ADVANCES IN PALLADIUM-CATALYZED CONJUNCTIVE CROSS-COUPLING

CHRISTOPHER ALEXANDER WILHELMSEN

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Christopher Alexander Wilhelmsen

Advisor: Professor James P. Morken

Abstract: The development of boron and palladium ligands for conjunctive cross-coupling provides access to new reactivity. Some of these advances are outlined in this dissertation. Chapter one describes an enantioselective and diastereoselective palladium catalyzed conjunctive cross-coupling of β-substituted alkenyl boron "ate" complexes to afford contiguous benzylic stereocenters. "Mac" diol was discovered as a useful boron ligand in conjunctive cross-coupling by reducing unwanted Suzuki-Miyaura cross-coupling. Chapter two describes the utilization of "mac" diol in the enantioselective conjunctive cross-coupling of α-substituted alkenyl boron "ate" complexes with carbamoyl chlorides. This transformation affords tertiary, β-boryl amides, which provide a complementary approach to Mannich, aldol, and conjugate borylation products. Water was an essential additive to enable high yield and high enantioselectivity, and its reaction role was investigated. The synthetic utility of this cross-coupling was demonstrated with the asymmetric synthesis of (+)-adalinine. Chapter three describes the thought process behind discovering a new palladium ligand for conjunctive cross-coupling. Phosphinooxazolines (PHOX) are useful and inexpensive ligands for enantioselective palladium-catalyzed conjunctive cross-coupling. A stereochemical model of this cross-coupling with this ligand was examined.

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List of Abbreviations

9-BBN: 9-Borabicyclo(3.3.1)nonane

Å: angstrom

Ac: acetyl

ACN: acetonitrile

AQ: 8-aminioquinoline

Ar: aryl

Ar_F: 3,5-bis(trifluoromethyl)phenyl

atm: atmosphere(s)

Aux: auxiliary

BHT: 2,6-di-*t*-butyl-4-methylphenol

Bn: benzyl

Boc: *tert*-butyloxycarbonyl

BOX: bis(oxazoline)

BQ: benzoquinone

COD: cyclooctadiene

conv: conversion

Cy: cyclohexyl

DART: direct analysis in real time

dba: dibenzylideneacetone

DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene

DCM: methylene chloride

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

DFT: density functional theory

DIBAL: diisobutylaluminium hydride

DIPEA: N,N-Diisopropylethylamine (Hünig's base)

D*i*-PrPF: 1,1'-Bis(diisopropylphosphino)ferrocene

DMAP: 4-dimethylaminopyridine

DME: 1,2-dimethoxyethane

DMF: dimethylformamide

DMP: Dess-Martin periodinane

DMS: dimethylsulfide

DMSO: dimethylsulfoxide

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

DPPM: Bis(diphenylphosphino)methane

DPPP: Bis(diphenylphosphino)propane

dr: diastereomeric ratio

DTBM: (3,5-di-*tert*-butyl-4-methoxyphenyl)

ee: enantiomer excess

ent: enantiomer

equiv.: equivalents

er: enantiomeric ratio

es: enantiospecificity

Et: ethyl

EWG: electron withdrawing group

h: hour(s)

HFIP: hexafluoroisopropanol

HMDS: bis(trimethylsilyl)amide

HMPA: hexamethylphosphoramide

HPLC: high pressure liquid chromatography

HRMS: high-resolution mass spectrometry

IPA: isopropyl alcohol

i-Pr: isopropyl

IR: infrared spectroscopy

LAH: Lithium aluminium hydride

Tf: triflyl

M: molar

mac: methylated acenapthoquinone

*m*CPBA: *m*-chloroperoxybenzoic acid

min: minute(s)

mmol: millimole

mol: mole

Ms: mesityl

MS: molecular sieves

NA: not available

nbd: norbornadiene

n-butyl: butyl

NCS: N-chlorosuccinimide

ND: not determined

neo: *neo*-pentyl glycol

NHC: N-hetereocyclic carbene

NMO: N-methylmorpholine N-oxide

NMR: nuclear magnetic resonance

n-propyl: propyl

Nuc: nucleophile

PCC: pyridinium chlorochromate

PDC: pyridinium dichromate

Ph: phenyl

PHIM: phosphinoimidazoline

PHOX: phosphinooxazoline

pin: pinacol

PMB: *p*-methoxybenzyl

PPTs/*p*TSA: pyridinium *p*-toluenesulfonic acid

psi: pounds per square inch

RBF: round-bottom flask

Rf: Retention factor

rt: room temperature

Sacc: saccharin

SFC: supercritical fluid chromatography

TBA: tetrabutylammonium

TBDMS: *tert*-butyldimethyl silyl

t-butyl: *tert*-butyl

Temp: temperature

TEMPO: 2,2,6,6-tetramethyl-1-

piperidinyloxy free radical

TFA: trifluoroacetate (acetic acid)

TFAA: trifluoroacetic anhydride

TFE: 2,2,2-trifluoroethanol

THF: tetrahydrofuran

TIPS: triisopropylsilyl

TLC: thin-layer chromatography

TMEDA: tetramethylethylenediamine

TMP: 2,2,6,6-tetramethylpiperidine

TMS: trimethylsilyl

tol: tolyl

TPAP: tetrapropylammonium perruthenate

Ts: tosyl

UV: ultraviolet

Table of Contents

Chapter 1

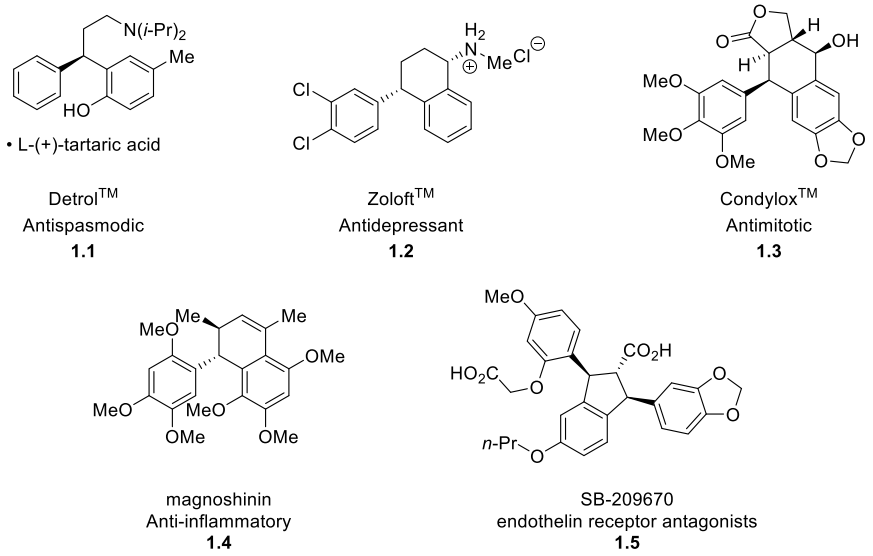
Diastereoselective and Enantioselective Palladium-Catalyzed Conjunctive Cross-Coupling Enabled by Boron Ligand Design

1.1 Background

1.1.1 Synthesis of Chiral Benzhydryl Compounds

Chiral 1,1-diaryl benzhydryl compounds are of immense importance to the synthetic and pharmaceutical community.[1] These compounds are known to be useful as analgesics, antiarrhythmics, anticancer, antidepressants, antifungals, and antihistamines as seen in Figure 1.1.1.1.

Figure 1.1.1.1*: Pharmaceutical Drugs with a Benzhydryl Motif*



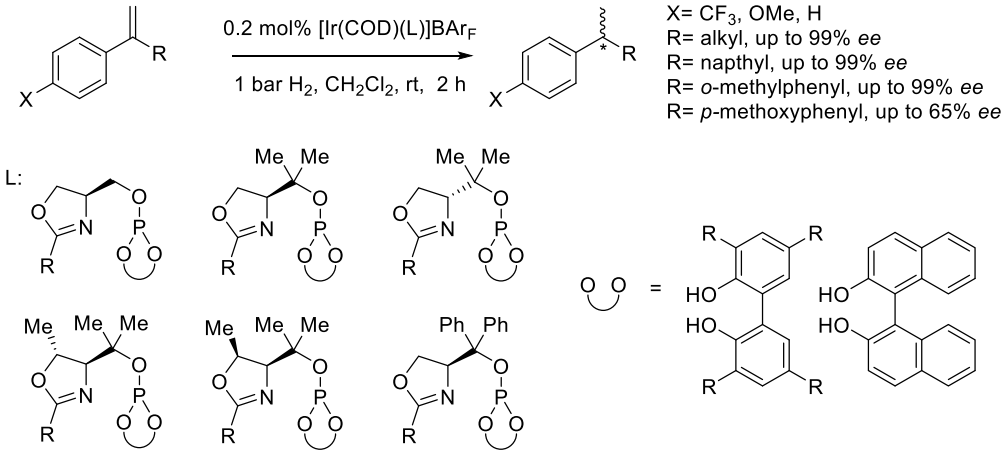
Perhaps due to their beneficial pharmacological properties, there are numerous methods to address their synthesis.[2] Among the most common asymmetric methods is metal-catalyzed enantioselective hydrogenation. However, this approach often requires a directing group on the

[1] Ameen, D.; Snape, T. J. *Med. Chem. Commun.* **2013**, *4*, 893-907
[2] Mondal, S.; Roy, D.; Panda, G. *ChemCatChem* **2018**, *10*, 1941-1967

1,1-diaryl alkene substrate to differentiate between the prochiral faces. Diéguez, Andersson, and coworkers were the first to achieve high enantioselectivities without the need of a directing group.[3]

In 2009, Diéguez used iridium phosphite-oxazoline catalysts for the enantioselective hydrogenation of 1,1-disubstituted olefins.[4] Screening a ligand library revealed catalysts that furnish high conversion and asymmetric induction in the construction of benzyl stereocenters. It should be noted that selective reactions were only observed with sterically biased substrates. Enantioselective synthesis of benzhydryl stereocenters without a steric bias was still challenging (Scheme 1.1.1.1).

Scheme 1.1.1.1: *Diéguez and Andersson Phosphite-Oxazoline Iridium-Catalyzed Enantioselective Hydrogenation of 1,1 Diaryl Alkenes*

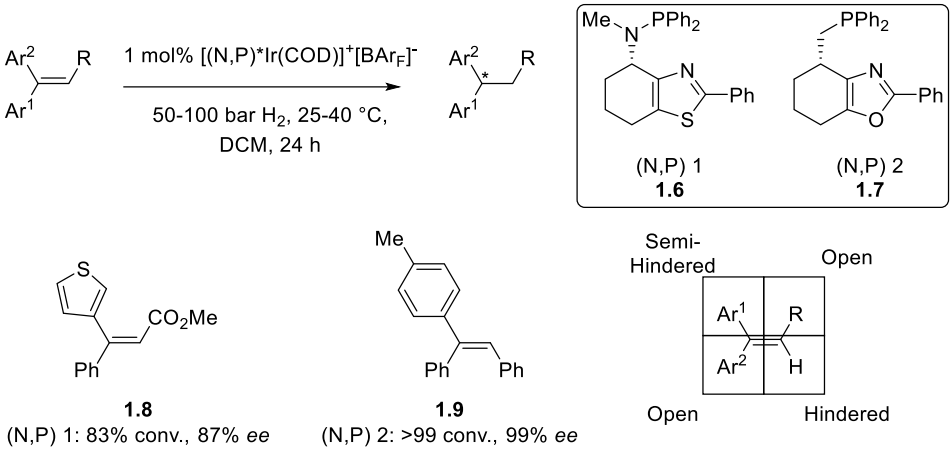


That same year, Andersson used various chiral P,N-ligated iridium catalysts to enantioselectively hydrogenate trisubstituted olefins (Table 1.1.1.1).[5] The authors claim that the C_1-symmetry of the ligand scaffold afforded excellent enantioselectivity. A large steric influence occupies the quadrant with hydrogen of the olefin and only a partially occupancy in the opposite

[3] Mazuela, J.; Norrby, P.; Andersson, P. G.; Pàmies, O.; Diéguez, M. *J. Am. Chem. Soc.* **2011**, *133*, 13634-13645
[4] Mazuela, J.; Verendel, J. J.; Coll, M.; Schäffner, B.; Börner. A.; Andersson, P. G.; Pàmies, O.; Diéguez, M. *J. Am. Chem. Soc.* **2009**, *131*, 12344-12353
[5] Tolstoy, P.; Engman, M.; Paptchikhine, A.; Bergquist, J.; Church, T. L.; Leung, A. W. M.; Andersson, P. G. *J. Am. Chem. Soc.* **2009**, *131*, 8855-8860

quadrant with Ar^1. Essentially, instead of discerning the steric difference between similar Ar^1 and Ar^2 groups, the ligand is designed to distinguish the size difference between the R group and hydrogen.

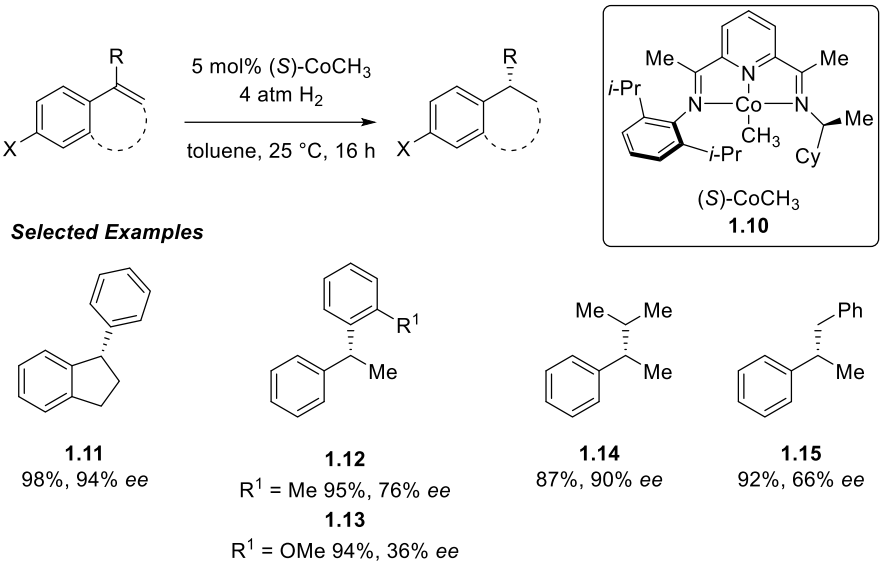
Table 1.1.1.1: *Andersson's Enantioselective Hydrogenation of Trisubstituted Alkenes*



In 2016, Chirik and coworkers developed a cobalt-catalyzed enantioselective hydrogenation of 1,1-disubstituted alkenes.[6] Once again, high enantioselectivity was achieved in the synthesis of benzylic stereocenters, but selective formation of benzhydryl stereocenters was only selective with cyclic, trisubstituted alkenes substrates (Table 1.1.1.2).

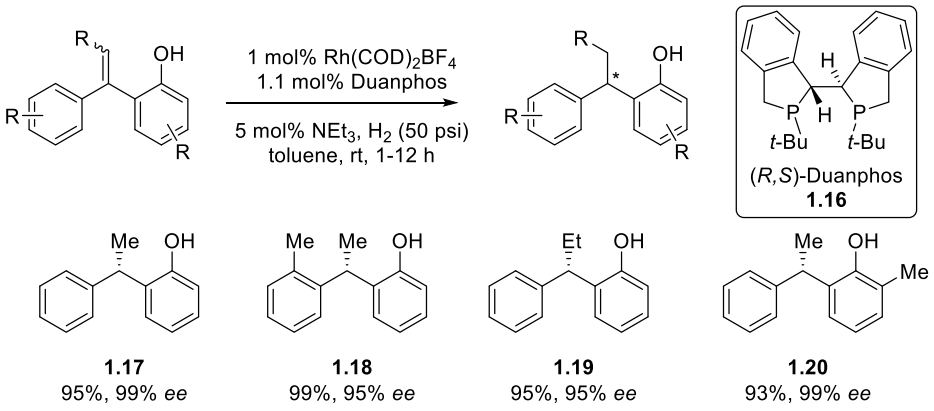
[6] Friedfeld, M. R.; Shevlin, M.; Margulieux, G. W.; Campeau, L. C.; Chirik, P. J. *J. Am. Chem. Soc.* **2016**, *138*, 3314-3324

Table 1.1.1.2: *Chirik's Cobalt-Catalyzed Enantioselective Hydrogenation*



In 2011, Wang and coworkers developed a highly enantioselective hydrogenation of 1,1 diaryl alkenes to afford enantioenriched benzhydryl stereocenters.[7] This reaction was enabled by Duanphos-ligated rhodium complexes, and the high levels of discrimination between the prochiral faces was attributed to the directing effect of the *ortho*-hydroxyl aryl group of the substrate (Table 1.1.1.3).

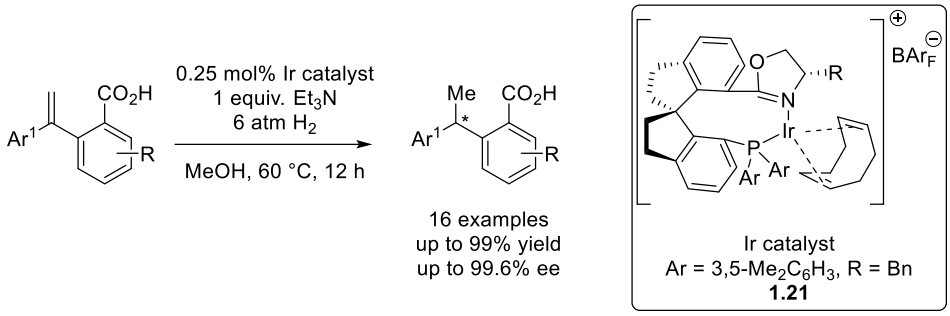
Table 1.1.1.3: *Wang's Hydroxyl Directed Enantioselective Rhodium-Catalyzed Hydrogenation*



[7] Wang, X.; Guram, A.; Caille, S.; Hu, J.; Preston, J. P.; Ronk, M.; Walker, S. *Org. Lett*. **2011**, *13*, 1881-1883

In 2013, Zhou and coworkers developed a carboxyl-directed asymmetric hydrogenation of 1,1 diarylethenes utilizing a P,N-ligated iridium catalyst.[8] A broad range of products were obtained in excellent yield and enantioselectivity (Scheme 1.1.1.2). The carboxylic acid directing group of the product can be easily removed via decarboxylation, or it can be transformed into other functional groups.

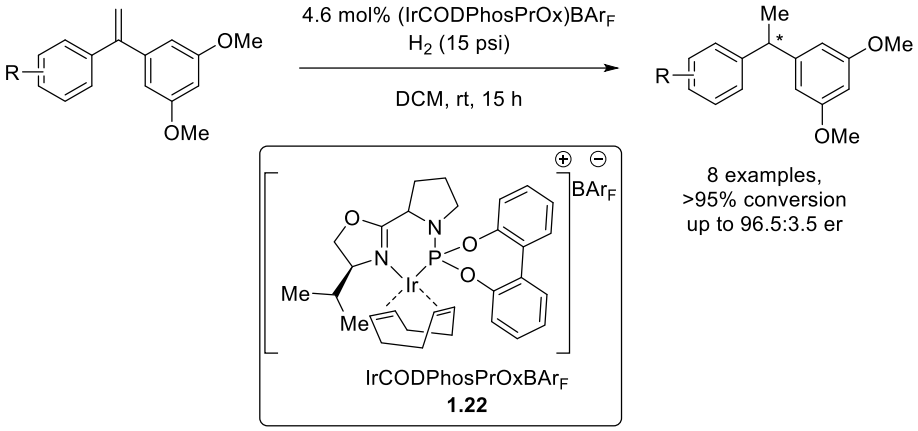
Scheme 1.1.1.2: *Zhou's Carboxy Directed Asymmetric Hydrogenation*



In 2013, Sigman and coworkers utilized a *meta*-directing group effect to facilitate an enantioselective hydrogenation of 1,1 diarylalkenes with an oxazoline-phosphoramidite-ligated iridium complex (Scheme 1.1.1.3).[9] Interestingly, the 3,5-dimethoxy substitution pattern was necessary for high yield and enantioselectivity. The authors noted a dramatic decrease in the enantioselectivity when manipulating the "directing" aryl group to 3-methoxy or other alkyl or ethereal substituents.

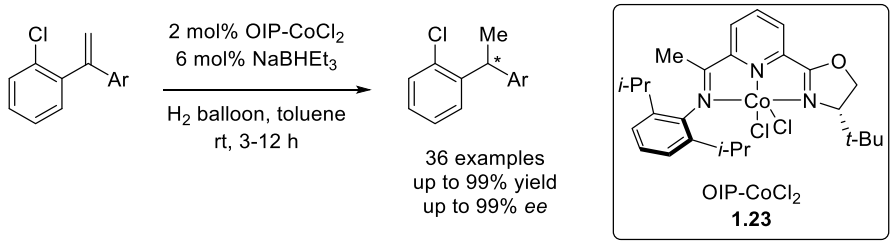
[8] Song, S.; Zhu, S.; Yu, Y.; Zhou, Q. *Angew. Chem. Int. Ed.* **2013**, *52*, 1556-1599
[9] Bess, E. N.; Sigman, M. S. *Org. Lett.* **2013**, *15*, 646-649

Scheme 1.1.1.3: *Sigman's Meta-Methoxy Directed Asymmetric Hydrogenation*



In 2016, Lu and coworkers developed a cobalt-catalyzed asymmetric hydrogenation of 1,1 diarylethenes. An *ortho*-chloro directing group is critical for the high facial selectivity.[10] A broad substrate scope was examined and the process generally occurred with excellent yield and enantioselectivity (Scheme 1.1.1.4). Notably, a transition metal-catalyzed proto-dechlorination can render the directing group traceless.

Scheme 1.1.1.4: *Lu's Ortho-Chloro Directed Cobalt-Catalyzed Asymmetric Hydrogenation*

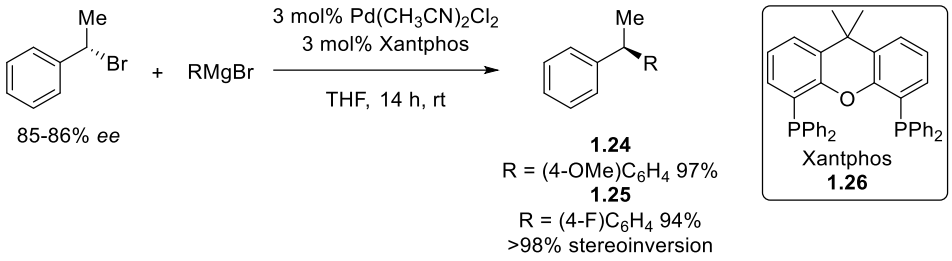


Despite the expansive literature reports associated with asymmetric hydrogenation of alkenes, reduction of 1,1-diaryl alkenes remains challenging and a general ligand class remains elusive.[11] An alternative disconnection for the synthesis of benzhydryl stereocenters was found in benzylic cross-coupling reactions. This method reduces the dependence on directing-group strategies and

[10] Chen, J.; Chen, C.; Ji, C.; Lu, Z. *Org. Lett.* **2016**, *18*, 1594-1597
[11] (a) Margarita, C.; Andersson, P. G. *J. Am. Soc. Chem.* **2017**, *139*, 1346-1356 (b) Kraft, S.; Ryan, K.; Kargbo, R. B. *J. Am. Soc. Chem.* **2017**, *139*, 11630-11641

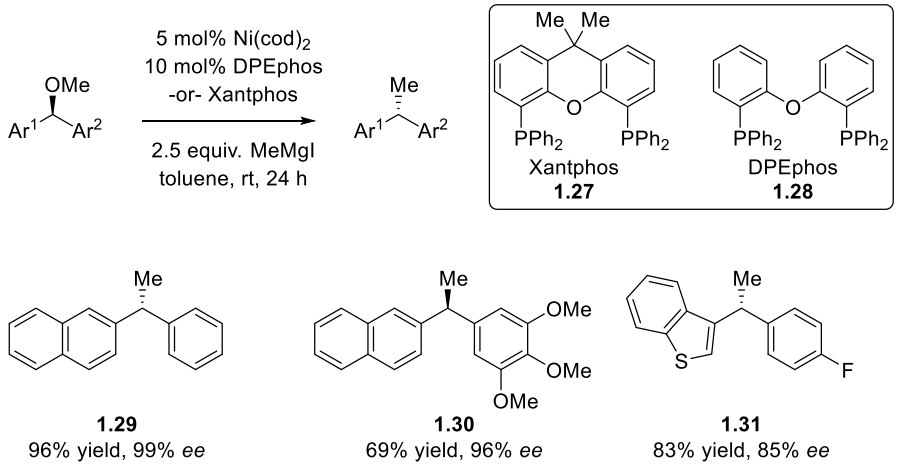
enables a broader substrate scope in some cases. In 2009, Juan Carretero and coworkers developed a stereospecific palladium-catalyzed Kumada cross-coupling of secondary benzylic bromides (Scheme 1.1.1.5).[12] Though there are only two examples, greater than 98% stereoinversion is observed when using an enantiometrically-enriched secondary benzylic bromide. Unfortunately, it was difficult to synthesize the prerequisite benzylic bromide in high enantioselectivity.

Scheme 1.1.1.5: *Carretero's Stereospecific Palladium-Catalyzed Kumada Cross-Coupling of Benzyl Bromides*



In 2011, Jarvo and coworkers addressed the problem associated with a benzylic bromide substrate by developing a stereospecific nickel-catalyzed Kumada cross-coupling of benzhydryl ethers to yield enantio-enriched diarylethanes (Table 1.1.1.4).[13] This method relies on the enantioselective synthesis of diaryl secondary alcohols.

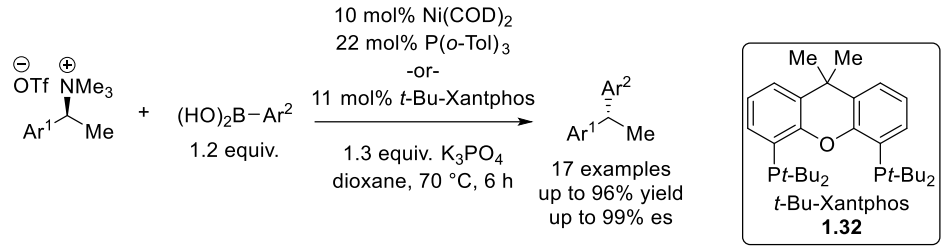
Table 1.1.1.4: *Jarvo's Stereospecific Nickel-Catalyzed Kumada Cross-Coupling of Benzhydryl Ethers*



[12] López-Pérez, A.; Adrio, J.; Carretero, J. C. *Org. Lett.* **2009**, *11*, 5514-5517
[13] Taylor, B. L. H.; Swift, E. C.; Waetzig, J. D.; Jarvo, E. R. *J. Am. Chem. Soc.* **2011**, *133*, 389-391

In a process related to Jarvo's, Watson and coworkers coupled benzylic ammonium salts with boronic acids in a stereospecific nickel-catalyzed reaction.[14] This methodology provides a complementary, alternative disconnection by forming a benzyl-aryl bond instead of a benzhydryl-alkyl bond (Scheme 1.1.1.6).

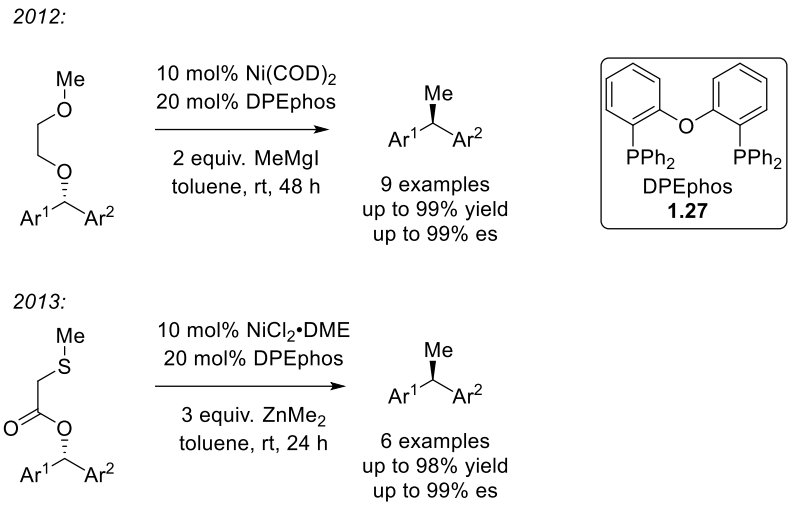
Scheme 1.1.1.6: *Watson's Stereospecific Nickel-Catalyzed Suzuki Cross-Coupling of Benzyl Ammonium Salts*



In 2012[15] and 2013,[16] Jarvo and coworkers continued to develop stereospecific transformations of benzhydryl ethers by using traceless directing group auxiliaries. These ethereal auxiliaries accelerate oxidative addition, and the overall reaction rate, of a nickel catalyzed reaction to yield enantioenriched benzhydryl stereocenters (Scheme 1.1.1.7). The advantage of this approach relative to her previous publication is it allows the incorporation of additional functionality, including hetereocycles. The use of organozinc reagents allows greater functionality in the reaction substrate scope.

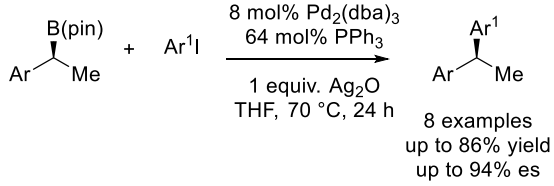
[14] Maity, P.; Shacklady-McAtee, D. M.; Yap, G. P. A.; Sirianni, E. R.; Watson, M. P. *J. Am. Chem. Soc.* **2013**, *135*, 280-285
[15] Greene, M. A.; Yonova, I. M.; Williams, F. J.; Jarvo, E. R. *Org. Lett.* **2012**, *14*, 4293-4296
[16] Wisniewska, H. M.; Swift, E. C.; Jarvo, E. R. *J. Am. Soc. Chem.* **2013**, *135*, 9083-9090

Scheme 1.1.1.7: *Jarvo's Traceless Auxiliary Strategy in Stereospecific Nickel-Catalyzed Cross-Coupling of Benzhydryl Ethers*



In 2009, Crudden and coworkers developed a stereospecific palladium-catalyzed cross-coupling of chiral benzylic organoboronic esters and aryl iodides. The reaction occurs with retention of configuration (Scheme 1.1.1.8).[17]

Scheme 1.1.1.8: *Crudden's Stereoretentive Palladium-Catalyzed Suzuki Cross-Coupling*

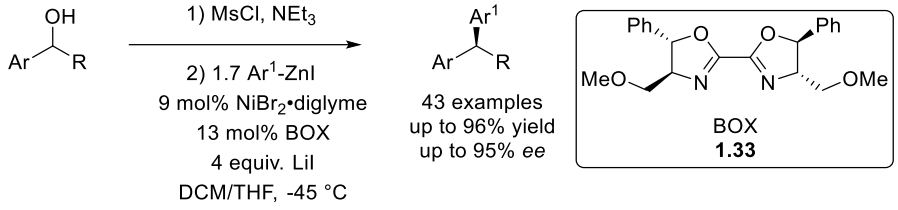


A natural extension of the benzylic cross-coupling is to replace stereospecific transformations, where the synthesis of enantiopure starting material can be challenging and the enantiomeric excess of the product can erode over the course of two steps, and move toward enantioconvergent cross-coupling reactions. The allows racemic starting benzylic electrophiles to be converted to enriched bisaryl motifs. In 2013, Fu and coworkers used racemic benzylic mesylates, which are

[17] Imao, D.; Glasspoole, B. W.; Laberge, V. S.; Crudden, C. M. *J. Am. Soc. Chem.* **2009**, *131*, 5024-5025

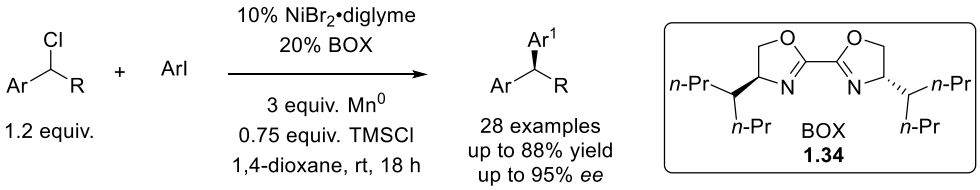
converted *in situ* to benzylic iodides, as electrophiles in an enantioconvergent nickel-catalyzed Negishi cross-coupling (Scheme 1.1.1.9).[18]

Scheme 1.1.1.9: *Fu's Enantioconvergent Nickel-Catalyzed Negishi Cross-Coupling*



As an extension of enantioconvergent cross-coupling, in 2017 Reisman and coworkers developed an enantioconvergent nickel-catalyzed reductive cross-coupling of racemic benzylic chlorides with aryl iodides (Scheme 1.1.1.10).[19] It is worth noting that the enantioconvergent methods furnish products in high yield and enantioselectivity without requiring a directing group. They also increased the scope of the primary alkyl chain (R group).

Scheme 1.1.1.10: *Reisman's Enantioconvergent Nickel-Catalyzed Reductive Cross-Coupling*

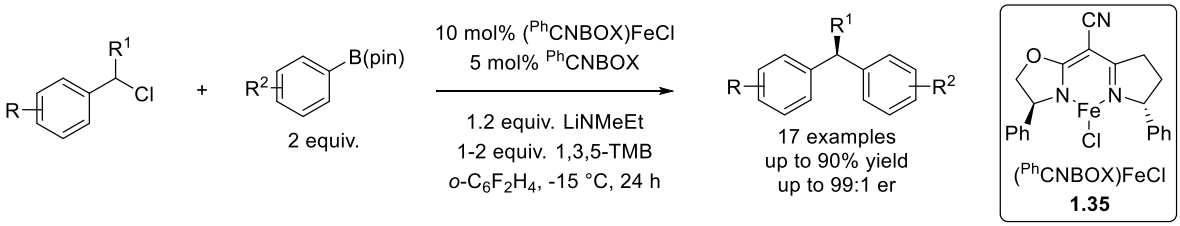


In 2020, Byers and coworkers reported the first enantioconvergent Suzuki-Miyaura cross-coupling of racemic benzyl chlorides and aryl pinacol boronates using a cyanobis(oxazoline) ligated iron-catalyst (Scheme 1.1.1.11).[20] A lithium methylethylamide facilitated the transmetallation of the boronate to the iron, and 1,3,5 trimethoxybenzene was proposed to increase catalyst lifetime for efficient catalysis. Good yields and enantioselectivities of the products were

[18] Do, H.; Chandrashekar, E. R. R.; Fu. G. C. *J. Am. Chem. Soc.* **2013**, *135*, 16288-16291
[19] Poremba, K. E.; Kadunce, N. T.; Suzuki, N.; Cherney, A. H.; Reisman, S. E. *J. Am. Chem. Soc.* **2017**, *139*, 5684-5687
[20] Tyrol, C. C.; Yone, N. S.; Gallin, C. F.; Byers, J. A. *Chem. Commun.* **2020**, *56*, 14661-14664

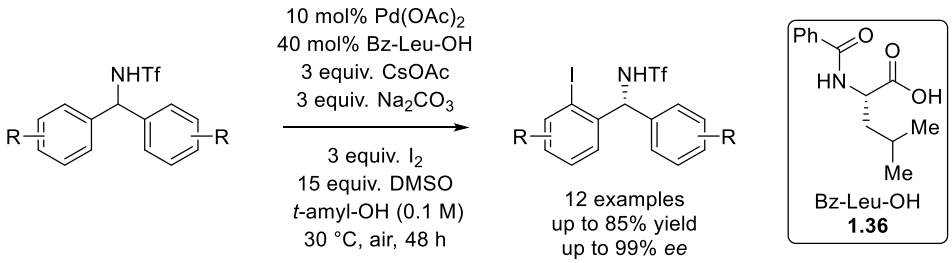
obtained for most products, but a notable increase in enantioselectivity was observed for *ortho*-substituted benzyl electrophiles.

Scheme 1.1.1.11: *Byers' Enantioconvergent Iron-Catalyzed Suzuki-Miyaura Cross-Coupling*



An alternative disconnection to furnish enantiomerically enriched benzhydryl motifs is an enantioselective palladium catalyzed C-H activation desymmetrization of diarylmethylamines. For example, Yu and coworkers developed a palladium-catalyzed enantioselective C-H iodination of diarylmethyltriflamide in 2013 (Scheme 1.1.1.12).[21] The *ortho* C-H iodination was enabled by a combination of a triflamide directing group, mixture of acetate and carbonate bases, polar additives, and an amino acid derived palladium ligand to obtain products in high yields and enantioselectivities. Notably, starting materials without *ortho*-substitution often underwent additionally iodination reactions to obtain diiodinated products.

Scheme 1.1.1.12: *Yu's Enantioselective Palladium-Catalyzed C-H Iodination Reaction*

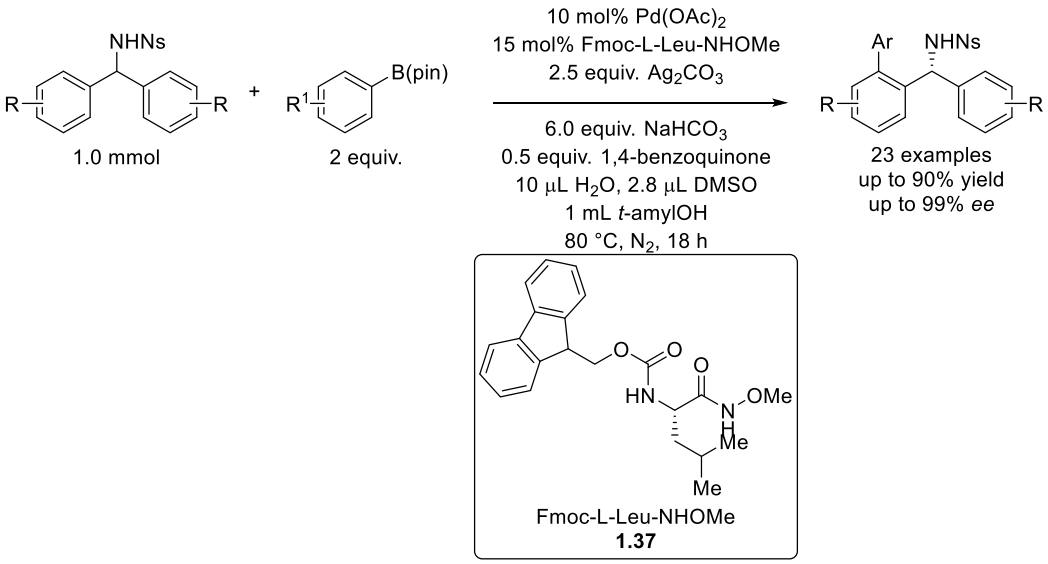


In 2015, Yu and coworkers extended this transformation to include arylboronates.[22] Along with optimization of oxidant, carbonate bases, polar additives, and palladium ligand, a notable advance

[21] Chu, L.; Wang, X.-C.; Moore, C. E.; Rheingold, A. L.; Yu, J. -Q. *J. Am. Chem. Soc.;* **2013**, *135*, 16344-16347
[22] Laforteza, B. N.; Chan, K. S. L.; Yu, J. -Q. *Angew. Chem. Int. Ed.* **2015**, *54*, 11143-11146

is the use of a sulfonamide directing group to enable high yields and enantioselectivities. The corresponding enriched sulfonamide product can undergo a deprotection reaction to yield the free amine.

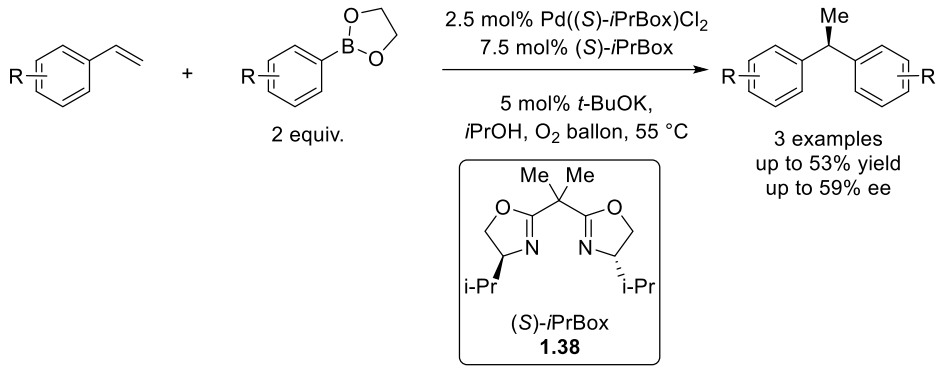
Scheme 1.1.1.13: *Yu's Enantioselective Palladium-Catalyzed C-H Arylation Reaction*



A carbon-carbon bond forming reaction was found in asymmetric hydroarylation reactions of styrenes. This complementary method relies on inexpensive and commercially available styrenyl feedstocks. In 2011, Sigman and coworkers reported one of the first examples of a palladium-catalyzed asymmetric hydroarylation of styrenes with arylboronates. This process is noteworthy for its use of oxygen as the terminal oxidant (Scheme 1.1.1.14).[23] Unfortunately, most products were generated in relatively low yield and enantioselectivity.

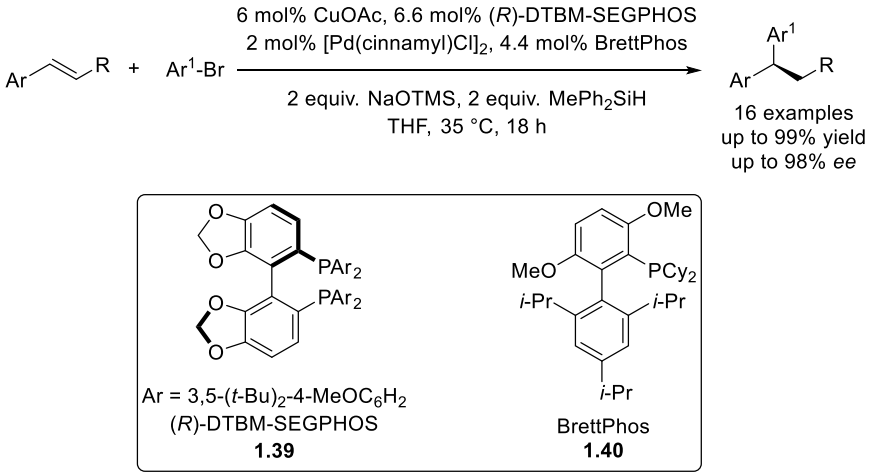
[23] Podhajsky, S. M.; Iwai, Y.; Cook-Sneathen, A.; Sigman, M. S. *Tetrahedron* **2011**, *67*, 4435-4441

Scheme 1.1.1.14: *Sigman's Asymmetric Palladium-Catalyzed Hydroarylation of Styrenes*



In 2016, Buchwald and coworkers developed a dual catalytic hydroarylation method wherein an enantioselective copper hydride addition to styrenes is followed by transmetallation to a palladium (II) aryl complex. Subsequent reductive elimination furnished the product in high yield and enantioselectivity (Scheme 1.1.1.15).[24]

Scheme 1.1.1.15: *Buchwald's Dual Catalyst Asymmetric Hydroarylation*

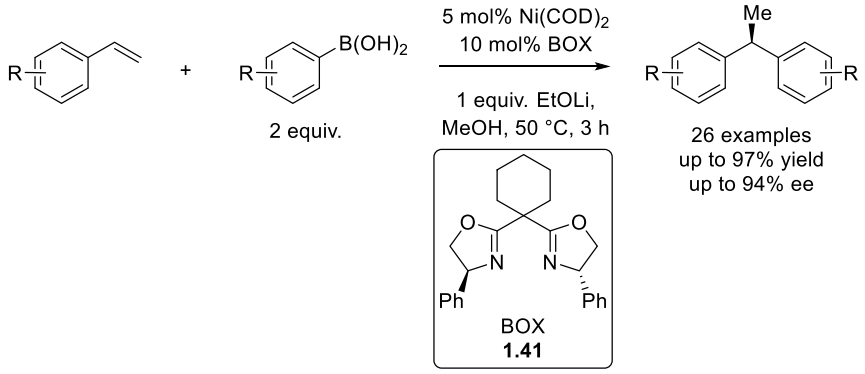


In 2019, Mei and coworkers developed a nickel-catalyzed asymmetric hydroarylation of styrenes with boronic acids (Scheme 1.1.1.16). Deuterium labeling experiments suggest that after 1,2 migratory insertion of the nickel-aryl species into styrene, methanol serves as a proton source

[24] Friis, S. D.; Pirnot, M. T.; Buchwald, S. L. *J. Am. Soc. Chem.* **2016**, *138*, 8372-8375

for protodemetallation. These products contain diarylmethyl stereocenters that were obtained in high yield and enantioselectivities.[25]

Scheme 1.1.1.16: *Mei's Nickel-Catalyzed Asymmetric Hydroarylation of Styrenes*

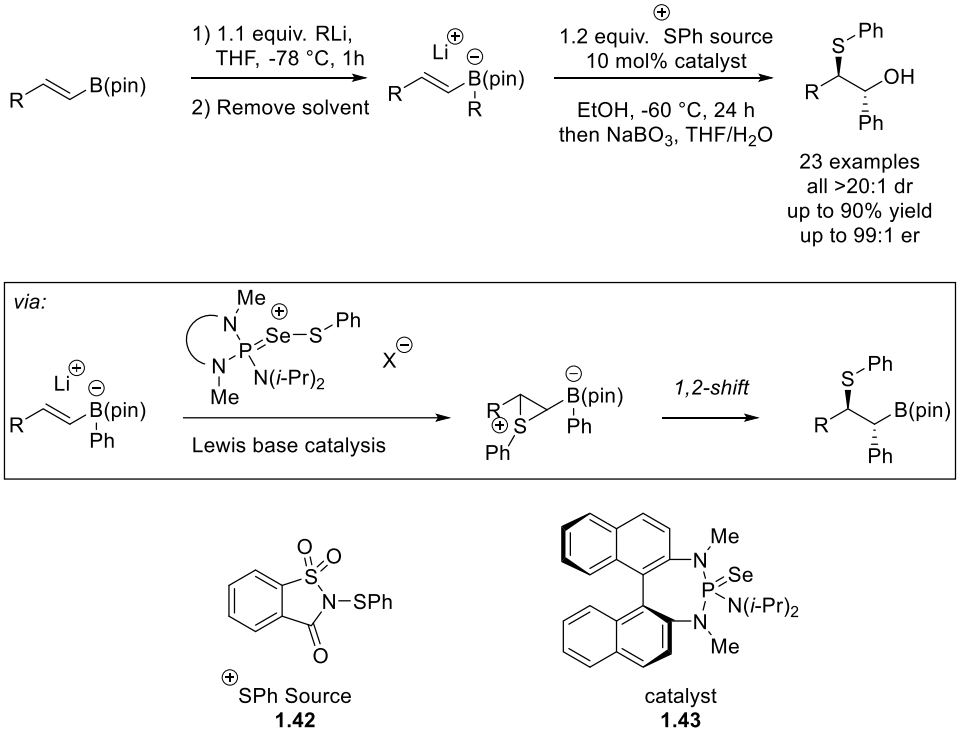


1.1.2 Generation of Contiguous Stereocenters via 1,2-Migration of β-Substituted Alkenyl Boronates

In 2018, Denmark and coworkers developed an enantioselective, selenophosphoramide-catalyzed carbosulfenylation of alkenylboronates.[26] This process was found to occur by 1,2 boronate migration., and is an extension of his intramolecular, enantioselective sulfenofunctionalization of alkenes.[27] The authors note that the tetracoordinate alkenyl boronate is sufficiently nucleophilic that it directly adds to the sulfur electrophile without any catalyst, even under cryogenic condition in dichloromethane. To minimize the strong background reaction, ethanol was used as a solvent, which was hypothesized to hydrogen-bond with the pinacol oxygens and reduce the nucleophilicity of the tetracoordinate boronate. Using the conditions described below, carbosulfenylation of alkenylboronates was achieved with high enantioselectivity (Scheme 1.1.2.1).

[25] Chen, Y.; Shuai, B.; Xu, X.; Li, Y.; Yang, Q.; Qiu, H.; Zhang, K.; Fang, P.; Mei, T. *J. Am. Chem. Soc.* **2019**, *141*, 3395-3399
[26] Tao, Z.; Robb, K. A.; Panger, J. L.; Denmark, S. E. *J. Am. Chem. Soc.* **2018**, *140*, 15621-15625
[27] Hartmann, E.; Kornfilt, D. J. P.; Wang, H.; Denmark, S. E. *Nat. Chem.* **2014**, *6*, 1056-1064

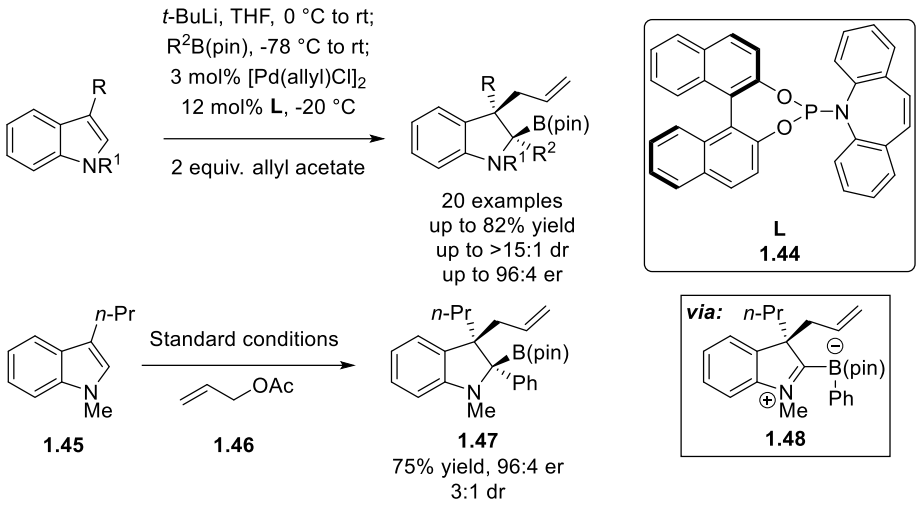
Scheme 1.1.2.1: *Denmark's Selenophosphoramide-Catalyzed Carbosulfenylation of β-Substituted Alkenylboronates*



In 2018, Ready and coworkers developed a palladium-catalyzed tandem allylation and 1,2 boronate rearrangement for the asymmetric synthesis of indolines bearing adjacent quaternary stereocenters.[28] This report is an extension of a process that was previously developed by the group in 2017. In this reaction sequence, an allyl electrophile reacts with palladium (0) species to form a palladium (II) π-allyl species. The indoyl derived boron "ate" complex adds to the palladium (II) π-allyl complex to generate an enantioenriched indoline and palladium (0). The author notes that not all substrates exhibit high diastereoselectivity, especially when "R" is a larger alkyl group. Variable diastereoselectivity indicates that the 1,2-metallate shift and nucleophilic attack is not a concerted process (Scheme 1.1.2.2).

[28] (a) Panda, S.; Ready, J. M. *J. Am. Chem. Soc.* **2017**, *139*, 6038-6041 (b) Panda, S.; Ready, J. M. *J. Am. Soc. Chem.* **2018**, *140*, 13242-13252

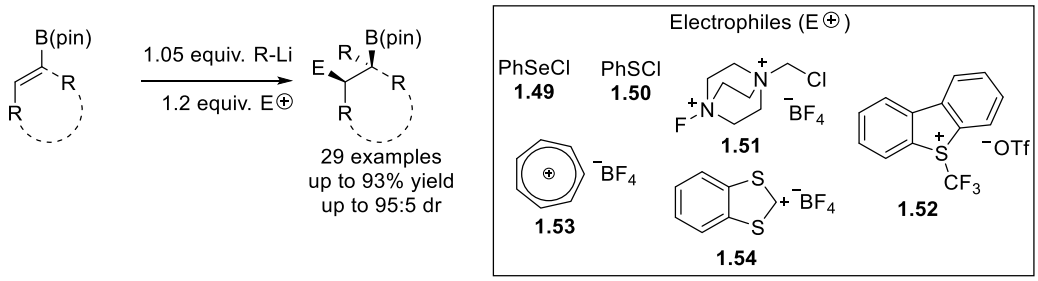
Scheme 1.1.2.2: *Ready's Palladium-Catalyzed Enantioselective Tandem Allylation/ 1,2-Boronate Rearrangement*



In 2017, Aggarwal and coworkers investigated the conjunctive functionalization of alkenyl boronate complexes with various electrophiles.[29] Though a 1,2-metallate shift of an alkenyl boron "ate" complex has been triggered by electrophiles before such as iodine (Zweifel olefination[30]) or a selenium electrophile[31], both reactions produce a difunctionalized intermediate that undergoes base-promoted elimination (Scheme 1.1.2.3). In this study, di- and tri-substituted alkenyl boron "ate" complexes were treated with different electrophiles and the resulting product stereoselectivity assessed. With many combinations of electrophiles, 1,2-metallate shifts were achieved with high diastereoselectivity and in high yield. However, low yields were obtained when using β,β-disubstituted alkenyl boronates. The major byproduct was found to be the corresponding deborylated alkene due to an elimination process. In addition, less than optimal diastereoselectivity was obtained in some cases and the author attributed this erosion in selectivity to the build-up of a cationic intermediate. The use of mixed solvent systems during the reaction was able to restore stereoselectivity in some cases.

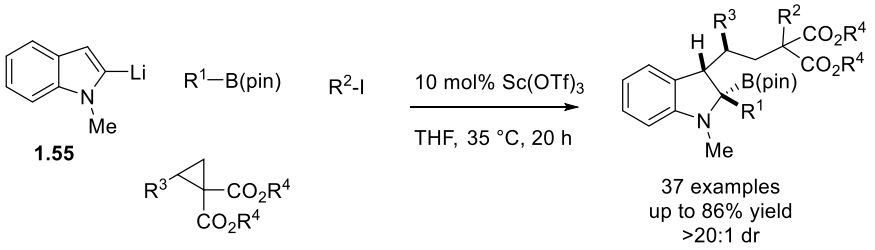
[29] Armstrong, R. J.; Sandford, C.; García-Ruiz, C.; Aggarwal, V. K. *Chem. Commun.* **2017**, *53*, 4922-4925
[30] Armstrong, R. J.; Aggarwal, V. K. *Synthesis* **2017**, *49*, 3323-3336
[31] Armstrong, R. J.; García-Ruiz, C.; Myers, E. L.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2017**, *56*, 786-790

Scheme 1.1.2.3: *Aggarwal's Stoichiometric Di-functionalization of β-Substituted Alkenyl Boronates*



In 2018, Studer and coworkers used scandium triflate as a catalyst to promote a 1,2-metallate shift that results in a dicarbofunctionalization of indolyl boronates.[32] In this process, after formation of an indolyl derived "ate" complex, addition to the cyclopropane moiety via a 1,2-metallate shift occurs, resulting in a ring opening of the cyclopropane and formation of a malonate anion intermediate. This anion is subsequently trapped with an alkyl iodide electrophile. It is noteworthy that the four-component reaction occurred with complete stereospecificity, regardless of variation of the reactive components. Interestingly, in the presence of two electrophiles, selective additions occur in the reaction sequence (Scheme 1.1.2.4).

Scheme 1.2.2.4: *Studer's Scandium Triflate-Catalyzed Four-Component Coupling*

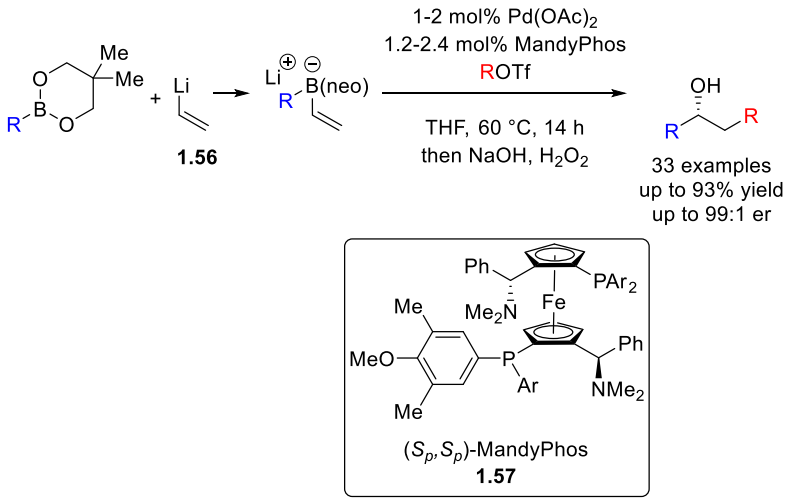


[32] Das, S.; Daniliuc, C. G.; Studer, A. *Angew. Chem. Int. Ed.* **2018**, *57*, 4053-4057

1.1.3 Palladium-Catalyzed Conjunctive Cross-Coupling

In 2016, our group developed the enantioselective palladium-catalyzed conjunctive cross-coupling (Scheme 1.1.3.1).[33] The term "conjunctive" reflects the merger of two nucleophilic components in a single cross-coupling. In this case, an organoboronate and an organolithium come together to form a tetracoordinate boron "ate" complex, which reacts with the electrophile.

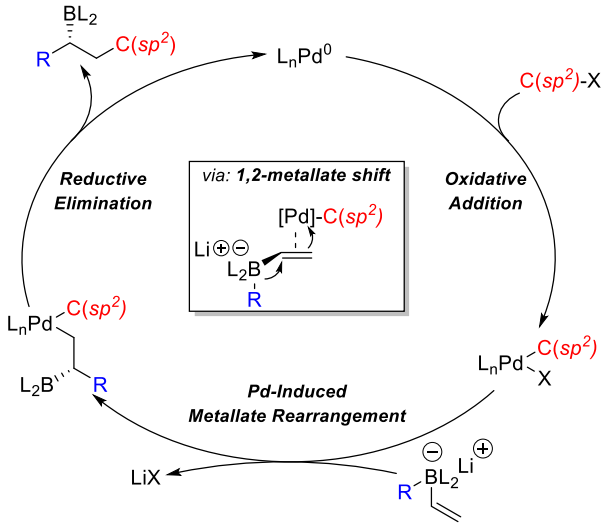
Scheme 1.1.3.1: *Palladium-Catalyzed Conjunctive Cross-Coupling*



Similar to Suzuki-Miyaura cross-coupling, conjunctive cross-coupling starts with oxidative addition of an aryl triflate to palladium (0) thereby forming a cationic palladium (II) complex (Scheme 1.1.3.2). Diverging from the Suzuki-Miyaura transmetallation, the vinyl component of the tetracoordinate boronate binds to the open coordination site of palladium. A subsequent palladium induced 1,2-metallate shift occurs, which is a process that is mechanistically similar to a Zweifel olefination. Finally, reductive elimination turns over the catalytic cycle. Simply, this is a three-component cross-coupling between an organoboronate, an organolithium, and an organotriflate to yield a chiral secondary organoboronate.

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

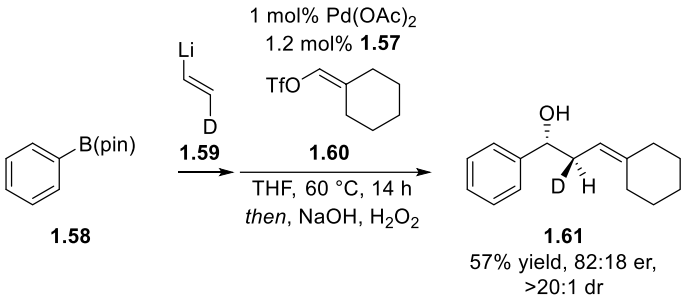
Scheme 1.1.3.2: *Catalytic Cycle for Palladium-Catalyzed Conjunctive Cross-Coupling*



The conjunctive cross-coupling reaction contains many interesting points of reaction design that should be emphasized. Of note, *neo*-pentylglycol was chosen as a ligand for boron because the corresponding "ate" complexes were determined to be the more nucleophilic than a pinacol derived boronate.[34] The use of triflate electrophiles was necessary to generate a cationic palladium (II) intermediate. A triflate counterion is ideal for the ionization of a palladium (II) intermediate and generate an open coordination site in order to activate the alkene of the "ate" complex. The nature of the palladium induced 1,2-metallate shift was experimentally determined by studying the diastereoselectivity of the reaction using a deuterium labeled vinyllithium reagent (Scheme 1.1.3.3). After forming a boron "ate" complex by reaction of labeled vinyllithium and phenyl B(pin), it was subjected to a reaction with an alkenyl triflate electrophile. The deuterium labeled product was obtained as a single diastereomer. This experiment showed that the metallate rearrangement occurs by a stereospecific *anti*-periplanar addition of the migrating group and palladium to the alkene.

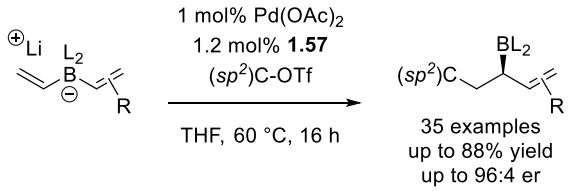
[34] (a) Berionni, G.; Leonov, A. I.; Mayer, P.; Ofial, A. R.; Mayr, H. *Angew. Chem. Int. Ed.* **2015**, *54*, 2780-2783 (b) Feeney, K.; Berionni, G.; Mayr, H.; Aggarwal, V. K. *Org. Lett.* **2015**, *17*, 2614-2617

Scheme 1.1.3.3: *Deuterium Labeled Experiment*



In 2017, our group investigated the use of bis(alkenyl)boronates as a cross-coupling partner in conjunctive cross-coupling.[35] The product of this reaction is a valuable chiral allylboronate (Scheme 1.1.3.4). It was noted that the more substituted alkenyl component of the boron "ate" complex migrates exclusively during the reaction. This suggests that the cationic palladium (II) intermediate selectively activates the less substituted alkene for a 1,2-metallate shift.

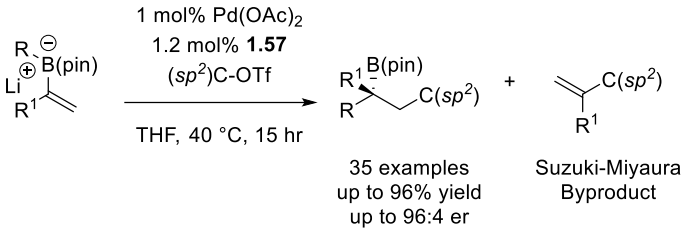
Scheme 1.1.3.4: *Palladium-Catalyzed Conjunctive Cross-Coupling of Bisalkenyl Boron "Ate" Complexes*



In 2018, our group investigated the use of α-substituted alkenylboronates in conjunctive cross-coupling.[36] Upon an enantioselective palladium-induced 1,2-metallate shift, the synthesis of tertiary organoboronates was achieved (Scheme 1.1.3.5). In the optimization of this transformation, neopentyl glycol derived isopropenyl boronates reacted with modest selectivity. Product ratios of 1:4.5 (conjunctive coupling:Suzuki coupling) were observed under some reaction conditions. However, use of a pinacolato isopropenyl boronate resulted in good selectivity for the desired product (up to 1:0.06 conjunctive:Suzuki).

[35] Edelstein, E. K.; Namirembe, S.; Morken, J. P. *J. Am. Soc. Chem.* **2017**, *139*, 5027-5030
[36] Myhill, J. A.; Zhang, L.; Lovinger, G. L.; Morken, J. P. *Angew. Chem. Int. Ed.* **2018**, *57*, 12799-12803

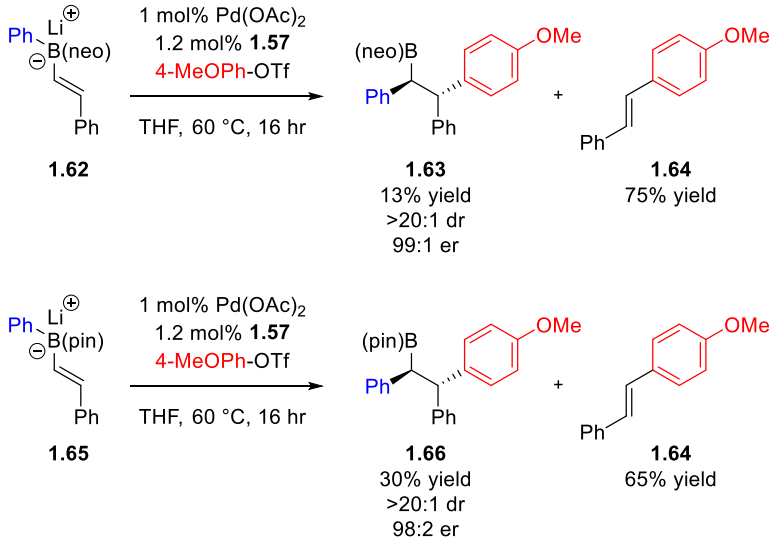
Scheme 1.1.3.5: *Palladium-Catalyzed Conjunctive Cross-Coupling of α-Substituted Alkenyl Boron " Ate" Complexes*



1.2 Diastereoselective and Enantioselective Palladium-Catalyzed Conjunctive Cross-Coupling

In 2018, we investigated the reactivity of conjunctive cross-coupling where the migrating group shifts to a β-substituted alkenyl component of a tetra-substituted boronate. Based on the previously described deuterium labeling experiment, we would get high diastereoselectivity and generate two contiguous stereocenters. However, as suggested from the results obtained from the conjunctive cross-coupling of bis(alkenyl)boronates and α-substituted alkenyl boronates, the steric demands involved in a 1,2 metallate shift to a β-substituted alkenyl boronate posed a challenge.

Scheme 1.2.1: *Initial Conjunctive Cross-Coupling Investigation of β-Substituted Alkenyl Boronates*

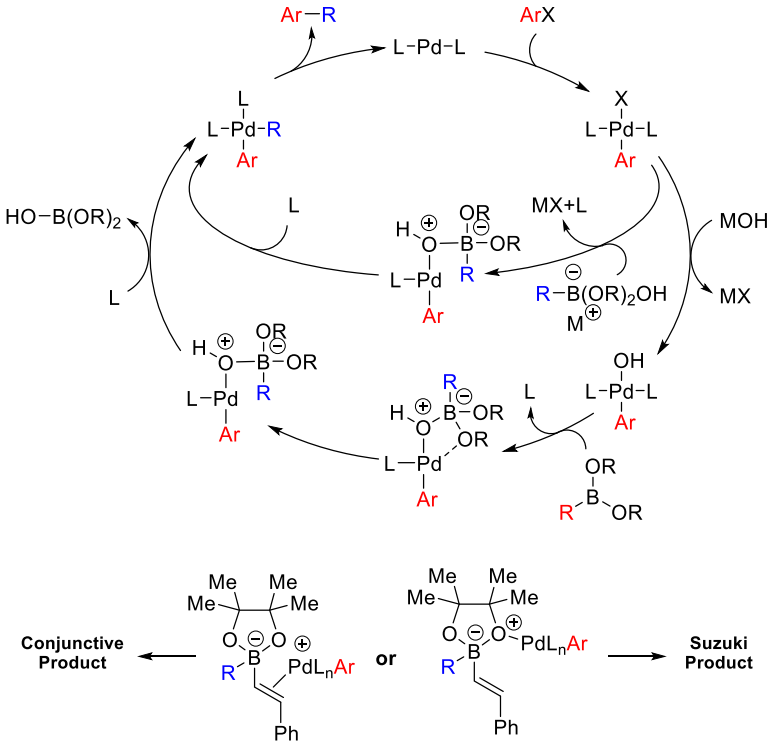


Preliminary coupling experiments were performed with a styrenyl B(neo) phenyl "ate" complex (**1.62**) and an aryl triflate (Scheme 1.2.1). However, the desired product was obtained in only 13% yield. Encouragingly, the product was generated with excellent enantioselectivity and diastereoselectivity. The major byproduct of the reaction was derived from styrenyl transmetallation and yielded stilbene by a Suzuki reaction. Under identical reaction conditions but using a pinacolato alkenyl boron "ate" complex, the conjunctive cross-coupling occurred with higher selectivity for the desired product and maintained high levels of diastereoselectivity and enantioselectivity. Given the distribution of products and in consideration of previous mechanistic experiments, we hypothesized that alkene binding to the cationic palladium is more challenging such that 1,2-metallate shift becomes a disfavored process (Scheme 1.2.2). Additionally, the more favorable process is the conversion of the "ate" complex to a Suzuki-Miyaura coupling product. Studies suggest that the Suzuki-Miyaura reaction proceeds from a four-centered transition state involving a bridging oxygen between palladium and boron.[37] Given the difficulty in utilizing new ligands for palladium that improve reactivity,[38] we opted to examine how the diol ligand structure might enhance reactivity. Our hypothesis was that if oxygen binding to palladium could be disfavored, we would change the selectivity to favor 1,2-metallate shift.

[37] (a) Matos, K.; Soderquist, J. A. *J. Org. Chem.* **1998**, *63*, 461-470 (b) Carrow, B. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 2116-2119 (c) Amatore, C.; Le Duc, G.; Jutand, A. *Chem. Eur. J.* **2013**, *19*, 10082-10093 (d) Thomas, A. A.; Wang, H.; Zahrt, A. F.; Denmark, S. E. *J. Am. Soc. Chem.* **2017**, *139*, 3805-3821 (e) Thomas, A. A.; Denmark, S. E. *Science* **2016**, *352*, 329-332

[38] Zhang, L 2017, *Catalytic Conjunctive Cross-Coupling and Catalytic Diboration Reactions*, Boston College, Chestnut Hill

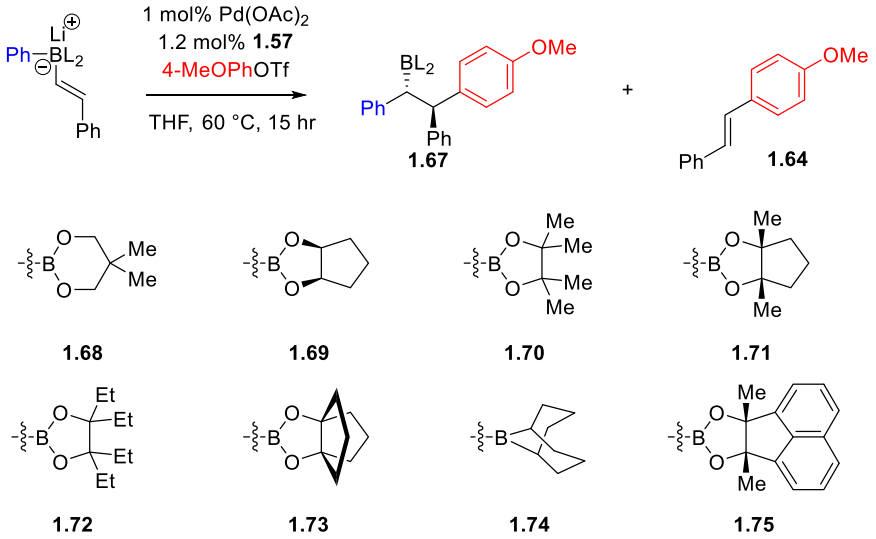
Scheme 1.2.2: *Suzuki-Catalytic Cycle and Hypothesis of Transmetallation Mechanism Dichotomy*



The approach of this survey is to examine ligands with unique steric and electronic features and determine their efficiency to minimize Suzuki-Miyaura coupling (Table 1.3.1). We started by testing a ubiquitous and bulky diol in pinacol, **1.70**. Gratifyingly, we observed that by increasing the steric bulk around the boronic ester oxygens, the selectivity shifted more favorably to the conjunctive cross-coupling product. Although we still observe more Suzuki-Miyaura coupling than desired product, the enantioselectivity and diastereoselectivity remain high. We next synthesized various diols and investigate their reactivity. 1,2-*cis* cyclopentane diol was synthesized by dihydroxylation of the corresponding alkene (**1.69)**. Despite the ease of synthesis, the subsequent reaction showed poor selectivity for the desired product. In comparison, the 1,2 dimethyl cyclopentane diol, **1.71**, was synthesized, and found to provide enhanced selectivity in favor of the conjunctive cross-coupling product. However, despite our best efforts, a facile

synthesis of the diol from commercial starting materials remained elusive and ultimately this diol was abandoned for practicality reasons.

Table 1.2.1: *Boron Ligand Survey*

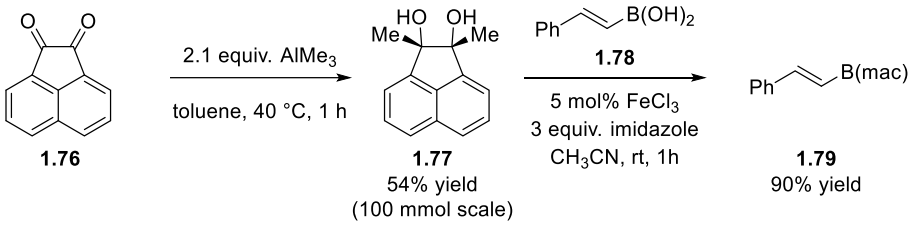


Entry	Boron Ligand	CCC:SM	Yield	dr	er
1	**1.68**	1:5.8	13%	> 20:1	99:1
2	**1.69**	1:>20	< 5%	NA	NA
3	**1.70**	1:2.0	35%	> 20:1	98:2
4	**1.71**	1.7:1	56%	> 20:1	99:1
5	**1.72**	1:2.0	30%	> 20:1	NA
6	**1.73**	1:3.0	20%	> 20:1	NA
7	**1.74**	>20:1	75%	> 20:1	67:33
8	**1.75**	4.2:1	76%	> 20:1	99:1

Bicyclo[3.3.0]octane diol, **1.73**, and tetraethyl diol, **1.72**, were also synthesized in hopes that a more sterically encumbering diols would further enhance selectivity. However, neither was able to provide better selectivity for conjunctive cross-coupling than pinacol. During our investigation, we also studied the reactivity of styrenyl 9-BBN compounds (**1.74**); the hypothesis was if there are no oxygens to coordinate with palladium, the direct transmetallation could be minimized and beneficial selectivity may be observed. Interestingly, high selectivity was observed for the desired conjunctive cross-coupling product. However, we were unable to obtain useful levels of

enantioselectivity after a thorough screening of conditions, solvents, and ligands for palladium. The low enantioselectivity of this reaction may be due to a highly reactive and electron rich boron "ate" complex. It is worth noting that the excellent selectivity for the conjunctive cross-coupling exhibited by the 9-BBN substrate, **1.74**, may be due to the steric bulk of the ligand being closer to the boron center.[39] This may prevent direct transmetallation. We speculated an approach to obtain a ligand similar to **1.71** but minimize synthesis complications and shorten the route length. **1.75** was synthesized from the corresponding diketone and trimethyl aluminum (Scheme 1.2.3).Under the indicated reaction conditions, full conversion of the diketone was observed, and the desired *cis*-diastereomer can be obtained in up to 7:1 dr. Gratifyingly, the *cis*-diastereomer can be isolated after a simple recrystallization. When applied to the conjunctive cross-coupling reaction, a 4.2:1 selectivity in favor of the desired product was observed. This new 1,2 diol was termed "mac" (methylated acenapthoquinone), and was a starting point for further examination.

Scheme 1.2.3: *Mac Diol Synthesis and Condensation with Boronic Acids*



1.76

1.77
54% yield
(100 mmol scale)

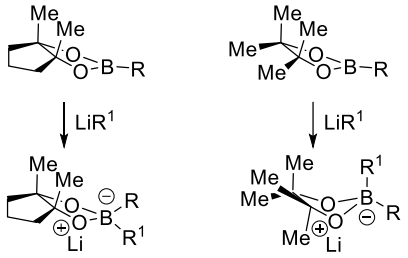
1.79
90% yield

Since we do not know the exact transition state for the Suzuki-Miyaura transmetallation in this system, it is difficult to determine with certainty the reason for the difference in selectivity between the various boronic esters. Nevertheless, we can speculate based on the structural differences between the boronic esters. **1.68** and **1.69** are derived from primary and secondary alcohols,

[39] Attempts were made to synthesize a diethyl styrenyl borane. This substrate would be used to probe whether the selective properties of a 9-BBN ligand are derived from the sterics being closer to the boron center than boronates or if oxygen is necessary for direct transmetallation. Unfortunately, clean synthesis the diethyl styrenyl starting material from hydroboration with diethylborane (from a conproportionation of borane and triethylborane) was not feasible in my hands.

respectively. It is possible that the oxygen atoms in these boronates are more exposed and could facilitate direct transmetallation. Ligand **1.74**, as previously stated, less transmetallation appears to occur with this substrate, and this may be due to the lack of Lewis basic oxygen necessary to interaction with palladium. These data points suggest that the boronic ester oxygens are necessary for transmetallation and the steric environment around the oxygens play a major role in controlling selectivity. Changing to a pinacolato ligand increased the selectivity for conjunctive crossing-coupling. This is presumably because of the increased sterics around the oxygens. Further increasing the sterics, however, to a tetraethyl diol, **1.72**, did not improve the selectivity. Perhaps simply increasing the bulkiness on the boronic ester could not only effect palladium binding to the oxygen, but to the alkene as well. Alternatively, ligand **1.73** may not provide enough steric bulk compared to methyl groups because the relevant steric are tied back in the bicycle. Alteration of the ligand to **1.71** provides an interesting data point where a turnover in selectivity is observed. Comparing the sterics between **1.70** and **1.71**, there appears to be little difference. It might be relevant to discuss the conformational differences between **1.70** and **1.71** (Scheme 1.2.4).

Scheme 1.2.4: *Possible Conformational Differences in **1.66** and **1.67** Ligated Boron "Ate" Complexes*



As a three-coordinate boron, the B(pin) boracycle is a planar five-membered ring.[40] This is likely due to the overlap of the empty p-orbital of the boron and the non-bonded lone pair of

[40] Fasano, V.; McFord, A. W.; Butts, C. P.; Collins, B. S. L.; Fey, N.; Alder, R. W.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2020**, *59*, 22403-22593

electrons on the oxygen atoms. As a consequence, the vicinal methyl groups are likely to be eclipsing each other. In a four-coordinate boron, where the B(pin) boracycle is likely to adopt an envelope conformation to minimize eclipsing interactions.[41] As a consequence, the vicinal methyl groups are gauche to each other and the eclipsing steric penalty is alleviated. Over the course of a metal induced 1,2 metallate shift, a tetra-coordinate B(pin) becomes three-coordinate. The barrier for 1,2 metallate shift could be relatively high as a relatively low energy (gauche methyl groups) and stable "ate" complex is converted to a relatively high energy three-coordinate borylcycle (eclipsing methyl groups). To summarize, the pinacol boronic ester might be a good electrophile to generate "ate" complexes, but it is a relatively poor ligand framework for 1,2-metallate shift. Due to the fused boracycle of **1.71**, conformational differences are not likely to arise between three and four coordinate boronates, and the vicinal methyl groups are going to be eclipsed for both species. Using the same analysis for B(pin), we could expect the barrier for 1,2 metallate shift to be lower because the eclipsing conformational penalty is present in both the ground state and the transition state. In summary, **1.71** is a better nucleophile for 1,2 metallate shift.

Mac diol, **1.75**, appears to have many merits that can improve selectivity. The fused boracycle, like **1.71**, may improve selectivity. In addition, the oxygen atoms are benzylic and this should render the "ate" complex less Lewis basic and therefore less likely to bind to palladium.

Notably, the three-coordinate B(mac) is a meso compound, but upon addition of an organolithium to form the boron "ate" complex, a mixture of diastereomers is formed (Scheme 1.2.5). Formation of a mixture of isomers might be a complication because it is possible that only one diastereomer is active under the catalytic conditions. ^{1}H NMR experiments revealed that the addition of phenyllithium to *n*-butylB(mac) occurs with diastereoselectivity (Figure 1.2.1), and a

[41] Berionni, G.; Leonov, A. I.; Mayer, P.; Ofial, A.; Mayr, H. *Angew. Chem. Int. Ed.* **2015**, *54*, 2780-2783

nuclear Overhauser effect experiment determined that the addition of the phenyllithium to boron occurs from the same side as the gem-dimethyl of the mac diol (Figure 1.2.2). Fortunately, interconversion of the diastereomers occurs at catalytically relevant temperatures. With this knowledge, the reaction should proceed to full conversion regardless of the amount of a more active diastereomer.

Scheme 1.2.5: *Isomerization of Tetra-Coordinate Mac-Ligated Boron "ate"*

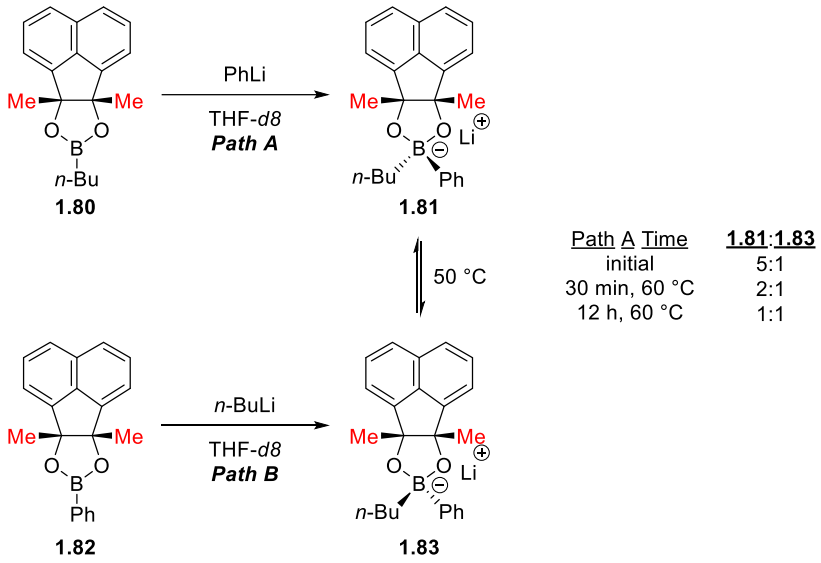


Figure 1.2.1: *^{1}H NMR of Isomerization of Boron "Ate" Complex Over Time*

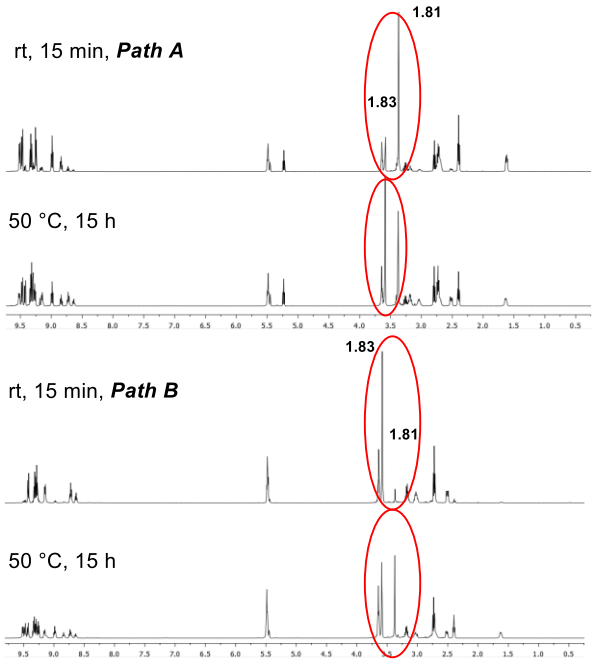
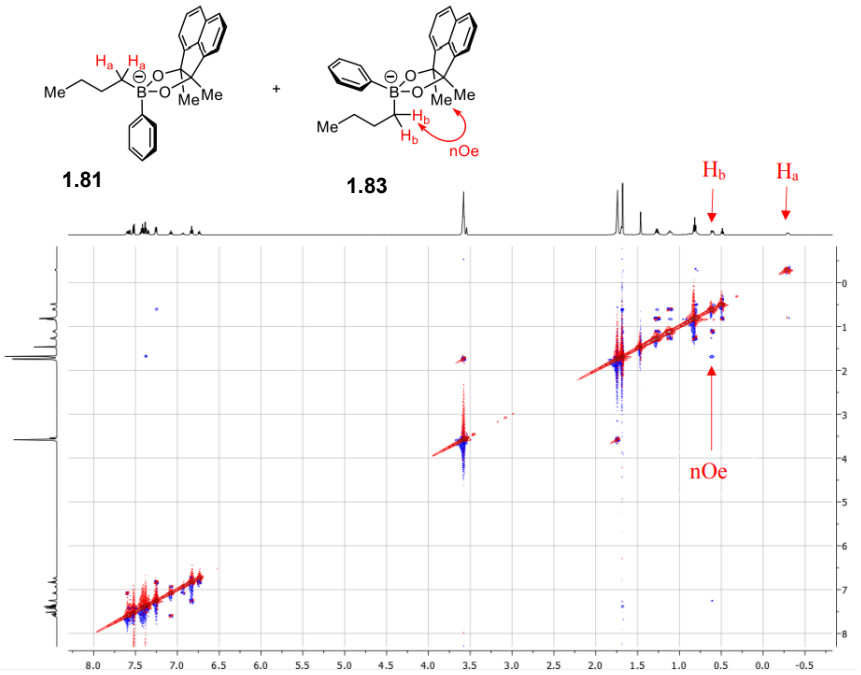


Figure 1.2.2: *nOe ^{1}H NMR to Determine Diastereomers of Boron "Ate" Complex*



During reaction optimization, cesium fluoride was discovered as an effective additive in this conjunctive cross-coupling. Cesium fluoride enabled conversion of the boron "ate" complex at a

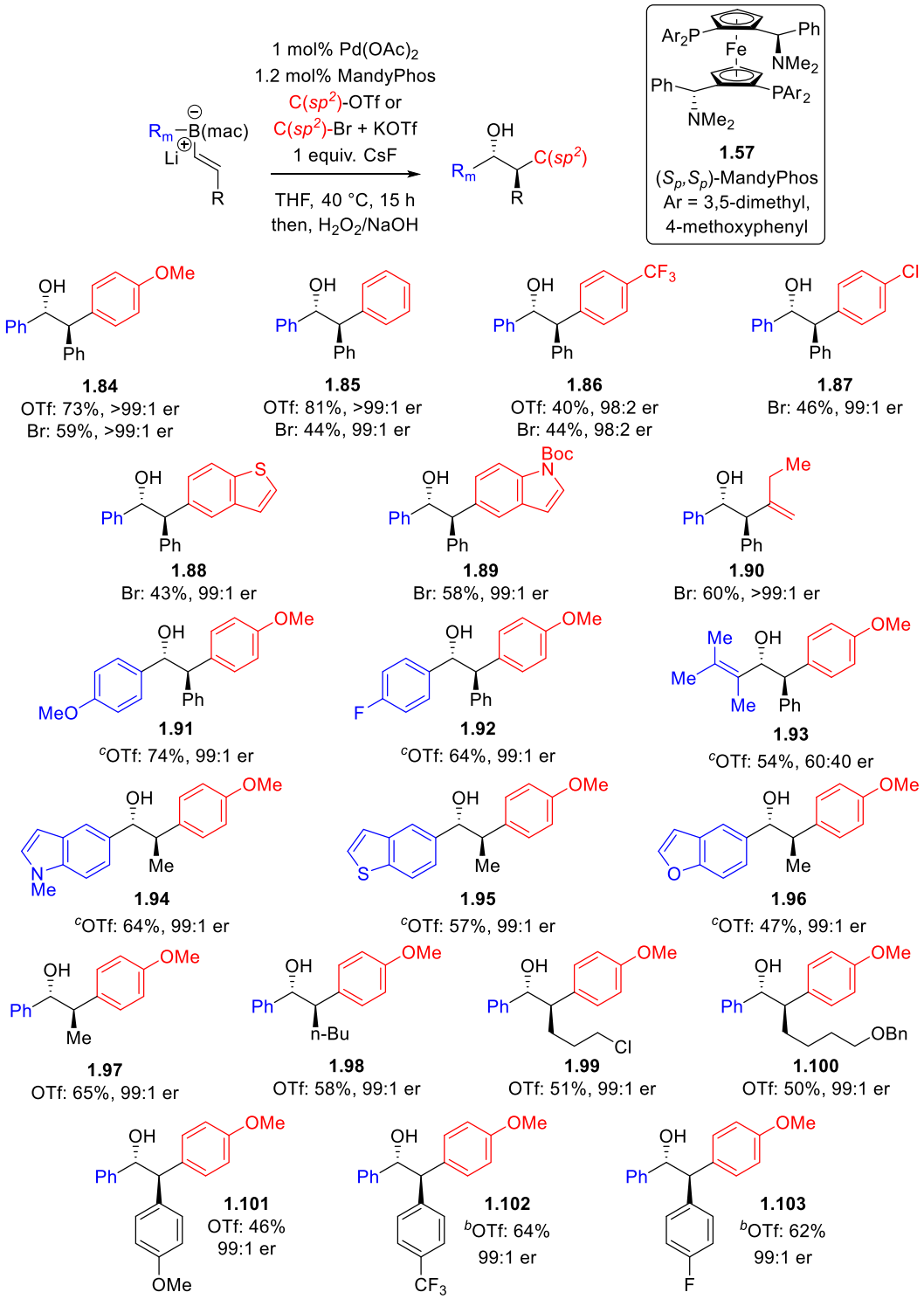
lower reaction temperature. We postulate that a salt metathesis may occur between cesium fluoride and a lithium derived boron "ate" complex to yield a cesium "ate" complex and lithium fluoride. A cesium "ate" would be more reactive in conjunctive cross-coupling because the greater atomic radius of the cesium cation. Cesium fluoride has also been used in other conjunctive cross-coupling methods.[42]

With a suitable ligand for boron in hand, the effects of the reaction components in the conjunctive cross-coupling were examined (Table 1.2.2). Interestingly, near perfect diastereoselectivity (>20:1) was obtained for every substrate. This observation indicates a concerted *anti* carbon-carbon and carbon-palladium bond formation during the 1,2-metallate shift. Using a boronate complex derived from phenyllithium and styrenyl B(mac), different electrophiles were examined. Various aryl triflates participated well in the reaction. Usually, the bromide electrophiles performed worse than the triflate analogs, but high enantioselectivity was maintained. Additionally, use of potassium triflate was necessary to alleviate an inhibiting effect of bromide salts.[43] Electron rich aryl electrophiles worked well under the reaction conditions. Switching to an electron deficient electrophile resulted in decreased yield of the desired product and increased amounts of Suzuki-Miyaura product. This is perhaps due to an exceptionally electron-deficient and reactive palladium (II) intermediate that is better able to bind to oxygen atoms for transmetallation. It was gratifying to see that useful functionality such as aryl chlorides, heterocycles, and alkenes was tolerated. Numerous migrating groups took part in the desired reaction. Once again, electron rich aryl migrating groups exhibited better reactivity than electron deficient ones. This may be due to the beneficial build-up of negative charge on the migrating carbon. Interestingly, alkene migration occurred with exceptionally low levels of

[42] Meng, Y.; Kong, Z.; Morken, J. P. *Angew. Chem. Int. Ed.* **2020**, *59*, 8456-8459
[43] Lovinger, G. J.; Aparece, M. D.; Morken, J. P. *J. Am. Chem. Soc.* **2017**, *139*, 3153-3160

enantioselectivity. Also, alkyl migrating groups yielded only the Suzuki-Miyaura product. The third and final component examined was the substitution of the alkenyl boronate. Alkyl substitution was well tolerated under the reaction conditions. As a consequence, other functional groups could be introduced, such as alkyl chlorides and protected alcohols. Additionally, aryl groups with different electronic properties were tolerated. Interestingly, an electron rich aryl group reacted with a near 1:1 Suzuki-Miyaura:conjunctive selectivity and apparent increased rate of reaction. In contrast, electron deficient aryl substituents required higher temperatures for increased conversion but selectivity and enantioselectivity remained high.

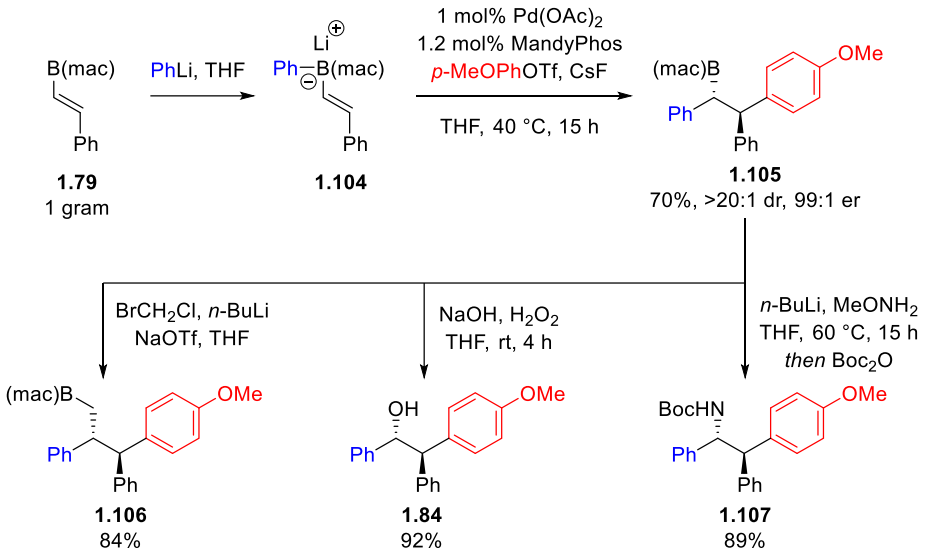
Table 1.2.2: *Substrate Scope of β-Substituted Alkenyl Boronates*



[a]Yields are isolated yields of purified material and represent and average yield of two different experiments. Enantiomeric ratios were determined by SFC analysis on a chiral stationary phase and are in comparison to authentic racemic materials. Diastereoselectivity was determined by analysis of the ^{1}H NMR spectrum. For reactions of organobromide electrophiles, an equivalent of KOTf was added. [b]Reaction at 60 °C. [c]Reaction conducted with 2 mol% Pd and 2.2 mol% (S_p,S_p-L1)

A notable feature of this reaction is that gram quantities of starting material coupled well and the boronic ester product could be isolated in high yield using silica gel chromatography (Scheme 1.2.6). Additionally, the isolated mac-derived boronic ester could be derivatized under similar conditions as a pinacol boronate. Homologation[44], oxidation, and amination[45] products were isolated in high yields.

Scheme 1.2.6: *Gram-Scale Catalytic Reaction and Transformations of Product*

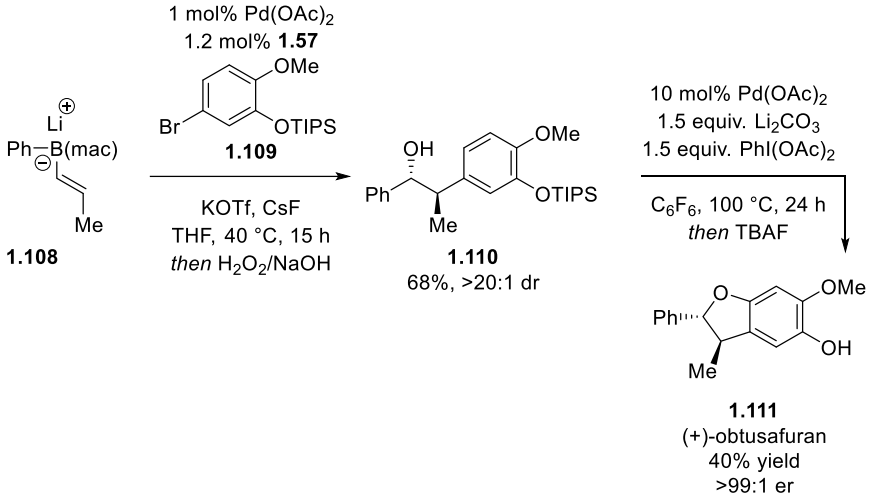


The ability to generate stereodefined benzyl stereocenters was applied in the synthesis of (+)-obtusafuran.[46] Obtusafuran was isolated from the heartwood of a cocobolo tree, *Dalbergia retusa*. To prepare this compound, a propenyl "mac" ligated boronate was converted to an "ate" complex by subjecting it to phenyl lithium (Scheme 1.3.6). The "ate" complex was then coupled with the necessary oxygenated aryl bromide under conjunctive cross-coupling conditions. Using this process, the required carbon skeleton was synthesized in one step from three separate components

[44] Sonawane, R. P.; Jheengut, V.; Rabalakos, C.; Larouche-Gauthier, R.; Scott, H. K.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2011**, *50*, 3760-3763
[45] Mlynarski, S. N.; Karns, A. S.; Morken, J. P. *J. Am. Chem. Soc.* **2012**, *134*, 16449-16451
[46] Gregson, M.; Ollis, W. D.; Redman, B. T.; Sutherland, I. O.; Dietrichs, H. H.; Gottlieb, O. R. *Phytochemistry* **1978**, *17*, 1395-1400

in high enantioselectivity, diastereoselectivity, and yield. It is worth noting that synthesis of a derivative of the requisite benzylic alcohol was previously accomplished in six linear steps.[47] Lastly, a palladium-catalyzed oxidative cyclization[48] and TBAF-mediated silyl deprotection yielded the natural product as, essentially, a single stereoisomer. Jesse Myhill is solely responsible of the synthesis of (+)-obtusafuran as described in Scheme 1.2.7.

Scheme 1.2.7: *Total Synthesis of (+)-Obtusafuran*



[47] Chen, C.; Weisel, M. *Synlett* **2013**, *24*, 189-192
[48] Wang, X.; Lu, Y.; Dai, H. X.; Yu, J. Q. *J. Am. Chem. Soc.* **2010**, *132*, 12203-12205

1.3 Experimental section

1.3.1 General information

^{1}H NMR spectra were recorded on either a Varian Gemini-500 (500 MHz), Varian Gemini-600 (600 MHz), or Varian Inova-500 (500 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 (126 MHz), Varian Gemini-600 (151 MHz) or a Varian Inova-500 (126 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 77.2 ppm). ^{11}B NMR spectra were recorded on a Varian Gemini-500 (128 MHz) or Varian Gemini-600 (160 MHz) spectrometer. ^{19}F NMR spectra were recorded on a Varian Gemini-500 (470 MHz) spectrometer. Infrared (IR) spectra were recorded on a Bruker alpha-P Spectrometer using compounds neat. 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) 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. 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 (magic stain). Analytical chiral supercritical fluid chromatography (SFC) was performed on a TharSFC Method Station II equipped with Waters 2998 Photodiode Array Detector with isopropanol or

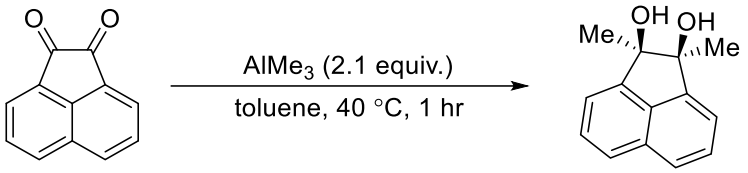
methanol as the modifier. X-ray crystal structure determination was performed using a Bruker Kappa Apex Duo automated single crystal diffractometer.

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 (DCM) 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, MandyPhos **1.57**, and 1,1'-Bis(diisopropylphosphino)ferrocene were purchased from Strem Chemicals, Inc. and used without further purification. 1,3-Bis(diphenylphosphino)propane was purchased from TCI and used without further purification. Acenaphthylene-1,2-dione, 4-methoxyphenyl trifluoromethanesulfonate, phenyl trifluoromethanesulfonate, and cesium fluoride were purchased from Oakwood Chemicals and used without further purification. Potassium trifluoromethanesulfonate was purchased from Oakwood Chemicals and dried by heating (100 ºC) under vacuum overnight. Alkenyl boronic acids were prepared by hydroboration of alkynes with $HBBr_2$ followed by hydrolysis.[49] All other reagents were purchased from Aldrich, Alfa Aesar, Acros, Combi Blocks, or Oakwood Chemicals and used without further purification.

[49] Holt, D.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2015**, *54*, 7857-7861

1.3.2 Experimental Procedures

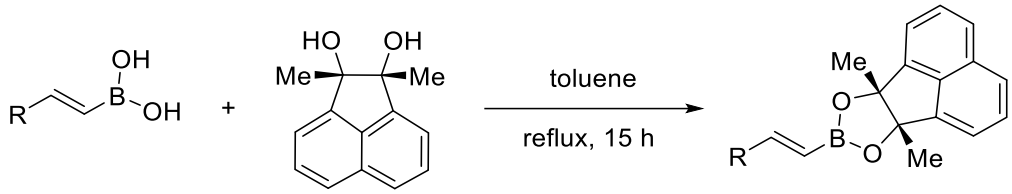
Preparation of 1,2-dimethyl-1,2-dihydroacenaphthylene-1,2-diol (mac) (1.77)



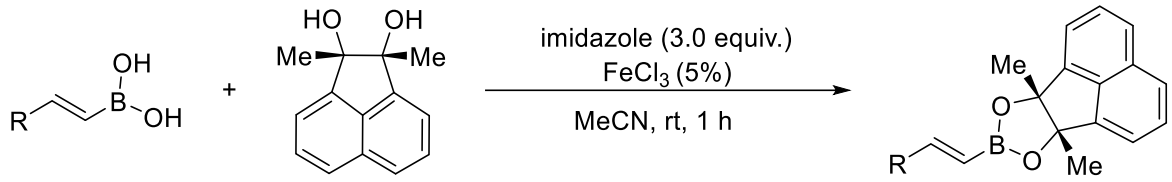
A flame-dried 3-neck 1000 mL RBF was equipped with stir bar, a reflux condenser fitted to the middle neck, and the other two necks were sealed with rubber septa. Acenaphthoquinone (18.22 g, 100 mmol) was added, and the flask was evacuated and backfilled with nitrogen. Dry toluene (100.0 mL, [substrate] = 1.00 M) was added via syringe, and the yellow suspension was stirred at 40 ºC. Trimethyl aluminum (20.1 mL, 210.0 mmol, 2.1 equiv.) was added dropwise via syringe (a 12 mL syringe was used to transfer 5 mL aliquots dropwise). Upon completion of addition, the reaction was allowed to stir for 1 hour at 40 ºC, then cooled to 0 ºC and quenched very slowly with 40 ml H_2O and 20 ml 1M HCl (caution: gas evolution). The reaction was diluted with EtOAc and filtered through a frit funnel, then the filtrate was poured into separatory funnel containing water (200 mL). The organic layer was washed three times with EtOAc (300 mL) then the combined organic layers were washed 3 times with brine, then dried over Na_2SO4, filtered, and concentrated. ^{1}H NMR analysis of the crude material indicates ~4.3:1 syn:anti diol. The crude product was dissolved in hot EtOAc (750 mL) and stored at -20 ºC overnight. The resulting precipitate was collected by filtration and rinsed with pentane to yield *syn*-1,2-dimethyl-1,2-dihydroacenaphthylene-1,2-diol as off-white crystals (11.5 g, 53.7 mmol, 54% yield). Suspected losses in yield due to insolubility when transferring between vessels. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74 (d, J = 8.2 Hz, 2H), 7.56 (t, J = 7.5 Hz, 2H), 7.48 (d, J = 6.9 Hz, 2H), 2.97 (s, 2H), 1.63 (s, 6H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 146.36, 134.51, 131.34, 128.68, 125.07, 119.33, 82.38,

23.53.; HRMS (DART) for $C_{14}H_{13}O$ $[M+H-H_2O]^+$: calculated: 197.0961, found: 197.0956.

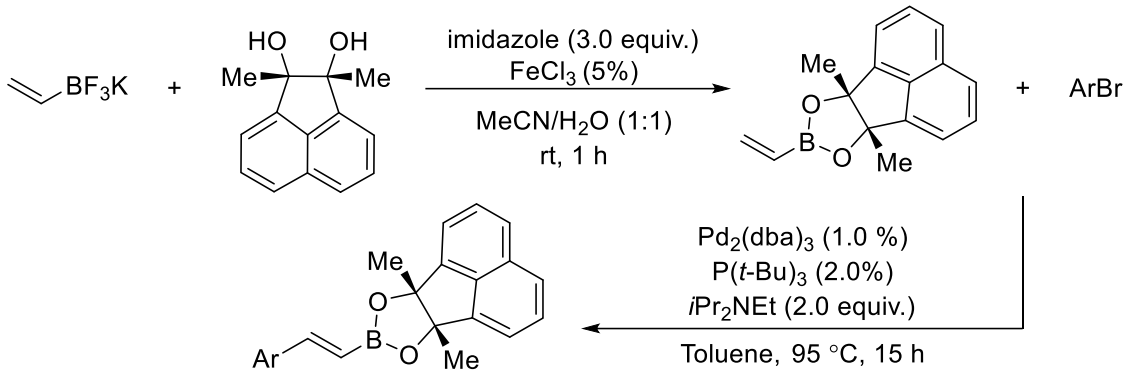
Procedures for the preparation of alkenyl boronic esters



Method A: To a 100-mL RBF equipped with a stir bar was added alkenyl boronic acid (3.0 mmol, 1.0 equiv.) and toluene (12 mL). 1,2-Dimethylacenaphthylene-1,2-diol (3.0 mmol, 1.0 equiv.) was added and a Dean-Stark apparatus equipped with a reflux condenser was attached to the flask. The reaction was heated to reflux for 15 hours then concentrated under vacuum. The crude product was purified by silica gel chromatography to afford the desired product. *This method can be used to synthesize boronic esters containing other diol ligands.*



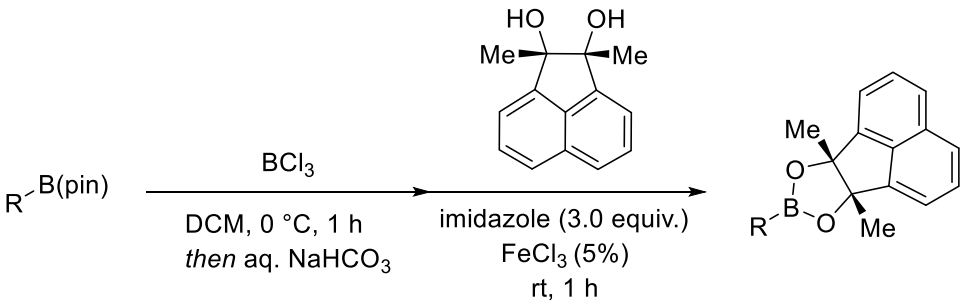
Method B: According to a modified literature procedure.[48] To a scintillation vial equipped with a stir bar was added alkenyl boronic acid (3.0 mmol, 1.0 equiv.) and MeCN (12.00 mL). To this solution was added sequentially 1,2-dimethylacenaphthylene-1,2-diol (3.00 mmol, 1.0 equiv.), imidazole (9.00 mmol, 3 equiv.), and $FeCl_3$ (60.00 µmol, 0.05 equiv.). The reaction was then stirred at room temperature open to air for 1 hour before being filtered through a pad of silica gel with Et_2O. The crude product was purified by silica gel chromatography to afford the desired product. *This method can be used to synthesize boronic esters containing other diol ligands.*



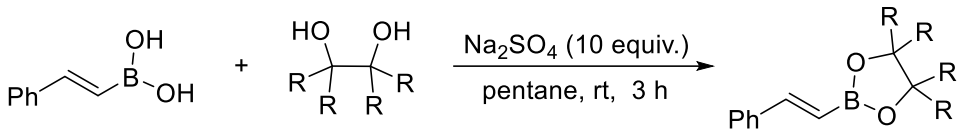
***Method C*:** VinylB(mac) was prepared according to a modified literature procedure, as follows.[48] To a solution of vinyl potassium trifluoroborate (343.9 mg, 2.57 mmol, 1.0 equiv.) in 50% acetonitrile/water (5 mL) was added sequentially open to air at room temperature, 1,2-dimethylacenaphthylene-1,2-diol (550 mg, 2.57 mmol, 1.0 equiv.), imidazole (524.3 mg, 7.70 mmol, 3.0 equiv.), and $FeCl_3$ (20.8 mg, 0.128 mmol, 0.05 equiv.). The reaction was allowed to stir 30 minutes, then filtered through a plug of silica gel with Et_2O and concentrated. The crude material was purified by silica gel column chromatography to afforded the desired product (typically 90% yield). The Heck reaction was carried out according to a modified literature procedure.[50] In an argon-filled glovebox, vinylB(mac) (750.30 mg, 3 mmol, 1.0 equiv.), aryl bromide (3.30 mmol, 1.1 equiv.), N,N-diisopropylethylamine (1.05 mL, 6.00 mmol, 2.0 equiv.), tris(dibenzylideneacetone)dipalladium(0) (27.47 mg, 30.00 µmol, 1.0 mol%), tri-*tert*-butylphosphine (10% weight in hexanes, 121.39 mg, 60.00 µmol, 2.0 mol%), and toluene (6.00 mL) were added to an oven-dried scintillation vial equipped with a stir-bar. The vial was sealed and removed from the glovebox. The reaction was then heated to 95 ºC overnight, filtered through a plug of silica gel with Et_2O, and concentrated. The crude product was purified by column

[50] Liu, Z.; Wei, W.; Xiong, L.; Feng, Q.; Shi, Y.; Wang, N.; Yu, L. *New J. Chem*. **2017**, *41*, 3172-3176

chromatography with silica gel. *This method can be used to synthesize boronic esters containing other diol ligands.*



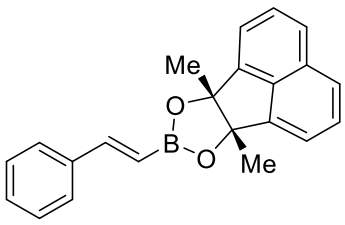
Method D: Boron trichloride (1 M solution in DCM, 17.5 mL, 17.5 mmol, 5.0 equiv.) was added to a solution of boronic acid pinacol ester (3.5 mmol, 1.0 equiv.) in DCM (3.50 mL) at – 78 ºC. The mixture was stirred at 0 ºC for 1 hour, then quenched with saturated aqueous sodium bicarbonate solution (3.5 mL), and the reaction was warmed to room temperature. To this solution was added 1,2-dimethylacenaphthylene-1,2-diol (3.5 mmol, 1.0 equiv.), imidazole (10.5 mmol, 3.0 equiv.), and $FeCl_3$ (0.18 mmol, 0.05 equiv.). The reaction was stirred for 1 hour at room temperature then filtered through a plug of silica gel with Et_2O and concentrated. The crude product was purified by column chromatography with silica gel. *This method can be used to synthesize boronic esters containing other diol ligands.*



Method E: To a 100-mL RBF equipped with a stir bar was added alkenyl boronic acid (3.0 mmol, 1.0 equiv.) and pentane (12 mL, 0.25 M). The diol (3.0 mmol, 1.0 equiv.) was added followed by anhydrous sodium sulfate (30 mmol, 10.0 equiv.). The reaction was allowed to stir at room temperature for 3 hours, then the reaction mixture was filtered through a cotton plug with Et_2O and concentrated. The crude product was purified by silica gel chromatography to afford the desired product.

