Stereoselective Synthesis of Organoboron Reagents and their Application Toward the Synthesis of Amphidinolides C and F:

Author: Sheila Namirembe

Stereoselective Synthesis of Organoboron Reagents and their Application Toward the Synthesis of Amphidinolides C and F

Sheila Namirembe

A dissertation

submitted to the Faculty of

the department of chemistry

in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

Boston College

Morrissey College of Arts and Sciences
Graduate School

May 2020

Stereoselective Synthesis of Organoboron Reagents and their Application Toward the Synthesis of Amphidinolides C and F

Sheila Namirembe

Advisor: Professor James P. Morken

Abstract: This dissertation details three main projects that focus on stereoselective synthesis of organoboron reagents and their application to total synthesis studies. The first chapter describes the development of an enantioselective palladium-catalyzed conjuntive cross-coupling of bis(alkenyl)borates to access chiral allylboron reagents. These reagents are of high synthetic value that is demonstrated through various applications. The second chapter describes the development of a diastereoselective amine-modified boron-Wittig reaction with ketone electrophiles to access trisubstituted alkenyl boronic esters. The synthetic utility of these trisubstituted alkenyl boronic esters is demonstrated through a novel palladium-catalyzed cross-coupling reaction. The third chapter encompassess studies toward the total synthesis of natural products amphidinolides C and F. It highlights the application of methods developed in the Morken laboratory in the context of challenging total synthesis. It also highlights the potential for newly developed conjunctive cross-coupling and boron-Wittig reactions to solve problems in total synthesis.

ACKNOWLEDGEMENTS

I would like to extend my deeprest gratitude and appreciation for my advisor, Prof. James P. Morken for his support during these past five years. Jim is extremely knowledgeable and his passion and enthusiasm for chemistry is unmatched. Jim is an educator who cares about the scientific growth of his students, but at the same time creating an environment that is condusive for personal growth. Jim has challenged me to think critically, and molded me into an independent chemist. I would not trade the experience in the Morken lab for another!

I would like to thank Profs. X. Peter Zhang and Marc L. Snapper for serving as members of my thesis committee and taking the time out of their busy schedules to read my thesis. I am indebted to Profs. Marc L. Snapper and Shih-Yuan Liu for their help in advancing my scientific career after Boston College.

The work that is presented in this thesis is a testament to the collaborative nature of the Morken laboratory and I have many co-workers to thank. First, I am grateful for Dr. Emma K. Edelstein, who took me under her wings as a mentee during my first year of graduate school. Thank you for being patient, and helping me navigate the first year of graduate school. I would also like to thank the undergraduate students that gave me an opportunity to mentor them; Chenpeng Gao, Ryan P. Wexler, Andrea Grote and Joy Zhou. I would like to further thank Chenpneg Gao and Ryan P. Wexler for their hardwork and help with the boron-Wittig reaction. Lastly, but definitely not least, I would like to thank Dr. Lu Yan. You made working on amphidinolide C and F incredibly energizing. It was great to have a co-worker who was always open to seeing problems from a different

persective, but also accepting criticism at the same time. Thank you for making the journey bearable even when several routes we had designed completely fell apart midway and we had to go back to the drawing board. Through this, I learned to always have plans A, B, C and D for back up! I would like to thank Dr. Bryan T. Ingoglia, Elton Kativhu and Alex J. Vendola for taking the time to read my dissertation and provide feedback. I am grateful for the friendships that were fostered in the Morken lab with various colleagues. You made life in and out of lab both fun and enjoyable. For this, I have many people to thank (in no particular order); Dr. Emma K. Edelstein, Dr. Lu Yan, Dr. Gabriel J. Lovinger, Mark D. Aparece, Dr. Chunyin Law, Alex J. Vendola, Elton Kativhu and Dr. Bryan T. Ingonglia.

My academic journey to this point would not have been possible if it weren't for the "village" that raised me and allowed me to pursue my passion. I am grateful for the many men and women at various institutions (College of the Holy Cross, United World College of the Atlantic, and King's College Budo) that have mentored me over the years, believed in me, opened doors of opportunity, and challenged me to bring my best self to the table. I would not have made it this far if our paths had not crossed, so thank you!

I am grateful for my sisters who have stood by me over the last many years. Thank you for constant love and support. I would also like to thank Innocent Mugyenzi for his unwavering love, support and understanding especially during the last two years.

To my mother, I fall short of words to express my sincere gratitude. Thank you for believing me in without a doubt, for allowing me to follow my pursuits and being a constant source of support, love, morale and everything in between. You inspire me in so many ways to be a better person and leave the world a better place!

Dedicated to my mother

Annet Nsubuga.

TABLE OF CONTENTS

List of Abbreviations

Å: angstrom

Ac: acetyl acac: acetylacetonyl

atm: atmosphere(s)

$B_2(cat)_2$: bis(catecholato)diboron

$B_2(pin)_2$: bis(pinacolato)diboron

$B_2(pro)_2$: bis(propanediol)diboron

9- BBN: 9-borabicylco[3.3.1]nonane

BINAP: 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl

Bn: benzyl

cat: catechol

cod: 1,5-cyclooctadiene

conv: conversion

COSY: correlation spectroscopy

Cy: cyclohexyl

d: day(s)

DART: direct analysis in real time

dba: dibenzylideneacetone

DCM: dichloromethane

DFT: density functional theory

DI: deionized

DME: dimethoxyethane

DMF: N,N-dimethylformamide dmpd: 2,4-dimethylpenane-2,4-diol

DMPU: 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone

DMSO: dimethyl sulfoxide

DCyPF: 1,1'-bis(dicyclohexylphosphino)ferrocene

DPPF: 1,1'-bis(diphenylphosphino)ferrocene

d.r.: diastereomeric ratio

e.e.: enantiomeric excess

eq.: equation(s)

equiv.: equivalent(s)

er: enantiomeric ratio

ESI: electrospray ionization

EtOAc: ethyl acetate

h: hour(s)

HMTETA: 1,1,4,7,10,10-Hexamethyltriethylenetetramine

HPLC: high performance liquid chromatography

HRMS: high resolution mass spectrometry

HREIMS: high resolution electrospray ionization mass spectrometry

Hz: hertz

IPA: isopropanol

IR: infrared spectroscopy

LDA: lithium diisopropylamide

LiTMP: lithium 2,2,6,6-tetramethylpiperidide

M: molar

MeCN: acetonitrile

Me_6TREN: Tris[2-(dimethylamino)ethyl]amine

min: minutes

MOM: methoxymethyl

MS: molecular sieves

nbd: norbornadiene

NBS: N-bromosuccinimide

neo: neopentyl glycol

NHC: *N*-heterocyclic carbene

NMR: nuclear magnetic resonance

NOESY: nuclear overhauser effect spectroscopy

NR: no reaction

$Pd(OAc)_2$: palladium (II) acetate

Pd(dppf)Cl_2: [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)

pin: pinacol

pmb: *p*-methoxybenzyl

PMDTA: *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine

ppm: parts per million

Pyr: pyrimidine

rac: racemic

rt: room temperature

Ruphos: 2-dicyclohexylphosphino-2,6′-diisopropoxybiphenyl

SFC: supercritical fluid chromatography

TBAF: tetrabutylammonium fluoride

TBDPS: *t*-buttyldiphenylsilyl

TBS: *t*-butyldimethylsilyl

TBS-DHG: (2R,3S,4R)-2-(((tertbutyldimethylsilyl)oxy)methyl)tetrahydr o-2H-pyran-3,4-diol

temp: temperature

TEMPO: 2,2,6,6-tetramethyl-1-piperidinyloxy free radical

TES: triethylsilane

TIPS: triisopropylsily

TMEDA: *N*,*N*,*N*′,*N*′-Tetramethylethylenediamine

Tf: trifluomethanesulfonyl

TFA: trifluoroacetate

TFAA: trifluoroacetic anyhyride

TMTAN: 1,4,7-Trimethyl-1,4,7-triazacyclononane

TMS: trimethylsilyl

Tol: toluene

Ts: *p*-toluenesulfonyl

UV: ultraviolet

Xylyl: dimethylphenyl

Chapter 1

Enantioselective conjunctive cross-coupling of bis(alkenyl) boronates: a general synthesis of chiral allylboron reagents.

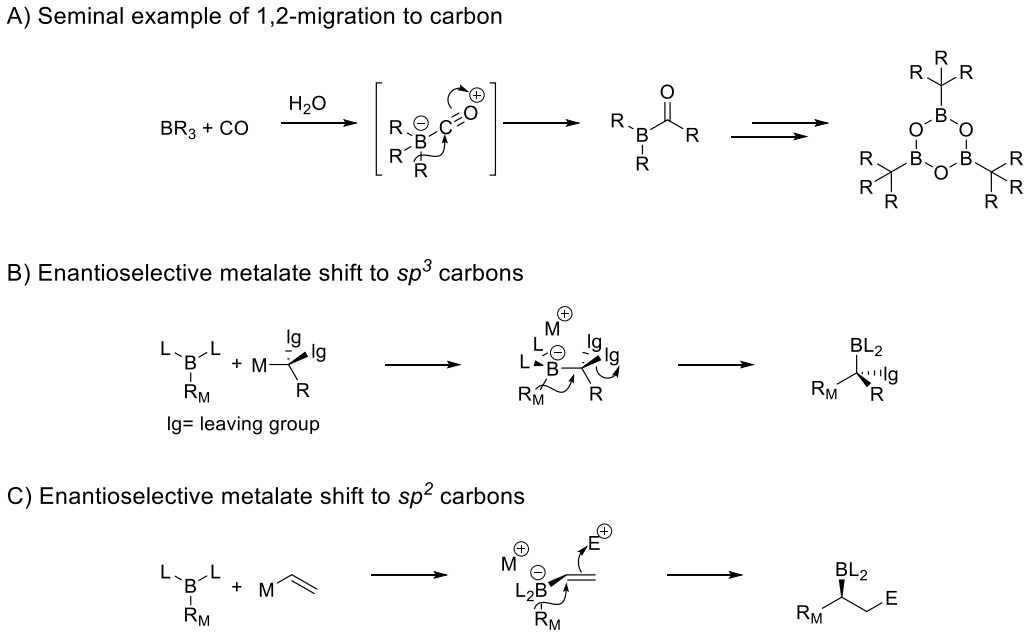
1.1 Introduction

In 1962, M. Hillman at DuPont's Experimental Station Laboratory described a reaction between trialkylboranes and carbon monoxide wherein coordination of CO to boron was followed by 1,2-migration of an alkyl group from boron to carbon (Scheme 1.1 A).[1] Notably, the remaining B-alkyl groups also underwent migration – likely facilitated by the presence of water – such that a new isolable organoboron product was generated. This reaction proved to be the first example of what would turn out to be a broad range of organoboron homologation reactions, a class of transformations that establish a new C–C bond while retaining a versatile organoboron functional group in the product. A noteworthy aspect of many such homologation reactions is that they can be conducted in a stereoselective fashion and enable new methods for stereoselective synthesis. A particularly exciting direction surrounds homologation processes that can be facilitated by the influence of an external catalyst, especially when that catalytic entity can be employed to accomplish stereoselective transformations. Two such generalized strategies are depicted in Scheme 1.1. In the first approach (Scheme 1.1 B), organoboron compounds are treated with carbanions that bear enantiotopic leaving groups such that the migration step is stereochemistry-determining and can be influenced by an external activator. In the

[1] Hillman, M. E. D. *J. Am. Chem. Soc.* **1962**, *84*, 4715–4720.

second approach (Scheme 1.1 C), a 1,2-metalate shift is facilitated by subjecting alkenylboron-derived "ate" complexes to an external π-activator: if the prochiral faces of the reacting alkene can be distinguished, then this strategy provides new opportunities for the stereoselective synthesis of organoboron reagents.

Scheme 1.1 1,2-metalate shifts involving organoboron compounds



1.2. Background

A variety of important metalate shift-based transformations that operate through the use of stoichiometric chiral reagents have been developed.[2] However, this discussion will be focused on catalyst promoted metalate shifts such as those described in Scheme 1.1 B and 1.1 C.

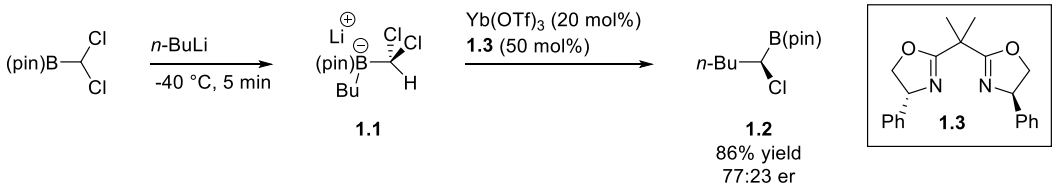
[2] Leonori, D.; V. K. Aggarwal. *Acc. Chem. Res.* **2014**, *47*, 3174–3183.

1.2.1 Catalytic metalate shifts involving migration to sp^3 carbon atoms

Stereoselective homologation by 1,2-metalate shift to sp^3 carbons has been broadly developed, both with chiral diolato ligands on boron[3] and through the use of enantiomerically-enriched homologation reagents comprised of organometallic compounds that bear a leaving group.[2] Catalytic and enantioselective differentiation of two enantiotopic leaving groups on the C*(sp^3)* atom is not a trivial task. Hints that such a process might operate can be found in seminal studies by Matteson who found that with chiral pinanediol-derived boronic esters, $ZnCl_2$ was required for high levels of stereoselectivity during homologation with dichloromethyllithium. It was proposed that Zn^{2+} engaged in bidentate chelation between a pinacol oxygen and a chloride leaving group.[4] In 1997, Jadhav rendered such a process catalytic and enantioselective with the use of an external chiral Lewis acid catalyst that could discriminate between the enantiotopic pro-*R* and pro-*S* chloride atoms of an *in situ* generated (dichloromethyl)-boron "ate" complex, **1.1** (Scheme 1.2).[5] This reaction afforded chiral α-chloroalkylboronic esters (**1.2**), which are important intermediates for stereodirected synthesis.[6] Of note, the chiral ytterbium salt used for this process could be employed in a substoichiometric fashion. While, there is still ample room for development of this type of process with respect to selectivity and catalyst efficiency, Jadhav's contribution indicates that the elementary steps are indeed viable.

[3] Matteson, D. S.; Majumdar, D. *J. Am. Chem. Soc.* **1980**, *102*, 7590–7591.
[4] For a discussion: Matteson, D. S. *Tetrahedron* **1998**, *54*, 10555–10607.
[5] Jadhav, P. K.; Man, H.-W. *J. Am. Chem. Soc.* **1997**, *119*, 846–847.
[6] Matteson, D. S. *Chem. Rev.* **1989**, *89*, 1535–1551.

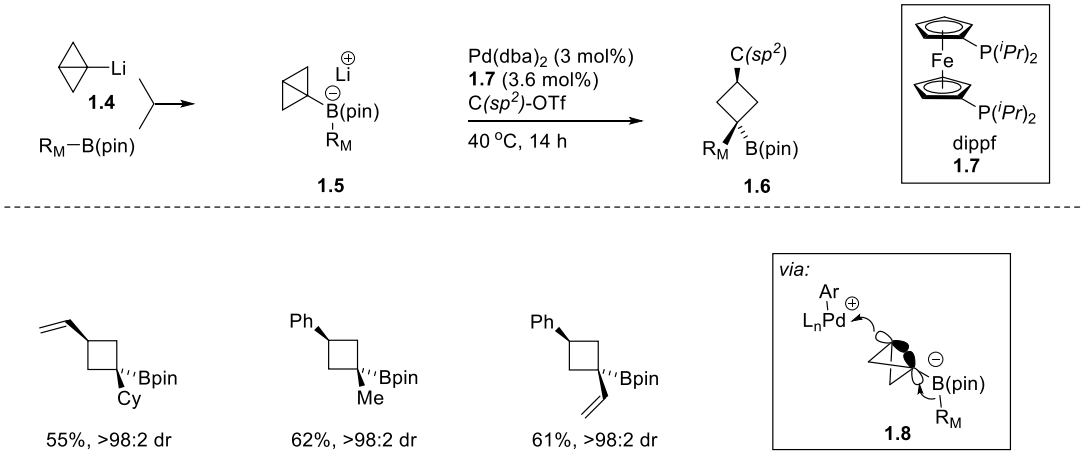
Scheme 1.2 Catalytic asymmetric homologation by selective halide displacement.



A recent report by Aggarwal describes a different catalytic metalate shift that involves migration of a carbon from boron to an attached sp^3-hybridized carbon atom.[7] When borate complex **1.5** – a structure that is prepared from readily available organolithium **1.4** – was treated with 3 mol% of a palladium complex and organotriflate electrophiles, efficient conversion to cyclobutanes (**1.6**) occurs (Scheme 1.3). In this reaction, the thermodynamic driving force for the metalate shift is the relief of approximately 66 kcal/mol of ring strain present in the bicyclo [1.1.0] butane motif. Importantly, the team found that triflate electrophiles were essential for the formation of cationic palladium that is needed to facilitate the 1,2-migration reaction. On the basis of the stereochemical outcome of this process, it appears that subsequent to oxidative addition, an intermediate cationic Pd complex reacts at the β carbon of the strained bicycle (**1.8**, Scheme 1.3). Unlike most transmetalation reactions of organoboronates, the α-carbon of bicycle **1.5** is rendered inaccessible by the boron ligand framework. Instead, the authors propose Pd approaches from the backside of the β-carbon, taking advantage of the p-character at the atoms in the strained ring. While this pathway is plausible, it is none the less remarkable that direct transmetalation of the migrating group, resulting in Suzuki-Miyaura coupling of the R_M group is not a problem.

[7] Fawcett, A.; Biberger, T.; Aggarwal, V. K. *Nature Chem.* **2019**, *11*, 117–122.

Scheme 1.3 Catalytic ring-opening of strained bicycles by 1,2-metalate shift.



1.2.2 Catalytic metalate shifts involving migration to *sp* and *sp*^{2} carbon atoms

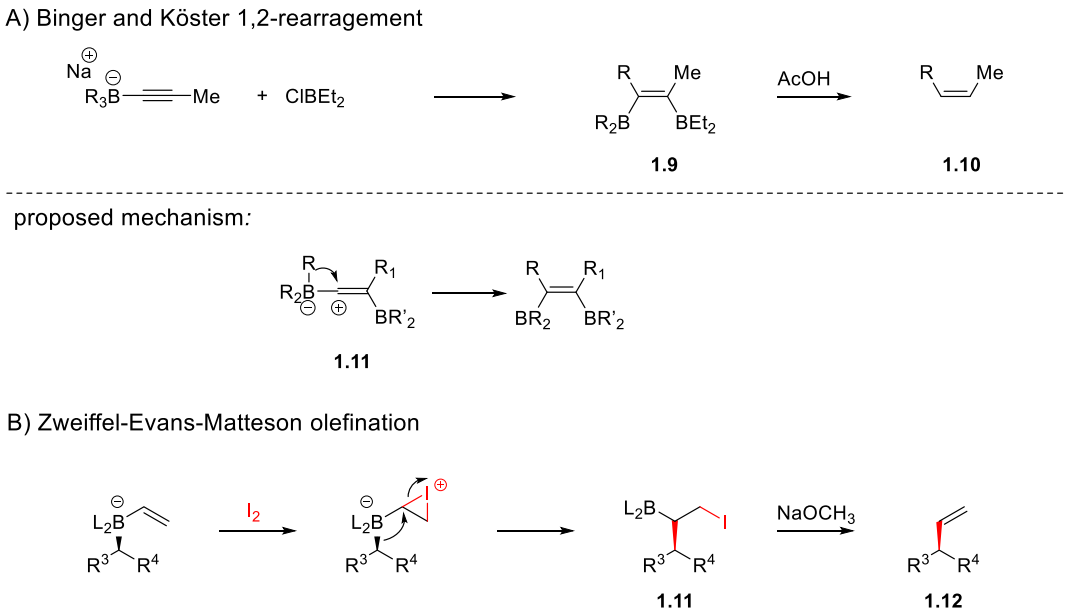
Association of alkenyl- and alkynylboron derived "ate" complexes with external π-acidic electrophiles can prompt a 1,2-migration from boron to the adjacent unsaturated carbon atom. This mode of activation was first observed by Binger and Köster with main group electrophiles, specifically a chlorodiethylborane-induced rearrangement of alkynylborates (Scheme 1.4 A) that was postulated to occur by the mechanism depicted in Scheme 1.4 B.[8] Upon treatment of the vicinal diboron product **1.9** with acetic acid, the *cis*-alkene **1.10** was isolated. This outcome secured the configurational assignment of organoboron **1.9** and suggests a metalate shift by *anti*-addition of the electrophile and the migrating group across the olefin, a pathway that is followed by the preponderance of metalate rearrangements.

Metalate shifts in alkenylborates were first proposed by Zweifel[9] in iodine-promoted rearrangements of trialkylborane-derived substrates, and later expanded to

[8] Binger, P.; Köster, R. *Tetrahedron Lett.* **1965**, *6*, 1901–1906.
[9] Zweifel, G.; Arzoumanian, H.; Whitney, C. C. *J. Am. Chem. Soc.* **1967**, *89*, 3652–3653.

boronic esters by Matteson[10] and Evans.[11] In these processes (Scheme 1.4 B), subsequent to iodine-prompted rearrangement, base promoted boron-iodine elimination from intermediate **1.11** generates an alkene-containing product, **1.12**. In addition to the examples in Scheme 1.4, a broad range of other main group electrophiles have been shown to promote the 1,2-metalate shift with unsaturated organoboron compounds.[12]

Scheme 1.4 Early stoichiometric electrophile-induced metalate shifts involving unsaturated boron "ate" complexes



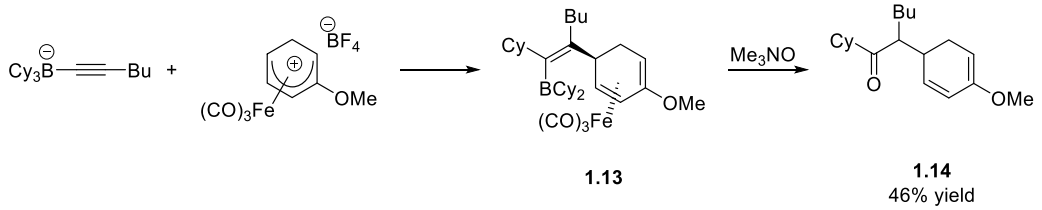
Catalytic reactions that involve 1,2-metalate shifts of alkenyl- and alkynylborates most often employ transition metal-based complexes. With transition metal promotion, metalate rearrangements have been observed to occur through both inner sphere (direct

[10] Matteson, D. S.; Jesthi, P. K. *J. Organomet. Chem.* **1976**, *110*, 25–37.
[11] Evans, D. A.; Crawford, T. C.; Thomas, R. C.; Walker, J. A. *J. Org. Chem.* **1976**, *41*, 3947–3953.
[12] Negishi, E.-I.; Idacavage, M. J. *Org. React.* **1985**, *33*, 1–246.

binding of the metal to the alkene) and outer sphere (nucleophilic attack of the "ate" complex on a metal-bound ligand) pathways.

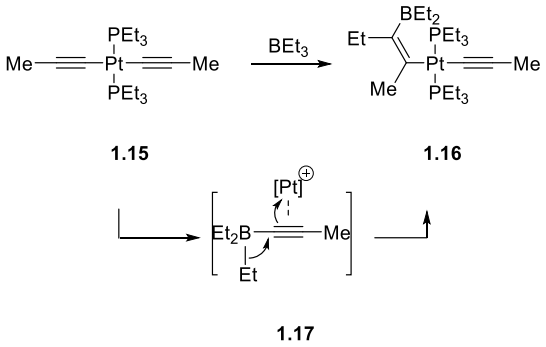
Scheme 1.5 Stoichiometric metalate shifts involving outer sphere and inner sphere addition to transition metal complexes.

A) Pelter: outer sphere Fe-promoted metalate rearragment



1.13 **1.14** 46% yield

B) Wrackemeyer: inner sphere Pt-promoted metalate rearragment



1.15 **1.16**

1.17

Precedent for the outer sphere path was provided by Pelter who found that an alkynylborate would react with a cationic η^5-dienyl iron complex by addition *anti* to the iron center, providing compounds such as **1.13** (Scheme 1.5 A).[13] Treatment of **1.13** with excess trimethylamine N-oxide served to both oxidize the alkenylboron to a ketone as well as oxidatively decomplex iron from the diene, yielding **1.14**.

Evidence for inner sphere activation was first obtained by Wrackmeyer, who found that treatment of platinum bis(acetylide) complex **1.15** with triethylborane resulted in formation

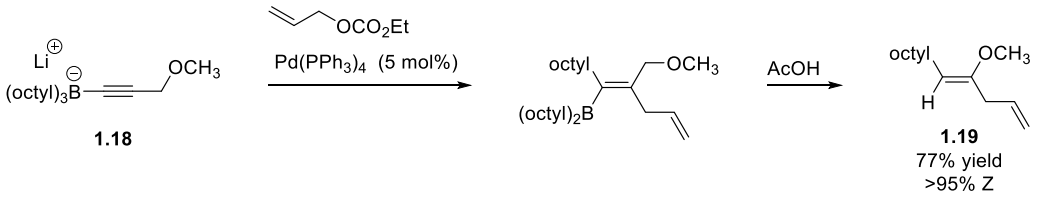
[13] Pelter A.; Gould, K. J.; Kane-Maguire, P, A. L. *J. Chem. Soc., Chem. Commun.* **1974**, 1029–1030.

of platinaborylalkene **1.16** (Scheme 1.5 B).[14] This unusual rearrangement was proposed to occur by transmetalation from Pt to BEt_3 to form an "ate" complex, followed by activation of the generated "ate" complex by the platinum cation (**1.17**); subsequent metalate shift generates the alkenylplatinum complex product.

1.2.3 Catalytic allylic substitutions involving metalate shifts

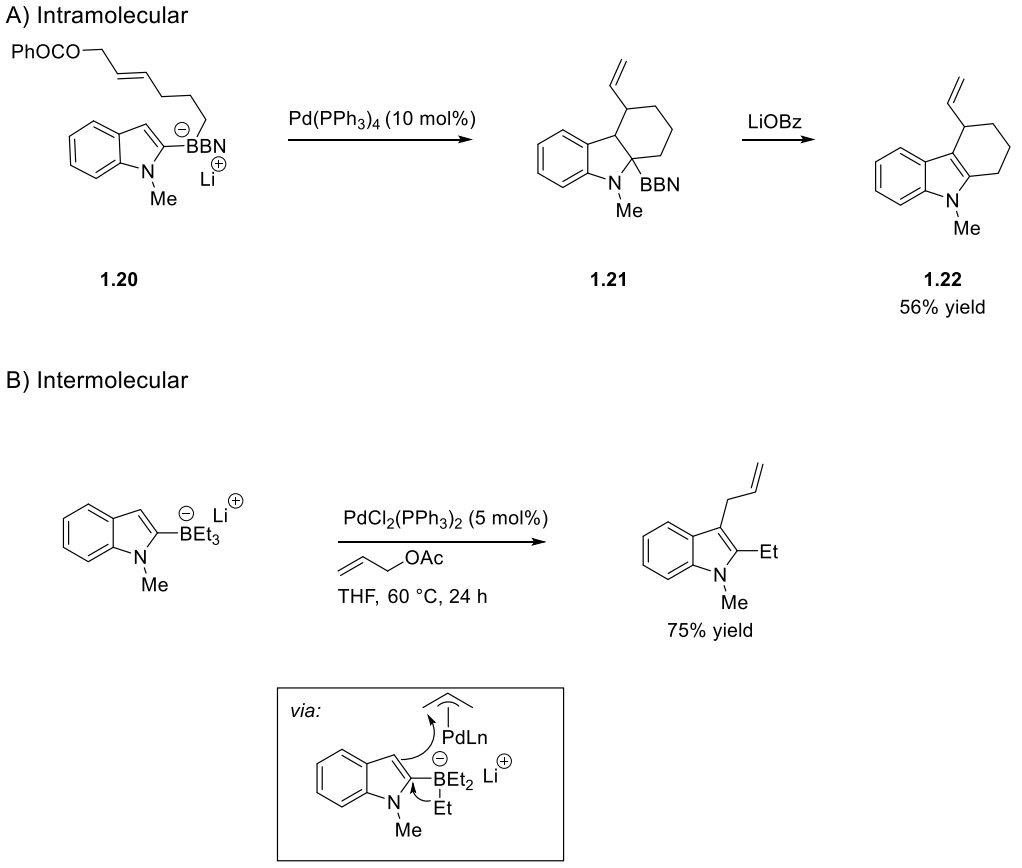
Reactions that occur by outer sphere attack of "ate" complexes on metal-bound ligands comprise the first examples of catalytic reactions involving metalate shifts. In 1990, the Deng laboratory found that treatment of lithium trialkylalkynylborates **1.18** (Scheme 1.6) with allyl carbonate and 5 mol% $Pd(PPh_3)_4$ resulted in the stereoselective formation of borylated skipped dienes; these compounds could be subjected to protodeborylation with acetic acid to furnish the hydrocarbon **1.19**.[15] Generally, this process was found to occur with very high levels of stereocontrol, providing products derived from *anti* addition of the migrating group and Pd(allyl) complex across the alkyne.

Scheme 1.6 Catalytic synthesis of skipped dienes by addition of an alkynylborate to a Pd(allyl) complex with concomitant metalate shift



[14] Sebald, A.; Wrackmeyer, B. *J. Chem. Soc., Chem. Commun.* **1983**, 309–310.
[15] Chan, Y.; Li, N. S.; Deng, M.-Z. *Tetrahedron Lett.* **1990**, *31*, 2405–2406.

Scheme 1.7 Ishikura's Pd-catalyzed addition of indole borates to allyl electrophiles.

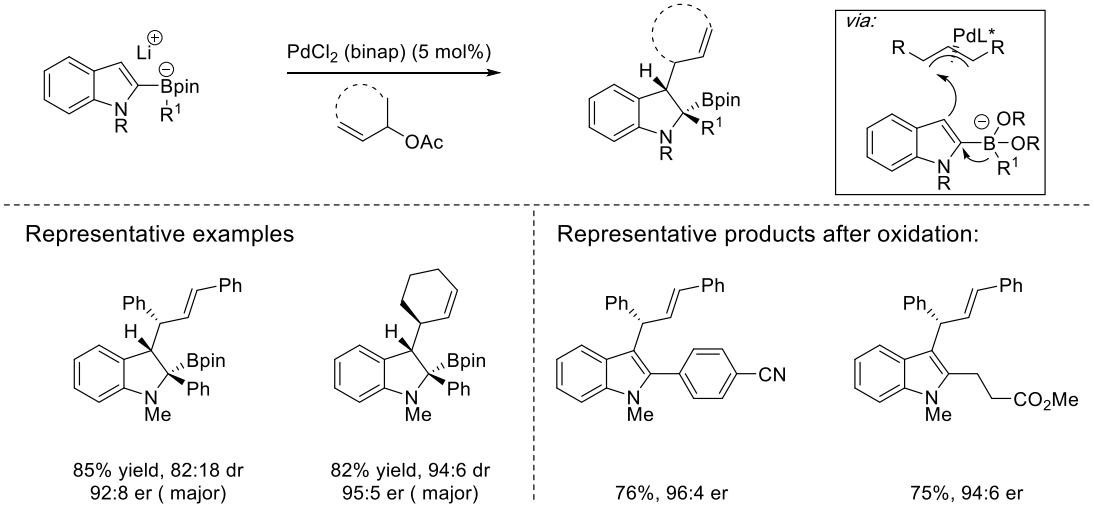


Beginning in 1991, Ishikura disclosed a series of studies involving indole-derived "ate" complexes.[16] As depicted in Scheme 1.7, the transition metal-catalyzed 1,2- metalate rearrangement from indole derived borate complex **1.20** onto a tethered Pd(allyl) complex provides ring-fused product **1.22** by way of **1.21**. The proposed mechanism suggests initial oxidative addition from Pd(0) to generate a palladium π–allyl complex, which then induces a chemoselective 1,2-migration reaction. Notably, the primary alkyl group undergoes migration in preference to the 9-BBN carbon atoms. Although the migration reaction itself serves to temporarily dearomatize the indole nucleus providing an added barrier to the

[16] Ishikura, M.;. Terashima,M. *J. Chem. Soc., Chem. Commun.* **1991**, 1219–1221.

metalate shift, the reaction nevertheless proceeds efficiently. Subsequent to rearrangement, the alkyl BBN undergoes a deborylative re-aromatization; a process that likely requires an oxidation. In addition to these intramolecular examples, intermolecular addition to allyl acetate (Scheme 1.7 B) and addition to epoxy dienes,[17] as well as and propargylic carbonates,[18] were also effective.

Scheme 1.8 Ready's catalytic asymmetric coupling of indolylborates and allyl acetates.



With precedent established for catalytic addition of indole-derived borates to Pd(allyl) complexes, Ready studied an asymmetric version of this reaction.[19] Generation of three contiguous stereogenic centres in indoles and indolines is a desired but challenging one-step synthetic transformation. This three-component coupling allows enantio-, regio- and diastereoselective palladium-catalyzed C–C bond formation at C-2 and C-3 of the

[17] Ishikura, M. Kato,H. *Tetrahedron*. **2002**, *58*, 9827–9838.
[18] Ishikura, M.; Matsuzaki, Y.; Agata, I.; Katagiri, N. *Tetrahedron*. **1998**, *54*, 13929–13942.
[19] (a) Panda, S.; Ready, J. M. *J. Am. Chem. Soc.* **2017**, *139*, 6038–6041. (b) Panda, S.; Ready, J. M. *J. Am. Chem. Soc.* **2018**, *140*, 13242–13252.

indole in a single flask process (Scheme 1.8). This method provides a powerful inroad to pharmaceutically relevant motifs from a simple lithiated indole, a substituted allyl acetate electrophile, and an organoboron nucleophile. While the initial indoline product contains a boronic ester, oxidation provides a convenient route to the substituted indole derivative. The Ready group further applied this method to the synthesis of indolines with quaternary stereocenters at C3.[19]

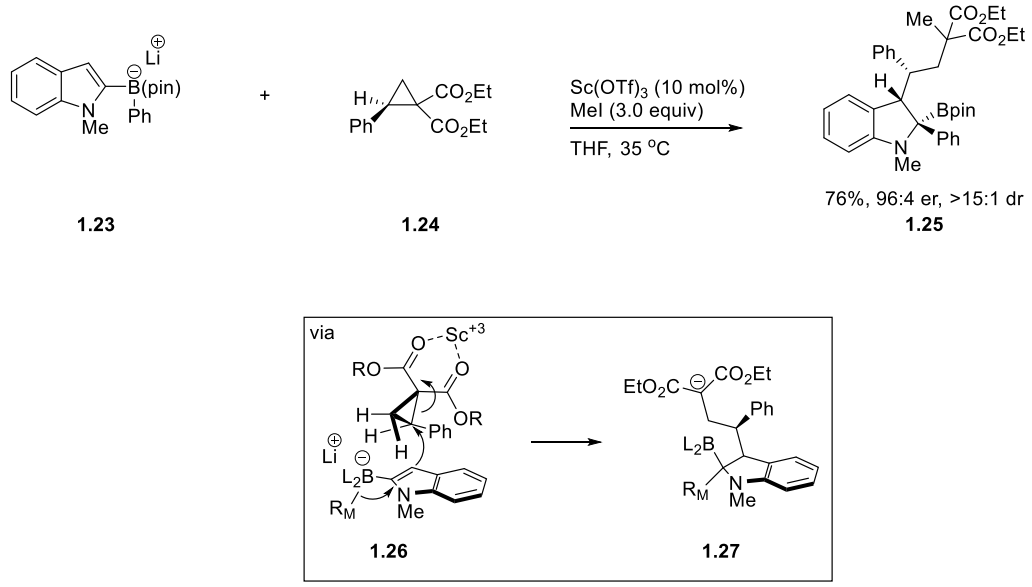
1.2.4 Reaction of indolylborates with activated cyclopropanes

Studer expanded the scope of electrophiles that can activate 2-indolylboron "ate" complexes to include donor-acceptor cyclopropanes (Scheme 1.9).[20] Treatment of phenyl-substituted cyclopropane **1.24** with 10 mol% $Sc(OTf)_3$ is sufficient to activate the strained ring for nucleophilic attack by indolylborate **1.23**, thereby generating a substituted indoline **1.27**, which contains a malonate anion; subsequent trapping with alkyl halides delivers the reaction product **1.25** and likely facilitates turnover of the catalyst. Of note, this protocol allows the formation of three new C–C bonds in a highly diastereoselective fashion. By using a chiral donor-acceptor cyclopropane, the stereochemical course of the process could be followed and allowed a plausible mechanism to be proposed (inset, Scheme 1.9) that suggests the ring opening is stereospecific: the 1,2-migration occurs in an *anti*-fashion with respect to the cyclopropane attack, and the cyclopropane substituent (Ph) is directed away from the large boron framework (Scheme 1.9). While stereoinduction with chiral substrates allows for construction of non-racemic products with this process, use of achiral

[20] Das, S.; Daniliuc, C. G.; Studer, A. *Angew. Chem. Int. Ed.* **2018**, *57*, 4053–4057.

cyclopropanes in conjunction with chiral Lewis acid catalysts would be a plausible and exciting strategy for absolute stereochemical control in this reaction.

Scheme 1.9 Studer's catalytic stereoselective coupling of indolylborates and cyclopropanes by way of a metalate shift.



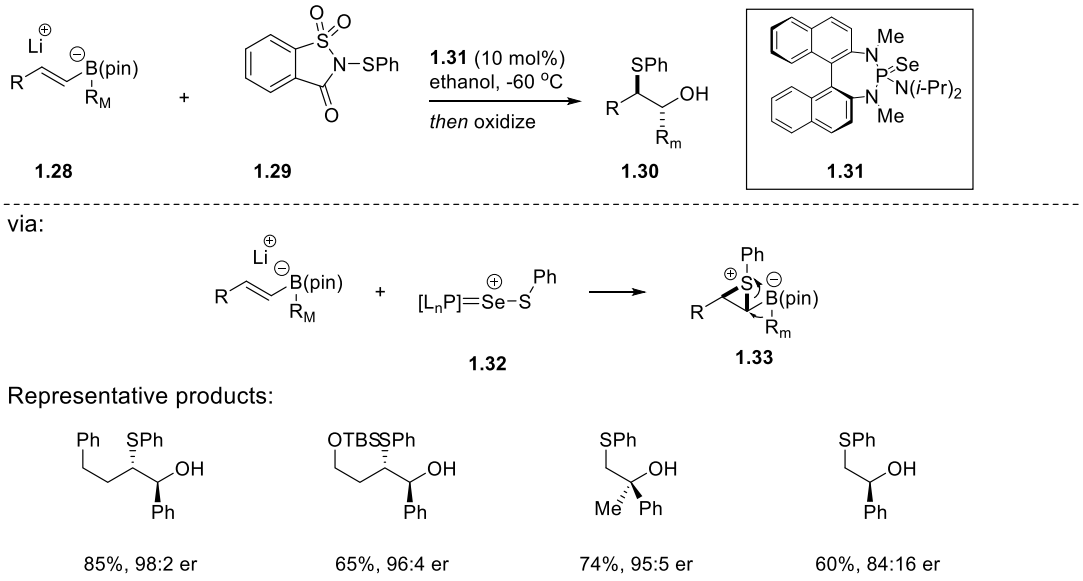
1.2.5 Catalytic activation of alkenylboronates by sulfenium ion transfer

Recently, Denmark established an enantio- and diastereoselective Lewis base-catalyzed carbosulfenylation of alkenylboron compounds (Scheme 1.10).[21] In a creative reaction design, these authors first generated a series of prochiral alkenylboron-derived "ate" complexes and then subjected them to catalytic stereoselective sulfenium ion transfer using chiral selenium-based catalyst designs the group had developed for sulfenofunctionalization reactions.[22] In the context of alkenylboronates, reaction of the olefin with a cationic donor-acceptor complex **1.32** results in selective formation of a

[21] Tao, Z.; Robb, K. A.; Panger, J. L.; Denmark, S. E. *J. Am. Chem. Soc.* **2018**, *140*, 15621–15625.
[22] For an overview: Denmark, S. E.; Hartmann, E.; Kornfilt, D. J. P.; Wang, H. *Nat. Chem.*, **2014**, *6*, 1056–1064.

thiiranium ion, **1.33** which undergoes stereospecific opening by a 1,2-metalate shift. This rearrangement applies to mono-, di- and trisubstituted alkenylboron substrates and affords products (**1.30**) with vicinal stereogenic centers in high levels of enantioselectivity.

Scheme 1.10 Denmark's catalytic asymmetric metalate rearrangement through sulfenium ion catalysis.



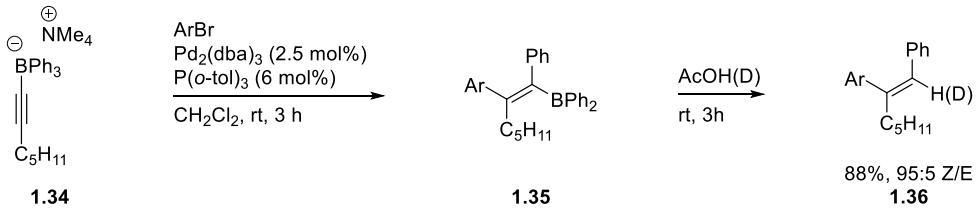
1.2.6 Activation of alkynyltrialkylboronates with Pd complexes

In 2007, Murakami developed the first system wherein a transition metal complex appeared to activate an unsaturated boronate for 1,2-metalate rearrangement by direct bonding between a metal and the substrate (Scheme 1.11).[23] An (aryl)Pd(II) complex, generated by oxidative addition between Pd(0) and an aryl halide, induced rearrangement of an alkynyltrialkylborate(1.**34**), ultimately furnishing a trisubstituted (*Z*)-alkenylboron (**1.35**) as the product. A variety of aryl migrating groups and aryl bromide electrophiles were competent in the reaction, whereas aryl chlorides, and triflates were found to be poor

[23] Ishida, N.; Miura, T.; Murakami, M. *Chem. Commun.*, **2007**, 4381–4383.

substrates. The organoborane products (**1.35**) underwent efficient protodeboronation to give trisubstituted alkenes (**1.36**) in excellent yield and diastereoselectivity. This reaction was further developed to engage alkynyltrialkylborates with electrophilic ammonium salts, 2-bromopyridine-N-oxide, and allyl electrophiles.[24]

Scheme 1.11 Murakami's Pd-catalyzed coupling of alkynylborates and aryl bromides.

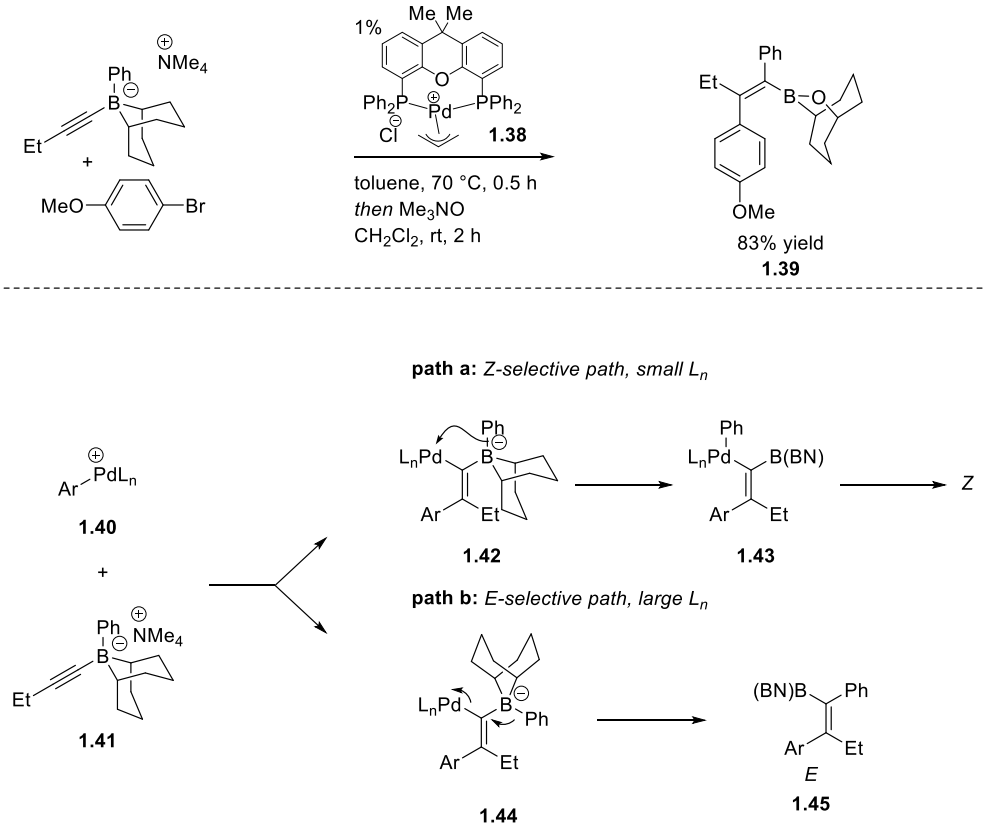


Later, the Murakami group reported the *E*-selective synthesis of trisubstituted alkenyl-9-BBN derivatives via a (Xantphos)palladium-catalyzed reaction of alkynylborates and aryl halides (Scheme 1.12).[25] Mechanistically, the *trans*-addition product (**1.39**) was proposed to arise via the mechanism depicted in Scheme 1.12. After oxidative addition, a cationic palladium complex (**1.40**) is proposed to undergo carbopalladation of the alkynylborate (**1.41**). Subsequently, the aryl group migrates from boron to the α-carbon (path b) and reductively displaces Pd with inversion at the sp^2 carbon, thereby giving net *anti* addition of the electrophile and migrating group across the alkyne (product **1.45**). The stereochemical outcome was largely dependent on the ligand: with less encumbered tri(*o*-tolyl)phosphine, 1,3-migration of the phenyl group from boron to palladium (path a, intramolecular transmetalation) is thought to occur and the *Z* isomer is obtained. In contrast, with Xantphos, a bulky bidentate phosphine ligand, transmetalation

[24] (a) Ishida, N.; Narumi, M.; Murakami, M. *Org. Lett.* **2008**, *10*, 12879–1281. (b) Naoki, I.; Tatsuo, S.; Shota, M.; Tomoya, M.; Murakami, M. *Bull. Chem. Soc. Jpn.* **2010**, *83*, 1380–1385. (c) Ishia, N.; Ikemoto, W. S.; Narumi, M.; Murakami, M. *Org. Lett.* **2011**, *13*, 3008–3011.
[25] Ishida, N.; Shimamoto, Y.; Murakami, M. *Org. Lett.* **2009**, *11*, 5434–5437.

is inhibited and 1,2-migration of the phenyl group onto the α carbon occurs, resulting in the *E* product. In terms of the migrating groups, electron rich and electron poor arenes could participate. Electron rich and electron deficient aryl halide electrophiles were also competent in the reaction. A wide range of functional groups such thiophenyl, silyl ether, ester, and phthalimide were also tolerated in the reaction.

Scheme 1.12 Murakami's Pd-catalyzed coupling of alkynylborates and aryl bromides.



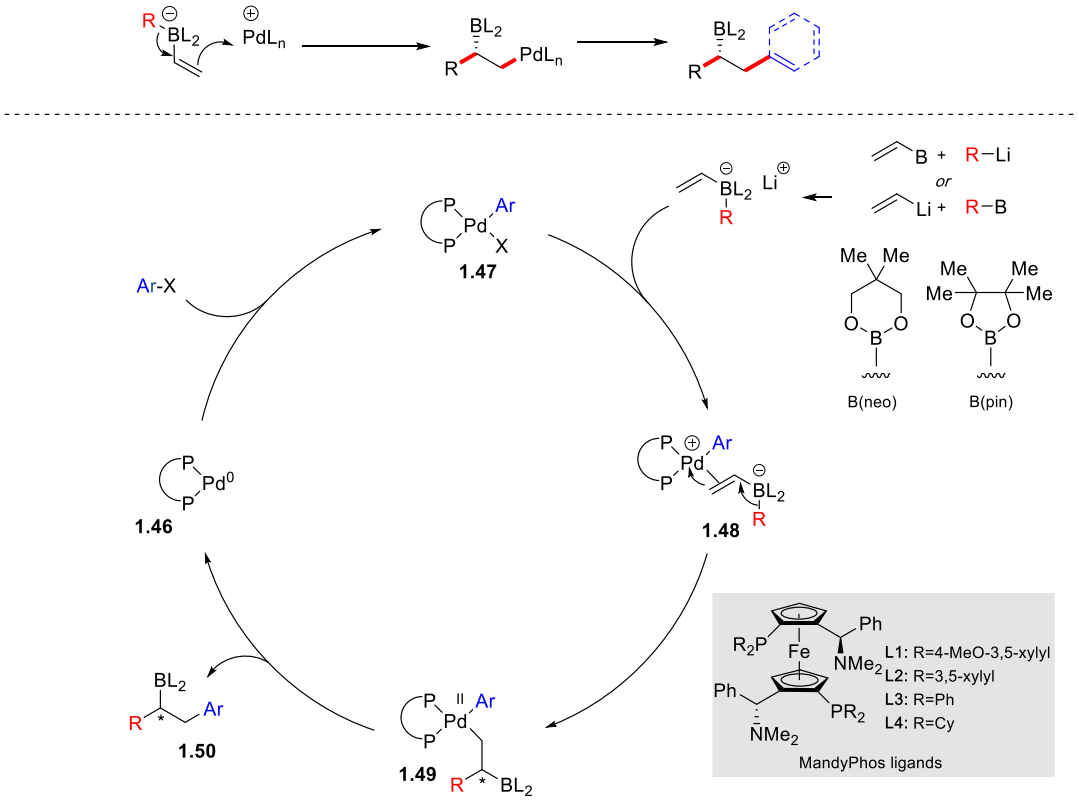
1.3 Conjunctive Cross-Coupling

1.3.1 Activation of alkenyboronic ester derived "ate" with Pd complexes

In 2015, the Morken group began investigating the use of transition metal complexes to activate alkenylboron-derived "ate" complexes. These studies would lead to the first examples of catalysis of metalate shifts involving direct activation of the π system by metal-π bonding, and also provide the first examples of enantioselective processes. Mechanistically, it was considered that after oxidative addition of a transition metal to an electrophile (**1.46→1.47**, Scheme 1.13), if the metal complex could activate the alkenylboronate for a 1,2-metalate shift (**1.48→1.49**), reductive elimination would generate C–C coupled product **1.50**. The overall reaction has been termed "conjunctive cross-coupling" to indicate the merger of two ostensibly nucleophilic reagents; an organoboron and an organolithium together. In regards to catalysis, to facilitate olefin binding to complex **1.47**, aryl triflates were employed as electrophiles and this choice would prove to be critical: in the absence of specially-chosen additives, as little as 1 mol% halide arising from either the catalyst, the electrophile, or during the synthesis of "ate" complexes, leads to significant inhibition of the reaction. A similarly critical choice was the decision to employ wide bite-angle bidentate ligands for palladium: this selection was made in an effort to speed reductive elimination relative to β-hydrogen elimination from intermediate **1.49**, and so far, only these ligands, particularly the MandyPhos[26] class (Scheme 1.13), reliably deliver the conjunctive coupling product.

[26] Almena Perea, J. J.; Lotz, M.; Knochel, P. *Tetrahedron Asymm.* **1999**, *10*, 375–384.

Scheme 1.13 Mechanistic hypothesis for catalytic conjunctive cross-coupling by metal-induced metalate rearrangement.

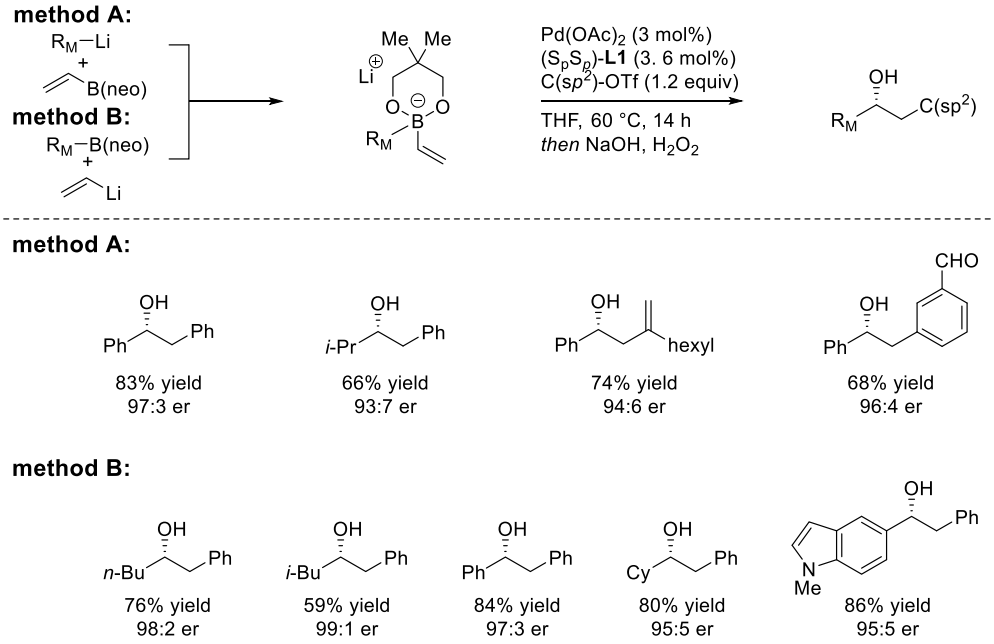


Initial experiments employed neopentyl glycol-derived boronic esters and a catalyst prepared from $Pd(OAc)_2$ and MandyPhos (Scheme 1.14).[27] Cross-couplings with a range of aryl and alkenyl triflates were found to furnish chiral secondary boronic esters in good yield and with excellent enantioselectivity. Both aromatic and aliphatic groups underwent efficient migration in these reactions and it is also notable that the reaction can accommodate sensitive functional groups, such as an aldehyde in the electrophilic partner. A last noteworthy feature in regards to synthesis utility is similar reaction outcomes are

[27] Zhang, L.; Lovinger, G. J.; Edelstein, E. K.; Szymaniak, A. A.; Chierchia, M. P.; Morken, J. P. *Science*, **2016**, *351*, 70–74.

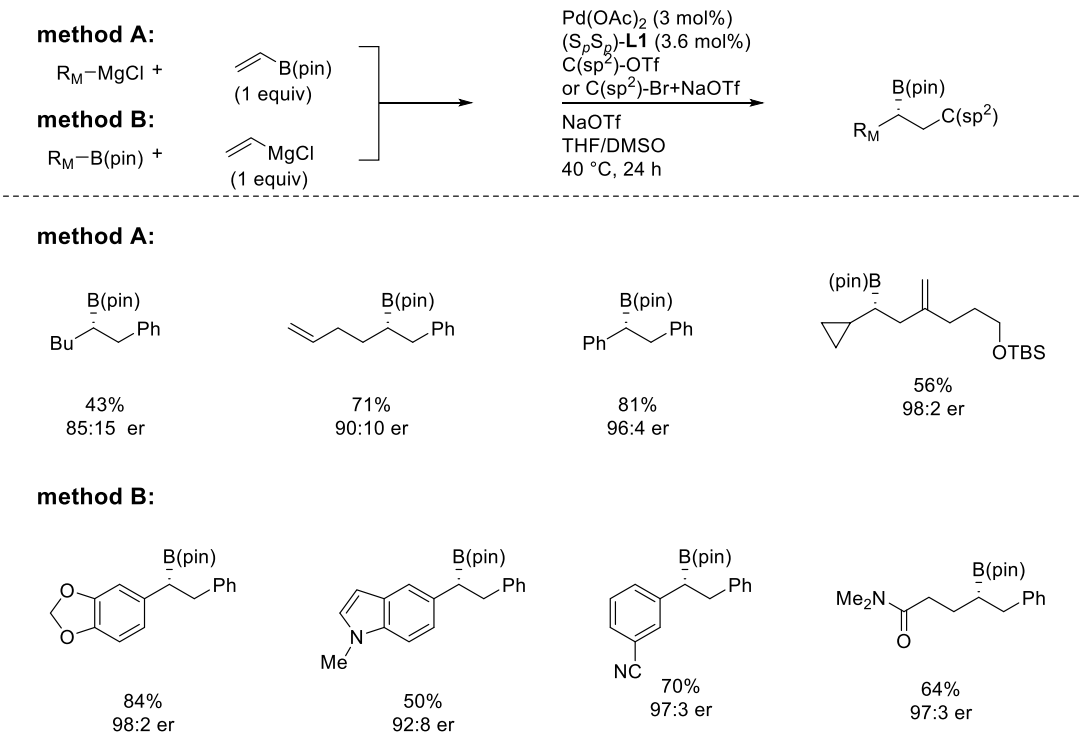
observed whether the “ate” complex was prepared from organolithium reagents and vinyl boron compounds (Scheme 1.14, method A) or from organoboron reagents and vinyllithium (Scheme 1.14, method B).

Scheme 1.14 Catalytic enantioselective conjunctive cross-coupling.



Halide inhibition is a significant problem (vide supra) in the palladium-catalyzed conjunctive cross-coupling process. For instance, when organolithium reagents employed in Scheme 1.14 were prepared from halide precursors, they required recrystallization to remove halide contaminants. The origin of this problem was attributed to halide's ability to outcompete the “ate” complex for binding to Pd(II).

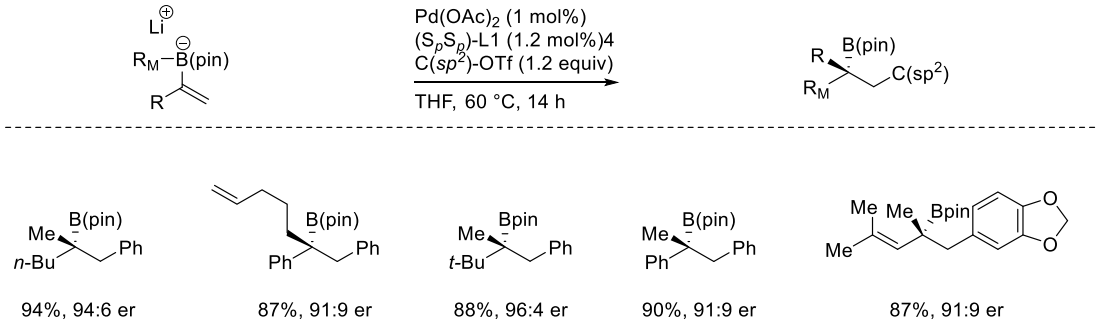
Scheme 1.15 Catalytic conjunctive cross-coupling employing Grignard reagents



To address this issue, and to enable the use of Grignard reagents in place of reactive organolithium compounds, NaOTf was employed as an additive (Scheme 1.15).[28] This salt was found to not only remove halide from the reaction milieu (sequestration is likely due to both strong NaCl ionic bonding and the insolubility of NaCl in the reaction solvent), but NaOTf also facilitates formation of "ate" complexes from the Grignard reagents and organoboron compounds. Through the use of this additive and DMSO as a co-solvent (DMSO appears to stabilize the "ate" complex in the reaction medium), a broad range of practical conjunctive coupling reactions were enabled (Scheme 1.15). An impressive array of functional groups were accommodated on the migrating group, with amides, carbamates, esters, acetals, and nitriles surviving the reaction intact.

[28] Lovinger, G. J.; Aparece, M. D.; Morken, J. P. *J. Am. Chem. Soc.* **2017**, *139*, 3153–3160.

Scheme 1.16 Synthesis of tertiary organoboronic esters by conjunctive cross-coupling of α-substituted vinylboron "ate" complexes.



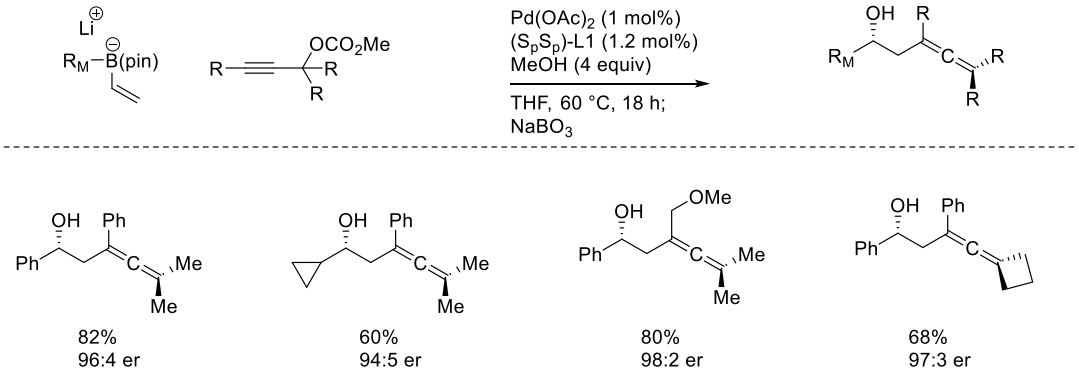
Tertiary boronic esters are precursors to tertiary alcohols and amines. Moreover, through the use of C–C bond-forming homologation reactions, tertiary boronic esters can provide access to compounds with quaternary centers. Extending the conjunctive coupling reaction to the construction of these important motifs entails the use of α-substituted alkenyl boronic esters as substrates. With such substitution, direct transmetalation becomes a competing reaction pathway, resulting in significant amounts of Suzuki-Miyaura coupling products. However, use of boronic esters bearing a pinacoldiolato group led to a significant suppression of the direct cross-coupling products and allowed production of tertiary boronic ester-containing conjunctive coupling products in good yield and with high enantioselectivity (Scheme 1.16).[29]

The electrophile scope of the Pd-catalyzed conjunctive cross-coupling was expanded to include propagylic carbonates to afford enantionenriched β-allenyl boronic esters in good yield and with great stereoselectivity. Key to this transformation was the use

[29] Myhill, J. A.; Zhang, L.; Lovinger, G. J.; Morken, J. P. *Angew. Chem. Int. Ed.* **2018**, *130*, 12981–12985.

of methanol which promoted an alkoxy group exchange of the boron- ate complex during the reaction (Scheme 1.17).[30]

Scheme 1.17 Synthesis of β-allenyl boronic esters by Pd-catalyzed conjunctive coupling

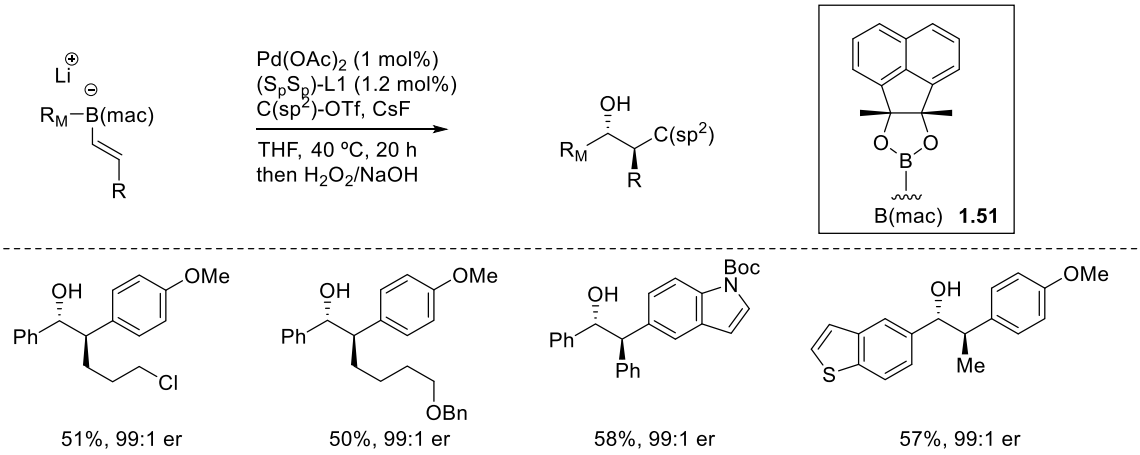


A recent advancement from the Morken laboratory involves reactions of β-substituted alkenyl boronic esters (Scheme 1.19).[31] Conjunctive coupling with these substrates provides reaction products bearing vicinal stereogenic centers. In the development phase of this process, it was found that with either neopentyl glycol or pinacol boronic ester derivatives, the predominant product arose from Suzuki-Miyaura reaction. This outcome is not surprising since C–Pd bond formation during the metalate shift is now impeded by additional substitution at the β-carbon; in contrast, the rate of transmetalation leading to direct Suzuki-Miyaura products is likely unaltered by the additional substitution. On the basis of the hypothesis that a more encumbered boron ligand might tilt chemoselectivity back towards the metalate-shift-based pathway by precluding access of Pd to the α-carbon, a number of different encumbered ligands were investigated. A practical solution was found in the use of the methylated acenapthoquinone, "mac" ligand

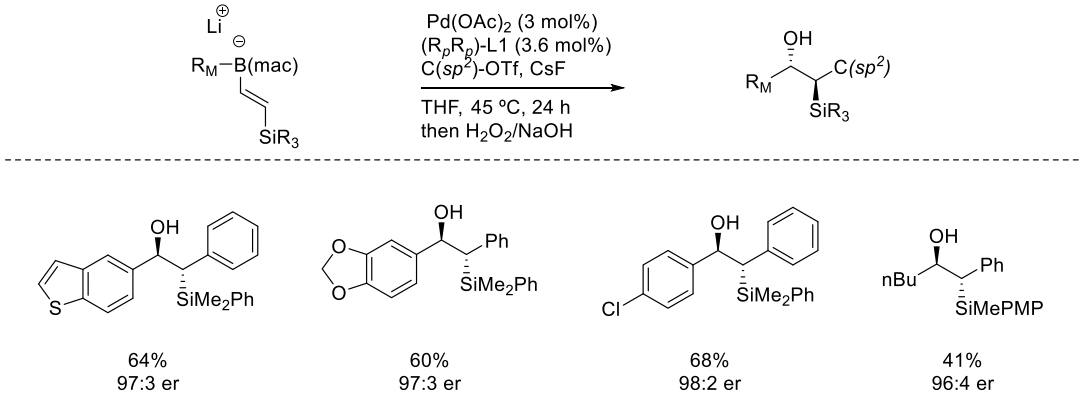
[30] Aparece, M. D.; Hu, W.; Morken, J. P. *ACS Catal*. **2019**, *9*, 11381–11385.
[31] Myhill, J. A.; Wilhelmsen, C. A.; Zhang, L.; Morken, J. P. *J. Am. Chem. Soc.* **2018**, *140*, 15181–15185.

(Scheme 1.19), readily prepared in a single step by methylation of acenapthoquinone. As depicted in Scheme 1.19, conjunctive-coupling with B(mac) derived substrates proceeds in useful yields and with outstanding levels of diastereo- and enantioselectivity.

Scheme 1.19 Conjunctive coupling of β-substituted alkenylboronates



Scheme 1.20 Synthesis of anti 1,2 silylboronates by conjunctive coupling



The conjunctive cross-coupling was extended to β-metalloalkenylboronates to access *anti* vicinal silylboronates (Scheme 1.20).[32] These vicinal dimetalloid compounds are important because both the silicon and boron can be independently transformed into

[32] Meng, Y.; Kong, Z.; Morken, J. P. *Angew. Chem. Int. Ed.* **2020**, *59*, 1–5.

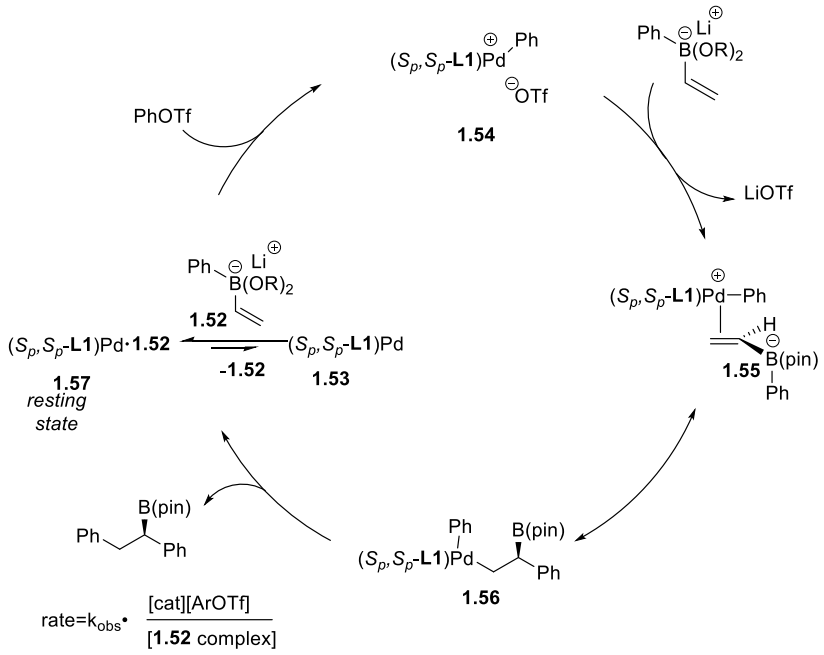
other functional groups in a stereospecific fashion. In particular these products could be elaborated into *anti*-1,2- diols and *anti*-1,2- amino alcohols.

1.3.1.1 Palladium-catalyzed conjunctive cross-coupling mechanistic studies

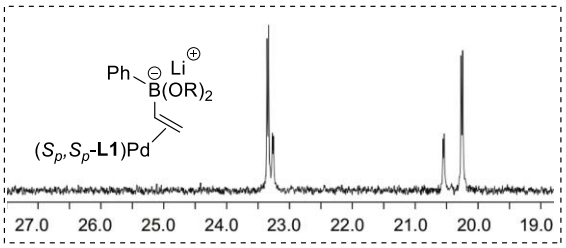
The mechanism of the Pd-catalyzed conjunctive coupling with alkenylboronic ester derivatives has been studied with a variety of techniques.[29] Kinetic analysis was conducted by *in situ* NMR and revealed that the reaction is overall zero-order. Analysis of individual components showed the reaction to be first order in electrophile and catalyst but inverse order in "ate" complex. This observation is most explained by a mechanism (Scheme 1.21 A) where the oxidative addition (**1.53→1.54**) is turnover-limiting, while Pd(0) is removed from the catalytic cycle by formation of a complex with the boronate (**1.53→1.57**). Thus the electrophile and the "ate" complex compete for Pd(0), and the net result is a zero-order process. Of note, for the inhibition by "ate" complex to have an order of $[ate]^{-1}$ and perfectly balance a first-order oxidative addition, the equilibrium between complexes **1.53** and **1.57** must strongly favor **1.57**, making **1.57** the resting state of the reaction. Analysis of Pd complexes by ^{31}P NMR in the absence of electrophile are consistent with the formation of the palladium- bound "ate" complex ((Scheme 1.21 B) two diastereomeric complexes are observed), and it is worth noting that this is the sole species detected by ^{31}P NMR spectroscopy throughout the entire course of the catalytic reaction.

Scheme 1.21 (A) Kinetic analysis of conjunctive coupling reveals reaction rate law. (B) Observation of the catalyst resting state supports kinetic analysis.

A) Kinetic analysis of conjunctive coupling reveals reaction rate law



B) ^{31}P NMR of Pd/Mandyphos with excess 'ate' complex

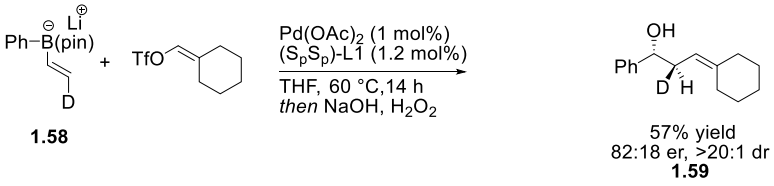


The stereochemical course of conjunctive coupling reactions is consistent with a Pd-promoted 1,2-metalate shift (Scheme 1.22). When deuterium-labelled substrate **1.58** is employed in these reactions, a single diastereoisomer (**1.59**) of product is obtained whose configurational assignment is consistent with *anti*-addition of the migrating group and the electrophile across the alkene.[27] Note that this stereochemical pathway is also observed in

the reactions of β-substituted substrates described above in Schemes 1.19 and 1.20. Along with this evidence, DFT calculations[30] of the reaction shows that the 1,2-metalate shift step itself has a barrier of only 5.0 kcal/mol and is exergonic by 28.2 kcal/mol.

Scheme 1.22 Stereochemical and DFT calculation for 1,2-metalate shift transition state. Ligand on Pd for DFT is dppf.

A) Stereochemical analysis

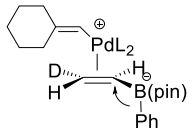


1.58

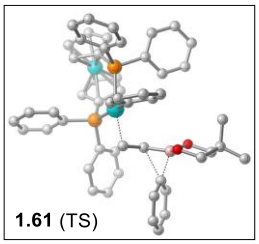
57% yield
82:18 er, >20:1 dr
1.59

B) DFT analysis of transiton state

via:



1.60

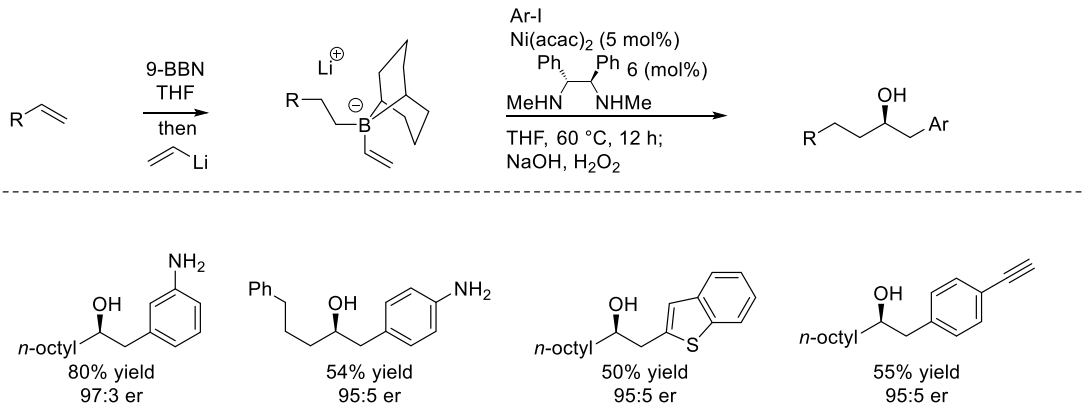


1.61 (TS)

1.3.2 Conjunctive cross-coupling with Ni-based catalysts

While conjunctive coupling with Pd-based catalysts is efficient across a range of alkenyl boronic ester-derived substrates, it is restricted to C*(sp²)* electrophiles. To expand the scope of this reaction to a broader array of electrophilic partners, Ni-based catalysts have been examined in conjunctive couplings. To initiate these studies, couplings of aryl halide electrophiles were examined.[33] While these electrophiles would not undergo coupling with boronic ester-derived "ate" complexes and Ni catalysis, as depicted in Scheme 1.23, it was found that 9-BBN-derived "ate" complexes were competent coupling partners and provide a complementary path to conjunctive coupling products relative to Pd catalysis. In the presence of a chiral diamine ligand, these processes could also be accomplished with excellent levels of enantioselectivity. The underlying reason for the influence of the boron ligand in this system is not clearly understood and, indeed, boronic esters were later found to be compatible in Ni catalysis with alternate electrophiles and Nickel ligands (*vide infra*).

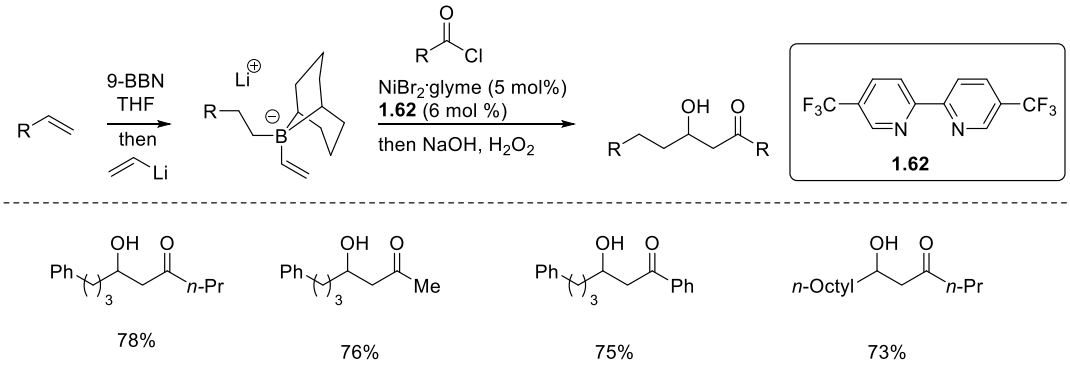
Scheme 1.23 Conjunctive coupling with Ni-based catalysts.



[33] Chierchia, M.; Law, C.; Morken, J. P.; *Angew. Chem. Int. Ed.* **2017**, *56*, 11870–11874.

Recently, the scope of C(*sp*^{2}) electrophiles that engage in the Ni-based conjunctive cross-coupling reaction has been broadened to include carbonyl-derived electrophiles.[34] This transformation (Scheme 1.24) employed carboxylic acid derived electrophiles (acyl chlorides and symmetrical anyhydrides) to generate β-boryl carbonyls. This method provides an alternative to conjugate borylation to access these synthetically useful motifs.

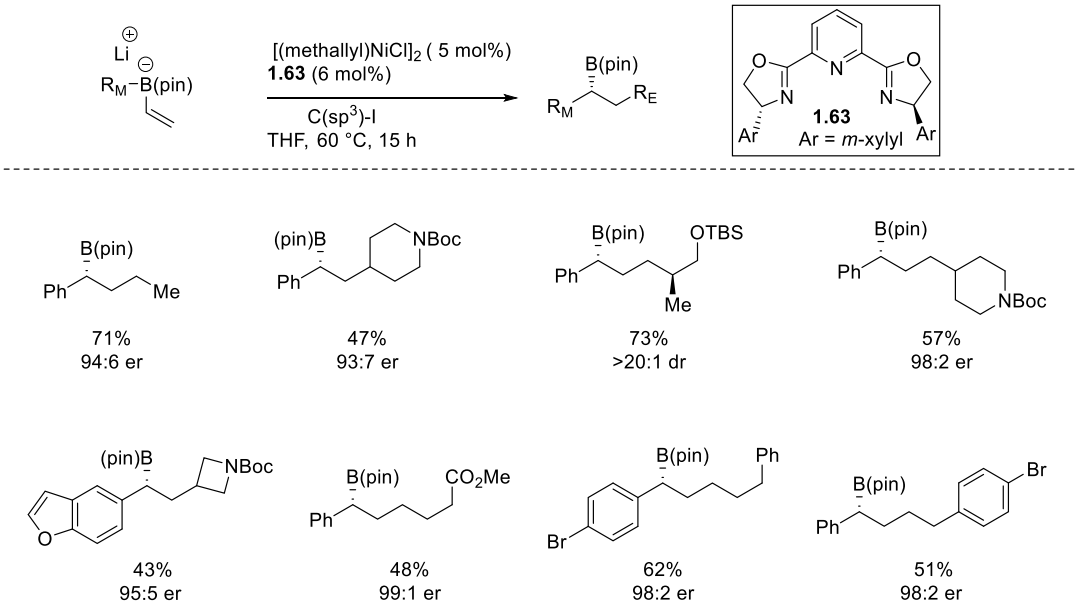
Scheme 1.24 Conjunctive coupling with Ni-based catalysts and acyl electrophiles



With the ability to employ Ni catalysts as activators for metalate shifts, efforts towards development of a conjunctive coupling reaction that employed C(*sp*^{3}) electrophiles were undertaken.[35] Ni(pybox) complexes were found to effectively couple B(pin)-derived "ate" complexes and alkyl electrophiles. As noted in Scheme 1.25, the electrophile can bear a number of different functional groups, or none at all, and high levels of stereoselectivity can be achieved.

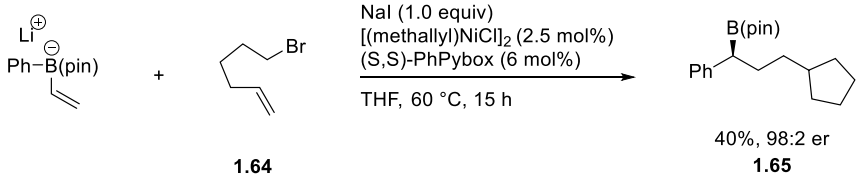
[34] Law, C.; Meng, Y.; Koo, S. M.; Morken, J. P. *Angew.Chem*. **2019**, *131*, 6726–6730.
[35] Lovinger, G. J.; Morken, J. P. *J. Am. Chem. Soc.* **2017**, *139*, 17293–17296.

Scheme 1.25 Ni-catalyzed conjunctive coupling with C(sp^3) electrophiles.



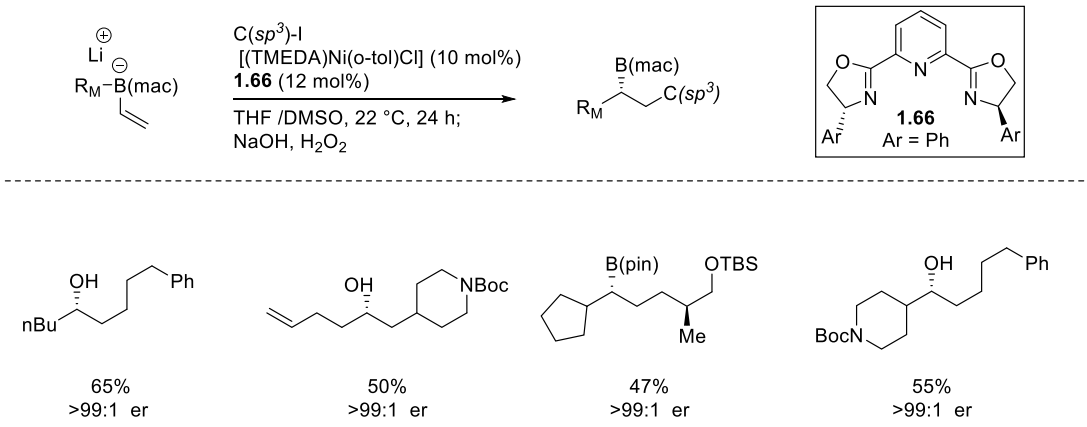
Isotope labelling experiments conducted on the systems depicted in Schemes 1.23, and 1.24 show that *anti* addition of migrating group and the electrophile to the alkene occurs. This feature is analogous to the Pd-based process. However, it should be noted that the Ni-based reaction of C*(sp^3)* electrophiles appears to follow a different course, with oxidative addition occurring by a radical based process. For example, the electrophile 5-bromo-1-hexene (**1.64**) undergoes cyclization prior to engaging in cross-coupling to give **1.65** (Scheme 1.26), thereby suggesting the intermediacy of carbon-centered radicals in the Ni-catalyzed process. In line with this hypothesis, it was found that iodomethylcyclopropane undergoes ring-opening during coupling, and the coupling reaction of other C*(sp^3)* halides is subject to inhibition by the radical scavenger TEMPO.

Scheme 1.26 Ni-catalyzed conjunctive coupling mechanistic probe with C*(sp³)* electrophiles.



Whereas the previous discussed Ni-catalyzed conjunctive cross-coupling was effective at engaging alkyl electrophiles, it was limited to aryl migrating groups (Scheme 1.25). The reaction scope has since been expanded to include alkyl migrating groups (Scheme 1.27).[36] This was achieved by changing the nickel precatalyst, using Pybox **1.66** as an ancillary ligand and an acenapthoquinone derived boron ligand to ensure efficient reactivity and excellent stereoselectivity

Scheme 1.27: Ni-catalyzed conjunctive coupling with C*(sp³)* electrophiles and alkyl migrating groups

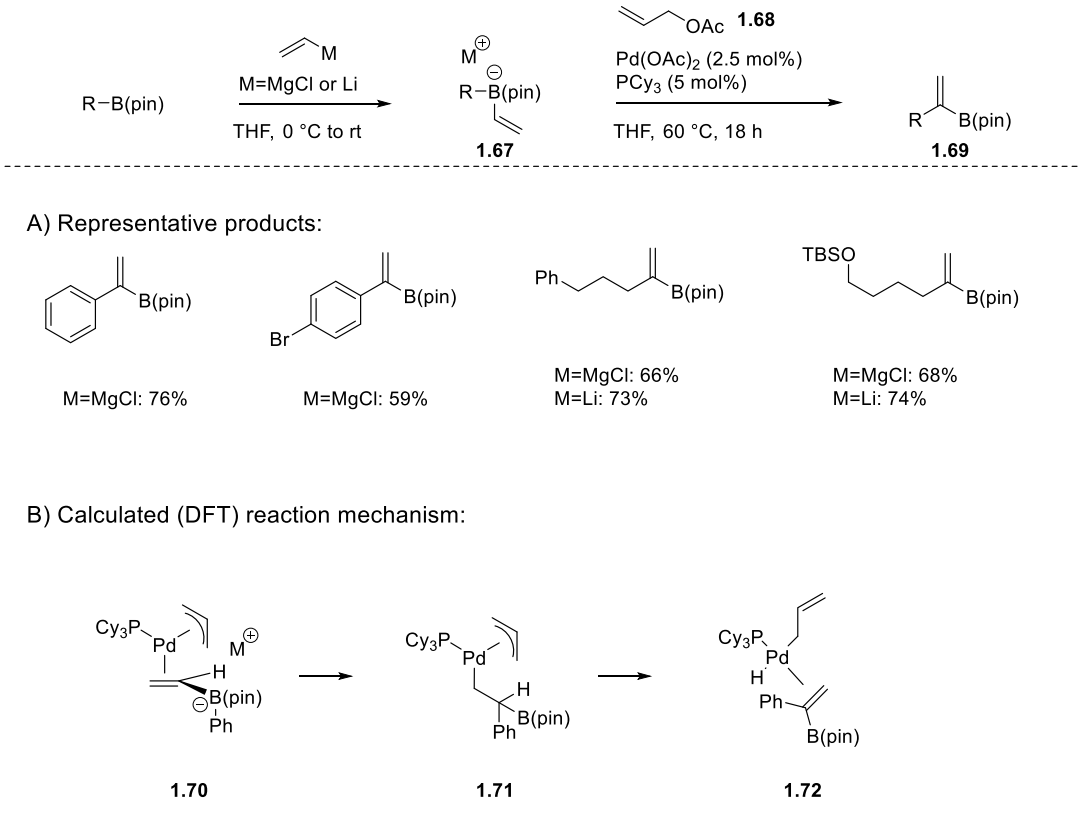


[36] Koo, S. M.; Vendola, J. A.; Momm, S. N. Morken, J. P. *Org. Lett.* **2020**, *22*, 666−669.

1.3.3 Vinylidenation of organoboronic ester enabled by catalytic metalate shift

Palladium-catalyzed reaction of alkenylboron "ate" complexes with allyl acetate produces new alkenylboronic esters by a process that appears to entail metal-activated 1,2-boronate rearrangement.[37] This process is depicted in Scheme 1.28, where it can be seen that aryl and alkyl boronic esters undergo "vinylidenation" when their derived "ate" complex (**1.67**) is subjected to catalytic $Pd(OAc)_2/PCy_3$ and allyl acetate. Mechanistically, this reaction is considered to be initiated by activation of the "ate" complex upon binding to (π-allyl)Pd complex **1.70**.

Scheme 1.28 A metalate shift in the course of Pd-catalyzed vinylidenation of boronic esters.



[37] Aparece, M. D.; Gao, C.; Lovinger, G. J.; Morken, J. P. *Angew. Chem. Int. Ed.*, **2018**, *58*, 592–595.

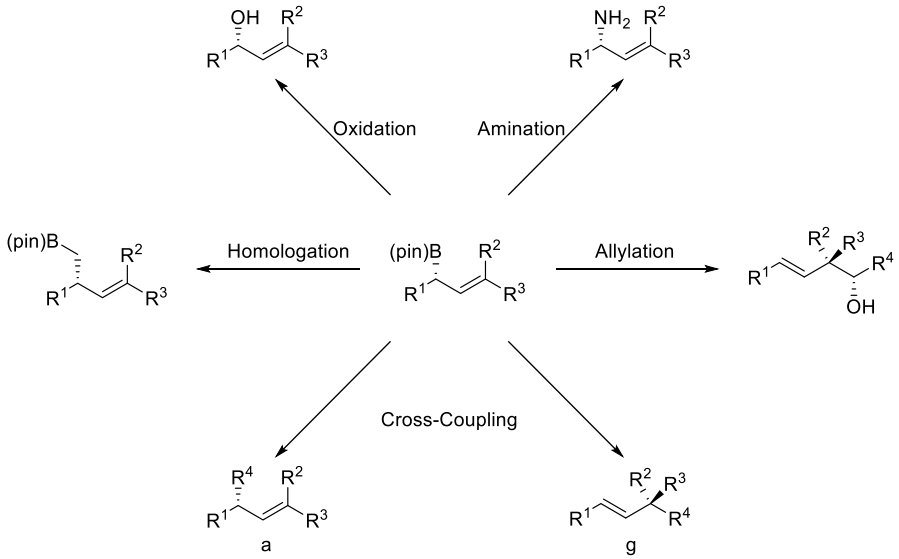
While this pathway appears to be in contradistinction to the outer sphere addition reactions developed by Ishikura and Ready, it is worth noting that unlike the above described reactions, in the process depicted in Scheme 1.28 B, a monodentate ligand structure was employed, which can be expected to provide ready access to coordinatively unsaturated structures requisite for alkene binding. The metalate shift step is calculated to occur with an 11.5 kcal/mol activation barrier; subsequent β-hydrogen elimination ($DDG^{\neq}$ = 20.8 kcal/mol) and reductive elimination are expected to produce propene as well as the vinylidenation product (**1.69**).

1.4 Conjunctive cross-coupling of bis(alkenyl) boron "ates": a general synthesis of chiral allylboron reagents.

1.4.1 Utility of allylboron reagents

Chiral allylboron reagents are a uniquely versatile class of synthetic intermediates due to their chemical and configurational stability.[38] More importantly, they can undergo stereospecific reactions that convert them to allylic alcohols[39], and amines.[40] Additionally, they can also engage in carbon – carbon bond forming reactions such as cross-coupling[41], homologation[42] carbonyl, and imine allylation[43] (Scheme 1.29).

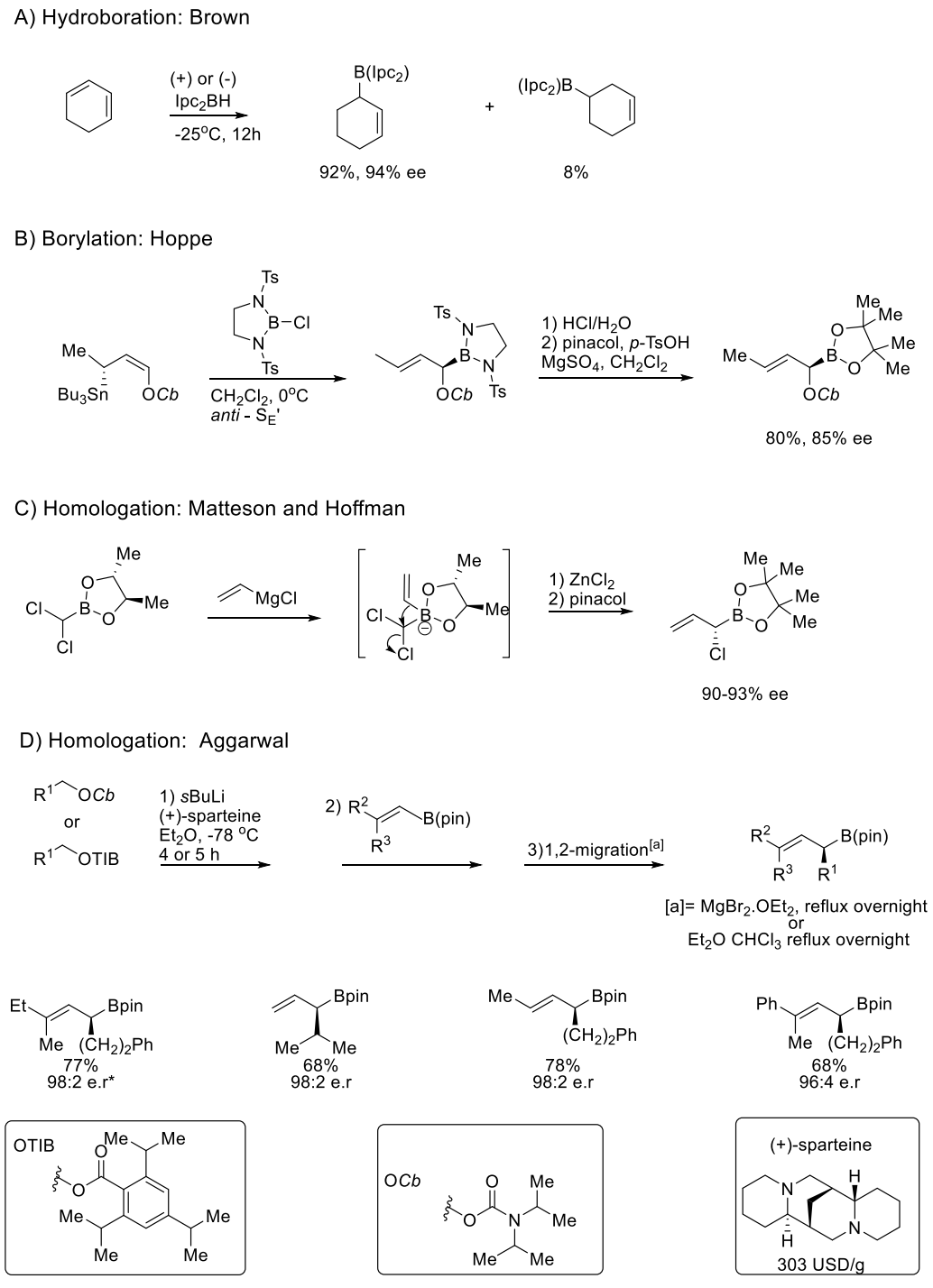
Scheme 1.29 Representative utility of allylboron reagents



[38] Diner, C.; Szabó K. J. *J. Am. Chem. Soc.* **2017**, *139*, 2–14.
[39] Brown, H. C. *Tetrahedron* **1986**, *42*, 5505.
[40] (a) Morken, J.P.; *J. Am. Chem. Soc*. **2017**, *139*, 5027. (b) Edelstein, E. K.; Namirembe, S.; Morken, J. P. *J. Am. Chem. Soc.* **2017**, *130,* 5027.
[41] (a) Buchwald, S. L. *J. Am. Chem. Soc*. **2012**, *135*, 10642. (b) Aggarwal, V. K.; Crudden, C. M.; *Chem. Eur. J*. **2013**, *19*, 17698.
[42] Sadhu, M, K.; Matteson, D. S. *J. Am. Chem. Soc*. **1983**, *105*, 2077.
[43] Chen, L.-Y. J; Scott, K.H.; Willis, L. C.; Aggarwal, V. K. *J. Am. Chem. Soc*. **2013**, *135*, 5316.

1.4.2 Previous methods for the synthesis of chiral allylboron reagents.

Scheme 1.30 Representative stoichiometric methods of synthesizing allylboron reagents



A variety of stoichiometric and catalytic methods have been developed to synthesize chiral allylboron reagents. Stoichiometric methods that employ hydroboration,[44] borylation of allyl tin reagents[45] and homologation[46] have been used to synthesize allylboron reagents (Scheme 1.30 A-D). Whereas these methods achieve the synthesis of chiral allylboron reagents, only the Aggarwal homologation protocol achieves access to geometrically diverse chiral allyboronic esters (Scheme 1.30 D). However, the synthetic utility of this method is limited by the high cost and scarcity of sparteine- the stoichiometric chiral reagent.

Because of their demonstrated utility, catalytic asymmetric methods have been developed to access chiral allylboron reagents. A myriad of copper-catalyzed allylic borylation methods have been developed, namely by the Sawamura[47] and Hoveyda[48] groups, which require stereodefined allylic carbonates as starting materials to afford terminal allylboronic esters (Scheme 1.31 A and B). The McQuade group improved upon this methodology by engaging *E/Z* diastereomeric mixtures of allylic ethers in the copper-catalyzed allylic borylation to access enantioenriched terminal allyl boronic esters (Scheme 1.31 C).[49]

One of the most difficult-to- access yet synthetically useful classes of allylboronates are differentially γ,γ disubstituted chiral secondary allylic boronates. These are valuable

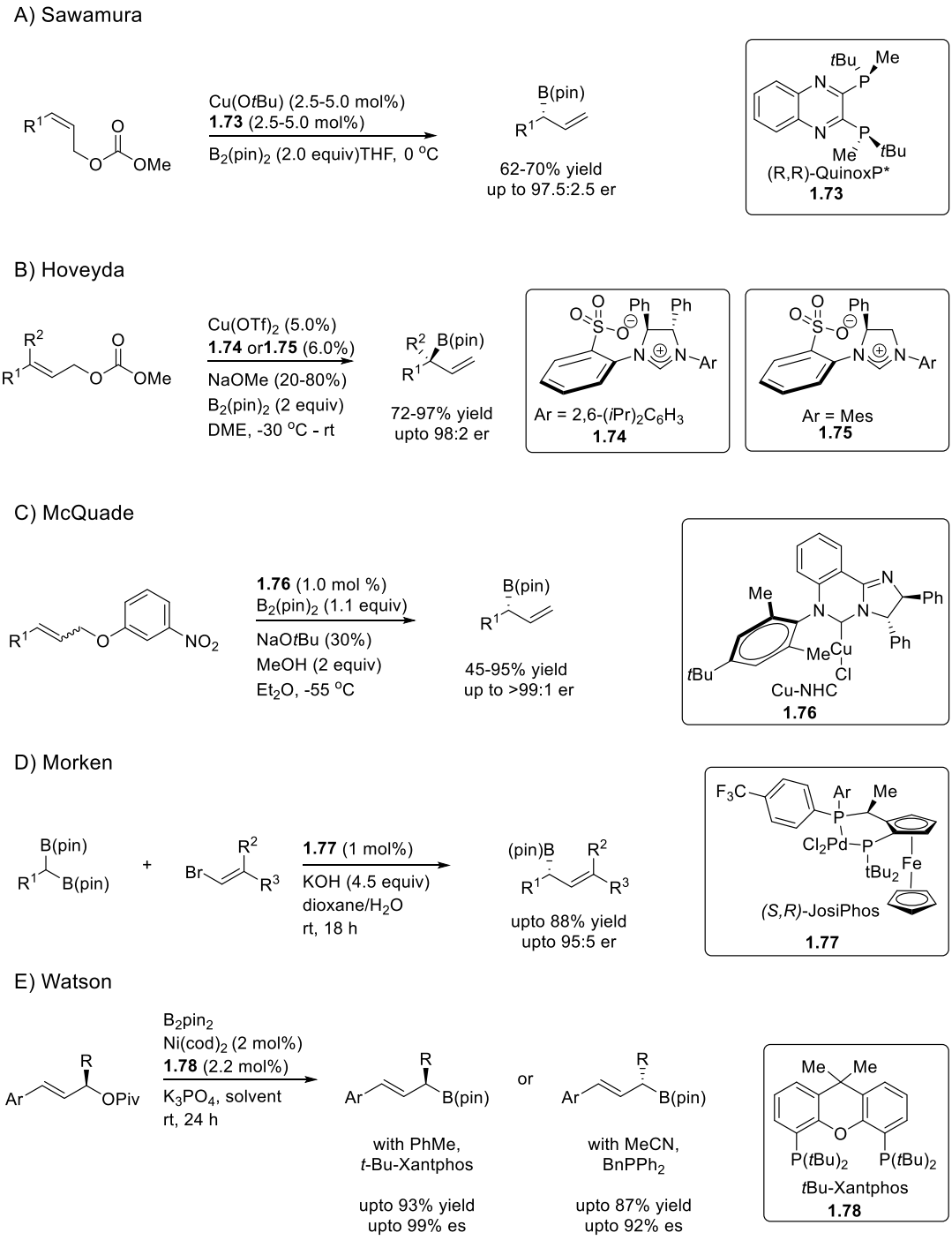
[44] Brown, H. C.; Jadhav, K .P.; Bhat, S. K. *J. Am. Chem. Soc*. **1985**, *107*, 2564–2565.
[45] Beckmann, D.; Hoppe, D. *Synlett* **2004**, *13*, 2275–2280.
[46] (a) Beckmann, E.; Hoppe, D. *Synthesis* **2005**, *2*, 217-222. (b) Hoffman, W. R. *Angew. Chem. Int. Ed*. **1984**, *23*, 437–438. (c) Sadhu, M. K.; Matteson, D.S.; Hurst, D. G.; Kurosky, M. J. O*rganometallics*. **1984**, *3*, 804.
[47] (a) Ito, H.; Sawamura, M. *J. Am. Chem. Soc*. **2007**, *129*, 14856. (b) Ito, H.; Sawamura, M. *Nature. Chem*, **2010**, *2*, 972.
[48] Guzman-Martinez, A.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2010**, *132*, 10634.
[49]Park, K. J.; Lackey, H .H.; Ondrusek, A. B.; McQuade, D. T. *J. Am. Chem. Soc.* **2011**, *133*, 2410.

reagents because they are precursors to quaternary centers upon allylation. Previous work in the Morken group has since addressed this challenge by an enantiotopic group-selective cross-coupling of readily available achiral geminal bis(boronates) (Scheme 1.31 D).[50]

The Watson group developed a stereospecific and enantioselective nickel-catalyzed Miyaura borylation of allylic pivalates, which delivers α-stereogenic γ-aryl-substituted allylboronates in good yield and with good enantioselectivity (Scheme 1.31 E).[51] The reaction can proceed by either a stereoretentive or stereoinvertive pathway via the influence of the solvent and ligand. In non-polar solvents such as toluene and with a Ni/*t*-BuXantPhos catalyst, the oxidative addition is proposed to be directed by the pivalate group via a 7 membered closed transition state resulting in retention. While in the presence of polar solvents, such as acetonitrile and a Ni/$BnPPh_2$ catalyst, the stereochemistry of the product is inverted. It is hypothesized that MeCN, which has a high propensity to bind to transition metals, coordinates to the nickel catalyst better than the pivalate group. This prevents the directed oxidative addition but allows the undirected oxidative addition pathway to operate through an open transition state that subsequently affords the stereoinverted product. Thus, both enantiomers of the chiral allylboronate are accessible from one starting material. Besides the Morken and Watson examples discussed above, other catalytic methods to access internal allylboron reagents include diene diboration[52], conjugate 1,4 or 1,6-borylation of activated dienes. [53]

[50] Potter, B.; Szymaniak, A. A.; Edelstein, K. E.; Morken. J. P. *J. Am. Chem. Soc*. **2014**, *136*, 17918.
[51] Zhou, Q.; Srinivas, D. H.; Zhang, S.; Watson, M. P. *J. Am. Chem. Soc*. **2016**, *138*, 11989.
[52] (a) Pelz, N. F.; Woodward, A. R.; Burks, H. E.; Sieber, J. D.;. Morken, J. P *J. Am. Chem. Soc.* **2004***, 126*, 16328. (b) Kliman, L. T.; Mlynarski, S. N.; Morken. J. P.; *J. Am. Chem. Soc.* **2012**, *51*, 521.
[53] (a) Luo, Y.; Roy, I. D.; Madec, A. G. E.; Lam, H. W. *Angew. Chem., Int. Ed*. **2014**, *53*, 4186. (b) Sim, H.-S.; Feng, X.; Yun, J. *Chem. - Eur. J.* **2009**, *15,* 1939.

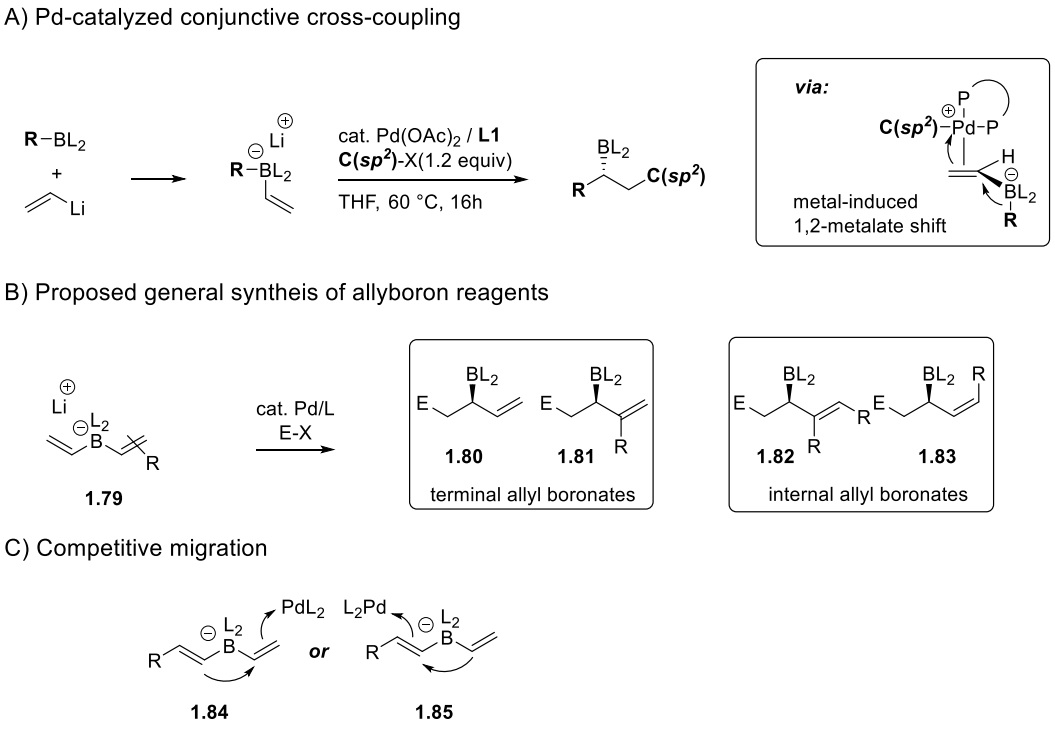
Scheme 1.31 Representative catalytic methods for the synthesis of chiral allylboron reagents.



1.4.3 Reaction development

Although various methods exist that construct chiral allylboron reagents, none provide general access to chiral allylboron reagents with different substitution patterns on the olefin moiety in a catalytic fashion. To address this synthetic challenge, we sought to engage bis(alkenyl)boron "ate" complexes in a palladium-catalyzed conjunctive cross-coupling.[54]

Scheme 1.32 Conjunctive cross-coupling of bis(alkenyl)borates



Previous work in our group has shown that in the presence of a cationic palladium complex, an alkenylboron "ate" complex undergoes a 1,2-metalate shift thereby adding carbon and palladium across the pendent olefin in an *anti* fashion, yielding enantioenriched boronic esters upon reductive elimination (Scheme 1.32 A). Both aryl and alkyl groups were found to undergo migration. We hypothesized that if cationic palladium could

[54] See reference 40 (b)

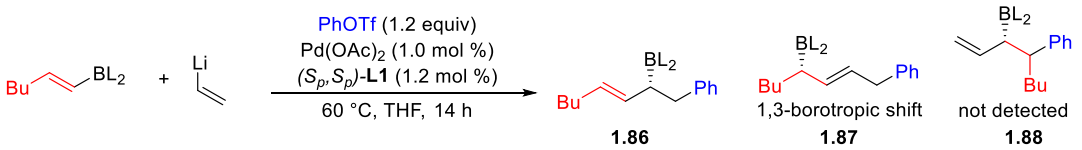
selectively bind to the less substituted olefin of a bis(alkenyl)boron "ate" complex (**1.79**), the more substituted olefin would migrate, and subsequent reductive elimination would provide both terminal and internal allylboron reagents (Scheme 1.32 B).

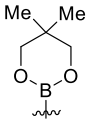
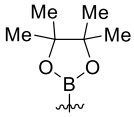
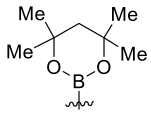
1.4.3.1 Boron and metal ligand survey

The demonstrated ability of conjunctive cross-coupling reactions to accommodate aromatic C(sp^2) migrating groups was encouraging; however, for alkene migration, several critical issues remained uncertain. First, it was unclear whether the Pd complex could selectively bind and activate one alkene in the bis(alkenyl)boron "ate" substrate or whether indiscriminant activation of both alkenes would lead to product mixtures (Scheme 1.32 C). Second, it was ambiguous whether the allyl boronate functional group in the product – a motif that can engage in rapid transmetalation[55]– would be consumed by Suzuki-Miyaura reactions with the organic electrophile. Lastly, both the chemical and configurational stabilities of the "ate" complex and reaction products in the conjunctive coupling process were unknown. With these potential challenges in mind, we set out to optimize the ligand on boron and palladium as we deemed these parameters important for reaction yield and stereoselectivity.

[55](a) Yamamoto, Y.; Takada, S.; Miyaura, N.; Iyama, T.; Tachikawa, H. *Organometallics* **2009**, *28*, 152. (b) Ardolino, M. J.; Morken, J. P. *J. Am. Chem. Soc*. **2014**, *136*, 7092.

Scheme 1.33 Examination of boron ligand effect on reactivity and enantioselectivity



entry	BL_2	yield (%)	er
1		<5	-
2		<10	97:3
3		85	92:8
4		80	79:21

At the outset, we surveyed the ligands on boron, using Mandyphos ligand **1.92** which had been previously reported to give high enantioselectivity in palladium-catalyzed conjunctive coupling processes (Scheme 1.33). Using an unencumbered propanediol as the boron ligand generated only a trace amount of product (entry 1). Analysis of the ^{11}B NMR spectrum revealed that in this case, the boron "ate" complex was unstable during the course of the reaction. Employing neopentyl glycol as the boron ligand only afforded a trace amount of product as well, albeit with excellent enantioselectivity (entry 2). In this case, the product (**1.86**) was unstable and underwent a 1,3-borotropic shift[56] to furnish compound

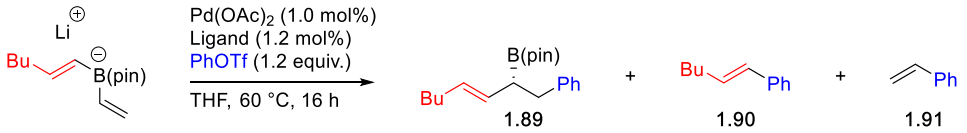
[56] (a) Hancock, K. G.; Kramer, J. D. *J. Am. Chem. Soc.* **1973**, *95*, 6463. (b) Hancock, K. G.; Kramer, J. D. *J. Organomet. Chem.* **1974**, *64*, C29. (c) Henriksen, U.; Snyder, J. P.; Halgren, T. A. *J. Org. Chem*. **1981**, *46*, 3767. (d) Bîhl, M.; Schleyer, P. v. R.; Ibrahim, M. A.; Clark, T. *J. Am. Chem. Soc*. **1991**, *113*, 2466. (e) Bubnov, Y. N.; Gurskii, M. E.; Gridnev, I. D.; Ignatenko, A. V.; Ustynyuk, Y. A.; Mstislavsky, V. I. *J. Organomet. Chem.* **1992**, *424*, 127. (f) Gridnev, I. D.; Gursky, M. E.; Bubnov, Y. N. *Organometallics* **1996**, *15*, 3696. (g) Bubnov, Y. N. *Pure Appl. Chem.* **1987**, *59*, 895. (h) Choi, J. Y.; Kim, C. K.; Kim, C. K.; Lee, I. *J. Phys. Chem. A* **2002**, *106*, 5709. (i) Ess, D. H.; Kister, J.; Chen, M.; Roush, W. R. *Org. Lett.*

1.87. Gratifyingly, when pinacol was employed as the boron ligand, the desired product **1.86** was obtained in excellent yield and with good enantioselectivity (entry 3). Compound **1.87** was not detected, indicating that the palladium catalyst binds to the least substituted olefin to induce selective migration of the more substituted olefin. Further increasing the steric bulk around boron by using dimethylpentane diol as the ligand resulted in diminished enantioselectivity but good yield (entry 4). With the optimal boron ligand in hand, efforts to improve enantioselectivity by changing the ligand on palladium were undertaken.

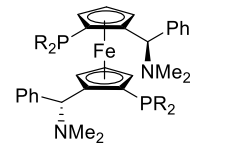
A variety of monodentate and bidentate ligand frameworks on palladium delivered the conjunctive cross-coupling product (**1.89**) in variable yields and enantioselectivities (Scheme 1.34). Monodentate phosphine ligands **1.99** and **1.100** afforded the desired product in low yield and with poor enantioselectivity (Scheme 1.34, entries 8 and 9). Bidentate ligands such as Ferrotane **1.102**, Binaphane **1.103** and Josiphos **1.101** also afforded the product in unsatisfactory yield and with poor enantioselectivity (entries 10-12). While the aforementioned ligands provided uniformly regioselective reactions, their chemoselectivity [**1.89**:(**1.90**+**1.91**)] and enantioselectivity were worse than to those obtained with MandyPhos **1.92**.

2009, *11*, 5538. (j) Gurskii M. E.; Belyakov, P. A.; Lyssenko, K. A.; Semenova, A. L.; Bubnov, Y. N. *Russian Chem. Bull. Int. Ed.* **2014**, *63*, 480. (k) Zweifel, G.; Horng, A. *Synthesis*, **1973**, 672. (l) Kramer, G. W.; Brown, H. C. *J. Organomet. Chem*. **1977**, *132*, 9. (m) Zweifel, G.; Backlund, S. J.; Leung, T. *J. Am. Chem. Soc*. **1978**, 100, 5561. (n) Brown, H. C.; Liotta, R.; Kramer, G. W. *J. Am. Chem. Soc.* **1979**, *101*, 2966. (o) Hoffmann, R. W.; Zeib, H. J. *J. Org. Chem.* **1981**, *46*, 1309. (p) Wang, K. K.; Nikam, S. S.; Ho, C. D. *J. Org. Chem.* **1983**, *48*, 5376. (q) Brown, H. C.; Jadhav, P. K.; Bhat, K. S. *J. Am. Chem. Soc.* **1985**, *107*, 2564. (r) Brown, H. C.; Rangaishenvi, M. V.; Jayaraman, S. *Organometallics* **1992**, *11*, 1948. (s) Lombardo, M.; Morganti, A.; Tozzi, M.; Trombini, C. *Eur. J. Org. Chem.* **2002**, 2823. (t) Burgos, C. H.; Canales, E.; Matos, K.; Soderquist, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 8044. (u) Gonzalez, A. Z.; Soderquist, J. A. *Org. Lett.* **2007**, *9*, 1081. (v) Canales, E.; Gonzalez, A. Z.; Soderquist, J. A. *Angew. Chem. Int. Ed*. **2007**, *46*, 397. (w) Fang, G. Y.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2007**, *46*, 359. (x) González, A. Z.; Román, J. G.; Alicea, E.; Canales, E.; Soderquist, J. A. *J. Am. Chem. Soc.* **2009**, *131*, 1269. (y) Chen, J. L.-Y.; Scott, H. K.; Hesse, M. J.; Willis, C. L.; Aggarwal, V. K. *J. Am. Chem.* Soc, **2013**, *135*, 5316. (z) Chen, M.; Roush, W. R.; *J. Am. Chem. Soc.* **2013**, *135*, 9512. (aa) van der Mei, F. W.; Miyamoto, H.; Silverio, D. L.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2016**, *55*, 4701.

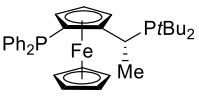
Scheme 1.34 Palladium ligand survey



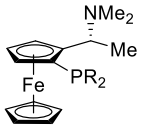
entry	ligand	yield (%)	1.89: (1.90 + 1.91)	er
1	**1.92**	85	8:1	92:8
2	**1.93**	77	8:1	89:11
3	**1.94**	70	5:1	89:11
4	**1.95**	<2	na	na
5	**1.96**	85	6:1	92:8
6	**1.97**	78	7:1	72:28
7	**1.98**	<10	1:5	na
8	**1.99**	40	1:1	77:23
9	**1.100**	30	>10:1	59:41
10	**1.101**	58	>20:1	70:30
11	**1.102**	29	1:1	69:31
12	**1.103**	40	>20:1	53:47



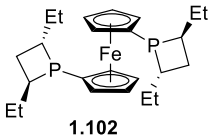
1.92: R= 4-OMe, 3,5-MePh
1.93: R = Ph
1.94: R = m-xylyl
1.95: R = *p*-CF_3Ph
1.96: R = *p*-MeOPh
1.97: R = Cy
1.98: R= 2-furyl



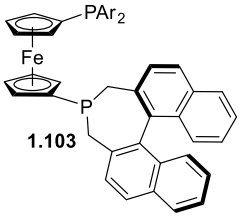
1.101



1.99: R = Ph
1.100: R = *t*-Bu



1.102



1.103

Further investigation of the MandyPhos class of ligands revealed that electron-deficient ligand **1.95** gave no product, which could be attributed to slow oxidative addition. Ligand **1.97** which is sterically and electronically different than **1.92** afforded the product in good yield but with poor enantioselectivity (entry 6). Ligand **1.98**, which was assumed to be smaller but electronically similar to **1.92** gave only trace product (entry 7). Further exploration of the Mandyphos ligand substructure revealed that an electron-rich phenyl ring with methyl substituents on the 3 and 5 positions were important to achieve high yield and enantioselectivity as in entries 2, 3, and 5; thus ligand **1.92** which combines these factors gave the highest yield and enantioselectivity (entry 1). Further optimization of solvent, temperature and catalyst loading resulted in negligible changes. With the optimal

ancillary ligand (**1.92**) and pinacol as the boron ligand, the substrate scope was subsequently investigated.

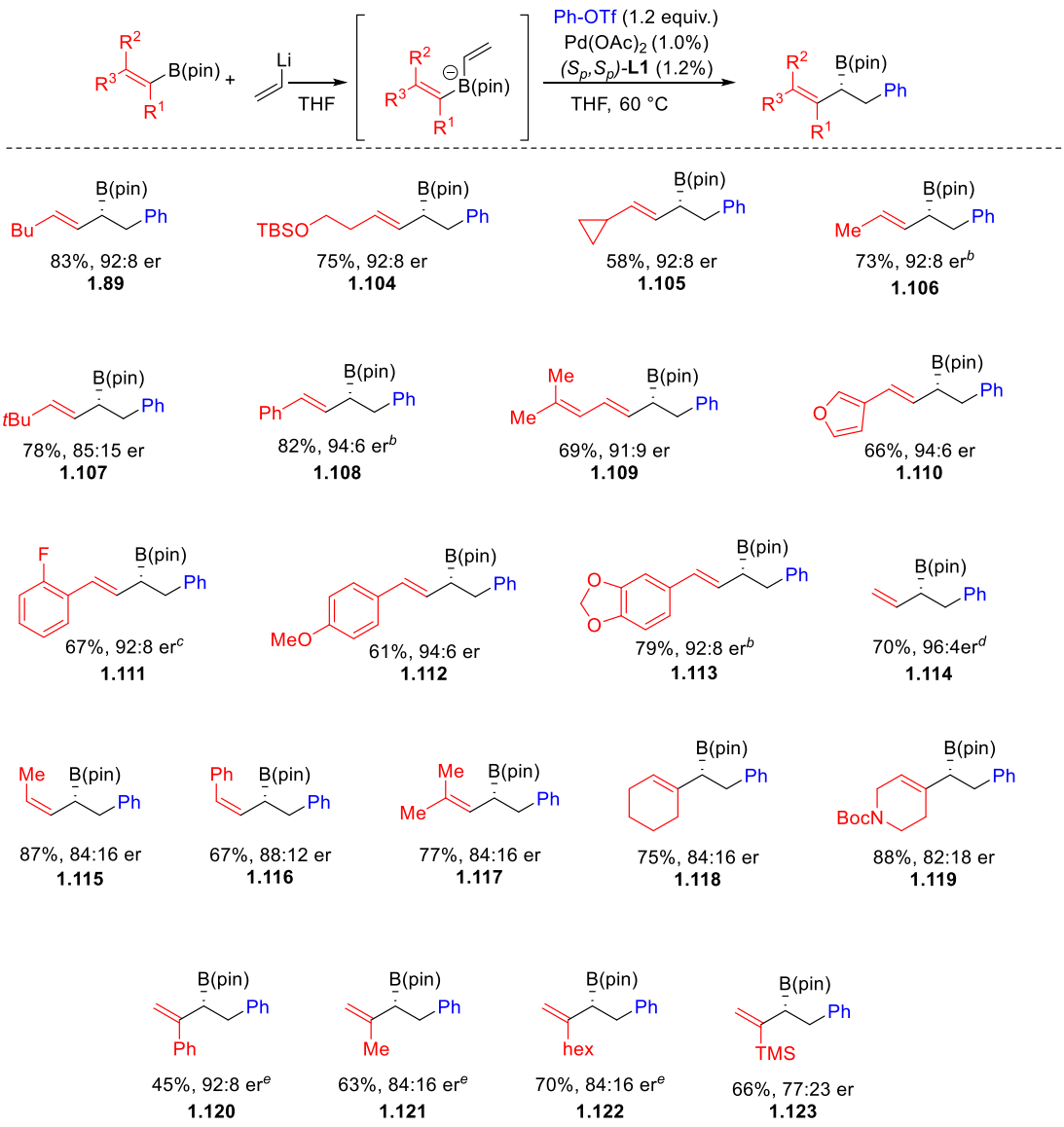
1.4.4 Substrate scope

1.4.4.1 Migrating group scope

A variety of migrating groups were explored with phenyl triflate as the electrophile (Scheme 1.35). (*E)*-Alkenyl migrating groups delivered the conjunctive product in good yield and with high enantioselectivity (products **1.89** -**1.107**). In addition, (*E)*-styrenyl migrating groups afforded the desired product in good yield and with high enantioselectivity (products **1.108**, **1.110**-**11**). A dienyl migrating group was also tolerated in the reaction (product **1.109**). Furthermore, (*Z*)-alkenyl and (*Z*)-styrenyl reagents delivered the corresponding products in good yield and with synthetically useful levels of enantioselectivity. A simple vinyl group migrated to yield the conjunctive product **1.114** in respectable yield and with excellent enantioselectivity. α-Substituted alkenes were also tolerated as migrating groups and generated the products **1.120- 1.123** in good yield but with slightly diminished enantioselectivity. Compounds **1.120**-**1.122** were produced in optimal yield when DMSO was used as co-solvent; with THF as the sole solvent, the product was formed in about than an hour or less and rapidly underwent a 1,3-borotropic shift to afford the more substituted alkene with concomitant loss of stereochemical purity during the course of the reaction. The use of DMSO as a co-solvent slowed down the conjunctive coupling reaction as it required more than two hours to achieve full conversion. In addition, we hypothesized that DMSO coordinates to the empty p-orbital of the allyl boronic ester product, thus preventing the 1,3-borotropic shift. Functional groups such as a silyl ether (**1.104)** and Boc protected amine (**1.119)** were tolerated in the reaction, as well

as heterocycles **1.110** and **1.113** in the migrating partner. In all the above cases, the configuration of the migrating alkene is preserved in the product, a feature that highlights the utility of this methodology as the alkene configuration can be engineered by controlling the starting alkenylboron reagent.

Scheme 1.35 Migrating group scope

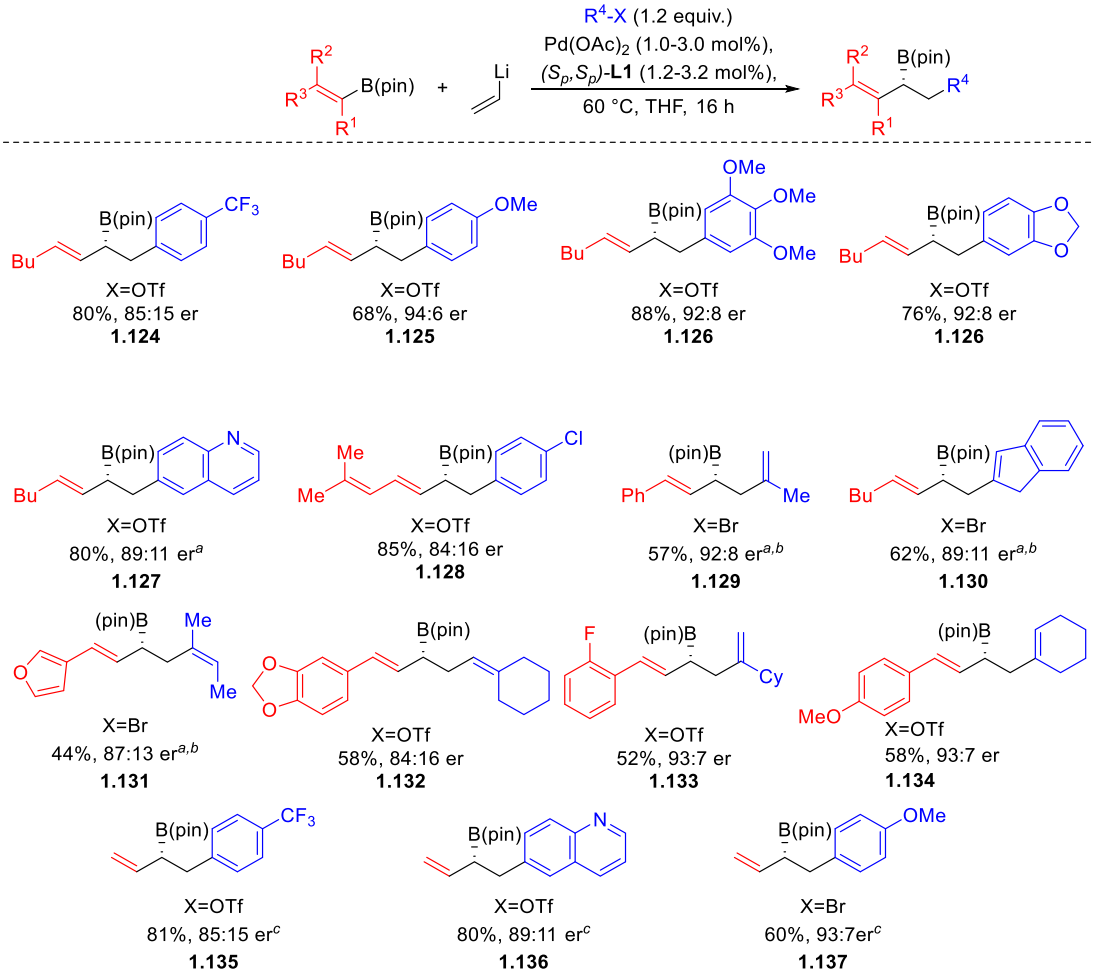


[a] reaction time;1.5-16 h, [b]2% $Pd(OAc)_2$, 2.2% **L1**, [c]isolated as OH,[d]3% $Pd(OAc)_2$, 3.2% **L1**
[e]solvent as 1:1 THF: DMSO

1.4.4.2 Electrophile scope

A wide array of aryl and alkenyl triflates were suitable reaction partners. Both electron-rich, heteroaryl and electron-deficient aryl triflates generated products in good yield, though the later showed slightly diminished enantioselectivity. Aryl bromides also engaged in the reaction provided potassium triflate was added as a halide scavenger (Scheme 1.36).

Scheme 1.36 Electrophile scope



[a] 2% $Pd(OAc)_2$, 2.2% L_1, [b] KOTf (2.0 equiv.), [c] 3% $Pd(OAc)_2$, 2.2% L_1, 5h

1.4.5 Practical applications

1.4.5.1 Grignard nucleophiles

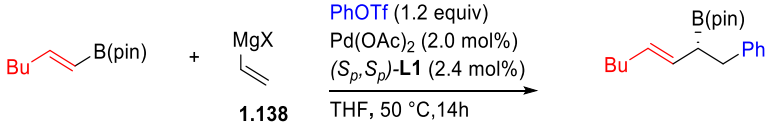
To enhance the operational utility of this reaction, we sought to engage Grignard nucleophiles in place of organolithiums as Grignard reagents are readily available and more functional group tolerant than organolithium reagents. Previous work in our group showed that Grignard derived alkenyl boron "ate" complexes engaged in the palladium-catalyzed conjunctive cross-coupling and both aryl and alkyl groups migrated in this reaction (Scheme 1.15). Central to this transformation was the use of sodium triflate as an additive that served a dual role. First, it facilitated the formation of the boron "ate" complexes from Grignard reagents. Second, it sequestered halide ions from the reaction thus overcoming halide inhibition. Mg-based alkylboron "ate" complexes were found to be less stable than their aryl counterparts, even in the presence of NaOTf. However, in the presence of DMSO as a co-solvent, the Mg-based alkylboron "ate" complexes were more stable and afforded conjunctive products in high yield.[57]

We investigated the reactivity of Mg-based bis(alkenyl)boron "ate" complexes by reacting an alkenyl boronic ester with vinylmagnesium chloride in THF (Table 1.1 entry 1). This reaction yielded no desired product; a similar observation was made with vinylmagnesium bromide (entry 2). ^{11}B NMR analysis of these reactions revealed no bis(alkenyl)boron "ate" complex formation. When either sodium or potassium triflate-additives previously shown to increase nucleophilicity of Grignard reagents, and also sequester halides-was added to the reaction mixture, there was no product formation

[57] See reference 2828

(entries 3-6). ^{11}B NMR analysis showed only trace "ate" complex formation even in the presence of the alkali metal triflate additives.

Table 1.1 Optimization of the Mg-based bis(alkenyl)boronate system.



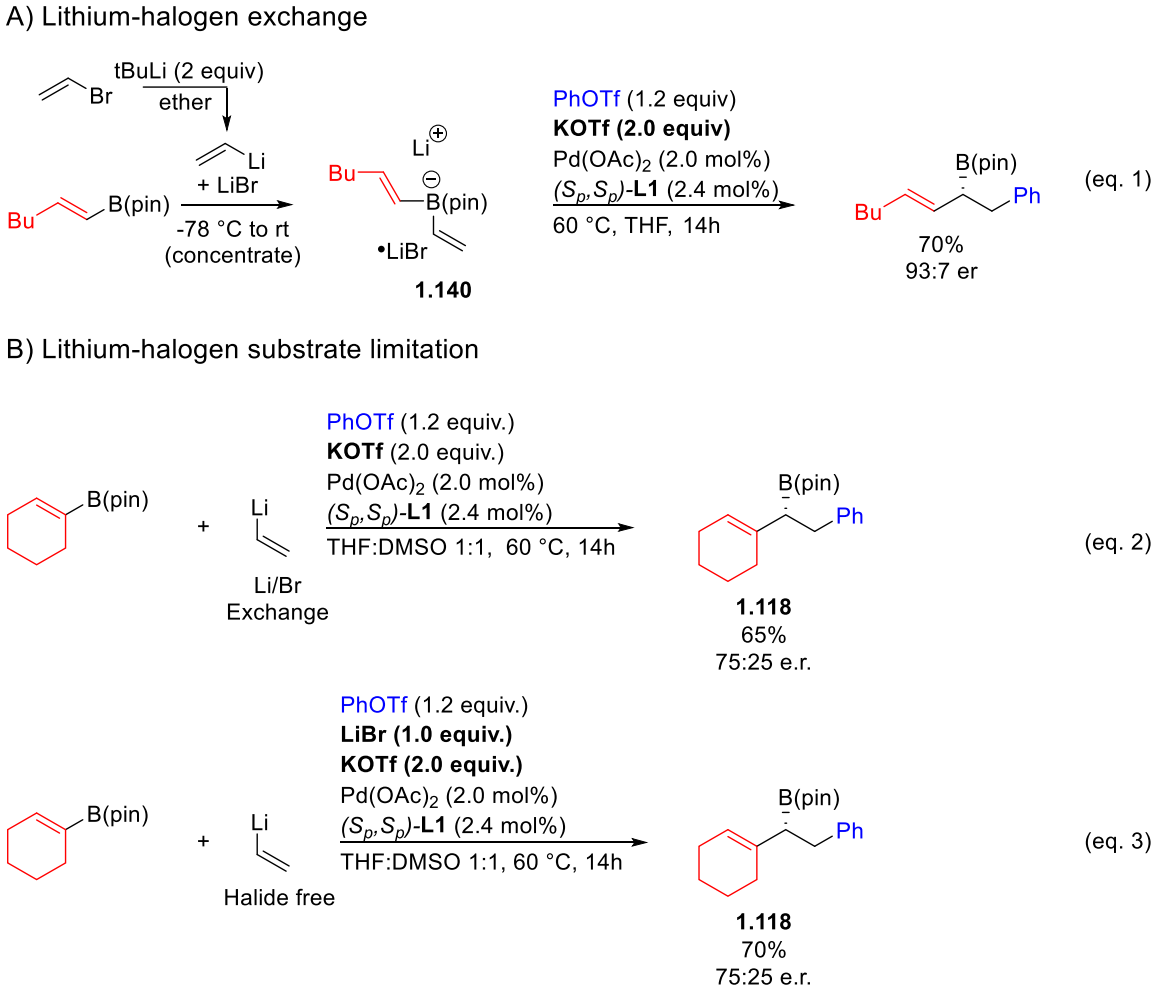
Entry	X	Change from standard conditions	Result
1	Cl	-	0%
2	Br	-	0%
3	Cl	2 equiv. KOTf	0%
4	Cl	2 equiv. NaOTf	0%
5	Br	2 equiv. KOTf	0%
6	Br	2 equiv. NaOTf	0%
7	Cl	2 equiv. NaOTf 1:1 THF: DMSO	62%, 92:8 e.r.
8	Br	2 equiv. KOTf 1:1 THF: DMSO	55%, 92:8 e.r
9	Cl	**2 equiv. NaOTf** **3:1 THF: DMSO**	**69%, 92:8 er**

It was not until a THF/DMSO mixture and either potassium or sodium triflate was used that complete boron "ate" complex formation was observed by ^{11}B NMR analysis. With these new conditions that allowed for "ate" complex formation, the desired product was also obtained in good yield and with good enantioselectivity (entries 7 and 8). DMSO is hypothesized to increase the polarity of the reaction medium, shifts the equilibrium towards "ate" complex formation and stabilize the "ate". Further optimization showed that the combination of sodium triflate with vinylmagnesium chloride in a 3:1 THF:DMSO volumetric ratio resulted in the best yield and enantioselectivity (entry 9). The ability to

engage Mg-based bis(alkenyl)borates increases the ease of application of this conjunctive reaction and complements the lithium-based system.

1.4.5.2 Lithium-Halogen Exchange

Scheme 1.37 Development and limitations of the lithium-halogen exchange



The vinyllithium utilized in the reaction development discussed above was derived from a lithium-tin exchange between tetravinyltin and *n*-butyllithium. This afforded halide free vinyllithium that was utilized in the reaction without additives. To broaden the synthetic utility of the reaction and also overcome the toxicity associated with tin reagents, vinyllithium along with a stoichiometric amount of lithium bromide were generated via a

lithium-halogen exchange (Scheme 1.37, eq. 1). During the optimization studies, *tert*-butyllithium was a better nucleophile than *n*-BuLi for the lithium-bromide exchange. In addition, diethyl ether was superior than tetrahydrofuran as the solvent medium for the lithium-halogen exchange. This was attributed to *t*-BuLi's ability to deprotonate the C2 acidic hydrogen of the THF ring faster than it deprotonates the most acidic hydrogen in diethyl ether.[58] Vinyllithium synthesized from lithium-halogen exchange was used in the reaction with the help of two equivalents of potassium triflate as the halide scavenger to achieve an efficient and stereoselective reaction (Scheme 1.37 A, eq. 1). When more densely substituted alkenyl migrating groups such as cyclohexenyl boronic ester in eq. 2 were employed, the product **1.118** was obtained in good yield but with diminished enantioselectivity (75:25 er) using vinyllithium derived from lithium-bromine exchange. In contrast, when halide free vinyllithium was used, compound **1.118** was obtained in 84:16 er. To understand the origin of this difference in selectivity, the halide free vinyllithium reaction was doped with one equivalent of lithium bromide and 2 equivalents of potassium triflate (eq. 3). The conjunctive product was obtained in good yield and with the same enantiomeric ratio (75:25 er) as in eq. 2. This result suggested that potassium triflate, which is important to overcome halide inhibition, might alter the transition state which results in the observed diminished enantioselectivity with densely substituted alkenyl migrating groups.

[58] Clayden, J.; Yasin, S. A. *New J. Chem*. **2002**, *26*, 191−192.

Scheme 1.38 Storable ate complex

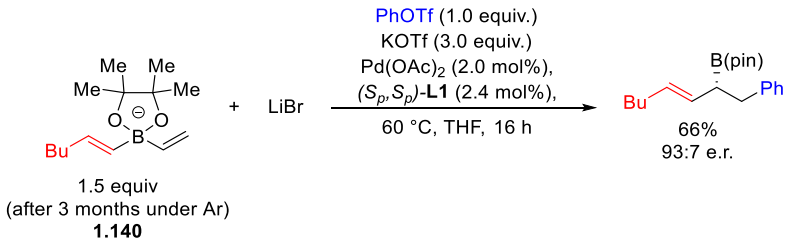
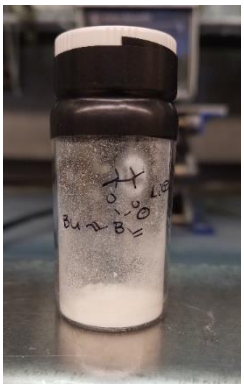


Figure 1.1



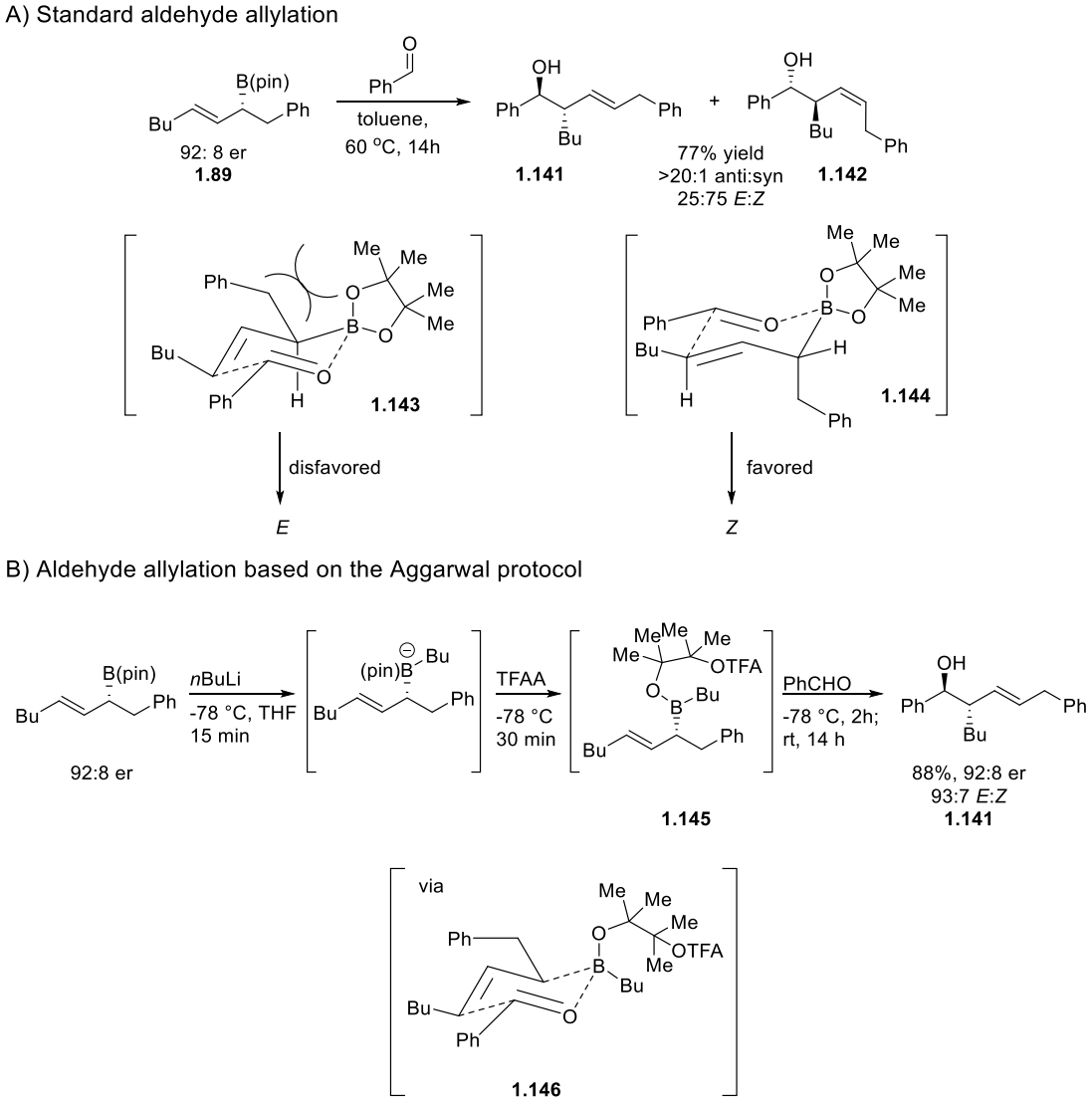
The intermediate boron 'ate" complexes were often free-flowing crystalline solids when evaporated to dryness under vaccum. To determine the long term stabiliy of these materials as potential "off-the shelf" coupling partners, we prepared bis(alkenyl) boron "ate" complex (**1.140**) on gram scale and stored it at room temperature under argon. To our delight, this "ate" complex even after 3 months of storage, furnished the allylic boronate in 66% yield and the same enantioselectivity as the freshly prepared material (Scheme 1.38).

1.5 Synthetic Utility

1.5.1 Aldehyde allylation

Scheme 1.39 Aldehyde allylation

To highlight the synthetic utility of the products, we performed an aldehyde allylation reaction. Using standard conditions,[59] allylboronic ester **1.89** and benzaldehyde were mixed, and the product was obtained as a 70:30 *Z*:*E* mixture (Scheme 1.39 A). The



[59] Hoffman, R. W.; Schäfer, F.; Haeberlin, E.; Rohde, T.; Körber, K. Synthesis, **2000**, *14*, 2060−2068.

impact of the α-substituent on the stereochemical outcome of allylboration and crotylation of aldehydes has been widely studied by various groups.[60] Literature precedent shows that with small ligands such as propanediol on boron, the *E* product is obtained, whereas large ligands on boron predominantly favor the *Z* diastereomer. The pinacol ligand on boron is known to give a 70:30 *Z*:*E* diasteromeric mixture.[61] This observation was in accord with the experimental stereochemical outcome we observed from the allylboration reaction (Scheme 1.39 A). This result can be rationalized by transition states **1.143** and **1.144**. In transition state **1.143**, there is a penalizing steric interaction between the equatorial benzyl substituent and the pinacol methyl groups thus disfavoring the formation of the *E* diastereomer. Transition state **1.144,** in contrast, places the benzyl in the axial position, thus minimizing the steric penalty with the pinacol methyl groups. As a result, **1.144** is favored and leads to the *Z* diastereomer.

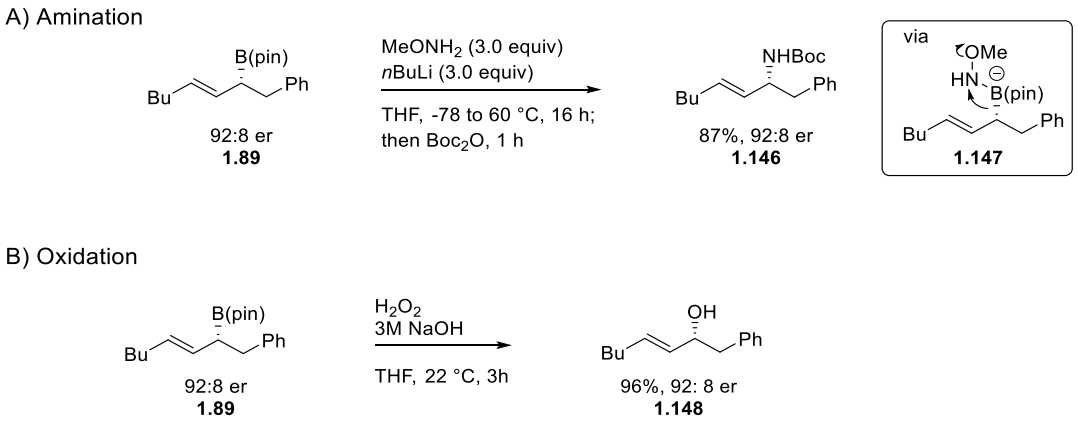
To improve the diastereoselectivity of the allylboration reaction, the protocol developed by Aggarwal was employed.[62] Addition of *n*-BuLi to pinacol boronic ester **1.89**, followed by acylation of the alkoxide with trifluoroacetic anhydride afforded the more reactive allyl borinic ester **1.145,** which underwent allylboration to afford homoallyl alcohol **1.141** in excellent yield and with high *E* diastereoselectivity (Scheme 1.39 B). In accord with the transition state (**1.146**) proposed by Aggarwal, it is plausible that the ring opened allyl borinic ester avoids the steric clash between the pinacol methyl groups and the equatorial benzyl substituent hence leading to the *E* product as the major diastereomer.

[60] Lachance, H.; Hall, D. G. Allylboration of Carbonyl Compounds. Organic Reactions; Denmark, S. E., Ed.; John Wiley & Sons: New York, **2008**, pp 1−573.
[61] Carosi, L.; Lachance, H.; Hall, D. G. *Tetrahedron Lett.* **2005**, *46*, 8981.
[62] See reference 43

1.5.2 Amination and oxidation

The allylboron products could undergo stereospecific amination[63], which to the best of our knowledge, is the first example of such a transformation from an allylboron reagent. Methoxyamine was deprotonated using *n*-butyllithium to generate the corresponding nitrogen anion, which adds to the empty p-orbital on allylboron **1.89** to generate "ate" complex **1.147**. Subsequent 1,2- metalate shift from **1.147** generates allyl amine **1.146** in good yield and with preservation of enantioselectivity (Scheme 1.40 A). The product could also be oxidized to the corresponding allyl alcohol) in nearly quantitative yield (Scheme 1.40 B).

Scheme 1.40 Allylboron amination and oxidation



[63] Mlynarski, S.; Karns, A. S.; Morken, J. P. *J. Am. Chem. Soc.* 2**012**, *40*, 16449−16451.

1.6 Conclusion

The scope of the palladium-catalyzed conjunctive cross-coupling has been expanded to include bis(alkenyl)borates. This proceeds by selective activation of the less sterically encumbered alkene and subsequent migration of the more substituted olefin. This protocol serves as a general catalytic and enantioselective method for the synthesis of α-chiral terminal and internal allyl boron reagents that employs readily accessible alkenyl boronic esters, organolithium and Grignard reagents.

1.7 Experimental Section

1.7.1 General Information

^{1}H NMR spectra were recorded on either a Varian Gemini-500 (500 MHz) or Varian Gemini-600 (600 MHz) spectrometer. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 7.26 ppm). Data are reported as follows: integration, chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, br = broad, app = apparent), and coupling constants (Hz). ^{13}C NMR spectra were recorded on either a Varian Gemini-500 (125 MHz) or a Varian Gemini-600 (150 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 77.16 ppm). ^{11}B NMR spectra were recorded on a Varian Gemini-500 (160 MHz). Chemical shifts are reported in ppm with an external standard ($BF_3 \cdot Et_2O$: 0 ppm). ^{19}F NMR spectra were recorded on a Varian Gemini-500 (470 MHz) spectrometer or Varian Gemini-600 (564 MHz) spectrometer. Infrared (IR) spectra were recorded on a Bruker alpha-P Spectrometer. Frequencies are reported in wavenumbers (cm^{-1}) as follows: strong (s), broad (br), medium (m), and weak (w). Optical rotations were measured on a Rudolph Analytical Research Autopol IV Polarimeter. High-resolution mass spectrometry (DART and ESI) was performed at the Mass Spectrometry Facility, Boston College, Chestnut Hill, MA. Liquid chromatography was performed using forced flow (flash chromatography) on silica gel (SiO_2, 230 x 450 Mesh) purchased from Silicycle or with a Biotage Isolera One equipped with full wavelength scan. Thin layer chromatography (TLC) was performed on 25 μm silica gel glass backed plates from Silicycle. Visualization was performed using ultraviolet light (254 nm), ceric ammonium molybdate (CAM) in ethanol, phosphomolybdic acid and

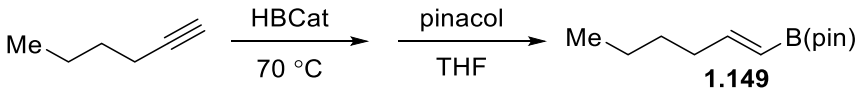
cerium(IV) sulfate in ethanol with sulfuric acid (Seebach), ninhydrin, or potassium permanganate.

Analytical chiral supercritical fluid chromatography (SFC) was performed on a TharSFC Method Station II equipped with Waters 2998 Photodiode Array Detector with isopropanol or methanol as the modifier.

All reactions were conducted in oven- or flame-dried glassware under an inert atmosphere of nitrogen or argon. Tetrahydrofuran (THF), diethyl ether (Et_2O), dichloromethane (CH_2Cl_2) and toluene were purified using Pure Solv MD-4 solvent purification system, from Innovative Technology, Inc., by passing the solvent through two activated alumina columns after purging with argon. Palladium (II) acetate, 1,1′-Bis(dicyclohexylphosphino)ferrocene, and 1,1′-Bis(diphenylphosphino)ferrocene were purchased from Strem Chemicals, Inc. and used without further purification. (S_p,S_p)-**L1** was generously donated by Solvias. All other reagents were purchased from either Aldrich, Alfa Aesar, Acros, Oakwood Chemicals, Combi Blocks, or TCI and were used without further purification.

1.7.2 Experimental Information

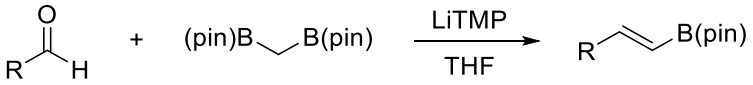
1.7.2.1 Procedures for the Synthesis of Alkenyl Boronic Esters

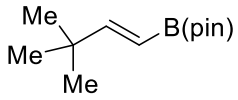


1.149

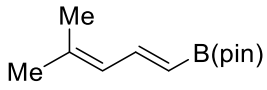
(E)-2-(Hex-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.149). Prepared according to the procedure reported in the literature[64] with 1-Hexyne (2.30 mL, 20.0 mmol, 1.0 equiv.), catecholborane (2.34 mL, 22.0 mmol, 1.1 equiv.), pinacol (2.84 g, 24 mmol, 1.2 equiv.), and THF (50 mL). The crude residue was purified on silica gel flash chromatography with the Biotage Isolera One with 7-47% CH_2Cl_2 in hexanes to afford the title compound as a clear colorless oil which was then distilled under reduced pressure to afford a clear colorless oil (2.84 g, 68%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.63 (1H, dt, *J* = 17.4, 6.6 Hz), 5.42 (1H, d, *J* = 17.4 Hz), 2.17-2.12 (2H, m), 1.42-1.36 (2H, m), 1.35-1.28 (2H, m), 1.26 (12H, s), 0.88 (1H, t, *J* = 7.2 Hz). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 154.9, 83.1, 35.7, 30.5, 24.9, 22.4, 14.1. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 29.6. **IR** (neat) ν_{max} 2977.7 (w), 2928.4 (w), 2872.8 (w), 1638.0 (m), 1466.5 (w), 1358.9 (s), 1316.4 (s), 1144.1 (s), 997.7 (m), 970.9 (m), 849.6 (m) cm^{-1}. **HRMS** (DART+) for $C_{12}H_{24}BO_2$ $[M+H]^+$ calculated: 211.1869, found: 211.1862.

(64) Yoo, K. S.; Yoon, S. H.; Jung K. W. *J. Am. Chem. Soc.* **2006**, *128*, 16384.

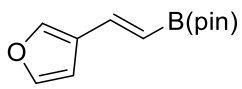




(E)-2-(3,3-Dimethylbut-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaboro la ne (1.150). Prepared according to the procedure reported in the literature[65] with pivalaldehyde (0.48 mL, 4.4 mmol, 1.1 equiv.), bis[pinacolato) boryl]methane (1.07 g, 4.0 mmol, 1.0 equiv.), lithium tetramethyl piperidide (0.65 g, 4.4 mmol, 1.1 equiv.), and THF (15 mL). The crude residue was purified on silica gel flash chromatography with 2% ethyl acetate in hexanes to afford the title compound as a clear colorless oil (0.55 g, 65% yield). All spectral data was in accord with the literature.[66]



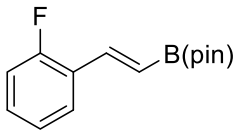
(E)-4,4,5,5-Tetramethyl-2-(4-methylpenta-1,3-dien-1-yl)-1,3,2-dioxa bor olane (1.151). Prepared according to the procedure reported, and all spectral data in accord with the literature.[2]



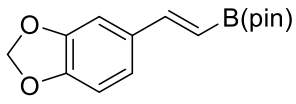
(E)-2-(2-(Furan-3-yl)vinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.152). Prepared according to the procedure reported in the literature[2] with 3-furancarboxaldehyde (0.43 mL, 5.0 mmol, 1.0 equiv.), bis[(pinacolato) boryl]methane (1.60 g, 6.0 mmol, 1.2 equiv.), lithium tetramethyl piperidide (0.88 g, 6.0 mmol, 1.2 equiv.), and THF (20.0 mL). The crude residue was

(65) Coombs, J. R.; Zhang, L.; Morken, J. P. *Org. Lett.* **2015**, *17*, 1708.
(66) Stulgies, B.; Prinz, P.; Magull, J.; Rauch, K.; Meindl, K.; Ruhl, S.; de Meijere. A. *Chem. Eur. J.* **2004**, *11*, 308.

purified with the Biotage Isolera One in 10-50% CH_2Cl_2 in hexanes to afford the title compound as a white solid (0.744 g, 68%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.49 (1H, s), 7.38-7.35 (1H, m), 7.27 (1H, d, J = 18.0 Hz), 6.60 (1H, d, J = 1.2 Hz), 5.83 (1H, d, J = 18.6 Hz), 1.29 (12H, s). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 143.9, 142.4, 139.5, 126.0, 107.5, 83.4, 25.0. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 29.7. **IR** (neat) ν_{max} 3104.6 (w), 2938.0 (w), 1630.1 (s), 1560.4 (w), 1373.1 (m), 1347.1 (s), 1322.8 (s), 1237.0 (m), 1140.7 (s), 1086.3 (m), 1023.2 (m), 994.2 (m), 965.6 (m), 869.3 (m), 846.5 (m), 793.5 (m) cm^{-1}. **HRMS** (DART+) for $C_{12}H_{18}BO_3$ $[M+H]^+$ calculated: 221.1349, found: 221.1352.



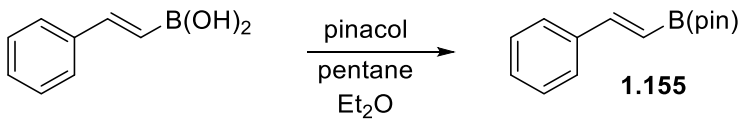
(E)-2-(2-Fluorostyryl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.153). Prepared according to the procedure reported in the literature[2] with 2-fluorobenzaldehyde (0.93 mL, 8.8 mmol, 1.1 equiv.), bis[Ipinacolato) boryl]methane (2.14 g, 8.0 mmol, 1.0 equiv.), lithium tetramethyl piperidide (1.30 g, 8.8 mmol, 1.1 equiv.), and THF (30 mL). The crude residue was purified on silica gel flash chromatography with 2% ethyl acetate in hexanes to afford the title compound as a pale yellow oil (1.55 g, 78% yield). All spectral data was in accord with the literature.[67]

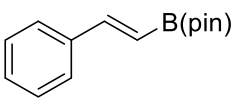


(E)-2-(2-(Benzo[d][1,3]dioxol-5-yl)vinyl)-4,4,5,5-tetramethyl-1,3,2 -dioxaborolane (1.154). Prepared according to the procedure reported in the literature[2] with piperonal (0.45 g, 3.0 mmol, 1.0 equiv.), bis[(pinacolato)boryl]methane (0.88 g, 3.3 mmol, 1.1 equiv.), lithium

(67) Jang, H.; Zhugralin, A. R.; Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, 7859.

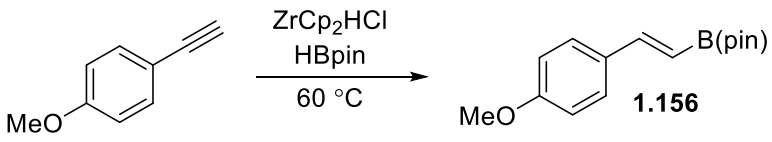
tetramethylpiperidide (0.49 g, 3.3 mmol, 1.1 equiv.), and THF (12 mL). The crude residue was purified with the Biotage Isolera One in 10-50% CH_2Cl_2 in hexanes to afford the title compound as a white solid (0.49 g, 59% yield). All spectral data was in accord with the literature.[68]

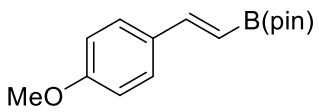




(E)-4,4,5,5-Tetramethyl-2-styryl-1,3,2-dioxaborolane (1.155). Prepared according to the procedure reported in the literature[69] with *trans*-2-phenylvinylboronic acid (1.0 g, 6.8 mmol, 1.0 equiv.), pinacol (0.84 g, 7.1 mmol, 1.05 equiv.), and a pentane/Et_2O 2:1 mixture (8 mL). The crude residue was purified on a silica gel plug with CH_2Cl_2 to afford the title compound as a white solid (1.47 g, 94%). All spectral data was in accord with the literature.[70]

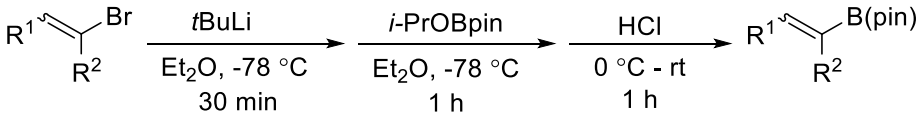
(68) Reid, W. B.; Spillane, J. J.; Krause, S. B.; Watson, D. A. *J. Am. Chem. Soc.* **2016**, *138*, 5539.
(69) Zhang, L.; Lovinger, G. J.; Edelstein, E. K.; Szymaniak, A. A.; Chierchia, M. P.; Morken, J. P. *Science*. **2016**, *351*, 70.
(70) Tucker, C. E.; Davidson, J.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 3482.

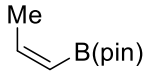




(E)-2-(4-Methoxystyryl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.156). Prepared according to the procedure reported in the literature[71] with slight modification. In an Ar-filled glove box, an oven dried round bottom flask equipped with a magnetic stir bar was charged with bis(cyclopentadienyl) zirconium IV chloride hydride (Shwartz's reagent, 0.077 g, 0.3 mmol, 0.06 equiv.) and sealed with a rubber septum. Outside the glove box, under N_2, 4-ethynyl anisole (0.650 mL, 5.0 mmol, 1.0 equiv.) was added followed by pinacolborane (0.73 mL, 5.0 mmol, 1.0 equiv.) dropwise. The reaction mixture was allowed to stir at room temperature for 16 h under N_2. The reaction mixture was quenched with H_2O (10 mL) and then allowed to stir for 10 min at room temperature. The aqueous layer was then extracted with Et_2O (2x 20 mL). The organic layer was drier over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified on silica gel chromatography with 5% ethyl acetate in hexanes to afford the title compound as a white solid (1.14 g, 87% yield). All spectral data was in accord with the literature.[3]

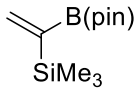
(71) Crestey, F.; Hooyberghs, G.; Kristensen, J. L. *Tetrahedron*. **2012**, *68*, 1417.





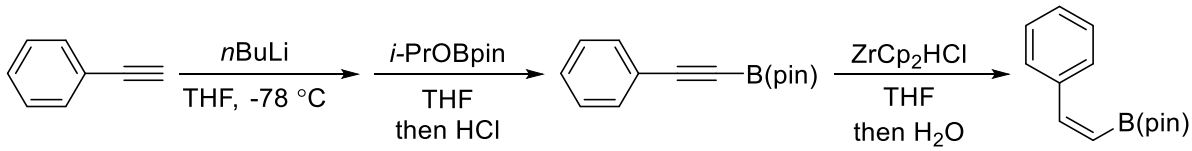
(Z)-4,4,5,5-Tetramethyl-2-(prop-1-en-1-yl)-1,3,2-dioxaborolane (1.157). A round bottom flask equipped with a magnetic stir bar was flame dried and back-filled with N_2 then charged with diethyl ether (20 mL) and *cis*-1-bromo-1-propene (0.85 mL, 10.0 mmol, 1.0 equiv.) The mixture was cooled to -78 °C, and *t*ert-butyllithium (11.1 mL, 1.8 M in pentane, 20 mmol, 2.0 equiv.) was added dropwise cautiously. The mixture was allowed to stir for 30 minutes at -78 °C. Another round bottom flask equipped with a magnetic stir bar was flame dried and back-filled with N_2 then charged with diethyl ether (20 mL) and 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.65 mL, 13.0 mmol, 1.3 equiv.). The solution was cooled to 0 °C and the freshly prepared alkenyl lithium solution was added dropwise and rinsed with additional diethyl ether (5 mL). The resulting solution was allowed to stir for 30 minutes at -78 °C then was allowed to warm to room temperature and allowed to stir for an additional 30 minutes. The solution was then cooled to 0 °C and HCl (1M, 15 mL) was added dropwise. The resulting solution was allowed to warm to room temperature and allowed to stir for one hour. The mixture was transferred to a separatory funnel and the aqueous layer was extracted with diethyl ether (3x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified using the Biotage Isolera one (50 g column) with 10-40% CH_2Cl_2 in hexanes to afford the title compound as a clear colorless oil (0.360 g, 21% yield). All spectral data was in accord with the literature.[72]

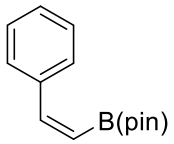
(72) Althaus, M.; Mahmood, A.; Suárez, J. R.; Thomas, S. P.; Aggarwal, V. K.. *J. Am. Chem. Soc.* **2010**, *132*, 4025.



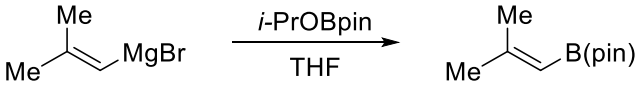
Trimethyl(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)silane (1.158). A round bottom flask equipped with a magnetic stir bar was flame dried and back-filled with N_2 then charged with diethyl ether (15 mL) and (1-bromovinyl)trimethylsilane (1.20 mL, 7.7 mmol, 1.0 equiv.) The mixture was cooled to -78 °C, and *t*ert-butyllithium (9.06 mL, 1.7 M in pentane, 15.4 mmol, 2.0 equiv.) added dropwise cautiously. The mixture was allowed to stir for 30 minutes at -78 °C. Another round bottom flask equipped with a magnetic stir bar was flame dried and back-filled with N_2 then charged with diethyl ether (15 mL) and 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.04 mL, 10.0 mmol, 1.3 equiv.). The solution was cooled to 0 °C and the freshly prepared alkenyl lithium solution was added dropwise and rinsed with additional diethyl ether (5 mL). The resulting solution was allowed to stir for 30 minutes at -78 °C then was warmed to room temperature and allowed to stirred for an additional 30 minutes. The solution was then cooled to 0 °C and HCl (1M, 12 mL) was added dropwise. The resulting solution was allowed to warm to room temperature then allowed to stir for one hour. The mixture was transferred to a separatory funnel and the aqueous layer was extracted with diethyl ether (3x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified on silica gel with 5% ethyl acetate in hexanes to afford the title compound as a clear colorless oil (1.29 g, 72% yield). All spectral data was in accord with the literature.[73]

(73) Kurahashi, T.; Hata, T.; Masai, H.; Kitagawa, H.; Shimizu, M.; Hiyama, T. *Tetrahedron* **2002**, *58*, 6381.

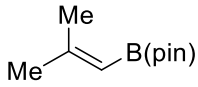




(Z)-4,4,5,5-Tetramethyl-2-styryl-1,3,2-dioxaborolane (S-10). Prepared according to the procedures reported in the literature.[74,75] All spectral data was in accord with the literature.[76]



1.159



4,4,5,5-Tetramethyl-2-(2-methylprop-1-en-1-yl)-1,3,2-dioxaborolane (1.159). Prepared according to the procedure reported in the literature[77] with 2-methyl-1-propenylmagnesium bromide (0.35 M in THF, 13.0 mL, 4.55 mmol, 1.0 equiv.), 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.39 mL, 6.83 mmol. 1.5 equiv.) and THF (5.0 mL). The crude residue was purified on silica gel flash chromatography with 5% ethyl acetate in hexanes to afford a clear colorless oil which was then distilled under reduced pressure to afford the title compound as a clear colorless oil (0.607 g, 73% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.11 (1H, s), 1.98 (3H, s), 1.86 (3H, s), 1.25 (12H, s). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 159.6, 82.7, 29.1, 25.0, 22.8. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 29.4. **IR** (neat) ν_{max} 2977.7 (w), 2931.6 (w), 1643.3 (m), 1445.2 (m),

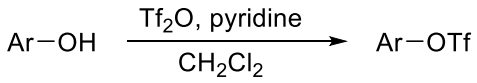
(74) Nishihara, Y.; Miyasaka, M.; Okamoto, M.; Takahashi, H.; Inoue, E.; Tanemura, K; Takagi, K. *J. Am. Chem. Soc.* **2007**, *129*, 12634.
(75) Luan, Y.; Barbato, K. S.; Moquist, P. N.; Kodama, T.; Schaus, S. E. *J. Am Chem. Soc.* **2015**, *137*, 3233.
(76) Gunanathan, C.; Holscher, M.; Pang, F.; Leitner, W. *J. Am. Chem. Soc.* **2012**, *134*, 14349.
(77) Myslinska, M.; Heise, G. L.; Walsh, D. J. *Tetrahedron Lett.* **2012**, *53*, 2937.

1397.1 (s), 1378.6 (s), 1357.7 (s), 1316.2 (s), 1264.3 (s), 1143.1 (s), 970.6 (m), 852.1 (m) cm^{-1}. **HRMS** (DART+) for $C_{10}H_{20}BO_2$ $[M+H]^+$ calculated: 183.1556, found: 183.1560.

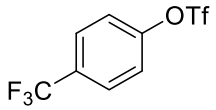
All other boronic esters were purchased and used without further purification. Vinyl boronic acid pinacol ester, *trans*-1-propenylboronic acid pinacol ester, isopropenyl boronic acid pinacol ester, cyclohexen-1-ylboronic acid pinacol ester, and 3,6-dihydro-2H-pyridine-1-N-Boc-4-boronic acid pinacol ester were purchased from Combi Blocks. *(trans)*-2-cyclopropylvinyl boronic acid pinacol ester, *trans*-4-(*tert*-Butyldimethylsiloxy)-1-buten-1-ylboronic acid pinacol ester, and 1-phenylvinyl boronic acid pinacol ester were purchased from Sigma Aldrich.

1.7.2.2 Procedures for the Synthesis of Trifluoromethanesulfonates

General Procedure for the Synthesis of Aryl Trifluoromethanesulfonates:

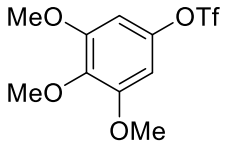


Aryl Trifluoromethanesulfonates were made according to literature procedure with slight modification.[78] To a solution of the corresponding phenol (1.0 equiv.) and pyridine (2.0 equiv.) in CH_2Cl_2 at 0 °C, a solution of trifluoromethanesulfonic anhydride (1.2 equiv.) in CH_2Cl_2 was added dropwise. The mixture was then allowed to warm to room temperature and allowed to stir for 1 hour. The mixture was diluted with Et_2O, and quenched with 3M HCl *(aq).* The organic layer was washed with $NaHCO_3$ *(aq, sat.)* then brine. The solution was dried over Na_2SO_4, filtered with Et_2O, and the solvent was removed under reduced pressure to afford the crude aryl trifluoromethanesulfonates which were purified on silica gel or with vacuum distillation.

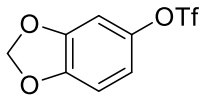


4-(Trifluoromethyl)phenyl trifluoromethanesulfonate (1.160). Prepared according to the general procedure for the synthesis of aryl trifluoromethanesulfonates above with 4-trifluoromethylphenol (0.811 g, 5.0 mmol), trifluoromethanesulfonic anhydride (1.0 mL, 6.0 mmol), pyridine (0.809 mL, 10.0 mmol), and CH_2Cl_2 (10.0 mL). The crude residue was distilled under reduced pressure to afford the title compound as a clear colorless oil (1.35 g, 92% yield). All spectral data was in accord with the literature.[79]

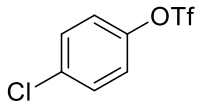
(78) Goosen, L. J.; Linder, C.; Rodríguez, N.; Lange, P. P. *Chem. Eur. J.* **2009**, *15*, 9336.
(79) Gill, D.; Hester, A. J.; Lloyd-Jones, G. C. *Org. Biomol. Chem.,* **2004**, *2*, 2547.



3,4,5-Trimethoxyphenyl trifluoromethanesulfonate (1.161). Prepared according to the general procedure for the synthesis of aryl trifluoromethanesulfonates above with 3,4,5-trimethoxyphenol (0.921 g, 5.0 mmol), trifluoromethanesulfonic anhydride (1.0 mL, 6.0 mmol), pyridine (0.809 mL, 10.0 mmol), and CH_2Cl_2 (8.0 mL). The crude residue was purified with silica gel chromatography (20% ethyl acetate in hexanes) to afford the title compound as an off white solid (1.55 g, 98% yield). All spectral data was in accord with the literature.[80]



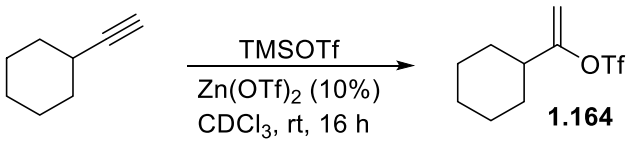
Benzo[d][1,3]dioxol-5-yl trifluoromethanesulfonate (1.162). Prepared according to the general procedure for the synthesis of aryl trifluoromethanesulfonates above with sesamol (0.83 g, 6.0 mmol), trifluoromethanesulfonic anhydride (1.21 mL, 7.20 mmol), pyridine (0.97 mL, 12.0 mmol), and CH_2Cl_2 (12.0 mL). The crude residue was distilled under reduced pressure to afford the title compound as a yellow oil (1.57 g, 97% yield). All spectral data was in accord with the literature.[81,82]

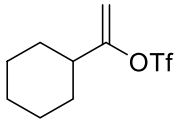


4-Chlorophenyl trifluoromethanesulfonate (1.163). Prepared according to the general procedure for the synthesis of aryl trifluoromethanesulfonates above with 4-chlorophenol (1.29 g, 10 mmol), trifluoromethanesulfonic anhydride (2.0 mL, 12.0 mmol), pyridine (1.62 mL, 20.0 mmol), and CH_2Cl_2 (20.0 mL). The crude residue was distilled under reduced pressure to afford

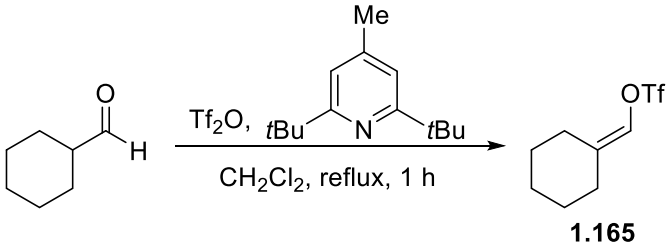
(80) Macmillan, D.; Anderson, D. *Org. Lett.* **2004**, *6*, 4659.
(81) Smythe, L. A.; Phillips, E. M.; Chan, V. S.; Napolitano, J. G.; Henry, R.; Shekhar, S. *J. Org. Chem.* **2016**, *81*, 1285.
(82) Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5478.

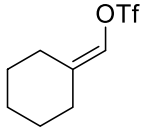
the title compound as a clear colorless oil (2.32 g, 89% yield). All spectral data was in accord with the literature.[83]





1-Cyclohexylvinyl trifluoromethanesulfonate (1.164). Prepared according to the procedure reported, and all spectral data was in accord with the literature.[84].



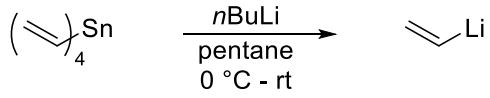


Cyclohexylidenemethyl trifluoromethanesulfonate (1.165). Prepared according to the procedure reported, and all spectral data in accord with the literature.[85] All other trifluoromethanesulfonates were purchased and used without further purification. 4-methoxyphenyl trifluoromethanesulfonate was purchased from Oakwood. 6-Quinolinyl trifluoromethanesulfonate and 1-cylcohexenyl trifluoromethanesulfonate were purchased from Sigma Aldrich.

(83) Proutiere, F.; Schoenebeck, F. *Angew. Chem. Int. Ed.* **2011**, *50*, 8192.
(84) Al-huniti, M. H.; Lepore, S. D. *Org. Lett*. **2014**, *16*, 4154.
(85) Stang, P. J.; Treptow, W. *Synthesis*. **1980**, *4*, 283.

1.7.2.3 Procedures for the Synthesis of Halide-Free Vinyl Lithium

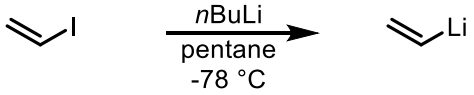
Lithium-tin exchange:



To an oven-dried 250 mL round bottom flask equipped with a stir bar in an Ar-filled glovebox was added tetravinyltin (5.67 g, 25.0 mmol, 1.0 equiv.) and pentane (100 mL). The reaction flask was sealed with a rubber septum, removed from the glovebox, and cooled to 0 ℃. Under N_2, *n*-butyllithium (18.9 mL. 2.65 M in hexanes, 2.0 equiv.) was added *via* syringe pump over an hour. Vinyllithium formation was observed as a white suspension in the reaction flask within 2-3 minutes of initial *n*BuLi addition. Upon completion of slow addition at 0 ℃, the flask was allowed to warm to room temperature and left to stir an additional 2 hours. The reaction flask was then sealed, and returned to an Ar-filled glovebox. The vinyllithium suspension was vacuum filtered through a fritted funnel and the solid vinyl lithium was consecutively washed with pentane (3x 30 mL), then dried under reduced pressure. Caution should be taken with the pentane filtrate, as organotin waste is toxic and is to be disposed of accordingly. Caution should also be taken with the dry vinyllithium, as it is a very fine powder and pyrophoric. The solid vinyl lithium was dissolved in THF (approximately 40 mL) and then filtered through acrodisc syringe filters to afford the vinyllithium solution in quantitative yield as a pale yellow solution which is stored under Ar in the freezer of the glovebox. The molarity of the solution is determined by titration with BHT in the presence of 1,10-phenanthroline and generally ranges from 1.3 – 1.9 M.

Note: Freshly titrated good quality (clear or pale yellow and particulate free) *n*butyllithium was used to afford the vinyllithium solution as a pale yellow solution. Older bottles of *n*BuLi that have turned darker yellow and cloudy will afford vinyllithium as a dark yellow or orange solution in THF. While this vinyllithium is still efficient in the reaction, higher Pd/ligand loadings (3% vs. 1%) may be required.

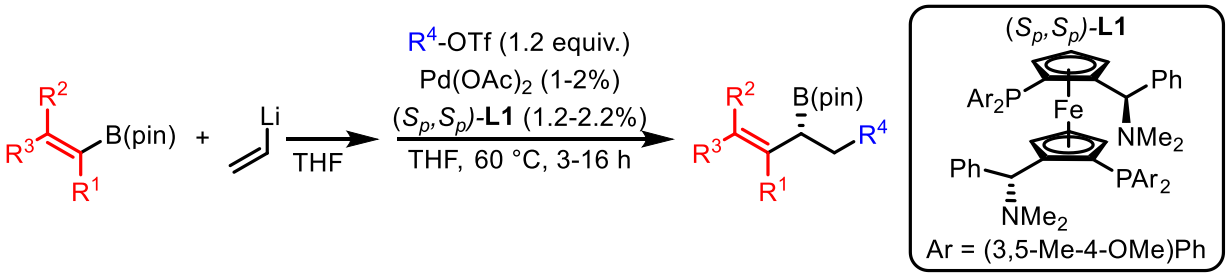
Lithium-iodide exchange:



Halide-free vinyl Lithium can also be prepared from lithium halogen exchange with vinyl iodide followed by repeated recrystallization.[6]

1.7.2.4 General Procedures for Conjunctive Cross-Coupling

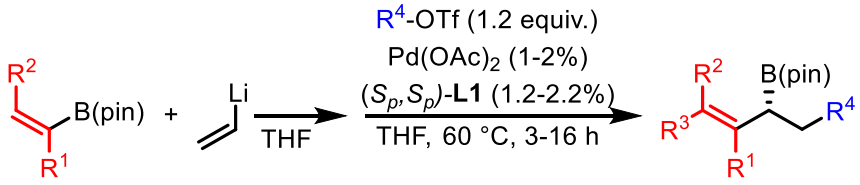
***Method A**:* Halide-free vinyl lithium with liquid trifluoromethanesulfonate electrophiles of



reported density

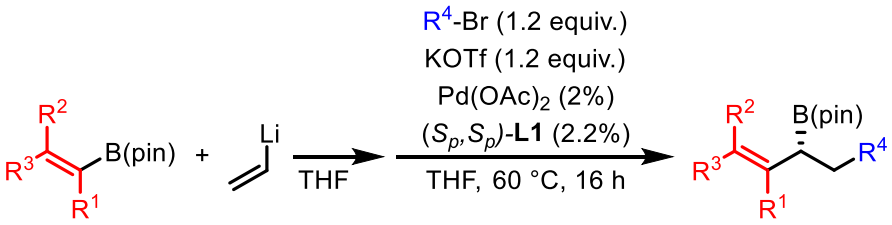
To an oven-dried 2-dram vial equipped with a magnetic stir bar in an Ar-filled glovebox was added alkenyl boronic ester (0.30 mmol, 1.0 equiv.) and THF (0.60 mL). The vial was sealed with a septum cap, removed from the glove box, cooled to 0 °C, and under N_2, vinyl lithium (solution in THF, 0.30 mmol, 1.0 equiv.) was added. The reaction vial was allowed to warm to room temperature and allowed to stir for 5 minutes. $Pd(OAc)_2$ and (S_p,S_p)-**L1** were added as a solution in THF (0.30 – 0.60 mL) that had been pre-stirred for 10 minutes then THF was added to bring the concentration to 0.2 M. The triflate (0.36 mmol, 1.2 equiv.) was added. The reaction vial was taped to seal, heated to 60 °C, and allowed to stir for 3-16 hours. The resulting mixture was cooled to room temperature, filtered through a silica gel plug with diethyl ether, and concentrated under reduced pressure to afford the crude reaction residue which was purified on silica gel.

