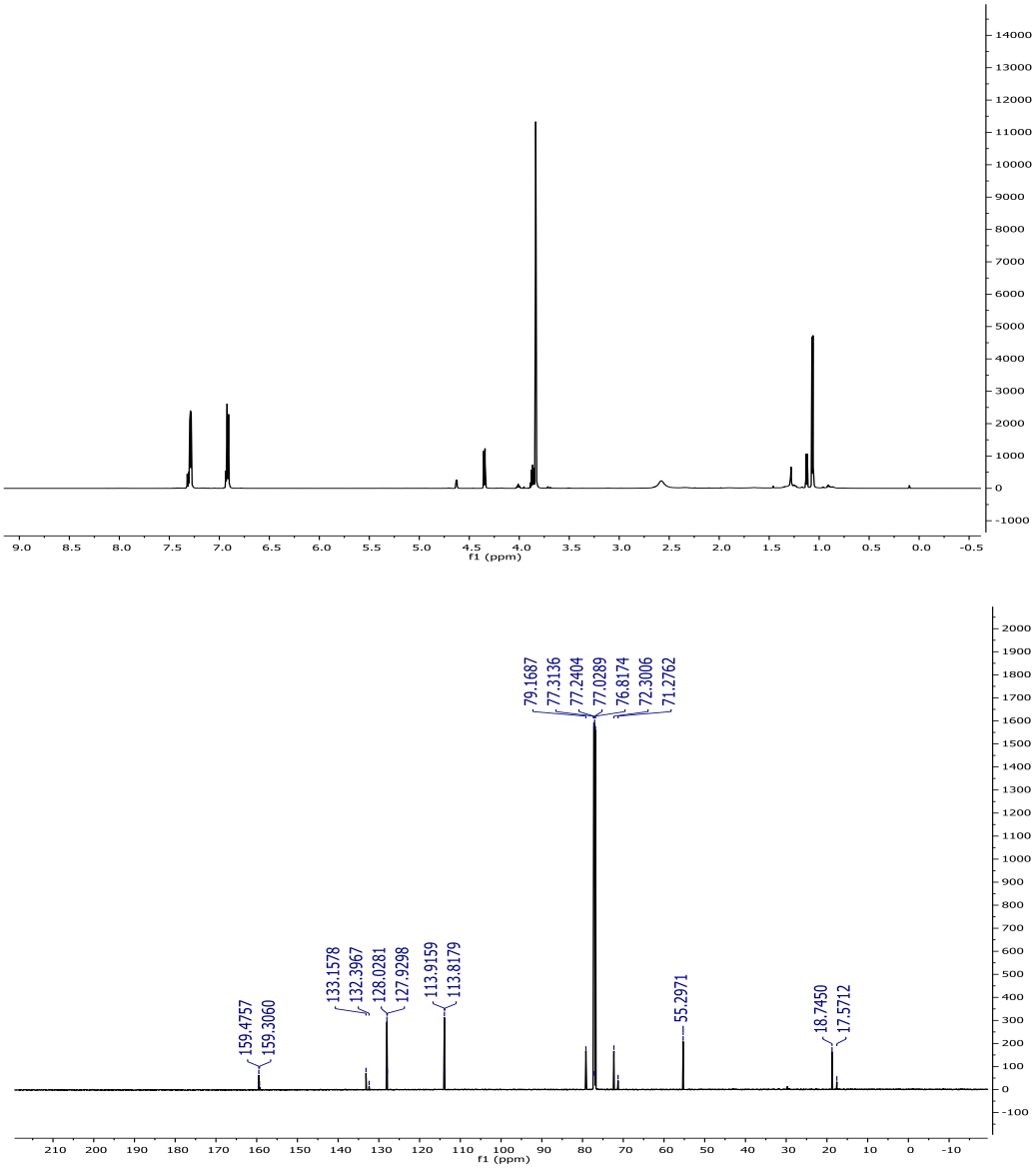
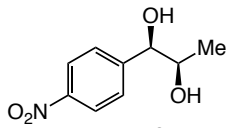


Figure 1.4. ^{1}H and ^{13}C{^{1}H} NMR spectra of 1.7.



1.8

1-(4-nitrophenyl)propane-1,2-diol (1.8). Following Procedure A, the crude oxidation mixture was purified by silica gel chromatography (1:1 hexanes:ethyl acetate) to yield diol **1.8** as an orange oil in 34% yield (6.6 mg) and 96:4 d.r (syn:anti). ***Syn*** **diastereomer:** **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 8.28 – 8.21 (m, 2H), 7.61 – 7.55 (m, 2H), 4.56 (d, 1H, *J* = 6.7 Hz), 3.88 (quint, 1H, *J* = 6.4 Hz), 2.94 (s, 2H), 1.16 (d, 1H, *J* = 6.3 Hz). **^{13}C NMR** (151 MHz, CDCl3): δ 148.33, 147.72, 127.73, 123.66, 78.34, 72.02, 19.09. ***Anti*** **diastereomer:** **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 8.28 – 8.21 (m, 2H), 7.61 – 7.55 (m, 2H), 4.89 (d, 1H, *J* = 3.9 Hz), 4.12 (qd, 1H, *J* = 6.4, 3.9 Hz), 2.34 (s, 2H), 1.07 (d, 3H *J* = 6.4 Hz). **^{13}C NMR** (151 MHz, CDCl3): δ 148.33, 147.60, 127.38, 123.49, 76.35, 71.03, 16.89. **HRMS (ESI$^+$)** calcd for $C_9H_{11}O_4NNa^+$ 220.0586, found: 220.0581 [M+Na]. **IR (ν/cm^{-1}):** 3400 (br, s), 2982 (s), 1528 (s), 1381 (s), 1248 (m), 1217 (m), 1022 (w), 954 (m), 821 (w). **$[\alpha]^{22}_D$** = –32.1 ° (*c* = 0.572, CH_2Cl_2, l = 100 mm). Enantiomeric excess was determined by HPLC analysis compared to the authentic racemic material. Absolute stereochemistry was inferred from the stereochemistry obtained for compound **1.4**. *Diacel CHIRALPAK IA Column; 92:8 hexanes:ethyl acetate; 1.0 mL/min; 210 nm. Syn*-diastereomer: (1*S,2S*) enantiomer: 162.0 min; (1*R,2R*) enantiomer 175.7 min: 95:5 e.r.

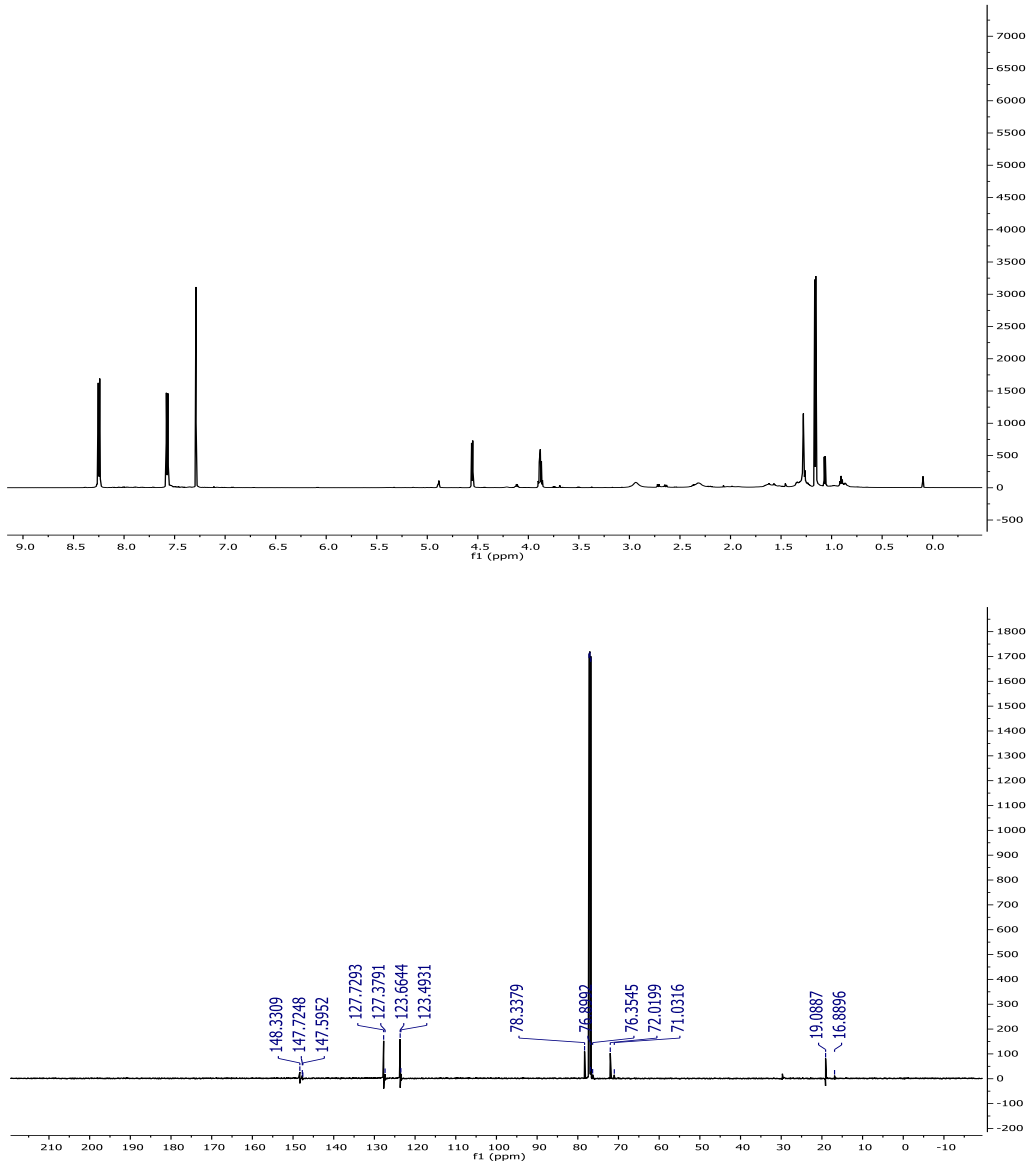
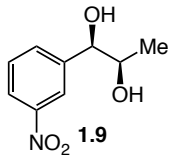


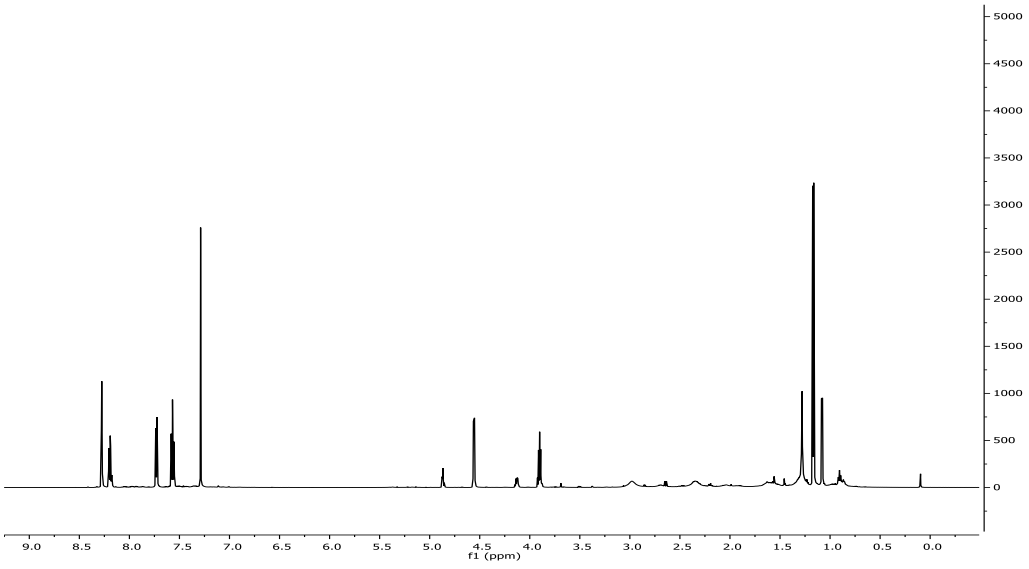
Figure 1.5. ^{1}H and ^{13}C{^{1}H} NMR spectra of 1.8.



1.9

1-(3-nitrophenyl)propane-1,2-diol (1.9). Following Procedure A, the crude oxidation mixture was purified by silica gel chromatography (1:1 hexanes:ethyl acetate) to yield diol **1.9** as a yellow oil in 35% yield (6.6 mg) and 84:16 d.r (syn:anti). ***Syn* diastereoemer: ^{1}H NMR** ($CDCl_3$, 600 MHz): δ 8.25 (t, 1H, J = 2.0 Hz), 8.20 – 8.12 (m,

1H), 7.70 (dt, 1H, *J* = 7.7, 1.4 Hz), 7.54 (td, 1H, *J* = 7.9, 3.3 Hz), 4.53 (d, 1H, *J* = 6.8 Hz), 3.87 (quint, 1H, *J* = 6.4 Hz), 2.95 (s, 2H), 1.14 (d, 2H, *J* = 6.3 Hz). **^{13}C NMR** (151 MHz, $CDCl_3$): δ 148.34, 143.28, 133.00, 129.43, 123.06, 121.89, 78.21, 72.01, 19.09. ***Anti* diastereoemer: ^{1}H NMR** ($CDCl_3$, 600 MHz): δ 4.84 (m, 1H), 4.10 (qd, 1H, *J* = 6.4, 3.9 Hz), 2.30 (s, 2H), 1.05 (d, 3H, *J* = 6.4 Hz). **^{13}C NMR** (151 MHz, $CDCl_3$): δ 148.34, 142.44, 132.75, 129.21, 122.72, 121.66, 76.26, 70.97, 17.02. **HRMS (ESI$^+$)** calcd for $C_9H_{11}O_4NNa^+$ 220.0586, found: 220.0581 [M+Na]. **IR (neat):** 3402 (br, s), 2987 (s), 1528 (s), 1345 (s), 1260 (m) 1220 (m), 1025 (w), 954 (m), 821 (w). **$[\alpha]^{22}_D$** = –45.2 ° (*c* = 0.657, CH_2Cl_2, l = 100 mm). Enantiomeric excess was determined by HPLC analysis compared to the authentic racemic material. Absolute stereochemistry was inferred from the stereochemistry obtained for compound **1.4**. *Diacel CHIRALPAK IC Column; 97:3 hexanes:iPrOH; 1.0 mL/min; 210 nm. Syn*-diastereomer: (1*S,2S*) enantiomer: 35.8 min; (1*R,2R*) enantiomer 52.3 min: 95:5 e.r.



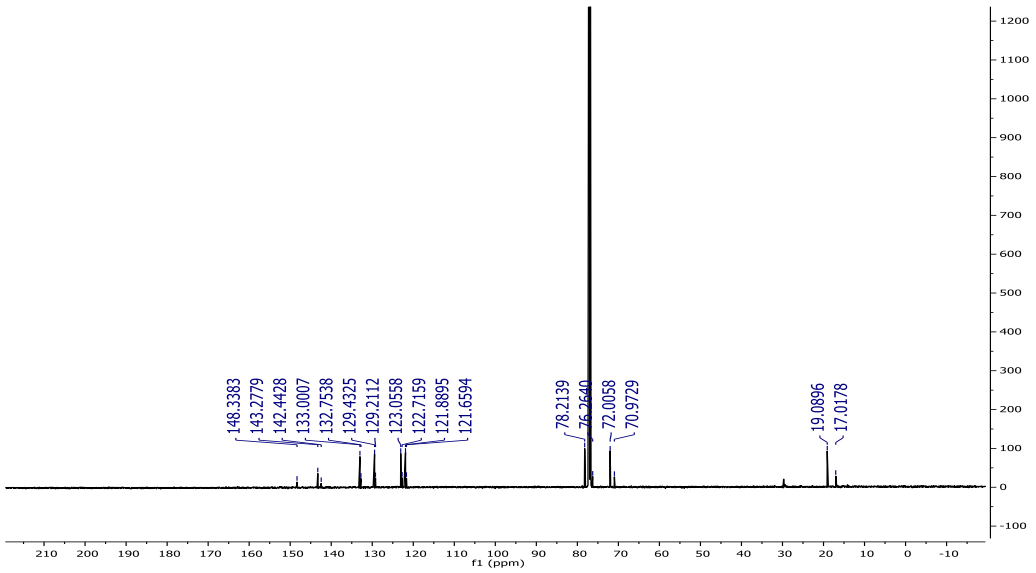
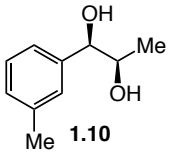


Figure 1.6. ^{1}H and ^{13}C{^{1}H} NMR spectra of 1.9.



1.10

1-(3-tolyl)propane-1,2-diol (1.10). Following Procedure A, the crude oxidation mixture was purified by silica gel chromatography (1:1 hexanes:ethyl acetate) to yield diol **1.10** as a colorless oil in 76% yield (12.6 mg) and 96:4 d.r (syn:anti). ***Syn* diastereomer: ^{1}H NMR** ($CDCl_3$, 600 MHz): δ 7.26 – 7.22 (m, 1H), 7.19 – 7.10 (m, 3H), 4.34 (d, 1H J = 7.3 Hz), 3.90 – 3.83 (m, 1H), 2.63 (s, 1H), 2.53 (s, 1H), 1.06 (d, 3H, J = 6.3 Hz). **^{13}C NMR** ($CDCl_3$, 151 MHz): δ 141.00, 138.23, 128.91, 128.41, 127.44, 123.94, 79.53, 75.07, 21.46, 18.79. **Anti diastereomer: ^{1}H NMR** ($CDCl_3$, 600 MHz): δ 7.26 – 7.22 (m, 1H), 7.19 – 7.10 (m, 3H), 4.66 (d, J = 4.5 Hz, 1H), 4.03 (qd, J = 6.4, 4.7 Hz, 1H), 2.63 (s, 1H), 2.53 (s, 1H), 1.13 (dd, J = 6.4, 0.8 Hz, 3H). **^{13}C NMR** ($CDCl_3$, 151 MHz): δ 140.30, 138.09, 128.63, 128.30, 127.29, 123.73, 77.64, 71.31, 21.50, 17.44. **HRMS (ESI^{+})** calcd for $C_{10}H_{14}O_2Na^{+}$: 189.0893, found: 189.0888 ($M + Na^{+}$). **IR (ν/cm^{-1}):** 3417 (br, s), 2917 (s), 1646 9 (s), 1456 (m), 1130 (m), 1038 (w), 544 (m). **$[\alpha]^{22}_{D}$** = +49.2 ° (c = 0.675, CH_2Cl_2, l = 100 mm).

Enantiomeric excess was determined by HPLC analysis compared to the authentic racemic material. Absolute stereochemistry was inferred from the stereochemistry obtained for compound **1.4**. *Diacel CHIRALPAK IA Column; 99:1 hexanes:iPrOH; 1.0 mL/min; 210 nm. Syn*-diastereomer: (1*S,2S*) enantiomer: 23.3 min; (1*R,2R*) enantiomer 40.2 min: 98:2 e.r.

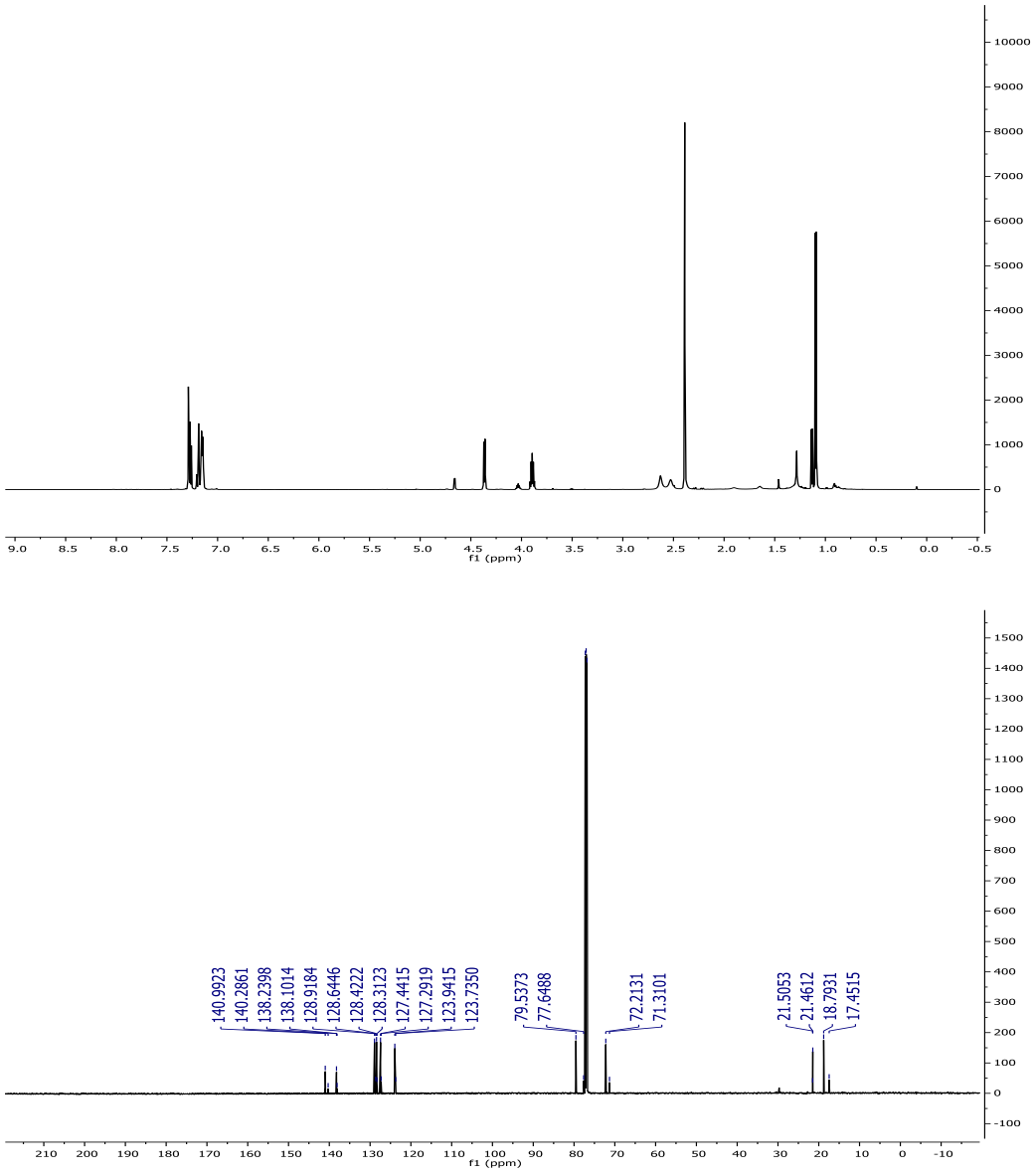
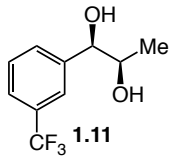


Figure 1.7. ^{1}H and ^{13}C{^{1}H} NMR spectra of 1.10.



1.11

1-(3-(trifluoromethyl)phenyl)propane-1,2-diol (1.11). Following Procedure A, the crude oxidation mixture was purified by silica gel chromatography (1:1 hexanes:ethyl acetate) to yield diol **1.11** as a colorless oil in 59% yield (12.9 mg) and 96:4 d.r (syn:anti). ***Syn* diastereomer: ^{1}H NMR** ($CDCl_3$, 600 MHz): δ 7.64 (s, 1H), 7.56 (dd, 2H, *J* = 16.0, 7.7 Hz), 7.48 (t, 1H, *J* = 7.7 Hz), 4.45 (d, 1H, *J* = 7.1 Hz), 3.85 (quint, 1H, *J* = 6.5 Hz), 3.44 (s, 1H), 2.89 (s, 1H), 1.10 (d, 3H, *J* = 6.3 Hz). **^{13}C NMR** ($CDCl_3$, 151 MHz): δ 142.27, 131.11, 130.90, 130.68, 130.47, 130.33, 128.86, 124.95, 124.83, 124.81, 123.71, 123.68, 123.66, 123.63, 78.72, 72.04, 18.88. ***Anti* diastereomer: ^{1}H NMR** ($CDCl_3$, 600 MHz): δ 7.65 (s, 1H), 7.56 (dd, 2H, *J* = 16.0, 7.7 Hz), 7.48 (t, 1H, *J* = 7.7 Hz) 4.79 (d, 1H, *J* = 3.9 Hz), 4.05 (dd, 1H, *J* = 6.4, 4.0 Hz), 3.17 (s, 1H), 2.89 (s, 1H), 1.06 (d, 3H, *J* = 6.5 Hz). **^{13}C NMR** ($CDCl_3$, 151 MHz): δ 141.54, 130.71, 130.47, 130.02, 128.65, 124.45, 124.42, 123.42, 123.39, 123.15, 76.65, 71.10, 16.90. **HRMS (ESI^{+})** calcd for $C_{10}H_{11}F_3O_2Na^{+}$: 243.0609, found: 243.0604 [M+Na]. **IR (ν/cm^{-1}):** 3416 (br, s), 2918 (s), 2849 (s), 1647 (m), 1454 (m), 1329 (w), 1166 (w), 1073 (m), 1127 (w), 802 (m), 705 (w). **$[\alpha]^{22}_{D}$** = +37.5 ˚ (*c* = 0.225, CH_2Cl_2, l = 100 mm). Enantiomeric excess was determined by HPLC analysis compared to the authentic racemic material. Absolute stereochemistry was inferred from the stereochemistry obtained for compound **1.4**. *Diacel CHIRALPAK IC Column; 99:1 hexanes:iPrOH; 1.0 mL/min; 210 nm. Syn*-diastereomer: (1*R,2R*) enantiomer: 12.7 min; (1*S,2S*) enantiomer 13.4 min: 94:6 e.r.

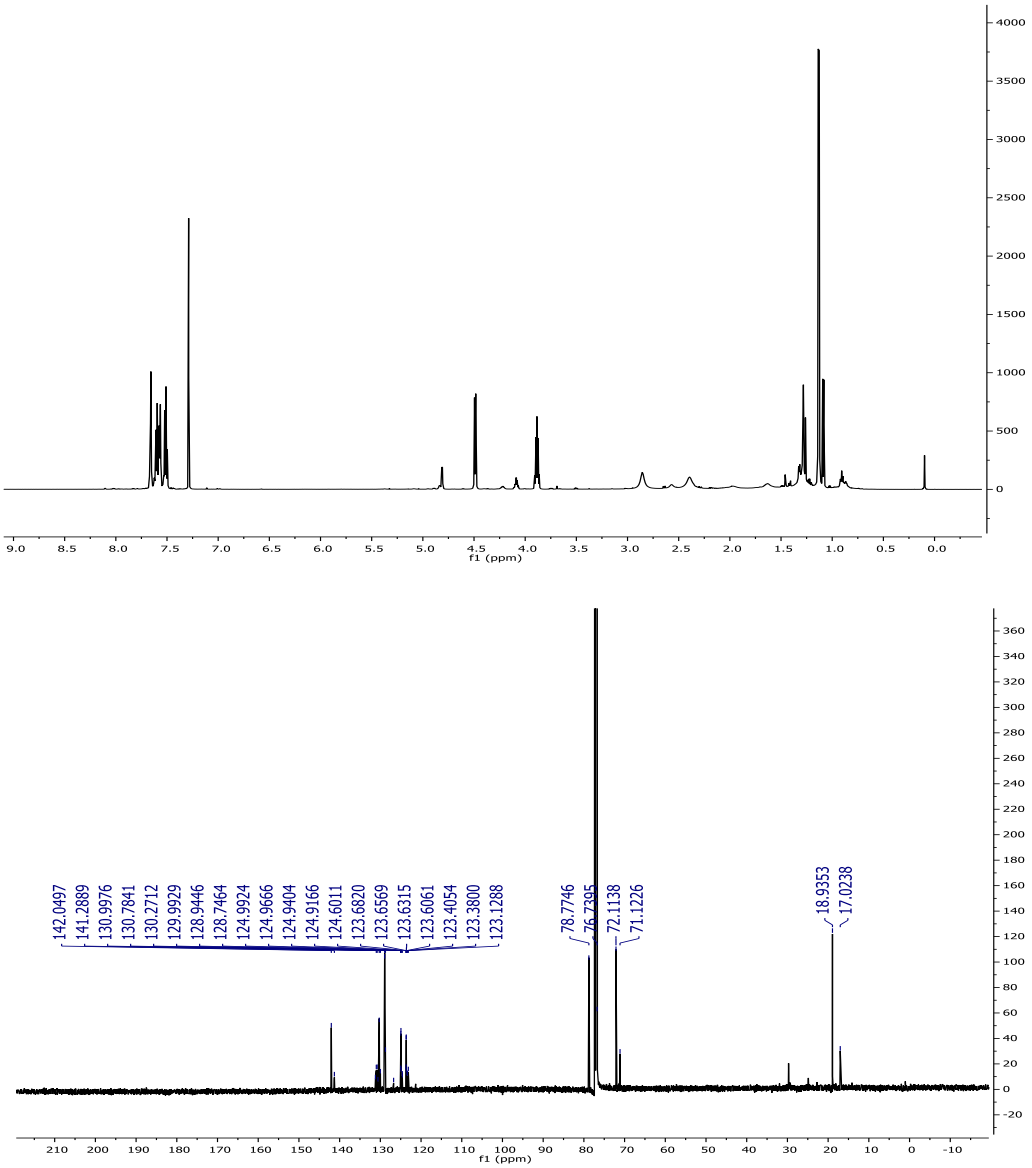
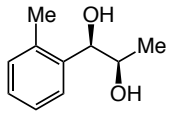


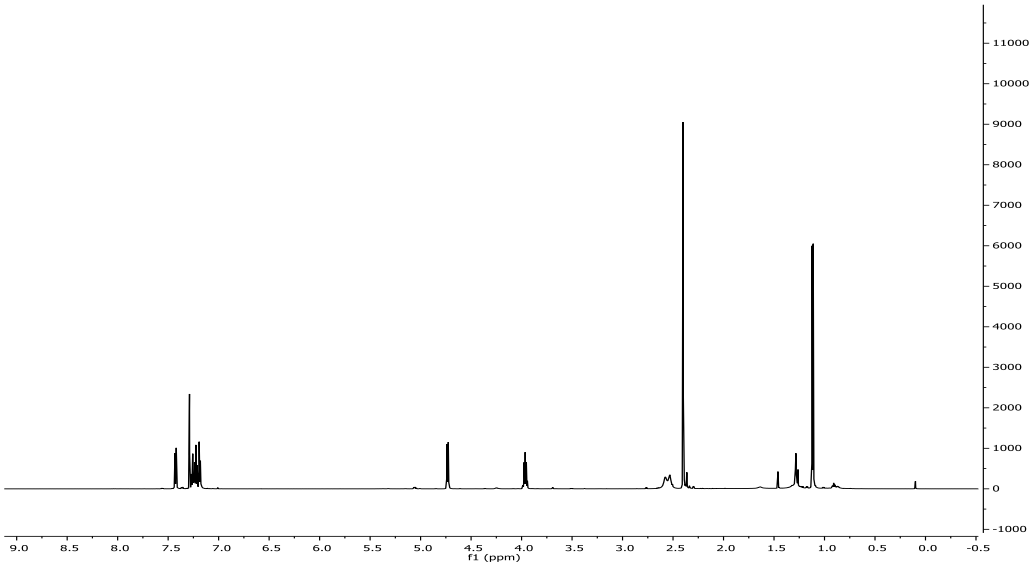
Figure 1.8. ^{1}H and ^{13}C{^{1}H} NMR spectra of 1.11.



1.12

1-(2-tolyl)propane-1,2-diol (1.12). Following Procedure A, the crude oxidation mixture was purified by silica gel chromatography (1:1 hexanes:ethyl acetate) to yield diol **1.12** as a colorless oil in 68% yield (10.8 mg) as a single detectable diastereomer (*syn*). **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 7.38 (dd, 1H, J = 7.5, 1.5 Hz), 7.24 – 7.11 (m, 3H), 4.68 (d, 1H,

J = 7.3 Hz), 3.91 (quint, 1H, *J* = 6.6 Hz), 2.91 (br, d, 2H), 2.36 (s, 3H), 1.06 (d, 3H, *J* = 6.4 Hz). **^{13}C NMR** ($CDCl_3$, 151 MHz): δ 139.42, 135.44, 130.53, 127.67, 126.44, 126.27, 75.01, 72.10, 19.59, 18.54. **HRMS (ESI$^+$)** calcd for $C_{10}H_{14}O_2Na^+$: 189.0893, found: 189.0888 (M + Na^+). **IR (ν/cm^{-1}):** 3292 (br, s), 2918 (s), 2360 (s), 1645 (s), 1467 (m), 1035 (w), 545 (m). **$[\alpha]^{22}_D$** = +46.3 ° (*c* = 0.564, CH_2Cl_2, l = 100 mm). Enantiomeric excess was determined by HPLC analysis compared to the authentic racemic material. Absolute stereochemistry was inferred from the stereochemistry obtained for compound **1.4**. *Diacel CHIRALPAK IA Column; 99:1 hexanes:iPrOH; 1.0 mL/min; 210 nm. Syn*-diastereomer: (1*S,2S*) enantiomer: 24.8 min; (1*R,2R*) enantiomer 27.9 min: 93:7 e.r.



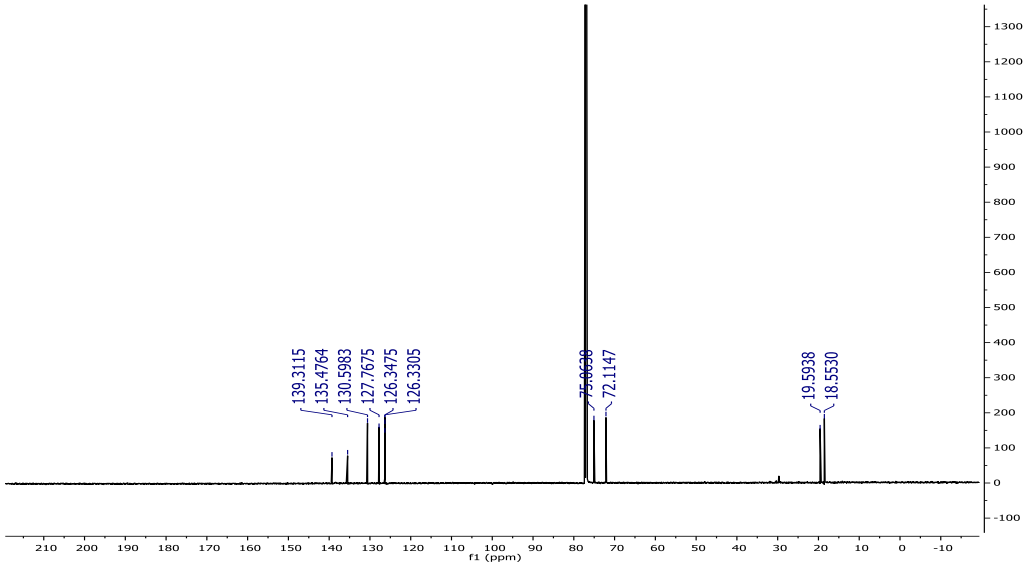
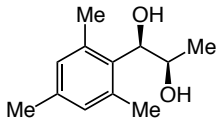


Figure 1.9. ^{1}H and ^{13}C{^{1}H} NMR spectra of 1.12.



1.13

1-mesitylpropane-1,2-diol (1.13). Following Procedure A, the crude oxidation mixture was purified by silica gel chromatography (1:1 hexanes:ethyl acetate) to yield diol **1.13** as a colorless oil in 65% yield (12.7 mg) as a single detectable diastereomer (*syn*). **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 6.9 (s, 2H), 4.92 (d, 1H, J = 9.1 Hz), 4.35 (dq, 1H, J = 9.1, 6.3 Hz), 2.45 (s, 6H), 2.38 (s, 3H), 1.06 (d, 3H, J = 6.6 Hz). **^{13}C NMR** ($CDCl_3$, 151 MHz): δ 137.17, 136.88, 133.24, 130.29, 76.36, 69.84, 21.15, 20.77, 18.65. **HRMS (ESI^{+})** calcd for $C_{12}H_{18}O_2Na^{+}$ 217.1205, found: 217.1120 [M+Na]. **IR (v/cm^{-1}):** 3293 (br, s), 2920 (s), 1644 (m), 1454 (m), 1121 (w), 1040 (w), 1015 (m), 705 (w). **$[\alpha]^{22}_{D}$** = +64.5 ° (c = 0.679, CH_2Cl_2, l = 100 mm). Enantiomeric excess was determined by HPLC analysis compared to the authentic racemic material. Absolute stereochemistry was inferred from the stereochemistry obtained for compound **1.4**. *Diacel CHIRALPAK IA Column; 99:1 hexanes:iPrOH; 0.75*

mL/min; 210 nm. Syn-diastereomer: (1*S,2S*) enantiomer: 39.7 min; (1*R,2R*) enantiomer 42.3 min: 93:7 e.r.

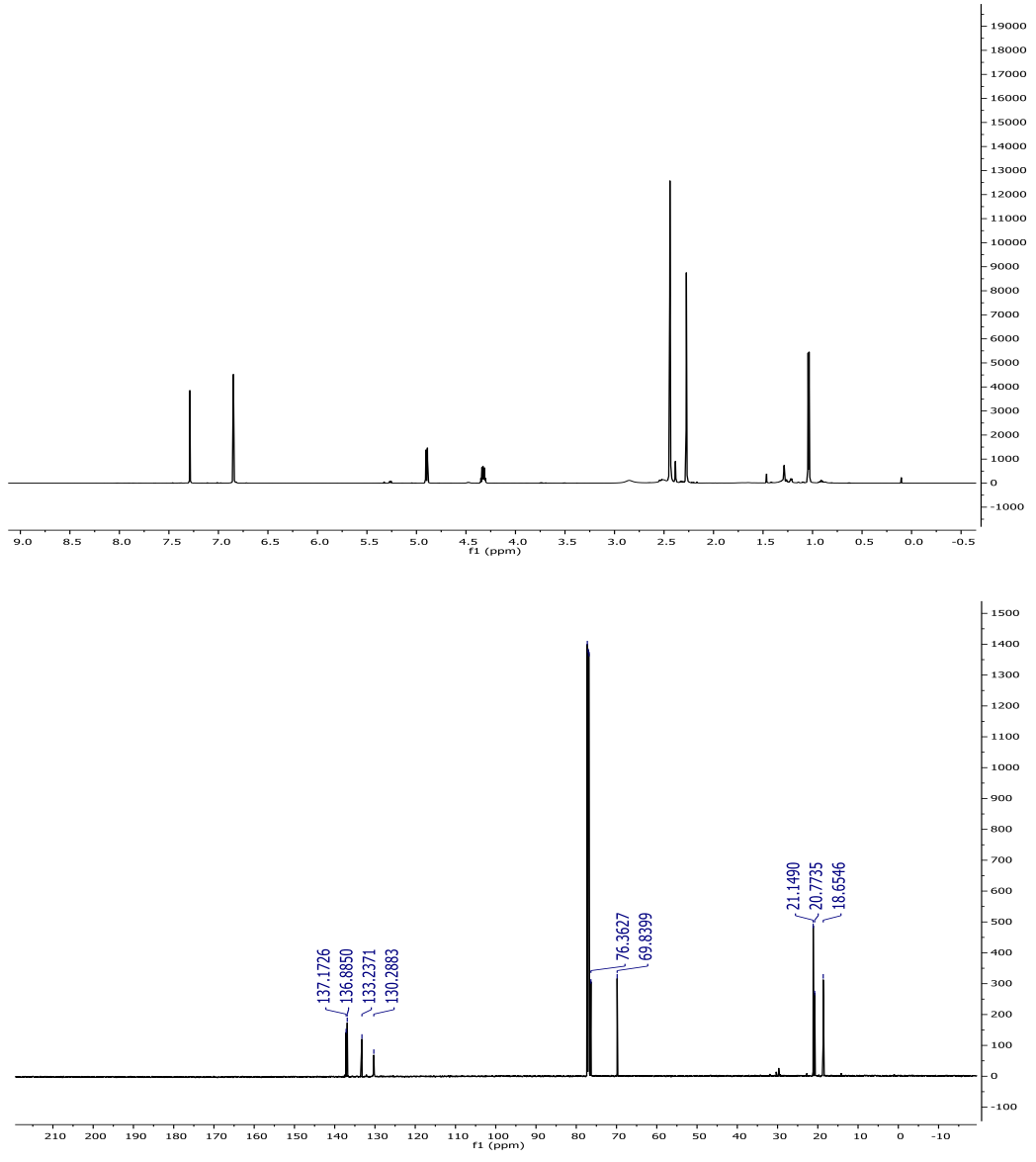
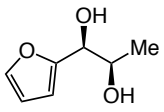


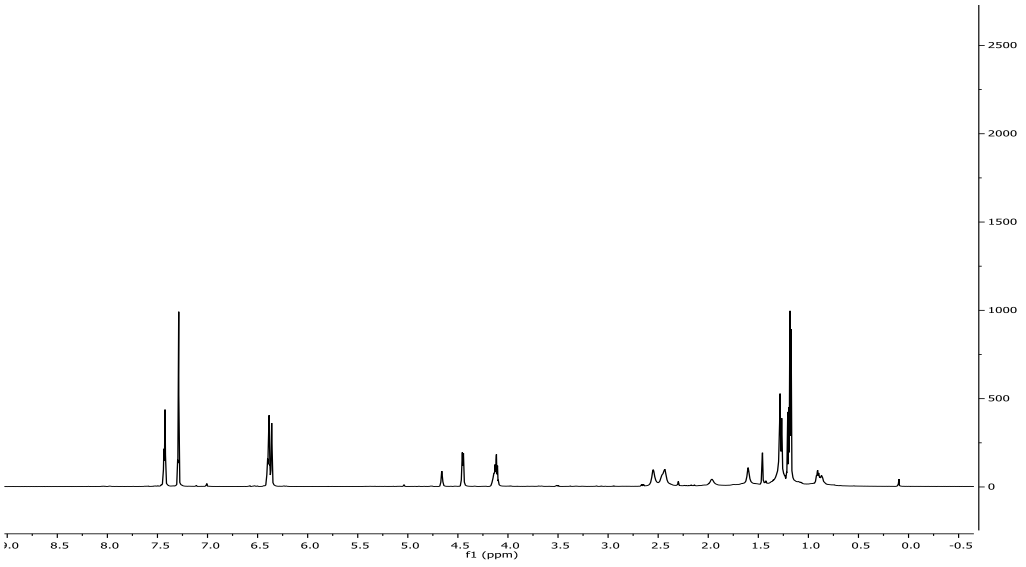
Figure 1.10. ^{1}H and ^{13}C{^{1}H} NMR spectra of 1.13.



1.14

1-(furan-3-yl)propane-1,2-diol (1.14). Following Procedure A, the crude oxidation mixture was purified by silica gel chromatography (1:1 hexanes:ethyl acetate) to yield diol

1.14 as a colorless oil in 56% yield (7.9 mg) and 96:4 d.r. (syn:anti). ***Syn* diastereomer: ^{1}H NMR** ($CDCl_3$, 600 MHz): δ 7.42 (d, 1H, *J* = 1.0 Hz), 6.40-6.38 (m, 2H), 4.41 (m, 1H), 4.45 (d, 1H, *J* = 7.0 Hz), 4.12 (m, 1H), 2.71 (s, 2H), 1.18 (d, 3H, *J* = 6.3 Hz). **^{13}C NMR** ($CDCl_3$, 151 MHz): δ 153.88, 142.40, 110.35, 107.72, 72.60, 69.86, 18.81. ***Anti* diastereomer: ^{1}H NMR** ($CDCl_3$, 600 MHz): δ 7.44 (d, 1H, *J* = 3.6 Hz), 6.37-6.35 (m, 2H), 4.67 (d, 1H, *J* = 4.4 Hz), 4.15 (m, 1H), 2.61 (br s, 2H), 1.21 (d, 3H, *J* = 6.0 Hz). **^{13}C NMR** ($CDCl_3$, 101 MHz): δ 153.53, 142.34, 110.35, 107.92, 71.80, 69.97, 18.29. **HRMS (ESI^{+})** calcd for $C_7H_{10}O_3Na^{+}$ 165.0528, found: 165.05221 [M+Na]. **IR (ν/cm^{-1}):** 3416 (br, s), 2980 (s), 1643 (s), 1454 (m), 1380 (m), 1148 (w), 1011 (m), 674 (w). **$[\alpha]^{22}_{D}$** = +15.4 ° (*c* = 0.232, CH_2Cl_2, l = 100 mm). Enantiomeric excess was determined by HPLC analysis compared to the authentic racemic material. Absolute stereochemistry was inferred from the stereochemistry obtained for compound **1.4**. *Diacel CHIRALPAK IA Column; 99:1 hexanes:iPrOH; 1.0 mL/min; 210 nm. Syn*-diastereomer: (1*S,2S*) enantiomer: 30.4 min; (1*R,2R*) enantiomer 32.8 min: 95:5 e.r.



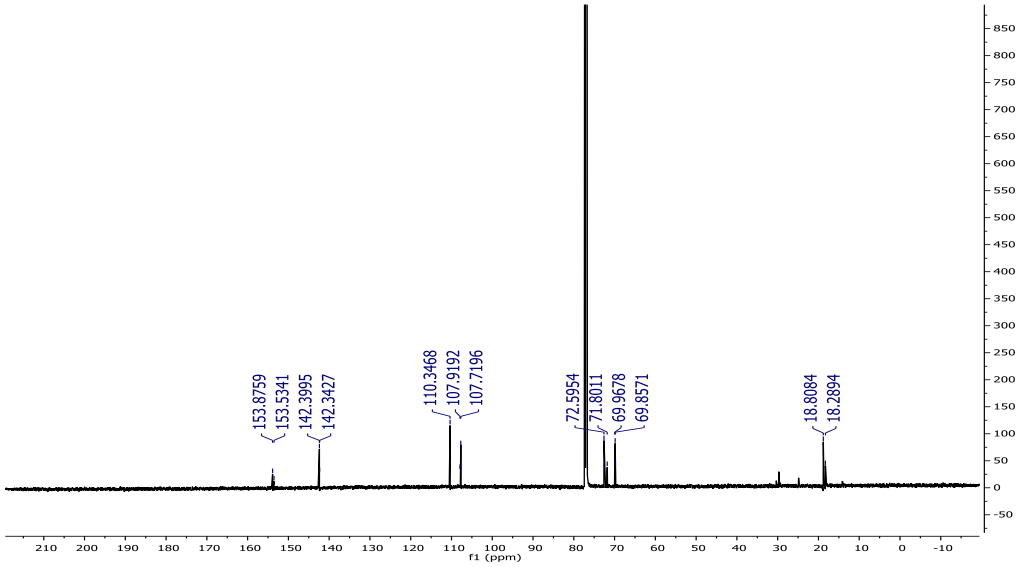
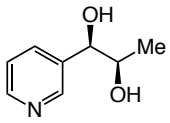


Figure 1.11. ^{1}H and ^{13}C{^{1}H} NMR spectra of 1.14.



1.15

1-(pyridin-3-yl)propane-1,2-diol (1.15). Following Procedure A, the crude oxidation mixture was purified by silica gel chromatography (1:1 hexanes:ethyl acetate) to yield diol **1.15** as a colorless oil in 68% yield (10.4 mg) and 84:16 d.r (syn:anti). ***Syn* diastereomer: ^{1}H NMR** ($CDCl_3$, 600 MHz): δ 8.60 (br, d, 2H, J = 11.6 Hz), 7.77 (d, 1H, J = 8.0 Hz), 7.34 (m, 1H), 4.47 (d, 1H, J = 7.0 Hz), 3.90 (m, 1H), 1.13 (d, 3H, J = 4 Hz). **^{13}C NMR** (CDCl3, 151 MHz) δ 149.09, 148.34, 134.63, 123.44, 77.26, 77.05, 76.84, 75.21, 70.98, 17.20. **Anti Diastereomer: ^{1}H NMR** ($CDCl_3$, 600 MHz): δ 8.60 (br d, 2H, J = 11.6 Hz), 7.77 (d, 1H, J = 8.0 Hz), 7.34 (m, 1H), 4.78 (d, 1H, J = 4.0 Hz), 4.11 (m, 1H), 1.09 (d, 3H, J = 6.3 Hz). **^{13}C NMR** (CDCl3, 151 MHz) δ 149.09, 148.34, 134.63, 123.44, 77.26, 77.05, 76.84, 75.21, 70.98, 17.20. **HRMS (ESI^{+})** calcd for $C_8H_{12}O_2N^{+}$ 154.168, found: 154.182 [M+H]. **IR (neat):** 3322 (br, s), 2963 (s), 1584 (s), 1470 (m), 1370 (m), 1302 (m), 1290 (m), 1085 (w), 900 (m), 808 (w). **$[\alpha]^{22}_{D}$** = +14.2 ° (c = 0.145, CH_2Cl_2, l = 100 mm).

Enantiomeric excess was determined by HPLC analysis compared to the authentic racemic material. Absolute stereochemistry was inferred from the stereochemistry obtained for compound **1.4**. *Diacel CHIRALPAK IC Column; 85:15 hexanes:iPrOH; 0.5 mL/min; 210 nm. Syn*-diastereomer: (1*R*,2*R*) enantiomer: 37.2 min; (1*S*,2*S*) enantiomer 39.8 min: 90:10 e.r.

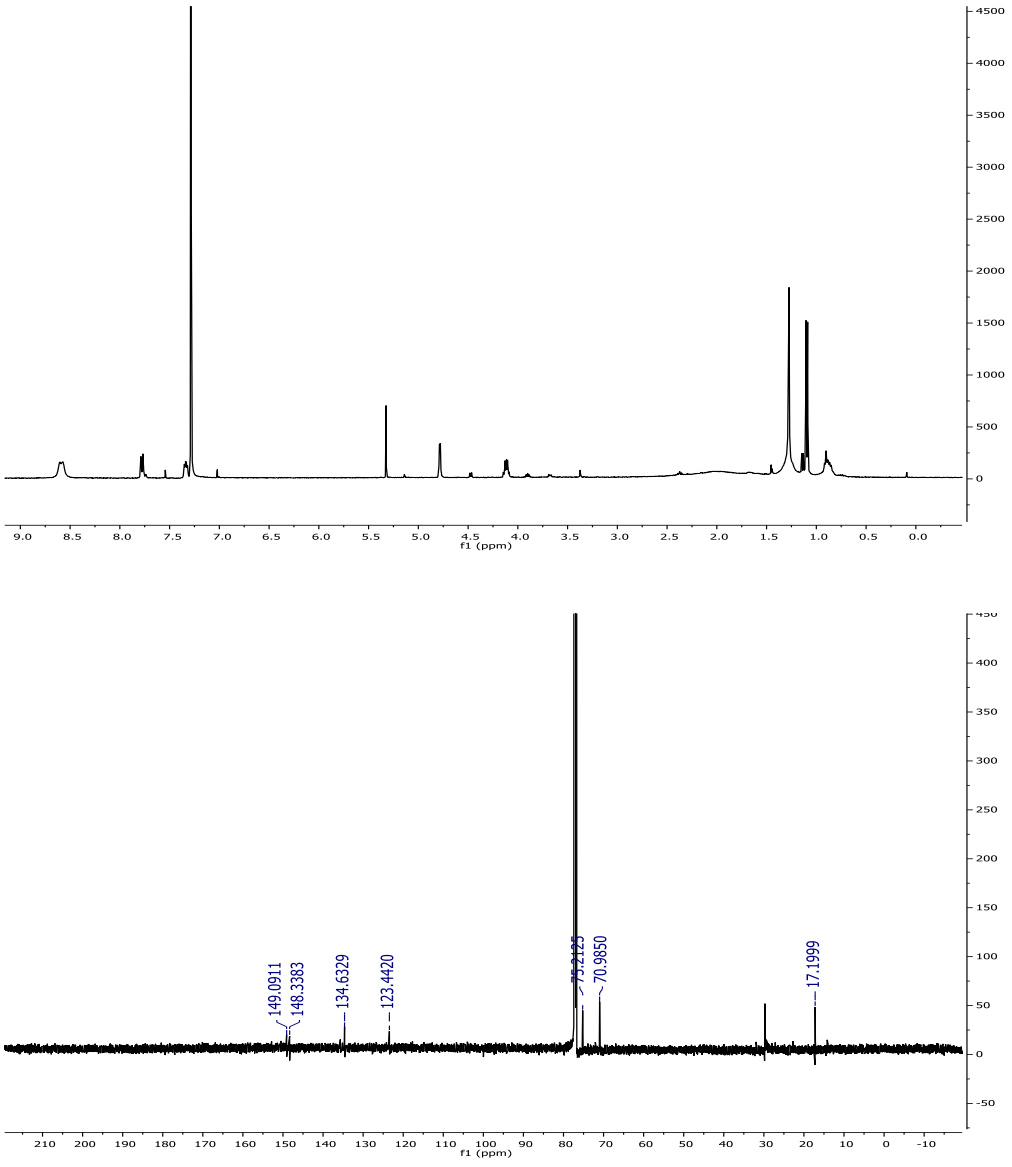
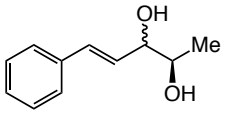


Figure 1.12. ^{1}H and ^{13}C{^{1}H} NMR spectra of 1.15.

1.8.3 Preparation of vinyl 1,2-diols



1.16

(*2R,E*)-5-phenylpent-4-ene-2,3-diol (1.16). Following Procedure C, the crude oxidation mixture was purified by silica gel chromatography (2:1 to 1:1 hexanes:ethyl acetate), the product diol **1.16** was isolated as a colorless oil in 59% yield (10.5 mg) and 54:46 d.r (*anti:syn*). ***anti*-diastereomer: ^{1}H NMR** ($CDCl_3$, 600 MHz): δ 7.40 (t, 2H, *J* = 6.8 Hz), 7.33 (d, 2H, *J* = 7.2 Hz), 7.26 (t, 1H, *J* = 6.6 Hz), 6.67 (d, 1H, *J* = 12.6 Hz), 6.27 (dd, 1H, J = 16.2, 7.2 Hz), 4.26 (dd, 1H, *J* = 7.2, 1.2 Hz), 3.97 (m, 1H), 1.20 (d, 1H, *J* = 6.6 Hz); **^{13}C NMR** ($CDCl_3$, 151 MHz): δ 136.51, 133.26, 128.76, 128.12, 127.18, 126.70, 76.70, 70.45, 17.88; ***syn*-diastereomer: ^{1}H NMR** ($CDCl_3$, 600 MHz): δ 7.40 (t, 2H, *J* = 6.8 Hz), 7.33 (d, 2H, *J* = 7.2 Hz), 7.26 (t, 1H, *J* = 6.6 Hz), 6.69 (d, 1H, *J* = 13.2 Hz), 6.19 (dd, 1H, J = 16.2, 7.2 Hz), 4.04 (td, 1H, *J* = 8.4, 1.2 Hz), 3.75 (quint, 1H, *J* = 6.0 Hz), 1.23 (d, 1H, *J* = 6.0 Hz); **^{13}C NMR** ($CDCl_3$, 151 MHz): δ 136.47, 133.02, 128.77, 128.45, 128.09, 126.70, 77.92, 71.08, 19.16; **IR** (ν/cm^{-1}): 3385 (OH, br, s), 3027 (w), 2972 (w), 2925 (m), 2870 (w), 2851 (w), 1457 (m), 1375 (w), 1070 (w), 1027 (w), 968 (m), 748 (m), 693 (m), 505 (w); **HRMS**-(ESI$^+$) $[M+Na]^+$ calcd for $C_{11}H_{14}NaO_2^+$ 201.0892, found: 201.0887. Enantiomeric purity was determined by HPLC analysis compared to the authentic racemic material. Absolute stereochemistry was inferred from the stereochemistry obtained for compound **1.20** and **1.23** (defunctionalization experiment, see section 1.8.4 below).[26] *Diacel CHIRALPAK IB Column; 98:2 hexanes:iPrOH; 0.75 mL/min; 22 °C, 210 nm. Syn*-diastereomers: (2*S*,3*S*)-enantiomer: 87.4 min.; (2*R*,3*R*)-enantiomer: 113.1 min.: 92:8 e.r.; *anti*-diastereomers: (2*R,*3*S*)-enantiomer: 89.8 min.; (2*S,*3*R*)-enantiomer: 142.5 min.: 97:3 e.r.

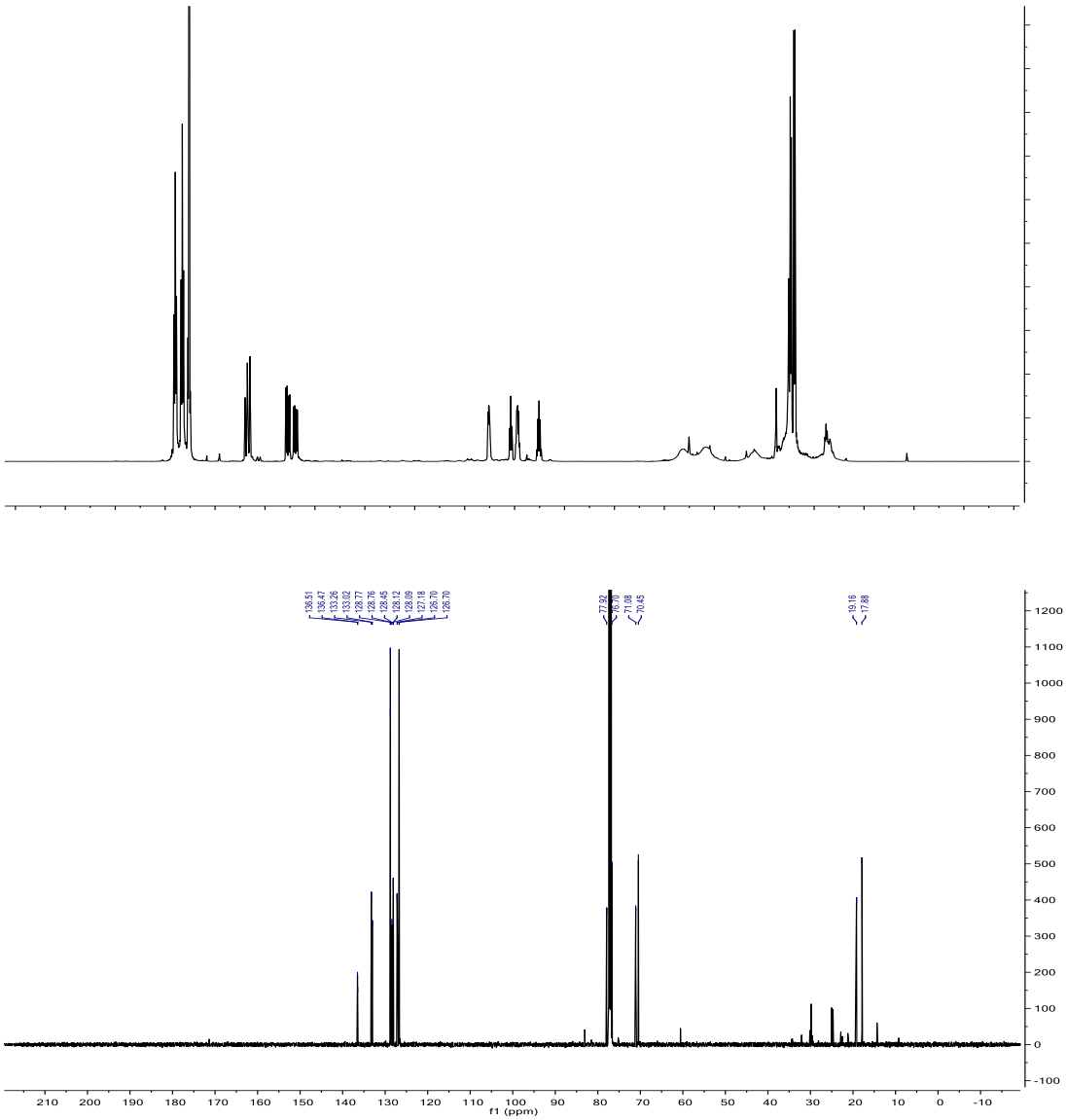
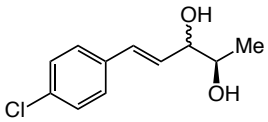


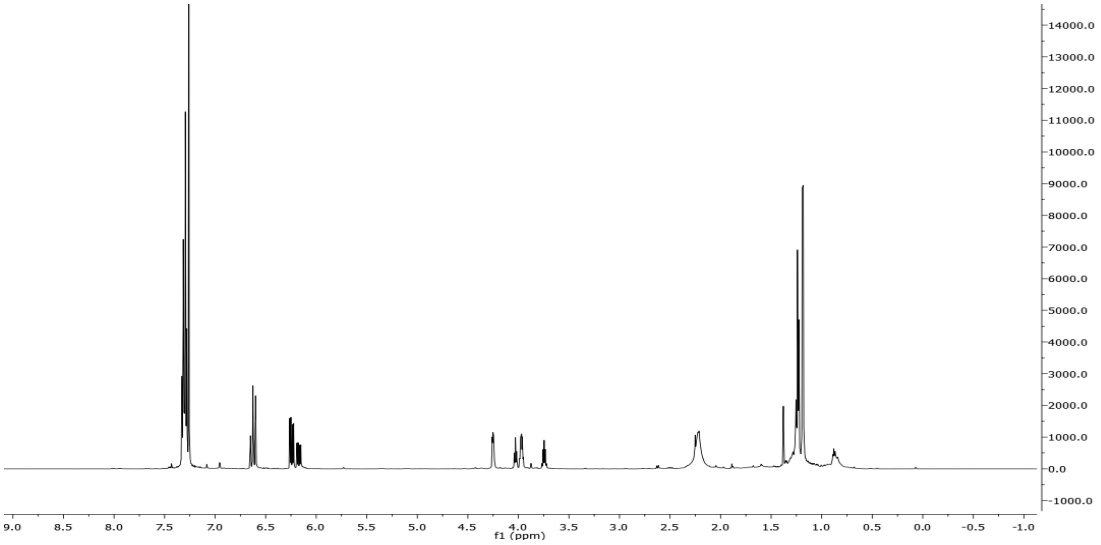
Figure 1.13. ^{1}H and ^{13}C{^{1}H} NMR spectra of 1.16.



1.17

(*2R,E*)-5-(4-chlorophenyl)pent-4-ene-2,3-diol (1.17). Following Procedure C, the crude oxidation mixture was purified by silica gel chromatography (2:1 to 1:1 hexanes:ethyl acetate), the product diol **1.17** was isolated as a colorless oil in 38% yield (8.1 mg) and 54:46 d.r (*anti:syn*). ***anti*-diastereomer: ^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.28-7.32 (m, 4H), 6.60

(d, 1H, *J* = 15.0 Hz), 6.24 (dd, 1H, *J* = 16.2, 7.2 Hz), 4.25 (dd, 1H, *J* = 7.2, 1.2 Hz), 3.97 (m, 1H), 1.19 (d, 1H, *J* = 6.6 Hz); ***syn*-diastereomer: ^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.28-7.32 (m, 4H), 6.64 (d, 1H, *J* = 13.8 Hz), 6.17 (dd, 1H, J = 16.2, 7.2 Hz), 4.03 (t, 1H, *J* = 6.6 Hz), 3.75 (quint, 1H, *J* = 6.0 Hz), 1.23 (d, 1H, *J* = 7.8 Hz); **mixture of *syn*- and *anti*-diastereomers: ^{13}C NMR** (151 MHz, $CDCl_3$): δ 135.04, 134.98, 133.74, 133.69, 131.86, 131.66, 129.15, 128.93, 128.92, 127.89, 77.67, 76.47, 71.02, 70.42, 19.25, 17.88; **IR** (ν/cm^{-1}): 3384 (OH, br, s), 2973 (m), 2927 (m), 2870 (m), 1491 (m), 1472 (w), 1457 (w), 1405 (w), 1374 (w), 1135 (w), 1091 (m), 1012 (m), 969 (m), 853 (w), 824 (w); **HRMS**-(ESI^{+}) $[M+Na]^{+}$ calcd for $C_{11}H_{13}ClNaO_2^{+}$ 235.0502, found: 235.0496. Enantiomeric purity was determined by HPLC analysis compared to the authentic racemic material. Absolute stereochemistry was inferred from the stereochemistry obtained for compounds **1.20** and **1.23**. *Diacel CHIRALPAK IA Column; 90:10 hexanes:EtOAc; 1.00 mL/min; 22 °C, 254 nm. Syn*-diastereomers: (2*S*,3*S*)-enantiomer: 67.6 min.; (2*R*,3*R*)-enantiomer: 71.3 min.: 94:6 e.r.; *anti*-diastereomers: (2*R,*3*S*)-enantiomer: 89.8 min.; (2*S,*3*R*)-enantiomer: 103.6 min.; 97:3 e.r.



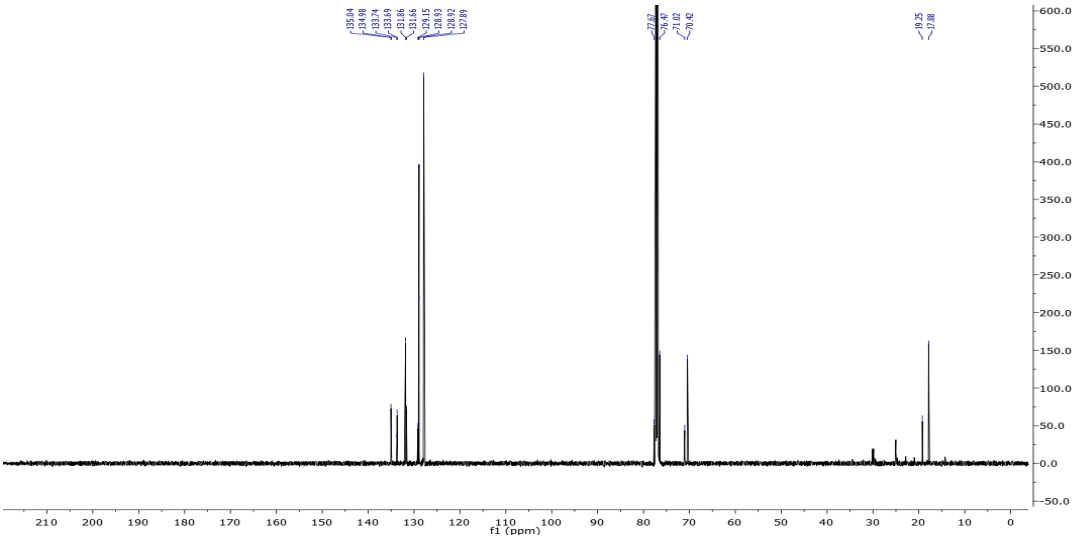
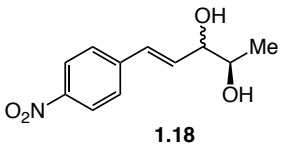


Figure 1.14. ^{1}H and ^{13}C{^{1}H} NMR spectra of 1.17.



1.18

(2*R*,*E*)-5-(4-nitrophenyl)pent-4-ene-2,3-diol (1.18). Following Procedure C, the crude oxidation mixture was purified by silica gel chromatography (1:1 pentane:ethyl acetate), the product diol **1.18** was isolated as a viscous orange oil in 46% yield (10.2 mg) and 55:45 d.r (*syn:anti*). ***syn*-diastereomer: ^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.19 (d, 2H, *J* = 8.4 Hz), 7.52 (d, 2H, *J* = 8.4 Hz), 6.78 (d, 1H, *J* = 16.8 Hz), 6.40 (dd, 1H, *J* = 16.2, 6.0 Hz), 4.11 (t, 1H, *J* = 6.6 Hz), 3.79 (quint, 1H, *J* = 6.6 Hz), 1.27 (d, 1H, *J* = 6.0 Hz); ***anti*-diastereomer: ^{1}H NMR** (600 MHz, $CDCl_3$): 8.19 (d, 2H, *J* = 8.4 Hz), 7.53 (d, 2H, *J* = 8.4 Hz), 6.75 (d, 1H, *J* = 16.2 Hz), 6.46 (dd, 1H, *J* = 15.6, 6.0 Hz), 4.33 (m, 1H), 4.02 (m, 1H), 1.21 (d, 1H, *J* = 6.0 Hz); **mixture of *syn*- and *anti*-diastereomers: ^{13}C NMR** (151 MHz, $CDCl_3$): δ 147.23, 147.20, 143.06, 142.99, 133.52, 132.34, 130.48, 130.36, 127.22, 127.20, 124.17, 75.99, 70.91, 70.41, 19.39, 17.89; **IR** (ν/cm^{-1}): 3392 (OH, br, s), 2976 (w), 2926 (w), 2855 (w), 1596 (m), 1515 (m), 1345 (m), 1110 (w), 1076 (w), 1027 (w), 975 (w), 913 (w),

849 (w), 747 (w); **HRMS**-(ESI$^+$) $[M+Na]^+$ calcd for $C_{11}H_{13}NNaO_4^+$ 246.0742, found: 246.0738. Enantiomeric purity was determined by SFC analysis compared to the authentic racemic material. Absolute stereochemistry was inferred from the stereochemistry obtained for compounds **1.20** and **1.23**. *Regis RegisPack (RP, cat# 783104) column; 93:7 CO_2:MeOH; 1.00 mL/min; 40 °C, 210 nm (SFC). Syn*-diastereomers: (2*S*,3*S*)-enantiomer: 66.7 min.; (2*R*,3*R*)-enantiomer: 81.5 min.: 95:5 e.r.; *anti*-diastereomers: (2*R*,3*S*)-enantiomer: 81.5 min.; (2*S*,3*R*)-enantiomer: 99.7 min.: 95:5 e.r.

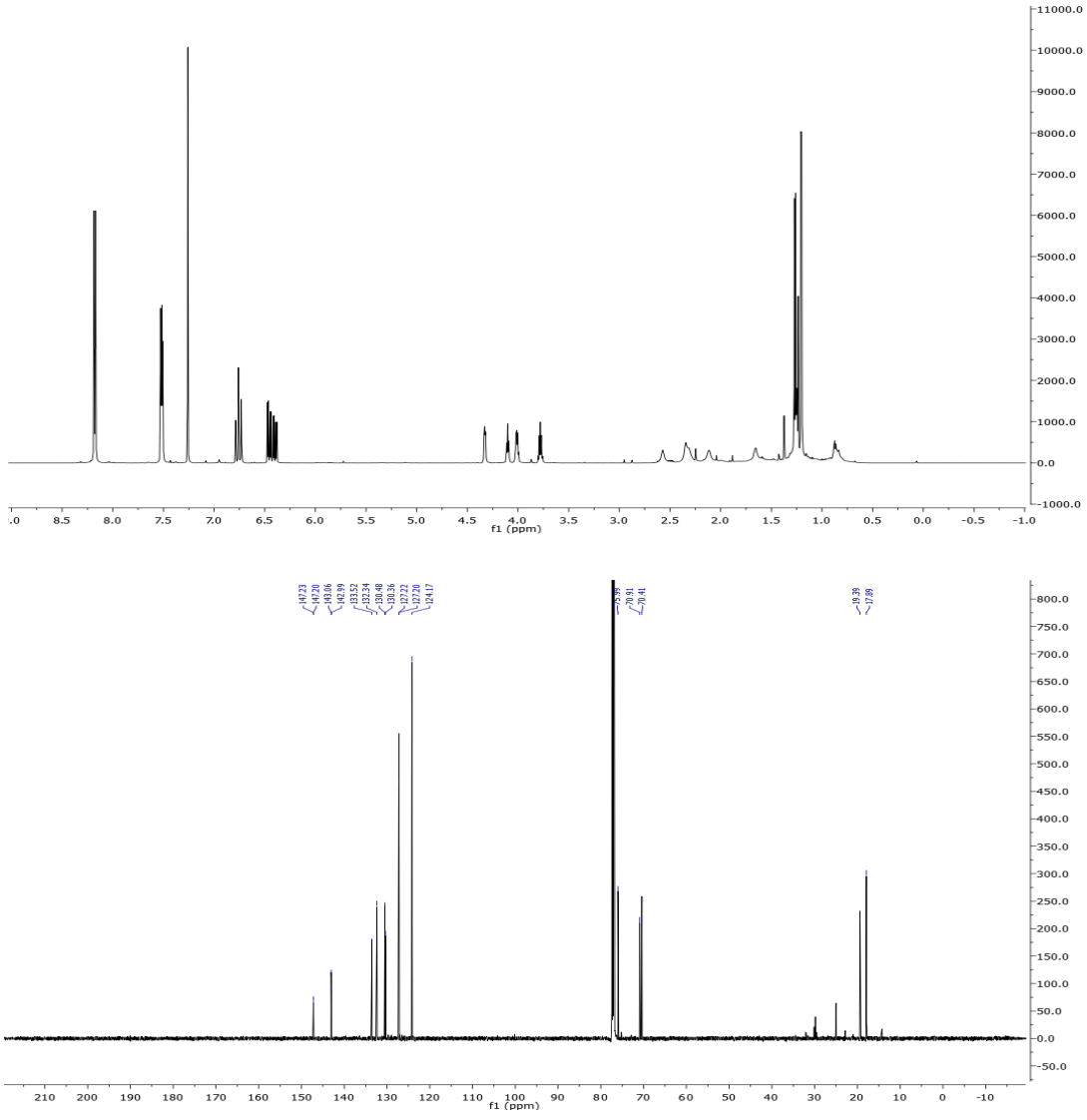
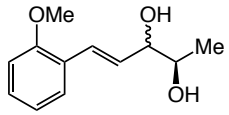
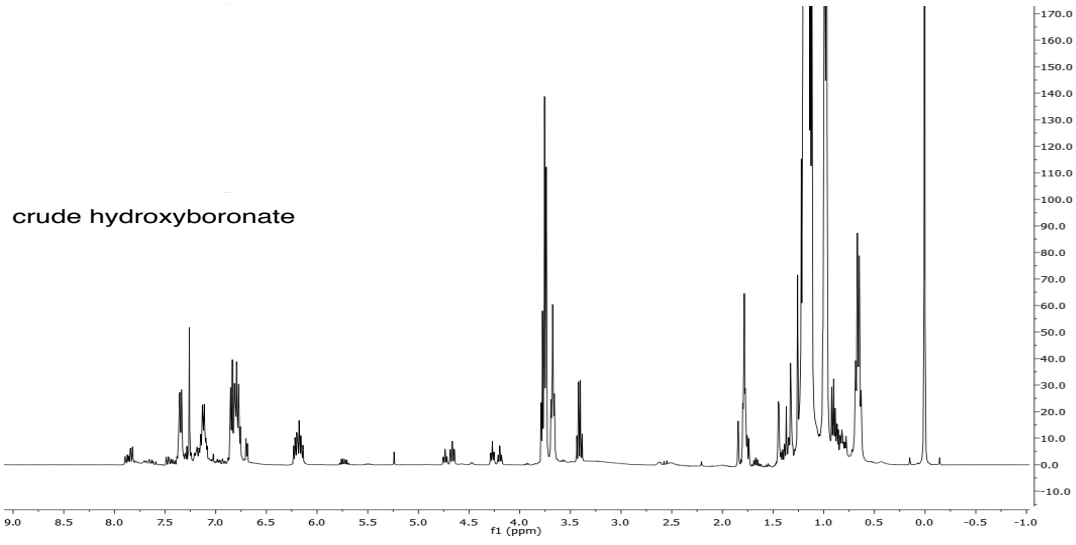


Figure 1.15. ^{1}H and ^{13}C{^{1}H} NMR spectra of 1.18.



1.19

(2*R*,*E*)-5-(2-methoxyphenyl)pent-4-ene-2,3-diol (1.19). Following Procedure C, the crude oxidation mixture was purified by silica gel chromatography (1:1 pentane:ethyl acetate), the product diol **1.19** was isolated as an unstable pale yellow oil inseparable from pinacol in maximum 75% yield (15.7 mg) and 55:45 d.r (*syn:anti*). A ^{1}H NMR spectrum of the crude hydroxyboronate product and ^{1}H and ^{13}C NMR spectra of the unstable (impure) diol **1.19** are provided, in addition to IR and HRMS data. The product is not sufficiently stable to obtain a complete set of clean characterization data, nor was it possible to assay the enantiomeric purity of the products via HPLC. **IR** (ν/cm^{-1}): 3418 (OH, br, s), 2979 (s), 2939 (m), 2838 (w), 1598 (w), 1490 (m), 1466 (m), 1439 (m), 1370 (m), 1245 (m), 1156 (m), 1112 (m), 1030 (m), 975 (w), 951 (m), 884 (w), 829 (w), 751 (w), 671 (w); **HRMS**-(ESI^{+}) [M+Na]$^{+}$ calcd for $C_{12}H_{16}NaO_3^{+}$ 231.0997, found: 231.0991.



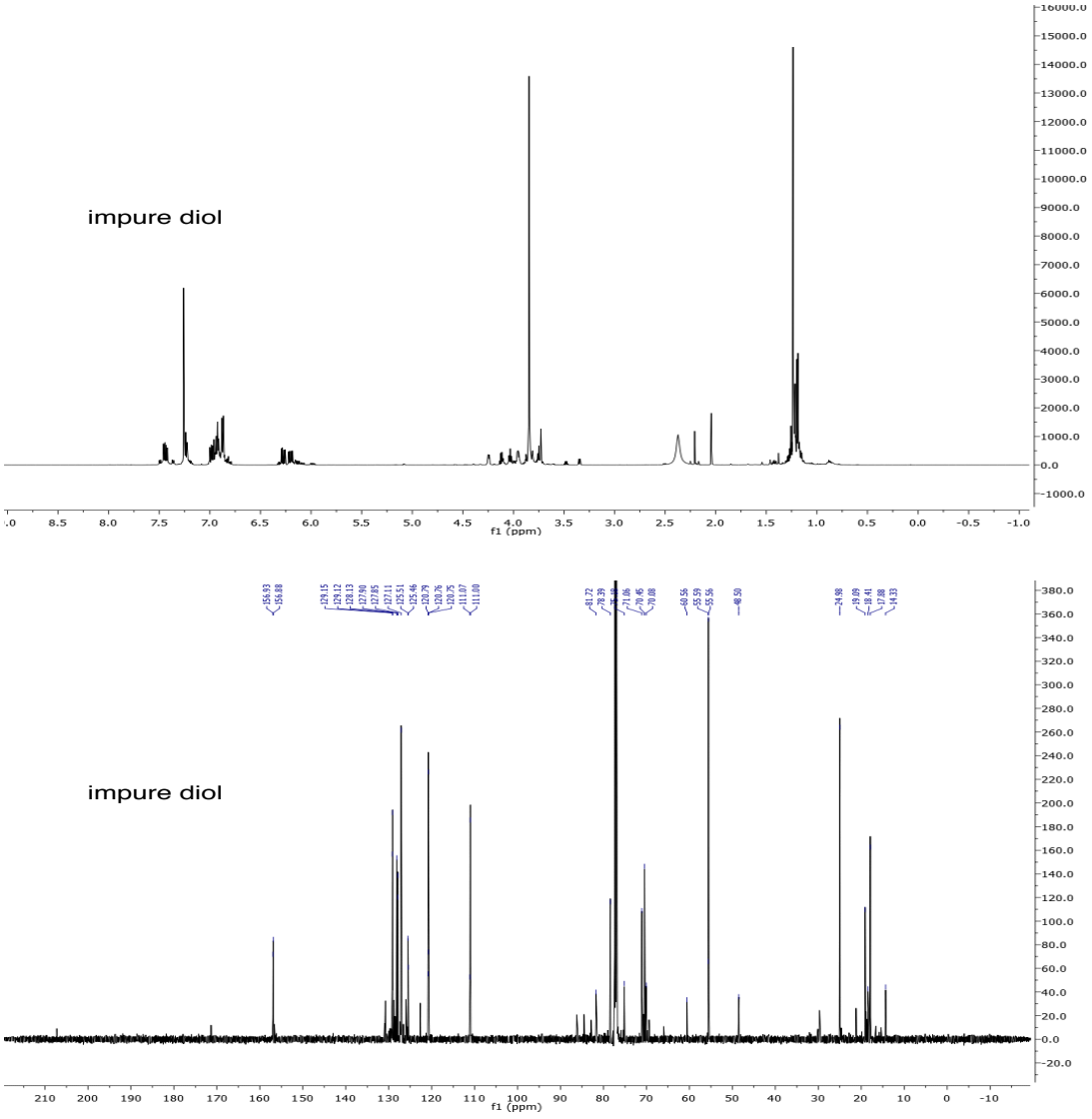
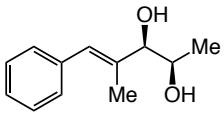


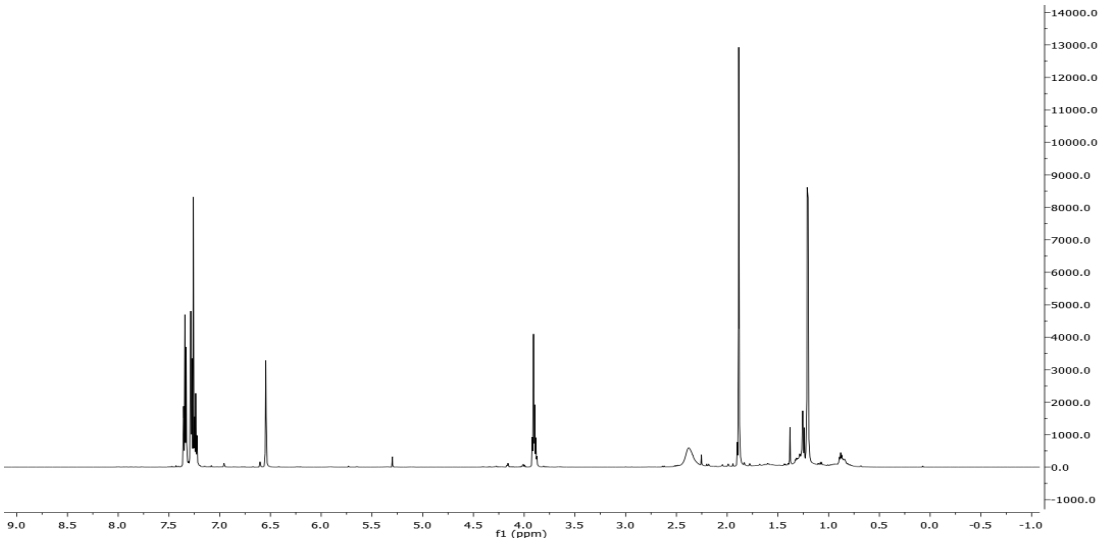
Figure 1.16. ^{1}H of crude hydroxyboronate and ^{1}H and ^{13}C{^{1}H} NMR spectra of diol 1.19.



1.20

(*2R,3R,E*)-4-methyl-5-phenylpent-4-ene-2,3-diol (1.20). Following Procedure B, the crude oxidation mixture was purified by silica gel chromatography (2:1 to 1:1 hexanes:ethyl acetate), the product diol **1.20** was isolated as a colorless oil in 54% yield (10.4 mg) and 97:3 d.r (*syn:anti*). ***syn*-diastereomer: ^{1}H NMR** ($CDCl_3$, 600 MHz): δ 7.34 (t, 2H,

J = 7.2), 7.28 (d, 2H, *J* = 7.8), 7.23 (t, 1H, *J* = 7.2), 6.54 (s, 1H), 3.87-3.91 (m, 2H), 1.88 (d, 3H, *J* = 1.2), 1.20 (d, 3H, *J* = 6.0); **^{13}C NMR** ($CDCl_3$, 151 MHz): δ 137.35, 137.21, 129.12, 128.57, 128.31, 126.87, 83.20, 69.22, 19.23, 13.82; **IR** (ν/cm^{-1}): 3385 (OH, br, s), 3024 (w), 2970 (m), 2925 (m), 2862 (m), 1457 (m), 1374 (w), 1273 (w), 1127 (m), 1072 (w), 1040 (m), 1012 (m), 918 (w), 885 (w), 865 (w), 751 (m), 699 (m), 592 (w), 506 (m); **HRMS**-(ESI$^+$) $[M+Na]^+$ calcd for $C_{12}H_{16}NaO_2^+$ 215.1048, found: 215.1043; **$[\alpha]_D^{19}$** = +50.2° (*c* = 0.485, CH_2Cl_2, *l* = 100 mm), Lit.: $[\alpha]_D^{25}$ = +69.8° (*c* = 1.2, EtOH),[26] Lit.: $[\alpha]_D^{20}$ = +76° (*c* = 1.0, EtOH).[27] Enantiomeric purity was determined by HPLC analysis compared to the authentic racemic material. Absolute stereochemistry was determined by comparison of the $[\alpha]_D$ value to those previously reported. *Diacel CHIRALPAK IC Column; 90:10 hexanes:EtOAc; 1.00 mL/min; 22 °C, 254 nm. Syn*-diastereomers: (2*S*,3*S*)-enantiomer: 20.4 min.; (2*R*,3*R*)-enantiomer: 22.6 min.: 90:10 e.r.



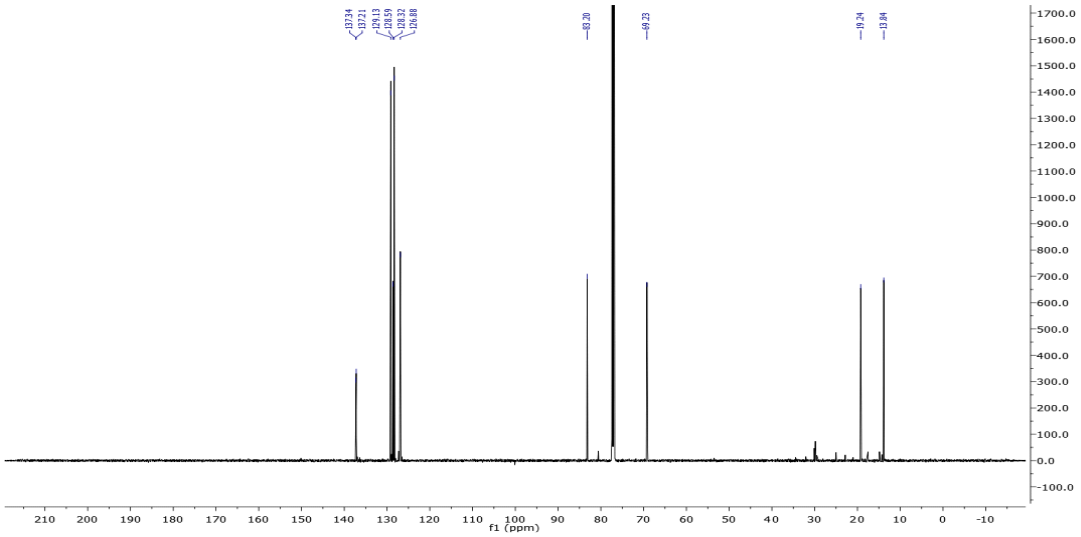
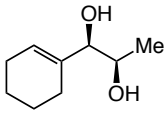


Figure 1.17. ^{1}H and ^{13}C{^{1}H} NMR spectra of 1.20.



1.21

(*1R*,2R)-1-(cyclohex-1-en-1-yl)propane-1,2-diol (1.21). Following Procedure B, the crude oxidation mixture was purified by silica gel chromatography (2:1 to 1:1 hexanes:ethyl acetate), the product diol **1.21** was isolated as a colorless oil in 34% yield (5.3 mg) and 96:4 d.r (*syn:anti*). ***syn*-diastereomer: ^{1}H NMR** (600 MHz, $CDCl_3$): δ 5.72 (m, 1H), 3.77 (quint, 1H, J = 6.6 Hz), 3.67 (d, 1H, J = 7.2 Hz), 2.10-2.14 (m, 2H), 2.03 (m, 2H), 1.49-1.69 (m, 4H), 1.12 (d, 3H, J = 6.6 Hz); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 137.33, 126.09, 81.78, 69.08, 25.19, 24.26, 22.71, 22.65, 19.07; **IR** (ν/cm^{-1}): 3384 (OH, br, s), 2964 (w), 2927 (m), 2857 (w), 2836 (w), 1507 (w), 1489 (w), 1457 (w), 1437 (w), 1372 (w), 1240 (w), 1126 (w), 1064 (w), 1020 (m), 918 (w), 838 (w), 816 (w), 777 (w), 696 (w), 506 (w); **HRMS**-(ESI^{+}) $[M+Na]^{+}$ calcd for $C_9H_{16}NaO_2^{+}$ 179.1048, found: 179.1044; **$[\alpha]_D^{20}$** = +2.7° (c = 0.245, CH_2Cl_2, l = 100 mm). Enantiomeric purity was determined by HPLC analysis compared to the authentic racemic material. Absolute stereochemistry was inferred from the

stereochemistry obtained for compound **1.20** and **1.23**. *Diacel CHIRALPAK IC Column; 99:1 hexanes:iPrOH; 0.75 mL/min; 22 °C, 190 nm. Syn*-diastereomers: (1*R*,2*R*)-enantiomer: 75.5 min.; (1*S*,2*S*)-enantiomer: 81.1 min.: 83:17 e.r.

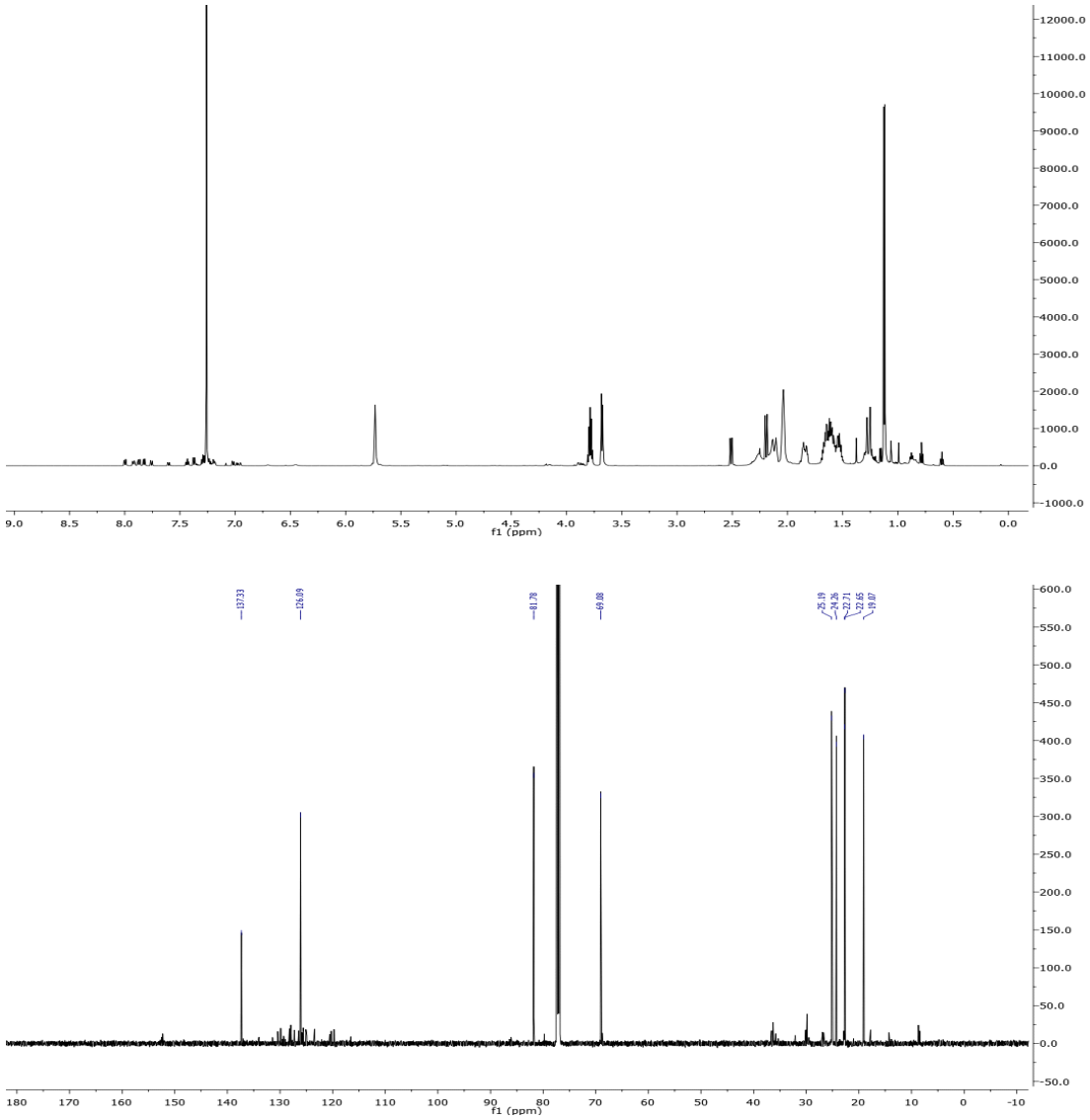
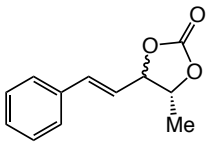


Figure 1.18. ^{1}H and ^{13}C{^{1}H} NMR spectra of 1.21.

1.8.4 Control of C–B stereogenic center



1.22

(4*R*)-4-methyl-5-((*E*)-styryl)-1,3-dioxolan-2-one (1.22). Diol **1.16** ((2R,*E*)-5-phenylpent-4-ene-2,3-diol) was transformed to the title cyclic carbonate **1.22** according to a modified literature procedure.[21] A flame-dried 20-mL scintillation vial equipped with a magnetic stir bar was flushed with N_2 and charged with diol **1.16** (44.7 mg, 0.251 mmol) and 1.9 mL of anhydrous THF. Carbonyldiimidazole (61.0 mg, 0.376 mmol) was added to the stirring solution and the headspace was purged with N_2. The solution was allowed to stir for 5 h, during which time it was monitored by TLC (2:1 hexanes:ethyl acetate, UV visualization). Water was added to quench the reaction when the diol was observed to be consumed. The crude reaction mixture was purified by silica gel column chromatography (2:1 hexanes:ethyl acetate) and the 52:48 d.r. mixture of carbonate diastereomers **1.22** was isolated as a viscous oil in 60% yield (30.7 mg). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.40-7.43 (m, 4H), 7.35-7.38 (m, 4H), 7.32-7.34 (m, 2H), 6.78 (d, 2H, *J* = 16.2 Hz), 6.16 (m, 2H), 5.28 (t, 1H, *J* = 5.3 Hz), 4.95 (quintt, 1H, *J* = 7.2 Hz), 4.77 (t, 1H, *J* = 7.8 Hz), 4.53 (m, 1H), 1.53 (d, 3H, *J* = 6 Hz), 1.40 (d, 3H, *J* = 6.6 Hz); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 154.53, 154.39, 137.11, 136.86, 135.15, 134.93, 129.29, 129.15, 128.98, 128.98, 127.12, 127.06, 121.84, 119.79, 84.73, 80.67, 78.76, 76.58, 18.19, 15.90; **IR** (ν/cm^{-1}): 2979 (w), 2953 (w), 2919 (m), 2851 (w), 1798 (CO, s), 1450 (w), 1351 (w), 1186 (m), 1070 (m), 1020 (m), 971 (w), 776 (w), 753 (w), 693 (w), 536 (w); **HRMS**-(ESI$^+$) $[M+Na]^+$ calcd for $C_{12}H_{12}NaO_3^+$ 227.0684, found: 227.0679. The enantiomeric purity of the diol starting material (**1.16**) for the carbonate protection/defunctionalization sequence was independently determined by HPLC analysis: *Diacel CHIRALPAK IB Column; 98:2 hexanes:iPrOH; 0.75 mL/min; 22 °C, 210 nm. Syn*-diastereomers: (2*S*,3*S*)-enantiomer: 90.4 min.; (2*R*,3*R*)-enantiomer: 118.9 min.:

90:10 e.r.*; anti*-diastereomers: (*2R*,3*S*)-enantiomer: 94.9 min.; (2*S*,3*R*)-enantiomer: 147.5 min.: 97:3 e.r.

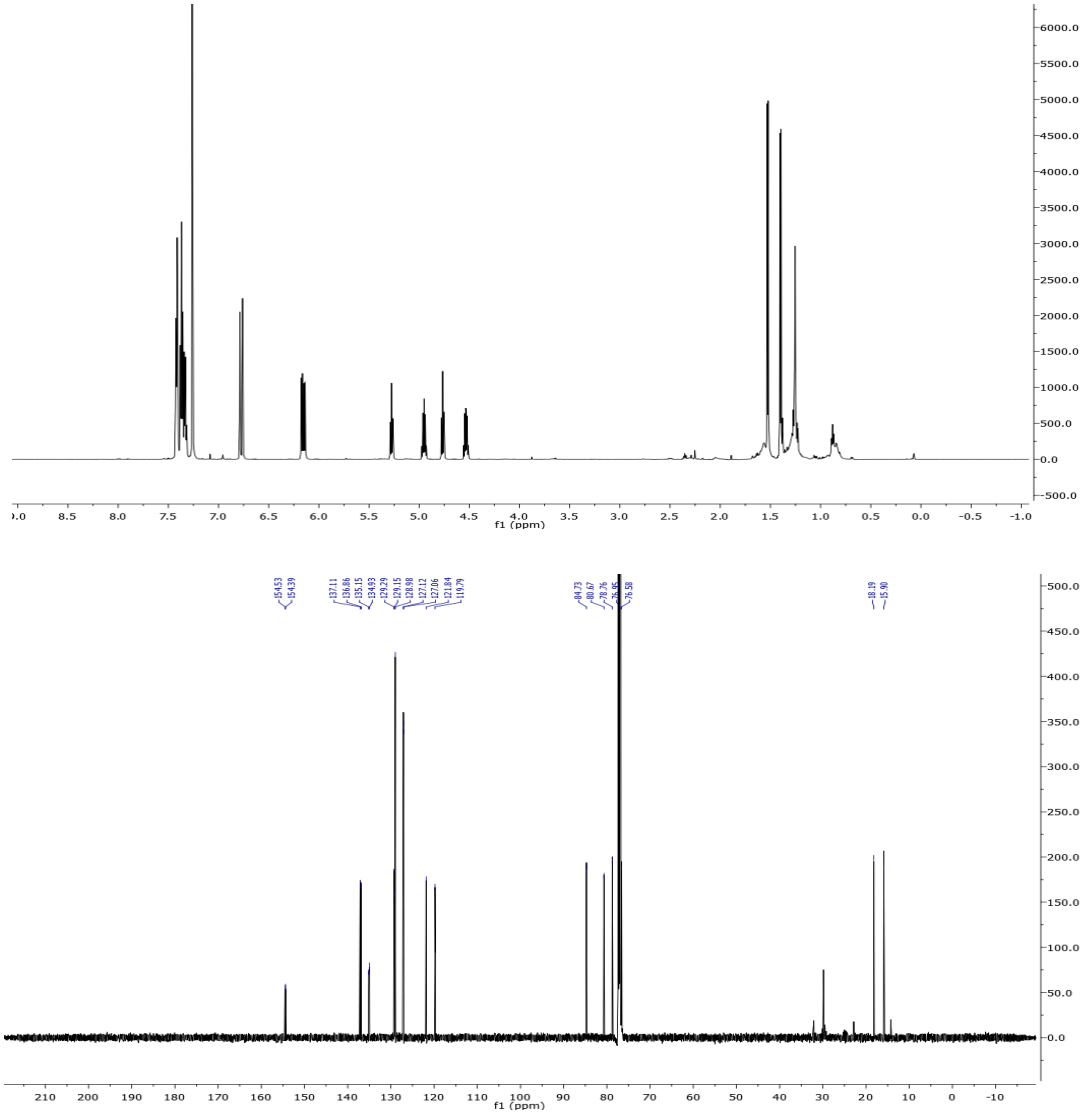
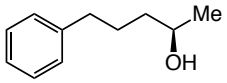


Figure 1.19. ^{1}H and ^{13}C{^{1}H} NMR spectra of 1.22.



1.23

(*R*)-5-phenylpentan-2-ol (1.23). Compound **1.22** was defunctionalized and then hydrogenated to the title alcohol **1.23** according to a modified literature procedure.[21] In an N_2-filled glove box, an 8-mL vial equipped with a magnetic stir bar and septum cap was

charged with carbonate (14.8 mg, 0.0725 mmol) and a 560 μL THF solution containing $Pd_2(dba)_3$ (0.67 mg, 0.000725 mmol) and PPh_3 (0.38 mg, 0.00145). The vial was removed from the glove box, cooled to 0 °C, and charged with Et_3N (50 μL, 0.363 mmol) and HCOOH (27 μL, 0.725 mmol). The reaction was monitored by TLC (2:1 hexanes/diethyl ether, UV visualization), and after 5 hours the solvent was removed by purging with a stream of H_2 gas. Pd/C (15 mg (5 wt %), 0.00725 mmol) was added to the vial, in addition to 1.0 mL of wet methanol. The septum cap was replaced and the headspace was purged with H_2 gas. The solution was allowed to vigorously stir at 22 °C for 1 h before being filtered through a plug of silica gel with ethyl acetate. The crude reaction mixture was purified by silica gel column chromatography (2:1 hexanes:diethyl ether) to yield the title compound as a clear, colorless oil in 50% yield (6.0 mg). The title compound was found to be identical to literature spectra.[28] HPLC analysis of compound **1.23** in comparison to a previously prepared racemic sample provided an enantiomeric ratio of 92:8 e.r., which can be compared to the average e.r. of the two diol diastereomers (52:48 (*syn:*anti); ***syn***: 90:10 e.r.*;* ***anti***: 97:3 e.r.) from which it was derived. The measured optical rotation $\mathbf{[\alpha]_D^{20}}$ = –7.4° (*c* = 0.455, CH_2Cl_2, *l* = 100 mm) matches the sign and approximate magnitude of the opposite enantiomer of that reported in the literature (lit.[28] $[\alpha]_D^{20}$ = +8.0° (*c* = 1.0, $CHCl_3$, 97% *ee,* (*S*)-isomer) and lit.[29] $[\alpha]_D^{27}$ = +8.47° (*c* = 3.0, $CHCl_3$, (*S*)-isomer)). Enantiomeric purity was determined by HPLC analysis compared to the authentic racemic material. Absolute stereochemistry was determined by comparison with the signs of the previously reported $[\alpha]_D$ values (above). *Diacel CHIRALPAK IC Column; 99:1 hexanes:iPrOH; 0.20 mL/min; 22 °C, 210 nm.* (*R*)-enantiomer: 118.3 min., (*S*)-enantiomer: 126.6 min.: 92:8 e.r.

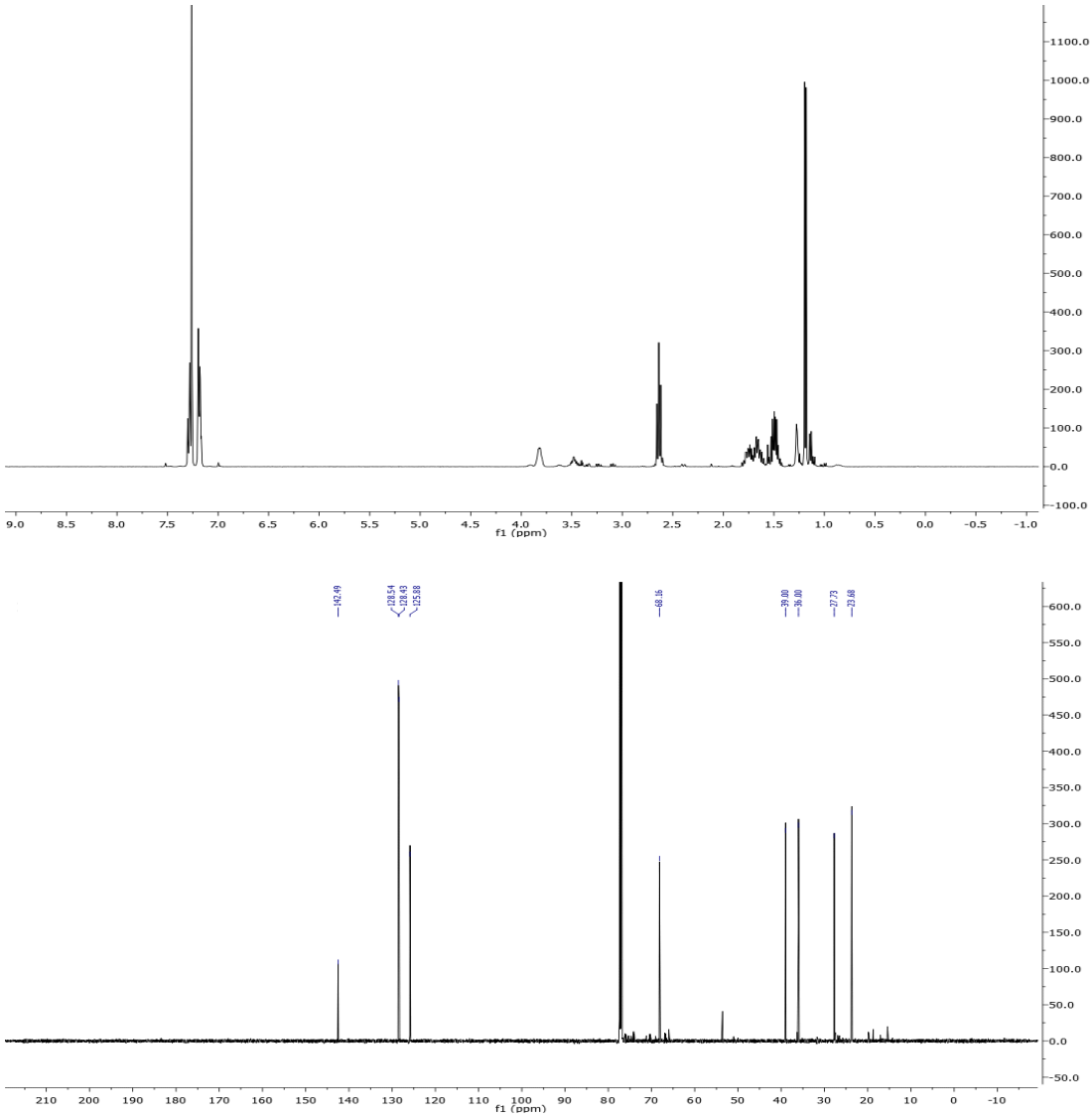
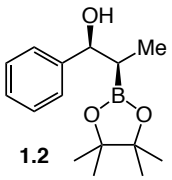


Figure 1.20. ^{1}H and ^{13}C{^{1}H} NMR spectra of 1.23.

1.8.5 Functionalizations of 1,2-hydroxyboronates

1.8.5.1 Boron homologation



1.2

(1*S*,2*R*)-1-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-ol (1.2). Following Procedure A, the product was obtained in 75% yield and 85:15 *syn:anti* d.r

(based on hexamethyldisiloxane as an internal standard). The crude residue was purified by silica gel column chromatography (20:1 hexanes:ethyl acetate to 2:1 hexanes:diethyl ether) and the title compound was isolated as a clear, colorless oil in 53% yield (140 mg) and 89:11 d.r. (*syn:anti*). ***syn*-diastereomer: ^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.30-7.36 (m, 5H), 4.60 (dd, 1H, *J* = 8.0, 4.8 Hz), 2.78 (d, 1H, *J* = 4.8 Hz), 1.54 (quint, 1H, *J* = 7.6 Hz), 1.24 (s, 12H), 0.88 (d, 3H, *J* = 7.2 Hz); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 144.46, 128.24, 127.34, 126.44, 83.53, 77.54, 24.84, 24.72, 12.47; **IR** (ν/cm^{-1}): 3481 (OH, br, s), 3085 (w), 3062 (w), 3030 (w), 2978 (s), 2932 (m), 2876 (m), 1494 (w), 1458 (m), 1381 (m), 1320 (m), 1275 (w), 1247 (w), 1215 (w), 1167 (w), 1145 (m), 1111 (w), 1073 (w), 1059 (w), 1009 (w), 966 (w), 910 (w), 863 (w), 844 (w), 764 (w), 701 (w), 675 (w); **HRMS**-(ESI$^+$) $[M+Na]^+$ calcd for $C_{15}H_{23}BNaO_3^+$ 285.1638, found: 285.1634; $[\alpha]_D^{21}$ = –10.6° (*c* = 7.00, CH_2Cl_2, *l* = 100 mm). The enantiomeric purity of the hydroxyboronate starting material (**1.2**) for the TBS-protection/homologation sequence was independently determined by HPLC analysis via oxidation of a small portion of hydroxyboronate **1.2** to diol **1.4** according to the general oxidation procedure. *Diacel CHIRALPAK IA Column; 99:1 hexanes:iPrOH; 1.00 mL/min; 22 °C, 210 nm. Syn*-diastereomers: (*S*,*S*)-enantiomer: 29.5 min.; (*R*,*R*)-enantiomer: 37.0 min.: ***93:7 e.r.***

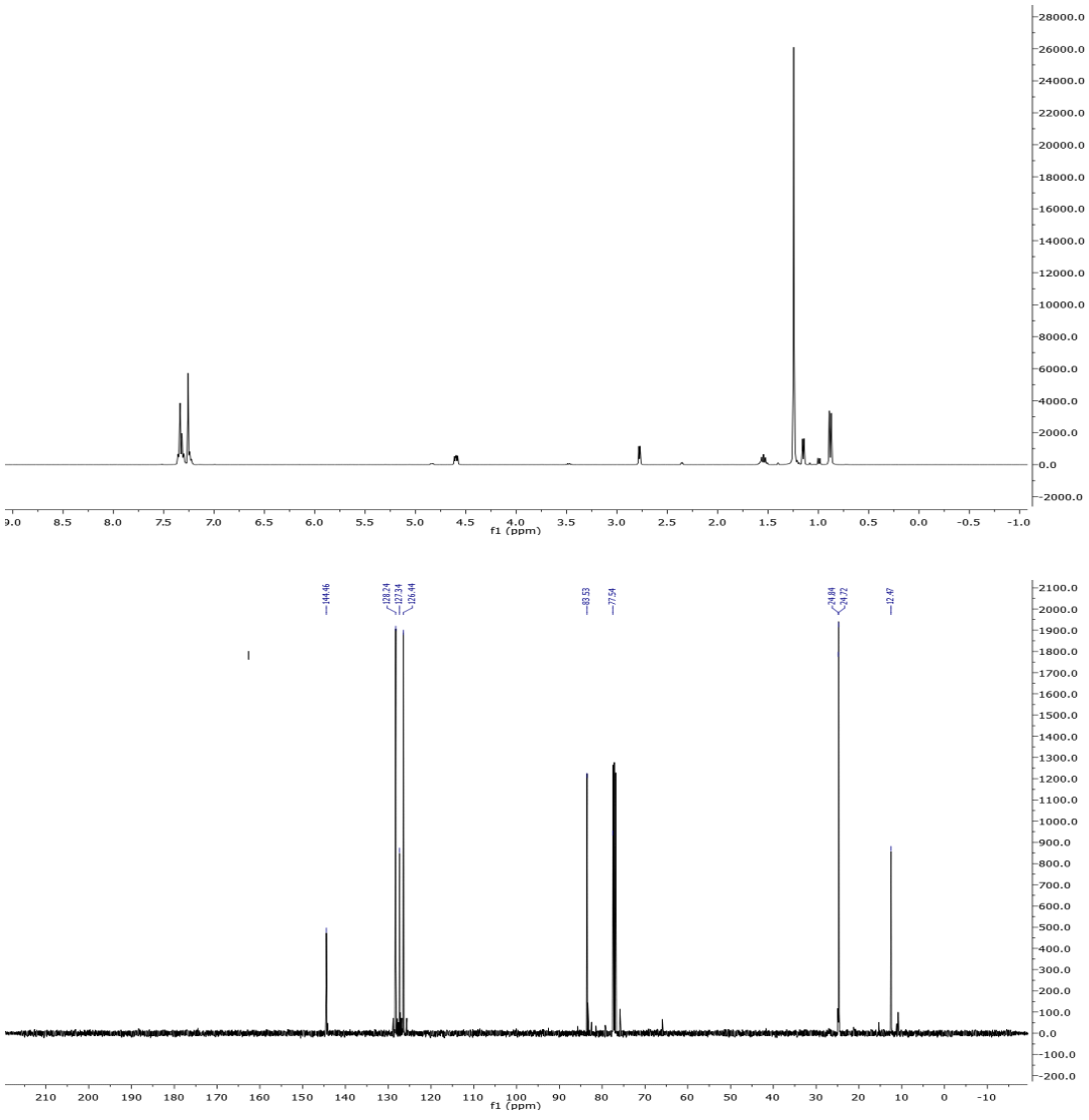
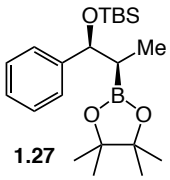


Figure 1.21. ^{1}H and ^{13}C{^{1}H} NMR spectra of 1.2.



1.27

***tert*-butyldimethyl((1*S*,2*R*)-1-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propoxy)silane (1.27).** The title benzylic *tert*-butyldimethylsilyl ether **1.27** was prepared from hydroxyboronate **1.2** according to a standard literature procedure.[30] A flame-dried 8-mL vial equipped with a magnetic stir bar was charged with hydroxyboronate **1.2** (65.5 mg,

0.250 mmol) and 2.0 mL of anhydrous DMF. Imidazole (34.0 mg, 0.500 mmol) was added, followed by tert-butyldimethylsilyl chloride (56.5 mg, 0.375 mmol). The vial was capped with a screw-cap septum and purged with N_2 for 5 minutes before being allowed to stir at 22 °C for 24 h (TLC monitoring; 2:1 hexanes:diethyl ether, $R_f = 0.7$, UV and Seebach stain). The reaction was quenched with 1.0 mL of a saturated aqueous solution of NH_4Cl, and the aqueous layer was extracted three times with ethyl acetate. The combined organic layers were then washed twice with saturated aqueous $NaHCO_3$, followed by two washes with saturated aqueous NaCl. The resulting organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (25:1 pentane:diethyl ether) and **1.27** was isolated as a colorless oil in 76% yield (71.8 mg) and 89:11 d.r. (*syn:anti*). ***syn*-diastereomer: ^{1}H NMR** ($CDCl_3$, 600 MHz): δ 7.30 (dd, 2H, *J* = 7.8, 1.2 Hz), 7.26 (t, 2H, *J* = 7.2 Hz), 7.19 (tt, 1H, *J* = 7.2, 1.8 Hz), 4.71 (d, 1H, *J* = 7.8 Hz), 1.49 (quint, 1H, *J* = 7.8 Hz), 1.24 (d, 12H, *J* = 5.4 Hz), 0.86 (s, 9H), 0.75 (d, 3H, *J* = 7.2 Hz), 0.02 (s, 3H), –0.29 (s, 3H); **^{13}C NMR** ($CDCl_3$, 151 MHz): δ 145.21, 127.74, 127.01, 126.91, 83.06, 77.78, 26.07, 25.35, 24.81, 18.26, 11.68, –4.34, –4.64; **IR** (ν/cm^{-1}): 3086 (w), 3063 (w), 3030 (w), 2978 (m), 2957 (m), 2929 (m), 2886 (m), 2857 (m), 1493 (w), 1471 (w), 1462 (m), 1402 (w), 1380 (m), 1371 (m), 1319 (m), 1255 (m), 1211 (w), 1184 (w), 1166 (w), 1146 (m), 1110 (w), 1078 (w), 1060 (m), 1029 (w), 1006 (w), 967 (w), 861 (m), 836 (m), 816 (w), 775 (m), 754 (w), 701 (m), 670 (w), 588 (w), 533 (w), 510 (w). **HRMS**-(ESI$^+$) $[M+Na]^+$ calcd for $C_{21}H_{37}BNaO_3Si^+$ 399.2503, found: 399.2498; **$[\alpha]_D^{17}$** = –23.8° (*c* = 3.59, CH_2Cl_2, *l* = 100 mm).

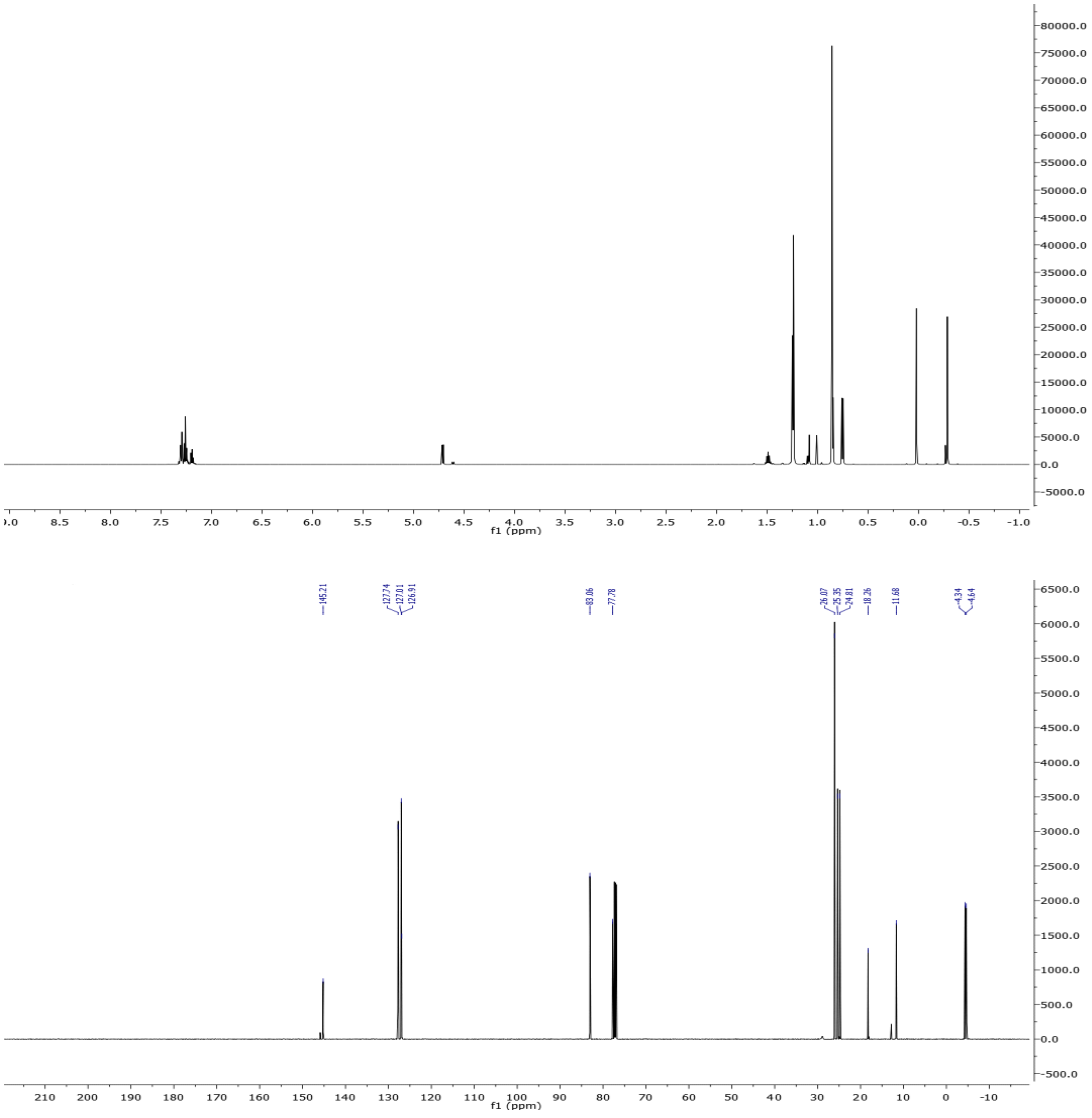
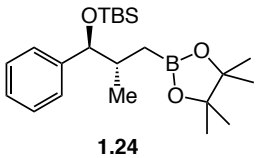


Figure 1.22. ^{1}H and ^{13}C{^{1}H} NMR spectra of 1.27.



1.24

***tert*-butyldimethyl((1*S*,2*S*)-2-methyl-1-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propoxy)silane (1.24).** Homologated pinacol boronic ester **1.24** was prepared from TBS-protected **1.27** according to a modified literature procedure.[31] To a stirred solution of TBS-protected **1.27** (35.0 mg, 0.0930 mmol) and dibromomethane (16 µL, 0.233

mmol) in anhydrous THF (0.93 mL) at –78 °C in a flame-dried 8-mL vial equipped with a magnetic stir bar, was added *n*-BuLi (1.6 M in hexanes, 0.205 mmol) dropwise. The resulting mixture was stirred for 10 min. at –78 °C and then warmed to 22 °C and allowed to stir for 2 h. The reaction was quenched with 1.0 mL of a saturated aqueous solution of NH_4Cl, and the aqueous layer was diluted with 1.0 mL of deionized water and extracted three times with diethyl ether. The resulting organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (25:1 pentane:diethyl ether; TLC in 4:1 hexanes:diethyl ether, $R_f = 0.65$, Seebach stain) and the title compound **1.24** was isolated as a colorless oil in 75% yield (27.3 mg) and 91:9 d.r. (*syn:anti*). ***syn*-diastereomer: ^{1}H NMR** ($CDCl_3$, 600 MHz): δ 7.24-7.27 (m, 4H), 7.18-7.21 (m, 1H), 4.39 (d, 1H, $J = 6.0$ Hz), 1.97 (m, 1H), 1.23 (d, 12H, $J = 3.0$ Hz), 1.03 (dd, 1H, $J =$ 15.6, 4.2 Hz), 0.87 (s, 9H), 0.80 (d, 3H, $J = 7.2$ Hz), 0.62 (dd, 1H, $J = 15.6$, 10.2 Hz), 0.01 (s, 3H), –0.24 (s, 3H); **^{13}C NMR** ($CDCl_3$, 151 MHz): δ 144.15, 127.63, 127.24, 126.78, 82.98, 80.32, 37.99, 26.05, 25.14, 24.83, 18.41, 18.36, –4.48, –4.87; **IR** (ν/cm^{-1}): 3087 (w), 3063 (w), 3028 (w), 2977 (m), 2957 (m), 2929 (m), 2888 (m), 2857 (m), 1493 (w), 1471 (w), 1463 (w), 1370 (m), 1318 (m), 1255 (m), 1214 (w), 1165 (w), 1146 (m), 1087 (m), 1063 (m), 1027 (w), 1006 (w), 970 (w), 941 (w), 913 (w), 860 (m), 837 (m), 775 (m), 746 (w), 702 (m), 671 (w), 629 (w), 577 (w), 548 (w), 502 (w). **HRMS**-(ESI$^+$) $[M+Na]^+$ calcd for $C_{22}H_{39}BNaO_3Si^+$ 413.2660, found: 413.2654; $[\alpha]_D^{22} = –24.2°$ ($c = 1.37$, CH_2Cl_2, $l = 100$ mm).