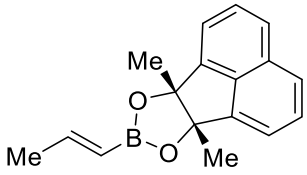
***When to Use Each Method*:**

In instances when boronic acids or potassium trifluoroborates are readily available, Method B is preferred due to operational simplicity, reaction efficiency, and simple product purification. However, if the substrate contains acid-sensitive functionality then Method A or Method E should be used instead. Additionally, if the resulting boronic ester is not stable to silica gel chromatography, then Method E is preferred. In instances when a pinacol boronic ester is more easily obtained than the corresponding boronic acid, Method D is utilized (this method should be avoided if the substrate contains acid-sensitive functionality). Method B is utilized for the synthesis of styrenyl boronic esters as an alternative to the hydroboration of terminal alkynes.



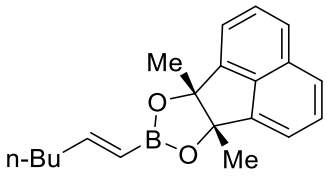
6b,9a-dimethyl-8-((E)-styryl)-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (1.79). The title compound was prepared according to Method A with [(E)-styryl]boronic acid (500 mg, 3.38 mmol, 1.0 equiv.), 1,2-dimethylacenaphthylene-1,2-diol (723 mg, 3.38 mmol, 1.0 equiv.), and toluene (15 mL). The crude product was purified by silica gel chromatography with 5-10% EtOAc / hexane to yield the title compound (1.05 g, 3.21 mmol, 95% yield) as a white solid.

The title compound was also prepared according to Method B with [(E)-styryl]boronic acid (443.90 mg, 3 mmol, 1.0 equiv.), MeCN (12 mL), $FeCl_3$ (24.33 mg, 150 µmol, 0.05 equiv.), imidazole (612.72 mg, 9.00 mmol, 3.0 equiv.), and 1,2-dimethylacenaphthylene-1,2-diol (642.78 mg, 3.00 mmol, 1.0 equiv.). The crude product was purified by silica gel chromatography with 5-10% EtOAc / hexane to yield the title compound (881 mg, 2.70 mmol, 90% yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (dd, J = 6.9, 2.1 Hz, 2H), 7.67 – 7.57 (m, 4H), 7.42 (d, J = 7.2 Hz, 2H), 7.36 (d, J = 18.4 Hz, 1H), 7.33 – 7.23 (m, 3H), 6.10 (d, J = 18.4 Hz, 1H), 1.85 (s, 6H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 152.4, 147.4, 140.1, 137.4, 134.1, 131.5, 131.2, 131.2, 129.7, 128.0, 122.2, 94.7, 79.9, 79.7, 79.5, 24.8.; ^{11}B NMR: (160 MHz, $CDCl_3$) δ 30.3.; IR (neat) ν_{max} 3024.6 (w), 2972.4 (w), 2932.9 (w), 1622.7 (s), 1450.0 (m), 1433.7 (m), 1313.1 (s), 1139.6 (s), 788.5 (m), 480.5 (m) cm^{-1}. HRMS (DART) for $C_{22}H_{20}BO_2$ $[M+H]^+$ calculated: 327.1556, found: 327.1543.



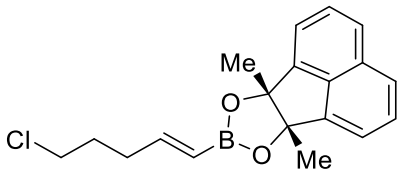
6b,9a-dimethyl-8-((E)-prop-1-en-1-yl)-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (S-1). The title compound was prepared according to Method B with [(E)-prop-1-

enyl]boronic acid (379 mg, 4.41 mmol, 1.0 equiv.), MeCN (11 mL), 1,2-dimethylacenaphthylene-1,2-diol (1.35 g, 4.41 mmol, 1.0 equiv.), imidazole (901 mg, 13.2 mmol, 3.0 equiv.), and FeCl3 (36 mg, 221 μmol, 0.05 equiv.). The crude product was purified by silica gel chromatography with 5-10% EtOAc / hexane to yield the title compound (1.12 g, 4.24 mmol, 96% yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, J = 8.1 Hz, 2H), 7.65 – 7.52 (m, 4H), 6.69 – 6.56 (m, 1H), 5.40 (d, J = 17.8 Hz, 1H), 1.84 – 1.74 (m, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.98, 144.8, 134.7, 131.3, 128.4, 125.2, 119.4, 91.7, 22.1, 21.6. ^{11}B NMR: (160 MHz, $CDCl_3$) δ 29.9; IR (neat) ν_{max} 3044.5 (w), 2973.6 (m), 2933.7 (w), 1639.4 (s), 1347.6 (m), 1214.4 (m), 1077.7 (m), 777.8 (m) cm^{-1}. HRMS (DART) for for $C17H18BO_2$ $[M+H]^+$: calculated: 265.1400, found: 265.1393.

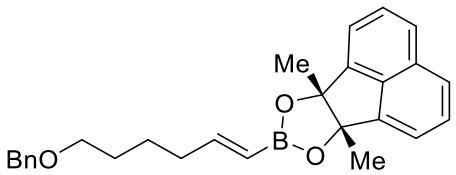


8-((E)-hex-1-en-1-yl)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (S-2). The title compound was prepared according to Method B with [(E)-hex-1-enyl]boronic acid (213 mg, 1.67 mmol, 1.0 equiv.), MeCN (6.7 mL), 1,2-dimethylacenaphthylene-1,2-diol (357 g, 1.67 mmol, 1.0 equiv.), imidazole (340 mg, 5.00 mmol, 3.0 equiv.), and $FeCl_3$ (13.5 mg, 83 μmol, 0.05 equiv.). The crude product was purified by silica gel chromatography with 5-10% EtOAc / hexane to yield the title compound (465 mg, 1.52 mmol, 91% yield) as a yellow oil which solidified upon standing. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (dd, J = 7.9, 1.1 Hz, 2H), 7.65 – 7.51 (m, 4H), 6.61 (dt, J = 18.0, 6.5 Hz, 1H), 5.38 (d, J = 17.9 Hz, 1H), 2.14 – 2.06 (m, 2H), 1.81 (s, 6H), 1.41 – 1.21 (m, 4H), 0.85 (t, J = 7.2 Hz, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.0, 144.9, 134.7, 131.3, 128.4, 125.2, 119.4, 91.7, 35.4, 30.3, 22.2, 22.1, 13.9. ^{11}B NMR: (160 MHz, $CDCl_3$) δ 30.0; IR (neat) ν_{max} 3045.2 (w), 2956.9 (m), 2928.2 (m), 2856.8 (w), 1638.0 (m),

1355.2 (m), 1310.6 (m), 1116.4 (m), 1078.4 (m), 805.8 cm^{-1}. HRMS (DART) for $C_{20}H_{24}BO_2$ $[M+H]^+$: calculated: 307.1869, found: 307.1882.

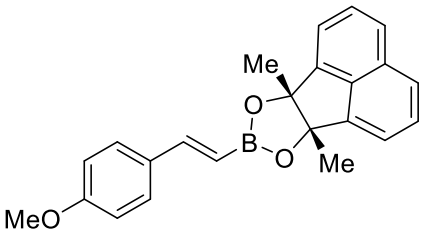


8-((E)-5-chloropent-1-en-1-yl)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (S-3). The title compound was prepared according to Method B with (E)-(5-chloropent-1-en-1-yl) boronic acid (367 mg, 2.46 mmol, 1.0 equiv.), MeCN (13 mL), 1,2-dimethylacenaphthylene-1,2-diol (527 mg, 2.46 mmol, 1.0 equiv.), imidazole (503 mg, 7.39 mmol, 3.0 equiv.), and $FeCl_3$ (20 mg, 123 μmol, 0.05 equiv.). The crude product was purified by silica gel chromatography with 5-10% EtOAc / hexane to yield the title compound (530 mg, 1.62 mmol, 66% yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (dt, *J* = 8.0, 1.1 Hz, 2H), 7.63 – 7.53 (m, 4H), 6.59 – 6.50 (m, 1H), 5.42 (dq, *J* = 17.9, 1.5 Hz, 1H), 3.50 – 3.45 (m, 2H), 2.28 – 2.21 (m, 2H), 1.88 – 1.81 (m, 2H), 1.80 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 152.5, 144.9, 134.8, 131.5, 128.6, 125.4, 119.6, 91.9, 44.4, 32.8, 31.0, 22.2. ^{11}B NMR: (160 MHz, $CDCl_3$) δ 29.73; IR (neat) ν_{max} 3042.8 (w), 2975.0 (w), 2933.3 (w), 1637.7 (m), 1347.5 (m), 1311.14 (m), 1114.9 (m), 1076.1 (m), 825.3 (m), 777.6 (s), 640.4 (m) cm^{-1}. HRMS (DART) for $C_{19}H_{20}BClO_2$ $[M+H]^+$ calculated: 327.1323, found: 327.1334.



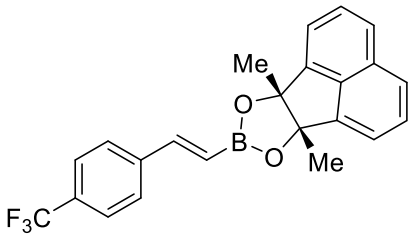
8-((E)-6-(benzyloxy)hex-1-en-1-yl)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (S-4). The title compound was prepared according to Method B with (E)-(6-(benzyloxy)hex-1-en-1-yl)boronic acid (497 mg, 2.12 mmol, 1.0 equiv.), MeCN (13 ml), 1,2-dimethylacenaphthylene-1,2-diol (453 mg, 2.12 mmol, 1.0 equiv.), imidazole (433 mg,

6.37 mmol, 3.0 equiv.) and $FeCl_3$ (17.2 mg, 106 μmol, 0.05 equiv.). The crude product was purified by silica gel chromatography with 5-10% EtOAc / hexane to yield the title compound (629 mg, 1.53 mmol, 72% yield) as a thick, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 – 7.76 (m, 2H), 7.63 – 7.54 (m, 4H), 7.39 – 7.26 (m, 5H), 6.65 – 6.55 (m, 1H), 5.42 – 5.35 (m, 1H), 4.47 (s, 2H), 3.46 – 3.40 (m, 2H), 2.16 – 2.07 (m, 2H), 1.81 (s, 6H), 1.64 – 1.53 (m, 2H), 1.51 – 1.42 (m, 2H) ^{13}C NMR (151 MHz, $CDCl_3$) δ 154.5, 144.9, 138.7, 134.7, 131.4, 128.5, 128.4, 127.6, 127.5, 125.3, 119.5, 91.7, 72.9, 70.2, 35.5, 29.3, 24.8, 22.2. ^{11}B NMR: (160 MHz, $CDCl_3$) δ 29.94; IR (neat) ν_{max} 3031.0 (w), 2972.4 (w), 2932.6 (w), 2855.4 (w), 1637.1 (m), 1354.9 (m), 1339.4 (m), 1114.4 (m), 1076.0 (m), 805.8 (m), 777.9 (m), 733.4 (m), 696.6 (m), 641.8 (m) cm^{-1}. HRMS (DART) for $C_{27}H_{29}BO_3$ $[M+H]^+$ calculated: 413.2288, found:413.2304.

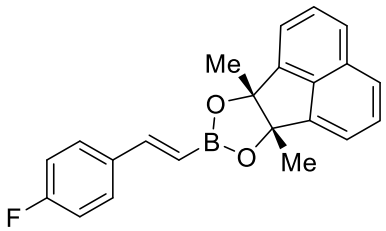


8-((E)-4-methoxystyryl)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (S-5). The title compound was prepared according to Method B with [(E)-2-(4-methoxyphenyl)vinyl]boronic acid (186 mg, 1.04 mmol, 1.0 equiv.), MeCN (4.2 mL), 1,2-dimethylacenaphthylene-1,2-diol (223.49 mg, 1.04 mmol, 1.0 equiv.), imidazole (213 mg, 3.13 mmol, 3.0 equiv.), and $FeCl_3$ (8.5 mg, 52.2 μmol, 0.05 equiv.). The crude product was purified by silica gel chromatography with 5-10% EtOAc / hexane to yield the title compound (353 mg, 0.99 mmol, 95% yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (dd, J = 6.7, 2.2 Hz, 2H), 7.65 – 7.56 (m, 4H), 7.40 – 7.35 (m, 2H), 7.32 (d, J = 18.4 Hz, 1H), 6.83 (d, J = 8.5 Hz, 2H), 5.95 (d, J = 18.3 Hz, 1H), 3.79 (s, 3H), 1.85 (s, 6H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.2, 149.2, 144.78, 134.7, 131.4, 130.3, 128.5, 128.4, 125.3, 119.4, 113.9, 91.9, 55.2, 22.1. ^{11}B NMR: (160 MHz, $CDCl_3$) δ 31.0.; IR (neat) ν_{max} 3041.3 (w),

2972.0 (w), 2932.7 (w), 2836.1 (w), 1623.7 (m), 1603.1 (m), 1509.4 (m), 1312.9 (m), 1252.7 (m), 1116.0 (m), 1077.2 (m), 815.7 (m) cm^{-1}. HRMS (DART) for $C_{23}H_{22}BO_3$ $[M+H]^+$: calculated: 357.1662, found: 357.1664.

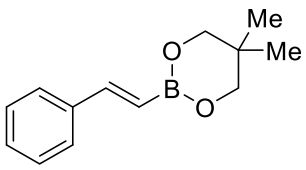


6b,9a-dimethyl-8-((E)-4-(trifluoromethyl)styryl)-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (S-6). The title compound was prepared according to Method B with [(E)-2-[4-(trifluoromethyl)phenyl]vinyl]boronic acid (164 mg, 0.76 mmol, 1.0 equiv.), MeCN (3.0 mL), 1,2-dimethylacenaphthylene-1,2-diol (163 mg, 0.76 mmol, 1.0 equiv.), imidazole (155 mg, 2.28 mmol, 3.0 equiv.), and $FeCl_3$ (6.2 mg, 38 μmol). The crude product was purified by silica gel chromatography with 5-10% EtOAc / hexane to yield the title compound (276 mg, 0.70 mmol, 92% yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (dt, J = 7.2, 1.6 Hz, 2H), 7.70 – 7.59 (m, 4H), 7.56 (d, J = 8.1 Hz, 2H), 7.50 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 18.3 Hz, 1H), 6.20 (d, J = 18.4 Hz, 1H), 1.87 (s, 6H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.8, 144.5, 140.7, 134.7, 131.4, 130.4 (q, $^2J_{C-F}$ = 32.4 Hz), 128.5, 127.1, 125.5 (q, $^3J_{C-F}$ = 3.8 Hz), 125.4, 124.1 (partially buried, q, $^1J_{C-F}$ = 271.8 Hz), 119.5, 92.2, 29.7, 22.1. ^{11}B NMR: (160 MHz, $CDCl_3$) δ 30.3.; ^{19}F NMR (470 MHz, $CDCl_3$) δ 62.7.; IR (neat) ν_{max} 3045.7 (w), 2974.7 (w), 2929.0 (w), 1626.9 (m), 1457.6 (m), 1415.8 (m), 1263.2 (m), 1210.6 (m), 825.1 (m), 778.6 (m) cm^{-1}. HRMS (DART) for $C_{23}H_{19}BO_2F_3$ $[M+H]^+$: calculated: 395.1430, found: 395.1441.



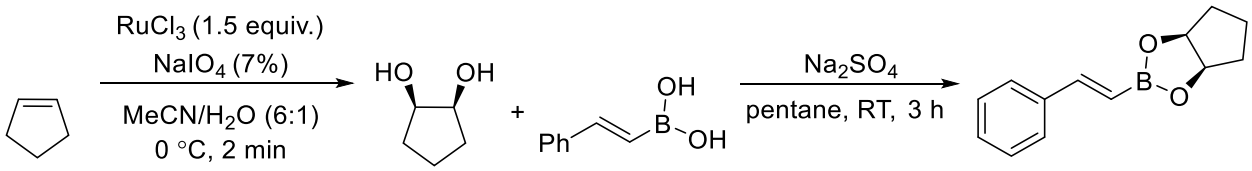
8-((E)-4-fluorostyryl)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (S-7). The title compound was prepared according to Method B with [(E)-2-(4-

fluorophenyl)vinyl]boronic acid (277 mg, 1.67 mmol, 1.0 equiv.), MeCN (6.67 mL), 1,2-dimethylacenaphthylene-1,2-diol (357 mg, 1.67 mmol, 1.0 equiv.), imidazole (304 mg, 5.00 mmol, 3.0 equiv.), and $FeCl_3$ (14 mg, 83.3 μmol, 0.05 equiv.). The crude product was purified by silica gel chromatography with 5-10% EtOAc / hexane to yield the title compound (535 mg, 1.55 mmol, 93% yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (dd, J = 7.1, 1.8 Hz, 2H), 7.66 – 7.56 (m, 4H), 7.46 – 7.36 (m, 2H), 7.32 (d, J = 18.4 Hz, 1H), 7.05 – 6.92 (m, 2H), 6.01 (d, J = 18.4 Hz, 1H), 1.85 (s, 6H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.1 (d, $^1J_{C-F}$ = 248.5 Hz), 148.3, 144.7, 134.7, 133.7, 133.6, 131.4, 128.6 (d, $^3J_{C-F}$ = 8.2 Hz), 128.5, 125.3, 119.5, 115.5 (d, $^2J_{C-F}$ = 21.6 Hz), 92.0, 22.1. ^{11}B NMR: (160 MHz, $CDCl_3$) δ 30.1; ^{19}F NMR: (470 MHz, $CDCl_3$) δ -112.41; IR (neat) ν_{max} 3045.2 (w), 2976.5 (m), 2933.9 (w), 1620.8 (m), 1506.5 (m), 1415.7 (m), 1156.6 (m), 904.0 (m), 778.7 (m) cm^{-1}. HRMS (DART) for $C_{22}H_{19}BO_2F$ $[M+H]^+$: calculated: 345.1462, found: 345.1470.

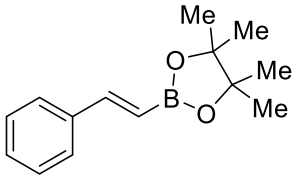


(E)-5,5-dimethyl-2-styryl-1,3,2-dioxaborinane (S-8). The title compound was prepared according to Method E using neopentyl glycol (208 mg, 2.00 mmol, 1 equiv.), (E)-styrylboronic acid (296 mg, 2.00 mmol, 1.0 equiv.), and pentane (20 mL). The crude product was purified by silica gel chromatography with 10% EtOAc / hexanes to yield the title compound (278 mg, 1.29 mmol, 64% yield) as a white solid. Spectral data are in accordance with the literature.[51]

[51] Kobayashi, Y.; Nakayama, Y.; Mizojiri, R. *Tetrahedron* **1998**, *54*, 1053-1062



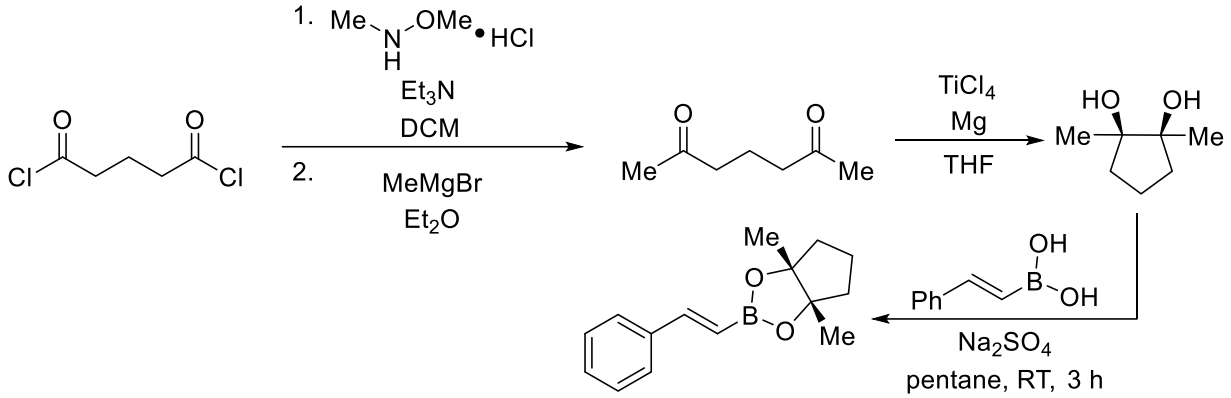
(E)-2-styryltetrahydro-4H-cyclopenta[d][1,3,2]dioxaborole (S-9). The title compound was prepared according to Method E using *syn*-cyclopentane-1,2-diol (prepared using a literature procedure[52]) (109 mg, 1.07 mmol, 1 equiv.) with (E)-styrylboronic acid (158.3 mg, 1.07 mmol, 1 equiv.) and pentane (4 mL). The mixture was allowed to stir overnight in a sealed vial at room temperature. The crude product was purified by silica gel chromatography with 10% EtOAc: hexanes to yield the title compound (174 mg, 0.812 mmol, 76%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 – 7.47 (m, 2H), 7.40 (d, J = 18.5 Hz, 1H), 7.37 – 7.32 (m, 2H), 7.32 – 7.28 (m, 1H), 6.17 (d, J = 18.5 Hz, 1H), 4.97 – 4.86 (m, 2H), 2.03 – 1.94 (m, 2H), 1.74 – 1.55 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.9, 137.6, 129.1, 128.7, 127.2, 82.5, 34.9, 21.7. ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.2.; IR (neat) ν_{max} 3025.0 (w), 2960.5 (w), 1622.4 (m), 1357.7 (s), 1032.5 (m), 746.8 (s) cm^{-1}. HRMS (DART) for $C_{13}H_{16}BO_2$ $[M+H]^+$ calculated: 215.1243, found: 215.1252.



(E)-4,4,5,5-tetramethyl-2-styryl-1,3,2-dioxaborolane (S-10). The title compound was prepared according to a literature procedure[53] using phenylacetylene (2.14 mg, 21.00 mmol, 1.05 equiv.), pinacolborane (2.56 g, 20.0 mmol, 1.0 equiv.) and Bis(cyclopentadienyl)zirconium(IV) chloride hydride (258 mg, 1 mmol, 0.05 equiv.). The crude product was purified by silica gel chromatography with 5-

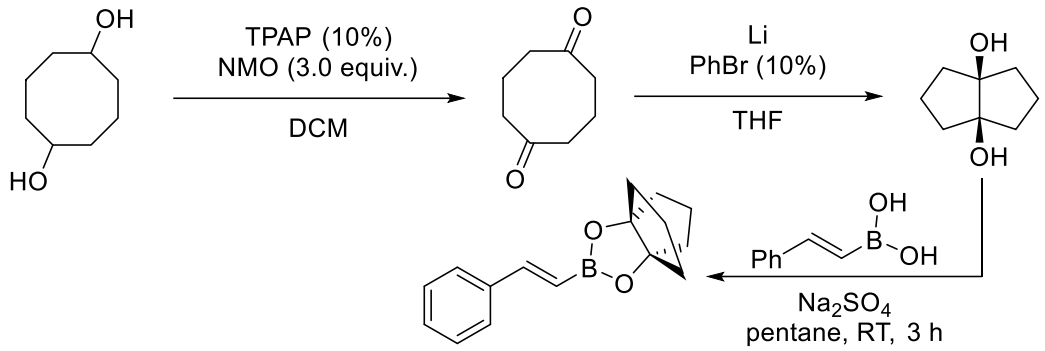
[52] Shing, T. K. M.; Tam, E. K. W.; Tai, V. W.-F.; Chung, I. H. F.; Jiang, Q. *Chem. Eur. J*. **1996**, *2*, 50-57
[53] Pereira, S.; Srebnik, M. *Organometallics* **1995**, *14*, 3127-3128

10% EtOAc / hexanes to yield the title compound (4.25 mg, 18.4 mmol, 92% yield) as a white solid. Spectral data are in accordance with the literature.[54]

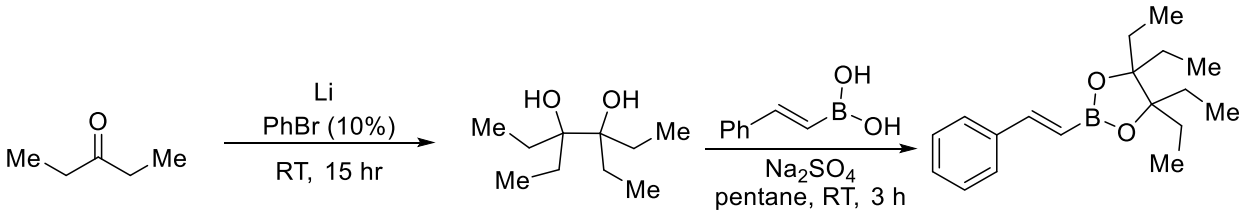


(E)-3a,6a-dimethyl-2-styryltetrahydro-4H-cyclopenta[d][1,3,2]dioxaborole (S-11). The title compound was prepared according to a series of literature reactions[55, 56], then Method E using the cis-1,2-dimethylcyclopentane-1,2-diol (38.6 mg, 296 µmol, 1.0 equiv.) with (E)-styrylboronic acid (43.9 mg, 296 µmol, 1.0 equiv.), and pentane (1 mL). The crude product was purified by silica gel chromatography with 10% EtOAc / hexanes to yield the title compound as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.51 – 7.46 (m, 2H), 7.40 – 7.27 (m, 4H), 6.15 (d, J = 18.4 Hz, 1H), 2.05 (dd, J = 12.9, 5.5 Hz, 2H), 1.69 – 1.50 (m, 4H), 1.37 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 149.4, 137.7, 129.0, 128.7, 127.2, 90.6, 42.0, 23.4, 21.4. ^{11}B NMR (160 MHz, $CDCl_3$) δ 29.7.; IR (neat) ν_{max} 2966.4 (w), 1623.2 (m), 1353.0 (s). HRMS (DART) for $C_{15}H_{19}BO_2$ $[M+H]^+$ calculated: 243.1556, found: 243.1563.

[54] Tucker, C. E.; Davidson, J.; Knochel, P. *J. Org. Chem*. **1992**, *57*, 3482-3485
[55] Doi, R.; Shibuya, M.; Murayama, T.; Yamamoto, Y.; Iwabuchi, Y. *J. Org. Chem*. **2015**, *80*, 401-413
[56] Chanteau, S. H.; Tour, J. M. *J. Org. Chem.* **2003**, *68,* 8750-8766

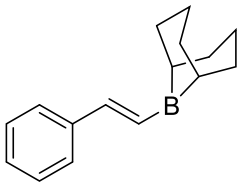


8-((E)-styryl)tetrahydro-1H,4H-3a,6a-(epoxyboranooxy)pentalene (S-12). The title compound was prepared according to Method E with (E)-styrylboronic acid (70.5 mg, 477 μmol, 1.0 equiv.), tetrahydropentalene-3a,6a(1H,4H)-diol (67 mg, 477 μmol, 1.0 equiv.) and 1 mL of pentane. The crude product was purified by silica gel chromatography with 5% EtOAc / hexanes to the yield the title compound (121.1 mg, 338 μmol, 71% yield) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.51 – 7.47 (m, 2H), 7.39 (d, *J* = 18.4 Hz, 1H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.29 (t, *J* = 7.3 Hz, 1H), 6.15 (d, *J* = 18.4 Hz, 1H), 2.02 – 1.96 (m, 4H), 1.87 – 1.78 (m, 2H), 1.75 – 1.61 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.6, 137.6, 129.0, 128.7, 127.2, 99.8, 39.0, 25.0. ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.7.; IR (neat) ν_{max} 3025.0 (w), 2960.5 (w), 1622.4 (m), 1357.7 (s), 1032.5 (m), 746.8 (m). HRMS (DART) for $C_{16}H_{19}BO_2$ $[M+H]^+$ calculated: 255.1556 found: 255.1552.



(E)-4,4,5,5-tetraethyl-2-styryl-1,3,2-dioxaborolane (S-13). The title compound was prepared according to Method E using 3,4-diethylhexane-3,4-diol (prepared according to a literature

procedure[57]) (79.5 mg, 0.46 mmol, 1.0 equiv.), (E)-styrylboronic acid (67.5 mg, 0.46 mmol, 1.0 equiv.) and pentane (1.5 mL). The crude product was purified by silica gel chromatography with 10% EtOAc / hexanes to yield the title compound (115 mg, 0.40 mmol, 88%) as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 – 7.48 (m, 2H), 7.41 (d, J = 18.4 Hz, 1H), 7.36 – 7.32 (m, 2H), 7.31 – 7.27 (m, 1H), 6.20 (d, J = 18.3 Hz, 1H), 1.80 – 1.67 (m, 8H), 0.96 (t, J = 7.5 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.4, 137.8, 128.9, 128.7, 127.2, 88.5, 26.6, 9.0. ^{11}B NMR (192 MHz, $CDCl_3$) δ 29.1.; IR (neat) ν_{max} 2975.3 (w), 2973.5 (w), 2882.9 (w), 1624.2 (m), 1346.2 (s) cm^{-1}. HRMS (DART) for $C_{18}H_{27}BO_2$ $[M+H]^+$ calculated: 287.2182, found: 287.2189.



(E)-9-styryl-9-borabicyclo[3.3.1]nonane (S-14). In an argon-filled glovebox, to an oven-dried scintillation vial was added phenylacetylene (102.13 mg, 1 mmol, 1.0 equiv.), followed by 9-borabicyclo[3.3.1]nonane (0.5 M solution in THF, 2.00 mL, 1.0 mmol, 1.0 equiv.). The solution was allowed to stir for 3 hours at room temperature then used without further purification as a ~0.5 M solution in THF.

Procedure for boron 'ate' complex NMR studies

In an argon-filled glovebox, boronic ester (0.2 mmol, 1.0 equiv.) and THF (0.4 mL) were added to an oven-dried 2-dram vial with stir bar. The vial was sealed with a septum cap and removed from the glovebox, then cooled to 0 ºC. The organolithium reagent (0.2 mmol, 1.0 equiv.) was added dropwise and reaction was allowed to stir at room temperature for 15 minutes before the solvent was carefully removed under vacuum. The vial was brought back into the glovebox and

[57] Zhao, H.; Li, D.-J.; Deng, L. Liu, L.; Guo, Q.-X. *Chem. Commun.* **2003**, 506-507

the ‘ate’ complex was dissolved in THF-*d8*, then transferred to an oven-dried NMR tube. The NMR tube was sealed and a ^{1}H NMR spectrum was obtained (Scheme 1.3.5). The NMR tube was then heated to 60 ºC for 12 hours before another ^{1}H NMR spectrum was obtained.

Figure 1.2.1 ^{1}H NMR spectra of boron ‘ate’ complex from nBuB(mac)

^{1}H NMR (500 MHz, THF-d_8)

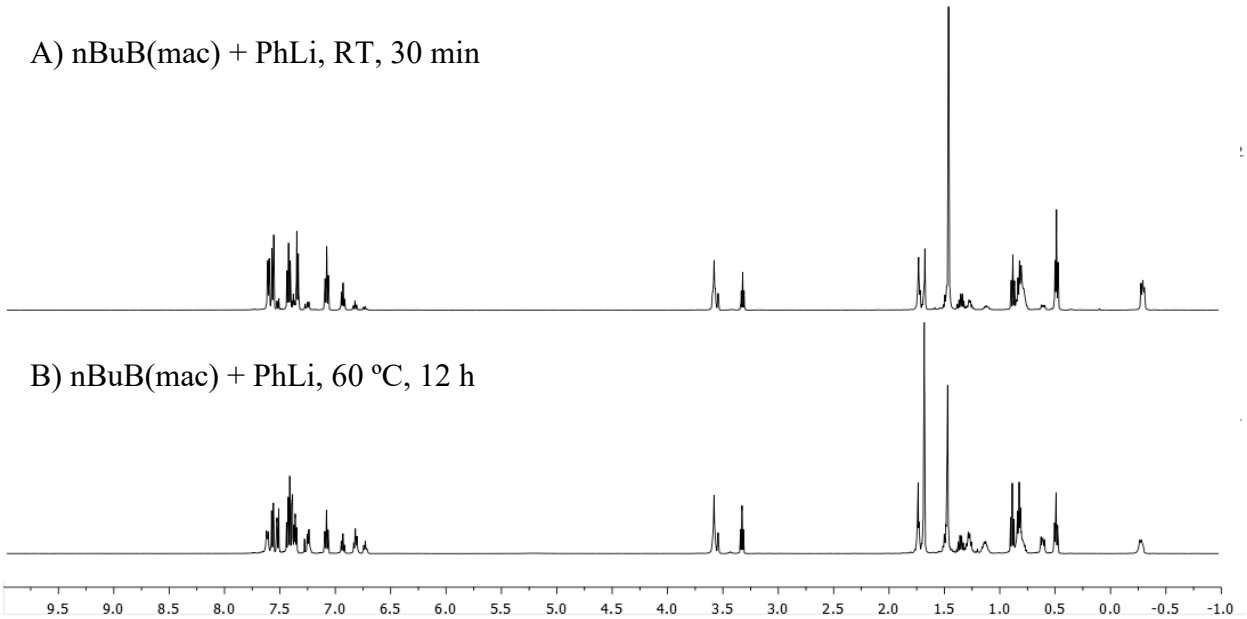


Figure 1.2.1 ^{1}H NMR spectra of boron ‘ate’ complex from PhB(mac)

^{1}H NMR (500 MHz, THF-*d8*)

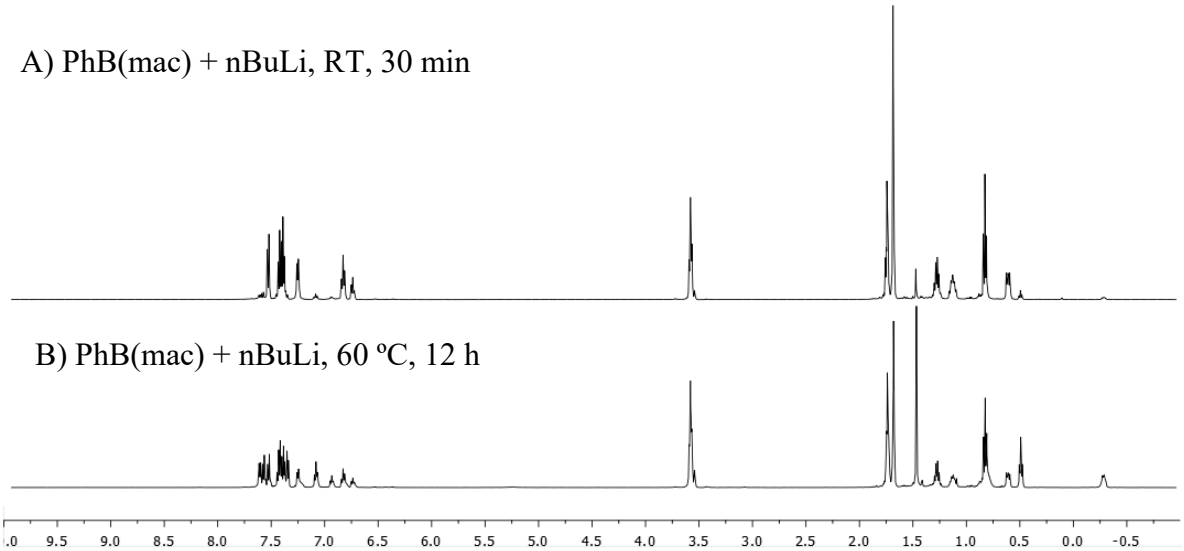
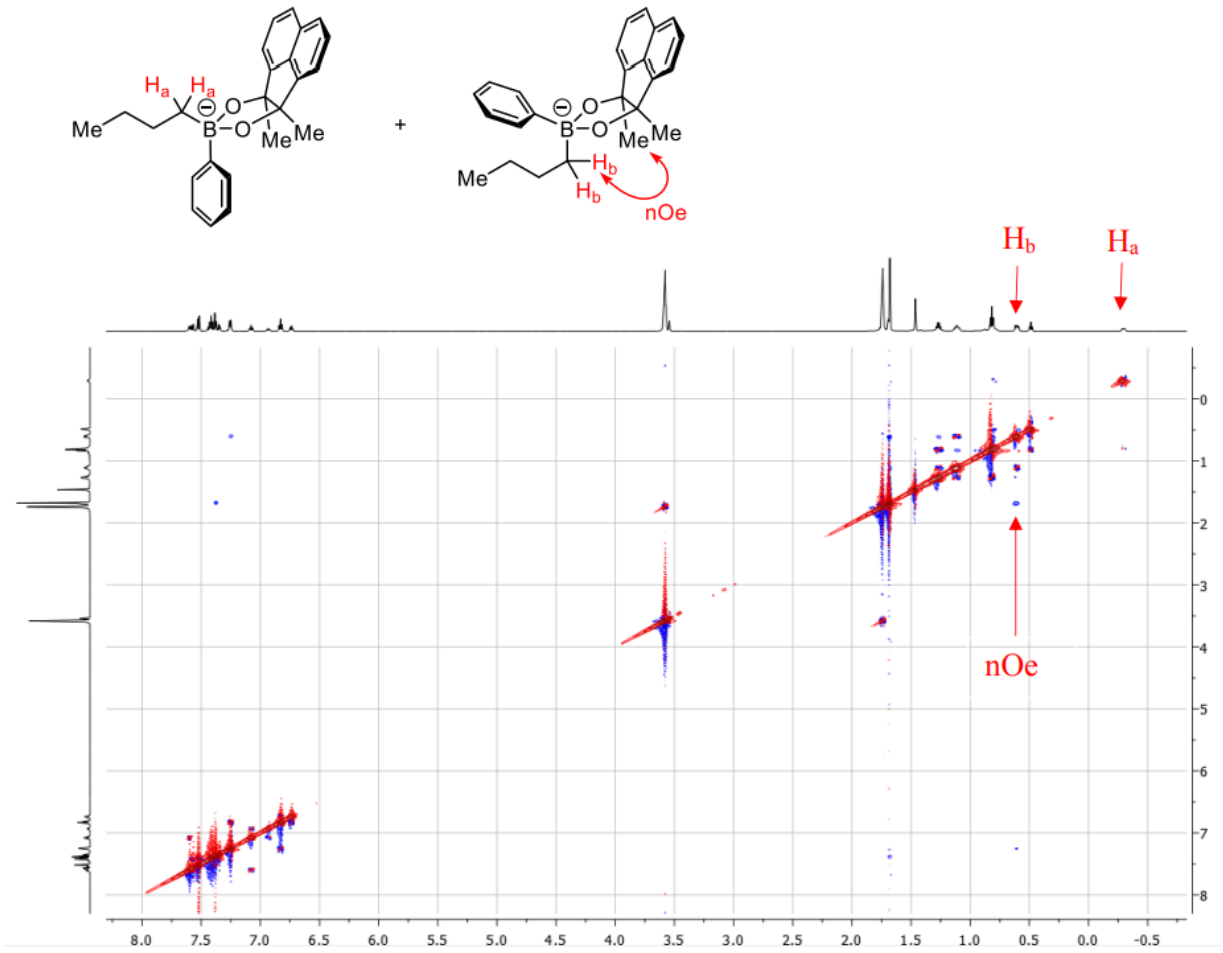
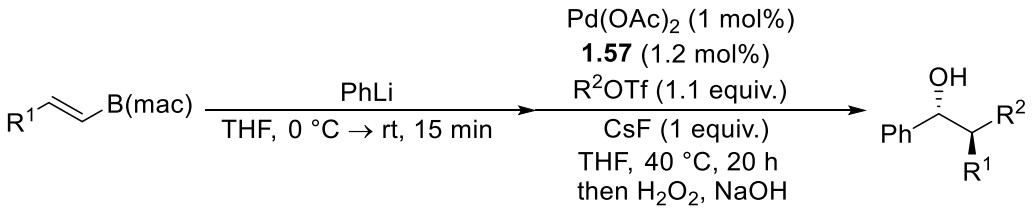


Figure 1.2.2: nOe ^{1}H NMR to Determine Diastereomers of Boron "Ate" Complex



Representative procedure for the conjunctive cross-coupling reaction

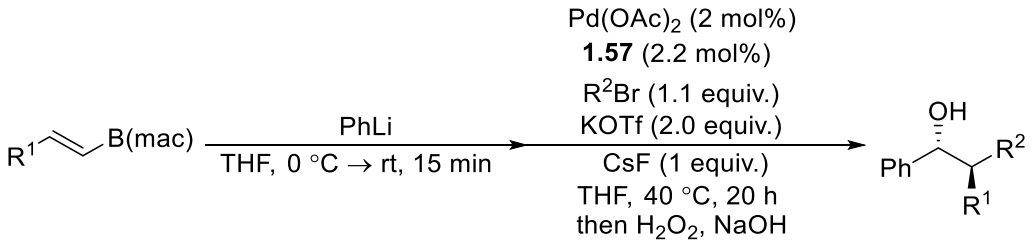
Method A:



To an oven-dried 2-dram vial equipped with a magnetic stir bar in an Ar-filled glovebox was added alkenyl boronic acid "mac" ester (0.20 mmol, 1.00 equiv.) and THF (0.4 mL). The vial was sealed with a septum cap, and removed from the glovebox. The reaction vial was cooled to 0 °C, and a

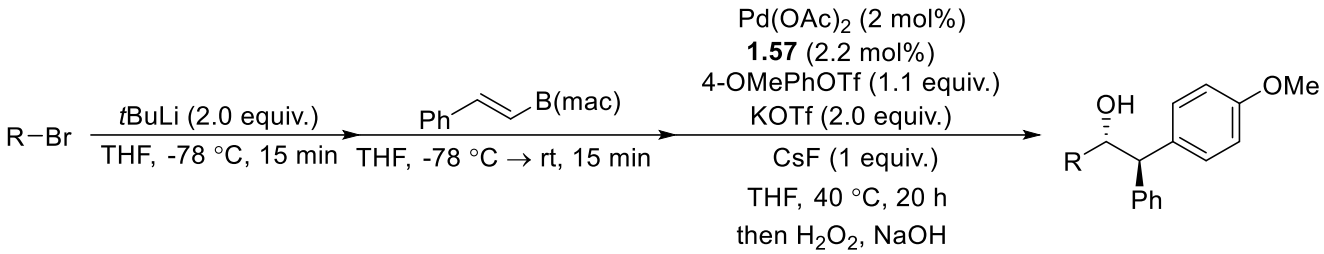
phenyllithium solution (1.9 M in dibutyl ether, 0.20 mmol, 1.0 equiv.) was added at 0 °C. The reaction vial was allowed to warm to room temperature and stirred for 15 minutes, then the solvent was carefully removed under reduced pressure, and the reaction vial was brought back into the glovebox. Cesium fluoride (0.20 mmol, 1.0 equiv.) was added to the reaction vial, followed by THF (0.6 mL), and the vial was stirred at room temperature for 5 minutes. To a separate oven-dried 2-dram vial equipped with a magnetic stir bar in the glovebox was added $Pd(OAc)_2$ (0.002 mmol, 0.01 equiv.), **1.57** (0.0024 mmol, 0.012 equiv.), and THF (0.2 mL). The $Pd(OAc)_2$/**1.57** solution was allowed to stir for 15 minutes at room temperature, then it was transferred into the reaction vial, followed by aryl triflate (0.22 mmol, 1.10 equiv.). The reaction vial was sealed with a polypropylene cap, taped, and brought out of the glovebox where it was allowed to stir at 40 °C for 20 hours. The resulting mixture was cooled to room temperature, filtered through a celite plug with diethyl ether, and concentrated under reduced pressure. The crude product was diluted with THF (3 mL) and cooled to 0 °C before 3M NaOH (2 mL) was added, followed by 30% H_2O_2 (1.0 mL) dropwise. The reaction was allowed to warm to room temperature and stirred for 4 hours, then quenched at 0 °C by dropwise addition of saturated aq. $Na_2S_2O_3$ solution (3 mL). This solution was allowed to stir at room temperature for 10 minutes. The mixture was diluted with Et_2O and transferred to a separatory funnel, and the aqueous layer was washed with Et_2O three times. The combined organic layers were washed with brine then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was subsequently purified via silica gel (treated with 2% triethylamine / hexanes prior to use) column chromatography to afford the desired product.

Method B:



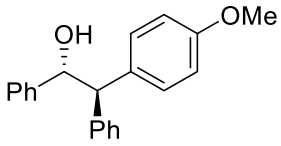
To an oven-dried 2-dram vial equipped with a magnetic stir bar in an Ar-filled glovebox was added alkenyl boronic acid "mac" ester (0.20 mmol, 1.00 equiv.) and THF (0.4 mL), sealed with a septum cap, and removed from the glovebox. The reaction vial was cooled to 0 °C, and a phenyllithium solution (1.9M in dibutyl ether, 0.20 mmol, 1.0 equiv.) was added at 0 °C. The reaction vial was allowed to warm to room temperature and stirred for 15 minutes. Then, the solvent was carefully removed under reduced pressure, and the reaction vial was brought back into the glovebox. Cesium fluoride (0.20 mmol, 1.0 equiv.) was added to the reaction vial, followed by THF (0.4 mL), and the vial was stirred at room temperature for 5 minutes, then potassium trifluoromethanesulfonate (0.40 mmol, 2.0 equiv.) was added. To a separate oven-dried 2-dram vial equipped with a magnetic stirbar in the glovebox was added $Pd(OAc)_2$ (0.004 mmol, 0.020 equiv.), **1.57** (0.0044 mmol, 0.022 equiv.), and THF (0.4 mL). The $Pd(OAc)_2$/**1.57** solution was allowed to stir for 15 minutes at room temperature, then transferred into the reaction vial, followed by aryl/alkenyl bromide (0.22 mmol, 1.10 equiv.). The reaction vial was sealed with a polypropylene cap, taped, and brought out of the glovebox where it was allowed to stir at 40 °C for 20 hours. The same oxidation and purification procedure was done as in Method A.

Method C:



To an oven-dried 2-dram vial equipped with a magnetic stir bar in an Ar-filled glovebox was added aryl/alkenyl bromide (0.20 mmol, 1.00 equiv.) and THF (0.2 mL), and sealed with a septum cap. To a separate oven-dried 1-dram vial was added styrenyl B(mac) (S-1) (0.2 mmol, 1.0 equiv,) and THF (0.4 mL). Both vials were removed from the glove box. The 2-dram reaction vial was cooled to -78 °C, and a *tert*-butyllithium solution (0.40 mmol, 2.0 equiv.) was added dropwise at -78 °C and the reaction was allowed to stir at that temperature for 15 minutes. The solution of styrenyl B(mac) (S-1) from the 1-dram vial was then added to the reaction vial slowly, and the reaction was warmed to room temperature and stirred for 15 minutes, then the solvent was carefully removed under reduced pressure, and the reaction vial was brought back into the glovebox. Cesium fluoride (0.20 mmol, 1.0 equiv.) was added to the reaction vial, followed by THF (0.4 mL), and the vial was stirred at room temperature for 5 minutes, then potassium trifluoromethanesulfonate (0.40 mmol, 2.0 equiv) was added. To a separate oven-dried 2-dram vial equipped with a magnetic stir bar in the glovebox was added $Pd(OAc)_2$ (0.004 mmol, 0.02 equiv.), **1.57** (0.0044 mmol, 0.022 equiv.), and THF (0.4 mL). The $Pd(OAc)_2$/**1.57** solution was allowed to stir for 15 minutes at room temperature then transferred into the reaction vial, followed by and 4-methoxyphenyl trifluoromethanesulfonate (0.22 mmol, 1.10 equiv.). The reaction vial was sealed with a polypropylene cap, taped, and brought out of the glovebox where it was allowed to stir at 40 °C for 20 hours. The same oxidation and purification procedure was done as in Method A.

1.3.3 Characterization of conjunctive cross-coupling products and analysis of stereochemistry



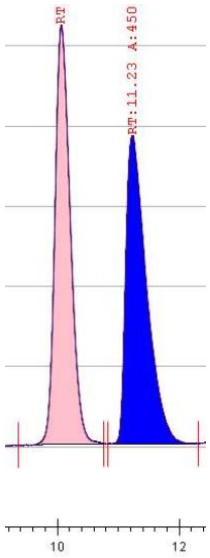
(1R,2R)-2-(4-methoxyphenyl)-1,2-diphenylethan-1-ol (1.84). The reaction was performed according to the general procedure (**Method A**) with styrenyl B(mac) (**1.79**) (65.2 mg, 0.20 mmol, 1.0 equiv.), phenyllithium (1.9 M in dibutyl ether, 0.11 mL, .20 mmol, 1.0 equiv.), 4-methoxyphenyl trifluoromethanesulfonate (56.4 mg, 0.22 mmol, 1.1 equiv.), palladium (II) acetate (0.45 mg, 2.0 μmol, 0.010 equiv.), **1.57** (2.5 mg, 2.4 μmol) , 0.012 equiv.), and cesium fluoride (30.4 mg, 0.2 mmol, 1.0 equiv.) in THF (0.80 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (5-20% EtOAc in hexanes, stain in magic stain) to afford a white solid (46 mg, 76% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ (d, J = 8.2 Hz, 2H), 7.29 – 7.05 (m, 10H), 6.89 (d, J = 8.2 Hz, 2H), 5.36 (d, J = 8.5 Hz, 1H), 4.22 (d, J = 8.5 Hz, 1H), 3.80 (s, 3H), 2.16 (br, 1H).; ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.5, 142.3, 141.9, 132.8, 130.0, 128.5, 128.2, 128.0, 127.5, 126.9, 126.3, 114.2, 76.9, 59.4, 55.2.; IR (neat): ν_{max} 3385.3 (br), 3060.4 (w), 3028.0 (m), 2906.4 (m), 2834.7 (w), 1609.2 (m), 1509.4 (s), 1245.9 (s), 1075.1 (s), 785.0 (m), 697.3 (s), 596.5 (m) cm^{-1}. HRMS (DART) for $C_{21}H_{19}O$ $[M+H-H_2O]^+$: calculated: 287.1436, found: 287.1431. $[\alpha]^{20}_D$: -43.242 (c = 1.200, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Diastereomer ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. Racemic compound was prepared according to the procedure described above with $Pd(OAc)_2$ (2 mol%) and 1,3-Bis(diphenylphosphino)propane (2.4 mol%) as the catalyst. Absolute stereochemistry was assigned by analogy from crystal structure of compound **1.105**.

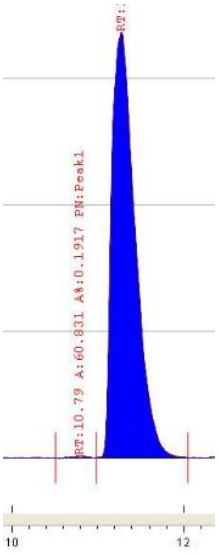
Chiral SFC (OD-H, 12% IPA, 4 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (1R,2R)-2-(4-methoxyphenyl)-1,2-diphenylethan-1-ol.

Racemic Material

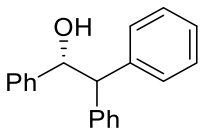


Peak No	% Area	Area	RT (min)
1	50.2496	4554.7092	10.06
2	49.7504	4509.4626	11.23
Total:	100	9064.1718	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	0.1917	60.831	10.79
2	99.8083	31665.4228	11.27
Total:	100	31726.2538	



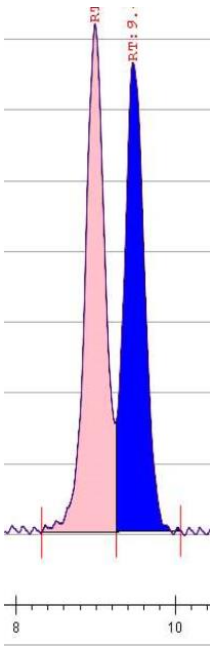
(R)-1,2,2-triphenylethan-1-ol (1.85). The reaction was performed according to the general procedure (**Method A**) with styrenyl B(mac) (**1.79**) (65.2 mg, 0.20 mmol, 1.0 equiv.), phenyllithium (1.9 M in dibutyl ether, 0.11 mL, .20 mmol, 1.0 equiv.), phenyl trifluoromethanesulfonate (49.8 mg, 0.22 mmol, 1.1 equiv.), palladium (II) acetate (0.45 mg, 2.0 μmol, 0.010 equiv.), **1.57** (2.5 mg, 2.4 μmol) , 0.012 equiv.), cesium fluoride (30.4 mg, 0.2 mmol, 1.0 equiv.) in THF (0.80 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (2-10% EtOAc in hexanes, stain in magic stain) to afford a white solid (47 mg, 86% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 (d, J = 7.3 Hz, 2H), 7.36 (t, J = 7.6 Hz, 2H), 7.31 – 7.19 (m, 6H), 7.19 – 7.08 (m, 5H), 5.41 (dd, J = 8.8, 2.7 Hz, 1H), 4.27 (d, J = 8.8 Hz, 1H), 2.13 (d, J = 2.9 Hz, 1H).; ^{13}C NMR (126 MHz, $CDCl_3$): δ 142.2, 141.5, 140.9, 128.9, 128.8, 128.6, 128.2, 128.0, 127.6, 127.0, 126.9, 126.4, 76.8, 60.3.; IR (neat): ν_{max} 3341.8 (br), 3060.0 (m), 3027.2 (m), 2908.2 (w), 1598.9 (m), 1493.5 (m), 1451.3 (m), 1301.2 (m), 743.9 (s), 697.0 (s), 598.8 (s) cm^{-1}. HRMS (DART) for $C_{20}H_{17}$ $[M+H-H_2O]^+$: calculated: 257.1325, found: 257.1324. $[\alpha]^{20}_D$: -63.355 (c = 0.960, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Racemic compound was prepared according to the procedure described above with $Pd(OAc)_2$ (2 mol%) and 1,3-Bis(diphenylphosphino)propane (2.4 mol%) as the catalyst. Absolute stereochemistry was assigned by analogy from crystal structure of compound **1.105**.

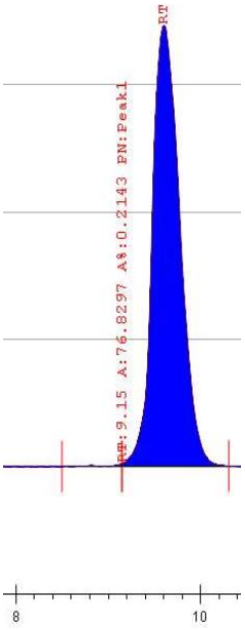
Chiral SFC (Chiralcel OD-H, 10% IPA, 4 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (R)-1,2,2-triphenylethan-1-ol.

Racemic Material



Peak No	% Area	Area	RT (min)
1	51.9085	2512.8466	8.99
2	48.0915	2328.0711	9.47
Total:	100	4840.9177	

Standard Conditions



Peak No	% Area	Area	RT (min)
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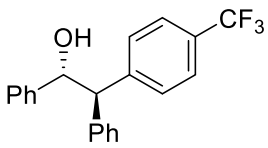
2	99.7857	35770.1731	9.6
Total:	100	35847.0028	



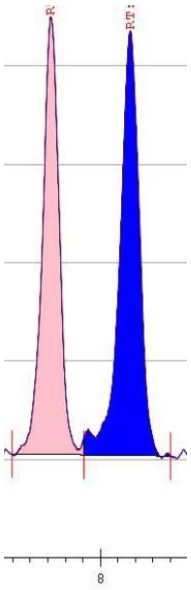
(1R,2R)-1,2-diphenyl-2-(4-(trifluoromethyl)phenyl)ethan-1-ol (1.86). The reaction was performed according to the general procedure (**Method B**) with styrenyl B(mac) (**1.79**) (65.2 mg, 0.20 mmol, 1.0 equiv.), phenyllithium (1.9 M in dibutyl ether, 0.11 mL, .20 mmol, 1.0 equiv.), 1-bromo-4-(trifluoromethyl)benzene (49.5 mg, 0.22 mmol, 1.1 equiv.), palladium (II) acetate (0.90 mg, 4.0 µmol, 0.020 equiv.), **1.57** (5.0 mg, 4.8 µmol) , 0.024 equiv.), cesium fluoride (30.4 mg, 0.2 mmol, 1.0 equiv.), and potassium trifluoromethanesulfonate (75.3 mg, 0.40 mmol, 2.0 equiv.) in THF (0.80 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (2-10% EtOAc in hexanes, stain in magic stain) to afford a pale yellow oil (30 mg, 44% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58 (d, J = 8.0 Hz, 2H), 7.52 (d, J = 8.0 Hz, 2H), 7.28 – 7.08 (m, 10H), 5.44 (d, J = 8.3 Hz, 1H), 4.33 (d, J = 8.3 Hz, 1H), 2.06 (br, 1H).; ^{13}C NMR (151 MHz, $CDCl_3$): δ 147.9, 144.8, 143.5, 132.1, 131.6 (q, $^{2}J_{C-F}$ = 32.4 Hz), 131.2, 131.09, 131.06, 130.9, 130.5, 129.4, 129.3, 128.0 (q, $^{3}J_{C-F}$ = 3.7 Hz), 126.9 (partially buried, q, $^{1}J_{C-F}$ = 271.8 Hz), 79.3, 62.3, 33.0.; ^{19}F NMR (470 MHz, $CDCl_3$): δ -62.4.; IR (neat): ν_{max} 3359.1 (br), 3063.1 (w), 3029.7 (m), 2924.1 (w), 1618.8 (m), 1324.7 (s),1163.9 (m), 1113.7 (m), 1068.7 (m), 746.9 (m) cm^{-1}. HRMS (DART) for $C_{21}H_{16}F_3$ $[M+H-H_2O]^+$: calculated: 325.1204, found: 325.1211. $[\alpha]^{20}_D$: -50.989 (c = 1.055, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Diastereomer ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. Racemic compound was prepared according to the procedure described above with $Pd(OAc)_2$ (2 mol%) and 1,3-Bis(diphenylphosphino)propane (2.4 mol%) as the catalyst. Absolute stereochemistry was assigned by analogy from crystal structure of compound **1.105**.

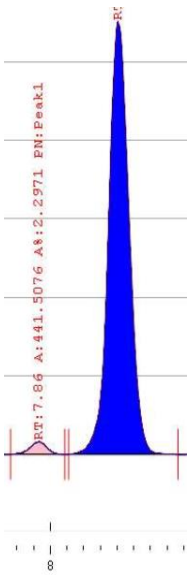
Chiral SFC (Chiralcel OD-H, 10% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (1R,2R)-1,2-diphenyl-2-(4-(trifluoromethyl)phenyl)ethan-1-ol.

Racemic Material

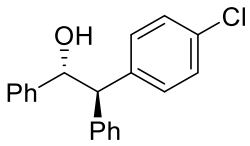


Peak No	% Area	Area	RT (min)
1	46.6539	1187.7833	7.43
2	53.3461	1358.1622	8.34
Total:	100	2545.9455	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	2.2971	441.5076	7.86
2	97.7029	18778.9673	8.81
Total:	100	19220.4749	



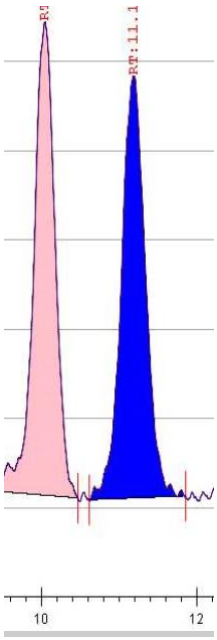
(1R,2R)-2-(4-chlorophenyl)-1,2-diphenylethan-1-ol (1.87). The reaction was performed according to the general procedure (**Method B**) with styrenyl B(mac) (**1.79**) (65.2 mg, 0.20 mmol, 1.0 equiv.), phenyllithium (1.9 M in dibutyl ether, 0.11 mL, .20 mmol, 1.0 equiv.), 1-bromo-4-chlorobenzene (42.1 mg, 0.22 mmol, 1.1 equiv.), palladium (II) acetate (0.90 mg, 4.0 μmol, 0.020 equiv.), **1.57** (5.0 mg, 4.8 μmol) , 0.024 equiv.), cesium fluoride (30.4 mg, 0.2 mmol, 1.0 equiv.), and potassium trifluoromethanesulfonate (75.3 mg, 0.40 mmol, 2.0 equiv.) in THF (0.80 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (2-10% EtOAc in hexanes, stain in magic stain) to afford a pale yellow oil (29 mg, 47% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 – 7.06 (m, 14H), 5.38 (d, J = 8.2 Hz, 1H), 4.24 (d, J = 8.2 Hz, 1H), 2.05 (br, 1H).; ^{13}C NMR (126 MHz, $CDCl_3$): δ 142.4, 141.4, 139.6, 132.8, 130.6, 128.9, 128.7, 128.54, 128.53, 128.3, 127.9, 126.9, 126.8, 76.9, 59.4.; IR (neat): ν_{max} 3350.5, 3061.4, 3028.4, 2920.9, 1491.2, 1453.2, 1014.8, 799.1, 734.8, 698.5 cm^{-1}. HRMS (DART) for $C_{20}H_{16}Cl$ $[M+H-H_2O]^+$: calculated: 291.0941, found: 291.0930. $[\alpha]^{20}_D$: -32.43 (c = 1.00, $CHCl_3$, l = 50 mm).

Analysis of Stereochemistry:

Diastereomer ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. Racemic compound was prepared according to the procedure described above with $Pd(OAc)_2$ (2 mol%) and 1,3-Bis(diphenylphosphino)propane (2.4 mol%) as the catalyst. Absolute stereochemistry was assigned by analogy from crystal structure of compound **1.105**.

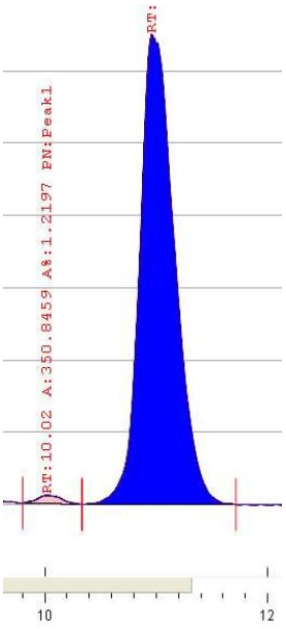
Chiral SFC (Chiralcel OD-H, 10% IPA, 4 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (1R,2R)-2-(4-chlorophenyl)-1,2-diphenylethan-1-ol.

Racemic Material

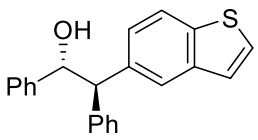


Peak No	% Area	Area	RT (min)
1	50.1967	2046.2136	10.04
2	49.8033	2030.1811	11.19
Total:	100	4076.3947	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	1.2197	350.8459	10.02
2	98.7803	28413.5011	10.96
Total:	100	28764.347	



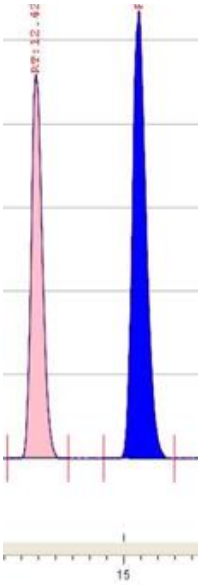
(1R,2R)-2-(benzo[b]thiophen-5-yl)-1,2-diphenylethan-1-ol (1.88). The reaction was performed according to the general procedure (**Method B**) with styrenyl B(mac) (**1.79**) (65.2 mg, 0.2 mmol, 1 equiv.), phenyllithium in dibutyl ether solution (1.9 M) (0.105 mL, 0.2 mmol, 1 equiv.), 5-bromobenzothiophene (46.9 mg, 0.22 mmol, 1.10 equiv.), palladium (II) acetate (0.45 mg, 0.002 mmol, 0.010 equiv.), **1.57** (2.30 mg, 0.0022 mmol, 0.011 equiv.), potassium triflate (75.3 mg, 0.4 mmol, 2 equiv.), and cesium fluoride (30.4 mg, 0.2 mmol, 1 equiv.) in THF (0.8 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (5-20% EtOAc in hexanes, stain in magic stain) to afford a white solid (28.4 mg, 43% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.44 (d, *J* = 5.4 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.32 (d, *J* = 5.4 Hz, 1H), 7.25 – 7.03 (m, 10H), 5.48 (d, *J* = 8.7 Hz, 1H), 4.40 (d, *J* = 8.6 Hz, 1H), 2.16 (s, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 142.4, 141.8, 140.2, 138.6, 137.2, 128.7, 128.4, 128.2, 127.7, 127.1, 127.0, 126.5, 125.7, 124.0, 123.8, 122.9, 77.0, 60.3. IR (neat): ν_{max} 3356.7 (bm), 3062.1 (m), 3027.3 (m) 2921.4 (m), 2855.0 (w), 1728.2 (w), 1600.1 (m), 1551.5 (m), 1491.9 (m), 1049.7 (m), 753.0 (s), 696.9 (s), 553.5 (m) cm^{-1}. HRMS (DART) for $C_{22}H_{18}OS$ $[M+H-H2O]^+$: calculated: 313.1051, found: 313.1049. $[\alpha]^{20}_D$: -38.828 (c = 0.855, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Diastereomer ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. Racemic compound was prepared according to the procedure described above with styrenyl B(mac), and $Pd(OAc)_2$ (2 mol%) and a mixture of **ent-1.57** and **1.57** (2.4 mol%) as the catalyst as the catalyst. Absolute stereochemistry was assigned by analogy from crystal structure of compound **1.105**.

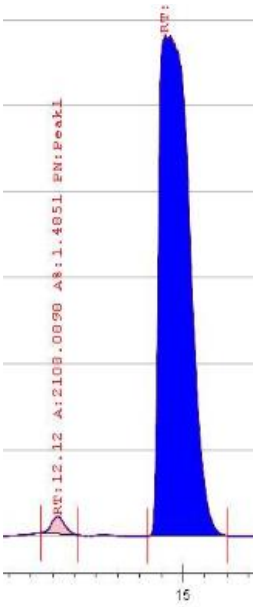
Chiral SFC (Chiralcel ODR-H, 15% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (1R,2R)-2-(benzo[b]thiophen-5-yl)-1,2-diphenylethan-1-ol

Racemic Material

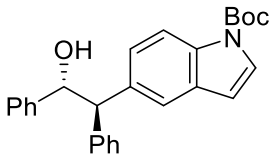


Peak No	% Area	Area	RT (min)
1	41.0665	10437.3868	12.42
2	58.9335	14978.4344	15.44
Total:	100	25415.8212	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	1.4851	2108.0898	12.12
2	98.5149	139837.4666	14.59
Total:	100	141945.5564	



tert-butyl 5-((1R,2R)-2-hydroxy-1,2-diphenylethyl)-1H-indole-1-carboxylate (1.89). The reaction was performed according to the general procedure (**Method B**) with styrenyl B(mac) (**1.79**) (65.2 mg, 0.20 mmol, 1.0 equiv.), phenyllithium (1.9 M in dibutyl ether, 0.11 mL, .20 mmol, 1.0 equiv.), tert-butyl 5-bromoindole-1-carboxylate (65.2 mg, 0.22 mmol, 1.1 equiv.), palladium (II) acetate (0.90 mg, 4.0 µmol, 0.020 equiv.), **1.57** (5.0 mg, 4.8 µmol) , 0.024 equiv.), cesium fluoride (30.4 mg, 0.2 mmol, 1.0 equiv.), and potassium trifluoromethanesulfonate (75.3 mg, 0.40 mmol, 2.0 equiv.) in THF (0.80 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (2-20% EtOAc in hexanes, stain in magic stain) to afford a white solid (49 mg, 59% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.0 Hz, 1H), 7.68 – 7.56 (m, 2H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.31 – 7.04 (m, 10H), 6.55 (d, *J* = 3.7 Hz, 1H), 5.46 (d, *J* = 8.6 Hz, 1H), 4.37 (d, *J* = 8.6 Hz, 1H), 2.23 (s, 1H), 1.68 (s, 9H).; ^{13}C NMR (151 MHz, $CDCl_3$): δ 149.9, 142.5, 142.1, 135.3, 134.4, 131.2, 128.7, 128.4, 128.2, 127.7, 127.1, 126.5, 126.4, 125.4, 121.3, 115.6, 107.5, 83.9, 77.1, 60.4, 28.4.; IR (neat): ν_{max} 3412. 5 (br), 3061.8 (m), 2978.7 (m), 1730.4 (s), 1492.63 (m), 1371.9 (s), 1163.0 (s), 1083.6 (m), 754.3 (s), 698.7 (s) cm^{-1}. HRMS (DART) for $C_{27}H_{26}NO_2$ $[M+H-H_2O]^+$: calculated: 396.1964, found: 396.1953. $[\alpha]^{20}_D$: -45.59 (c = 1.033, $CHCl_3$, *l* = 50 mm).

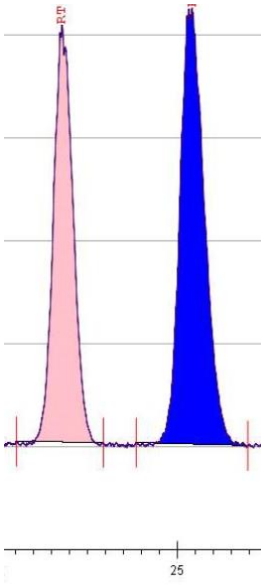
Analysis of Stereochemistry:

Diastereomer ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. Racemic compound was prepared according to the procedure described above with $Pd(OAc)_2$ (2 mol%) and a 1:1 mixture of **ent-1.57** and **1.57** (2.4 mol%) as the catalyst. Absolute stereochemistry was assigned by analogy from crystal structure of compound **1.105**.

Chiral SFC (Chiralcel OD-H, 10% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of tert-

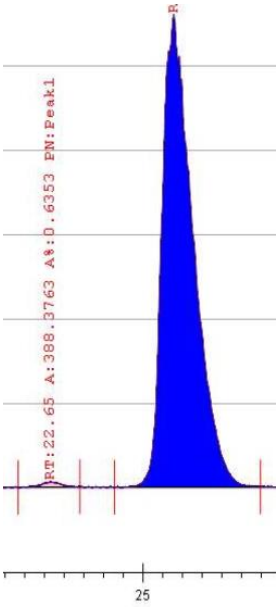
butyl 5-((1R,2R)-2-hydroxy-1,2-diphenylethyl)-1H-indole-1-carboxylate.

Racemic Material

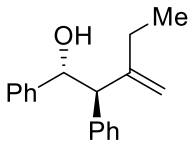


Peak No	% Area	Area	RT (min)
1	43.259	7639.7137	21.79
2	56.741	10020.7002	25.41
Total:	100	17660.4139	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	0.6353	388.3763	22.65
2	99.3647	60747.6108	25.78
Total:	100	61135.9871	



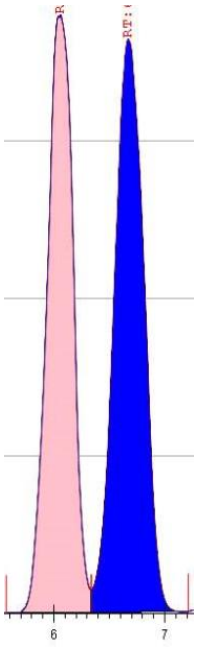
(1R,2S)-3-methylene-1,2-diphenylpentan-1-ol (1.90). The reaction was performed according to the general procedure (**Method B**) with styrenyl B(mac) (**1.79**) (65.2 mg, 0.20 mmol, 1.0 equiv.), phenyllithium (1.9 M in dibutyl ether, 0.11 mL, .20 mmol, 1.0 equiv.), 2-bromo-1-butene (29.7 mg, 0.22 mmol, 1.1 equiv.), palladium (II) acetate (0.90 mg, 4.0 µmol, 0.020 equiv.), **1.57** (5.0 mg, 4.8 µmol) , 0.024 equiv.), cesium fluoride (30.4 mg, 0.2 mmol, 1.0 equiv.), and potassium trifluoromethanesulfonate (75.3 mg, 0.40 mmol, 2.0 equiv.) in THF (0.80 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (2-10% EtOAc in hexanes, stain in magic stain) to afford a pale yellow oil (32 mg, 63% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.21 – 7.04 (m, 8H), 6.97 (dt, J = 7.5, 1.4 Hz, 2H), 5.37 (s, 1H), 5.22 (s, 1H), 5.06 (d, J = 9.8 Hz, 1H), 3.54 (d, J = 9.9 Hz, 1H), 2.64 (s, 1H), 2.11 – 1.95 (m, 2H), 1.03 (td, J = 7.4, 1.2 Hz, 3H).; ^{13}C NMR (151 MHz, $CDCl_3$): δ 154.4, 144.4, 142.2, 131.3, 130.6, 130.5, 130.0, 129.6, 129.2, 111.9, 78.6, 64.0, 31.7, 14.8.; IR (neat): ν_{max} 3440.4 (br), 3062.1 (w), 3028.4 (m), 2964.4 (m), 1641.4 (w), 1492.4 (m), 1453.0 (m), 1218.9 (m), 1074.2 (m), 755.3 (s), 696.9 (s) cm^{-1}. HRMS (DART) for $C_{18}H_{19}$ $[M+H-H_2O]^+$: calculated: 235.1487, found: 235.1481. $[\alpha]^{20}_D$: -209.087 (c = 1.020, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Diastereomer ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. Racemic compound was prepared according to the procedure described above with $Pd(OAc)_2$ (2 mol%) and a 1:1 mixture of **ent-1.57** and **1.57** (2.4 mol%) as the catalyst. Absolute stereochemistry was assigned by analogy from crystal structure of compound **1.105**.

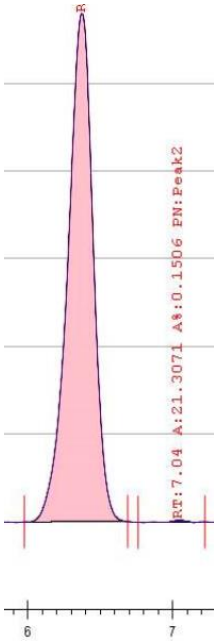
Chiral SFC (Chiralcel OJ-H, 5% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (1R,2S)-3-methylene-1,2-diphenylpentan-1-ol.

Racemic Material

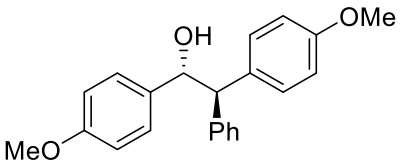


Peak No	% Area	Area	RT (min)
1	47.9207	31092.8311	6.06
2	52.0793	33791.1063	6.67
Total:	100	64883.9374	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	99.8494	14123.3123	6.37
2	0.1506	21.3071	7.04
Total:	100	14144.6194	



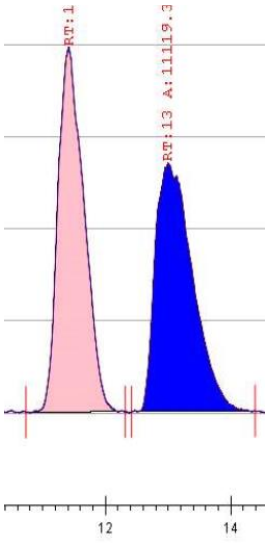
(1R,2R)-1,2-bis(4-methoxyphenyl)-2-phenylethan-1-ol (1.91). The reaction was performed according to the general procedure (**Method C**) with styrenyl B(mac) (**1.79**) (65.2 mg, 0.20 mmol, 1.0 equiv.), 4-bromoanisole (37.4 mg, 0.20 mmol, 1.0 equiv.), *tert*-butyllithium (1.7 M in pentane, 0.24 mL, 0.40 mmol, 2.0 equiv.), 4-methoxyphenyl trifluoromethanesulfonate (56.4 mg, 0.22 mmol, 1.1 equiv.), palladium (II) acetate (0.90 mg, 4.0 μmol, 0.020 equiv.), **1.57** (5.0 mg, 4.8 μmol) , 0.024 equiv.), cesium fluoride (30.4 mg, 0.2 mmol, 1.0 equiv.), and potassium trifluoromethanesulfonate (75.3 mg, 0.40 mmol, 2.0 equiv.) in THF (0.80 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (5-20% EtOAc in hexanes, stain in magic stain) to afford a white solid (52 mg, 79% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, J = 8.6 Hz, 2H), 7.19 – 7.03 (m, 6H), 6.89 (d, J = 8.6 Hz, 2H), 6.82 – 6.69 (m, 3H), 5.31 (d, J = 8.7 Hz, 1H), 4.18 (d, J = 8.8 Hz, 1H), 3.79 (s, 3H), 3.75 (s, 3H), 2.08 (br s, 1H).; ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.9, 158.5, 142.0, 134.5, 133.1, 129.9, 128.5, 128.2, 128.0, 126.2, 116.0, 114.8, 114.2, 113.4, 76.5, 59.5, 55.8, 55.24, 55.16.; IR (neat): ν_{max} 3389.0 (b), 3028.0 (w), 3000.8 (m), 2931.9 (m), 2835.0 (m), 1610.7 (m), 1584.3 (s), 1301.9 (w), 1246.2 (s), 1176.8 (m), 1302.9 (m), 828.5 (m), 699.9 (m) cm^{-1}. HRMS (DART) for $C_{22}H_{21}O_2$ $[M+H-H_2O]^+$: calculated: 317.152, found: 317.1547. $[\alpha]^{20}_D$: -37.908 (c = 0.633, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Diastereomer ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. Racemic compound was prepared according to the procedure described above with $Pd(OAc)_2$ (2 mol%) and 1,3-Bis(diphenylphosphino)propane (2.4 mol%) as the catalyst. Absolute stereochemistry was assigned by analogy from crystal structure of compound **1.105**.

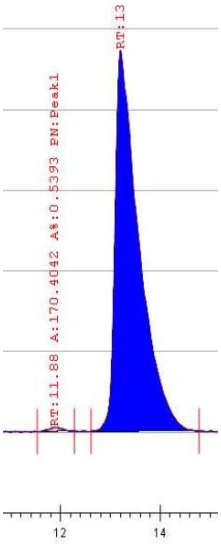
Chiral SFC (Chiralcel OD-H, 15% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (1R,2R)-1,2-bis(4-methoxyphenyl)-2-phenylethan-1-ol.

Racemic Material

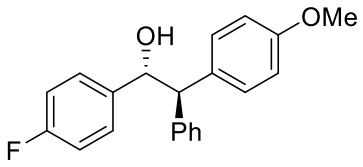


Peak No	% Area	Area	RT (min)
1	50.557	11369.8668	11.42
2	49.443	11119.3306	13
Total:	100	22489.1974	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	0.5393	170.4042	11.88
2	99.4607	31426.3547	13.2
Total:	100	31596.7589	



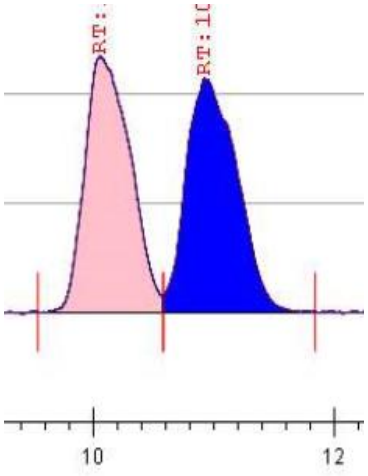
(1R,2R)-1-(4-fluorophenyl)-2-(4-methoxyphenyl)-2-phenylethan-1-ol (1.92). The reaction was performed according to the general procedure (**Method C**) with styrenyl B(mac) (**1.79**) (65.2 mg, 0.20 mmol, 1.0 equiv.), 1-bromo-4-fluorobenzene (35.0 mg, 0.20 mmol, 1.0 equiv.), *tert*-butyllithium (1.7 M in pentane, 0.24 mL, 0.40 mmol, 2.0 equiv.), 4-methoxyphenyl trifluoromethanesulfonate (56.4 mg, 0.22 mmol, 1.1 equiv.), palladium (II) acetate (0.90 mg, 4.0 μmol, 0.020 equiv.), **1.57** (5.0 mg, 4.8 μmol) , 0.024 equiv.), cesium fluoride (30.4 mg, 0.2 mmol, 1.0 equiv.), and potassium trifluoromethanesulfonate (75.3 mg, 0.40 mmol, 2.0 equiv.) in THF (0.80 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (5-20% EtOAc in hexanes, stain in magic stain) to afford a white solid (45 mg, 70% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, J = 8.6 Hz, 2H), 7.23 – 7.13 (m, 4H), 7.13 – 7.05 (m, 3H), 6.96 – 6.86 (m, 4H), 5.33 (d, J = 8.8 Hz, 1H), 4.14 (d, J = 8.8 Hz, 1H), 3.80 (s, 3H), 2.16 (br, 1H).; ^{13}C NMR (126 MHz, $CDCl_3$): δ 162.1 (d, $^{1}J_{C-F}$ = 245.3 Hz), 158.6, 141.6, 138.01, 137.99, 132.5, 129.9, 128.4 (d, $^{3}J_{C-F}$ = 8.3 Hz), 128.4, 128.3, 126.4, 114.8 (d, $^{2}J_{C-F}$ = 21.4 Hz), 114.7, 114.3, 76.3, 59.8, 55.2.; ^{19}F NMR (470 MHz, $CDCl_3$) δ -115.0.; IR (neat): ν_{max} 3378.7 (br), 3060.3 (w), 3029.1 (m), 2908.1 (m), 2835.9 (m), 1605.9 (m), 1508.8 (s), 1220.3 (m), 1178.9 (m), 1033.6 (m),699.4 (m), 567.7 (m) cm^{-1}. HRMS (DART) for $C_{21}H_{18}FO$ $[M+H-H_2O]^+$: calculated: 305.1342, found: 305.1342. $[\alpha]^{20}_D$: -58.335 (c = 0.813, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Diastereomer ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. Racemic compound was prepared according to the procedure described above with $Pd(OAc)_2$ (2 mol%) and 1,3-Bis(diphenylphosphino)propane (2.4 mol%) as the catalyst. Absolute stereochemistry was assigned by analogy from crystal structure of compound **1.105**.

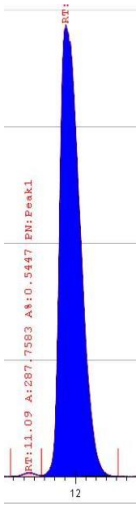
Chiral SFC (Chiralcel OD-H, 12% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (1R,2R)-1-(4-fluorophenyl)-2-(4-methoxyphenyl)-2-phenylethan-1-ol.

Racemic Material

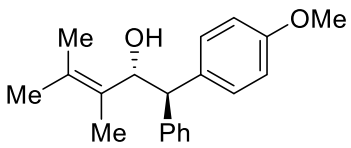


Peak No	% Area	Area	RT (min)
1	49.5931	6149.1124	10.05
2	50.4069	6250.0104	10.92
Total:	100	12399.1228	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	0.5447	287.7583	11.09
2	99.4553	52539.5337	11.81
Total:	100	52827.292	



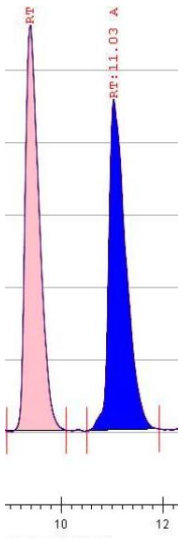
(1R,2R)-1-(4-methoxyphenyl)-3,4-dimethyl-1-phenylpent-3-en-2-ol (1.93). The reaction was performed according to the general procedure (**Method C**) with styrenyl B(mac) (**1.79**) (65.2 mg, 0.20 mmol, 1.0 equiv.), 2-bromo-3-methyl-but-2-ene (29.8 mg, 0.20 mmol, 1.0 equiv.), *tert*-butyllithium (1.7 M in pentane, 0.24 mL, 0.40 mmol, 2.0 equiv.), 4-methoxyphenyl trifluoromethanesulfonate (56.4 mg, 0.22 mmol, 1.1 equiv.), palladium (II) acetate (0.90 mg, 4.0 μmol, 0.020 equiv.), **1.57** (5.0 mg, 4.8 μmol) , 0.024 equiv.), cesium fluoride (30.4 mg, 0.2 mmol, 1.0 equiv.), and potassium trifluoromethanesulfonate (75.3 mg, 0.40 mmol, 2.0 equiv.) in THF (0.80 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (5-20% EtOAc in hexanes, stain in magic stain) to afford a white solid (33 mg, 56% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, J = 8.6 Hz, 2H), 7.23 – 7.15 (m, 4H), 7.15 – 7.10 (m, 1H), 6.90 (d, J = 8.7 Hz, 2H), 5.28 (d, J = 10.2 Hz, 1H), 4.06 (d, J = 10.1 Hz, 1H), 3.79 (s, 3H), 1.66 (s, 3H), 1.60 (s, 1H), 1.54 (s, 3H), 1.51 (s, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.5, 142.1, 133.7, 129.8, 129.7, 128.1, 127.9, 126.8, 126.2, 114.3, 73.1, 55.7, 55.2, 21.0, 20.1, 12.3.; IR (neat): ν_{max} 3448.0 (br), 3027.5 (w), 2993.8 (m), 2928.2 (m), 2858.4 (m), 1609.7 (m), 1510.4 (s), 1248.5 (s), 1178.1 (m), 1034.7 (m), 699.5 (m) cm^{-1}. HRMS (DART) for $C_{20}H_{23}O$ $[M+H-H_2O]^+$: calculated: 279.1749, found: 279.1751. $[\alpha]^{20}_D$: -8.766 (c = 0.920, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Diastereomer ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. Racemic compound was prepared according to the procedure described above with $Pd(OAc)_2$ (2 mol%) and 1,3-Bis(diphenylphosphino)propane (2.4 mol%) as the catalyst. Absolute stereochemistry was assigned by analogy from crystal structure of compound **1.105**.

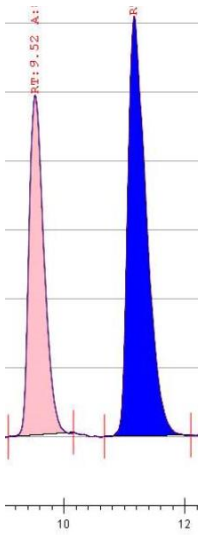
Chiral SFC (Chiralcel ODR-H, 5% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (1R,2R)-1-(4-methoxyphenyl)-3,4-dimethyl-1-phenylpent-3-en-2-ol.

Racemic Material

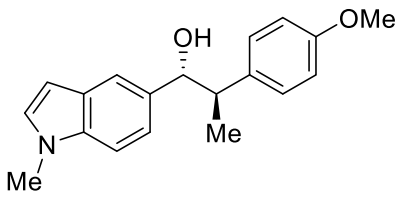


Peak No	% Area	Area	RT (min)
1	50.1135	21398.0761	9.39
2	49.8865	21301.1734	11.03
Total:	100	42699.2495	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	39.509	8442.2713	9.52
2	60.491	12925.7029	11.16
Total:	100	21367.9742	



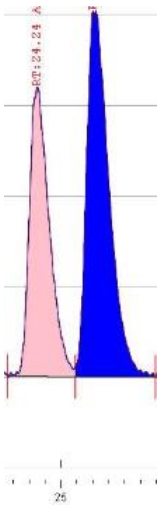
(1R,2R)-2-(4-methoxyphenyl)-1-(1-methyl-1H-indol-5-yl)propan-1-ol (1.94). The reaction was performed according to the general procedure (**Method C**) with (*E*)-propenyl B(mac) (**S-1**) (52.8 mg, 0.2 mmol, 1 equiv.), *tert*-butyllithium (1.7 M in pentane, 0.24 mL, 0.40 mmol, 2 equiv.), 5-bromo-1-methyl-indole (42.0 mg, 0.20 mmol, 1.0 equiv.), palladium (II) acetate (0.90 mg, 0.004 mmol, 0.020 equiv.), **1.57** (5.0 mg, 0.0048 mmol, 0.024 equiv.), potassium triflate (75.3 mg, 0.4 mmol, 2 equiv.), and cesium fluoride (30.4 mg, 0.2 mmol, 1 equiv.) in THF (0.8 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (5-20% EtOAc in hexanes, stain in magic stain) to afford a white solid (37.8 mg, 64% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 1.5 Hz, 1H), 7.32 (d, *J* = 8.5 Hz, 1H), 7.30 – 7.24 (m, 3H), 7.07 (d, *J* = 3.1 Hz, 1H), 6.92 (d, *J* = 8.6 Hz, 2H), 6.49 (d, *J* = 3.0 Hz, 1H), 4.72 – 4.67 (m, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.07 (dq, *J* = 8.9, 7.1 Hz, 1H), 1.86 (d, *J* = 2.1 Hz, 1H), 1.03 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.5, 136.7, 136.2, 133.9, 129.3, 129.1, 128.4, 120.7, 119.7, 114.2, 109.3, 101.2, 80.7, 77.4, 77.2, 76.9, 55.4, 47.7, 33.1, 19.0.; IR (neat): ν_{max} 3435.4 (br), 2956.7 (m), 2923.9 (m) 2852.4 (m), 1610.4 (w), 1582.3 (w), 1511.8 (s), 1245.0 (s), 770.3 (m) cm^{-1}. HRMS (DART) for $C_{19}H_{21}NO_2$ $[M+H]^+$: calculated: 296.1645, found: 296.1639. $[\alpha]^{20}_D$: +95.6726 (c = 1.09, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Diastereomer ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. Racemic compound was prepared according to the procedure described above with (E)-propenyl B(mac) and $Pd(OAc)_2$ (2 mol%) and a mixture of **ent-1.57** and **1.57** (2.4 mol%) as the catalyst. Absolute stereochemistry was assigned by analogy from crystal structure of compound **1.105**.

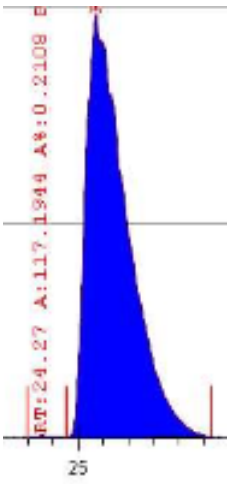
Chiral SFC (Chiralcel ODR-H, 10% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – (1R,2R)-2-(4-methoxyphenyl)-1-(1-methyl-1H-indol-5-yl)propan-1-ol.

Racemic Material

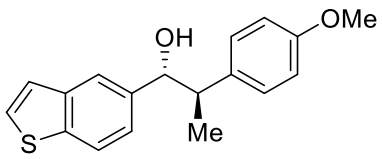


Peak No	% Area	Area	RT (min)
1	41.1283	6949.1704	24.24
2	58.8717	9947.1451	26.01
Total:	100	16896.3155	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	0.2108	117.1944	24.27
2	99.7892	55478.6465	25.36
Total:	100	55595.8409	



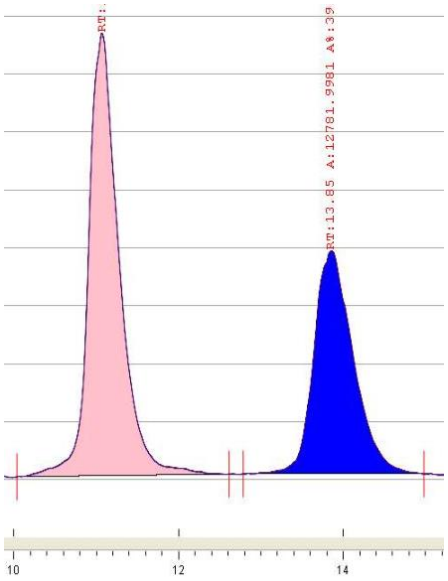
(1R,2R)-1-(benzo[b]thiophen-5-yl)-2-(4-methoxyphenyl)propan-1-ol (1.95). The reaction was performed according to the general procedure (**Method C**) with (*E*)-propenyl B(mac) (**S-1**) (52.8 mg, 0.2 mmol, 1 equiv.), *tert*-butyllithium (1.7 M in pentane, 0.24 mL, 0.40 mmol, 2 equiv.), 5-bromobenzothiophene (42.6 mg, 0.20 mmol, 1.0 equiv.), palladium (II) acetate (0.90 mg, 0.004 mmol, 0.020 equiv.), **1.57** (5.0 mg, 0.0048 mmol, 0.024 equiv.), potassium triflate (75.3 mg, 0.4 mmol, 2 equiv.), and cesium fluoride (30.4 mg, 0.2 mmol, 1 equiv.) in THF (0.8 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (5-20% EtOAc in hexanes, stain in magic stain) to afford a white solid (35 mg, 59% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.5 Hz, 1H), 7.81 (s, 1H), 7.46 (d, *J* = 5.4 Hz, 1H), 7.41 – 7.31 (m, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 6.92 (d, *J* = 8.6 Hz, 2H), 4.72 (d, *J* = 8.7 Hz, 1H), 3.82 (s, 3H), 3.09 – 2.97 (m, 1H), 1.95 (br, 1H), 1.07 (d, *J* = 7.1 Hz, 3H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.7, 139.8, 139.3, 139.1, 135.4, 129.2, 126.9, 124.1, 123.5, 122.5, 122.3, 114.3, 80.1, 55.5, 47.7, 18.7.; IR (neat): ν_{max} 3416 (br), 2961 (m), 2928 (m), 1610 (m), 1583 (w), 1511 (s), 1246 (s), 787 (m) cm^{-1}. HRMS (DART) for $C_{18}H_{17}OS$ $[M+H-H_2O]^+$: calculated: 281.0995, found: 281.1002. $[\alpha]^{20}_D$: +52.99 (c = 1.00, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Diastereomer ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. Racemic compound was prepared according to the procedure described above with (E)-propenyl B(mac) and $Pd(OAc)_2$ (2 mol%) and a mixture of **ent-1.57** and **1.57** (2.4 mol%) as the catalyst. Absolute stereochemistry was assigned by analogy from crystal structure of compound **1.105**.

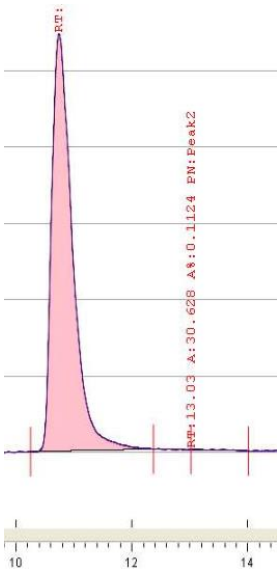
Chiral SFC (Chiralcel AS-H, 10% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – (1R,2R)-1-(benzo[b]thiophen-5-yl)-2-(4-methoxyphenyl)propan-1-ol

Racemic Material

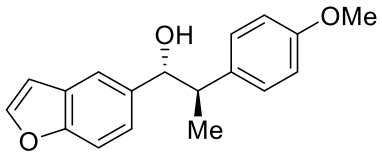


Peak No	% Area	Area	RT (min)
1	60.608	19666.2012	11.07
2	39.392	12781.9981	13.85
Total:	100	32448.1993	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	99.8876	27219.7084	10.74
2	0.1124	30.628	13.03
Total:	100	27250.3364	



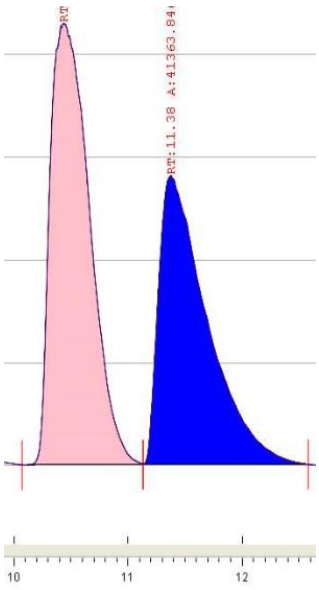
(1R,2R)-1-(benzofuran-5-yl)-2-(4-methoxyphenyl)propan-1-ol (1.96). The reaction was performed according to the general procedure (**Method C**) with (*E*)-propenyl B(mac) (**S-1**) (52.8 mg, 0.2 mmol, 1 equiv.), *tert*-butyllithium (1.7 M in pentane, 0.24 mL, 0.40 mmol, 2 equiv.), 5-bromobenzofuran (39.4 mg, 0.20 mmol, 1.0 equiv.), palladium (II) acetate (0.90 mg, 0.004 mmol, 0.020 equiv.), **1.57** (5.0 mg, 0.0048 mmol, 0.024 equiv.), potassium triflate (75.3 mg, 0.4 mmol, 2 equiv.), and cesium fluoride (30.4 mg, 0.2 mmol, 1 equiv.) in THF (0.8 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (5-20% EtOAc in hexanes, stain in magic stain) to afford a white solid (28 mg, 50% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 – 7.57 (m, 2H), 7.49 (d, *J* = 8.5 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 1H), 7.28 – 7.21 (m, 2H), 6.94 – 6.89 (m, 2H), 6.80 – 6.75 (m, 1H), 4.70 (d, *J* = 8.8 Hz, 1H), 3.82 (s, 3H), 3.08 – 2.94 (m, 1H), 1.93 (br, *J* = 2.1 Hz, 1H), 1.05 (d, *J* = 7.0 Hz, 3H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.7, 154.8, 145.5, 137.5, 135.5, 129.2, 127.5, 123.5, 119.8, 114.3, 111.3, 106.8, 80.2, 55.5, 47.9, 18.8.; IR (neat): ν_{max} 3441(br), 2960 (m), 2927 (m) 1610 (m), 1583 (s), 1467 (m), 1246 (s), 1179 (m), 1032 (s), 741 (m) cm^{-1}. HRMS (DART) for $C_{18}H_{17}O_2$ $[M+H-H_2O]^+$: calculated: 265.1223, found: 265.1232. $[\alpha]^{20}_D$: +48.50 (c = 0.933, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Diastereomer ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. Racemic compound was prepared according to the procedure described above with (*E*)-propenyl B(mac) and $Pd(OAc)_2$ (2 mol%) and a mixture of **ent-1.57** and **1.57** (2.4 mol%) as the catalyst. Absolute stereochemistry was assigned by analogy from crystal structure of compound **1.105**.

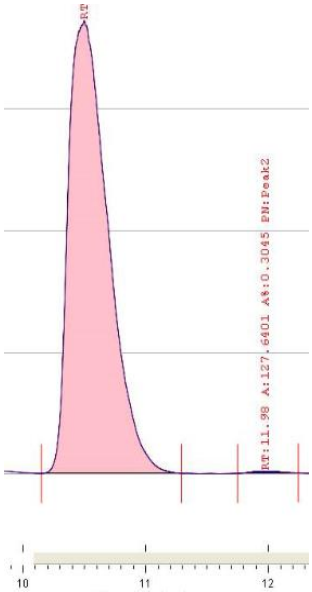
Chiral SFC (Chiralcel ODR-H, 8% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – (1R,2R)-1-(benzofuran-5-yl)-2-(4-methoxyphenyl)propan-1-ol.

Racemic Material

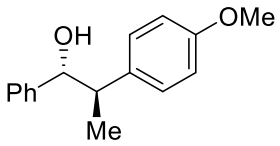


Peak No	% Area	Area	RT (min)
1	55.5182	51626.6428	10.44
2	44.4818	41363.8463	11.38
Total:	100	92990.4891	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	99.6955	41790.8039	10.5
2	0.3045	127.6401	11.98
Total:	100	41918.444	



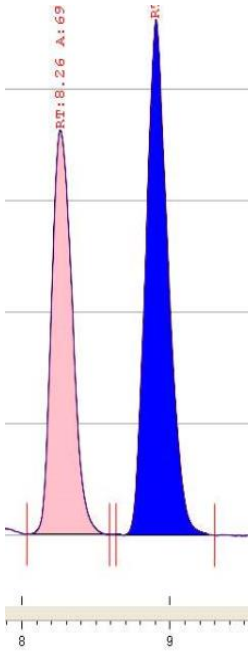
(1R,2R)-2-(4-methoxyphenyl)-1-phenylpropan-1-ol (1.97). The reaction was performed according to the general procedure (**Method A**) with (*E*)-propenyl B(mac) (**S-1**) (52.8 mg, 0.20 mmol, 1.0 equiv.), phenyllithium (1.9 M in dibutyl ether, 0.11 mL, .20 mmol, 1.0 equiv.), 4-methoxyphenyl trifluoromethanesulfonate (56.4 mg, 0.22 mmol, 1.1 equiv.), palladium (II) acetate (0.45 mg, 2.0 μmol, 0.010 equiv.), **1.57** (2.5 mg, 2.4 μmol) , 0.012 equiv.), cesium fluoride (30.4 mg, 0.2 mmol, 1.0 equiv.) in THF (1.60 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (2-20% EtOAc in hexanes, stain in magic stain) to afford a white solid (34 mg, 70% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.28 (m, 5H), 7.22 (d, J = 8.7 Hz, 2H), 6.91 (d, J = 8.7 Hz, 2H), 4.61 (d, J = 8.6 Hz, 1H), 3.82 (s, 3H), 3.04 – 2.92 (m, 1H), 1.88 (s, 1H), 1.07 (d, J = 7.1 Hz, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.5, 142.6, 135.2, 129.0, 128.2, 127.7, 127.0, 114.1, 79.8, 55.3, 47.3, 18.4.; IR (neat): ν_{max} 3444.8 (br), 3030.4 (w), 2961.7 (m), 2931.5 (m), 2834.8 (w), 1610.5 (w), 1583.1 (s), 1245.5 (s), 1178.3 (m), 1036.7 (m), 724.3 (m) cm^{-1}. HRMS (DART) for $C_{16}H_{17}O$ $[M+H-H_2O]^+$:calculated: 225.1274, found: 225.1270. $[\alpha]^{20}_D$: -69.455 (c = 1.000, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Diastereomer ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. Racemic compound was prepared according to the procedure described above with (E)-propenyl B(mac)**,** and $Pd(OAc)_2$ (2 mol%) and a mixture of **ent-1.57** and **1.57** (2.4 mol%) as the catalyst. Absolute stereochemistry was assigned by analogy from crystal structure of compound **1.105**.

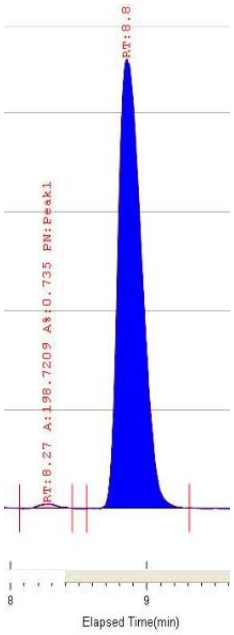
Chiral SFC (Chiralcel OJ-H, 10% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (1R,2R)-2-(4-methoxyphenyl)-1-phenylpropan-1-ol.