***Method B**:* Halide-free vinyl lithium with solid trifluoromethanesulfonate electrophiles or liquid trifluoromethanesulfonate electrophiles of un-reported density.



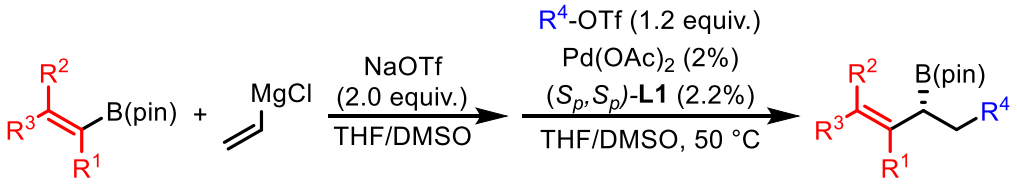
To an oven-dried 2-dram vial equipped with a magnetic stir bar in an Ar-filled glovebox was added alkenyl boronic ester (0.30 mmol, 1.0 equiv.) and THF (0.60 mL). The vial was sealed with a septum cap and removed from the glove box. Under N_2, the reaction vial was cooled to 0 °C and vinyl lithium (solution in THF, 0.30 mmol, 1.0 equiv.) was added. The reaction vial was allowed to warm to room temperature, allowed to stir for 5 minutes, and then returned to an Ar-filled glove box. $Pd(OAc)_2$ and (S_p,S_p)-**L1** were added as a solution in THF (0.30 – 0.60 mL) that had been pre-stirred for 10 minutes then THF was added to bring the concentration to 0.2 M. The triflate (0.36 mmol, 1.2 equiv.) was added. The reaction vial was sealed with a polypropylene cap, removed from the glove box, heated to 60 °C, and allowed to stir for 3-16 hours. The resulting mixture was cooled to room temperature, filtered through a silica gel plug with diethyl ether, and concentrated under reduced pressure to afford the crude reaction residue which was purified on silica gel.

***Method C**:* Halide-free vinyl lithium with bromide electrophiles



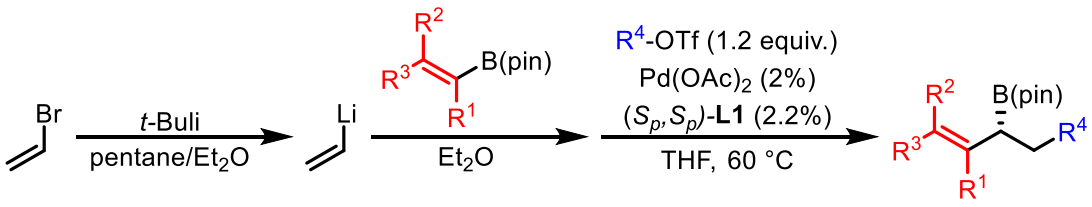
To an oven-dried 2-dram vial equipped with a magnetic stir bar in an Ar-filled glovebox was added alkenyl boronic ester (0.30 mmol, 1.0 equiv.) and THF (0.60 mL). The vial was sealed with a septum cap and removed from the glove box. Under N_2, the reaction vial was cooled to 0 ℃ and vinyl lithium (solution in THF, 0.30 mmol, 1.0 equiv.) was added. The reaction vial was allowed to warm to room temperature, allowed to stir for 5 minutes, and then returned to an Ar-filled glove box. Potassium trifluoromethanesulfonate (0.36 mmol, 1.2 equiv.) was added. $Pd(OAc)_2$ (0.006 mmol, 2%) and (S_p,S_p)-**L1** (0.0066 mmol, 2.2%) were added as a solution in THF (0.60 mL) that had been pre-stirred for 10 minutes then THF was added to bring the concentration to 0.2 M. The bromide (0.36 mmol, 1.2 equiv.) was added. The reaction vial was sealed with a polypropylene cap, removed from the glove box, heated to 60 ℃, and allowed to stir for 16 hours. The resulting mixture was cooled to room temperature, filtered through a silica gel plug with diethyl ether, and concentrated under reduced pressure to afford the crude reaction residue which was purified on silica gel.

***Method D**:* Vinyl magnesium chloride



To an oven-dried 2-dram vial equipped with a magnetic stir bar in an Ar-filled glovebox was added alkenyl boronic ester (0.30 mmol, 1.0 equiv.), sodium trifluoromethanesulfonate (0.60 mmol, 2.0 equiv.), THF (0.30 mL), and DMSO (0.3 mL). The vial was sealed with a septum cap and removed from the glove box. Under N_2, the reaction vial was cooled to 0 °C and vinyl magnesium chloride (solution in THF, 0.30 mmol, 1.0 equiv.) was added. The reaction vial was allowed to warm to room temperature, allowed to stir for 15 minutes, and then returned to an Ar-filled glove box. $Pd(OAc)_2$ (0.006 mmol, 0.02 equiv.) and (S_p,S_p)-**L1** (0.0066 mmol, 0.022 equiv.) were added as a solution in THF (0.6 mL) that had been pre-stirred for 10 minutes then THF was added to bring the concentration to 0.2 M. The triflate (0.36 mmol, 1.2 equiv.) was added. The reaction vial was sealed with a polypropylene cap, removed from the glove box, heated to 50 °C, and allowed to stir for 16 hours. The resulting mixture was cooled to room temperature, filtered through a silica gel plug with diethyl ether, and concentrated under reduced pressure to afford the crude reaction residue which was purified on silica gel.

***Method E**:* Vinyl lithium from lithium-bromide exchange



***Preparation of Vinyl Bromide Solution in diethyl ether**:* A 2-neck round bottom flask equipped with a magnetic stir bar and condensation funnel was flame dried and back-filled with N_2. Diethyl ether was added (8.0 mL). The condensation funnel was cooled to -78 °C. Vinyl bromide gas was condensed into the ether (approximately 20-30 drops) to afford a vinyl bromide solution in diethyl ether of approximately 0.9-2 M. The molarity of the solution was determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. This solution was stored under nitrogen or argon in the fridge.

Ate complex formation: An oven-dried 2 dram vial equipped with a magnetic stir bar was evacuated and back-filled with N_2 then charged with vinyl bromide (0.28 mL, 0.33 mmol, 1.2 M in Et_2O, 1.1 equiv.). The solution was cooled to -78 °C and *tert*-butyllithium (0.36 mL, 0.63 mmol, 1.75 M in pentane, 2.1 equiv.) was added dropwise. The reaction mixture was allowed to stir 30 min at -78 °C. Alkenyl boronic ester (0.30 mmol, 1.0 equiv.) was added as a solution in diethyl ether (0.40 mL). The solution was stirred for 5 minutes at -78 °C then allowed to warm to room temperature and left to stir for 10 minutes. The solvent was carefully removed under reduced pressure to afford the ate complex as a few flowing white solid which was brought into an Ar-filled glove box. This can be done on small scale and immediately used in a coupling reaction (yield based off of amount of boronic ester used) or on larger (gram) scale and stored under Ar to be used at a later time. The yield of

the coupling reaction in this case is based off of the electrophile amount, with the ate complex being used in excess (due to the difficulty of accurately quantifying the ate complex:LiBr ratio).

***Coupling Procedure when ate complex was made on small scale**:* In an Ar-filled glove box, to the dry ate complex was added potassium trifluoromethanesulfonate (0.60 mmol, 2.0 equiv.) followed by THF (0.60 mL). $Pd(OAc)_2$ (0.006 mmol, 0.02 equiv.) and (S_p,S_p)-**L1** (0.0066 mmol, 0.021 equiv.) were added as a solution in THF (0.60 mL, then 0.30 mL to rinse) that had been pre-stirred for 10 minutes. The triflate (0.36 mmol, 1.2 equiv.) was added. The reaction vial was sealed with a polypropylene cap, removed from the glove box, heated to 60 °C, and allowed to stir for 16 hours. The resulting mixture was cooled to room temperature, filtered through a silica gel plug with diethyl ether, and concentrated under reduced pressure to afford the crude reaction residue which was purified on silica gel.

***Coupling Procedure when ate complex was used after being stored**:* In an Ar-filled glove box, to a 2-dram vial equipped with a stir bar was added the dry ate complex (0.45 mmol, 1.5 equiv.), potassium trifluoromethanesulfonate (0.90 mmol, 3.0 equiv.) followed by THF (0.60 mL). $Pd(OAc)_2$ (0.006 mmol, 0.02 equiv.) and (S_p,S_p)-**L1** (0.0066 mmol, 0.021 equiv.) were added as a solution in THF (0.60 mL, then 0.30 mL to rinse) that had been pre-stirred for 10 minutes. The triflate (0.30 mmol, 1.0 equiv.) was added. The reaction vial was sealed with a polypropylene cap, removed from the glove box, heated to 60 °C, and allowed to stir for 16 hours. The resulting mixture was cooled to room temperature, filtered through a silica gel plug with diethyl ether, and concentrated under reduced pressure to afford the crude reaction residue which was purified on silica gel.

1.7.2.5 Oxidation procedures

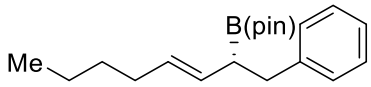
General Procedure for the Oxidation of Allylic Boronic Esters to Allylic Alcohols:

The boronic ester was diluted with THF (3.0 mL) and cooled to 0 °C. 30% H_2O_2 (1.0 mL) was added followed by 3M NaOH (2.0 mL). The reaction mixture was allowed to warm to room temperature and was allowed to stir for 3 hours open to air. The reaction mixture was then cooled to 0 °C and saturated aqueous $Na_2S_2O_3$ (4.0 mL) was added slowly to quench and the mixture was allowed to stir for 5 minutes at 0 °C. The mixture was allowed to warm to room temperature and the aqueous layer was extracted with diethyl ether (3 x 15.0 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified on silica gel to afford the desired allylic alcohol for chiral SFC separation.

Procedure for the Sodium Perborate Oxidation of Allylic Boronic Esters to Allylic Alcohols:

The boronic ester was diluted with THF (2.0 mL) and H_2O (2.0 mL). Sodium perborate monohydrate (300.0 mg, 10.0 equiv.) was added. The mixture was allowed to vigorously stir overnight for 14 hours open to air. The reaction mixture was transferred to a separatory funnel with ethyl acetate and brine. The aqueous layer was extracted with ethyl acetate (3 x 15.0 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified on silica gel to afford the desired allylic alcohol for chiral SFC separation.

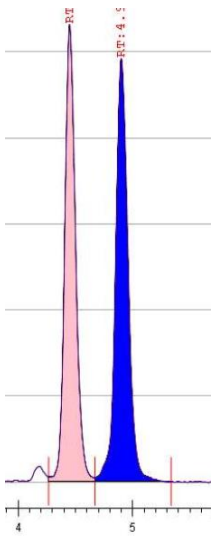
1.7.2.6 Characterization of Conjunctive Cross-Coupling Products and Analysis of Stereochemistry

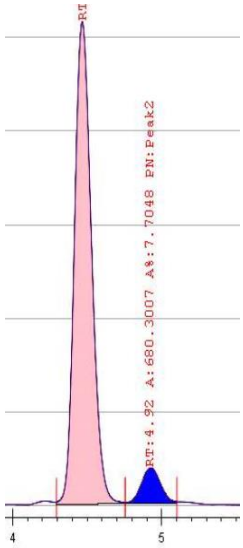


(R,E)-4,4,5,5-Tetramethyl-2-(1-phenyloct-3-en-2-yl)-1,3,2-dioxa borolane (1.89). The reaction was performed according to the general procedure ***(Method A)*** with (*E*)-2-(hex-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (63.0 mg, 0.30 mmol), phenyl trifluoromethanesulfonate (0.058 mL, 0.36 mmol), palladium (II) acetate (0.67 mg, 0.003 mmol, 1%), (S_p, S_p)-**L1** (3.79 mg, 0.0036 mmol, 1.2%), and was stirred at 60 °C for 3 hours. The crude residue was purified on silica gel with (20-50% CH_2Cl_2 in pentane) to afford a clear colorless oil. (75.1 mg, 80% yield, 92:8 er). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.25-7.18 (4H, m), 7.15-7.12 (1H, m), 5.44-5.35 (2H, m), 2.83 (1H, dd, *J* = 13.8, 9.0 Hz), 2.72 (1H, dd, *J* = 13.8, 7.8 Hz), 2.13 (1H, app q, *J* = 7.2 Hz), 1.96 (2H, app q, *J* = 6.0 Hz), 1.31-1.21 (4H, m), 1.16 (6H, s), 1.14 (6H, s), 0.86 (3H, t, *J* = 7.2 Hz). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 142.1, 130.7, 130.0, 129.1, 128.1, 125.7, 83.26, 37.4, 32.6, 31.9, 30.7 (C-B), 24.8, 24.7, 22.1, 14.1. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 32.6. **IR** (neat) ν_{max} 3026.8 (w), 2977.0 (w), 2957.0 (w), 2925.9 (w), 1465.7 (w), 1368.9 (s), 1322.2 (s), 1248.9 (w), 1142.0 (s), 967.3 (m), 862.5 (m), 698.2 (m) 671.7 (m) cm^{-1}. **HRMS** (DART+) for $C_{20}H_{32}BO_2$ $[M+H]^+$ calculated: 315.2495, found: 315.2504. **$[\alpha]^{20}_D$** -20.824 (c = 2.295, $CHCl_3$, *l* =50 mm).

Analysis of Stereochemistry: The boronic ester was oxidized according to the general procedure. The resulting allylic alcohol was compared to racemic alcohol prepared analogously with $Pd(OAc)_2$ (5 mol%) and 1,1′-bis(dicyclohexylphosphino)ferrocene (6 mol%) as the catalyst. Absolute stereochemistry determined as shown below.

Chiral SFC (Chiralcel OD-H, 35 °C, 3 mL/min, 6% isopropanol, 100 bar) – analysis of (R,E)-1-phenyloct-3-en-2-ol.

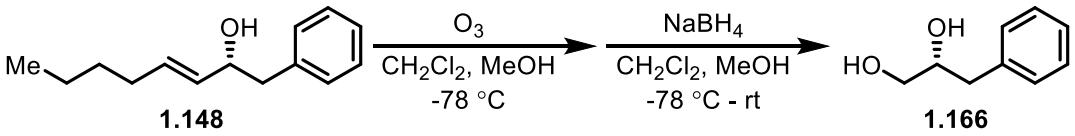




Peak No	% Area	Area	RT (min)
1	48.3975	3482.4261	4.45
2	51.6025	3713.034	4.9
Total:	100	7195.4601	

Peak No	% Area	Area	RT (min)
1	92.2952	8149.2151	4.47
2	7.7048	680.3007	4.92
Total:	100	8829.5158	

Absolute stereochemistry was determined by ozonolysis/reduction of the allylic alcohol to *(R)*-3-phenylpropane-1,2-diol (***1.166)*** and comparison of the optical rotation to the reported value.



To a 10-dram vial equipped with a magnetic was added *(R,E)*-1-phenyloct-3-en-2-ol ***(1.148)*** (100 mg). CH_2Cl_2 (4.0 mL), and methanol (4.0 mL). The solution was cooled to -78 °C. While open to the atmosphere, O_3 was bubbled through the solution for

approximately 1 min until the solution turned a pale blue color. Sodium borohydride (300 mg) was then added as a solid. The solution was left to stir for 5 min at -78 °C then was allowed to warm to room temperature and left to stir for 3 hours open to the atmosphere. H_2O was added (6 mL) and the solution was transferred to a separatory funnel with ethyl acetate. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 x 10.0 mL). Combined organic dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was then purified on silica gel with 50% ethyl acetate in hexanes to afford the product as a colorless solid. All spectral data was in accord with the literature.[86] The enantiomeric ratio was determined by chiral SFC analysis (92:8 er - *Chiralcel OJ-H, 35 °C, 3 mL/min, 4% isopropanol, 100 bar).*[87]

$[\alpha]^{20}_D$ +13.632 (c = 0.635, $CHCl_3$, *l* =50 mm).

Reported for *(R)*-3-phenylpropane-1,2-diol:

$[\alpha]^{20}_D$: +22.1 (95% *ee*, c = 1.0, $CHCl_3$).[23]

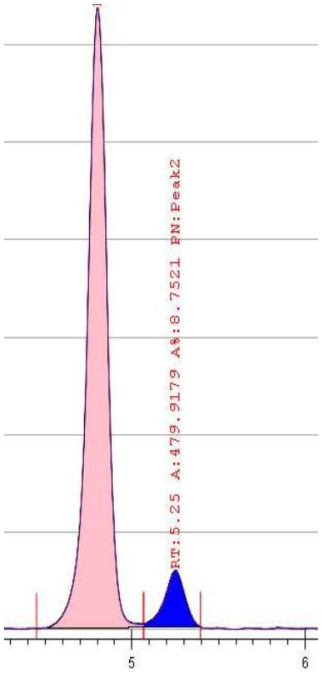
$[\alpha]^{20}_D$: +15.0 (99% *ee*, c = 1.0, $CHCl_3$).[88]

(86) Toribatake, K.; Nishiyama, H. *Angew. Chem. Int. Ed.* **2013**, *52*, 11011.
(87) Fang, L.; Yan, L.; Haeffner, F.; Morken, J. P. *J. Am. Chem. Soc.*, **2016**, *138*, 2508.
(88) Ramachary, D. B.; Barbas, C. F., III. *Org. Lett.*, **2005**, *7*, 1577.

1.7.2.7 Gram-Scale Glove Box Free Procedure

To a 50 mL round bottom flask equipped with a magnetic stir bar was added (*E*)-2-(hex-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.05 g, 5.0 mmol, 1.0 equiv.). The vial was sealed with a rubber septum and was purged with N_2. THF (10.0 mL) was added. The flask was cooled to 0 ℃ and vinyl lithium (3.14 mL, 1.59 M in THF, 5.0 mmol. 1 equiv.) was added dropwise cautiously. After the addition, the flask was allowed to warm to room temperature and left to stir for 15 minutes. During this time, to a 2 dram vial equipped with a magnetic stir bar was added palladium (II) acetate (11.2 mg, 0.05 mmol, 1%). and (S_p, S_p)-**L1** (63.2 mg, 0.06 mmol, 1.2%). The vial was purged with N_2, then THF was added (5.0 mL) and the solution was left to stir for 10 minutes. The Pd/Ligand solution was then added to the ate complex solution and rinsed with an additional 5.0 mL of THF. Phenyl trifluoromethanesulfonate (0.96 mL, 6.0 mmol, 1.2 equiv) was added. The reaction flask was taped to seal, and heated to 60 ℃ for 16 hours. The resulting mixture was cooled to room temperature, filtered through silica gel with Et_2O, and concentrated under reduced pressure to afford the crude reaction residue which was purified on silica gel with 20-60% CH_2Cl_2 in pentane to afford the desired product as a clear colorless oil (1.28 g, 81% yield, 91:9 er).

Analysis of Stereochemistry: The boronic ester was oxidized according to the general procedure. The racemic trace is shown above.*Chiral SFC (Chiralcel OD-H, 35 °C, 3 mL/min, 6% isopropanol, 100 bar) – analysis of (R,E)-1-phenyloct-3-en-2-ol.*



Peak No	% Area	Area	RT (min)
1	91.2479	5003.5457	4.8
2	8.7521	479.9179	5.25
Total:	100	5483.4636	

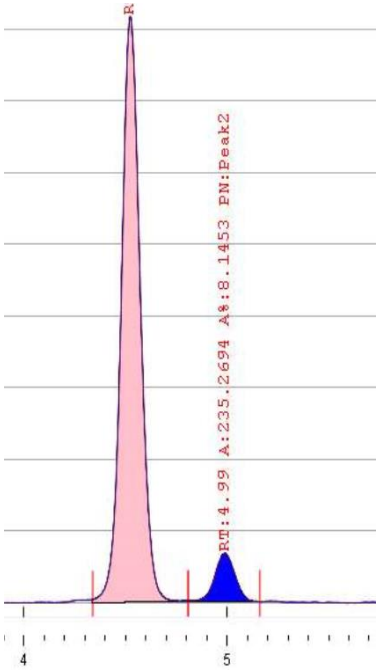
Scheme 2 (Eq 1) – Grignard Nucleophile

The reaction was performed according to the general procedure ***(Method D)*** with (*E*)-2-(hex-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (42.0 mg, 0.20 mmol), phenyl trifluoromethanesulfonate (0.041 mL, 0.24 mmol), sodium trifluoromethanesulfonate (68.8 mg, 0.40 mmol), palladium (II) acetate (0.90 mg, 0.004 mmol, 2%), (S_p, S_p)-**L1** (4.6 mg, 0.0044 mmol, 2.2%), and was stirred at 50 °C for 16 hours. The crude mixture was purified on silica gel (20-50% CH_2Cl_2 in pentane) to afford the title compound as a clear colorless oil (43.4 mg, 69% yield, 92:8 er).

Analysis of Stereochemistry:

The boronic ester was oxidized according to the general procedure. The racemic trace is shown above.

Chiral SFC (Chiralcel OD-H, 35 °C, 3 mL/min, 6% isopropanol, 100 bar) – analysis of (R,E)-1-phenyloct-3-en-2-ol.



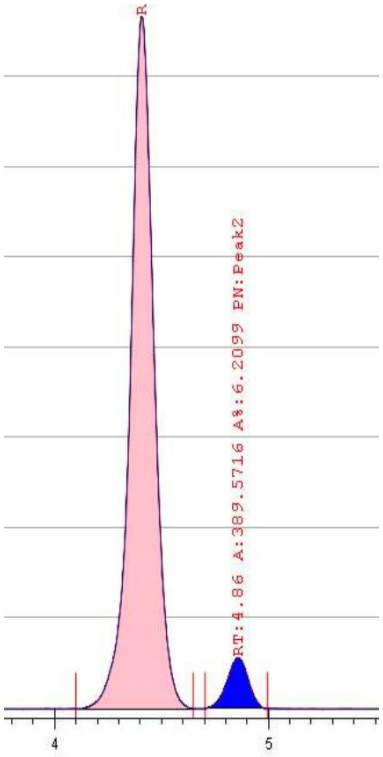
Peak No	% Area	Area	RT (min)
1	91.8547	2653.1353	4.52
2	8.1453	235.2694	4.99
Total:	100	2888.4047	

Scheme 2 (Eq 2) – Vinyl Lithium from Lithium Halogen Exchange

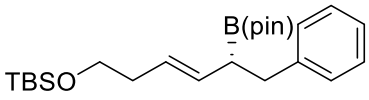
The reaction was performed according to the general procedure ***(Method E)*** with (*E*)-2-(hex-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (63.0 mg, 0.30 mmol), phenyl trifluoromethanesulfonate (0.058 mL, 0.36 mmol), potassium trifluoromethanesulfonate (112.9 mg, 0.60 mmol), palladium (II) acetate (1.35 mg, 0.006 mmol, 2%), (S_p, S_p)-**L1** (6.95 mg, 0.0066 mmol, 2.2%), and was stirred at 60 ℃ for 16 hours. The crude residue was purified on silica gel (20-50% CH_2Cl_2 in pentane) to afford the title compound as a clear colorless oil (66.2 mg, 70% yield, 93:7 er).

Analysis of Stereochemistry: The boronic ester was oxidized according to the general procedure. The racemic trace is shown above.

Chiral SFC (Chiralcel OD-H, 35 °C, 3 mL/min, 6% isopropanol, 100 bar) – analysis of (R,E)-1-phenyloct-3-en-2-ol.



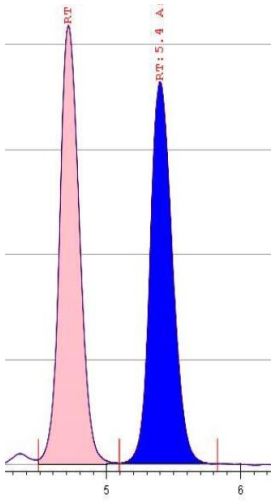
Peak No	% Area	Area	RT (min)
1	93.7901	5883.8062	4.41
2	6.2099	389.5716	4.86
Total:	100	6273.3778	

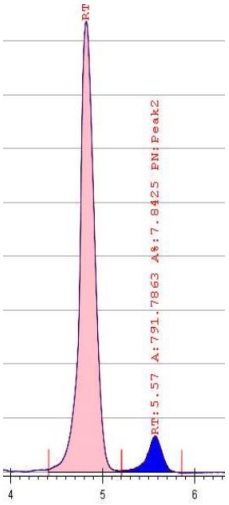


(R,E)-tert-Butyldimethyl((6-phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-3-en-1-yl)oxy)silane (1.104). The reaction was performed according to the general procedure ***(Method A)*** with *(E)*-tert-butyldimethyl((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-yl)oxy)silane (94.0 mg, 0.30 mmol), phenyl trifluoromethanesulfonate (0.058 mL, 0.36 mmol), palladium (II) acetate (0.67 mg, 0.003 mmol, 1%), (S_p, S_p)-**L1** (3.79 mg, 0.0036 mmol, 1.2%), and was stirred at 60 °C for 16 hours. The crude residue was purified on silica gel (30% CH_2Cl_2 in hexanes) to afford the title compound as a clear colorless oil. (92.4 mg, 74% yield, 92:8 er). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.24-7.21 (2H, m), 7.19 – 7.18 (2H, m), 7.15-7.13 (1H, m), 5.51 – 5.48 (1H, m), 5.38 (1H, dt, J = 15.0, 6.6 Hz), 3.54 (2H, t, J = 7.2 Hz), 2.83 (1H, dd, J = 13.8, 9.0 Hz), 2.73 (1H, dd, J = 13.2,

7.2 Hz), 2.20 (2H, app q, J = 7.2 Hz), 2.14 (1H, app q, J = 7.8 Hz,), 1.16 (6H, s), 1.14 (6H, s), 0.89 (9H, s), 0.04 (6H, s). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 141.9, 132.3, 129.1, 128.1, 126.6, 125.8, 83.3, 63.7, 37.3, 36.7, 30.9 (C-B), 26.1, 24.8, 24.7, 18.5, -5.1. **^{11}B NMR** (160 MHz, $CDCl_3$) 32.7. **IR** (neat) ν_{max} 3026.5 (w), 2977.2 (m), 2856.6 (w), 1496.0 (w), 1369.5 (s), 1323.7 (s), 1251.4 (m), 1251.4 (w), 1142.2 (s), 1095.2 (s), 937.5 (m), 832.7 (s), 774.0 (s), 746.7 (s), 670.0 (s) cm^{-1}. **HRMS** (DART+) for $C_{24}H_{41}BO_3Si$ $[M+H]^+$ calculated: 417.2996, found: 417.3012. **$[\alpha]^{20}_D$** -15.934 (c=1.660, $CHCl_3$, l =50 mm). ***Analysis of Stereochemistry:***The boronic ester was oxidized according to the general procedure. The resulting allylic alcohol was compared to racemic alcohol prepared analogously with $Pd(OAc)_2$ (5 mol%) and 1,1′-bis(diphenylphosphino)ferrocene (6 mol%) as the catalyst..

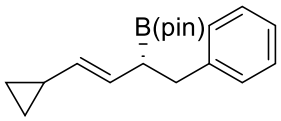
Chiral SFC (Chiralcel OJ-H, 35 °C, 3 mL/min, 2% isopropanol, 100 bar) – analysis of (R,E)-6-((tert-butyldimethylsilyl)oxy)-1-phenylhex-3-en-2-ol.





Peak No	% Area	Area	RT (min)
1	48.3975	3482.4261	4.45
2	51.6025	3713.034	4.9
Total:	100	7195.4601	

Peak No	% Area	Area	RT (min)
1	92.1575	9304.3558	4.82
2	7.8425	791.7863	5.57
Total:	100	10096.1421	

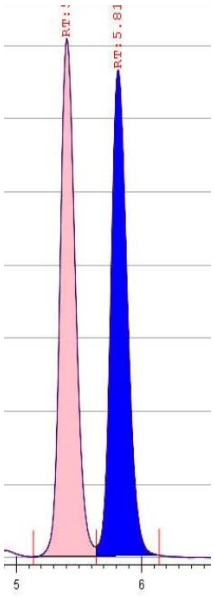


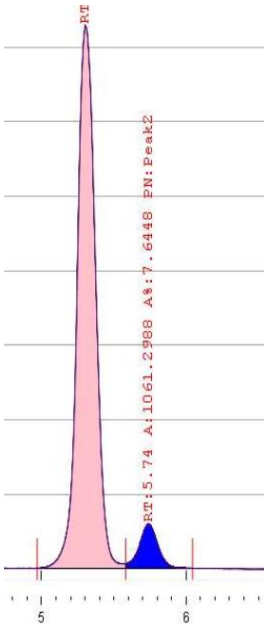
(R,E)-2-(4-Cyclopropyl-1-phenylbut-3-en-2-yl)-4,4,5,5-tetramethyl-1,3, 2-dioxaborolane (1.105). The reaction was performed according to the general procedure ***(Method A)*** with *(trans)*-2-cyclopropylvinyl boronic acid pinacol ester (54.0 mg, 0.30 mmol), phenyl trifluoromethanesulfonate (0.058 mL, 0.36 mmol), palladium (II) acetate (0.67 mg, 0.003 mmol, 1%), (S_p, S_p)-**L1** (3.79 mg, 0.0036 mmol, 1.2%), and was stirred at 60 °C for 16 hours. The crude residue was purified on silica gel (30% CH_2Cl_2 in hexanes) to afford the title compound as a clear colorless oil. (58.2 mg, 58% yield, 92:8 er). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.25-7.17 (4H, m), 7.16-7.11 (1H, m), 5.51 (1H, dd, *J* = 15.0, 8.4 Hz), 4.98 (1H, ddd, *J* = 15.0, 8.4, 1.2 Hz), 2.82 (1H, dd, *J* = 13.8, 9.6 Hz), 2.73 (1H, dd, *J* = 13.8, 7.2 Hz), 2.12 (1H, app q, *J* = 8.4 Hz), 1.37-1.29 (1H, m), 1.15 (6H, s), 1.14 (6H, s), 0.64-0.59 (2H, m), 0.29-0.25 (2H, m). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 142.0, 134.0, 129.1, 128.1, 127.7, 125.7, 83.3, 37.5, 30.5 (C-B), 24.8, 24.71, 13.9, 6.6, 6.5. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 32.7. **IR** (neat) ν_{max} 2977.2 (w), 2928.7 (w), 2857.0 (w), 1370.1 (s), 1322.2 (s), 1245.8 (w), 1213.5 (w), 1107.0 (s), 963.6 (m), 863.0 (m), 747.3 (w), 698.6 (m) cm^{-1}. **HRMS** (DART+) for $C_{19}H_{27}BO_2$ $[M+H]^+$ calculated: 299.2182, found: 299.2174. **$[\alpha]^{20}_D$** -24.103 (c = 2.605, $CHCl_3$, *l* =50 mm).

Analysis of Stereochemistry:

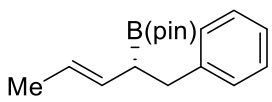
The boronic ester was oxidized according to the general procedure. The resulting allylic alcohol was compared to racemic alcohol prepared analogously with $Pd(OAc)_2$ (5 mol%) and 1,1′-bis(dicyclohexylphosphino)ferrocene (6 mol%) as the catalyst.

Chiral SFC (Chiralcel OD-H, 35 °C, 3 mL/min, 6% isopropanol, 100 bar) – analysis of (R,E)-4-cyclopropyl-1-phenylbut-3-en-2-ol.





Peak No	% Area	Area	RT (min)	Peak No	% Area	Area	RT (min)
1	49.8707	6023.307	5.4	1	92.3552	12821.2647	5.3
2	50.1293	6054.5441	5.81	2	7.6448	1061.2988	5.74
Total:	100	12077.8511		Total:	100	13882.5635	



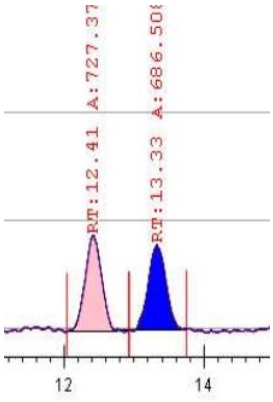
(R,E)-4,4,5,5-Tetramethyl-2-(1-phenylpent-3-en-2-yl)-1,3,2-dioxaborol ane (1.106). The reaction was performed according to the general procedure ***(Method A)*** with , *trans*-1-propenylboronic acid pinacol ester (50.4

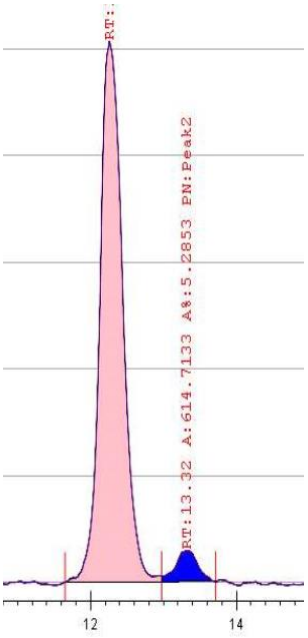
mg, 0.30 mmol), phenyl trifluoromethanesulfonate (0.058 mL, 0.36 mmol), palladium (II) acetate (1.35 mg, 0.006 mmol, 2%), (S_p, S_p)-**L1** (6.95 mg, 0.0066 mmol, 2.2%), and was stirred at 60 ℃ for 16 hours. The crude residue was purified on silica gel (20-40% CH_2Cl_2 in pentane) to afford the title compound as a clear colorless oil. (62.0 mg, 76% yield, 95:5 er). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.25-7.18 (4H, m), 7.16-7.12 (1H, m), 5.48-5.38 (2H, m), 2.83 (1H, dd, *J* = 13.2, 8.4 Hz), 2.73 (1H, dd, *J* = 13.2, 7.2 Hz), 2.14 (1H, app q, *J* = 7.20 Hz), 1.64 (3H, d, *J* = 6.0 Hz), 1.16 (6H, s), 1.14 (6H, s). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 142.0, 131.2, 129.0, 128.1, 125.7, 125.0, 83.3, 37.4, 30.7 (C-B), 24.8, 24.7, 18.3. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 32.69. **IR** (neat) ν_{max} 3025.6 (w), 2977.4 (w), 2855.3 (w), 1361.1 (s), 1321.4 (s), 1141.2 (s), 965.6 (s), 852.7 (m), 746.0 (m), 697.9 (s) cm^{-1}. **HRMS** (DART+) for $C_{17}H_{26}BO_2$ $[M+H]^+$ calculated: 273.2026, found: 273.2038. **$[\alpha]^{20}_D$** -20.604 (c = 1.830, $CHCl_3$, *l* =50 mm).

Analysis of Stereochemistry:

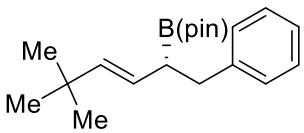
The boronic ester was oxidized according to the general procedure. The resulting allylic alcohol was compared to racemic alcohol prepared analogously with $Pd(OAc)_2$ (5 mol%) and 1,1′-bis(dicyclohexylphosphino)ferrocene (6 mol%) as the catalyst.

Chiral SFC (Chiralcel OD-H, 35 °C, 3 mL/min, 1% isopropanol, 100 bar) – analysis of (R,E)-1-phenylpent-3-en-2-ol





Peak No	% Area	Area	RT (min)	Peak No	% Area	Area	RT (min)
1	51.4452	727.3758	12.41	1	94.7147	11015.9784	12.26
2	48.5548	686.5082	13.33	2	5.2853	614.7133	13.32
Total:	100	1413.884		Total:	100	11630.6917	



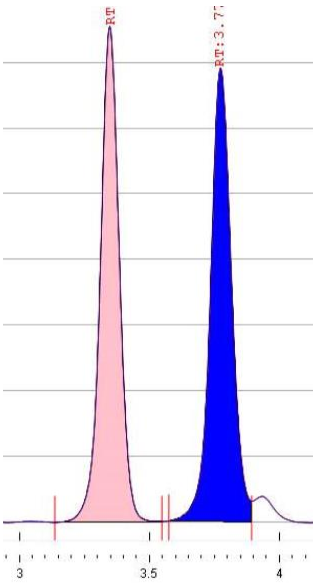
(R,E)-2-(5,5-Dimethyl-1-phenylhex-3-en-2-yl)-4,4,5,5-tetramethyl-1, 3,2-dioxaborolane (1.107). The reaction was performed according to the general procedure ***(Method A)*** with *(E)*-2-(3,3-dimethylbut-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaboro lane (63.0 mg, 0.30 mmol), phenyl

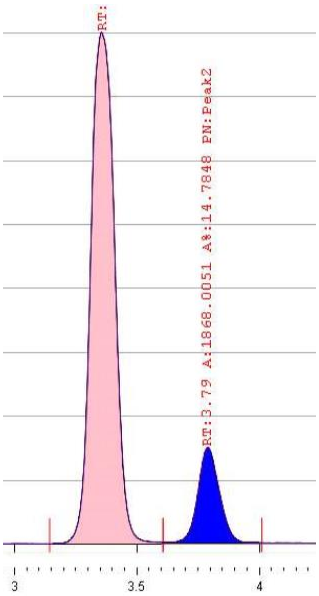
trifluoromethanesulfonate (0.058 mL, 0.36 mmol, 1%), palladium (II) acetate (0.67 mg, 0.003 mmol), (S_p, S_p)-**L1** (3.79 mg, 0.0036 mmol, 1.2%), and was stirred at 60 °C for 16 hours. The crude residue was purified on silica gel (30% CH_2Cl_2 in hexanes) to afford the title compound as a clear colorless oil. (76.4 mg, 81% yield, 85:15 er). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.25-7.18 (4H, m), 7.16-7.12 (1H, m), 5.45 (1H, d, *J* = 15.6 Hz), 5.35 (1H, dd, *J* = 15.6, 8.4 Hz), 2.84 (1H, dd, *J* = 13.8, 9.6 Hz), 2.73 (1H, dd, *J* = 13.2, 7.2 Hz), 2.11 (1H, app q, *J* = 8.4 Hz), 1.16 (6H, s), 1.15 (6H, s), 0.97 (9H, s). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 142.2, 141.8, 129.1, 128.1, 125.7, 124.7, 83.2, 37.4, 33.1, 30.6 (C-B), 30.0, 24.7, 24.6. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 32.6. **IR** (neat) ν_{max} 2975.9 (w), 2957.3 (w), 2864.1 (w), 1359.7 (s), 1321.5 (s), 1164.9 (s), 969.6 (m), 853.8 (m), 745.9 (m), 698.2 (s) cm^{-1}. **HRMS** (DART+) for $C_{20}H_{32}BO_2$ $[M+H]^+$ calculated: 315.2495, found: 315.2499. **$[\alpha]^{20}_D$** -20.647 (c = 2.720, $CHCl_3$, *l* =50 mm).

Analysis of Stereochemistry:

The boronic ester was oxidized according to the general procedure. The resulting allylic alcohol was compared to racemic alcohol prepared analogously with $Pd(OAc)_2$ (5 mol%) and 1,1′-bis(dicyclohexylphosphino)ferrocene (6 mol%) as the catalyst.

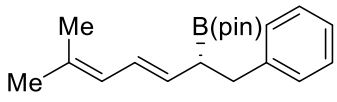
Chiral SFC (Chiralcel AD-H, 35 °C, 3 mL/min, 10% isopropanol, 100 bar) – analysis of (R,E)-5,5-dimethyl-1-phenylhex-3-en-2-ol.





Peak No	% Area	Area	RT (min)
1	49.7319	3826.6287	3.35
2	50.2681	3867.8818	3.77
Total:	100	7694.5105	

Peak No	% Area	Area	RT (min)
1	85.2152	10766.6026	3.36
2	14.7848	1868.0051	3.79
Total:	100	12634.6077	



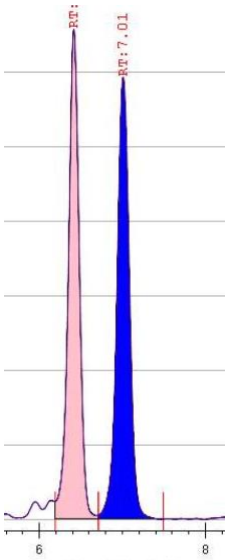
(R,E)-4,4,5,5-Tetramethyl-2-(6-methyl-1-phenylhepta-3,5-dien-2-yl) -1,3,2-dioxaborolane (1.109). The reaction was performed according to the general procedure ***(Method A)*** with *(E)*-4,4,5,5-tetramethyl-2-(4-methylpenta-1,3-dien-1-yl)-1,3,2-dioxa borolane (62.4 mg, 0.30 mmol), phenyl trifluoromethanesulfonate (0.058 mL, 0.36 mmol), palladium (II) acetate (0.67 mg, 0.003 mmol, 1%), (S_p, S_p)-**L1** (3.79 mg, 0.0036 mmol, 1.2%), and was stirred at 60 °C for 16 hours. The crude residue was purified on silica gel (30% CH_2Cl_2 in hexanes) to afford the title compound as a clear colorless oil (67.5 mg, 72% yield, 91:9 er). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.26-7.19 (4H, m), 7.17-711 (1H, m), 6.08 (1H, d, J = 15.6 Hz), 5.58 (1H, dd, J = 15.6, 8.4 Hz), 5.42 (1H, app q, J = 7.2 Hz), 2.88 (1H, dd, J = 13.8, 9.6 Hz), 2.79 (1H, dd, J = 13.2, 6.6 Hz), 2.24 (1H, app q, J = 8.4 Hz), 1.72-1.68 (6H, m), 1.15 (6H, s), 1.13 (6H,

s). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 142.0, 134.8, 134.7, 129.0, 128.2, 127.1, 125.8, 124.4, 83.3, 37.5, 31.1 (C-B), 24.74, 24.72, 13.8, 12.3. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 32.7. **IR** (neat) ν_{max} 2977.8 (w), 2926.9 (w), 2858.6 (w), 1453.4 (w), 1369.9 (m), 1323.4 (m), 1142.0 (s), 964.5 (m), 838.7 (w), 747.4 (w), 698.7 (m) cm^{-1}. **HRMS** (DART+) for $C_{20}H_{30}BO_2$ $[M+H]^+$ calculated: 313.2339, found: 313.2356. **$[\alpha]^{20}_D$** -29.155 (c = 3.290, $CHCl_3$, *l* =50 mm).

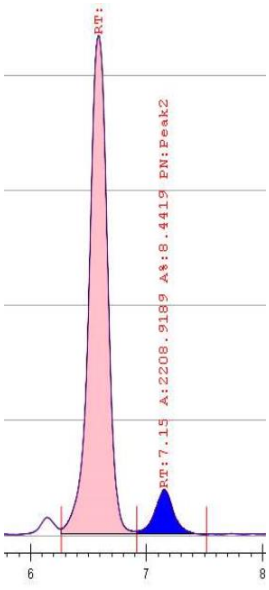
Analysis of Stereochemistry:

The boronic ester was oxidized according to the general procedure. The resulting allylic alcohol was compared to racemic alcohol prepared analogously with $Pd(OAc)_2$ (5 mol%) and 1,1′-bis(dicyclohexylphosphino)ferrocene (6 mol%) as the catalyst.

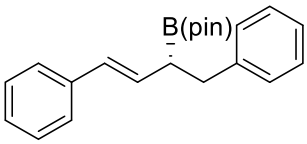
Chiral SFC (Chiralcel OD-H, 35 °C, 3 mL/min, 4% isopropanol, 100 bar) – analysis of (R,E)-6-methyl-1-phenylhepta-3,5-dien-2-ol



Peak No	% Area	Area	RT (min)
1	49.4096	6039.3736	6.42
2	50.5904	6183.7019	7.01
Total:	100	12223.0755	



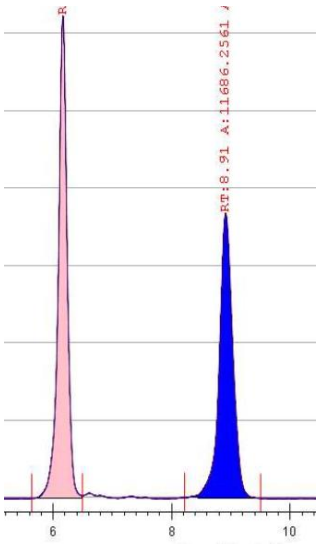
Peak No	% Area	Area	RT (min)
1	91.5581	23957.2234	6.59
2	8.4419	2208.9189	7.15
Total:	100	26166.1423	

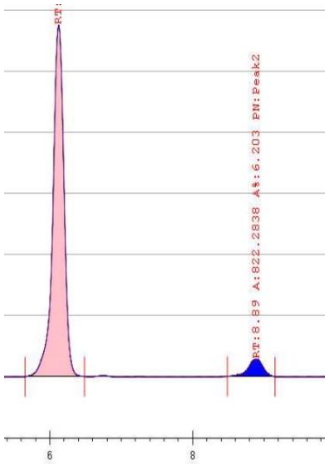


(R,E)-2-(1,4-Diphenylbut-3-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxa borolane (1.108). The reaction was performed according to the general procedure ***(Method A)*** with *(E)*-4,4,5,5-tetramethyl-2-styryl-1,3,2-dioxaborolane (69.0 mg, 0.30 mmol), phenyl trifluoromethanesulfonate (0.058 mL, 0.36 mmol), palladium (II) acetate (1.35 mg, 0.006 mmol, 2%), (S_p, S_p)-**L1** (6.95 mg, 0.0066 mmol, 2.2%), and was stirred at 60 °C for 16 hours. The crude residue was purified on silica gel (30-50% CH_2Cl_2 in pentane) to afford the title compound as a white solid (83.0 mg, 83% yield, 94:6 er).**^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.36-7.32 (2H, m), 7.31-7.26 (6H, m), 7.21-7.15 (2H, m), 6.40 (1H, d, J = 15.6 Hz), 6.29 (1H, dd, J = 16.2, 9.0 Hz), 2.99 (1H, dd, J = 13.8, 9.0 Hz), 2.89 (1H, dd, J = 13.8, 7.2 Hz), 2.40 (1H, app q, J = 8.4 Hz), 1.19 (6H, s), 1.17 (6H, s). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 141.6, 138.2, 131.1, 129.7, 129.0, 128.5, 128.2, 126.8, 126.1, 125.9, 83.5, 37.1, 31.5 (C-B), 24.8, 24.7. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 32.7. **IR** (neat) ν_{max} 3060.5 (w), 3025.6 (w), 2977.0 (w), 2929.0 (w), 1360.5 (s), 1324.0 (s), 1165.7 (s), 965.2 (s), 851.9 (m), 744.0 (m), 694.6 (s) cm^{-1}. **HRMS** (DART+) for $C_{22}H_{31}BNO_2$ $[M+NH_4]^+$ calculated: 352.2448, found: 352.2445. **$[\alpha]^{20}_D$** -46.339 (c = 2.485, $CHCl_3$, l =50 mm).

Analysis of Stereochemistry: The boronic ester was oxidized according to the general procedure. The resulting allylic alcohol was compared to racemic alcohol prepared analogously with $Pd(OAc)_2$ (5 mol%) and 1,1′-bis(dicyclohexylphosphino)ferrocene (6 mol%) as the catalyst.

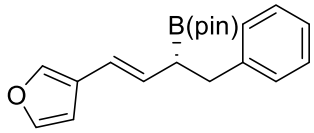
Chiral SFC (Chiralcel OD-H, 35 °C, 3 mL/min, 15% isopropanol, 100 bar) – analysis of (R,E)-1,4-diphenylbut-3-en-2-ol.





Peak No	% Area	Area	RT (min)
1	52.7666	13055.2669	6.16
2	47.2334	11686.2561	8.91
Total:	100	24741.523	

Peak No	% Area	Area	RT (min)
1	93.797	12433.9991	6.12
2	6.203	822.2838	8.89
Total:	100	13256.2829	

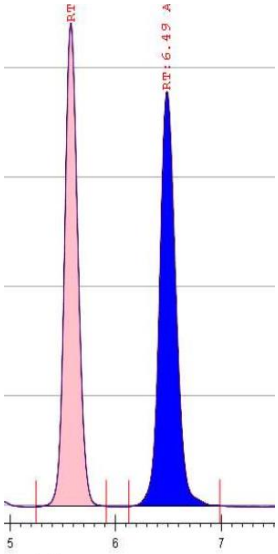


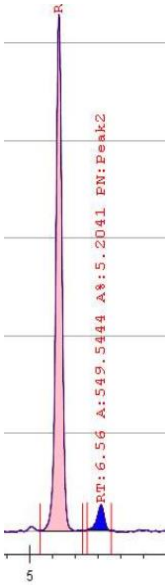
(R,E)-2-(4-(Furan-3-yl)-1-phenylbut-3-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.110). The reaction was performed according to the general procedure ***(Method A)*** with *(E)*-2-(2-(furan-3-yl)vinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (66.0 mg, 0.30 mmol), phenyl trifluoromethanesulfonate (0.058 mL, 0.36 mmol), palladium (II) acetate (0.67 mg, 0.003 mmol, 1%), (S_p, S_p)-**L1** (3.79 mg, 0.0036 mmol, 1.2%), and was stirred at 60 °C for 3 hours. The crude residue was purified on silica gel (30-50% CH_2Cl_2 in hexanes) to afford the title compound as a clear colorless oil (59.9 mg, 62% yield, 95:5 er).**^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.33-7.31 (2H, m), 7.25-7.21 (4H, m), 7.17-7.14 (1H, m), 6.50 (1H, s), 6.23 (1H,

d, *J* = 15.6 Hz), 5.98 (1H, dd, *J* = 16.2, 9.0 Hz), 2.93 (1H, dd, *J* = 13.8, 9.0 Hz), 2.84 (1H, dd, *J* = 13.8, 7.2 Hz), 2.32 (1H, app q, *J* = 8.4 Hz), 1.17 (6H, s), 1.15 (6H, s). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 143.3, 141.7, 139.4, 130.6, 129.0, 128.2, 125.9, 124.8, 119.3, 107.8, 83.5, 37.2, 31.3 (C-B), 24.8, 24.7. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 32.8. **IR** (neat) ν_{max} 3026.1 (w), 2977.7 (w), 2857.3 (w), 1361.1 (s), 1324.8 (s), 1140.8 (s), 1024.7 (m), 964.7 (m), 870.6 (m), 776.0 (m), 699.3 (m) cm^{-1}. **HRMS** (DART+) for $C_{20}H_{26}BO_3$ $[M+H]^+$ calculated: 325.1975, found: 325.1992. **$[\alpha]^{20}_D$** -32.738 (c = 1.000, $CHCl_3$, *l* =50 mm).

Analysis of Stereochemistry: The boronic ester was oxidized according to the general procedure. The resulting allylic alcohol was compared to racemic alcohol prepared analogously with $Pd(OAc)_2$ (5 mol%) and 1,1′-bis(dicyclohexylphosphino)ferrocene (6 mol%) as the catalyst.

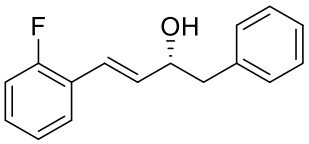
Chiral SFC (Chiralcel OD-H, 35 °C, 3 mL/min, 10% isopropanol, 100 bar) – analysis of (R,E)-4-(furan-3-yl)-1-phenylbut-3-en-2-ol.





Peak No	% Area	Area	RT (min)
1	48.9643	7714.1851	5.58
2	51.0357	8040.5251	6.49
Total:	100	15754.7102	

Peak No	% Area	Area	RT (min)
1	94.7959	10010.1928	5.64
2	5.2041	549.5444	6.56
Total:	100	10559.7372	

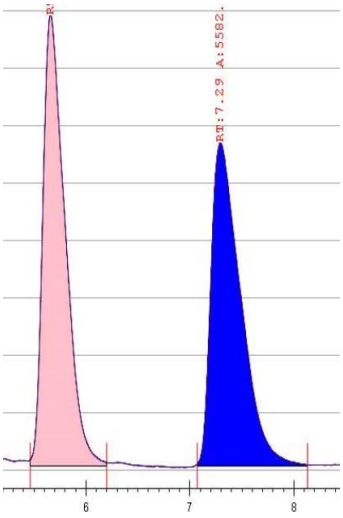


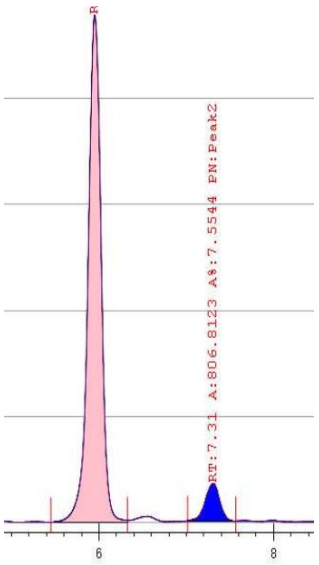
(R,E)-4-(2-Fluorophenyl)-1-phenylbut-3-en-2-ol (1.111-OH). The reaction was performed according to the general procedure ***(Method A)*** with *(E)*-2-(2-fluorostyryl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (74.4.0 mg, 0.30 mmol), phenyl trifluoromethanesulfonate (0.058 mL, 0.36 mmol), palladium (II) acetate (0.67 mg, 0.003 mmol, 1%), (S_p, S_p)-**L1** (3.79 mg, 0.0036 mmol, 1.2%), and was stirred at 60 ℃ for 16 hours. The crude residue was directly oxidized according to the general procedure. The crude residue was purified on silica gel (10% ethyl acetate in hexanes) to afford the title compound as a clear colorless oil (49.4 mg, 68% yield, 92:8 er). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.45-7.42 (1H, m), 7.35- 7.32 (2H, m), 7.28- 7.25 (3H, m), 7.23-7.20 (1H, m), 7.11- 7.08 (1H, m), 7.05- 7.02 (1H, m), 6.76 (1H, dd, *J* = 16.2 Hz), 6.38 (1H, dd, *J* = 16.2, 6 Hz), 4.57-4.53 (1H, m), 2.99 (1H, dd, *J* = 13.8, 4.8 Hz), 2.89 (1H, dd, *J* = 13.2, 7.8 Hz), 1.73 (1H, br s). **^{13}C NMR** (150 MHz, CDCl3) δ 160.5 (d, *J* = 247.5 MHz), 137.7, 134.3 (d, *J* = 24.0 Hz), 129.7, 129.1 (d, *J* = 3.0 Hz), 128.7, 127.7 (d, *J* = 4.5 Hz), 126.8, 124.6 (d, *J* = 12 Hz), 124.2 (d, *J* = 3.0 Hz), 123.0 (d, *J* = 4.5 Hz), 115.9 (d, *J* = 22.5 Hz), 73.7, 44.3. **^{19}F NMR** (564 MHz, CDCl3) δ -117.88 – -117.92 (m). **IR** (neat) ν_{max} 3376.8 (br), 3082.5 (w), 3062.2 (w), 2921.7 (w), 2852.4 (w), 1603.4 (w), 1578.8 (w), 1486.9 (m), 1454.1 (m), 1228.3 (m), 1087.2 (w), 1030.3 (w), 968.2 (w), 748.3 (m), 699.4 (m) cm^{-1}. **HRMS** (DART+) for $C_{16}H_{14}F$ $[M+H-H_2O]^+$ calculated:225.1080, found: 225.1078. **$[\alpha]^{20}_D$** -15.934 (c=1.660, $CHCl_3$, *l* =50 mm).

Analysis of Stereochemistry:

The alcohol was compared to racemic alcohol prepared analogously with $Pd(OAc)_2$ (5 mol%) and 1,1′-bis(dicyclohexylphosphino)ferrocene (6 mol%) as the catalyst.

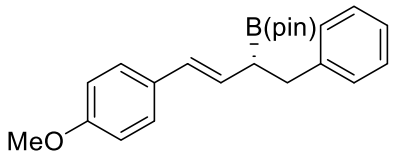
Chiral SFC (Chiralcel OD-H, 35 °C, 3 mL/min, 12% isopropanol, 100 bar) – analysis of (R,E)-4-(2-fluorophenyl)-1-phenylbut-3-en-2-ol.





Peak No	% Area	Area	RT (min)
1	51.0343	5818.8373	5.66
2	48.9657	5582.9876	7.29
Total:	100	11401.8249	

Peak No	% Area	Area	RT (min)
1	92.4456	9873.2163	5.95
2	7.5544	806.8123	7.31
Total:	100	10680.0286	

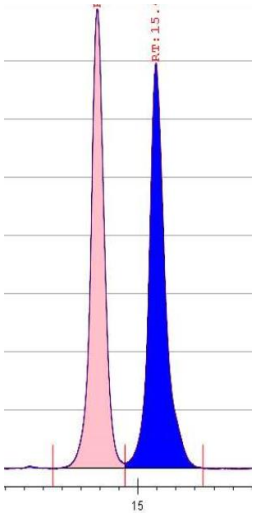


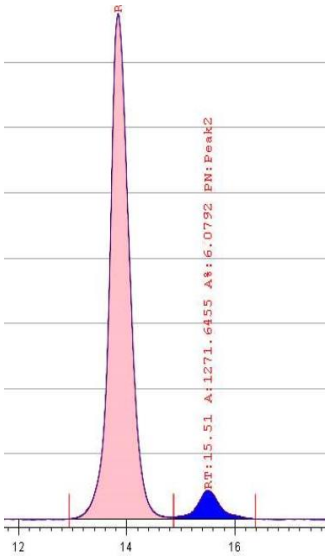
(R,E)-2-(4-(4-Methoxyphenyl)-1-phenylbut-3-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.112). The reaction was performed according to the general procedure ***(Method A)*** with *(E)*-2-(4-methoxystyryl)-4,4,5,5-tetramethyl-1,3,2-dioxaborola- ne (78.0 mg, 0.30 mmol), phenyl trifluoromethanesulfonate (0.058 mL, 0.36 mmol), palladium (II) acetate (0.67 mg, 0.003 mmol, 1%), (S_p, S_p)-**L1** (3.79 mg, 0.0036 mmol, 1.2%), and was stirred at 60 ℃ for 16 hours. The crude residue was purified on silica gel (30% CH_2Cl_2 in hexanes) to afford the title compound as a white solid (73.0 mg, 67% yield, 94:6 er). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.28-7.26 (6H, m), 7.19-7.16 (1H, m), 6.85-6.84 (2H, m), 6.35 (1H, d, J = 16.2 Hz), 6.14 (1H, dd, J = 15.6,8.4 Hz), 3.81 (3H, s), 2.97 (1H, dd, J = 13.8, 9 Hz), 2.88 (1H, dd, J = 13.8, 7.8 Hz), 2.39-2.35 (1H, app q, J = 8.4 Hz), 1.19 (6H, s), 1.17 (6H, s). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 158.7, 141.7, 131.1, 129.1, 129.0, 128.9, 128.2, 127.1, 125.9, 114.0, 83.5, 55.4, 37.3, 31.4 (C-B), 24.8, 24.7. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 30.2. **IR** (neat) ν_{max} 3060.9 (w), 3027.2 (w), 2932.4 (w)., 2835.3 (w), 1606.5 (m), 1495.9 (s), 1454.4 (w), 1361.1 (m), 1324.9 (m), 1245.6 (s), 1173.6 (m), 1140.3 (s), 1107.9 (w), 1034.1 (w), 965.5 (m), 852.6 (m), 814.4 (m) cm^{-1}. **HRMS** (DART+) for $C_{23}H_{39}BO_3$ $[M+H]^{+\cdot}$ calculated: 364.2210, found: 364.2192. **$[\alpha]^{20}_D$** -46.000 (c =2.805 , $CHCl_3$, l =50 mm).

Analysis of Stereochemistry:

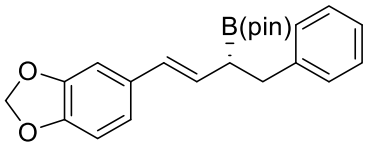
The boronic ester was oxidized according to the general procedure. The resulting allylic alcohol was compared to racemic alcohol prepared analogously with $Pd(OAc)_2$ (5 mol%) and 1,1′-bis(dicyclohexylphosphino)ferrocene (6 mol%) as the catalyst.

Chiral SFC (Chiralcel OD-H, 35 °C, 3 mL/min, 10% isopropanol, 100 bar) – analysis of (R,E)-4-(4-methoxyphenyl)-1-phenylbut-3-en-2-ol





Peak No	% Area	Area	RT (min)	Peak No	% Area	Area	RT (min)
1	48.6665	9698.8857	13.92	1	93.9208	19646.1689	13.84
2	51.3335	10230.4189	15.47	2	6.0792	1271.6455	15.51
Total:	100	19929.3046		Total:	100	20917.8144	

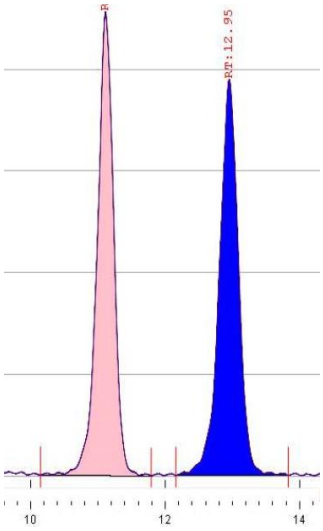


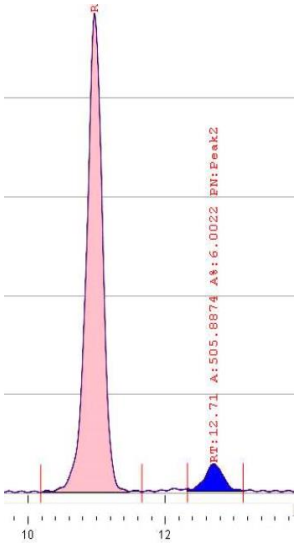
(R,E)-2-(4-(Benzo[d][1,3]dioxol-5-yl)-1-phenylbut-3-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.113). The reaction was performed according to the general procedure ***(Method A)*** with *(E)*-2-(2-(benzo[d][1,3]dioxol-5-yl)vinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (82.2 mg, 0.30 mmol), phenyl trifluoromethanesulfonate (0.058 mL, 0.36 mmol), palladium (II) acetate (1.35 mg, 0.006 mmol, 2%), (S_p, S_p)-**L1** (6.95 mg, 0.0066 mmol, 2.2%), and was stirred at 60 °C for 16 hours. The crude residue was purified on silica gel (30-70% CH_2Cl_2 in pentane) to afford the title compound as a white solid (94.0 mg, 83% yield, 94:6 er). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.27-7.23 (4H, m), 7.18-7.15 (1H,

m), 6.89 (1H, s), 6.74 (2H, m), 6.30 (1H, d, J = 15.6 Hz), 6.10 (1H, dd, J = 16.2, 9.0 Hz), 5.92 (2H, s), 2.96 (1H, dd, J = 13.8, 9.0 Hz), 2.86 (1H, dd, J = 13.8, 7.8 Hz), 2.35 (1H, app q, J = 8.4 Hz), 1.18 (6H, s), 1.16 (6H, s). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 148.0, 146.6, 141.7, 132.8, 129.4, 129.3, 129.0, 128.2, 125.9, 120.4, 108.3, 105.6, 101.0, 83.5, 37.2, 31.4 (C-B), 24.79, 24.75. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 32.6. **IR** (neat) ν_{max} 3026.3 (w), 2977.0 (w), 2927.3 (w), 2895.5 (w), 1489.0 (s), 1444.5 (m), 1355.2 (m), 1325.8 (m), 1248.3 (s), 1141.3 (s), 1039.2 (s), 966.3 (m), 931.5 (m) cm^{-1}. **HRMS** (DART+) for $C_{23}H_{28}BO_4$ $[M+H]^+$ calculated: 379.2081, found: 379.2077. **$[\alpha]^{20}_D$** -53.653 (c = 1.115, $CHCl_3$, l =50 mm).

Analysis of Stereochemistry: The boronic ester was oxidized according to the general procedure. The resulting allylic alcohol was compared to racemic alcohol prepared analogously with $Pd(OAc)_2$ (5 mol%) and 1,1′-bis(dicyclohexylphosphino)ferrocene (6 mol%) as the catalyst.

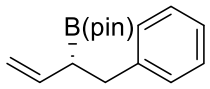
Chiral SFC (Chiralcel OD-H, 35 °C, 3 mL/min, 10% isopropanol, 100 bar) – analysis of (R,E)-4-(benzo[d][1,3]dioxol-5-yl)-1-phenylbut-3-en-2-ol





Peak No	% Area	Area	RT (min)
1	50.2042	3909.7758	11.11
2	49.7958	3877.9689	12.95
Total:	100	7787.7447	

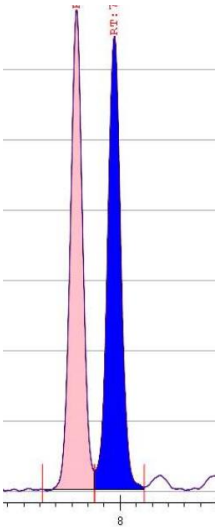
Peak No	% Area	Area	RT (min)
1	93.9978	7922.469	10.97
2	6.0022	505.8874	12.71
Total:	100	8428.3564	

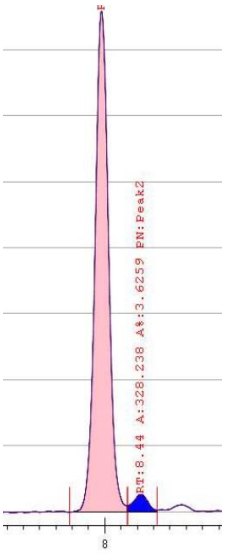


(R)-4,4,5,5-tetramethyl-2-(1-Phenylbut-3-en-2-yl)-1,3,2-dioxaborolane (1.114). The reaction was performed according to the general procedure ***(Method A)*** vinyl boronic acid pinacol ester (46.2 mg, 0.30 mmol), phenyl trifluoromethanesulfonate (0.058 mL, 0.36 mmol), palladium (II) acetate (2.0 mg, 0.009 mmol, 3%), (S_p, S_p)-**L1** (10.1 mg, 0.0096 mmol, 3.2%), and was stirred at 60 °C for 5 hours. The crude residue was purified on silica gel (30-50% CH_2Cl_2 in pentane) to afford the title compound as a clear colorless oil (51.3 mg, 66% yield, 96:4 er). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.26-7.19 (4H, m), 7.17-7.13 (1H, m), 5.85 (1H, ddd, *J* = 17.4, 9.6, 7.8 Hz), 5.00 (1H, dd, *J* = 17.2, 1.7 Hz), 4.95 (1H, dd, *J* = 10.2, 1.7 Hz), 2.89 (1H, dd, *J* = 13.2, 8.4 Hz), 2.78 (1H, dd, *J* = 13.2, 7.2 Hz), 2.23 (1H, app q, *J* = 7.8 Hz), 1.17 (6H, s), 1.16 (6H, s). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 141.7, 138.9, 129.0, 128.2, 125.8, 114.3, 83.4, 36.6, 32.2 (C-B), 24.8, 24.7. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 32.6. **IR** (neat) ν_{max} 3028.0 (w), 2977.6 (w), 2929.1 (w), 1631.5 (w), 1360.3 (s), 1323.9 (s), 1256.9 (m), 1213.0 (m), 1141.5 (s), 972.7 (m), 903.5 (m), 861.2 (m), 698.1 (s) cm^{-1}. **HRMS** (DART+) for $C_{16}H_{27}BNO_2$ $[M+NH_4]^+$ calculated: 276.2135, found: 276.2129. **$[\alpha]^{20}_D$** -2.509 (c = 1.275, $CHCl_3$, *l* =50 mm). ***Analysis of Stereochemistry:*** The boronic ester was oxidized according to the general procedure. The resulting allylic alcohol was compared to racemic alcohol prepared analogously with $Pd(OAc)_2$ (5 mol%) and 1,1′-bis(dicyclohexylphosphino)ferrocene (6 mol%) as the catalyst. Absolute stereochemistry assigned by comparison to the literature **$[\alpha]^{25}_D$** +3.88 (93% *ee,* c=1.34, $CHCl_3$) for *(S)* enantiomer.[89]

(89) Park, J. K.; Lackey, H. H.; Ondrusek, B. A.; McQuade, D. T. *J. Am. Chem. Soc.* **2011**, *133*, 2410.

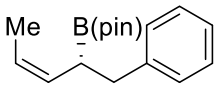
Chiral SFC (Chiralcel OD-H, 35 °C, 3 mL/min, 3% isopropanol, 100 bar) – analysis of (R)-1-phenylbut-3-en-2-ol





Peak No	% Area	Area	RT (min)
1	49.4	3633.7036	7.46
2	50.6	3721.9767	7.93
Total:	100	7355.6803	

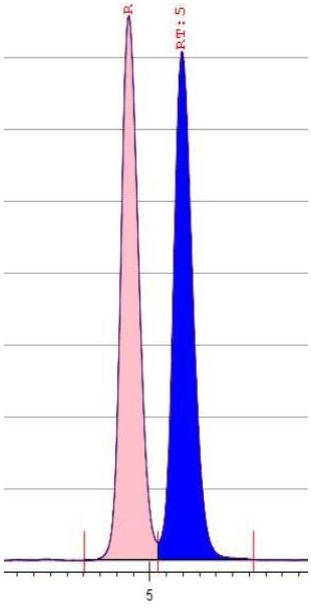
Peak No	% Area	Area	RT (min)
1	96.3741	8724.4002	7.96
2	3.6259	328.238	8.44
Total:	100	9052.6382	

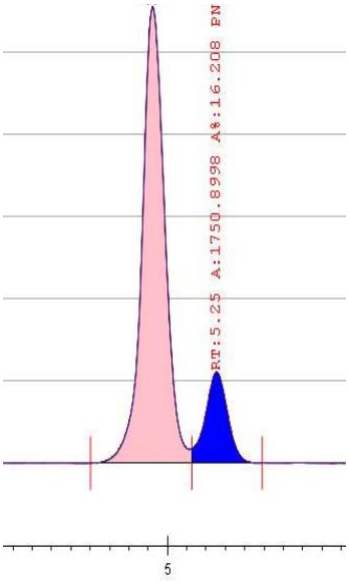


(R,Z)-4,4,5,5-Tetramethyl-2-(1-phenylpent-3-en-2-yl)-1,3,2-dioxaborolane (1.115). The reaction was performed according to the general procedure ***(Method A)*** with *(Z)*-4,4,5,5-tetramethyl-2-(prop-1-en-1-yl)-1,3,2-dioxaborolane (50.4 mg, 0.30 mmol), phenyl trifluoromethanesulfonate (0.058 mL, 0.36 mmol), palladium (II) acetate (0.67 mg, 0.003 mmol, 1%), (S_p, S_p)-**L1** (3.79 mg, 0.0036 mmol, 1.2%), and was stirred at 60 °C for 3 hours. The crude residue was purified on silica gel (20-50% CH_2Cl_2 in pentane) to afford the title compound as a clear colorless oil (68.3 mg, 84% yield, 84:16 er). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.26-7.19 (4H, m), 7.16-7.13 (1H, m), 5.46-5.40 (1H, m), 5.40-5.34 (1H, m), 2.88 (1H, dd, J = 13.2, 7.8 Hz), 2.70 (1H, dd, J = 13.8, 7.8 Hz), 2.46 (1H, app q, J = 7.8 Hz), 1.52 (3H, dd, J = 6.6, 1.8 Hz), 1.18 (6H, s), 1.17 (6H, s). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 142.1, 130.7, 129.0, 128.1, 125.8, 124.0,

83.3, 37.3, 26.2 (C-B), 24.8, 24.7, 13.2. **^{11}B** NMR (160 MHz, $CDCl_3$) δ 32.5. **IR** (neat) ν_{max} 2977.5 (w), 2927.4 (w), 2858.1 (w), 1353.8 (s), 1320.8 (s), 1261.8 (w), 1246.9 (w), 1141.1 (s), 965.5 (m), 732.6 (m), 698.1 (m) cm^{-1}. **HRMS** (DART+) for $C_{17}H_{25}BO_2$ $[M+H]^+$ calculated: 273.2026, found: 273.2034. **$[\alpha]^{20}_D$** -14.529 (c = 2.705, $CHCl_3$, *l* =50 mm).

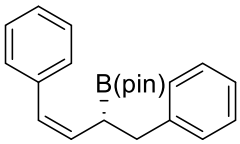
Analysis of Stereochemistry: The boronic ester was oxidized according to the general procedure. The resulting allylic alcohol was compared to racemic alcohol prepared analogously with $Pd(OAc)_2$ (5 mol%) and 1,1′-bis(dicyclohexylphosphino)ferrocene (6 mol%) as the catalyst*Chiral SFC (Chiralcel OD-H, 35 °C, 3 mL/min, 4% isopropanol, 100 bar) – analysis of (R,Z)-1-phenylpent-3-en-2-ol*





Peak No	% Area	Area	RT (min)
1	49.7819	5659.0577	4.87
2	50.2181	5708.6437	5.19
Total:	100	11367.7014	

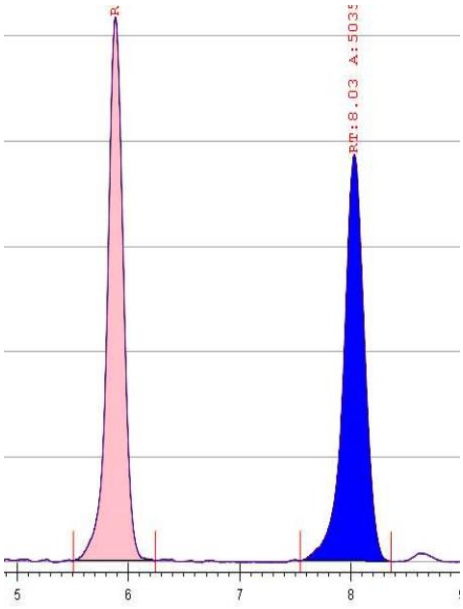
Peak No	% Area	Area	RT (min)
1	83.792	9051.8056	4.92
2	16.208	1750.8998	5.25
Total:	100	10802.7054	

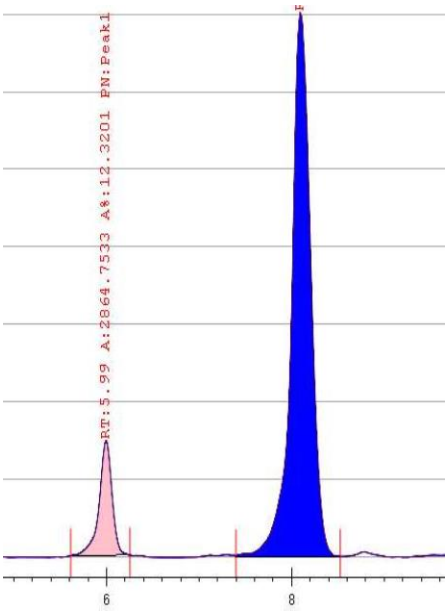


(R,Z)-2-(1,4-Diphenylbut-3-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborol-ane (1.116). The reaction was performed according to the general procedure ***(Method A)*** with *(Z)*-4,4,5,5-tetramethyl-2-styryl-1,3,2-dioxaborolane (69.0 mg, 0.30 mmol), phenyl trifluoromethane- sulfonate (0.058 mL, 0.36 mmol), palladium (II) acetate (0.67 mg, 0.003 mmol, 1%), (S_p, S_p)-**L1** (3.79 mg, 0.0036 mmol, 1.2%), and was stirred at 60 ℃ for 16 hours. The crude residue was purified on silica gel (30-50% CH_2Cl_2 in pentane) to afford the title compound as a clear colorless oil (71.1 mg, 71% yield, 88:12 er). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.34-7.28 (4H, m), 7.25-7.19 (3H, m), 7.18-7.13 (3H, m), 6.42 (1H, d, J = 12.0 Hz), 5.65 (1H, app t, J = 12.8 Hz), 2.95-2.82 (2H, m), 2.80 (1H, dd J = 12.0, 6.6 Hz), 1.17 (6H, s), 1.15 (6H, s). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 141.4, 137.8, 133.1, 129.0, 128.9, 128.6, 128.21, 128.20, 126.5, 125.9, 83.5, 37.9, 27.3(C-B), 24.8, 24.7. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 32.7. **IR** (neat) ν_{max} 3061.1 (w), 3025.1 (w), 2977.6 (w), 2926.9 (w), 1358.5 (s), 1324.0 (s), 1141.2 (s), 967.0 (w), 668.0 (s) cm^{-1}. **HRMS** (DART+) for $C_{22}H_{28}BO_2$ $[M+H]^+$ calculated: 335.2182, found: 335.2186. **$[\alpha]^{20}_D$** -124.343 (c = 1.065, $CHCl_3$, l =50 mm).

Analysis of Stereochemistry: The boronic ester was oxidized according to the general procedure. The resulting allylic alcohol was compared to racemic alcohol prepared analogously with $Pd(OAc)_2$ (5 mol%) and 1,1′-bis(diphenylphosphino)ferrocene (6 mol%) as the catalyst.

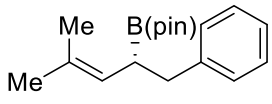
Chiral SFC (Chiralcel OD-H, 35 °C, 3 mL/min, 10% isopropanol, 100 bar) – analysis of (R,Z)-1,4-diphenylbut-3-en-2-ol.





Peak No	% Area	Area	RT (min)
1	50.5291	5143.6977	5.88
2	49.4709	5035.9734	8.03
Total:	100	10179.6711	

Peak No	% Area	Area	RT (min)
1	12.3201	2864.7533	5.99
2	87.6799	20387.8884	8.09
Total:	100	23252.6417	

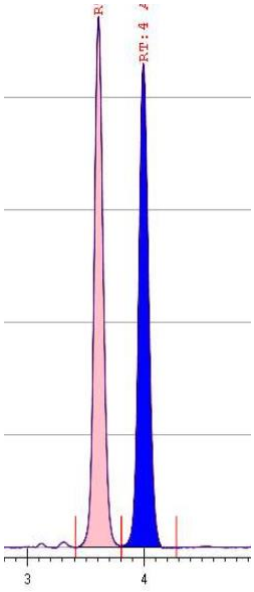


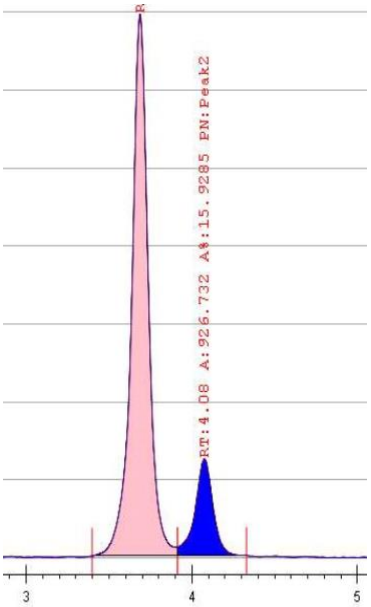
(R)-4,4,5,5-Tetramethyl-2-(4-methyl-1-phenylpent-3-en-2-yl)-1,3,2-diox aborolane (1.117). The reaction was performed according to the general procedure ***(Method A)*** with 4,4,5,5-tetramethyl-2-(2-methylprop-1-en-1-yl)-1,3,2-dioxaborolane (54.6 mg, 0.30 mmol), phenyl trifluoromethane- sulfonate (0.058 mL, 0.36 mmol), palladium (II) acetate (0.67 mg, 0.003 mmol, 1%), (S_p, S_p)-**L1** (3.79 mg, 0.0036 mmol, 1.2%), and was stirred at 60 °C for 3 hours. The crude residue was purified on silica gel (30-50% CH_2Cl_2 in pentane) to afford the title compound as a clear colorless oil (74.7 mg, 75% yield, 84:16 er). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.25-7.18 (4H, m), 7.16-7.11 (1H, m), 5.10 (1H, d, J = 9.6 Hz), 2.82 (1H, dd, J = 13.2, 7.8 Hz), 2.67 (1H,

dd, J = 14.4, 8.4 Hz), 2.31 (1H, app q, J = 8.4 Hz), 1.67 (3H, s), 1.51 (3H, s), 1.16 (6H, s), 1.14 (6H, s). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 142.2, 131.7, 129.0, 128.1, 125.7, 124.5, 83.2, 37.7, 27.0 (C-B), 26.0, 24.8, 24.7, 18.2. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 32.45. **IR** (neat) ν_{max} 3026.8 (w), 2925.0 (w), 2856.8 (w), 1361.2 (s), 1318.8 (s), 1141.5 (s), 967.1 (m), 864.2 (m), 832.8 (m), 749.2 (m), 698.2 (s) cm^{-1}. **HRMS** (DART+) for $C_{18}H_{28}BO_2$ $[M+H]^+$ calculated: 287.2182, found: 287.2187. **$[\alpha]^{20}_D$** -17.704 (c = 2.580, $CHCl_3$, l =50 mm).

Analysis of Stereochemistry: The boronic ester was oxidized according to the general procedure. The resulting allylic alcohol was compared to racemic alcohol prepared analogously with $Pd(OAc)_2$ (5 mol%) and 1,1′-bis(diphenylphosphino)ferrocene (6 mol%) as the catalyst..

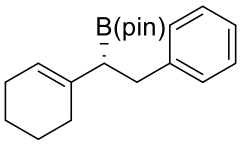
Chiral SFC (Chiralcel OD-H, 35 °C, 3 mL/min, 6% isopropanol, 100 bar) – analysis of (R)-4-methyl-1-phenylpent-3-en-2-ol.





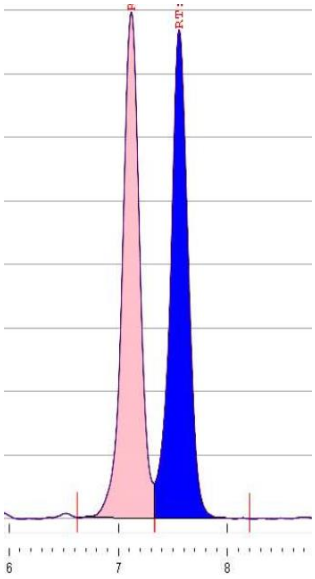
Peak No	% Area	Area	RT (min)
1	50.2447	2576.3053	3.61
2	49.7553	2551.2159	4
Total:	100	5127.5212	

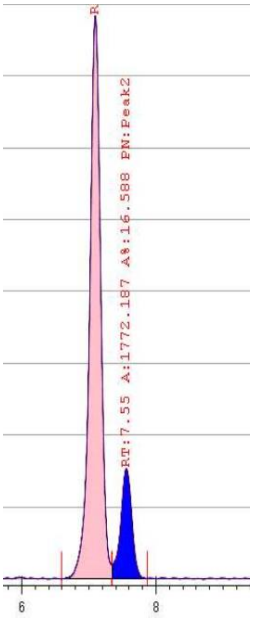
Peak No	% Area	Area	RT (min)
1	84.0715	4891.3346	3.69
2	15.9285	926.732	4.08
Total:	100	5818.0666	



(R)-2-(1-(Cyclohex-1-en-1-yl)-2-phenylethyl)-4,4,5,5-tetramethyl-1,3,2-di oxaborolane (1.118). The reaction was performed according to the general procedure ***(Method A)*** with 1-cyclohexen-1-yl-boronic acid pinacol ester (62.4 mg, 0.30 mmol), phenyl trifluoromethanesulfonate (0.058 mL, 0.36 mmol), palladium (II) acetate (0.67 mg, 0.003 mmol, 1%), (S_p, S_p)-**L1** (3.79 mg, 0.0036 mmol, 1.2%), and was stirred at 60 °C for 16 hours. The crude residue was purified on silica gel (30% CH_2Cl_2 in hexanes) to afford the title compound as a clear colorless oil (74.2 mg, 79% yield, 84:16 er). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.25-7.19 (4H, m), 7.15-7.12 (1H, m), 5.47-5.44 (1H, m), 2.88 (1H, dd, J = 13.8, 10.2 Hz), 2.79 (1H, dd, J = 13.2, 6.6 Hz), 1.63-1.57 (5H, m), 1.63-1.57 (2H, m), 1.56-1.50 (2H, m), 1.15 (6H, s), 1.13 (6H, s). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 142.5, 137.8, 129.0, 128.0, 125.6, 121.3, 83.2, 35.9, 29.0, 25.6, 24.74, 24.72, 23.4, 22.7. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 32.9. **IR** (neat) ν_{max} 2976.7 (w), 2923.8 (m), 2855.4 (w), 1479.1 (w), 1356.9 (s), 1316.8 (s), 1213.8 (w), 1164.6 (w), 1141.1 (s), 695.2 (m), 858.6 (m), 745.8 (m), 697.3 (s) cm^{-1}. **HRMS** (DART+) for $C_{20}H_{30}BO_2$ $[M+H]^+$ calculated: 313.2339, found: 313.2324. **$[\alpha]^{20}_D$** -5.010 (c = 2.235, $CHCl_3$, l =50 mm).

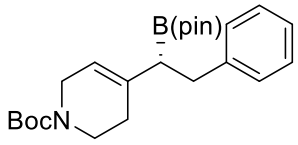
Analysis of Stereochemistry: The boronic ester was oxidized according to the general procedure. The resulting allylic alcohol was compared to racemic alcohol prepared analogously with $Pd(OAc)_2$ (5 mol%) and 1,1′-bis(dicyclohexylphosphino)ferrocene (6 mol%) as the catalyst..*Chiral SFC (Chiralcel OD-H, 35 °C, 3 mL/min, 6% isopropanol, 100 bar) – analysis of (R)-1-(cyclohex-1-en-1-yl)-2-phenylethan-1-ol.*





Peak No	% Area	Area	RT (min)
1	50.3541	8787.2088	7.12
2	49.6459	8663.6277	7.56
Total:	100	17450.8365	

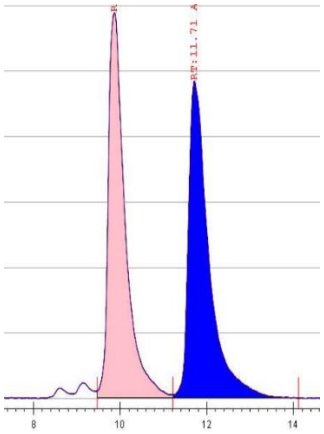
Peak No	% Area	Area	RT (min)
1	83.412	8911.3573	7.09
2	16.588	1772.187	7.55
Total:	100	10683.5443	

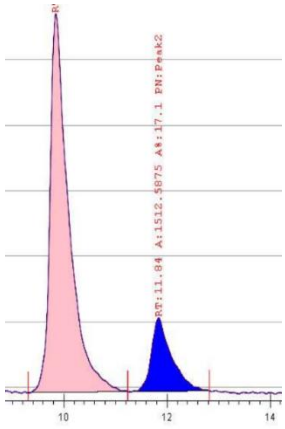


tert-Butyl (R)-4-(2-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)-3,6-dihydropyridine-1(2H)-carboxylate (1.119). The reaction was performed according to the general procedure ***(Method A)*** with 3,6-dihydro-2H-pyridine-1-N-Boc-4-boronic acid pinacol ester (92.8 mg, 0.30 mmol), phenyl trifluoromethanesulfonate (0.058 mL, 0.36 mmol), palladium (II) acetate (0.67 mg, 0.003 mmol, 1%), (S_p, S_p)-**L1** (3.79 mg, 0.0036 mmol, 1.2%), and was stirred at 60 °C for 16 hours. The crude residue was purified on silica gel (10% ethyl acetate in hexanes) to afford the title compound as a clear colorless oil (110.4 mg, 89% yield, 83:17 er). **^{1}H NMR** (500 MHz, $CDCl_3$, 55 °C) δ7.25-7.13 (5H,

m), 5.37 (1H, br s), 3.89-3.79 (2H, m), 3.48-3.40 (2H, m), 2.93- 2.88 (1H, m), 2.81-2.76 (1H, m) 2.12-2.08 (3H, m), 1.46 (9H, s), 1.16-1.13 (12H, m). **^{13}C NMR** (125 MHz, $CDCl_3$, 55 °C) δ 155.2, 142.0, 137.0, 129.0, 128.2, 125.9,118.4, 83.5, 79.4, 40.8, 43.8, 35.7, 28.9, 28.7, 25.0, 24.8. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 32.6. **IR** (neat) ν_{max} 3060.2 (w), 3025.2 (m), 2976.2 (w), 2929.1 (w), 2861.0 (w), 1695.6 (s), 1603.5 (w), 1494.8 (w), 1477.5 9w), 1415.8 (m), 1364.6 (s), 1323.0 (m), 1284.9 (w), 1213.9 (m), 1169.1 (s), 1142.6 (s), 1110.3 (m), 1054.2 (w), 967.3 (w), 864.4 (w), 837.0 (w) 699.9 (w) cm^{-1}. **HRMS** (DART+) for $C_{24}H_{37}BNO_4$ $[M+H]^+$ calculated: 414.2816, found: 414.2830. **$[\alpha]^{20}_D$** -9.921 (c = 3.925, $CHCl_3$, *l* =50 mm). ***Analysis of Stereochemistry:*** The boronic ester was oxidized according to the general procedure. The resulting allylic alcohol was compared to racemic alcohol prepared analogously with $Pd(OAc)_2$ (5 mol%) and 1,1′-bis(dicyclohexylphosphino)ferrocene (6 mol%) as the catalyst.

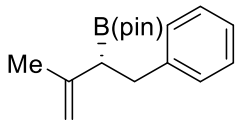
Chiral SFC (Chiralcel OJ-H, 35 °C, 3 mL/min, 5% isopropanol, 100 bar) – analysis of tert-butyl (R)-4-(1-hydroxy-2-phenylethyl)-3,6-dihydropyridine-1(2H)-carboxylate





Peak No	% Area	Area	RT (min)
1	50.1645	15952.1331	9.87
2	49.8355	15847.5096	11.71
Total:	100	31799.6427	

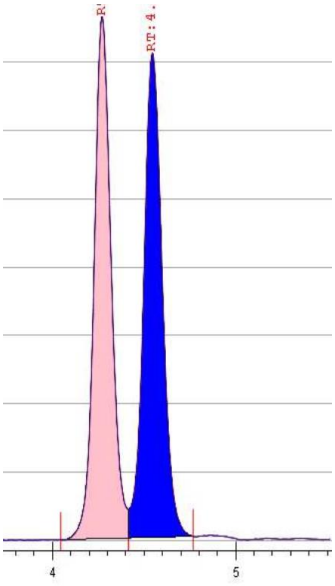
Peak No	% Area	Area	RT (min)
1	82.9	7332.9533	9.84
2	17.1	1512.5875	11.84
Total:	100	8845.5408	

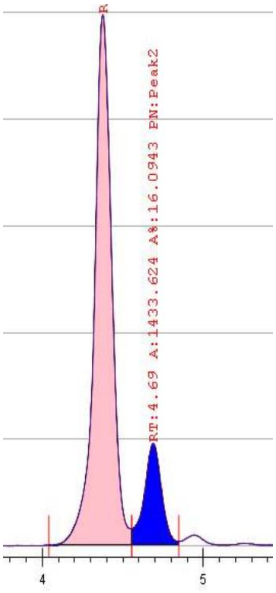


(R)-4,4,5,5-Tetramethyl-2-(3-methyl-1-phenylbut-3-en-2-yl)-1,3,2-dioxabo rolane (1.121). The reaction was performed according to the general procedure ***(Method A)*** with 2-isopropenyl boronic acid pinacol ester (50.4 mg, 0.30 mmol), phenyl trifluoromethanesulfonate (0.058 mL, 0.36 mmol), palladium (II) acetate (0.67 mg, 0.003 mmol, 1%), (S_p, S_p)-**L1** (3.79 mg, 0.0036 mmol, 1.2%), THF (0.60 mL), DMSO (0.30 mL), and was stirred at 60 °C for 1.5 hours. The crude residue was purified on silica gel (30-50% CH_2Cl_2 in pentane) to afford the title compound as a clear colorless oil (51.0 mg, 62% yield, 84:16 er). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.26-7.21 (4H, m), 7.17-7.13 (1H, m), 4.76 (1H, d, J = 1.8 Hz), 4.75 (1H, d, J = 1.2 Hz), 2.94 (1H, dd, J = 13.8, 9.6 Hz), 2.83 (1H, dd, J = 13.8, 7.2 Hz), 2.19 (1H, dd, J = 8.4, 7.2 Hz), 1.79 (3H, s), 1.17 (6H, s), 1.14 (6H, s). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 146.0, 142.1, 128.9, 128.1, 125.8, 110.1, 83.4, 35.8, 24.74, 24.72, 23.2. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 32.9. **IR** (neat) ν_{max} 3063.5 (w), 3027.9 (w), 2977.2 (m), 2930.8 (w), 1453.2 (w), 1358.0 (s), 1322.1 (s), 1269.1 (w), 1142.2 (s), 879.3 (w), 853.0 (w), 698.4 (m) cm^{-1}. **HRMS** (DART+) for $C_{17}H_{26}BO_2$ $[M+H]^+$ calculated: 273.2026, found: 273.2033. **$[\alpha]^{20}_D$** +10.981 (c = 0.960, $CHCl_3$, l =50 mm).

Analysis of Stereochemistry:The boronic ester was oxidized according to the general procedure. The resulting allylic alcohol was compared to racemic alcohol prepared analogously with $Pd(OAc)_2$ (5 mol%) and 1,1′-bis(dicyclohexylphosphino)ferrocene (6

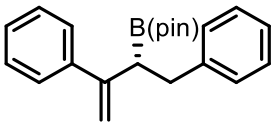
mol%) as the catalyst. *Chiral SFC (Chiralcel OD-H, 35 °C, 3 mL/min, 4% isopropanol, 100 bar) – analysis of (R)-3-methyl-1-phenylbut-3-en-2-ol.*





Peak No	% Area	Area	RT (min)
1	49.9272	2473.0193	4.27
2	50.0728	2480.2272	4.54
Total:	100	4953.2465	

Peak No	% Area	Area	RT (min)
1	83.9057	7474.0382	4.38
2	16.0943	1433.624	4.69
Total:	100	8907.6622	

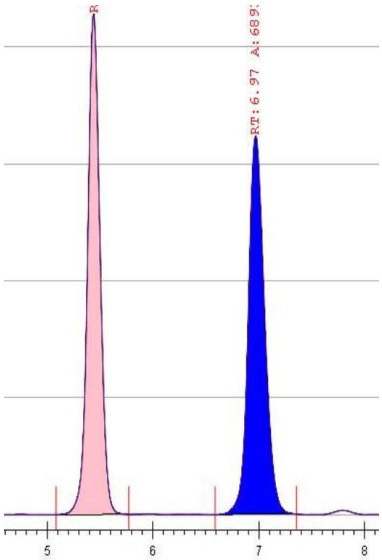


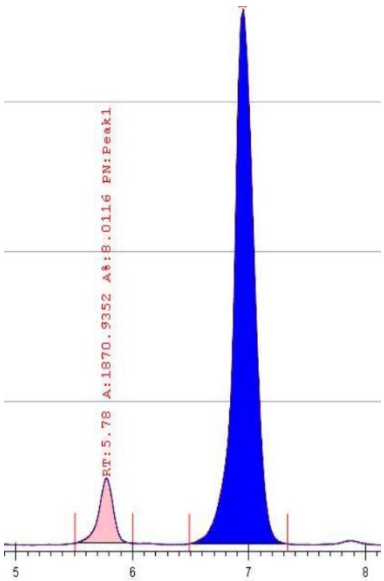
(R)-2-(1,3-Diphenylbut-3-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborol ane (1.120). The reaction was performed according to the general procedure ***(Method A)*** with 2-isopropenyl boronic acid pinacol ester (50.4 mg, 0.30 mmol), phenyl trifluoromethanesulfonate (0.058 mL, 0.36 mmol), palladium (II) acetate (0.67 mg, 0.003 mmol, 1%), (S_p, S_p)-**L1** (3.79 mg, 0.0036 mmol, 1.2%), THF (0.60 mL), DMSO (0.30 mL), and was stirred at 60 °C for 1.5 hours. The crude residue was purified on silica gel (30-50% CH_2Cl_2 in pentane) to afford the title compound as a clear colorless oil (47.5 mg, 47% yield, 92:8 er). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.45-7.41 (2H, m), 7.32-7.28 (2H, m), 7.26-7.22 (5H, m), 7.17-7.13 (1H, m), 5.33 (1H, s), 5.18 (1H, s),

3.04-2.96 (2H, m), 2.72 (1H, app t, J = 8.4 Hz), 1.05 (6H, s), 1.03 (6H, s). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 149.8, 143.0, 141.8, 129.0, 128.22, 128.18, 127.3, 126.8, 125.9, 112.3, 83.5, 36.8, 33.24 (C-B), 24.6. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 32.7. **IR** (neat) ν_{max} 3026.52 (w), 2977.0 (w), 2927.3 (w), 1494.1 (w), 1357.6 (s), 1325.7 (s), 1271.0 (m), 1212.1 (m), 1140.8 (s), 1028.9 (m), 974.5 (m), 861.5 (m), 697.0 (s) cm^{-1}. **HRMS** (DART+) for $C_{22}H_{28}BO_2$ $[M+H]^+$ calculated: 335.2182, found: 335.2172. **$[\alpha]^{20}_D$** +32.120 (c = 2.370, $CHCl_3$, l =50 mm).

Analysis of Stereochemistry: The boronic ester was oxidized according to the general procedure. The resulting allylic alcohol was compared to racemic alcohol prepared analogously with $Pd(OAc)_2$ (5 mol%) and 1,1′-bis(dicyclohexylphosphino)ferrocene (6 mol%) as the catalyst.

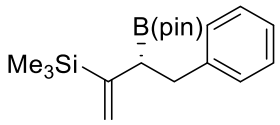
Chiral SFC (Chiralcel OD-H, 35 °C, 3 mL/min, 10% isopropanol, 100 bar) – analysis of (R)-1,3-diphenylbut-3-en-2-ol.





Peak No	% Area	Area	RT (min)
1	50.2874	6972.7526	5.44
2	49.7126	6893.0424	6.97
Total:	100	13865.795	

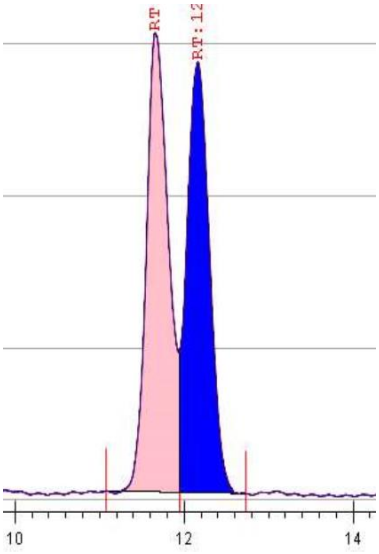
Peak No	% Area	Area	RT (min)
1	8.0116	1870.9352	5.78
2	91.9884	21481.7618	6.95
Total:	100	23352.697	

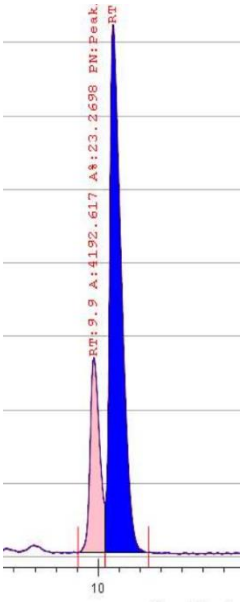


(R)-Trimethyl(4-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) but-1-en-2-yl)silane (1.123). The reaction was performed according to the general procedure ***(Method A)*** except in a 3:1 THF:DMSO solvent mixture with trimethyl(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)silane (67.9 mg, 0.30 mmol), phenyl trifluoromethanesulfonate (0.058 mL, 0.36 mmol), palladium (II) acetate (0.67 mg, 0.003 mmol, 1%), (S_p, S_p)-**L1** (3.79 mg, 0.0036 mmol, 1.2%), and was stirred at 60 ℃ for 1.5 hours. The crude residue was purified on silica gel (30% CH_2Cl_2 in hexanes) to afford the title compound as a clear colorless oil (48.8 mg, 66% yield, 77:23 er). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.25-7.21 (4H, m), 7.16-7.12 (1H, m), 5.81 (1H, d, J = 2.4 Hz), 5.48 (1H, d, J = 2.4 Hz), 2.95 (1H, dd, J = 13.8, 10.2 Hz), 2.77 (1H, dd, J = 13.2, 6.0 Hz), 2.25 (1H, dd, J = 10.2, 6.0 Hz), 1.14 (6H, s), 1.13 (6H, s), 0.06 (9H, s). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 152.8, 142.5, 129.1, 128.1, 125.7, 124.5, 83.2, 38.2, 32.33 (C-B), 24.8, 24.7, -1.5. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 32.4. **IR** (neat) ν_{max} 2977.5 (w), 2955.6 (w), 1357.4 (s), 1324.4 (s), 1247.0 (m), 1142.7 (s), 853.4 (s), 835.8 (s), 697.6 (m) cm^{-1}. **HRMS** (DART+) for $C_{19}H_{32}BO_2Si$ $[M+H]^+$ calculated: 331.2259, found: 331.2265. **$[\alpha]^{20}_D$** +9.083 (c = 1.670, $CHCl_3$, l =50 mm).

Analysis of Stereochemistry:The boronic ester was oxidized according to the general procedure. The resulting allylic alcohol was compared to racemic alcohol prepared analogously with $Pd(OAc)_2$ (5 mol%) and 1,1′-bis(dicyclohexylphosphino)ferrocene (6 mol%) as the catalyst.

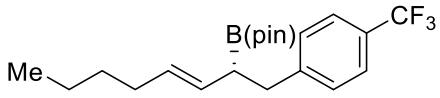
Chiral SFC (Chiralcel AD-H, 25 °C, 2.5 mL/min, 1% isopropanol, 100 bar) – analysis of (R)-1-phenyl-3-(trimethylsilyl)but-3-en-2-ol.





Peak No	% Area	Area	RT (min)
1	51.089	5505.9533	11.66
2	48.911	5271.2304	12.16
Total:	100	10777.1837	

Peak No	% Area	Area	RT (min)
1	23.2698	4192.617	9.9
2	76.7302	13824.7926	10.35
Total:	100	18017.4096	

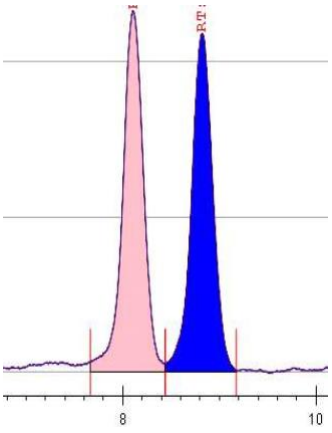


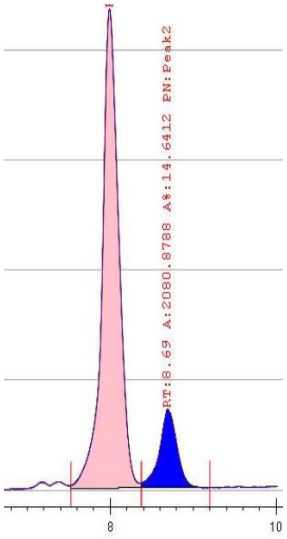
(R,E)-4,4,5,5-Tetramethyl-2-(1-(4-(trifluoromethylphenyl) oct-3-en-2-yl)-1,3,2-dioxaborolane (1.124). The reaction was performed according to the general procedure ***(Method B)*** *(E)*-2-(hex-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane ***(1)*** (63.0 mg, 0.30 mmol), 4-(trifluoromethyl)phenyl trifluoromethanesulfonate (105.9 mg, 0.36 mmol), palladium (II) acetate (0.67 mg, 0.003 mmol, 1%), (S_p, S_p)-**L1** (3.79 mg, 0.0036 mmol, 1.2%), and was stirred at 60 °C for 16 hours. The crude residue was purified on silica gel (20-40% CH_2Cl_2 in pentane) to afford the title compound as a clear colorless oil (93.2 mg,

81% yield, 85:15 er). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.49 (2H, d, *J* = 7.8 Hz), 7.30 (2H, d, *J* = 8.4 Hz), 5.42-5.33 (2H, m), 2.89 (1H, dd, *J* = 13.8, 8.4 Hz), 2.76 (1H, dd, *J* = 13.8, 7.8 Hz), 2.12 (1H, app q, *J* = 7.2 Hz), 1.96 (2H, app q, *J* = 6.0 Hz), 1.28-1.19 (4H, m), 1.17 (6H, s), 1.16 (6H, s), 0.85 (3H, t, *J* = 7.2 Hz). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 146.3, 131.3, 129.4, 129.3, 128.1 (q, *J* = 31.1 Hz), 125.0 (q, *J* = 4.7 Hz), 124.6 (q, *J* = 270.3 Hz), 83.4, 37.1, 32.5, 31.8, 30.5 (C-B), 24.8, 24.7, 22.1, 14.0. **^{19}F NMR** (564 MHz, $CDCl_3$) δ -62.3. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 32.7. **IR** (neat) ν_{max} 2978.2 (w), 2958.1 (w), 2926.8 (w), 1618.2 (w), 1370.5 (m), 1322.9 (s), 1162.9 (m), 1123.5 (s), 1067.4 (m), 967.8 (w), 848.6 (w) cm^{-1}. **HRMS** (DART+) for $C_{21}H_{31}BO_2F_3$ $[M+H]^+$ calculated: 383.2369, found: 383.2380. **$[\alpha]^{20}_D$** -15.987 (c = 1.015, $CHCl_3$, *l* =50 mm).

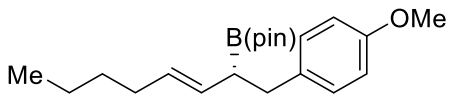
Analysis of Stereochemistry: The boronic ester was oxidized according to the general procedure. The resulting allylic alcohol was compared to racemic alcohol prepared analogously with $Pd(OAc)_2$ (5 mol%) and 1,1′-bis(diphenylphosphino)ferrocene (6 mol%) as the catalyst.

Chiral SFC (Chiralcel OD-H, 35 °C, 3 mL/min, 2% isopropanol, 100 bar) – analysis of (R,E)-1-(4-(trifluoromethyl)phenyl)oct-3-en-2-ol



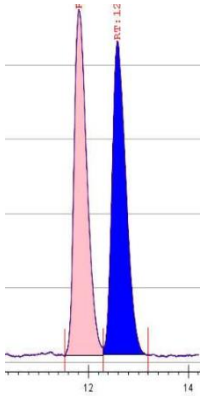


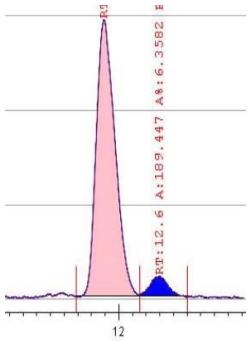
Peak No	% Area	Area	RT (min)	Peak No	% Area	Area	RT (min)
1	50.8736	1750.9453	8.11	1	85.3588	12131.5999	7.99
2	49.1264	1690.81	8.82	2	14.6412	2080.8788	8.69
Total:	100	3441.7553		Total:	100	14212.4787	



(R,E)-2-(1-(4-Methoxyphenyl)oct-3-en-2-yl)-4,4,5,5 tetra methyl-1,3,2-dioxaborolane (1.125)..The reaction was performed according to the general procedure ***(Method B)*** (*E*)-2-(hex-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (63.0 mg, 0.30 mmol), 4-methoxyphenyl trifluoromethanesulfonate (92.2 mg, 0.36 mmol), palladium (II) acetate (0.67 mg, 0.003 mmol, 1%), (S_p, S_p)-**L1** (3.79 mg, 0.0036 mmol, 1.2%), and was stirred at 60 °C for 16 hours. The crude residue was purified on silica gel (40-100% CH_2Cl_2 in pentane) to afford the title compound as a clear colorless oil (71.5 mg, 69% yield, 94:6 er).

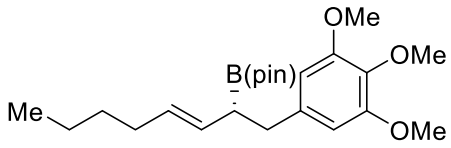
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.11 (2H, d, *J* = 8.4 Hz), 6.78 (2H, d, *J* = 8.4 Hz), 5.42-5.34 (2H, m), 3.77 (3H, s), 2.77 (1H, dd, *J* = 13.8, 9.0 Hz), 2.66 (1H, dd, *J* = 13.8, 7.8 Hz), 2.09 (1H, app q, *J* = 7.8 Hz), 1.96 (2H, app q, *J* = 6.0 Hz), 1.32-1.22 (4H, m), 1.16 (6H, s), 1.15 (6H, s), 0.86 (3H, t, *J* = 7.2 Hz). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 157.8, 134.3, 130.6, 130.1, 129.9, 113.5, 83.2, 55.4, 36.5, 32.6, 31.9, 31.0(C-B), 24.8, 24.7, 22.1, 14.1. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 32.8. **IR** (neat) ν_{max} 2976.2 (w), 2956.4 (w), 2925.4 (w), 2854.1 (w), 1611.8 (w), 1511.3 (s), 1369.7 (m), 1322.1 (m), 1244.4 (s), 1142.4 (s), 1038.7 (m), 967.8 (m) cm^{-1}. **HRMS** (DART+) for $C_{21}H_{37}BO_3N$ $[M+NH_4]^+$ calculated: 362.2866, found: 362.2883. **$[\alpha]^{20}_D$** -16.798 (c = 1.085, $CHCl_3$, *l* =50 mm). ***Analysis of Stereochemistry:*** The boronic ester was oxidized according to the general procedure. The resulting allylic alcohol was compared to racemic alcohol prepared analogously with $Pd(OAc)_2$ (5 mol%) and 1,1′-bis(dicyclohexylphosphino)ferrocene (6 mol%) as the catalyst. *Chiral SFC (Chiralcel ODR-H, 35 °C, 3 mL/min, 2% isopropanol, 100 bar) – analysis of (R,E)-1-(4-methoxyphenyl)oct-3-en-2-ol.*





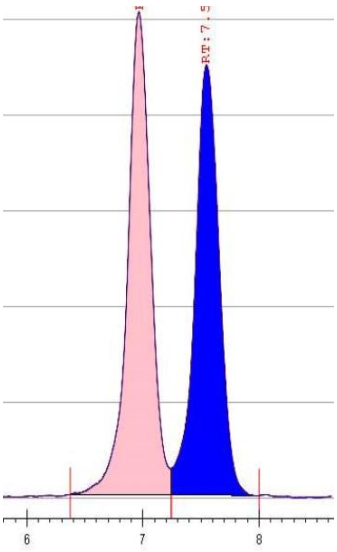
Peak No	% Area	Area	RT (min)
1	50.4606	4145.1496	11.81
2	49.5394	4069.4696	12.58
Total:	100	8214.6192	

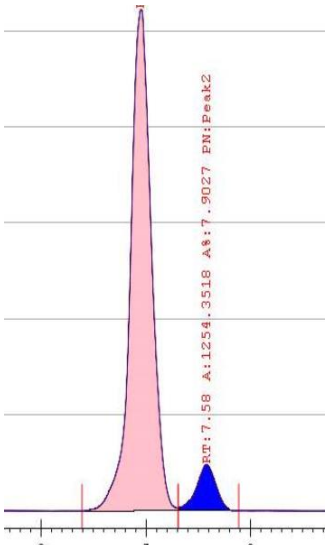
Peak No	% Area	Area	RT (min)
1	93.6418	2790.1234	11.78
2	6.3582	189.447	12.6
Total:	100	2979.5704	



(R,E)-4,4,5,5-Tetramethyl-2-(1-(3,4,5-trimethoxyphenyl) oct-3-en-2-yl)-1,3,2-dioxaborolane (1.126). The reaction was performed according to the general procedure ***(Method B)*** (*E*)-2-(hex-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborol- ane ***(1)*** (63.0 mg, 0.30 mmol), 3,4,5-trimethoxyphenyl trifluoromethanesulfonate (113.9 mg, 0.36 mmol), palladium (II) acetate (0.67 mg, 0.003 mmol, 1%), (S_p, S_p)-**L1** (3.79 mg, 0.0036 mmol, 1.2%), and was stirred at 60 °C for 16 hours. The crude residue was purified on silica gel (5-15% ethyl acetate in hexanes) to afford the title compound as a clear colorless oil (109.3 mg, 90% yield, 92:8 er). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.43 (2H, s), 5.43-5.36 (2H, m), 3.82 (6H, s), 3.79 (3H, s), 2.76 (1H, dd, *J* = 13.8, 9.0 Hz), 2.68 (1H, dd, *J* = 13.8, 7.2 Hz), 2.15-2.10 (1H, m), 1.99-1.95 (2H, m), 1.30-1.21 (4H, m), 1.16 (6H, s), 1.14 (6H, s), 0.85 (3H, t, *J* = 7.2 Hz). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 152.9, 137.9, 136.1, 130.7, 129.9, 105.9, 83.3, 60.9, 56.1, 37.6, 32.5, 31.9, 30.7 (C-B), 24.8, 24.7, 22.1, 14.0. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 32.8. **IR** (neat) ν_{max} 2975.2 (w), 2955.8 (w), 2972.9 (w), 2854.7 (w), 1588.4 (m), 1507.1 (m), 1457.2 (m), 1369.3 (m), 1323.3 (m), 1236.4 (m), 1127.5 (s), 1012.1 (m), 968.2 (m) cm^{-1}. **HRMS** (DART+) for $C_{23}H_{38}BO_5$ $[M+H]^+$ calculated: 405.2812, found: 405.2809. **$[\alpha]^{20}_D$** -16.763 (c = 0.985, $CHCl_3$, *l* =50 mm). ***Analysis of Stereochemistry:***The boronic ester was oxidized according to the general procedure. The resulting allylic alcohol was compared to racemic alcohol prepared analogously with $Pd(OAc)_2$ (5 mol%) and 1,1′-bis(diphenylphosphino)ferrocene (6 mol%) as the catalyst. *Chiral SFC (Chiralcel OD-H,*

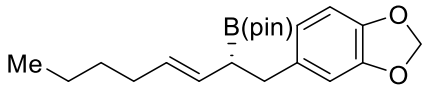
35 °C, 3 mL/min, 10% isopropanol, 100 bar) – analysis of (R,E)-1-(3,4,5-trimethoxyphenyl)oct-3-en-2-ol.





Peak No	% Area	Area	RT (min)
1	51.6616	6978.1858	6.97
2	48.3384	6529.3034	7.54
Total:	100	13507.4892	

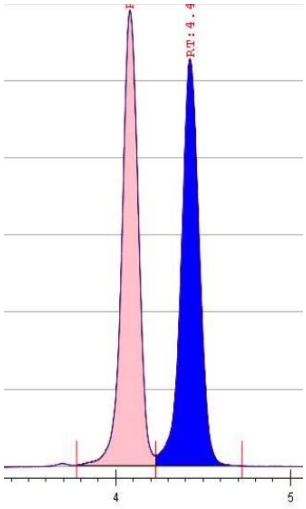
Peak No	% Area	Area	RT (min)
1	92.0973	14618.1541	6.95
2	7.9027	1254.3518	7.58
Total:	100	15872.5059	

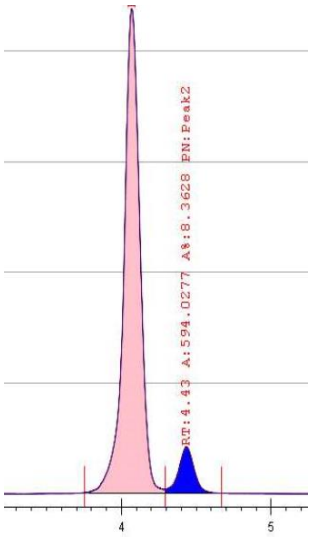


(R,E)-2-(1-(Benzo[d][1,3]dioxol-5-yl)oct-3-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.126). The reaction was performed according to the general procedure ***(Method B)*** with (*E*)-2-(hex-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane ***(1)*** (63.0 mg, 0.30 mmol), benzo[d][1,3]dioxol-5-yl trifluoromethanesulfonate (97.3 mg, 0.36 mmol), palladium (II) acetate (0.67 mg, 0.003 mmol, 1%), (S_p, S_p)-**L1** (3.79 mg, 0.0036 mmol, 1.2%), and was stirred at 60 °C for 16 hours. The crude residue was purified on silica gel (30-70% CH_2Cl_2 in pentane) to afford the title compound as a clear colorless oil (86.1 mg, 80% yield, 92:8 er). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.70-6.67 (2H, m), 6.65-6.63 (1H, m), 5.88 (2H, s), 5.31-5.33 (2H, m), 2.75 (1H, dd, *J* = 13.2, 8.4 Hz), 2.63 (1H, dd, *J* = 13.2, 7.2 Hz), 2.08-2.03 (1H, m), 1.98-1.94 (2H, m), 1.31-1.22 (4H, m), 1.18 (6H, s), 1.17 (6H, s), 0.86 (3H,

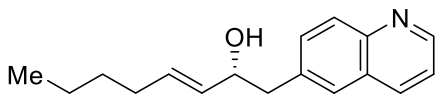
t, J = 7.2 Hz). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 147.3, 145.5, 136.0, 130.8, 129.9, 121.8, 109.6, 107.9, 100.7, 83.3, 37.1, 32.5, 31.9, 31.2 (C-B), 24.8, 24.7, 22.1, 14.1. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 33.0. **IR** (neat) ν_{max} 2977.0 (w), 2956.9 (w), 2926.0 (w), 2872.0 (w), 1503.4 (m), 1489.0 (s), 1441.5 (m), 1370.4 (m), 1324.2 (m), 1245.4 (s), 1142.9 (s), 1040.7 (s), 968.5 (m), 934.6 (w), 854.0 (w), 807.3 (w) cm^{-1}. **HRMS** (DART+) for $C_{21}H_{32}BO_4$ $[M+H]^+$ calculated: 359.2394, found: 359.2381. **$[\alpha]^{20}_D$** -19.441 (c = 1.055, $CHCl_3$, l =50 mm). ***Analysis of Stereochemistry:*** The boronic ester was oxidized according to the general procedure. The resulting allylic alcohol was compared to racemic alcohol prepared analogously with $Pd(OAc)_2$ (5 mol%) and 1,1′-bis(diphenylphosphino)ferrocene (6 mol%) as the catalyst.

Chiral SFC (Chiralcel OD-H, 35 °C, 3 mL/min, 10% isopropanol, 100 bar) – analysis of (R,E)-1-(benzo[d][1,3]dioxol-5-yl)oct-3-en-2-ol.





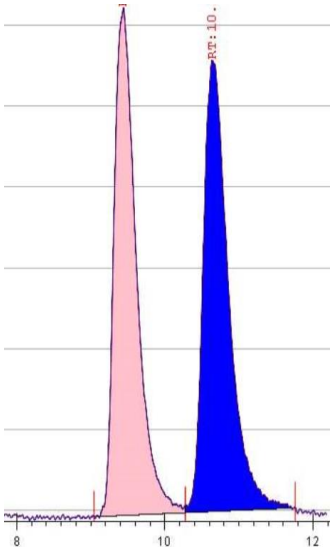
Peak No	% Area	Area	RT (min)	Peak No	% Area	Area	RT (min)
1	50.3749	3847.5712	4.08	1	91.6372	6509.1964	4.07
2	49.6251	3790.3087	4.43	2	8.3628	594.0277	4.43
Total:	100	7637.8799		Total:	100	7103.2241	

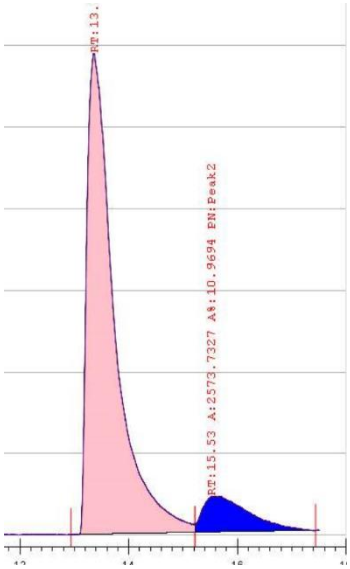


(R,E)-1-(Quinolin-6-yl)oct-3-en-2-ol (1.127-OH). The reaction was performed according to the general *procedure (**Method B**)* with (*E*)-2-(hex-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (63.0 mg, 0.30 mmol), 6-quinolinyl trifluoromethanesulfonate (97.3 mg, 0.36 mmol), palladium (II) acetate (1.35 mg, 0.006 mmol, 2%), (S_p, S_p)-**L1** (6.95 mg, 0.0066 mmol, 2.2%),, and was stirred at 60 ℃ for 16 hours. The crude residue was directly oxidized according to the sodium perborate oxidation procedure. The crude residue was purified on silica gel (20-40% ethyl acetate in hexanes) to afford the title compound as a clear colorless oil (62.6 mg, 82% yield, 89:11 er). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.88-8.84 (1H, m), 8.10 (1H, d, *J* = 6.0 Hz), 8.03 (1H, d, *J* = 12.0 Hz), 7.64 (1H, s), 7.61-7.57 (1H, m), 7.37 (1H, dd, *J* = 8.4, 4.2 Hz), 5.64 (1H, dt, *J* = 13.2, 6.6 Hz), 5.56 (1H, dd, *J* = 15.6, 7.2 Hz), 4.41 (1H, app q, *J* = 6.6 Hz), 3.05-2.96 (2H, m), 2.07-1.96 (2H, m), 1.93-1.75 (1H, br s), 1.34-1.27 (2H, m), 1.27-1.19 (2H, m), 0.85 (3H, t, *J* = 7.2 Hz). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 149.9, 147.3, 137.0, 135.9, 132.8, 132.0, 131.9, 129.3, 128.3, 128.0, 121.2, 73.6, 44.2, 32.0, 31.3, 22.2, 14.0. **IR** (neat) ν_{max} 3246.7 (br), 2954.3 (m), 2922.8 (m), 2854.4 (m), 1501.8 (s), 1464.8 (w), 1434.7 (w), 1378.1 (w), 1321.2 (w), 1232.1 (w), 1093.5 (w), 1034.1 (m) 969.1 (s), 831.4 (s), 797.4 (w), 772.5 (w) cm^{-1}. **HRMS** (DART+) for $C_{17}H_{22}NO$ $[M+H]^+$ calculated: 256.1701, found: 276.1711. **$[\alpha]^{20}_D$** -3.820 (c = 1.765, $CHCl_3$, *l* =50 mm).

Analysis of Stereochemistry: The alcohol was compared to racemic alcohol prepared analogously with $Pd(OAc)_2$ (5 mol%) and 1,1′-bis(diphenylphosphino)ferrocene (6 mol%) as the catalyst.

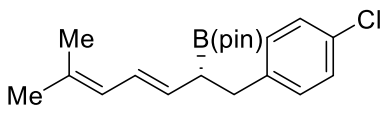
Chiral SFC (Chiralcel OJ-H, 35 °C, 3 mL/min, 6% isopropanol, 100 bar) – analysis of (R,E)-1-(quinolin-6-yl)oct-3-en-2-ol.





Peak No	% Area	Area	RT (min)
1	49.8505	2634.9339	9.44
2	50.1495	2650.734	10.64
Total:	100	5285.6679	

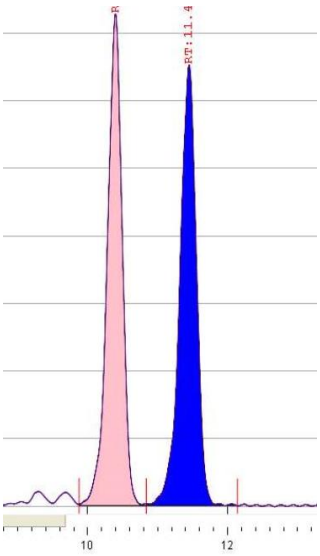
Peak No	% Area	Area	RT (min)
1	89.0306	20889.0524	13.37
2	10.9694	2573.7327	15.53
Total:	100	23462.7851	

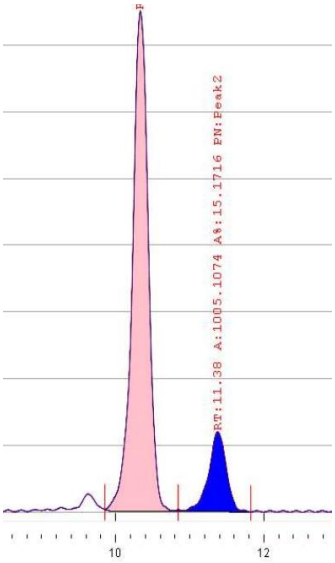


(R,E)-2-(1-(4-Chlorophenyl)-6-methylhepta-3,5-dien-2-yl)-4,4, 5,5-tetramethyl-1,3,2-dioxaborolane (1.128). The reaction was performed according to the general procedure ***(Method B)*** with *(E)*-4,4,5,5-tetramethyl-2-(4-methylpenta-1,3-dien-1-yl)-1,3,2-dioxa borolane (62.4 mg, 0.30 mmol), 4-chlorophenyl trifluoromethanesulfonate ***(S-15)*** (93.8 mg, 0.36 mmol), palladium (II) acetate (0.67 mg, 0.003 mmol, 1%), (S_p, S_p)-**L1** (3.79 mg, 0.0036 mmol, 1.2%), and was stirred at 60 °C for 5 hours. The crude residue was purified on silica gel (20-40% CH_2Cl_2 in pentane) to afford the title compound as a clear colorless oil (87.9 mg, 85% yield, 85:15 er). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.20 (2H, d, J = 8.4 Hz), 7.13 (2H, d, J = 8.4 Hz), 6.05 (1H, d, J = 15.6 Hz), 5.53 (1H, dd, J = 15.6, 9.0 Hz), 5.41 (1H, q, J = 6.6 Hz), 2.84 (1H, dd, J = 13.8, 9.0 Hz), 2.73 (1H, dd, J = 13.8, 7.2 Hz), 2.17 (1H, app q, J = 8.4 Hz), 1.72-

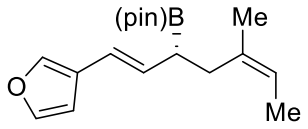
1.65 (6H, m), 1.16 (6H, s), 1.14 (6H, s). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 140.5, 135.0, 134.7. 131.5, 130.4, 128.2, 126.6, 124.7, 83.5, 36.8, 31.1 (C-B), 24.8, 24.7, 13.8, 12.2. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 32.5. **IR** (neat) ν_{max} 3025.4 (w), 2977.7 (w), 2925.4 (w), 1491.6 (m), 1360.9 (s), 1322.9 (s), 1141.7 (s), 1092.5 (w), 1015.2 (w), 964.6 (m) cm^{-1}. **HRMS** (DART+) for $C_{20}H_{29}BClO_2$ $[M+H]^+$ calculated: 347.1949, found: 347.1932. **$[\alpha]^{20}_D$** -27.905 (c = 1.080, $CHCl_3$, *l* =50 mm).

Analysis of Stereochemistry: The boronic ester was oxidized according to the general procedure. The resulting allylic alcohol was compared to racemic alcohol prepared analogously with $Pd(OAc)_2$ (5 mol%) and 1,1′-bis(cyclohexylphosphino)ferrocene (6 mol%) as the catalyst. *Chiral SFC (Chiralcel OD-H, 35 °C, 3 mL/min, 8% isopropanol, 100 bar) – analysis of (R,E)-1-(4-chlorophenyl)-6-methylhepta-3,5-dien-2-ol.*





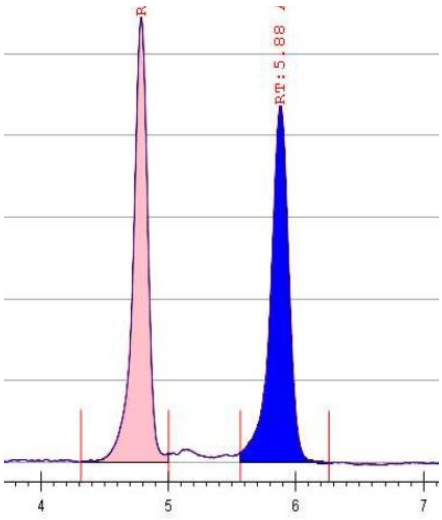
Peak No	% Area	Area	RT (min)	Peak No	% Area	Area	RT (min)
1	50.062	5417.8947	10.4	1	84.8284	5619.798	10.33
2	49.938	5404.468	11.45	2	15.1716	1005.1074	11.38
Total:	100	10822.3627		Total:	100	6624.9054	

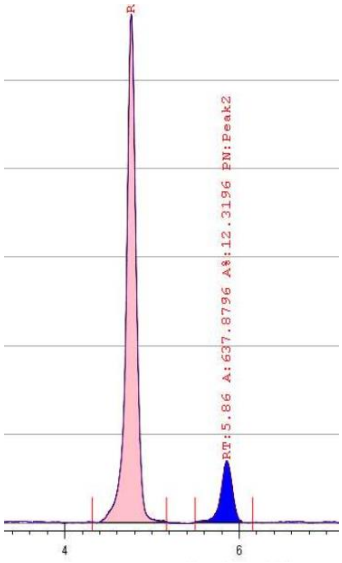


2-((R,1E,5Z)-1-(Furan-3-yl)-5-methylhepta-1,5-dien-3-yl)-4,4,5,5-tetr amethyl-1,3,2-dioxaborolane (1.131). The reaction was performed according to the general procedure ***(Method C)*** with *(E)*-2-(2-(furan-3-yl)vinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (66.0 mg, 0.30 mmol), *(Z)*-2-bromo-2-butene (0.037 mL, 0.36 mmol), potassium trifluoromethanesulfonate (67.7 mg, 0.36 mmol), palladium (II) acetate (1.35 mg, 0.006 mmol, 2%), (S_p, S_p)-**L1** (6.95 mg, 0.0066 mmol, 2.2%), and was stirred at 60 ℃ for 16 hours. The crude residue was purified on silica gel (30% CH_2Cl_2 in hexanes) to afford the title compound as a clear colorless oil (41.0 mg, 45% yield, 87:13 er). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.12-7.04 (2H, m), 6.26 (1H, s), 5.96 (1H, d, *J* = 18 Hz), 5.00-4.97 (1H, m), 5.00-4.97 (1H, m), 2.10 (1H, dd, *J*= 13.2, 7.8 Hz), 1.99 (1H, dd, *J* = 13.2, 7.8Hz), 1.91 (1H, q, *J* = 8.4 Hz), 1.45-1.44 (3H, m), 1.38-1.35 (3H, m), 1.001 (6H, s), 0.996 (6H, s). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 143.2, 139.3, 135.1, 131.2, 124.9, 120.1, 118.7, 107.8, 83.4, 32.6, 27.9 (C-B), 24.9, 24.7, 23.4, 13.7. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 32.6. **IR** (neat) ν_{max} 2977.2 (m), 2928.0 (w), 2857.9 (w), 1571.0 (w), 1507.6 (w), 1370.3 (s), 1360.7 (s), 1322.8 (s), 1271 (w), 1248.5 (w), 1140.9 (s), 1024.8 (m), 963.6 (m), 852.0 (m), 773.8 (m) cm^{-1}. **HRMS** (DART+) for $C_{18}H_{28}BO_3$ $[M+H]^+$ calculated: 303.2132, found: 303.2135. **$[\alpha]^{20}_D$** -11.905 (c = 1.375, $CHCl_3$, *l* =50 mm).

Analysis of Stereochemistry: The boronic ester was oxidized according to the general procedure. The resulting allylic alcohol was compared to racemic alcohol prepared analogously with $Pd(OAc)_2$ (5 mol%) and 1,1′-bis(dicyclohexylphosphino)ferrocene (6 mol%) as the catalyst.

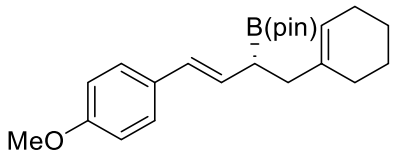
Chiral SFC (Chiralcel OD-H, 35 °C, 3 mL/min, 5% isopropanol, 100 bar) – analysis of (R,1E,5Z)-1-(furan-3-yl)-5-methylhepta-1,5-dien-3-ol





Peak No	% Area	Area	RT (min)
1	49.7388	2190.7246	4.79
2	50.2612	2213.7311	5.88
Total:	100	4404.4557	

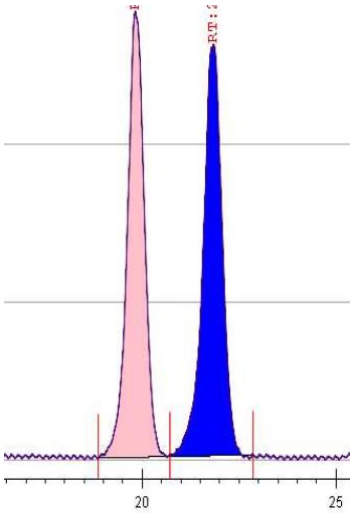
Peak No	% Area	Area	RT (min)
1	87.6804	4539.8875	4.76
2	12.3196	637.8796	5.86
Total:	100	5177.7671	

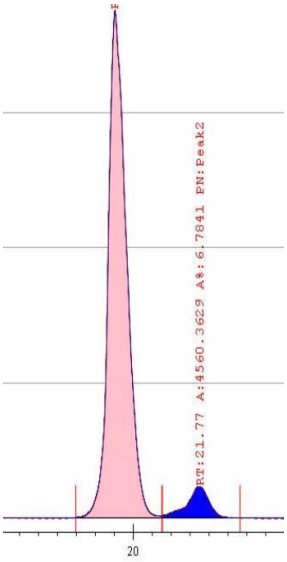


(R,E)-2-(1-(Cyclohex-1-en-1-yl)-4-(4-methoxyphenyl)but-3-en -2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.134). The reaction was performed according to the general procedure ***(Method A)*** with *(E)*-2-(4-methoxystyryl)-4,4,5,5-tetramethyl-1,3,2-dioxabor olane (78.0 mg, 0.30 mmol), 1-cyclohexenyl trifluoromethanesulfonate (0.059 mL, 0.36 mmol), palladium (II) acetate (0.67 mg, 0.003 mmol, 1%), (S_p, S_p)-**L1** (3.79 mg, 0.0036 mmol, 1.2%), and was stirred at 60 °C for 16 hours. The crude residue was purified on silica gel (30% CH_2Cl_2 in hexanes) to afford the

title compound as a white solid (63.6 mg, 58% yield, 93:7 er). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.25-7.24 (2H, m), 6.82-6.81 (2H, m), 6.31 (1H, d, *J* = 15.6 Hz), 6.07-6.03 (1H, m), 5.45 (1H, s), 3.79 (3H, s), 2.30-2.29 (1H, m), 2.22-2.18 (1H, m), 2.14-2.11 (1H, m), 1.96-1.87 (4H, m), 1.61-1.58 (2H, m), 1.53-1.50 (2H, m), 1.222-1.216 (12H, m). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 158.6, 137.3, 131.4, 129.7, 128.3, 127.1, 121.7, 114.0, 83.3, 55.4, 39.6, 28.6, 25.4, 24.9, 24.8, 23.1, 22.7. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 32.3. **IR** (neat) ν_{max} 2976.7 (w), 2926.2 (w), 2834.3 (w), 1607.6 (w), 1510.3 (m), 1464.8 (w), 1440.7 (w), 1378.4 (w), 1359.2 (w), 1246.7 (m), 1173.5 (m), 1107.7 (w), 1007.0 (w), 967.3 (w), 854.4 (w), 814.2 (w) cm^{-1}. **HRMS** (DART+) for $C_{23}H_{34}BO_3$ $[M+H]^+$ calculated: 369.2601, found: 369.2681. **$[\alpha]^{20}_D$** -2.112 (c =0.6900 , $CHCl_3$, *l* =50 mm).

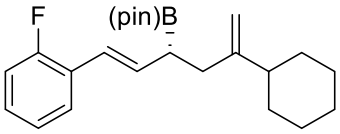
Analysis of Stereochemistry: The boronic ester was oxidized according to the general procedure. The resulting allylic alcohol was compared to racemic alcohol prepared analogously with $Pd(OAc)_2$ (5 mol%) and 1,1′-bis(dicyclohexylphosphino)ferrocene (6 mol%) as the catalyst. *Chiral SFC (Chiralcel OD-H, 35 °C, 3 mL/min, 6% isopropanol, 100 bar) – analysis of (R,E)-1-(cyclohex-1-en-1-yl)-4-(4-methoxyphenyl)but-3-en-2-ol.*





Peak No	% Area	Area	RT (min)
1	49.0866	4368.5593	19.82
2	50.9134	4531.1406	21.84
Total:	100	8899.6999	

Peak No	% Area	Area	RT (min)
1	93.2159	62661.1882	19.52
2	6.7841	4560.3629	21.77
Total:	100	67221.5511	



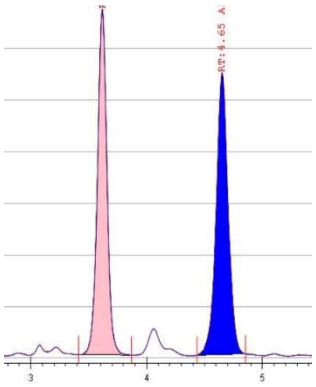
(R,E)-2-(5-Cyclohexyl-1-(2-fluorophenyl)hexa-1,5-dien-3-yl)-4,4, 5,5-tetramethyl-1,3,2-dioxaborolane (1.133). The reaction was performed according to the general procedure ***(Method B)*** with *(E)*-2-(2-fluorostyryl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (74.4.0 mg, 0.30 mmol), 1-cyclohexylvinyl trifluoromethanesulfonate ***(S-16)*** (93.0 mg, 0.36 mmol), palladium (II) acetate (0.67 mg, 0.003 mmol, 1%), (S_p, S_p)-**L1** (3.79 mg, 0.0036 mmol, 1.2%), and was

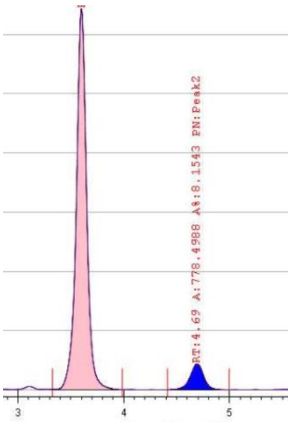
stirred at 60 °C for 16 hours. The crude residue was purified on silica gel (30% CH_2Cl_2 in hexanes) to afford the title compound as a clear colorless oil (63.3 mg, 54% yield, 92:8 er). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.43-7.40 (1H, m), 7.15-7.11 (1H, m), 7.06-7.03 (1H, m), 7.00-6.97 (1H, m), 6.54 (1H, d, *J* = 16.2 Hz), 6.31-6.27 (1H, m), 4.76-4.75 (2H, m), 2.41 (1H, dd, , *J* = 13.8 ,7.8 Hz), 2.32-2.25 (2H, m), 1.89-1.84 (1H, m), 1.80-1.74 (5H, m), 1.70-1.67 (1H, m), 1.30-1.25 (2H, m), 1.23-1.22 (12H, m), 1.17-1.24 (3H, m). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 160.0 (d, *J* = 253.5 Hz), 154.4, 134.4 (d, *J* = 4.5 Hz), 127.8 (d, *J* = 7.5 Hz), 127.0 (d, *J* = 4.5 Hz), 126.1 (d, *J* = 12.0 Hz), 124.0 (d, *J* = 3.0 Hz), 121.5 (d, *J* = 4.5 Hz), 115.6 (d, *J* = 22.5 Hz), 107.7, 83.5, 44.4, 36.2, 32.7, 28.4 (C-B), 27.01, 27.00, 26.6, 24.9, 24.8. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 32.71. **^{19}F NMR** (470 MHz, $CDCl_3$) δ **-**118.90 – -118.95 (m). **IR** (neat) ν_{max} 3037.7 (w), 2977.7 (m), 2851.5 (w), 1639.1 (w), 1485.9 (w), 1449.7 (w), 1369.9 (m), 1322.6 (m), 1229.0 (w), 1165.5 (s), 967.47 (m), 792.93s) cm^{-1}. **HRMS** (DART+) for $C_{24}H_{35}BFO_2$ $[M+H]^+$ calculated: 385.2714, found: 385.2715. **$[\alpha]^{20}_D$** -10.078 (c = 1.990, $CHCl_3$, *l* =50 mm).

Analysis of Stereochemistry:

The boronic ester was oxidized according to the general procedure. The resulting allylic alcohol was compared to racemic alcohol prepared analogously with $Pd(OAc)_2$ (1 mol%) and *rac*-Bis[(N,N-dimethylamino)(phenyl)methyl]-1,1'-bis(di(3,5 dimethylphenyl)phosphino)ferrocene (1.2 mol%) as the catalyst.

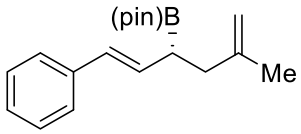
Chiral SFC (Chiralcel OD-H, 35 °C, 3 mL/min, 15% isopropanol, 100 bar) – analysis of (R,E)-5-cyclohexyl-1-(2-fluorophenyl)hexa-1,5-dien-3-ol.





Peak No	% Area	Area	RT (min)
1	49.6035	3830.5548	3.62
2	50.3965	3891.7986	4.65
Total:	100	7722.3534	

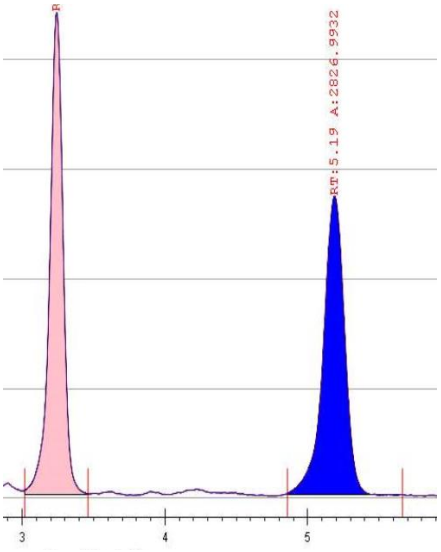
Peak No	% Area	Area	RT (min)
1	91.8457	8768.6539	3.6
2	8.1543	778.4988	4.69
Total:	100	9547.1527	

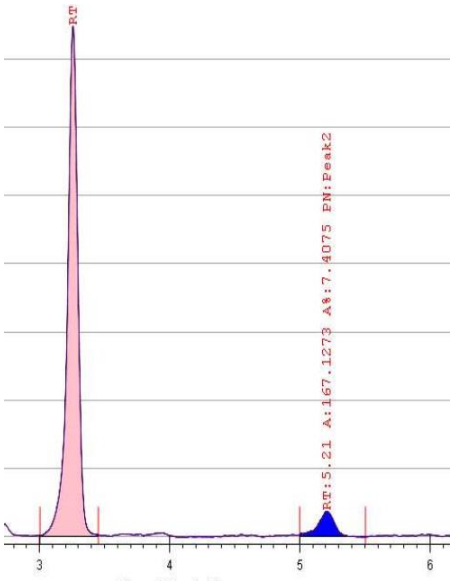


(R,E)-4,4,5,5-Tetramethyl-2-(5-methyl-1-phenylhexa-1,5-dien-3-yl)-1,3,2-dioxaborolane (1.129). The reaction was performed according to the general procedure ***(Method C)*** with *(E)*-4,4,5,5-tetramethyl-2-styryl-1,3,2-dioxaborolane (69.0 mg, 0.30 mmol), 2-bromopropene (0.034 mL, 0.36 mmol), potassium trifluoromethanesulfonate (67.7 mg, 0.36 mmol), palladium (II) acetate (1.35 mg, 0.006 mmol, 2%), (S_p, S_p)-**L1** (6.95 mg, 0.0066 mmol, 2.2%), and was stirred at 60 °C for 16 hours. The crude residue was purified on silica gel (30% CH_2Cl_2 in hexanes) to afford the title compound as a clear colorless oil (52.7 mg, 59% yield, 93:7 er). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.33-7.321 (2H, m), 7.28-7.26 (2H, m), 7.18-7.15 (1H, m), 6.39 (1H, d, *J*=15.6 Hz), 6.20 (1H, dd, *J* = 16.2, 8.4 Hz), 4.74 (1H, s), 4.72 (1H, s), 2.40-2.35 (1H, m), 2.27-2.22 (2H, m), 1.73 (3H, s), 1.23 (6H, s), 1.22 (6H, s). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 145.2, 138.3, 131.4, 129.2, 128.5, 126.7, 126.0, 110.8, 83.5, 38.9, 27.8 (C-B), 24.9, 24.8, 22.8. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 30.3. **IR** (neat) ν_{max} 3079.6 (w), 3024.1

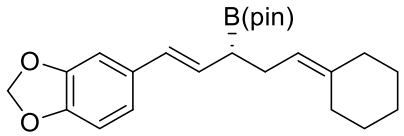
(w), 2977.1 (m), 2928.7 (m), 1647.5 (w), 1447.5 (w), 1369.8 (s), 1357.3 (s), 1322.6 (s). 1270.2 (m), 1140.3 (s), 964.5(s), 887.3 (m), 866.6 (m), 852.5 (m) cm^{-1}. **HRMS** (DART+) for $C_{19}H_{28}BO_2$ $[M+H]^+$ calculated: 299.2182, found: 299.2179. **$[\alpha]^{20}_D$** -7.231 (c = 2.050, $CHCl_3$, *l* =50 mm). ***Analysis of Stereochemistry:*** The boronic ester was oxidized according to the general procedure. The resulting allylic alcohol was compared to racemic alcohol prepared analogously with $Pd(OAc)_2$ (5 mol%) and 1,1′-bis(dicyclohexylphosphino)ferrocene (6 mol%) as the catalyst.

Chiral SFC (Chiralcel OD-H, 35 °C, 3 mL/min, 15% isopropanol, 100 bar) – analysis of (R,E)-5-methyl-1-phenylhexa-1,5-dien-3-ol.





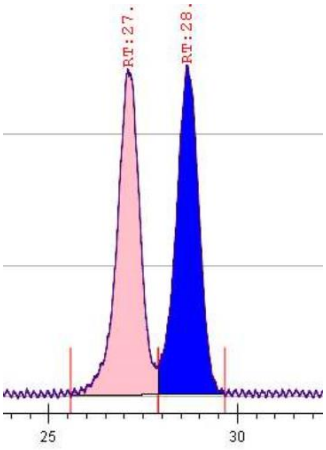
Peak No	% Area	Area	RT (min)	Peak No	% Area	Area	RT (min)
1	50.382	2870.5216	3.24	1	92.5925	2089.0663	3.26
2	49.618	2826.9932	5.19	2	7.4075	167.1273	5.21
Total:	100	5697.5148		Total:	100	2256.1936	

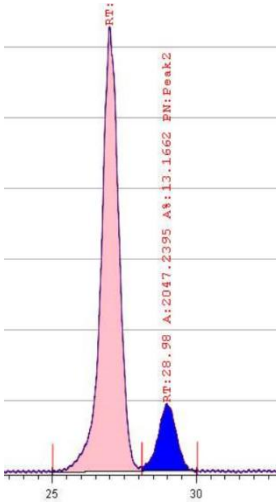


(R,E)-2-(1-(Benzo[d][1,3]dioxol-5-yl)-5-cyclohexylidenepent-1-en-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.132). The reaction was performed according to the general procedure ***(Method B)*** with *(E)*-2-(2-(benzo[d][1,3]dioxol-5-yl)vinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane ***(S-5)*** (82.2 mg, 0.30 mmol), cyclohexylidenemethyl trifluoromethanesulfonate (68.1 mg, 0.36 mmol), palladium (II) acetate (0.67 mg, 0.003 mmol, 1%), (S_p, S_p)-**L1** (3.79 mg, 0.0036 mmol, 1.2%), and was stirred at 60 °C for 16 hours. The crude residue was purified on silica gel (30% CH_2Cl_2 in hexanes) to afford the title compound as a clear colorless oil (67.8 mg, 57% yield, 87:13 er). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.89 (1H, s), 6.75-6.71 (2H, m), 6.28 (1H, d, J = 15.6 Hz), 6.05 (1H, dd, J = 15.6, 8.4 Hz), 5.92 (2H, s), 5.09-5.07 (1H, m), 2.34-2.29 (1H, m), 2.24-2.15 (2H, m), 2.13-2.09 (1H, m), 2.05-2.03 (2H, m), 1.97 (1H, app q, J = 16.2, 7.8 Hz), 1.53-1.44 (6H, m), 1.23 (12H, s). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 148.0, 146.5, 140.3, 133.0, 130.1, 128.7, 120.5, 120.3, 108.3, 105.6, 101.0, 83.4, 37.4, 30.1 (C-B), 29.1, 28.8, 28.7, 27.9, 27.1, 24.9. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 32.7. **IR** (neat) ν_{max} 2977.2 (w), 2925.6 (m), 2853.9 (w), 1603.9 (w), 1489.4 (w), 1371.1 (w), 1353.7 (w), 1323.8 (w), 1165.9 (m), 1039.9 (m), 966.0 (w), 931.4 (w), 864.2 (w), 802.0 (w) cm^{-1}. **HRMS** (DART+) for $C_{24}H_{37}BO_4N$ $[M+NH_4]^+$ calculated: 414.2816, found: 414.2810. **$[\alpha]^{20}_D$** -10.588 (c =1.430 , $CHCl_3$, l =50 mm).

Analysis of Stereochemistry: The boronic ester was oxidized according to the general procedure. The resulting allylic alcohol was compared to racemic alcohol prepared analogously with $Pd(OAc)_2$ (1 mol%) and *rac*-Bis[(N,N-dimethylamino)(phenyl)methyl]-1,1'-bis(di(3,5-dimethylphenyl)phosphino)ferrocene (1.2 mol%) as the catalyst.

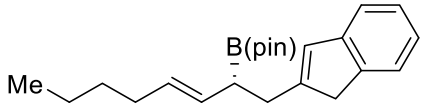
Chiral SFC (Chiralcel OD-H, 35 °C, 3 mL/min, 6% isopropanol, 100 bar) – analysis of (R,E)-1-(benzo[d][1,3]dioxol-5-yl)-5-cyclohexylidenepent-1-en-3-ol.





Peak No	% Area	Area	RT (min)
1	49.9792	2120.4947	27.1
2	50.0208	2122.2567	28.66
Total:	100	4242.7514	

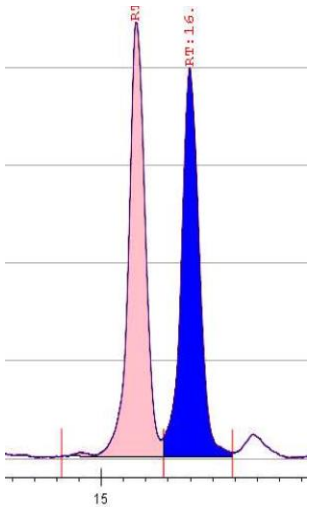
Peak No	% Area	Area	RT (min)
1	86.8338	13502.0201	26.98
2	13.1662	2047.2395	28.98
Total:	100	15549.2596	

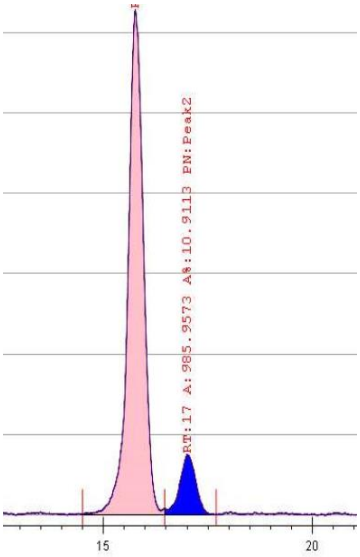


(R,E)-2-(1-(1H-Inden-2-yl)oct-3-en-2-yl)-4,4,5,5-tetrameth-yl-1,3,2-dioxaborolane (1.130). The reaction was performed according to the general procedure ***(Method C)*** with (*E*)-2-(hex-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane ***(1)*** (63.0 mg, 0.30 mmol), 2-bromoindene (70.2 mg, 0.36 mmol), potassium trifluoromethanesulfonate (67.7 mg, 0.36 mmol), palladium (II) acetate (1.35 mg, 0.006 mmol, 2%), (S_p, S_p)-**L1** (6.95 mg, 0.0066 mmol, 2.2%), and was stirred at 60 °C for 16 hours. The crude residue was purified on silica gel (30% CH_2Cl_2 in hexanes) to afford the title compound as a clear colorless oil (65.5 mg, 62% yield, 89:11 er). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.35 (1H, d. *J* = 7.5 Hz), 7.24 (1H, d, *J* = 7.5 Hz), 7.19 (1H, t, *J* = 7.0 Hz), 7.08 (1H, d, *J* = 7.5, 1.5 Hz), 6.51 (1H,

s), 5.48-5.39 (2H, m), 3.35-3.25 (2H, m), 2.73 (1H, dd, *J* = 15.5, 8.5 Hz), 2.59 (1H, dd, *J* = 15.0, 7.5 Hz), 2.16 (1H, app q, *J* = 7.5 Hz), 2.00-1.96 (2H, m), 1.33-1.21 (4H, m), 1.19 (12H, s), 0.84 (3H, t, *J* = 7.0 Hz). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 150.6, 145.8, 143.4, 130.6, 130.1, 126.8, 126.2, 123.6, 123.4, 120.0, 83.3, 41.5, 32.7, 32.6, 31.9, 28.4 (C-B), 24.8, 24.7, 22.1, 14.0. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 33.0. **IR** (neat) ν_{max} 2976.2 (w), 2956.7 (w), 2925.3 (w), 2871.8 (w), 1610.7(w), 1460.8 (s), 1369.4 (m), 1321.7 (m), 1271.6 (s), 1141.5 (w), 11040.0 (s), 967.4 (m), 909.2 (w), 750.2 (w) cm^{-1}. **HRMS** (DART+) for $C_{23}H_{34}BO_2$ $[M+H]^+$ calculated: 353.2652, found: 353.2658. **$[\alpha]^{20}_D$** -14.757 (c = 2.290, $CHCl_3$, *l* =50 mm). ***Analysis of Stereochemistry:*** The boronic ester was oxidized according to the general procedure. The resulting allylic alcohol was compared to racemic alcohol prepared analogously with $Pd(OAc)_2$ (5 mol%) and 1,1′-bis(dicyclohexylphosphino)ferrocene (6 mol%) as the catalyst.

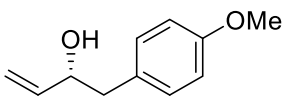
Chiral SFC (Chiralcel OD-H, 35 °C, 3 mL/min, 5% isopropanol, 100 bar) – analysis of (R,E)-1-(benzo[d][1,3]dioxol-5-yl)-5-cyclohexylidenepent-1-en-3-ol.





Peak No	% Area	Area	RT (min)
1	51.2225	11720.1404	15.77
2	48.7775	11160.6943	16.98
Total:	100	22880.8347	

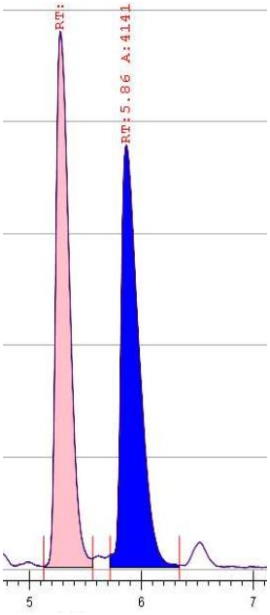
Peak No	% Area	Area	RT (min)
1	89.0887	8050.1743	15.76
2	10.9113	985.9573	17
Total:	100	9036.1316	

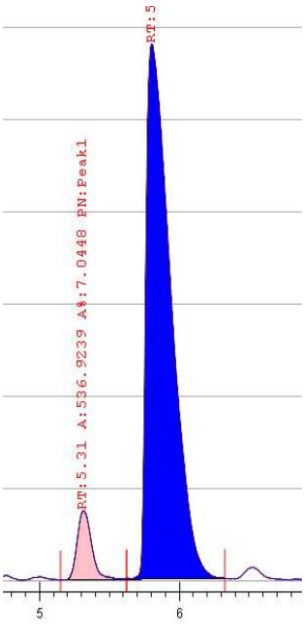


(R)-1-(4-Methoxyphenyl)but-3-en-2-ol (1.137-OH). The reaction was performed according to the general procedure ***(Method B)*** vinyl boronic acid pinacol ester (46.2 mg, 0.30 mmol), 4-methoxyphenyl trifluoromethanesulfonate (92.2 mg, 0.36 mmol), palladium (II) acetate (2.0 mg, 0.009 mmol, 3%), (S_p, S_p)-**L1** (10.1 mg, 0.0096 mmol, 3.2%), and was stirred at 60 ℃ for 5 hours. The crude residue was directly oxidized according to the sodium perborate oxidation procedure. The crude residue was purified on silica gel (10-20% ethyl acetate in hexanes) to afford the title compound as a clear colorless oil (32.5 mg, 61% yield, 93:7 er). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.15 (2H, d, *J* = 8.6 Hz), 6.86 (2H, d, *J* = 8.6 Hz), 5.93 (1H, ddd, *J* = 16.4, 10.5, 5.8 Hz), 5.25 (1H, dt, *J* = 17.2, 1.4 Hz), 5.13 (1H, dt, *J* = 10.4, 1.3 Hz), 4.30 (1H, app q, *J* = 6.0 Hz), 3.80 (3H, s), 2.83 (1H, dd, *J* = 13.7 5.1 Hz), 2.73 (1H, dd, *J* = 13.7, 8.0 Hz), 1.62 (1H, br s). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 158.5, 140.4, 130.7, 129.8, 115.0, 114.1, 73.9, 55.4, 43.1. **IR** (neat) ν_{max} 3387.6 (br), 2932.8 (w), 2915.2 (w), 2835.8 (w), 1611.7 (w), 1511.1 (s), 1244.0 (s), 1177.6 (m), 1118.4 (m), 1034.0 (s), 993.3 (m), 922.1 (w), 817.2 (w) cm^{-1}. **HRMS** (APPI+) for $C_{11}H_{13}O$ $[M+H-H_2O]^+$ calculated: 161.0961, found: 161.0968. **$[\alpha]^{20}_D$** -1.692 (c = 0.985, $CHCl_3$, *l* =50 mm).

Analysis of Stereochemistry: The alcohol was compared to racemic alcohol prepared analogously with $Pd(OAc)_2$ (5 mol%) and 1,1′-bis(dicyclohexylphosphino)ferrocene (6 mol%) as the catalyst.

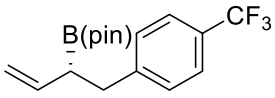
Chiral SFC (Chiralcel AS-H, 35 °C, 3 mL/min, 3% isopropanol, 100 bar) – analysis of (R)-1-(4-methoxyphenyl)but-3-en-2-ol





Peak No	% Area	Area	RT (min)
1	49.4008	4043.7152	5.27
2	50.5992	4141.8187	5.86
Total:	100	8185.5339	

Peak No	% Area	Area	RT (min)
1	7.0448	536.9239	5.31
2	92.9552	7084.6108	5.8
Total:	100	7621.5347	

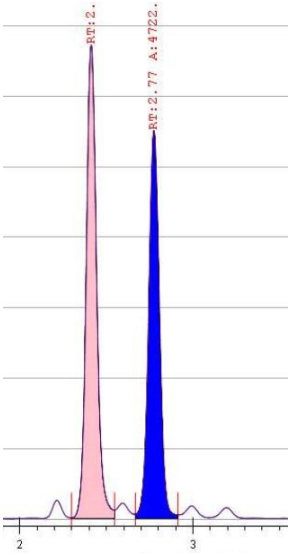


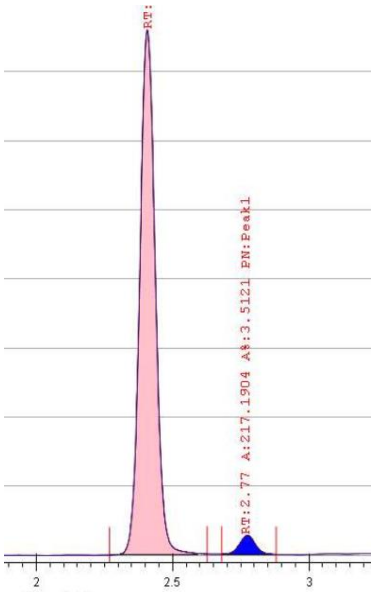
(R)-4,4,5,5-Tetramethyl-2-(1-(4-(trifluoromethyl)phenyl)but-3-en-2-yl)-1,3,2-dioxaborolane (1.135). The reaction was performed according to the general procedure ***(Method B)*** vinyl boronic acid pinacol ester (46.2 mg, 0.30 mmol), 4-(trifluoromethyl)phenyl trifluoromethanesulfonate (105.9 mg, 0.36 mmol), palladium (II) acetate (2.0 mg, 0.009 mmol, 3%), (S_p, S_p)-**L1** (10.1 mg, 0.0096 mmol, 3.2%), and was stirred at 60 °C for 5 hours. The crude residue was purified on silica gel (20-50% CH_2Cl_2 in pentane) to afford the title compound as a clear colorless oil (72.7 mg, 74% yield, 96:4 er). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.50 (2H, d, J = 8.0 Hz), 7.31 (2H, d, J = 8.0 Hz), 5.82 (1H, ddd, J = 17.2, 10.3, 8.3 Hz), 5.02-4.94 (2H, m), 2.94 (1H, dd, J = 13.29 8.2 Hz), 2.82 (1H, dd, J = 13.9, 7.8 Hz), 2.22 (1H, app q, J = 8.1 Hz), 1.17 (6H, s),

1.16 (6H, s). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 146.0, 138.3, 129.3, 128.2 (q, *J* = 32.2 Hz), 125.1 (q, *J* = 11.4 Hz), 124.6 (q, *J* = 268.8 Hz), 114.8, 83.6, 36.3, 31.9 (C-B), 24.8, 24.7. **^{19}F NMR** (470 MHz, $CDCl_3$) δ -62.3. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 32.5. **IR** (neat) ν_{max} 2979.1 (w), 2934.4 (w), 1618.2 (w), 1362.3 (m), 1322.5 (s), 1258.0 (w), 1213.4 (w), 1262.8 (m), 1121.9 (s), 1067.4 (s), 973.3 (w), 907.0 (w). 846.2 (m) cm^{-1}. **HRMS** (DART+) for $C_{17}H_{23}BF_3O_2$ $[M+H]^+$ calculated: 327.1743, found: 327.1754. **$[\alpha]^{20}_D$** -1.541 (c = 1.075, $CHCl_3$, *l* =50 mm).

Analysis of Stereochemistry: The boronic ester was oxidized according to the general procedure. The resulting allylic alcohol was compared to racemic alcohol prepared analogously with $Pd(OAc)_2$ (3 mol%) and *rac*-Bis[(N,N-dimethylamino)(phenyl)methyl]-1,1'-bis(di(3,5-dimethylphenyl)phosphino)ferrocene (3.2 mol%) as the catalyst..

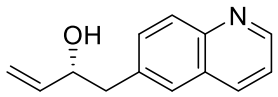
Chiral SFC (Chiralcel AD-H, 35 °C, 3 mL/min, 10% isopropanol, 100 bar) – analysis of (R)-1-(4-(trifluoromethyl)phenyl)but-3-en-2-ol





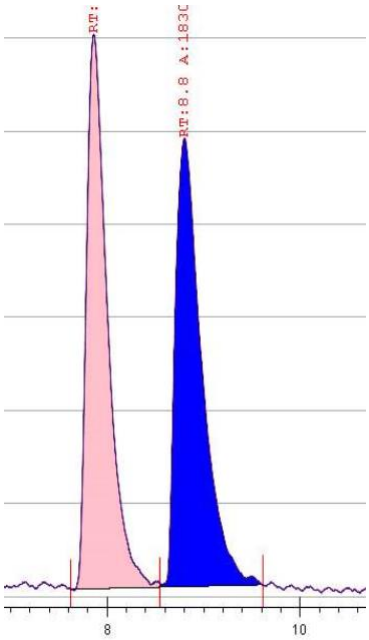
Peak No	% Area	Area	RT (min)
1	53.9736	5538.4164	2.41
2	46.0264	4722.9213	2.77
Total:	100	10261.3377	

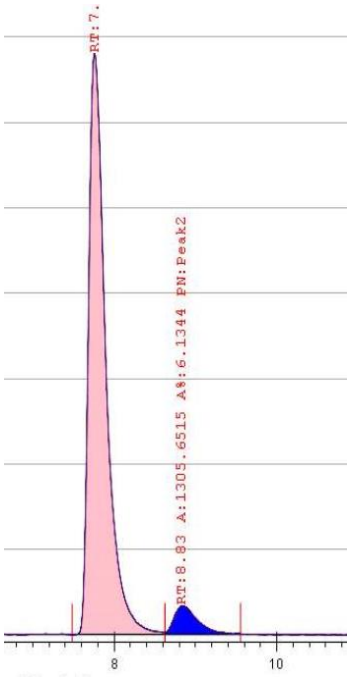
Peak No	% Area	Area	RT (min)
1	96.4879	5966.8512	2.41
2	3.5121	217.1904	2.77
Total:	100	6184.0416	



(R)-1-(4-Methoxyphenyl)but-3-en-2-ol (1.136-OH). The reaction was performed according to the general procedure ***(Method A)*** vinyl boronic acid pinacol ester (46.2 mg, 0.30 mmol), 6-quinolinyl trifluoromethanesulfonate (97.3 mg, 0.36 mmol), palladium (II) acetate (2.0 mg, 0.009 mmol, 3%), (S_p, S_p)-**L1** (10.1 mg, 0.0096 mmol, 3.2%), and was stirred at 60 °C for 5 hours. The crude residue was directly oxidized according to the sodium perborate oxidation procedure. The crude residue was purified on silica gel (20-60% ethyl acetate in hexanes) to afford the title compound as a clear colorless oil (40.9 mg, 68% yield, 94:6 er). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.84-8.81 (1H, m), 8.08 (1H, d, *J* = 8.3), 8.01 (1H, d, *J* = 8.6 Hz), 7.64 (1H, s), 7.60-7.57 (1H, m), 7.35 (1H, dd, *J* = 8.2, 4.2 Hz), 5.98 (1H, ddd, *J* = 16.8, 10.4, 5.8 Hz), 5.27 (1H, dt, *J* = 17.1, 1.4 Hz), 5.15 (1H, dt, *J* = 10.4, 1.3 Hz), 4.47 (1H, dt, *J* = 7.7, 5.8 Hz), 3.05 (1H, dd, *J* = 13.7, 5.2 Hz), 2.99 (1H, dd, *J* = 13.7, 7.9 Hz), 2.52 (1H, br s). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 150.0, 147.3, 140.3, 136.7, 136.0, 131.8, 129.4, 128.3, 128.0, 121.3, 115.4, 73.6, 43.8. **IR** (neat) ν_{max} 3223.1 (br), 3074.4 (w), 2918.6 (w), 2835.0 (w), 1594.2 (w), 1574.7 (w), 1502.6 (s), 1247.0 (w), 1320.3 (w), 1118.4 (m), 1034.4 (m), 994.4 (m), 921.0 (m), 827.5 (s), 798.6 (m), 772.0 (m) cm^{-1}. **HRMS** (APPI+) for $C_{13}H_{14}NO$ $[M+H]^+$ calculated: 200.1075, found: 200.1074. **$[\alpha]^{20}_D$** -1.630 (c = 1.805, $CHCl_3$, *l* =50 mm). ***Analysis of Stereochemistry***: The alcohol was compared to racemic alcohol prepared analogously with $Pd(OAc)_2$ (5 mol%) and 1,1′-bis(dicyclohexylphosphino)ferrocene (6 mol%) as the catalyst.

Chiral SFC (Chiralcel AD-H, 35 °C, 3 mL/min, 15% isopropanol, 100 bar) – analysis of (R)-1-(quinolin-6-yl)but-3-en-2-ol

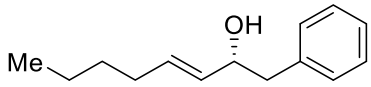




Peak No	% Area	Area	RT (min)
1	49.6291	1803.1808	7.86
2	50.3709	1830.132	8.8
Total:	100	3633.3128	

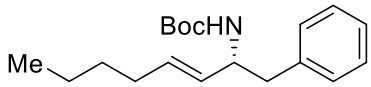
Peak No	% Area	Area	RT (min)
1	93.8656	19978.4281	7.76
2	6.1344	1305.6515	8.83
Total:	100	21284.0796	

1.7.2.8 Procedures and Characterization for Transformations of Allyl Boronates



(R,E)-1-Phenyloct-3-en-2-ol (1.148). Prepared according to the general procedure for the oxidation of allylic boronic esters with *(R,E)*-4,4,5,5-tetramethyl-2-(1-phenyloct-3-en-2-yl)-1,3,2-dioxaborolane (73.8 mg, 0.23 mmol) to afford the title compound as a clear colorless oil (45.7 mg, 96%, 92:8 er). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.33-7.29 (2H, m), 7.25-7.21 (3H, m), 5.67-5.61 (1H, m), 5.55-5.50 (1H, m), 4.32-4.28 (1H, m), 2.85 (1H, dd, *J* = 13.8, 5.4 Hz), 2.79 (1H, dd, *J* = 13.2, 7.8 Hz), 2.07-1.98 (2H, m), 1.58 (1H, br s), 1.38-1.25 (4H, m), 0.89 (3H, t, *J* = 7.2 Hz). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 138.2, 132.6, 132.0, 129.7, 128.5, 126.6, 73.8, 44.3, 32.0, 31.4, 22.3, 14.1. **IR** (neat) ν_{max} 3380.2 (br), 3028.1 (w), 2955.9 (m), 2924.7 (m), 2856.4 (m), 1495.0 (w), 1454.2 (w), 1093.1 (w), 1029.5 (s), 968.5 (s), 744.9 (s), 698.6 (s) cm^{-1}. **HRMS** (DART+) for $C_{14}H_{19}$ $[M+H-H_2O]^+$ calculated: 187.1487, found: 187.1488. **$[\alpha]^{20}_D$** -2.573 (c = 1.055, $CHCl_3$, *l* =50 mm).

SFC traces and stereochemistry determination shown above with compound **2**.



tert-Butyl (R,E)-(1-phenyloct-3-en-2-yl)carbamate (1.145). Prepared according to the procedure reported in the literature[90] with *(R,E)*-4,4,5,5-tetramethyl-2-(1-phenyloct-3-en-2-yl)-1,3,2-dioxaborolane ***(37)*** (103.0 mg, 0.33 mmol, 1.0 equiv.), methoxyamine (0.282 mL, 3.51 M in THF, 0.99 mmol, 3 equiv.), *n*butyllithium (0.374 mL, 2.65 M in hexanes, 0.99 mmol, 3 equiv.) and

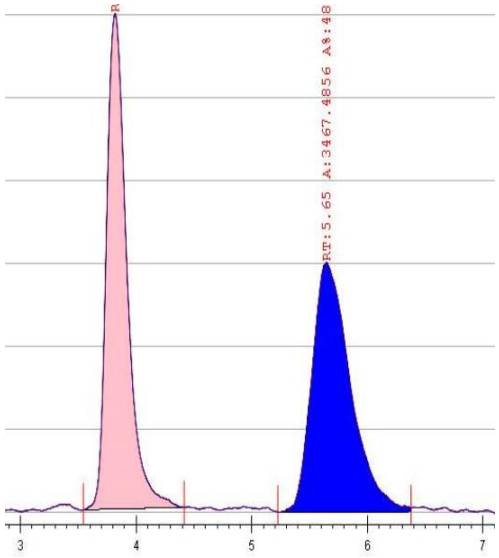
(90) Mlynarski, S. N.; Karns, A. S.; Morken, J. P. *J. Am. Chem. Soc.* **2012**, *134*, 16449.

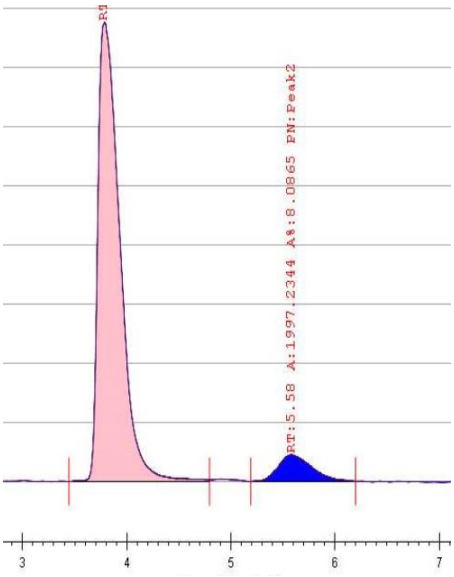
THF (2.5 mL), followed by di-*tert*-butyl dicarbonate (0.244 mL, 1.06 mmol, 3.2 equiv.). The crude residue was purified with the Biotage Isolera One in 2-10% ethyl acetate in hexanes to afford a white solid (0.0862 g, 86% yield, 92:8 er). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.30-7.26 (2H, m), 7.22-7.18 (1H, m), 7.18-7.14 (2H, m), 5.48 (1H, dt, *J* = 15.0, 6.6 Hz), 5.35 (1H, dd, *J* = 15.6, 6.0 Hz), 4.50-4.26 (2H, br m), 2.87-2.81 (1H, br m), 2.79 (1H, dd, *J* = 13.2, 7.2 Hz), 1.98 (2H, app q, *J* = 6.6 Hz), 1.41 (9H, s), 1.32-1.20 (4H, m), 0.86 (3H, t, *J* = 7.2 Hz). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 155.3, 137.9, 131.8, 129.8, 129.7, 128.3, 126.4, 79.3, 53.3, 42.1, 32.0, 31.4, 28.5, 22.2, 14.0. **IR** (neat) ν_{max} 3344.0 (br), 2957.9 (w), 2926.2 (m), 2857.0 (m), 1699.7 (s), 1495.1 (m), 1365.3 (m), 1246.1 (m), 1168.7 (s), 1013.0 (w), 969.0 (w), 699.5 (m) cm^{-1}. **HRMS** (DART+) for $C_{19}H_{30}NO_2$ $[M+H]^+$ calculated: 304.2277, found: 304.2287. **$[\alpha]^{20}_D$** -5.129 (c = 0.890, $CHCl_3$, *l* =50 mm).

Analysis of Stereochemistry:

The amine was compared to racemic amine prepared analogously with $Pd(OAc)_2$ (5 mol%) and 1,1′-bis(dicyclohexylphosphino)ferrocene (6 mol%) as the catalyst. Absolute stereochemistry determination shown below.

Chiral SFC (Chiralcel AS-H, 35 °C, 3 mL/min, 2% isopropanol, 100 bar) – analysis of tert-butyl (R,E)-(1-phenyloct-3-en-2-yl)carbamate.

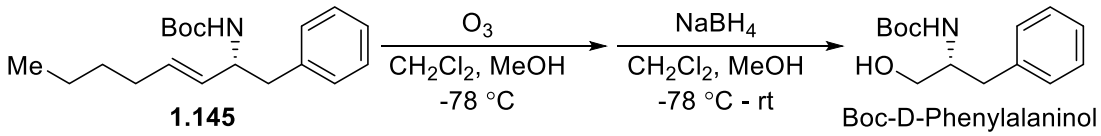




Peak No	% Area	Area	RT (min)
1	51.3155	3654.8706	3.82
2	48.6845	3467.4856	5.65
Total:	100	7122.3562	

Peak No	% Area	Area	RT (min)
1	91.9135	22701.2912	3.78
2	8.0865	1997.2344	5.58
Total:	100	24698.5256	

Absolute stereochemistry was determined by ozonolysis/reduction to Boc-D-Phenylalaninol and comparison of the optical rotation to the reported value.



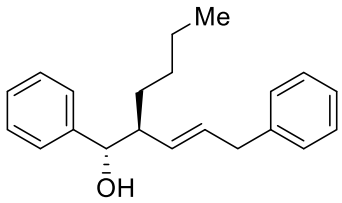
To a 10-dram vial equipped with a magnetic was added *tert*-butyl (*R,E*)-(1-phenyloct-3-en-2-yl)carbamate ***(41)*** (73.0 mg, 0.240 mmol, 1.0 equiv), CH_2Cl_2 (4.0 mL), and methanol (4.0 mL). The solution was cooled to -78 °C. While open to the atmosphere, O_3 was

bubbled through the solution for approximately 1 min until the solution turned a pale blue color. Sodium borohydride (272 mg, 7.2 mmol, 30 equiv.) was then added as a solid. The solution was left to stir for 5 min at -78 °C then was allowed to warm to room temperature and left to stir for 3 hours open to the atmosphere. H_2O was added (6 mL) and the solution was transferred to a separatory funnel with ethyl acetate. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3x 10 mL). Combined organic dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was then filtered through a small pad of silica gel with ethyl acetate to afford Boc-D-phenylalaninol as a white solid (60.0 mg, quantitative yield). All spectral data was in accord with commercially available material.