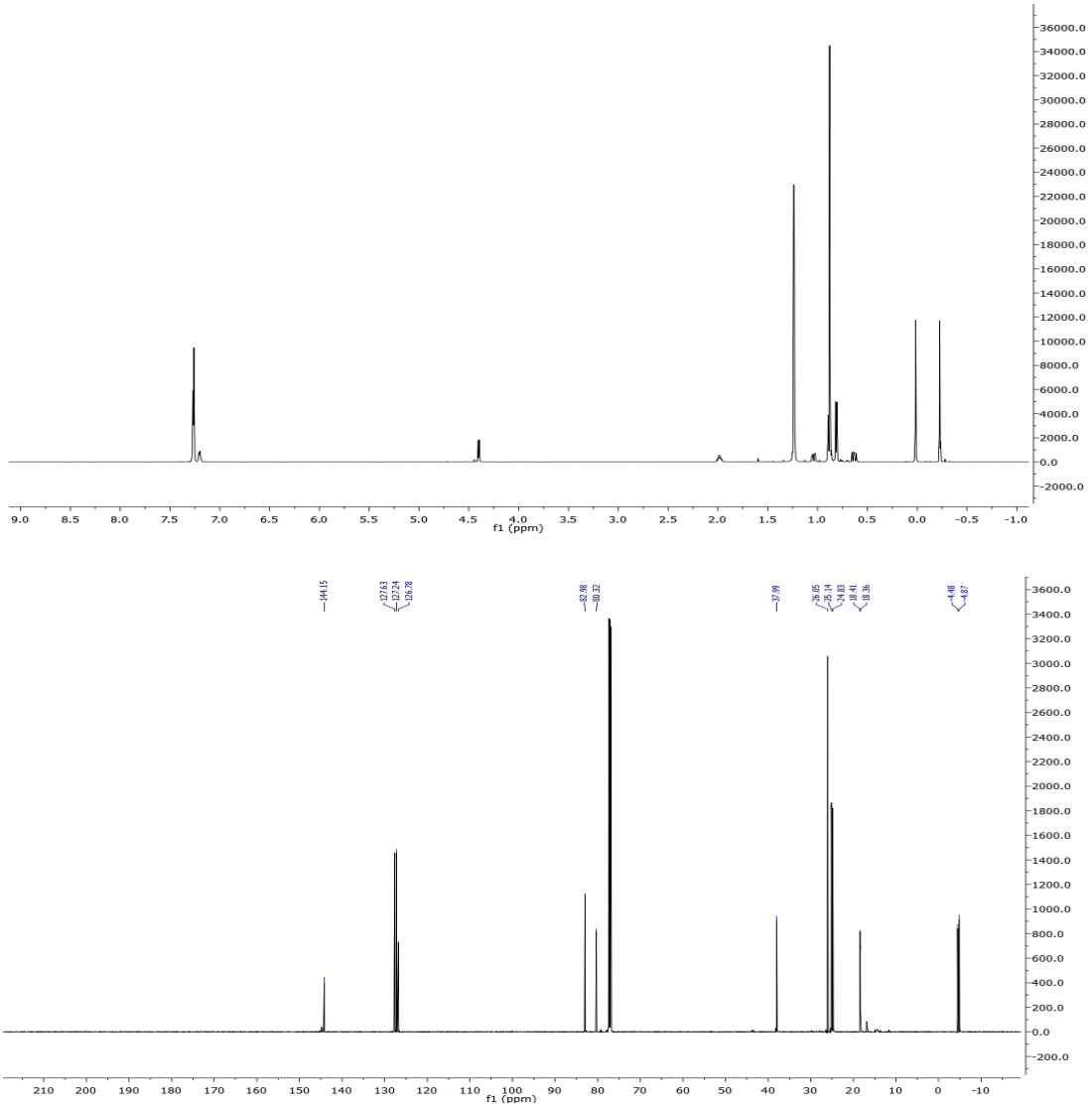
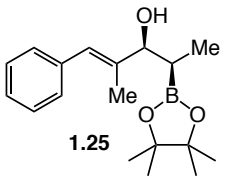


Figure 1.23. ^{1}H and ^{13}C{^{1}H} NMR spectra of 1.24.

1.8.5.2 Conversion to amine



1.25

(3*S*,4*R*,*E*)-2-methyl-1-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-1-en-3-ol (1.25). Following Procedure B, the title hydroxyboronate **1.25** was produced in 66% yield and 96:4 d.r. (*syn:anti*). The crude residue was purified by silica gel

column chromatography (20:1 hexanes:ethyl acetate to 2:1 hexanes:diethyl ether) and the title compound was isolated as a viscous, clear, yellow oil in 54% yield (115 mg) and 98:2 d.r. (*syn:anti*). ***syn*-diastereomer: ^{1}H NMR** ($CDCl_3$, 600 MHz): δ 7.35 (t, 2H, *J* = 7.2 Hz), 7.30 (d, 2H, *J* = 6.6 Hz), 7.23 (t, 1H, *J* = 7.2 Hz), 6.50 (s, 1H), 4.12 (dd, 1H, *J* = 9.0 Hz, 4.2 Hz), 2.61 (d, 1H, *J* = 4.2 Hz), 1.87 (d, 3H, *J* = 1.2 Hz), 1.51 (m, 1H, *J* = 7.8 Hz), 1.29 (d, 12H, *J* = 2.4 Hz), 0.98 (d, 3H, *J* = 7.8 Hz). **^{13}C NMR** ($CDCl_3$, 151 MHz): δ 139.72, 137.90, 129.16, 128.17, 126.68, 126.42, 83.60, 81.33, 24.96, 24.83, 12.88, 12.63; **IR** (ν/cm^{-1}): 3494 (OH, br, m), 2978 (m), 2930 (w), 2874 (w), 1491 (w), 1458 (m), 1381 (m), 1321 (m), 1274 (w), 1245 (w), 1215 (w), 1167 (w), 1145 (m), 1110 (w), 1056 (w), 998 (m), 966 (w), 917 (w), 845 (m), 751 (m), 700 (m), 669 (w), 516 (w), 504 (w); **HRMS**-(ESI$^+$) $[M+Na]^+$ calcd for $C_{18}H_{27}BNaO_3^+$ 325.1951, found: 325.1950; $[\alpha]_D^{19}$ = +20.9° (*c* = 4.23, CH_2Cl_2, *l* = 100 mm). The enantiomeric purity of the hydroxyboronate starting material (**1.25**) for the TBS-protection/amination sequence was independently determined by HPLC analysis via oxidation of a small portion of hydroxyboronate **1.25** to diol **1.20** according to the general oxidation procedure. *Diacel CHIRALPAK IC Column; 90:10 hexanes:EtOAc; 1.00 mL/min; 22 °C, 254 nm. Syn*-diastereomers: (*S*,*S*)-enantiomer: 20.3 min.; (*R*,*R*)-enantiomer: 22.4 min.: ***92:8 e.r.***

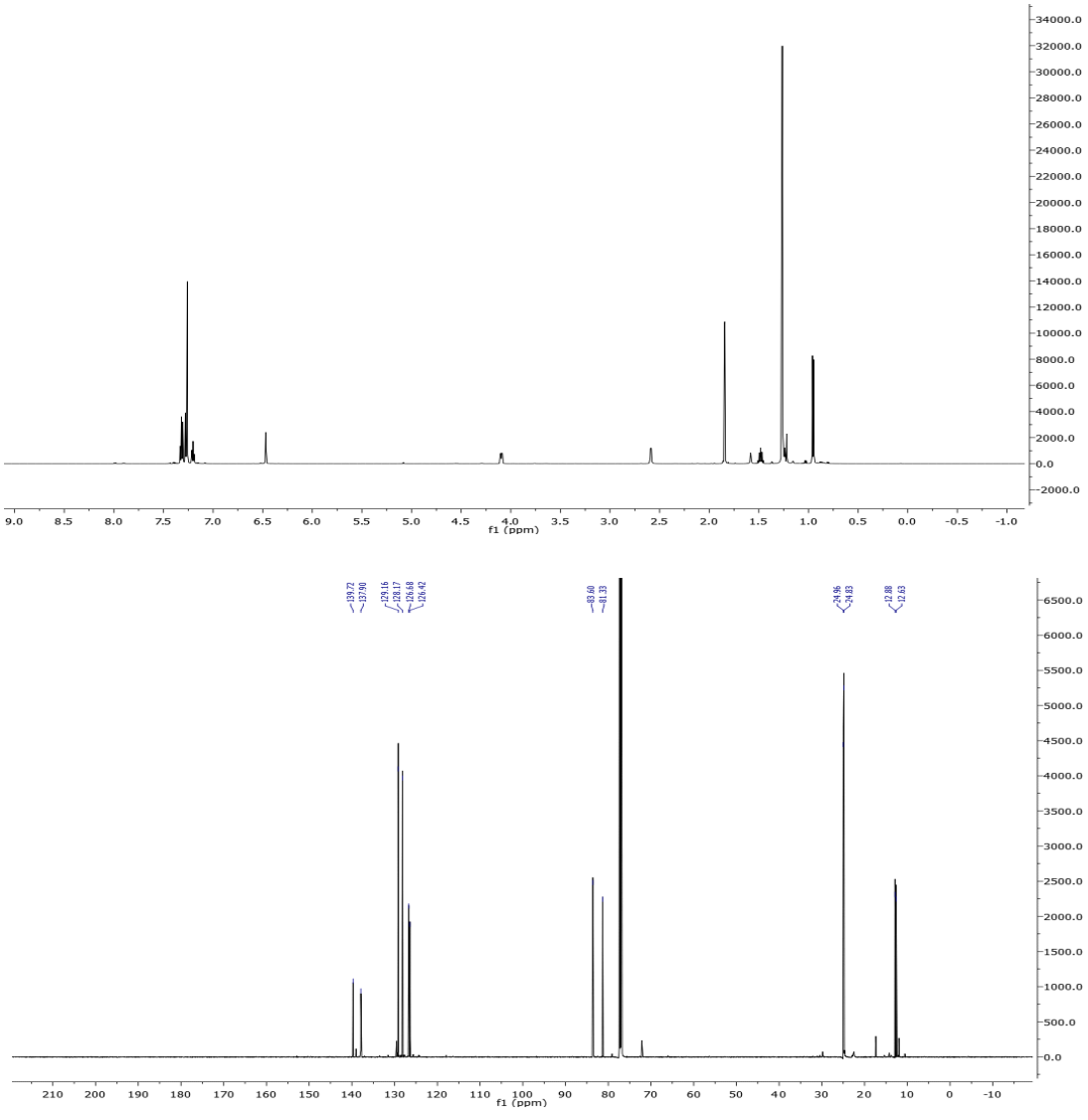
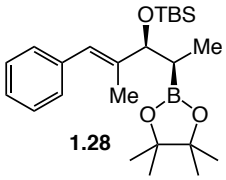


Figure 1.24. ^{1}H and ^{13}C{^{1}H} NMR spectra of 1.25.



1.28

***tert*-butyldimethyl(((3*S*,4*R*,*E*)-2-methyl-1-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-1-en-3-yl)oxy)silane (1.28).** The title allylic *tert*-butyldimethylsilyl ether **1.28** was prepared from hydroxyboronate **1.25** according to a literature procedure.[30] A flame-dried 8-mL vial equipped with a magnetic stir bar was charged with hydroxyboronate

1.25 (57.5 mg, 0.190 mmol) and 1.54 mL of anhydrous DMF. Imidazole (25.9 mg, 0.380 mmol) was added, followed by tert-butyldimethylsilyl chloride (43.0 mg, 0.285 mmol). The vial was capped with a screw-cap septum and purged with N_2 for 5 minutes before being allowed to stir at 22 °C for 20 h. The progress of the reaction was followed by TLC (2:1 hexanes:diethyl ether, $R_f = 0.75$, UV visualization). The reaction was quenched with 1.0 mL of a saturated aqueous solution of NH_4Cl, and the aqueous layer was extracted three times with ethyl acetate. The combined organic layers were then washed twice with saturated aqueous $NaHCO_3$, followed by two washes with saturated aqueous NaCl. The resulting organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (25:1 pentane:diethyl ether) and the title compound **1.28** was isolated as a colorless oil in 64% yield (50.6 mg) and as a single detectable diastereomer. ***syn*-diastereomer: ^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.33 (t, 2H, J = 7.6 Hz), 7.27 (d, 2H, J = 8.4 Hz), 7.21 (t, 1H, J = 7.2 Hz), 6.40 (s, 1H), 4.19 (d, 1H, J = 9.2 Hz), 1.80 (d, 3H, J = 1.2 Hz), 1.44 (quint, 1H, J = 8.4 Hz), 1.26 (d, 12H, J = 6.4 Hz), 0.91 (s, 9H), 0.85 (d, 3H, J = 7.6 Hz), 0.12 (s, 3H), 0.03 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 140.36, 138.20, 129.02, 128.18, 126.74, 126.27, 83.01, 81.99, 26.17, 25.41, 24.80, 18.36, 12.64, 12.52, –4.05, –4.65; **IR** (ν/cm^{-1}): 3082 (w), 3059 (w), 3025 (w), 2976 (m), 2955 (m), 2930 (m), 2889 (m), 2857 (m), 1462 (m), 1380 (m), 1320 (m), 1252 (m), 1146 (m), 1109 (w), 1058 (m), 1005 (m), 967 (w), 876 (m), 836 (m), 775 (m), 749 (w), 699 (m), 666 (w); **HRMS**-(ESI$^+$) $[M+Na]^+$ calcd for $C_{24}H_{41}BNaO_3Si^+$ 439.2816, found: 439.2811; **$[\alpha]_D^{19}$** = +16.2° (c = 2.53, CH_2Cl_2, l = 100 mm).

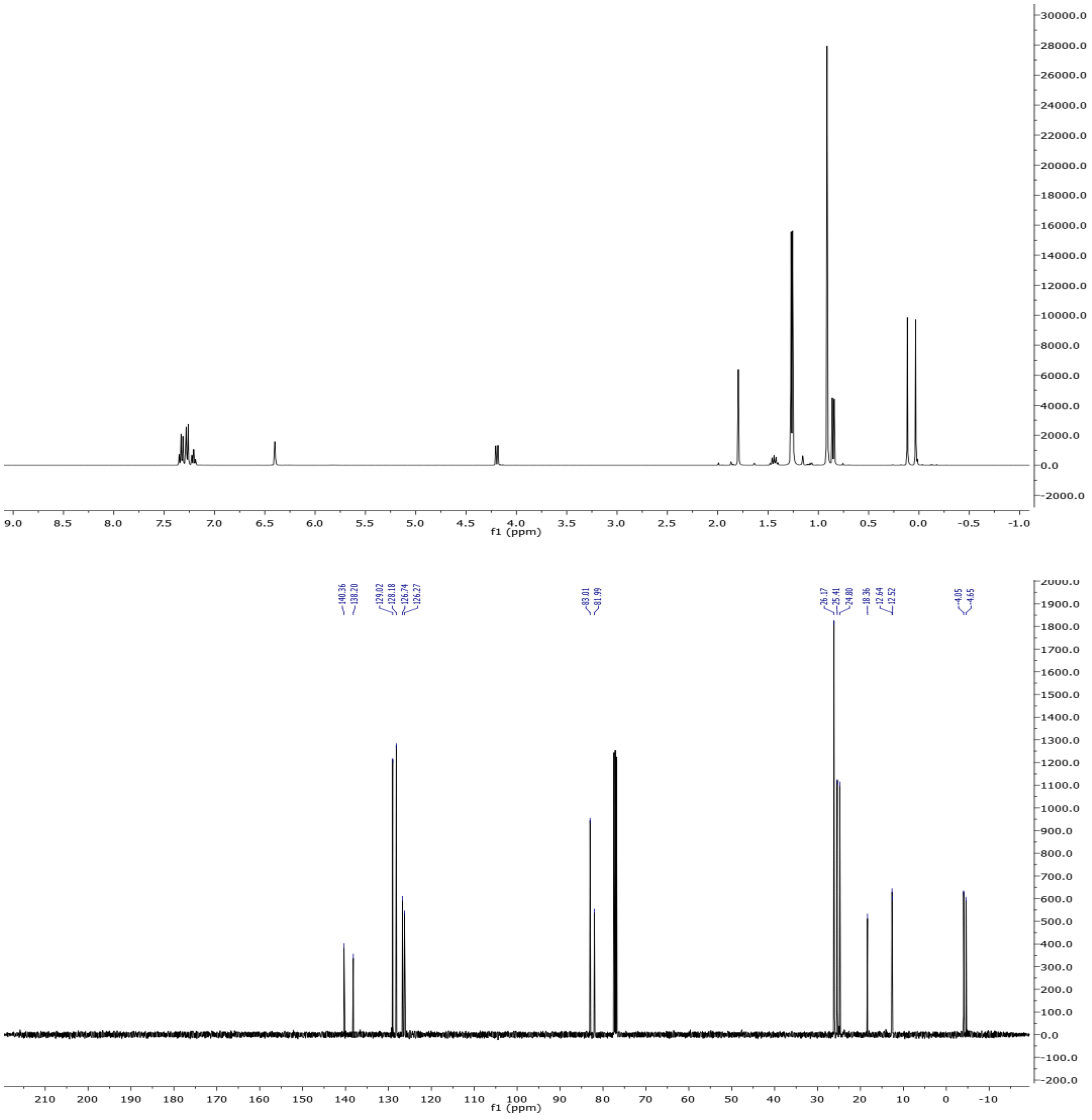
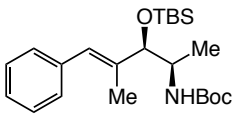


Figure 1.25. ^{1}H and ^{13}C{^{1}H} NMR spectra of 1.28.



1.26

***tert*-butyl((2*R*,3*R*,*E*)-3-((*tert*-butyldimethylsilyl)oxy)-4-methyl-5-phenylpent-4-en-2-yl)carbamate (1.26).** Carbamate **1.26** was prepared from compound **1.28** according to literature procedure.[3] A flame-dried 8-mL vial equipped with a magnetic stir bar was flushed with N_2 and charged with **1.28** (25.2 mg, 0.0605 mmol) and 500 μL of anhydrous THF. A

0.928 M solution of *O*-methylhydroxylamine (196 μL, 0.182 mmol) was added to a separate N_2-flushed, flame-dried 8-mL vial and then diluted with 418 μL of anhydrous THF. Both vials were cooled to –78 °C in a dry ice/acetone bath. A 1.59 M solution of *n*-butyllithium in hexanes (114 μL, 0.182 mmol) was added dropwise to the *O*-methylhydroxylamine solution and this was allowed to stir at –78 °C for 30 minutes. After this time, the *in* situ generated solution of lithium *O*-methylhydroxylamide was cannula transferred to the cooled solution of **1.28**. The resulting solution was allowed to warm to room temperature and was then heated to 60 °C with stirring for 20 h. After this time, the solution was allowed to cool to 22 °C and di-*tert*-butyl dicarbonate (44.5 μL, 0.194 mmol) was added via syringe. The solution was allowed to stir for 2 hours at 22 °C. The reaction was quenched with 3 mL of deionized water, and the aqueous layer was extracted four times with ethyl acetate. The combined organic layers were then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (10:1 pentane:diethyl ether), yielding both returned starting material (5.6 mg, 22%) and title carbamate **1.26**. The title compound was isolated as a colorless oil in 57% yield (14.0 mg). ***syn*-diastereomer: ^{1}H NMR** ($CDCl_3$, 600 MHz): δ 7.31 (t, 2H, *J* = 7.2 Hz), 7.24 (d, 2H, *J* = 7.8 Hz), 7.20 (t, 1H, *J* = 7.2 Hz), 6.49 (s, 1H), 4.65 (s, br, 1H), 3.97 (d, 1H, *J* = 3.0 Hz), 3.90 (s, br, 1H), 1.85 (d, 3H, *J* = 1.2 Hz), 1.37 (s, 9H), 1.19 (d, 3H, *J* = 6.6 Hz), 0.96 (s, 9H), 0.10 (s, 3H), 0.06 (s, 3H); **^{13}C NMR** ($CDCl_3$, 151 MHz): δ 155.81, 138.07, 137.90, 129.12, 128.13, 126.39, 126.13, 80.30, 79.01, 49.10, 28.56, 26.08, 19.54, 18.43, 15.32, –4.31, –4.96; **IR** (ν/cm^{-1}): 3449 (w), 3365 (br, w), 2972 (m), 2956 (m), 2930 (m), 2892 (w), 2885 (w), 2857 (m), 1716 (CO, s), 1496 (s), 1455 (m), 1390 (m), 1365 (m), 1253 (m), 1170 (s), 1106 (m), 1057 (m), 1007 (w), 942 (w), 865 (m), 837 (m), 776 (m), 751 (w), 699 (m), 512 (w). **HRMS**-(ESI$^+$)

$[M+Na]^+$ calcd for $C_{23}H_{39}NNaO_3Si^+$ 428.2597, found: 428.2594; $[\alpha]_D^{19}$ = –25.7° (*c* = 0.650, CH_2Cl_2, *l* = 100 mm).

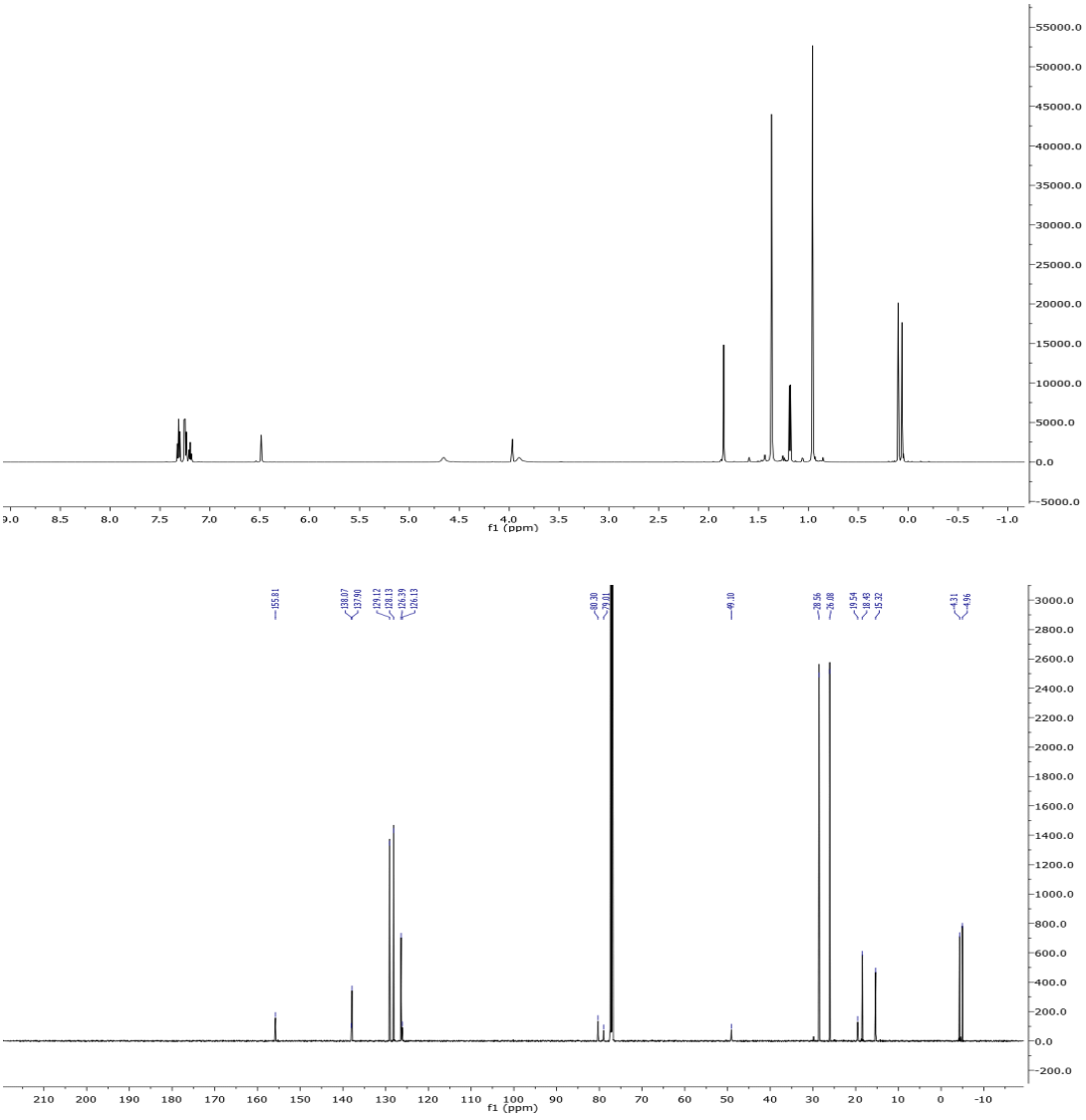


Figure 1.26. ^{1}H and ^{13}C{^{1}H} NMR spectra of 1.26.

2 Chapter 2: Silver(I)-Catalyzed Diastereoselective Synthesis of *anti*-1,2-Hydroxyboronates

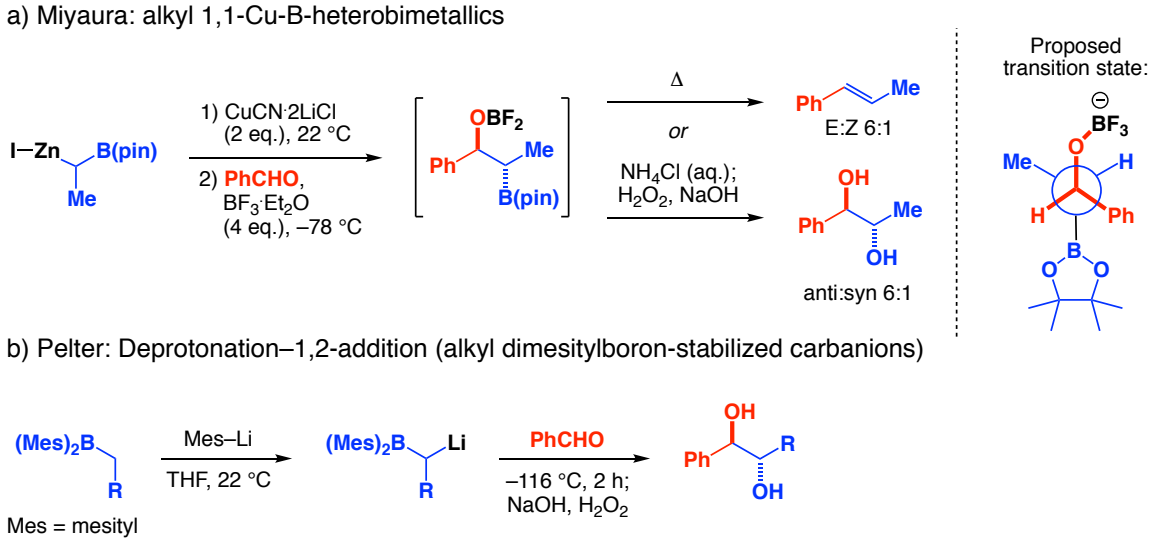
This chapter is adapted and reprinted with permission from Joannou, M. V.; Moyer, B. S.; Goldfogel, M. J.; Meek, S. J. *Angew. Chem. Int. Ed.* **2015**, *54*, 14141-14145. This chapter resulted from a collaboration with Dr. Matthew V. Joannou and Dr. Matthew J. Goldfogel.

2.1 Introduction

2.1.1 C–C bond-forming reactions of α-boryl anions / boron-stabilized alkyl nucleophiles

Functionalized secondary alkyl boronate esters are enabling reagents for chemical synthesis; thus, catalytic stereoselective methods for their preparation are a compelling objective (see section 1.1.1).[1] Carbon–carbon bond-forming reactions of boron-stabilized alkyl nucleophiles provide direct approaches to functionalized molecules containing C(sp^3)–B bonds. Specifically, alkylation of aldehydes with α-boryl nucleophiles serves to generate secondary alcohols bearing a vicinal alkyl boron unit.[32] Such processes form two contiguous stereogenic centers with a versatile C(sp^3)–B bond.[33,34] Despite progress in this area, several shortcomings preclude their synthetic utility, the most apparent of which are the lack of catalytic processes to afford products in high yield and stereoselectivity. Existing protocols for the stereoselective synthesis of 1,2-hydroxyboronates are achieved through organocuprates and deprotonations of bis(mesityl)-substituted alkyl boranes. Miyaura and co-workers reported one example of the stereoselective addition of Knochel's α-B(pin) cyanocuprate [B(pin) = (pinacolato)boron] to benzaldehyde to afford a 1,2-hydroxyboronate

in 6:1 d.r. (*anti/syn*), which can be stereospecifically converted to the boron-Wittig product upon heating (6:1 *trans/cis*) or the diol upon oxidation (6:1 *anti/syn*); the authors provide a steroechemical model to explain the selectivity (Scheme 2.1a).[32b] The drawback of this methodology resides in the necessity to employ both stoichiometric copper and superstoichiometric boron trifluoride diethyl etherate. Pelter *et al.* reported excellent levels of *anti*-selectivity for the addition of dimesityl-boron-stabilized carbanions to aldehydes (Scheme 2.1b). However, strong lithium bases and cryogenic conditions (–116 °C) are required for carbanion generation and reaction, thus limiting functional-group compatibility.[32c]



Scheme 2.1. Addition of α-boryl reagents to aldehydes.
a) Diastereoselective cuprate 1,2-addition. b) Deprotonation/1,2-addition of alkyl borons.

Bench-stable alkyl geminal diborons have emerged as useful difunctional reagents which provide effective methods to access α-boryl anion synthons. In the presence of an alkoxide or hydroxide activator, 1,1-diborons participate in alkylation and cross-coupling reactions. Morken and coworkers demonstrated that the corresponding borates decompose to α-boryl-stabilized carbanions, which undergo efficient and diastereoselective alkylation with

alkyl halides to generate substituted quaternary carbon atoms.[16,35] Catalytic reactions developed with difunctional alkyl organoboron reagents have focused on Suzuki cross-couplings.[17,36] Shibata and coworkers demonstrated that palladium-catalyzed cross-couplings of alkyl 1,1-diborons effectively proceed under ambient conditions to afford secondary alkyl boronates (see Scheme 1.4).[17a] More recently, the groups of Morken and Hall independently reported catalytic enantioselective variants for the stereoselective synthesis of secondary benzylic (see Scheme 1.5) and allylboronates.[18] Advances notwithstanding, catalytic diastereoselective protocols for the addition of 1,1-diborons to carbonyls remain limited. In Chapter 1, we discussed our report on the enantio- and diastereoselective copper(I)-catalyzed additions of substituted alkyl 1,1-diborons to aldehydes to afford 1,2-hydroxyboronates in high *syn*-selectivity. The reaction most likely proceeds *via* a chiral α-boron copper(I)–alkyl intermediate adding to the aldehyde, and simultaneously forming a new C–C bond and two vicinal stereogenic centers, one of which comprises a secondary alkyl boron unit for further synthetic elaboration.

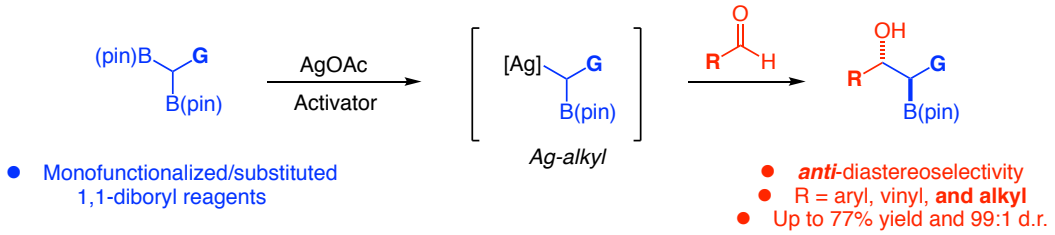
2.1.2 Research objectives

As a continuation of our laboratory's stated research objectives described in section 1.1.2, we sought to find a complementary protocol to our previously described Cu(I) manifold that is also broader in terms of reagent and substrate scope. We found that moving down the periodic table from Cu(I) to Ag(I) gave us a substantial increase in reactivity, as well as a reversal in diastereoselectivity that allowed us to produce complementary *anti*-1,2-hydroxyboronates with a variety of sterically voluminous, substituted 1,1-diboryl reagents. With further methodological tweaks, we were also able to adapt the Ag(I) system to work with enolizable alkyl aldehydes. Unfortunately, despite substantial efforts, no

enantioselective variant could be developed. Chapter 2 discusses our success in developing this complementary catalytic, diastereoselective protocol based on Ag(I).

2.2 Strategy for the synthesis of *anti*-1,2-hydroxyboronates

In Chapter 2, we outline the first catalytic protocol for the diastereoselective synthesis of *anti*-1,2-hydroxyboronates through the silver-catalyzed addition of 1,1-diboronates to aryl and alkyl aldehydes (Scheme 2.2). Reactions are promoted by 10 mol % of a readily available silver(I) salt catalyst in conjunction with an alkoxide or alkyl lithium activator. The products are delivered in up to 77% yield and 99:1 d.r. The reaction is also tolerant of several functional groups, including silyl-ether-protected alcohols, *N*-Boc-protected nitrogen atoms, esters, and acetal-protected aldehydes.



Scheme 2.2. Catalytic, *anti*-selective 1,2-addition of 1,1-diboronates to aldehydes.

2.3 Optimization of the catalytic reaction

Initial studies of catalytic reaction conditions identified silver(I) salts as effective promoters for the *anti*-selective addition of 1,1-diboryl reagents to aldehydes. The data illustrated in Table 2.1 summarize the optimization of the reaction conditions. As entry 1 shows, there is a significant nonselective background reaction with 130 mol % NaO*t*Bu at 22 °C and it affords **2.2** and **2.3** in 50:50 d.r. (63% conversion), and <2% conversion is observed at 0 °C (entry 2).[x] Catalytic AgOAc (10 mol%) was found to promote the addition

[x]Catalytic NaO*t*Bu does not promote the addition of **2.1** to benzaldehyde.

at 0 °C, but with no diastereoselectivity (entry 3). Monodentate (PPh_3; entry 4), and bidentate (*rac*-binap; entry 5) phosphines were evaluated for their ability to deliver **2.2** in high diastereoselectivity and yield, and *rac*-binap affords **2.2** in 42% conversion and 84:16 d.r. (*anti/syn*; entry 5). Decreasing the temperature to –25 °C results in lower conversions to **2.2**, but increases the *anti*-selectivity (92:8 d.r.; entry 6). Application of KO*t*Bu in place of NaO*t*Bu leads to an improved yield at –25 °C with no significant loss in d.r. value.[xi] Monodentate aryl (entry 8) and alkyl (entry 9) phosphines in the presence of KO*t*Bu were found to deliver **2.2** with a conversion and selectivity that are similar to those obtained with *rac*-binap. Optimal reaction conditions for the catalytic diastereoselective addition of **2.1** to benzaldehyde are those run in the absence of a phosphine ligand; this silver catalyzed reaction provides the same *anti* selectivity as that observed by the groups of Miyaura[32b] and Pelter[32c] in the 1,2-addition reactions of cyanocuprates, and therefore most likely proceeds *via* their proposed (non-ligated/phosphine-free) synclinal stereochemical model (Scheme 2.1) involving an α-boryl alkyl silver species.[xii] Treatment of benzaldehyde and **2.1** with 10 mol % AgOAc with KO*t*Bu in THF (–25 °C) delivers **2.2** in 84% yield (NMR analysis) and 97:3 d.r. (entry 10). No reaction is observed in the absence of a silver(I) salt (entry 11).[xiii]

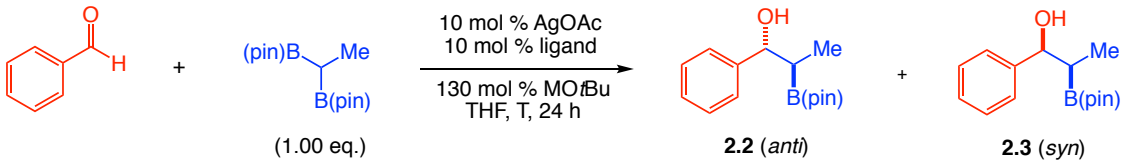
[xi]Preliminary enantioselective results have been obtained with chiral phosphine/Ag(I) complexes employing the optimal reaction conditions in Table 1: (a) 10 mol % AgOAc, 10 mol % (*R*)-Monophos, –25 °C; 61% conv., 90:10 d.r., 61:39 e.r.; (b) 10 mol % AgOAc, 10 mol % (*R*)-(+)-1-[(*R*)-2-(2'-dicyclohexylphosphinophenyl)ferrocenyl]ethyldi(bis-3,5-trifluoromethylphenyl)phosphine, –40 °C; 11% conv., 95:5 d.r., 77.5:22.5 e.r.

[xii]The role of silver(I) as a Lewis acid activator for the aldehyde cannot be completely ruled out. Monitoring a mixture of AgOAc (or the more soluble [(binap)AgOAc]) and benzaldehyde at 22 °C by ^{1}H and ^{13}C NMR spectroscopy shows no change in the chemical shift for the aldehyde signals. This indicates that there is unlikely to be a significant interaction between the silver(I) salt and the aldehyde at –25 °C.

[xiii]Use of silver(I) salts with more dissociating counter ions [*e.g.*, AgOTf, $AgBF_4$, $AgSbF_6$, $AgClO_4$, Ag(TFA)] afford <10% conversion.

Increasing the catalyst loading or reaction times result in only slight increases (<5%) in yield.[xiv]

Table 2.1. Optimization of reaction conditions for the synthesis of the *anti*-1,2-hydroxyboronate 2.2.[a]



Entry	Silver salt	Ligand	MO*t*Bu	T (°C)	NMR conv. (%)[b]	d.r. (**2.2**/**2.3**)[b]
1	—	—	NaO*t*Bu	22	63	50:50
2	—	—	NaO*t*Bu	0	<2	—
3	AgOAc	—	NaO*t*Bu	0	18	50:50
4[c]	AgOAc	PPh_3	NaO*t*Bu	0	47	54:46
5	AgOAc	*rac-binap*	NaO*t*Bu	0	42	84:16
6	AgOAc	*rac-binap*	NaO*t*Bu	–25	33	92:8
7[d]	AgOAc	*rac-binap*	KO*t*Bu	–25	50	93:7
8[c]	AgOAc	PPh_3	KO*t*Bu	–25	47	95:5
9	AgOAc	PCy_3	KO*t*Bu	–25	64	93:7
10	***AgOAc***	***—***	***KOtBu***	***–25***	***84***	***97:3***
11	—	—	KO*t*Bu	–25	<2	—

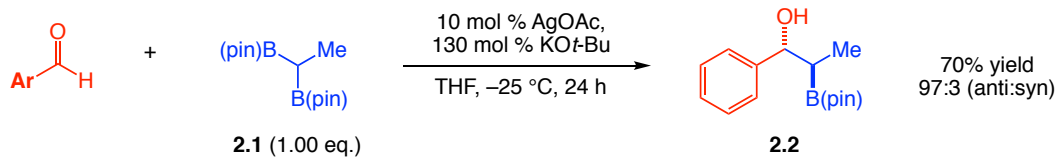
[a]Reactions performed under N_2 atm. [b]Conversion and diastereomeric ratio (d.r.) determined by analysis of either 400 MHz or 600 MHz ^{1}H NMR spectra of unpurified reaction mixtures using an internal standard. [c]20 mol % PPh_3. [d]Use of (*R*)-binap delivers **2.2** in 0% ee. The reaction conditions of entry 10 represent the optimized reaction conditions. binap = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl.

2.4 Ag(I)-catalyzed *anti*-1,2-additions of diboryl ethane to aryl and vinyl aldehydes

We next evaluated the scope of the silver(I)-catalyzed protocol for the addition of **2.1** to aryl- and alkenyl-substituted aldehydes (Scheme 2.3), and several points are noteworthy: 1) *para*-substituted aryl aldehydes bearing either halogens (**2.4** and **2.5**) or electron-donating methoxy (**2.6**) groups undergo diastereoselective additions to yield hydroxyboronates in good yield (64-73%) and high selectivity (up to 97:3 *anti/syn*). 2) Substitution at the *meta* and

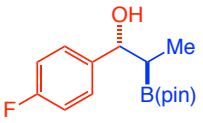
[xiv]Further optimization demonstrates that increasing the number of equivalents of KO*t*Bu or the boron reagent results in lower conversion and decreased *anti/syn* selectivity. For example, 200 mol % KO*t*Bu or 2.0 equivalents **2.1** affords **2.2**/**2.3** in 13% conv. in 86:14 d.r., and 48% conv. in 85:15 d.r., respectively.

ortho positions of the aryl aldehyde are tolerated, as demonstrated by the formation of **2.7-2.10** in 52-75% yield and 97:3 d.r. (*anti/syn*). 3) Synthesis of furyl-, pyridyl-, and Boc-indole-substituted products (**2.11-2.13**) demonstrate that heteroaryl aldehydes are effective substrates with no apparent inhibition. The expected 1,2-hydroxyboronates were isolated in 45-77% yield and 91:9-99:1 d.r.[xv] 4) Transformations with sterically unhindered alkenyl aldehydes proceed with diminished selectivity, thus producing the allylic alcohols **2.14** and **2.15** in 88:12 and 86:14 d.r., respectively. However, α-methylcinnamaldehyde-derived **2.16** was obtained in 64% yield and 92:8 d.r. With respect to the diastereoselectivity that accompanies diboryl ethane additions to cinnamyl aldehydes, these findings are generally congruent with (but still much higher than) the lower levels of diastereoselectivity obtained by emplying the Cu(I)-phosphoramidite protocol (see section 1.5).

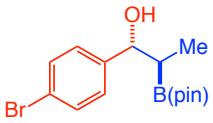


2.1 (1.00 eq.) **2.2**

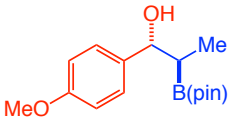
[xv]The lower yield of the pyridyl alcohol is attributed to slight decomposition during purification.



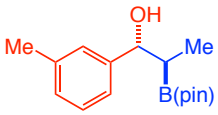
2.4
65% yield
97:3 d.r. (anti:syn)



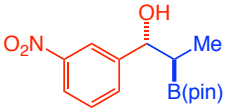
2.5
64% yield
97:3 d.r. (anti:syn)



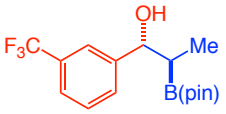
2.6
73% yield
96:4 d.r. (anti:syn)



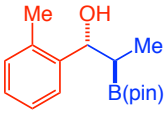
2.7
75% yield
97:3 d.r. (anti:syn)



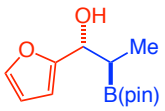
2.8[a]
53% yield
97:3 d.r. (anti:syn)



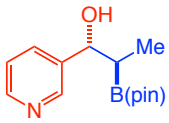
2.9
52% yield
97:3 d.r. (anti:syn)



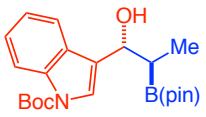
2.10
69% yield
99:1 d.r. (anti:syn)



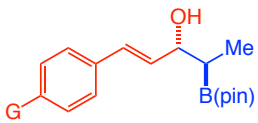
2.11
71% yield,
91:9 d.r. (anti:syn)



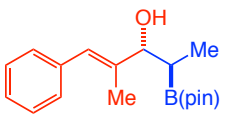
2.12
45% yield,
96:4 d.r. (anti:syn)



2.13
77% yield,
99:1 d.r. (anti:syn)



2.14; G=H, 65% yield, 88:12 d.r.
2.15; G=Cl, 40% yield, 86:14 d.r.
(anti:syn)



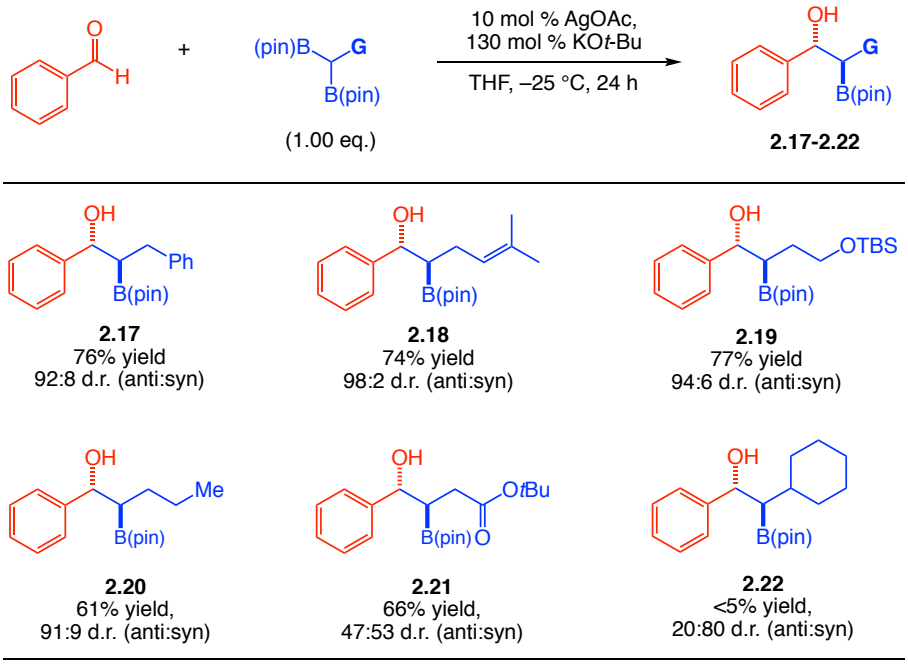
2.16
64% yield,
92:8 d.r. (anti:syn)

Yields of the purified products are an average of two runs. Diastereomeric ratio (d.r.) determined by analysis of either 400 MHz or 600 MHz ^{1}H NMR spectra of the unpurified reaction mixtures using hexamethyldisiloxane as an internal standard. [a]Yield determined by ^{1}H NMR spectroscopy.

Scheme 2.3. *Anti*-selective Ag(I)-catalyzed 1,2-addition of diboryl ethane to aryl and vinyl aldehydes.

2.5 Beyond diboryl ethane: Employing *substituted* 1,1-diboronates in the *anti*-selective 1,2-hydroxyboronate synthesis

Catalytic *anti*-selective 1,2-additions were extended to include substituted alkyl 1,1-diboron compounds (see **2.17-2.22**; Scheme 2.4). The transformations proceed effectively with 10 mol% AgOAc in up to 77% yield at –25 °C in 24 hours. The expected 1,2-hydroxyboronates, including those that contain functional groups such as a phenyl ring (**2.17**), an alkene (**2.18**), a silyl ether (**2.19**), an *n*-alkyl chain (**2.20**), or an ester (**2.21**), were obtained in up to 77% yield and greater than 98:2 d.r. (*anti/syn*) selectivity. Only in the case of a *tert*-butyl-ester-containing reagent was low diastereoselectivity observed; **2.21** was isolated in 66% yield and 47:53 d.r. (*anti/syn*). One shortcoming of the method relates to the use of β-branched 1,1-diboryl alkanes, and as an example, the cyclohexyl **2.22** is formed in less than 5% yield.



Yields of the purified products are an average of two runs. Diastereomeric ratio (d.r.) determined by analysis of either 400 MHz or 600 MHz ^{1}H NMR spectra of the unpurified reaction mixtures using hexamethyldisiloxane as an internal standard. G = attached group.

Scheme 2.4. Scope with respect to substituted 1,1-diboronates in the *anti*-selective 1,2-hydroxyboronate synthesis.

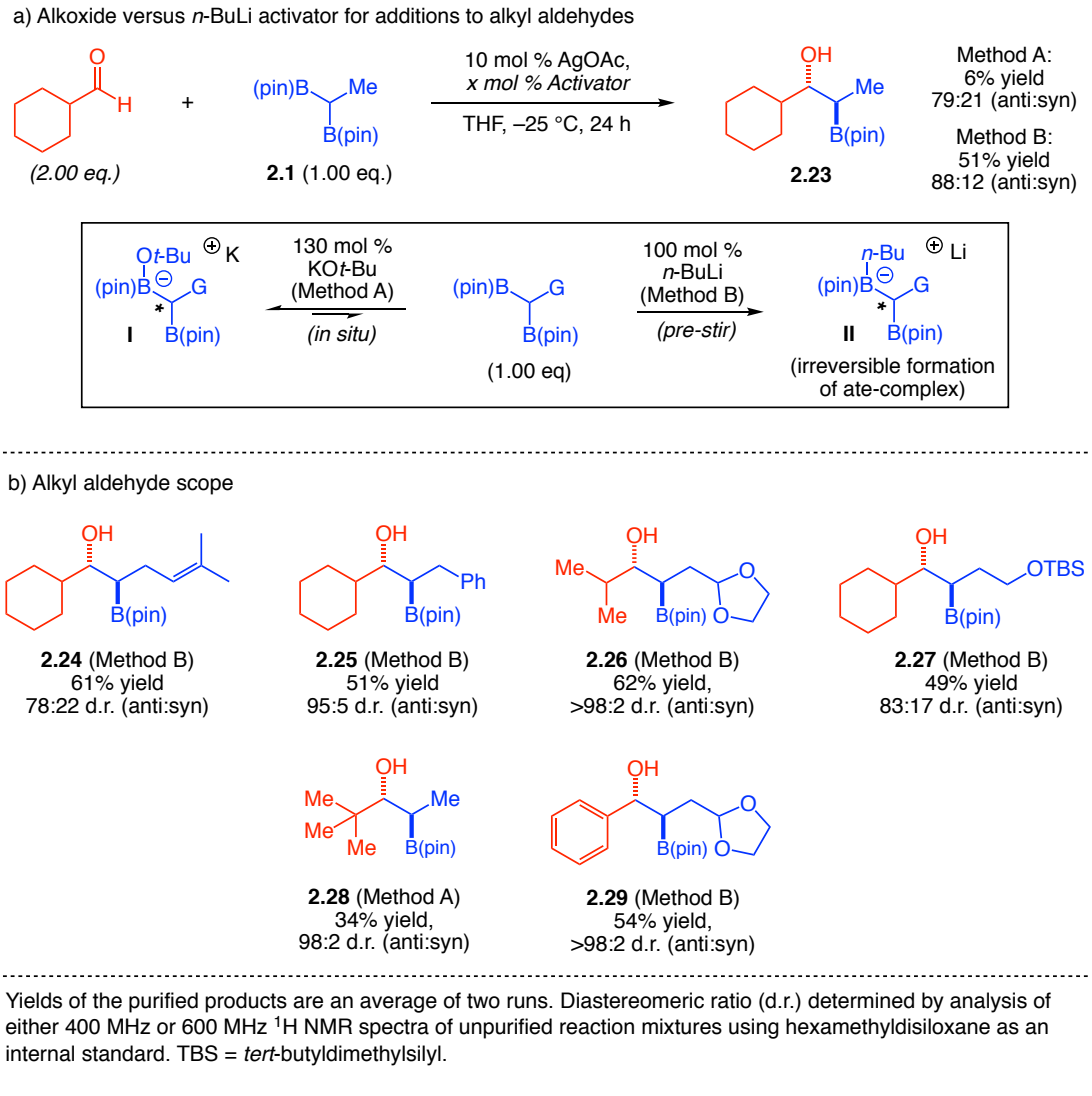
2.6 Ag(I)-catalyzed *anti*-1,2-additions of 1,1-diboronates to *alkyl* aldehydes

Addition of α-boryl nucleophiles was next extended to alkyl aldehydes (Scheme 2.5), which is a significant advancement over the Cu(I)-protocol discussed in Chapter 1. With cyclohexane carboxaldehyde, under otherwise identical reaction conditions (see Scheme 2.3), there was 6% conversion to **2.23** in 79:21 d.r. (Method A, Scheme 2.5a). We reasoned that deprotonation of the aldehyde by KO*t*Bu (or borate **I**) was responsible for low conversion to product.[xvi] To discourage enolization caused by unreacted alkoxide in solution, we substituted *n*-BuLi for KO*t*Bu (Method B, Scheme 2.5a), as an irreversible activation of the 1,1-diboryl alkane (**II**) should minimize undesired side reactions. Treatment of **2.1** with 1 equivalent of *n*-BuLi in the presence of AgOAc followed by cyclohexane carboxaldehyde at

[xvi]The presence of significant unreacted aldehyde upon aqueous workup supports this hypothesis.

–25 °C afforded **2.23** in 51% yield and 88:12 d.r. (*anti/syn*). A less than 5% conversion to **2.23** is observed in the absence of the silver(I) salt. The *n*-BuLi protocol proved effective for alkyl and aryl aldehydes in combination with substituted 1,1-diboron reagents which contain an alkene (**2.24**), phenyl ring (**2.25**), acetal (**2.26**), or silyl ether (**2.27**; Scheme 2.5b). In general, the yields and *anti*-selectivity of the 1,2-hydroxyboronate products are slightly lower than in the case of aryl aldehydes. Alkyl aldehydes lacking α-protons do not require *n*-BuLi as an activator.[xvii] For example, pivaldehyde undergoes diastereoselective (98:2 d.r., *anti/syn*) addition promoted by KO*t*Bu, but **2.28** is isolated in only 34% yield. The acetal-containing product **2.29**, while derived from an aryl aldehyde, requires Method B for formation (Method A furnishes the product in <5% yield). In general, aryl aldehydes work with Method B, but the resulting products are produced in lower yields and diastereoselectivities.

[xvii]On the other hand, a limitation to this methodology is that primary aldehydes (*e.g.* dihydrocinnamaldehyde) and α-acidic aldehydes (*e.g.* 2-phenylpropionaldehyde) do not work with either method.

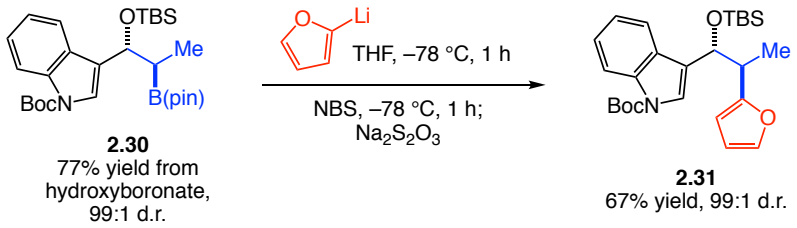


Yields of the purified products are an average of two runs. Diastereomeric ratio (d.r.) determined by analysis of either 400 MHz or 600 MHz ^{1}H NMR spectra of unpurified reaction mixtures using hexamethyldisiloxane as an internal standard. TBS = *tert*-butyldimethylsilyl.

Scheme 2.5. Ag(I)-catalyzed additions of 1,1-diboronates to alkyl aldehydes.

2.7 Functionalization of *anti*-1,2-hydroxyboronates: Stereospecific heteroarylation

To showcase the synthetic utility of *anti*-1,2-hydroxyboronates, the TBS-protected hydroxyboronate **2.30** (isolated in 77% yield from the parent hydroxyboronate) was subjected to stereospecific aryl coupling (Scheme 2.6). The boronate **2.30** was treated with 1.2 equivalents of α-lithiated furan at –78 °C, followed by *N*-bromosuccinimide, and finally a saturated solution of $Na_2S_2O_3$ to furnish 1,2-diarylated product **2.31** in 67% yield and 99:1 d.r.[6,37] As was discussed in Chapter 1, these compounds are amenable to numerous stereospecific transformations, including oxidation, amination, and carbon homologation.[3-7]



Scheme 2.6. Stereospecific heteroarylation of 1,2-hydroxyboronate products.

In conclusion, Chapter 2 has summarized our studies into the development of the first catalytic *anti*-selective addition of various substituted 1,1-diboryl alkanes to a range of aryl-, alkenyl-, and particularly alkyl-substituted aldehydes. This methodology is both complementary to the Cu(I)-protocol in that opposite diastereoselectivity is observed, in addition to being a major advancement over the previous methodology in terms of reagent (substituted 1,1-diboronates) and substrate (alkyl aldehydes) scope. Furthermore, functionalization of the *anti*-hydroxyboronates has been demonstrated by a stereospecific aryl coupling with furan. One direction for future investigations involves the development of enantioselective variants of this protocol.

2.8 Experimental Section

2.8.1 General Methods

All reactions were carried out in oven-dried (150 ˚C) or flame-dried glassware under an inert atmosphere of dried N_2 unless otherwise noted. Analytical thin-layer chromatography was performed on glass plates coated with 0.25 mm of 60 Å mesh silica gel. Plates were visualized by exposure to UV light (254 nm) and/or immersion into Seebach's or $KMnO_4$ stain followed by heating. Column chromatography was performed using silica gel P60 (mesh 230-400) supplied by Silicycle. Deactivated silica gel was prepared by stirring a slurry of the aforementioned silica gel in a 3% NaOAc aqueous solution for 15 minutes. The deactivated silica gel was collected by filtration and then dried in a 150 ˚C oven for 3 days.

All solvents were sparged with argon and then purified under a positive pressure of argon through an SG Water, USA Solvent Purification System. Tetrahydrofuran (OmniSolv) was passed successively through two columns of neutral alumina. The ambient temperature in the laboratory was approximately 22 ˚C.

2.8.1.1 Instrumentation

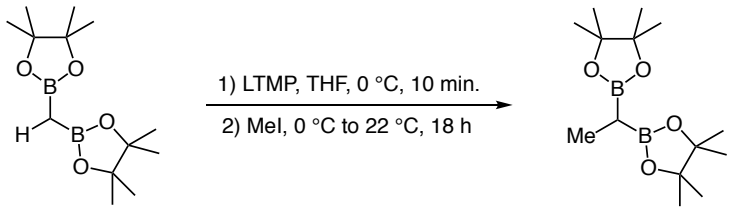
All ^{1}H NMR spectra were recorded on Bruker Spectrometers (AVANCE-600, AVANCE-500 and AVANCE-400). Chemical shifts are reported in ppm from tetramethylsilane and referenced to the residual protio solvent peak ($CDCl_3$: δ 7.26, THF-d_8: δ 1.72). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, qu = quartet, quint = quintet, br = broad, m = multiplet, app = apparent), integration, and coupling constants are given in Hz. ^{13}C NMR spectra were recorded on Bruker Spectrometers (AVANCE-600 and AVANCE-400) with carbon and proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane and referenced to the residual protio solvent peak ($CDCl_3$: δ 77.16). All IR spectra were recorded on a Jasco 260 Plus Fourier transform infrared spectrometer. Mass Spectrometry samples were analyzed with a hybrid LTQ FT (ICR 7T) (ThermoFisher, Bremen, Germany) mass spectrometer. Samples were introduced *via* a micro-electrospray source at a flow rate of 10 μL/min (solvent composition 10:1 MeOH:H_2O). Xcalibur (ThermoFisher, Breman, Germany) was used to analyze the data. Molecular formula assignments were determined with Molecular Formula Calculator (v. 1.2.3).

2.8.1.2 Reagents

All liquid aldehydes were distilled from CaH_2 or $CaSO_4$ under vacuum and then sparged with dry N_2. Solid aldehydes were purified *via* recrystallization, followed by

azeotropic drying with benzene. Silver acetate was purchased from Strem Chemicals and kept in an N_2 filled glove box. Diboryl methane was synthesized according to Scheme 1.12 (see section 1.8.1.3 above).

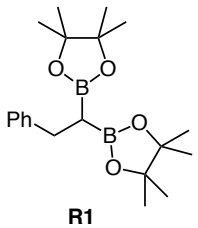
2.8.1.3 Representative synthesis of substituted diboryl reagents



Scheme 2.7. Representative synthesis of substituted diboryl reagents.

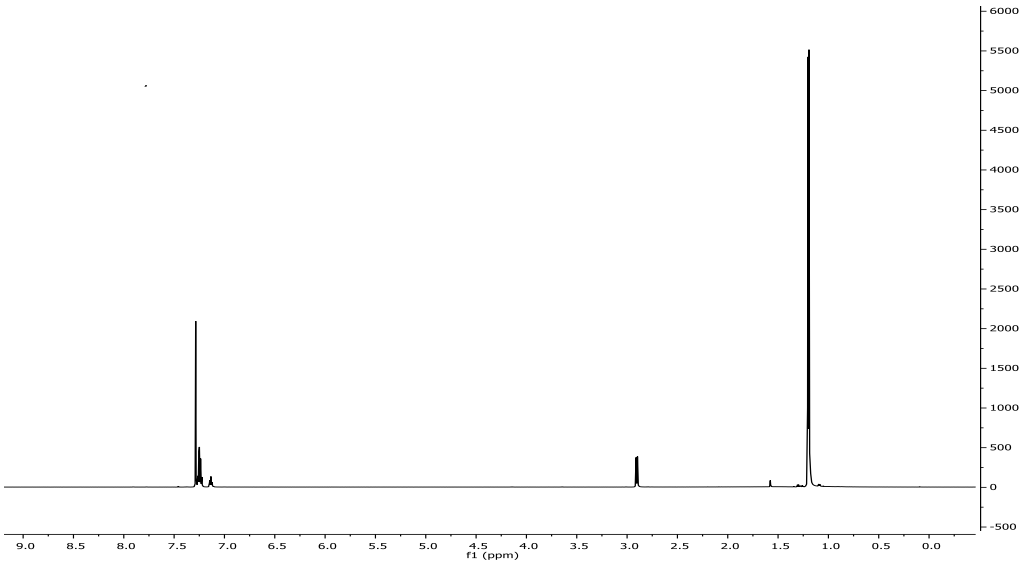
In an N_2-filled glove box, an oven-dried round-bottom flask was charged with diboryl methane (3.00 g, 11.2 mmol) and a magnetic stir-bar, capped with a rubber septum, and sealed with electrical tape. A separate oven-dried, conical shaped flask was charged with lithium 2,2,6,6-tetramethylpiperidine (1.73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

desired diboryl reagent (in this case, diboryl ethane; **1.1/2.1**, see section 1.8.1.4 for synthesis) in 89% yield (2.8 g).



R1

2,2'-(2-phenylethane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (R1). Following the representative procedure, diboryl methane was alkylated with benzyl bromide and the crude reaction mixture was purified *via* silica gel chromatography in 20:1 hexanes:EtOAc to yield the product in 90% yield (1.2 g). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.28 – 7.21 (m, 4H), 7.17 – 7.11 (m, 1H), 2.90 (d, J = 8.4 Hz, 2H), 1.21 (s, 7H), 1.20 (s, 6H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 144.6, 128.5, 128.1, 125.5, 83.2, 31.4, 24.9, 24.7. **IR** (ν/cm^{-1}): 2978 (m), 2930 (w), 2866 (w), 1453 (w), 1381 (w), 1360 (m), 1320 (s), 1268 (w), 1241 (w), 1215 (w), 1140 (s). **HRMS** (ESI+) $[M+Na]^+$ calcd for $C_{20}H_{32}B_2NaO_4^+$ 381.2385, found: 381.2380.



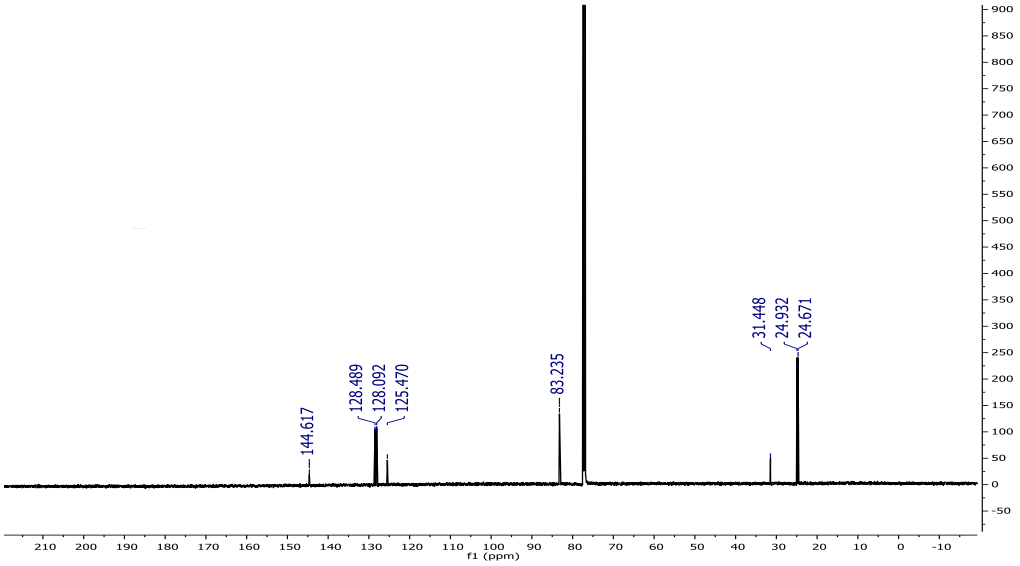
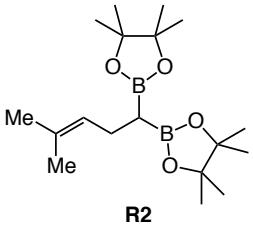


Figure 2.1. ^{1}H and ^{13}C{^{1}H} NMR spectra of R1.



R2

2,2'-(4-methylpent-3-ene-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (R2). Following the representative procedure, diboryl methane was alkylated with prenyl bromide. The crude reaction mixture was purified via silica gel chromatography in 20:1 hexanes:EtOAc to yield the product in 90% yield (1.1 g). **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 5.09 (t, 1H, J = 7.02 Hz), 2.21 (t, 2H, J = 7.8 Hz), 1.63 (s, 3H), 1.60 (s, 3H), 1.22 (s, 12H), 1.21 (s, 12H), 0.75 (t, 1H, J = 8.4 Hz). **^{13}C NMR** ($CDCl_3$, 151 MHz): δ 130.3, 127.1, 83.1, 25.9, 25.0, 24.6, 24.2, 18.0. **IR** (ν/cm^{-1}): 2978 (s), 2928 (m), 2862 (w), 1446 (w), 1370 (m), 1357 (m), 1319 (m), 1270 (w), 1246 (w), 1215 (w), 1141 (s). **HRMS** (ESI+) $[M+Na]^+$ calcd for $C_{18}H_{34}B_2NaO_4^+$ 359.2541, found: 359.2539.

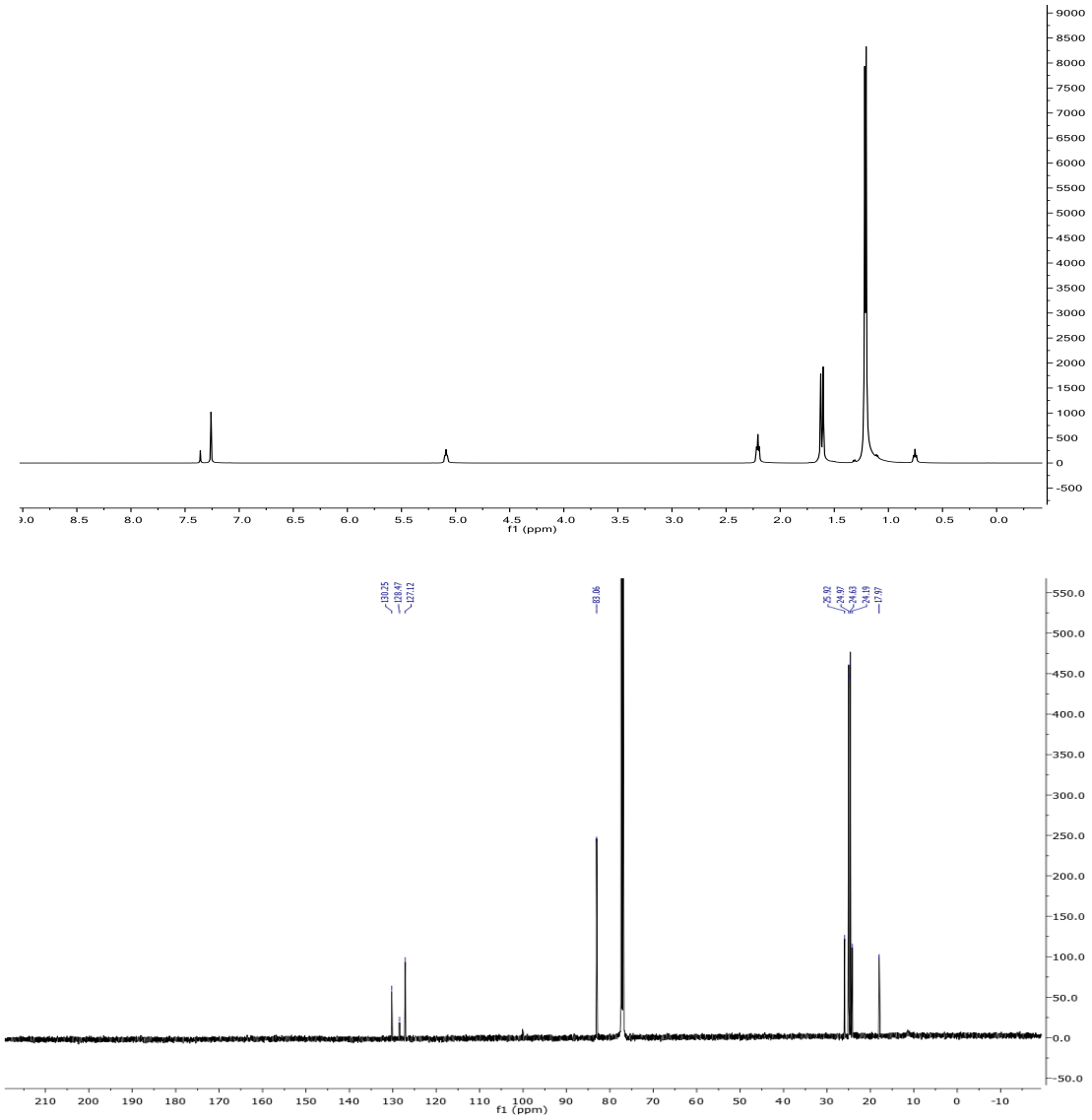
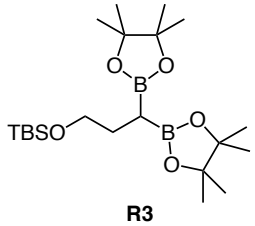


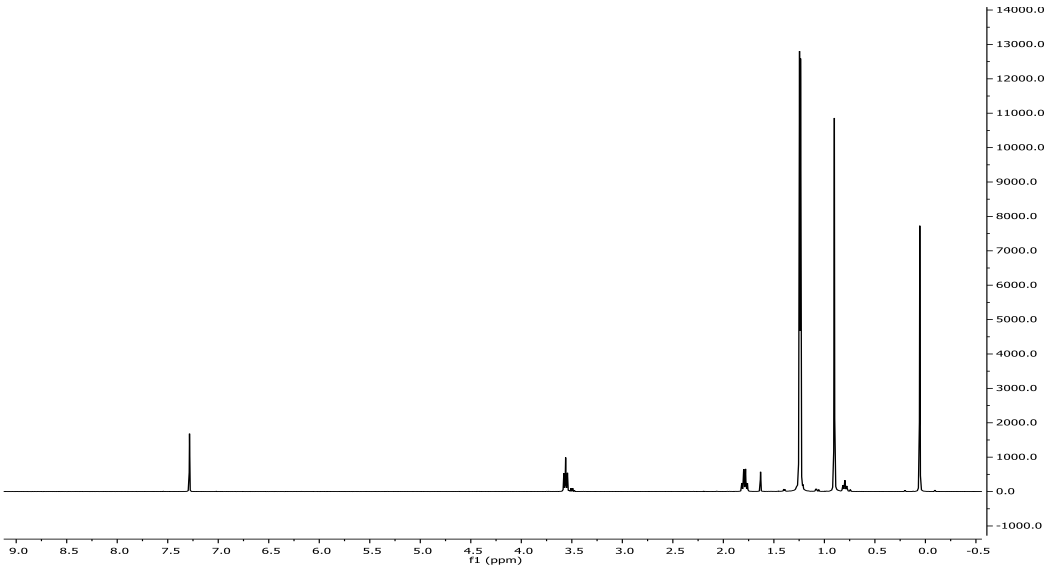
Figure 2.2. ^{1}H and ^{13}C{^{1}H} NMR spectra of R2.



R3

(3,3-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propoxy)(tert-butyl)dimethylsilane (R3). Following the representative procedure, diboryl methane was alkylated with (2-bromoethoxy)(tert-butyl)dimethylsilane. The crude reaction mixture was

purified via silica gel chromatography in 20:1 hexanes:EtOAc to yield the product in 92% yield (1.4 g). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 3.54 (t, 2H, J = 7.2 Hz), 1.76 (qu, 2H, J = 7.6 Hz), 1.22 (s, 12H), 1.21 (s, 12H), 0.87 (s, 9H), 0.77 (t, 1H J = 7.6 Hz), 0.03 (s, 6H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 83.1, 65.2, 28.9, 26.2, 25.1, 24.6, 18.6, –5.1. **IR** (ν/cm^{-1}): 2978 (m), 2956 (m), 2930 (m), 2886 (w), 2857 (m), 1471 (w), 1379 (m), 1362 (m), 1318 (m), 1270 (w), 1255 (w), 1215 (w), 1165 (w), 1141 (m), 1099 (m), 1037 (w), 1006 (w). **HRMS** (ESI+) $[M+Na]^+$ calcd for $C_{21}H_{44}B_2NaO_5Si^+$ 449.3042, found: 449.3040.



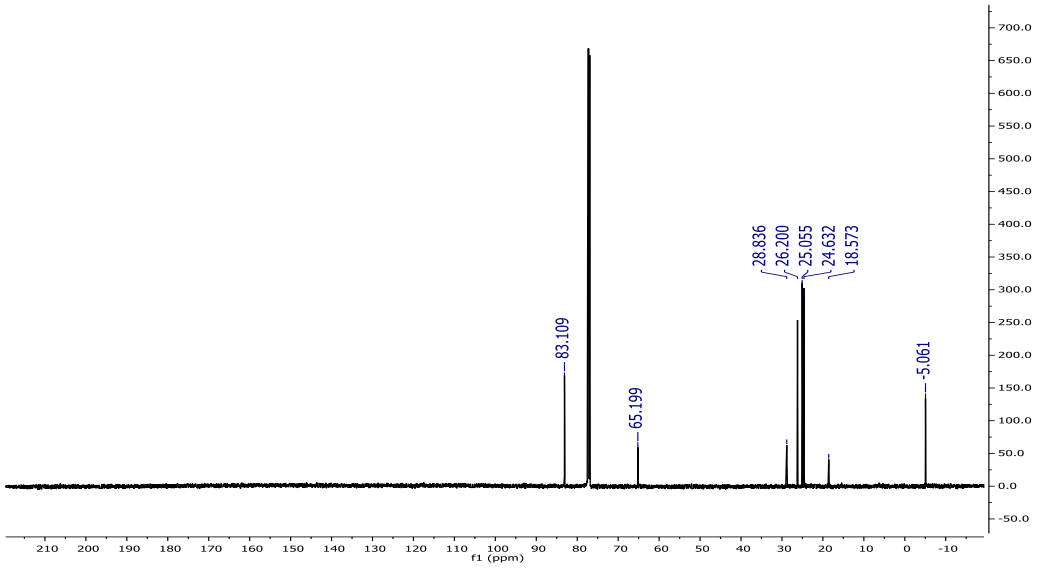
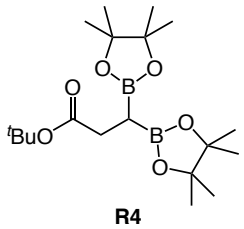


Figure 2.3. ^{1}H and ^{13}C{^{1}H} NMR spectra of R3.



R4

tert-butyl 3,3-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoate (R4).

Following the representative procedure, diboryl methane was alkylated with *tert*-butyl-2-bromoacetate. The crude reaction mixture was purified via silica gel chromatography in 20:1 hexanes:EtOAc to yield the product in 68% yield (485 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 2.52 (d, J = 8.5 Hz, 2H), 1.43 (s, 9H), 1.25 (s, 12H), 1.23 (s, 12H), 1.07 (t, *J* = 8.5 Hz, 1H). **^{13}C NMR** (126 MHz, CDCl3) δ 174.2, 83.1, 79.6, 31.7, 28.1, 24.9, 24.5. **IR** (ν/cm^{-1}): 2977 (s), 2894 (m), 2094 (w), 1729 (s), 1643 (s), 1468 (m), 1314 (w), 1268 (m), 1213 (m), 1140 (w). **HRMS** (ESI^{+}) $[2M+Na]^{+}$ calcd for $C_{38}H_{72}B_4NaO_{12}^{+}$ 787.5294, found: 787.5314.

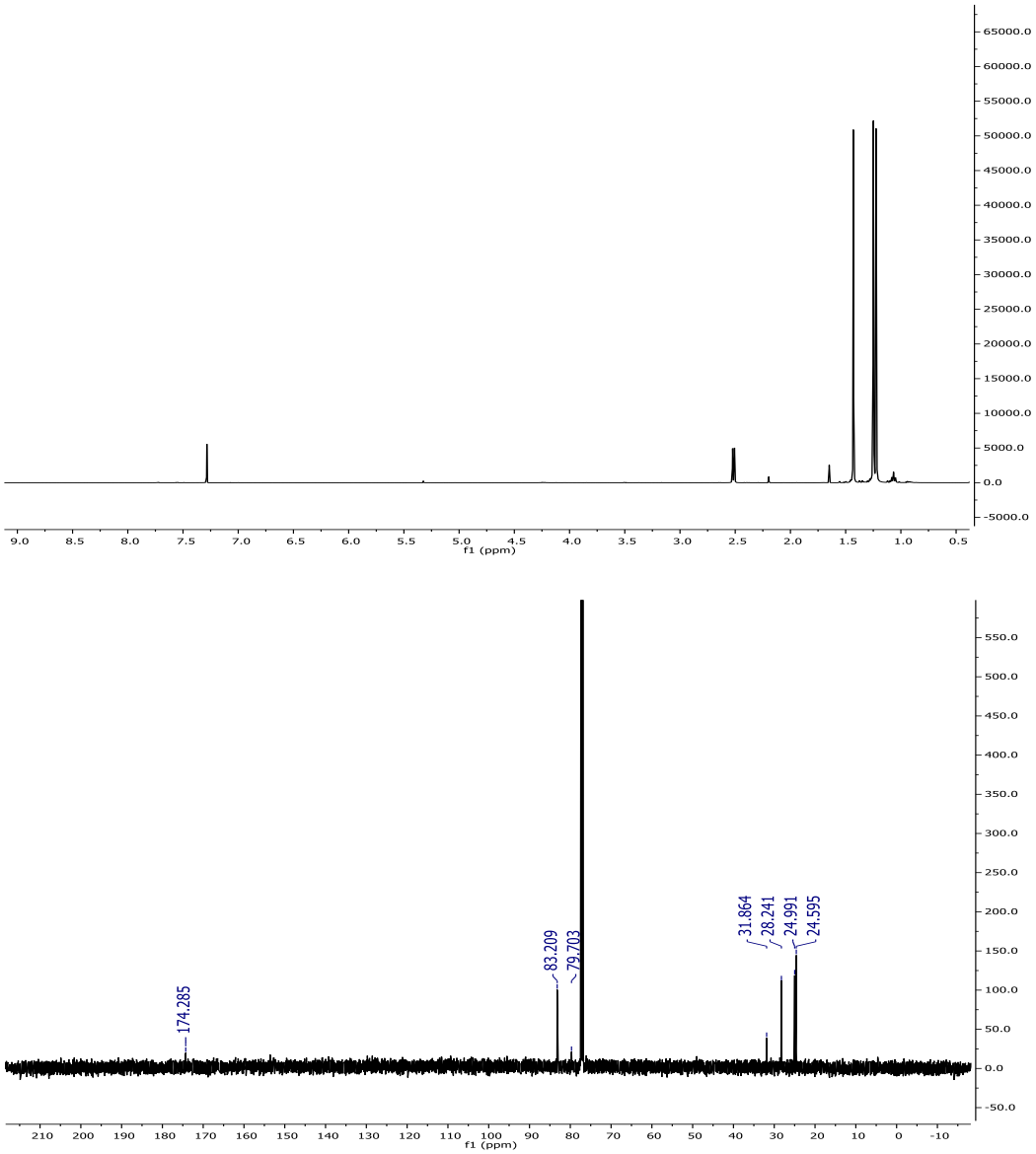
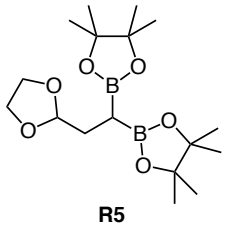


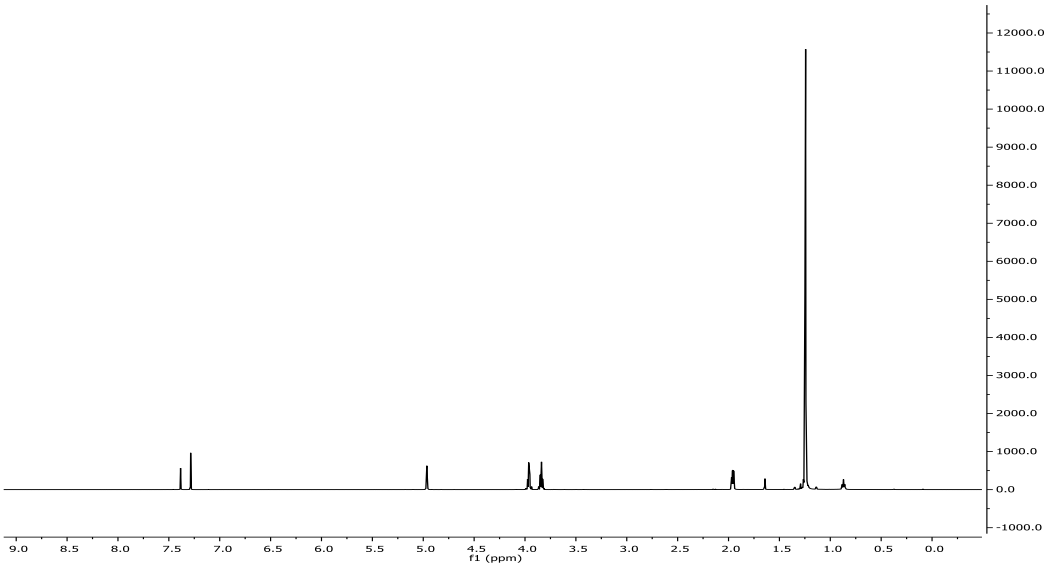
Figure 2.4. ^{1}H and ^{13}C{^{1}H} NMR spectra of R4.



R5

2,2'-(2-(1,3-dioxolan-2-yl)ethane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (R5). Following the representative procedure, diboryl methane was alkylated with 2-bromomethyl-1,3-dioxolane. The crude reaction mixture was purified *via*

silica gel chromatography in 20:1 hexanes:EtOAc to yield the product in 44% yield (440 mg). **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 4.94 (t, 1H, *J* = 3.9 Hz), 3.91-3.96 (m, 2H), 3.79-3.84 (m, 2H), 1.93 (dd, 2H, *J* = 7.6, 4.0 Hz), 1.22 (s, 12H), 1.22 (s, 12H), 0.84 (t, 1H, *J* = 7.6 Hz). **^{13}C NMR** ($CDCl_3$, 151 MHz): δ 128.5, 105.1, 83.1, 65.1, 30.1, 24.9, 24.7. **IR** (ν/cm^{-1}): 2978 (s), 2930 (m), 2886 (m), 1469 (w), 1440 (w), 1369 (m), 1321 (s), 1270 (w), 1245 (w), 1215 (w), 1140 (s), 1085 (w), 1034 (w). **HRMS** (ESI+) $[2M+NH_4]^+$ calcd for $C_{34}H_{68}B_4NaO_{12}^+$ 726.5113, found: 726.5150.



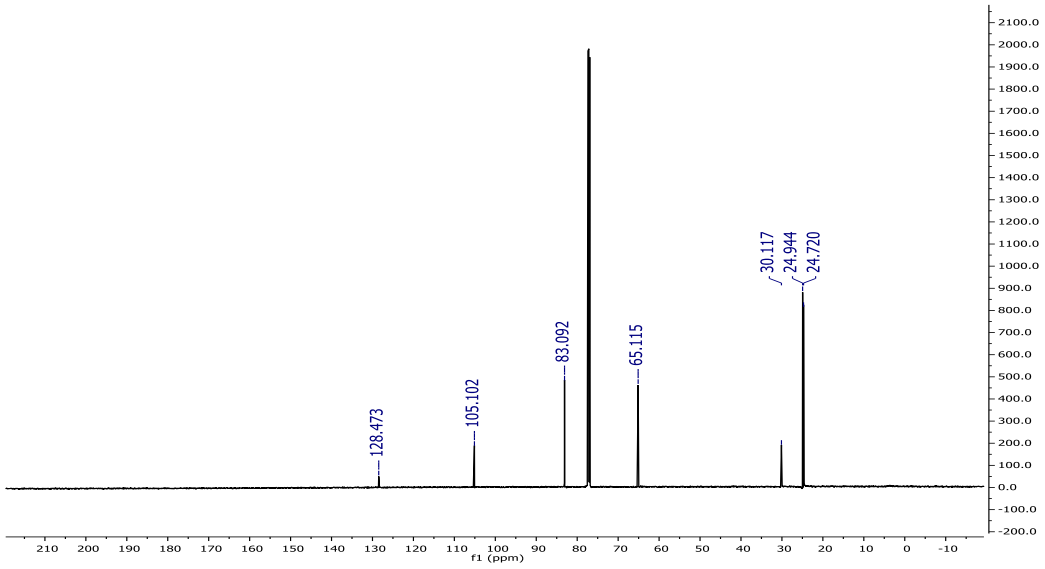
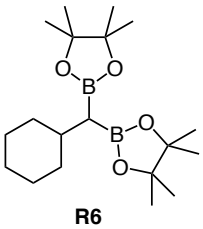


Figure 2.5. ^{1}H and ^{13}C{^{1}H} NMR spectra of R5.



R6

2,2'-(cyclohexylmethylene)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (R6).

Following the representative procedure, diboryl methane was alkylated with bromocyclohexane. The crude reaction mixture was purified *via* silica gel chromatography in 20:1 hexanes:EtOAc to yield the product in 20% yield (190 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.85 – 1.55 (m, 8H), 1.26 (s, 12H), 1.24 (s, 12H), 1.17 – 1.04 (m, 1H), 1.03 – 0.85 (m, 2H), 0.66 (d, J = 10.4 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 82.9, 36.1, 36.1, 26.9, 26.4, 25.0, 24.7. **IR** (v/cm^{-1}): 2978 (s), 2922 (m), 2851 (m), 2082 (m), 1639 (s), 1447 (m), 1315 (w), 1266 (m), 1140 (w). **HRMS** (ESI+) $[2M+Na]^+$ calcd for $C_{38}H_{72}B_4NaO_8^+$ 723.5630, found: 723.5603.

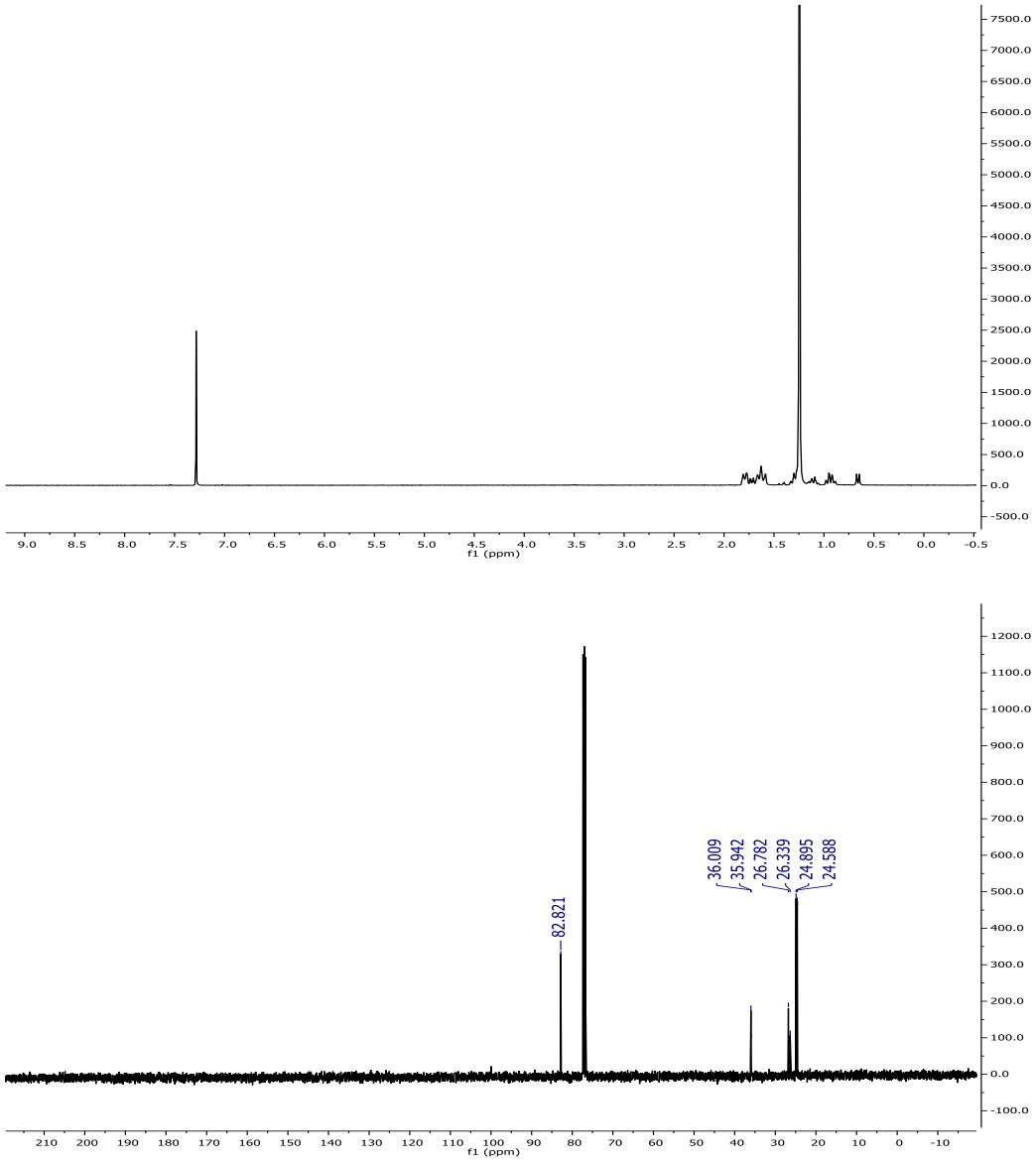
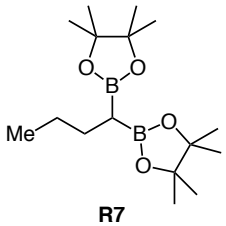


Figure 2.6. ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of R6.



R7

2,2'-(butane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (R7).

Following the representative procedure, diboryl methane was alkylated with 1-iodopropane. The crude reaction mixture was purified *via* silica gel chromatography in 20:1

hexanes:EtOAc to yield the product in 78% yield (442 mg). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.59 – 1.51 (m, 2H), 1.37 – 1.28 (m, 2H), 1.26 (s, 12H), 1.24 (s, 12H), 0.89 (t, J = 7.3 Hz, 3H), 0.76 (t, J = 7.9 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 82.9, 27.9, 25.6, 24.9, 24.5, 14.2. **IR** (ν/cm^{-1}): 2976 (s), 2840 (m), 1646 (m), 1314 (m), 1141 (m). **HRMS** (ESI+) $[2M+Na]^+$ calcd for $C_{32}H_{64}B_4NaO_8^+$ 643.4883, found: 643.4870.

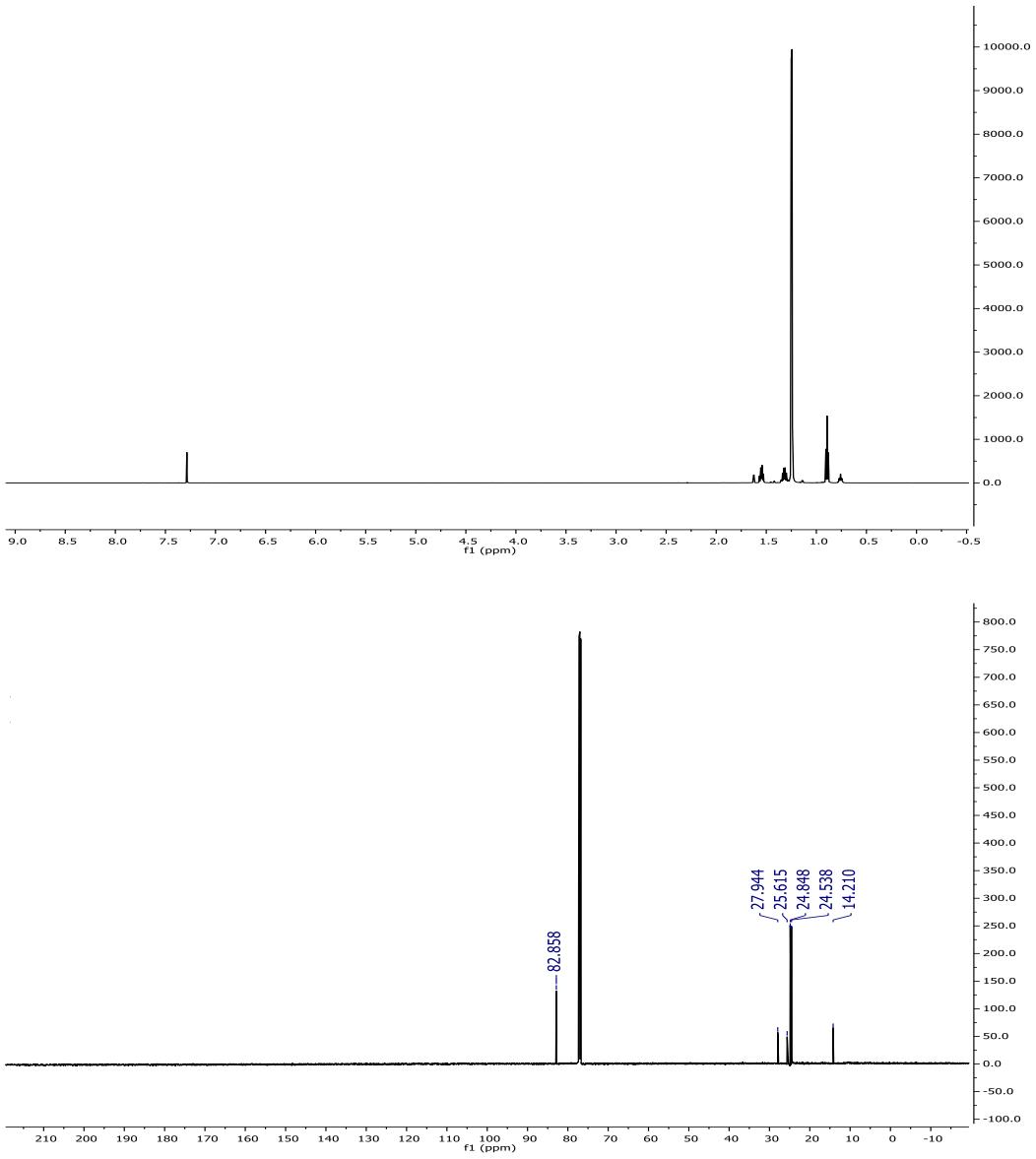
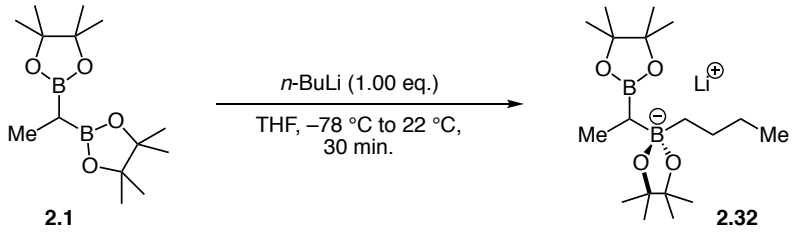


Figure 2.7. ^{1}H and ^{13}C{^{1}H} NMR spectra of R7.

2.8.1.4 Synthesis of *n*-BuLi-activated diboryl ethane (**2.32**)



Scheme 2.8. Synthesis of *n*-BuLi-activated diboryl ethane (2.32).

In an N_2-filled glove box, an 8-mL vial was equipped with a magnetic stir bar and charged with diboryl ethane (**2.1**; 100 mg, 0.355 mmol) and dissolved in 930 μL of anhydrous THF (0.33 M). The vial was sealed with a septa-lined cap and removed from the glove box. The reaction was allowed to cool to –78 ˚C (dry ice/acetone) and *n*-butyllithium was added to the solution under nitrogen (530 μL, 0.355 mmol, 0.67 M solution in hexanes). The reaction solidified instantaneously and the cooling bath was removed to allow the reaction to stir at ambient temperature for 30 minutes. The reaction was then brought back into the glove box where it was concentrated *in vacuo*, taken up in hexanes, and filtered through a plug of Celite. After concentrating the filtrate *in vacuo*, 1 mL of diethyl ether was added to the residue and removed *in vacuo* to yield a glassy solid. This solid was then scraped from the sides of the vial to yield a crystalline off-white powder in 98% yield (113 mg). **^{1}H NMR** (500 MHz, THF-d_8): δ 1.34 – 1.13 (m, 13H), 1.07 – 0.94 (m, 12H), 0.94 – 0.75 (m, 9H), 0.22 – 0.04 (m, 2H), -0.16 (qu, J = 7.2 Hz, 1H). **^{11}B NMR** (500 MHz, THF-d_8): 35.9 (s), 6.1 (s).

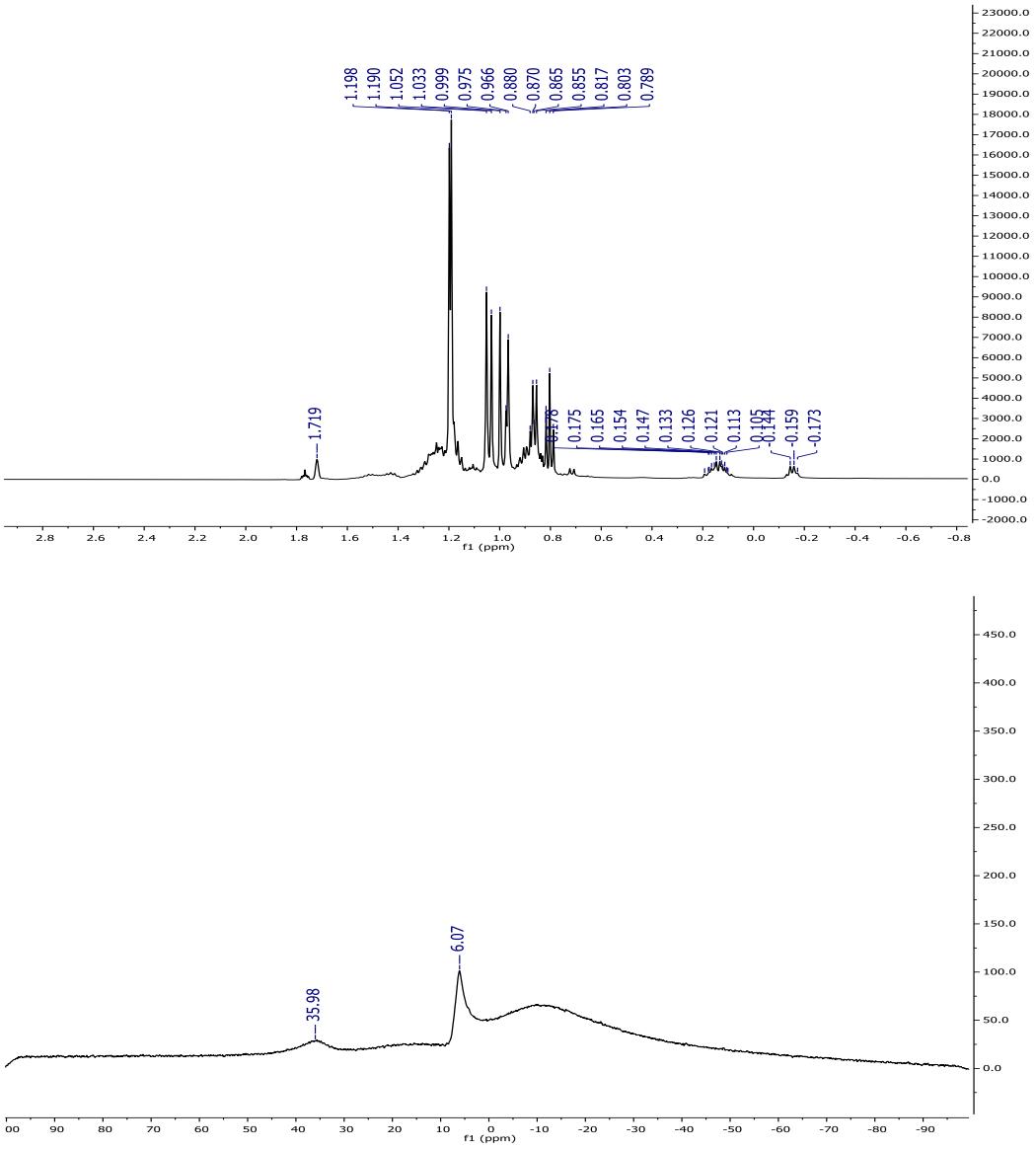
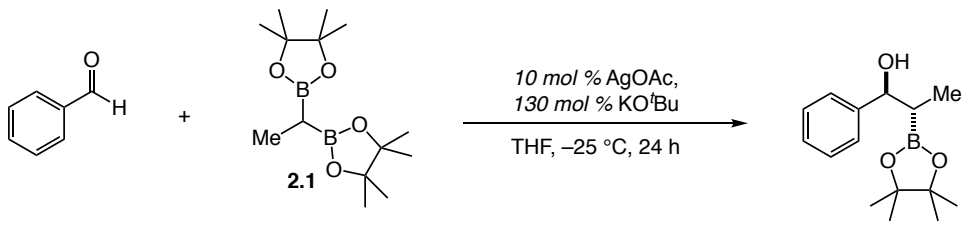


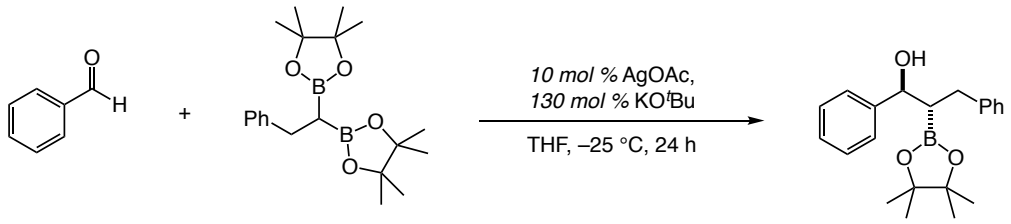
Figure 2.8. ^{1}H and ^{11}B NMR spectra of 2.21.

2.8.1.5 General procedures for the Ag-catalyzed 1,2-addition reaction



Scheme 2.9. General procedure A (aryl and vinyl aldehydes with diboryl ethane).

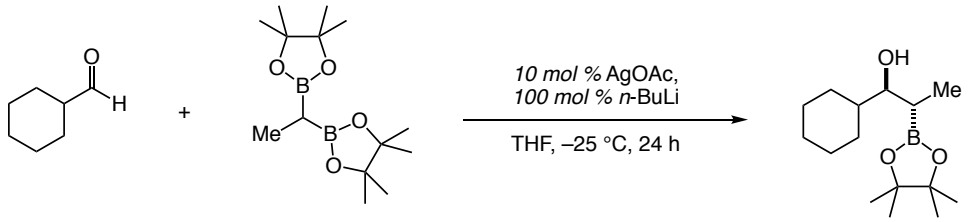
Procedure A (aryl and vinyl aldehydes with diboryl ethane, 2.1): In an N_2-filled glove box, an 8-mL vial equipped with a magnetic stir bar was charged with AgOAc (1.7 mg, 0.010 mmol) and KO^{t}Bu (14.6 mg, 0.13 mmol) and then shaken to evenly mix the solids. Diboryl ethane (**2.1**) was then added as a solution in THF down the side of the vial (29.7μL, 0.1 mmol in 0.8 mL of THF). The vial was sealed with a septa-lined cap and removed from the glove box and allowed to stir at 22 ˚C for 5 min. The reaction was then placed in a freezer set to –25 ˚C and allowed to stir for 30 more minutes. The aldehyde (0.1 mmol) was then added to the reaction *via* syringe under argon and allowed to stir for 24 hours. The reaction was quenched at –25 ˚C with 1.0 mL of a saturated aqueous solution of NH_4Cl, and the aqueous layer extracted three times with diethyl ether. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Conversion and diastereomeric ratios were determined by ^{1}H NMR using hexamethyldisiloxane as an internal standard.



Scheme 2.10. General procedure B (aryl aldehydes with R1-R7).

Procedure B (aryl aldehydes with R1-R7): In an N_2-filled glove box, an 8-mL vial equipped with a magnetic stir bar was charged with AgOAc (1.7 mg, 0.010 mmol) and KO^{t}Bu (14.6 mg, 0.13 mmol) and then shaken to evenly mix the solids. The diboryl reagent was then added as a solution in THF down the side of the vial (0.1 mmol in 0.8 mL of THF). The vial was sealed with a septa-lined cap and removed from the glove box and allowed to stir at 22 ˚C for 30 min. The reaction was then placed in a freezer set to –25 ˚C and allowed to stir for 10 minutes. The aldehyde (0.1 mmol) was then added to the reaction *via* syringe

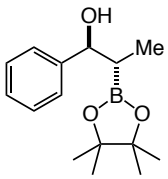
under argon and allowed to stir for 24 hours. The reaction was quenched at –25 ˚C with 1.0 mL of a saturated aqueous solution of NH_4Cl, and the aqueous layer extracted three times with diethyl ether. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Conversion and diastereomeric ratios were determined by ^1H NMR using hexamethyldisiloxane as an internal standard.



Scheme 2.11. General procedure C (alkyl aldehydes with all diboryl reagents).

Procedure C (alkyl aldehydes with all diboryl reagents): In an N_2-filled glove box, an 8-mL vial equipped with a magnetic stir bar was charged with AgOAc (1.7 mg, 0.010 mmol) and diboryl ethane (29.7 μL, 0.1 mmol), followed by 0.80 mL of anhydrous THF. The vial was sealed with a septa-lined cap and removed from the glove box and allowed to cool to –78 ˚C (dry-ice/acetone). *n*-butyllithium was then added at this temperature (69 μL, 0.10 mmol, 1.42 M solution in hexanes) and allowed to stir for 20 minutes. The reaction was transferred to a freezer set to –25 ˚C and allowed to stir for 10 minutes. The aldehyde (0.2 mmol) was then added to the reaction *via* syringe under argon and allowed to stir at –25 ˚C for 24 hours. The reaction was quenched at –25 ˚C with 1.0 mL of a saturated aqueous solution of NH_4Cl, and the aqueous layer extracted three times with diethyl ether. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Conversion and diastereomeric ratios were determined by ^1H NMR using hexamethyldisiloxane as an internal standard.

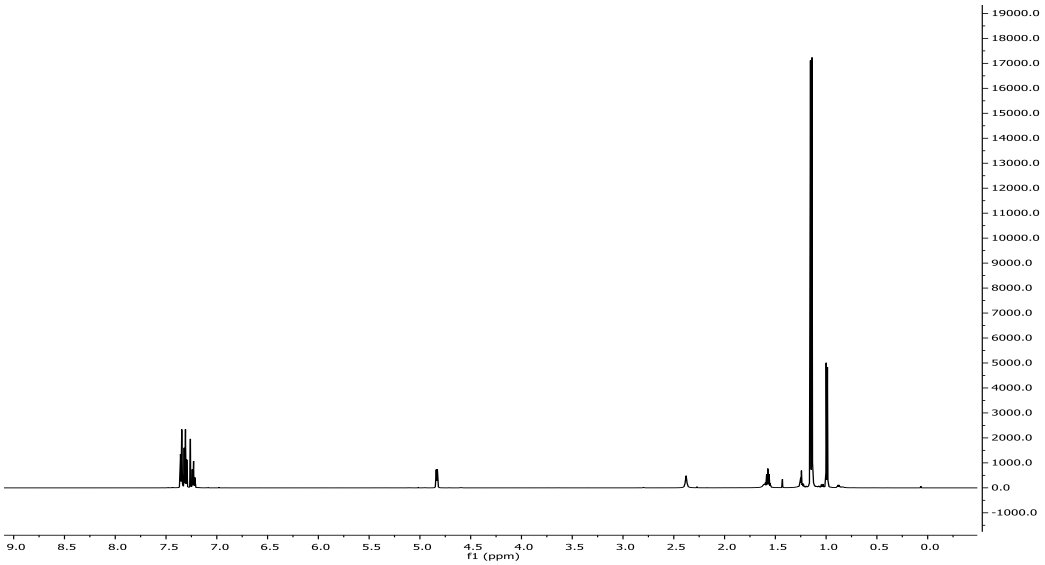
2.8.2 Preparation of aryl and vinyl *anti*-1,2-hydroxyboronates



2.2

1-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-ol (2.2).

Following general procedure A, the crude reaction mixture was purified by silica gel chromatography (NaOAc deactivated silica gel, 10:1 to 2:1 pentane:diethyl ether, Seebach Stain) to yield the hydroxyboronate as a colorless oil in 70% yield (18.3 mg) in 99:1 anti:syn diastereomeric ratio. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.35 (d, *J* = 7.3 Hz, 2H), 7.31 (t, *J* = 7.6 Hz, 2H), 7.23 (m, 1H), 4.84 (dd, *J* = 6.5, 4.1 Hz, 1H), 2.35 (d, *J* = 4.1 Hz, 1H), 1.58 (m, 1H), 1.16 (s, 6H), 1.15 (s, 6H), 0.99 (d, *J* = 7.4 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 144.1, 128.2, 127.2, 126.4, 83.4, 75.9, 24.7, 10.8. **IR** (ν/cm^{-1}): 3481 (s, br), 3085 (w), 3062 (w), 3030 (w), 2978 (s), 2932 (m), 2876 (m), 1494 (w), 1458 (m), 1381 (m), 1320 (m), 1275 (w), 1247 (w), 1215 (w), 1167 (w), 1145 (m), 1111 (w), 1073 (w), 1059 (w), 1009 (w). **HRMS (ESI+)** $[M+Na]^+$ calcd for $C_{15}H_{23}BNaO_3^+$ 285.1638, found: 285.1634.



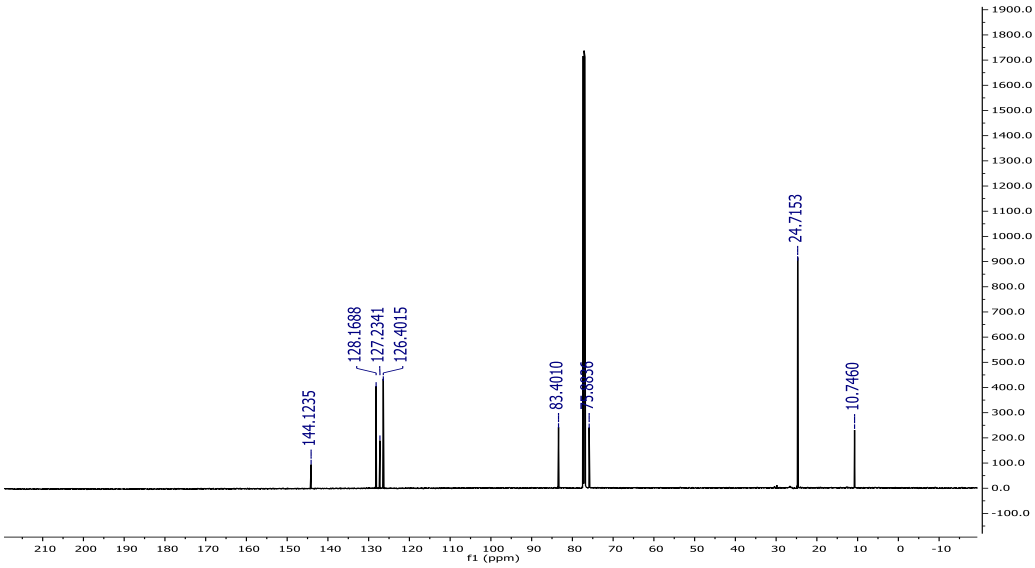
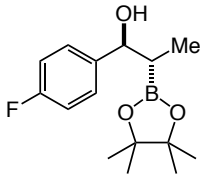


Figure 2.9. ^{1}H and ^{13}C{^{1}H} NMR spectra of 2.2.



2.4

1-(4-fluorophenyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-ol (2.4). Following general procedure A, the crude reaction mixture was purified by silica gel chromatography (NaOAc deactivated silica gel, 10:1 to 2:1 pentane:diethyl ether, Seebach Stain) to yield the hydroxyboronate as a colorless oil in 65% yield (18.2 mg) in 99:1 anti:syn diastereomeric ratio. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 2H), 7.08 – 6.92 (m, 2H), 4.81 (d, *J* = 6.7 Hz, 1H), 2.41 (s, 1H), 1.53 (qu, *J* = 7.3 Hz, 1H), 1.15 (s, 6H), 1.14 (s, 6H), 0.98 (d, *J* = 7.4 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 162.9, 161.2, 139.9, 139.9, 128.0, 128.0, 115.0, 114.8, 83.5, 75.2, 24.7, 24.7, 10.7. **IR** (ν/cm^{-1}): 3496 (s, br), 2979 (m), 2930 (w), 2877 (w), 1508 (s), 1457 (w), 1381 (s), 1320 (m), 1223 (m), 1144 (m), 1011 (m). **HRMS** (ESI^{+}) $[M+Na]^{+}$ calcd for $C_{15}H_{22}BFO_3Na^{+}$ 303.1544, found: 303.1537.

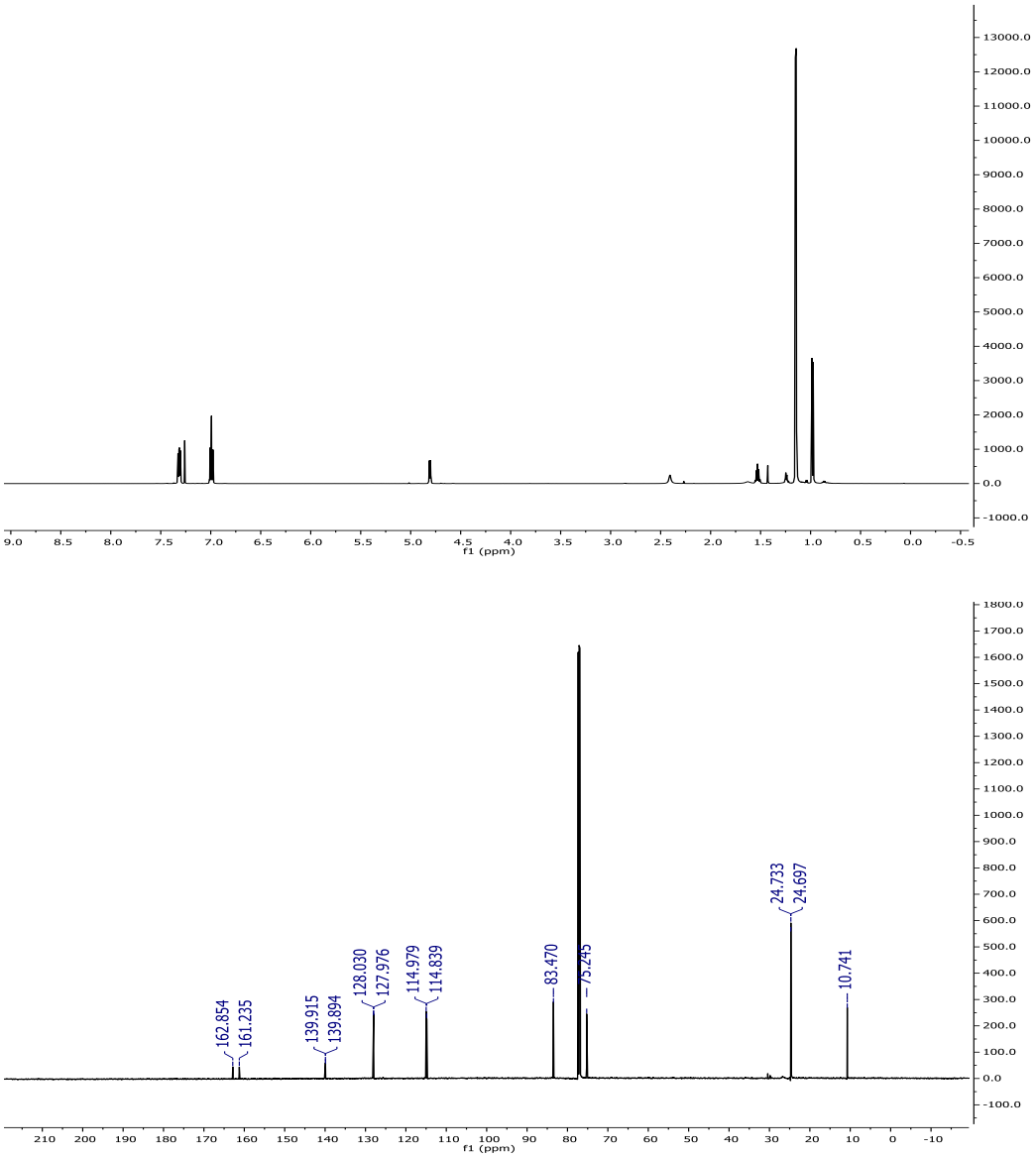
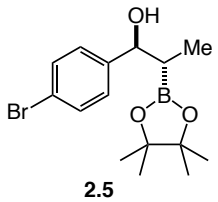


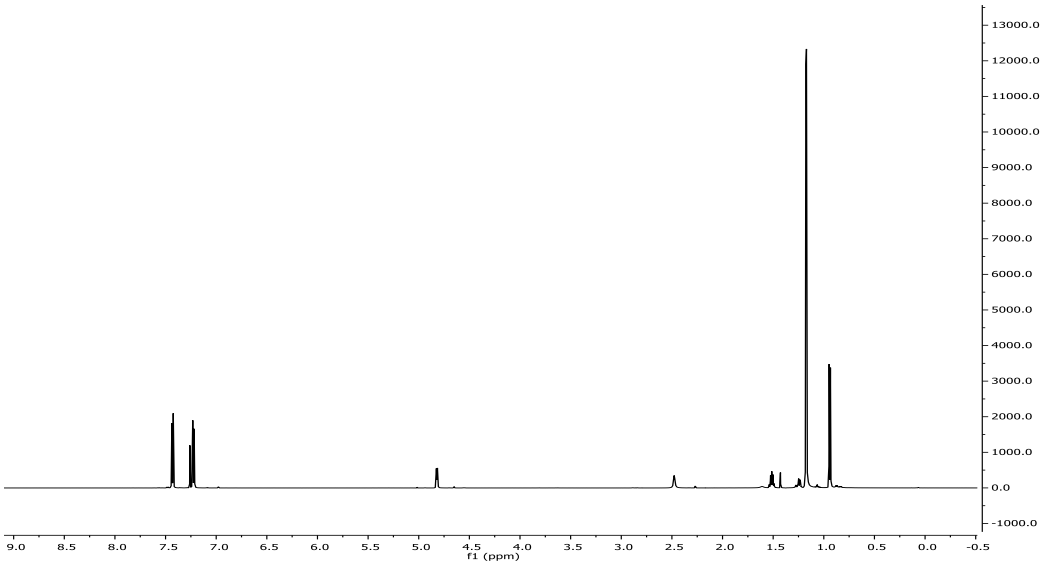
Figure 2.10. ^{1}H and ^{13}C{^{1}H} NMR spectra of 2.4.