Racemic Material

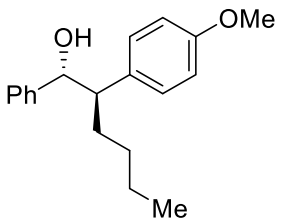


Peak No	% Area	Area	RT (min)
1	42.1696	6987.3301	8.26
2	57.8304	9582.2447	8.9
Total:	100	16569.5748	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	0.735	198.7209	8.27
2	99.265	26839.1094	8.85
Total:	100	27037.8303	



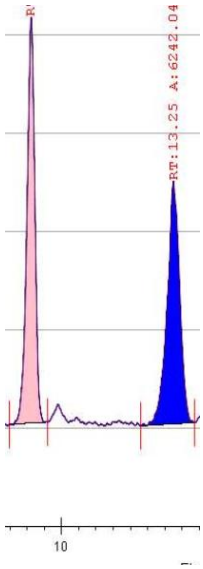
(1R,2R)-2-(4-methoxyphenyl)-1-phenylhexan-1-ol (1.98). The reaction was performed according to the general procedure (**Method A**) with (*E*)-hexenyl B(mac) (**S-2**) (61.2 mg, 0.20 mmol, 1.0 equiv.), phenyllithium (1.9 M in dibutyl ether, 0.11 mL, .20 mmol, 1.0 equiv.), 4-methoxyphenyl trifluoromethanesulfonate (56.4 mg, 0.22 mmol, 1.1 equiv.), palladium (II) acetate (0.45 mg, 2.0 μmol, 0.010 equiv.), **1.57** (2.5 mg, 2.4 μmol) , 0.012 equiv.), cesium fluoride (30.4 mg, 0.2 mmol, 1.0 equiv.) in THF (0.80 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (2-20% EtOAc in hexanes, stain in magic stain) to afford a white solid (36 mg, 63% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.24 (m, 5H), 7.16 (dd, J = 8.6, 1.8 Hz, 2H), 6.90 (dd, J = 8.6, 1.7 Hz, 2H), 4.66 (d, J = 8.4 Hz, 1H), 3.82 (s, 3H), 2.83 – 2.75 (m, 1H), 1.84 (br, 1H), 1.62 – 1.47 (m, 1H), 1.43 – 1.32 (m, 1H), 1.26 – 1.04 (m, 2H), 1.04 – 0.92 (m, 2H), 0.73 (td, J = 7.3, 1.6 Hz, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.5, 142.9, 133.1, 129.7, 128.2, 127.6, 127.0, 114.0, 76.8, 55.2, 53.5, 31.7, 29.5, 22.5, 13.9.; IR (neat): ν_{max} 3458.4 (br), 2996.4 (m), 2954.1 (m), 2857.2 (m), 1610.0 (m), 1507.1 (s), 1244.8 (s), 1177.1 (m), 1034.9 (m), 700.2 (s) cm^{-1}. HRMS (DART) for $C_{19}H_{23}O$ $[M+H-H_2O]^+$: calculated: 267.1749, found: 267.1756. $[\alpha]^{20}_D$: +37.172 (c = 1.300, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Diastereomer ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. Racemic compound was prepared according to the procedure described above with (*E*)-hexenyl B(mac), and $Pd(OAc)_2$ (2 mol%) and 1,3-Bis(diphenylphosphino)propane (2.4 mol%) as the catalyst. Absolute stereochemistry was assigned by analogy from crystal structure of compound **1.105**.

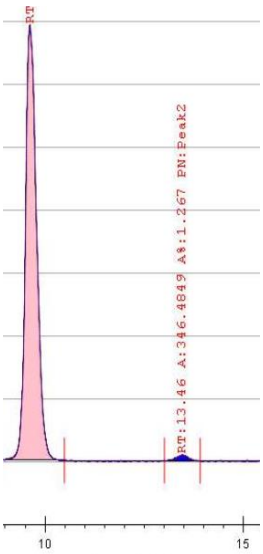
Chiral SFC (Chiralcel OJ-H, 5% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (1R,2R)-2-(4-methoxyphenyl)-1-phenylhexan-1-ol

Racemic Material

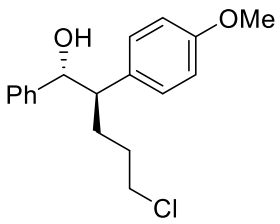


Peak No	% Area	Area	RT (min)
1	51.3895	6598.905	9.12
2	48.6105	6242.0449	13.25
Total:	100	12840.9499	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	98.733	27000.6134	9.62
2	1.267	346.4849	13.46
Total:	100	27347.0983	



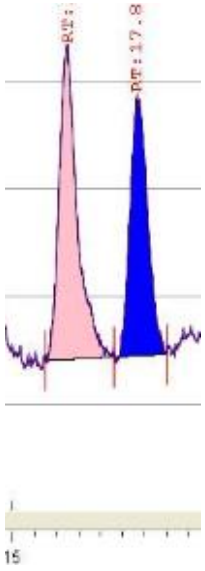
(1R,2R)-5-chloro-2-(4-methoxyphenyl)-1-phenylpentan-1-ol (1.99). The reaction was performed according to the general procedure (**Method A**) with (*E*)-5-chloro-pentenyl B(mac) (**S-3**) (65.3 mg, 0.2 mmol, 1.0 equiv.), phenyllithium in dibutyl ether solution (1.9 M) (0.105 mL, 0.2 mmol, 1.0 equiv.), (4-methoxyphenyl) trifluoromethanesulfonate (56.4 mg, 0.22 mmol, 1.10 equiv.), palladium (II) acetate (0.45 mg, 0.002 mmol, 0.010 equiv.), **1.57** (2.30 mg, 0.0022 mmol, 0.011 equiv.) and cesium fluoride (30.4 mg, 0.2 mmol, 1 equiv.) in THF (0.8 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (5-20% EtOAc in hexanes, stain in magic stain) to afford a white solid (31.1 mg, 51% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.25 (m, 5H), 7.17 – 7.11 (m, 2H), 6.91 – 6.85 (m, 2H), 4.65 (d, *J* = 8.2 Hz, 1H), 3.80 (s, 3H), 3.38 – 3.25 (m, 2H), 2.83 – 2.75 (m, 1H), 1.81 (s, 1H), 1.70 – 1.43 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.7, 142.5, 132.2, 129.6, 128.3, 127.8, 126.9, 114.2, 78.8, 55.2, 52.9, 44.8, 30.5, 29.3. IR (neat): ν_{max} 3466.9 (br), 2995.5 (w), 2953.4 (w), 1609.7 (w), 1510.6 (s), 1453.8 (w), 1301.7 (w), 1247.0 (s), 1178.4 (m), 1034.2 (m), 701.56 (m) cm^{-1}. HRMS (DART) for $C_{18}H_{21}ClO_2$ $[M+H-H_2O]^+$: calculated: 287.1203, found:287.1212. $[\alpha]^{20}_D$: +14.145 (c = 0.82, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Diastereomer ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. Racemic compound was prepared according to the procedure described above with (*E*)-5-chloro-pentenyl B(mac), and $Pd(OAc)_2$ (2 mol%) and a mixture of **ent-1.57** and **1.57** (2.4 mol%) as the catalyst. Absolute stereochemistry was assigned by analogy from crystal structure of compound **1.105**.

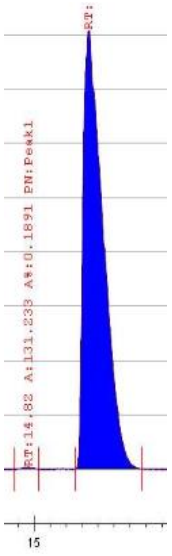
Chiral SFC (Chiralcel ODR-H, 5% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (1R,2R)-5-chloro-2-(4-methoxyphenyl)-1-phenylpentan-1-ol.

Racemic Material

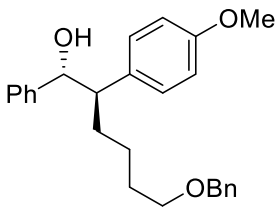


Peak No	% Area	Area	RT (min)
1	55.7361	839.1701	16.25
2	44.2639	666.443	17.83
Total:	100	1505.6131	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	0.1891	131.233	14.82
2	99.8109	69250.2415	16.72
Total:	100	69381.4745	



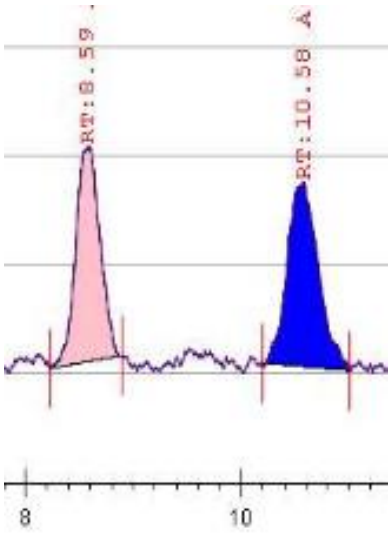
(1R,2R)-6-(benzyloxy)-2-(4-methoxyphenyl)-1-phenylhexan-1-ol (1.100). The reaction was performed according to the general procedure (**Method A**) with (*E*)-6-(benzyloxy)hexenyl B(mac) (**S-4**) (82.5 mg, 0.2 mmol, 1.0 equiv.), phenyllithium in dibutylether solution (1.9 M) (0.105 mL, 0.2 mmol, 1.0 equiv.), (4-methoxyphenyl) trifluoromethanesulfonate (56.4 mg, 0.22 mmol, 1.10 equiv.), palladium (II) acetate (0.45 mg, 0.002 mmol, 0.010 equiv.), **1.57** (2.30 mg, 0.0022 mmol, 0.011 equiv.), and cesium fluoride (30.4 mg, 0.2 mmol, 1 equiv.) in THF (0.8 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (5-20% EtOAc in hexanes, stain in magic stain) to afford a white solid (39.1 mg, 50.0% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ. 7.42 – 7.21 (m, 10H), 7.19 – 7.12 (m, 2H), 6.95 – 6.86 (m, 2H), 4.65 (d, J = 8.4, 2.4 Hz, 1H), 4.38 (s, 2H), 3.82 (s, 3H), 3.35 – 3.24 (m, 2H), 2.87 – 2.73 (m, 1H), 1.82 (s, 1H), 1.61 – 1.34 (m, 4H), 1.18 – 1.01 (m, 2H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.6, 142.9, 138.7, 133.0, 129.8, 128.40, 128.37, 127.8, 127.7, 127.6, 127.1, 114.2, 78.9, 72.9, 70.2, 55.3, 53.5, 31.9, 29.6, 24.0.; IR (neat): ν_{max} 3438.8 (br), 3060.1 (w), 3029.9 (w), 2932.3 (m), 2857.5 (m), 1609.6 (m), 1510 (s), 1453.3 (m), 1245.8 (s), 1177.5 (m), 1093.9 (m), 1029.1 (s), 698.4 (s) cm^{-1}. HRMS (DART) for $C_{26}H_{30}O_3$ $[M+H-H_2O]^+$: calculated: 373.2168, found: 373.215. $[\alpha]^{20}_D$: +18.497 (c = 0.955, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Diastereomer ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. Racemic compound was prepared according to the procedure described above with (*E*)-6-(benzyloxy)hexenyl B(mac), and $Pd(OAc)_2$ (2 mol%) and a mixture of **ent-1.57** and **1.57** (2.4 mol%) as the catalyst. Absolute stereochemistry was assigned by analogy from crystal structure of compound **1.105**.

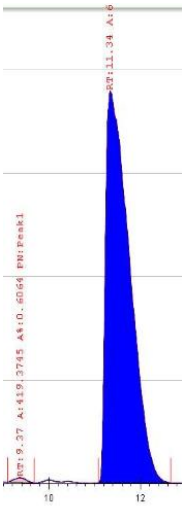
Chiral SFC (Chiralcel ODR-H ,15% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (1R,2R)-6-(benzyloxy)-2-(4-methoxyphenyl)-1-phenylhexan-1-ol.

Racemic Material

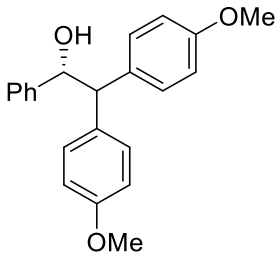


Peak No	% Area	Area	RT (min)
1	47.6343	616.1072	8.59
2	52.3657	677.3049	10.58
Total:	100	1293.4121	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	0.6064	419.3745	9.37
2	99.3936	68741.3181	11.34
Total:	100	69160.6926	



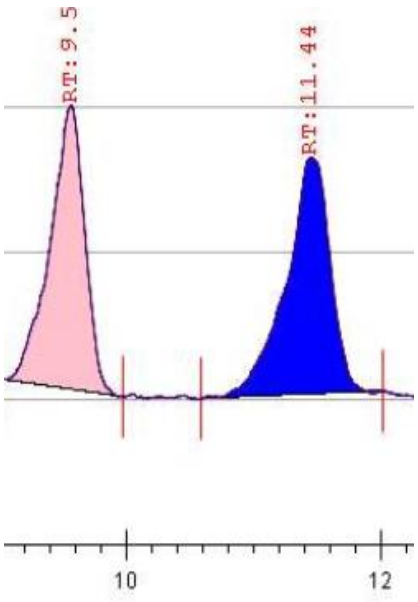
(R)-2,2-bis(4-methoxyphenyl)-1-phenylethan-1-ol (1.101). The reaction was performed according to the general procedure (**Method A**) with 4-methoxy-styrenyl B(mac) (**S-5**) (71.2 mg, 0.20 mmol, 1.0 equiv.), phenyllithium (1.9 M in dibutyl ether, 0.11 mL, .20 mmol, 1.0 equiv.), 4-methoxyphenyl trifluoromethanesulfonate (56.4 mg, 0.22 mmol, 1.1 equiv.), palladium (II) acetate (0.45 mg, 2.0 μmol, 0.010 equiv.), **1.57** (2.5 mg, 2.4 μmol) , 0.012 equiv.), cesium fluoride (30.4 mg, 0.2 mmol, 1.0 equiv.) in THF (0.80 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (2-20% EtOAc in hexanes, stain in magic stain) to afford a white solid (32 mg, 48% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, J = 7.6 Hz, 2H), 7.28 – 7.17 (m, 5H), 7.02 (d, J = 8.2 Hz, 2H), 6.89 (d, J = 8.5 Hz, 2H), 6.69 (d, J = 8.4 Hz, 2H), 5.30 (d, J = 8.6 Hz, 1H), 4.17 (d, J = 8.6 Hz, 1H), 3.79 (s, 3H), 3.71 (s, 3H), 2.13 (br, 1H).; ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.5, 157.9, 142.4, 134.1, 133.1, 129.9, 129.4, 128.0, 127.4, 126.9, 114.2, 113.6, 77.0, 58.6, 55.2, 55.1.; IR (neat): ν_{max} 3429.1 (br), 3060.9 (w), 3030.9 (w), 2932.3 (m), 2834.9 (m), 1608.3 (m), 1508.8 (s), 1245.1 (s), 1176.8 (m), 1032.8 (m), 814.5 (m), 700.5 (m) cm^{-1}. HRMS (DART) for $C_{22}H_{21}O_2$ $[M+H-H_2O]^+$: calculated: 317.1536, found: 317.1535. $[\alpha]^{20}_D$: -51.455 (c = 1.105, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Racemic compound was prepared according to the procedure described above $Pd(OAc)_2$ (2 mol%) and 1,3-Bis(diphenylphosphino)propane (2.4 mol%) as the catalyst. Absolute stereochemistry was assigned by analogy from crystal structure of compound **1.105**.

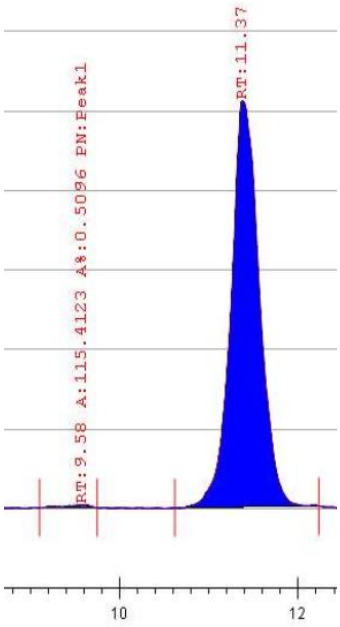
Chiral SFC (Chiralcel OJ-H, 15% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (R)-2,2-bis(4-methoxyphenyl)-1-phenylethan-1-ol

Racemic Material

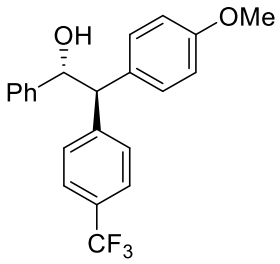


Peak No	% Area	Area	RT (min)
1	48.6093	3676.123	9.57
2	51.3907	3886.4641	11.44
Total:	100	7562.5871	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	0.5096	115.4123	9.58
2	99.4904	22531.7318	11.37
Total:	100	22647.1441	



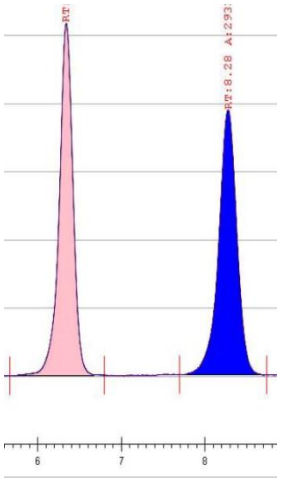
(1R)-2-(4-methoxyphenyl)-1-phenyl-2-(4-(trifluoromethyl)phenyl)ethan-1-ol (1.102). The reaction was performed according to the general procedure (**Method A**) at 60 ºC with 4-trifluoromethyl-styrenyl B(mac) (**S-6**) (78.8 mg, 0.20 mmol, 1.0 equiv.), phenyllithium (1.9 M in dibutyl ether, 0.11 mL, .20 mmol, 1.0 equiv.), 4-methoxyphenyl trifluoromethanesulfonate (56.4 mg, 0.22 mmol, 1.1 equiv.), palladium (II) acetate (1.35 mg, 6.0 μmol, 0.030 equiv.), **1.57** (6.7 mg, 6.4 μmol) , 0.032 equiv.), cesium fluoride (30.4 mg, 0.2 mmol, 1.0 equiv.) in THF (0.80 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (2-20% EtOAc in hexanes, stain in magic stain) to afford a yellow oil (51 mg, 69% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 (d, J = 8.1 Hz, 2H), 7.34 – 7.12 (m, 9H), 6.90 (d, J = 8.8 Hz, 2H), 5.35 (d, J = 8.4 Hz, 1H), 4.27 (d, J = 8.4 Hz, 1H), 3.80 (s, 3H), 2.16 (s, 1H).; ^{13}C NMR (151 MHz, $CDCl_3$): δ 161.4, 148.7, 144.5, 134.5, 132.6, 131.5, 131.2 (q, $^{2}J_{C\text{-}F}$ = 32.4 Hz), 130.9, 130.8, 130.5, 129.5, 127.8 (q, $^{3}J_{C\text{-}F}$ = 3.9 Hz), 126.8 (q, $^{1}J_{C\text{-}F}$ = 271.8 Hz), 117.0, 79.3, 61.8, 57.9.; ^{19}F NMR (564 MHz, $CDCl_3$): δ -62.48.; IR (neat): ν_{max} 3405.1 (br), 3033,4 (w), 2929.2 (m), 2837.9 (w), 1612.4 (m), 1510.8 (s), 1324.0 (s), 1249.5 (s), 1162.8 (s), 1115.1 (s), 1035.4 (s), 814.5 (s), 754.3 (s), 700.4 (s), 605.7 (s) cm^{-1}. HRMS (DART) for $C_{22}H_{18}F_3O$ $[M+H-H_2O]^+$: calculated: 355.1310, found: 355.1311. $[\alpha]^{20}_D$: -27.50 (c = 1.115, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Diastereomer ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. Racemic compound was prepared according to the procedure described above with $Pd(OAc)_2$ (2 mol%) and 1,3-Bis(diphenylphosphino)propane (2.4 mol%) as the catalyst. Absolute stereochemistry was assigned by analogy from crystal structure of compound **1.105**.

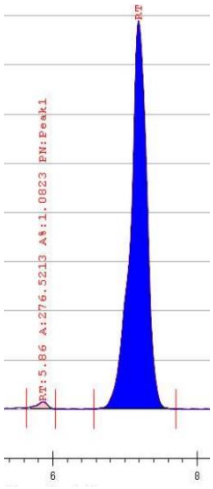
Chiral SFC (Chiralcel OJ-H, 10% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (1R)-2-(4-methoxyphenyl)-1-phenyl-2-(4-(trifluoromethyl)phenyl)ethan-1-ol

Racemic Material

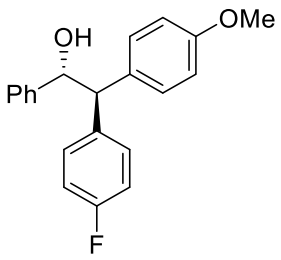


Peak No	% Area	Area	RT (min)
1	50.2702	2965.8056	6.34
2	49.7298	2933.9292	8.28
Total:	100	5899.7348	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	1.0823	276.5213	5.86
2	98.9177	25273.2809	7.19
Total:	100	25549.8022	



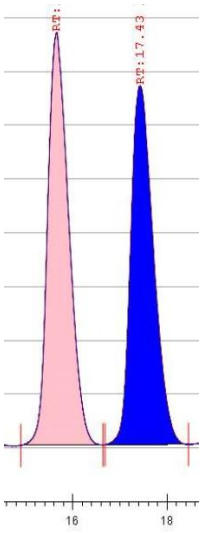
(1R)-2-(4-fluorophenyl)-2-(4-methoxyphenyl)-1-phenylethan-1-ol (1.103). The reaction was performed according to the general procedure (**Method A**) at 60 ºC with 4-fluoro-styrenyl B(mac) (**S-7**) (68.8 mg, 0.20 mmol, 1.0 equiv.), phenyllithium (1.9 M in dibutyl ether, 0.11 mL, .20 mmol, 1.0 equiv.), 4-methoxyphenyl trifluoromethanesulfonate (56.4 mg, 0.22 mmol, 1.1 equiv.), palladium (II) acetate (0.45 mg, 2.0 µmol, 0.010 equiv.), **1.57** (2.5 mg, 2.4 µmol) , 0.012 equiv.), cesium fluoride (30.4 mg, 0.2 mmol, 1.0 equiv.) in THF (0.80 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (2-20% EtOAc in hexanes, stain in magic stain) to afford a yellow oil (38 mg, 59% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, J = 8.6 Hz, 2H), 7.26 – 7.17 (m, 5H), 7.08 – 7.03 (m, 2H), 6.90 (d, J = 8.9 Hz, 2H), 6.83 (t, J = 8.6 Hz, 2H), 5.29 (d, J = 8.6 Hz, 1H), 4.19 (d, J = 8.7 Hz, 1H), 3.80 (s, 3H), 2.14 (br, 1H).; ^{13}C NMR (126 MHz, $CDCl_3$): δ 161.3 (d, $^{1}J_{C\text{-}F}$ = 244.7 Hz), 158.6, 142.2, 137.7, 137.7, 132.6, 129.9 (d, $^{3}J_{C\text{-}F}$ = 8.0 Hz), 129.8, 128.1, 127.6, 126.8, 115.0 (d, $^{2}J_{C\text{-}F}$ = 21.0 Hz), 114.2, 77.0, 58.7, 55.3.; ^{19}F NMR (470 MHz, $CDCl_3$): δ -116.7.; IR (neat): ν_{max} 3383.7 (br), 3062.4 (w), 3031.9 (w), 2905.6 (w), 2835.8 (w), 1605.4 (s), 1247.9 (m), 1033.8 (m), 819.4 (m), 752.9 (m), 700.4 (m), 576.7 (m) cm^{-1}. HRMS (DART) for $C_{21}H_{18}OF$ $[M+H-H_2O]^+$:calculated: 305.1336, found: 305.1369. $[\alpha]^{20}_D$: -42.020 (c = 1.315, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Diastereomer ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. Racemic compound was prepared according to the procedure described above with $Pd(OAc)_2$ (2 mol%) and 1,3-Bis(diphenylphosphino)propane (2.4 mol%) as the catalyst. Absolute stereochemistry was assigned by analogy from crystal structure of compound **1.105**.

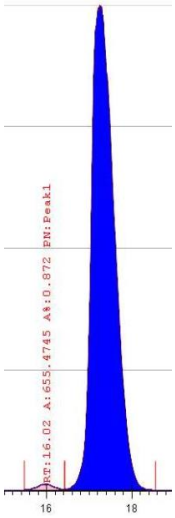
Chiral SFC (Chiralcel OD-H, 9% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (1R)-2-(4-fluorophenyl)-2-(4-methoxyphenyl)-1-phenylethan-1-ol.

Racemic Material



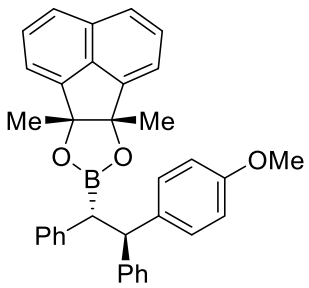
Peak No	% Area	Area	RT (min)
1	51.6168	23769.3094	15.65
2	48.3832	22280.2598	17.43
Total:	100	46049.5692	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	0.872	655.4745	16.02
2	99.128	74514.8681	17.25
Total:	100	75170.3426	

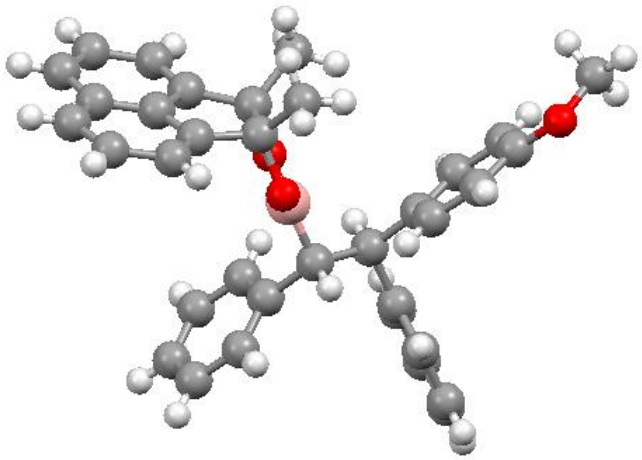
1.3.4 Gram-scale reaction and transformations of products



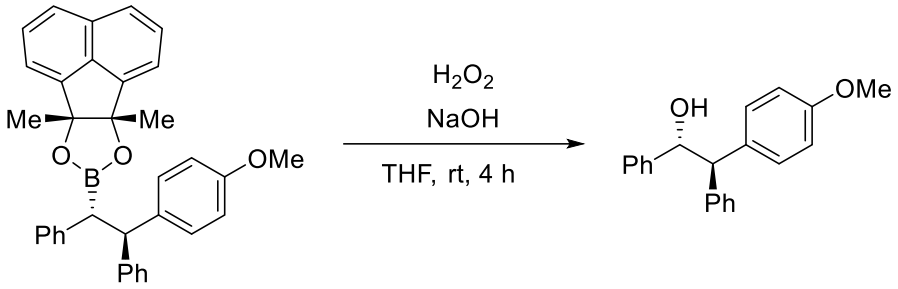
8-((1R,2R)-2-(4-methoxyphenyl)-1,2-diphenylethyl)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (1.105). The reaction was performed according to the general procedure (**Method A**) with styrenyl B(mac) (**1.79**) (1.00 g, 3.07 mmol, 1.0 equiv.), phenyllithium (1.9 M in dibutyl ether, 1.6 mL, 3.07 mmol, 1.0 equiv.), 4-methoxyphenyl trifluoromethanesulfonate (864.0 mg, 3.37 mmol, 1.1 equiv.), palladium (II) acetate (6.9 mg, 30 μmol, 0.010 equiv.), **1.1** (38.7 mg, 37 μmol), 0.012 equiv.), and cesium fluoride (465.7 mg, 3.07 mmol, 1.0 equiv.) in THF (12.3 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (2-10% EtOAc in hexanes, stain in magic stain) to afford a white solid (1.1 g, 70 % yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, J = 8.1 Hz, 2H), 7.58 – 7.49 (m, 2H), 7.41 (dd, J = 16.5, 6.9 Hz, 2H), 7.15 (d, J = 7.2 Hz, 2H), 7.09 (t, J = 7.6 Hz, 2H), 7.05 – 6.90 (m, 8H), 6.18 (d, J = 8.7 Hz, 2H), 4.25 (d, J = 12.6 Hz, 1H), 3.61 (s, 3H), 3.15 (d, J = 12.6 Hz, 1H), 1.55 (d, J = 14.6 Hz, 6H).; ^{13}C NMR (151 MHz, $CDCl_3$): δ 159.9, 147.1, 146.9, 146.8, 143.4, 139.0, 137.4, 137.3, 133.9, 131.8, 131.1, 131.0, 130.84, 130.77, 130.66, 130.5, 130.4, 130.3, 128.2, 127.92, 127.89, 127.7, 127.6, 122.2, 121.8, 121.7, 115.5, 94.5, 94.4, 57.5, 56.7, 24.9, 24.40, 24.35.; ^{11}B NMR (160 MHz, $CDCl_3$) δ 33.2.; IR (neat): ν_{max} 3058.3 (w), 3026.7 (w), 2972.6 (w), 2932.0 (w), 1607.0 (m), 1494.3 (m), 1316.6 (m), 1176.6 (m), 1034.5 (m), 846.8 (m), 699.6 (m) cm^{-1}. HRMS (DART) $C_{35}H_{35}BO_3N$ $[M+H]^+$: calculated: 528.2716, found: 528.2725. $[\alpha]^{20}_D$: -80.816 (c = 0.667, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Diastereomer ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. Racemic compound was prepared according to the procedure described above with $Pd(OAc)_2$ (2 mol%) and 1,3-Bis(diphenylphosphino)propane (2.4 mol%) as the catalyst. Enantiomeric ratio was determined by chiral SFC analysis of the corresponding alcohol (see Compound **1.84**). Absolute stereochemistry was determined by single crystal X-ray diffraction.

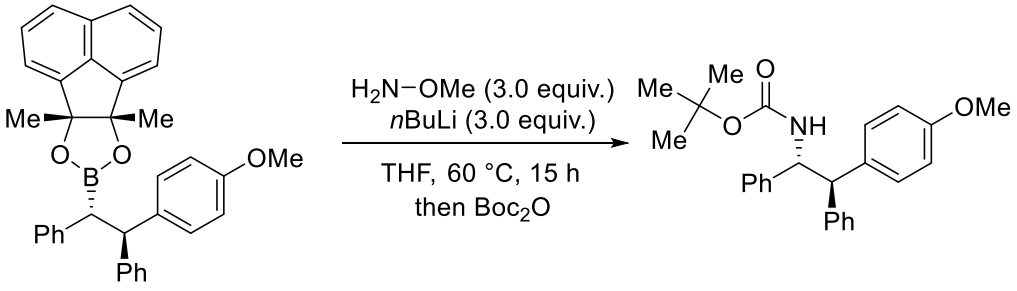


Oxidation



(1R,2R)-2-(4-methoxyphenyl)-1,2-diphenylethan-1-ol (1.84). 8-((1R,2R)-2-(4-methoxyphenyl)-1,2-diphenylethyl)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (**1.105**) (51.0 mg, 0.1 mmol, 1.0 equiv.) was dissolved in THF (2 mL) and cooled to 0 °C. 3M NaOH (1.0 mL) was added, followed by 30% H_2O_2 (0.5 mL), dropwise. The reaction mixture was allowed to stir at room temperature for 4 hours. The reaction mixture was cooled to 0 °C and saturated aq. $Na_2S_2O_3$ solution (3 mL) was added dropwise. After stirring at room temperature for 10 minutes, the reaction mixture was poured into a separatory funnel and the aqueous layer was washed three times with Et_2O. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography with silica gel (silica gel was treated with 2% triethylamine / hexanes prior to use.) (2%-20% EtOAc / hexane, stain in magic stain) to afford the desired product as a white solid (28.0 mg, 92.0% yield).

Amination



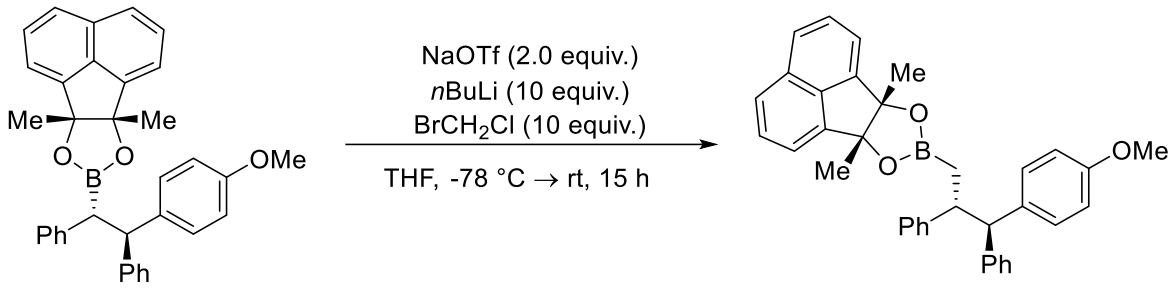
tert-butyl ((1R,2R)-2-(4-methoxyphenyl)-1,2-diphenylethyl)carbamate (1.107). The title compound was prepared according to a literature procedure.[51] A flame-dried, 2-dram vial equipped with a magnetic stir bar and septum was purged with N_2. After 5 minutes, O-methylhydroxylamine (2 M in THF, 150.00 µL, 0.3 mmol, 3.0 equiv.) was added and diluted with THF (1 mL). The reaction flask was cooled to -78 °C. A solution of *n*-butyllithium (2.5 M in hexanes, 120.00 µL, 0.3 mmol, 3.0 equiv.) was added dropwise and the reaction was allowed to stir at -78 °C for 30 min. A separate flame-dried 1-dram vial was charged with 8-((1R,2R)-2-(4-methoxyphenyl)-1,2-diphenylethyl)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (**1.105**) (51.0 mg, .1 mmol, 1.0 equiv.) and diluted with THF (0.5 mL) under N_2. The solution of boronic ester was then added dropwise to the solution of deprotonated *O*-methylhydroxylamine dropwise via syringe. The reaction vial was warmed to room temperature and then heated to 60 °C. After stirring at 60 °C for 12 h, the reaction flask was cooled to room temperature and tert-butoxycarbonyl tert-butyl carbonate (1 M in THF, 320.00 µL, 0.32 mmol, 3.2 equiv.) was added and reaction was allowed to stir for 2 h at room temperature. The reaction was filtered through a plug of celite with Et_2O and concentrated in vacuo to give the crude reaction mixture and subsequently purified by silica gel column chromatography (silica gel was treated with 2% triethylamine / hexanes prior to use) (5%-20% EtOAc / hexane, stain in magic stain) to afford the desired product as a white solid (36.0 mg, 89.2% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 – 7.01 (m, 12H), 6.87 – 6.80 (m, 2H), 5.35 (br, J = 59.7 Hz, 1H), 4.86 (br, 1H), 4.17 (d, J = 9.3 Hz, 1H), 3.78 (s, 3H), 1.32 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.4, 155.0, 142.0, 129.8, 128.4, 128.2, 128.0, 127.0, 126.9, 126.3, 113.9, 57.3, 55.2, 28.3.; IR (neat): ν_{max} 3402.9 (m), 3029.3 (w), 2975.3 (m), 2934.1 (w), 1682.8 (s), 1511.6 (s), 1248.6 (m), 1169.4 (m), 1015.3 (m), 696.5 (m) cm^{-1}. HRMS (DART) for $C_{26}H_{30}NO_3$ $[M+H]^+$: calculated: 404.2226, found: 404.2226. $[\alpha]^{20}_D$: -66.337 (c = 1.150, $CHCl_3$, *l*

= 50 mm).

Analysis of Stereochemistry:

The enantiospecificity was determined by the diastereomer ratio (>20:1) as detected by ^{1}H NMR.

Homologation



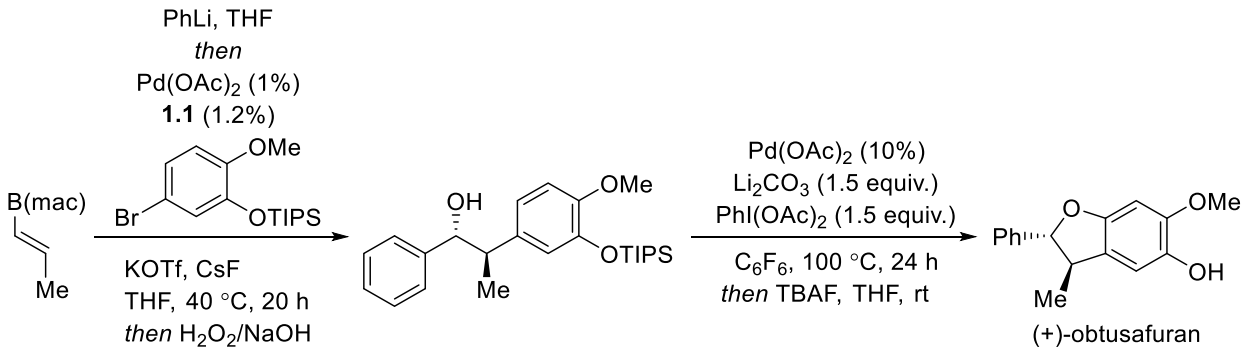
8-((2R,3R)-3-(4-methoxyphenyl)-2,3-diphenylpropyl)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (1.106). The title compound was prepared according to a literature procedure with slight modification.[52] In an argon-filled glovebox, an oven-dried 2-dram equipped with magnetic stir bar was charged with 8-((1R,2R)-2-(4-methoxyphenyl)-1,2-diphenylethyl)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (**1.105**) (51.0 mg, 0.1 mmol, 1.0 equiv.), sodium triflate (34.4 mg, 0.2 mmol, 2.0 equiv.), bromo(chloro)methane (129.4 mg, 1.0 mmol, 10 equiv.), and THF (0.75 mL). The vial was sealed with a septum cap and removed from glovebox. The reaction was cooled to -78 °C and *n*-butyllithium (2.5 M in hexane, 400.00 µL, 1.0 mmol, 10 equiv.) was added dropwise. The resulting mixture was stirred for 1 hour at –78 °C, then allowed to slowly warm to room temperature and stirred overnight. The reaction was filtered through a plug of celite with Et_2O and concentrated in vacuo. The crude product was purified by silica gel column chromatography (2%-5% EtOAc / hexane, stain in magic stain) to afford the desired product as a white solid (44.0 mg, 83.9% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76 (dd, J = 5.1, 3.1 Hz, 2H), 7.56 (dt, J = 8.2, 7.1 Hz, 2H), 7.46

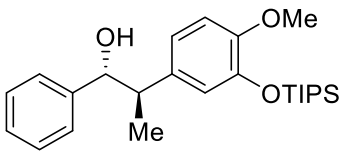
(ddd, J = 11.0, 6.9, 0.8 Hz, 2H), 7.32 – 7.23 (m, 2H), 7.17 – 7.08 (m, 2H), 7.08 – 7.00 (m, 4H), 6.98 – 6.90 (m, 1H), 6.90 – 6.78 (m, 3H), 6.75 (dd, J = 204.7, 8.8 Hz, 2H), 4.04 (d, J = 11.4 Hz, 1H), 3.72 (s, 3H), 3.62 (td, J = 11.1, 4.6 Hz, 1H), 1.54 (s, 3H), 1.48 (s, 3H), 1.11 (dd, J = 15.0, 4.6 Hz, 1H), 0.99 (dd, J = 15.1, 11.1 Hz, 1H).; ^{13}C NMR (151 MHz, $CDCl_3$): δ 160.5, 147.40, 147.37, 147.32, 146.8, 139.0, 137.2, 134.0, 132.0, 131.0, 130.9, 130.6, 130.5, 130.1, 128.1, 128.1, 127.7, 121.88, 121.85, 116.5, 94.2, 94.1, 79.9, 79.7, 79.5, 61.8, 57.8, 48.7, 24.5, 24.3.; IR (neat): ν_{max} 3059.9 (m), 3027.5 (m), 2970.5 (m), 2931.8 (m), 1608.9 (s), 1582.9 (s), 1357.0 (s), 1250.1 (s), 1175.5 (m), 1077.3 (m), 806.8 (m), 724.7 (s), 667.3 (s) cm^{-1}. HRMS (DART) for $C_{36}H_{37}BO_3N$ $[M+NH_4]^+$: calculated: 542.2866, found: 542.2894. $[\alpha]^{20}_D$: +20.029 (c = 1.000, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

The enantiospecificity was determined by the diastereomer ratio (>20:1) as detected by ^{1}H NMR.

1.3.5 Synthesis of (+)-obtusafuran

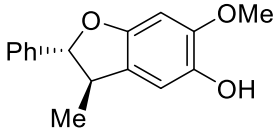




(1R,2R)-2-(4-methoxy-3-((triisopropylsilyl)oxy)phenyl)-1-phenylpropan-1-ol (1.110). The reaction was performed according to the general procedure (**Method B**) with (*E*)-propenyl B(mac) (**S-1**) (52.8 mg, 0.2 mmol, 1.0 equiv.), phenyllithium (1.9 M in dibutyl ether, 0.11 mL, 0.20 mmol, 1.0 equiv.), (5-bromo-2-methoxyphenoxy)triisopropylsilane (79.1 mg, 0.22 mmol, 1.1 equiv.), palladium (II) acetate (0.45 mg, 0.002 mmol, 0.010 equiv.), **1.57** (2.5 mg, 0.0024 mmol, 0.012 equiv.), potassium triflate (37.6 mg, 0.2 mmol, 1.0equiv.), and cesium fluoride (30.4 mg, 0.2 mmol, 1.0 equiv.) in THF (0.8 mL, 0.25 M). The crude mixture was purified by silica gel chromatography (5-20% EtOAc in hexanes, stain in magic stain) to afford a white solid (56 mg, 68% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 – 7.31 (m, 4H), 7.31 – 7.23 (m, 1H), 6.86 – 6.76 (m, 3H), 4.57 (d, J = 8.3 Hz, 1H), 3.80 (s, 3H), 2.91 (q, J = 7.4 Hz, 1H), 1.90 (br, 1H), 1.35 – 1.18 (m, 3H), 1.18 – 0.98 (m, 21H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 150.1, 145.8, 142.6, 135.5, 128.4, 127.8, 127.13, 121.07, 120.3, 112.4, 79.8, 55.7, 47.7, 18.4, 18.11, 18.08, 18.05, 13.1. IR (neat): ν_{max} 2943, 2866, 1509, 1443, 1278, 1165, 1029, 883, 700 cm^{-1}. HRMS (DART) for $C_{25}H_{39}O_3Si$ $[M+H]^+$: calculated: 415.2663, found: 415.2659. $[\alpha]^{20}_D$: +37.25 (c = 1.02, $CHCl_3$, l = 50 mm).

Analysis of Stereochemistry:

Diastereomer ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. Absolute stereochemistry was assigned by analogy.



(2R,3R)-6-methoxy-3-methyl-2-phenyl-2,3-dihydrobenzofuran-5-ol ((+)-obtusafuran) (1.111). The reaction was performed according to a literature procedure.[52a, b] In an argon-filled glovebox, to an oven-dried 1-dram vial was added 2-

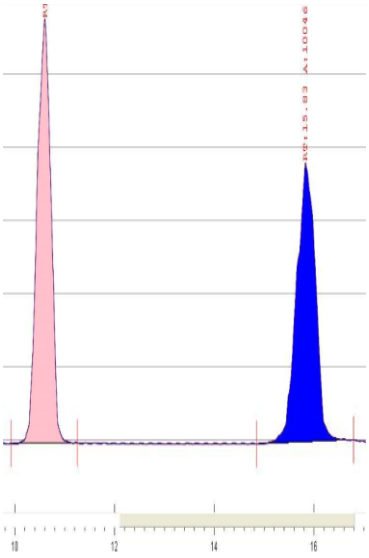
(4-methoxy-3-triisopropylsilyloxy-phenyl)-1-phenyl-propan-1-ol (56 mg, 135 μmol, 1.0 equiv.), lithium carbonate (14.97 mg, 203 μmol, 1.5 equiv.), diacetoxyiodobenzene (64.84 mg, 203 μmol, 1.5 equiv.), palladium (II) acetate (3mg, 14 μmol, 0.10 equiv.), and hexafluorobenzene (0.14 mL, 1 M). The vial was sealed with a screwcap and placed in a 100 ºC oil bath. After stirring at this temperature for 24 hours, the reaction was cooled down to room temperature and filtered through a plug of silica gel with Et_2O. The crude mixture was concentrated, then dissolved in THF (0.54 mL). Tetrabutylammonium fluoride hydrate (53 mg, 203 μmol, 1.5 equiv.) was added and the reaction was stirred at room temperature for 24 hours then filtered through a plug of silica gel with Et_2O. The solvent was evaporated and the crude product was purified by silica gel chromatography (5-20% EtOAc in hexanes, stain in magic stain) to afford a white solid (14 mg, 54 μmol, 40% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 – 7.29 (m, 5H), 6.73 (s, 1H), 6.51 (s, 1H), 5.28 (s, 1H), 5.12 (d, J = 8.5 Hz, 1H), 3.87 (s, 3H), 3.45 – 3.32 (m, 1H), 1.39 (d, J = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.6, 146.4, 141.2, 140.1, 128.8, 128.7, 128.3, 126.3, 126.2, 123.1, 109.7, 94.4, 93.0, 56.4, 45.9, 18.6. $[\alpha]^{20}_D$: +56.2 (c = 0.90, MeOH, l = 50 mm).

Analysis of Stereochemistry:

Racemic compound was prepared according to a literature procedure.[58] Absolute stereochemistry was determined by comparison of optical rotation to the literature[54] (Measured: $[\alpha]^{20}_D$: +56.2 (c = 0.90, MeOH, l = 50 mm), literature: $[\alpha]^{20}_D$: +50 (c = 0.33, MeOH), 99:1 *e.r.* for (2R,3R)-6-methoxy-3-methyl-2-phenyl-2,3-dihydrobenzofuran-5-ol), and the absolute stereochemistry was assigned to be (2R,3R)-6-methoxy-3-methyl-2-phenyl-2,3-dihydrobenzofuran-5-ol.

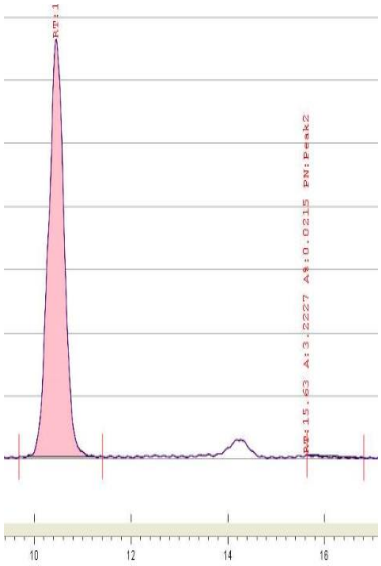
[58] Engler, T. A.; Combrink, K. D.; Letavic, M. A.; Lynch Jr.; K. O.; Ray, J. E. *J. Org. Chem*. **1994**, *59*, 6567-6587

Racemic material

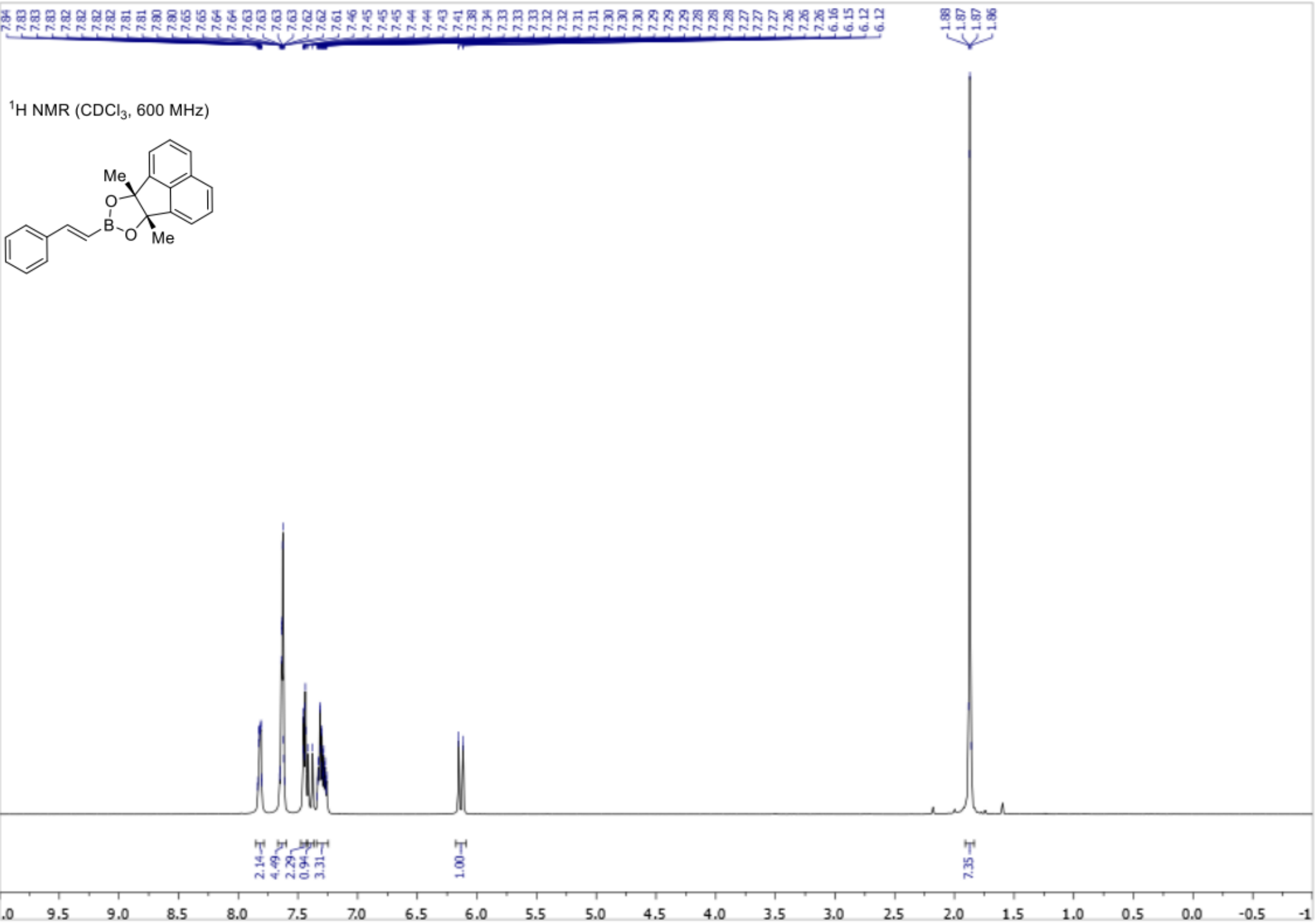


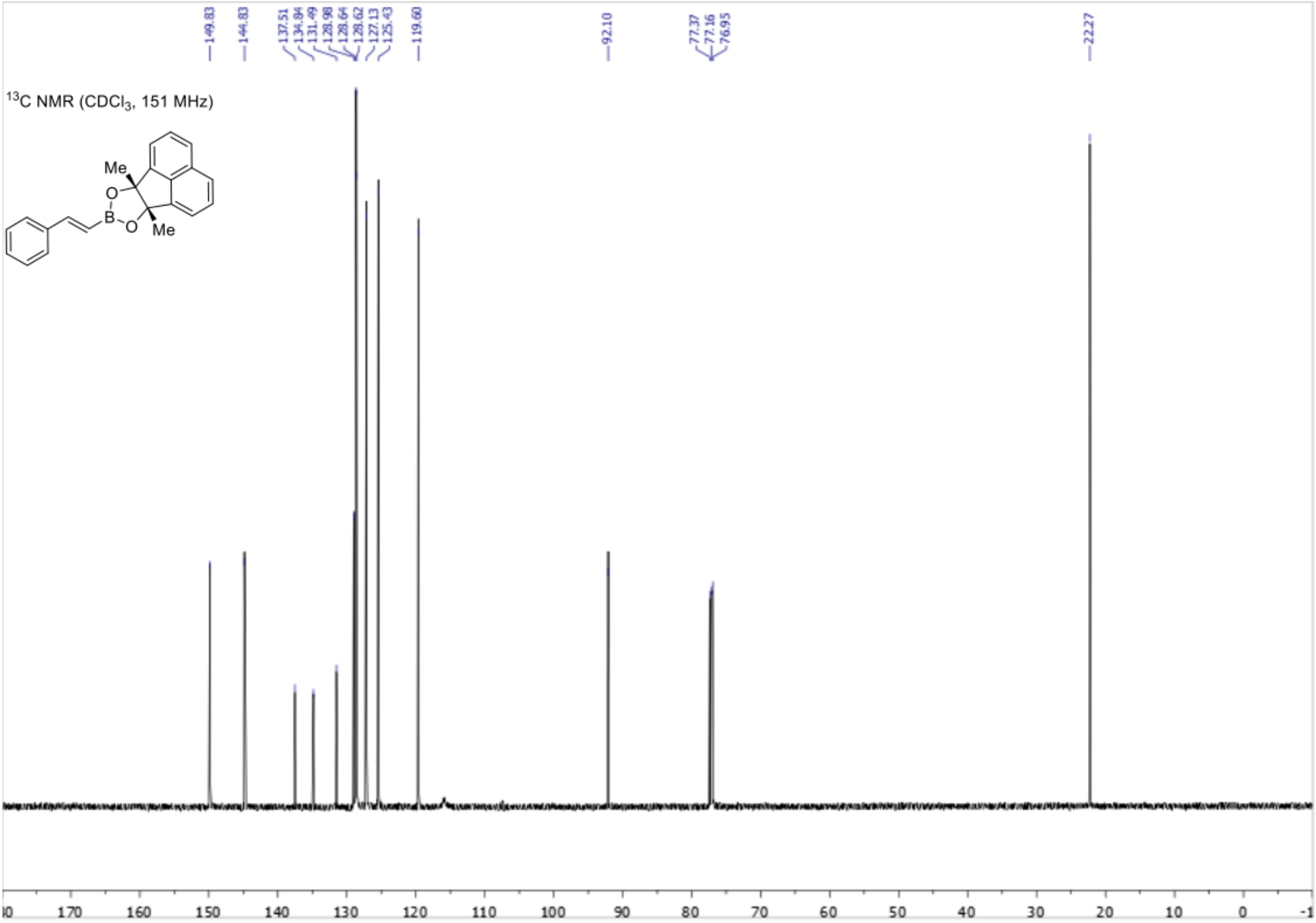
Peak No	% Area	Area	RT (min)
1	52.64	11166.1069	10.61
2	47.36	10046.088	15.83
Total:	100	21212.1949	

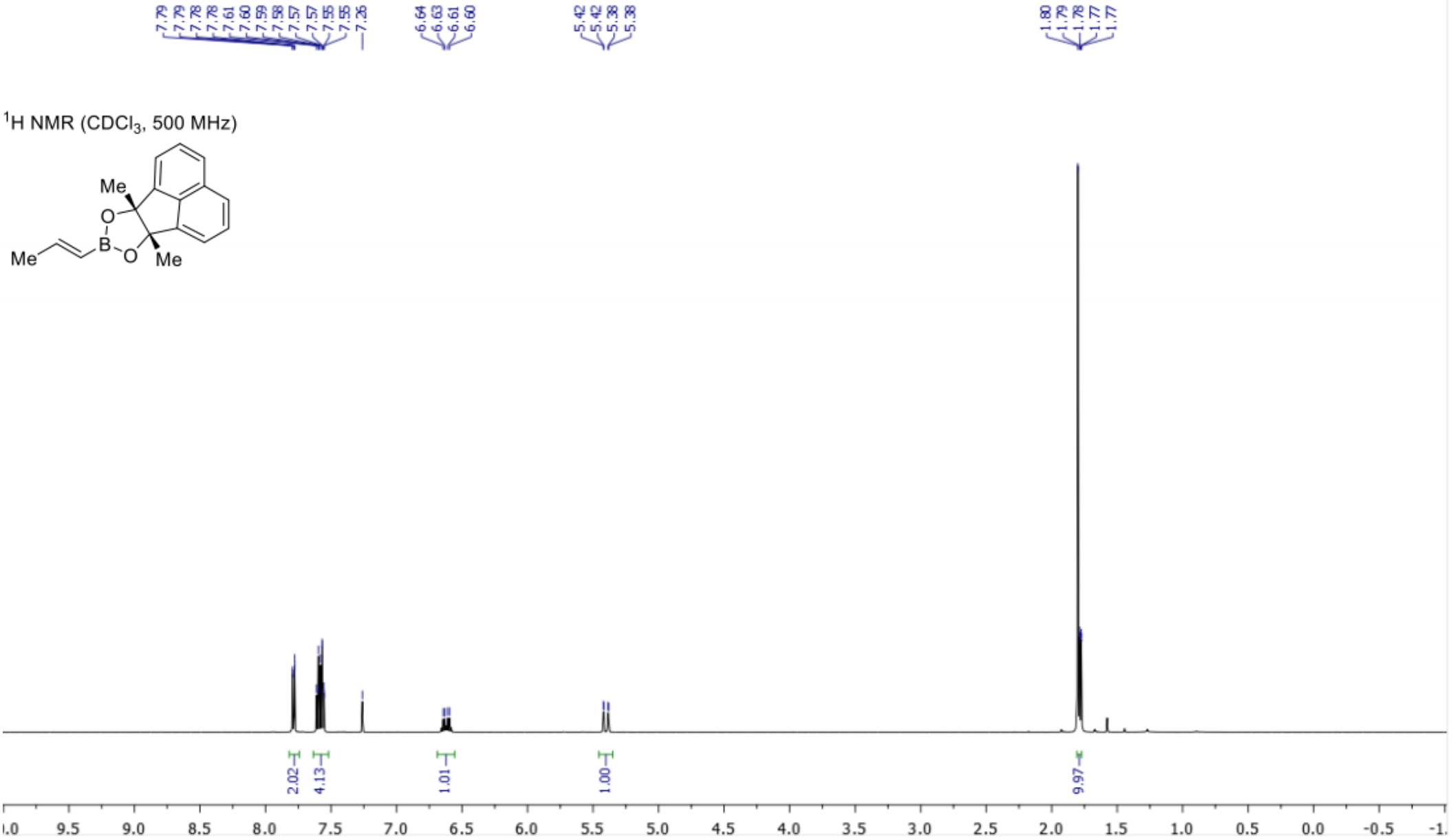
Standard Conditions

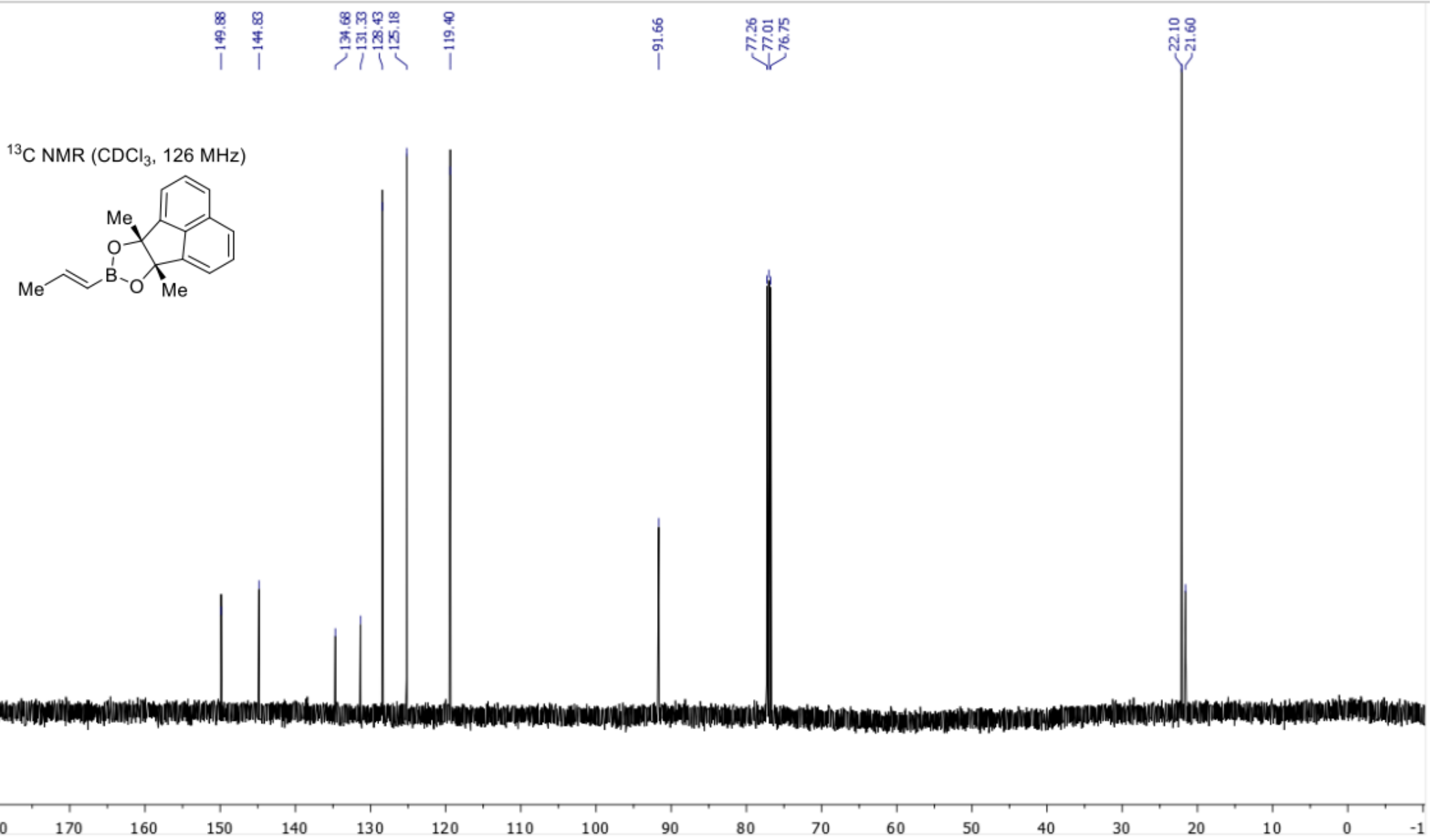


Peak No	% Area	Area	RT (min)
1	99.9785	14956.6731	10.45
2	0.0215	3.2227	15.63
Total:	100	14959.8958	

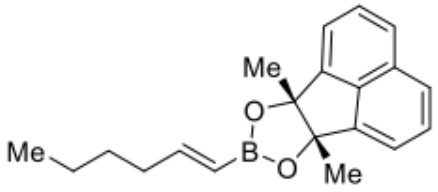

^{1}H NMR ($CDCl_3$, 600 MHz)
Me
O
B
O
Me

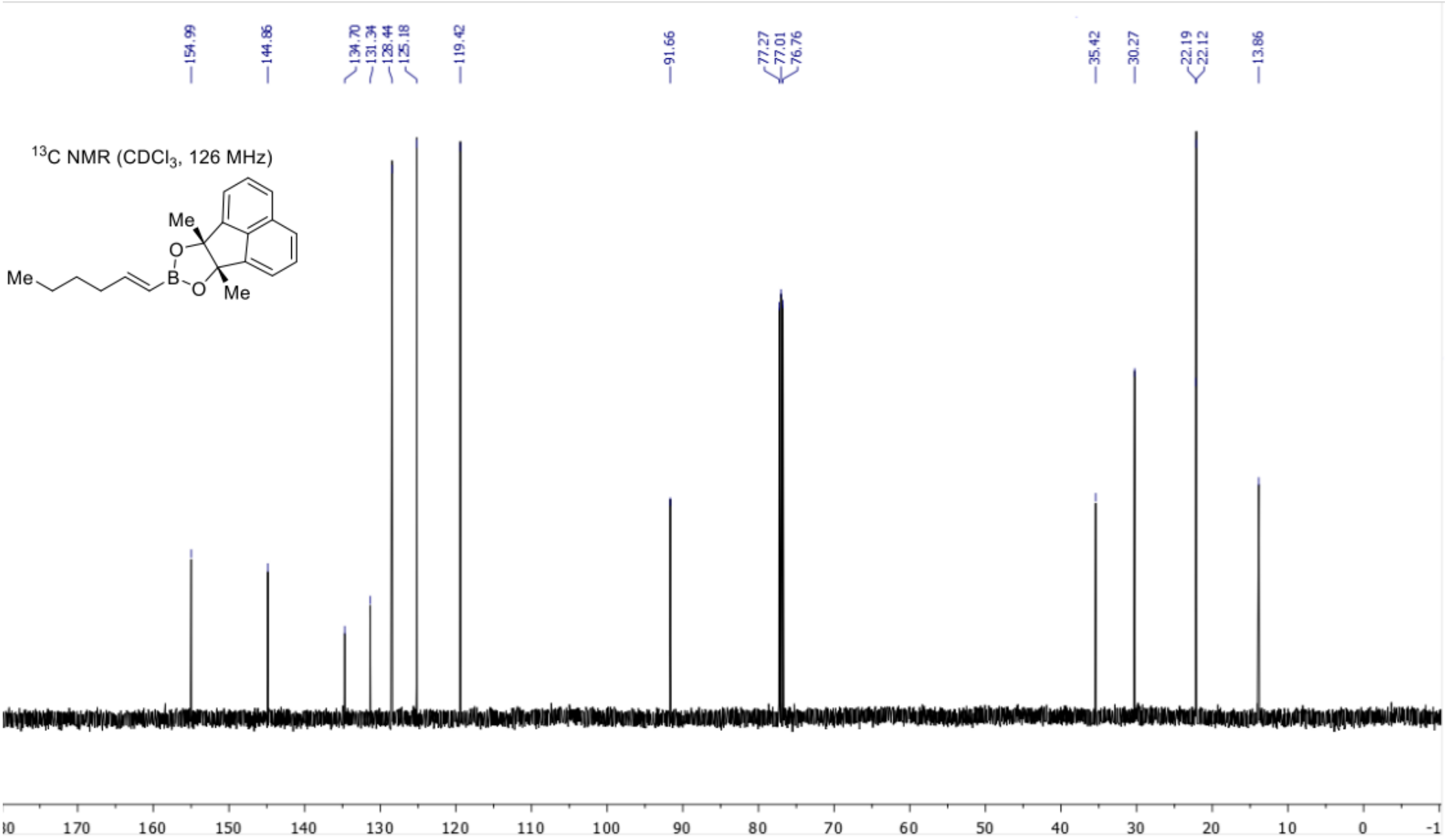

149.83
144.83
137.51
134.84
131.49
128.98
128.64
128.62
127.13
125.43
119.60
92.10
77.37
77.16
76.95
22.27
13C NMR (CDCl3, 151 MHz)
Me
O
B
O
Me
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


7.79
7.79
7.78
7.78
7.61
7.60
7.59
7.58
7.57
7.57
7.55
7.55
7.26
6.64
6.63
6.61
6.60
5.42
5.42
5.38
5.38
1.80
1.79
1.78
1.77
1.77
^{1}H NMR ($CDCl_3$, 500 MHz)
Me
O
B
O
Me
Me
2.02
4.13
1.01
1.00
9.97
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

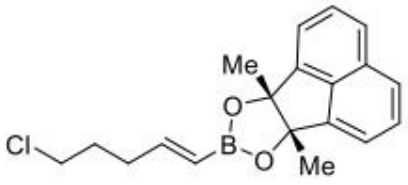

149.88
144.83
134.68
131.33
128.43
125.18
119.40
91.66
77.26
77.01
76.75
22.10
21.60
13C NMR (CDCl3, 126 MHz)
Me
O
B
O
Me
Me
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1

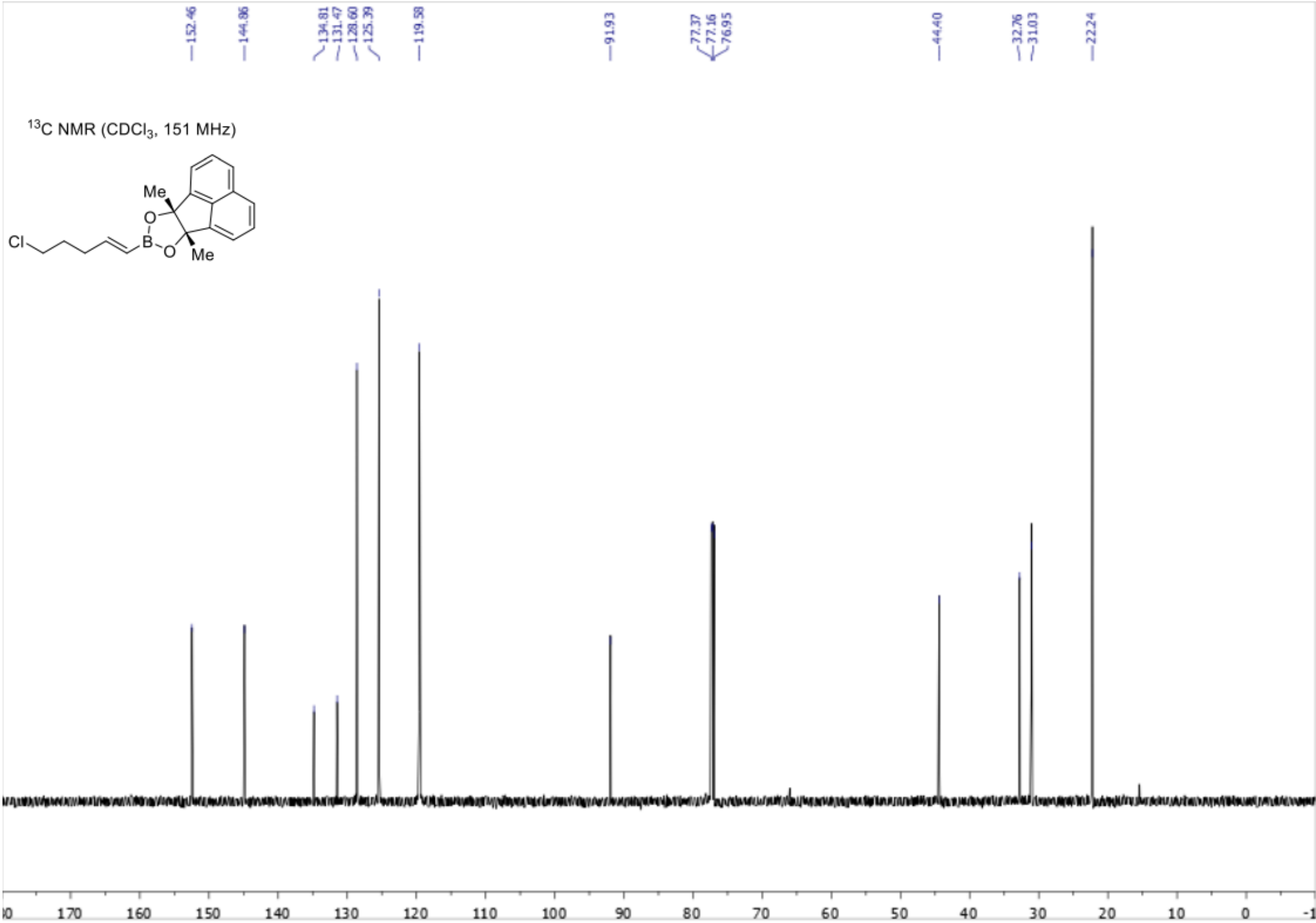
^{1}H NMR ($CDCl_3$, 500 MHz)



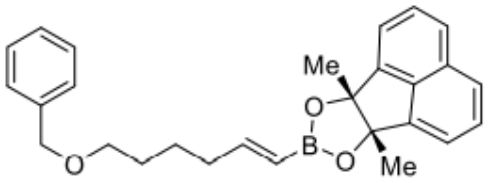

154.99
144.86
134.70
131.34
128.44
125.18
119.42
91.66
77.27
77.01
76.76
35.42
30.27
22.19
22.12
13.86
^{13}C NMR ($CDCl_3$, 126 MHz)
Me
O
B
O
Me
Me
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

^{1}H NMR ($CDCl_3$, 500 MHz)



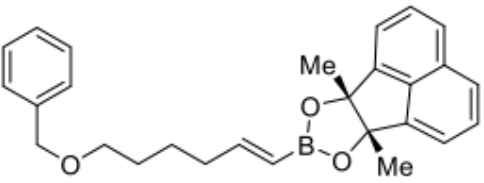

152.46
144.86
134.81
131.47
128.60
125.39
119.58
91.93
77.37
77.16
76.95
44.40
32.76
31.03
22.24
^{13}C NMR ($CDCl_3$, 151 MHz)
Me
O
B
O
Me
Cl
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

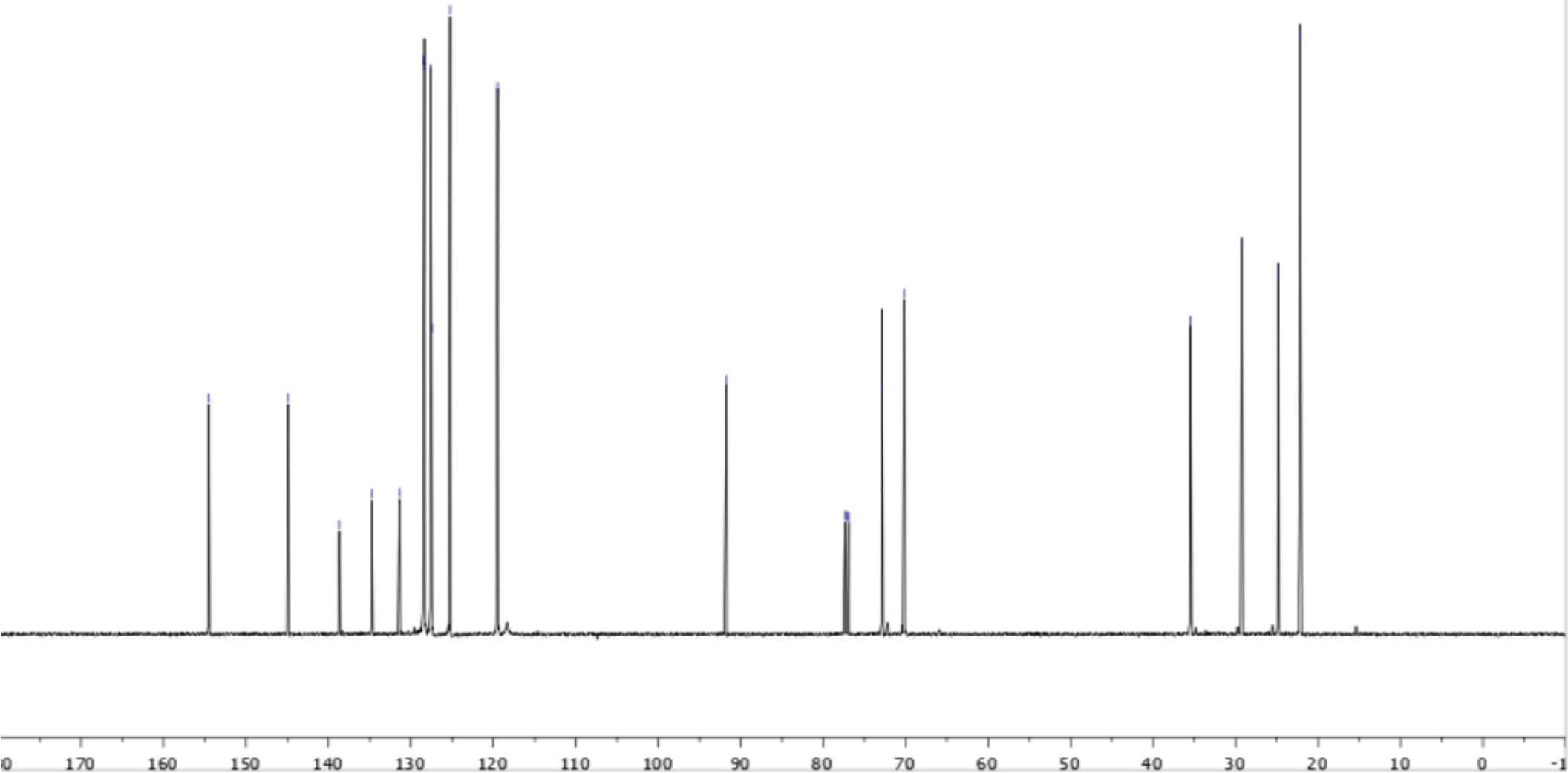
^{13}C NMR ($CDCl_3$, 151 MHz)

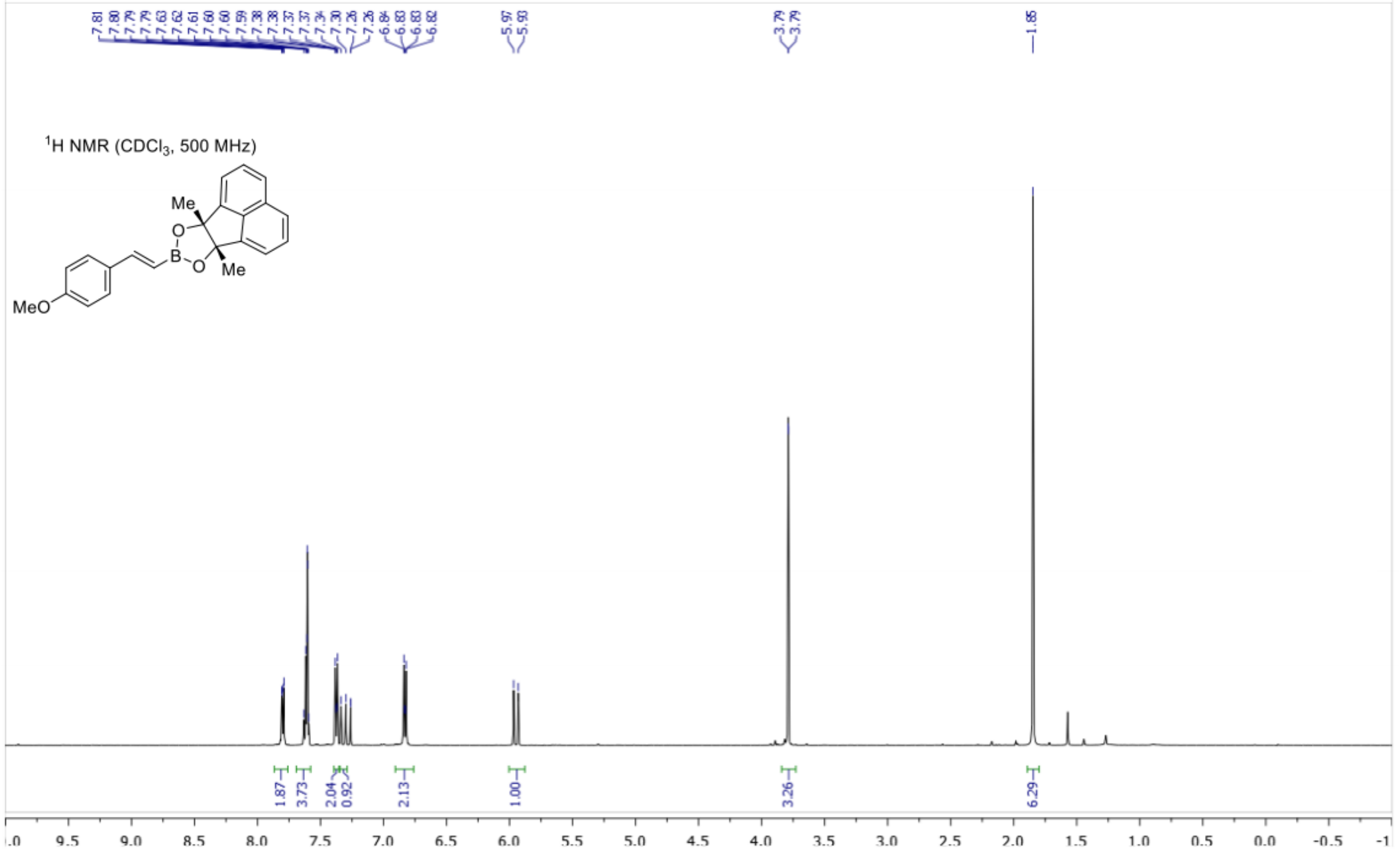


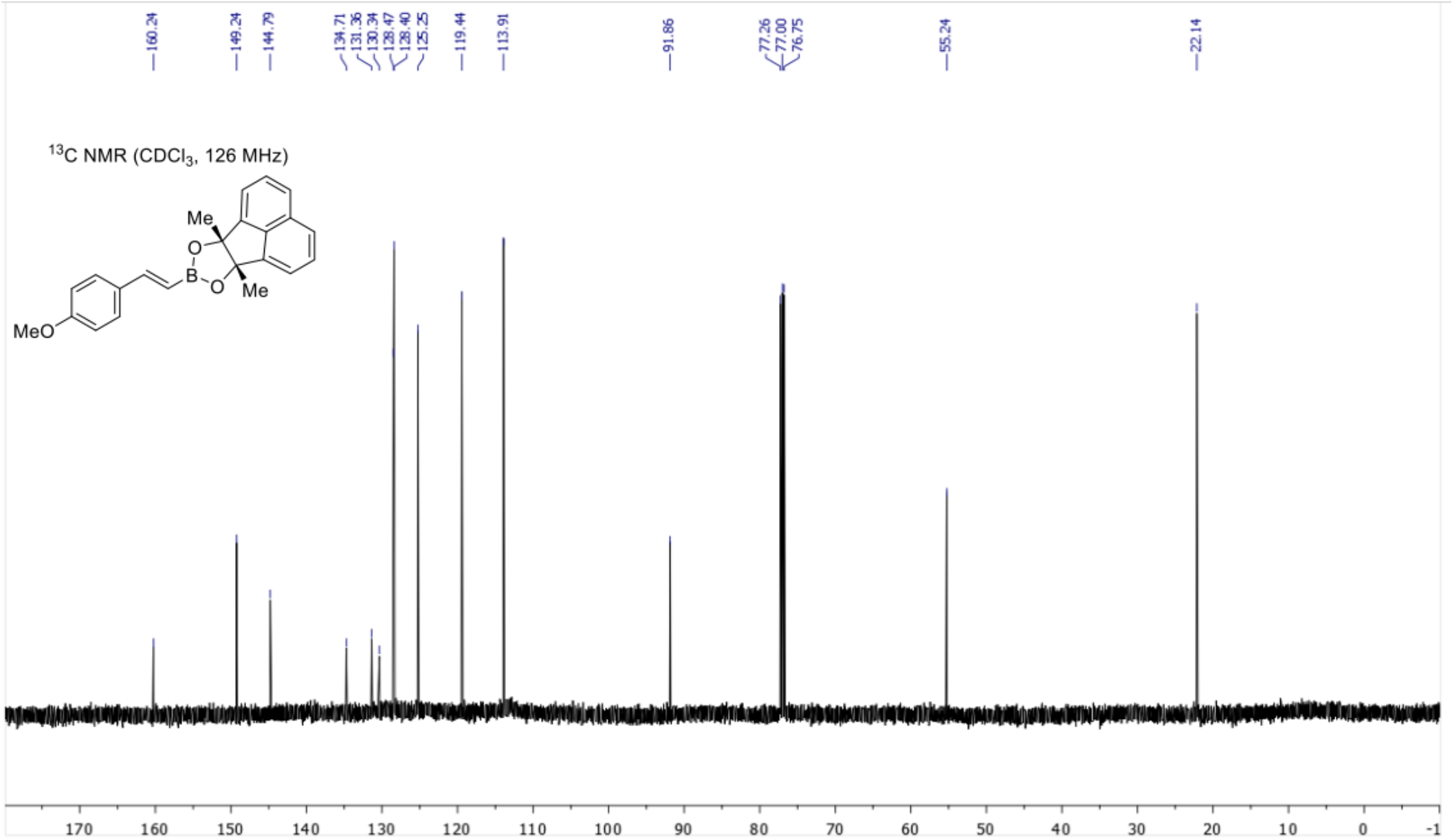
154.51
144.89
138.66
134.74
131.38
128.50
128.36
127.61
127.49
125.26
119.48
91.73
77.37
77.16
76.95
72.89
70.15
35.50
29.26
24.79
22.18

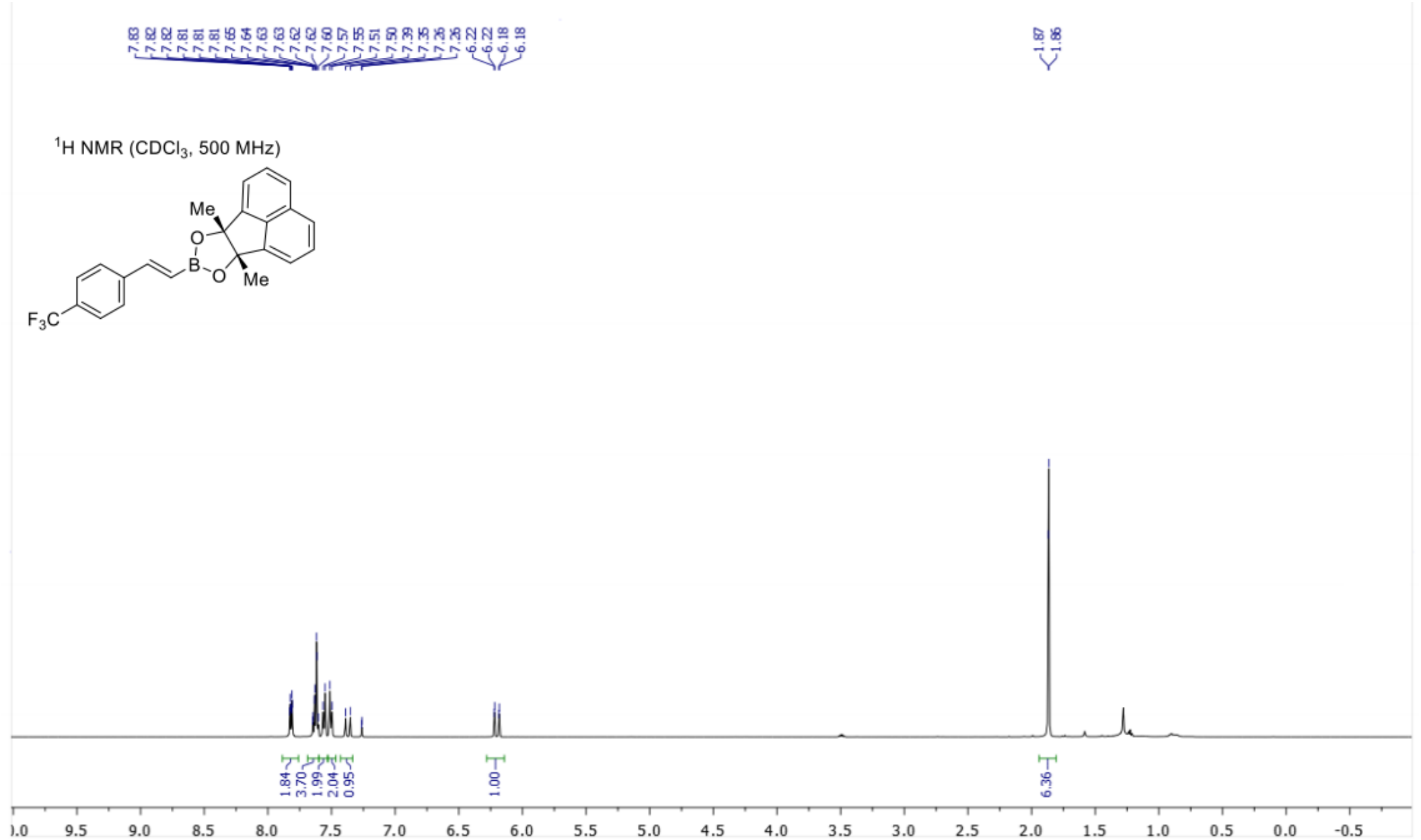
^{13}C NMR ($CDCl_3$, 151 MHz)

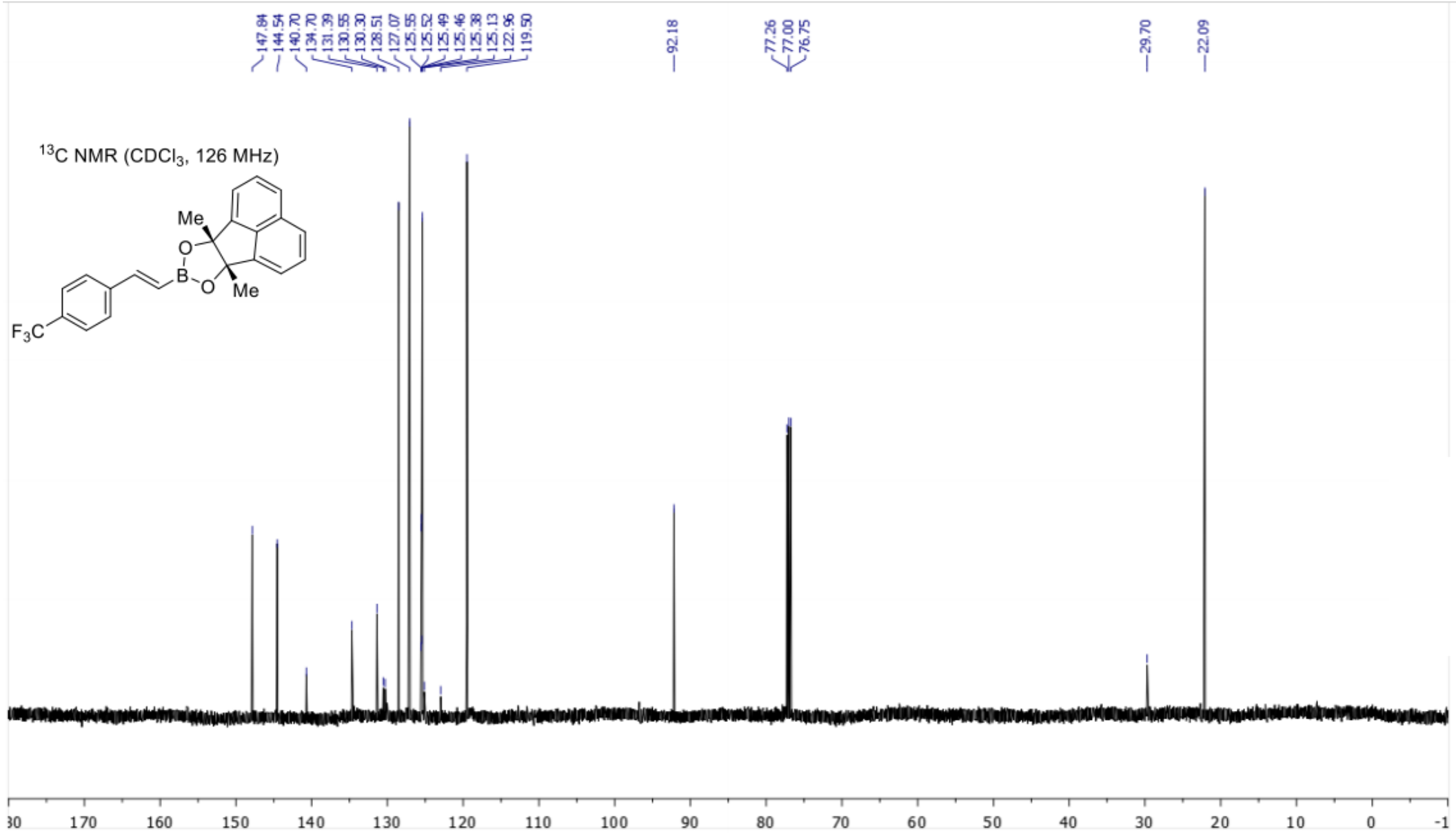


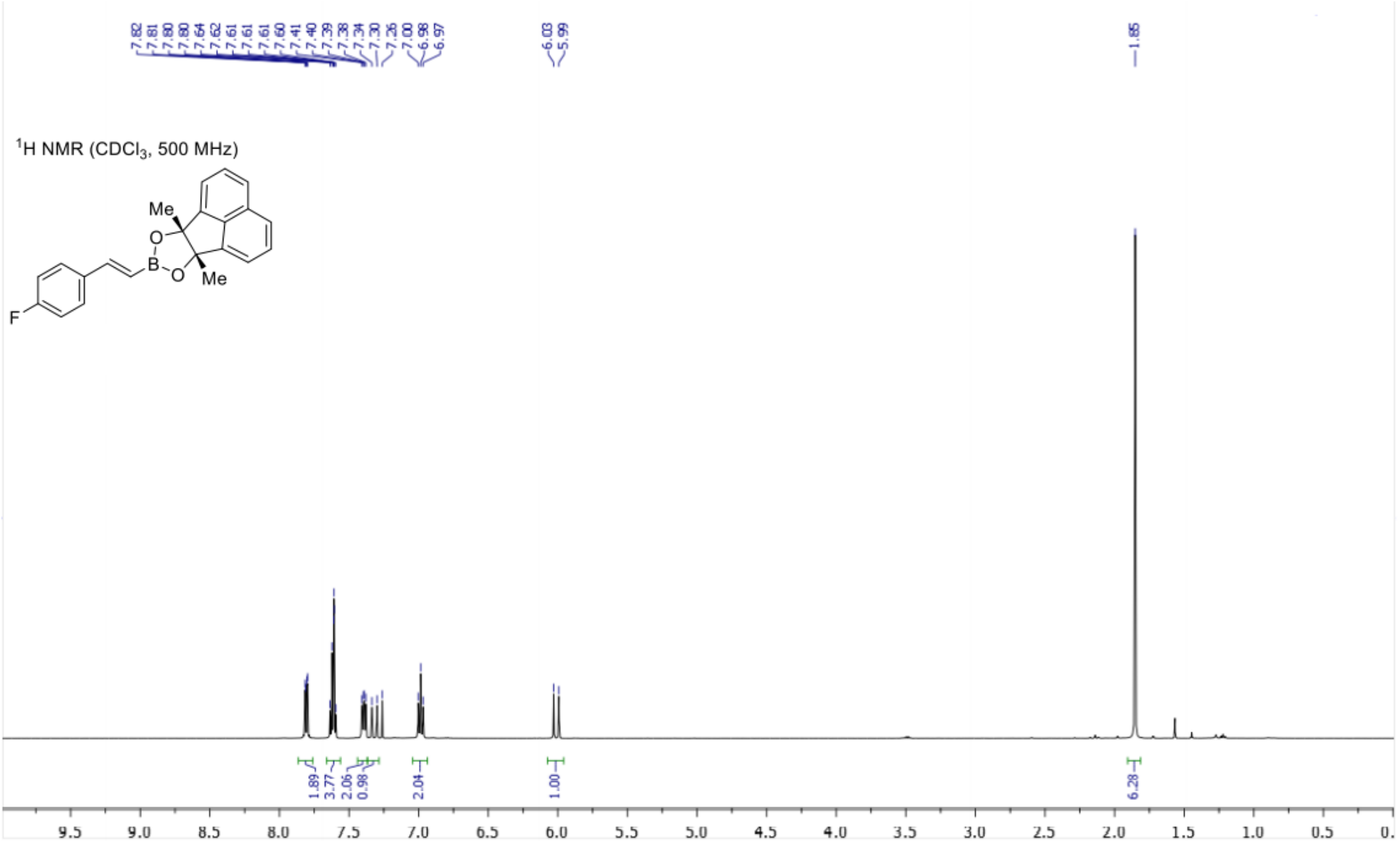


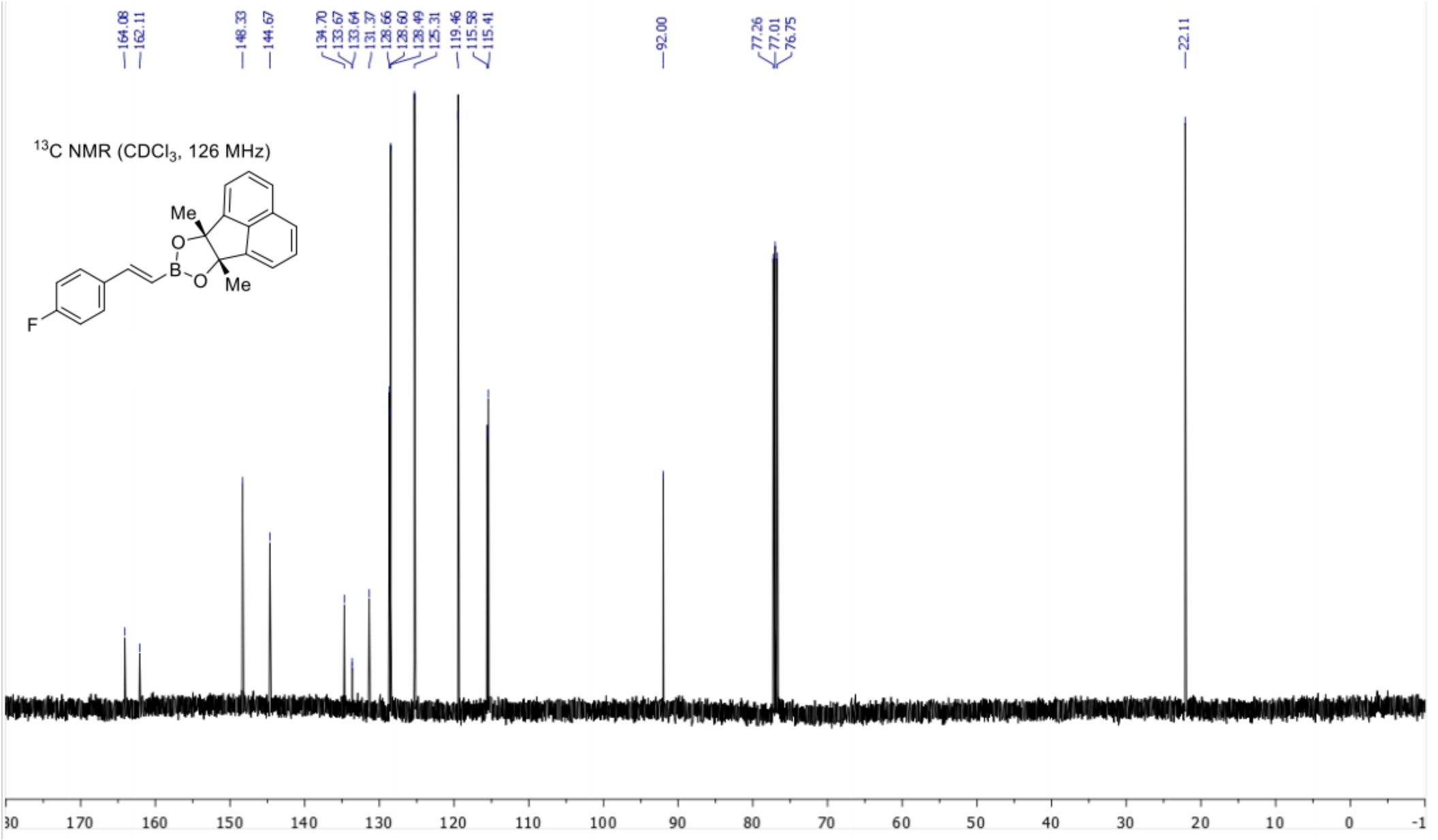

7.81
7.80
7.79
7.79
7.63
7.62
7.61
7.60
7.60
7.59
7.38
7.38
7.37
7.37
7.34
7.30
7.26
7.26
6.84
6.83
6.83
6.82
5.97
5.93
3.79
3.79
1.85
1H NMR (CDCl3, 500 MHz)
Me
O
B
O
Me
MeO
1.87
3.73
2.04
0.92
2.13
1.00
3.26
6.29
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

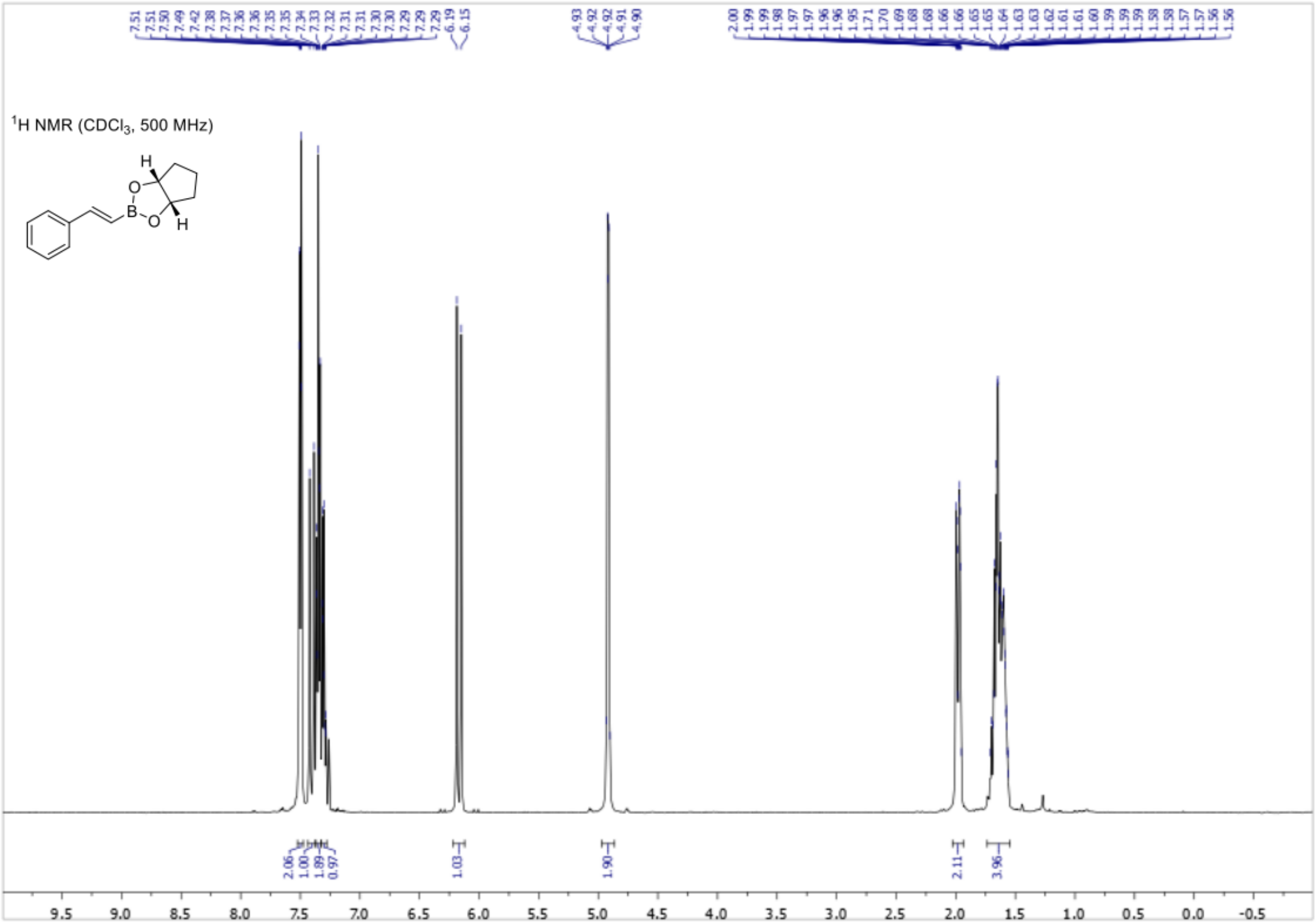

160.24
149.24
144.79
134.71
131.36
130.34
128.47
128.40
125.25
119.44
113.91
91.86
77.26
77.00
76.75
55.24
22.14
13C NMR (CDCl3, 126 MHz)
Me
O
B
O
Me
MeO
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1

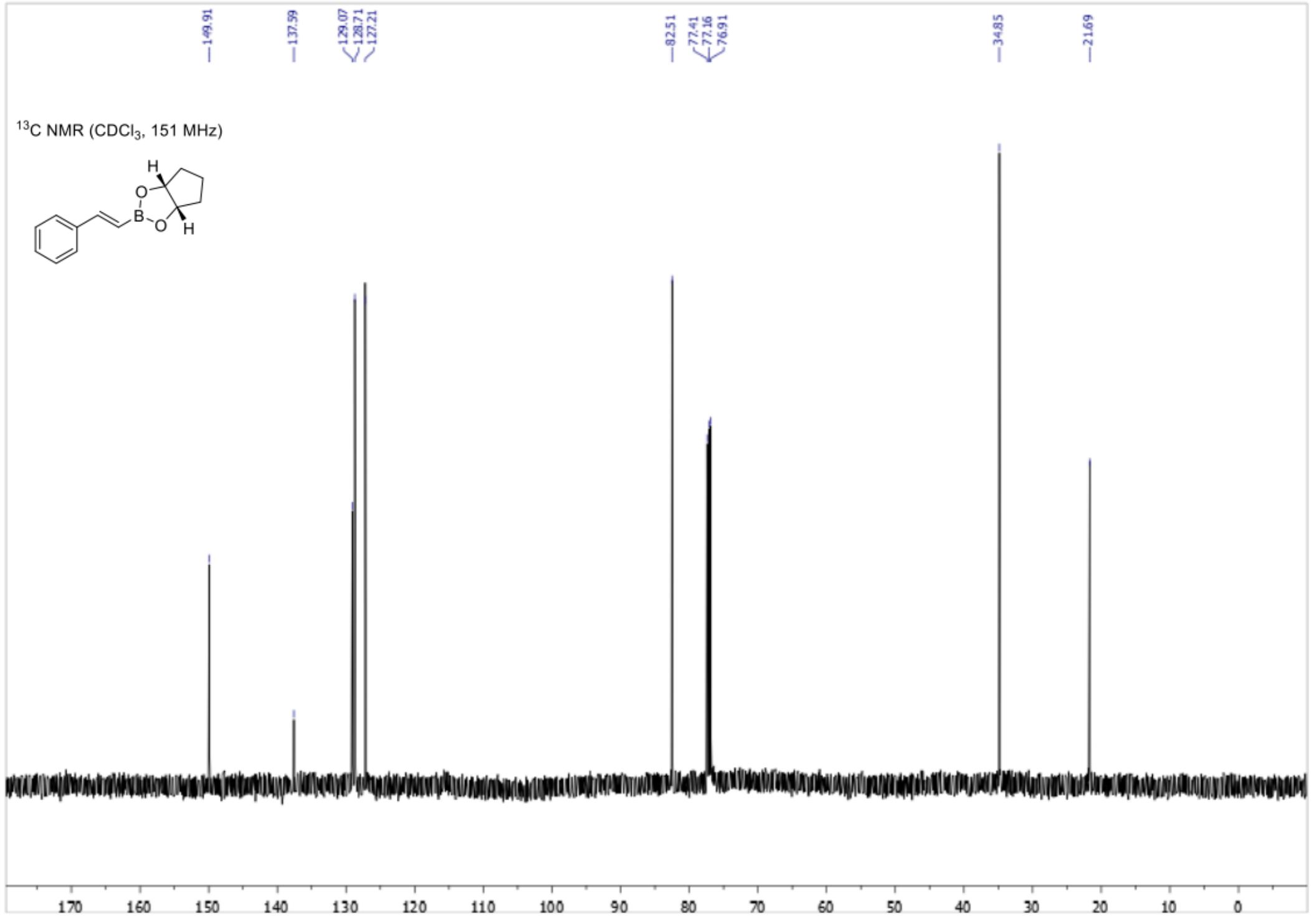

7.83
7.82
7.82
7.81
7.81
7.81
7.65
7.64
7.63
7.63
7.62
7.62
7.60
7.57
7.55
7.51
7.50
7.39
7.35
7.26
7.26
6.22
6.22
6.18
6.18
1.87
1.86
1H NMR (CDCl3, 500 MHz)
Me
O
B
O
Me
F3C
1.84
3.70
1.99
2.04
0.95
1.00
6.36
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