$[\alpha]^{20}_D$ +19.639 (92:8 er, c = 1.235, $CHCl_3$, *l* =50 mm).

Reported for Boc-*D*-phenylalaninol: **$[\alpha]^{21}_D$**: +21.6 (98% *ee*, c = 1.0, $CHCl_3$).[91]

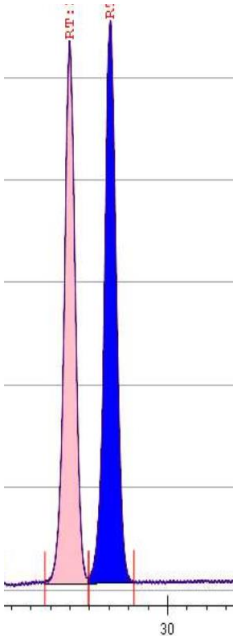
(91) Maji, B.; Yamamoto, H. *Angew. Chem. Int. Ed.* **2014**, *53*, 8714.

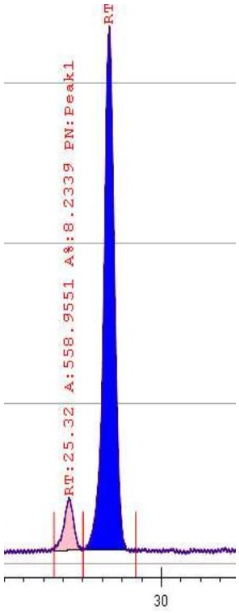


(1S,2S)-1-Phenyl-2-((E)-3-phenylprop-1-en-1-yl)hexan-1-ol (1.141). Prepared according to the procedure reported in the literature[92] with *(R,E)*-4,4,5,5-tetramethyl-2-(1-phenyloct-3-en-2-yl)-1,3,2-dioxaboro lane ***(1.89)*** (70.0 mg, 0.22 mmol, 1.0 equiv.) to afford the title compound as clear colorless oil (57.9 mg, 88% yield, 92:8 er, 93:7 dr). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.37-7.27 (7H, m), 7.22-7.20 (1H, m), 7.17-7.16 (2H, m), 5.76-5.71 (1H, m), 5.39-5.35 (1H, m), 4.41 (1H, d, *J* = 7.2 Hz), 3.43 (2H, d, *J* = 7.2 Hz), 2.32-2.27 (1H, m), 2.18 (1H, s), 1.34-1.12 (6H, m), 0.81 (3H, t, *J* = 6.6 Hz). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 142.8, 140.6, 133.7, 132.3, 128.59, 128.57, 128.3, 127.6, 127.1, 126.2, 77.1, 51.7, 39.3, 30.7, 29.70, 22.6, 14.1. **IR** (neat) ν_{max} 3433.0 (br), 3083.7 (w), 3061.7 (w), 3027.2 (m), 2955.4 (m), 2857.4 (w) 1602.9 (w), 1493.7 (m), 1453.0 (m), 1029.4 (w), 973.7 (w),m 745.4 (m), 698.7 (s) cm^{-1}. **HRMS** (DART+) for $C_{21}H_{25}$ $[M+H-H_2O]^+$ for calculated: 277.1956 ,found: 277.1968. **$[\alpha]^{20}_D$** -38.066 (c =1.630 , $CHCl_3$, *l* =50 mm). The allylation product was compared to racemic product prepared analogously with $Pd(OAc)_2$ (5 mol%) and 1,1′-bis(dicyclohexylphosphino)ferrocene (6 mol%) as the catalyst.

Chiral SFC (Chiralcel AD-H, 35 °C, 3 mL/min, 5% isopropanol, 100 bar) – analysis of (1S,2S)-1-phenyl-2-((E)-3-phenylprop-1-en-1-yl)hexan-1-ol

(92) Chen, J. L.-Y.; Scott, H. K.; Hesse, M. J.; Willis, C. L.; Aggarwal, V. K.. *J. Am. Chem. Soc.* **2013**, *135*, 5316.



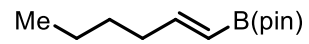


Peak No	% Area	Area	RT (min)
1	47.304	10483.4877	24.97
2	52.696	11678.4715	27.06
Total:	100	22161.9592	

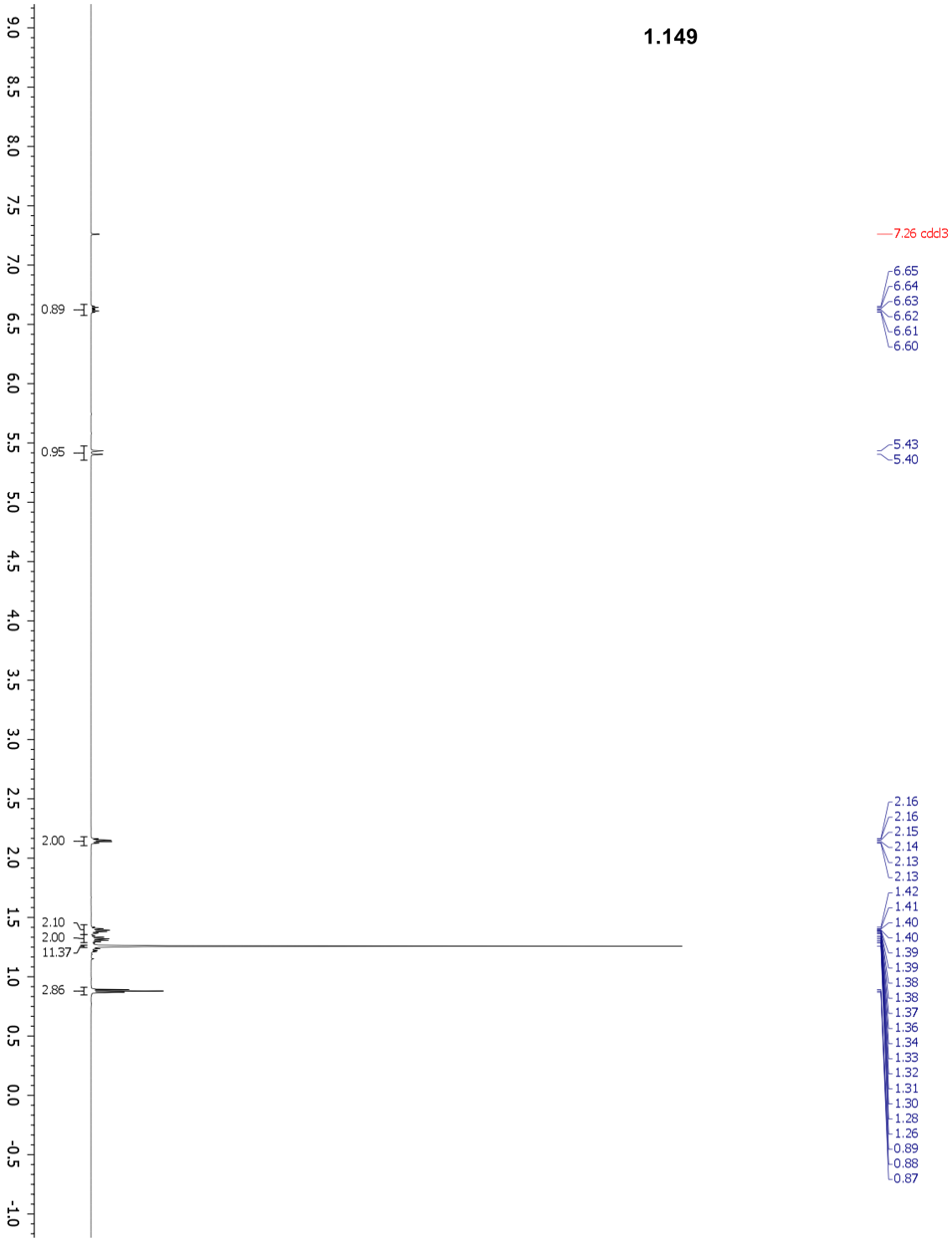
Peak No	% Area	Area	RT (min)
1	8.2339	558.9551	25.32
2	91.7661	6229.4965	27.36
Total:	100	6788.4516	

1.7.3 NMR Spectra

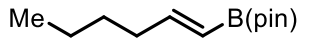
^{1}H NMR ($CDCl_3$, 600 MHz)



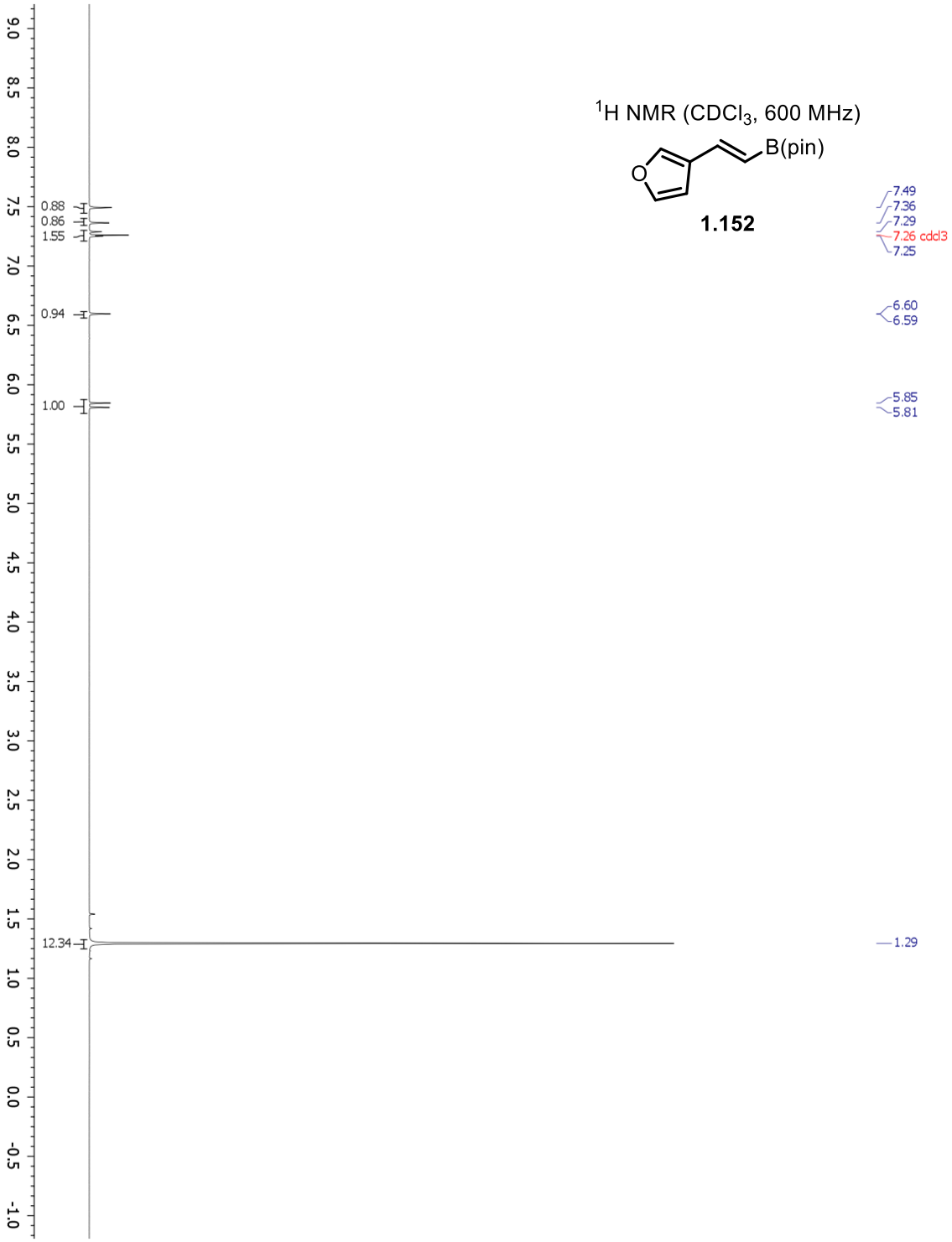
1.149

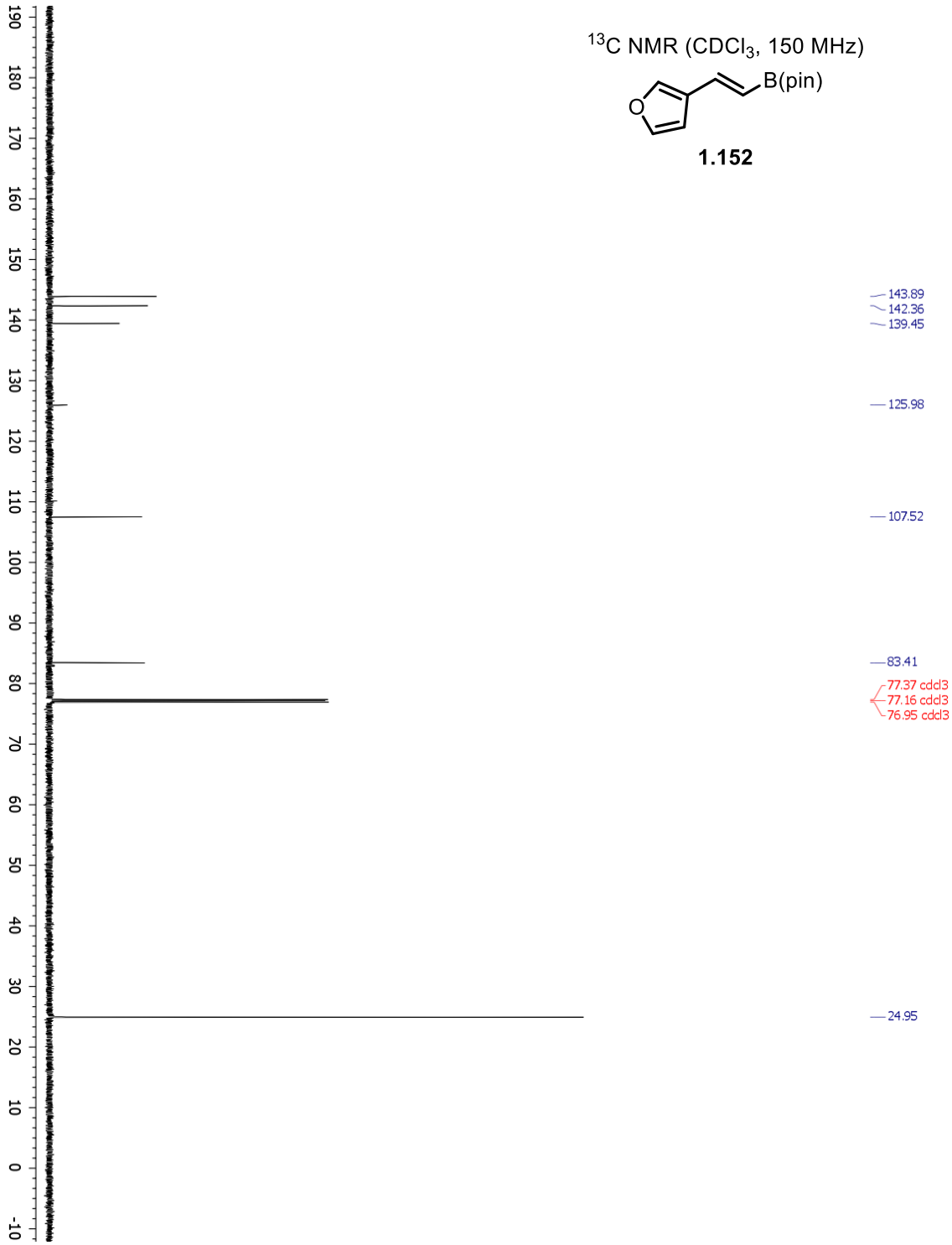


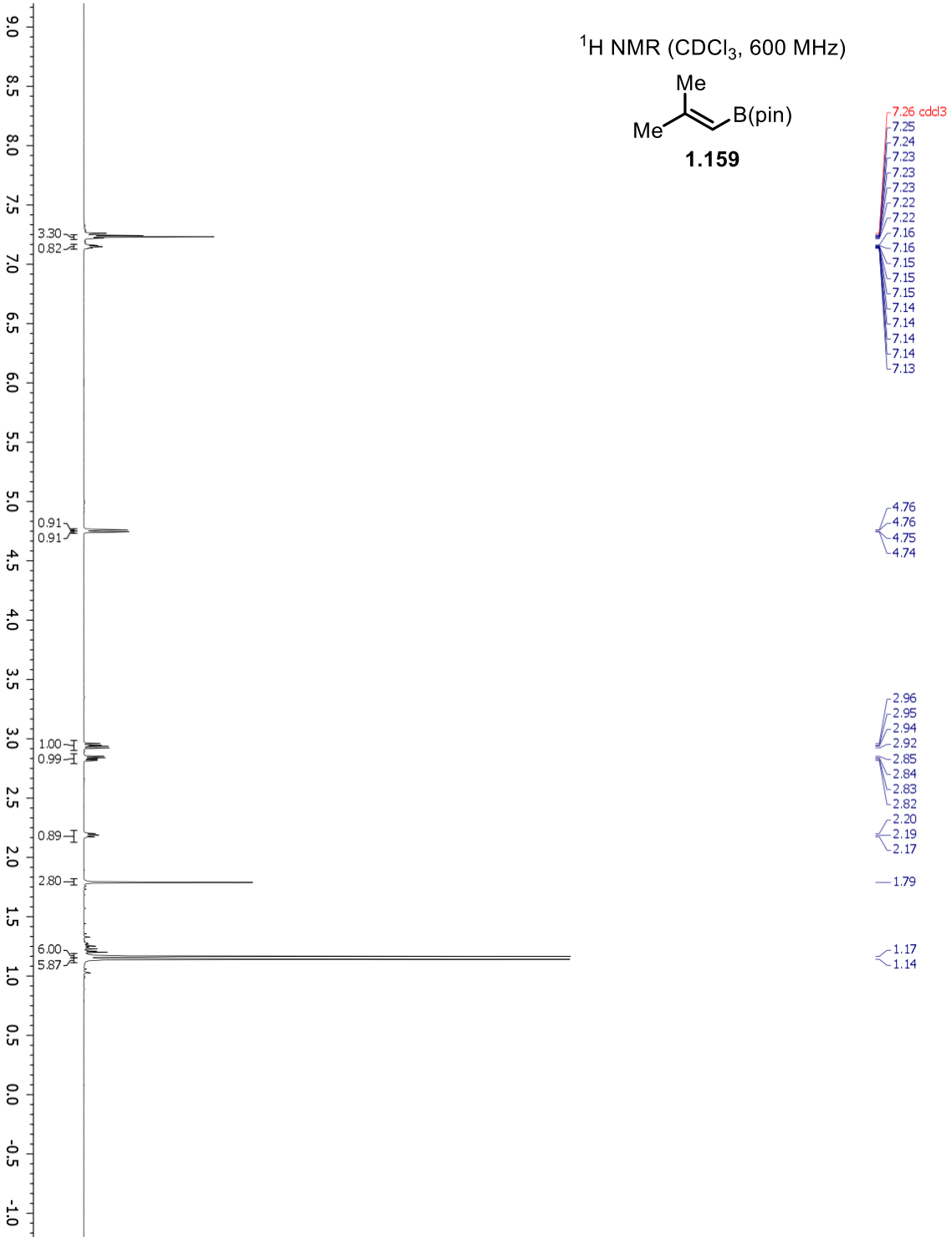
^{13}C NMR ($CDCl_3$, 150 MHz)

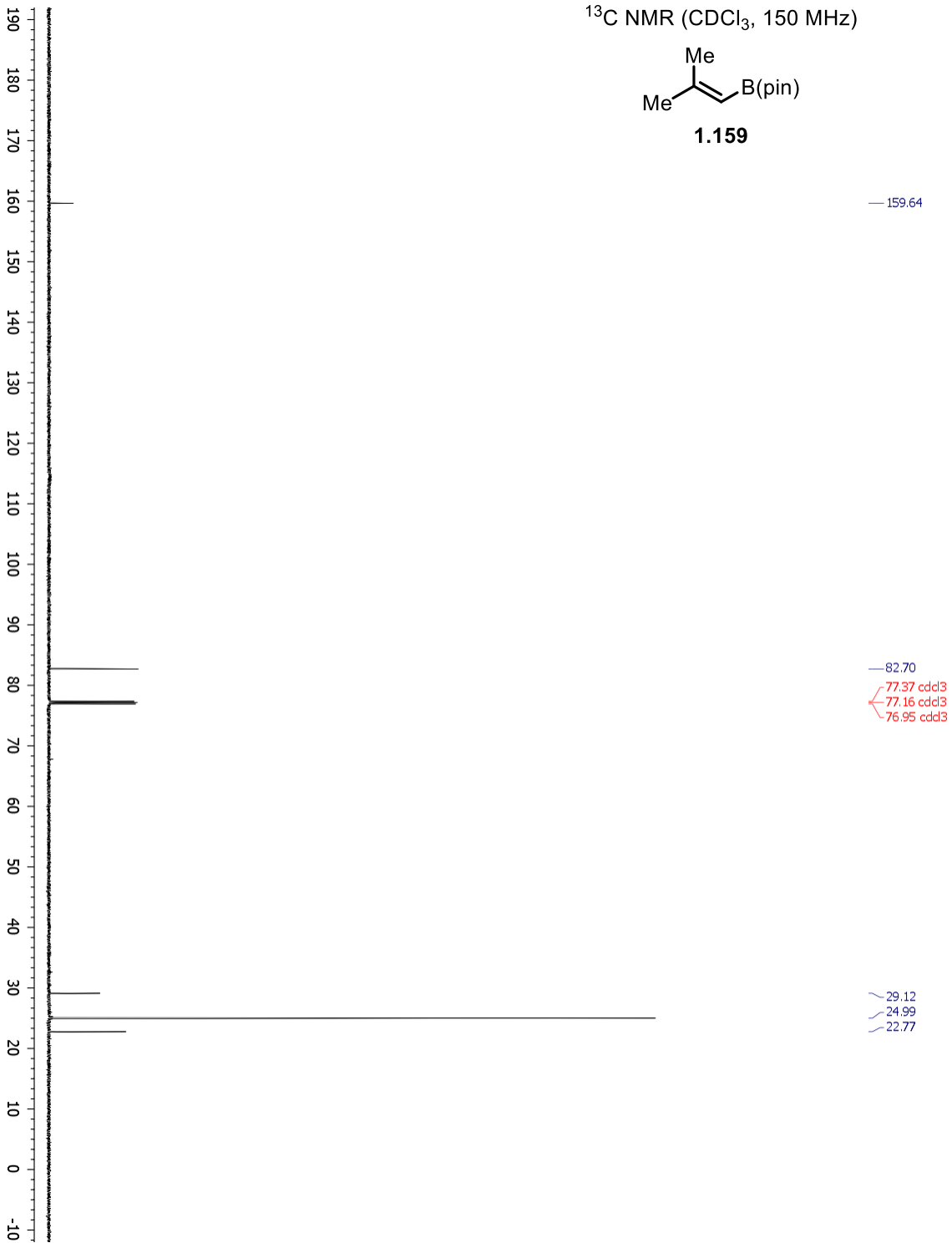


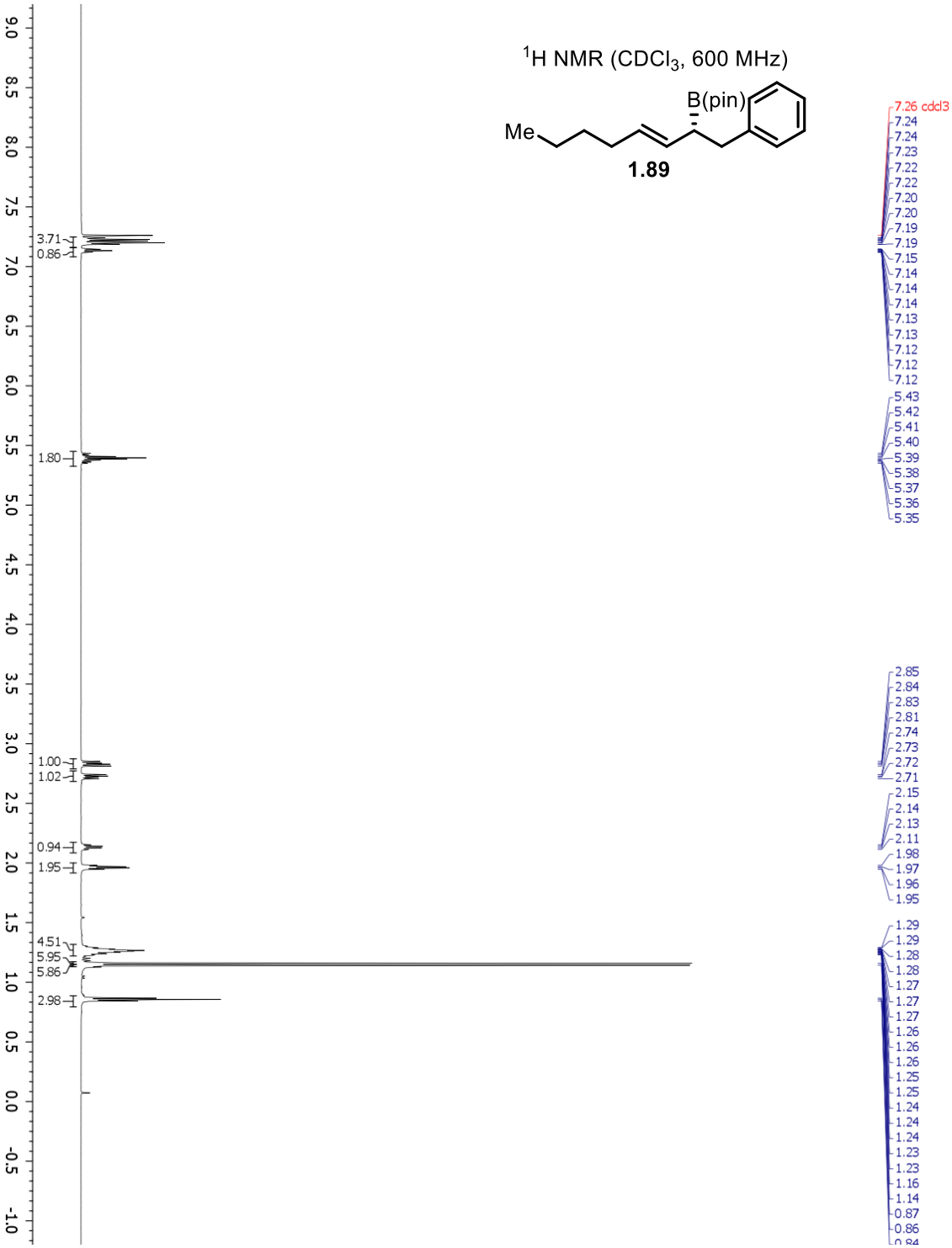
1.149

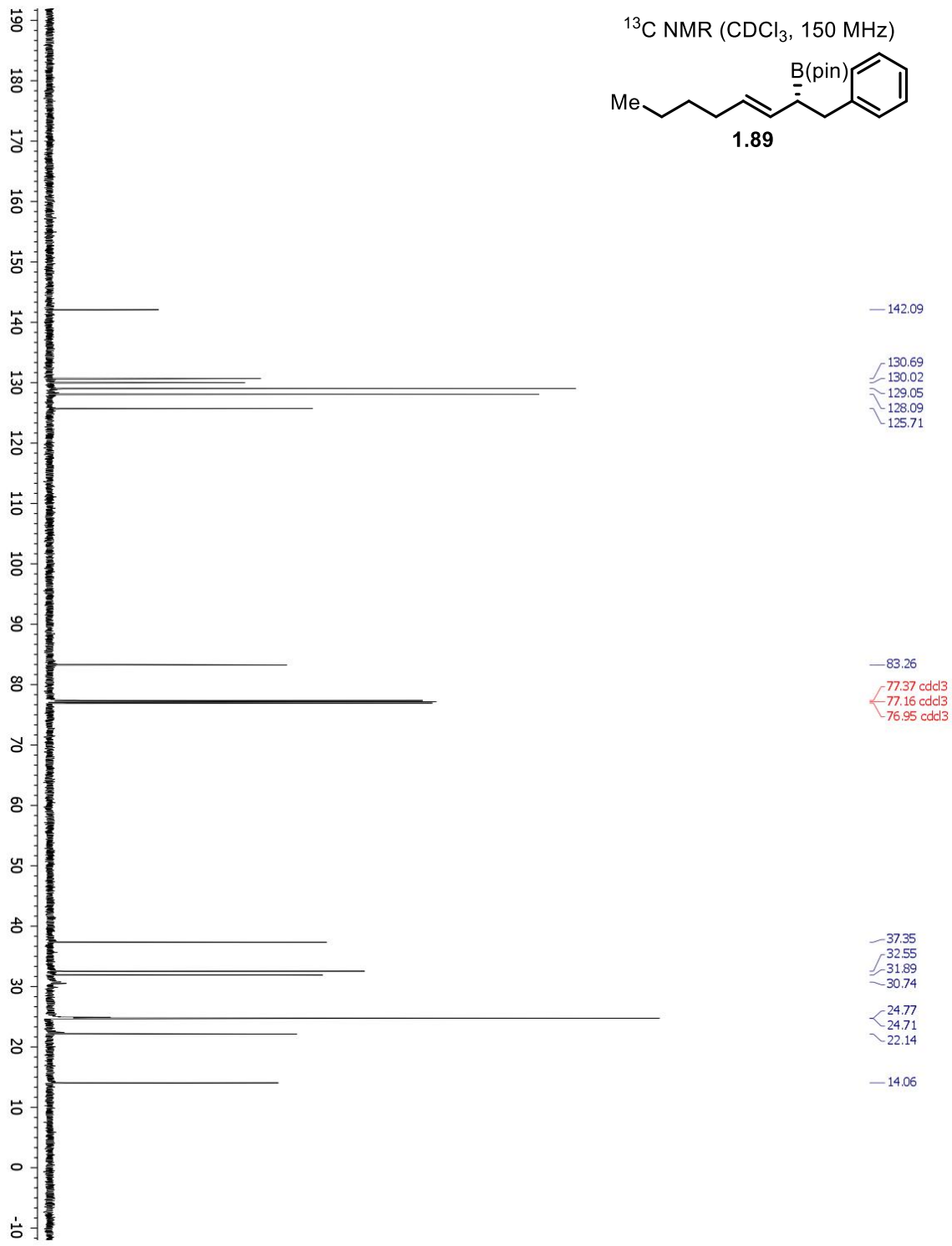

^{1}H NMR ($CDCl_3$, 600 MHz)
B(pin)
O
1.152
0.88
0.86
1.55
0.94
1.00
12.34
7.49
7.36
7.29
7.26 cdcl3
7.25
6.60
6.59
5.85
5.81
1.29

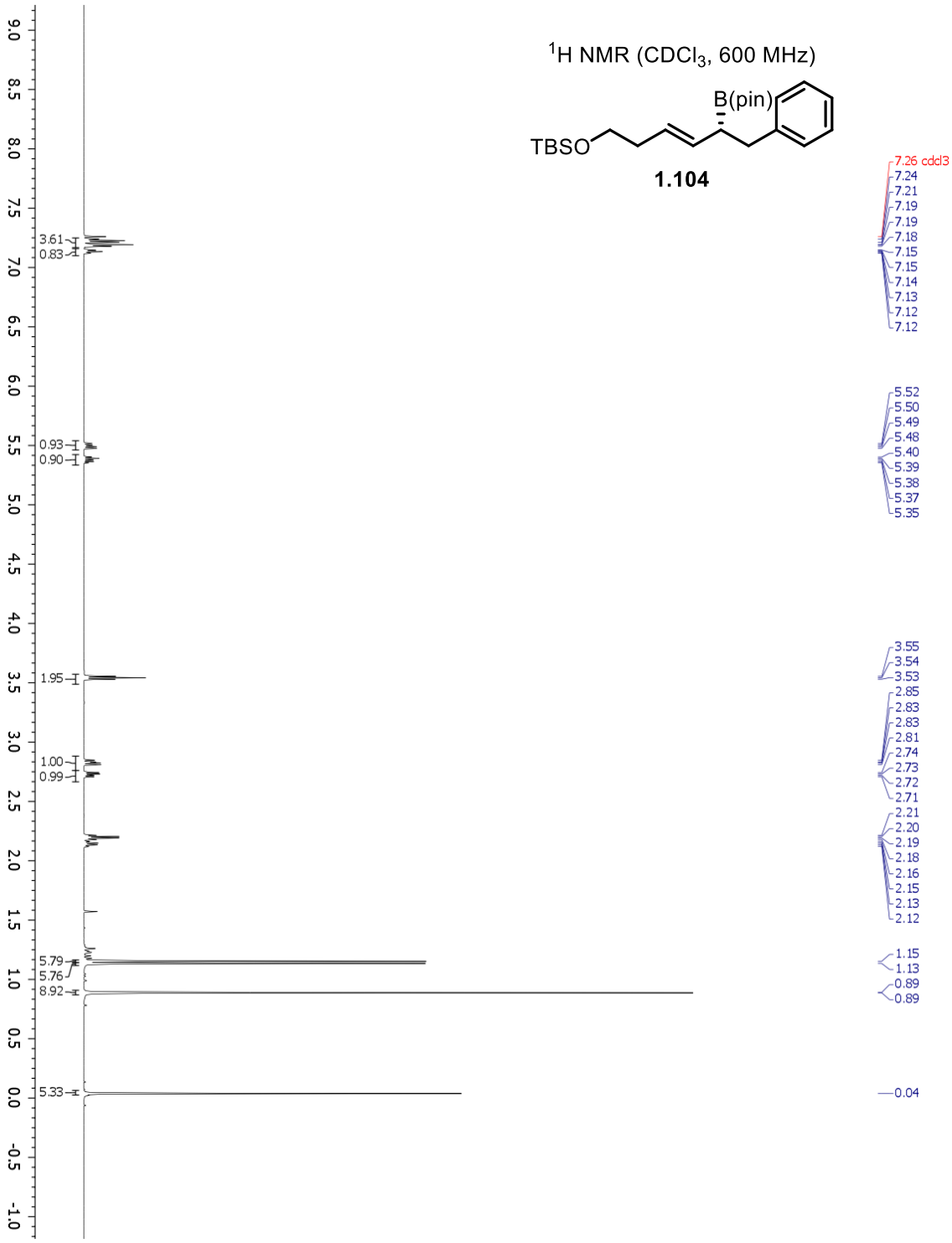

^{13}C NMR ($CDCl_3$, 150 MHz)
B(pin)
O
1.152
143.89
142.36
139.45
125.98
107.52
83.41
77.37 cdcl3
77.16 cdcl3
76.95 cdcl3
24.95

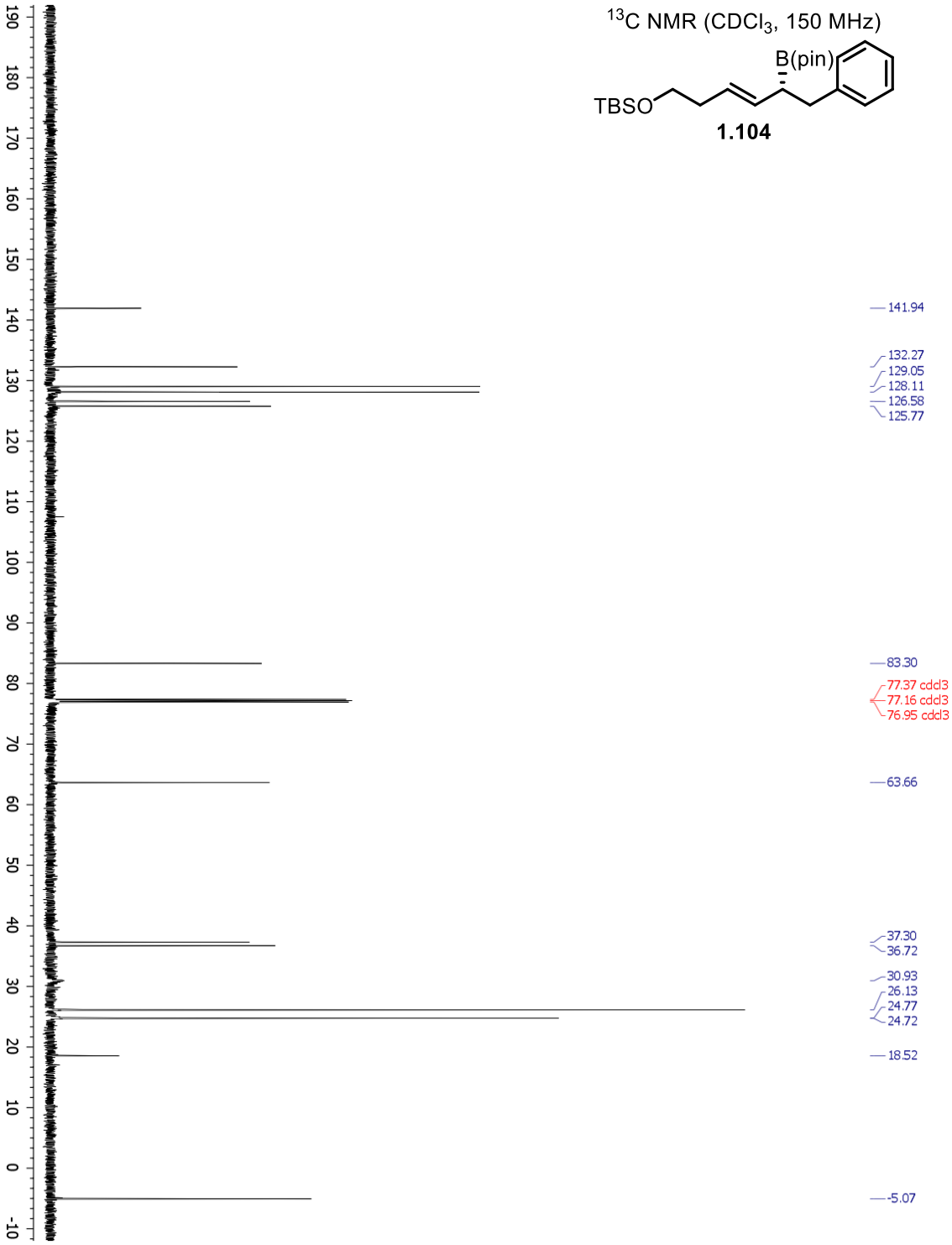

^{1}H NMR ($CDCl_3$, 600 MHz)
Me
Me
B(pin)
1.159
7.26 cdcl3
7.25
7.24
7.23
7.23
7.23
7.23
7.22
7.22
7.16
7.16
7.15
7.15
7.15
7.14
7.14
7.14
7.14
7.13
4.76
4.76
4.75
4.74
2.96
2.95
2.94
2.92
2.85
2.84
2.83
2.82
2.20
2.19
2.17
1.79
1.17
1.14
3.30
0.82
0.91
0.91
1.00
0.99
0.89
2.80
6.00
5.87

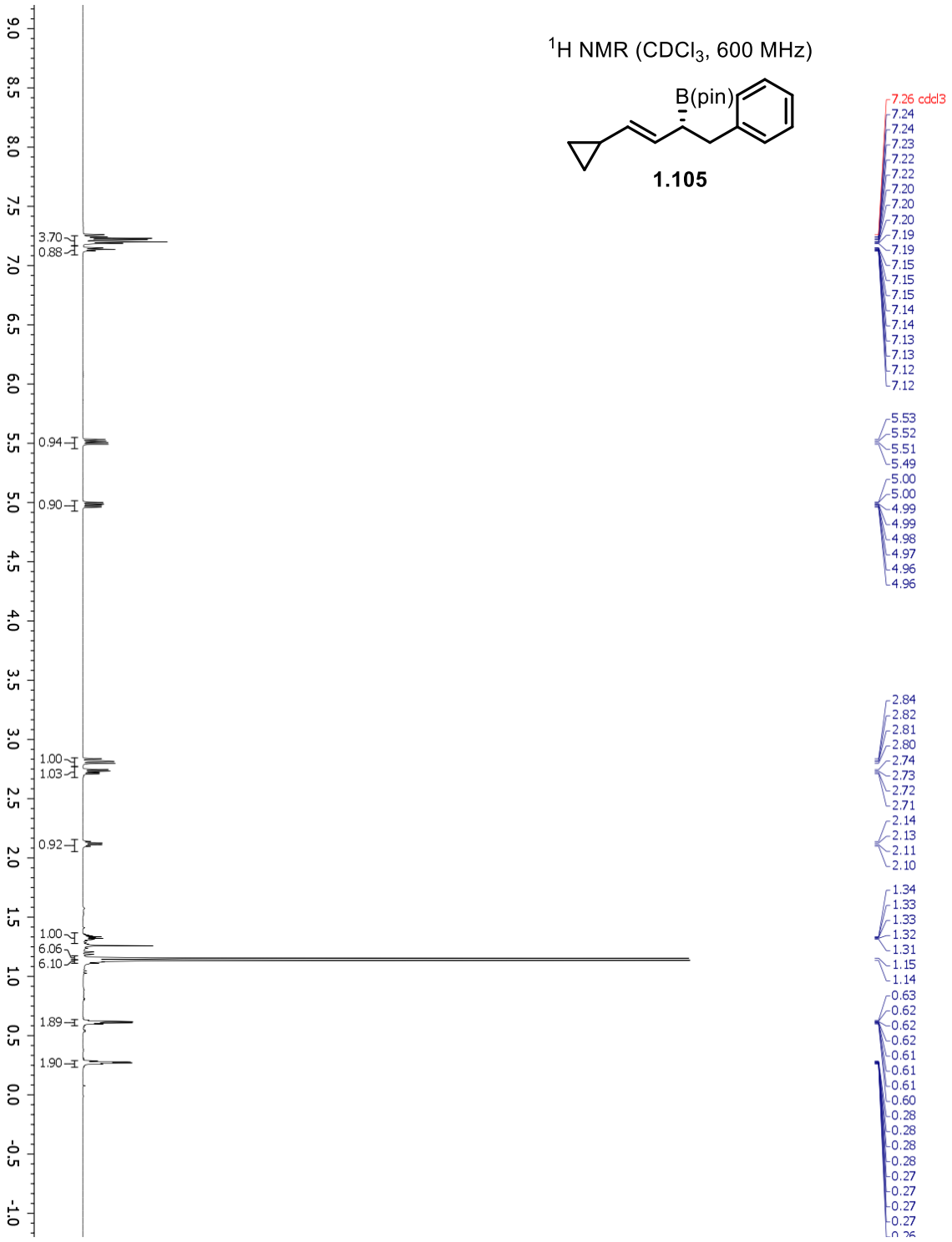

^{13}C NMR ($CDCl_3$, 150 MHz)
Me
Me
B(pin)
1.159
159.64
82.70
77.37 cdcl3
77.16 cdcl3
76.95 cdcl3
29.12
24.99
22.77
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

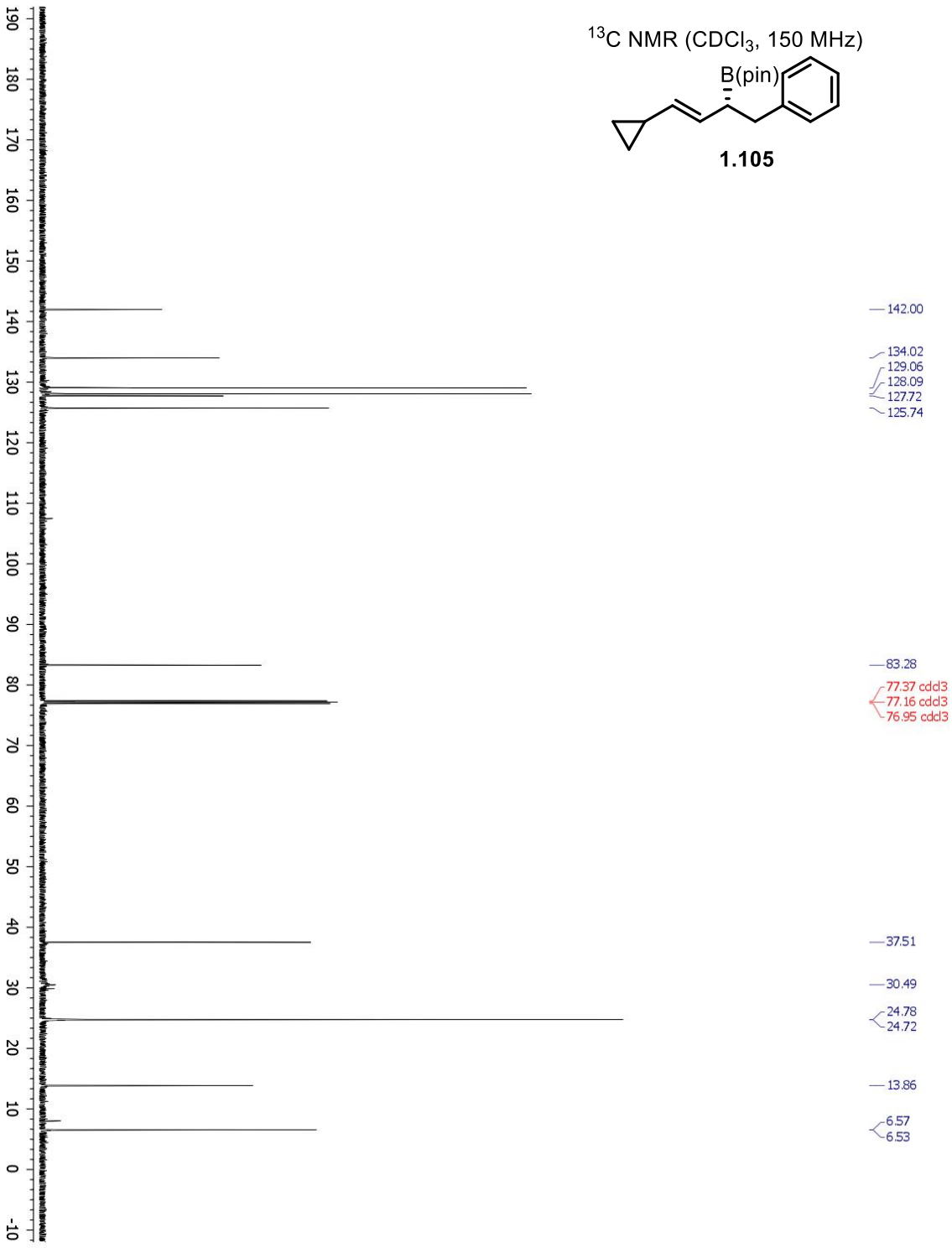

^{1}H NMR ($CDCl_3$, 600 MHz)
B(pin)
Me
1.89
7.26 cdcl3
3.71
0.86
1.80
1.00
1.02
0.94
1.95
4.51
5.95
5.86
2.98

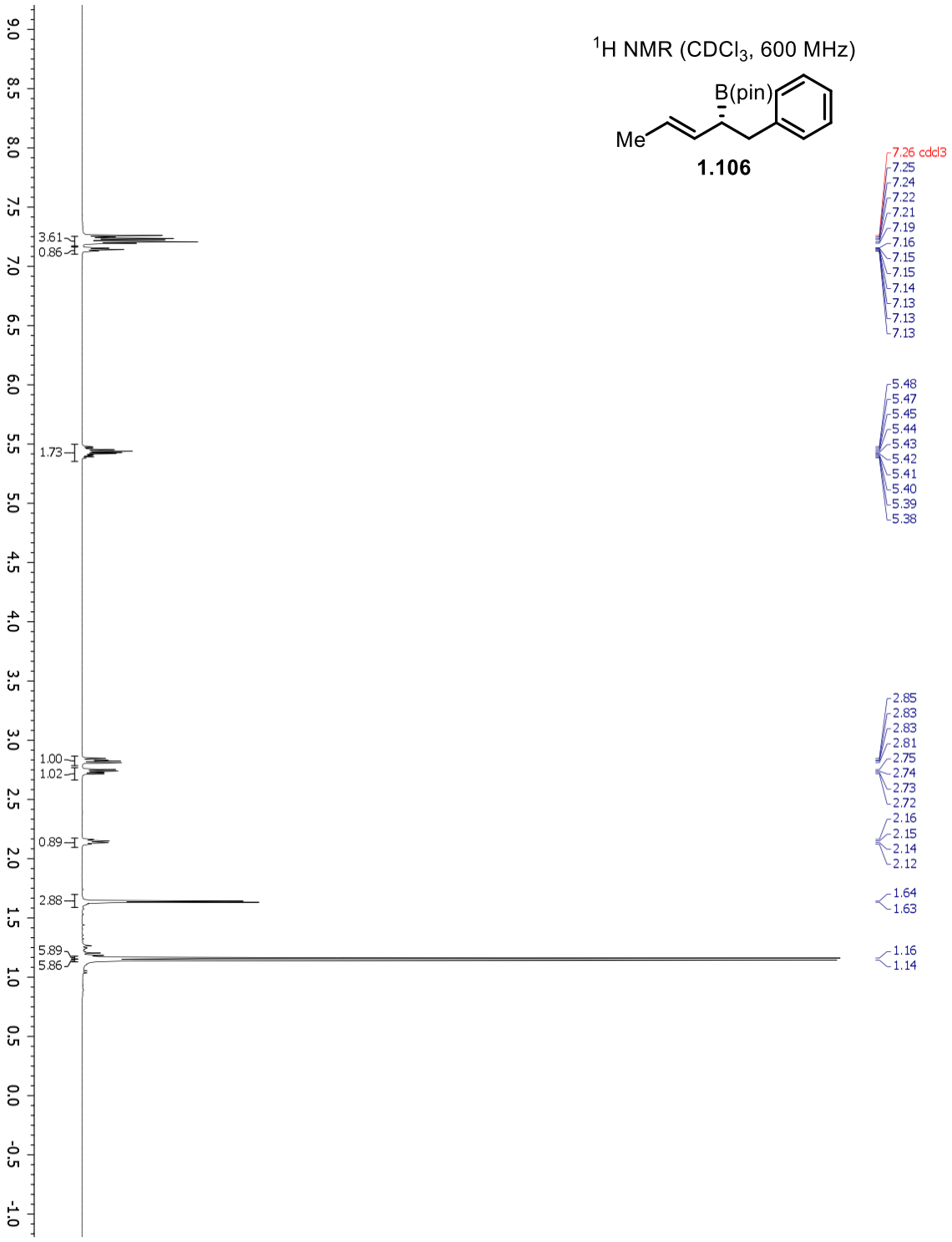

^{13}C NMR ($CDCl_3$, 150 MHz)
B(pin)
Me
1.89
142.09
130.69
130.02
129.05
128.09
125.71
83.26
77.37 cdcl3
77.16 cdcl3
76.95 cdcl3
37.35
32.55
31.89
30.74
24.77
24.71
22.14
14.06

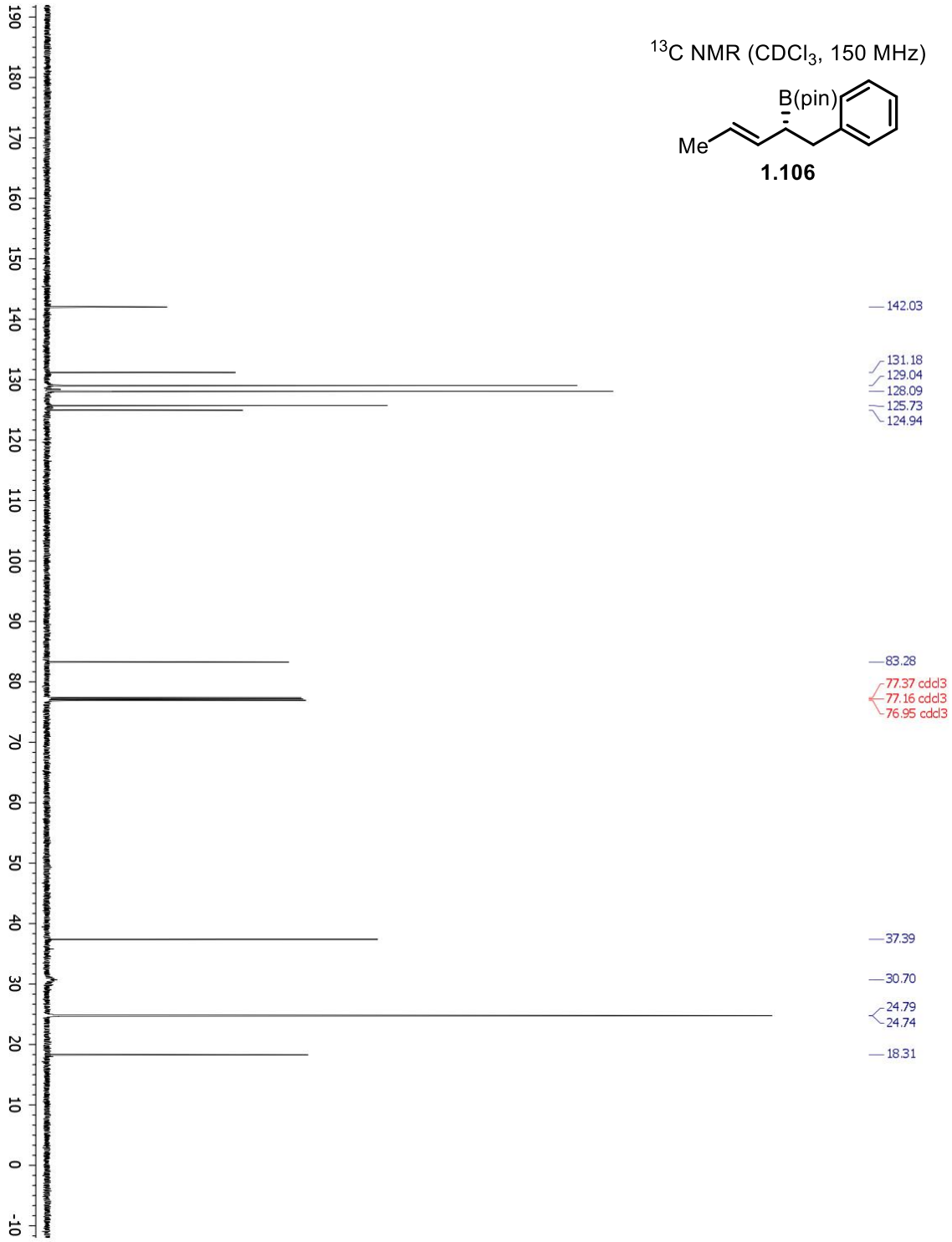

^{1}H NMR ($CDCl_3$, 600 MHz)
B(pin)
TBSO
1.104
7.26 cdcl3
7.24
7.21
7.19
7.19
7.18
7.15
7.15
7.14
7.13
7.12
7.12
5.52
5.50
5.49
5.48
5.40
5.39
5.38
5.37
5.35
3.55
3.54
3.53
2.85
2.83
2.83
2.81
2.74
2.73
2.72
2.71
2.21
2.20
2.19
2.18
2.16
2.15
2.13
2.12
1.15
1.13
0.89
0.89
0.04
3.61
0.83
0.93
0.90
1.95
1.00
0.99
5.79
5.76
8.92
5.33

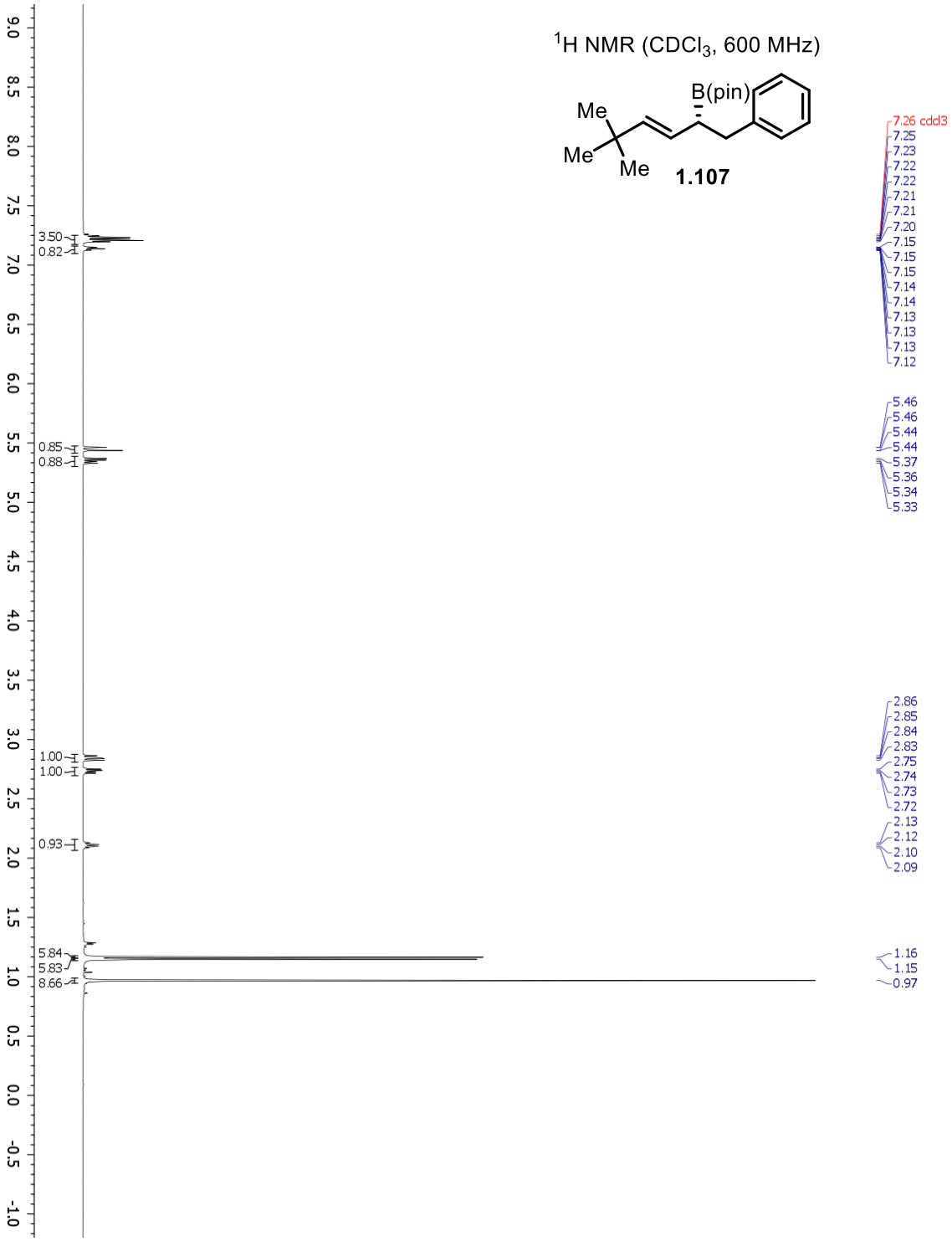

^{13}C NMR ($CDCl_3$, 150 MHz)
B(pin)
TBSO
1.104
141.94
132.27
129.05
128.11
126.58
125.77
83.30
77.37 cdcl3
77.16 cdcl3
76.95 cdcl3
63.66
37.30
36.72
30.93
26.13
24.77
24.72
18.52
-5.07

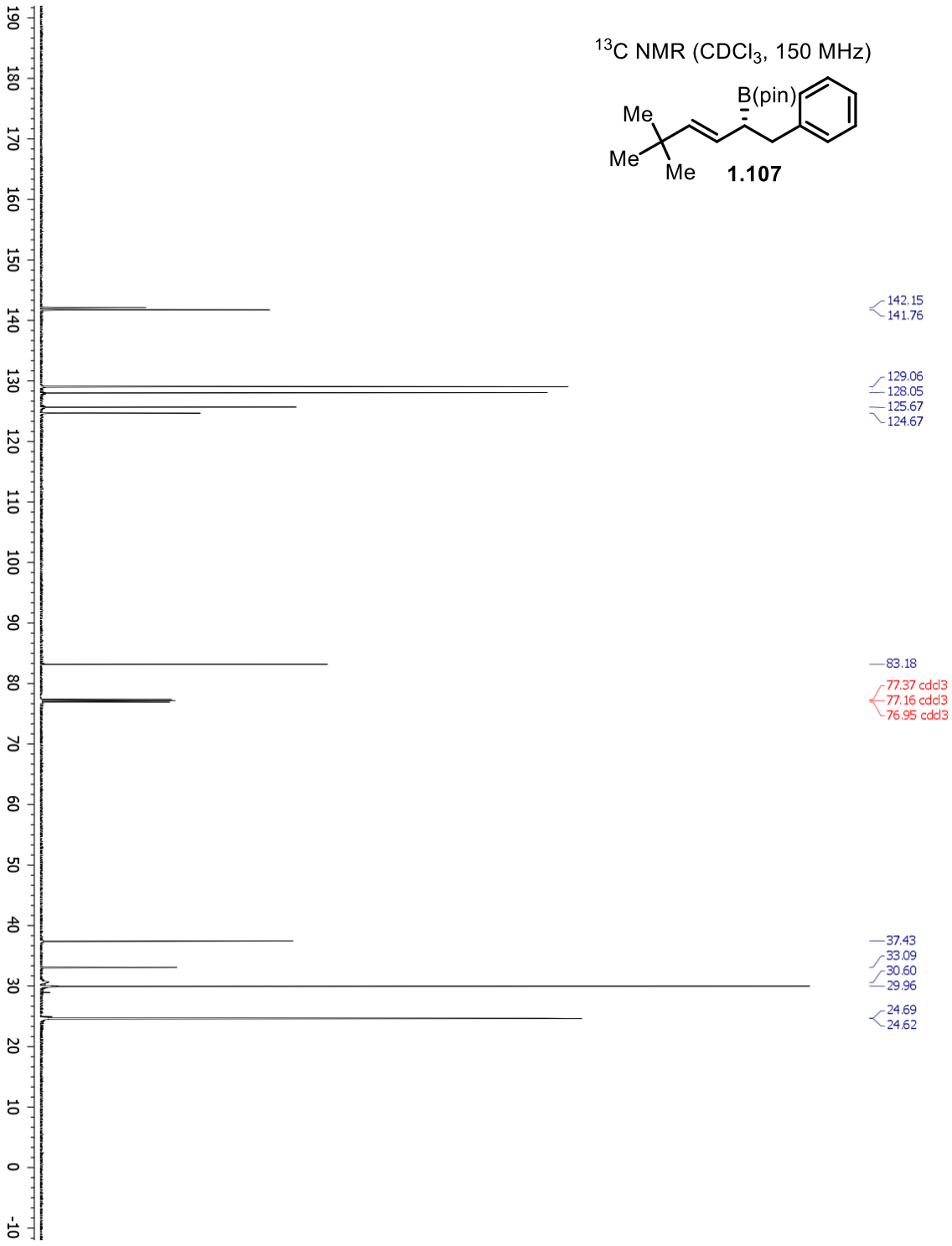

^{1}H NMR ($CDCl_3$, 600 MHz)
B(pin)
1.105
3.70
0.88
0.94
0.90
1.00
1.03
0.92
1.00
6.06
6.10
1.89
1.90
7.26 cdcl3
7.24
7.24
7.23
7.22
7.22
7.20
7.20
7.20
7.19
7.19
7.15
7.15
7.15
7.14
7.14
7.13
7.13
7.12
7.12
5.53
5.52
5.51
5.49
5.00
5.00
4.99
4.99
4.98
4.97
4.96
4.96
2.84
2.82
2.81
2.80
2.74
2.73
2.72
2.71
2.14
2.13
2.11
2.10
1.34
1.33
1.33
1.32
1.31
1.15
1.14
0.63
0.62
0.62
0.62
0.61
0.61
0.61
0.60
0.28
0.28
0.28
0.28
0.27
0.27
0.27
0.27

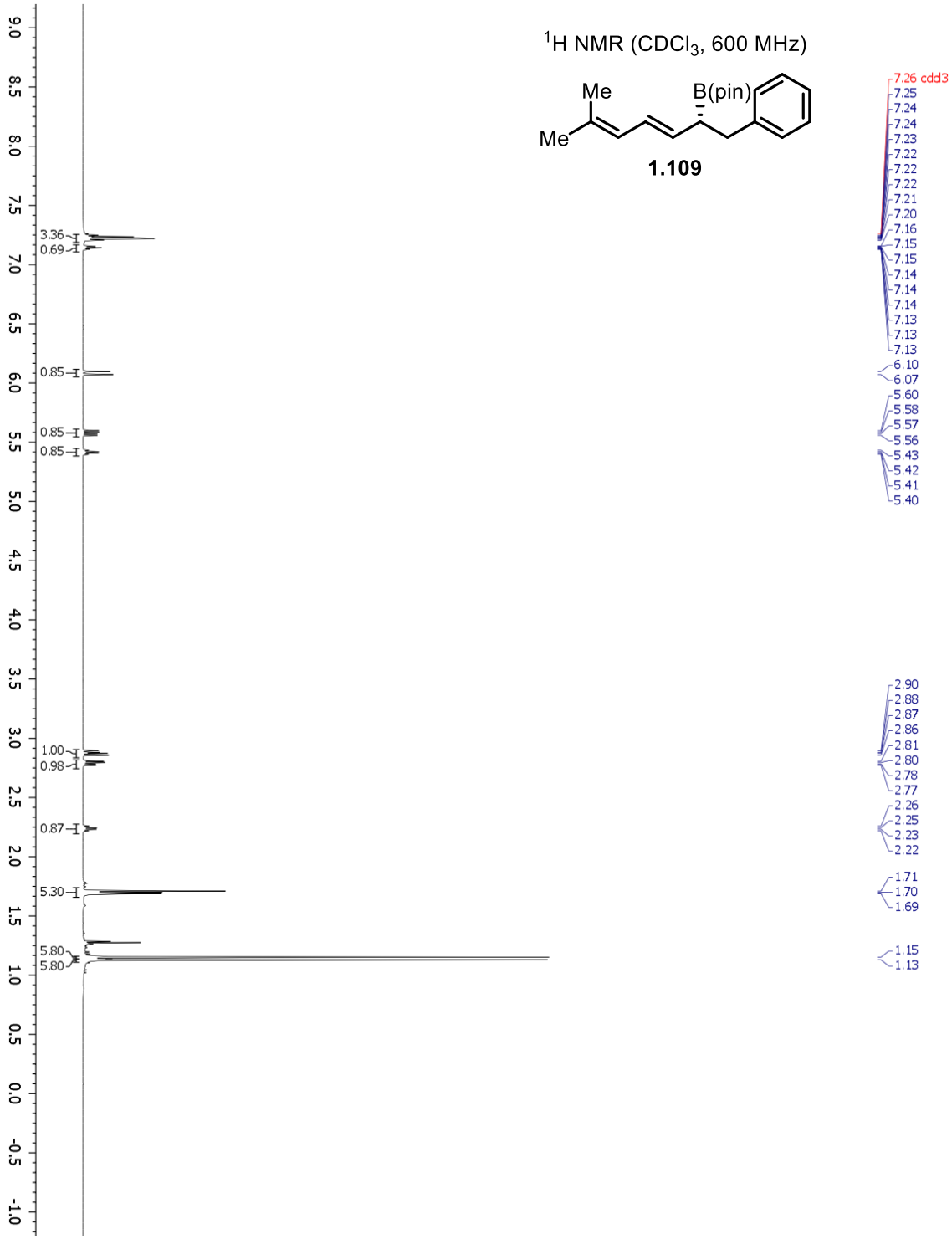

^{13}C NMR ($CDCl_3$, 150 MHz)
B(pin)
1.105
142.00
134.02
129.06
128.09
127.72
125.74
83.28
77.37 cdcl3
77.16 cdcl3
76.95 cdcl3
37.51
30.49
24.78
24.72
13.86
6.57
6.53

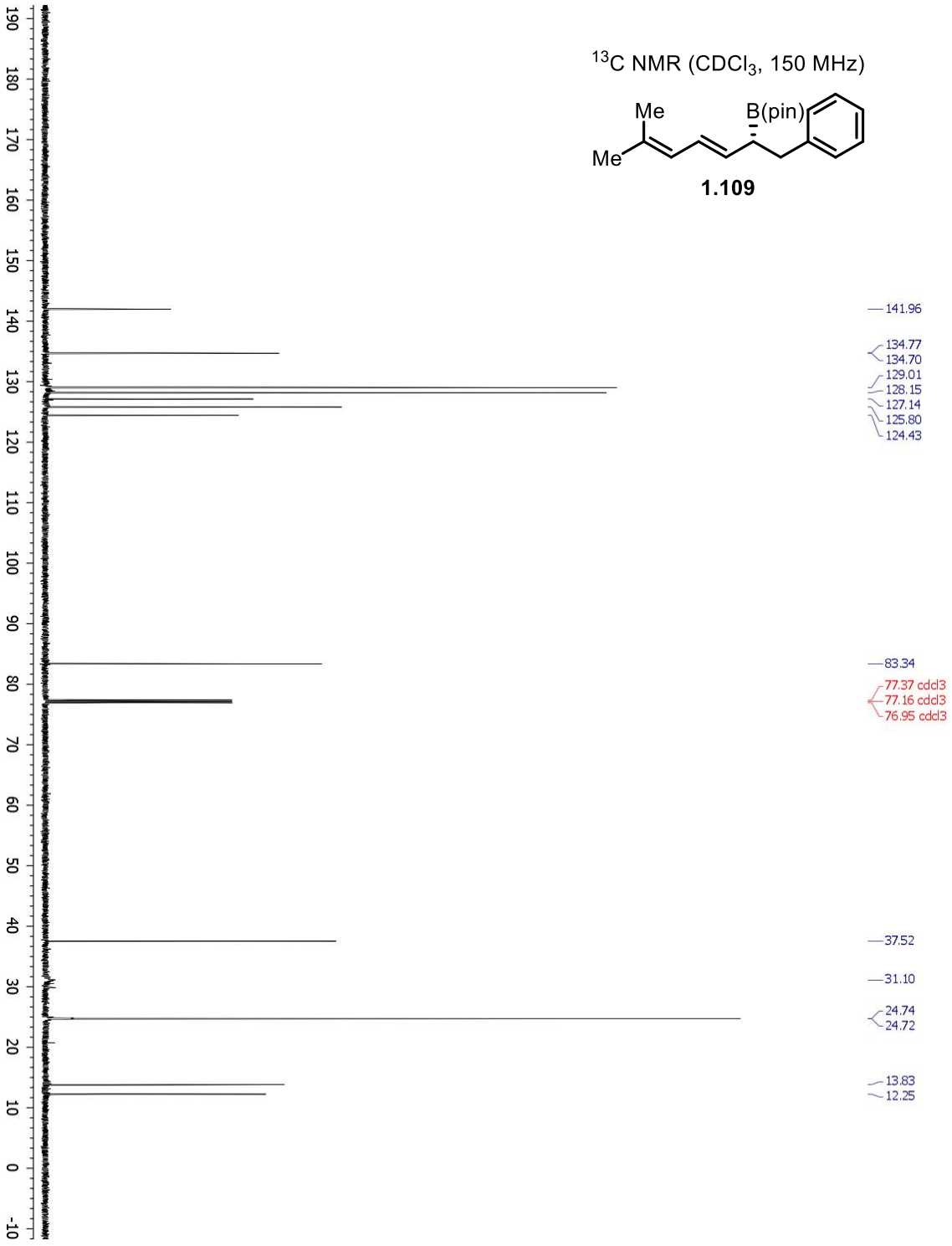

^{1}H NMR ($CDCl_3$, 600 MHz)
B(pin)
Me
1.106
7.26 cdcl3
7.25
7.24
7.22
7.21
7.19
7.16
7.15
7.15
7.14
7.13
7.13
7.13
5.48
5.47
5.45
5.44
5.43
5.42
5.41
5.40
5.39
5.38
2.85
2.83
2.83
2.81
2.75
2.74
2.73
2.72
2.16
2.15
2.14
2.12
1.64
1.63
1.16
1.14
3.61
0.86
1.73
1.00
1.02
0.89
2.88
5.89
5.86
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0

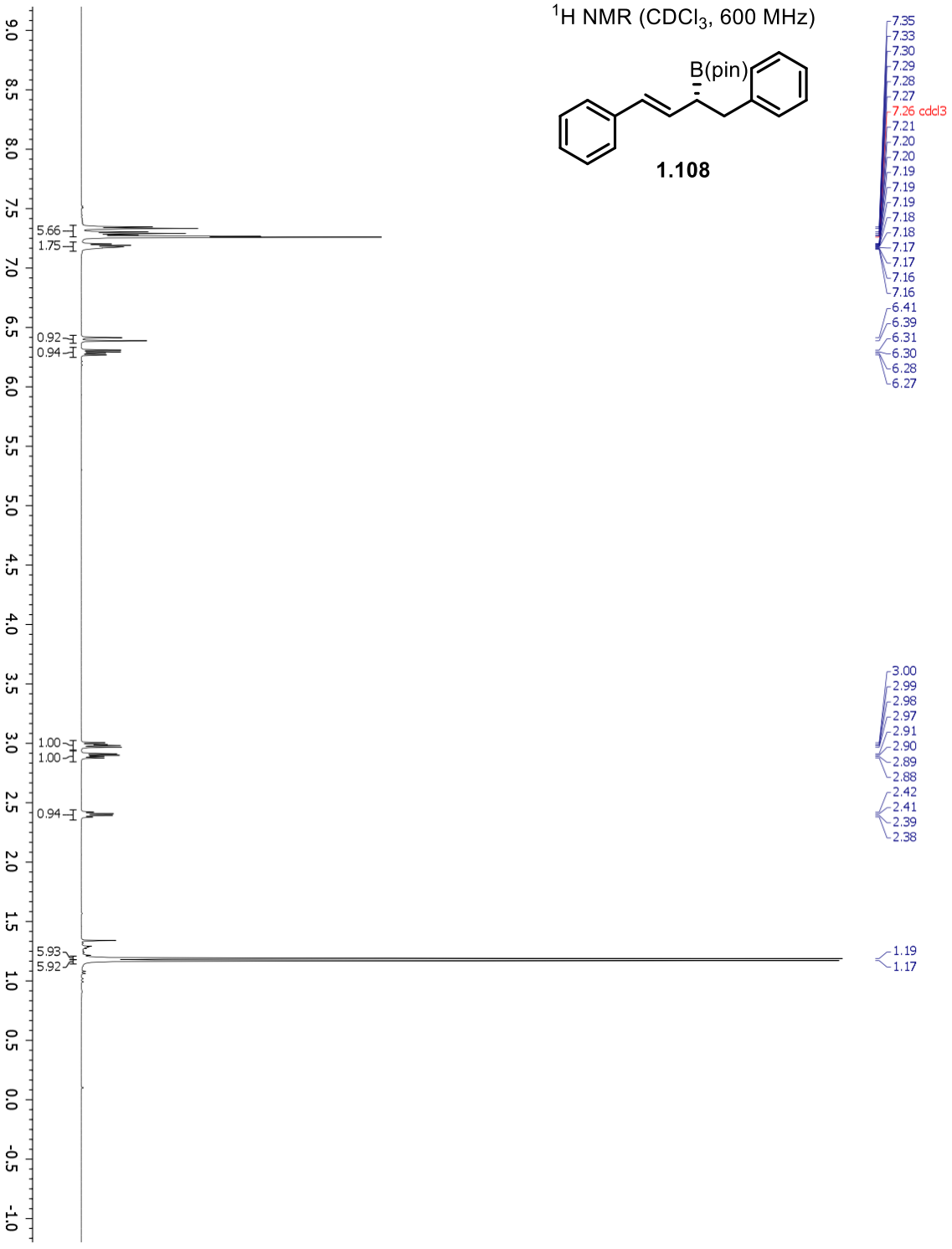

^{13}C NMR ($CDCl_3$, 150 MHz)
B(pin)
Me
1.106
142.03
131.18
129.04
128.09
125.73
124.94
83.28
77.37 cdcl3
77.16 cdcl3
76.95 cdcl3
37.39
30.70
24.79
24.74
18.31

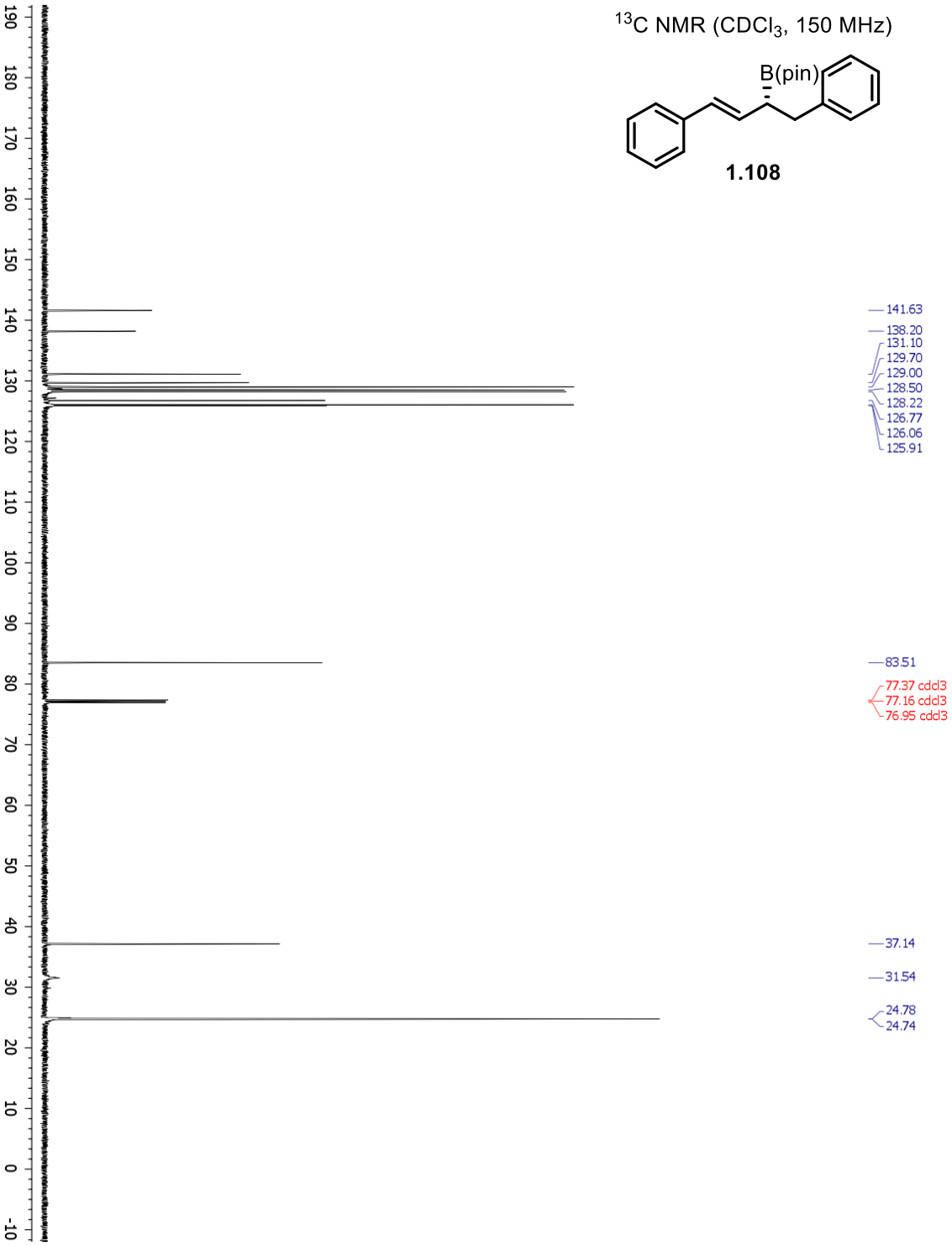

^{1}H NMR ($CDCl_3$, 600 MHz)
B(pin)
Me
Me
Me
1.107
7.26 cdcl3
7.25
7.23
7.22
7.22
7.21
7.21
7.20
7.15
7.15
7.15
7.14
7.14
7.13
7.13
7.13
7.12
5.46
5.46
5.44
5.44
5.37
5.36
5.34
5.33
2.86
2.85
2.84
2.83
2.75
2.74
2.73
2.72
2.13
2.12
2.10
2.09
1.16
1.15
0.97
3.50
0.82
0.85
0.88
1.00
1.00
0.93
5.84
5.83
8.66

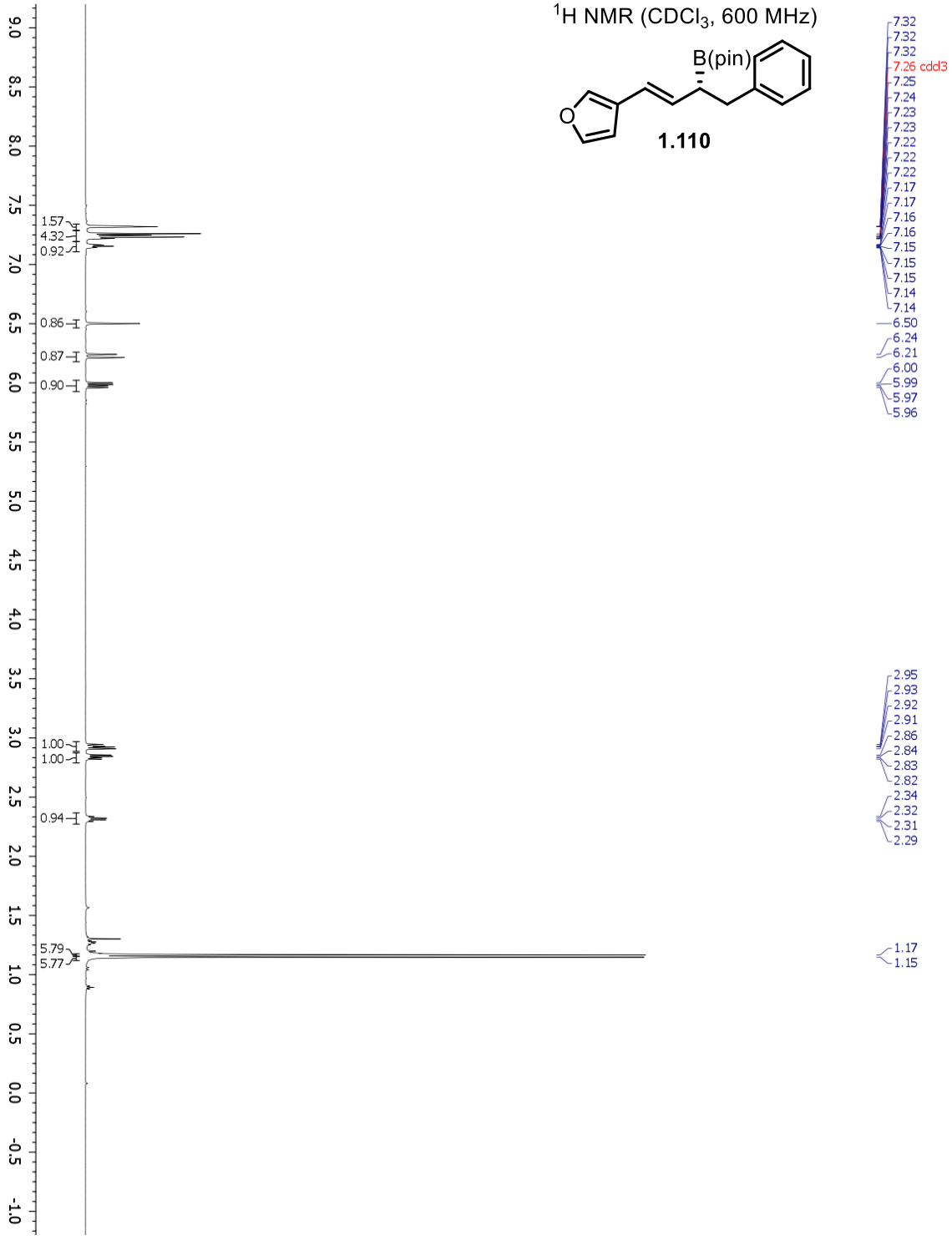

^{13}C NMR ($CDCl_3$, 150 MHz)
B(pin)
Me
Me
Me
1.107
142.15
141.76
129.06
128.05
125.67
124.67
83.18
77.37 cdcl3
77.16 cdcl3
76.95 cdcl3
37.43
33.09
30.60
29.96
24.69
24.62

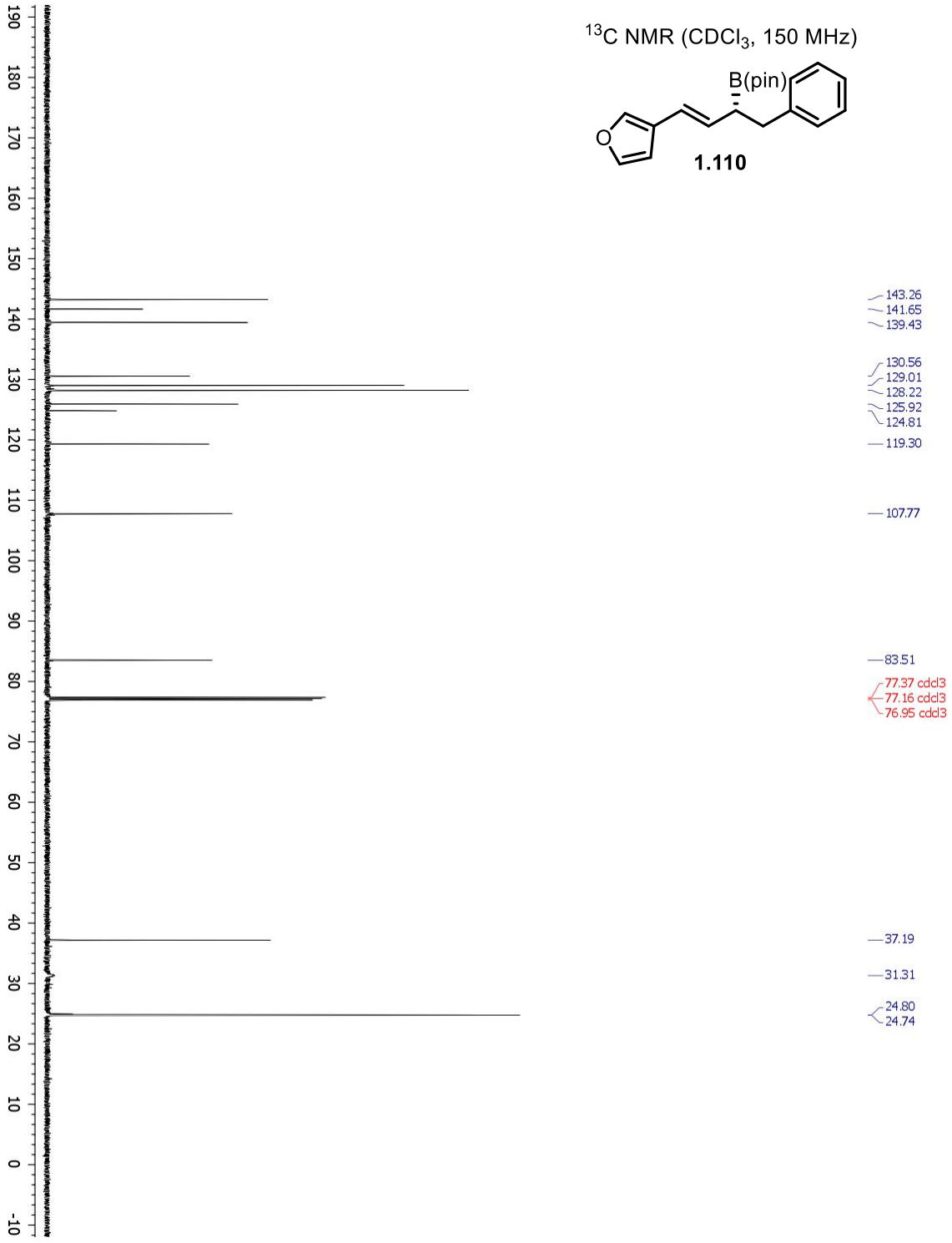

^{1}H NMR ($CDCl_3$, 600 MHz)
Me
B(pin)
Me
1.109
7.26 cdcl3
3.36
0.69
0.85
0.85
0.85
1.00
0.98
0.87
5.30
5.80
5.80
2.90
2.26
1.71
1.15

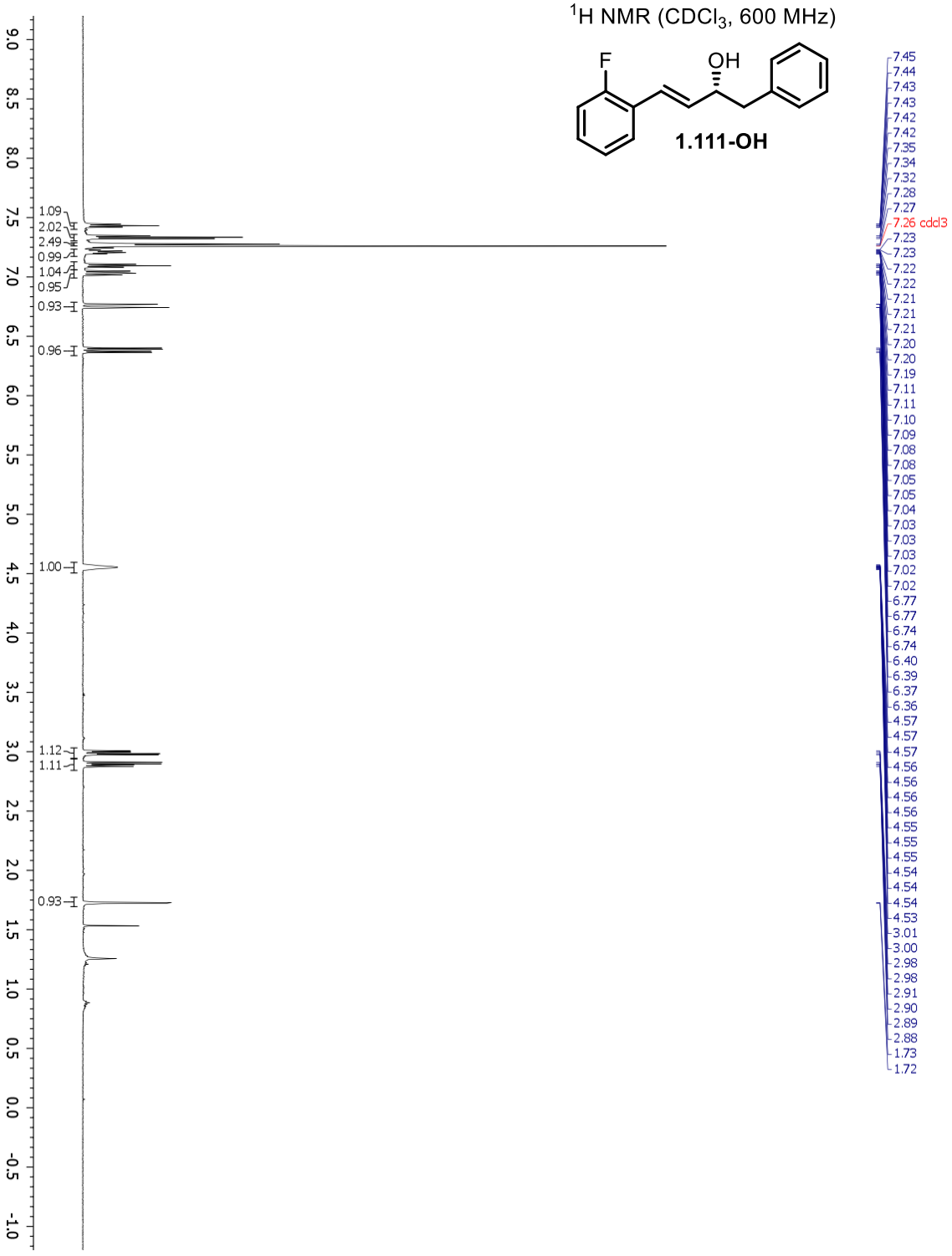

13C NMR (CDCl3, 150 MHz)
Me
B(pin)
Me
1.109
141.96
134.77
134.70
129.01
128.15
127.14
125.80
124.43
83.34
77.37 cdcl3
77.16 cdcl3
76.95 cdcl3
37.52
31.10
24.74
24.72
13.83
12.25

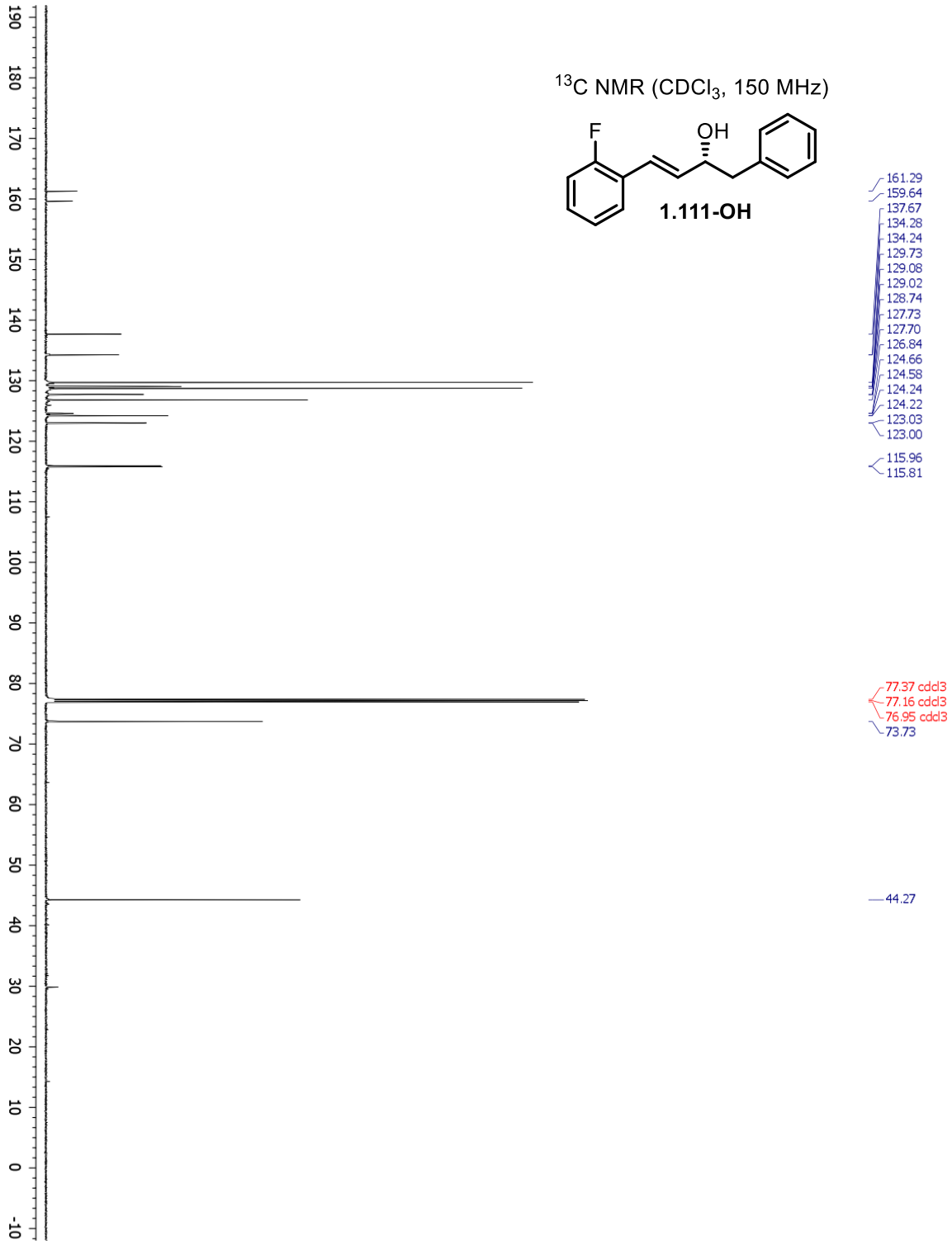

^{1}H NMR ($CDCl_3$, 600 MHz)
B(pin)
1.108
7.35
7.33
7.30
7.29
7.28
7.27
7.26 cdcl3
7.21
7.20
7.20
7.19
7.19
7.19
7.18
7.18
7.17
7.17
7.16
7.16
6.41
6.39
6.31
6.30
6.28
6.27
3.00
2.99
2.98
2.97
2.91
2.90
2.89
2.88
2.42
2.41
2.39
2.38
1.19
1.17
5.66
1.75
0.92
0.94
1.00
1.00
0.94
5.93
5.92

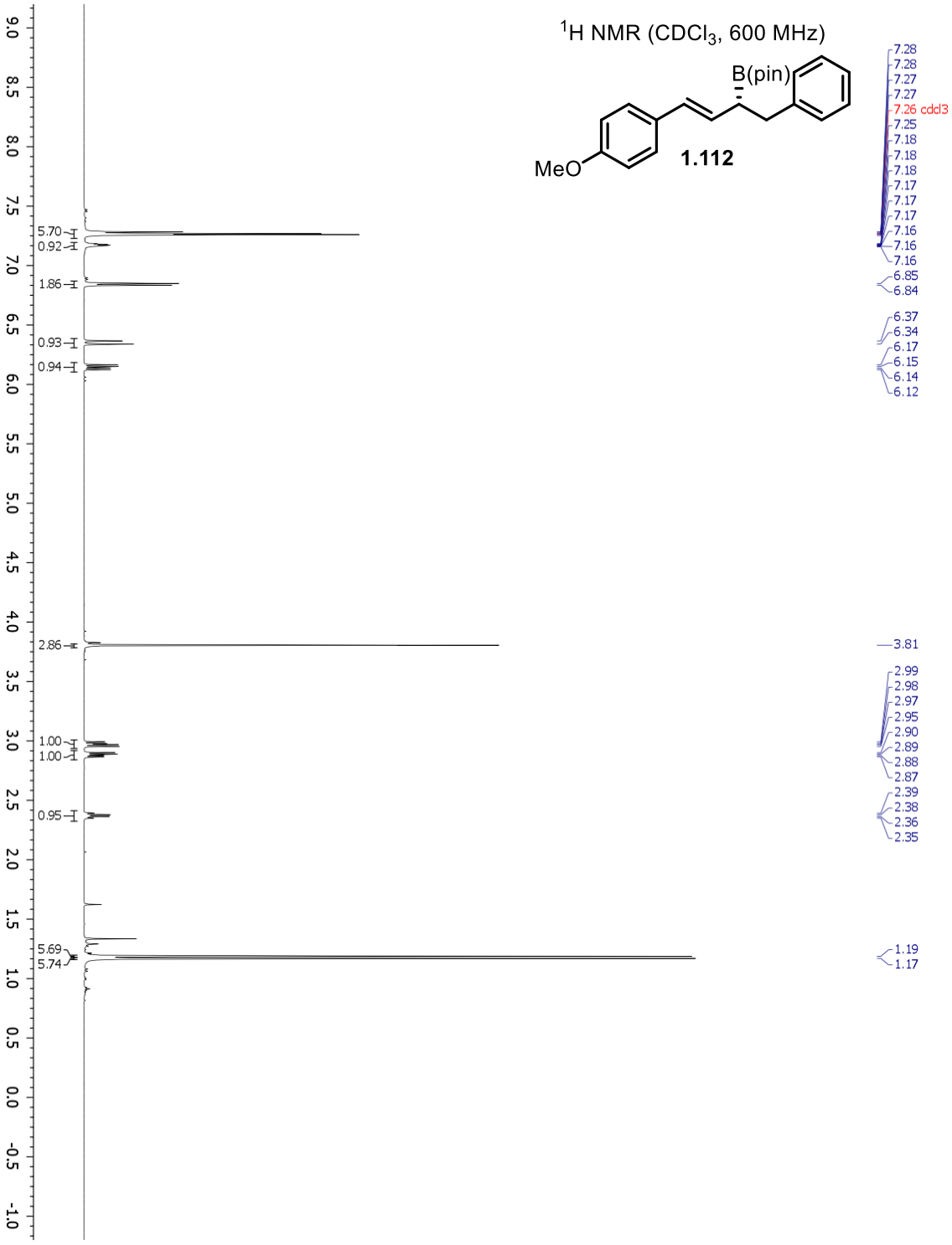

^{13}C NMR ($CDCl_3$, 150 MHz)
B(pin)
1.108
141.63
138.20
131.10
129.70
129.00
128.50
128.22
126.77
126.06
125.91
83.51
77.37 cdcl3
77.16 cdcl3
76.95 cdcl3
37.14
31.54
24.78
24.74

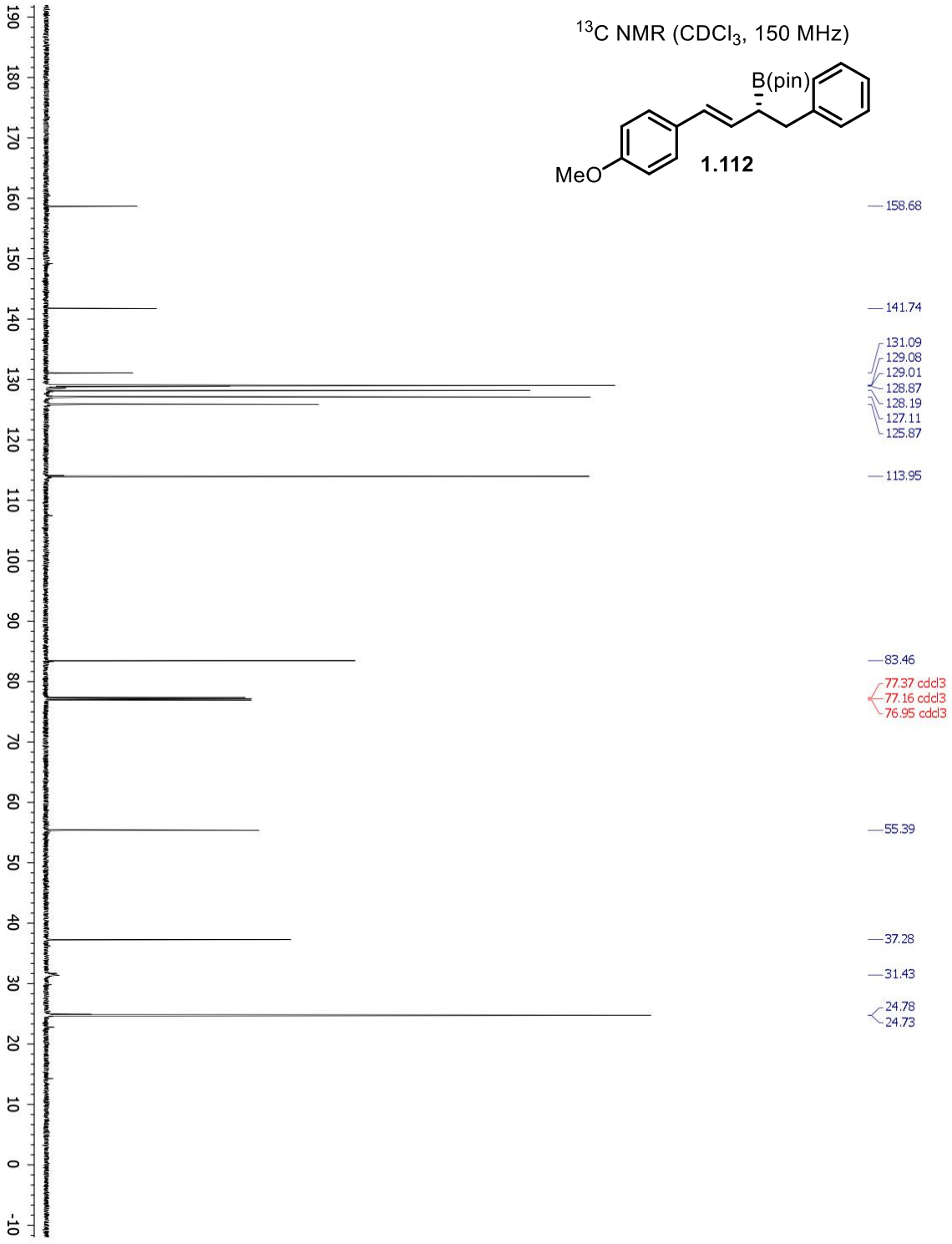

^{1}H NMR ($CDCl_3$, 600 MHz)
B(pin)
O
1.110
7.32
7.32
7.32
7.26 cdcl3
7.25
7.24
7.23
7.23
7.22
7.22
7.22
7.17
7.17
7.16
7.16
7.15
7.15
7.15
7.14
7.14
6.50
6.24
6.21
6.00
5.99
5.97
5.96
2.95
2.93
2.92
2.91
2.86
2.84
2.83
2.82
2.34
2.32
2.31
2.29
1.17
1.15
1.57
4.32
0.92
0.86
0.87
0.90
1.00
1.00
0.94
5.79
5.77
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0

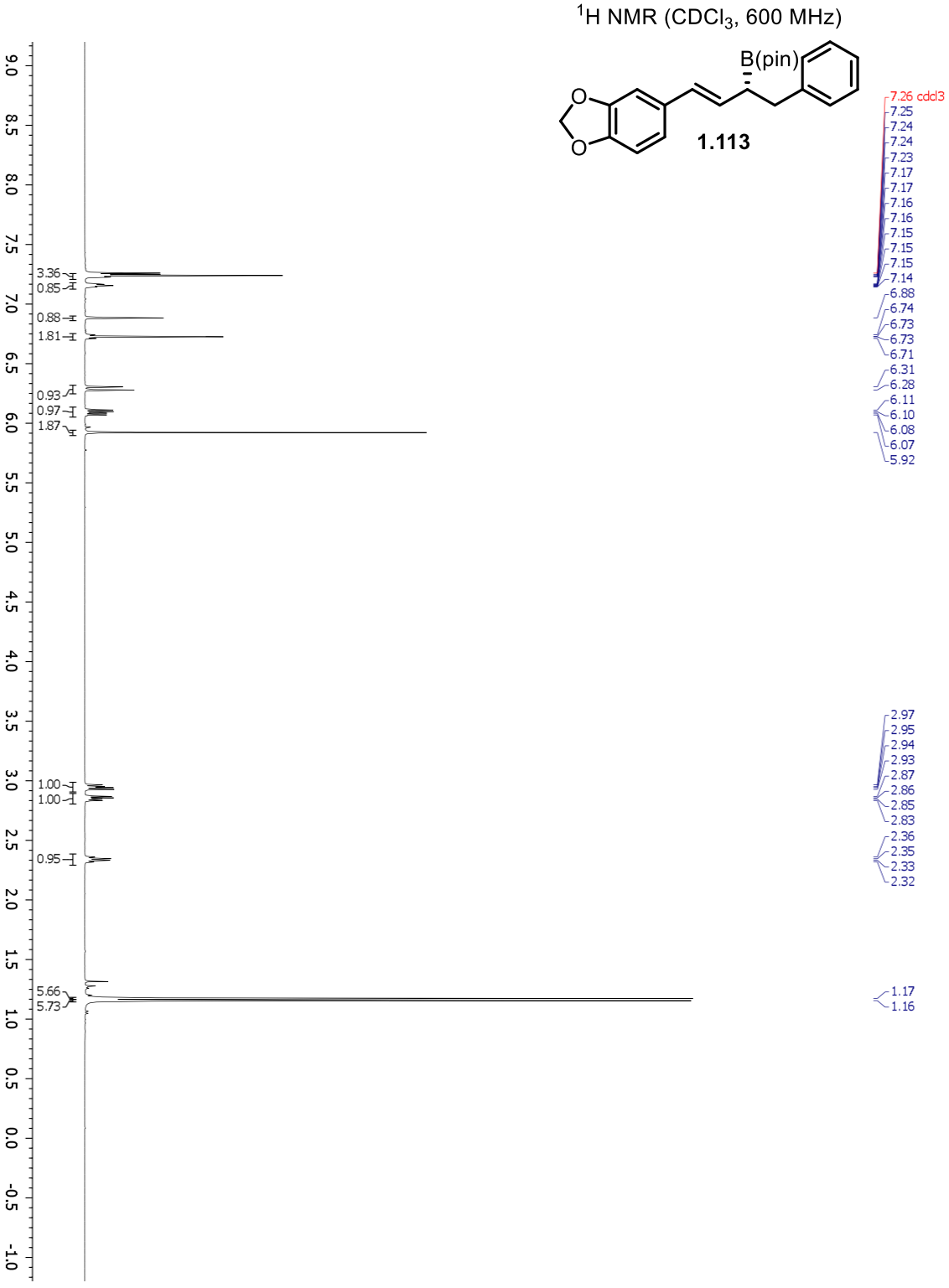

^{13}C NMR ($CDCl_3$, 150 MHz)
B(pin)
O
1.110
143.26
141.65
139.43
130.56
129.01
128.22
125.92
124.81
119.30
107.77
83.51
77.37 cdcl3
77.16 cdcl3
76.95 cdcl3
37.19
31.31
24.80
24.74

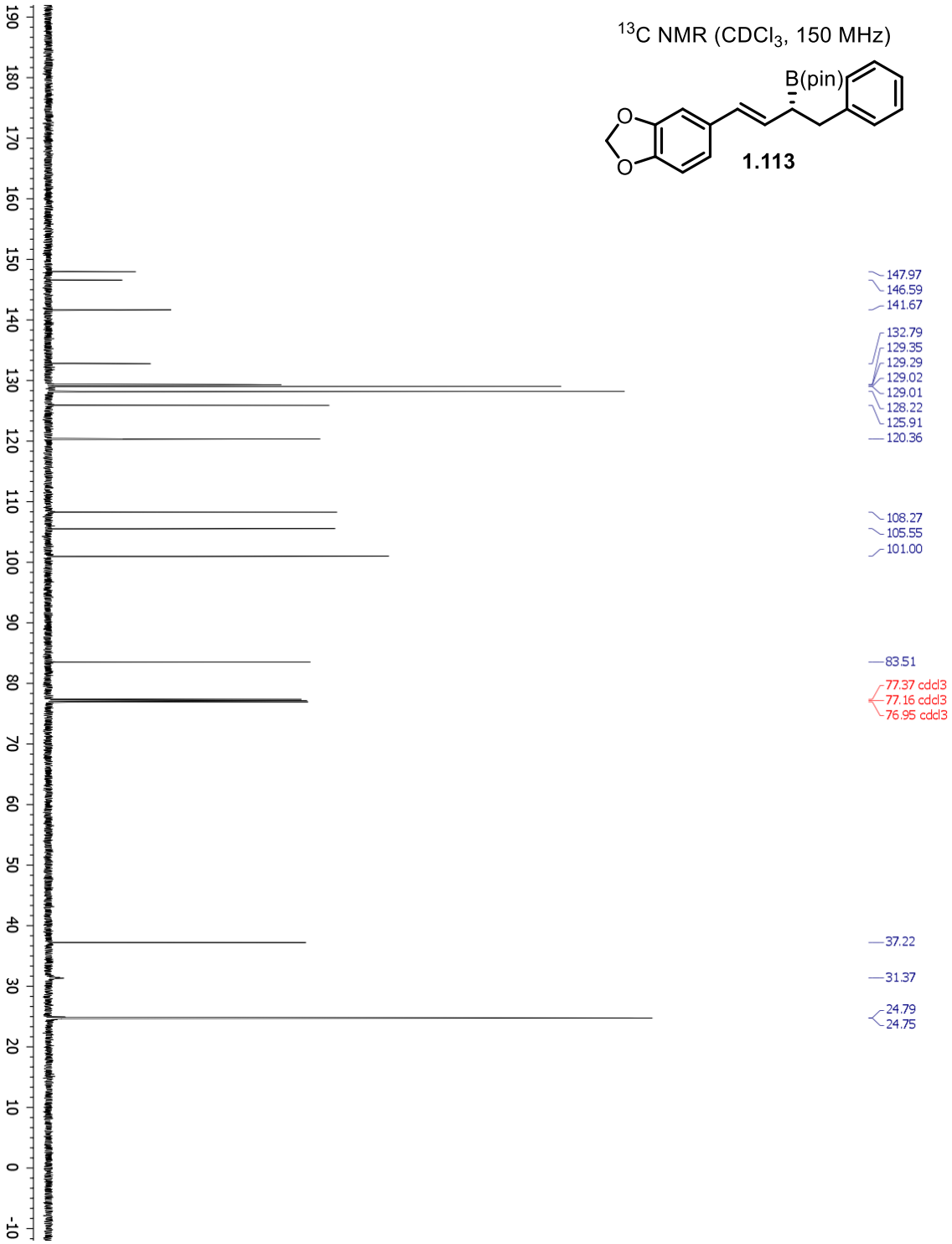

^{1}H NMR ($CDCl_3$, 600 MHz)
F
OH
1.111-OH
1.09
2.02
2.49
0.99
1.04
0.95
0.93
0.96
1.00
1.12
1.11
0.93
7.45
7.44
7.43
7.43
7.42
7.42
7.35
7.34
7.32
7.28
7.27
7.26 cddl3
7.23
7.23
7.22
7.22
7.21
7.21
7.21
7.20
7.20
7.19
7.11
7.11
7.10
7.09
7.08
7.08
7.05
7.05
7.04
7.03
7.03
7.03
7.02
7.02
6.77
6.77
6.74
6.74
6.40
6.39
6.37
6.36
4.57
4.57
4.57
4.56
4.56
4.56
4.56
4.55
4.55
4.55
4.54
4.54
4.54
4.53
3.01
3.00
2.98
2.98
2.91
2.90
2.89
2.88
1.73
1.72

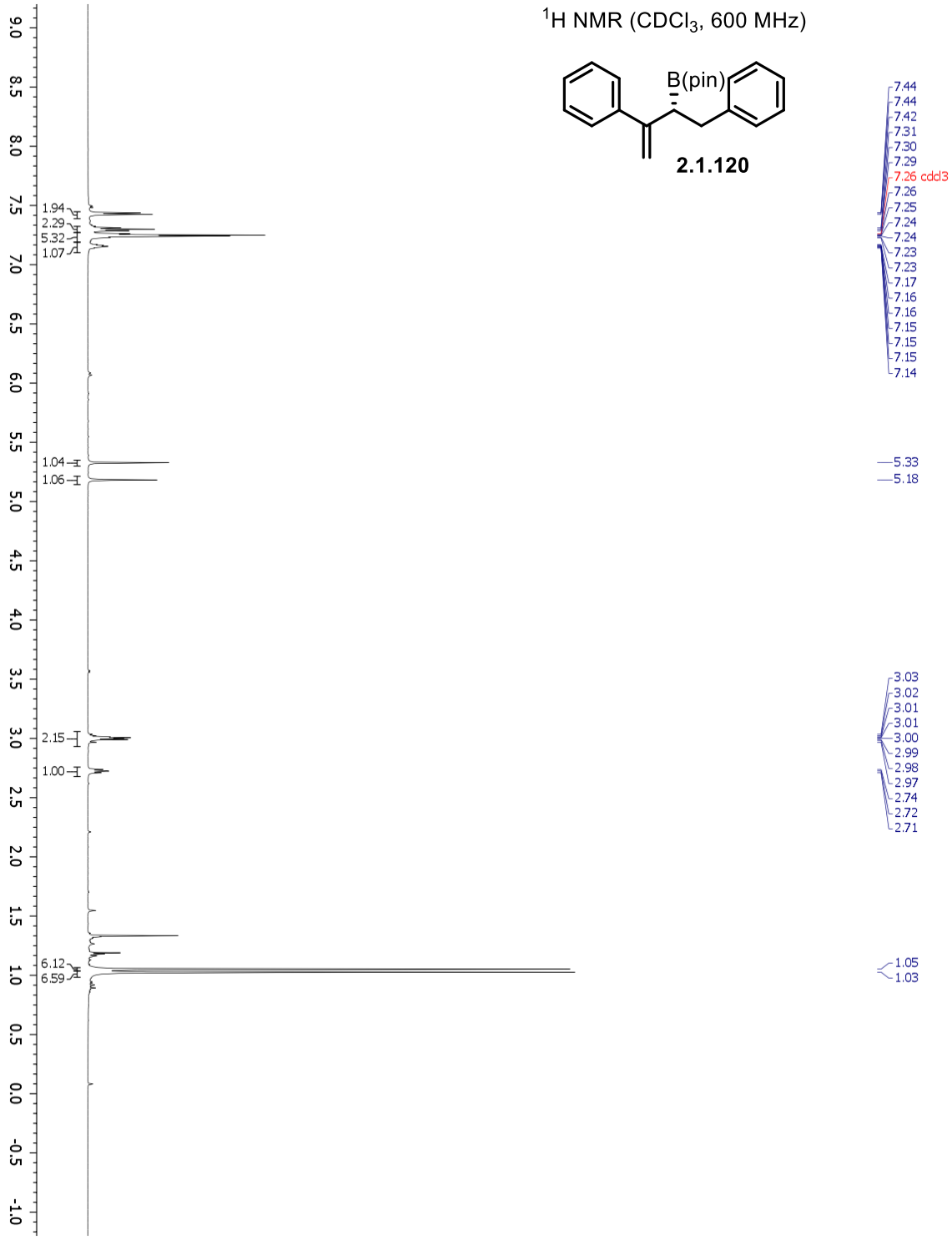

^{13}C NMR ($CDCl_3$, 150 MHz)
F
OH
1.111-OH
161.29
159.64
137.67
134.28
134.24
129.73
129.08
129.02
128.74
127.73
127.70
126.84
124.66
124.58
124.24
124.22
123.03
123.00
115.96
115.81
77.37 cdd3
77.16 cdd3
76.95 cdd3
73.73
44.27

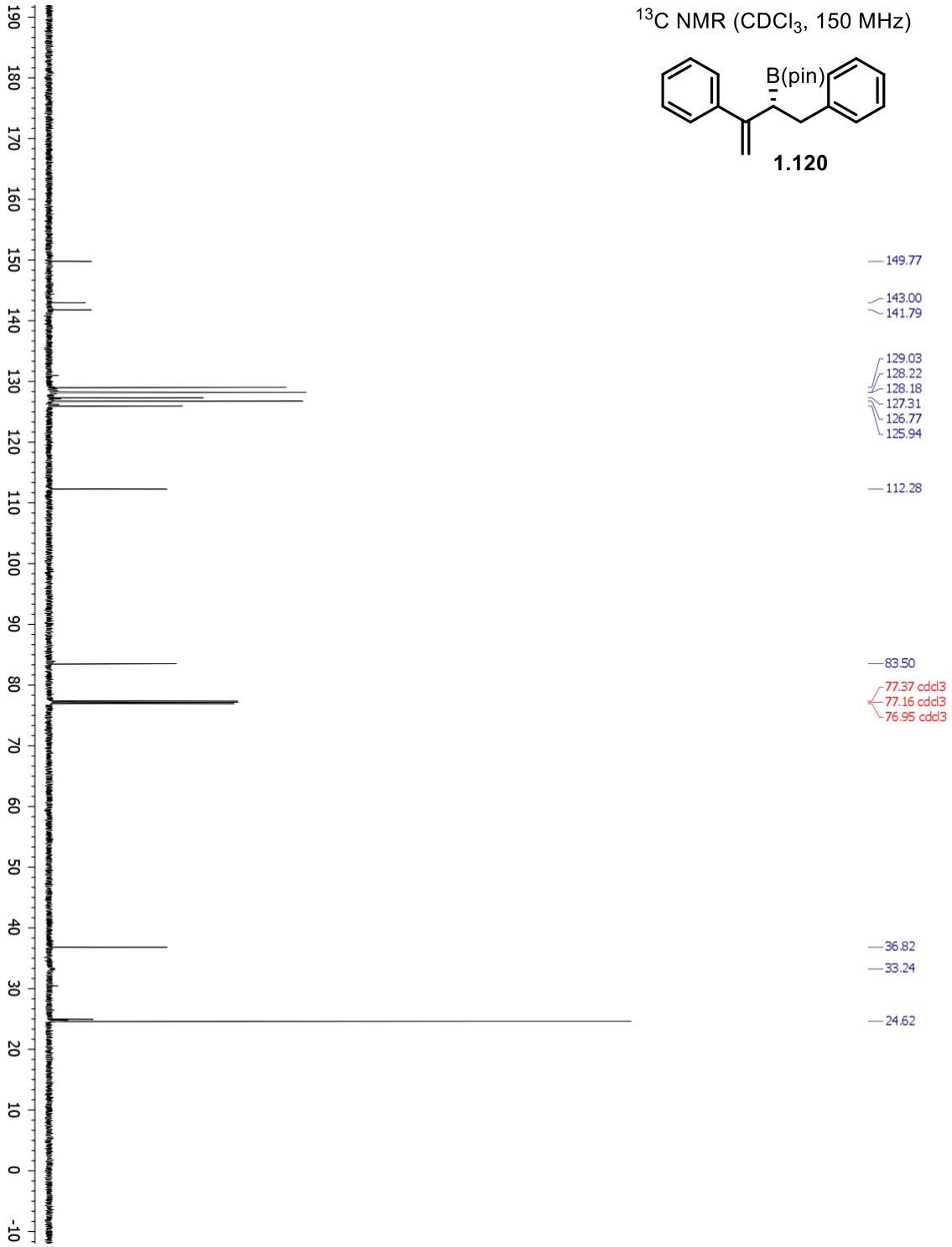

^{1}H NMR ($CDCl_3$, 600 MHz)
B(pin)
MeO
1.112
7.28
7.28
7.27
7.27
7.26 cddl3
7.25
7.18
7.18
7.18
7.17
7.17
7.17
7.16
7.16
7.16
6.85
6.84
6.37
6.34
6.17
6.15
6.14
6.12
3.81
2.99
2.98
2.97
2.95
2.90
2.89
2.88
2.87
2.39
2.38
2.36
2.35
1.19
1.17
5.70
0.92
1.86
0.93
0.94
2.86
1.00
1.00
0.95
5.69
5.74


^{13}C NMR ($CDCl_3$, 150 MHz)
B(pin)
MeO
1.112
158.68
141.74
131.09
129.08
129.01
128.87
128.19
127.11
125.87
113.95
83.46
77.37 cdcl3
77.16 cdcl3
76.95 cdcl3
55.39
37.28
31.43
24.78
24.73

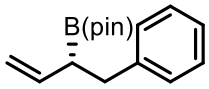

^{1}H NMR ($CDCl_3$, 600 MHz)
B(pin)
1.113
7.26 cdcl3
7.25
7.24
7.24
7.23
7.17
7.17
7.16
7.16
7.15
7.15
7.15
7.14
6.88
6.74
6.73
6.73
6.71
6.31
6.28
6.11
6.10
6.08
6.07
5.92
2.97
2.95
2.94
2.93
2.87
2.86
2.85
2.83
2.36
2.35
2.33
2.32
1.17
1.16
3.36
0.85
0.88
1.81
0.93
0.97
1.87
1.00
1.00
0.95
5.66
5.73


^{13}C NMR ($CDCl_3$, 150 MHz)
B(pin)
O
O
1.113
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
147.97
146.59
141.67
132.79
129.35
129.29
129.02
129.01
128.22
125.91
120.36
108.27
105.55
101.00
83.51
77.37 cdcl3
77.16 cdcl3
76.95 cdcl3
37.22
31.37
24.79
24.75

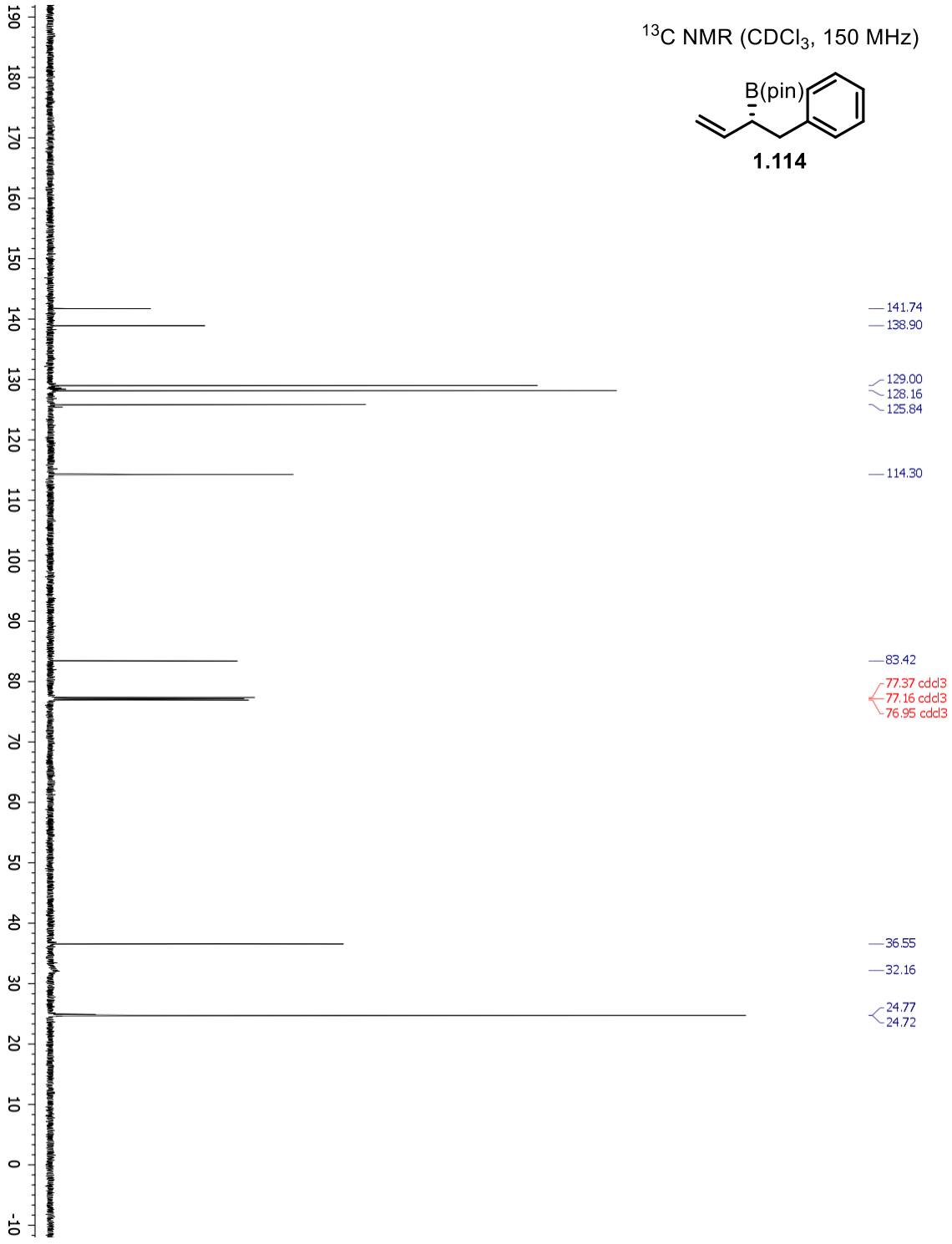

^{1}H NMR ($CDCl_3$, 600 MHz)
B(pin)
2.1.120
7.44
7.44
7.42
7.31
7.30
7.29
7.26 cdcl3
7.26
7.25
7.24
7.24
7.23
7.23
7.17
7.16
7.16
7.15
7.15
7.15
7.14
5.33
5.18
3.03
3.02
3.01
3.01
3.00
2.99
2.98
2.97
2.74
2.72
2.71
1.05
1.03
1.94
2.29
5.32
1.07
1.04
1.06
2.15
1.00
6.12
6.59

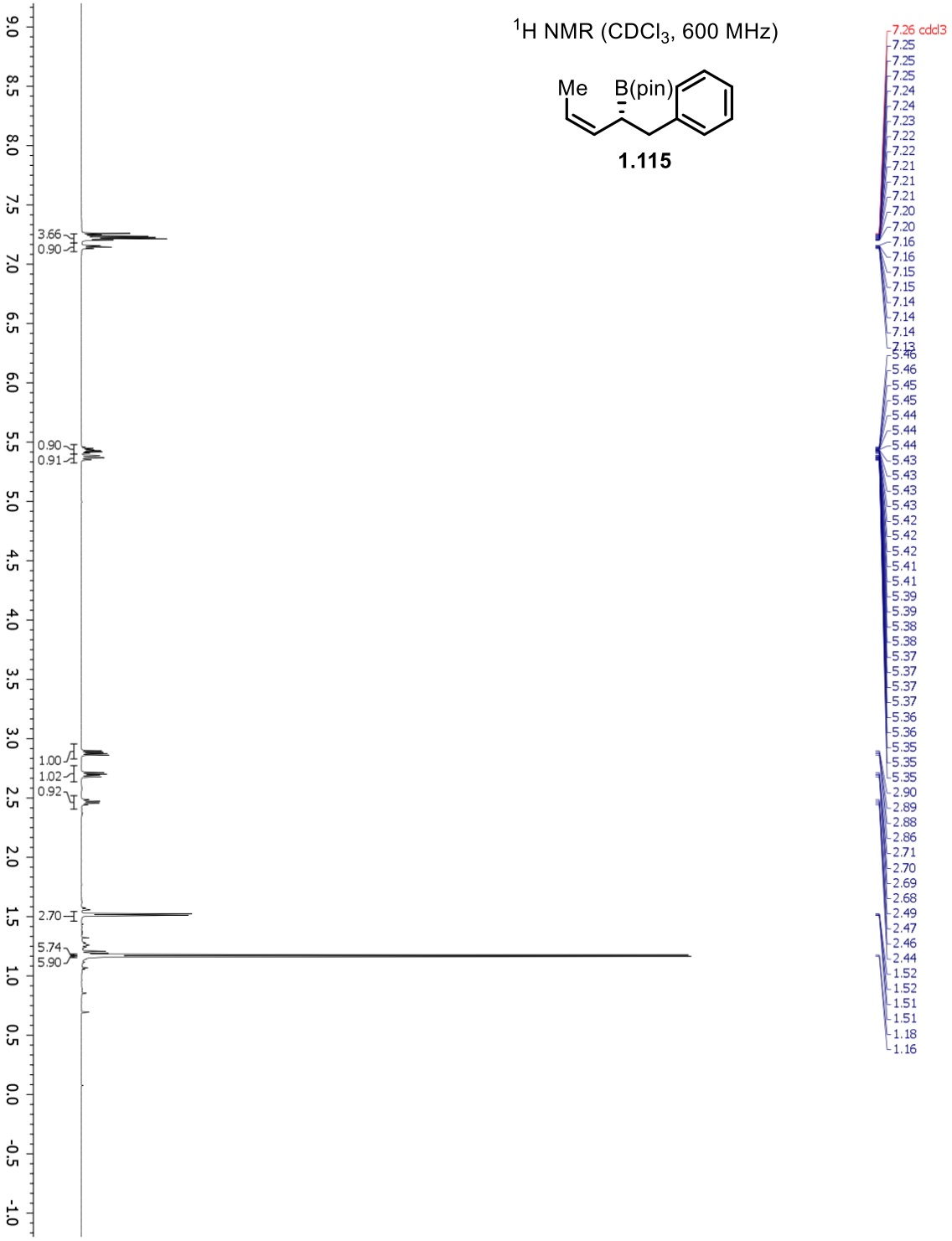

^{13}C NMR ($CDCl_3$, 150 MHz)
B(pin)
1.120
149.77
143.00
141.79
129.03
128.22
128.18
127.31
126.77
125.94
112.28
83.50
77.37 cdcl3
77.16 cdcl3
76.95 cdcl3
36.82
33.24
24.62

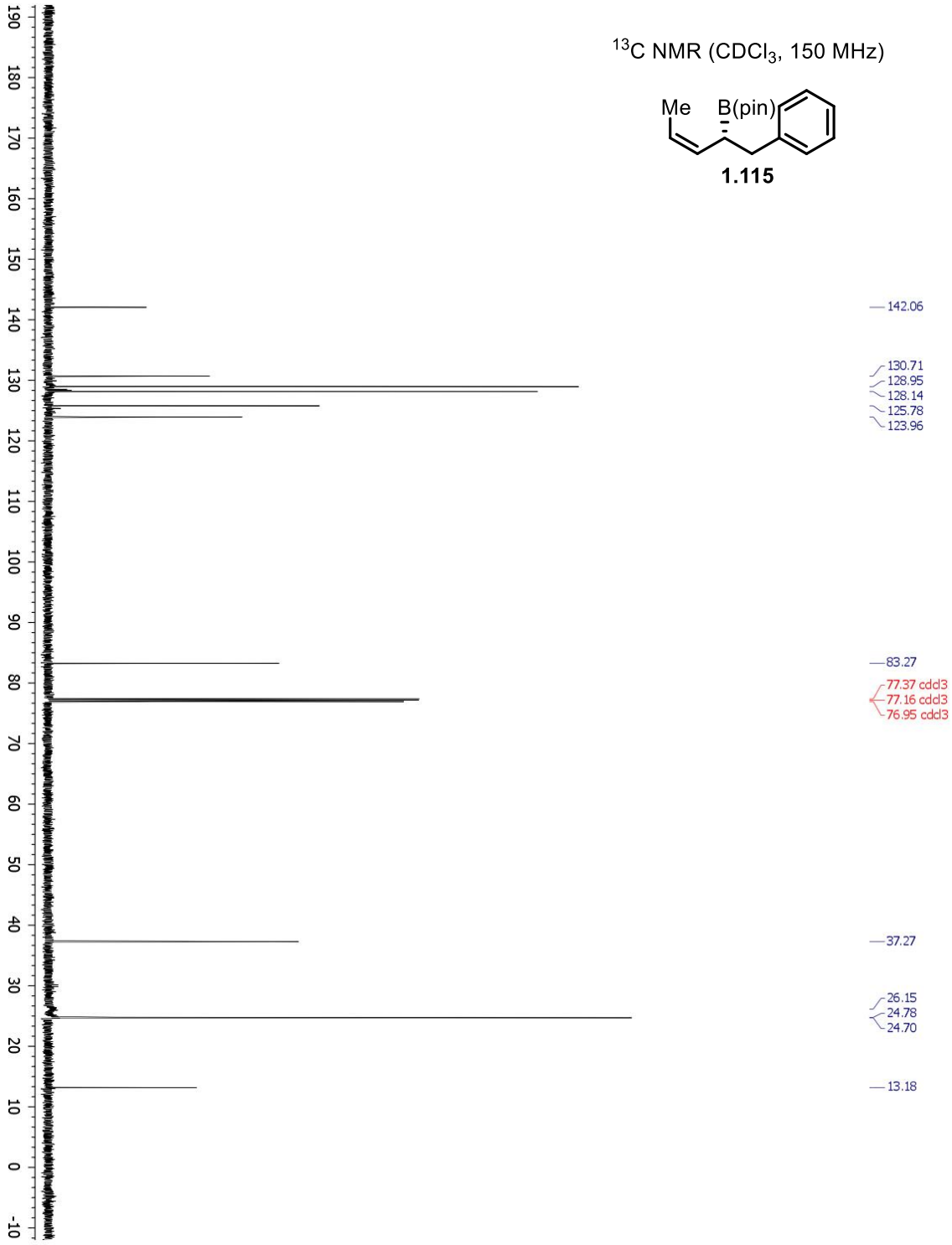
^{1}H NMR ($CDCl_3$, 600 MHz)

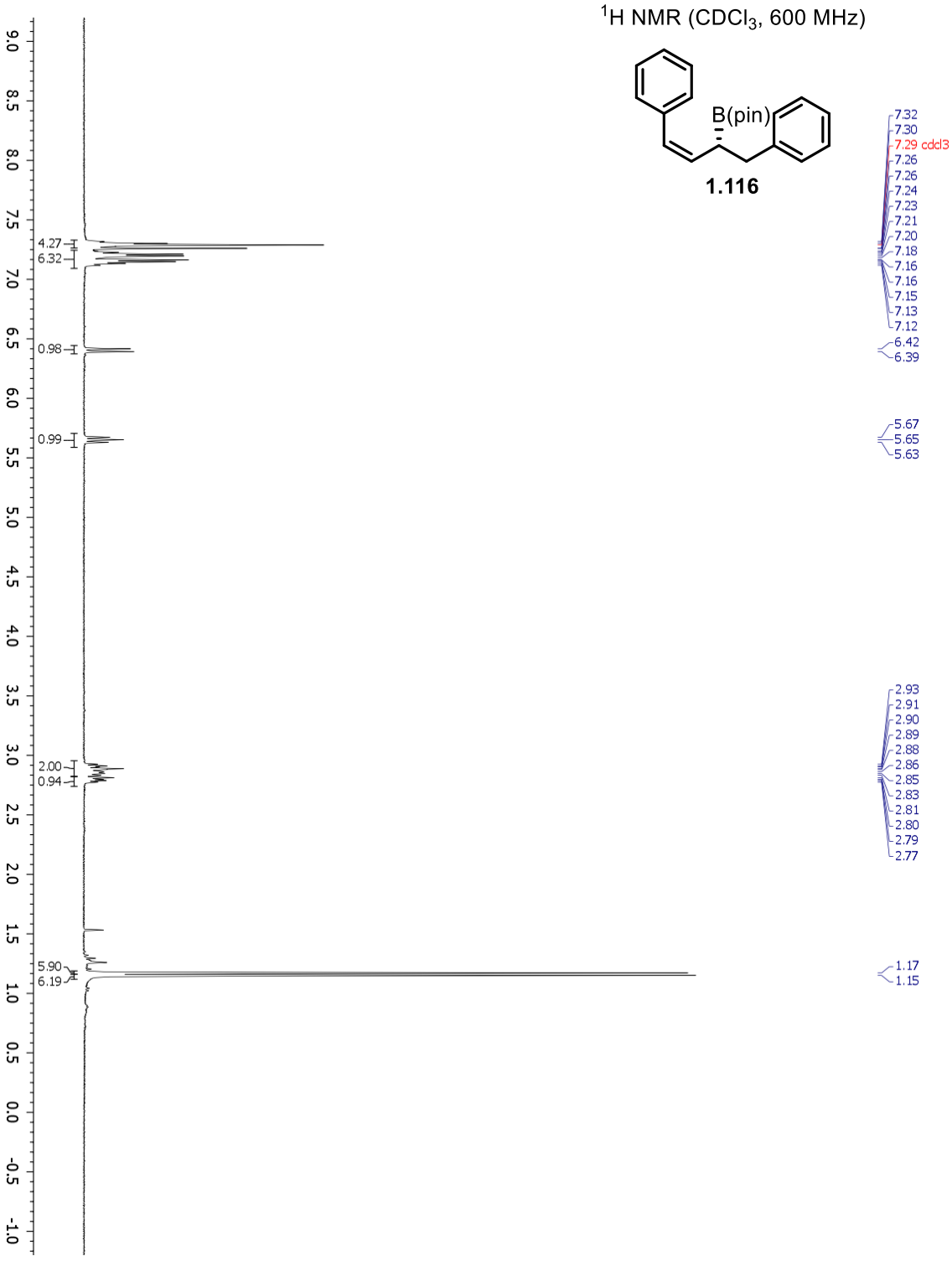


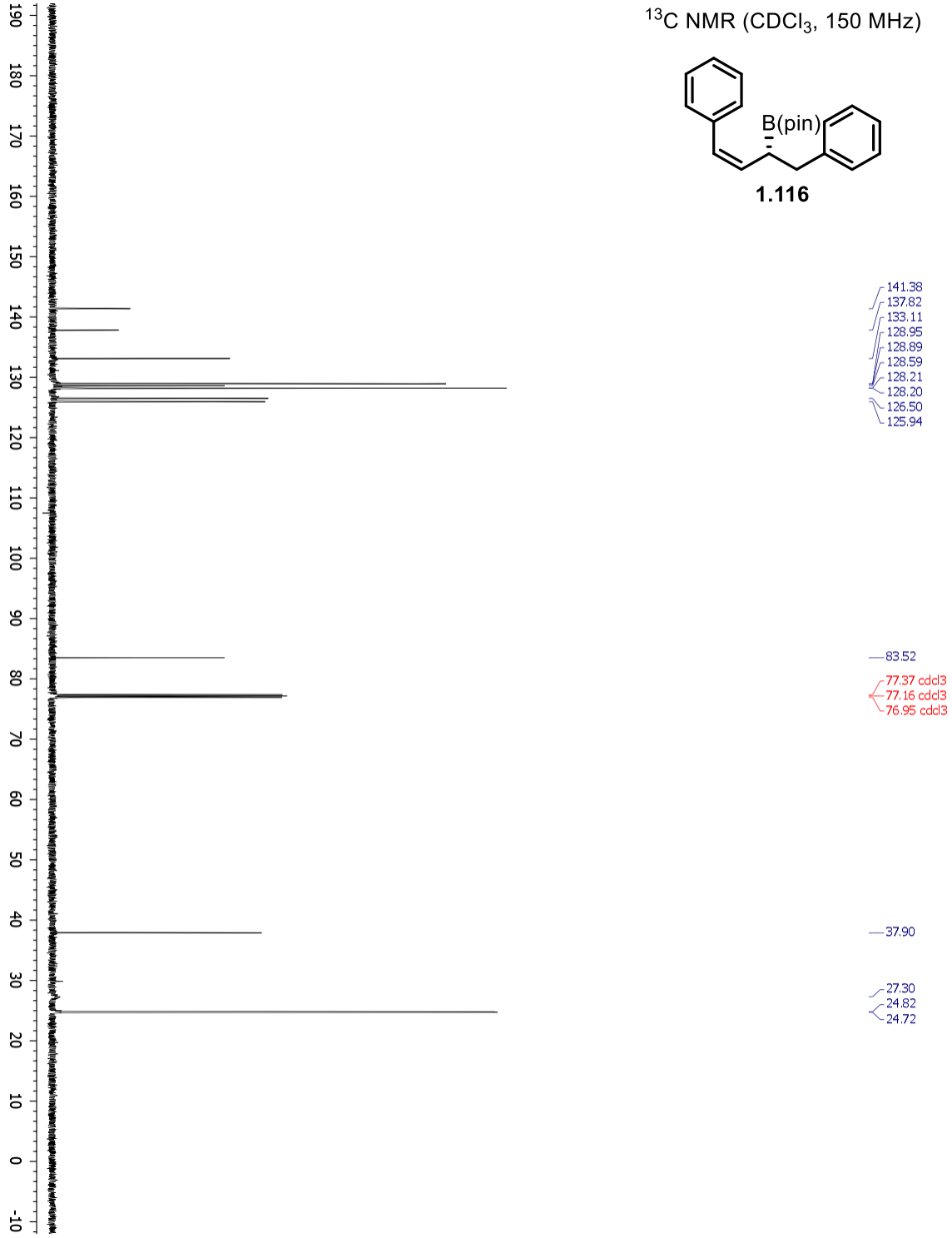
1.114

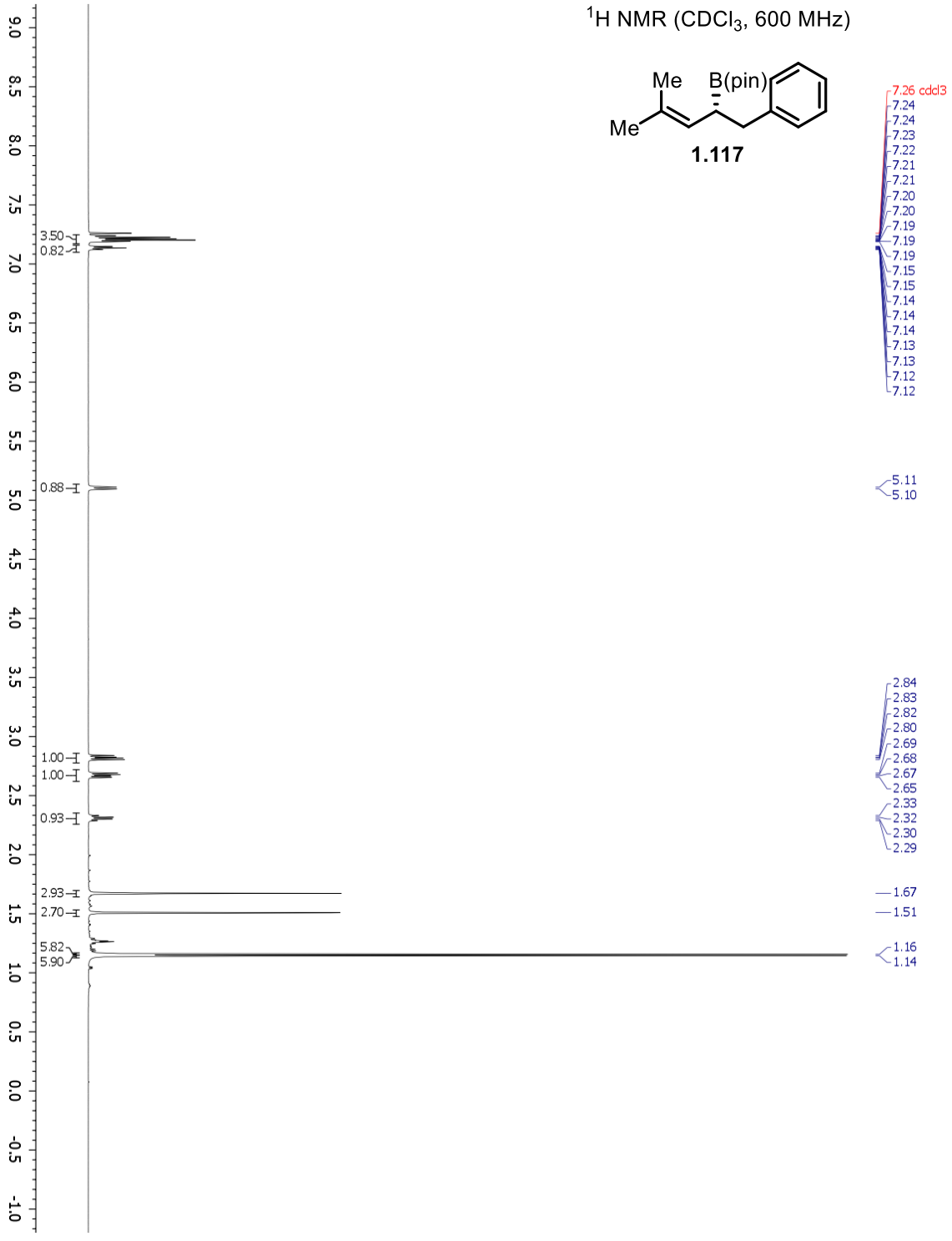

^{13}C NMR ($CDCl_3$, 150 MHz)
B(pin)
1.114
141.74
138.90
129.00
128.16
125.84
114.30
83.42
77.37 cdcl3
77.16 cdcl3
76.95 cdcl3
36.55
32.16
24.77
24.72


^{1}H NMR ($CDCl_3$, 600 MHz)
Me
B(pin)
1.115
3.66
0.90
0.90
0.91
1.00
1.02
0.92
2.70
5.74
5.90
7.26 cdcl3

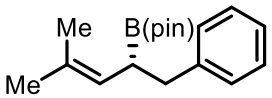

^{13}C NMR ($CDCl_3$, 150 MHz)
Me
B(pin)
1.115
142.06
130.71
128.95
128.14
125.78
123.96
83.27
77.37 cdcl3
77.16 cdcl3
76.95 cdcl3
37.27
26.15
24.78
24.70
13.18


^{1}H NMR ($CDCl_3$, 600 MHz)
B(pin)
1.116
4.27
6.32
0.98
0.99
2.00
0.94
5.90
6.19
7.32
7.30
7.29 cdcl3
7.26
7.26
7.24
7.23
7.21
7.20
7.18
7.16
7.16
7.15
7.13
7.12
6.42
6.39
5.67
5.65
5.63
2.93
2.91
2.90
2.89
2.88
2.86
2.85
2.83
2.81
2.80
2.79
2.77
1.17
1.15

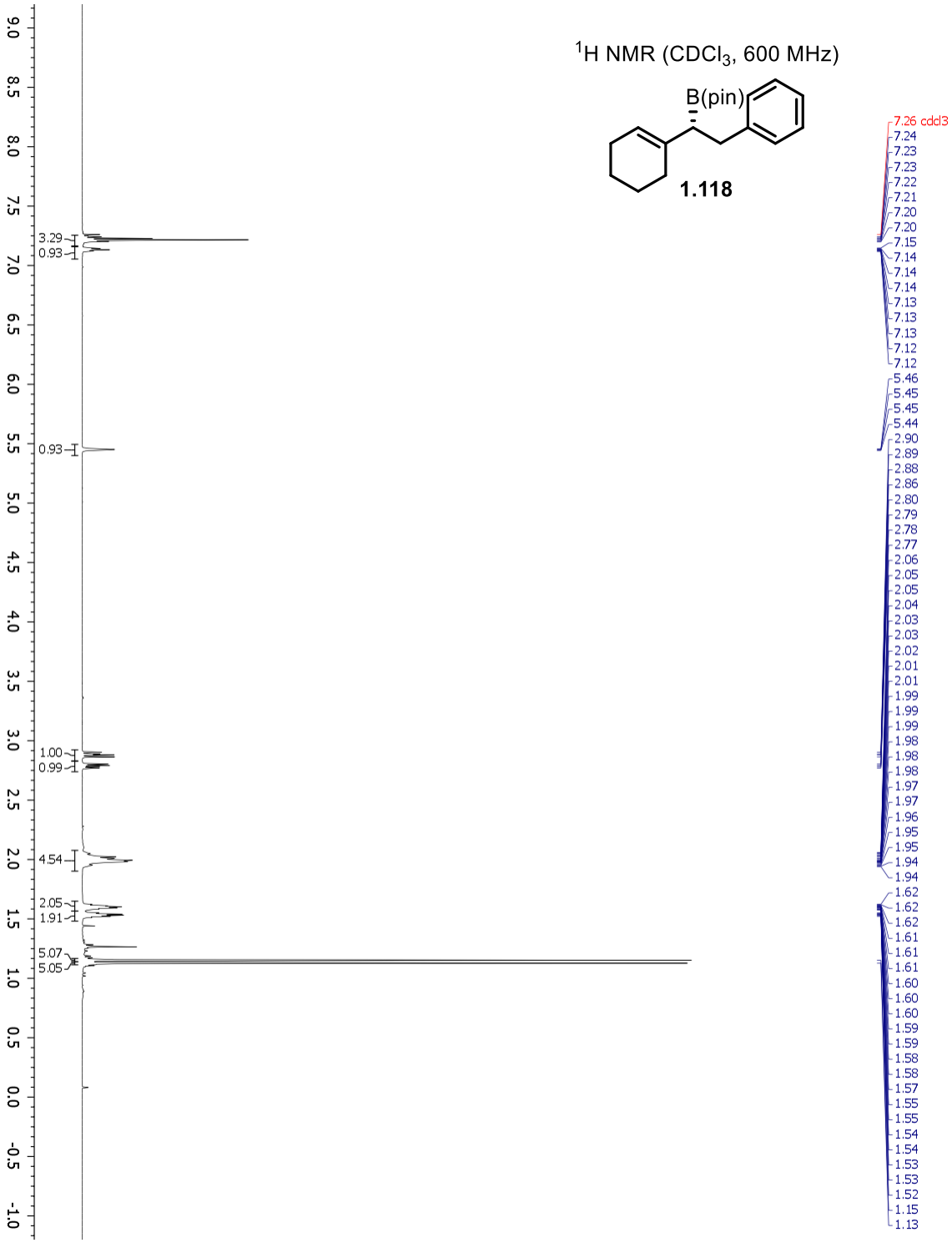

^{13}C NMR ($CDCl_3$, 150 MHz)
B(pin)
1.116
141.38
137.82
133.11
128.95
128.89
128.59
128.21
128.20
126.50
125.94
83.52
77.37 cdcl3
77.16 cdcl3
76.95 cdcl3
37.90
27.30
24.82
24.72

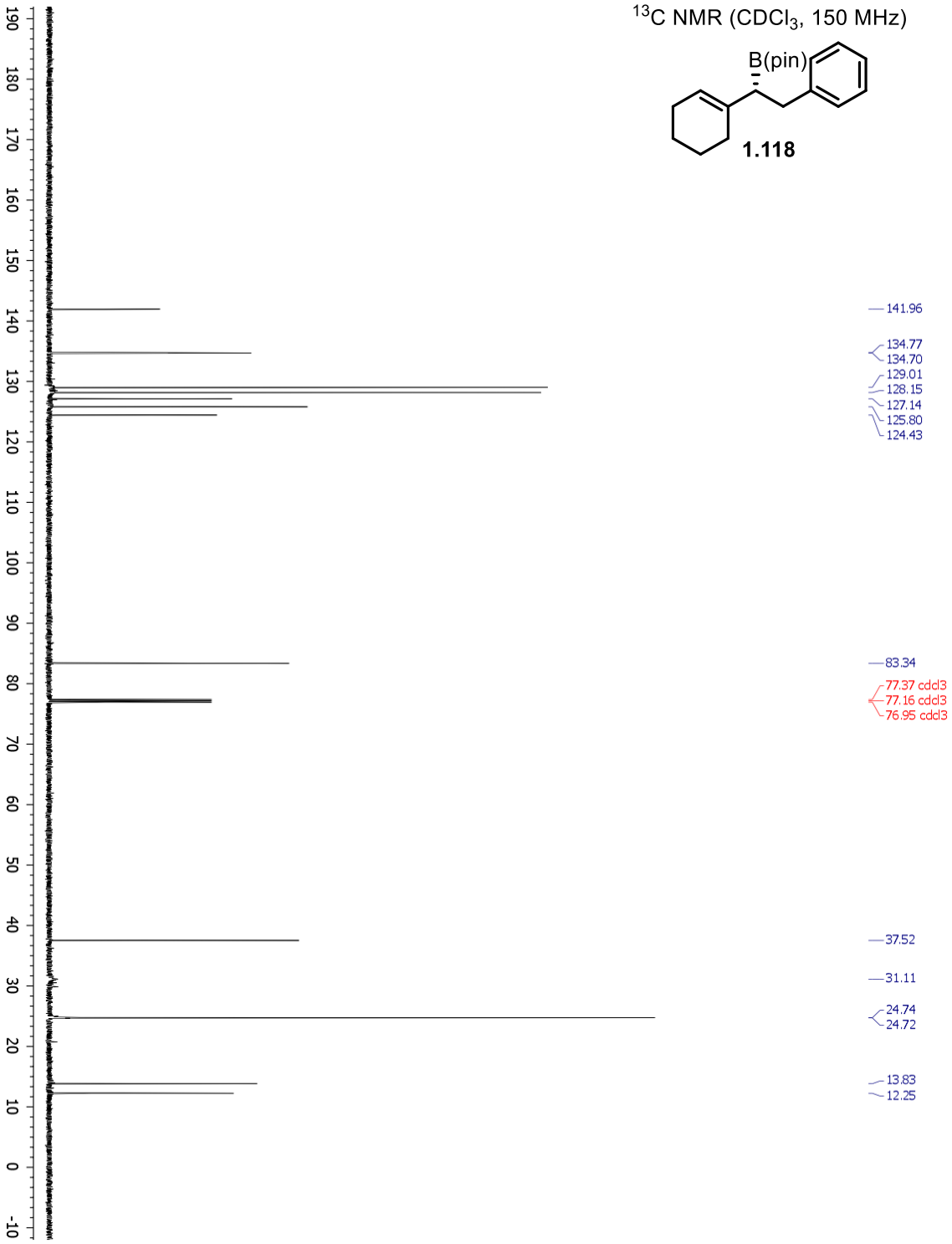

^{1}H NMR ($CDCl_3$, 600 MHz)
Me
B(pin)
Me
1.117
7.26 cdcl3
7.24
7.24
7.23
7.22
7.21
7.21
7.20
7.20
7.19
7.19
7.19
7.15
7.15
7.14
7.14
7.14
7.13
7.13
7.12
7.12
5.11
5.10
2.84
2.83
2.82
2.80
2.69
2.68
2.67
2.65
2.33
2.32
2.30
2.29
1.67
1.51
1.16
1.14
3.50
0.82
0.88
1.00
1.00
0.93
2.93
2.70
5.82
5.90
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0

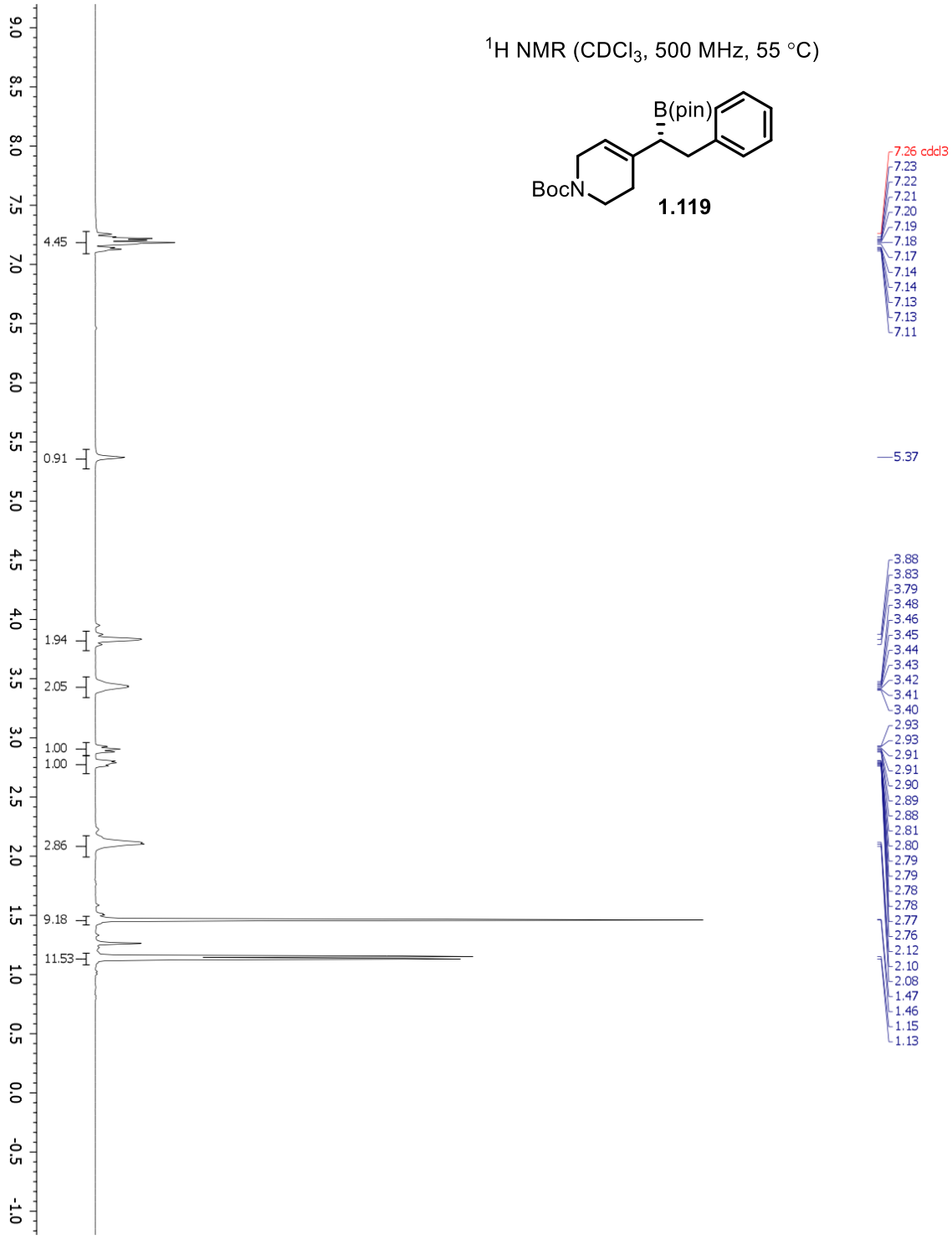
^{13}C NMR ($CDCl_3$, 150 MHz)



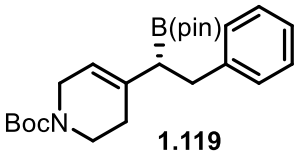
1.117


^{1}H NMR ($CDCl_3$, 600 MHz)
B(pin)
1.118
3.29
0.93
0.93
1.00
0.99
4.54
2.05
1.91
5.07
5.05
7.26 cdcl3

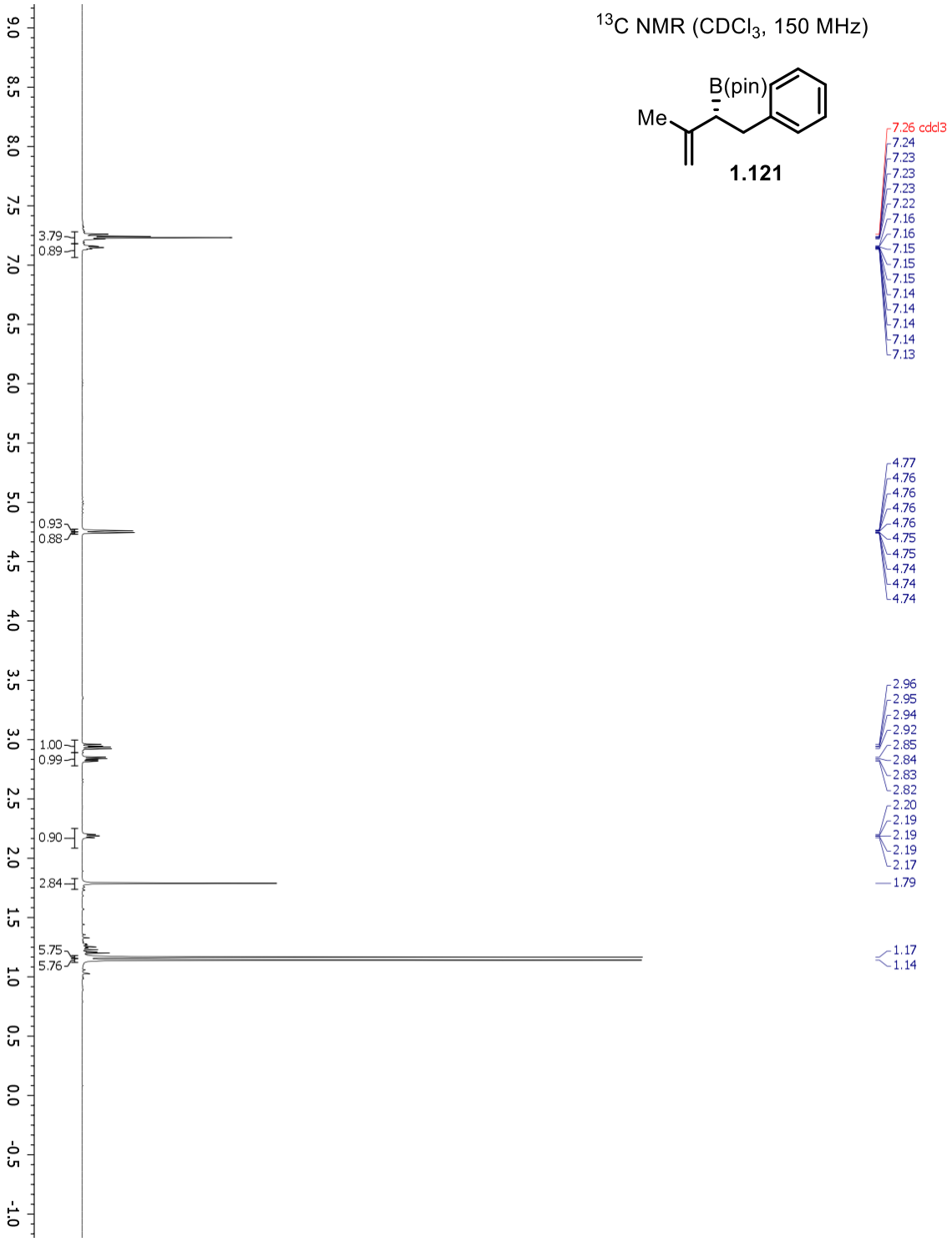

^{13}C NMR ($CDCl_3$, 150 MHz)
B(pin)
1.118
141.96
134.77
134.70
129.01
128.15
127.14
125.80
124.43
83.34
77.37 cdcl3
77.16 cdcl3
76.95 cdcl3
37.52
31.11
24.74
24.72
13.83
12.25


^{1}H NMR ($CDCl_3$, 500 MHz, 55 °C)
B(pin)
BocN
1.119
4.45
0.91
1.94
2.05
1.00
1.00
2.86
9.18
11.53
7.26 cdcl3
7.23
7.22
7.21
7.20
7.19
7.18
7.17
7.14
7.14
7.13
7.13
7.11
5.37
3.88
3.83
3.79
3.48
3.46
3.45
3.44
3.43
3.42
3.41
3.40
2.93
2.93
2.91
2.91
2.90
2.89
2.88
2.81
2.80
2.79
2.79
2.78
2.78
2.77
2.76
2.12
2.10
2.08
1.47
1.46
1.15
1.13

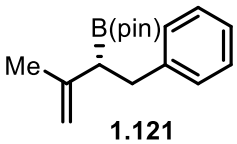
^{13}C NMR ($CDCl_3$, 125 MHz, 55 °C)



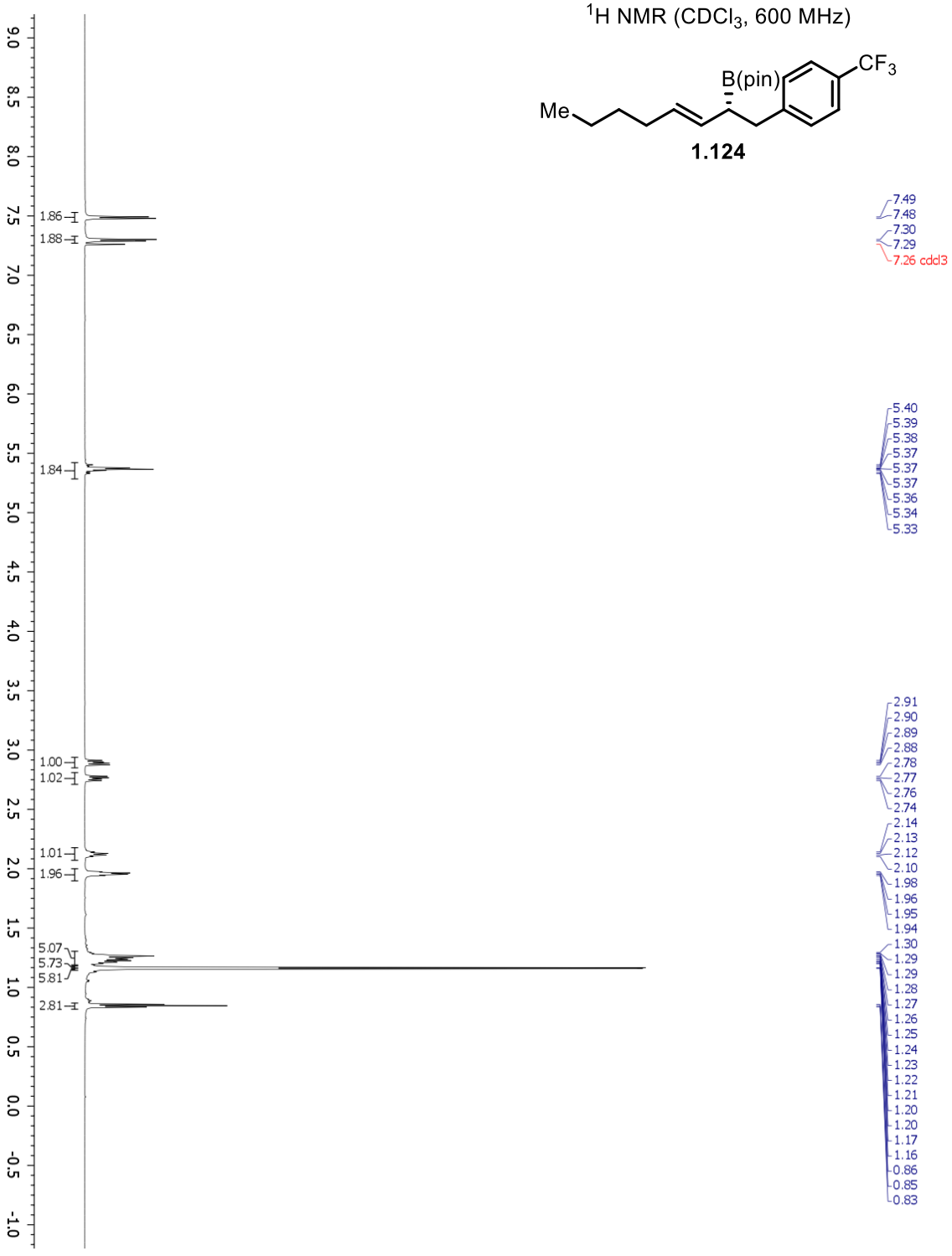
1.119

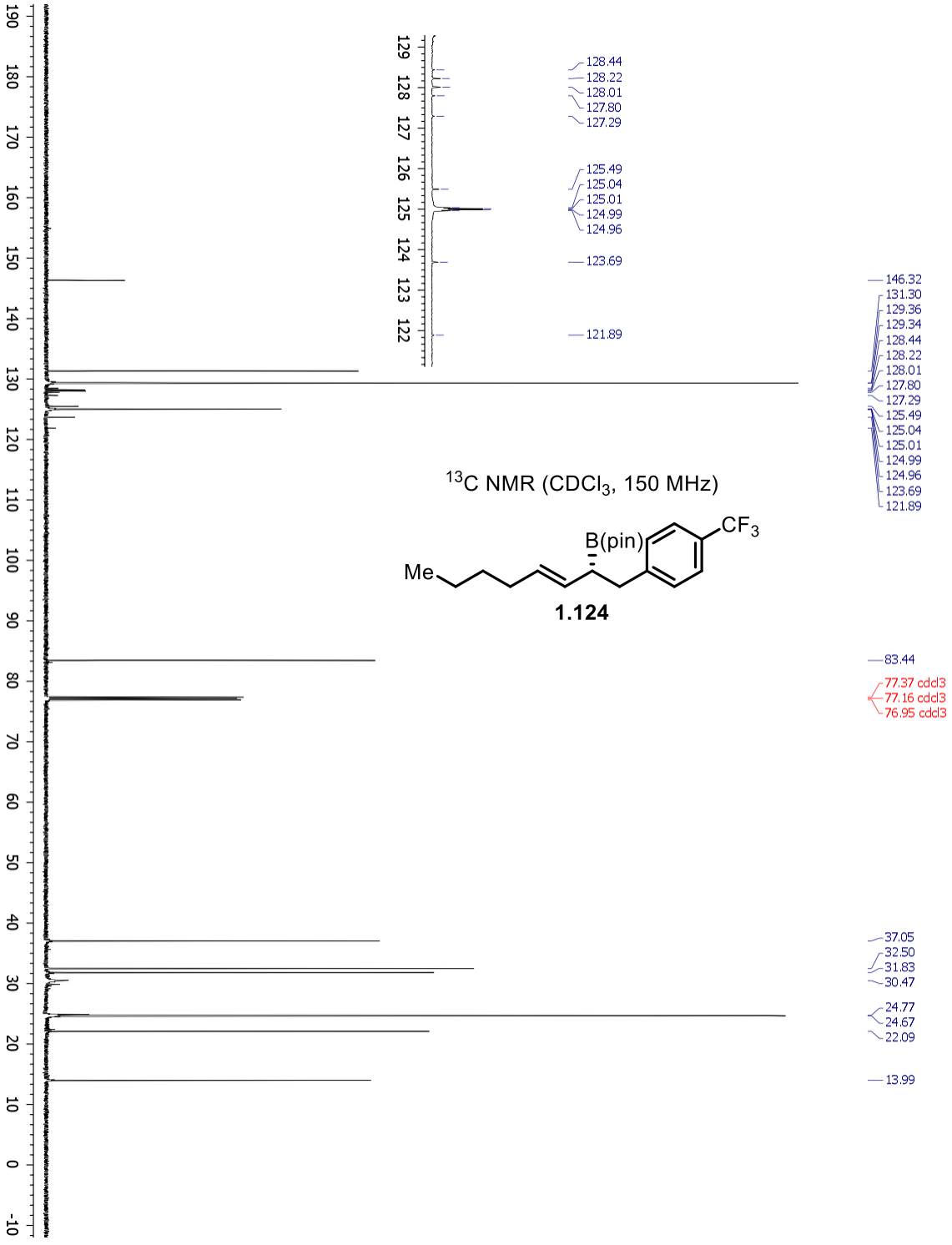

^{13}C NMR ($CDCl_3$, 150 MHz)
B(pin)
Me
1.121
7.26 cdcl3
7.24
7.23
7.23
7.23
7.22
7.16
7.16
7.15
7.15
7.15
7.14
7.14
7.14
7.14
7.13
4.77
4.76
4.76
4.76
4.76
4.75
4.75
4.74
4.74
4.74
2.96
2.95
2.94
2.92
2.85
2.84
2.83
2.82
2.20
2.19
2.19
2.19
2.17
1.79
1.17
1.14
3.79
0.89
0.93
0.88
1.00
0.99
0.90
2.84
5.75
5.76

^{1}H NMR ($CDCl_3$, 600 MHz)



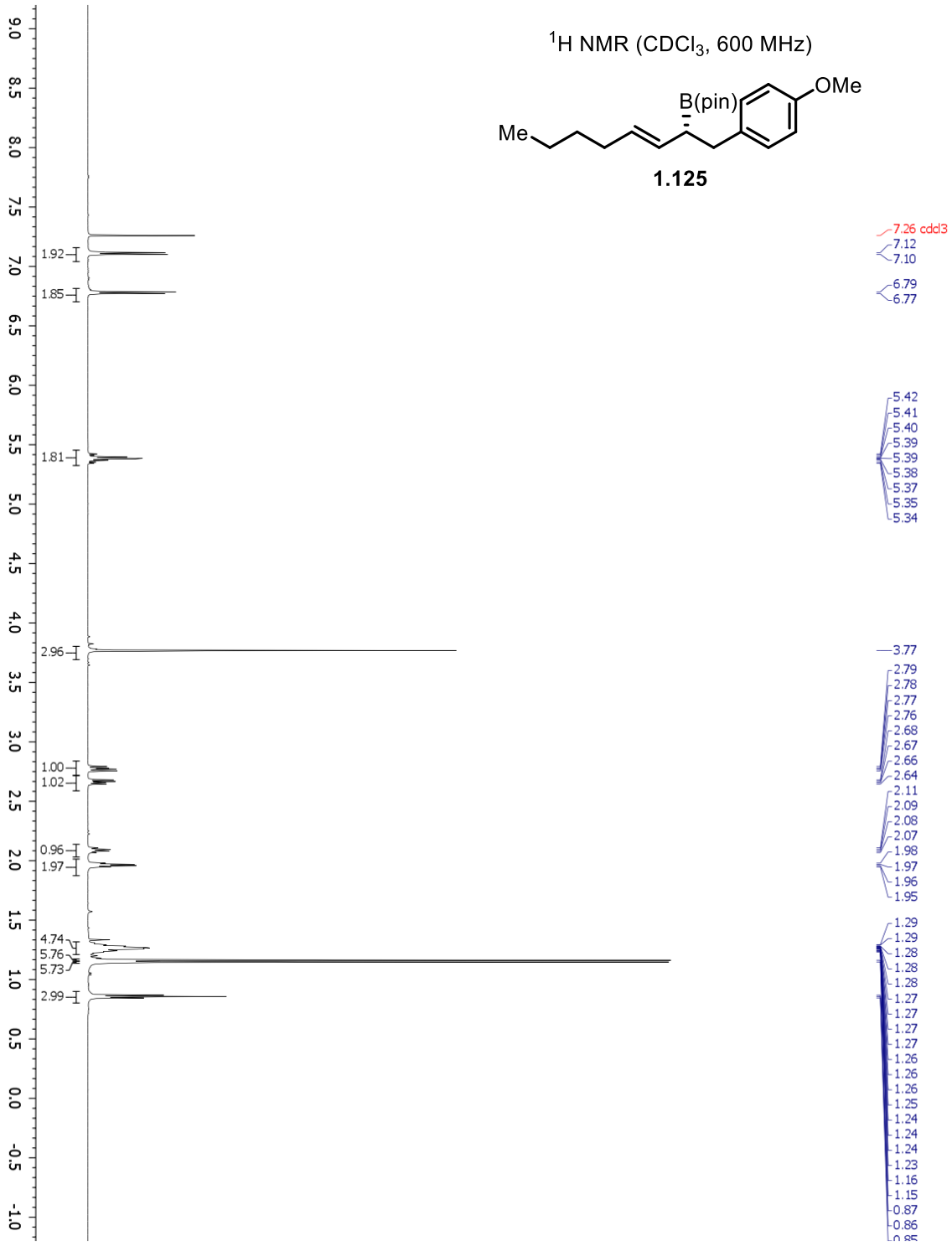
1.121

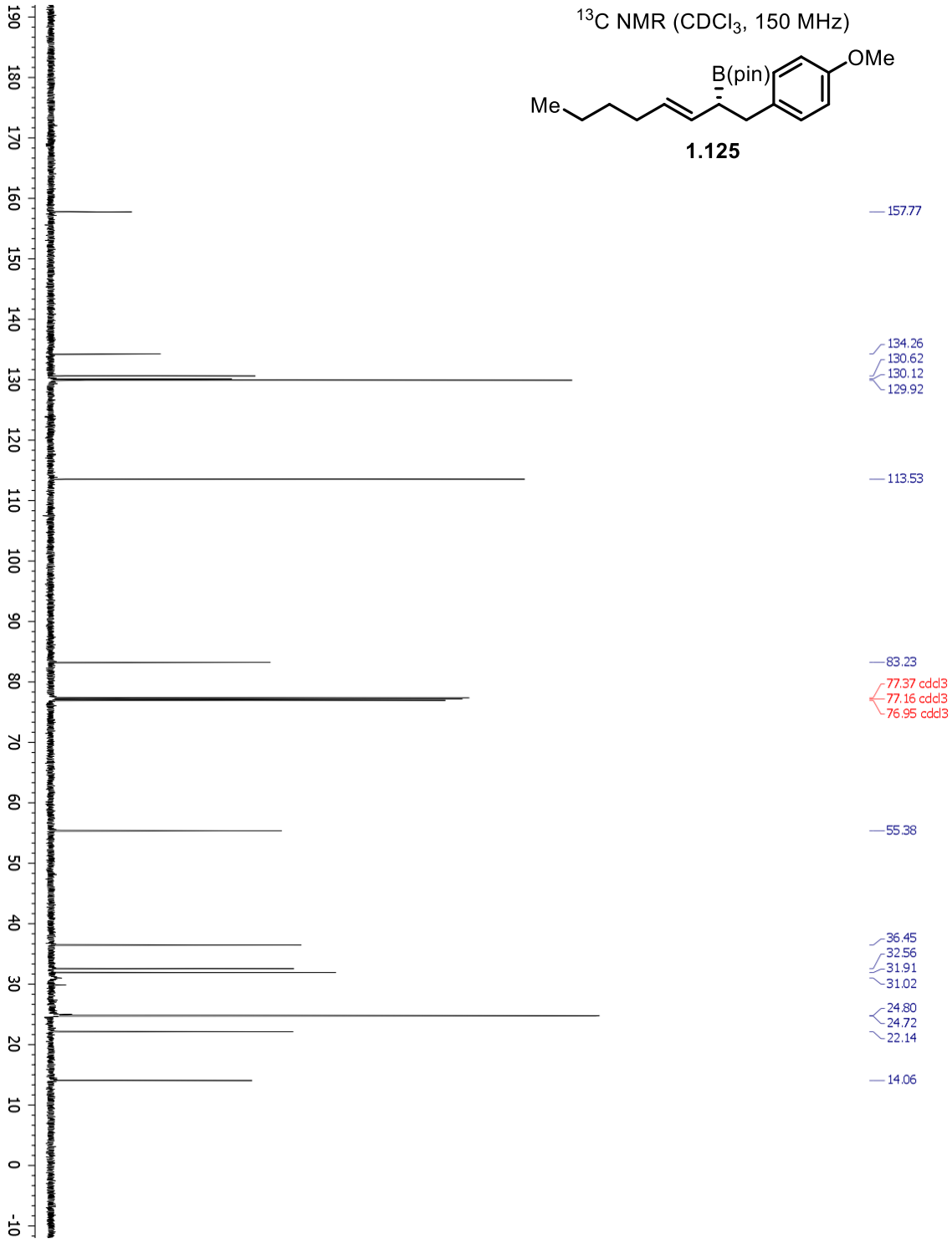

^{1}H NMR ($CDCl_3$, 600 MHz)
B(pin)
CF_3
Me
1.124
7.49
7.48
7.30
7.29
7.26 cdcl3
5.40
5.39
5.38
5.37
5.37
5.37
5.36
5.34
5.33
2.91
2.90
2.89
2.88
2.78
2.77
2.76
2.74
2.14
2.13
2.12
2.10
1.98
1.96
1.95
1.94
1.30
1.29
1.29
1.28
1.27
1.26
1.25
1.24
1.23
1.22
1.21
1.20
1.20
1.17
1.16
0.86
0.85
0.83
1.86
1.88
1.84
1.00
1.02
1.01
1.96
5.07
5.73
5.81
2.81