2.5

1-(4-bromophenyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-ol (2.5). Following general procedure A, the crude reaction mixture was purified by silica gel (NaOAc deactivated silica gel, 10:1 to 2:1 pentane:diethyl ether, Seebach Stain) to yield the

hydroxyboronate as a white crystalline solid in 65% yield (22.2 mg) in >99:1 anti:syn diastereomeric ratio. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.47 – 7.38 (m, 2H), 7.25 – 7.18 (m, 2H), 4.82 (d, J = 6.1 Hz, 1H), 2.48 (s, 1H), 1.56 – 1.46 (m, 1H), 1.18 (s, 6H), 1.17 (s, 6H), 0.94 (d, J = 7.4 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 143.1, 131.2, 128.1, 120.9, 83.6, 75.0, 24.8, 24.7, 10.3. **IR** (ν/cm^{-1}): 3467 (s, br), 2978 (s), 2931 (w), 2876 (w), 1653 (w), 1457 (w), 1374 (s), 1320 (s), 1144 (s), 1010 (m). **HRMS** (ESI^{+}) $[M+Na]^{+}$ calcd for $C_{15}H_{22}BBrO_3Na^{+}$ 365.0743, found: 365.0716.



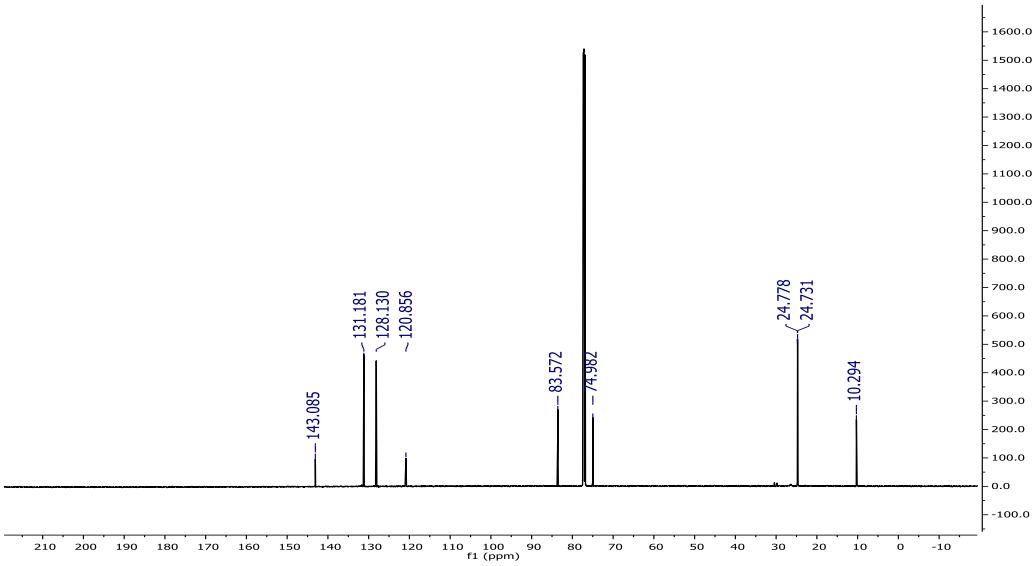
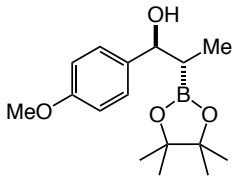


Figure 2.11. ^{1}H and ^{13}C{^{1}H} NMR spectra of 2.5.



2.6

1-(4-methoxyphenyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-ol (2.6). Following general procedure A, the crude reaction mixture was purified by silica gel chromatography (NaOAc deactivated silica gel, 10:1 to 2:1 pentane:diethyl ether, Seebach Stain) to yield the hydroxyboronate as a colorless oil in 73% yield (21.3 mg) in 99:1 anti:syn diastereomeric ratio. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.29 – 7.26 (m, 2H), 6.86 – 6.82 (m, 2H), 4.76 (d, *J* = 7.1 Hz, 1H), 3.79 (s, 1H), 2.29 (s, 1H), 1.55 (qu, *J* = 7.3 Hz, 1H), 1.14 (s, 6H), 1.13 (s, 6H), 1.01 (d, *J* = 7.2 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 158.8, 136.5, 127.6, 113.5, 83.3, 75.7, 55.4, 24.7, 24.7, 11.1. **IR** (ν/cm^{-1}): 3495 (s, br), 2978 (s), 2932 (w), 2873 (w), 1615 (m), 1514 (s), 1457 (m), 1374 (s), 1319 (m), 1248 (s), 1173 (m), 1144 (m). **HRMS** (ESI^{+}) $[M+Na]^{+}$ calcd for $C_{16}H_{25}BO_4Na^{+}$ 315.1744, found: 315.1737.

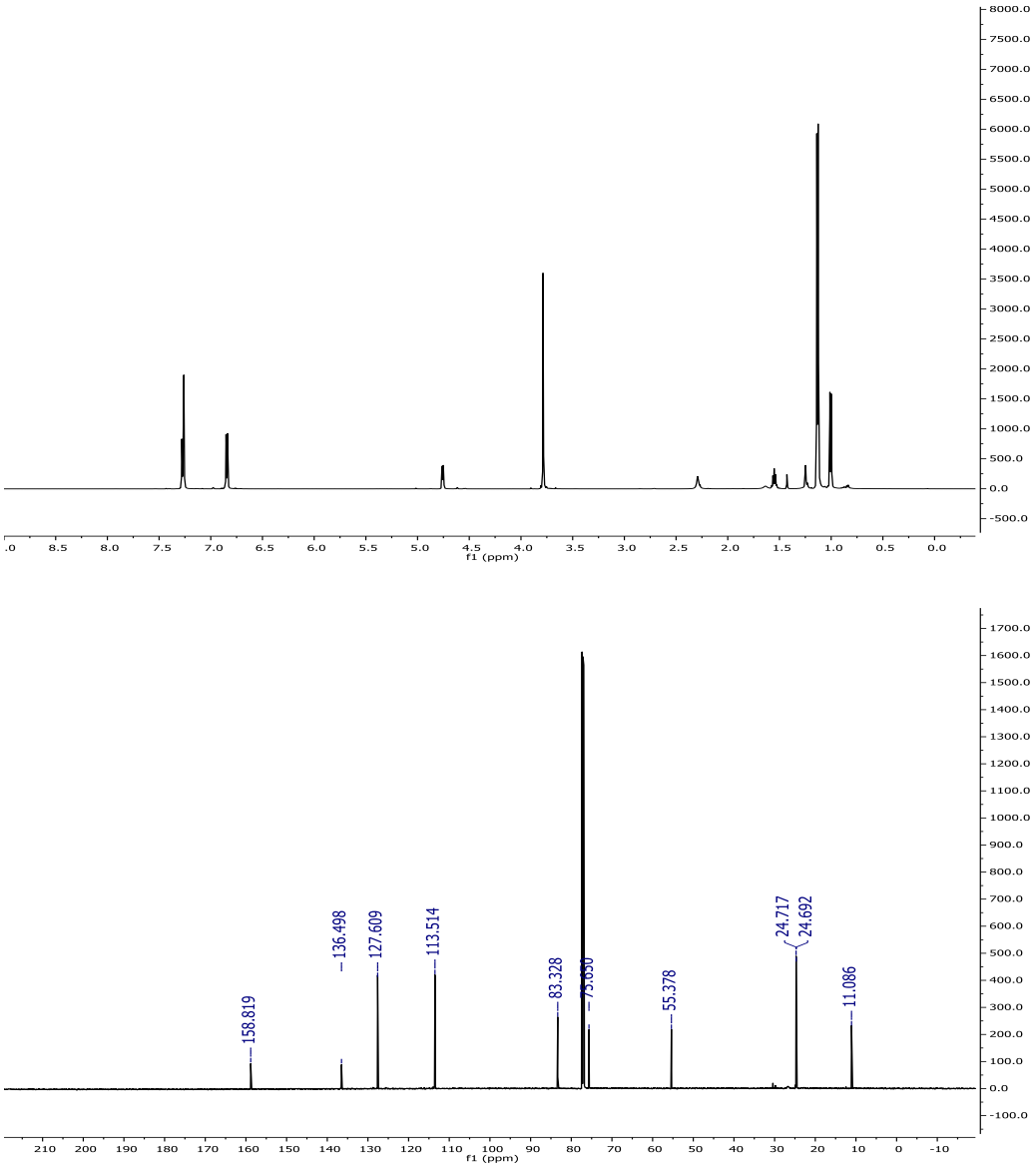
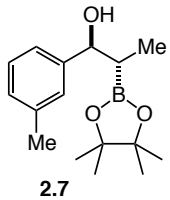


Figure 2.12. ^{1}H and ^{13}C{^{1}H} NMR spectra of 2.6.

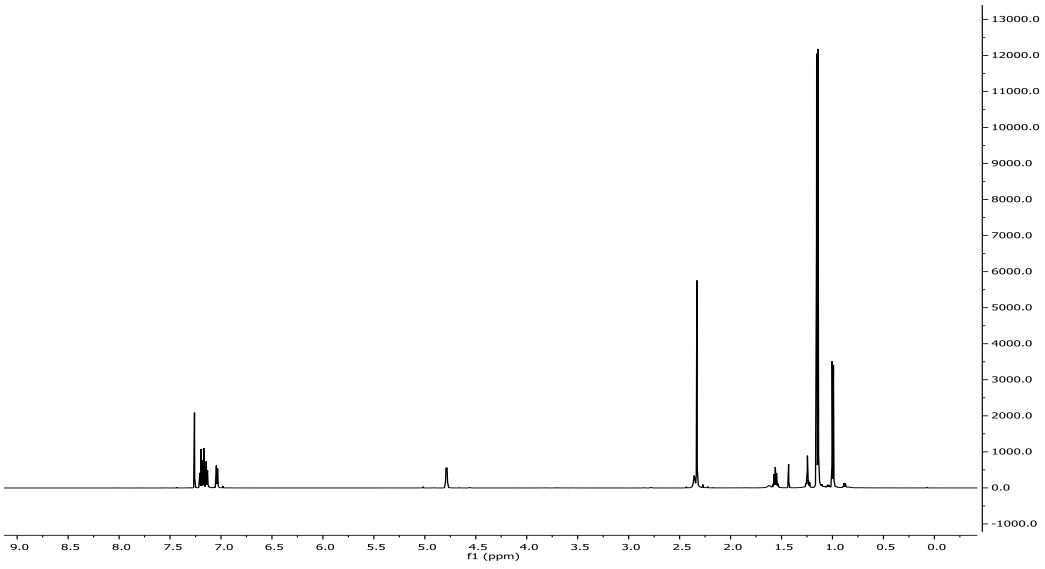


2.7

2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(m-tolyl)propan-1-ol (2.7).

Following general procedure A, the crude reaction mixture was purified by silica gel (NaOAc deactivated silica gel, 10:1 to 2:1 pentane:diethyl ether, Seebach Stain) to yield the

hydroxyboronate as a colorless oil in 75% yield (20.7 mg) in 97:3 anti:syn diastereomeric ratio. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.20 (t, *J* = 7.5 Hz, 1H), 7.17 (s, 1H), 7.15 – 7.12 (m, 1H), 7.04 (d, *J* = 7.3 Hz, 1H), 4.79 (d, *J* = 6.7 Hz, 1H), 2.35 (s, 1H), 2.33 (s, 3H), 1.56 (quint, *J* = 7.3 Hz, 1H), 1.16 (s, 6H), 1.14 (s, 6H), 1.00 (d, *J* = 7.4 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 144.1, 137.6, 128.1, 127.9, 127.1, 123.5, 83.4, 76.0, 24.7, 21.6, 10.9. **IR** (ν/cm^{-1}): 3487 (s, br), 2978(s), 2929 (m), 2874 (w), 1457 (m), 1380 (s), 1319 (m), 1145 (s), 1006 (m). **HRMS** (ESI^+) $[M+Na]^+$ calcd for $C_{16}H_{25}BO_3Na^+$ 299.1795, found: 299.1788.



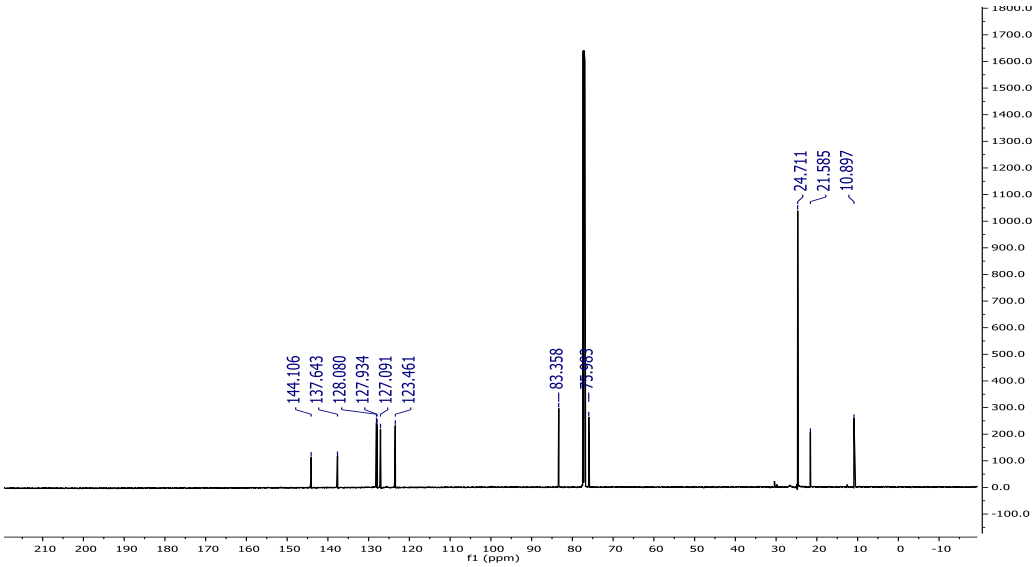
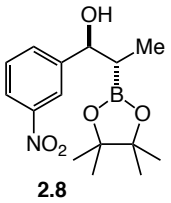


Figure 2.13. ^{1}H and ^{13}C{^{1}H} NMR spectra of 2.7.



2.8

1-(3-nitrophenyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-ol (2.8). Following general procedure A, the crude reaction mixture was purified by silica gel chromatography (NaOAc deactivated silica gel, 10:1 to 2:1 pentane:diethyl ether, Seebach Stain) to yield the hydroxyboronate as a colorless oil in 36% yield (11.1 mg) in 99:1 anti:syn diastereomeric ratio. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.28 (t, *J* = 2.0 Hz, 1H), 8.13 (ddd, *J* = 8.2, 2.3, 1.0 Hz, 1H), 7.75 – 7.68 (m, 1H), 7.51 (t, *J* = 7.9 Hz, 1H), 5.02 (d, *J* = 5.6 Hz, 1H), 2.77 (s, 1H), 1.60 (qd, *J* = 7.5, 5.6 Hz, 1H), 1.23 (s, 12H), 0.95 (d, *J* = 7.5 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 148.2, 146.3, 132.6, 129.0, 122.1, 121.4, 83.8, 74.6, 24.8, 24.8, 10.0. **IR** (ν/cm^{-1}): 3567 (br, s), 2979 (s), 2930 (m), 2877 (w), 1698 (m), 1558 (m), 1540 (s), 1457 (m), 1351 (s), 1318 (m), 1142 (m), 1018 (w). **HRMS** (ESI^{+}) $[M+H]^{+}$ calcd for $C_{15}H_{22}BNO_5^{+}$ 306.1513, found: 306.1519.

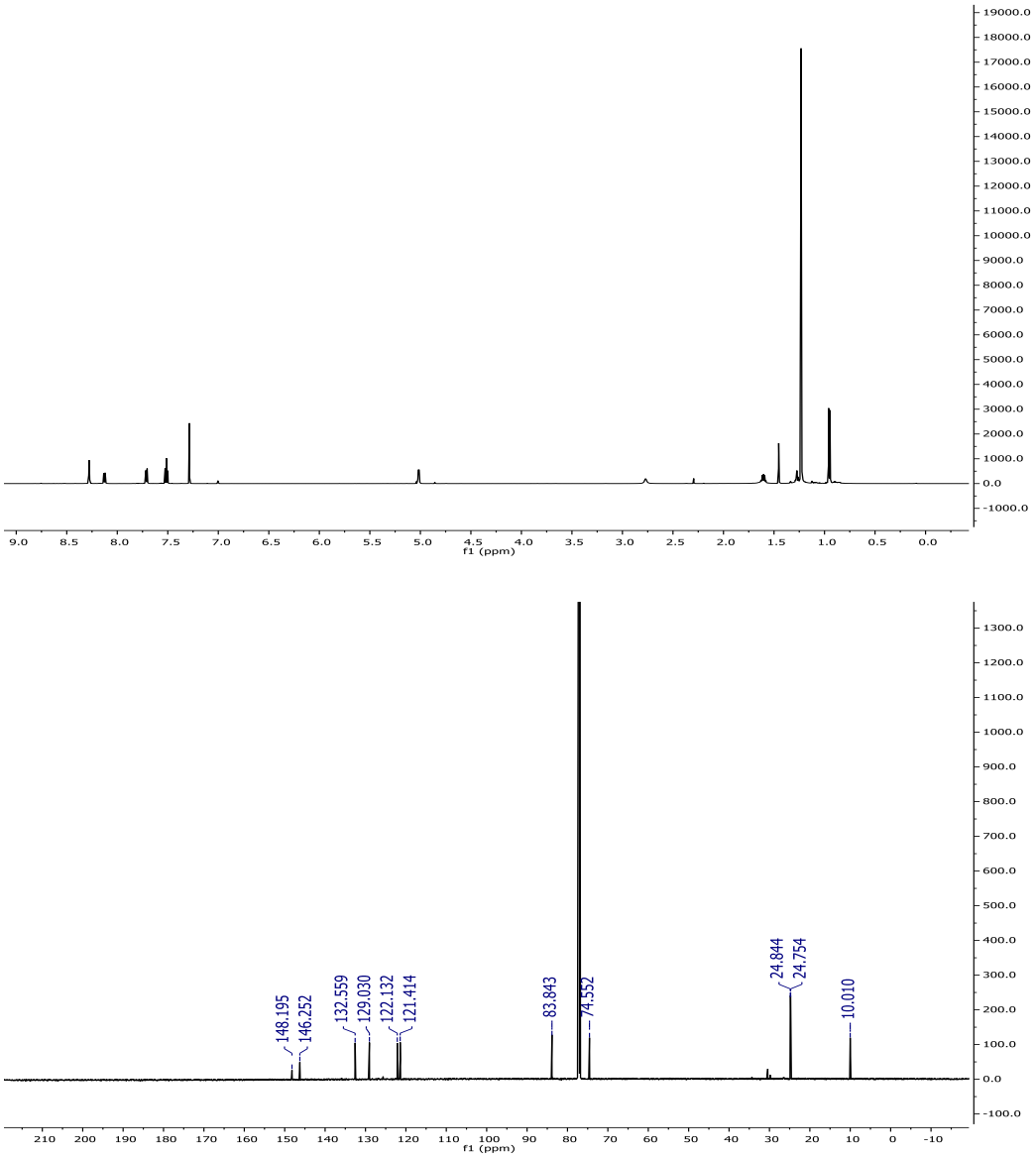
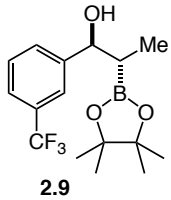


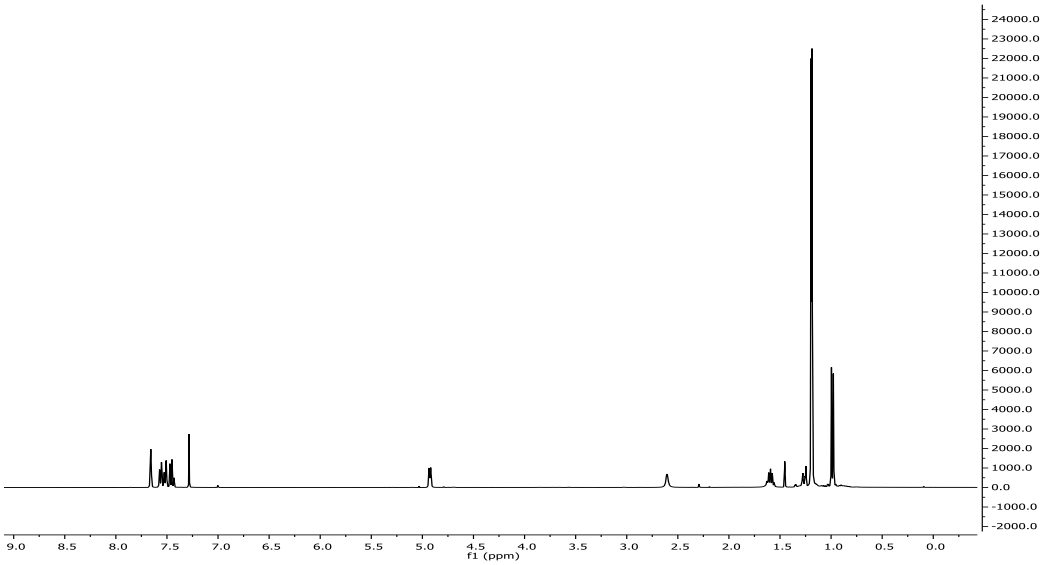
Figure 2.14. ^{1}H and ^{13}C{^{1}H} NMR spectra of 2.8.



2.9

2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(3-(trifluoromethyl)phenyl) propan-1-ol (2.9). Following general procedure A, the crude reaction mixture was purified by silica gel chromatography (NaOAc deactivated silica gel, 10:1 to 2:1 pentane:diethyl

ether, Seebach Stain) to yield the hydroxyboronate as a colorless oil in 52% yield (17.2 mg) in 98:2 anti:syn diastereomeric ratio. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.52 (d, *J* = 7.7 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 1H), 4.93 (d, *J* = 6.3 Hz, 1H), 2.61 (s, 1H), 1.59 (quint, *J* = 7.1 Hz, 1H), 1.20 (s, 6H), 1.19 (s, 6H), 0.99 (d, *J* = 7.4 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.0, 130.5, 130.1, 129.7, 128.5, 125.6, 123.9, 123.9, 123.2, 123.2, 122.9, 83.5, 75.1, 24.6, 10.4. **IR** (ν/cm^{-1}): 3459 (br, s), 2980 (s), 2934 (w), 2879 (w), 1451 (m), 1382 (m), 1329 (s), 1165 (s), 1144 (m), 1126 (s), 1073 (m), 1019 (m). **HRMS** (ESI^{+}) $[M+Na]^{+}$ calcd for $C_{16}H_{22}BF_3O_3Na^{+}$ 353.1512, found: 353.1509.



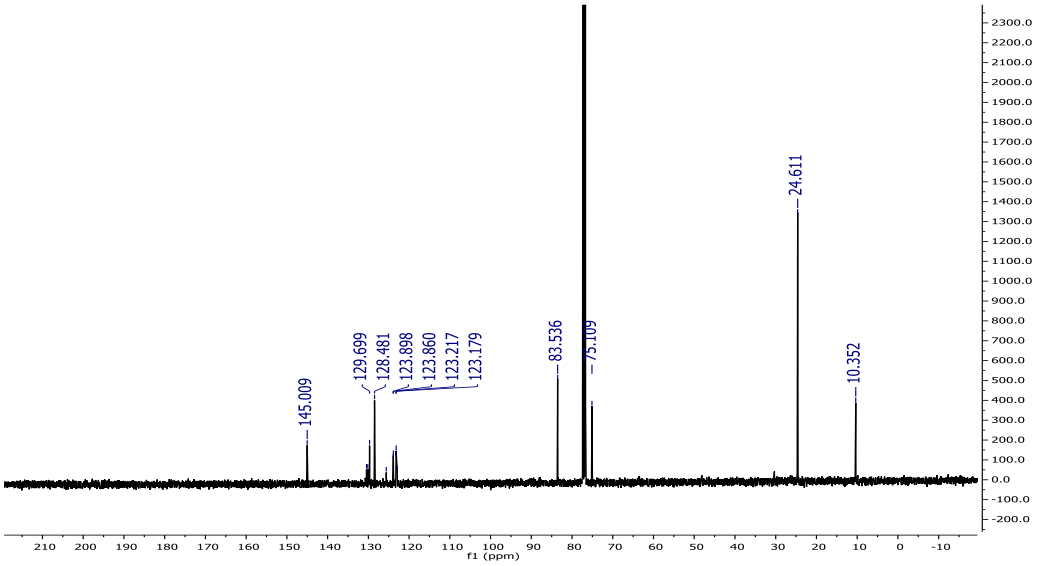
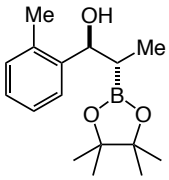


Figure 2.15. ^{1}H and ^{13}C{^{1}H} NMR spectra of 2.9.



2.10

2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(o-tolyl)propan-1-ol (2.10).

Following general procedure A, the crude reaction mixture was purified by silica gel chromatography (NaOAc deactivated silica gel, 10:1 to 2:1 pentane:diethyl ether, Seebach Stain) to yield the hydroxyboronate as a colorless oil in 69% yield (19.0 mg) in >99:1 anti:syn diastereomeric ratio. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.21 (td, *J* = 7.4, 1.6 Hz, 1H), 7.16 (td, *J* = 7.3, 1.4 Hz, 1H), 7.14 – 7.11 (m, 1H), 5.08 (d, *J* = 6.8 Hz, 1H), 2.40 (s, 3H), 1.67 – 1.60 (m, 1H), 1.15 (s, 6H), 1.13 (s, 6H), 1.06 (d, *J* = 7.3 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 142.0, 134.9, 130.4, 127.1, 126.4, 125.9, 83.3, 72.0, 24.7, 24.6, 19.4, 10.9. **IR** (ν/cm^{-1}): 3482 (br, s), 2978 (s), 2931 (m), 2874 (w), 1459 (m), 1380 (s), 1319 (s), 1145 (s), 1008 (m). **HRMS** (ESI^{+}) $[M+Na]^{+}$ calcd for $C_{16}H_{25}BO_3Na^{+}$ 299.1795, found: 299.1788.

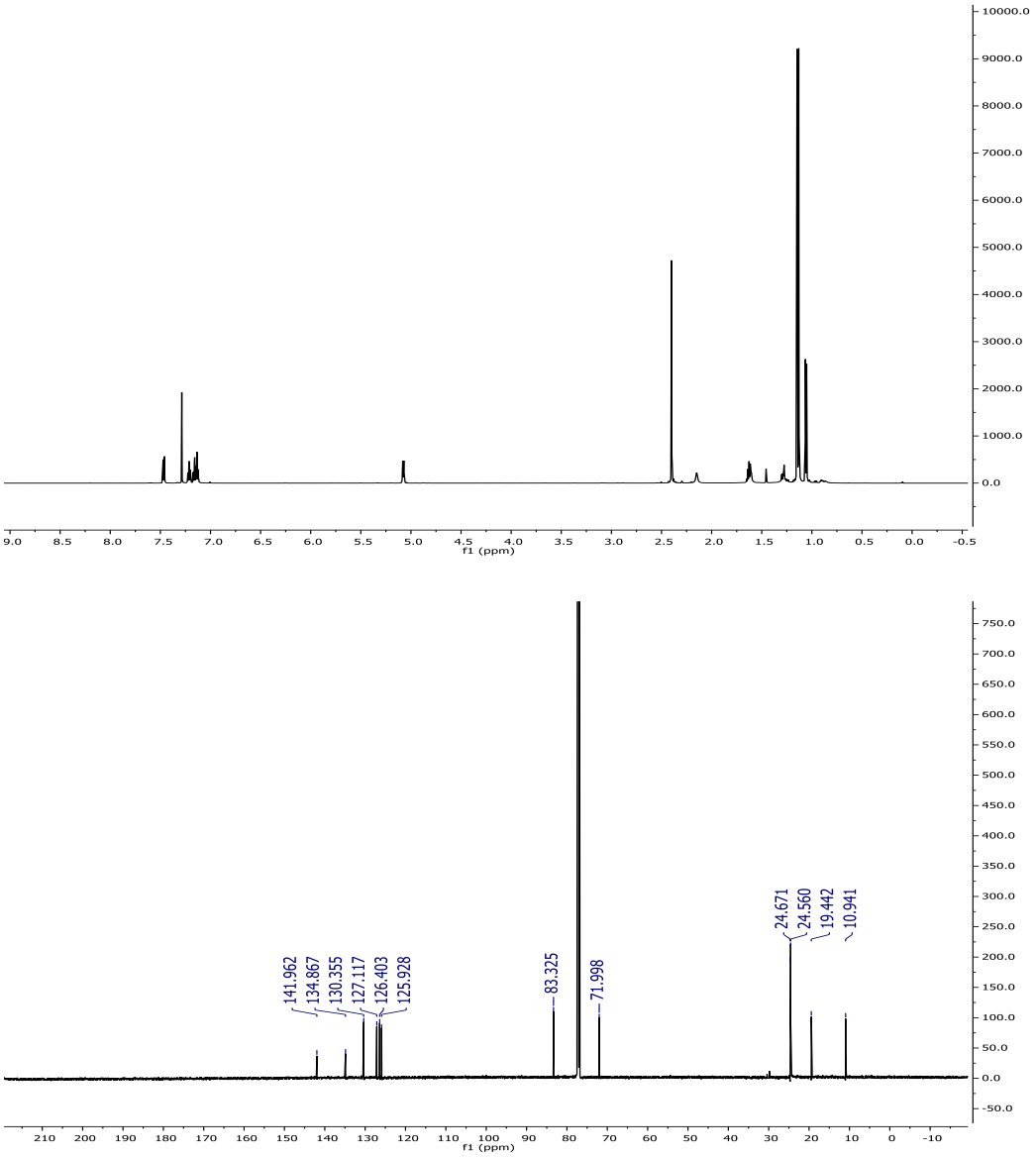
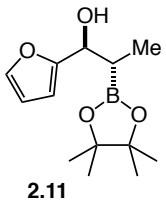


Figure 2.16. ^{1}H and ^{13}C{^{1}H} NMR spectra of 2.10.

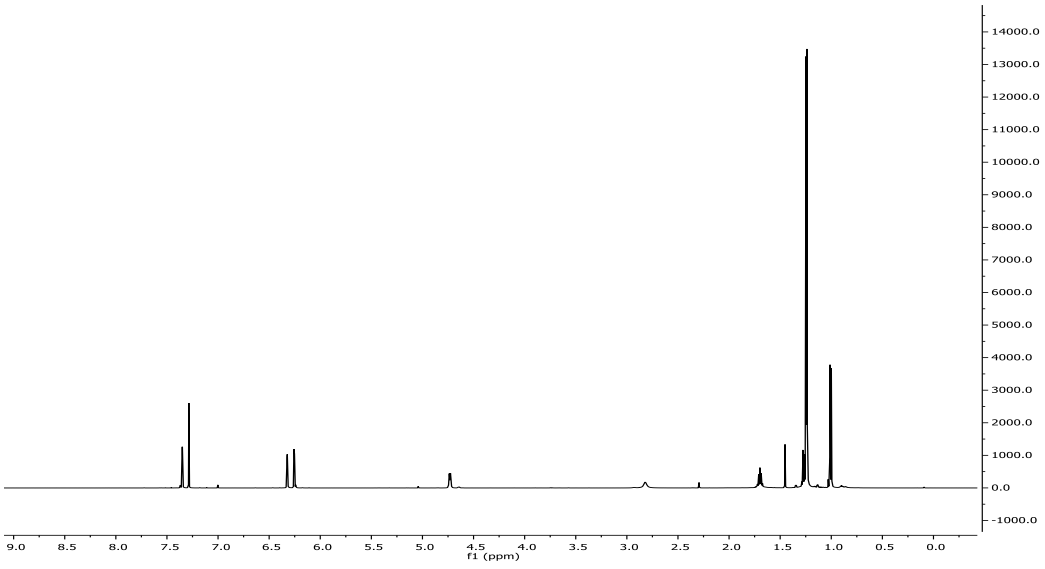


2.11

1-(furan-2-yl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-ol (2.11).

Following general procedure A, the crude reaction mixture was purified by silica gel (NaOAc deactivated silica gel, 10:1 to 2:1 pentane:diethyl ether, Seebach Stain) to yield the

hydroxyboronate as a yellow oil in 71% yield (17.8 mg) in 94:6 anti:syn diastereomeric ratio. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.35 (dd, *J* = 1.9, 0.8 Hz, 1H), 6.32 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.25 (dt, *J* = 3.2, 0.7 Hz, 1H), 4.73 (d, *J* = 7.1 Hz, 1H), 2.82 (s, 1H), 1.70 (quint, *J* = 7.4 Hz, 1H), 1.25 (s, 6H), 1.24 (s, 6H), 1.01 (d, *J* = 7.5 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 156.6, 141.4, 110.0, 106.4, 83.5, 70.1, 24.7, 24.6, 11.3. **IR** (ν/cm^{-1}): 3469 (s, br), 2979 (s), 2932 (m), 2878 (w), 1458 (m), 1381 (s), 1322 (m), 1145 (s), 1009 (m). **HRMS** (ESI^+) $[M+Na]^+$ calcd for $C_{13}H_{21}BO_4Na^+$ 275.1431, found: 275.1427.



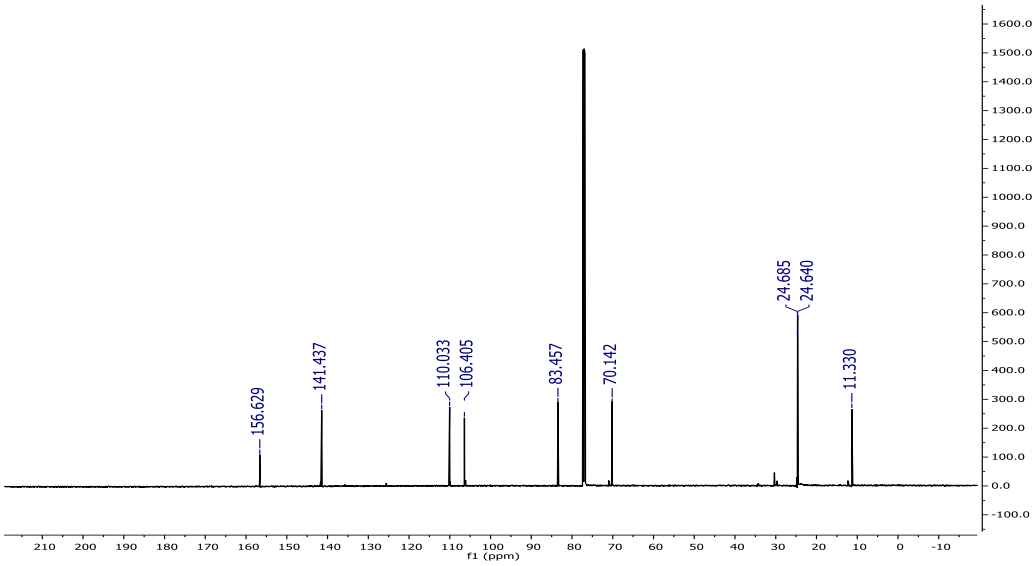
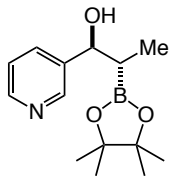


Figure 2.17. ^{1}H and ^{13}C{^{1}H} NMR spectra of 2.11.



2.12

1-(pyridin-3-yl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-ol

(2.12). Following general procedure A, the crude reaction mixture was purified by silica gel chromatography (NaOAc deactivated silica gel, 10:1 to 2:1 pentane:diethyl ether, Seebach Stain) to yield the hydroxyboronate as a colorless oil in 45% yield (11.8 mg) in 99:1 anti:syn diastereomeric ratio. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.59 (d, *J* = 2.2 Hz, 1H), 8.50 (dd, *J* = 4.8, 1.7 Hz, 1H), 7.73 (dt, *J* = 7.9, 2.0 Hz, 1H), 7.27 (dd, *J* = 4.8, 0.8 Hz, 1H), 4.93 (d, *J* = 6.3 Hz, 1H), 2.74 (s, 1H), 1.67 – 1.53 (m, 1H), 1.20 (s, 6H), 1.19 (s, 6H), 1.00 (d, *J* = 7.4 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 148.5, 148.2, 139.3, 134.1, 123.2, 83.7, 73.5, 24.8, 24.7, 10.4. **IR** (v/cm^{-1}): 3433 (s), 2359 (s), 2085 (w), 1643 (m), 1378 (w), 1320 (w), 1142 (m). **HRMS** (ESI)$^{+}$ $[M+H]^{+}$ calcd for $C_{14}H_{23}BNO_3^{+}$ 264.1772, found: 264.1761.

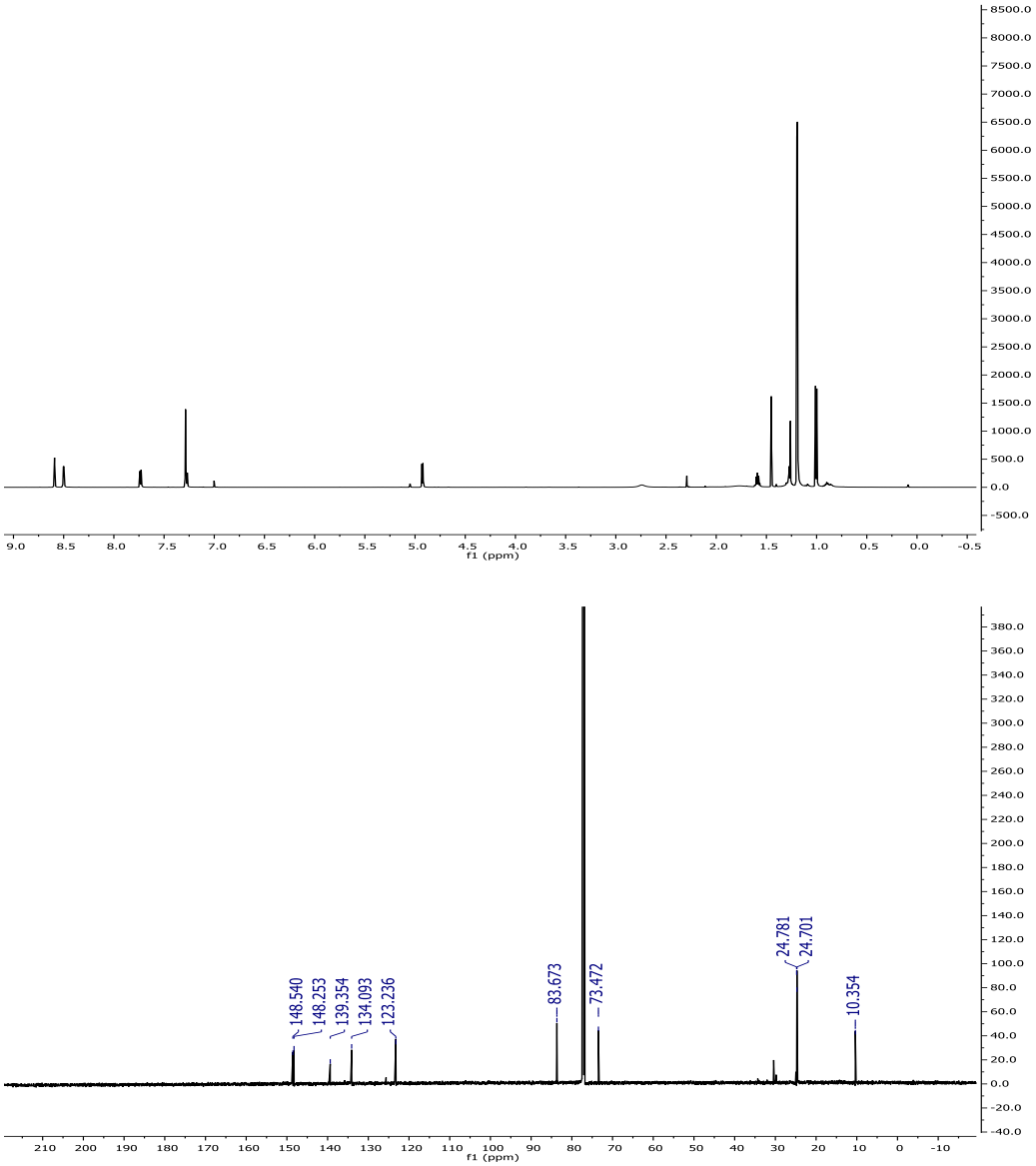
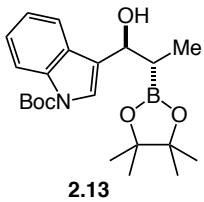


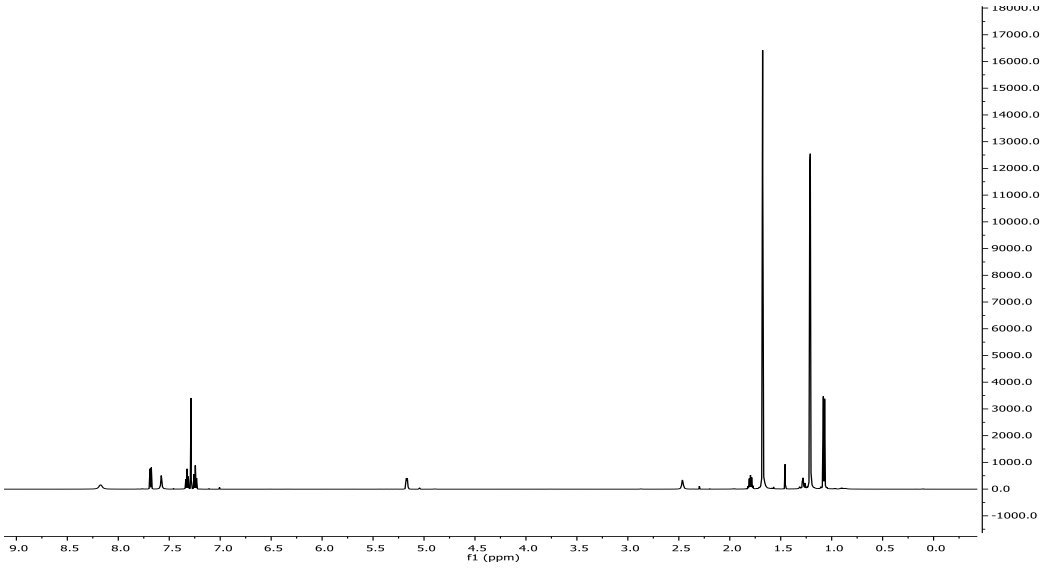
Figure 2.18. ^{1}H and ^{13}C{^{1}H} NMR spectra of 2.12.



2.13

***tert*-butyl 3-(*anti*-1-hydroxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl)-1*H*-indole-1-carboxylate (2.13).** Following general procedure A, the crude reaction mixture was purified by silica gel chromatography (NaOAc deactivated silica gel,

10:1 to 2:1 pentane:diethyl ether, Seebach Stain) to yield the hydroxyboronate as a colorless oil in 77% yield (30.9 mg) in >99:1 anti:syn diastereomeric ratio. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.25 – 8.09 (m, 1H), 7.68 (dt, *J* = 7.8, 0.9 Hz, 1H), 7.58 (s, 1H), 7.33 (ddd, *J* = 8.4, 7.2, 1.2 Hz, 1H), 7.24 (ddd, *J* = 8.0, 7.3, 1.0 Hz, 1H), 5.17 (dd, *J* = 6.4, 2.3 Hz, 1H), 2.46 (d, *J* = 4.5 Hz, 1H), 1.85 – 1.75 (m, 1H), 1.68 (s, 9H), 1.21 (s, 6H), 1.21 (s, 6H), 1.08 (d, *J* = 7.5 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 149.8, 135.8, 129.1, 125.6, 124.4, 123.7, 122.8, 122.5, 120.0, 115.3, 83.5, 69.4, 28.3, 24.8, 24.7, 10.8. **IR (ν/cm^{-1}):** 3502 (s, br), 2978 (s), 2932 (m), 2877 (w), 1733 (s), 1455 (s), 1372 (s), 1321 (m), 1255 (m), 1159 (s), 1081 (m), 1011 (m). **HRMS** (ESI^+) $[M+Na]^+$ calcd for $C_{22}H_{32}BNO_5Na^+$ 424.2271, found: 424.2272.



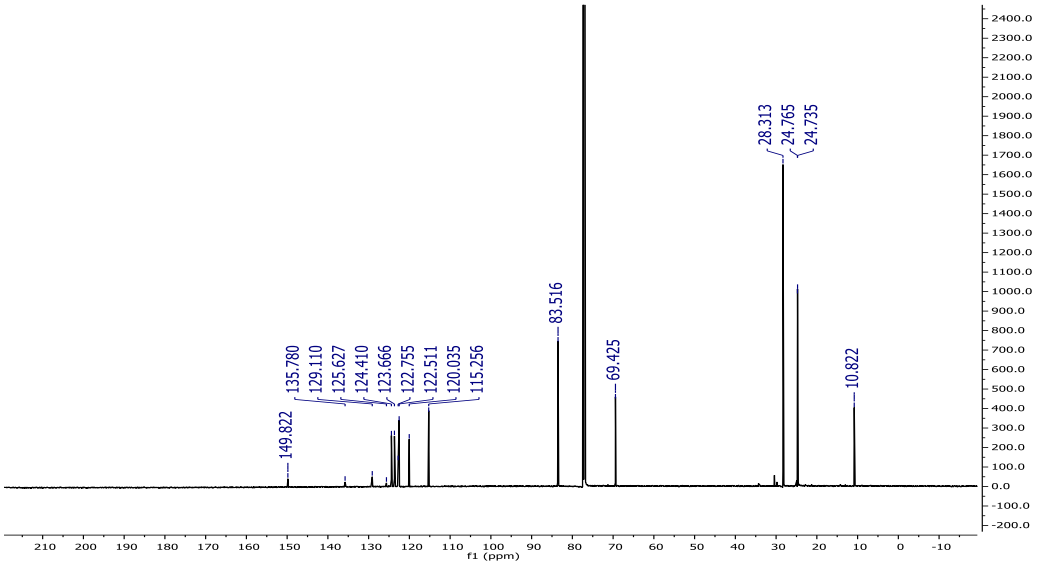
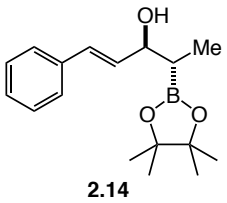


Figure 2.19. ^{1}H and ^{13}C{^{1}H} NMR spectra of 2.13.



2.14

***(E)*-1-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-1-en-3-ol (2.14).**

Following general procedure A, the crude reaction mixture was purified by silica gel chromatography (NaOAc deactivated silica gel, 10:1 to 2:1 pentane:diethyl ether, Seebach Stain) to yield the hydroxyboronate as a yellow oil in 65% yield (18.7 mg) in 88:12 anti:syn diastereomeric ratio. ***anti*-diastereomer: ^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.42 – 7.37 (m, 2H), 7.35 – 7.31 (m, 2H), 7.27 – 7.22 (m, 1H), 6.61 (dd, J = 15.9, 1.2 Hz, 1H), 6.28 (dd, J = 15.9, 6.5 Hz, 1H), 4.41 – 4.33 (m, 1H), 2.39 (s, 1H), 1.53 – 1.46 (m, 1H), 1.25 (s, 12H), 1.07 (d, J = 7.5 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 137.0, 131.7, 130.3, 128.5 127.4, 126.4, 83.4, 75.0, 24.8, 24.7, 11.0. ***syn*-diastereomer: ^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.43 – 7.36 (m, 2H), 7.36 – 7.30 (m, 2H), 7.27 – 7.22 (m, 1H), 6.59 (dd, J = 15.0, 1.2 Hz, 1H), 6.25 (dd, J = 17.2, 6.5 Hz, 1H), 4.27 (m, 1H), 2.55 (s, 1H), 1.41 (quint, J = 7.4 Hz, 1H), 1.28 (s, 6H),

1.27 (s, 6H), 1.07 (d, J = 8.0 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 137.0, 132.5, 131.7, 130.2, 127.4, 126.4, 83.5, 75.8, 24.9, 24.7, 12.1. **IR** (ν/cm^{-1}): 3446 (s, br), 3026 (w), 2978 (s), 2931 (m), 2875 (w), 1457 (m), 1380 (s), 1320 (m), 1144 (s), 1006 (m). **HRMS** (ESI$^+$) $[M+Na]^+$ calcd for $C_{17}H_{25}BO_3Na^+$ 311.1795, found: 311.1788.

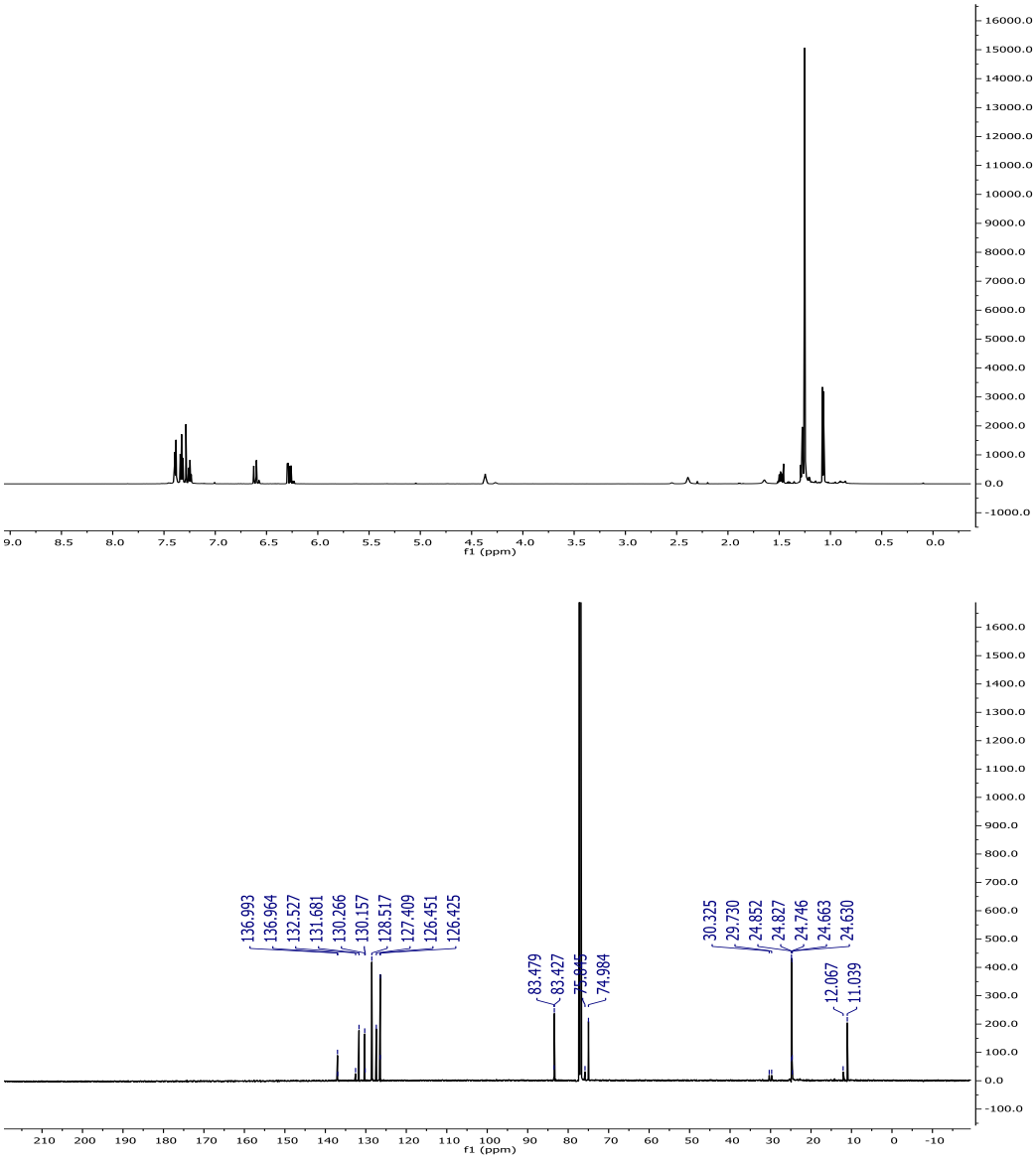
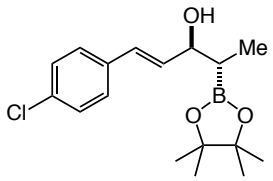


Figure 2.20. ^{1}H and ^{13}C{^{1}H} NMR spectra of 2.14.



2.15

(*E*)-1-(4-chlorophenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-1-en-3-ol (2.15). Following general procedure A, the crude reaction mixture was purified by silica gel chromatography (NaOAc deactivated silica gel, 10:1 to 2:1 pentane:diethyl ether, Seebach Stain) to yield the hydroxyboronate as a colorless oil in 40% yield (12.9 mg) in 88:12 anti:syn diastereomeric ratio. ***anti* diastereomer**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.31 – 7.25 (m, 5H), 6.54 (dd, *J* = 15.9, 1.3 Hz, 1H), 6.23 (dd, *J* = 15.8, 6.4 Hz, 1H), 4.39 – 4.28 (m, 1H), 2.36 (s, 1H), 1.48 – 1.43 (m, 1H), 1.22 (s, 6H), 1.22 (s, 6H), 1.04 (d, *J* = 7.5 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 135.5, 133.0, 132.4, 129.0, 128.7, 127.6, 83.5, 74.8, 24.8, 24.7, 11.0. ***syn*-diastereomer: ^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 5H), 6.56 – 6.51 (m, 1H), 6.25 – 6.20 (m, 1H), 4.25 (t, *J* = 6.5 Hz, 1H), 2.57 (s, 1H), 1.43 – 1.36 (m, 1H), 1.27 (s, 6H), 1.26 (s, 6H), 1.06 (d, *J* = 7.5 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 133.2, 129.2, 128.8, 128.8, 127.6, 125.5, 83.5, 75.7, 24.8, 24.7, 12.1. **IR** (v/cm^{-1}): 3433 (s), 2385 (m), 2083 (s), 1642 (m), 1490 (w), 1378 (m), 1320 (m), 1140 (w). **HRMS** (ESI^+) $[M+Na]^+$ calcd for $C_{17}H_{24}BClO_3Na$ 345.1405, found: 345.1394.

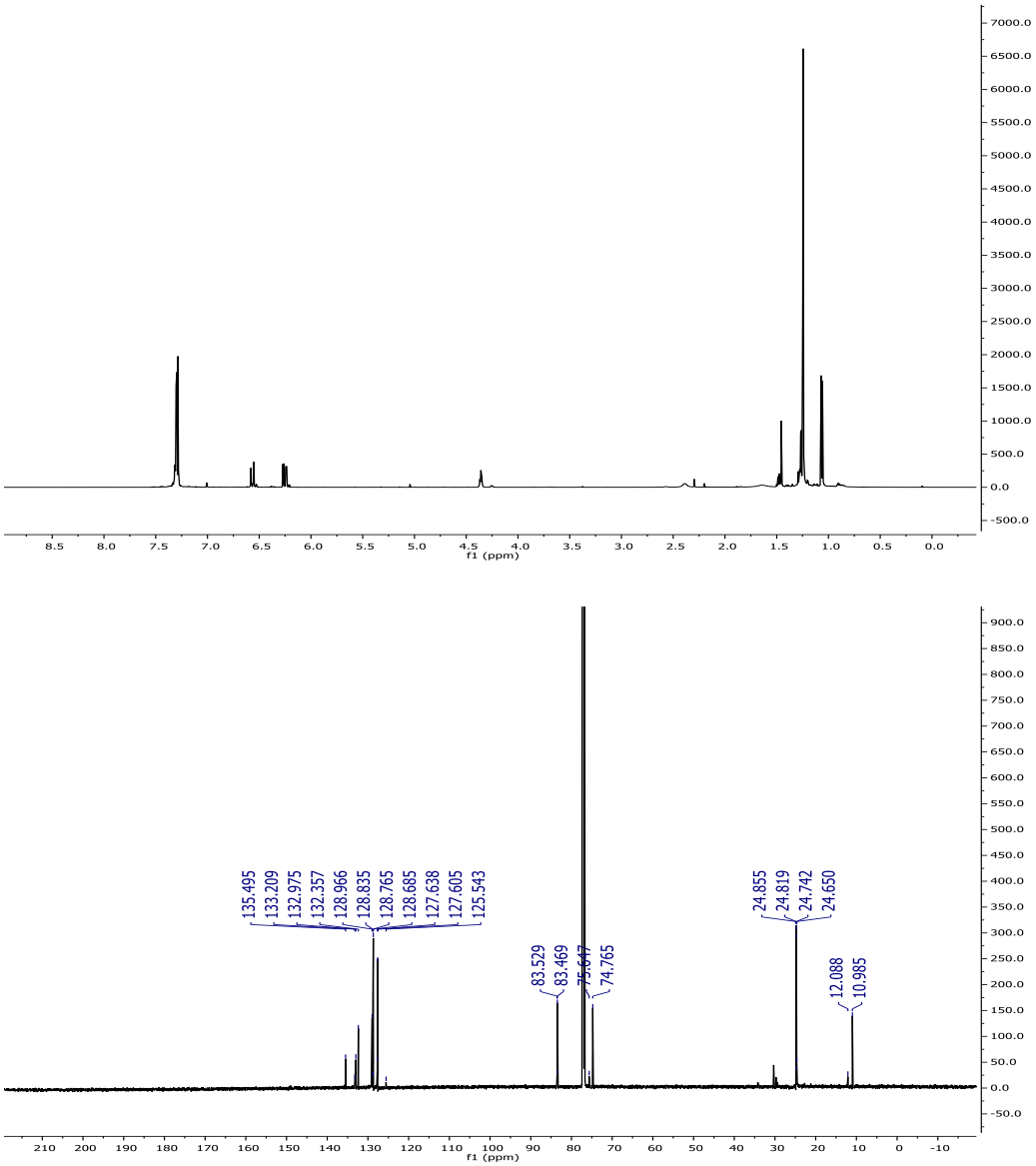
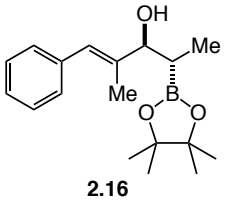


Figure 2.21. ^{1}H and ^{13}C{^{1}H} NMR spectra of 2.15.

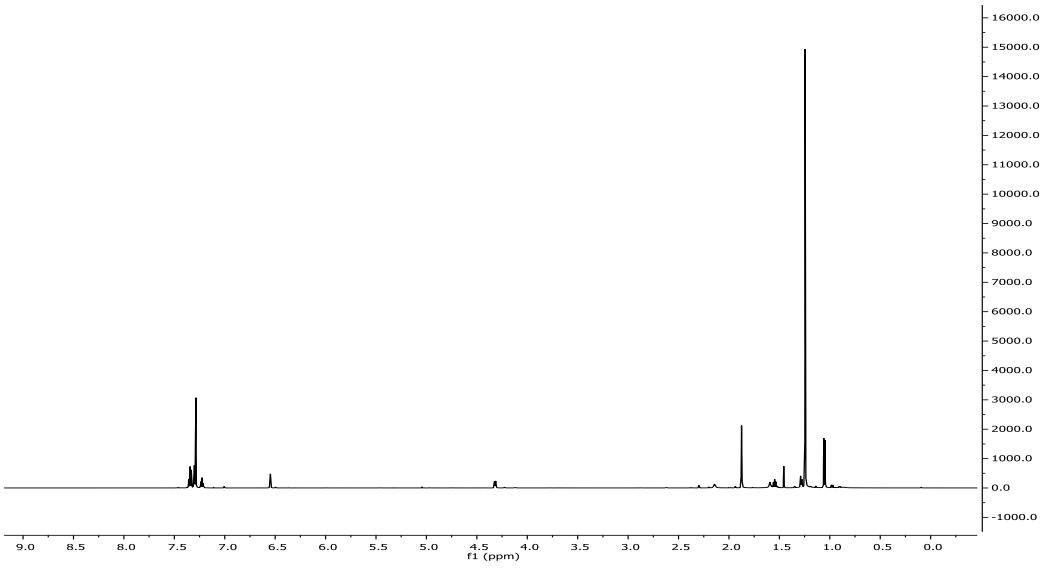


2.16

***(E)*-1-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-1-en-3-ol (2.16).**

Following general procedure A, the crude reaction mixture was purified by silica gel chromatography (NaOAc deactivated silica gel, 10:1 to 2:1 pentane:diethyl ether, Seebach

Stain) to yield the hydroxyboronate as a colorless oil in 64% yield (18.5 mg) in 93:7 anti:syn diastereomeric ratio. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.38 – 7.32 (m, 2H), 7.29 (d, *J* = 8.8 Hz, 2H), 7.23 (td, *J* = 7.2, 1.5 Hz, 1H), 6.55 (s, 1H), 4.32 (d, *J* = 7.0 Hz, 1H), 2.14 (s, 1H), 1.88 (s, 3H), 1.55 (m, 1H), 1.24 (s, 12H), 1.05 (d, *J* = 7.4 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 139.8, 137.9, 129.1, 128.1, 126.3, 125.6, 83.4, 79.1, 24.9, 24.8, 14.2, 10.5. **IR** (ν/cm^{-1}): 3429 (s), 2568 (m), 2082 (m), 1643 (s), 1143 (m). **HRMS** (ESI^+) $[M+Na]^+$ calcd for $C_{18}H_{27}BO_3Na^+$ 325.1943, found: 325.1940.



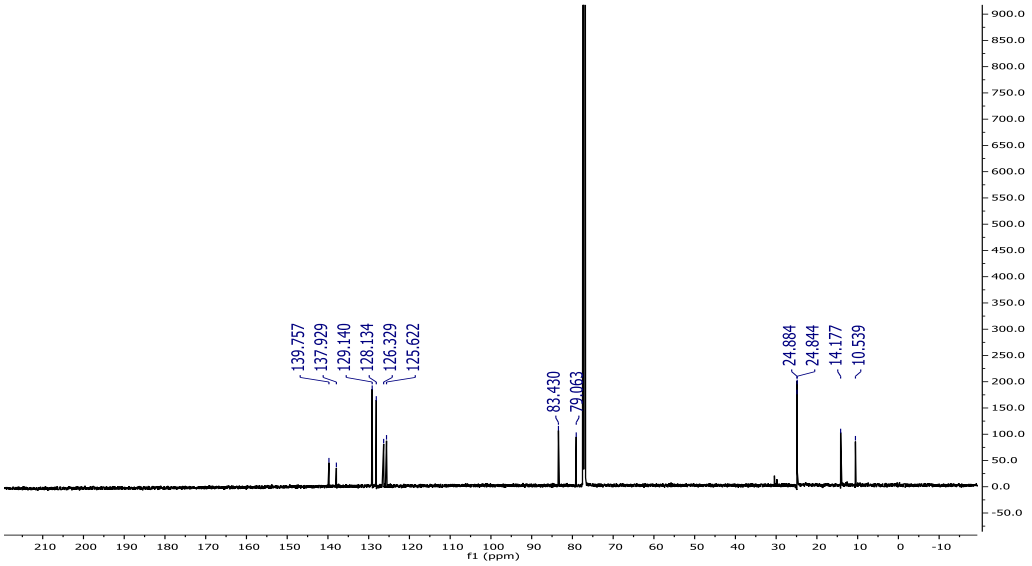
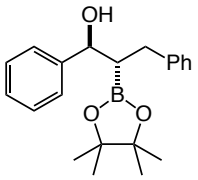


Figure 2.22. ^{1}H and ^{13}C{^{1}H} NMR spectra of 2.16.

2.8.3 Preparation of *anti*-1,2-hydroxyboronates from substituted 1,1-diboronates



2.17

1,3-diphenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-ol (2.17).

Following general procedure B, the crude reaction mixture was purified by silica gel chromatography (NaOAc deactivated silica gel, 10:1 to 5:1 pentane:diethyl ether, Seebach Stain) to yield the hydroxyboronate as a colorless oil in 76% yield (25.7 mg) in 92:8 anti:syn diastereomeric ratio. ***anti* diastereomer**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.43 – 7.38 (m, 1H), 7.35 (m, 1H), 7.34 – 7.29 (m, 2H), 7.27 – 7.17 (m, 5H), 7.17 – 7.10 (m, 1H), 4.83 (dd, *J* = 8.1, 3.6 Hz, 1H), 3.06 (dd, *J* = 13.6, 5.6 Hz, 1H), 2.81 – 2.68 (m, 1H), 2.24 (d, *J* = 3.7 Hz, 1H), 2.02 (ddd, *J* = 11.1, 8.0, 5.7 Hz, 1H), 0.90 (s, 6H), 0.89 (s, 6H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 143.9, 141.7, 129.1, 128.4, 128.3, 126.8, 126.0, 125.9, 83.4, 76.0, 34.5, 24.7, 24.7. ***syn*-diastereomer**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.43 – 7.38 (m, 1H), 7.35 (m, 1H), 7.34 –

7.29 (m, 2H), 7.27 – 7.17 (m, 5H), 7.17 – 7.10 (m, 1H), 4.70 (t, J = 6.7 Hz, 1H), 2.81 – 2.68 (m, 2H), 2.62 (d, J = 7.2 Hz, 1H), 1.99 – 1.91 (m, 1H), 1.08 (s, 6H), 1.07 (s, 6H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 144.9, 141.3, 129.0, 128.4, 128.3, 127.8, 127.3, 126.0, 83.6, 75.1, 34.5, 24.9. 24.7. **IR** (ν/cm^{-1}): 3467 (s, br), 3061 (w), 3028 (m), 2979 (s), 2927 (m), 2865 (w), 1455 (m), 1380 (s), 1325 (m), 1247 (m), 1143 (s). **HRMS** (ES$^+$) $[M+Na]^+$ calcd for $C_{21}H_{27}BO_3Na^+$ 361.1951, found: 361.1949.

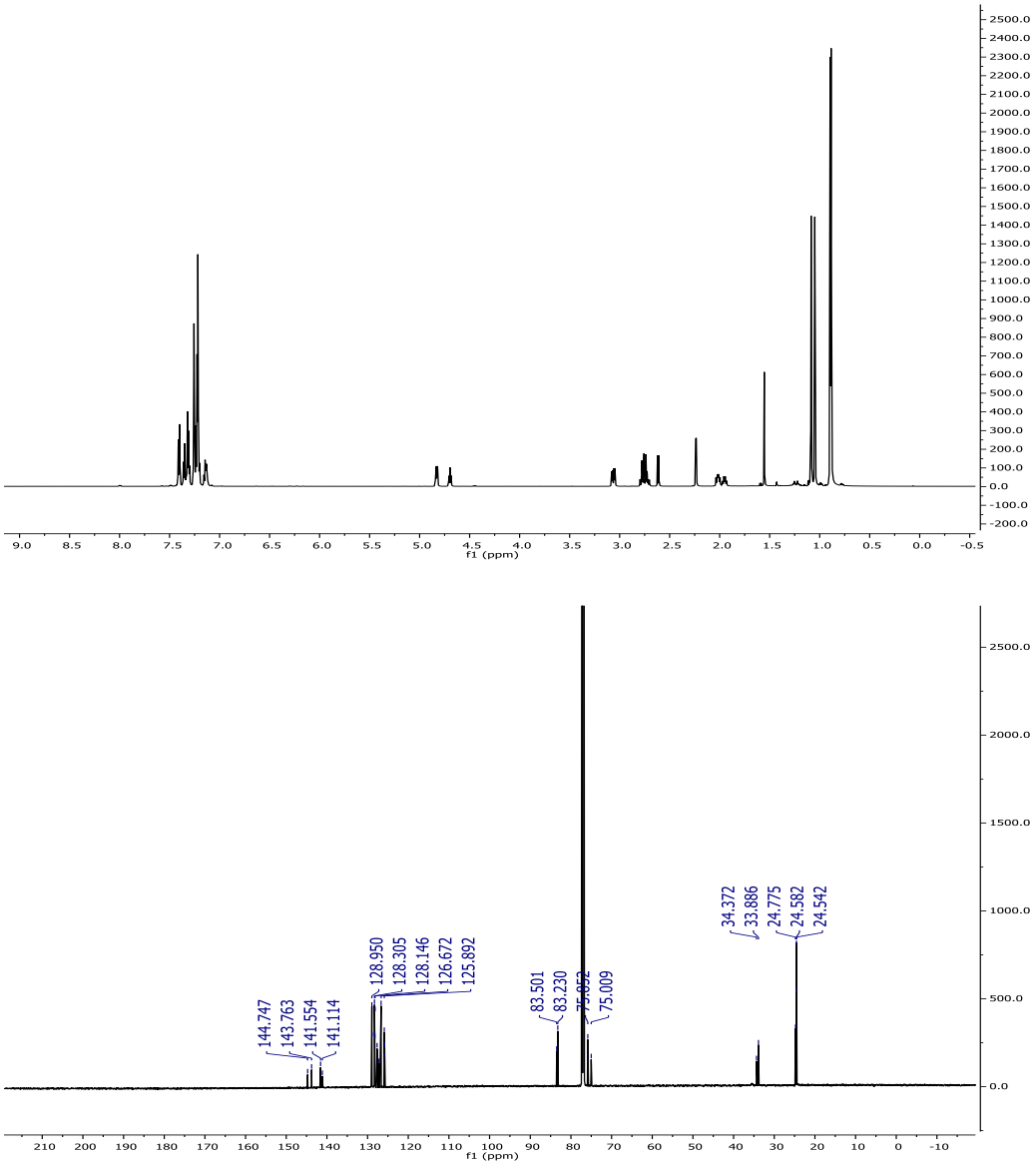
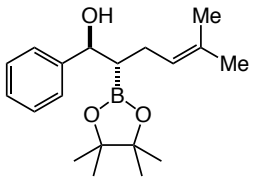


Figure 2.23. ^{1}H and ^{13}C{^{1}H} NMR spectra of 2.17.



2.18

5-methyl-1-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-4-en-1-ol (2.18). Following general procedure B, the crude reaction mixture was purified by silica gel chromatography (NaOAc deactivated silica gel, 10:1 to 5:1 pentane:diethyl ether, Seebach Stain) to yield the hydroxyboronate as a colorless oil in 74% yield (23.4 mg) in 98:2 anti:syn diastereomeric ratio. ***anti*-diastereomer: ^{1}H NMR** ($CDCl_3$, 600 MHz): δ 7.37 (d, J = 6.6 Hz, 2H), 7.30 (t, J = 7.8 Hz, 2H), 7.22 (tt, J = 7.2, 1.8 Hz, 1H), 5.17 (t, J = 7.5 Hz, 1H), 4.77 (d, J = 9.0 Hz, 1H), 2.33 (d, J = 4.2 Hz, 1H), 2.28-2.31 (m, 1H), 2.23-2.26 (m, 1H), 1.66 (s, 3H), 1.63-1.64 (m, 1H), 1.60 (s, 3H), 1.05 (s, 6H), 1.02 (s, 6H). **^{13}C NMR** ($CDCl_3$, 151 MHz): δ 144.1, 132.2, 128.3, 127.6, 126.8, 124.0, 83.3, 75.8, 26.5, 26.0, 24.7, 24.6, 18.0. ***syn*-diastereomer: ^{1}H NMR** ($CDCl_3$, 600 MHz): δ 7.34 (d, J = 7.2 Hz, 2H), 7.30 (t, J = 7.8 Hz, 2H), 7.22 (tt, J = 7.2, 1.8 Hz, 1H), 5.11 (t, J = 7.2 Hz, 1H), 4.70 (t, J = 6.6 Hz, 1H), 2.65 (d, J = 6.0 Hz, 1H), 2.11-2.16 (m, 1H), 2.00-2.04 (m, 1H), 1.65 (s, 3H), 1.58-1.59 (m, 1H), 1.55 (s, 3H), 1.19 (s, 12H). **^{13}C NMR** ($CDCl_3$, 151 MHz): δ 144.9, 132.3, 127.3, 126.2, 123.5, 83.5, 75.7, 27.1, 25.9, 25.0, 24.6, 18.0. **IR** (ν/cm^{-1}): 3478 (s, br, OH), 3061 (w), 3030 (w), 2978 (m), 2925 (m), 2857 (m), 1453 (w), 1410 (w), 1379 (s), 1323 (m), 1245 (m), 1213 (w), 1166 (w), 1144 (s), 1108 (w), 1052 (w), 1008 (w). **HRMS (ESI+)** $[2M+Na]^+$ calcd for $C_{38}H_{58}B_2NaO_6^+$ 655.4318, found: 655.4309.

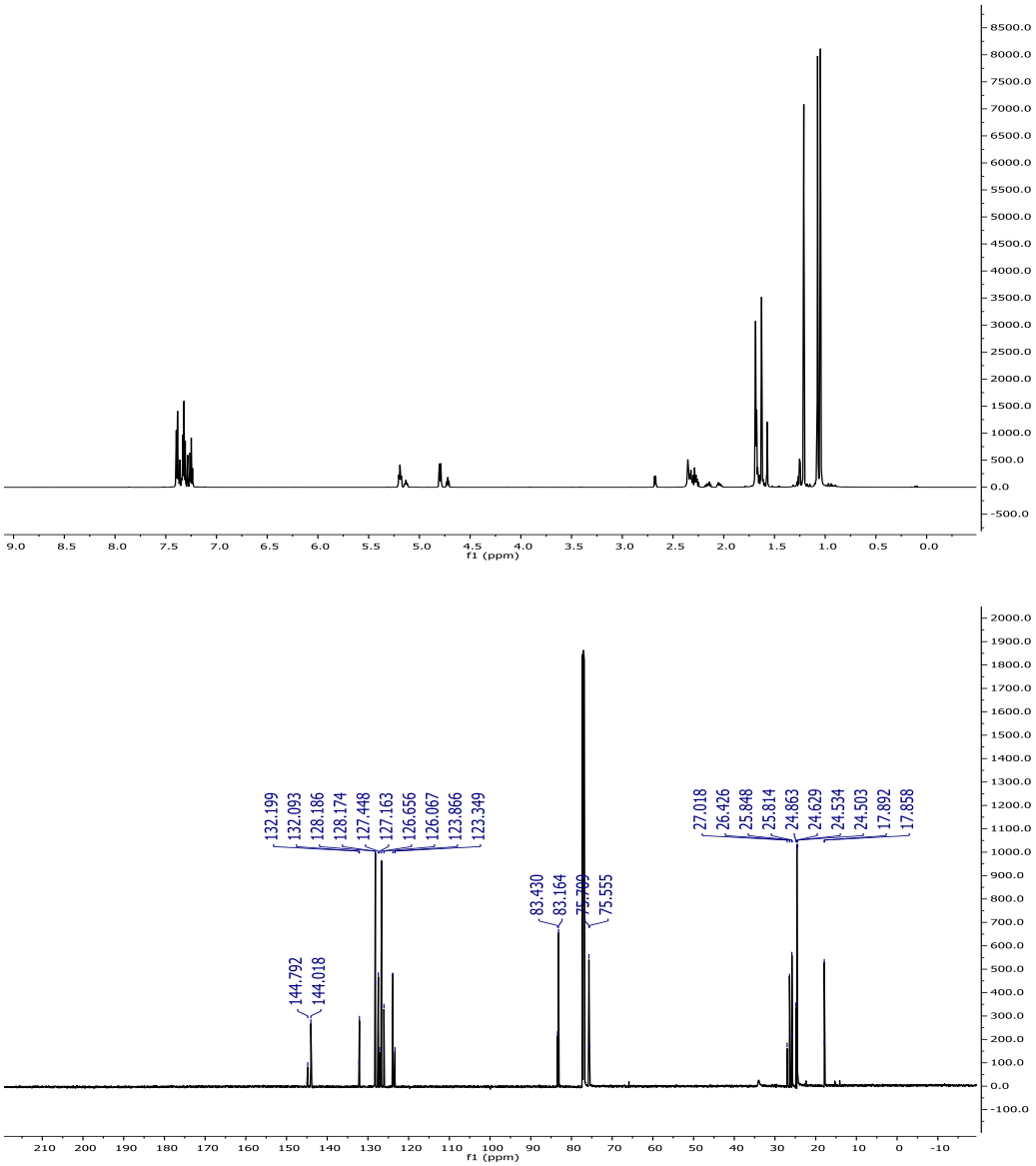
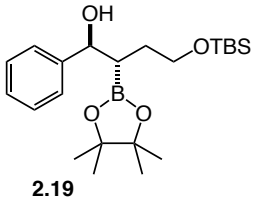


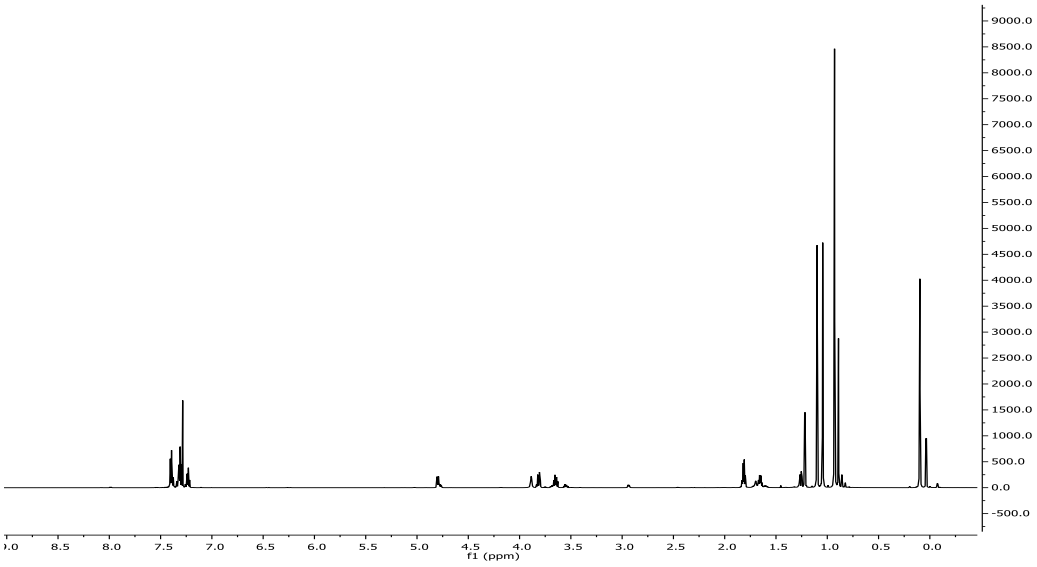
Figure 2.24. ^{1}H and ^{13}C{^{1}H} NMR spectra of 2.18.



2.19

4-((*tert*-butyldimethylsilyl)oxy)-1-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-1-ol (2.19). Following general procedure B, the crude reaction mixture was purified by silica gel chromatography (NaOAc deactivated silica gel, 10:1 to 5:1

pentane:diethyl ether, Seebach Stain) to yield the hydroxyboronate as a colorless oil in 77% yield (31.3 mg) in 94:6 anti:syn diastereomeric ratio. ***anti*-diastereomer: ^{1}H NMR** ($CDCl_3$, 600 MHz): δ 3.77 (dt, *J* = 10.2, 6.0 Hz, 1H), 3.57-3.61 (m, 1H), 3.48 (qu, *J* = 5.4 Hz, 1H), 2.77 (d, *J* = 6.6 Hz, 1H), 1.90 (m, 1H), 1.68-1.78 (m, 4H), 1.56-1.64 (m, 2H), 1.32-1.43 (m, 2H), 1.24 (s, 9H), 1.08-1.22 (m, 3H), 0.94-1.06 (m, 2H), 0.89 (s, 6H), 0.88 (s, 6H), 0.06 (s, 6H). **^{13}C NMR** ($CDCl_3$, 151 MHz): δ 83.3, 76.8, 63.5, 42.2, 33.2, 30.1, 29.3, 27.9, 26.6, 26.4, 26.3, 26.1, 24.9, 24.9, 18.5, –5.2. ***syn*-diastereomer: ^{1}H NMR** ($CDCl_3$, 600 MHz): δ 3.67 (ddd, *J* = 10.0, 7.5, 6.1 Hz, 1H), 3.56-3.61 (m, 1H), 3.34 (qu, *J* = 7.2 Hz, 1H), 2.25 (d, *J* = 8.4 Hz, 1H), 1.95 (m, 1H), 1.68-1.78 (m, 4H), 1.56-1.64 (m, 2H), 1.32- 1.43 (m, 2H), 1.24 (s, 9H), 1.08-1.22 (m, 3H), 0.94-1.06 (m, 2H), 0.89 (s, 6H), 0.88 (s, 6H), 0.04 (s, 6H). **^{13}C NMR** ($CDCl_3$, 151 MHz): δ 83.4, 77.9, 62.9, 43.7, 36.5, 31.8, 30.0, 28.6, 26.7, 26.6, 26.3, 26.1, 25.0, 24.9, 18.5, –5.1, –5.1. **IR** (ν/cm^{-1}): 3474 (s, br, OH), 2978 (m), 2954 (m), 2929 (m), 2885 (m), 2857 (m), 1471 (w), 1372 (m), 1321 (m), 1254 (m), 1214 (w), 1167 (w), 1144 (m), 1096 (m), 1025 (w). **HRMS (ESI+)** $[M+Na]^+$ calcd for $C_{22}H_{39}BNaO_4Si^+$ 429.2609, found: 429.2607.



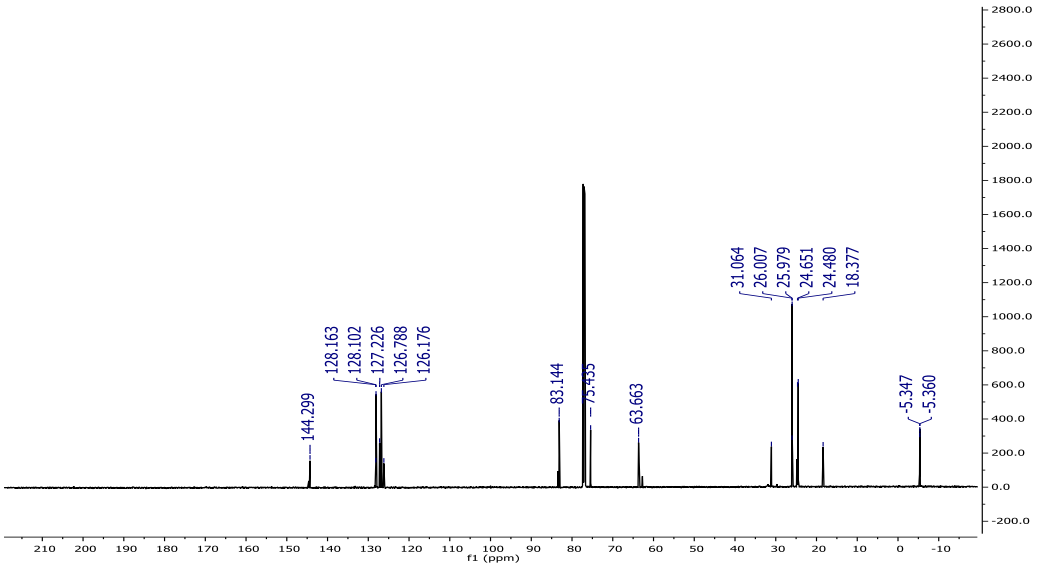
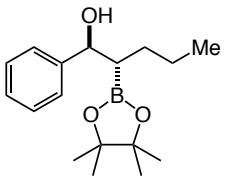


Figure 2.25. ^{1}H and ^{13}C{^{1}H} NMR spectra of 2.19.



2.20

1-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentan-1-ol (2.20).

Following general procedure B, the crude reaction mixture was purified by silica gel chromatography (NaOAc, deactivated silica gel, 5:1 pentane:diethyl ether to 2:1 pentane diethyl ether, Seebach Stain) to yield the hydroxyboronate as a colorless oil in 60% yield (17.4 mg) in 94:6 anti:syn diastereomeric ratio. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.41 – 7.37 (m, 2H), 7.33 (dd, *J* = 8.4, 6.8 Hz, 2H), 7.28 – 7.23 (m, 1H), 4.78 (d, *J* = 7.6 Hz, 1H), 2.26 (s, 1H), 1.62 (ddt, *J* = 12.5, 10.1, 4.5 Hz, 2H), 1.58 – 1.50 (m, 2H), 1.43 – 1.36 (m, 2H), 1.35 – 1.22 (m, 2H), 1.12 (s, 6H), 1.07 (s, 6H), 0.92 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 144.3, 128.3, 127.5, 126.7, 83.3, 75.8, 30.0, 24.8, 24.7, 22.7, 14.6. **IR** (v/cm^{-1}): 3432 (s), 2090 (s), 1642 (m), 1454 (m), 1379 (m), 1320 (w), 1247 (m), 1143 (w). **HRMS** (ESI)$^{+}$ $[2M+Na]^{+}$ calcd for $C_{34}H_{54}B_2O_6Na^{+}$ 603.4004, found: 603.3987.

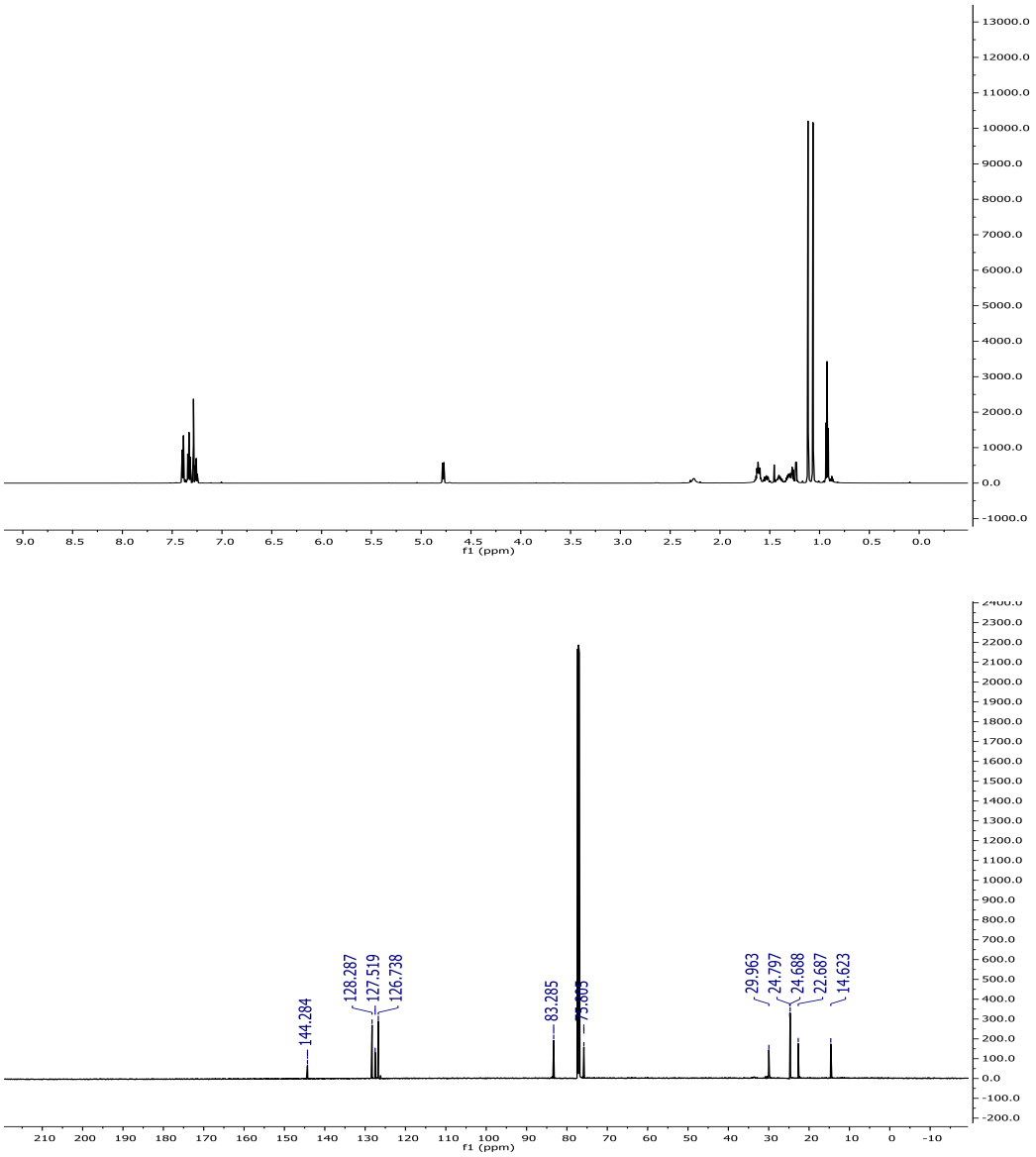
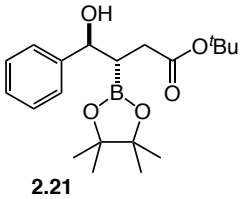


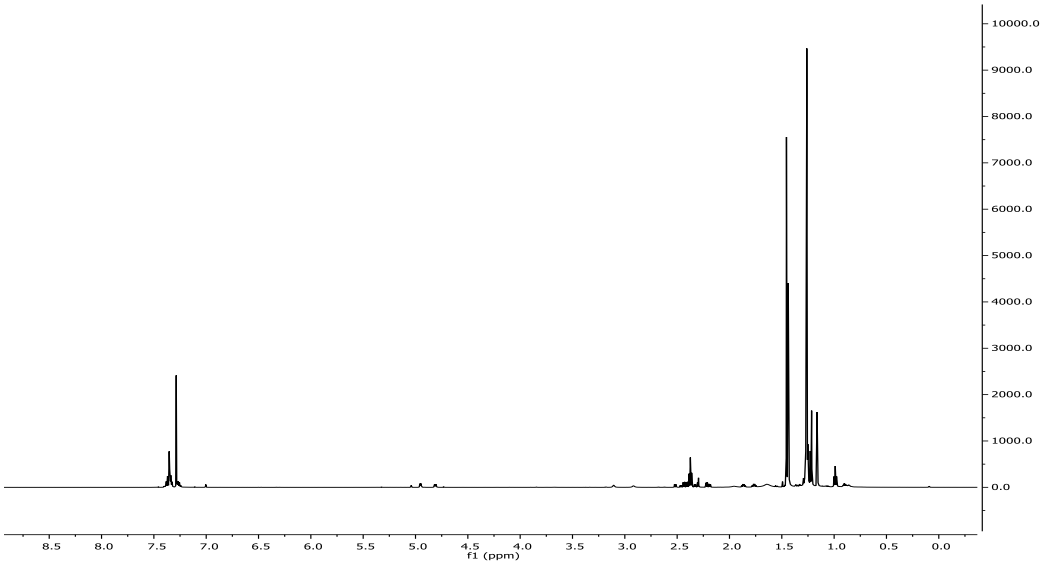
Figure 2.26. ^{1}H and ^{13}C{^{1}H} NMR spectra of 2.20.



2.21

tert-butyl-4-hydroxy-4-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoate (2.21). Following general procedure B, the crude reaction mixture was purified by silica gel chromatography (NaOAc deactivated silica gel, 10:1 to 5:1

pentane:diethyl ether, Seebach Stain) to yield the hydroxyboronate as a colorless oil in 66% yield (23.9 mg) in a 47:53 anti:syn diastereomeric ratio. ***anti*-diastereomer: ^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.46 – 7.29 (m, 4H), 7.28 – 7.23 (m, 1H), 4.95 (d, J = 6.1 Hz, 1H), 3.11 (s, 1H), 2.54 – 2.17 (m, 2H), 1.87 (dt, J = 8.3, 6.1 Hz, 1H), 1.46 (s, 9H), 1.26 (s, 12H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 174.1, 143.7, 128.2, 127.2, 126.2, 83.1, 79.8, 74.3, 33.9, 32.7, 30.0, 28.1, 24.9, 24.8, 24.8. ***syn*-diastereomer: ^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.46 – 7.29 (m, 4H), 7.28 – 7.23 (m, 1H), 4.81 (d, J = 8.2 Hz, 1H), 2.92 (s, 1H), 2.54 – 2.17 (m, 9H), 1.80 – 1.73 (m, 1H), 1.44 (s, 9H), 1.28 (s, 6H), 1.27 (s, 6H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.1, 143.7, 128.3, 127.4, 126.3, 83.7, 83.5, 80.5, 80.4, 75.0, 32.7, 30.3, 28.1, 28.1, 24.8, 24.7, 24.5, 24.5. **IR** (v/cm^{-1}): 3429 (s), 2359 (s), 2341 (s), 2094 (w), 1643 (m), 1139 (m). **HRMS** (ESI)$^{+}$ $[2M+Na]^{+}$ calcd for $C_{40}H_{62}B_2O_{10}Na^{+}$ 747.4428, found: 747.4407.



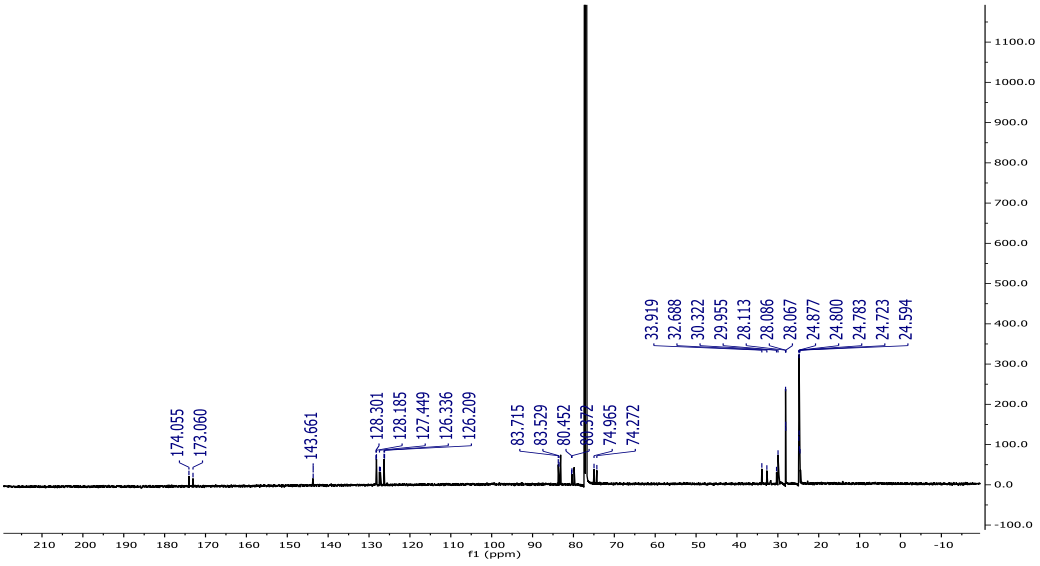
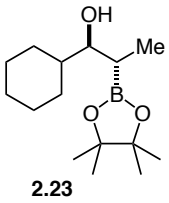


Figure 2.27. ^{1}H and ^{13}C{^{1}H} NMR spectra of 2.21.

2.8.4 Preparation of *anti*-1,2-hydroxyboronates from alkyl aldehydes and substituted 1,1-diboronates



2.23

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

Following general procedure C, the crude reaction mixture was purified by silica gel chromatography (NaOAc deactivated silica gel, 20:1 pentane:ethyl acetate to 5:1 pentane:diethyl ether, Seebach Stain) to yield the hydroxyboronate as a crystalline white solid in 38% yield (10.3 mg) and 88:12 anti:syn diastereomeric ratio. ***anti*-diastereomer: ^{1}H NMR** ($CDCl_3$, 600 MHz): δ 3.46 (m, 1H), 1.92-1.95 (m, 2H), 1.71-1.77 (m, 2H), 1.62-1.65 (m, 2H), 1.56-1.59 (m, 1H), 1.32-1.40 (m, 2H), 1.09-1.24 (m, 3H), 0.98-1.02 (m, 1H), 1.24 (s, 12H), 0.96 (d, J = 7.8 Hz, 3H). **^{13}C NMR** ($CDCl_3$, 151 MHz): δ 83.4, 77.4, 41.1, 29.7, 28.6, 26.6, 26.5, 26.3, 24.9, 24.8, 9.2. **IR** (ν/cm^{-1}): 3522 (s, br, OH), 2977 (m), 2925 (s),

2851 (m), 1450 (m), 1379 (s), 1317 (m), 1273 (w), 1214 (w), 1166 (w), 1145 (m), 1008 (w).

HRMS (ESI+) $[2M+Na]^+$ calcd for $C_{30}H_{58}B_2NaO_6^+$ 559.4318, found: 559.4314.

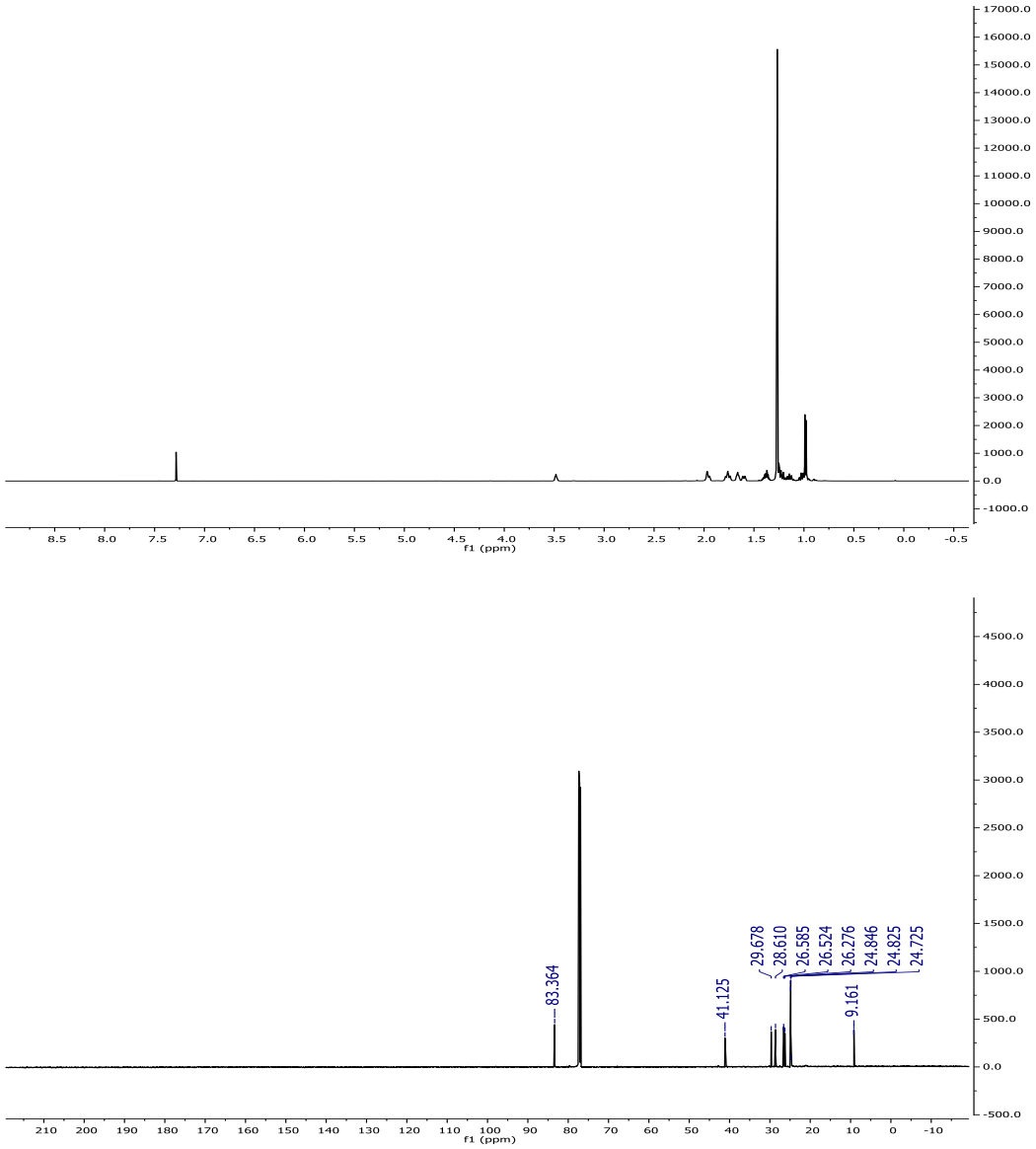
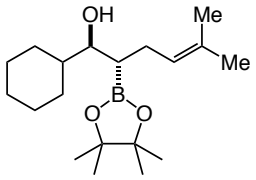


Figure 2.28. ^{1}H and ^{13}C{^{1}H} NMR spectra of 2.23.



2.24

1-cyclohexyl-5-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-4-en-1-ol (2.24). Following general procedure C, the crude reaction mixture was purified by silica gel chromatography (NaOAc deactivated silica gel, 20:1 pentane:ethyl acetate to 5:1 pentane:diethyl ether, Seebach Stain) to yield the hydroxyboronate as a colorless, crystalline white solid in 61% yield (19.5 mg) and 78:22 anti:syn diastereomeric ratio. ***anti*-diastereomer: ^{1}H NMR** ($CDCl_3$, 600 MHz): δ 5.15 (t, J = 7.2 Hz, 1H), 3.48 (t, J = 6.6 Hz, 1H), 2.17-2.26 (m, 2H), 1.86-1.92 (m, 2H), 1.72-1.77 (m 2H), 1.66 (s, 3H), 1.62 (s, 3H), 1.57-1.60 (m, 1H), 1.32-1.39 (m, 2H), 1.22 (s, 6H), 1.22 (s, 6H), 1.08-1.21 (m, 4H), 0.95-1.06 (m, 1H). **^{13}C NMR** ($CDCl_3$, 151 MHz): δ 131.9, 124.5, 83.3, 42.4, 30.3, 27.4, 26.7, 26.6, 26.4, 26.0, 25.3, 24.9, 24.8, 18.0. ***syn*-diastereomer: ^{1}H NMR** ($CDCl_3$, 600 MHz): δ 5.11 (t, J = 7.2 Hz, 1H), 3.32 (qu, J = 7.2 Hz, 1H), 2.10-2.16 (m, 2H), 2.04 (d, 1H, J = 9.0 Hz), 1.86-1.92 (m, 2H), 1.72-1.77 (m 2H), 1.66 (s, 3H), 1.62 (s, 3H), 1.57-1.60 (m, 1H), 1.32-1.39 (m, 2H), 1.23 (s, 12H), 1.08-1.21 (m, 4H), 0.95-1.06 (m, 1H). **^{13}C NMR** ($CDCl_3$, 151 MHz): δ 132.0, 124.1, 83.4, 78.2, 44.1, 30.0, 28.5, 27.7, 26.7, 26.6, 25.9, 25.0, 24.7, 18.0. **IR** (ν/cm^{-1}): 3517 (s, br, OH), 2928 (m), 2925 (s), 2852 (m), 1449 (m), 1378 (s), 1320 (m), 1245 (w), 1213 (w), 1165 (w), 1144 (s), 1110 (w), 1044 (w). **HRMS** (ESI+) $[2M+Na]^+$ calcd for $C_{38}H_{70}B_2NaO_6^+$ 667.5257, found: 667.5249.

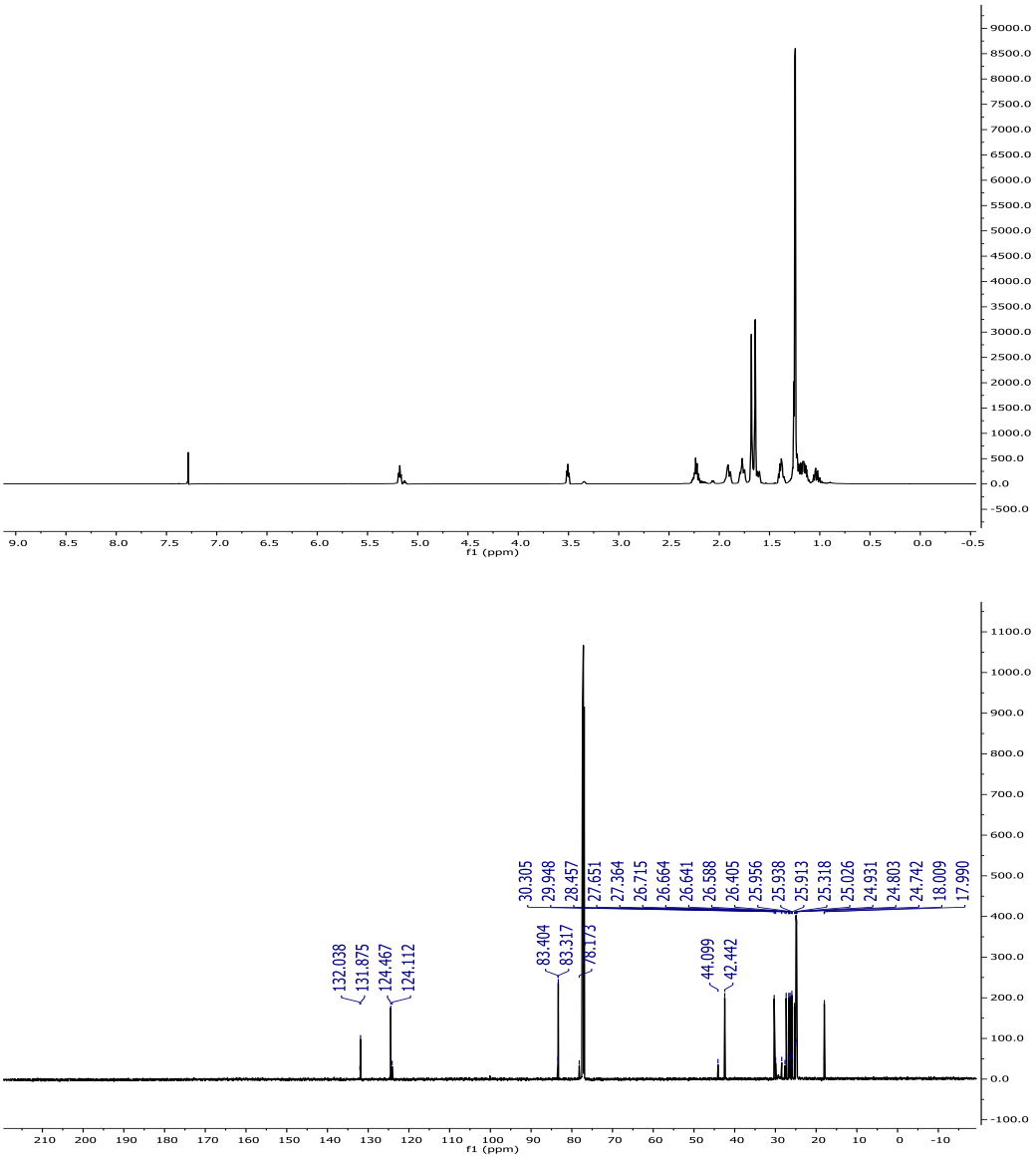
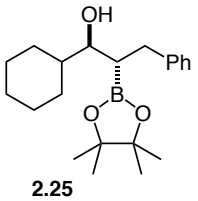


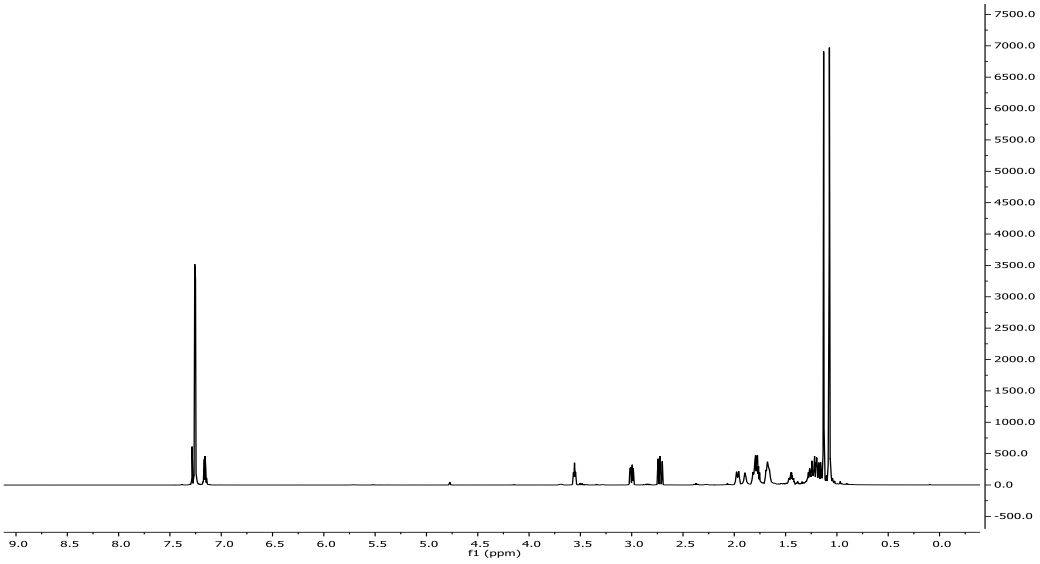
Figure 2.29. ^{1}H and ^{13}C{^{1}H} NMR spectra of 2.24.



2.25

1-cyclohexyl-3-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-ol (2.25). Following general procedure C, the crude reaction mixture was purified by silica gel chromatography (NaOAc deactivated silica gel, 20:1 pentane:ethyl acetate to 5:1

pentane:diethyl ether, Seebach Stain) to yield the hydroxyboronate as a colorless, crystalline white solid in 49% yield (17.0 mg) and 95:5 anti:syn diastereomeric ratio. ***anti-diastereomer:*** **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 7.23 (m, 2H), 7.23 (m, 2H), 7.13 (m, 1H), 3.53 (t, J = 6.0 Hz, 1H), 2.98 (dd, J = 13.8 Hz, 6.0 Hz, 1H), 2.70 (dd, J = 13.2, 11.4 Hz, 1H), 1.93-1.96 (m, 1H), 1.87 (s, 1H), 1.73-1.80 (m, 3H), 1.63-1.67 (m, 2H), 1.39-1.46 (m, 1H), 1.12-1.27 (m, 5H), 1.11 (s, 6H), 1.05 (s, 6H). **^{13}C NMR** ($CDCl_3$, 151 MHz): δ 142.2, 129.1, 128.2, 125.8, 83.4, 77.3, 42.4, 32.7, 30.3, 27.4, 26.7, 26.6, 26.3, 24.9, 24.8. **IR** (ν/cm^{-1}): 3511 (s, br, OH), 3061 (w), 3027 (w), 2978 (m), 2925 (s), 2852 (w), 1496 (w), 1450 (m), 1372 (s), 1323 (m), 1249 (w), 1211 (w), 1166 (w), 1143 (m), 1100 (w), 1084 (w), 1072 (w), 1040 (w). **HRMS** (ESI+) $[2M+Na]^+$ calcd for $C_{42}H_{66}B_2NaO_6^+$ 711.4943, found: 711.4936.



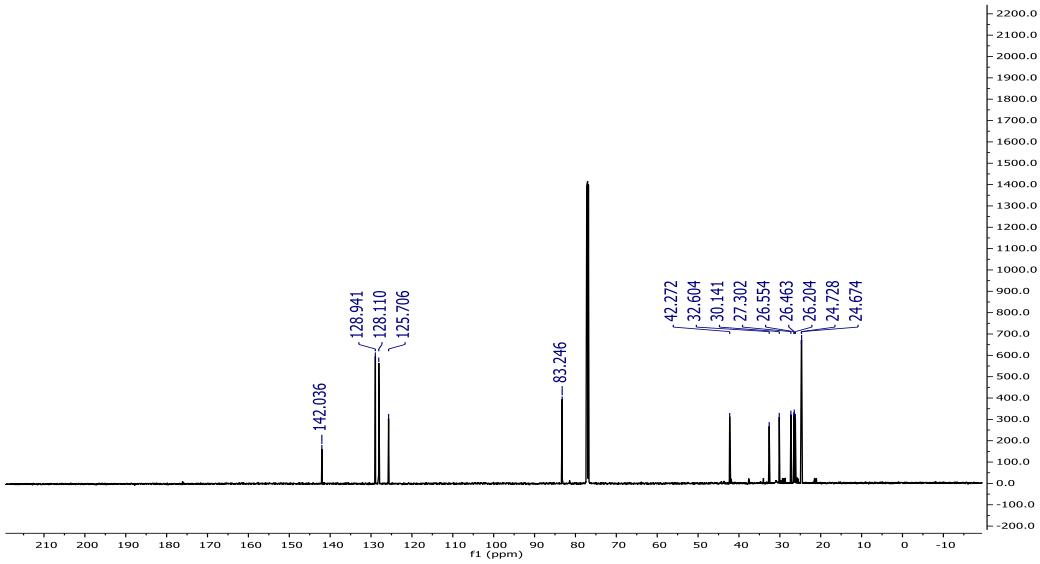
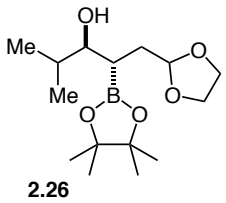


Figure 2.30. ^{1}H and ^{13}C{^{1}H} NMR spectra of 2.25.



2.26

1-(1,3-dioxolan-2-yl)-4-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentan-3-ol (2.26). Following general procedure C, the crude reaction mixture was purified by silica gel chromatography (NaOAc deactivated silica gel, 20:1 pentane:ethyl acetate to 5:1 pentane:diethyl ether, Seebach Stain) to yield the hydroxyboronate as a colorless oil in 62% yield (18.6 mg) and >98:2 anti:syn diastereomeric ratio. ***anti*-diastereomer: ^{1}H NMR** ($CDCl_3$, 600 MHz): 4.99 (t, 1H, J = 4.2 Hz), 3.94-3.98 (m, 2H), 3.80-3.85 (m, 2H), 3.43 (t, 1H, J = 6.1 Hz), 2.32 (s, 1H), 1.88-1.95 (m, 2H), 1.67-1.73 (m, 1H), 1.40-1.44 (m, 1H), 1.24 (s, 12H), 0.92 (dd, J = 13.8, 6.7 Hz, 6H). **^{13}C NMR** ($CDCl_3$, 151 MHz): δ 104.4, 83.4, 77.1, 65.0, 65.0, 32.2, 30.5, 24.9, 24.9, 20.1, 17.1. **IR** (ν/cm^{-1}): 3495 (s, br), 2976 (m), 2931 (m), 2875 (m), 1470 (w), 1373 (s), 1318 (m), 1249 (w), 1213

(w), 1144 (s), 1095 (w). **HRMS** (ESI+) $[2M+H]^+$ calcd for $C_{30}H_{59}B_2O_{10}^+$ 601.4294, found: 601.4317.

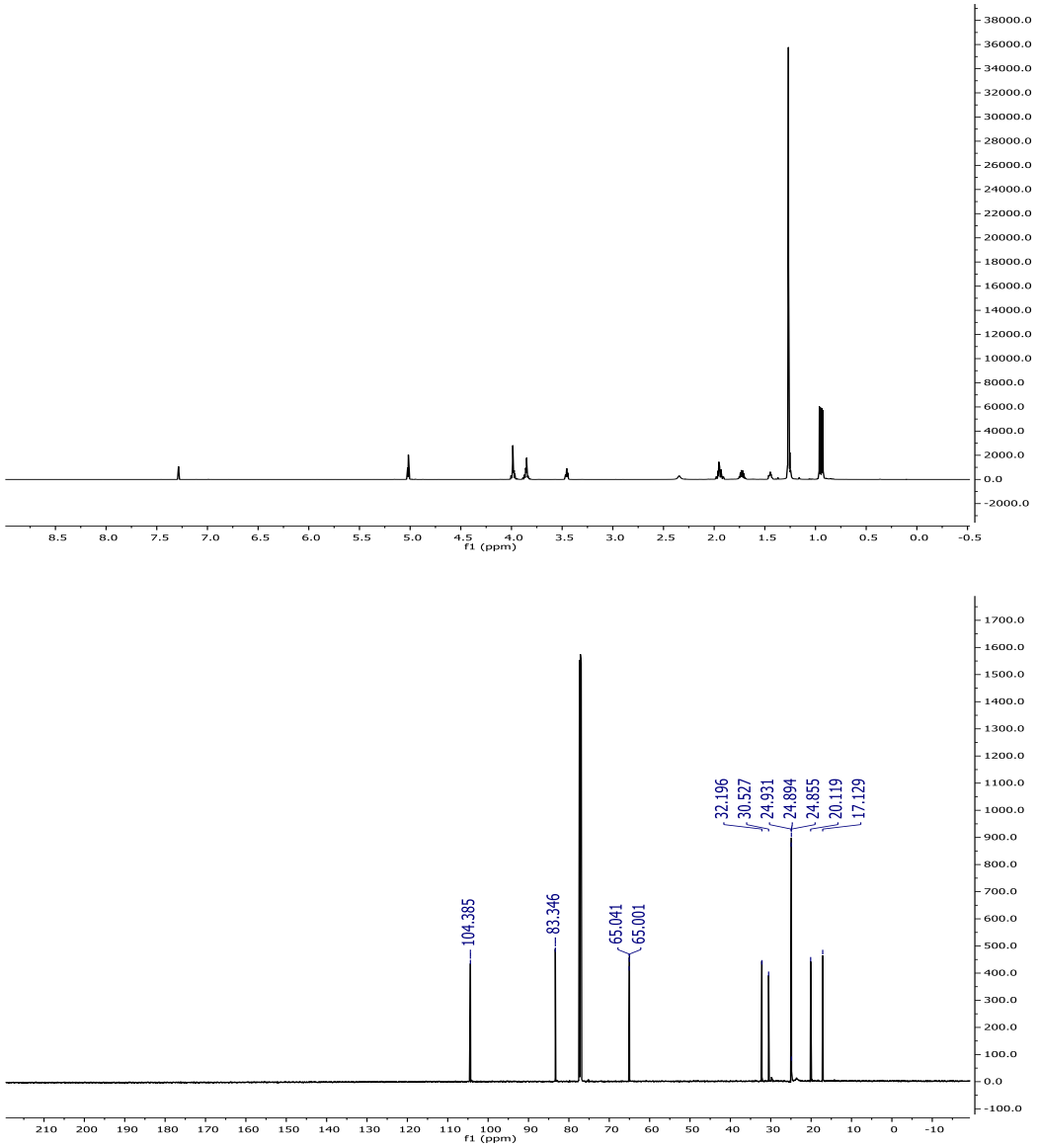
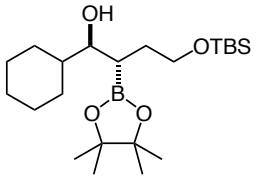


Figure 2.31. ^{1}H and ^{13}C{^{1}H} NMR spectra of 2.26.



2.27

4-((*tert*-butyldimethylsilyl)oxy)-1-cyclohexyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-1-ol (2.27). Following general procedure C, the crude reaction mixture was purified by silica gel chromatography (NaOAc deactivated silica gel, 20:1 pentane:ethyl acetate to 5:1 pentane:diethyl ether, Seebach Stain) to yield the hydroxyboronate as a colorless, crystalline white solid in 49% yield (20.3 mg) and 90:10 anti:syn diastereomeric ratio. ***anti*-diastereomer: ^{1}H NMR** ($CDCl_3$, 600 MHz): δ 3.77 (dt, *J* = 10.2, 6.0 Hz, 1H), 3.57-3.61 (m, 1H), 3.48 (qu, *J* = 5.4 Hz, 1H,), 2.77 (d, *J* = 6.6 Hz, 1H), 1.90 (m, 1H), 1.68-1.78 (m, 4H), 1.56-1.64 (m, 2H), 1.32- 1.43 (m, 2H), 1.24 (s, 9H), 1.08-1.22 (m, 3H), 0.94-1.06 (m, 2H), 0.89 (s, 6H), 0.88 (s, 6H), 0.06 (s, 6H). **^{13}C NMR** ($CDCl_3$, 151 MHz): δ 83.3, 76.8, 63.5, 42.2, 33.2, 30.1, 29.3, 27.9, 26.6, 26.4, 26.3, 26.1, 24.9, 24.9, 18.5, –5.2. ***syn*-diastereomer: ^{1}H NMR** ($CDCl_3$, 600 MHz): δ 3.67 (ddd, *J* = 10.0, 7.5, 6.1 Hz, 1H), 3.56-3.61 (m, 1H), 3.34 (qu, *J* = 7.2 Hz, 1H), 2.25 (d, *J* = 8.4 Hz, 1H), 1.95 (m, 1H), 1.68-1.78 (m, 4H), 1.56-1.64 (m, 2H), 1.32- 1.43 (m, 2H), 1.24 (s, 9H), 1.08-1.22 (m, 3H), 0.94-1.06 (m, 2H), 0.89 (s, 6H), 0.88 (s, 6H), 0.04 (s, 6H). **^{13}C NMR** ($CDCl_3$, 151 MHz): δ 83.4, 77.9, 62.9, 43.7, 36.5, 31.8, 30.0, 28.6, 26.7, 26.6, 26.3, 26.1, 25.0, 24.9, 18.5, –5.1, –5.1. **IR** (ν/cm^{-1}): 3464 (s, br, OH), 2977 (m), 2927 (s), 2854 (m), 1471 (m), 1449 (m), 1372 (m), 1317 (m), 1254 (m), 1214 (w), 1166 (w), 1145 (m), 1094 (m), 1007 (w). **HRMS** (ESI+) $[M+Na]^+$ calcd for $C_{22}H_{45}BNaO_4Si^+$ 435.3078, found: 435.3077.