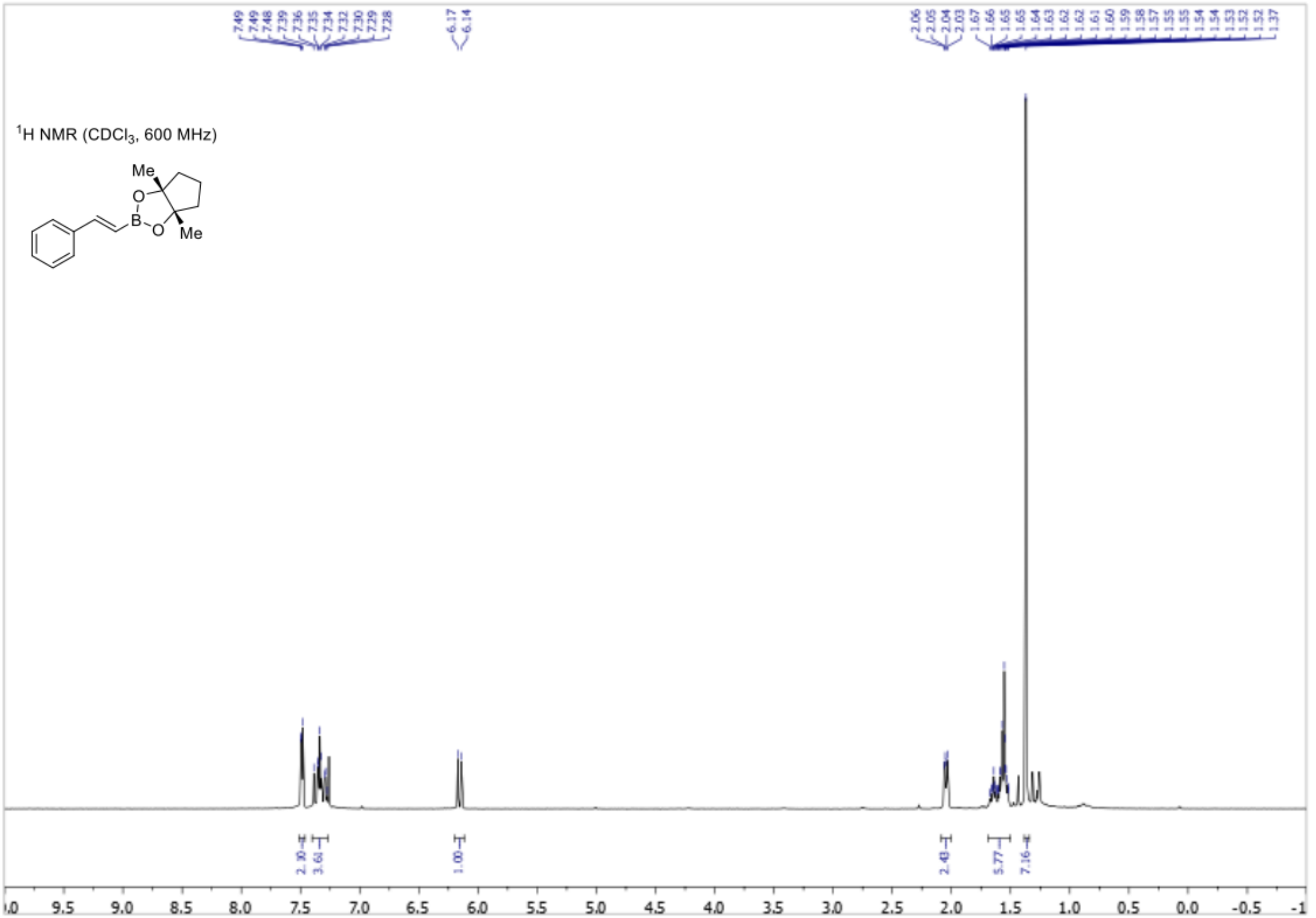

147.84
144.54
140.70
134.70
131.39
130.55
130.30
128.51
127.07
125.55
125.52
125.49
125.46
125.38
125.13
122.96
119.50
92.18
77.26
77.00
76.75
29.70
22.09
13C NMR (CDCl3, 126 MHz)
Me
O
B
O
Me
F3C
30
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1

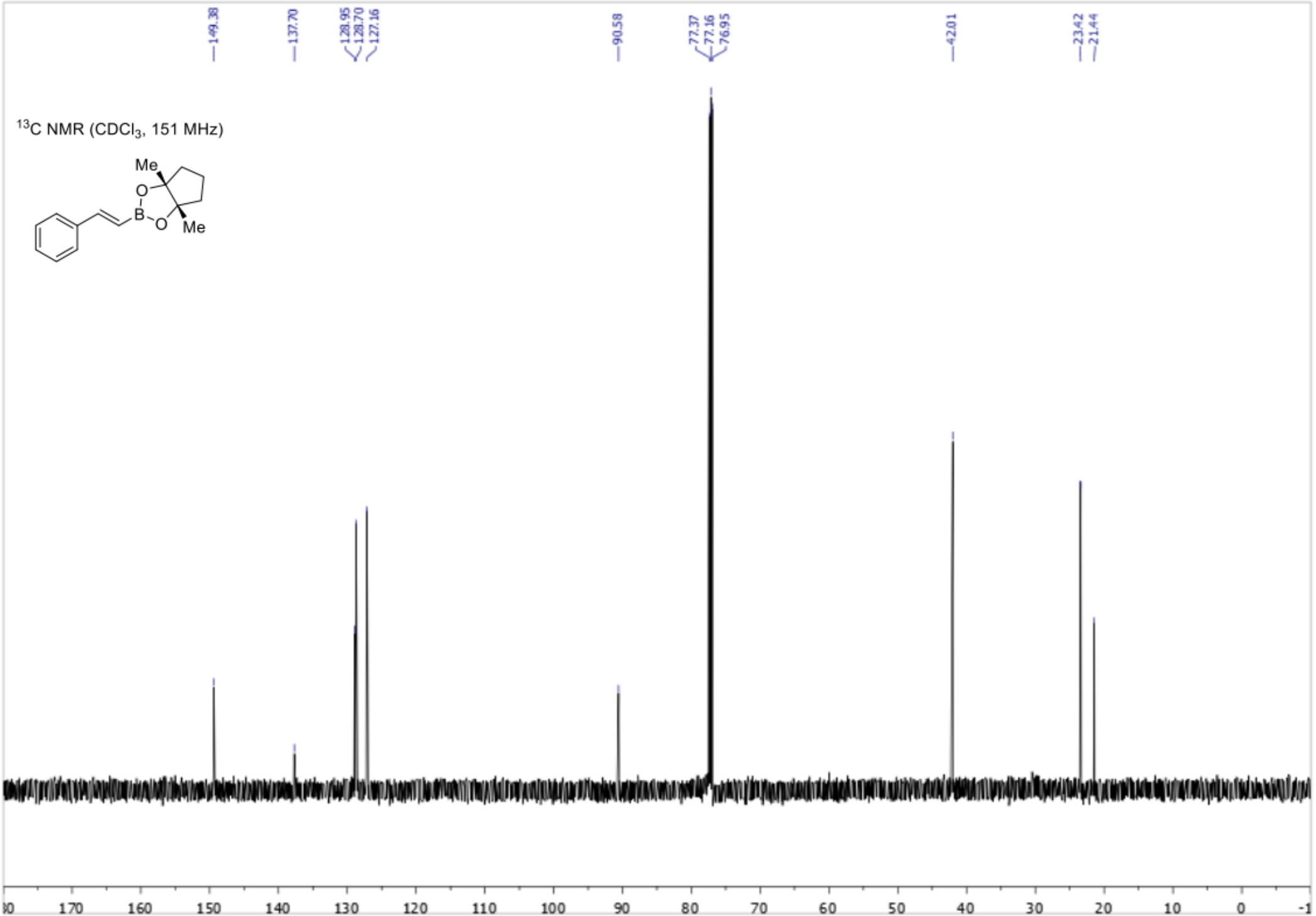

7.82
7.81
7.80
7.80
7.64
7.62
7.61
7.61
7.61
7.60
7.41
7.40
7.39
7.38
7.34
7.30
7.26
7.00
6.98
6.97
6.03
5.99
1.85
^{1}H NMR ($CDCl_3$, 500 MHz)
Me
O
B
O
Me
F
1.89
3.77
2.06
0.98
2.04
1.00
6.28
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5


164.08
162.11
148.33
144.67
134.70
133.67
133.64
131.37
128.66
128.60
128.49
125.31
119.46
115.58
115.41
92.00
77.26
77.01
76.75
22.11
13C NMR (CDCl3, 126 MHz)
Me
O
B
O
Me
F
30
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1

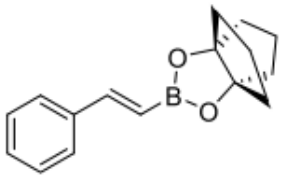

7.51 7.51 7.50 7.49 7.42 7.38 7.37 7.36 7.36 7.35 7.35 7.34 7.33 7.32 7.31 7.31 7.30 7.30 7.29 7.29 7.29 6.19 6.15
4.93 4.92 4.92 4.91 4.90
2.00 1.99 1.99 1.98 1.97 1.97 1.96 1.96 1.95 1.71 1.70 1.69 1.68 1.68 1.66 1.66 1.65 1.65 1.64 1.63 1.63 1.62 1.61 1.61 1.60 1.59 1.59 1.59 1.58 1.58 1.57 1.57 1.56 1.56
^{1}H NMR ($CDCl_3$, 500 MHz)
H
O
B
O
H
2.06
1.00
1.89
0.97
1.03
1.90
2.11
3.96
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

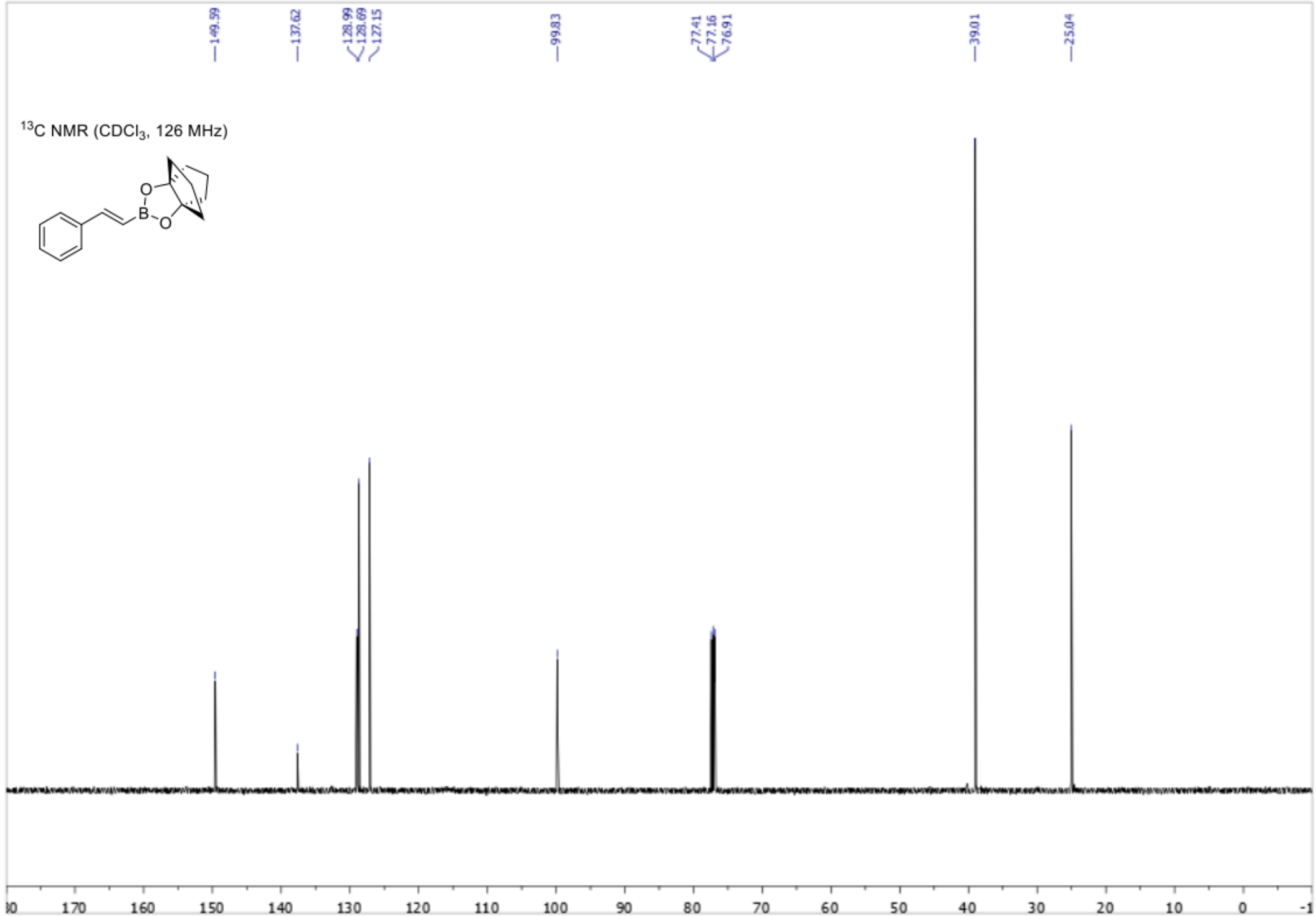

149.91
137.59
129.07
128.71
127.21
82.51
77.41
77.16
76.91
34.85
21.69
13C NMR (CDCl3, 151 MHz)
H
O
B
O
H
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

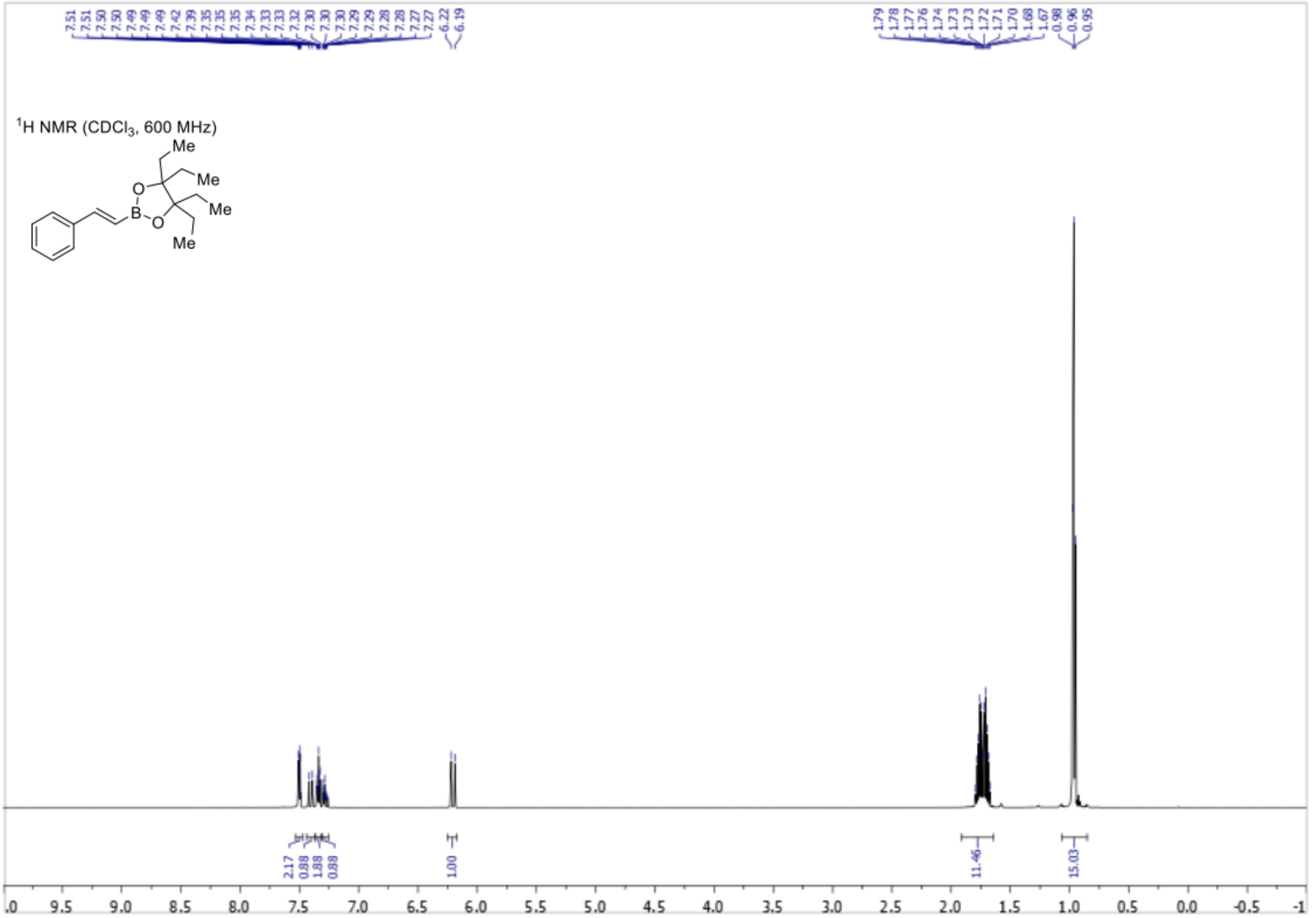

7.49
7.49
7.48
7.39
7.36
7.35
7.34
7.32
7.30
7.29
7.28
6.17
6.14
2.06
2.05
2.04
2.03
1.67
1.66
1.65
1.65
1.64
1.63
1.62
1.62
1.61
1.60
1.59
1.58
1.57
1.55
1.55
1.54
1.54
1.53
1.52
1.52
1.37
^{1}H NMR ($CDCl_3$, 600 MHz)
Me
O
B
O
Me
2.30
3.61
1.00
2.43
5.77
7.16
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

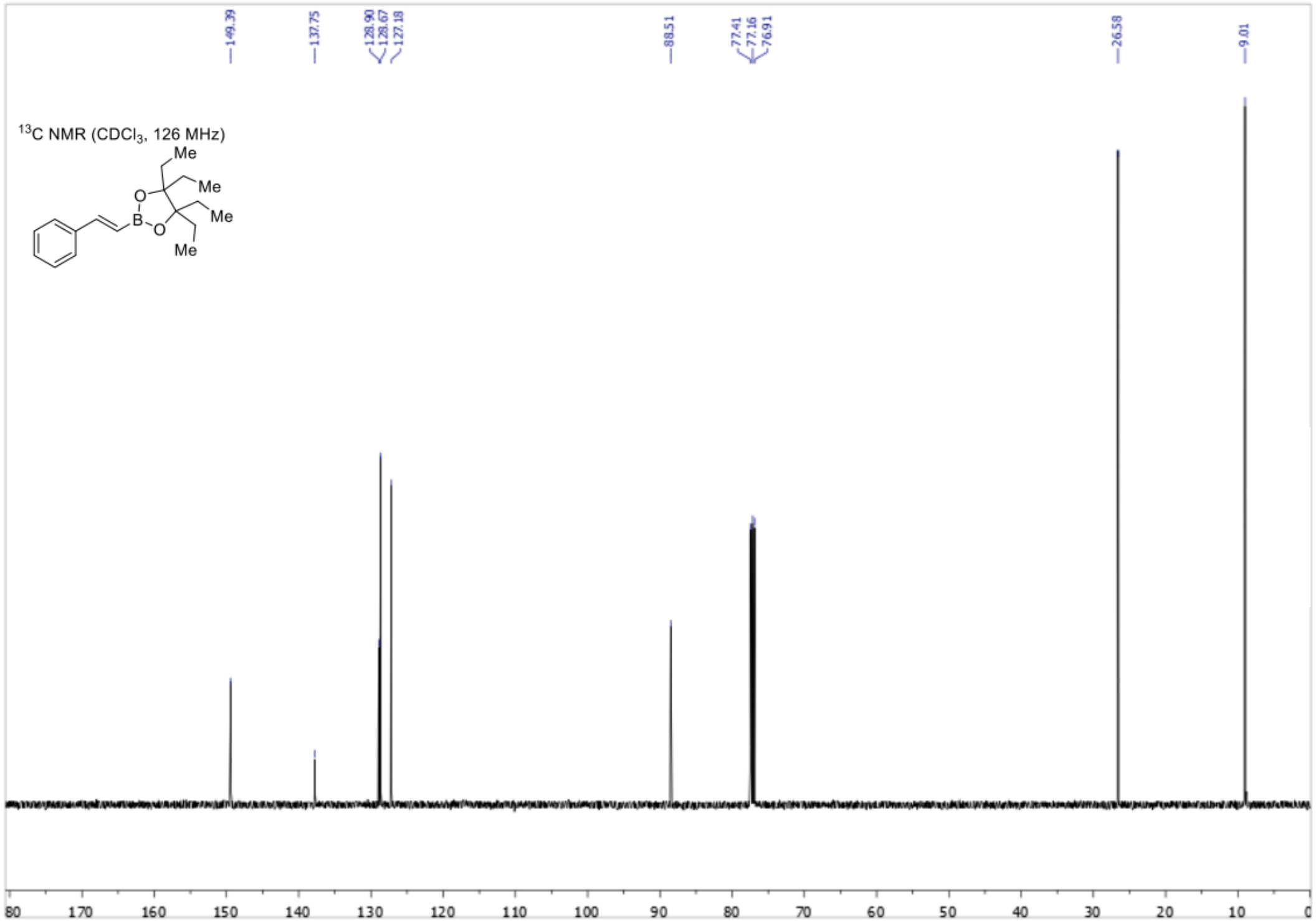

149.38
137.70
128.95
128.70
127.16
90.58
77.37
77.16
76.95
42.01
23.42
21.44
^{13}C NMR ($CDCl_3$, 151 MHz)
Me
O
B
O
Me
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

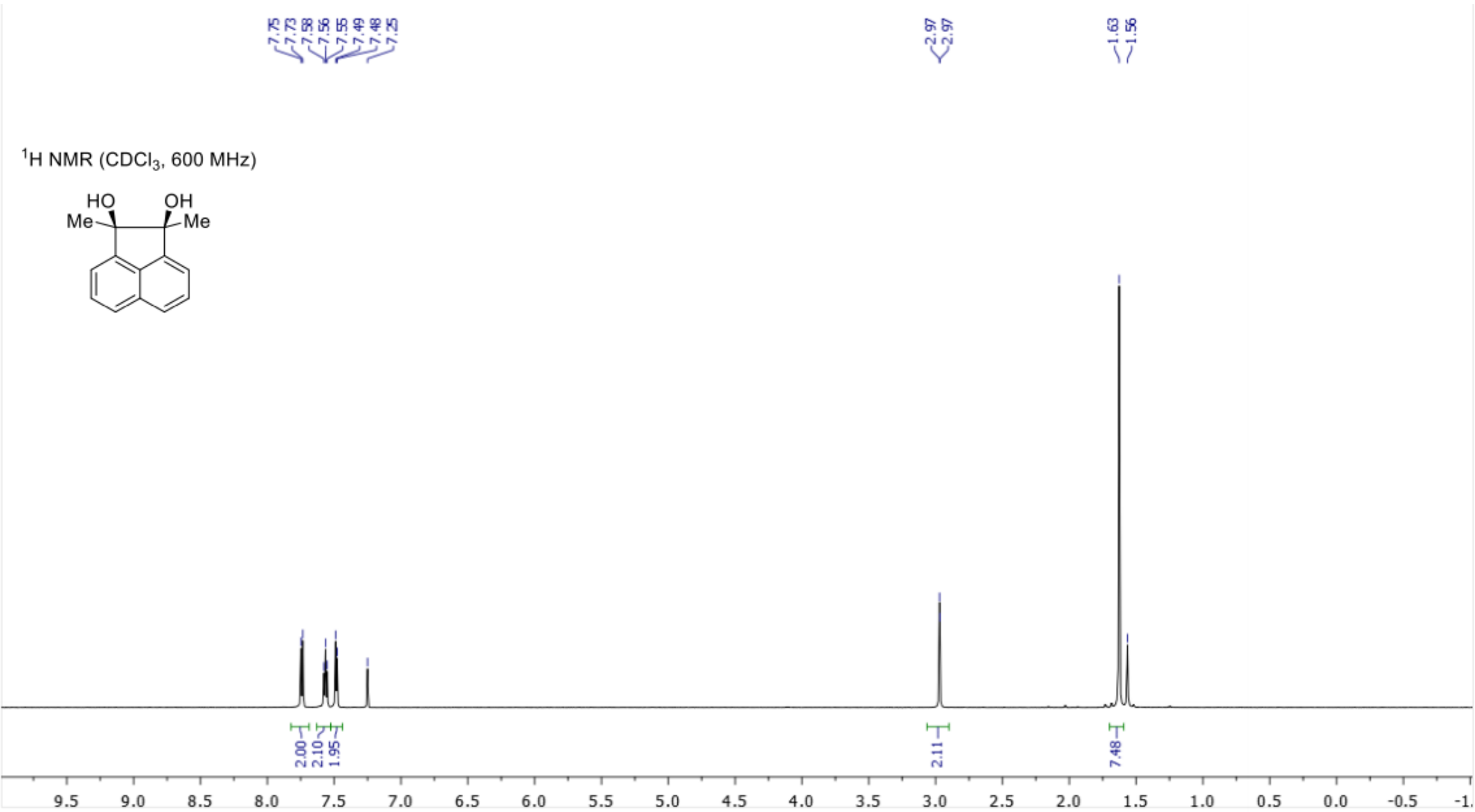
^{1}H NMR ($CDCl_3$, 500 MHz)




149.59
137.62
128.99
128.69
127.15
99.83
77.41
77.16
76.91
39.01
25.04
13C NMR (CDCl3, 126 MHz)
O
B
O
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


7.51 7.51 7.50 7.50 7.49 7.49 7.49 7.42 7.39 7.35 7.35 7.35 7.34 7.33 7.33 7.32 7.30 7.30 7.30 7.29 7.29 7.28 7.28 7.27 7.27 6.22 6.19
1.79 1.78 1.77 1.76 1.74 1.73 1.73 1.72 1.71 1.70 1.68 1.67 0.98 0.96 0.95
1H NMR (CDCl3, 600 MHz)
Me
Me
Me
Me
O
B
O
2.17 0.88 1.88 0.88 1.00 11.46 15.03
.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


149.39
137.75
128.90
128.67
127.18
88.51
77.41
77.16
76.91
26.58
9.01
^{13}C NMR ($CDCl_3$, 126 MHz)
Me
Me
Me
Me
O
B
O
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10


7.75
7.73
7.58
7.56
7.55
7.49
7.48
7.25
2.97
2.97
1.63
1.56
^{1}H NMR ($CDCl_3$, 600 MHz)
HO
OH
Me
Me
2.00
2.10
1.95
2.11
7.48
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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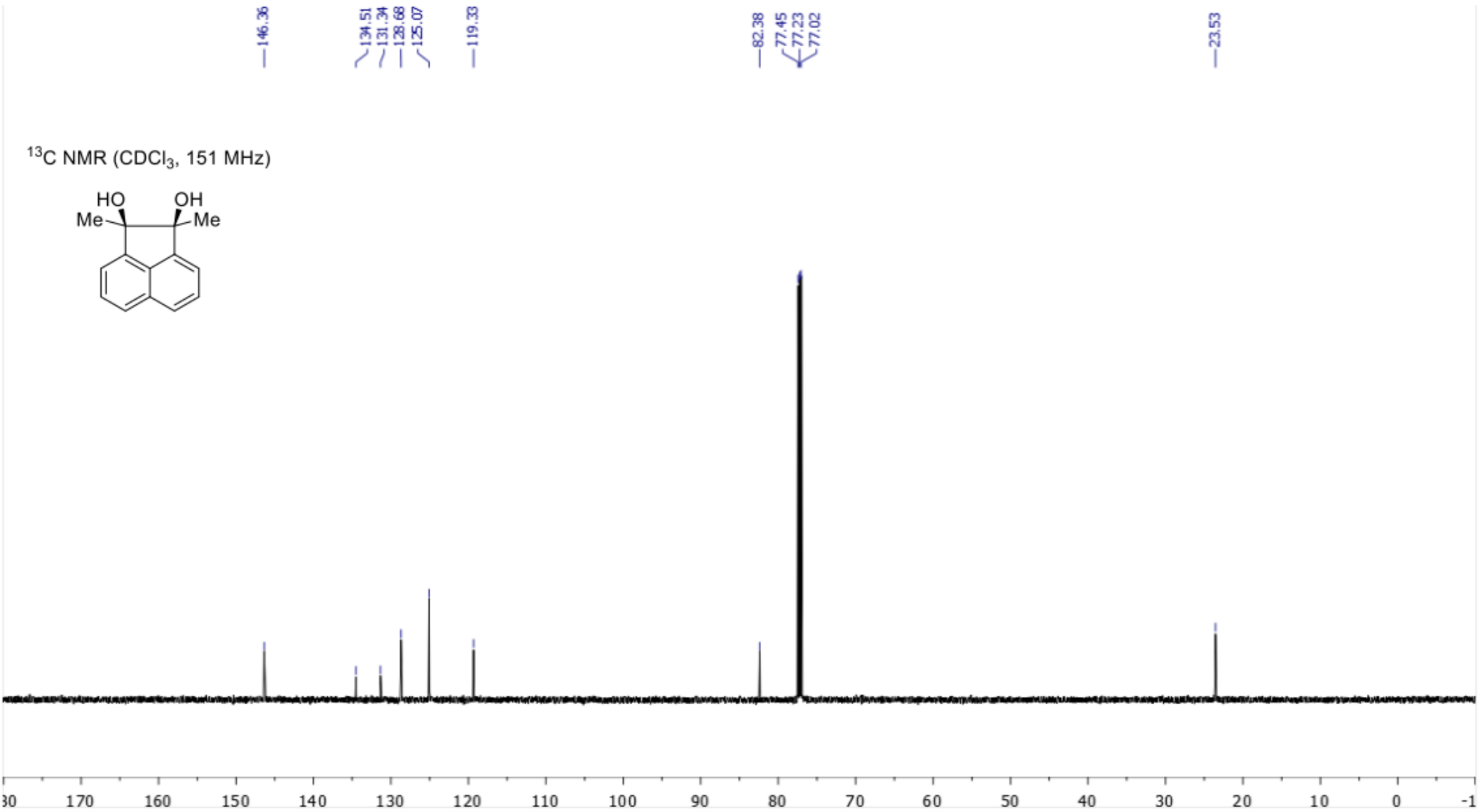
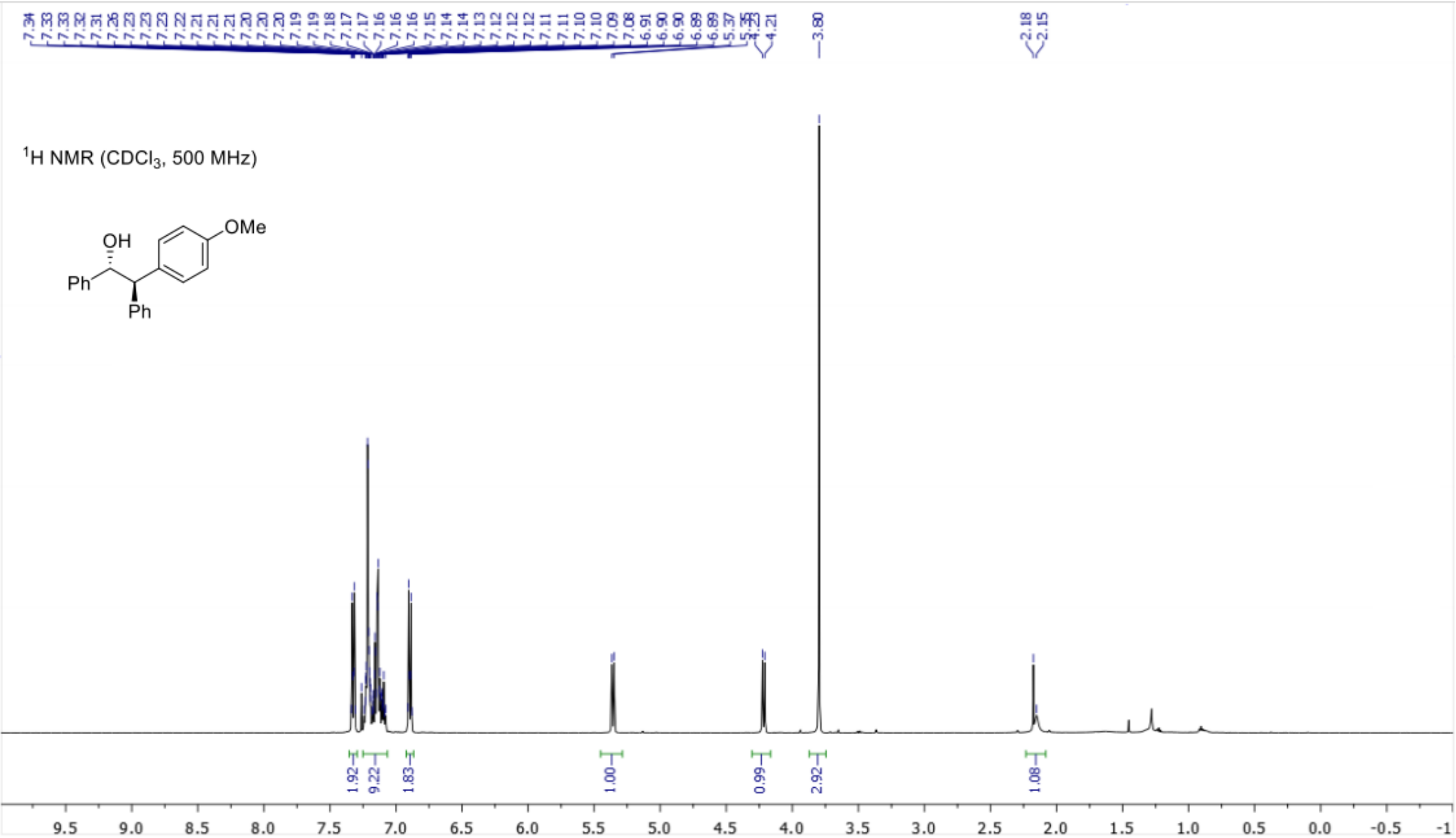
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5


146.36
134.51
131.34
128.68
125.07
119.33
82.38
77.45
77.23
77.02
23.53
^{13}C NMR ($CDCl_3$, 151 MHz)
HO
OH
Me
Me
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0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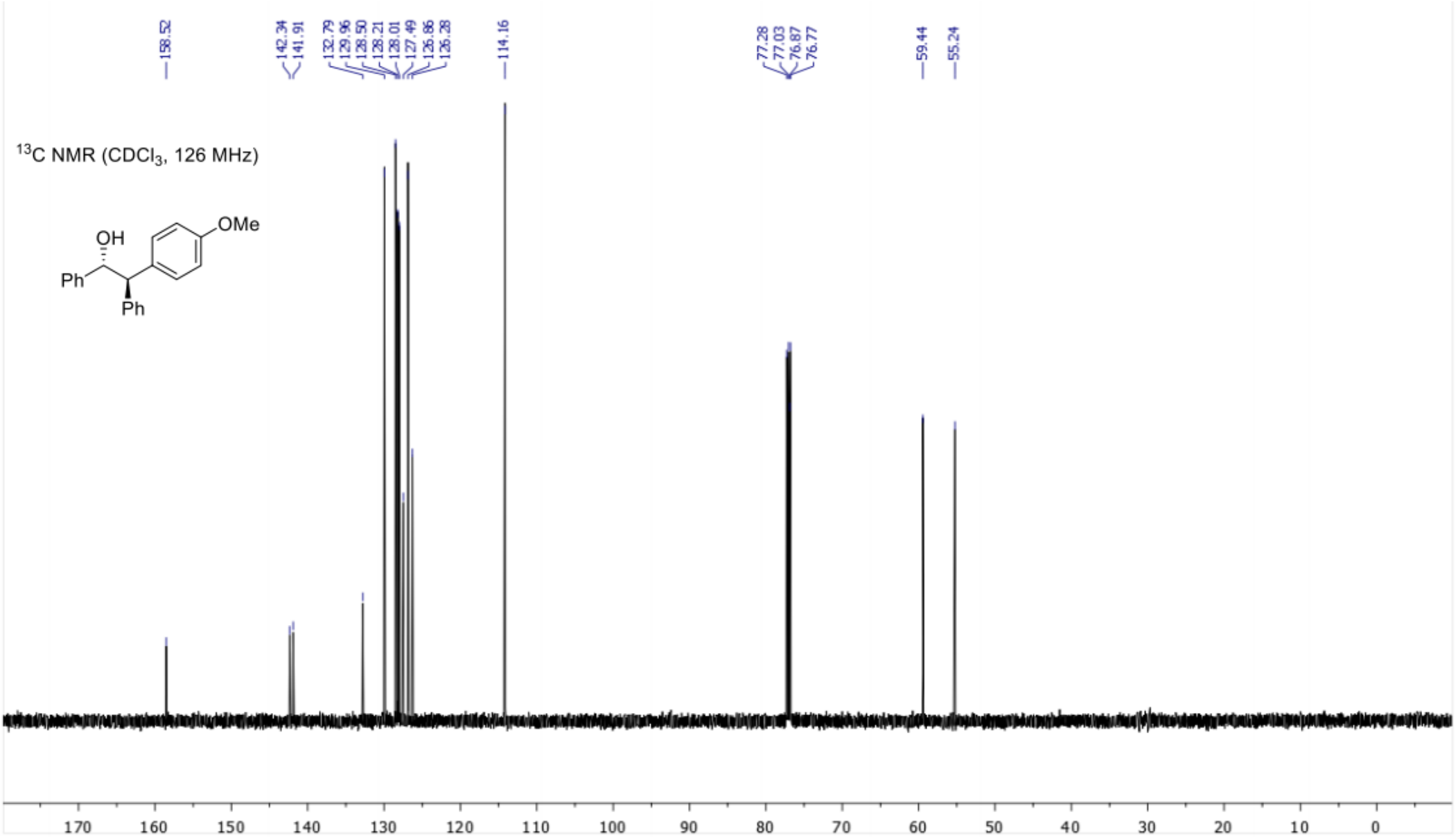
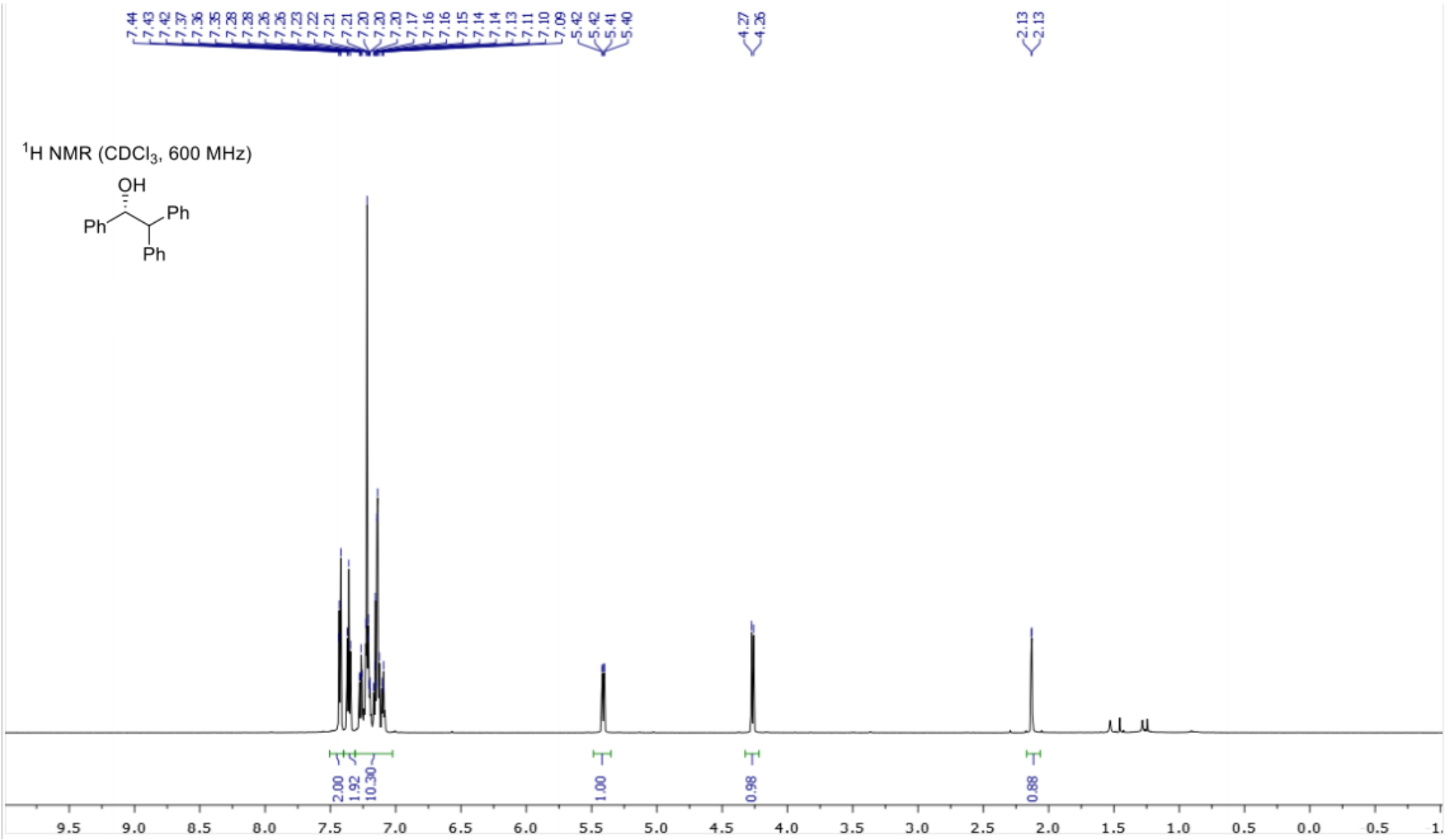
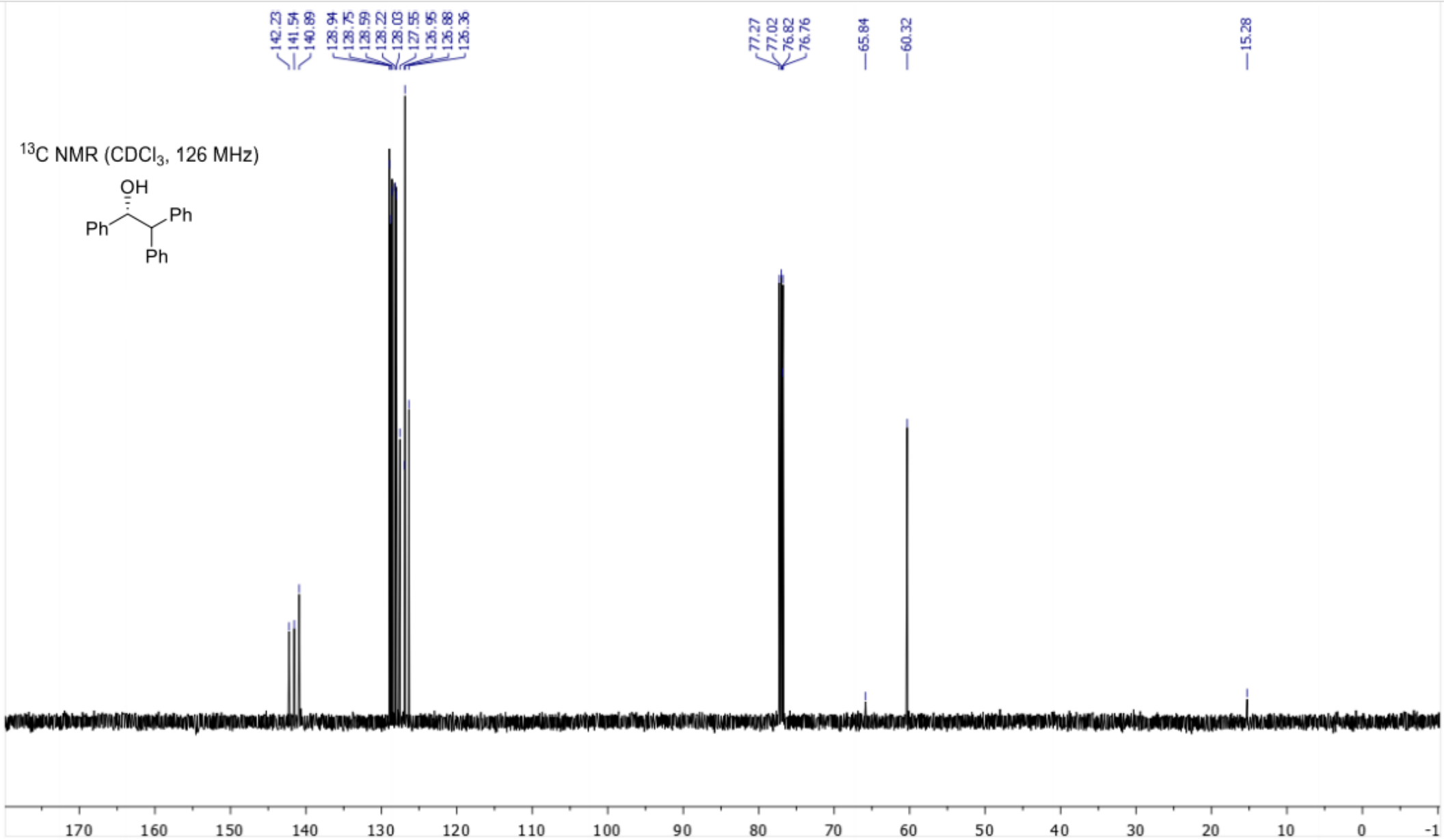
7.33
7.33
7.32
7.31
7.26
7.23
7.23
7.23
7.22
7.21
7.21
7.21
7.20
7.20
7.20
7.19
7.19
7.18
7.17
7.17
7.16
7.16
7.16
7.15
7.14
7.14
7.13
7.12
7.12
7.12
7.11
7.11
7.10
7.10
7.09
7.08
6.91
6.90
6.90
6.89
6.89
5.37
5.35
4.23
4.21
3.80
2.18
2.15
1H NMR (CDCl3, 500 MHz)
OH
OMe
Ph
Ph
1.92
9.22
1.83
1.00
0.99
2.92
1.08
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


158.52
142.34
141.91
132.79
129.96
128.50
128.21
128.01
127.49
126.86
126.28
114.16
77.28
77.03
76.87
76.77
59.44
55.24
13C NMR (CDCl3, 126 MHz)
OH
OMe
Ph
Ph
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


7.44
7.43
7.42
7.37
7.36
7.35
7.28
7.28
7.26
7.26
7.23
7.22
7.21
7.21
7.20
7.20
7.20
7.20
7.17
7.16
7.16
7.15
7.14
7.14
7.13
7.11
7.10
7.09
5.42
5.42
5.41
5.40
4.27
4.26
2.13
2.13
^{1}H NMR ($CDCl_3$, 600 MHz)
OH
Ph
Ph
Ph
2.00
1.92
10.30
1.00
0.98
0.88
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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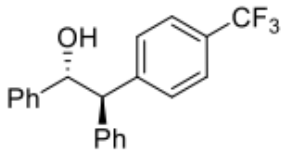
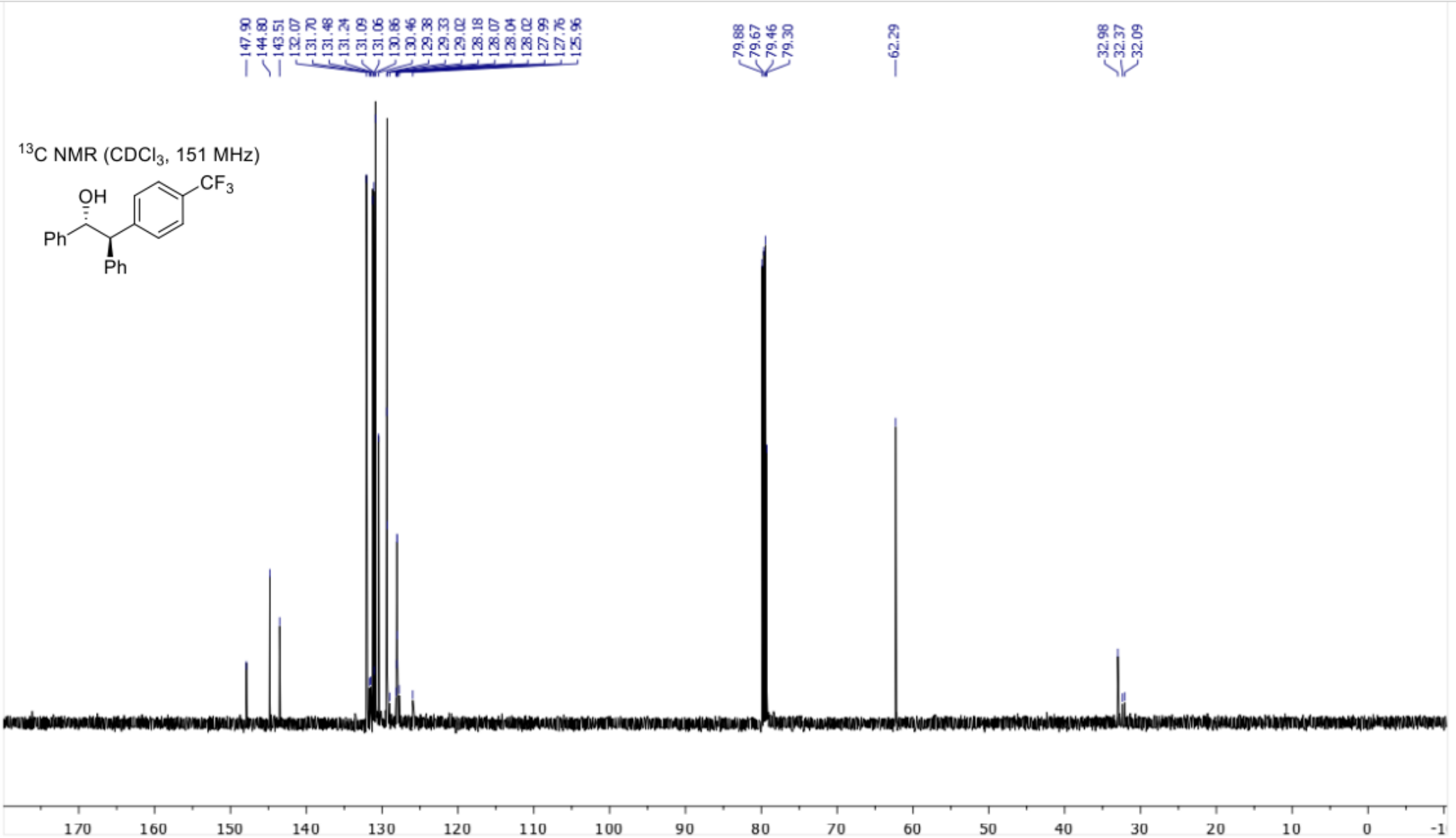
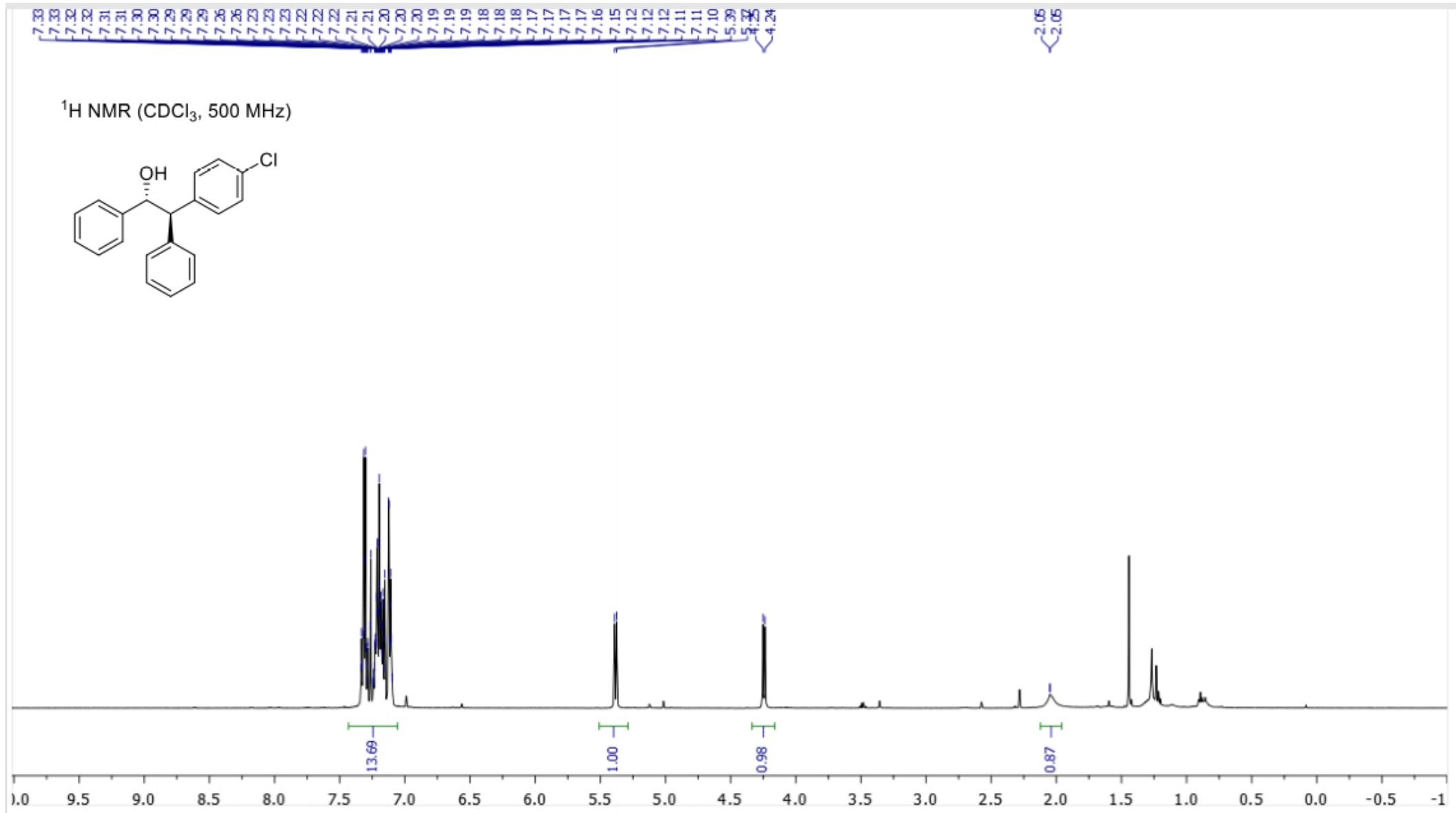
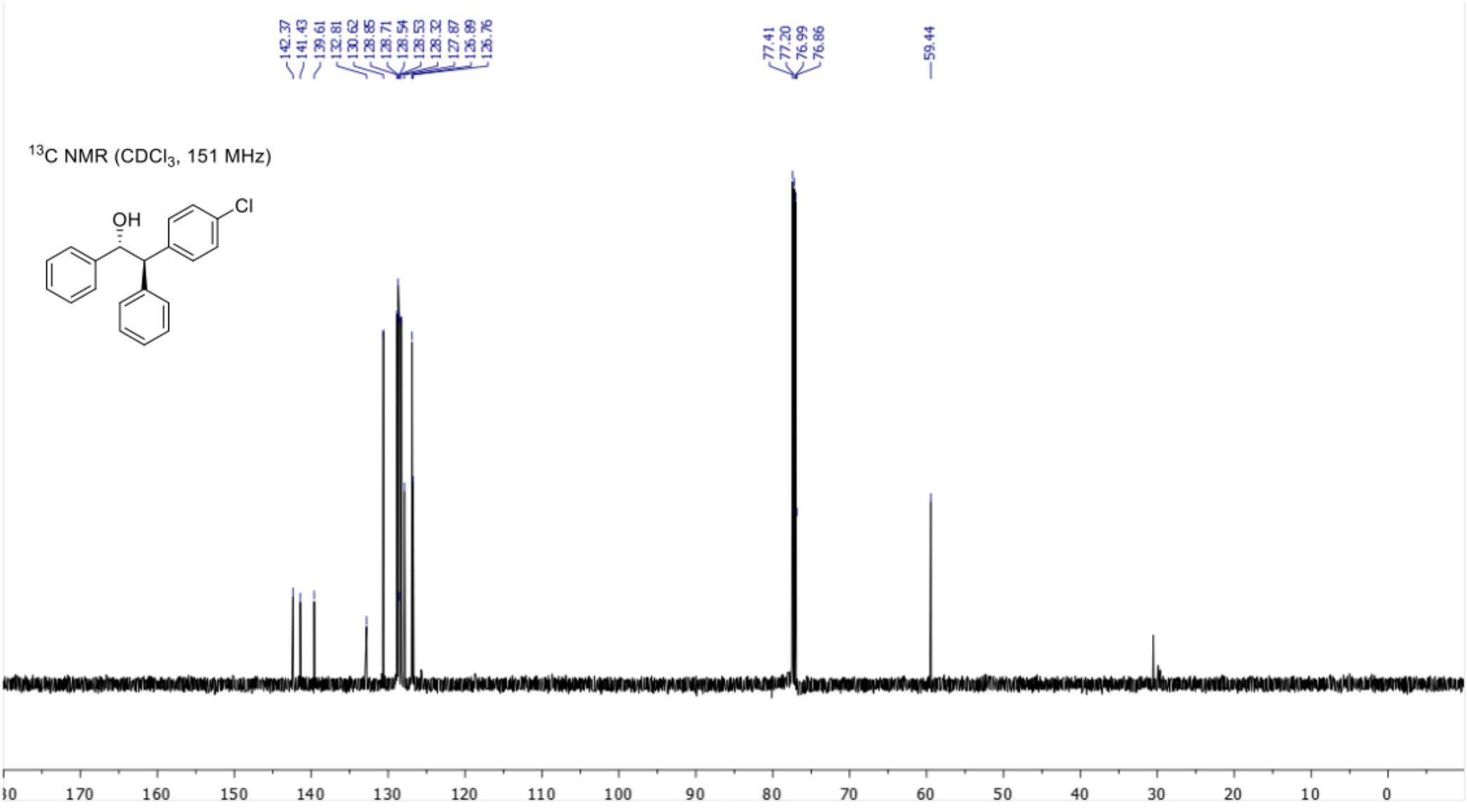
141.54
140.89
128.94
128.75
128.59
128.22
128.03
127.55
126.95
126.88
126.36
77.27
77.02
76.82
76.76
65.84
60.32
15.28
13C NMR (CDCl3, 126 MHz)
OH
Ph
Ph
Ph
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1

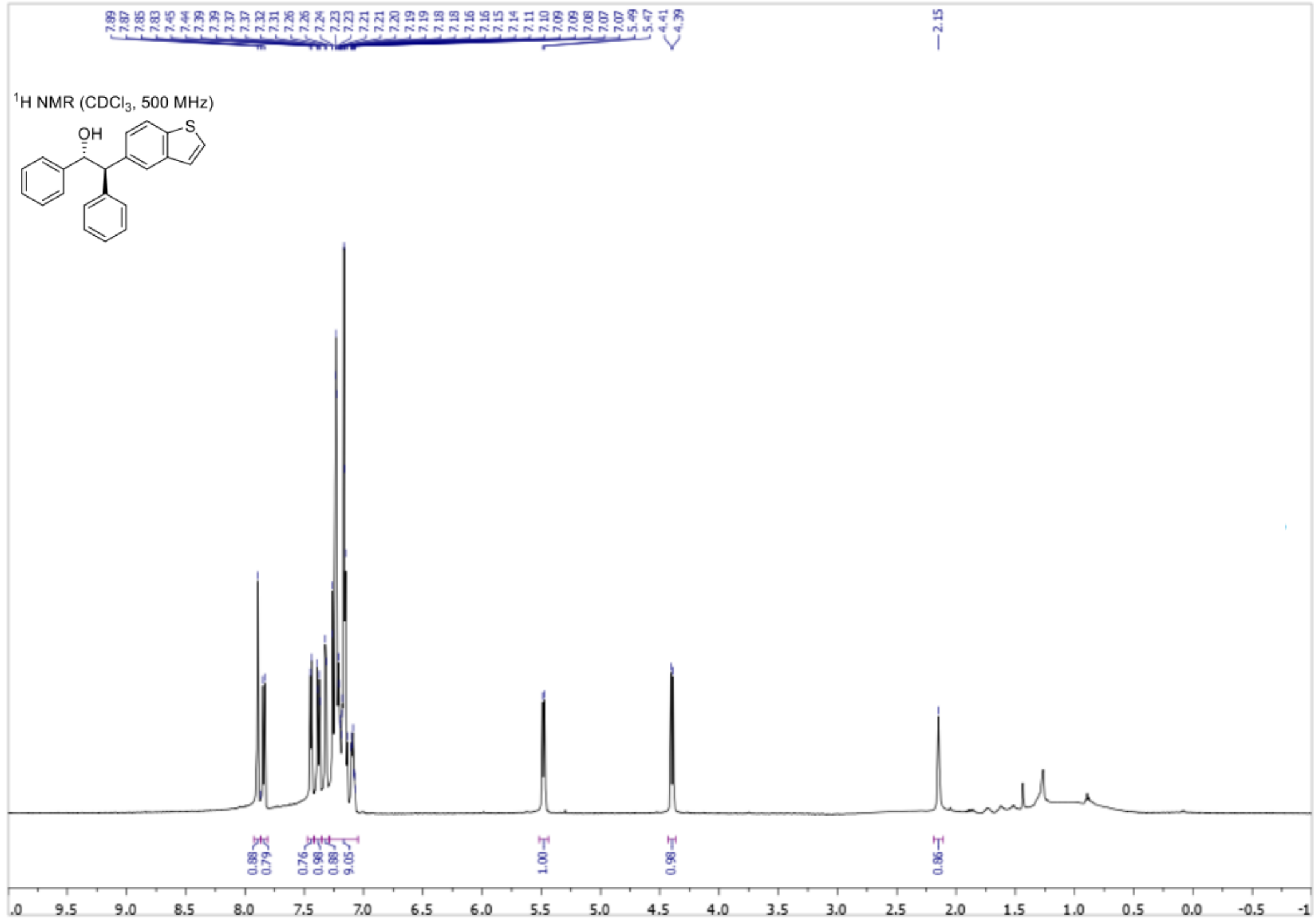
^{1}H NMR ($CDCl_3$, 600 MHz)

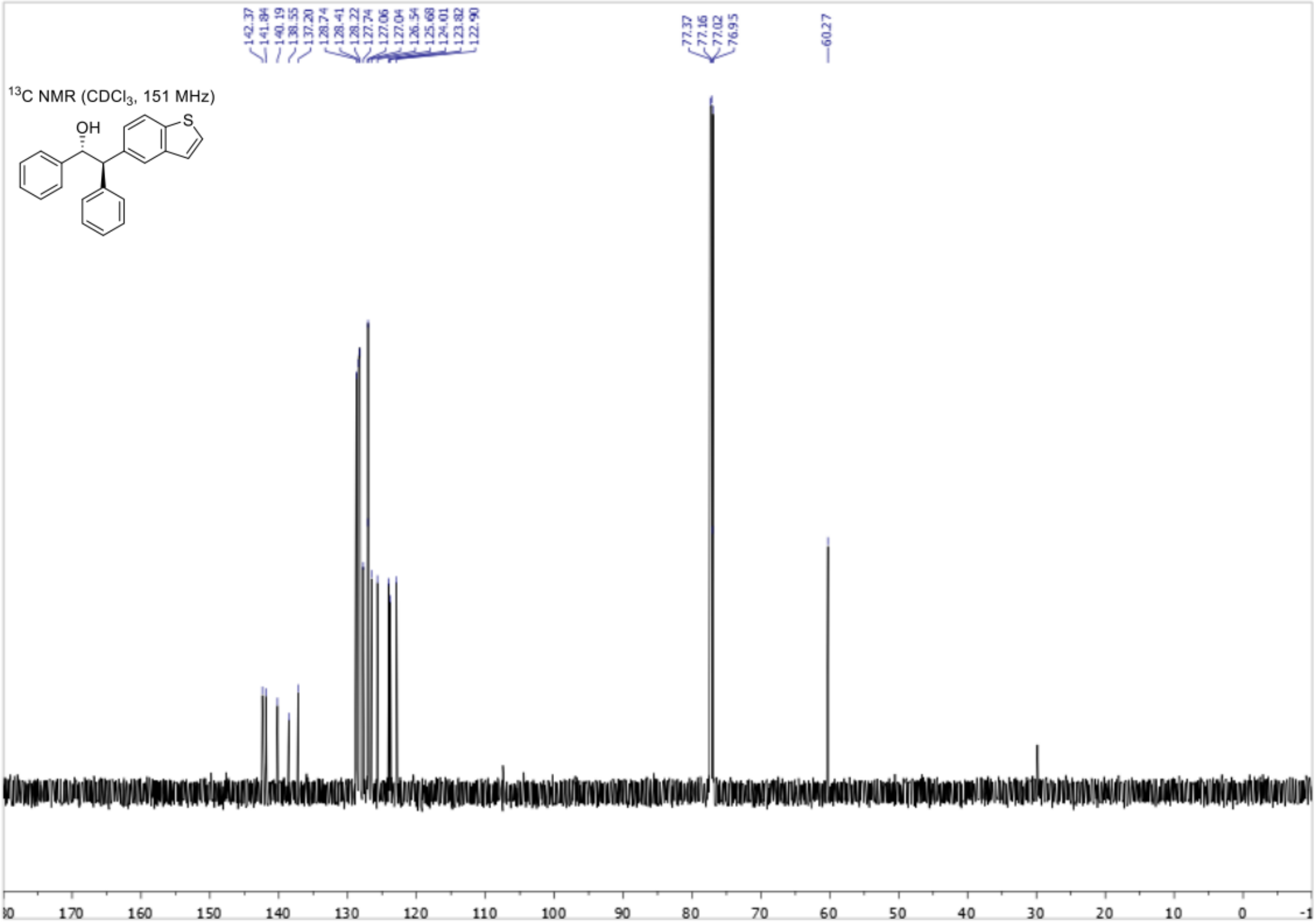


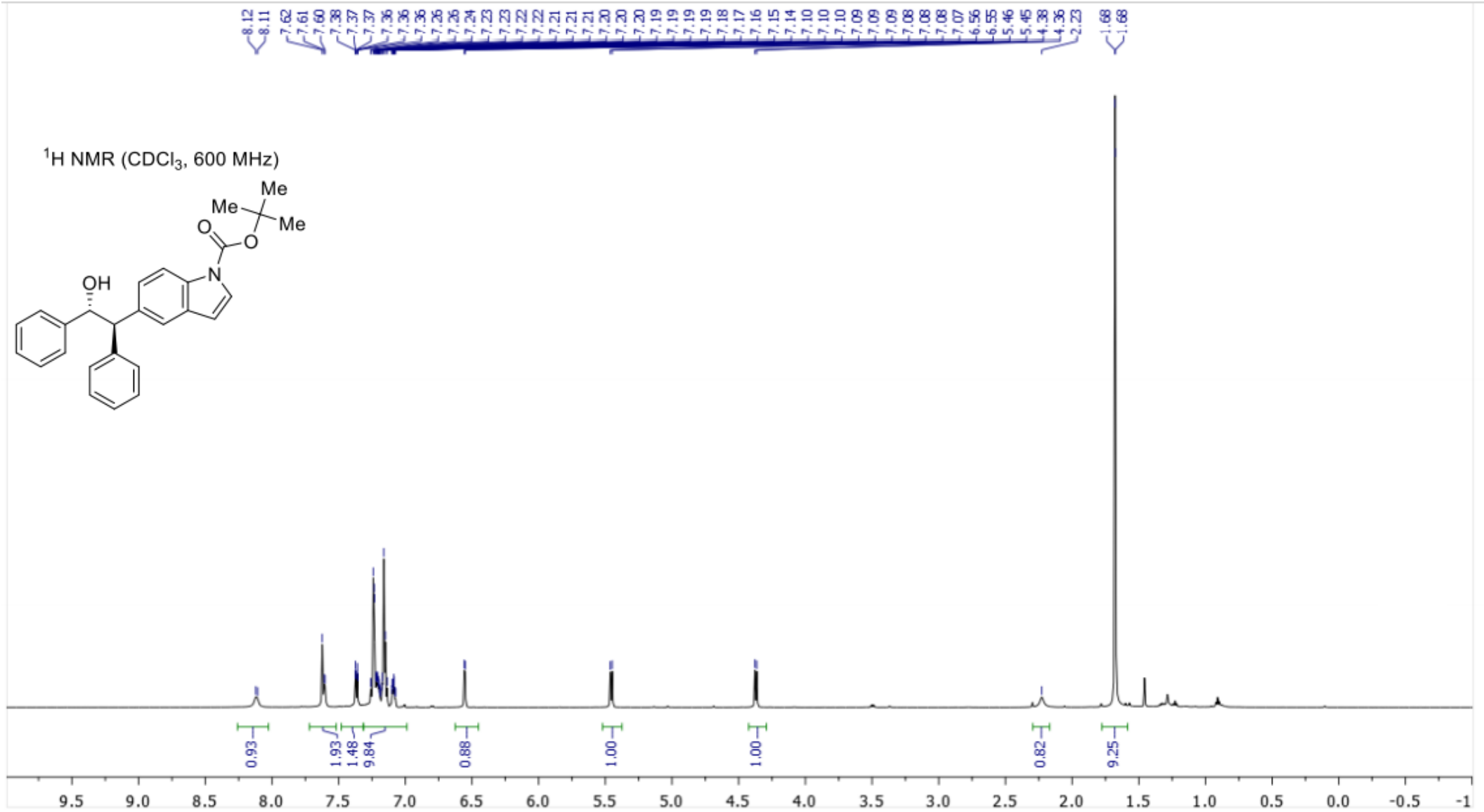

147.90
144.80
143.51
132.07
131.70
131.48
131.24
131.09
131.06
130.86
130.46
129.38
129.33
129.02
128.18
128.07
128.04
128.02
127.99
127.76
125.96
79.88
79.67
79.46
79.30
62.29
32.98
32.37
32.09
13C NMR (CDCl3, 151 MHz)
OH
CF3
Ph
Ph
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1

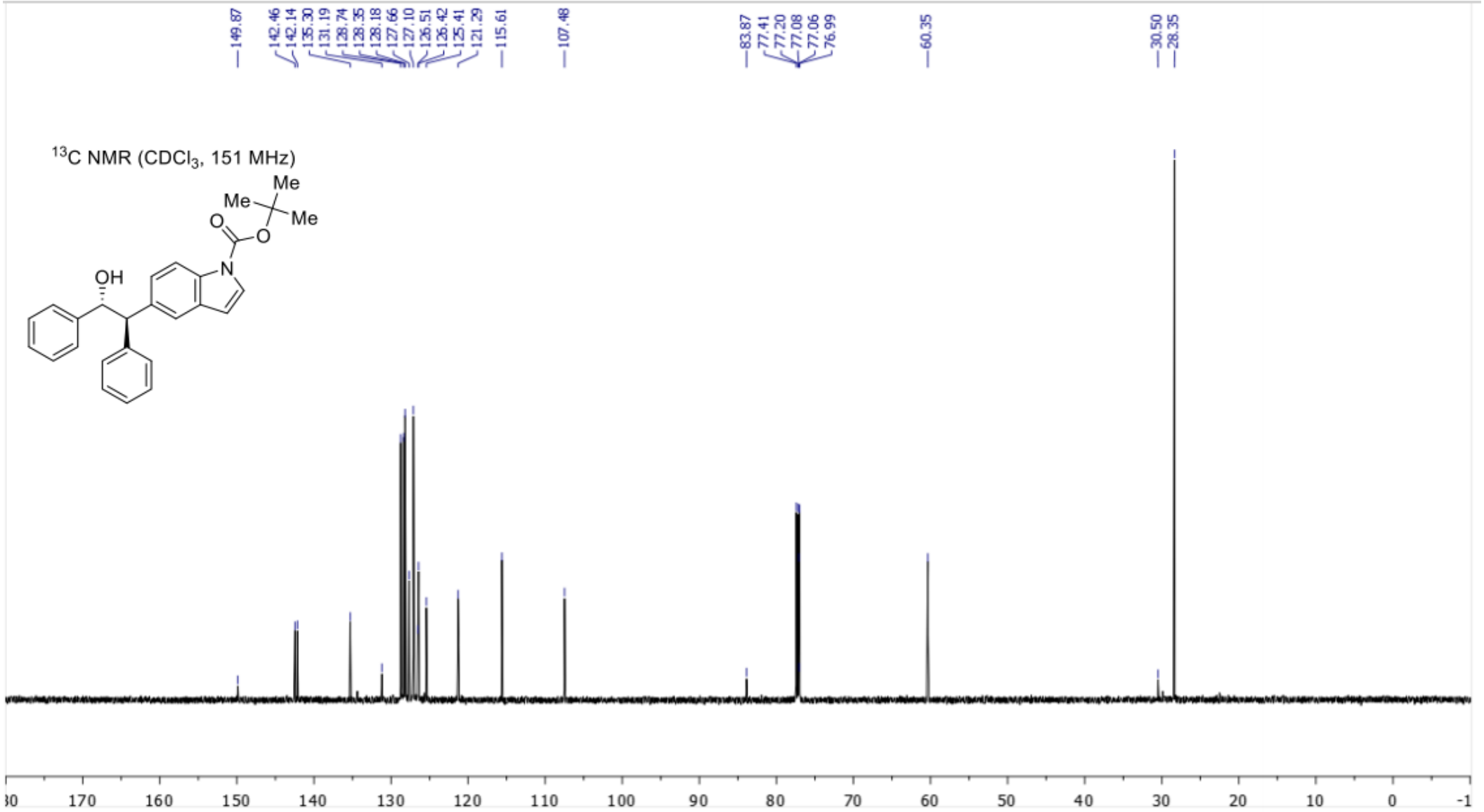

7.33 7.33 7.32 7.32 7.31 7.31 7.30 7.30 7.29 7.29 7.29 7.26 7.26 7.23 7.23 7.22 7.22 7.22 7.21 7.21 7.20 7.20 7.20 7.19 7.19 7.18 7.18 7.18 7.17 7.17 7.17 7.17 7.16 7.15 7.12 7.12 7.12 7.11 7.10 5.39 4.24
2.05 2.05
1H NMR (CDCl3, 500 MHz)
OH
Cl
13.69
1.00
0.98
0.87
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 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


142.37
141.43
139.61
132.81
130.62
128.85
128.71
128.54
128.53
128.32
127.87
126.89
126.76
77.41
77.20
76.99
76.86
59.44
13C NMR (CDCl3, 151 MHz)
OH
Cl
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


7.89
7.87
7.85
7.83
7.45
7.44
7.39
7.39
7.37
7.37
7.32
7.31
7.26
7.26
7.24
7.23
7.23
7.21
7.21
7.20
7.19
7.19
7.18
7.18
7.16
7.16
7.15
7.14
7.11
7.10
7.09
7.09
7.08
7.07
7.07
5.49
5.47
4.41
4.39
2.15
1H NMR (CDCl3, 500 MHz)
OH
S
0.88
0.79
0.76
0.98
0.88
9.05
1.00
0.98
0.86
.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


142.37
141.84
140.19
138.55
137.20
128.74
128.41
128.22
127.74
127.06
127.04
126.54
125.68
124.01
123.82
122.90
77.37
77.16
77.02
76.95
60.27
13C NMR (CDCl3, 151 MHz)
OH
S
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


8.12
8.11
7.62
7.61
7.60
7.38
7.37
7.37
7.36
7.36
7.36
7.26
7.26
7.24
7.23
7.23
7.22
7.22
7.21
7.21
7.21
7.20
7.20
7.20
7.19
7.19
7.19
7.19
7.18
7.17
7.16
7.15
7.14
7.10
7.10
7.10
7.09
7.09
7.09
7.08
7.08
7.08
7.07
6.56
6.55
5.46
5.45
4.38
4.36
2.23
1.68
1.68
1H NMR (CDCl3, 600 MHz)
Me
Me
Me
O
O
N
OH
0.93
1.93
1.48
9.84
0.88
1.00
1.00
0.82
9.25
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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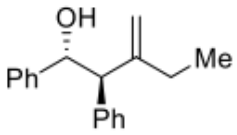
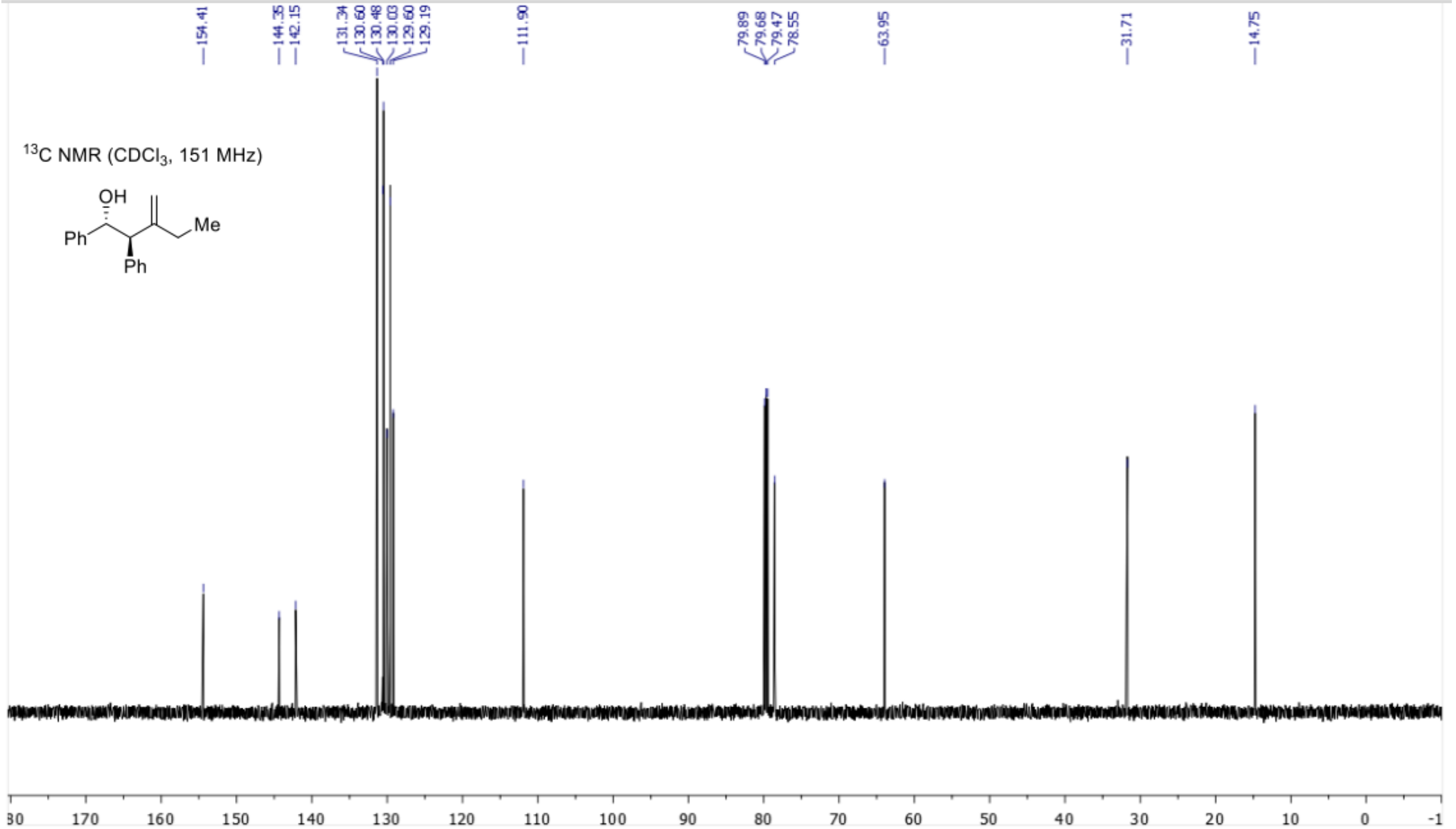
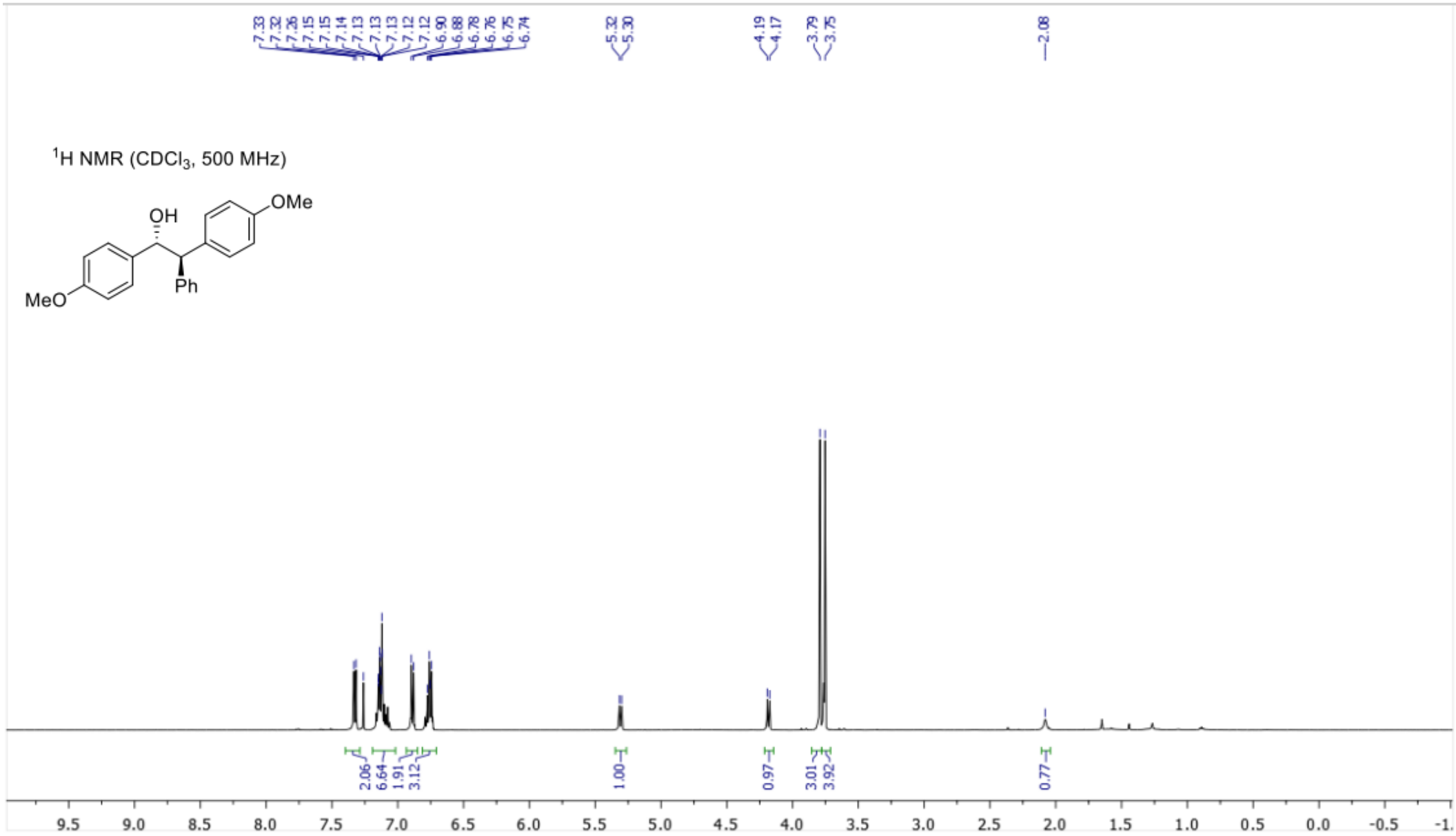
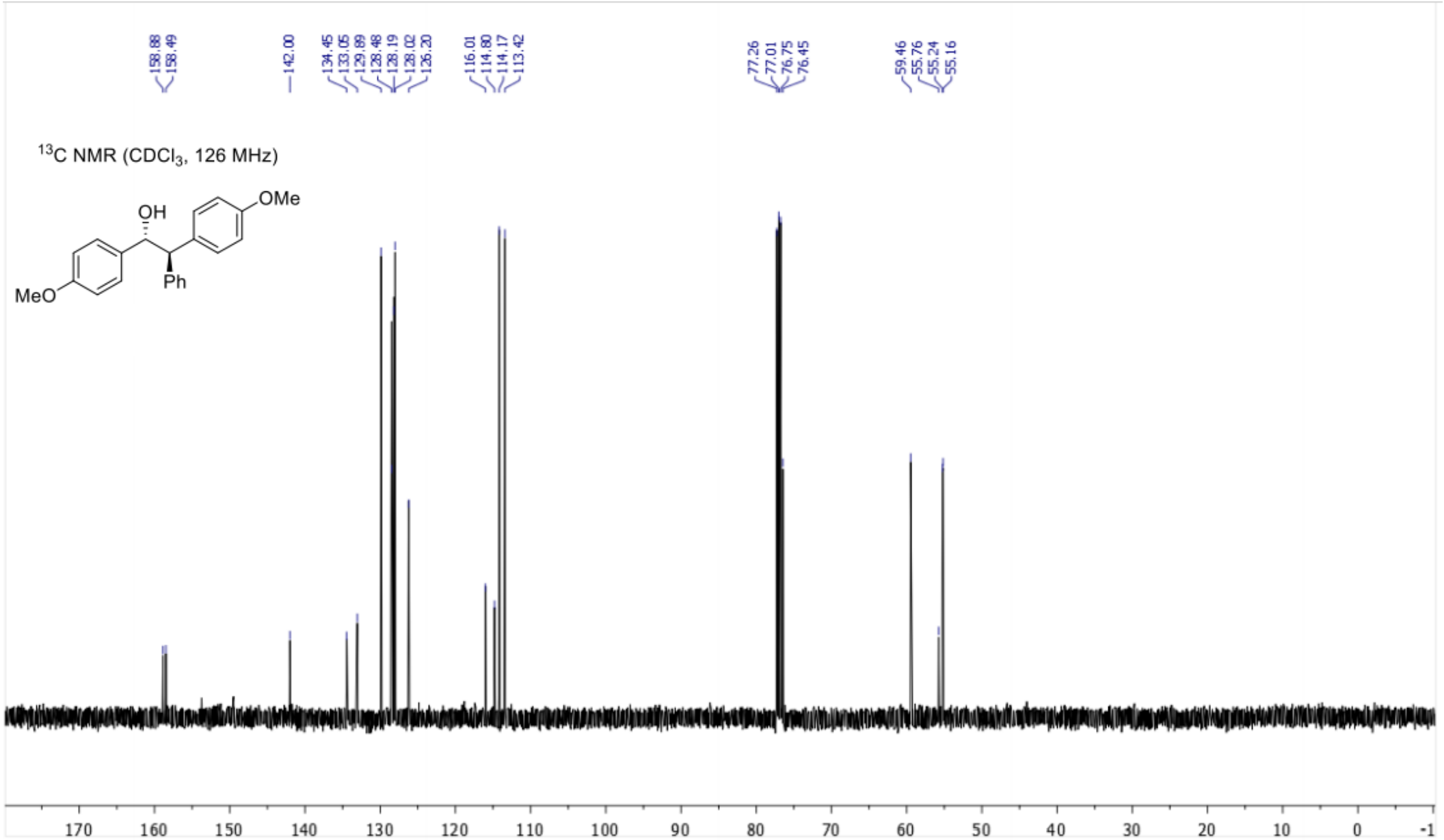
142.46
142.14
135.30
131.19
128.74
128.35
128.18
127.66
127.10
126.51
126.42
125.41
121.29
115.61
107.48
83.87
77.41
77.20
77.08
77.06
76.99
60.35
30.50
28.35
13C NMR (CDCl3, 151 MHz)
Me
Me
Me
O
O
N
OH
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1

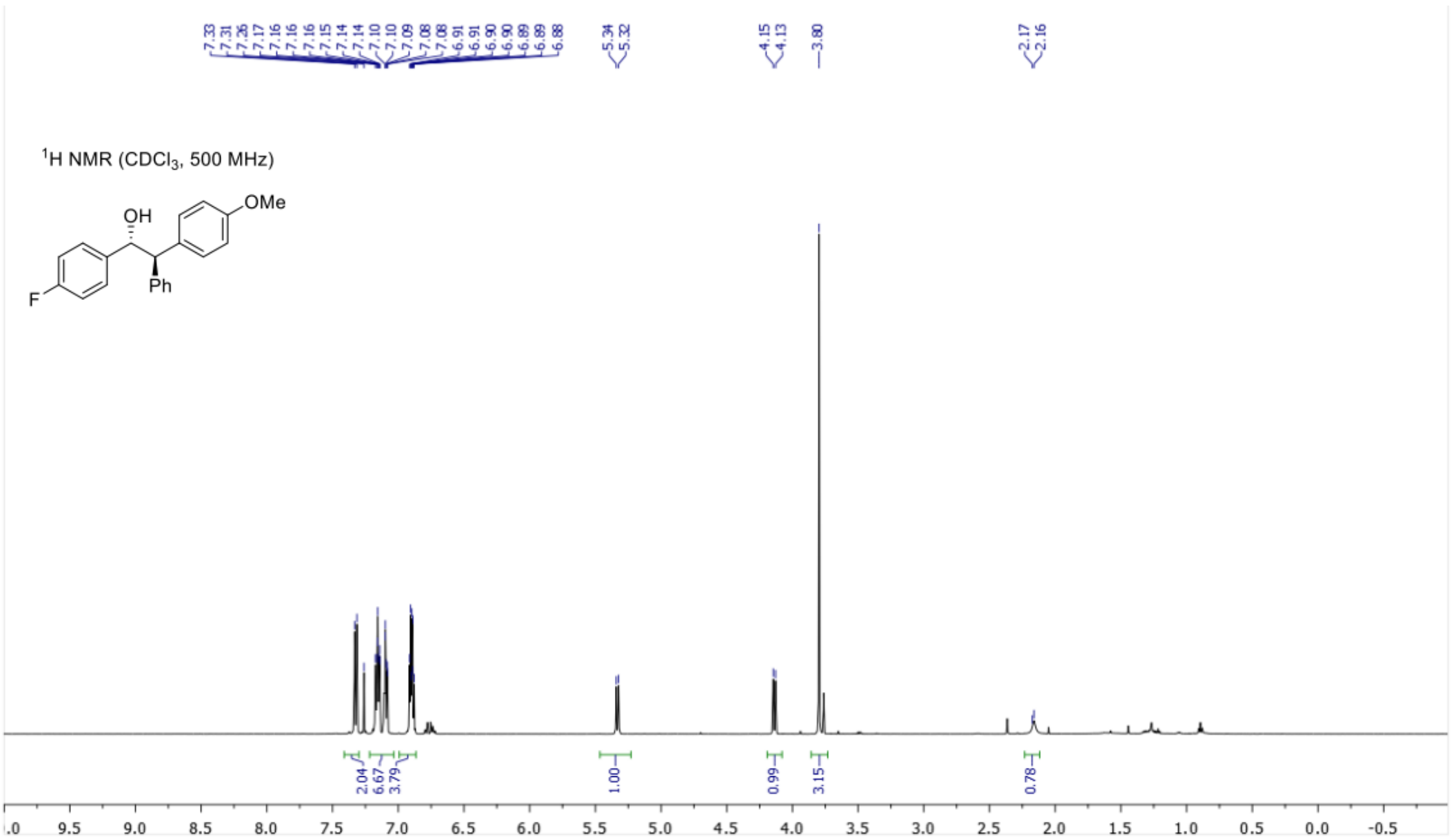
^{1}H NMR ($CDCl_3$, 600 MHz)

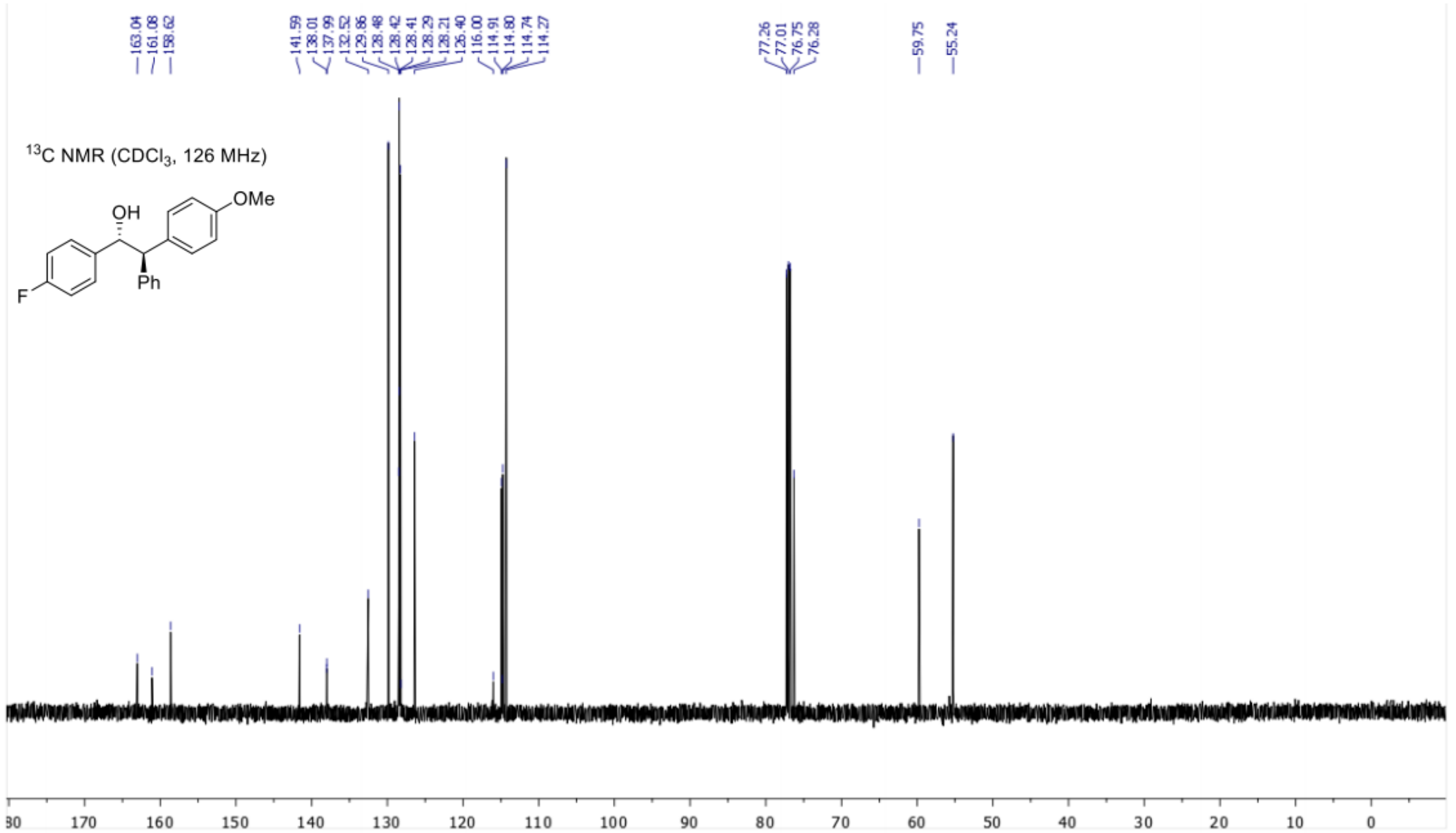


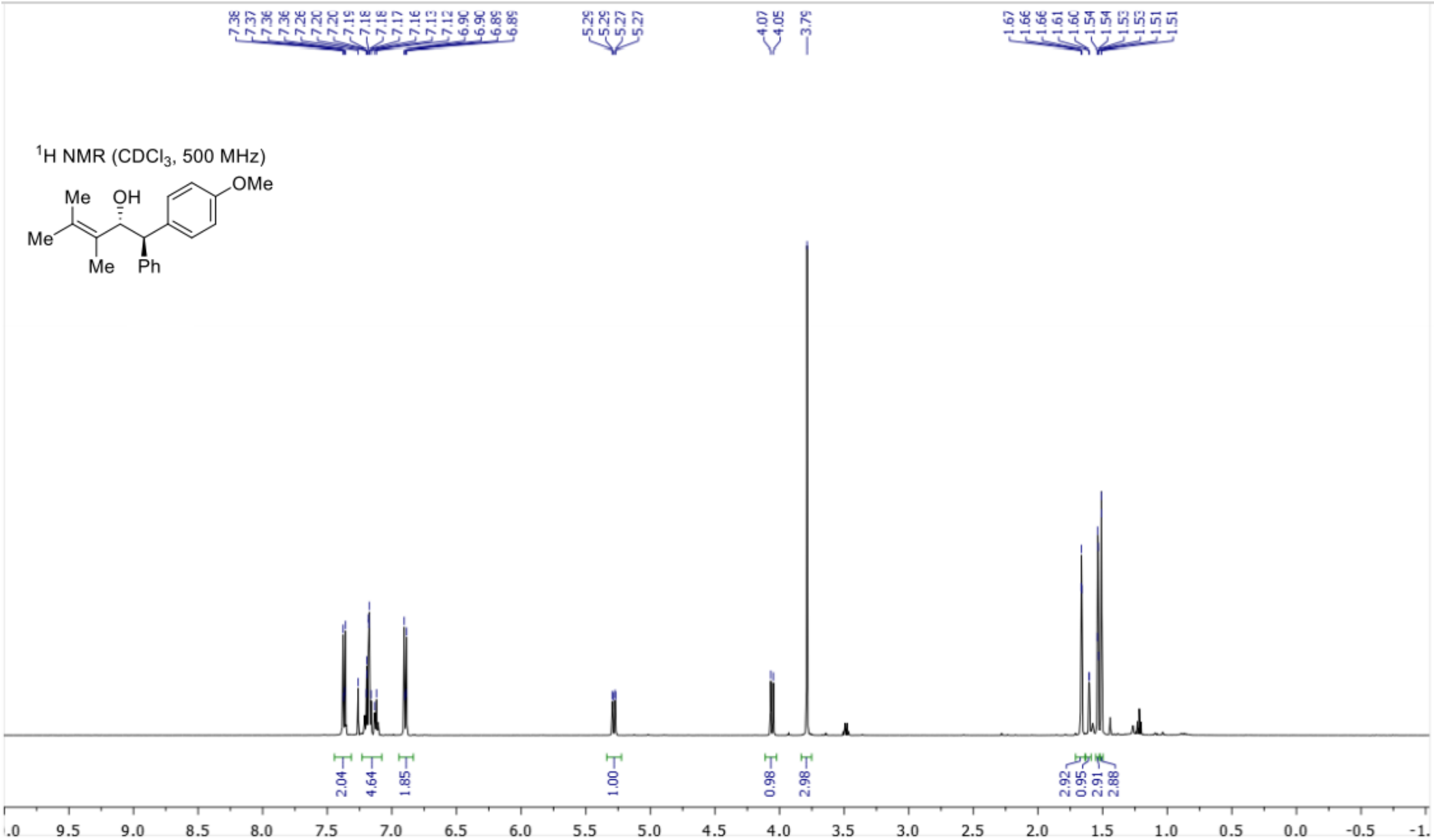

154.41
144.35
142.15
131.34
130.60
130.48
130.03
129.60
129.19
111.90
79.89
79.68
79.47
78.55
63.95
31.71
14.75
^{13}C NMR ($CDCl_3$, 151 MHz)
OH
Ph
Me
Ph
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1


7.33
7.32
7.26
7.15
7.15
7.14
7.13
7.13
7.13
7.12
7.12
6.90
6.88
6.78
6.76
6.75
6.74
5.32
5.30
4.19
4.17
3.79
3.75
2.08
^{1}H NMR ($CDCl_3$, 500 MHz)
OH
OMe
Ph
MeO
2.06
6.64
1.91
3.12
1.00
0.97
3.01
3.92
0.77
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


158.88
158.49
142.00
134.45
133.05
129.89
128.48
128.19
128.02
126.20
116.01
114.80
114.17
113.42
77.26
77.01
76.75
76.45
59.46
55.76
55.24
55.16
13C NMR (CDCl3, 126 MHz)
OH
OMe
Ph
MeO
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1


7.33
7.31
7.26
7.17
7.16
7.16
7.15
7.14
7.14
7.10
7.10
7.09
7.08
7.08
6.91
6.91
6.90
6.90
6.89
6.89
6.88
5.34
5.32
4.15
4.13
3.80
2.17
2.16
^{1}H NMR ($CDCl_3$, 500 MHz)
OH
OMe
Ph
F
2.04
6.67
3.79
1.00
0.99
3.15
0.78
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


163.04
161.08
158.62
141.59
138.01
137.99
132.52
129.86
128.48
128.42
128.41
128.29
128.21
126.40
116.00
114.91
114.80
114.74
114.27
77.26
77.01
76.75
76.28
59.75
55.24
13C NMR (CDCl3, 126 MHz)
OH
OMe
Ph
F
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