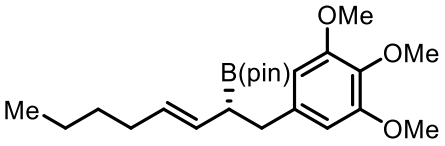
^{13}C NMR ($CDCl_3$, 150 MHz)

1.124


^{1}H NMR ($CDCl_3$, 600 MHz)
B(pin)
OMe
Me
1.125
7.26 cdcl3
7.12
7.10
6.79
6.77
5.42
5.41
5.40
5.39
5.39
5.38
5.37
5.35
5.34
3.77
2.79
2.78
2.77
2.76
2.68
2.67
2.66
2.64
2.11
2.09
2.08
2.07
1.98
1.97
1.96
1.95
1.29
1.29
1.28
1.28
1.28
1.27
1.27
1.27
1.27
1.26
1.26
1.26
1.25
1.24
1.24
1.24
1.23
1.16
1.15
0.87
0.86
1.92
1.85
1.81
2.96
1.00
1.02
0.96
1.97
4.74
5.76
5.73
2.99

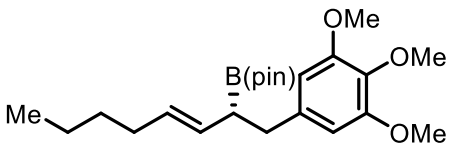

^{13}C NMR ($CDCl_3$, 150 MHz)
B(pin)
OMe
Me
1.125
157.77
134.26
130.62
130.12
129.92
113.53
83.23
77.37 cdcl3
77.16 cdcl3
76.95 cdcl3
55.38
36.45
32.56
31.91
31.02
24.80
24.72
22.14
14.06

^{1}H NMR ($CDCl_3$, 600 MHz)

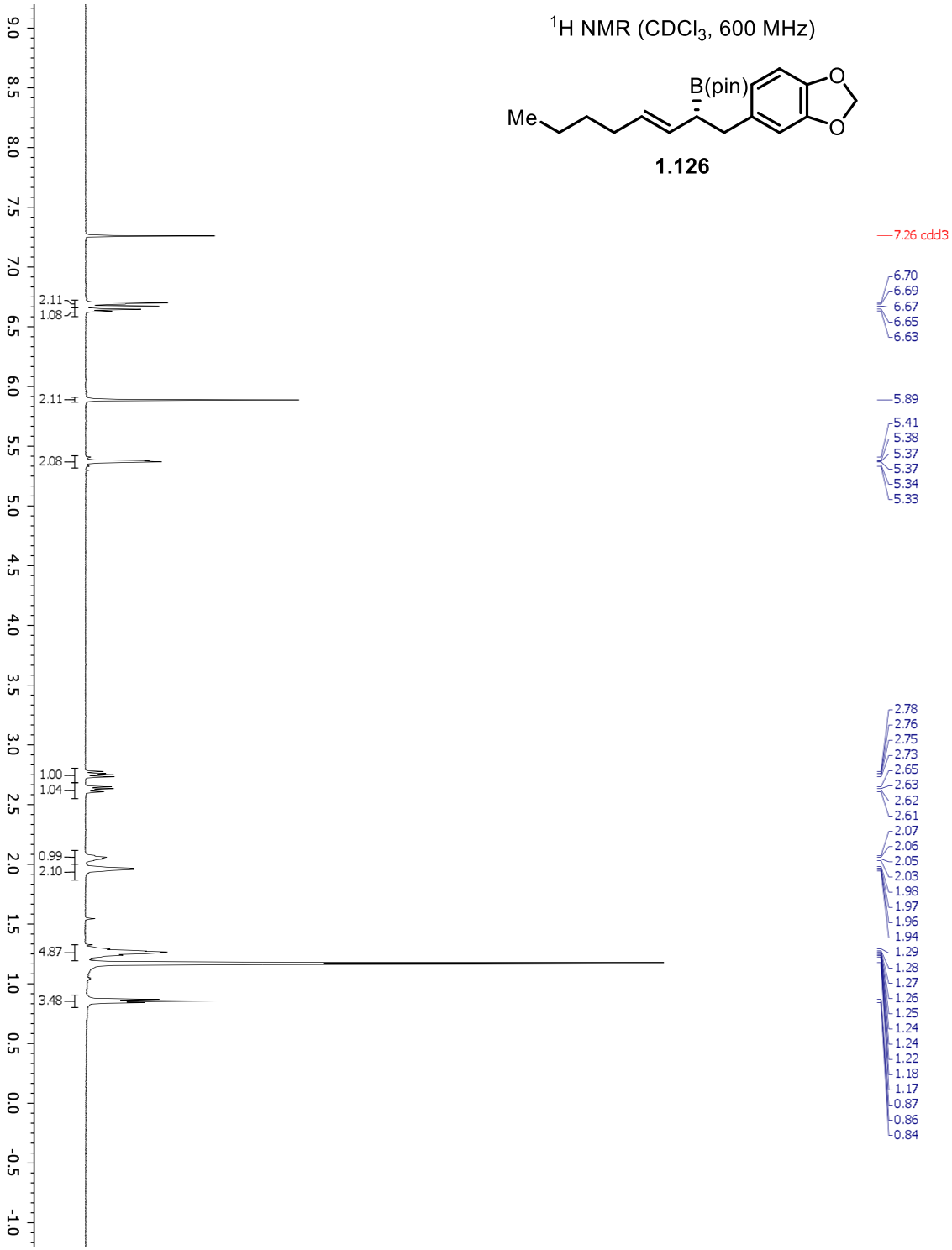


1.126

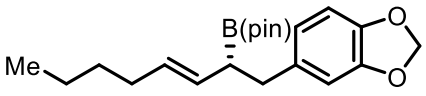
^{13}C NMR ($CDCl_3$, 150 MHz)



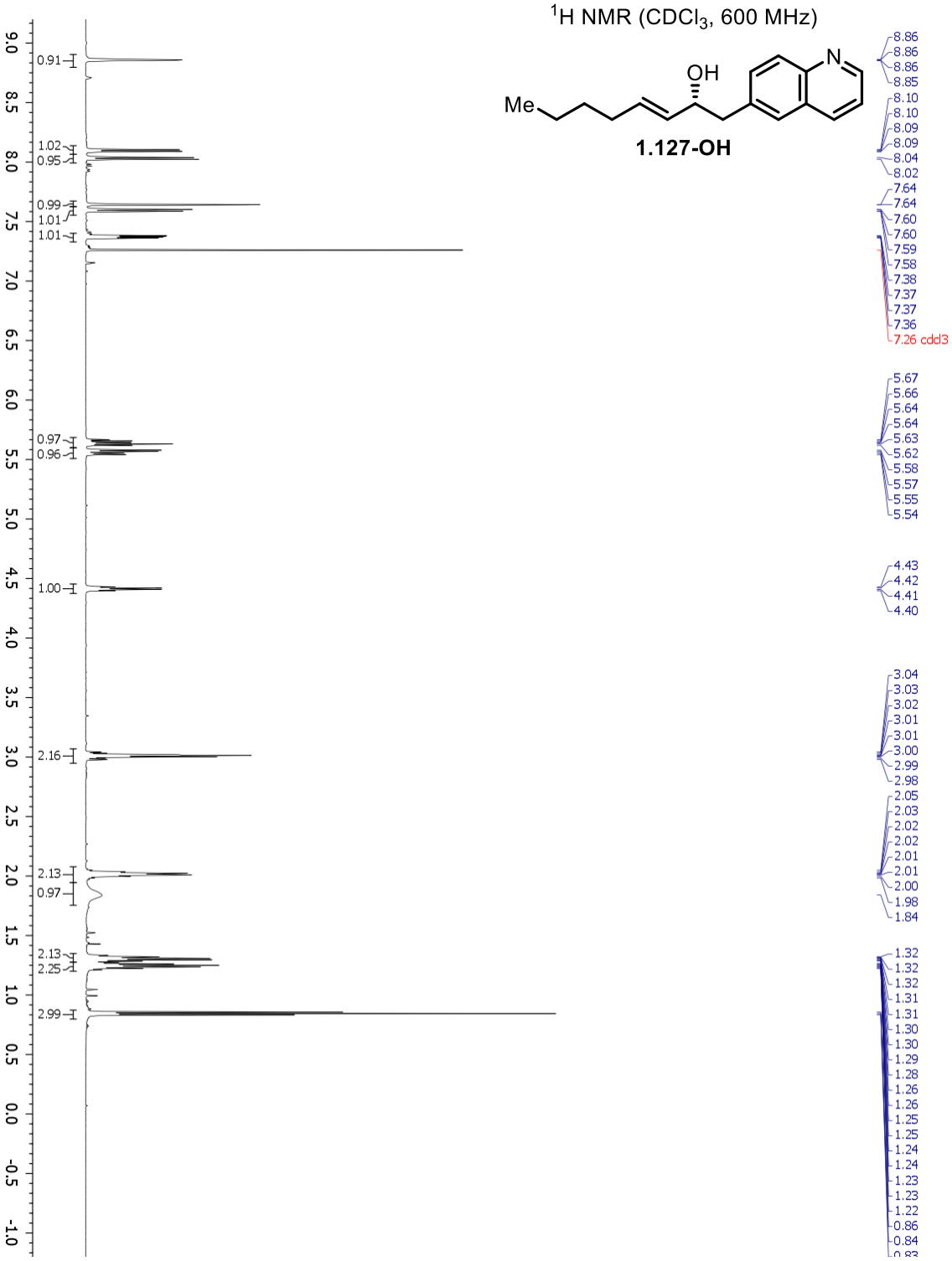
1.126

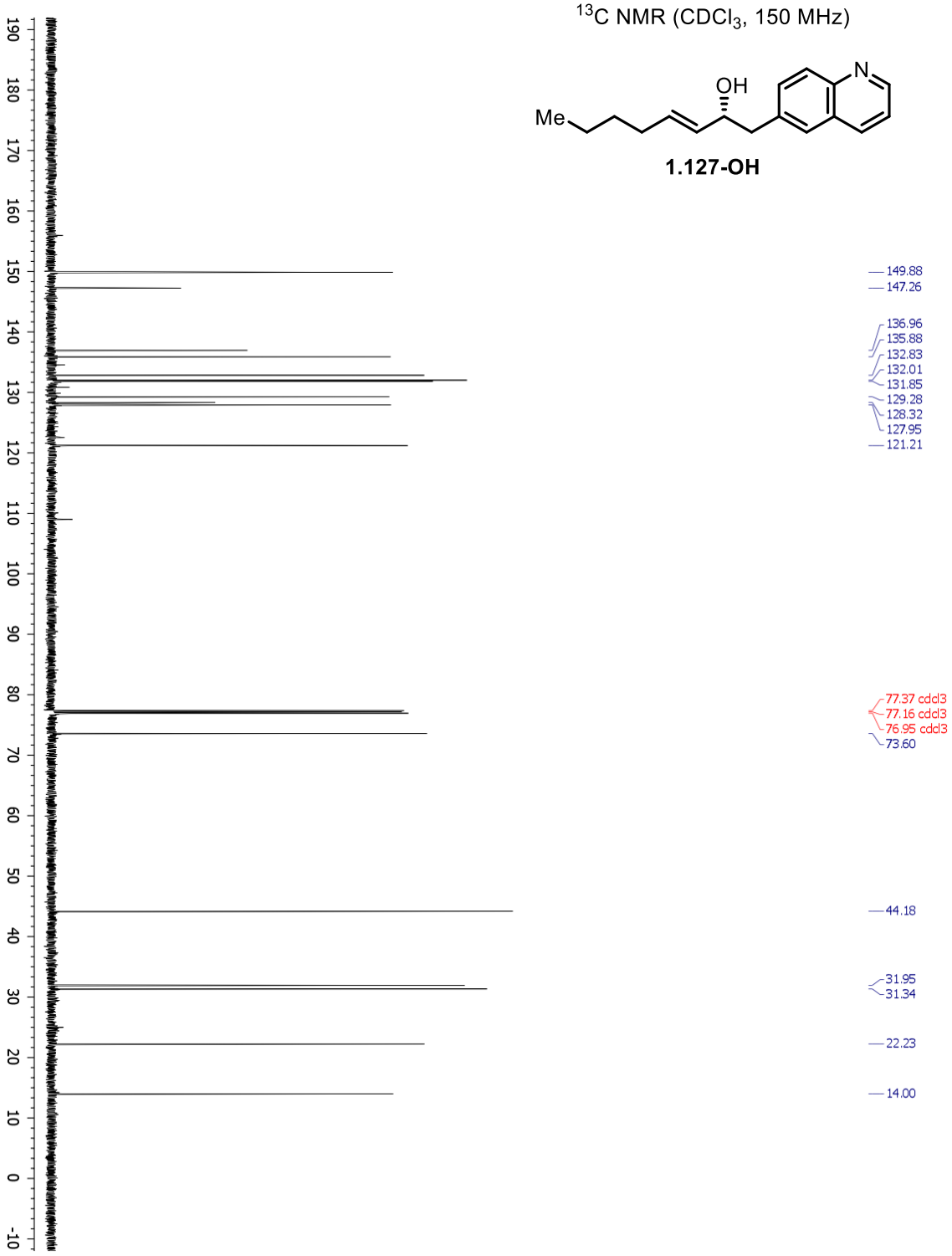

^{1}H NMR ($CDCl_3$, 600 MHz)
B(pin)
Me
O
O
1.126
7.26 cdcl3
6.70
6.69
6.67
6.65
6.63
5.89
5.41
5.38
5.37
5.37
5.34
5.33
2.78
2.76
2.75
2.73
2.65
2.63
2.62
2.61
2.07
2.06
2.05
2.03
1.98
1.97
1.96
1.94
1.29
1.28
1.27
1.26
1.25
1.24
1.24
1.22
1.18
1.17
0.87
0.86
0.84
2.11
1.08
2.11
2.08
1.00
1.04
0.99
2.10
4.87
3.48

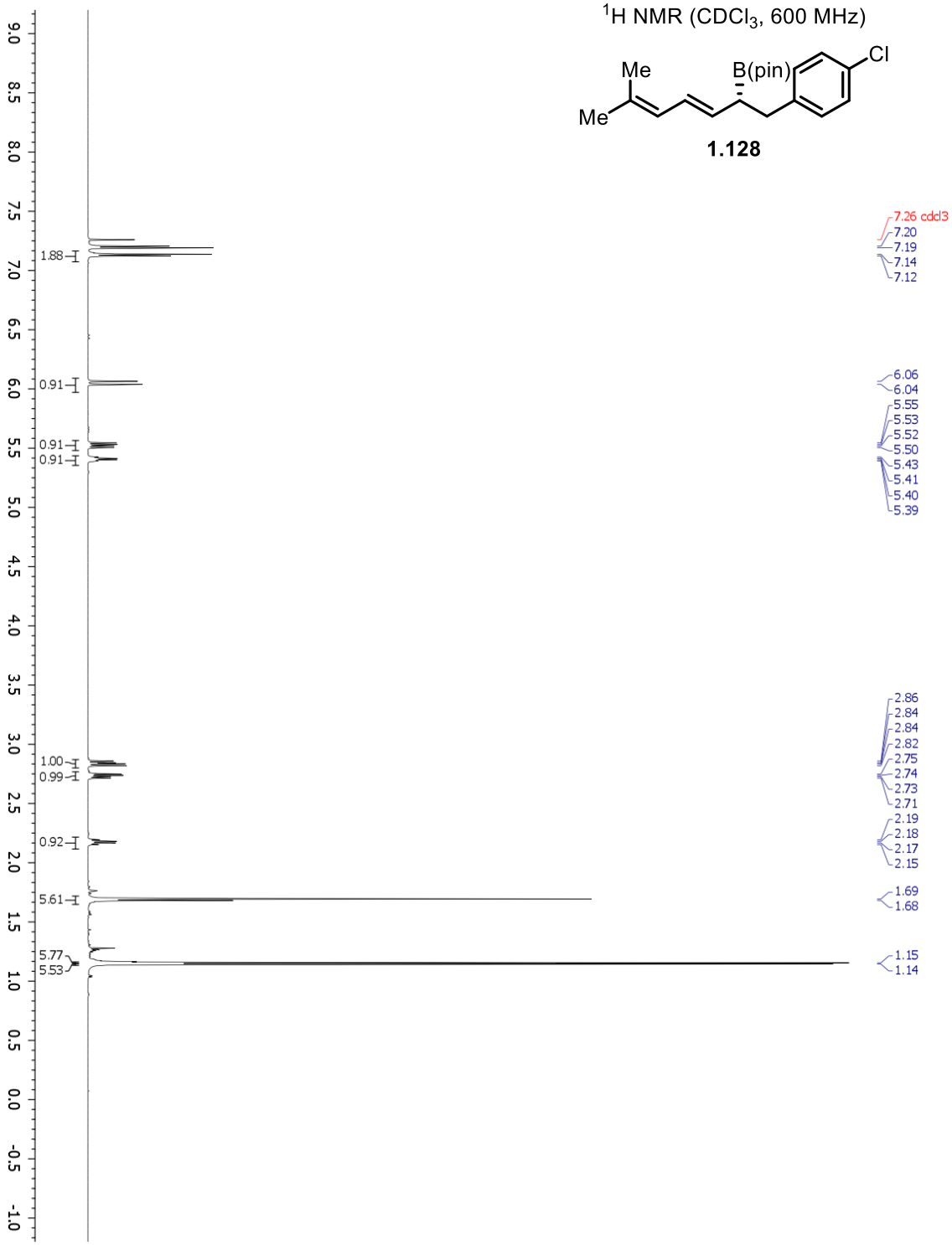
^{13}C NMR ($CDCl_3$, 150 MHz)

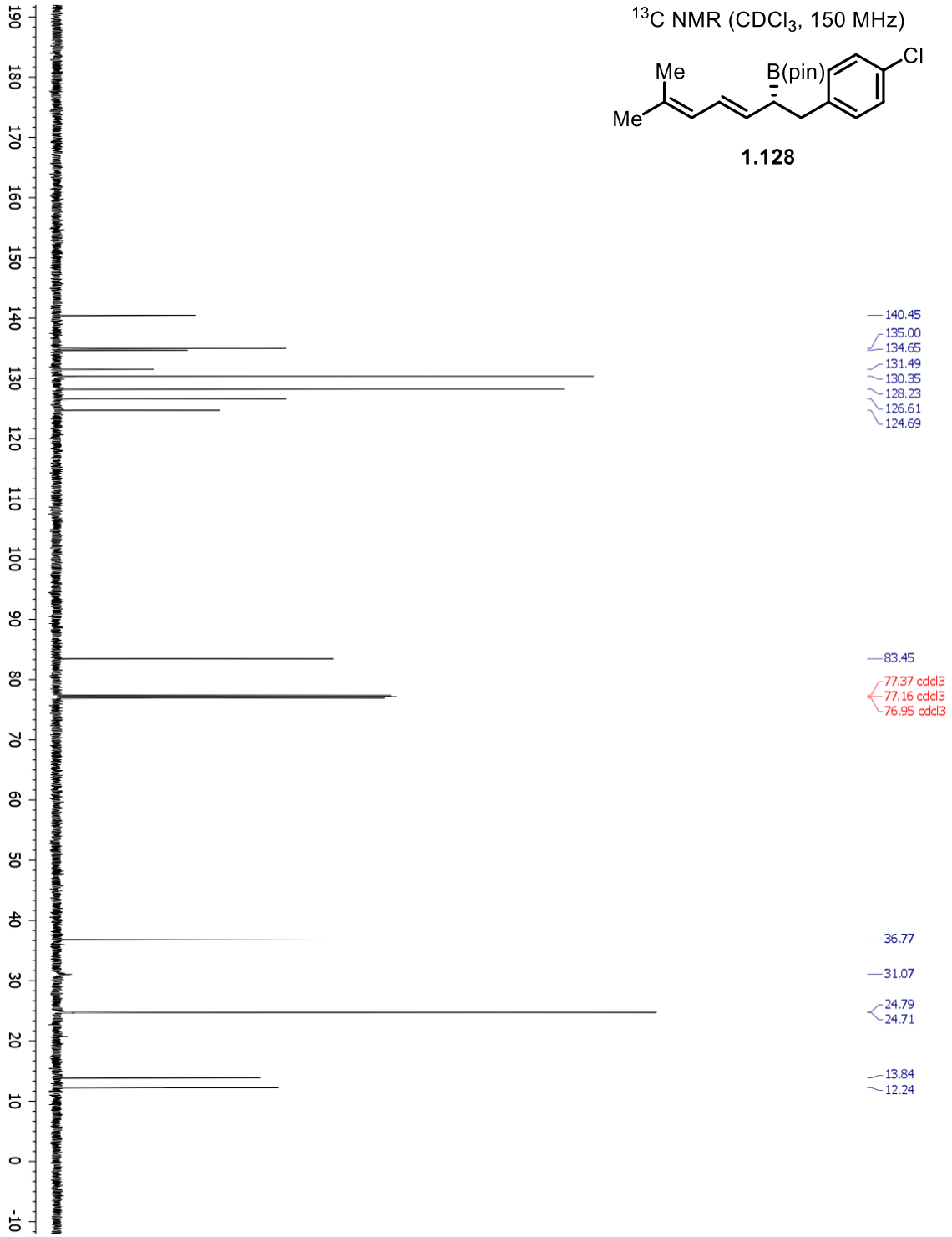


1.126

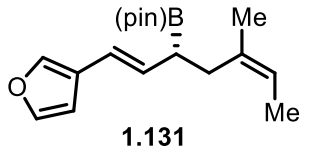

^{1}H NMR ($CDCl_3$, 600 MHz)
Me
OH
N
1.127-OH
0.91
1.02
0.95
0.99
1.01
1.01
0.97
0.96
1.00
2.16
2.13
0.97
2.13
2.25
2.99
8.86
8.86
8.86
8.85
8.10
8.10
8.09
8.09
8.04
8.02
7.64
7.64
7.60
7.60
7.59
7.58
7.38
7.37
7.37
7.36
7.26 cdcl3
5.67
5.66
5.64
5.64
5.63
5.62
5.58
5.57
5.55
5.54
4.43
4.42
4.41
4.40
3.04
3.03
3.02
3.01
3.01
3.00
2.99
2.98
2.05
2.03
2.02
2.02
2.01
2.01
2.00
1.98
1.84
1.32
1.32
1.32
1.31
1.31
1.30
1.30
1.29
1.28
1.26
1.26
1.25
1.25
1.24
1.24
1.23
1.23
1.22
0.86
0.84


^{13}C NMR ($CDCl_3$, 150 MHz)
OH
N
Me
1.127-OH
149.88
147.26
136.96
135.88
132.83
132.01
131.85
129.28
128.32
127.95
121.21
77.37 cdcl3
77.16 cdcl3
76.95 cdcl3
73.60
44.18
31.95
31.34
22.23
14.00

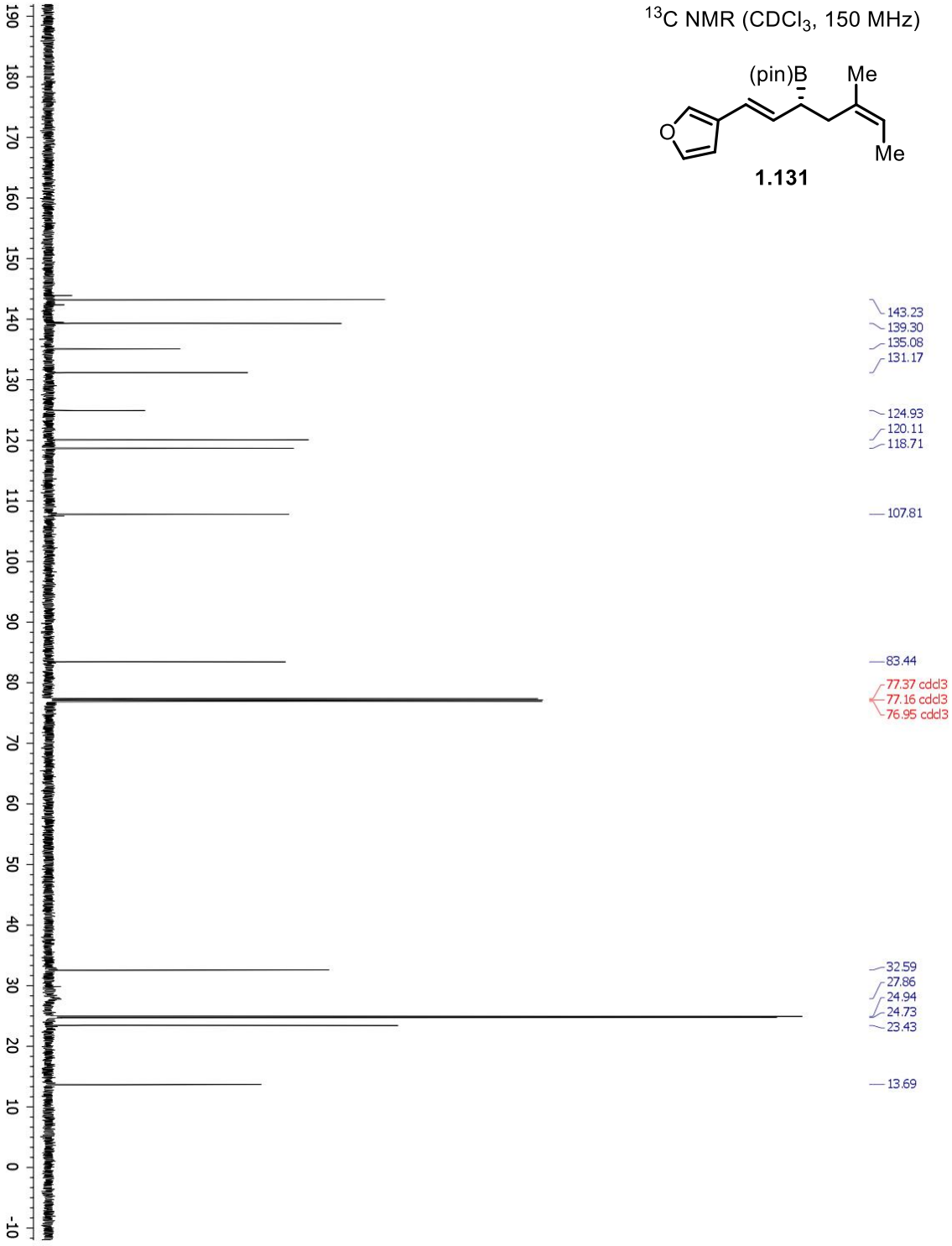

^{1}H NMR ($CDCl_3$, 600 MHz)
Me
B(pin)
Cl
Me
1.128
7.26 cdcl3
7.20
7.19
7.14
7.12
6.06
6.04
5.55
5.53
5.52
5.50
5.43
5.41
5.40
5.39
2.86
2.84
2.84
2.82
2.75
2.74
2.73
2.71
2.19
2.18
2.17
2.15
1.69
1.68
1.15
1.14
1.88
0.91
0.91
0.91
1.00
0.99
0.92
5.61
5.77
5.53


^{13}C NMR ($CDCl_3$, 150 MHz)
Me
B(pin)
Cl
Me
1.128
140.45
135.00
134.65
131.49
130.35
128.23
126.61
124.69
83.45
77.37 cdcl3
77.16 cdcl3
76.95 cdcl3
36.77
31.07
24.79
24.71
13.84
12.24

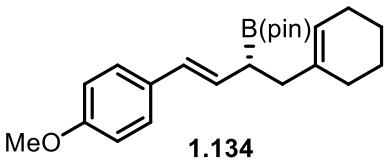
^{1}H NMR ($CDCl_3$, 600 MHz)



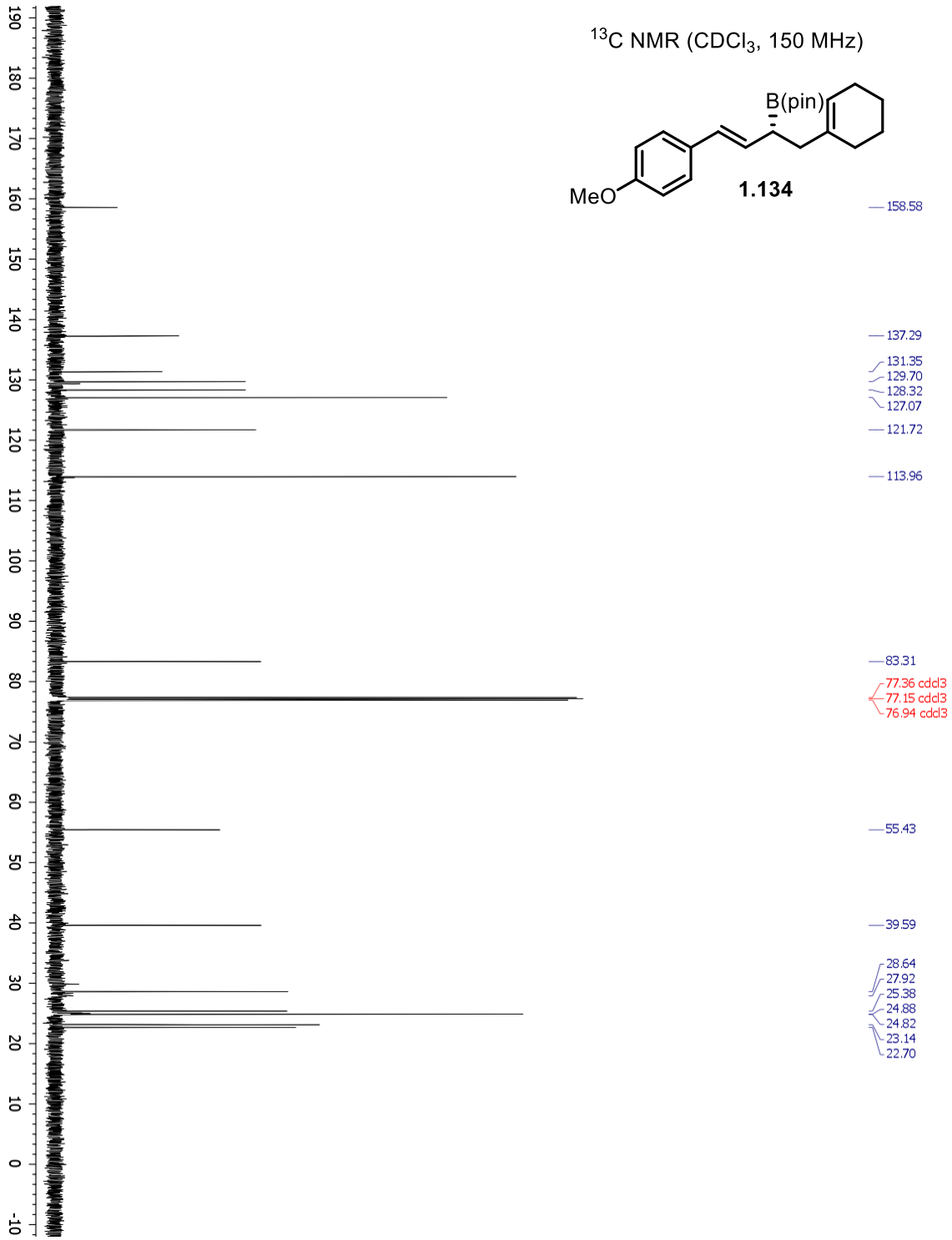
1.131

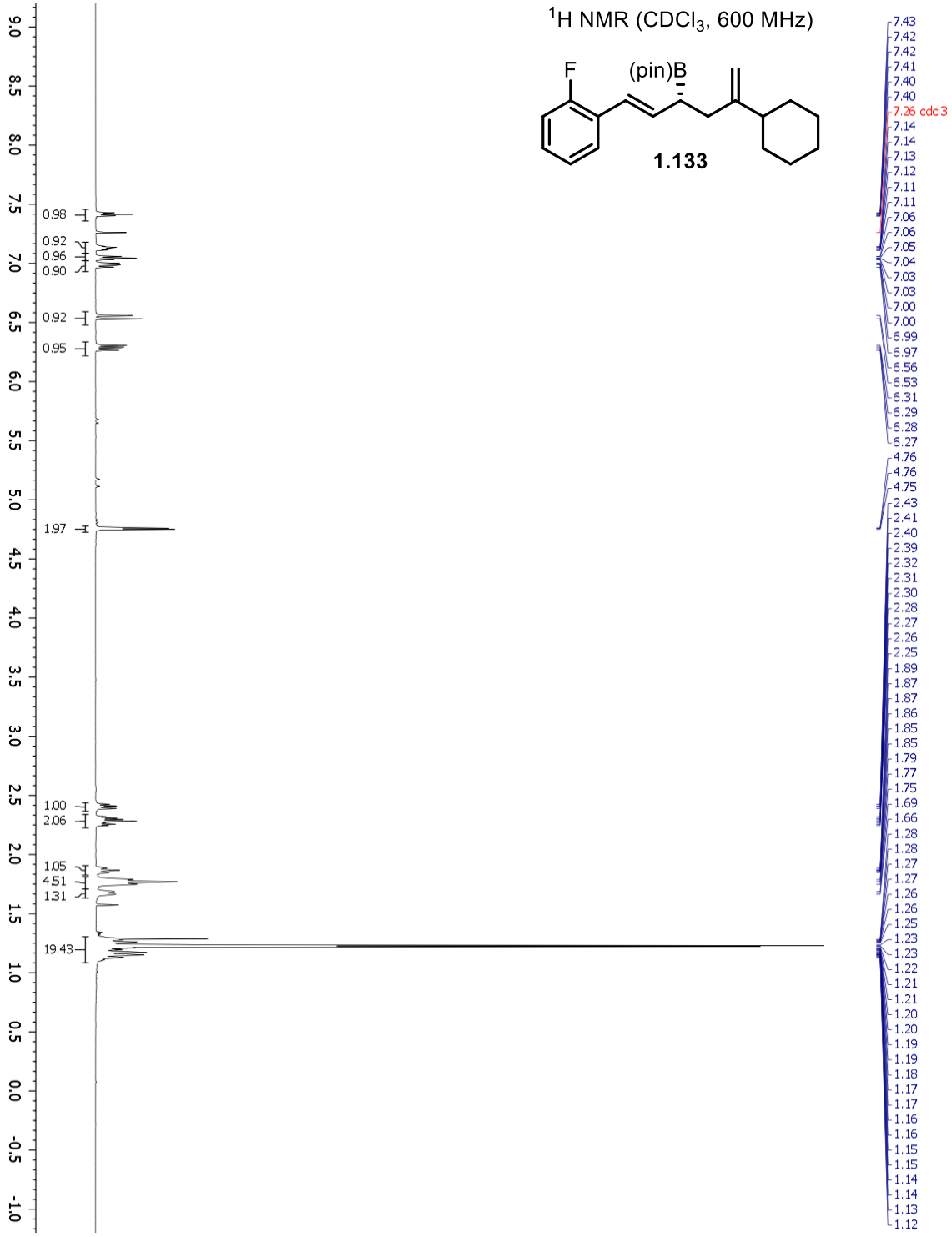

^{13}C NMR ($CDCl_3$, 150 MHz)
(pin)B
Me
O
Me
1.131
143.23
139.30
135.08
131.17
124.93
120.11
118.71
107.81
83.44
77.37 cdcl3
77.16 cdcl3
76.95 cdcl3
32.59
27.86
24.94
24.73
23.43
13.69

^{1}H NMR ($CDCl_3$, 600 MHz)

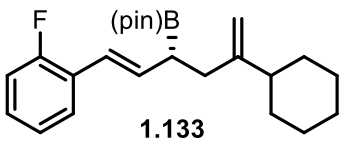


1.134

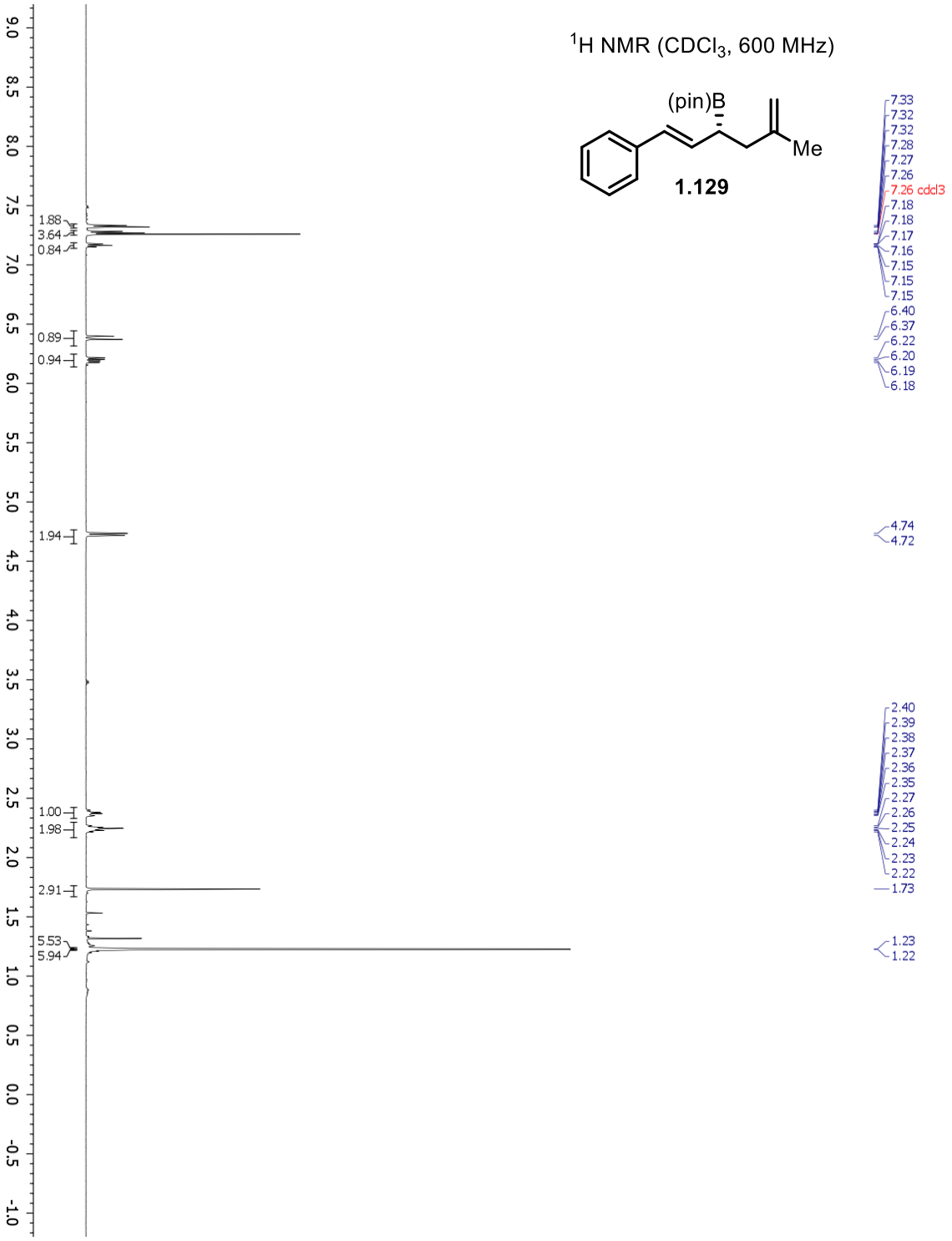

^{13}C NMR ($CDCl_3$, 150 MHz)
B(pin)
MeO
1.134
158.58
137.29
131.35
129.70
128.32
127.07
121.72
113.96
83.31
77.36 cdcl3
77.15 cdcl3
76.94 cdcl3
55.43
39.59
28.64
27.92
25.38
24.88
24.82
23.14
22.70

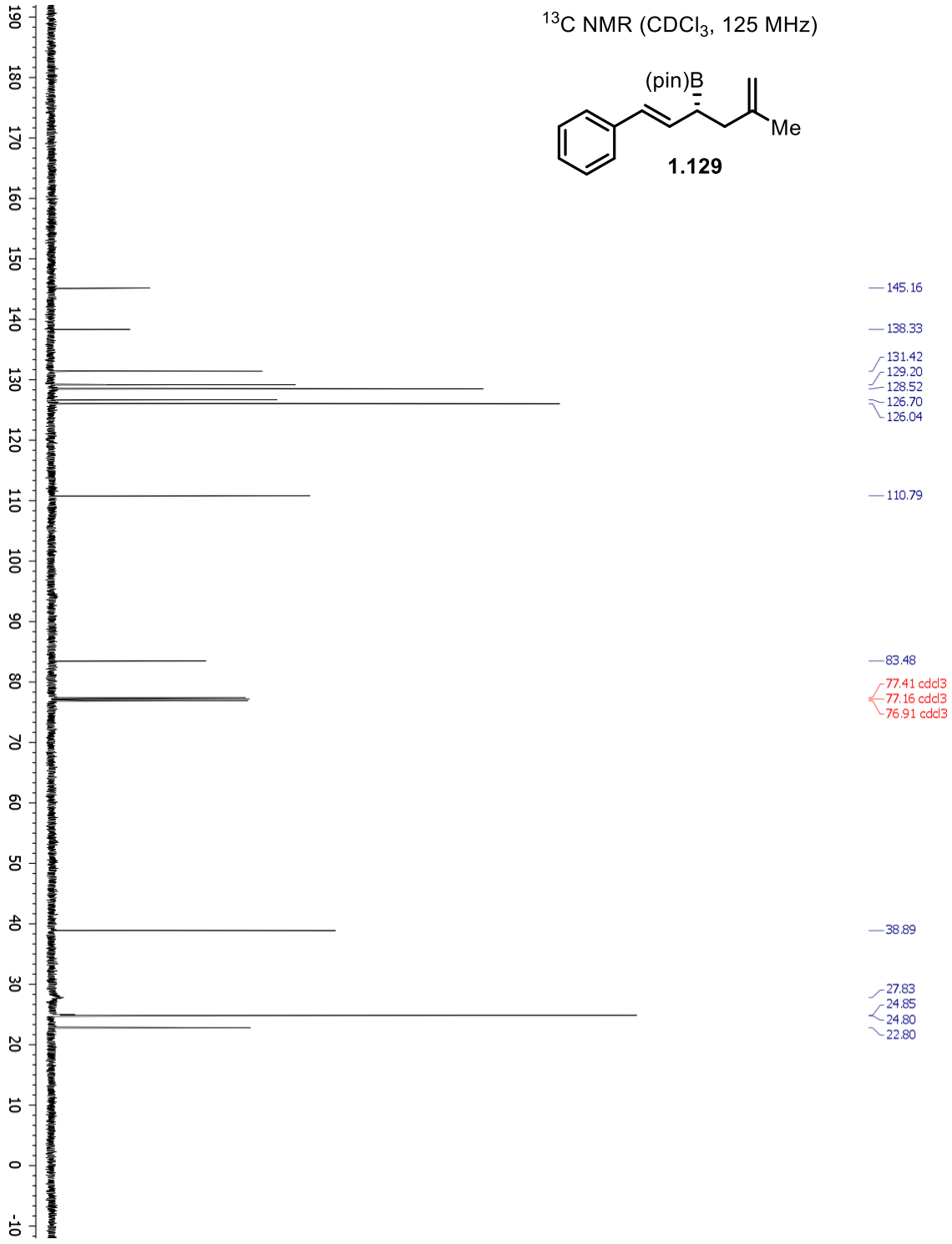

^{1}H NMR ($CDCl_3$, 600 MHz)
F
(pin)B
1.133
0.98
0.92
0.96
0.90
0.92
0.95
1.97
1.00
2.06
1.05
4.51
1.31
19.43
7.26 cdcl3

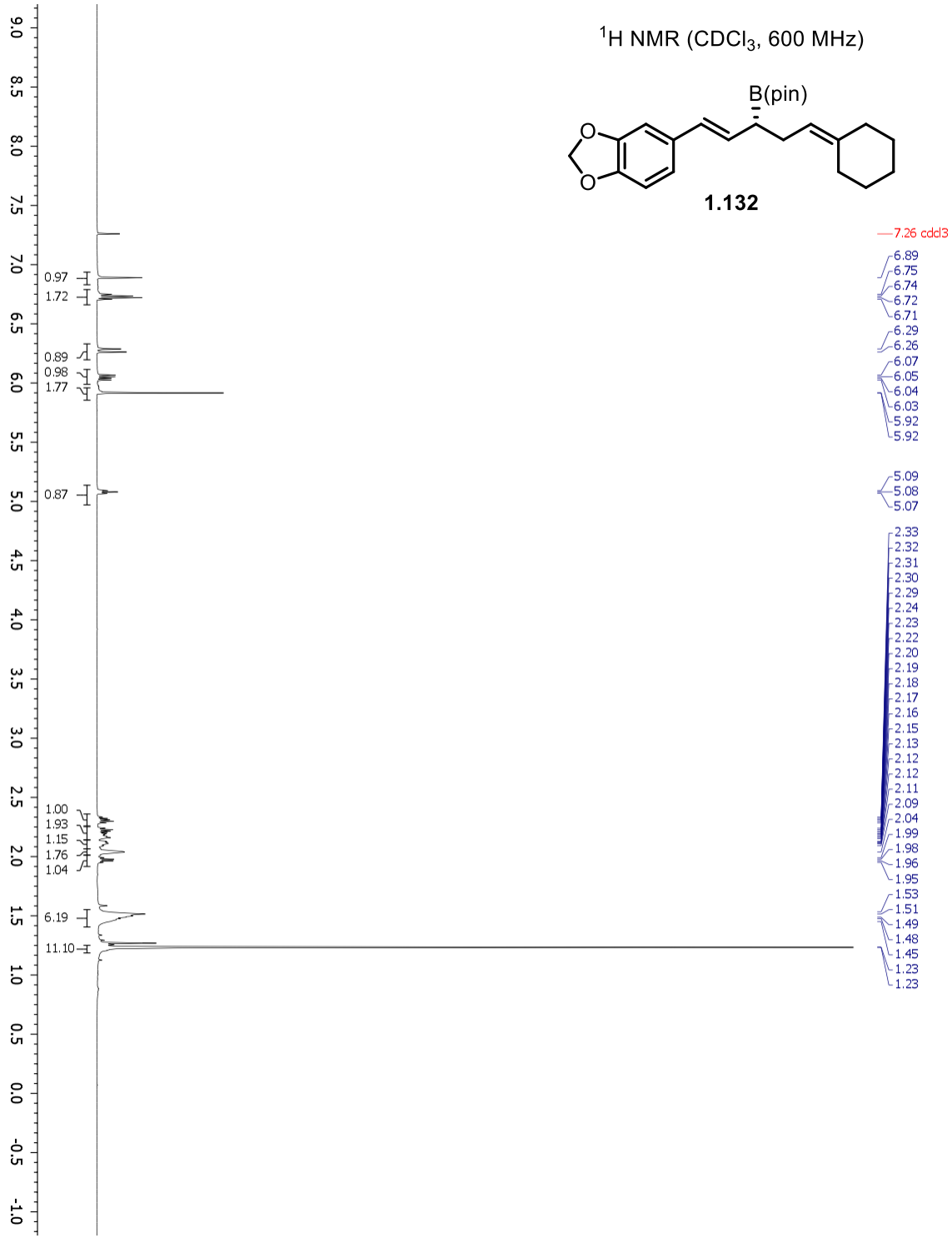
^{13}C NMR ($CDCl_3$, 150 MHz)



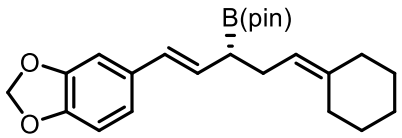
1.133


^{1}H NMR ($CDCl_3$, 600 MHz)
(pin)B
Me
1.129
7.33
7.32
7.32
7.28
7.27
7.26
7.26 cdcl3
7.18
7.18
7.17
7.16
7.15
7.15
7.15
6.40
6.37
6.22
6.20
6.19
6.18
4.74
4.72
2.40
2.39
2.38
2.37
2.36
2.35
2.27
2.26
2.25
2.24
2.23
2.22
1.73
1.23
1.22
1.88
3.64
0.84
0.89
0.94
1.94
1.00
1.98
2.91
5.53
5.94

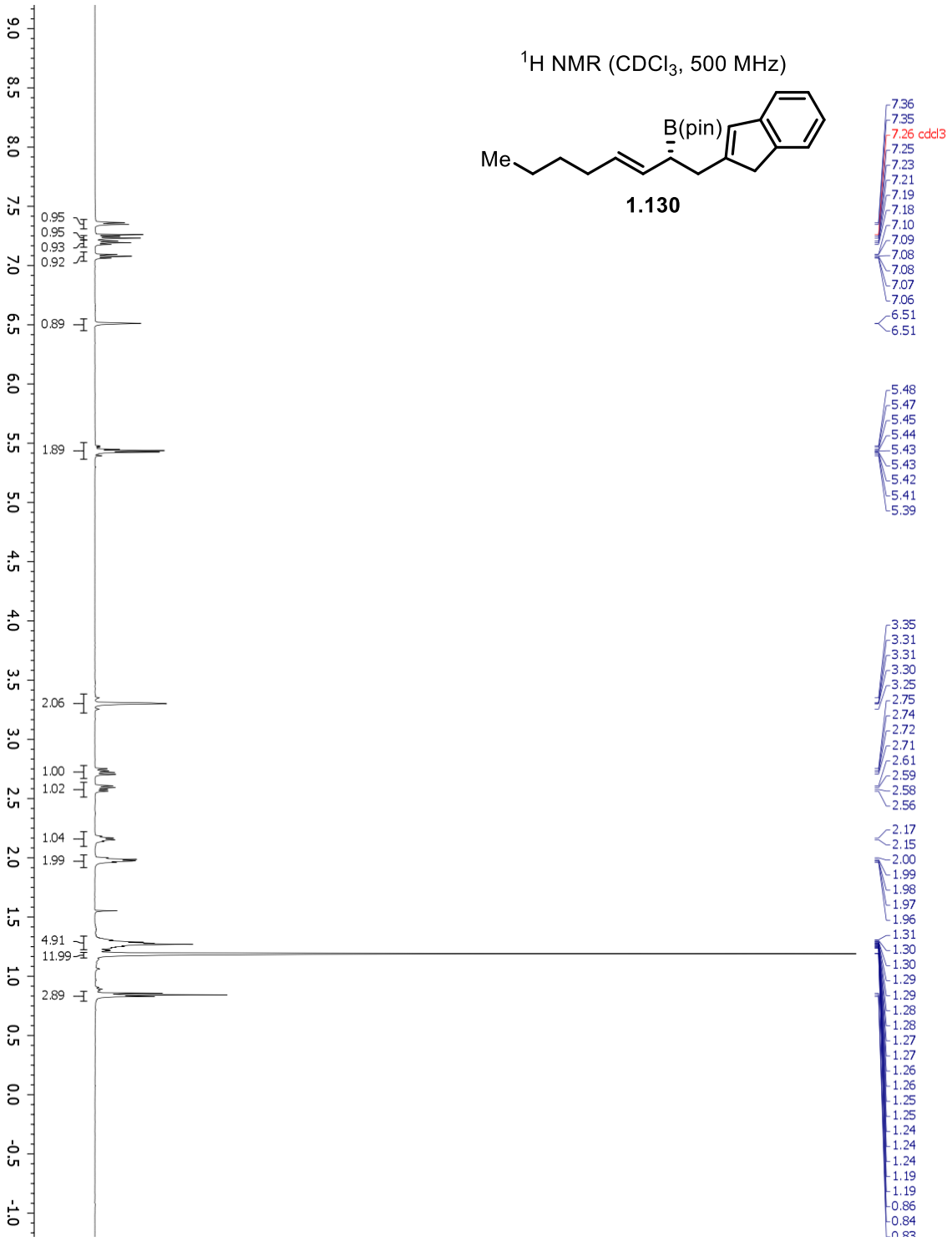

^{13}C NMR ($CDCl_3$, 125 MHz)
(pin)B
Me
1.129
145.16
138.33
131.42
129.20
128.52
126.70
126.04
110.79
83.48
77.41 cdcl3
77.16 cdcl3
76.91 cdcl3
38.89
27.83
24.85
24.80
22.80

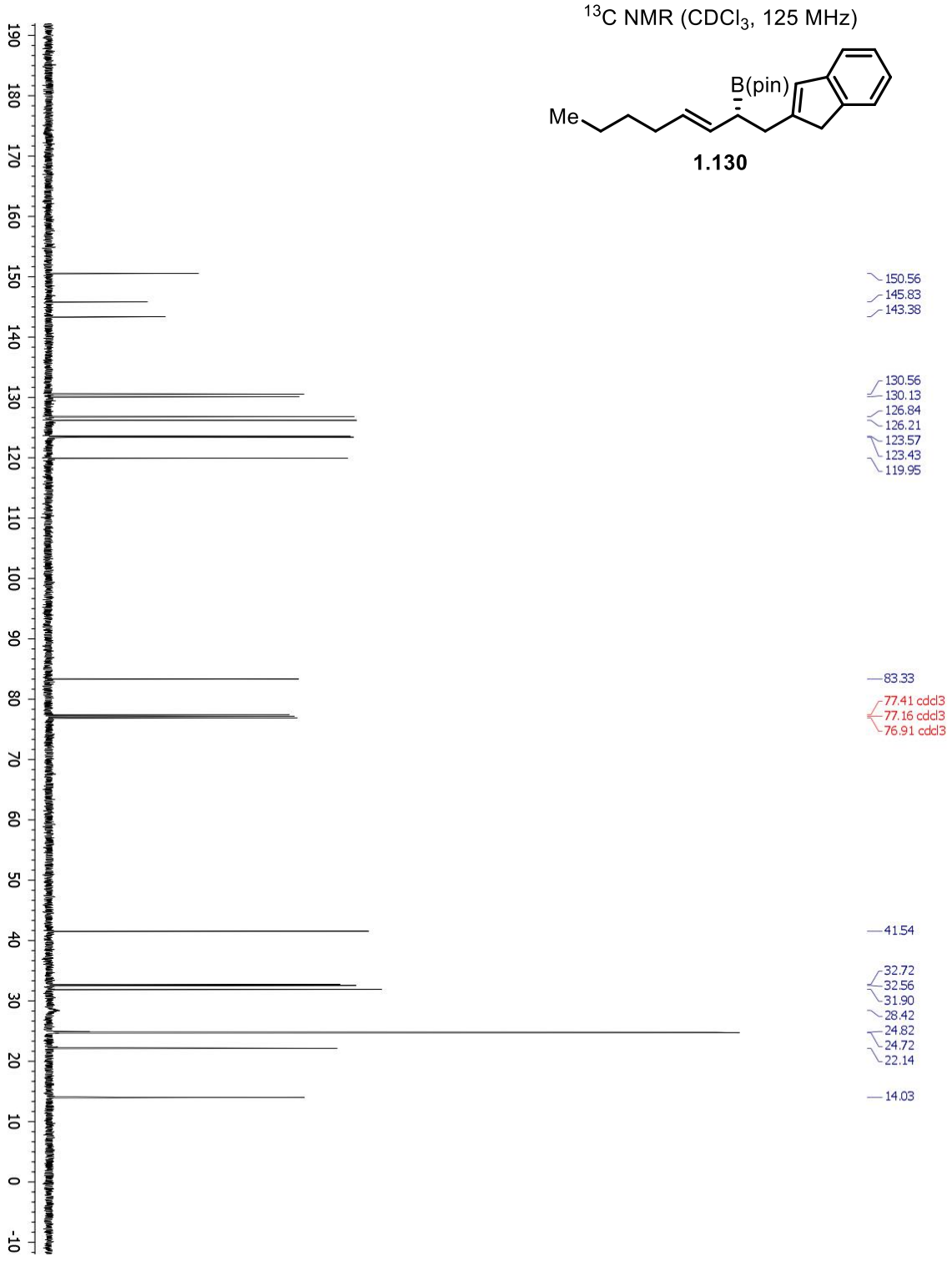

^{1}H NMR ($CDCl_3$, 600 MHz)
B(pin)
1.132
7.26 cdcl3
6.89
6.75
6.74
6.72
6.71
6.29
6.26
6.07
6.05
6.04
6.03
5.92
5.92
5.09
5.08
5.07
2.33
2.32
2.31
2.30
2.29
2.24
2.23
2.22
2.20
2.19
2.18
2.17
2.16
2.15
2.13
2.12
2.12
2.11
2.09
2.04
1.99
1.98
1.96
1.95
1.53
1.51
1.49
1.48
1.45
1.23
1.23
0.97
1.72
0.89
0.98
1.77
0.87
1.00
1.93
1.15
1.76
1.04
6.19
11.10

^{13}C NMR ($CDCl_3$, 150 MHz)

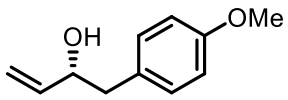


1.132

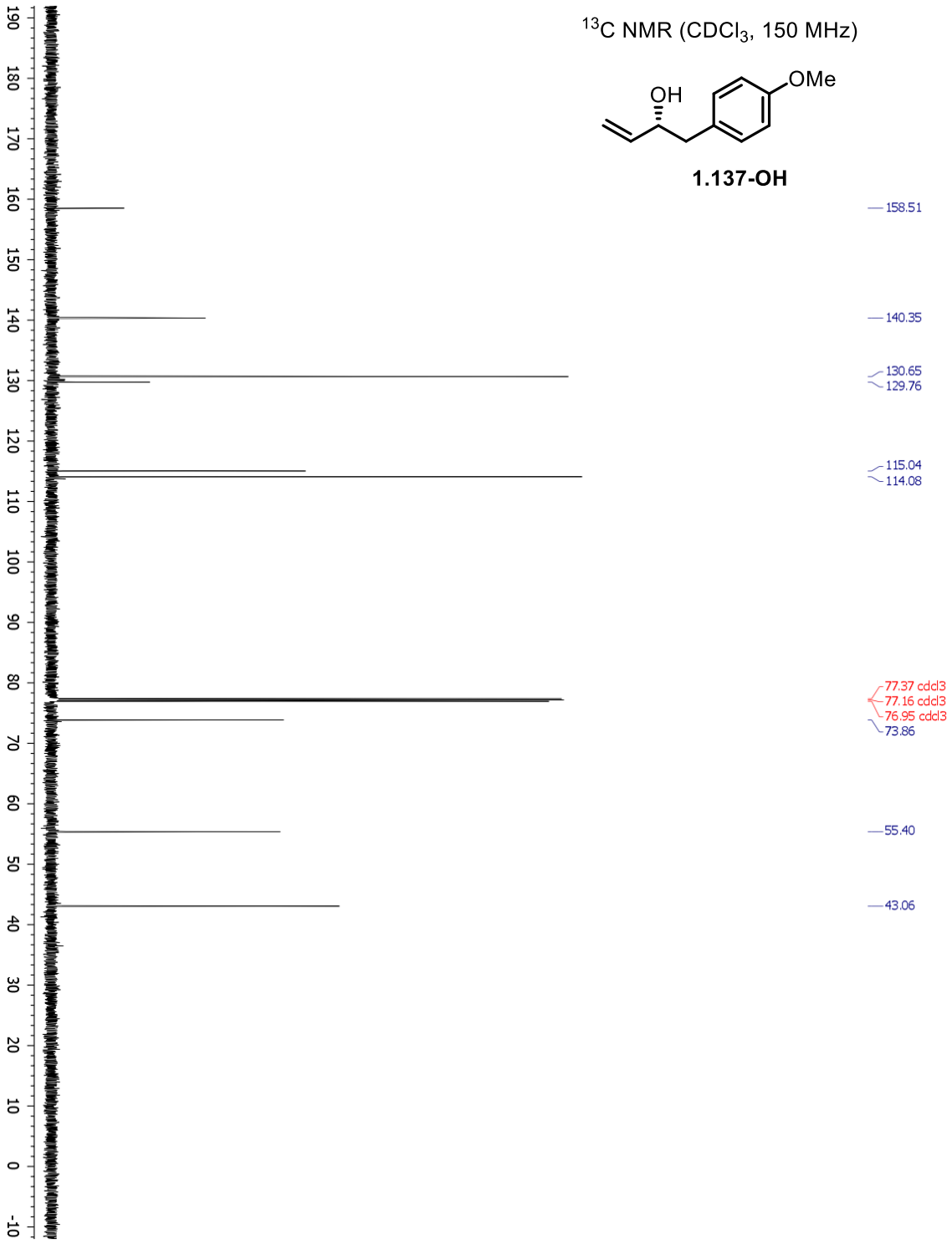

^{1}H NMR ($CDCl_3$, 500 MHz)
B(pin)
Me
1.130
0.95
0.95
0.93
0.92
0.89
1.89
2.06
1.00
1.02
1.04
1.99
4.91
11.99
2.89
7.36
7.35
7.26 cdcl3
7.25
7.23
7.21
7.19
7.18
7.10
7.09
7.08
7.08
7.07
7.06
6.51
6.51
5.48
5.47
5.45
5.44
5.43
5.43
5.42
5.41
5.39
3.35
3.31
3.31
3.30
3.25
2.75
2.74
2.72
2.71
2.61
2.59
2.58
2.56
2.17
2.15
2.00
1.99
1.98
1.97
1.96
1.31
1.30
1.30
1.29
1.29
1.28
1.28
1.27
1.27
1.26
1.26
1.25
1.25
1.24
1.24
1.24
1.19
1.19
0.86
0.84


^{13}C NMR ($CDCl_3$, 125 MHz)
B(pin)
Me
1.130
150.56
145.83
143.38
130.56
130.13
126.84
126.21
123.57
123.43
119.95
83.33
77.41 cdcl3
77.16 cdcl3
76.91 cdcl3
41.54
32.72
32.56
31.90
28.42
24.82
24.72
22.14
14.03

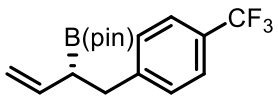
^{1}H NMR ($CDCl_3$, 600 MHz)



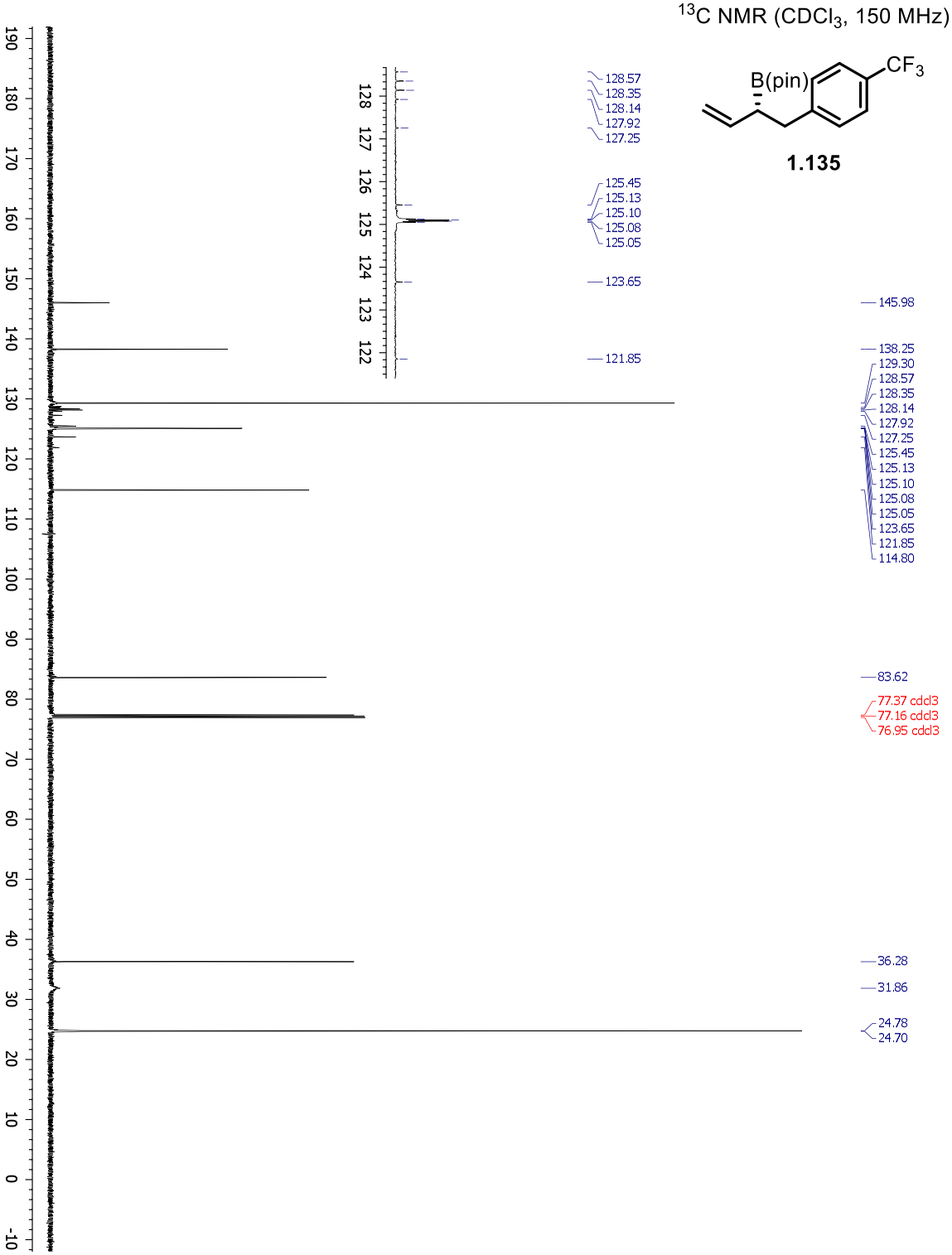
1.137-OH


^{13}C NMR ($CDCl_3$, 150 MHz)
OH
OMe
1.137-OH
158.51
140.35
130.65
129.76
115.04
114.08
77.37 cdcl3
77.16 cdcl3
76.95 cdcl3
73.86
55.40
43.06

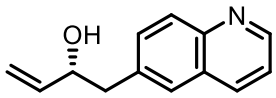
^{1}H NMR ($CDCl_3$, 600 MHz)



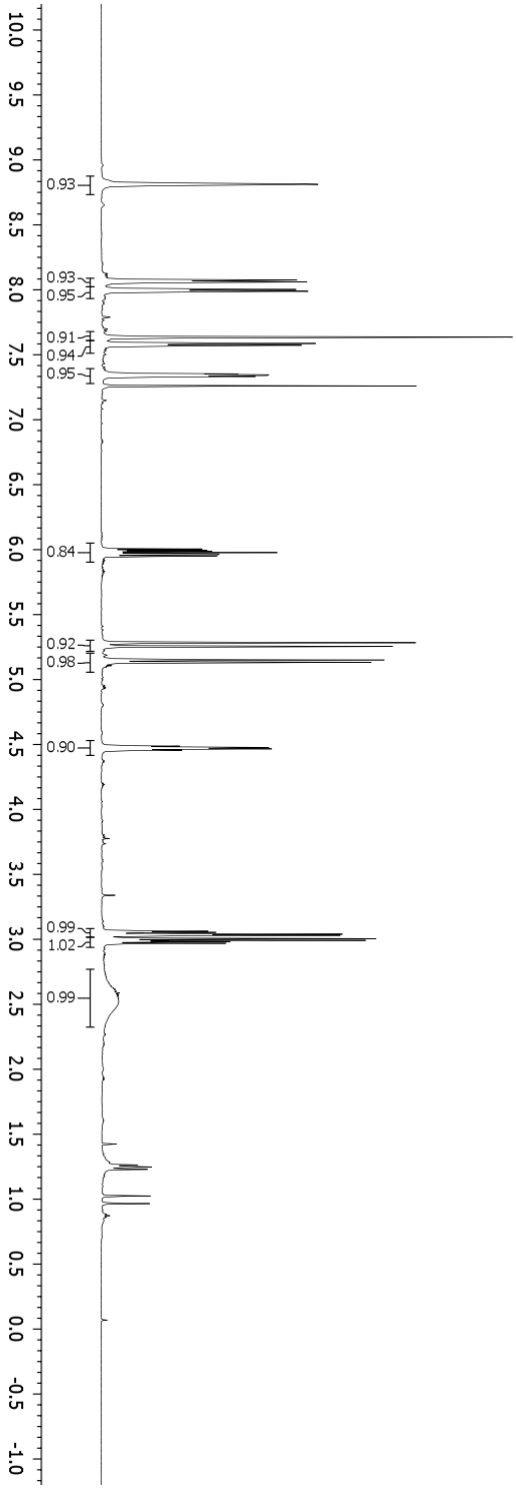
1.135

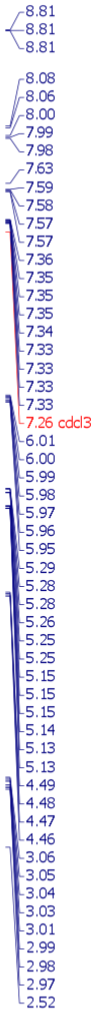

^{13}C NMR ($CDCl_3$, 150 MHz)
B(pin)
CF_3
1.135
128.57
128.35
128.14
127.92
127.25
125.45
125.13
125.10
125.08
125.05
123.65
121.85
145.98
138.25
129.30
128.57
128.35
128.14
127.92
127.25
125.45
125.13
125.10
125.08
125.05
123.65
121.85
114.80
83.62
77.37 cdcl3
77.16 cdcl3
76.95 cdcl3
36.28
31.86
24.78
24.70

^{1}H NMR ($CDCl_3$, 600 MHz)

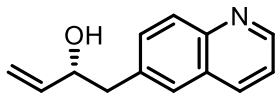


1.136-OH

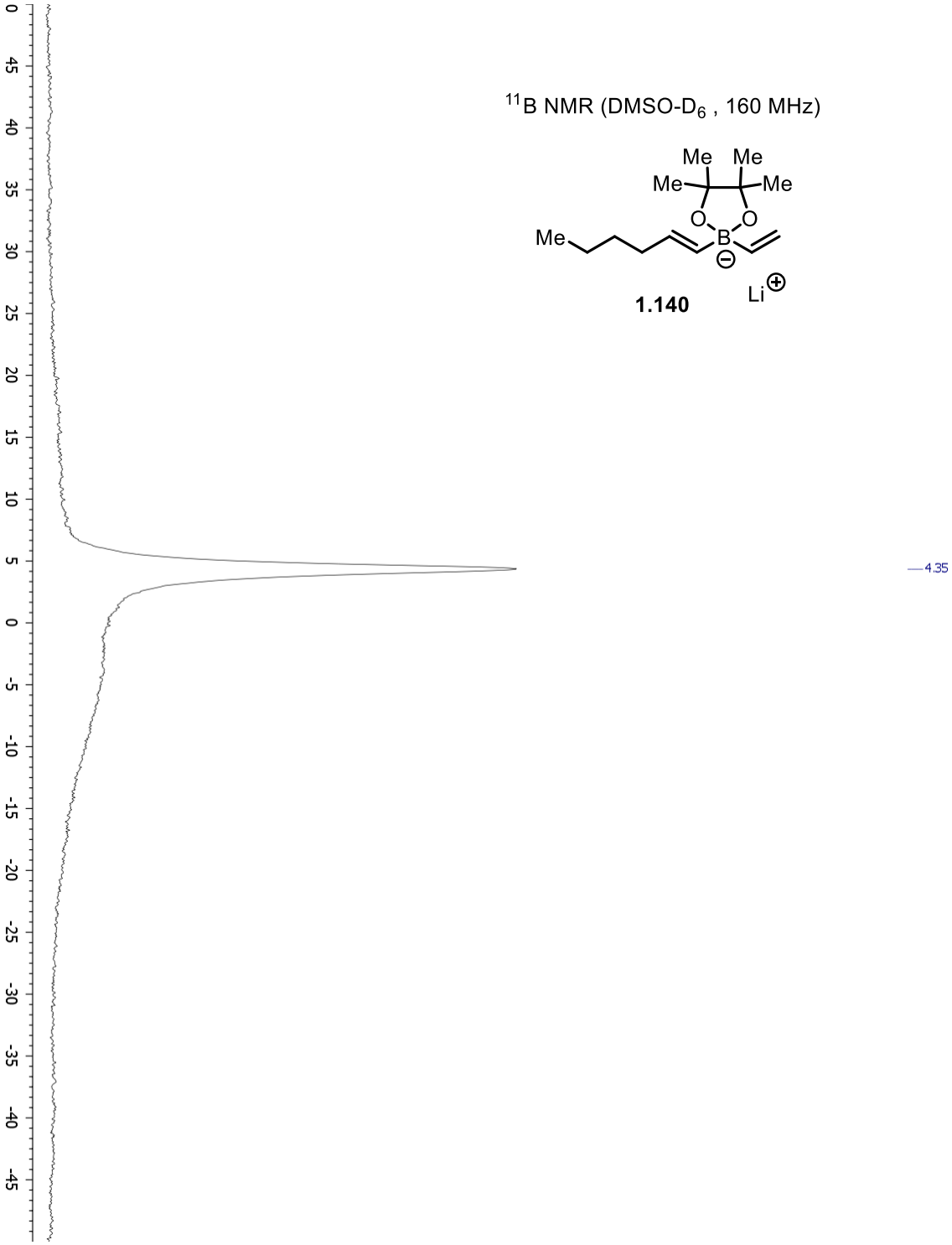




^{13}C NMR ($CDCl_3$, 150 MHz)

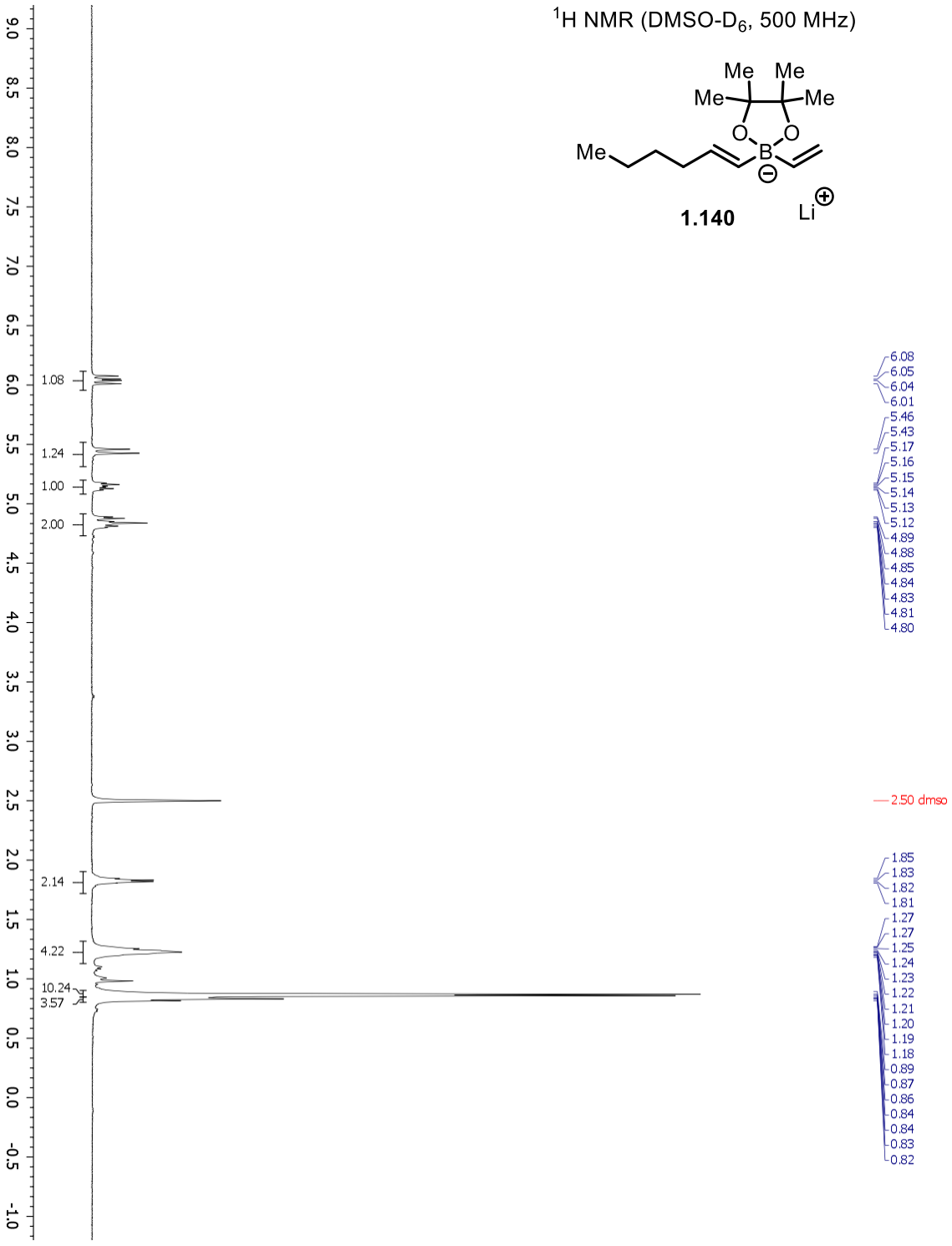


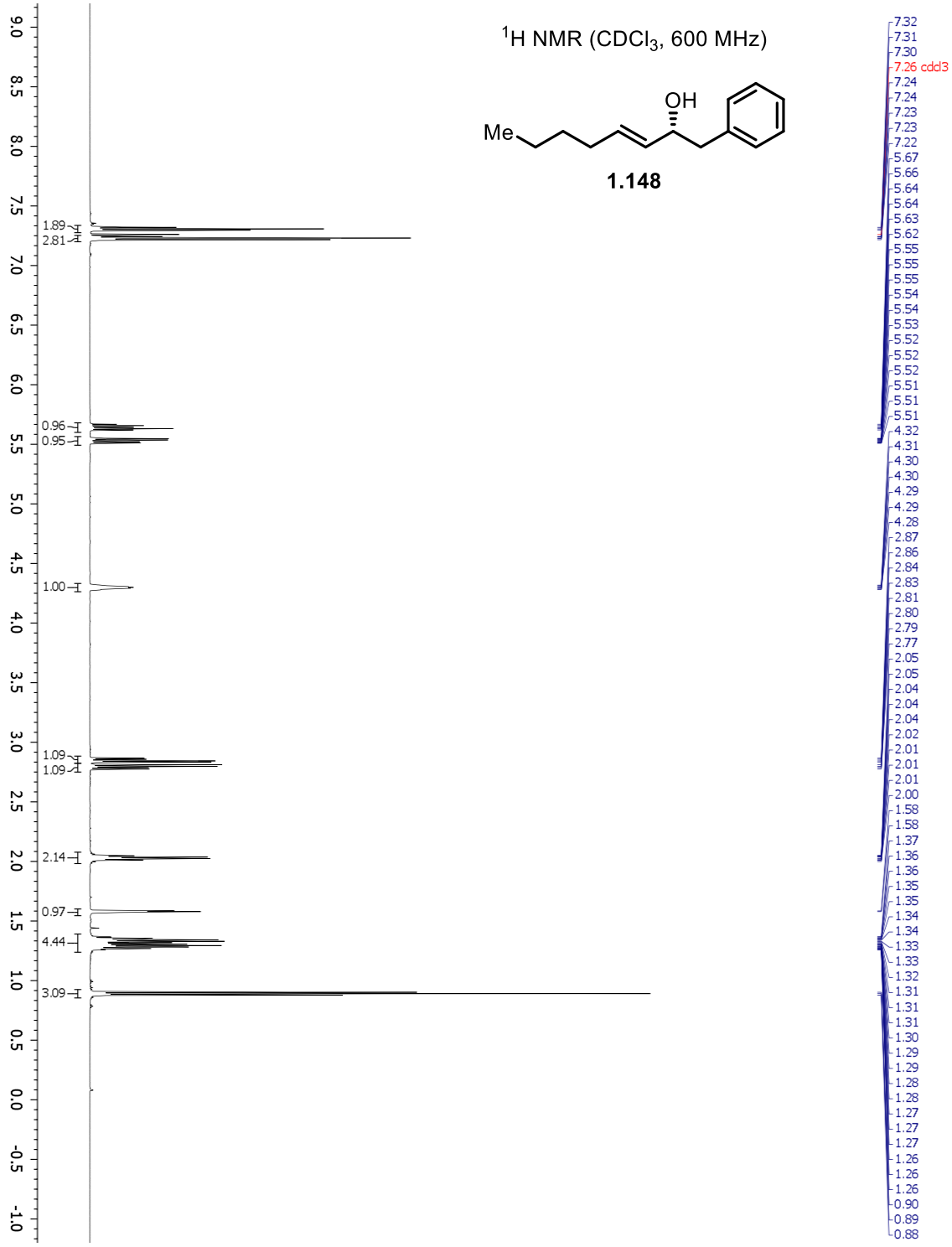
1.136-OH

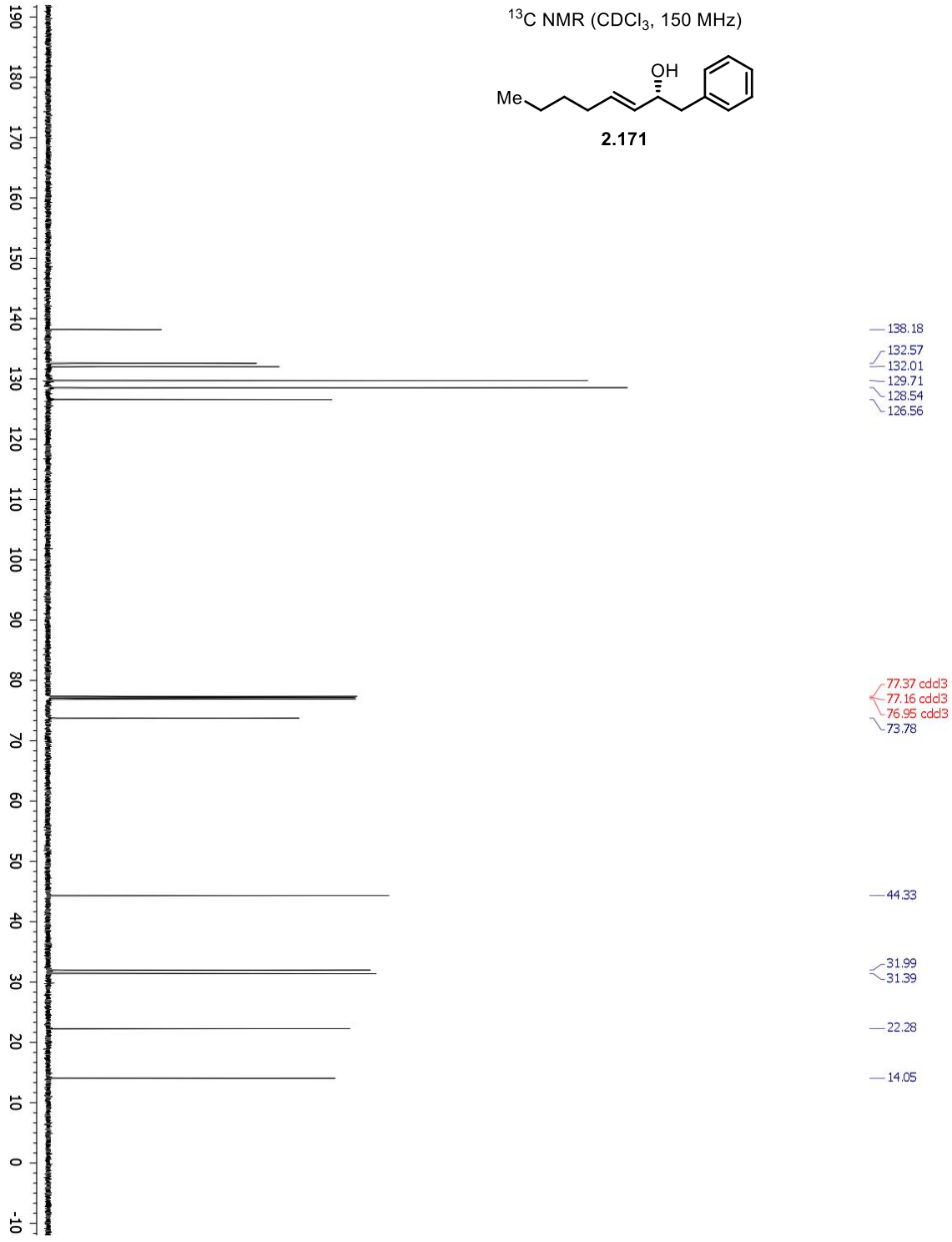


^{11}B NMR (DMSO-D_6 , 160 MHz)

1.140


^{1}H NMR (DMSO-D$_6$, 500 MHz)
Me
Me
Me
Me
O
O
B
Me
Li
1.140
1.08
1.24
1.00
2.00
2.14
4.22
10.24
3.57
6.08
6.05
6.04
6.01
5.46
5.43
5.17
5.16
5.15
5.14
5.13
5.12
4.89
4.88
4.85
4.84
4.83
4.81
4.80
2.50 dmso
1.85
1.83
1.82
1.81
1.27
1.27
1.25
1.24
1.23
1.22
1.21
1.20
1.19
1.18
0.89
0.87
0.86
0.84
0.84
0.83
0.82


^{1}H NMR ($CDCl_3$, 600 MHz)
OH
Me
1.148
1.89
2.81
0.96
0.95
1.00
1.09
1.09
2.14
0.97
4.44
3.09
7.26 cdcl3


^{13}C NMR ($CDCl_3$, 150 MHz)
OH
Me
2.171
138.18
132.57
132.01
129.71
128.54
126.56
77.37 cdcl3
77.16 cdcl3
76.95 cdcl3
73.78
44.33
31.99
31.39
22.28
14.05

Chapter 2

Stereoselective synthesis of trisubstituted alkenyl boronic esters by boron-Wittig reaction of ketones

2.1 Introduction

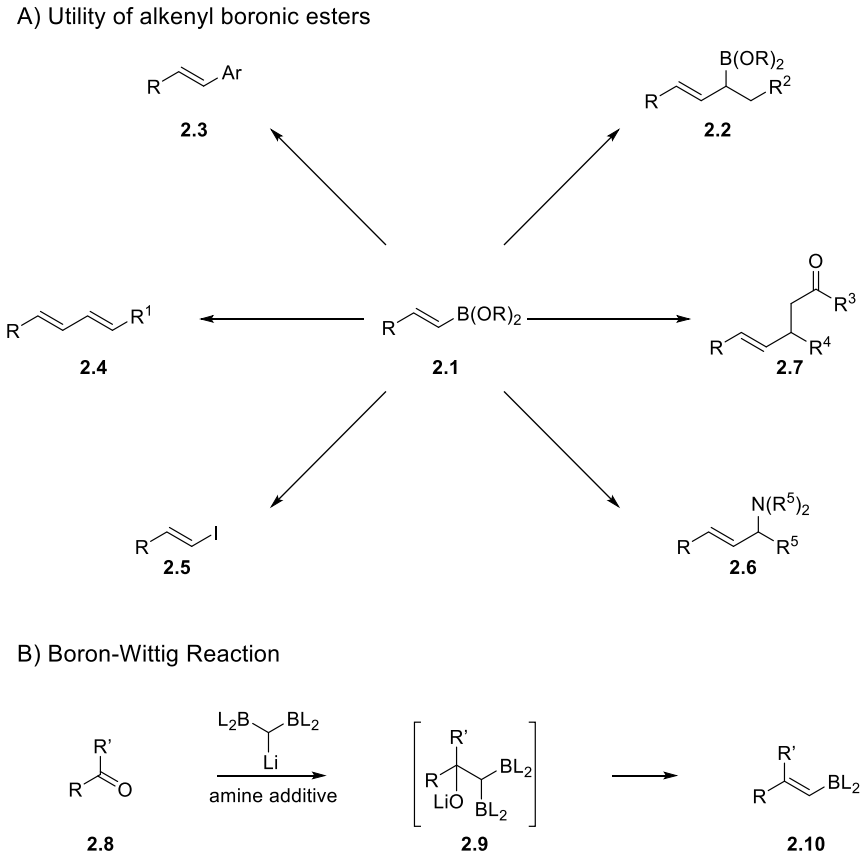
Alkenyl boronic esters are versatile synthetic motifs.[1] Not only are they chemically and configurationally stable, but they also undergo a myriad of transformations (Scheme 2.1 A). These include a variety of C–C bond-forming reactions such as the Petasis reaction,[2] transition metal-catalyzed[3] and metal-free[4] conjugate additions, and conjunctive cross-coupling[5] among others. More notably, highly substituted alkenyl boronic esters can engage in Suzuki-Miyaura[6] cross-coupling with aryl and alkenyl electrophiles to access geometrically-defined styrenes and dienes respectively, that are challenging to access in the context of natural product synthesis.[7] Other synthetic applications include, but are not limited to, halodeboration, and radical reactions.[8]

A literature survey shows a variety of ways to synthesize disubstituted alkenyl boronic esters.[9] However, there are limited methods to access stereodefined trisubstituted alkenyl boronic esters. In this chapter, the development of a modified boron-Wittig reaction

[1] Hall, D. G. Boronic Acids; Wiley-VCH: Weinheim, **2011**.
[2] (a)Petasis, N. A.; Goodman, A.; Zavialov, I. A. Tetrahedron, **1997**, *53*, 16463. (b) Koolmeister, T.; Södergren, M.; Scobie, M. Tetrahedron Lett. **2002**, *43*, 5965 (c) Nielsen, E.T.; Givskov, M.; Wu, P. *Chem. Rev.* **2019**, *119*, 11245 – 11290.
[3] Hayashi, T.; Yamasaki, K. *Chem. Rev*. **2003**, *103*, 2829.
[4] Chong. J. M.; Wu, R, T. *J. Am. Chem. Soc*. **2007**, *129*, 4908.
[5] Namirembe, S.; Morken, J P. *Chem. Soc. Rev*. **2019**, *48*, 3464 – 3474.
[6] Miyaura, N.; Suzuki, A. *Chem. Rev*. **1995**, *95*, 2457.
[7] Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442.
[8] Carreras, J.; Caballero, A.; Pérez, P. J. *Chem. Asian. J.* **2019**, *14*, 329.
[9] See reference 8

with ketone electrophiles – a reaction that is an inroad to stereodefined trisubstituted alkenyl boronic esters – will be discussed (Scheme 2.1 B).

Scheme 2.1 Representative applications of alkenyl boronic esters and boron-Wittig reaction



2.2. Background

2.2.1. Representative synthesis of trisubstituted alkenyl boronic esters

The majority of the existing catalytic methods (described below) to synthesize trisubstituted alkenyl boronic esters rely mainly on functionalization of alkynes and alkenes. These methodologies rely on carboboration of terminal alkynes, hydroboration of

internal alkynes and dehydrogenative borylation of alkenes using catalytic amounts of copper, ruthenium, rhodium, zirconium, iron or palladium.

2.2.1.1. Representative synthesis of trisubstituted alkenyl boronic esters via carboboration

Carboboration of terminal alkynes is one of the effective routes to the synthesis of trisubstituted alkenylboron reagents. Initial efforts in this area were pioneered by the Suiginome group using palladium and nickel catalysis.[10] They required use of pre-functionalized alkynes and unstable boron reagents such as chloroaminoboranes, which limit the method's utility. Nonetheless, they laid the groundwork for future reaction development in this area.

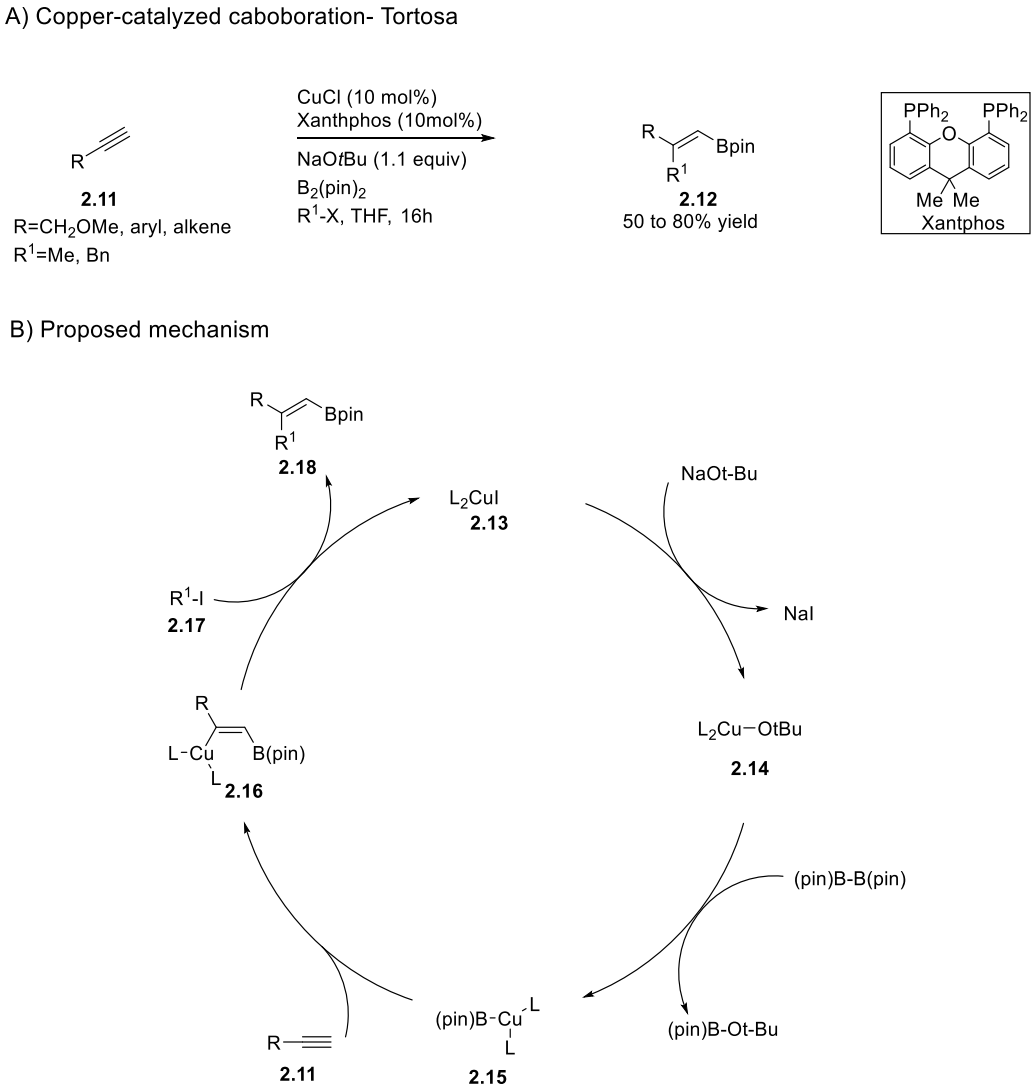
2.2.1.1.1. Copper-catalyzed carboboration of terminal alkynes

The Tortosa group demonstrated the first copper-catalyzed *syn* carboboration of simple terminal alkynes (Scheme 2.2 A).[11] The proposed mechanism (Scheme 2.2 B) of the reaction starts with transmetalation of Cu(I) species (**2.13)** with NaO*t*Bu to form L_2CuO*t*Bu (**2.14**). A second transmetalation between L_2CuO*t*Bu (**2.14**) and B_2pin_2 affords Cu–Bpin species (**2.15**), which undergoes a migratory insertion to the terminal alkyne (**2.11**) to form a C-B bond and an alkenyl copper species (**2.15**). The alkenyl copper species then undergoes a nucleophilic displacement on the alkyl iodide (**2.17**) to form the desired product (**2.18**) and regenerate the catalyst (**2.13**). Overall, this new carboboration

[10] (a) Suginome, M.; Yamamoto, A.; Murakami, M. *J. Am. Chem.Soc*. **2003**, *125*, 6358. (b) Yamamoto, A.; Suginome, M. *J. Am. Chem.Soc*. **2005**, *127*, 15706. (c) Suginome, M.; Yamamoto, A.; Murakami, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 2380. (d) Suginome, M.; Shirakura, M.; Yamamoto, A. *J. Am. Chem. Soc*. **2006**, *128*, 14438. (e) Daini, M.; Yamamoto, A.; Suginome, M. *J. Am. Chem. Soc.* **2008**, *130*, 2918.
[11] Alfaro, R.; Parra, A.; Alemán, J.; Ruano, J. L. G.; Tortosa, M. *J. Am. Chem. Soc.* **2012**, *134*, 15165 – 15168.

method could employ methyl iodide, allyl iodide or benzyl bromide as electrophiles. In addition, terminal aromatic alkynes underwent carboboration with high regioselectivity but reactions of simple terminal alkynes remained elusive.

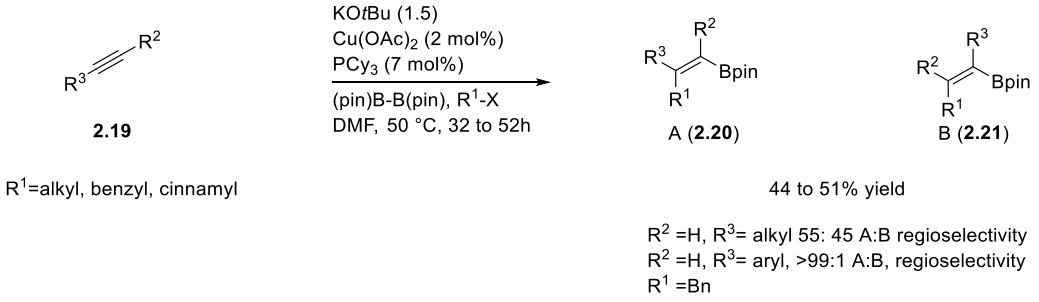
Scheme 2.2 Tortosa copper-catalyzed carboboration and proposed mechanism



Near the same time as Tortosa, the Yoshida group independently reported a copper-catalyzed carboboration that utilized a much cheaper $P(Cy)_3$ ligand and complemented the

Tortosa work (Scheme 2.3).[12] Another improvement of the carboboration protocol by the Yoshida group was the ability to engage other longer chain alkyl bromides, tosylates and benzyl chlorides albeit in low yield. The limitation of the Yoshida method is similar to that encountered by the Tortosa group: when simple terminal alkyl alkynes were employed in the reaction, they suffered from poor regioselectivity.

Scheme 2.3 Copper-catalyzed carboboration by Yoshida



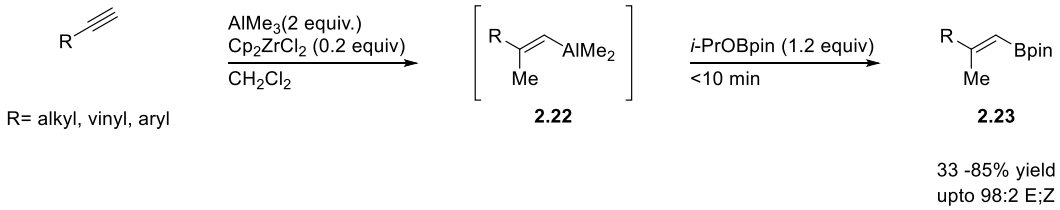
2.2.1.1.2 Zr-catalyzed carboboration of terminal alkynes

Inspired by Negishi's carboalumination[13], the Aggarwal group developed a zirconium-catalyzed methylboration of terminal alkynes as a route to trisubstituted alkenyl boronic esters (Scheme 2.4).[14] In this reaction, a terminal alkyne undergoes carboalumination to afford alkenylaluminum species **2.22** which transmetalates with isopropoxy boronate to generate the trisubstituted alkenyl boronic ester **2.23**. This transformation was achieved in good yield and with high selectivity. However, the utility of this methodology is limited because there are few trialkylaluminium reagents that are

[12] Yoshida, H.; Kageyuki, I.; Takaki, K. *Org. Lett.* **2013**, *15*, 952 – 955
[13] Negishi, E.; Yoshida, T. *J. Am. Chem. Soc.* **1981**, *16*, 4985–4987.
[14] Zhurakovskyi, O.; Dias, R. M. P.; Noble, A.; Aggarwal, V. K. *Org. Lett*. **2018**, *20*, 3136–3139.

easily accessible and the pyrophoric nature of trimethylaluminum is undesirable, especially on large scale.

Scheme 2.4. Zirconium-catalyzed carboboration of terminal alkynes



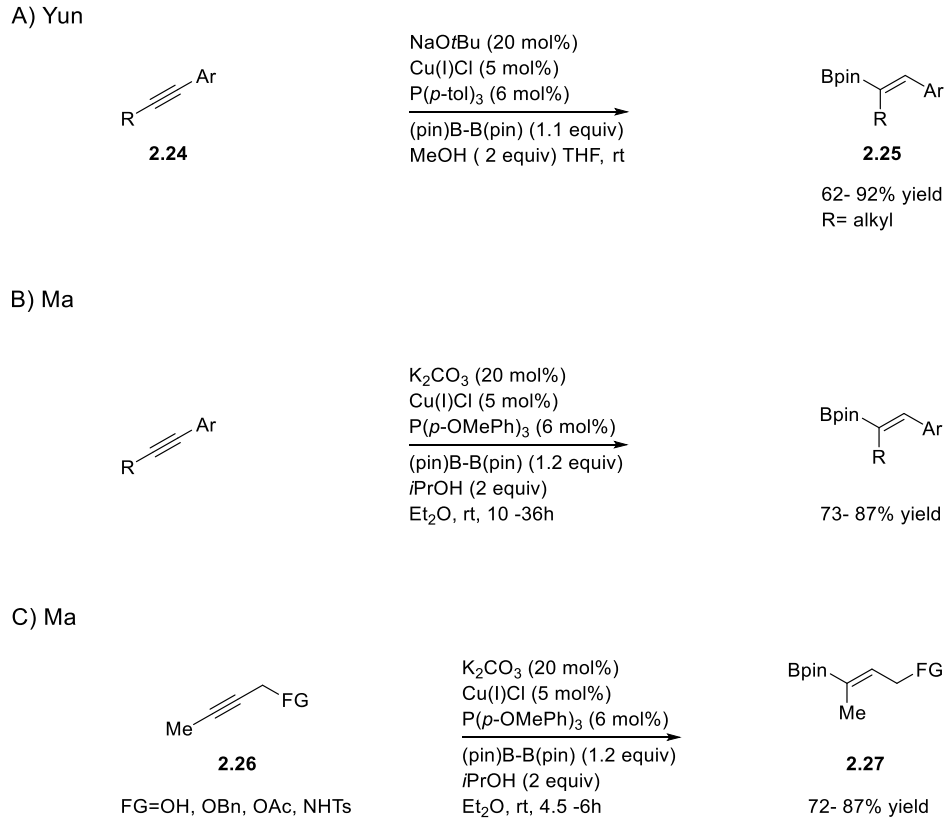
2.2.1.2. Representative examples of metal-catalyzed hydroboration of internal alkynes

One of the classic ways to synthesize alkenyl boronic esters is through hydroboration of terminal alkynes, which proceeds with predictable regio- and stereoselectivity.[15] More challenging, is the regioselective hydroboration of internal unsymmetrical alkynes. Strides have been made to address this challenge by some groups using well designed copper/ ligand catalysts.[16] Of note is the work developed by Jaesook Yun,[17] and Shengmin Ma described below.[18]

[15] (a) Pelter, A.; Singaram, S.; Brown, H. *Tet. Lett*. **1983**, *24*, 1433–1436. (b) Tucker, C. E.; Davidson, J.; Knochel, P. *J. Org. Chem*. **1992**, *57*, 3482–3485. (c) Pereira, S.; Srebnik, M. *Organometallics*, **1995**, *14*, 3127–3128. (d) Ohmura, T.; Yamamoto, Y.; Miyaura, N. *J. Am. Chem. Soc*. **2000**, *122*, 4990–4991.(e) Wang, Y.D.; Kimball, G.; Prashad, A.S.; Wang, Y. *Tet. Lett*, 2**005**, *46*, 8777–8780 (f) Jang,H.; Zhugralin, A.R.; Lee,Y.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2011**, *133*, 7859–7871.
[16] (a) Semba, K.; Fujihara, T.; Terao, J.; Tsuji, Y. *Chem. Eur. J*. **2012**, *18*, 4179. (b) Lipshutz, B. H.; Bošković, . Ž. V.; Aue, D. H. *Angew. Chem., Int. Ed*. **2008**, *47*, 10183–10186. (c) Bidal, Y. D.; Lazreg, F.; Cazin, C. S. J. *ACS Catal*. **2014**, *4*, 1564−1569.
[17] Kim, H, R.; Yun, J. *Chem. Commu.,* **2011**, *47*, 2943–2945.
[18] Yuan, W.; Ma, S. *Org. Biomol. Chem*. **2012**, *10*, 7266–7268.

2.2.1.2.1. Copper catalyzed *syn*-hydroboration of alkynes

Scheme 2.5 Copper catalyzed hydroboration of internal alkynes



In 2011, the Yun group reported a regio- and stereoselective hydroboration of unsymmetrical aryl/alkyl alkynes using Cu(I) catalyst, B_2pin_2 and MeOH (Scheme 2.5 A).[19] The hydroboration proceeded in a *syn* fashion such that boron was added to the carbon β to the arene to afford trisubstituted alkenyl boronic esters in moderate to excellent yield. Similar to the Yun work, the Ma group also engaged aryl/alkyl alkynes using a Cu(I) catalyst, B_2pin_2 and *i*-PrOH to effect a *syn* hydroboration (Scheme 2.5 B).[20] As an advancement from previous reported methods, they were able to engage functionalized

[19] See reference 16
[20] See reference 17

dialkyl alkynes, namely propagylic derivatives, to ensure good control over regioselectivity (Scheme 2.5 C). Although regioselective hydroboration of unsymmetrical aryl/alkyl alkynes has been accomplished, a general strategy for the regioselective hydroboration of simple unsymmetrical unactivated dialkyl alkynes remains an unsolved problem.

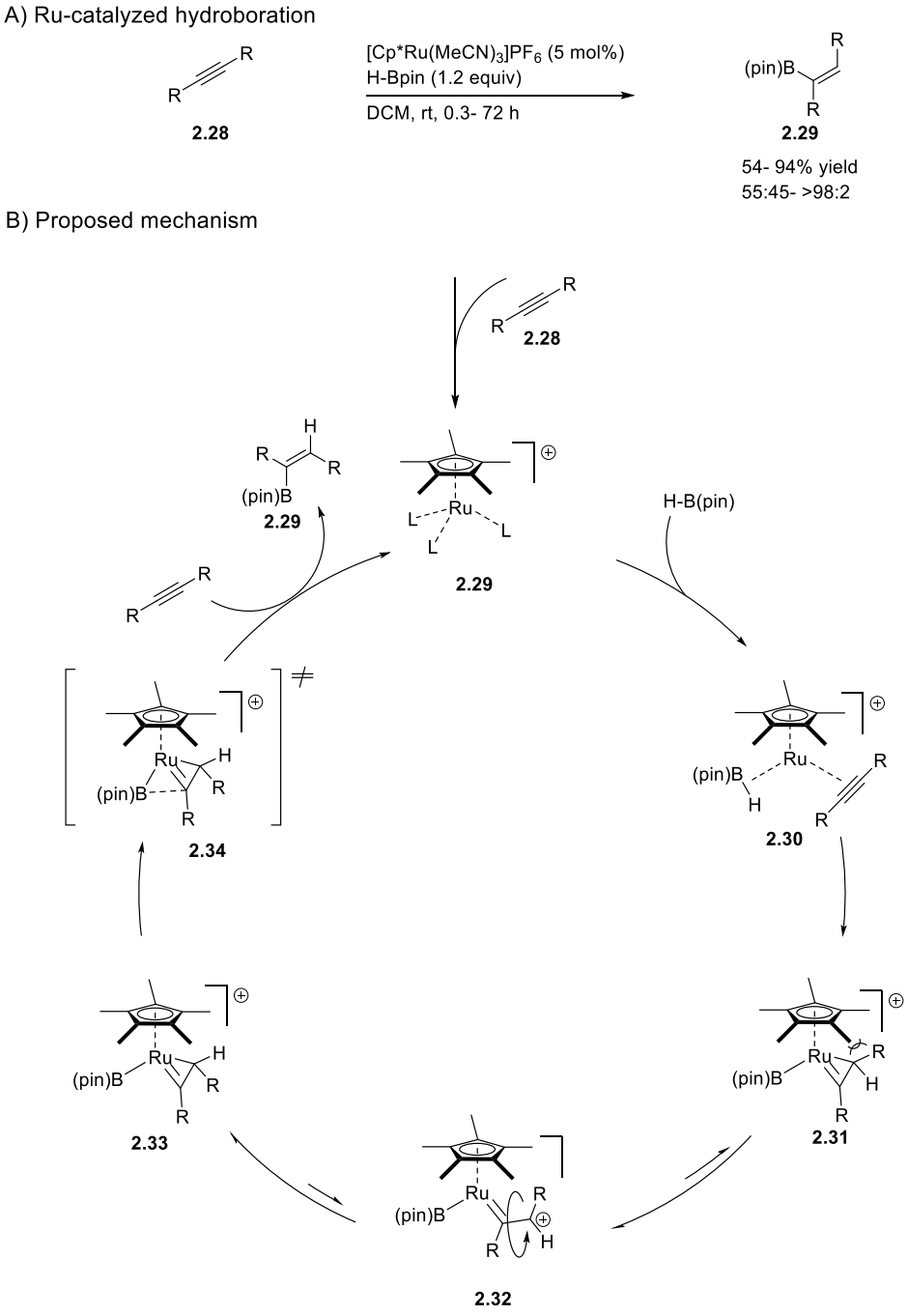
2.2.1.2.2 *Trans*-hydroboration of dialkyl alkynes

Trans hydroboration of alkynes is a non-trivial undertaking that has been demonstrated in literature using Ir/ Rh,[21] Ru,[22] Co[23] and Cu[24] with terminal alkynes. The Liu group also demonstrated a palladium-catalyzed *trans* hydroboration of terminal and internal enynes.[25] More challenging is the *trans* hydroboration of internal alkynes to access trisubstituted alkenyl boronic esters.

Fürstner reported the first *trans*-selective hydroboration of internal dialkyl alkynes using $[Cp^*Ru(MeCN)_3]PF_6$.[26] Symmetrical dialkyl alkynes were reported to undergo *trans* hydroboration to afford trisubstituted alkenyl boronic esters with high trans-selectivity (Scheme 2.6 A). However, unsymmetrical dialkyl alkynes afforded trisubstituted alkenyl boronic esters as mixtures of regioisomers with low diastereoselectivity.

[21] Ohmura, T.; Yamamoto, Y.; Miyaura, N. *J. Am. Chem. Soc*. **2000**, *122*, 4990.
[22] Gunanathan, C.; Hoelscher, M.; Pan, F.; Leitner, W. *J. Am. Chem. Soc*. **2012**, *134*, 14349.
[23] Obligacion, J. V.; Neely, J. M.; Yazdani, A. N.; Pappas, I.; Chirik, P. J. *J. Am. Chem. Soc*. **2015**, *137*, 5855.
[24] Jang, W. J.; Lee, W. L.; Moon, J. H.; Lee, J. Y.; Yun, J. *Org. Lett*. **2016**, *18*, 1390.
[25] Xu, S.; Zhang, Y.; Li, B.; Liu, S.-Y. *J. Am. Chem. Soc*. **2016**, *138*, 14566 –14569.
[26] Sundararaju, B.; Fürstner, A. *Angew. Chem., Int. Ed*. **2013**, *52*, 14050.

Scheme 2.6 Ru-catalyzed *trans*-hydroboration of internal alkynes and proposed mechanism.



The mechanism proposed by Fürstner (Scheme 2.6 B), commences with alkyne binding to the cationic Ru^{2+} to form complex **2.29.** This is followed by intermediate **2.29** binding

to H-Bpin to form intermediate **2.30** and subsequent formation of the metallocyclopropene (intermediate **2.31**) via inner sphere H delivery. The steric penalty between allylic R group of intermediate **2.31** and the Cp ring is considered to be the driving force for the isomerization to intermediate **2.33,** which is less sterically encumbered via **2.31**. Reductive elimination from intermediate **2.34** affords the trisbustituted akenyl boronic ester in which the boron and hydrogen atoms end up *anti* to establish the *E* diastereomer.

2.2.1.3. Representative dehydrogenative borylation of 1,1-disubstituted alkenes.

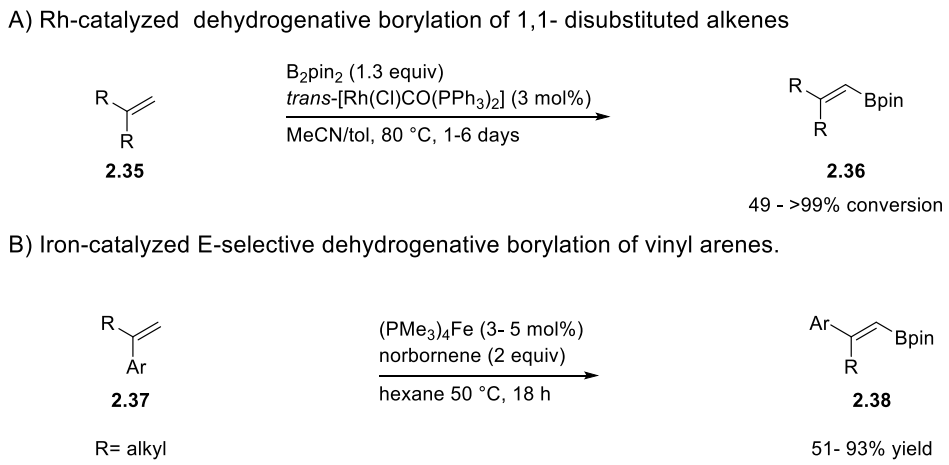
Metal-catalyzed dehydrogenative borylation of alkenes is another method that has been developed to synthesize trisubstituted alkenylboron reagents. This has been effected by using H-Bpin or $B_2(pin)_2$ with a proton source to convert alkene feedstock chemicals into versatile trisubstituted alkenyl boronic esters.

2.2.1.3.1 Rhodium and iron-catalyzed dehydrogenative borylation of 1,1-disubstituted alkenes

In 2003, Marder and co-workers[27] pioneered the rhodium-catalyzed dehydrogenative borylation of 1,1-disubstituted alkenes (Scheme 2.7 A) to afford trisubstituted alkenyl boronic esters. The reaction proceeded in good yield and with good stereoselectivity but required high temperature and long reaction times. In 2016, Ge improved upon the dehydrogenative borylation of 1,1- disubstituted alkenes by using iron catalysis (Scheme 2.7 B).[28] The reaction proceeded in shorter reaction time with moderate to excellent yield but was limited to vinyl arene substrates.

[27] Coapes, R. B.; Souza, F. E. S.; Thomas, R. L.; Hall, J. J.; Marder, T. B. *Chem. Commun*. **2003**, *5*, 614–615.
[28] Wang, C.; Wu, C.; Ge, S. *ACS Catal*. **2016**, *6*, 7585–7589.

Scheme 2.7 Rh and Fe-catalyzed dehydrogenative borylation

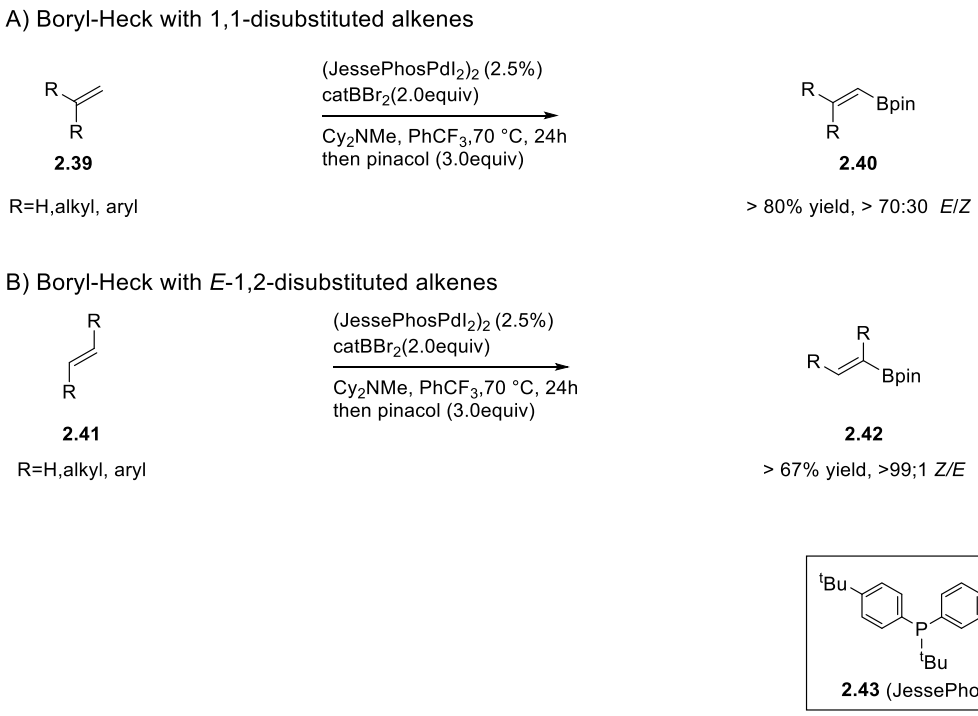


2.2.1.3. Palladium-catalyzed boryl-Heck reaction of alkenes

In 2018, the Watson group reported a boryl-Heck reaction that converted simple 1,1-disusbstitued and 1,2-disubstituted alkenes into trisubstituted alkenyl boronic esters (Scheme 2.8). [29] In comparison to the aforementioned methodology (Ge and Marder), this boryl-Heck could now engage simple dialkyl alkenes and afford the resulting trisubstituted alkenyl boronic esters in good yield and with excellent diastereoselectivity. This method is limited by the need to have high purity *E*-1,2-disubstituted alkenes to ensure high diastereoselectivity in the boryl-Heck reaction (Scheme 2. 8 B).

[29] (a) Reid, W. B.; Watson, D. A. *Org. Lett*. **2018**, *20*, 6832 − 6835. (b) Reid, W. B.; Spillane, J. J.; Krause, S. B.; Watson, D. A. *J. Am. Chem. Soc*. **2016**, *138*, 5539.

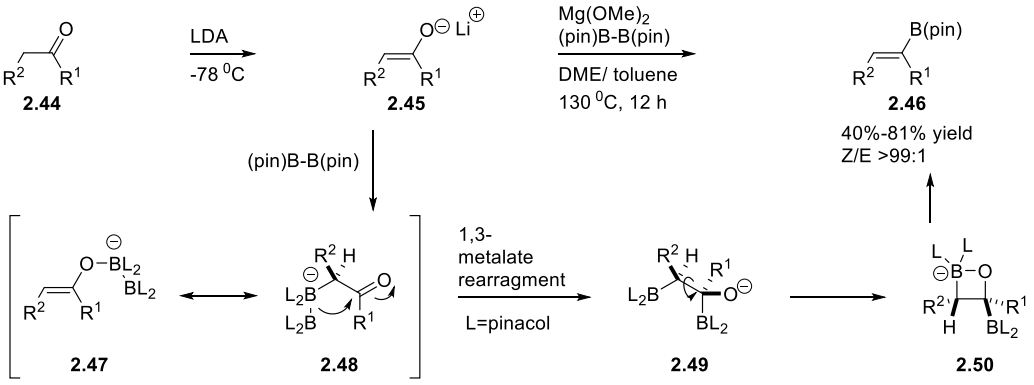
Scheme 2.8 Palladium-catalyzed boryl-Heck



2.2.1.4. 1,3- Metalate rearrangement-borylation of ketones

Similar to alkenes, ketones are easily accessible building blocks and their utility as synthetic precursors is appealing. The Liu group developed a 1,3- metalate rearrangement-

Scheme 2.9 1,3- Rearrangement of boron-enolate



borylation of ketone enolates as a way to access trisubstituted alkenyl boronic esters

(Scheme 2.9).[30] A plausible operating mechanism was proposed as depicted in Scheme 2.9. Deprotonation of ketone **2.44** at -78 °C generates the lithium enolate **2.45**. This enolate (**2.45**) attacks B_2pin_2 to form boron enolate **2.48** which is in equilibrium with α-boryl ketone **2.47**. $Mg(OMe)_2$ is proposed to act as a Lewis acid that binds to the carbonyl oxygen to increase its electrophilicity toward the 1,3-migration of boron to afford intermediate **2.49.** Upon rotation and oxo-nucleophilic addition to boron, intermediate **2.49** is transformed into the four membered ring intermediate **2.50** which undergoes stereospecific B-O elimination to generate the *Z* alkenyl boronic ester.

2.2.3 History of the boron-Wittig reaction

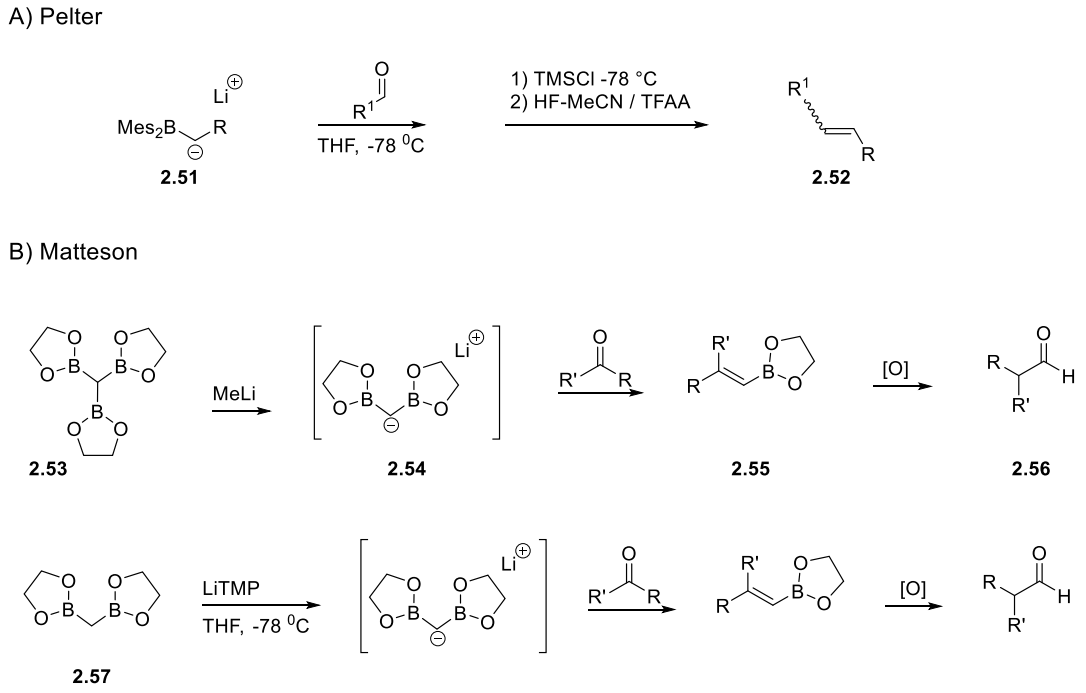
2.2.3.1 Reaction with aldehydes

The seminal boron-Wittig reaction was pioneered by Pelter[31] and Matteson.[32] Pelter utilized dimesityl alkyl boranes to synthesize either *E* or *Z* alkenes under different reaction conditions (Scheme 2.10 A), whereas Matteson utilized geminal bis(ethylene glycolboronates) (Scheme 2.10 B). Initial studies by Matteson employed methyllithium to deborylate tris(boronate) **2.53** to afford the olefination reagent **2.54**. Later, LiTMP was found to be an effective base at deprotonating the α-position of the methylene diboron **2.57** to generate boron-stabilized anion **2.54**.[33] Subsequent boron-Wittig reaction using reagent **2.54** and aldehydes or ketones afforded ethylene glycol derived alkenyl boronic ester

[30] Hu, Y.; Sun, W.; Zhang, T.; Xu, Nuo.; Xu, J.; Lan, Y.; Liu, C. *Angew. Chem. Int. Ed*. **2019**, *58*, 15813–15818.
[31] (a) Pelter, A.; Buss, D.; Colclough, E.; Singaram, B. *Tetrahedron*. **1993**, *49*, 7077. (b) Pelter, A.; Buss, E.; Colclough, E. *J. Chem. Soc., Chem. Commun.* **1987**, *4*, 297.
[32] (a) Matteson, D. S.; Moody, R. J.; Jesthi, P. K. *J. Am. Chem. Soc*. **1975**, *97*, 5608–5609. (b) Matteson, D. S.; Moody, R. J. *Organometallics*. **1982**, *1*, 20–28.
[33] See reference 30 (b).

intermediates. Owing to their air and moisture sensitivity, these ethylene glycol derived alkenyl boronic esters (**2.55**) were oxidized to afford the homologated aldehyde (**2.56**).

Scheme 2.10 Seminal boron-Wittig with aldehydes

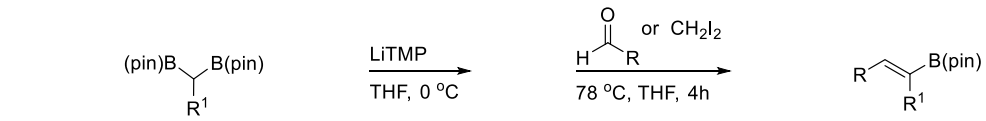


Because alkenylboron reagents found a place in potentially solving challenging synthesis problems as shown by Kishi in the total synthesis of palytoxin,[34] the Morken lab deemed it a worthwhile pursuit and embarked on developing a stereoselective synthesis of isolable alkenyl boronic esters from aldehydes (Scheme 2.11). [35] In the Morken protocol, pinacol derived diborylmethane was deprotonated using LiTMP (similar to the Matteson conditions, Scheme 2.10 B), and subsequent addition of the aldehyde delivered air-and moisture-stable 1,2-disubstituted alkenylboronic esters in good yield and with excellent

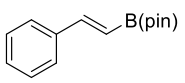
[34] Armstrong, R. W.; Beau, J.-M.; Cheon, S. H.; Christ, W. J.; Fujioka, H.; Ham, W.-H.; Hawkins, L. D.; Jin, H.; Kang, S. H.; Kishi, Y.; Martinelli, M. J.; McWhorter, W. W., Jr.; Mizuno, M.; Nakata, M.; Stutz, A. E.; Talamas, F. X.; Taniguchi, M.; Tino, J. A.; Ueda, K.; Uenishi, J.; White, J. B.; Yonaga, M. *J. Am. Chem. Soc*. **1989**, *111*, 7525.
[35] Coombs, J. R.; Zhang, L. Morken, J.P. *Org. Lett.* **2015**, *7*, 1708–1711.

diastereoselectivity (Scheme 2.11 A). When diiodomethane was employed as the electrophile, a variety of 1,1-disubstituted alkenyl boronic esters were obtained (Scheme 2.11 B). Using α-substituted diborylmethane and aldehydes, the boron-Wittig reaction generated trisubstituted alkenyl boronic esters in good yield but low diastereoselectivity (Scheme 2.11 C).

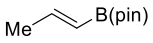
Scheme 2.11 Representative substrate scope: boron-Wittig reaction with aldehydes and diiodoomethane



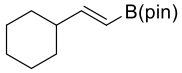
A) R^1= H, electrophile = aldehyde



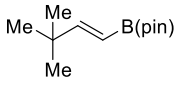
2.58
76%
>97:3 E/Z



2.59
63%
97:3 E/Z

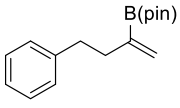


2.60
79%
>97:3 E/Z

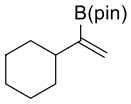


2.61
48%
97:3 E/Z

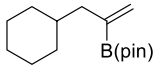
B) R_1= H, electrophile = CH_2I_2



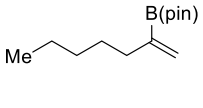
2.62
87%



2.63
84%

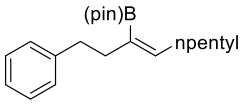


2.64
73%

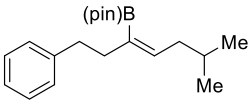


2.65
78%

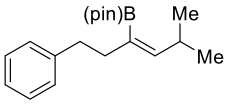
C) R^1= alkyl, electrophile = aldehyde



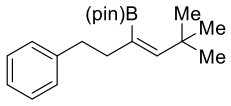
2.66
88%
88:12 Z/E



2.67
93%
76:24 Z/E



2.68
89%
61:39 E/Z

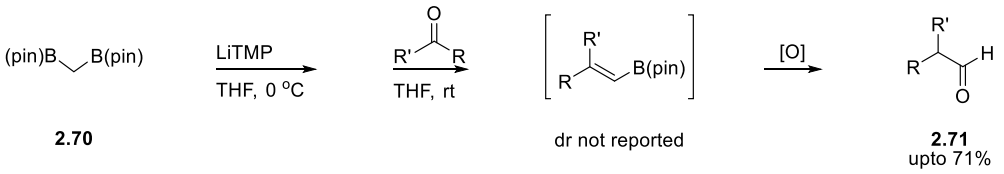


2.69
65 %
>97:3 E/Z

2.3. Reaction development with ketones

Previously, Pattison[36], Shibata, and Endo[37] investigated the boron-Wittig reaction with ketones (Scheme 2.11). The Pattison group did not probe the diastereoselectivity of the alkenyl boronic ester products but instead oxidized them to the corresponding aldehyde (Scheme 2.12). On the other hand, Shibata and Endo focused on the synthesis of tetrasubstituted alkenyl boronic esters.

Scheme 2.12 Ketone homologation via boron-Wittig reaction (Pattison)

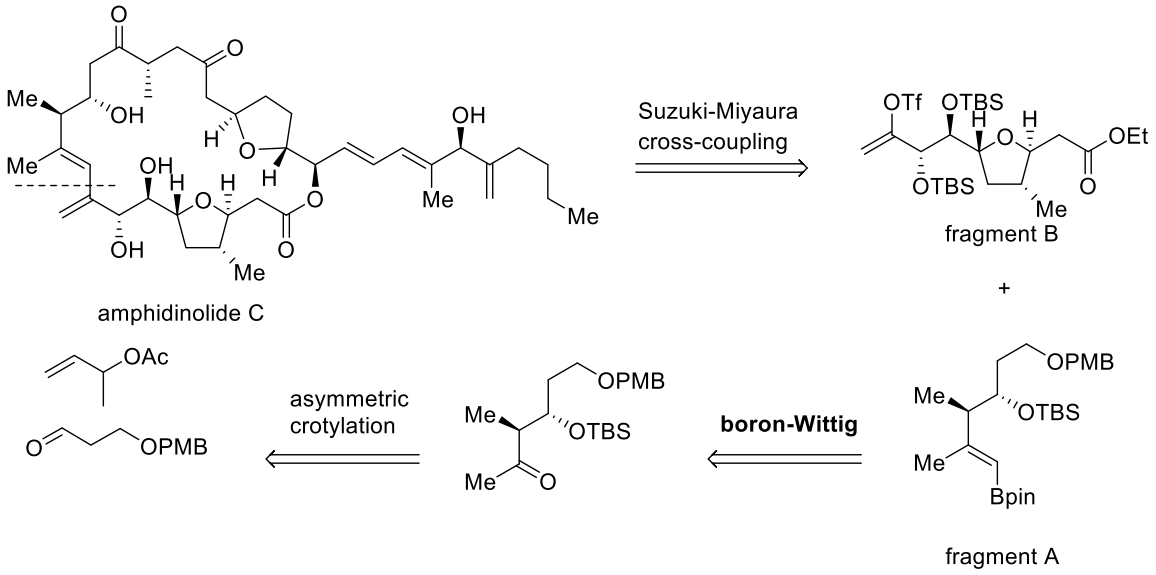


2.3.1 Development of a diastereoselective boron-Wittig reaction with ketones

While studying the total synthesis of amphidinolide C and related natural products, we saw the potential to effect a Suzuki-Miyaura cross–coupling to construct the diene from a trisubstituted alkenyl boronic ester and an alkenyl electrophile (Scheme 2.13). Due to the easy access to the ketone moiety, we deemed it paramount to develop the stereoselective boron-Wittig reaction with ketones[38] in order address this synthetic challenge posed by amphidinolide C.

[36] Stephens, T. C.; Pattison, G. *Org. Lett.* **2017**, *19*, 3498–3501.
[37] (a) Endo, K.; Hirokami, M.; Shibata, T. *J.Org. Chem*. **2010**, *75*, 3469. (b) Endo, K.; Sakamoto, A.; Ohkubo, T.; Shibata, T. *Chem. Lett*. **2011**, *40*, 1440.
[38] Namirembe, S.; Gao, C.; Wexler, R. P.; Morken, J. P. *Org. Lett.* **2019**, *21*, 4392−4394.

Scheme 2.13 Reaction development inspiration from amphidinolides C



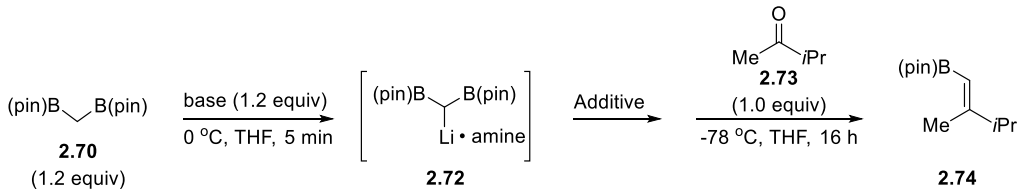
2.3.2 Metal cation effects

Initial investigations employed isopropylmethyl ketone (**2.73**) as a model substrate and conditions previously used for aldehyde substrates: LiTMP (1.2 equiv), diborylmethane (1.0 equiv) in THF (0.25M) (Table 2.1 entry 1).[39] This generated the trisubstituted alkenyl boronic ester (**2.74)** in moderate yield and with 75:25 *E/Z* diastereoselectivity. We considered that various reaction elements might be crucial for controlling the diastereoselectivity. These included choice of base and corresponding metal cation, solvent, and temperature. To understand the solvent effects, reactions were conducted in 1:1 solvent mixtures of THF with either toluene, dichloromethane or acetonitrile. All the solvent combinations investigated gave lower yield and diminished diastereoselectivity as compared to just THF as the reaction solvent. Therefore, our efforts were turned towards

[39] See reference 33

investigating the effect of the amine and metal cation on the stereochemical outcome of the reaction.

Table 2.1 Investigation of additive effects on the boron-Wittig reaction with ketones.



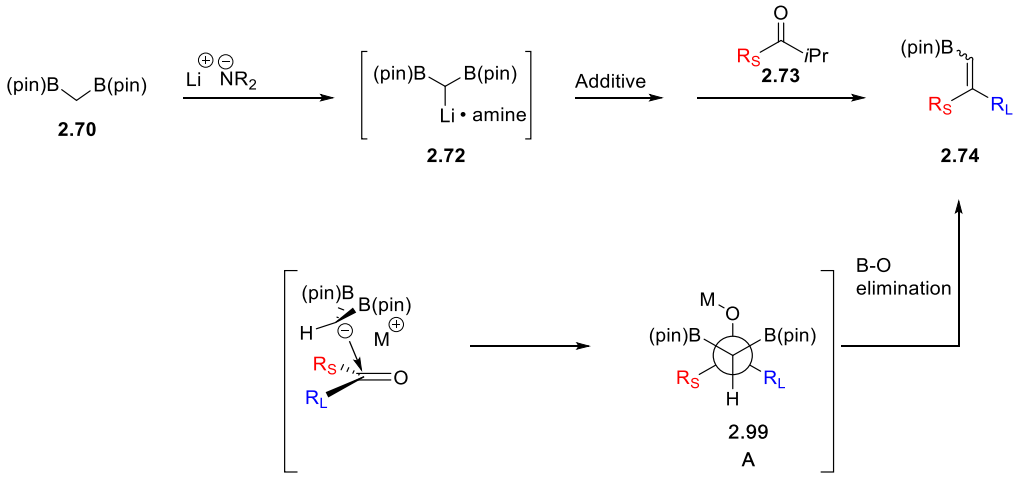
Entry	Base	Additive	Equiv	Conversion (%)	*E:Z*
1	LiTMP	none	-	54	75:25
2	LiTMP	CsF	1.2	71	57:43
3	LiTMP	CsF	2.0	66	52:48
4	LiTMP	KF	1.2	45	59:41
5	LiTMP	KF	2.0	64	68:32
6	LiTMP	12-crown 4	1.2	nr	-
7	LiTMP	12-crown 4	2.0	nr	-
8	LDA	none	-	52	77:23

Previous studies by Pattison indicated that strong non-nucleophilic lithium amine bases, LiTMP and LDA with pKa of 36 and 37 respectively, were effective at deprotonating diborylmethane **2.70**.[40] Despite the limited access to amine bases with different metal cations than Li^+ whose pKa was greater than 36, we speculated that the metal ion might serve multiple roles in the reaction and was a worthwhile subject of investigation. First, it might serve as a Lewis acid to activate the ketone for 1,2-addition. Second, after nucleophilic attack of the diborylmethylene anion on the ketone to afford the

[40] See reference 35

intermediate **2.99** (Scheme 2.14), the cation might affect the nucleophilicity of the resulting alkoxide. As a result, this might affect the rate of the alkoxide nucleophilic addition to the empty p-orbital on boron and subsequent elimination. Third, the cation size might also affect the arrangement of the different groups in the transition state, preferentially favoring boron-oxygen elimination to one diastereomer.

Scheme 2.14. Proposed metal ion effect



As previously depicted in Table 2.1, efforts were made to investigate the influence of the cation on the stereochemical outcome of the boron-Wittig reaction. We hypothesized that perhaps having large metal counter ions such as Cs^+ or K^+ might affect the diastereoselectivity. To test this, after deprotonation of diborylmethane **2.70** using LiTMP to afford anion **2.72**, the fluoride salt (CsF or KF) was added to the reaction in the glovebox. This was followed by addition of the ketone at -78 ºC (Table 2.1, entries 2-5). During the course of the reaction, we speculate that transmetalation between the fluoride salt and a lithium complex - an energetically favorable process - generates LiF whose lattice energy

(-1034 kJ/mol) is large than that of either CsF (-744 kJ/mol) or KF (-812 kJ/mol).[41] This leaves either a cesium or potassium alkoxide that adds to the empty p orbital on boron to effect the B-O elimination. Unfortunately, the addition of either CsF or KF to the reaction resulted in lower diastereoselectivity (entries 2-5) than the additive free reaction (entry 1). To further understand the role of the cation, it was found that sequestering the Li^+ counter ion using 12-crown-4 inhibited the reaction (entries 6 and 7). This experimental result underpinned the importance of Li^+ as a Lewis acid that activates the ketone for the initial 1,2-addition. In addition, the lack of improvement in diastereoselectivity with either CsF or KF additives rendered Li^+ as the optimal cation for the reaction.

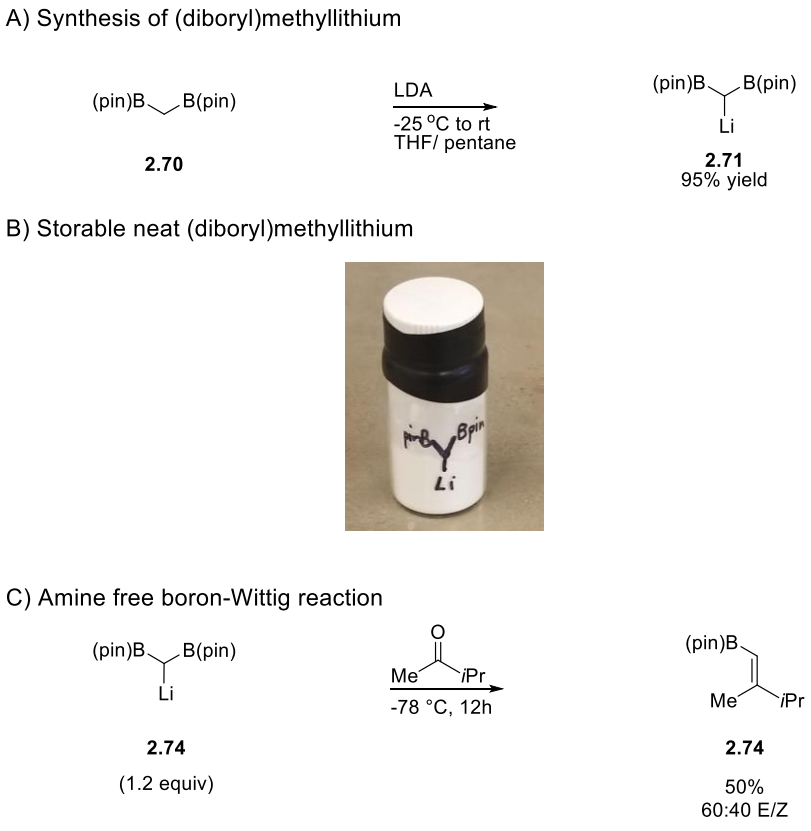
Given that entry 1 had given the best result so far in the optimization studies: 54% conversion and 72: 25 *E*/*Z*, efforts were turned toward investigating the effect of the amine. On attempting to use LDA, in place of LiTMP, a slight increase in diastereoselectivity to 77:23 E/Z (entry 8) from 75:25 *E/Z* with LiTMP was observed. LDA and LiTMP differ mainly in structure of their amines. Diisopropylamine is acyclic while 2,2,6,6-tetramethylpiperidine is cyclic and more bulky around the nitrogen atom. Although the selectivity improvement while using LDA was only small, this result was reproducible and prompted us to investigate the role of amines in the reaction.

To probe this effect, amine free (diboryl)methyllithium **2.71** (Scheme 2.15) was required. To synthesize **2.71**, the protocol developed by the Cho[42] group was adopted with careful attention to reaction temperature and concentration (Scheme 2.15). To a 1 M solution of **2.70** in dry pentane was added a freshly prepared 10 M -25 ^oC cold solution of

[41] Datta, A.; Gopikrishnan, C.; Jose, D. *AIP Advances*. **2012**, *2*, 12131−12138
[42] Lee, Y.; Park, J.; Cho, S. H. *Angew. Chem. Int. Ed*. **2018**, *57*, 12930.

LDA in one portion; formation of a white precipitate was immediately observed. The reaction was allowed to stir and warmed to room temperature for 20 minutes. In the glovebox, the white solid was filtered using a fritted funnel and carefully washed with THF and pentane to wash away the remaining amine without dissolving the solid (diboryl)methyllithium. The solvent was removed in vacuo and the white solid could be stored under nitrogen in the glove box freezer for at least six months.

Scheme 2.15 Preparation of amine free (diboryl)methyllithium



When amine free (diboryl)methyllithium (**2.71**) was employed as the olefination reagent, the product **2.74** was isolated in 50% yield and with 60:40 *E/Z* diastereoselectivity (Scheme 2.15 C), in contrast to the (diboryl)methyllithium derived from in situ deprotonation of $CH_2(Bpin)_2$ with LiTMP which delivered the product in 54% yield and

75:25 *E/Z* ratio. This result suggested that amine additives could have an effect on the diastereoselectivity and this hypothesis was further probed.

2.3.3 Investigation of amine additives

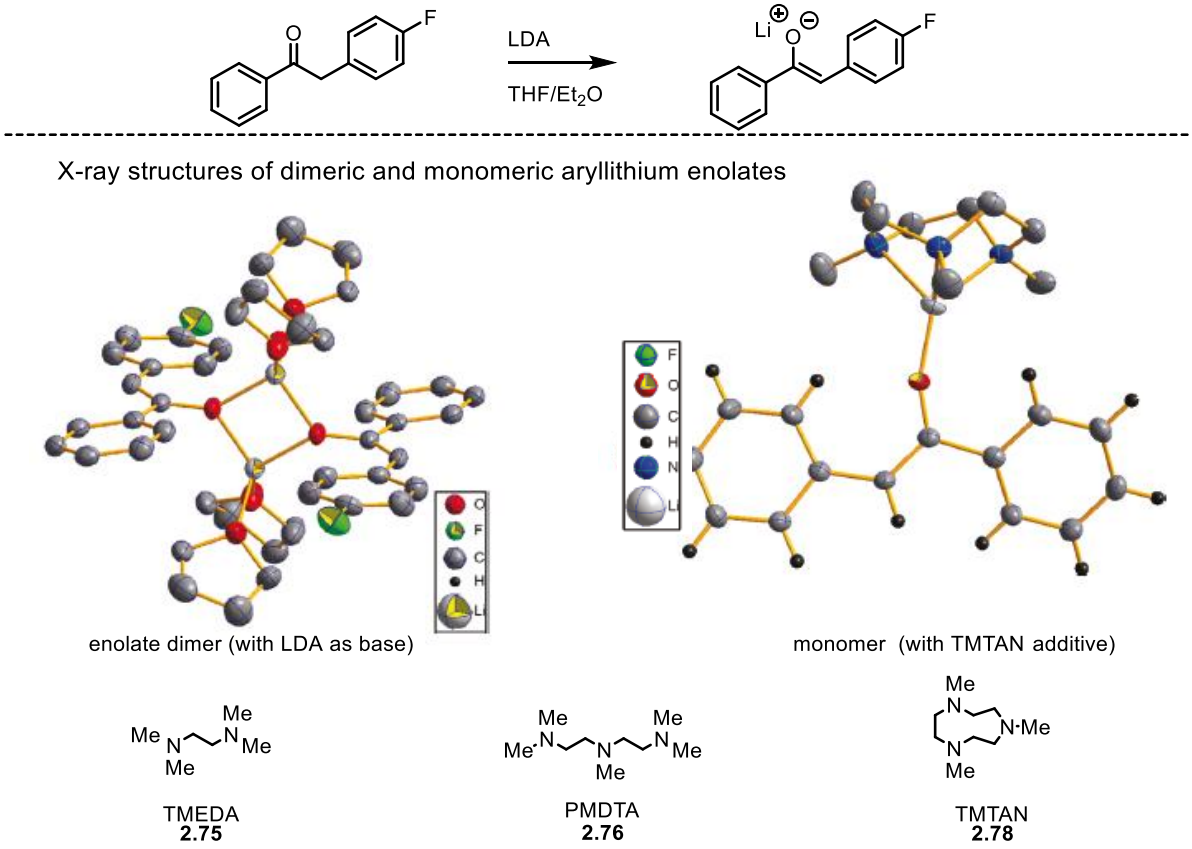
A variety of amines are known to chelate organolithium species, affect the their aggregation state and alter reactivity.[43,44] Based on the above experimental results that displayed an effect of the amine on the diastereoselectivity, we speculated that there might be a complex equilibrium mixture of organolithium species with different solvation and aggregation states and that each might have unique kinetics and selectivities in the boron-Wittig reaction. The effect of amine additives on the aggregation state of various organolithium reagents has been extensively studied by the groups of Collum and Reich.[45]

Research conducted by the Reich group on various aryllithium enolates showed that different amine additives can alter their aggregation states. Among the amines studied included TMEDA; a diamine, PMDTA; an acyclic triamine, and TMTAN; a cyclic triamine. TMEDA was found to promote formation of dimeric organolithium species, PMDTA and TMTAN were found to promote formation of monomeric organolithium species.[46] In their studies, 2-(4-fluorophenyl)-1-phenylethan-1-one was deprotonated using LDA to generate the lithium enolate (Scheme 2.16). This aryllithium enolate was found to be mainly dimeric in a THF/Et_2O solution as depicted in the X-ray structure below (Scheme 2.15).[47] When either PMDTA or TMTAN was added to the aryllithium enolate,

[43] Reich, J. H. *Chem. Rev*. **2013**, *113*, 7130−7178.
[44] Reich, J. H.; Green, D. P.; Medina, A. M.; Goldenberg, W. S.; Gudmundsson, Ö. B.; Dykstra, R. R.; Phillips, H. N. *J. Am. Chem. Soc*. **1998**, *29*, 7201-7210.
[45] Reich, J. H. *Chem. Rev*. **2013**, *113*, 7130−7178.
[46] Kolonko, K. J.; Biddle, M. M.; Guzi, I. A.; Reich, H. J. *J. Am. Chem.* Soc. **2009**, *131*, 11525.
[47] Kolonko, K. J.; Guzei, I. A.; Reich, H. J. *J. Org. Chem*. **2010**, *75*, 6163.

deaggregation from the dimeric to the monomeric species was observed by ^{7}Li and ^{19}F NMR. The TMTAN bound monomeric complex structure was determined by X-ray crystallography as depicted in Scheme 2.16.

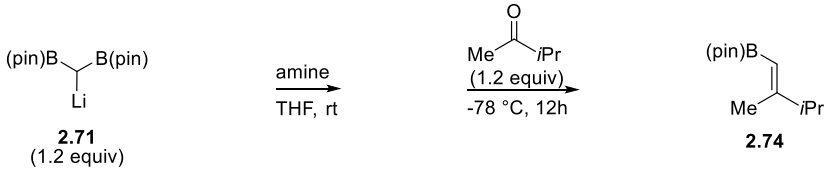
Scheme 2.16 Amine additive effect on aryllithium enolate aggregation (Reich)



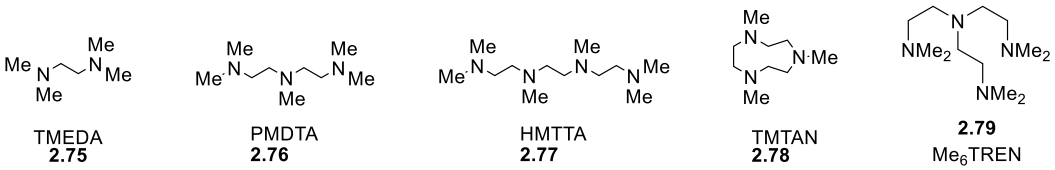
While both TMTAN and PMDTA were effective at converting dimeric lithium species to monomeric ones, the cyclic TMTAN was found to have a higher kinetic affinity for lithium than PMDTA. Free TMTAN was not detected until 1 equivalent had been added to the aryllithium enolate solution. Whereas with PMDTA, addition of 1 equivalent to the aryllithium enolate solution generated only 55% of the monomeric enolate. Consequently,

the cyclic TMTAN proposed was more efficient at promoting the formation of monomeric aryllithium enolate species than the acyclic PMDTA[48].

Table 2.2 Amine additive effects on the boron-Wittig reaction



Entry	Additive	Equiv	Yield (%)	E/Z
1	-	-	50	60:40
2	TMEDA	1.5	54	78:22
3	PMDTA	1.2	62	90:10
4	PMDTA	1.5	63	94:6
5	HMTETA	1.5	50	78:22
6	TMTAN	1.5	63	93:7
7	Me_6TREN	1.5	60	79:21



Inspired by the literature precedent from the Reich group, we speculated that amine additives might affect the aggregation state of the organolithium alkoxides and the overall stereochemical outcome of the boron-Wittig reaction. The reaction with TMEDA, a diamine that promotes formation of dimeric organolithium species, afforded the product with increased diastereoselectivity (78:22 *E*/*Z,* Table 2.2, entry 2) than the amine free reaction (60:40 *E*/*Z*, Table 2.2, entry 1). When triamines PMDTA (entries 3 and 4), and TMTAN (entry 6), were added to the reaction, a large increase in diastereoselectivity to

[48] See reference 45

90:10 – 94:6 and 93:7 *E/Z* was observed respectively. Reactions with tetramines, HMTETA (entry 5) and Me_6TREN (entry 7) as amine additives generated the desired product in moderate diastereoselectivity. Further changes in temperature and solvent did not improve diastereoselectivity.

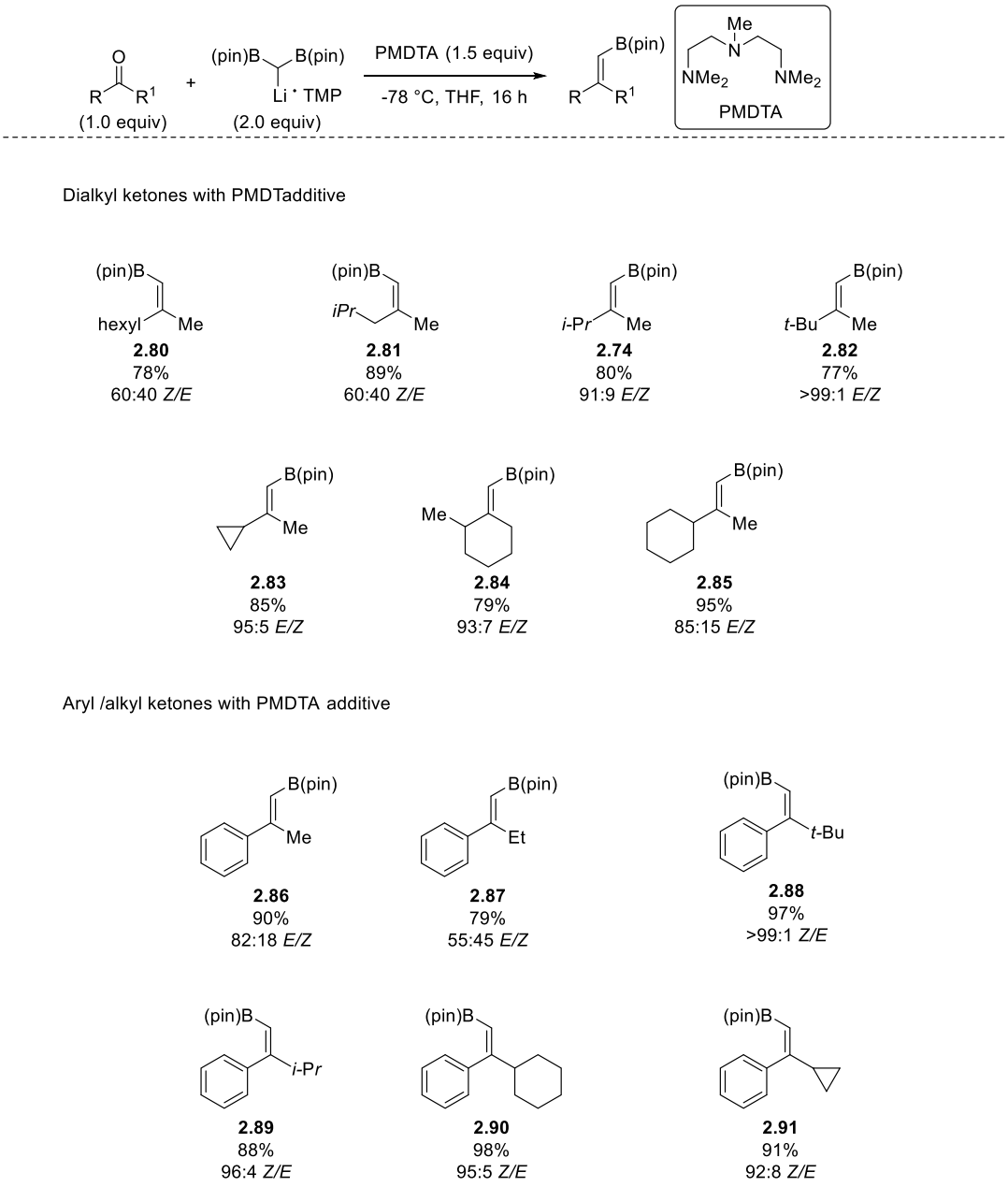
An operationally convenient protocol was developed in which diborylmethane was deprotonated *in situ* by LiTMP, followed by amine addition. Further reaction optimization revealed that the amount of the amine additive affected both conversion and diastereoselectivity and was the subject of further optimization. With PMDTA and TMTAN, the reaction required 1.5 and 0.5 equivalents of amine respectively for optimum yield and stereoselectivity. This result was in agreement with the observation made by the Reich group as discussed above in which they suggest that TMTAN has a higher kinetic affinity for lithium than PMDTA. In addition, further diluting the reaction from 0.25 M to 0.09 M and using two equivalents of diborylmethane ensured high conversion of the starting ketone. These conditions were used to investigate the substrate scope.

2.4 Substrate scope

The investigation of the substrate scope commenced with aliphatic ketones. Reactions of these substrates were found to be most selective when PMDTA (1.5 equivalent) was used as the amine additive (Scheme 2.17, method A). Aliphatic ketones bearing α-substituents afforded boron-Wittig products with high levels of diastereoselectivity favoring the *E* isomer (compounds **2.74**, **2.82**, **2.83**, and **2.84**). In contrast, aliphatic ketones that lacked steric bias between the two groups generated alkenyl boronic esters with moderate levels of diastereoselectivity (compounds **2.80** and **2.81**) and favored the *Z*- isomer. Examination of aromatic (aryl/alkyl) ketones with PMDTA revealed

that the alkenyl boronic esters were obtained in high *Z* diastereoselectivity as long as the alkyl group had an α-substituent. (Scheme 2.17, compounds **2.88**, **2.89**, **2.90**, and **2.91**).

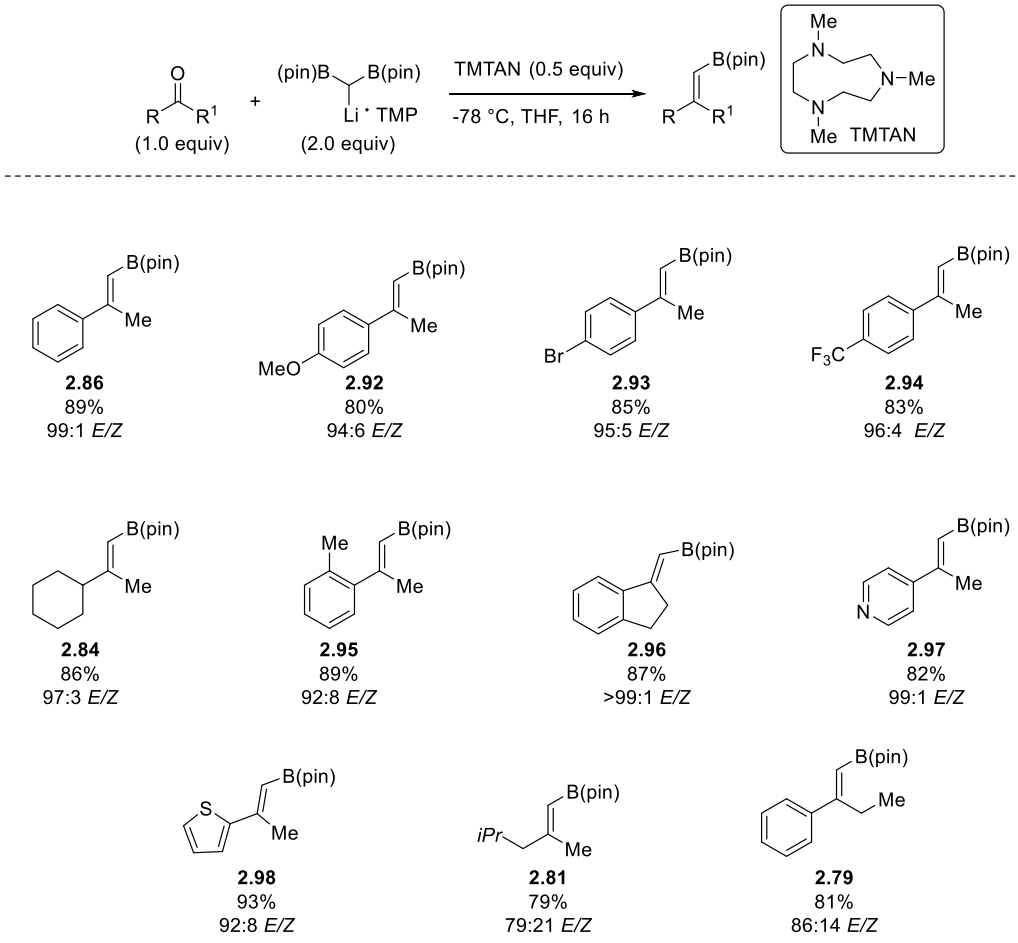
Scheme 2.17 Method A: substrate scope with PMDTA amine additive



Acetophenone which lacks an α-substituent afforded the alkenyl boronic ester (**2.86**) in moderate diastereoselectivity (82:18 *E/Z*) with PMDTA (Scheme 2.17, method A).

Because of the potential synthetic utility of alkenyl boronic esters derived from arylmethyl ketones, acetophenone was further investigated with TMTAN amine additive

Scheme 2.18 Method B: substrates scope with TMTAN



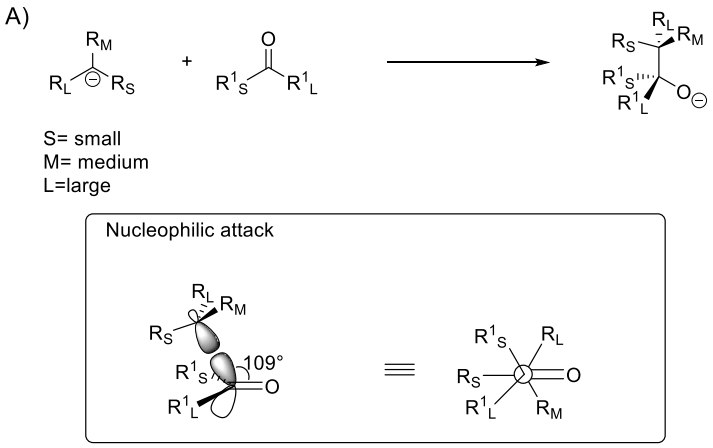
Gratifyingly with the addition of 0.5 equivalents of TMTAN (Scheme 2.18), acetophenone was converted to the desired alkenyl boronic ester in high yield and with excellent diastereoselectivity (99:1 E/Z, compound **2.86**). In addition, electron-rich and electron-poor arylmethyl ketones were competent in the reaction. Heteroaryl methyl ketones were also suitable substrates in the reaction and afforded the desired alkenyl boronic esters in excellent yield and with high diastereoselectivity (compounds **2.97** and **2.98**). Dialkyl ketones that are less sterically encumbered were now able to furnish the

alkenyl boronic ester products in moderate *E* diastereoslectvity with TMTAN **(**compounds **2.81,** and **2.79**).

2.5 Origin of diastereoselectivity

Bassindale and Taylor proposed a predictive model for the origin of diastereoselectivity in reactions between prochiral carbanion and prochiral carbonyl compounds (Scheme 2.19 A). If nucleophilic attack by the carbanion on the carbonyl occurred irreversibly, the stereochemical outcome was dependent on the steric influence of the different groups. Therefore, the most favorable nucleophilic attack was proposed to occur at at least 109º such that the small group, R_S is situated between the large R^1_L and and small R^1_S groups of the carbonyl (Scheme 2.19A).[49]

Scheme 2.19 Proposed origin of selectivity in [2+2]: Taylor and Bassindale

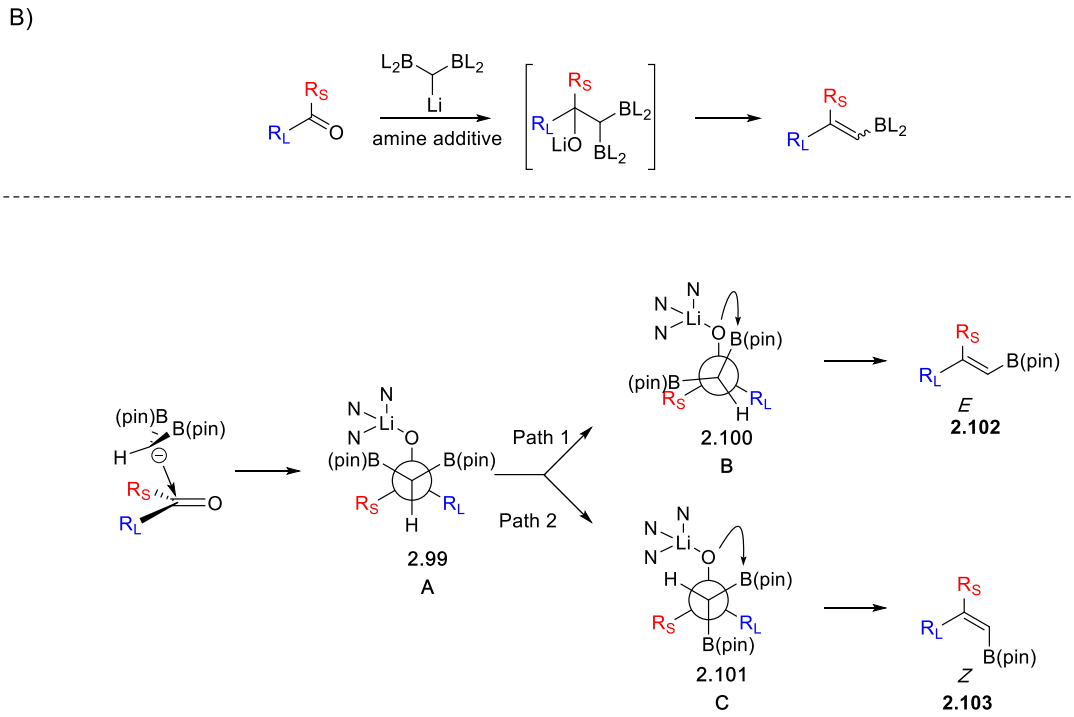


In regard to the boron-Wittig reaction, the diastereoselectivity model (Scheme 2.19 B) proposed considers that nucleophilic attack on the ketone occurs in accord with the Taylor-Basindale model (Scheme 2.19 A) in which the smallest group (H) would likely sit

[49] Bassindale, A. R.; Ellis, R. J.; Lau, J. C.-Y.; Taylor, P. G. *J. Chem. Soc., Chem. Commun*. **1986**, 98.

between the two carbonyl substituents. Nucleophilic attack in this fashion generates intermediate A (**2.99**). If B-O elimination is faster than bond rotation, then reaction through path 1 might dominate; intermediate B, (**2.100**) has the non-eliminating boron situated in proximity to the small group and B-O elimination would furnish the *E* diastereomer (**2.102**). However, if B-O elimination is slow, allowing for bond rotation to happen, intermediate A (**2.99)** might be converted to C (**2.101**) (path 2 dominates); the small H is close to the large triamine ligand on the lithium and B-O elimination would furnish the *Z* diastereomer (**2.103**).

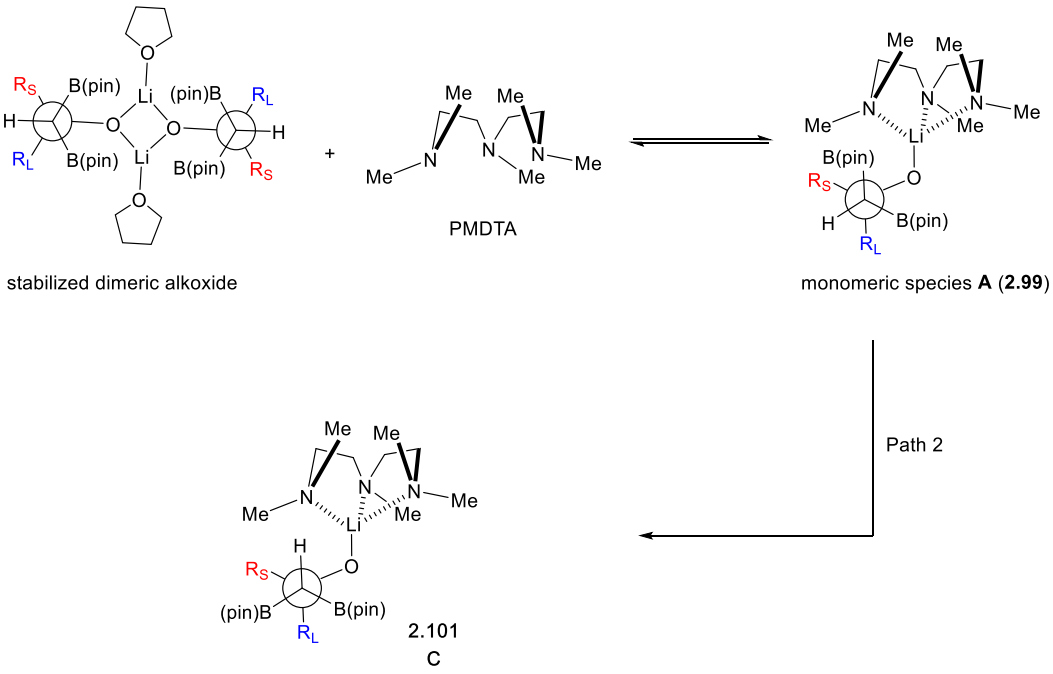
Scheme 2.19 Proposed origin of selectivity in the Boron-Wittig with ketones



The role of the amine in the boron-Wittig reaction, specifically its influence on the diastereoselectivity is empirical. Lithium aggregation studies conducted by the Reich group showed that PMDTA and TMTAN converted dimeric lithium enolate species to

monomeric species. They showed that TMTAN was more effective than PMDTA at forming monomeric lithium enolate species.[50] In regard to the boron-Wittig reaction, we speculate that the intermediacy of dimeric alkoxides (Scheme 2.20) may serve to stabilize the addition product A (**2.99)** and thereby allow path 2 through intermediate C (**2.101**) to operate (Scheme 2.20). Whereas with TMTAN, rapid elimination through intermediate B, (**2.100**, path 1, Scheme 2.19) occurs thus furnishing a greater proportion of the *E* product

Scheme 2.20 Proposed PMDTA-promoted deaggregation of dimeric alkoxides to monomers

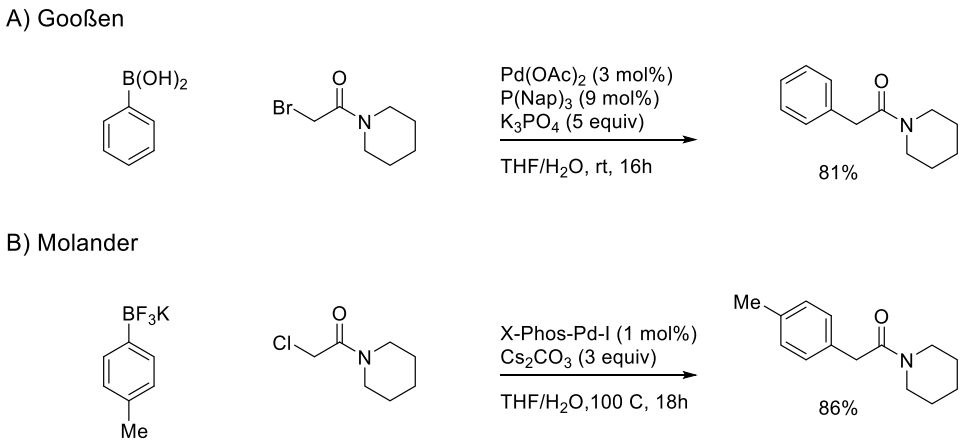


[50] See references 44 and 45.

2.6 Practical Applications

Somewhat surprisingly, palladium-catalyzed Suzuki-Miyaura cross-coupling between an α-bromo amide/ ester and a trisubstituted alkenyl boronic ester to afford β,γ-unsaturated esters and amides is unknown, yet it is needed for one route we envisioned for the total synthesis of amphidinolide C and F. This cross-coupling would provide an easy access to this class of compounds. A literature survey revealed a variety of palladium-catalyzed cross-coupling between α-halo amides and arylboronic acid derivatives.[51] Of note are the seminal examples using boronic acids by Gooßen[52] and aryltrifluoroborate salts by Molander[53] (Scheme 2.21).

Scheme 2.21 Selected examples of Pd-catalyzed Suzuki cross coupling between arylboronic acid derivatives and α-halo carbonyls

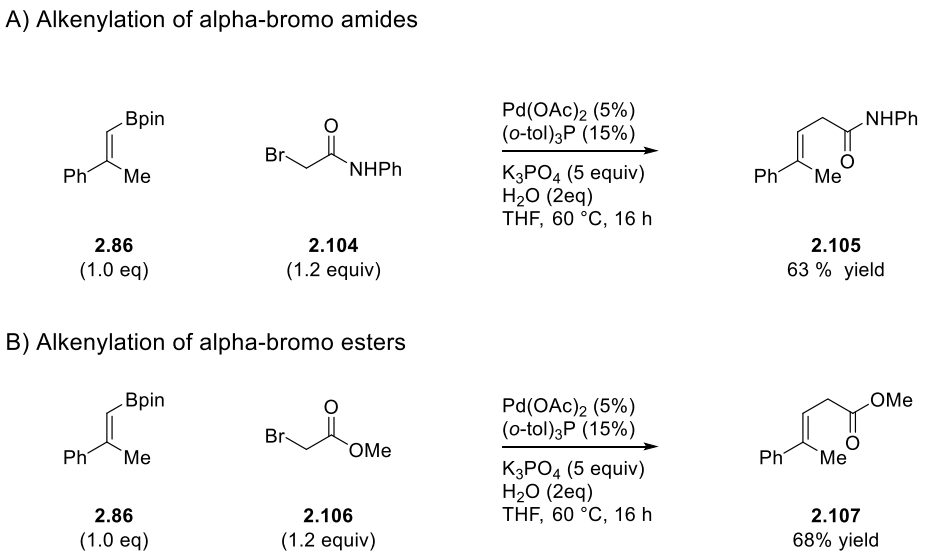


The ease of access to the products especially the β,γ-unsaturated amides is of synthetic significance as they are used in amide directed hydroboration[54] and the previous methods of synthesis were lengthy. Gratifyingly, we found that using a $Pd(OAc)_2$/(*o*-

[51] Cossy, J.; Guérinot, A.; Barde, E. *Synthesis* **2019**, *51*, 178 – 184.
[52] Gooßen, L. J. *Chem. Commun*. **2001**, 669.
[53] Traister, K. M.; Barcellos, T.; Molander, G. A. *J. Org. Chem*. **2013**, 78, 4123.
[54] Smith S. M.; Takacs, J. M. *J. Am. Chem. Soc.* **2010**, *132*, 1740 – 174.

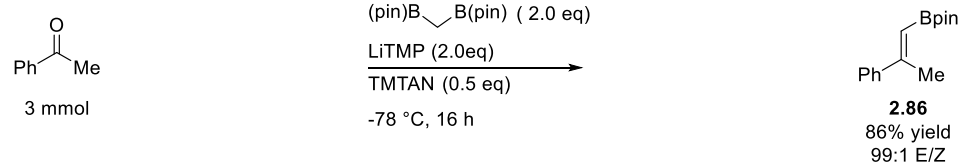
tol)$_3$Ph catalyst, potassium phosphate base and THF/H_2O effected the Suzuki-Miyaura cross-coupling between α-halo amides/ esters with trisubstituted alkenyl boronic esters in synthetically useful yields (Scheme 2.22).

Scheme 2.22: Alkenylation of α-bromo amides and esters



It is also notable that the boron-Wittig reaction could be performed on large scale with acetophenone to afford the desired trisubstituted alkenyl boronic ester (**2.86**) in high yield and diastereoselectivity (Scheme 2.23).