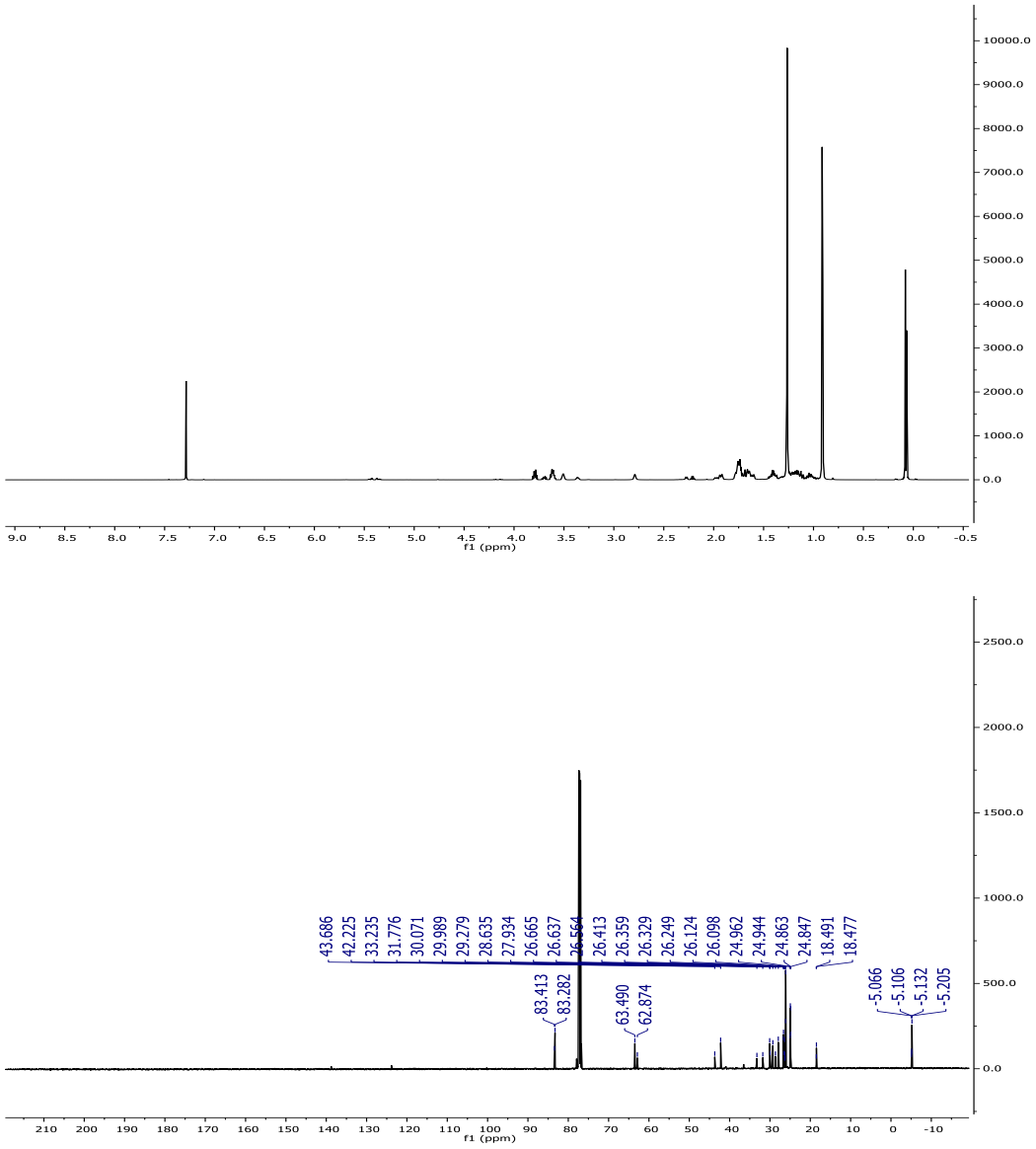
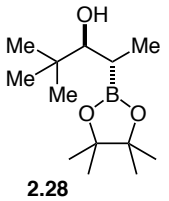


Figure 2.32. ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of 2.27.

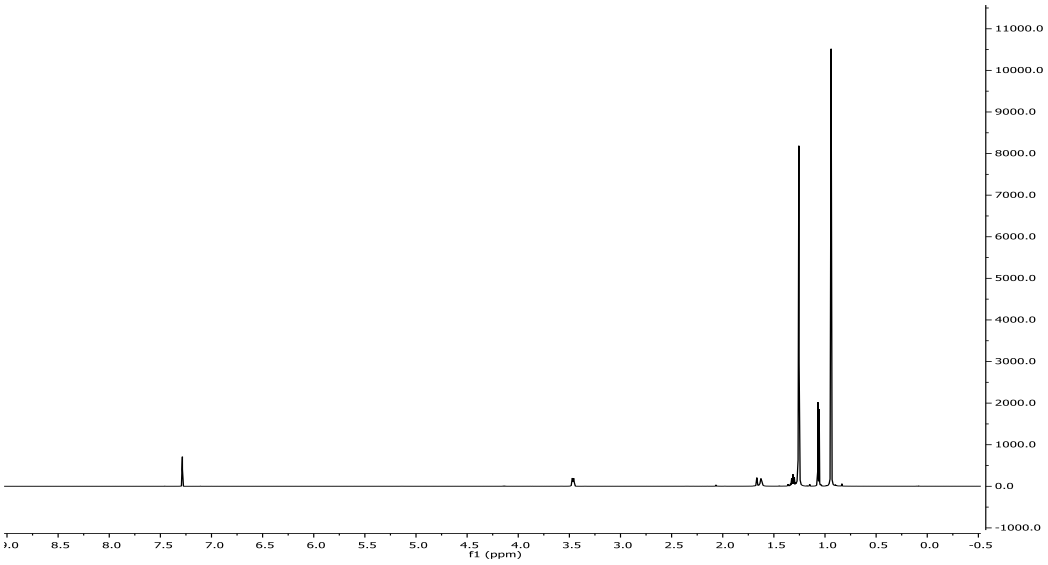


2.28

2,2-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentan-3-ol (2.28).

Following general procedure B, the crude reaction mixture was purified by silica gel chromatography (NaOAc deactivated silica gel, 20:1 pentane:ethyl acetate to 5:1

pentane:diethyl ether, Seebach Stain) to yield the hydroxyboronate as a colorless, crystalline white solid in 33% yield (7.9 mg) and >98:2 anti:syn diastereomeric ratio. **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 3.44 (d, 1H, *J* = 7.8 Hz), 1.60 (s, 1H), 1.29 (quint, 1H, *J* = 7.8 Hz), 1.23 (s, 12H), 1.04 (d, 3H, *J* = 7.2 Hz), 0.92 (s, 9H). **^{13}C NMR** ($CDCl_3$, 151 MHz): δ 83.2, 79.9, 36.1, 26.7, 24.8, 24.8, 12.0. **IR** (ν/cm^{-1}): 3539 (s, br, OH), 2978 (m), 2953 (m), 2871 (w), 1481 (w), 1458 (w), 1379 (m), 1334 (w), 1314 (m), 1166 (w), 1145 (m), 1106 (w), 1039 (w). **HRMS** (ESI+) $[2M+Na]^+$ calcd for $C_{26}H_{54}B_2NaO_6^+$ 507.4004, found: 507.3998.



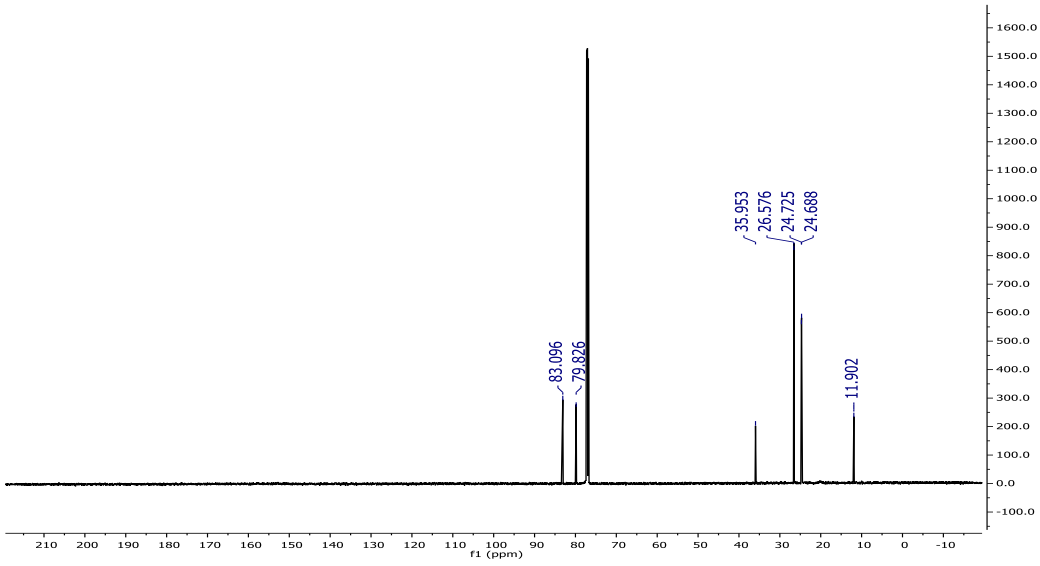
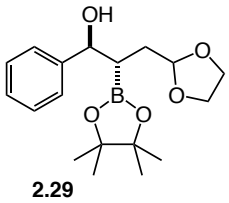


Figure 2.33. ^{1}H and ^{13}C{^{1}H} NMR spectra of 2.28.



2.29

3-(1,3-dioxolan-2-yl)-1-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-ol (2.29). Following general procedure C, the crude reaction mixture was purified by silica gel chromatography (NaOAc-deactivated silica gel; 2:1 pentane:diethyl ether to 1:1 pentane:diethyl ether, Seebach stain) to yield the hydroxyboronate as a colorless, crystalline white solid in 54% yield (18.0 mg) and >98:2 anti:syn diastereomeric ratio. **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 7.38 (d, *J* = 7.2 Hz, 2H), 7.30 (t, *J* = 7.8 Hz, 2H), 7.22 (t, *J* = 7.2 Hz, 1H), 4.99 (t, *J* = 4.1 Hz, 1H), 4.75 (d, 1H, *J* = 8.0 Hz), 3.94-3.99 (m, 2H), 3.81-3.86 (m, 2H), 2.72 (s, 1H), 2.03 (dt, *J* = 14.2, 4.2 Hz, 1H), 1.95 (ddd, *J* = 14.1, 9.7, 4.3 Hz, 1H), 1.73 (ddd, *J* = 9.7, 8.1, 4.6 Hz, 1H), 1.10 (s, 6H), 1.01 (s, 6H). **^{13}C NMR** ($CDCl_3$, 151 MHz): δ 143.9, 128.3, 127.6, 126.9, 104.2, 83.3, 75.2, 65.1, 65.0, 31.8, 24.9, 24.7. **IR** (ν/cm^{-1}): 3468 (s, br), 2977 (m), 2926 (m), 2887 (m), 1455 (w), 1378 (s), 1321 (m), 1249 (w), 1212 (w),

1144 (s), 1032 (m). **HRMS** (ESI+) $[2M+Na]^+$ calcd for $C_{36}H_{54}B_2NaO_{10}^+$ 691.3801, found: 691.3827.

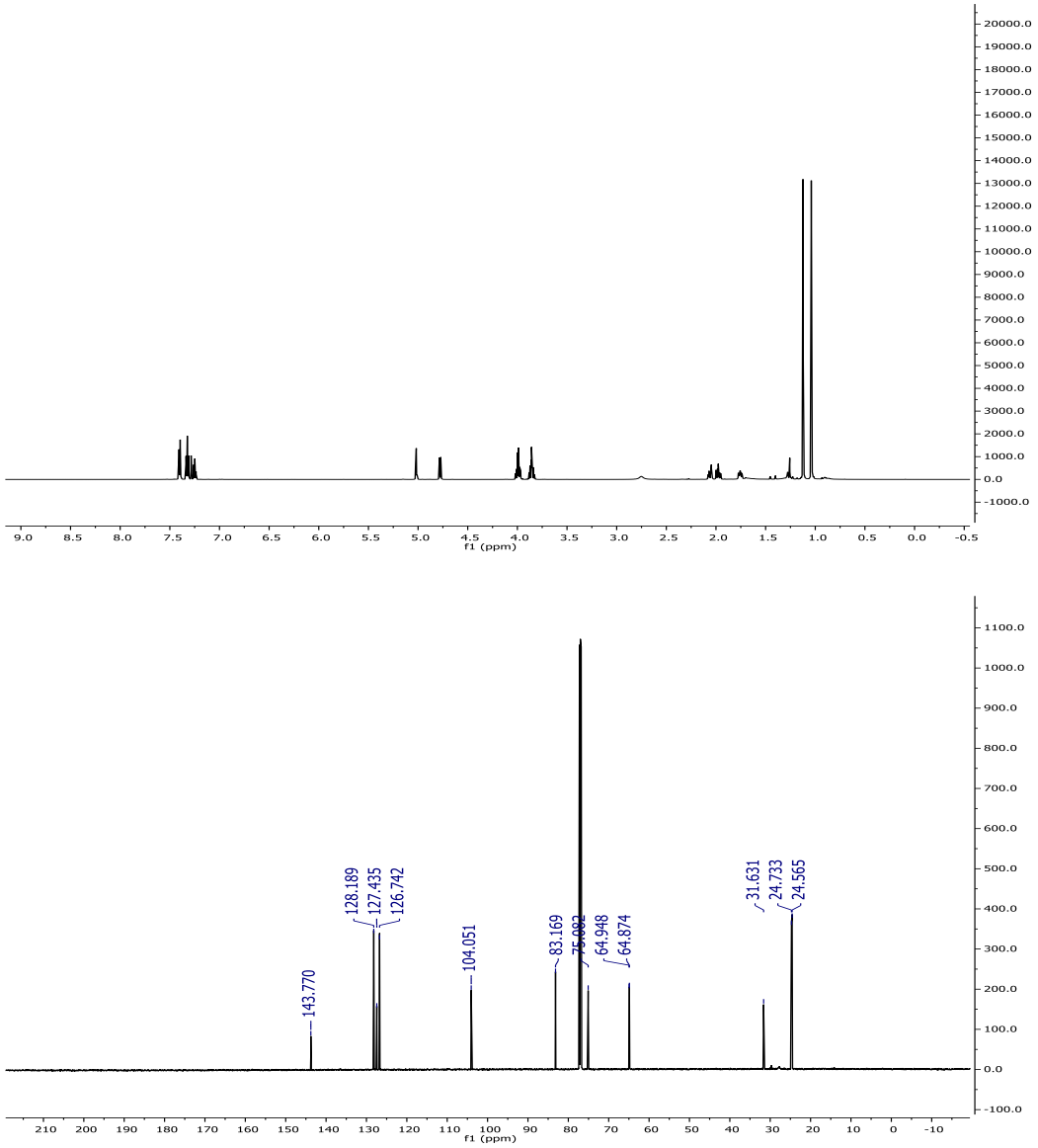
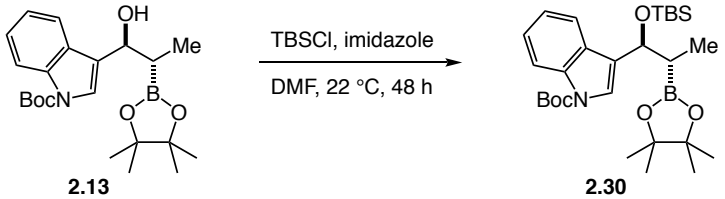


Figure 2.34. ^{1}H and ^{13}C{^{1}H} NMR spectra of 2.29.

2.8.5 Functionalization of *anti*-1,2-hydroxyboronates



2.13 **2.30**

Synthesis of TBS-protected hydroxyboronate **2.30**: An 8-mL vial containing hydroxyboronate **2.13** (21.6 mg, 0.0538 mmol) was charged with imidazole (9.9 mg, 0.145 mmol) and *tert*-butyldimethylchlorosilane (16.3 mg, 0.108 mmol) and then sealed with a septa-lined cap. Anhydrous DMF (0.360 mL) was added under N_2 and the reaction was purged for 10 minutes and allowed to stir at ambient temperature for 48 hours. The reaction was quenched by the addition of 1.5 mL of a saturated aqueous solution of NH_4Cl and the aqueous layer extracted three times with ethyl acetate. The combined organic extracts were washed twice with a saturated aqueous solution of $NaHCO_3$ and once with brine. The organic extract was dried over $MgSO_4$ and concentrated *in vacuo*. The crude reaction mixture was purified by silica gel chromatography (NaOAc deactivated silica gel; 25:1 pentane:diethyl ether, Seebach Stain) to yield the TBS-protected hydroxyboronate in 77% yield (21.3 mg) as a colorless oil in 99:1 *anti*:*syn* diastereoselectivity. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.76 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.42 (s, 1H), 7.31 – 7.23 (m, 1H), 7.18 (ddd, *J* = 8.0, 7.2, 1.1 Hz, 1H), 4.91 (d, *J* = 9.3 Hz, 1H), 1.73 (dq, *J* = 9.3, 7.2 Hz, 1H), 4.94 (d, *J* = 9.3 Hz, 1H), 1.65 (s, 9H), 1.11 (d, *J* = 7.3 Hz, 3H), 1.08 (s, 6H), 1.01 (s, 6H), 0.86 (s, 9H), 0.05 (s, 3H), -0.24 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 149.9, 135.8, 129.0, 125.4, 124.1, 122.4, 122.2, 121.6, 114.9, 83.23, 82.9, 71.1, 28.3, 26.0, 24.7, 24.5, 18.4, 12.6, -4.4, -4.9. **IR** (v/cm^{-1}): 2990 (s), 2922 (m), 2879 (w), 1734 (s), 1446 (s), 1318 (m), 1255 (m), 1159 (s), 1145 (m), 1081 (m), 1011 (m). **HRMS** (ESI$^+$): $[M+Na]^+$ calcd for $C_{28}H_{46}BNO_5SiNa^+$ 538.3137, found: 538.3139.

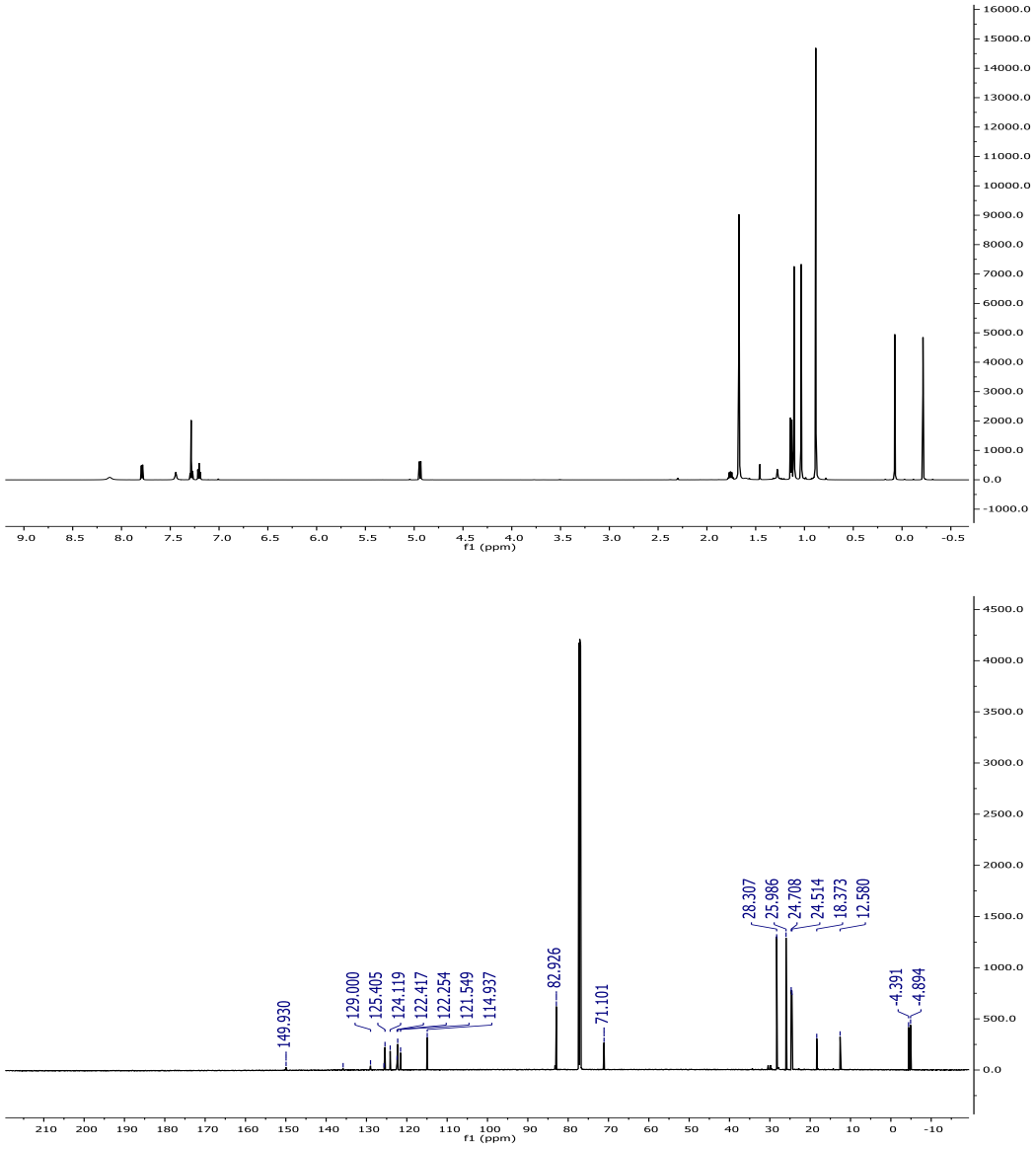
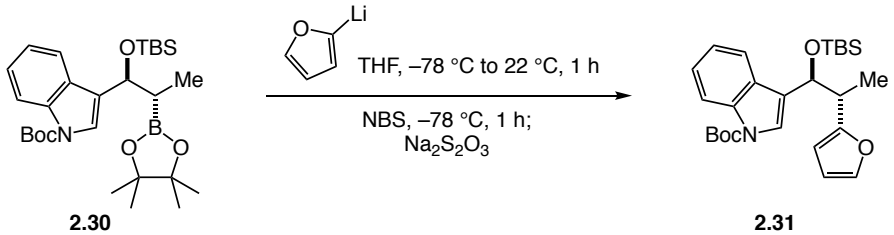


Figure 2.35. ^{1}H and ^{13}C{^{1}H} NMR spectra of 2.30.



2.30 **2.31**

Arylation of **2.30** with lithiated furan: **2.31** was prepared according to a literature procedure.[6] A flame-dried 8-mL vial was charged with furan (2.60 µL, 0.0363 mmol) and anhydrous THF (0.120 mL). The reaction was allowed to cool to –78 ˚C (dry-ice/acetone)

and then charged with *n*-butyllithium (21.7 μL, 0.0363 mmol, 1.67 M solution in hexanes). The cooling bath was removed and the reaction was allowed to stir at ambient temperature for 1 hour. The mixture was allowed to cool back down to –78 ˚C (dry-ice/acetone) and then charged with **2.30** as a 0.4 M solution in THF (15.6 mg, 0.0303 mmol) and allowed to stir at that temperature for 1.5 hour. NBS (6.50 mg, 0.0363 mmol) was then added to the reaction as a 0.3 M solution in THF. After allowing the reaction to stir for 1.5 hours, 1 mL of a saturated aqueous solution of $Na_2S_2O_3$ was added to the reaction and allowed to stir at ambient temperature for 30 minutes. The layers were separated and extracted three times with diethyl ether. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude reaction mixture was purified by silica gel chromatography (40:1 pentane:diethyl ether, Seebach stain) to give the product **2.31** as a colorless oil in 67% yield (9.0 mg) and >99:1 *anti*:*syn* diastereoselectivity as a mixture rotamers (85:15). 25% of the starting material **2.30** was recovered from the reaction. (^{13}C NMR shows signals for only one diastereomer, indicating that the ^{1}H NMR contains rotamers). Rotamer 1: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.64 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.47 (s, 1H), 7.36 (dd, *J* = 1.9, 0.8 Hz, 1H), 7.33 (ddd, *J* = 8.4, 7.2, 1.2 Hz, 1H), 7.25 (ddd, *J* = 8.1, 7.2, 1.1 Hz, 1H), 6.29 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.03 (dt, *J* = 3.2, 0.9 Hz, 1H), 5.33 (dd, *J* = 3.7, 1.1 Hz, 1H), 3.28 (td, *J* = 7.1, 3.8 Hz, 1H), 1.69 (s, 9H), 1.24 (d, *J* = 7.0 Hz, 3H), 0.88 (s, 9H), -0.20 (s, 3H), -0.20 (s, 3H). Rotamer 2: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.64 – 7.61 (m, 1H), 7.46 (d, *J* = 5.1 Hz, 1H), 7.36 (dd, *J* = 1.9, 0.8 Hz, 1H), 7.33 (ddd, *J* = 8.4, 7.2, 1.2 Hz, 1H), 7.27 – 7.22 (m, 1H), 6.19 (d, *J* = 3.2 Hz, 1H), 5.99 (dd, *J* = 3.3, 1.0 Hz, 1H), 5.31 (dd, *J* = 3.8, 1.2 Hz, 1H), 3.25 (m, 1H), 1.69 (s, 9H), 1.21 (d, *J* = 7.0 Hz, 3H), 0.89 (s, 9H), -0.15 (s, 3H), -0.17 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 157.8, 140.6, 124.1, 123.6, 123.3, 122.3,

119.9, 115.2, 110.2, 105.9, 100.0, 70.9, 65.9, 40.1, 34.1, 28.2, 25.8, 22.4, 18.2, 15.3, 14.1, 11.5, -5.0, -5.8. **IR** (v/cm^{-1}): 2990 (s), 2901 (m), 2864 (w), 2525 (s), 2050 (m), 1736 (s), 1439 (s), 1324 (m), 1260 (m), 1148 (s), 1141 (m), 1082 (m), 1011 (m). **HRMS** (ESI^{+}): $[M+Na]^{+}$ cald for $C_{26}H_{37}NO_4SiNa^{+}$ 478.2384, found: 478.2389.

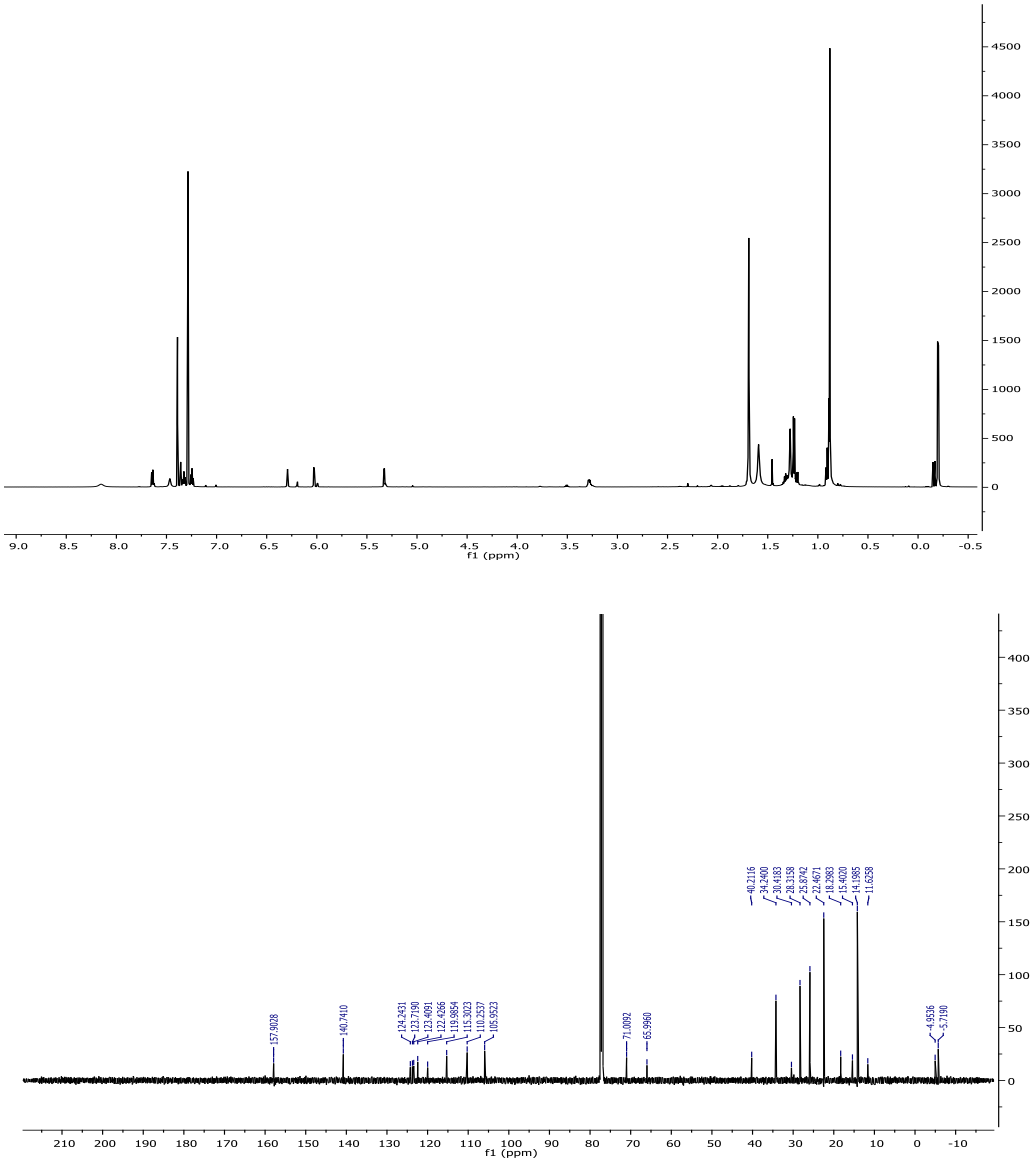


Figure 2.36. ^{1}H and ^{13}C{^{1}H} NMR spectra of 2.31.

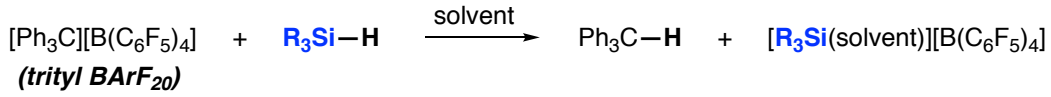
3 Chapter 3: Taming Silylium Ions for Synthesis: *N*-Heterocycle Synthesis *via* Stereoselective C–C Bond Formation

This chapter is adapted from a submission of Moyer, B. S.; Gagné, M. R. *Synlett* (manuscript accepted).

3.1 Applying highly reactive silylium ion catalysts to organic synthesis

3.1.1 Background

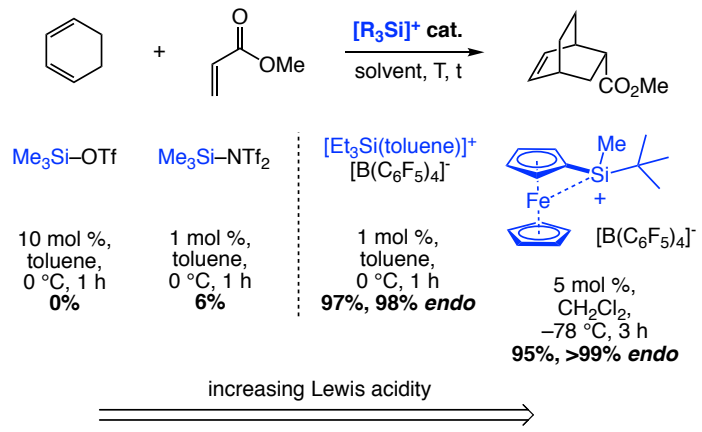
The development of catalytic, synthetic applications of silylium ions has been frustrated by the technicality that, except for in the most extreme cases,[38] they do not exist.[39] Despite their apparent structural similarity to carbenium ions and their reduced Pauling electronegativity (1.8 vs. 2.5), silylium ions are highly Lewis acidic.[40] Their increased size and longer bond lengths reduce the efficiency of stabilizing π-conjugative and hyperconjugative effects, endowing them with a high affinity for both σ- and π-Lewis bases, including solvent molecules and counteranions. Therefore, as silylium ionicity falls on a continuum, the most "free" examples so far reported are paired with either $[B(C_6F_5)_4]^-$ (*i.e.* $BArF_{20}$) or $[HCB_{11}R_5X_6]^-$ (halogenated carboranes) as weakly coordinating anions (WCAs) in aromatic or halocarbon solvents.[41] In particular, the reactive $[R_3Si]^+$ equivalent is readily accessible as the solvent-stabilized Lewis pair $[R_3Si(solvent)][B(C_6F_5)_4]$ *via* simple Bartlett-Condon-Schneider hydride abstraction from $R_3Si–H$ by the commercially available salt $[Ph_3C][B(C_6F_5)_4]$ (abbreviated herein trityl $BArF_{20}$; Scheme 3.1).[42]



Scheme 3.1. Bartlett-Condon-Schneider hydride abstraction.

To date, catalytic applications of silylium ions in synthesis include alkene hydrosilylation,[43] carbonyl reduction,[44] imine reduction,[45] C–F bond activation (hydrodefluorination),[46] and C–C bond formation (namely Diels-Alder reactions; Scheme 3.2).[47] The C–C bond-forming reactions are arguably the most relevant to organic synthesis, as they are useful in building more complex organic scaffolds. The silylium ion-catalyzed variant of a classic Diels-Alder reaction (Scheme 3.2, below) is a state of the art example (*note:* there are now enantioselective derivatives, see ref. 47) that illustrates the continuum encompassing the classical silicon Lewis acid catalysts that have been used in numerous synthetic applications (*e.g.* Mukaiyama aldol, Hosomi-Sakurai allylation, etc.)[48] and more reactive silylium ion catalysts such as Lambert's salt and Oestreich's ferrocene-based salt. The differences are apparent in the conversions and temperatures of operation: low conversions[xviii] at 0 °C to RT for the former and quantitative conversions at –78 °C to 0 °C for the latter. Other (non-Diels-Alder) synthetic examples of note, albeit not technically catalytic or self-regenerative in silylium, include applications in C–C[49] and Si–C[50] bond formation ((sila)-Friedel-Crafts reactions).

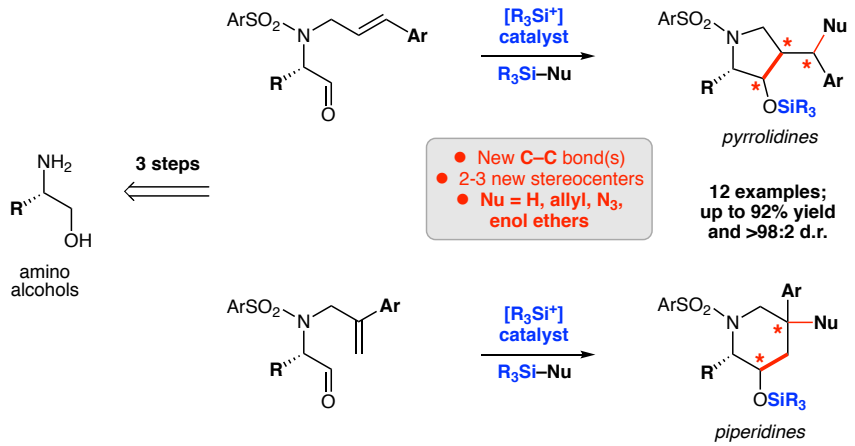
[xviii] Higher conversions using $Me_3Si–NTf_2$ are attainable with higher catalyst loadings (~10 mol %) and/or with certain other Diels-Alder systems; this example was chosen to illustrate the reactivity differences.



Scheme 3.2. Comparison between various reported "silylium ion" catalysts.

3.1.2 Research objectives

Few examples exist in which silylium ions are employed to catalyze the construction of C–C bonds. Our group has long been interested in the synthetic applications of silylium ion chemistry in the context of catalytic hydrosilylation with $B(C_6F_5)_3$ (BCF) and its derivatives,[51] and has published numerous manuscripts ranging from the deoxygenation/ defunctionalization of sugars (cellulosics) and other simple sugar-derivatives to the late-stage diversification of natural products.[52] Chapter 3 discusses our lab's progress in applying easily accessible silylium ions as catalysts in the stereoselective synthesis of various *N*-heterocyclic pyrrolidine and piperidine scaffolds *via* a *Prins* cyclization (Scheme 3.3). The substrates for this protocol are acyclic amino aldehydes that are obtained from the corresponding amino alcohols in three synthetic steps. Chapter 3 is followed by an appendix (A), which summarizes some of our most recent and unpublished work resulting from screening alternative Lewis acids (most notably BCF) as catalysts for the *Prins* cyclization.

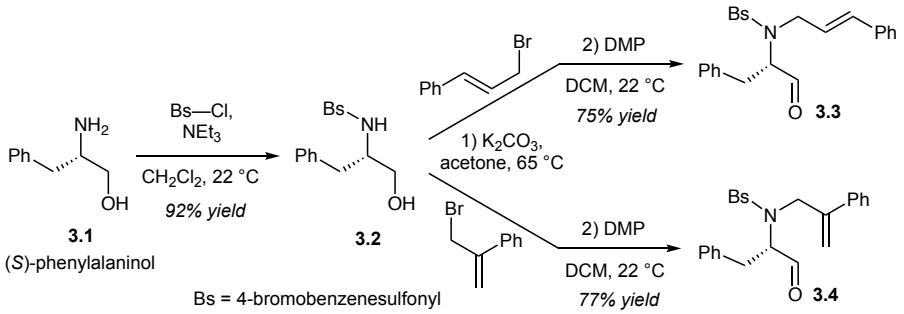


Scheme 3.3. Silylium ion-catalyzed *Prins* cyclization.

3.2 Substrate synthesis

Aldehyde substrates can be obtained in three high-yielding linear steps starting from the corresponding amino alcohols; for experimental details and analytical data, see section 3.7.2. Representative syntheses of (*S*)-phenylalaninol-derivatives **3.3** and **3.4** are illustrated in Scheme 3.4. First, (*S*)-phenylalaninol **3.1** was sulfonylated with 4-bromobenzenesulfonyl chloride (Bs, brosyl) in the presence of triethylamine to afford the Bs-amino alcohol **3.2** in 92% yield.[xix] **3.3** was then alkylated with either cinnamyl bromide or 2-phenylallyl bromide in the presence of potassium carbonate to yield the corresponding *N*-alkylated Bs-amino alcohols (not shown). These were then oxidized with Dess-Martin periodinane (DMP) to yield, respectively, the cinnamyl-amino aldehyde **3.3** in 75% yield (2 steps) and the 2-phenylallyl-amino aldehyde **3.4** in 77% yield (2 steps).

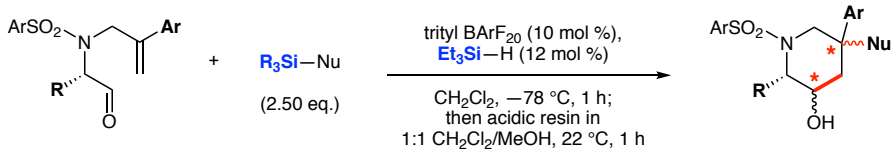
[xix]The choice of arylsulfonyl protecting group was based on yield and general ease of substrate synthesis. Other *N*-protecting groups (*e.g.* Boc, Ac, Bz, TFA, and *p*-Ns) were found to be difficult to install in satisfactory yields and so were not investigated for compatibility in the *Prins* cyclization.



Scheme 3.4. Representative substrate syntheses.

3.3 *N*-heterocycle synthesis *via* stereoselective C–C bond formation

Representative conditions for the silylium ion-catalyzed *Prins*-cyclization are given below in Scheme 3.5; attempts to further optimize the reaction with respect to trialkylhydrosilane, solvent, concentration, and catalyst loading were unfruitful. Using 10 mol % of the *in situ*-generated silylium ion equivalent $[Et_3Si][B(C_6F_5)_4]$ in CH_2Cl_2 at –78 °C, an appropriately substituted aldehyde rapidly cyclizes and the resulting carbocation is trapped by a silyl-protected nucleophile (R_3Si–Nu) to form a substituted piperidine derivative, following subsequent acid-catalyzed removal of the silyl residue.



Scheme 3.5. Representative reaction conditions.

3.4 Silylium ion-catalyzed *Prins* cyclization employing various R_3Si–Nu (Et_3Si–H, Me_3Si–allyl, and Me_3Si–N_3) as trapping nucleophiles

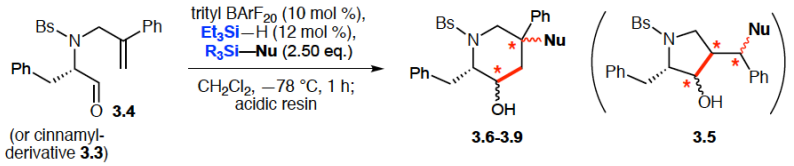
The trapping nucleophile (R_3Si–Nu) scope of the silylium-catalyzed *Prins*-cyclization was investigated; the best examples are listed in Table 3.1.[xx] Reaction of cinnamyl-amino aldehyde **3.3** with Et_3Si–H resulted in the formation of pyrrolidine **3.5** in 77% yield as a

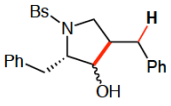
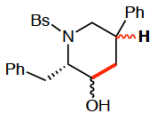
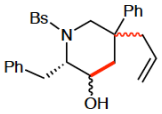
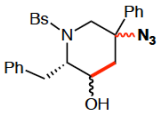
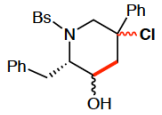
[xx]Other R_3Si–Nu sources, including TMS–I, TMS–CN, and TMS–OAc, provided complex mixtures of products by ^1H and ^{13}C NMR.

mixture of three diastereomers in 76:13:11 d.r. (entry 1). The reaction of 2-phenylallyl-amino aldehyde **3.4** with $Et_3Si–H$ resulted in piperidine **3.6** in 92% yield and 60:21:19 d.r. (entry 2). Reaction of **3.4** with allyltrimethylsilane led to an 84% yield of piperidine **3.7**, which contains an all-carbon quaternary center (66:34 d.r., entry 3); from a mechanistic perspective, this transformation could be considered a vinylogous analog of the named *Hosomi-Sakurai* allylation.[48b,53] When trimethylsilyl azide ($Me_3Si–N_3$) was employed as the trapping nucleophile, alkyl azide **3.8** was obtained in 78% yield and 79:21 d.r. (entry 4). When chlorotrimethylsilane ($Me_3Si–Cl$) was employed as the trapping nucleophile, no chloride-trapped product was observed (<5%; **3.9**, entry 5); $Me_3Si–Cl$ is apparently insufficiently nucleophilic under these conditions, even upon warming to RT.[xxi] Fortuitously, the $TiCl_4$-promoted classic *Prins* cyclization (see 3.7.5.1) is complementary in that it produces the chloride-trapped piperidine **3.9** in 99% isolated yield and 85:9:6 d.r. favoring the vicinal *cis*-diastereomer ($^3J_{CH\text{-}CH}$ = 5.9 Hz).

[xxi]The substrate is consumed; in the absence of a suitable trapping nucleophile, catalytic $[Et_3Si][B(C_6F_5)_4]$ leads to a 54% NMR yield of eliminated products **3.22** and **3.23** in 78:22 *cis:trans* d.r. (see section 3.6).

Table 3.1. Scope of trapping nucleophiles.



Entry	R_3Si–Nu	Product	Yield% (NMR)[c]	d.r.[d]
1	Et_3Si—H	 **3.5**	77%	76:13:11
2[e]	Et_3Si—H	 **3.6**	92%	60:21:19
3[f,g,h]	Me_3Si 	 **3.7**	84%	66:34
4[h,i]	Me_3Si—N_3	 **3.8**	78%	79:21
5[j]	Me_3Si—Cl	 **3.9**	(<5%)	n.d.[b]

[a]Reactions were run in duplicate on a 0.05-0.1 mmol scale. [b]Bs = 4-bromo-benzenesulfonyl; n.d. = "not determined". [c]Dimethylformamide (DMF) used as ^{1}H NMR internal standard. [d]d.r. after purification. [e]1.20 eq. Et_3Si–H provided **3.6** in 69% NMR yield and 51:29:20 d.r.. [f]The reaction was warmed from –78 to –30 °C overnight. [g]1.10 eq. Me_3Si–allyl provided **3.7** in 57% NMR yield and 58:42 d.r.. [h]The relative configurations of **3.7** and **3.8** were assigned in analogy to the X-ray crystal structure of **3.20** (*vide infra*). [i]1.10 eq. R_3Si–N_3; 2.50 eq. provided **3.8** in 85% yield and 62:38 d.r.. [j]The reaction was slowly warmed from –78 to 22 °C over 8 h.

3.5 Silylium ion-catalyzed *Prins* cyclization employing silyl enol ethers

With silyl enol ether trapping nucleophiles, various novel hetero(poly)cyclic piperidines (**3.13-3.19**) are accessible in fair to good yields and as single diastereomers (Table 3.2). These novel bridged tricyclic piperidine scaffolds contain two stereocenters, one of which is an all-carbon quaternary center. The initial intramolecular *Prins* cyclization and intermolecular carbocation trapping create the two new C–C bonds (red) in

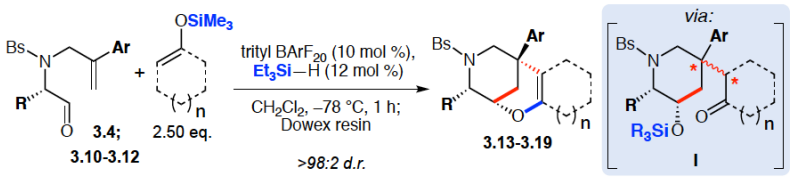
intermediate **I**; subsequent treatment of **I** with Brønsted acid (*e.g.* Dowex resin 50W-X8) catalyzes annulation (blue bond) and elimination to diastereomerically pure (>98:2 d.r.) tricyclic product. It is noteworthy that the annulation selects for a single diastereomer of trapped product; the yields likely reflect this.[xxii]

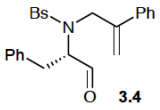
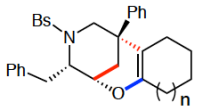
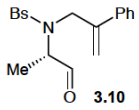
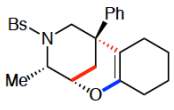
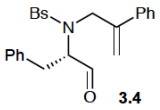
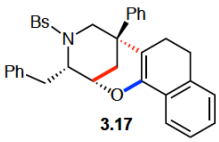
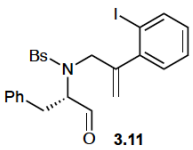
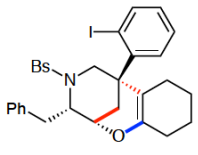
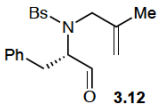
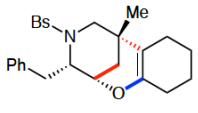
Entry 1 documents the effects of changing the ring size of the silyl enol ether; cyclopentanone-derived **3.13** is obtained in only trace amounts (^{13}C NMR and HR-MS, see 3.7.4.2 and Figure 3.8 therein), presumably due to ring strain, while cyclohexanone- and cycloheptanone-derivatives **3.14** and **3.15** are obtained in 64% and 22% yields, respectively. Alaninol-derivative **3.16** was obtained in 38% yield (entry 2) and the more hindered valinol-derivative was not obtainable under any conditions (not shown; see compound **3.40** in section 3.7.4.2). The presence of a conjugated aryl group on the silyl enol ether is also not well tolerated; see α-tetralone-derivative **3.17** (11% yield, entry 3).[xxiii] Aryl iodide **11**, showcasing aryl substitution on the 2-phenylpropene fragment, undergoes cyclization and annulation to **3.18** in 24% yield (entry 4); such products could potentially be employed in cross-coupling reactions for further synthetic elaboration. Methyl-substituted **3.19**, derived from the corresponding 2-methylpropenyl-substituted starting material **3.12**, was obtained in 22% yield (entry 5).

[xxii] Analysis of crude pre- and post-annulation ^{13}C NMR suggests the reason for exclusively high d.r. but low yield is most likely due to double diastereo-differentiation during annulation of intermediate **I**; diastereomers with a *trans*-configuration of the C–O and C–Nu bonds decompose and/or are easily separated away from the *cis*-bridged products. We have not attempted to isolate or characterize the intermediate ketone diastereomers (**I**).

[xxiii] Reaction with the corresponding acyclic acetophenone-derived silyl enol ether yielded only trace cyclized product (see section 3.7.4.2 and Figure 3.13 therein).

Table 3.2. Silyl enol ethers as trapping nucleophiles.



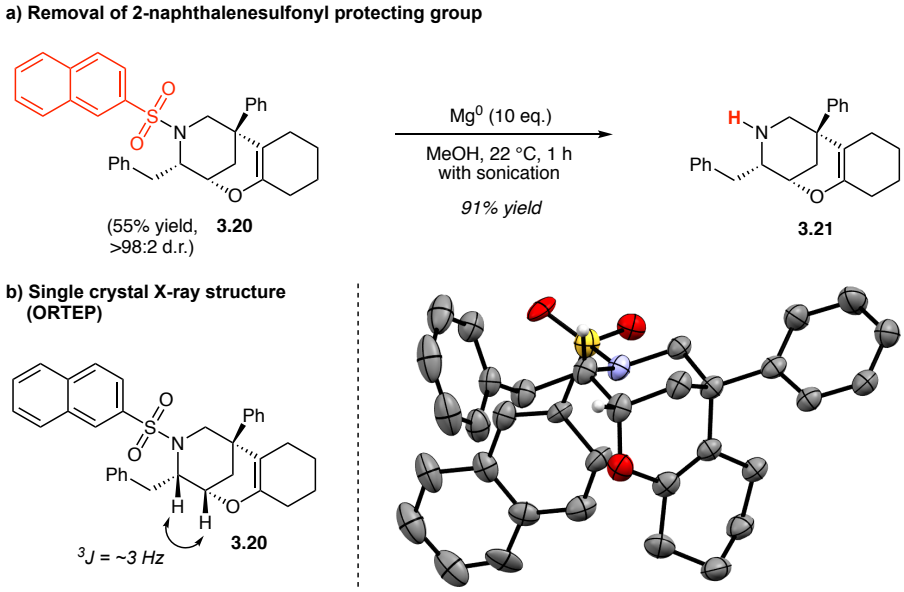
Entry	Substrate	Product	Yield% (NMR)[c]
1	 3.4	 3.13-3.15	n = 0: **3.13**; (trace) n = 1: **3.14**; 64%[d] n = 2: **3.15**; 22%
2	 3.10	 3.16	38%
3	 3.4	 3.17	11% (17%)
4[e]	 3.11	 3.18	24%
5[e]	 3.12	 3.19	22%

[a]Reactions were run in duplicate on a 0.05-0.1 mmol scale. [b]Bs = 4-bromo-benzenesulfonyl. [c]Dimethylformamide (DMF) used as ^{1}H NMR internal standard. [d]**3.14** was obtained in 52% yield using 1.10 eq. of silyl enol ether. [e]The reaction was warmed from –78 to –30 °C overnight, which increased yield and reproducibility.

3.5.1 Removal of aryl sulfonamide protecting groups and X-ray structure for **3.20**

In light of the knowledge that deprotection of simple aryl sulfonamides (*e.g.* tosyl (Ts), brosyl (Bs)) often requires aggressive reagents,[54] we endeavored to demonstrate removal under mild conditions. The 2-naphthalene sulfonamide-protected **3.20** was synthesized for this purpose (55%, see preparation of **3.20** in section 3.7.4.2 and Figure 3.16 therein for analytical data), and employing a modification of a previously reported reductive protocol,[55] provided free amine **3.21** (91% yield, Scheme 3.6a; for

experimental details and analytical data, see section 3.7.4.4). It is also notable that the more potent Na-naphthalenide reductant was able to effect the Bs-deprotection of **3.14** (93% yield, see section 3.7.4.4). X-ray analysis of **3.20** (CSD-1548662; Scheme 3.6b, see also section 3.7.4.3) confirmed the relative stereochemistry of the C–O bond and amino R-group to be *cis*-(axial-equatorial), respectively, consistent with $^{3}J_{CH\text{-}CH}$ = 3 Hz.[56]

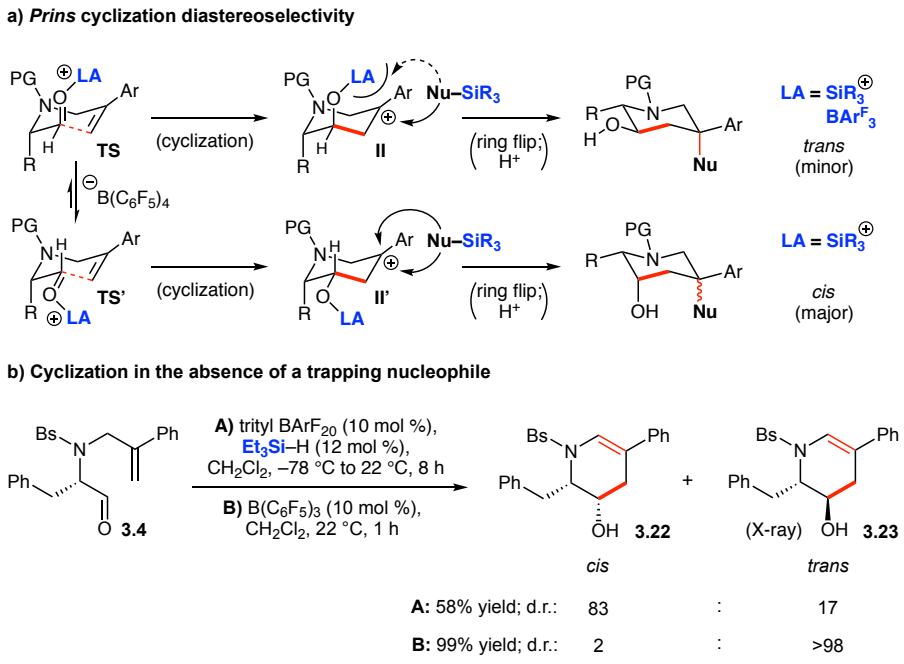


Scheme 3.6. Deprotection (a) and X-ray structure (b) of piperidine 3.20.

3.6 Mechanism: *Prins* cyclization diastereoselectivity; cyclization in the absence of trapping nucleophiles / cyclizations using other Lewis Acids

Based on the similarity in reactivity and observed vicinal *cis*-diastereoselectivity in the products resulting from both our putative silylium ion manifold and classical $TiCl_4$-promoted *Prins* cyclization conditions (see section 3.7.5.1), we suggest the mechanism in Scheme 3.7a: The strongly Lewis acidic silylium ion catalyst $[R_3Si][B(C_6F_5)_4]$ activates the aldehyde to nucleophilic attack by the appended alkene

via chair-like transition states **TS** and **TS'**;[xxiv] experimentation has shown **TS'** to be favored to arrive at the *cis*-diastereomer (**II'**). The ensuing trap of **II** and **II'** by R_3Si–Nu regenerates the $[R_3Si][B(C_6F_5)_4]$ catalyst.[xxv] The multiple observed diastereomers can be explained by invoking high facial discrimination in **II** *via* a 1,3-diaxial interaction, whereas **II'** contains almost no inherent facial bias.



Scheme 3.7. Proposed mechanism of the silylium-catalyzed *Prins* cyclization

Corroboration of our proposed mechanism was obtained by running the *Prins* cyclization in the absence of suitable trapping nucleophiles; upon warming to room temperature, elimination (an effective carbonyl-ene reaction) occurs to yield *cis*- and *trans*-

[xxiv] DFT calculations (ωB97X-D//6-311+G**//CPCM:CH_2Cl_2) on 2-methyl-1-(phenylsulfonyl)piperidine show the lowest energy axial conformer to be 3.3 kcal/mol more stable than the lowest energy equatorial conformer. We speculate that this is paralleled in **TS** and **TS'**.

[xxv] Interestingly, 10 mol % $HBArF_{24}$ ($[H(OEt_2)_2][B(C_6H_3(CF_3)_2)_4]$, Brookhart's acid) as catalyst provided hydride-trapped **3.6** (Table 3.1) in an inferior 47% NMR yield but 45:36:19 d.r. favoring the same diastereomers as those resulting from the putative silylium ion catalysis (*cf.* Table 3.1, Entry 2; see section 3.7.5.2 for experimental details). This suggests that the reaction can be catalyzed by Brønsted acid and that co-catalysis could be operative *via* adventitious water. See: Schmidt, R. K.; Muether, K.; Mueck-Lichtenfeld, C.; Grimme, S.; Oestreich, M. *J. Am. Chem. Soc.* **2012**, *134*, 4421.

tetrahydropyridine diastereomers **3.22** and **3.23**, respectively (58% yield, 83:17 d.r., Scheme 3.7b; see 3.7.5.3 for details).[xxvi] Intriguingly, application of the neutral Lewis acid $B(C_6F_5)_3$ at RT provides *trans*-**3.23** in 99% yield (see 3.7.5.4 for details).[xxvii] We attribute this reversal of diastereoselectivity to the larger steric environment (and lower reactivity) of $B(C_6F_5)_3$ only allowing for activation of the aldehyde in an exclusively *trans*-diaxial conformation.

In summary, we have developed a straightforward synthetic protocol that utilizes readily accessible, *in situ*-generated silylium ions to stereoselectively catalyze the conversion of acyclic amino alcohol-derived substrates into stereodefined *N*-heterocyclic pyrrolidine and piperidine derivatives. This represents an early and nascent example of how silylium ions can be harnessed in complexity-generating organic transformations. We hope that their high reactivity can be further modulated to better control and increase their selectivity.

3.7 Experimental Section

3.7.1 General Methods

All catalytic reactions were set up in a nitrogen-filled glovebox and run outside the glovebox under nitrogen atmosphere in oven-dried (130 °C) 1 dram (4 mL) vials with magnetic stirring unless otherwise specified. All catalytic reactions were run in duplicate

[xxvi] The relative stereochemistry of *cis*- and *trans*-tetrahydropyridine products was determined *via* X-ray crystallography and comparison of ^1H and ^{13}C NMR data (see **3.42**, section 3.7.5.4; for X-ray data, see section 3.7.5.5).

[xxvii] a) Attempts to intercept the carbocation with $R_3Si–Nu$ in the presence of BCF have been unsuccessful; $Et_3Si–H$ hydrosilylates the aldehyde in 32% NMR yield (see section A.5.4.1 for details), along with producing 44% of *trans*-tetrahydropyridine **3.23** and 7% and 12%, respectively, of minor diastereomers *B* and *C* of piperidine **3.6**. Unfortunately, variation of addition order and temperature did not allow for the clean, high-yielding production of any single product, especially piperidine **3.6**. b) Aldehyde hydrosilylation has been well documented; see Ref. 51.

on 0.05-0.1 mmol scale unless otherwise specified. Catalytic reactions that were performed at –78 °C were pre-cooled in vacuum dewars containing an acetone/$CO_{2(s)}$ mixture that was maintained throughout the course of the reaction. All other reactions were performed at ambient temperature (22 ºC, RT) unless otherwise specified. All solvents were subjected to three freeze-pump-thaw cycles and stored over activated molecular sieves in the glovebox prior to use. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Column chromatography was performed using SilaFlash P60 40-63 μm (230-400 mesh). Catalytic reaction products were purified *via* silica gel column chromatography on a 1.5 cm x 22 cm column using mixtures of *n*-pentane and ethyl acetate as eluents and gravity as pressure. Thin layer chromatography (TLC) was performed on SiliCycle Silica Gel 60 F254 plates and was visualized with UV light, cerium ammonium molybdate (CAM) stain, or potassium permanganate ($KMnO_4$) stain. General deprotection procedure: *Where indicated, catalytic reactions were treated with an acidic resin before attempted isolation to remove labile silyl protecting groups.* The catalytic reactions were quenched by addition of an excess of Et_3N (50 μL) or *i*-$PrNH_2$ (50 μL) at –78 °C (unless otherwise stated) and allowed to warm to room temperature before concentration *in vacuo* and placement under high vacuum for at least 1 h to remove excess amine. *Note: Complete removal of excess amine is necessary for the reproducibility of subsequent acid-catalyzed deprotections; repeated azeotroping with CH_2Cl_2 and drying under high vacuum facilitates removal of excess base.* The resulting residue was taken up in 2 mL of 1:1 CH_2Cl_2/MeOH, approximately 10-20 beads of Dowex resin (50W-X8) were added, and the reaction was stirred at 22 °C for 1 h (or the time indicated). *Note: Other, less aggressive acidic resins can also afford deprotected product, including pyridinium p-*

toluene sulfonate polymer-bound resin (PPTS) with extent of labeling 3.5 mmol/g toluene sulfonate loading purchased through Aldrich. The solution was then filtered by gravity through a plug of sand and cotton, rinsed through with excess CH_2Cl_2 (x2), concentrated *in vacuo*, and placed under high vacuum for at least 1 h before NMR analysis.

3.7.1.1 Instrumentation

All NMR spectra were recorded on a Bruker Avance 600 MHz spectrometer at standard temperature and pressure. All deuterated solvents were used as received from Cambridge Isotope Laboratories, Inc. The residual solvent protons (^1H) or the solvent carbons (^{13}C) were used as internal references. The following abbreviations are used in reporting NMR data: s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; sept, septet; dd, doublet of doublets; dt, doublet of triplets; dq, doublet of quartets; td, triplet of doublets; dt, doublet of triplets; tt, triplet of triplets; quint d, quintet of doublets; ddd, doublet of doublet of doublets; and m, multiplet. Where necessary, 2D COSY, 2D HSQC, and ^{13}C DEPT-135 data were used for peak assignment. All IR spectra were recorded on a Jasco 260 Plus Fourier transform infrared spectrometer with reporting from 4000-1000 cm^{-1} using the following abbreviations: s, strong; m, medium; w, weak; br, broad. High resolution mass spectra were obtained on a hybrid LTQ FT (ICR 7T) (ThermoFisher, Bremen, Germany) mass spectrometer where samples were introduced via a micro-electrospray source at a flow rate of 3 μL/min. The data were analyzed using Xcalibur (ThermoFisher, Breman, Germany) and theoretical masses were calculated using IsoPro 3.1. Specific rotations were obtained on a Jasco DIP-1000 digital polarimeter equipped with a sodium lamp at STP utilizing a 3.5 x 100 mm cell. X-ray crystallographic data were recorded on a Bruker APEX-II CCD diffractometer. A NesLab cryobath CB-80 was

utilized for reduced temperature reactions where temperature was verified by low-temperature thermometer. Sonication was performed in a Fisher Scientific FS60 Ultrasonic Cleaner with a frequency of 42 kHz.

3.7.1.2 Chemicals

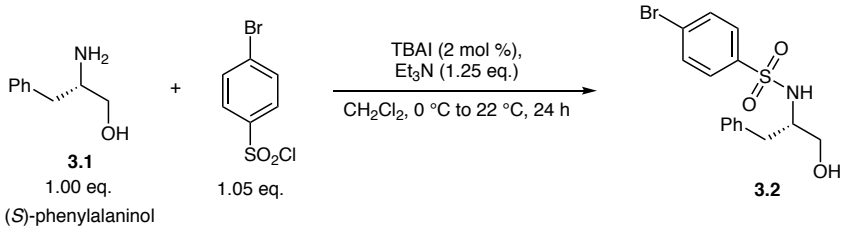
Me_2EtSiH, Et_3SiH, t-$BuMe_2SiH$, and *i*-Pr_3SiH were purchased from Gelest and stored over pre-activated molecular sieves in a dry, N_2-filled glovebox. Dichloromethane (CH_2Cl_2) and tetrahydrofuran (THF) were purchased from Sigma-Aldrich and used as received. Methanol was purchased from Fisher and used as received. Dichloromethane (for air/water free reactions) and toluene were passed through an alumina column in a solvent purification system prior to use. Trityl tetra(pentafluorophenyl)borate ($[Ph_3C][B(C_6F_5)_4]$, trityl $BArF_{20}$) was purchased from Strem and used as received. All aldehyde substrates were azeotropically dried three times with either dry toluene (solvent purification system) or benzene (freshly distilled over calcium hydride), followed by placement under high vacuum (~100 mtorr) overnight, before being stored at room temperature in a dry, N_2-filled glovebox. *Note: Based on periodic checks via ^{1}H NMR, the aldehydes appear to be stable for at least 6-12 months when stored at room temperature and under nitrogen in a glove box. The aldehydes often start to turn yellow→orange→brown over weeks to months of time, but no decomposition can be detected from periodic (homogenous) NMR aliquots.* Silyl enol ethers were prepared from their corresponding freshly distilled (over CaH_2) parent ketones using modified literature procedures,[57] purified *via* aluminum oxide chromatography (Aldrich; activated, neutral, Brockmann activity I slurried with 10% H_2O), and stored in a dry, N_2-filled glovebox. All obtained silyl enol ethers matched previously reported ^{1}H and $^{13}C\{^1H\}$ NMR data. Trityl tetra(pentafluorophenyl)borate

(97%, trityl $BArF_{20}$) was purchased from Strem Chemicals (catalog # 05-5000) and stored at room temperature in a dry, N_2-filled glove box. Tetrakis[3,5-bis(trifluoromethyl)phenyl] borate ($HBArF_{24}$) was prepared according to literature procedure and stored at –35 °C in a dry, N_2-filled glove box.[58]

3.7.2 Substrate synthesis and characterization

3.7.2.1 Synthesis of *N*-arylsulfonyl-protected amino alcohols

Preparation of aryl sulfonamide 3.2:

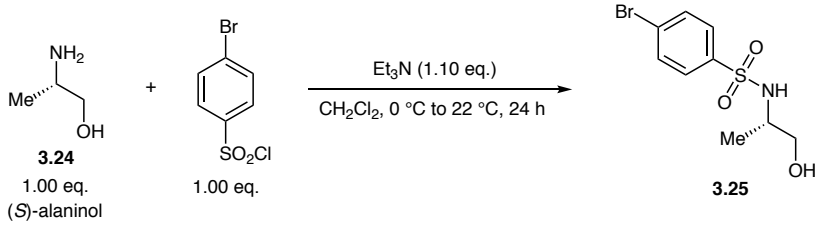


To a flame-dried 250 mL round-bottom flask equipped with a magnetic stir bar was added (*S*)-phenylalaninol (**3.1**, 26.5 mmol, 4.00 g, 1.00 eq.) and tetrabutylammonium iodide (0.530 mmol, 196 mg, 0.02 eq.). The flask was capped with a septum, an N_2 needle was inserted, and the headspace of the flask was purged with anhydrous N_2. CH_2Cl_2 (133 mL) and Et_3N (33.1 mmol, 4.62 mL, 1.25 eq.) were added. The flask was placed in an ice-water bath and cooled to 0 °C. The septum was quickly removed and 4-bromobenzene sulfonyl chloride (brosyl chloride, Bs–Cl; 27.8 mmol, 7.10 g, 1.05 eq.) was added quickly and the flask resealed. The homogeneous solution was warmed to 22 °C and stirred for 24 h. After 24 h, the solution was decanted into a separatory funnel and diluted with excess CH_2Cl_2 and washed with deionized water. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (x4). The combined organics were dried over

Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (9:1 dichloromethane:methanol; R_f = 0.35 in 1:1 hexanes:ethyl acetate) to yield the desired *N*-Bs amino alcohol **3.2** as an off-white, crystalline solid in 92% yield (9.05 g).

(*S*)-4-bromo-*N*-(1-hydroxy-3-phenylpropan-2-yl)benzenesulfonamide (3.2). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.52-7.44 (m, 4H), 7.21-7.15 (m, 3H), 6.96 (d, 2H, *J* = 6.5 Hz), 4.76 (d, 1H, *J* = 7.2 Hz), 3.69 (ddd, 1H, *J* = 11.3, 6.1, 4.0 Hz), 3.60 (dt, 1H, *J* = 11.1, 4.8 Hz), 3.45 (dddd, 1H, *J* = 11.4, 8.4, 6.2, 4.3 Hz), 2.83 (dd, 1H, *J* = 14.0, 6.2 Hz), 2.67 (dd, 1H, *J* = 13.9, 8.3 Hz), 2.01 (t, 1H, *J* = 5.6 Hz); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 138.8, 136.6, 132.4, 129.2, 128.9, 128.5, 127.7, 127.0, 64.7, 57.0, 38.0.

Preparation of aryl sulfonamide 3.25:

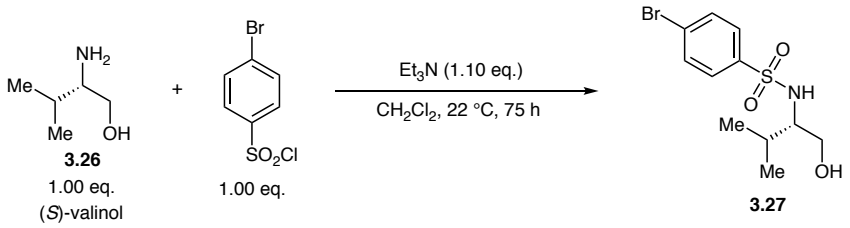


To a flame-dried 100 mL round-bottom flask equipped with a magnetic stir bar was added (*S*)-alaninol (**3.24**, 20.0 mmol, 1.56 mL, 1.00 eq.). The flask was capped with a septum, an N_2 needle was inserted, and the headspace of the flask was purged with anhydrous N_2. CH_2Cl_2 (40 mL) and Et_3N (22.0 mmol, 3.07 mL, 1.10 eq.) were added. The flask was placed in an ice-water bath and cooled to 0 °C. The septum was quickly removed and 4-bromobenzenesulfonyl chloride (brosyl chloride, Bs–Cl; 20.0 mmol, 5.11 g, 1.00 eq.) was added quickly and the flask resealed. The solution was warmed to 22 °C and

stirred for 24 h. After 24 h, the solution was decanted into a separatory funnel and diluted with excess CH_2Cl_2 and washed with deionized water. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (x4). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (9:1 dichloromethane:methanol; $R_f = 0.5$ in 2:1 ethylacetate:hexanes) to yield the desired *N*-Bs amino alcohol **3.25** as a white, crystalline solid in 91% yield (5.32 g).

(*S*)-4-bromo-*N*-(1-hydroxypropan-2-yl)benzenesulfonamide (3.25). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.76 (d, 2H, *J* = 8.6 Hz), 7.66 (d, 2H, *J* = 8.6 Hz), 4.82 (d, 1H, *J* = 7.2 Hz), 3.58 (d, 1H, *J* = 10.2 Hz), 3.49-3.39 (m, 2H), 1.88 (br s, 1H), 1.07 (d, 3H, *J* = 6.5 Hz); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 139.7, 132.6, 128.8, 127.9, 66.3, 51.6, 18.0.

Preparation of aryl sulfonamide 3.27:

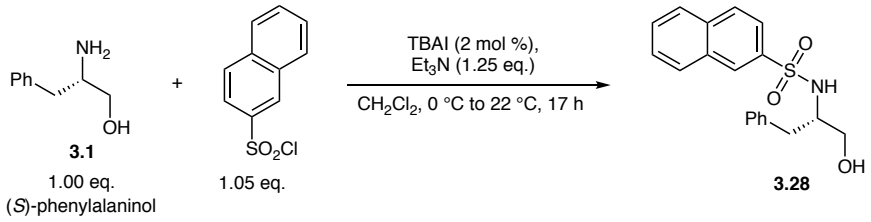


To a flame-dried 100 mL round-bottom flask equipped with a magnetic stir bar was added (*S*)-valinol (**3.26**, 19.4 mmol, 2.16 mL, 1.00 eq.). The flask was capped with a septum, an N_2 needle was inserted, and the headspace of the flask was purged with anhydrous N_2. CH_2Cl_2 (39 mL) and Et_3N (21.3 mmol, 2.97 mL, 1.10 eq.) were added. The septum was quickly removed and 4-bromobenzenesulfonyl chloride (brosyl chloride, Bs–Cl; 19.4 mmol, 4.96 g, 1.00 eq.) was added quickly and the flask resealed. The solution

was stirred for 75 h. After this time, the solution was decanted into a separatory funnel and diluted with excess CH_2Cl_2 and washed with deionized water. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (x4). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (9:1 dichloromethane:methanol) to yield the desired *N*-Bs amino alcohol **3.27** as an off-white, crystalline solid in 84% yield (5.24 g).

(*S*)-4-bromo-*N*-(1-hydroxy-3-methylbutan-2-yl)benzenesulfonamide (3.27). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.76 (d, 2H, *J* = 8.6 Hz), 7.65 (d, 2H, *J* = 8.5 Hz), 4.83 (d, 1H, *J* = 8.6 Hz), 3.63-3.54 (m, 2H), 3.09-3.04 (m, 1H), 1.84-1.78 (m, 2H), 0.81 (d, 6H, *J* = 6.2 Hz); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 139.9, 132.5, 128.8, 127.8, 63.1, 61.2, 29.7, 19.3, 18.6.

Preparation of aryl sulfonamide 3.28:



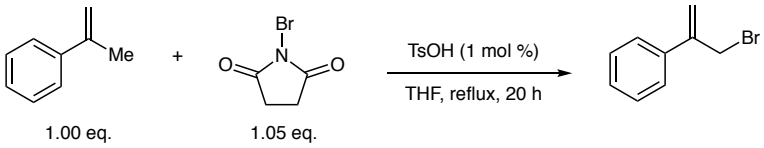
To a flame-dried 100 mL round-bottom flask equipped with a magnetic stir bar was added (*S*)-phenylalaninol (**3.1**, 6.61 mmol, 1.00 g, 1.00 eq.) and tetrabutylammonium iodide (0.13 mmol, 49 mg, 0.02 eq.). The flask was capped with a septum, an N_2 needle was inserted, and the headspace of the flask was purged with anhydrous N_2. CH_2Cl_2 (33 mL) and Et_3N (8.27 mmol, 1.15 mL, 1.25 eq.) were added. The flask was placed in an ice-water bath and cooled to 0 °C. The septum was quickly removed and 2-

naphthalenesulfonyl chloride (Naph–Cl; 6.94 mmol, 1.57 g, 1.05 eq.) was added quickly and the flask resealed. The solution was warmed to 22 °C and stirred for 17 h. After 17 h, the solution was decanted into a separatory funnel and diluted with excess CH_2Cl_2 and washed with deionized water. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (x4). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (1:1 hexanes:ethyl acetate; $R_f = 0.3$) to yield the desired *N*-arylsulfonyl amino alcohol **3.28** as a white, crystalline solid in 87% yield (1.97 g).

(*S*)-*N*-(1-hydroxy-3-phenylpropan-2-yl)naphthalene-2-sulfonamide (3.28). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.29 (d, 1H, *J* = 1.8 Hz), 7.90 (t, 2H, *J* = 8.3 Hz), 7.83 (d, 1H, *J* = 8.6 Hz), 7.66 (td, 1H, *J* = 6.9, 1.3 Hz), 7.62 (td, 1H, *J* = 6.8, 1.4 Hz), 7.59 (dd, 1H, *J* = 8.6, 1.9 Hz), 7.06-7.01 (m, 3H), 6.90 (dd, 2H, *J* = 8.0, 1.9), 4.83 (d, 1H, *J* = 7.0 Hz), 3.67 (ddd, 1H, *J* = 10.6, 6.3, 3.9 Hz), 3.57 (dt, 1H, *J* = 11.1, 5.0 Hz), 3.51 (qd, 1H, *J* = 7.1, 3.4 Hz), 2.79 (dd, 1H, *J* = 13.9, 6.6 Hz), 2.68 (dd, 1H, *J* = 13.9, 7.7 Hz), 1.06 (t, 1H, *J* = 6.6 Hz); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 136.5, 134.9, 132.2, 129.7, 129.4, 129.1, 129.0, 128.8, 128.6, 128.0, 127.7, 126.9, 122.2, 64.4, 56.8, 38.0.

3.7.2.2 Preparation of allyl bromides

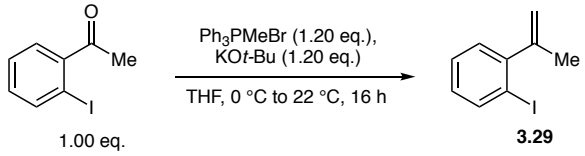
Preparation of 2-phenylallyl bromide:



2-Phenylallyl bromide was synthesized according to modified literature procedure.[59] A flame-dried round-bottom flask equipped with a magnetic stir bar was charged with α-methylstyrene (100 mmol, 13.0 mL, 1.00 eq.), *N*-bromosuccinimide (105 mmol, 18.7 g, 1.05 eq.), tosic acid monohydrate ($TsOH \cdot H_2O$; 1.00 mmol, 190 mg, 0.0100 eq.) and anhydrous THF (300 mL). The homogeneous solution was brought to reflux and vigorously stirred for 20 h. The reaction was allowed to cool to room temperature. The solution was decanted into a separatory funnel, diluted with hexanes and deionized water, and the organic layer was separated. The aqueous layer was then washed with three portions of hexanes. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford a yellow oil. The crude residue was purified by silica gel column chromatography (hexanes; $R_f = 0.5$) to provide the desired 2-phenylallyl bromide as a clear, light yellow oil in 58% yield (11.4 g). The spectral data of the bromide matched those previously reported.

(3-bromoprop-1-en-2-yl)benzene ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.52-7.49 (m, 2H), 7.41-7.32 (m, 3H), 5.57 (s, 1H), 5.50 (s, 1H), 4.40 (s, 2H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 144.3, 137.7, 128.6, 128.4, 126.2, 117.4, 34.4.

Preparation of 1-iodo-2-(prop-1-en-2-yl)benzene (3.29):

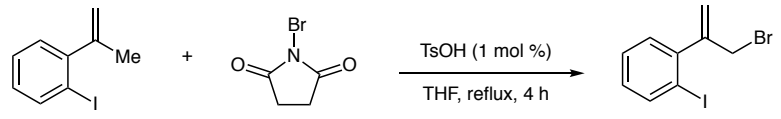


The title compound **(3.29)** was synthesized *via* modification to a general literature procedure.[59] A flame-dried Schlenk flask equipped with a magnetic stir bar was charged

with *anhydrous* potassium *tert*-butoxide (14.6 mmol, 1.64 g, 1.20 eq.) and methyltriphenylphosphonium bromide (14.6 mmol, 5.23 g, 1.20 eq.). The flask was placed under vacuum, backfilled with nitrogen, and then placed in a 0°C ice-water bath. Anhydrous THF (16 mL) was added down the side of the flask and the bright yellow mixture was stirred at 0°C for 45 minutes. Then a solution of 2'-iodoacetophenone (12.2 mmol, 1.74 mL, 1.00 eq.) in anhydrous THF (8 mL) was added drop-wise. The solution was gradually warmed to room temperature with stirring for 16 h. The solution was filtered, the filtrand washed with diethyl ether, and the resulting filtrate concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (hexanes; R_f = 0.65) to provide the desired 1-iodo-2-(prop-1-en-2-yl)benzene (**3.29**) as a clear, colorless oil in 89% yield (2.64 g).

1-iodo-2-(prop-1-en-2-yl)benzene (3.29) ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.83 (d, 1H, *J* = 7.9 Hz), 7.30 (t, 1H, *J* = 7.5 Hz), 7.18 (d, 1H, *J* = 7.6 Hz), 6.94 (t, 1H, *J* = 7.7 Hz), 5.22 (s, 1H), 4.89 (s, 1H), 2.07 (s, 1H); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 148.9, 148.6, 139.3, 128.6, 128.5, 128.2, 116.2, 97.1, 24.1.

Preparation of 2-(o-iodophenyl)allyl bromide 3.30:



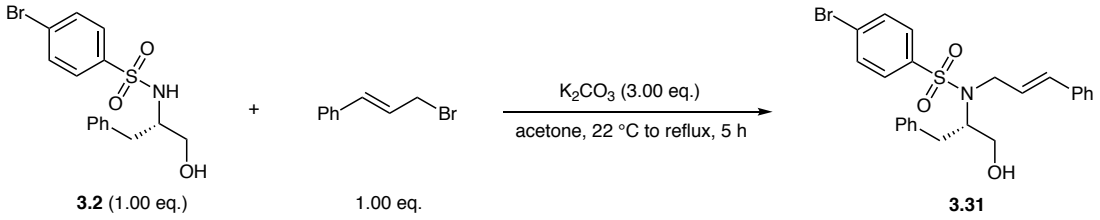
The title compound (**3.30**) was synthesized according to modified literature procedure.[59] A flame-dried round-bottom flask equipped with a magnetic stir bar was charged with 1-iodo-2-(prop-1-en-2-yl)benzene (**3.29**) (10.6 mmol, 2.57 g, 1.00 eq.), *N*-

bromosuccinimide (11.1 mmol, 1.97 g, 1.05 eq.), tosic acid monohydrate ($TsOH \cdot H_2O$; 0.11 mmol, 20 mg, 0.010 eq.) and anhydrous THF (32 mL). The homogeneous solution was brought to reflux and vigorously stirred for 4 h. The reaction was then cooled to room temperature. The solution was decanted into a separatory funnel, diluted with hexanes and deionized water, and the organic layer was separated. The aqueous layer was then washed with three portions of hexanes. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford a yellow oil. The crude residue was purified by silica gel column chromatography (hexanes; $R_f = 0.5$) to provide the desired 1-(3-bromoprop-1-en-2-yl)-2-iodobenzene (**3.30**) as a clear, colorless oil in 10% yield (347 mg). Note: 63% (1.62 g) of the starting material was able to be cleanly recovered (27% yield BORSM).

1-(3-bromoprop-1-en-2-yl)-2-iodobenzene (3.30) ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.86 (dd, 1H, *J* = 7.9, 1.2 Hz), 7.36 (td, 1H, *J* = 7.5, 1.2 Hz), 7.27 (dd, 1H, *J* = 7.6, 1.8 Hz), 7.02 (td, 1H, *J* = 7.7, 1.8 Hz), 5.65 (s, 1H), 5.19 (s, 1H), 4.31 (s, 2H); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 148.0, 144.3, 139.3, 130.7, 129.6, 128.1, 121.1, 97.5, 35.9.

3.7.2.3 *N*-alkylation of *N*-arylsulfonyl-protected amino alcohols

Preparation of *N*-alkylated amino alcohol 3.31:

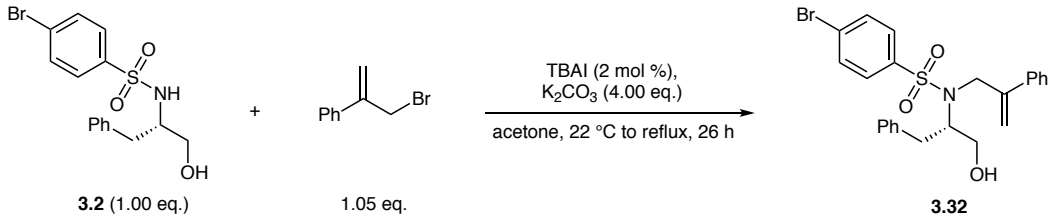


3.2 (1.00 eq.) 1.00 eq. **3.31**

To a flame-dried 50 mL round-bottom flask equipped with a magnetic stir bar was added aryl sulfonamide **3.2** (2.97 mmol, 1.10 g, 1.00 eq.) and powdered, anhydrous potassium carbonate (8.91 mmol, 1.23 g, 3.00 eq.). The flask was capped with a septum, an N_2 needle was inserted, and the headspace of the flask was purged with anhydrous N_2. Anhydrous acetone (22 mL) was added to dissolve the substrate, followed by cinnamyl bromide (2.97 mmol, 440 μL, 1.00 eq.). The flask was equipped with a reflux condenser, placed in an oil bath, and heated to reflux (approximately 60-65 °C oil bath temperature). The heterogeneous mixture was vigorously stirred for 5 h and then cooled to room temperature. The mixture was filtered through a cotton plug to remove potassium salts and then concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (3:1 hexanes:ethyl acetate; $R_f = 0.3$) to yield the *N*-alkylated amino alcohol product **3.31** as a clear, colorless, glassy solid in 89% yield (1.29 g).

(*S*)-4-bromo-*N*-cinnamyl-*N*-(1-hydroxy-3-phenylpropan-2-yl)benzenesulfonamide (3.31). ^{1}**H NMR** ($CDCl_3$, 600 MHz): δ 7.50-7.44 (m, 4H), 7.35-7.31 (m, 2H), 7.31-7.27 (m, 3H), 7.24-7.21 (m, 3H), 7.08-7.04 (m, 2H), 6.56 (d, 1H, J = 16.0 Hz), 6.10 (ddd, 1H, J = 16.0, 7.4, 6.0 Hz), 4.21 (qd, 1H, J = 7.8, 4.6 Hz), 4.13 (ddd, 1H, J = 16.0, 6.0, 1.6 Hz), 4.06 (ddd, 1H, J = 16.0, 7.4, 1.3 Hz), 3.75 (ddt, 1H, J = 11.6, 8.3, 4.8 Hz), 3.68 (dt, 1H, J = 11.3, 5.1 Hz), 2.85 (dd, 1H, J = 13.9, 7.6 Hz), 2.78 (dd, 1H, J = 13.9, 7.4 Hz), 1.85 (br s, 1H, J = 4.8 Hz); ^{13}**C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 139.9, 137.6, 136.1, 133.5, 132.3, 129.1, 128.9, 128.9, 128.8, 128.4, 127.5, 126.9, 126.6, 126.2, 63.1, 62.2, 46.9, 36.5.

Preparation of *N*-alkylated amino alcohol 3.32:

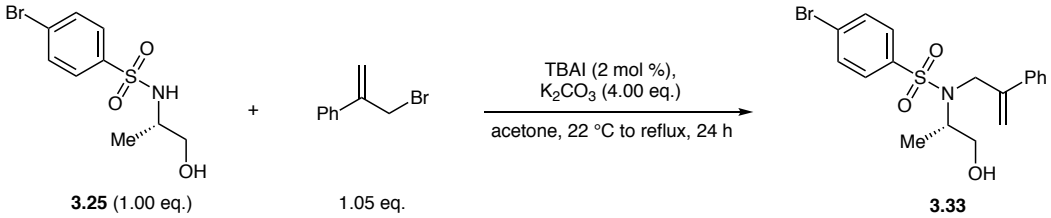


To a flame-dried 250 mL round-bottom flask equipped with a magnetic stir bar was added aryl sulfonamide **3.2** (10.0 mmol, 3.70 g, 1.00 eq.), tetrabutylammonium iodide (0.20 mmol, 75 mg, 0.02 eq.), and powdered, anhydrous potassium carbonate (40.0 mmol, 5.53 g, 4.00 eq.). The flask was capped with a septum, an N_2 needle was inserted, and the headspace of the flask was purged with anhydrous N_2. Anhydrous acetone (75 mL) was added to dissolve the substrate, followed by 2-phenylallyl bromide (10.5 mmol, 1.51 mL, 1.05 eq.). The flask was equipped with a reflux condenser, placed in an oil bath, and heated to reflux (approximately 60-65 °C oil bath temperature). The heterogeneous mixture was vigorously stirred for 26 h and then cooled to room temperature. The mixture was filtered through a cotton plug to remove potassium salts and then concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (3:1 hexanes:ethyl acetate; $R_f = 0.3$) to yield the *N*-alkylated amino alcohol product **3.32** as a crystalline white solid in 91% yield (4.41 g).

(*S*)-4-bromo-*N*-(1-hydroxy-3-phenylpropan-2-yl)-*N*-(2-phenylallyl)benzene sulfonamide (3.32). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.62 (d, 2H, $J = 8.6$ Hz), 7.58 (d, 2H, $J = 8.6$ Hz), 7.42-7.39 (m, 2H), 7.38-7.33 (m, 3H), 7.24-7.18 (m, 3H), 6.95 (dd, 2H, $J =$ 7.7, 1.7 Hz), 5.49 (s, 1H), 5.44 (s, 1H), 4.54 (d, 1H, $J = 16.3$ Hz), 4.35 (d, 1H, $J = 15.8$ Hz), 3.95 (tdd, 1H, $J = 9.1, 5.0, 4.1$ Hz), 3.61 (ddd, 1H, $J = 12.1, 8.5, 5.5$ Hz), 3.49 (ddd,

1H, J = 12.1, 7.2, 4.0 Hz), 2.77 (dd, 1H, J = 13.5, 9.8 Hz), 2.62 (dd, 1H, J = 13.5, 5.0 Hz), 1.51 (dd, 1H, J = 7.2, 5.6 Hz); **$^{13}C\{^{1}H\}$ NMR** ($CDCl_3$, 151 MHz): δ 145.1, 139.4, 138.4, 137.7, 132.5, 129.1, 129.1, 129.0, 128.8, 128.5, 127.9, 126.9, 126.8, 116.8, 62.5, 62.3, 49.4, 36.1.

Preparation of *N*-alkylated amino alcohol 3.33:

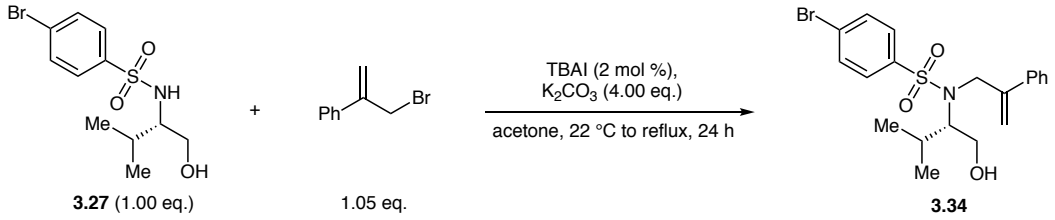


3.25 (1.00 eq.) 1.05 eq. **3.33**

To a flame-dried 100 mL round-bottom flask equipped with a magnetic stir bar was added aryl sulfonamide **3.25** (5.10 mmol, 1.50 g, 1.00 eq.), tetrabutylammonium iodide (0.10 mmol, 38 mg, 0.02 eq.), and powdered, anhydrous potassium carbonate (20.4 mmol, 2.82 g, 4.00 eq.). The flask was capped with a septum, an N_2 needle was inserted, and the headspace of the flask was purged with anhydrous N_2. Anhydrous acetone (38 mL) was added to dissolve the substrate, followed by 2-phenylallyl bromide (5.35 mmol, 770 µL, 1.05 eq.). The flask was equipped with a reflux condenser, placed in an oil bath, and heated to reflux (approximately 60-65 °C oil bath temperature). The heterogeneous mixture was vigorously stirred for 24 h and then cooled to room temperature. The mixture was filtered through a cotton plug to remove potassium salts and then concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (25:1 dichloromethane:methanol; R_f = 0.25 in 2:1 hexanes:ethyl acetate) to yield the *N*-alkylated amino alcohol product **3.33** as a white, crystalline solid in 97% yield (2.03 g).

(*S*)-4-bromo-*N*-(1-hydroxypropan-2-yl)-*N*-(2-phenylallyl)benzenesulfonamide (3.33). **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 7.66-7.62 (m, 4H), 7.44 (d, 2H, *J* = 6.9 Hz), 7.36 (t, 2H, *J* = 7.7 Hz), 7.34 (t, 1H, *J* = 7.1 Hz), 5.45 (s, 1H), 5.38 (s, 1H), 4.60 (d, 1H, *J* = 16.1 Hz), 4.08 (d, 1H, *J* = 16.1 Hz), 3.94 (dqd, 1H, *J* = 8.8, 7.0, 4.6 Hz), 3.49 (ddd, 1H, *J* = 11.7, 8.8, 4.6 Hz), 3.38 (ddd, 1H, *J* = 11.7, 8.2, 4.8 Hz), 1.51 (dd, 1H, *J* = 8.3, 4.7 Hz), 0.91 (d, 3H, *J* = 7.0 Hz); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 145.0, 139.3, 138.3, 132.5, 129.0, 128.8, 128.5, 127.8, 126.8, 116.2, 64.7, 56.3, 48.3, 13.7.

Preparation of *N*-alkylated amino alcohol 3.34:

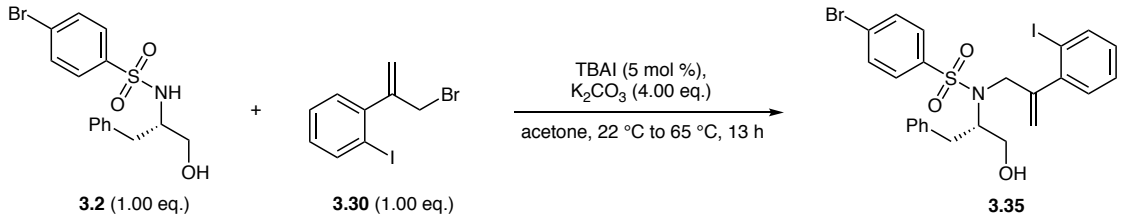


To a flame-dried 100 mL round-bottom flask equipped with a magnetic stir bar was added aryl sulfonamide **3.27** (4.66 mmol, 1.50 g, 1.00 eq.), tetrabutylammonium iodide (0.093 mmol, 34 mg, 0.02 eq.), and powdered, anhydrous potassium carbonate (18.6 mmol, 2.57 g, 4.00 eq.). The flask was capped with a septum, an N_2 needle was inserted, and the headspace of the flask was purged with anhydrous N_2. Anhydrous acetone (35 mL) was added to dissolve the substrate, followed by 2-phenylallyl bromide (4.89 mmol, 703 μL, 1.05 eq.). The flask was equipped with a reflux condenser, placed in an oil bath, and heated to reflux (approximately 60-65 °C oil bath temperature). The heterogeneous mixture was vigorously stirred for 24 h and then cooled to room temperature. The mixture was filtered through a cotton plug to remove potassium salts and then concentrated *in*

vacuo. The crude residue was purified by silica gel chromatography (3:1 hexanes:ethyl acetate; R_f = 0.5 in 2:1 hexanes:ethyl acetate) to yield the *N*-alkylated amino alcohol product **3.34** as a clear, colorless, viscous oil in 86% yield (1.76 g).

(*S*)-4-bromo-*N*-(1-hydroxy-3-methylbutan-2-yl)-*N*-(2-phenylallyl)benzenesulfonamide (3.34). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.66 (d, 2H, *J* = 8.6 Hz), 7.59 (d, 2H, *J* = 8.6 Hz), 7.32-7.29 (m, 3H), 7.26-7.24 (m, 2H), 5.42 (s, 1H), 5.39 (s, 1H), 4.40 (d, 1H, *J* = 16.0 Hz), 4.28 (d, 1H, *J* = 16.2 Hz), 3.70 (dt, 1H, *J* = 12.6, 3.9 Hz), 3.59 (ddd, 1H, *J* = 12.3, 6.1, 2.8 Hz), 3.47 (ddd, 1H, *J* = 10.3, 8.5, 3.6 Hz), 1.89 (dsept, 1H, *J* = 10.3, 6.6 Hz), 1.62 (br, m, 1H), 0.88 (d, 3H, *J* = 6.5 Hz), 0.58 (d, 3H, *J* = 6.6 Hz); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 145.0, 140.0, 139.0, 132.2, 129.4, 128.7, 128.4, 127.6, 126.7, 117.5, 67.3, 62.4, 49.4, 28.2, 20.9, 20.4.

Preparation of *N*-alkylated amino alcohol 3.35:



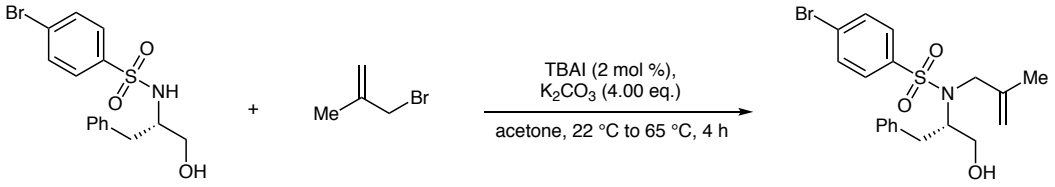
3.2 (1.00 eq.) **3.30** (1.00 eq.) **3.35**

To a flame-dried 20 mL scintillation vial equipped with a magnetic stir bar was added aryl sulfonamide **3.2** (1.07 mmol, 398 mg, 1.00 eq.), tetrabutylammonium iodide (0.054 mmol, 20 mg, 0.05 eq.), and powdered, anhydrous potassium carbonate (4.30 mmol, 594 mg, 4.00 eq.). The vial was capped with a septum, an N_2 needle was inserted, and the headspace of the vial was purged with anhydrous N_2. Anhydrous acetone (8.1 mL) was added to dissolve the substrate, followed by 1-(3-bromoprop-1-en-2-yl)-2-

iodobenzene (**3.30**, 1.07 mmol, 347 mg, 1.00 eq.). The vial was capped, placed in an oil bath, and heated to 65 °C. The heterogeneous mixture was vigorously stirred for 13 h and then cooled to room temperature. The mixture was filtered through a cotton plug to remove potassium salts and then concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (3:1 hexanes:ethyl acetate; $R_f = 0.3$) to yield the *N*-alkylated amino alcohol product **3.35** as a white, sticky solid in 77% yield (507 mg).

(*S*)-4-bromo-*N*-(1-hydroxy-3-phenylpropan-2-yl)-*N*-(2-(2-iodophenyl)allyl)benzene sulfonamide (3.35). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.85 (d, 1H, *J* = 7.9 Hz), 7.63 (d, 2H, *J* = 8.7 Hz), 7.55 (d, 2H, *J* = 8.5 Hz), 7.33 (t, 1H, *J* = 7.4 Hz), 7.28-7.21 (m, 3H), 7.12 (d, 1H, *J* = 7.6 Hz), 7.08 (d, 2H, *J* = 8.1 Hz), 7.04 (t, 1H, *J* = 7.7 Hz), 5.62 (s, 1H), 5.20 (s, 1H), 4.22 (d, 1H, *J* = 17.3 Hz, 1H), 4.17 (d, 1H, *J* = 17.2 Hz, 1H), 4.09-4.03 (m, 1H), 3.73 (ddd, 1H, *J* = 13.3, 7.9, 5.8 Hz), 3.67 (ddd, 1H, *J* = 11.6, 6.3, 4.1 Hz), 2.90 (dd, 1H, *J* = 13.7, 9.2 Hz), 2.78 (dd, 1H, *J* = 13.7, 5.6 Hz), 1.89 (t, 1H, *J* = 6.1 Hz); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 148.0, 144.8, 139.5, 139.2, 137.7, 132.4, 130.1, 129.5, 129.1, 129.0, 128.8, 128.4, 127.8, 126.9, 118.7, 97.7, 63.2, 63.0, 50.3, 36.5.

Preparation of *N*-alkylated amino alcohol 3.36:



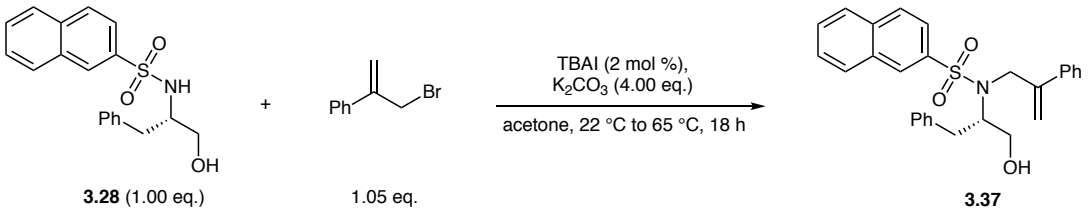
3.2 (1.00 eq.) 1.05 eq. **3.36**

To a flame-dried 20 mL scintillation vial equipped with a magnetic stir bar was added aryl sulfonamide **3.2** (2.03 mmol, 750 mg, 1.00 eq.), tetrabutylammonium iodide

(0.041 mmol, 15 mg, 0.02 eq.), and powdered, anhydrous potassium carbonate (8.10 mmol, 1.12 g, 4.00 eq.). The vial was capped with a septum, an N_2 needle was inserted, and the headspace of the vial was purged with anhydrous N_2. Anhydrous acetone (15 mL) was added to dissolve the substrate, followed by 3-bromo-2-methylpropene (2.13 mmol, 221 μL, 1.05 eq.). The vial was capped, placed in an oil bath, and heated to 65 °C. The heterogeneous mixture was vigorously stirred for 4 h and then cooled to room temperature. The mixture was filtered through a cotton plug to remove potassium salts and then concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (3:1 hexanes:ethyl acetate; $R_f = 0.3$) to yield the *N*-alkylated amino alcohol product **3.36** as a light yellow, viscous oil in 93% yield (800 mg).

(*S*)-4-bromo-*N*-(1-hydroxy-3-phenylpropan-2-yl)-*N*-(2-methylallyl)benzene sulfonamide (3.36). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.62 (d, 2H, *J* = 8.6 Hz), 7.57 (d, 2H, *J* = 8.6 Hz), 7.24-7.16 (m, 3H), 7.00 (dd, 2H, *J* = 7.2, 2.2 Hz), 5.06 (s, 1H), 5.00 (s, 1H), 4.01-3.93 (m, 2H), 3.86 (d, 1H, *J* = 15.8 Hz), 3.70 (ddd, 1H, *J* = 11.8, 8.1, 6.2 Hz), 3.60 (ddd, 1H, *J* = 11.8, 5.9, 4.2 Hz), 2.80 (dd, 1H, *J* = 13.6, 9.0 Hz), 2.71 (dd, 1H, *J* = 13.7, 5.8 Hz), 1.93 (t, 1H, *J* = 6.1 Hz), 1.80 (s, 3H); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 142.7, 139.7, 137.7, 132.4, 129.0, 128.8, 128.8, 127.7, 126.8, 114.5, 62.7, 62.4, 51.6, 36.0, 20.2.

Preparation of *N*-alkylated amino alcohol 3.37:



3.28 (1.00 eq.) 1.05 eq. **3.37**

To a flame-dried 20 mL scintillation vial equipped with a magnetic stir bar was added aryl sulfonamide **3.28** (2.20 mmol, 750 mg, 1.00 eq.), tetrabutylammonium iodide (0.044 mmol, 16 mg, 0.02 eq.), and powdered, anhydrous potassium carbonate (8.79 mmol, 1.22 g, 4.00 eq.). The vial was capped with a septum, an N_2 needle was inserted, and the headspace of the vial was purged with anhydrous N_2. Anhydrous acetone (8.8 mL) was added to dissolve the substrate, followed by 2-phenylallyl bromide (2.31 mmol, 332 μL, 1.05 eq.). The vial was capped, placed in an oil bath, and heated to 65 °C. The heterogeneous mixture was vigorously stirred for 18 h and then cooled to room temperature. The mixture was filtered through a cotton plug to remove potassium salts and then concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (3:1 hexanes:ethyl acetate; $R_f = 0.25$) to yield the *N*-alkylated amino alcohol product **3.37** as a white, crystalline solid in 93% yield (937 mg).

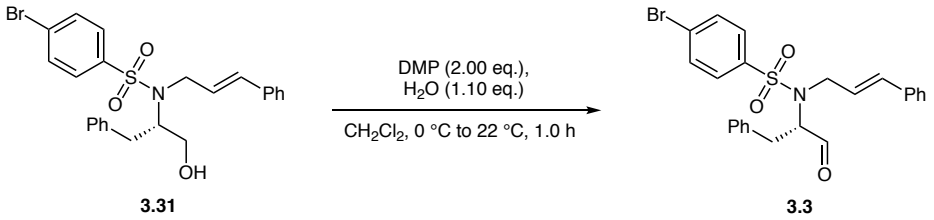
(*S*)-*N*-(1-hydroxy-3-phenylpropan-2-yl)-*N*-(2-phenylallyl)naphthalene-2-sulfonamide (3.37). **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 8.43 (br s, 1H), 7.96 (d, 1H, *J* = 8.0 Hz), 7.92 (dd, 2H, *J* = 8.4, 5.0 Hz), 7.75 (dd, 1H, *J* = 8.8, 1.3 Hz), 7.67 (t, 1H, *J* = 7.0 Hz), 7.64 (t, 1H, *J* = 7.1 Hz), 7.43 (dd, 2H, *J* = 6.6, 2.9 Hz), 7.34-7.31 (m, 3H), 7.09 (t, 3H, *J* = 3.2 Hz), 6.83 (dd, 2H, *J* = 6.3, 3.1 Hz), 5.50 (s, 1H), 5.47 (s, 1H), 4.68 (d, 1H, *J* = 16.1 Hz), 4.38 (d, 1H, *J* = 16.1 Hz), 3.99 (tt, 1H, *J* = 8.7, 4.1 Hz), 3.61 (ddd, 1H, *J* = 12.2, 8.6, 5.4 Hz), 3.48 (ddd, 1H, *J* = 11.8, 7.6, 3.8 Hz), 2.74 (dd, 1H, *J* = 13.3, 10.4 Hz), 2.53 (dd, 1H, *J* = 13.3, 4.4 Hz), 1.60 (dd, 1H, *J* = 7.6, 5.4 Hz); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 145.4, 138.4, 137.7, 137.0, 135.0, 132.3, 129.7, 129.4, 129.2, 129.1, 129.0, 128.8, 128.7, 128.5, 128.1, 127.8, 126.8, 126.7, 122.7, 116.5, 62.4, 62.2, 49.4, 36.0.

3.7.2.4 Synthesis of amino aldehydes

General procedure 3.1

To a flame-dried scintillation vial or round-bottom flask equipped with a magnetic stir bar was added *N*-alkylated amino alcohol (1.00 eq.) and Dess-Martin periodinane (DMP; 2.00 eq.). The flask was capped with a septum, an N_2 needle was inserted, the headspace of the flask was purged with anhydrous N_2, and the flask was placed in a 0 °C ice-water bath. Anhydrous CH_2Cl_2 (0.1 M in substrate) was added down the side of the flask with vigorous stirring, resulting in a colorless, homogeneous solution. Deionized water (1.10 eq.) was injected *via* microliter syringe and the ice-water bath was removed, allowing the solution to warm to RT. The solution rapidly became heterogeneous and milky white upon addition of the water. The heterogeneous mixture was vigorously stirred for approximately 1.0 h, at which time thin layer chromatography on SiO_2 showed complete conversion. The mixture was again cooled to 0 °C in an ice-water bath and quenched by the drop-wise addition of an equal volume of 1:1 sat. $NaHCO_{3\,(aq.)}$: sat. $Na_2S_2O_{3\,(aq.)}$ (sodium thiosulfate). After evolution of $CO_{2\,(g)}$ was complete, the solution was warmed to RT and stirred for an additional 30 minutes. The resulting homogeneous solution was then decanted into a separatory funnel, diluted with excess CH_2Cl_2, and washed with deionized water. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (x4). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified first by filtration with CH_2Cl_2 through a short plug of neutral aluminum oxide (Brockmann activity I slurried with 10% H_2O), followed by silica gel chromatography (mixtures of hexanes:ethyl acetate) to yield the pure amino aldehyde products.

Preparation of amino aldehyde 3.3:



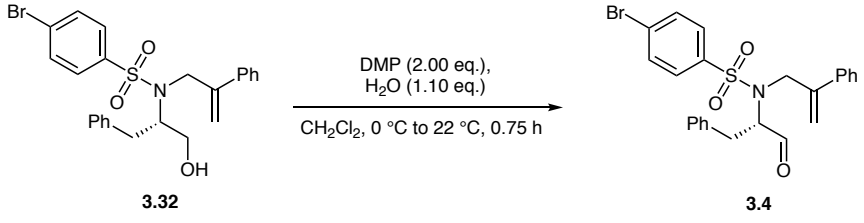
3.31 **3.3**

Following general procedure 3.1, *N*-alkylated amino alcohol **3.31** (0.905 mmol, 440 mg, 1.00 eq.) was oxidized with DMP (2.00 eq.) over 1.0 h. The crude residue was purified by silica gel chromatography (4:1 hexanes:ethyl acetate; $R_f = 0.4$) to yield the amino aldehyde product **3.3** as an off-white crystalline solid in 84% yield (370 mg).

(*S*)-4-bromo-*N*-cinnamyl-*N*-(1-oxo-3-phenylpropan-2-yl)benzenesulfonamide (3.3).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 9.72 (s, 1H), 7.47 (d, 2H, $J = 8.6$ Hz), 7.40 (d, 2H, $J = 8.6$ Hz), 7.35-7.30 (m, 2H), 7.30-7.26 (m, 3H), 7.26-7.20 (m, 3H), 7.06 (d, 2H, $J = 6.6$ Hz), 6.42 (d, 1H, $J = 15.8$ Hz), 5.98 (dt, 1H, $J = 15.9, 7.0$ Hz), 4.59 (dd, 1H, $J = 9.5, 5.2$ Hz), 4.03-3.92 (m, 2H), 3.45 (dd, 1H, $J = 14.7, 5.2$ Hz), 2.83 (dd, 1H, $J = 14.7, 9.5$ Hz); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 198.9, 139.2, 136.9, 135.8, 135.6, 132.4, 129.1, 128.9, 128.9, 128.8, 128.6, 127.9, 127.0, 126.7, 123.7, 67.7, 48.6, 33.3; **$[\alpha]_D^{26}$** = –129.0° (c = 1.070, CH_2Cl_2, l = 100 mm).

Preparation of amino aldehyde 3.4:

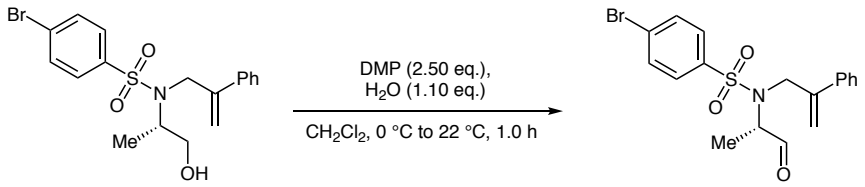


3.32 **3.4**

Following general procedure 3.1, *N*-alkylated amino alcohol **3.32** (4.79 mmol, 2.33 g, 1.00 eq.) was oxidized with DMP (2.00 eq.) over 0.75 h. *Note: In our hands, 1.75-2.00 eq. of DMP are necessary to attain full conversion.* The crude residue was purified by silica gel chromatography (4:1 hexanes:ethyl acetate; $R_f = 0.5$) to yield the amino aldehyde product **3.4** as a beige solid in 85% yield (1.98 g).

(*S*)-4-bromo-*N*-(1-oxo-3-phenylpropan-2-yl)-*N*-(2-phenylallyl)benzenesulfonamide (3.4). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 9.15 (s, 1H), 7.61-7.55 (m, 4H), 7.32-7.27 (m, 3H), 7.23-7.20 (m, 3H), 7.20-7.18 (m, 2H), 7.00-6.96 (m, 2H), 5.41 (s, 1H), 5.04 (s, 1H), 4.37 (d, 1H, $J = 14.8$ Hz), 4.10 (dd, 1H, $J = 8.3, 5.5$ Hz), 3.94 (d, 1H, $J = 14.8$ Hz), 3.41 (dd, 1H, $J = 14.6, 5.5$ Hz), 2.82 (dd, 1H, $J = 14.6, 8.3$ Hz); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 197.9, 142.9, 138.8, 137.6, 137.5, 132.6, 129.3, 129.2, 128.8, 128.8, 128.6, 128.4, 127.0, 126.7, 119.3, 67.5, 51.5, 33.6; **$[\alpha]_D^{25}$** = –100.7° (c = 1.525, CH_2Cl_2, l = 100 mm).

Preparation of amino aldehyde 3.10:

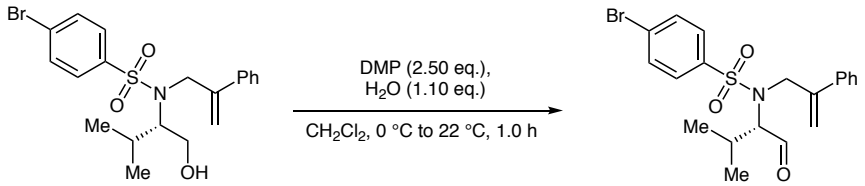


3.33 **3.10**

Following general procedure 3.1, *N*-alkylated amino alcohol **3.33** (2.44 mmol, 1.00 g, 1.00 eq.) was oxidized with DMP (2.50 eq.) over 1.0 h. The crude residue was purified by silica gel chromatography (3:1 hexanes:ethyl acetate; $R_f = 0.5$) to yield the amino aldehyde product **3.10** as a white, crystalline solid in 54% yield (524 mg).

(*S*)-4-bromo-*N*-(1-oxopropan-2-yl)-*N*-(2-phenylallyl)benzenesulfonamide (3.10). **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 9.17 (s, 1H), 7.66 (s, 4H), 7.36-7.32 (m, 5H), 5.49 (s, 1H), 5.29 (s, 1H), 4.47 (d, 1H, *J* = 14.9 Hz), 4.17 (d, 1H, *J* = 14.9 Hz), 4.07 (q, 1H, *J* = 7.0 Hz), 1.18 (d, 3H, *J* = 7.0 Hz); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 199.5, 142.5, 138.6, 137.4, 132.7, 129.1, 128.8, 128.6, 128.4, 126.8, 118.8, 61.5, 50.0, 11.0; **$[\alpha]_D^{26}$** = –3.04° (c = 0.540, CH_2Cl_2, l = 100 mm).

Preparation of amino aldehyde 3.38:

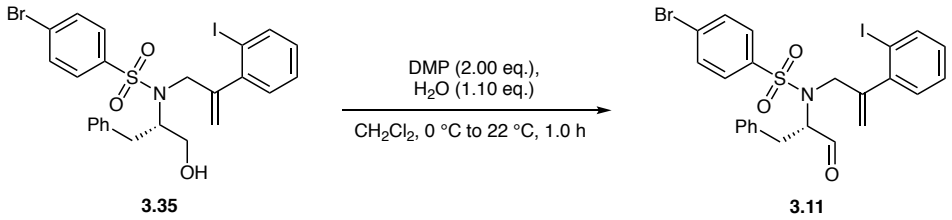


3.34 **3.38**

Following general procedure 3.1, *N*-alkylated amino alcohol **3.34** (1.71 mmol, 750 mg, 1.00 eq.) was oxidized with DMP (2.50 eq.) over 1.0 h. The crude residue was purified by silica gel chromatography (4:1 hexanes:ethyl acetate) to yield the amino aldehyde product **3.38** as a clear, colorless, viscous oil in 94% yield (701 mg).

(*S*)-4-bromo-*N*-(3-methyl-1-oxobutan-2-yl)-*N*-(2-phenylallyl)benzenesulfonamide (3.38). **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 9.36 (s, 1H), 7.61-7.58 (m, 4 H), 7.31-7.26 (m, 3H), 7.25-7.21 (m, 2H), 5.43 (s, 1H), 5.30 (s, 1H), 4.40 (d, 1H, *J* = 15.7 Hz), 4.28 (d, 1H, *J* = 15.8), 3.70 (d, 1H, *J* = 10.1), 2.32 (dsept, 1H, *J* = 10.1, 6.6 Hz), 1.03 (d, 3H, *J* = 6.5 Hz), 0.79 (d, 3H, *J* = 6.7 Hz); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 198.4, 143.3, 139.1, 138.3, 132.4, 129.3, 128.7, 128.4, 128.4, 126.7, 118.8, 71.5, 51.3, 27.9, 20.5, 20.3; **$[\alpha]_D^{26}$** = –3.13° (c = 0.565, CH_2Cl_2, l = 100 mm).

Preparation of amino aldehyde 3.11:

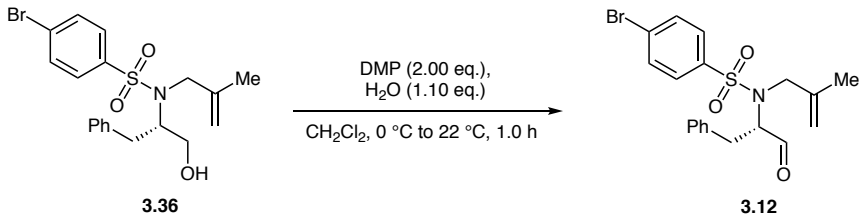


3.35 **3.11**

Following general procedure 3.1, *N*-alkylated amino alcohol **3.35** (0.804 mmol, 492 mg, 1.00 eq.) was oxidized with DMP (2.00 eq.) over 1.0 h. The crude residue was purified by silica gel chromatography (4:1 hexanes:ethyl acetate; $R_f = 0.4$) to yield the amino aldehyde product **3.11** as a light yellow, waxy solid in 79% yield (386 mg).

(*S*)-4-bromo-*N*-(2-(2-iodophenyl)allyl)-*N*-(1-oxo-3-phenylpropan-2-yl)benzene sulfonamide (3.11). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 9.62 (s, 1H), 7.68 (dd, 1H, *J* = 8.0, 1.2 Hz), 7.47 (d, 2H, *J* = 8.7 Hz), 7.44 (d, 2H, *J* = 8.7 Hz), 7.34-7.30 (m, 2H), 7.28-7.24 (m, 3H), 7.20 (td, 1H, *J* = 7.5, 1.2 Hz), 6.96 (td, 1H, *J* = 7.7, 1.7 Hz), 6.82 (dd, 1H, *J* = 7.6, 1.7 Hz), 5.14 (s, 1H), 5.09 (s, 1H), 4.21 (dd, 1H, *J* = 8.7, 5.2 Hz), 4.15 (d, 1H, *J* = 15.7 Hz), 3.59 (dd, 1H, *J* = 14.5, 5.2 Hz), 3.41 (d, 1H, *J* = 15.7 Hz), 3.08 (dd, 1H, *J* = 14.5, 8.7 Hz); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 197.6, 145.9, 143.4, 139.7, 137.8, 137.7, 132.4, 129.5, 129.5, 129.4, 129.4, 129.0, 128.5, 128.2, 127.2, 121.9, 97.5, 67.9, 52.4, 35.0; **$[\alpha]_D^{26}$** = –58.2° (c = 0.645, CH_2Cl_2, l = 100 mm).

Preparation of amino aldehyde 3.12:

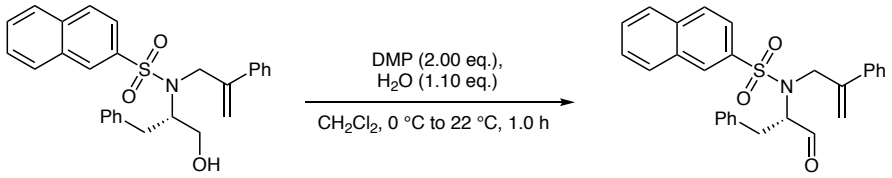


3.36 **3.12**

Following general procedure 3.1, *N*-alkylated amino alcohol **3.36** (1.91 mmol, 812 mg, 1.00 eq.) was oxidized with DMP (2.00 eq.) over 1.0 h. The crude residue was purified by silica gel chromatography (4:1 hexanes:ethyl acetate; $R_f = 0.4$) to yield the amino aldehyde product **3.12** as an off-white, crystalline solid in 75% yield (603 mg).

(*S*)-4-bromo-*N*-(2-methylallyl)-*N*-(1-oxo-3-phenylpropan-2-yl)benzenesulfonamide (3.12). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 9.70 (s, 1H), 7.57 (s, 4H), 7.22-7.17 (m, 3H), 7.01-6.97 (m, 2H), 4.96 (s, 1H), 4.81 (s, 1H), 4.20 (dd, 1H, J = 8.5, 5.7 Hz), 3.78 (d, 1H, J = 14.7 Hz), 3.52 (d, 1H, J = 14.7 Hz), 3.43 (dd, 1H, J = 14.6, 5.7 Hz), 2.83 (dd, 1H, J = 14.6, 8.5 Hz), 1.66 (s, 3H); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 198.2, 139.6, 139.1, 137.2, 132.5, 129.1, 129.1, 128.9, 128.1, 127.0, 117.7, 67.4, 53.3, 33.3, 19.9. **$[\alpha]_D^{25}$** = –52.3° (c = 0.650, CH_2Cl_2, l = 100 mm).

Preparation of amino aldehyde 3.39:



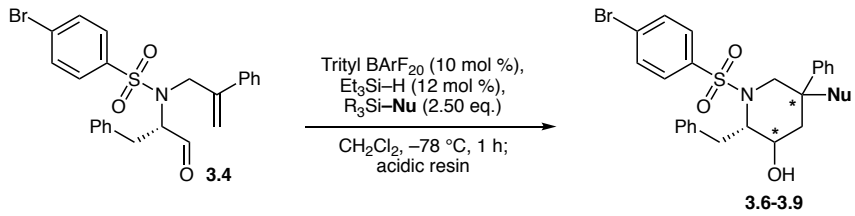
3.37 **3.39**

Following general procedure 3.1, *N*-alkylated amino alcohol **3.37** (1.37 mmol, 625 mg, 1.00 eq.) was oxidized with DMP (2.00 eq.) over 1.0 h. The crude residue was purified by silica gel chromatography (4:1 hexanes:ethyl acetate; $R_f = 0.4$) to yield the amino aldehyde product **3.39** as an off-white to light yellow crystalline solid in 95% yield (591 mg).

(*S*)-*N*-(1-oxo-3-phenylpropan-2-yl)-*N*-(2-phenylallyl)naphthalene-2-sulfonamide (3.39). **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 9.19 (s, 1H), 8.39 (d, 1H, *J* = 1.9 Hz), 7.95 (d, 2H, *J* = 9.3 Hz), 7.92 (d, 1H, *J* = 8.7 Hz), 7.75-7.60 (m, 3H), 7.26-7.22 (m, 1H), 7.19-7.13 (m, 4H), 7.15-7.12 (m, 3H), 6.91 (d, 2H, *J* = 6.4 Hz), 5.39 (s, 1H), 4.99 (s, 1H), 4.46 (d, 1H, *J* = 14.7 Hz), 4.11 (dd, 1H, *J* = 8.0, 5.5 Hz), 3.97 (d, 1H, *J* = 14.7 Hz), 3.42 (dd, 1H, *J* = 14.5, 5.4 Hz), 2.84 (dd, 1H, *J* = 14.5, 8.1 Hz); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 198.1, 142.9, 137.8, 137.4, 136.4, 135.1, 132.2, 129.7, 129.5, 129.5, 129.3, 129.2, 128.6, 128.6, 128.5, 128.0, 127.9, 126.7, 126.7, 122.8, 119.1, 67.3, 51.5, 33.5; **$[\alpha]_D^{26}$** = –110.5° (c = 0.515, CH_2Cl_2, l = 100 mm).