7.38
7.37
7.36
7.36
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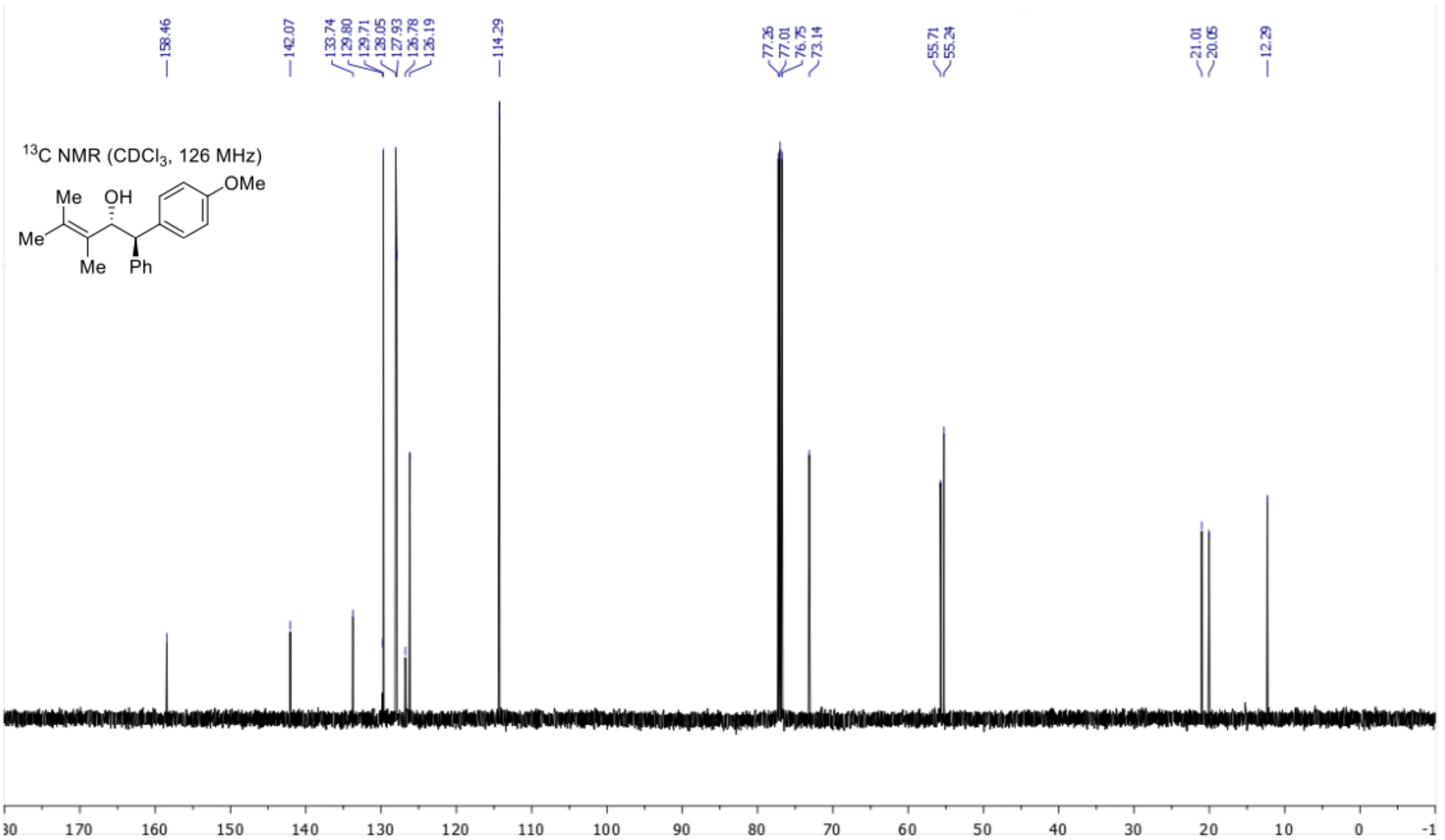
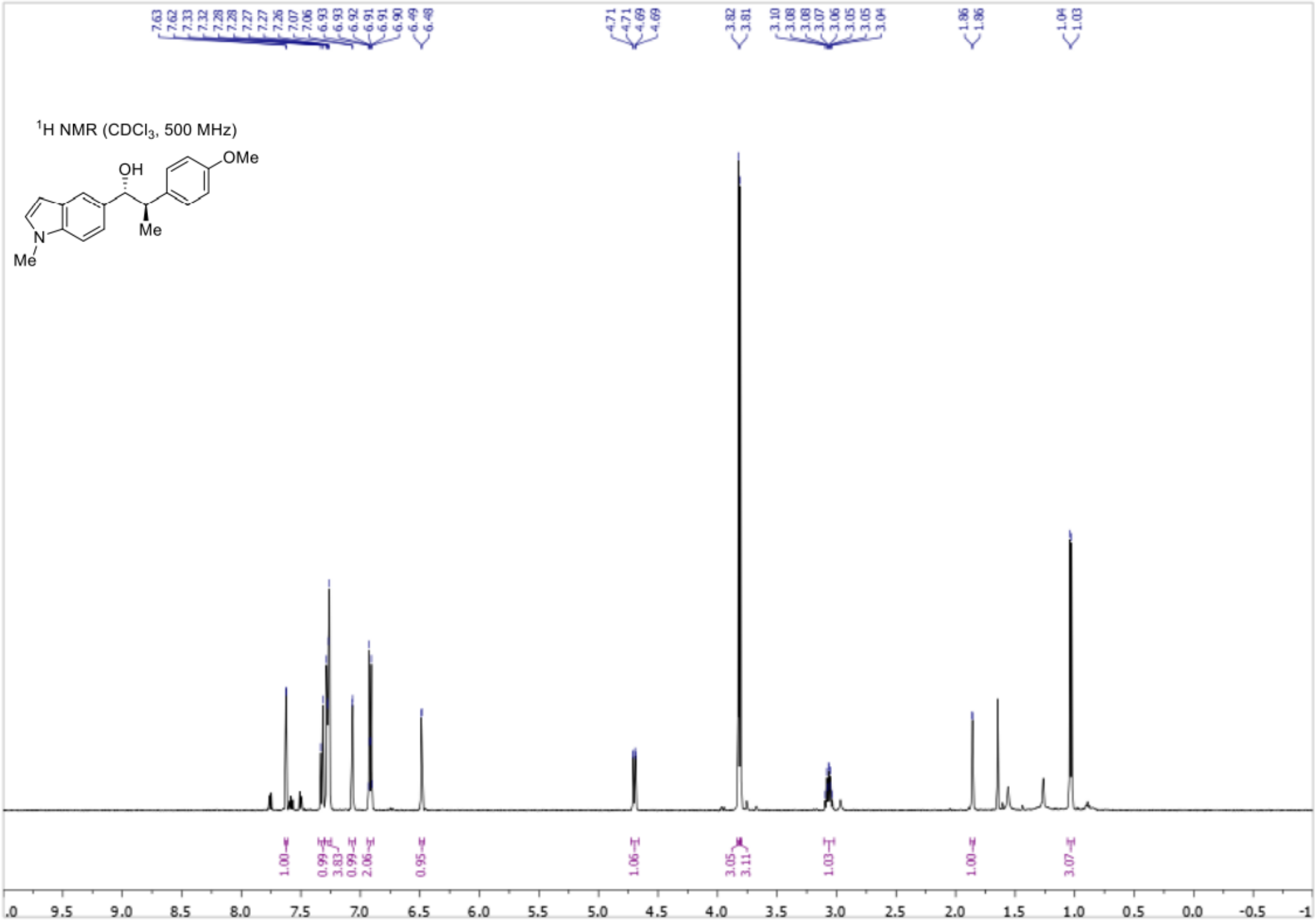
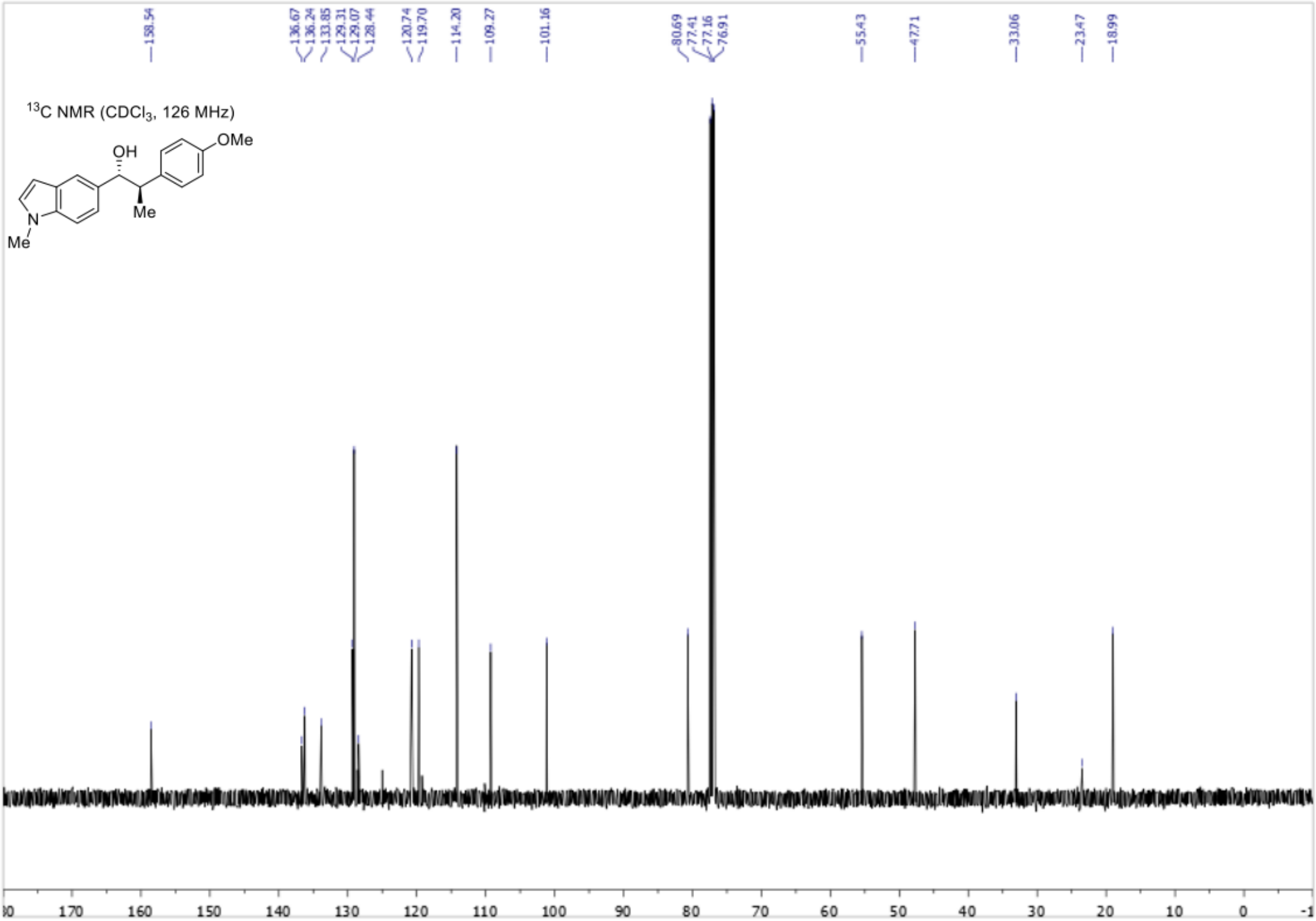
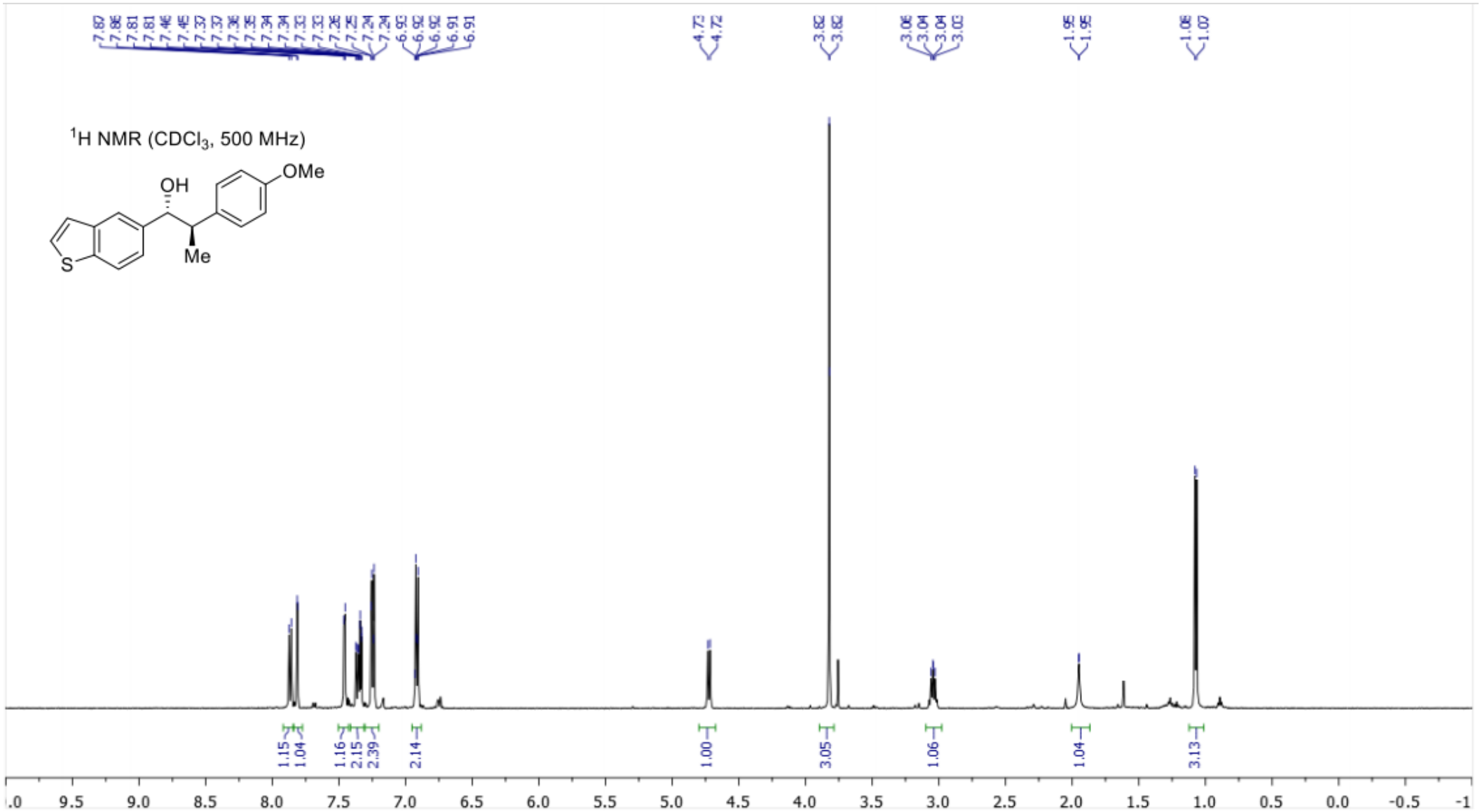
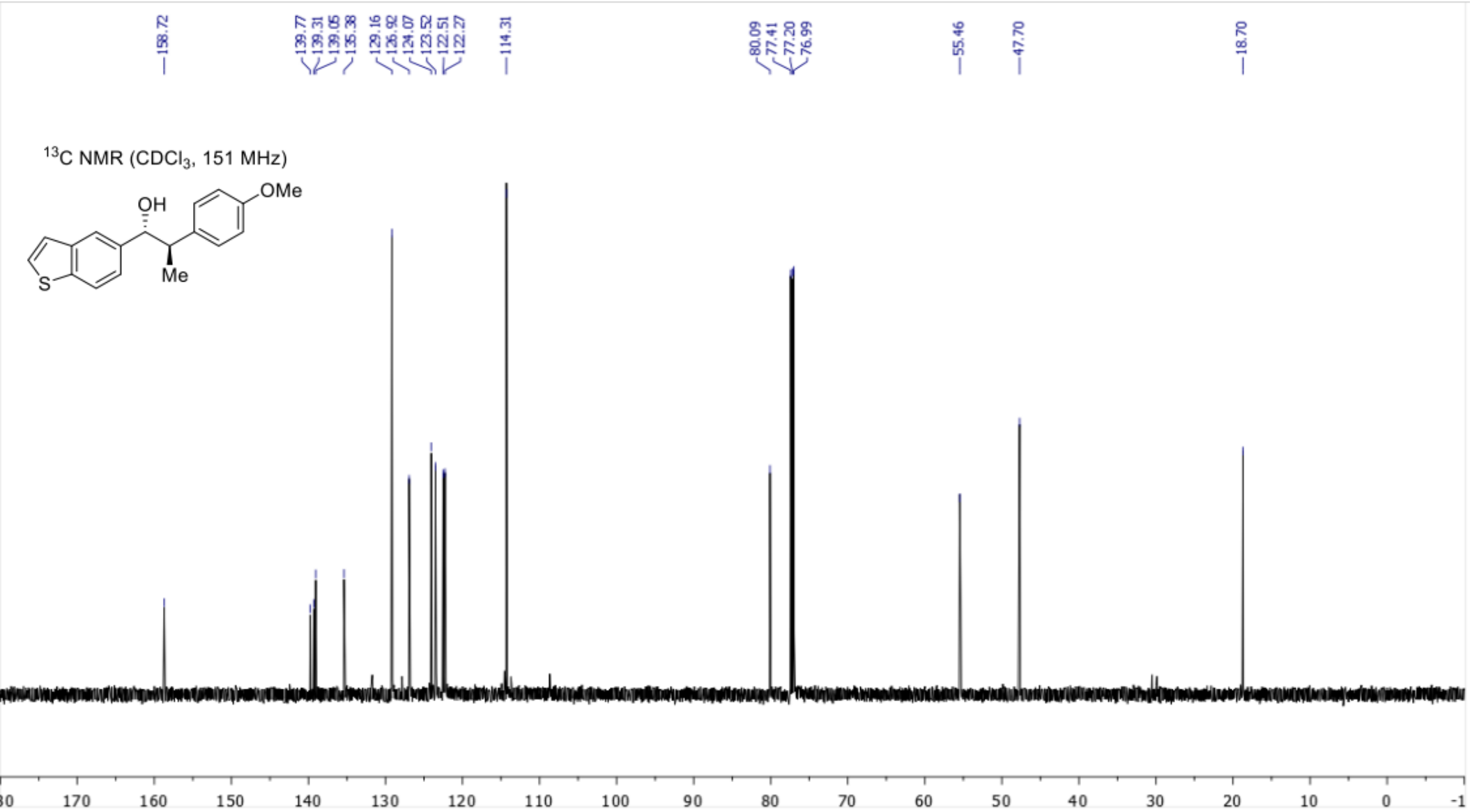
7.20
7.20
7.19
7.18
7.18
7.17
7.16
7.13
7.12
6.90
6.90
6.89
6.89
5.29
5.29
5.27
5.27
4.07
4.05
3.79
1.67
1.66
1.66
1.61
1.60
1.54
1.54
1.53
1.53
1.51
1.51
1H NMR (CDCl3, 500 MHz)
Me
OH
OMe
Me
Me
Ph
2.04
4.64
1.85
1.00
0.98
2.98
2.92
0.95
2.91
2.88
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

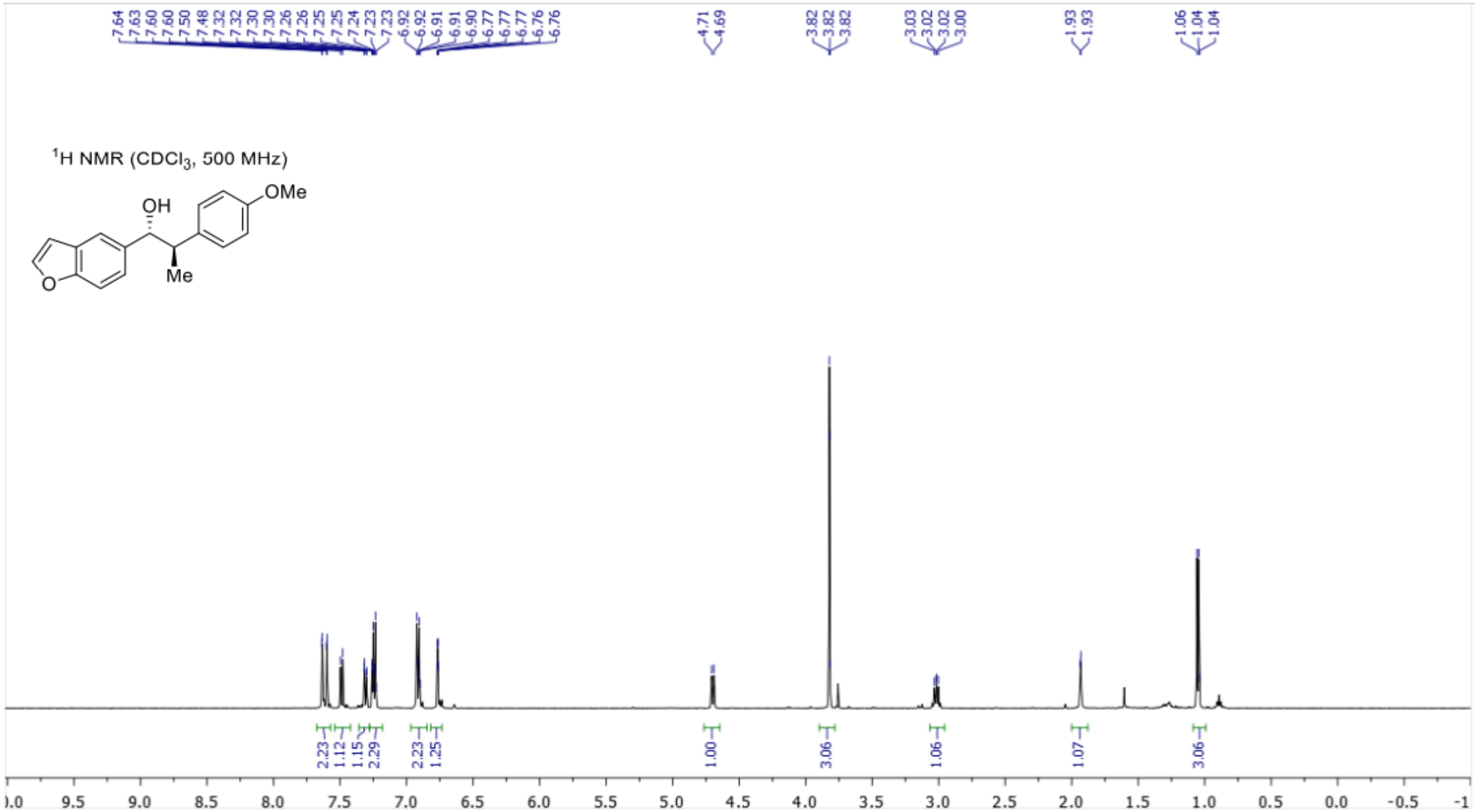

158.46
142.07
133.74
129.80
129.71
128.05
127.93
126.78
126.19
114.29
77.26
77.01
76.75
73.14
55.71
55.24
21.01
20.05
12.29
13C NMR (CDCl3, 126 MHz)
Me
OH
OMe
Me
Me
Ph
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

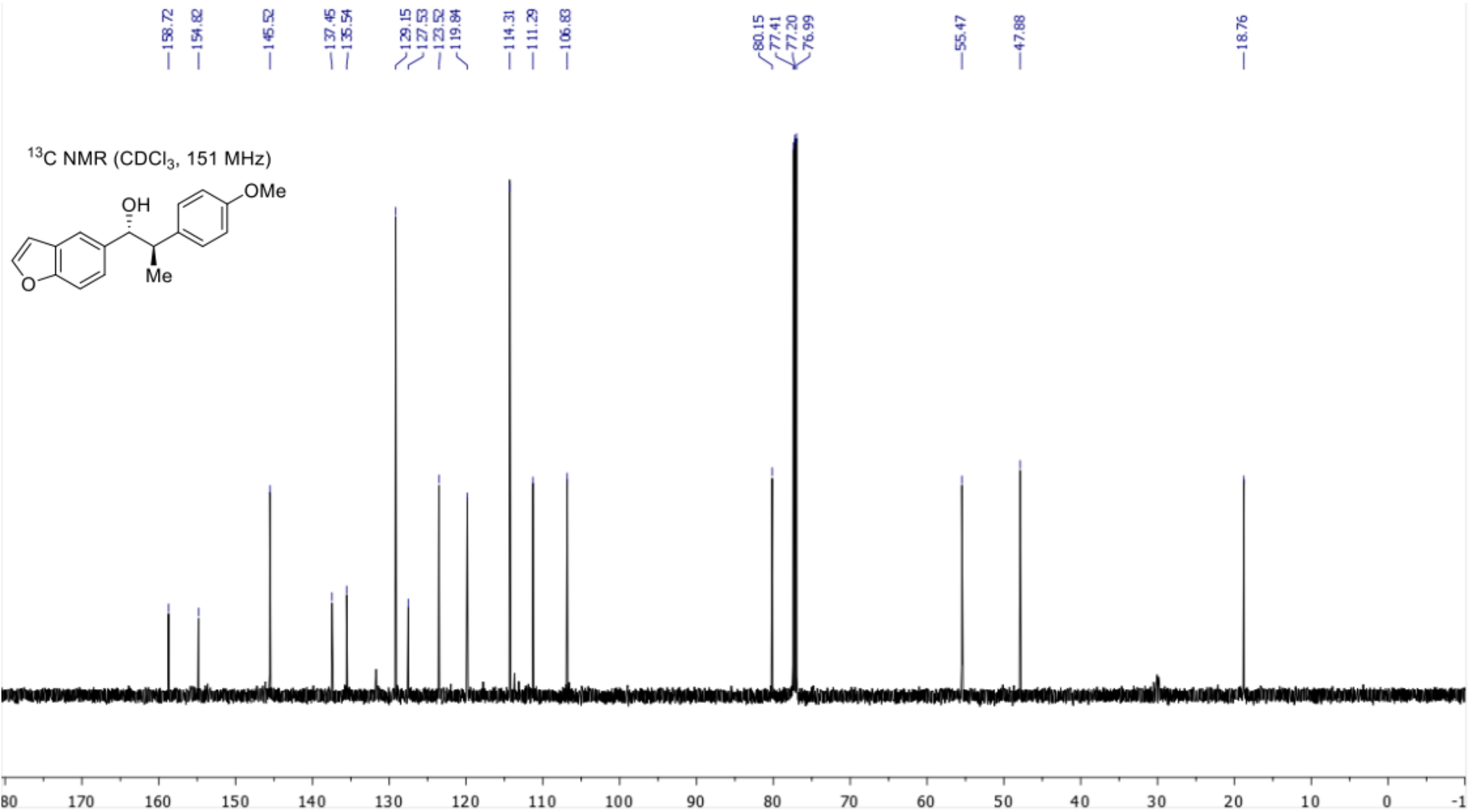

7.63
7.62
7.33
7.32
7.28
7.28
7.27
7.27
7.26
7.07
7.06
6.93
6.93
6.92
6.91
6.91
6.90
6.49
6.48
4.71
4.71
4.69
4.69
3.82
3.81
3.10
3.08
3.08
3.07
3.06
3.05
3.05
3.04
1.86
1.86
1.04
1.03
1H NMR (CDCl3, 500 MHz)
OH
OMe
Me
N
Me
1.00
0.99
3.83
0.99
2.06
0.95
1.06
3.05
3.11
1.03
1.00
3.07
.0
9.5
9.0
8.5
8.0
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


158.54
136.67
136.24
133.85
129.31
129.07
128.44
120.74
119.70
114.20
109.27
101.16
80.69
77.41
77.16
76.91
55.43
47.71
33.06
23.47
18.99
13C NMR (CDCl3, 126 MHz)
OH
OMe
Me
N
Me
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


^{1}H NMR ($CDCl_3$, 500 MHz)
OH
OMe
Me
S


158.72
139.77
139.31
139.05
135.38
129.16
126.92
124.07
123.52
122.51
122.27
114.31
80.09
77.41
77.20
76.99
55.46
47.70
18.70
13C NMR (CDCl3, 151 MHz)
OH
OMe
Me
S
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


7.64
7.63
7.60
7.60
7.50
7.48
7.32
7.32
7.30
7.30
7.26
7.26
7.25
7.25
7.24
7.23
7.23
6.92
6.92
6.91
6.91
6.90
6.77
6.77
6.77
6.76
6.76
4.71
4.69
3.82
3.82
3.82
3.03
3.02
3.02
3.00
1.93
1.93
1.06
1.04
1.04
^{1}H NMR ($CDCl_3$, 500 MHz)
OH
OMe
Me
O
2.23
1.12
1.15
2.29
2.23
1.25
1.00
3.06
1.06
1.07
3.06
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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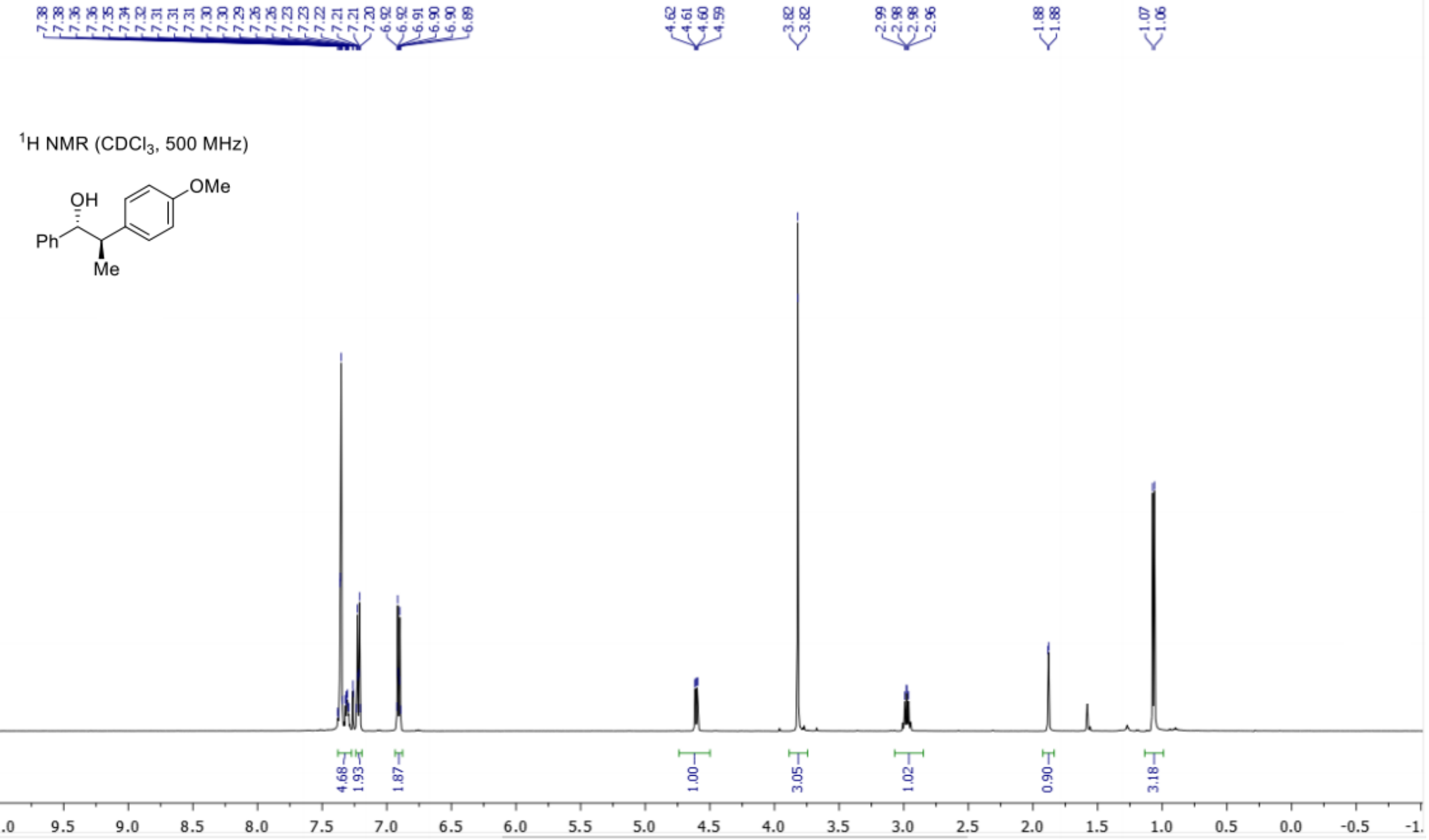
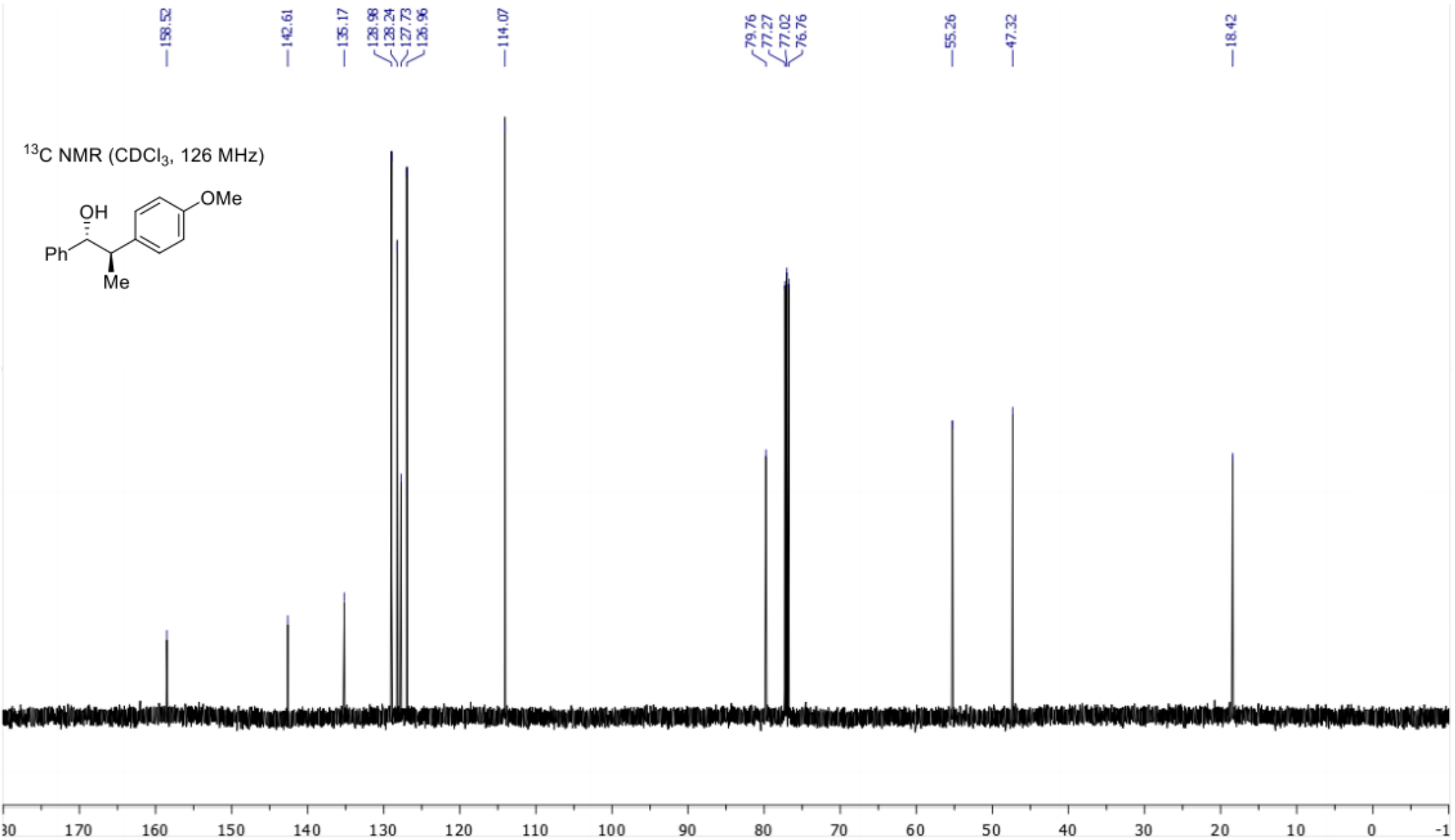
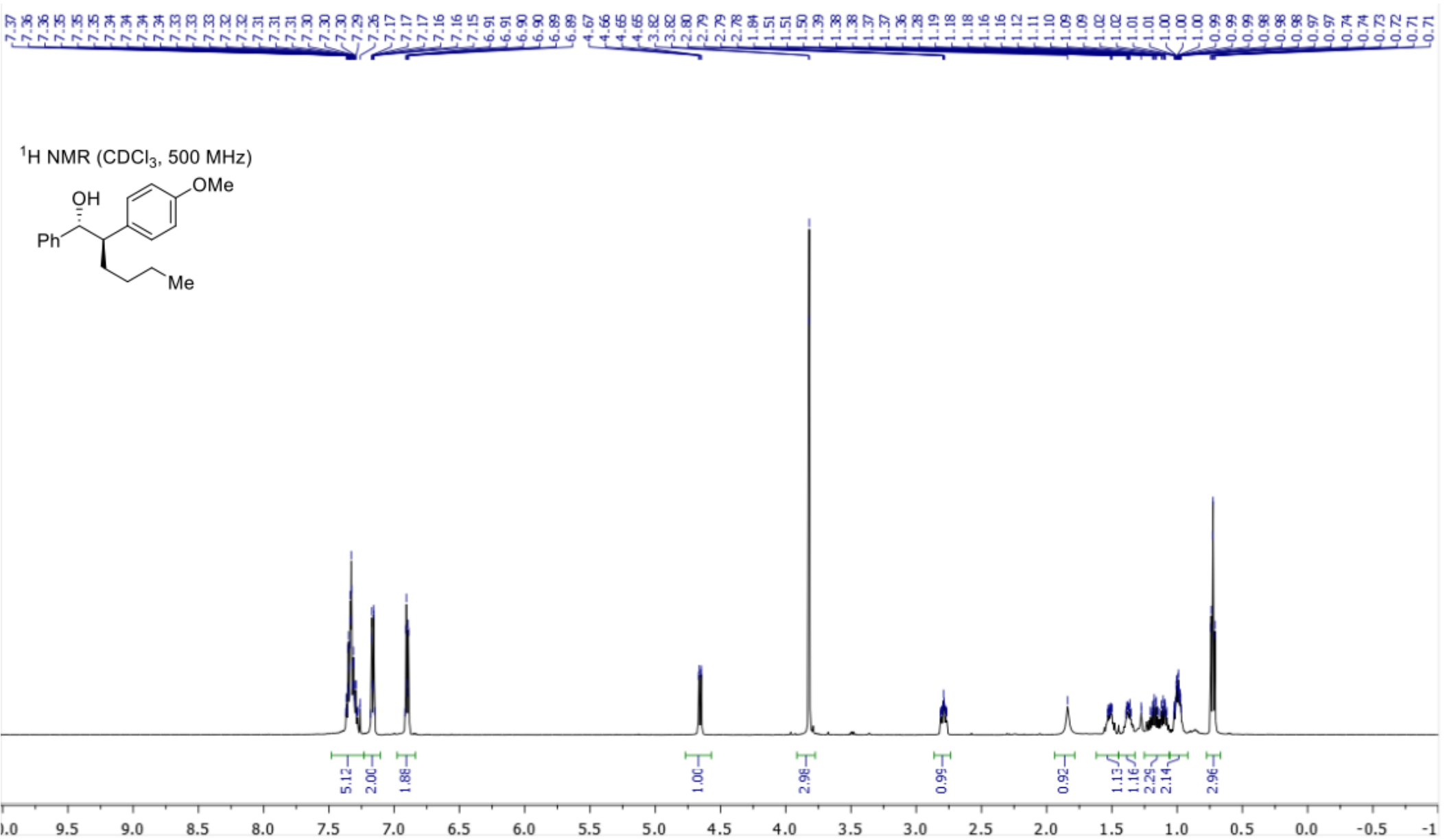
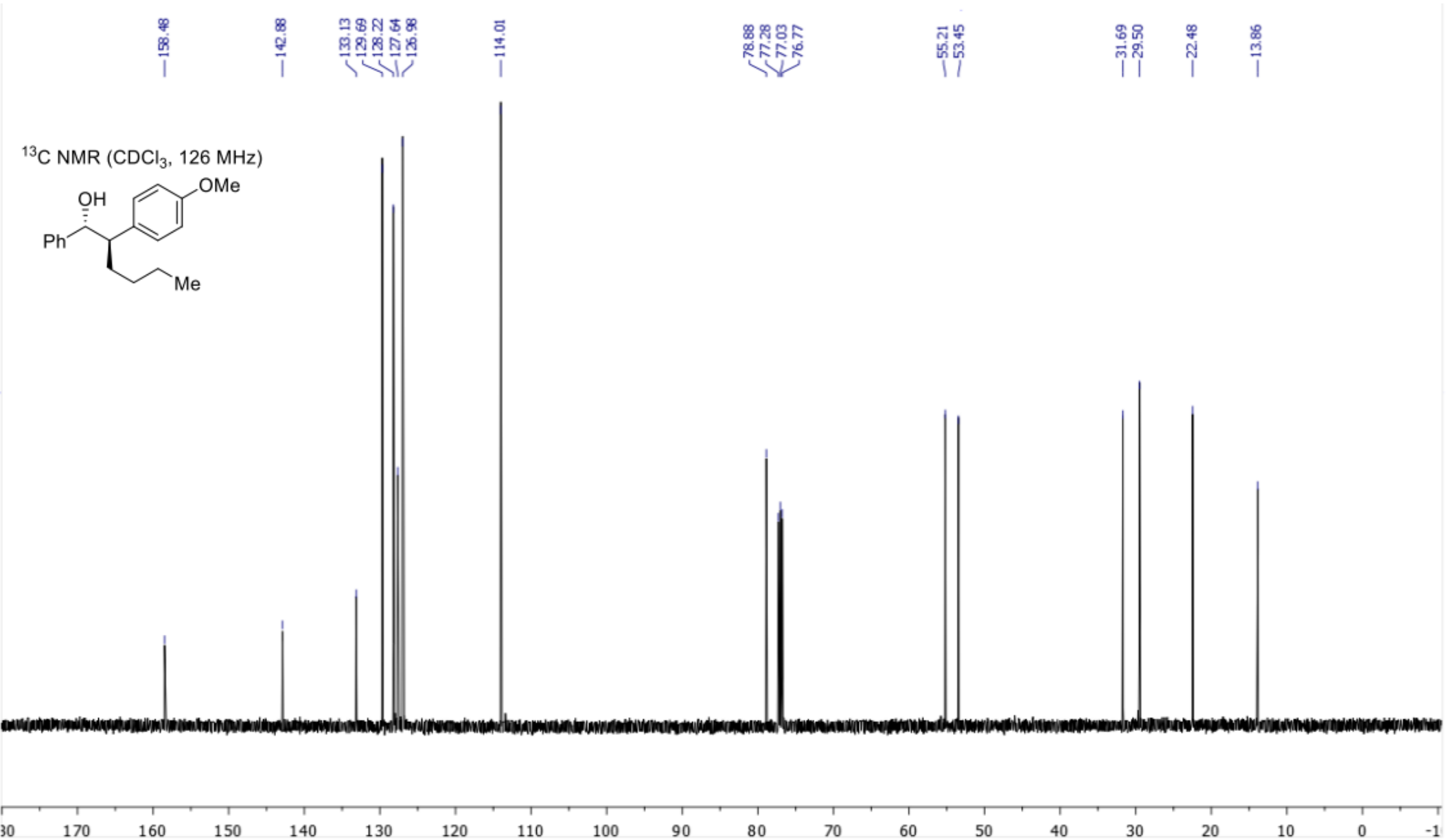
154.82
145.52
137.45
135.54
129.15
127.53
123.52
119.84
114.31
111.29
106.83
80.15
77.41
77.20
76.99
55.47
47.88
18.76
13C NMR (CDCl3, 151 MHz)
OH
OMe
Me
O
80
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1


7.38
7.38
7.36
7.36
7.35
7.34
7.32
7.31
7.31
7.31
7.30
7.30
7.29
7.26
7.26
7.23
7.23
7.22
7.21
7.21
7.20
6.92
6.92
6.91
6.90
6.90
6.89
4.62
4.61
4.60
4.59
3.82
3.82
2.99
2.98
2.98
2.96
1.88
1.88
1.07
1.06
1H NMR (CDCl3, 500 MHz)
OH
OMe
Ph
Me
4.68
1.93
1.87
1.00
3.05
1.02
0.90
3.18
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


158.52
142.61
135.17
128.98
128.24
127.73
126.96
114.07
79.76
77.27
77.02
76.76
55.26
47.32
18.42
^{13}C NMR ($CDCl_3$, 126 MHz)
OH
OMe
Ph
Me
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


^{1}H NMR ($CDCl_3$, 500 MHz)
OH
OMe
Ph
Me
5.12
2.00
1.88
1.00
2.98
0.99
0.92
1.13
1.16
2.29
2.14
2.96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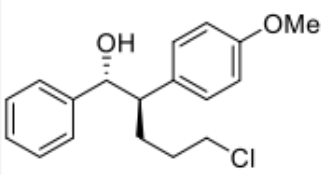
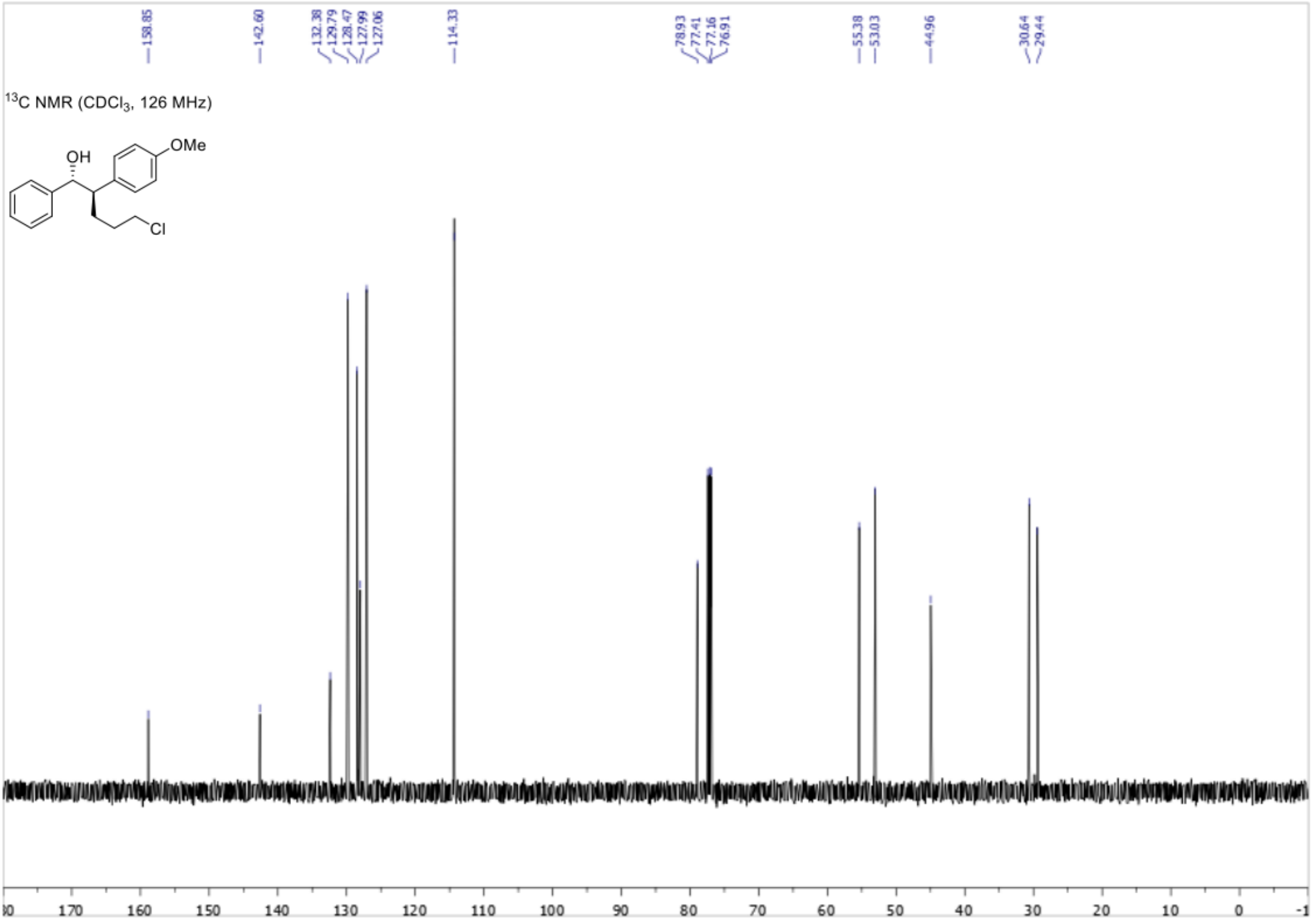
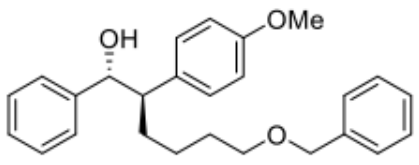
142.88
133.13
129.69
128.22
127.64
126.98
114.01
78.88
77.28
77.03
76.77
55.21
53.45
31.69
29.50
22.48
13.86
13C NMR (CDCl3, 126 MHz)
OH
OMe
Ph
Me
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

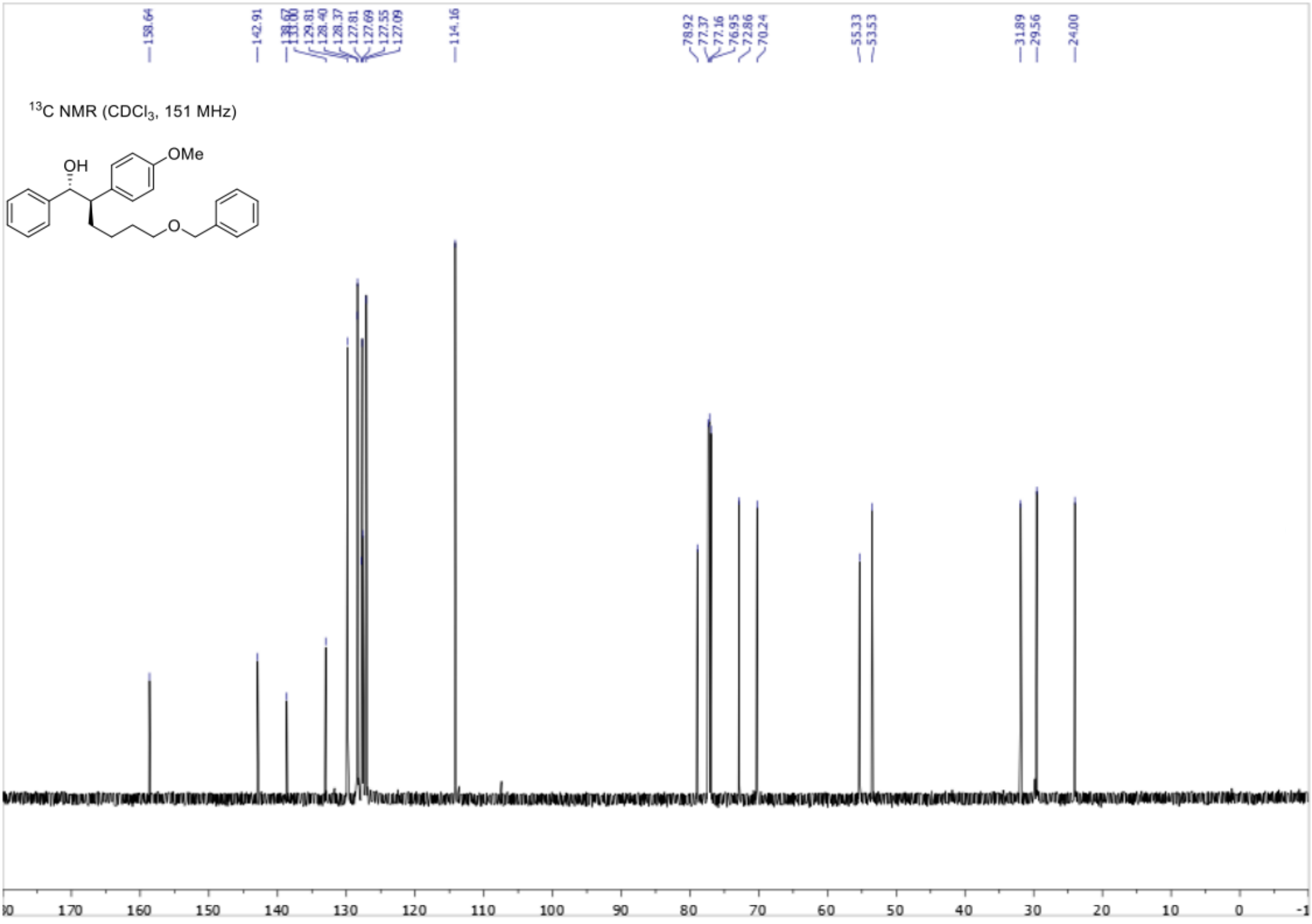
^{1}H NMR ($CDCl_3$, 500 MHz)

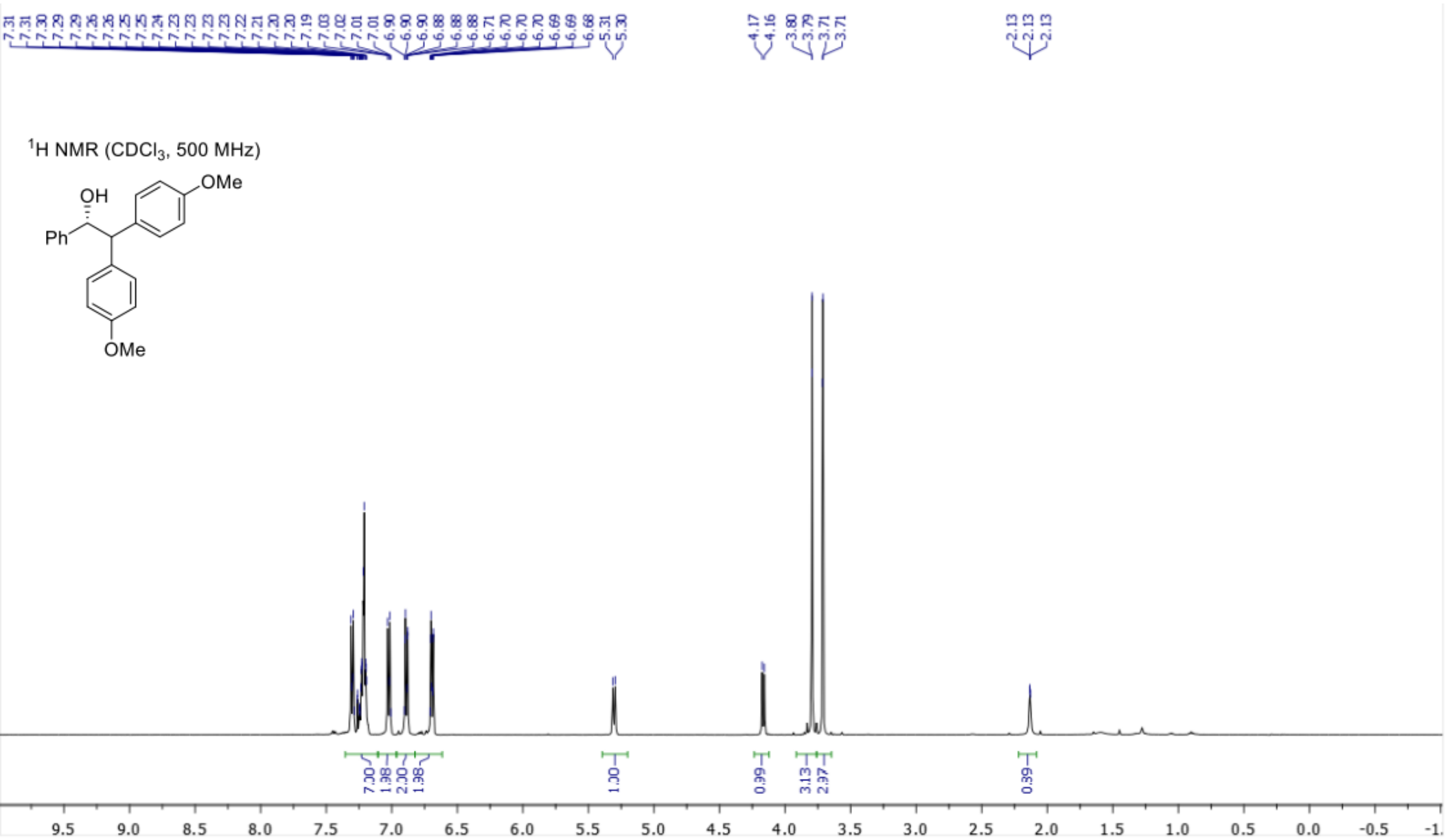


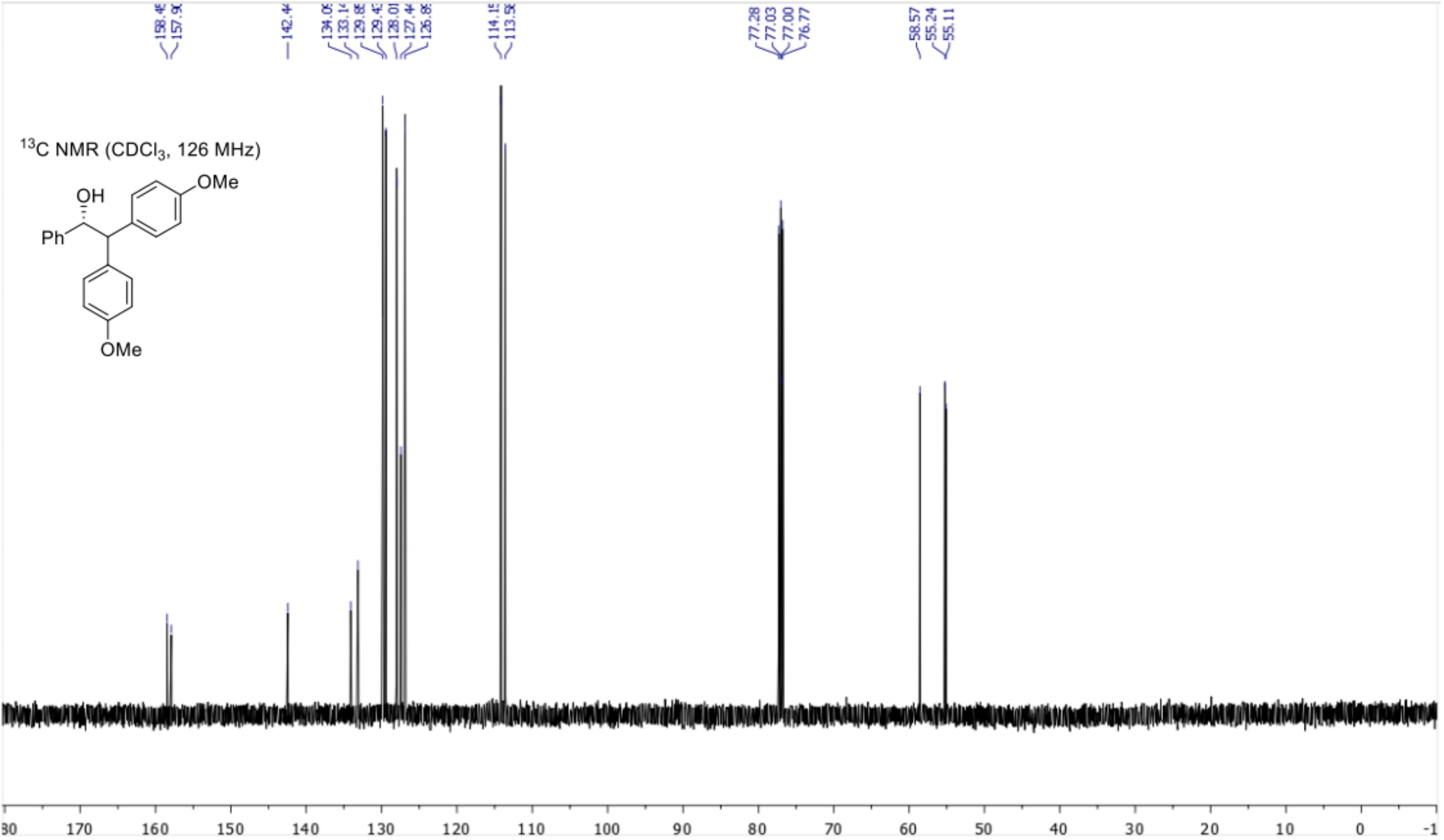

158.85
142.60
132.38
129.79
128.47
127.99
127.06
114.33
78.93
77.41
77.16
76.91
55.38
53.03
44.96
30.64
29.44
13C NMR (CDCl3, 126 MHz)
OH
OMe
Cl
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

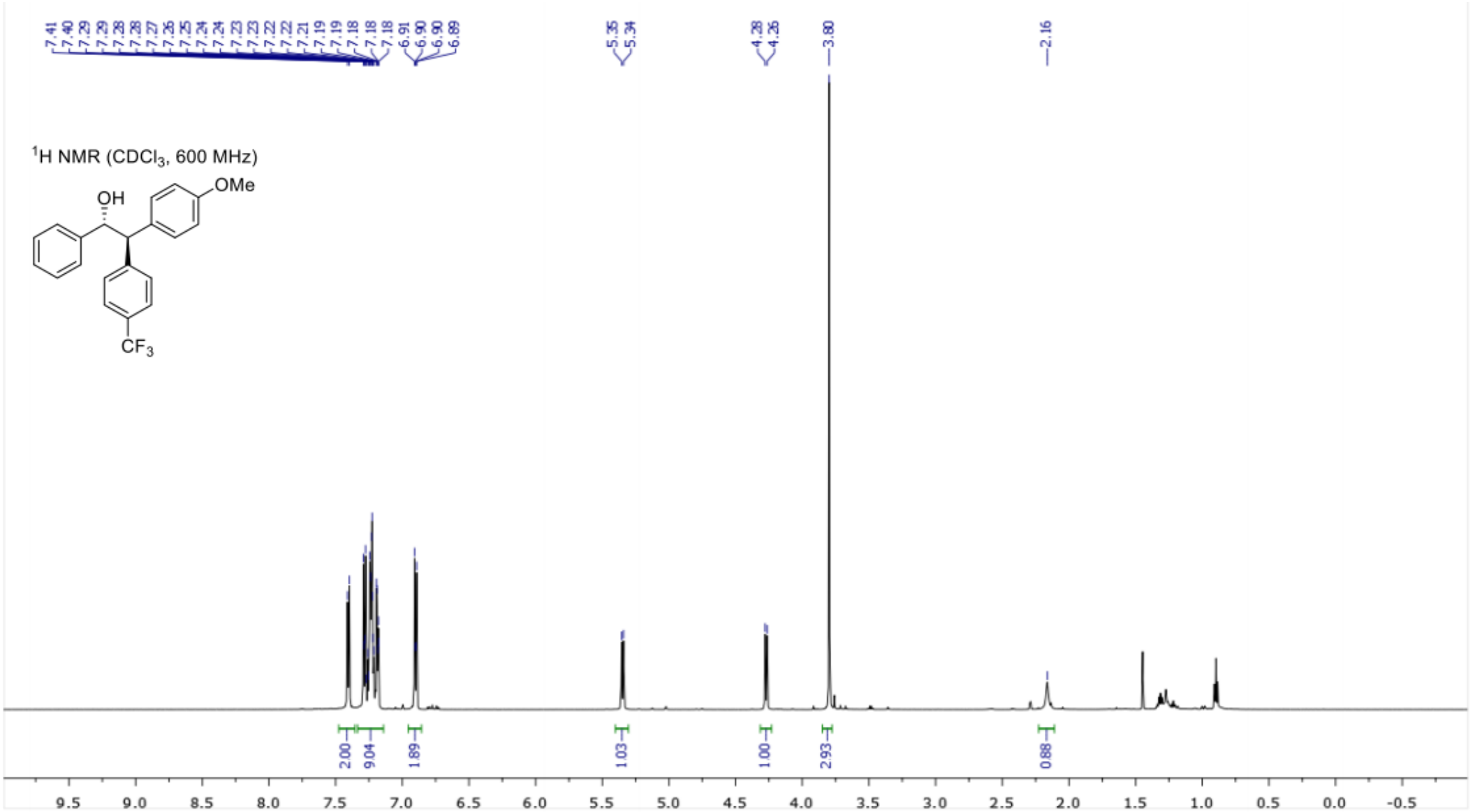
^{1}H NMR ($CDCl_3$, 600 MHz)

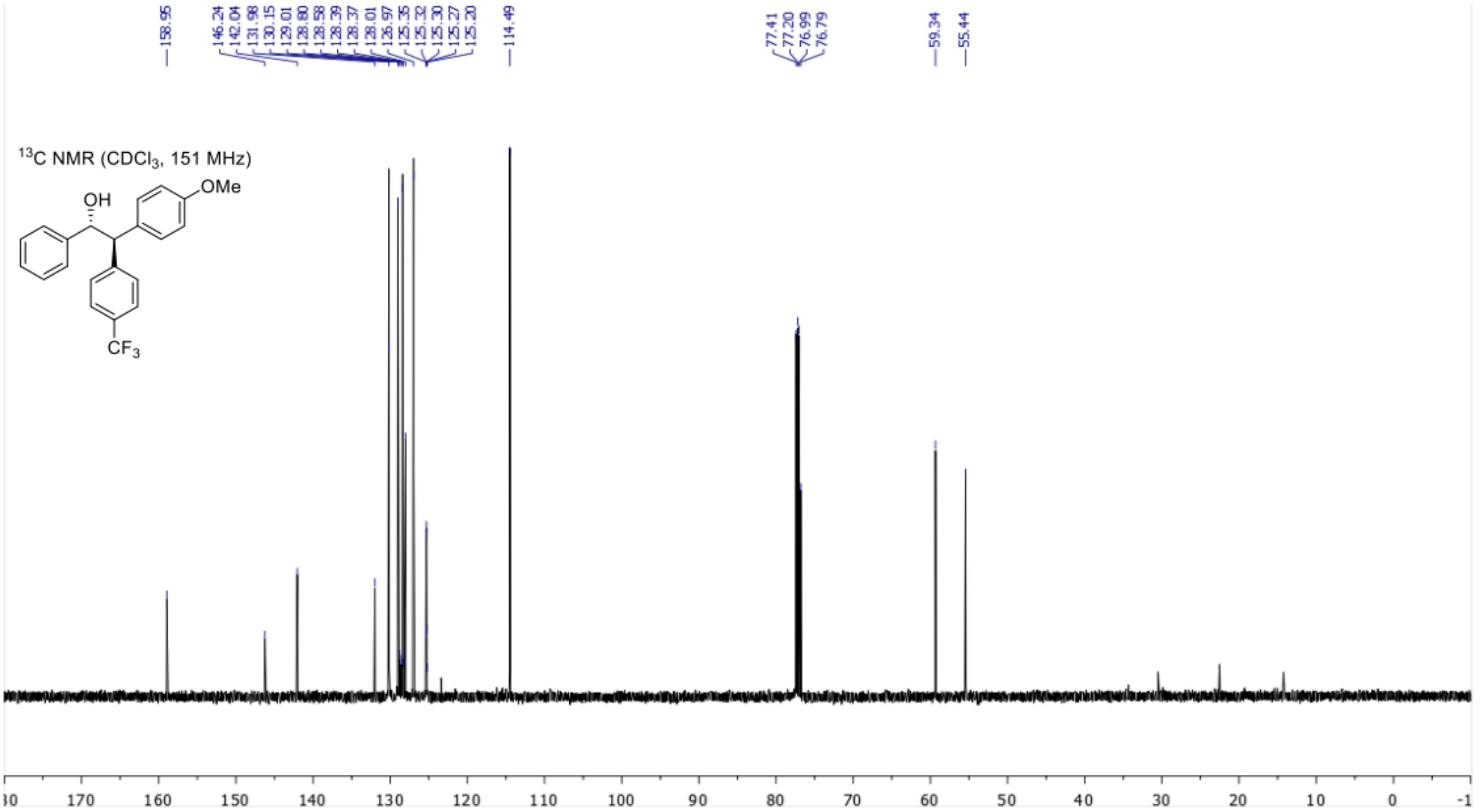


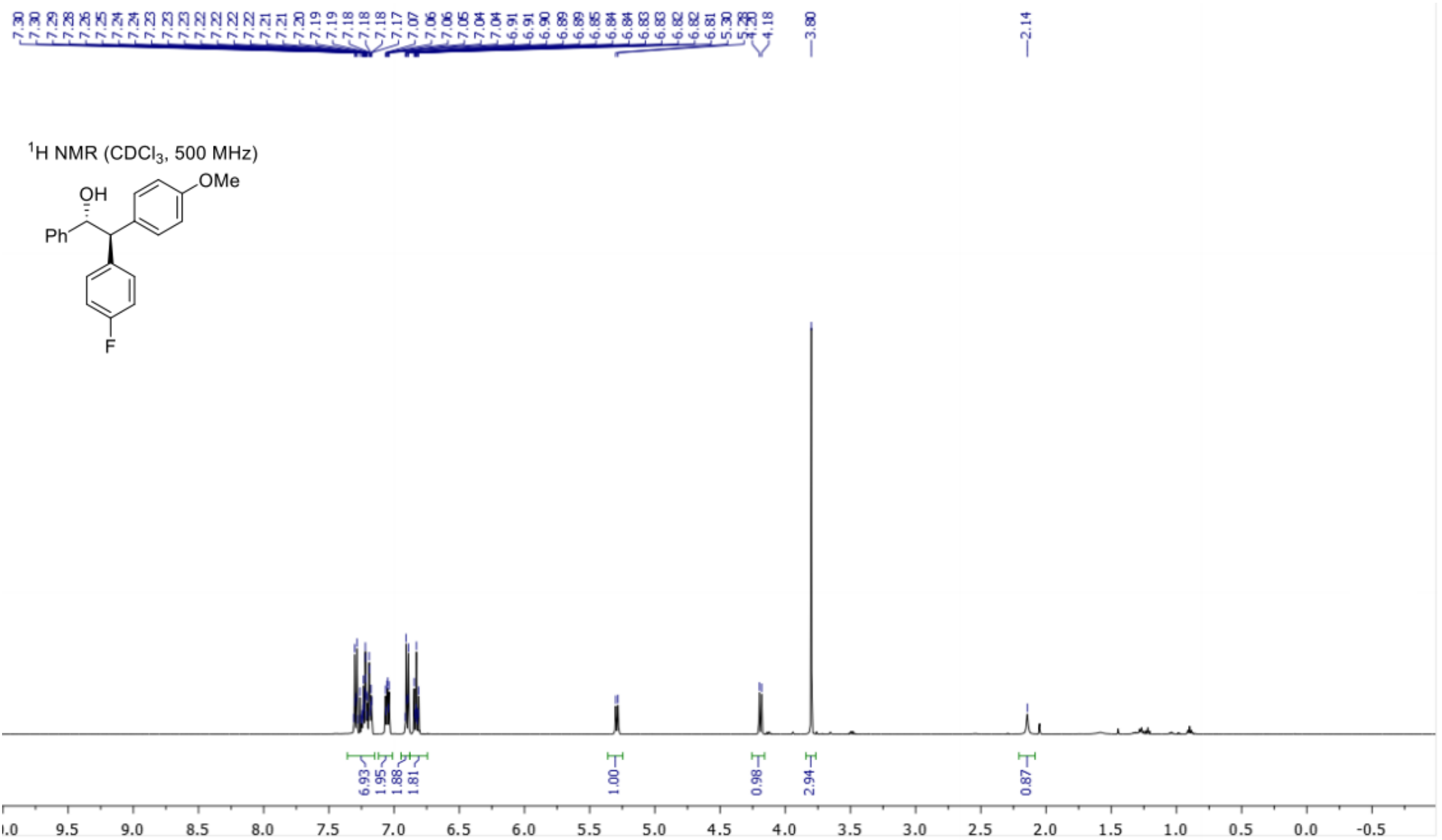

158.64
142.91
138.67
133.60
129.81
128.40
128.37
127.81
127.69
127.55
127.09
114.16
78.92
77.37
77.16
76.95
72.86
70.24
55.33
53.53
31.89
29.56
24.00
^{13}C NMR ($CDCl_3$, 151 MHz)
OH
OMe
O
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

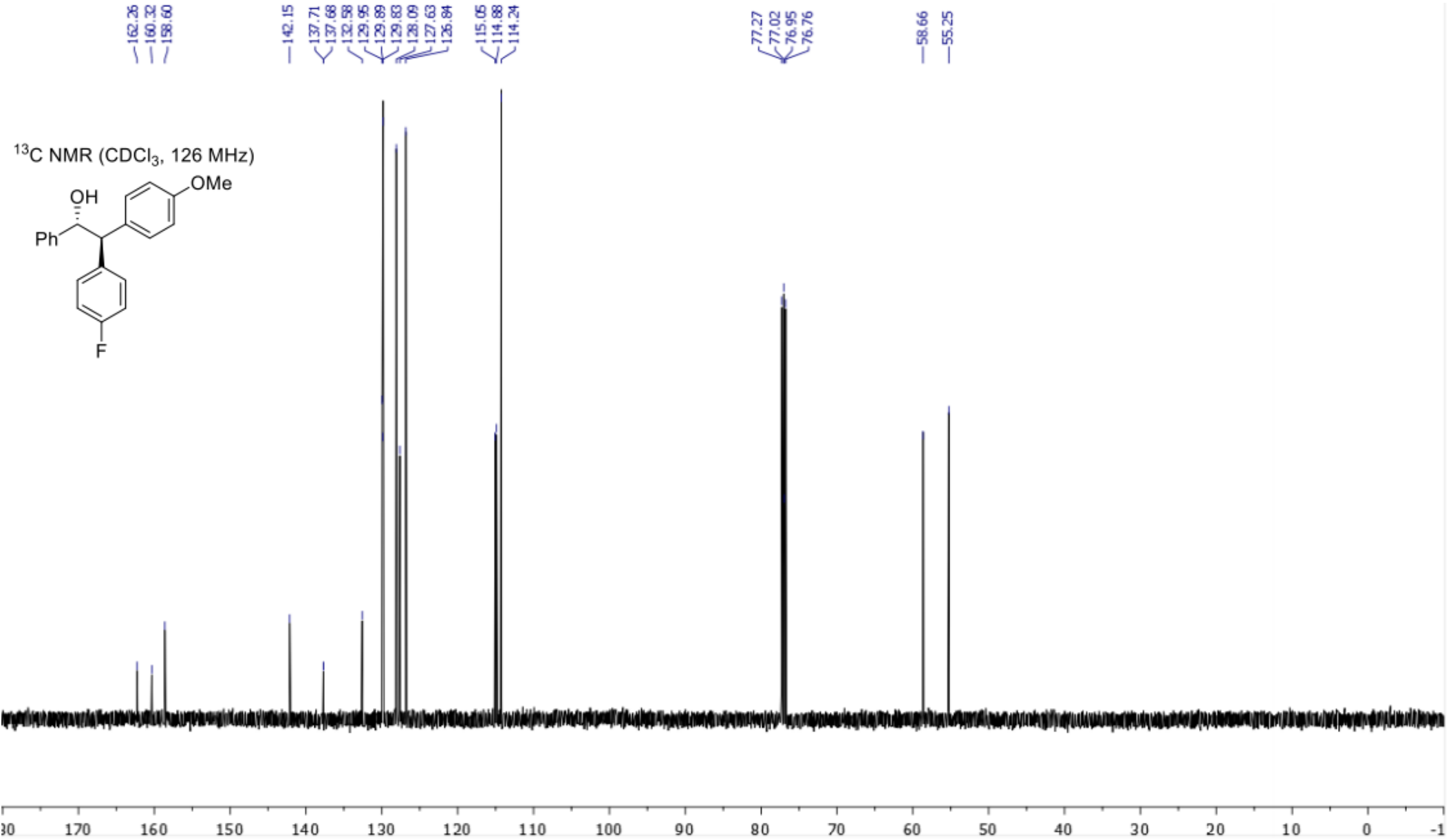

7.31
7.31
7.30
7.29
7.29
7.26
7.26
7.25
7.25
7.24
7.23
7.23
7.23
7.23
7.22
7.21
7.20
7.20
7.19
7.03
7.02
7.01
7.01
6.90
6.90
6.90
6.88
6.88
6.88
6.71
6.70
6.70
6.70
6.69
6.69
6.68
5.31
5.30
4.17
4.16
3.80
3.79
3.71
3.71
2.13
2.13
2.13
1H NMR (CDCl3, 500 MHz)
OH
Ph
OMe
OMe
7.00
1.98
2.00
1.98
1.00
0.99
3.13
2.97
0.39
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

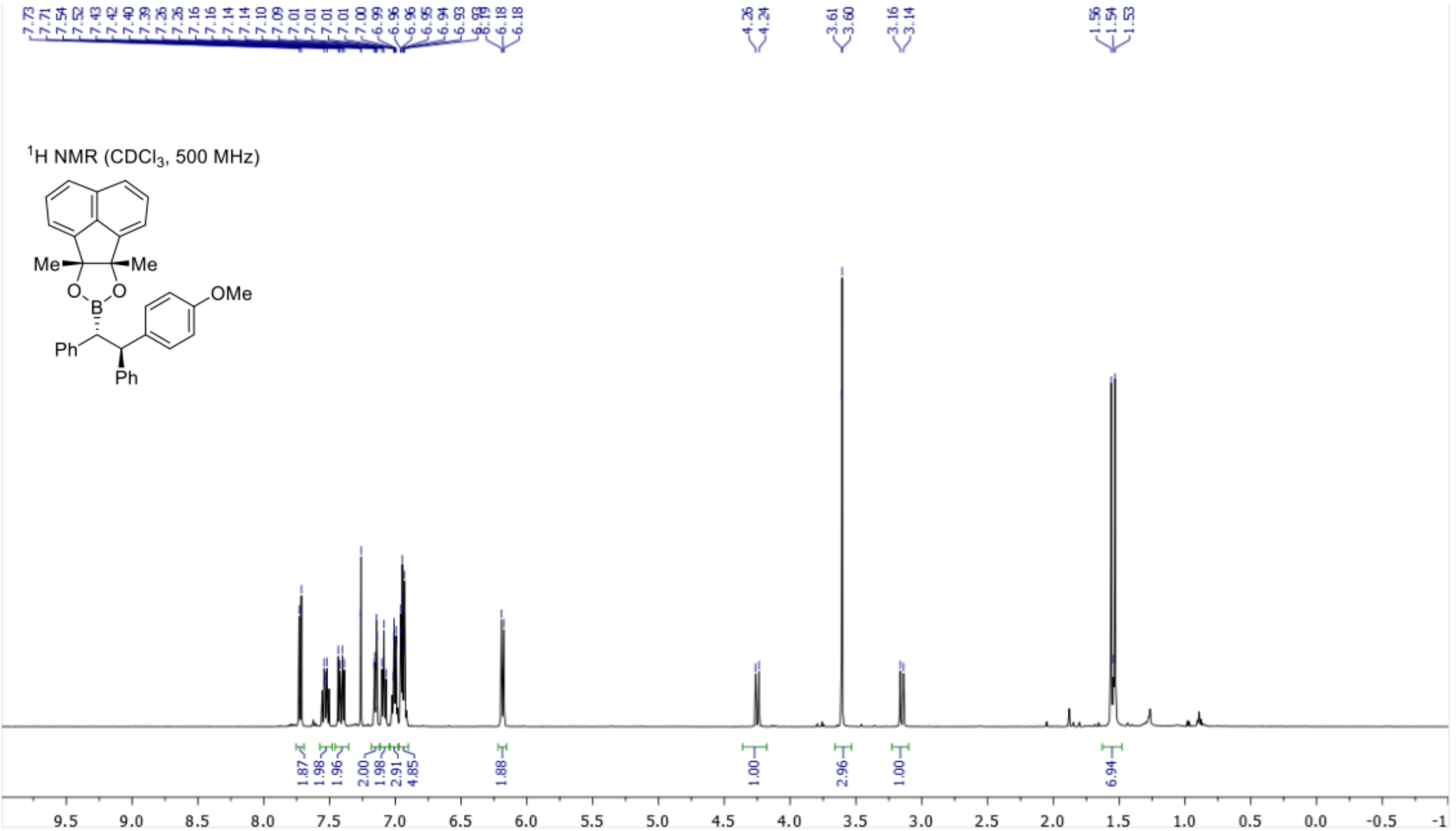

13C NMR (CDCl3, 126 MHz)
OH
Ph
OMe
OMe
158.45
157.90
142.44
134.05
133.14
129.88
129.43
128.01
127.44
126.89
114.15
113.58
77.28
77.03
77.00
76.77
58.57
55.24
55.11
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

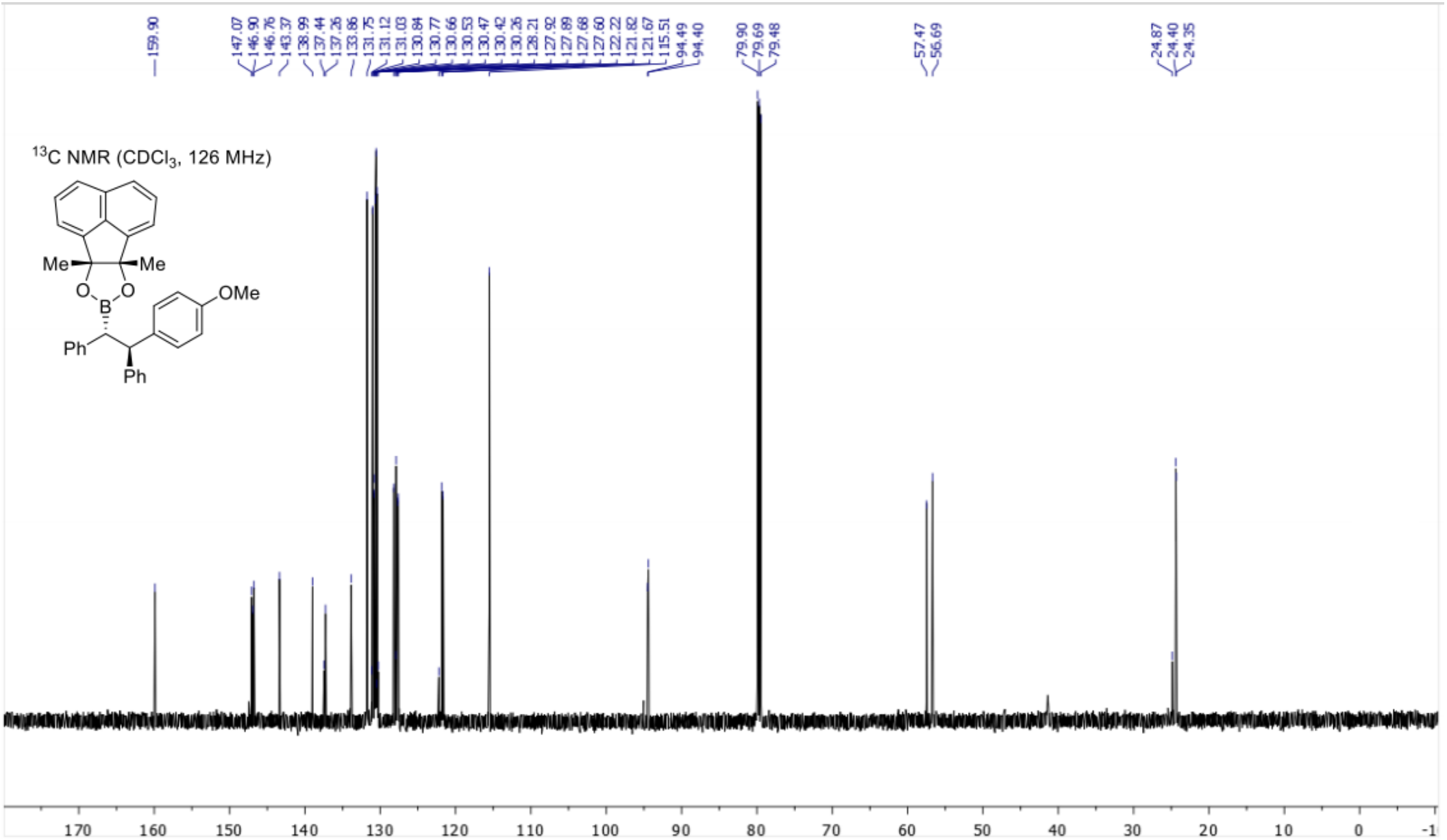

7.41
7.40
7.29
7.29
7.28
7.28
7.27
7.26
7.25
7.24
7.24
7.23
7.23
7.22
7.22
7.21
7.19
7.19
7.18
7.18
7.18
6.91
6.90
6.90
6.89
5.35
5.34
4.28
4.26
3.80
2.16
1H NMR (CDCl3, 600 MHz)
OH
OMe
CF3
2.00
9.04
1.89
1.03
1.00
2.93
0.88
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

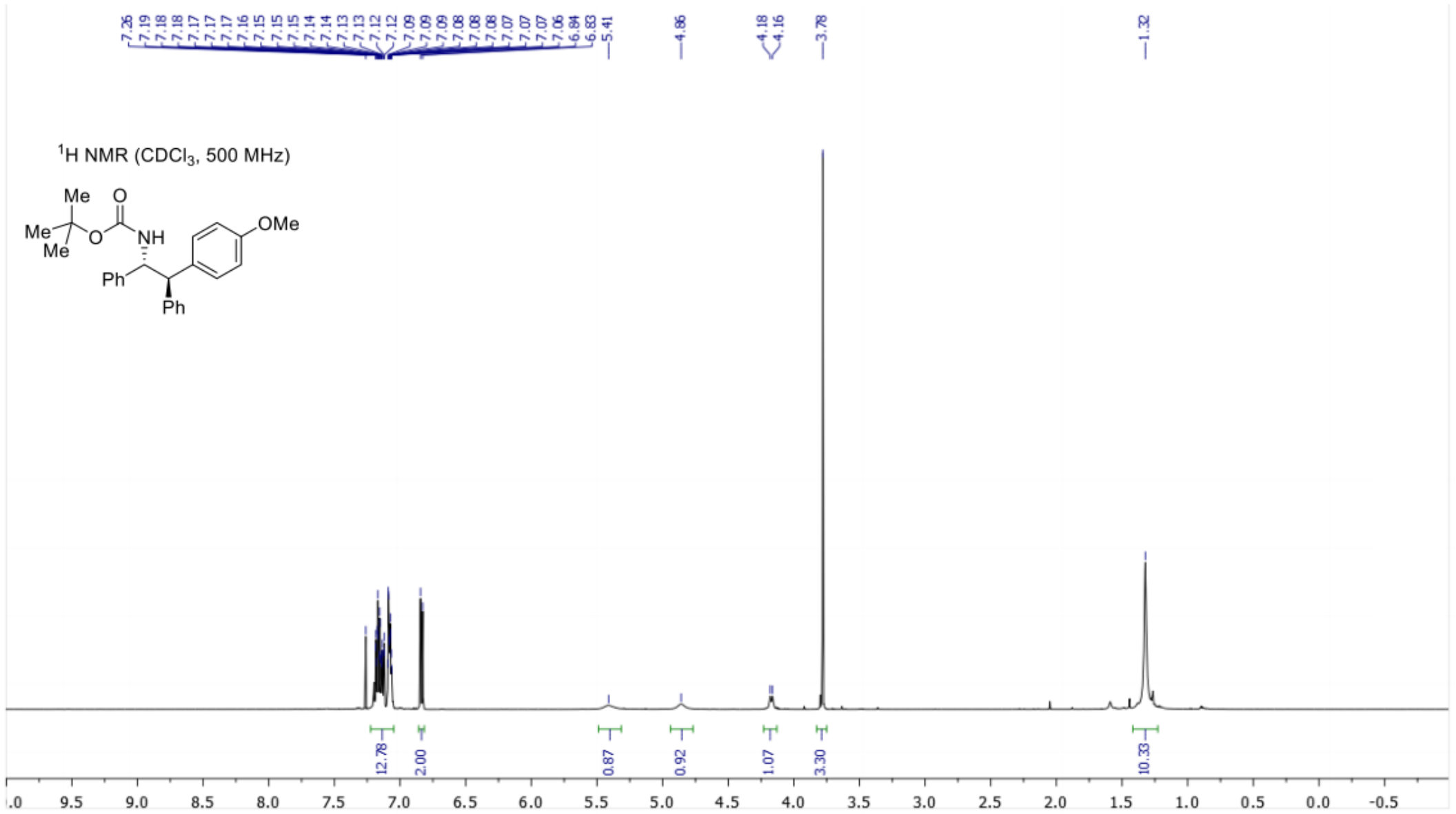

158.95
146.24
142.04
131.98
130.15
129.01
128.80
128.58
128.39
128.37
128.01
126.97
125.35
125.32
125.30
125.27
125.20
114.49
77.41
77.20
76.99
76.79
59.34
55.44
13C NMR (CDCl3, 151 MHz)
OH
OMe
CF3
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


7.30 7.30 7.29 7.28 7.26 7.25 7.24 7.24 7.23 7.23 7.23 7.22 7.22 7.22 7.22 7.21 7.21 7.20 7.19 7.19 7.18 7.18 7.18 7.17 7.07 7.06 7.06 7.05 7.04 7.04 6.91 6.91 6.90 6.89 6.89 6.85 6.84 6.84 6.83 6.83 6.82 6.82 6.81 5.30 5.28 4.20 4.18
3.80
2.14
1H NMR (CDCl3, 500 MHz)
OH
OMe
Ph
F
6.93
1.95
1.88
1.81
1.00
0.98
2.94
0.87
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


162.26
160.32
158.60
142.15
137.71
137.68
132.58
129.95
129.89
129.83
128.09
127.63
126.84
115.05
114.88
114.24
77.27
77.02
76.95
76.76
58.66
55.25
13C NMR (CDCl3, 126 MHz)
OH
OMe
Ph
F
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


7.73
7.71
7.54
7.52
7.43
7.42
7.40
7.39
7.26
7.26
7.16
7.16
7.14
7.14
7.10
7.09
7.01
7.01
7.01
7.01
7.00
6.99
6.96
6.96
6.95
6.94
6.93
6.18
6.18
4.26
4.24
3.61
3.60
3.16
3.14
1.56
1.54
1.53
1H NMR (CDCl3, 500 MHz)
Me
Me
O
O
B
OMe
Ph
Ph
1.87
1.98
1.96
2.00
1.98
2.91
4.85
1.88
1.00
2.96
1.00
6.94
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


159.90
147.07
146.90
146.76
143.37
138.99
137.44
137.26
133.86
131.75
131.12
131.03
130.84
130.77
130.66
130.53
130.47
130.42
130.26
128.21
127.92
127.89
127.68
127.60
122.22
121.82
121.67
115.51
94.49
94.40
79.90
79.69
79.48
57.47
56.69
24.87
24.40
24.35
13C NMR (CDCl3, 126 MHz)
Me
Me
O
O
B
OMe
Ph
Ph
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1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7.14
7.13
7.13
7.12
7.12
7.09
7.09
7.09
7.08
7.08
7.08
7.07
7.07
7.07
7.06
6.84
6.83
5.41
4.86
4.18
4.16
3.78
1.32
^{1}H NMR ($CDCl_3$, 500 MHz)
Me
O
Me
O
NH
OMe
Me
Ph
Ph
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2.00
0.87
0.92
1.07
3.30
10.33
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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3.5
3.0
2.5
2.0
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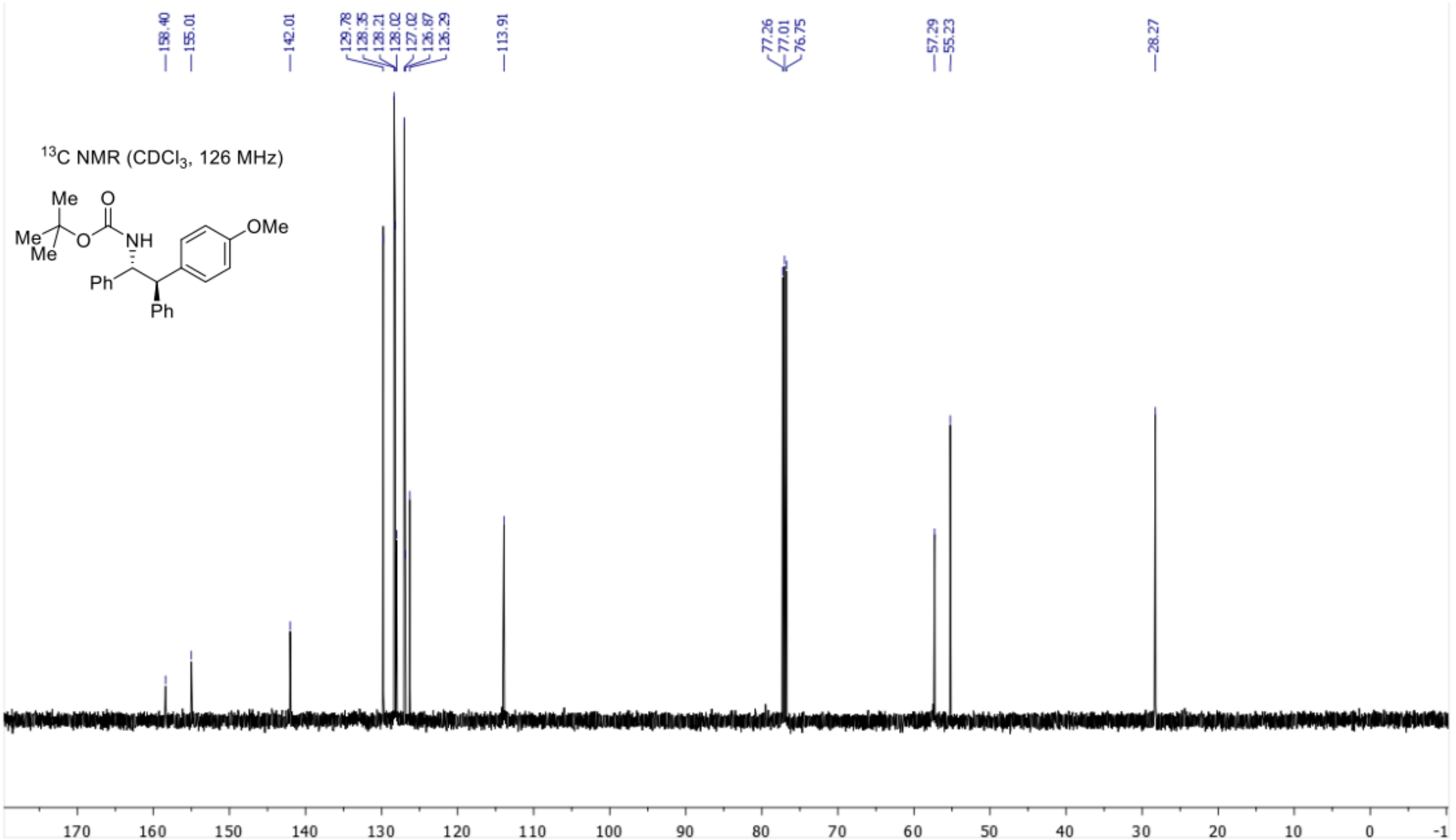
-0.5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127.02
126.87
126.29
113.91
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77.01
76.75
57.29
55.23
28.27
^{13}C NMR ($CDCl_3$, 126 MHz)
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O
Me
Me
O
NH
OMe
Ph
Ph
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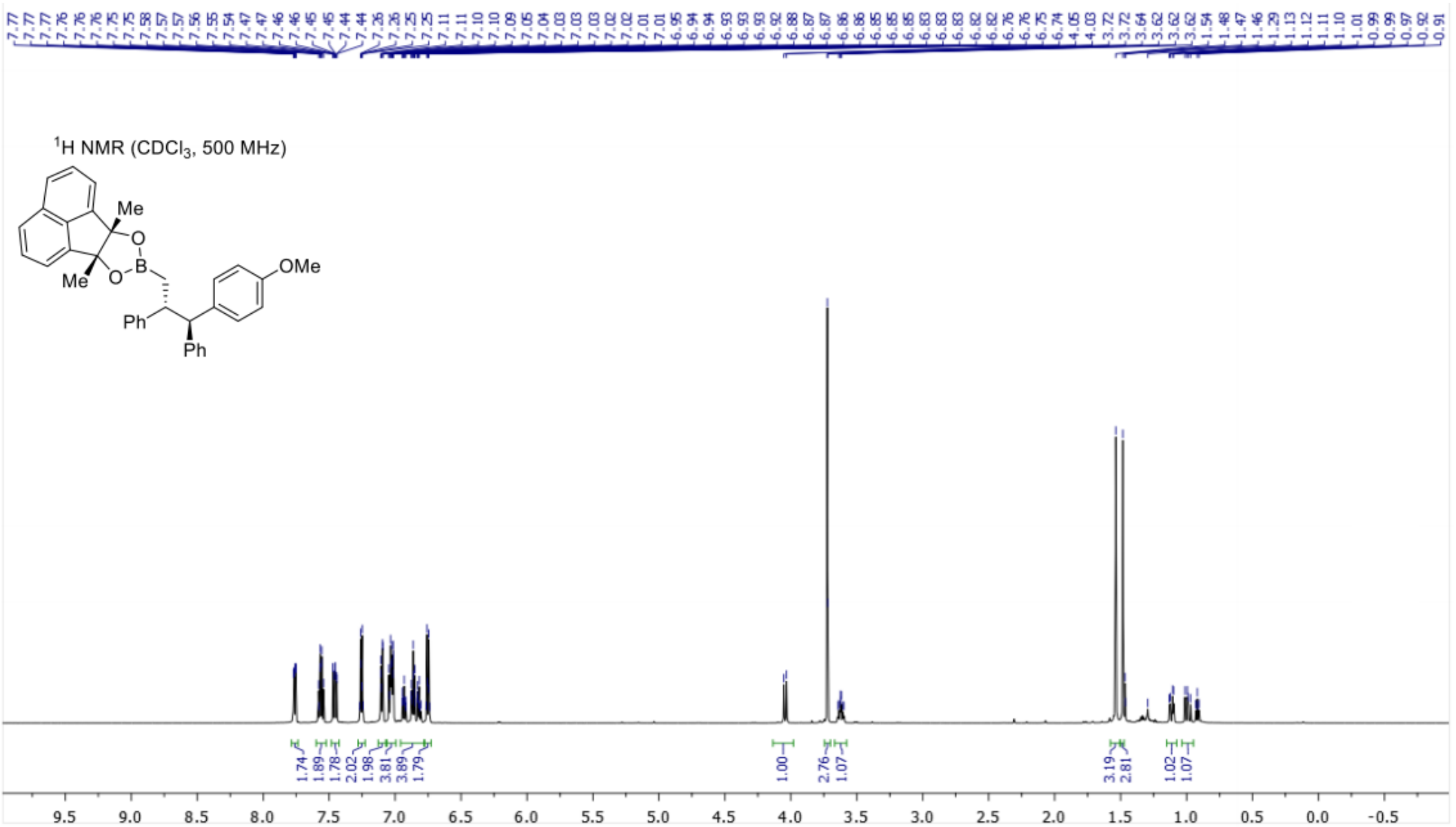
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B
Me
O
OMe
Ph
Ph
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1.98
3.81
3.89
1.79
1.00
2.76
1.07
3.19
2.81
1.02
1.07
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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3.5
3.0
2.5
2.0
1.5
1.0
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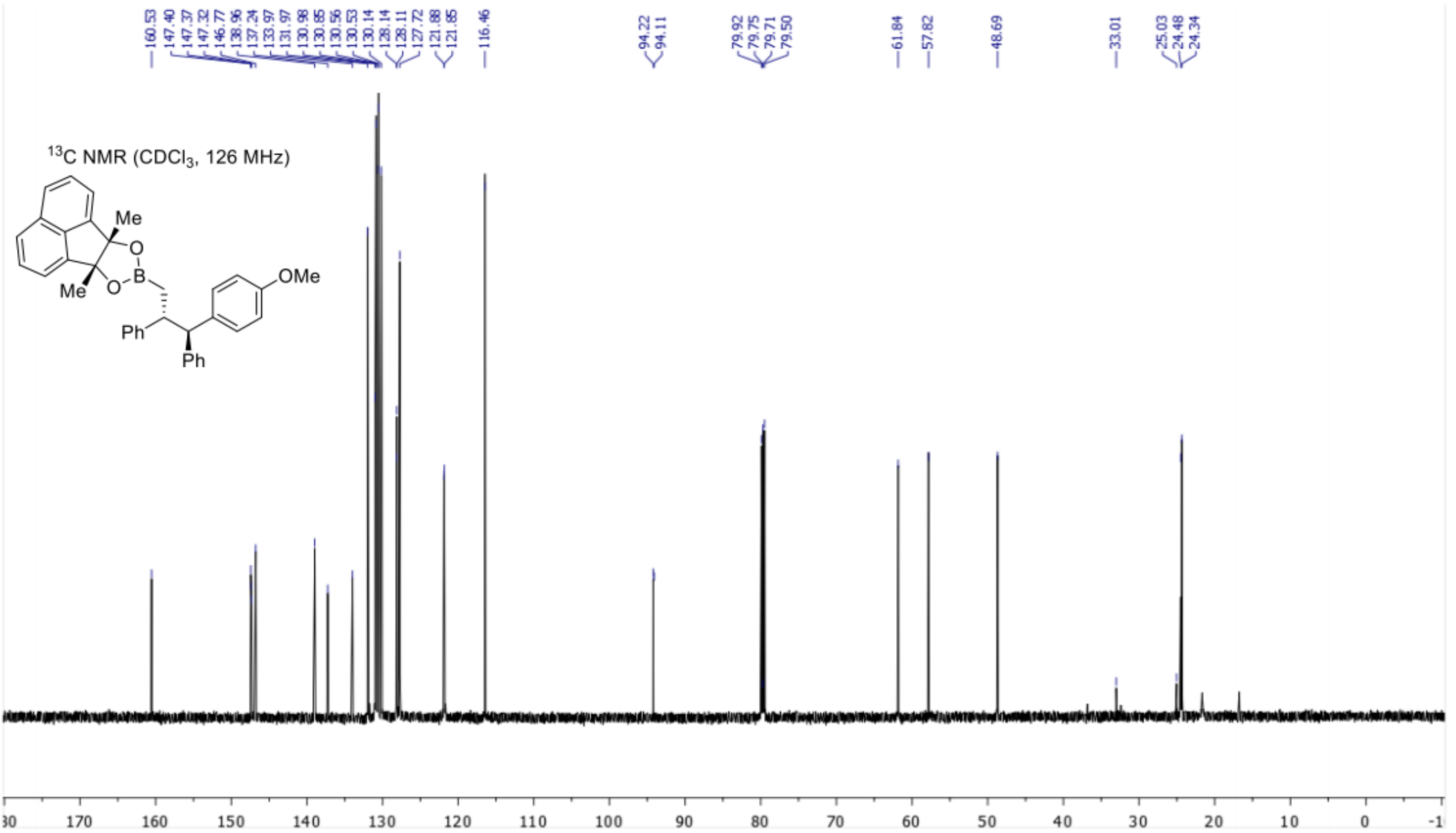
0.0
-0.5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130.14
128.14
128.11
127.72
121.88
121.85
116.46
94.22
94.11
79.92
79.75
79.71
79.50
61.84
57.82
48.69
33.01
25.03
24.48
24.34
13C NMR (CDCl3, 126 MHz)
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O
B
O
Me
OMe
Ph
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150
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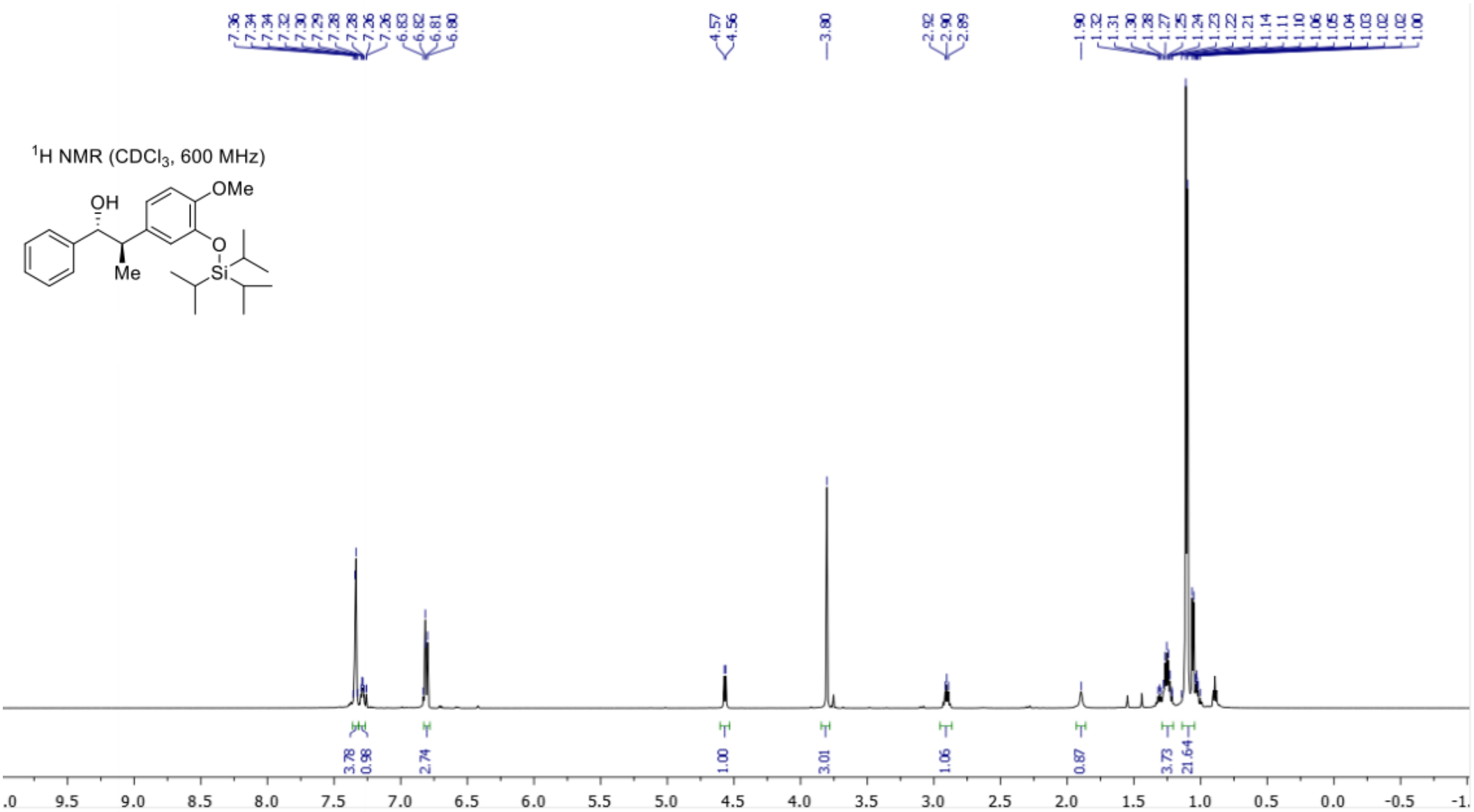
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6.80
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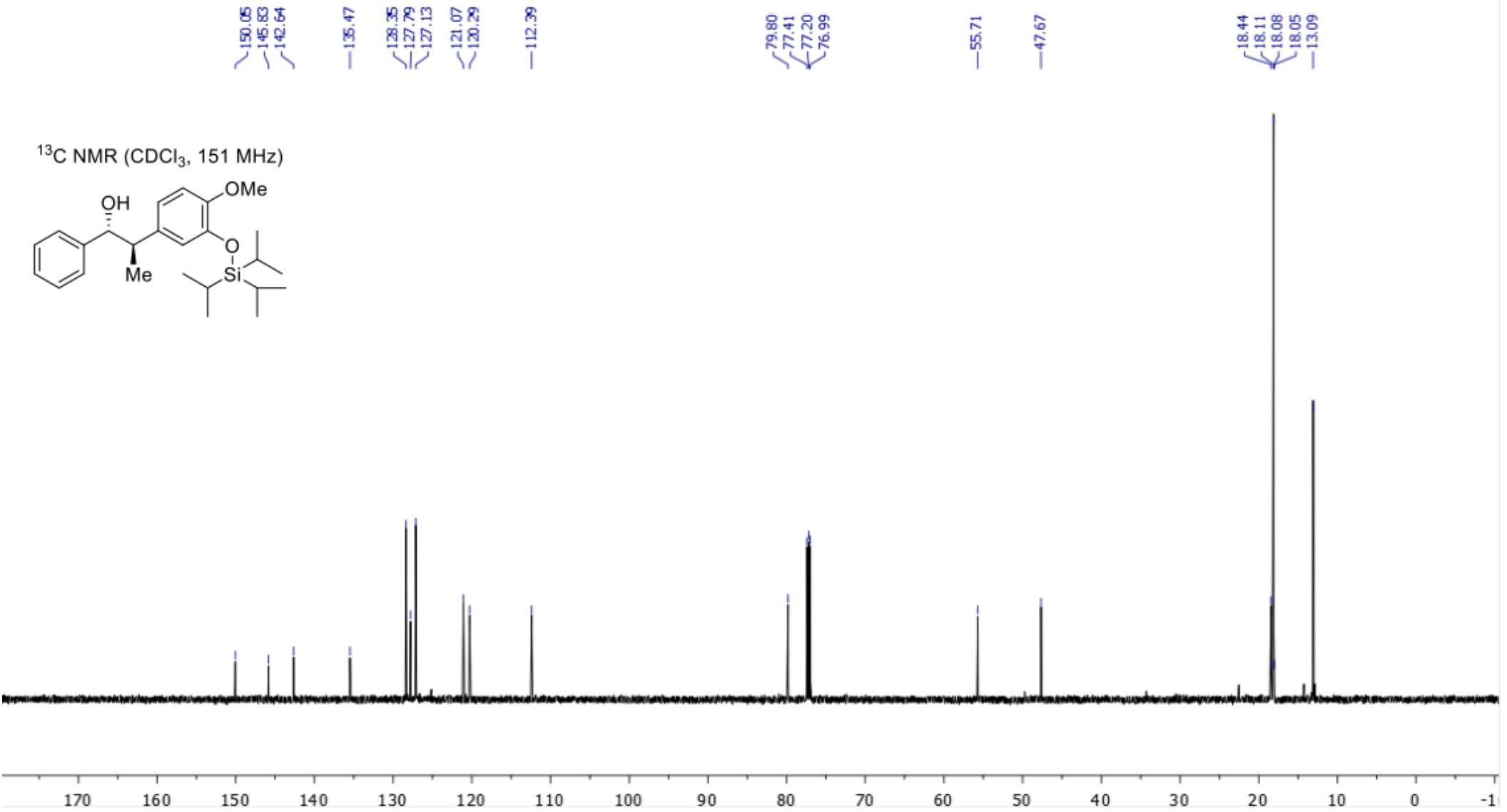
4.56
3.80
2.92
2.90
2.89
1.90
1.32
1.31
1.30
1.28
1.27
1.25
1.24
1.23
1.22
1.21
1.14
1.11
1.10
1.06
1.05
1.04
1.03
1.02
1.02
1.00
1H NMR (CDCl3, 600 MHz)
OH
OMe
O
Si
Me
3.78
0.98
2.74
1.00
3.01
1.06
0.87
3.73
21.64
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5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145.83
142.64
135.47
128.35
127.79
127.13
121.07
120.29
112.39
79.80
77.41
77.20
76.99
55.71
47.67
18.44
18.11
18.08
18.05
13.09
13C NMR (CDCl3, 151 MHz)
OH
OMe
Me
O
Si
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160
150
140
130
120
110
100
90
80
70
60
50
40
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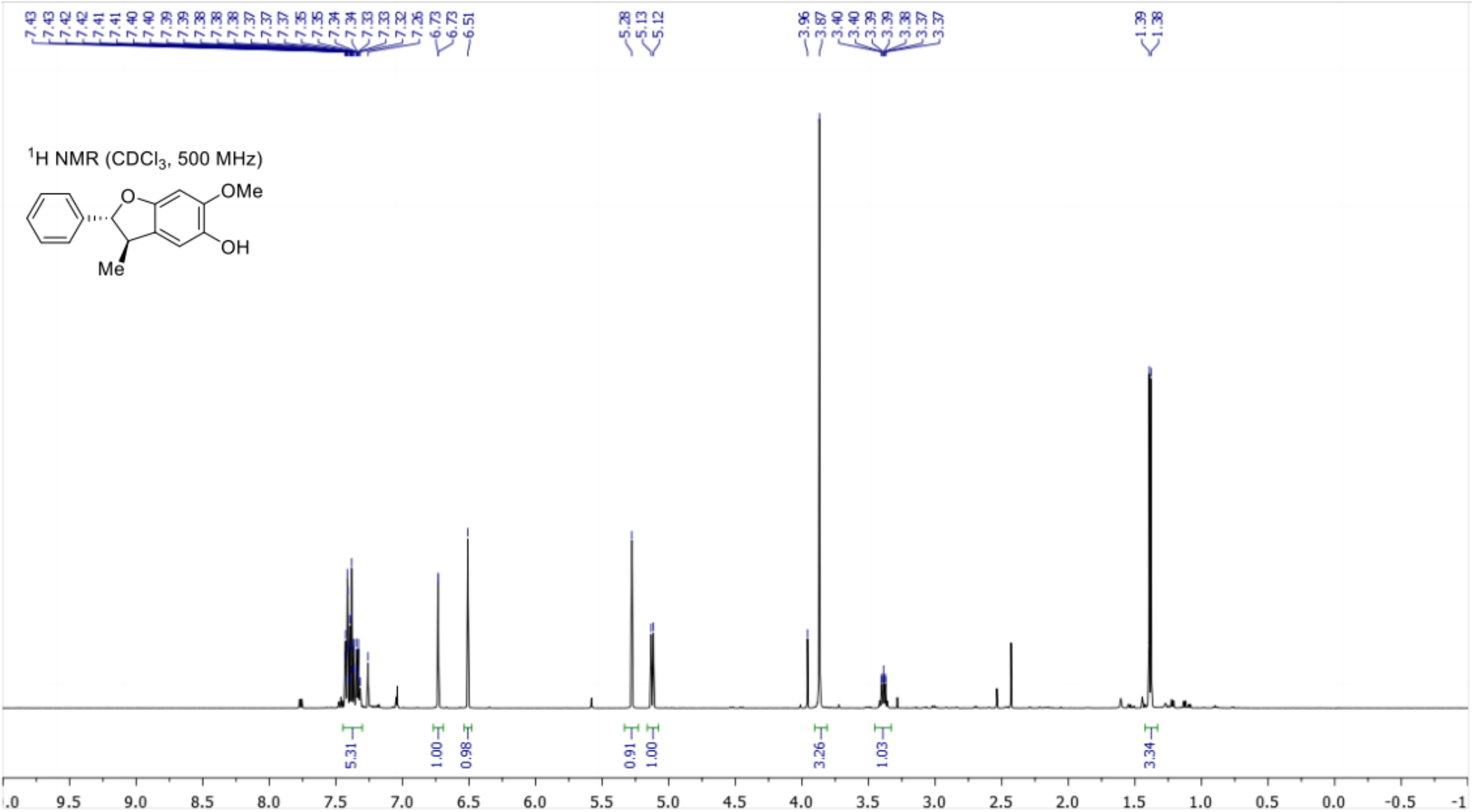
10
0
-1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7.35
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7.33
7.33
7.32
7.26
6.73
6.73
6.51
5.28
5.13
5.12
3.96
3.87
3.40
3.40
3.39
3.39
3.38
3.37
3.37
1.39
1.38
1H NMR (CDCl3, 500 MHz)
O
OMe
OH
Me
5.31
1.00
0.98
0.91
1.00
3.26
1.03
3.34
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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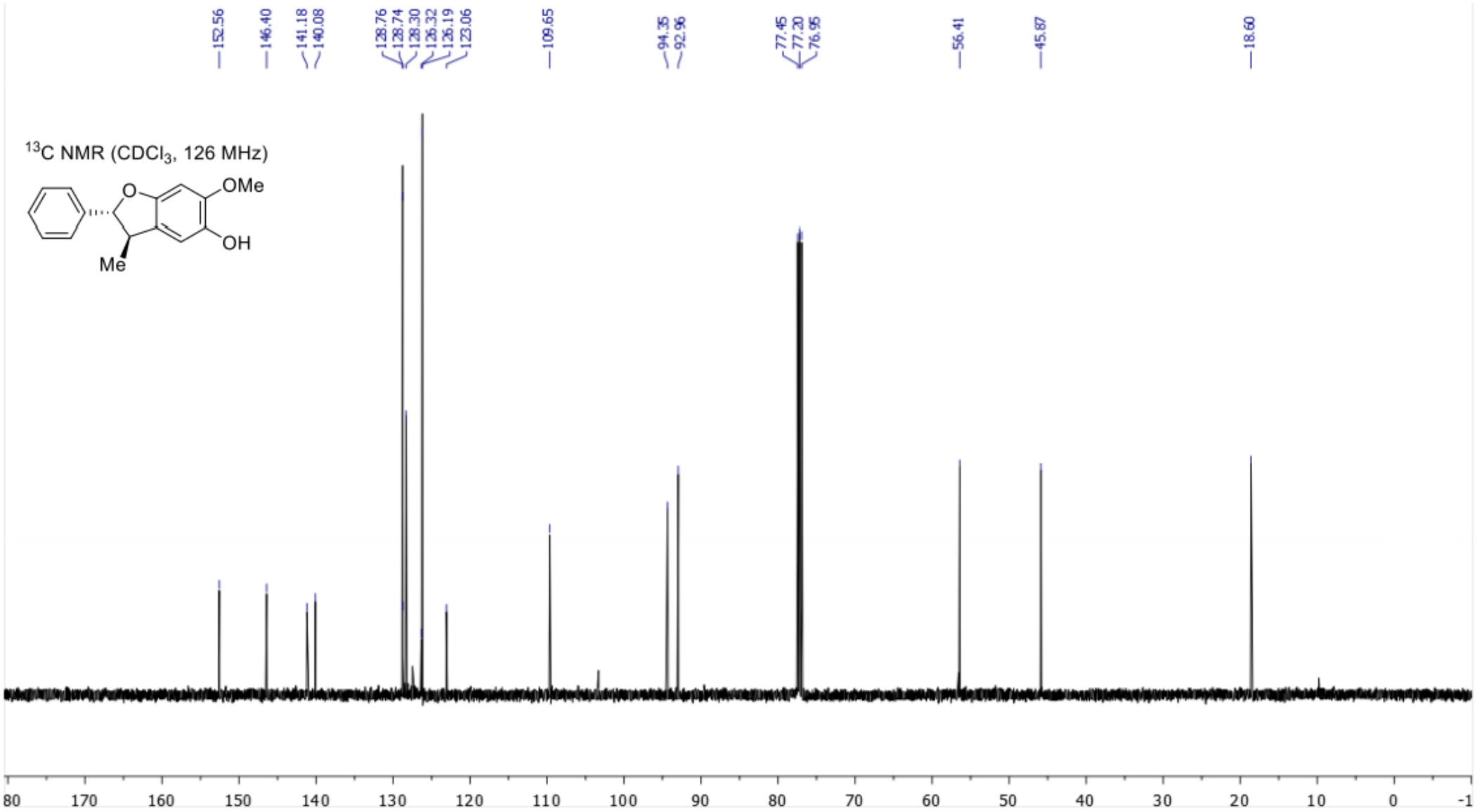
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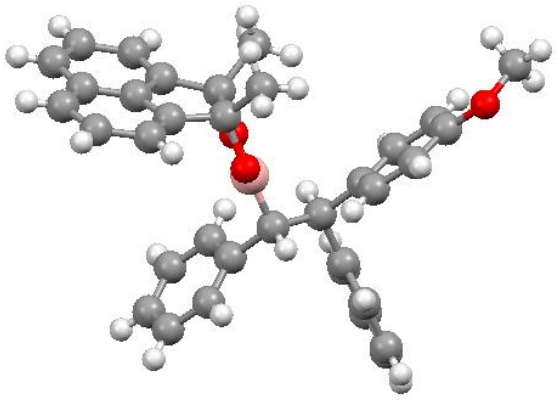
126.19
123.06
109.65
94.35
92.96
77.45
77.20
76.95
56.41
45.87
18.60
13C NMR (CDCl3, 126 MHz)
O
OMe
OH
Me
80
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1

1.5.7 Crystal Structure Data

Table 1. Crystal data and structure

refinement for C35H31BO3.