Scheme 2.23 Practical large scale boron-Wittig



2.7 Conclusion

An amine modified boron-Wittig reaction that engages ketone electrophiles and furnishes trisubstituted alkenyl boronic esters has been developed. This transformation provides an efficient and diastereoselective alternative to access a variety of these synthetically useful motifs from readily available starting materials. Further computational studies are needed to understand the role of the amine additives. Future studies should also be geared towards increasing the stereoselectvity for ketones that lack steric bias between the two groups.

2.8 Experimental

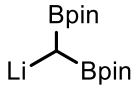
2.8.1 General Information

^{1}H NMR spectra were recorded on either a Varian Gemini-500 (500 MHz) or Varian Gemini-600 (600 MHz) spectrometer. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 7.26 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet), and coupling constants (Hz). ^{13}C NMR spectra were recorded on either a Varian Gemini-500 (125 MHz) or a Varian Gemini-600 (150 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 77.16 ppm). 2D-NOESY spectra were recorded on Varian Gemini-600 (150 MHz). ^{11}B NMR spectra were recorded on a Varian Gemini-500 (128 MHz) or Varian Gemini-600 (160 MHz) spectrometer. Chemical shifts are reported in ppm with an external standard ($BF_3 \cdot Et_2O$: 0 ppm). Infrared (IR) spectra were recorded on a Bruker alpha-P Spectrometer. Frequencies are reported in wavenumbers (cm^{-1}) as follows: strong (s), broad (br), medium (m), and weak (w). High-resolution mass spectrometry (DART) was performed at the Mass Spectrometry Facility, Boston College, Chestnut Hill, MA. Liquid chromatography was performed using forced flow (flash chromatography) on silica gel (SiO_2, 230 x 450 Mesh) purchased from Silicycle or with a Biotage Isolera One equipped with full wavelength scan. Thin layer chromatography (TLC) was performed on 25 μm silica gel glass backed plates from Silicycle. Visualization was performed using ultraviolet light (254 nm), ceric ammonium molybdate (CAM) in ethanol, or phosphomolybdic acid and cerium (IV) sulfate in ethanol with sulfuric acid (Seebach).

All reactions were conducted in oven- or flame-dried glassware under an inert atmosphere of nitrogen or argon. Tetrahydrofuran (thf), diethyl ether (Et_2O), were purified using Pure Solv MD-4 solvent purification system, from Innovative Technology, Inc., by passing the solvent through two activated alumina columns after purging with argon. Calcium hydride was purchased from Acros. Diisopropylamine was purchased from Fisher, 2,2,6,6-tetramethylpiperidine was purchased from Oakwood and distilled over calcium hydride before use. 1,4,7-Trimethyl-1,4,7-triazacyclononane was purchased from Matrix Scientific, *N*,*N*,*N*′,*N*″,*N*‴-Pentamethyldiethylenetriamine was purchased from TCI America, 1,1,4,7,10,10-Hexamethyltriethylenetetramine was purchased from Sigma Aldrich, Tris[2-(dimethylamino)ethyl]amine was purchased from Alfa Aesar and were used without further purification. N,N,N',N'-Tetramethylethylenediamine was purchased from ThermoFisher and distilled over calcium hydride before use**.** Copper iodide was purchased from Strem Chemicals and used as received. $B_2(pin)_2$ was obtained from Oakwood and used without further purification. Palladium acetate was purchased from Strem and used as received. Tris-o-tolyphosphine was purchased from Strem and used as received.

All other reagents, including ketones were purchased from either Aldrich, Alfa Aesar, Acros, Oakwood Chemicals, Combi Blocks, Fluka or TCI and were used without further purification.

2.8.2 Experimental Information

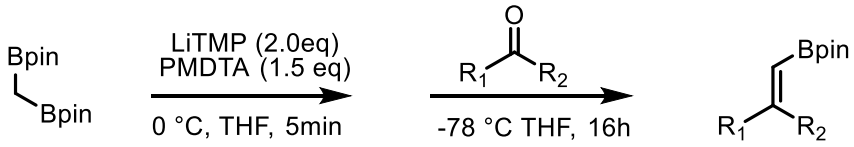


(bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)lithium (2.74). The title compound was prepared from known literature procedure[55]. NMR spectral data were in agreement with literature.

bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane (2.70). The title compound was prepared from known literature procedure[56]. NMR and mass spectral data were in agreement with literature.

2.8.2.1 General Procedures for the Synthesis of trisubstitiuted alkenylborons

Method A

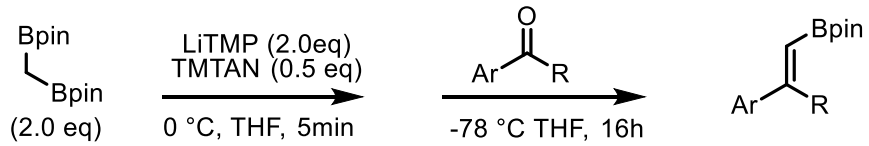


In a glove box, an oven dried 16 dram vial with a magnetic stir bar was charged with LiTMP (147.2 mg, 1.00 mmol, 2.0 equiv), 2.50 ml of THF was added, then PMDTA (130.0 mg, 0.75 mmol 1.5 equiv), sealed with septa and removed from the glovebox. Under nitrogen, the reaction vial was cooled to 0 °C, and a solution of bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane (268.0 mg 1.00 mmol, 2.0 equiv) in THF (2.0 mL) was added in one portion. The reaction was allowed to stir for 5 minutes. The reaction was cooled to -78 °C and ketone (0.5 mmol, 1 equiv) in 1 ml THF was added was added. The reaction vial was allowed to stir for 16 hours at -78 °C. Upon completion, the reaction was opened to air, and filtered through a silica plug with eluting diethyl ether. The mixture was

[55] Lee, Y.; Park, J.; Cho, S. H. *Angew. Chem.* **2018**, *57*, 12930.
[56] Coombs, J. R.; Zhang, L.; Morken, J. P. *Org. Lett.* **2015**, *17,* 1708.

concentrated under reduced pressure. The trisubstituted alkenyl boronate products were isolated by SiO2 chromatography.

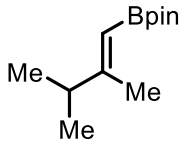
Method B



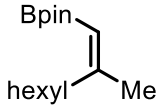
In a glove box, an oven dried 16 dram vial with a magnetic stir bar was charged with LiTMP (147.2 mg, 1.00 mmol, 2.0 equiv), 2.50 ml of THF, then TMTAN (42.8 mg, 0.25 mmol, 0.5 equiv), vial sealed with septa and removed from the glovebox. Under nitrogen, the reaction vial was cooled to 0 °C, and a solution of bis(4,4,5,5- tetramethyl-1,3,2-dioxaborolan-2-yl)methane (268.0 mg 1.00 mmol, 2.0 equiv) in THF (2.0 mL) was added in one portion. The reaction was allowed to stir for 5 minutes. The reaction was cooled to -78 °C and ketone (0.5 mmol) in 1 ml THF was added. The reaction vial was allowed to stir for 16 hours at -78 °C. Upon completion, the reaction was opened to air, and filtered through a silica plug with diethyl ether. The mixture was concentrated under reduced pressure. The trisubstituted alkenyl boronate products were isolated by SiO2 chromatography.

2.8.2.2 Characterization of Boron-Wittig products

Note: Due to boron quadrupole, carbon atoms attached to the boron are sufficiently broadened and rendered undetectable in ^{13}C NMR.

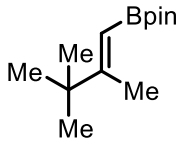


***(E)*-2-(2,3-dimethylbut-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.74).** Prepared according to general procedure (Method A) using LiTMP (147.2 mg, 1.00 mmol), bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane (268.0 mg, 1.00 mmol) PMDTA (130.0 mg, 1.5 mmol), 3-methylbutan-2-one (43.1 mg , 0.5 mmol) and THF (5.5 ml). The crude reaction mixture was purified by column chromatography on silica gel (30% DCM /hexanes) to afford the desired product as a clear colorless oil (105 mg, 80%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.14 (s, 1H), 2.33 – 2.23 (m, 1H), 1.97 (s, 3H), 1.27 (s, 12H), 1.02 (d, J = 6.9 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.6, 82.7, 39.0, 25.0, 21.5, 19.0. ^{11}B NMR: (160 MHz, $CDCl_3$) δ 3085 IR (neat) ν_{max} 2991 (m), 2993 (m), 1635 (s), 1459 (m), 1385 (s), 1317 (s), 1144 (s). HRMS (DART+) for $C_{12}H_{24}BO_2$ $[M+H]^+$ calculated: 211.1864, found: 211.1860.

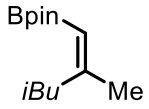


***(Z)*-4,4,5,5-tetramethyl-2-(2-methyloct-1-en-1-yl)-1,3,2-dioxaborolane (2.80).** Prepared according to general procedure (Method A) using LiTMP (147.2 mg, 1.00 mmol), bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane (268.0 mg, 1.00 mmol) PMDTA (130.0 mg, 1.5 mmol), 2-octanone (56.2 mg , 0.5 mmol) and THF (5.5 ml). The crude reaction mixture was purified by column chromatography on

silica gel (30% DCM /hexanes) to afford the desired product as a clear colorless oil (93 mg, 78%). All spectral data are in accord with the literature.[57]

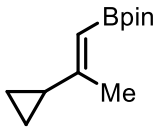


***(E)*-4,4,5,5-tetramethyl-2-(2,3,3-trimethylbut-1-en-1-yl)-1,3,2-dioxaborolane (2.82).** Prepared according to general procedure (Method A) using LiTMP (147.2 mg, 1.00 mmol), bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane (268.0 mg, 1.00 mmol) PMDTA (130.0 mg, 1.5 mmol), 3,3-dimethylbutan-2-one (50.0 mg , 0.5 mmol) and THF (5.5 ml). The crude reaction mixture was purified by column chromatography on silica gel (30% DCM /hexanes) to afford the desired product as a clear colorless oil (87 mg, 77%). All spectral data are in accord with the literature.[3]

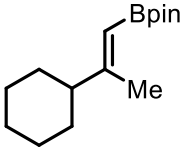


***(Z)*-2-(2,4-dimethylpent-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.81).** Prepared according to general procedure (Method A) using LiTMP (147.2 mg, 1.00 mmol), bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane (268.0 mg, 1.00 mmol) PMDTA (130.0 mg, 1.5 mmol), 4-methylpentan-2-one (50. mg , 0.5 mmol) and THF (5.5 ml). The crude reaction mixture was purified by column chromatography on silica gel (30% DCM /hexanes) to afford the desired product as a clear colorless oil (100 mg, 89%). All spectral data are in accord with the literature.[58]

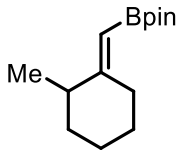
[57] Zhurakovskyi, O.; Dias, R. M. P.; Noble, A.; Aggarwal, V. K. *Org. Lett.* **2018,** *20*, 3136.
[58] Wang, C.; Tobrman, T.; Xu, Z.; Negishi, E. -I. *Org. Lett.* **2009,** *11,* 4092.



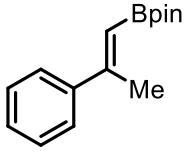
***(E)*-2-(2-cyclopropylprop-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.83).** Prepared according to general procedure (Method A) using LiTMP (147.2 mg, 1.00 mmol), bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane (268.0 mg, 1.00mmol) PMDTA, (130.0 mg, 1.5 mmol), cyclo propylmethyl ketone (42.1 mg , 0.5 mmol) and THF (5.5 ml). The crude reaction mixture was purified by column chromatography on silica gel (30% DCM /hexanes) to afford the desired product as a clear colorless oil (89 mg, 85%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.09 (s, 1H), 1.89 (s, 3H), 1.48 (tt, J = 8.3, 5.2 Hz, 1H), 1.25 (s, 12H), 0.70 – 0.65 (m, 2H), 0.61 – 0.57 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.9, 82.6, 77.4, 77.2, 77.0, 25.0, 21.1, 18.5, 6.80. ^{11}B NMR: (160 MHz, CDCl3) δ 30.56. IR (neat) ν_{max} 3082 (w), 2975 (m), 2927 (m), 1623 (s), 1283 (s) 1213 (s), 1142 (s). HRMS (DART+) for $C_{12}H_{22}BO_2$ $[M+H]^+$ calculated: 209.1707, found: 209.1705.



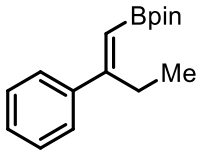
***(E)*-2-(2-cyclohexylprop-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.85).** Prepared according to general procedure (Method B) using LiTMP (147.2 mg, 1.00 mmol), bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane (268.0 mg, 1.00mmol) TMTAN (42.8 mg, 0.5 mmol), 1-cylohexylethanone (63.1 mg , 0.5 mmol) and THF (5.5 ml). The crude reaction mixture was purified by column chromatography on silica gel (30% DCM /hexanes) to afford the desired product as a clear colorless oil (100 mg, 89%). All spectral data are in accord with the literature.[3]



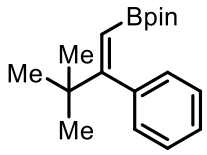
***(E)*-4,4,5,5-tetramethyl-2-((2-methylcyclohexylidene)methyl)-1,3,2-dioxaborolane (2.84).** Prepared according to general procedure (Method A) using LiTMP (147.2 mg, 1.00 mmol), bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane (268.0 mg, 1.00mmol), PMDTA (130.0 mg, 1.5 mmol), 2-methylcyclohexanone (56.1 mg , 0.5 mmol) and THF (5.5 ml). The crude reaction mixture was purified by column chromatography on silica gel (30% DCM /hexanes) to afford the desired product as a clear colorless oil (89 mg, 85%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.03 (s, 1H), 3.11 – 3.01 (m, 2H), 2.20 – 2.07 (m, 1H), 2.05 – 1.97 (m, 1H), 1.83 – 1.65 (m, 3H), 1.51 – 1.31 (m, 3H), 1.27 (s, 12H), 1.19 – 1.10 (m, 1H), 1.03 (d, J = 6.6 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.6, 82.6, 40.8, 37.2, 33.5, 29.1, 25.9, 25.0, 24.9, 18.7. ^{11}B NMR: (160 MHz, CDCl3) δ 30.76. IR (neat) ν_{max} . 2974 (m), 2922 (m), 2850 (m), 1633 (s), 1401 (m), 1369 (s), 1267 (s). .HRMS (DART+) for $C_{14}H_{26}BO_2$ $[M+H]^+$ calculated: 237.2020, found: 237.2019.



***(E)*-4,4,5,5-tetramethyl-2-(2-phenylprop-1-en-1-yl)-1,3,2-dioxaborolane (2.86).** Prepared according to general procedure (Method B) using LiTMP (147.2 mg, 1.00 mmol), bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane (268.0 mg, 1.00mmol) TMTAN (42.8mg, 0.25mmol), acetophenone (60.07mg, 0.5mmol) and THF (5.5ml). The crude reaction mixture was purified by column chromatography on silica gel (30% DCM/hexanes) to afford the desired product as a clear, colorless oil (110.7mg, 91%). All spectral data are in accord with the literature.[3]

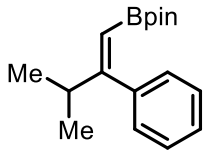


***(Z)*-4,4,5,5-tetramethyl-2-(2-phenylbut-1-en-1-yl)-1,3,2-dioxaborolane (2.87).** Prepared according to general procedure (Method A) using LiTMP (147.2 mg, 1.00 mmol), bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane (268.0 mg, 1.00mmol), PMDTA (130.0 mg, 1.5 mmol), propiophenone (67.1 mg , 0.5 mmol) and THF (5.5 ml). The crude reaction mixture was purified by column chromatography on silica gel (30% DCM /hexanes) to afford the desired product as a clear colorless oil (102 mg, 79%). All spectral data are in accord with the literature.[59]

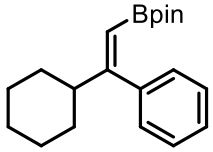


***(Z)*-2-(3,3-dimethyl-2-phenylbut-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.88).** Prepared according to general procedure (Method A) using LiTMP (147.2 mg, 1.00 mmol), bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane (268.0 mg, 1.00 mmol), PMDTA (130.0 mg, 1.5 mmol), 2,2-dimethylpropiophenone (81.1 mg , 0.5 mmol) and THF (5.5 ml). The crude reaction mixture was purified by column chromatography on silica gel (30% DCM /hexanes) to afford the desired product as a clear colorless oil (139 mg, 97%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 – 7.19 (m, 3H), 7.12 – 7.02 (m, 3H), 5.62 (s, 1H), 1.09 (s, 9H), 0.96 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.9, 142.5, 129.5, 126.8, 126.1, 82.7, 37.6, 29.4, 24.5. ^{11}B NMR: (160 MHz, $CDCl_3$) δ 31.05. IR (neat) ν_{max} 2972 (m), 1618 (m), 1368 (s), 1353 (s), 1142 (s). HRMS (DART+) for $C_{18}H_{28}BO_2$ $[M+H]^+$ calculated: 287.2177, found: 287.2193.

[59] Molloy, J. J.; Metternich, J. B.; Daniliuc, C. G.; Watson, A. J. B.; Gilmour, A. *Angew. Chem.* **2018***, 130,* 3222.

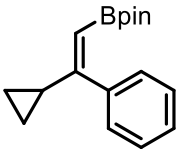


***(Z)*-4,4,5,5-tetramethyl-2-(3-methyl-2-phenylbut-1-en-1-yl)-1,3,2-dioxaborolane (2.89).** Prepared according to general procedure (Method A) using LiTMP (147.2 mg, 1.00 mmol), bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane (268.0 mg, 1.00mmol), PMDTA (130.0 mg, 1.5 mmol), 2,2-dimethylpropiophenone (81.1 mg , 0.5 mmol) and THF (5.5 ml). The crude reaction mixture was purified by column chromatography on silica gel (30% DCM /hexanes) to afford the desired product as a clear colorless oil (139 mg, 97%). ^{1}H NMR (600 MHz, CDCl3) δ 7.32 – 7.17 (m, 5H), 5.45 (s, 1H), 2.77 – 2.49 (m, 1H), 1.09 (s, 12H), 1.05 (d, *J* = 6.8 Hz, 6H).^{13}C NMR (126 MHz, cdcl$_3$) δ 168.3, 143.6, 128.2, 127.5, 126.9, 82.9, 37.0, 24.7, 21.8. ^{11}B NMR: (160 MHz, CDCl3) δ 31.25. IR (neat) ν_{max} . 2972 (m), 2927 (w), 2869 (w), 1639 (m), 1314 (m), 1260 (m), 1141.9 (s). HRMS (DART+) for $C_{17}H_{26}BO_2$ $[M+H]^+$ calculated: 273.2020, found: 273.2027.

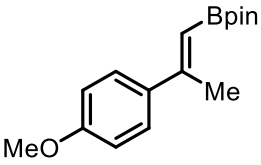


***(Z)*-2-(2-cyclohexyl-2-phenylvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.90).** Prepared according to general procedure (Method A) using LiTMP (147.2 mg, 1.00 mmol), bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane (268.0 mg, 1.00mmol), PMDTA (130.0 mg, 1.5 mmol), cyclohexyl phenyl ketone (94.1 mg , 0.5 mmol) and THF (5.5 ml). The crude reaction mixture was purified by column chromatography on silica gel (30% DCM /hexanes) to afford the desired product as a white solid (153.3 mg, 98%). ^{1}H NMR (600 MHz, CDCl3) δ 7.28 – 7.25 (m, 3H), 7.20 – 7.15 (m, 2H), 5.41 (s, 1H), 1.29 – 1.11 (m, 5H), 1.08 (s, 12H).^{13}C NMR (151 MHz, $CDCl_3$) δ 167.5, 143.8, 128.2, 127.5, 126.9, 82.9, 47.2, 32.3, 26.8, 26.4, 24.7. ^{11}B NMR: (160 MHz, $CDCl_3$) δ 31.15. IR (neat) ν_{max} 2975

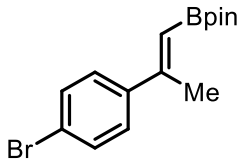
(m), 2921 (m), 2894 (m), 1622 (m), 1377 (w), 1347 (m), 1339 (m), 1142 (s), 1108 (m). HRMS (DART+) for $C_{20}H_{30}BO_2$ $[M+H]^+$ calculated: 313.2333, found: 313.2342.



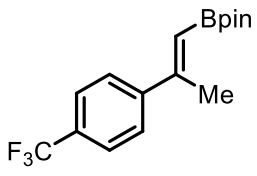
***(Z)*-2-(2-cyclopropyl-2-phenylvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.91).** Prepared according to general procedure (Method A) using LiTMP (147.2 mg, 1.00 mmol), bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane (268.0 mg, 1.00mmol), PMDTA (130.0 mg, 1.5 mmol), cyclopropyl phenyl ketone (73.1 mg , 0.5 mmol) and THF (5.5 ml). The crude reaction mixture was purified by column chromatography on silica gel (30% DCM /hexanes) to afford the desired product as a clear colourles oil (122.7 mg, 90%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.18 (m, 5H), 5.26 (s, 1H), 1.71 – 1.61 (m, 1H), 1.10 (s, 12H), 0.83 – 0.74 (m, 2H), 0.68 – 0.51 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.8, 142.5, 128.3, 127.4, 127.3, 82.8, 24.6, 20.0, 7.9. ^{11}B NMR: (160 MHz, $CDCl_3$) δ 31.05. IR (neat) ν_{max} 2975 (m), 1617 (m), 1383 (m), 1339 (m), 1261 (m), 1141 (s). HRMS (DART+) for $C_{17}H_{24}BO_2$ $[M+H]^+$ calculated: 271.1864 found: 271.1863



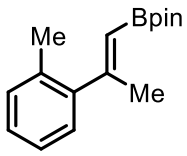
***(E)*-2-(2-(4-methoxyphenyl)prop-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.92).** Prepared according to general procedure (Method B) using LiTMP (147.2 mg, 1.00 mmol), bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane (268.0 mg, 1.00 mmol) TMTAN (42.8mg, 0.25 mmol), 4'-methoxyacetophenone (150.2 mg, 0.5 mmol) and THF (5.5 ml). The crude reaction mixture was purified by column chromatography on silica gel (5% ethyl acetate/hexanes) to afford the desired product as a white solid (121.2mg, 88%). All spectral data are in accord with the literature.[3]



***(E)*-2-(2-(4-bromophenyl)prop-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.93).** Prepared according to general procedure (Method B) using LiTMP (147.2 mg, 1.00 mmol), bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane (268.0 mg, 1.00 mmol) TMTAN (42.8mg, 0.25 mmol), 4'-bromoacetophenone (99.5 mg, 0.5 mmol) and THF (5.5 ml). The crude reaction mixture was purified by column chromatography on silica gel (30% DCM /hexanes) to afford the desired product as a clear colorless oil (137 mg, 84%). All spectral data are in accord with the literature.[3]

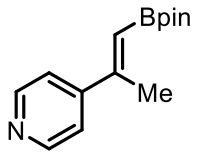


***(E)*-4,4,5,5-tetramethyl-2-(2-(4-(trifluoromethyl)phenyl)prop-1-en-1-yl)-1,3,2-dioxaborolane (2.94).** Prepared according to general procedure (Method B) using LiTMP (147.2 mg, 1.00 mmol), bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane (268.0 mg, 1.00mmol) TMTAN (42.8 mg, 0.25 mmol), 4'-(trifluoromethyl)acetophenone (94.1 mg , 0.5 mmol) and THF (5.5 ml). The crude reaction mixture was purified by column chromatography on silica gel (30% DCM /hexanes) to afford the desired product as a clear colorless oil (130 mg, 83%). All spectral data are in accord with the literature.[3]

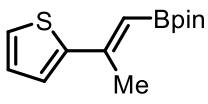


***(E)*-4,4,5,5-tetramethyl-2-(2-(o-tolyl)prop-1-en-1-yl)-1,3,2-dioxaborolane. (2.95).** Prepared according to general procedure (Method B) using LiTMP (147.2 mg, 1.00 mmol), bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane (268.0 mg, 1.00 mmol) TMTAN (42.8mg, 0.25 mmol), 2'-methylacetophenone (67.1 mg, 0.5 mmol) and THF (5.5 ml). The crude reaction mixture was purified by column chromatography on silica gel (30% DCM /hexanes) to afford the desired product as a clear colorless oil (116.2 mg, 90%). ^{1}H NMR (600 MHz, $CDCl_3$) δ

7.19 – 7.05 (m, 4H), 5.27 (s, 1H), 2.32 (s, 3H), 2.30 (s, 3H), 1.34 (s, 12H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 161.1, 146.9, 133.6, 130.2, 126.8, 125.6, 83.0, 25.0, 23.1, 20.0. ^{11}B NMR: (160 MHz, $CDCl_3$) δ 30.6. IR (neat) ν_{max} 2975 (w), 2926 (m), 1629 (m), 1483 (m), 1349 (s), 1296 (s), 1210 (m), 1141 (s), HRMS (DART+) for $C_{16}H_{24}BO_2$ $[M+H]^+$ calculated: 259.1864, found: 259.1865

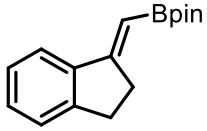


***(E)*-4-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-1-en-2-yl)pyridine (2.97).** Prepared according to general procedure (Method B) using LiTMP (147.2 mg, 1.00 mmol), bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane (268.0 mg, 1.00 mmol) TMTAN (42.8mg, 0.25 mmol), 4-acetylpyridine (64.3 mg, 0.5 mmol) and THF (5.5 ml). The crude reaction mixture was purified by column chromatography on silica gel (30% DCM /hexanes) to afford the desired product as a pale yellow solid (101.2 mg, 82%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (dd, 2H), 7.34 (dd, 2H), 5.90 (s, 1H), 2.38 (s, 3H), 1.32 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.7, 150.8, 150.0, 120.4, 83.4, 25.0, 19.5. ^{11}B NMR: (160 MHz, CDCl3) δ 30.66. IR (neat) ν_{max} 2972 (m), 2924 (w), 1623 (m), 1593 (m), 1356 (s), 1213 (m), 1142 (s). HRMS (DART+) for $C_{14}H_{21}NBO_2$ $[M+H]^+$ calculated: 246.1660, found: 246.1661.



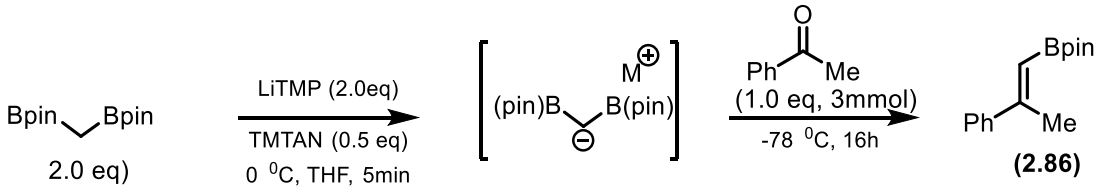
***(E)*-4,4,5,5-tetramethyl-2-(2-(thiophen-2-yl)prop-1-en-1-yl)-1,3,2-dioxaborolane (2.98).** Prepared according to general procedure (Method B) using LiTMP (147.2 mg, 1.00 mmol), bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane (268.0 mg, 1.00mmol) TMTAN (42.8 mg, 0.25 mmol), 2-acetylthiophene (63.1 mg , 0.5 mmol) and THF (5.5 ml). The crude reaction mixture was

purified by column chromatography on silica gel (30% DCM /hexanes) to afford the desired product as a clear colorless oil (123.6 mg, 98%). All spectral data are in accord with the literature.[6]



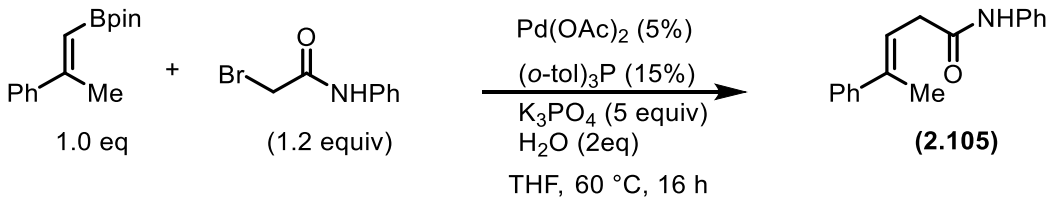
***(E)*-2-((2,3-dihydro-1H-inden-1-ylidene)methyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.96).** Prepared according to general procedure (Method B) using LiTMP (147.2 mg, 1.00 mmol), bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane (268.0 mg, 1.00 mmol) TMTAN (42.8mg, 0.25 mmol), 1-indanone (66.1 mg, 0.5 mmol) and THF (5.5 ml). The crude reaction mixture was purified by column chromatography on silica gel (30% DCM /hexanes) to afford the desired product as a white solid (108mg, 84%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.7 Hz, 1H), 7.26 (m, 2H), 7.21 (t, *J* = m,1H), 5.84 (s, 1H), 3.11 – 3.04 (m, 2H), 3.03 – 2.96 (m, 2H), 1.30 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.9, 148.2, 141.9, 129.5, 126.5, 125.5, 121.3, 82.8, 31.9, 30.3, 25.0. ^{11}B NMR: (160 MHz, CDCl3) δ 31.05. IR (neat) ν_{max} 2973 (m), 2926 (w), 1623 (s), 1602 (w), 1472 (m), 1357 (s), 1317 (m), 1210 (m), 1141 (s). HRMS (DART+) for $C_{16}H_{22}BO_2$ $[M+H]^+$ calculated: 257.1707, found: 209.1705.

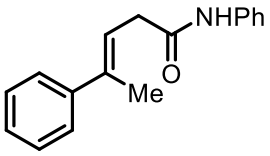
2.8.2.3 Procedure for large scale reaction



In a glove box, a flamed dried 100 ml round bottom flask with a magnetic stir bar was charged with LiTMP (883.1 mg, 6.00 mmol,), 20 ml of THF, then TMTAN (256.9 mg, 1.5 mmol), sealed with septa and removed from the glovebox. Under Nitrogen, the reaction vial was cooled to 0 °C, and a solution of bis(4,4,5,5-tetramethyl1,3,2-dioxaborolan-2-yl)methane (1.61 mg, 3.00 mmol) in THF (5 mL) was added and the reaction was allowed to stir for 5 minutes. Then the reaction was cooled to -78 °C and acetophenone (360.4 mg, 3mmol) in 8.3 ml THF was added. The reaction vial was allowed to stir for 16 hours at- 78 °C. Upon completion, the reaction opened to air, and filtered through a short silica gel column with diethyl ether. The mixture was concentrated under reduced pressure. Columned in 30% DCM/ hexanes to yield the desired product, compound 9 as a clear oil. (630 mg, 86%, 99:1 E/Z).

2.8.2.4 Procedure for cross-coupling reaction

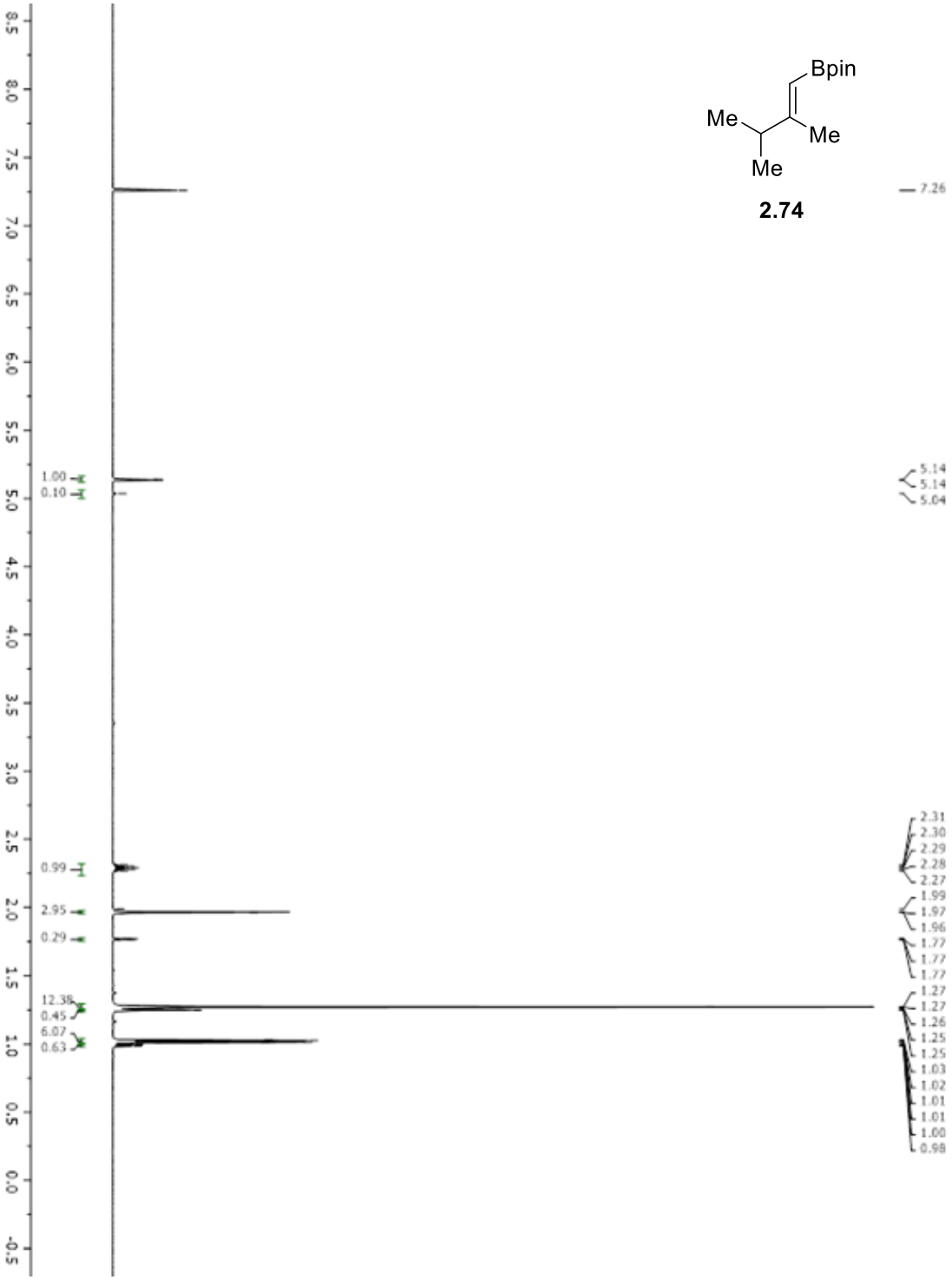


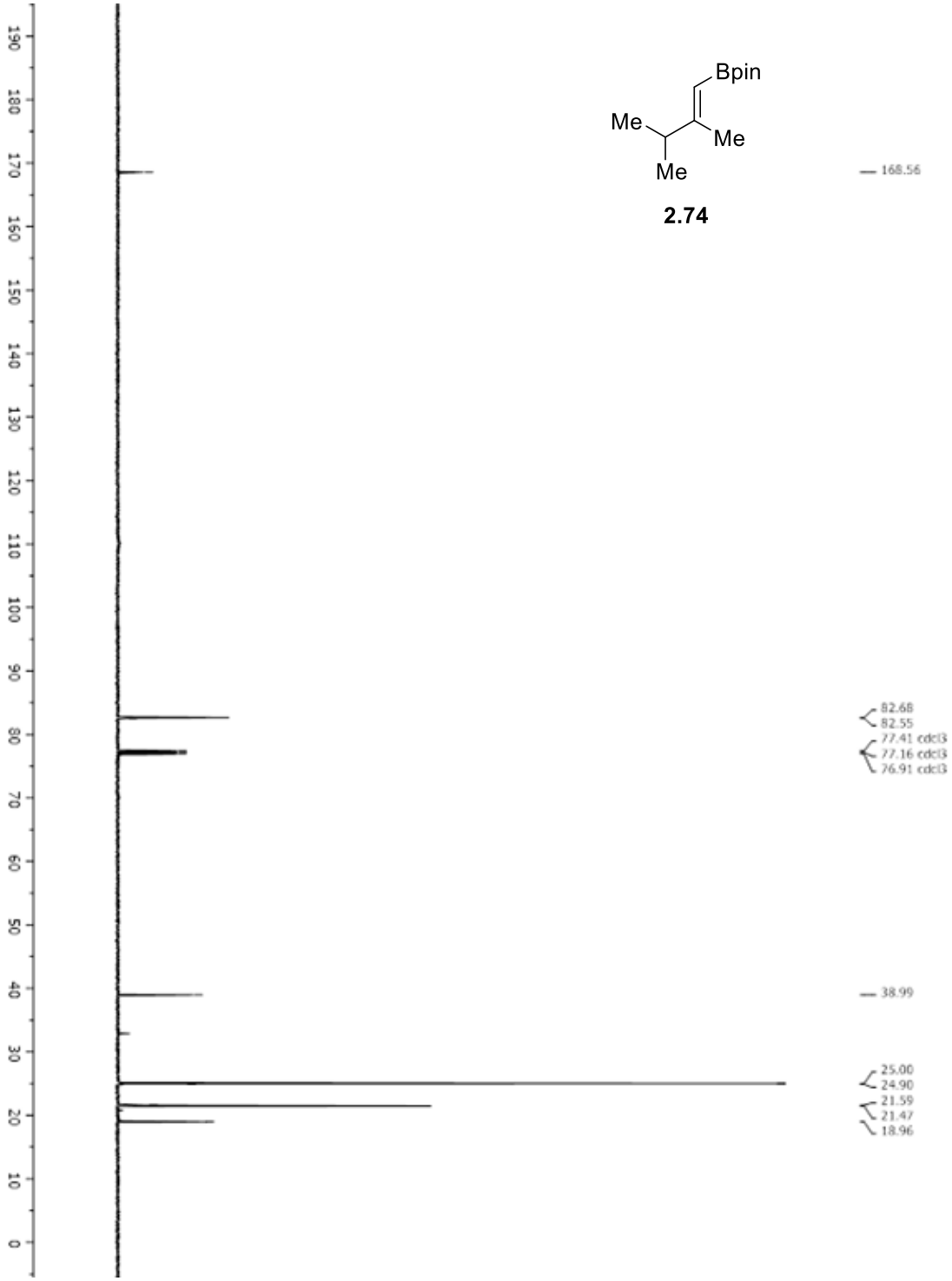


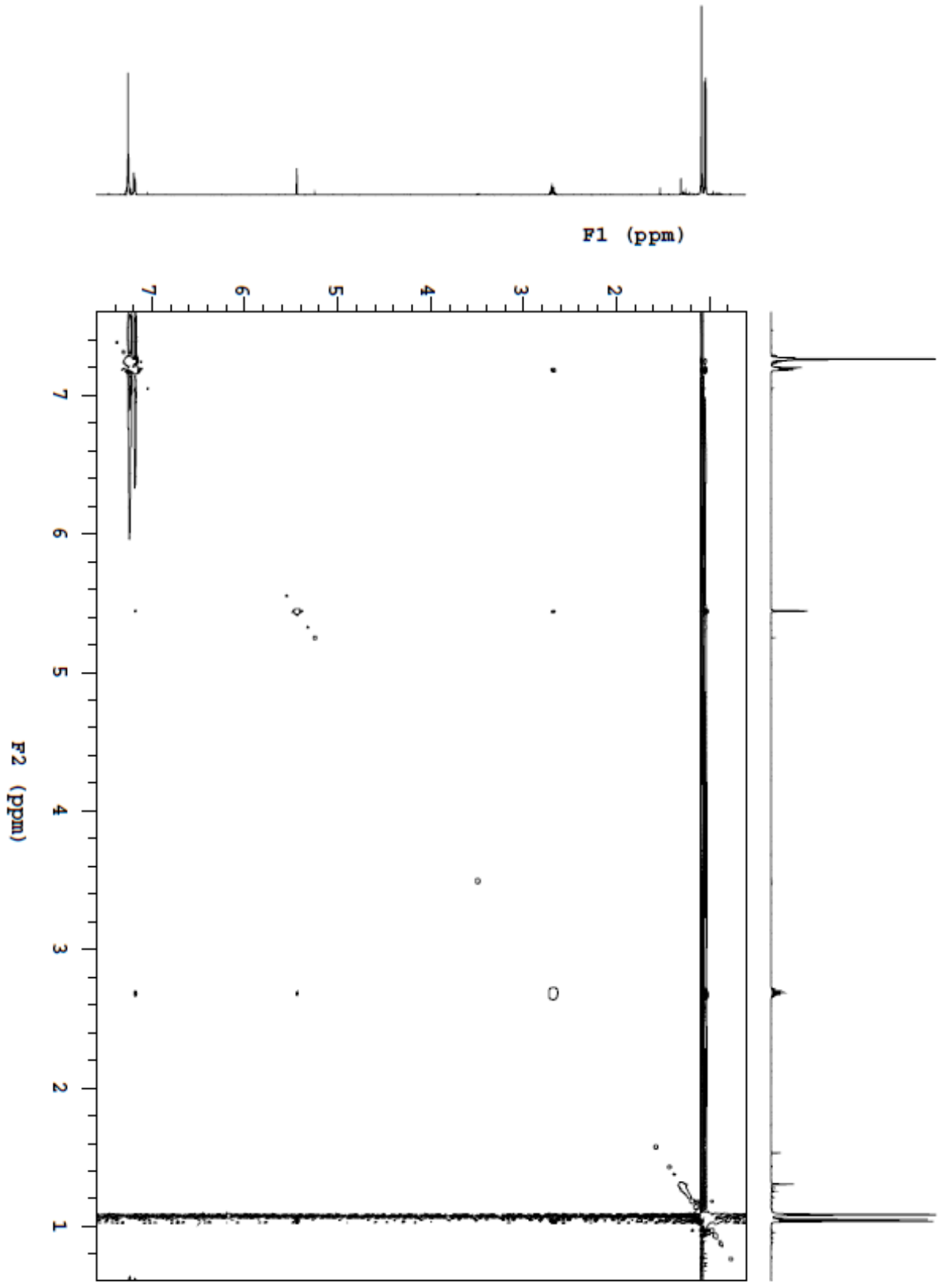
(*E*)-N,4-diphenylpent-3-enamide (2.105). To a 2 dram vial with a magnetic stir bar in a glove box was added Palladium acetate (3.3mg, 0.05mmol), tris-o-tolyphosphine (13.7 mg, 0.15 mmol), 0.4 ml THF and stirred at ambient temperature for 10 minutes. In a separate 2 dram vial with a magnetic stir bar was added *(E)*-4,4,5,5-tetramethyl-2-(2-phenylprop-1-en-1-yl)-1,3,2-dioxaborolane (72.3 mg, 0.3 mmol), 2-bromo-N-phenyl-acetamide (77.1mg, 0.36 mmol), tripotassium phosphate (318.4mg, 1.5mmol), and 0.6 ml THF. To this solution was added the pre complexed palladium/ligand solution in THF. Rinsed the palladium/ ligand vial with 0.2ml of THF and added this to the reaction solution, sealed and brought outside of the glove box. Under Nitrogen, water (nitrogen sparged for 30 minutes) (0.11 ml, 0.6 mmol) was added to the reaction, taped and stirred at 60 °C for 16 hours. Quenched with water, extracted with ethyl acetate, dried with sodium sulfate, concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography on silica gel (5% ethyl acetate /hexanes) to afford the desired product as a faint yellow solid (47.5 mg, 63%). All spectral and mass spec data were in accord with the literature.[60]

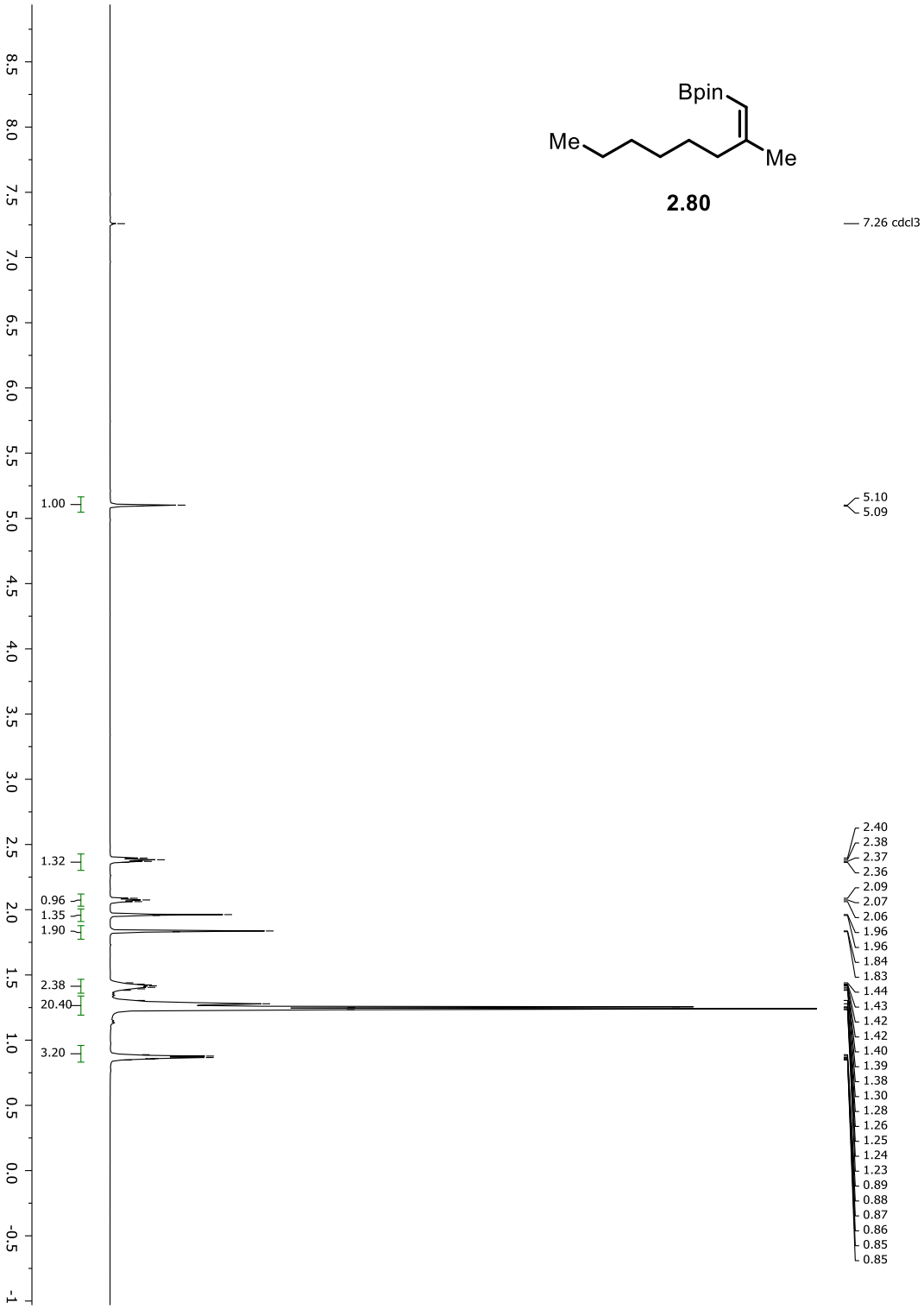
[60] Fang, X.; Haoguan, L.; Jackstell, R.; Beller, M. *J. Am. Chem. Soc.* **2014**, *136*, 16039.

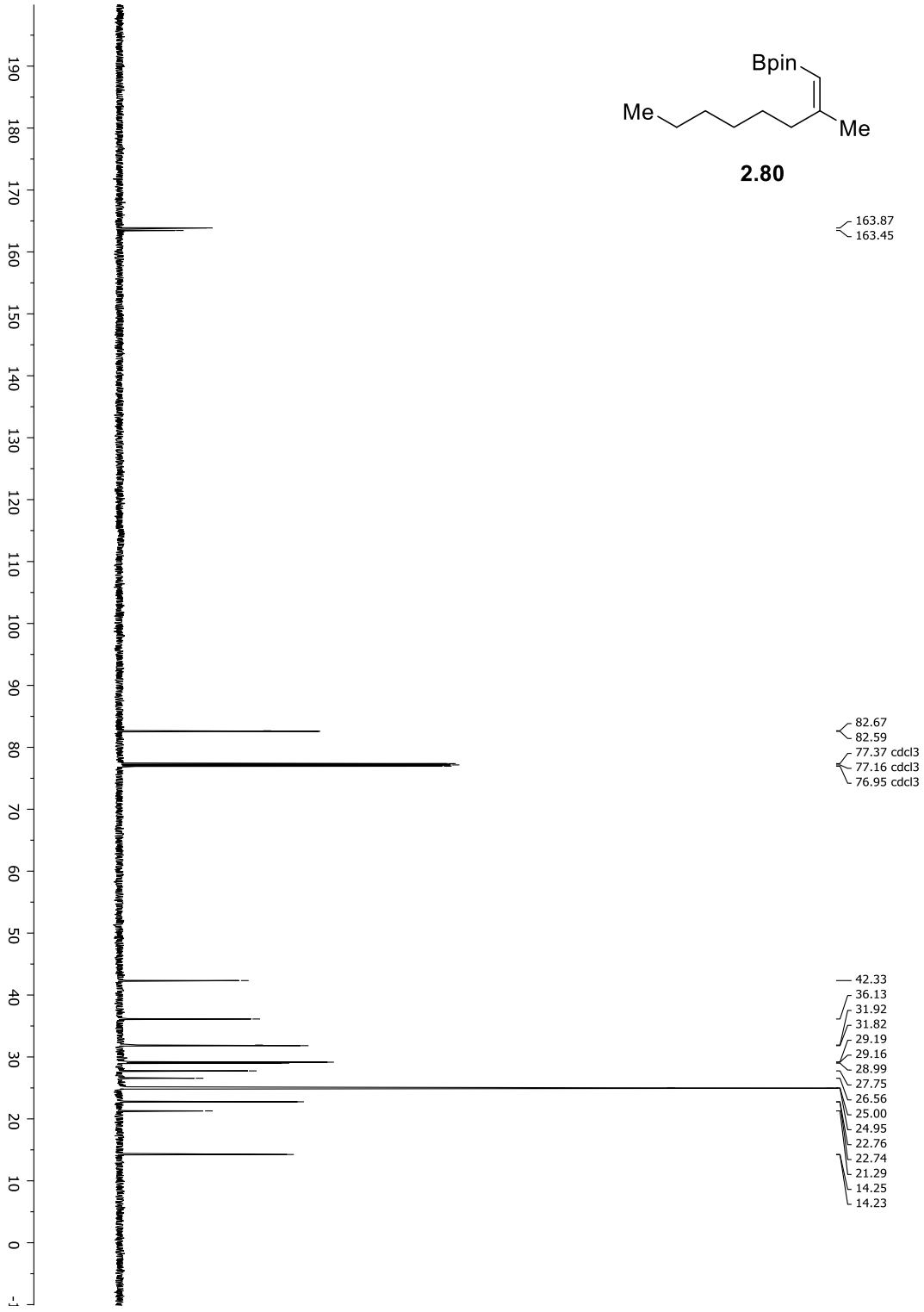
2.8.3 NMR Spectra

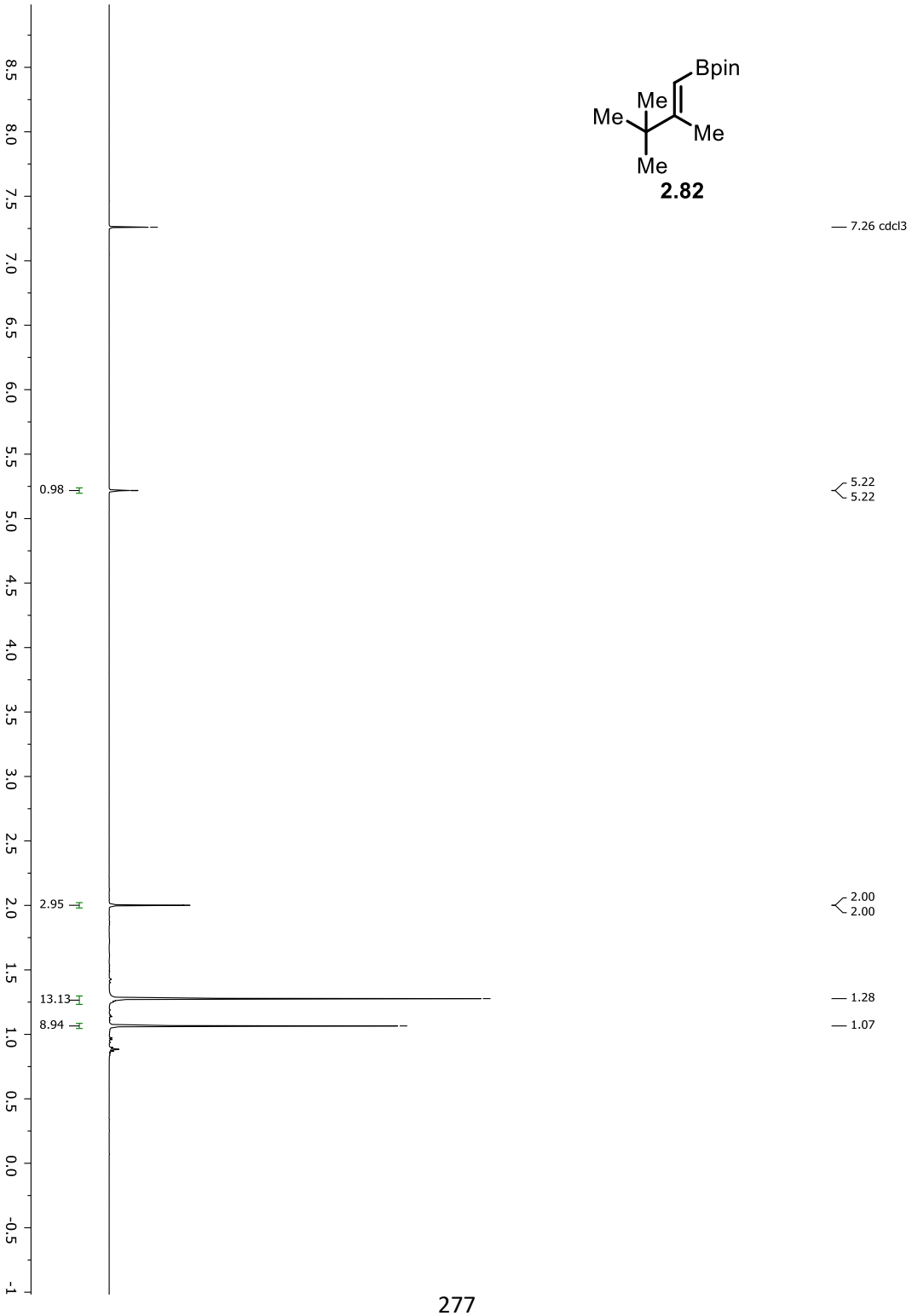


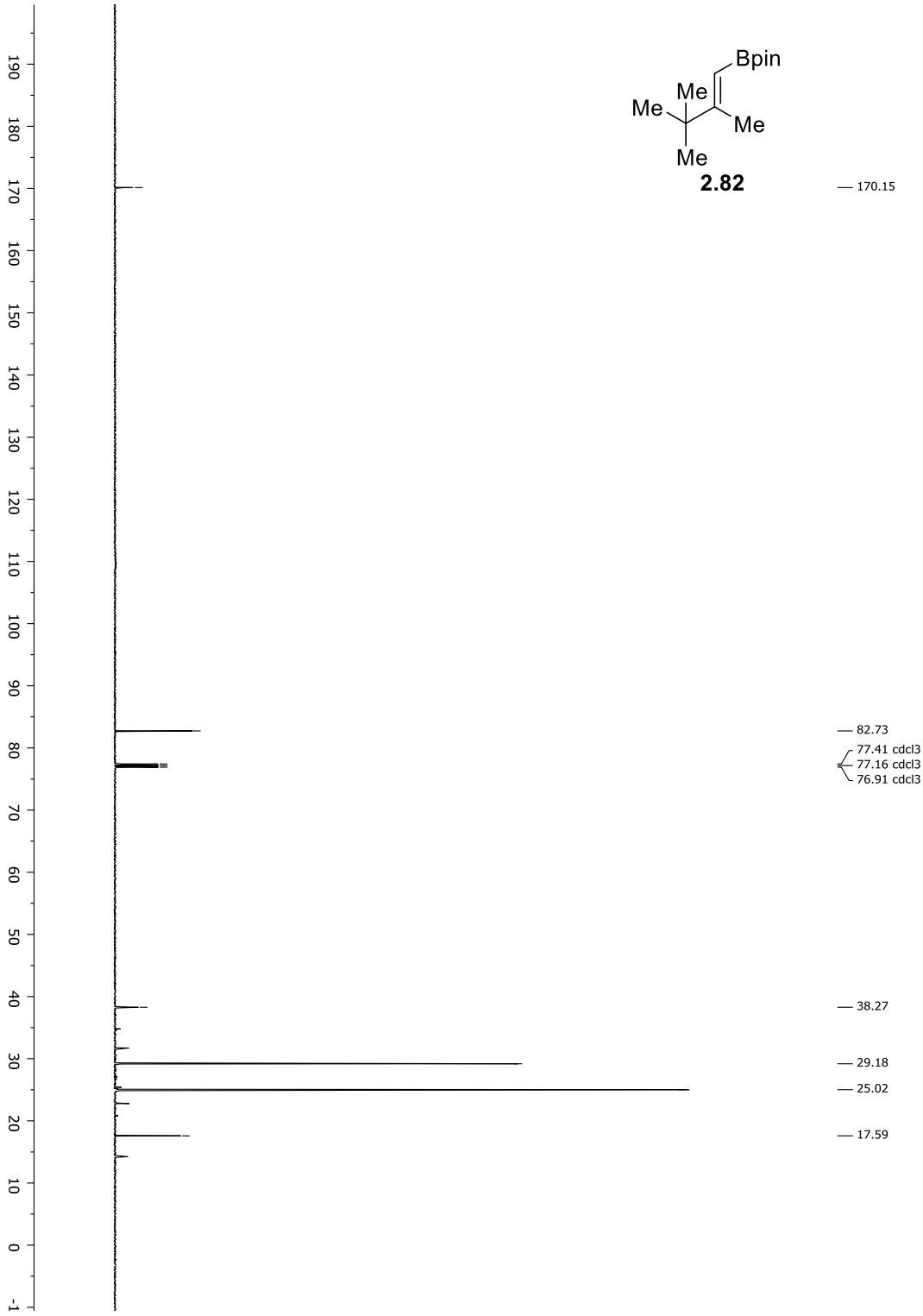

Bpin
Me
Me
Me
2.74
168.56
82.68
82.55
77.41 cdcl3
77.16 cdcl3
76.91 cdcl3
38.99
25.00
24.90
21.59
21.47
18.96

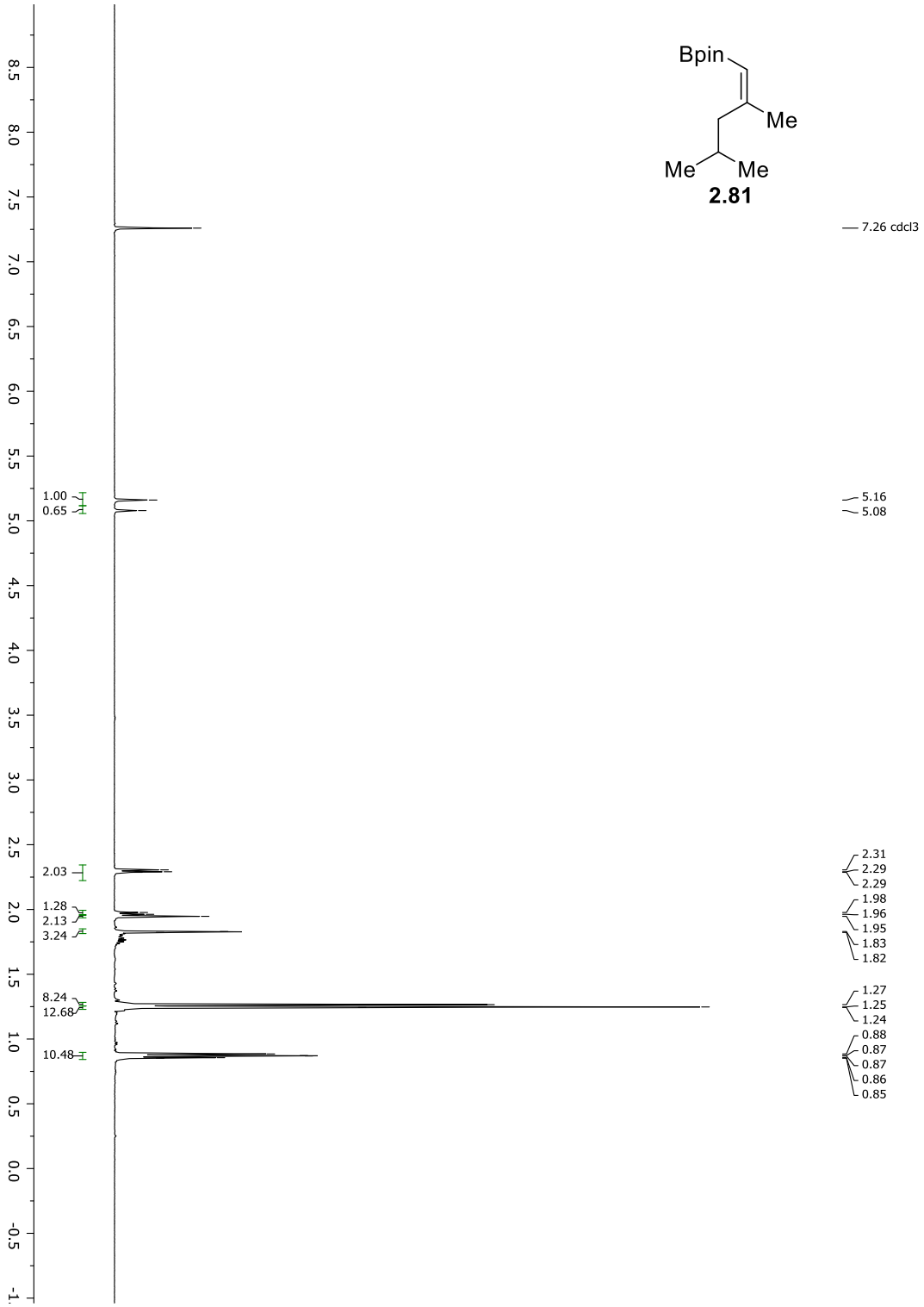

F1 (ppm)
F2 (ppm)
7
6
5
4
3
2
1

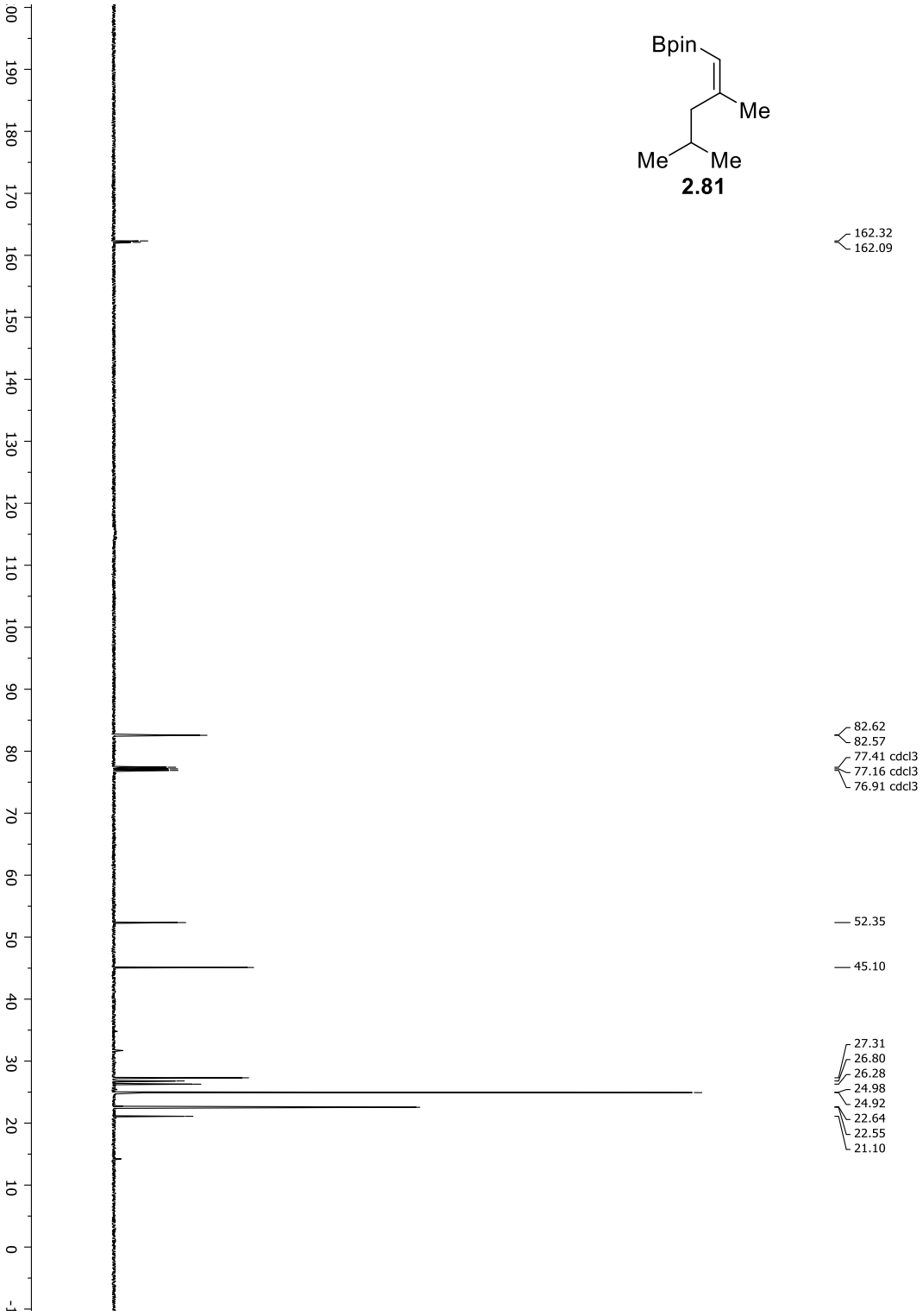

Bpin
Me
Me
2.80
7.26 cdcl3
5.10
5.09
1.00
1.32
0.96
1.35
1.90
2.38
20.40
3.20
2.40
2.38
2.37
2.36
2.09
2.07
2.06
1.96
1.96
1.84
1.83
1.44
1.43
1.42
1.42
1.40
1.39
1.38
1.30
1.28
1.26
1.25
1.24
1.23
0.89
0.88
0.87
0.86
0.85
0.85

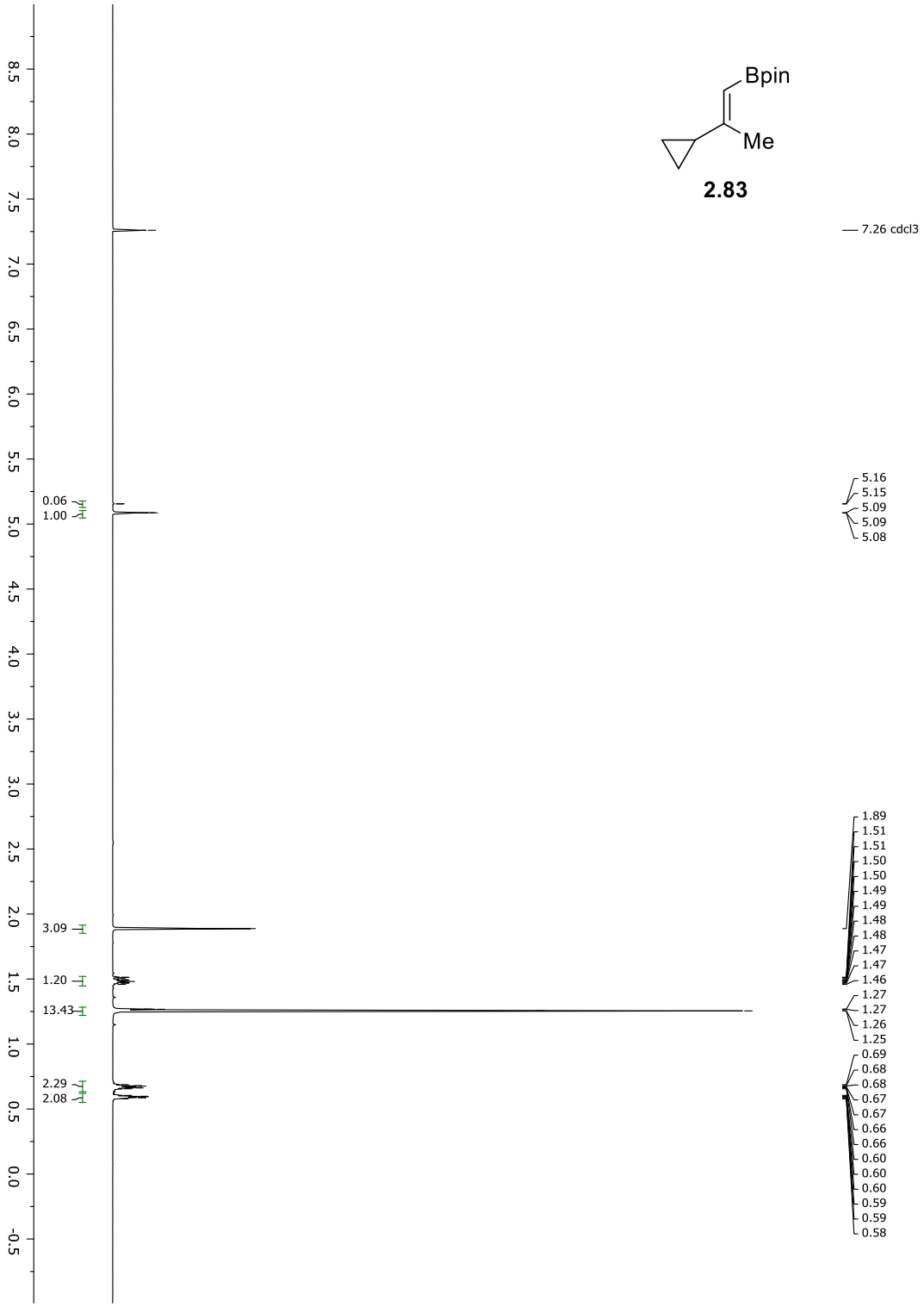

Bpin
Me
Me
2.80
163.87
163.45
82.67
82.59
77.37 cdcl3
77.16 cdcl3
76.95 cdcl3
42.33
36.13
31.92
31.82
29.19
29.16
28.99
27.75
26.56
25.00
24.95
22.76
22.74
21.29
14.25
14.23

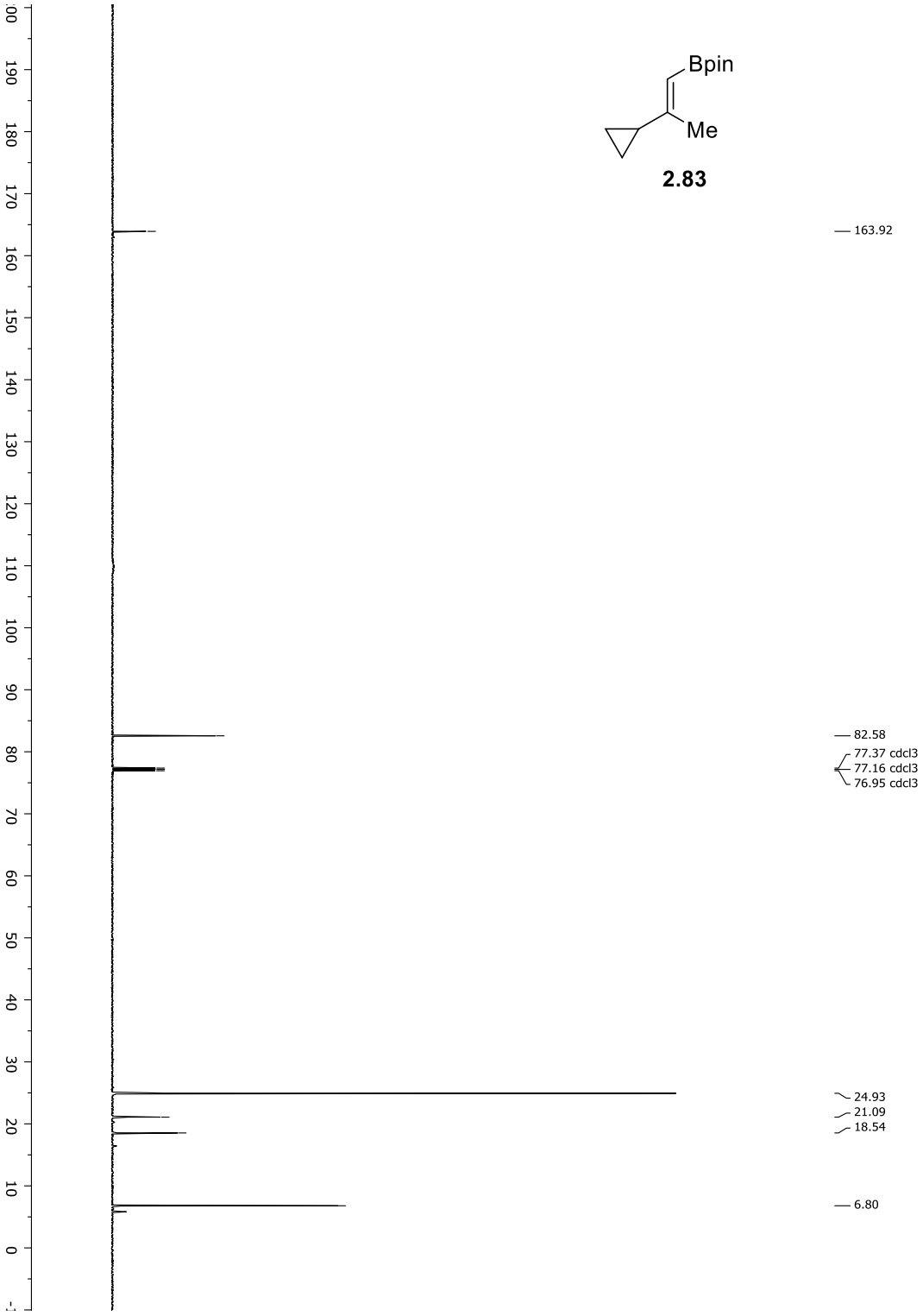

Bpin
Me
Me
Me
Me
2.82
7.26 cdcl3
5.22
5.22
2.00
2.00
1.28
1.07
0.98
2.95
13.13
8.94
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1


Bpin
Me
Me
Me
Me
2.82
170.15
82.73
77.41 cdcl3
77.16 cdcl3
76.91 cdcl3
38.27
29.18
25.02
17.59
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1

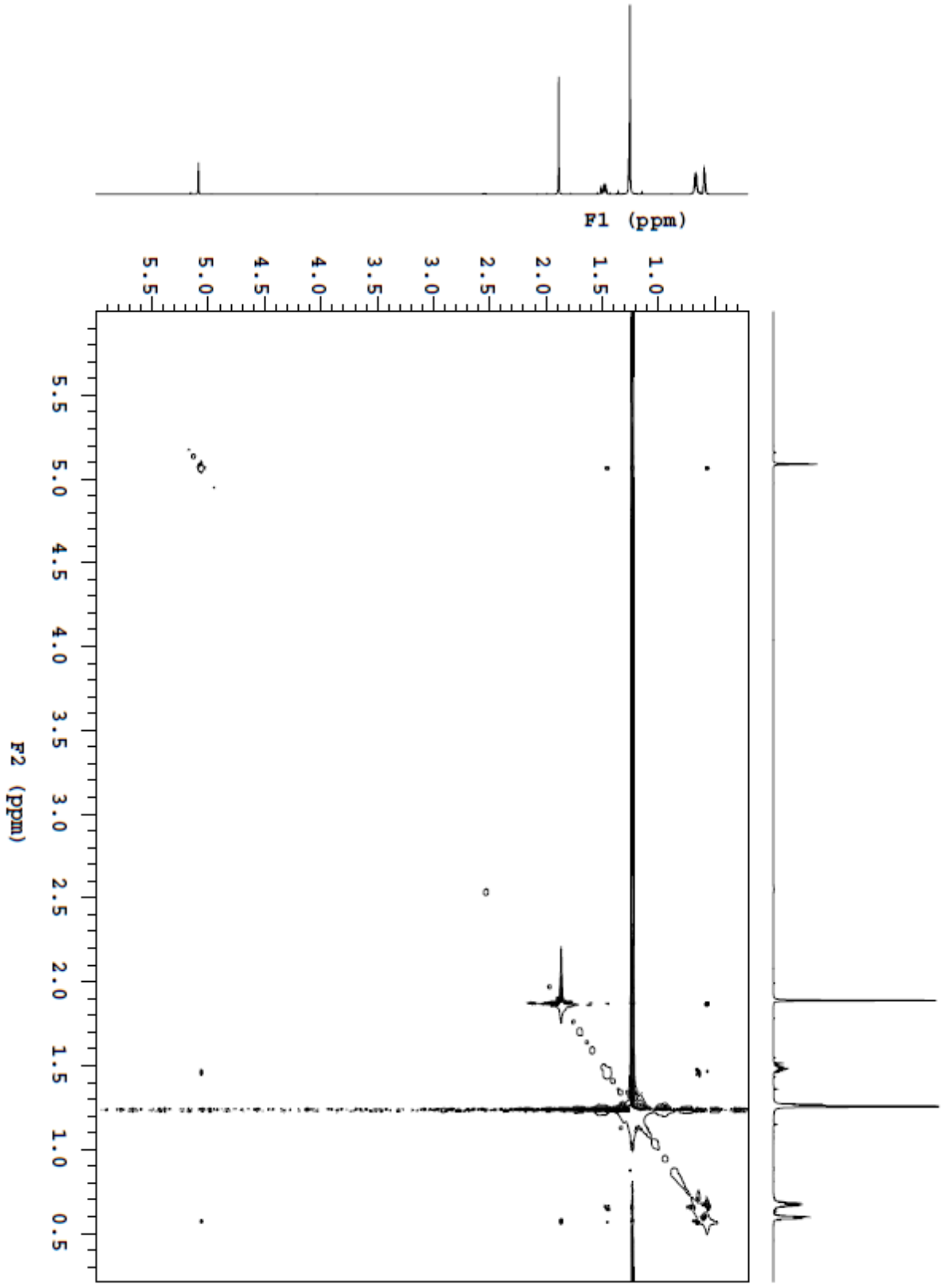

Bpin
Me
Me
Me
2.81
7.26 cdcl3
5.16
5.08
2.31
2.29
2.29
1.98
1.96
1.95
1.83
1.82
1.27
1.25
1.24
0.88
0.87
0.87
0.86
0.85
1.00
0.65
2.03
1.28
2.13
3.24
8.24
12.68
10.48

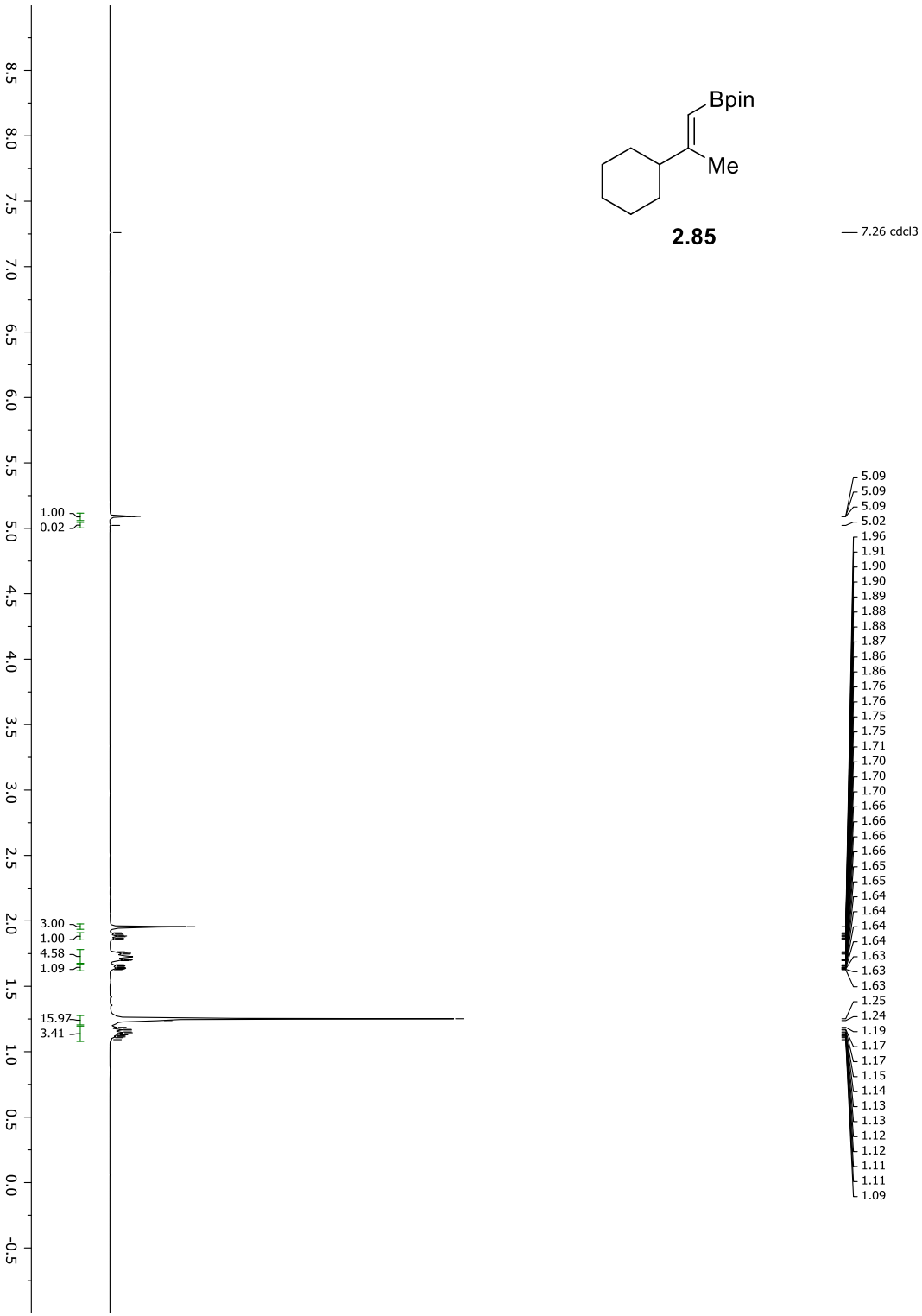

Bpin
Me
Me
Me
2.81
162.32
162.09
82.62
82.57
77.41 cdcl3
77.16 cdcl3
76.91 cdcl3
52.35
45.10
27.31
26.80
26.28
24.98
24.92
22.64
22.55
21.10

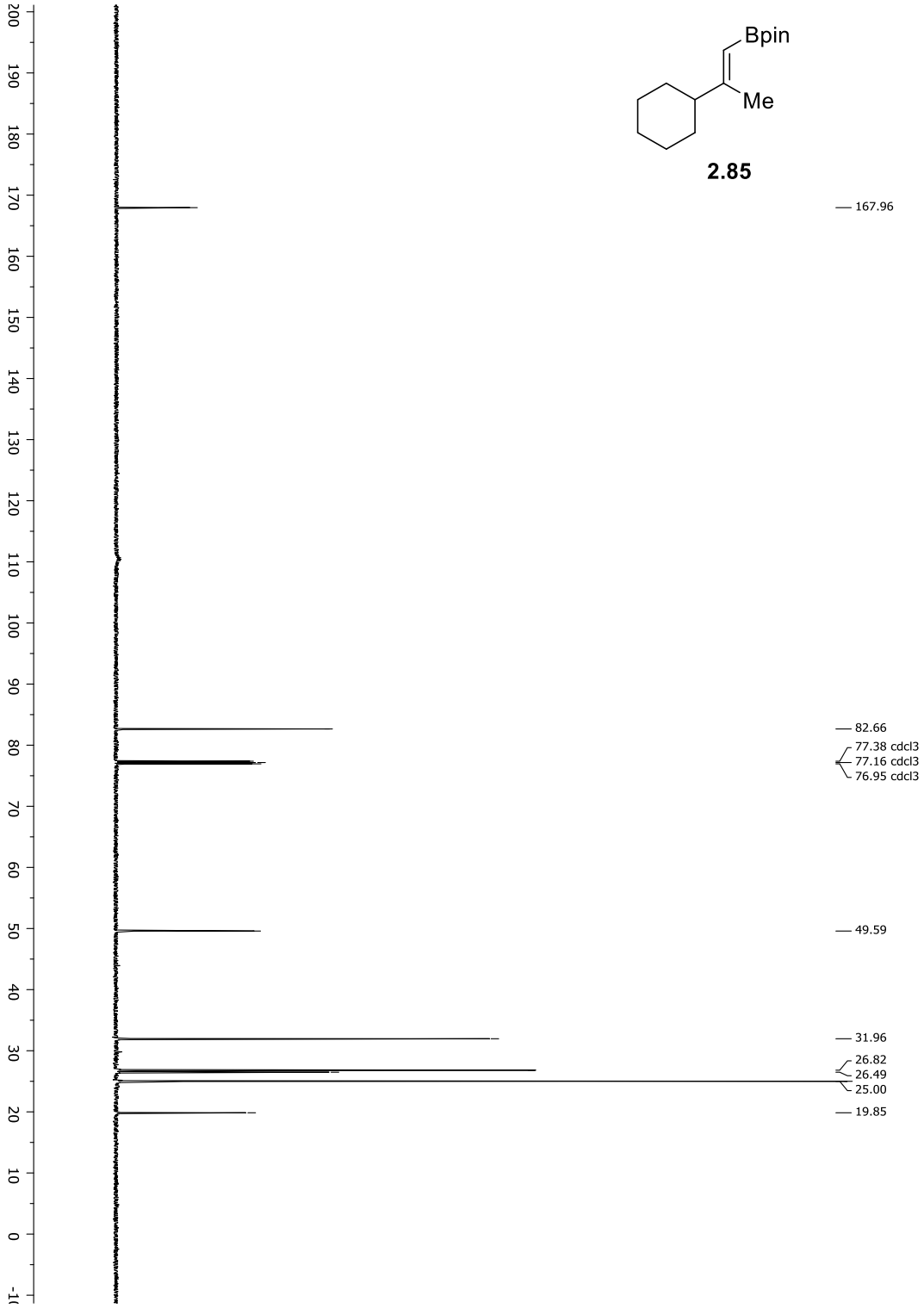

Bpin
Me
2.83
7.26 cdcl3
5.16
5.15
5.09
5.09
5.08
1.89
1.51
1.51
1.50
1.50
1.49
1.49
1.48
1.48
1.47
1.47
1.46
1.27
1.27
1.26
1.25
0.69
0.68
0.68
0.67
0.67
0.66
0.66
0.60
0.60
0.60
0.59
0.59
0.58
0.06
1.00
3.09
1.20
13.43
2.29
2.08
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

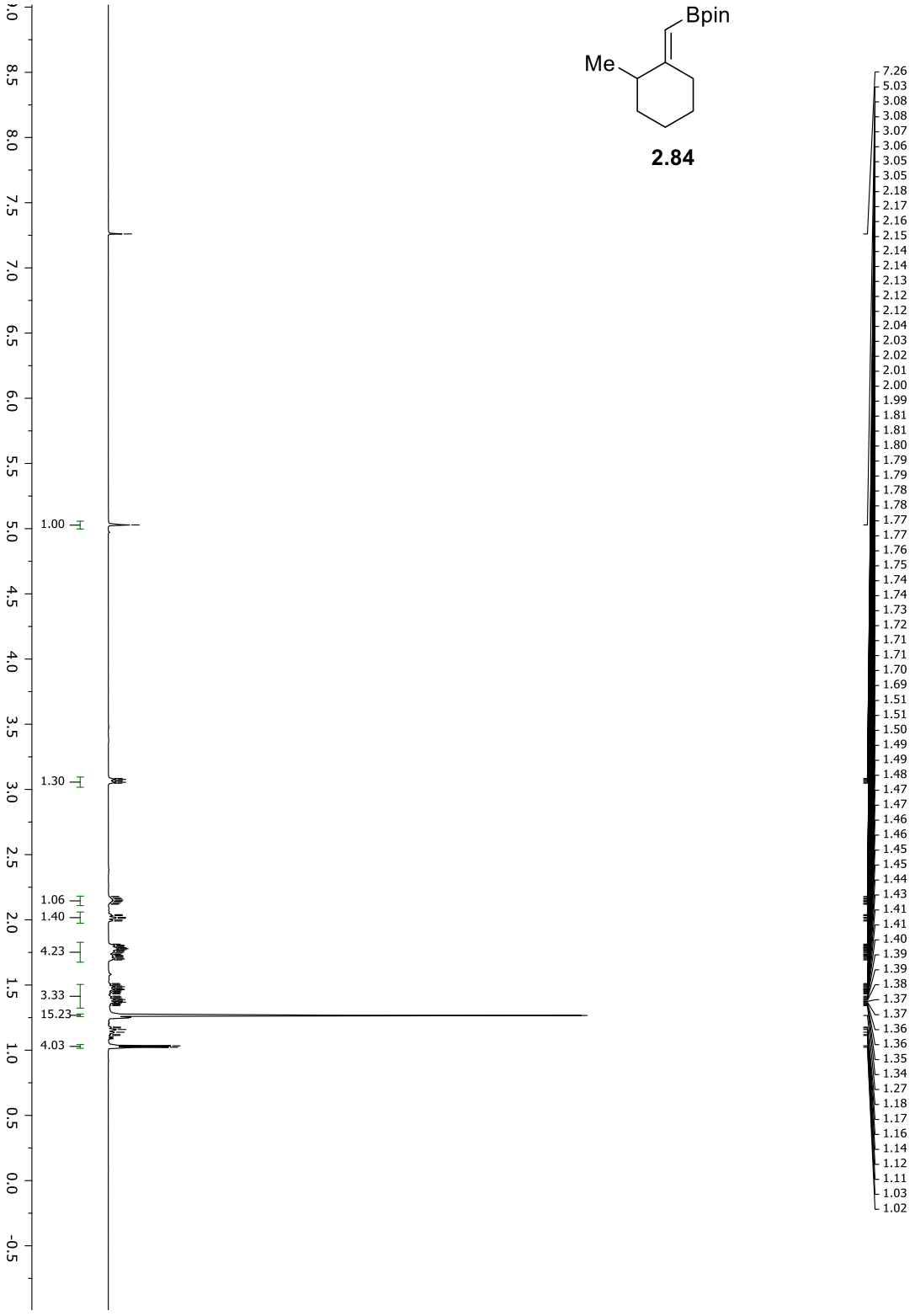

Bpin
Me
2.83
163.92
82.58
77.37 cdcl3
77.16 cdcl3
76.95 cdcl3
24.93
21.09
18.54
6.80

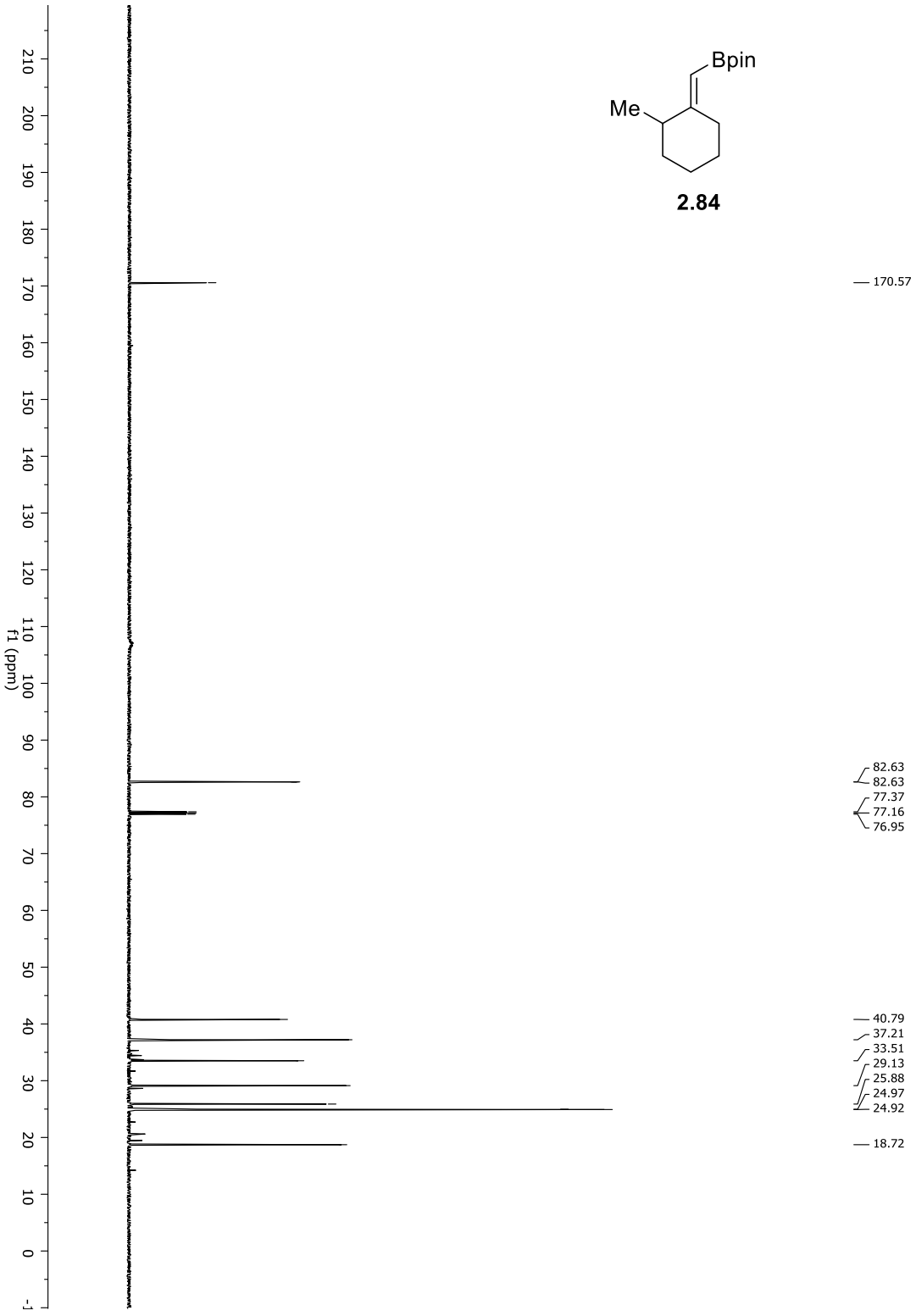
1HNMR NOESY for compound **2.83**



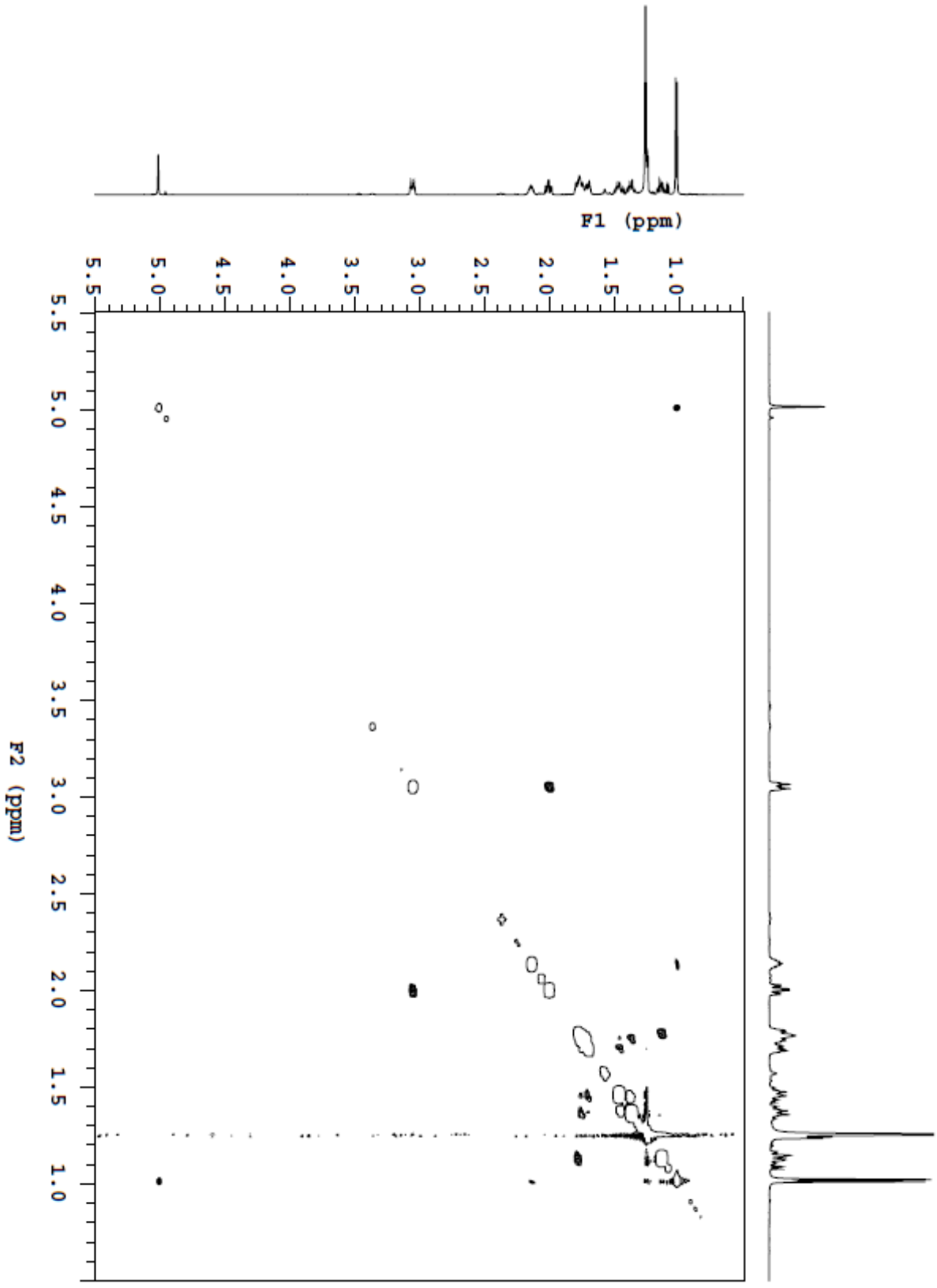

Bpin
Me
2.85
7.26 cdcl3
1.00
0.02
3.00
1.00
4.58
1.09
15.97
3.41
5.09
5.09
5.09
5.02
1.96
1.91
1.90
1.90
1.89
1.88
1.88
1.87
1.86
1.86
1.76
1.76
1.75
1.75
1.71
1.70
1.70
1.70
1.66
1.66
1.66
1.66
1.65
1.65
1.64
1.64
1.64
1.64
1.63
1.63
1.63
1.25
1.24
1.19
1.17
1.17
1.15
1.14
1.13
1.13
1.12
1.12
1.11
1.11
1.09

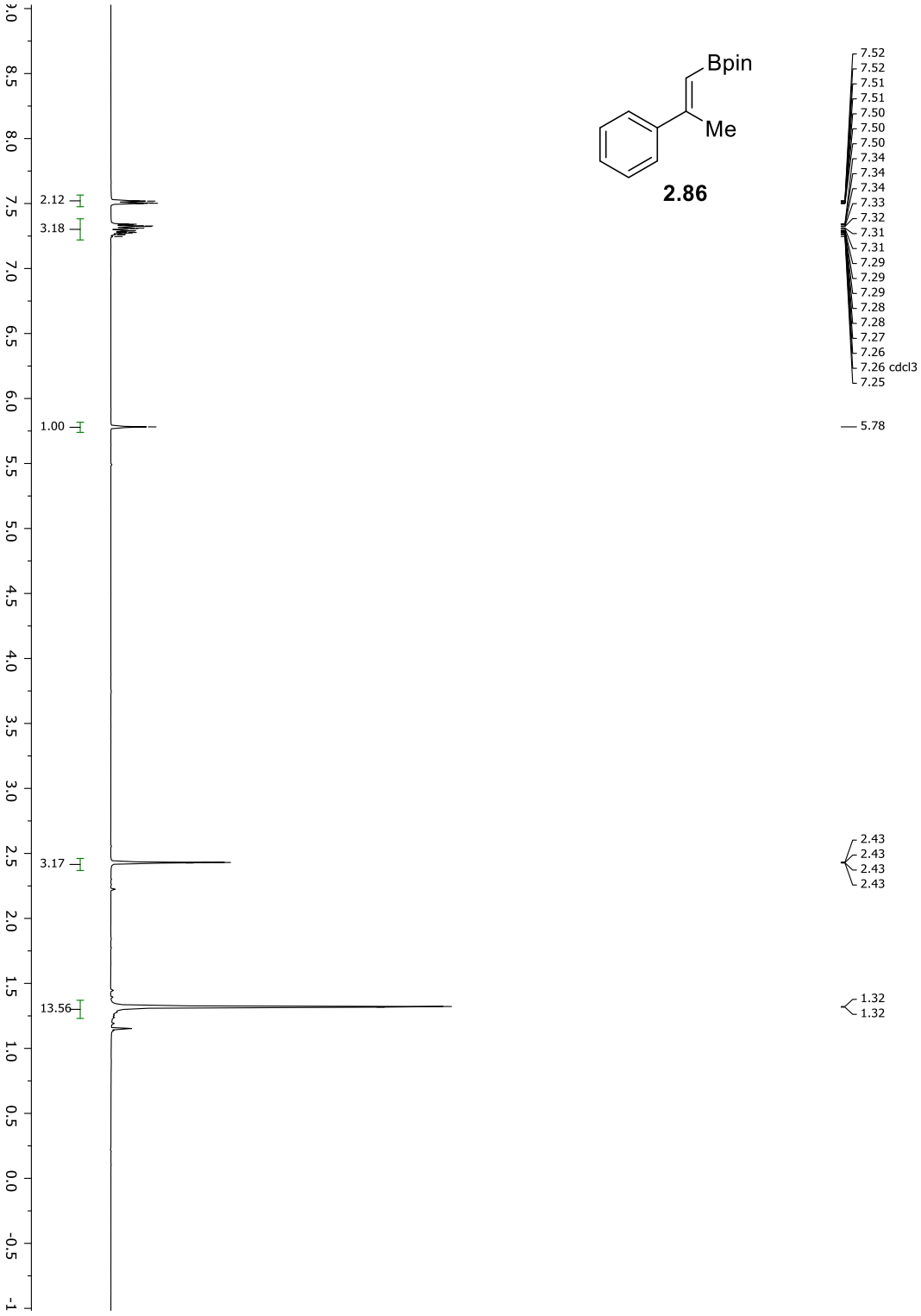

Bpin
Me
2.85
167.96
82.66
77.38 cdcl3
77.16 cdcl3
76.95 cdcl3
49.59
31.96
26.82
26.49
25.00
19.85

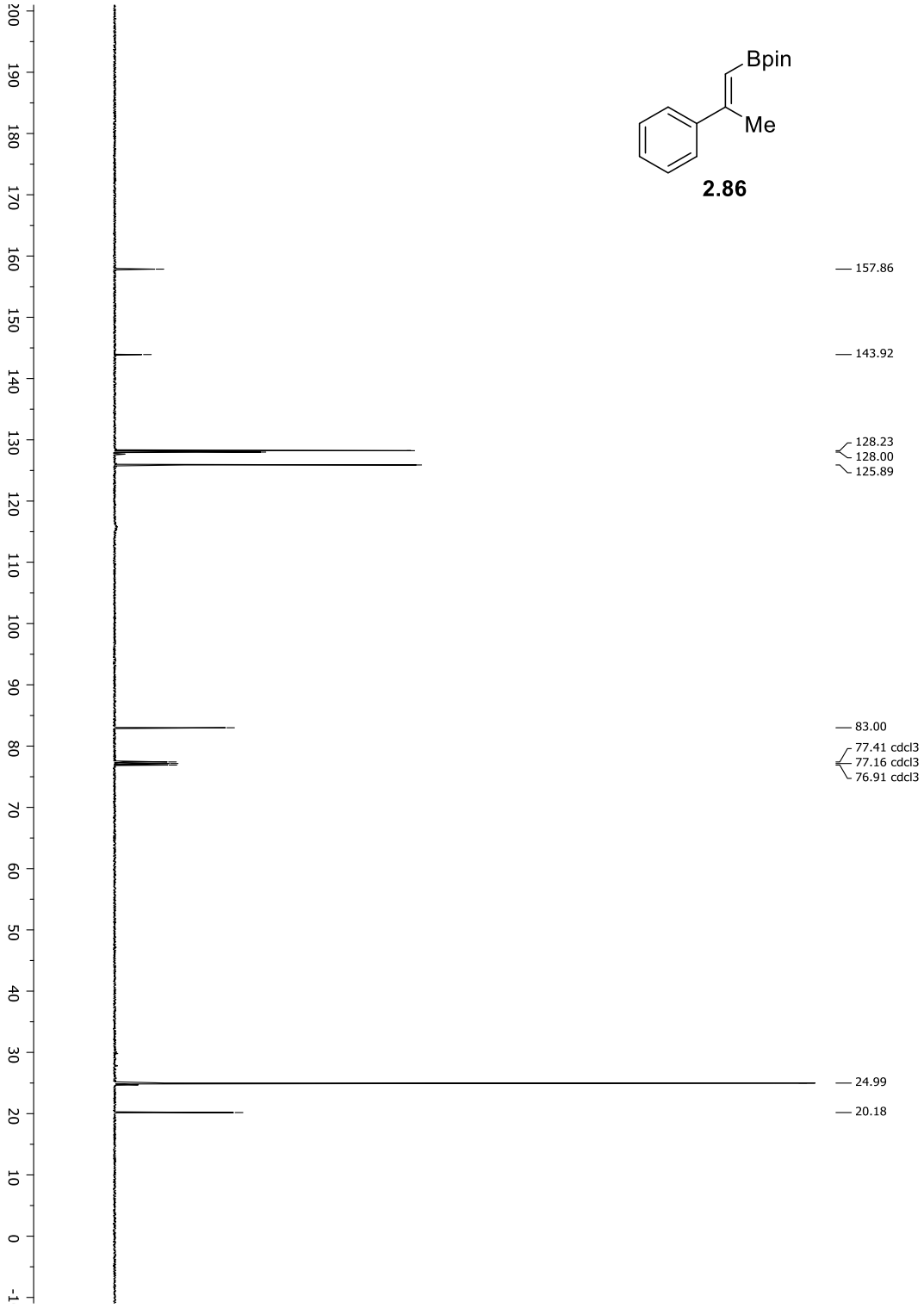

Bpin
Me
2.84
1.00
1.30
1.06
1.40
4.23
3.33
15.23
4.03
7.26
5.03
3.08
3.08
3.07
3.06
3.05
3.05
2.18
2.17
2.16
2.15
2.14
2.14
2.13
2.12
2.12
2.04
2.03
2.02
2.01
2.00
1.99
1.81
1.81
1.80
1.79
1.79
1.78
1.78
1.77
1.77
1.76
1.75
1.74
1.74
1.73
1.72
1.71
1.71
1.70
1.69
1.51
1.51
1.50
1.49
1.49
1.48
1.47
1.47
1.46
1.46
1.45
1.45
1.44
1.43
1.41
1.41
1.40
1.39
1.39
1.38
1.37
1.37
1.36
1.36
1.35
1.34
1.27
1.18
1.17
1.16
1.14
1.12
1.11
1.03
1.02

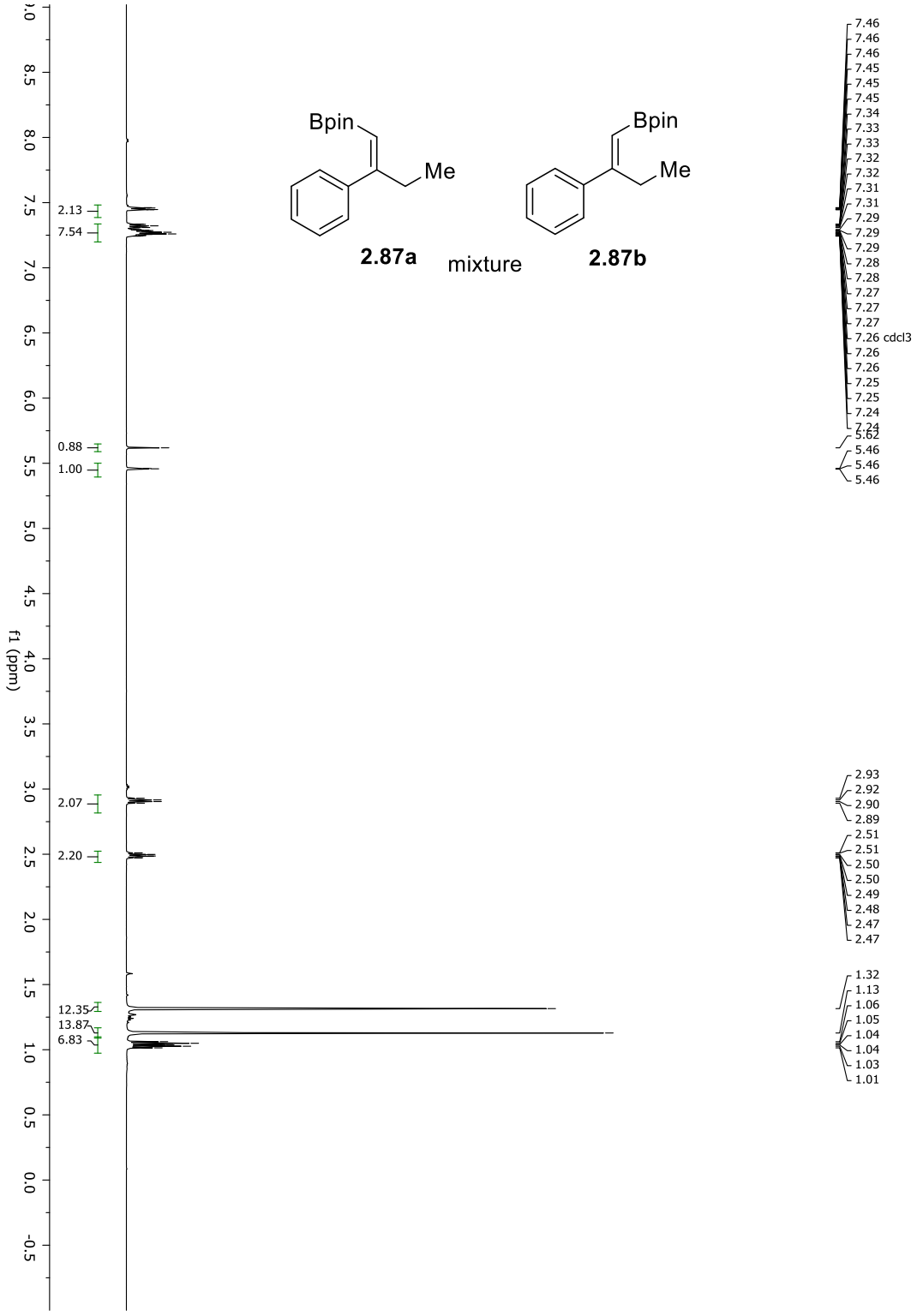

Bpin
Me
2.84
170.57
82.63
82.63
77.37
77.16
76.95
40.79
37.21
33.51
29.13
25.88
24.97
24.92
18.72
f1 (ppm)

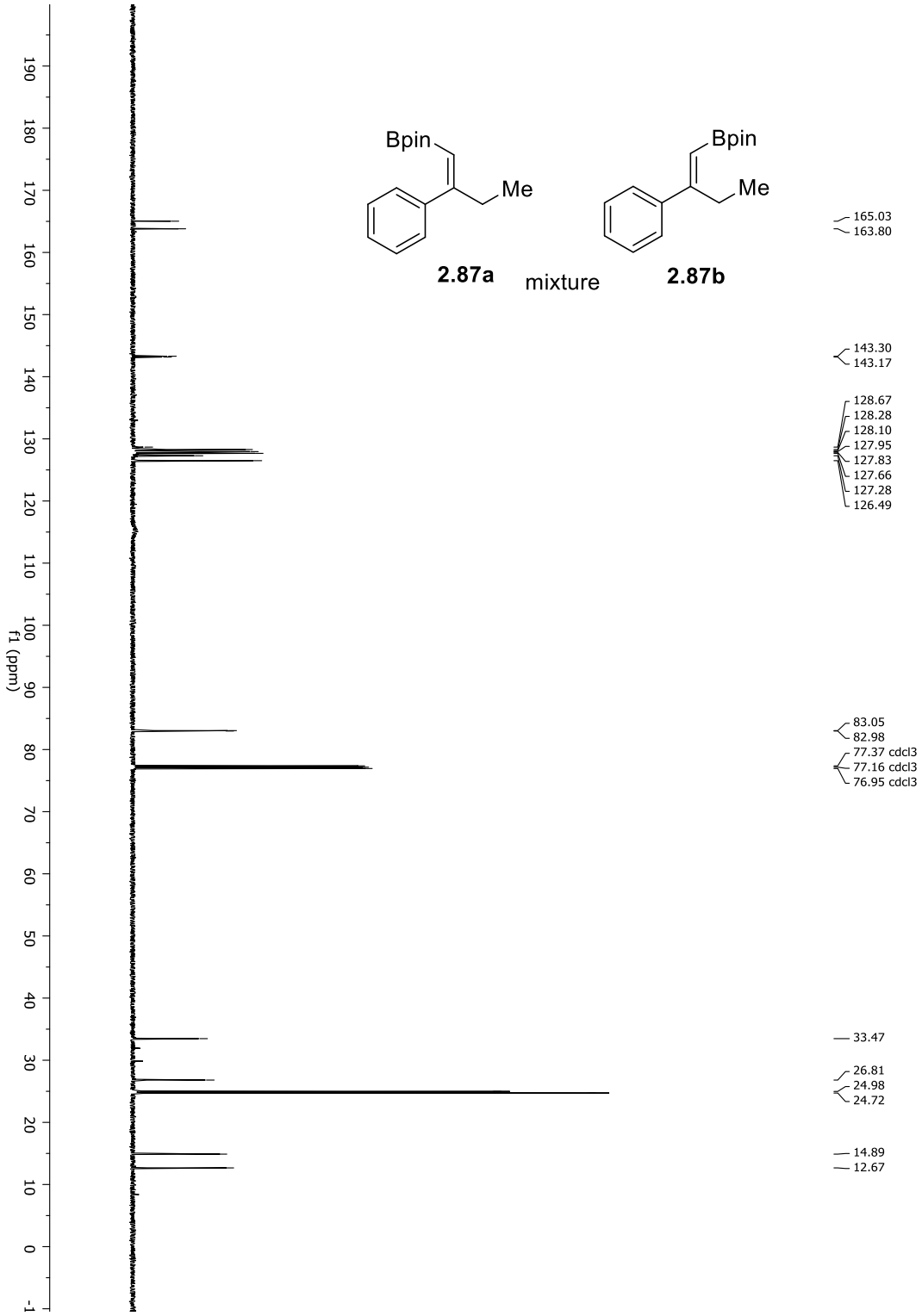
1HNMR NOESY for compound **2.84**

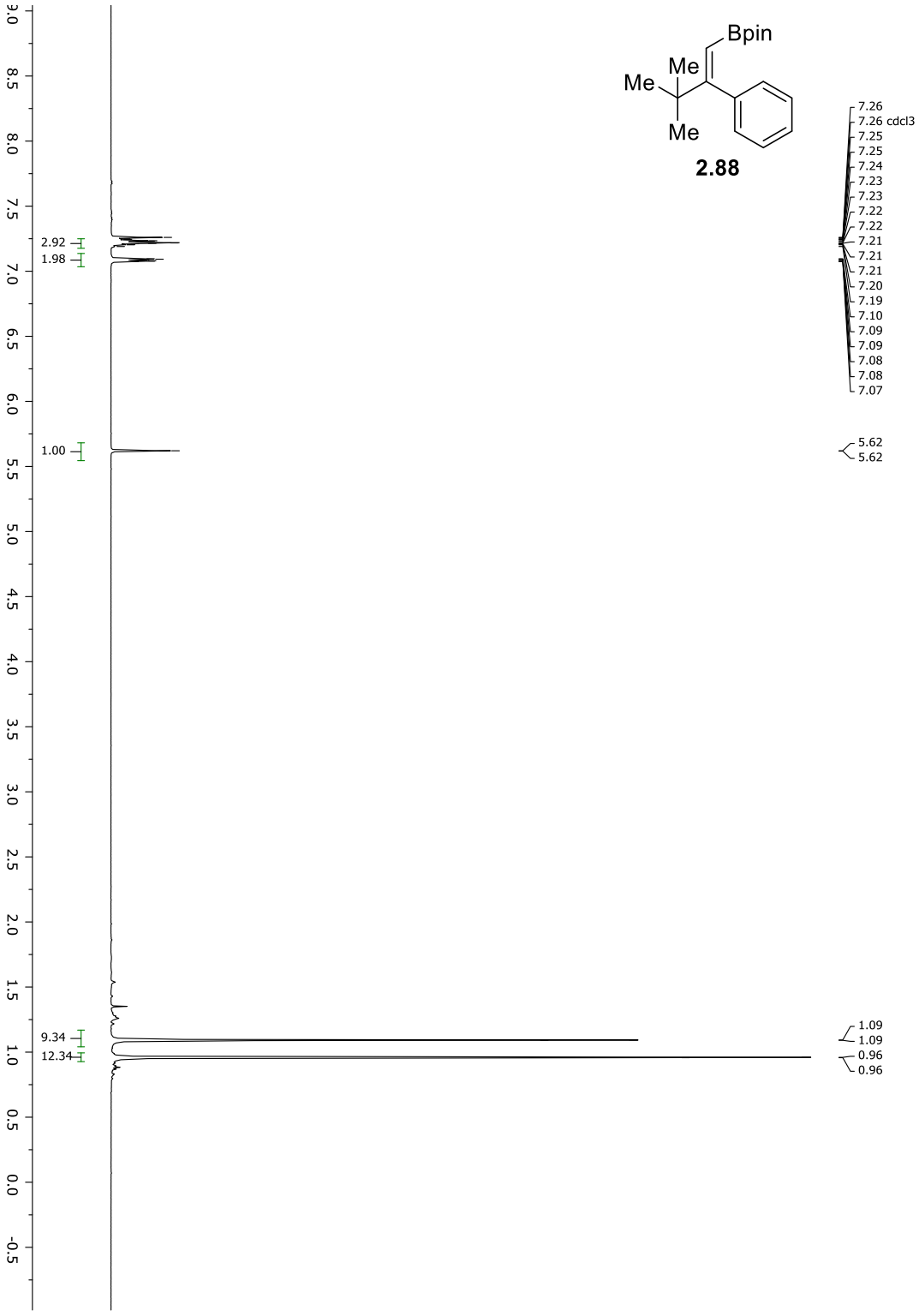


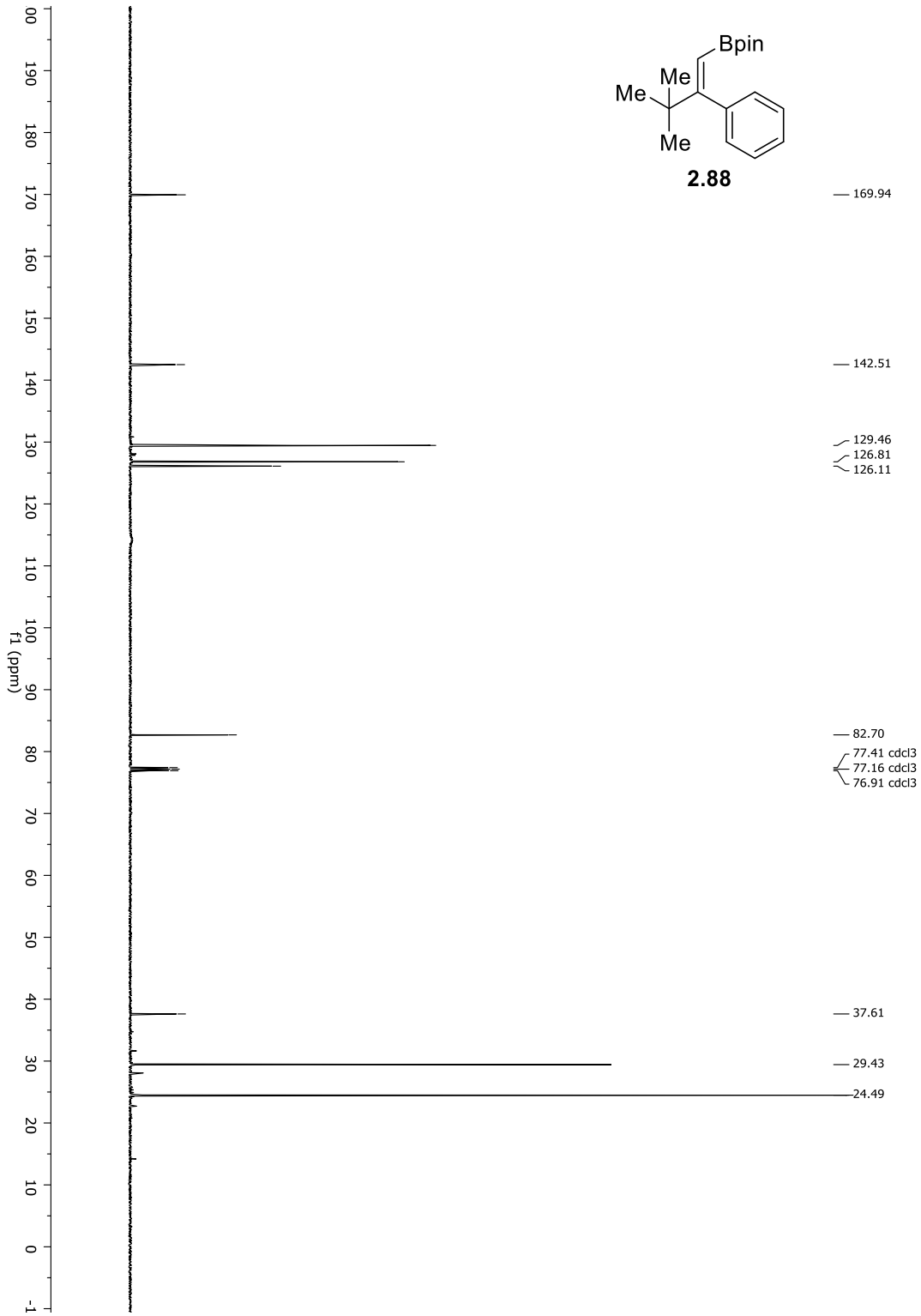

Bpin
Me
2.86
7.52
7.52
7.51
7.51
7.50
7.50
7.50
7.34
7.34
7.34
7.33
7.32
7.31
7.31
7.29
7.29
7.29
7.28
7.28
7.27
7.26
7.26 cdcl3
7.25
5.78
2.43
2.43
2.43
2.43
1.32
1.32
2.12
3.18
1.00
3.17
13.56


Bpin
Me
2.86
157.86
143.92
128.23
128.00
125.89
83.00
77.41 cdcl3
77.16 cdcl3
76.91 cdcl3
24.99
20.18

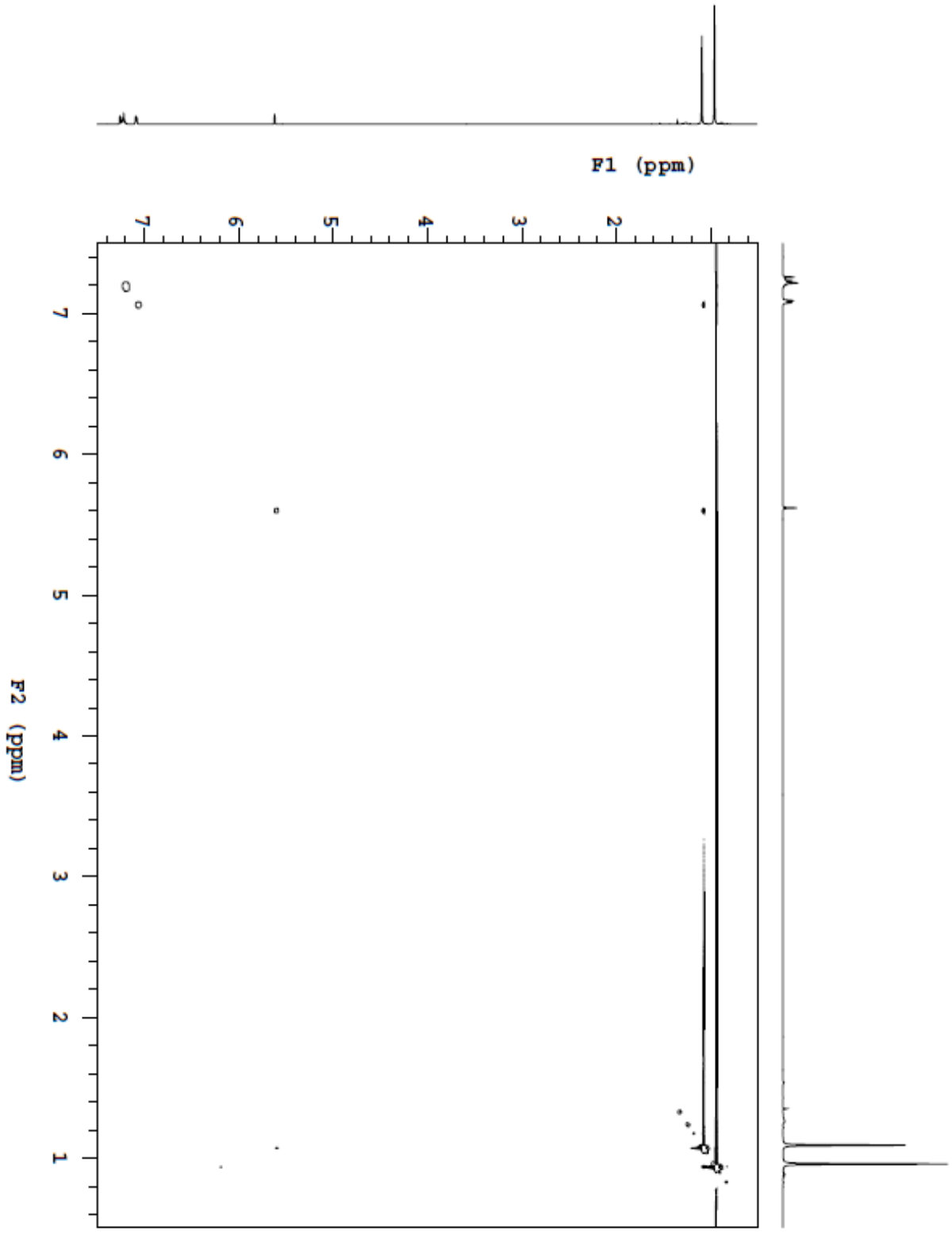

Bpin
Me
2.87a
mixture
Bpin
Me
2.87b
f1 (ppm)
2.13
7.54
0.88
1.00
2.07
2.20
12.35
13.87
6.83
7.46
7.46
7.46
7.45
7.45
7.45
7.34
7.33
7.33
7.32
7.32
7.31
7.31
7.29
7.29
7.29
7.28
7.28
7.27
7.27
7.27
7.26 cdcl3
7.26
7.26
7.25
7.25
7.24
7.24
5.62
5.46
5.46
5.46
2.93
2.92
2.90
2.89
2.51
2.51
2.50
2.50
2.49
2.48
2.47
2.47
1.32
1.13
1.06
1.05
1.04
1.04
1.03
1.01

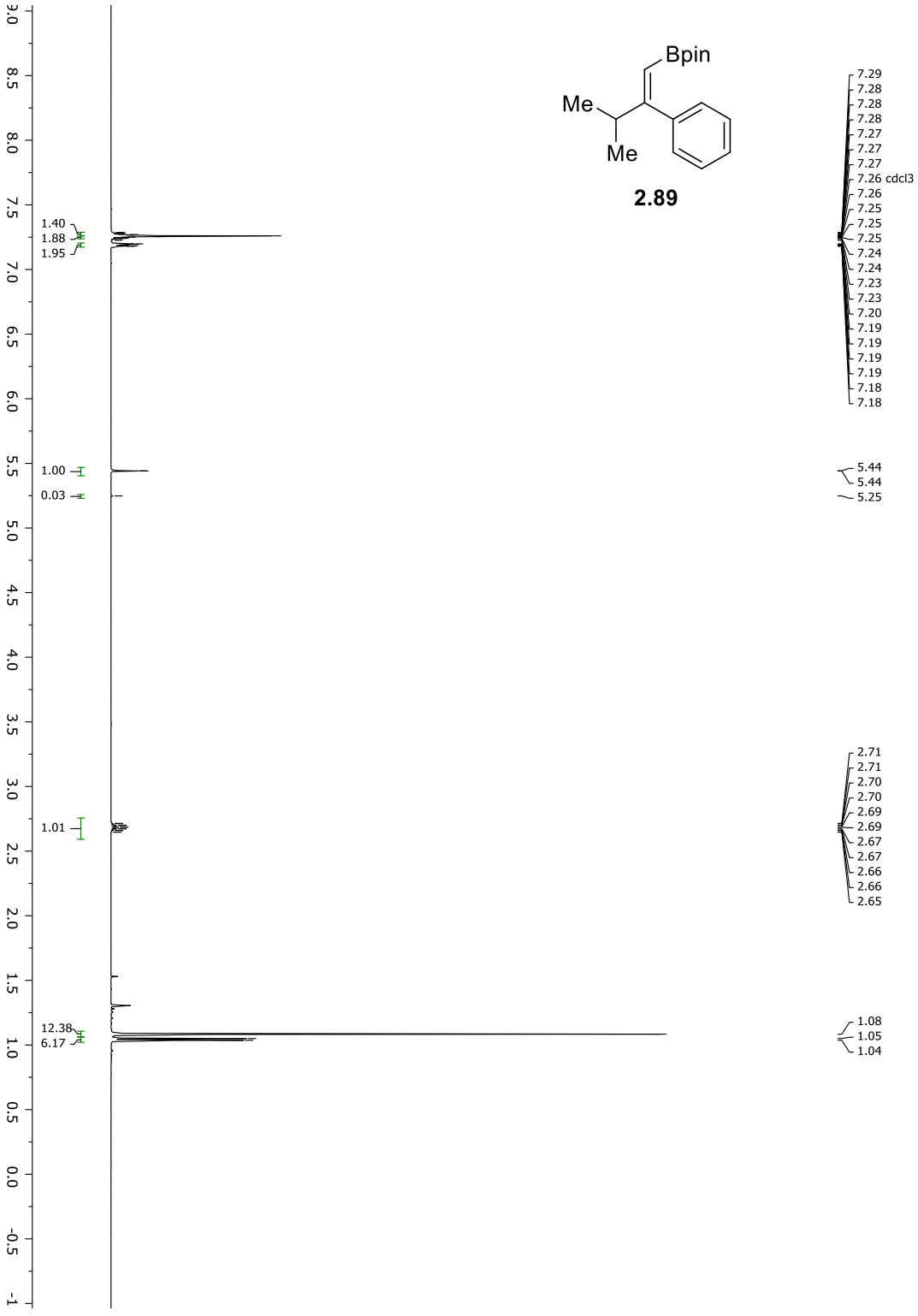

Bpin
Me
Bpin
Me
2.87a
mixture
2.87b
165.03
163.80
143.30
143.17
128.67
128.28
128.10
127.95
127.83
127.66
127.28
126.49
83.05
82.98
77.37 cdcl3
77.16 cdcl3
76.95 cdcl3
33.47
26.81
24.98
24.72
14.89
12.67
f1 (ppm)

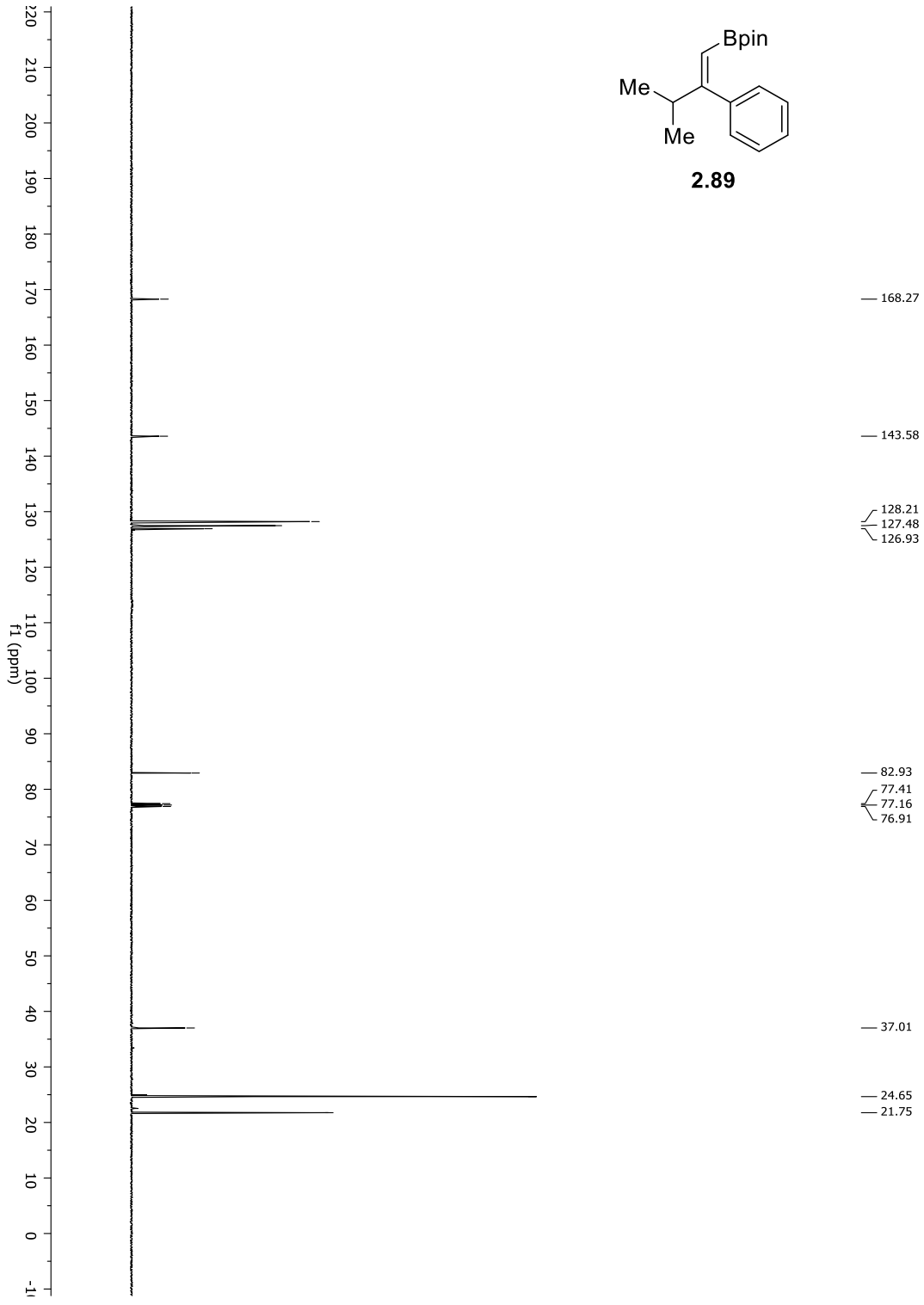

Bpin
Me
Me
Me
2.88
7.26
7.26 cdcl3
7.25
7.25
7.24
7.23
7.23
7.22
7.22
7.21
7.21
7.21
7.20
7.19
7.10
7.09
7.09
7.08
7.08
7.07
5.62
5.62
1.09
1.09
0.96
0.96
2.92
1.98
1.00
9.34
12.34


Bpin
Me
Me
Me
2.88
169.94
142.51
129.46
126.81
126.11
82.70
77.41 cdcl3
77.16 cdcl3
76.91 cdcl3
37.61
29.43
24.49
f1 (ppm)

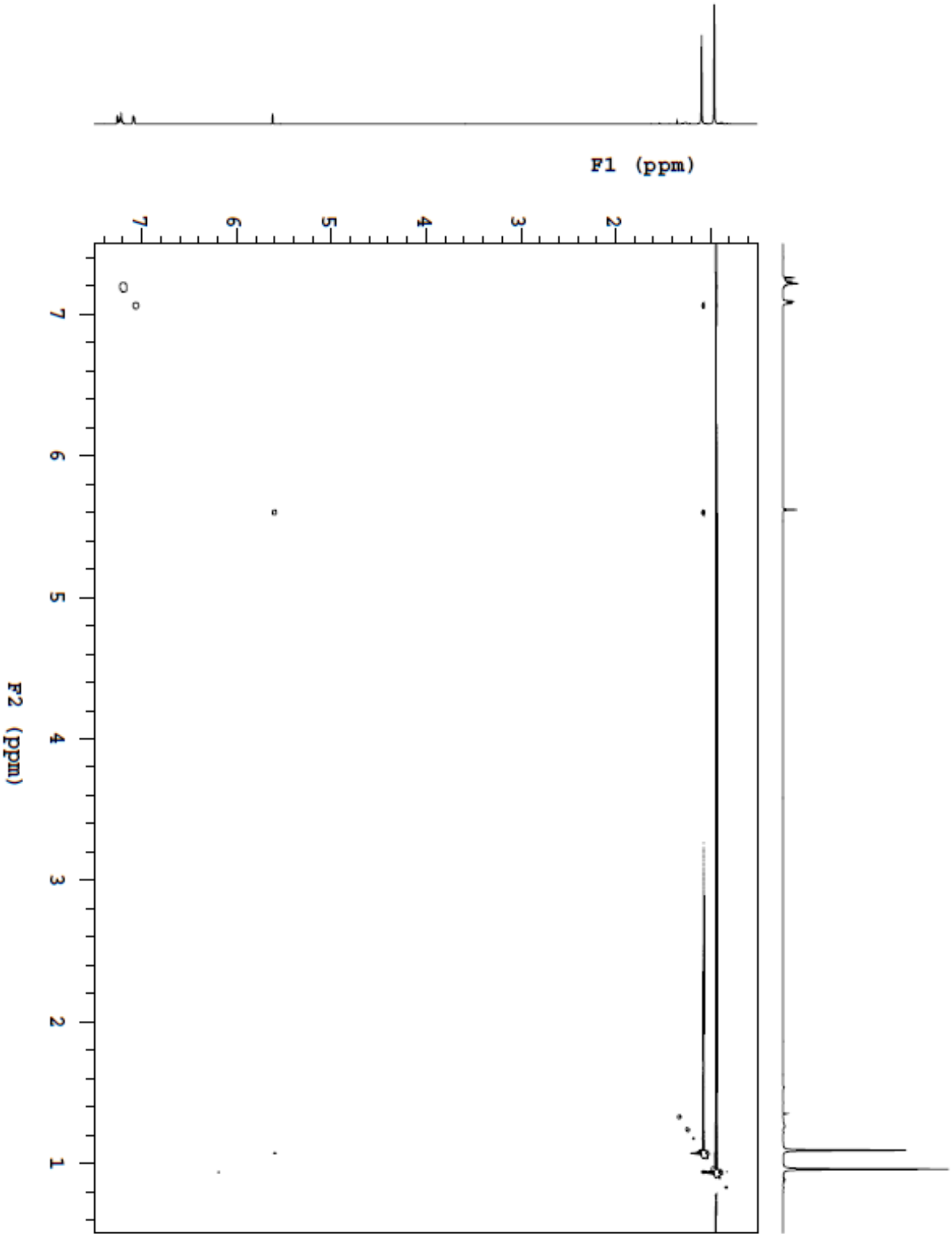
1HNMR NOESY for compound **2.88**

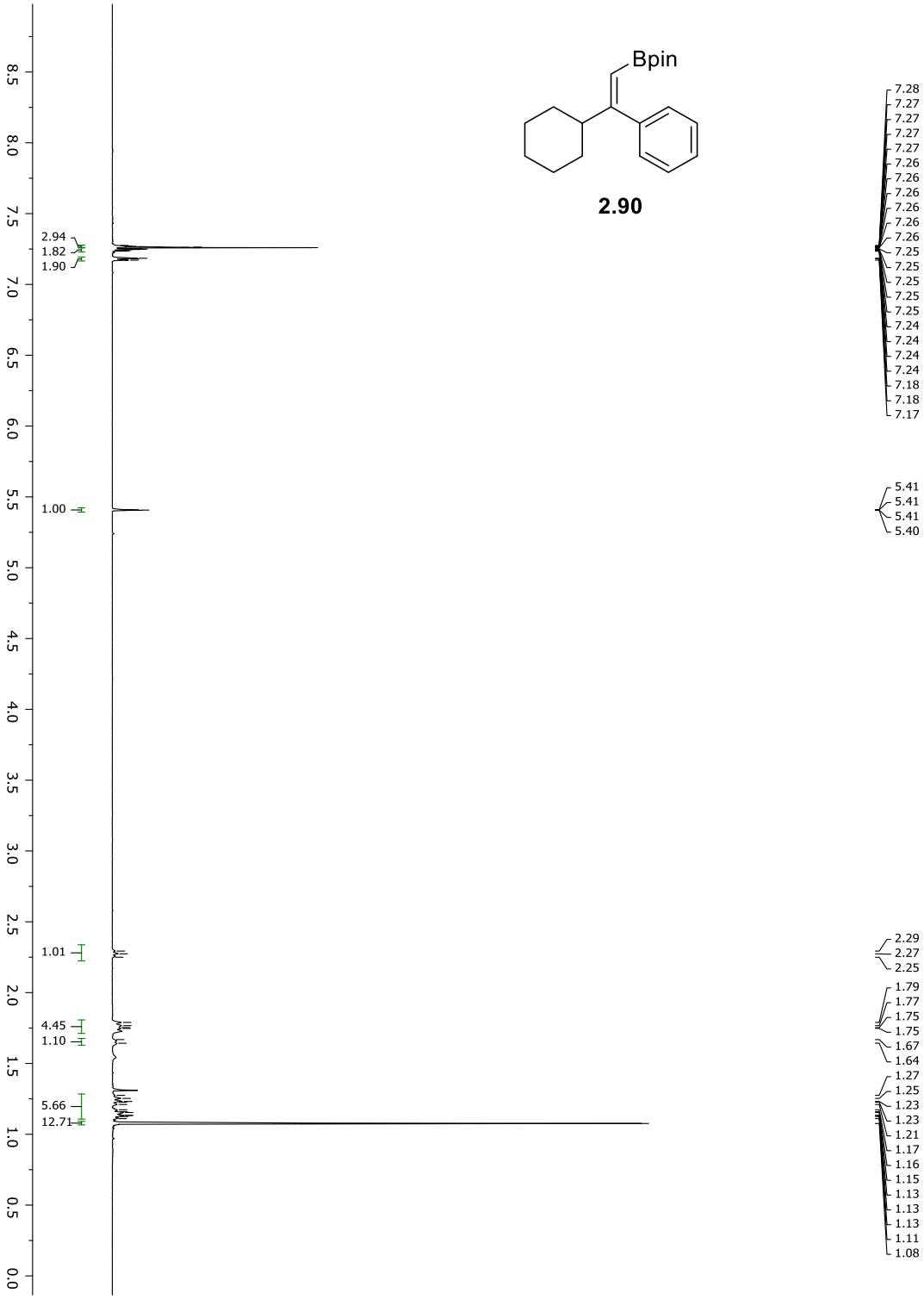


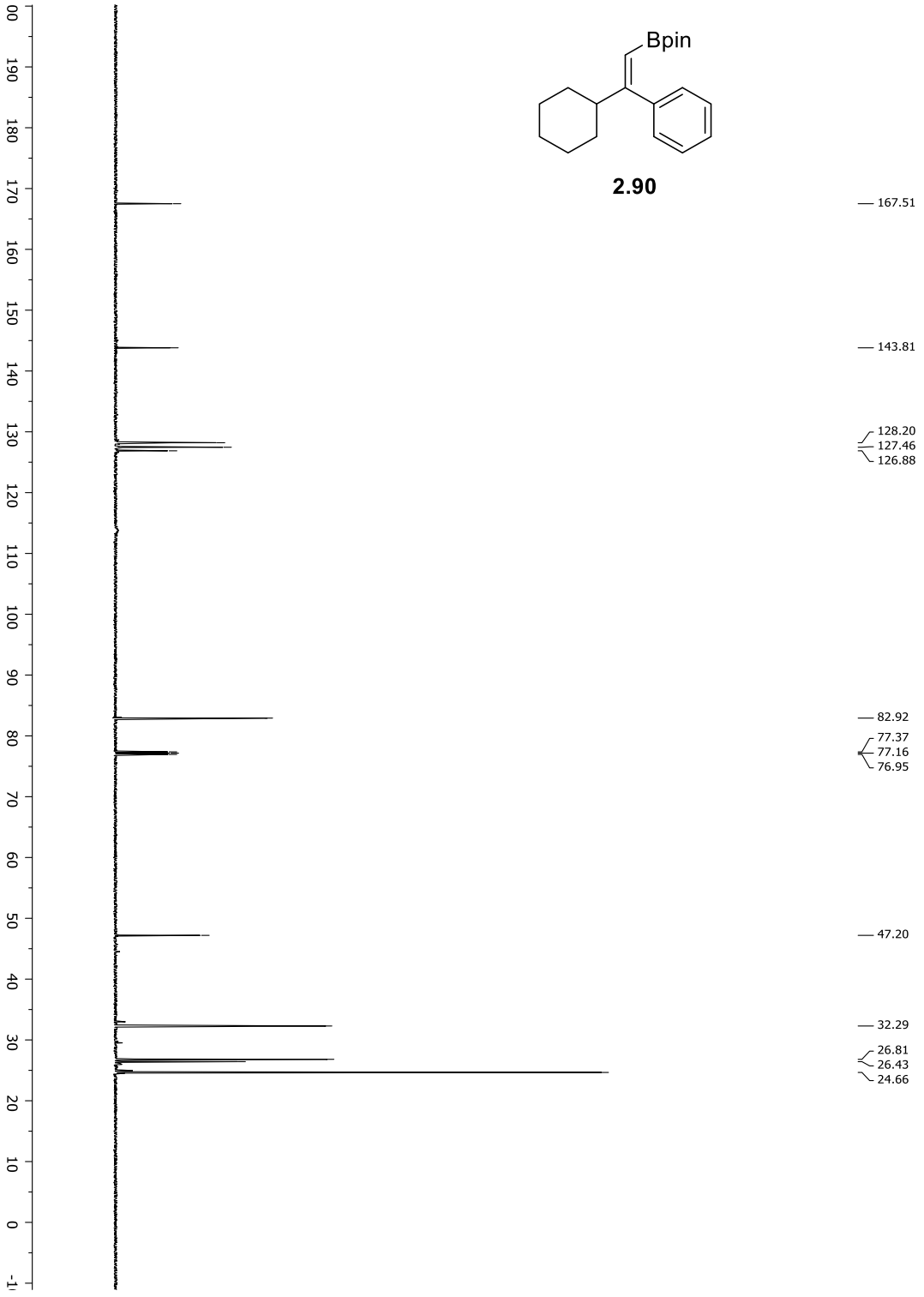

Bpin
Me
Me
2.89
1.40
1.88
1.95
1.00
0.03
1.01
12.38
6.17
7.29
7.28
7.28
7.28
7.27
7.27
7.27
7.26 cdcl3
7.26
7.25
7.25
7.25
7.24
7.24
7.23
7.23
7.20
7.19
7.19
7.19
7.19
7.18
7.18
5.44
5.44
5.25
2.71
2.71
2.70
2.70
2.69
2.69
2.67
2.67
2.66
2.66
2.65
1.08
1.05
1.04


Bpin
Me
Me
2.89
168.27
143.58
128.21
127.48
126.93
82.93
77.41
77.16
76.91
37.01
24.65
21.75
f1 (ppm)

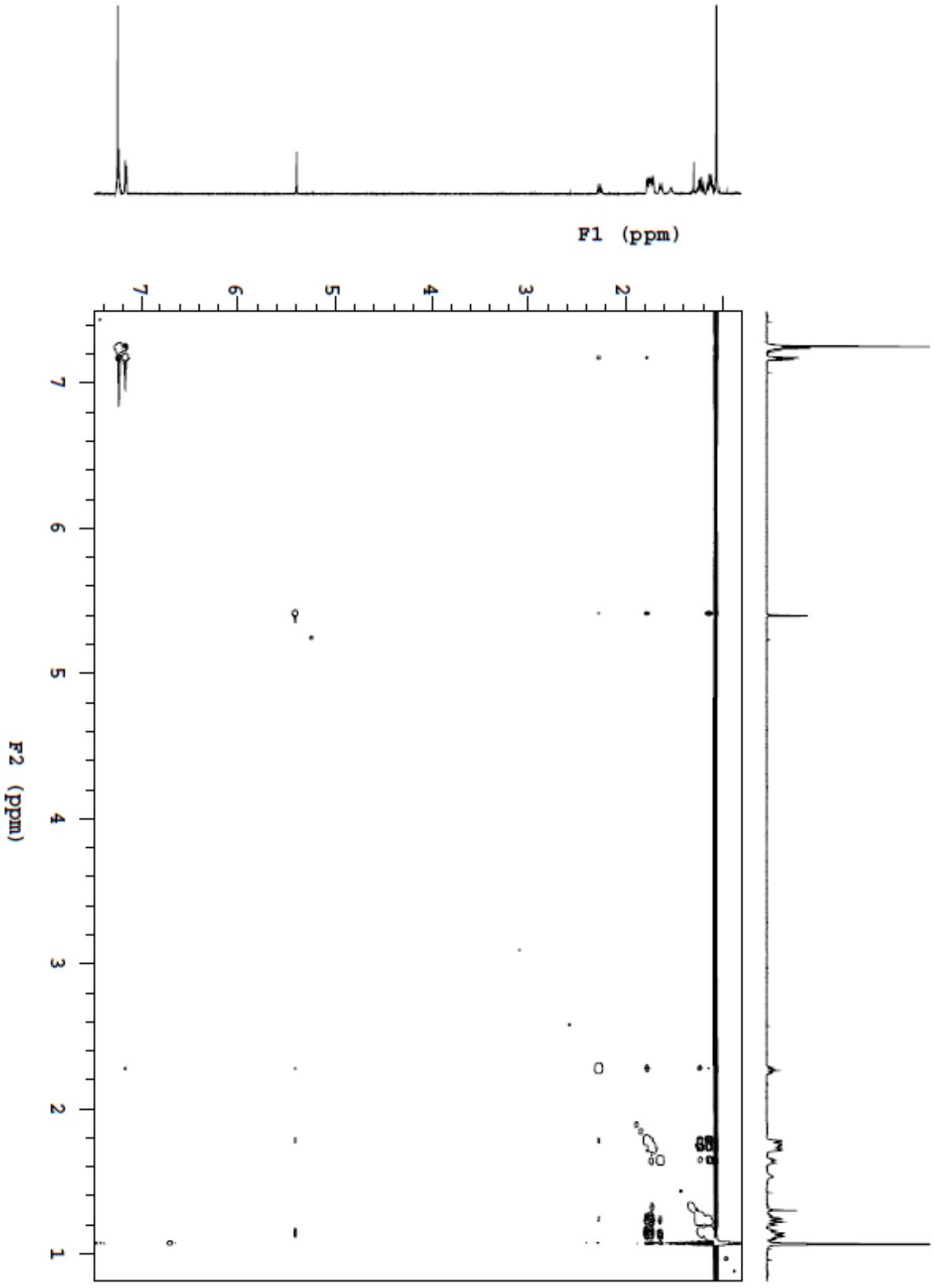
1HNMR NOESY for compound **2.89**

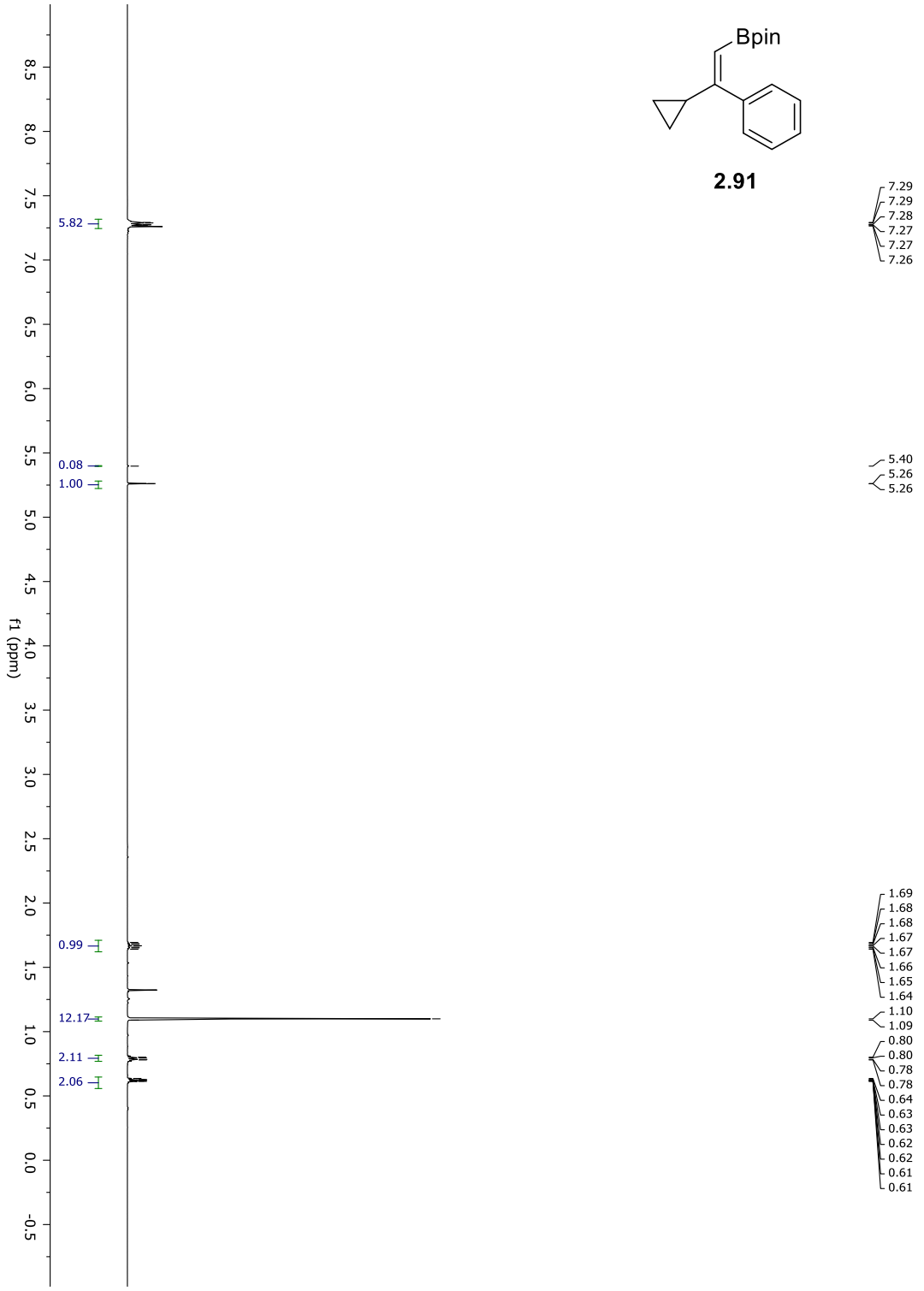


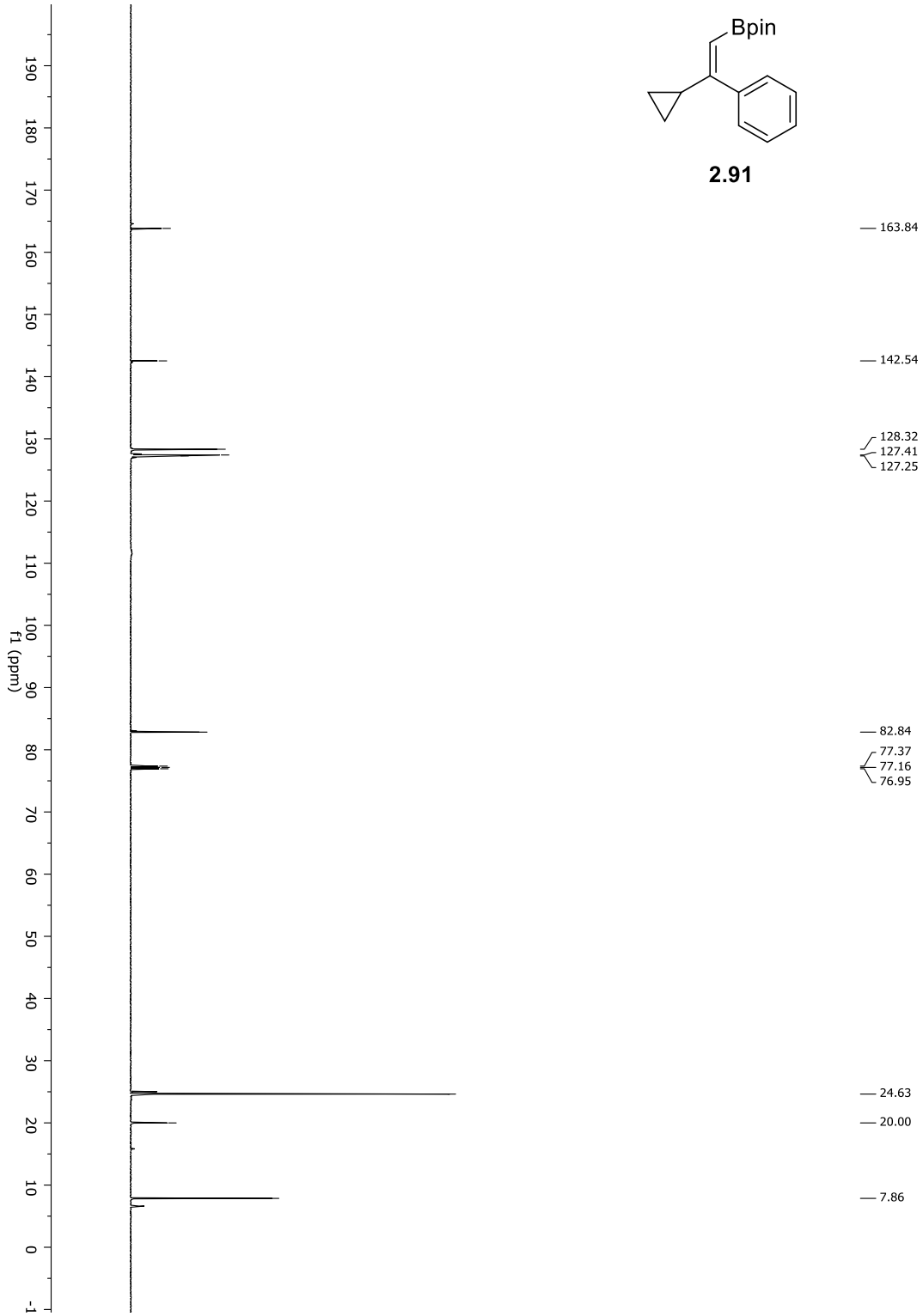

Bpin
2.90
2.94
1.82
1.90
1.00
1.01
4.45
1.10
5.66
12.71
7.28
7.27
7.27
7.27
7.27
7.26
7.26
7.26
7.26
7.26
7.26
7.25
7.25
7.25
7.25
7.25
7.25
7.24
7.24
7.24
7.24
7.18
7.18
7.17
5.41
5.41
5.41
5.40
2.29
2.27
2.25
1.79
1.77
1.75
1.75
1.67
1.64
1.27
1.25
1.23
1.23
1.21
1.17
1.16
1.15
1.13
1.13
1.13
1.11
1.08


Bpin
2.90
167.51
143.81
128.20
127.46
126.88
82.92
77.37
77.16
76.95
47.20
32.29
26.81
26.43
24.66

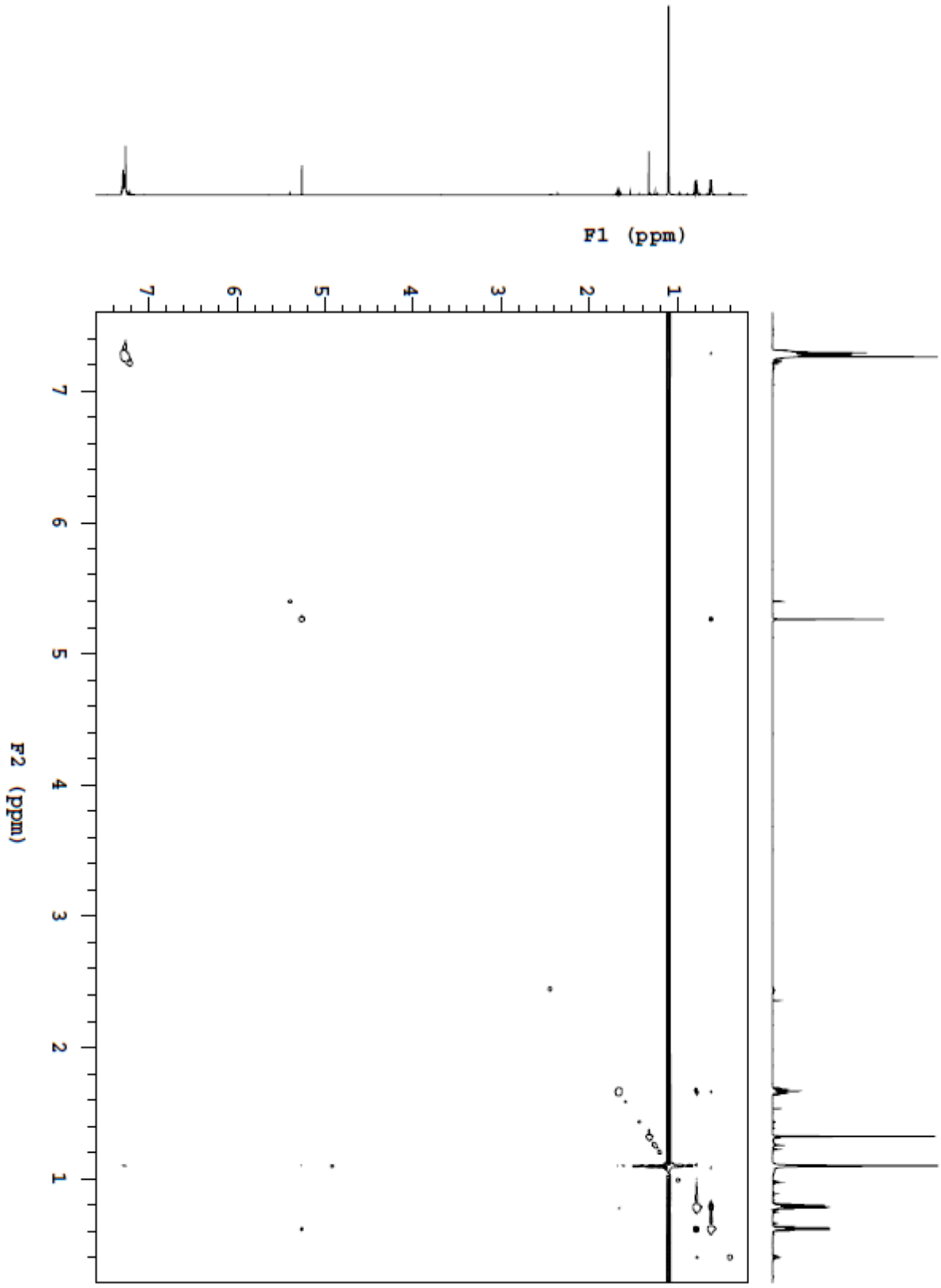
1HNMR NOESY for compound **2.83**

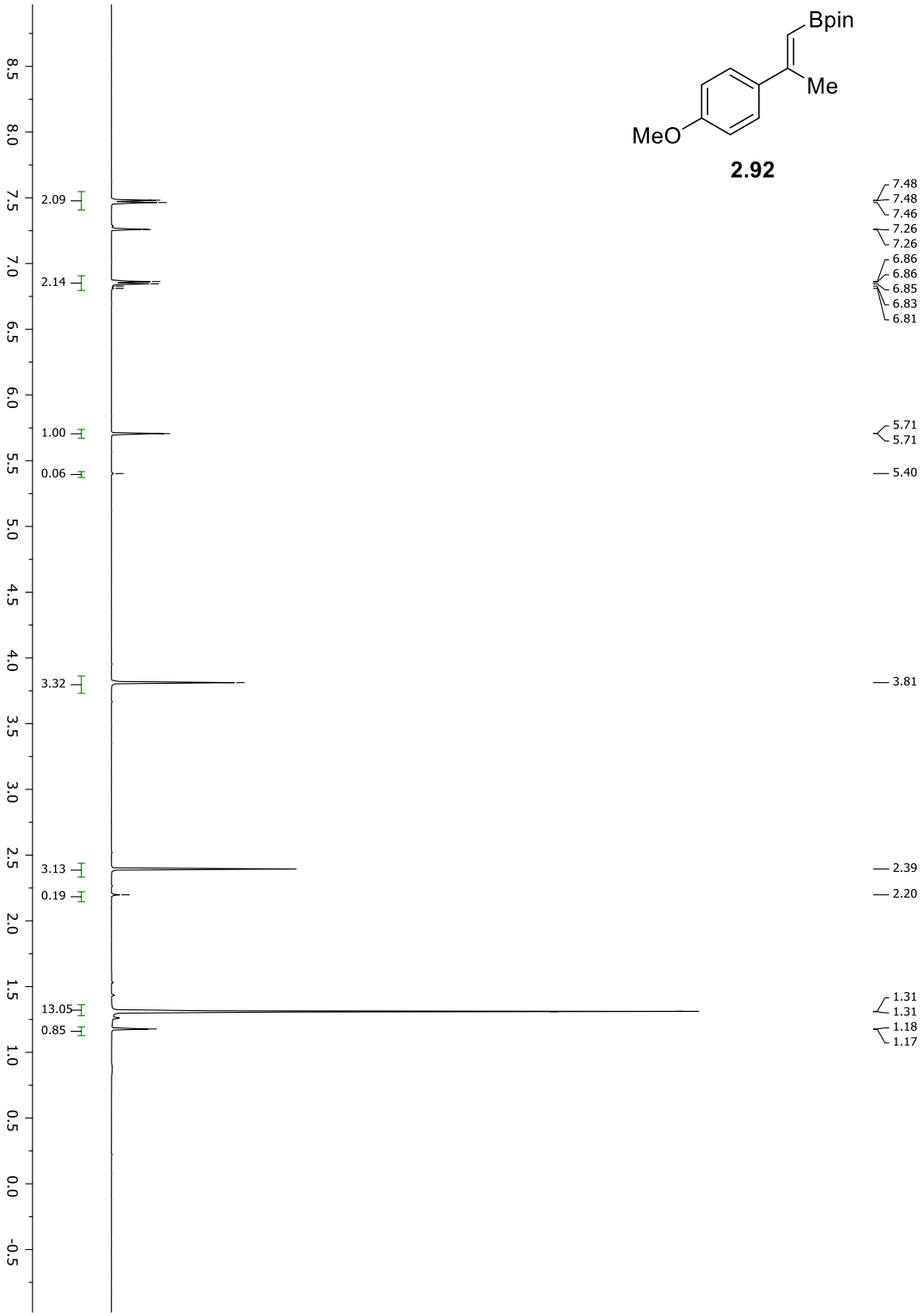


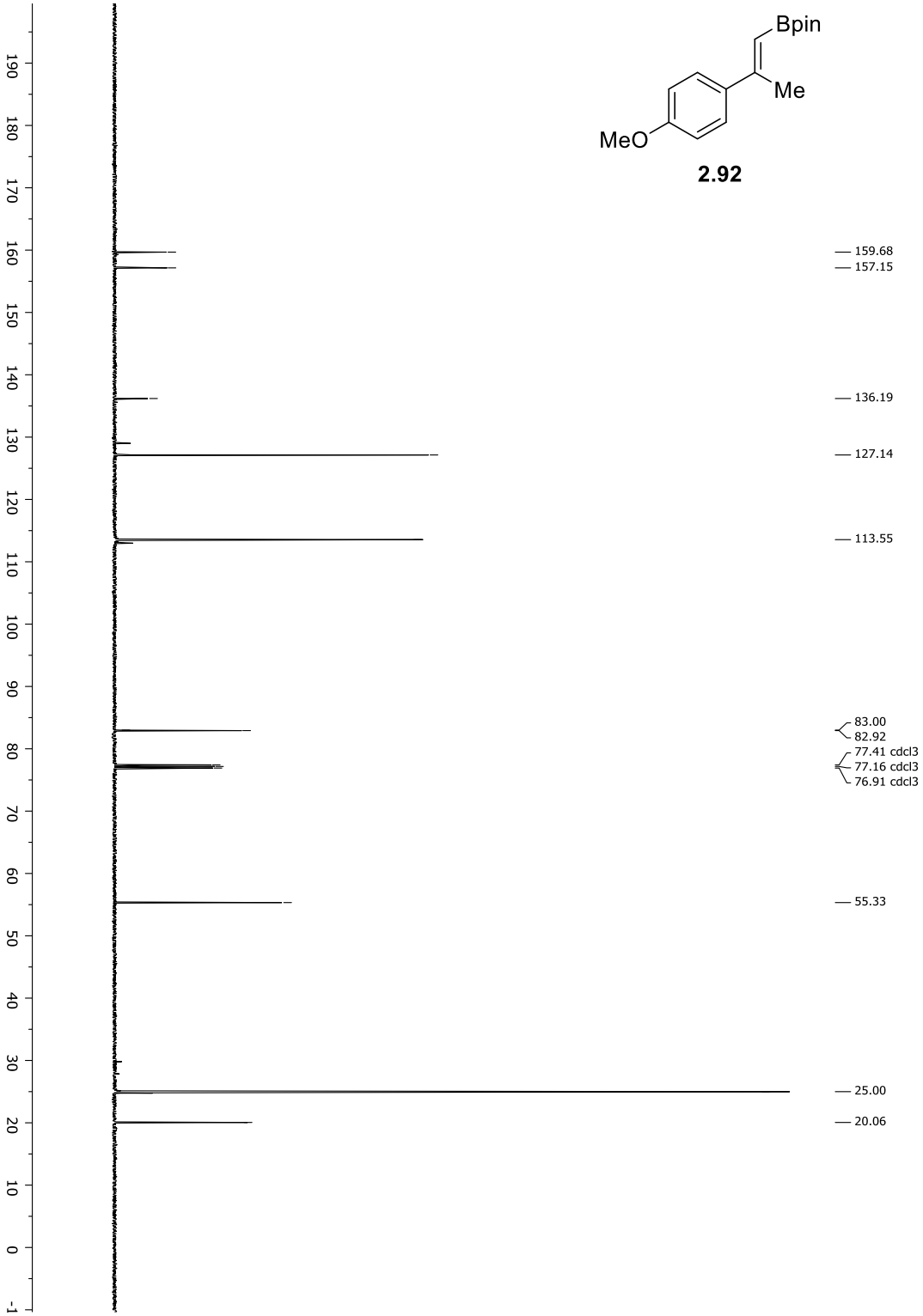

Bpin
2.91
f1 (ppm)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
5.82
0.08
1.00
0.99
12.17
2.11
2.06
7.29
7.29
7.28
7.27
7.27
7.26
5.40
5.26
5.26
1.69
1.68
1.68
1.67
1.67
1.66
1.65
1.64
1.10
1.09
0.80
0.80
0.78
0.78
0.64
0.63
0.63
0.62
0.62
0.61
0.61

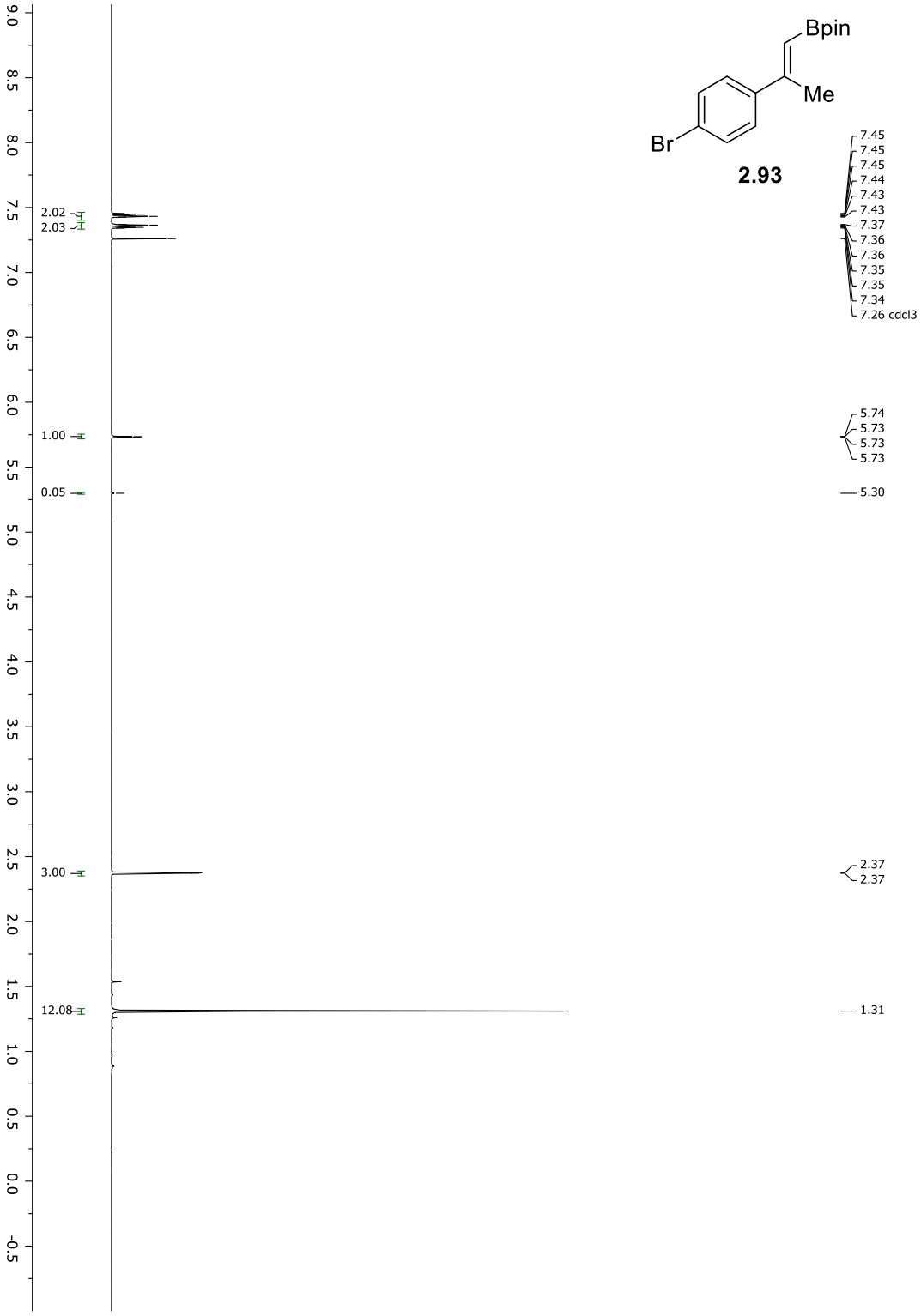

Bpin
2.91
163.84
142.54
128.32
127.41
127.25
82.84
77.37
77.16
76.95
24.63
20.00
7.86
f1 (ppm)