3.7.3 *Prins* cyclization products obtained by employing $Et_3Si–H$, $Me_3Si–allyl$, and $Me_3Si–N_3$ as trapping nucleophiles

3.7.3.1 General procedures



Prins cyclization and trapping with $R_3Si–Nu$ (non-silyl enol ether):

In a dry, N_2-filled glove box, aldehyde **3.4** (1.00 eq.) and $[Ph_3C][B(C_6F_5)_4]$ (trityl $BArF_{20}$; 0.10 eq.) were weighed into a screw cap 1 dram vial equipped with a stir bar and sealed with a septum cap. In a separate screw cap 1 dram vial, Et_3SiH (0.12 eq.) and $R_3Si–Nu$ (2.50 eq.) were dissolved in CH_2Cl_2 (0.05 M in substrate) and the vial sealed with a septum cap. Both vials were removed from the glove box and placed under a positive N_2 atmosphere *via* piercing of the septa with N_2 needles, and the vial containing the aldehyde

and trityl $BArF_{20}$ was cooled to –78 °C in an acetone/$CO_{2(s)}$ bath. Using careful inert atmosphere technique, the room temperature solution in CH_2Cl_2 was syringed drop-wise and slowly down the side of the vial into the vigorously stirring solution over approximately 5 minutes. During the addition, the solution turned clear bright yellow in color, which persisted throughout the course of the reaction. The solution was stirred for an additional 1 h at –78 °C, quenched at the cryogenic temperature with 50 μL *i*-$PrNH_2$ (resulting in rapid loss of color), and warmed to room temperature. The residue was repeatedly washed with CH_2Cl_2 and concentrated *in vacuo* (x3; to remove excess base), and then placed under high vacuum for ≥1 h to remove excess *i*-$PrNH_2$ (residual base must be removed before the acid-catalyzed deprotection step; this can be facilitated by repetitive azeotroping with CH_2Cl_2).

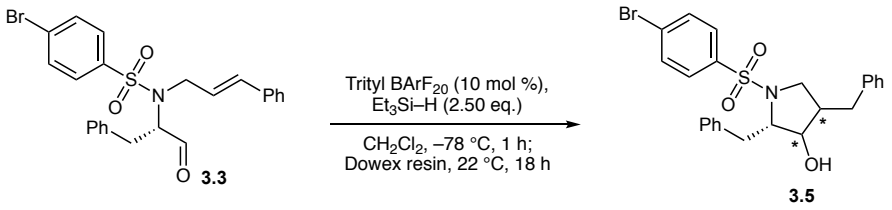
Acid-catalyzed silyl ether cleavage (deprotection):

The crude residue was taken up in 2 mL of 1:1 CH_2Cl_2/MeOH, approximately 10-20 beads of Dowex resin (50W-X8) were added and the reaction was stirred at 22 °C for 1-24 h (–$OSiMe_3$ requires significantly less time (~1 h) compared to –$OSiEt_3$ or larger (~overnight)). Note: for potentially sensitive products, less aggressive acidic resins can also afford deprotected product, including pyridinium *p*-toluene sulfonate polymer-bound resin (PPTS). The solution was then filtered by gravity through a plug of sand and cotton to remove the Dowex beads, rinsed with 2x1mL CH_2Cl_2, and concentrated *in vacuo*. Dimethylformamide (0.050 mmol, 3.9 μL) was added as an internal standard and the residue taken up in $CDCl_3$ for ^1H and ^{13}C NMR analyses to determine conversion, product identity, NMR yield, and crude diastereomeric ratios (d.r.). After re-concentration *in vacuo*, the crude residue was purified by silica gel chromatography (mixtures of *n*-

pentane:ethyl acetate), providing analytically pure heterocycles **3.6-3.9** for which isolated yields and post-purification diastereomeric ratios are reported.

3.7.3.2 Preparation and characterization

Preparation of pyrrolidine 3.5:

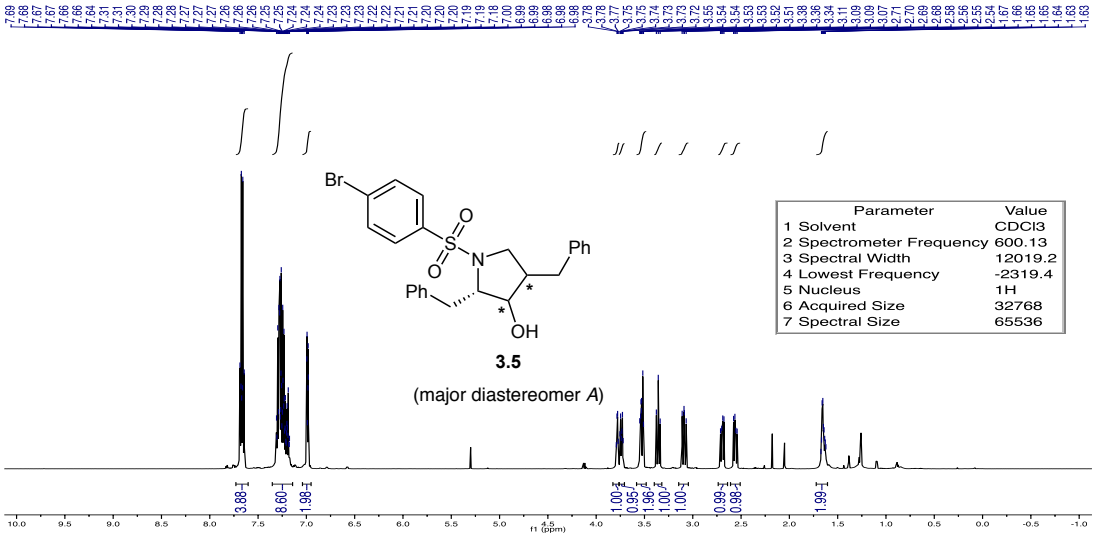


In a dry, N_2-filled glove box, aldehyde **3.3** (0.100 mmol, 48.4 mg, 1.00 eq.) and $[Ph_3C][B(C_6F_5)_4]$ (trityl $BArF_{20}$, 0.010 mmol, 9.2 mg, 0.10 eq.) were weighed into a screw cap 1 dram vial equipped with a stir bar and sealed with a septum cap. In a separate screw cap 1 dram vial, Et_3SiH (0.250 mmol, 40 μL, 2.50 eq.) was dissolved in 2.00 mL of CH_2Cl_2 and the vial sealed with a septum cap. Both vials were removed from the glove box and placed under a positive N_2 atmosphere *via* piercing of the septa with N_2 needles, and the vial containing the aldehyde and trityl $BArF_{20}$ was cooled to –78 °C in an acetone/$CO_{2(s)}$ bath. The room temperature solution in CH_2Cl_2 was syringed drop-wise and slowly down the side of the vial into the vigorously stirring solution over approximately 10 minutes. The solution was stirred for an additional 1 h at –78 °C, quenched at the cryogenic temperature with 50 μL *i*-$PrNH_2$, and warmed to room temperature. The residue was repeatedly washed with CH_2Cl_2 and concentrated *in vacuo* (x3), and was then placed under high vacuum for ≥1 h to remove excess *i*-$PrNH_2$. The resulting residue was taken up in 2 mL of 1:1 CH_2Cl_2/MeOH, approximately 10-20 beads of Dowex resin (50W-X8) were added, and the reaction was stirred at 22 °C for 18 h. The solution was then filtered by

gravity through a plug of sand and cotton, rinsed with 2x1mL CH_2Cl_2, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (3:1 *n*-pentane:ethyl acetate; R_f = 0.3-0.4) to yield pyrrolidine **3.5** as a white, crystalline solid in 77% yield (37.5 mg average on a 0.1 mmol scale) and as a mixture of three partially separable diastereomers in 76:13:11 d.r. (major diastereomer *A* separates from co-eluting minor diastereomers *B* and *C*).

(2*S*)-2,4-dibenzyl-1-((4-bromophenyl)sulfonyl)pyrrolidin-3-ol (3.5). ***Major diastereomer (A):*** **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 7.70-7.64 (m, 4H), 7.32-7.16 (m, 8H), 6.99 (d, 2H, *J* = 6.8 Hz), 3.78 (q, 1H, *J* = 3.9 Hz), 3.74 (dt, 1H, *J* = 11.5, 4.1 Hz), 3.55-3.50 (m, 2H), 3.36 (t, 1H, *J* = 11.8 Hz), 3.09 (dd, 1H, *J* = 13.5, 11.4 Hz), 2.69 (dd, 1H, *J* = 13.8, 7.3 Hz), 2.56 (dd, 1H, *J* = 13.9, 7.9 Hz), 1.69-1.60 (m, 2H); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 139.3, 138.4, 137.0, 132.6, 129.0, 128.9, 128.9, 128.8, 128.5, 127.9, 126.8, 126.6, 72.2, 67.8, 52.3, 45.3, 36.0, 32.4; **^{13}C NMR DEPT-135** ($CDCl_3$, 151 MHz): δ 132.6 (CH), 129.0 (CH), 128.9 (CH), 128.9 (CH), 128.8 (CH), 128.5 (CH), 126.8 (CH), 126.6 (CH), 72.2 (CH), 67.8 (CH), 52.3 (CH_2), 45.3 (CH), 36.0 (CH_2), 32.4 (CH_2); **IR** (ν/cm^{-1}): 3529 (s, br, OH), 3085 (w), 3061 (w), 3027 (w), 3002 (w), 2925 (m), 2856 (w), 1603 (w), 1574 (m), 1495 (m), 1470 (w), 1454 (m), 1389 (m), 1347 (s), 1295 (w), 1275 (w), 1162 (s), 1126 (w), 1088 (m), 1068 (m), 1032 (w), 1009 (m); **HRMS**-(ESI$^+$) $[M+H]^+$ calcd for $C_{24}H_{25}NO_3SBr^+$ 486.0739, found: 486.0738; **$[\alpha]_D^{25}$** = +40.1° (c = 1.13, CH_2Cl_2, l = 100 mm). ***Minor diastereomers (B, C):*** **^{1}H NMR** ($CDCl_3$, 600 MHz; aliphatic resonances only, distinguished by 1D TOCSY): δ 4.02 (ddd, 1H, *J* = 8.5, 6.8, 3.8 Hz, *C*), 3.79-3.75 (m, 1H, *B*), 3.63 (td, 1H, *J* = 6.8, 4.4 Hz, *C*), 3.51-3.47 (m, 1H, *B*), 3.46-3.42 (m, 1H, *B*), 3.44 (dd, 1H, *J* = 10.3, 7.0 Hz, *C*), 3.38 (dd, 1H, *J* = 11.8, 7.3 Hz, *B*), 3.18 (dd, 1H, *J* = 13.8, 4.4 Hz,

C), 3.07 (dd, 1H, *J* = 13.8, 9.0 Hz, *C*), 2.99-2.91 (m, 2H, *B*), 2.94 (dd, 1H, *J* = 10.1, 7.1 Hz, *C*), 2.78 (dd, 1H, *J* = 13.8, 5.3 Hz, *B*), 2.62 (dd, 1H, *J* = 13.6, 5.2 Hz, *C*), 2.38 (dd, 1H, *J* = 13.9, 9.7 Hz, *B*), 2.34 (dd, 1H, *J* = 13.9, 8.6 Hz, *C*), 2.30-2.22 (m, 1H, *C*), 1.70 (ttd, 1H, *J* = 9.6, 7.4, 5.3 Hz, *B*), 1.53 (d, 1H, *J* = 4.3 Hz, *C*), 1.07 (d, 1H, *J* = 3.8 Hz, *B*); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 138.9, 138.6, 138.5, 137.2, 137.0, 136.2, 132.6, 132.5, 129.8, 129.7, 129.1, 129.1, 129.0, 128.9, 128.9, 128.8, 128.8, 128.7, 128.5, 128.1, 127.8, 127.1, 126.7, 126.7, 79.4 (*B*), 75.8 (*C*), 68.2 (*B*), 63.8 (*C*), 51.6 (*B*), 50.3 (*C*), 46.6 (*B*), 44.9 (*C*), 40.5 (*B*), 36.6 (*C*), 36.5 (*C*), 36.4 (*B*); **IR** (ν/cm^{-1}): 3516 (s, br, OH), 3086 (w), 3061 (w), 3027 (w), 2924 (m), 2855 (w), 1603 (w), 1574 (m), 1496 (m), 1471 (w), 1454 (m), 1389 (m), 1346 (s), 1275 (w), 1164 (s), 1088 (m), 1069 (m), 1031 (w), 1008 (m); **HRMS**-(ESI^{+}) $[M+H]^+$ calcd for $C_{24}H_{25}NO_3SBr^+$ 486.0739, found: 486.0741.



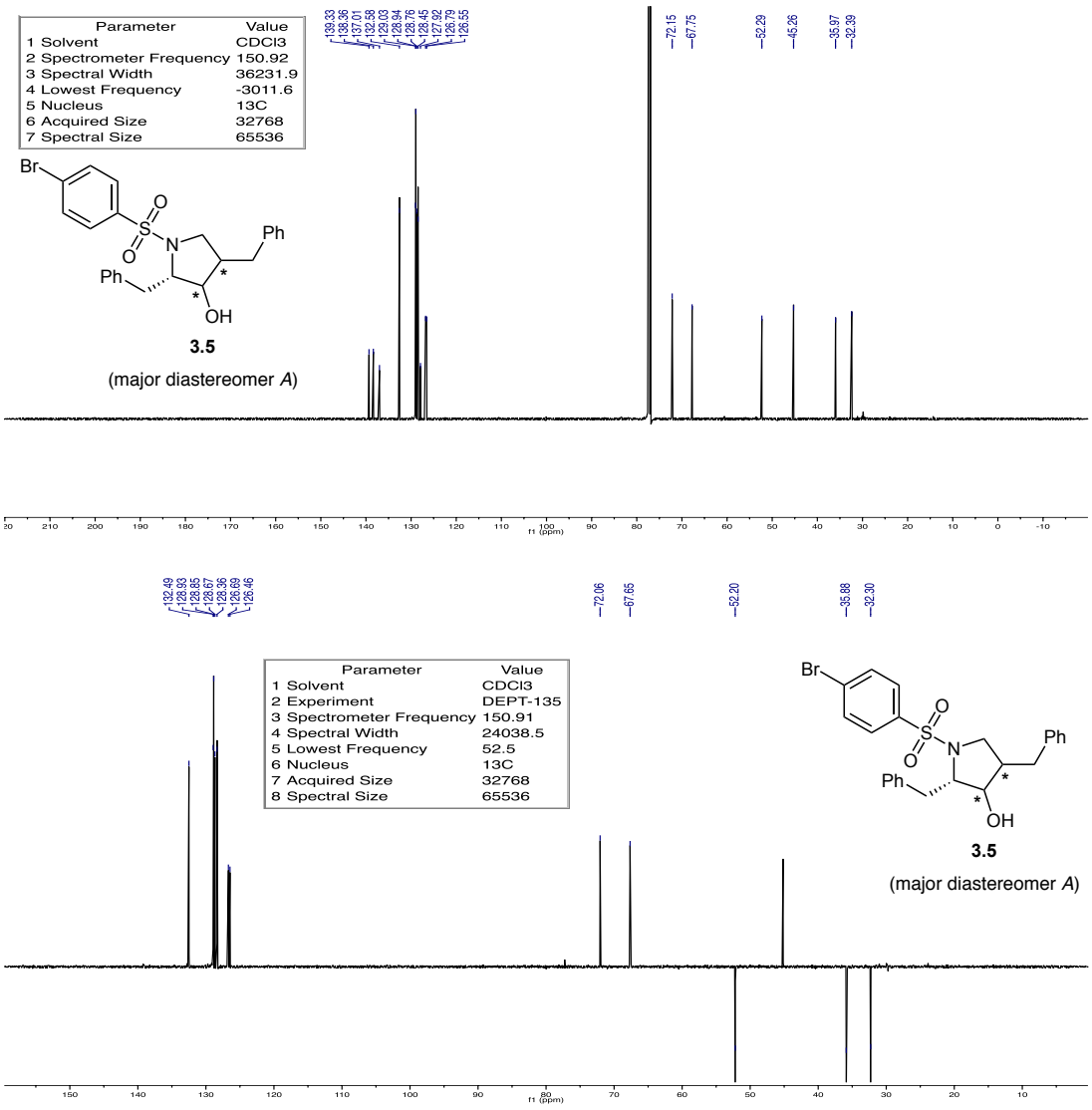


Figure 3.1. ^{1}H, ^{13}C{^{1}H}, and ^{13}C DEPT-135 NMR spectra for pyrrolidine 3.5 (major diastereomer A).

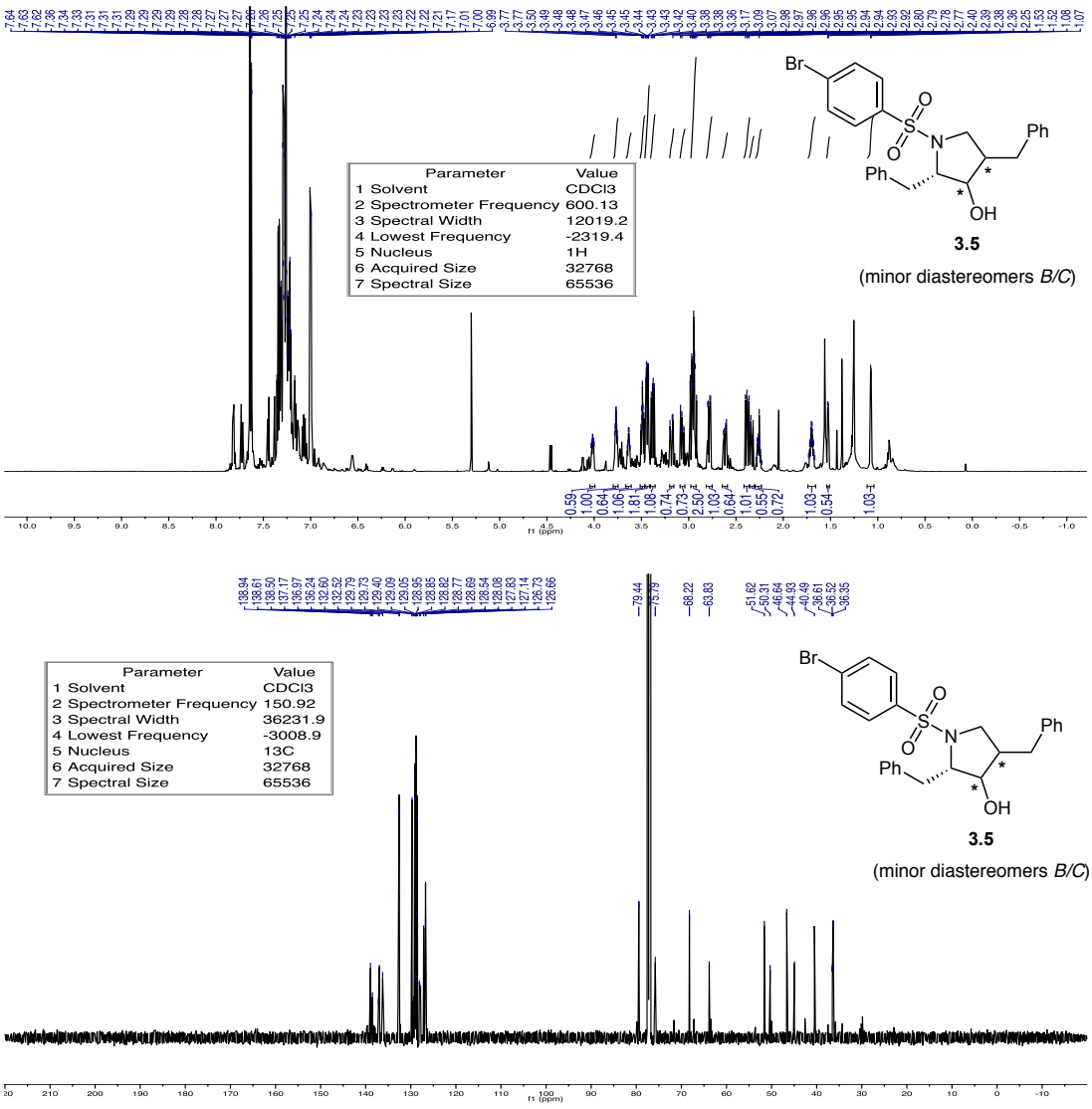
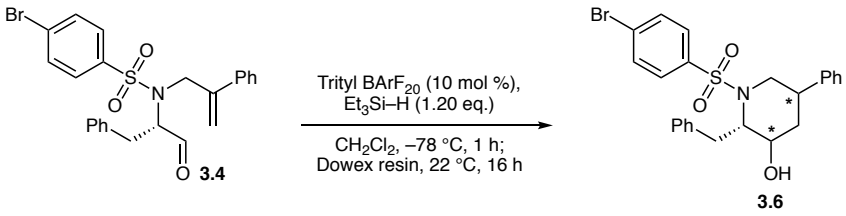


Figure 3.2. ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra for pyrrolidine 3.5 (minor diastereomers B/C)

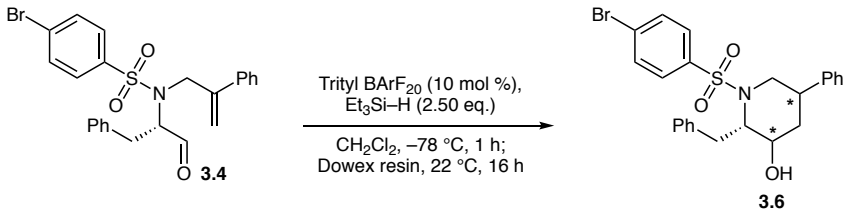
Preparation of piperidine 3.6 with <u>1.20 eq.</u> $Et_3Si–H$:



In a dry, N_2-filled glove box, aldehyde **3.4** (0.0500 mmol, 24.2 mg, 1.00 eq.) and

$[Ph_3C][B(C_6F_5)_4]$ (trityl $BArF_{20}$, 0.0050 mmol, 4.6 mg, 0.10 eq.) were weighed into a screw cap 1 dram vial equipped with a stir bar and sealed with a septum cap. In a separate screw cap 1 dram vial, Et_3SiH (0.060 mmol, 9.6 μL, 1.20 eq.) was dissolved in 1.00 mL of CH_2Cl_2 and the vial sealed with a septum cap. Both vials were removed from the glove box and placed under a positive N_2 atmosphere *via* piercing of the septa with N_2 needles, and the vial containing the aldehyde and trityl $BArF_{20}$ was cooled to –78 °C in an acetone/$CO_{2(s)}$ bath. The room temperature solution in CH_2Cl_2 was syringed drop-wise and slowly down the side of the vial into the vigorously stirring solution over approximately 5 minutes. The solution was stirred for an additional 1 h at –78 °C, quenched at the cryogenic temperature with 50 μL Et_3N, and warmed to room temperature. The residue was repeatedly washed with CH_2Cl_2 and concentrated *in vacuo* (x3), and was then placed under high vacuum for ≥1 h to remove excess Et_3N. The resulting residue was taken up in 2 mL of 1:1 CH_2Cl_2/MeOH, approximately 10-20 beads of Dowex resin (50W-X8) were added, and the reaction was stirred at 22 °C for 16 h. The solution was then filtered by gravity through a plug of sand and cotton, rinsed with 2x1mL CH_2Cl_2, and concentrated *in vacuo*. Dimethylformamide (0.050 mmol, 3.9 μL) was added as an internal standard and the residue taken up in $CDCl_3$ for ^1H and ^{13}C NMR analyses to determine crude NMR yield and diastereomeric ratios; the desired piperidine **3.6** was produced in 69% yield and in 51:29:20 d.r.

Preparation of piperidine 3.6 with <u>2.50 eq.</u> $Et_3Si–H$:



In a dry, N_2-filled glove box, aldehyde **3.4** (0.0500 mmol, 24.2 mg, 1.00 eq.) and $[Ph_3C][B(C_6F_5)_4]$ (trityl $BArF_{20}$, 0.0050 mmol, 4.6 mg, 0.10 eq.) were weighed into a screw cap 1 dram vial equipped with a stir bar and sealed with a septum cap. In a separate screw cap 1 dram vial, Et_3SiH (0.125 mmol, 20.0 μL, 2.50 eq.) was dissolved in 1.00 mL of CH_2Cl_2 and the vial sealed with a septum cap. Both vials were removed from the glove box and placed under a positive N_2 atmosphere *via* piercing of the septa with N_2 needles, and the vial containing the aldehyde and trityl $BArF_{20}$ was cooled to –78 °C in an acetone/$CO_{2(s)}$ bath. The room temperature solution in CH_2Cl_2 was syringed drop-wise and slowly down the side of the vial into the vigorously stirring solution over approximately 5 minutes. The solution was stirred for an additional 1 h at –78 °C, quenched at the cryogenic temperature with 50 μL Et_3N, and warmed to room temperature. The residue was repeatedly washed with CH_2Cl_2 and concentrated *in vacuo* (x3), and was then placed under high vacuum for ≥1 h to remove excess Et_3N. The resulting residue was taken up in 2 mL of 1:1 CH_2Cl_2/MeOH, approximately 10-20 beads of Dowex resin (50W-X8) were added, and the reaction was stirred at 22 °C for 16 h. The solution was then filtered by gravity through a plug of sand and cotton, rinsed with 2x1mL CH_2Cl_2, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (3:1 *n*-pentane:ethyl acetate; R_f = 0.2-0.3) to yield piperidine **3.6** as a white, crystalline solid in 92% yield (22.3

mg average per reaction over two 0.05 mmol scale trials) and as a mixture of three inseparable diastereomers in 60:21:19 d.r. (partial separation of minor diastereomer C and application of 1D TOCSY experiments allowed for full characterization of diastereomers). **(2*S*)-2-benzyl-1-((4-bromophenyl)sulfonyl)-5-phenylpiperidin-3-ol (3.6).** ***Major diastereomer A:*** **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 7.38-7.32 (m, 4H), 7.30-7.25 (m, 4H), 7.17 (t, 2H, *J* = 8.3 Hz), 7.07 (d, 2H, *J* = 7.1 Hz), 6.99 (d, 2H, *J* = 8.6 Hz), 4.54 (dq, 1H, *J* = 11.6, 4.0 Hz), 4.26 (dt, 1H, *J* = 11.8, 4.9 Hz), 3.63 (dd, 1H, *J* = 14.1, 4.4 Hz), 3.19 (dd, 1H, *J* = 14.3, 3.7 Hz), 3.11 (ddt, 1H, *J* = 12.6, 8.9, 4.6 Hz), 3.00 (dd, 1H, *J* = 14.1, 12.0 Hz), 2.82 (dd, 1H, *J* = 14.4, 11.6 Hz), 2.25 (s, br, 1H), 2.13 (dt, 1H, *J* = 12.9, 4.2 Hz), 2.06 (dd, 1H, *J* = 12.2, 12.2 Hz); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 141.0, 139.2, 138.5, 132.0, 129.3, 128.9, 128.8, 128.6, 127.4, 127.2, 127.1, 126.5, 69.4, 59.1, 45.6, 42.1, 34.4, 29.4; ***Minor diastereomer B:*** **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 7.44 (d, 2H, *J* = 8.6 Hz), 7.34 (d, 2H, *J* = 9.1 Hz), 7.30-7.21 (m, 8H), 7.13 (dd, 2H, *J* = 6.6, 2.9 Hz), 4.42 (t, 1H, *J* = 8.0 Hz), 4.02-3.97 (m, 1H), 3.74 (dd, 1H, *J* = 13.9, 4.4 Hz), 3.35-3.24 (m, 1H), 3.11 (t, 1H, *J* = 13.1 Hz), 2.89 (d, 2H, *J* = 7.9 Hz), 2.48 (s, br, 1H), 2.13 (dt, 1H, *J* = 14.6, 5.8 Hz), 2.09-2.02 (m, 1H); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 141.8, 139.3, 137.4, 132.2, 129.1, 129.0, 128.9, 128.9, 127.3, 127.3, 127.0, 126.8, 66.2, 60.5, 46.3, 35.6, 35.6, 33.0; ***Minor diastereomer C:*** **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 7.53-7.48 (m, 4H), 7.32-7.26 (m, 4H), 7.26-7.21 (m, 4H), 7.17 (d, 2H, *J* = 6.7 Hz), 4.02 (dd, 1H, *J* = 13.4, 4.3 Hz), 3.89 (dt, 1H, *J* = 6.4, 3.3 Hz), 3.76 (ddd, 1H, *J* = 9.7, 5.0, 2.9 Hz), 3.36 (dd, 1H, *J* = 12.8, 7.8 Hz), 3.31 (tt, 1H, *J* = 8.4, 4.3 Hz), 3.26 (dd, 1H, *J* = 13.7, 9.7 Hz), 3.01 (dd, 1H, *J* = 13.7, 5.1 Hz), 2.18-2.13 (m, 1H), 1.87 (ddd, 1H, *J* = 13.9, 8.9, 3.4 Hz); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 141.7, 139.9, 138.2, 132.4, 129.4, 128.8, 128.8, 128.6, 127.6, 127.4, 127.0, 126.8, 65.1,

63.6, 51.8, 37.5, 36.0, 34.0; **IR** (ν/cm^{-1}): 3512 (s, br, OH), 3087 (w), 3061 (w), 3028 (m), 3004 (w), 2934 (s), 2871 (m), 1603 (w), 1575 (m), 1496 (m), 1471 (m), 1454 (m), 1389 (m), 1327 (s), 1267 (m), 1212 (w), 1155 (s), 1115 (w), 1100 (w), 1088 (m), 1068 (m), 1030 (w), 1011 (m); **HRMS**-(ESI$^+$) $[M+H]^+$ calcd for $C_{24}H_{25}NO_3SBr^+$ 486.0739, found: 486.0741.

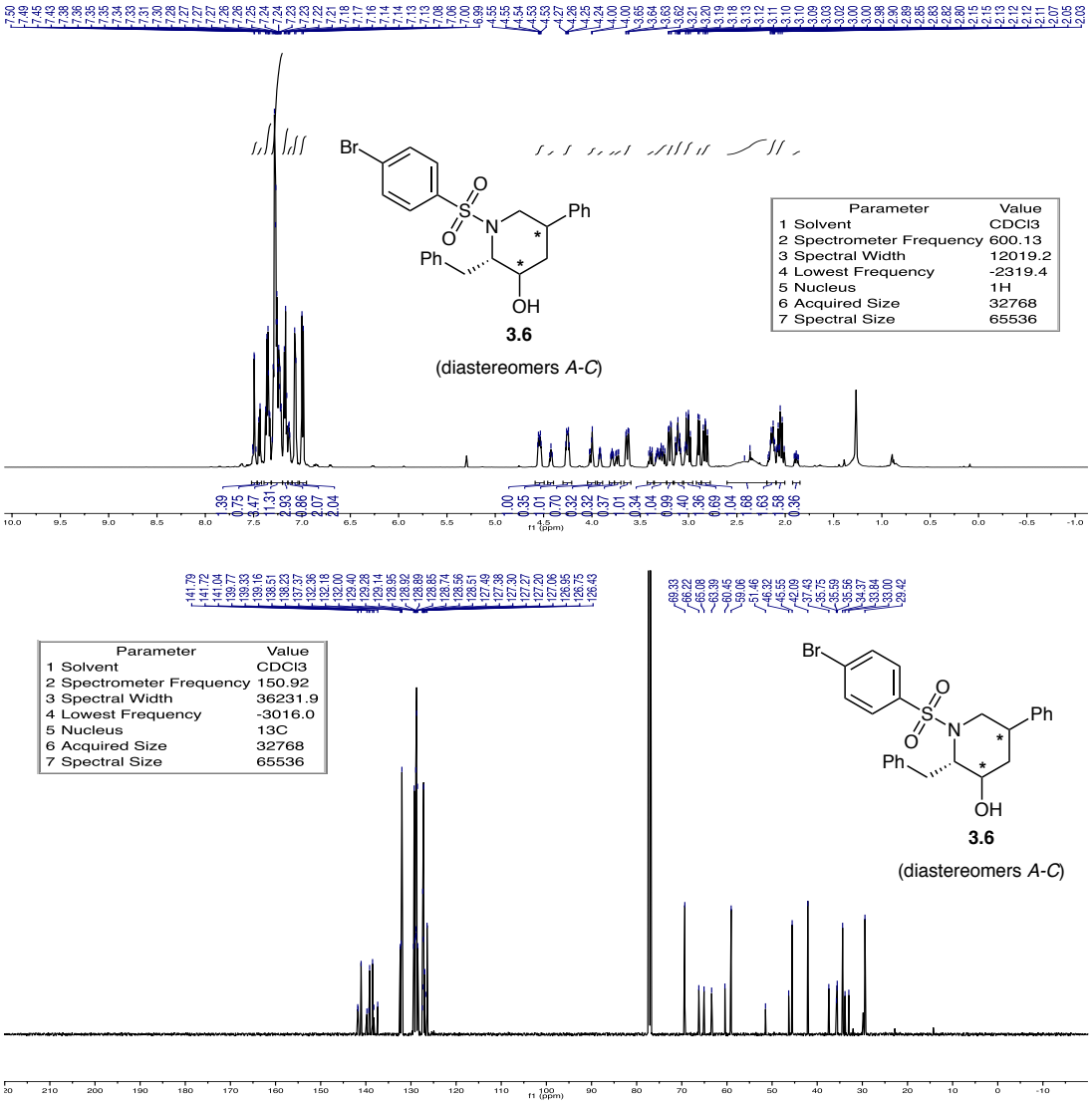


Figure 3.3. ^{1}H and ^{13}C{^{1}H} spectra for piperidine 3.6 (diastereomers A-C).

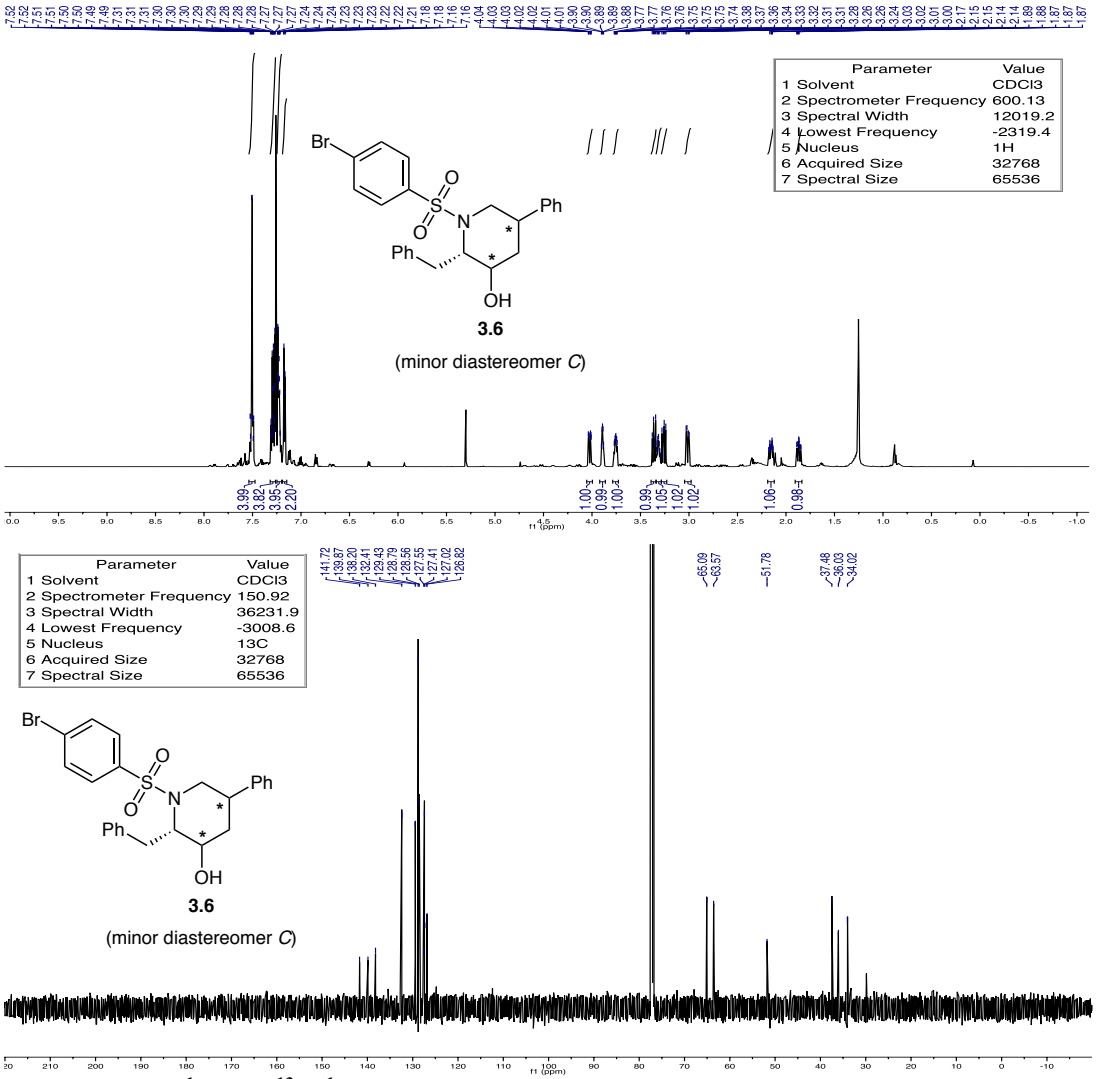
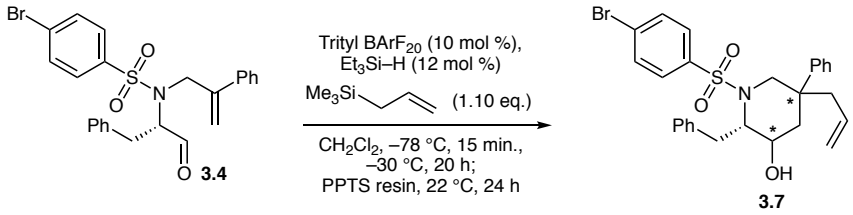


Figure 3.4. ^{1}H and ^{13}C{^{1}H} NMR spectra for piperidine 3.6 (minor diastereomer C).

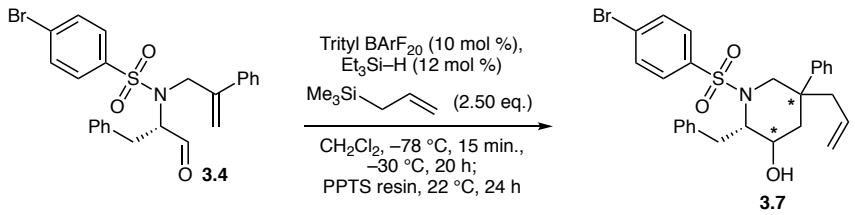
Preparation of piperidine 3.7 with <u>1.10 eq.</u> allyltrimethylsilane (Me_3Si–allyl):



In a dry, N_2-filled glove box, aldehyde **3.4** (0.0500 mmol, 24.2 mg, 1.00 eq.) and $[Ph_3C][B(C_6F_5)_4]$ (trityl $BArF_{20}$, 0.0050 mmol, 4.6 mg, 0.10 eq.) were weighed into a

screw cap 1 dram vial equipped with a stir bar and sealed with a septum cap. In a separate screw cap 1 dram vial, Et_3SiH (0.0060 mmol, 1.0 μL, 0.12 eq.) and allyltrimethylsilane (0.0550 mmol, 8.7 μL, 1.10 eq.) were dissolved in 1.00 mL of CH_2Cl_2 and the vial sealed with a septum cap. Both vials were removed from the glove box and placed under a positive N_2 atmosphere *via* piercing of the septa with N_2 needles, and the vial containing the aldehyde and trityl $BArF_{20}$ was cooled to –78 °C in an acetone/$CO_{2(s)}$ bath. The room temperature solution in CH_2Cl_2 was syringed drop-wise and slowly down the side of the vial into the vigorously stirring solution over approximately 5 minutes. The solution was stirred for an additional 15 minutes at –78 °C, after which time the reaction was transferred to a –30 °C cryobath and stirred overnight for 20 h (this was necessary for increased yield and reproducibility). The reaction was then quenched at the cryogenic temperature with 50 μL *i*-$PrNH_2$ and warmed to room temperature. The residue was repeatedly washed with CH_2Cl_2 and concentrated *in vacuo* (x3), and was then placed under high vacuum for ≥1 h to remove excess *i*-$PrNH_2$. The resulting residue was taken up in 2 mL of 1:1 CH_2Cl_2/MeOH, a spatula tip of PPTS resin was added, and the reaction was stirred at 22 °C for 24 h. The solution was then filtered by gravity through a plug of sand and cotton, rinsed with 2x1mL CH_2Cl_2, and concentrated *in vacuo*. Dimethylformamide (0.050 mmol, 3.9 μL) was added as an internal standard and the residue taken up in $CDCl_3$ for ^1H and ^{13}C NMR analyses to determine crude NMR yield and diastereomeric ratios (d.r.); the desired allyl-piperidine **3.7** was produced in 57% yield and in 58:42 d.r.

Preparation of piperidine 3.7 with <u>2.50 eq.</u> allyltrimethylsilane (Me_3Si–allyl):

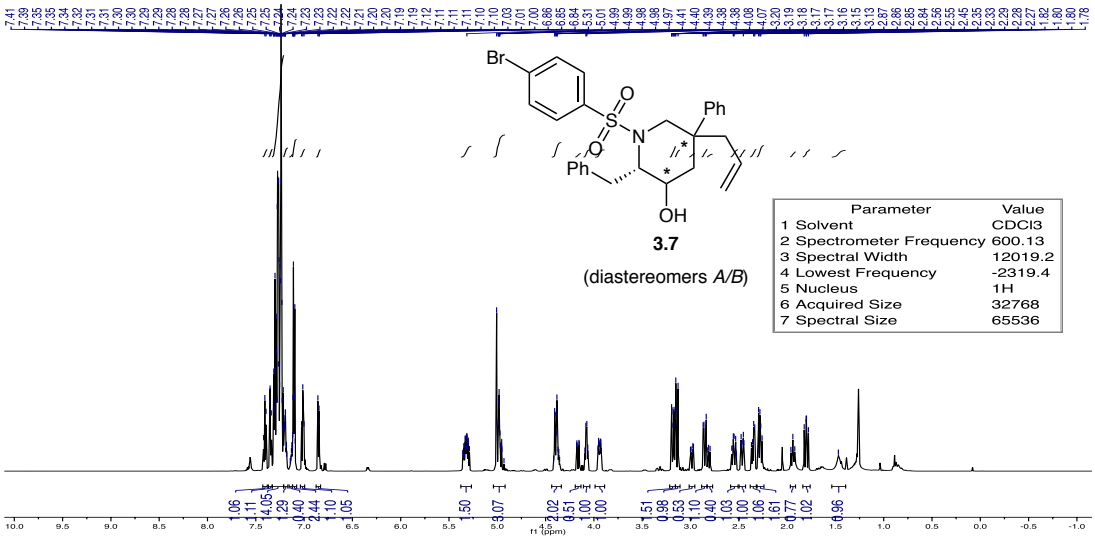


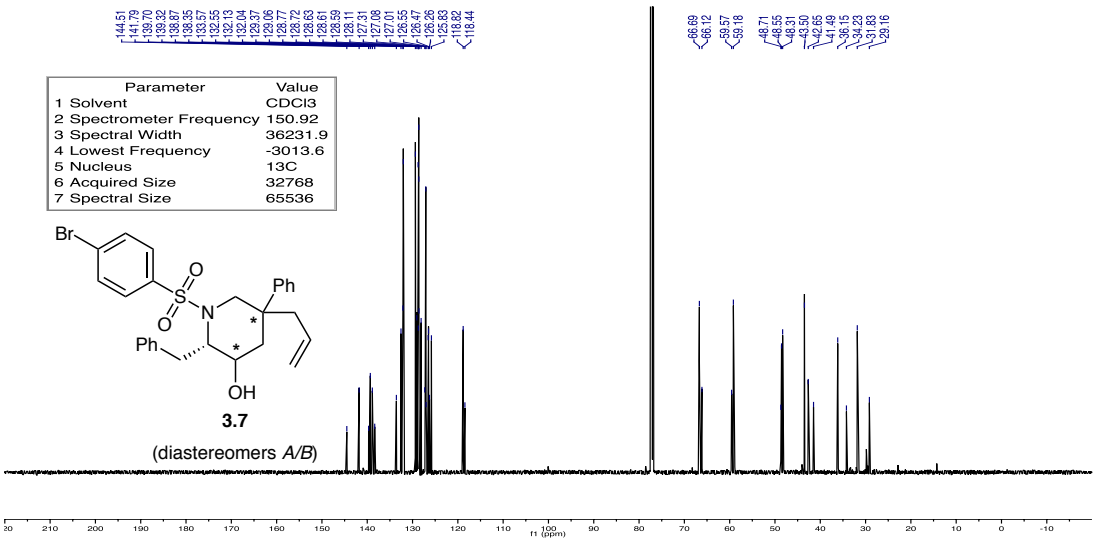
In a dry, N_2-filled glove box, aldehyde **3.4** (0.0500 mmol, 24.2 mg, 1.00 eq.) and $[Ph_3C][B(C_6F_5)_4]$ (trityl $BArF_{20}$, 0.0050 mmol, 4.6 mg, 0.10 eq.) were weighed into a screw cap 1 dram vial equipped with a stir bar and sealed with a septum cap. In a separate screw cap 1 dram vial, Et_3SiH (0.0060 mmol, 1.0 μL, 0.12 eq.) and allyltrimethylsilane (0.125 mmol, 19.9 μL, 2.50 eq.) were dissolved in 1.00 mL of CH_2Cl_2 and the vial sealed with a septum cap. Both vials were removed from the glove box and placed under a positive N_2 atmosphere *via* piercing of the septa with N_2 needles, and the vial containing the aldehyde and trityl $BArF_{20}$ was cooled to –78 °C in an acetone/$CO_{2(s)}$ bath. The room temperature solution in CH_2Cl_2 was syringed drop-wise and slowly down the side of the vial into the vigorously stirring solution over approximately 5 minutes. The solution was stirred for an additional 15 minutes at –78 °C, after which time the reaction was transferred to a –30 °C cryobath and stirred overnight for 20 h (this was necessary for increased yield and reproducibility). The reaction was then quenched at the cryogenic temperature with 50 μL *i*-$PrNH_2$ and warmed to room temperature. The residue was repeatedly washed with CH_2Cl_2 and concentrated *in vacuo* (x3), and was then placed under high vacuum for ≥1 h to remove excess *i*-$PrNH_2$. The resulting residue was taken up in 2 mL of 1:1 CH_2Cl_2/MeOH, a spatula tip of PPTS resin was added, and the reaction was stirred at 22 °C for 24 h. The solution was then filtered by gravity through a plug of sand and cotton,

rinsed with 2x1mL CH_2Cl_2, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (4:1 *n*-pentane:ethyl acetate; $R_f = 0.3$) to yield allyl-piperidine **3.7** as a clear, colorless oil in 84% yield (22.1 mg average per reaction over two 0.05 mmol scale trials) and as a mixture of two inseparable diastereomers in 66:34 d.r..

(2*S*)-5-allyl-2-benzyl-1-((4-bromophenyl)sulfonyl)-5-phenylpiperidin-3-ol (3.7). ^{1}H NMR ($CDCl_3$, 600 MHz; non-aromatic resonances delineated as major diastereomer *A* and minor diastereomer *B*): δ 7.41 (t, 1H, *J* = 7.7 Hz), 7.35 (d, 1H, *J* = 7.2 Hz), 7.33-7.20 (m, 20H), 7.22-7.16 (m, 1H), 7.15-7.12 (m, 1H), 7.10 (d, 2H, *J* = 8.6 Hz), 7.01 (t, 1H, *J* = 7.6 Hz), 6.85 (d, 1H, *J* = 7.2 Hz), 5.37-5.27 (m, 2H, *A*,*B*), 5.03-4.91 (m, 4H, 2*A*,2*B*), 4.43-4.34 (m, 3H, *A*,2*B*), 4.17 (d, 1H, *J* = 13.9 Hz, *B*), 4.08 (q, 1H, *J* = 5.9 Hz, *A*), 3.94 (ddd, 1H, *J* = 12.2, 5.7, 3.9 Hz, *A*), 3.21-3.15 (m, 2H, *A*,*B*), 3.14 (d, 1H, *J* = 14.0 Hz, *A*), 2.98 (dd, 1H, *J* = 14.5, 3.8 Hz, *B*), 2.85 (dd, 1H, *J* = 14.2, 5.1 Hz, *A*), 2.81 (dd, 1H, *J* = 14.5, 9.2 Hz, *B*), 2.58-2.52 (m, 2H, 2*B*), 2.46 (dt, 1H, *J* = 13.9, 2.9 Hz, *A*), 2.35 (dd, 1H, *J* = 13.6, 6.8 Hz, *A*), 2.30-2.25 (m, 2H, *A*,*B*), 1.94 (t, 1H, *J* = 12.2 Hz, *B*), 1.80 (dd, 1H, *J* = 14.0, 12.1 Hz, *A*), 1.46 (s, br, 2H, *A*,*B*); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz; aliphatic resonances delineated as major diastereomer *A* and minor diastereomer *B*): δ 144.5, 141.8, 139.7, 139.3, 138.9, 138.4, 133.6, 132.6, 132.1, 132.0, 129.4, 129.1, 128.8, 128.7, 128.6, 128.6, 128.6, 128.1, 127.3, 127.1, 127.0, 127.0, 126.6, 126.5, 126.3, 125.8, 118.8, 118.4, 66.7 (*A*), 66.1 (*B*), 59.6 (*B*), 59.2 (*A*), 48.7 (*B*), 48.6 (*A*), 48.3 (*A*), 43.5 (*A*), 42.7 (*B*), 41.5 (*B*), 36.2 (*A*), 34.2 (*B*), 31.8 (*A*), 29.2 (*B*); **^{13}C NMR DEPT-135** ($CDCl_3$, 151 MHz): δ 133.6 (CH), 132.6 (CH), 132.1 (CH), 132.0 (CH), 129.4 (CH), 129.1 (CH), 128.8 (CH), 128.7 (CH), 128.6 (CH), 128.6 (CH), 128.6 (CH), 128.1 (CH), 127.1 (CH), 127.0 (CH), 126.6 (CH), 126.5 (CH), 126.3 (CH), 125.8 (CH), 118.8 (CH_2), 118.4 (CH_2), 66.7 (CH), 66.1 (CH), 59.6

(CH), 59.2 (CH), 48.7 (CH_2), 48.6 (CH_2), 48.3 (CH_2), 41.5 (CH_2), 36.2 (CH_2), 34.2 (CH_2), 31.8 (CH_2), 29.2 (CH_2); **IR** (ν/cm^{-1}): 3519 (s, br, OH), 3086 (w), 3061 (w), 3027 (w), 3005 (w), 2926 (s), 2870 (w), 1638 (w), 1602 (w), 1576 (m), 1497 (m), 1470 (m), 1454 (m), 1446 (m), 1416 (w), 1389 (m), 1334 (s), 1276 (w), 1266 (w), 1158 (s), 1089 (m), 1069 (m), 1029 (w); **HRMS**-(ESI$^+$) $[M+H]^+$ calcd for $C_{27}H_{29}NO_3SBr^+$ 526.1052, found: 526.1055.





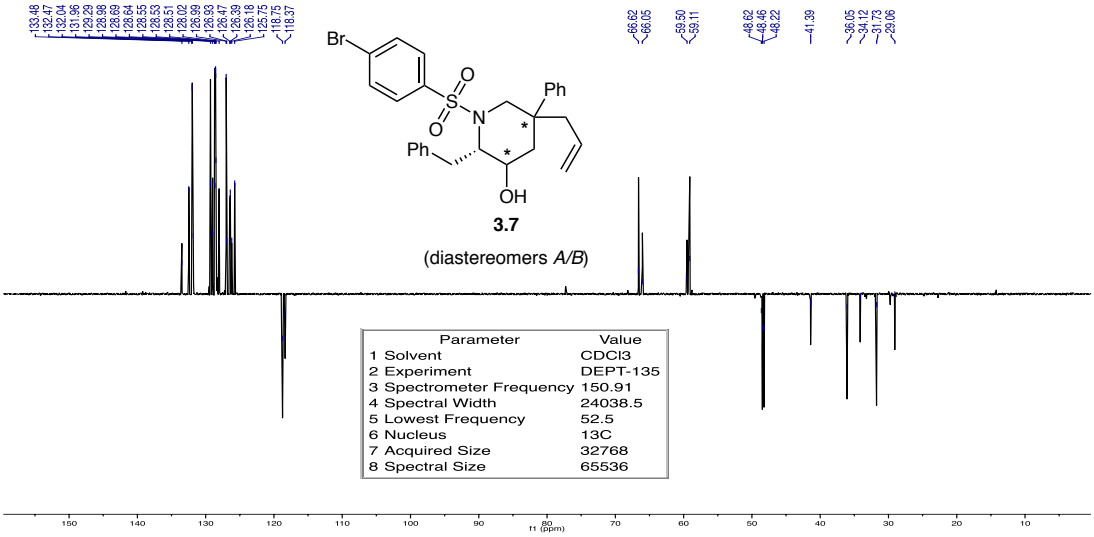
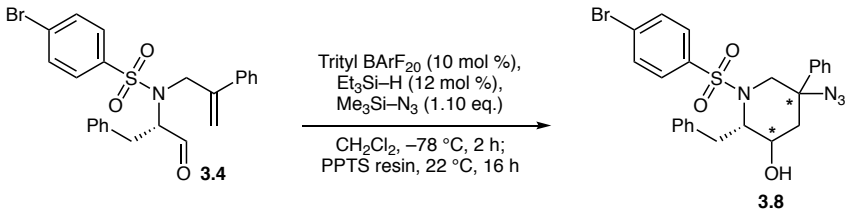


Figure 3.5. ^{1}H, $^{13}C\{^{1}H\}$, and ^{13}C DEPT-135 NMR spectra for allyl-piperidine 3.7 (diastereomers A/B).

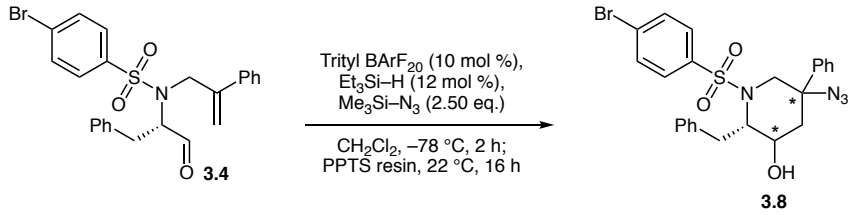
Preparation of piperidine 3.8 with <u>1.10 eq.</u> $Me_3Si–N_3$:



In a dry, N_2-filled glove box, aldehyde **3.4** (0.0500 mmol, 24.2 mg, 1.00 eq.) and $[Ph_3C][B(C_6F_5)_4]$ (trityl $BArF_{20}$, 0.0050 mmol, 4.6 mg, 0.10 eq.) were weighed into a screw cap 1 dram vial equipped with a stir bar and sealed with a septum cap. In a separate screw cap 1 dram vial, Et_3SiH (0.0060 mmol, 1.0 μL, 0.12 eq.) and $Me_3Si–N_3$ (0.0550 mmol, 7.2 μL, 1.10 eq.) were dissolved in 1.00 mL of CH_2Cl_2 and the vial sealed with a septum cap. Both vials were removed from the glove box and placed under a positive N_2 atmosphere *via* piercing of the septa with N_2 needles, and the vial containing the aldehyde and trityl $BArF_{20}$ was cooled to –78 °C in an acetone/$CO_{2(s)}$ bath. The room temperature

solution in CH_2Cl_2 was syringed drop-wise and slowly down the side of the vial into the vigorously stirring solution over approximately 5 minutes. The solution was stirred for an additional 2 h at –78 °C, after which time the reaction was quenched at the cryogenic temperature with 50 μL *i*-$PrNH_2$ and warmed to room temperature. The residue was repeatedly washed with CH_2Cl_2 and concentrated *in vacuo* (x3), and was then placed under high vacuum for ≥1 h to remove excess *i*-$PrNH_2$. The resulting residue was taken up in 2 mL of 1:1 CH_2Cl_2/MeOH, a spatula tip of PPTS resin was added, and the reaction was stirred at 22 °C for 16 h. The solution was then filtered by gravity through a plug of sand and cotton, rinsed with 2x1mL CH_2Cl_2, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (3:1 *n*-pentane:ethyl acetate; R_f = 0.3-0.4) to yield azido-piperidine **3.8** as a white, crystalline solid in 78% yield (41.0 mg average per reaction over two 0.05 mmol scale trials) and as a mixture of two separable diastereomers in 79:21 d.r..

Preparation of piperidine 3.8 with <u>2.50 eq.</u> $Me_3Si–N_3$:



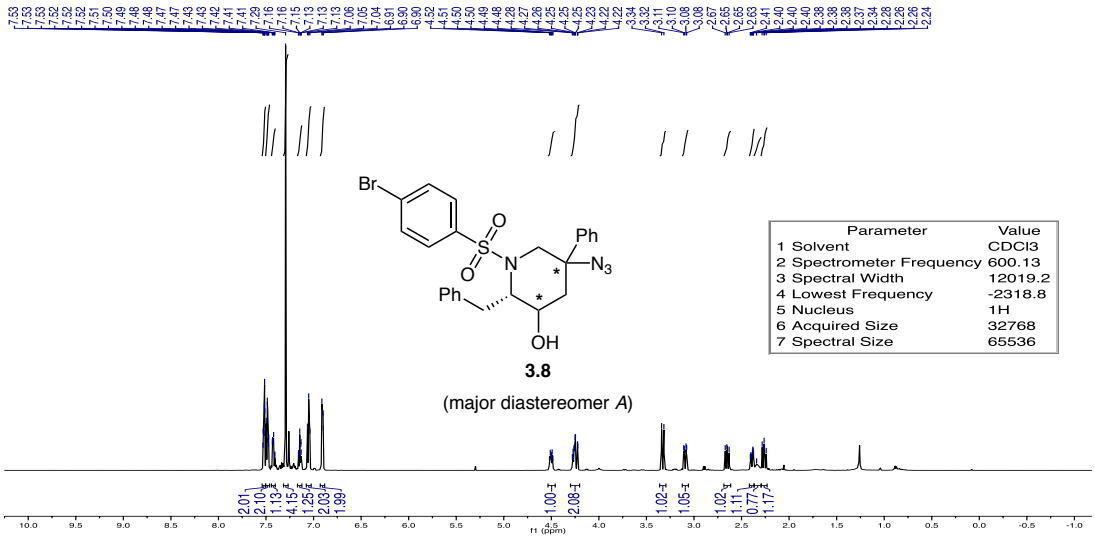
In a dry, N_2-filled glove box, aldehyde **3.4** (0.0500 mmol, 24.2 mg, 1.00 eq.) and $[Ph_3C][B(C_6F_5)_4]$ (trityl $BArF_{20}$, 0.0050 mmol, 4.6 mg, 0.10 eq.) were weighed into a screw cap 1 dram vial equipped with a stir bar and sealed with a septum cap. In a separate screw cap 1 dram vial, Et_3SiH (0.0060 mmol, 1.0 μL, 0.12 eq.) and $Me_3Si–N_3$ (0.125 mmol, 16.4 μL, 2.50 eq.) were dissolved in 1.00 mL of CH_2Cl_2 and the vial sealed with a

septum cap. Both vials were removed from the glove box and placed under a positive N_2 atmosphere *via* piercing of the septa with N_2 needles, and the vial containing the aldehyde and trityl $BArF_{20}$ was cooled to –78 °C in an acetone/$CO_{2(s)}$ bath. The room temperature solution in CH_2Cl_2 was syringed drop-wise and slowly down the side of the vial into the vigorously stirring solution over approximately 5 minutes. The solution was stirred for an additional 2 h at –78 °C, after which time the reaction was quenched at the cryogenic temperature with 50 μL *i*-$PrNH_2$ and warmed to room temperature. The residue was repeatedly washed with CH_2Cl_2 and concentrated *in vacuo* (x3), and was then placed under high vacuum for ≥1 h to remove excess *i*-$PrNH_2$. The resulting residue was taken up in 2 mL of 1:1 CH_2Cl_2/MeOH, a spatula tip of PPTS resin was added, and the reaction was stirred at 22 °C for 16 h. The solution was then filtered by gravity through a plug of sand and cotton, rinsed with 2x1mL CH_2Cl_2, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (3:1 *n*-pentane:ethyl acetate; R_f = 0.3-0.4) to yield azido-piperidine **3.8** as a white, crystalline solid in 85% yield (45.0 mg average per reaction over two 0.05 mmol scale trials) and as a mixture of two separable diastereomers in 62:38 d.r..

(2*S*)-5-azido-2-benzyl-1-((4-bromophenyl)sulfonyl)-5-phenylpiperidin-3-ol (3.8).

Major diastereomer A: **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 7.52 (d, 2H, *J* = 7.1 Hz), 7.48 (t, 2H, *J* = 8.1 Hz), 7.42 (t, 1H, *J* = 6.3 Hz), 7.29 (s, 4H), 7.14 (t, 1H, *J* = 7.1 Hz), 7.05 (t, 2H, *J* = 7.6 Hz), 6.91 (d, 2H, *J* = 7.2 Hz), 4.50 (dt, 1H, *J* = 11.3, 4.8 Hz), 4.28-4.26 (m, 1H), 4.24 (dd, 1H, *J* = 14.0, 2.0 Hz), 3.33 (d, 1H, *J* = 14.6 Hz), 3.09 (dd, 1H, *J* = 14.4, 3.9 Hz), 2.65 (dd, 1H, *J* = 14.4, 10.3 Hz), 2.39 (ddd, 1H, *J* = 13.7, 4.3, 2.3 Hz), 2.34 (s, br, 1H), 2.26 (dd, 1H, *J* = 13.7, 11.7 Hz); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 139.2, 139.1, 137.8,

132.0, 129.4, 129.1, 129.1, 128.6, 128.5, 127.3, 126.4, 125.7, 66.3, 65.6, 59.3, 47.5, 36.2, 29.4; **^{13}C NMR DEPT-135** ($CDCl_3$, 151 MHz): δ 132.0 (CH), 129.4 (CH), 129.1 (CH), 129.1 (CH), 128.6 (CH), 128.5 (CH), 126.4 (CH), 125.7 (CH), 65.6 (CH), 59.3 (CH), 47.5 (CH_2), 36.2 (CH_2), 29.4 (CH_2); **IR** (ν/cm^{-1}): 3514 (s, br, OH), 3087 (w), 3061 (w), 3028 (w), 3004 (w), 2931 (s), 2853 (w), 2105 (s, N_3), 1602 (w), 1576 (m), 1496 (m), 1471 (m), 1448 (m), 1389 (m), 1332 (s), 1304 (m), 1264 (m), 1248 (m), 1200 (w), 1154 (s), 1103 (m), 1088 (m), 1069 (m), 1030 (w), 1011 (m); **HRMS**-(ESI^+) $[M+Na]^+$ calcd for $C_{24}H_{23}N_4O_3NaSBr^+$ 549.0572, found: 549.0579; $\mathbf{[\alpha]_D^{24}}$ = –53.9° (c = 1.61, CH_2Cl_2, l = 100 mm). ***Minor diastereomer B:*** **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 7.50-7.48 (m, 2H), 7.42-7.39 (m, 3H), 7.35 (d, 2H, *J* = 8.6 Hz), 7.25-7.19 (m, 5H), 7.15-7.12 (m, 2H), 4.26 (d, 1H, *J* = 13.8 Hz), 4.01-3.91 (m, 2H), 3.55 (d, 1H, *J* = 13.5 Hz), 3.20 (dd, 1H, *J* = 14.0, 7.3 Hz), 2.87 (dd, 1H, *J* = 14.0, 5.6 Hz), 2.58 (d, 1H, *J* = 12.7 Hz), 2.23 (dd, 1H, *J* = 13.8, 10.1 Hz), 1.99 (s, br, 1H); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 139.0, 138.3, 137.2, 132.3, 129.3, 129.2, 129.1, 128.8, 128.5, 127.7, 127.0, 126.7, 66.3, 64.5, 60.2, 49.5, 37.3, 31.8; **^{13}C NMR DEPT-135** ($CDCl_3$, 151 MHz): δ 132.3 (CH), 129.3 (CH), 129.2 (CH), 129.1 (CH), 128.8 (CH), 128.5 (CH), 127.0 (CH), 126.7 (CH), 66.3 (CH), 60.2 (CH), 49.5 (CH_2), 37.3 (CH_2), 31.8 (CH_2); **IR** (ν/cm^{-1}): 3517 (s, br, OH), 3087 (w), 3061 (w), 3029 (w), 2924 (s), 2851 (m), 2099 (s, N_3), 1603 (w), 1575 (m), 1496 (m), 1470 (m), 1454 (m), 1389 (m), 1335 (s), 1312 (m), 1264 (m), 1244 (m), 1160 (s), 1101 (m), 1087 (m), 1069 (m), 1030 (w), 1011 (m); **HRMS**-(ESI^+) $[M+Na]^+$ calcd for $C_{24}H_{23}N_4O_3NaSBr^+$ 549.0572, found: 549.0578; $\mathbf{[\alpha]_D^{25}}$ = –12.1° (c = 0.440, CH_2Cl_2, l = 100 mm).


Br
O
S
O
N
Ph
N3
Ph
*
*
OH
3.8
(major diastereomer A)
Parameter Value
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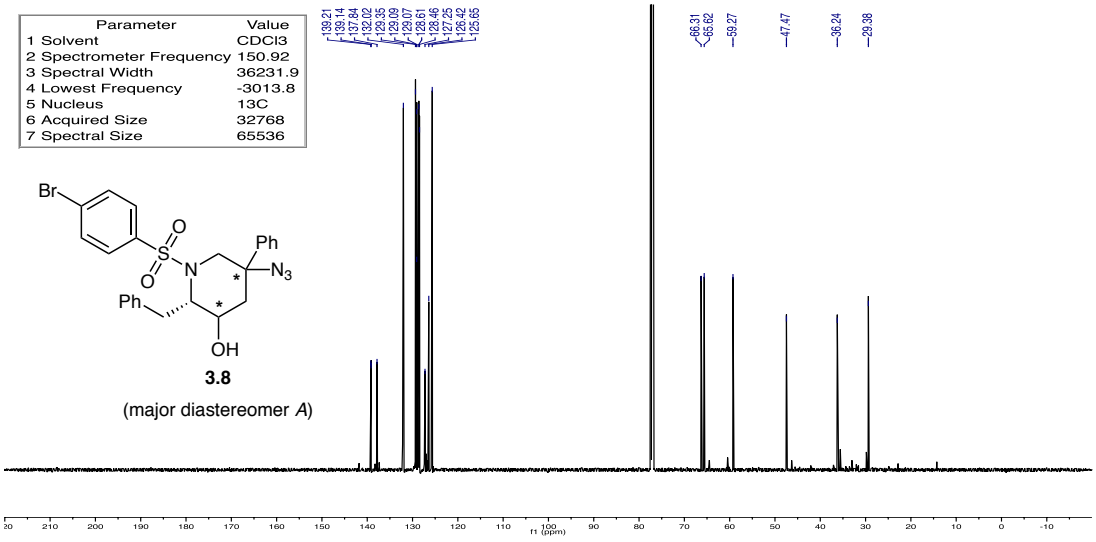
3 Spectral Width 12019.2
4 Lowest Frequency -2318.8
5 Nucleus 1H
6 Acquired Size 32768
7 Spectral Size 65536
f1 (ppm)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3 Spectral Width 36231.9
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6 Acquired Size 32768
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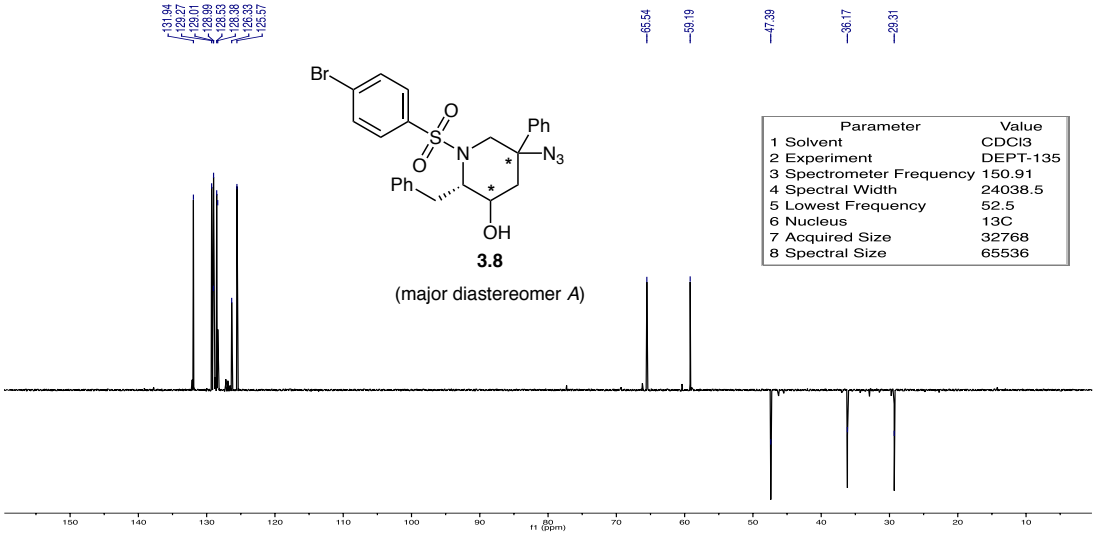
Br
O
S
O
N
Ph
N3
Ph
*
*
OH
3.8
(major diastereomer A)
f1 (ppm)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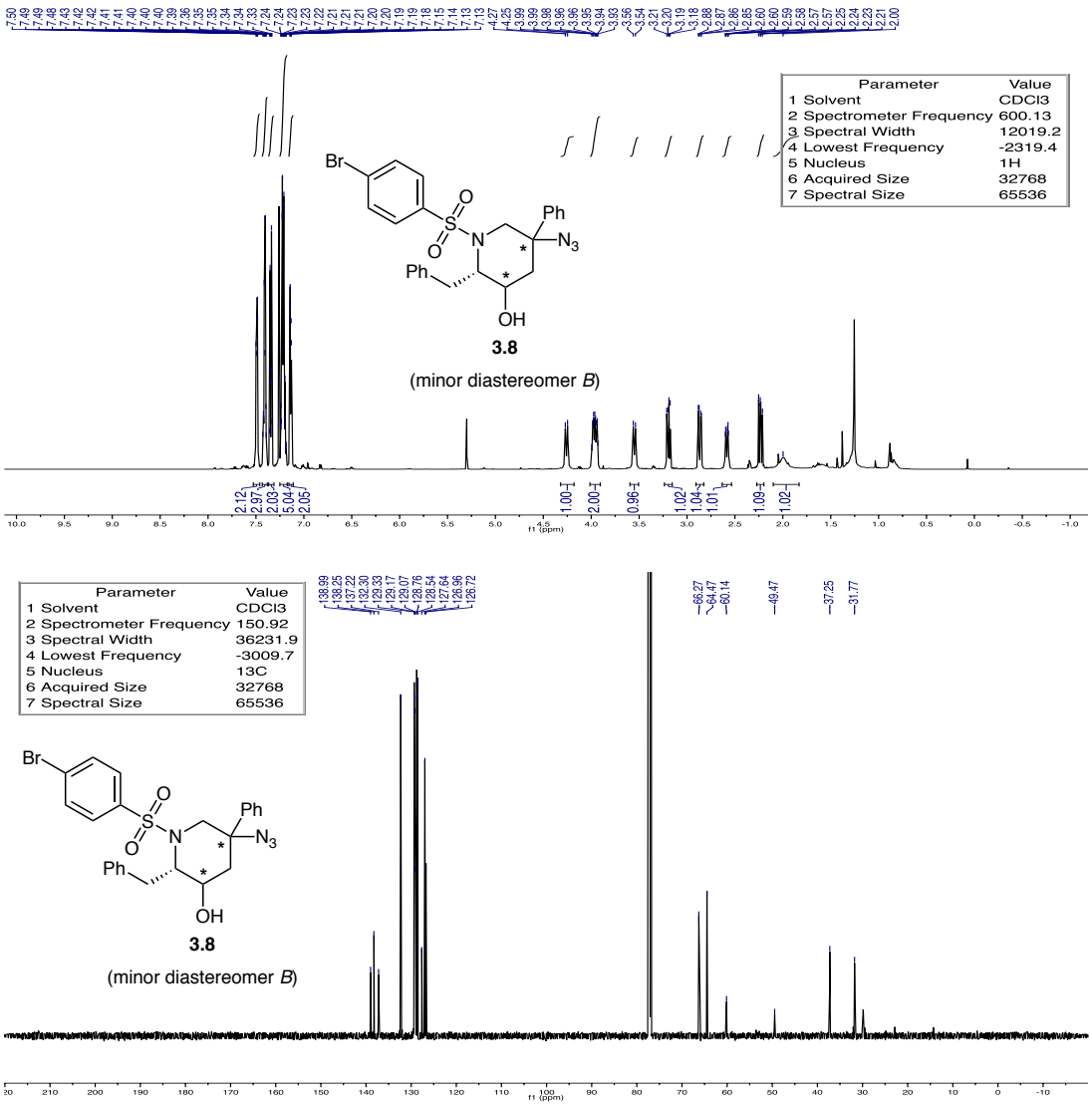
8 Spectral Size 65536
Br
O
S
O
N
Ph
N3
Ph
*
*
OH
3.8
(major diastereomer A)
f1 (ppm)

Figure 3.6. ^{1}H, $^{13}C\{^{1}H\}$, and ^{13}C DEPT-135 NMR spectra for azido-piperidine 3.8 (major diastereomer A).



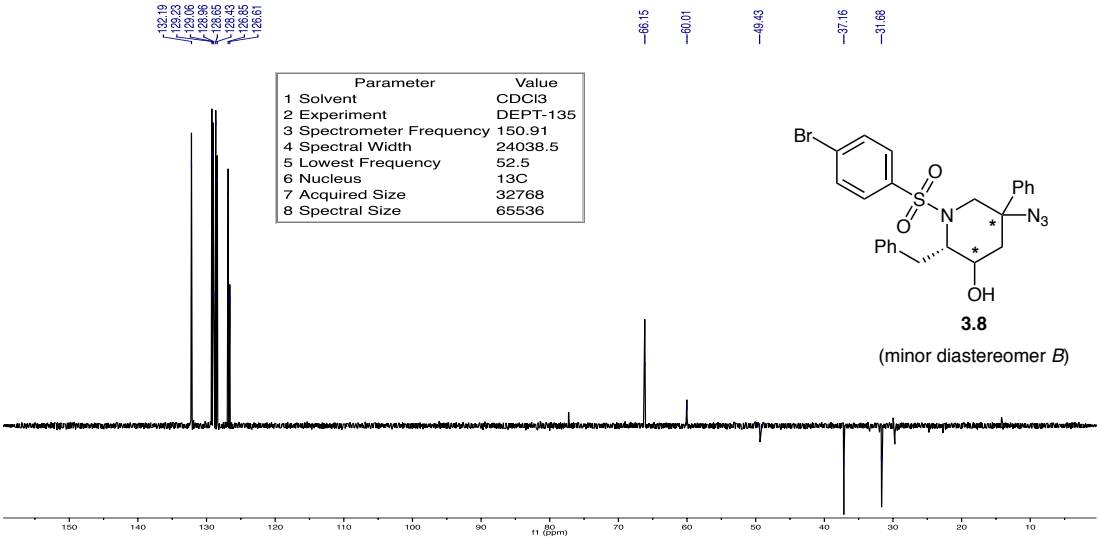
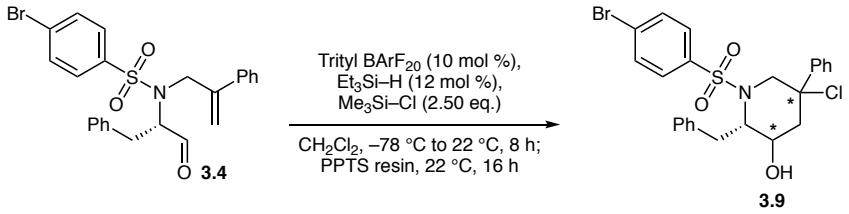


Figure 3.7. ^{1}H, ^{13}C{^{1}H}, and ^{13}C DEPT-135 NMR spectra for azido-piperidine 3.8 (minor diastereomer B).

Preparation of piperidine 3.9:

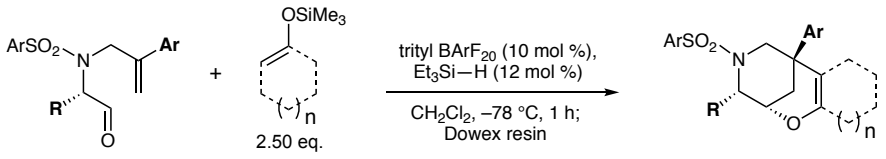


In a dry, N_2-filled glove box, aldehyde **3.4** (0.0500 mmol, 24.2 mg, 1.00 eq.) and $[Ph_3C][B(C_6F_5)_4]$ (trityl $BArF_{20}$, 0.0050 mmol, 4.6 mg, 0.10 eq.) were weighed into a screw cap 1 dram vial equipped with a stir bar and sealed with a septum cap. In a separate screw cap 1 dram vial, Et_3SiH (0.0060 mmol, 1.0 μL, 0.12 eq.) was dissolved in 1.00 mL of CH_2Cl_2 and the vial sealed with a septum cap. Both vials were removed from the glove box and placed under a positive N_2 atmosphere *via* piercing of the septa with N_2 needles. Freshly distilled Me_3Si–Cl (0.125 mmol, 15.9 μL, 2.50 eq.) was syringed from a Schlenk flask into the vial containing the solution of Et_3SiH in CH_2Cl_2. The vial containing the aldehyde and trityl $BArF_{20}$ was cooled to –78 °C in an acetone/$CO_{2(s)}$ bath. The room

temperature solution in CH_2Cl_2 was syringed drop-wise and slowly down the side of the vial into the vigorously stirring solution over approximately 5 minutes. The stirring solution was allowed to gradually warm from –78 °C to 22 °C in the dewar over the course of 8 h, after which time the reaction was quenched at room temperature with 50 μL *i*-$PrNH_2$ and warmed to room temperature. The residue was repeatedly washed with CH_2Cl_2 and concentrated *in vacuo* (x3), and was then placed under high vacuum for ≥1 h to remove excess *i*-$PrNH_2$. The resulting residue was taken up in 2 mL of 1:1 CH_2Cl_2/MeOH, a spatula tip of PPTS resin was added, and the reaction was stirred at 22 °C for 16 h. The solution was then filtered by gravity through a plug of sand and cotton, rinsed with 2x1mL CH_2Cl_2, and concentrated *in vacuo*. Dimethylformamide (0.050 mmol, 3.9 μL) was added as an internal standard and the residue taken up in $CDCl_3$ for ^1H and ^{13}C NMR analyses to determine conversion, product identity, crude NMR yield, and diastereomeric ratios (d.r.): The starting material was completely consumed; <5% of the desired chloride-trapped piperidine **3.9** was formed. Elimination was instead observed and tetrahydropiperidine diastereomers **3.22** and **3.23** were obtained in 54% NMR yield and in 78:22 *cis:trans* d.r. (see Scheme 3.7).

3.7.4 *Prins* cyclization products obtained by employing silyl enol ethers as trapping nucleophiles

3.7.4.1 General procedures



Prins cyclization and trapping with silyl enol ether:

In a dry, N_2-filled glove box, aldehyde (1.00 eq.) and $[Ph_3C][B(C_6F_5)_4]$ (trityl $BArF_{20}$; 0.10 eq.) were weighed into a screw cap 1 dram vial equipped with a stir bar and sealed with a septum cap. In a separate screw cap 1 dram vial, Et_3SiH (0.12 eq.) and silyl enol ether (2.50 eq.) were dissolved in CH_2Cl_2 (0.05 M in substrate) and the vial sealed with a septum cap. Both vials were removed from the glove box and placed under a positive N_2 atmosphere *via* piercing of the septa with N_2 needles, and the vial containing the aldehyde and trityl $BArF_{20}$ was cooled to –78 °C in an acetone/$CO_{2(s)}$ bath. Using careful inert atmosphere technique, the room temperature solution in CH_2Cl_2 was syringed drop-wise and slowly down the side of the vial into the vigorously stirring solution over approximately 5 minutes. During the addition, the reaction turned clear bright yellow in color, which persisted throughout the course of the reaction. The solution was stirred for an additional 1 h at –78 °C, quenched at the cryogenic temperature with 50 μL *i*-$PrNH_2$ (resulting in rapid loss of color), and warmed to room temperature. The residue was repeatedly washed with CH_2Cl_2 and concentrated *in vacuo* (x3; to remove excess base), and was then placed under high vacuum for ≥1 h to remove excess *i*-$PrNH_2$ (when issues of reproducibility arise, they are often the result of incomplete removal of residual base; this can be rectified by repetitive washing with CH_2Cl_2).

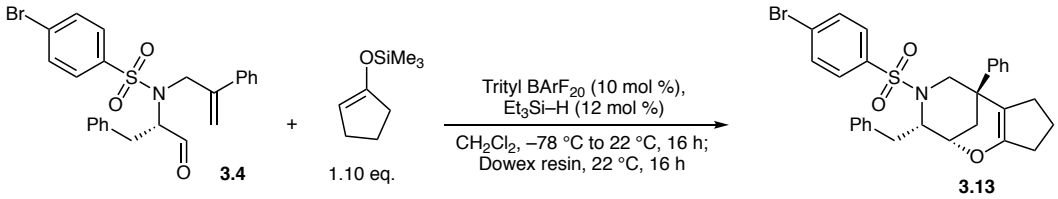
Acid-catalyzed annulation and elimination:

The crude residue was taken up in 2 mL of 1:1 CH_2Cl_2/MeOH, approximately 10-20 beads of Dowex resin (50W-X8) were added, and the reaction was stirred at 22 °C for 1 h. The solution was then filtered by gravity through a plug of sand and cotton to remove the Dowex beads, rinsed with 2x1mL CH_2Cl_2, and concentrated *in vacuo*.

Dimethylformamide (0.050 mmol, 3.9 μL) was added as an internal standard and the residue taken up in $CDCl_3$ for ^1H and ^{13}C NMR analyses to determine conversion, product identity, NMR yield, and crude diastereomeric ratios (d.r.). After re-concentration *in vacuo*, the crude residue was purified by silica gel chromatography (mixtures of *n*-pentane:ethyl acetate), providing analytically pure heterocycle for which isolated yields and post-purification diastereomeric ratios are reported.

3.7.4.2 Preparation and Characterization

Preparation of piperidine 3.13:



In a dry, N_2-filled glove box, aldehyde **3.4** (0.0500 mmol, 24.2 mg, 1.00 eq.) and $[Ph_3C][B(C_6F_5)_4]$ (trityl $BArF_{20}$, 0.0050 mmol, 4.6 mg, 0.10 eq.) were weighed into a screw cap 1 dram vial equipped with a stir bar and sealed with a septum cap. In a separate screw cap 1 dram vial, Et_3SiH (0.0060 mmol, 1.0 μL, 0.12 eq.) and cyclopentanone-derived silyl enol ether (0.0550 mmol, 9.8 μL, 1.10 eq.) were dissolved in 1.00 mL of CH_2Cl_2 and the vial sealed with a septum cap. Both vials were removed from the glove box and placed under a positive N_2 atmosphere *via* piercing of the septa with N_2 needles, and the vial containing the aldehyde and trityl $BArF_{20}$ was cooled to –78 °C in an acetone/$CO_{2(s)}$ bath. The room temperature solution in CH_2Cl_2 was syringed drop-wise and slowly down the side of the vial into the vigorously stirring solution over approximately 5 minutes. The solution was stirred and allowed to slowly warm to room temperature in the

dewar overnight for 16 h. The reaction was then quenched with 50 μL Et_3N. The solution was diluted with CH_2Cl_2, concentrated *in vacuo* (x2), and then placed under high vacuum for ≥1 h to remove excess Et_3N. The resulting residue was taken up in 2 mL of 1:1 CH_2Cl_2/MeOH, approximately 10-20 beads of Dowex resin (50W-X8) were added, and the mixture was stirred at 22 °C for 16 h. The mixture was then filtered by gravity through a plug of sand and cotton, rinsed with 2x1mL CH_2Cl_2, and concentrated *in vacuo*. Dimethylformamide (0.050 mmol, 3.9 μL) was added as an internal standard and the residue taken up in $CDCl_3$ for ^1H and ^{13}C NMR analyses to determine conversion, product identity, NMR yield, and crude diastereomeric ratios (d.r.). Despite full consumption of starting materials, only trace **3.13** is visible by ^{13}C.

(2*S*,3*S*,6*R*)-3-benzyl-4-((4-bromophenyl)sulfonyl)-6-phenyl-2,3,4,5,6,7,8,9-octahydro-2,6-methanocyclopenta[*g*][1,4]oxazocine (3.13). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 151 MHz): δ 109.6 (diagnostic vinyl ether peak); **HRMS**-(ESI$^+$) $[M+H]^+$ calcd for $C_{29}H_{29}NO_3SBr^+$ 550.1052, found: 550.1054.

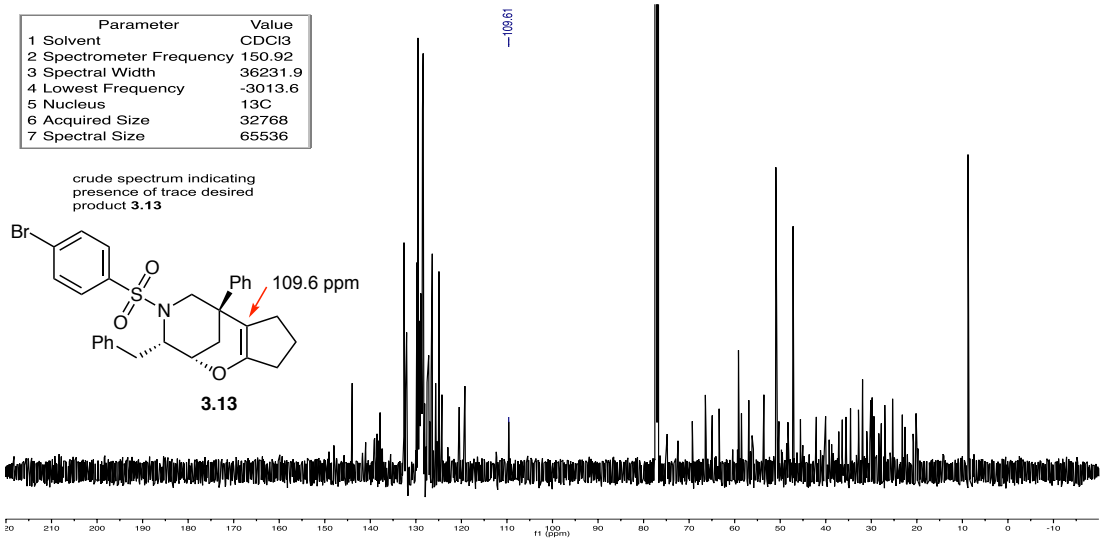
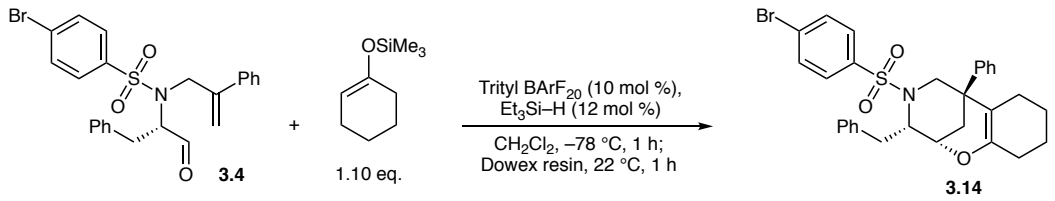


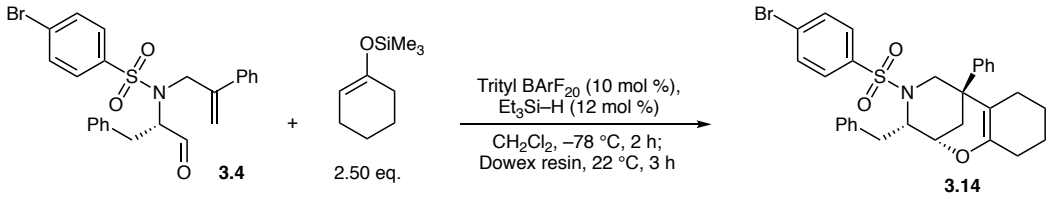
Figure 3.8. $^{13}C\{^1H\}$ spectrum for piperidine 3.13.

Preparation of piperidine 3.14 with <u>1.10 eq.</u> silyl enol ether:



In a dry, N_2-filled glove box, aldehyde **3.4** (0.0500 mmol, 24.2 mg, 1.00 eq.) and $[Ph_3C][B(C_6F_5)_4]$ (trityl $BArF_{20}$, 0.0050 mmol, 4.6 mg, 0.10 eq.) were weighed into a screw cap 1 dram vial equipped with a stir bar and sealed with a septum cap. In a separate screw cap 1 dram vial, Et_3SiH (0.0060 mmol, 1.0 μL, 0.12 eq.) and cyclohexanone-derived silyl enol ether (0.0550 mmol, 10.6 μL, 1.10 eq.) were dissolved in 1.00 mL of CH_2Cl_2 and the vial sealed with a septum cap. Both vials were removed from the glove box and placed under a positive N_2 atmosphere *via* piercing of the septa with N_2 needles, and the vial containing the aldehyde and trityl $BArF_{20}$ was cooled to –78 °C in an acetone/$CO_{2(s)}$ bath. The room temperature solution in CH_2Cl_2 was syringed drop-wise and slowly down the side of the vial into the vigorously stirring solution over approximately 5 minutes. The solution was stirred for an additional 1 h at –78 °C, quenched at the cryogenic temperature with 50 μL Et_3N, and warmed to room temperature. The solution was diluted with CH_2Cl_2, concentrated *in vacuo*, and then placed under high vacuum for ≥1 h to remove excess Et_3N. The resulting residue was taken up in 2 mL of 1:1 CH_2Cl_2/MeOH, approximately 10-20 beads of Dowex resin (50W-X8) were added, and the mixture was stirred at 22 °C for 1 h. The mixture was then filtered by gravity through a plug of sand and cotton, rinsed with 2x1mL CH_2Cl_2, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (5:1 *n*-pentane:ethyl acetate; $R_f = 0.6$) to yield the tricyclic piperidine product **3.14** as a white, crystalline solid in 52% yield (14.7 mg).

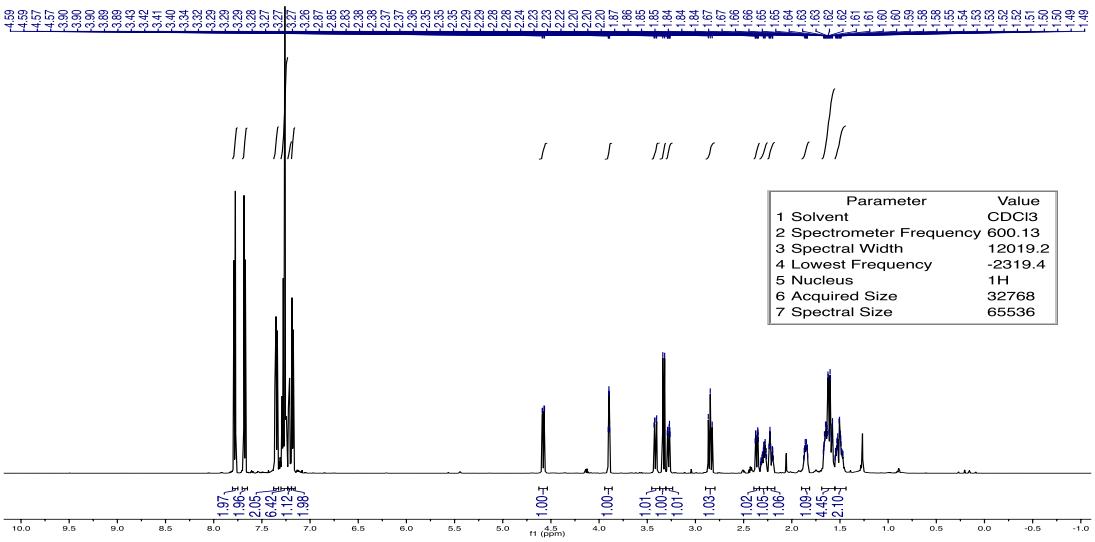
Preparation of piperidine 3.14 with <u>2.50 eq.</u> silyl enol ether:



In a dry, N_2-filled glove box, aldehyde **3.4** (0.100 mmol, 48.4 mg, 1.00 eq.) and $[Ph_3C][B(C_6F_5)_4]$ (trityl $BArF_{20}$, 0.010 mmol, 9.2 mg, 0.10 eq.) were weighed into a screw cap 1 dram vial equipped with a stir bar and sealed with a septum cap. In a separate screw cap 1 dram vial, Et_3SiH (0.012 mmol, 1.9 μL, 0.12 eq.) and cyclohexanone-derived silyl enol ether (0.250 mmol, 48 μL, 2.50 eq.) were dissolved in 2.00 mL of CH_2Cl_2 and the vial sealed with a septum cap. Both vials were removed from the glove box and placed under a positive N_2 atmosphere *via* piercing of the septa with N_2 needles, and the vial containing the aldehyde and trityl $BArF_{20}$ was cooled to –78 °C in an acetone/$CO_{2(s)}$ bath. The room temperature solution in CH_2Cl_2 was syringed drop-wise and slowly down the side of the vial into the vigorously stirring solution over approximately 10 minutes. The solution was stirred for an additional 2 h at –78 °C, quenched at the cryogenic temperature with 50 μL Et_3N, and warmed to room temperature. The residue was repeatedly washed with CH_2Cl_2 and concentrated *in vacuo* (x3), and was then placed under high vacuum for ≥1 h to remove excess Et_3N. The resulting residue was taken up in 2 mL of 1:1 CH_2Cl_2/MeOH, approximately 10-20 beads of Dowex resin (50W-X8) were added, and the mixture was stirred at 22 °C for 3 h. The mixture was then filtered by gravity through a plug of sand and cotton, rinsed with 2x1mL CH_2Cl_2, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (5:1 *n*-pentane:ethyl acetate; $R_f = 0.6$) to yield the tricyclic piperidine product **3.14** as a white, crystalline solid in 64% yield (36.4 mg average

per reaction over two 0.1 mmol scale trials).

(2*R*,3*S*,6*S*)-3-benzyl-4-((4-bromophenyl)sulfonyl)-6-phenyl-3,4,5,6,7,8,9,10-octahydro-2*H*-2,6-methanobenzo[*g*][1,4]oxazocine (3.14). **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 7.77 (d, 2H, *J* = 8.6 Hz), 7.67 (d, 2H, *J* = 8.6 Hz), 7.35 (t, 2H, *J* = 7.9 Hz), 7.30-7.27 (m, 3H), 7.25-7.24 (m, 2H), 7.21 (t, 1H, *J* = 7.4 Hz), 7.18 (d, 2H, *J* = 6.6 Hz), 4.57 (dd, 1H, *J* = 11.6, 2.7 Hz), 3.89 (dt, 1H, *J* = 4.0, 1.9 Hz), 3.41 (dd, 1H, *J* = 12.7, 3.6 Hz), 3.32 (d, 1H, *J* = 11.5 Hz), 3.27 (ddd, 1H, *J* = 11.6, 3.6, 1.8 Hz), 2.83 (t, 1H, *J* = 11.6 Hz), 2.36 (dt, 1H, *J* = 13.2, 4.2 Hz), 2.32-2.25 (m, 1H), 2.23-2.18 (m, 1H), 1.87-1.82 (m, 1H), 1.67-1.56 (m, 4H), 1.55-1.45 (m, 2H); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 150.1, 143.3, 141.9, 138.0, 132.4, 129.8, 128.7, 128.6, 128.4, 127.5, 126.8, 126.7, 126.4, 106.3, 67.3, 65.4, 54.1, 39.1, 39.0, 35.8, 27.8, 24.7, 23.3, 23.1; **^{13}C NMR DEPT-135** ($CDCl_3$, 151 MHz): δ 132.4 (CH), 129.8 (CH), 128.7 (CH), 128.6 (CH), 128.4 (CH), 126.8 (CH), 126.7 (CH), 126.4 (CH), 67.3 (CH), 65.4 (CH), 54.1 (CH_2), 39.0 (CH_2), 35.8 (CH_2), 27.8 (CH_2), 24.7 (CH_2), 23.3 (CH_2), 23.1 (CH_2); **IR** (ν/cm^{-1}): 3086 (w), 3060 (w), 3027 (w), 2931 (s), 2885 (m), 2857 (m), 2840 (m), 1679 (m), 1602 (w), 1575 (m), 1496 (m), 1471 (w), 1452 (w), 1446 (m), 1389 (w), 1373 (m), 1331 (s), 1266 (w), 1236 (m), 1215 (w), 1166 (s), 1153 (s), 1138 (m), 1126 (m), 1089 (m), 1067 (m), 1023 (w), 1009 (m); **HRMS**-(ESI^{+}) $[M+H]^{+}$ calcd for $C_{30}H_{31}NO_3SBr^{+}$ 564.1208, found: 564.1207; **$[\alpha]_D^{26}$** = +28.9° (c = 3.640, CH_2Cl_2, l = 100 mm).



Parameter	Value
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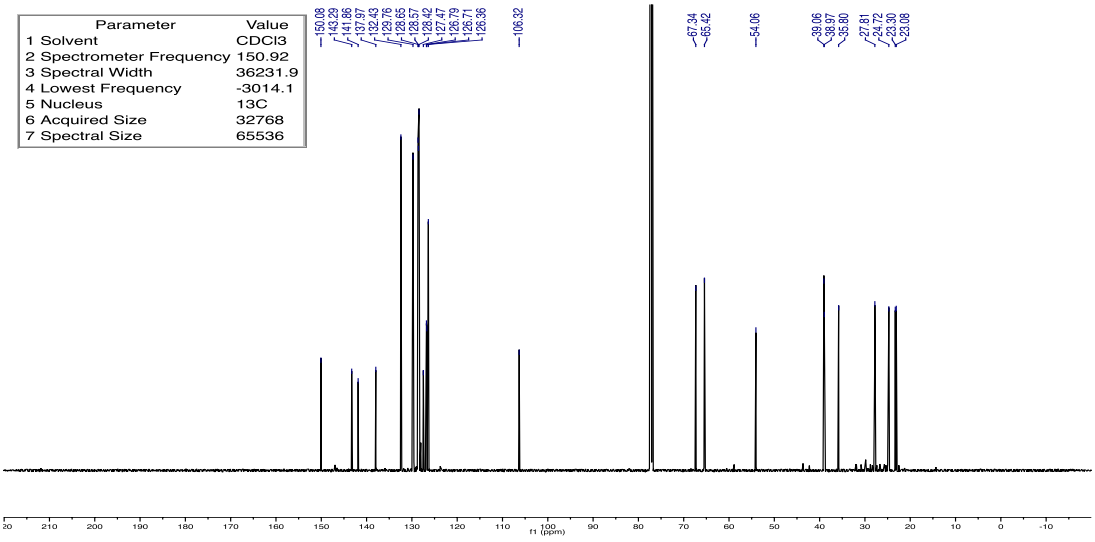
4 Lowest Frequency	-2319.4
5 Nucleus	1H
6 Acquired Size	32768
7 Spectral Size	65536



Parameter	Value
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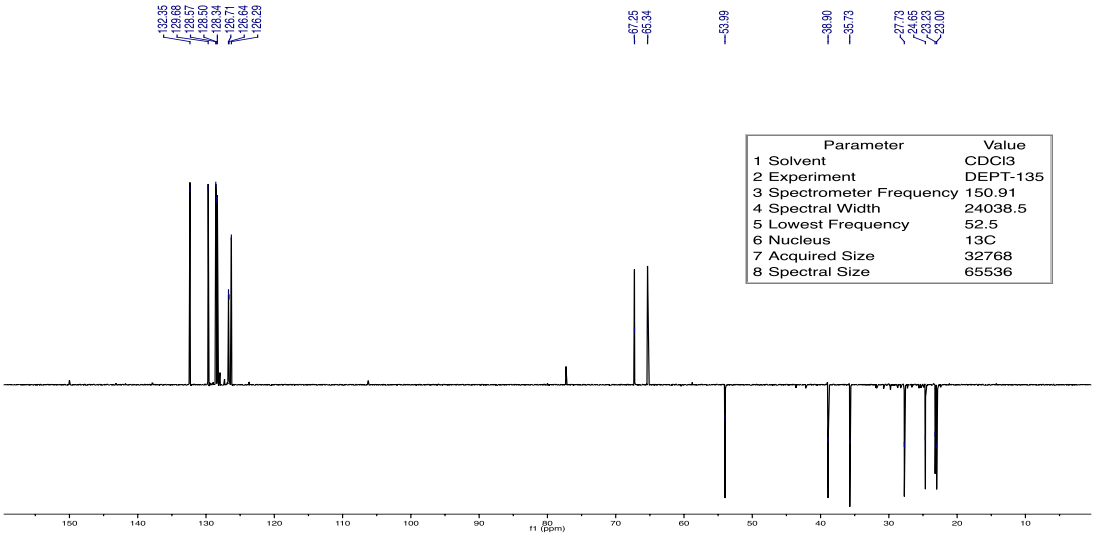
4 Lowest Frequency	-3014.1
5 Nucleus	13C
6 Acquired Size	32768
7 Spectral Size	65536



Parameter	Value
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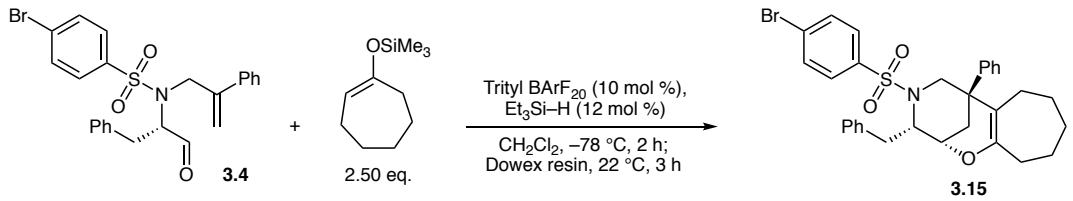
2 Experiment	DEPT-135
3 Spectrometer Frequency	150.91
4 Spectral Width	24038.5
5 Lowest Frequency	52.5
6 Nucleus	13C
7 Acquired Size	32768
8 Spectral Size	65536

Figure 3.9. ^{1}H, $^{13}C\{^{1}H\}$, and ^{13}C DEPT-135 spectra for piperidine 3.14.

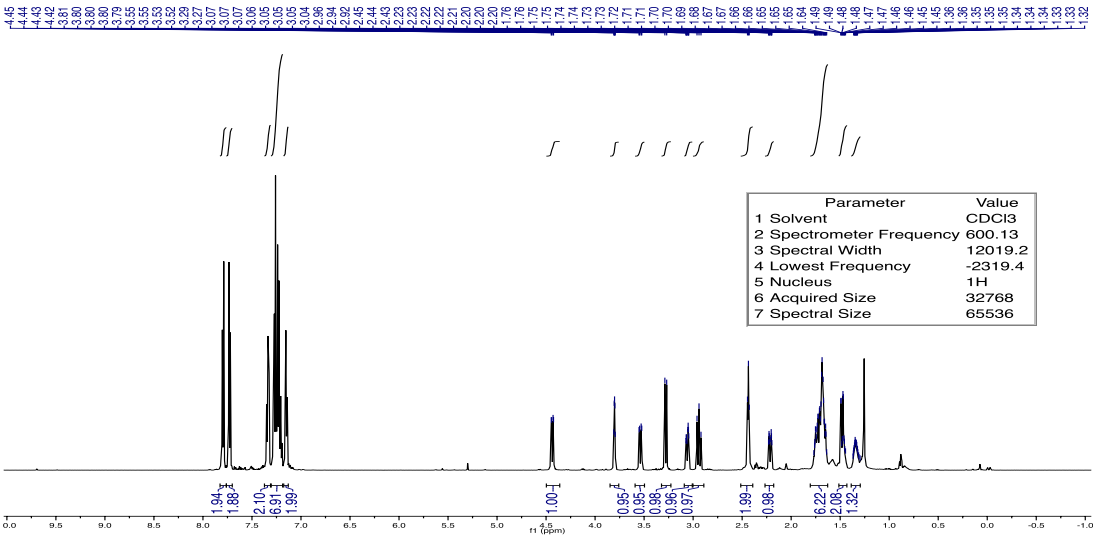
Preparation of piperidine 3.15:



In a dry, N_2-filled glove box, aldehyde **3.4** (0.100 mmol, 48.4 mg, 1.00 eq.) and $[Ph_3C][B(C_6F_5)_4]$ (trityl $BArF_{20}$, 0.010 mmol, 9.2 mg, 0.10 eq.) were weighed into a screw cap 1 dram vial equipped with a stir bar and sealed with a septum cap. In a separate screw cap 1 dram vial, Et_3SiH (0.012 mmol, 1.9 μL, 0.12 eq.) and cycloheptanone-derived silyl enol ether (0.250 mmol, 53 μL, 2.50 eq.) were dissolved in 2.00 mL of CH_2Cl_2 and the vial sealed with a septum cap. Both vials were removed from the glove box and placed under a positive N_2 atmosphere *via* piercing of the septa with N_2 needles, and the vial containing the aldehyde and trityl $BArF_{20}$ was cooled to –78 °C in an acetone/$CO_{2(s)}$ bath. The room temperature solution in CH_2Cl_2 was syringed drop-wise and slowly down the side of the vial into the vigorously stirring solution over approximately 10 minutes. The solution was stirred for an additional 2 h at –78 °C, quenched at the cryogenic temperature with 50 μL Et_3N, and warmed to room temperature. The residue was repeatedly washed with CH_2Cl_2 and concentrated *in vacuo* (x3), and was then placed under high vacuum for ≥1 h to remove excess Et_3N. The resulting residue was taken up in 2 mL of 1:1 CH_2Cl_2/MeOH, approximately 10-20 beads of Dowex resin (50W-X8) were added, and the mixture was stirred at 22 °C for 3 h. The mixture was then filtered by gravity through a plug of sand and cotton, rinsed with 2x1mL CH_2Cl_2, and concentrated *in vacuo*. The crude residue was

purified by silica gel chromatography (5:1 *n*-pentane:ethyl acetate; $R_f = 0.65$) to yield the tricyclic piperidine product **3.15** as a white, crystalline solid in 22% yield (12.9 mg average per reaction over two 0.1 mmol scale trials).

(2*R*,3*S*,6*S*)-3-benzyl-4-((4-bromophenyl)sulfonyl)-6-phenyl-2,3,4,5,6,7,8,9,10,11-decahydro-2,6-methanocyclohepta[*g*][1,4]oxazocine (3.15). **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 7.80 (d, 2H, *J* = 8.6 Hz), 7.73 (d, 2H, *J* = 8.6 Hz), 7.34 (t, 2H, *J* = 8.7 Hz), 7.29-7.19 (m, 6H), 7.15 (d, 2H, *J* = 6.9 Hz), 4.44 (dd, 1H, *J* = 11.2, 2.7 Hz), 3.80 (dt, 1H, *J* = 4.1, 2.0 Hz), 3.54 (dd, 1H, *J* = 12.8, 3.6 Hz), 3.28 (d, 1H, *J* = 11.1 Hz), 3.06 (ddd, 1H, *J* = 11.6, 3.6, 1.9 Hz), 2.94 (t, 1H, *J* = 12.2 Hz), 2.44 (t, 2H, *J* = 5.4 Hz), 2.21 (dt, 1H, *J* = 13.4, 4.0 Hz), 1.79-1.62 (m, 6H), 1.48 (dd, 1H, *J* = 13.3, 2.2 Hz), 1.48-1.43 (m, 1H), 1.38-1.30 (m, 1H); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): 155.5, 144.2, 140.0, 138.0, 132.6, 129.7, 128.7, 128.7, 128.6, 127.7, 126.8, 126.7, 126.2, 110.1, 67.3, 64.8, 55.0, 40.8, 39.1, 36.2, 33.9, 32.2, 28.8, 27.2, 25.8; **^{13}C NMR DEPT-135** ($CDCl_3$, 151 MHz): δ 132.6, 129.7, 128.7, 128.7, 128.6, 126.8, 126.7, 126.2, 67.3 (CH), 64.8 (CH), 55.0 (CH_2), 39.1 (CH_2), 36.2 (CH_2), 33.9 (CH_2), 32.2 (CH_2), 28.8 (CH_2), 27.2 (CH_2), 25.8 (CH_2); **IR** (ν/cm^{-1}): 3086 (w), 3060 (w), 3027 (w), 2924 (s), 2849 (m), 1669 (m), 1602 (w), 1575 (m), 1496 (m), 1471 (w), 1445 (m), 1389 (w), 1373 (w), 1337 (s), 1265 (w), 1237 (m), 1168 (s), 1125 (m), 1090 (m), 1068 (m), 1030 (w), 1008 (m); **HRMS**-(ESI$^+$) $[M+H]^+$ calcd for $C_{31}H_{33}NO_3SBr^+$ 578.1365, found: 578.1382; **$[\alpha]_D^{25}$** = +32.9° (c = 0.405, CH_2Cl_2, l = 100 mm).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5 Nucleus 1H
6 Acquired Size 32768
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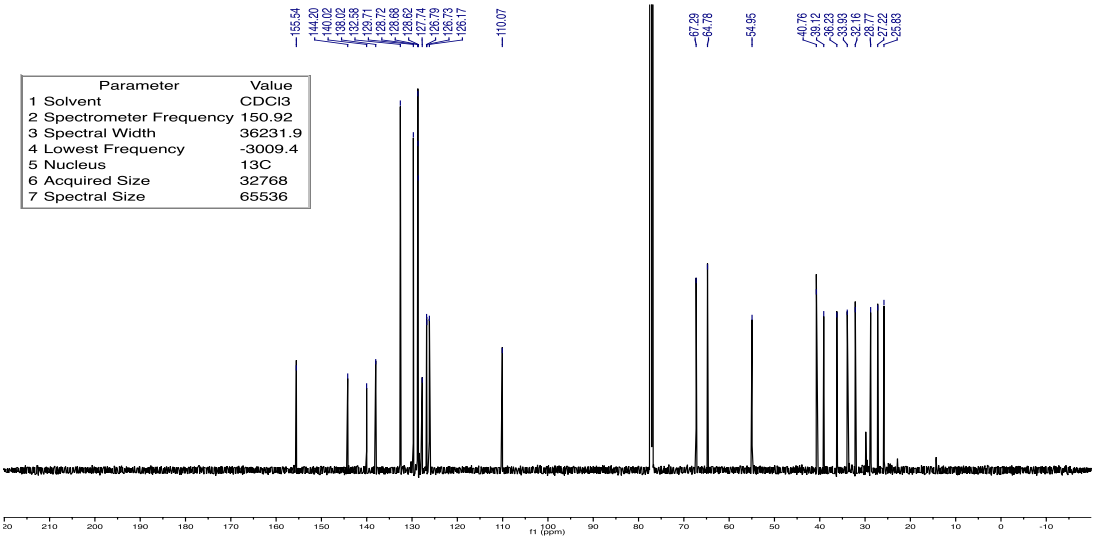
f1 (ppm)


Parameter Value
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3 Spectral Width 36231.9
4 Lowest Frequency -3009.4
5 Nucleus 13C
6 Acquired Size 32768
7 Spectral Size 65536
f1 (ppm)

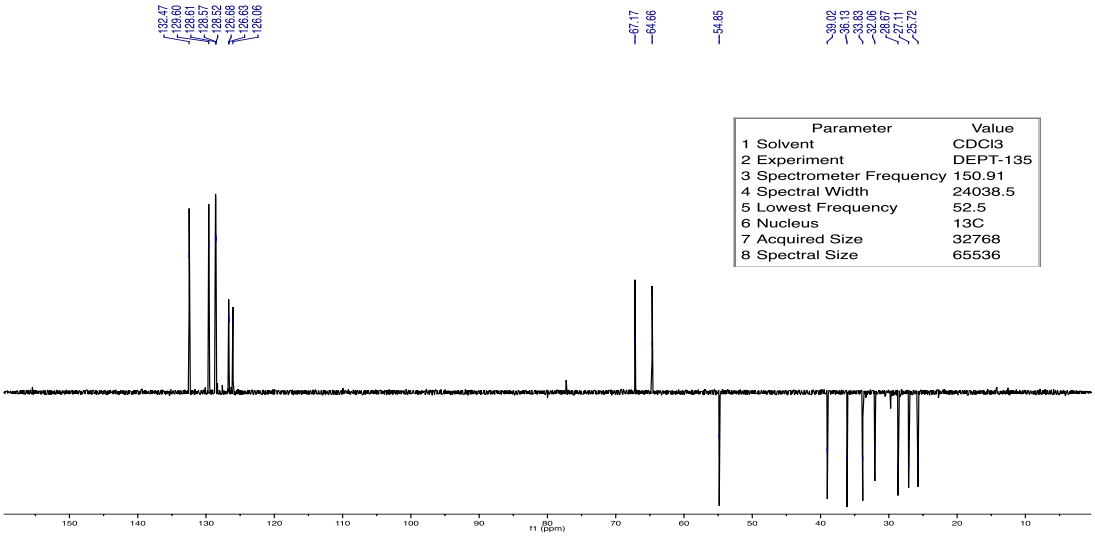
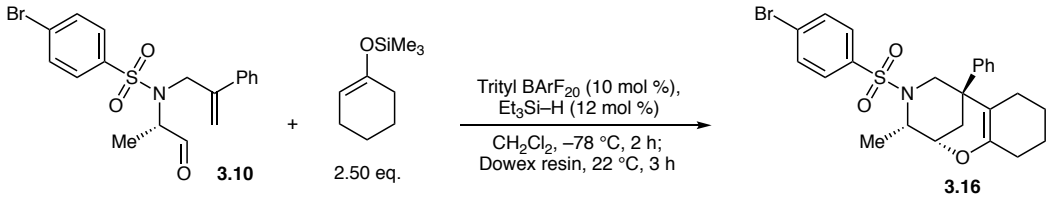

Parameter Value
1 Solvent CDCl3
2 Experiment DEPT-135
3 Spectrometer Frequency 150.91
4 Spectral Width 24038.5
5 Lowest Frequency 52.5
6 Nucleus 13C
7 Acquired Size 32768
8 Spectral Size 65536
f1 (ppm)

Figure 3.10. ^{1}H, $^{13}C\{^{1}H\}$, and ^{13}C DEPT-135 spectra for piperidine 3.15.

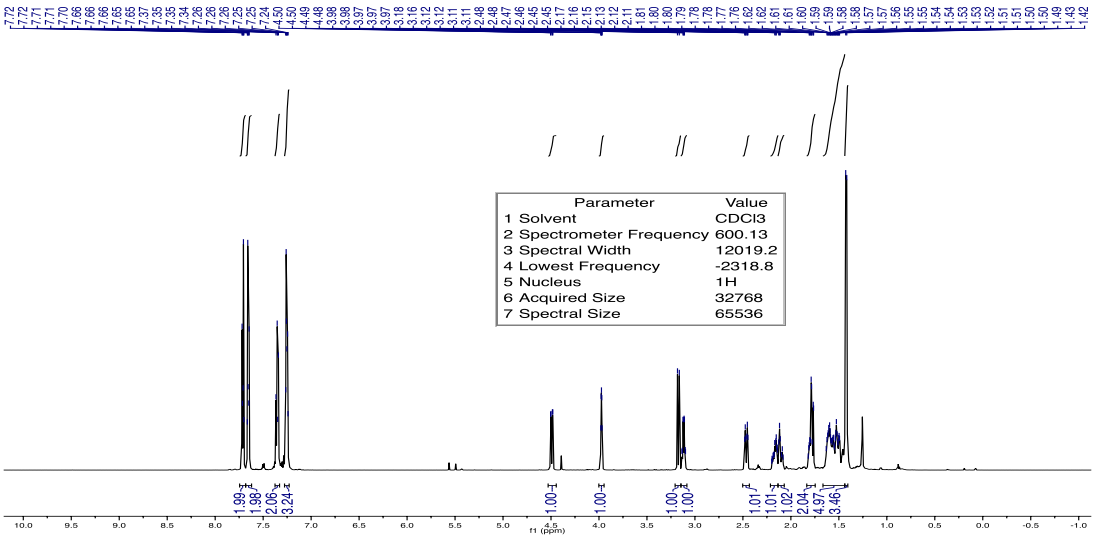
Preparation of piperidine 3.16:



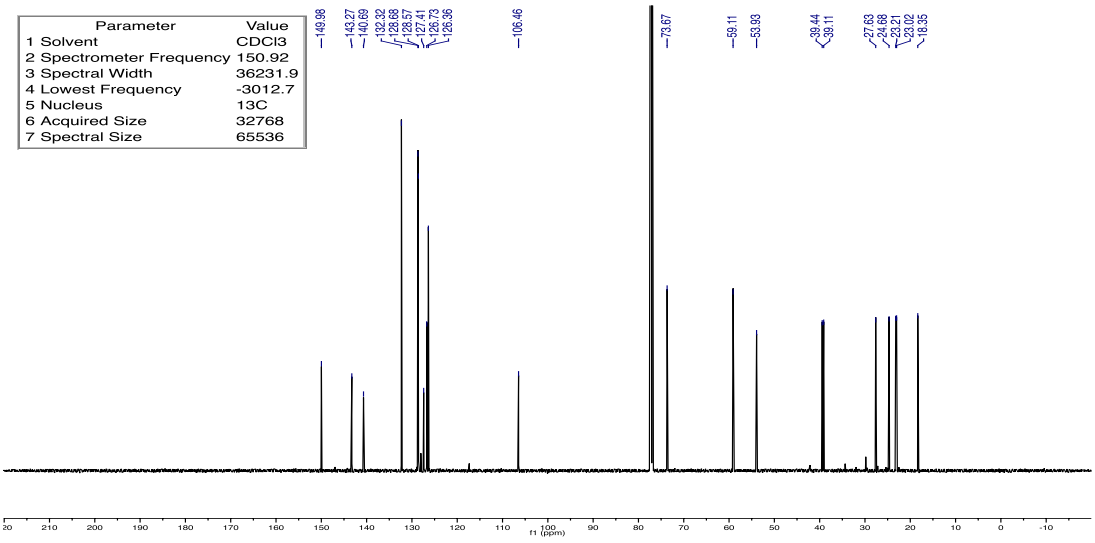
In a dry, N_2-filled glove box, aldehyde **3.10** (0.100 mmol, 40.8 mg, 1.00 eq.) and $[Ph_3C][B(C_6F_5)_4]$ (trityl $BArF_{20}$, 0.010 mmol, 9.2 mg, 0.10 eq.) were weighed into a screw cap 1 dram vial equipped with a stir bar and sealed with a septum cap. In a separate screw cap 1 dram vial, Et_3SiH (0.012 mmol, 1.9 μL, 0.12 eq.) and cyclohexanone-derived silyl enol ether (0.250 mmol, 48 μL, 2.50 eq.) were dissolved in 2.00 mL of CH_2Cl_2 and the vial sealed with a septum cap. Both vials were removed from the glove box and placed under a positive N_2 atmosphere *via* piercing of the septa with N_2 needles, and the vial containing the aldehyde and trityl $BArF_{20}$ was cooled to –78 °C in an acetone/$CO_{2(s)}$ bath. The room temperature solution in CH_2Cl_2 was syringed drop-wise and slowly down the side of the vial into the vigorously stirring solution over approximately 10 minutes. The solution was stirred for an additional 2 h at –78 °C, quenched at the cryogenic temperature with 50 μL Et_3N, and warmed to room temperature. The residue was repeatedly washed with CH_2Cl_2 and concentrated *in vacuo* (x3), and was then placed under high vacuum for ≥1 h to remove excess Et_3N. The resulting residue was taken up in 2 mL of 1:1 CH_2Cl_2/MeOH, approximately 10-20 beads of Dowex resin (50W-X8) were added, and the mixture was stirred at 22 °C for 3 h. The mixture was then filtered by gravity through a plug of sand and cotton, rinsed with 2x1mL CH_2Cl_2, and concentrated *in vacuo*. The crude residue was

purified by silica gel chromatography (5:1 *n*-pentane:ethyl acetate; $R_f = 0.5$) to yield the tricyclic piperidine product **3.16** as a white, crystalline solid in 38% yield (18.7 mg average per reaction over two 0.1 mmol scale trials).