Identification code C35H31BO3
Empirical formula C35 H31 B O3
Formula weight 510.41
Temperature 100(2) K
Wavelength 1.54178 Å
Crystal system Triclinic
Space group P1
Unit cell dimensions a = 10.1118(3) Å D= 83.3770(10)°.
b = 11.8308(4) Å E= 70.4740(10)°.
c = 12.5795(4) Å J = 72.0230(10)°.
Volume 1348.98(8) Å3
Z 2
Density (calculated) 1.257 Mg/m3
Absorption coefficient 0.611 mm-1
F(000) 540
Crystal size 0.600 x 0.560 x 0.480 mm3
Theta range for data collection 3.728 to 66.684°.
Index ranges -12<=h<=12, -14<=k<=14, -14<=l<=14
Reflections collected 25450
Independent reflections 9064 [R(int) = 0.0484]
Completeness to theta = 66.684° 98.5 %
Absorption correction Semi-empirical from equivalents
Max. and min. transmission 0.7528 and 0.6878
Refinement method Full-matrix least-squares on F2
Data / restraints / parameters 9064 / 3 / 709
Goodness-of-fit on F2 1.022
Final R indices [I>2sigma(I)] R1 = 0.0449, wR2 = 0.1164
R indices (all data) R1 = 0.0450, wR2 = 0.1165
Absolute structure parameter -0.16(14)
Extinction coefficient n/a
Largest diff. peak and hole 0.242 and -0.207 e.Å-3

Table 2. Atomic coordinates (x 104) and equivalent isotropic displacement parameters (Å2x 103)
for C35H31BO3. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(1)	4672(2)	8507(2)	6018(2)	28(1)
O(2)	4074(2)	3215(2)	8406(2)	16(1)
O(3)	5215(2)	2995(2)	6498(2)	16(1)
B(1)	3926(3)	3316(2)	7359(2)	15(1)
C(1)	4580(4)	9395(3)	6731(3)	29(1)
C(2)	3893(3)	7698(3)	6483(2)	22(1)
C(3)	4155(3)	6776(3)	5788(2)	24(1)
C(4)	3429(3)	5910(2)	6171(2)	20(1)
C(5)	2434(3)	5938(2)	7248(2)	17(1)
C(6)	2195(3)	6869(3)	7936(2)	24(1)
C(7)	2915(3)	7755(3)	7556(3)	25(1)
C(8)	1550(3)	5039(2)	7672(2)	15(1)
C(9)	2394(3)	3790(2)	7145(2)	15(1)
C(10)	1524(3)	2892(2)	7575(2)	16(1)
C(11)	1382(4)	2187(3)	6836(3)	27(1)
C(12)	639(4)	1334(3)	7230(3)	35(1)
C(13)	16(3)	1175(3)	8371(3)	30(1)
C(14)	133(3)	1874(3)	9120(3)	27(1)
C(15)	886(3)	2723(3)	8725(2)	23(1)

C(16) 56(3) 5519(2) 7494(2) 14(1)
C(17) -68(3) 5735(2) 6408(2) 17(1)
C(18) -1439(3) 6192(2) 6266(2) 22(1)
C(19) -2694(3) 6438(2) 7193(3) 24(1)
C(20) -2586(3) 6229(2) 8266(3) 23(1)
C(21) -1214(3) 5775(2) 8411(2) 20(1)
C(22) 5634(3) 2852(2) 8288(2) 15(1)
C(23) 6414(3) 2646(2) 6972(2) 15(1)
C(24) 6085(3) 1633(2) 8817(2) 14(1)
C(25) 5863(3) 1260(2) 9918(2) 17(1)
C(26) 6493(3) 46(3) 10149(2) 23(1)
C(27) 7314(3) -762(2) 9304(2) 21(1)
C(28) 7579(3) -398(2) 8157(2) 17(1)
C(29) 8460(3) -1100(2) 7193(2) 20(1)
C(30) 8637(3) -601(2) 6125(2) 21(1)
C(31) 7984(3) 620(2) 5944(2) 18(1)
C(32) 7149(3) 1316(2) 6867(2) 15(1)
C(33) 6940(3) 809(2) 7950(2) 15(1)
C(34) 5932(3) 3813(2) 8795(2) 21(1)
C(35) 7470(3) 3368(2) 6381(2) 22(1)
O(4) 5748(2) 1425(2) 2607(2) 25(1)
O(5) 4948(2) 6967(2) 3036(2) 19(1)
O(6) 5674(2) 6822(2) 1110(2) 17(1)
B(2) 6079(3) 6697(3) 2057(2) 17(1)
C(36) 4884(3) 968(3) 3601(3) 30(1)
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C(38) 7034(3) 2789(3) 1721(2) 24(1)
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C(51) 9681(3) 4669(2) 2649(2) 16(1)
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C(54) 12669(3) 3652(2) 2366(3) 24(1)
C(55) 12182(3) 3892(2) 1432(2) 21(1)
C(56) 10707(3) 4401(2) 1575(2) 18(1)
C(57) 3578(3) 7328(2) 2778(2) 16(1)
C(58) 4083(3) 7232(2) 1441(2) 15(1)
C(59) 2813(3) 8640(2) 3005(2) 16(1)
C(60) 2130(3) 9262(3) 3986(2) 20(1)
C(61) 1443(3) 10503(3) 3918(2) 23(1)
C(62) 1459(3) 11091(2) 2912(3) 22(1)
C(63) 2201(3) 10468(2) 1879(2) 19(1)
C(64) 2337(3) 10928(2) 769(3) 23(1)
C(65) 3079(3) 10200(3) -144(2) 24(1)
C(66) 3703(3) 8962(2) -29(2) 20(1)
C(67) 3573(3) 8492(2) 1035(2) 15(1)
C(68) 2848(3) 9244(2) 1970(2) 15(1)
C(69) 2639(3) 6545(3) 3455(2) 25(1)
C(70) 3580(3) 6360(2) 979(2) 21(1)

Chapter 2

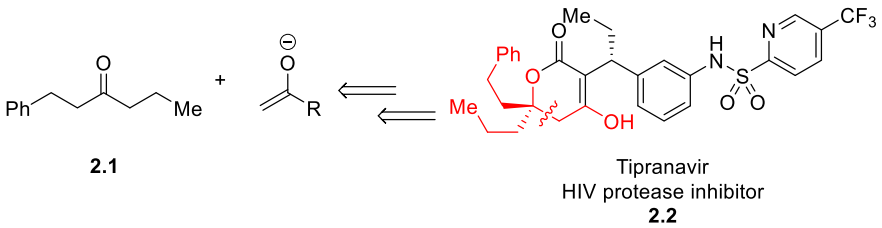
Enantioselective Conjunctive Cross-Coupling of Alkenyl Boronates with Carbamoyl Chlorides: Asymmetric Synthesis of Tertiary β-Boryl Amides

2.1 Background

2.1.1 Synthesis of Challenging Tertiary Alcohols β to Carbonyl Motifs: Case Study of the Enantioselective Synthesis of Tipranavir

Revealing deficiencies in current synthetic methods is among the many benefits of total synthesis.[59] An example is the total synthesis of tipranavir (Figure 2.1.1.1).

Figure 2.1.1.1: *Chemical Structure of Tipranavir*



Tipranavir is a rare example of a nonpeptidic HIV protease inhibitor, and it is currently being commercially manufactured by Boehringer Ingelheim under the trade name, Aptivus. Among the many interesting structural features of this molecule, the tertiary alcohol β to the carbonyl functional group is synthetically interesting. A logical retrosynthetic disconnection would be an asymmetric aldol reaction. However, a selective carbon-carbon bond forming reaction at the prochiral atom would require a diastereomeric transition state that distinguishes between a phenyl ethyl group and a sterically similar propyl group, which is challenging. Perhaps not surprisingly, since the elucidation of tipranavir's bioactivity in the 1990s, there have only been two catalytic

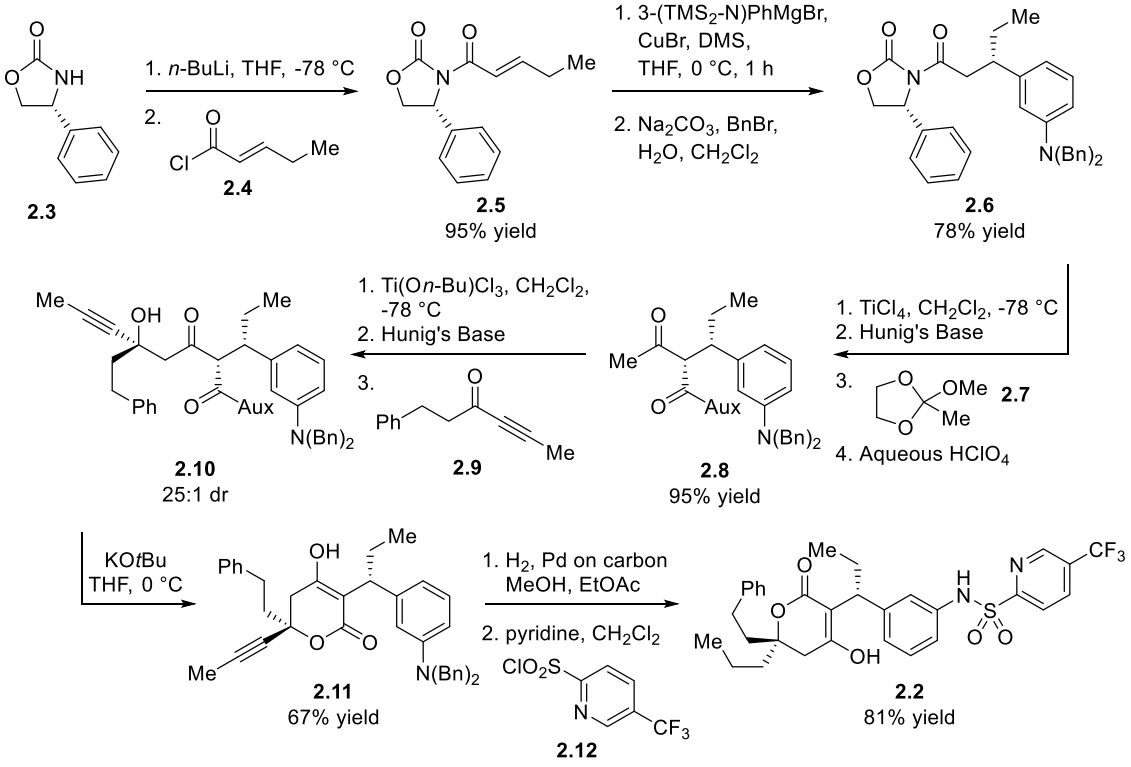
[59] (a) Nicolaou, K. C. *J. Org. Chem.* **2009**, *74*, 951-972 (b) Nicolaou, K. C.; Rigol, S. *Nat. Prod. Rep.* **2020**, *37*, 1404-1435

enantioselective methods described in the literature to address this challenging stereocenter. The following is a compilation of the methods used address this motif.

In 1997, Gammill and coworkers, at what was previously called Pharmacia and Upjohn Inc., developed the first asymmetric synthesis of tipranavir (Scheme 2.1.1.1).[60] To establish the multiple stereocenters, a chiral amino alcohol was used in a chiral auxiliary strategy. The enantio-enriched oxazolidone was acylated to give enone **2.5**. A diastereoselective cuprate addition to the enone and subsequent double benzyl protection of the aniline nitrogen afforded **2.6** as a single diastereomer. After using Lewis acidic $TiCl_4$ and Hunig's base to diastereoselectively generate a titanium enolate, an aldol reaction delivered methyl ketone **2.8** in high yield as a single diastereomer. Many stereoselective aldol reactions were considered to synthesize tertiary alcohol **2.10**. It was found that ynone **2.9** was a good electrophile in this case and furnished the desired diastereomer in 25:1 dr. It is worth noting, however, that the ideal ketone, 1-phenylhexan-3-one, only afforded a 3:2 mixture of diastereomers. Base-mediated removal of the auxiliary and cyclization yielded the desired lactone. Hydrogenation conditions with catalytic palladium on carbon removed the benzyl protecting groups and reduced the alkyne to set up a subsequent sulfonamide condensation to yield tipranavir.

[60] Judge, T. M.; Phillips, G.; Morris, J. K.; Lovasz, K. D.; Romines, K. R.; Luke, G. P.; Tulinsky, J.; Tustin, J. M.; Chrusciel, R. A, Dolak, L. A.; Mizsak, S. A.; Watt, W.; Morris, J.; Vander Velda, S. L.; Strohbach, J. W.; Gammill, R. B. *J. Am. Chem. Soc.* **1997**, *119*, 3627-3628

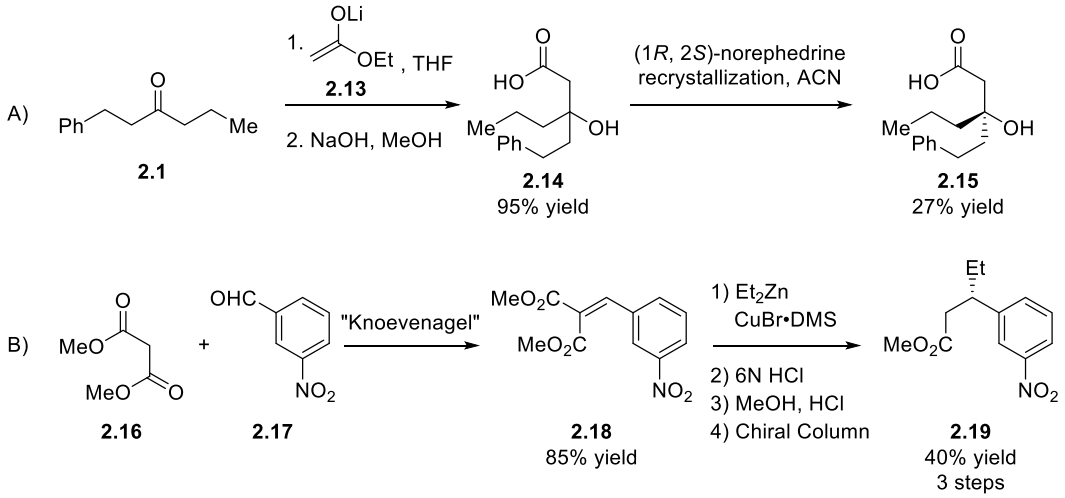
Scheme 2.1.1.1: *Gammill's Total Synthesis of Tipranavir*



In 1998, Wicnienski and coworkers from the same company reported an alternative route to tipranavir (Scheme 2.2.3.2).[61] To synthesize the tertiary alcohol, a racemic aldol reaction was conducted with ketone **2.1** to afford the carboxylic acid **2.14** after hydrolysis. A resolution was performed with the chiral amino alcohol norephedrine, to acquire the correct enantiomer of alcohol. It is also worth noting that to gain access to the other stereocenter within the target molecule (**2.19**), the racemate was more easily resolved with chiral chromatography.

[61] Fors, K. S.; Gage, J. R.; Heier, R. F.; Kelly, R. C.; Perrault, W. R.; Wicnienski, N. *J. Org. Chem.* **1998**, *63*, 7348-7356

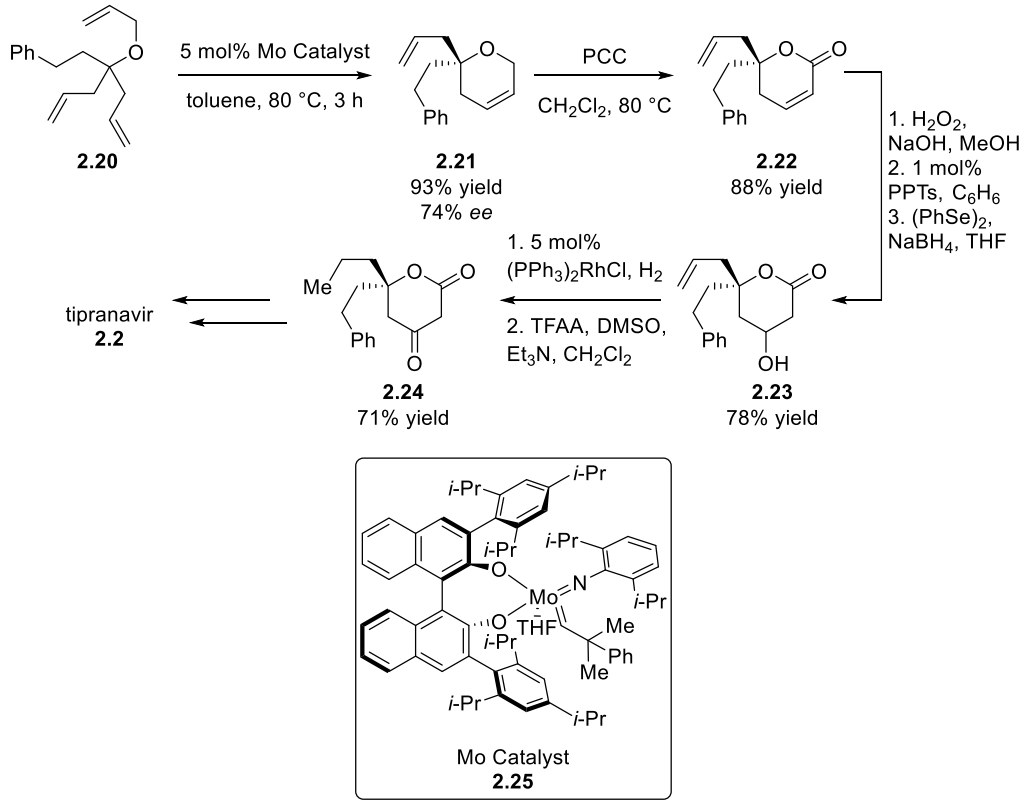
Scheme 2.1.1.2: *Wicnienski's Synthesis of Stereocenters in Tipranavir*



In 2001, Amir Hoveyda, Richard Schrock, and coworkers described the first catalytic enantioselective approach to tipranavir using an enantioselective olefin-metathesis strategy (Scheme 2.1.1.3).[62] Starting from a prochiral ether, an enantioselective ring-closing metathesis was performed using a chiral molybdenum catalyst to give cyclic ether **2.21**. This established the desired stereocenter in a single catalytic step, albeit in moderate enantioselectivity. A regioselective allylic oxidation afforded lactone **2.22**. An epoxidation and reductive opening furnished alcohol **2.23**. Reduction of the olefin afforded the desired propyl group and oxidation of the alcohol gives diketone **2.24**, which is an intermediate used at Boehringer-Ingelheim for the synthesis of tipranavir.

[62] Cefalo, D. R.; Kiely, A. F.; Wuchrer, M.; Jamieson, J. Y.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 3139-3140

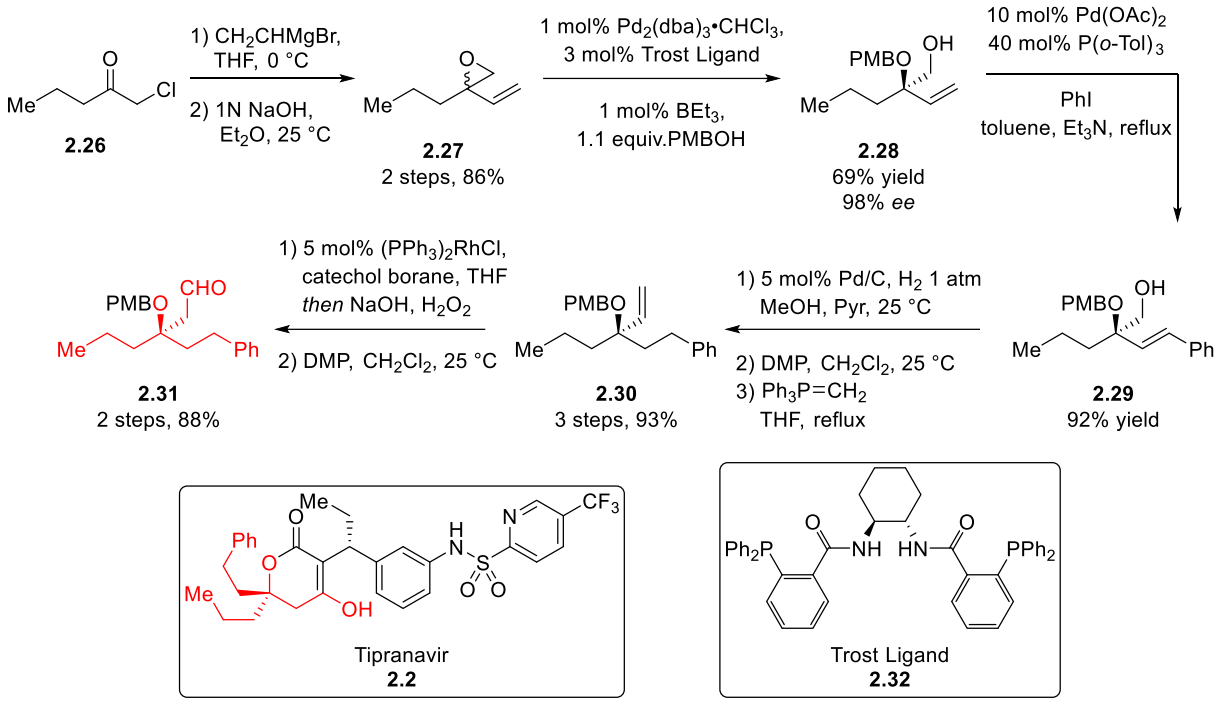
Scheme 2.1.1.3: *Hoveyda's and Schrock's Asymmetric Ring-Closing Metathesis Strategy to Tertiary Ethers*



In 2002, Barry Trost and Neil G. Andersen used a chiral palladium catalyst to establish the tertiary alcohol stereocenter in tipranavir by a catalytic dynamic kinetic asymmetric transformation of allyl electrophiles (Scheme 2.1.1.4).[63] To synthesize the racemic epoxide **2.27**, vinyl magnesium bromide was added to ketone **2.26**. Under basic conditions, the tertiary alkoxide cyclized to afford the epoxide as a racemate. Using a Trost ligand-ligated palladium catalyst, a dynamic kinetic asymmetric etherification yielded *p*-methoxybenzyl protected tertiary alcohol **2.28** in good yield and excellent enantioselectivity. A subsequent Heck reaction installed the phenyl group with the appropriate carbon chain. A palladium-on-carbon mediated hydrogenation of the styryl group furnished the phenyl ethyl side chain. Four more steps were employed to homologate the primary alcohol and oxidize it to an aldehyde (**2.31**).

[63] Trost, B.; Andersen, N. G. *J. Am. Chem. Soc.* **2002**, *124*, 14320-14321

Scheme 2.1.1.4: *Trost's Dynamic Kinetic Strategy to Asymmetric Aldol Product*



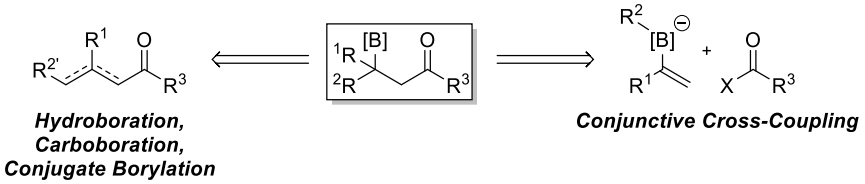
To summarize the methods used in the synthesis of tipranavir, industrial methods utilized stoichiometric amounts of chiral reagents in order to perform diastereoselective transformations or resolutions. Despite the relatively poor atom economy of chiral material compared to catalytic methods, a single chiral auxiliary was able to set three stereocenters, including a difficult tertiary alcohol, from an asymmetric aldol reaction. However, it is worth noting the necessary additional steps for auxiliary installation and removal, as well as the further substrate manipulation (i.e., reduction of the alkyne) required to obtain high diastereoselectivity. Likewise, fewer steps can be performed at the expense of large amounts of material when resolutions or chiral separations are employed. In the development of enantioselective catalytic methods, powerful and clever disconnections can be used in important pharmaceutical molecules. Simple prochiral or racemic starting materials can be catalytically converted into enantio-enriched building blocks. However, substrate dependent reactivity sometimes affords less than ideal enantioselectivity or numerous, post-catalysis modification steps may be required. In conclusion, there is opportunity to address

alternative disconnections to important motifs, such as in tipranavir, within total synthesis. Conjunctive cross-coupling can address the synthesis of such challenging stereocenters by providing an alternative disconnection.

2.1.2 Enantioselective Synthesis of β-Boryl Carbonyls via Olefin Functionalization

β-Boryl carbonyl compounds are configurationally and chemically stable precursors to asymmetric conjugate addition, Mannich addition and aldol addition products. As previously described in the synthesis of tipranavir, alternative disconnections to access challenging tertiary alcohols beta to carbonyl functionality are still necessary to study. Among the disconnections that provide access to β-boryl carbonyls are boron-carbon bond formation via olefin functionalization. These methods include hydroboration,[64] carboboration,[65] and conjugate borylation[66] (Scheme 2.1.2.1). The following represents the state of the art for methods in β-boryl carbonyl synthesis.

Scheme 2.1.2.1: *Synthesis of β-Boryl Carbonyls*



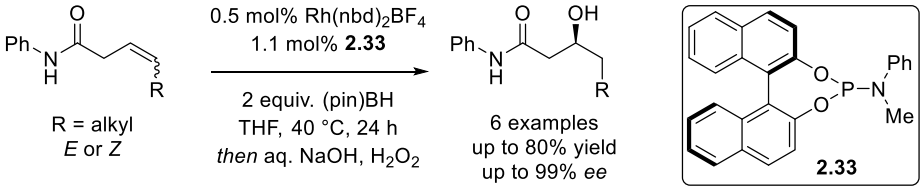
[64] (a) Bochat, A. J.; Shoba, V. M.; Takacs, J. M. *Angew. Chem. Int. Ed.* **2019**, *58*, 9434-9538 (b) Smith, S. M.; Thacker, N. C.; Takacs, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 3734-3735 (c) Smith, S. M.; Takacs, J. M. *J. Am. Chem. Soc.* **2011**, *132*, 1740-1741 (d) Smith, S. M.; Uteuliyev, M.; Takacs, J. M. *Chem. Commun.* **2011**, *47*, 7812-7814 (e) Smith, S. M.; Takacs, J. M. *Org. Lett.* **2010**, *12*, 4612-4615 (f) Gao, T. -T.; Zhang, W. -W.; Sun, X.; Lu, H. -X.; Li, B. -J. *J. Am. Chem. Soc.* **2019**, *141*, 4670-4677

[65] (a) Liu, Z.; Li, X.; Zeng, T.; Engle, K. M. *ACS Catal.* **2019**, *9*, 3260-3265 (b) Bai, Z.; Zheng, S.; Bai, Z.; Song, F.; Wang, H.; Peng, Q.; Chen, G.; He, G. *ACS Catal.* **2019**, *9*, 6502-6509

[66] (a) Chen, I. -H.; Yin, L.; Itano, W.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 11664-11665 (b) Mun, S.; Lee, J. -E.; Yun, J. *Org. Lett.* **2006**, *8*, 4887-4889 (c) Lee, J. -E.; Yun, J. *Angew. Chem. Int. Ed.* **2008**, *47*, 145-147 (d) Sim, H. -S.; Feng, X.; Yun, J. *Chem. Eur. J.* **2009**, *15*, 1939-1943 (e) Chea, H.; Sim, H.; Yun, J. *Adv. Synth. Catal.* **2009**, *351*, 855-858 (f) Chen, I. -H.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2010**, *12*, 4098-4101 (g) Feng, X.; Yun, J. *Chem. Eur. J.* **2010**, *16*, 13609-13612 (h) O'Brien, J. M.; Lee, K. -S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10630-10633 (i) Radomkit, S.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2014**, *53*, 3387-3459 (j) For a non-selective variant: Lee, K. -S.; Zhugralin, A. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 7253-7255 (k) Liu, B.; Wu, H. -H.; Zhang, J. *ACS Catal.* **2018**, *8*, 8318-8323

Directed metal-catalyzed enantioselective hydroboration is one method to synthesize enantioenriched, chiral β-boryl carbonyl compounds. Reactions that employ carbonyl directing groups are currently limited to the synthesis of the secondary organoboronates, but tertiary organoboronates have been synthesized using an oxime directing group.[67] James Takacs and coworkers disclosed several studies on directed catalytic enantioselective hydroboration. Many of these processes used β,γ-unsaturated amides as an alkene substrates to yield enantioenriched β-boryl amides. In 2008, Takacs reported the asymmetric amide-directed hydroboration of β,γ-unsaturated amides (Scheme 2.1.2.2).[68] Interestingly, using the *E* or the *Z* isomer of the unsaturated amide afforded the same yield and enantiomer. Regioselectivity was also high; only three to four percent of the γ-boryl product was formed. Symmetric γ,γ-trisubstituted olefins were also competent substrates, but a different ligand was required to maintain high enantioselectivity and good conversion. Notably, the amide component was important for high enantioselectivity and regioselectivity. Additionally, an excess of HB(pin) was needed for full conversion due to the formation of borate dimers.

Scheme 2.1.2.2: *Takac's Amide-Directed Asymmetric Hydroboration*

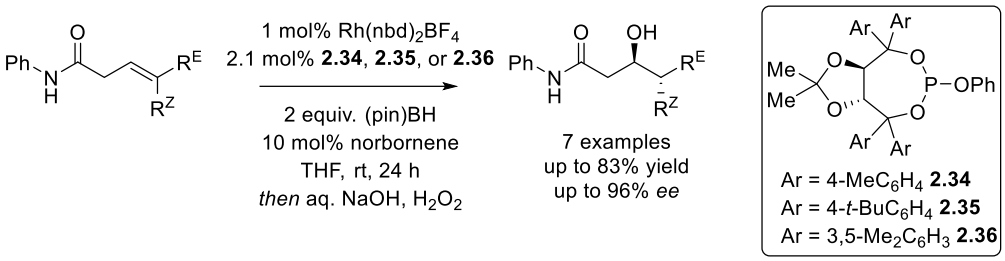


In 2010, Takacs and coworkers expanded the alkene scope to include non-symmetric γ,γ-trisubstituted olefins.[69] This method generated compounds with contiguous stereocenters (Scheme 2.1.2.3). Interestingly, using an *E* alkene afforded the *anti*-diastereomer to the exclusion of the

[67] Bochat, A. J.; Shoba, V. M.; Takacs, J. M. *Angew. Chem. Int. Ed.* **2019**, *58*, 9434-9538
[68] Smith, S. M.; Thacker, N. C.; Takacs, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 3734-3735
[69] Smith, S. M.; Takacs, J. M. *J. Am. Chem. Soc.* **2011**, *132*, 1740-1741

syn-diastereomer. However, when using a *Z* alkene, the *syn*-diastereomer is obtained exclusively. The authors noted that over the course of the reaction, the enantioselectivity was poor during the first hour, but upon full conversion the product is obtained in higher er. This observation suggests a transient catalyst is active in the beginning of the reaction, but it is replaced by a more enantioselective catalyst as the reaction progresses. Although the role is not well understood, sacrificial alkenes were surveyed, and norbornene was found to increase the enantioselectivity slightly.[70]

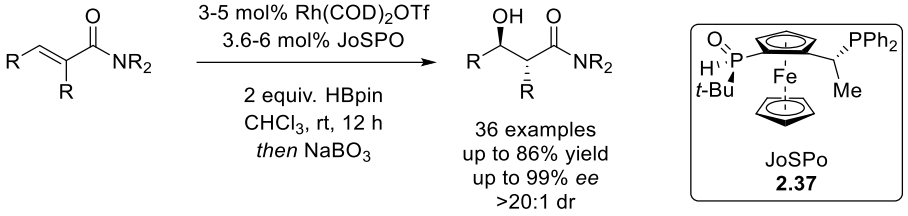
Scheme 2.1.2.3: *Takac's Amide-Directed Asymmetric Hydroboration of Tri-Substituted Olefins*



In 2019, Bi-Jie Li and coworkers reported the first catalytic enantioselective hydroboration of α,β-unsaturated amides to yield β-boryl amides (Scheme 2.1.2.4).[71] Usually, a metal-catalyzed hydroboration of α,β-unsaturated carbonyl results in net hydrogenation of the olefin. This hydrogenation is due to hydride addition to the β-carbon and generation of a α-boryl carbonyl, which is subsequently protodeborylated during aqueous work up. However, in the Li study a JoSPO-ligated rhodium (I) complex enabled a reversal in the regioselectivity. Furthermore, the stereospecific hydroboration of the alkene of an α,β-disubstituted amide enabled high diastereoselectivity.

[70] For other examples of Catalytic Asymmetric Hydroboration: (a) Smith, S. M.; Uteuliyev, M.; Takacs, J. M. *Chem. Commun.* **2011**, *47*, 7812-7814 (b)) Smith, S. M.; Takacs, J. M. *Org. Lett.* **2010**, *12*, 4612-4615
[71] Gao, T. -T.; Zhang, W. -W.; Sun, X.; Lu, H. -X.; Li, B. -J. *J. Am. Chem. Soc.* **2019**, *141*, 4670-4677

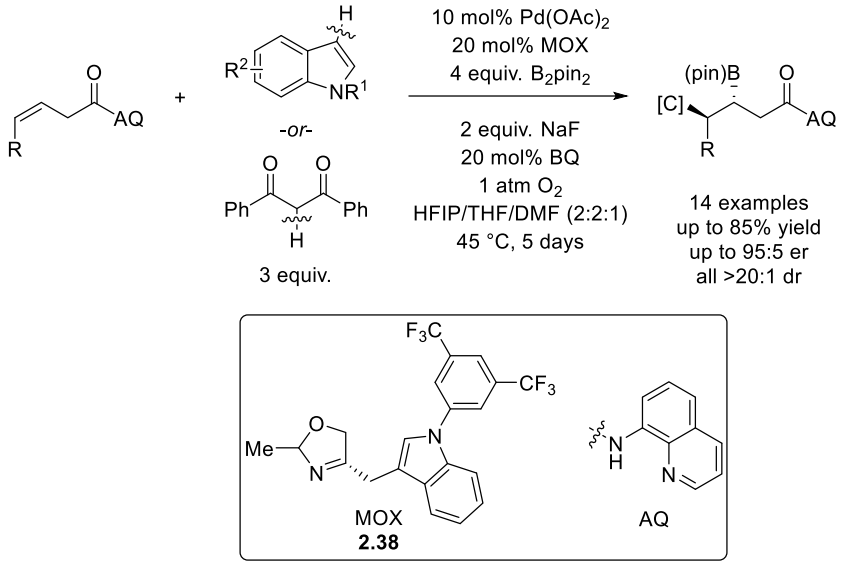
Scheme 2.1.2.4: *Li's Enantioselective Hydroboration of α, β Unsaturated Amides*



Enantioselective carboboration provides a similar disconnection as hydroboration. However, this method, like hydroboration, requires a directing group within the substrate molecule. In 2019, Keary Engle and coworkers reported a directed palladium-catalyzed enantioselective *anti*-carboboration of alkenyl amide substrates (Scheme 2.1.2.5).[72] 8-aminioquinoline (AQ) amide was vital to this method as a directing group. An intensive ligand screening process identified MOX (monodentate oxazoline) ligands as the optimal ligand for conversion and enantio-induction. Substrates are mostly limited to indole-derived carbon nucleophiles and β,γ-unsaturated amides. It is worth noting that the products from *Z*-alkene substrates were obtained with excellent diastereoselectivity. Interestingly, *E*-olefin substrates also gave the same major diastereomer, suggesting *E*/*Z* isomerization under the reaction conditions.

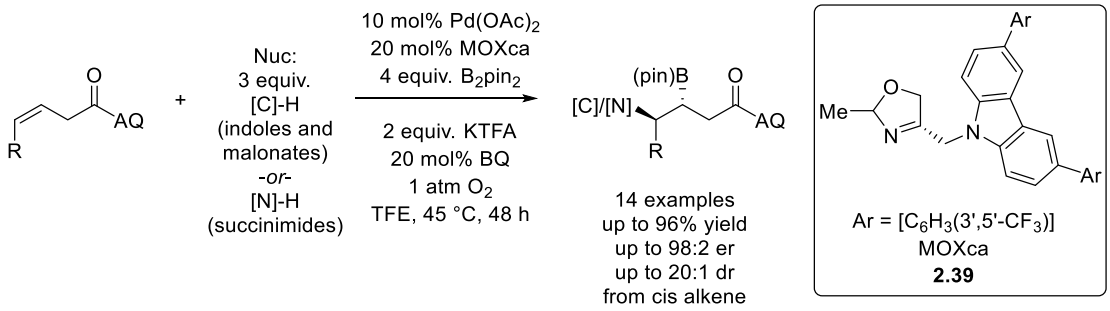
[72] Liu, Z.; Li, X.; Zeng, T.; Engle, K. M. *ACS Catal.* **2019**, *9*, 3260-3265

Scheme 2.1.2.5: *Engle's Directed Enantioselective Nucleopalladation Reaction*



Later that year, a collaborative effort between Peng, Chen, He and coworkers developed a very similar protocol utilizing a MOX ligand, an aminoquinoline amide directing group, *Z*-olefin substrates, and similar conditions (Scheme 2.2.1.6).[73] Along with indole-based carbon nucleophiles, cyclic malonate nucleophiles and imide nitrogen nucleophiles were operative in the reaction.

Scheme 2.1.2.6: *He's Enantioselective Aminoboration and Carboboration Reaction*



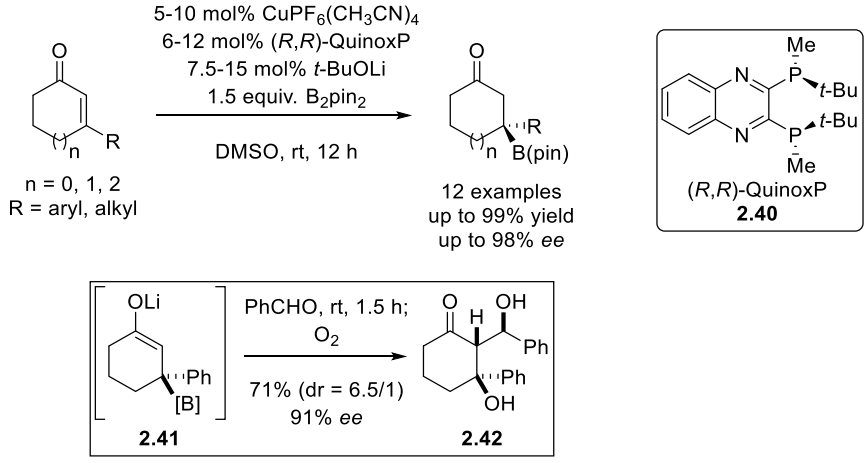
The last alkene borylation functionalization described here is a boryl addition to Michael acceptors. This disconnection is a well-studied reaction compared to the previously mentioned

[73] Bai, Z.; Zheng, S.; Bai, Z.; Song, F.; Wang, H.; Peng, Q.; Chen, G.; He, G. *ACS Catal.* **2019**, *9*, 6502-6509

methods. Additionally, this method is one of the few methods that enable the enantioselective synthesis of tertiary organoboronates, which will be the focus of the discussion.

In 2009, Masakatsu Shibasaki and coworkers were among the first to develop an asymmetric synthesis of tertiary β-boryl carbonyl compounds by means of a boryl conjugate addition (Scheme 2.1.2.7).[74] At this time, there were a plethora of symmetric conjugate addition methods that employ β-disubstituted enones, but addition to β,β-trisubstituted enones were challenging. Interestingly, in prior studies, protic additives such as methanol were used to facilitate the turnover of the catalytic cycle.[75] However, under Shibasaki's reaction conditions, methanol was detrimental to reactivity. In terms of mechanism, it was inferred that the initial product of the reaction was a boron enolate. Taking advantage of the enolate reactivity, the authors were able to perform a diastereoselective aldol addition at the end of the reaction.

Scheme 2.1.2.7: *Shibasaki's Enantioselective Boryl Conjugate Addition to Trisubstituted Enones*

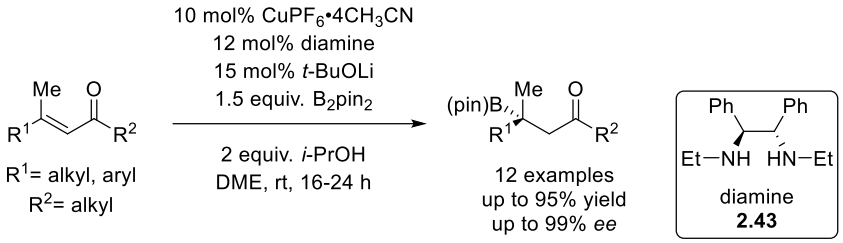


In 2010, Shibasaki and coworkers expanded the substrate scope of boron conjugate addition to include acyclic enones (Scheme 2.1.2.8).[76] This advance was enabled by the use of a different

[74] Chen, I. -H.; Yin, L.; Itano, W.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 11664-11665
[75] (a) Mun, S.; Lee, J. -E.; Yun, J. *Org. Lett.* **2006**, *8*, 4887-4889 (b) Lee, J. -E.; Yun, J. *Angew. Chem. Int. Ed.* **2008**, *47*, 145-147 (c) Sim, H. -S.; Feng, X.; Yun, J. *Chem. Eur. J.* **2009**, *15*, 1939-1943 (d) Chea, H.; Sim, H.; Yun, J. *Adv. Synth. Catal.* **2009**, *351*, 855-858
[76] Chen, I. -H.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2010**, *12*, 4098-4101

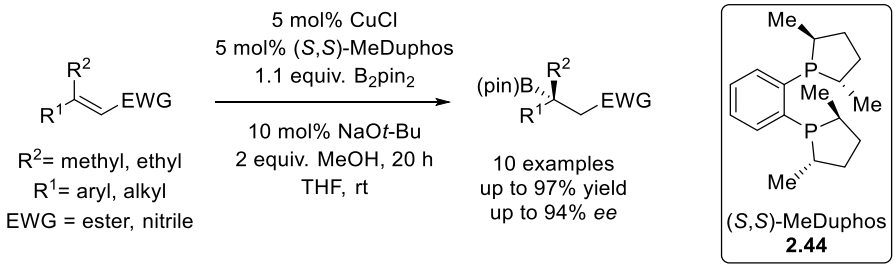
ligand and a protic additive. An interesting reaction feature was proposed involving the chiral secondary diamine ligand. One of the secondary amines is deprotonated under the reaction conditions, which activated the copper-catalyst for facile transmetallation to form a copper-boryl intermediate. This intermediate in turn is the active catalyst for borylation.

Scheme 2.1.2.8: *Shibasaki's Enantioselective Boryl Conjugate Addition to Acyclic Enones*



In the same year, Jaesook Yun and coworkers expanded conjugate borylation to include tertiary β-boryl esters substrates (Scheme 2.1.2.9).[77] Importantly, this method could be applied to acyclic unsaturated nitriles. Excellent enantioselectivity for the reaction of β-aryl, β-alkyl olefins was observed. However, the authors note the difficulty with facial selectivity for β,β-dialkyl substrates, and the decrease in enantioselectivity when using nitrile or larger ester electron-withdrawing groups.

Scheme 2.1.2.9: *Yun's Copper-Catalyzed Asymmetric Boryl Conjugate Addition of Michael Acceptors*

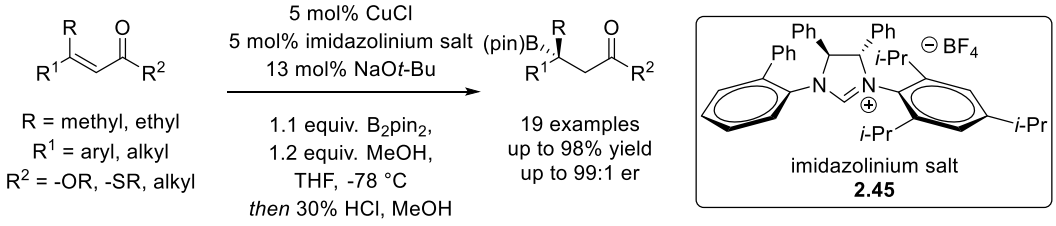


In 2010, Amir Hoveyda and coworkers developed an NHC-ligated copper-catalyzed boron conjugate addition to α,β-unsaturated esters, ketones and thioesters (2.1.2.10).[78] It is noteworthy

[77] Feng, X.; Yun, J. *Chem. Eur. J.* **2010**, *16*, 13609-13612
[78] O'Brien, J. M.; Lee, K. -S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10630-10633

that the major byproduct of the reaction with more congested substrates is the saturated carbonyl. Interestingly, the authors postulate that the copper-boryl intermediate may react too slowly with the substrate. As a consequence, the copper-boryl intermediate undergoes an exchange reaction with methanol to form copper-hydride and methyl borate. The copper hydride, a smaller nucleophile, is then able to reduce the olefin substrate.

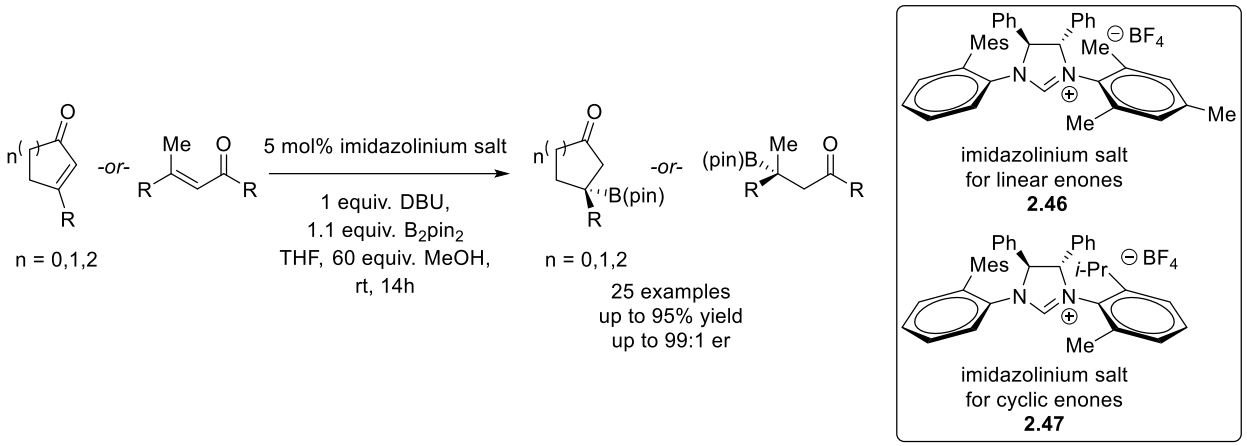
Scheme 2.1.2.10: *Hoveyda's Copper-Catalyzed Asymmetric Boryl Conjugate Addition of Michael Acceptors*



In 2014, Amir Hoveyda and coworkers reported the first example of an enantioselective Lewis base-catalyzed conjugate borylation to obtain tertiary β-boryl carbonyls (Scheme 2.1.2.11).[79] High yields and enantioselectivities were achieved for both cyclic and acyclic ketones using a chiral NHC catalyst. The diversity of the scope and the functional group tolerance is noteworthy. Interestingly, catalytic amounts of DBU can be used in some cases to achieve similar levels of reactivity.

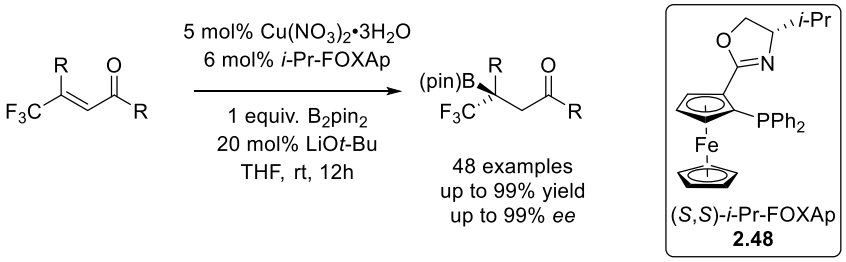
[79] (a) Radomkit, S.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2014**, *53*, 3387-3459 (b) For a non-selective variant: Lee, K. -S.; Zhugralin, A. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 7253-7255

Scheme 2.1.2.11: *Hoveyda's NHC-Catalyzed Conjugate Boryl Addition*



In 2018, Junliang Zhang and coworkers extended the scope of conjugate borylation to include substrates bearing β-trifluoromethyl groups in the synthesis of tertiary β-boryl ketones and esters (Scheme 2.1.2.12).[80] Before this report, synthesis of stereocenters containing both boryl and trifluoromethyl groups were challenging because reaction conditions promoted B-F elimination. Impressively, the authors developed mild enough reaction conditions that high yields and enantioselectivity could be obtained for a broad substrate scope.

Scheme 2.1.2.12: *Zhang's Copper-Catalyzed Conjugate Borylation*



In conclusion, enantioselective borylations of olefins is an excellent strategy to synthesize diverse β-boryl carbonyl containing compounds in high yield and enantioselectivity. The benefits of targeting a boron containing product are numerous. For example, enantioselective methods for

[80] Liu, B.; Wu, H. -H.; Zhang, J. *ACS Catal.* **2018**, *8*, 8318-8323

hydroboration,[81] carboboration,[82] or conjugate-borylation[83] are more feasible and well-studied than the corresponding enantioselective hydration or carbohydroxylation reaction. Also, a single β-boryl product could be subsequently transformed to yield asymmetric aldol[84] or conjugate addition products.[85] There are, however, some limitations to these methods that are worth addressing. For example, carboboration and hydroboration are unable to furnish tertiary β-boryl carbonyls enantioselectively. Additionally, enantioselective conjugate borylation has some limitations with substrate scope. For example, there are no enantioselective methods to synthesize tertiary β-boryl amides or lactams.[86] Additionally, the stereoselective synthesis of β,β-trisubstituted Michael acceptors can be challenging outside of stereospecific carboalumination of terminal alkynes.[87] However, the carboalumination process is largely limited to trimethyl or triethylaluminium reagents. Some Horner-Emmons reactions have been applied to sterically biased substrates, but more often these reaction yield mixtures of diastereomers that are difficult to separate.[88] There are some stereoselective copper-catalyzed conjugate addition reactions of aryl

[81] (a) Bochat, A. J.; Shoba, V. M.; Takacs, J. M. *Angew. Chem. Int. Ed.* **2019**, *58*, 9434-9538 (b) Smith, S. M.; Thacker, N. C.; Takacs, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 3734-3735 (c) Smith, S. M.; Takacs, J. M. *J. Am. Chem. Soc.* **2011**, *132*, 1740-1741 (d) Smith, S. M.; Uteuliyev, M.; Takacs, J. M. *Chem. Commun.* **2011**, *47*, 7812-7814 (e) Smith, S. M.; Takacs, J. M. *Org. Lett.* **2010**, *12*, 4612-4615 (f) Gao, T. -T.; Zhang, W. -W.; Sun, X.; Lu, H. -X.; Li, B. -J. *J. Am. Chem. Soc.* **2019**, *141*, 4670-4677

[82] (a) Liu, Z.; Li, X.; Zeng, T.; Engle, K. M. *ACS Catal.* **2019**, *9*, 3260-3265 (b) Bai, Z.; Zheng, S.; Bai, Z.; Song, F.; Wang, H.; Peng, Q.; Chen, G.; He, G. *ACS Catal.* **2019**, *9*, 6502-6509

[83] (a) Chen, I. -H.; Yin, L.; Itano, W.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 11664-11665 (b) Mun, S.; Lee, J. -E.; Yun, J. *Org. Lett.* **2006**, *8*, 4887-4889 (c) Lee, J. -E.; Yun, J. *Angew. Chem. Int. Ed.* **2008**, *47*, 145-147 (d) Sim, H. -S.; Feng, X.; Yun, J. *Chem. Eur. J.* **2009**, *15*, 1939-1943 (e) Chea, H.; Sim, H.; Yun, J. *Adv. Synth. Catal.* **2009**, *351*, 855-858 (f) Chen, I. -H.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2010**, *12*, 4098-4101 (g) Feng, X.; Yun, J. *Chem. Eur. J.* **2010**, *16*, 13609-13612 (h) O'Brien, J. M.; Lee, K. -S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10630-10633 (i) Radomkit, S.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2014**, *53*, 3387-3391 (j) For a non-selective variant: Lee, K. -S.; Zhugralin, A. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 7253-7255 (k) Liu, B.; Wu, H. -H.; Zhang, J. *ACS Catal.* **2018**, *8*, 8318-8323

[84] Radomkit, S.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2014**, *53*, 3387-3391

[85] Liu, Z.; Chen, J.; Lu, H. -X.; Li, X.; Gao, Y.; Coombs, J. R.; Goldfogel, M. J.; Engle, K. M. *Angew. Chem Int. Ed.* **2019**, *58*, 17068-17073

[86] For examples of secondary β-boryl amides: (a) Chea, H.; Sim, H. -S.; Yun J. *Adv. Synth. Catal.* **2009**, *351*, 855-858 (b) Shiomi, T.; Adachi, T.; Toribatake, K.; Zhou, Li.; Hishiyama, H. *Chem. Commun.* **2009**, 5987-5789

[87] Wipf, P.; Lim, S. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1068-1070

[88] Feng, X.; Yun, J. *Chem. Eur. J.* **2010**, *16*, 13609-13612

boronic acids to alkynoates that give β,β-diaryl or β,β-aryl,alkyl Michael acceptors in high selectivity.[89] However, stereoselective synthesis and isolation of β,β-dialkyl Michael acceptors (not methyl or ethyl) remains challenging. Conjunctive cross-coupling can address some of the previously mentioned challenges associated with the enantioselective synthesis of tertiary, β-boryl carbonyl compounds by providing an alternative disconnection. Tertiary organoboronates have been synthesized using palladium-catalyzed conjunctive cross-coupling.[90] Changing to a carbonyl electrophiles and coupling with α-substituted alkenyl boron "ate" complexes could gain access to these motifs (tertiary, β-boryl carbonyl compounds) that would be otherwise difficult to synthesis. It is worth studying a variety of palladium-catalyzed cross-coupling of carbonyl electrophiles to be familiar with possible challenges in reactivity.

2.1.3 Palladium-Catalyzed Cross-Coupling of Carbamoyl Chlorides

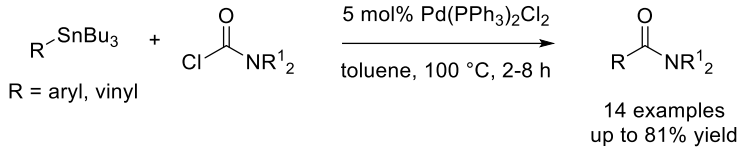
Carbamoyl chlorides undergo a plethora of metal-catalyzed and non-metal-catalyzed transformations to, for example, furnish carbamates, isocynates, and ureas.[91] Given the ubiquity of amides in directed coupling reactions[92] and in drug molecules[93], there are surprisingly few palladium-catalyzed carbon-carbon bond coupling reactions to synthesize amides from carbamoyl electrophiles.[94] With the notable gap in synthesis of tertiary β-boryl amides, we considered it worth

[89] (a) Yamamoto, Y.; Kirai, N.; Harada, Y. *Chem. Commun.* **2008**, 2010-2012 (b) Swant, K. B.; Jennings, M. P. *Eur. J. Org. Chem.* **2004**, 3201-3204
[90] Myhill, J. A.; Zhang, L.; Lovinger, G. J.; Morken, J. P. *Angew. Chem. Int. Ed.* **2018**, *57*, 12799-12803
[91] Shrestha, M.; Wu, X.; Huang, W.; Qu, J.; Chen, Y. *Org. Chem. Front.* **2021**, *8*, 4024-4045
[92] (a) Sambiagio, C.; Schönbauer, D.; Blieck, R.; Dao-Huy, T.; Pototschnig, G.; Schaaf, P. Wiesinger, T.; Zia, M. F.; Wencel-Delord, J.; Besset, T.; Maes, B. U. W.; Schnürch, M. *Chem. Soc. Rev.* **2018**, *47*, 6603-6743 (b) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879-933 (c) Xiong, T.; Li, Y.; Lv, Y.; Zhang, Q. *Chem. Commun.* **2010**, *46*, 6831-6833 (d) Zhang, M.; Zhang, Y.; Jie, X.; Zhao, H.; Li, G.; Su, W. *Org. Chem. Front.* **2014**, *1*, 843-895 (e) Hoveyda, A. H.; Fu, G. C.; Evans, D. A. *Chem. Rev.* **1993**, *93*, 1307-1370 (f) Bhadra, S.; Yamamoto, H. *Chem. Rev.* **2018**, *118*, 3391-3446
[93] Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337-2347
[94] Allen, C. L.; Williams, J. M. J. *Chem. Soc. Rev.* **2011**, *40*, 3405-3415

studying the reactivity of carbamoyl chloride electrophiles in cross-coupling reactions. These lessons might be applied in a conjunctive cross-coupling method.

In 1991, Bernard Jousseasume and coworkers developed one of the first methods to cross-couple carbamoyl chlorides with organotin reagents using a palladium catalyst (Scheme 2.1.3.1).[95] Though the study mostly focused on the cross-coupling of chloroformates, which have been previously employed using similar conditions, this was the first reported cross-coupling of carbamoyl chlorides. It was found that, aryl and vinyl tributyltin reagents reacted with carbamoyl chlorides to yield tertiary amides in synthetically useful yields. The authors noted when using chloroformates as the electrophile that the symmetrical diketone was the major side product. It is speculated that chloroformate decomposes into phosgene, which undergoes further transformations under the reaction conditions. Increased yields of the desired product were observed when a slow addition of the electrophile was performed, and when a 10% HMPA solvent mixture was used. However, carbamoyl chlorides did not decompose under the reaction conditions, and HMPA was not necessary to obtain good yields.

Scheme 2.1.3.1: *Jousseaume's Palladium-Catalyzed Cross-Coupling of Carbamoyl Chloride and Organotin Reagents*

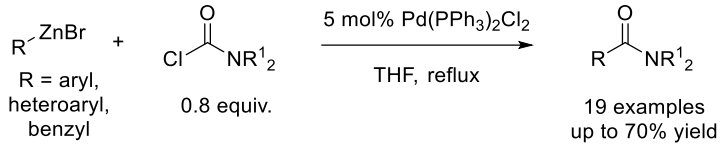


In 2012, Seung-Hoi Kim and coworkers reported the only Negishi cross-coupling with carbamoyl chlorides (Scheme 2.1.3.2).[96] A variety of aryl and benzyl organozinc reagent were efficiently coupled under the reaction conditions to provide access to tertiary amides. However,

[95] Balas, L.; Jousseaume, B.; Shin, H.; Verlhac, J. -B.; Wallian, F. *Organometallics* **1991**, *10*, 366-368
[96] Rieke, R. D.; Kim, S. -H. *Tetrahedron Letters* **2012**, *53*, 3478-3481

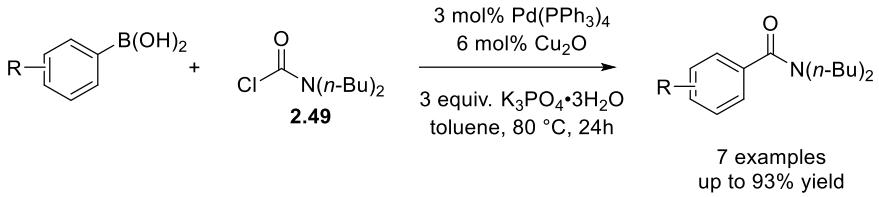
only a few heteroaryl zinc reagents participated in the reaction. The authors noted the major side product of this reaction was ring opening of THF.

Scheme 2.1.3.2: *Kim's Palladium-Catalyzed Cross-Coupling of Carbamoyl Chlorides and Organozinc Reagents*



A common and well-studied cross-coupling with carbamoyl chlorides is Suzuki-Miyaura cross-coupling. In 2005, Min-Zhi Deng and coworkers reported the first palladium-catalyzed cross-coupling of arylboronic acids with chloroformates or carbamoyl chlorides (Scheme 2.1.3.3).[97] Ethyl chloroformate cross-coupled with many substituted aryl boronic acids. Notably, *N*,*N*-dibutyl carbamoyl chloride cross-coupled with a number of aryl boronic acids in higher yield than the chloroformates. Interestingly, the coupling reaction required specific conditions in order to achieve good reactivity. Though the author did not provide a rationale, a specific palladium source, base, and a catalytic amount of copper oxide[98] were all necessary for the reaction, and any deviations from the optimized conditions resulted in dramatically reduced yields.

Scheme 2.1.3.3: *Deng's Palladium-Catalyzed Cross-Coupling of Arylboronic Acids and Carbamoyl Chlorides*

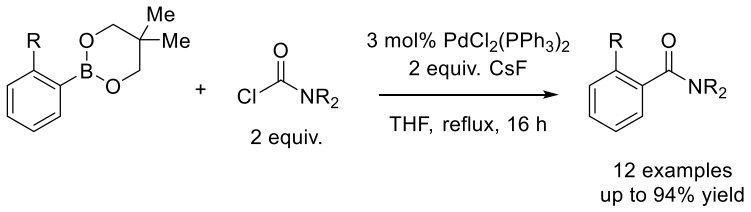


In 2005, Jesper Kristensen and coworkers developed a modified condition to cross-couple *ortho*-substituted aryl boronic esters and carbamoyl chlorides in high yield (Scheme 2.1.3.4).[99]

[97] Duan, Y. -Z.; Deng, M. -Z. *Synlett* **2005**, *2*, 355-357
[98] Other examples of copper oxide used as a co-catalyst: (a) Liu, X. -X.; Deng, M. -Z. *Chem. Commun.* **2002**, 622-623 (b) Duan, Y. -Z.; Deng, M. -Z. *Tetrahedron Letters* **2003**, *44*, 3423-3426
[99] Lysén, M.; Kelleher, S.; Begtrup, M.; Kristensen, J. L. *J. Org. Chem.* **2005**, *70*, 5342-5343

After examining numerous reaction conditions, cesium fluoride was found to be the optimal base for this reaction. However, it was necessary to have an excess of electrophile because the carbamoyl chloride slowly converted to carbamoyl fluoride, which is less reactive.

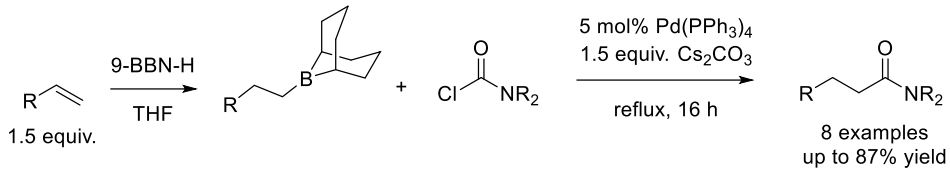
Scheme 2.1.3.4: *Kristensen's Palladium-Catalyzed Cross-Coupling of Aryl Boronic Esters and Carbamoyl Chlorides*



In 2007, Yoshiji Takemoto and coworkers developed a one-pot hydroboration and palladium-catalyzed Suzuki-Miyaura amidation of olefins using carbamoyl chlorides as electrophiles (Scheme 2.1.3.5).[100] This was the first report of an alkyl borane cross-coupling to yield alkyl tertiary amides. Notably, it was observed that potassium phosphates and carbonates facilitated low reactivity and little conversion of the electrophile. Reactions with cesium fluoride provided some product, but the major product of the reaction was generation of carbamoyl fluoride. Cesium carbonate facilitated the best yields. The optimized conditions were also applicable to other boron reagents, such as, triethyl borane, phenylboronic acid, and styrylboronic acid. In terms of mechanism, the authors suggested that a carbonate reacted with carbamoyl chloride to generate the mixed anhydride of the carbonic acid and carbamic acid. These mixed anhydrides were thought to be the participating electrophiles under the reaction conditions, but these species were not observed using spectroscopy.

[100] Yasui, Y.; Tsuchida, S.; Miyabe, H.; Takemoto, Y. *J. Org. Chem.* **2007**, *72*, 5898-5900

Scheme 2.1.3.5: *Takemoto's Palladium-Catalyzed Cross-Coupling of Alkylboranes and Carbamoyl Chlorides*

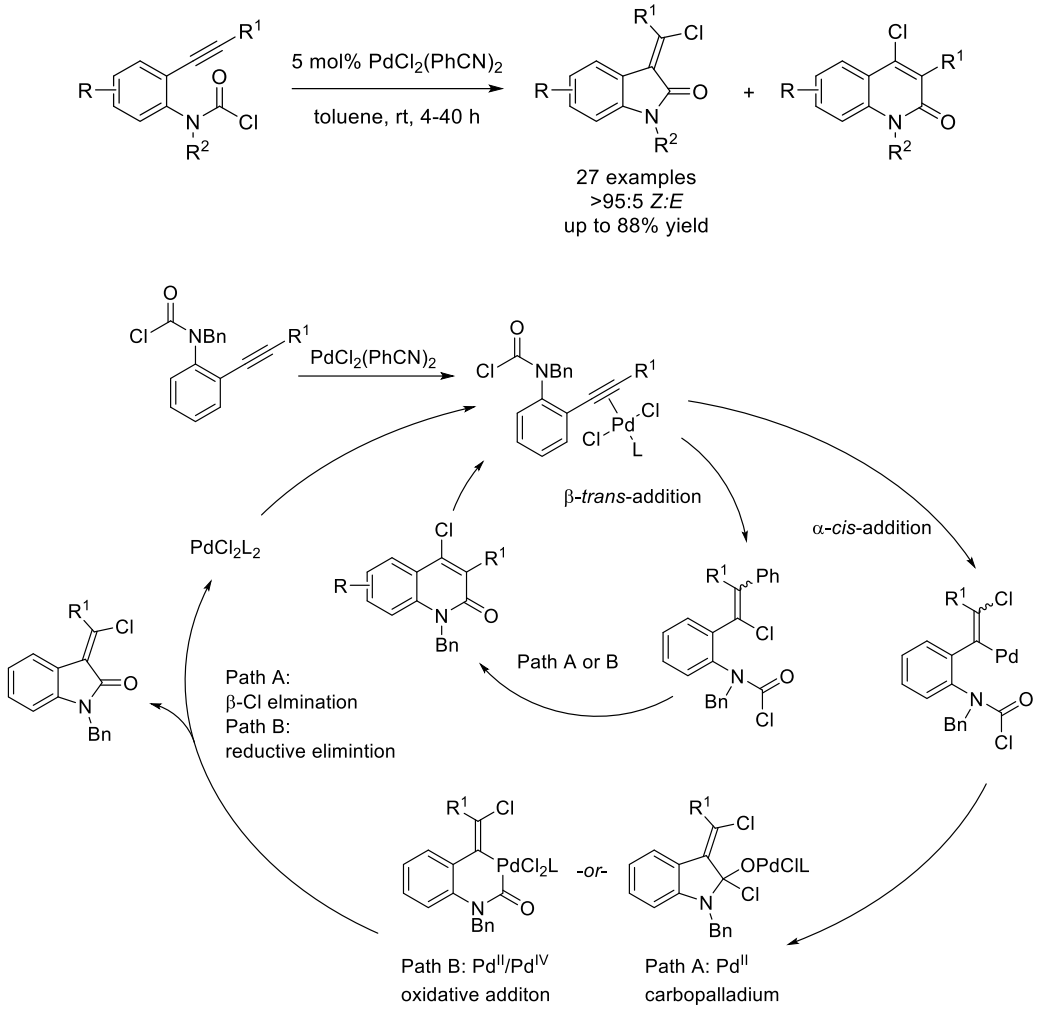


It was not until 2016 that a different palladium-catalyzed reaction with carbamoyl chlorides was described in a collaborative effort by Franziska Schoeneback, Mark Lautens, and coworkers (Scheme 2.1.3.6).[101] The reaction is a stereoselective synthesis of methylene oxindoles enabled by a palladium-catalyzed intramolecular chloroamidation of alkynes with a tethered carbamoyl chloride. Though there are multiple reaction pathways possible, DFT calculations suggested that after α-cis-addition (chloropalladation), the reaction proceeds through a palladium (IV) intermediate to generate the product.

In summary, carbamoyl chlorides undergo numerous palladium-catalyzed transformations with a variety of transmetallating partners to gain access to tertiary amides. Though there are a limited number of examples, each report contains interesting observations concerning the reactivity of these electrophiles and, in particular, the additives used therein.

[101] Le, C. M.; Sperger, T.; Fu, R.; Hou, X.; Lim. Y. H.; Schoenebeck, F.; Lautens, M. *J. Am. Soc. Chem.* **2016**, *138*, 14441-14448

Scheme 2.1.3.6: *Schoenback's and Lauten's Palladium-Catalyzed Carbochlorination Reaction*



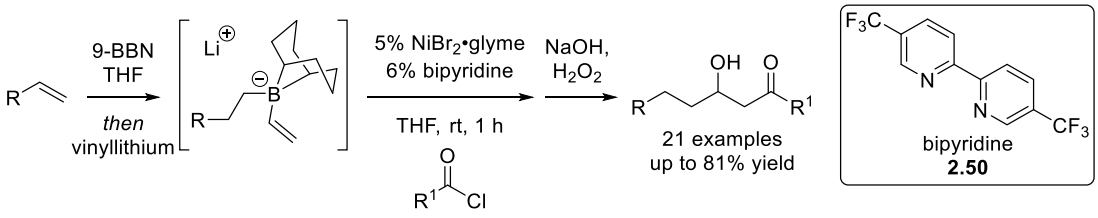
2.2 Conjunctive Cross-Coupling of Carbonyl Electrophiles

Access to enantioenriched chiral tertiary β-boryl carbonyl motifs is largely limited to the conjugate borylations of stereodefined Michael acceptors.[102] Other methods for the synthesis of

[102] (a) Chen, I. -H.; Yin, L.; Itano, W.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 11664-11665 (b) Mun, S.; Lee, J. -E.; Yun, J. *Org. Lett.* **2006**, *8*, 4887-4889 (c) Lee, J. -E.; Yun, J. *Angew. Chem. Int. Ed.* **2008**, *47*, 145-147 (d) Sim, H. -S.; Feng, X.; Yun, J. *Chem. Eur. J.* **2009**, *15*, 1939-1943 (e) Chea, H.; Sim, H.; Yun, J. *Adv. Synth. Catal.* **2009**, *351*, 855-858 (f) Chen, I. -H.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2010**, *12*, 4098-4101 (g) Feng, X.; Yun, J. *Chem. Eur. J.* **2010**, *16*, 13609-13612 (h) O'Brien, J. M.; Lee, K. -S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10630-10633 (i) Radomkit, S.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2014**, *53*, 3387-3391 (j) For a non-selective variant: Lee, K. -S.; Zhugralin, A. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 7253-7255 (k) Liu, B.; Wu, H. -H.; Zhang, J. *ACS Catal.* **2018**, *8*, 8318-8323

secondary boronates include asymmetric hydroboration of α,β- or β,γ-unsaturated amides[103] and asymmetric carboboration of β,γ-unsaturated amides.[104] In 2019, an alternative disconnection was realized using conjunctive cross-coupling.[105] Conjunctive cross-coupling had been limited in scope to aryl, alkenyl, and alkyl electrophiles, but bipyridine-nickel complex enabled cross-coupling of carboxylic acid derivatives with 9-BBN derived "ate" complexes (Scheme 2.2.1). Acid chlorides, anhydrides, and mixed anhydrides were excellent cross-coupling partners to yield both alkyl and aryl ketones. In some cases, the reaction was complete within 2 minutes, but it was difficult to render the reaction enantioselective, even after surveying a variety of ligand architectures.

Scheme 2.2.1: *Nickel-Catalyzed Conjunctive Cross-Coupling of Acyl Electrophiles with 9-BBN "ate" complexes*



Aside from the lack of effective stereocontrol, there are other aspects of the reaction that could be improved. For example, this nickel-catalyzed process was limited to 9-BBN derived "ate" complexes, and boronic esters are arguably more useful derivatives as they are often bench stable and can subsequently be transformed into a broader array of products.[106] Additionally, the synthesis of enantioenriched tertiary boronates has already been accomplished with palladium-

[103] (a) Bochat, A. J.; Shoba, V. M.; Takacs, J. M. *Angew. Chem. Int. Ed.* **2019**, *58*, 9434-9538 (b) Smith, S. M.; Thacker, N. C.; Takacs, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 3734-3735 (c) Smith, S. M.; Takacs, J. M. *J. Am. Chem. Soc.* **2011**, *132*, 1740-1741 (d) Smith, S. M.; Uteuliyev, M.; Takacs, J. M. *Chem. Commun.* **2011**, *47*, 7812-7814 (e) Smith, S. M.; Takacs, J. M. *Org. Lett.* **2010**, *12*, 4612-4615 (f) Gao, T. -T.; Zhang, W. -W.; Sun, X.; Lu, H. -X.; Li, B. -J. *J. Am. Chem. Soc.* **2019**, *141*, 4670-4677

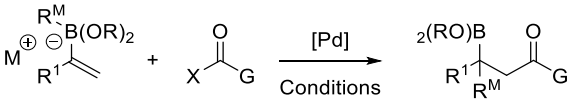
[104] (a) Liu, Z.; Li, X.; Zeng, T.; Engle, K. M. *ACS Catal.* **2019**, *9*, 3260-3265 (b) Bai, Z.; Zheng, S.; Bai, Z.; Song, F.; Wang, H.; Peng, Q.; Chen, G.; He, G. *ACS Catal.* **2019**, *9*, 6502-6509

[105] Law, C.; Meng, Y.; Koo, S. M.; Morken, J. P. *Angew. Chem. Int. Ed.* **2019**, *58*, 6654-6658

[106] Sandford, C.; Aggarwal, V. K. *Chem. Commun.* **2017**, *53*, 5481-5494

catalyzed conjunctive cross-coupling.[107] So, there is opportunity to explore α-substituted alkenyl boron "ate" complexes as cross-coupling partners to gain access to valuable tertiary β-boryl carbonyls. For these reasons, numerous carbonyl electrophiles were surveyed in the palladium-catalyzed conjunctive cross-coupling of α-substituted alkenyl boron "ate" complexes to synthesis enriched tertiary β-boryl carbonyls (Scheme 2.2.2).

Scheme 2.2.2: *Initial Investigation of Carbonyl Electrophiles*



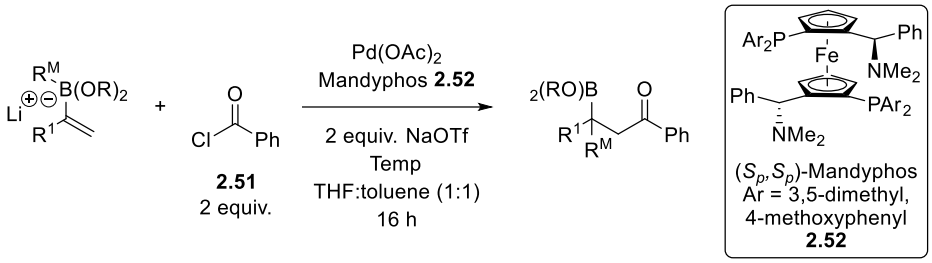
Initial investigation of different carbonyl electrophiles revealed diverse reaction profiles when comparing a variety of "X" groups and carbonyl groups. Acid chlorides are ideal electrophiles since many are commercially available or can be directly prepared from carboxylic acids. Also, acid chlorides have been successfully used in nickel-catalyzed conjunctive cross-coupling reactions.

Based on previous observations and hypotheses, sodium triflate was chosen as the optimal additive to minimize halogen inhibition and thereby enable effective conversion to product.[108] Reaction conditions were first investigated using a vinyl boron pinacol ester. A phenyl derived "ate" complex and benzoyl chloride did not couple under the reaction conditions (Table 2.2.1, entry 1). Notably, vinyl boron "mac" esters only provided some improved reactivity for phenyl and butyl migrating groups (entries 2-3). Interestingly, the corresponding isopropenyl B(pin) enabled higher yield of the tertiary β-boryl ketone (entry 4). The alpha-substituent may reduce undesirable Suzuki-Miyaura cross-coupling, and methyl group may polarize the olefin for beneficial palladium-induced 1,2-metallate shift. Curiously, isopropenyl B(mac) enabled poorer

[107] Myhill, J. A.; Zhang, L.; Lovinger, G. J.; Morken, J. P. *Angew. Chem. Int. Ed.* **2018**, *57*, 12799-12803
[108] Lovinger, G. J.; Aparece, M. D.; Morken, J. P. *J. Am. Chem. Soc.* **2017**, *139*, 3153-3160

conversion to product under similar conditions (entry 5). Unfortunately, high catalyst loading was necessary for effective reactivity (entry 7), and other changes to the reaction conditions were not fruitful, including temperature (entries 8 and 9).

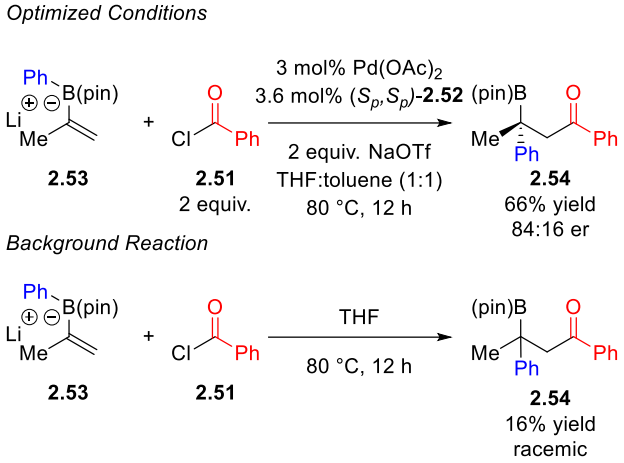
Table 2.2.1: *Optimization of Conjunctive Cross-Coupling with Benzoyl Chloride*



Entry	mol% $Pd(OAc)_2$	mol% MandyPhos	"OR"	R^M	R^1	Temp ˚C	Outcome	er
1	3.0	3.6	pinacol	Ph	H	80	No Product, ~25% Suzuki	ND
2	3.0	3.6	mac	Ph	H	80	37% Product	72:28
3	3.0	3.6	mac	*n*-Bu	H	80	18% Product	84:16
4	3.0	3.6	pinacol	Ph	Me	80	66% Product	84:16
5	3.0	3.6	mac	Ph	Me	80	29% Product	ND
6	3.0	3.6	pinacol	*n*-Bu	Me	80	39% Product	84:16
7	1.0	1.2	pinacol	Ph	Me	80	40% Product	ND
8	3.0	3.6	pinacol	Ph	Me	60	55% Product	89:11
9	3.0	3.6	pinacol	Ph	Me	100	52% Product	ND

Subjecting the "ate" complex and electrophile to reaction conditions without a palladium catalyst yielded a small amount of the racemic tertiary β-boryl product (Scheme 2.2.3). This background reaction may explain the lower enantioselectivity observed under catalytically relevant conditions.

Scheme 2.2.3: *Optimized Conditions for Benzoyl Chloride Electrophile and Observable Background Reaction*

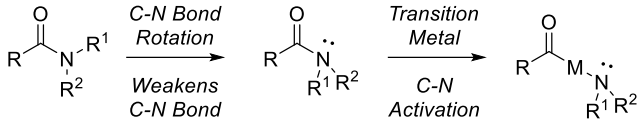


Perhaps acid chlorides undergo a relatively facile non-catalytic addition-elimination mechanism with "ate" complexes instead of participating in a concerted oxidative addition mechanism and subsequent desired catalysis.[109] Switching the electrophile may reduce the amount of undesired background reaction and increase the enantioselectivity of the process. Acid fluorides and twisted amides are excellent alternative to acid chloride derivatives to address this reactivity problem. Acid fluorides exhibit an interesting reaction profile by being more stable than acid chlorides and anhydrides but more reactive than esters and amides.[110] Many acid fluoride derivatives are not commercially available, but there are many ways to synthesize them, and they are stable to silica gel chromatography. Conversely, acid fluorides slowly react with glass and some commonly used laboratory plastics.[111] Additionally, twisted amides are a useful, bench stable alternative to acid chlorides in transition-metal catalyzed coupling reactions.[112] Steric bulk on the amide (R, R^1, and R^2) minimizes orbital overlap between the lone pair of electrons on

[109] (a) Goossen, L. J.; Koley, D.; Hermann, H. L.; Thiel, W. *J. Am. Chem. Soc.* **2005**, *127*, 11102-11114 (b) Liu, C.; Ji, C, -L.; Hong, X.; Szostak, M. *Angew. Chem. Int. Ed.* **2018**, *57*, 16721-16726
[110] Ogiwara, Y.; Sakai, N. *Angew. Chem. Int. Ed.* **2020**, *59*, 574-594
[111] Malapit, C. A.; Bour, J. R.; Brigham, C. E.; Sanford, M. S. *Nature* **2018**, *563*, 100-104
[112] Meng, G.; Szostak, M. *Org. Biomol. Chem.* **2016**, *14*, 5690-5707

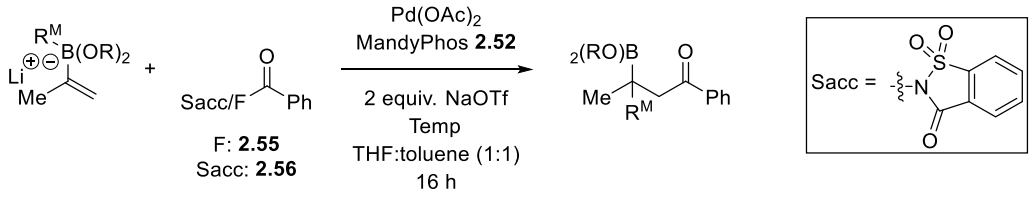
nitrogen and C-O π* causing ground-state destabilization (Scheme 2.2.4). This weakens the carbon-nitrogen bond enough to function as an electrophile in transition-metal catalysis.

Scheme 2.2.4: *Twisted-Amides for Transition-Metal C-N Activation*



Optimized conditions were developed for aroyl fluoride and aroyl saccharin[113] electrophiles (Table 2.2.2). Conditions were found to be similar as conditions used with acid chloride electrophiles with some exceptions. Lower catalyst loading was possible while obtaining similar levels of conversion (entries 3-6). "Mac" diol was used as a ligand for boron to minimize unwanted Suzuki-Miyaura cross-coupling product and fewer equivalents of benzoyl fluoride were necessary (entry 4). Saccharin derived twisted-amide electrophiles participated nearly identically in the reaction conditions when compared to acyl fluorides (entries 5-6). Reduced background reaction with these less electrophilic electrophiles was observed and higher enantioselectivity was obtained. However, the conversion to product remained at an unsatisfactory level.

Table 2.2.2: *Optimization of Conjunctive Cross-Coupling with Benzoyl Fluoride and Saccharin*



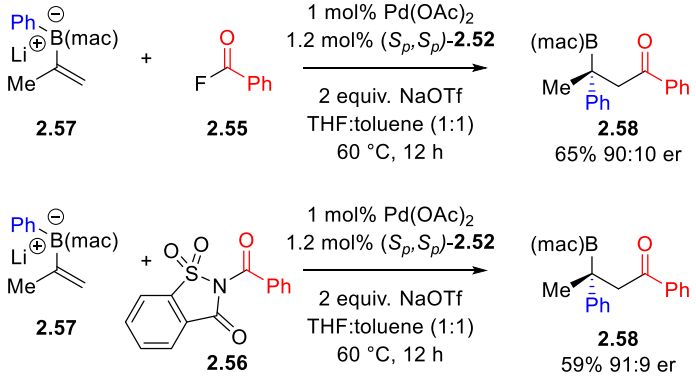
Entry	mol% $Pd(OAc)_2$	mol% MandyPhos	"OR"	R^M	E^+ (equiv.)	Temp ˚C	Outcome	er
1	3.0	3.6	pinacol	Ph	F (2).	60	66% product	90:10
2	3.0	3.6	pinacol	*n*-Bu	F (2)	60	65% Product	80:20
3	1.0	1.2	pinacol	Ph	F (2)	60	59% Product	ND
4	1.0	1.2	mac	Ph	F (1.2)	60	65% Product	90:10
5	1.0	1.2	pinacol	Ph	Sacc (1.2)	60	54% Product	ND
6	1.0	1.2	mac	Ph	Sacc (1.2)	60	59% Product	91:9

[113] Liu, C.; Meng, G.; Liu, Y.; Liu, R.; Lalancette, R.; Szostak, R.; Szostak, M. *Org. Lett.* **2016**, *18*, 4194-4197

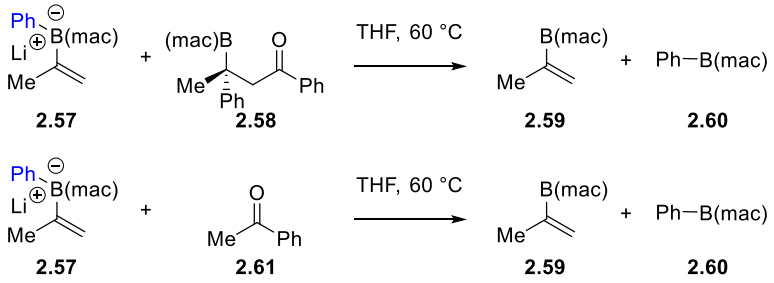
A control experiment was performed to determine the compatibility of the starting "ate" complex with the product of the reaction. The hypothesis was that the acidic α-protons of the product protonated the basic, tetracoordinate boron "ate" complex to yield the tricoordinate organoboronate and the corresponding propene or benzene (Scheme 2.2.5). Indeed, under reaction conditions similar to conjunctive cross-coupling, the boron "ate" complex decomposed in the presence of the product. This decomposition was also observed when replacing the tertiary organoboronate with acetophenone.

Scheme 2.2.5: *Acyl Fluoride and Saccharin Electrophiles in Conjunctive Cross-Coupling*

Optimized Conditions for Acyl Fluoride and Saccharin:



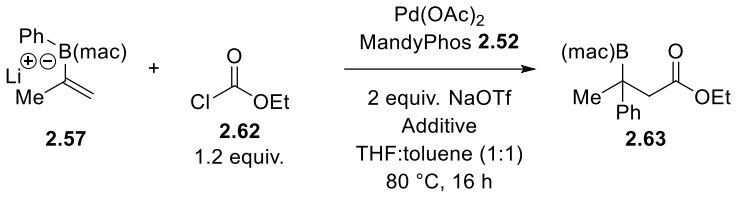
Starting Material Decomposition with Product:



The products derived from chloroformate electrophiles are expected to have a higher pKa than the corresponding aryl ketone products. The ester can also be easily transformed to other carbonyl motifs. Notably, elevated reaction temperatures were necessary to achieve effective conversion. However, when compared to the reactivity of aroyl fluoride or saccharin electrophiles, a similar

yield and enantioselectivity of the ester product was afforded using ethyl chloroformate as an electrophile (Table 2.3.3 entry 1). Polar solvent additives were hypothesized to slow the reaction and furnish the product in higher enantioselectivity. Indeed, the optimal polar additive was discovered through a solvent survey (entries 2-4). Five equivalents of dimethylformamide enabled the best results, but, interestingly, more equivalents of the additive provided increased enantioselectivity with reduced product yield.

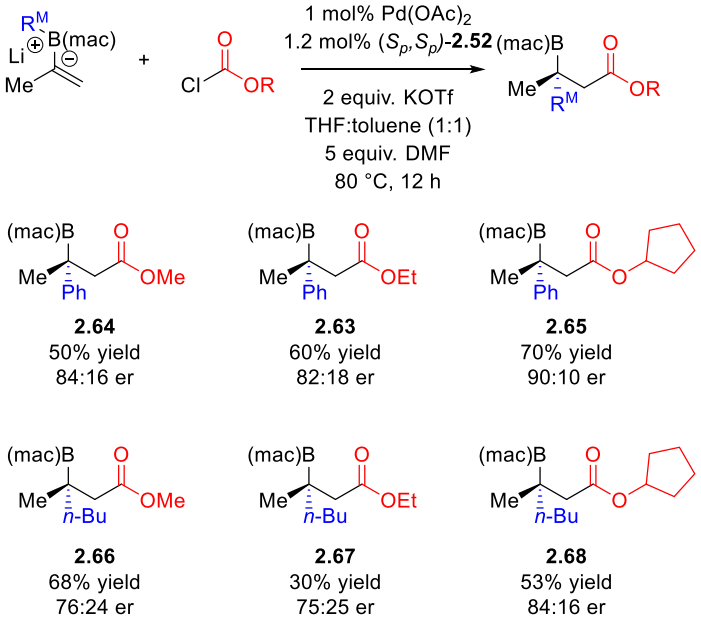
Table 2.2.3: *Optimization of Conjunctive Cross-Coupling with Ethyl Chloroformate*



Entry	mol% $Pd(OAc)_2$	mol% MandyPhos	Additive (equiv.)	Outcome	er
1	1.0	1.2	none	60% product	82:18
2	1.0	1.2	DMSO (3 equiv.)	61% Product	86:14
3	1.0	1.2	ACN (3 equiv.)	63% Product	80:20
4	1.0	1.2	DMF (3 equiv.)	74% Product	86:14
5	1.0	1.2	DMF (5 equiv.)	77% Product	85:15
6	1.0	1.2	DMF (7 equiv.)	68% Product	89:11
7	1.0	1.2	DMF (9 equiv.)	63% Product	91:9
8	1.0	1.2	DMF (11 equiv.)	56% Product	91:9

Potassium triflate instead of sodium triflate enabled more consist reactivity and generality for the chloroformate electrophile scope. Unfortunately, varied yields and enantioselectivities were observed when changing the R group of the chloroformate electrophile. Generally, larger chloroformate electrophiles reacted with higher conversion to product and gave higher enantioselectivity (Table 2.2.4). However, boronate complexes with alkyl migrating groups yielded products with lower enantioselectivity and diminished selectivity.

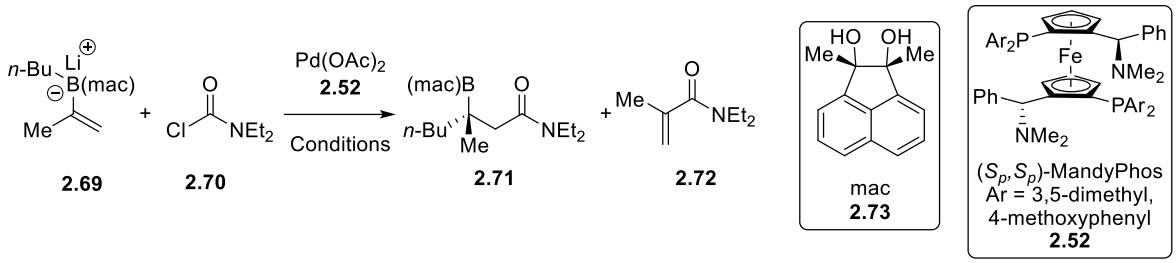
Table 2.2.4: *Conjunctive Cross-Coupling with Chloroformate Electrophiles*



Carbamoyl chloride electrophiles were investigated in conjunctive cross-coupling. Some reports suggest that under identical conditions carbamoyl chlorides are more reactive in palladium-catalyzed reactions than chloroformates.[114] Indeed, effective cross-coupling occurred at room temperature and using cesium fluoride as an additive (Table 2.2.5). Cesium fluoride was chosen as an additive because of previous results for increasing reactivity of the corresponding "ate" complex[115] and increased reactivity with carbamoyl chloride in Suzuki-Miyaura cross-coupling.[116] Investigation of different reaction conditions started with the coupling of a *n*-BuLi derived isopropenyl B(pin) "ate" complex with *N,N*-diethylcarbamoyl chloride using $Pd(OAc)_2$ and MandyPhos (entry 1). Poor selectivity for the desired conjunctive product was observed, and direct-transmetallation was the main product. Changing the boron ligand to a "mac" diol yielded good levels of selectivity for the desired product and moderate enantioselectivity (entry 2).

[114] Duan, Y. -Z.; Deng, M. -Z. *Synlett* **2005**, *2*, 355-357
[115] (a) Myhill, J. A.; Wilhelmsen, C. A.; Zhang, L.; Morken, J. P. *J. Am. Chem. Soc.* **2018**, *140*, 15181-15185 (b) Meng, Y.; Kong, Z.; Morken, J. P. *Angew. Chem. Int. Ed.* **2020**, *59*, 8456-8459
[116] Yasui, Y.; Tsuchida, S.; Miyabe, H.; Takemoto, Y. *J. Org. Chem.* **2007**, *72*, 5898-5900

Table 2.2.5: *Optimization of Conjunctive Cross-Coupling using Carbamoyl Chloride Electrophiles*



[a]Entry	mol% $Pd(OAc)_2$	mol% MandyPhos	Temp	Time	Additives	% **2.71** (% **2.72**)	er
[b]1	1	1.2	60 ˚C	12 h	2 equiv. CsF	16% (55%)	ND
2	1	1.2	60 ˚C	12 h	2 equiv. CsF	72% (7%)	82:18
3	1	1.2	40 ˚C	24 h	2 equiv. CsF	64% (13%)	87:13
4	1	1.2	rt	48 h	2 equiv. CsF	27% (3%)	91:9
5	1	1.2	rt	48 h	2 equiv. NaOTf	32% (18%)	84:16
6	1	1.2	rt	48 h	2 equiv. KOTf	25% (10%)	80:20
7	5	6	rt	48 h	2 equiv. CsF	80% (3%)	92:8
8	3	3.6	rt	72 h	2 equiv. CsF, 1 equiv. H_2O	86% (3%)	94:6

[a]%CCC refers to isolated yield of desired purified conjunctive coupling product. %SM refers to yield of Suzuki-Miyaura product as determine by 1H NMR using 1,1,2,2-tetrachloroethane as an internal standard. er refers to the enantiomeric ratio.[b] Pinacol was used as a boron ligand instead of "mac" diol

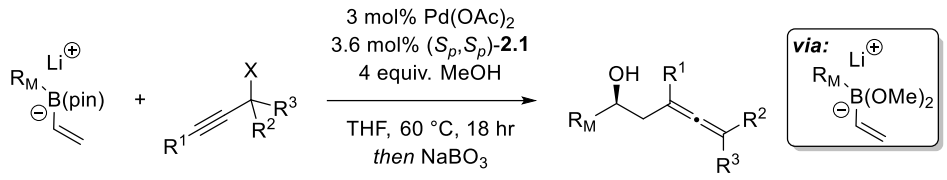
Lowering the reaction temperature and increasing the reaction time had the desired effect of increasing enantioselectivity (entry 3). However, conversion to product was reduced along with an increased formation of Suzuki-Miyaura product. Further reducing the reaction temperature resulted in increased enantioselectivity but poor conversion to product (entry 4). A survey of common additives in conjunctive cross-coupling did not result in improved selectivity and enantioselectivity (entries 5-6). Unsurprisingly, simply increasing the catalyst loading allowed for complete conversion within 48 hours. Good yields and enantioselectivities were exhibited with some substrates under these reaction conditions. Due to inconsistent reaction yields and selectivities with aryl migrating groups, numerous solvents and additives were screened. However, this did not yield satisfactory results. Inspired by recent studies within our lab[117] and others,[118]

[117] Aparece, M. D.; Hu, W.; Morken, J. P. *ACS Catal.* **2019**, *9*, 11381-11385
[118] Tao, Z.; Robb, K. A.; Panger, J. L.; Denmark, S. E. *J. Am. Chem. Soc.* **2018**, *140*, 15621-15625

various alcohols were investigated in hopes to improve reaction scope. Ultimately, water was found to provide excellent levels of selectivity and enantioselectivity with numerous substrates.

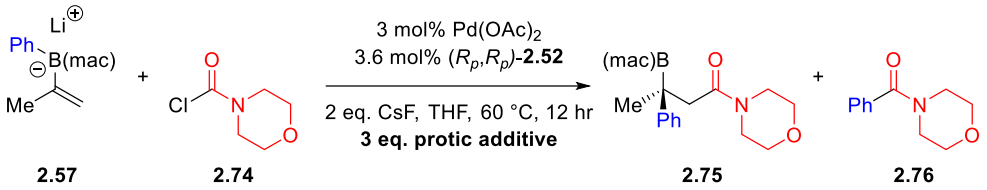
The impact of protic additives was demonstrated first in 2019 with the conjunctive cross-coupling of propargyl electrophiles (Scheme 2.2.6). Methanol was used as an additive, and NMR studies suggested exchange of the alcohol with the boron ligands enabled effective catalysis.

Scheme 2.2.6: *Morken's Conjunctive Cross-Coupling of Propargyl Electrophiles*



Reaction of aryl migrating groups yielded mostly Suzuki byproduct (Table 2.2.6). Addition of methanol did not have the desired effect. Instead of the desired effect of exchanging boron ligands, methanol reacted with carbamoyl chloride to yield the corresponding carbamate, and HCl destroyed the ate complex. On the other hand, water enabled the desired selectivity for the conjunctive cross-coupling product, and interestingly, a more acidic solvent such as trifluoroethanol still yielded the desired product. However, the poor reactivity exhibited with phenol indicated a limit to the acidic groups. Given the sensitivity of the electrophile to nucleophilic alcohols, and the boron "ate" complexes' low tolerance of acidic residues, the role of water was investigated further.

Table 2.2.6: *Investigation of Protic Additives in Conjunctive Cross-Coupling of Morpholine Carbamoyl Chloride*

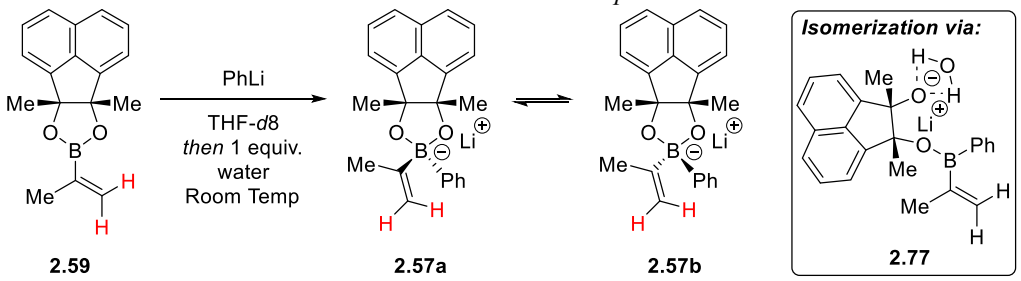


2.57 **2.74** **2.75** **2.76**

Protic Additive	pKa	"ate" Conv. (%)	**2.75** (%)	**2.76** (%)
None	N/A	>95	10	80
Methanol	15.5	>95	0	<10
Water	15.7	>95	85	<10
Trifluoroethanol	12.5	>95	55	<10
Phenol	10	>90	0	<10

The function of water was investigated by NMR analysis (Scheme 2.2.7). ^{1}H NMR experiments suggested that water accelerates the rate of isomerization for a relevant "ate" complex (Figure 2.2.1). With one equivalent of water, a change in the relative concentration of each diastereomer was observed over time such that a nearly 1:1 ratio was observed within one hour.

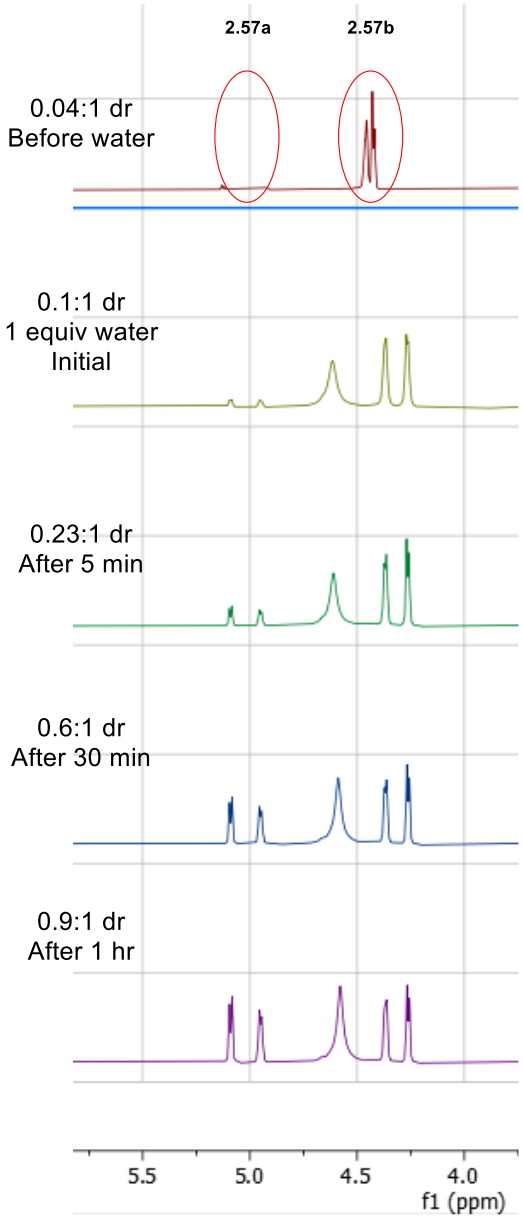
Scheme 2.2.7: *Water Mediated "Ate" Complex Isomerization Studies*



2.59 **2.57a** **2.57b** **2.77**

An identical experiment was performed in the absence of water, and only 0.2:1 dr was observed after 36 hours. These observations, along with the increased selectivity observed for conjunctive cross-coupling in the presence of water, suggest that water may act as an H-bond donor to the Lewis basic oxygens of the "ate" complex to facilitate isomerization. Though there are many possibilities and roles for water, one may be that a specific diastereomer is necessary for effective catalysis, and water helps accelerate the process that replenishes the reactive isomer from its less reactive counterpart.