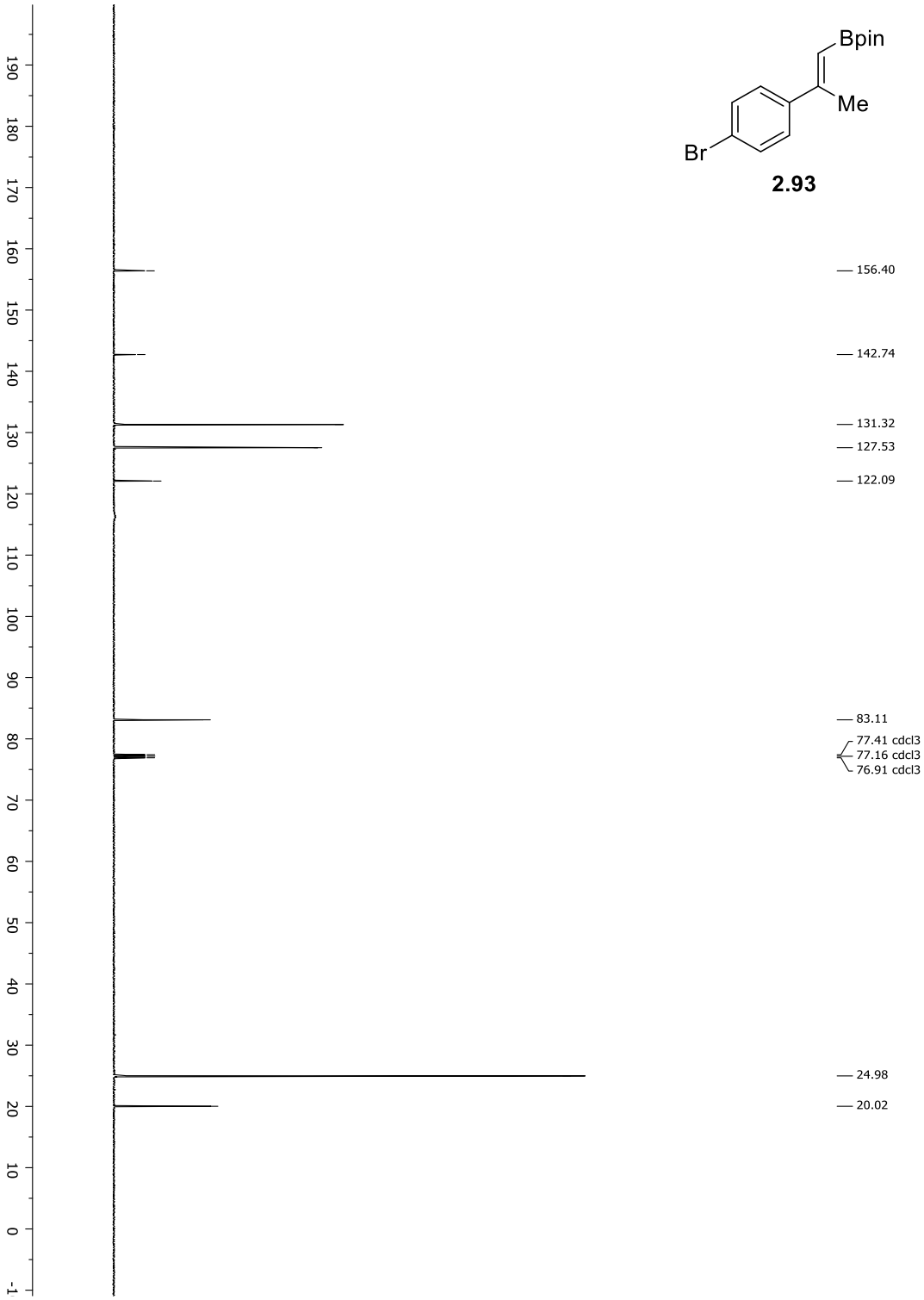
1HNMR NOESY for compound **2.91**

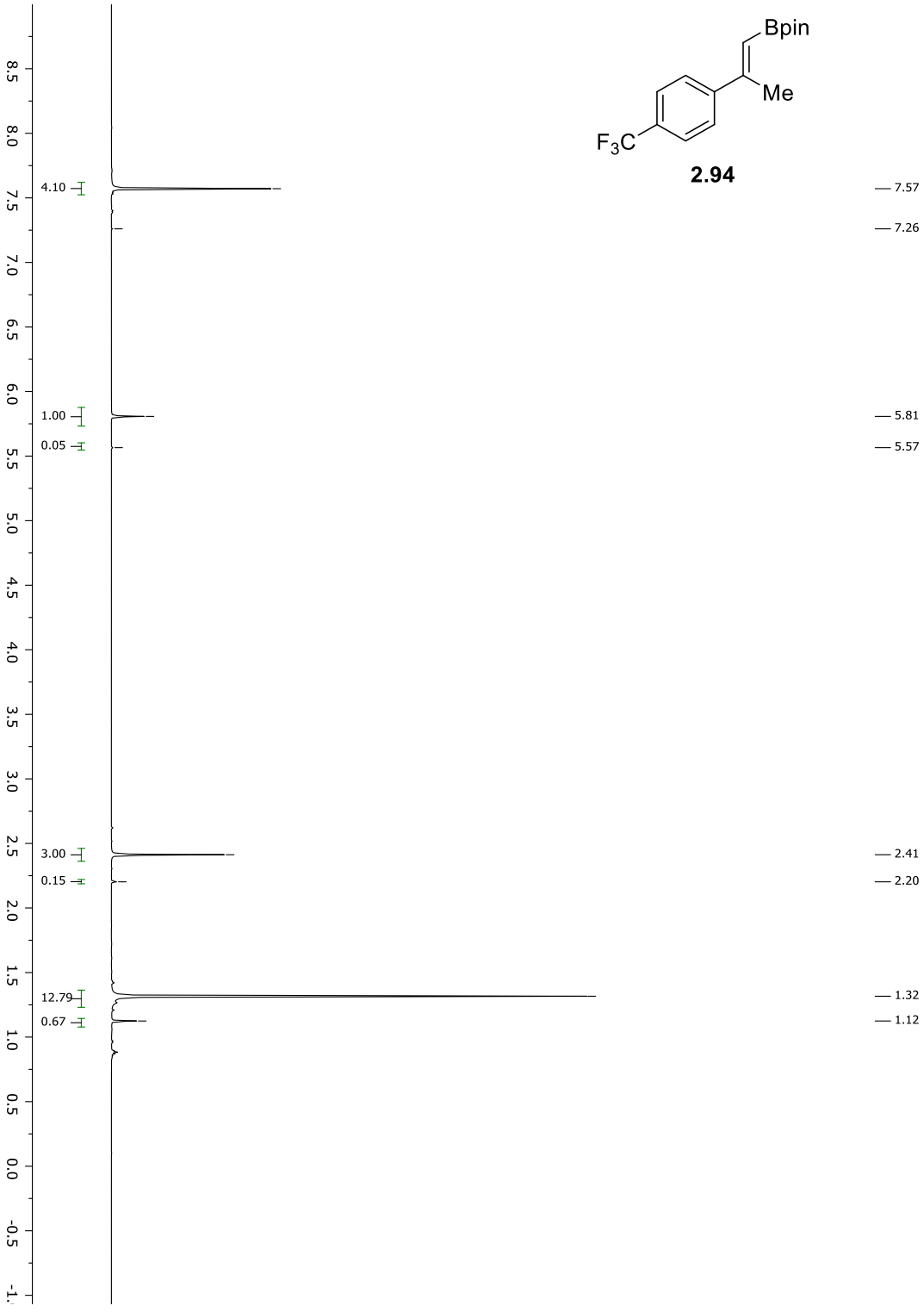


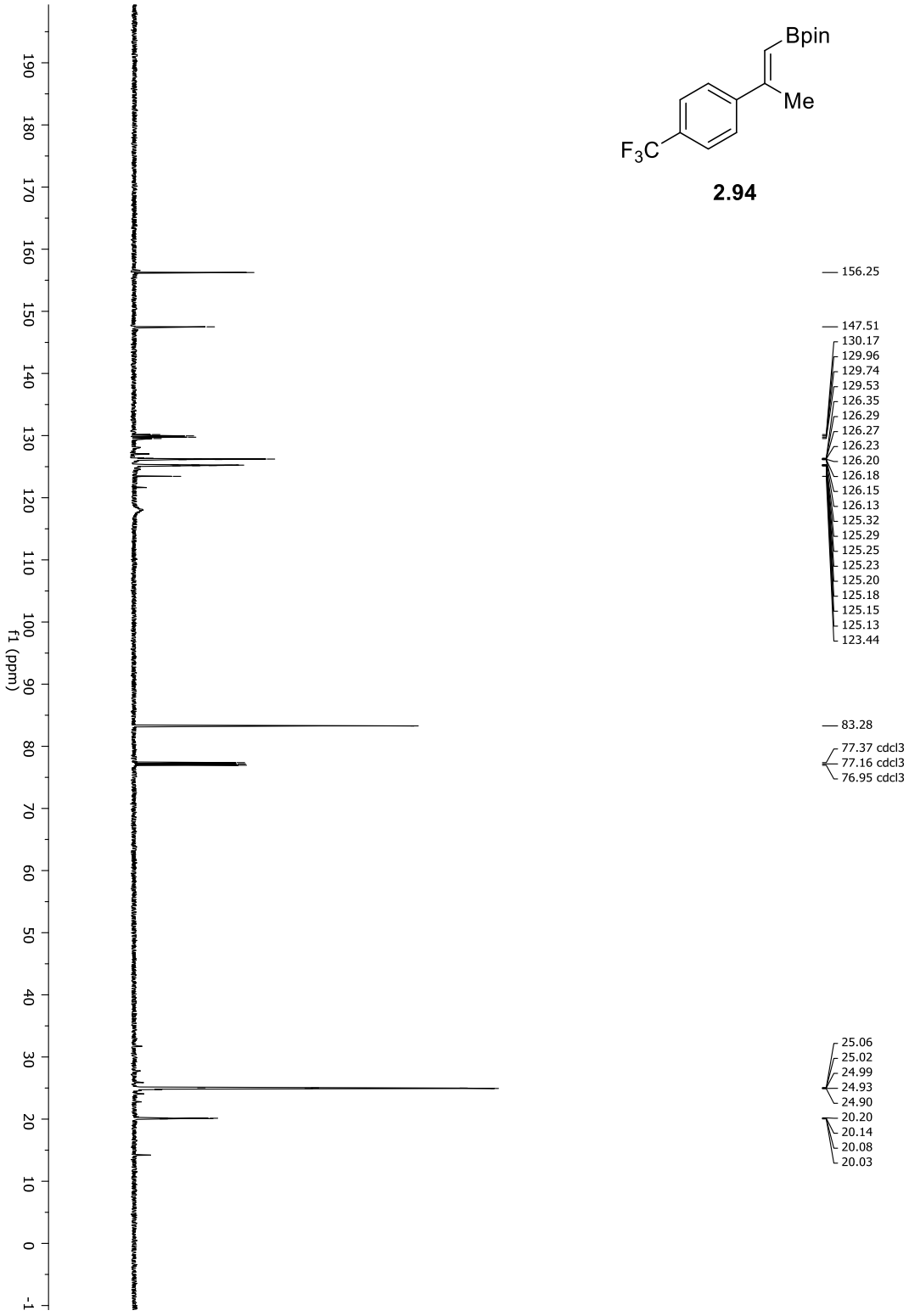

Bpin
Me
MeO
2.92
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
2.09
2.14
1.00
0.06
3.32
3.13
0.19
13.05
0.85
7.48
7.48
7.46
7.26
7.26
6.86
6.86
6.85
6.83
6.81
5.71
5.71
5.40
3.81
2.39
2.20
1.31
1.31
1.18
1.17

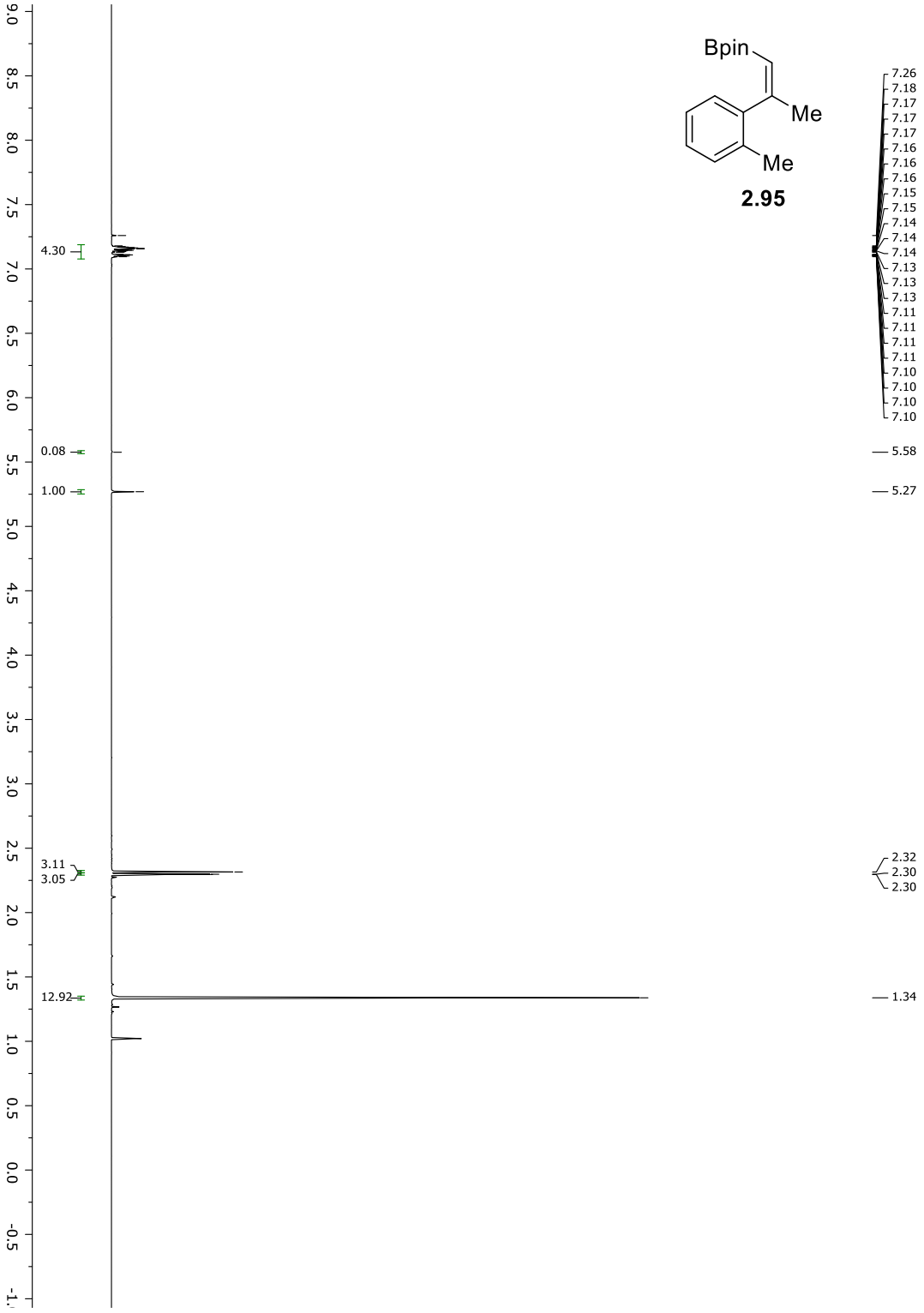

Bpin
Me
MeO
2.92
159.68
157.15
136.19
127.14
113.55
83.00
82.92
77.41 cdcl3
77.16 cdcl3
76.91 cdcl3
55.33
25.00
20.06

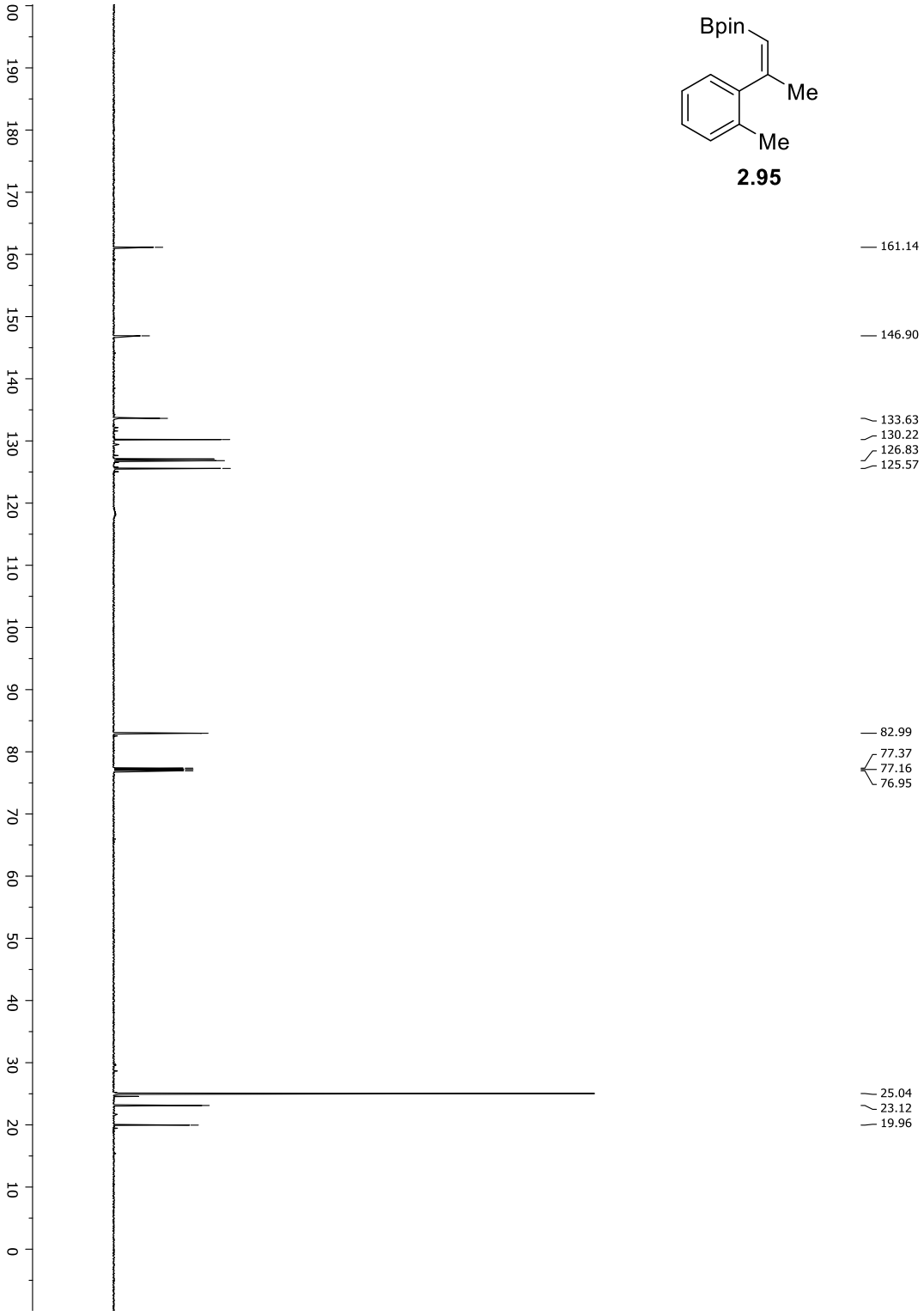

Bpin
Me
Br
2.93
7.45
7.45
7.45
7.44
7.43
7.43
7.37
7.36
7.36
7.35
7.35
7.34
7.26 cdcl3
5.74
5.73
5.73
5.73
5.30
2.37
2.37
1.31
2.02
2.03
1.00
0.05
3.00
12.08


Bpin
Me
Br
2.93
156.40
142.74
131.32
127.53
122.09
83.11
77.41 cdcl3
77.16 cdcl3
76.91 cdcl3
24.98
20.02

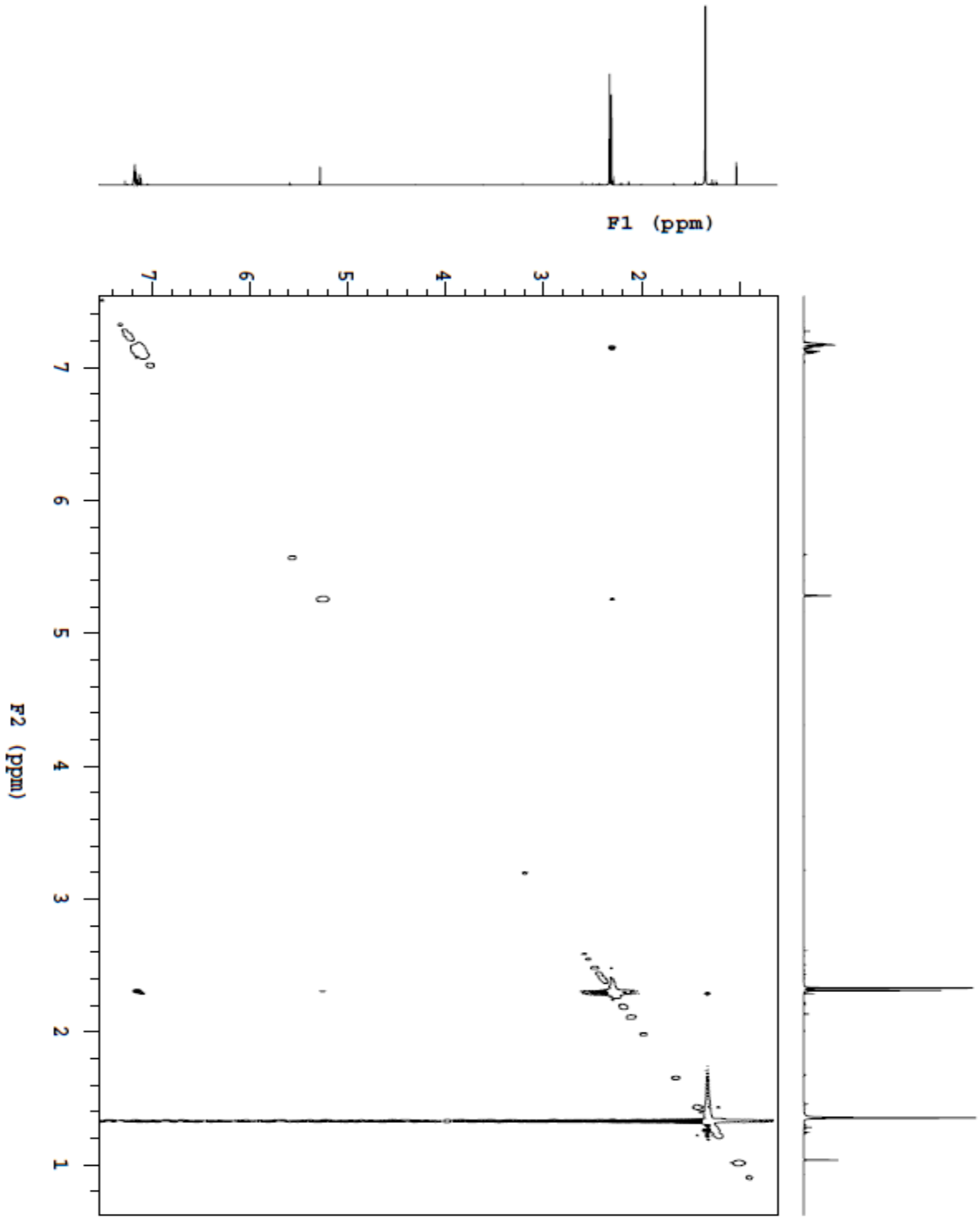

Bpin
Me
F3C
2.94
4.10
1.00
0.05
3.00
0.15
12.79
0.67
7.57
7.26
5.81
5.57
2.41
2.20
1.32
1.12

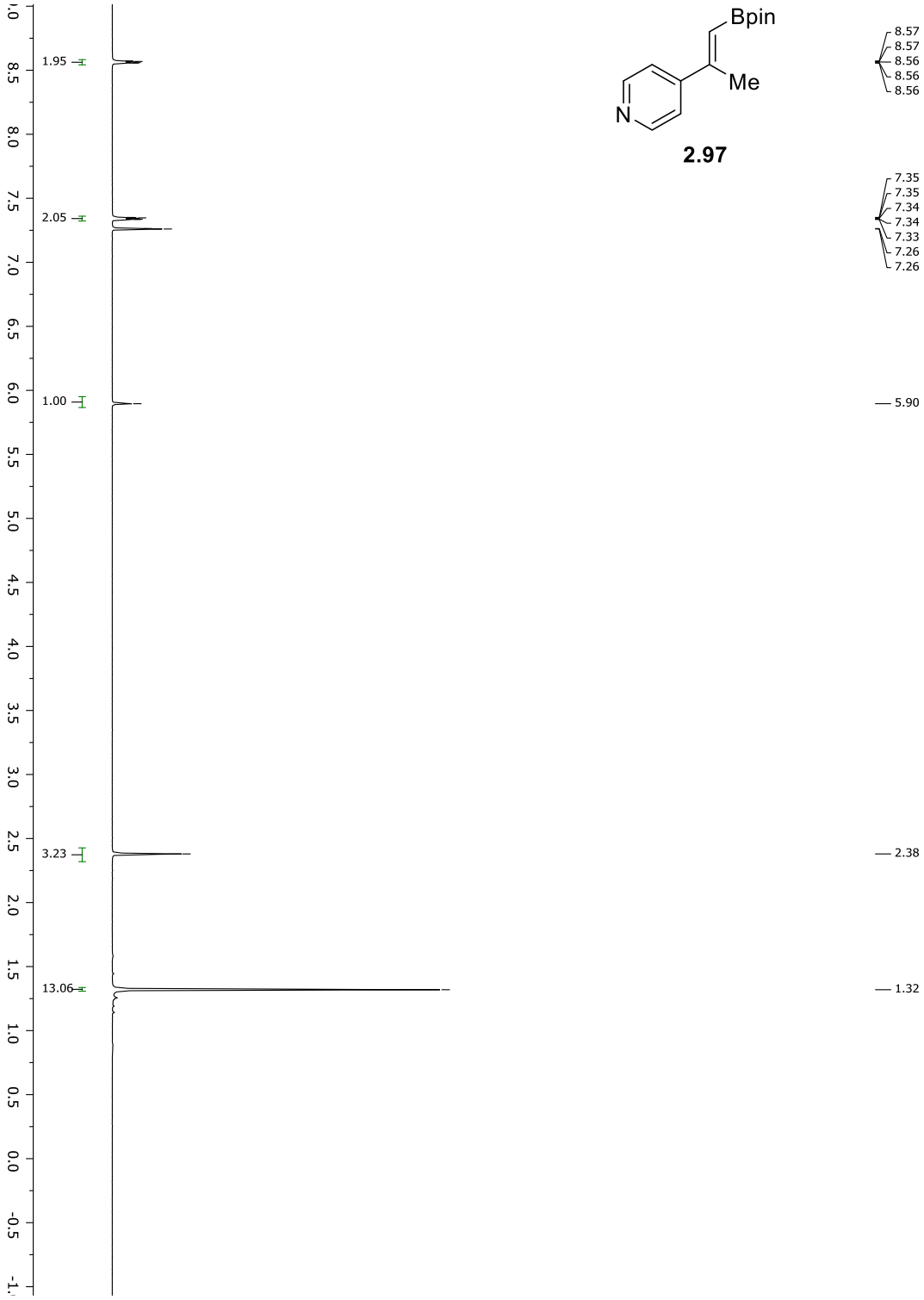

Bpin
Me
F3C
2.94
156.25
147.51
130.17
129.96
129.74
129.53
126.35
126.29
126.27
126.23
126.20
126.18
126.15
126.13
125.32
125.29
125.25
125.23
125.20
125.18
125.15
125.13
123.44
83.28
77.37 cdcl3
77.16 cdcl3
76.95 cdcl3
25.06
25.02
24.99
24.93
24.90
20.20
20.14
20.08
20.03
f1 (ppm)

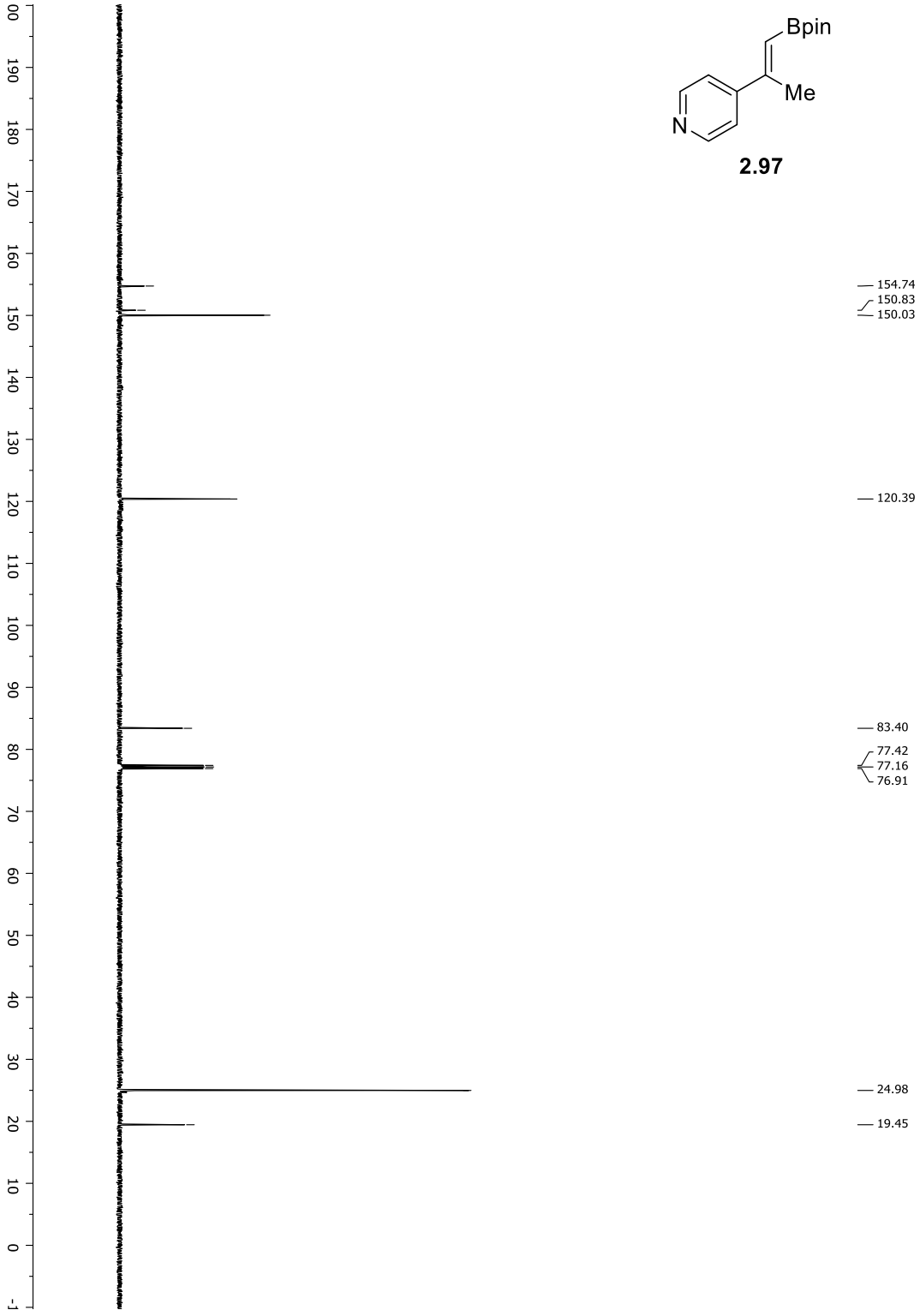

Bpin
Me
Me
2.95
4.30
0.08
1.00
3.11
3.05
12.92
7.26
7.18
7.17
7.17
7.17
7.16
7.16
7.16
7.15
7.15
7.14
7.14
7.14
7.13
7.13
7.13
7.11
7.11
7.11
7.11
7.10
7.10
7.10
7.10
5.58
5.27
2.32
2.30
2.30
1.34


Bpin
Me
Me
2.95
161.14
146.90
133.63
130.22
126.83
125.57
82.99
77.37
77.16
76.95
25.04
23.12
19.96

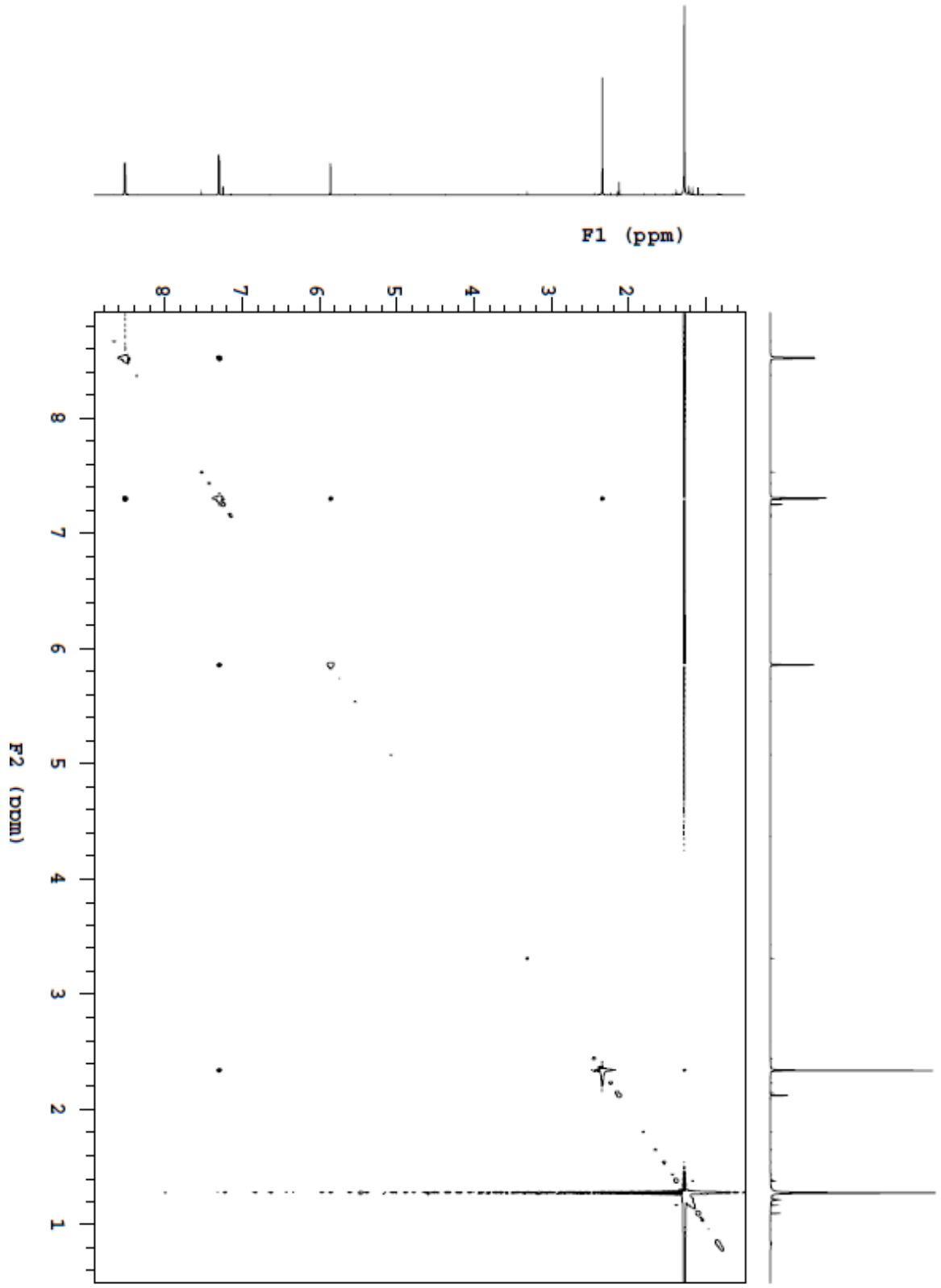
1HNMR NOESY for compound **2.95**

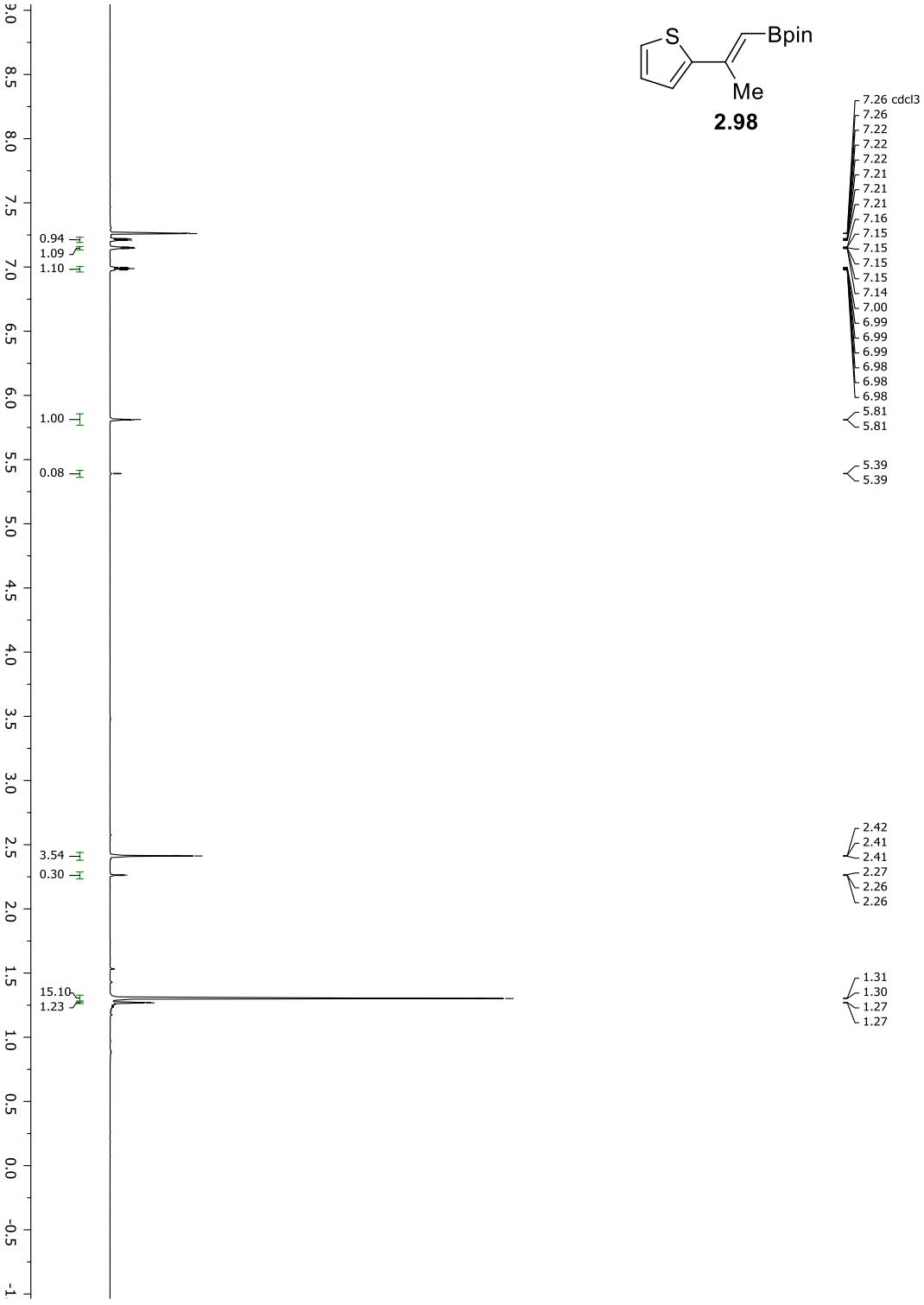


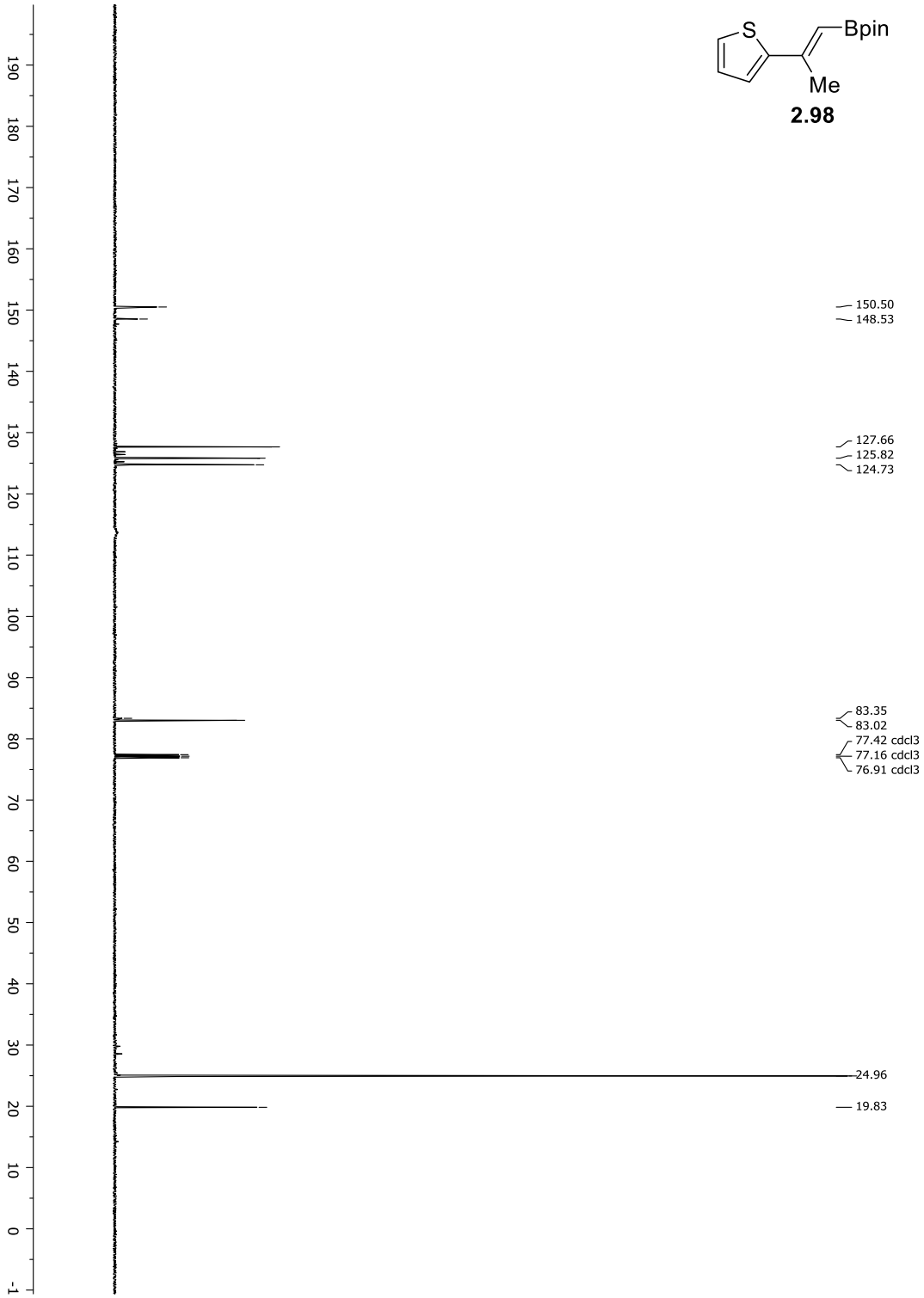

Bpin
Me
N
2.97
8.57
8.57
8.56
8.56
8.56
7.35
7.35
7.34
7.34
7.33
7.26
7.26
5.90
2.38
1.32
1.95
2.05
1.00
3.23
13.06

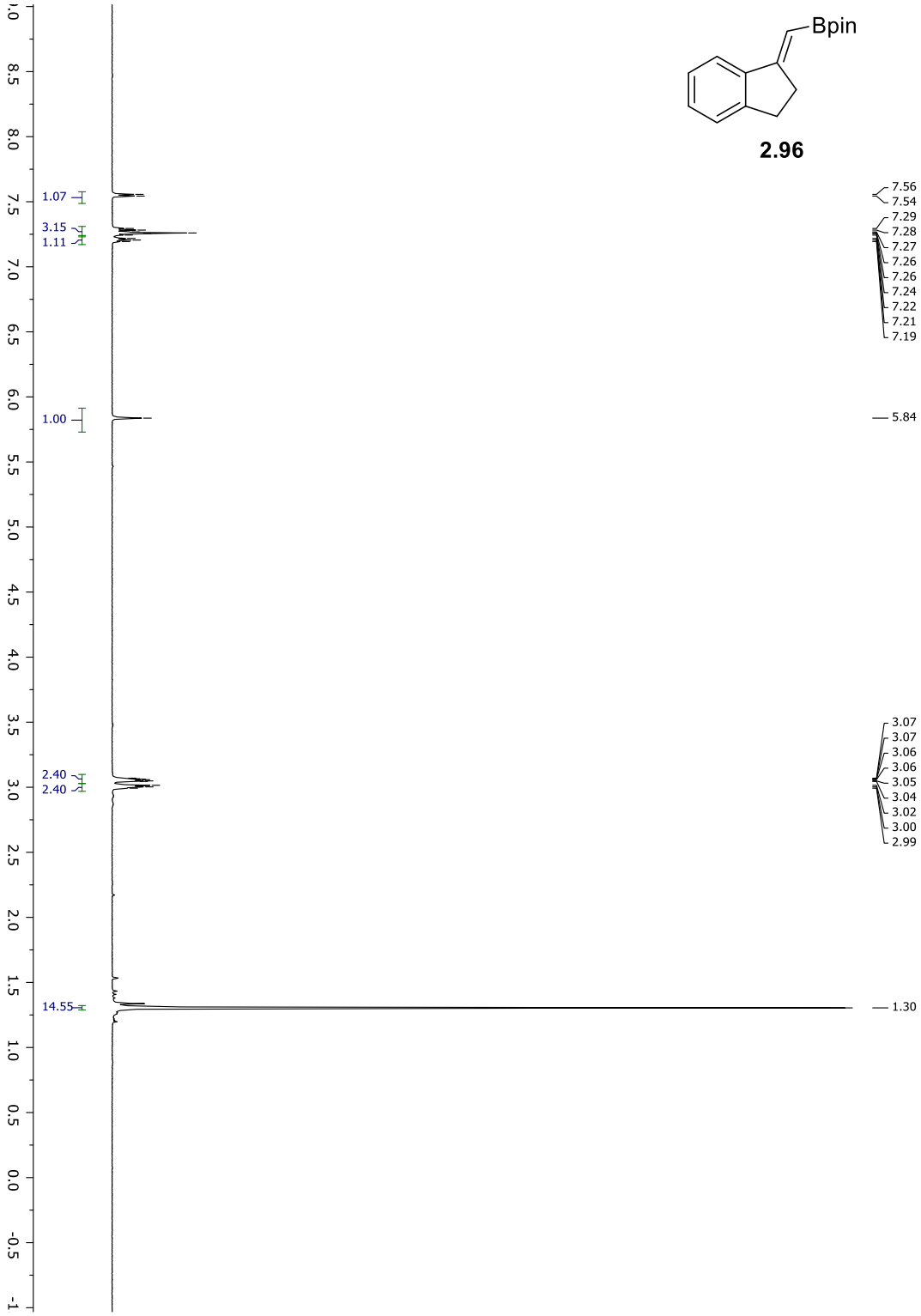

Bpin
Me
N
2.97
154.74
150.83
150.03
120.39
83.40
77.42
77.16
76.91
24.98
19.45

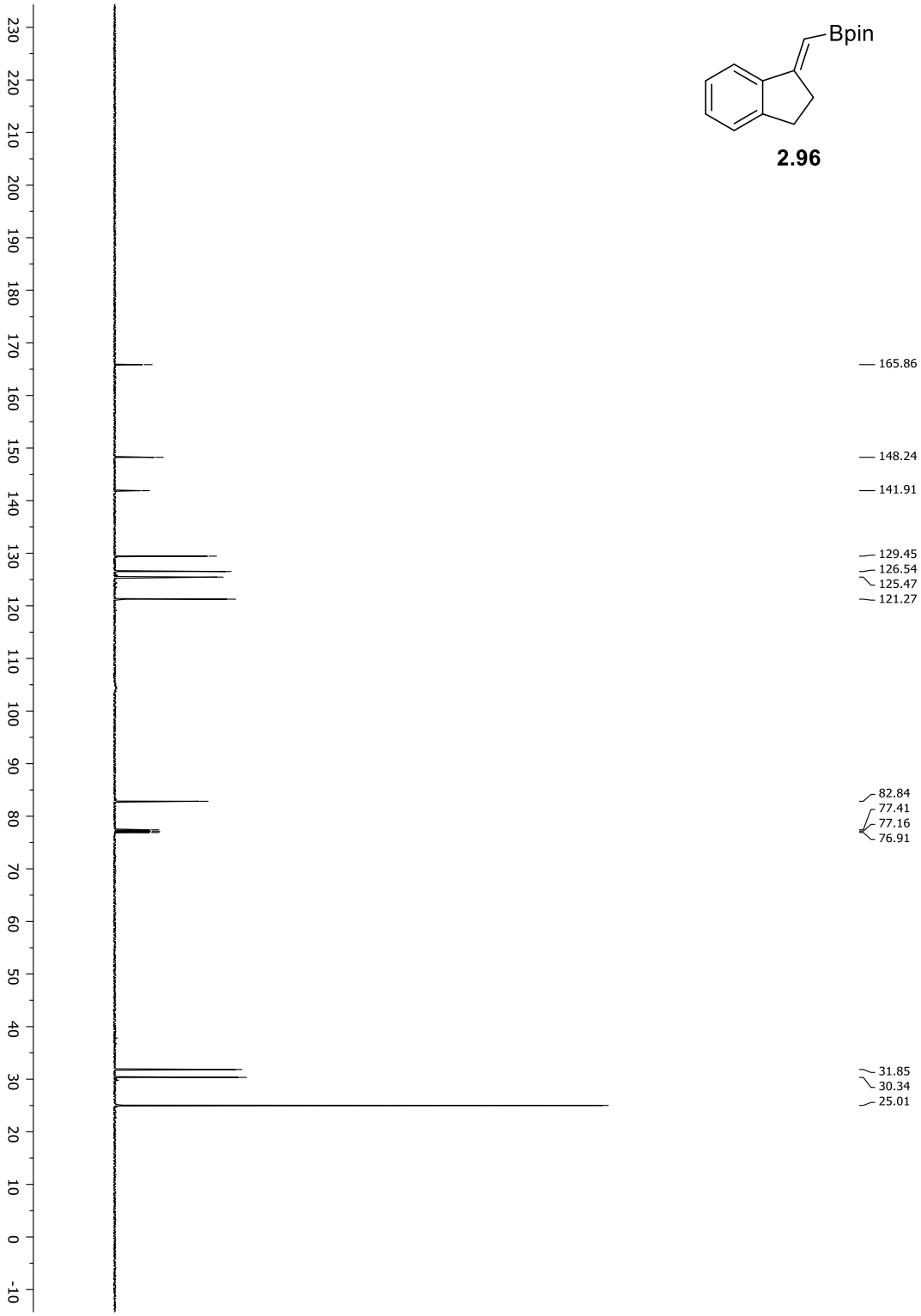
^{1}HNMR NOESY for compound **2.97**



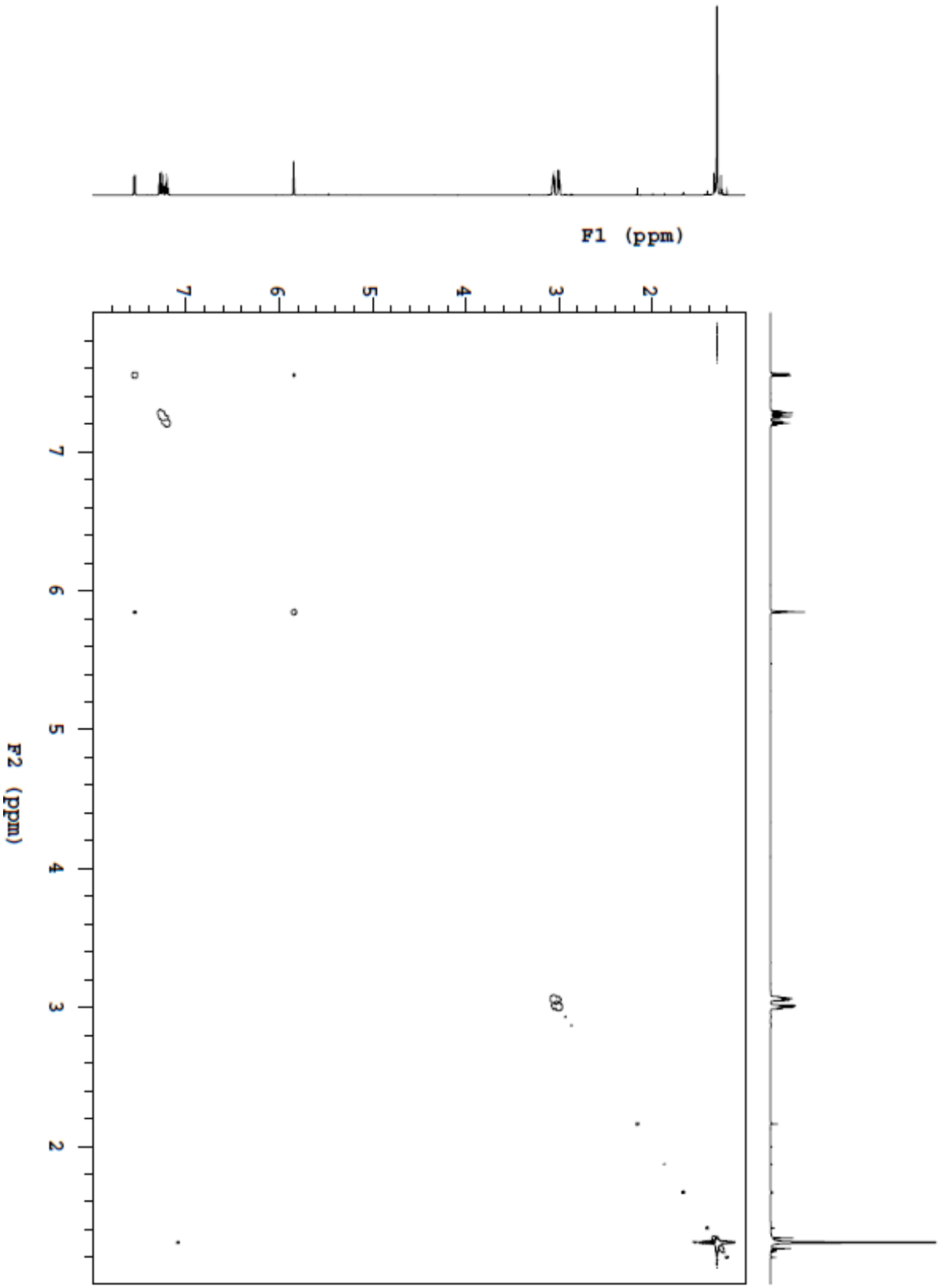

S
Bpin
Me
2.98
7.26 cdcl3
7.26
7.22
7.22
7.22
7.21
7.21
7.21
7.16
7.15
7.15
7.15
7.15
7.14
7.00
6.99
6.99
6.99
6.98
6.98
6.98
5.81
5.81
5.39
5.39
2.42
2.41
2.41
2.27
2.26
2.26
1.31
1.30
1.27
1.27
0.94
1.09
1.10
1.00
0.08
3.54
0.30
15.10
1.23
3.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1

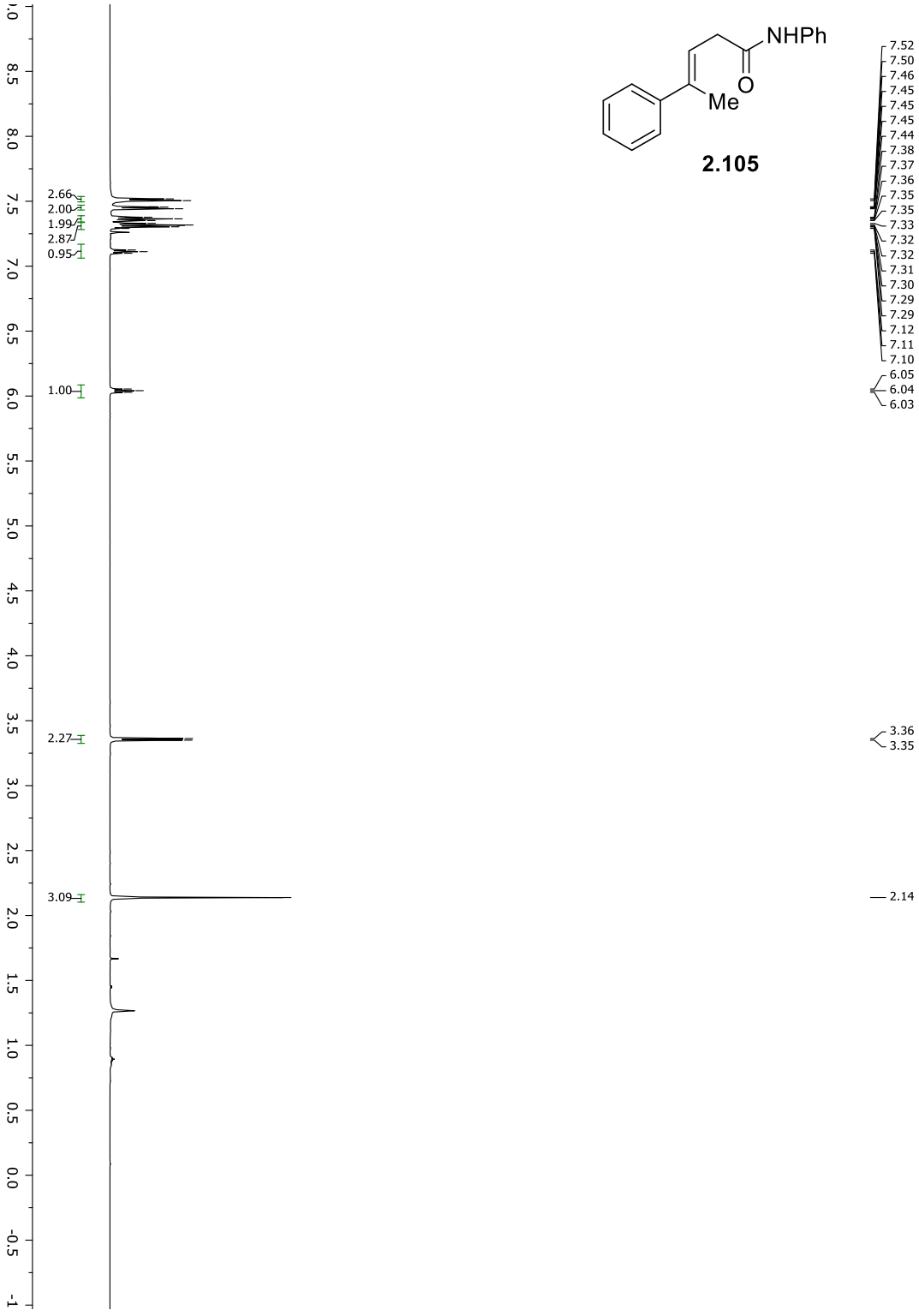

S
Bpin
Me
2.98
150.50
148.53
127.66
125.82
124.73
83.35
83.02
77.42 cdcl3
77.16 cdcl3
76.91 cdcl3
24.96
19.83
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1

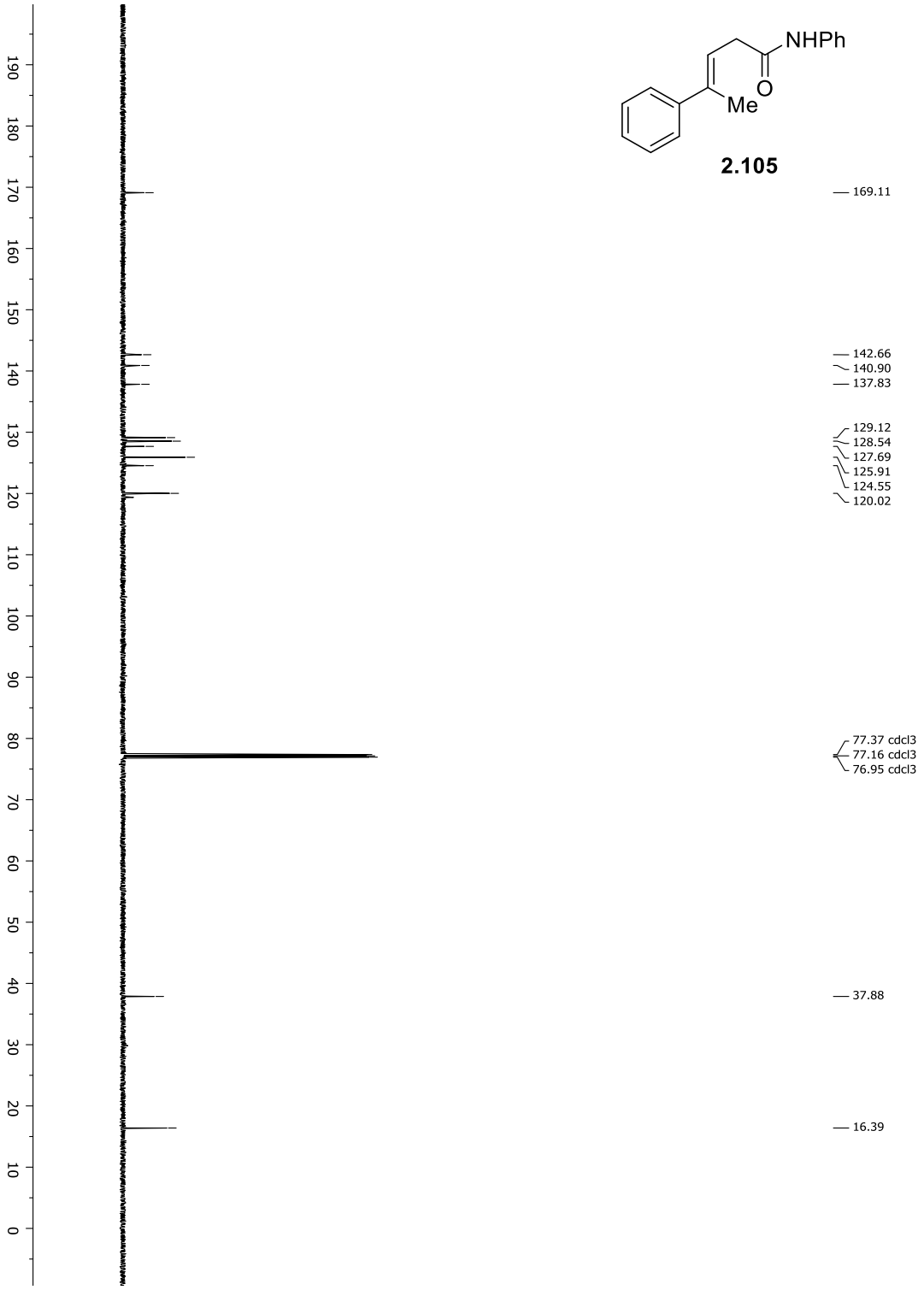

Bpin
2.96
1.07
3.15
1.11
1.00
2.40
2.40
14.55
7.56
7.54
7.29
7.28
7.27
7.26
7.26
7.24
7.22
7.21
7.19
5.84
3.07
3.07
3.06
3.06
3.05
3.04
3.02
3.00
2.99
1.30


Bpin
2.96
165.86
148.24
141.91
129.45
126.54
125.47
121.27
82.84
77.41
77.16
76.91
31.85
30.34
25.01

^{1}HNMR NOESY for compound **2.96**




NHPh
O
Me
2.105
2.66
2.00
1.99
2.87
0.95
1.00
2.27
3.09
7.52
7.50
7.46
7.45
7.45
7.45
7.44
7.38
7.37
7.36
7.35
7.35
7.33
7.32
7.32
7.31
7.30
7.29
7.29
7.12
7.11
7.10
6.05
6.04
6.03
3.36
3.35
2.14

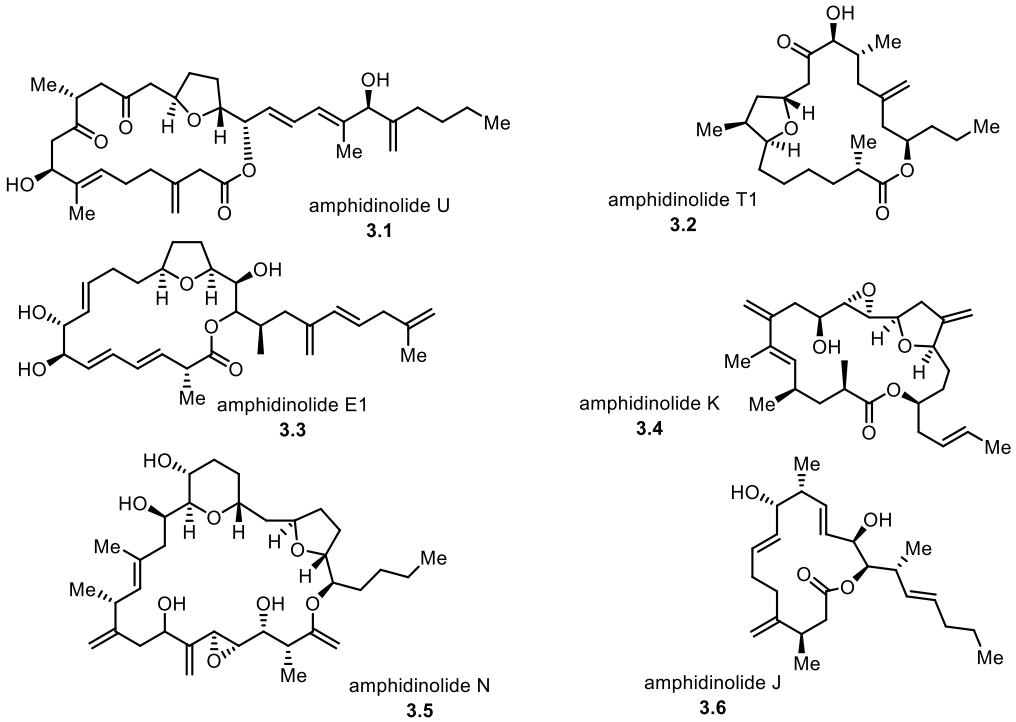

NHPh
O
Me
2.105
169.11
142.66
140.90
137.83
129.12
128.54
127.69
125.91
124.55
120.02
77.37 cdcl3
77.16 cdcl3
76.95 cdcl3
37.88
16.39

Chapter 3
Studies towards the Total synthesis of Amphidinolide C and F.

3.1 Introduction

Amphidinolides are a family of macrolide natural products isolated from dinoflagellates *Amphidinium spp.*[1] As of 2003, thirty-four macrolides had been isolated from *Amphidinium sp* by the Kobayashi group (Scheme 3.1).[1d] These are designated A-H, J-Y, G2, G3, H2-H5, T2-T5 and differ in their macrolactone core and side chains

Scheme 3.1 Representative examples of the amphidinolide family of natural products

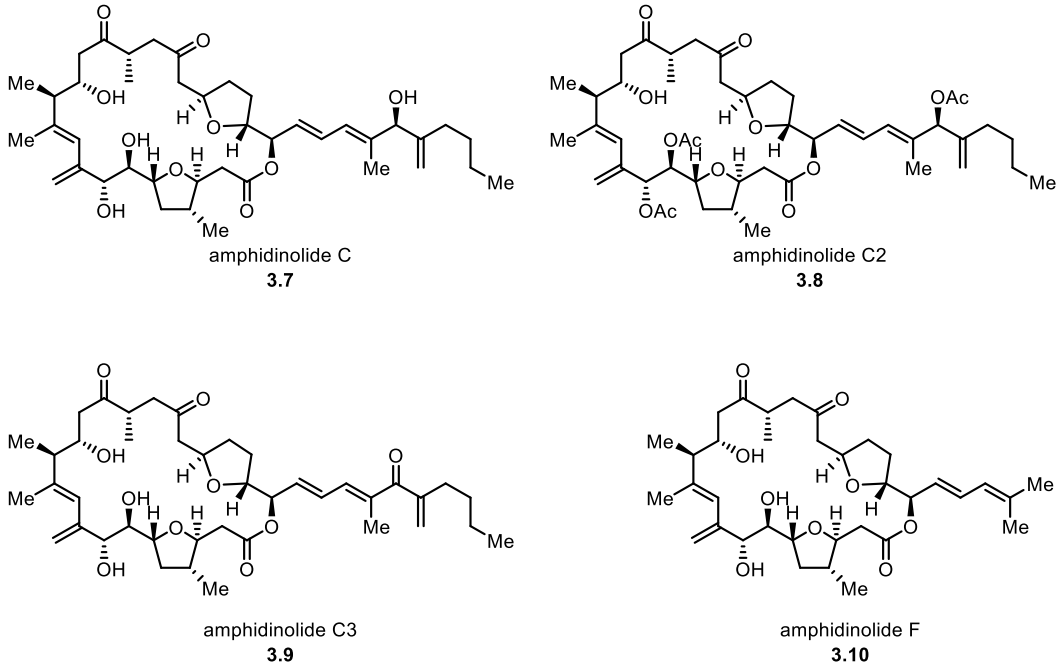


[1] (a) Kobayashi, J.; Ishibashi, M. *Chem. Rev*. **1993**, *93*, 1753. (b) Chakraborty, T. K.; Das, S. *Curr. Med. Chem*. 2**001**, *1*, 131. (c) Kobayashi, J.; Kubota, T. *J. Nat. Prod*. **2007**, *70*, 451. (d) Kobayashi, J. *J. Antibiot*. **2008**, *61*, 271.

3.2 Background

3.2.1 Isolation and structure determination of amphidinolides C, C2, C3 and F

Scheme 3.2A Amphidinolides C, C2, C3 and F

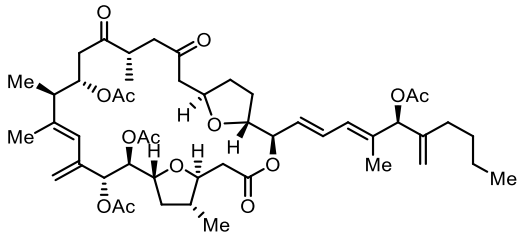


From the inner cells of Okinawan flatworm *Amphiscolops sp,* Kobayashi and co-workers isolated the symbiotic dinoflagellate Am*phidinium sp*.[2] The combined harvested cells were extracted with methanol and toluene to afford a solution that was further subjected to silica gel chromatography with methanol/chloroform and acetone/hexanes as eluents. This was followed by reversed-phase HPLC using 88% methanol as the eluents to afford amphidinolide C **(3.7)** as a colorless solid (0.0015%). Its optical rotation was found to be $[\alpha]_D^{26} = -106^o$ (c=1.0, $CHCl_3$). The molecular formula was found to be $C_{41}H_{62}O_{10}$ as determined by FABMS (M^++H, m/z 715) and HREIMS (M+-H_2O, m/z 696.4236 for

[2] Kobayashi, J.; Ishibashi, M.; Walchli, M. R.; Nakamura, H.; Hirata, Y.; Sasaki, T.; Ohizumi, Y. *J. Am. Chem. Soc.* **1988**, *110*, 490-494

$C_{14}H_{60}O_9$, Δ -10 mmu). Extensive ^{1}HNMR and ^{13}C NMR studies (NOESY, COSY, HMBC) were carried out on the tetraacetate amphidinolide C (**3.11)** to elucidate the structure of amphidinolide C (**3.7).**

Scheme 3.2B Tetraacetate amphidinolide C



tetraacetate amphidinolide C
3.11

Later, the Kobyashi group also reported the isolation and structural elucidation of amphidinolide C2 (**3.8**)[3] and amphidinolide C3 (**3.9**).[4] Amphidinolide F (**3.10**), which possess the same macrolactone as amphidinolide C but a different side chain has also been isolated and characterized in a similar manner by the Kobayashi group.[5]

[3] Kubota, T.; Sakuma, Y.; Tsuda, M.; Kobayashi, J. I. *Mar. Drugs*. **2004**, *2*, 83-87.
[4] Kobayashi, J.; Kubota, T.; Suzuki, A.; Yamada, M.; Baba, S. *Heterocycles.* **2010**, *82*, 333.
[5] Kobayashi, J.; Tsuda, M.; Ishibashi, M.; Shigemori, H.; Yamasu, T.; Hirota, H.; Sasaki, T. *J. Antibiot*. **1991**, *44*, 1259–1261.

3.2.2 Biological activity of amphidinolides C, C2, C3 and F

Amphidinolide C was the first 25-membered macrolactone that was reported to exhibit potent antineoplastic activity.[2] During their studies on amphidinolide natural products, Kobayashi and co-workers found that despite their structural similarities, amphidinolides C, C2, C3 and F exhibited remarkably different biological activities for the murine lymphoma L1210 and human epidermoid carcinoma KB cell lines.[6] **(Table 3.1).**

Table 3.1 Biological activity towards cancer cell lines

	C	C2	C3	F
L1210 (IC_{50}) μg/mL)	0.058	0.8	7.6	1.5
KB (IC_{50}) (μg/mL)	0.0046	3.0	10	3.2

Amphidinolide C is much more cytotoxic than amphidinolide F, suggesting that perhaps its side chain is responsible for the observed difference in biological activity. In addition, amphidinolide C2 and C3, which have different C(29) oxidation/ protection than amphidinolide C, have lower cytotoxicity. This observation alludes to the importance of the C(29) free hydroxyl group on the amphidinolide C side chain.

3.3 Previous Total Syntheses of amphidinolide C and F

Amphidinolides C and F have the same macrolactone skeleton but their side chains differ. Because of their difference in biological activity (Table 3.1), combined with the low isolated amounts from nature, organic chemists have gained continued interest in their total

[6] (a)Kobayashi, J.; Ishibashi, M. *Chem. Rev*. **1993**, *93*, 1753. (b) Chakraborty, T. K.; Das, S. *Curr. Med. Chem*. 2**001**, 1, 131. (c) Kobayashi, J.; Kubota, T. *J. Nat. Prod*. **2007**, *70*, 451. (d) Kobayashi, J. *J. Antibiot*. **2008**, *61*, 271.

syntheses. Various groups have attempted to synthesize different fragments[7] of amphidinolide C and F. To date, there have been two total syntheses of amphidinolide C by the Carter[8] and Fürstner[9] groups. In addition, three total syntheses of amphidinolide F have been reported in the literature by the Carter, [10] Fürstner[11] and Figadère[12] groups.

3.3.1 Total Synthesis of Amphidinolide C and F by Rich G. Carter

In 2012[12] and 2013,[10] the Carter group reported the first total syntheses of Amphidinolide F and C respectively. The Carter group utilized a similar approach to access both amphidinolide C and F where late stage Yamaguchi macrolactonization would afford the macrolactone (Scheme 3.3). The synthetically challenging C_{14} and C_{15} (in **3.12**) bond would be accessed via a series of sulfone alkylation and oxidative desulfurization reactions[13] starting from the two main fragments (**3.13** and **3.14).** The Western fragment (**3.14**) would be generated via a 1,2-addition of alkenyllithium derived from alkenyl iodide **3.15** to deliver the desired aldehyde (**3.16**). This aldehyde (**3.16**) and the Eastern fragment would be assembled from common advanced intermediate (**3.17**).

---

[7] (a) Shotwell, J. B.; Roush, W. R. *Org. Lett.* **2004**, *6*, 3865−3868. (b) Mohapatra, D. K.; Rahaman, M.; Chorghade, S.; Gurjar, M. K. Synlett. **2007**, *18*, 567−570. (c) Bates, R. H.; Shotwell, J. B.; Roush, W. R. *Org. Lett.* **2008**, *10*, 4343−4346. (d) Armstrong, A.; Pyrkotis, C. *Tetrahedron Lett.* **2009**, *50*, 3325−3328. (e)Mohapatra, D. K.; Dasari, P.; Rahaman, H.; Pal, R. *Tetrahedron Lett.* **2009**, *50*, 6276−6279. (f) Paudyal, M.P.; Rath, N. P.; Spilling, C. D. *Org. Lett.* **2010**, *12*, 2954−2957. (g) Ferrié, L.; Figadère, B. *Org. Lett.* **2010**,*12*, 4976−4979. (h) Roy, S.; Spilling, C. D. *Org. Lett.* **2010**, *12*, 5326−5329. (h) Morra, N. A.; Pagenkopf,B. L. *Org. Lett.* **2011**, *13*, 572−575. (i) Wu, D.; Forsyth, C. J. *Org. Lett.* **2013**, *15*, 1178−1181. (j) Clark, J.S.; Yang, G.; Osnowski, A. P. *Org. Lett.* **2013**, *15*, 1460−1463. (k) Clark, J. S.; Yang, G.; Osnowski, A. P.*Org. Lett.* **2013**, *15*, 1464−1467. (l) Morra, N. A.; Pagenkopf, B. L. *Tetrahedron.* **2013**, *69*, 8632−8644. (m) Morra, N. A.; Pagenkopf, B. L. *Eur. J. Org. Chem.* **2013**, 756−760.

[8] Mahapatra, S.; Carter, R. G. *J. Am. Chem. Soc.* **2013**, *135*, 10792–10803.

[9] Valot, G.; Mailhol, D.; Regens, C. S.; Omalley, D. P.; Godineau, E.; Takikawa, H.; Philipps, P.; Fürstner, A. *Chem. Eur. J*. **2015**, *21*, 2398–2408.

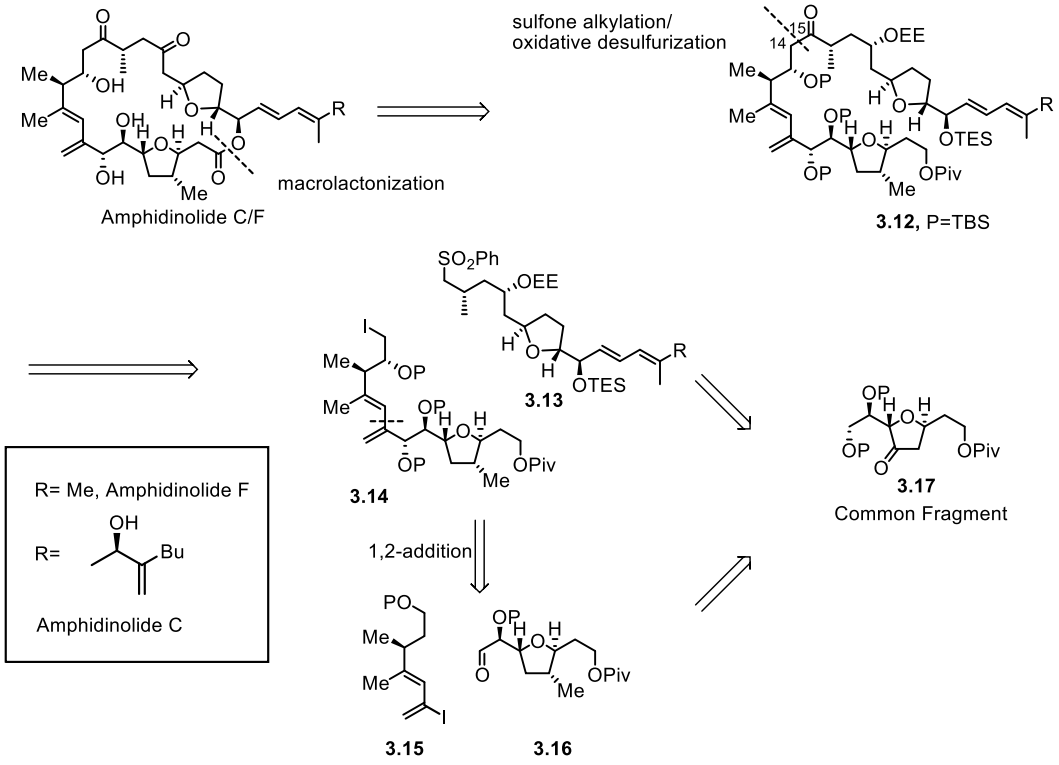
[10] Mahapatra, S.; Carter, R. G. *Angew. Chem. Int. Ed*. **2012**, *51*, 7948 –7951.

[11] Valot, G.; Mailhol, D.; Regens, C. S.; Omalley, D. P.; Godineau, E.; Takikawa, H.; Philipps, P.; Fürstner, A. *Angew. Chem. Int. Ed*. **2013**, *52*, 9534 –9538.

[12] Ferrié, L.; Fenneteau, J.; Figadère, B. *Org. Lett.* **2018**, *20*, 3192−3196.

[13] Zhou, X.-T.; Carter, R. G. *Angew. Chem., Int. Ed*. **2006**, *45*, 1787−1790.

Scheme 3.3. Carter retrosynthetic analysis of Amphidinolide C and F

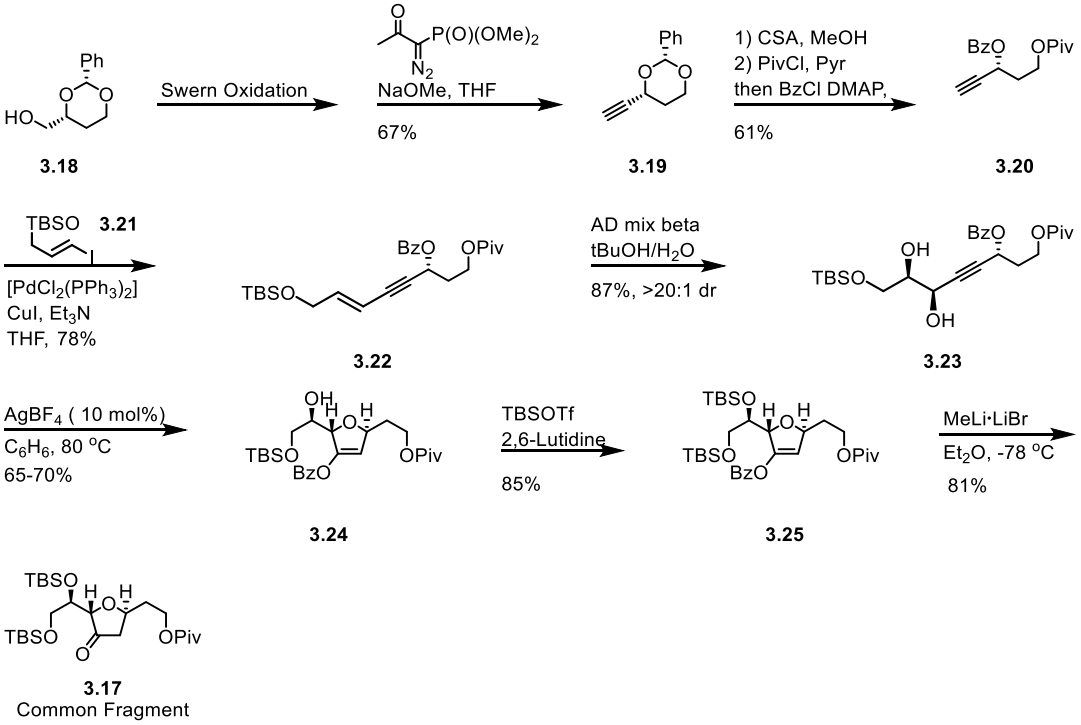


The Carter synthesis of the common precursor[12] to both Amphidinolide C and F commenced with known alcohol[14] **3.18** (Scheme 3.4). Swern oxidation of alcohol **3.18,** followed by Seyferth-Gilbert homologation produced the desired alkyne **3.19** in moderate yield. Acid-promoted acetal deprotection, pivalate protection and subsequent palladium/copper catalyzed Sonagashira cross-coupling generated desired enyne **3.22** in good yield. Sharpless asymmetric dihydroxylation afforded the desired diol **3.23** in excellent yield and diastereoselectivity. A strategic silver-catalyzed cyclization[15] was effected to deliver the trans-dihydrofuran **3.24** in synthetically useful yield and excellent

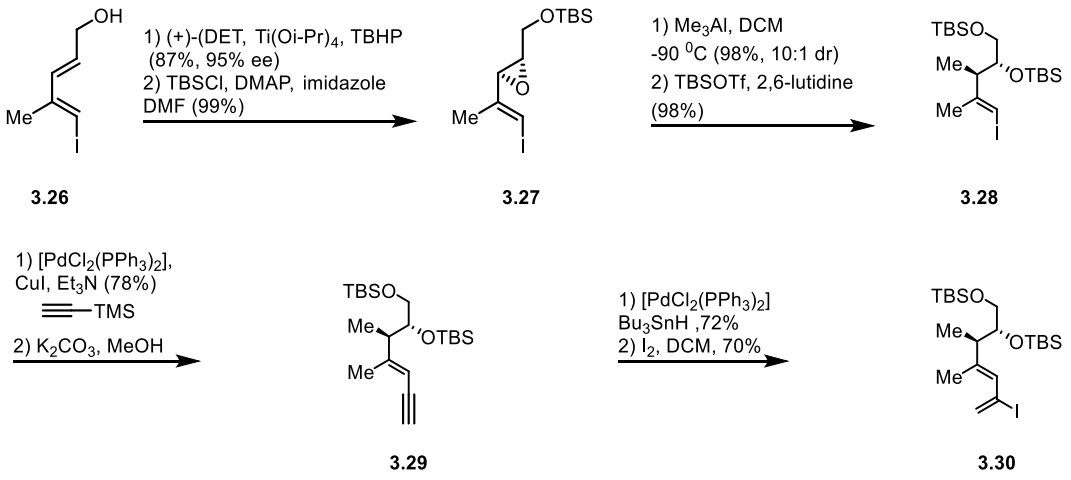
[14](a) Flögel, O.; Amombo, M. G. O.; Reißig, H.-U.; Zahn, G.; Brüdgam, I.; Hartl, *Chem. Eur. J.* **2003**, *9*, 1405–1415. (b) Herradon, B. *Tetrahedron: Asymmetry* **1991**, *2*, 191-194.
[15] Shigemasa, Y.; Yasui, M.; Ohrai, S.; Sasaki, M.; Sashiwa, H.; Saimoto, H. *J. Org. Chem*. **1991**, *56*, 910 – 912.

diastereoselectivity. Silyl protection, followed by enol benzoate removal furnished the desired common intermediate **3.17** in excellent yield.

Scheme 3.4 Synthesis of common fragment **3.17**



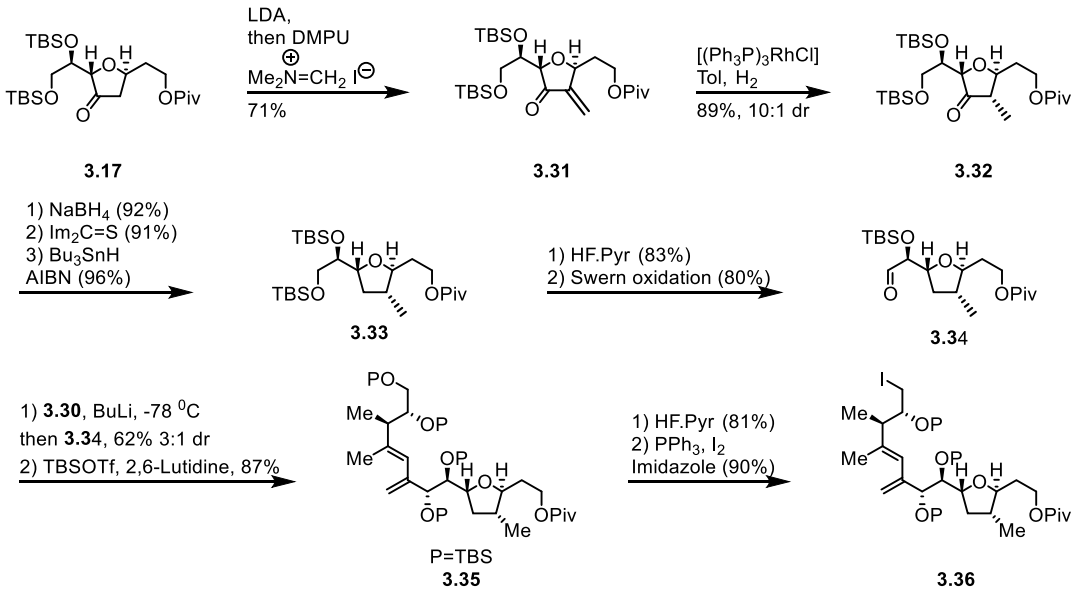
Scheme 3.5 Synthesis of Fragment **3.30**



The Carter group had previously reported synthetic effort to access fragment **3.30** (Scheme 3.5).[16] Starting from known alkenyl iodide **3.26**,[17] Sharpless asymmetric epoxidation was effected in excellent yield and enantioselectivity. This was followed by silyl protection to provide **3.27** in quantitative yield**.** A non-trivial trimethyl aluminum-mediated[18] epoxide opening satisfactorily gave the desired product in good diastereoselectivity and regioselectivity. Silyl protection afforded compound **3.28** in nearly quantitative yield. In this 2012 revised route, Carter utilized a Sonagashira cross-coupling followed by TMS deprotection to engender enyne **3.29**. The sequence was completed with a regioselective hydrostannylation that led to the desired dienyl iodide **3.30**.

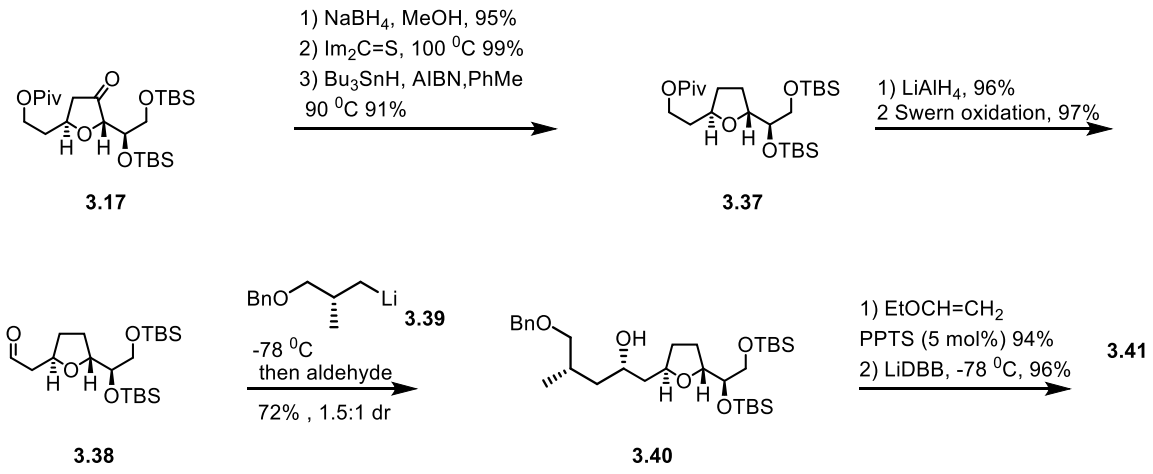
[16] Mahapatra, S.; Carter, R. G. *Org. Biomol. Chem*. **2009**, *7*, 4582 – 4585.
[17] (a) Menche, D.; Hassfeld, J.; Li, J.; Rudolph, S. *J. Am. Chem. Soc.* **2007**, *129*, 6100–6101. (b) Harris, H.; Jarowicki, K.; Kocienski, P.; Bell, R. *Synlett* 1**996**, 903–905. (c) Hanisch, I.; Bruckner, R. *Synlett*, **2000**, 374–378. (d) Yin, N.; Wang G.; Qian. M.; Negishi, E. *Angew. Chem. Int. Ed.* **2006**, *45*, 2916–2920.
[18] Shanmugam, P.; Miyashita, M. *Org. Lett.* **2003,** *5*, 3265–3268.

Scheme 3.6. Synthesis of Eastern fragment **3.36**



Methylenation of advanced intermediate **3.17** was effected using Eschenmoser's salt to afford enone **3.31** in good yield (Scheme 3.6). Subsequent hydrogenation using Wilkinson's catalyst generated compound **3.32** in 10:1 dr. Reduction of the ketone to the alcohol, followed by thiolation, and Barton-McCombie deoxygenation reliably delivered **3.33**. Deprotection of the primary silyl ether and subsequent Swern oxidation furnished the desired aldehyde **3.34** in excellent yield. Lithium-halogen exchange on dienyl iodide **3.30** gave the desired alkenyllithium which was added to aldehyde **3.34** to access the secondary alcohol in low diastereoselectivity but synthetically useful yield. The alcohol was protected as the silyl ether **3.35** in high yield. Deprotection of the primary silyl ether in **3.35** followed by Appel reaction delivered the primary alkyl iodide **3.36** in excellent yield.

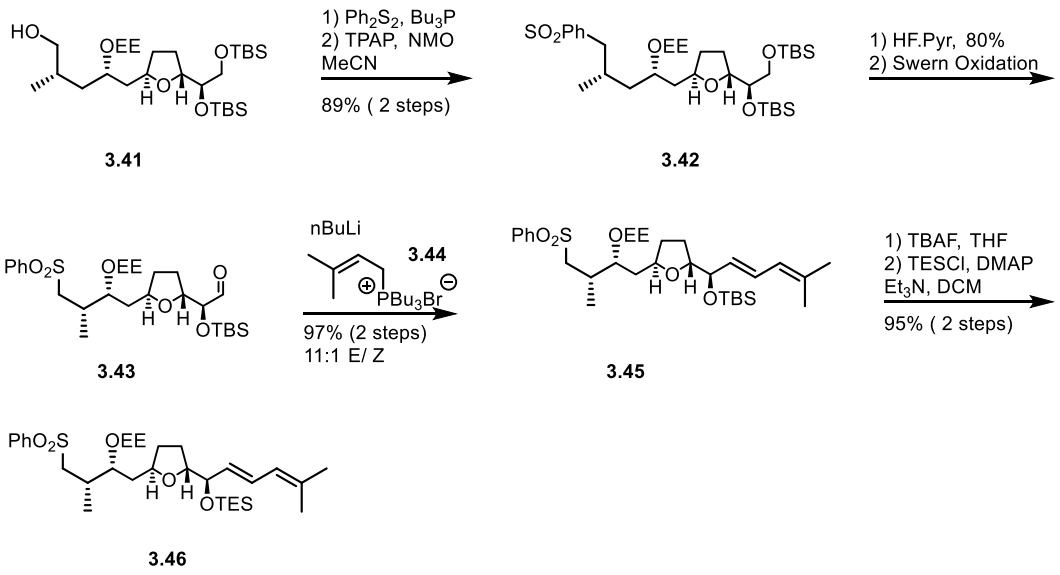
Scheme 3.7 Synthesis of fragment **3.46**



Starting from common intermediate **3.17,** sodium borohydride reduction was effected followed by thiolate formation under thermal conditions and subsequent Barton-McCombie de-oxygenation afforded the desired tetrahydrofuran **3.37** (Scheme 3.7). Pivalate deprotection and oxidation of the resulting primary alcohol yielded aldehyde **3.38,** which when reacted with organolithium[19] **3.39** gave the desired secondary alcohol **3.40** in good yield albeit with poor diastereoselectivity. Alcohol **3.40** was protected as a labile ethoxyethyl ether and subsequent debenzylation using the Freeman reagent[20] furnished the primary alcohol **3.41** in excellent yield.

[19] (a) White, D. J.; Kawaski, M. *J. Org. Chem*. **1992**, *57*, 5292 – 5300. (b) Vong, G.B.; Abraham, S.; Xiang, X. A.; Theodorakis, A. E. *Org. Lett*. **2003**, *5*, 1617 – 1620. (c) Kopecky, J.D.; Rychnovsky, D.S.; *J. Am. Chem. Soc.* **2001**, *123*, 8420 – 8421.
[20] Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *45*, 1924−1930.

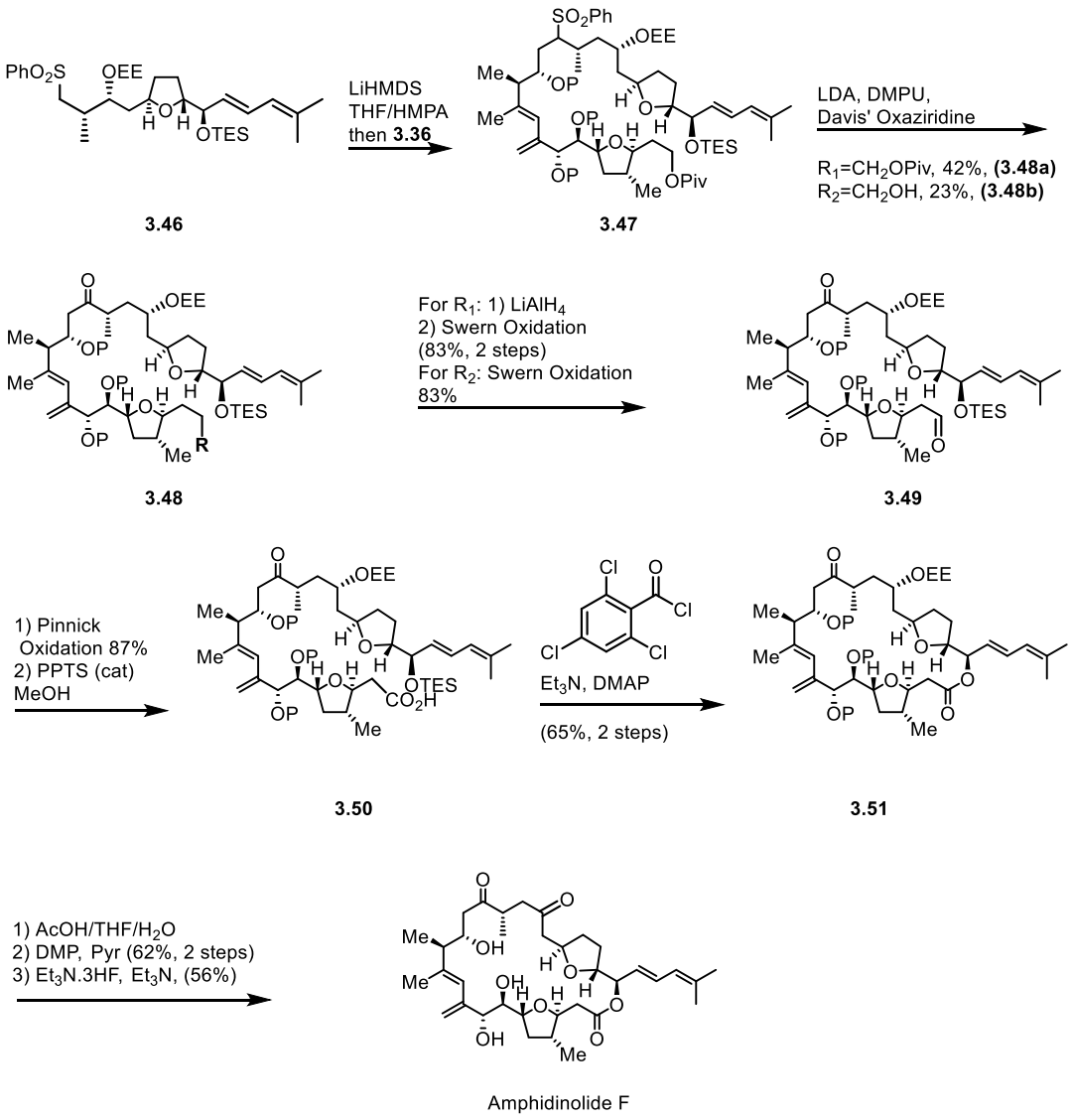
Scheme 3.8 Synthesis of fragment **3.46** continued



Thiolation, followed by oxidation of sulfur to the dioxide provided **3.42** (Scheme 3.8). Deprotection of the primary silyl ether in **3.42**, followed by Swern oxidation produced the desired aldehyde **3.43** which underwent olefination to install the side chain in compound **3.45**. Conversion of the allylic TBS ether to the TES ether afforded the desired fragment **3.46** in excellent yield.

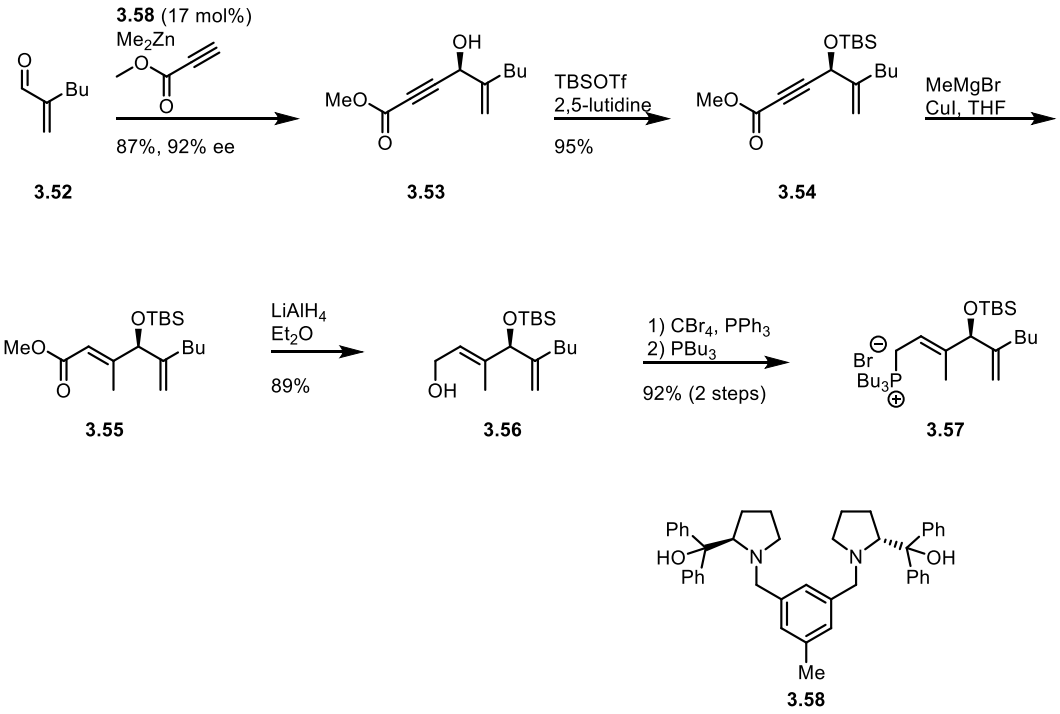
In Carter's end game assembly of amphidinolide F, sulfone **3.46** was lithiated, followed by addition of the alkyl iodide **3.36** to deliver the advanced intermediate **3.47** **(**Scheme 3.9). Oxidative desulfurization furnished a mixture of **3.48a** and **3.48b** which were converted to the corresponding aldehyde **3.49**. Pinnick oxidation followed by deprotection of the TES ether yielded the desired acid **3.50**. Yamaguchi esterification reliably led to macrolactone **3.51**. Subsequent deprotection of the ethoxylether and DMP oxidation assembled the 1,4-diketone and finally global silyl ether removal furnished ampidinolide F.

Scheme 3.9. Carter End Game towards the synthesis of Amphidinolide F



3.3.2 Total Synthesis of Amphidinolide C by Rich G. Carter

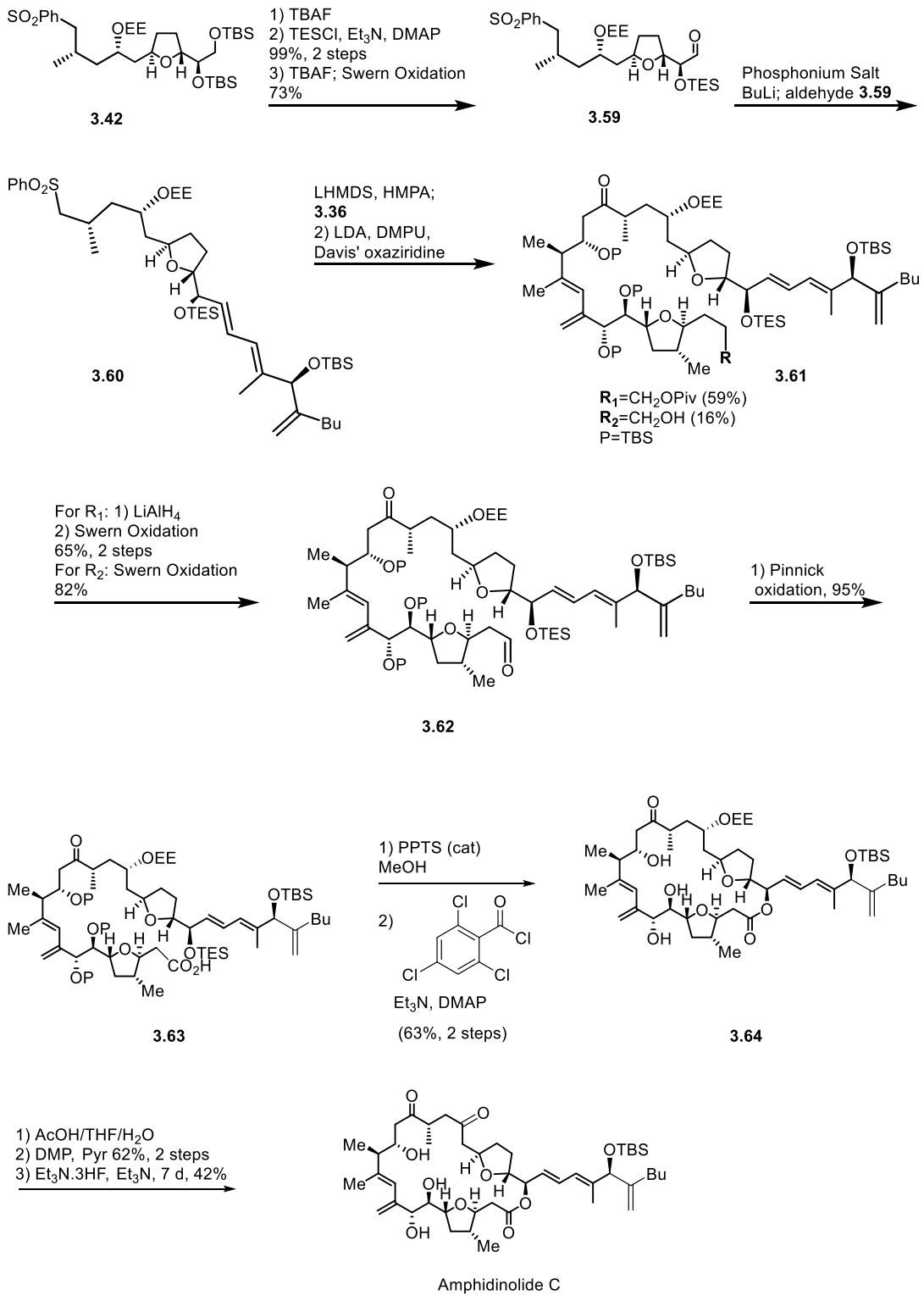
Scheme 3.10 Side chain synthesis: phosphonium salt synthesis



Known aldehyde **3.52**[21] underwent Trost asymmetric alkynylation[22] to generate the desired enantiomerically enriched propagyl alcohol **3.53** (Scheme 3.10). Silyl protection followed by organocuprate conjugate addition gave the desired (*E)*-alkene **3.55** as the sole diastereomer. Reduction of the ester **3.55** to afford the primary alcohol **3.56** proceeded in excellent yield, followed by bromination and nucleophilic displacement generated the tributylphosphonium salt **3.57**.

[21] Ragoussis, V.; Giannikopoulos, A.; Skoka, E.; Grivas, P. *J. Agric. Food. Chem*. **2007**, *55*, 5050−5052.
[22] Trost, B. M.; Weiss, A. H.; Wangelin, A. K.-V. *J. Am. Chem. Soc.* **2006**, *128*, 8−9.

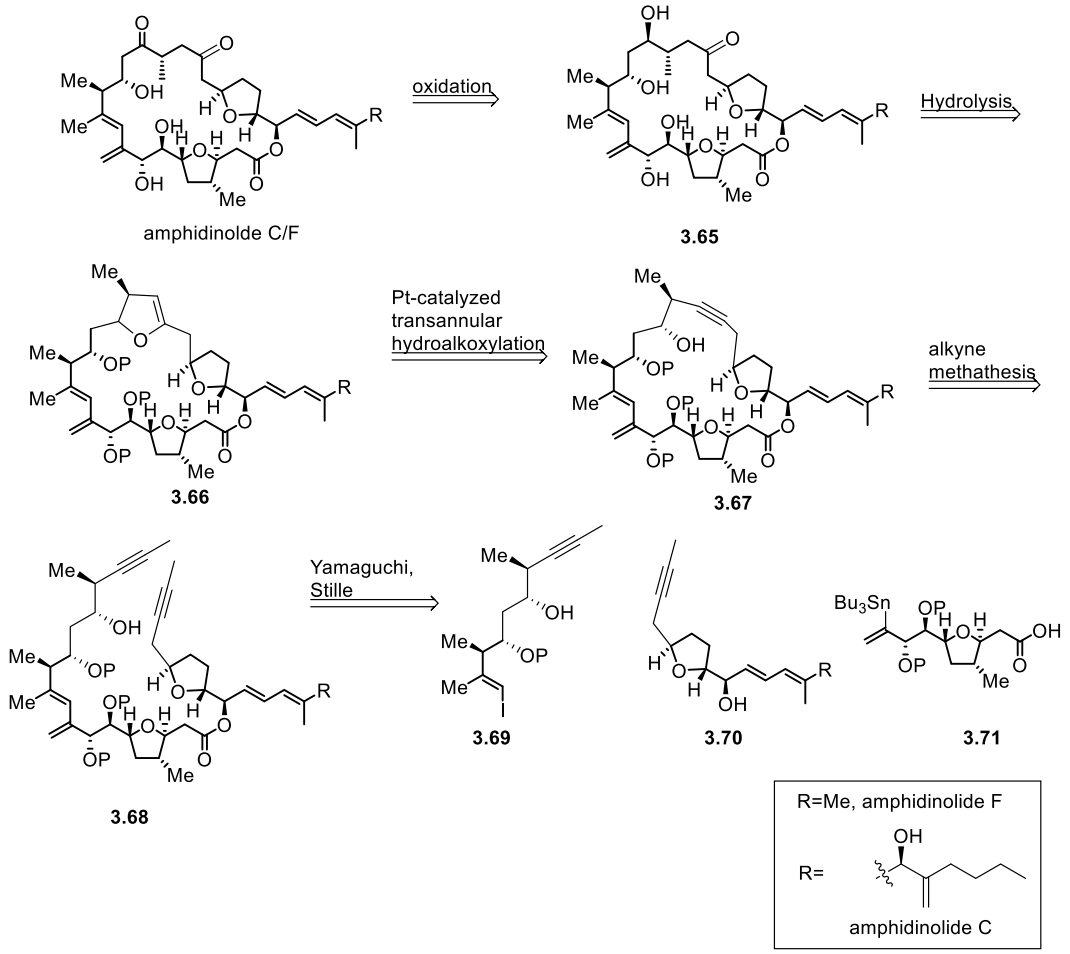
Scheme 3.11. End game enroute to amphidinolide C by Carter



Global TBAF deprotection of **3.42,** followed by bis TES protection, deprotection of the primary TES ether and subsequent Swern oxidation furnished aldehyde **3.59** in good yield. The subsquent end game steps for amphidinolide C are synonymous to those described above for amphidinolide F (Scheme 3.11).

3.3.3 Total synthesis of amphidinolide F and C by Alois Fürstner

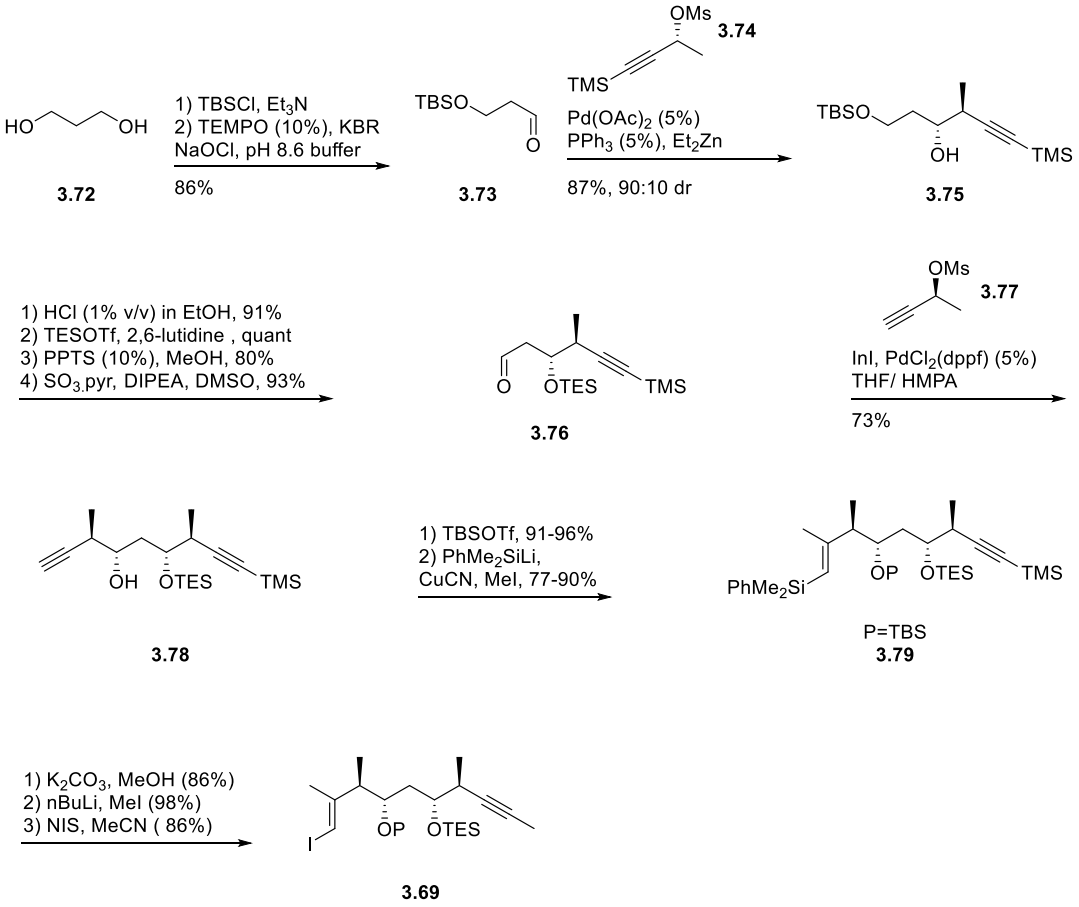
Scheme 3.12 Fürstner retrosynthetic analysis of amphidinolide C and F



To access both amphidinolide C and F, the Fürstner group sought to adopt nearly identical approaches to both molecules due to the similarity of their macrolactone core.[11]

To complete the targets, they envisioned a late stage oxidation of **3.65** (Scheme 3.12). This was proceeded by hydrolysis of dihydrofuran **3.66**. Platinum-catalyzed transannular hydroalkoxylation of **3.67** would provide **3.66** while **3.67** would be generated from alkyne metathesis of **3.68**. Stille cross-coupling of **3.69** and **3.70**, followed by Yamaguchi esterification with fragment **3.71** would deliver the desired advanced intermediate **3.68**

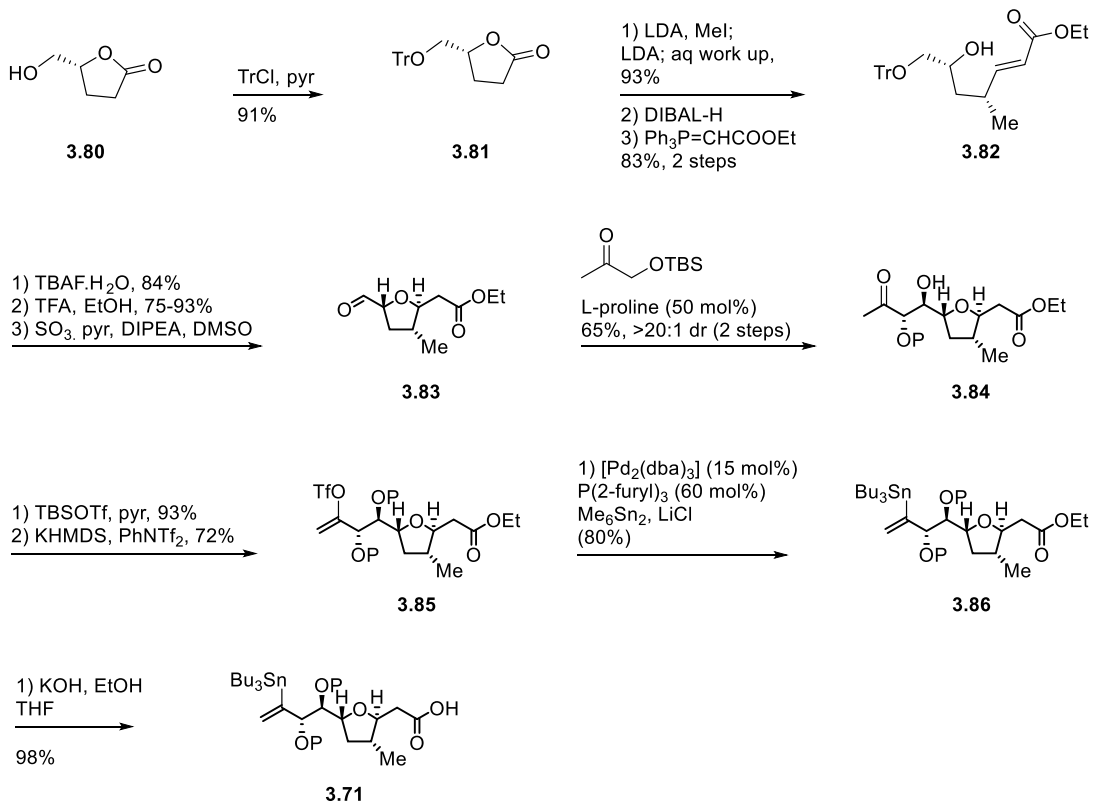
Scheme 3.13. Fragment synthesis



Propane-1,3-diol (**3.72**) was mono silyl protected, followed by oxidation to generate the corresponding aldehyde (**3.73**) (Scheme 3.13). This underwent an *anti*-propagylation to deliver **3.75** in good diastereoselectivity and excellent yield**.** Compound **3.75** was further transformed into the corresponding aldehyde **3.76** after a series of

protecting group manipulations and oxidation. Aldehyde **3.76** was subjected to propargylation to produce the dialkyne **3.78**. Subsequent silyl protection proceeded in high yield, and this was followed by silylcupration and methyl iodide quench to afford **3.79**. Compound **3.79** underwent TMS deprotection to provide the corresponding alkyne that was alkylated and subsequently converted the alkenylsilane to the alkenyl iodide to access **3.69.**

Scheme 3.14. Amphidinolide C and F southern fragment synthesis



Commercially available lactone **3.80**[23] was trityl protected to afford **3.81** (Scheme 3.14). Compound **3.81** was alkylated, the lactone moiety was reduced to the corresponding

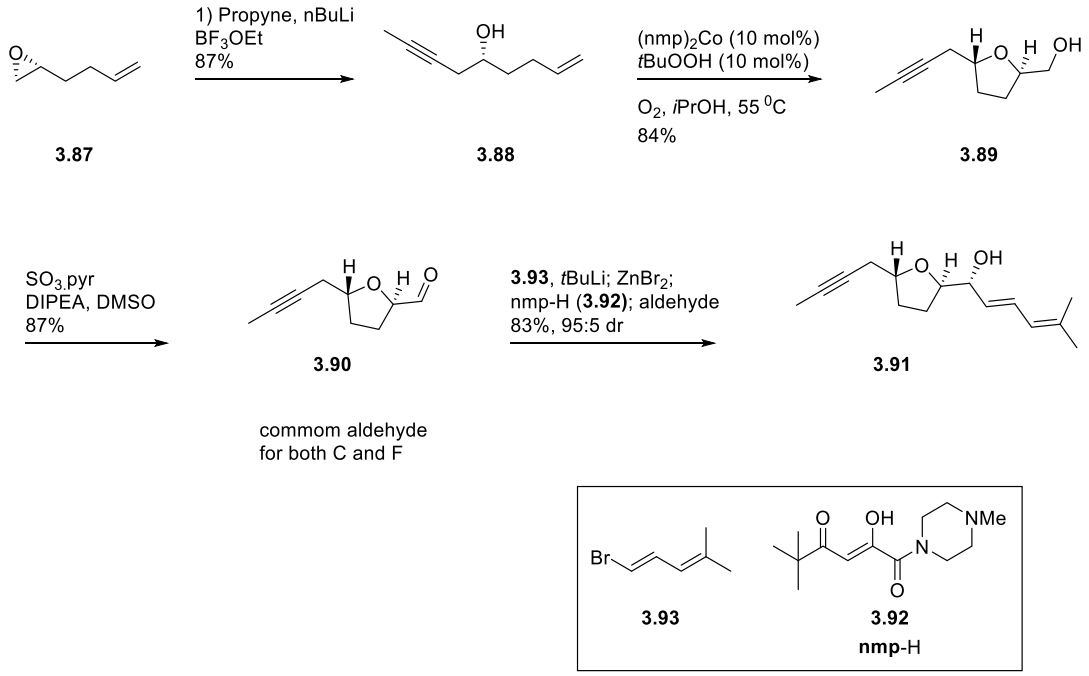
[23] Cai, X.; Chorghade, S.M.; Fura, A.; Grewal, S. G.; Jauregui, A.K.; Lounsbury, A. H.; Scannell, T. R.; Yeh, C. G.;Young, A. M.; Yu, S.; Guo, L.; Moriarty, M. R.; Penmasta, R.; Rao, S. M.; Singhal, K. R.; Song, Z.; Staszewski, P. J.; Tuladhar, M. S.; Yang, S. *Org. Process Res. Dev*. **1998**, *2*, 73–76.

aldehyde and further olefinated to afford the desired enone **3.82** in high yield. TBAF mediated oxo-Michael addition proceeded in high yield, followed by deprotection of the trityl group and oxidation to prepare the corresponding aldehyde **3.83** which was not isolated but carried forward as the crude material. A proline-catalyzed aldol reaction on aldehyde **3.83** yielded the desired anti-aldol compound **3.84** in excellent diastereoselectivity. Silyl protection of the secondary alcohol and conversion of ketone to the alkenyl triflate afforded compound **3.85.** Palladium-catalyzed stannanation afforded the alkenyl stannane **3.86**. This was further subjected to saponification to furnish the corresponding carboxylic acid (**3.71**) in nearly quantitative yield.

Enantiopure epoxide[24] **3.87** was opened using propynyllithium to afford the desired alcohol **3.88** (Scheme 3.15). This was subjected to an intramolecular cobalt-catalyzed oxidative cyclization[25] to synthesize the desired trans-tetrahydrofuran ring **3.89** in good yield and nearly perfect diastereoselectivity. Oxidation of the primary alcohol generated aldehyde **3.90** and this reacted with the organozinc derived from alkenyl bromide **3.93** to deliver **3.91** in great yield and diastereoselectivity.

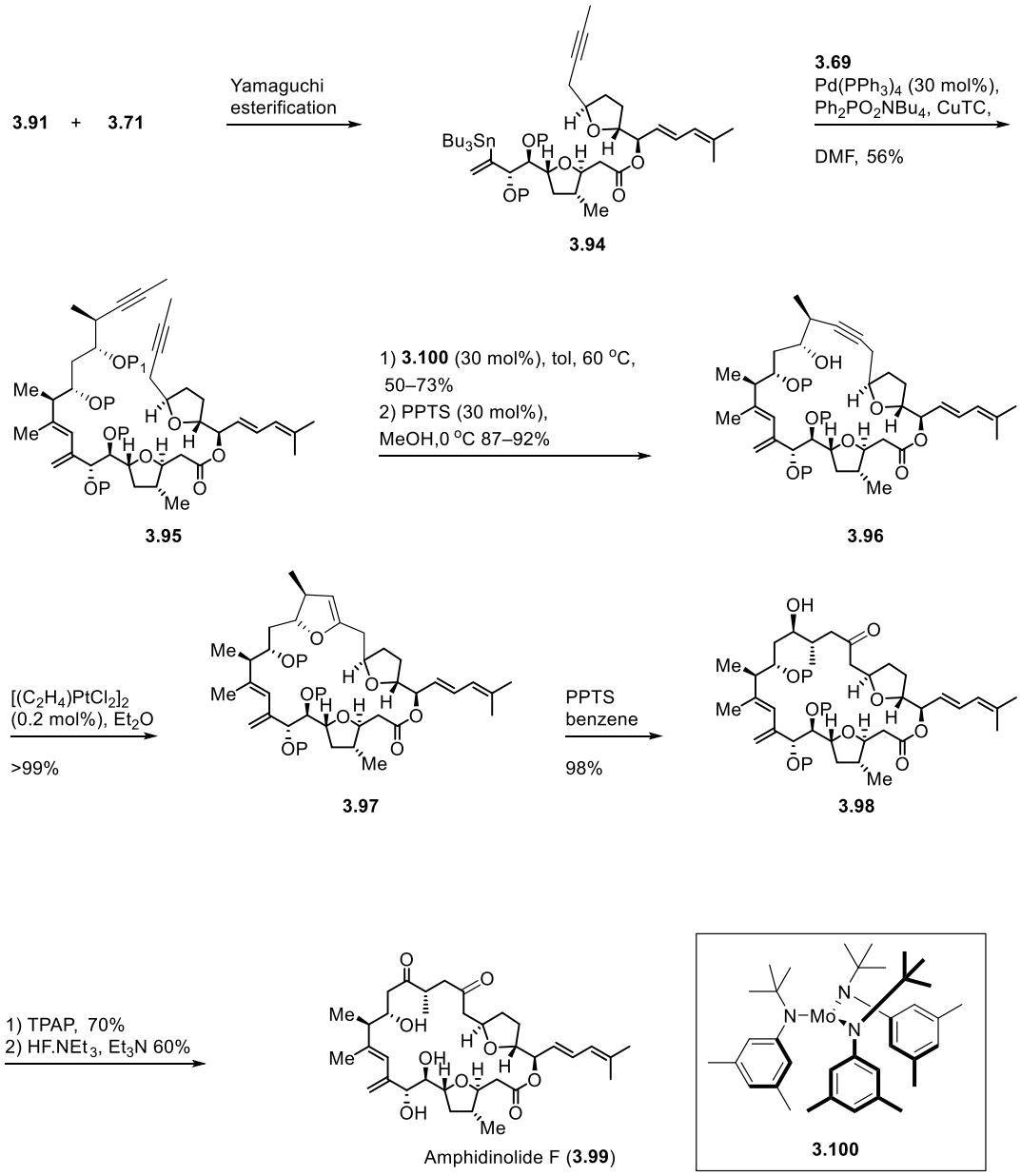
[24] Tokunaga, M.; Larrow,F.J.; Kakiuchi, F.; Jacobsen, N. E. *Science*, 1**997**, *277*, 936 –938 (b) Keith, M.J.; Larrow, F.J.; Jacobsen, N. E. *Adv. Synth. Catal*. **2001**, *343*, 5 –26.
[25] (a) Palmer, C.; Morra, A. N.; Stevens, C. A.; Bajtos, B.; Machin, P. B. (b) Pagenkopf, L. B.; *Org. Lett*. **2009**, *11*, 5614 –5617. (c) Morra, A. N.; Pagenkopf, L. B.; *Eur. J. Org. Chem*. **2013**, 756–760 (d) Inoki, S.; Mukaiyama, T. *Chem. Lett.* **1990**, 67– 70. (e) Menéndez Pérez, B.; Schuch, D.; Hartung*, J. Org. Biomol. Chem*. 2**008**, *6*, 3532–3541.

Scheme 3.15. Synthesis of amphidinolide F Eastern fragment (**3.91**) and common intermediate THF ring (**3.89**) for amphidinolide C- Fürstner

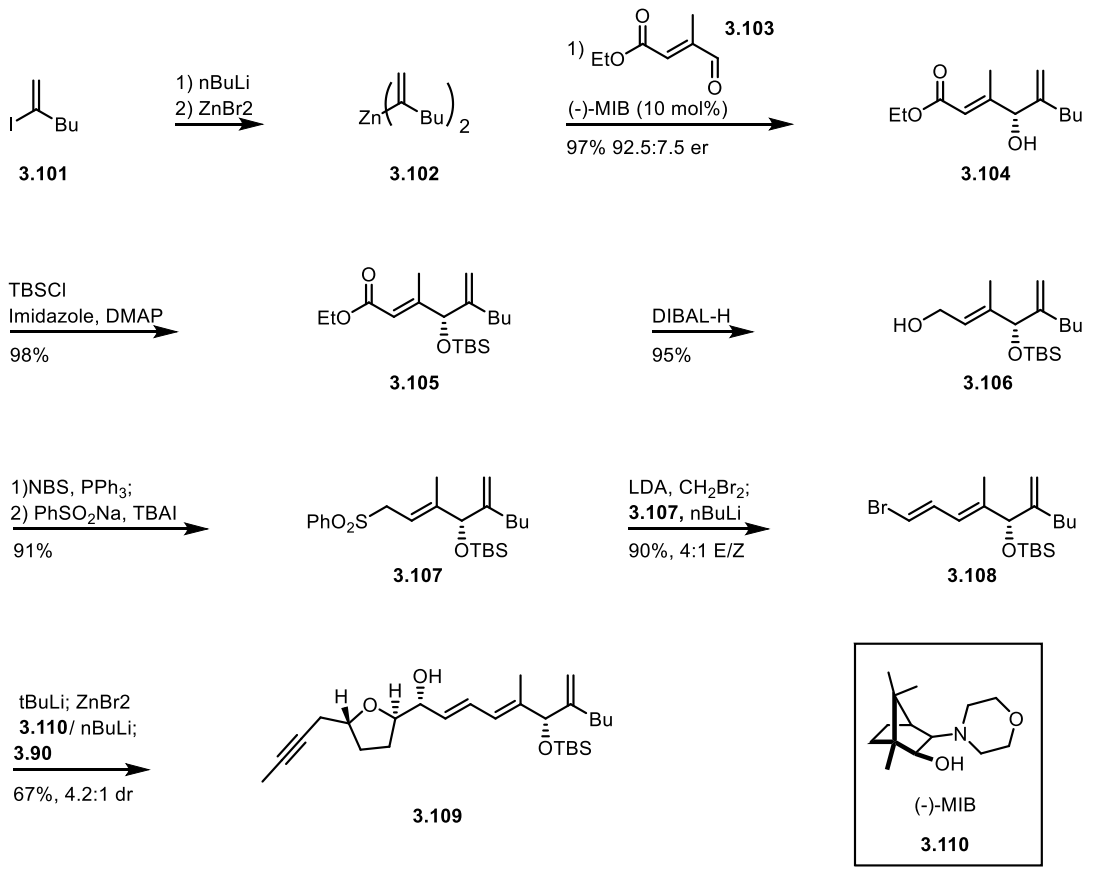


To accomplish the end game for Amphidinolide F, a Yamaguchi esterification between **3.91** and **3.71** generated advanced intermediate **3.94** (Scheme 3.16). Compound **3.94** underwent a Stille cross-coupling with **3.69** to yield *S*-cis diene **3.95** in moderate yield. Alkyne metathesis followed by TES deprotection generated compound **3.96**. Platinum-catalyzed transannulation yielded dihydrofuran **3.97** in quantitative yield. Compound **3.97** was subjected to a mild hydrolysis to prepare the 1,4-dioxygenation pattern in **3.98** quantitatively. Oxidation of the primary alcohol resulted in the 1,4-diketone and global deprotection of the silyl ether generated the desired amphidinolide C.

Scheme 3.16. Fürstner fragment synthesis continued and end game for amphidinolide F

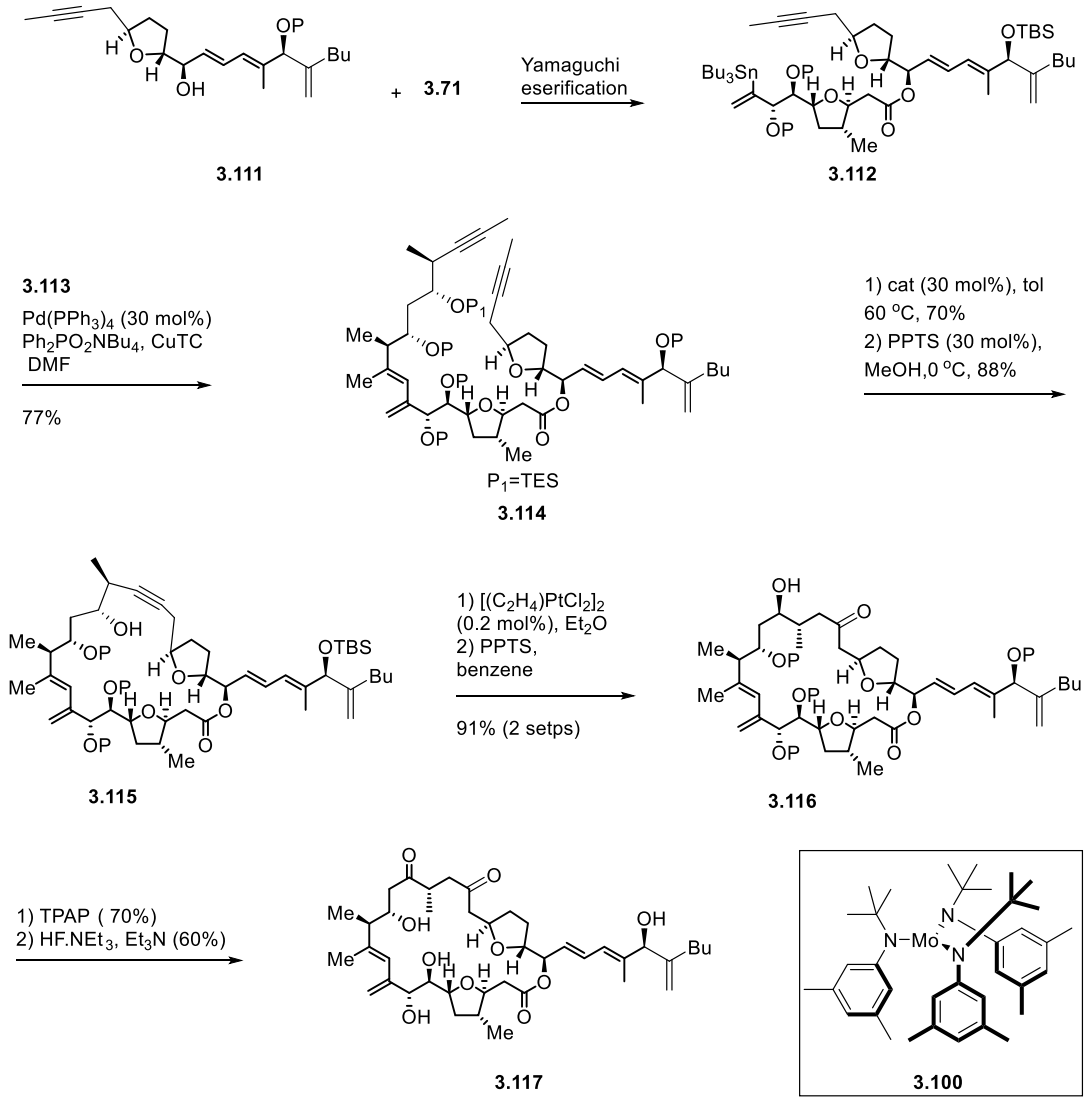


Scheme 3.17. Synthesis of side chain for amphidinolide C and Eastern fragment.



Alkenyl iodide **3.101**, was converted to the dialkenyl organozinc **3.102** and subjected to an asymmetric 1,2-addition to prepare the bis allyl alcohol **3.104** in great yield and enantioselectivity (Scheme 3.17). Silyl protection of alcohol **3.104** and reduction of the ester generated the allylic primary alcohol **3.106**. Bromination of **3.106** followed by nucleophilic displacement afforded sulfoxide **3.107** in great yield over two steps. Compound **3.107** was converted to the corresponding dienylbromide **3.108** in moderate diastereoselectivity. Lithium- halogen exchange was performed on **3.108**, followed by transmetallation to provide the desired organozinc that engaged in an asymmetric 1,2-addition to deliver **3.109** with the desired diastereomer as the major product.

Scheme 3.18. Fürstner end game to synthesize amphidinolide C.

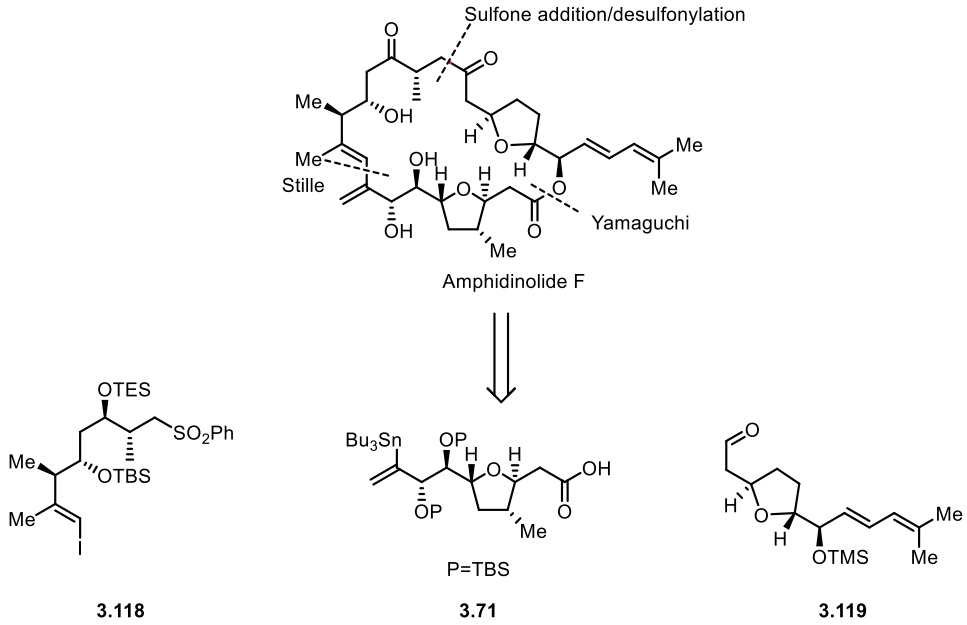


To accomplish the synthesis of amphidinolide C, Fürstner's end game utilized a Yamaguchi esterification between **3.111** and **3.71** to generate compound **3.112** (Scheme 3.18). Subsequent Stille cross-coupling with **3.113,** followed by an intramolecular ring closing alkyne metathesis were robust enough to afford **3.115**. Platinum-catalyzed transannular hydroalkoxylation followed by hydrolysis afforded **3.116** in 91% yield over

two steps**.** Oxidation of intermediate **3.116** produced the 1,4-diketone and global deprotection of the silyl ethers provided amphidinolide C.

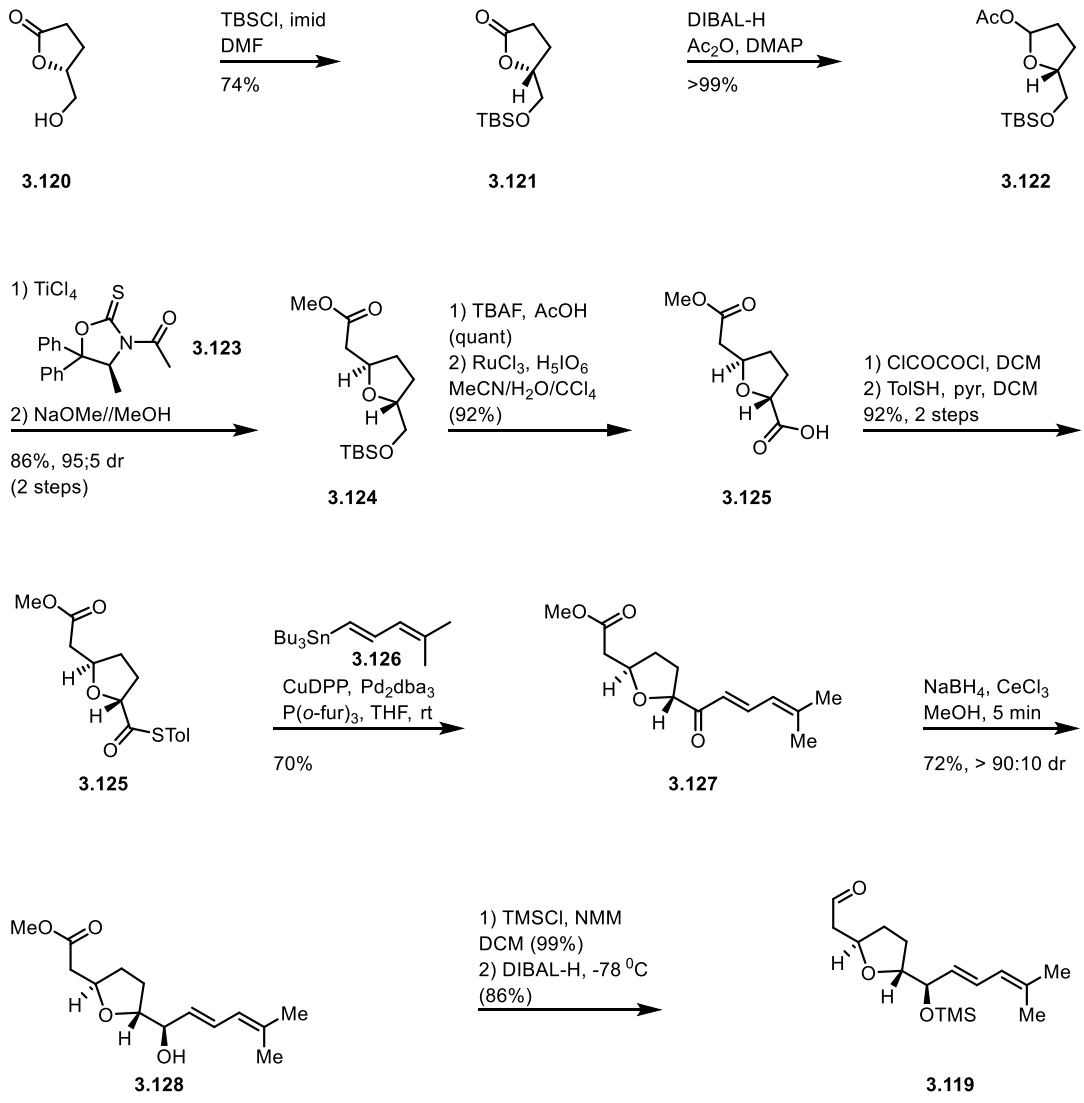
3.3.4 Total synthesis of amphidinolide F by Bruno Figadère

Scheme 3.19. Retrosynthetic analysis



Figadère's retrosynthetic analysis of amphidinolide F[14] envisioned a sulfone condensation/desulfonylation protocol, a Stille cross-coupling and Yamaguchi marcolactonization to connect fragments **3.118**, **3.71** and **3.119** (Scheme 3.19).

Scheme 3.20. Eastern fragment synthesis of amphidinolide F



Known lactone[26] **3.120** was silyl protected to generate **3.121** which was reduced and subsequently acetylated to afford ketal **3.122** (Scheme 3.20). Compound **3.122** underwent C-glycosylation with the titanium enolate of bulky N-acetyloxazolidinethiones,

[26] Commercially available or prepared from (R)-glutamic acid. See:(a) Boukouvalas, J. In Encyclopedia of Reagents for Organic Synthesis; John Wiley & Sons, Ltd., **2001**. Dihydro-5-(hydroxymethyl)-2(3H)-furanone: (b) Shiro, Y.; Kato, K.; Fuji, M.; Ida, Y.; Akita, H. *Tetrahedron.* **2006**, 62, 8687−8695. (c) Cai, X.; Chorghade, M. S.; Fura, A.; Grewal, G. S.; Jauregui, K. A.; Lounsbury, H. A.; Scannell, R. T.; Yeh, C. G.; Young, M. A.; Yu, S. *Org. Process Res. Dev*. **1999**, *3*, 73−76.

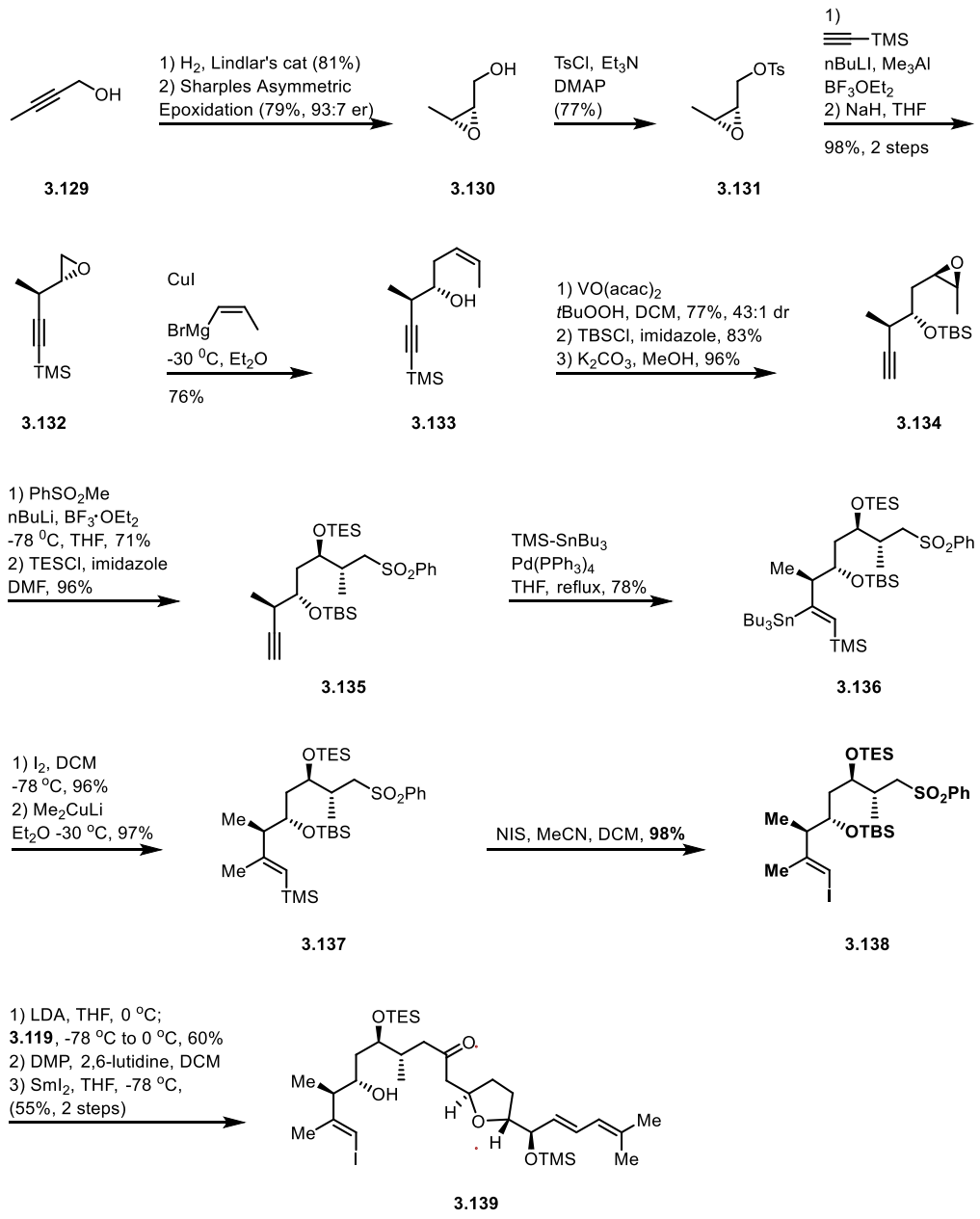
and methanolysis of the auxillary **3.123** to deliver **3.124** in excellent yield and diastereoselectivity. Silyl ether **3.124** was deprotected and the corresponding primary alcohol was oxidized to afford the carboxylic acid **3.125**. Compound **3.125** was converted to the more reactive acyl chloride and then to the thioester. At this stage, **3.125** was subjected to Liebeskind−Srogl cross-coupling[27,28] with dienyl stannane **3.126 to** generate compound **3.127**. Luche reduction of the dienone **3.127** afforded the desired alcohol **3.128** in good yield and diastereoselectivity. TMS protection of compound **3.128** proceeded quantitatively, followed by reduction of the ester to aldehyde **3.119**.

Propagyl alcohol **3.129** was reduced using Lindlar's catalyst and the corresponding allylic alcohol was subjected to a Sharpless asymmetric epoxidation to give compound **3.130** (Scheme 3.21). The primary alcohol **3.130** was activated as the tosylate and the epoxide was regioselectively opened up using TMS-acetylide. The intermediate sodium alkoxide underwent an intramolecular nucleophilic substitution to generate epoxide **3.132**. A second epoxide opening with an organocuprate produced alcohol **3.133**. A hydroxyl directed $VO(acac)_2$ epoxidation proceeded in good yield and excellent diastereoselectivity. This was followed by TBS protection and deprotection of the TMS- alkyne to deliver **3.134**. Regioselective epoxide opening and subsequent TES protection gave access to compound **3.135**. Palladium-catalyzed trimethyl silyl-stannylation of **3.135** afforded **3.136.**

[27] (a) Wittenberg, R.; Srogl, J.; Egi, M.; Liebeskind, L. S. *Org. Lett*. **2003**, 5, 3033−3035. (b) Li, H.; Yang, H.; Liebeskind, L. S. *Org. Lett*. **2008**, *10*, 4375−4378

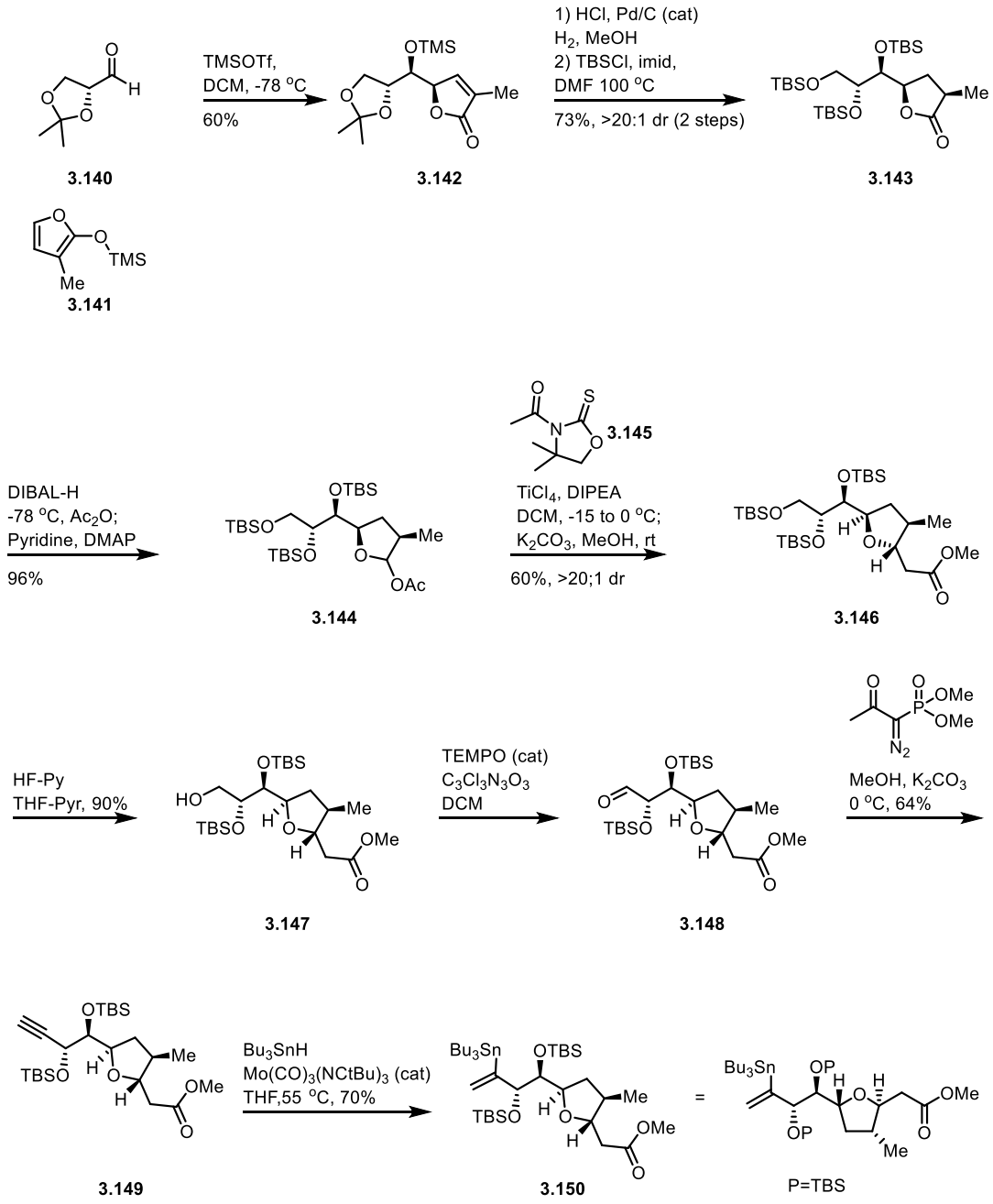
[28] Liebeskind, L. S.; Srogl, J. *J. Am. Chem. Soc.* **2000**, *122*, 11260−11261. (b) Yang, H.; Li, H.; Wittenberg, R.; Egi, M.; Huang, W.; Liebeskind, L. S. *J. Am. Chem. Soc*. **2007**, *129*, 1132−1140
(c) Prokopcová H.; Kappe, C. O. Angew. Chem. 2009, 121, 2312−2322; *Angew. Chem., Int. Ed.* **2009**, *48*, 2276−2286.

Scheme 3.21 Fragment **3.139** synthesis



Iodolyisis of **3.136** proceeded in excellent yield. The iodide was displaced by dimethylcuprate to engender compound **3.137**. The alkenyl TMS was then converted to the desired alkenyl iodide **3.138**. Carefully orchestrated sulfonylation, followed by desufonylation of **3.138** delivered the desired advanced intermediate **3.139**.

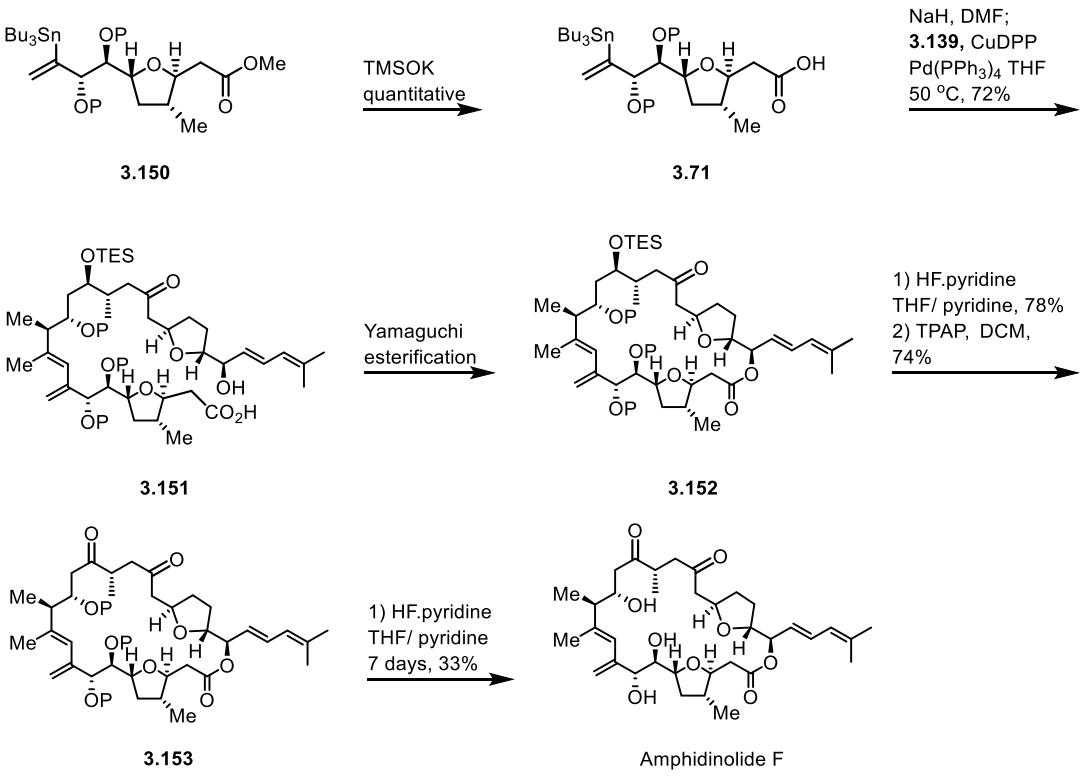
Scheme 3.22. Southern fragment synthesis



A vinylogous aldol reaction between **3.140** and **3.141** enabled the assembly of **3.142** in synthetically useful yield (Scheme 3.22). Hydrogenation of **3.142** under acidic medium in methanol and subsequent silyl protection afforded the tris silyl ether **3.143** in excellent diastereoselectivity and good yield. Lactone **3.143** was reduced and subsequently

acetylated to generate **3.144** in excellent yield. C-glycosylation of **3.144**, followed by methanolysis transformed it into compound **3.146** in excellent diastereoselectivity. Selective deprotection of the primary TBS ether in **3.146** afforded **3.147,** which was oxidized to aldehyde **3.148**. Compound **3.148** was transformed into alkyne **3.149** using the Bestmann-Ohira reagent. Regioselective hydrostannation of **3.149** generated alkenyl stannane **3.150**.

Scheme 3.23 Amphidinolide F end game



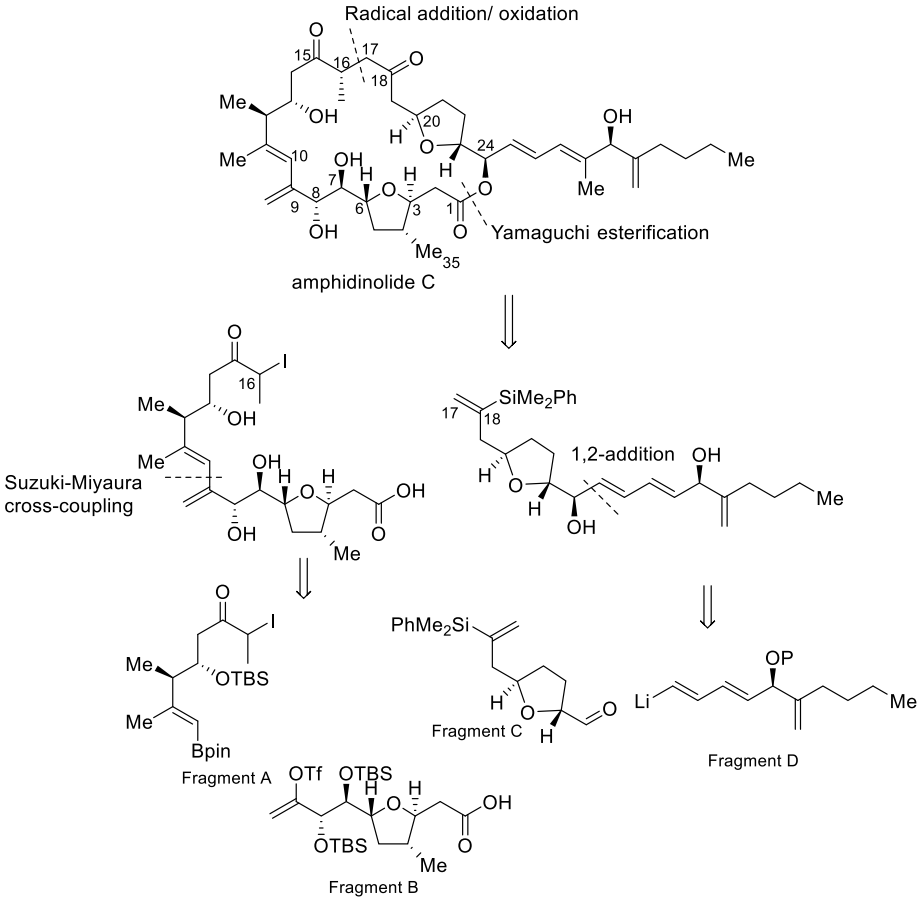
To accomplish the total synthesis of amphidinolide F, ester **3.150** was hydrolyzed to **3.71** quantitatively (Scheme 3.23). Stille cross-coupling between **3.71** and **3.139** reliably afforded **3.151**. Yamaguchi esterification generated intermediate **3.152**. TES ether deprotection, followed by oxidation transformed **3.152** into compound **3.153**. Global TBS ether deprotection then furnished amphidinolide F.

To date, the total synthesis of amphidinolide C has been accomplished by the Fürstner and Carter group. The total synthesis of amphidinolide F has been accomplished by the Fürstner (21 steps for longest linear sequence, 39 steps total) Carter (36 steps for longest linear sequence, 62 steps total) and Figadère groups. Our group sought to undertake studies towards the total synthesis of amphidinolide C and F to demonstrate the synthetic efficiency that can be accomplished using new existing methodology. This would in part reduce the step count, and also allow rapid access to the aforementioned natural products for further biological studies.

3.4 Studies towards the total synthesis of amphidinolides C and F

3.4.1 Development of the retrosynthesis

Scheme 3.25 Retrosynthetic approach to amphidinolide C and F – Route 1



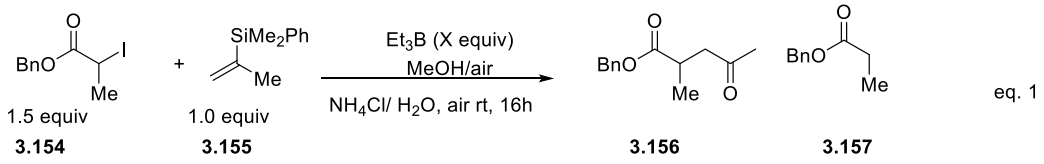
The first retrosynthetic route we envisioned considered a Yamaguchi esterification to complete the lactone of amphidinolide C and F. The western and eastern fragments would be assembled through a substrate controlled stereoselective radical addition onto an alkenylsilane, followed by oxidation to construct the 1,4-diketone. Suzuki-Miyaura cross-coupling of fragments A and B would furnish the western fragment. 1,2-Addition would connect fragments C and D to afford the eastern fragment (Scheme 3.25).

To assess the viability of the route in Scheme 3.25, we examined model coupling reactions (Scheme 3.26). In the literature, the proposed radical addition and oxidation reaction is known to occur between a terminal alkenylsilane and a primary α-iodo ester.[29] Our proposed route required a secondary α-iodo ketone (Scheme 3.25, fragment A). Preliminary studies showed that simple secondary α-iodo ketones suffer from poor solubility in the reaction solvent because they lacked polar functional groups that are present in fragment A. Alternatively, we set out to investigate the feasibility of the radical addition and oxidation by engaging a more soluble secondary α-iodo ester (Scheme 3.26, eq. 1). At the outset, we employed conditions previously used for primary α-iodo esters: 2.0 equiv Et_3B, MeOH in aqueous NH_4Cl and open to air. This reaction afforded a trace amount of desired 1,4-diketone product **3.156** and dehalogenated ester **3.157** (Table 3.2, entry 1). Increasing the amount of Et_3B from two to five and nine equivalents afforded the desired product in 22% and 37% yield respectively (entries 2-3). We attempted other conditions to effect the radical addition between C_{16} and C_{17}. When we employed conditions previously used for the *γ*-alkylation of enones by Mohr,[30] no addition/elimination product **3.158** was observed but we recovered starting material and the dehalogenated ester (Scheme 3.26, eq. 2). We attempted an atom transfer radical addition of the α-iodo ester onto an alkenylsilane catalyzed by a visble light-active iridium catalyst[31] (Scheme 3.26, eq. 3). Although the conditions in equation 3 had been reported to effect a radical addition to terminal alkenes, no product was observed when we employed

[29] Kondo, J.; Shinokubo, H.; Oshima, K. *Angew.Chem.Int.Ed*. **2003**, *42*, 825–827.
[30] Chen, X.; Liu, X.; Mohr, T. J. *J. Am. Chem. Soc*. **2016**, *138*, 6364-6367.
[31] Nguyen, J. D.; Tuckler, J. W.; Konieczynska, M. D.; Stephenson, C. R. J. *J. Am. Chem. Soc*. **2011**, *133*, 4160–4163.

an alkenylsilane. Given the low optimized yield in eq. 1 and the uncertainty of the chemoselectivity of the radical addition step when employed in the real system, we deemed it desirable to redesign this step in the total synthesis in order to have a more reliable route.

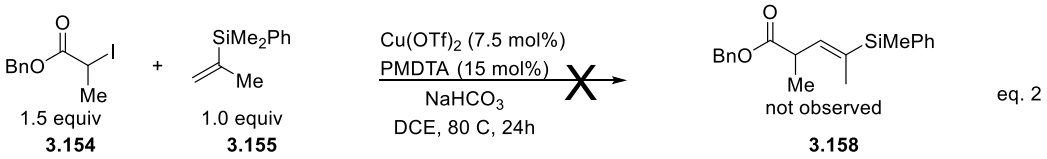
Scheme 3.26 Model studies for the radical 1,4-addition and oxidation



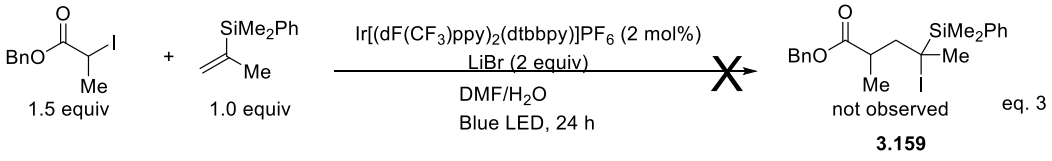
eq. 1

Table 3.2

Entry	Et_3B equivalents	Product yield
1	2	<5%
2	5	22%
3	9	37%



eq. 2

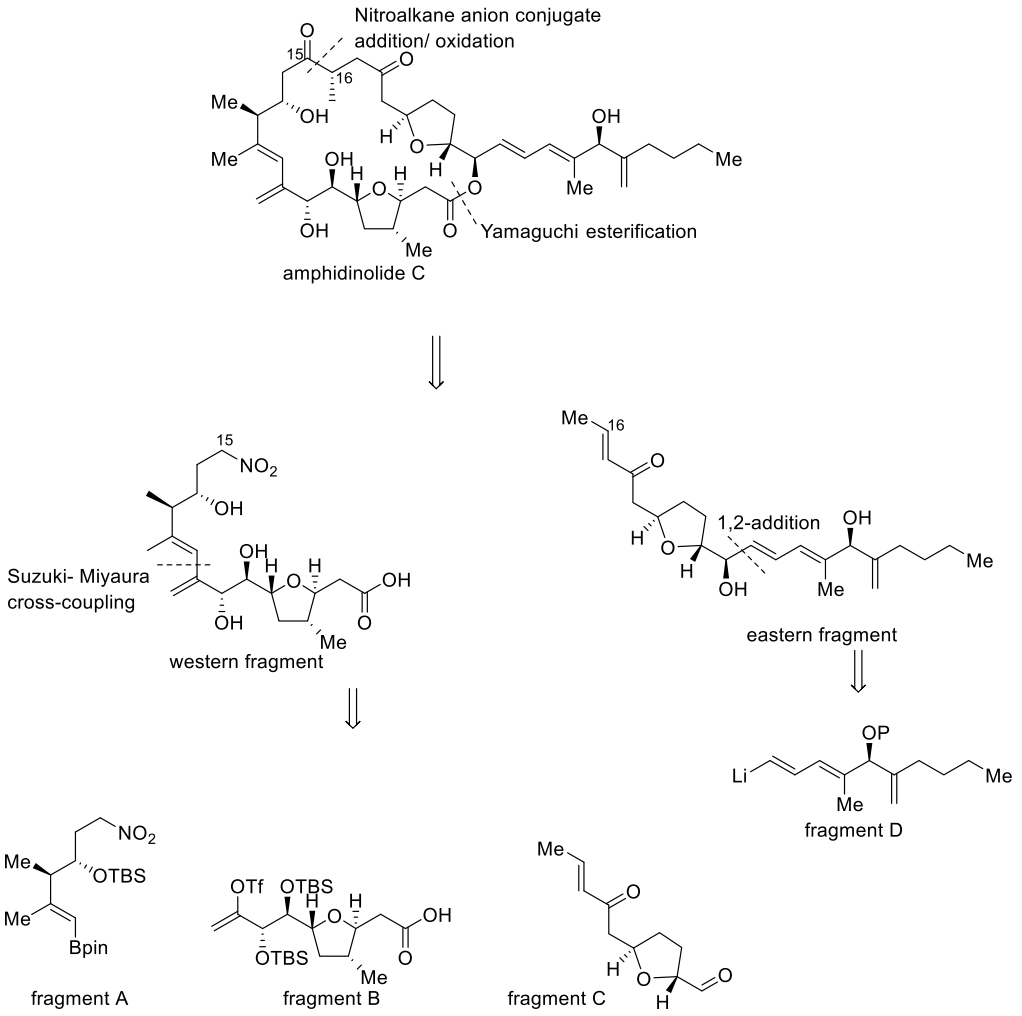


eq. 3

The second retrosynthetic route we proposed utilized a nitroalkane conjugate addition between C_{15} and C_{16}, followed by oxidation to afford the 1,4-diketone moiety, with the rest of the disconnections remaining unchanged (Scheme 3.27). The nitroalkane conjugate addition is anionic, and hence would avoid the chemoselectivity problem that would have been encountered in the radical addition reaction of substrates bearing additional alkenes. The choice of the nitroalkane was also crucial: these conjugate additions

usually require mild basic conditions[32] which might also facilitate retro Michael reactions and decompose the *trans*-THF rings in fragments B and C.

Scheme 3.27 Retrosynthetic approach to amphidinolide C and F – Route 2

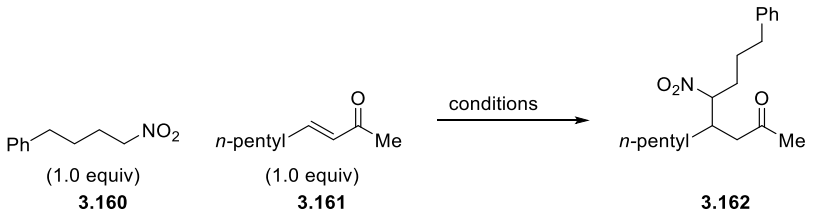


Studies were initiated to probe the feasibility of the nitroalkane conjugate addition (Table 3.3). Nitroalkane **3.160** and enone **3.161** were used as model substrates. In the literature, DBU in MeCN has been widely used to promote nitroalkane conjugate additions

[32] Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A.; Petrini, M. *Chem. Rev*. **2005,** *105*, 933–971.

to enones.[33] When two equivalents of DBU in acetonitrile were employed at 40 °C, the conjugate addition proceeded with 58% conversion after 24 hours to afford product **3.162** (Table 3.3 entry 1). Reducing the DBU amount from two to one equivalent increased the conversion to 73% (entry 2). Increasing the temperature from 40 °C to 60 °C and letting the reaction stir for 48 hours only showed a slight increase in conversion to 76% (entry 3). Further optimization showed that using THF instead of MeCN at 60 °C with one equivalent of DBU ensured full conversion after 48 hours (entry 4).

Table 3.3 Nitroalkane conjugation addition model study



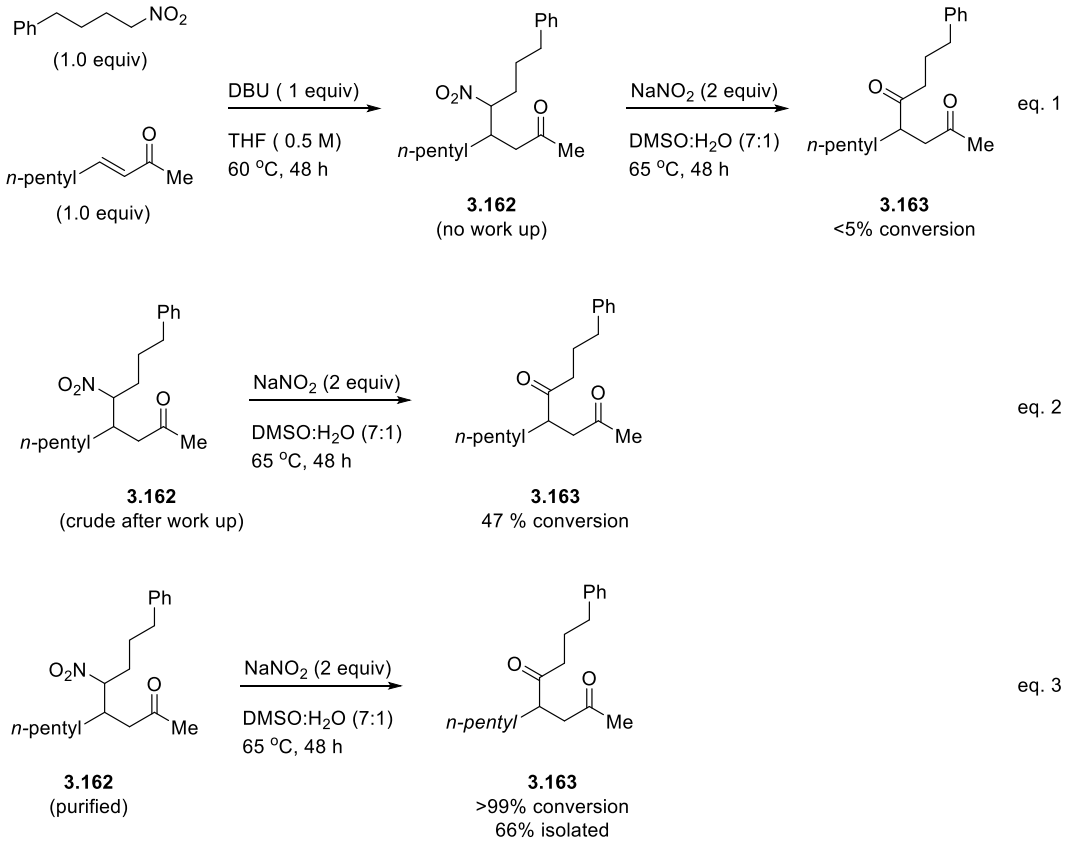
Entry	DBU (equiv)	solvent	temp (°C)	time (hrs)	conversion (%)
1	2.0	MeCN	40	24	58
2	1.0	MeCN	40	24	73
3	1.0	MeCN	60	48	76
4	1.0	THF	60	48	.>99

With the proof of principle that the nitroalkane conjugate addition to the enone could indeed be effected in the model substrate, we set out to investigate the subsequent oxidation step. A variety of Nef[34] reactions have been reported to effect a nitroalkane oxidation to a carbonyl. However, majority of these use harsh conditions that we deemed

[33](a) Ono, N.; Kamimura, A.; Kaji, A. *Synthesis.* **1984**, 226. (b) Pollini, G. P.; Barco, A.; De Giuli, G. *Synthesis.* **1972**, 44. (c) Chavan, S. P.; Pasupathy, K.; Venkatraman, M. S.; Kale, R. R. *Tetrahedron Lett.* **2004**, *45*, 6879. (d) Ballini, R.; Barboni, L.; Bosica, G.; Fiorini, D. *Synthesis*. **2002**, *18*, 2725–2728.
[34] Ballini, R.; Petrini, M. *Adv. Synth. Catal*. **2015**, *357*, 2371–2402.

incompatible with the THF rings in the target compound as they are prone to retro-Michael reactions. Other mild protocols have also been developed using weakly basic conditions.[35]

Scheme 3.28 Nitroalkane oxidation model studies

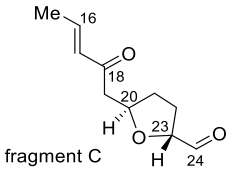


At the outset, we employed conditions developed by Mioskowski:[36] $NaNO_2$ in DMSO/H_2O at 65 °C in a one pot conjugate addition followed by oxidation protocol (Scheme 3.28, eq. 1). This afforded less than 5% of 1,4-diketone **3.163**. We speculated that the presence of DBU from the first conjugate addition might inhibit the subsequent oxidation step. Using crude nitroalkane after aqueous work up in the oxidation step

[35] Aghahosseini, H.; Ramazani, A.; Jalayer, N. S.; Ranjdoost, Z.; Souldozi, A.; Ślepokura, K.; Lis, T. *Org. Lett.* **2019**, *22*, 8893–8898.
[36] Tománková, Z.; Setnička, V.; Urbanová, M.; Matějka, P.; Král, V.; Volka, K.; Bouř, P. *J. Org. Chem.* **2004**, *26*, 8997–9001.

generated the desired product in 47% yield (eq. 2). Gratifyingly, when purified starting nitroalkane was employed in the reaction, quantitative conversion to 1,4-diketone **3.163** was observed and the product was isolated in 66% yield (eq. 3). Encouraged by the nitroalkane conjugate addition and oxidation in the model substrates, we continued to study the synthesis of the other fragments we proposed in the second retrosynthetic route in Scheme 3.27.

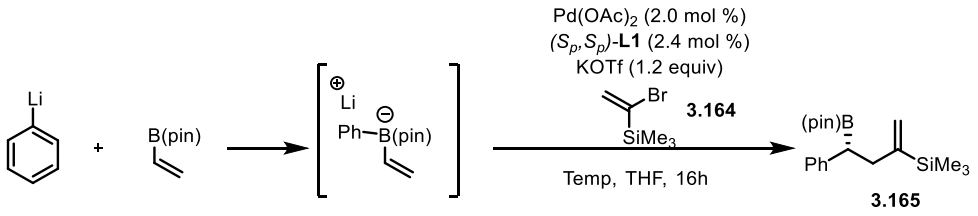
3.4.2 Studies towards the synthesis of fragment C



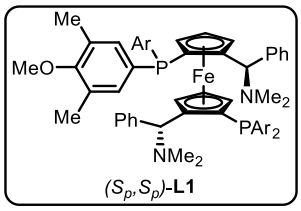
The first route we envisioned for the synthesis of fragment C utilized a palladium-catalyzed conjunctive[37] cross-coupling with a 1-bromoalkenylsilane electrophile to set stereocentre C_{20} (Table 3.4). Whereas alkenylbromides have been previously used as electrophiles in the conjunctive coupling, bromoalkenylsilane elctrophiles had not been demonstrated to engage in the reaction. When we employed conditions previously developed for the conjunctive coupling with alkenylbromides, the product **3.165** was obtained in 68% and 92:8 er. (Table 3.4 entry 1). A brief optimization showed that the best yield (86%), and enantiomeric ratio (96:4 er), were obtained when the reaction was conducted at room temperature with 2 mol% $Pd(OAc)_2$ and 2.4 mol% Mandyphos in THF (entry 3).

[37] See chapter 1, reference 5.