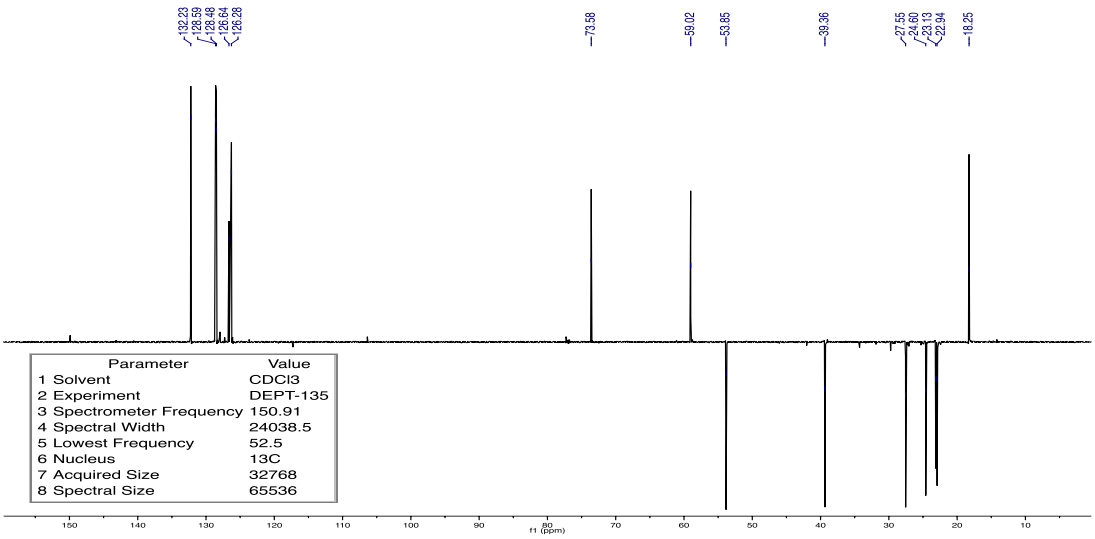
(2*R*,3*S*,6*S*)-4-((4-bromophenyl)sulfonyl)-3-methyl-6-phenyl-3,4,5,6,7,8,9,10-octahydro-2*H*-2,6-methanobenzo[*g*][1,4]oxazocine (3.16). **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 7.71 (d, 2H, *J* = 8.5 Hz), 7.65 (d, 2H, *J* = 8.5 Hz), 7.35 (t, 2H, *J* = 7.7 Hz), 7.26-7.24 (m, 3H), 4.49 (dd, 1H, *J* = 11.3, 2.6 Hz), 3.97 (dt, 1H, *J* = 3.8, 1.9 Hz), 3.17 (d, 1H, *J* = 11.3 Hz), 3.12 (qd, 1H, *J* = 6.7, 1.8 Hz), 2.46 (dt, 1H, *J* = 13.1, 3.3 Hz), 2.21-2.12 (m, 1H), 2.10 (dt, 1H, *J* = 17.4, 4.9 Hz), 1.83-1.79 (m, 1H), 1.78 (dd, 1H, *J* = 13.0, 2.1 Hz), 1.65-1.43 (m, 5H), 1.42 (d, 3H, *J* = 6.6 Hz); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 150.0, 143.3, 140.7, 132.3, 128.7, 128.6, 127.4, 126.7, 126.4, 106.5, 73.7, 59.1, 53.9, 39.4, 39.1, 27.6, 24.7, 23.2, 23.0, 18.4; **^{13}C NMR DEPT-135** ($CDCl_3$, 151 MHz): δ 132.3, 128.7, 128.6, 126.7, 126.4, 73.7 (CH), 59.1 (CH), 53.9 (CH_2), 39.1 (CH_2), 27.6 (CH_2), 24.7 (CH_2), 23.2 (CH_2), 23.0 (CH_2), 18.4 (CH_3); **IR** (ν/cm^{-1}): 3087 (w), 3059 (w), 3024 (w), 2982 (w), 2931 (s), 2886 (w), 2855 (m), 2841 (m), 1678 (m), 1603 (w), 1575 (m), 1496 (w), 1471 (m), 1446 (m), 1389 (m), 1372 (m), 1325 (s), 1286 (w), 1270 (w), 1248 (w), 1235 (w), 1217 (w), 1174 (s), 1154 (s), 1136 (m), 1089 (m), 1068 (m), 1037 (m), 1010 (m); **HRMS**-(ESI$^+$) $[M+H]^+$ calcd for $C_{24}H_{27}NO_3SBr^+$ 488.0895, found: 488.0895; **$[\alpha]_D^{26}$** = +2.02° (c = 1.865, CH_2Cl_2, l = 100 mm).



Parameter	Value
1 Solvent	CDCl3
2 Spectrometer Frequency	600.13
3 Spectral Width	12019.2
4 Lowest Frequency	-2318.8
5 Nucleus	1H
6 Acquired Size	32768
7 Spectral Size	65536



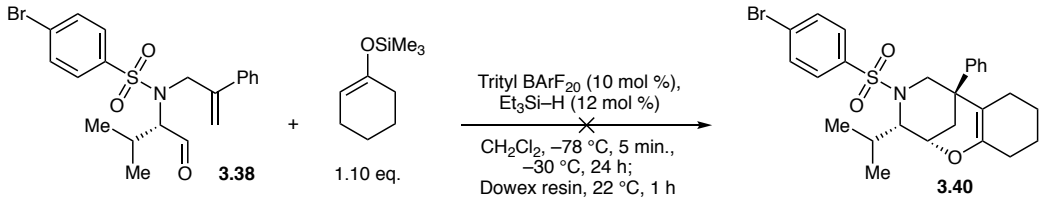
Parameter	Value
1 Solvent	CDCl3
2 Spectrometer Frequency	150.92
3 Spectral Width	36231.9
4 Lowest Frequency	-3012.7
5 Nucleus	13C
6 Acquired Size	32768
7 Spectral Size	65536



Parameter	Value
1 Solvent	CDCl3
2 Experiment	DEPT-135
3 Spectrometer Frequency	150.91
4 Spectral Width	24038.5
5 Lowest Frequency	52.5
6 Nucleus	13C
7 Acquired Size	32768
8 Spectral Size	65536

Figure 3.11. ^{1}H, $^{13}C\{^{1}H\}$, and ^{13}C DEPT-135 spectra for piperidine 3.16.

Preparation of piperidine 3.40:

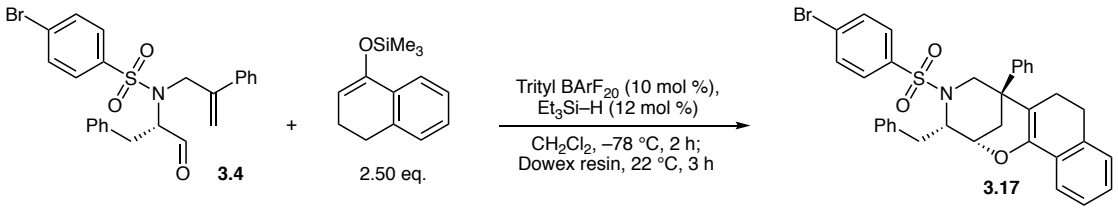


In a dry, N_2-filled glove box, aldehyde **3.38** (0.0500 mmol, 21.8 mg, 1.00 eq.) and $[Ph_3C][B(C_6F_5)_4]$ (trityl $BArF_{20}$, 0.0050 mmol, 4.6 mg, 0.10 eq.) were weighed into a screw cap 1 dram vial equipped with a stir bar and sealed with a septum cap. In a separate screw cap 1 dram vial, Et_3SiH (0.0060 mmol, 1.0 μL, 0.12 eq.) and cyclohexanone-derived silyl enol ether (0.0550 mmol, 10.6 μL, 1.10 eq.) were dissolved in 1.00 mL of CH_2Cl_2 and the vial sealed with a septum cap. Both vials were removed from the glove box and placed under a positive N_2 atmosphere *via* piercing of the septa with N_2 needles, and the vial containing the aldehyde and trityl $BArF_{20}$ was cooled to –78 °C in an acetone/$CO_{2(s)}$ bath. The room temperature solution in CH_2Cl_2 was syringed drop-wise and slowly down the side of the vial into the vigorously stirring solution over approximately 5 minutes. The solution was stirred for an additional 5 minutes at –78 °C, after which time the reaction was transferred to a –30 °C cryobath and stirred overnight for 24 h. The reaction was then quenched at the cryogenic temperature with 50 μL Et_3N and warmed to room temperature. The solution was diluted with CH_2Cl_2, concentrated *in vacuo* (x2), and then placed under high vacuum for ≥1 h to remove excess Et_3N. The resulting residue was taken up in 2 mL of 1:1 CH_2Cl_2/MeOH, approximately 10-20 beads of Dowex resin (50W-X8) were added, and the mixture was stirred at 22 °C for 1 h. The solution was then filtered by gravity

through a plug of sand and cotton, rinsed with 2x1mL CH_2Cl_2, and concentrated *in vacuo*. Dimethylformamide (0.050 mmol, 3.9 μL) was added as an internal standard and the residue taken up in $CDCl_3$ for ^1H and ^{13}C NMR analyses to determine conversion, product identity, NMR yield, and crude diastereomeric ratios (d.r.). Despite full consumption of starting materials, no trace of **3.40** is visible by ^1H or ^{13}C NMR.

(2*S*,3*S*,6*R*)-4-((4-bromophenyl)sulfonyl)-3-isopropyl-6-phenyl-3,4,5,6,7,8,9,10-octahydro-2*H*-2,6-methanobenzo[*g*][1,4]oxazocine (3.40). The starting material was consumed with no generation of desired product detectable by ^1H and $^{13}C\{^1H\}$ NMR or HRMS-(ESI+).

Preparation of piperidine 3.17:

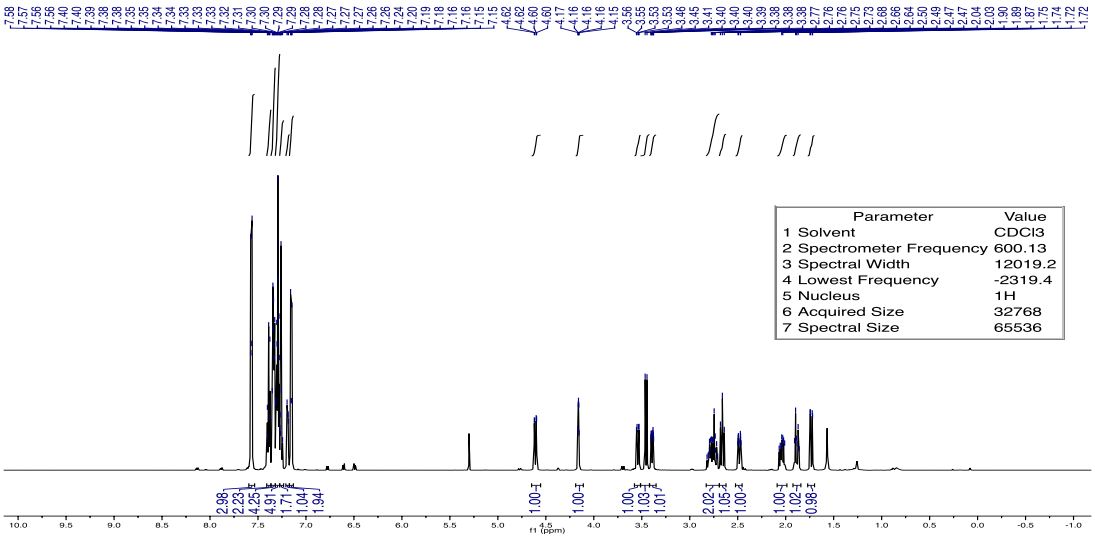


In a dry, N_2-filled glove box, aldehyde **3.4** (0.100 mmol, 48.4 mg, 1.00 eq.) and $[Ph_3C][B(C_6F_5)_4]$ (trityl $BArF_{20}$, 0.010 mmol, 9.2 mg, 0.10 eq.) were weighed into a screw cap 1 dram vial equipped with a stir bar and sealed with a septum cap. In a separate screw cap 1 dram vial, Et_3SiH (0.012 mmol, 1.9 μL, 0.12 eq.) and α-tetralone-derived silyl enol ether (0.250 mmol, 54.6 mg, 2.50 eq.) were dissolved in 2.00 mL of CH_2Cl_2 and the vial sealed with a septum cap. Both vials were removed from the glove box and placed under a positive N_2 atmosphere *via* piercing of the septa with N_2 needles, and the vial containing the aldehyde and trityl $BArF_{20}$ was cooled to –78 °C in an acetone/$CO_{2(s)}$ bath. The room

temperature solution in CH_2Cl_2 was syringed drop-wise and slowly down the side of the vial into the vigorously stirring solution over approximately 10 minutes. The solution was stirred for an additional 2 h at –78 °C, quenched at the cryogenic temperature with 50 μL Et_3N, and warmed to room temperature. The residue was repeatedly washed with CH_2Cl_2 and concentrated *in vacuo* (x3), and was then placed under high vacuum for ≥1 h to remove excess Et_3N. The resulting residue was taken up in 2 mL of 1:1 CH_2Cl_2/MeOH, approximately 10-20 beads of Dowex resin (50W-X8) were added, and the mixture was stirred at 22 °C for 3 h. The mixture was then filtered by gravity through a plug of sand and cotton, rinsed with 2x1mL CH_2Cl_2, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (10:1 *n*-pentane:ethyl acetate; $R_f = 0.3$), followed by washing with *n*-pentane to remove co-eluting α-tetralone, to yield the tetracyclic piperidine product **3.17** as a white, crystalline solid in 11% yield (6.8 mg average per reaction over two 0.1 mmol scale trials).

(2*R*,3*S*,6*S*)-3-benzyl-4-((4-bromophenyl)sulfonyl)-6-phenyl-3,4,5,6,7,8-hexahydro-2*H*-2,6-methanonaphtho[2,1-*g*][1,4]oxazocine (3.17). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.57 (d, 3H, *J* = 8.6 Hz), 7.39 (t, 2H, *J* = 7.7 Hz), 7.35-7.31 (m, 5H), 7.31-7.27 (m, 4H), 7.26 (t, 1H, *J* = 5.9 Hz), 7.19 (d, 1H, *J* = 6.3 Hz), 7.15 (d, 2H, *J* = 8.6 Hz), 4.61 (dd, 1H, *J* = 11.7, 2.7 Hz), 4.16 (dt, 1H, *J* = 3.9, 1.8 Hz), 3.54 (dd, 1H, *J* = 12.5, 3.5 Hz), 3.46 (d, 1H, *J* = 11.7 Hz), 3.39 (ddd, 1H, *J* = 11.9, 3.6, 1.7 Hz), 2.85-2.70 (m, 2H), 2.66 (t, 1H, *J* = 12.1 Hz), 2.48 (dt, 1H, *J* = 13.5, 4.1 Hz), 2.04 (ddd, 1H, *J* = 15.8, 11.7, 6.5 Hz), 1.88 (dt, 1H, *J* = 15.9, 6.6 Hz), 1.73 (dd, 1H, *J* = 13.4, 2.1 Hz); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 147.5, 143.7, 141.5, 137.8, 136.2, 132.2, 131.0, 129.9, 128.9, 128.8, 128.6, 127.9, 127.5, 127.4, 127.1, 127.0, 126.7, 126.2, 121.5, 110.2, 68.0, 65.5, 53.3, 40.3, 38.9, 35.7, 28.2,

23.8; **^{13}C NMR DEPT-135** ($CDCl_3$, 151 MHz): δ 132.2, 129.9, 128.9, 128.8, 128.6, 127.9, 127.5, 127.1, 127.0, 126.7, 126.2, 121.5, 68.0 (CH), 65.5 (CH), 53.3 (CH_2), 38.9 (CH_2), 35.7 (CH_2), 28.2 (CH_2), 23.8 (CH_2); **IR** (ν/cm^{-1}): 3086 (w), 3060 (w), 3027 (w), 3002 (w), 2952 (m), 2930 (m), 2854 (w), 1645 (m), 1601 (w), 1574 (m), 1496 (m), 1470 (w), 1446 (w), 1427 (w), 1389 (w), 1371 (w), 1329 (m), 1314 (s), 1266 (w), 1243 (w), 1232 (w), 1154 (s), 1121 (w), 1088 (m), 1069 (m), 1025 (w), 1011 (w); **HRMS**-(ESI$^+$) $[M+H]^+$ calcd for $C_{34}H_{31}NO_3SBr^+$ 612.1208, found: 612.1212; **$[\alpha]_D^{25}$** = +2.53° (c = 0.675, CH_2Cl_2, l = 100 mm).



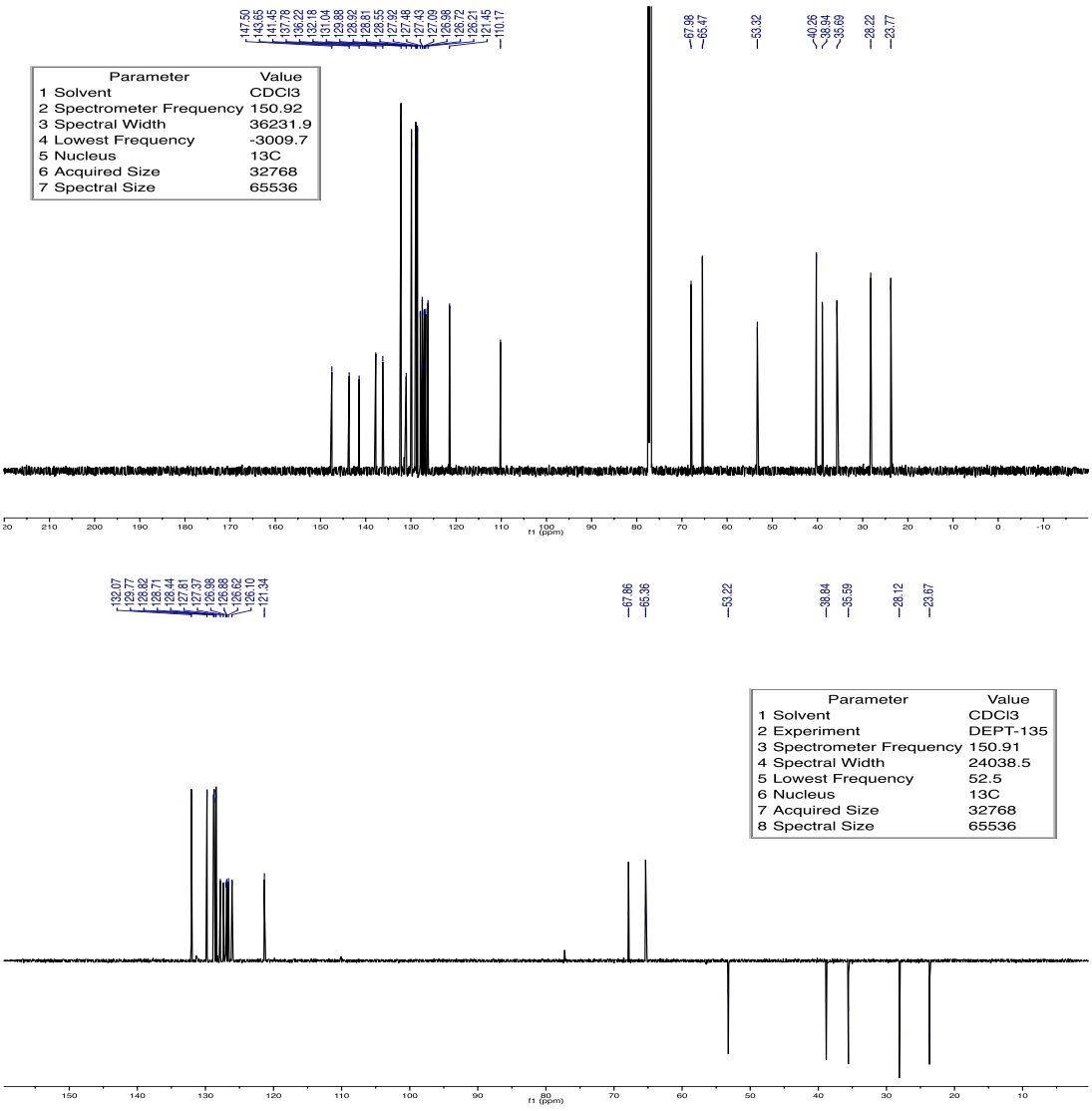
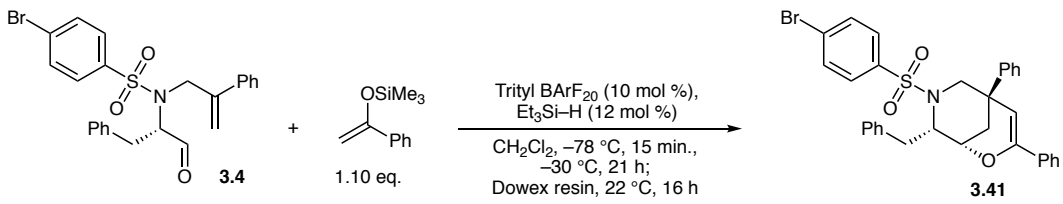


Figure 3.12. ^{1}H, ^{13}C{^{1}H}, and ^{13}C DEPT-135 spectra for piperidine 3.17.

Preparation of piperidine 3.41:



In a dry, N_2-filled glove box, aldehyde **3.4** (0.0500 mmol, 24.2 mg, 1.00 eq.) and

$[Ph_3C][B(C_6F_5)_4]$ (trityl $BArF_{20}$, 0.0050 mmol, 4.6 mg, 0.10 eq.) were weighed into a screw cap 1 dram vial equipped with a stir bar and sealed with a septum cap. In a separate screw cap 1 dram vial, Et_3SiH (0.0060 mmol, 1.0 μL, 0.12 eq.) and acetophenone-derived silyl enol ether (0.0550 mmol, 11.3 μL, 1.10 eq.) were dissolved in 1.00 mL of CH_2Cl_2 and the vial sealed with a septum cap. Both vials were removed from the glove box and placed under a positive N_2 atmosphere *via* piercing of the septa with N_2 needles, and the vial containing the aldehyde and trityl $BArF_{20}$ was cooled to –78 °C in an acetone/$CO_{2(s)}$ bath. The room temperature solution in CH_2Cl_2 was syringed drop-wise and slowly down the side of the vial into the vigorously stirring solution over approximately 5 minutes. The solution was allowed to stir for an additional 15 minutes at –78 °C, after which time the reaction was transferred to a –30 °C cryobath and stirred overnight for 21 h. The reaction was then quenched at the cryogenic temperature with 50 μL Et_3N and warmed to room temperature. The solution was diluted with CH_2Cl_2, concentrated *in vacuo* (x2), and then placed under high vacuum for ≥1 h to remove excess Et_3N. The resulting residue was taken up in 2 mL of 1:1 CH_2Cl_2/MeOH, approximately 10-20 beads of Dowex resin (50W-X8) were added, and the mixture was stirred at 22 °C for 16 h. The mixture was then filtered by gravity through a plug of sand and cotton, rinsed with 2x1mL CH_2Cl_2, and concentrated *in vacuo*. Dimethylformamide (0.050 mmol, 3.9 μL) was added as an internal standard and the residue taken up in $CDCl_3$ for ^1H and ^{13}C NMR analyses to determine conversion, product identity, NMR yield, and crude diastereomeric ratios (d.r.). Despite full consumption of starting materials, only trace **3.41** is visible by ^{13}C.

(1*S*,5*S*,8*S*)-8-benzyl-7-((4-bromophenyl)sulfonyl)-3,5-diphenyl-2-oxa-7-azabicyclo[3.3.1]non-3-ene (3.41). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 151 MHz): δ 101.9 (diagnostic

vinyl ether peak); **HRMS**-(ESI$^+$) $[M+H]^+$ calcd for $C_{32}H_{29}NO_3SBr^+$ 586.1052, found: 586.1054.

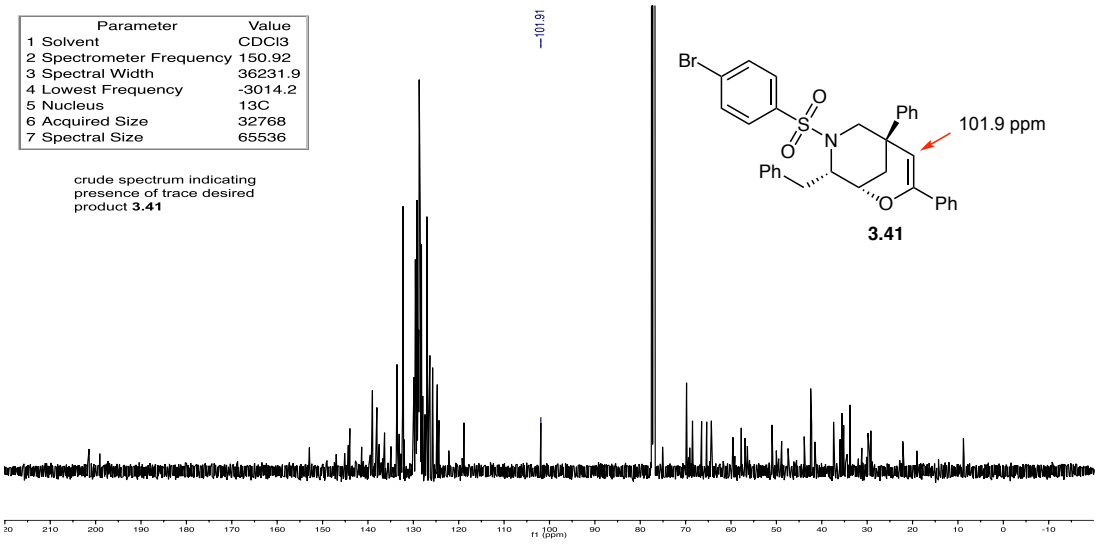
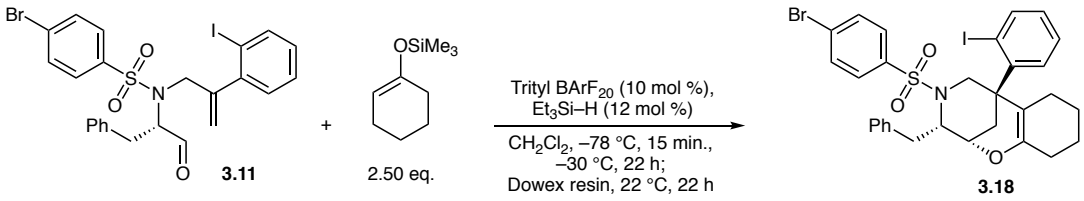


Figure 3.13. $^{13}C\{^1H\}$ spectrum for piperidine 3.41.

Preparation of piperidine 3.18:

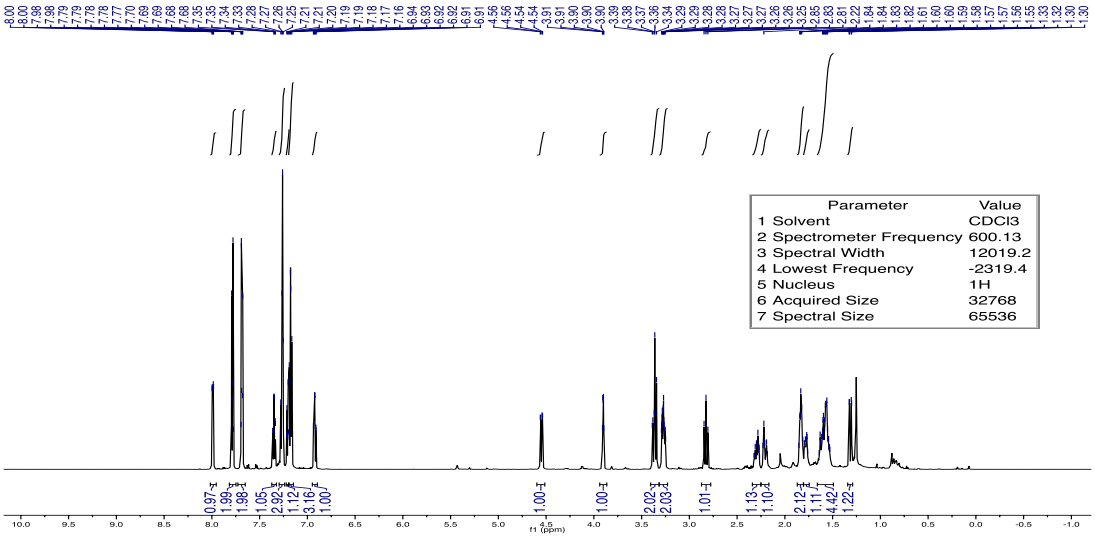


In a dry, N_2-filled glove box, aldehyde **3.11** (0.0500 mmol, 30.5 mg, 1.00 eq.) and $[Ph_3C][B(C_6F_5)_4]$ (trityl $BArF_{20}$, 0.0050 mmol, 4.6 mg, 0.10 eq.) were weighed into a screw cap 1 dram vial equipped with a stir bar and sealed with a septum cap. In a separate screw cap 1 dram vial, Et_3SiH (0.0060 mmol, 1.0 µL, 0.12 eq.) and cyclohexanone-derived silyl enol ether (0.125 mmol, 24.1 µL, 2.50 eq.) were dissolved in 1.00 mL of CH_2Cl_2 and the vial sealed with a septum cap. Both vials were removed from the glove box and placed under a positive N_2 atmosphere *via* piercing of the septa with N_2 needles, and the vial

containing the aldehyde and trityl $BArF_{20}$ was cooled to –78 °C in an acetone/$CO_{2(s)}$ bath. The room temperature solution in CH_2Cl_2 was syringed drop-wise and slowly down the side of the vial into the vigorously stirring solution over approximately 5 minutes. The solution was allowed to stir for an additional 15 minutes at –78 °C, after which time the reaction was transferred to a –30 °C cryobath and stirred overnight for 22 h (this was necessary for increased yield and reproducibility). The reaction was then quenched at the cryogenic temperature with 50 μL *i*-$PrNH_2$ and warmed to room temperature. The residue was repeatedly washed with CH_2Cl_2 and concentrated *in vacuo* (x3), and was then placed under high vacuum for ≥1 h to remove excess *i*-$PrNH_2$. The resulting residue was taken up in 2 mL of 1:1 CH_2Cl_2/MeOH, approximately 10-20 beads of Dowex resin (50W-X8) were added, and the mixture was stirred at 22 °C for 22 h. The mixture was then filtered by gravity through a plug of sand and cotton, rinsed with 2x1mL CH_2Cl_2, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (5:1 *n*-pentane:ethyl acetate; $R_f = 0.5$) to yield the tricyclic piperidine product **3.18** as a light yellow oil in 24% yield (8.2 mg average per reaction over two 0.05 mmol scale trials).

(2*S*,3*S*,6*S*)-3-benzyl-4-((4-bromophenyl)sulfonyl)-6-(2-iodophenyl)-3,4,5,6,7,8,9,10-octahydro-2*H*-2,6-methanobenzo[*g*][1,4]oxazocine (3.18). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.99 (dd, 1H, *J* = 7.9, 1.4 Hz), 7.79 (d, 2H, *J* = 8.6 Hz), 7.68 (d, 2H, *J* = 8.6 Hz), 7.35 (td, 1H, *J* = 7.7, 1.4 Hz), 7.26 (t, 2H, *J* = 3.8 Hz), 7.22-7.15 (m, 4H), 6.92 (td, 1H, *J* = 7.6, 1.5 Hz), 4.55 (dd, 1H, *J* = 11.1, 3.0 Hz), 3.90 (dt, 1H, *J* = 4.2, 1.8 Hz), 3.40-3.33 (m, 2H), 3.30-3.23 (m, 2H), 2.83 (t, 1H, *J* = 12.1 Hz), 2.33-2.25 (m, 1H), 2.21 (dt, 1H, *J* = 16.8, 5.5 Hz), 1.86-1.80 (m, 2H), 1.81-1.75 (m, 1H), 1.65-1.50 (m, 3H), 1.31 (dd, 1H, *J* = 13.3, 1.9 Hz); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 151.7, 143.7, 142.8, 141.9, 137.8, 132.5, 129.8,

128.7, 128.6, 128.4, 128.4, 127.6, 127.5, 126.9, 103.4, 96.3, 67.1, 65.7, 55.4, 40.9, 35.9, 34.1, 27.8, 24.8, 23.3, 22.4; **^{13}C NMR DEPT-135** ($CDCl_3$, 151 MHz): δ 143.7 (CH), 132.5 (CH), 129.8 (CH), 128.7 (CH), 128.6 (CH), 128.4 (CH), 128.4 (CH), 127.5 (CH), 126.9 (CH), 67.1 (CH), 65.7 (CH), 55.4 (CH_2), 35.9 (CH_2), 34.1 (CH_2), 27.8 (CH_2), 24.8 (CH_2), 23.3 (CH_2), 22.4 (CH_2); **IR** (ν/cm^{-1}): 3084 (w), 3060 (w), 3027 (w), 3002 (w), 2929 (s), 2857 (m), 2836 (m), 1684 (m), 1602 (w), 1575 (m), 1496 (w), 1470 (w), 1457 (m), 1388 (m), 1374 (m), 1352 (m), 1333 (s), 1265 (w), 1232 (m), 1209 (w), 1164 (s), 1154 (s), 1128 (w), 1112 (w), 1089 (m), 1067 (m), 1053 (w), 1009 (m); **HRMS**-(ESI$^+$) $[M+H]^+$ calcd for $C_{30}H_{30}NO_3SBrI^+$ 690.0175, found: 690.0185; **$[\alpha]_D^{25}$** = +21.6° (c = 0.820, CH_2Cl_2, l = 100 mm).



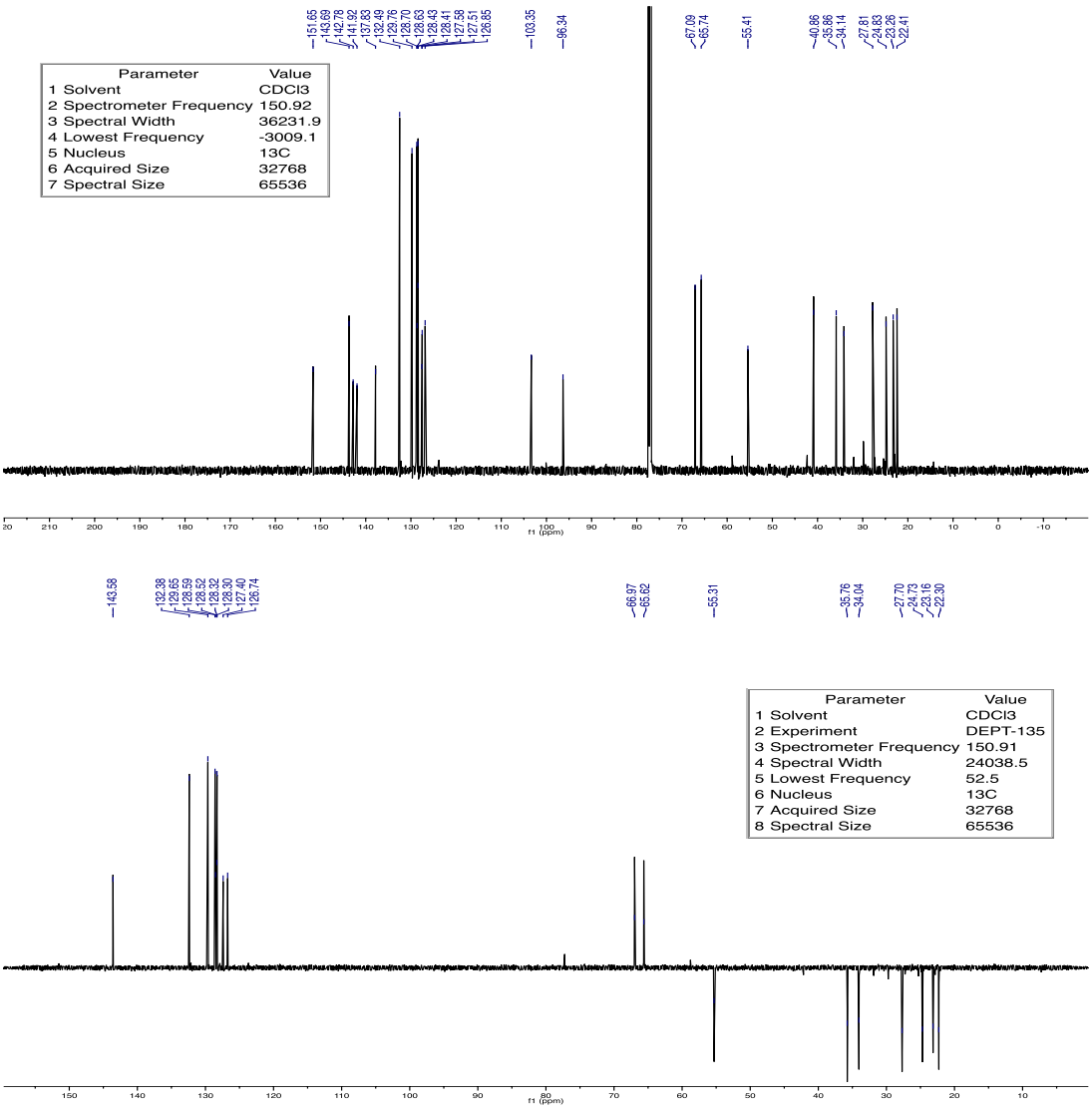
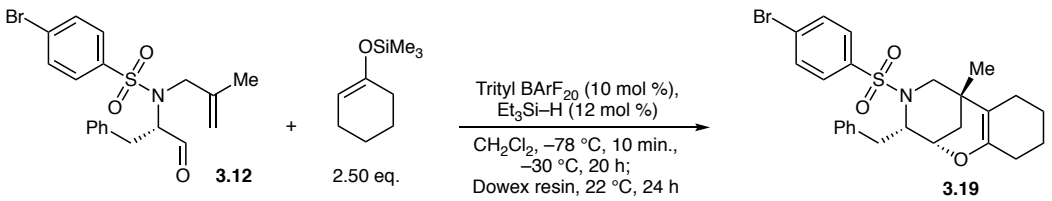


Figure 3.14. ^{1}H, ^{13}C{^{1}H}, and ^{13}C DEPT-135 spectra for piperidine 3.18.

Preparation of piperidine 3.19:

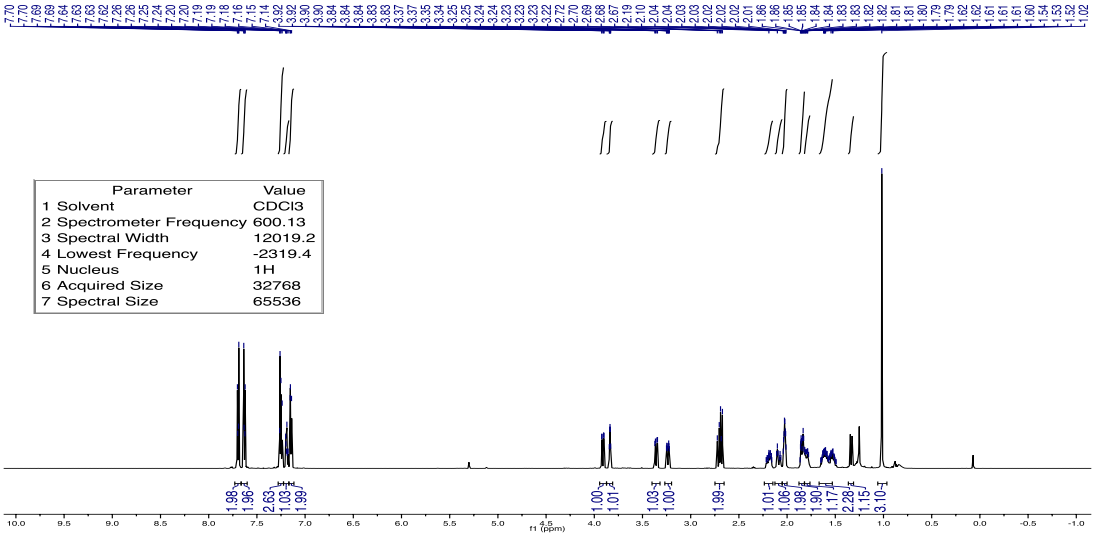


In a dry, N_2-filled glove box, aldehyde **3.12** (0.0500 mmol, 21.1 mg, 1.00 eq.) and

$[Ph_3C][B(C_6F_5)_4]$ (trityl $BArF_{20}$, 0.0050 mmol, 4.6 mg, 0.10 eq.) were weighed into a screw cap 1 dram vial equipped with a stir bar and sealed with a septum cap. In a separate screw cap 1 dram vial, Et_3SiH (0.0060 mmol, 1.0 μL, 0.12 eq.) and cyclohexanone-derived silyl enol ether (0.125 mmol, 24.1 μL, 2.50 eq.) were dissolved in 1.00 mL of CH_2Cl_2 and the vial sealed with a septum cap. Both vials were removed from the glove box and placed under a positive N_2 atmosphere *via* piercing of the septa with N_2 needles, and the vial containing the aldehyde and trityl $BArF_{20}$ was cooled to –78 °C in an acetone/$CO_{2(s)}$ bath. The room temperature solution in CH_2Cl_2 was syringed drop-wise and slowly down the side of the vial into the vigorously stirring solution over approximately 5 minutes. The solution was allowed to stir for an additional 15 minutes at –78 °C, after which time the reaction was transferred to a –30 °C cryobath and stirred overnight for 20 h (this was necessary for increased yield and reproducibility). The reaction was then quenched at the cryogenic temperature with 50 μL *i*-$PrNH_2$ and warmed to room temperature. The residue was repeatedly washed with CH_2Cl_2, concentrated *in vacuo* (x3), and was then placed under high vacuum for ≥1 h to remove excess *i*-$PrNH_2$. The resulting residue was taken up in 2 mL of 1:1 CH_2Cl_2/MeOH, approximately 10-20 beads of Dowex resin (50W-X8) were added, and the mixture was stirred at 22 °C for 24 h. The mixture was then filtered by gravity through a plug of sand and cotton, rinsed with 2x1mL CH_2Cl_2, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (10:1 *n*-pentane:ethyl acetate; $R_f = 0.4$) to yield the tricyclic piperidine product **3.19** as a white solid in 22% yield (5.5 mg average per reaction over three 0.05 mmol scale trials).

(2*S*,3*S*,6*S*)-3-benzyl-4-((4-bromophenyl)sulfonyl)-6-methyl-3,4,5,6,7,8,9,10-octahydro-2*H*-2,6-methanobenzo[*g*][1,4]oxazocine (3.19). **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 7.69 (d,

2H, J = 8.5 Hz), 7.63 (d, 2H, J = 8.5 Hz), 7.25 (t, 2H, J = 7.4 Hz), 7.19 (t, 1H, J = 7.3 Hz), 7.15 (d, 2H, J = 7.0 Hz), 3.91 (dd, 1H, J = 11.9, 2.4 Hz), 3.84 (dt, 1H, J = 4.0, 2.0 Hz), 3.36 (dd, 1H, J = 12.6, 3.7 Hz), 3.24 (ddd, 1H, J = 11.5, 3.7, 2.0 Hz), 2.70 (t, 1H, J = 12.0 Hz), 2.68 (d, 1H, J = 11.9 Hz), 2.23-2.14 (m, 1H), 2.09 (dt, 1H, J = 16.9, 4.9 Hz), 2.05-2.00 (m, 2H), 1.84 (dt, 2H, J = 12.9, 2.8 Hz), 1.83-1.75 (m, 1H), 1.67-1.47 (m, 2H), 1.33 (dd, 1H, J = 13.0, 2.0 Hz), 1.02 (s, 3H); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 148.1, 141.9, 138.2, 132.3, 129.8, 128.6, 128.4, 127.3, 126.7, 106.7, 67.3, 65.1, 56.7, 37.2, 35.7, 31.1, 27.5, 23.4, 22.9, 22.9, 22.0; **^{13}C NMR DEPT-135** ($CDCl_3$, 151 MHz): δ 132.3 (CH), 129.8 (CH), 128.6 (CH), 128.4 (CH), 126.7 (CH), 67.3 (CH), 65.1 (CH), 56.7 (CH_2), 37.2 (CH_2), 35.7 (CH_2), 27.5 (CH_2), 23.4 (CH_2), 22.9 (CH_2), 22.9 (CH_2), 22.0 (CH_3); **IR** (ν/cm^{-1}): 3086 (w), 3061 (w), 3028 (w), 2929 (s), 2875 (m), 2855 (m), 2840 (m), 1679 (m), 1603 (w), 1575 (m), 1495 (w), 1471 (w), 1455 (m), 1387 (m), 1357 (m), 1331 (s), 1315 (m), 1267 (w), 1244 (w), 1189 (m), 1156 (s), 1142 (m), 1130 (m), 1114 (w), 1091 (m), 1068 (m), 1052 (w), 1036 (w), 1008 (m); **HRMS**-(ESI$^+$) $[M+H]^+$ calcd for $C_{25}H_{29}NO_3SBr^+$ 502.1052, found: 502.1054; **$[\alpha]_D^{25}$** = +0.699° (c = 0.830, CH_2Cl_2, l = 100 mm).



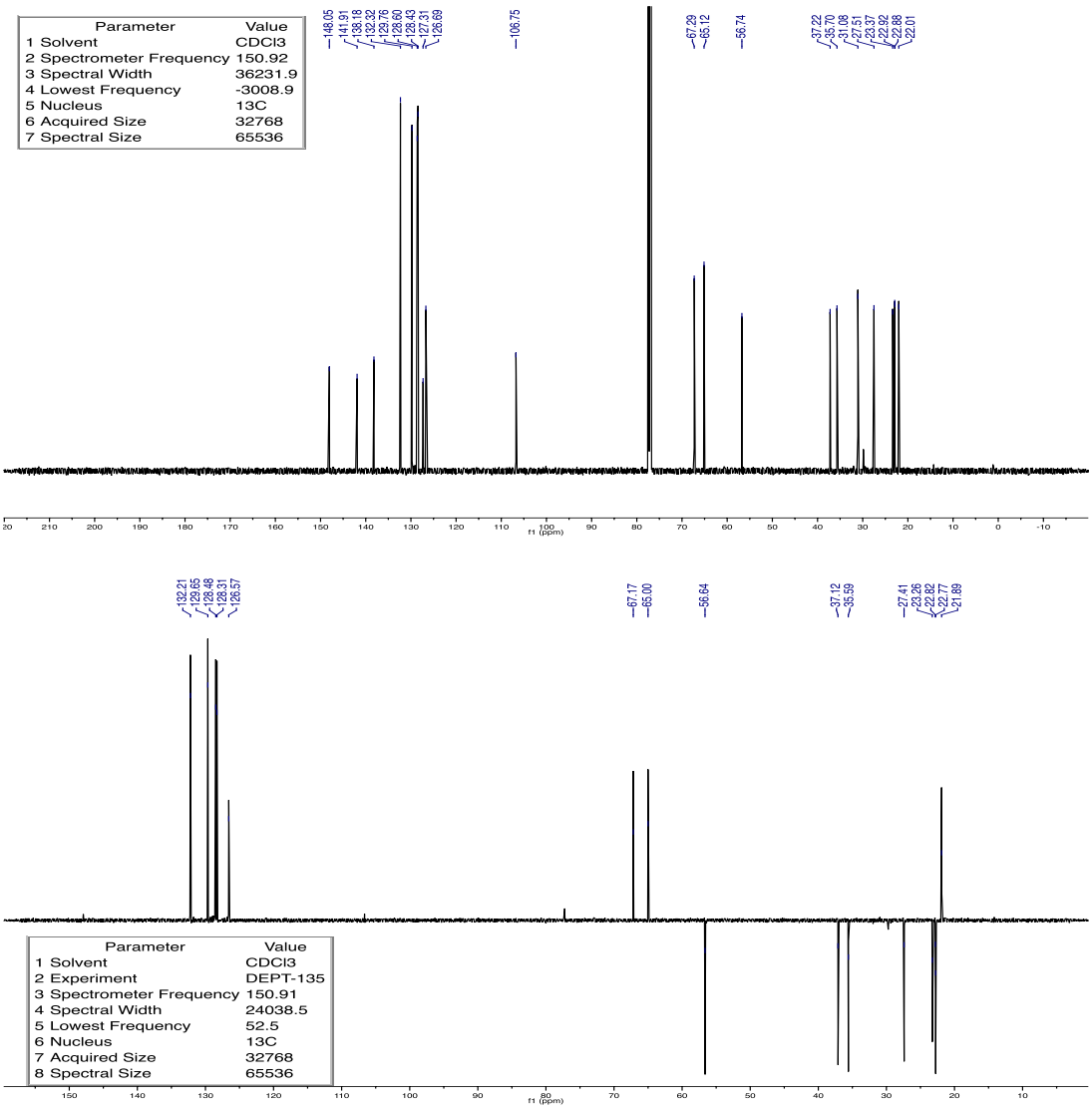
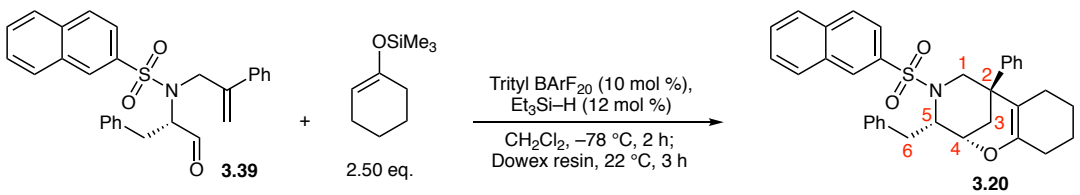


Figure 3.15. ^{1}H, ^{13}C{^{1}H}, and ^{13}C DEPT-135 spectra for piperidine 3.19.

Preparation of piperidine 3.20:

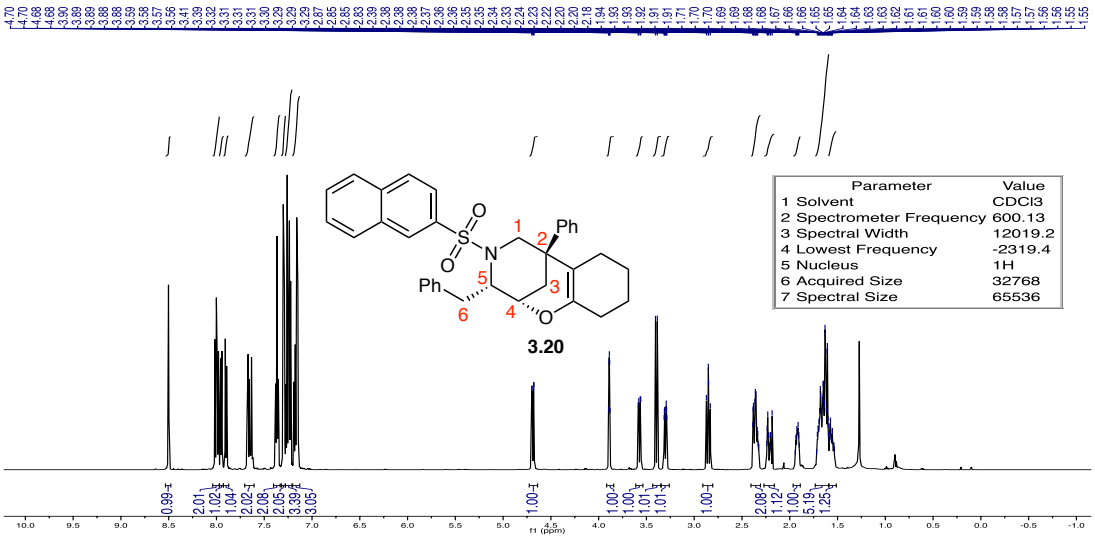


In a dry, N_2-filled glove box, aldehyde **3.39** (0.150 mmol, 68.3 mg, 1.00 eq.) and $[Ph_3C][B(C_6F_5)_4]$ (trityl $BArF_{20}$, 0.015 mmol, 13.8 mg, 0.10 eq.) were weighed into a

screw cap 1 dram vial equipped with a stir bar and sealed with a septum cap. In a separate screw cap 1 dram vial, Et_3SiH (0.018 mmol, 2.9 μL, 0.12 eq.) and cyclohexanone-derived silyl enol ether (0.375 mmol, 72 μL, 2.50 eq.) were dissolved in 3.00 mL of CH_2Cl_2 and the vial sealed with a septum cap. Both vials were removed from the glove box and placed under a positive N_2 atmosphere *via* piercing of the septa with N_2 needles, and the vial containing the aldehyde and trityl $BArF_{20}$ was cooled to –78 °C in an acetone/$CO_{2(s)}$ bath. The room temperature solution in CH_2Cl_2 was syringed drop-wise and slowly down the side of the vial into the vigorously stirring solution over approximately 10 minutes. The solution was stirred for an additional 2 h at –78 °C, quenched at the cryogenic temperature with 50 μL Et_3N, and warmed to room temperature. The residue was repeatedly washed with CH_2Cl_2 and concentrated *in vacuo* (x3), and was then placed under high vacuum for ≥1 h to remove excess Et_3N. The resulting residue was taken up in 2 mL of 1:1 CH_2Cl_2/MeOH, approximately 10-20 beads of Dowex resin (50W-X8) were added, and the mixture was stirred at 22 °C for 3 h. The mixture was then filtered by gravity through a plug of sand and cotton, rinsed with 2x1mL CH_2Cl_2, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (5:1 *n*-pentane:ethyl acetate; $R_f = 0.5$) to yield the tricyclic piperidine product **3.20** as a white, crystalline solid in 55% yield (44.3 mg).

(2*R*,3*S*,6*S*)-3-benzyl-4-(naphthalen-2-ylsulfonyl)-6-phenyl-3,4,5,6,7,8,9,10-octahydro-2*H*-2,6-methanobenzo[*g*][1,4]oxazocine (3.20). ^{1}H NMR ($CDCl_3$, 600 MHz; piperidine ring protons assigned in red): δ 8.50 (d, 1H *J* = 1.9 Hz), 8.01 (d, 1H, *J* = 8.7 Hz), 7.99 (d, 1H, *J* = 8.2 Hz), 7.95 (d, 1H, *J* = 8.0 Hz), 7.90 (dd, 1H, *J* = 8.7, 1.9 Hz), 7.67 (ddd, 1H, *J* = 8.2, 6.9, 1.4 Hz), 7.63 (ddd, 1H, *J* = 8.2, 6.8, 1.4 Hz), 7.37 (t, 2H, *J* = 7.7 Hz), 7.29 (dd,

2H, J = 8.2, 1.3 Hz), 7.27-7.22 (m, 3H), 7.18 (d, 1H, J = 7.4 Hz), 7.16 (dd, 2H, J = 7.1, 1.6 Hz), 4.69 (dd, 1H, J = 11.4, 2.7 Hz, 1), 3.89 (dt, 1H, J = 4.0, 1.9 Hz, 4), 3.57 (dd, 1H, J = 12.7, 3.5 Hz, 6), 3.40 (d, 1H, J = 11.5 Hz, 1), 3.30 (ddd, 1H, J = 11.6, 3.6, 1.8 Hz, 5), 2.85 (t, 1H, J = 12.8, 11.6 Hz, 6), 2.39-2.32 (m, 2H, 3), 2.24-2.19 (m, 1H), 1.94-1.90 (m, 1H), 1.72-1.53 (m, 6H, 3); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz; piperidine ring carbons assigned in red): δ 150.1, 143.5, 139.6, 138.2, 134.8, 132.4, 129.8, 129.4, 129.3, 128.9, 128.6, 128.6, 128.1, 127.8, 127.7, 126.7, 126.6, 126.4, 122.5, 106.3, 67.4 (4), 65.5 (5), 54.1 (1), 39.1 (2), 39.0 (3), 35.8 (6), 27.8, 24.8, 23.4, 23.1; **^{13}C NMR DEPT-135** ($CDCl_3$, 151 MHz): δ 129.8 (CH), 129.4 (CH), 129.3 (CH), 128.9 (CH), 128.6 (CH), 128.6 (CH), 128.1 (CH), 127.8 (CH), 127.7 (CH), 126.7 (CH), 126.6 (CH), 126.4 (CH), 122.5 (CH), 67.4 (CH), 65.5 (CH), 54.1 (CH_2), 39.0 (CH_2), 35.8 (CH_2), 27.8 (CH_2), 24.8 (CH_2), 23.4 (CH_2), 23.1 (CH_2); **IR** (ν/cm^{-1}): 3059 (w), 3027 (w), 2928 (s), 2855 (m), 1679 (m), 1602 (w), 1496 (m), 1445 (m), 1373 (m), 1327 (s), 1267 (w), 1236 (w), 1166 (s), 1151 (s), 1130 (m), 1074 (m), 1063 (w), 1021 (w); **HRMS**-(ESI$^+$) $[M+H]^+$ calcd for $C_{34}H_{34}NO_3S^+$ 536.2260, found: 536.2259; **$[\alpha]_D^{26}$** = +11.7° (c = 1.70, CH_2Cl_2, l = 100 mm). A single crystal X-ray structure was obtained from this compound *via* recrystallization (solvent vapor) from a mixture of C_6H_6/*n*-pentane. The data indicate a surprising *cis*-(axial-equatorial) configuration of the C–O bond and the amino R-group, respectively.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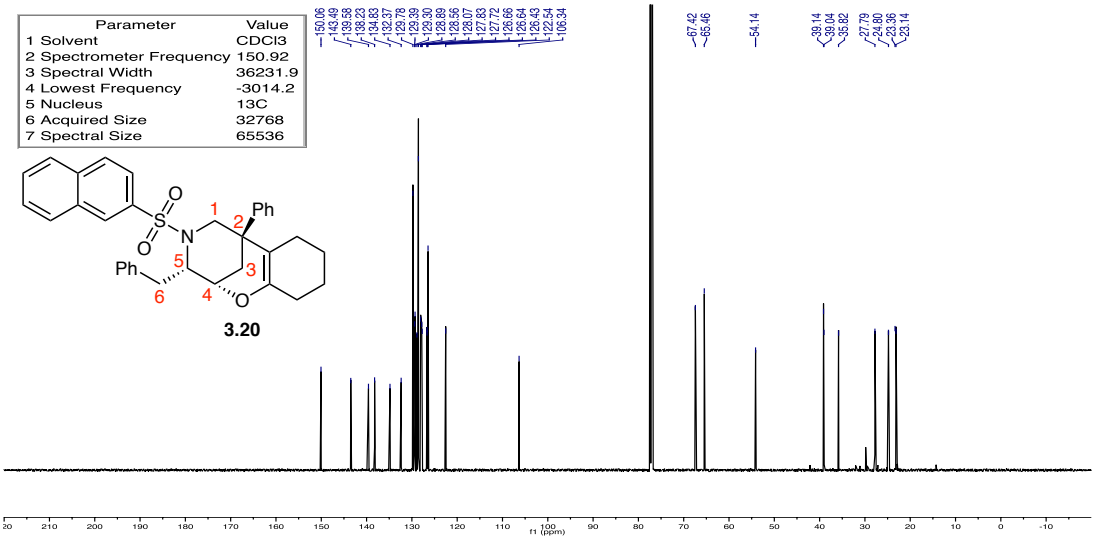
3.20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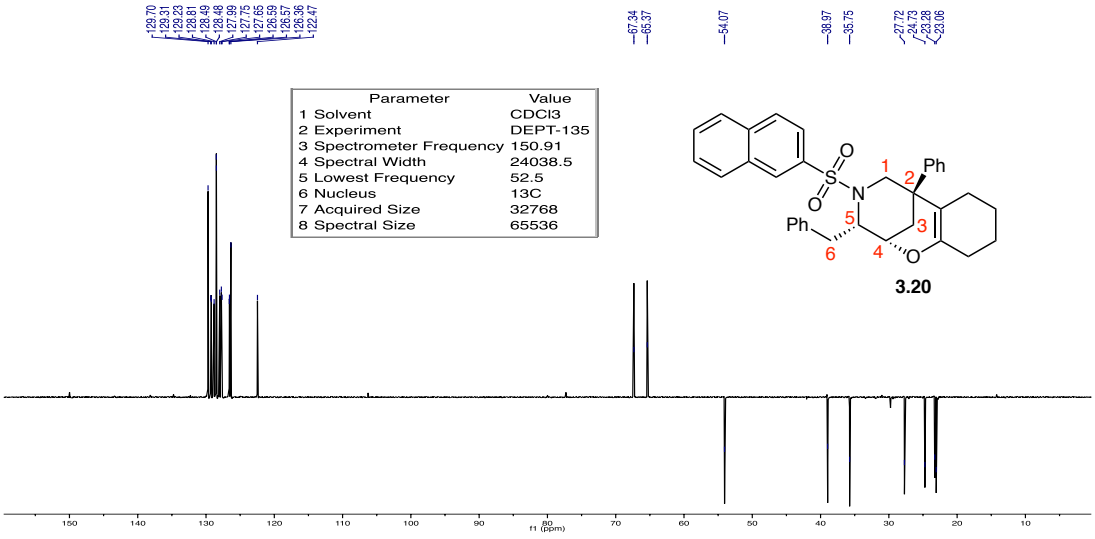
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3.20

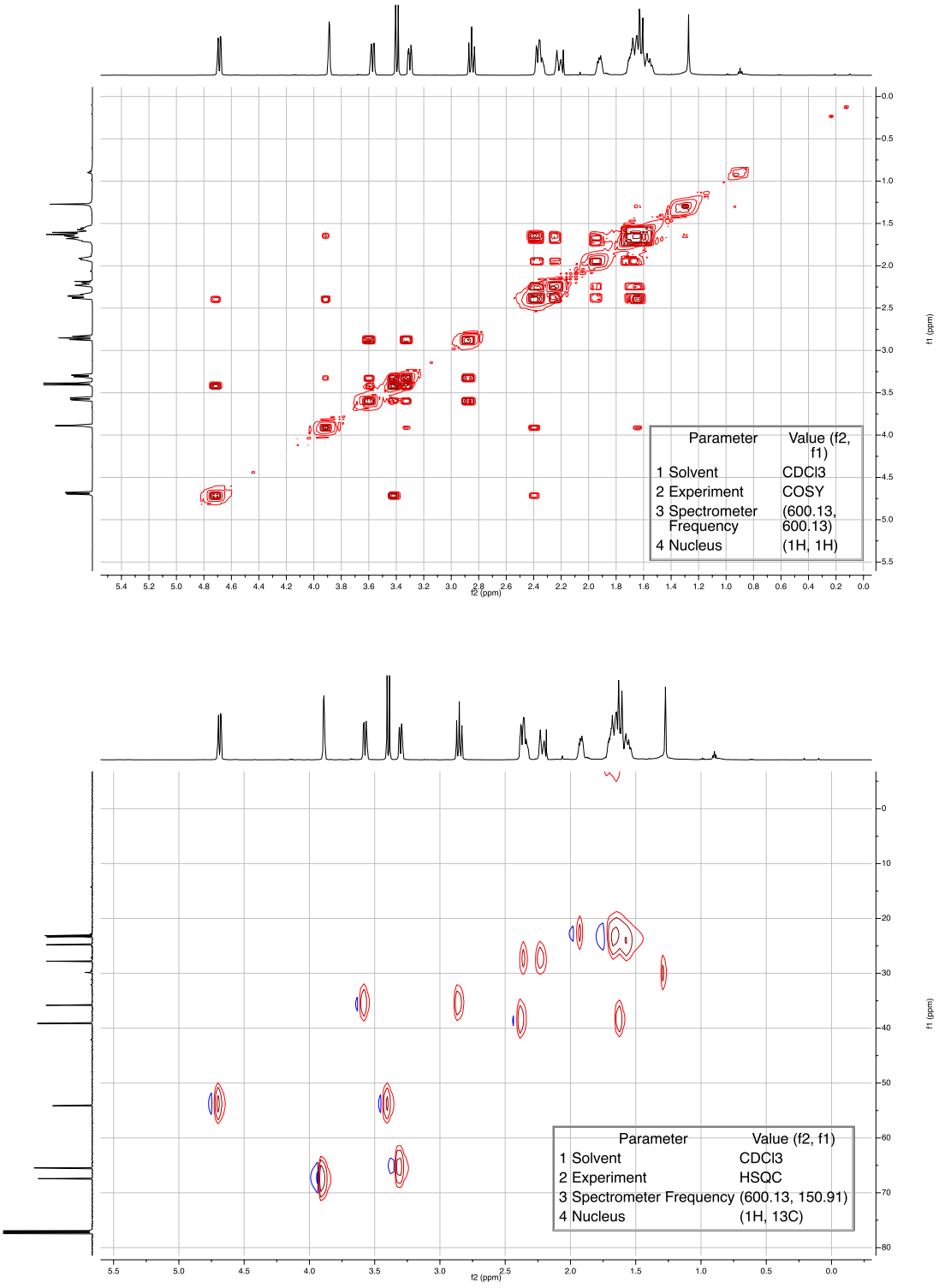


Figure 3.16. ^{1}H, ^{13}C{^{1}H}, ^{13}C DEPT-135, 2D COSY, and 2D HSQC spectra for piperidine 3.20.

3.7.4.3 X-ray crystallographic data and structure for **3.20**

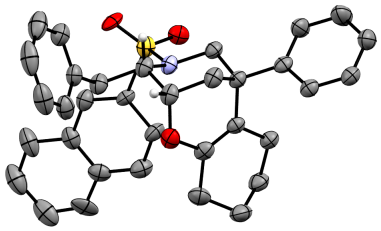


Figure 3.17. ORTEP representation of solid state molecular structure of 3.20.

The ORTEP representation of the solid state molecular structure of **3.20** (CSD-1548662) is shown in Figure 3.17; ellipsoids are drawn at 50% probability, the majority of hydrogen atoms are omitted for clarity.[56] There is disorder in the orientation of the 2-naphthalenesulfonyl group; only one of two adopted conformations of the naphthyl group is shown for clarity. The X-ray crystallographic data are shown in Table 3.3.

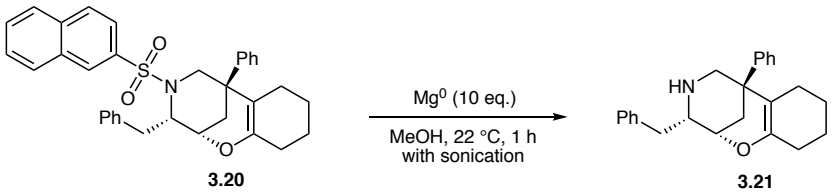
Table 3.3. Solid state molecular structure data for 3.20.

Empirical formula	$C_{34}H_{33}NO_3S$	D_{calcd} (Mg m^{-3})	1.333
F_w	535.70	Radiation	Cu $_{K\alpha}$, λ = 1.54178 Å
Colour, habit	Colourless, Plate	Absorption coeff. (μ) (mm^{-1})	1.37
Crystal dimensions (mm)	0.23 x 0.10 x 0.06	Absorption correction	Numerical
Crystal system	Monoclinic	F(000)	1137
Space group	$P2_1/c$	θ_{min} *to* θ_{max} (°)	3.4 to 66.7
Z	4	Measured reflections	39148
a (Å)	13.1751(2)	Independent reflections	4720 (R_{int}=0.047)
b (Å)	10.6097(2)	Data/restraints/parameters	4720/150/454
c (Å)	19.5344(3)	Maximum shift/error	<0.001
α (°)	90.00	Goodness-of-fit on F^2	1.19
β (°)	102.0226(9)	Final R indices ($I > 2\sigma(I)$)	R_1 = 0.054 wR_2 = 0.114
γ (°)	90.00	R indices (all data)	R_1 = 0.067 wR_2 = 0.119
Collection ranges	h = –15→15	Extinction coefficient	N/A

	$k = -12 \rightarrow 12$ $l = -23 \rightarrow 22$		
Temperature (K)	100	Largest diff. peak and hole (e Å^{-3})	0.21 and –0.38
Volume (Å^3)	2670.70(8)		

3.7.4.4 Removal of aryl sulfonamide protecting groups

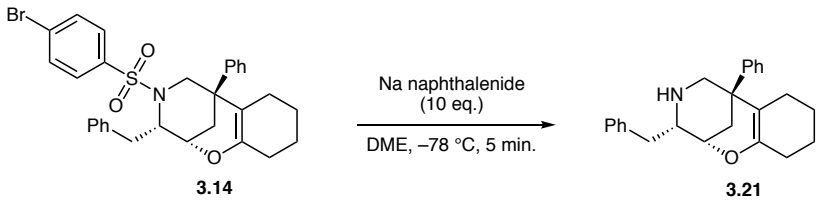
Deprotection of piperidine 3.20:



3.20 **3.21**

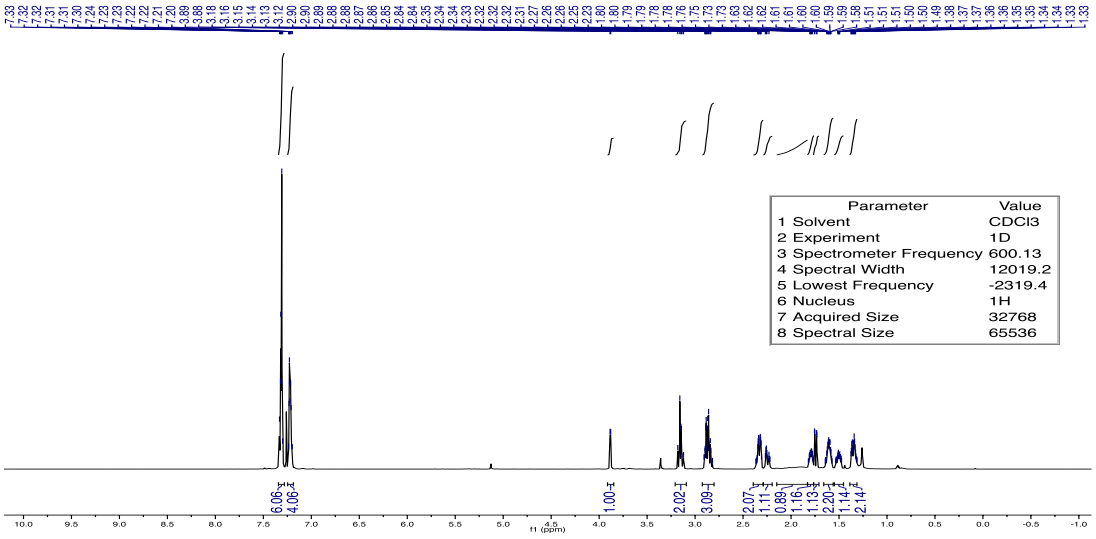
2-naphthalenesulfonyl-protected piperidine **3.20** (0.0609 mmol, 32.6 mg, 1.00 eq.) and elemental magnesium (50 mesh; 0.609 mmol, 14.8 mg, 10.0 eq.) were weighed into a screw cap 1 dram vial equipped with a stir bar and sealed with a septum cap. The vial was purged with a stream of dry N_2 for 5 minutes, at which time anhydrous methanol (1.82 mL) was added *via* syringe. The milky white suspension was sonicated for 1 h, during which time the substrate and magnesium dissolved to produce a homogeneous gray solution; TLC (25:1 CH_2Cl_2:MeOH; product $R_f = 0.4$) showed spot-to-spot conversion. The reaction was quenched with saturated aqueous NH_4Cl, diluted with excess CH_2Cl_2 and rinsed into a separatory funnel, basified with excess aqueous 1M NaOH (until pH ≥ 10), diluted with saturated aqueous NaCl, and then extracted with CH_2Cl_2 (x5). The combined organic washes were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (25:1 dichloromethane:methanol with trace triethylamine; $R_f = 0.4$) to yield the free piperidine **3.21** as a clear, colorless oil in 91% yield (19.1 mg).

Deprotection of piperidine 3.14:



The reductive deprotection of brosyl-protected piperidine **14** was effected *via* application of a modified literature procedure.[6] A stock solution of sodium naphthalenide was prepared by dissolving finely chopped sodium metal (4.06 mmol, 93 mg) and naphthalene (4.47 mmol, 572 mg) in 5.00 mL of freshly distilled 1,2-dimethoxyethane (DME) and stirring at 22 °C for 2 h. Note: the solution rapidly became dark green in color. Piperidine **14** (0.0406 mmol, 22.9 mg, 1.00 eq.) was weighed into a screw cap 1 dram vial equipped with a stir bar and sealed with a septum cap. The vial was purged with a stream of dry N_2 for 5 minutes, at which time anhydrous DME (500 μL) was added *via* syringe and the vial was cooled to –78 °C in an acetone/$CO_{2(s)}$ bath. Sodium naphthalenide solution (approx. 0.406 mmol, 600 μL, 10-12 eq.) was added dropwise via syringe. The dark green solution was vigorously stirred for an additional 5 minutes at –78 °C, at which time the solution froze. The reaction was quenched at the cryogenic temperature by the addition of 500 μL of saturated aqueous $NaHCO_3$, warmed to room temperature, and rinsed into a separatory funnel with excess CH_2Cl_2. The organic layer was basified with aqueous 1M NaOH (10 mL), diluted with saturated aqueous NaCl (10 mL), and then extracted with CH_2Cl_2 (x5). The combined organic washes were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (25:1 dichloromethane:methanol with trace triethylamine; $R_f = 0.4$) to yield the free amine product **21** as a light yellow oil in 93% yield (13.0 mg).

(2*R*,3*S*,6*S*)-3-benzyl-6-phenyl-3,4,5,6,7,8,9,10-octahydro-2*H*-2,6-methanobenzo[*g*][1,4] oxazocine (3.21). **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 7.34-7.29 (m, 6H), 7.24-7.19 (m, 4H), 3.88 (d, 1H, *J* = 4.1 Hz), 3.19-3.10 (m, 2H), 2.91-2.81 (m, 3H), 2.37-2.29 (m, 2H), 2.27-2.21 (m, 1H), 1.90 (br s, 1H, N*H*), 1.82-1.77 (m, 1H), 1.74 (dd, *J* = 13.1, 1.8 Hz, 1H), 1.63-1.58 (m, 2H), 1.54-1.47 (m, 1H), 1.37-1.33 (m, 2H); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 151.0, 144.9, 139.1, 129.6, 128.5, 128.4, 126.8, 126.3, 126.2, 106.3, 69.1, 63.8, 51.7, 39.4, 39.1, 39.0, 27.8, 24.9, 23.6, 23.3; **^{13}C NMR DEPT-135** ($CDCl_3$, 151 MHz): δ 129.6 (CH), 128.5 (CH), 128.4 (CH), 126.8 (CH), 126.3 (CH), 126.2 (CH), 69.1 (CH), 63.8 (CH), 51.7 (CH_2), 39.4 (CH_2), 39.1 (CH_2), 27.8 (CH_2), 24.9 (CH_2), 23.6 (CH_2), 23.3 (CH_2); **IR** (ν/cm^{-1}): 3084 (w), 3059 (w), 3026 (w), 2927 (s), 2854 (s), 1669 (m), 1603 (w), 1556 (w), 1495 (m), 1446 (m), 1372 (w), 1348 (w), 1266 (w), 1232 (m), 1215 (w), 1150 (m), 1136 (m), 1108 (w), 1058 (w), 1032 (w); **HRMS**-(ESI^{+}) $[M+H]^{+}$ calcd for $C_{24}H_{28}NO^{+}$ 346.2171, found: 346.2164; **$[\alpha]_D^{25}$** = +117° (c = 0.955, CH_2Cl_2, l = 100 mm).



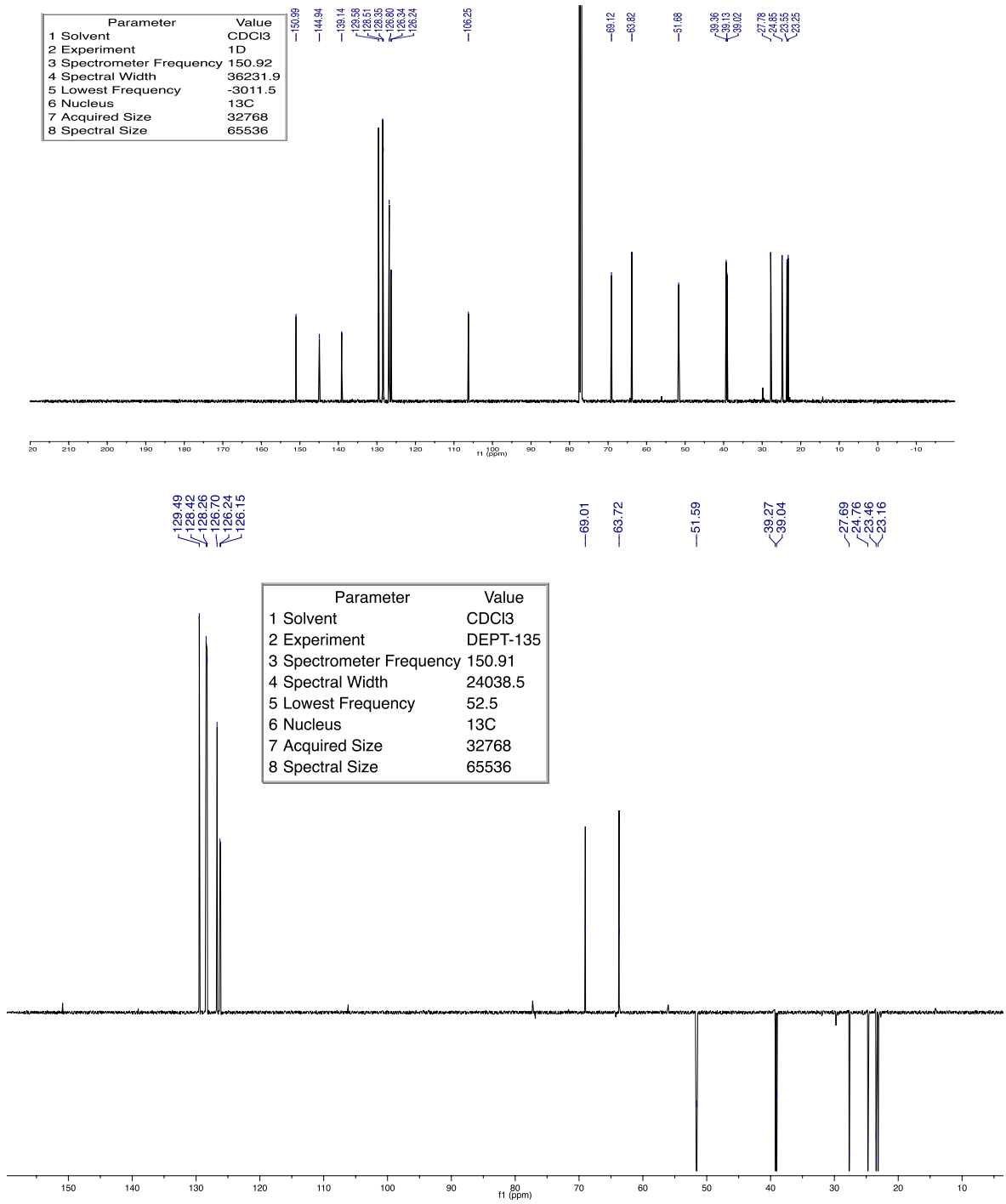
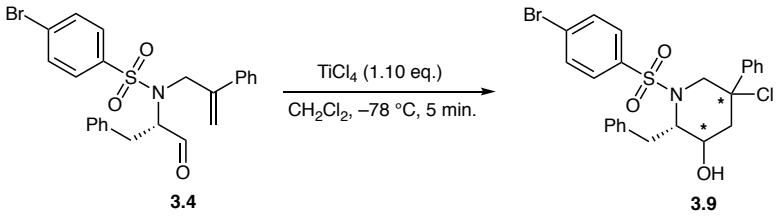


Figure 3.18. ^{1}H, $^{13}C\{^{1}H\}$, and ^{13}C DEPT-135 spectra for free piperidine 3.21.

3.7.5 *Prins* cyclizations in the absence of trapping nucleophiles / cyclizations using other Lewis Acids

3.7.5.1 *Prins* cyclization promoted by $TiCl_4$

Preparation of chloro-piperidine 3.9

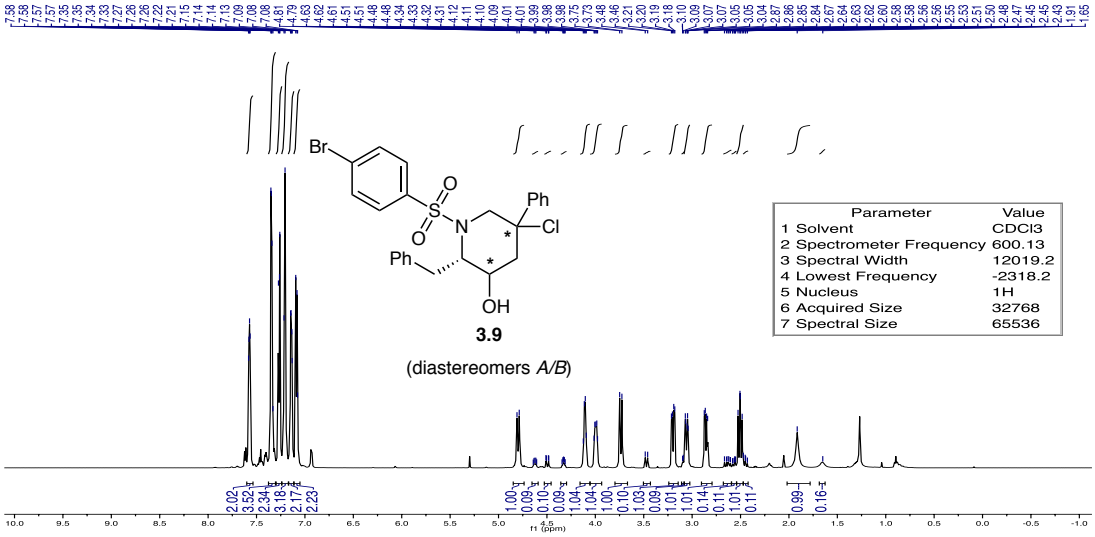


In a dry, N_2-filled glove box, aldehyde **3.4** (0.100 mmol, 48.4 mg) was weighed into a screw cap 1 dram vial equipped with a stir bar. CH_2Cl_2 (1.00 mL, 0.1 M) was added and the vial was sealed with a septum cap. Simultaneously, a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 was prepared in a 1 dram vial and the vial was sealed with a septum cap. Both vials were removed from the glove box. The vial containing the substrate was equipped with a nitrogen line and cooled to –78 °C in an acetone/$CO_{2(s)}$ bath. The 1.0 M $TiCl_4$ solution in CH_2Cl_2 (0.110 mmol, 110 μL) was taken up by syringe and added drop-wise to the rapidly stirring solution of substrate at –78 °C over 30 seconds. The color was observed to change from light yellow to deep reddish-orange. After 5 minutes, the solution was quenched (resulting in rapid loss of color) by drop-wise addition of a CH_2Cl_2 solution (800 μL) containing NEt_3 (80 μL) and MeOH (30 μL). The solution was stirred at –78 °C for 10 minutes, and was then allowed to warm to room temperature over 10 minutes. The reaction was worked up by dilution with CH_2Cl_2, followed by sequential washes with saturated aqueous NH_4Cl, $NaHCO_3$, and NaCl, followed by drying over anhydrous $MgSO_4$ and concentration *in vacuo*. The crude residue was purified by silica gel chromatography (3:1 *n*-pentane:ethyl acetate; R_f = 0.3-0.4) to yield chloro-piperidine **3.9** as a white, crystalline

solid in 99% yield (51.5 mg) and as a mixture of three partially separable diastereomers in 85:9:6 d.r. (see section 3.4 and Table 3.1 therein).

(2*S*)-2-benzyl-1-((4-bromophenyl)sulfonyl)-5-chloro-5-phenylpiperidin-3-ol (3.9). ***Major diastereomer A*** *(co-eluted with minor diastereomer B)**:*** **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 7.59-7.55 (m, 2H), 7.36-7.33 (m, 3H), 7.27 (d, 2H, *J* = 8.4 Hz), 7.24-7.18 (m, 3H), 7.16-7.13 (m, 2H), 7.09 (d, 2H, *J* = 8.2 Hz), 4.80 (d, 1H, *J* = 13.9 Hz), 4.11 (q, 1H, *J* = 6.1 Hz), 3.99 (dt, 1H, *J* = 10.6, 4.6 Hz), 3.74 (d, 1H, *J* = 13.9 Hz), 3.20 (dd, 1H, *J* = 14.3, 6.4 Hz), 3.06 (dt, 1H, *J* = 13.9, 3.1 Hz), 2.86 (dd, 1H, *J* = 14.3, 6.4 Hz), 2.50 (dd, 1H, *J* = 13.8, 11.9 Hz), 1.91 (s, br, 1H); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 139.5, 138.4, 138.4, 132.2, 129.3, 128.8, 128.8, 128.7, 128.5, 127.6, 127.1, 126.6, 66.9, 66.1, 58.9, 50.8, 41.5, 31.0; **^{13}C NMR DEPT-135** ($CDCl_3$, 151 MHz): δ 132.2 (CH), 129.3 (CH), 128.8 (CH), 128.8 (CH), 128.7 (CH), 128.5 (CH), 127.1 (CH), 126.6 (CH), 66.9 (CH), 58.9 (CH), 50.8 (CH_2), 41.5 (CH_2), 31.0 (CH_2); **IR** (ν/cm^{-1}): 3520 (s, br, OH), 3087 (w), 3061 (w), 3028 (w), 2953 (w), 2926 (w), 2853 (w), 1603 (w), 1575 (m), 1496 (m), 1470 (m), 1449 (m), 1389 (m), 1335 (s), 1311 (m), 1277 (m), 1266 (m), 1231 (w), 1159 (s), 1098 (m), 1086 (m), 1069 (s), 1031 (w); **HRMS**-(ESI^+) $[M–Cl^-]^+$ calcd for $C_{24}H_{23}NO_3SBr^+$ 484.0582, found: 484.0588; $[\alpha]_D^{25}$ = –22.2° (c = 2.35, CH_2Cl_2, l = 100 mm). ***Minor diastereomer B*** *(co-eluted with major diastereomer A; aliphatic peaks reported where visible)**:*** **^{1}H NMR** ($CDCl_3$, 600 MHz; aliphatic only): δ 4.62 (dt, 1H, *J* = 10.6, 4.7 Hz), 4.50 (dd, 1H, *J* = 14.9, 2.3 Hz), 4.33 (dt, 1H, *J* = 9.7, 4.9 Hz), 3.47 (d, 1H, *J* = 14.9 Hz), 3.10-3.08 (m, 1H), 2.67-2.60 (m, 1H), 2.57 (dt, 1H, *J* = 13.7, 3.4 Hz), 2.45 (dd, 1H, *J* = 14.0, 11.4 Hz); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz; aliphatic only): δ 70.6, 66.2, 59.3, 51.1, 40.3, 30.0; **^{13}C NMR DEPT-135** ($CDCl_3$, 151 MHz; aliphatic only): δ 66.2 (CH), 59.3 (CH), 51.1 (CH_2), 40.3

(CH_2), 30.0 (CH_2). ***Minor diastereomer C:*** **^{1}H NMR** ($CDCl_3$, 600 MHz): δ ^{1}H NMR 7.81 (d, 2H, *J* = 8.6 Hz), 7.62 (d, 2H, *J* = 8.6 Hz), 7.55 (d, 2H, *J* = 7.8 Hz), 7.45 (t, 2H, *J* = 7.7 Hz), 7.41-7.22 (m, 4H), 7.14 (d, 2H, *J* = 6.9 Hz), 4.56 (dd, 1H, *J* = 15.2, 2.5 Hz), 4.34 (dd, 1H, *J* = 11.0, 4.7 Hz), 3.86 (ddt, 1H, *J* = 11.4, 4.1, 2.0 Hz), 3.67 (d, 1H, *J* = 14.8 Hz), 3.30 (d, 1H, *J* = 11.4 Hz), 2.93 (dd, 1H, *J* = 13.6, 4.6 Hz), 2.74 (dd, 1H, *J* = 13.6, 10.9 Hz), 2.70 (d, 1H, *J* = 14.9 Hz), 2.53 (dd, 1H, *J* = 15.6, 4.0 Hz); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 141.8, 139.5, 136.8, 132.4, 129.2, 129.2, 129.1, 128.8, 128.0, 127.3, 127.2, 125.3, 68.6, 65.5, 61.5, 51.6, 37.6, 36.3; **^{13}C NMR DEPT-135** ($CDCl_3$, 151 MHz): δ 132.4 (CH), 129.2 (CH), 129.2 (CH), 129.1 (CH), 128.8 (CH), 127.3 (CH), 127.2 (CH), 125.3 (CH), 65.5 (CH), 61.5 (CH), 51.6 (CH_2), 37.6 (CH_2), 36.3 (CH_2); **IR** (ν/cm^{-1}): 3566 (m, br, OH), 3086 (w), 3061 (w), 3028 (w), 2921 (s), 2850 (m), 1733 (w), 1716 (w), 1698 (w), 1684 (w), 1647 (w), 1636 (w), 1601 (w), 1575 (m), 1558 (w), 1541 (w), 1521 (w), 1507 (w), 1496 (m), 1472 (w), 1456 (m), 1448 (w), 1419 (w), 1389 (m), 1340 (s), 1266 (m), 1214 (w), 1163 (s), 1090 (m), 1068 (m), 1030 (m), 1010 (m); **HRMS**-(ESI$^+$) $[M–Cl^-]^+$ calcd for $C_{24}H_{23}NO_3SBr^+$ 484.0582, found: 484.0589.



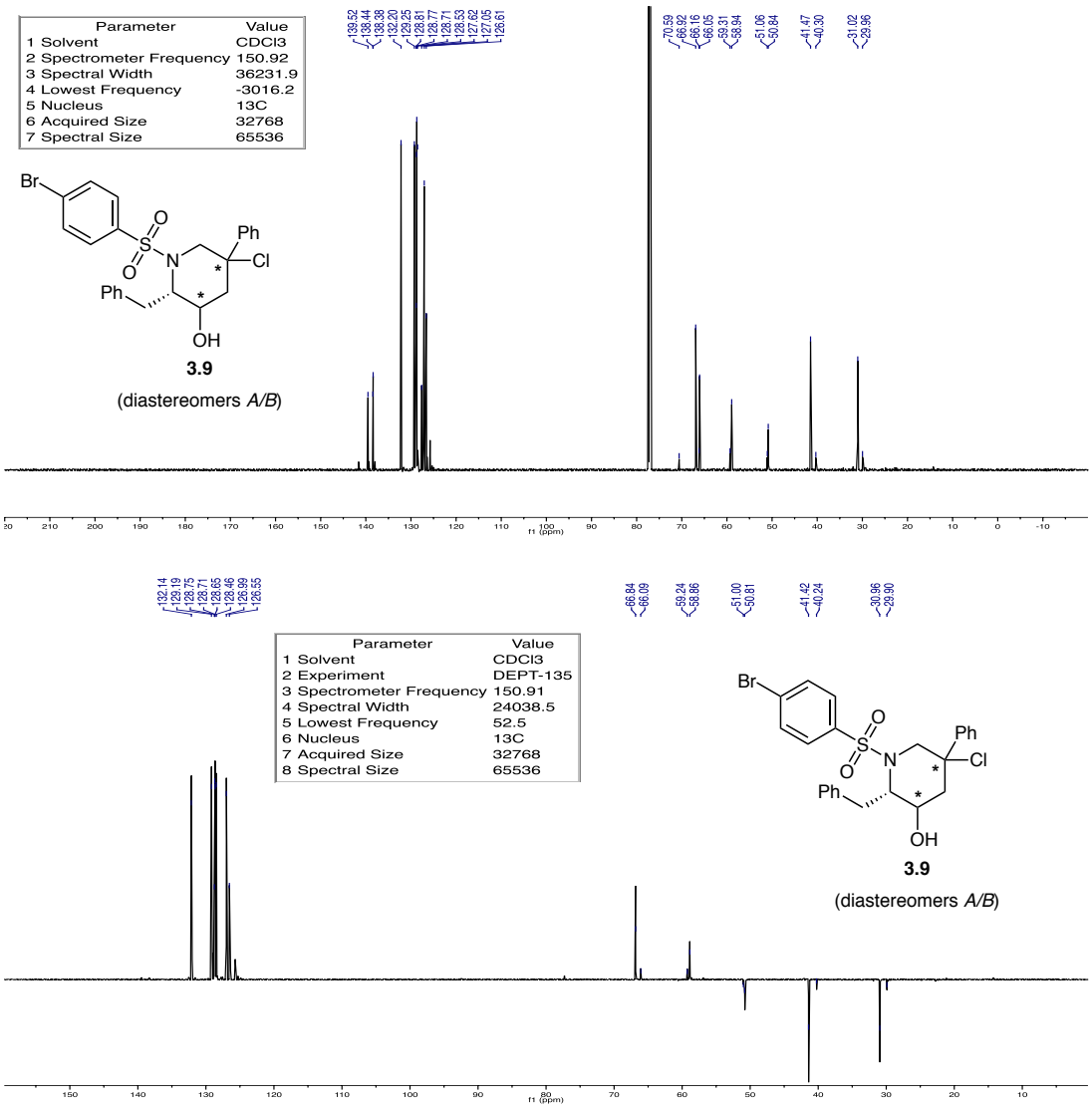
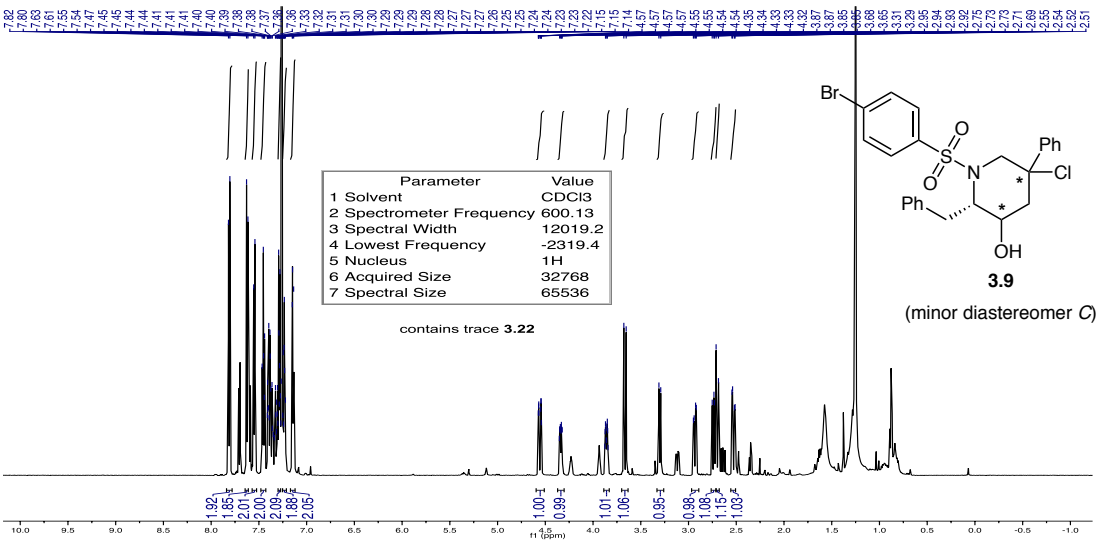


Figure 3.19. ^{1}H, ^{13}C{^{1}H}, and ^{13}C DEPT-135 NMR spectra of chloro-piperidine 3.9 (diastereomers A/B).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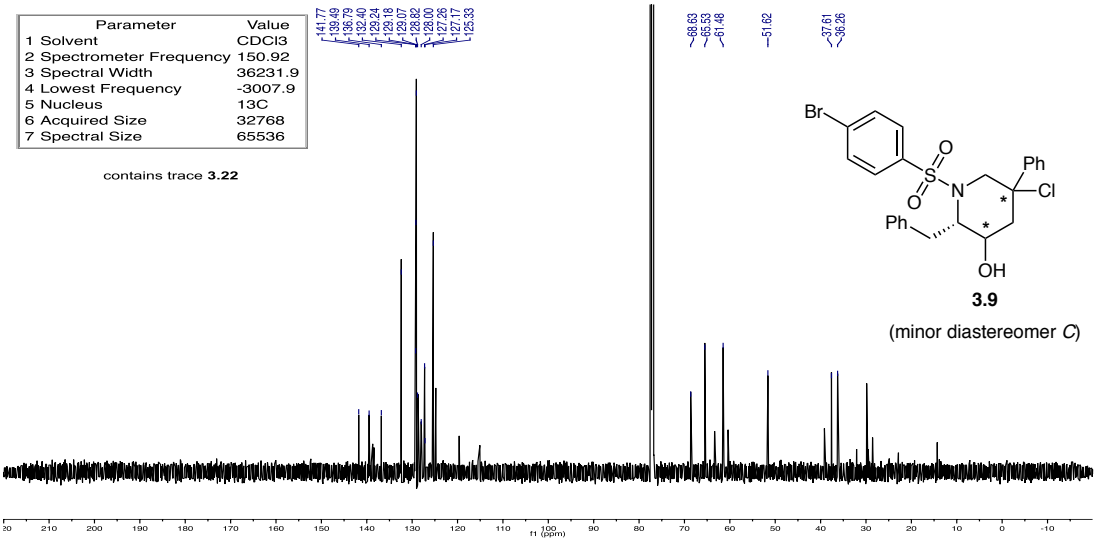
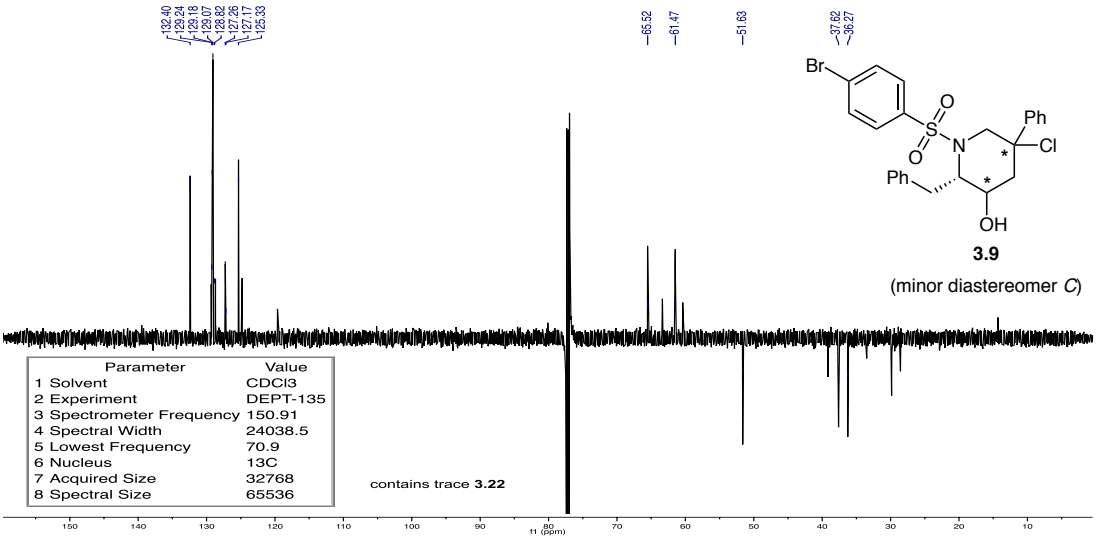
2 Spectrometer Frequency 600.13
3 Spectral Width 12019.2
4 Lowest Frequency -2319.4
5 Nucleus 1H
6 Acquired Size 32768
7 Spectral Size 65536
contains trace 3.22
Br
Ph
Cl
Ph
OH
3.9
(minor diastereomer C)


Parameter Value
1 Solvent CDCl3
2 Spectrometer Frequency 150.92
3 Spectral Width 36231.9
4 Lowest Frequency -3007.9
5 Nucleus 13C
6 Acquired Size 32768
7 Spectral Size 65536
contains trace 3.22
Br
Ph
Cl
Ph
OH
3.9
(minor diastereomer C)


Parameter Value
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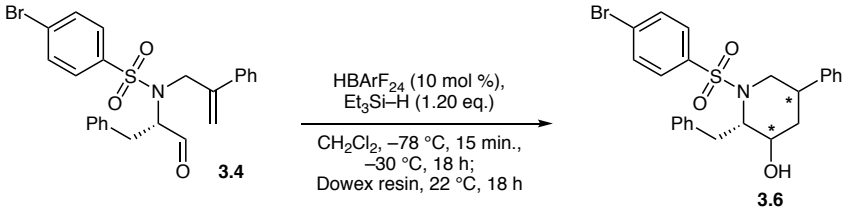
2 Experiment DEPT-135
3 Spectrometer Frequency 150.91
4 Spectral Width 24038.5
5 Lowest Frequency 70.9
6 Nucleus 13C
7 Acquired Size 32768
8 Spectral Size 65536
contains trace 3.22
Br
Ph
Cl
Ph
OH
3.9
(minor diastereomer C)

Figure 3.20. ^{1}H, $^{13}C\{^{1}H\}$, and ^{13}C DEPT-135 NMR spectra of chloro-piperidine 3.9 (minor diastereomer C).

3.7.5.2 *Prins* cyclization catalyzed by $HBArF_{24}$ (Brookhart's acid)

Alternate preparation of piperidine 3.6

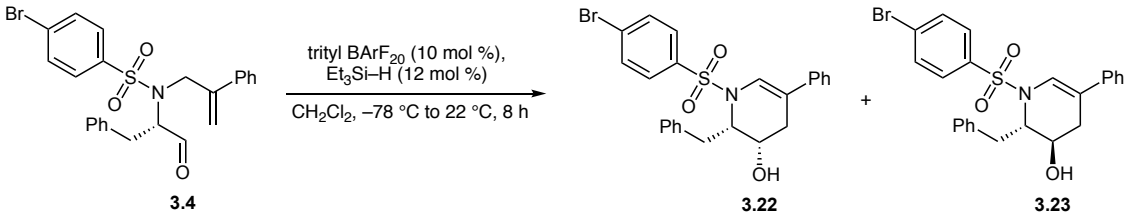


In a dry, N_2-filled glove box, aldehyde **3.4** (0.0500 mmol, 24.2 mg, 1.00 eq.) and $[H(OEt_2)_2][B(C_6H_3(CF_3)_2)_4]$ ($HBArF_{24}$ (Brookhart's acid), 0.0050 mmol, 5.1 mg, 0.10 eq.) were weighed into a screw cap 1 dram vial equipped with a stir bar and sealed with a septum cap. In a separate screw cap 1 dram vial, Et_3SiH (0.0600 mmol, 9.6 μL, 1.20 eq.) was dissolved in 1.00 mL of CH_2Cl_2 and the vial sealed with a septum cap. Both vials were removed from the glove box and placed under a positive N_2 atmosphere *via* piercing of the septa with N_2 needles, and the vial containing the aldehyde and $HBArF_{24}$ was cooled to –78 °C in an acetone/$CO_{2(s)}$ bath. The room temperature solution in CH_2Cl_2 was syringed drop-wise and slowly down the side of the vial into the vigorously stirring solution over approximately 5 minutes. The solution was stirred for an additional 15 minutes at –78 °C, after which time the reaction was transferred to a –30 °C cryobath and stirred overnight for 18 h. The reaction was then quenched at the cryogenic temperature with 50 μL Et_3N and warmed to room temperature. The residue was repeatedly washed with CH_2Cl_2 and concentrated *in vacuo* (x3), and was then placed under high vacuum for ≥1 h to remove excess Et_3N. The resulting residue was taken up in 2 mL of 1:1 CH_2Cl_2/MeOH,

approximately 10-20 beads of Dowex resin (50W-X8) were added, and the mixture was stirred at 22 °C for 18 h. The mixture was then filtered by gravity through a plug of sand and cotton, rinsed with 2x1mL CH_2Cl_2, and concentrated *in vacuo*. Dimethylformamide (0.050 mmol, 3.9 μL) was added as an internal standard and the residue taken up in $CDCl_3$ for ^1H and ^{13}C NMR analyses to determine crude NMR yield and diastereomeric ratios (d.r.); the desired piperidine **3.6** was produced in 47% yield and in 45:36:19 d.r. favoring the same diastereomers as those resulting from the putative silylium ion catalysis (see section 3.4 and Table 3.1 therein).

3.7.5.3 Silylium-ion catalyzed *Prins* cyclization in the absence of trapping nucleophiles

Preparation of tetrahydropyridines 3.22 and 3.23

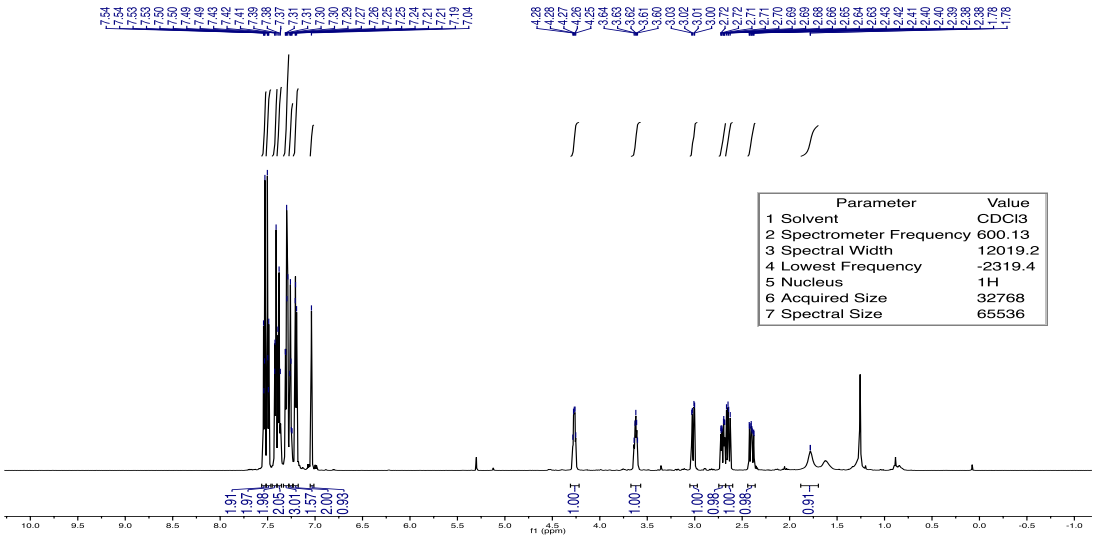


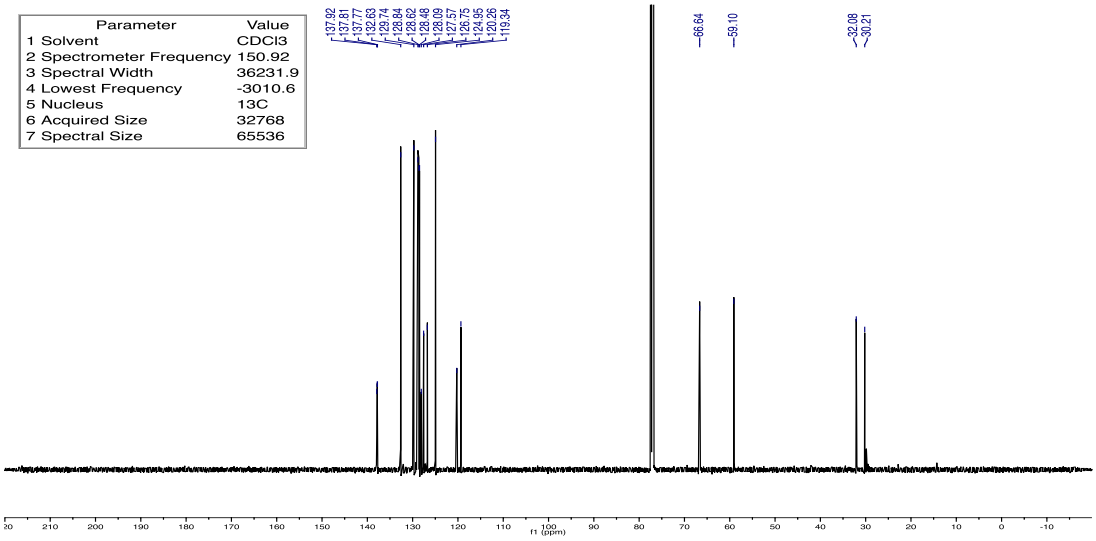
In a dry, N_2-filled glove box, aldehyde **3.4** (0.100 mmol, 48.4 mg) and $[Ph_3C][B(C_6F_5)_4]$ (trityl $BArF_{20}$, 0.0100 mmol, 9.2 mg) were weighed into a screw cap 1 dram vial equipped with a magnetic stir bar and sealed with a septum cap. In a separate screw cap 1 dram vial, Et_3SiH (0.0120 mmol, 1.9 μL) was dissolved in 2.00 mL of CH_2Cl_2 and the vial sealed with a septum cap. Both vials were removed from the glove box and placed under a positive N_2 atmosphere *via* piercing of the septa with N_2 needles, and the vial containing the aldehyde and trityl $BArF_{20}$ was cooled to –78 °C in an acetone/$CO_{2(s)}$ bath. The room temperature solution in CH_2Cl_2 was syringed drop-wise and slowly down

the side of the vial over 5 minutes with magnetic stirring. During addition, the reaction turned clear bright yellow in color, which persisted throughout the course of the reaction. The reaction was allowed to freely and *slowly* (in the dewar) warm to 22 °C with stirring over the course of 8 hours, after which time the reaction was quenched with 100 μL of *i*-$PrNH_2$ and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (gradient of 5:1 to 3:1 *n*-pentane:ethyl acetate; R_f = 0.2-0.3) to yield *cis*-tetrahydropyridine **3.22** and *trans*-tetrahydropyridine **3.23** as clear, colorless oils in 58% yield (28.0 mg on a 0.1 mmol scale) and as a mixture of two chromatographically separable diastereomers in 83:17 *cis:trans* diastereomeric ratio (see section 3.6 and Scheme 3.7 therein).

(2*S*,3*S*)-2-benzyl-1-((4-bromophenyl)sulfonyl)-5-phenyl-1,2,3,4-tetrahydropyridin-3-ol (3.22). ***Cis-diastereomer:*** **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 7.54 (d, 2H, *J* = 8.6 Hz), 7.50 (d, 2H, *J* = 8.6 Hz), 7.42 (d, 2H, *J* = 7.3 Hz), 7.38 (t, 2H, *J* = 7.6 Hz), 7.30 (t, 3H, *J* = 7.1 Hz), 7.26 (t, 1H, *J* = 3.6 Hz), 7.20 (d, 2H, *J* = 6.7 Hz), 7.04 (s, 1H), 4.27 (dt, 1H, *J* = 9.2, 4.3 Hz), 3.62 (dt, 1H, *J* = 10.5, 5.4 Hz), 3.02 (dd, 1H, *J* = 13.9, 4.2 Hz), 2.70 (ddd, 1H, *J* = 17.1, 6.0, 1.6 Hz), 2.65 (dd, 1H, *J* = 13.9, 9.5 Hz), 2.40 (ddd, 1H, *J* = 17.2, 10.4, 1.9 Hz), 1.78 (s, br, 1H); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 137.9, 137.8, 137.8, 132.6, 129.7, 128.8, 128.6, 128.5, 128.1, 127.6, 126.8, 125.0, 120.3, 119.3, 66.6, 59.1, 32.1, 30.2; **^{13}C NMR DEPT-135** ($CDCl_3$, 151 MHz): δ 132.6 (CH), 129.7 (CH), 128.8 (CH), 128.6 (CH), 128.5 (CH), 127.6 (CH), 126.8 (CH), 125.0 (CH), 119.3 (CH), 66.6 (CH), 59.1 (CH), 32.1 (CH_2), 30.2 (CH_2); **IR** (ν/cm^{-1}): 3532 (s, br, OH), 3086 (w), 3061 (w), 3028 (w), 2925 (m), 2849 (w), 1632 (m), 1601 (w), 1574 (m), 1496 (m), 1471 (w), 1455 (w), 1445 (w), 1389 (w), 1349 (s), 1265 (w), 1220 (w), 1166 (s), 1093 (m), 1070 (m), 1053 (w), 1018 (w), 1006

(m); **HRMS**-(ESI$^+$) $[M+H]^+$ calcd for $C_{24}H_{23}NO_3SBr^+$ 484.0582, found: 484.0590; $[\alpha]_D^{25}$ = –41.4° (c = 1.150, CH_2Cl_2, l = 100 mm).





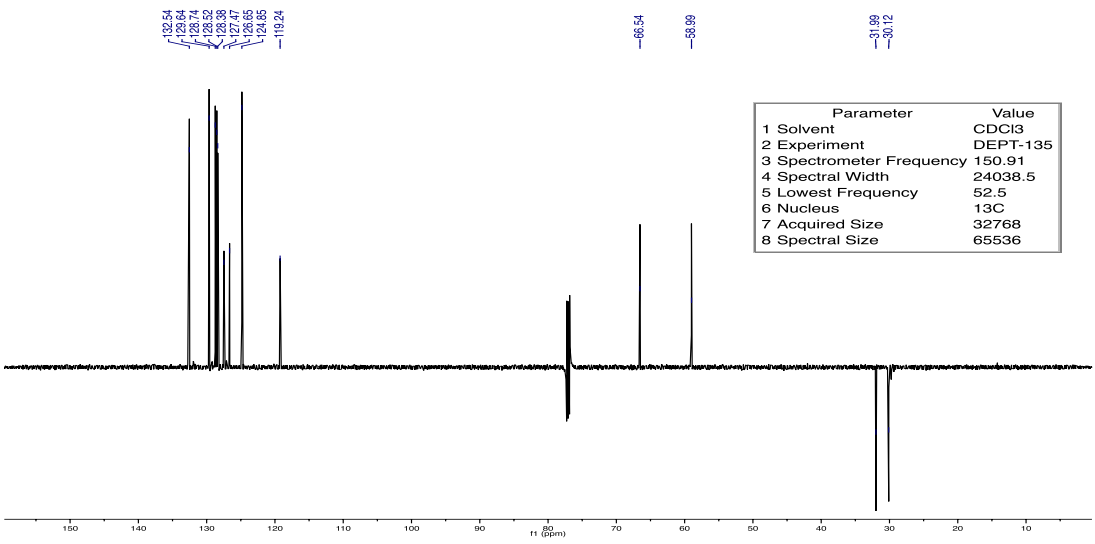
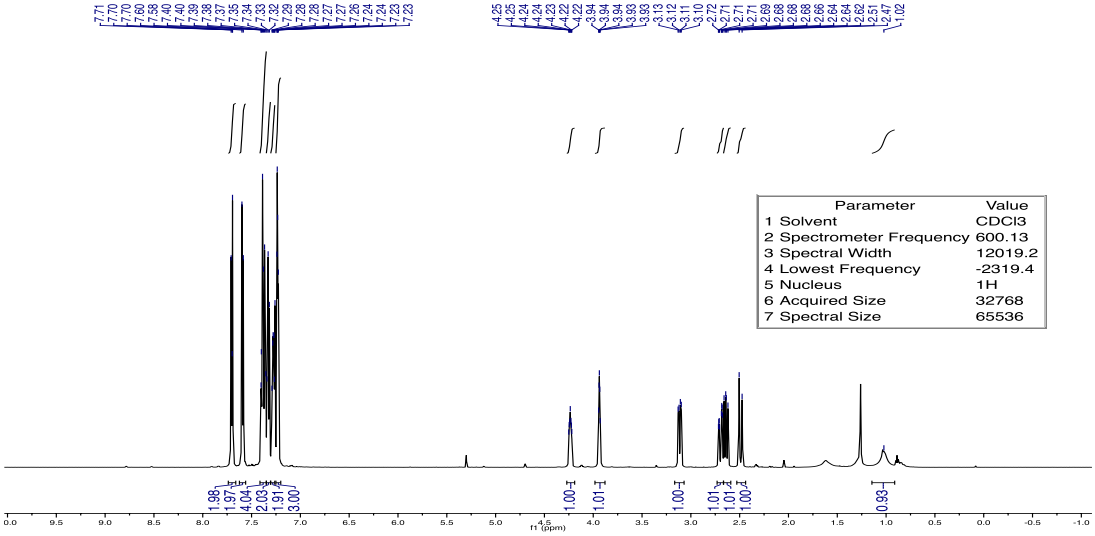
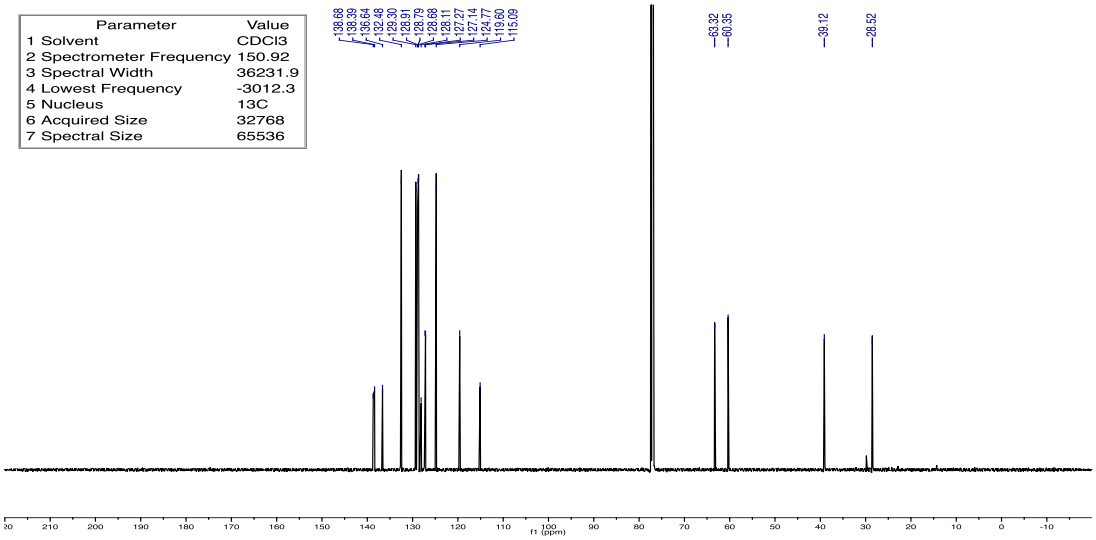


Figure 3.21. ^{1}H, ^{13}C{^{1}H}, and ^{13}C DEPT-135 NMR spectra for *cis*-tetrahydropyridine 3.22.

(2*S*,3*R*)-2-benzyl-1-((4-bromophenyl)sulfonyl)-5-phenyl-1,2,3,4-tetrahydropyridin-3-ol (3.23). ***Trans-diastereomer:*** **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 7.70 (d, 2H, *J* = 8.4 Hz), 7.59 (d, 2H, *J* = 8.3 Hz), 7.41-7.35 (m, 4H), 7.33 (t, 2H, *J* = 7.4 Hz), 7.30-7.26 (m, 2H), 7.25-7.22 (m, 3H), 4.23 (ddd, 1H, *J* = 9.5, 5.7, 2.6 Hz), 3.94 (dd, 1H, *J* = 4.3, 2.3 Hz), 3.11 (dd, 1H, *J* = 13.8, 5.6 Hz), 2.70 (ddd, 1H, *J* = 18.0, 4.4, 2.0 Hz), 2.64 (dd, 1H, *J* = 13.8, 10.1 Hz), 2.49 (d, 1H, *J* = 18.1 Hz), 1.03 (s, br, 1H); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 138.7, 138.4, 136.6, 132.5, 129.3, 128.9, 128.8, 128.7, 127.3, 127.1, 124.8, 119.6, 115.1, 63.3, 60.4, 39.1, 28.5; **^{13}C NMR DEPT-135** ($CDCl_3$, 151 MHz): δ 132.5, 129.3, 128.9, 128.8, 128.7, 128.1, 127.3, 127.1, 124.8, 119.6, 63.3 (CH), 60.4 (CH), 39.1 (CH_2), 28.5 (CH_2); **IR** (ν/cm^{-1}): 3542 (s, br, OH), 3085 (w), 3060 (w), 3028 (w), 2923 (m), 2850 (w), 1639 (m), 1599 (w), 1574 (m), 1495 (m), 1471 (w), 1454 (w), 1446 (w), 1389 (m), 1352 (s), 1266 (w), 1215 (w), 1198 (w), 1164 (s), 1092 (s), 1067 (m), 1058 (m), 1032 (w), 1009

(w); **HRMS**-(ESI$^+$) $[M+H]^+$ calcd for $C_{24}H_{23}NO_3SBr^+$ 484.0582, found: 484.0591; $[\alpha]_D^{25}$ = –21.4° (c = 1.20, CH_2Cl_2, l = 100 mm).





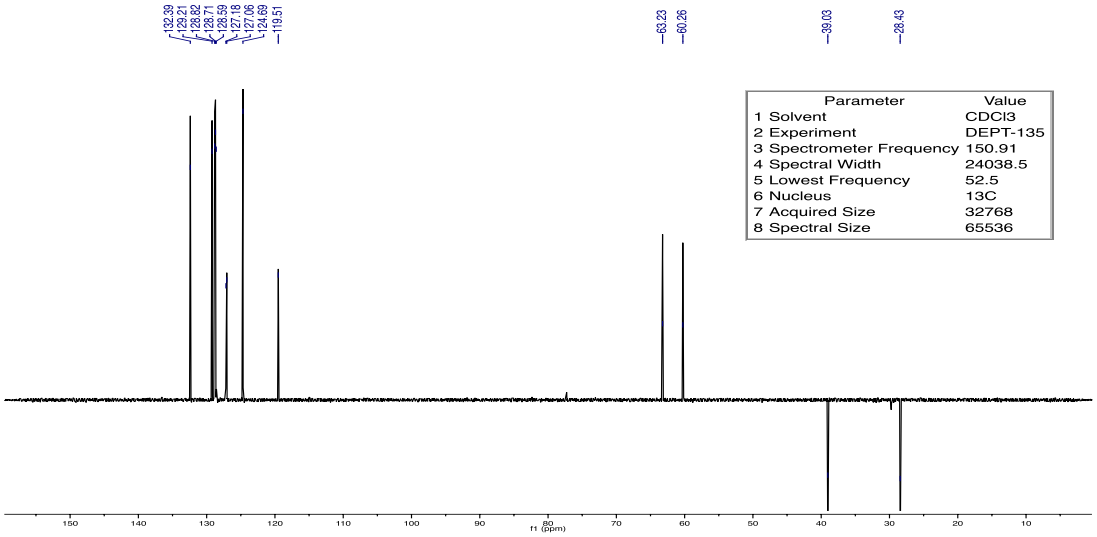
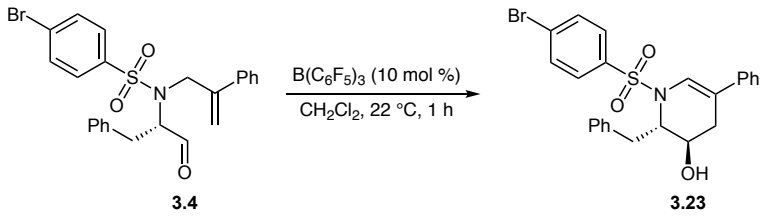


Figure 3.22. ^{1}H, ^{13}C{^{1}H}, and ^{13}C DEPT-135 NMR spectra for *trans*-tetrahydropyridine 3.23.