Figure 2.2.1: *^{1}H NMR Experiment of "Ate" Complex Isomerization with Water*



A kinetic study was performed to determine whether a specific diastereomer reacts faster than the other under catalytically relevant conditions (Figure 2.2.2). An “ate” complex was prepared from isopropenyl B(mac) and phenyl lithium (the same as described from Scheme 2.2.7) without additional water (Scheme 2.2.8). In a THF solution, the “ate” complex was allowed to isomerize at 60 ˚C to obtain a 1.0:1.0 ratio of diastereomers. This solution was then subject to catalytic conditions (without water) and the reaction was monitored over time. It appeared that both

diastereomers of the "ate" complex were consumed at the same rate at 60 ˚C. It is also worth noting that a substantial amount of Suzuki-Miyaura product was observed at the end of the experiment as observed in Table 2.2.6. Unfortunately, conversion of "ate" complex did not occur at room temperature under these conditions. A similar experiment was performed using an "ate" complex derived from *n*-butyllithium and isopropenyl B(mac). This "ate" complex isomerizes rapidly at room temperature without the assistance of water, and both diastereomers of the "ate" appear to be consumed at the same rate. Therefore, we cannot conclude that a specific diastereomer reacts faster than another under these reaction conditions.

Scheme 2.2.8: *Conjunctive Cross-Coupling of 1:1 dr Mixture of "Ate" Complex Without Water*

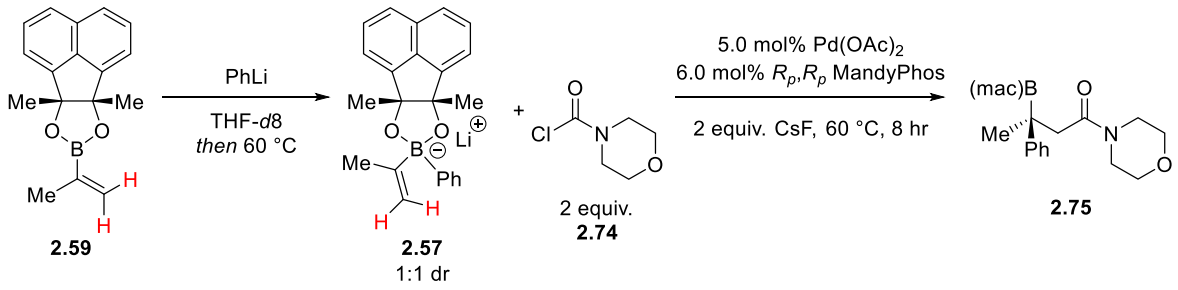
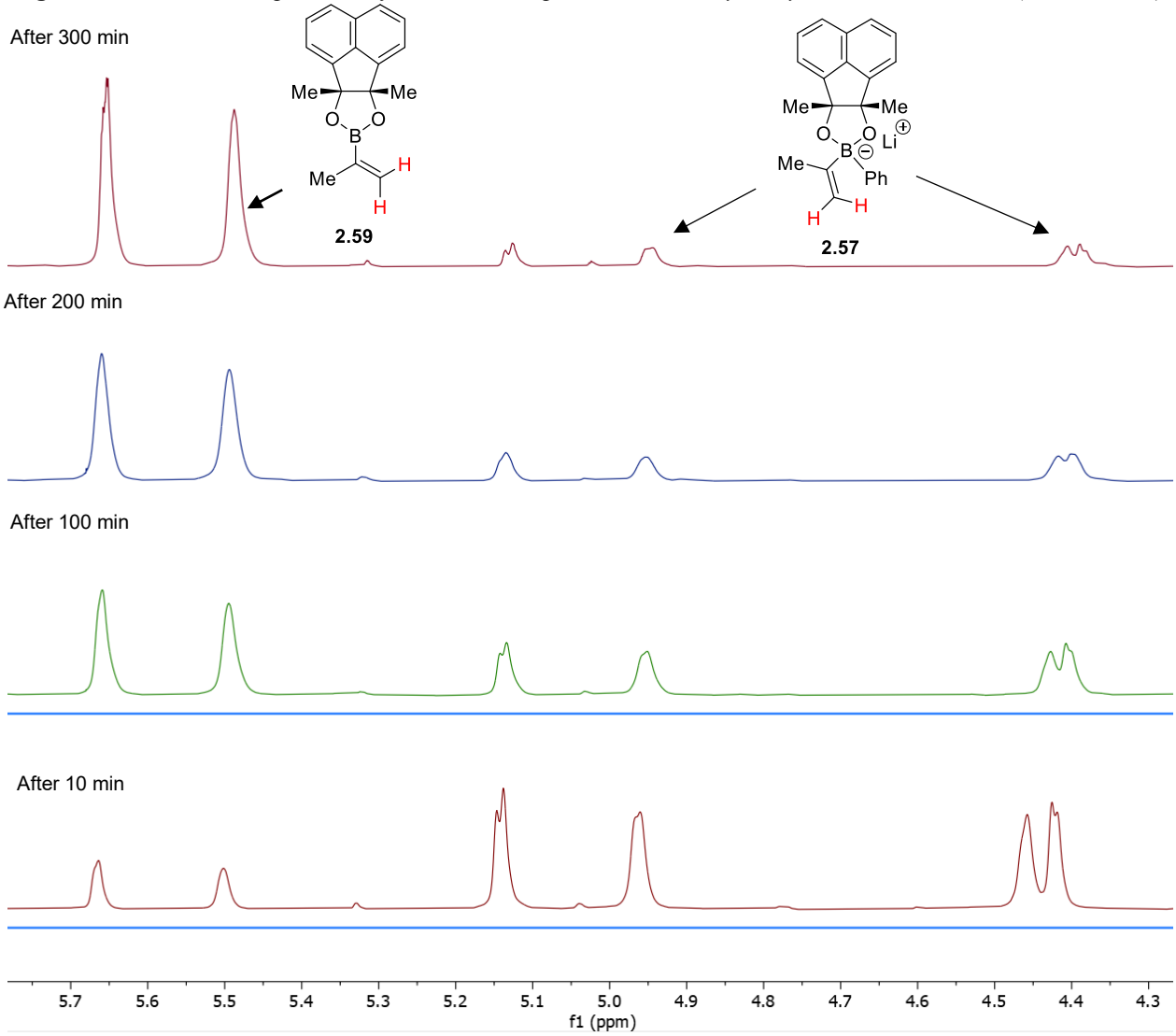


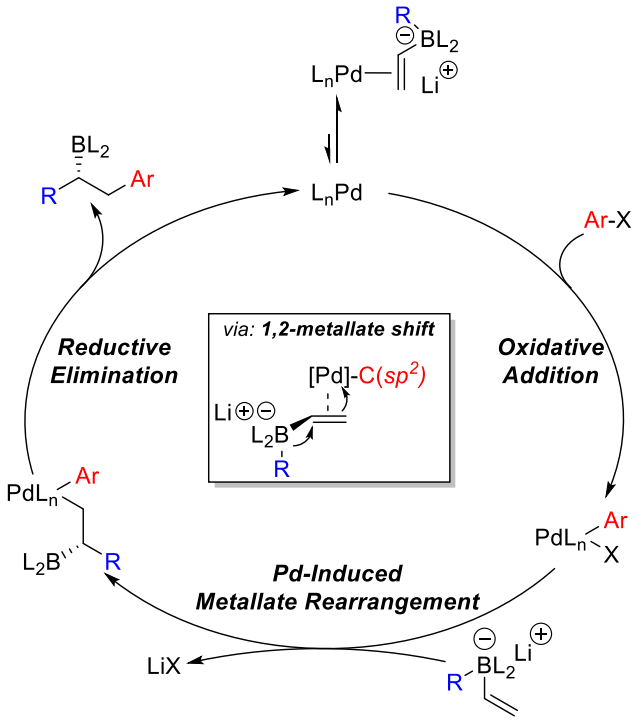
Figure 2.2.2: *1H NMR Experiment of "Ate" Consumption Under Catalytically Relevant Conditions (Scheme 2.2.8)*



A kinetic study was performed to determine the resting state within the catalytic cycle. Previously, kinetic studies in palladium-catalyzed conjunctive cross-coupling determined that the resting state in the catalytic cycle was a MandyPhos-ligated palladium (0) species with a boron "ate" complex when using an aryl triflate as an electrophile (Figure 2.2.3).[119] Thus, the turnover limiting step of this catalytic cycle is disassociation of the "ate" complex from palladium and subsequent oxidative addition.

[119] Myhill, J. A.; Zhang, L.; Lovinger, G. L.; Morken, J. P. *Angew. Chem Int. Ed.* **2018**, *57*, 12799-12803

Figure 2.2.3: *Catalytic Cycle for Conjunctive Cross-Coupling*

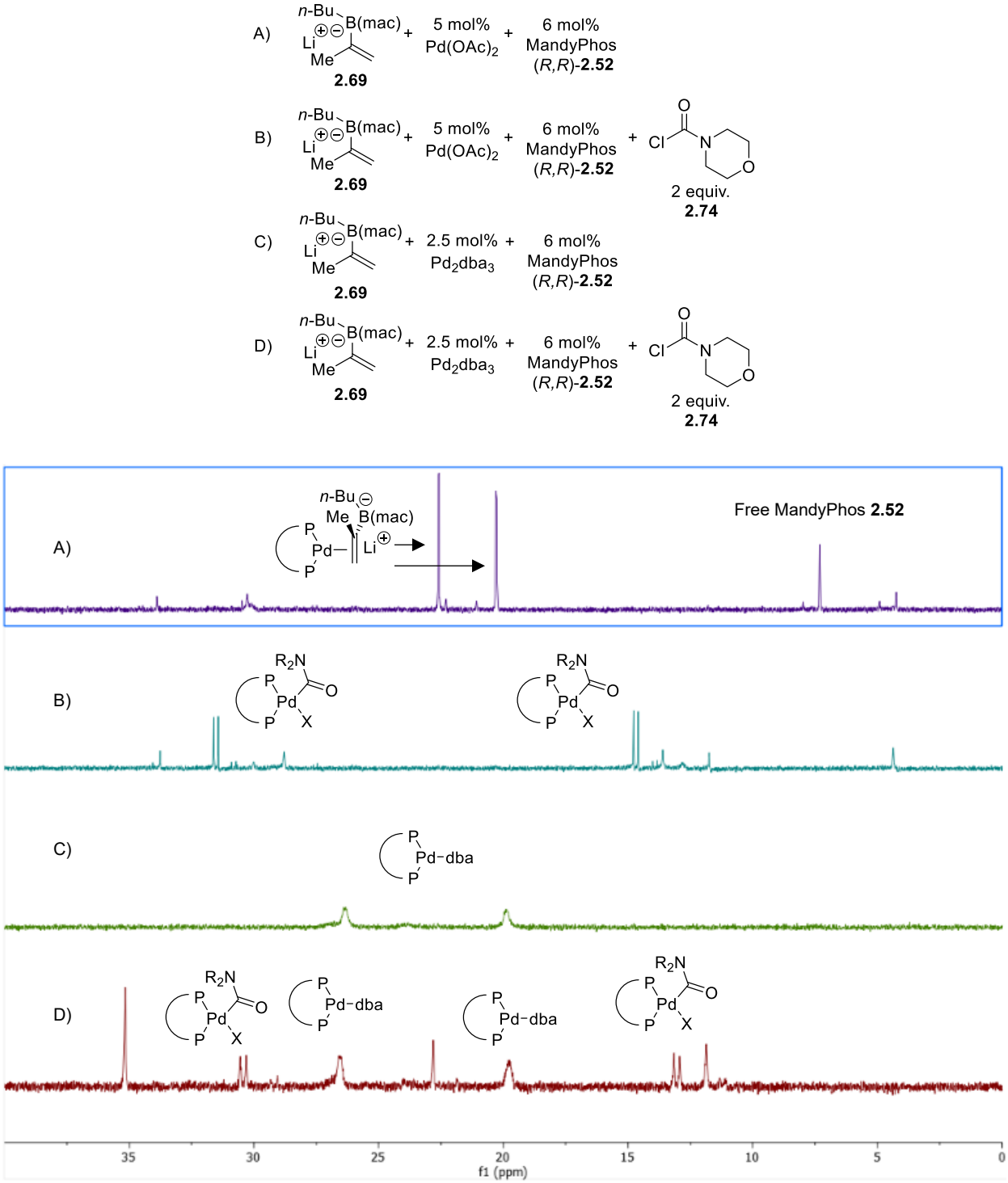


Several phosphorus NMR experiments support these kinetic observations. An ^{31}P NMR spectrum was obtained when palladium acetate, MandyPhos, and an "ate" complex react together under catalytically relevant conditions. An "ate" complex is believed to reduce palladium (II) to palladium (0) under these reaction conditions. This is supported by conducting the same with a palladium (0) precatalyst, $Pd_2(dba)_3$, which yielded the same spectrum. As expected from the kinetic studies, the same spectrum was obtained when phenyl triflate was added to the reaction mixture. These phosphorus NMR experiments support the notion of a catalytic resting state comprised of an "ate" complex and MandyPhos-ligated palladium (0) species.

However, a different kinetic profile may be operative for a carbamoyl chloride electrophile. A simple probe of the catalytic resting state is to perform ^{31}P NMR experiments. Several samples were prepared as outlined below in Figure 2.2.4. Equation "A" describes an "ate" complex and

MandyPhos-ligated palladium (0) like in the previous study. The phosphorus NMR experiment furnishes a spectrum very similar to what was described in 2018.

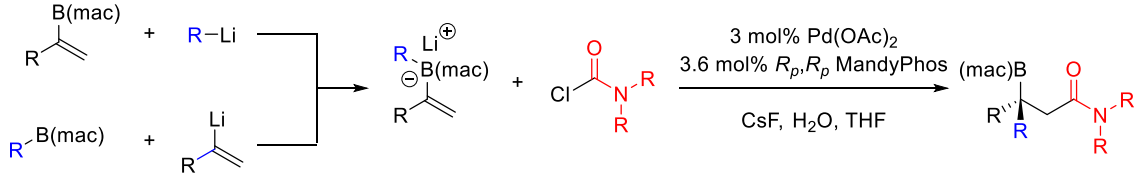
Figure 2.2.4: *^{31}P NMR of Conjunctive Cross-Coupling*



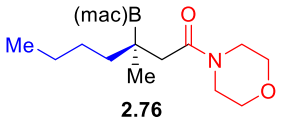
However, when adding morpholine carbamoyl chloride and allowing the reaction to proceed for 24 hours (~50% conversion), a different ^{31}P spectrum was observed (equation "B"). The major phosphorous appeared to be a doublet of doublets, which may indicate an asymmetric MandyPhos-ligated palladium species. In an attempt to afford the same catalytic resting state from a different palladium source, $Pd_2(dba)_3$ was utilized again. Interesting, equation "C" afforded a different ^{31}P spectrum from equation "A" unlike in the previous study. Perhaps dibenzylideneacetone is ligated to palladium under these reaction condition to provide different chemical shifts. However, a similar doublet of doublets appeared with the addition of the carbamoyl chloride (equation "D"). Though this spectrum appears similar to equation "B", the chemical shifts are not identical. Still, equations "B" and "D" may yield a similar catalytic resting state species. At this time, it is difficult to determine the true chemical makeup of this resting state, but it may involve a carbamoyl-palladium (II) intermediate.

With optimized conditions in hand, the performance of migrating groups was examined using a morpholine-derived carbamoyl chloride as a standard electrophile (Table 2.2.7). This electrophile was chosen because the morpholine amide readily undergoes subsequent transformations. Various commercially available organolithium-derived "ate" complexes participated in the reaction (**2.75**-**2.80**). Interestingly, the *tert*-butyl-derived "ate" complex required heating for efficient coupling, but high enantioselectivity was still maintained. Additionally, many commercially available carbamoyl chlorides performed well (**2.81**-**2.83**). However, larger carbamoyl chlorides required higher temperatures for conversion and near-racemic reaction products were obtained. Gratifyingly, novel α-substituted alkenyl B(mac)s can be synthesized and their corresponding "ate" complexes were compatible cross-coupling partners (**2.84** and **2.85**). These reactants furnished difficult-to-prepare tertiary β-boryl carbonyl

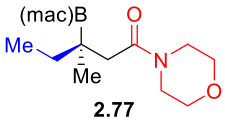
Table 2.2.7: *Representative Substrates in Palladium-Catalyzed Conjunctive Cross-Coupling of Carbamoyl Chlorides*



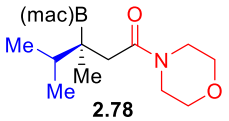
Commerical Organolithiums:



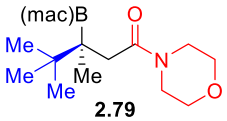
2.76
86% yield, 95:5 er



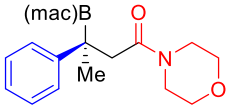
2.77
63% yield, 97:3 er



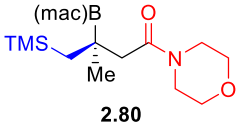
2.78
52% yield, 91:9 er



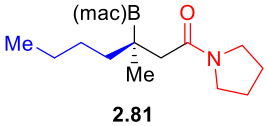
2.79
[a]59% yield, 96:4 er



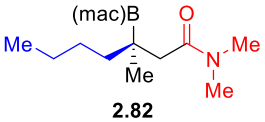
2.75
[b]81% yield, 96:4 er



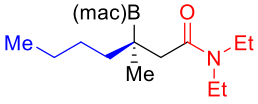
2.80
48% yield, 97:3 er



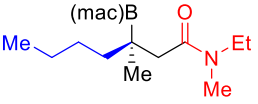
2.81
85% yield, 96:4 er



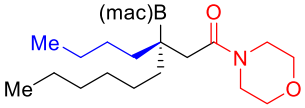
2.82
85% yield, 93:7 er



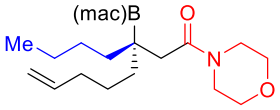
2.69
[c]86% yield, 94:6 er



2.83
89% yield, 94:6 er

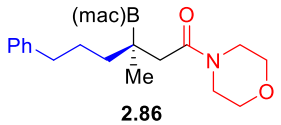


2.84
75% yield, 94:6 er

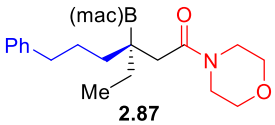


2.85
74% yield, 95:5 er

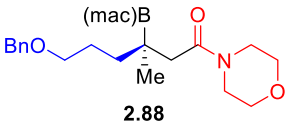
Lithium Halogen Exchange:



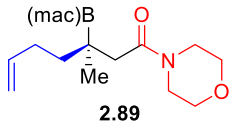
2.86
51% yield, 96:4 er



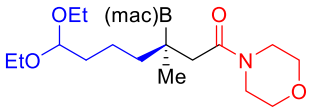
2.87
51% yield, 94:6 er



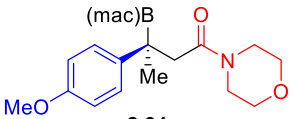
2.88
66% yield, 95:5 er



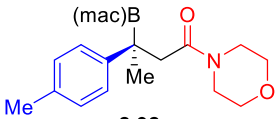
2.89
68% yield, 94:6 er



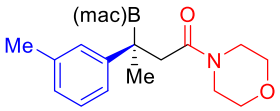
2.90
68% yield, 94:6 er



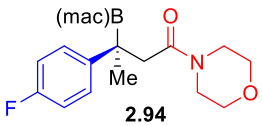
2.91
[d]42% yield, 95:5 er



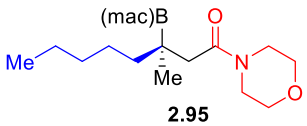
2.92
[d]61% yield, 95:5 er



2.93
[d]65% yield, 96:4 er



2.94
[d]65% yield, 96:4 er



2.95
[e]67% yield, 94:6 er

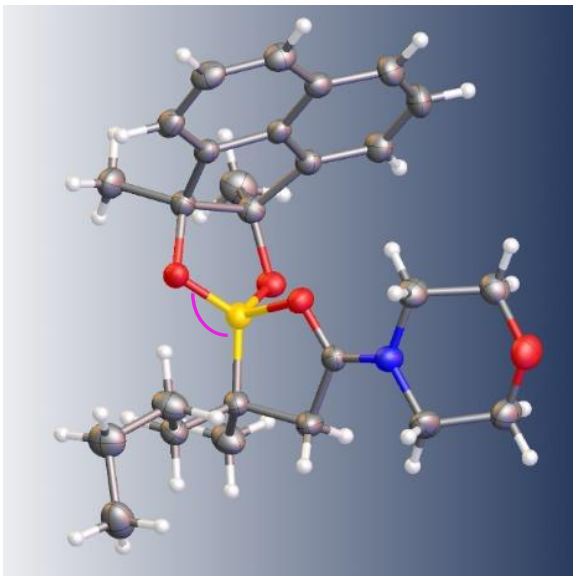
Yields are isolated yields of purified material and represent an average yield of two separate experiments. Enantiomeric ratios were determined by SFC analysis on a chiral stationary phased and are in comparison to authentic racemic materials. For commercial organolithiums, reaction was conducted with 3% Pd and 3.6% (S_p,S_p-MandyPhos) in THF (0.22 M) with 2 equiv. carbamoyl chloride, 2 equiv. CsF, 1 equiv. water at room temperature for 2 days. [a]Reaction conducted at 40 °C for 3 days. [b]Reaction conducted in .166 M THF at 60 °C for 12 hours. [c]Reaction conducted at rt for 3 days. For lithium halogen exchange, reaction was conducted with 3% Pd and 3.6% (S_p,S_p-MandyPhos) in THF (0.22 M) with 2 equiv. carbamoyl chloride, 3 equiv. CsF, 6 equiv. water at room temperature for 2 days. [d]Reaction conducted in .166 M THF at 60 °C for 12 hours. [e]Pentyllithium derived "ate" was made from pentylbromide and lithium metal (see SI for details)

compounds in high yields and enantioselectivities. Lithium-halogen exchange afforded migrating groups that are not available from commercial sources. With this reaction, aryl bromides can be made into competent "ate" complex coupling partners using isopropenyl B(mac). Additionally, numerous alkyl and aryl B(mac) "ate" complexes derived from lithium-halogen exchange of commercial isopropenyl bromide were also good coupling partners. Lastly, alkyllithium reagents generated from alkyl halides and lithium metal can be used in conjuctive cross-coupling.

The catalytic conjunctive coupling can be performed using gram-scale starting material and a reduced catalyst loading (Scheme 2.2.8). The products are usually easy-to-handle crystalline solids, and the absolute configuration was assigned with x-ray crystallography. The crystal structure of **2.76** unveiled interesting characteristics of the product motif (Figure 2.2.2). Perhaps the most obvious feature is an intramolecular Lewis acid-base adduct formed between boron and the oxygen of the amide. The normally planar, sp^2 hybridized boron becomes pyramidalized because of the electron donation of the Lewis-basic oxygen atom of the amide to the empty p-orbital of boron. This interaction is readily apparent in solution as suggested by the large up field shift in the ^{11}B resonance (24-29 ppm) compared to simple alkyl boronic esters (~35 ppm).

Figure 2.2.2: *Crystal structure of 2.76*

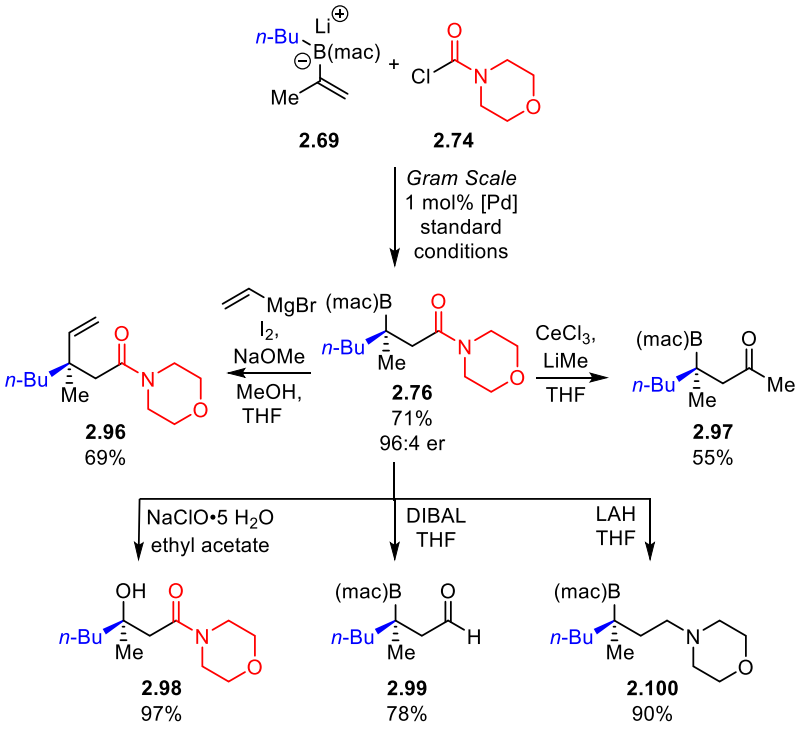
O-B-C angle = 117.84˚



The product of the coupling was used in subsequent transformations. The boronate was subject to mild oxidation conditions to yield the corresponding tertiary alcohol in high yield.[120] Other more basic oxidations can also be performed without substantial loss of product yield from retro-aldol side reactions. We were pleased to see that orthogonal carbon-carbon bond forming reactions can be performed. For example, a Zweifel olefination product was obtained in good yields without considerable vinyl magnesium bromide addition to the morpholine amide.[121] Interestingly, cerium-based organometallics can be used to selectively modify the morpholine amide to an alkyl ketone in the presence of a boronic ester.[122] Additionally, DIBAL can reduce the amide to form an aldehyde, and a tertiary amine can also be obtained from a LAH-mediate reduction.

[120] Radomkit, S.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2014**, *53*, 3387-3391
[121] Sonawane, R. P.; Jheengut, V.; Rabalakos, C.; Larouche-Gauthier, R.; Scott, H. K.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2011**, *50*, 3760-3763
[122] Kurosu, M.; Kishi, Y. *Tetrahedron Letters* **1998**, *39*, 4793-4796

Scheme 2.2.8: *Representative Transformation of Conjunctive Cross-Coupling Product*



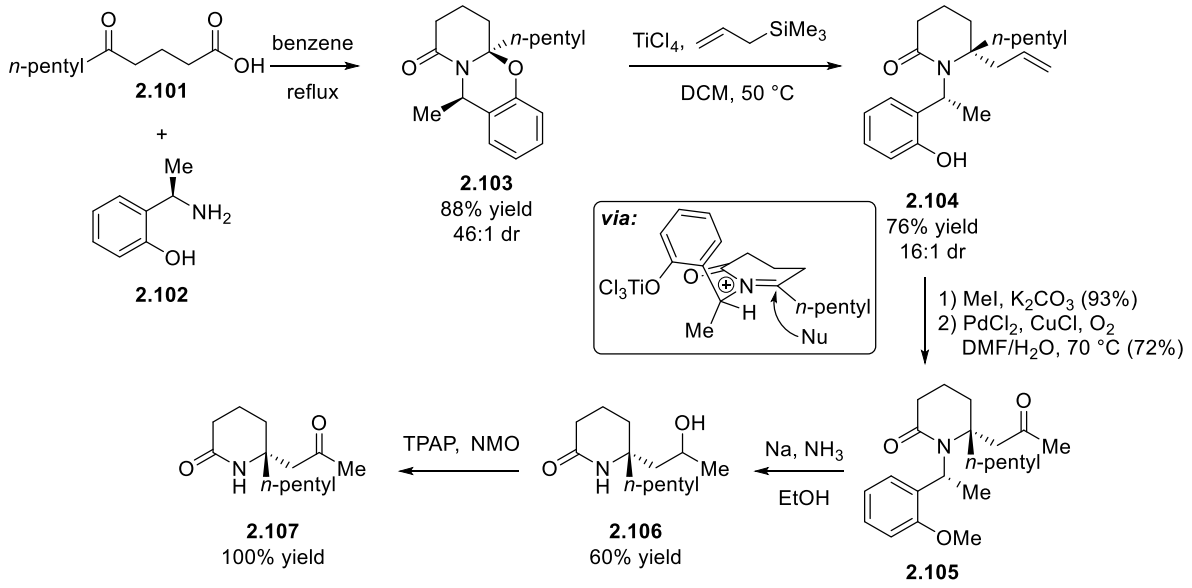
2.3 Total Synthesis of (+)-Adalinine

The enantioselective synthesis of tertiary β-boryl amides and their subsequent selective transformations provide a useful disconnection strategy for products that might otherwise be difficult to obtain with current methods. This benefit was demonstrated with the enantioselective synthesis of (+)-adalinine. (-)-Adalinine is a piperidine alkaloid that was isolated in 1996 from the European two-spotted ladybird beetle, *Adalia bipunctata*.[123] Though the exact biological function of this molecule is still not entirely known, the beetle discharges this compound as a defense mechanism. From a synthetic chemist's point of view, (-)-adalinine has a challenging, nitrogen-containing, quaternary center that is β to a methyl ketone. Biosynthetic studies suggest that the alkaloid is derived from a retro-Mannich process.[124]

[123] Lognay, G.; Hemptinne, J. L.; Chan, F. Y.; Gaspar, C. H.; Marlier, M.; Braekman, J. C.; Daloze, D.; Pasteels, J. M. *J. Nat. Prod.* **1996**, *59*, 510-511
[124] Laurent, P.; Lebrun, B.; Braekman, J. -C.; Daloze, D.; Pasteels, J. M. *Tetrahedron* **2001**, *57*, 3403-3412

There have been several asymmetric syntheses of this molecule that address the challenging stereocenter. In 1999, Kibayashi and coworkers utilized a chiral auxiliary strategy (Scheme 2.3.1).[125] A chiral aminophenol **2.102** was condensed onto a carboxylic acid 5-one **2.101** to prepare the desired lactam **2.103**. An efficient and diastereoselective Lewis acid-mediated Sakurai allylation reaction afforded the desired stereocenter. Methylation of the phenol and subsequent Wacker oxidation furnished the desired methyl ketone **2.104**. A Birch reduction removed the auxiliary and reduced the ketone to the secondary alcohol **2.106**. A ruthenium-mediated oxidation returned the carbinol to the desired oxidation state and furnishes the natural product **2.107**.

Scheme 2.3.1: *Kibayashi's Total Synthesis of (-)-Adalinine*



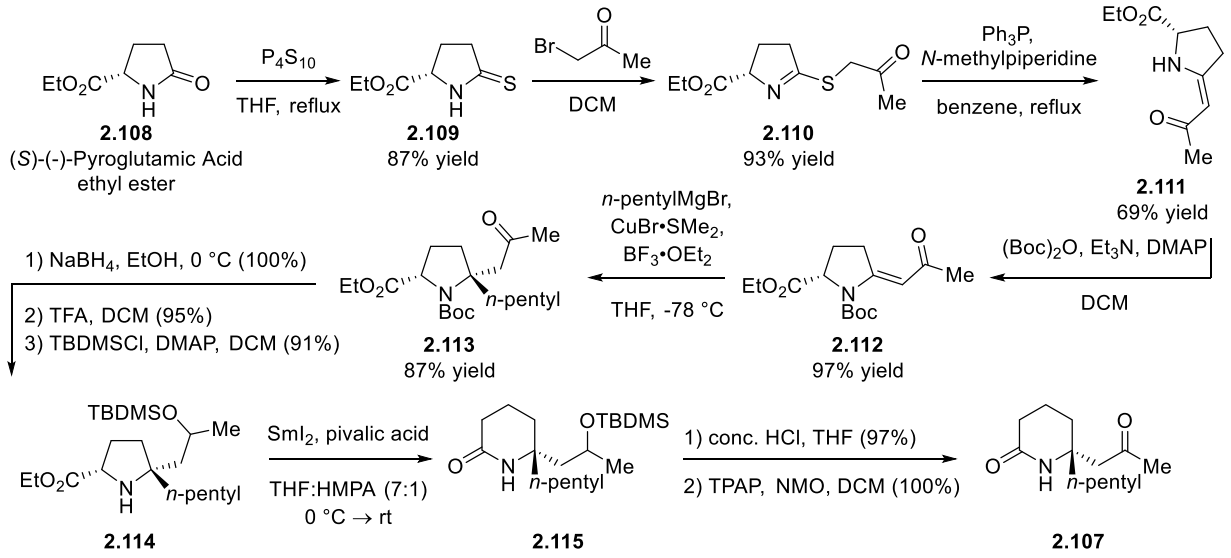
In 2000, Honda and coworkers synthesized (-)-adalinine using a diasteroselective strategy starting from the naturally occurring chiral starting material (*S*)-(-)-pyroglutamic acid ethyl ester **2.108** (Scheme 2.3.2).[126] *En route* to the desired stereocenter, the lactam was converted to the thiolactam in an efficient manner. The thiolactone was then alkylated with bromoacetone, and

[125] Yamazaki, N.; Ito, T.; Kibayashi, C. *Tetrahedron Letters* **1999**, *40*, 739-742

[126] Honda, T.; Kimura, M. *Org. Lett.* **2000**, *2*, 3925-3927

subsequent desulfurization coupling reaction afforded the methyl ketone **2.110** as a single olefin isomer. Conditions to protect the secondary amine as a carbamate resulted in isomerization of the enone; subsequent diastereoselective cuprate addition then established the desired stereocenter in excellent yield. Reduction of the methyl ketone, followed by protection of the resulting alcohol, yielded the silyl ether. Removal of the Boc group set up a samarium iodide-mediated ring expansion of the lactam. Deprotection of the silyl ether and subsequent ruthenium-mediated oxidation furnished the natural product.

Scheme 2.3.2: *Honda's Total Synthesis of (-)-Adalinine*

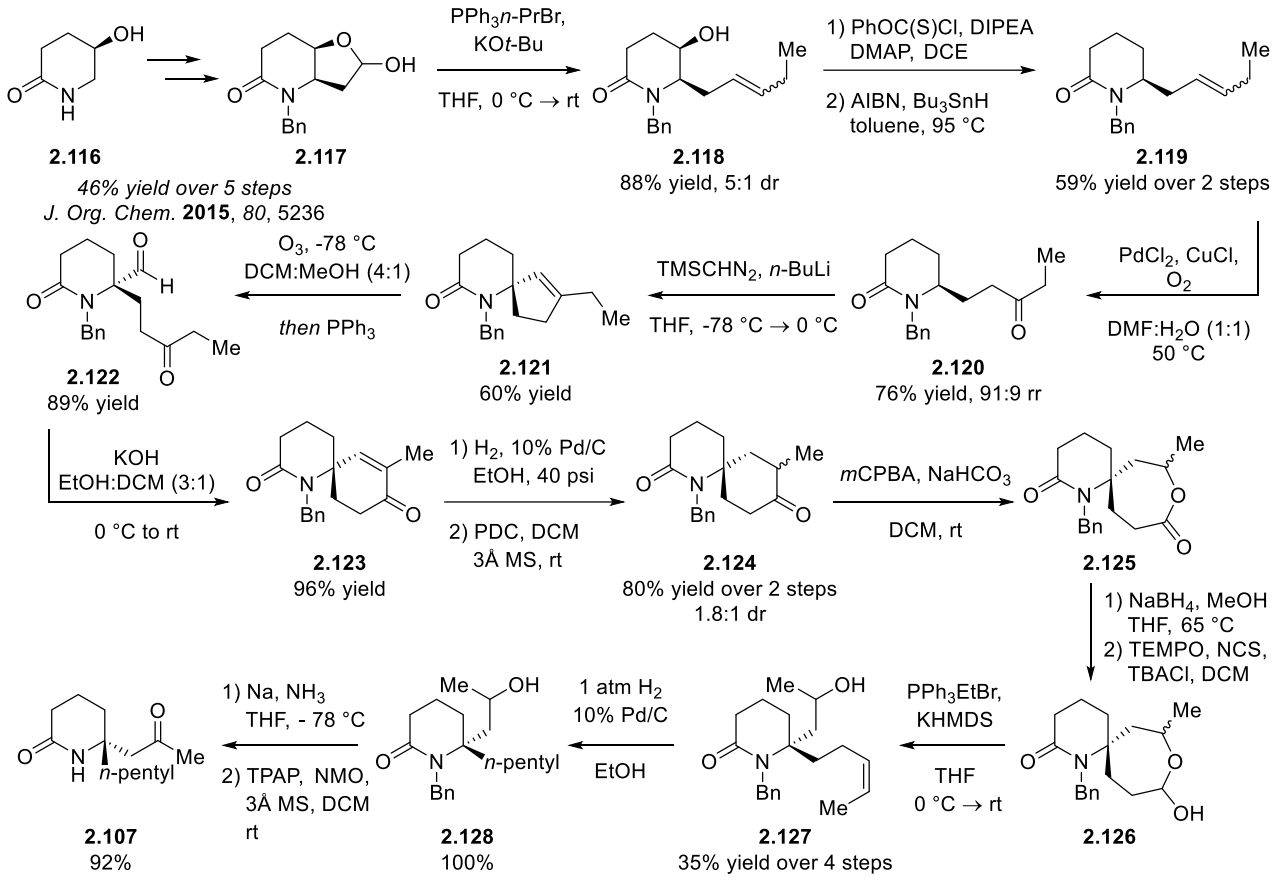


In 2016, Wee and coworkers synthesized (-)-adalinine from alcohol **2.116** (Scheme 2.3.3).[127] The five-step preparation of bicycle **2.117** was previously described in a prior publication from within the same group.[128] A Wittig-olefination yielded the corresponding alkene **2.118**. Having served its purpose to establish the vicinal stereocenter, the original carbinol stereocenter was destroy under Barton-McCombie deoxygenation conditions. A regioselective Wacker oxidation

[127] Annadi, K.; Wee, A. G. H. *J. Org. Chem.* **2016**, *81*, 1021-1038
[128] Annadi, K.; Wee, A. G. H. *J. Org. Chem.* **2015**, *80*, 5236-5251

afforded the ketone **2.120** in high regioselectivity. This set up an alkylidene carbene C-H activation and cyclization that furnished the spiro bicycle **2.121** and quaternary stereocenter. Several steps were performed to obtain the desired methyl ketone and pentyl group. An ozone-mediated oxidative cleavage of the tri-substituted olefin yielded the dicarbonyl **2.122**, and subsequent aldol condensation under basic conditions afforded a new spiro bicycle **2.123**. Hydrogenation of the enone and re-oxidation of the alcohol furnished ketone **2.124**.

Scheme 2.3.3: *Wee's Total Synthesis of (-)-Adalinine*



A regioselective Baeyer-Villiger oxidation afforded lactone **2.125**. This oxidation installed the oxygen atom that would later be the oxygen of the methyl ketone. To open the lactone and build the pentyl group, a sodium borohydride enabled reduction of the lactone yielded the corresponding diol, then selective oxidation of the primary alcohol and subsequent cyclization gave the

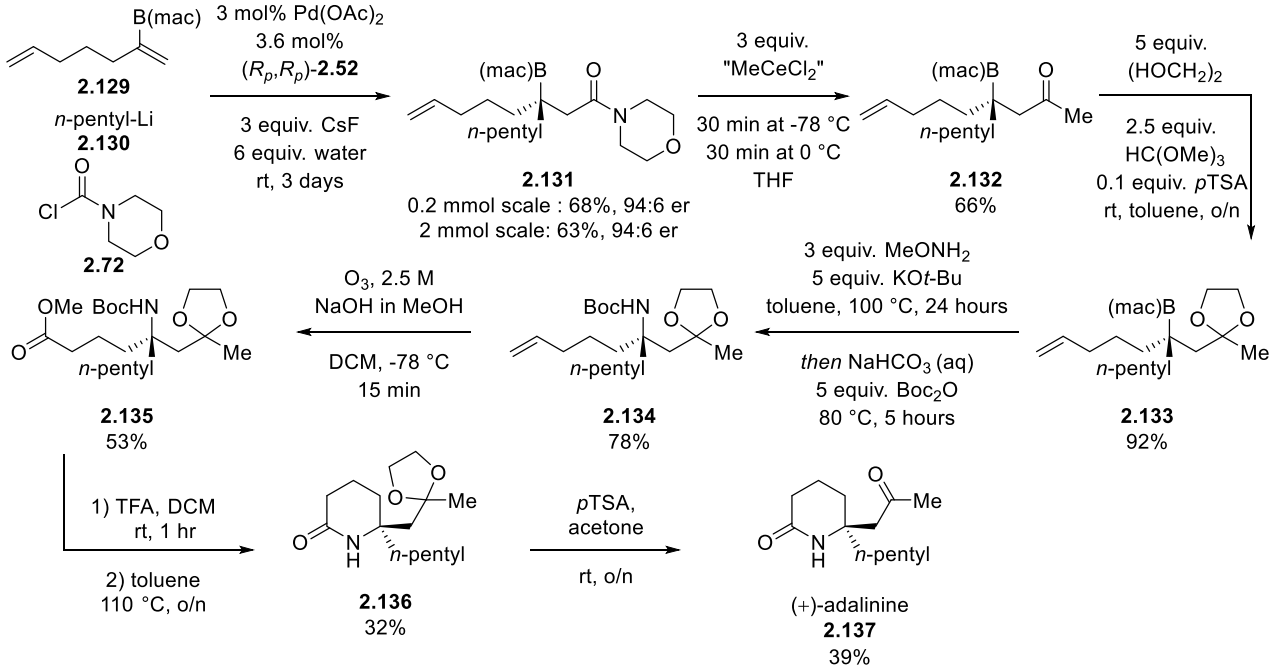
hemiacetal **2.126**. Once again, a Wittig-olefination opened the hemiacetal to yield the necessary carbon skeleton and oxidation pattern for the product. A palladium-on-carbon mediated hydrogenation of the olefin furnished the pentyl group. A Birch reduction removed the benzyl protecting group, and a ruthenium-mediated oxidation afforded the ketone and the natural product.

We sought to establish conjunctive cross-coupling as a means to synthesize difficult boryl containing quaternary stereocenters, and this method has been demonstrated in the total synthesis of (+)-adalinine (Scheme 2.3.4). Conjunctive cross-coupling was used to establish most of the skeletal structure and the necessary stereocenter. Compound **2.131** was synthesized in 68% yield and 94:6 er from **2.129** B(mac). Transformation of the morpholine amide to the desired methyl ketone **2.132** in the presence of the tertiary boronate was accomplished using a slight modification of the previously described method. Unfortunately, amination conditions with this ketone or the precursor amide substrate was not feasible because direct addition of the methoxyamine to the carbonyl motif and deprotonation were believed to be the side reactions under these conditions and a facile methyl ketone protection was necessary. Nevertheless, with ketal **2.133**, an enantiospecific amination generated the necessary nitrogen-containing stereocenter.[129] Oxidative cleavage of the terminal olefin was accomplished by ozonolysis in 53% yield. One-pot ozone-mediated oxidative cleavage and subsequent cyclization methods have been previously reported.[130] Unfortunately, nitrogen protection was necessary for the isolation of the prerequisite tertiary amine product and cyclization did not occur. Instead of the desired lactam, the tethered ester was isolated. With the correct oxidation state of the carbon skeleton in place, operationally-simple BOC deprotection and cyclization steps were conducted to afford the desired lactam. Column

[129] Edelstein, E. K.; Grote, A. C.; Palkowitz. M. D.; Morken, J. P. *Synlett* **2018**, *29*, 1749-1752
[130] Marshall, J. A.; Garofalo, A. W. *J. Org. Chem.* **1993**, *58*, 3675-3680

chromatography was necessary for the removal of an unidentified byproduct prior to ketal deprotection that delivered the desired natural product (+)-adalinine.

Scheme 2.3.4: *Total Synthesis of (+)-Adalinine Using Conjunctive Cross-Coupling*



In summary, this conjunctive cross-coupling method enabled the rapid construction of highly enriched tertiary-boryl amides with high yields and selectivity from simple and easily accessible starting materials. Reactions employing the "mac" diol derived boronate, cesium fluoride, and water afforded a broad substrate scope and high reaction fidelity. The usefulness of this rapid increase in molecular complexity was demonstrated in the asymmetric synthesis of (+)-adalinine.

2.4 Experimental Section

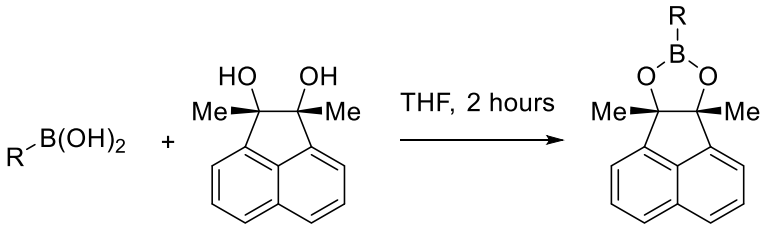
2.4.1 General information

^{1}H NMR spectra were recorded on either a Varian Gemini-500 (500 MHz), Varian Gemini-600 (600 MHz), or Varian Inova-500 (500 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 (126 MHz), Varian Gemini-600 (151 MHz) or a Varian Inova-500 (126 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 77.2 ppm). ^{11}B NMR spectra were recorded on a Varian Gemini-500 (128 MHz) or Varian Gemini-600 (160 MHz) spectrometer. ^{19}F NMR spectra were recorded on a Varian Gemini-500 (470 MHz) spectrometer. Infrared (IR) spectra were recorded on a Bruker alpha-P Spectrometer using compounds neat. 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) 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. 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 (magic stain). Analytical chiral supercritical fluid chromatography (SFC) was performed on a TharSFC Method Station II equipped with Waters 2998 Photodiode Array Detector with isopropanol or

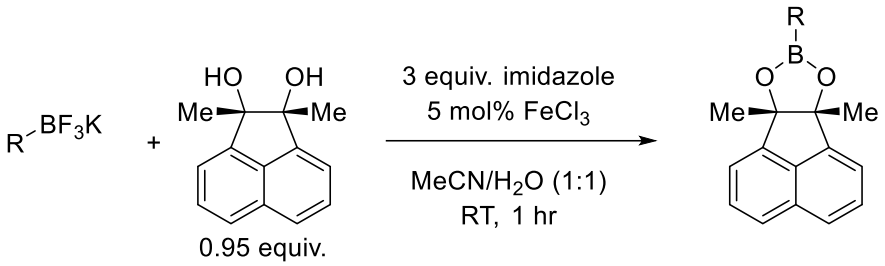
methanol as the modifier. X-ray crystal structure determination was performed using a Bruker Kappa Apex Duo automated single crystal diffractometer.

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 (DCM) 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 nitrogen. All carbamoyl chlorides were purchased from commercial sources and were distilled using a short path distillation apparatus. All other reagents were purchased from Aldrich, Alfa Aesar, Acros, Combi Blocks, TCI Chemicals or Oakwood Chemicals and used without further purification.

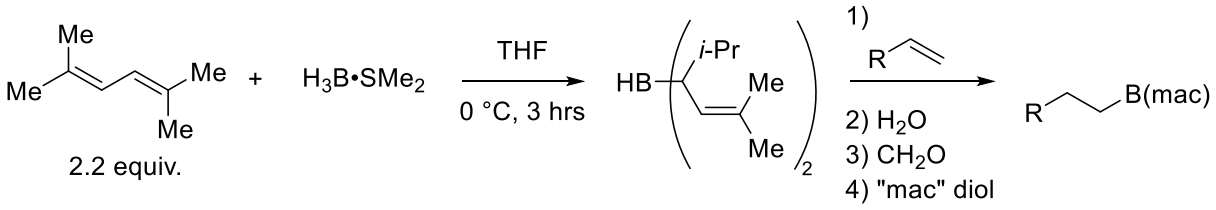
2.4.2 Procedures for Preparation of Boronic Esters



Method A: To a 50 mL round bottom flask equipped with a magnetic stir bar was charged with boronic acid (2.0 mmol, 1.0 equiv.), "mac" diol (2.0 mmol, 1.0 equiv.), and THF (10 mL). Reaction was allowed to stir at room temperature and open to air. Reaction conversion was monitored by TLC (within 2 hours). Upon completion, reaction mixture was concentrated under vacuum. The crude product was purified by a silica gel plug using dichloromethane as an eluten. *This method can be used with conveniently available and easily handled boronic acids.*



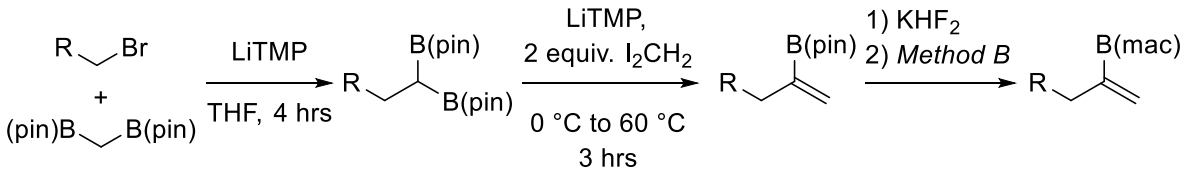
Method B: Organoboronates were prepared according to a modified literature procedure, as follows.[131] To a 250 mL round bottom flask equipped with a magnetic stir bar was charged open to air and at room temperature with potassium trifluroborate (8.0 mmol, 1.0 equiv.) and 1:1 acetonitrile:water (60 mL). Iron trichloride (0.4 mmol, 0.05 equiv.), imidazole (24.0 mmol, 3 equiv.), and "mac" diol (7.6 mmol, 0.95 equiv.) were added sequentially. Reaction mixture was allowed to stir vigorously for 1 hour. Reaction was diluted with water and ethyl acetate. Reaction mixture was transferred to a separatory funnel and collected the organic layer. The aqueous layer was washed three times with ethyl acetate. The collected organic layers were washed with brine, dried with sodium sulfate, filtered into a round bottom flask, and concentrated under vacuum. A silica plug eluted with DCM was used to purify the resulting crude. The crude can be further purified by recrystallization using hot ethyl acetate. *This method can be used when the corresponding boronic acid is unavailable or difficult to handle.*



Method C: Organoboronates were prepared according to a modified literature procedure, as follows.[132] To a flame-dried 100 mL round bottom flask equipped with a magnetic stir bar was

[131] Wood, J. L.; Marciasini, L. D.; Vaultier, M.; Pucheault, M. *Synlett.* **2014**, *25*, 551-555
[132] Kalinin, A. V.; Scherer, S.; Snieckus, V. *Angew. Chem. Int. Ed.* **2003**, *42*, 3399-3404

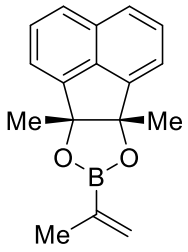
charged with 2mL THF and 2,5-dimethylhexa-2,4-diene (4.4 mmol, 2.2 equiv.). The resulting solution was chilled in an ice bath and borane dimethylsulfide (2 mmol, 1 equiv.) was added dropwise. Upon the completion of the dropwise addition, the reaction was allowed to stir at that temperature for 3 hours. After, alkene (2 mmol, 1 equiv.) was added dropwise and, upon completion, allowed to stir at room temperature for 2 hours. Then, the reaction was cooled by an ice bath and water (14 mmol, 7 equiv.) was added dropwise to the reaction. Paraformaldehyde (2 mmol, 1 equiv.) was added directly at room temperature and was allowed to stir for 2 hours. After, "mac" diol (2 mmol, 1 equiv.) was added directly. The diol slowly disappears over the course of an hour and then resulting mixture was subject an aqueous work up. Reaction was washed with water. The aqueous layer was washed with ethyl acetate times. The organic layers were collected and washed with brine, dried with sodium sulfate, filtered and concentrated under vacuum. Crude is purified using silica gel chromatography. *This method can be used to gain access to alkyl boronic esters from available terminal alkene.*



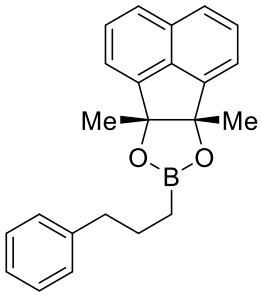
Method D: 1,1 bisboronates are prepared using the following methodology precedent.[133] The following boron-Wittig reaction was performed using the following methodology precedent.[134] The same alpha substituted alkenyl B(pin) used in this publication were prepared as the previously mentioned literature precedent and obtained intermediate NMR spectra are in good agreement with

[133] Liu, X.; Sun, C.; Mlynarski, S.; Morken, J. P. *Org. Lett.* **2018**, *20*, 1898-1901
[134] Myhill, J. A.; Zhang, L.; Lovinger, G. L.; Morken, J. P. *Angew. Chem. Int. Ed.* **2018**, *57*, 12799-12803

reported spectra. Transformation from the B(pin) to the corresponding B(mac) was performed from a literature precedent[135] and *Method B*.



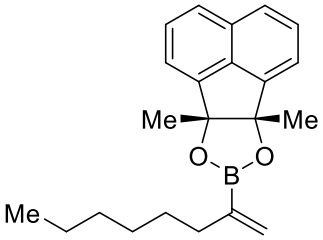
(6bR,9aS)-6b,9a-dimethyl-8-(prop-1-en-2-yl)-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (2.59). The title compound was prepared according to *Method B* with potassium isopropenyltrifluoroborate (4.83 g, 32.67 mmol, 1 equiv.), 1,2-dimethylacenaphthylene-1,2-diol, "mac", (7 g, 32.67 mmol, 1 equiv.), iron (III) chloride (265 mg, 1.63 mmol, 0.05 equiv.), and imidazole (6.67 g, 98.01 mmol, 3 equiv.) in 250 mL water: acetonitrile mixture in 1:1 ratio. The resulting crude was purified by recrystallization using hot ethyl acetate to yield the title compound (6.42 g, 24.6 mmol, 74% yield) as a white crystalline solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (dd, *J* = 7.9, 1.1 Hz, 2H), 7.63 – 7.54 (m, 4H), 5.72 (dq, *J* = 3.9, 1.3 Hz, 1H), 5.57 (dq, *J* = 3.6, 1.7 Hz, 1H), 1.80 (s, 6H), 1.75 (t, *J* = 1.5 Hz, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.0, 134.9, 131.5, 130.6, 128.6, 125.3, 119.7, 92.2, 22.3, 21.3.; ^{11}B NMR (160 MHz, $CDCl_3$) δ 29.91.; IR (neat): ν_{max} 2991.17 (w), 2974.88 (w), 1620.42 (m), 1301.58 (s), 1175.17 (m), 1115.72 (m), 1076.48 (m) cm^{-1}. HRMS (DART) for $C_{17}H_{18}BO_2$ $[M+H]^+$: Calc'd: 265.13944, found: 265.14002.



(6bR,9aS)-6b,9a-dimethyl-8-(3-phenylpropyl)-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (S-1). The title compound was prepared according to *Method C* with 2,5-dimethylhexa-2,4-diene (1.57 mL, 11.00 mmol, 2.2 equiv.), 1,2-dimethylacenaphthylene-1,2-diol (1.07 g, 2 mmol, 1 equiv.), allylbenzene (0.662 mL, 5 mmol, 1 equiv.), borane dimethylsulfide (0.474 mL, 5 mmol, 1 equiv.), paraformaldehyde (150.2 mg, 5 mmol, 1 equiv.),

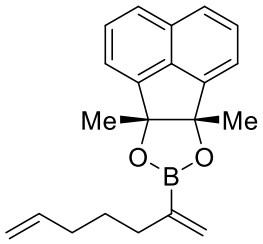
[135] Koo, S. M.; Vendola, A. J.; Momm, S. N.; Morken, J. P. *Org. Lett.* **2020**, *22*, 666-669

and water (0.625 mL, ~35 mmol, ~7 equiv.) in 5 mL THF. The resulting crude was purified by silica gel column chromatography using 5% ethyl acetate:hexanes to isolate the title compound (1.30 g, 3.78 mmol, 76% yield) as a white solid. Product Rf = 0.6 in 10% ethyl acetate:hexanes (UV active and stains green with *para*-anisaldehyde stain).; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (dd, *J* = 8.1, 1.0 Hz, 2H), 7.64 – 7.51 (m, 4H), 7.24 – 7.17 (m, 2H), 7.15 – 7.03 (m, 3H), 2.50 (t, *J* = 7.7 Hz, 2H), 1.76 (s, 6H), 1.67 (p, *J* = 7.9 Hz, 2H), 0.78 (t, *J* = 7.9 Hz, 2H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.0, 142.7, 134.8, 131.5, 128.6, 128.6, 128.2, 125.6, 125.4, 119.5, 91.8, 38.5, 26.1, 22.2.; ^{11}B NMR (160 MHz, $CDCl_3$) δ 34.13.; IR (neat): ν_{max} 3022.89 (w), 2969.40 (w), 2928.92 (w), 1369.86 (m), 1114.50 (m), 1075.89 (m), 824.16 (m), 776.59 (m) cm^{-1}. HRMS (DART) for $C_{23}H_{24}BO_2$ $[M+H]^+$: Calc'd: 343.18639, found: 343.18711.

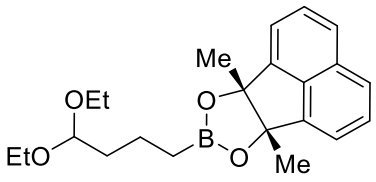


(6bR,9aS)-6b,9a-dimethyl-8-(oct-1-en-2-yl)-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (S-2). The title compound was prepared according to *Method D* with trifluoro-(1-methyleneheptyl)-potassio-boron (2.49 g, 11.42 mmol, 1 equiv.), iron (III) trichloride (92.6 mg, 0.57 mmol, 0.05 equiv.), imidazole (2.33 g, 34.3 mmol, 3 equiv.), and 1,2-dimethylacenaphthylene-1,2-diol (2.45 g, 11.42 mmol, 1 equiv.) in an 85 mL 1:1 water: acetonitrile mixture. The resulting crude was purified by silica gel column chromatography using 25% DCM:hexanes (unoptimized column conditions) to isolate the title compound (484 mg, 1.45 mmol, 13% yield) as a white solid. Product Rf = 0.8 in 50% DCM:hexanes (UV active and stains with potassium permanganate stain).; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 7.9, 1.1 Hz, 2H), 7.70 – 7.48 (m, 4H), 5.82 – 5.70 (m, 1H), 5.56 (dt, *J* = 3.5, 1.6 Hz, 1H), 2.10 (tt, *J* = 7.4, 1.3 Hz, 2H), 1.81 (s, 6H), 1.35 (dt, *J* = 12.4, 4.5 Hz, 2H), 1.27 – 1.18 (m, 6H), 0.90 – 0.81 (m, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.1, 134.9, 131.5, 129.1, 128.6, 125.3, 119.6, 92.1, 35.2, 31.9, 29.1,

24.9, 22.7, 22.3, 14.23, 14.22.; ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.26.; IR (neat): ν_{max} 2922.51 (w), 1362.82 (m), 1114.30 (m), 1075.82 (m), 823.21 (m), 775.26 (m) cm^{-1}. HRMS (DART) for $C_{22}H_{28}BO_2$ $[M+H]^+$: Calc'd: 335.21769, found: 335.21699.



(6bR,9aS)-8-(hepta-1,6-dien-2-yl)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (2.129). The title compound was prepared according to *Method D* with trifluoro-(1-methylenehex-5-enyl)-potassio-boron (1.68 g, 8.33 mmol, 1 equiv.), iron (III) trichloride (67.6 mg, 0.42 mmol, 0.05 equiv.), imidazole (1.7 g, 25 mmol, 3 equiv.), and 1,2-dimethylacenaphthylene-1,2-diol (1.78 g, 8.33 mmol, 1 equiv.) in 62 mL 1:1 water: acetonitrile mixture. The resulting crude was purified by silica gel column chromatography using 25% DCM:hexanes (unoptimized column conditions) to isolate the title compound (824 mg, 2.59 mmol, 31% yield) as a white solid. Product Rf = 0.7 in 50% DCM:hexanes (UV active and stains with potassium permanganate stain).; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.0 Hz, 2H), 7.62 – 7.54 (m, 4H), 5.82 – 5.72 (m, 2H), 5.57 – 5.53 (m, 1H), 4.99 – 4.92 (m, 1H), 4.90 (ddd, *J* = 10.0, 2.1, 1.1 Hz, 1H), 2.10 (t, *J* = 7.7 Hz, 2H), 1.99 (q, *J* = 7.2 Hz, 2H), 1.80 (s, 6H), 1.49 – 1.41 (m, 2H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.0, 139.1, 134.8, 131.4, 129.6, 128.5, 125.3, 119.6, 114.3, 92.1, 34.7, 33.5, 28.4, 24.9, 22.3.; ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.33.; IR (neat): ν_{max} 3059.03 (w), 2972.49 (w), 2925.66 (w), 1297.80 (m), 1114.14 (m), 1075.33 (m), 775.76 (m) cm^{-1}. HRMS (DART) for $C_{21}H_{24}BO_2$ $[M+H]^+$: Calc'd: 319.18639, found: 319.18765.



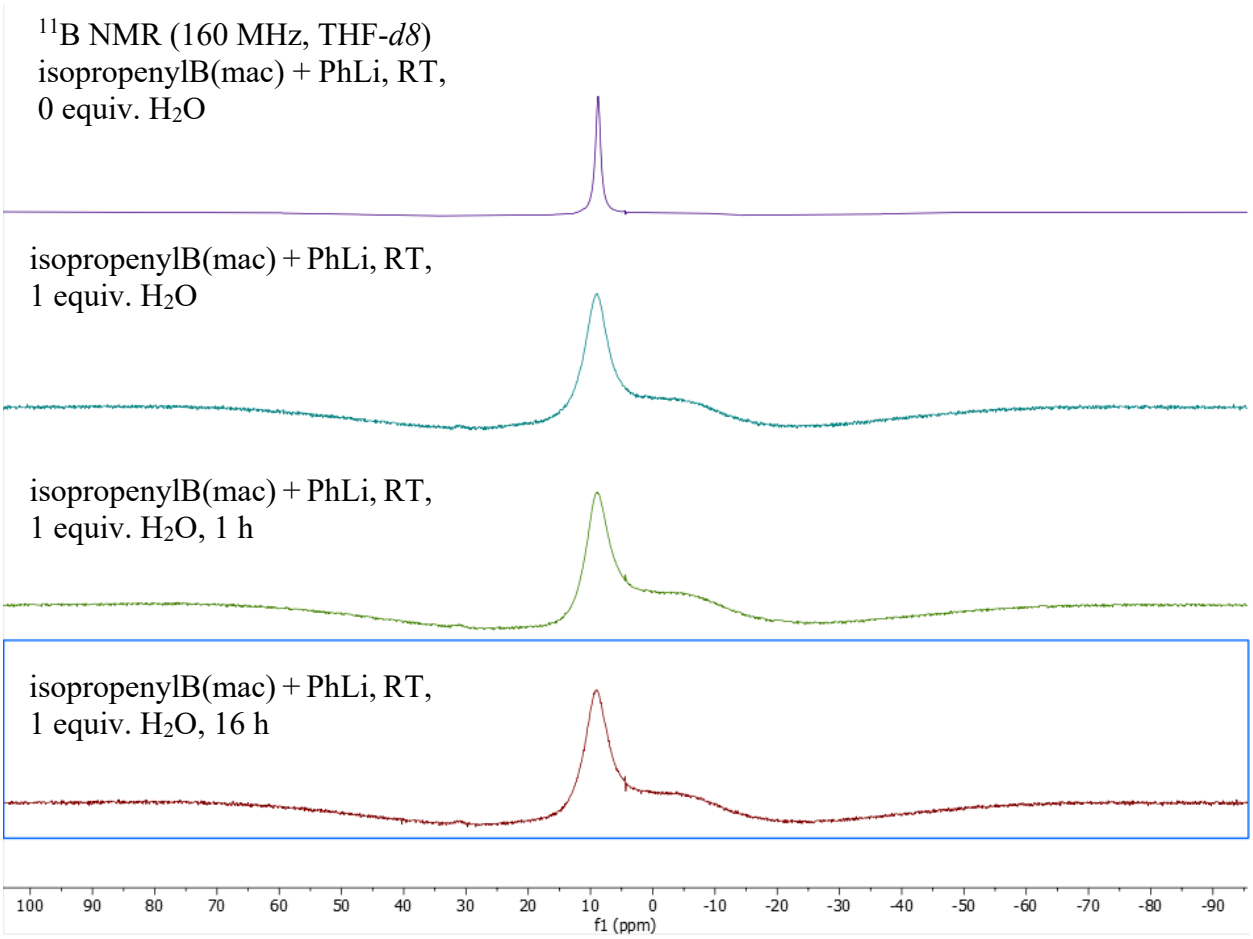
Compound (6bR,9aS)-8-(4,4-diethoxybutyl)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (S-3). The title compound was prepared according to *Method C* with 2,5-dimethylhexa-2,4-diene (0.63 mL, 4.4 mmol, 2.2 equiv.), 1,2-dimethylacenaphthylene-1,2-diol

(428.5 mg, 2 mmol, 1 equiv.), 4,4-diethoxybut-1-ene (0.339 mL, 2 mmol, 1 equiv.), borane dimethylsulfide (0.19 mL, 2 mmol, 1 equiv.), paraformaldehyde (60 mg, 2 mmol, 1 equiv.), and water (0.625 mL, ~35 mmol, ~7 equiv.) in 2 mL THF. The resulting crude was purified by silica gel column chromatography using 10% ethyl acetate:hexanes to isolate the title compound (420 mg, 1.14 mmol, 57% yield) as a white solid. Product Rf = 0.2 in 10% ethylacetate:hexanes (UV active and stains green with *para*-anisaldehyde stain).; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.87 – 7.70 (m, 2H), 7.63 – 7.50 (m, 4H), 4.41 (t, J = 5.7 Hz, 1H), 3.55 (dq, J = 9.5, 7.1 Hz, 2H), 3.40 (dq, J = 9.5, 7.1 Hz, 2H), 1.77 (s, 6H), 1.55 – 1.50 (m, 2H), 1.41 (dt, J = 15.5, 7.6 Hz, 2H), 1.15 (t, J = 7.1 Hz, 6H), 0.75 (t, J = 7.8 Hz, 2H).; ^{13}C NMR (600 MHz, $CDCl_3$) δ 145.0, 134.7, 131.5, 128.7, 128.42, 125.4, 125.2, 119.7, 119.4, 102.9, 102.7, 91.8, 77.4, 77.2, 76.9, 60.9, 60.72, 60.68, 60.51, 36.0, 22.3, 22.2, 19.3, 15.7, 15.5, 15.3, 15.2.; ^{11}B NMR (160 MHz, $CDCl_3$) δ 36.3.; IR (neat): ν_{max}, 2974.12 (m), 2934.96 (m), 2876.52 (m), 1724.83 (s), 1374.35(m), 1117.10 (s), 1078.41 (s). HRMS (DART) for $C_{20}H_{24}BO_3$ $[M\text{-}C_2H_5O^-]^+$: Calc'd 323.18130, found: 323.18212.

2.4.3 NMR Studies

Preparation of Boron "Ate" Complex: ^{11}B Study

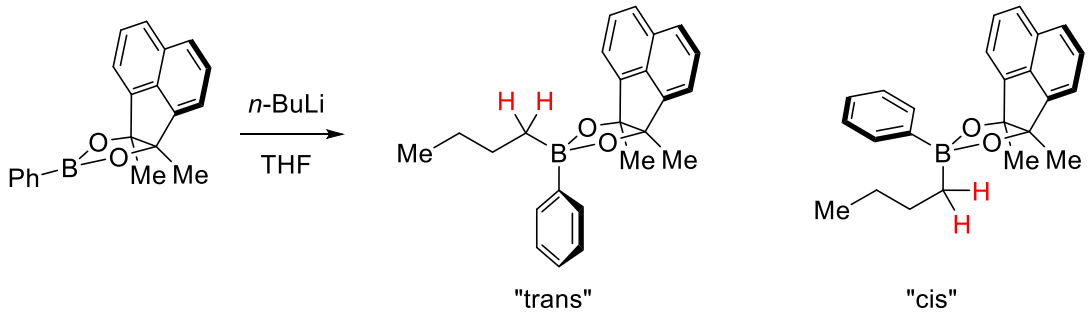
In an argon-filled glovebox, to an oven dried vial and stir bar was added isopropenyl B(mac) (52.8 mg, 0.2 mmol, 1 equiv.) and 4 mL THF. In a separate oven dried vial and stir bar was added bromobenzene (31.4 mg, 0.2 mmol, 1 equiv.) and 1 mL diethyl ether. Out of the glovebox, *tert*-butyllithium (0.235 mL, 1.7 M in pentane, 2 equiv.) was added to the bromobenzene dropwise at -78 ˚C under a nitrogen atmosphere. The reaction was allowed to stir at that temperature for 15 minutes. Lithium halogen exchange solution was added dropwise to the B(mac) solution at 0 ˚C. Upon completion, reaction was allowed to stir for 30 minutes at room temperature. Upon completion, reaction was concentrated to yield a white solid and brought back into the glovebox. "Ate" was dissolved in 5 mL THF-*d8.* Water was added directly to NMR tube just prior to running NMR experiment.

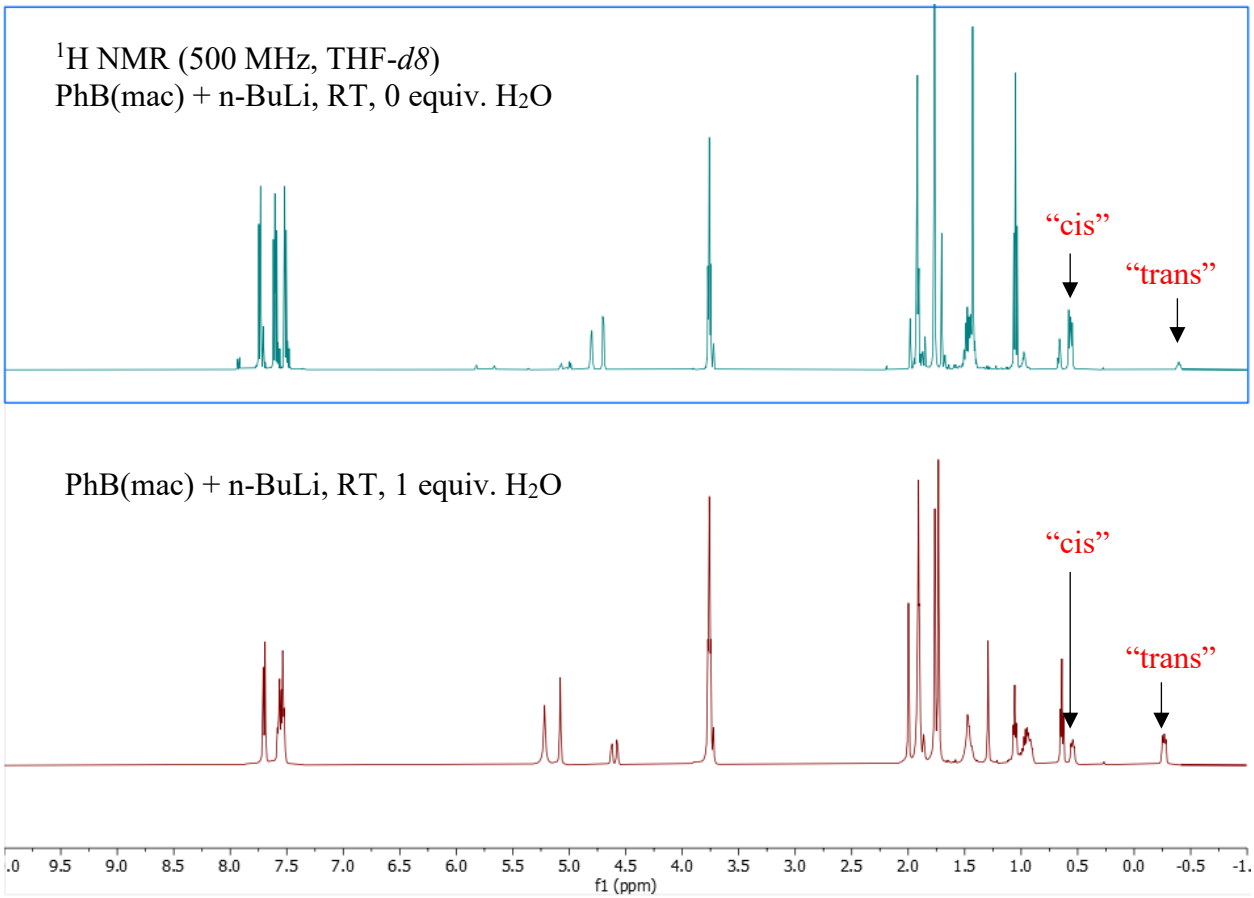


Preparation of Boron "Ate" Complex: ^{1}H Isomerization Study

In an argon-filled glovebox, to an oven dried vial and stir bar was added phenyl B(mac) (60.0 mg, 0.2 mmol, 1 equiv.) and 4 mL THF. Out of the glovebox, commercial *n*-butyllithium (0.125 mL, 1.6 M in hexanes, 1 equiv.) was added dropwise to the B(mac) solution at 0 ˚C. Upon completion, reaction was allowed to stir for 30 minutes at room temperature. Upon completion, reaction was concentrated to yield a white solid and brought back into the glovebox. 'Ate' was dissolved in 5 mL THF-*d8.* Water was added directly to NMR tube just prior to running NMR experiment. Diastereomer determination of the 'ate' complex was performed in a prior study.[136]

[136] Myhill, J. A.; Wilhelmsen, C. A.; Zhang, L.; Morken, J. P. *J. Am. Chem. Soc.* **2018**, *140*, 15181-15185





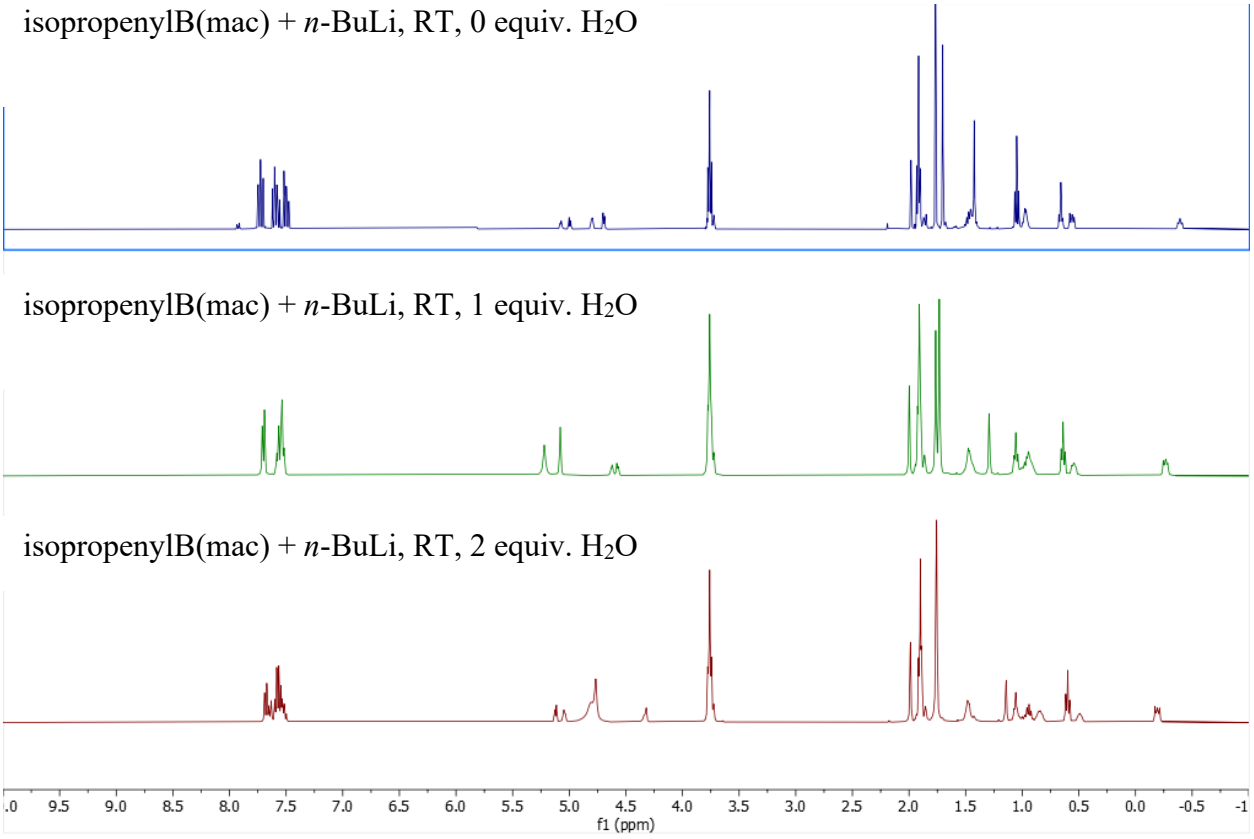
Discussion: Initial 'ate' complex formation yielded a 7.3:1 dr of cis to trans. Upon direct addition of water to the NMR tube and immediate performance of ^{1}H NMR experiment, rapid isomerization yielded a dr of 0.8:1 cis to trans of the resulting 'ate' without assistance of heat or prolonged time.

Preparation of Boron "Ate" Complex: ^{1}H and ^{13}C Study

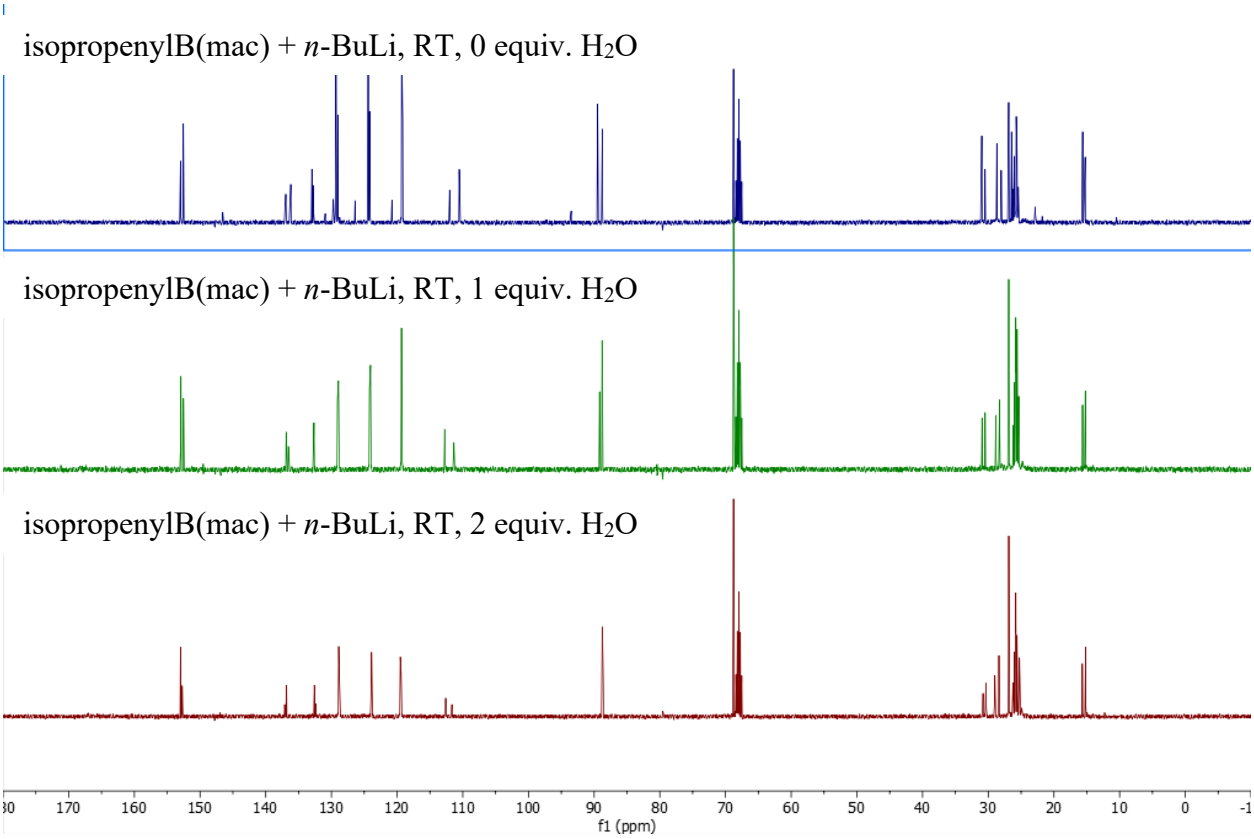
In an argon-filled glovebox, to an oven dried vial and stir bar was added isopropenyl B(mac) (52.8 mg, 0.2 mmol, 1 equiv.) and 4 mL THF. Out of the glovebox, commercial *n*-butyllithium (0.125

mL, 1.6 M in hexanes, 1 equiv.) was added dropwise to the B(mac) solution at 0 ˚C. Upon completion, reaction was allowed to stir for 30 minutes at room temperature. Upon completion, reaction was concentrated to yield a white solid and brought back into the glovebox. 'Ate' was dissolved in 5 mL THF-*d8.* Water was added directly to NMR tube just prior to running NMR experiment.

^{1}H NMR (400 MHz, THF-*d8*)

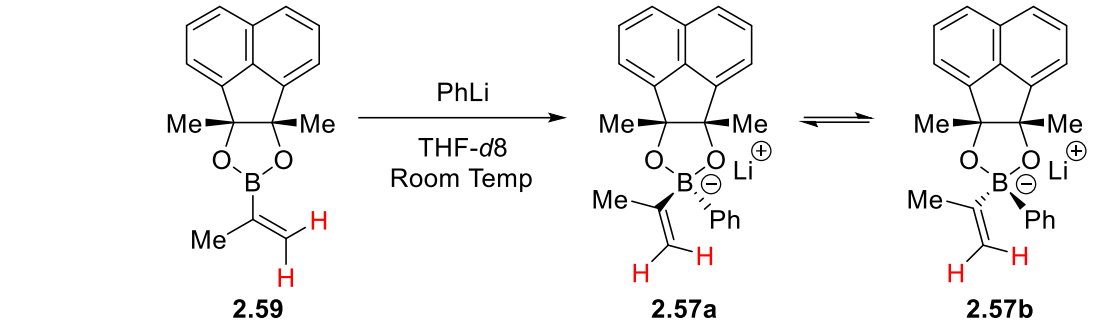


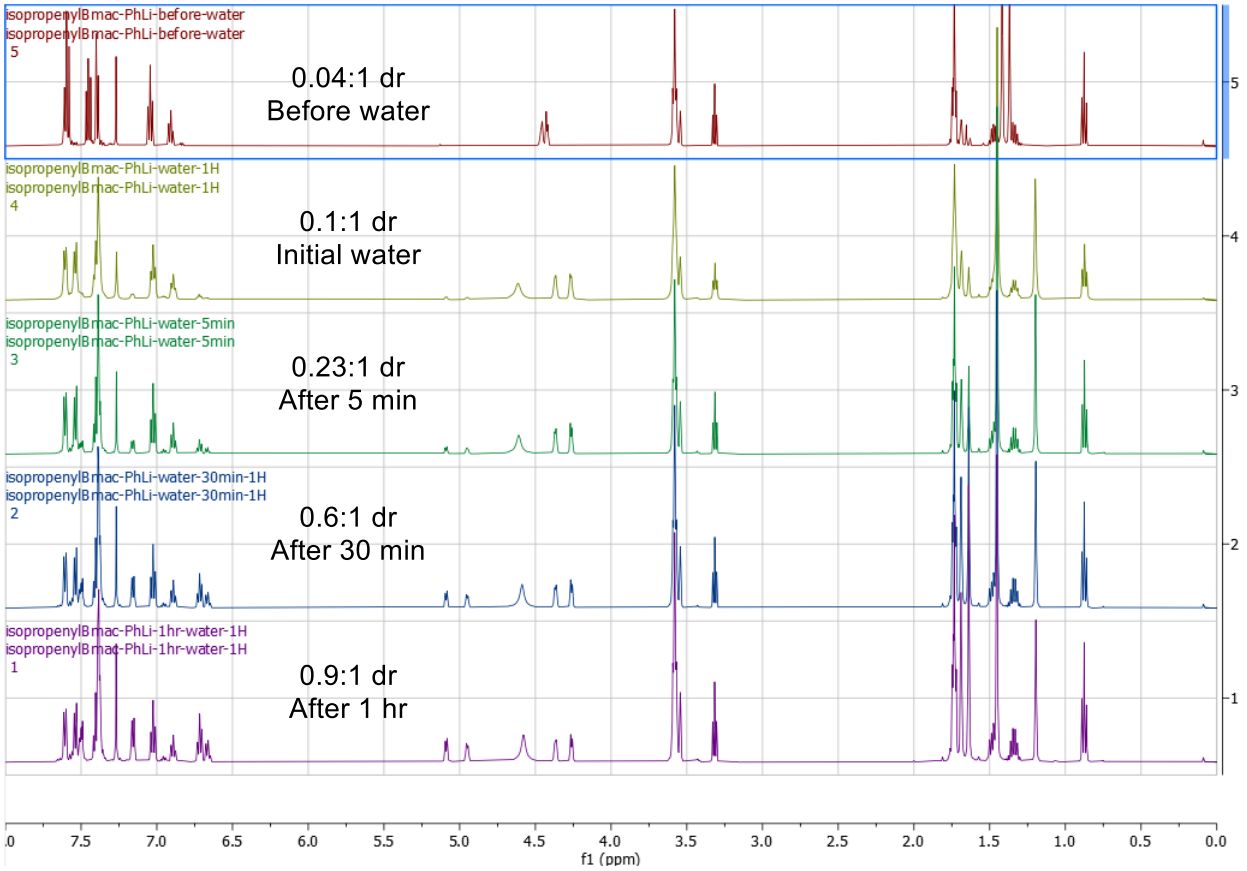
^{13}C NMR (101 MHz, THF-*d8*)



Preparation of Boron "Ate" Complex: ^{1}H Isomerization Study

In an argon-filled glovebox, to an oven dried vial and stir bar was added isopropenyl B(mac) (26.4 mg, 0.1 mmol, 1 equiv.) and 2 mL THF. Out of the glovebox, commercial phenyllithium (0.055 mL, 1.8 M in dibutyl ether, 1 equiv.) was added dropwise to the B(mac) solution at 0 ˚C. Upon completion, reaction was allowed to stir for 30 minutes at room temperature. Upon completion, reaction was concentrated to yield a white solid and brought back into the glovebox. 'Ate' was dissolved in 5 mL THF-*d8.* Water was added directly to NMR tube just prior to running NMR experiment.

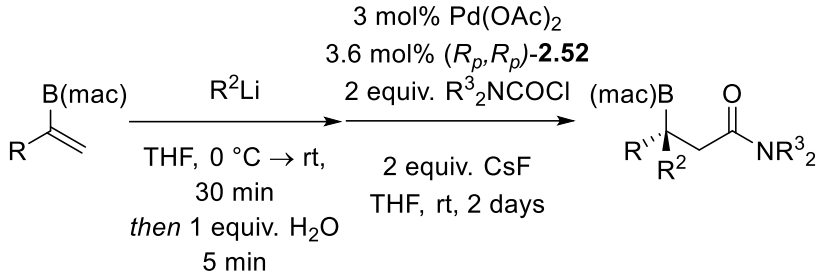




Discussion: Initial 'ate' complex formation yielded a 0.04:1 dr. Upon direct addition of water to the NMR tube and immediate performance of ^{1}H NMR experiment, rapid isomerization yielded a dr of 0.9:1 cis to trans of the resulting 'ate' without assistance of heat or prolonged time within an hour. A second experiment without water, identical dr of the initial "ate" complex was observed and after 36 hours at room temperature, an 0.2:1 dr was observed. No "ate" complex decomposition was observed with either experiment.

2.4.4 General Procedures for Conjunctive Cross Coupling

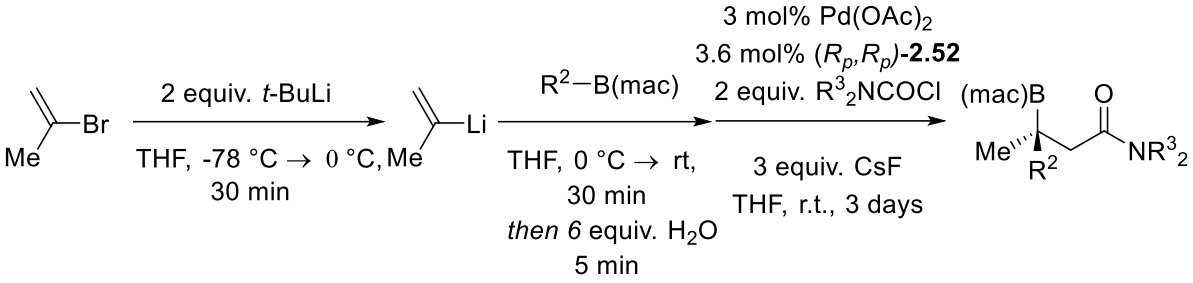
Method A:



To an oven-dried 2-dram vial equipped with a magnetic stir bar in an argon-filled glovebox was added alkenyl boronic acid "mac" ester (0.2 mmol, 1.0 equiv.) and THF (0.4 mL). This vial was sealed with a septum cap, and then removed from the glovebox. The vial was placed under a nitrogen atmosphere and cooled to 0 ˚C using an ice bath. Commercial alkyllithium solution (0.2 mmol, 1.0 equiv.) was added dropwise to the stirring solution often resulting in a color change. Upon completion of addition, reaction was allowed to warm to room temperature and stirred for 30 minutes at that temperature. Then, deionized water (0.2 mmol, 1 equiv.) was added via syringe and allowed to stir for an additional 5 minutes usually resulting a colorless solution. The solvent was carefully removed under reduced pressure to yield a white solid and was brought back into the glovebox. To a separate oven-dried 2-dram vial equipped with a magnetic stir bar in the glovebox was added $Pd(OAc)_2$ (0.006 mmol, 0.03 equiv.), (R_p,R_p)-**2.52** (0.0072 mmol, 0.036 equiv.), and 0.2 mL THF. This palladium solution was allowed to stir for 15 minutes at room temperature. Cesium fluoride (0.4 mmol, 2 equiv.) was added to the white solid "ate" vial, followed by palladium solution, then 0.4 mL THF, and finally carbamoyl chloride (0.4 mmol, 2 equiv.) by mass. The reaction vial was sealed with a polypropylene cap, taped, and brought out of the glovebox. The reaction was stirred at room temperature for 2 days. The resulting mixture was

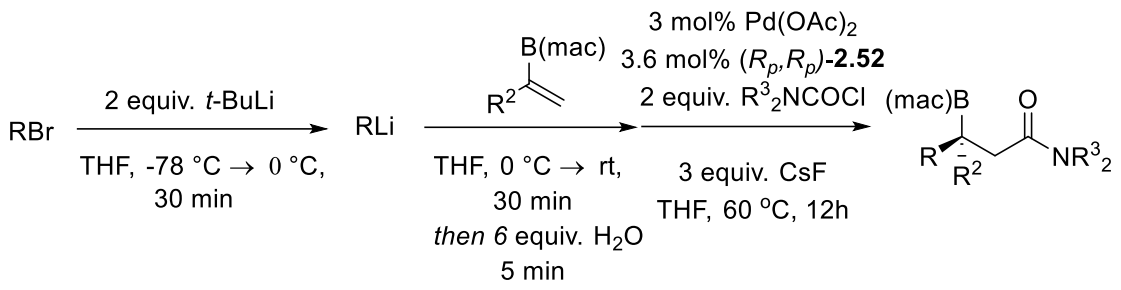
filtered through a silica plug eluted with diethyl ether and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography to afford the desired product.

Method B:



To an oven-dried 2-dram vial equipped with a magnetic stir bar in an argon-filled glovebox was added alkyl boronic acid "mac" ester (0.2 mmol, 1.0 equiv.) and THF (0.4 mL). This vial was sealed with a septum cap, and then removed from the glovebox. The vial was placed under a nitrogen atmosphere and cooled to 0 ˚C using an ice bath. To a separate oven-dried 10 ml round bottom flask equipped with a magnetic stir bar was added isopropenyl bromide (1.0 mmol, 5.0 equiv.) and THF (2.5 ml) under argon. Commercial *tert*-butyllithium solution (2.0 mmol, 2 equiv. to isopropenyl bromide) was added dropwise to the stirring solution under nitrogen at -78 ˚C. Reaction was stirred at this temperature for 30 min then slowly warmed to and kept at 0 ˚C. Concentration of this alkenyllithium solution was titrated by BHT using 1,10-phenathroline as indicator. Suitable amount of this aryllithium solution (0.2 mmol, 1 equiv.) was added into boronic ester solution via syringe at 0 ˚C. The rest of procedure is identical to *Method A*, except for stirring the reaction at room temperature for 3 days.

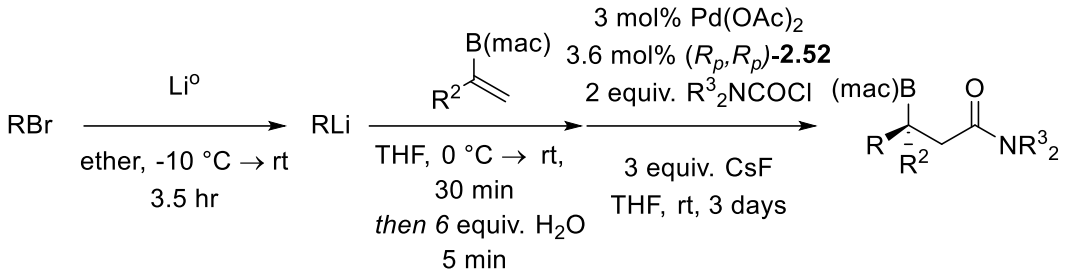
Method C:



To an oven-dried 2-dram vial equipped with a magnetic stir bar in an argon-filled glovebox was added alkenyl boronic acid "mac" ester (0.2 mmol, 1.0 equiv.) and THF (0.4 mL). This vial was sealed with a septum cap, and then removed from the glovebox. The vial was placed under a nitrogen atmosphere and cooled to 0 ˚C using an ice bath. To a separate oven-dried 10 ml round bottom flask equipped with a magnetic stir bar was added aryl bromide (1.0 mmol, 5.0 equiv.) and THF (2.5 ml) under argon. Commercial tert-butyllithium solution (2.0 mmol, 2 equiv. to RBr) was added dropwise to the stirring solution under nitrogen at -78 ˚C. Reaction was stirred at this temperature for 30 min then slowly warmed to and kept at 0 ˚C. Concentration of this aryllithium solution was titrated by BHT using 1,10-phenathroline as indicator. Suitable amount of this aryllithium solution (0.2 mmol, 1 equiv.) was added into boronic ester solution via syringe at 0 ˚C. Reaction was allowed to warm up to room temperature and stirred for 30 min. Then, deionized water (1.2 mmol, 6 equiv.) was added via syringe and allowed to stir for an additional 5 minutes. The solvent was carefully removed under reduced pressure and was brought back into the glovebox. To a separate oven-dried 2-dram vial equipped with a magnetic stir bar in the glovebox was added $Pd(OAc)_2$ (0.006 mmol, 0.03 equiv.), (R_p,R_p)-**2.52** (0.0072 mmol, 0.036 equiv.), and 0.2 mL THF. This palladium solution was allowed to stir for 15 minutes at room temperature. Cesium fluoride (0.6 mmol, 3 equiv.) was added to the "ate" vial, followed by palladium solution, 0.4 mL THF, and finally carbamoyl chloride (0.4 mmol, 2 equiv.). The reaction vial was sealed with a polypropylene cap, taped, and brought out of the glovebox. The reaction was stirred at 60

˚C for 12h. The resulting mixture was filtered through a silica plug eluted with diethyl ether and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography to afford the desired product.

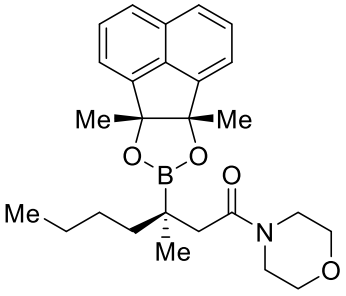
Method D:



To an oven-dry, round bottom flask equipped with a magnetic stirring bar was added freshly prepared lithium slots (277.6 mg, 40 mmol) and diethyl ether (5 mL) in the glovebox. The mixture was cooled in a brine /ice bath and stirred vigorously as solution of pentyl bromide (1.24 mL, 10 mmol) in diethyl ether (5 mL) was added slowly over 120 min using a syringe pump. After the addition, the mixture was allowed to warm to room temperature and stirred for an additional 90 min. Mixture was titrated using L-menthol and using 1,10-phenathroline as indicator. To an oven-dried vial and magnetic stir bar, was added alkenyl boronic acid "mac" ester (0.2 mmol, 1 equiv.) and THF in the glovebox. This vial was sealed with a septum cap, and then removed from the glovebox. The vial was placed under a nitrogen atmosphere and cooled to 0 ˚C using an ice bath. Alkyllithium solution (0.2 mmol, 1.0 equiv.) was added dropwise to the stirring solution often resulting in a color change. Upon completion of addition, reaction was allowed to warm to room temperature and stirred for 30 minutes at that temperature. Then, deionized water (1.2 mmol, 6 equiv.) was added via syringe and allowed to stir for an additional 5 minutes usually resulting a colorless solution. The solvent was carefully removed under reduced pressure to yield a white solid

and was brought back into the glovebox. To a separate oven-dried 2-dram vial equipped with a magnetic stir bar in the glovebox was added $Pd(OAc)_2$ (0.006 mmol, 0.03 equiv.), (R_p,R_p)-**2.52** (0.0072 mmol, 0.036 equiv.), and 0.2 mL THF. This palladium solution was allowed to stir for 15 minutes at room temperature. Cesium fluoride (0.6 mmol, 3 equiv.) was added to the white solid "ate" vial, followed by palladium solution, then 1.0 mL THF, and finally carbamoyl chloride (0.4 mmol, 2 equiv.) by mass. The reaction vial was sealed with a polypropylene cap, taped, and brought out of the glovebox. The reaction was stirred at room temperature for 3 days. The resulting mixture was filtered through a silica plug eluted with diethyl ether and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography to afford the desired product.

2.4.5 Characterization of Conjunctive Cross Coupling Products and Analysis of Stereochemistry



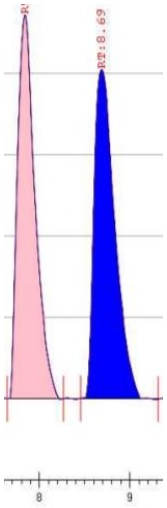
(S)-3-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-3-methyl-1-morpholinoheptan-1-one (2.76). The reaction was performed according to the general procedure *Method A* using isopropenyl B(mac) (**2.59**) (52.8 mg, 0.2 mmol, 1.0 equiv.), *n*-butyllithium (2.5 M in hexanes, 0.08 mL, 0.2 mmol, 1.0 equiv.), 4-morpholinecarbonyl chloride (59.8 mg, 0.4 mmol, 2.0 equiv.), palladium (II) acetate (1.35 mg, 0.006 mmol, 0.03 equiv.), (R_p,R_p)-**2.52** (7.58 mg, 0.0072 mmol, 0.036 equiv.), cesium fluoride (60.8 mg, 0.4 mmol, 2.0 equiv.), and water (3.6 μL, 0.2 mmol, 1 equiv.) in THF (0.6 mL, 0.33 M). The crude mixture was purified by silica gel chromatography (deactivated silica using 2% triethylamine:hexanes, eluted with 10% acetone:hexanes) to afford a white solid (75.5 mg, 86.7% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 – 7.68 (m, 2H), 7.59 – 7.46 (m, 4H), 3.68 – 3.52 (m, 4H), 3.45 – 3.34 (m, 4H), 2.41 (d, *J* = 16.5 Hz, 2H), 2.11 (d, *J* = 16.6 Hz, 2H), 1.76 (d, *J* = 20.4 Hz, 6zH), 1.29 – 1.18 (m, 1H), 1.03 (td, *J* = 12.4, 4.3 Hz, 1H), 0.96 – 0.80 (m, 6H), 0.68 – 0.54 (m, 1H), 0.46 (t, *J* = 7.1 Hz, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.4, 146.8, 146.6, 135.2, 131.3, 128.4, 128.3, 124.6, 124.5, 119.03, 118.99, 90.9, 90.8, 66.9, 66.6, 45.9, 44.9, 42.7, 38.9, 27.5, 23.4, 22.4, 22.2, 22.1, 13.9.; ^{11}B NMR (160 MHz, $CDCl_3$) δ 29.50.; IR (neat): ν_{max} 2958.36 (m), 2924.25 (m), 2854.17 (m), 1631.30 (s), 1115.11 (s), 781.52 (s) cm^{-1}. HRMS (DART) for $C_{26}H_{35}BNO_4$ $[M+H]^+$: Calc'd: 436.26537, found: 436.26719. $[\alpha]^{20}_D$: 0.764 (c = 1.0 g/100 mL, $CHCl_3$, *l* = 50 mm)

Analysis of Stereochemistry:

Racemic compound was prepared according to the procedure described above with $Pd(OAc)_2$ (3 mol%) and BrettPhos (3.6 mol%) as the catalyst. Crude material was used for SFC without purification.

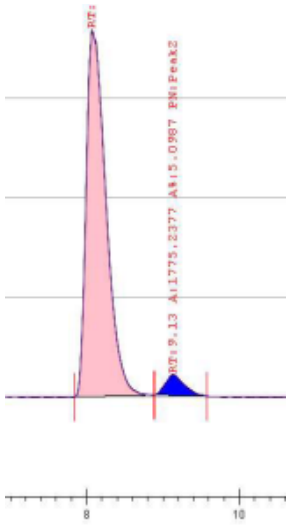
Chiral SFC (AD-H, 2% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of 3-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-3-methyl-1-morpholinoheptan-1-one

Racemic

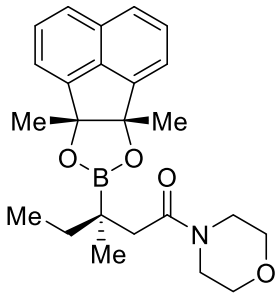


Peak No	% Area	Area	RT (min)
1	49.8614	12781.9478	7.84
2	50.1386	12853.0154	8.69
Total:	100	25634.9632	

Enriched



Peak No	% Area	Area	RT (min)
1	94.9013	33042.3678	8.07
2	5.0987	1775.2377	9.13
Total:	100	34817.6055	



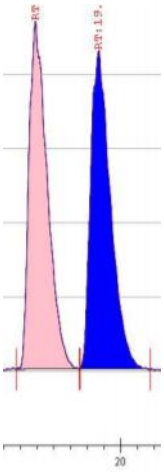
(S)-3-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-3-methyl-1-morpholinopentan-1-one (2.77). The reaction was performed according to the general procedure *Method A* using isopropenyl B(mac) (**2.59**) (52.8 mg, 0.2 mmol, 1.0 equiv.), ethyllithium (0.5 M in benzene, 0.40 mL, 0.2 mmol, 1.0 equiv.), 4-morpholinecarbonyl chloride (59.8 mg, 0.4 mmol, 2.0 equiv.), palladium (II) acetate (1.35 mg, 0.006 mmol, 0.03 equiv.), (R_p,R_p)- **2.52** (7.58 mg, 0.0072 mmol, 0.036 equiv.), cesium fluoride (60.8 mg, 0.4 mmol, 2.0 equiv.), and water (3.6 μL, 0.2 mmol, 1 equiv.) in THF (0.6 mL, 0.33 M). The crude mixture was purified by silica gel chromatography eluted with 20% ethyl acetate:hexanes to isolate the title compound (51.1 mg, 0.125 mmol, 63% yield) as a white solid. Product Rf = 0.4 in 40% ethyl acetate: hexanes (UV active and stains blue with *para*-anisaldehyde stain). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 – 7.68 (m, 2H), 7.59 – 7.48 (m, 4H), 3.67 – 3.50 (m, 4H), 3.43 – 3.32 (m, 4H), 2.40 (d, *J* = 16.5 Hz, 1H), 2.12 (d, *J* = 16.5 Hz, 1H), 1.77 (s, 3H), 1.74 (s, 3H), 1.35 – 1.25 (m, 1H), 1.17 – 1.06 (m, 1H), 0.84 (s, 3H), 0.50 (t, *J* = 7.5 Hz, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.3, 146.8, 146.6, 135.2, 131.3, 128.4, 128.3, 124.6, 124.5, 119.0, 90.9, 90.8, 66.9, 66.6, 45.9, 44.4, 42.6, 31.4, 22.4, 22.1, 21.6, 9.5.; ^{11}B NMR (160 MHz, $CDCl_3$) δ 29.57.; IR (neat): ν_{max} 3038.45 (w), 2963.49 (m), 2920.65 (m), 2855.46 (m), 1630.97 (s), 1458.89 (m), 1115.31 (s), 781.21 (m) cm^{-1}. HRMS (DART) for $C_{24}H_{31}BNO_4$ $[M+H]^+$: Calc'd: 408.23407, found: 408.23393. $[\alpha]^{20}_D$: -1.158 (c = 1.0 g/100 mL, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

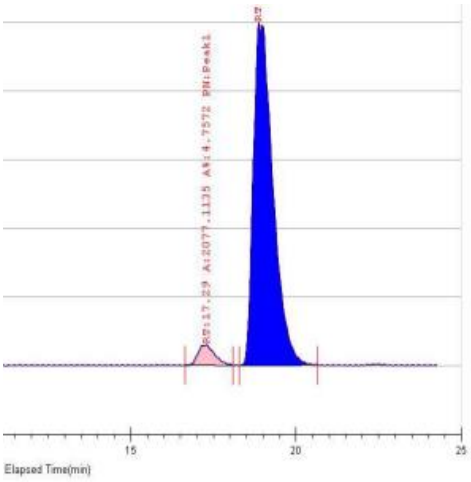
Racemic compound was prepared according to the procedure described above with $Pd(OAc)_2$ (3 mol%) and BrettPhos (3.6 mol%) as the catalyst. Crude material was used for SFC without purification.