Table 3.4 Fragment C-synthesis- optimization of conjunctive cross coupling



Entry	Temp (°C)	conc (M)	Yield (Bpin %)	er (OH)
1*	60	0.25	68	92:8
2	40	0.25	81	96:4
3	23	0.25	86	96:4
4	4	0.25	55	97:3
5	23	0.20	86	96:4
6	23	0.15	82	95:5

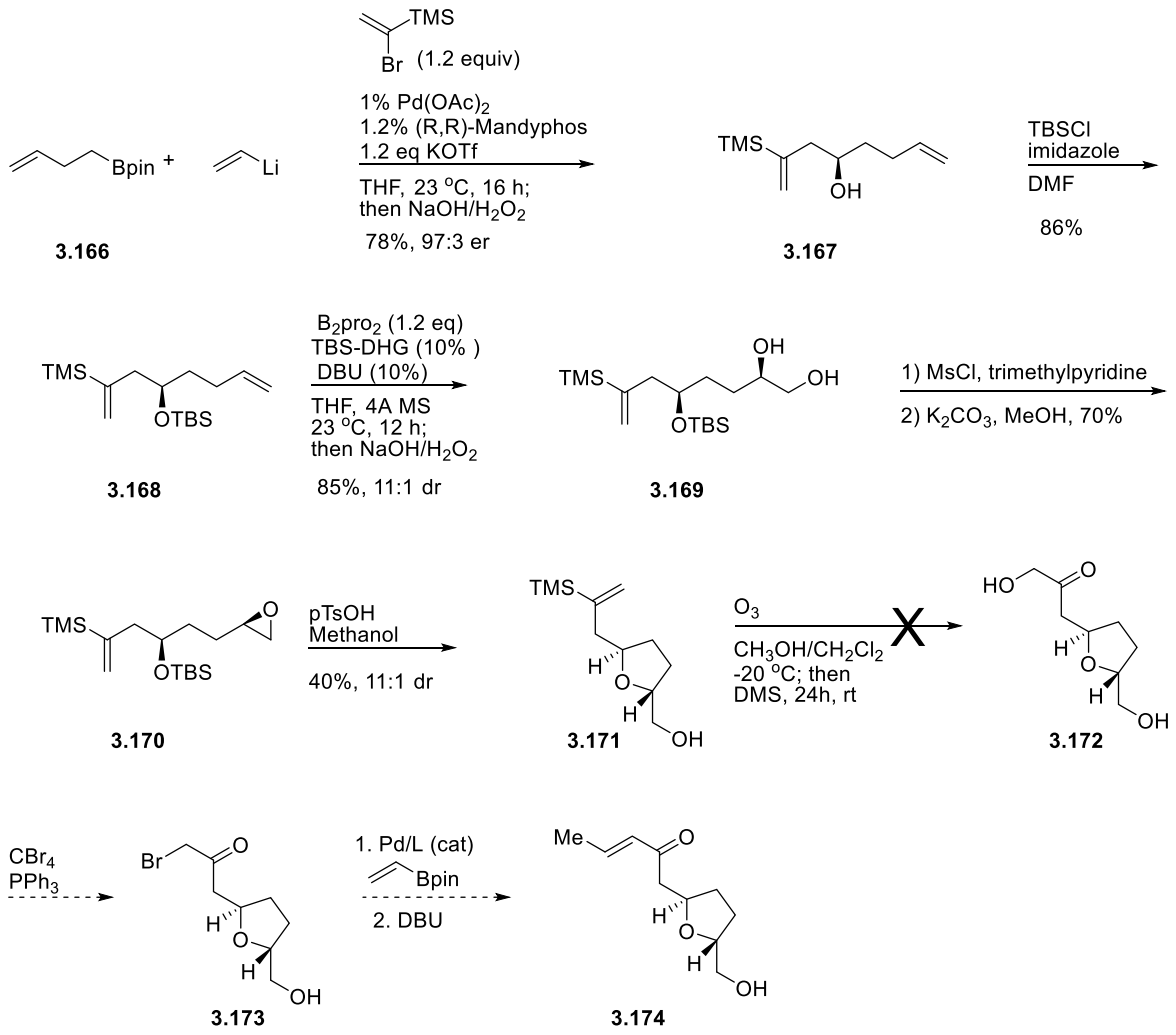


* $Pd(OAc)_2$ (5.0 mol%), (S_p,S_p)-**L1** (6.0 mol%)

To access the complete fragment C, we utilized a palladium-catalyzed conjunctive cross-coupling of homo-allylboron **3.166**, vinyllithium and 1-bromoalkenylsilane followed by oxidation to synthesize alcohol **3.167** (Scheme 3.29). Silyl protection proceeded in 86% yield followed by a chemoselective carbohydrate/DBU co-catalyzed diboration[38] of the terminal alkene and oxidation to afford the desired diol **3.169** in 85% yield and with 11:1 diastereoselectivity. The primary alcohol in **3.169** was activated as the mesylate, and base-promoted cyclization delivered epoxide **3.170** in 70% yield. A one step silyl ether deprotection, followed by intramolecular cyclization transformed **3.170** into the desired *trans*-THF derivative **3.171** in moderate yield and with good diastereoselectivity.

[38] (a) Fang, L.; Yan, L.; Haeffner; Morken, J. P. *J. Am. Chem. Soc*. **2016**, *138*, 2508. (b) Yan, L.; Meng, Y.; Haeffner, F.; Leon, R. M.; Crockett, M. P.; Morken, J. P. *J. Am. Chem. Soc*. **2018**, 140, 3663.

Scheme 3.29 Synthesis of fragment C- Route 1



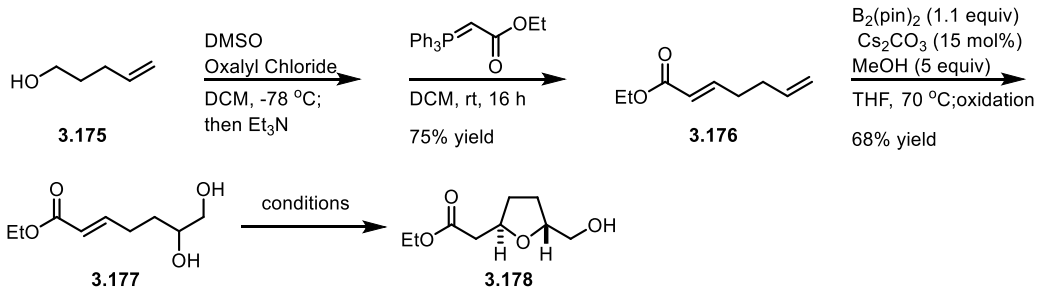
At this point, we had anticipated that ozonolysis might provide a handle to manipulate the alkenylsilane in **3.171** into the α-hydroxyl ketone **3.172** based on literature precedent.[39] However, we were unsuccessful with the ozonolysis of the alkenysilane. Starting material was fully consumed but not converted to the desired α-hydroxyl ketone **3.172** and we were unable to identify the product of this ozonolysis. If the ozonolysis had been successfully, we had speculated that bromination would afford **3.173**, cross coupling with vinylBpin and

[39] Buechi, G.; Wuest, H. *J. Am. Chem. Soc.* **1978**, *100*, 294–295.

olefin isomerization would afford **3.174**. Not being discouraged, we revised the route to access fragment C as discussed below.

The initial studies for the second route to fragment C were initiated with a racemic model synthesis that would allow for optimization of the key transformations (Schemes 3.30 A and B). Commercially available alcohol **3.175** was subjected to a Swern oxidation, followed by Horner-Wadsworth-Emmons olefination to provide unsaturated ester **3.176** (Scheme 3.30A). Racemic transition-metal-free diboration[40] was effected to afford diol **3.177** in 68% yield. With the diol in hand, we set out to synthesize the *trans*-THF ring. DBU promoted cyclization afforded tetrahydrofuran ring as 1:1 mixture of *cis* and *trans* diastereomers (Table 3.5, entry 1).

Scheme 3.30A Fragment C synthesis**-** route 2 (racemic)



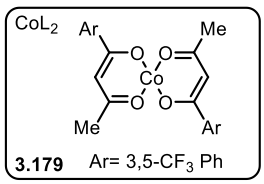


Table 3.5

Entry	conditions	result
1	2.0 equiv DBU	78%, 1;1 dr
2	air, CoL_2 (15 mol%) *gamma*-Terpinene, 80 °C, 16 h	complex mixture

[40] Bonet, A.; Pubill-Ulldemolins, C.; Bo, C.; Gulyás, H.; Fernández, E. *Angew. Chem. Int. Ed*. **2011**, *31*, 7158–7161.

2,5-Disubstitued-THF rings like those in amphidinolides C and F are encountered in many other biologically active natural products and a variety of methods have been developed to access them.[41] A wide array of methods have been developed to access *cis*-2,5-disubstituted[42] THF rings but the synthesis of 2,5-*trans*-THF rings is more challenging. We were encouraged by the cobalt-catalyzed oxidative cyclization of bis-homoallylic alcohols developed by Mukayima to access THF rings.[43] This work was complemented by Hartung who developed a cobalt-catalyzed aerobic oxidation of (*E*)- and (*Z*)-bis-homoallylic alcohols to access *trans*-THF rings.[44] We adopted and modified conditions developed by Forsyth[45] to effect a Mukaiyama aerobic alkenol cylization catalyzed by Hartung's complex to afford the desired *trans*-THF ring (Scheme 3.30 A). When diol **3.177** was used as the substrate under cobalt catalysis, we observed a complex mixture of products (Table 3.5, entry 2). We speculated that the primary free hydroxyl group might interfere with the reaction and proceeded to protected it as the silyl ether **3.180** (Scheme 3.30 B).

[41] Jalce, G.; Franck, X.; Figadère, B. *Tetrahedron. Asymmetry*. **2009**, *20*, 2537−2581.
[42] Pullin, D. C. R.; Lipiński, M. R.; Donohoe, J. T. *Pure Appl. Chem*. **2013,** *6***,** 1175−1184.
[43] Inoki, S.; Mukayima, T. *Chem. Lett*. 1**990**, 67−70.
[44] Pérez, B. M.; Hartung, J. *Tetrahedron Lett.* **2009**, *50*, 960.
[45] Wu, D.; Forsyth, J. C. *Org. Lett*. **2013**, *6*, 1178−1181.

Scheme 3.30B Optimization of the cobalt-catalyzed cyclization

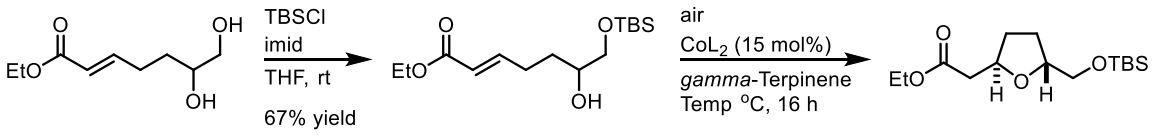


Table 3.6

Entry	Temp	Change from standard	Result
1	80	-	24%, >20:1 dr
2	70	-	24%, >20:1 dr
3	70	continous air flow inlet	35,> 20:1 dr
4	70	catalyst added twice; at t=0, then t=4h. compressed air flow inlet	>95% conversion, >20:1 dr

When silyl ether **3.180** was engaged in the reaction, the desired product **3.181** was afforded in 24% yield and >20:1 *trans*:*cis* diastereoselectivity (Table 3.6, entry 1). Further reaction optimization showed that constant air flow was important as we observed increased yield from 24% to 35% when a compressed air inlet was used as opposed to a static atmosphere (entries 2-3). When the catalyst was added sequentially at the beginning of the reaction and again after 4 hours, nearly full conversion of starting material to the desired product **3.181** as a single diastereomer was observed (entry 4).

Scheme 3.31 Racemic route- optimization for enone **3.184** synthesis

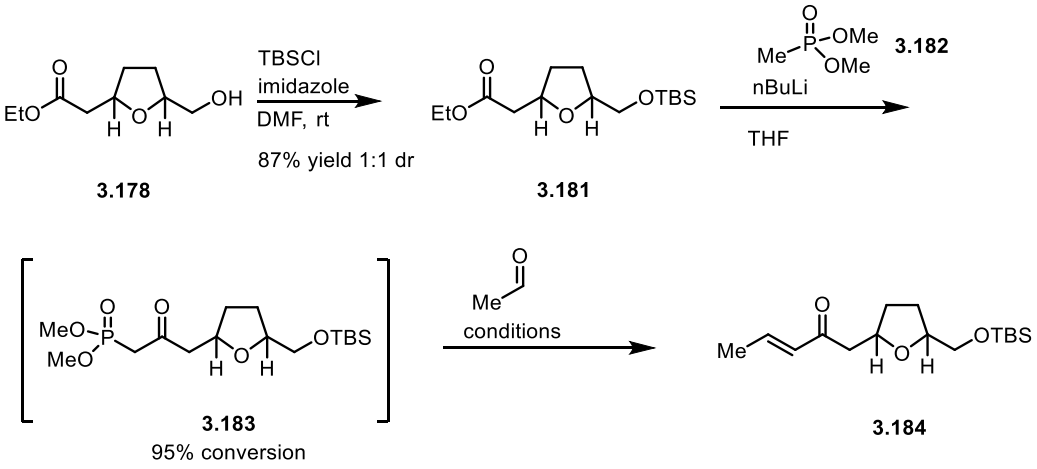


Table 3.7

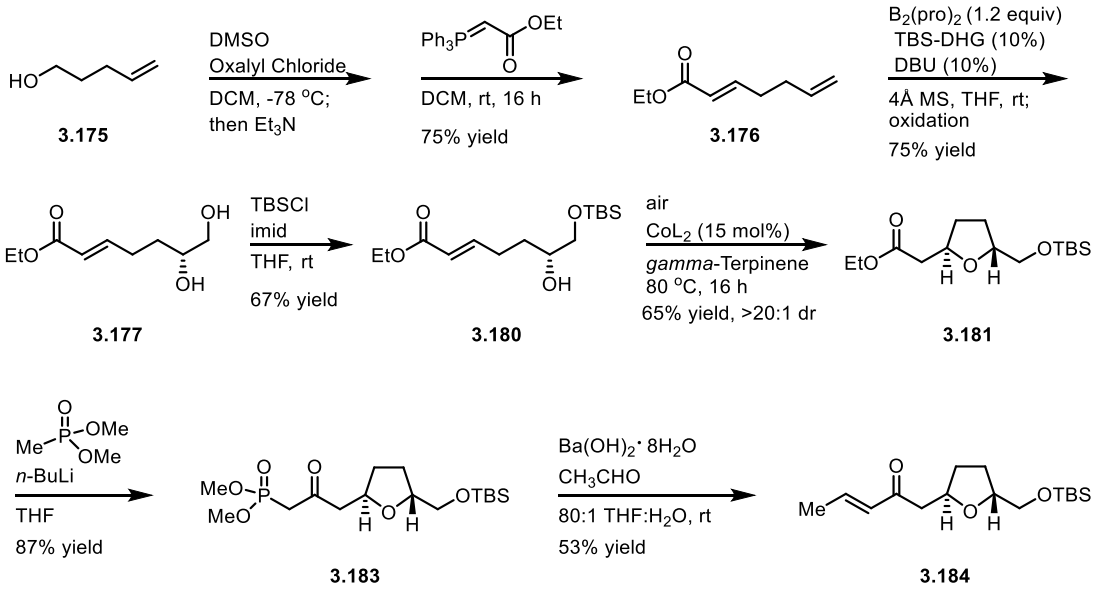
Entry	Conditions	Result
1	3.0 eq LDA THF, -78C	7%
2	LiBr/ Et_3N THF, -rt	7%
3	LiBr/ DBU THF, rt	20%
4	$Ba(OH)_2$ $8H_2O$ 80:1 THF:H_2O, rt	53%

The next efforts were geared toward accessing the enone to afford the model fragment C **3.184** (Scheme 3.31). Silyl protection of the primary alcohol in **3.178** afforded the silyl ether **3.181** in 87% yield. Compound **3.181** underwent a Claisen condensation with the lithium salt of dimethyl methyl phosphonate **3.182** to afford phosphoester **3.183**. To access enone **3.184**, a variety of conditions were explored to promote the Horner-Wadsworth-Emmons reaction. With LDA as the base, only 7% of the desired enone **3.184** was observed (Table 3.**7**, entry 1). Using Roush/Masamune conditions:[46] LiBr and Et_3N,

[46] (a) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfield, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. Tetrahedron Lett. 1984, 25, 218. (b) Evans, A. M.; Morken, J. P. *Org. Lett*. **2005**, *15*, 3371–3373.

also afforded the enone in poor yield of 7% (entry 2). Switching the base from Et_3N to DBU increased the yield to 20% (entry 3). Gratifyingly, when barium hydroxide octahydrate[47] was used as base in THF/H_2O the desired enone **3.184** was obtained in 58% yield (entry 4).

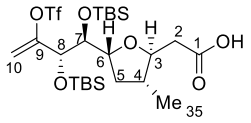
Scheme 3.32 Forward synthesis of fragment C



To access the enantiomerically enriched fragment C, optimized reactions from Schemes 3.30 and 3.31 were applied to the route in Scheme 3.32. Unsaturated ester **3.176** underwent an asymmetric carbohydrate/DBU co-catalyzed diboration to afford chiral diol **3.177** which was silyl protected to afford the desired *trans*-THF ring in 65% yield and greater than 20:1 dr. The rest of the steps to afford the desired fragment C are similar to those optimized in Schemes 3.30 and 3.31 above.

[47] Paterson, I.; Yeung, K.-S.; Smaill, J. B. *Synlett* **1993**, *10*, 774–776.

3.4.3 Studies toward the synthesis of fragment B



Fragment B

Scheme 3.33 Studies towards the synthesis of fragment B: conjunctive coupling-route 1

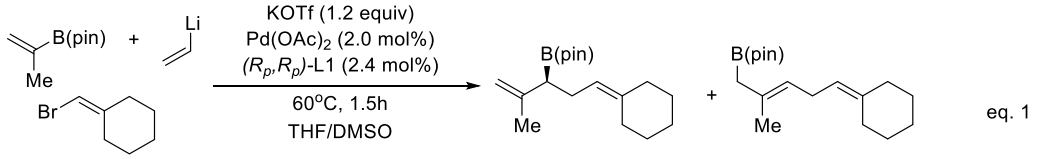
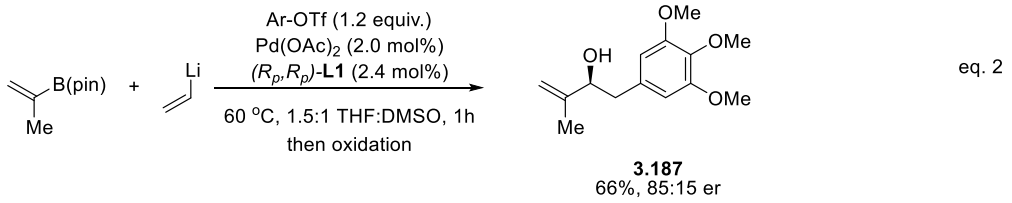


Table 3.8

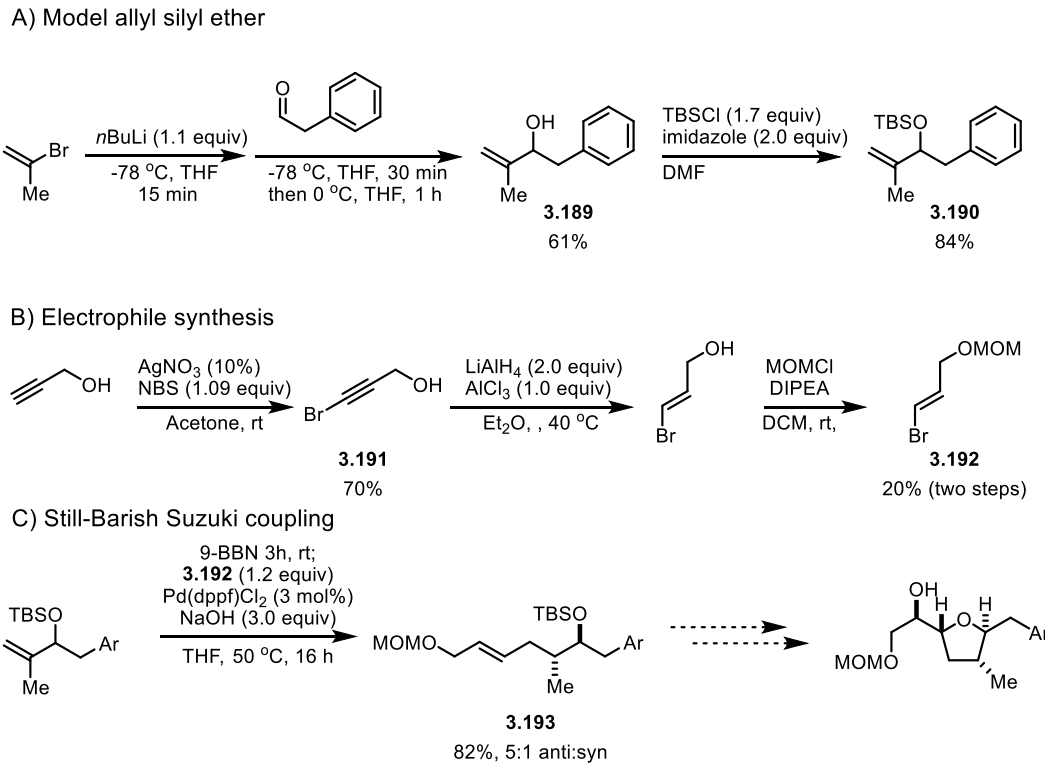
THF:DMSO	A:B	yield A (OH)	er
3:1	2.5:1	67%	73:27
1:1	1.5:1	nd	nd



The first route we envisioned for fragment B employed a Pd-catalyzed conjunctive cross-coupling of a bis(alkenyl)borate. In the first attempt, we employed isopropenyl Bpin, vinyllithium and an alkenylbromide to afford allylboron **3.185** (Scheme 3.33, eq 1). We had envisioned that the olefin from the electrophile would be a precursor to the C_1 carboxylic acid and further manipulation of the 1,1-disubstituted alkene in the product (**3.185**) would set the methyl stereocentre at C_4 and further lead to fragment B. The conjunctive reaction (eq. 1) proceeded to full conversion but afforded a mixture of desired allylboron **3.185** and its 1,3-borotropic shift product **3.186**. Although product **3.185** was isolated in synthetically useful yield, it had poor enantioselectivity (Table 3.8). As an alternative, we sought to engage an electon-rich triflate as the electrophile which would

also be a suitable carboxylic acid precursor (Scheme 3.33, eq. 2). This reaction proceed in 66% yield and 85:15 er. Before continuing with the manipulation of allylalcohol **3.187**, we probed downstream reactions that we had envisioned would be crucial for this first route to be implemented.

Scheme 3.34 Model studies for Fragment B – route 1



Specifically, we wanted to understand the diastereoselectivity of the Still-Barish[48] hydroboration of the 1,1-disubtituted alkene in **3.187** and the subsequent yield of the Suzuki cross-coupling with a suitable electrophile. To study this, the model route depicted in Scheme 3.34 was investigated. Lithium-halogen exchange followed by 1,2-addition to the aldehyde and TBS protection afforded silyl ether **3.190** in 61% yield (Scheme 3.34 A).

[48] Still, W. C.; Barrish, J. C. *J. Am. Chem. Soc*. **1983**, *105*, 2487.

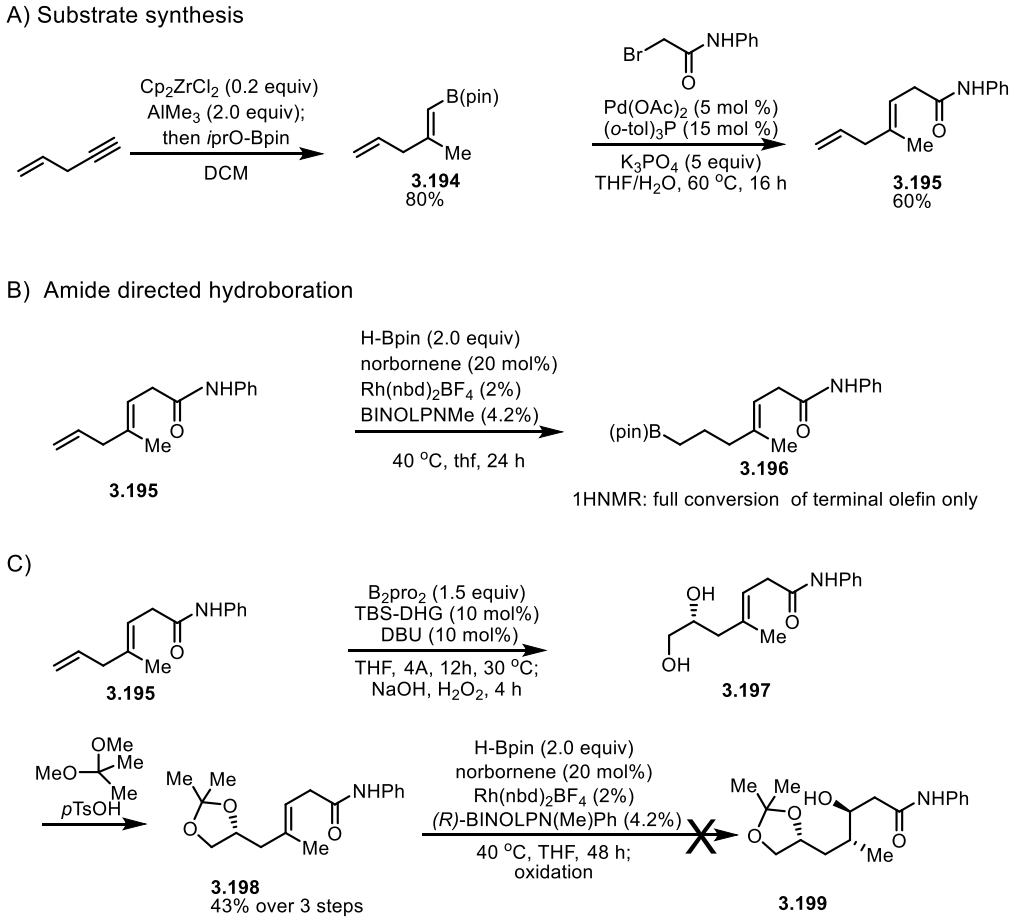
To access the electrophile, propargyl alcohol was brominated, reduced to allyl alcohol **3.191** which was protected as MOM ether **3.192** (Scheme 3.34 B). Using conditions developed by Still and Barish, the allylsilyl ether **3.190** was hydroborated using 9-BBN and the resulting alkylborane was subjected to a palladium-catalyzed Suzuki cross-coupling[49] to afford product **3.193** as a 5:1 mixture of *anti*:*syn* diastereomers in 82% yield. The diastereoselectivity achieved in this reaction was deemed too low, especially at the beginning of a route sequence, and would have required a challenging separation of diastereomers. Because of this, we considered a second alternative route to access fragment B as shown in Scheme 3.35.

The second route that we considered relied on an asymmetric amide-directed hydroboration of a trisubstituted alkene to set the C_4 methyl stereocenter in fragment B. To test this hypothesis, substrate **3.195** was required (Scheme 3.35). To synthesize this, Aggarwal's zirconium-catalyzed methylboration[50] of a skipped enyne afforded alkenylboron **3.194**, and subsequent Suzuki-Miyaura cross-coupling afforded the α,γ-unsaturated amide **3.195**. Using conditions developed by Takacs,[51] the amide-directed hydroboration of compound **3.195** afforded the hydroboration product of the terminal alkene (Scheme 3.35 B). This result suggested that hydroboration of the terminal alkene was faster than the amide directed hydroboration of the trisubstituted alkene. To circumvent this chemoselectivity problem, the terminal alkene was diborated and protected as acetal **3.198.** When acetal **3.198** was subjected to the Takacs hydroboration conditions, no desired product was obtained and instead we recovered the starting material (Scheme

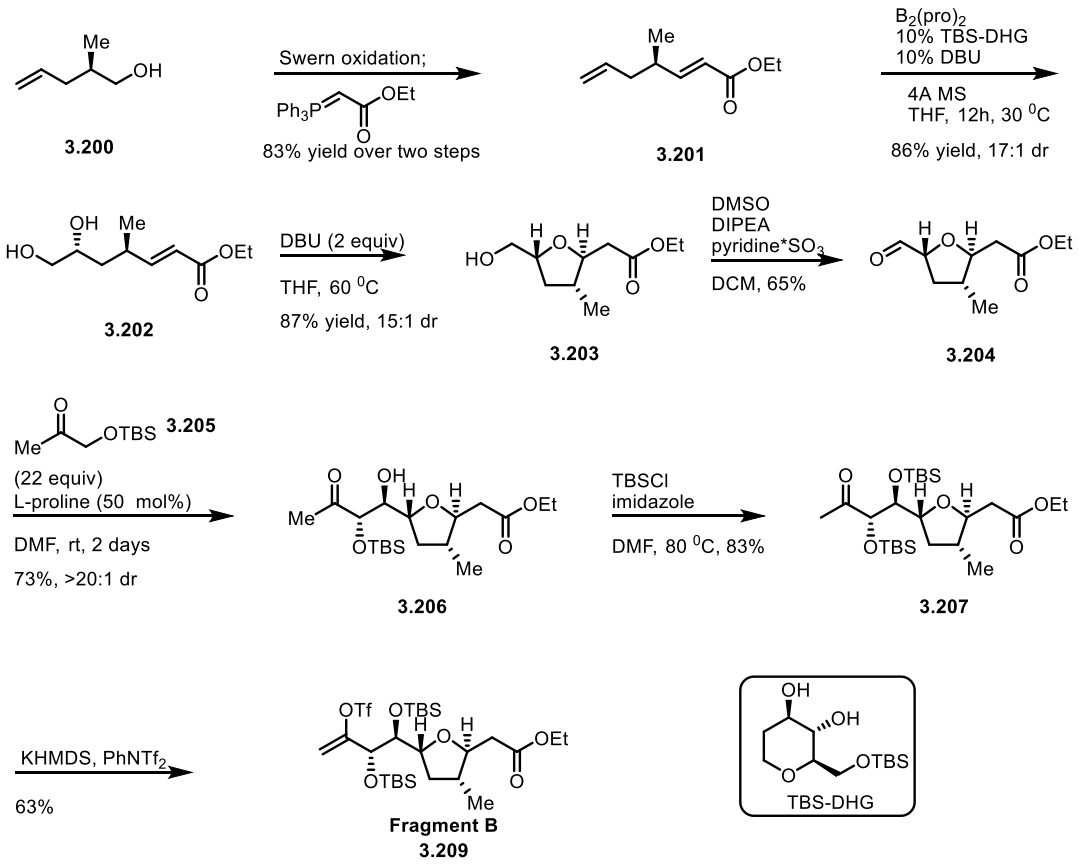
[49] Chemler, R. S.; Trauner, D.; Danishefsky, J. S. *Angew. Chem. Int. Ed*. **2001**, *40*, 4544 –4568.
[50] See chapter 2, reference 14.
[51] Smith, M. S.; Takacs, M. J. *J. Am. Chem. Soc.* **2010,** *132*, 1740–1741.

3.35 C). We speculate that the acetal functional group increases the steric bulk of the substrate and renders the hydroboration more challenging even with the amide directing group present. With the above two failed routes to access fragment B, a third route was designed and executed as depicted in Scheme 3.36.

Scheme 3.35 Studies toward the synthesis of fragment B: amide-directed hydroboration-route 2



Scheme 3.36 Synthesis of fragment B- route 3



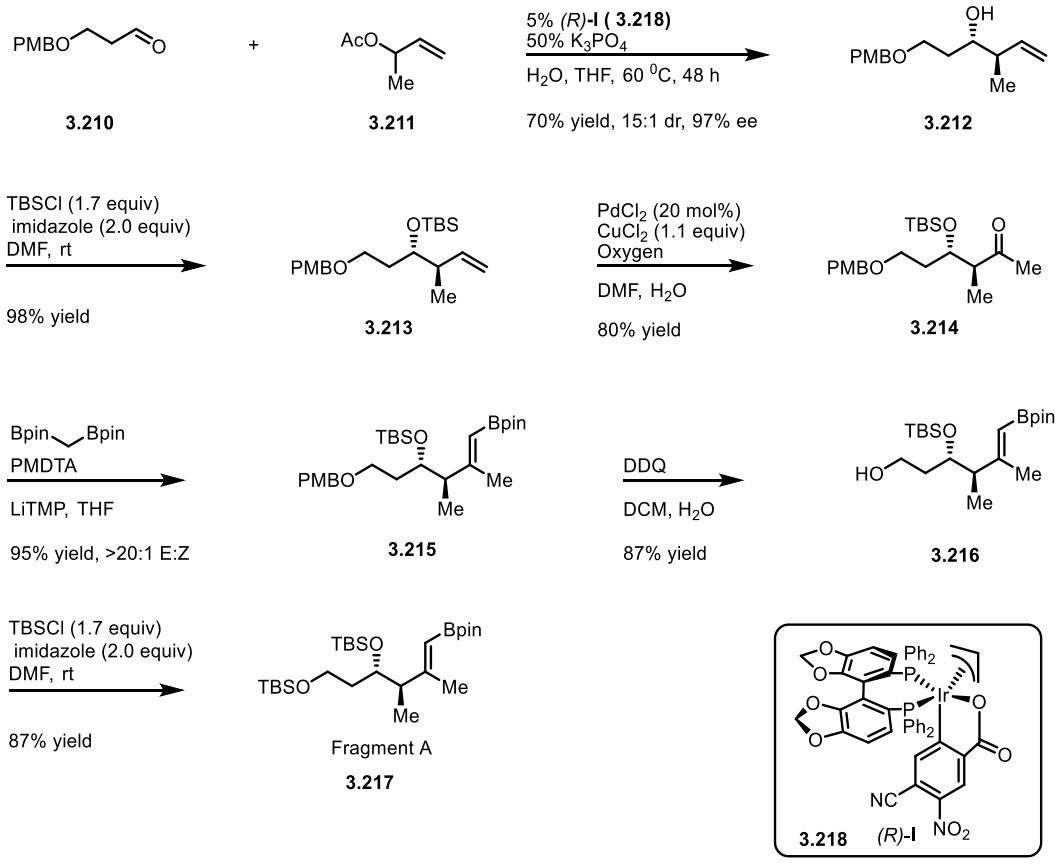
To access fragment B in route 3, we started from easily accessible chiral alcohol **3.200**[52] which was oxidized to the aldehyde and a subsequent Horner-Wadsworth-Emmons olefination furnished unsaturated ester **3.201** (Scheme 3.36). Using a previously developed Morken group methodology, the terminal alkene of compound **3.201** was chemoselectively diborated and oxidized to yield the diol **3.202** in 86% yield and 17:1 diastereoselectivity. DBU promoted the intramolecular cyclization of **3.202** to **3.203** in 87% yield and 15:1 diastereoselectivity**.** Parikh-Doering oxidation transformed alcohol **3.203** into aldehyde

[52](a) Meiries, S.; Bartoli, A.; Decostanzi, M.; Parrain, J.-L.; Commeiras, L. *Org. Biomol. Chem*. **2013**,*11*,4882. (b) May, E. A.; Willoughby, H. P.; Hoye, R. T.; *J. Org. Chem.* **2008**, *73*, 3292-3294. (c) Volker, P. McCaskill, S. J.; Guenter, V. K.; *Angew. Chem. Int. Ed*. **2016**, *55*, 4252–4255.

3.204 in 64% yield. This aldehyde was particularly unstable, even under argon in the freezer, and had to be used the same day as it was purified. L-Proline catalyzed *anti*-aldol reaction of aldehyde **3.204** and ketone **3.205** generated advanced intermediate **3.206** in 73% yield as a single diastereomer. Silyl protection of the secondary alcohol in DMF at 80 ^{0}C resulted in compound **3.207**. The ketone **3.207** was deprotonated at -78 ^{0}C and the resulting kinetic enolate reacted with Comin's reagent to deliver fragment B (**3.209**) in 63% yield.

3.4.4 Studies toward synthesis of fragment A

Scheme 3.37 Synthesis of fragment A



For the second half of the western fragment, we set out to synthesize fragment A. Asymmetric Krische crotylation[53] of aldehyde **3.210** delivered compound **3.212** in 70% yield and 15:1 diastereoselectivity (Scheme 3.37). Silyl protection proceeded nearly quantitatively to afford silyl ether **3.213.** Wacker[54] oxidation of the terminal alkene delivered ketone **3.214** in 80% yield**.** At this juncture in the synthesis, we applied the recently developed modified boron-Wittig[55] reaction to ketone **3.214** to afford the alkenyl boronic ester **3.2.15** as a single *E* diasteoereomer. ^{1}HNMR NOESY was used to confirm the *E* configuration of the olefin. PMB deprotection proceeded in good yield without destroying the alkenyl boronic ester functional group to furnish the free hydroxyl fragment A **3.216**. It was discovered that starting out with the PMB ether aldehyde **3.210** was crucial because when a silyl ether was used, it was cleaved during the Wacker oxidation and eroded the yield of the oxidation step. Subsequent TBS protection of **3.216** afforded the desired silyl ether protected fragment A (**3.217**).

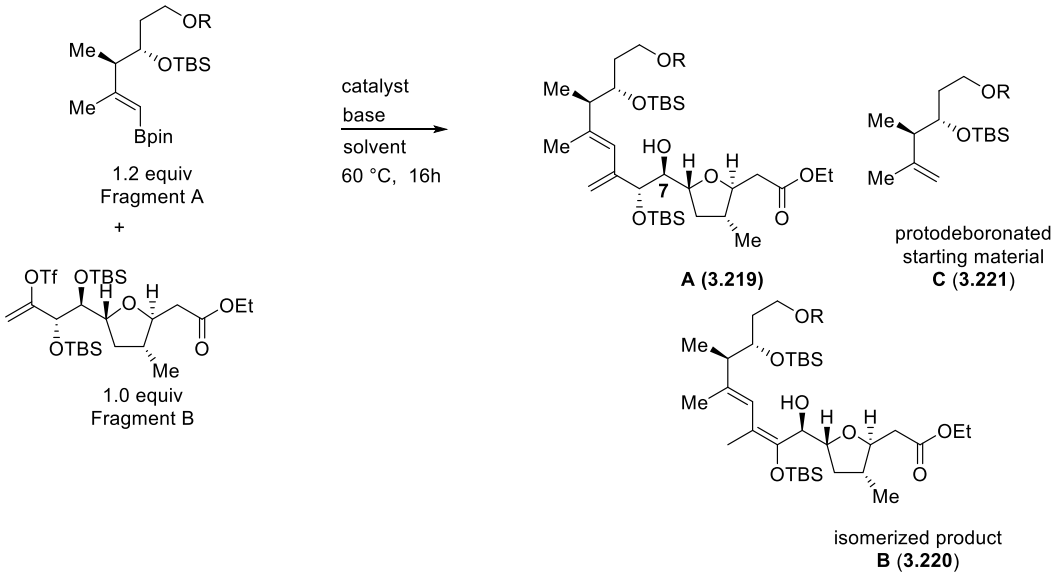
3.4.5 Assembly of the Western Fragment

Previous syntheses of amphidinolides C and F have relied on the Stille cross-coupling to assemble the western fragment. Whereas this methodology is feasible, it utilizes tin, which is toxic and poses safety concerns on large scale. Alternatively, the Suzuki-Miyaura cross-coupling we envisioned relies on the use of an easily accessible alkenyl boronic esters which are less toxic than their alkenylstannane counterparts. During

[53] (a) Kim, I. S.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc*. **2008**, *130*, 6340−6341. (b) Kim, I. S.; Ngai, M. Y.; Krische, M. J. *J. Am. Chem. Soc*. **2008**, *130*, 14891−14899. (c) Gao, X.; Townsend, I. A.; Krische, M. J. *J. Org. Chem*. **2011**, 76, 2350−2354. (d) DechertSchmitt, A. M.; Schmitt, D. C.; Krische, M. J. *Angew. Chem., Int. Ed*. **2013**, 52, 3195−3198.
[54] Czuba, I. R.; Zammit, S.; Rizzacasa, M. A. *Org. Biomol. Chem*. **2003**, *1*, 2044–2056.
[55] (a) Coombs, J. R.; Zhang, L.; Morken, J. P. *Org. Lett*. **2015**, 17, 1708. (b) Namirembe, S.; Gao, C; Wexler, R. P.; Morken, J. P. *Org. Lett.* **2019**, *11*, 4392-4394.

our studies, various conditions were investigated to execute the Suzuki-Miyaura cross-coupling.

Table 3.9 Suzuki-Miyaura cross-coupling investigation



Entry	R	cat	base	solvent	A:B:C
1	H	$Pd(PPh_3)Cl_2$ (30 mol %)	K_3PO_4 (30 eq)	THF/H_2O	40:20:30
2	PMB	$Pd(dppf)Cl_2$ (30 mol %)	K_3PO_4 (5 eq)	THF/H_2O	50:10:30
3*	PMB	$Pd(dppf)Cl_2$ (30 mol %)	K_3PO_4 (5 eq)	THF/H_2O	60:00:30
4	PMB	$Pd(dppf)Cl_2$ (30 mol %)	$Ba(OH)_2.8H_2O$ (5 equiv)	DMF	00:60:30
5*	TBS	$Pd(dppf)Cl_2$ (30 mol %)	K_3PO_4 (5 eq)	THF/H_2O	60:00:30
6*	PMB	Ruphos Pd G3 (30 mol%)	K_3PO_4 (5 eq)	THF/H_2O	00:00:100
7*	PMB	Xphos Pd G3 (30 mol%)	K_3PO_4 (5 eq)	THF/H_2O	20:00:70

* reaction run in the dark

At the outset of the Suzuki-Miyaura cross-coupling, we were aware of the potential challenges that would be associated with the reaction. First, the *cis*-diene in the product **3.219** could isomerize to the *trans* compound **3.220** during the course of the reaction. Second, the rate of transmetalation as compared to that of protodeboronation of the alkenyl boronic ester was of concern.

Initially, we investigated the Suzuki cross-coupling using alkenyl boronic ester **3.216** (R=H). After 16 hours at 60 ^{0}C, (Table 3.9, entry 1) we observed 40% conversion to the desired Suzuki-Miyaura product **3.219** in which the C_7 silyl ether had been deprotected during the reaction. The mass balance was accounted for by the protodeboronated alkenyl boronic ester (**3.221**) and isomerized diene (**3.220**) (Table 3.9). We speculated that the free hydroxyl group in the starting material might interfere with the coupling, so we proceeded by protecting it as either the silyl or PMB ether for the rest of the optimization studies. Indeed, when we used the PMB protected substrate and 5 equivalents of K_3PO_4 instead of 30, we observed a 50% conversion to the Suzuki product and 10% isomerized product (entry 2). When we employed $Ba(OH)_2 \cdot 8H_2O$[56] as the base and DMF as the solvent, the only product observed was isomerized **3.220** (entry 4). Buchwald pre-catalysts were explored (entries 6 and 7) and were inferior to $Pd(dppf)Cl_2$. We also found that when the reaction was run in the dark,[57] we did not observe isomerization of the diene and were able to isolate the desired product (**3.219**) in 52 to 64% yield (entry 3).

[56]Gopalarathnam, A.; Nelson, S. G. *Org. Lett.* **2006**, *8*, 7–10.
[57] Morrison, R. J.; Mei, F. W. V. D.; Romiti, F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2019**, *142*, 436-447.

3.5 Conclusion

We have accomplished the synthesis of C(1)-C(15) and C(16)-C(24) of amphidinolide C and F. These studies have allowed us to learn about the critical aspects of these natural products that will allow for completion of their syntheses. The key steps to access fragment A included a catalytic *anti*- diastereo and enantioselecive Krische crotylation and a modified boron-Wittig olefination. The assembly of fragment B highlights the carbohydrate/DBU co-catalyzed diboration and an *anti*-aldol reaction. Construction of fragment C was accomplished using asymmetric diboration and a cobalt-catalyzed diastereoselective cyclization. Advancement has been made as this is the first time a Suzuki-Miyaura cross-coupling has been demonstrated to assemble two advanced intermediates in the synthesis amphidinolide C and F. Future studies should be aimed at synthesizing the side chains, and connecting the Eastern and Western fragments to accomplish the total syntheses.

3.6 Experimental information

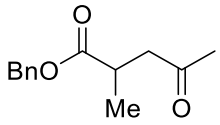
3.6.1 General Information

^{1}H NMR spectra were recorded on either a Varian Gemini-500 (500 MHz) or Varian Gemini-600 (600 MHz) spectrometer. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 7.26 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet), and coupling constants (Hz). ^{13}C NMR spectra were recorded on either a Varian Gemini-500 (125 MHz) or a Varian Gemini-600 (150 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 77.16 ppm). 2D-NOESY spectra were recorded on Varian Gemini-600 (150 MHz). ^{11}B NMR spectra were recorded on a Varian Gemini-500 (128 MHz) or Varian Gemini-600 (160 MHz) spectrometer. Chemical shifts are reported in ppm with an external standard ($BF_3 \cdot Et_2O$: 0 ppm). Infrared (IR) spectra were recorded on a Bruker alpha-P Spectrometer. Frequencies are reported in wavenumbers (cm^{-1}) as follows: strong (s), broad (br), medium (m), and weak (w). High-resolution mass spectrometry (DART) was performed at the Mass Spectrometry Facility, Boston College, Chestnut Hill, MA. Optical rotations were measured on a Rudolph Analytical Research Autopol IV Polarimeter. Liquid chromatography was performed using forced flow (flash chromatography) on silica gel (SiO_2, 230 x 450 Mesh) purchased from Silicycle. Thin layer chromatography (TLC) was performed on 25 μm silica gel glass backed plates from Silicycle. Visualization was performed using ultraviolet light (254 nm), ceric ammonium molybdate (CAM) in ethanol, or phosphomolybdic acid and cerium (IV) sulfate in ethanol with sulfuric acid (seebach).

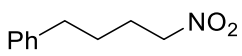
Analytical chiral supercritical fluid chromatography (SFC) was performed on a TharSFC Method Station II equipped with Waters 2998 Photodiode Array Detector with isopropanol or methanol as the modifier. Tetrahydrofuran (THF), diethyl ether (Et_2O), dichloromethane (CH_2Cl_2) and toluene were purified using Pure Solv MD-4 solvent purification system, from Innovative Technology, Inc., by passing the solvent through two activated alumina columns after purging with argon. Anhydrous dimethyl formamide (DMF), isopropanol (IPA), 4Å molecular sieves were purchased from Sigma Aldrich and used without further purification. All other reagents were purchased from either Aldrich, Alfa Aesar, Acros, Oakwood Chemicals, Combi Blocks, Strem, or TCI and were used without further purification.

3.6.2 Experimental section

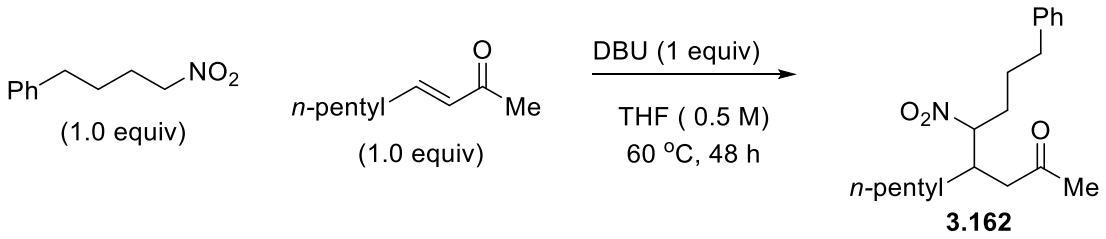
3.6.2.1 Conjugate additions



Benzyl 2-methyl-4-oxopentanoate (3.156). The title compound was prepared according to known literature procedure.[58] NMR and mass spectra data was in accord with the literature.[59]



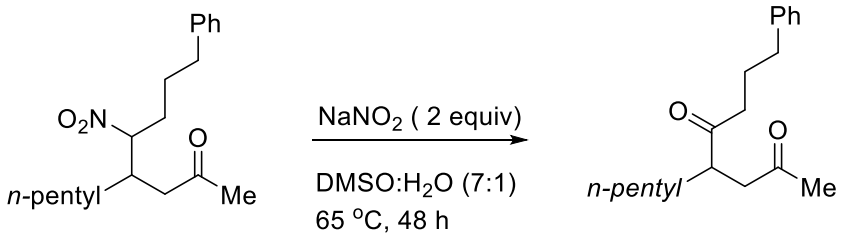
(4-nitrobutyl)benzene (3.160). The title compound was prepared from the corresponding amine according to known literature procedure.[60] NMR and mass spectra data was in accord with the literature.[61]



4-(1-nitro-4-phenylbutyl)nonan-2-one (3.162). To an oven dried 2 dram vial with a stir bar was added nitroalkane **3.160** (1.0 equiv), exchanged air with nitrogen and added anhydrous THF (0.5M). Under nitrogen at room temperature, added DBU (1.0 equiv) dropwise and saw an instant color change from colorless to faint pink. Added *(E)*-non-3-en-2-one dropwise and stirred under nitrogen for 48 hours at 60 °C. Diluted with water and extracted with hexanes. Dried the organic layer with sodium sulfate and concentrated in vacuo. Purified by silica gel chromatography to afford the desired product as a clear colorless oil, 66% yield **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.35 – 7.26 (m, 2H), 7.23

[58] Kondo, J.; Shinokubo, H.; Oshima, K. *Angew. Chem. Int. Ed*. **2003**, *42*, 825–827.
[59] Liu, Q-Z.; Chu, W-D.; Chen, B. *RSC Adv.* **2019**, *9*, 1487– 1490.
[60] Schreiner, P. R. *J. Org. Chem.* **2008**, *73*, 7789– 7792
[61] Glorius, F. *Chem. Eur. J.* **2016**, 22, 9, 971– 9974.

– 7.08 (m, 3H), 4.66 – 4.55 (m, 1H), 2.70 – 2.58 (m, 3H), 2.49 – 2.30 (m, 2H), 2.14 (s, 3H), 1.72 – 1.53 (m, 4H), 1.38 – 1.16 (m, 8H), 0.87 (t, *J* = 6.9 Hz, 3H).



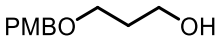
3.162
(purified)

3.163

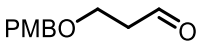
4-pentyl-8-phenyloctane-2,5-dione (3.163). The title compound was prepared according to known literature procedure with slight modification.[62] A solution of the nitroalkane **3.162** (1 mmol), and sodium nitrite (2 mmol), in DMSO/water (7:1 V:V; 0.4M) was stirred at 65 °C until disappearance of the starting material (by TLC). An equal volume of water was then added and the aqueous layer was extracted several times with diethyl ether. The combined organic layers were dried over sodium sulfate, concentrated and the resulting crude was purified by column chromatography to afford the desired product as a clear colorless oil, 66% isolated yield. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.36 – 7.11 (m, 5H), 3.01 – 2.90 (m, 2H), 2.67 – 2.58 (m, 2H), 2.51 (dt, *J* = 17.6, 7.3 Hz, 1H), 2.46 – 2.38 (m, 1H), 2.13 (s, 3H), 2.00 – 1.80 (m, 2H), 1.64 – 1.46 (m, 2H), 1.37 – 1.15 (m, 8H), 0.87 (t, *J* = 6.9 Hz, 3H). **^{13}C NMR** (126 MHz, cdcl$_3$) δ 213.40, 207.69, 142.02, 128.62, 128.45, 125.96, 77.41, 77.16, 76.91, 46.45, 44.87, 41.68, 35.24, 31.92, 31.49, 30.47, 30.10, 29.85, 26.92, 25.15, 22.56, 14.12.

[62] Tománková, Z.; Setnička, V.; Urbanová, M.; Matějka, P.; Král, V.; Volka, K.; Bouř, P. *J. Org. Chem.* **2004**, *26*, 8997–9001.

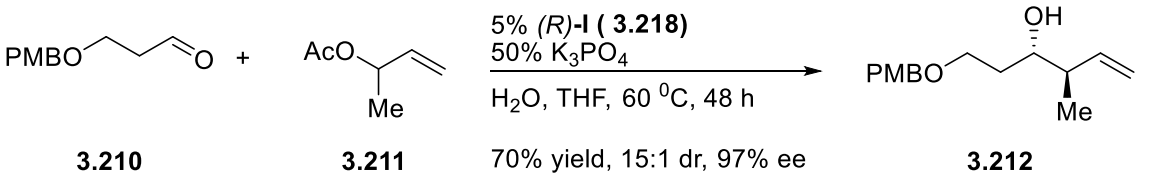
3.6.2.2 Fragment A

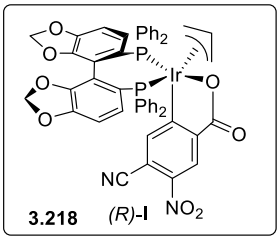


3-((4-methoxybenzyl)oxy)propan-1-ol (3.209) The title compound was prepared from known literature procedure. NMR spectral data were in agreement with literature.[63]



3-((4-methoxybenzyl)oxy)propanal (3.210) The title compound was prepared from known literature procedure. NMR spectral data were in agreement with literature.[64]

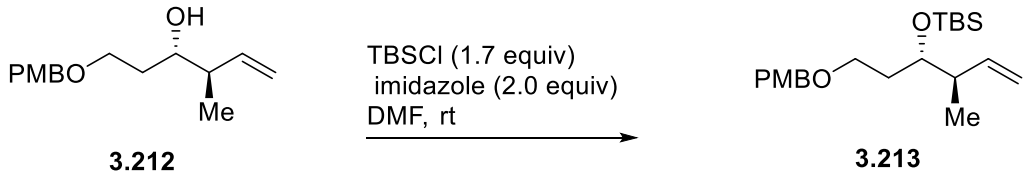




***(3S,4R)*-1-((4-methoxybenzyl)oxy)-4-methylhex-5-en-3-ol (3.212)**. The title compound was prepared according to known literature procedure[65] with slight modification. In the glove box, an oven dried 4 dram vial with a magnetic stir bar was charged with 3-(4-methoxybenzyloxy)propanal **3.201** (310.8 mg, 1.6 mmol, 1.0 equiv), [(*R*)-(+)-5,5'-Bis(diphenylphosphino)-4,4'-bi-1,3-benzodioxole][4-cyano-3-

[63] Gao, D.; Li, B.; O'Doherty, G. A. *Org. Lett,* **2019**, *21,* 8334–8338.
[64] See reference 1
[65] Gao, X.; Townsend, I. A.; Krische, M. J. *J. Org. Chem*. **2011**, *76*, 2350−2354

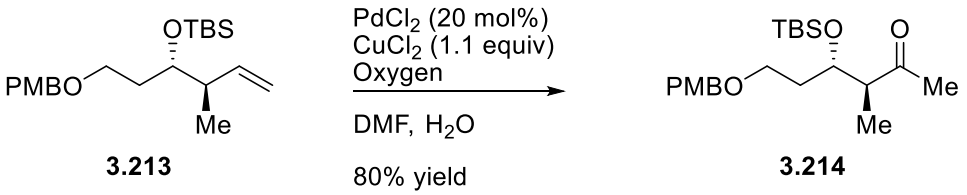
nitrobenzenecarboxylato][1,2,3-n-2-propenyl]iridium(III) **3.218** (41.4 mg, 0.04 mmol, 0.025 equiv), K_3PO_4 (169.8 mg, 0.8 mmol, 0.5 equiv), THF (0.8 mL, 2.0 M). The vial was sealed with a teflon septum and removed from the glove box. Under nitrogen, isopropanol (0.244 ml, 3.20 mmol, 2.0 equiv) was added, followed by but-3-en-2-yl acetate **3.211** (0.051 ml, 3.2 mmol, 2.0 equiv). The reaction flask was allowed to stir at ambient temperature for 0.5 hours then placed in an oil bath at 60 °C and allowed to stir for 48 hours. The reaction was concentrated in vacuo. The residue was purified by silica gel chromatography (2 to 5% ethyl acetate in hexane) to afford compound the product as a clear colorless oil in (70%, 282 mg, 20:1 dr). NMR spectra and mass spec data were in accord with the reported literature.[66] **[α]** $^{26.7}$ **D**: +5.13 (c= 1.94, $CHCl_3$, *l*=50 mm), 97% ee.



Tert-butyl(((*3S,4R)*-1-((4-methoxybenzyl)oxy)-4-methylhex-5-en-3-yl)oxy)dimethylsilane (3.213). To a solution of alcohol **3.212** (250 mg, 1.0 mmol, 1 equiv) in DMF (1.1 ml, 0.9M), was added TBSCl (263.4 mg, 1.75 mmol, 1.75 equiv), imidazole (136 mg, 2.0 mmol, 2 equiv). Sealed and stirred overnight for 16 hours at ambient temperature. Quenched with water and extracted three times with diethyl ether. The combined organic layers were dried over sodium sulfate and concentrated in vacuo. The crude reaction mixture was purified by silica gel chromatography in 5% ethyl acetates in

[66] See reference 3

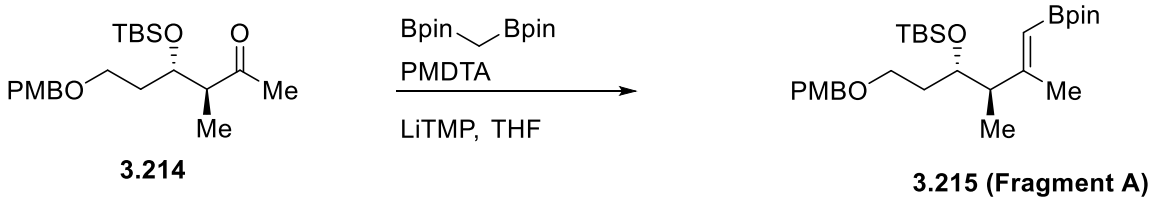
hexanes to yield a clear colorless oil (93%, 341 mg). Spectral data were in accord with the literature.[67]



***(3S,4S)*-4-((tert-butyldimethylsilyl)oxy)-6-((4-methoxybenzyl)oxy)-3-methylhexan-2-one (3.214).** The title compound was synthesized using known literature procedure with slight modification.[68] In the glove box, an oven dried round bottom flask with a stir bar was charged with $PdCl_2$ (25.9 mg, 0.146 mmol, 0.2 equiv) and CuCl (79.5 mg, 0.8 mmol, 1.1 equiv). Sealed and brought outside of the glove box. To this suspension was added DMF (2.5 ml), water (2.0 ml) and stirred at ambient temperature for 2 hours under an oxygen atmosphere. A solution of alkene **3.213** in DMF (2.5 ml) and water (2.0 ml) was slowly added by canula and the resulting reaction mixture was heated at 75 °C for 23 hours. Cooled to room temperature, diluted with diethyl ether, cold 5% aqueous HCl was added and the organic layer was washed with saturated aqueous $NaHCO_3$. The organic layer was dried over sodium sulfate and the crude reaction mixture was purified by silica gel chromatography in 5% ethyl acetate in hexanes to afford the product as a clear colorless oil (79%, 220 mg). **^{1}H NMR** (500 MHz, $CDCl_3$)δ 7.25 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.3 Hz, 2H), 4.47 – 4.33 (m, 2H), 4.11 (td, J = 6.3, 4.2 Hz, 1H), 3.80 (s, 3H), 3.52 (td, J = 6.6, 1.5 Hz, 2H), 2.78 – 2.63 (m, 1H), 2.14 (s, 3H), 1.82 – 1.71 (m, 1H), 1.71 – 1.59 (m, 1H),

[67] Eggen, M.; Mossman, C. J.; Buck, S. B.; Nair, S. K.; Bhat, L.; Ali, S. M.; Reiff, E. A.; Boge, T. C.; Georg, G. I. *J. Org. Chem.* **2000**, *65*, 7792–7799.
[68] Czuba, I. R.; Zammit, S.; Rizzacasa, M. A. *Org. Biomol. Chem*., **2003**, *1*, 2044–2056.

1.04 (d, J = 7.0, 0.7 Hz, 3H), 0.86 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 211.5, 159.3, 130.8, 129.3, 113.9, 72.7, 71.0, 66.0, 55.4, 52.6, 46.7, 33.7, 30.4, 26.0, 18.1, 11.8, -4.5, -4.7. **HRMS**-(DART+) for $C_{21}H_{40}N_{O4}Si$ $[M+NH4]^+$: calculated: 398.2721, found: 398.2719. **IR** (neat): 2951 (m), 2927 (m), 2854 (m), 1713 (s), 1512 (m), 1359 (w), 1247 (s), 1099 (s), 1038 (s), 834 (s). **[α] $^{26.7}$ D**: +30.217 (c=0.9, $CHCl_3$, l=50 mm).

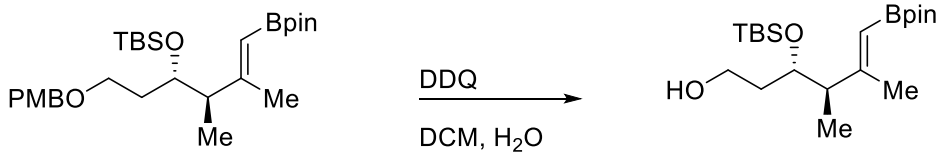


3.214 **3.215 (Fragment A)**

Tert-butyl(((*3S,4R,E)*-1-((4-methoxybenzyl)oxy)-4,5-dimethyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-5-en-3-yl)oxy)dimethylsilane (3.215). The title compound was prepared according to known literature procedure.[69] In a glove box, an oven dried round bottom flask with a magnetic stir bar was charged with LiTMP (170 mg, 1.16 mmol, 2.0 equiv), 2.50 ml of THF was added, then PMDTA (150.3 mg, 0.87 mmol 1.5 equiv), sealed with a rubber septa and removed from the glovebox. Under nitrogen, the reaction vial was cooled to 0 °C, and a solution of bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane (131.0 mg 1.16 mmol, 2.0 equiv) in THF (2.5 mL) was added in one portion. The reaction was allowed to stir for 5 minutes. The reaction was cooled to -78 °C and ketone **3.214** (220mg, 0.58 mmol, 1.0 equiv) in 1.4 ml THF was added dropwise. The reaction was allowed to stir for 16 hours at -78 °C. Upon completion, the

[69] Namirembe, S.;.Gao, C; Wexler, P. R.; Morken, J. P. *Org. Lett.,* **2019***, 21*, 4392–4394.

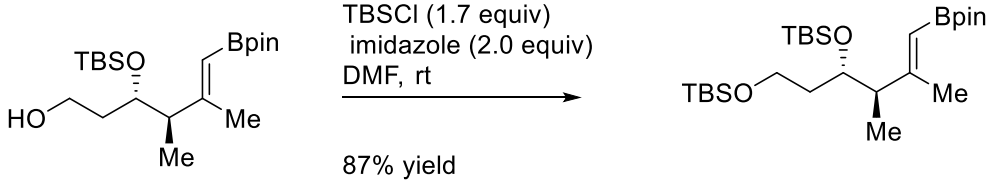
reaction was opened to air, and filtered through a silica gel plug with eluting diethyl ether. The mixture was concentrated under reduced pressure. The crude reaction mixture was purified by silica gel chromatography in 2 to 5% ethyl acetate in hexanes to afford the alkenyl boronic ester as a clear colorless oil (85%, 248mg, >20: 1 E/Z). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.15 (s, 1H), 4.47 – 4.34 (m, 2H), 3.92 (dt, *J* = 7.2, 4.6 Hz, 1H), 3.80 (s, 3H), 3.54 – 3.41 (m, 2H), 2.40 – 2.29 (m, 1H), 1.99 (s, 3H), 1.72 – 1.60 (m, 2H), 1.26 (s, 12H), 1.01 (d, *J* = 7.0 Hz, 3H), 0.87 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 164.2, 159.2, 130.9, 129.3, 113.9, 82.7, 72.6, 71.6, 67.3, 55.4, 50.0, 32.7, 26.1, 25.07, 25.0, 20.9, 18.2, 13.3, -4.3, -4.5. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 29.25. **IR** (neat): 2953 (m), 2926 (m), 2854 (m), 1634 (m), 1512 (m), 1361 (w), 1319 (s), 1247 (s), 1144 (s), 1101 (m), 834 (s). **HRMS**-(DART+) for $C_{28}H_{50}BO_5Si$ $[M+H]^+$: calculated: 505.3515, found: 505.3525. **[α] $^{26.7}$ D**: +9.332 (c=1.05, $CHCl_3$, *l*=50 mm).



3.215 **3.216**

(*3S,4R,E*)-3-((tert-butyldimethylsilyl)oxy)-4,5-dimethyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-5-en-1-ol (3.216).To a 20 ml scintillation vial with stirbar and compound **5** (142 mg, 281.42 umol), was added CH_2Cl_2(1.8 ml) and water (0.2ml). The mixture was allowed to stir for 2 minutes at room temperature. DDQ (70.27 mg, 309.56 umol) was then added. The reaction wasallowed to stir at room temperature for 3hours. Upon the completion of the reaction, water (3 ml) was added. The mixture was transferred

to a separotary funnel. Layers were separated. The aqueous layer was extracted byCH_2Cl_2 three times. The organic layers were combined, dried over sodium sulfate, filtered and concentrated under vacuo. The crude product was purified through silica gelcolumn with 10% ethyl acetate in hexane as eluent. The product was afforded as clear oil (94.1 mg, 87%). **1H NMR** (600 MHz, $CDCl_3$) δ 5.18 (s, 1H), 3.98 (ddd, J = 7.1, 5.5, 4.2Hz, 1H), 3.72 (dtt, J = 15.5, 9.9, 5.1 Hz, 2H), 2.42 (p, J = 6.6 Hz, 1H), 2.00 (s, 3H), 1.75– 1.57 (m, 2H), 1.26 (s, 12H), 1.01 (d, J = 7.0 Hz, 3H), 0.89 (s, 9H), 0.08 (d, J = 14.0 Hz, 6H). **13C NMR** (151 MHz, CDCl3) δ 163.8, 82.9, 73.6, 60.8, 49.5, 34.2, 26.1, 25.1, 25.1, 21.2, 18.2, 13.2, -4.2, -4.4. **HRMS**-(DART+) for C11H41BO4 [M+H]+: calculated: 385.2920, found:385.2937. **IR** (neat): 2953.1 (m), 2927.2 (m), 2854.3 (w), 1634.4 (m), 1369.2 (s), 1320.0 (s), 1254.3 (s), 1101.8 (m), 1049.0 (m), 835. 0(s), 773.4(m). $[\alpha]_D^{20}$ = +5.774 (c=1.05, CHCl3, l=50 mm).

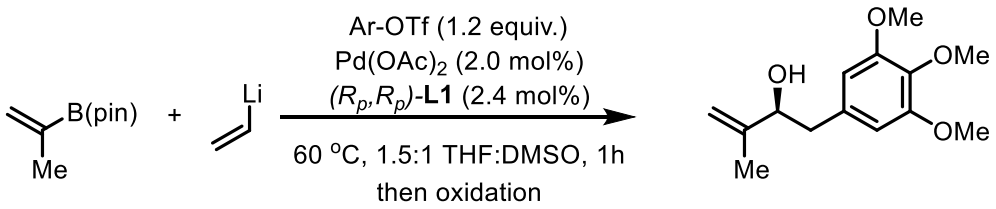


3.216 **3.217**

(*S*)-2,2,3,3,9,9,10,10-octamethyl-5-((R,E)-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-2-yl)-4,8-dioxa-3,9-disilaundecane (**3.217**). To an 2 dram vial with a stir bar was added alcohol **3.216** (84.4 mg, 0.22 mmol), DMF (0.5 ml, 0.44 M), TBSCl (56.3 mg, 0.373 mmol, 1.7 equiv), and imidazole (29.9 mg, 0.440 mmol, 0.22 mmol). Sealed vial and stirred overnight at room temperature. Quenched with distilled water and extracted with hexanes four times. The combined organic layers were dried over

sodium sulfate, and concentrated in vacuo. The crude material was purified using silicagel chromatography to afford the desired product as a clear colorless oil, 95.5 mg, 87%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.15 (s, 1H), 4.01 – 3.85 (m, 1H), 3.70 – 3.54 (m, 2H), 2.44 – 2.17 (m, 1H), 1.99 (s, 3H), 1.58 – 1.46 (m, 2H), 1.26 (s, 12H), 1.01 (d, *J* = 7.0 Hz, 3H), 0.88 (s, 9H), 0.87 (s, 6H), 0.05 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 164.35, 82.71, 77.41, 77.16, 76.91, 71.08, 60.16, 49.94, 35.63, 26.10, 26.06, 25.03, 25.00, 20.93, 18.39, 18.24, 13.11, -4.37, -4.45, -5.09, -5.17. **HRMS**-(DART+) for C26H55BO4Si4 [M+H]+: calculated: 499.3805, found: 499.3813. **IR**(neat): 2956.0 (m), 2928.9(m), 2857.1(m), 2358.5(s), 1635.6 (s), 1255.49 (m), 1146.4(s). **$[\alpha]_D^{20}$** = +3.31(c=1.86, $CHCl_3$, l=50 mm).

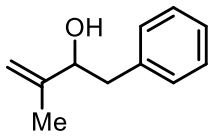
3.6.2.3 Fragment B



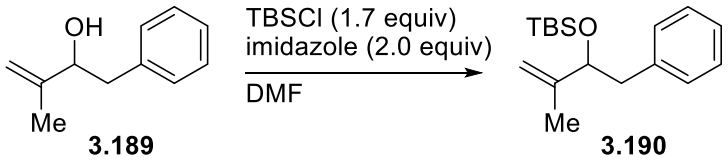
3.187
66%, 85:15 er

***(S)*-3-methyl-1-(3,4,5-trimethoxyphenyl)but-3-en-2-ol (3.187).** The title compound was prepared according to known procedure[70] to affording the desired product as a clear colorless oil, 66% yield, 85:15 er. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.46 (s, 2H), 5.02 (s, 1H), 4.89 (s, 1H), 4.26 (dd, *J* = 8.5, 4.4 Hz, 1H), 3.86 (s, 6H), 3.83 (s, 3H), 2.98 (s, 3H), 2.86 (dd, *J* = 13.7, 3.9 Hz, 1H), 2.69 (dd, *J* = 13.8, 9.1 Hz, 1H).

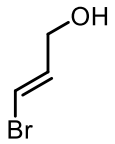
[70] See chapter 2, Experimental information.



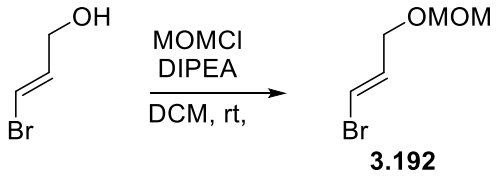
3-methyl-1-phenylbut-3-en-2-ol (3.189). The title compound was synthesized according to literature known literature procedure. NMR and mass spectra data was in accord with the literature.[71]



tert-butyldimethyl((3-methyl-1-phenylbut-3-en-2-yl)oxy)silane (3.190). To alcohol **3.189** (1.94 g, 11.96 mmol, 1 equiv) in a round bottom flask was added DMF (17 ml, 0.7 M), TBSCl (3.06 g, 20.3 mmol, 1.7 equiv) and imidazole (1.63 g, 23.9 mmol, 2.0 equiv) and stirred overnight. Quenched with water and stirred for 30 minutes. Extracted the aqueous layer with hexanes. Dried the combined organic layers with sodium sulfate and concentrated in vacuo. The crude material was purified by silica gel chromatography in 10% ethyl acetate in hexanes to afford the desired product was a clear colorless oil 2.84 g, 85%. The spectra and mass spec data were in according with the literature.[72]

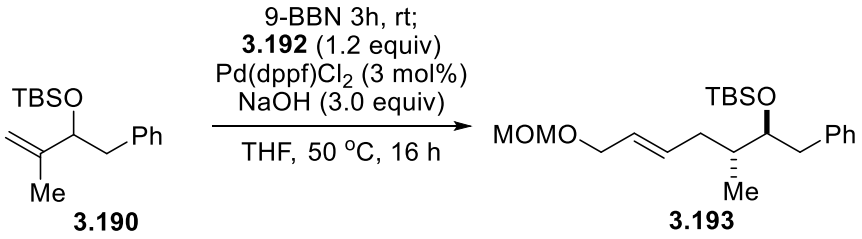


(E)-3-bromoprop-2-en-1-ol. The tile compound was prepared according to known literature procedure and the NMR and mass spectra data was in accord with the literature. [73]



[71] Schleicher, D. K.; Jamison, F, T. *Beilstein J. Org. Chem.* **2013,** *9,* 1533–1550
[72] See reference 70.
[73] Malapel-Andrieu, B.; Mérour, J-Y.Tet. Lett, **1998**, *39*,143–146.

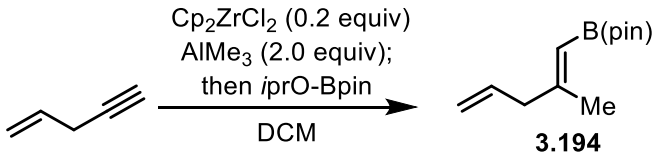
***(E)*-1-bromo-3-(methoxymethoxy)prop-1-ene (3.192).** The title compound was prepared according to known literature procedure.[74] A solution of *(E)*-3-bromoprop-2-en-1-ol. (08.93 mmol) and i-PrNEt$_2$ (326.73 mmol) in 40 mL of dry CH_2Cl_2 was cooled to -15 ºC and a solution of MOMCl (13.36 mmol) in 10 mL of CH_2Cl_2 was added dropwise. A cooling bath was removed and reaction mixture was stirred overnight at room temperature under inert atmosphere. Then mixture was diluted with 50 mL of CH_2Cl_2 followed by addition of 50 mL of H_2O. After separation of phases, aqueous one was washed with additional portion of CH_2Cl_2 (10 mL) and dried over magnesium sulfate. Concentrated in vacuo and purified by silicagel chromatography in 10% ethyl acetate in hexanes to afford the desired product in 20% yield as clear colorless oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.40 – 6.35 (m, 1H), 6.33 – 6.26 (m, 1H), 4.63 (s, 2H), 4.02 (dd, *J* = 6.0, 1.5 Hz, 2H), 3.37 (s, 3H).



***(9R,10S,E)*-10-benzyl-9,12,12,13,13-pentamethyl-2,4,11-trioxa-12-silatetradec-6-ene (3.193**). To an oven dried 2 dram vial with a stir bar was added allyl silyl ether **(3.190)** (55.30mg, 0.2 mmol, 1.0 equiv) flushed with nitrogen and added 0.2 ml of THF. Under nitrogen, added a solution of 9-BBN in THF (0.5 M, 440. uL, 1.1 equiv) dropwise at room temperature and allowed the reaction to stir for 3 hours. The vial was pumped into the glove box, added Pd(dppf)Cl$_2$ (4.90 mg, 0.06 mmol, 0.03 equiv), NaOH (24 mg, 0.6 mmol, 3

[74] Mames, A.; Stecko, S.; Mikolajczyk, P.; Soluch, M.; Bartlomiej, F.; Chmielewski, M. *J. Org. Chem.* **2010**, *22*, 7580–7587.

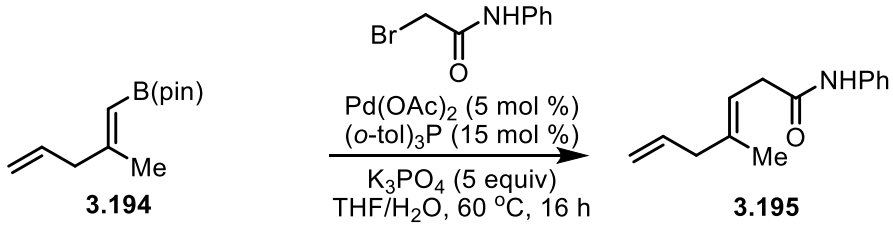
equiv) and alkenyl bromide **(3.192).** Sealed with a teflon cap and brought outside the glovebox. Heated the reaction at 50 C for 16 hours. Cooled to room temperature and quenched the reaction with water. Extracted with ethyl acetate and dried the combined organic layers over sodium sulfate. Concentrated in vacuo. The crude dr was determined to be 5:1. The crude material was columned using silica gel chromatography to afford the product as a clear colorless oil in 82% yield, 75.7 mg. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.28 (s, 3H), 7.19 (td, *J* = 8.5, 4.1 Hz, 2H), 5.73 (dt, *J* = 14.6, 7.0 Hz, 1H), 5.64 (d, *J* = 1.3 Hz, 1H), 4.67 (s, 2H), 4.06 (d, *J* = 6.2 Hz, 2H), 3.78 (dd, *J* = 7.9, 4.1 Hz, 1H), 3.39 (s, 3H), 2.74 (dd, *J* = 13.4, 4.8 Hz, 1H), 2.61 (dd, *J* = 13.4, 8.1 Hz, 1H), 2.32 – 2.21 (m, 1H), 2.01 – 1.92 (m, 1H), 0.94 (d, 3H), 0.84 (s, 9H), -0.08 (s, 3H).



***(E)*-4,4,5,5-tetramethyl-2-(2-methylpenta-1,4-dien-1-yl)-1,3,2-dioxaborolane (3.194).** The title compound was prepared according to a known literature procedure.[75] Zirconocene dichloride (29 mg, 0.1 mmol, 0.2 eq) was placed into a non-dry 25 mL pear-shaped flask and the atmosphere was exchanged with nitrogen 3 times. Reagent-grade DCM (500 ppm water, as stated by the vendor) was added (1.1 mL) to give a clear colorless solution, which was then cooled to 0 °C. AlMe3 (2 M in toluene, 0.50 mL, 1.0 mmol, 2 eq) was added dropwise at 0 °C and the resulting clear yellowish solution was stirred for 5–10 min. Neat starting pent-1-en-4-yne (0.50 mmol) was then added with a syringe, the ice bath was removed, and the mixture was stirred at 23 °C overnight (14 hr). Neat i-PrOBpin (0.12 mL,

[75] Zhurakovskyi, O.; Dias, P. M. P.; Noble, A.; Aggarwal, K. V. *Org. Lett.* **2018**, *10*, 3136–3139.

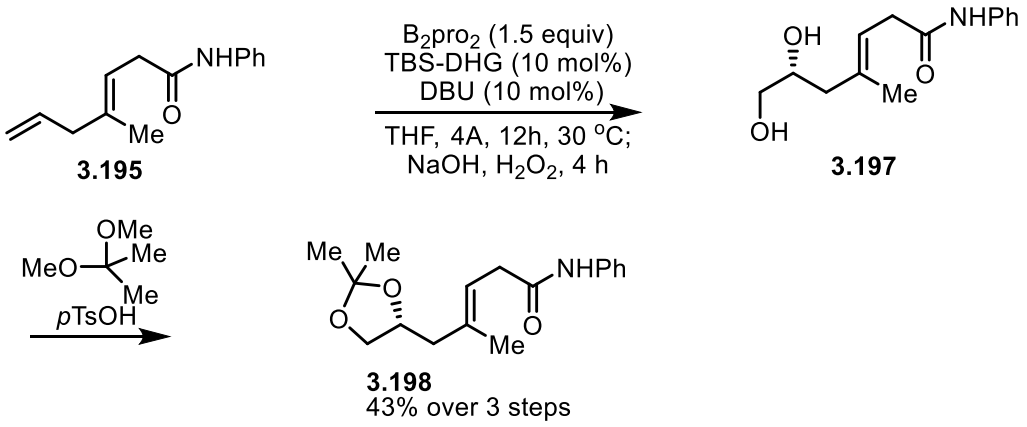
0.6 mmol, 1.2 eq) was then added at 0 °C in one portion, the ice bath was removed, and the mixture was stirred at 23 °C for 60 min. The Al–B exchange is fast. The reaction mixture was then cooled to 0 °C and diluted with 25 mL of reagent-grade DCM. A solution of HCl (3 M in H_2O, 3.3 mL) was added dropwise (caution: gas evolution!) and the mixture was stirred at 0 °C for 10 min, until gas evolution ceased. The mixture was then diluted with 3 M HCl (33 mL) and extracted with DCM (4×3 mL). The combined organic layer was washed with brine (4 mL) and dried over Na_2SO_4. The solution was passed through a plug of silica , washing the plug with 10 mL of DCM, then concentrated. A 3-5 mg aliquot was submitted for NMR analysis to measure regioselectivity. Purification of the crude sample by silica chromatography in 2-10% ethyl ether in pentanes then provided the target vinyl boronate in 80% yield. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.86 – 5.69 (m, 1H), 5.16 (s, 1H), 5.11 – 4.97 (m, 2H), 2.83 (d, *J* = 7.0 Hz, 2H), 1.99 (s, 3H), 1.27 (s, 12H).



***(E)*-4-methyl-N-phenylhepta-3,6-dienamide (3.195).** The title compound was prepared according to known literature procedure.[76] To a 2 dram vial with a magnetic stir bar in a glove box was added Palladium acetate (3.3mg, 0.05mmol), tris-o-tolyphosphine (13.7mg, 0.15mmol), 0.4 ml THF and stirred at ambient temperature for 10 minutes. In a separate 2 dram vial with a magnetic stir bar was added (E)-4,4,5,5-tetramethyl-2-(2-methylpenta-1,4-dien-1-yl)-1,3,2-dioxaborolane **(3.194).** (0.3mmol), 2-bromo-N-phenyl-acetamide

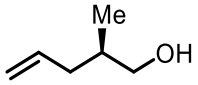
[76] See Chapter 2

(77.1mg, 0.36mmol), tripotassium phosphate (318.4mg, 1.5mmol), and 0.6 ml THF. To this solution was added the pre complexed palladium/ligand solution in THF. Rinsed the palladium/ ligand vial with 0.2ml of THF and added this to the reaction solution, sealed and brought outside of the glove box. Under Nitrogen, water (nitrogen sparged for 30 minutes) (0.11ml, 0.6mmol) was added to the reaction, taped and stirred at 60 °C for 16 hours. Quenched with water, extracted with ethyl acetate, dried with sodium sulfate, concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography on silica gel (5% ethyl acetate /hexanes) to afford the desired product as a faint yellow solid 60%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.58 – 7.44 (m, 2H), 7.39 – 7.32 (m, 2H), 7.20 – 7.01 (m, 1H), 5.92 – 5.78 (m, 1H), 5.56 – 5.43 (m, 1H), 5.19 – 5.03 (m, 1H), 3.18 (d, *J* = 7.5 Hz, 3H), 2.88 (d, *J* = 6.9 Hz, 3H), 1.75 (s, 3H).

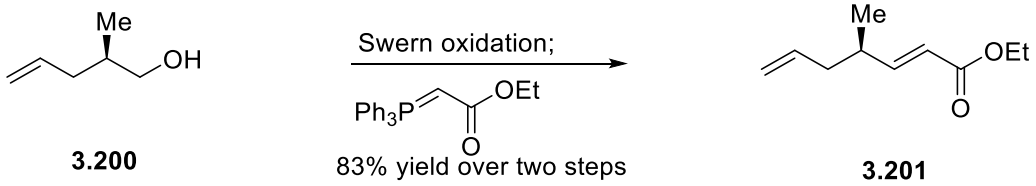


***(R,E)*-5-(2,2-dimethyl-1,3-dioxolan-4-yl)-4-methyl-N-phenylpent-3-enamide (3.198)**. *(E)*-4-methyl-N-phenylhepta-3,6-dienamide **(3.195)** was diborated in accord with previously reported protocol for compound **3.177**. Note: The diol after oxidation was very polar and ethyl acetate extraction led to a big mass loss so the crude was used instead for the protection step. To the crude oxidized product in a round bottom flask was added acetonide and *p*TsOH and stirred overnight. Extracted with ethyl acetate, dried over sodium

sulfate and concentrated in vacuo. The crude material was purified by silicagel chromatography in 40% ethyl acetate, 10% methanol in hexanes to afford the desired product as faint yellow solid in 43% yield. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.2 Hz, 2H), 7.35 – 7.27 (m, 2H), 7.13 – 7.03 (m, 1H), 5.53 (t, *J* = 7.8 Hz, 1H), 4.38 – 4.28 (m, 1H), 4.13 (ddd, *J* = 8.0, 6.1, 1.6 Hz, 1H), 3.66 (ddd, *J* = 7.9, 5.8, 1.6 Hz, 1H), 3.25 (dd, *J* = 17.3, 8.6 Hz, 1H), 3.09 (dd, *J* = 17.3, 7.0 Hz, 1H), 2.46 – 2.14 (m, 2H), 1.77 (s, 3H), 1.42 (s, 3H), 1.36 (s, 3H).



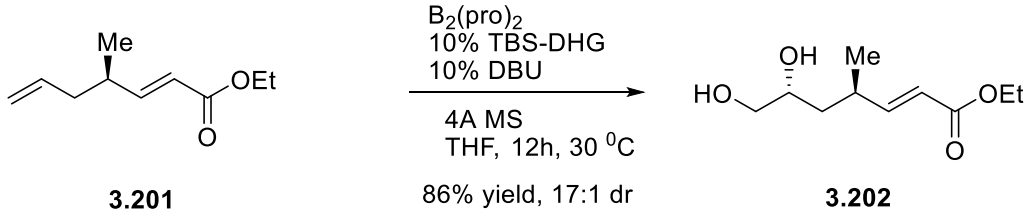
(*R*)-2-methylpent-4-en-1-ol (3.200). The title compound was prepared according to known literature procedure.[77]



Ethyl *(R,E)*-4-methylhepta-2,6-dienoate (3.201). The title compound was prepared according to known literature procedure with slight modification.[78] To a flame dried round bottom flask was added oxalyl chloride (7.6 ml, 89.9 mmol, 1.5 equiv), DCM (30 ml). Cooled to -78 °C, added a solution of DMSO (12.8ml, 179.8 mmol, 3 equiv) in DCM (30 ml) dropwise over 15 minutes and then a solution of 4- penten-1-0l alcohol (**3.200**) (2.58 ml, 59.9 mmol, 1 equiv) in 60 ml of DCM. The reaction was allowed to stir for 30 minutes at -78 °C. Et_3N (41.8 ml, 299.5 mmol, 5 equiv) was added dropwise over 15 minutes. The reaction mixture was stirred for 2 hours at -78 °C and allowed to warm to room temperature

[77] Boerth, J. A.; Hummel, J. R.; Ellman, J. A. *Angew. Chem. Int. Ed*., **2016**, *128*, 4324–4327.
[78] Srinivas, B.; Reddy, D. S.; Mallampudi, N. A.; Mohapatra, D. K. *Org. Lett*., **2018**, *20*, 6910−6914.

overnight for 14 hours. TLC analysis after the overnight reaction showed full consumption of alcohol. (2-ethoxy-2-oxoethyl)triphenylphosphonium bromide was added in one portion and the reaction was stirred overnight. The reaction mixture was quenched with saturated aqueous ammonium chloride (150 ml) and extracted the aqueous layer with DCM (3x 150 ml). The combined organic layers were dried over sodium sulfate, and concentrated under reduced pressure. The crude was then dissolved in diethyl ether, white precipitate crushes out which was filtered off on silica gel. The reconcentrated crude mixture was purified by silica gel chromatography in 10% diethyl ether in pentanes to give a sweet smelling colorless oil (83% 7.7 g). Spectral data was in accord with the literature.[79]



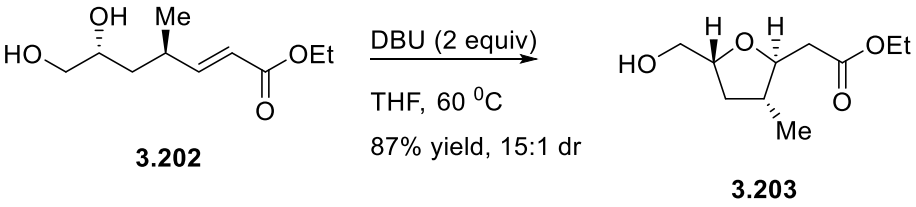
3.201 **3.202**

Ethyl *(4R,6R,E)*-6,7-dihydroxy-4-methylhept-2-enoate (3.202). The title compound was prepared according to the literature procedure[80]. In the glovebox, an oven dried round bottom flask equipped with a magnetic star bar was charged with TBS-DHG catalyst (312.0 mg, 1.19 mmol, 0.1 equiv), propanediol diboron (4.04 g, 23.8 mmol, 2.0 equiv), 4Å molecular sieves (1.19 g), the alkene substrate **3.201** (2.0 g, 11.9 mmol, 1.0 equiv) and THF (11.90 mL). DBU (177.0 µl, 1.19 mmol, 0.1 equiv) was then added to the solution. The flask was sealed with a septum and brought outside of the glove box and allowed to stir in a 30 °C oil bath for 16 hours. The reaction was warmed to room temperature. Under

[79] See reference 9
[80] Feng, R.; Lu, Y.; Deng, G.; Xu, J.; Wu, Z.; Li, H.; Liu, Q.; Kadowaki, N.; Abe, M.; Zeng, X. *J. Am. Chem. Soc.,* **2018**, *140*, 3663.

nitrogen, added 25 ml of THF. Cooled the reaction to -78 °C. 48 ml of 30% hydrogen peroxide was added dropwise over 15 minutes (reaction is extremely exothermic) followed by 96 ml of pH7 phosphate buffer and stirred at -78 °C for another 5 minutes. Transferred the reaction flask to an ice bath at 0°C and slowly allowed the reaction to warm to room temperature over 45 minutes and stirred for another 4 hours at room temperature. Transferred the reaction mixture to a 500ml flask and cooled the reaction to 0 °C. 90 ml of saturated sodium thiosulfate was added dropwise over 15 minutes (extremely exothermic quench) and allowed the reaction to stir for another 30 minutes while warming to ambient temperature. Extracted the aqueous layer (250 ml x 5) with ethyl acetate. The combined organics were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude reaction mixture which was purified by silica gel chromatography in 50% ethyl acetate in hexanes to afford the desired diol as clear colorless oil in 68-79% yield and 17:1 dr.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.92 (dd, J = 15.7, 7.7 Hz, 1H), 5.81 (d, J = 15.7 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.78 (tt, J = 7.6, 4.6 Hz, 1H), 3.65 (dd, J = 11.0, 2.9 Hz, 1H), 3.43 (dd, J = 11.0, 7.5 Hz, 1H), 2.64 – 2.49 (m, 1H), 2.17-1.98 (m,2H (OH)), 1.60 (ddd, J = 15.0, 8.6, 6.6 Hz, 1H), 1.42 – 1.35 (m, 1H), 1.28 (t, J = 7.1 Hz, 3H), 1.09 (d, J = 6.7 Hz, 3H). **^{13}C NMR** (151 MHz, CDCl3) δ 167.1, 154.2, 120.0, 70.1, 67.0, 60.5, 39.2, 33.2, 19.2, 14.5. **HRMS-(DART+)** for $C_{10}H_{19}O_4$ $[M+H]^+$: calculated: 203.1278, found: 203.1274. **IR** (neat): 3384.1 (br), 2957 (m), 2929 (m), 2871 (w), 1714 (s), 1700 (s), 1649 (m), 1279 (s), 1037 (s), 835 (w).**[α]** $^{26.7}$**D**: -18.997 (c=1.0, $CHCl_3$, *l*=50 mm).



3.202 **3.203**

Ethyl 2-(*(2S,3R,5R)*-5-(hydroxymethyl)-3-methyltetrahydrofuran-2-yl)acetate (3.203). A flame dried round bottom flask with a magnetic stir bar was charged with diol **3.202** (1.3 g, 6.43 mmol, 1.0 equiv). The flask was sealed with a rubber septum and purged three times with nitrogen. Under nitrogen, added THF (32.1 ml), followed by DBU (1.92 ml, 12.9mmol, 2.0 equiv). Removed nitrogen inlet and taped septum. Allowed the reaction to stir at 60°C for 16 hours. Warmed to room temperature, and concentrated in vacuo. The crude reaction mixture was purified by silica gel chromatography in 50% ethyl acetate in hexanes to afford the desired product as a clear colorless oil, 85% (1.11g, 85%, >20:1 dr). Spectral data was in accord with the literature.[81]

Absolute configuration was confirmed by comparison of the optical rotation with the reported literature.

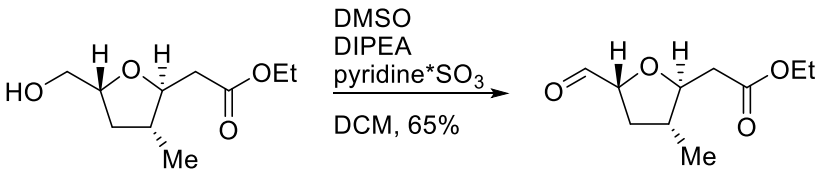
$[\alpha]^{28.7}_{D}$= -35.7483(>20:1 dr c = 3.90, $CHCl_3$, *l* =50 mm).

Reported optical rotation:

$[\alpha]^{24.3}_{D}$: -44.9 (91:9 dr, c=3.00, $CHCl_3$)[82]

$[\alpha]^{20}_{D}$: -28.0 (>20:1 dr, c = 1.95, CH_2Cl_2)[83]

[81] Valot, G.; Mailhol, D.; Regens, S. C.; O'Malley, P.D.; Godineau, E.; Takika-wa, H.; Philipps, P.; Fürstner, A. *Chem. Eur. J*., **2015**, *21*, 2398 – 2408.
[82] Bates, R. H.; Shotwell, J. B.; Roush, W. R. *Org. Lett.,* **2008**, *10*, 4343−4346.
[83] See reference 12

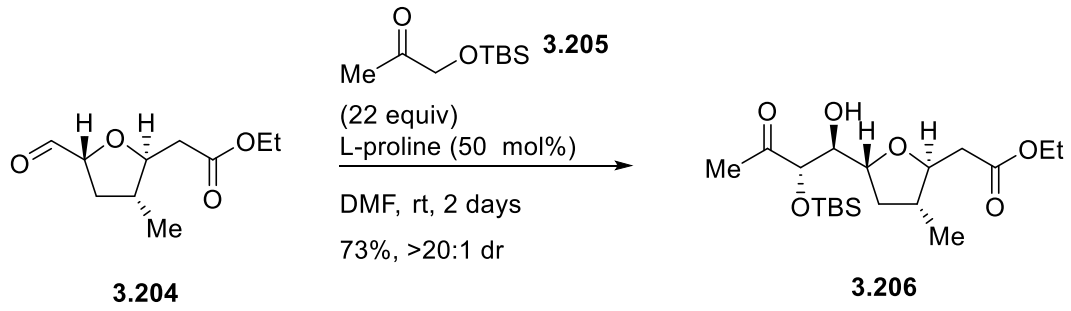


3.203 **3.204**

Ethyl 2-(*(2S,3R,5R)*-5-formyl-3-methyltetrahydrofuran-2-yl)acetate (3.204). The title compound was prepared according to known literature procedure with slight modification[84]. To a flame dried round bottom flask with a magnetic stir bar was added alcohol **3.203** (1.05 g, 5.19 mmol), followed by 58 ml of DCM. The reaction flask was cooled to 0 °C, added DMSO (1.84 ml, 26.0 mmol, 5 equiv), Et_3N (6.47 ml, 46.4 mmol, 8.9 equiv) and the mixture was stirred for 5 minutes. SO3•Pyr (2.48 g, 15.6 mmol, 3.0 equiv) was added in one portion and the reaction mixture stirred for another 2 h at 0 °C. The reaction was diluted with DCM and subsequently quenched by adding saturated aqueous sodium bicarbonate and let to warm ambient temperature. The aqueous layer was extracted with dichloromethane three times. The combined organic layers were dried over sodium sulfate, and concentrated under reduced pressure. The crude mixture was columned by silica gel chromatography to afford the product as a clear colorless oil (65%, 1.05 g). Spectral data was in agreement with the reported literature.[85]

Note: The aldehyde was used the same day as purified. Decomposition was observed when stored under nitrogen at 0 °C overnight.

[84] See reference 13.
[85] See reference 13.



Ethyl 2-(*(2S,3R,5R)*-5-((1S,2S)-2-((tert-butyldimethylsilyl)oxy)-1-hydroxy-3-oxobutyl)-3-methyltetrahydrofuran-2-yl)acetate (3.206). The title compound was prepared according to known literature procedure[86]. To a flame dried round bottom flask with a magnetic stir bar was added aldehyde **3.204** (997 mg, 4.98 mmol, 1 equiv), 1-[tert-butyl(dimethyl)silyl]oxypropan-2-one (**3.205**) (20.6 g, 109. 5 mmol, 22 equiv), DMF (3.61 ml) and then L-proline (286.6 mg, 2.49 mmol, 0.5 equiv). Exchanged the air in the reaction flask with nitrogen and stirred at ambient temperature for 48 hours. The reaction mixture was purified by silica gel chromatography in 5% to 10% ethyl acetate in hexanes to afford the product as a clear colorless (73%, 1.43 g, >20:1 dr). Spectral data were in accord with the reported literature.[87]

Absolute configuration was determined by comparing optical rotation with the reported literature

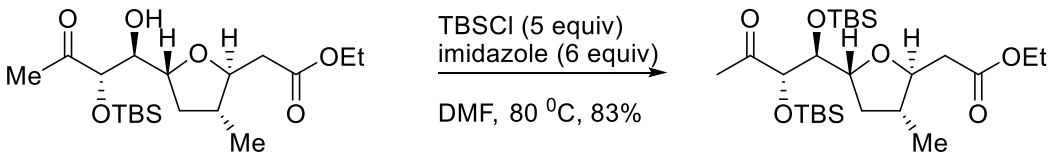
Experimental optical rotation

$[\alpha]^{28.7}_D$: -7.43 (>20:1 dr, c = 4.795, $CHCl_3$, *l* =50 mm).

Reported literature optical rotation:

[86] See reference 12.
[87] See reference 12.

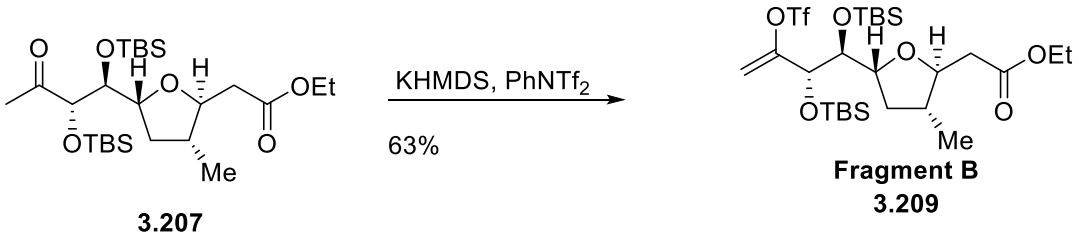
$[\alpha]^{20}_{D}$: -4.3 (>20:1 dr c = 0.49, CH_2Cl_2)[88]



3.206 **3.207**

Ethyl2-((*2S,3R,5R*)-5-((*5S,6S)*-6-acetyl-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladecan-5-yl)-3-methyltetrahydrofuran-2-yl)acetate (3.207). To a flame dried round bottom flask with a magnetic stir bar was added compound **3.207** (605 mg, 1.56 mmol, 1 equiv), DMF (1.56ml, 5 M), TBSCl (1.17g, 7.78 mmol, 5 equiv) and imidazole (636 mg, 9.34 mmol, 6 equiv). Sealed with a rubber septum and heated the reaction flask at 80 °C for 16 hours. Cooled reaction flask to ambient temperature, quenched with distilled water and allowed the reaction to stir for 30 minutes. Extracted 3 x 50 ml with diethyl ether. The combined organic layers were dried over sodium sulfate and concentrated in vacuo. The crude reaction mixture was purified by silica gel chromatography using 2% ethyl acetate in hexanes to afford the desired product as a clear colorless oil (94%, 734 mg). Spectral data was in accord with the literature.[89]

[88] See reference 12.
[89] See reference 12.

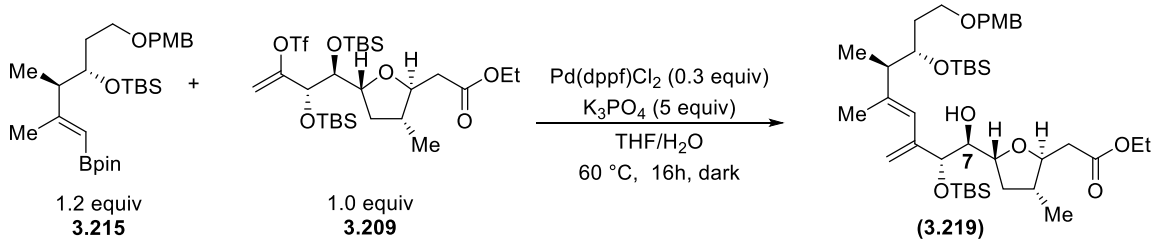


3.207 **Fragment B 3.209**

Ethyl 2-(*(2S,3R,5R)*-3-methyl-5-(*(5S,6S)*-2,2,3,3,8,8,9,9-octamethyl-6-(1-(((trifluoromethyl)sulfonyl)oxy)vinyl)-4,7-dioxa-3,8-disiladecan-5-yl)tetrahydrofuran-2-yl)acetate (3.209). The title compound was prepared according to known literature procedure[90] with slight modification. To a flame dried round bottom flask with a magnetic stir bar was added ketone (200mg, 0.398 mmol, 1 equiv), sealed and purged three times with nitrogen. Under nitrogen, added THF (2.1 ml), and cooled to -78° C. Added a pre-cooled (-78 °C) solution of KHMDS in THF (1.69 ml, 0.25 M, 1.08 equiv) dropwise and stirred for 1 hour at -78°C. The solution turned from colorless to yellow. To this solution at -78 °C was added a pre-cooled solution of phenyl triflimide in THF (1.81 ml, 0.55 M, 2.5 equiv) (the phenyl triflimide was azeotropically dried with toluene prior to use). The reaction was stirred at -78 °C for 2 hours and allowed to warm room temperature overnight. Quenched with saturated ammonium chloride and extracted with diethyl ether. The combined organic layers were dried over sodium sulfate and concentrated in vacuo. The crude reaction mixture was purified by silica gel chromatography using 0 to 0.7% methyl tert-butyl ether in hexanes to yield the alkenyl triflate as a clear colorless oil (64%, 163 mg). Spectral data was in accord with the reported literature. [91]

[90] See reference 12.
[91] Valot, G.; Mailhol, D.; Regens, C. S.; Omalley, D. P.; Godineau, E.; Takikawa, H.; Philipps, P.; Fürstner, A. *Angew. Chem. Int. Ed*., **2013**, *52*, 9534–9538.

3.6.2.4 Western fragment

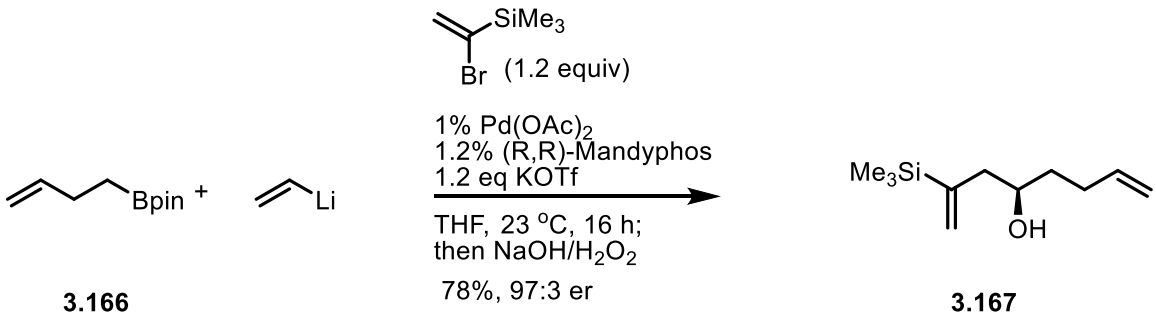


Ethyl 2-((*2S,3R,5R)*-5-((*1S,2R,6R,7S,E)*-2,7-bis((tert-butyldimethylsilyl)oxy)-1-hydroxy-9-((4-methoxybenzyl)oxy)-5,6-dimethyl-3-methylenenon-4-en-1-yl)-3-methyltetrahydrofuran-2-yl)acetate (**3.219**). In the glove box, an oven dried two dram vial with a stir bar was charged with alkenyk triflate **3.209** (64 mg, 0.1 mmol, 1 equiv), alkenyl boronic ester **3.215** (61.0 mg, 0.121 mmol, 1.2 equiv), THF (0.916 ml), followed by Pd(dppf)Cl_2 (22.13mg, 0.30 mmol, 0.3 equiv) and then potassium phosphate (107 mg, 0.504 mmol, 5 equiv). Sealed vial with a teflon septum and brought outside of the glove box. Under nitrogen added 0.09 ml of water (degassed for 30 minutes prior to use), wrapped vial in aluminum foil, taped and stirred at 60 ^oC for 16 hours. Warmed to room temperature, filtered the reaction mixture through a silica gel plug with diethyl ether and concentrated in vacuo. The crude reaction mixture was purified by silica gel chromatography in 4 to 10% ethyl acetate in hexanes to yield compound **3.219** as a clear colorless oil (61%, 45.7 mg).

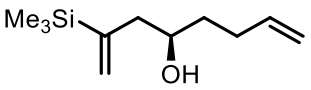
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.74 (s, 1H), 5.23 (s, 1H), 4.97 (s, 1H), 4.39 (q, *J* = 11.5 Hz, 2H), 4.23 – 4.08 (m, 3H), 4.02 (d, *J* = 7.2 Hz, 1H), 3.97 – 3.91 (m, 1H), 3.90 – 3.82 (m, 1H), 3.80 (s, 3H), 3.47 (t, *J* = 7.7 Hz, 2H), 3.29 – 3.20 (m, 1H), 2.48 (dd, *J* = 6.3, 3.2 Hz, 2H), 2.37 – 2.28 (m, 1H), 2.08 – 1.90 (m, 3H), 1.80 (s, 3H), 1.71 – 1.56 (m, 3H), 1.31 – 1.23 (m, 5H), 1.08 – 0.98 (m, 6H), 0.88

(d, *J* = 1.0 Hz, 18H), 0.06 (d, *J* = 1.9 Hz, 12H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.5, 159.2, 145.9, 142.0, 131.0, 129.3, 122.7, 115.9, 113.9, 82.1, 78.3, 76.5, 74.2, 72.6, 71.6, 67.3, 60.5, 55.4, 48.6, 40.3, 40.0, 37.6, 33.1, 26.1, 26.0, 18.3, 18.2, 17.9, 16.5, 14.4, 13.5, -4.3, -4.4, -4.5, -4.9. **IR (neat):** 2925 (br), 2856 (s), 1613 (m), 1513 (m), 1360 (m), 1302 (m), 1247 (s), 1097 (s), 1040 (s). **HRMS** (ESI+) for $C_{41}H_{72}O_8Si_2$ $[M+Na]^+$ calculated: 771.4664, found: 771.4656. **$[\alpha]^{20}_D$** =-17.204 (c = 1.73, $CHCl_3$, *l* =50 mm).

3.6.2.4 Fragment C

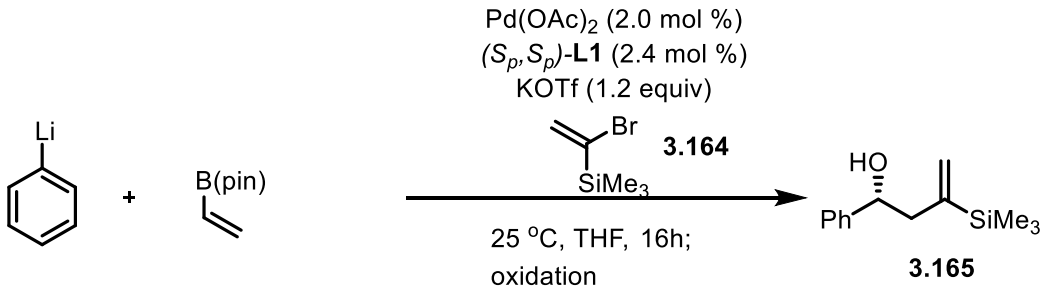


3.166 **3.167**

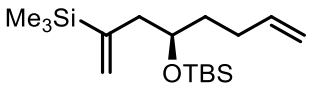


(*R*)-2-(trimethylsilyl)octa-1,7-dien-4-ol (3.167). To an oven-dried 20 ml scintillation vial with stir bar was added reagent **3.166** (502 mg, 2.76 mmol) and 3.0 ml of THF. The vial was sealed with a rubber septa and removed from the glovebox. Under nitrogen, thhe vial was cooled down to 0 °C followed by dropwise addition of vinyllithium (1.63 M, 1.69 mL). The vial was allowed to warm up to room temperature and stir at room temperature for additional 30 minutes. The vial was then brought back to the glovebox. To another oven dried 2-dram vial with stir bar was added Palladium (II) acetate (12.38 mg, 55.14 umol), (*R,R*)-Mandyphos (69.69 mg, 66.17 umol) and THF (2 ml). The mixture was allowed to stir at room temperature in the glovebox for 15 minutes. To the 20 ml scintillation vial just brought into the glovebox

was added potassium trifluoromethanesulfonate (622.59 mg, 3.31 mmol), 1-bromovinyl(trimethyl)silane (593.28 mg, 3.31 mmol) and THF (6 ml). The $Pd(OAc)_2$ and Mandyphos solution was then added. The vial was sealed with a rubber septa and removed from the glovebox. The vial was allowed to stir at 40 ^oC for 16 hours. Upon the completion of the reaction, the mixture was transferred to a 100 ml round bottom flask and cooled to0 ^oC. THF (10 ml) and 3M sodium hydroxide (15 ml) was then added and followed by dropwise addition of 30% H_2O_2 (8ml) aqueous solution. The mixture was allowed to stir at room temperature for 4 hours. Upon the completion of the oxidation, the flask was cooled down to 0 ^oC, sodium thiosulfate (15 ml) was added dropwise. The mixture was then transferred to a separatory funnel. The aqueous layer was extracted with ethyl acetate 3 times. The organic layers were combined, dried over sodium sulfate, filtered and condensed to crude product. The crude product was purified through silica gel column with 25% ethyl acetate in hexane as eluent. The product was afforded as clear oil (427.1 mg, 78%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.83 (ddt, J = 16.9, 10.2, 6.7 Hz, 1H), 5.67 (s, 1H), 5.50 (d, J = 3.0 Hz, 1H), 5.10 – 4.92 (m, 2H), 3.77 – 3.55 (m, 1H), 2.44 (dd, J = 13.4, 3.3 Hz, 1H), 2.23 (dq, J = 15.0, 7.9, 7.4 Hz, 1H), 2.15 (td, J = 13.5, 8.7 Hz, 2H), 1.74 (s, 1H), 1.57 (q, J = 8.0 Hz, 2H), 0.10 (s, 9H). **^{13}C NMR** (151 MHz, CDCl3) δ 149.6, 138.70, 138.69, 128.1, 114.9, 69.2, 45.1, 36.4, 30.3, -1.14, -1.15. HRMS-(DART+) for $C_{11}H_{23}OSi$ $[M+H]^+$: calculated: 199.1513, found:199.1508. **IR** (neat): 2951.6 (w), 2925.6 (w), 2854.0 (w), 1246.9 (m), 927.3 (m), 909.0 (m), 832.4(s), 772.9 (m), 756.5 (m). **$[\alpha]^{20}_D$** = +5.599 (c=1.0, $CHCl_3$, *l*=50 mm).

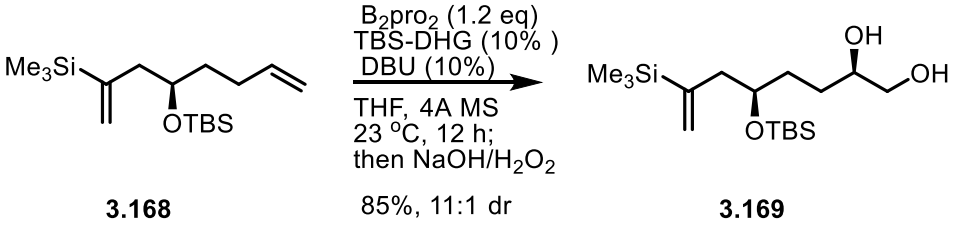


***(R)*-1-phenyl-3-(trimethylsilyl)but-3-en-1-ol (3.165).** The title compound was prepared according to the procedure above for the synthesis of compound **3.166**. 85% yield, 97:3 er. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 – 7.32 (m, 3H), 7.30 – 7.23 (m, 2H), 5.75 (s, 1H), 5.56 (s, 1H), 4.79 – 4.69 (m, 0H), 2.65 (dd, 0H), 2.46 (dd, 0H), 0.15 (s, 9H).



(*R*)-tert-butyldimethyl((2-(trimethylsilyl)octa-1,7-dien-4-yl)oxy)silane (3.167). To a 20 ml scintillation vial with stir bar and compound **3.166** (77 mg, 388.15 umol) was added imidazole (66.06 mg, 970.38 umol) and DMF (1 mL). The mixture was allowed to stir at room temperature for 5 minutes. TBSCl (117.00 mg, 776.30 umol) was then added. The reaction was allowed to stir at room temperature for 16 hours. Upon the completion of the reaction, water (3 ml) was added. The mixture was then transferred to a sep funnel. The layers were separated. The aqueous layer was extracted by hexane for 3 times. The organic layers were combined, dried over sodium sulfate, filtered and condensed to crude product. The crude product was purified through silica gel column with 1% to 2% ethyl acetate in hexane as eluent. The product was afforded as clear oil (104 mg, 86%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.81 (ddt, J = 13.3, 10.2, 6.6 Hz, 1H), 5.60 (s, 1H), 5.41 (d, J = 2.8 Hz, 1H), 4.96 (dd, J = 33.2, 13.9 Hz, 2H), 3.87 – 3.74 (m, 2H), 2.40 (dd, J = 13.6, 5.2 Hz, 1H), 2.24 (dd, J = 13.6, 8.4 Hz, 1H), 2.20

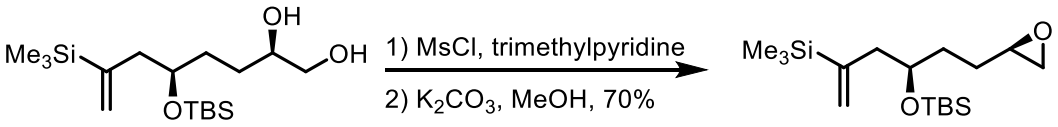
– 2.11 (m, 1H), 2.04 (dq, J = 14.6, 6.3 Hz, 1H), 1.61 – 1.49 (m, 1H), 1.41 (dtd, J = 13.5, 7.8, 6.7, 2.9 Hz, 1H), 0.89 (s, 9H), 0.09 (s, 9H), 0.06 (d, J = 2.3 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.9, 139.2, 127.7, 114.4, 71.2, 44.9, 36.0, 29.8, 26.2, 18.4, -1.0, -3.8, -4.2. HRMS-(DART+) for $C_{17}H_{37}OSi_2$ $[M+H]^+$: calculated: 313.2378, found:313.2376. IR (neat): 2951.9 (m), 2926.7 (m), 2854.7 (w), 1248.1 (m), 1090.1 (m), 929.0 (w), 834.1 (s), 772.6 (m), 756.8 (w). **$[\alpha]^{20}_D$** = +11.816 (c=1.1, $CHCl_3$, *l*=50 mm).



3.168 85%, 11:1 dr **3.169**

(2*R*,5*R*)-5-((tert-butyldimethylsilyl)oxy)-7-(trimethylsilyl)oct-7-ene-1,2-diol (3.166). To an oven-dried two dram flask with stir bar was added TBS-DHG (5.25 mg, 20.00 umol), B_2pro_2 (67.91 mg, 400.00 umol), and 4Å molecular sieves (30 mg). THF (0.2 ml), compound **3.165** (62.53 mg, 0.2 mmol) and DBU (3.04 mg, 20.00 umol) was then added. The vial was sealed with teflon cap and removed from the glovebox. The reaction was allowed to stir at 30 °C for 12 hours. Upon the completion of the reaction, THF (0.2 ml), 3M sodium hydroxide (0.6 ml) were added. The vial was cooled down 0 °C, 30% aqueous H_2O_2 was added in drop. The reaction was allowed to stir at room temperature for additional three hours. Upon the completion of the oxidation, saturated sodium thiosulfate (1 ml) was added in drop. The reaction was then transferred to a separatory funnel. The aqueous layer was extracted by ethyl acetate for 3 times. The organic layers were combined, dried over sodium sulfate, filtered and concentrated in vacuo. The crude product was purified through silica gel column with 30% to 40 % ethyl acetate as eluent. The product was afforded as clear oil (58.9 mg, 85%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.61 (s,

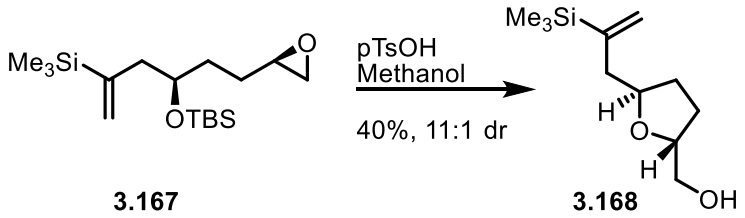
1H), 5.40 (d, J = 2.9 Hz, 1H), 3.87 – 3.80 (m, 1H), 3.68 (tt, J = 7.5, 4.2 Hz, 1H), 3.62 (dd, J = 11.0, 3.1 Hz, 1H), 3.43 (dd, J = 11.0, 7.7 Hz, 1H), 2.41 (dd, J = 13.6, 5.1 Hz, 1H), 2.25 (dd, J = 13.7, 8.7 Hz, 1H), 1.61 – 1.52 (m, 2H), 1.52 – 1.44 (m, 2H), 0.89 (s, 9H), 0.09 (s, 9H), 0.06 (s, 6H). **^{13}C NMR** (151 MHz, Chloroform-d) δ 148.7, 127.7, 72.5, 71.4, 67.0, 44.6, 31.9, 28.6, 26.1, 18.3, -1.0, -3.9, -4.2. HRMS-(DART+) for $C_{17}H_{39}O_3Si_2$ $[M+H]^+$: calculated: 347.2432, found: 347.2426. **IR** (neat): 2950.0 (w), 2925.7 (w), 2853.9 (w), 1246.8 (m), 1054.8 (m), 831.1 (s), 772.0 (s), 756.8 (m). **$[\alpha]^{20}_D$** =+8.119 (c=1.0, $CHCl_3$, *l*=50 mm).



3.166 **3.167**

Tert-butyldimethyl(((*R*)-1-((*R*)-oxiran-2-yl)-5-(trimethylsilyl)hex-5-en-3-yl)oxy)silane (3.167). To a 20 ml scintillation vial with stir bar and compound **3.166** (160 mg, 461.56 umol) was added CH_2Cl_2 (3 ml) and 2,4,6-trimethylpyridine (559.32 mg, 4.62 mmol, 610.61 uL). The vial was cooled down to 0 ^oC. Methanesulfonyl chloride (58.16 mg, 507.72 umol, 39.30 uL) was then added. The vial was allowed to stir at 0 ^oC for 2 hour. Upon the completion of the reaction, water (5 ml) was added. The mixture was transferred to a separatory funnel. The aqueous layer was extracted with CH_2Cl_2 three times. The organic layers were combined, dried over sodium sulfate, filtered and condensed to crude product. The crude product was taken to the next step without further purification. To a 20 ml scintillation vial with stir bar and crude product from the last step (195.81 mg, 461.00 umol) was added methanol (5 mL). The mixture was allowed to stir for 5 minutes and potassium carbonate (223.00 mg, 1.61 mmol, 97.38 uL) was added. The mixture was

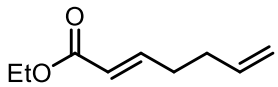
stirring for another 1 hour at room temperature. Upon the completion of the reaction, water (5 ml) was added. The mixture was transferred to a separatory funnel. The aqueous layer was extracted by diethyl ether for 3 times. The organic layers were combined, dried over sodium sulfate, filtered and condensed to crude product. The crude product was purified through silica gel column with 5% to 10% ethyl acetate in hexane as eluent. The product was afforded as clear oil, (106.1 mg, 70%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.61 (s, 1H), 5.41 (d, J = 2.4 Hz, 1H), 3.91 – 3.79 (m, 1H), 2.90 (s, 1H), 2.73 (t, J = 4.2 Hz, 1H), 2.48 – 2.43 (m, 1H), 2.40 (dd, J = 13.5, 4.9 Hz, 1H), 2.22 (dd, J = 13.6, 8.5 Hz, 1H), 1.73 – 1.64 (m, 1H), 1.64 – 1.39 (m, 3H), 0.88 (s, 9H), 0.09 (s, 9H), 0.05 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.7, 127.8, 71.0, 52.6, 47.4, 44.8,32.3, 28.2, 26.1, 18.3, -1.0, -3.8, -4.3. **HRMS**-(DART+) for $C_{17}H_{37}O_2Si_2$ $[M+H]^+$: calculated: 329.2327, found: 329.2324. **IR** (neat): 2951.3 (w), 2925.6 (w), 2853.9 (w), 1246.8 (m), 1093.1 (m), 1054.9 (m), 833.6 (s), 773.0 (m), 757.7 (m). **$[\alpha]^{20}_{D}$** = +12.598 (c=1.0, $CHCl_3$, *l*=50 mm).



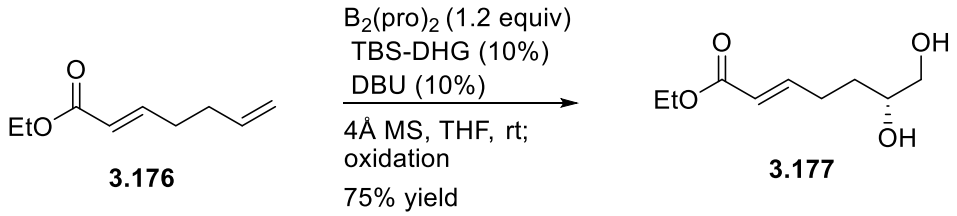
3.167 **3.168**

***(2R,5R)*-5-(2-(trimethylsilyl)allyl)tetrahydrofuran-2-yl)methanol (3.168).** To a 20 ml scintillation vial with stir bar and compound **3.167** (71 mg, 216.04 umol) was added THF (1ml). TBAF (1 M, 324.07 uL) was then added. The mixture was allowed to stir at room temperature for 14 hours. Upon the completion of the reaction, volatiles were removed in vacuo. The residue the filtered through silica gel plug with diethyl ether as eluent. The solvents was then removed in vacuo to afford the crude product. The crude product was

taken to next step without further purification. To a 20 ml scintillation vial with stir bar and the crude product from the last step (46.31 mg, 0.216 mmol) was added CH_2Cl_2 (1 ml) and *(1S)*-(+)-10-camphorsulfonic acid (55.19 mg, 237.60 umol). The mixture was allowed to stir at room temperature for 2 hours. Upon the completion of the reaction, volatiles were removed in vacuo. The residue was purified through silica gel column with 10% to 25% ethyl acetate in hexane as eluent. The product was afforded as clear oil (28.7 mg, 62% over 2 steps). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.63 (s, 1H), 5.40 (d, J = 2.9 Hz, 1H), 4.08 – 4.02 (m, 1H), 4.00 (ddd, J = 10.3, 7.1, 3.6 Hz, 1H), 3.69 (dd, J = 11.4, 3.3 Hz, 1H), 3.48 (dd, J = 11.4, 5.6 Hz, 1H), 2.52 (dd, J = 14.2, 6.3 Hz, 1H), 2.24 (dd, J = 14.2, 7.2 Hz, 1H), 1.99 – 1.92 (m, 1H), 1.92 – 1.85 (m, 1H), 1.77 – 1.68 (m, 1H), 1.56 – 1.47 (m, 1H), 0.09 (s, 9H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 149.2, 126.5, 79.6, 79.1, 65.4, 42.8, 31.5, 27.1, -1.2. **HRMS**-(DART+) for $C_{11}H_{23}O2_{Si}$ $[M+H]^+$: calculated: 215.1462, found:215.1450. **IR** (neat): 3427.5 (br), 2950.6 (m), 2870.5 (w), 1246.0 (m), 1047.8 (m), 927.6(w), 835.2 (s), 756.6 (m), 718.5 (w). **$[\alpha]^{20}_D$** = +8.779 (c=1.28, $CHCl_3$, *l*=50 mm).



Ethyl *(E)*-hepta-2,6-dienoate (3.176). The title compound was prepared in accord with the literature. NMR and mass spectra data was in accord with the literature.[92]

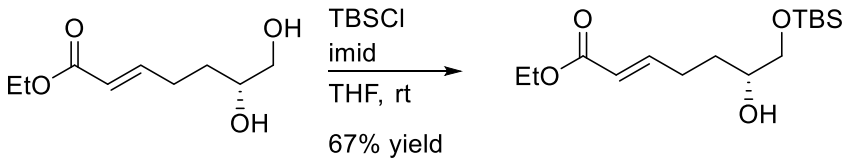


[92] Mohapatra, K.D.; Mallampudi, A. N.; Reddy, S.D.; Srinivas, B. *Org. Lett.* **2018**, *21*, 6910−6914.

Ethyl *(R,E)*-6,7-dihydroxyhept-2-enoate (3.177). The title compound was prepared according to the literature procedure.[93] In the glovebox, an oven dried round bottom flask equipped with a magnetic star bar was charged with TBS-DHG catalyst (102.1 mg, 0.389 mmol, 0.1 equiv), propanediol diboron (1.32 g, 7.78 mmol, 2.0 equiv), 4Å molecular sieves (389 mg g), the alkene substrate **3.176** (600.0 mg, 3.89 mmol, 1.0 equiv) and THF (3.89 mL). DBU (96.0 µl, 0.389 mmol, 0.1 equiv) was then added to the solution. The flask was sealed with a septum and brought outside of the glove box and allowed to stir in a 30 °C oil bath for 16 hours. The reaction was warmed to room temperature. Under nitrogen, added 15 ml of THF. Cooled the reaction to -78 °C. 36 ml of 30% hydrogen peroxide was added dropwise over 15 minutes (reaction is extremely exothermic) followed by 76 ml of pH7 phosphate buffer and stirred at -78 °C for another 5 minutes. Transferred the reaction flask to an ice bath at 0°C and slowly allowed the reaction to warm to room temperature over 45 minutes and stirred for another 4 hours at room temperature. Transferred the reaction mixture to a 500ml flask and cooled the reaction to 0 °C. 60 ml of saturated sodium thiosulfate was added dropwise over 15 minutes (extremely exothermic quench) and allowed the reaction to stir for another 30 minutes while warming to ambient temperature. Extracted the aqueous layer (150 ml x 5) with ethyl acetate. The combined organics were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude reaction mixture which was purified by silica gel chromatography in 50% ethyl acetate in hexanes to afford the desired diol as clear colorless oil in 75% yield. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.97 (d, J = 15.6 Hz, 1H), 5.86 (dd, J = 15.6, 1.0 Hz, 1H), 4.19 (q, J = 7.1 Hz, 3H), 3.79 – 3.70 (m, 1H), 3.69 – 3.62 (m, 1H), 3.51 – 3.40 (m, 1H), 2.44 – 2.23 (m, 2H),

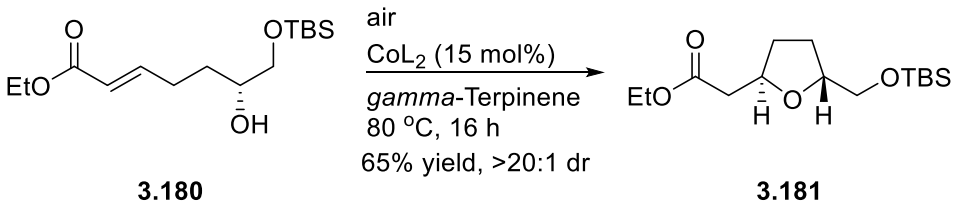
[93] Zeng, X.; Abe, M.; Kadowaki, N.; Liu, Q.; Li, H.; Wu, Z.; Xu, J.; Deng, G.; Lu, Y.; Feng, R. *J. Am. Chem. Soc.* **2018**, *10*, 3663−3673.

2.11 (s, 1H), 1.80 (s, 1H), 1.67 – 1.57 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 3H). **HRMS** (DART+) for $C_9H_{16}O_4$ $[M+H]^+$ calculated: 189.1116, found: 189.1121. **$[\alpha]^{26.3}_D$** +5. (c = 5.4, $CHCl_3$, *l* =50 mm).



3.177 **3.180**

Ethyl (R,E)-7-((tert-butyldimethylsilyl)oxy)-6-hydroxyhept-2-enoate ***(3.180)*** To a solution of ethyl (*E*)-6,7-dihydroxyhept-2-enoate (**3.177**) (1.33 g, 1.0 equiv, 7.06 mmol) in THF (32.83ml), was added imidazole (480 mg, 7.06 mmol, 1.0 equiv) at 0 ºC, and TBSCl (1.06g, 7.06 mmol,1.0 equiv). Stirred at 0 ºC for 1 hour then rt, overnight. Diluted with water and extracted four times with ethyl acetate. Dried with sodium sulfate and concentrated in vacuo. Columned by silica gel chromatography in 20% ethyl acetate in hexanes to afford the product as clear colorless oil, 1.44g, 67% yield. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.02 – 6.91 (m, 1H), 5.83 (d, *J* = 15.7 Hz, 1H), 4.16 (t, *J* = 7.1 Hz, 2H), 3.69 – 3.53 (m, 2H), 3.40 (ddd, *J* = 9.8, 7.0, 1.2 Hz, 1H), 2.46 – 2.34 (m, 2H), 2.29 (ddd, *J* = 7.9, 4.9, 1.6 Hz, 1H), 1.62 – 1.45 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.77, 148.71, 121.79, 77.41, 77.16, 76.91, 71.07, 67.19, 31.29, 28.44, 26.01, 18.42, 14.40, -5.23, -5.28. **HRMS** (DART+) for $C_{15}H_{30}SiO_4$ $[M+H]^+$ calculated: 303.1986, found: 303.1971.

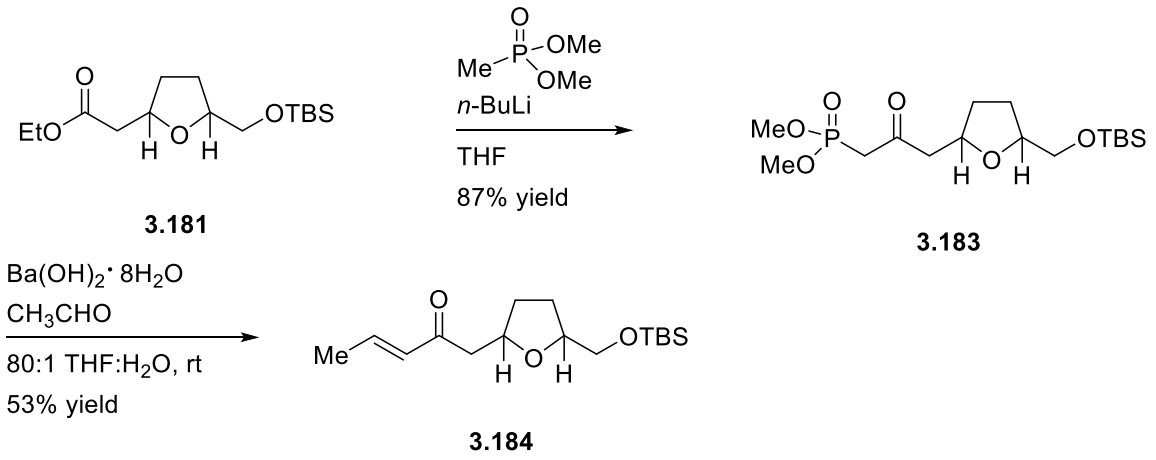


3.180 **3.181**

Ethyl 2-*((2R,5R)*-5-(((tert butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)acetate (3.181). The title compound was prepared according to literature precedent with slight modification.[94] To a solution of ethyl (R,E)-7-((tert-butyldimethylsilyl)oxy)-6-hydroxyhept-2-enoate **(3.180)** (448.6 mg, 1.48 mmol, 1.0 equiv) in γ-terpinene (9.51 ml, 59.3 mmol, 40 equiv) was added (73 mg, 0.111 mmol, 0.075 equiv) of Hartung's cobalt complex cobalt complex at rt. the solution was heated at 70C under compressed air flow . after 4 hours added the remaining cobalt complex (73 mg, 0.111 mmol, 0.075 equiv) and stirred under compressed air flow for 16 hours overnight with an outlet needle The crude mixture was loaded onto a silica gel column directly and flushed with hexane to remover γ-terpinene and then 10% ethyl acetate in hexanes to afford the desired product as a clear colorless oil in 65% yield and >20:1 dr. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.38 – 4.30 (m, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 4.10 – 4.04 (m, 1H), 3.65 – 3.51 (m, 2H), 2.63 – 2.49 (m, 1H), 2.47 – 2.38 (m, 1H), 2.17 – 2.05 (m, 1H), 2.03 – 1.94 (m, 1H), 1.84 – 1.71 (m, 1H), 1.59 (dt, *J* = 12.2, 8.2 Hz, 1H), 1.25 (t, *J* = 7.2 Hz, 3H), 0.88 (d, *J* = 1.6 Hz, 9H), 0.05 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.52, 79.52, 77.41, 77.16, 76.91, 75.83, 65.92, 60.54, 41.03, 31.87, 27.99, 26.08, 18.50, 14.35, -5.17. **HRMS** (DART+) for $C_{15}H_{31}SiO_4$ $[M+H]^+$ calculated: 303.1986, found: 303.1987.

[94] Wu, D.; Forsyth, J. C. *Org. Lett*. **2013**, *6*, 1178−1181.

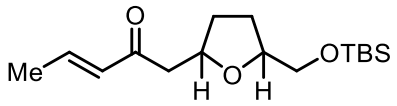
Note: Enone optimization characterization based on racemic trans-THF substrate with 1:1 dr



Dimethyl (3-(5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-2-oxopropyl)phosphonate (3.183). The title compound was synthesized according to literature procdure with a slight modification [95]A dry 2 dram vial was charged with [methoxy(methyl)phosphoryl]oxymethane (126.75 mg, 1.02 mmol, 109.27 uL) 1.05 ml THF. The solution was cooled to -78 °C, and n-BuLi (2.30 M, 444.15 uL) hexanes was slowly added. After 40 min, ethyl 2-[5-[[tert-butyl(dimethyl)silyl]oxymethyl]tetrahydrofuran-2-yl]acetate **(3.181)** (103 mg, 340.52 umol)) ester in 0.45 ml of THF was transferred via canula into the resultant slurry. After stirring an additional hour, the reaction was poured into saturated aqueous ammonium chloride and was extracted with EtOAc. The organic layers were combined, washed with brine, dried over MgSO4 and concentrated in vacuo. The crude material was purified by silica gel chromatography in 40% ethyl acetate, 10% methanol in hexanes to afford the

[95] Evans, A. M.; Morken, J. P. *Org. Lett*. **2005**, *15*, 3371–3373.

desired product as a colorless oil in 95% yield. Note: This product could also be carried forward as the crude material without loss in yield for the Honer-Wadsworth-Emmons olefination step.

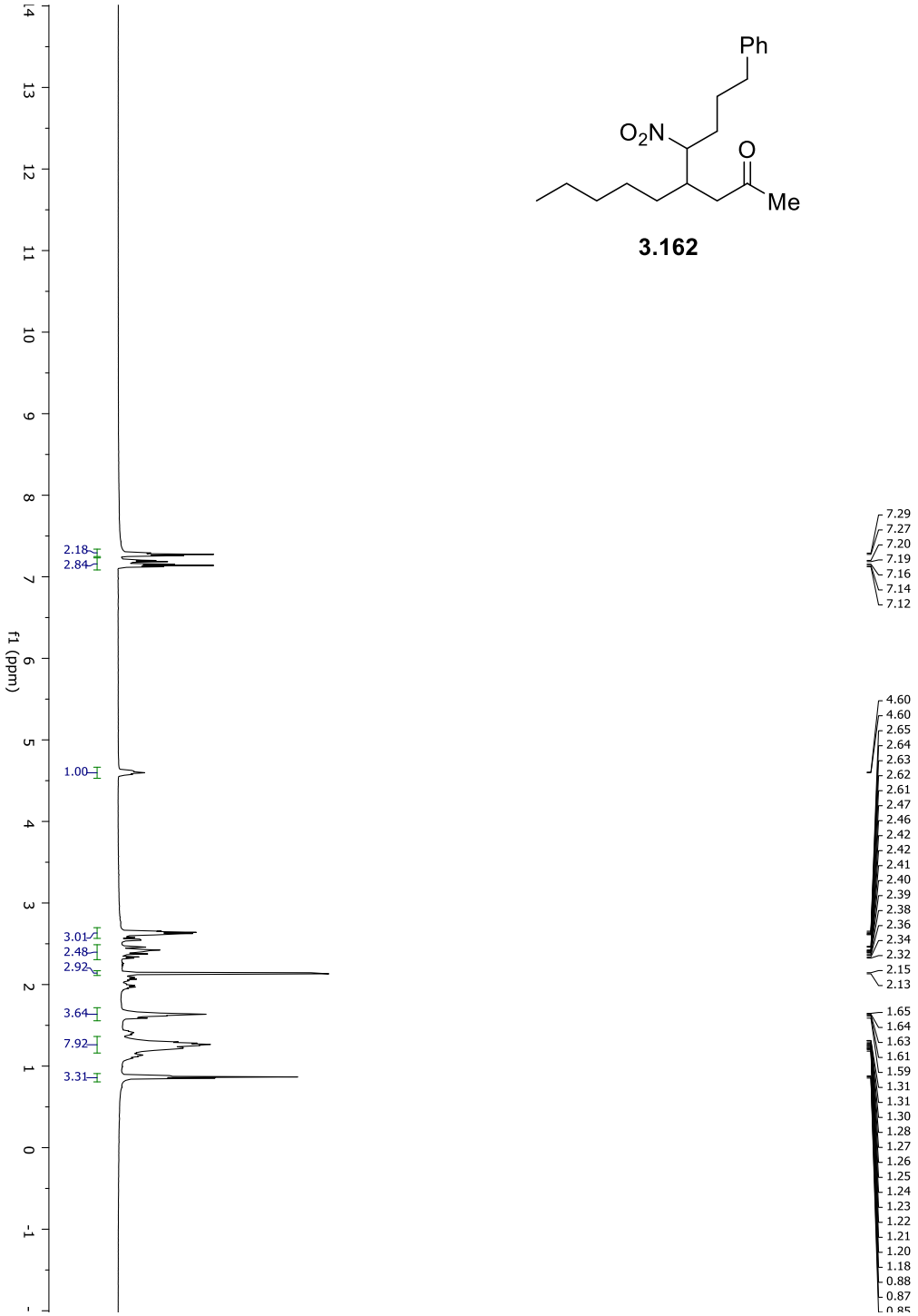


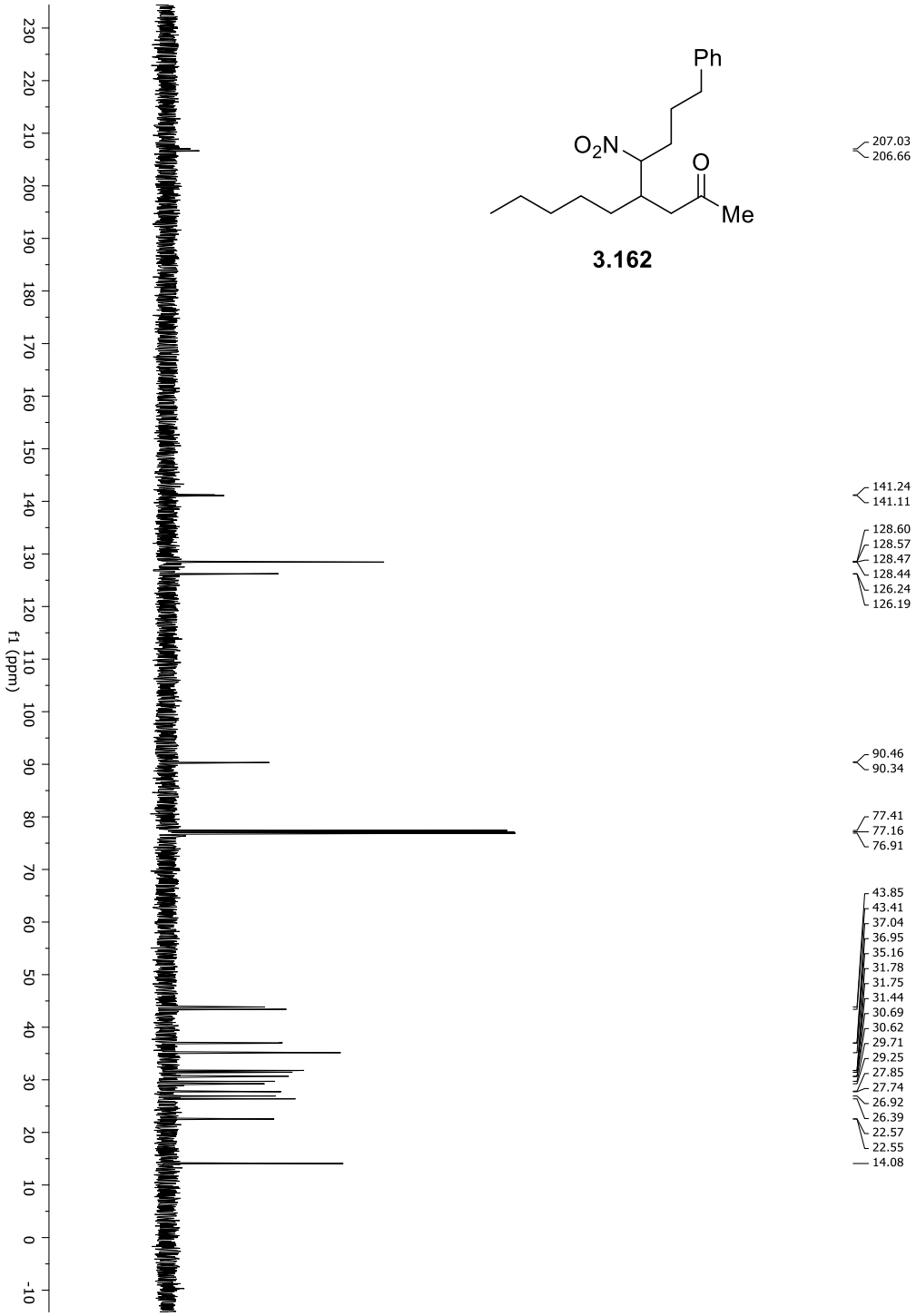
***(E)-1-(5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)pent-3-en-2-one (3.184*).** The title compound was prepared according to literature procedure with slight modification.[96] A mixture of ketophosphate **(3.183)** (1.0 mmol, 1.0 equiv) and barium hydroxide octahydrate (0.8 equiv, heated to 123 ^{o}C for 2 hours before use) in THF (2.5 ml) was stirred at room temperature for 30 minutes. A solution of acetaldehyde (pulled in a syringe that had been cooled to in dry ice because the aldehyde is very votile at room temperature) (1 mmol, 1.0 equiv) in wet thf (2.5 ml, 40:1 THF/H_2O) was then added. The reaction was allowed to stir overnight, dilued with DCM and washed with saturated aqueous sodium bicarbonate and then brine. The combined organic layers were dried over sodium sulfate and concentrated in vacuo. The crude was purified with silica gel chromatography in 5% ethyl acetate in hexanes to afford the desired product as a clear colorless oil in 58% and 1:1 dr.

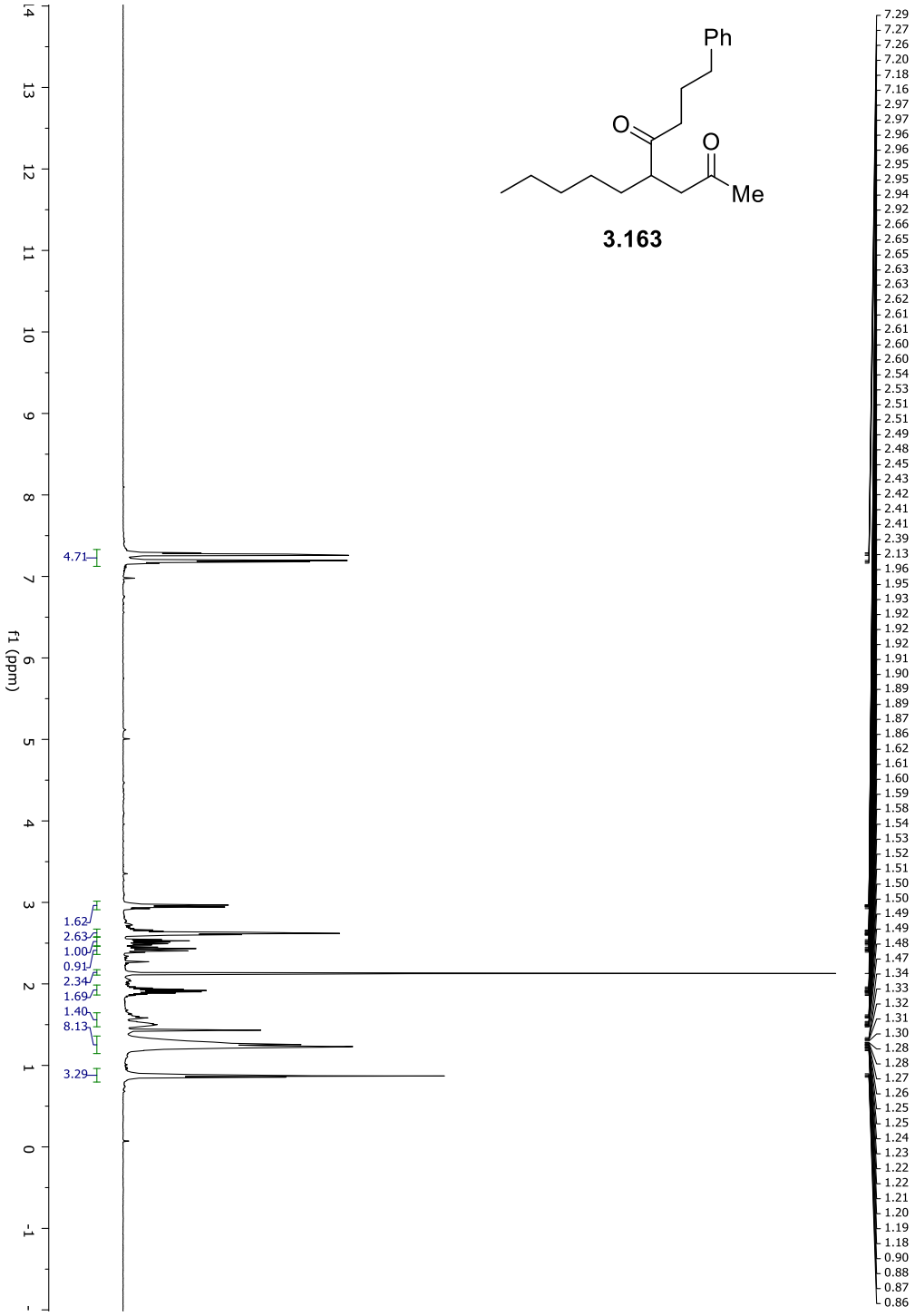
^{1}H NMR (600 MHz, $CDCl_3$) δ 6.92 – 6.79 (m, 1H), 6.14 (d, *J* = 15.7, 1.7 Hz, 2H), 4.40 – 4.24 (m, 1H), 4.10 – 3.91 (m, 0H), 3.63 – 3.52 (m, 2H), 3.02 – 2.87 (m, 1H), 2.68 – 2.56 (m, 1H), 2.21 – 2.02 (m, 1H), 2.01 – 1.95 (m, 1H), 1.90 (d, 3H), 1.83 – 1.71 (m, 1H), 1.57 – 1.44 (m, 1H), 0.89 (s, 9H), 0.05 (s, 11H).

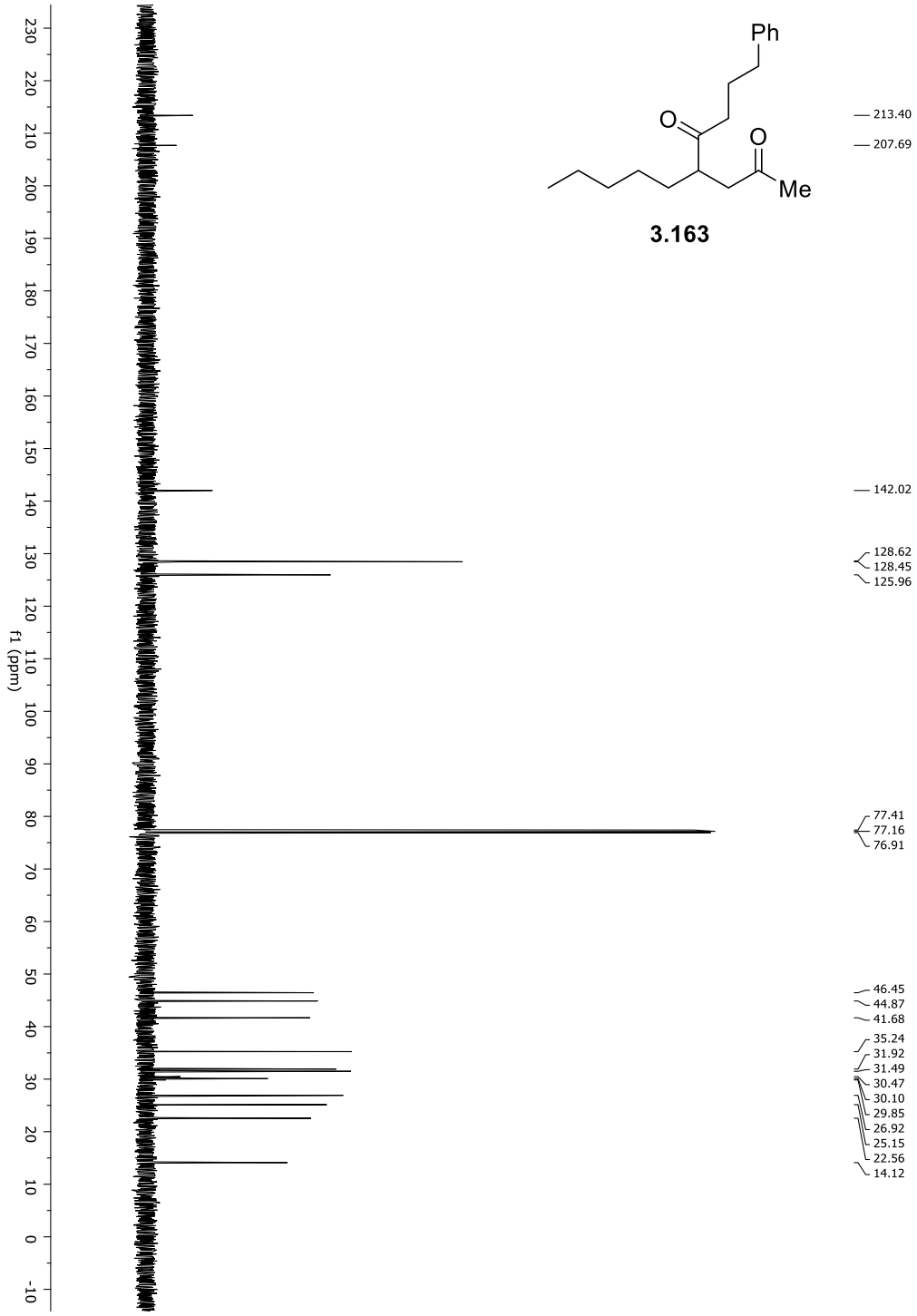
[96] Paterson, I.; Yeung, K.-S.; Smaill, J. B. *Synlett* **1993**, *10*, 774–776.