3.7.5.4 *Prins* cyclization catalyzed by $B(C_6F_5)_3$

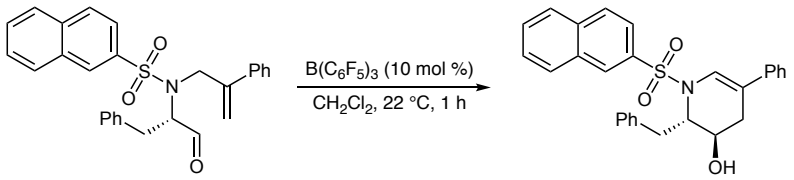
Independent preparation of *trans*-tetrahydropyridine 3.23



In a dry, N_2-filled glove box, aldehyde **3.4** (0.0500 mmol, 24.2 mg) and $B(C_6F_5)_3$ (BCF, 0.0050 mmol, 2.6 mg) were weighed into a screw cap 1 dram vial equipped with a magnetic stir bar. CH_2Cl_2 (1.00 mL, 0.05 M) was added and the vial was sealed with a septum cap and removed from the glove box. The solution was stirred at 22 °C for 1 h, after which time the catalyst was quenched with 50 μL of Et_3N and the solvent was removed *in vacuo*. The crude residue was purified by silica gel chromatography (5:1 *n*-pentane:ethyl acetate; $R_f = 0.3$) to yield the tetrahydropyridine product **3.23** as a clear, colorless oil in 99% yield (24.0 mg on a 0.05 mmol scale) and as a single diastereomer

(>98:2). Analytical data match that of *trans*-tetrahydropyridine **3.23** (*vide supra*) obtained as the minor product of silylium-catalyzed *Prins*-cyclization in the absence of trapping nucleophiles (see section 3.6 and Scheme 3.7 therein). Absolute configuration was assigned by analogy between the ^{1}H NMR spectra of *trans*-tetrahydropyridine products **3.23** and **3.42** (*vide infra*).

Preparation of *trans*-tetrahydropyridine 3.42 via $B(C_6F_5)_3$-catalyzed *Prins* cyclization:

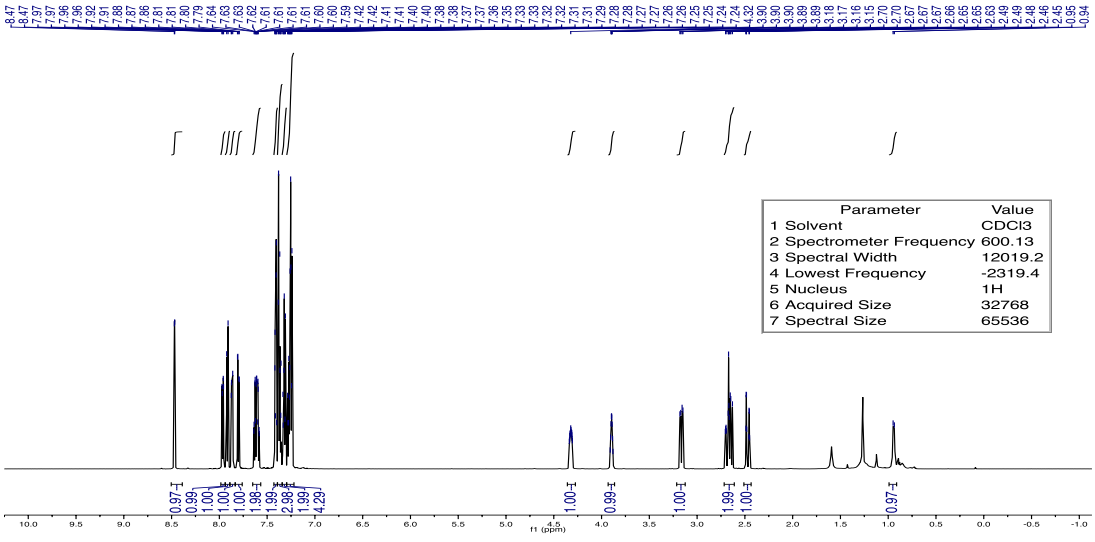


3.39 **3.42**

In a dry, N_2-filled glove box, aldehyde **3.39** (0.0500 mmol, 22.8 mg) and $B(C_6F_5)_3$ (BCF, 0.0050 mmol, 2.6 mg) were weighed into a screw cap 1 dram vial equipped with a stir bar. CH_2Cl_2 (1.00 mL, 0.05 M) was added and the vial was sealed with a septum cap and removed from the glove box. The solution was stirred at 22 °C for 1 h, after which time the catalyst was quenched with 50 μL of Et_3N and the solvent was removed *in vacuo*. The crude residue was purified by silica gel chromatography (5:1 *n*-pentane:ethyl acetate; $R_f = 0.3$) to yield the tetrahydropyridine product **3.42** as a white, crystalline solid in 99% yield (22.6 mg on a 0.05 mmol scale) and as a single diastereomer (≥98:2).

(2*S*,3*R*)-2-benzyl-1-(naphthalen-2-ylsulfonyl)-5-phenyl-1,2,3,4-tetrahydropyridin-3-ol (3.42). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.47 (d, 1H, *J* = 2.0 Hz), 7.96 (dd, 1H, *J* = 8.0, 1.5 Hz), 7.92 (d, 1H, *J* = 8.7 Hz), 7.87 (d, 1H, *J* = 7.3 Hz), 7.80 (dd, 1H, *J* = 8.7, 1.9 Hz), 7.64-7.57 (m, 2H), 7.41 (dd, 2H, *J* = 8.2, 1.4 Hz), 7.39-7.35 (m, 3H), 7.34-7.30 (m, 2H), 7.29-7.23 (m, 4H), 4.35-4.29 (m, 1H), 3.92-3.87 (m, 1H), 3.16 (dd, 1H, *J* = 13.7, 5.4 Hz), 2.72-

2.62 (m, 2H), 2.47 (dd, 1H, J = 18.1, 1.6 Hz), 0.94 (d, 1H, J = 7.8 Hz); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 138.9, 136.7, 136.2, 135.0, 132.2, 129.7, 129.5, 129.3, 129.1, 128.9, 128.8, 128.5, 128.1, 127.8, 127.1, 127.1, 124.8, 122.2, 120.0, 114.4, 63.3, 60.3, 39.2, 28.4; **^{13}C NMR DEPT-135** ($CDCl_3$, 151 MHz): δ 129.7 (CH), 129.5 (CH), 129.3 (CH), 129.1 (CH), 128.9 (CH), 128.8 (CH), 128.5 (CH), 128.1 (CH), 127.8 (CH), 127.1 (CH), 127.1 (CH), 124.8 (CH), 122.2 (CH), 120.0 (CH), 63.3 (CH), 60.3 (CH), 39.2 (CH_2), 28.4 (CH_2); **IR** (ν/cm^{-1}): 3540 (m, br, OH), 3058 (w), 3028 (w), 2925 (m), 2853 (w), 1639 (m), 1596 (w), 1496 (w), 1454 (w), 1447 (w), 1348 (s), 1267 (w), 1216 (w), 1198 (w), 1161 (s), 1132 (m), 1076 (m), 1056 (m), 1032 (w); **HRMS**-(ESI$^+$) $[M+H]^+$ calcd for $C_{28}H_{26}NO_3S^+$ 456.1634, found: 456.1644; **$[\alpha]_D^{25}$** = –74.1° (c = 1.06, CH_2Cl_2, l = 100 mm). A single crystal X-ray structure was obtained from this compound *via* recrystallization (solvent vapor) from a mixture of $CDCl_3$/*n*-pentane. The data indicate a *trans*-di-pseudoequatorial configuration between the amino alcohol R-group and the hydroxyl group.



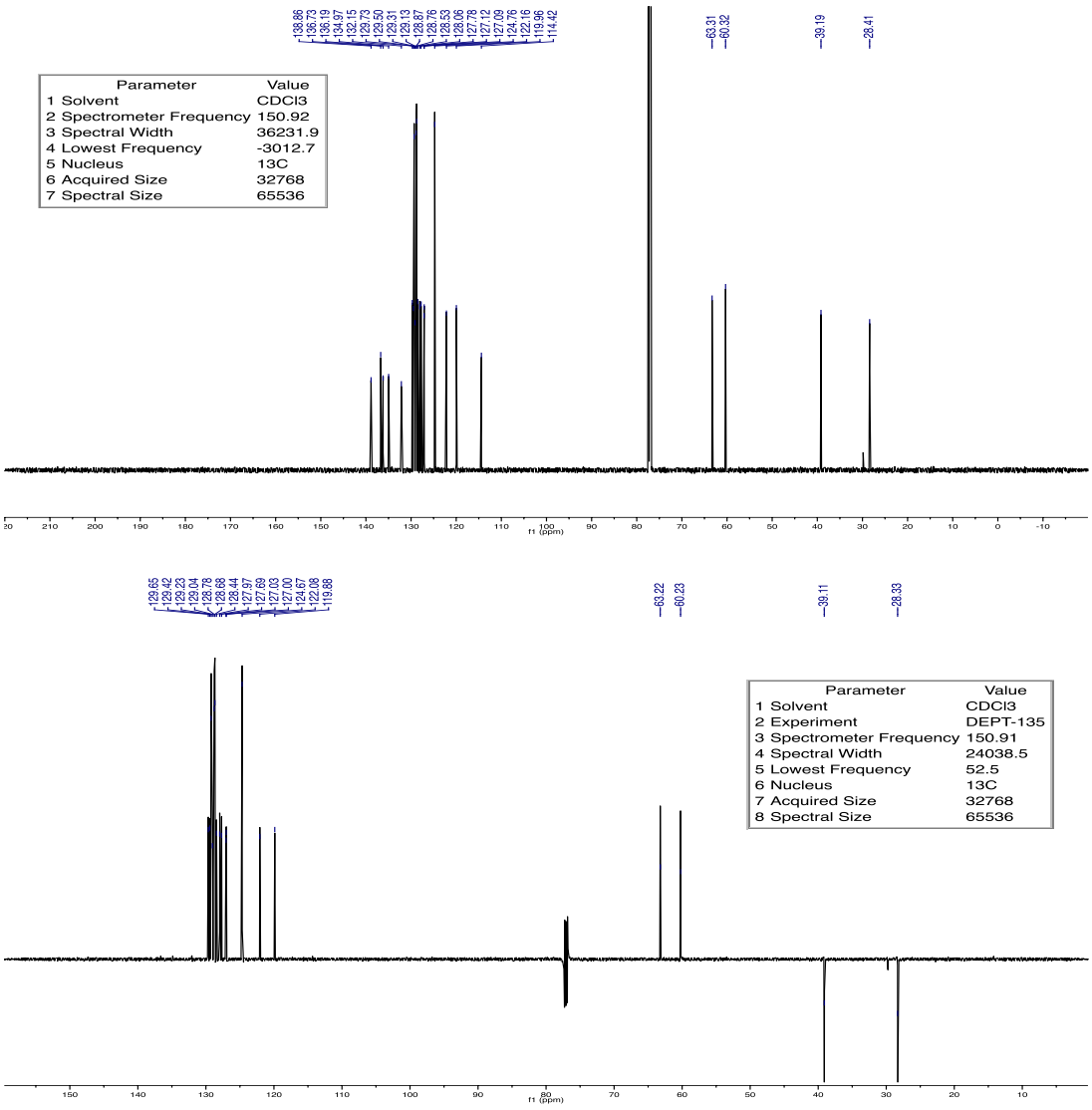


Figure 3.23. ^{1}H, $^{13}C\{^{1}H\}$, and ^{13}C DEPT-135 NMR spectra for *trans*-tetrahydropyridine 3.42.

3.7.5.5 X-ray crystallographic data and structure for **3.42**

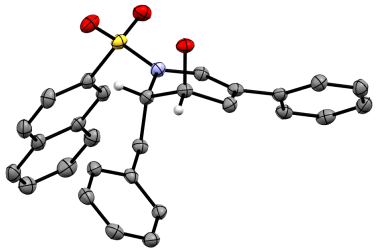


Figure 3.24. ORTEP representation of solid state molecular structure of 3.42.

The ORTEP representation of the solid state molecular structure of **3.42** (CSD-1548661) is shown in Figure 3.24; ellipsoids drawn at 50% probability, the majority of hydrogen atoms are omitted for clarity.[60] The X-ray crystallographic data are shown in Table 3.4.

Table 3.4. Solid state molecular structure data for 3.42.

Empirical formula	$C_{28}H_{25}NO_3S$	D_{calcd} (Mg m^{-3})	1.361
F_w	455.57	Radiation	Cu $K\alpha$, λ = 1.54178 Å
Colour, habit	Colourless, block	Absorption coeff. (μ) (mm^{-1})	1.55
Crystal dimensions (mm)	0.31 x 0.09 x 0.07	Absorption correction	Numerical
Crystal system	Orthorhombic	$F(000)$	960
Space group	$P2_12_12_1$	θ_{min} *to* θ_{max} (°)	2.5 to 68.1
Z	4	Measured reflections	35988
a (Å)	5.6499(1)	Independent reflections	4067 (R_{int}=0.049)
b (Å)	11.1424(2)	Data/restraints/parameters	4067/0/302
c (Å)	35.3036(7)	Maximum shift/error	<0.001
α (°)	90.00	Goodness-of-fit on F^2	1.06
β (°)	90.00	Final R indices ($I > 2\sigma(I)$)	R_1 = 0.030 wR_2 = 0.073
γ (°)	90.00	R indices (all data)	R_1 = 0.032 wR_2 = 0.074
Collection ranges	h = –6→6 k = –13→13 l = –42→42	absolute structure parameter	0.038(7)
Temperature (K)	100	Extinction coefficient	N/A
Volume ($Å^3$)	2222.48(7)	Largest diff. peak and hole (e $Å^{-3}$)	0.23 and –0.29

APPENDIX A: APPLYING $B(C_6F_5)_3$ TO *N*-HETEROCYCLE SYNTHESIS

The results and data contained within Appendix A are unpublished and represent further investigations with respect to substrate scope of the published discovery in section 3.6 above that $B(C_6F_5)_3$ catalyzes a stereospecific *Prins* cyclization followed by an elimination (formally a carbonyl-ene reaction) to form *trans*-tetrahydropyridine products in exceptionally high yield and diastereoselectivity. Background, breadth of amino alcohol-derived substrate scope, and reactivity of various fluoroaryl borane catalysts are discussed.

A.1 Introduction

Tris(pentafluorophenyl)borane (BCF) has proven itself to be a robust, selective, and versatile catalyst, improving the efficiency of many catalytic processes and opening the door to multiple potential reactivity pathways. To that extent, BCF is best known for its frustrated Lewis pair (FLP) reactivity and its peculiar affinity for silane activation ($R_3Si–H$; η^1-binding) in hydrosilylation methodology.[51a] However, BCF can serve many roles, including as a traditional oxophilic Lewis acid catalyst towards a variety of Lewis basic functional groups such as carbonyls and C–C π-bonds.[52d,61] It is in this latter capacity that we decided to apply BCF as a neutral, less reactive, and potentially more selective alternative to the silylium ion ($[R_3Si]^+$) protocol discussed in Chapter 3.

A.2 Substrate scope

The serendipitous discovery (section 3.6, Scheme 3.7) that neutral perfluoroaryl borane Lewis acids (*e.g.* BCF) could catalyze a stereospecific *Prins* cyclization to the complementary *trans*-diastereomer[xxviii], followed by elimination (overall carbonyl-ene

[xxviii] The relative configuration of the tetrahydropyridine products was assigned in analogy to the X-ray crystal structure of **3.42** (see section 3.7.5.4; for X-ray data, see section 3.7.5.5).

reaction) to produce *trans*-tetrahydropyridine scaffolds in exceptionally high yield and diastereoselectivity and under very mild conditions (*e.g.* room temperature) led us to further investigate the potential substrate scope of this *N*-heterocycle-forming transformation.[xxix] The amino aldehyde substrates for this expanded scope were obtained analogously to the syntheses described in Scheme 3.4; for experimental details and complete analytical data, see section A.5.1-3.

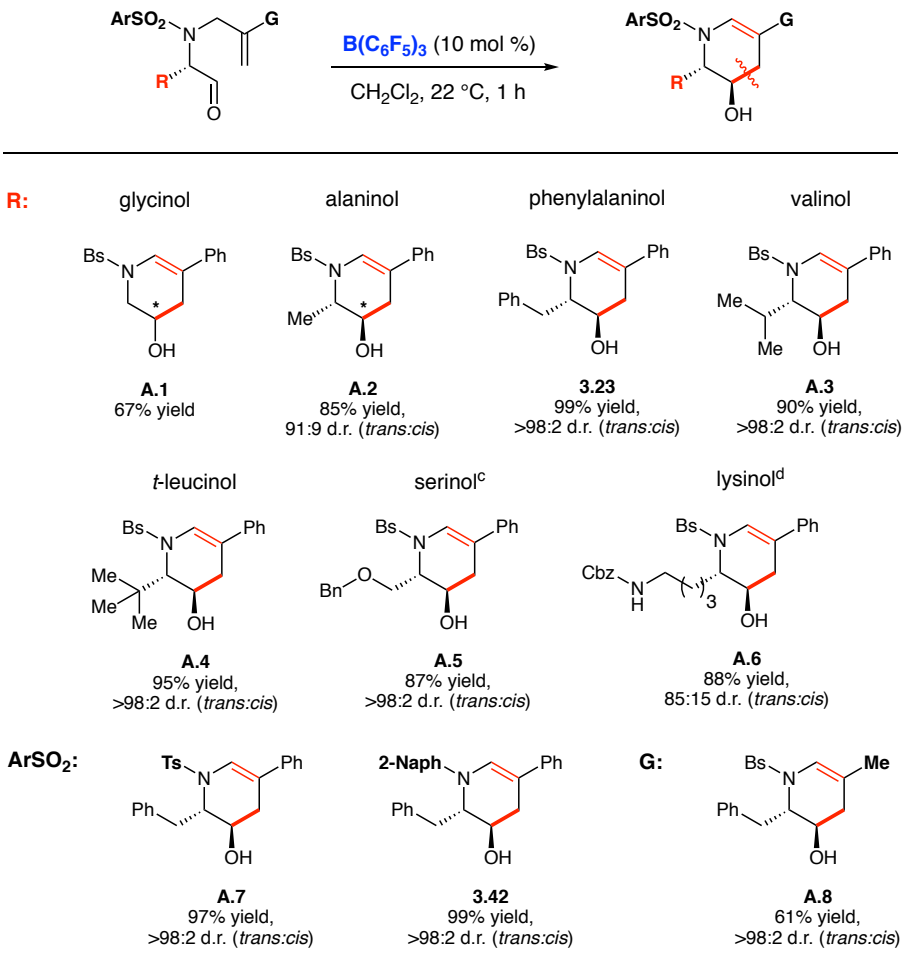
Representative, unoptimized conditions for the BCF-catalyzed *Prins* cyclization/elimination are given below in Table A.1. 10 mol % of BCF in CH_2Cl_2 at 22 °C is sufficient to induce rapid cyclization and elimination to yield free tetrahydropyridine products from a variety of substituted aldehydes (see section A.5.4 for experimental details and analytical data). Products **3.23** and **A.1-A.6** showcase steric and functional group variation in the amino alcohol-derived sidechain (**R**). "Glycinol"-derived **A.1**, which lacks an R-group, was obtained in 67% yield (the lower yield is most likely due to enolization and subsequent decomposition of the substrate) and as a racemate; this reaction could potentially be an interesting model with which to screen chiral perfluoroaryl borane derivatives.[62] Alaninol-derivative **A.2** was obtained in 85% yield and 91:9 d.r. (*trans:cis*); comparison of this result to the previously reported phenylalaninol-derivative **3.23** (99% yield and >98:2 d.r.) illuminates the minimum steric demand necessary to achieve high

[xxix] a) Attempts to intercept the carbocation with $R_3Si–Nu$ in the presence of BCF have been unsuccessful; $Et_3Si–H$ hydrosilylates the aldehyde in 32% NMR yield (see section A.5.4.1 for details), along with producing 44% of *trans*-tetrahydropyridine **3.23** and 7% and 12%, respectively, of minor diastereomers *B* and *C* of piperidine **3.6**. Unfortunately, variation of addition order and temperature did not allow for the clean, high-yielding production of any single product, especially piperidine **3.6**. b) Aldehyde hydrosilylation has been well documented; see Ref. 51.

diastereoselectivity.[xxx] Conforming to this apparent trend in sterics, valinol- and *tert*-leucinol-derivatives **A.3** and **A.4** were obtained in 90% and 95% yields, respectively, and in >98:2 d.r. Serinol-derivative **A.5** and lysinol-derivative **A.6** both illustrate the functional group/heteroatom tolerance of BCF and the potential for an expanded number of subsequent synthetic manipulations on the products. Serinol-derivative **A.5** was produced in 94% NMR yield and 94:6 d.r. (*trans:cis)* and was able to be isolated in 87% as a single diastereomer (>98:2 d.r.). Lysinol-derivative **A.6** was produced and isolated in 88% yield and 85:15 d.r. (*trans:cis*).

[xxx]In agreement with our observations in section 3.6, 10 mol % $HBArF_{24}$ ($[H(OEt_2)_2][B(C_6H_3(CF_3)_2)_4]$, Brookhart's acid) as catalyst provided the corresponding alaninol-derived *cis*-tetrahydropyridine (**A.2'**) in 81% yield and 72:28 d.r. (*cis:trans*); see A.5.4.2 for experimental details and analytical data.

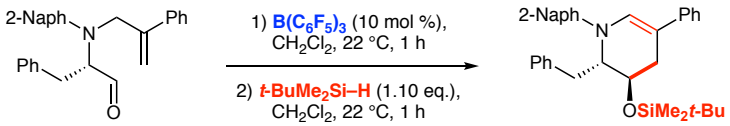
Table A.1. *Trans*-tetrahydropyridine substrate scope.



[a]Reactions were run on a 0.05 mmol scale. [b]Bs = 4-bromobenzenesulfonyl; Ts = *p*-toluenesulfonyl; 2-Naph = 2-naphthalenesulfonyl; [c]94% NMR yield in 94:6 d.r. (*trans:cis*) before purification; DMF as internal standard. [d]3 h reaction time necessary for completion.

Table A.1 also discloses a preliminary screen of *N*-protecting groups (**ArSO$_2$)** and allyl group substitution (**G**). Tosyl(Ts)- and 2-naphthalenesulfonyl(2-Naph)-protected products **A.7** and **3.42**, respectively, were obtained in 97% and 99% yields and both in >98:2 d.r., indicating that slightly less electron-withdrawing aryl sulfonamide groups do not impede the reaction or harm diastereoselectivity. Methyl-substituted **A.8**, derived from the corresponding 2-methylpropenyl-substituted starting material **3.12**, was obtained in 61% yield.

With respect to functionalization, Scheme A.1 demonstrates the ease with which these free tetrahydropyridine products can be protected preceding further functionalization.[xxxi] *In situ* addition of *tert*-butyldimethylhydrosilane (1.10 eq.) results in quantitative dehydrocoupling (with concomitant slow evolution of hydrogen gas) in <1 h to the corresponding silyl ether **A.9** (see section A.5.4.3). It is also worth noting that this one-pot transformation substantiates the catalytic competence of the BCF catalyst and lends further evidence against Brønsted acid co-catalysis *via* $[H]^+$.

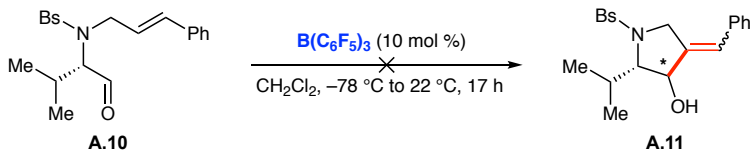


3.39 **A.9**

Scheme A.1. *In situ* BCF-catalyzed cyclization and dehydrocoupling / silyl-protection.

Application of this BCF-catalytic manifold to the corresponding cinnamyl amino aldehyde substrates to produce pyrrolidines was unsuccessful (Scheme A.2; see section A.5.4.4). Subjection of **A.10** to BCF (10 mol %) at the very mild conditions of slowly warming from –78 °C to 22 °C overnight resulted in 32% consumption of starting material and apparent decomposition; no pyrrolidine **A.11** was formed. We hypothesize that the driving force of the *Prins* cyclization / elimination reaction is the generation of a conjugated styrenyl enamide; absent a 1,2-hydride migration preceding the elimination (to form a 2,3-dihydropyrrole, not shown), a styrenyl enamide cannot form from the cinnamyl amino aldehyde substrates (*e.g.* **A.10**).

[xxxi] Although not discussed herein, other synthetic transformations/deprotections of the tetrahydropyridines, such as catalytic hydrogenation of the styrenyl enamide moiety or removal of the arylsulfonyl protecting group, were unsuccessful.

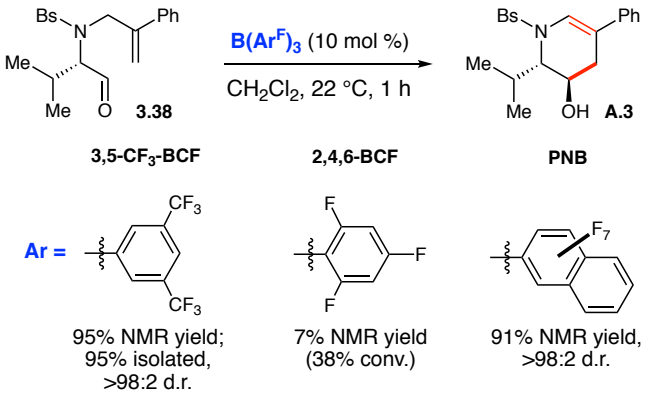


Scheme A.2. BCF-catalyzed cyclization / elimination to produce pyrrolidines.

A.3 Reactivity of various perfluoroaryl borane catalysts

We conducted a brief screen of perfluoroaryl borane Lewis acids as catalysts for the *Prins* cyclization / elimination manifold using substrate **3.38** (Scheme A.3; see section A.5.4.5). In comparison to BCF (Table A.1 above; 90% yield, >98:2 d.r.), **3,5-CF_3-BCF** provided the same *trans*-tetrahydropyridine product **A.3** in almost identical 95% yield and >98:2 d.r. Anomalously, the similarly Lewis acidic **2,4,6-BCF** provided only 7% NMR yield of the desired **A.3**, despite 38% consumption of the starting material.[xxxii] Finally, the more sterically hindered, but highly Lewis acidic **PNB** catalyst provided desired **A.3** in 91% NMR yield and >98:2 d.r. These results are generally in line with the reactivity and diastereoselectivity expected of large, neutral Lewis acid catalysts in this *Prins* cyclization reaction; modification of the perfluoroaryl borane catalyst could potentially be used to increase marginal diastereoselectivity in the examples where BCF itself was suboptimal (*e.g.* alaninol-, serinol-, and lysinol-derivatives **A.2**, **A.5**, and **A.6**, respectively, Table A.1 above).

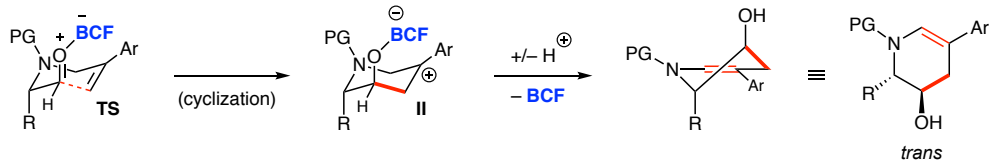
[xxxii] A recent computational study quantified the hydride donor abilities of these Lewis acids and validated the inverse relationship (proxy) between computed hydride donor ability and experimental Lewis acidity; Hydride donor ability for HBR_3^- ΔG (kcal/mol): **BCF** (65), **3,5-CF_3-BCF** (53), **2,4,6-BCF** (52), **PNB** (69). See Heiden, Z. M.; Lathem, A. P. *Organometallics* **2015**, *34*, 1818.



Scheme A.3. Perfluoroaryl borane catalyst screen.

A.4 Mechanism

As discussed in section 3.6 above (Scheme 3.7), the mechanism of the BCF-catalyzed cyclization is proposed to proceed *via* **TS → II** (Scheme A.4 below). The neutral, Lewis acidic perfluoroaryl borane catalyst activates the aldehyde to nucleophilic attack by the appended alkene exclusively *via* chair-like transition state **TS**; the larger steric environment (and lower reactivity) of BCF only allows for activation of the aldehyde in an enclusively *trans*-diaxial conformation (**TS**) to minimize interactions between BCF and the amino R-group.[xxxiii] The cyclization is then followed by rapid (at RT) intra- or intermolecular elimination of the resulting carbocation (**II**) by an alkoxide functionality to form the *trans*-tetrahydropyridine product and concomitantly regenerate the free perfluoroaryl borane catalyst.



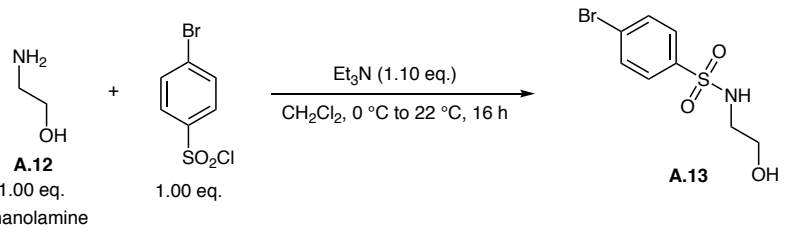
Scheme A.4. Proposed mechanism of the BCF-catalyzed *Prins* cyclization / elimination.

[xxxiii] DFT calculations (ωB97X-D//6-311+G**//CPCM:CH_2Cl_2) on 2-methyl-1-(phenylsulfonyl)piperidine show the lowest energy axial conformer to be 3.3 kcal/mol more stable than the lowest energy equatorial conformer. We speculate that this is paralleled in **TS**.

A.5 Experimental Section

A.5.1 Synthesis of *N*-arylsulfonyl-protected amino alcohols

Preparation of aryl sulfonamide A.13:



To a flame-dried 50 mL round-bottom flask equipped with a magnetic stir bar was added ethanolamine (**A.12**, 10.0 mmol, 604 μL, 1.00 eq.). The flask was capped with a septum, an N_2 needle was inserted, and the headspace of the flask was purged with anhydrous N_2. CH_2Cl_2 (20 mL) and Et_3N (11.0 mmol, 1.53 mL, 1.10 eq.) were added. The flask was placed in an ice-water bath and cooled to 0 °C. The septum was quickly removed and 4-bromobenzenesulfonyl chloride (brosyl chloride, Bs–Cl; 10.0 mmol, 2.56 g, 1.00 eq.) was added quickly and the flask resealed. The homogeneous solution was warmed to 22 °C and stirred for 16 h. After 16 h, the solution was decanted into a separatory funnel and diluted with excess CH_2Cl_2 and washed with deionized water. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (x4). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (9:1 dichloromethane:methanol; $R_f = 0.6$) to yield the desired *N*-Bs amino alcohol **A.13** in 85% yield (2.38 g).

4-bromo-*N*-(2-hydroxyethyl)benzenesulfonamide (A.13). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.74 (d, 2H, $J = 8.6$ Hz), 7.67 (d, 2H, $J = 8.6$ Hz), 5.02 (s, 1H), 3.72 (q, 2H, $J = 5.0$ Hz),

3.12 (q, 2H, J = 5.8 Hz), 1.88 (s, 1H); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 138.8, 132.6, 128.8, 128.0, 61.4, 45.2.

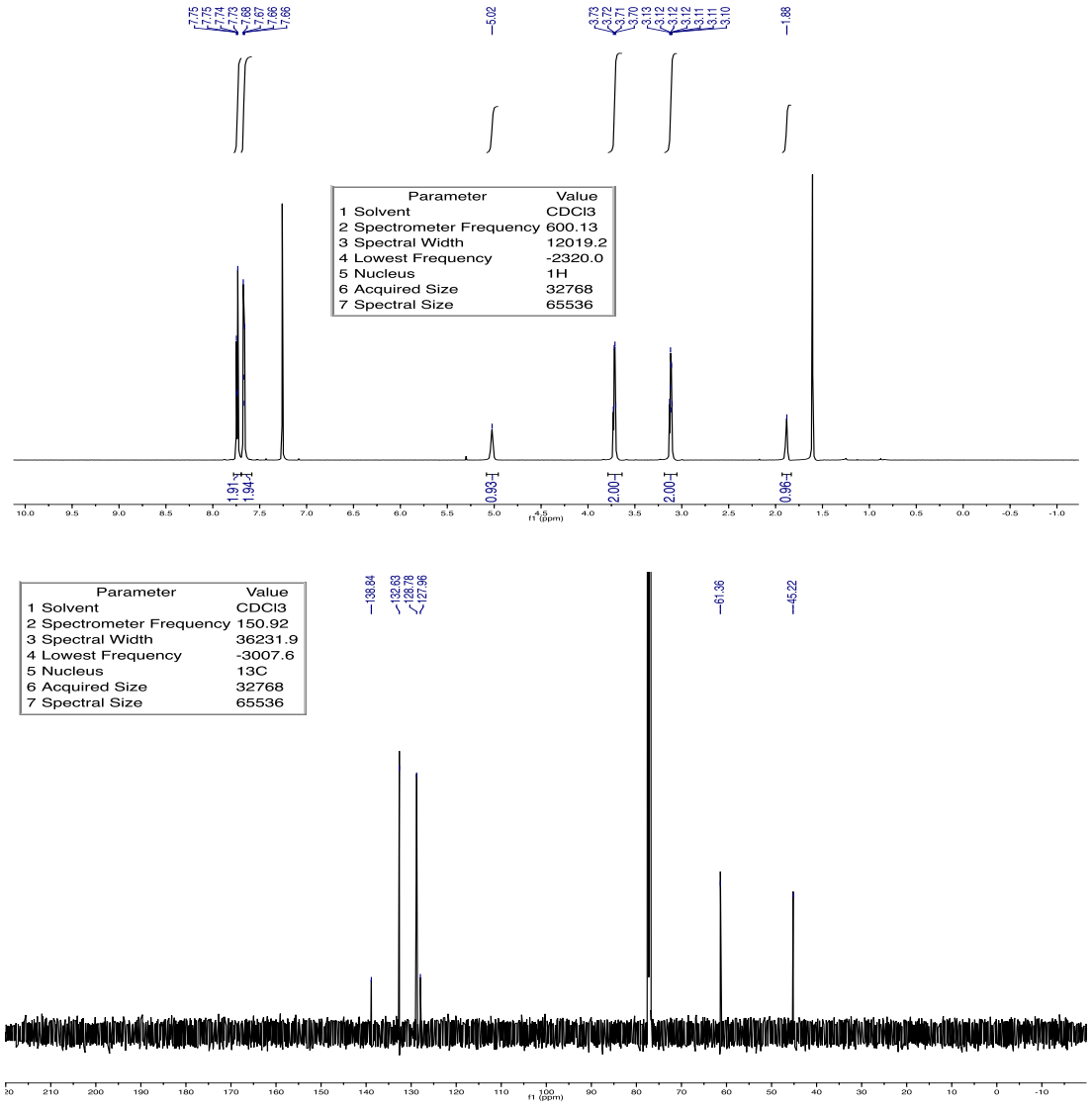
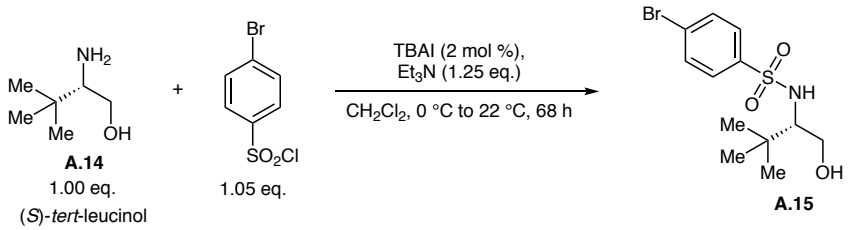


Figure A.1. ^{1}H and ^{13}C{^{1}H} NMR spectra of A.13.

Preparation of aryl sulfonamide A.15:



To a flame-dried 50 mL round-bottom flask equipped with a magnetic stir bar was added (*S*)-*tert*-leucinol (**A.14**, 8.53 mmol, 1.00 g, 1.00 eq.) and tetrabutylammonium iodide (0.171 mmol, 63 mg, 0.02 eq.). The flask was capped with a septum, an N_2 needle was inserted, and the headspace of the flask was purged with anhydrous N_2. CH_2Cl_2 (17 mL) and Et_3N (10.7 mmol, 1.49 mL, 1.25 eq.) were added. The flask was placed in an ice-water bath and cooled to 0 °C. The septum was quickly removed and 4-bromobenzenesulfonyl chloride (brosyl chloride, Bs–Cl; 8.96 mmol, 2.29 g, 1.05 eq.) was added quickly and the flask resealed. The homogeneous solution was warmed to 22 °C and stirred for 68 h. After 68 h, the solution was decanted into a separatory funnel and diluted with excess CH_2Cl_2 and washed with deionized water. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (x4). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (1:1 hexanes:ethyl acetate; $R_f = 0.5$) to yield the desired *N*-Bs amino alcohol **A.15** in 94% yield (2.70 g).

(S)-4-bromo-N-(1-hydroxy-3,3-dimethylbutan-2-yl)benzenesulfonamide (A.15).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.77 (d, 2H, J = 8.6 Hz), 7.65 (d, 2H, J = 8.6 Hz), 4.95 (d, 1H, J = 9.3 Hz), 3.68-3.57 (m, 2H), 3.03 (ddd, 1H, J = 9.6, 6.1, 3.8 Hz), 2.00 (dd, 1H, J =

6.9, 4.2 Hz); **$^{13}C\{^{1}H\}$ NMR** ($CDCl_3$, 151 MHz): δ 139.9, 132.4, 128.9, 127.8, 64.2, 62.2, 34.3, 27.1.

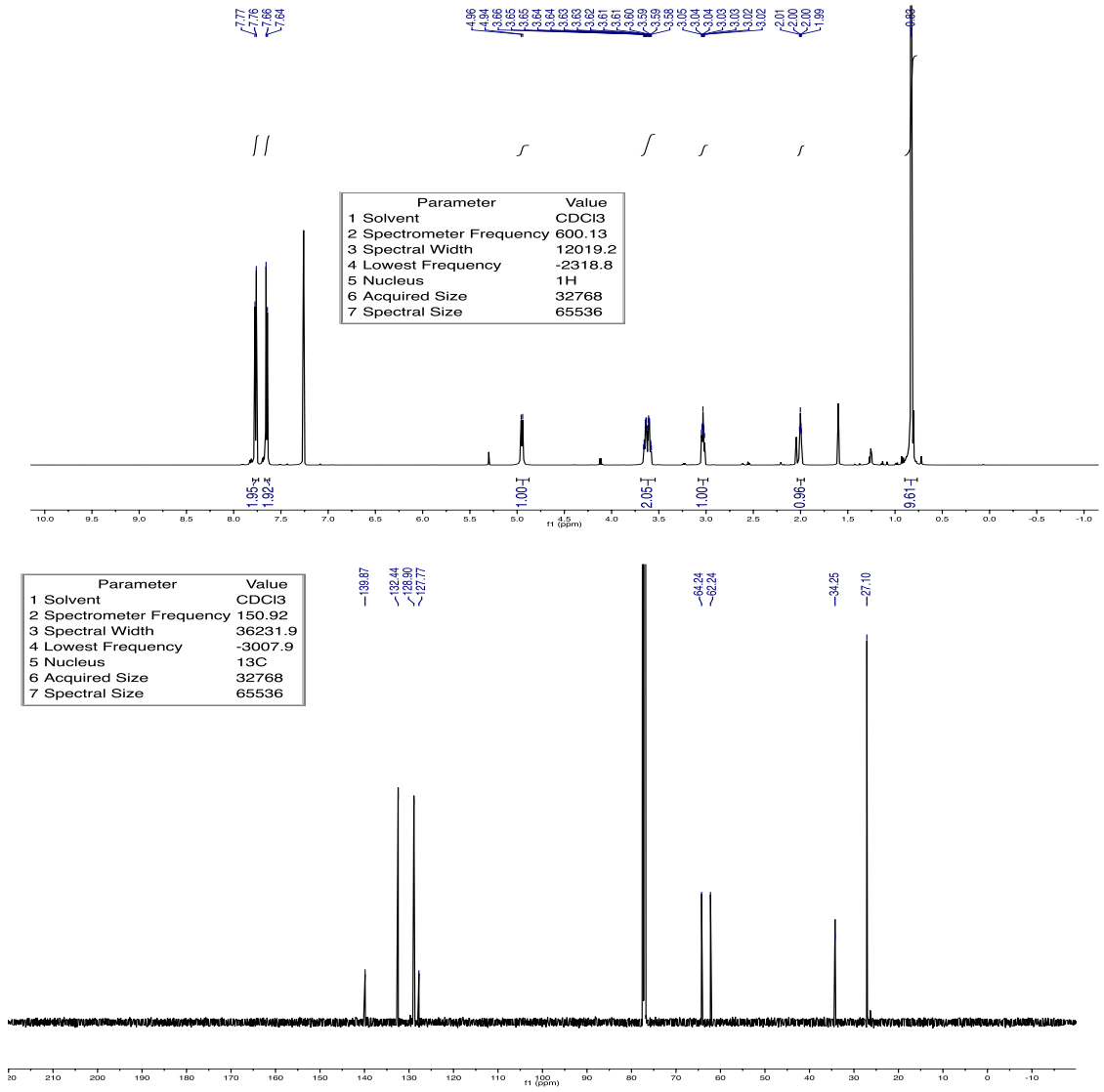
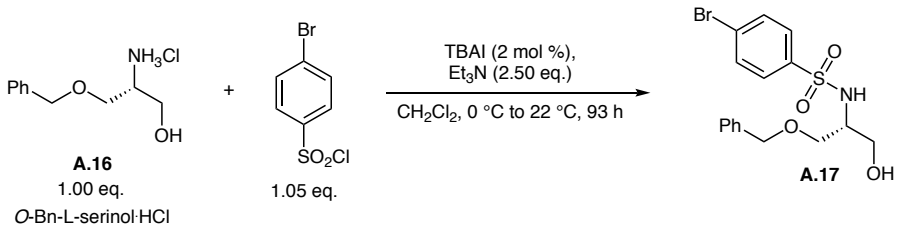


Figure A.2. ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of A.15.

Preparation of aryl sulfonamide A.17:



To a flame-dried 25 mL round-bottom flask equipped with a magnetic stir bar was added *O*-benzyl-L-serinol hydrochloride (**A.16**, CAS Reg. No. 58577-87-0; 2.30 mmol, 500 mg, 1.00 eq.) and tetrabutylammonium iodide (0.0460 mmol, 17.0 mg, 0.02 eq.). The flask was capped with a septum, an N_2 needle was inserted, and the headspace of the flask was purged with anhydrous N_2. CH_2Cl_2 (10.0 mL) and Et_3N (5.75 mmol, 800 μL, 2.50 eq.) were added. The flask was placed in an ice-water bath and cooled to 0 °C. The septum was quickly removed and 4-bromobenzenesulfonyl chloride (brosyl chloride, Bs–Cl; 2.41 mmol, 616 mg, 1.05 eq.) was added quickly and the flask resealed. The homogeneous solution was warmed to 22 °C and stirred for 93 h. After 93 h, the solution was decanted into a separatory funnel and diluted with excess CH_2Cl_2 and washed with deionized water. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (x4). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (10:1 dichloromethane:methanol; R_f = 0.4 in 1:1 hexanes:ethyl acetate) to yield the desired *N*-Bs amino alcohol **A.17** as an off-white, crystalline solid in 78% yield (721 mg).

(*R*)-*N*-(1-(benzyloxy)-3-hydroxypropan-2-yl)-4-bromobenzenesulfonamide (A.17).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.69 (d, 2H, *J* = 8.5 Hz), 7.59 (d, 2H, *J* = 8.6 Hz), 7.38-7.31 (m, 3H), 7.23-7.20 (m, 2H), 5.22 (d, 1H, *J* = 7.3 Hz), 4.40 (q, 2H, *J* = 13.7 Hz), 3.72

(dt, 1H, J = 11.4, 3.9 Hz), 3.58-3.52 (m, 2H), 3.45-3.39 (m, 2H), 2.12 (dd, 1H, J = 8.2, 4.2 Hz); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 139.6, 137.2, 132.5, 128.8, 128.7, 128.3, 127.9, 127.8, 73.7, 70.3, 63.3, 54.4.

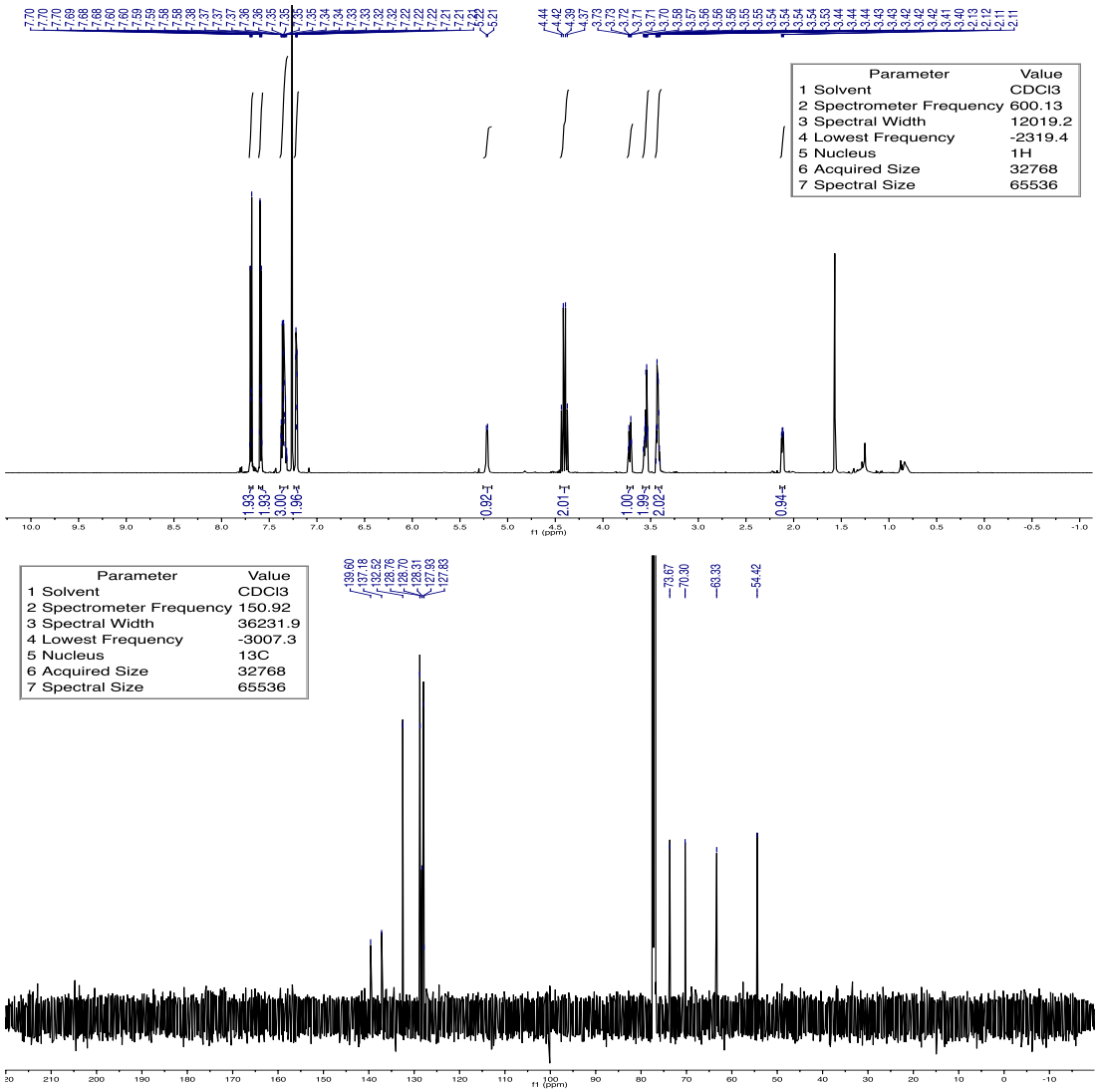
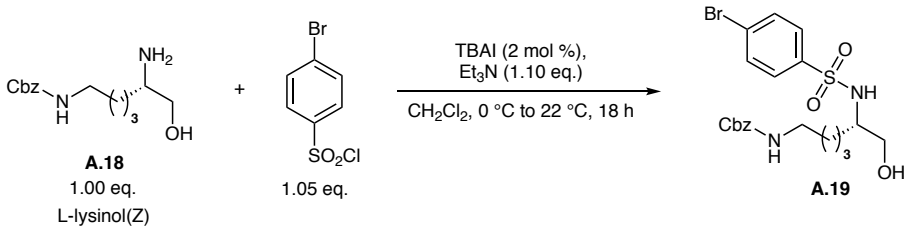


Figure A.3. ^{1}H and ^{13}C{^{1}H} NMR spectra of A.17.

Preparation of aryl sulfonamide A.19:



To a flame-dried 25 mL round-bottom flask equipped with a magnetic stir bar was added L-lysinol(Z) (**A.18**, CAS Reg. No. 101250-90-2; 1.88 mmol, 500 mg, 1.00 eq.) and tetrabutylammonium iodide (0.0375 mmol, 14.0 mg, 0.02 eq.). The flask was capped with a septum, an N_2 needle was inserted, and the headspace of the flask was purged with anhydrous N_2. CH_2Cl_2 (9.4 mL) and Et_3N (2.06 mmol, 290 μL, 1.10 eq.) were added. The flask was placed in an ice-water bath and cooled to 0 °C. The septum was quickly removed and 4-bromobenzenesulfonyl chloride (brosyl chloride, Bs–Cl; 1.97 mmol, 503 mg, 1.05 eq.) was added quickly and the flask resealed. The homogeneous solution was warmed to 22 °C and stirred for 18 h. After 18 h, the solution was decanted into a separatory funnel and diluted with excess CH_2Cl_2 and washed with deionized water. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (x4). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (1:2 hexanes:ethyl acetate; $R_f = 0.3$) to yield the desired *N*-Bs amino alcohol **A.19** as a white, crystalline powder in 72% yield (660 mg).

benzyl (*S*)-(5-((4-bromophenyl)sulfonamido)-6-hydroxyhexyl)carbamate (A.19).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.73 (d, 2H, *J* = 8.5 Hz), 7.63 (d, 2H, *J* = 8.5 Hz), 7.37 (d, 4H, *J* = 4.3 Hz), 7.35-7.31 (m, 1H), 5.16 (d, 1H, *J* = 7.9 Hz), 5.12 (d, 2H, *J* = 2.2 Hz), 4.78 (t, 1H, *J* = 6.2 Hz), 3.51-3.41 (m, 2H), 3.24-3.18 (m, 1H), 3.18-3.11 (m, 2H), 2.22 (t, 1H, *J*

= 5.9 Hz), 1.57-1.51 (m, 1H), 1.51-1.44 (m, 1H), 1.43-1.36 (m, 2H), 1.23-1.18 (m, 1H), 1.17-1.09 (m, 1H); **$^{13}C\{^{1}H\}$ NMR** ($CDCl_3$, 151 MHz): δ 157.2, 140.0, 136.5, 132.5, 128.7, 128.7, 128.4, 128.3, 127.7, 67.1, 64.4, 55.6, 39.7, 30.6, 29.8, 21.7.

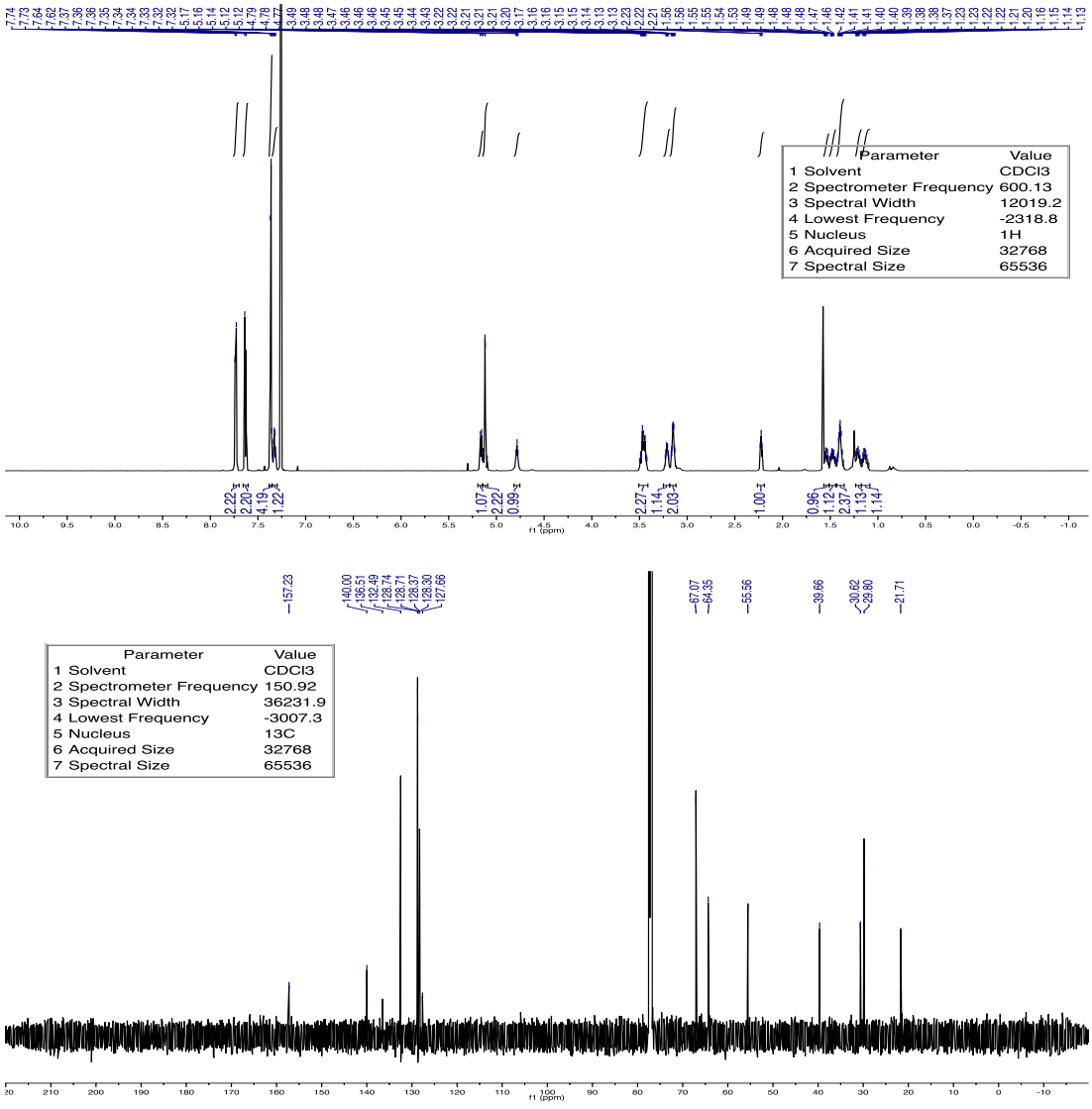
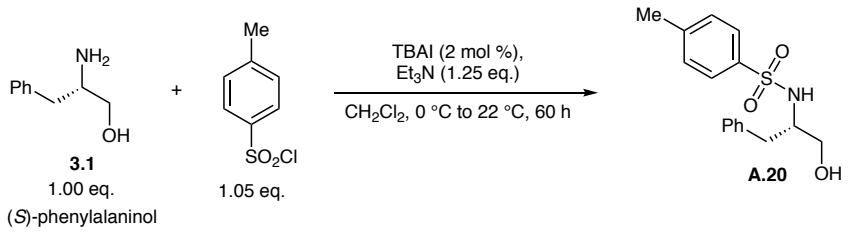


Figure A.4. ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of A.19.

Preparation of aryl sulfonamide A.20:



To a flame-dried 100 mL round-bottom flask equipped with a magnetic stir bar was added (*S*)-phenylalaninol (**3.1**, 6.61 mmol, 1.00 g, 1.00 eq.) and tetrabutylammonium iodide (0.132 mmol, 49 mg, 0.02 eq.). The flask was capped with a septum, an N_2 needle was inserted, and the headspace of the flask was purged with anhydrous N_2. CH_2Cl_2 (29 mL) and Et_3N (8.26 mmol, 1.15 mL, 1.25 eq.) were added. The flask was placed in an ice-water bath and cooled to 0 °C. The septum was quickly removed and 4-bromobenzene-sulfonyl chloride (tosyl chloride, Ts–Cl; 6.94 mmol, 1.32 g, 1.05 eq.) was added quickly and the flask resealed. The homogeneous solution was warmed to 22 °C and stirred for 60 h. After 60 h, the solution was decanted into a separatory funnel and diluted with excess CH_2Cl_2 and washed with deionized water. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (x4). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (1:1 hexanes:ethyl acetate; $R_f = 0.3$) to yield the desired *N*-Ts amino alcohol **A.20** as a yellow oil in 91% yield (1.84 g).

(*S*)-*N*-(1-hydroxy-3-phenylpropan-2-yl)-4-methylbenzenesulfonamide (A.20).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.58 (d, 2H, J = 8.3 Hz), 7.20 (d, 2H, J = 8.1 Hz), 7.19-7.17 (m, 3H), 6.98-6.95 (m, 2H), 4.88 (d, 1H, J = 7.1 Hz), 3.64 (ddd, 1H, J = 10.6, 6.4, 3.9 Hz), 3.53 (dt, 1H, J = 10.8, 5.0 Hz), 3.44 (qdd, 1H, J = 7.2, 4.8, 3.9 Hz), 2.78 (dd, 1H, J =

13.8, 7.0 Hz), 2.68 (dd, 1H, J = 13.8, 7.3 Hz), 2.41 (s, 3H), 2.21 (t, 1H, J = 5.9 Hz); **$^{13}C\{^{1}H\}$ NMR** ($CDCl_3$, 151 MHz): δ 143.6, 136.8, 136.8, 129.8, 129.3, 128.8, 127.1, 126.9, 64.2, 56.7, 37.9, 21.7.

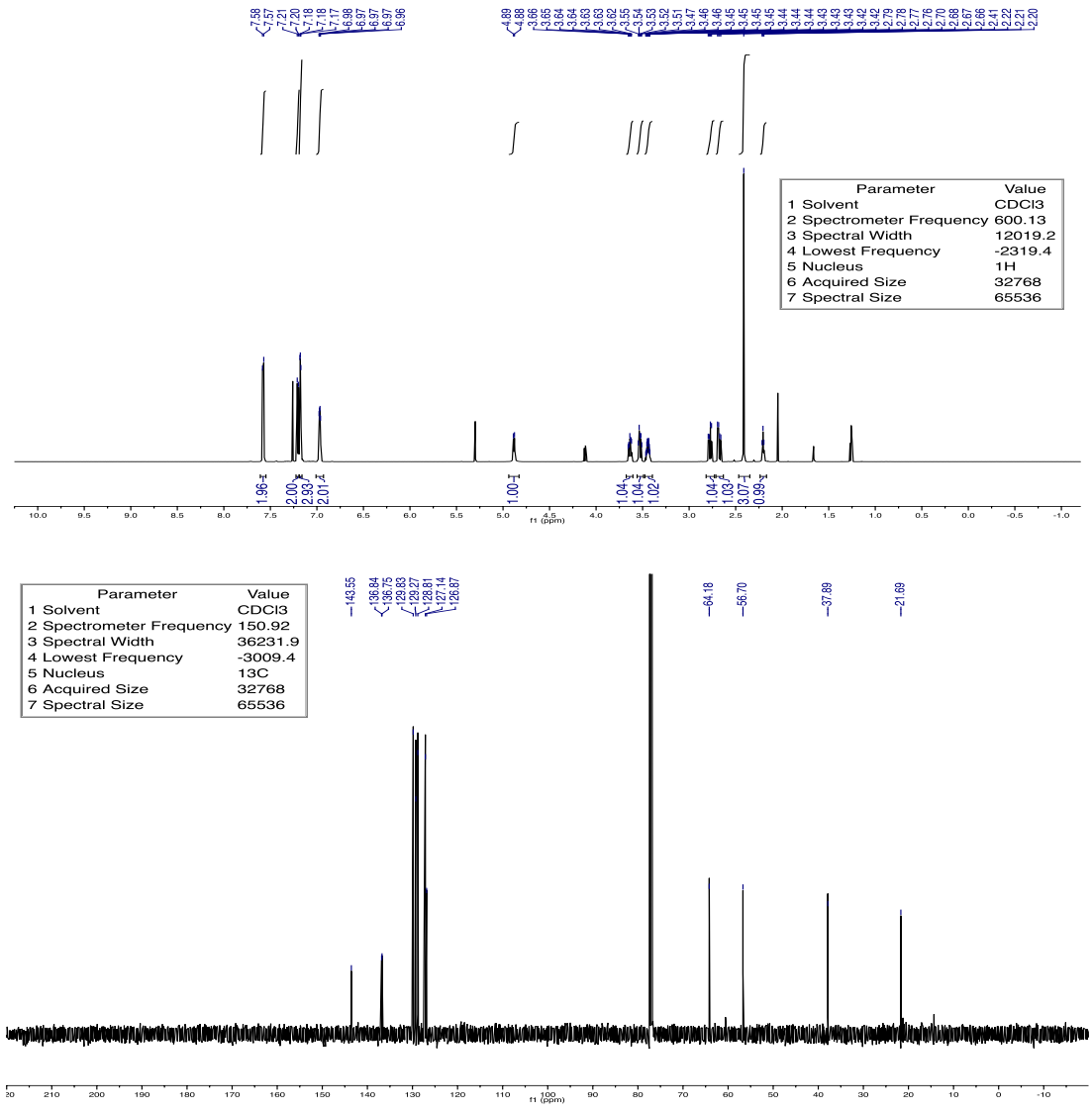
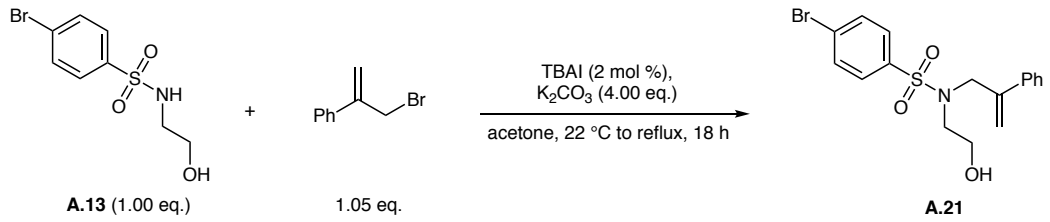


Figure A.5. ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of A.20.

A.5.2 *N*-alkylation of *N*-arylsulfonyl-protected amino alcohols

Preparation of *N*-alkylated amino alcohol A.21:



A.13 (1.00 eq.) 1.05 eq. **A.21**

To a flame-dried 20 mL scintillation vial equipped with a magnetic stir bar was added aryl sulfonamide **A.13** (2.00 mmol, 560 mg, 1.00 eq.), tetrabutylammonium iodide (0.040 mmol, 15 mg, 0.02 eq.), and powdered, anhydrous potassium carbonate (8.00 mmol, 1.11 g, 4.00 eq.). The vial was capped with a septum, an N_2 needle was inserted, and the headspace of the vial was purged with anhydrous N_2. Anhydrous acetone (15 mL) was added to dissolve the substrate, followed by 2-phenylallyl bromide (2.10 mmol, 302 μL, 1.05 eq.). The vial was sealed, placed in an oil bath, and heated to reflux (approximately 60-65 °C oil bath temperature). The heterogeneous mixture was vigorously stirred for 18 h and then cooled to room temperature. The mixture was filtered through a cotton plug to remove potassium salts and then concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (1:1 hexanes:ethyl acetate; $R_f = 0.45$) to yield the alkylated amino alcohol product **A.21** as a viscous yellow oil in 99% yield (793 mg).

4-bromo-N-(2-hydroxyethyl)-N-(2-phenylallyl)benzenesulfonamide (A.21). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.64-7.59 (m, 4H), 7.43-7.40 (m, 2H), 7.37-7.31 (m, 3H), 5.49 (s, 1H), 5.23 (s, 1H), 4.28 (s, 2H), 3.60 (q, 2H, $J = 5.6$ Hz), 3.19 (t, 2H, $J = 5.4$ Hz), 1.94 (t, 1H, $J = 6.0$ Hz); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 142.9, 137.8, 137.6, 132.5, 129.1, 128.8, 128.5, 128.0, 126.6, 117.3, 60.9, 53.5, 50.0.

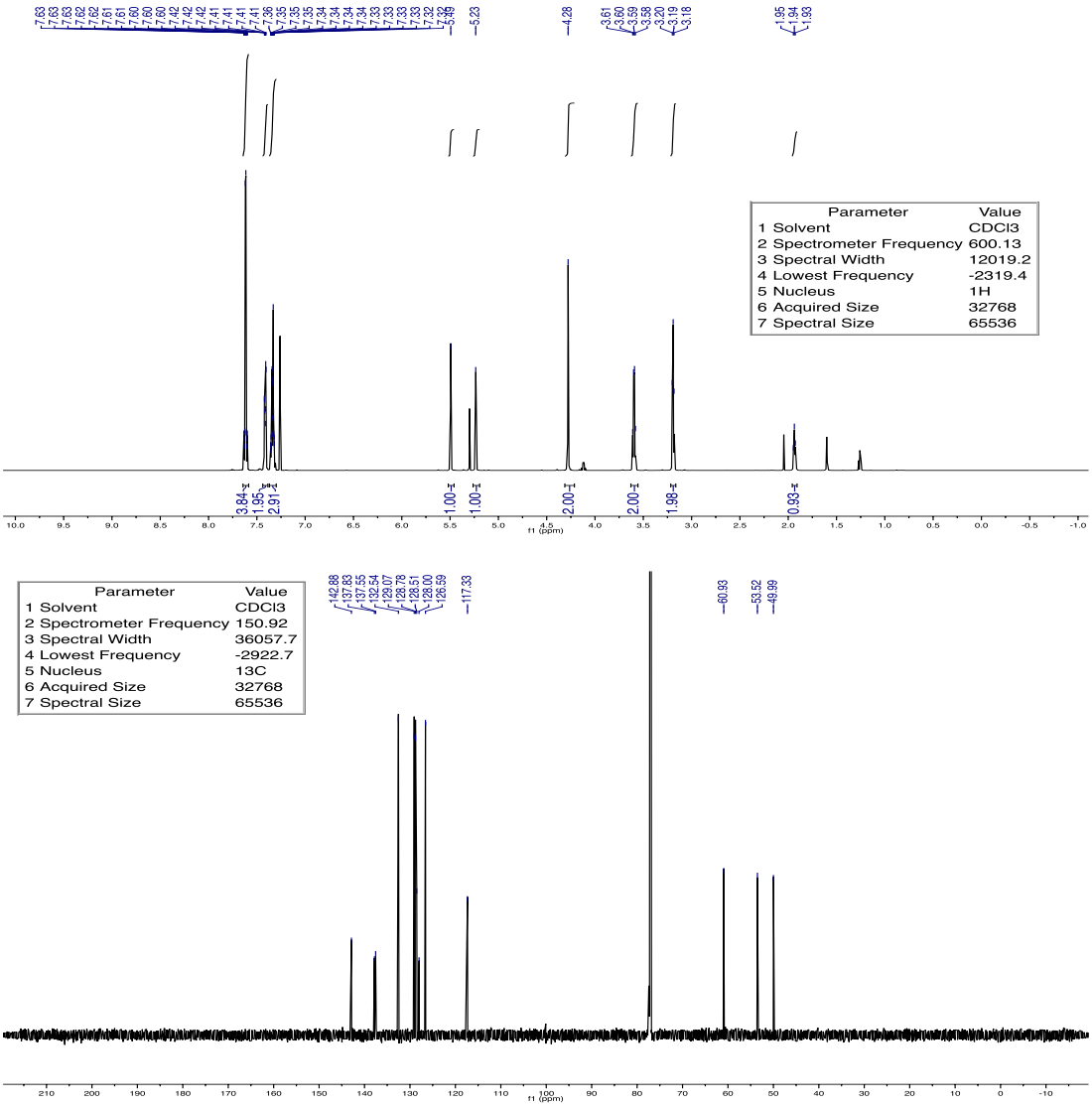
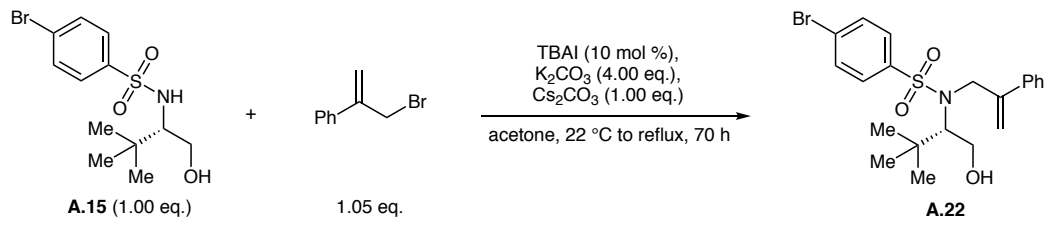


Figure A.6. ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of A.21.

Preparation of *N*-alkylated amino alcohol A.22:



A.15 (1.00 eq.) 1.05 eq. **A.22**

To a flame-dried 50 mL round-bottom flask equipped with a magnetic stir bar was added aryl sulfonamide **A.15** (3.00 mmol, 1.01 g, 1.00 eq.), tetrabutylammonium iodide (0.300 mmol, 111 mg, 0.10 eq.), and powdered, anhydrous potassium carbonate (12.0 mmol, 1.66 g, 4.00 eq.). The flask was capped with a septum, an N_2 needle was inserted, and the headspace of the flask was purged with anhydrous N_2. Anhydrous acetone (23 mL) was added to dissolve the substrate, followed by 2-phenylallyl bromide (3.15 mmol, 453 μL, 1.05 eq.). The flask was sealed, placed in an oil bath, and heated to reflux (approximately 60-65 °C oil bath temperature). The heterogeneous mixture was vigorously stirred for 45 h, at which time cesium carbonate (3.00 mmol, 977 mg, 1.00 eq.) was added and the mixture refluxed for another 25 h. The mixture was cooled to room temperature and filtered through a cotton plug to remove potassium and cesium salts and was then concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (4:1 hexanes:ethyl acetate; $R_f = 0.35$) to yield the alkylated amino alcohol product **A.22** as a glassy solid in 61% yield (829 mg).

(S)-4-bromo-N-(1-hydroxy-3,3-dimethylbutan-2-yl)-N-(2-phenylallyl)benzene sulfonamide (A.22). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.71 (d, 2H, J = 8.6 Hz), 7.58 (d, 2H, J = 8.6 Hz), 7.30-7.24 (m, 3H), 7.12-7.06 (m, 2H), 5.48 (s, 1H), 5.34 (s, 1H), 4.34-4.24 (m, 2H), 3.88 (s, br, 1H), 3.75-3.70 (m, 1H), 3.58 (s, br, 1H), 1.27 (s, br, 1H), 0.98 (s, 9H); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 143.7, 140.4, 139.8, 131.9, 129.9, 128.6, 128.2, 127.4, 126.4, 117.7, 69.1, 59.7, 49.2, 34.8, 28.4.

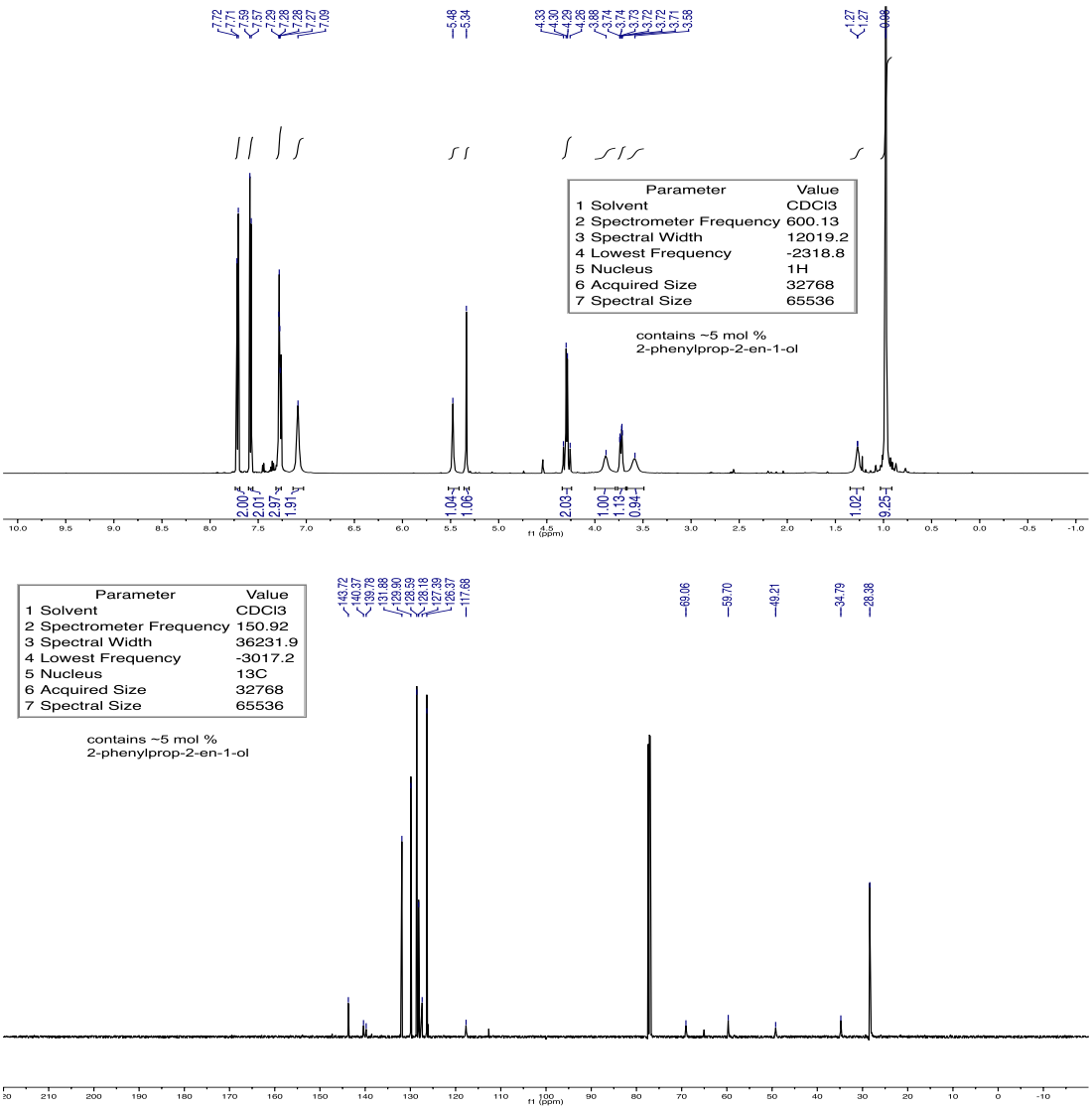


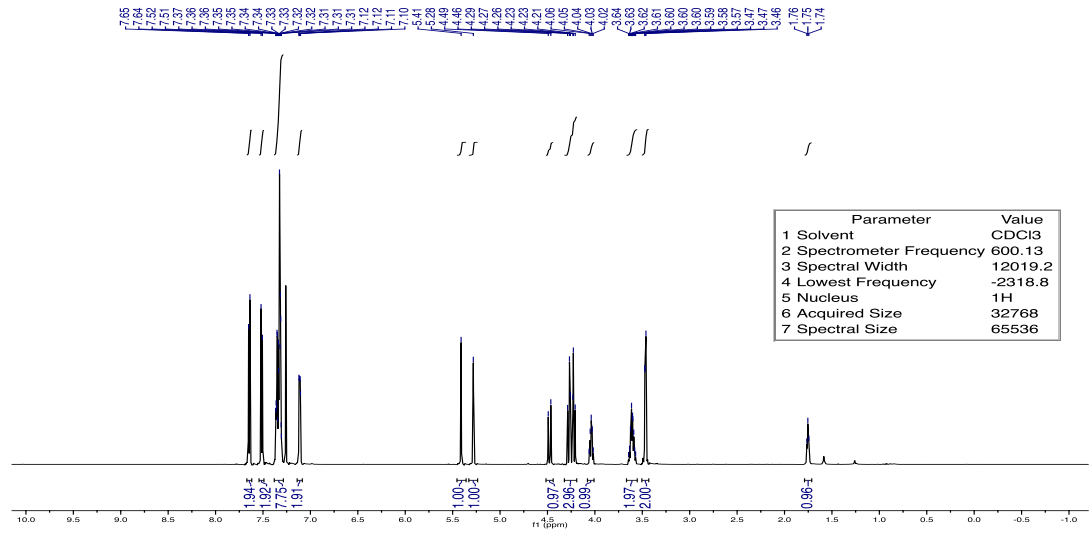
Figure A.7. ^{1}H and ^{13}C{^{1}H} NMR spectra of A.22.

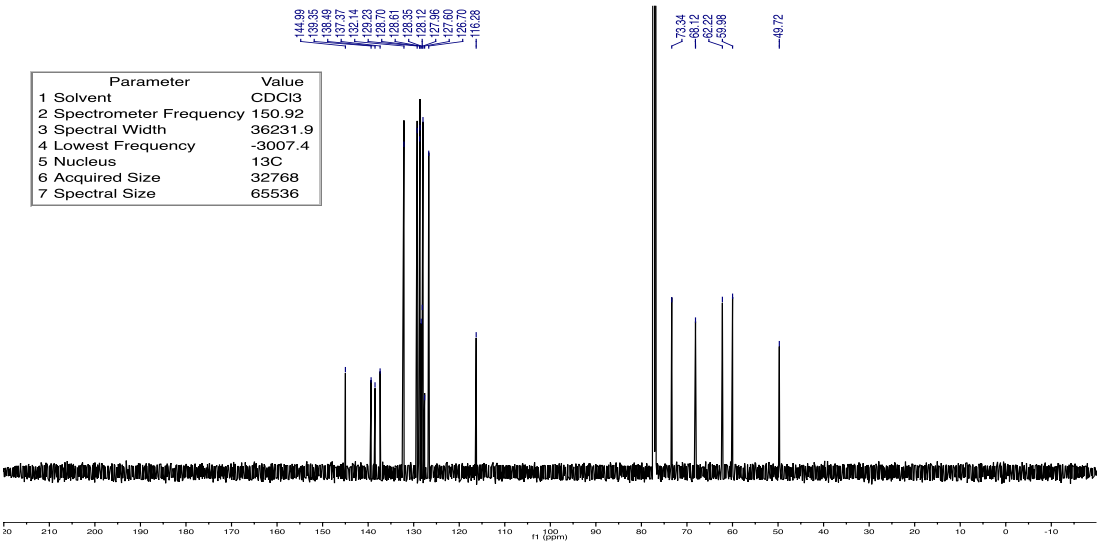
Preparation of *N*-alkylated amino alcohol A.23:

A.17 (1.00 eq.) 1.05 eq. **A.23**

To a flame-dried 20 mL scintillation vial equipped with a magnetic stir bar was added aryl sulfonamide **A.17** (1.25 mmol, 500 mg, 1.00 eq.), tetrabutylammonium iodide (0.025 mmol, 9.2 mg, 0.02 eq.), and powdered, anhydrous potassium carbonate (5.00 mmol, 691 mg, 4.00 eq.). The vial was capped with a septum, an N_2 needle was inserted, and the headspace of the vial was purged with anhydrous N_2. Anhydrous acetone (9.4 mL) was added to dissolve the substrate, followed by 2-phenylallyl bromide (1.31 mmol, 189 μL, 1.05 eq.). The vial was sealed, placed in an oil bath, and heated to reflux (approximately 60-65 °C oil bath temperature). The heterogeneous mixture was vigorously stirred for 7 h and then cooled to room temperature. The mixture was filtered through a cotton plug to remove potassium salts and then concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (2:1 hexanes:ethyl acetate; $R_f = 0.3$) to yield the *N*-alkylated amino alcohol product **A.23** as a clear, colorless oil in 92% yield (597 mg).

(*R*)-*N*-(1-(benzyloxy)-3-hydroxypropan-2-yl)-4-bromo-*N*-(2-phenylallyl)benzene sulfonamide (A.23). **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 7.64 (d, 2H, J = 8.5 Hz), 7.51 (d, 2H, J = 8.5 Hz), 7.39-7.30 (m, 8H), 7.11 (dd, 2H, J = 7.4, 2.0 Hz), 5.41 (s, 1H), 5.28 (s, 1H), 4.48 (d, 1H, J = 16.3 Hz), 4.30-4.20 (m, 3H), 4.04 (p, 1H, J = 6.5 Hz), 3.65-3.56 (m, 2H), 3.50-3.44 (m, 2H), 1.75 (t, 1H, J = 6.4 Hz); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 145.0, 139.4, 138.5, 137.4, 132.1, 129.2, 128.7, 128.6, 128.4, 128.1, 128.0, 127.6, 126.7, 116.3, 73.3, 68.1, 62.2, 60.0, 49.7; **^{13}C NMR DEPT135** ($CDCl_3$, 151 MHz): δ 132.1 (CH), 129.2 (CH), 128.7 (CH), 128.6 (CH), 128.4 (CH), 128.1 (CH), 128.0 (CH), 126.7 (CH), 116.3 (CH_2), 73.3 (CH_2), 68.1 (CH_2), 62.2 (CH_2), 60.0 (CH), 49.7 (CH_2).


7.65 7.64 7.52 7.51 7.37 7.36 7.36 7.35 7.35 7.34 7.34 7.33 7.33 7.32 7.32 7.31 7.31 7.31 7.12 7.12 7.11 7.10 5.41 5.28 4.49 4.46 4.29 4.27 4.26 4.23 4.23 4.21 4.06 4.05 4.04 4.03 4.02 3.64 3.63 3.62 3.61 3.60 3.60 3.60 3.59 3.58 3.57 3.47 3.47 3.46 1.76 1.75 1.74
Parameter Value
1 Solvent CDCl3
2 Spectrometer Frequency 600.13
3 Spectral Width 12019.2
4 Lowest Frequency -2318.8
5 Nucleus 1H
6 Acquired Size 32768
7 Spectral Size 65536
1.94 1.92 7.75 1.91 1.00 1.00 0.97 2.96 0.99 1.97 2.00 0.96
f1 (ppm)


144.99 139.35 138.49 137.37 132.14 129.23 128.70 128.61 128.35 128.12 127.96 127.60 126.70 116.28
73.34 68.12 62.22 59.98 49.72
Parameter Value
1 Solvent CDCl3
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5 Nucleus 13C
6 Acquired Size 32768
7 Spectral Size 65536
f1 (ppm)

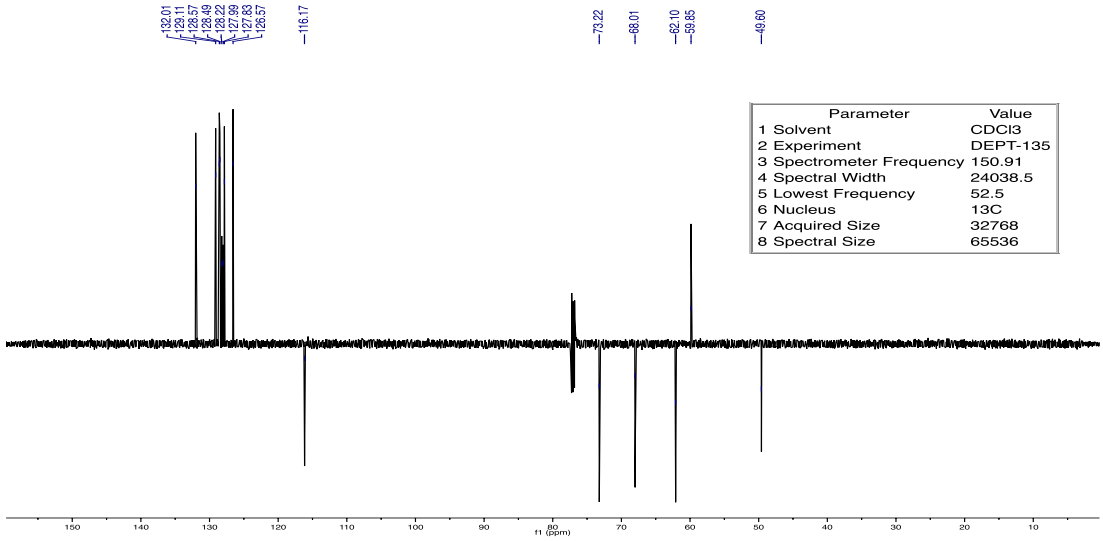
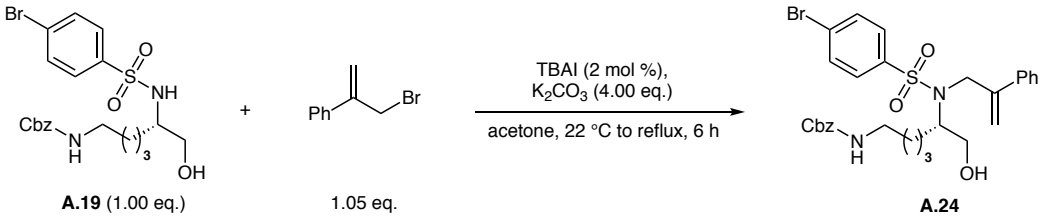


Figure A.8. ^{1}H, $^{13}C\{^{1}H\}$, and ^{13}C DEPT-135 NMR spectra of A.23.

Preparation of *N*-alkylated amino alcohol A.24:

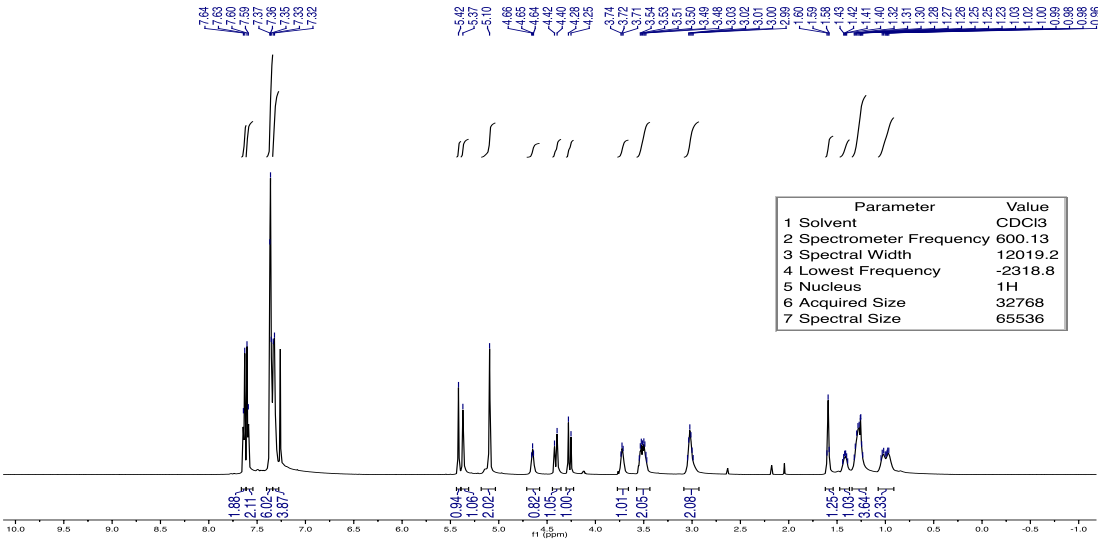


A.19 (1.00 eq.) 1.05 eq. **A.24**

To a flame-dried 20 mL scintillation vial equipped with a magnetic stir bar was added aryl sulfonamide **A.19** (0.906 mmol, 440 mg, 1.00 eq.), tetrabutylammonium iodide (0.018 mmol, 6.7 mg, 0.02 eq.), and powdered, anhydrous potassium carbonate (3.62 mmol, 501 mg, 4.00 eq.). The vial was capped with a septum, an N_2 needle was inserted, and the headspace of the vial was purged with anhydrous N_2. Anhydrous acetone (6.8 mL) was added to dissolve the substrate, followed by 2-phenylallyl bromide (0.951 mmol, 137 μL, 1.05 eq.). The vial was sealed, placed in an oil bath, and heated to reflux (approximately 60-65 °C oil bath temperature). The heterogeneous mixture was vigorously stirred for 6 h and then cooled to room temperature. The mixture was filtered through a

cotton plug to remove potassium salts and then concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (1:1 hexanes:ethyl acetate; $R_f = 0.3$) to yield the *N*-alkylated amino alcohol product **A.24** as a clear, amorphous solid in 98% yield (532 mg).

benzyl (*S*)-(5-((4-bromo-*N*-(2-phenylallyl)phenyl)sulfonamido)-6-hydroxyhexyl) carbamate (A.24). **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 7.63 (d, 2H, *J* = 8.2 Hz), 7.60 (d, 2H, *J* = 8.3 Hz), 7.39-7.34 (m, 6H), 7.33 (d, 4H, *J* = 8.0 Hz), 5.42 (s, 1H), 5.37 (s, 1H), 5.10 (s, 2H), 4.67-4.63 (m, 1H), 4.41 (d, 1H, *J* = 16.0 Hz), 4.27 (d, 1H, *J* = 16.0 Hz), 3.75-3.69 (m, 1H), 3.58-3.43 (m, 2H), 3.08-2.96 (m, 2H), 1.63-1.56 (m, 1H), 1.47-1.37 (m, 1H), 1.34-1.21 (m, 3H), 1.08-0.89 (m, 2H); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 156.5, 145.0, 139.6, 138.5, 136.7, 132.4, 129.2, 128.7, 128.7, 128.4, 128.3, 128.3, 127.7, 126.8, 116.9, 66.8, 63.2, 60.9, 48.9, 40.7, 29.8, 28.9, 23.9; **^{13}C NMR DEPT135** ($CDCl_3$, 151 MHz): δ 132.4 (CH), 129.2 (CH), 128.7 (CH), 128.7 (CH), 128.4 (CH), 128.3 (CH), 128.3 (CH), 126.8 (CH), 116.9 (CH_2), 66.8 (CH_2), 63.2 (CH_2), 60.9 (CH), 48.9 (CH_2), 40.7 (CH_2), 29.8 (CH_2), 28.9 (CH_2), 23.9 (CH_2).



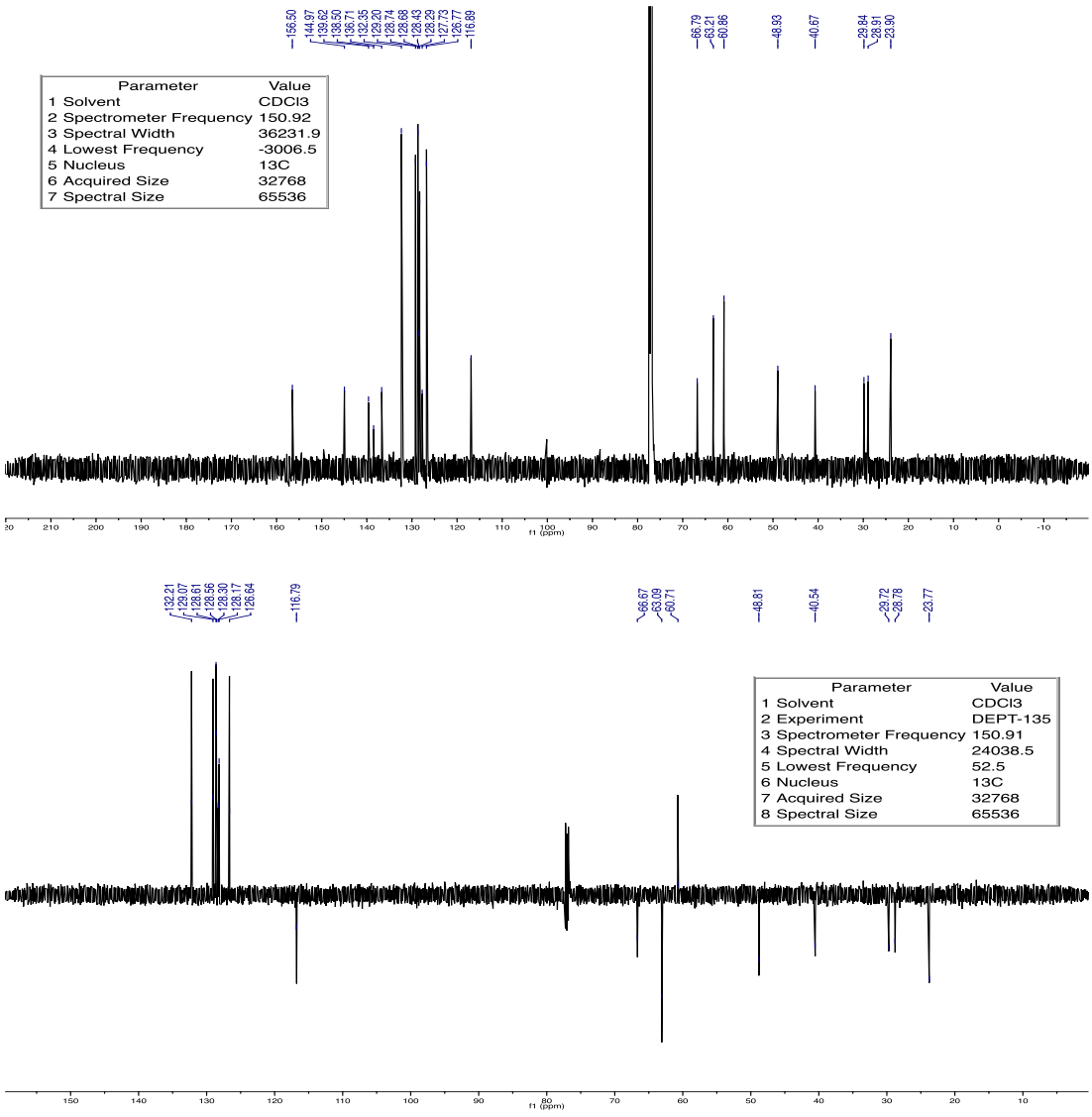
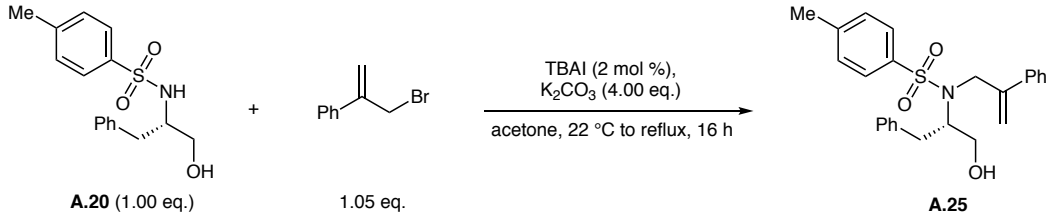


Figure A.9. ^{1}H, $^{13}C\{^{1}H\}$, and ^{13}C DEPT-135 NMR spectra of A.24.

Preparation of *N*-alkylated amino alcohol A.25:



A.20 (1.00 eq.) 1.05 eq. **A.25**

To a flame-dried 20 mL scintillation vial equipped with a magnetic stir bar was added aryl sulfonamide **A.20** (2.51 mmol, 765 mg, 1.00 eq.), tetrabutylammonium iodide (0.0501 mmol, 18.5 mg, 0.02 eq.), and powdered, anhydrous potassium carbonate (10.0 mmol, 1.39 g, 4.00 eq.). The vial was capped with a septum, an N_2 needle was inserted, and the headspace of the vial was purged with anhydrous N_2. Anhydrous acetone (10.0 mL) was added to dissolve the substrate, followed by 2-phenylallyl bromide (2.63 mmol, 378 μL, 1.05 eq.). The vial was sealed, placed in an oil bath, and heated to reflux (approximately 60-65 °C oil bath temperature). The heterogeneous mixture was vigorously stirred for 16 h and then cooled to room temperature. The mixture was filtered through a cotton plug to remove potassium salts and then concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (3:1 hexanes:ethyl acetate; $R_f = 0.3$) to yield the alkylated amino alcohol product **A.25** as a viscous, light yellow oil in 90% yield (953 mg).

(*S*)-*N*-(1-hydroxy-3-phenylpropan-2-yl)-4-methyl-*N*-(2-phenylallyl)benzene sulfonamide (A.25). **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 7.72 (d, 2H, *J* = 8.2 Hz), 7.46-7.43 (m, 2H), 7.39-7.33 (m, 3H), 7.30 (d, 2H, *J* = 8.2 Hz), 7.23-7.19 (m, 2H), 7.19-7.15 (m, 1H), 6.93 (d, 2H, *J* = 6.7 Hz), 5.50 (s, 1H), 5.45 (s, 1H), 4.60 (d, 1H, *J* = 16.2 Hz), 4.31 (d, 1H, *J* = 16.1 Hz), 3.91 (ddt, 1H, *J* = 10.7, 8.3, 4.0 Hz), 3.56 (ddd, 1H, *J* = 12.1, 8.6, 5.3 Hz), 3.44 (ddd, 1H, *J* = 11.9, 7.8, 3.8 Hz), 2.72 (dd, 1H, *J* = 13.3, 10.6 Hz), 2.52 (dd, 1H, *J* = 13.3, 4.2 Hz), 2.44 (s, 3H), 1.60-1.54 (m, 1H); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 145.3, 143.9, 138.4, 137.9, 137.3, 129.9, 129.1, 128.8, 128.7, 128.5, 127.7, 126.8, 126.8, 116.3, 62.3, 62.0, 49.3, 35.8, 21.7.

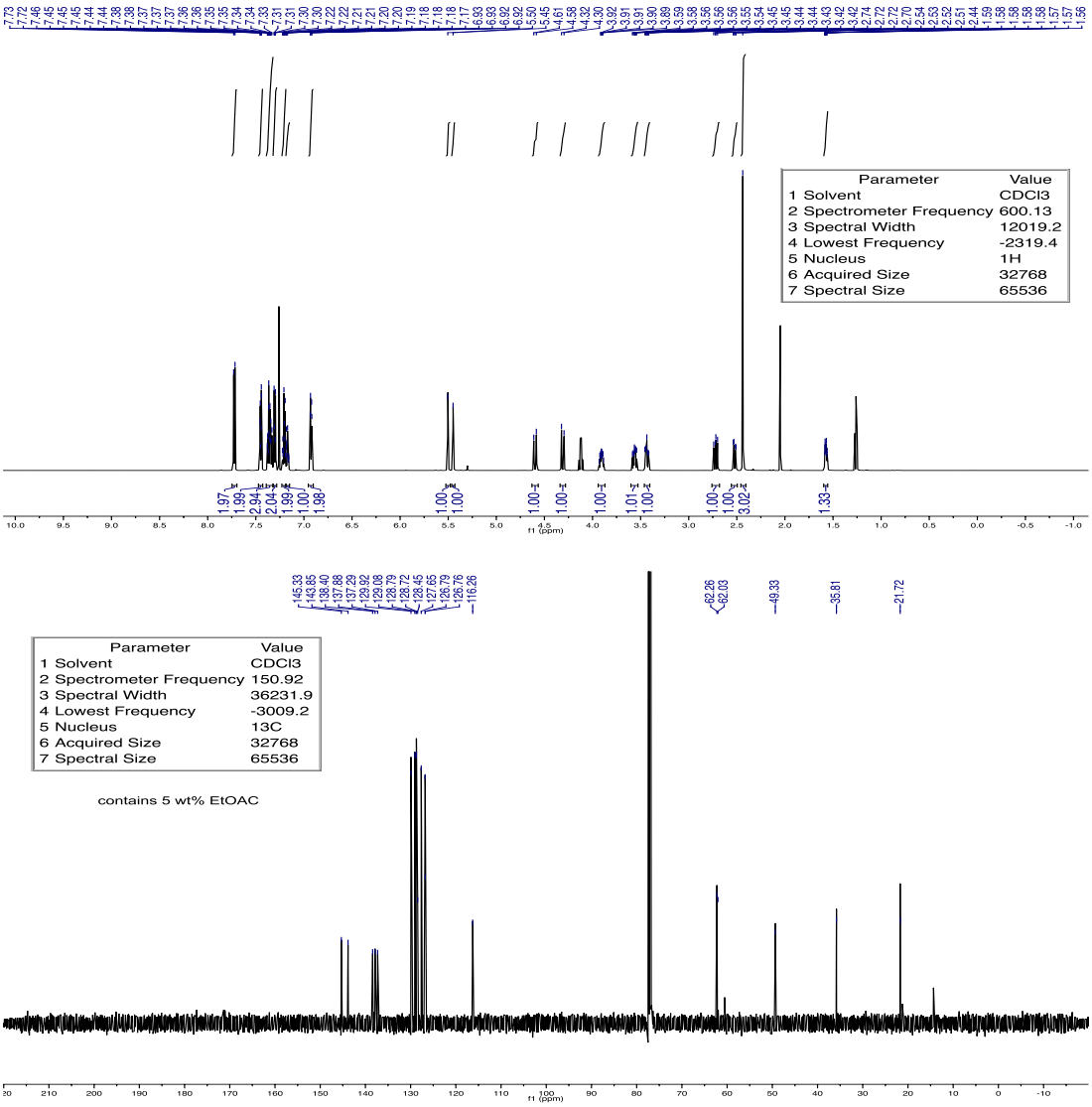
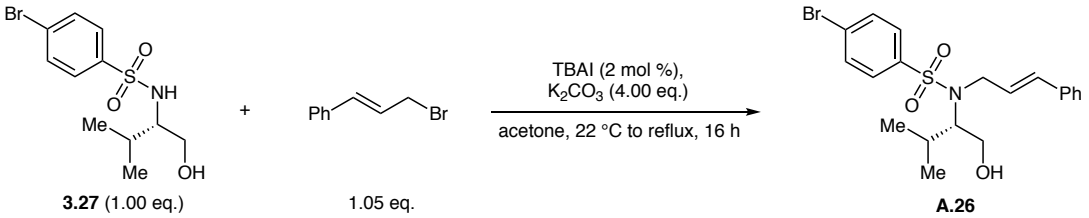


Figure A.10. ^{1}H and ^{13}C{^{1}H} NMR spectra of A.25.

Preparation of *N*-alkylated amino alcohol A.26:



To a flame-dried 50 mL round-bottom flask equipped with a magnetic stir bar was added aryl sulfonamide **3.27** (2.33 mmol, 750 mg, 1.00 eq.), tetrabutylammonium iodide

(0.047 mmol, 17 mg, 0.02 eq.), and powdered, anhydrous potassium carbonate (9.31 mmol, 1.29 g, 4.00 eq.). The flask was capped with a septum, an N_2 needle was inserted, and the headspace of the flask was purged with anhydrous N_2. Anhydrous acetone (17.5 mL) was added to dissolve the substrate, followed by cinnamyl bromide (2.44 mmol, 362 μL, 1.05 eq.). The flask was sealed, placed in an oil bath, and heated to reflux (approximately 55-60 °C oil bath temperature). The heterogeneous mixture was vigorously stirred for 16 h and then cooled to room temperature. The mixture was filtered through a cotton plug to remove potassium salts and then concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (3:1 hexanes:ethyl acetate; $R_f = 0.3$) to yield the alkylated amino alcohol product **A.26** as a colorless, viscous oil in 91% yield (925 mg).

(S)-4-bromo-N-cinnamyl-N-(1-hydroxy-3-methylbutan-2-yl)benzenesulfonamide (A.26). **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 7.72 (d, 2H, *J* = 8.6 Hz), 7.57 (d, 2H, *J* = 8.6 Hz), 7.34-7.30 (m, 2H), 7.29-7.24 (m, 3H), 6.52 (d, 1H, *J* = 15.9 Hz), 6.13 (dt, 1H, *J* = 15.9, 6.8 Hz), 4.10 (ddd, 1H, *J* = 16.1, 6.9, 1.4 Hz), 3.94 (ddd, 1H, *J* = 16.0, 6.9, 1.4 Hz), 3.80 (ddd, 1H, *J* = 11.6, 5.6, 3.5 Hz), 3.65 (ddd, 1H, *J* = 11.6, 8.8, 5.4 Hz), 3.59 (ddd, 1H, *J* = 10.1, 8.6, 3.6 Hz), 1.93-1.82 (m, 1H), 1.76 (t, 1H, *J* = 5.7 Hz), 0.94 (d, 3H, *J* = 6.6 Hz), 0.79 (d, 3H, *J* = 6.7 Hz); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 140.5, 136.2, 133.4, 132.2, 129.2, 128.8, 128.1, 127.4, 126.6, 126.1, 66.8, 62.2, 46.8, 28.2, 20.9, 20.3.

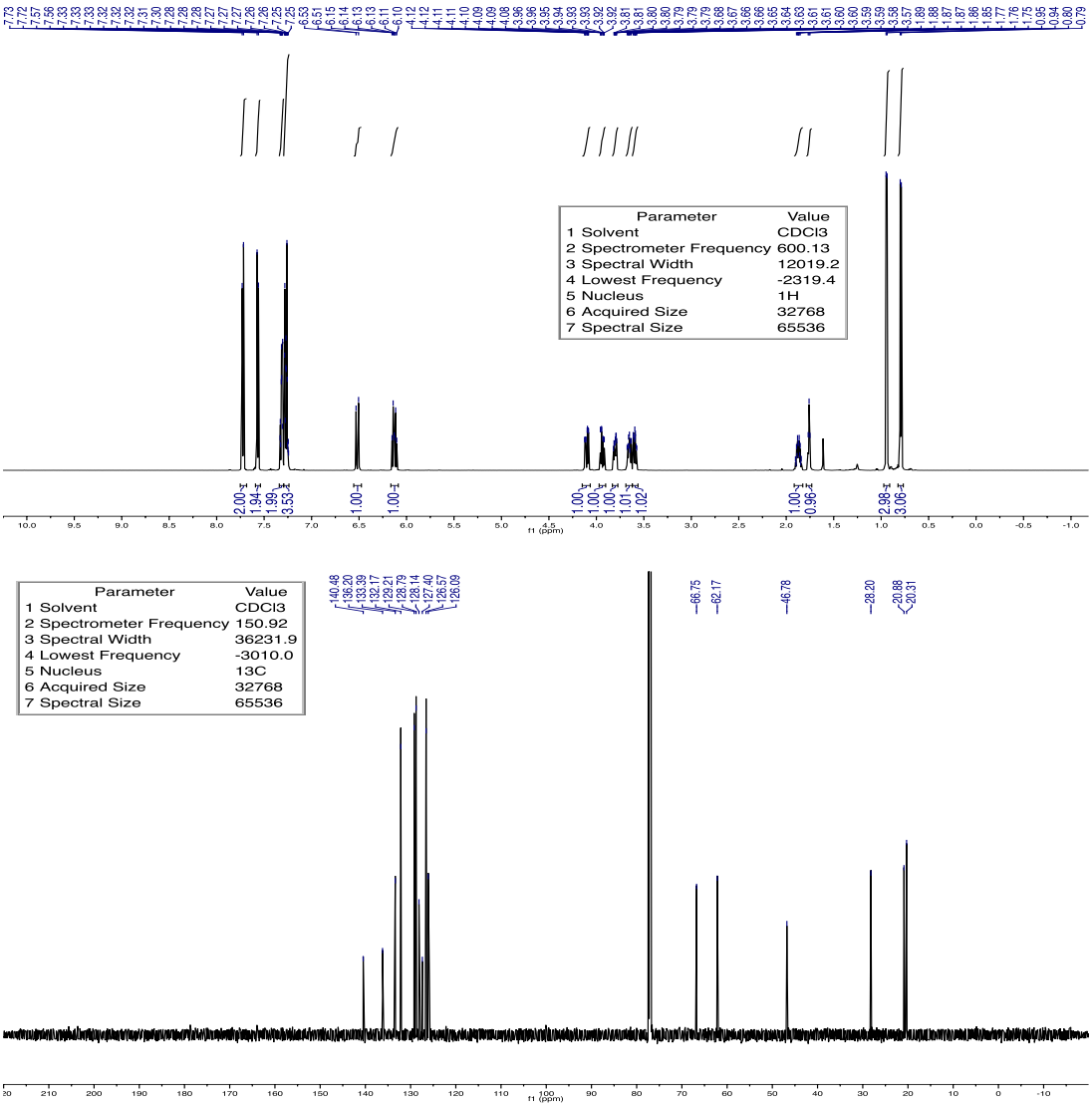
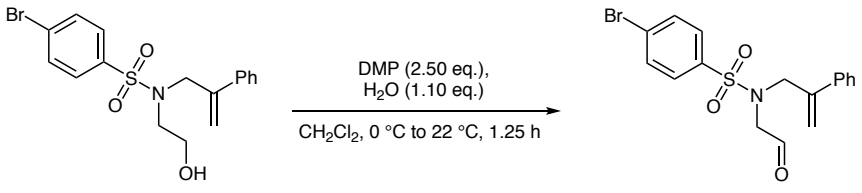


Figure A.11. ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of A.26.

A.5.3 Synthesis of amino aldehydes

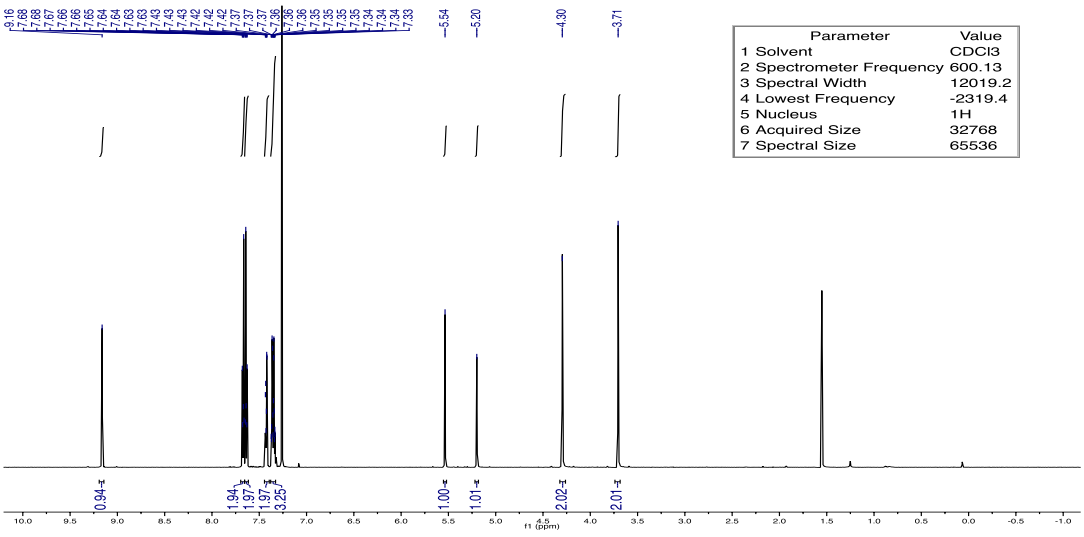
Preparation of amino aldehyde A.27:



A.21 **A.27**

Following general procedure 3.1 (section 3.7.2.4 above), *N*-alkylated amino alcohol **A.26** (1.01 mmol, 400 mg, 1.00 eq.) was oxidized with DMP (2.50 eq.) over 1.25 h. The crude residue was purified by silica gel chromatography (3:1 hexanes:ethyl acetate; $R_f = 0.4$) to yield the amino aldehyde product **A.27** as a white, crystalline solid in 68% yield (270 mg).

4-bromo-N-(2-oxoethyl)-N-(2-phenylallyl)benzenesulfonamide (A.27). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 9.16 (s, 1H), 7.67 (d, 2H, *J* = 8.6 Hz), 7.64 (d, 2H, *J* = 8.6 Hz), 7.43 (dd, 2H, *J* = 8.0, 1.7 Hz), 7.38-7.32 (m, 3H), 5.54 (s, 1H), 5.20 (s, 1H), 4.30 (s, 2H), 3.71 (s, 2H); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 197.8, 141.8, 137.0, 137.0, 132.7, 129.1, 128.9, 128.8, 128.4, 126.6, 118.5, 55.4, 53.2.



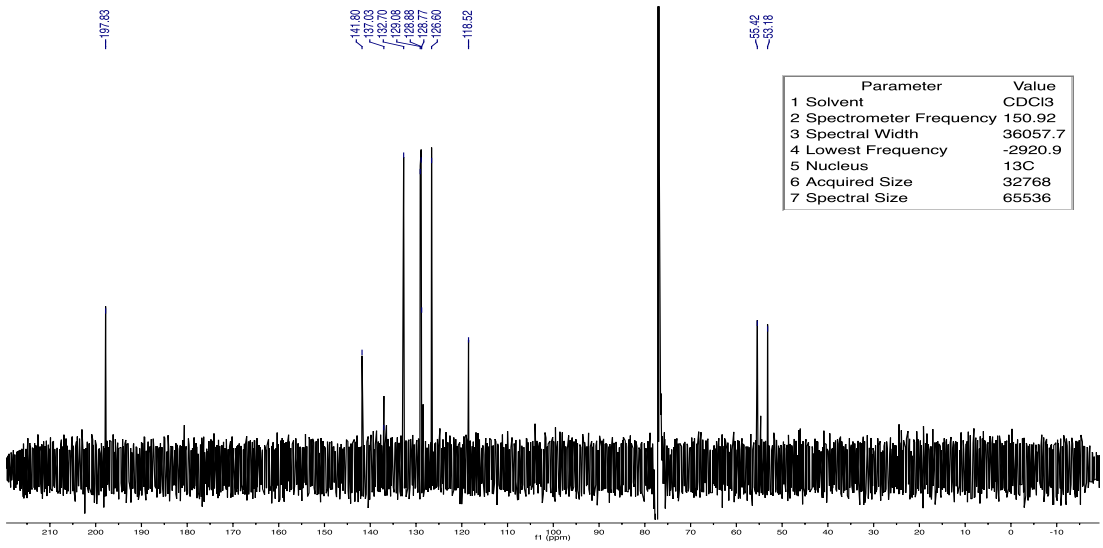
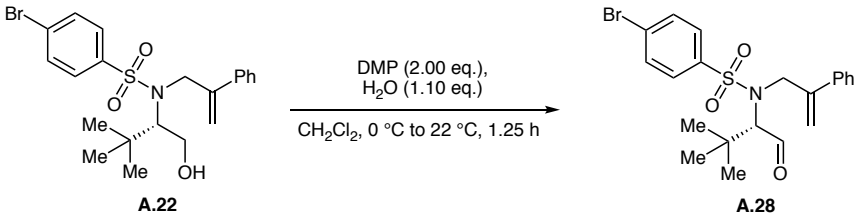


Figure A.12. ^{1}H and ^{13}C{^{1}H} NMR spectra of A.27.

Preparation of amino aldehyde A.28:



A.22 **A.28**

Following general procedure 3.1 (section 3.7.2.4 above), *N*-alkylated amino alcohol **A.22** (1.00 mmol, 452 mg, 1.00 eq.) was oxidized with DMP (2.00 eq.) over 1.25 h. The crude residue was purified by silica gel chromatography (5:1 hexanes:ethyl acetate; $R_f = 0.4$) to yield the amino aldehyde product **A.28** as a colorless, viscous oil in 92% yield (415 mg).

(S)-4-bromo-N-(3,3-dimethyl-1-oxobutan-2-yl)-N-(2-phenylallyl)benzenesulfonamide (A.28). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 9.50 (s, 1H), 7.66 (d, 2H, J = 8.6 Hz), 7.62 (d, 2H, J = 8.6 Hz), 7.31-7.28 (m, 3H), 7.22-7.18 (m, 2H), 5.59 (s, 1H), 5.55 (s, 1H), 4.52 (dt, 1H, J = 17.9, 1.9 Hz), 4.14 (s, 1H), 4.01 (d, 1H, J = 17.9 Hz), 1.21 (s, 9H); **^{13}C{^{1}H} NMR** ($CDCl_3$,

151 MHz): δ 198.6, 143.5, 139.4, 138.1, 132.4, 129.5, 128.6, 128.5, 128.2, 126.3, 116.9, 75.1, 52.6, 36.4, 28.4; $[\alpha]_D^{25}$ = –18.4° (c = 0.675, CH_2Cl_2, l = 100 mm).

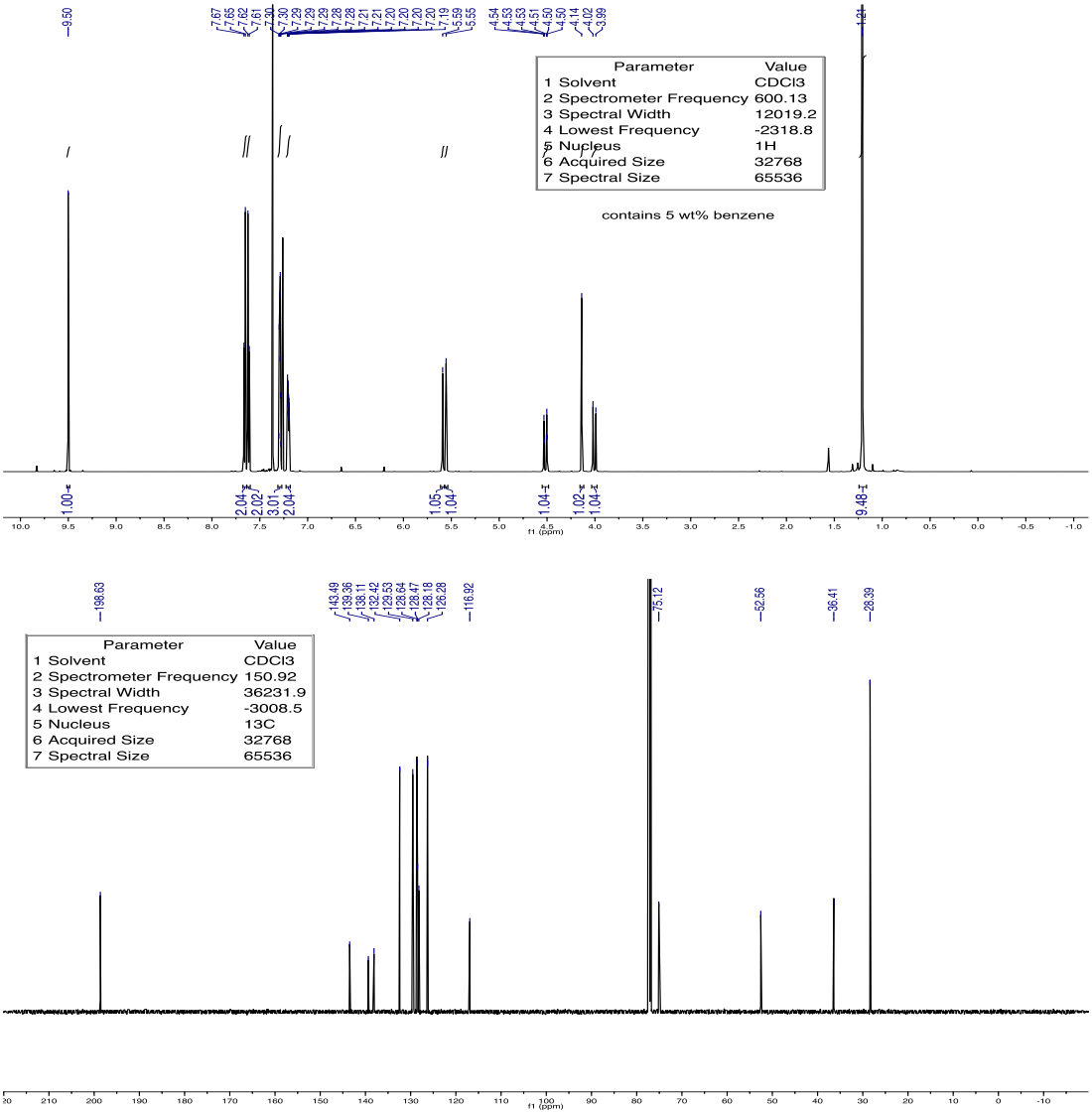
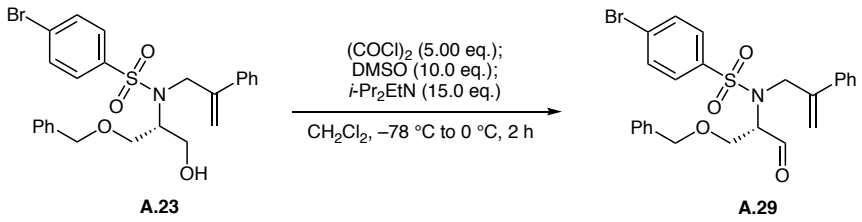


Figure A.13. ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of A.28.