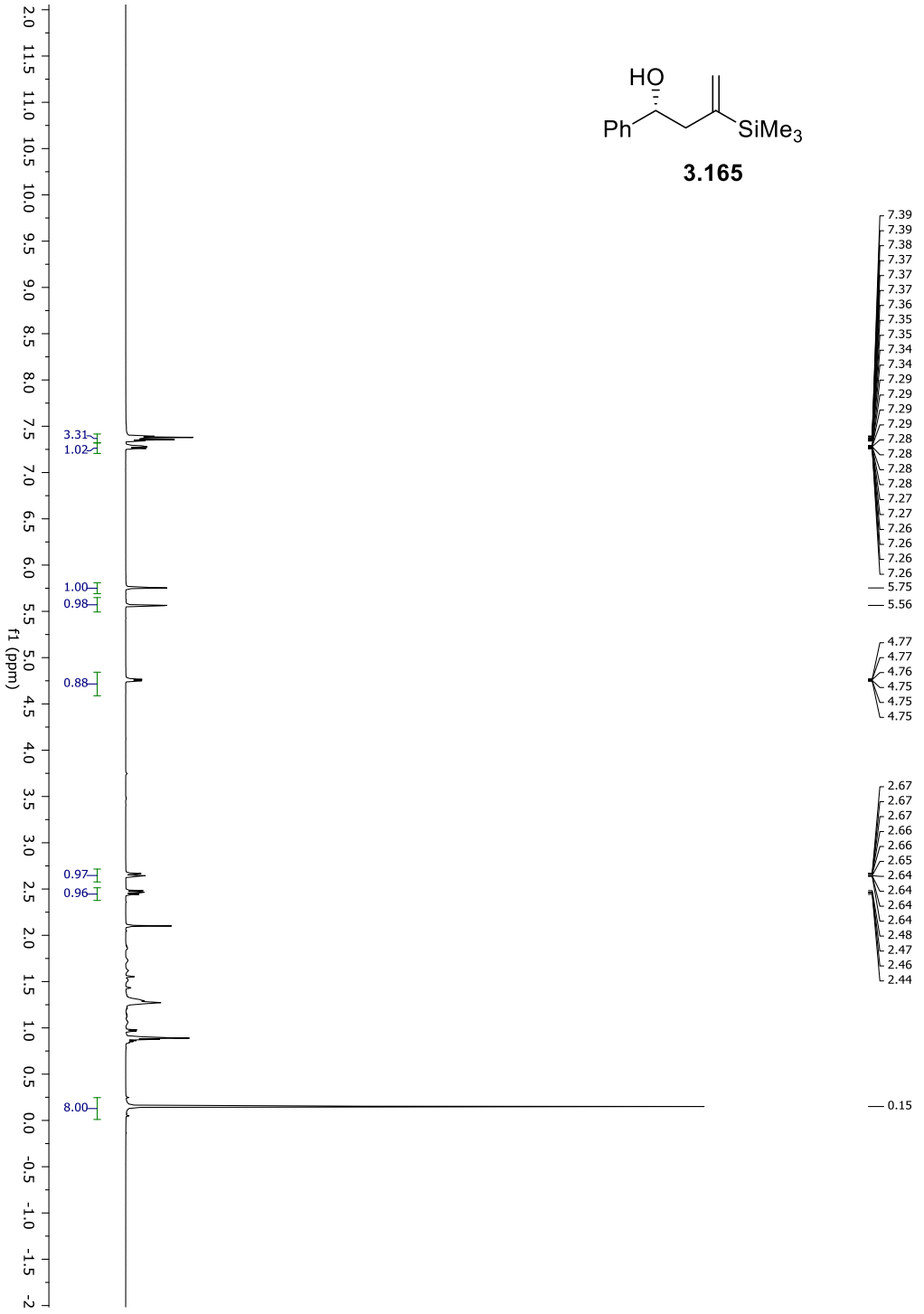
3.6.3 NMR Spectra

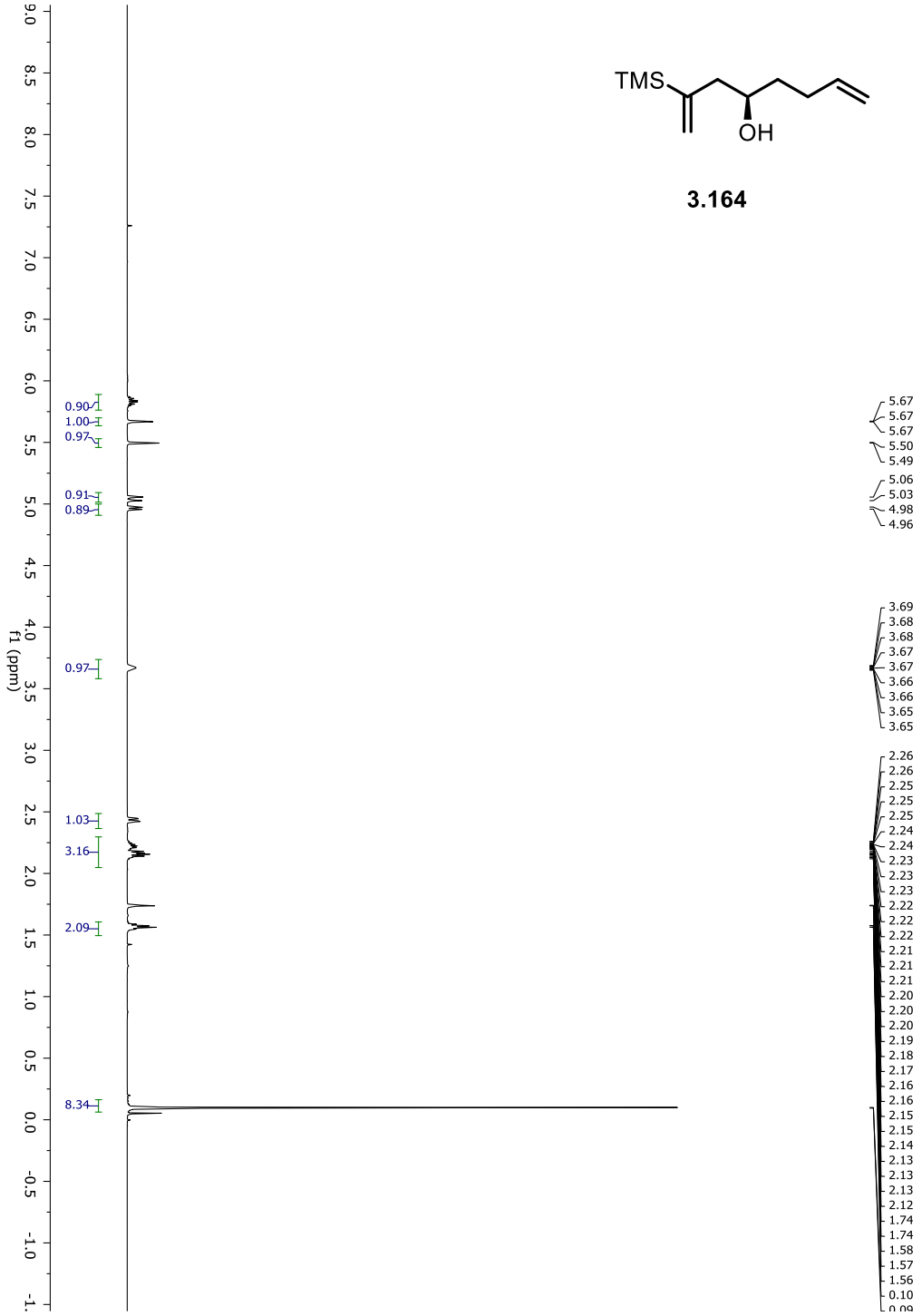


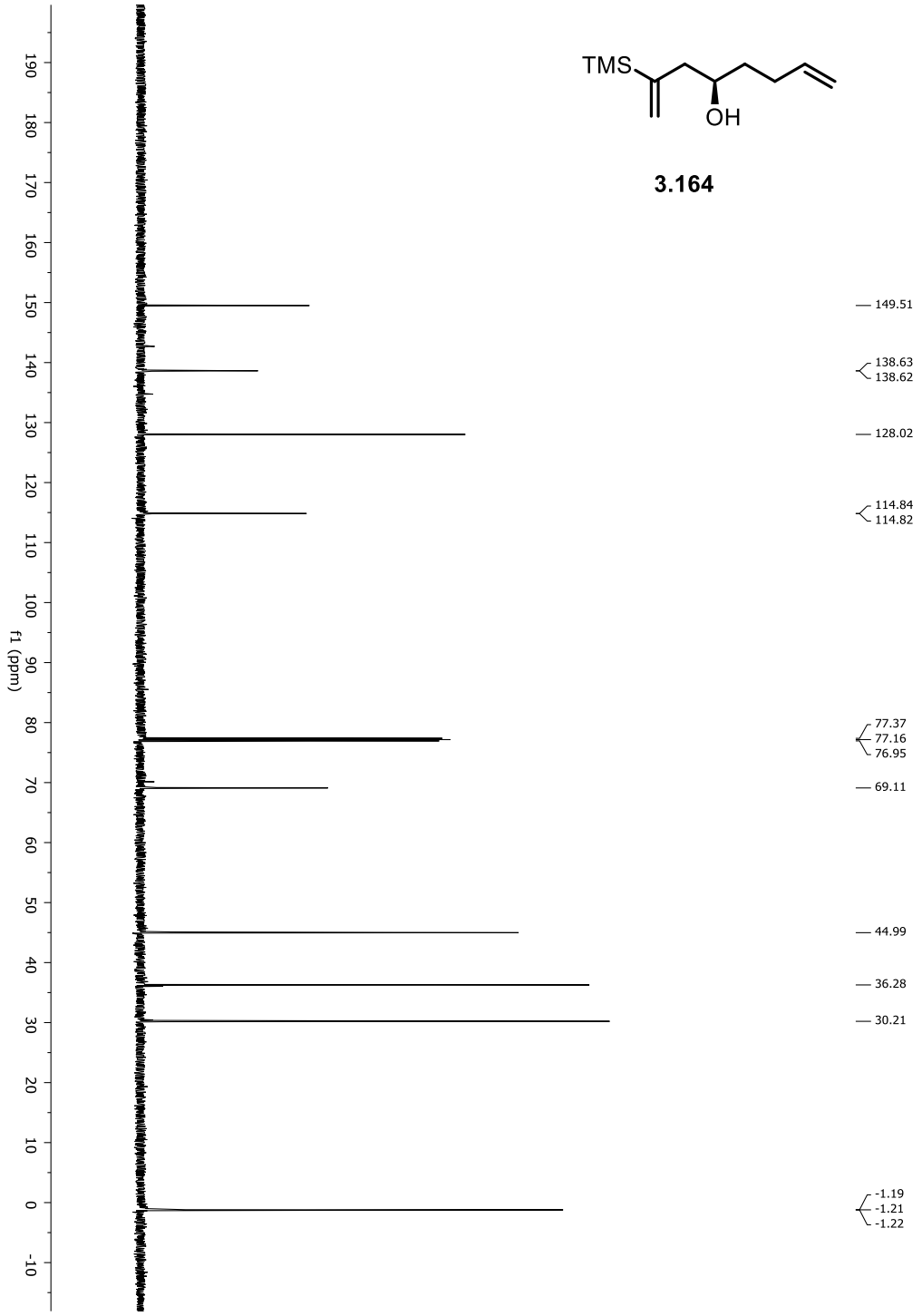

Ph
O2N
O
Me
3.162
207.03
206.66
141.24
141.11
128.60
128.57
128.47
128.44
126.24
126.19
90.46
90.34
77.41
77.16
76.91
43.85
43.41
37.04
36.95
35.16
31.78
31.75
31.44
30.69
30.62
29.71
29.25
27.85
27.74
26.92
26.39
22.57
22.55
14.08
f1 (ppm)

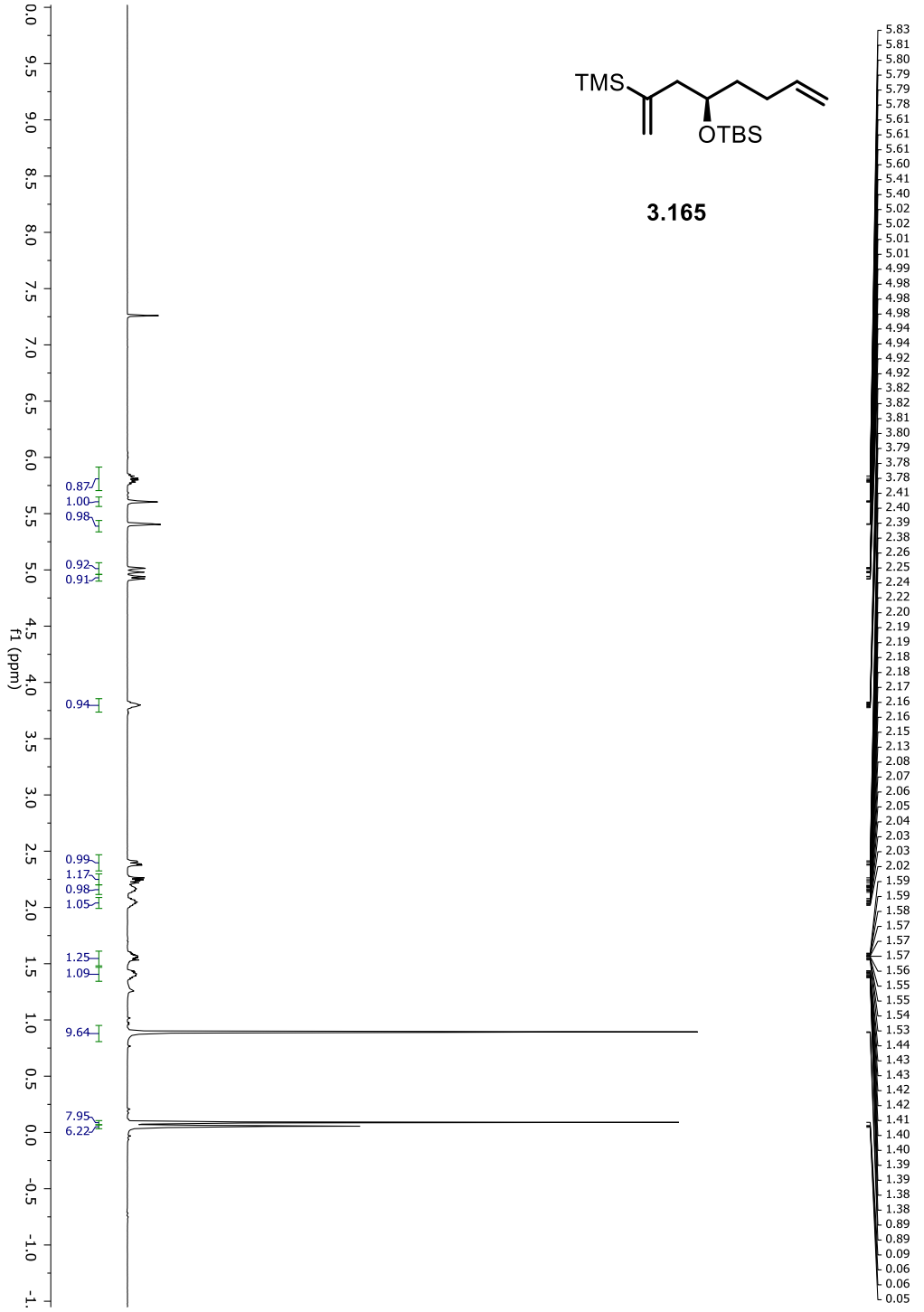

Ph
O
O
Me
3.163
f1 (ppm)
4.71
1.62
2.63
1.00
0.91
2.34
1.69
1.40
8.13
3.29

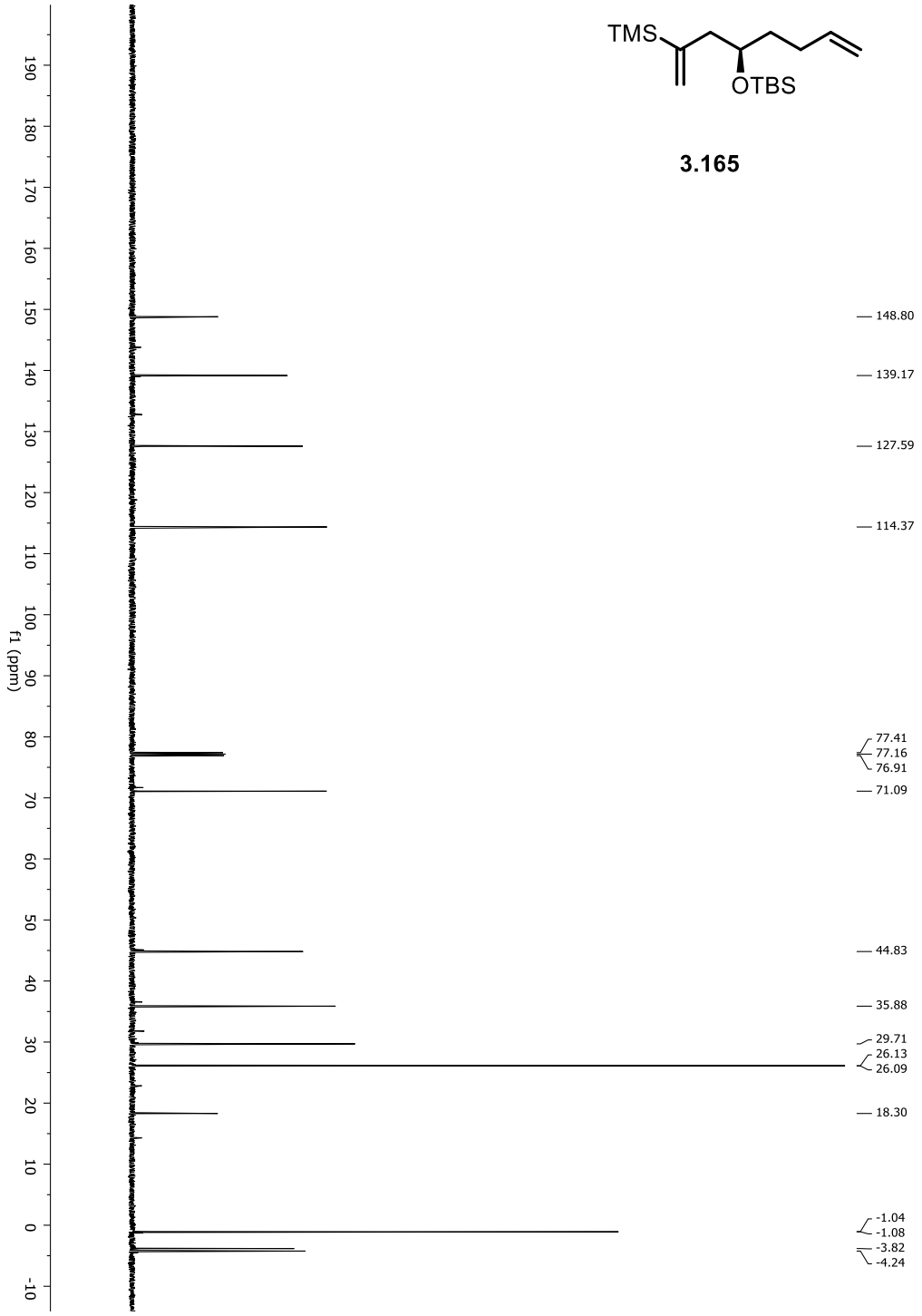

Ph
O
O
Me
3.163
213.40
207.69
142.02
128.62
128.45
125.96
77.41
77.16
76.91
46.45
44.87
41.68
35.24
31.92
31.49
30.47
30.10
29.85
26.92
25.15
22.56
14.12
f1 (ppm)

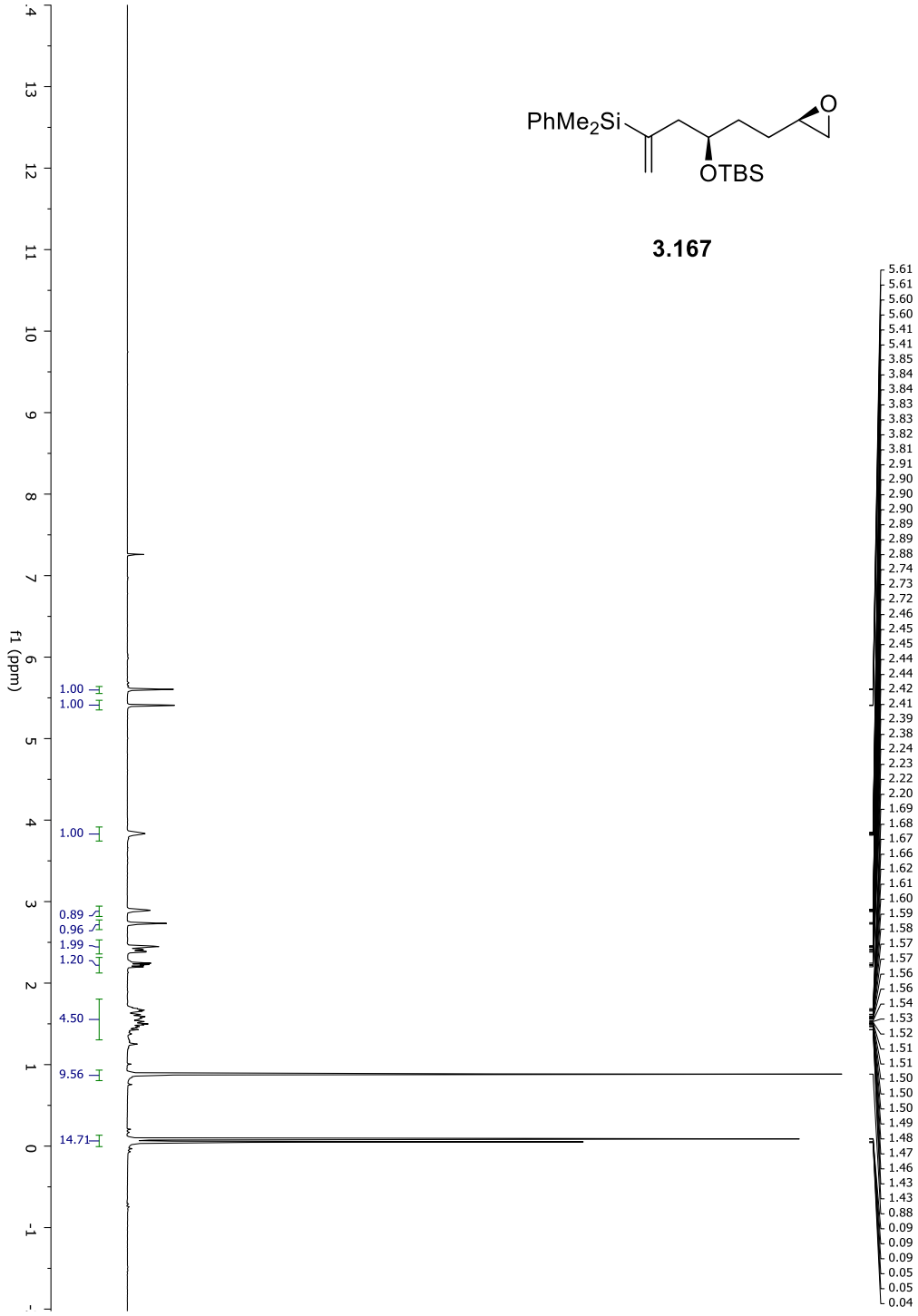

HO
Ph
SiMe3
3.165
f1 (ppm)
3.31
1.02
1.00
0.98
0.88
0.97
0.96
8.00
7.39
7.38
7.37
7.36
7.35
7.34
7.29
7.28
7.27
7.26
5.75
5.56
4.77
4.76
4.75
2.67
2.66
2.65
2.64
2.48
2.47
2.46
2.44
0.15

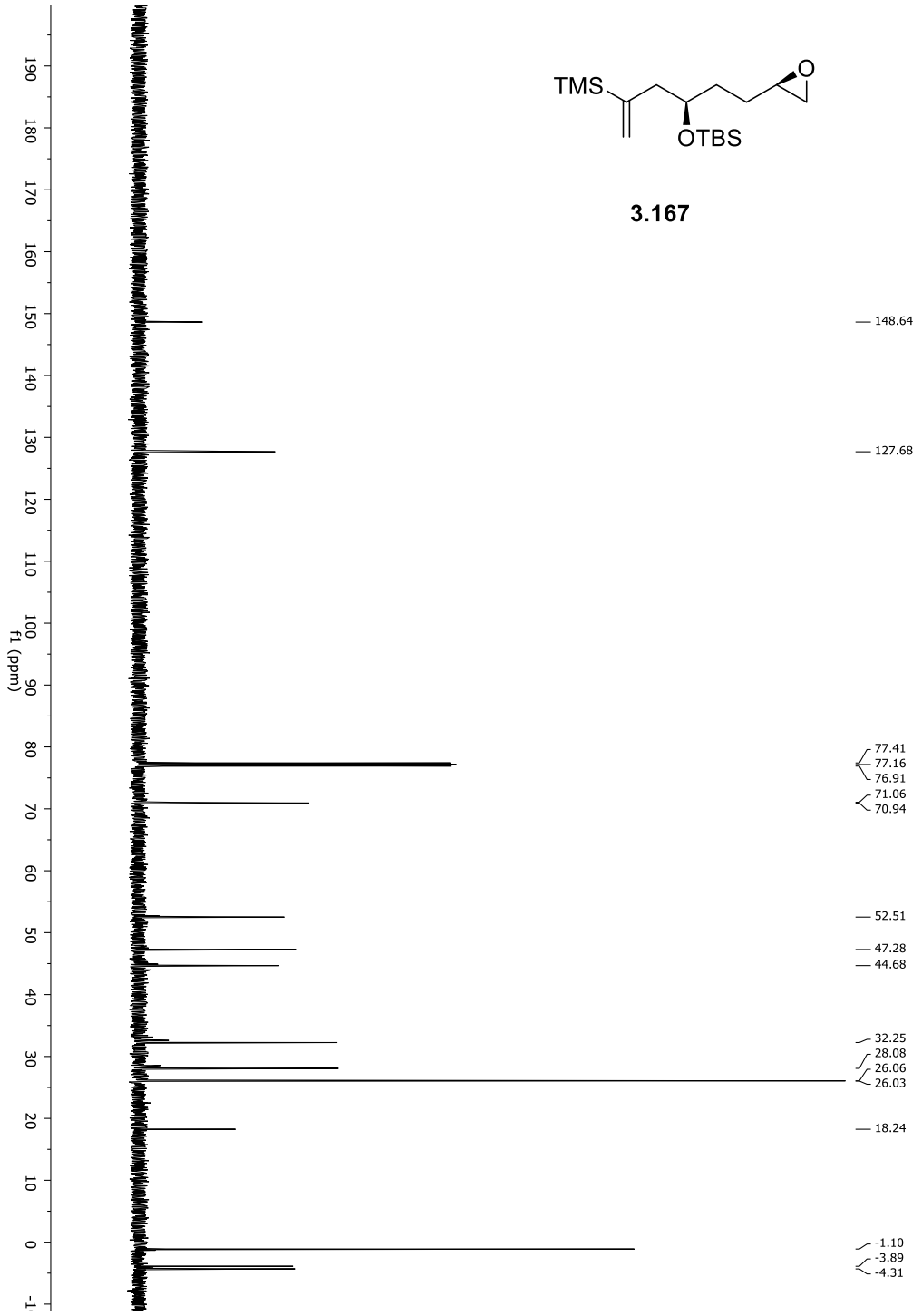

TMS
OH
3.164
f1 (ppm)
0.90
1.00
0.97
0.91
0.89
0.97
1.03
3.16
2.09
8.34
5.67
5.67
5.67
5.50
5.49
5.06
5.03
4.98
4.96
3.69
3.68
3.68
3.67
3.67
3.66
3.66
3.65
3.65
2.26
2.26
2.25
2.25
2.25
2.24
2.24
2.23
2.23
2.23
2.22
2.22
2.22
2.21
2.21
2.21
2.20
2.20
2.20
2.19
2.18
2.17
2.16
2.16
2.15
2.15
2.14
2.13
2.13
2.13
2.12
1.74
1.74
1.58
1.57
1.56
0.10

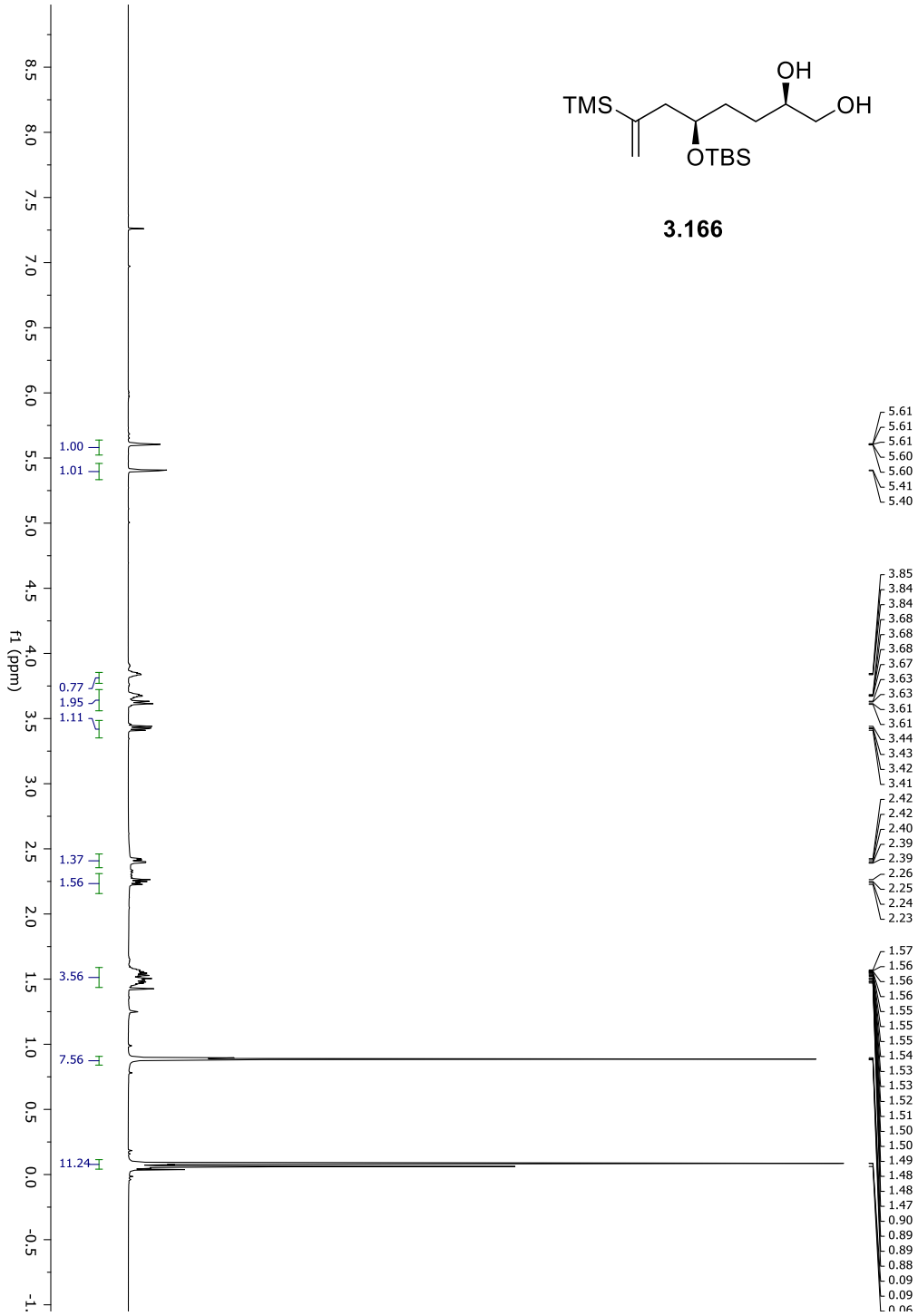

TMS
OH
3.164
f1 (ppm)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
149.51
138.63
138.62
128.02
114.84
114.82
77.37
77.16
76.95
69.11
44.99
36.28
30.21
-1.19
-1.21
-1.22

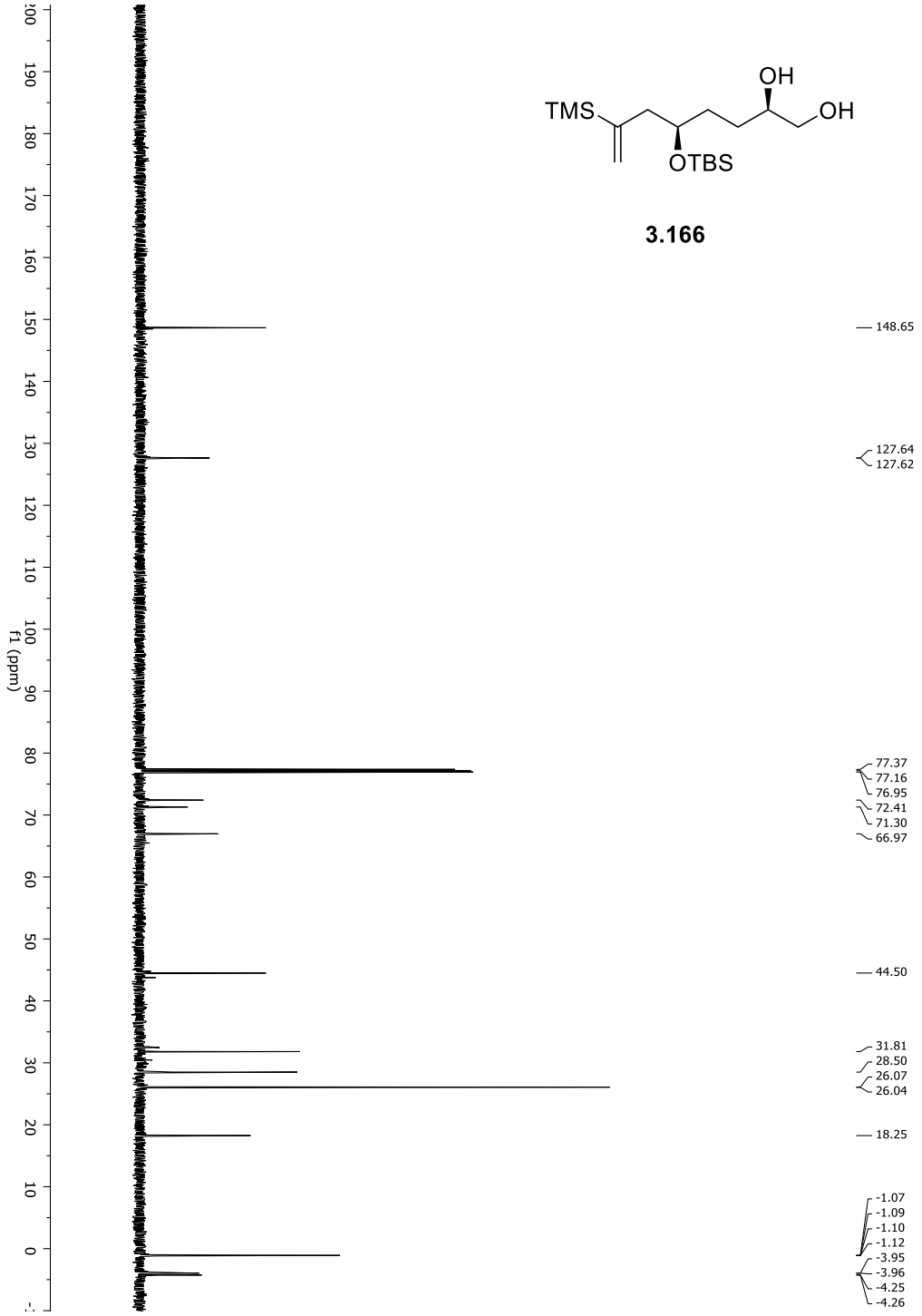

TMS
OTBS
3.165
f1 (ppm)
0.87
1.00
0.98
0.92
0.91
0.94
0.99
1.17
0.98
1.05
1.25
1.09
9.64
7.95
6.22

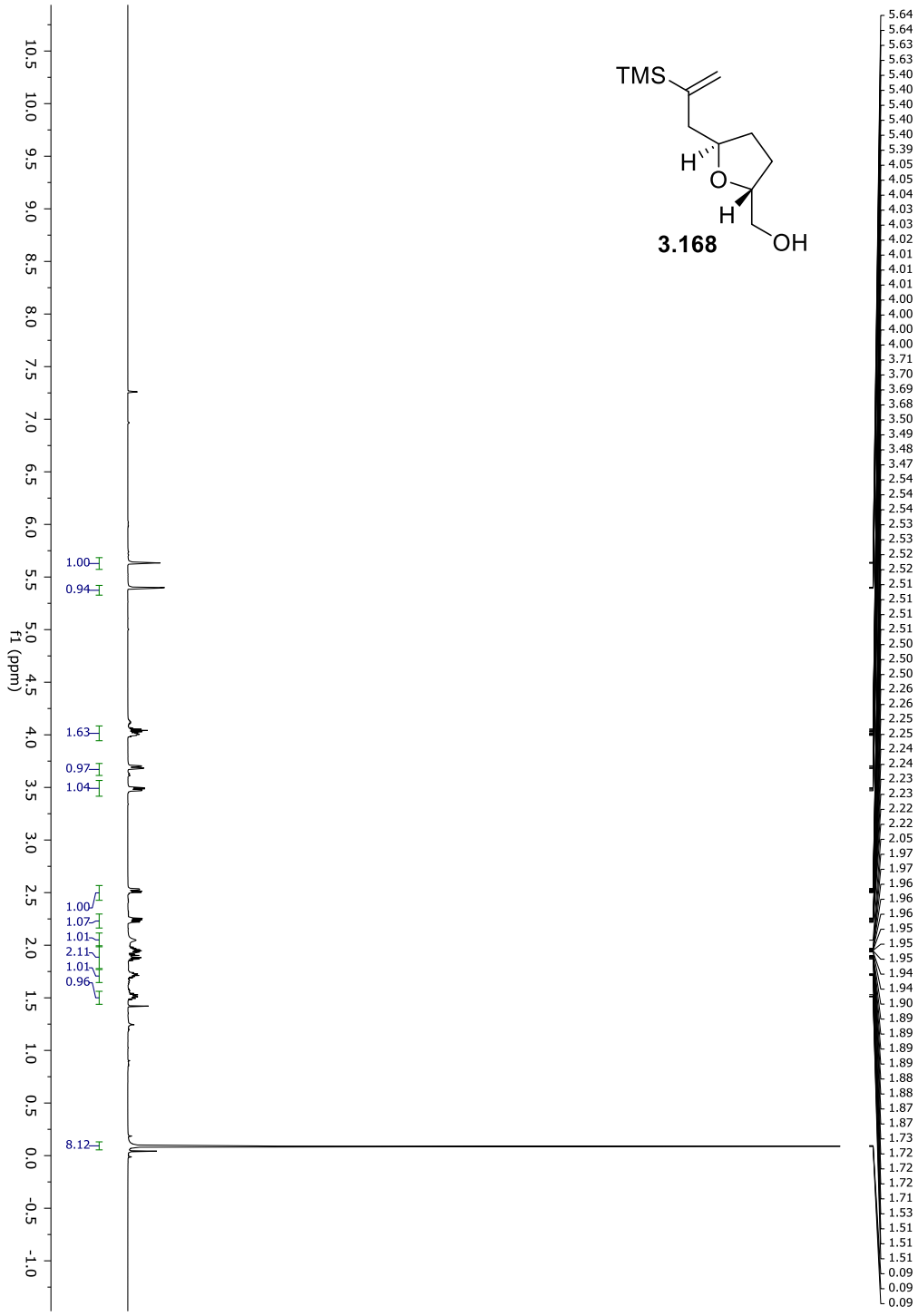

TMS
OTBS
3.165
f1 (ppm)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
148.80
139.17
127.59
114.37
77.41
77.16
76.91
71.09
44.83
35.88
29.71
26.13
26.09
18.30
-1.04
-1.08
-3.82
-4.24

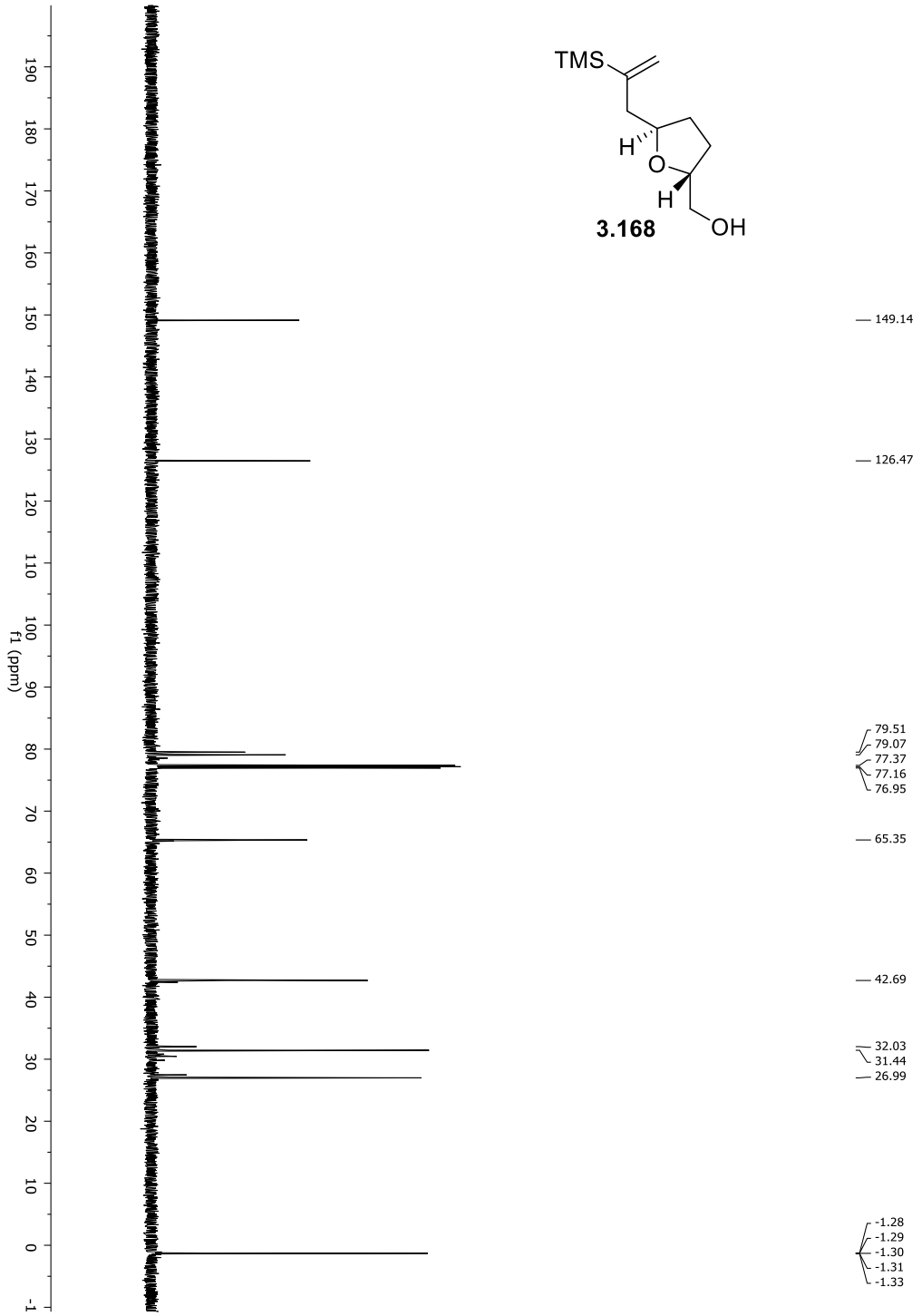

PhMe2Si
O
OTBS
3.167
f1 (ppm)
1.00
1.00
1.00
0.89
0.96
1.99
1.20
4.50
9.56
14.71

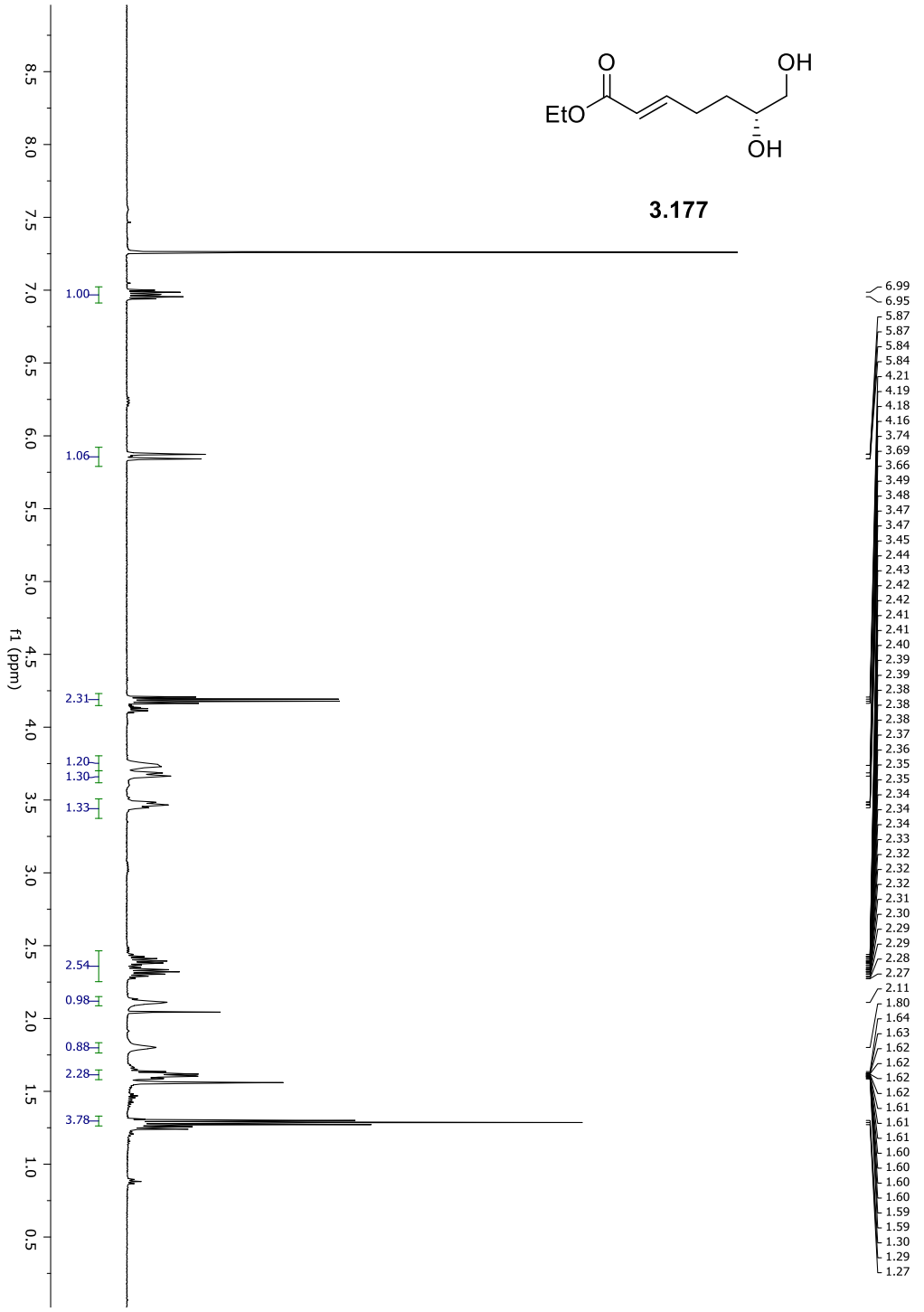

TMS
O
OTBS
3.167
f1 (ppm)
148.64
127.68
77.41
77.16
76.91
71.06
70.94
52.51
47.28
44.68
32.25
28.08
26.06
26.03
18.24
-1.10
-3.89
-4.31

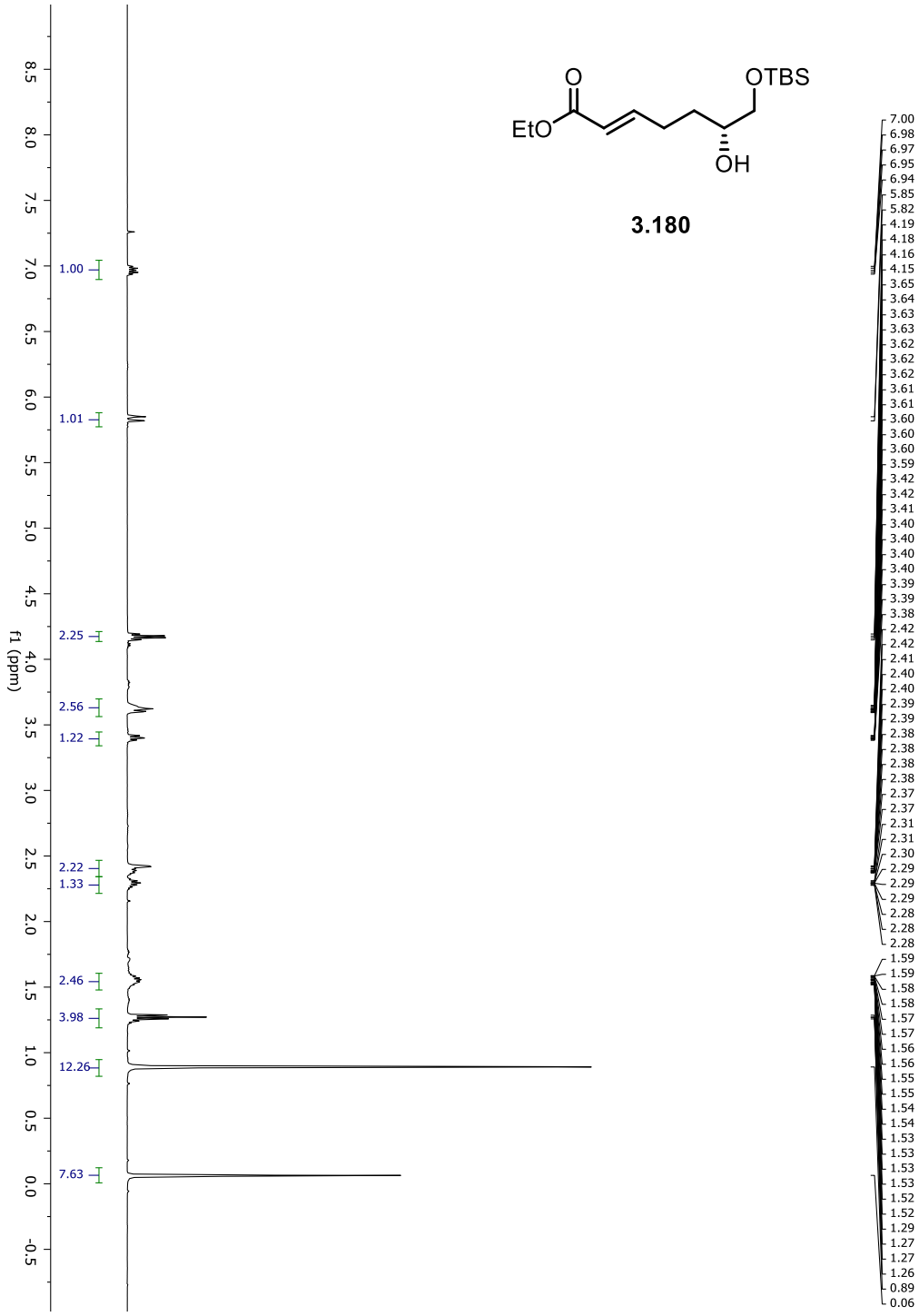

OH
TMS
OH
OTBS
3.166
f1 (ppm)
1.00
1.01
0.77
1.95
1.11
1.37
1.56
3.56
7.56
11.24

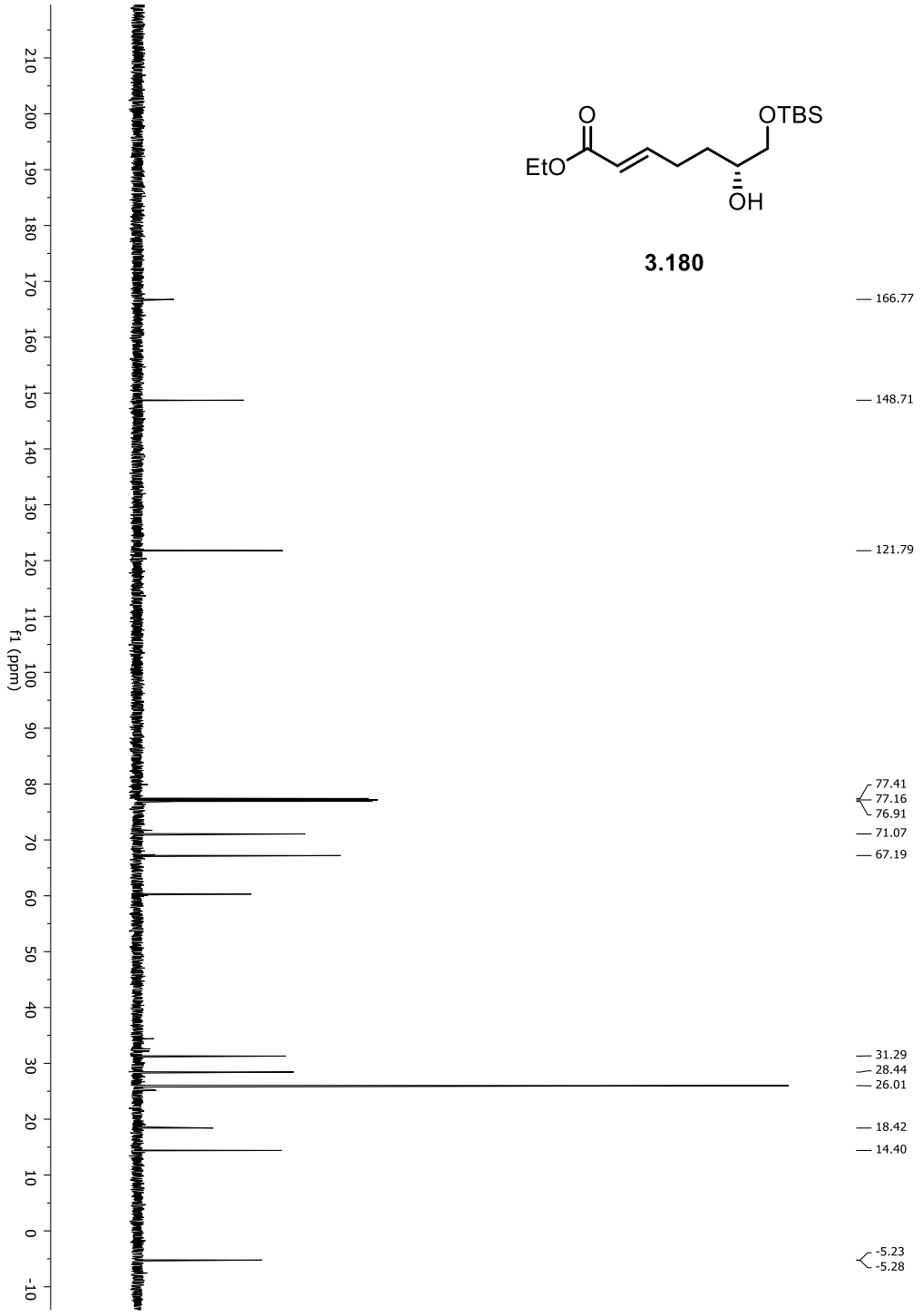

OH
TMS
OH
OTBS
3.166
148.65
127.64
127.62
77.37
77.16
76.95
72.41
71.30
66.97
44.50
31.81
28.50
26.07
26.04
18.25
-1.07
-1.09
-1.10
-1.12
-3.95
-3.96
-4.25
-4.26
f1 (ppm)

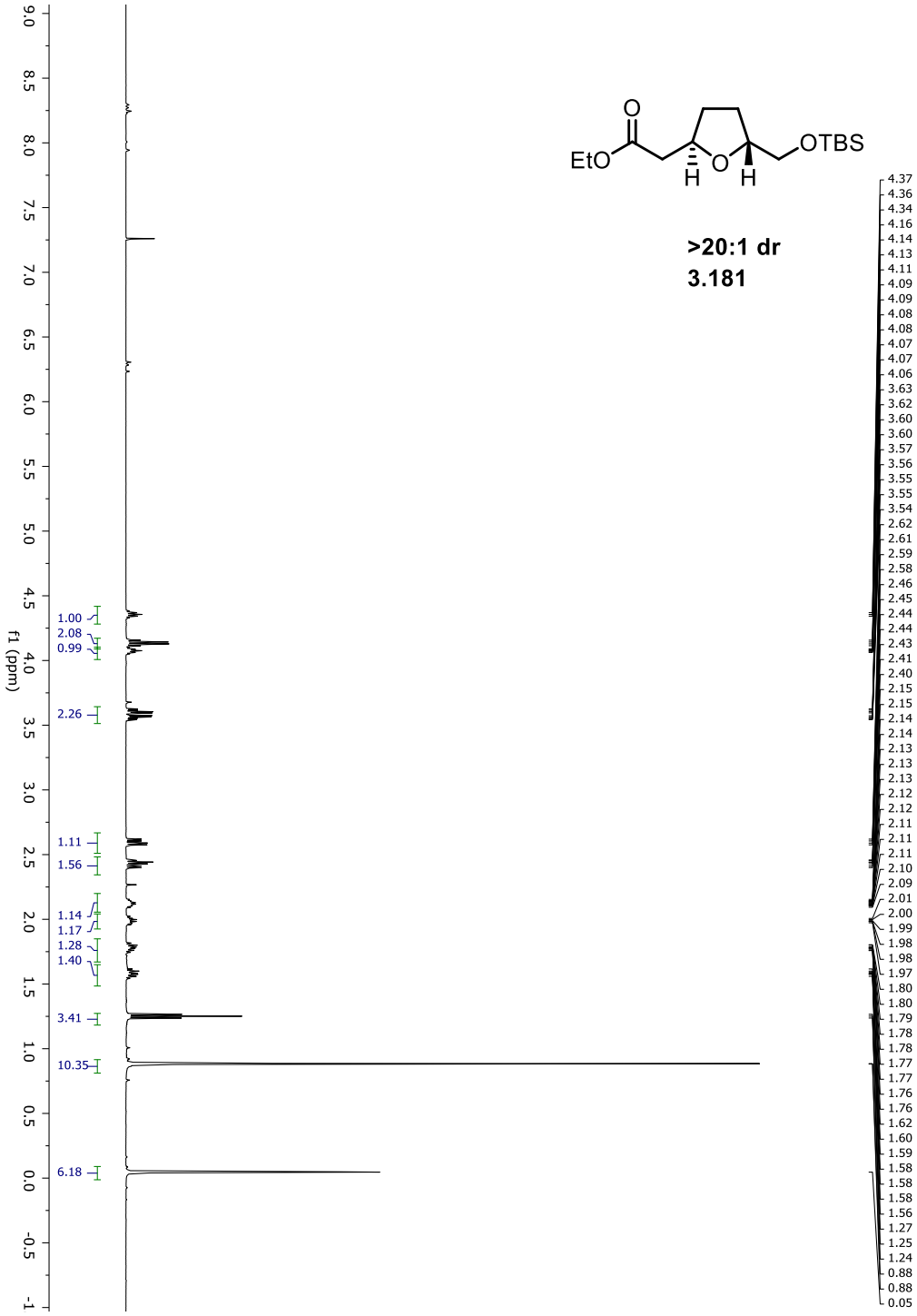

TMS
H
O
H
OH
3.168
f1 (ppm)
1.00
0.94
1.63
0.97
1.04
1.00
1.07
1.01
2.11
1.01
0.96
8.12

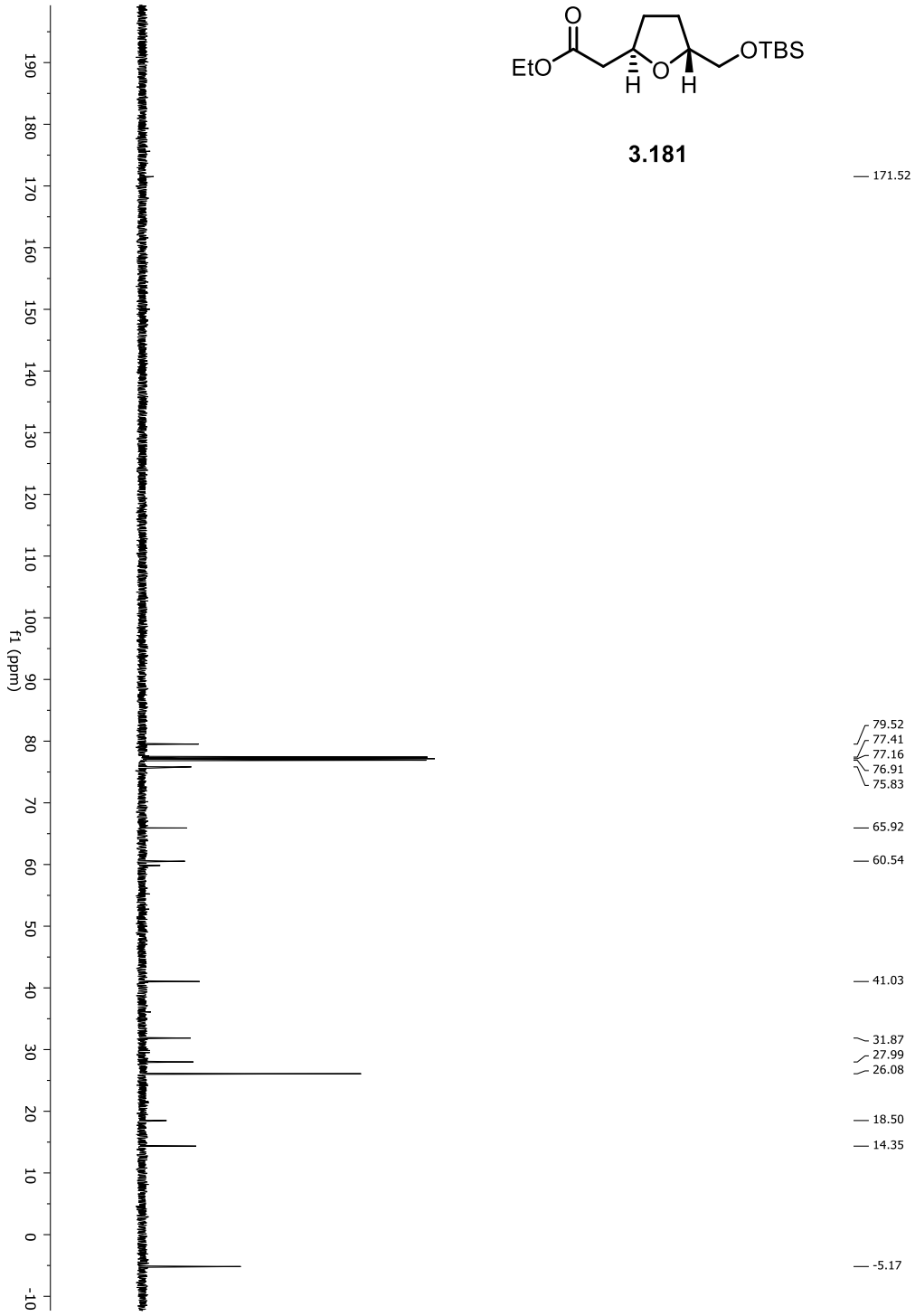

TMS
H
O
H
OH
3.168
f1 (ppm)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
149.14
126.47
79.51
79.07
77.37
77.16
76.95
65.35
42.69
32.03
31.44
26.99
-1.28
-1.29
-1.30
-1.31
-1.33

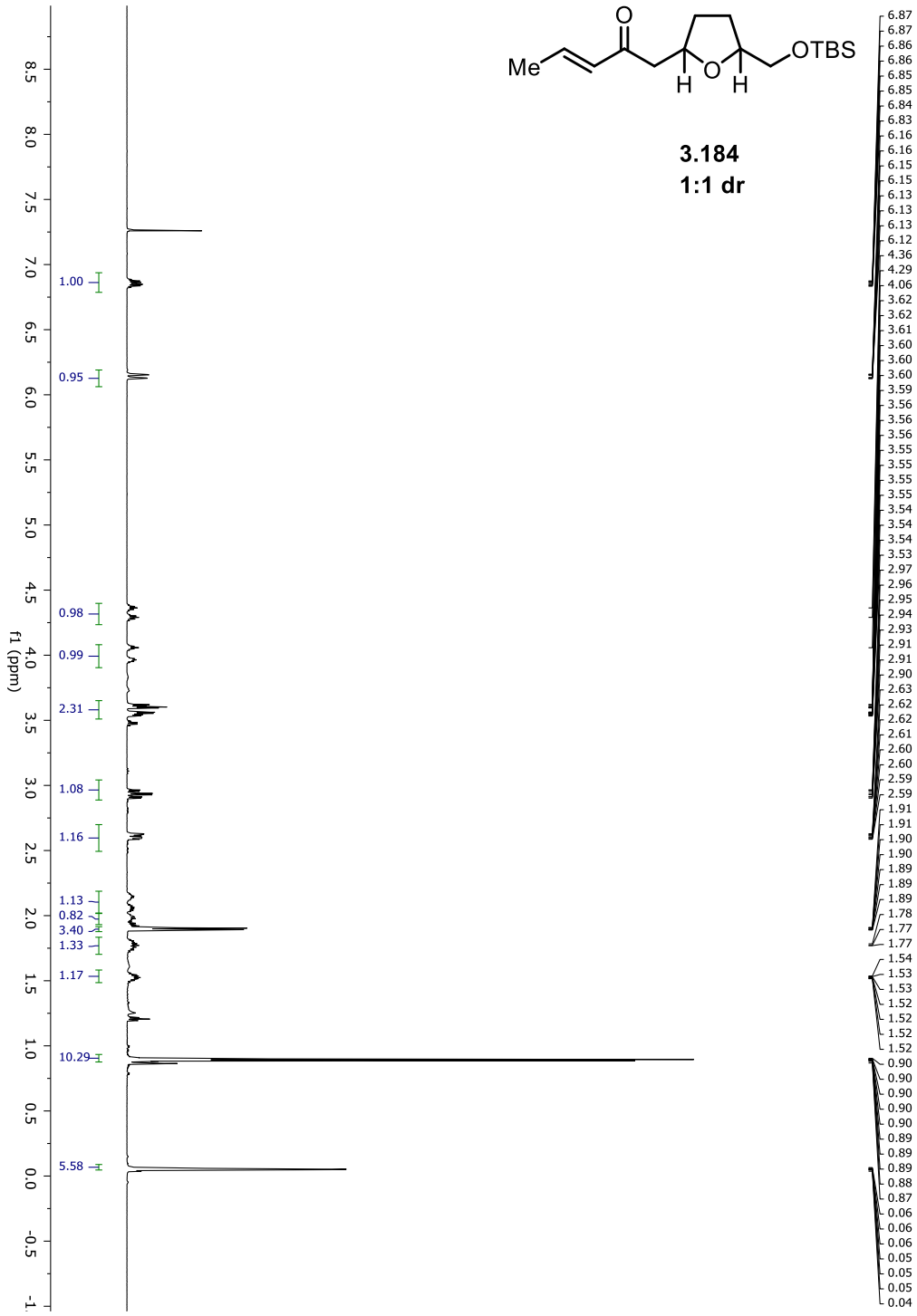

O
OH
EtO
OH
3.177
f1 (ppm)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
1.00
1.06
2.31
1.20
1.30
1.33
2.54
0.98
0.88
2.28
3.78
6.99
6.95
5.87
5.87
5.84
5.84
4.21
4.19
4.18
4.16
3.74
3.69
3.66
3.49
3.48
3.47
3.47
3.45
2.44
2.43
2.42
2.42
2.41
2.41
2.40
2.39
2.39
2.38
2.38
2.38
2.38
2.37
2.36
2.35
2.35
2.34
2.34
2.34
2.34
2.33
2.32
2.32
2.32
2.32
2.31
2.30
2.29
2.29
2.28
2.27
2.11
1.80
1.64
1.63
1.62
1.62
1.62
1.62
1.61
1.61
1.61
1.61
1.60
1.60
1.60
1.60
1.59
1.59
1.30
1.29
1.27

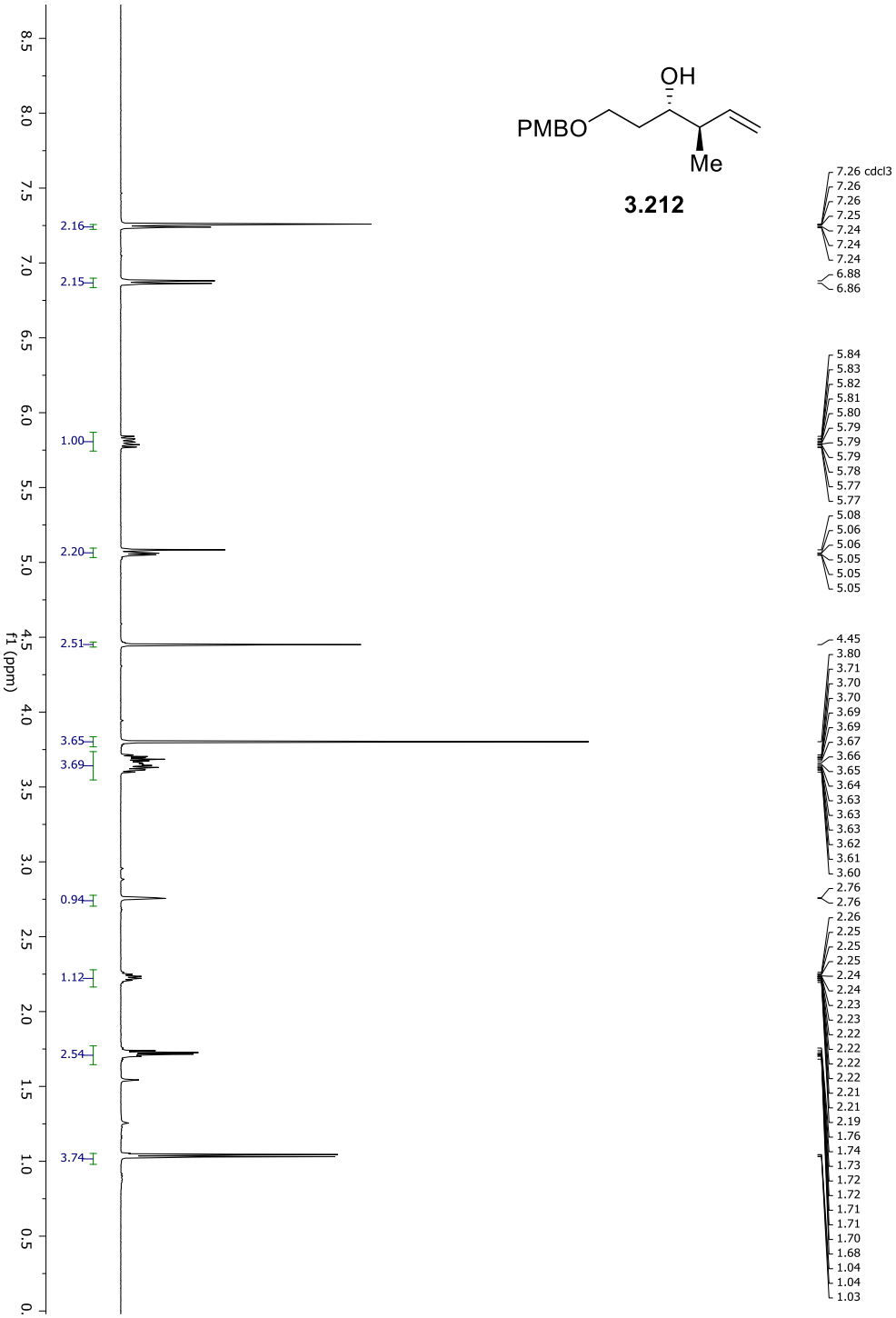

O
OTBS
EtO
OH
3.180
f1 (ppm)
1.00
1.01
2.25
2.56
1.22
2.22
1.33
2.46
3.98
12.26
7.63

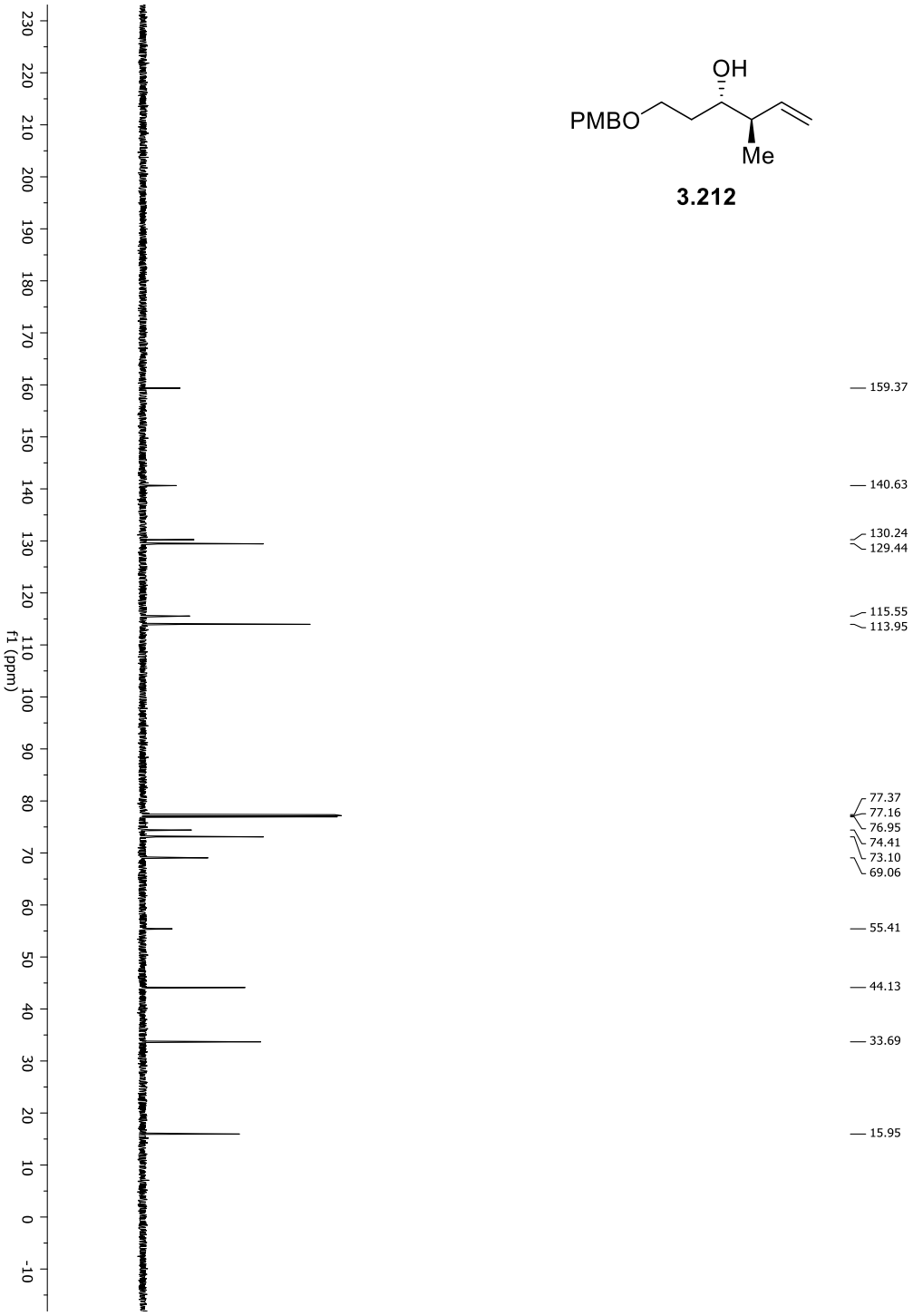

O
OTBS
EtO
OH
3.180
166.77
148.71
121.79
77.41
77.16
76.91
71.07
67.19
31.29
28.44
26.01
18.42
14.40
-5.23
-5.28
f1 (ppm)

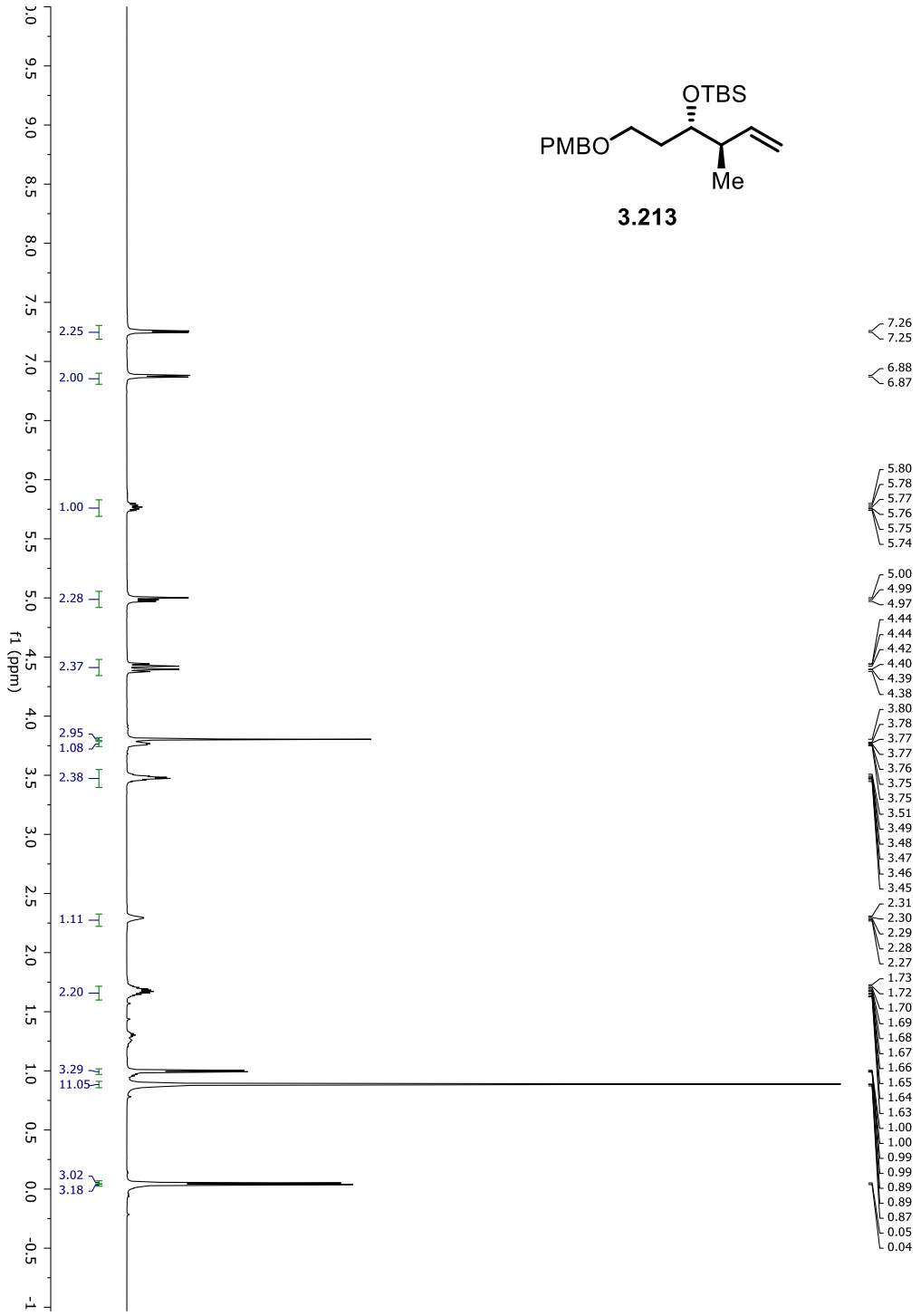

EtO
O
O
H
H
OTBS
>20:1 dr
3.181
f1 (ppm)
1.00
2.08
0.99
2.26
1.11
1.56
1.14
1.17
1.28
1.40
3.41
10.35
6.18

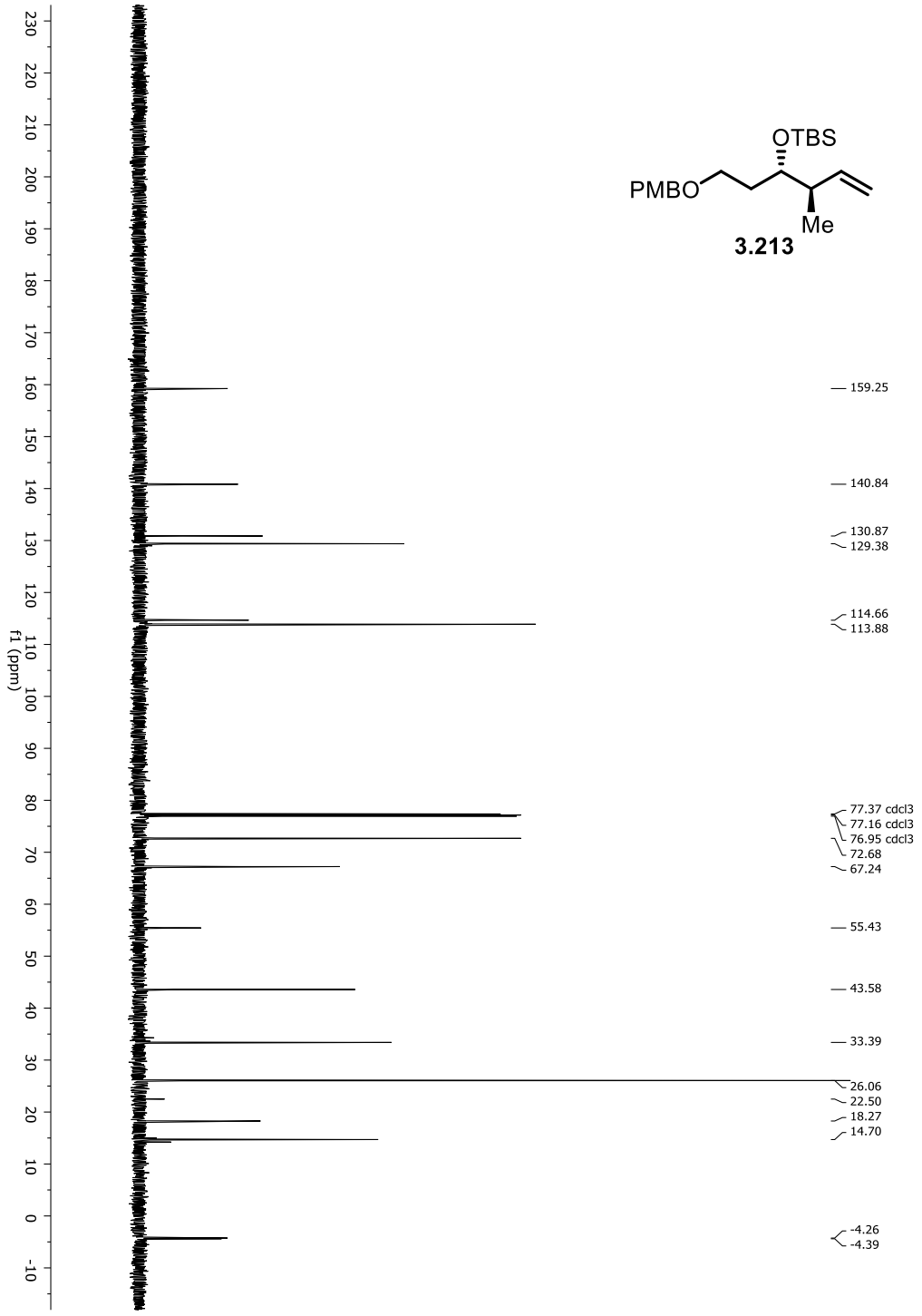

EtO
O
O
H
H
OTBS
3.181
f1 (ppm)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
171.52
79.52
77.41
77.16
76.91
75.83
65.92
60.54
41.03
31.87
27.99
26.08
18.50
14.35
-5.17

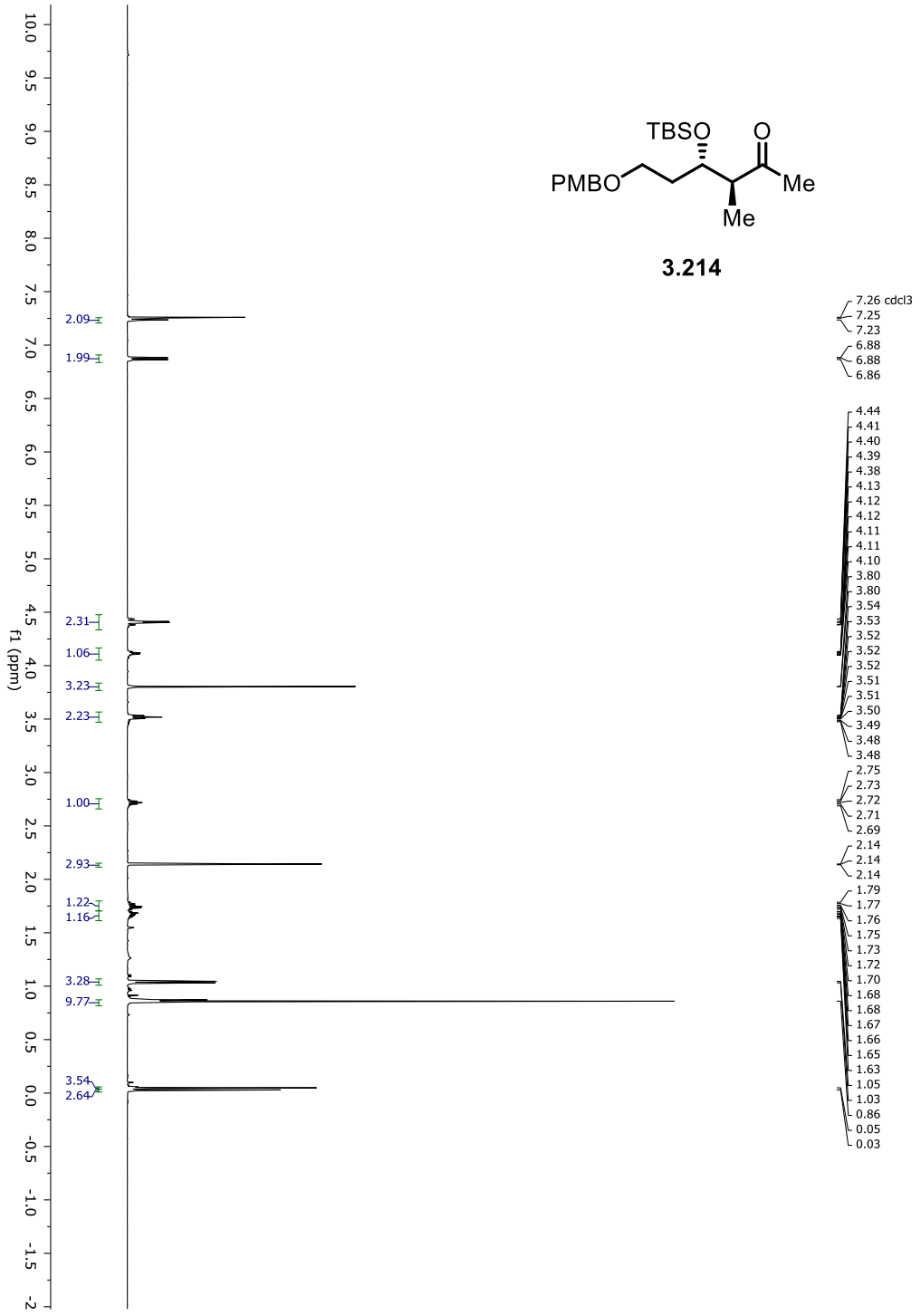

Me
O
H
O
H
OTBS
3.184
1:1 dr
f1 (ppm)
1.00
0.95
0.98
0.99
2.31
1.08
1.16
1.13
0.82
3.40
1.33
1.17
10.29
5.58

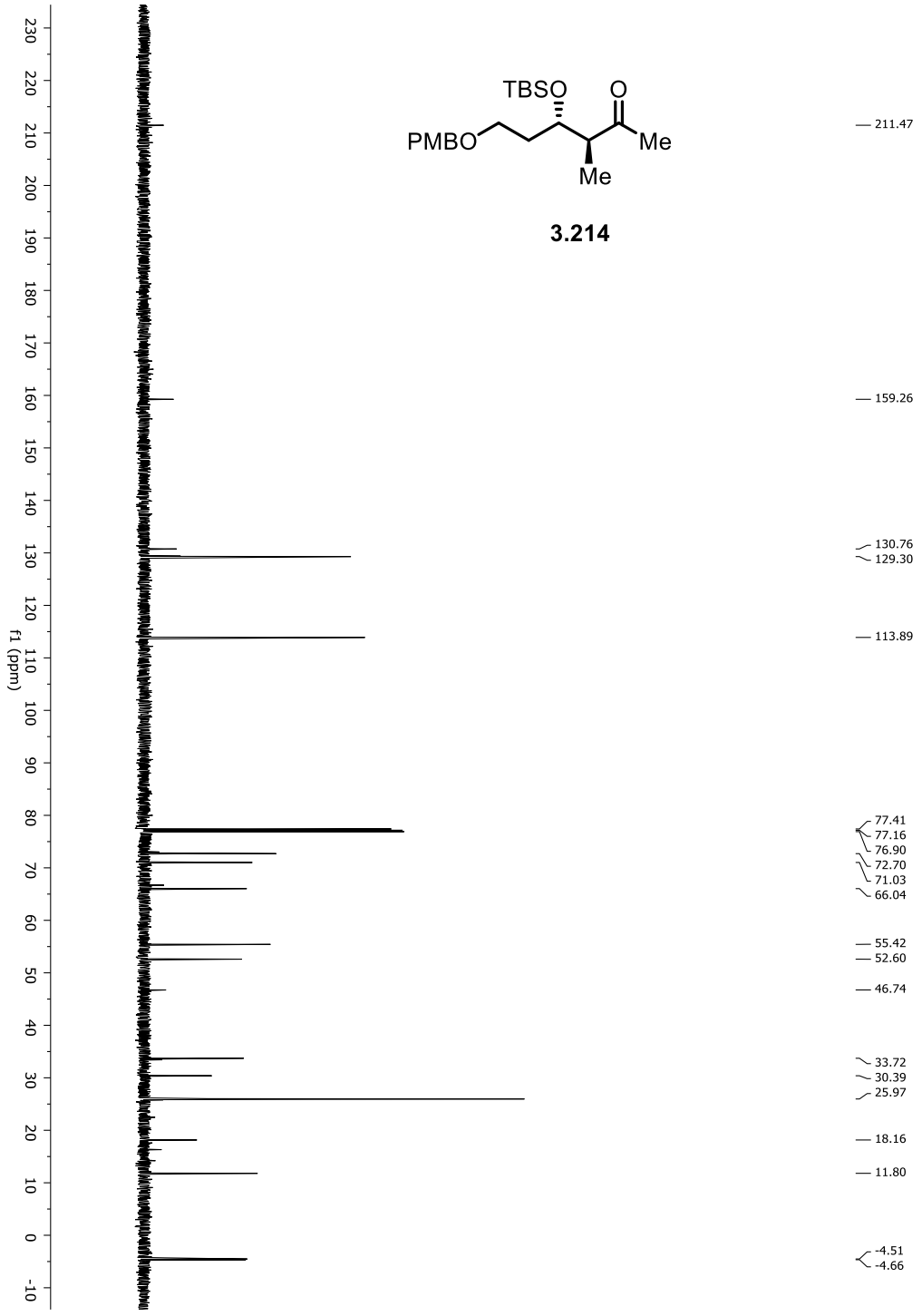

OH
PMBO
Me
3.212
f1 (ppm)
2.16
2.15
1.00
2.20
2.51
3.65
3.69
0.94
1.12
2.54
3.74
7.26 cdcl3
7.26
7.26
7.25
7.24
7.24
7.24
6.88
6.86
5.84
5.83
5.82
5.81
5.80
5.79
5.79
5.79
5.78
5.77
5.77
5.08
5.06
5.06
5.05
5.05
5.05
4.45
3.80
3.71
3.70
3.70
3.69
3.69
3.67
3.66
3.65
3.64
3.63
3.63
3.63
3.62
3.61
3.60
2.76
2.76
2.26
2.25
2.25
2.25
2.24
2.24
2.23
2.23
2.22
2.22
2.22
2.22
2.21
2.21
2.19
1.76
1.74
1.73
1.72
1.72
1.71
1.71
1.70
1.68
1.04
1.04
1.03

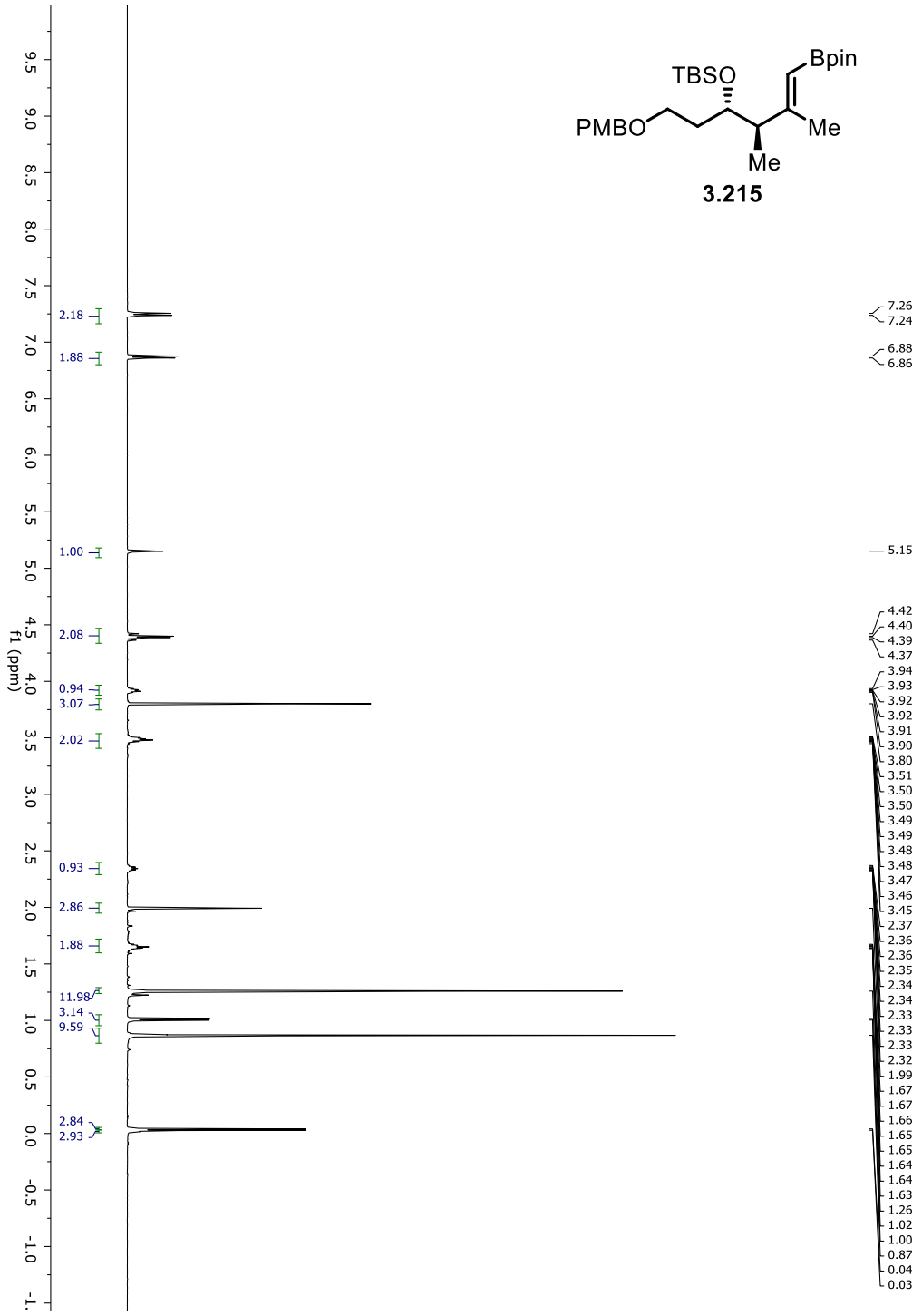

OH
PMBO
Me
3.212
f1 (ppm)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
159.37
140.63
130.24
129.44
115.55
113.95
77.37
77.16
76.95
74.41
73.10
69.06
55.41
44.13
33.69
15.95

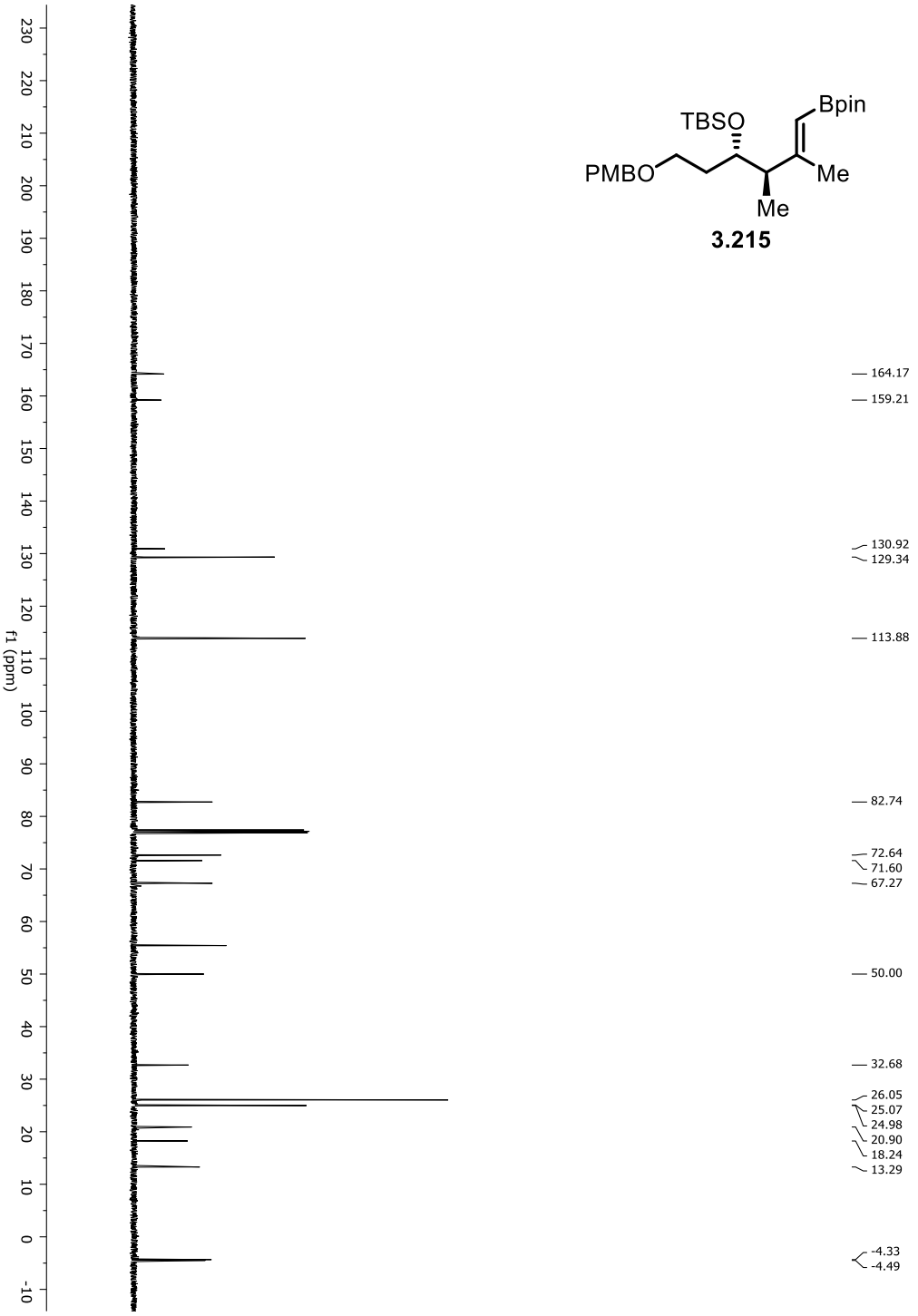

OTBS
PMBO
Me
3.213
f1 (ppm)
2.25
2.00
1.00
2.28
2.37
2.95
1.08
2.38
1.11
2.20
3.29
11.05
3.02
3.18
7.26
7.25
6.88
6.87
5.80
5.78
5.77
5.76
5.75
5.74
5.00
4.99
4.97
4.44
4.44
4.42
4.40
4.39
4.38
3.80
3.78
3.77
3.77
3.76
3.75
3.75
3.51
3.49
3.48
3.47
3.46
3.45
2.31
2.30
2.29
2.28
2.27
1.73
1.72
1.70
1.69
1.68
1.67
1.66
1.65
1.64
1.63
1.00
1.00
0.99
0.99
0.89
0.89
0.87
0.05
0.04


OTBS
PMBO
Me
3.213
f1 (ppm)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
159.25
140.84
130.87
129.38
114.66
113.88
77.37 cdcl3
77.16 cdcl3
76.95 cdcl3
72.68
67.24
55.43
43.58
33.39
26.06
22.50
18.27
14.70
-4.26
-4.39

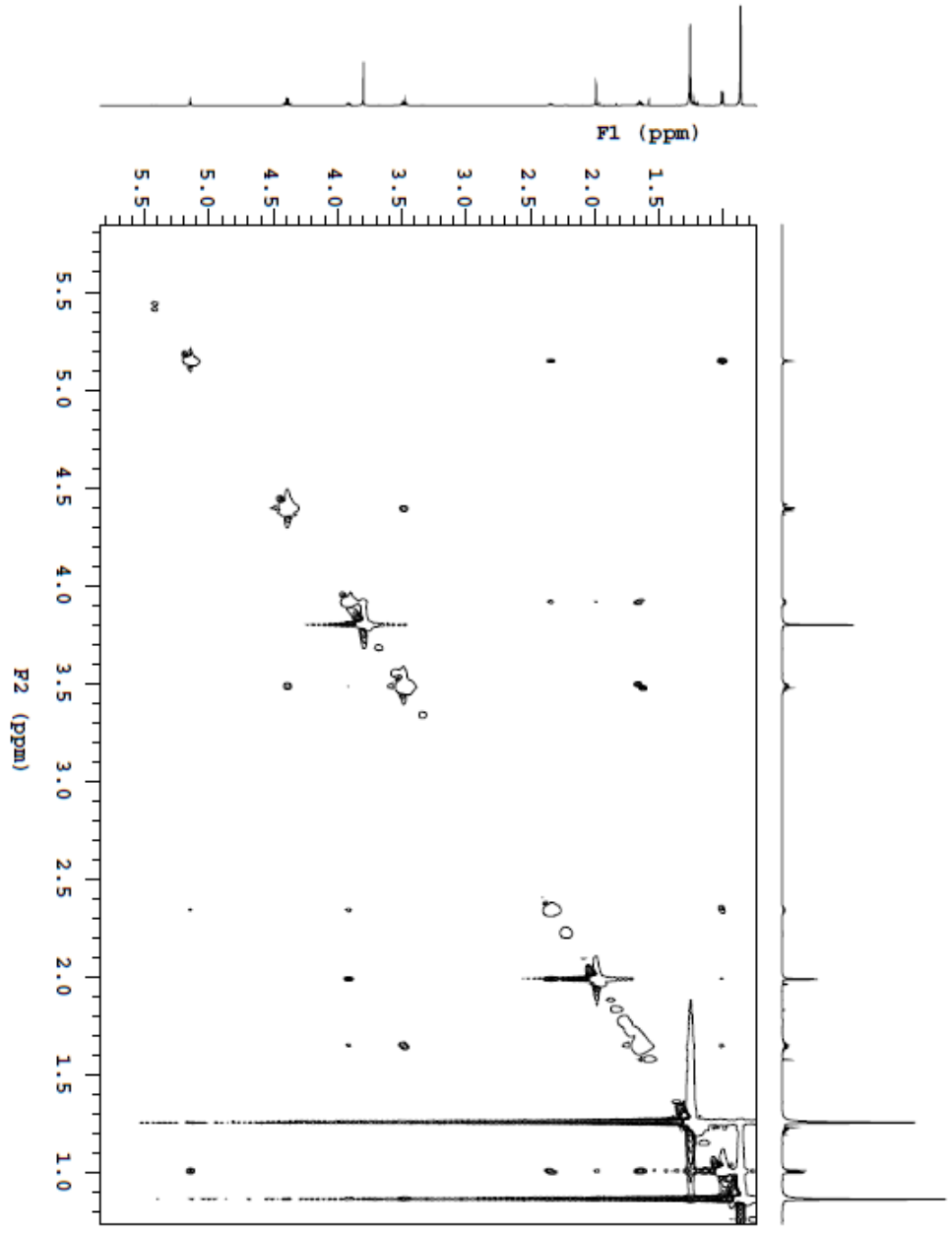

TBSO
O
PMBO
Me
Me
3.214
f1 (ppm)
2.09
1.99
2.31
1.06
3.23
2.23
1.00
2.93
1.22
1.16
3.28
9.77
3.54
2.64
7.26 cdcl3
7.25
7.23
6.88
6.88
6.86
4.44
4.41
4.40
4.39
4.38
4.13
4.12
4.12
4.11
4.11
4.10
3.80
3.80
3.54
3.53
3.52
3.52
3.52
3.51
3.51
3.50
3.49
3.48
3.48
2.75
2.73
2.72
2.71
2.69
2.14
2.14
2.14
1.79
1.77
1.76
1.75
1.73
1.72
1.70
1.68
1.68
1.67
1.66
1.65
1.63
1.05
1.03
0.86
0.05
0.03

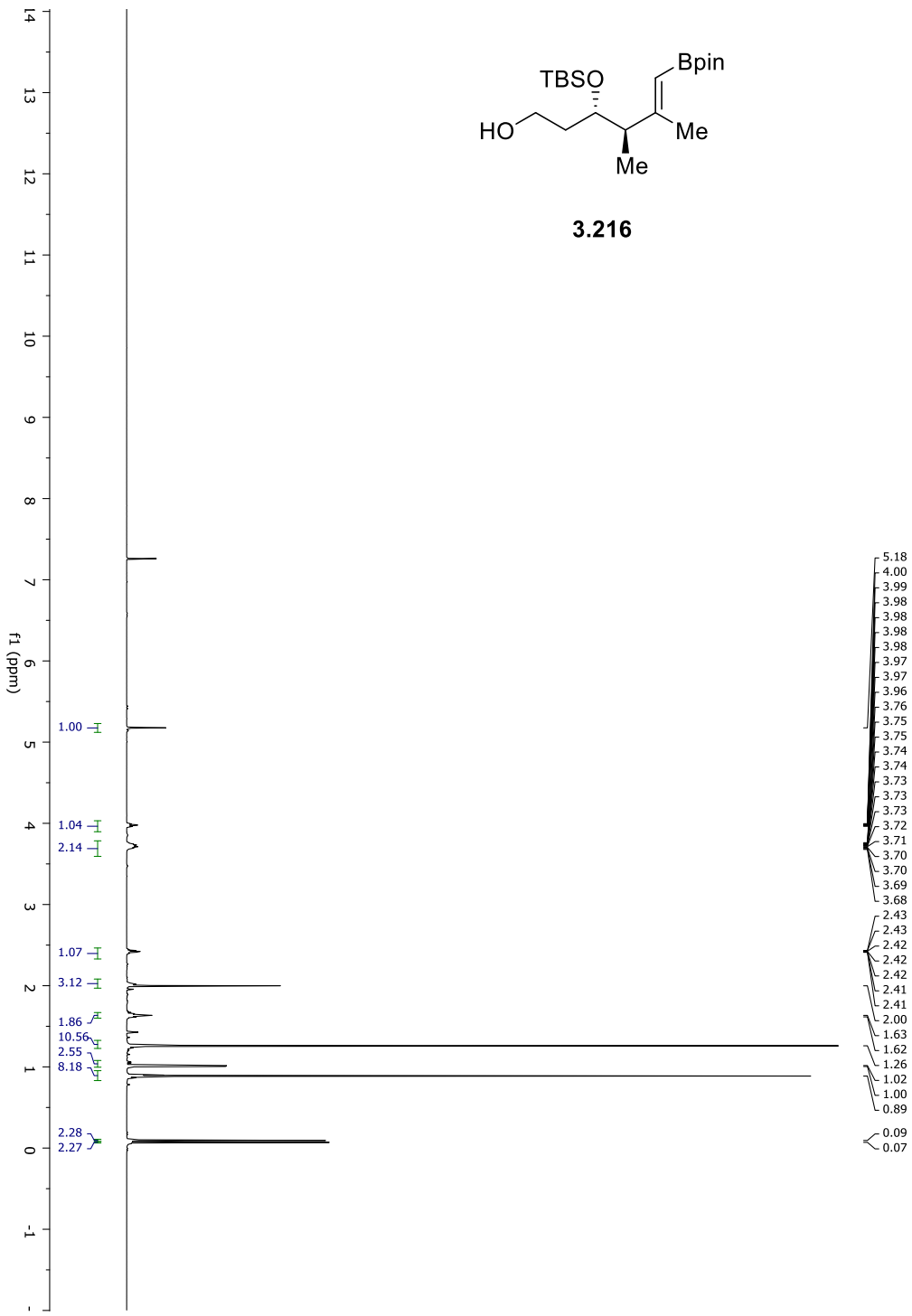

TBSO
O
PMBO
Me
Me
3.214
211.47
159.26
130.76
129.30
113.89
77.41
77.16
76.90
72.70
71.03
66.04
55.42
52.60
46.74
33.72
30.39
25.97
18.16
11.80
-4.51
-4.66
f1 (ppm)

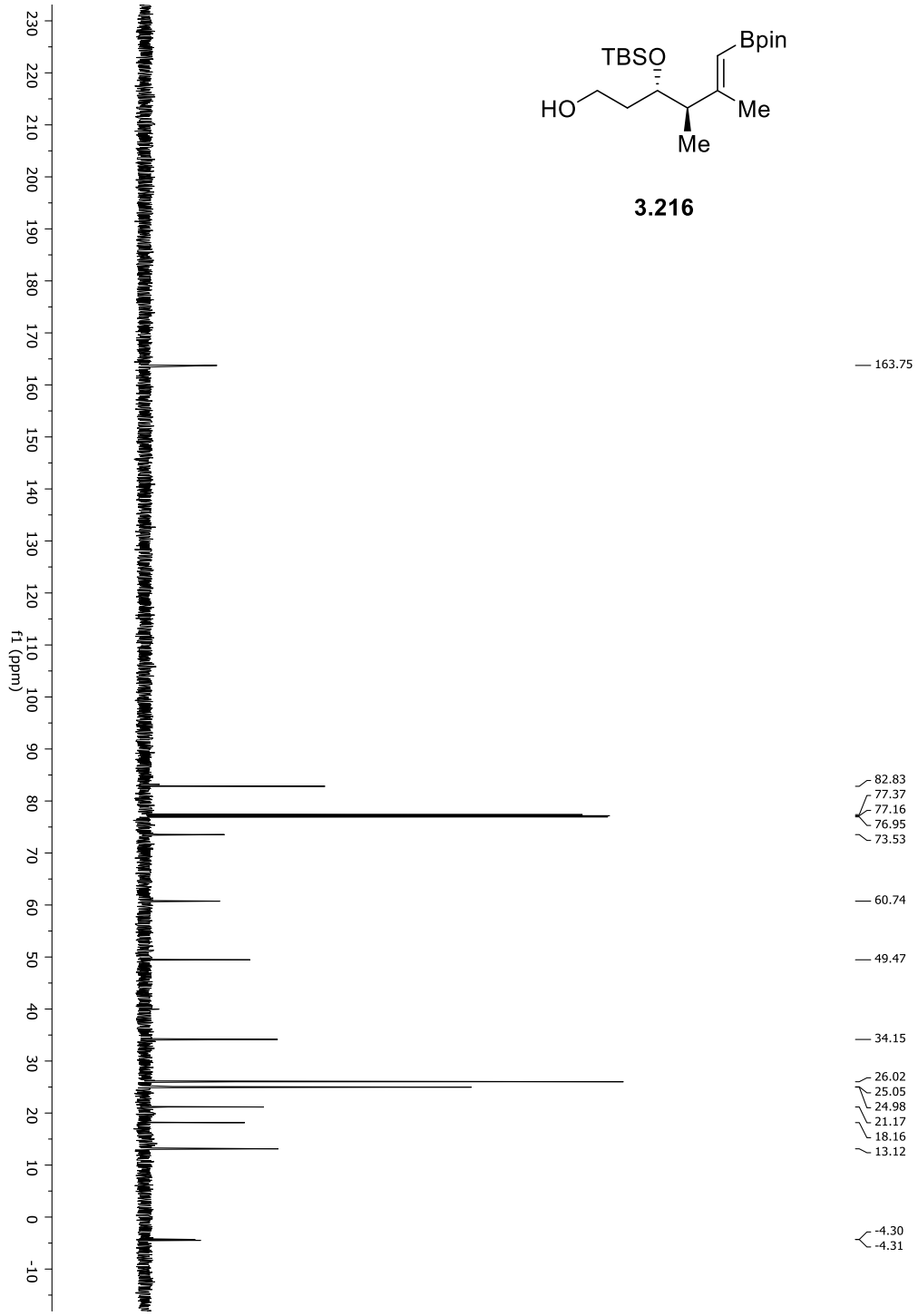

TBSO
Bpin
PMBO
Me
Me
3.215
f1 (ppm)
2.18
1.88
1.00
2.08
0.94
3.07
2.02
0.93
2.86
1.88
11.98
3.14
9.59
2.84
2.93
7.26
7.24
6.88
6.86
5.15
4.42
4.40
4.39
4.37
3.94
3.93
3.92
3.92
3.91
3.90
3.80
3.51
3.50
3.50
3.49
3.49
3.48
3.48
3.47
3.46
3.45
2.37
2.36
2.36
2.35
2.34
2.34
2.33
2.33
2.33
2.32
1.99
1.67
1.67
1.66
1.65
1.65
1.64
1.64
1.63
1.26
1.02
1.00
0.87
0.04
0.03

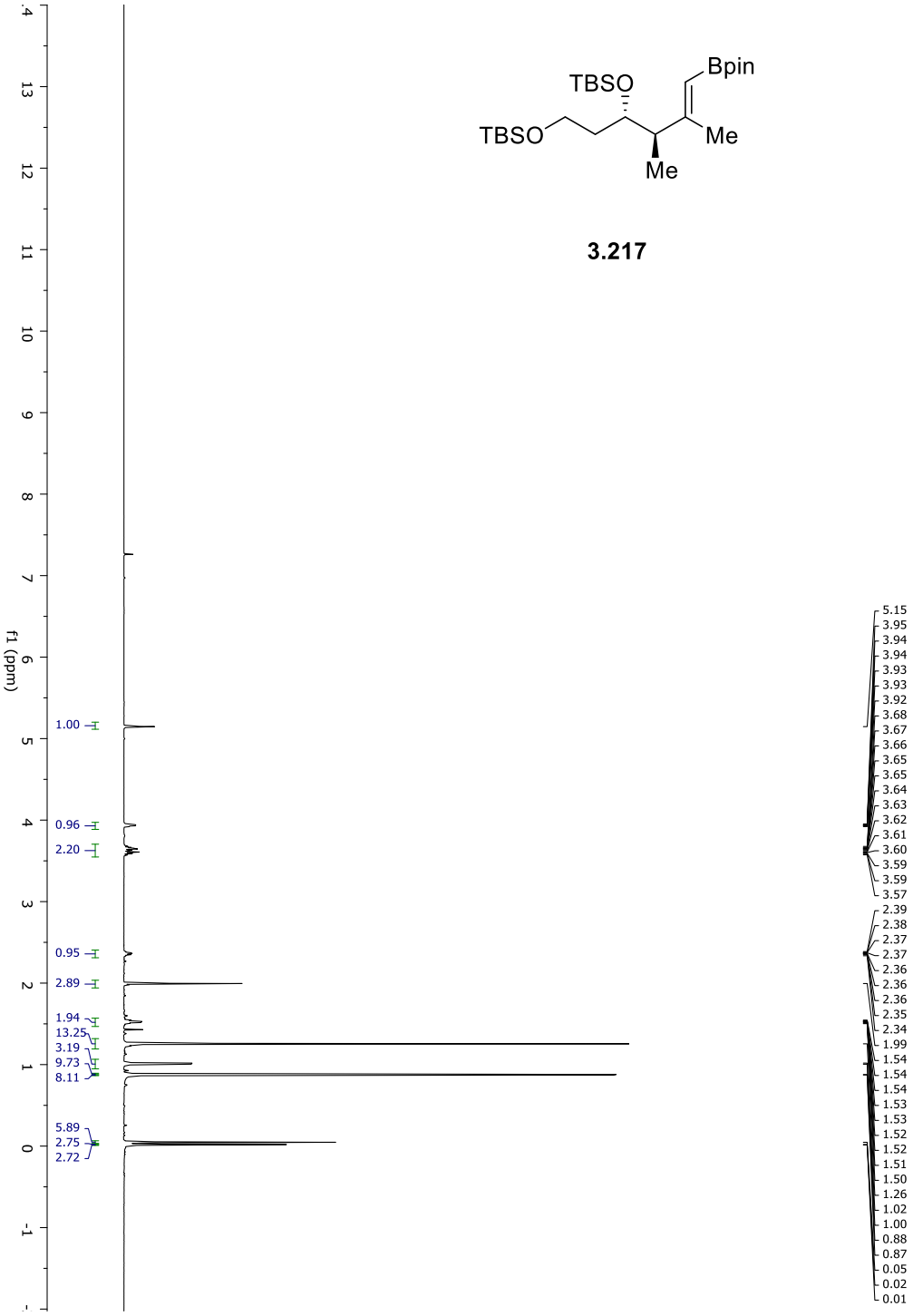

Bpin
TBSO
PMBO
Me
Me
3.215
f1 (ppm)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
164.17
159.21
130.92
129.34
113.88
82.74
72.64
71.60
67.27
50.00
32.68
26.05
25.07
24.98
20.90
18.24
13.29
-4.33
-4.49

[1]HNMR NOESY for compound **3.215**

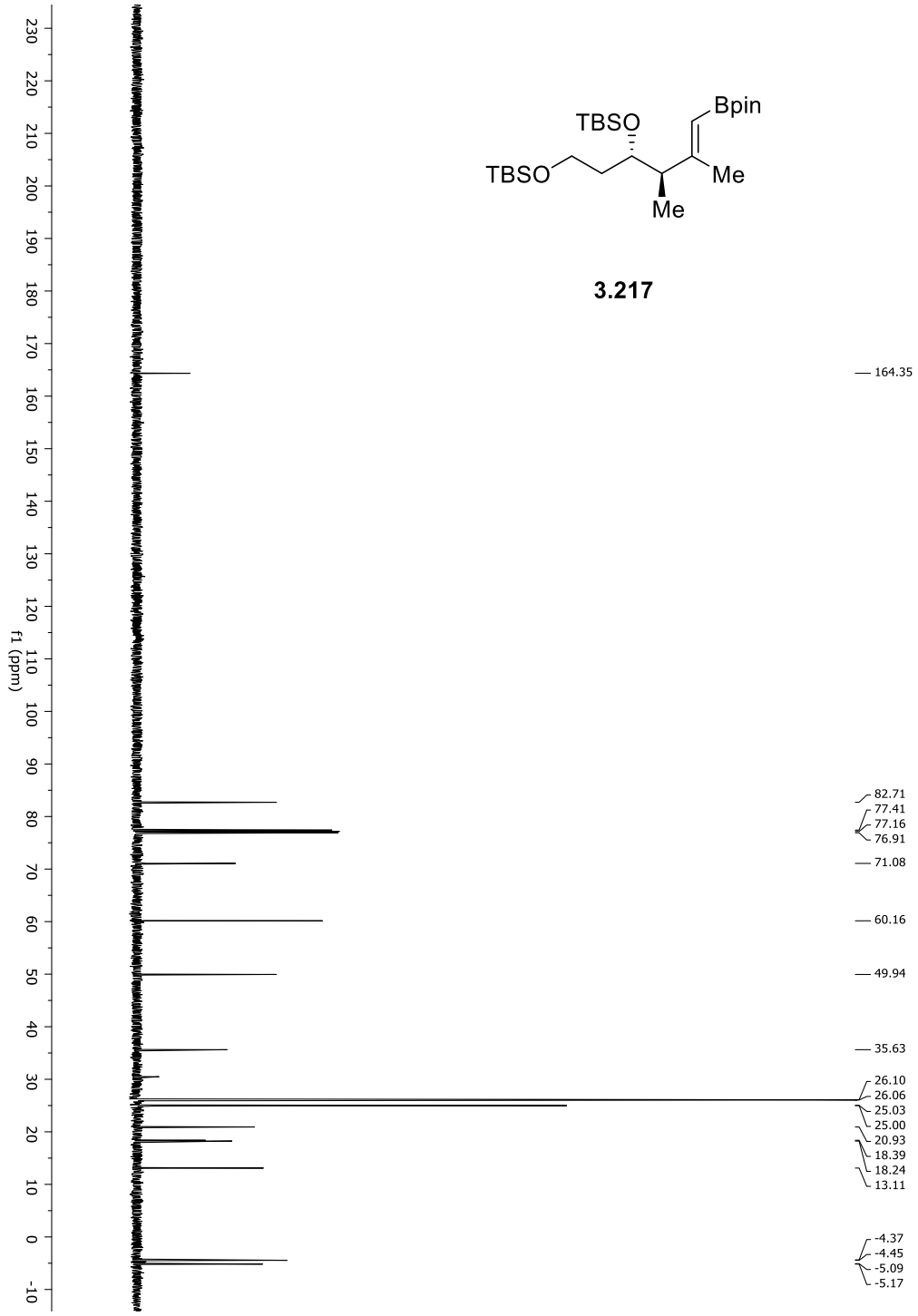


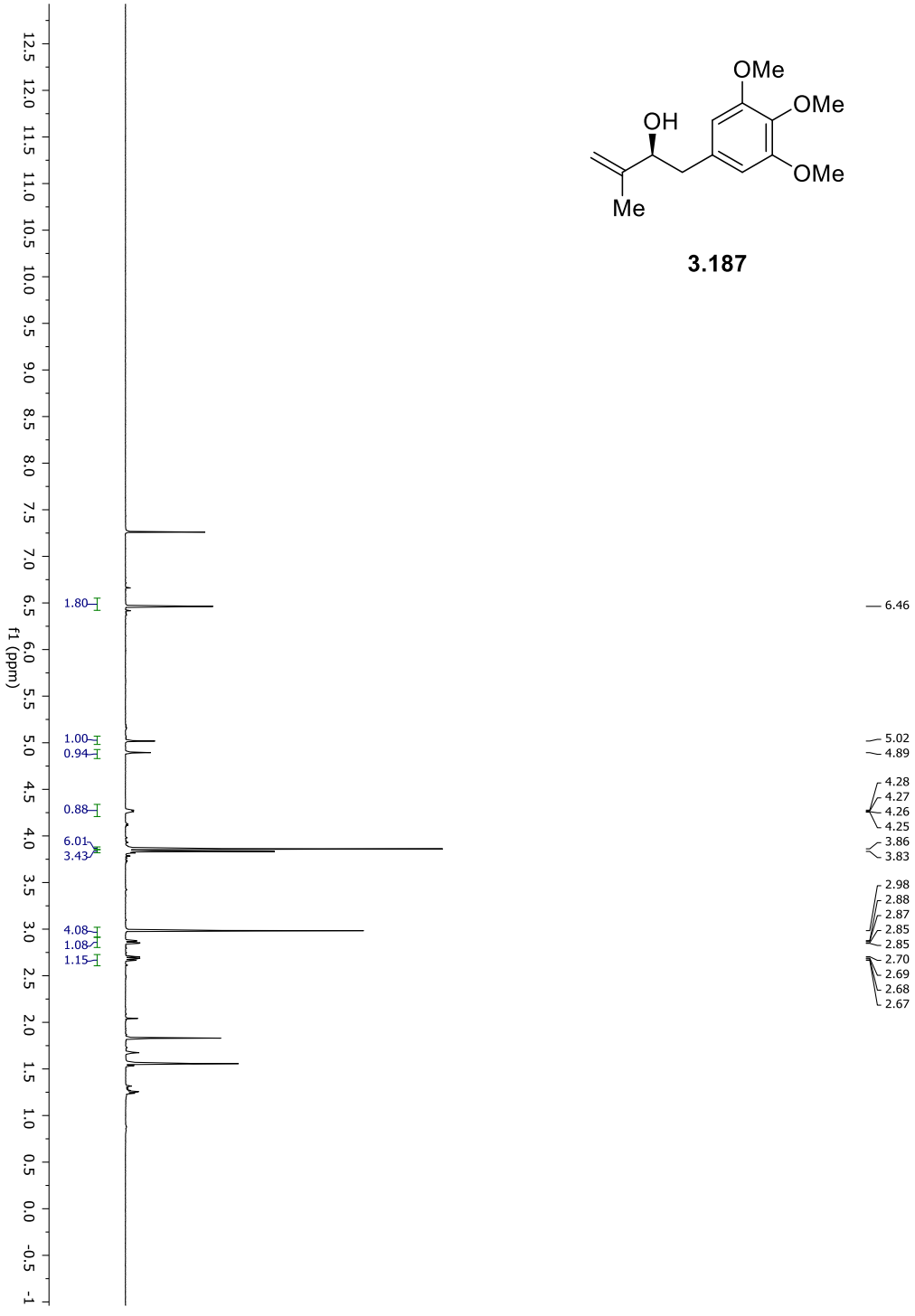

TBSO
Bpin
HO
Me
Me
3.216
f1 (ppm)
1.00
1.04
2.14
1.07
3.12
1.86
10.56
2.55
8.18
2.28
2.27
5.18
4.00
3.99
3.98
3.98
3.98
3.98
3.98
3.97
3.97
3.96
3.76
3.75
3.75
3.74
3.74
3.73
3.73
3.73
3.72
3.71
3.70
3.70
3.69
3.68
2.43
2.43
2.42
2.42
2.42
2.41
2.41
2.00
1.63
1.62
1.26
1.02
1.00
0.89
0.09
0.07

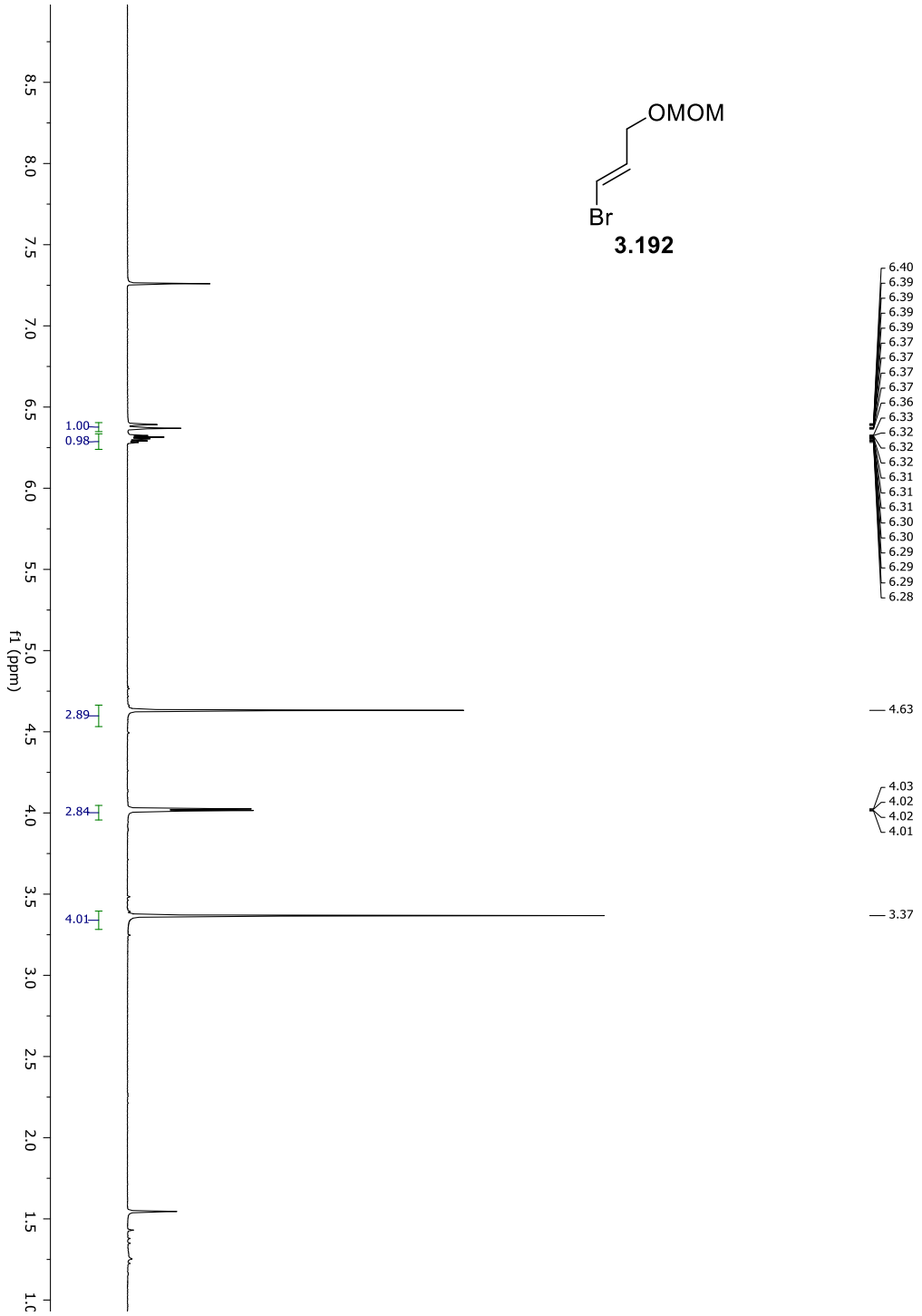

TBSO
Bpin
HO
Me
Me
3.216
f1 (ppm)
163.75
82.83
77.37
77.16
76.95
73.53
60.74
49.47
34.15
26.02
25.05
24.98
21.17
18.16
13.12
-4.30
-4.31

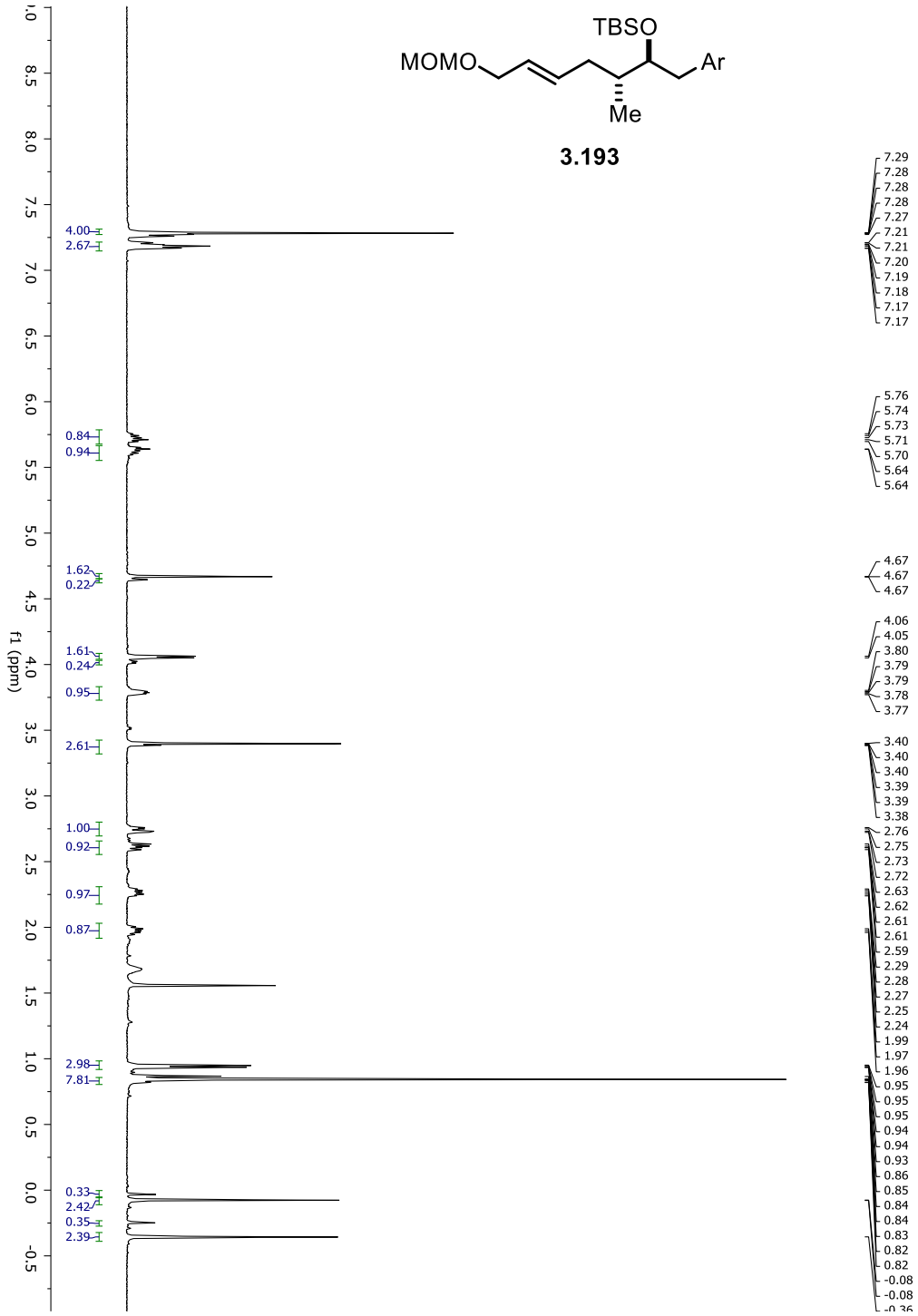

TBSO
Bpin
TBSO
Me
Me
f1 (ppm)
1.00
0.96
2.20
0.95
2.89
1.94
13.25
3.19
9.73
8.11
5.89
2.75
2.72
5.15
3.95
3.94
3.94
3.93
3.93
3.92
3.68
3.67
3.66
3.65
3.65
3.64
3.63
3.62
3.61
3.60
3.59
3.59
3.57
2.39
2.38
2.37
2.37
2.36
2.36
2.36
2.35
2.34
1.99
1.54
1.54
1.54
1.53
1.53
1.52
1.52
1.51
1.50
1.26
1.02
1.00
0.88
0.87
0.05
0.02
0.01

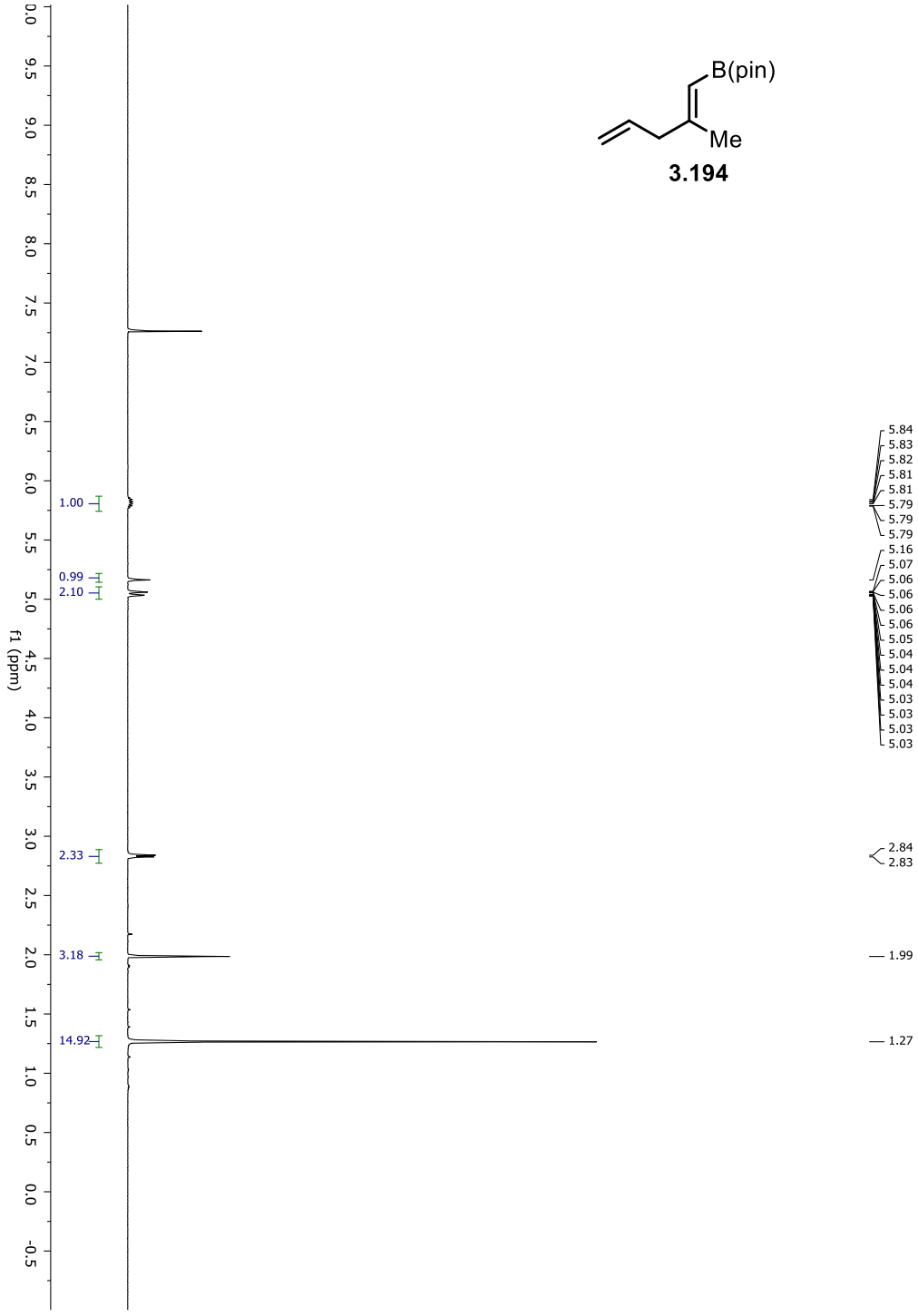
3.217

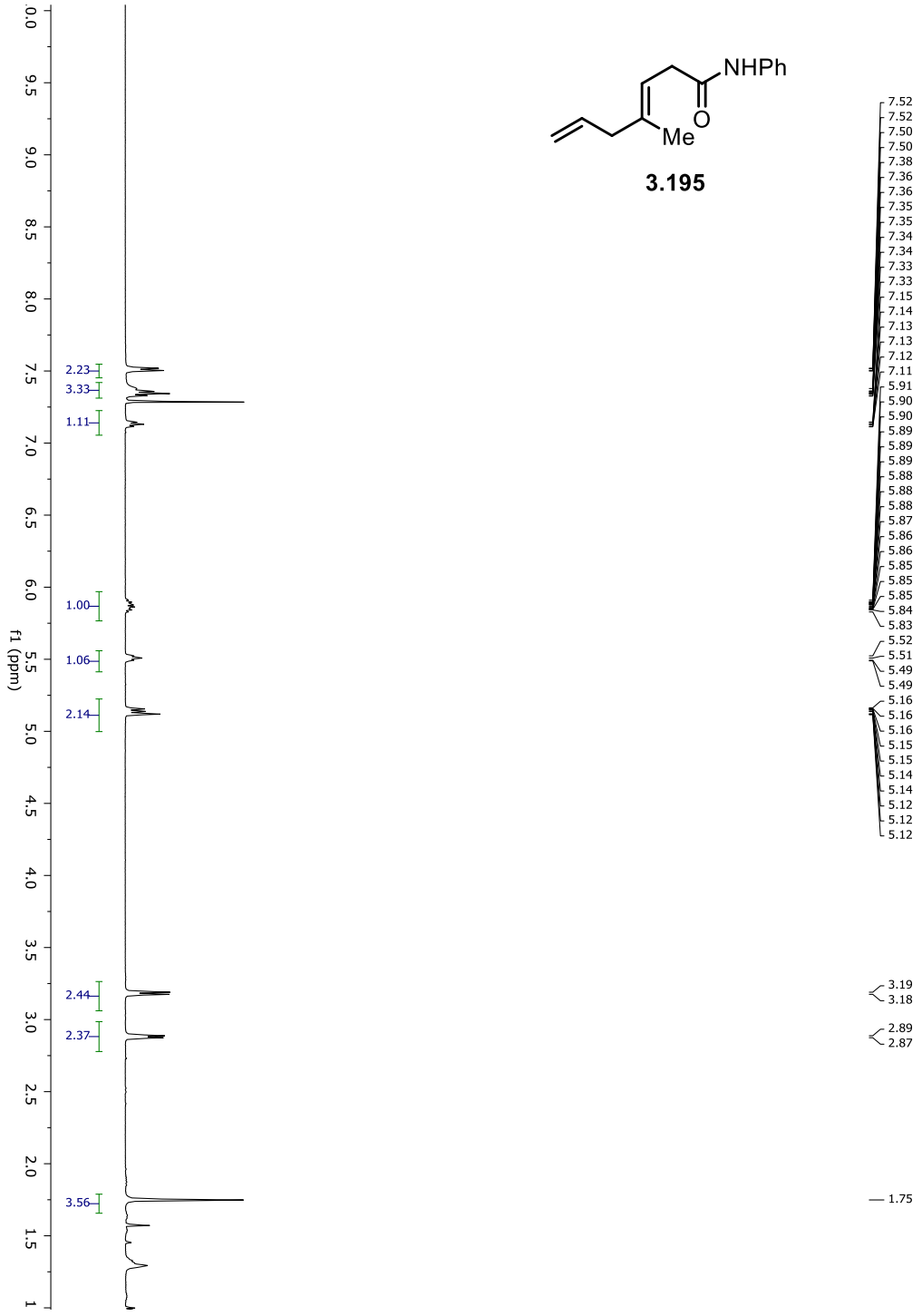

TBSO
Bpin
TBSO
Me
Me
3.217
f1 (ppm)
164.35
82.71
77.41
77.16
76.91
71.08
60.16
49.94
35.63
26.10
26.06
25.03
25.00
20.93
18.39
18.24
13.11
-4.37
-4.45
-5.09
-5.17

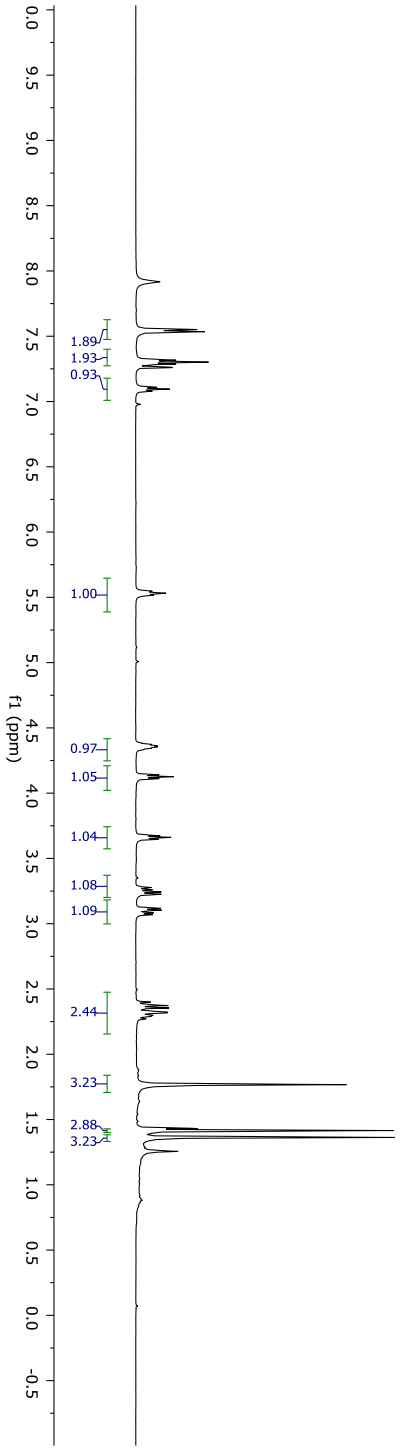

OMe
OMe
OH
OMe
Me
3.187
f1 (ppm)
1.80
1.00
0.94
0.88
6.01
3.43
4.08
1.08
1.15
6.46
5.02
4.89
4.28
4.27
4.26
4.25
3.86
3.83
2.98
2.88
2.87
2.85
2.85
2.70
2.69
2.68
2.67

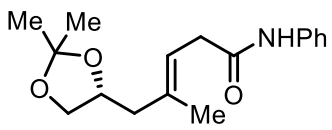

OMOM
Br
3.192
f1 (ppm)
1.00
0.98
2.89
2.84
4.01
6.40
6.39
6.39
6.39
6.39
6.37
6.37
6.37
6.37
6.36
6.33
6.32
6.32
6.32
6.31
6.31
6.31
6.30
6.30
6.29
6.29
6.29
6.28
4.63
4.03
4.02
4.02
4.01
3.37


TBSO
MOMO
Ar
Me
3.193
f1 (ppm)
4.00
2.67
0.84
0.94
1.62
0.22
1.61
0.24
0.95
2.61
1.00
0.92
0.97
0.87
2.98
7.81
0.33
2.42
0.35
2.39
7.29
7.28
7.28
7.28
7.27
7.21
7.21
7.20
7.19
7.18
7.17
7.17
5.76
5.74
5.73
5.71
5.70
5.64
5.64
4.67
4.67
4.67
4.06
4.05
3.80
3.79
3.79
3.78
3.77
3.40
3.40
3.40
3.39
3.39
3.38
2.76
2.75
2.73
2.72
2.63
2.62
2.61
2.61
2.59
2.29
2.28
2.27
2.25
2.24
1.99
1.97
1.96
0.95
0.95
0.95
0.94
0.94
0.93
0.86
0.85
0.84
0.84
0.83
0.82
0.82
-0.08
-0.08

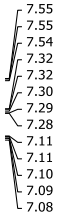

B(pin)
Me
3.194
f1 (ppm)
1.00
0.99
2.10
2.33
3.18
14.92
5.84
5.83
5.82
5.81
5.81
5.79
5.79
5.79
5.16
5.07
5.06
5.06
5.06
5.06
5.05
5.04
5.04
5.04
5.03
5.03
5.03
5.03
2.84
2.83
1.99
1.27

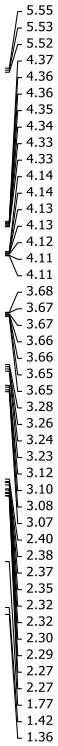

NHPh
O
Me
3.195
f1 (ppm)
2.23
3.33
1.11
1.00
1.06
2.14
2.44
2.37
3.56
7.52
7.52
7.50
7.50
7.38
7.36
7.36
7.35
7.35
7.34
7.34
7.33
7.33
7.15
7.14
7.13
7.13
7.12
7.11
5.91
5.90
5.90
5.89
5.89
5.89
5.88
5.88
5.88
5.87
5.86
5.86
5.85
5.85
5.85
5.84
5.83
5.52
5.51
5.49
5.49
5.16
5.16
5.16
5.15
5.15
5.14
5.14
5.12
5.12
5.12
3.19
3.18
2.89
2.87
1.75

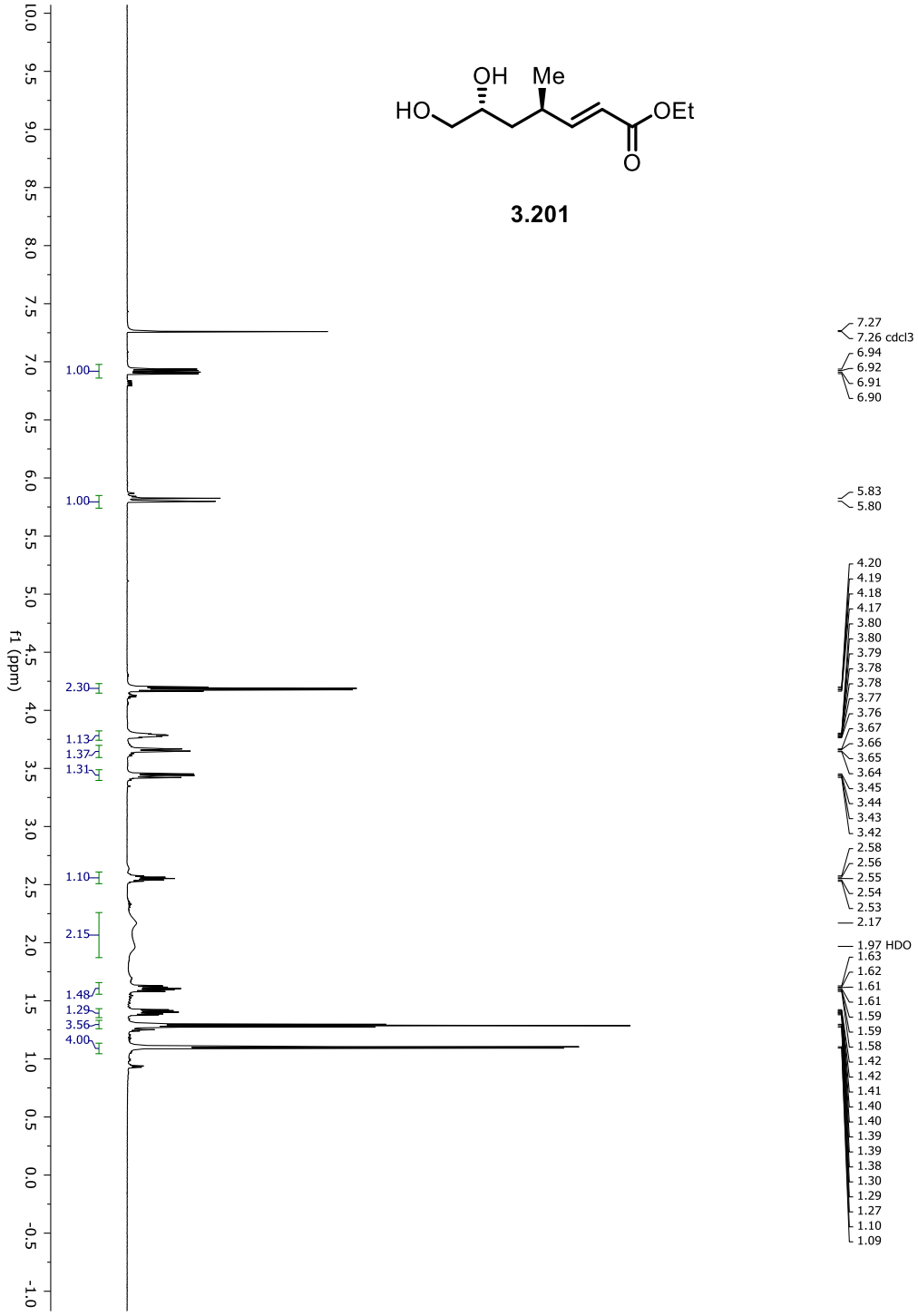

f1 (ppm)
1.89
1.93
0.93
1.00
0.97
1.05
1.04
1.08
1.09
2.44
3.23
2.88
3.23

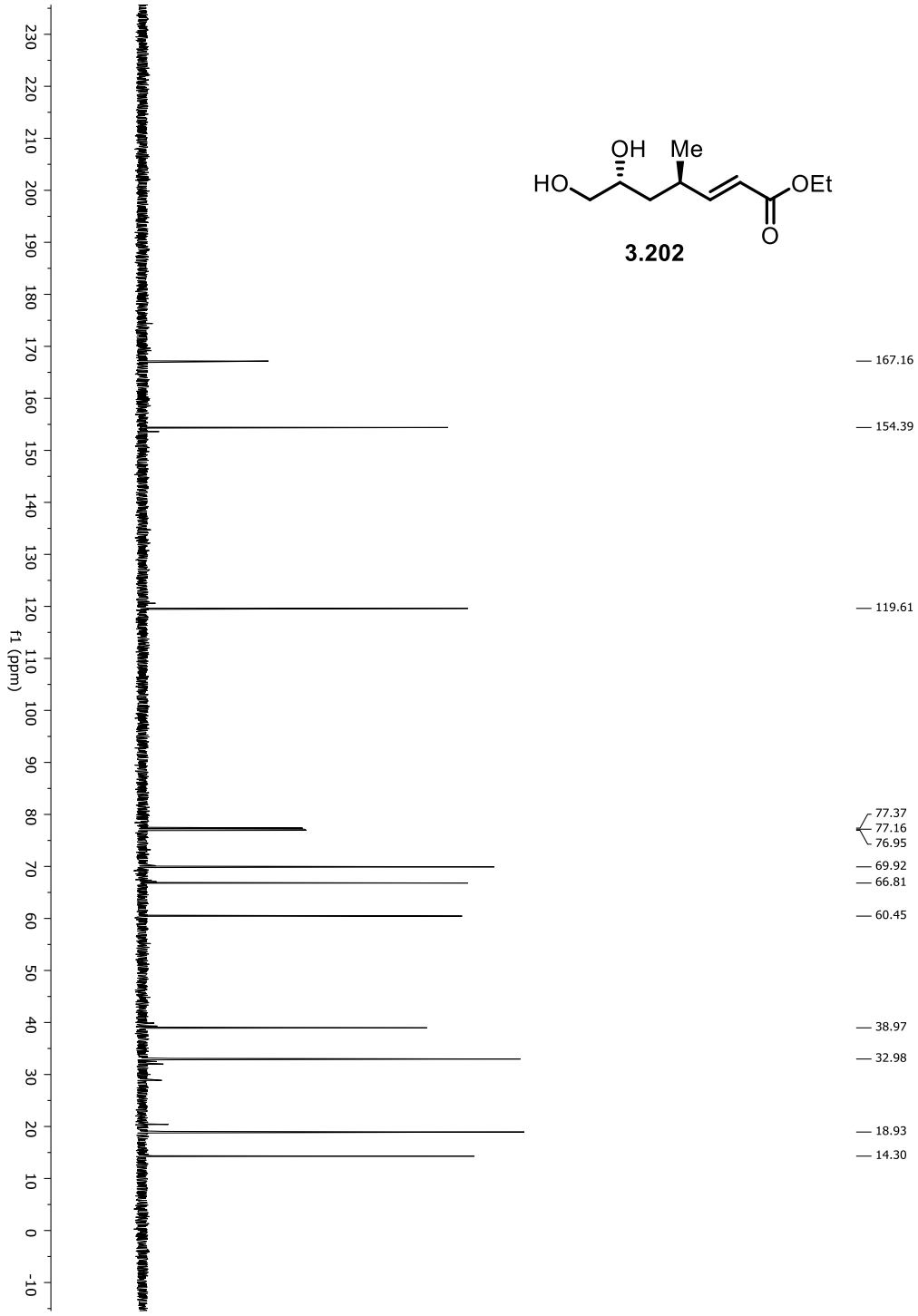

Me
Me
O
O
NHPh
O
Me

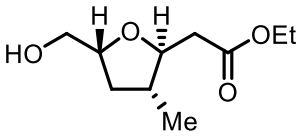
3.198


7.55
7.55
7.54
7.32
7.32
7.30
7.29
7.28
7.11
7.11
7.10
7.09
7.08


5.55
5.53
5.52
4.37
4.36
4.36
4.35
4.34
4.33
4.33
4.14
4.14
4.13
4.13
4.12
4.11
4.11
3.68
3.67
3.67
3.66
3.66
3.65
3.65
3.28
3.26
3.24
3.23
3.12
3.10
3.08
3.07
2.40
2.38
2.37
2.35
2.32
2.32
2.30
2.29
2.27
2.27
1.77
1.42
1.36

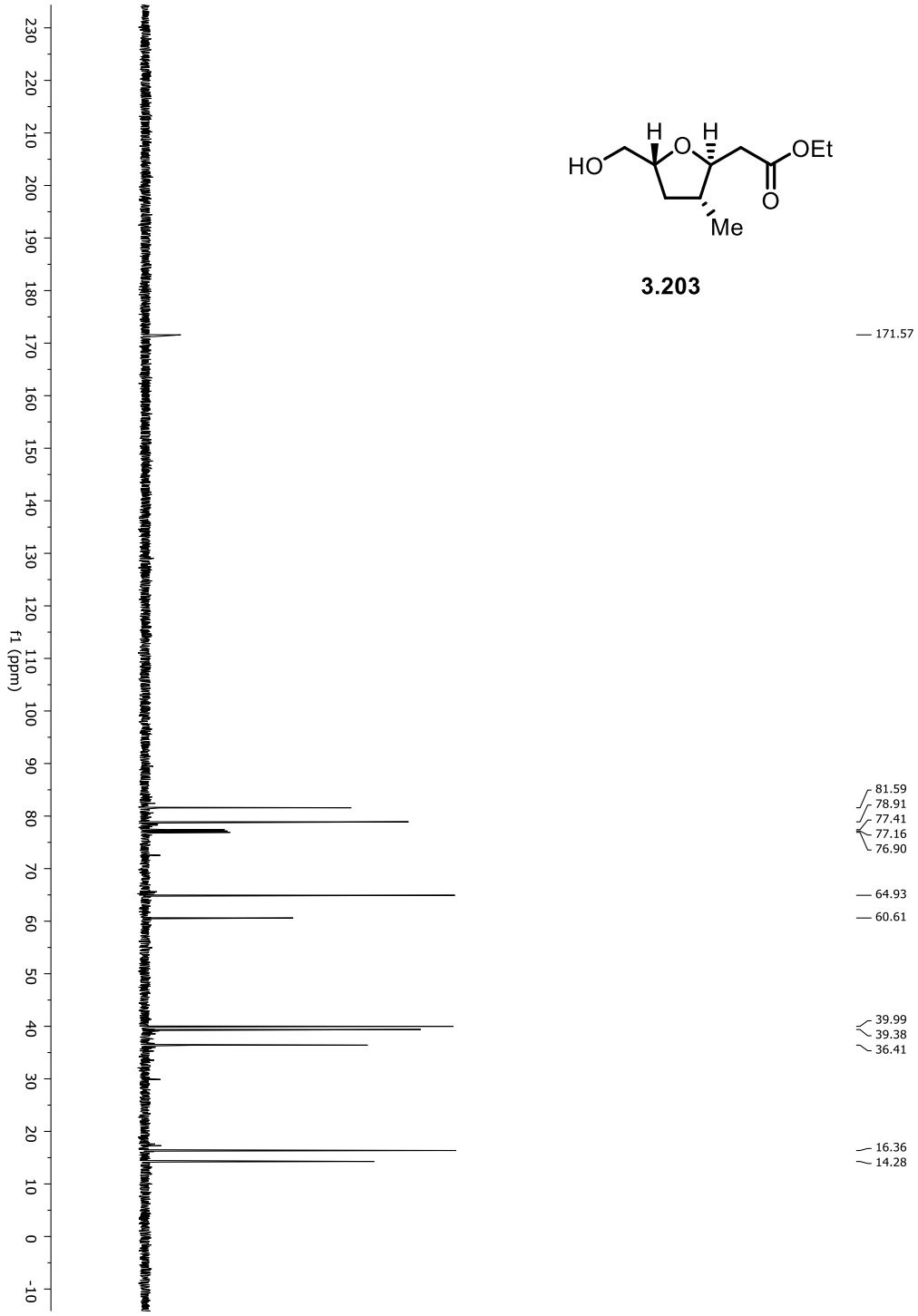

OH
Me
HO
OEt
O
3.201
f1 (ppm)
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
1.00
1.00
2.30
1.13
1.37
1.31
1.10
2.15
1.48
1.29
3.56
4.00
7.27
7.26 cdcl3
6.94
6.92
6.91
6.90
5.83
5.80
4.20
4.19
4.18
4.17
3.80
3.80
3.79
3.78
3.78
3.77
3.76
3.67
3.66
3.65
3.64
3.45
3.44
3.43
3.42
2.58
2.56
2.55
2.54
2.53
2.17
1.97 HDO
1.63
1.62
1.61
1.61
1.59
1.59
1.58
1.42
1.42
1.41
1.40
1.40
1.39
1.39
1.38
1.30
1.29
1.27
1.10
1.09


OH
Me
HO
OEt
O
3.202
167.16
154.39
119.61
77.37
77.16
76.95
69.92
66.81
60.45
38.97
32.98
18.93
14.30
f1 (ppm)


H
O
H
HO
OEt
O
Me

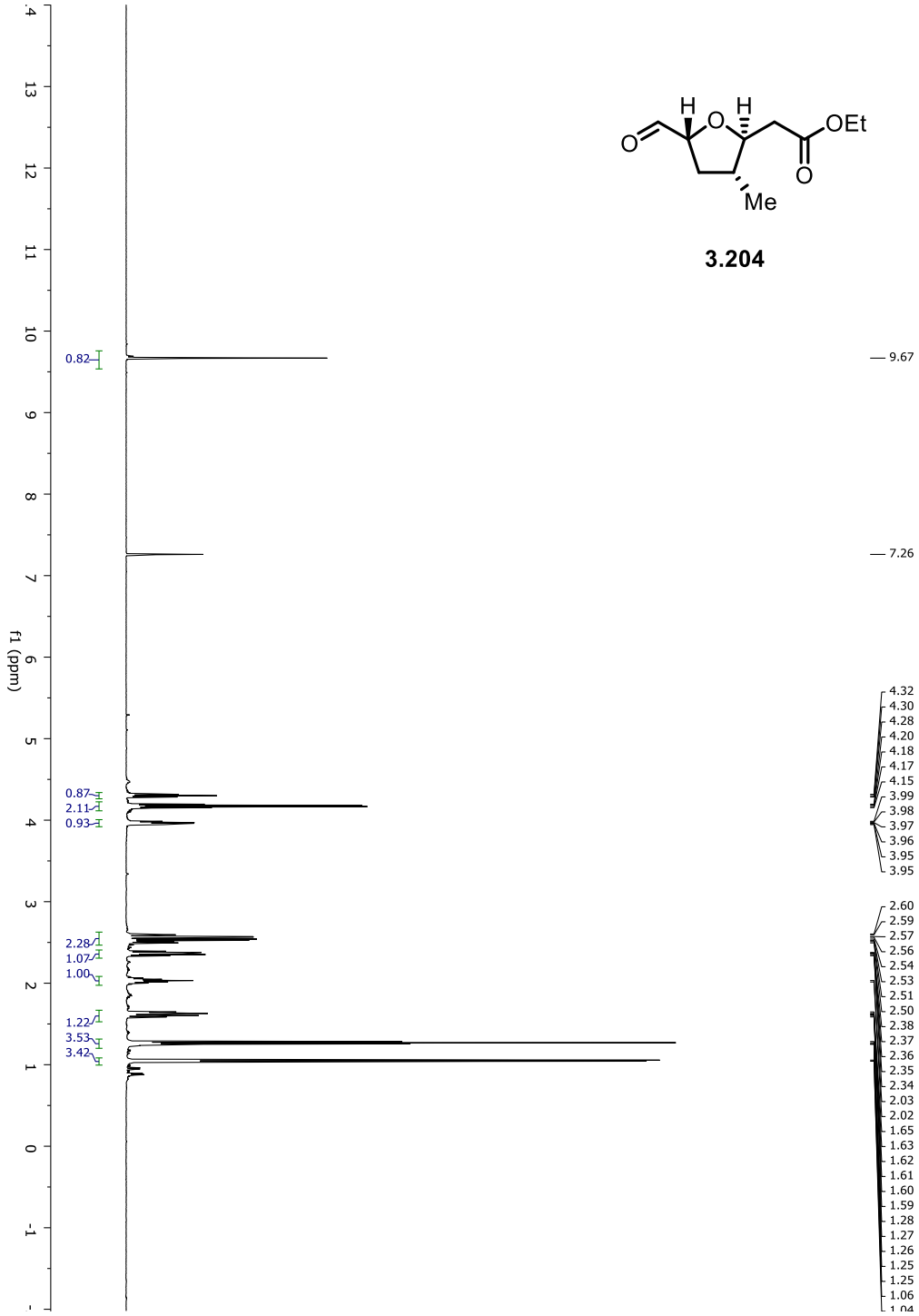
3.203

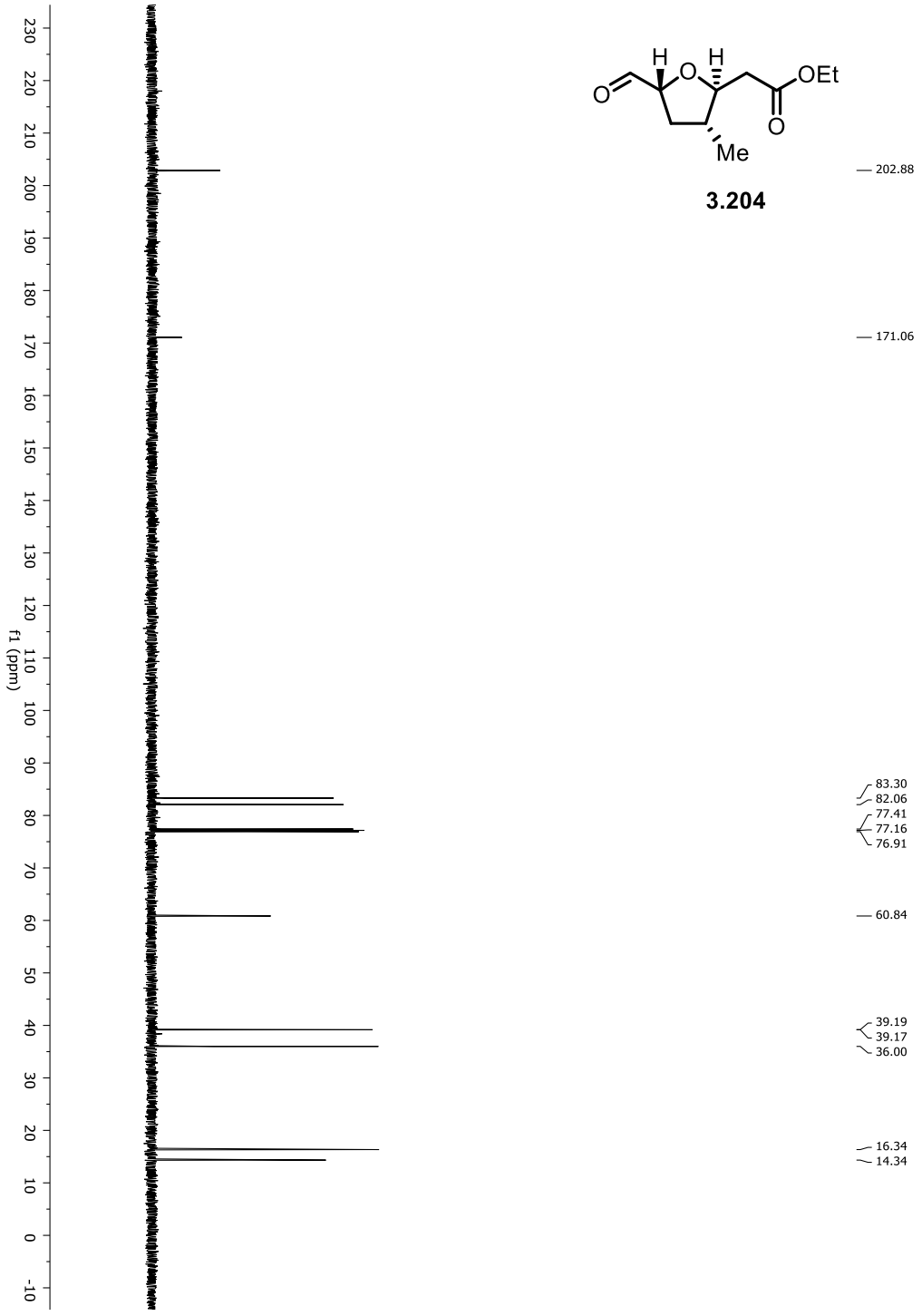
f1 (ppm)
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1
2.96
0.94
1.00
1.05
2.15
2.95
1.05
3.19
3.14
7.26 cdcl3
4.19
4.18
4.18
4.17
4.15
4.14
4.13
4.13
4.12
4.11
4.11
4.10
4.10
4.09
3.88
3.87
3.87
3.86
3.85
3.84
3.83
3.67
3.65
3.51
3.50
3.48
3.47
2.56
2.55
2.53
2.52
2.50
2.48
2.47
2.45
2.12
2.11
2.10
2.09
2.08
2.08
2.07
2.03
2.01
2.01
2.00
1.99
1.99
1.98
1.47
1.44
1.44
1.43
1.42
1.40
1.28
1.27
1.25
1.05
1.04


f1 (ppm)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
171.57
81.59
78.91
77.41
77.16
76.90
64.93
60.61
39.99
39.38
36.41
16.36
14.28

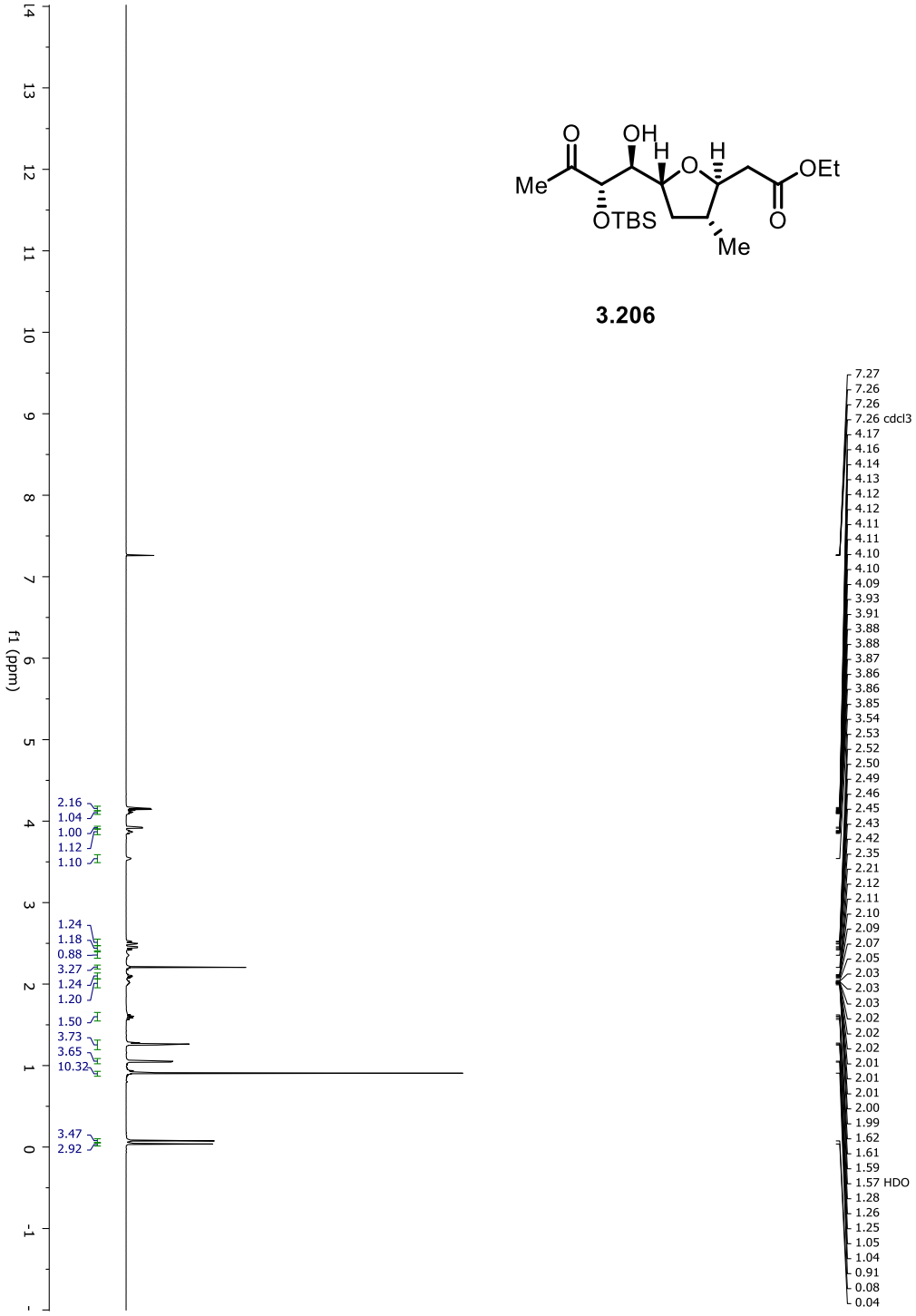
H
O
H
HO
OEt
O
Me

3.203


H
O
H
O
OEt
O
Me
3.204
f1 (ppm)
0.82
0.87
2.11
0.93
2.28
1.07
1.00
1.22
3.53
3.42
9.67
7.26
4.32
4.30
4.28
4.20
4.18
4.17
4.15
3.99
3.98
3.97
3.96
3.95
3.95
2.60
2.59
2.57
2.56
2.54
2.53
2.51
2.50
2.38
2.37
2.36
2.35
2.34
2.03
2.02
1.65
1.63
1.62
1.61
1.60
1.59
1.28
1.27
1.26
1.25
1.25
1.06

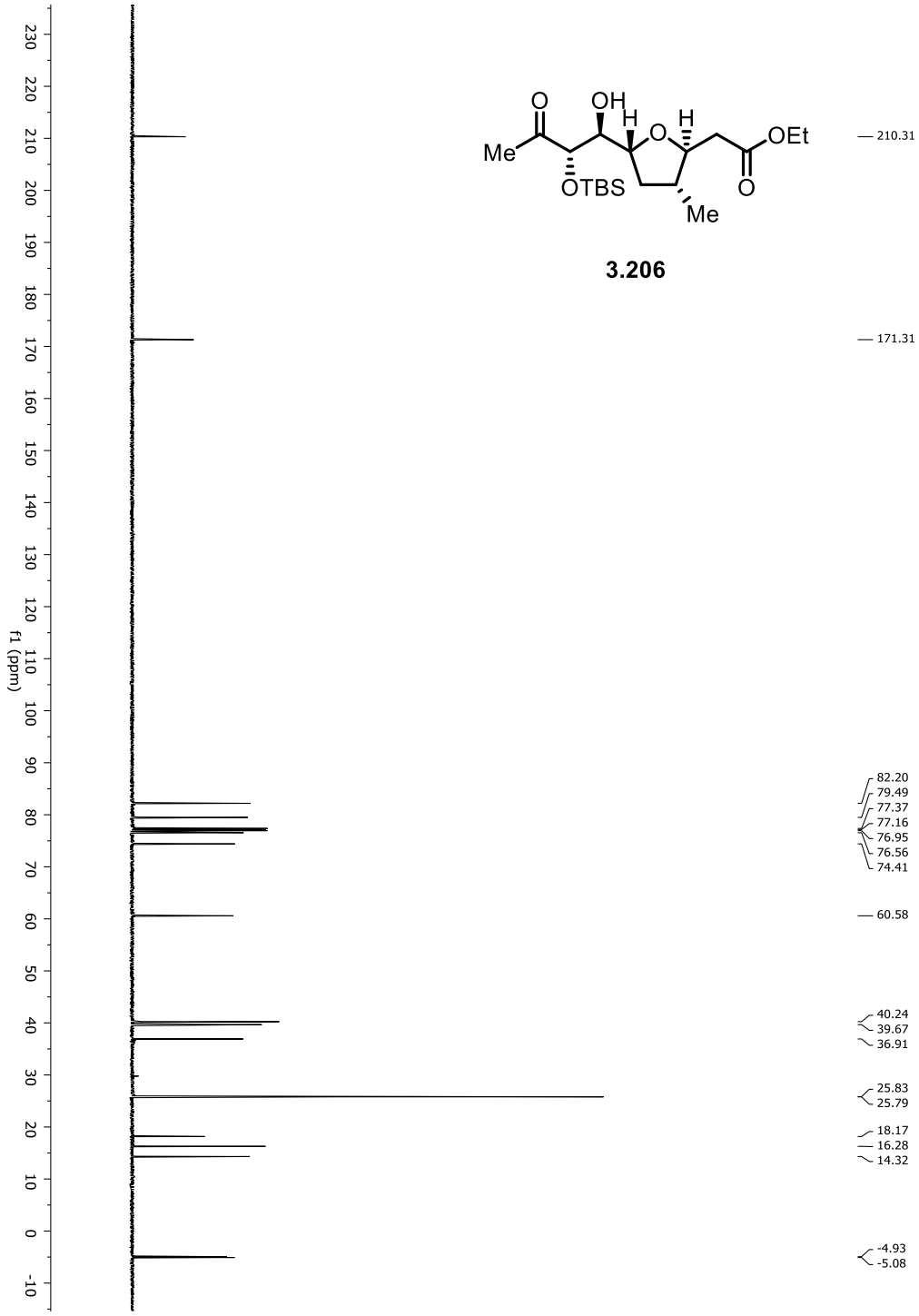

f1 (ppm)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
H
O
H
O
OEt
O
Me
202.88
171.06
83.30
82.06
77.41
77.16
76.91
60.84
39.19
39.17
36.00
16.34
14.34

3.204

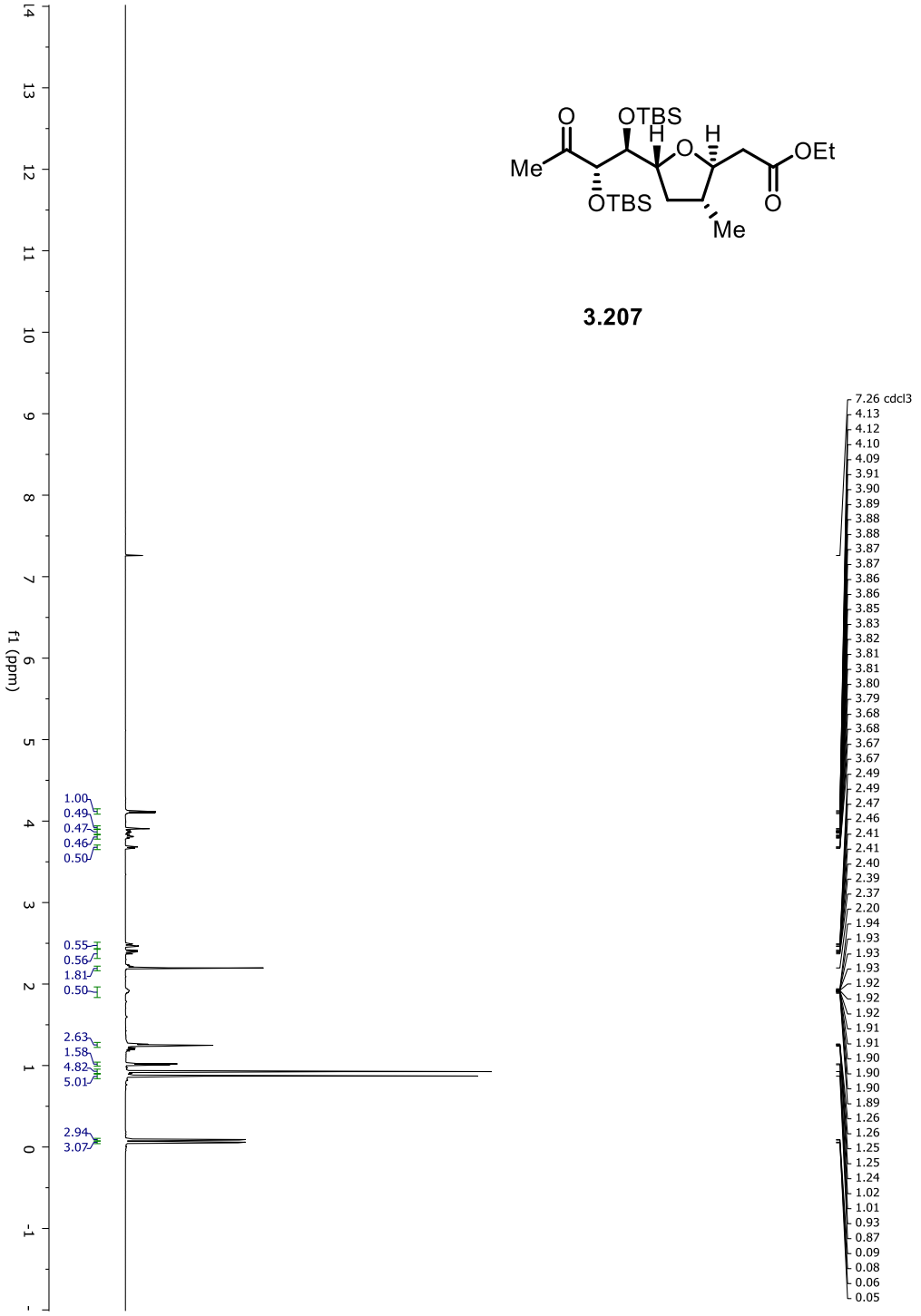

f1 (ppm)
2.16
1.04
1.00
1.12
1.10
1.24
1.18
0.88
3.27
1.24
1.20
1.50
3.73
3.65
10.32
3.47
2.92
7.27
7.26
7.26
7.26 cdcl3
4.17
4.16
4.14
4.13
4.12
4.12
4.11
4.11
4.10
4.10
4.09
3.93
3.91
3.88
3.88
3.87
3.86
3.86
3.85
3.54
2.53
2.52
2.50
2.49
2.46
2.45
2.43
2.42
2.35
2.21
2.12
2.11
2.10
2.09
2.07
2.05
2.03
2.03
2.03
2.02
2.02
2.02
2.01
2.01
2.01
2.00
1.99
1.62
1.61
1.59
1.57 HDO
1.28
1.26
1.25
1.05
1.04
0.91
0.08
0.04

O
OH
H
H
O
OEt
Me
OTBS
O
Me

3.206

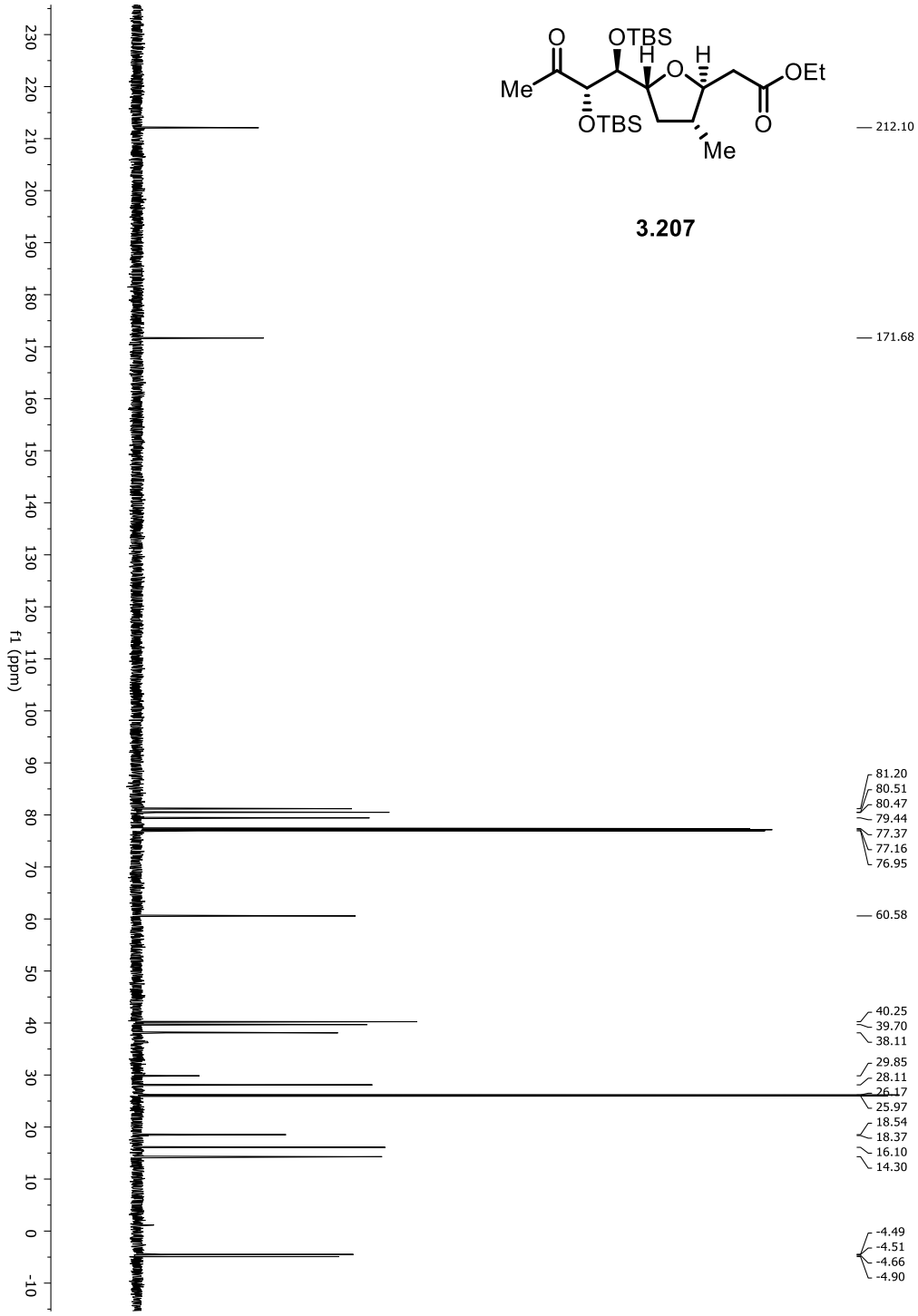

f1 (ppm)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
O
OH
H
O
H
OEt
Me
OTBS
O
Me
210.31
171.31
82.20
79.49
77.37
77.16
76.95
76.56
74.41
60.58
40.24
39.67
36.91
25.83
25.79
18.17
16.28
14.32
-4.93
-5.08

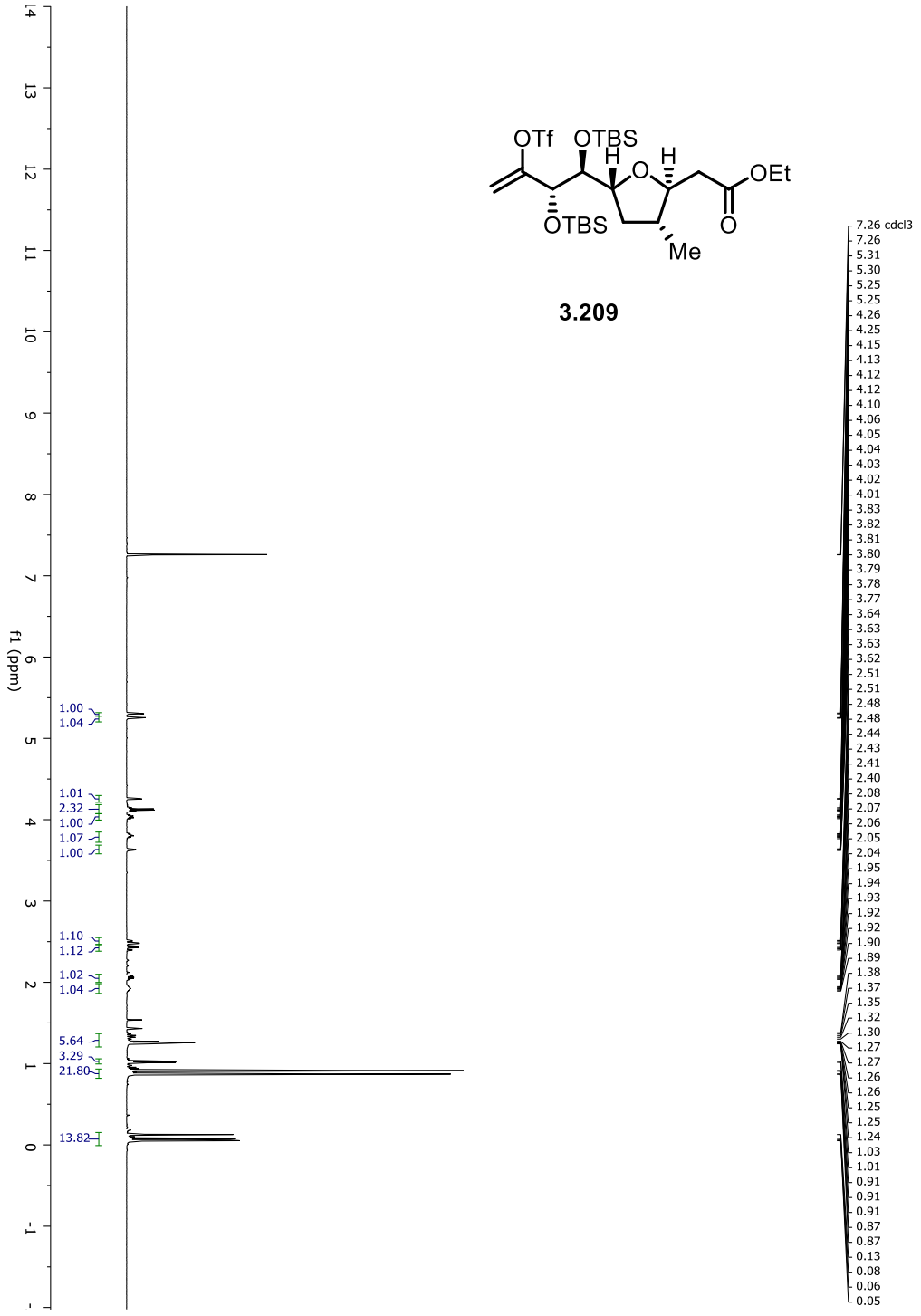
3.206

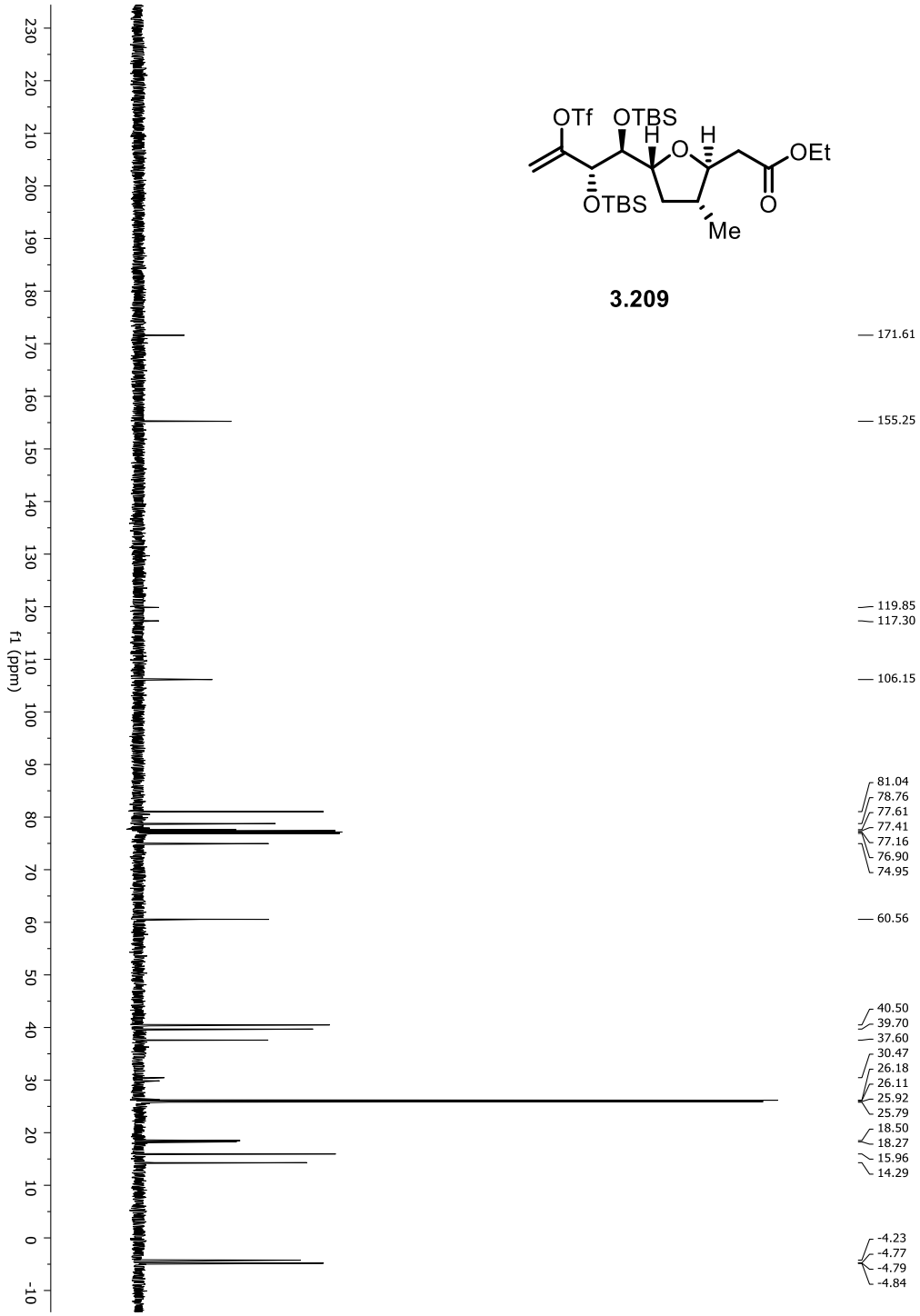

f1 (ppm)
1.00
0.49
0.47
0.46
0.50
0.55
0.56
1.81
0.50
2.63
1.58
4.82
5.01
2.94
3.07
7.26 cdcl3
4.13
4.12
4.10
4.09
3.91
3.90
3.89
3.88
3.88
3.87
3.87
3.86
3.86
3.85
3.83
3.82
3.81
3.81
3.80
3.79
3.68
3.68
3.67
3.67
2.49
2.49
2.47
2.46
2.41
2.41
2.40
2.39
2.37
2.20
1.94
1.93
1.93
1.93
1.92
1.92
1.92
1.91
1.91
1.90
1.90
1.90
1.89
1.26
1.26
1.25
1.25
1.24
1.02
1.01
0.93
0.87
0.09
0.08
0.06
0.05

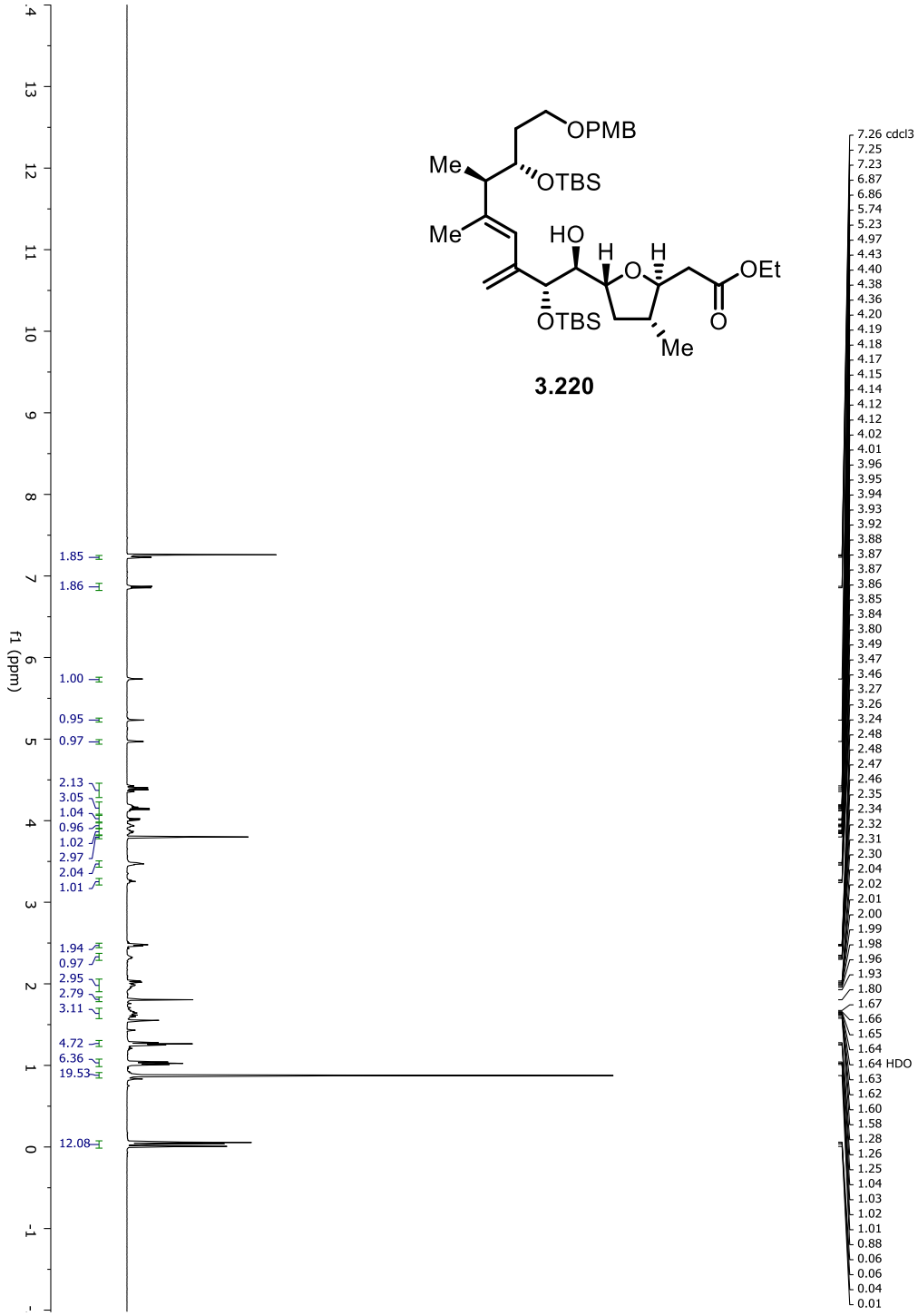
O
OTBS
H
H
O
OEt
Me
OTBS
O
Me

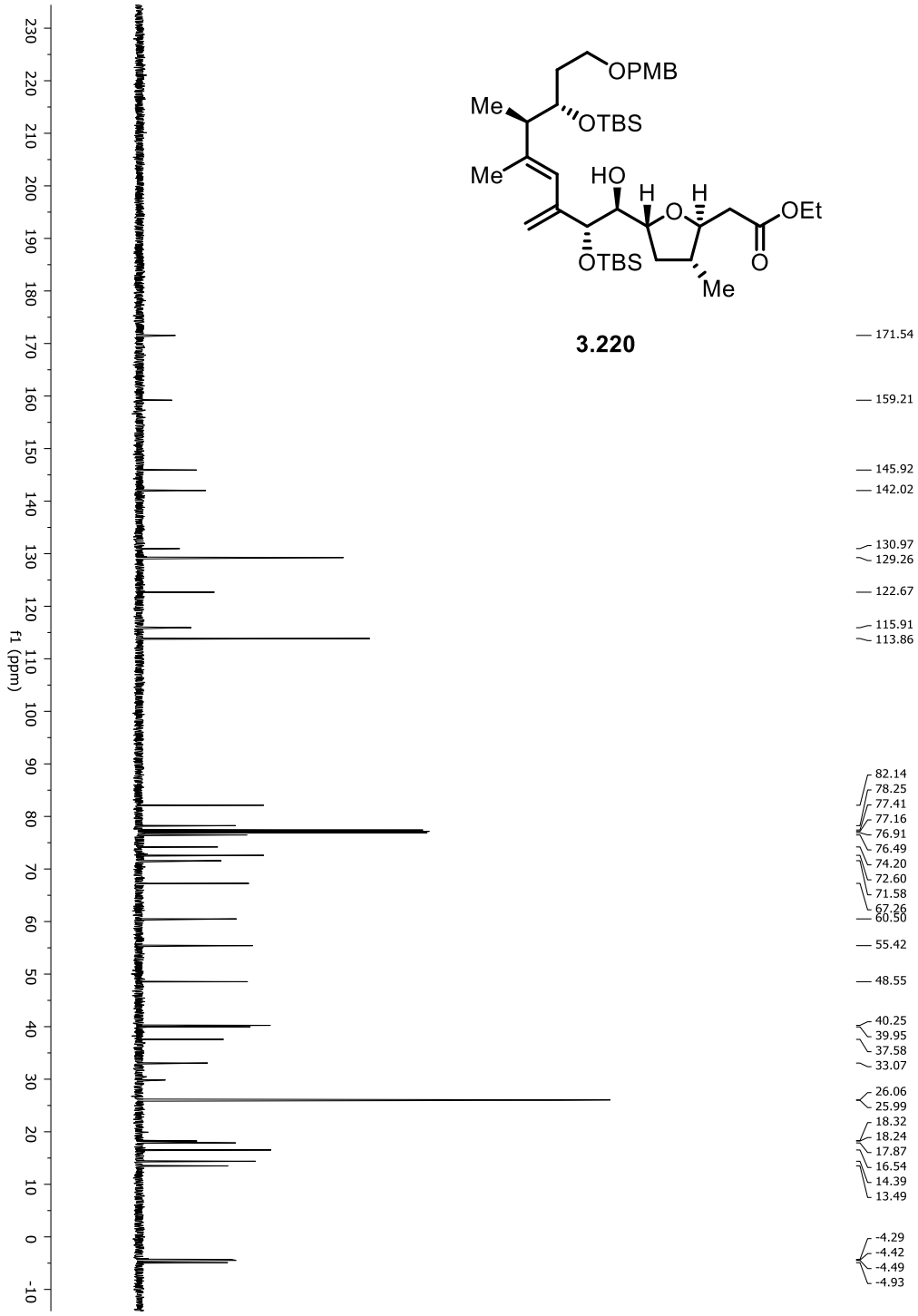
3.207


O
OTBS
H
H
O
OEt
Me
OTBS
O
Me
3.207
212.10
171.68
81.20
80.51
80.47
79.44
77.37
77.16
76.95
60.58
40.25
39.70
38.11
29.85
28.11
26.17
25.97
18.54
18.37
16.10
14.30
-4.49
-4.51
-4.66
-4.90
f1 (ppm)


OTf
OTBS
H
O
H
OEt
OTBS
O
Me
3.209
f1 (ppm)
1.00
1.04
1.01
2.32
1.00
1.07
1.00
1.10
1.12
1.02
1.04
5.64
3.29
21.80
13.82
7.26 cdcl3
7.26
5.31
5.30
5.25
5.25
4.26
4.25
4.15
4.13
4.12
4.12
4.10
4.06
4.05
4.04
4.03
4.02
4.01
3.83
3.82
3.81
3.80
3.79
3.78
3.77
3.64
3.63
3.63
3.62
2.51
2.51
2.48
2.48
2.44
2.43
2.41
2.40
2.08
2.07
2.06
2.05
2.04
1.95
1.94
1.93
1.92
1.92
1.90
1.89
1.38
1.37
1.35
1.32
1.30
1.27
1.27
1.26
1.26
1.25
1.25
1.24
1.03
1.01
0.91
0.91
0.91
0.87
0.87
0.13
0.08
0.06
0.05


OTf
OTBS
H
O
H
OEt
OTBS
O
Me
3.209
171.61
155.25
119.85
117.30
106.15
81.04
78.76
77.61
77.41
77.16
76.90
74.95
60.56
40.50
39.70
37.60
30.47
26.18
26.11
25.92
25.79
18.50
18.27
15.96
14.29
-4.23
-4.77
-4.79
-4.84
f1 (ppm)


OPMB
Me
OTBS
Me
HO
H
H
O
OEt
OTBS
O
Me
3.220
f1 (ppm)
1.85
1.86
1.00
0.95
0.97
2.13
3.05
1.04
0.96
1.02
2.97
2.04
1.01
1.94
0.97
2.95
2.79
3.11
4.72
6.36
19.53
12.08
7.26 cdcl3
HDO


OPMB
Me
OTBS
Me
HO
H
O
H
OEt
OTBS
O
Me
3.220
f1 (ppm)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
171.54
159.21
145.92
142.02
130.97
129.26
122.67
115.91
113.86
82.14
78.25
77.41
77.16
76.91
76.49
74.20
72.60
71.58
67.26
60.50
55.42
48.55
40.25
39.95
37.58
33.07
26.06
25.99
18.32
18.24
17.87
16.54
14.39
13.49
-4.29
-4.42
-4.49
-4.93