Preparation of amino aldehyde A.29:



A.23 **A.29**

To a flame-dried, N_2-filled, 25 mL round-bottom flask equipped with a magnetic stir bar and rubber septum were added anhydrous CH_2Cl_2 (1.0 mL) and oxalyl chloride (2.91 mmol, 249 μL, 5.00 eq.). The solution was cooled to –78 °C in an acetone/$CO_{2(s)}$ bath. A solution of dimethylsulfoxide (DMSO; 5.81 mmol, 416 μL, 10.0 eq.) in CH_2Cl_2 (1.0 mL) was added dropwise and the resulting solution stirred for 15 minutes at –78 ° C. Then a solution of the *N*-alkylated amino alcohol **A.23** (0.581 mmol, 300 mg, 1.00 eq.) in CH_2Cl_2 (1.0 mL) was slowly added dropwise and the resulting solution stirred for an additional 30 minutes at –78 °C. Finally, Hünig's base (*i*-Pr_2EtN; 8.72 mmol, 1.52 mL, 15.0 eq.) was slowly added dropwise. The resulting solution was stirred at –78 °C for 1 h and then warmed to 0 °C in an ice bath and stirred for an addition 1 h. The solution was poured into ice-cold 1 M $HCl_{(aq.)}$ and extracted with CH_2Cl_2 (x4). The combined organic layers were washed with pH 7.0 phosphate buffer (x4), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (3:1 hexanes:ethyl acetate; $R_f = 0.4$) to yield the amino aldehyde product **A.29** as a viscous, yellow oil in 93% yield (278 mg).

(*S*)-*N*-(1-(benzyloxy)-3-oxopropan-2-yl)-4-bromo-*N*-(2-phenylallyl)benzenesulfonamide (A.29). **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 9.09 (s, 1H), 7.68 (d, 2H, *J* = 8.0 Hz), 7.56 (d, 2H, *J* = 8.3 Hz), 7.39-7.35 (m, 2H), 7.35-7.30 (m, 6H), 7.10-7.06 (m, 2H), 5.48 (s, 1H), 5.20 (s, 1H), 4.46-4.36 (m, 2H), 4.32-4.25 (m, 2H), 4.11 (d, 1H, *J* = 11.4 Hz), 3.90 (dd, 1H, *J* = 10.5, 4.9 Hz), 3.72 (dd, 1H, *J* = 10.4, 8.9 Hz); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 197.8, 143.0,

138.8, 137.4, 137.2, 132.3, 129.3, 128.8, 128.6, 128.5, 128.1, 128.0, 127.8, 126.8, 118.5, 73.4, 66.5, 65.2, 51.9; $[\alpha]_D^{25} = -2.48°$ (c = 0.730, CH_2Cl_2, l = 100 mm).

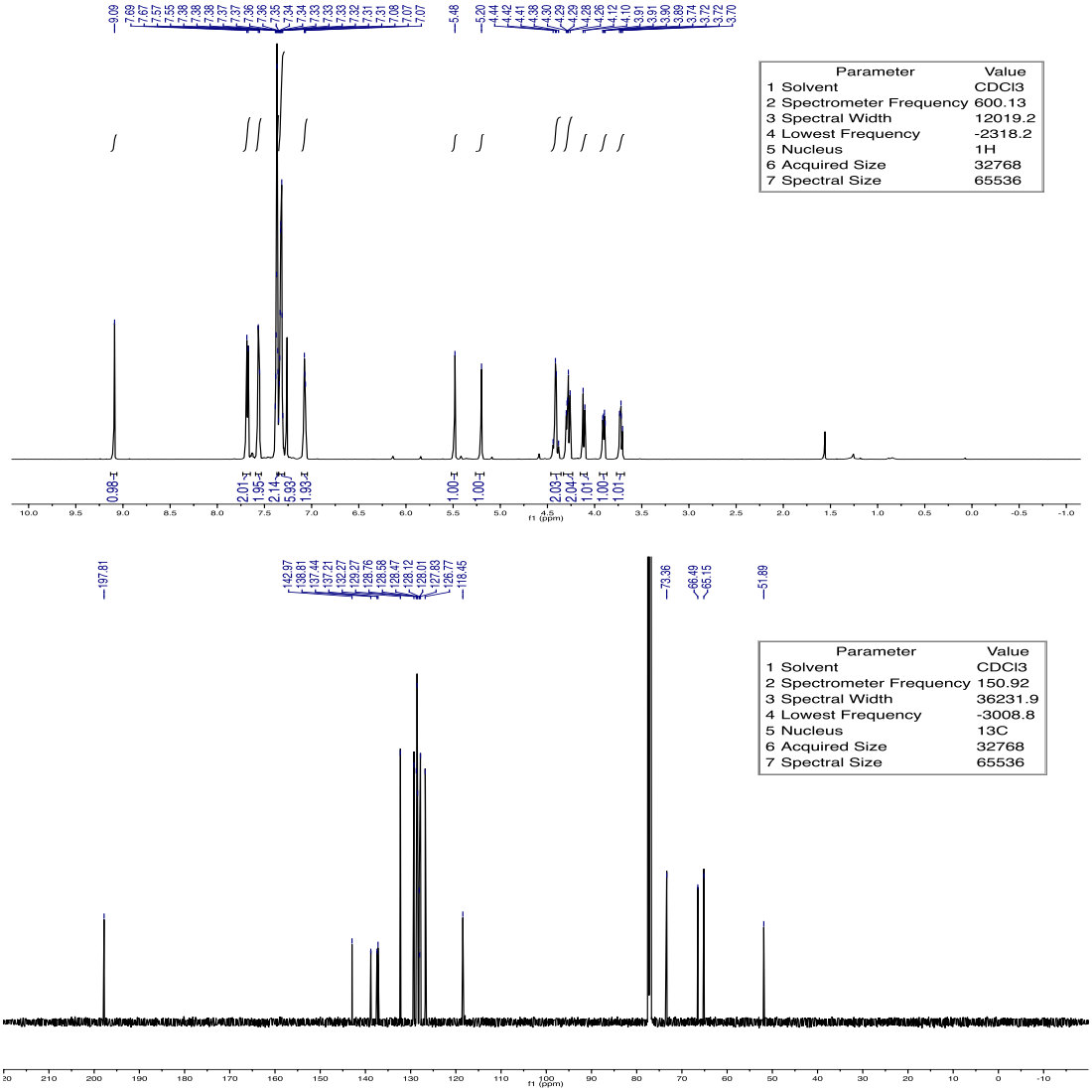
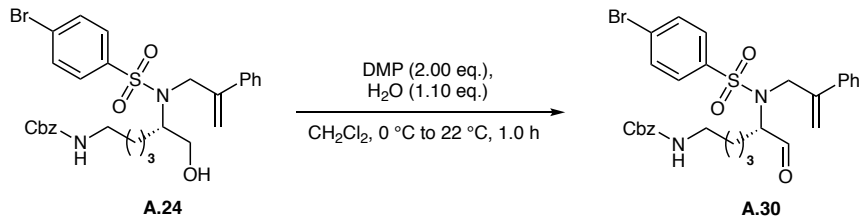


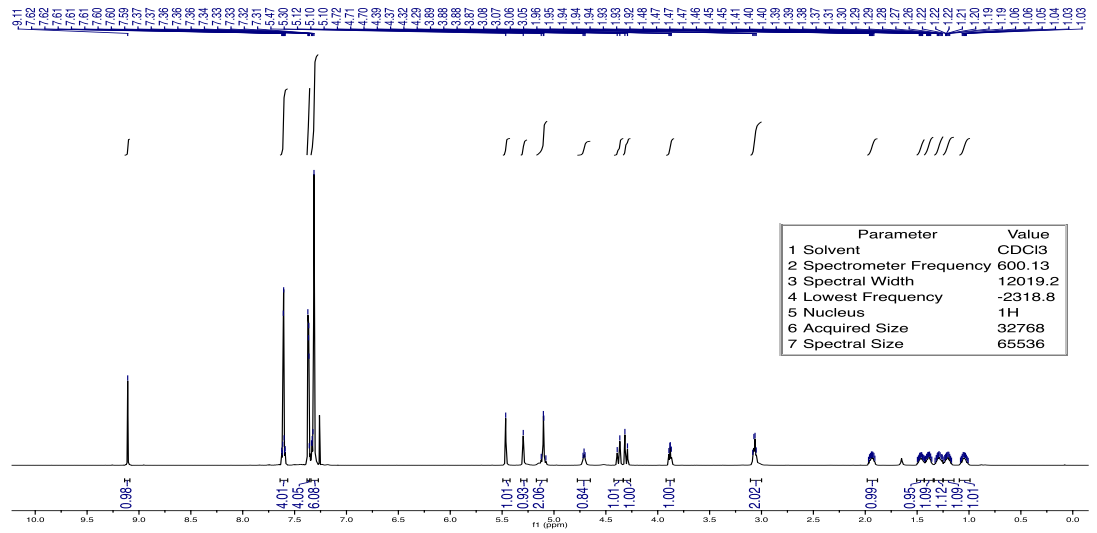
Figure A.14. ^{1}H and ^{13}C{^{1}H} NMR spectra of A.29.

Preparation of amino aldehyde A.30:



Following general procedure 3.1 (section 3.7.2.4 above), *N*-alkylated amino alcohol **A.24** (0.866 mmol, 521 mg, 1.00 eq.) was oxidized with DMP (2.00 eq.) over 1.0 h. The crude residue was purified by silica gel chromatography (2:1 hexanes:ethyl acetate; $R_f = 0.3$) to yield the amino aldehyde product **A.30** as a light yellow, amorphous solid in 62% yield (320 mg).

benzyl (*S*)-(5-((4-bromo-*N*-(2-phenylallyl)phenyl)sulfonamido)-6-oxohexyl)carbamate (A.30). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 9.11 (s, 1H), 7.63-7.58 (m, 4H), 7.39-7.35 (m, 4H), 7.31 (s, 6H), 5.47 (s, 1H), 5.30 (s, 1H), 5.10 (d, 2H, *J* = 2.3 Hz), 4.74-4.68 (m, 1H), 4.38 (d, 1H, *J* = 15.0 Hz), 4.30 (d, 1H, *J* = 15.0 Hz), 3.88 (dd, 1H, *J* = 8.0, 6.0 Hz), 3.07 (q, 2H, *J* = 6.7 Hz), 1.94 (ddt, 1H, *J* = 14.2, 11.3, 5.7 Hz), 1.47 (tdd, 1H, *J* = 13.7, 9.3, 5.2 Hz), 1.39 (dq, 1H, *J* = 16.9, 6.6 Hz), 1.29 (ddt, 1H, *J* = 19.0, 12.5, 6.4 Hz), 1.21 (ddt, 1H, *J* = 20.4, 10.2, 5.2 Hz), 1.05 (dtd, 1H, *J* = 20.9, 10.4, 5.1 Hz); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 199.0, 156.5, 142.9, 138.9, 137.5, 136.7, 132.6, 129.1, 128.8, 128.7, 128.6, 128.3, 128.3, 128.2, 126.8, 119.1, 66.8, 65.8, 51.0, 40.6, 29.8, 26.7, 23.9; **^{13}C NMR DEPT135** ($CDCl_3$, 151 MHz): δ 132.6 (CH), 129.1 (CH), 128.8 (CH), 128.7 (CH), 128.6 (CH), 128.3 (CH), 128.3 (CH), 126.8 (CH), 119.1 (CH_2), 66.8 (CH_2), 65.8 (CH), 51.0 (CH_2), 40.6 (CH_2), 29.8 (CH_2), 26.7 (CH_2), 23.9 (CH_2); **$[\alpha]_D^{25}$** = –2.12° (c = 1.38, CH_2Cl_2, l = 100 mm).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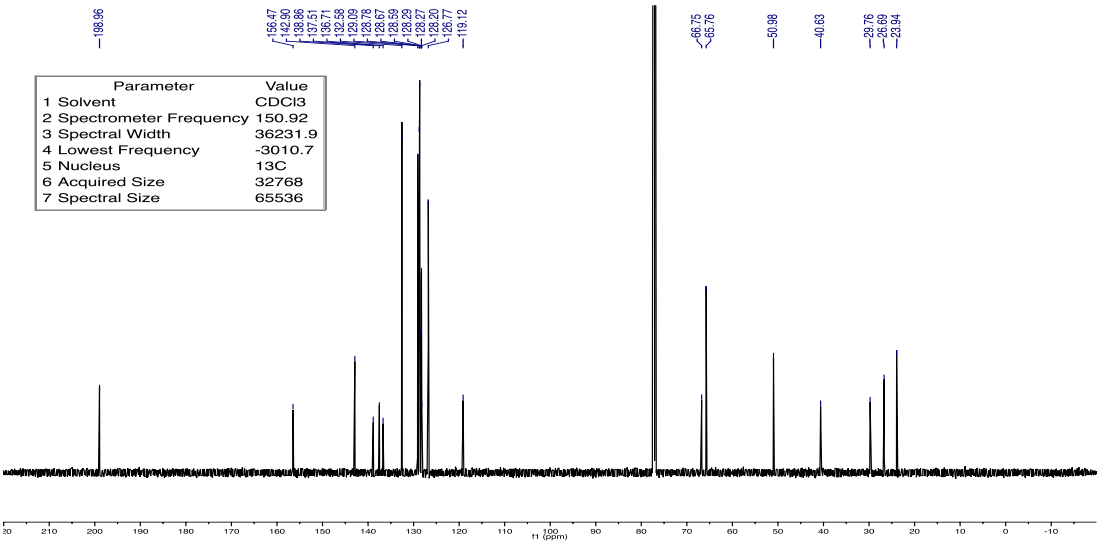
2 Spectrometer Frequency 600.13
3 Spectral Width 12019.2
4 Lowest Frequency -2318.8
5 Nucleus 1H
6 Acquired Size 32768
7 Spectral Size 65536
f1 (ppm)


Parameter Value
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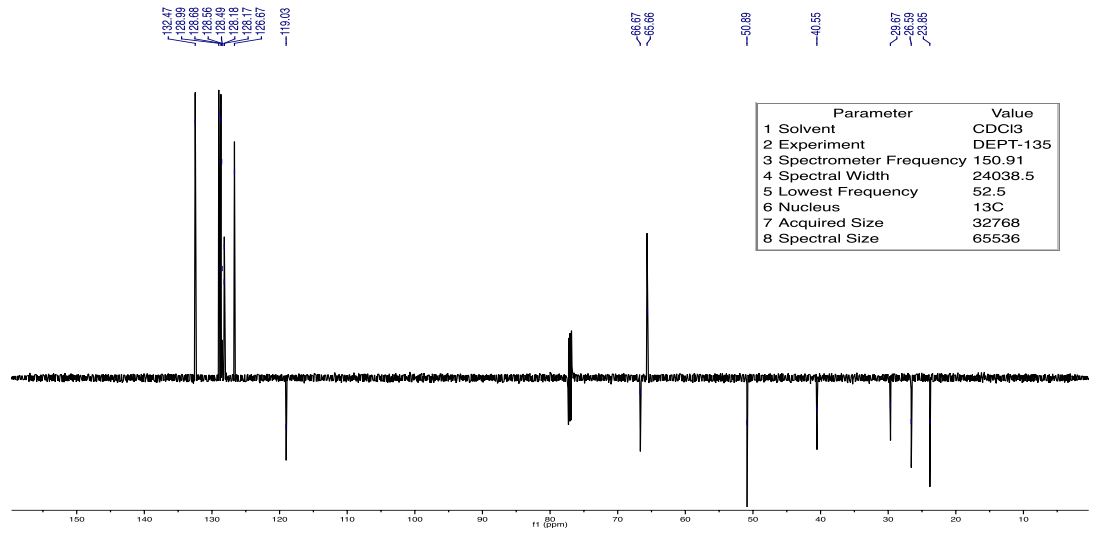
3 Spectral Width 36231.9
4 Lowest Frequency -3010.7
5 Nucleus 13C
6 Acquired Size 32768
7 Spectral Size 65536
f1 (ppm)


Parameter Value
1 Solvent CDCl3
2 Experiment DEPT-135
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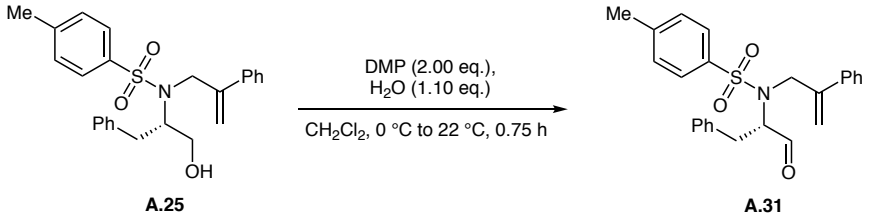
4 Spectral Width 24038.5
5 Lowest Frequency 52.5
6 Nucleus 13C
7 Acquired Size 32768
8 Spectral Size 65536
f1 (ppm)

Figure A.15. ^{1}H, $^{13}C\{^{1}H\}$, and ^{13}C DEPT-135 NMR spectra of A.30.

Preparation of amino aldehyde A.31:



A.25 **A.31**

Following general procedure 3.1 (section 3.7.2.4 above), *N*-alkylated amino alcohol **A.25** (1.19 mmol, 500 mg, 1.00 eq.) was oxidized with DMP (2.00 eq.) over 0.75 h. The crude residue was purified by silica gel chromatography (4:1 hexanes:ethyl acetate; $R_f = 0.4$) to yield the amino aldehyde product **A.31** as a clear, colorless, viscous oil in 86% yield (427 mg).

(*S*)-4-methyl-*N*-(1-oxo-3-phenylpropan-2-yl)-*N*-(2-phenylallyl)benzenesulfonamide (A.31). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 9.12 (s, 1H), 7.68 (d, 2H, *J* = 8.3 Hz), 7.31 (d, 2H, *J* = 8.1 Hz), 7.29-7.24 (m, 3H), 7.21-7.17 (m, 5H), 6.97-6.94 (m, 2H), 5.39 (s, 1H), 4.95 (s, 1H), 4.40 (d, 1H, *J* = 14.7 Hz), 4.02 (dd, 1H, *J* = 7.9, 5.5 Hz), 3.83 (d, 1H, *J* = 14.7), 3.39 (dd, 1H, *J* = 14.5, 5.5 Hz), 2.80 (dd, 1H, *J* = 14.4, 7.9 Hz), 2.48 (s, 3H); **$^{13}C\{^{1}H\}$ NMR** ($CDCl_3$, 151 MHz): δ 197.9, 144.2, 142.8, 138.0, 137.4, 136.8, 130.0, 129.3, 128.7, 128.6, 128.5, 128.0, 126.8, 126.7, 118.8, 67.3, 51.5, 33.4, 21.8; **$[\alpha]_D^{26}$** = –118.0° (c = 0.570, CH_2Cl_2, l = 100 mm).

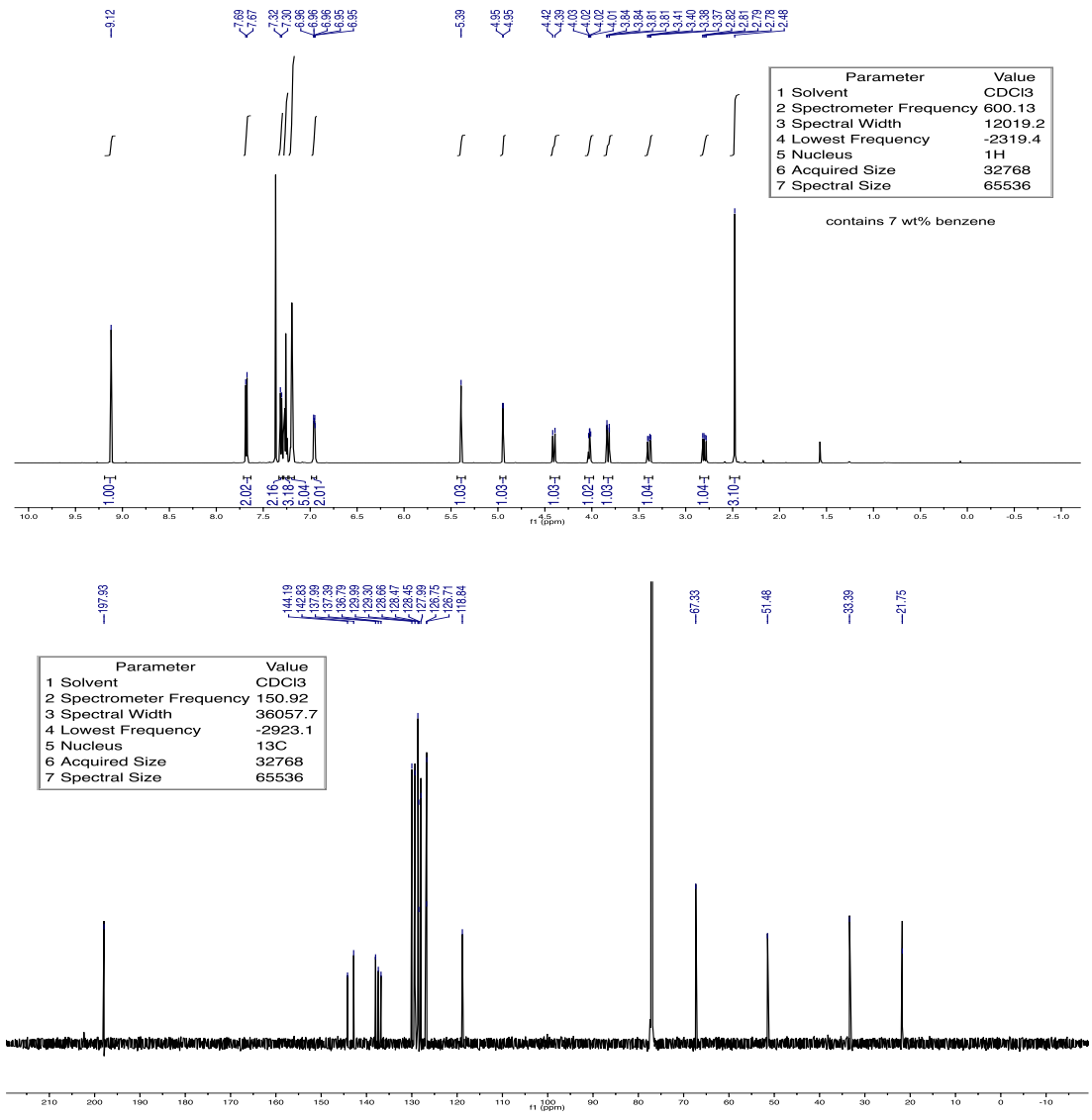
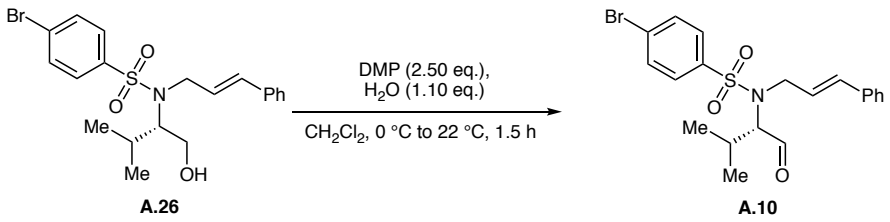


Figure A.16. ^{1}H and ^{13}C{^{1}H} NMR spectra of A.31.

Preparation of amino aldehyde A.10:

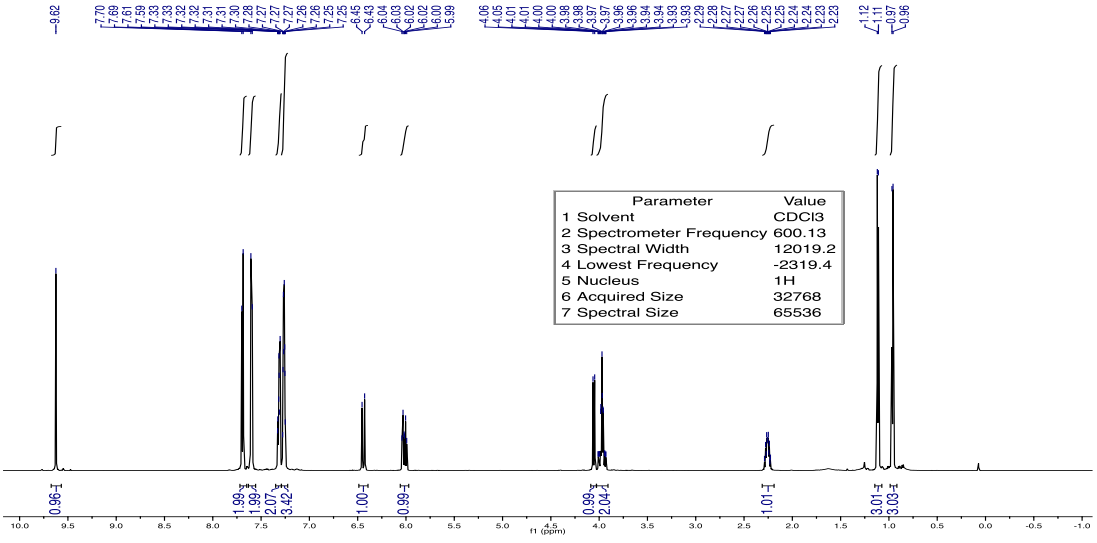


A.26 **A.10**

Following general procedure 3.1 (section 3.7.2.4 above), *N*-alkylated amino alcohol **A.26** (0.969 mmol, 425 mg, 1.00 eq.) was oxidized with DMP (2.50 eq.) over 1.5 h. The crude residue was purified by silica gel chromatography (4:1 hexanes:ethyl acetate; $R_f = 0.4$) to yield the amino aldehyde product **A.10** as a colorless, viscous oil in 86% yield (362 mg).

(S)-4-bromo-N-cinnamyl-N-(3-methyl-1-oxobutan-2-yl)benzenesulfonamide (A.10).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 9.62 (s, 1H), 7.69 (d, 2H, J = 8.6 Hz), 7.60 (d, 2H, J = 8.6 Hz), 7.34-7.29 (m, 2H), 7.28-7.24 (m, 3H), 6.44 (d, 1H, J = 15.8 Hz), 6.02 (dt, 1H, J = 15.9, 7.0 Hz), 4.05 (d, 1H, J = 10.3 Hz), 4.02-3.92 (m, 2H), 2.30-2.21 (m, 1H), 1.11 (d, 3H, J = 6.5 Hz), 0.96 (d, 3H, J = 6.7 Hz); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 198.7, 139.8, 135.9, 134.6, 132.4, 129.1, 128.8, 128.3, 127.9, 126.6, 124.8, 71.7, 48.7, 27.3, 20.4, 20.3; **$[\alpha]_D^{24}$** = –2.75° (c = 1.11, CH_2Cl_2, l = 100 mm).



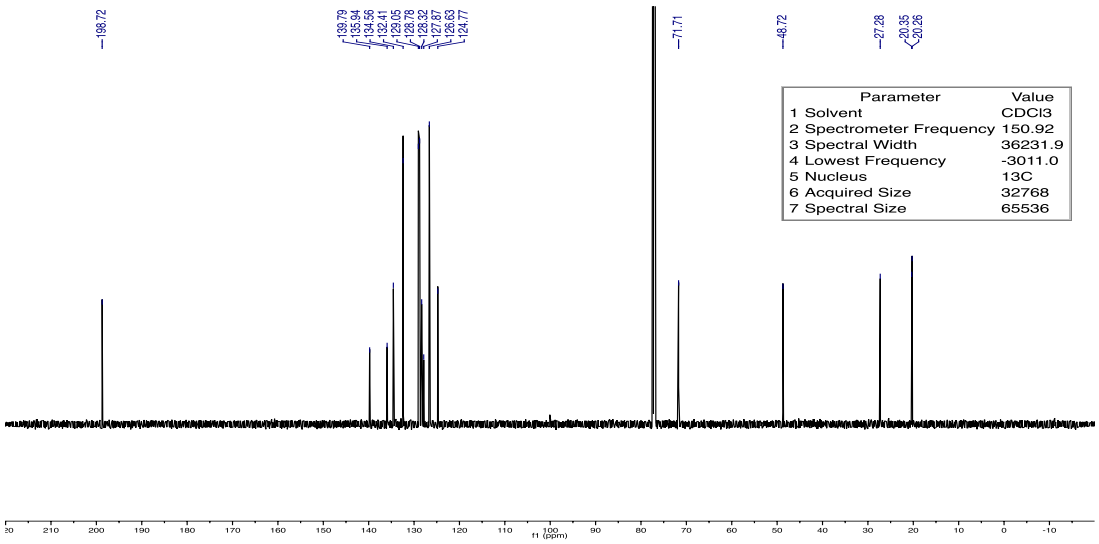
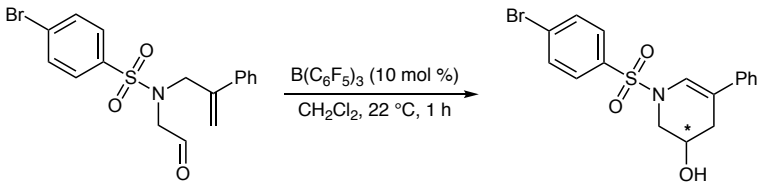


Figure A.17. ^{1}H and ^{13}C{^{1}H} NMR spectra of A.10.

A.5.4 BCF-catalyzed *Prins* cyclizations (carbonyl-ene reactions)

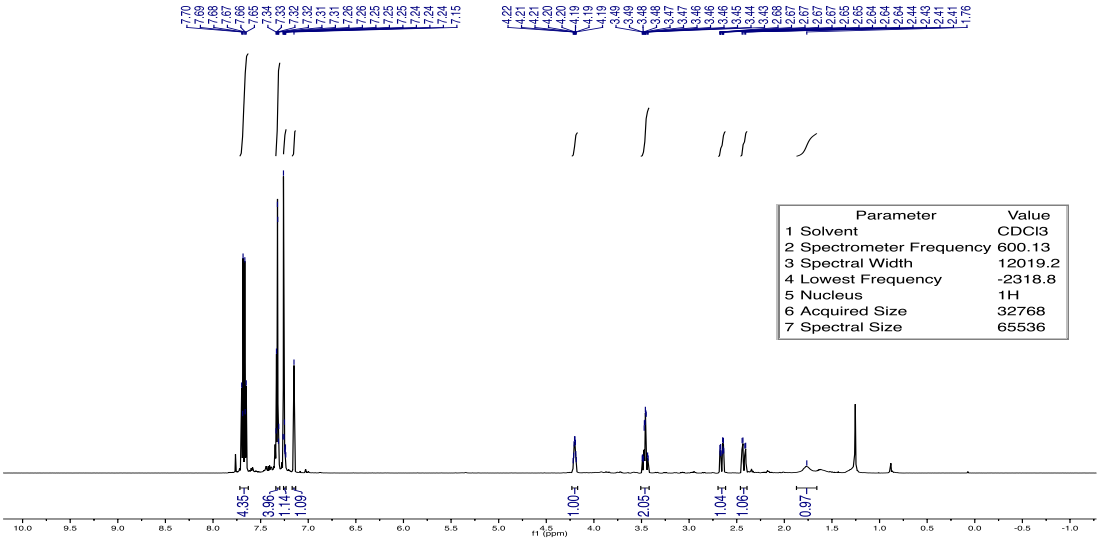
Preparation of tetrahydropyridine A.1



A.27 **A.1**

In a dry, N_2-filled glove box, amino aldehyde **A.27** (0.0500 mmol, 19.7 mg) and $B(C_6F_5)_3$ (BCF, 0.0050 mmol, 2.6 mg) were weighed into a screw cap 1 dram vial equipped with a magnetic stir bar. CH_2Cl_2 (1.00 mL, 0.05 M) was added and the vial was sealed with a septum cap and removed from the glove box. The solution was stirred at 22 °C for 1 h, after which time the catalyst was quenched with 50 µL of Et_3N and the solvent was removed *in vacuo*. The crude residue was purified by silica gel chromatography (2:1 *n*-pentane:ethyl acetate; R_f = 0.3) to yield the tetrahydropyridine product **A.1** as a colorless, viscous oil in 67% yield (13.2 mg).

1-((4-bromophenyl)sulfonyl)-5-phenyl-1,2,3,4-tetrahydropyridin-3-ol (A.1). **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 7.71-7.64 (m, 4H), 7.36-7.30 (m, 4H), 7.27-7.23 (m, 1H), 4.22-4.18 (m, 1H), 3.50-3.42 (m, 2H), 2.69-2.63 (m, 1H), 2.42 (dd, 1H, J = 17.1, 5.2 Hz), 1.76 (s, br, 1H); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 138.8, 137.0, 132.8, 128.8, 128.7, 128.4, 127.3, 124.8, 121.2, 116.8, 63.1, 48.8, 32.9; **^{13}C NMR DEPT135** ($CDCl_3$, 151 MHz): δ 132.8 (CH), 128.8 (CH), 128.7 (CH), 127.3 (CH), 124.8 (CH), 121.2 (CH), 63.1 (CH), 48.8 (CH_2), 32.9 (CH_2); **IR** (ν/cm^{-1}): 3525 (s, br, OH), 3086 (w), 3058 (w), 3031 (w), 2924 (m), 2850 (w), 1639 (m), 1598 (w), 1574 (m), 1496 (w), 1471 (w), 1446 (w), 1389 (m), 1351 (s), 1265 (w), 1218 (w), 1168 (s), 1089 (m), 1068 (m), 1049 (w), 1026 (w), 1008 (w); **HRMS**-(ESI^{+}) $[M+H]^{+}$ calcd for $C_{17}H_{17}NO_3SBr^{+}$ 394.0112, found: 394.0108.



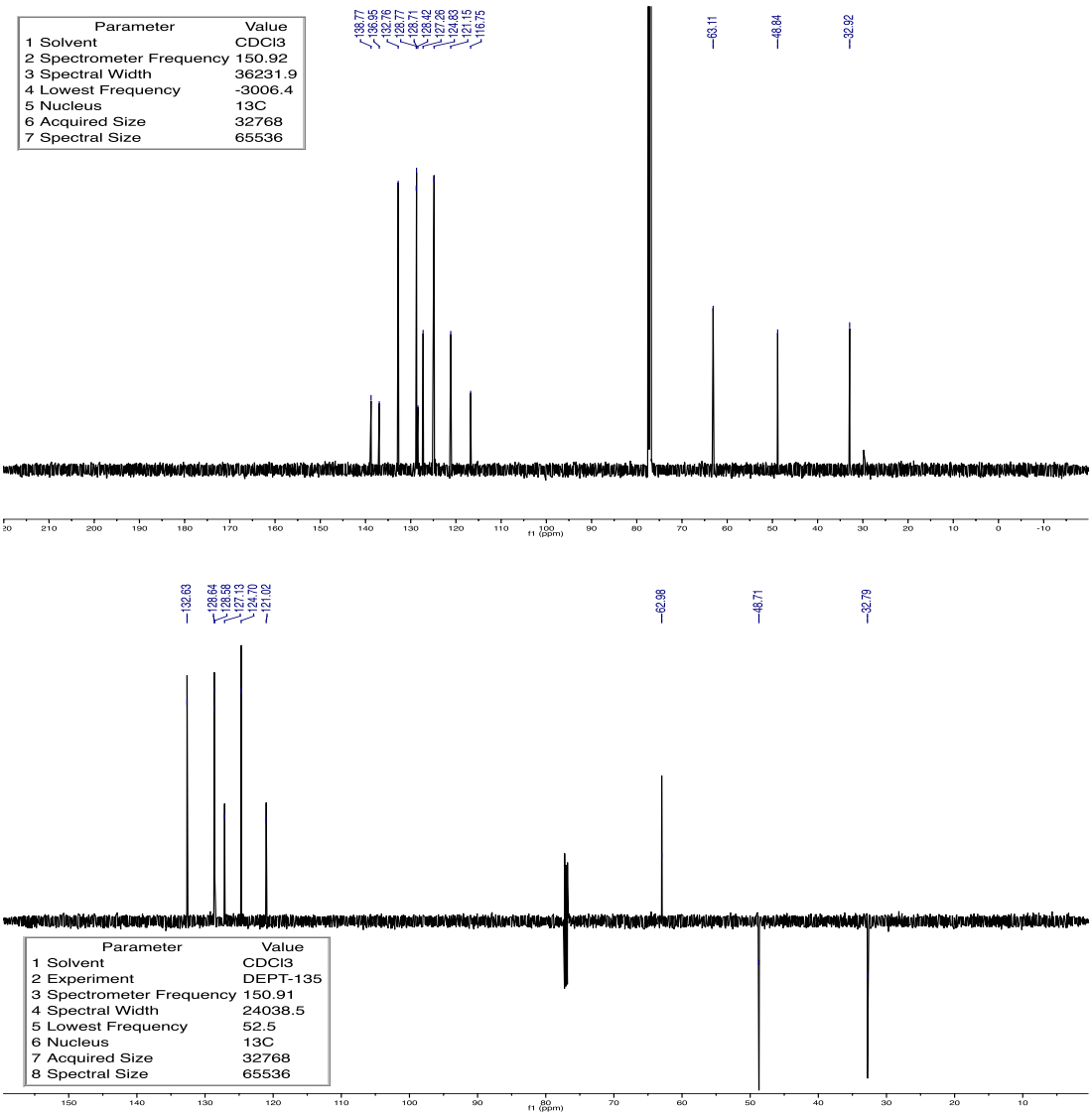


Figure A.18. ^{1}H, $^{13}C\{^{1}H\}$, and ^{13}C DEPT-135 NMR spectra of A.1.

Preparation of *trans*-tetrahydropyridine A.2

3.10 **A.2**

In a dry, N_2-filled glove box, amino aldehyde **3.10** (0.0500 mmol, 20.4 mg) and $B(C_6F_5)_3$ (BCF, 0.0050 mmol, 2.6 mg) were weighed into a screw cap 1 dram vial equipped with a magnetic stir bar. CH_2Cl_2 (1.00 mL, 0.05 M) was added and the vial was sealed with a septum cap and removed from the glove box. The solution was stirred at 22 °C for 1 h, after which time the catalyst was quenched with 50 μL of Et_3N and the solvent was removed *in vacuo*. The crude residue was purified by silica gel chromatography (3:1 *n*-pentane:ethyl acetate; $R_f = 0.3$) to yield the tetrahydropyridine product **A.2** as a white, crystalline solid in 85% yield (17.3 mg) and 91:9 *trans:cis* d.r..

(2S,3R)-1-((4-bromophenyl)sulfonyl)-2-methyl-5-phenyl-1,2,3,4-tetrahydropyridin-3-ol (A.2). **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 7.73 (d, 2H, *J* = 8.6 Hz), 7.62 (d, 2H, *J* = 8.6 Hz), 7.38-7.32 (m, 4H), 7.27-7.23 (m, 1H), 7.20 (s, 1H), 4.11-4.05 (m, 1H), 3.99-3.95 (m, 1H), 2.58 (ddd, 1H, *J* = 18.0, 4.2, 2.1 Hz), 2.48 (d, 1H, *J* = 18.3 Hz), 1.19 (d, 3H, *J* = 6.8 Hz), 1.10 (s, br, 1H); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 138.8, 138.6, 132.5, 128.8, 128.6, 128.1, 127.1, 124.7, 119.5, 114.2, 66.3, 54.8, 28.3, 18.1; **^{13}C NMR DEPT135** ($CDCl_3$, 151 MHz): δ 132.5 (CH), 128.8 (CH), 128.6 (CH), 127.1 (CH), 124.7 (CH), 119.5 (CH), 66.3 (CH), 54.8 (CH), 28.3 (CH_2), 18.1 (CH_3); **IR** (ν/cm^{-1}): 3545 (s, br, OH), 3086 (w), 3058 (w), 3032 (w), 2979 (w), 2919 (m), 2849 (w), 1639 (m), 1598 (w), 1574 (m), 1496 (w), 1471 (w), 1446 (w), 1389 (m), 1350 (s), 1266 (m), 1202 (w), 1166 (s), 1118 (m), 1090 (m), 1067 (m), 1028 (w), 1003 (s); **HRMS**-(ESI$^+$) $[M+H]^+$ calcd for $C_{18}H_{19}NO_3SBr^+$ 408.0269, found: 408.0263; **$[\alpha]_D^{26}$** = –11.6° (c = 0.865, CH_2Cl_2, l = 100 mm).

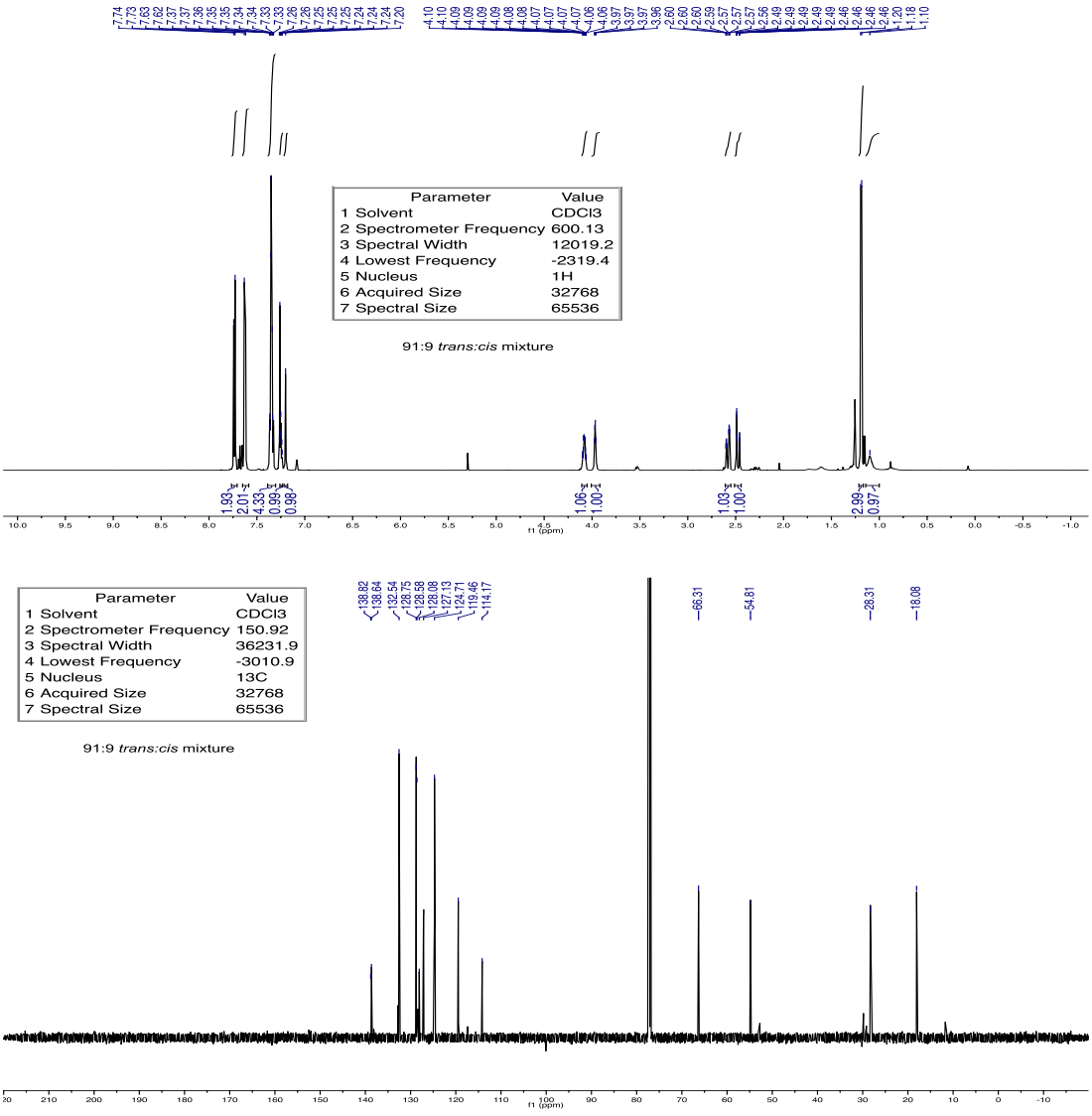


Figure A.19. ^{1}H and ^{13}C{^{1}H} spectra of *trans*-A.2.

Preparation of tetrahydropyridine A.3

3.38 **A.3**

In a dry, N_2-filled glove box, amino aldehyde **3.38** (0.0500 mmol, 21.8 mg) and $B(C_6F_5)_3$ (BCF, 0.0050 mmol, 2.6 mg) were weighed into a screw cap 1 dram vial equipped with a magnetic stir bar. CH_2Cl_2 (1.00 mL, 0.05 M) was added and the vial was sealed with a septum cap. The solution was stirred at 22 °C for 1 h, after which time the catalyst was quenched with 50 μL of Et_3N and the solvent was removed *in vacuo*. The crude residue was purified by silica gel chromatography (5:1 *n*-pentane:ethyl acetate; $R_f = 0.3$) to yield the tetrahydropyridine product **A.3** as a white, crystalline solid in 90% yield (19.6 mg) and >98:2 d.r..

(2S,3R)-1-((4-bromophenyl)sulfonyl)-2-isopropyl-5-phenyl-1,2,3,4-tetrahydropyridin-3-ol (A.3). **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 7.72 (d, 2H, *J* = 8.6 Hz), 7.60 (d, 2H, *J* = 8.6 Hz), 7.34 (d, 4H, *J* = 4.4 Hz), 7.28-7.22 (m, 1H), 7.16 (s, 1H), 4.25 (s, 1H), 3.73 (dd, 1H, *J* = 10.2, 3.0 Hz), 2.54 (ddd, 1H, *J* = 18.6, 4.6, 1.7 Hz), 2.42 (d, 1H, *J* = 18.5 Hz), 1.62 (ddt, 1H, *J* = 13.3, 10.1, 6.7 Hz), 1.13 (d, 3H, *J* = 6.7 Hz), 1.00 (d, 3H, *J* = 6.7 Hz), 0.74 (s, br, 1H); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 138.7, 138.6, 132.3, 128.9, 128.8, 127.9, 127.3, 124.7, 119.8, 117.2, 65.3, 63.6, 29.7, 29.1, 20.8, 19.2; **IR** (ν/cm^{-1}): 3542 (s, br, OH), 3085 (w), 3058 (w), 3027 (w), 2966 (m), 2928 (m), 2874 (w), 2850 (w), 1638 (m), 1598 (w), 1574 (m), 1496 (w), 1471 (m), 1446 (w), 1389 (m), 1369 (w), 1348 (s), 1266 (m), 1201 (w), 1164 (s), 1090 (s), 1067 (m), 1057 (m), 1028 (m), 1009 (m); **HRMS**-(ESI$^+$) $[M+H]^+$ calcd for $C_{20}H_{23}NO_3SBr^+$ 436.0582, found: 436.0577; **$[\alpha]_D^{26}$** = –85.7° (c = 1.04, CH_2Cl_2, l = 100 mm).

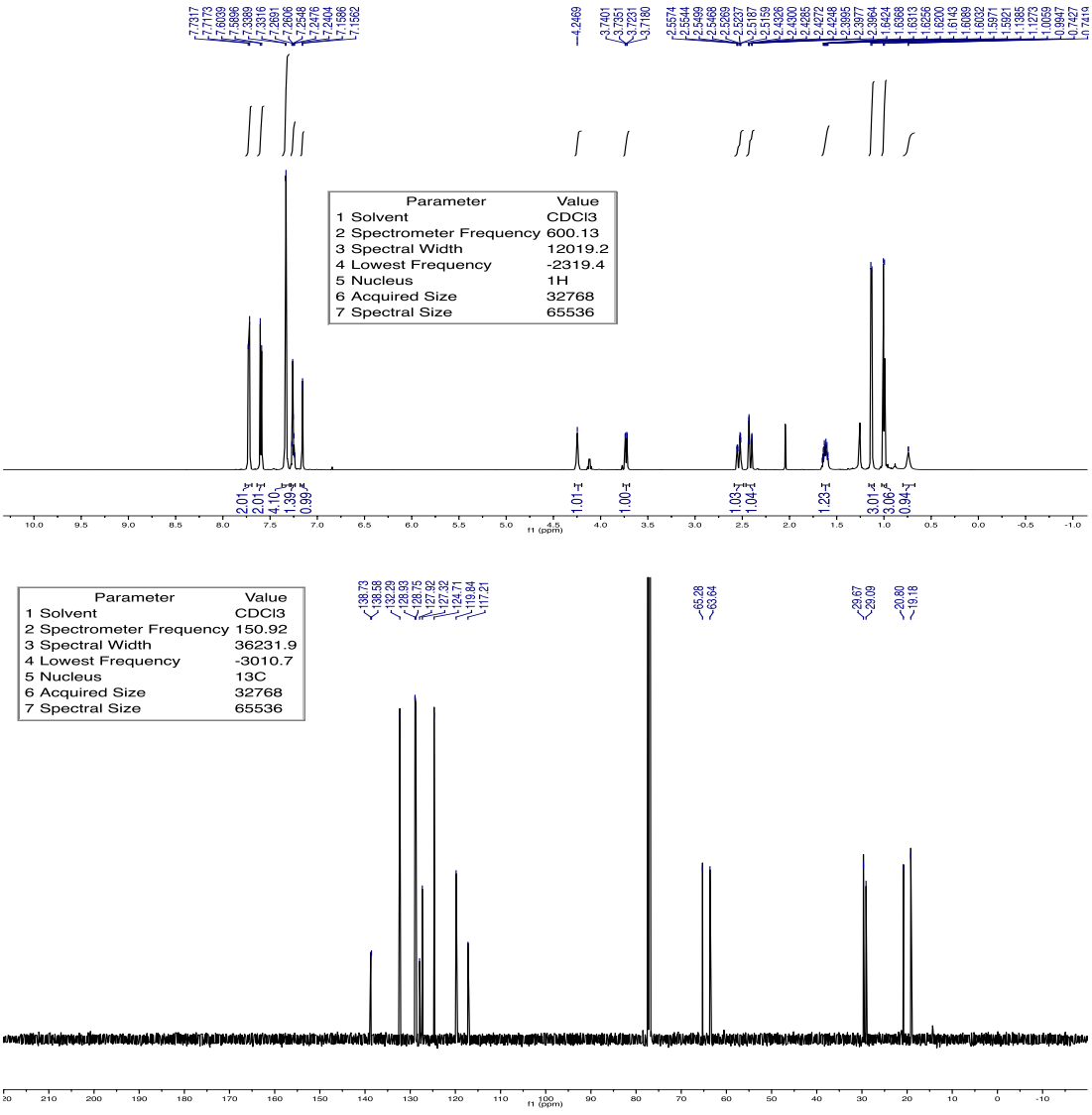


Figure A.20. ^{1}H and ^{13}C{^{1}H} NMR spectra of A.3.

Preparation of tetrahydropyridine A.4

A.28 **A.4**

In a dry, N_2-filled glove box, amino aldehyde **A.28** (0.0500 mmol, 22.5 mg) and $B(C_6F_5)_3$ (BCF, 0.0050 mmol, 2.6 mg) were weighed into a screw cap 1 dram vial equipped with a magnetic stir bar. CH_2Cl_2 (1.00 mL, 0.05 M) was added and the vial was sealed with a septum cap and removed from the glove box. The solution was stirred at 22 °C for 1 h, after which time the catalyst was quenched with 50 μL of Et_3N and the solvent was removed *in vacuo*. The crude residue was purified by silica gel chromatography (5:1 *n*-pentane:ethyl acetate; $R_f = 0.2$) to yield the tetrahydropyridine product **A.4** as a white, crystalline solid in 95% yield (21.4 mg) and >98:2 d.r..

(2S,3R)-1-((4-bromophenyl)sulfonyl)-2-(tert-butyl)-5-phenyl-1,2,3,4-tetrahydropyridin-3-ol (A.4). **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 7.73 (d, 2H, *J* = 8.6 Hz), 7.58 (d, 2H, *J* = 8.6 Hz), 7.36-7.32 (m, 2H), 7.31-7.29 (m, 2H), 7.28-7.25 (m, 1H), 7.16 (s, 1H), 4.33-4.30 (m, 1H), 3.90-3.87 (m, 1H), 2.60 (ddd, 1H, *J* = 18.7, 4.9, 1.7 Hz), 2.40 (dd, 1H, *J* = 18.7, 1.6 Hz), 1.05 (s, 9H), 0.73 (s, br, 1H); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 138.7, 138.2, 132.1, 129.4, 128.8, 128.0, 127.4, 124.8, 121.9, 118.7, 67.5, 63.8, 34.8, 31.2, 27.9.; **IR** (ν/cm^{-1}): 3586 (m), 3460 (s, br, OH), 3146 (w), 3081 (m), 3056 (m), 3032 (w), 2966 (s), 2917 (m), 2871 (w), 1637 (m), 1595 (w), 1573 (w), 1495 (w), 1474 (m), 1445 (w), 1392 (m), 1364 (m), 1338 (s), 1302 (w), 1272 (w), 1238 (w), 1224 (w), 1196 (m), 1170 (s), 1090 (m), 1068 (w), 1050 (w), 1039 (w), 1028 (w), 1017 (m), 1008 (w); **HRMS**-(ESI$^+$) $[M+H]^+$ calcd for $C_{21}H_{25}NO_3SBr^+$ 450.0739, found: 450.0733; **$[\alpha]_D^{26}$** = –78.1° (c = 1.07, CH_2Cl_2, l = 100 mm).

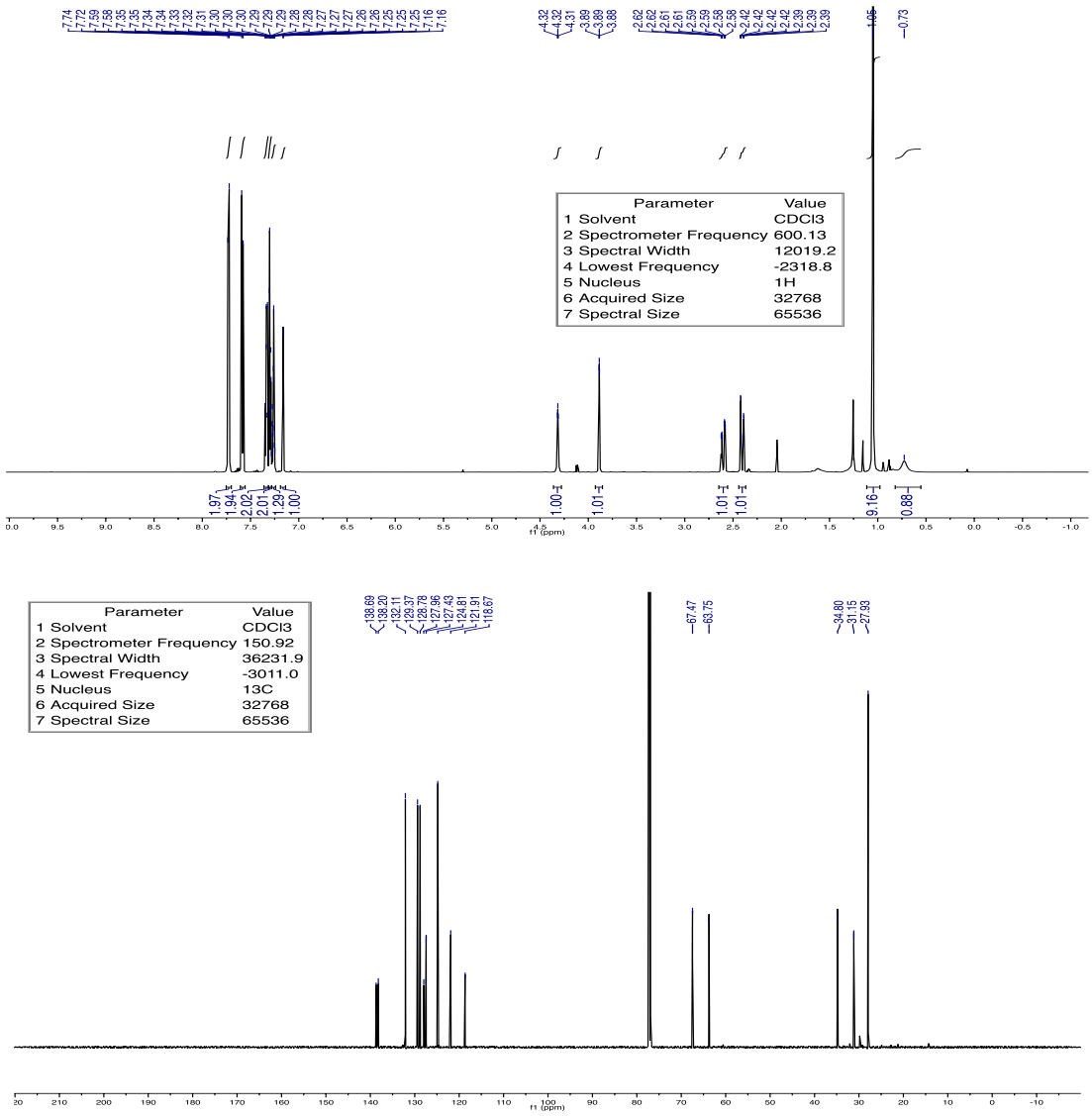


Figure A.21. ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of A.4.

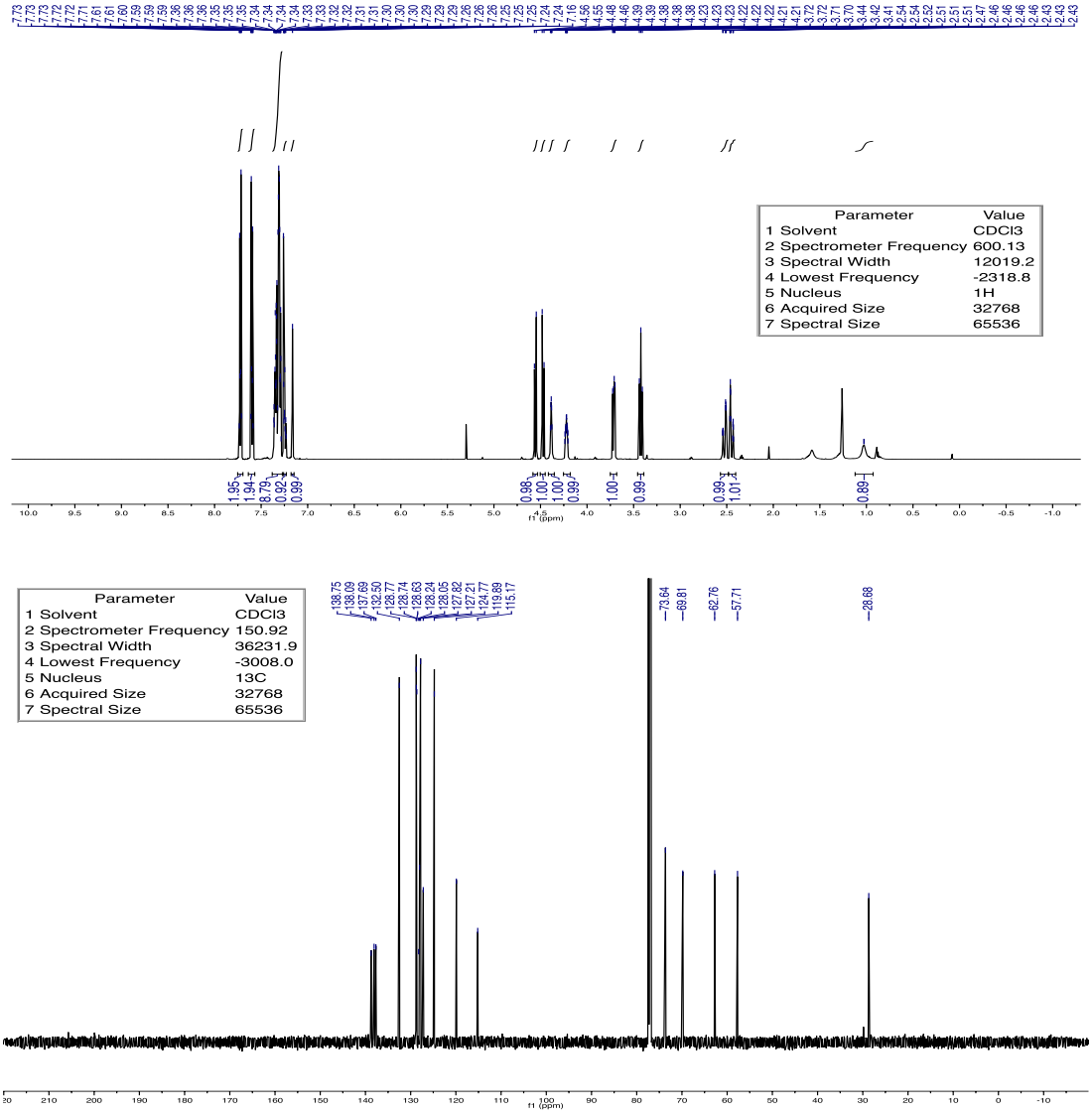
Preparation of tetrahydropyridine A.5

A.29 **A.5**

In a dry, N_2-filled glove box, amino aldehyde **A.29** (0.0500 mmol, 25.7 mg) and $B(C_6F_5)_3$ (BCF, 0.0050 mmol, 2.6 mg) were weighed into a screw cap 1 dram vial equipped with a magnetic stir bar. CH_2Cl_2 (1.00 mL, 0.05 M) was added and the vial was sealed with a septum cap and removed from the glove box. The solution was stirred at 22 °C for 1 h, after which time the catalyst was quenched with 50 μL of Et_3N and the solvent was removed *in vacuo*. ^1H and ^{13}C NMR analysis indicated that the desired tetrahydropyridine product **A.5** was produced in 94% yield and in 94:6 d.r.. The crude residue was purified by silica gel chromatography (3:1 *n*-pentane:ethyl acetate; $R_f = 0.3$) to yield the tetrahydropyridine product **A.5** as a crystalline, white solid in 87% yield (22.3 mg) and as a single (enriched) diastereomer in >98:2 d.r..

(2*S*,3*R*)-2-((benzyloxy)methyl)-1-((4-bromophenyl)sulfonyl)-5-phenyl-1,2,3,4-tetrahydropyridin-3-ol (A.5). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.72 (d, 2H, *J* = 8.7 Hz), 7.60 (d, 2H, *J* = 8.6 Hz), 7.37-7.28 (m, 9H), 7.26-7.23 (m, 1H), 7.16 (s, 1H), 4.55 (d, 1H, *J* = 11.9 Hz), 4.47 (d, 1H, *J* = 11.8 Hz), 4.41-4.36 (m, 1H), 4.25-4.20 (m, 1H), 3.71 (dd, 1H, *J* = 9.8, 5.4 Hz), 3.42 (t, 1H, *J* = 9.5 Hz), 2.53 (ddd, 1H, *J* = 18.0, 4.2, 2.1 Hz), 2.45 (ddt, 1H, *J* = 18.0, 2.3, 1.3 Hz), 1.03 (s, br, 1H); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 138.8, 138.1, 137.7, 132.5, 128.8, 128.7, 128.6, 128.2, 128.1, 127.8, 127.2, 124.8, 119.9, 115.2, 73.6, 69.8, 62.8, 57.7, 28.7; **^{13}C NMR DEPT135** ($CDCl_3$, 151 MHz): δ 132.5 (CH), 128.8 (CH), 128.7 (CH), 128.6 (CH), 128.1 (CH), 127.8 (CH), 127.2 (CH), 124.8 (CH), 119.9 (CH), 115.2, 73.6 (CH_2), 69.8 (CH_2), 62.8 (CH), 57.7 (CH), 28.7 (CH_2); **IR** (ν/cm^{-1}): 3540 (s, br, OH), 3086 (w), 3060 (w), 3030 (w), 2922 (m), 2861 (m), 1640 (m), 1598 (w), 1574 (m), 1496 (w), 1471 (w), 1453 (w), 1447 (w), 1389 (m), 1353 (s), 1276 (w), 1203 (w), 1166 (s), 1092 (s), 1068

(m), 1059 (m), 1028 (w), 1009 (m); **HRMS**-(ESI$^+$) $[M+H]^+$ calcd for $C_{25}H_{25}NO_4SBr^+$ 514.0687, found: 514.0681; $[\alpha]_D^{25}$ = –18.7° (c = 0.920, CH_2Cl_2, l = 100 mm).



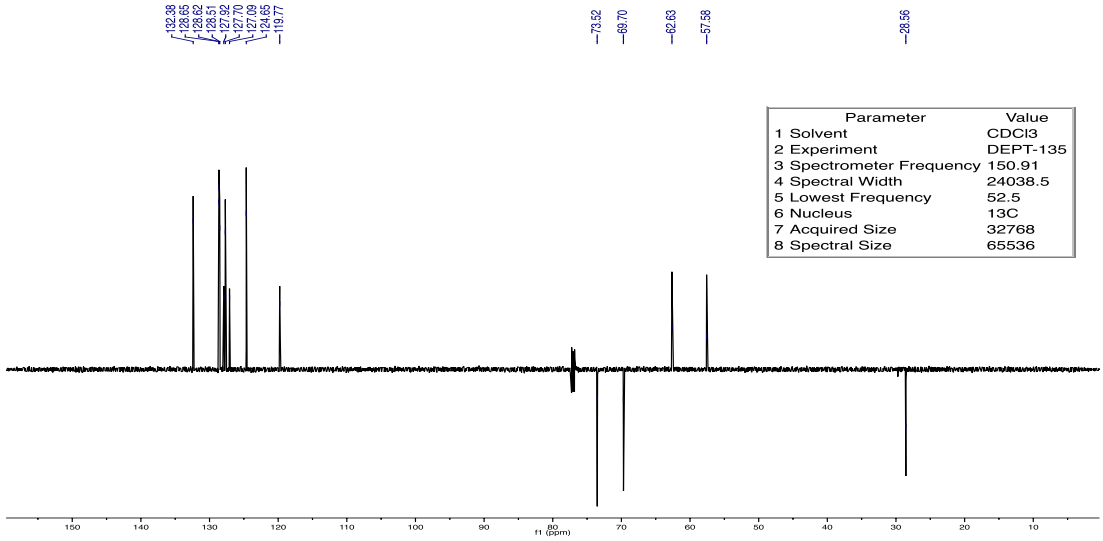
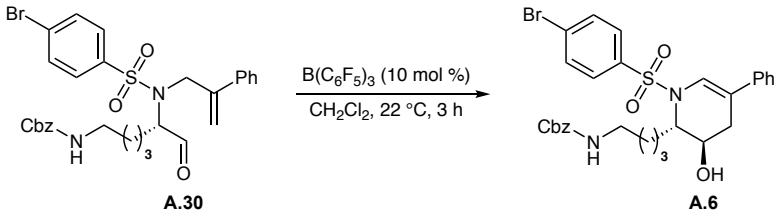


Figure A.22. ^{1}H, ^{13}C{^{1}H}, and ^{13}C DEPT-135 NMR spectra of A.5.

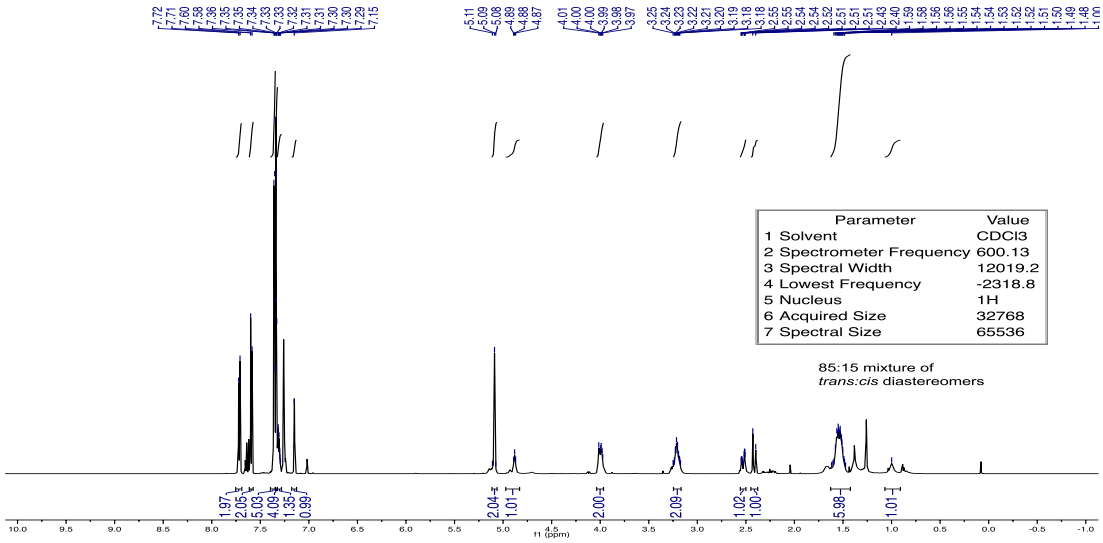
Preparation of tetrahydropyridine A.6



A.30 **A.6**

In a dry, N_2-filled glove box, amino aldehyde **A.30** (0.0500 mmol, 30.0 mg) and $B(C_6F_5)_3$ (BCF, 0.0050 mmol, 2.6 mg) were weighed into a screw cap 1 dram vial equipped with a magnetic stir bar. CH_2Cl_2 (1.00 mL, 0.05 M) was added and the vial was sealed with a septum cap and removed from the glove box. The solution was stirred at 22 °C for 3 h, after which time the catalyst was quenched with 50 µL of Et_3N and the solvent was removed *in vacuo*. *Note: incomplete conversion was observed in a separate experiment that was quenched after just 1 h.* The crude residue was purified by silica gel chromatography (2:1 *n*-pentane:ethyl acetate; R_f = 0.2) to yield the tetrahydropyridine product **A.6** as an amorphous,

white solid in 88% yield (26.5 mg) and as a mixture of two chromatographically inseparable diastereomers in 85:15 *trans:cis* d.r. (no diastereoenrichment occured during purification). **benzyl (4-((2*S*,3*R*)-1-((4-bromophenyl)sulfonyl)-3-hydroxy-5-phenyl-1,2,3,4-tetrahydro-pyridin-2-yl)butyl)carbamate (A.6).** **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 7.72 (d, 2H, *J* = 8.6 Hz), 7.59 (d, 2H, *J* = 8.6 Hz), 7.36-7.35 (m, 5H), 7.34-7.32 (m, 4H), 7.32-7.28 (m, 1H), 7.15 (s, 1H), 5.09 (s, 2H), 4.88 (t, 1H, *J* = 6.1 Hz), 4.04-3.96 (m, 2H), 3.25-3.16 (m, 2H), 2.56-2.50 (m, 1H), 2.41 (d, 1H, *J* = 18.2 Hz), 1.63-1.46 (m, 6H), 1.00 (s, 1H); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 156.6, 138.7, 138.6, 136.8, 132.8, 132.4, 128.8, 128.8, 128.6, 128.2, 128.0, 127.3, 124.8, 119.5, 115.9, 66.7, 65.1, 59.1, 40.9, 31.6, 29.8, 28.8, 22.9; **^{13}C NMR DEPT135** ($CDCl_3$, 151 MHz): δ 132.8 (CH), 132.4 (CH), 128.8 (CH), 128.8 (CH), 128.6 (CH), 128.2 (CH), 127.3 (CH), 124.8 (CH), 119.5 (CH), 66.7 (CH_2), 65.1 (CH), 59.1 (CH), 40.9 (CH_2), 31.6 (CH_2), 29.8 (CH_2), 28.8 (CH_2), 22.9 (CH_2); **IR** (ν/cm^{-1}): 3410 (s, br, OH), 3087 (w), 3060 (w), 3033 (w), 2931 (s), 2862 (m), 1700 (s, C=O), 1638 (m), 1597 (w), 1574 (m), 1525 (s), 1496 (w), 1470 (w), 1454 (w), 1446 (w), 1389 (m), 1349 (s), 1250 (s), 1164 (s), 1090 (m), 1067 (m), 1028 (w), 1009 (w); **HRMS**-(ESI^{+}) $[M+H]^{+}$ calcd for $C_{29}H_{32}N_2O_5SBr^{+}$ 599.1215, found: 599.1208; **$[\alpha]_D^{25}$** = –11.6° (c = 1.19, CH_2Cl_2, l = 100 mm).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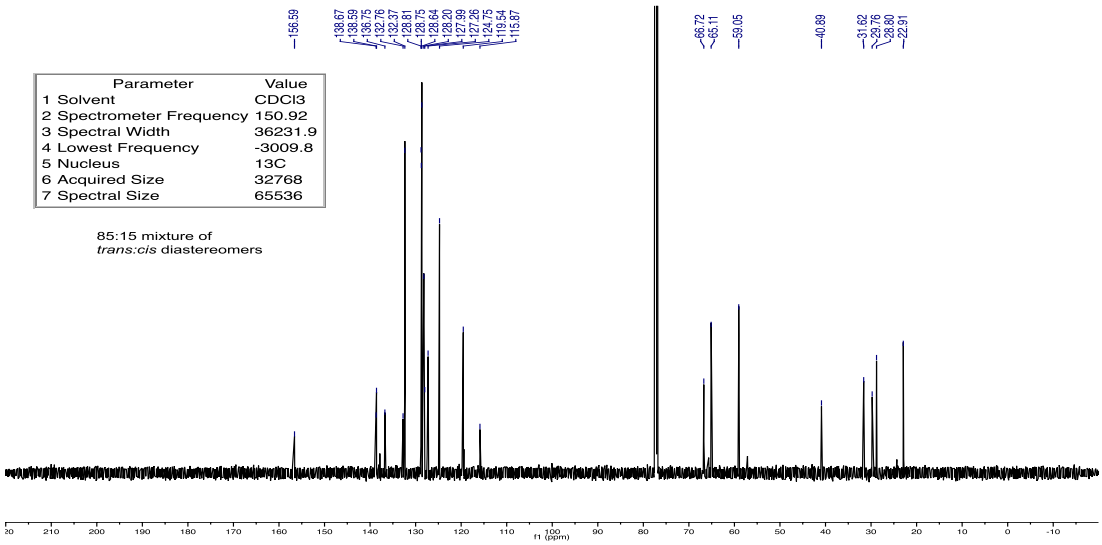
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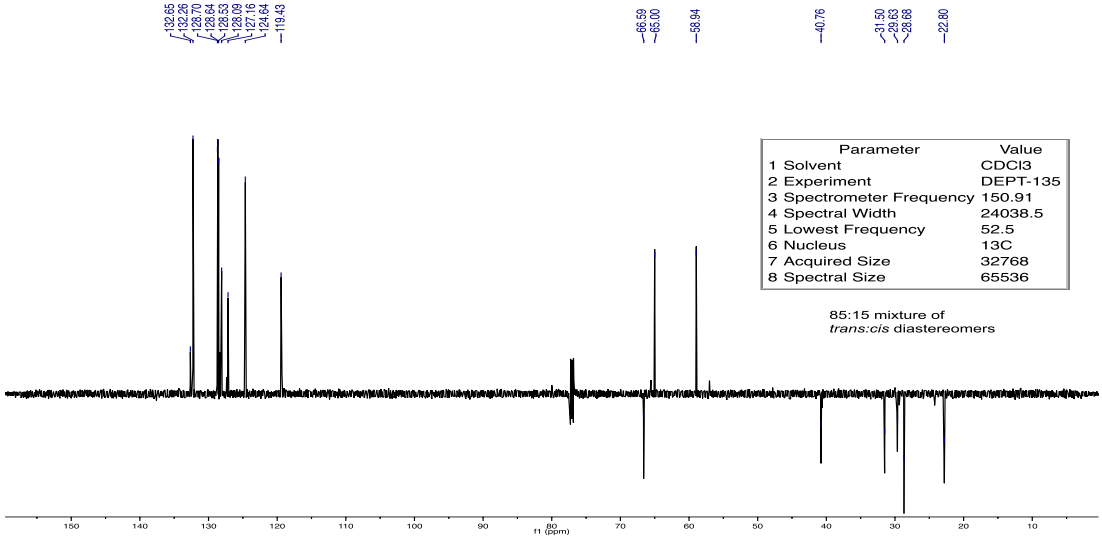
trans:cis diastereomers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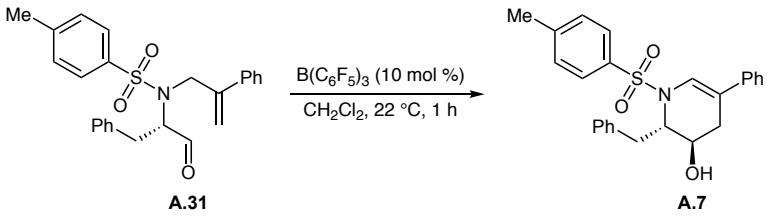
3 Spectrometer Frequency 150.91
4 Spectral Width 24038.5
5 Lowest Frequency 52.5
6 Nucleus 13C
7 Acquired Size 32768
8 Spectral Size 65536
85:15 mixture of
trans:cis diastereomers

Figure A.23. ^{1}H, ^{13}C{^{1}H}, and ^{13}C DEPT-135 NMR spectra of A.6.

Preparation of tetrahydropyridine A.7

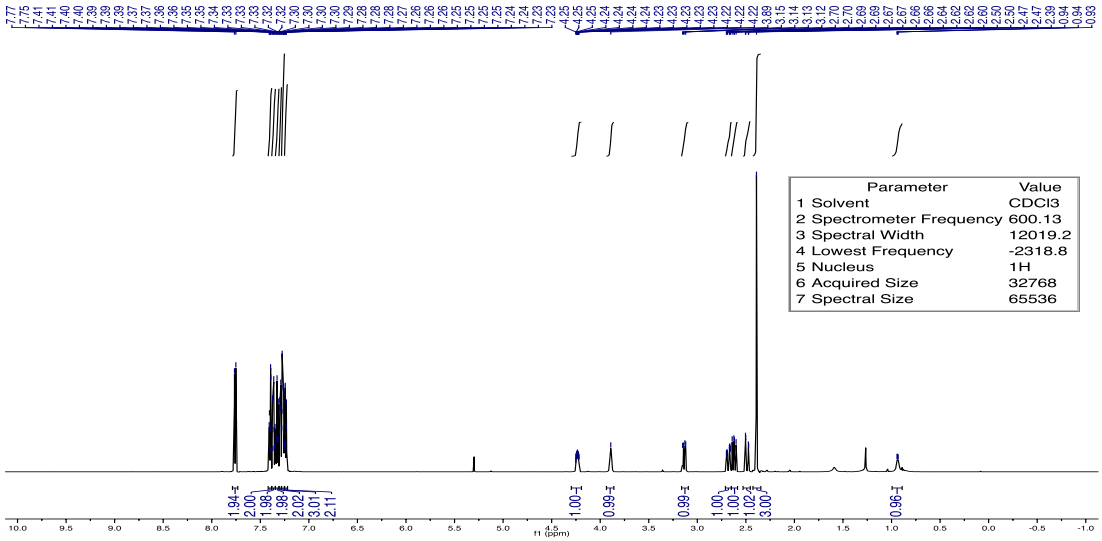


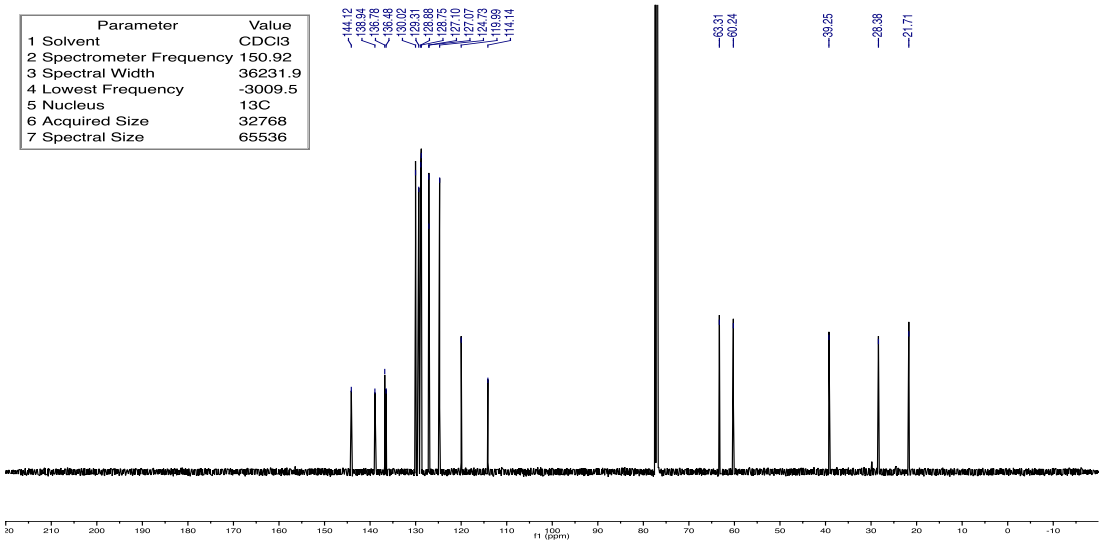
A.31 **A.7**

In a dry, N_2-filled glove box, amino aldehyde **A.31** (0.0500 mmol, 21.1 mg) and $B(C_6F_5)_3$ (BCF, 0.0050 mmol, 2.6 mg) were weighed into a screw cap 1 dram vial equipped with a magnetic stir bar. CH_2Cl_2 (1.00 mL, 0.05 M) was added and the vial was sealed with a septum cap and removed from the glove box. The solution was stirred at 22 °C for 1 h, after which time the catalyst was quenched with 50 μL of Et_3N and the solvent was removed *in vacuo*. The crude residue was purified by silica gel chromatography (5:1 to 3:1 *n*-pentane:ethyl acetate; R_f = 0.3 in 3:1) to yield the tetrahydropyridine product **A.7** as a white, crystalline solid in 97% yield (20.4 mg) and >98:2 d.r..

(2*S*,3*R*)-2-benzyl-5-phenyl-1-tosyl-1,2,3,4-tetrahydropyridin-3-ol (A.7). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.76 (d, 2H, *J* = 8.4 Hz), 7.42-7.39 (m, 2H), 7.36 (t, 2H, *J* = 8.0 Hz), 7.33 (t, 2H, *J* = 7.6 Hz), 7.29 (d, 2H, *J* = 6.0 Hz), 7.28-7.26 (m, 3H), 7.24 (d, 2H, *J* = 7.1 Hz), 4.27-4.20 (m, 1H), 3.89 (s, br, 1H), 3.14 (dd, 1H, *J* = 13.8, 5.3 Hz), 2.68 (ddd, 1H, *J* = 18.0, 4.4, 2.0 Hz), 2.62 (dd, 1H, *J* = 13.8, 10.4 Hz), 2.49 (dd, 1H, *J* = 18.0, 1.6 Hz), 2.39 (s, 3H), 0.96-0.91 (m, 1H); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 144.1, 138.9, 136.8, 136.5, 130.0, 129.3, 128.9, 128.8, 127.1, 127.1, 124.7, 120.0, 114.1, 63.3, 60.2, 39.3, 28.4, 21.7; **^{13}C NMR DEPT135** ($CDCl_3$, 151 MHz): δ 130.0 (CH), 129.3 (CH), 128.9 (CH), 128.8 (CH), 127.1 (CH), 127.1 (CH), 124.7 (CH), 120.0 (CH), 63.3 (CH), 60.2 (CH), 39.3 (CH_2), 28.4 (CH_2),

21.7 (CH_3); **IR** (ν/cm^{-1}): 3541 (s, br, OH), 3084 (w), 3060 (w), 3028 (w), 3003 (w), 2924 (m), 2854 (w), 1639 (m), 1598 (m), 1495 (m), 1454 (w), 1447 (w), 1349 (s), 1307 (w), 1266 (w), 1216 (w), 1198 (w), 1185 (w), 1161 (s), 1093 (s), 1056 (m), 1032 (m); **HRMS**-(ESI$^+$) $[M+H]^+$ calcd for $C_{25}H_{26}NO_3S^+$ 420.1634, found: 420.1628; $\mathbf{[\alpha]_D^{25}}$ = –20.6° (c = 1.02, CH_2Cl_2, l = 100 mm).





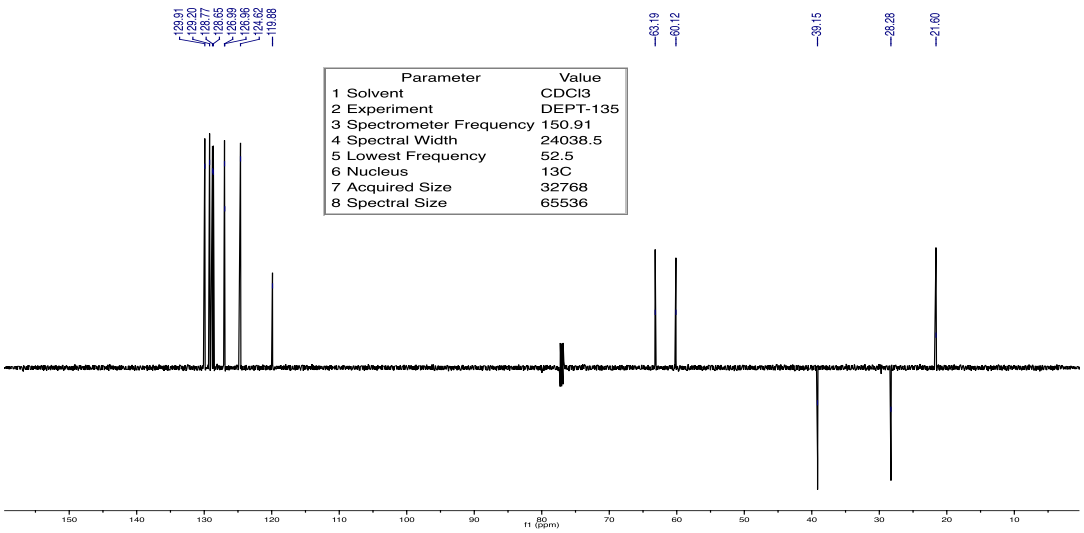
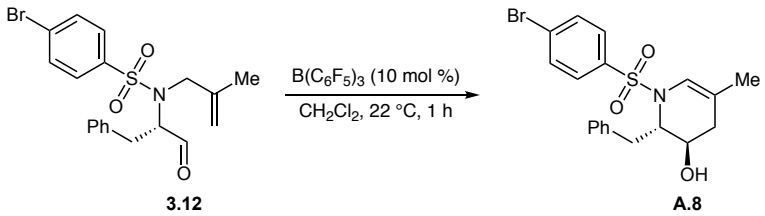


Figure A.24. ^{1}H, ^{13}C{^{1}H}, and ^{13}C DEPT-135 NMR spectra of A.7.

Preparation of tetrahydropyridine A.8

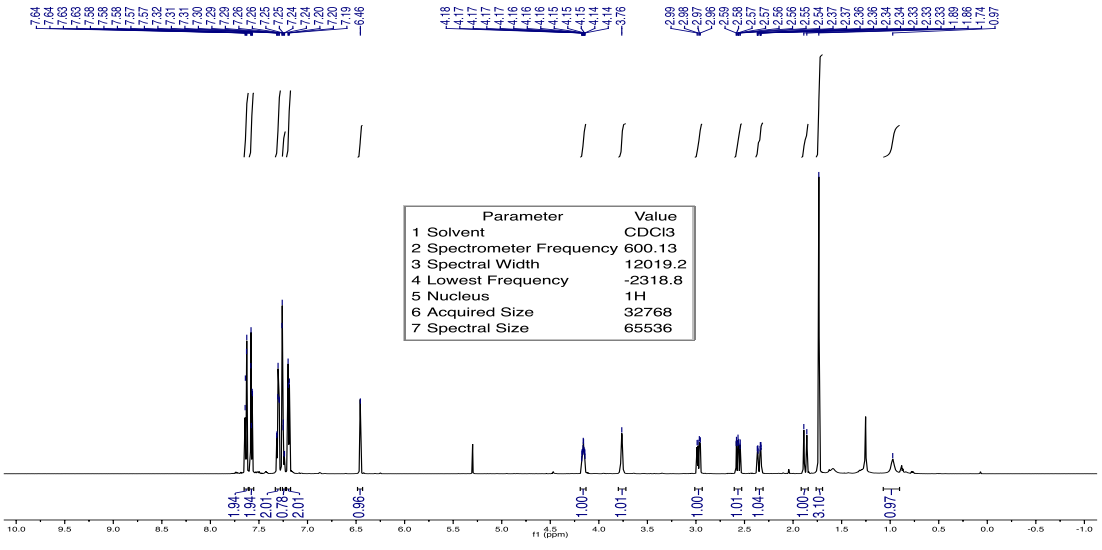


3.12 **A.8**

In a dry, N_2-filled glove box, amino aldehyde **3.12** (0.0500 mmol, 21.1 mg) and $B(C_6F_5)_3$ (BCF, 0.0050 mmol, 2.6 mg) were weighed into a screw cap 1 dram vial equipped with a magnetic stir bar. CH_2Cl_2 (1.00 mL, 0.05 M) was added and the vial was sealed with a septum cap and removed from the glove box. The solution was stirred at 22 °C for 1 h, after which time the catalyst was quenched with 50 µL of Et_3N and the solvent was removed *in vacuo*. The crude residue was purified by silica gel chromatography (5:1 *n*-pentane:ethyl

acetate; R_f = 0.3) to yield the tetrahydropyridine product **A.8** as a colorless oil in 61% yield (12.8 mg) and >98:2 d.r..

(2*S*,3*R*)-2-benzyl-1-((4-bromophenyl)sulfonyl)-5-methyl-1,2,3,4-tetrahydropyridin-3-ol (A.8). **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 7.63 (d, 2H, *J* = 8.5 Hz), 7.58 (d, 2H, *J* = 8.6 Hz), 7.30 (t, 2H, *J* = 7.7 Hz), 7.24 (t, 1H, *J* = 7.5 Hz), 7.19 (d, 2H, *J* = 7.9 Hz), 6.46 (s, 1H), 4.18-4.13 (m, 1H), 3.76 (s, br, 1H), 2.97 (dd, 1H, *J* = 13.8, 6.0 Hz), 2.56 (dd, 1H, *J* = 13.7, 9.5 Hz), 2.35 (d, 1H, *J* = 18.4 Hz), 1.87 (d, 1H, *J* = 18.5 Hz), 1.73 (s, 3H), 0.97 (s, br, 1H); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 138.7, 136.9, 132.4, 129.3, 128.8, 128.7, 127.8, 127.0, 116.9, 113.2, 63.7, 60.1, 38.8, 31.5, 20.9; **^{13}C NMR DEPT135** ($CDCl_3$, 151 MHz): δ 132.4 (CH), 129.3 (CH), 128.8 (CH), 128.7 (CH), 127.0 (CH), 116.9 (CH), 63.7 (CH), 60.1 (CH), 38.8 (CH_2), 31.5 (CH_2), 20.9 (CH_3); **IR** (ν/cm^{-1}): 3533 (s, br, OH), 3086 (w), 3062 (w), 3028 (w), 2917 (m), 2852 (w), 1677 (w), 1602 (w), 1574 (m), 1495 (w), 1471 (w), 1454 (w), 1389 (m), 1370 (w), 1346 (m), 1274 (w), 1216 (w), 1182 (m), 1160 (s), 1092 (m), 1067 (m), 1052 (m), 1011 (m); **HRMS**-(ESI$^+$) $[M+H]^+$ calcd for $C_{19}H_{21}NO_3SBr^+$ 422.0425, found: 422.0420; **$[\alpha]_D^{26}$** = +77.7° (c = 0.640, CH_2Cl_2, l = 100 mm).



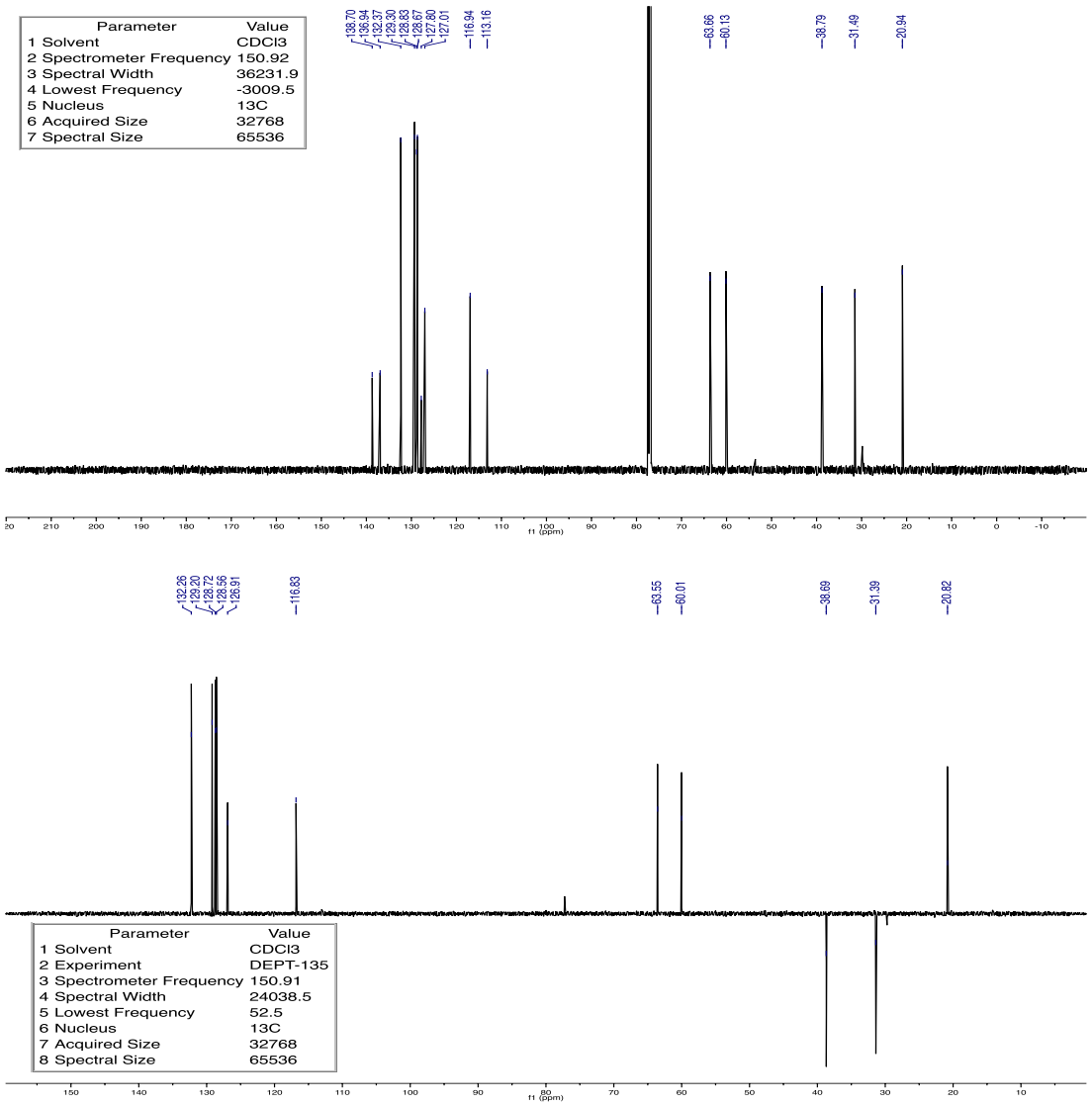


Figure A.25. ^{1}H, ^{13}C{^{1}H}, and ^{13}C DEPT-135 NMR spectra of A.8.

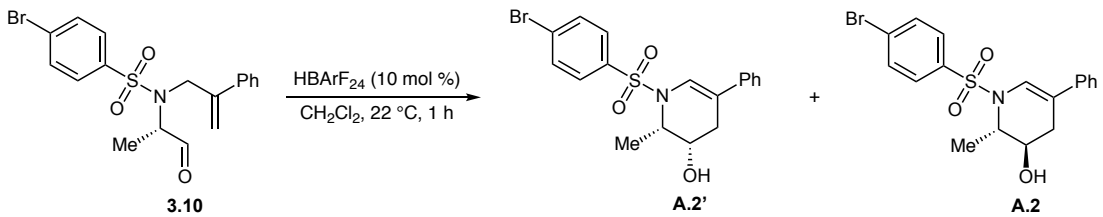
A.5.4.1 BCF-catalyzed aldehyde hydrosilylation

In a dry, N_2-filled glove box, amino aldehyde **3.4** (0.0500 mmol, 24.2 mg) was weighed into a screw cap 1 dram vial equipped with a magnetic stir bar. In a separate 1 dram

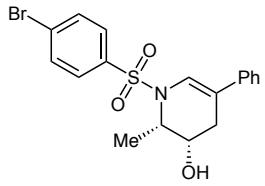
vial was added $B(C_6F_5)_3$ (BCF, 0.0050 mmol, 2.6 mg), followed by CH_2Cl_2 (1.00 mL, 0.05 M) and Et_3SiH (0.0550 mmol, 8.8 μL). The solution in CH_2Cl_2 was added all at once to the neat substrate; vigorous bubbling was observed. The solution was stirred at 22 °C for 5 minutes, after which time the catalyst was quenched with 50 μL of Et_3N and the solvent was removed *in vacuo*. *Note: The residue was treated with PPTS resin to facilitate NMR identification and quantification of the products.* The residue was repeatedly washed with CH_2Cl_2 and concentrated *in vacuo* (x3), and was then placed under high vacuum overnight to remove excess Et_3N. The resulting residue was taken up in 2 mL of 1:1 CH_2Cl_2/MeOH, a spatula tip of PPTS resin was added, and the mixture was stirred at 22 °C for 24 h. The mixture was then filtered through a short plug of neutral aluminum oxide (Brockmann activity I slurried with 10% H_2O) and concentrated *in vacuo*. Dimethylformamide (0.050 mmol, 3.9 μL) was added as an internal standard and the residue taken up in $CDCl_3$ for ^1H and ^{13}C NMR analyses; full conversion of starting material was observed with concomitant production of amino alcohol **3.32** (32%; resulting from the deprotection of silyl ether **A.32**), in addition to 44% of *trans*-tetrahydropyridine **3.23** and 7% and 12%, respectively, of minor diastereomers *B* and *C* of piperidine **3.6**.

A.5.4.2 $HBarF_{24}$-catalyzed *Prins* cyclization

Preparation of *cis*-tetrahydropyridine A.2'

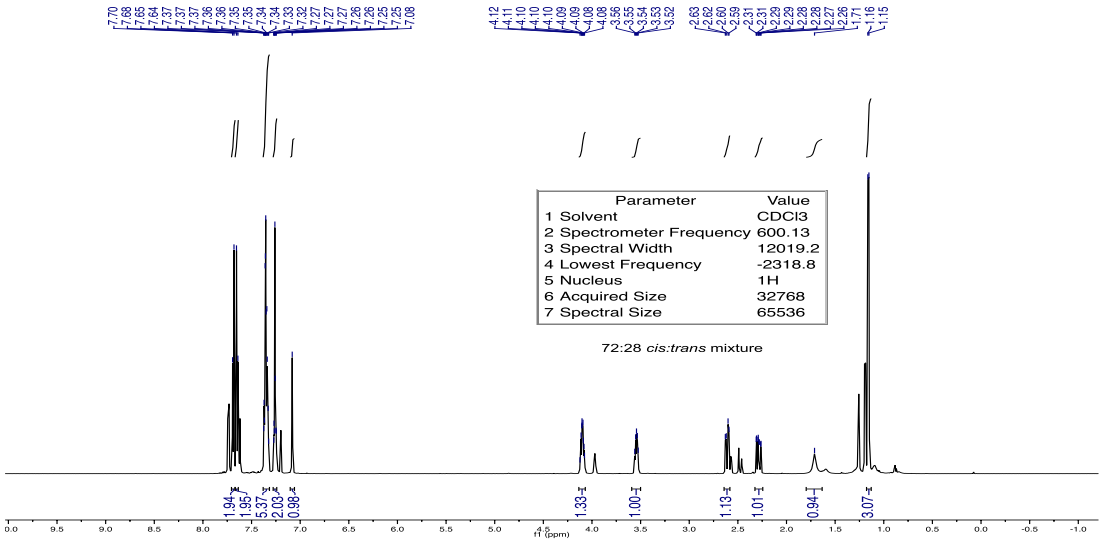


In a dry, N_2-filled glove box, amino aldehyde **3.10** (0.0500 mmol, 20.4 mg) and $[H(OEt_2)_2][B(C_6H_3(CF_3)_2)_4]$ ($HBArF_{24}$ (Brookhart's acid); 0.0050 mmol, 5.1 mg) were weighed into a screw cap 1 dram vial equipped with a magnetic stir bar. CH_2Cl_2 (1.00 mL, 0.05 M) was added and the vial was sealed with a septum cap and removed from the glove box. The solution was stirred at 22 °C for 1 h, after which time the catalyst was quenched with 50 μL of Et_3N and the solvent was removed *in vacuo*. The crude residue was purified by silica gel chromatography (3:1 *n*-pentane:ethyl acetate; $R_f = 0.3$) to yield the tetrahydropyridine product **A.2'/A.2** as a white, crystalline solid in 81% yield (16.6 mg) and 72:28 *cis:trans* d.r..



A.2'

(2S,3S)-1-((4-bromophenyl)sulfonyl)-2-methyl-5-phenyl-1,2,3,4-tetrahydropyridin-3-ol (A.2'). *Cis*-diastereomer: ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.69 (d, 2H, J = 8.7 Hz), 7.65 (d, 2H, J = 8.7 Hz), 7.38-7.32 (m, 4H), 7.28-7.24 (m, 1H), 7.08 (s, 1H), 4.13-4.07 (m, 1H), 3.57-3.51 (m, 1H), 2.61 (dd, 1H, J = 16.8, 5.7 Hz), 2.29 (ddd, 1H, J = 16.8, 10.5, 2.1 Hz), 1.71 (s, 1H), 1.16 (d, 3H, J = 6.7 Hz); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 138.3, 138.2, 132.8, 128.8, 128.4, 128.2, 127.3, 124.8, 119.4, 117.4, 66.2, 52.8, 29.2, 11.8; **^{13}C NMR DEPT135** ($CDCl_3$, 151 MHz): δ 132.8 (CH), 128.8 (CH), 128.4 (CH), 127.3 (CH), 124.8 (CH), 119.4 (CH), 66.2 (CH), 52.8 (CH), 29.2 (CH_2), 11.8 (CH_3).


Parameter Value
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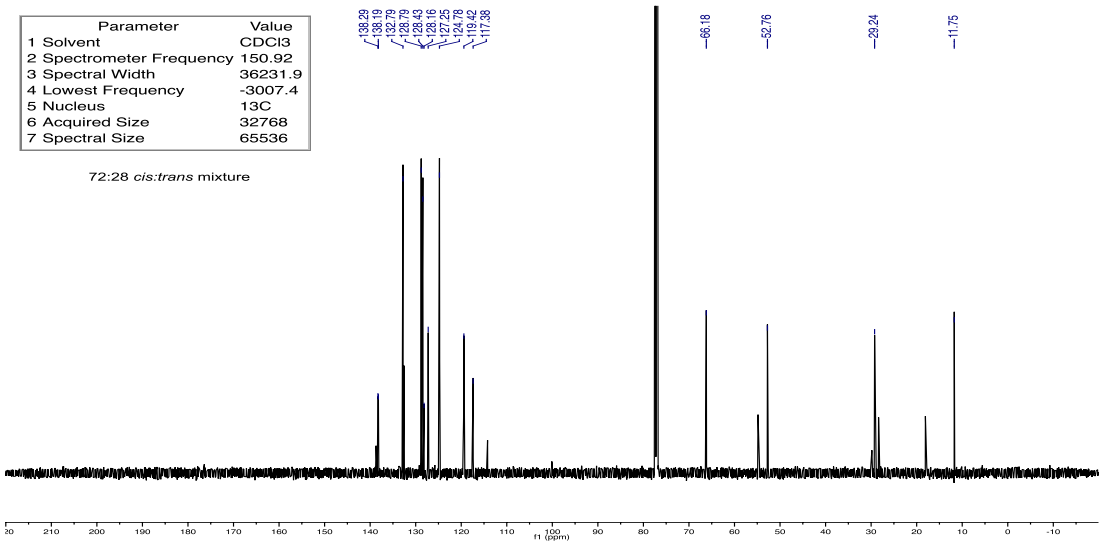
3 Spectral Width 12019.2
4 Lowest Frequency -2318.8
5 Nucleus 1H
6 Acquired Size 32768
7 Spectral Size 65536
72:28 cis:trans mixture
f1 (ppm)


Parameter Value
1 Solvent CDCl3
2 Spectrometer Frequency 150.92
3 Spectral Width 36231.9
4 Lowest Frequency -3007.4
5 Nucleus 13C
6 Acquired Size 32768
7 Spectral Size 65536
72:28 cis:trans mixture
f1 (ppm)

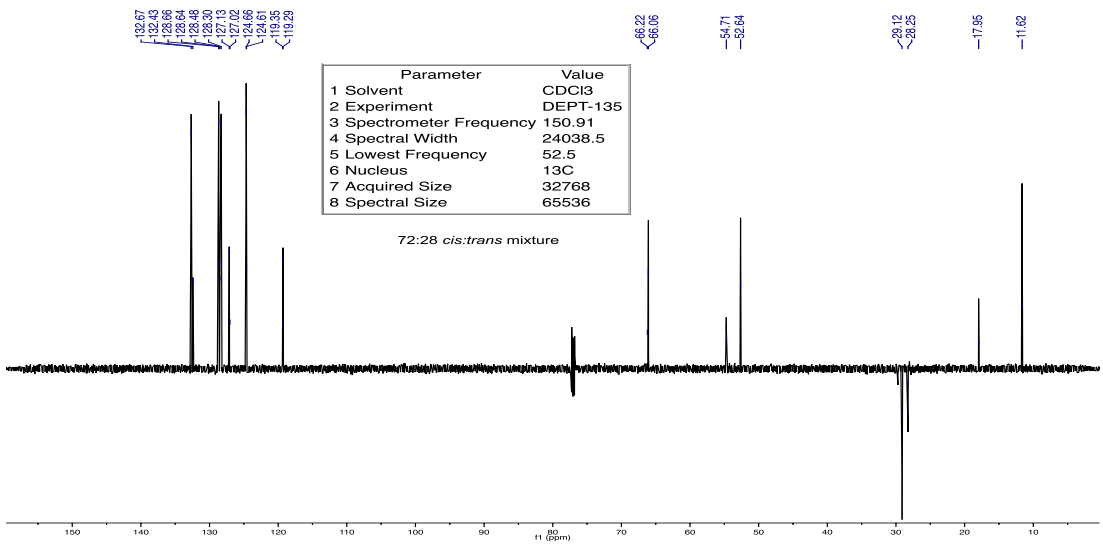
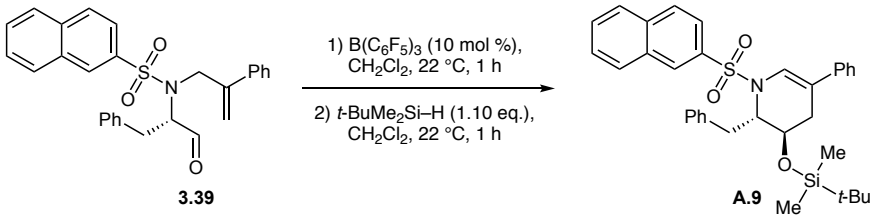


Figure A.26. ^{1}H, ^{13}C{^{1}H}, and ^{13}C DEPT-135 NMR spectra of *cis*-A.2'.

A.5.4.3 *In situ* BCF-catalyzed cyclization and dehydrocoupling / silyl-protection

Preparation of silyl-protected tetrahydropyridine A.9



In a dry, N_2-filled glove box, amino aldehyde **3.39** (0.250 mmol, 114 mg) and $B(C_6F_5)_3$ (BCF, 0.0250 mmol, 12.8 mg) were weighed into a screw cap 1 dram vial equipped with a magnetic stir bar. CH_2Cl_2 (2.50 mL, 0.10 M) was added and the vial was sealed with a septum cap. The solution was stirred at 22 °C for 1 h, after which time *t*-$BuMe_2SiH$ (0.275 mmol, 46 μL, 1.10 eq.) was added dropwise *via* syringe with concomitant slow evolution of bubbles. The solution was stirred for an additional 1 h, after which time the catalyst was quenched with 100 μL of Et_3N and the solvent was removed *in vacuo*. The crude residue was purified by silica gel chromatography (9:1 hexanes:ethyl acetate; $R_f = 0.5$) to yield the silyl-

protected tetrahydropyridine product **A.9** as a colorless, viscous oil in 94% yield (134 mg) and 91:9 *trans:cis* d.r..

(2S,3R)-2-benzyl-3-((tert-butyldimethylsilyl)oxy)-1-(naphthalen-2-ylsulfonyl)-5-phenyl-1,2,3,4-tetrahydropyridine (A.9). **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 8.46 (s, 1H), 7.95 (dd, 1H, *J* = 8.2, 1.5 Hz), 7.88 (d, 1H, *J* = 8.7 Hz), 7.85 (d, 1H, *J* = 8.0 Hz), 7.81 (dd, 1H, *J* = 8.8, 1.9 Hz), 7.63-7.55 (m, 2H), 7.41 (d, 2H, *J* = 8.2 Hz), 7.39-7.31 (m, 5H), 7.29-7.23 (m, 4H), 4.18 (ddd, 1H, *J* = 11.1, 5.7, 3.3 Hz), 3.94 (dt, 1H, *J* = 4.3, 2.1 Hz), 3.28 (dd, 1H, *J* = 13.7, 4.7 Hz), 2.67-2.60 (m, 2H), 2.38 (d, 1H, *J* = 17.1 Hz), 0.38 (s, 9H), –0.46 (s, 3H), –0.49 (s, 3H); **^{13}C{^{1}H} NMR** ($CDCl_3$, 151 MHz): δ 139.8, 137.4, 137.2, 135.1, 132.3, 129.6, 129.4, 129.2, 128.9, 128.8, 128.7, 128.3, 127.9, 127.5, 127.0, 126.6, 124.7, 122.7, 120.4, 113.6, 63.6, 61.0, 39.9, 28.8, 25.7, 18.2, –5.0, –5.2.; **IR** (ν/cm^{-1}): 3083 (w), 3059 (w), 3028 (w), 2952 (m), 2928 (m), 2884 (w), 2855 (m), 1644 (m), 1598 (w), 1495 (w), 1470 (w), 1462 (w), 1455 (w), 1447 (w), 1387 (w), 1350 (s), 1328 (w), 1254 (m), 1229 (m), 1215 (w), 1198 (w), 1163 (s), 1132 (m), 1100 (w), 1078 (s), 1057 (w), 1029 (w), 1004 (w); **HRMS**-(ESI^{+}) $[M+H]^+$ calcd for $C_{34}H_{40}NO_3SiS^+$ 570.2498, found: 570.2490; **$[\alpha]_D^{27}$** = –78.6° (c = 0.750, CH_2Cl_2, l = 100 mm).

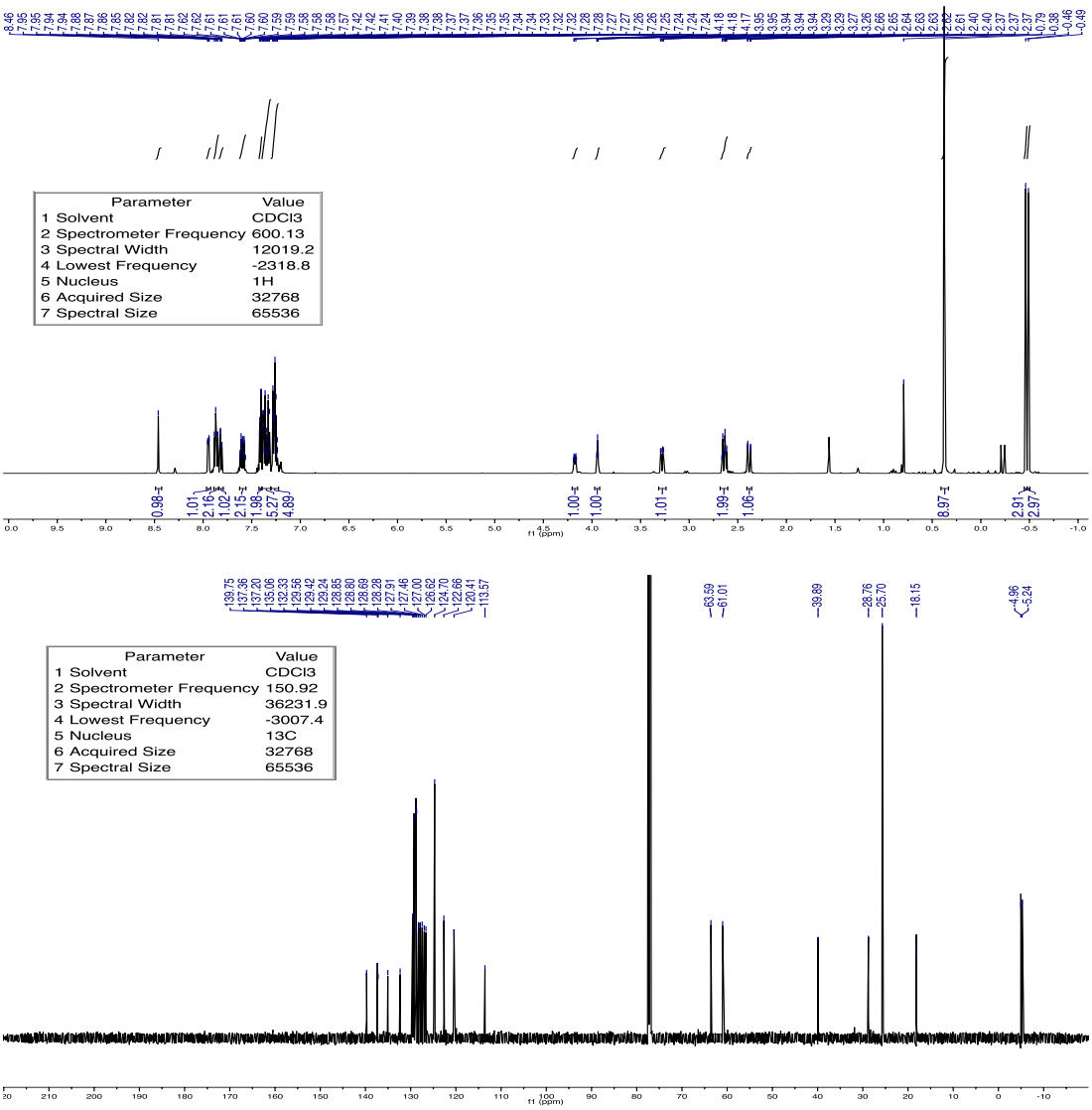
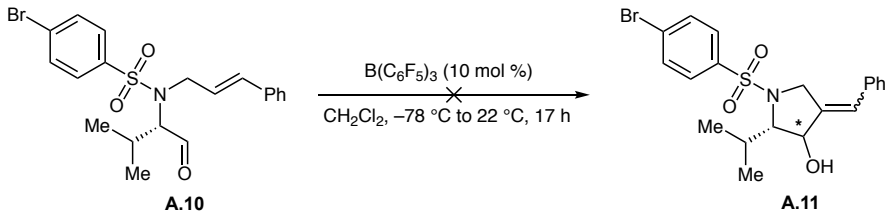


Figure A.27. ^{1}H and ^{13}C{^{1}H} NMR spectra of A.9.

A.5.4.4 BCF-catalyzed cyclization / elimination to produce pyrrolidines

Preparation of pyrrolidine A.11



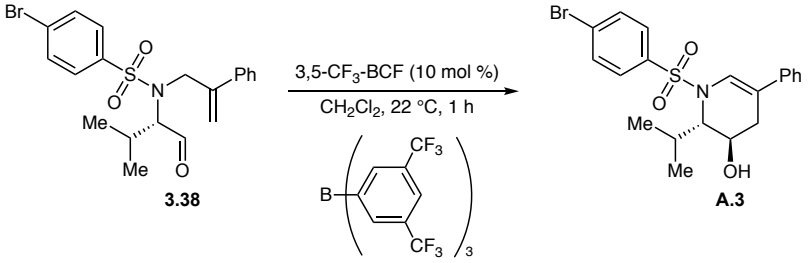
A.10 **A.11**

In a dry, N_2-filled glove box, cinnamyl amino aldehyde **A.10** (0.0500 mmol, 21.8 mg) and $B(C_6F_5)_3$ (BCF, 0.0050 mmol, 2.6 mg) were weighed into a screw cap 1 dram vial equipped with a magnetic stir bar and sealed with a septum cap. The vial was removed from the glove box and cooled to –78 °C in an acetone/$CO_{2(s)}$ bath. CH_2Cl_2 (1.00 mL, 0.05 M) was added slowly dropwise down the side of the vial. The solution was allowed to slowly warm to room temperature overnight in the dewar with magnetic stirring. After 17 h, the catalyst was quenched with 50 μL of Et_3N and the solvent was removed *in vacuo*. Dimethylformamide (0.050 mmol, 3.9 μL) was added as an internal standard and the residue taken up in $CDCl_3$ for ^1H and ^{13}C NMR analyses to determine conversion, product identity, NMR yield, and crude diastereomeric ratios (d.r.). Despite 32% consumption of starting material, no trace of **A.11** is visible by ^1H or ^{13}C NMR.

(2S)-4-benzylidene-1-((4-bromophenyl)sulfonyl)-2-isopropylpyrrolidin-3-ol (A.11). 32% of the starting material was consumed with no generation of desired product detectable by ^1H and $^{13}C\{^1H\}$ NMR. The substrate appears to slowly decompose under the reaction conditions.

A.5.4.5 Perfluoroaryl borane catalyst screen

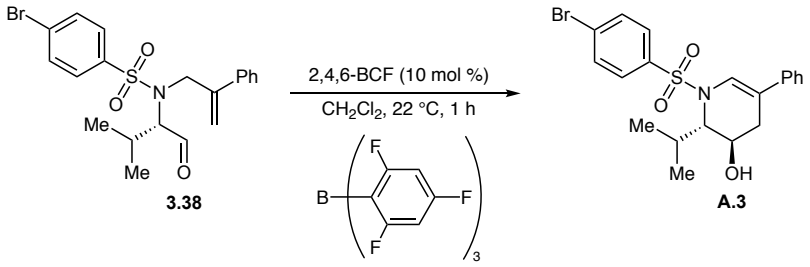
Preparation of tetrahydropyridine A.3



In a dry, N_2-filled glove box, amino aldehyde **3.38** (0.0500 mmol, 21.8 mg) and $B(C_6H_3(CF_3)_2)_3$ (3,5-CF_3-BCF; 0.0050 mmol, 3.3 mg) were weighed into a screw cap 1 dram

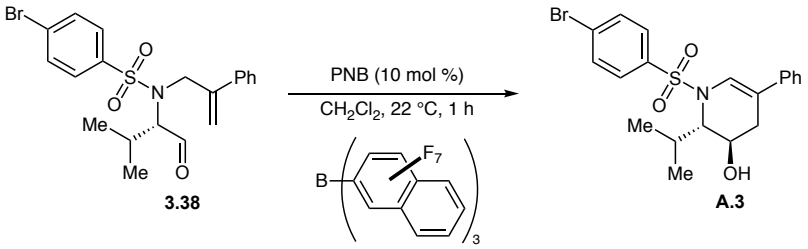
vial equipped with a magnetic stir bar. CH_2Cl_2 (1.00 mL, 0.05 M) was added and the vial was sealed with a septum cap. The solution was stirred at 22 °C for 1 h, after which time the catalyst was quenched with 50 μL of Et_3N and the solvent was removed *in vacuo*. Dimethylformamide (0.050 mmol, 3.9 μL) was added as an internal standard and the residue taken up in $CDCl_3$ for ^1H and ^{13}C NMR analyses; the desired tetrahydropyridine **A.3** was produced in 95% NMR yield and >98:2 d.r.. The crude residue was purified by silica gel chromatography (5:1 *n*-pentane:ethyl acetate; $R_f = 0.3$) to yield the tetrahydropyridine product **A.3** as a white, crystalline solid in 95% yield (20.7 mg) and >98:2 d.r..

Preparation of tetrahydropyridine A.3



In a dry, N_2-filled glove box, amino aldehyde **3.38** (0.0500 mmol, 21.8 mg) and $B(C_6H_2F_3)_3$ (2,4,6-BCF; 0.0050 mmol, 2.0 mg) were weighed into a screw cap 1 dram vial equipped with a magnetic stir bar. CH_2Cl_2 (1.00 mL, 0.05 M) was added and the vial was sealed with a septum cap. The solution was stirred at 22 °C for 1 h, after which time the catalyst was quenched with 50 μL of Et_3N and the solvent was removed *in vacuo*. Dimethylformamide (0.050 mmol, 3.9 μL) was added as an internal standard and the residue taken up in $CDCl_3$ for ^1H and ^{13}C NMR analyses; the desired tetrahydropyridine **A.3** was produced in 7% NMR yield (62% returned starting material).

Preparation of tetrahydropyridine A.3



In a dry, N_2-filled glove box, amino aldehyde **3.38** (0.0500 mmol, 21.8 mg) and B(2-($C_{10}F_7$))$_3$ (PNB; 0.0050 mmol, 3.9 mg) were weighed into a screw cap 1 dram vial equipped with a magnetic stir bar. CH_2Cl_2 (1.00 mL, 0.05 M) was added and the vial was sealed with a septum cap. The solution was stirred at 22 °C for 1 h, after which time the catalyst was quenched with 50 μL of Et_3N and the solvent was removed *in vacuo*. Dimethylformamide (0.050 mmol, 3.9 μL) was added as an internal standard and the residue taken up in $CDCl_3$ for ^1H and ^{13}C NMR analyses; the desired tetrahydropyridine **A.3** was produced in 91% NMR yield and >98:2 d.r..

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