Chiral SFC (AD-H, 3% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of 3-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-3-methyl-1-morpholinopentan-1-one

Racemic

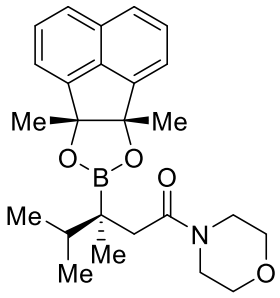


Enriched



Peak No	% Area	Area	RT (min)
1	50.2044	35423.6397	17.45
2	49.7956	35135.2579	19.35
Total:	100	70558.8976	

Peak No	% Area	Area	RT (min)
1	4.7572	2077.1135	17.29
2	95.2428	41585.0067	18.86
Total:	100	43662.1202	



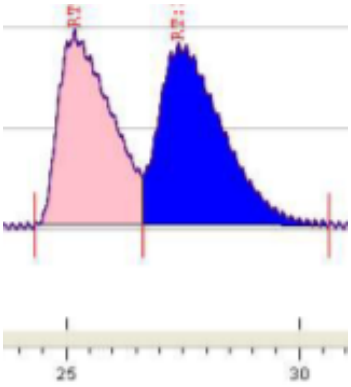
(S)-3-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-3,4-dimethyl-1-morpholinopentan-1-one (2.78). The reaction was performed according to the general procedure *Method A* using isopropenyl B(mac) (**2.59**) (52.8 mg, 0.2 mmol, 1.0 equiv.), isopropyllithium (0.7 M in pentane, 0.285 mL, 0.2 mmol, 1.0 equiv.), 4-morpholinecarbonyl chloride (59.8 mg, 0.4 mmol, 2.0 equiv.), palladium (II) acetate (1.35 mg, 0.006 mmol, 0.03 equiv.), (R_p,R_p)- **2.52** (7.58 mg, 0.0072 mmol, 0.036 equiv.), cesium fluoride (60.8 mg, 0.4 mmol, 2.0 equiv.), and water (3.6 μL, 0.2 mmol, 1 equiv.) in THF (0.6 mL, 0.33 M). The crude mixture was purified by silica gel chromatography (deactivated silica using 2% triethylamine:hexanes, eluted with 10% acetone:hexanes) to isolate the title compound (44.9 mg, 0.106 mmol, 53% yield) as a white solid. Product Rf = 0.5 in 3% triethylamine: 30% acetone: 67% hexanes (UV active and stains blue with *para*-anisaldehyde stain).; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70 (t, *J* = 8.5 Hz, 2H), 7.58 – 7.47 (m, 4H), 3.74 – 3.52 (m, 3H), 3.51 – 3.45 (m, 1H), 3.40 – 3.34 (m, 2H), 3.33 – 3.22 (m, 2H), 2.41 (d, *J* = 16.5 Hz, 1H), 2.14 (d, *J* = 16.5 Hz, 1H), 1.77 (s, 3H), 1.73 (s, 3H), 1.61 (hept, *J* = 7.0 Hz, 1H), 0.77 (s, 3H), 0.63 (d, *J* = 6.9 Hz, 3H), 0.44 (d, *J* = 6.7 Hz, 3H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.9, 147.3, 146.8, 135.3, 131.2, 128.4, 128.2, 124.5, 124.3, 118.93, 118.88, 90.6, 90.5, 66.8, 66.5, 45.9, 44.0, 42.7, 33.8, 22.6, 22.2, 19.1, 17.3, 16.2.; ^{11}B NMR (160 MHz, $CDCl_3$) δ 29.16. IR (neat): ν_{max} 3041.66 (w), 2957.17 (m), 2924.93 (m), 1610.73 (s), 1114.45 (s), 751.42 (m) cm^{-1}. HRMS (DART) for $C_{25}H_{33}BNO_4$ $[M+H]^+$: Calc'd: 422.24972, found: 422.24937. $[\alpha]^{20}_D$: -1.109 (c = 1.0 g/100 mL, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

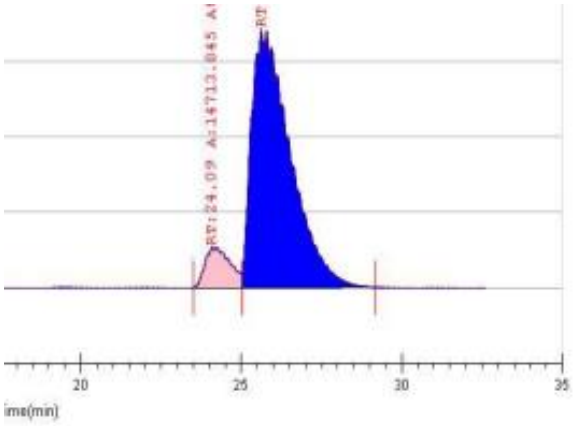
Racemic compound was prepared according to the procedure described above with $Pd(OAc)_2$ (3 mol%) and BrettPhos (3.6 mol%) as the catalyst. Crude material was used for SFC without purification.

Chiral SFC (AD-H, 3% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of ***3-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-3,4-dimethyl-1-morpholinopentan-1-one***

Racemic

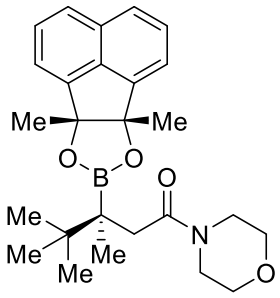


Enriched



Peak No	% Area	Area	RT (min)
1	46.7015	7435.5062	25.18
2	53.2985	8485.8432	27.4
Total:	100	15921.3494	

Peak No	% Area	Area	RT (min)
1	9.2566	14713.845	24.09
2	90.7434	144242.1529	25.62
Total:	100	158955.9979	



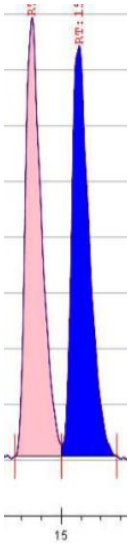
(S)-3-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-3,4,4-trimethyl-1-morpholinopentan-1-one (2.79). The reaction was performed according to the general procedure *Method A* at 40 °C using isopropenyl B(mac) (**2.59**) (52.8 mg, 0.2 mmol, 1.0 equiv.), *tert*-butyllithium (1.7 M in pentane, 0.117 mL, 0.2 mmol, 1.0 equiv.), 4-morpholinecarbonyl chloride (59.8 mg, 0.4 mmol, 2.0 equiv.), palladium (II) acetate (1.35 mg, 0.006 mmol, 0.03 equiv.), (R_p,R_p)- **2.52** (7.58 mg, 0.0072 mmol, 0.036 equiv.), cesium fluoride (60.8 mg, 0.4 mmol, 2.0 equiv.), and water (3.6 µL, 0.2 mmol, 1 equiv.) in THF (0.6 mL, 0.33 M). The crude mixture was purified by silica gel chromatography (deactivated silica using 2% triethylamine:hexanes, eluted with 10% acetone:hexanes) to isolate the title compound (51.2 mg, 0.118 mmol, 59% yield) as a white solid. Product Rf = 0.5 in 3% triethylamine: 30% acetone: 67% hexanes (UV active and stains blue with *para*-anisaldehyde stain).; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 (t, J = 7.2 Hz, 2H), 7.61 – 7.46 (m, 4H), 3.72 – 3.54 (m, 4H), 3.51 – 3.32 (m, 4H), 2.64 (d, J = 16.2 Hz, 1H), 2.03 (d, J = 16.2 Hz, 1H), 1.80 (s, 3H), 1.73 (s, 3H), 0.91 (3, 2H), 0.61 (s, 9H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.3, 146.7, 146.4, 135.1, 131.2, 128.3, 128.3, 124.6, 124.5, 119.1, 119.0, 91.1, 90.8, 67.0, 66.6, 45.8, 42.4, 39.4, 33.9, 26.9, 22.3, 22.0, 19.0.; ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.87.; IR (neat): ν_{max} 3039.63 (w), 2964.30 (m), 2856.85 (m), 1632.87 (s), 1433.38 (m), 1214.53 (m), 1115.72 (s), 782.20 (m) cm^{-1}. HRMS (DART) for $C_{26}H_{35}BNO_4$ $[M+H]^+$: Calc'd: 436.26537, found: 436.26514. $[\alpha]^{20}_D$: -14.961 (c = 1.0 g/100 mL, $CHCl_3$, l = 50 mm).

Analysis of Stereochemistry:

Racemic compound was prepared according to the procedure described above with $Pd(OAc)_2$ (3 mol%) and BrettPhos (3.6 mol%) as the catalyst. Crude material was used for SFC without purification.

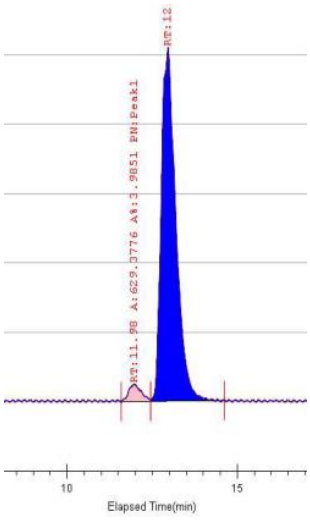
Chiral SFC (AD-H, 3% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of ***3-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-3,4,4-trimethyl-1-morpholinopentan-1-one***

Racemic

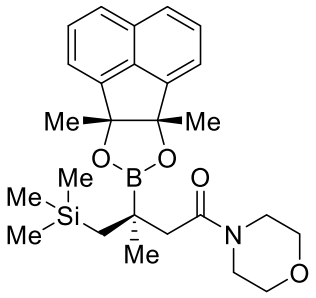


Peak No	% Area	Area	RT (min)
1	49.6785	22549.8309	14.26
2	50.3215	22841.6879	15.46
Total:	100	45391.5188	

Enriched



Peak No	% Area	Area	RT (min)
1	3.9851	629.3776	11.98
2	96.0149	15163.6949	12.96
Total:	100	15793.0725	



(S)-3-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-3-methyl-1-morpholino-4-(trimethylsilyl)butan-1-one (2.80). The reaction was performed according to the general procedure *Method A* using isopropenyl B(mac) (**2.59**) (52.8 mg, 0.2 mmol, 1.0 equiv.), $TMSCH_2Li$ (1.0 M in pentane, 0.2 mL, 0.2 mmol, 1.0 equiv.), 4-morpholinecarbonyl chloride (59.8 mg, 0.4 mmol, 2.0 equiv.), palladium (II) acetate (1.35 mg, 0.006 mmol, 0.03 equiv.), (R_p,R_p)- **2.52** (7.58 mg, 0.0072 mmol, 0.036 equiv.), cesium fluoride (60.8 mg, 0.4 mmol, 2.0 equiv.), and water (3.6 μL, 0.2 mmol, 1 equiv.) in THF (0.6 mL, 0.33 M). The crude mixture was purified by silica gel chromatography (deactivated silica using 2% triethylamine:hexanes, eluted with 10% acetone:hexanes) to afford a white solid (45.4 mg, 48.8% yield). Product Rf = 0.7 in 2% triethylamine:38% acetone:60% hexanes (stains blue with *para*-anisaldehyde stain and UV active).; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 (dd, *J* = 8.0, 4.5 Hz, 2H), 7.58 – 7.49 (m, 4H), 3.67 – 3.51 (m, 4H), 3.43 – 3.34 (m, 4H), 2.46 (d, *J* = 16.3 Hz, 1H), 2.21 (d, *J* = 16.3 Hz, 1H), 1.80 (s, 3H), 1.74 (s, 3H), 0.93 (s, 3H), 0.67 (d, *J* = 14.5 Hz, 1H), 0.49 (d, *J* = 14.5 Hz, 1H), -0.35 (s, 9H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.5, 146.32, 146.29, 135.5, 131.3, 128.34, 128.28, 124.7, 124.6, 119.2, 119.1, 91.30, 91.25, 67.0, 66.7, 48.2, 45.9, 42.3, 27.8, 24.9, 22.3, 22.2, 0.4.; ^{11}B NMR (160 MHz, $CDCl_3$) δ 32.11. IR (neat): ν_{max} 3043.43 (w), 2965.72 (m), 2913.22 (m), 2852.48 (m), 1624.02 (s), 1115.38 (s), 834.20 (s) cm^{-1}. HRMS (DART) for $C_{26}H_{36}BNO_4Si$ $[M+H]^+$: Calc'd: 466.25794 , found: 466.25735. $[\alpha]^{20}_D$: -0.350 (c = 1.0 g/100 mL, $CHCl_3$, *l* = 50 mm)

Analysis of Stereochemistry:

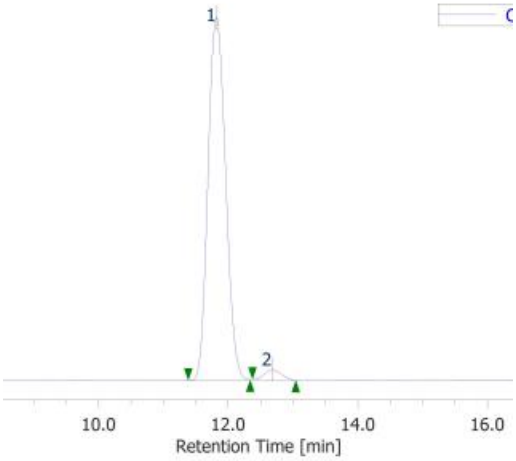
Racemic compound was prepared according to the procedure described above with $Pd(OAc)_2$ (3 mol%) and BrettPhos (3.6 mol%) as the catalyst. Crude material was used for SFC without purification.

Chiral SFC (AD-H, 10% IPA, 1 mL/min, 100 bar, 35 °C, 210-270 nm) - 3-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-3-methyl-1-morpholino-4-(trimethylsilyl)butan-1-one

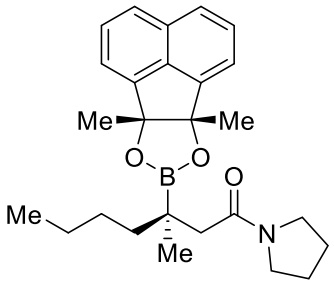
Racemic

tR [min]	Area [μV·sec]	Height [μV]	Area%
12.053	925972	52546	51.837
12.910	860338	47421	48.163

Enriched



tR [min]	Area [μV·sec]	Height [μV]	Area%
11.817	20166942	1072189	97.361
12.677	546667	29978	2.639



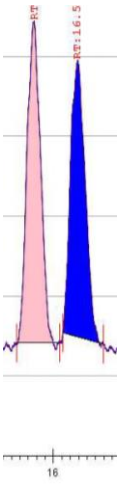
(S)-3-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-3-methyl-1-(pyrrolidin-1-yl)heptan-1-one (2.81). The reaction was performed according to the general procedure *Method A* using isopropenyl B(mac) (**2.59**) (52.8 mg, 0.2 mmol, 1.0 equiv.), *n*-butyllithium (2.5 M in hexanes, 0.08 mL, 0.2 mmol, 1.0 equiv.), 1-pyrrolidinecarbonyl chloride (53.4 mg, 0.4 mmol, 2 equiv.), palladium (II) acetate (1.35 mg, 0.006 mmol, 0.03 equiv.), (R_p,R_p)- **2.52** (7.58 mg, 0.0072 mmol, 0.036 equiv.), cesium fluoride (60.8 mg, 0.4 mmol, 2.0 equiv.), and water (3.6 μL, 0.2 mmol, 1 equiv.) in THF (0.6 mL, 0.33 M). The crude mixture was purified by silica gel chromatography (deactivated silica using 2% triethylamine:hexanes, eluted with 10% acetone:hexanes) to isolate the title compound (70.3 mg, 0.167 mmol, 83.8% yield) as a white solid. Product Rf = 0.45 in 3% triethylamine: 30% acetone: 67% hexanes (UV active and stains blue with *para*-anisaldehyde stain).; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 7.5, 1.3 Hz, 2H), 7.58 – 7.47 (m, 4H), 3.45 – 3.21 (m, 4H), 2.41 (d, *J* = 16.8 Hz, 1H), 2.05 (d, *J* = 16.8 Hz, 1H), 1.89 (pd, *J* = 7.0, 6.6, 5.1 Hz, 2H), 1.85 – 1.71 (m, 8H), 1.16 (ddd, *J* = 12.9, 11.3, 4.3 Hz, 1H), 1.00 (td, *J* = 12.5, 4.1 Hz, 1H), 0.93 – 0.73 (m, 6H), 0.63 – 0.52 (m, 1H), 0.44 (t, *J* = 7.0 Hz, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.3, 147.5, 147.27, 147.26, 135.2, 131.3, 128.23, 128.22, 124.3, 124.2, 118.9, 118.8, 90.4, 90.3, 46.9, 46.6, 46.2, 38.7, 27.5, 25.8, 24.5, 23.4, 22.7, 22.4, 22.3, 13.9.; ^{11}B NMR (160 MHz, $CDCl_3$) δ 26.41.; IR (neat): ν_{max} 3037.54 (w), 2951.87 (m), 2924.79 (m), 2868.52 (m), 1619.44 (s), 1447.82 (m), 1115.92 (s), 1080.74 (m), 780.53 (m) cm^{-1}. HRMS (DART) for $C_{26}H_{35}BNO_3$ $[M+H]^+$: Calc'd: 420.27045, found: 420.27052. $[\alpha]^{20}_D$: 1.750 (c = 1.0 g/100 mL, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Racemic compound was prepared according to the procedure described above with $Pd(OAc)_2$ (3 mol%) and BrettPhos (3.6 mol%) as the catalyst. Crude material was used for SFC without purification.

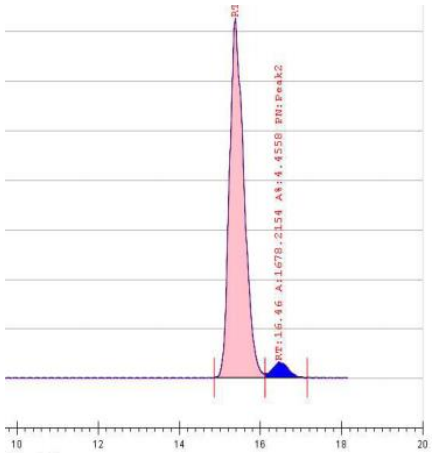
Chiral SFC (ODR-H, 5% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of 3-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-3-methyl-1-(pyrrolidin-1-yl)heptan-1-one

Racemic

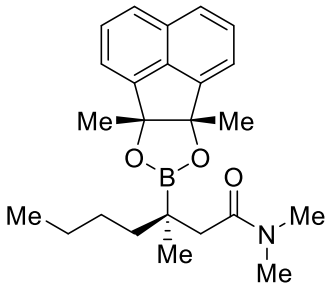


Peak No	% Area	Area	RT (min)
1	51.751	4461.181	15.54
2	48.249	4159.2896	16.57
Total:	100	8620.4706	

Enriched



Peak No	% Area	Area	RT (min)
1	95.5442	35985.6187	15.38
2	4.4558	1678.2154	16.46
Total:	100	37663.8341	



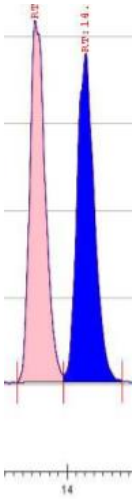
(S)-3-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-N,N,3-trimethylheptanamide (2.82). The reaction was performed according to the general procedure *Method A* using isopropenyl B(mac) (**2.59**) (52.8 mg, 0.2 mmol, 1.0 equiv.), *n*-butyllithium (2.5 M in hexanes, 0.08 mL, 0.2 mmol, 1.0 equiv.), dimethylcarbamoyl chloride (43.0 mg, 0.4 mmol, 2 equiv.), palladium (II) acetate (1.35 mg, 0.006 mmol, 0.03 equiv.), (R_p,R_p)- **2.52** (7.58 mg, 0.0072 mmol, 0.036 equiv.), cesium fluoride (60.8 mg, 0.4 mmol, 2.0 equiv.), and water (3.6 µL, 0.2 mmol, 1 equiv.) in THF (0.6 mL, 0.33 M). The crude mixture was purified by silica gel chromatography (deactivated silica using 2% triethylamine:hexanes, eluted with 10% acetone:hexanes) to isolate the title compound (66.4 mg, 0.168 mmol, 84% yield) as a white solid. Product Rf = 0.5 in 3% triethylamine: 30% acetone: 67% hexanes (UV active and stains blue with *para*-anisaldehyde stain).; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 – 7.62 (m, 2H), 7.57 – 7.46 (m, 4H), 2.91 (s, 3H), 2.79 (s, 3H), 2.41 (d, *J* = 16.8 Hz, 1H), 2.13 (d, *J* = 16.9 Hz, 1H), 1.77 (s, 3H), 1.73 (s, 3H), 1.19 (td, *J* = 12.1, 4.4 Hz, 1H), 1.02 (td, *J* = 12.5, 4.0 Hz, 1H), 0.96 – 0.75 (m, 6H), 0.61 (qq, *J* = 10.3, 5.8, 3.3 Hz, 1H), 0.47 (t, *J* = 7.0 Hz, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.2, 147.6, 147.3, 135.2, 131.3, 128.3, 128.2, 124.3, 124.2, 118.9, 118.8, 90.3, 90.2, 45.5, 38.7, 37.3, 36.0, 27.5, 23.5, 22.7, 22.5, 13.9.; ^{11}B NMR (160 MHz, $CDCl_3$) δ 26.12.; IR (neat): ν_{max} 3039.72 (w), 2951.95 (m), 2924.44 (m), 1628.73 (s), 1115.27 (s), 1080.98 (m), 780.72 (m) cm^{-1}. HRMS (DART) for $C_{24}H_{33}BNO_3$ $[M+H]^+$: Calc'd: 394.25480, found: 394.25579. $[\alpha]^{20}_D$: 0.789 (c = 1.0 g/100 mL, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

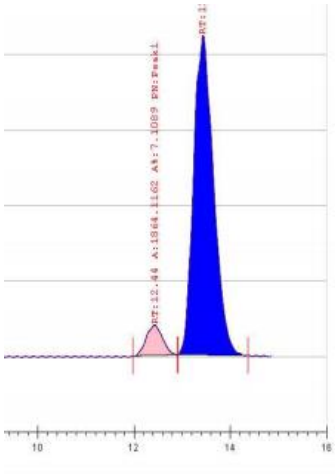
Racemic compound was prepared according to the procedure described above with $Pd(OAc)_2$ (3 mol%) and BrettPhos (3.6 mol%) as the catalyst. Crude material was used for SFC without purification.

Chiral SFC (OJ-H, 2% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of ***3-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-N,N,3-trimethylheptanamide***

Racemic

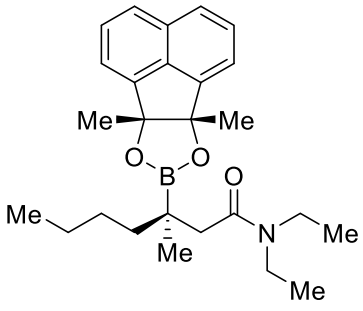


Enriched



Peak No	% Area	Area	RT (min)
1	49.8769	20381.4443	13.27
2	50.1231	20482.0161	14.42
Total:	100	40863.4604	

Peak No	% Area	Area	RT (min)
1	7.1089	1864.1162	12.44
2	92.8911	24358.1538	13.43
Total:	100	26222.27	



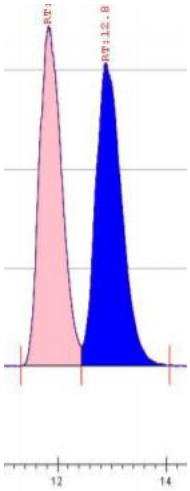
(S)-3-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-N,N-diethyl-3-methylheptanamide (2.71). The reaction was performed according to the general procedure *Method A* using isopropenyl B(mac) (**2.59**) (52.8 mg, 0.2 mmol, 1.0 equiv.), *n*-butyllithium (2.5 M in pentane, 0.080 mL, 0.2 mmol, 1.0 equiv.), diethylcarbamoyl chloride (54.2 mg, 0.4 mmol, 2.0 equiv.), palladium (II) acetate (1.35 mg, 0.006 mmol, 0.03 equiv.), (R_p,R_p)- **2.52** (7.58 mg, 0.0072 mmol, 0.036 equiv.), cesium fluoride (60.8 mg, 0.4 mmol, 2.0 equiv.), and water (3.6 µL, 0.2 mmol, 1 equiv.) in THF (0.6 mL, 0.33 M). The crude mixture was purified by silica gel chromatography (deactivated silica using 2% triethylamine:hexanes, eluted with 10% acetone:hexanes) to isolate the title compound (69.6 mg, 0.165 mmol, 83% yield) as a white solid. Product Rf = 0.7 in 3% triethylamine: 30% acetone: 67% hexanes (UV active and stains blue with *para*-anisaldehyde stain).; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71 – 7.64 (m, 2H), 7.54 – 7.46 (m, 4H), 3.27 – 3.19 (m, 2H), 3.18 – 3.10 (m, 1H), 3.01 – 2.92 (m, 1H), 2.41 (d, *J* = 16.7 Hz, 1H), 2.10 (d, *J* = 16.7 Hz, 1H), 1.74 (s, 3H), 1.72 (s, 3H), 1.32 – 1.19 (m, 1H), 1.10 (t, *J* = 7.2, 1.4 Hz, 3H), 1.08 – 1.02 (m, 1H), 1.00 – 0.87 (m, 3H), 0.85 (t, *J* = 7.2 Hz, 3H), 0.79 (s, 3H), 0.78 – 0.71 (m, 1H), 0.55 (t, *J* = 7.0 Hz, 3H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 176.6, 148.3, 148.0, 135.3, 131.2, 128.22, 128.16, 123.96, 123.93, 118.7, 89.7, 89.7, 45.4, 42.6, 41.6, 38.4, 27.6, 23.6, 23.0, 22.8, 22.5, 14.0, 13.8, 12.6.; ^{11}B NMR (160 MHz, $CDCl_3$) δ 22.65. IR (neat): ν_{max} 3038.37 (w), 2962.00 (m), 2926.54 (m), 1612.60 (s), 1459.92 (m), 1116.46 (s), 780.66 (m) cm^{-1}. HRMS (DART) for $C_{26}H_{37}BNO_3$ $[M+H]^+$: Calc'd: 422.28610, found: 422.28726. $[\alpha]^{20}_D$: -17.896 (c = 1.0 g/100 mL, $CHCl_3$, *l* = 50 mm)

Analysis of Stereochemistry:

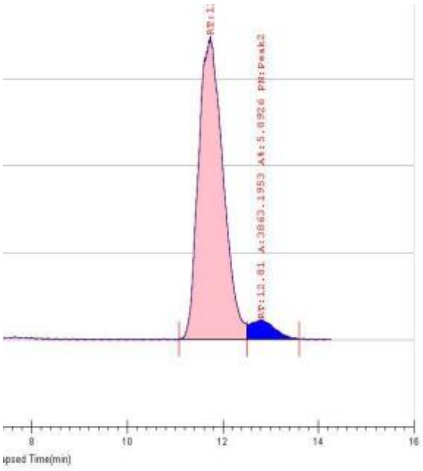
Racemic compound was prepared according to the procedure described above with $Pd(OAc)_2$ (3 mol%) and BrettPhos (3.6 mol%) as the catalyst. Crude material was used for SFC without purification.

Chiral SFC (AD-H, 3% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of ***3-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-N,N-diethyl-3-methylheptanamide***

Racemic

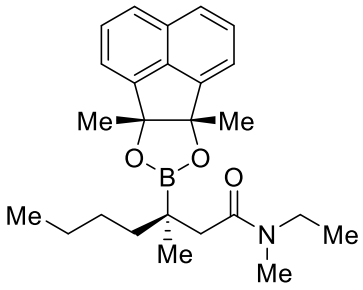


Enriched



Peak No	% Area	Area	RT (min)
1	49.1834	49469.1302	11.83
2	50.8166	51111.8831	12.89
Total:	100	100581.0133	

Peak No	% Area	Area	RT (min)
1	94.1074	61697.0746	11.74
2	5.8926	3863.1953	12.81
Total:	100	65560.2699	



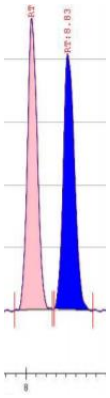
(S)-3-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-N-ethyl-N,3-dimethylheptanamide (2.83). The reaction was performed according to the general procedure *Method A* using isopropenyl B(mac) (**2.59**) (52.8 mg, 0.2 mmol, 1.0 equiv.), *n*-butyllithium (2.5 M in pentane, 0.080 mL, 0.2 mmol, 1.0 equiv.), methylethylcarbamoyl chloride (48.6 mg, 0.4 mmol, 2.0 equiv.), palladium (II) acetate (1.35 mg, 0.006 mmol, 0.03 equiv.), (R_p,R_p)- **2.52** (7.58 mg, 0.0072 mmol, 0.036 equiv.), cesium fluoride (60.8 mg, 0.4 mmol, 2.0 equiv.), and water (3.6 μL, 0.2 mmol, 1 equiv.) in THF (0.6 mL, 0.33 M). The crude mixture was purified by silica gel chromatography (deactivated silica using 2% triethylamine:hexanes, eluted with 10% acetone:hexanes) to isolate the title compound (72.0 mg, 0.177 mmol, 88% yield) as a white solid. Product Rf = 0.45 in 3% triethylamine: 30% acetone: 67% hexanes (UV active and stains blue with *para*-anisaldehyde stain).; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 – 7.65 (m, 2H), 7.57 – 7.47 (m, 4H), 3.28 (tq, J = 13.9, 7.2 Hz, 1H), 3.22 – 3.04 (m, 1H), 2.81 (d, J = 57.0 Hz, 3H), 2.41 (dd, J = 19.7, 16.8 Hz, 1H), 2.11 (t, J = 16.9 Hz, 1H), 1.75 (d, J = 1.8 Hz, 3H), 1.72 (d, J = 3.8 Hz, 3H), 1.32 – 1.15 (m, 1H), 1.11 (t, J = 7.2 Hz, 1.5H), 1.08 – 0.98 (m, 1H), 0.97 – 0.83 (m, 4.5H), 0.79 (d, J = 13.2 Hz, 3H), 0.74 – 0.60 (m, 1H), 0.55 – 0.46 (m, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.4, 147.9, 147.9, 147.61, 147.60, 135.28, 135.25, 131.3, 128.23, 128.19, 124.15, 124.13, 124.08, 118.77, 118.74, 118.73, 90.02, 89.98, 45.9, 45.1, 44.8, 43.6, 38.6, 38.6, 34.8, 33.4, 27.54, 27.51, 23.51, 23.50, 22.8, 22.6, 22.5, 22.4, 13.97, 13.96, 13.2, 12.0.; ^{11}B NMR (160 MHz, $CDCl_3$) δ 24.51.; IR (neat): ν_{max} 3034.49 (w), 2958.52 (m), 2926.22 (m), 1622.61 (s), 1116.41 (s), 1082.17 (m), 780.557 (m) cm^{-1}. HRMS (DART) for $C_{25}H_{35}BNO_3$ $[M+H]^+$: Calc'd: 408.27045, found: 408.27120. $[\alpha]^{20}_D$: -2.742 (c = 1.0 g/100 mL, $CHCl_3$, *l* = 50 mm)

Analysis of Stereochemistry:

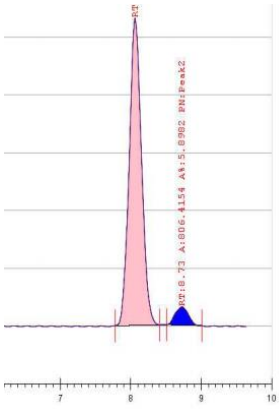
Racemic compound was prepared according to the procedure described above with $Pd(OAc)_2$ (3 mol%) and BrettPhos (3.6 mol%) as the catalyst. Crude material was used for SFC without purification.

Chiral SFC (ODR-H, 5% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of 3-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-N-ethyl-N,3-dimethylheptanamide

Racemic

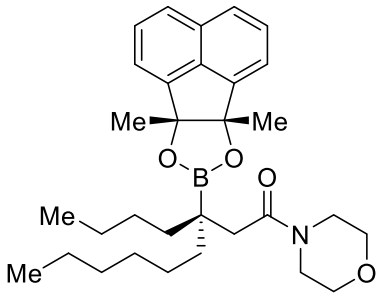


Enriched



Peak No	% Area	Area	RT (min)
1	49.9839	6331.9047	8.11
2	50.0161	6335.9956	8.83
Total:	100	12667.9003	

Peak No	% Area	Area	RT (min)
1	94.1018	12865.813	8.06
2	5.8982	806.4154	8.73
Total:	100	13672.2284	



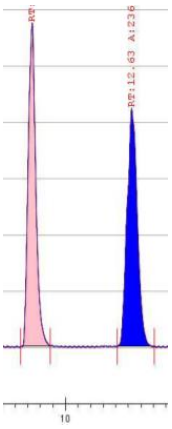
(R)-3-butyl-3-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-1-morpholinononan-1-one (2.84). The reaction was performed according to the general procedure *Method A* using alkenyl B(mac) (**S-2**) (66.9 mg, 0.2 mmol, 1.0 equiv.), *n*-butyllithium (2.5 M in pentane, 0.080 mL, 0.2 mmol, 1.0 equiv.), 4-morpholinecarbonyl chloride (59.8 mg, 0.4 mmol, 2.0 equiv.), palladium (II) acetate (1.35 mg, 0.006 mmol, 0.03 equiv.), (R_p,R_p)- **2.52** (7.58 mg, 0.0072 mmol, 0.036 equiv.), cesium fluoride (60.8 mg, 0.4 mmol, 2.0 equiv.), and water (3.6 µL, 0.2 mmol, 1 equiv.) in THF (0.6 mL, 0.33 M). The crude mixture was purified by silica gel chromatography (deactivated silica using 2% triethylamine:hexanes, eluted with 10% acetone:hexanes) to isolate the title compound (73.3 mg, 0.145 mmol, 73% yield) as a white solid. Product Rf = 0.8 in 3% triethylamine: 30% acetone: 67% hexanes (UV active and stains blue with *para*-anisaldehyde stain).; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.0 Hz, 2H), 7.57 – 7.47 (m, 4H), 3.62 (t, *J* = 4.8 Hz, 2H), 3.57 (t, *J* = 4.9 Hz, 2H), 3.43 – 3.37 (m, 4H), 2.28 (s, 2H), 1.75 (s, 6H), 1.34 – 1.15 (m, 4H), 1.10 – 0.84 (m, 10H), 0.78 (t, *J* = 7.3 Hz, 3H), 0.75 – 0.68 (m, 2H), 0.61 (t, *J* = 7.3 Hz, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.7, 146.91, 146.88, 135.2, 131.3, 128.3, 124.47, 124.46, 119.0, 90.7, 66.9, 66.7, 46.0, 42.8, 41.0, 33.7, 33.2, 31.8, 30.1, 26.4, 24.1, 23.5, 22.6, 22.34, 22.30, 14.20, 14.15.; ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.67.; IR (neat): ν_{max} 2952.73 (m), 2922.96 (m), 2852.40 (m), 1631.22 (s), 1115.08 (s), 781.34 (m) cm^{-1}. HRMS (DART) for $C_{31}H_{45}BNO_4$ $[M+H]^+$: Calc'd: 506.34362, found: 506.34187. $[\alpha]^{20}_D$: 0.754 (c = 1.0 g/100 mL, $CHCl_3$, *l* = 50 mm)

Analysis of Stereochemistry:

Racemic compound was prepared according to the procedure described above with $Pd(OAc)_2$ (3 mol%) and BrettPhos (3.6 mol%) as the catalyst. Crude material was used for SFC without purification.

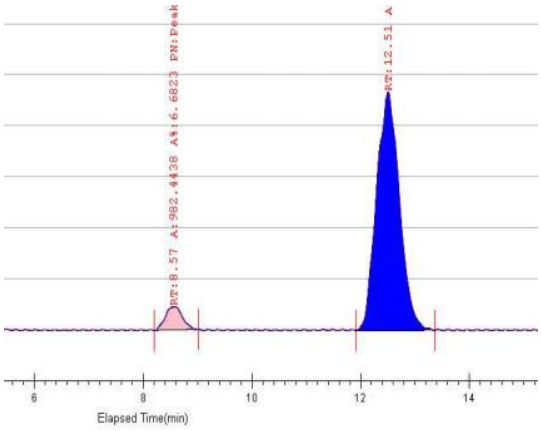
Chiral SFC (AD-H, 5% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of 3-butyl-3-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-1-morpholinononan-1-one

Racemic

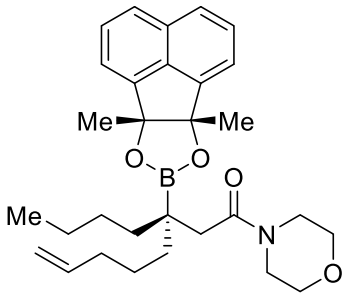


Peak No	% Area	Area	RT (min)
1	50.3539	24020.049	8.68
2	49.6461	23682.3939	12.63
Total:	100	47702.4429	

Enriched



Peak No	% Area	Area	RT (min)
1	6.6823	982.4438	8.57
2	93.3177	13719.8128	12.51
Total:	100	14702.2566	



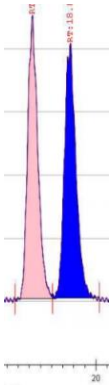
(R)-3-butyl-3-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho [1,2-d][1,3,2]dioxaborol-8-yl)-1-morpholinooct-7-en-1-one (2.85). The reaction was performed according to the general procedure *Method A* using alkenyl B(mac) (**2.129**) (63.4 mg, 0.2 mmol, 1.0 equiv.), *n*-butyllithium (2.5 M in pentane, 0.080 mL, 0.2 mmol, 1.0 equiv.), 4-morpholinecarbonyl chloride (59.8 mg, 0.4 mmol, 2.0 equiv.), palladium (II) acetate (1.35 mg, 0.006 mmol, 0.03 equiv.), (R_p,R_p)- **2.52** (7.58 mg, 0.0072 mmol, 0.036 equiv.), cesium fluoride (60.8 mg, 0.4 mmol, 2.0 equiv.), and water (3.6 µL, 0.2 mmol, 1 equiv.) in THF (0.6 mL, 0.33 M). The crude mixture was purified by silica gel chromatography (deactivated silica using 2% triethylamine:hexanes, eluted with 1% triethylamine: 10% acetone: 89% hexanes) to isolate the title compound (75.0 mg, 0.153 mmol, 76% yield) as a white solid. Product Rf = 0.6 in 3% triethylamine: 30% acetone: 67% hexanes (UV active and stains blue with *para*-anisaldehyde stain).;^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.9 Hz, 2H), 7.60 – 7.44 (m, 4H), 5.50 (ddt, *J* = 17.1, 10.4, 6.6 Hz, 1H), 4.81 – 4.77 (m, 1H), 4.76 (t, *J* = 1.4 Hz, 1H), 3.62 (t, *J* = 4.9 Hz, 2H), 3.56 (t, *J* = 4.8 Hz, 2H), 3.38 (q, *J* = 4.8 Hz, 4H), 2.28 (d, *J* = 2.1 Hz, 2zH), 1.80-1.72 (m, 8H), 1.34 – 1.14 (m, 4H), 1.08 – 0.82 (m, 5H), 0.82 – 0.69 (m, 1H), 0.61 (t, *J* = 7.3 Hz, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.9, 146.94, 146.92, 139.4, 135.2, 131.3, 128.3, 124.45, 124.43, 118.9, 113.8, 90.59, 90.57, 66.8, 66.6, 66.3, 46.0, 42.8, 41.1, 34.5, 33.3, 33.2, 26.5, 23.7, 23.5, 22.4, 22.3, 14.1.; ^{11}B NMR (160 MHz, $CDCl_3$) δ 28.87. IR (neat): ν_{max} 2951.95 (m), 2924.15 (m), 2854.90 (m), 1635.36 (s), 1115.79 (s), 781.86 (s) cm^{-1}. HRMS (DART) for $C_{30}H_{41}BNO_4$ $[M+H]^+$: Calc'd: 490.31232, found: 490.31170. $[\alpha]^{20}_D$: -3.012 (c = 1.0 g/100 mL, $CHCl_3$, *l* = 50 mm)

Analysis of Stereochemistry:

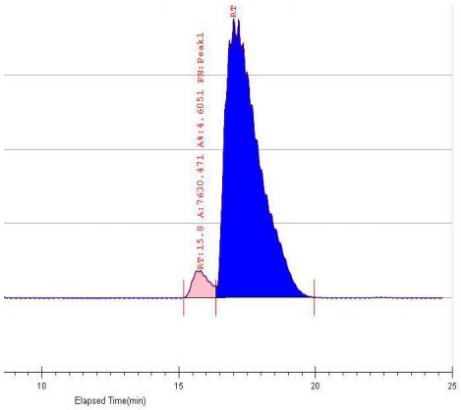
Racemic compound was prepared according to the procedure described above with $Pd(OAc)_2$ (3 mol%) and BrettPhos (3.6 mol%) as the catalyst. Crude material was used for SFC without purification.

Chiral SFC (AD-H, 3% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of 3-butyl-3-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho [1,2-d][1,3,2]dioxaborol-8-yl)-1-morpholinooct-7-en-1-one

Racemic

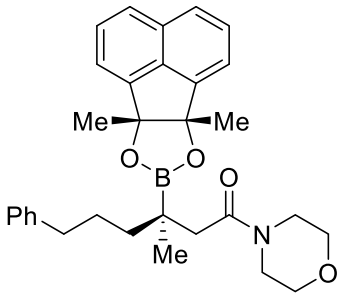


Enriched



Peak No	% Area	Area	RT (min)
1	49.5859	7099.1143	17.15
2	50.4141	7217.6763	18.85
Total:	100	14316.7906	

Peak No	% Area	Area	RT (min)
1	4.6051	7630.471	15.8
2	95.3949	158064.9338	17.01
Total:	100	165695.4048	



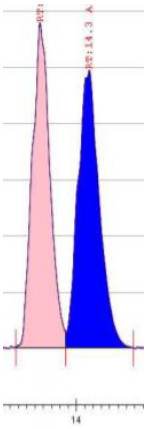
(S)-3-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-3-methyl-1-morpholino-6-phenylhexan-1-one (2.86). The reaction was performed according to the general procedure *Method B* using phenylpropyl B(mac) (**S-1**) (68.5 mg, 0.2 mmol, 1.0 equiv.), *tert*-butyllithium (1.7 M in pentane, 0.235 mL, 0.4 mmol, 2.0 equiv.), 2-bromopropene (24.2 mg, 0.2 mmol, 1.0 equiv.), 4-morpholinecarbonyl chloride (59.8 mg, 0.4 mmol, 2.0 equiv.), palladium (II) acetate (1.35 mg, 0.006 mmol, 0.03 equiv.), (R_p,R_p)- **2.52** (7.58 mg, 0.0072 mmol, 0.036 equiv.), cesium fluoride (91.1 mg, 0.6 mmol, 3.0 equiv.), and water (21.6 µL, 1.2 mmol, 6 equiv.) in THF (0.6 mL, 0.33 M). The crude mixture was purified by silica gel chromatography (eluted with 10% acetone:hexanes) to afford a white solid (52.1 mg, 52.4% yield). Product Rf. = 0.1 in 20% ethyl acetate:hexanes (UV active and stains blue green with PAA). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 11.2, 7.9 Hz, 2H), 7.61 – 7.48 (m, 4H), 7.19 – 7.05 (m, 3H), 6.70 (d, *J* = 7.3 Hz, 2H), 3.71 – 3.52 (m, 4H), 3.48 – 3.30 (m, 4H), 2.42 (d, *J* = 16.5 Hz, 1H), 2.20 (t, *J* = 7.2 Hz, 2H), 2.12 (d, *J* = 16.5 Hz, 1H), 1.77 (d, *J* = 26.4 Hz, 6H), 1.35 – 1.23 (m, 2H), 1.16 – 0.97 (m, 2H), 0.86 (s, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.3, 146.8, 146.5, 142.8, 135.1, 131.3, 128.38, 128.35, 128.2, 128.1, 125.4, 124.7, 124.5, 119.1, 119.0, 91.0, 90.9, 66.9, 66.6, 45.9, 45.0, 42.7, 39.1, 36.6, 27.1, 22.4, 22.3, 22.1.; ^{11}B NMR (160 MHz, cdcl$_3$) δ 27.34. IR (neat): ν_{max} 2965.68 (m), 2926.24 (m), 2853.77 (m), 1625.83 (s), 1114.5 (s), 749.03 (s) cm^{-1}. HRMS (DART) for $C_{31}H_{37}BNO_4$ $[M+H]^+$: Calc'd: 498.28102, found: 498.28230. $[\alpha]^{20}_D$: 4.017 (c = 1.0 g/100 mL, $CHCl_3$, *l* = 50 mm)

Analysis of Stereochemistry:

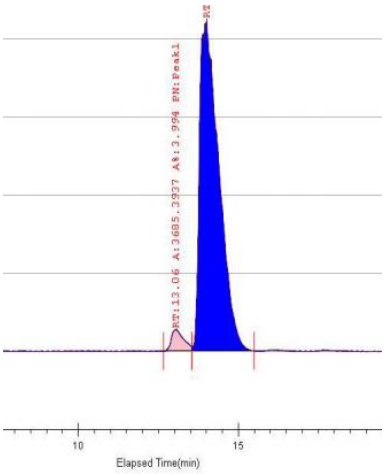
Racemic compound was prepared according to the procedure described above with $Pd(OAc)_2$ (3 mol%) and BrettPhos (3.6 mol%) as the catalyst. Crude material was used for SFC without purification.

Chiral SFC (AD-H, 7% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) - 3-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-3-methyl-1-morpholino-6-phenylhexan -1-one

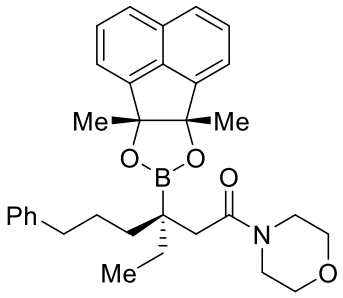
Racemic



Enriched



Peak No	% Area	Area	RT (min)	Peak No	% Area	Area	RT (min)
1	49.0635	17155.3916	13.12	1	3.994	3685.3937	13.06
2	50.9365	17810.3047	14.3	2	96.006	88588.3607	14.01
Total:	100	34965.6963		Total:	100	92273.7544	



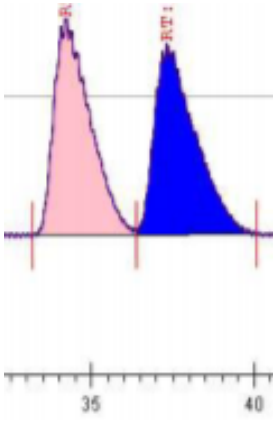
(S)-3-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-3-ethyl-1-morpholino-6-phenylhexan-1-one (2.87). The reaction was performed according to the general procedure *Method B* using phenylpropyl B(mac) (**S-1**) (68.5 mg, 0.2 mmol, 1.0 equiv.), *tert*-butyllithium (1.7 M in pentane, 0.235 mL, 0.4 mmol, 2.0 equiv.), 2-bromobut-1-ene (27.0 mg, 0.2 mmol, 1.0 equiv.), 4-morpholinecarbonyl chloride (59.8 mg, 0.4 mmol, 2.0 equiv.), palladium (II) acetate (1.35 mg, 0.006 mmol, 0.03 equiv.), (R_p,R_p)- **2.52** (7.58 mg, 0.0072 mmol, 0.036 equiv.), cesium fluoride (91.1 mg, 0.6 mmol, 3.0 equiv.), and water (21.6 μL, 1.2 mmol, 6 equiv.) in THF (0.6 mL, 0.33 M).. The crude mixture was purified by silica gel chromatography eluted with 10% acetone:hexanes to isolate the title compound (52.7 mg, 0.103 mmol, 51% yield) as a white solid. Product Rf = 0.6 in 30% acetone: 70% hexanes (UV active and stains blue with *para*-anisaldehyde stain).; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 (dd, *J* = 7.9, 4.1 Hz, 2H), 7.60 – 7.47 (m, 4H), 7.17 (t, *J* = 7.8 Hz, 2H), 7.11 (t, *J* = 7.3 Hz, 1H), 6.83 (d, *J* = 7.9 Hz, 2H), 3.61 (t, *J* = 4.9 Hz, 2H), 3.56 (t, *J* = 4.9 Hz, 2H), 3.40 – 3.35 (m, 4H), 2.35 – 2.21 (m, 4H), 1.76 (d, *J* = 8.9 Hz, 6H), 1.48 – 1.18 (m, 5H), 1.16 – 1.06 (m, 1H), 0.55 (t, *J* = 7.4 Hz, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.8, 146.94, 146.91, 143.0, 135.2, 131.3, 128.33, 128.32, 128.3, 128.1, 125.4, 124.51, 124.47, 119.0, 118.9, 90.63, 90.60, 66.8, 66.6, 45.9, 42.8, 40.8, 36.7, 33.5, 26.4, 25.7, 22.4, 22.3, 8.3.; ^{11}B NMR (160 MHz, $CDCl_3$) δ 27.42.; IR (neat): ν_{max} 2968.52 (m), 2938.22 (m), 2820.51 (m), 1628.66 (s), 1115.37 (s), 781.37 (s) cm^{-1}. HRMS (DART) for $C_{32}H_{39}BNO_4$ $[M+H]^+$: Calc'd: 512.29667, found: 512.29809. $[\alpha]^{20}_D$: 3.845 (c = 1.0 g/100 mL, $CHCl_3$, *l* = 50 mm)

Analysis of Stereochemistry:

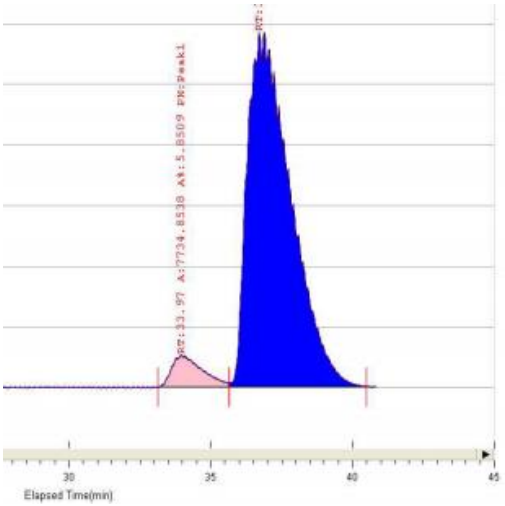
Racemic compound was prepared according to the procedure described above with $Pd(OAc)_2$ (3 mol%) and BrettPhos (3.6 mol%) as the catalyst. Crude material was used for SFC without purification.

Chiral SFC (AD-H, 4% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) - 3-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-3-ethyl-1-morpholino-6-phenylhexan-1-one

Racemic

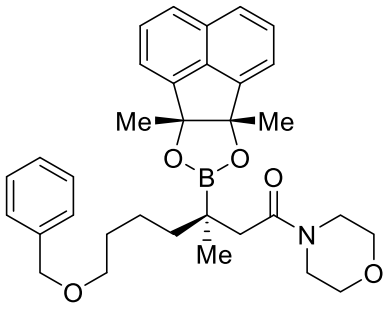


Enriched



Peak No	% Area	Area	RT (min)
1	50.3249	11948.8765	34.22
2	49.6751	11794.5779	37.31
Total:	100	23743.4544	

Peak No	% Area	Area	RT (min)
1	5.8509	7734.8538	33.97
2	94.1491	124465.0053	36.7
Total:	100	132199.8591	



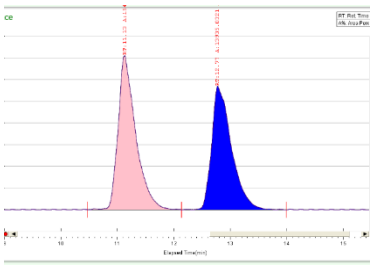
(S)-7-(benzyloxy)-3-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-3-methyl-1-morpholinoheptan-1-one (2.88). The reaction was performed according to the general procedure *Method B* using 1-benzyloxyl butyl B(mac) (77.2 mg, 0.2 mmol, 1.0 equiv.), 4-morpholine carbonyl chloride (59.8 mg, 0.4 mmol, 2.0 equiv.), palladium (II) acetate (1.35 mg, 0.006 mmol, 0.03 equiv.), (R_p,R_p)- **2.52** (7.58 mg, 0.0072 mmol, 0.036 equiv.), cesium fluoride (91.2 mg, 0.6 mmol, 3.0 equiv.), and water (21.6 µL, 1.2 mmol, 6 equiv.) in THF (0.6 mL, 0.33 M). The crude mixture was purified by silica gel chromatography (deactivated silica using 2% triethylamine:hexanes, eluted with 10% ethyl acetate:hexanes) to isolate the title compound (74.1 mg, 0.137 mmol, 68.5% yield) as a white solid. Product Rf = 0.60 in 2% triethylamine: 20% acetone: 78% hexanes (UV active and stains blue with *para*-anisaldehyde stain).; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.5 Hz, 2H), 7.53 – 7.47 (m, 4H), 7.34 – 7.31 (m, 2H), 7.26 (dd, *J* = 8.0, 6.0 Hz, 3H), 4.32 (s, 2H), 3.62 – 3.52 (m, 4H), 3.42 – 3.31 (m, 4H), 3.04 – 2.89 (m, 2H), 2.40 (d, *J* = 16.6 Hz, 1H), 2.11 (d, *J* = 16.6 Hz, 1H), 1.74 (d, *J* = 22.4 Hz, 6H), 1.22 (dq, *J* = 12.9, 7.3, 5.5 Hz, 2H), 1.15 (dq, *J* = 13.0, 7.2 Hz, 1H), 1.09 – 0.99 (m, 2H), 0.83 (s, 3H), 0.66 (ddp, *J* = 12.3, 7.1, 4.5, 4.1 Hz, 1H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.7, 146.9, 146.6, 128.38, 128.33, 128.27, 127.7, 127.5, 124.5, 124.4, 119.0, 118.9, 90.75, 90.69, 72.8, 70.5, 66.8, 66.5, 47.3, 45.9, 44.9, 42.8, 38.9, 30.3, 29.8, 22.1, 22.1, 21.8.; ^{11}B NMR (160 MHz, $CDCl_3$) δ 28.4.; IR (neat): ν_{max}, 2967.42 (m), 2927.64 (m), 2856.12 (m), 1624.96 (s), 1462.80 (m), 1115.49 (s), 1082.27 (s), 782.46 (s) cm^{-1}. HRMS (DART) for $C_{33}H_{40}BNO_5$ $[M+H]^+$: Calc'd: 542.30723, found: 542.30691. $[\alpha]^{20}_D$: 6.789 (c = 1.0 g/mL, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Racemic compound was prepared according to the procedure described above with $Pd(OAc)_2$ (3 mol%) and BrettPhos (3.6 mol%) as the catalyst. Crude material was used for SFC without purification.

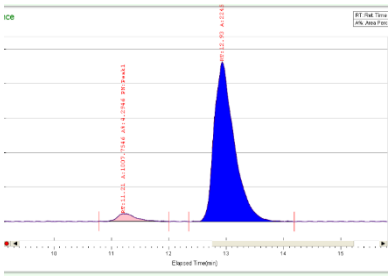
Chiral SFC (Chiralcel AD-H, 8% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (S)-7-(benzyloxy)-3-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho-[1,2-d][1,3,2]dioxaborol-8-yl)-3-methyl-1-morpholinoheptan-1-one

Racemic

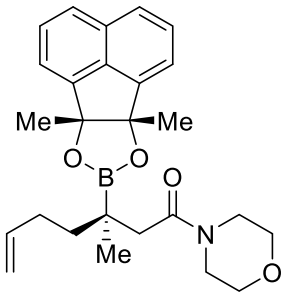


Peak No.	% Area	Area	RT (min)
1	52.537	15424.7692	11.13
2	47.463	13935.0321	12.77
Total	100	29359.8013	

Enriched



Peak No.	% Area	Area	RT (min)
1	4.2946	1007.7546	11.21
2	95.7054	22457.9527	12.93
Total	100	23465.7073	



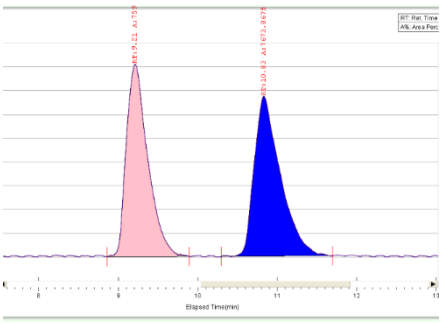
(S)-3-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-3-methyl-1-morpholinohept-6-en-1-one (2.89). The reaction was performed according to the general procedure *Method B* using 1-butenyl B(mac) (55.6 mg, 0.2 mmol, 1.0 equiv.), 4-morpholine carbonyl chloride (59.8 mg, 0.4 mmol, 2.0 equiv.), palladium (II) acetate (1.35 mg, 0.006 mmol, 0.03 equiv.), (R_p,R_p)- **2.52** (7.58 mg, 0.0072 mmol, 0.036 equiv.), cesium fluoride (91.2 mg, 0.6 mmol, 3.0 equiv.), and water (21.6 μL, 1.2 mmol, 6 equiv.) in THF (0.6 mL, 0.33 M). The crude mixture was purified by silica gel chromatography (deactivated silica using 2% triethylamine:hexanes, eluted with 10% ethyl acetate:hexanes) to isolate the title compound (59.6 mg, 0.138 mmol, 68.8% yield) as a white solid. Product Rf = 0.60 in 2% triethylamine: 30% acetone: 68% hexanes (UV active and stains blue with *para*-anisaldehyde stain).; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71 (dd, *J* = 8.0, 4.6 Hz, 2H), 7.56 – 7.47 (m, 4H), 5.47 (ddt, *J* = 16.9, 10.1, 6.7 Hz, 1H), 4.64 – 4.45 (m, 2H), 3.58 (d, *J* = 33.8 Hz, 4H), 3.36 (d, *J* = 4.4 Hz, 4H), 2.41 (d, *J* = 16.5 Hz, 1H), 2.14 (d, *J* = 16.6 Hz, 1H), 1.74 (d, *J* = 22.4 Hz, 7H), 1.49 (s, 1H), 1.32 (td, *J* = 12.4, 4.7 Hz, 1H), 1.15 (td, *J* = 12.5, 5.0 Hz, 1H), 0.84 (s, 3H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.6, 146.9, 146.6, 139.8, 135.2, 131.3, 128.4, 128.3, 124.6, 124.5, 119.0, 113.5, 90.8, 90.7, 66.8, 66.6, 45.9, 44.9, 42.8, 38.6, 29.9, 22.4, 22.2, 22.1.; ^{11}B NMR (160 MHz, $CDCl_3$) δ 28.2. IR (neat): ν_{max}, 2969.72 (m), 2925.36 (m), 2857.31 (m), 1622.65 (s), 1464.55 (m), 1116.37 (s), 1082.78 (s), 782.54 (s) cm^{-1}. HRMS (DART) for $C_{26}H_{32}BNO_4$ $[M+H]^+$: Calc'd: 434.24972, found: 434.25053. $[\alpha]^{20}_D$: 1.899 (c = 1.0 g/mL, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Racemic compound was prepared according to the procedure described above with $Pd(OAc)_2$ (3 mol%) and BrettPhos (3.6 mol%) as the catalyst. Crude material was used for SFC without purification.

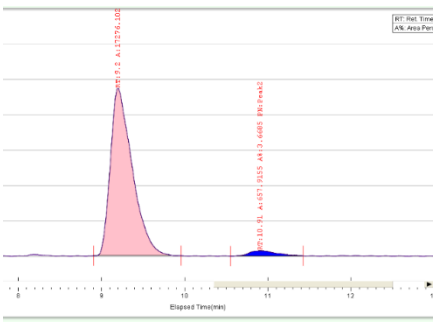
Chiral SFC (Chiralcel AD-H, 5% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (S)-3-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]-dioxaborol-8-yl)-3-methyl-1-morpholinohept-6-en-1-one.

Racemic

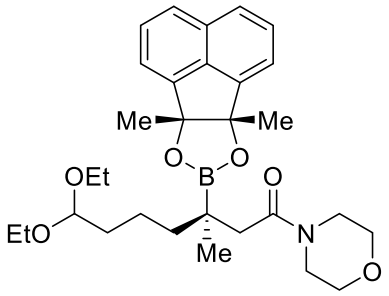


Peak No.	% Area	Area	RT (min)
1	49.7446	7595.8763	9.21
2	50.2554	7673.8675	10.83
Total	100	15269.7438	

Enriched



Peak No.	% Area	Area	RT (min)
1	96.3315	17276.102	9.20
2	3.6685	657.9155	10.91
Total	100	17934.0175	



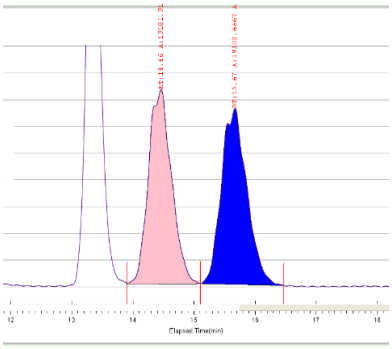
(S)-3-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-7,7-diethoxy-3-methyl-1-morpholinoheptan-1-one (2.90). The reaction was performed according to the general procedure *Method B* using 5,5-diethoxypentyl B(mac) (**S-3**) (73.6 mg, 0.2 mmol, 1.0 equiv.), isopropenyllithium (0.50 mL, 0.4 M, 0.2 mmol, 1.0 equiv.), 4-morpholine carbonyl chloride (59.8 mg, 0.4 mmol, 2.0 equiv.), palladium (II) acetate (1.35 mg, 0.006 mmol, 0.03 equiv.), (R_p,R_p)- **2.52** (7.58 mg, 0.0072 mmol, 0.036 equiv.), cesium fluoride (91.2 mg, 0.6 mmol, 3.0 equiv.), and water (21.6 μL, 1.2 mmol, 6 equiv.) in THF (0.6 mL, 0.33 M). The crude mixture was purified by silica gel chromatography (deactivated silica using 2% triethylamine:hexanes, eluted with 20% ethyl acetate:hexanes) to isolate the title compound (61.0 mg, 0.116 mmol, 58.3% yield) as an off-white solid. Product Rf = 0.50 in 2% triethylamine: 20% ethyl acetate: 78% hexanes (UV active and stains blue with *para*-anisaldehyde stain).; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74 – 7.67 (m, 2H), 7.56 – 7.49 (m, 4H), 3.99 (t, J = 5.7 Hz, 1H), 3.63 – 3.43 (m, 6H), 3.39 – 3.25 (m, 6H), 2.41 (d, J = 16.6 Hz, 1H), 2.13 (d, J = 16.6 Hz, 1H), 1.75 (d, J = 17.2 Hz, 6H), 1.30 – 1.18 (m, 4H), 1.11 (dq, J = 14.1, 7.1 Hz, 8H), 0.84 (s, 3H).; 13C NMR (151 MHz, $CDCl_3$) δ 173.6, 146.9, 146.7, 135.1, 131.2, 128.34, 128.25, 124.5 124.4, 118.96, 118.94, 103.2, 90.8, 90.7, 77.4, 77.2, 76.9, 66.8, 66.5, 61.3, 60.7, 45.9, 44.7, 42.7, 38.8, 34.5, 30.4, 22.4, 22.2, 22.1, 20.6, 15.5, 15.4.; ^{11}B NMR (160 MHz, $CDCl_3$) δ 28.4.; IR (neat): ν_{max}, 2968.45 (m), 2927.12 (m), 2860.33 (m), 1654.11 (s), 1462.10 (m), 1111.50 (s), 1088.47 (s). HRMS (DART) for $C_{28}H_{37}BNO_5$ $[M\text{-}C_2H_5O^-]^+$: Calc'd 478.27593, found: 478.27607. $[\alpha]^{20}_D$: 8.030 (c = 1.0 g/mL, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Racemic compound was prepared according to the procedure described above with $Pd(OAc)_2$ (3 mol%) and BrettPhos (3.6 mol%) as the catalyst. Crude material was used for SFC without purification.

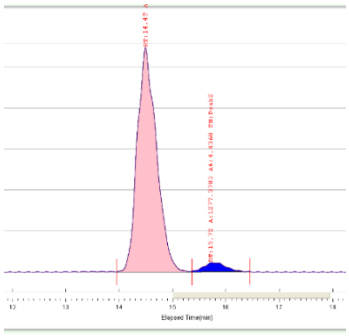
Chiral SFC (Chiralcel OJ-H, 3% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (S)-3-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho-[1,2-d][1,3,2]dioxaborol-8-yl)-7,7-diethoxy-3-methyl-1-morpholinoheptan-1-one

Racemic

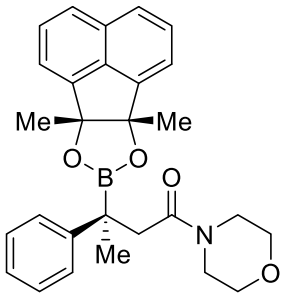


Peak No.	% Area	Area	RT (min)
1	50.1035	19181.9141	14.46
2	49.8965	19102.6667	15.67
Total	100	38284.5808	

Enriched



Peak No.	% Area	Area	RT (min)
1	95.5632	27513.1068	14.49
2	4.4368	1277.3783	15.72
Total	100	28790.4851	



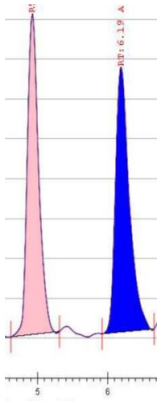
(S)-3-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-1-morpholino-3-phenylbutan-1-one (2.75). The reaction was performed according to the general procedure *Method A* at 60 °C using isopropenyl B(mac) (**2.59**) (52.8 mg, 0.2 mmol, 1.0 equiv.), phenyllithium (1.9 M in dibutyl ether, 0.105 mL, 0.2 mmol, 1.0 equiv.), 4-morpholinecarbonyl chloride (59.8 mg, 0.4 mmol, 2.0 equiv.), palladium (II) acetate (1.35 mg, 0.006 mmol, 0.03 equiv.), (R_p,R_p)- **2.52** (7.58 mg, 0.0072 mmol, 0.036 equiv.), cesium fluoride (60.8 mg, 0.4 mmol, 2.0 equiv.), and water (10.8 μL, 0.6 mmol, 3 equiv.) in THF (0.6 mL, 0.33 M). The crude mixture was purified by silica gel chromatography (deactivated silica using 2% triethylamine:hexanes, eluted with 2% triethylamine, 20% acetone, 78% hexanes) to isolate the title compound (74.2 mg, 0.162 mmol, 81% yield) as a white solid. Product Rf = 0.3 in 3% triethylamine: 30% acetone: 67% hexanes (UV active and stains blue with *para*-anisaldehyde stain).; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71 (t, *J* = 7.2 Hz, 2H), 7.52 (dt, *J* = 23.1, 6.8 Hz, 3H), 7.42 (d, *J* = 6.9 Hz, 1H), 7.04 – 6.92 (m, 5H), 3.70 – 3.56 (m, 3H), 3.53 – 3.47 (m, 1H), 3.44 (t, *J* = 4.9 Hz, 2H), 3.32 (t, *J* = 5.0 Hz, 2H), 3.03 (d, *J* = 16.4 Hz, 2H), 2.55 (d, *J* = 16.5 Hz, 2H), 1.73 (d, *J* = 12.8 Hz, 6H), 1.22 (s, 3H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.8, 148.2, 147.4, 146.9, 135.4, 131.2, 128.4, 128.1, 127.8, 126.5, 124.7, 124.2, 119.0, 118.7, 90.5, 90.4, 66.6, 66.4, 46.1, 43.6, 43.4, 26.9, 22.6, 22.5.; ^{11}B NMR (160 MHz, $CDCl_3$) δ 24.77. IR (neat): ν_{max} 2964.82 (m), 2924.49 (m), 2855.63 (m), 1610.994 (s), 1113.43 (s), 1082.75 (s), 752.21 (s) cm^{-1}. HRMS (DART) for $C_{28}H_{31}BNO_4$ $[M+H]^+$: Calc'd: 456.23407, found: 456.23432. $[\alpha]^{20}_D$: -33.002 (c = 1.0 g/100 mL, $CHCl_3$, *l* = 50 mm)

Analysis of Stereochemistry:

Racemic compound was prepared according to the procedure described above with $Pd(OAc)_2$ (3 mol%) and BrettPhos (3.6 mol%) as the catalyst. Crude material was used for SFC without purification.

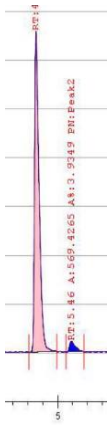
Chiral SFC (AD-H, 10% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of 3-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-1-morpholino-3-phenylbutan-1-one

Racemic

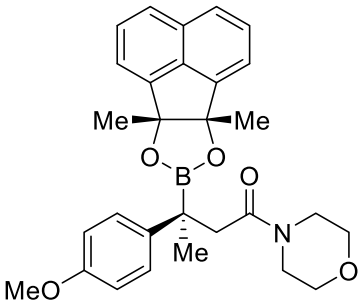


Peak No	% Area	Area	RT (min)
1	49.846	18104.0436	4.92
2	50.154	18215.8814	6.19
Total:	100	36319.925	

Enriched



Peak No	% Area	Area	RT (min)
1	96.0651	13901.8187	4.27
2	3.9349	569.4265	5.46
Total:	100	14471.2452	



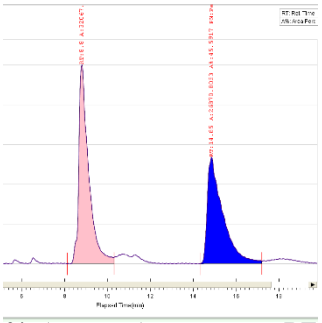
(R)-3-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-1-morpholino-3-(4-methoxyphenyl)butan-1-one (2.91). The reaction was performed according to the general procedure *Method C* using isopropenyl B(mac) (**2.59**) (52.8 mg, 0.2 mmol, 1.0 equiv.), 4-morpholine carbonyl chloride (59.8 mg, 0.4 mmol, 2.0 equiv.), palladium (II) acetate (1.35 mg, 0.006 mmol, 0.03 equiv.), (R_p,R_p)- **2.52** (7.58 mg, 0.0072 mmol, 0.036 equiv.), cesium fluoride (91.2 mg, 0.6 mmol, 3.0 equiv.), and water (21.6 μL, 1.2 mmol, 6 equiv.) in THF (0.6 mL, 0.33 M). The crude mixture was purified by silica gel chromatography (deactivated silica using 2% triethylamine:hexanes, eluted with 20% ethyl acetate:hexanes) to isolate the title compound (39.9 mg, 0.085 mmol, 42.5% yield) as a white solid. Product Rf = 0.50 in 2% triethylamine: 30% acetone: 68% hexanes (UV active and stains blue with *para*-anisaldehyde stain).; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 (dd, *J* = 8.1, 6.1 Hz, 2H), 7.50 (dt, *J* = 22.2, 7.0 Hz, 3H), 7.41 (d, *J* = 6.9 Hz, 1H), 6.88 (d, *J* = 8.6 Hz, 2H), 6.52 (d, *J* = 8.5 Hz, 2H), 3.68 (s, 3H), 3.59 (s, 3H), 3.51 (s, 1H), 3.42 (t, *J* = 4.9 Hz, 2H), 3.32 (t, *J* = 4.9 Hz, 1H), 2.95 (d, *J* = 16.4 Hz, 1H), 2.51 (d, *J* = 16.4 Hz, 1H), 1.72 (s, 6H), 1.17 (s, 3H).; ^{13}C NMR (151 MHz, $CDCl_3$): δ 174.5, 156.8, 147.3, 146.9, 140.3, 135.3, 131.2, 128.4, 128.1, 127.4, 124.2, 119.0, 118.8, 113.2, 90.5, 90.4, 66.7, 66.4, 55.2, 47.3, 46.0, 44.0, 43.3, 29.8, 26.7, 22.6, 22.5.; ^{11}B NMR (160 MHz, $CDCl_3$) δ 26.7.; IR (neat): ν_{max}, 2967.16 (m), 2926.18 (m), 2856.57 (m), 1611.09 (s), 1511.37 (m), 1114.97 (s), 1084.11 (s), 783.13 (s) cm^{-1}. HRMS (DART) for $C_{29}H_{32}BNO_4$ $[M+H]^+$: Calc'd: 486.24463, found: 486.24476. $[\alpha]^{20}_D$: 12.287 (c = 1.0 g/mL, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Racemic compound was prepared according to the procedure described above with $Pd(OAc)_2$ (3 mol%) and 50% (S_p, S_p)-**2.1** :50% (R_p, R_p)-**2.1** (3.6 mol%) as the catalyst. Crude material was used for SFC without purification.

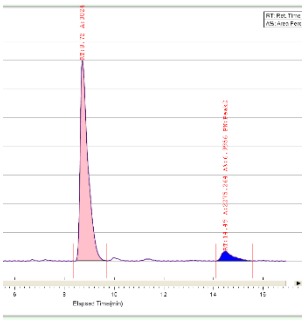
Chiral SFC (Chiralcel AD-H, 8% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (R)-3-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]-dioxaborol-8-yl)-1-morpholino-3-(4-methoxyphenyl)butan-1-one.

Racemic

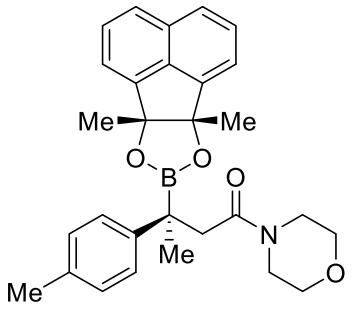


Peak No.	% Area	Area	RT (min)
1	54.4083	32067.1859	8.8
2	45.5917	26870.8053	14.85
Total	100	58937.9912	

Enriched



Peak No.	% Area	Area	RT (min)
1	93.0044	30248.742	8.72
2	6.9956	2275.264	14.10
Total	100	32524.006	



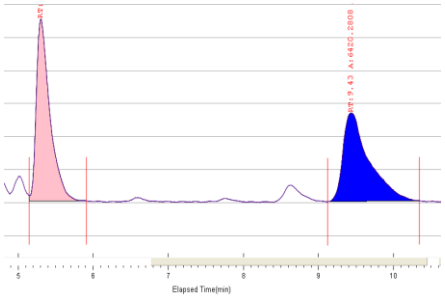
(R)-3-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-1-morpholino-3-(p-tolyl)butan-1-one (2.92). The reaction was performed according to the general procedure *Method C* using isopropenyl B(mac) (**2.59**) (52.8 mg, 0.2 mmol, 1.0 equiv.), 4-morpholine carbonyl chloride (59.8 mg, 0.4 mmol, 2.0 equiv.), palladium (II) acetate (1.35 mg, 0.006 mmol, 0.03 equiv.), (R_p,R_p)- **2.52** (7.58 mg, 0.0072 mmol, 0.036 equiv.), cesium fluoride (91.2 mg, 0.6 mmol, 3.0 equiv.), and water (21.6 μL, 1.2 mmol, 6 equiv.) in THF (0.6 mL, 0.33 M). The crude mixture was purified by silica gel chromatography (deactivated silica using 2% triethylamine:hexanes, eluted with 20% ethyl acetate:hexanes) to isolate the title compound (57.7 mg, 0.123 mmol, 61.5% yield) as a white solid. Product Rf = 0.40 in 2% triethylamine: 40% acetone: 58% hexanes (UV active and stains blue with *para*-anisaldehyde stain).; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 (dd, *J* = 8.0, 4.7 Hz, 2H), 7.53 – 7.46 (m, 3H), 7.41 (d, *J* = 6.6 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 2H), 6.79 (d, *J* = 7.9 Hz, 2H), 3.66 – 3.56 (m, 3H), 3.50 (d, *J* = 6.2 Hz, 1H), 3.43 (t, *J* = 4.8 Hz, 2H), 3.34 – 3.29 (m, 2H), 2.97 (d, *J* = 16.4 Hz, 1H), 2.52 (d, *J* = 16.5 Hz, 1H), 2.18 (s, 3H), 1.72 (d, *J* = 6.2 Hz, 6H), 1.19 (s, 3H).; ^{13}C NMR (151 MHz, $CDCl_3$): δ 174.5, 147.3, 146.9, 145.1, 135.4, 134.0, 131.2, 128.6, 128.4, 128.1, 126.3, 124.3, 119.0, 118.8, 90.6, 90.5, 66.7, 66.5, 46.0, 43.2, 29.8, 26.7, 22.6, 22.5, 20.9.; ^{11}B NMR (160 MHz, $CDCl_3$) δ 26.66.; IR (neat): ν_{max}, 2968.42 (m), 2923.58 (m), 2857.29 (m), 1613.81 (s), 1445.53 (m), 1116.82 (s), 1084.44 (s), 782.76 (s) cm^{-1}. HRMS (DART) for $C_{29}H_{32}BNO_4$ $[M+H]^+$: Calc'd: 470.24972, found: 470.25116. $[\alpha]^{20}_D$: 12.287 (c = 1.0 g/mL, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Racemic compound was prepared according to the procedure described above with $Pd(OAc)_2$ (3 mol%) and BrettPhos (3.6 mol%) as the catalyst. Crude material was used for SFC without purification.

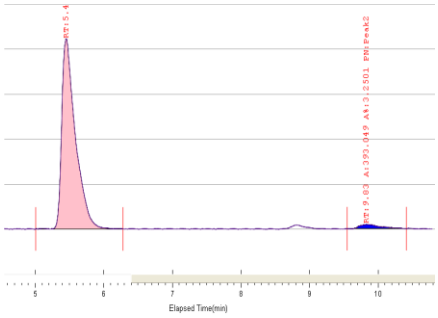
Chiral SFC (Chiralcel AD-H, 8% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (R)-3-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho-[1,2-d][1,3,2]-dioxaborol-8-yl)-1-morpholino-3-(p-tolyl)butan-1-one.

Racemic

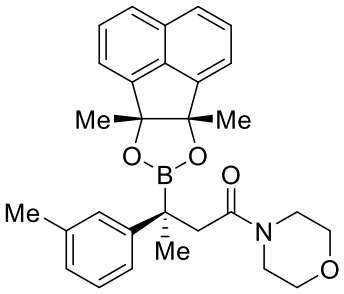


Peak No.	% Area	Area	RT (min)
1	51.805	6901.1975	5.3
2	48.195	6420.2808	9.43
Total	100	13321.4783	

Enriched



Peak No.	% Area	Area	RT (min)
1	96.7499	11700.4772	5.45
2	3.2501	393.049	9.83
Total	100	12093.5262	



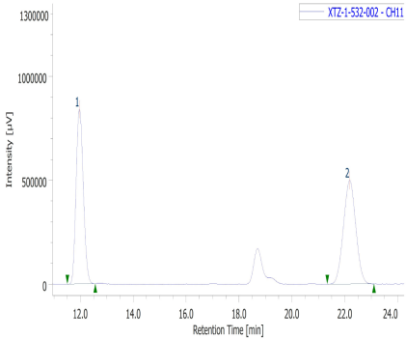
(R)-3-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-1-morpholino-3-(m-tolyl)butan-1-one (2.93). The reaction was performed according to the general procedure *Method C* using isopropenyl B(mac) (**2.59**) (52.8 mg, 0.2 mmol, 1.0 equiv.), 4-morpholine carbonyl chloride (59.8 mg, 0.4 mmol, 2.0 equiv.), palladium (II) acetate (1.35 mg, 0.006 mmol, 0.03 equiv.), (R_p,R_p)- **2.52** (7.58 mg, 0.0072 mmol, 0.036 equiv.), cesium fluoride (91.2 mg, 0.6 mmol, 3.0 equiv.), and water (21.6 µL, 1.2 mmol, 6 equiv.) in THF (0.6 mL, 0.33 M). The crude mixture was purified by silica gel chromatography (deactivated silica using 2% triethylamine:hexanes, eluted with 20% ethyl acetate:hexanes) to isolate the title compound (61.7 mg, 0.132 mmol, 65.8% yield) as a white solid. Product Rf = 0.40 in 2% triethylamine: 40% acetone: 58% hexanes (UV active and stains blue with *para*-anisaldehyde stain).; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70 (t, *J* = 8.2 Hz, 2H), 7.57 – 7.46 (m, 3H), 7.42 (d, *J* = 6.6 Hz, 1H), 6.89 (t, *J* = 7.6 Hz, 1H), 6.81 – 6.72 (m, 2H), 6.68 (d, *J* = 2.0 Hz, 1H), 3.69 – 3.59 (m, 3H), 3.55 – 3.50 (m, 1H), 3.45 (t, *J* = 4.8 Hz, 2H), 3.38 (t, *J* = 4.9 Hz, 2H), 2.99 (d, *J* = 16.4 Hz, 1H), 2.55 (d, *J* = 16.5 Hz, 1H), 1.95 (s, 3H), 1.73 (s, 6H), 1.20 (s, 3H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.6, 148.1, 147.4, 146.8, 137.1, 135.3, 131.2, 128.4, 128.2, 127.7, 127.6, 125.5, 124.3, 123.3, 119.0, 118.8, 90.6, 90.5, 66.7, 66.5, 46.1, 43.6, 43.3, 29.8, 27.0, 22.5, 21.4.; ^{11}B NMR (160 MHz, $CDCl_3$) δ 26.2.; IR (neat): ν_{max}, 2966.32 (m), 2923.45 (m), 2855.91 (m), 1607.14 (s), 1458.33 (m), 1115.59 (s), 1083.84 (s), 782.14 (s) cm^{-1}. HRMS (DART) for $C_{29}H_{32}BNO_5$ $[M+H]^+$: Calc'd: 470.24972, found: 470.25025. $[\alpha]^{20}_D$: 16.398 (c = 1.0 g/mL, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Racemic compound was prepared according to the procedure described above with $Pd(OAc)_2$ (3 mol%) and BrettPhos (3.6 mol%) as the catalyst.

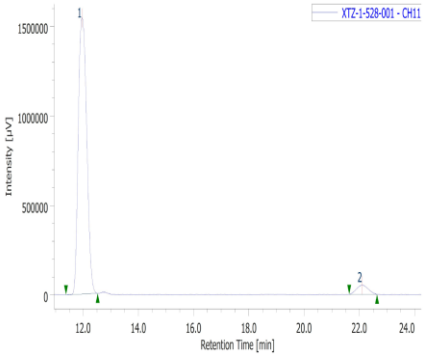
Chiral SFC (Chiralcel AD-H, 15% IPA, 1 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (R)-3-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho-[1,2-d][1,3,2]-dioxaborol-8-yl)-1-morpholino-3-(m-tolyl)butan-1-one

Racemic

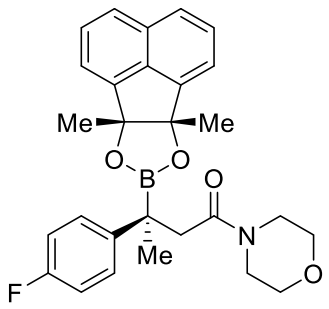


Peak No.	% Area	Area	RT (min)
1	49.715	15995171	11.97
2	50.285	16178867	22.18
Total	100	32174038	

Enriched



Peak No.	% Area	Area	RT (min)
1	95.605	32804267	11.96
2	4.395	1508131	22.10
Total	100	34312398	



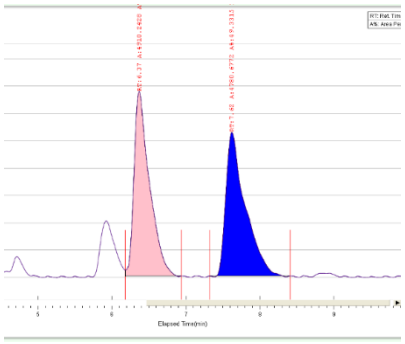
(R)-3-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-1-morpholino-3-(4-fluorophenyl)butan-1-one (2.94). The reaction was performed according to the general procedure *Method C* using isopropenyl B(mac) (**2.59**) (52.8 mg, 0.2 mmol, 1.0 equiv.), 4-morpholine carbonyl chloride (59.8 mg, 0.4 mmol, 2.0 equiv.), palladium (II) acetate (1.35 mg, 0.006 mmol, 0.03 equiv.), (R_p,R_p)- **2.52** (7.58 mg, 0.0072 mmol, 0.036 equiv.), cesium fluoride (91.2 mg, 0.6 mmol, 3.0 equiv.), and water (21.6 μL, 1.2 mmol, 6 equiv.) in THF (0.6 mL, 0.33 M). The crude mixture was purified by silica gel chromatography (deactivated silica using 2% triethylamine:hexanes, eluted with 20% ethyl acetate:hexanes) to isolate the title compound (62.0 mg, 0.131 mmol, 65.5% yield) as a white solid. Product Rf = 0.50 in 2% triethylamine: 30% acetone: 68% hexanes (UV active and stains blue with *para*-anisaldehyde stain).; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71 (dd, *J* = 8.1, 6.0 Hz, 2H), 7.56 – 7.48 (m, 3H), 7.38 (d, *J* = 6.8 Hz, 1H), 6.86 (dd, *J* = 8.6, 5.5 Hz, 2H), 6.61 (t, *J* = 8.8 Hz, 2H), 3.68 – 3.58 (m, 3H), 3.54 (dt, *J* = 11.8, 5.0 Hz, 1H), 3.47 (t, *J* = 5.0 Hz, 2H), 3.38 (t, *J* = 4.9 Hz, 2H), 3.01 (d, *J* = 16.5 Hz, 1H), 2.54 (d, *J* = 16.5 Hz, 1H), 1.72 (s, 6H), 1.17 (s, 3H).; ^{13}C NMR (151 MHz, $CDCl_3$): δ 174.8, 148.2, 147.4, 146.9, 135.4, 131.2, 128.4, 128.1, 127.8, 126.5, 124.7, 124.2, 119.0, 118.7, 90.5, 90.4, 66.8, 66.7, 66.5, 47.4, 46.1, 43.6, 43.4, 26.9, 22.7, 22.5.; ^{11}B NMR (160 MHz, $CDCl_3$) δ 24.4.; ^{19}F NMR (470 MHz, $CDCl_3$) δ -112.9.; IR (neat): ν_{max}, 2966.59 (m), 2923.55 (m), 2855.36 (m), 1616.33 (s), 1508.68 (m), 1115.30 (s), 1084.33 (s), 782.30 (s) cm^{-1}. HRMS (DART) for $C_{28}H_{29}BF\,NO_4$ $[M+H]^+$: Calc'd: 474.22464, found: 474.22438. $[\alpha]^{20}_D$: 10.499 (c = 1.0 g/mL, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Racemic compound was prepared according to the procedure described above with $Pd(OAc)_2$ (3 mol%) and BrettPhos (3.6 mol%) as the catalyst. Crude material was used for SFC without purification.

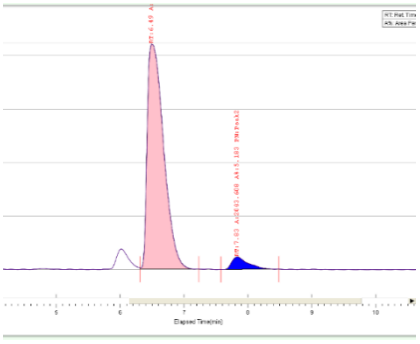
Chiral SFC (Chiralcel AD-H, 8% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (R)-3-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]-dioxaborol-8-yl)-1-morpholino-3-(4-fluoroxyphenyl)butan-1-one.

Racemic

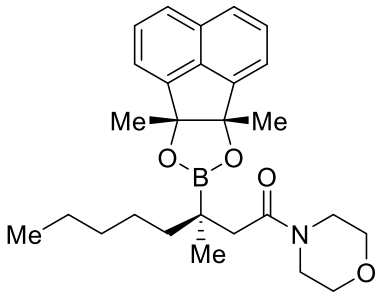


Peak No.	% Area	Area	RT (min)
1	50.6685	4910.2428	6.37
2	49.3315	4780.6772	7.62
Total	100	9690.92	

Enriched



Peak No.	% Area	Area	RT (min)
1	94.817	37385.3649	6.49
2	5.183	2043.608	7.83
Total	100	39428.9729	



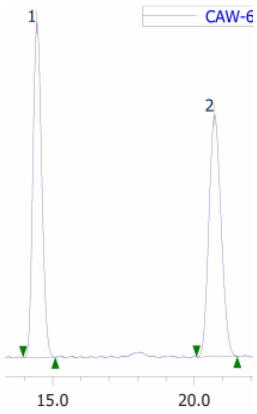
(R)-3-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-3-methyl-1-morpholinooctan-1-one (2.95). The reaction was performed according to the general procedure *Method D* using isopropenyl B(mac) (**2.59**) (52.8 mg, 0.2 mmol, 1.0 equiv.), pentyllithium (0.83 M in ether, 0.244 mL, 0.2 mmol, 1.0 equiv.), 4-morpholinecarbonyl chloride (59.8 mg, 0.4 mmol, 2.0 equiv.), palladium (II) acetate (1.35 mg, 0.006 mmol, 0.03 equiv.), (R_p,R_p)- **2.52** (7.58 mg, 0.0072 mmol, 0.036 equiv.), cesium fluoride (91.1 mg, 0.6 mmol, 3.0 equiv.), and water (21.6 µL, 1.2 mmol, 6 equiv.) in THF (1.2 mL, 0.13 M). The crude mixture was purified by silica gel chromatography (deactivated silica using 2% triethylamine:hexanes, eluted with 10% acetone:hexanes) to afford a white solid (60.8 mg, 67.7% yield). Product Rf = 0.45 in 2% triethylamine:29% acetone:70% hexanes (stains blue with *para*-anisaldehyde stain and UV active).; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 – 7.68 (m, 2H), 7.58 – 7.48 (m, 4H), 3.66 – 3.51 (m, 4H), 3.45 – 3.33 (m, 4H), 2.41 (d, *J* = 16.5 Hz, 1H), 2.11 (d, *J* = 16.5 Hz, 1H), 1.76 (d, *J* = 21.0 Hz, 6H), 1.25 – 1.17 (m, 1H), 1.07 – 0.99 (m, 1H), 0.99 – 0.75 (m, 8H), 0.69 – 0.60 (m, 1H), 0.57 (t, *J* = 7.0 Hz, 3H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.3, 146.8, 146.5, 135.2, 131.3, 128.32, 128.26, 124.6, 124.5, 119.01, 118.97, 90.9, 90.8, 66.9, 66.6, 45.9, 45.0, 42.6, 39.2, 32.5, 24.9, 22.40, 22.38, 22.2, 22.1, 13.9.; ^{11}B NMR (192 MHz, $CDCl_3$) δ 28.91.; IR (neat): ν_{max} 3040.36 (w), 2956.84 (m), 2922.60 (m), 2853.61 (m), 1632.62 (s), 1415.01 (m), 1213.07 (m), 1115.10 (s), 781.42 (w) cm^{-1}. HRMS (DART) for $C_{27}H_{27}BNO_4$ $[M+H]^+$: Calc'd: 450.28102 found: 450.28026. $[\alpha]^{20}_D$: -0.725 (c = 1.0 g/100 mL, $CHCl_3$, *l* = 50 mm)

Analysis of Stereochemistry:

Racemic compound was prepared according to the procedure described above with $Pd(OAc)_2$ (3 mol%) and BrettPhos (3.6 mol%) as the catalyst. Crude material was used for SFC without purification.

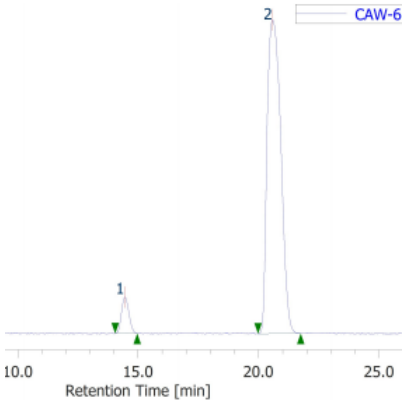
Chiral SFC (AD-H, 10% IPA, 1 mL/min, 100 bar, 35 °C, 210-270 nm) - 3-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-3-methyl-1-morpholinooctan-1-one

Racemic



#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	11	14.447	6564595	303341	50.087
2	Unknown	11	20.707	6541692	218807	49.913

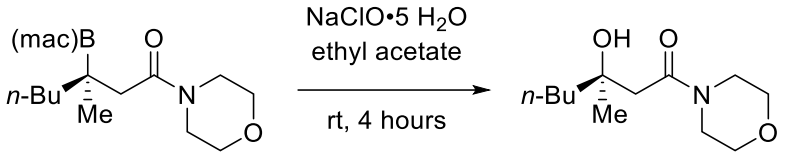
Enriched



#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	11	14.450	4520529	210467	5.926
2	Unknown	11	20.577	71765271	1816991	94.074

2.4.6 Transformations of Product

Oxidation

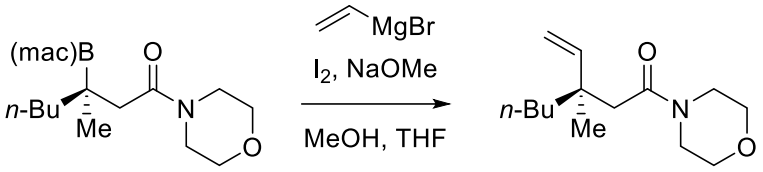


(R)-3-hydroxy-3-methyl-1-morpholinoheptan-1-one (2.98). The title compound was prepared according to a literature procedure with slight modification.[137] 3-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-3-methyl-1-morpholinoheptan-1-one (**2.76**) (43.5 mg, 0.1 mmol, 1 equiv.) was dissolved in 1 mL ethyl acetate and one drop of water was cooled to 0 ˚C using an ice/water bath. Solid sodium hypochlorite pentahydrate (49.4 mg, 0.3 mmol, 3 equiv.) was added directly. Reaction was allowed to warm to room temperature and stir vigorously for 4 hours. Reaction was quenched with 1 mL saturated aqueous sodium thiosulfate and 1 mL saturated aqueous ammonium chloride. Aqueous layer was extracted three times with ethyl acetate. The collected organic layers were washed with brine, dried with magnesium sulfate, filtered, and concentrated under vacuum. Crude mixture was purified using silica gel column chromatography (silica was deactivated with 2% triethylamine:hexanes and eluted with 40% ethyl acetate:hexanes) to yield the desired product as clear oil (22.2 mg, 96.8% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.75 – 3.60 (m, 6H), 3.53 – 3.44 (m, 2H), 2.46 – 2.36 (m, 2H), 1.58 – 1.47 (m, 2H), 1.34 – 1.27 (m, 4H), 1.25 (s, 1H), 1.23 (s, 3H), 0.91 (t, J = 7.0 Hz, 3H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.7, 71.4, 67.0, 66.7, 46.2, 42.3, 41.8, 41.3, 27.1, 26.4, 23.4, 14.3.; IR (neat): ν_{max} 3424.76 (bm), 2955.09 (m), 2923.37 (m), 2853.99 (m), 1617.23 (s), 1115.24 (s) cm^{-1}. HRMS

[137] Radomkit, S.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2014**, *53*, 3387-3391

(DART) for $C_{12}H_{24}NO_3$ $[M+H]^+$: Calc'd: 230.17507, found: 230.17604. $[\alpha]^{20}_D$: 2.060 (c = 4.3 mg/mL, $CHCl_3$, *l* = 50 mm).

Olefination

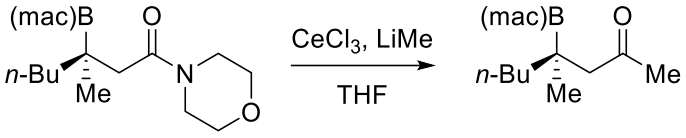


(R)-3-methyl-1-morpholino-3-vinylheptan-1-one (2.96). The title compound was prepared according to a literature procedure with slight modification.[138] To an oven dry vial and stir bar was added 3-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-3-methyl-1-morpholinoheptan-1-one (**2.76**) (87.1 mg, 0.2 mmol, 1 equiv.) and 2 mL dry THF under nitrogen atmosphere. The resulting was chilled to 0 ˚C using an ice/water bath. Vinyl magnesium bromide solution 1M in THF (0.8 mL, 0.8 mmol, 4 equiv.) was added dropwise via syringe. Reaction was allowed to warm up to room temperature and stir for 30 minutes. The resulting orange solution was then cooled to -78 ˚C using a dry ice/acetone bath and a solution of iodine (203 mg, 0.8 mmol, 4 equiv.) in 1.5 mL anhydrous MeOH was added dropwise via syringe. The resulting red mixture was allowed to stir for 30 minutes at that temperature. A solution of sodium methoxide (86.4 mg, 1.6 mmol, 8 equiv.) in 2 mL anhydrous methanol was added dropwise via syringe. The resulting mixture was allowed to warm to room temperature and stir for 1 hour. Reaction was quenched with saturated aqueous sodium thiosulfate. The aqueous layer was extracted three times with ethyl acetate. The collected organics were dried with magnesium sulfate, filtered and concentrated under vacuum to yield an orange oil. The crude mixture was purified

[138] Sonawane, R. P.; Jheengut, V.; Rabalakos, C.; Larouche-Gauthier, R.; Scott, H. K.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2011**, *50*, 3760-3763

using silica gel chromatography (eluted with 50% diethyl ether:pentane) to yield a clear oil (33.1 mg, 69.1% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.02 (d, *J* = 10.8 Hz, 1H), 4.95 (d, *J* = 17.5 Hz, 1H), 3.77 – 3.55 (m, 6H), 3.55 – 3.41 (m, 2H), 2.42 – 2.27 (m, 2H), 1.56 – 1.40 (m, 2H), 1.35 – 1.16 (m, 4H), 1.13 (s, 3H), 0.88 (t, *J* = 7.1 Hz, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.0, 146.4, 112.1, 67.2, 66.8, 47.2, 42.8, 41.9, 40.9, 39.9, 26.5, 23.5, 23.1, 14.3.; IR (neat): ν_{max} 2955.24 (m), 2925.66 (m), 2855.78 (m), 1636.43 (s), 1456.33 (m), 1419.09 (m), 1115.47 (s) cm^{-1}. HRMS (DART) for $C_{14}H_{26}NO_2$ $[M+H]^+$: Calc'd: 240.19581, found: 240.19561. $[\alpha]^{20}_D$: -6.019 (c = 1g/100 mL, $CHCl_3$, *l* = 50 mm).

Methylation

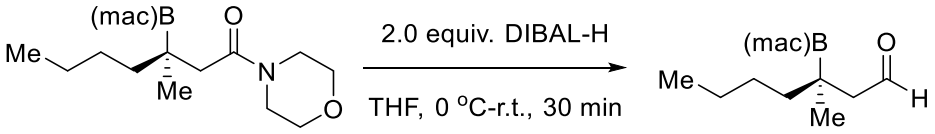


(S)-4-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-4-methyloctan-2-one (2.97). The title compound was prepared according to a literature procedure with slight modification.[139] In the glovebox, an oven-dried 25 mL round bottom flask and magnetic stir bar was charged with cerium chloride (296 mg, 1.2 mmol) and 5 mL of anhydrous THF. Out of the glovebox, the white slurry was placed under positive pressure of nitrogen atmosphere and cooled to -78 ˚C using a dry ice/acetone bath. 1.6 M methyllithium in diethyl ether solution (075 mL, 1.2 mmol) was added dropwise via syringe at that temperature. After stirring for 10 minutes, the mixture was warmed 0 ˚C using an ice/water bath and stir for an additional 10 minutes. This mixture was cooled to -78 ˚C without stirring and the supernatant was used. This supernatant (0.2 M "$MeCeCl_2$", 3 mL, 0.6 mmol, 6 equiv.) was added dropwise to a solution of 3-((6bR,9aS)-6b,9a-

[139] Kurosu, M.; Kishi, Y. *Tetrahedron Letters.* **1998**, *39*, 4793-4796

dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-3-methyl-1-morpholinoheptan-1-one (**2.76**) (43.5 mg, 0.1 mmol, 1 equiv.) in 0.5 mL THF that was chilled to -78 ˚C. After allowing the reaction to stir at -78 ˚C for 15 minutes and was quenched with 1 mL methanol. At room temperature was diluted with water and the aqueous layer was extracted three times with ethyl acetate. The collected organics were washed with brine, dried with magnesium sulfate, filtered, and concentrated under vacuum. The crude mixture was purified using silica gel chromatography (eluted with 5% acetone:hexanes) to yield a white solid (20.1 mg, 55.1% yield) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.2 Hz, 2H), 7.64 – 7.46 (m, 4H), 2.61 (d, *J* = 17.8 Hz, 1H), 2.31 (d, *J* = 17.8 Hz, 1H), 2.04 (s, 3H), 1.83 (s, 3H), 1.74 (s, 3H), 1.33 – 1.20 (m, 1H), 1.19 – 1.07 (m, 1H), 1.03 – 0.95 (m, 1H), 0.96 – 0.73 (m, 5H), 0.61 – 0.47 (m, 1H), 0.41 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.3, 145.5, 135.0, 131.4, 128.5, 125.0, 119.4, 91.82, 91.77, 55.15, 38.99, 30.18, 27.37, 23.17, 21.94, 21.88, 21.45, 13.78. ^{11}B NMR (160 MHz, $CDCl_3$) δ 35.04. IR (neat): ν_{max} 3041.97 (w), 2953.67 (m), 2953.367 (m), 2867.94 (m), 1709.60 (s), 1116.56 (s), 781.19 (s) cm^{-1}. HRMS (DART) for $C_{23}H_{29}BO_3$ $[M+H]^+$: Calc'd: 364.22825, found: 365.22882. $[\alpha]^{20}_D$: 3.599 (c = 1g/100 mL, $CHCl_3$, *l* = 50 mm).

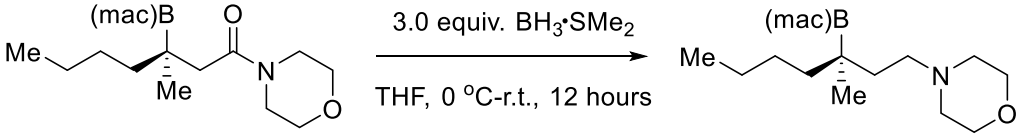
Reduction to Aldehyde



(S)-3-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-3-methylheptanal (2.99). To an oven-dried 2-dram vial equipped with a magnetic stir bar in an argon-filled glovebox was added 3-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-3-methyl-1-morpholinoheptan-1-one (**2.76**) (43.5 mg, 0.1 mmol, 1.0

equiv.) and THF (1.0 mL). This flask was sealed with a septum, and then removed from the glovebox. The flask was placed under a nitrogen atmosphere and cooled to 0 ˚C using an ice bath. Commercial DIBAL-H solution (1 M in hexane, 0.20 mL, 2.0 equiv.) was added dropwise. Reaction was allowed to warm up to room temperature and stirred for 30 min. Then, reaction was quenched by 0.5 mL methanol and filtered through a silica plug eluted with diethyl ether and concentrated under reduced pressure. The crude mixture was purified by silica gel chromatography (eluted with 5% ethyl acetate in hexane) to isolate the title compound (25.0 mg, 0.0714 mmol, 70.5% yield) as a white solid. Product Rf = 0.55 in 10% ethyl acetate: 90% hexane (UV active and stains pale yellow with potassium permanganate stain).; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.62 (s, 1H), 7.77 (d, *J* = 8.1 Hz, 2H), 7.60 – 7.51 (m, 4H), 2.53 (d, *J* = 17.1 Hz, 1H), 2.23 (d, *J* = 17.1 Hz, 1H), 1.77 (d, *J* = 23.6 Hz, 6H), 1.25 – 1.19 (m, 2H), 1.17 – 1.11 (m, 1H), 0.95 – 0.92 (m, 2H), 0.89 (s, 3H), 0.80 – 0.74 (m, 1H), 0.53 (t, *J* = 7.1 Hz, 3H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 203.4, 145.1, 145.0, 134.9, 131.4, 128.51, 128.49, 125.25, 125.23, 119.49, 119.44, 92.1, 54.2, 39.3, 27.6, 23.2, 22.1, 22.0, 21.9, 13.9.; ^{11}B NMR (160 MHz, $CDCl_3$) δ 31.9.; IR (neat): ν_{max}, 2955.93 (m), 2928.01 (m), 2870.23 (m), 1719.90 (s), 1467.28 (m), 1117.15 (s), 1087.32 (s), 781.85 (s) cm^{-1}. HRMS (DART) for $C_{22}H_{27}BO_3$ $[M+H]^+$: Calc'd: 351.21260, found: 351.21289. $[\alpha]^{20}_D$: 2.001 (c = 1.0 g/mL, $CHCl_3$, *l* = 50 mm).

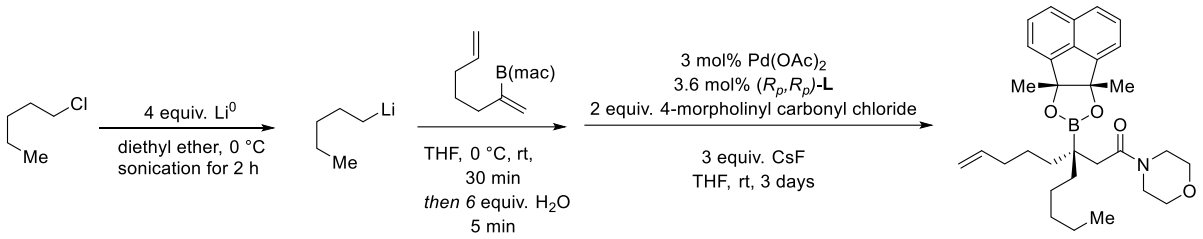
Reduction to Amine



4-((S)-3-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-3-methylheptyl)morpholine (2.100). To an oven-dried 2-dram vial equipped with a magnetic stir

bar in an argon-filled glovebox was added 3-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-3-methyl-1-morpholinoheptan-1-one (**2.76**) (43.5 mg, 0.1 mmol, 1.0 equiv.) and THF (1.0 mL). This flask was sealed with a septum, and then removed from the glovebox. The flask was placed under a nitrogen atmosphere and cooled to 0 ˚C using an ice bath. Borane dimethyl sulfide (neat, 22.8 mg, 0.30 mmol, 3.0 equiv.) was added. Reaction was allowed to warm up to room temperature and stirred for 12 hours. Then, reaction was quenched by 3 mL H_2O and extracted with diethyl ether for 3 times. Ether solution was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude mixture was purified by silica gel chromatography (eluted with 10% ethyl acetate in hexane) to isolate the title compound (36.8 mg, 0.0873mmol, 87.3% yield) as a colorless oil. Product Rf = 0.55 in 20% ethyl acetate: 80% hexane (UV active and stains pale yellow with potassium permanganate stain).; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.1 Hz, 2H), 7.62 – 7.53 (m, 4H), 3.87 (q, *J* = 8.7 Hz, 2H), 3.23 (dd, *J* = 31.7, 12.5 Hz, 2H), 2.60 (dd, *J* = 25.3, 12.3 Hz, 2H), 2.41 (td, *J* = 12.2, 4.7 Hz, 1H), 2.17 (td, *J* = 12.3, 3.8 Hz, 1H), 2.06 (q, *J* = 9.6 Hz, 2H), 1.77 (s, 6H), 1.68 – 1.63 (m, 1H), 1.55 – 1.51 (m, 1H), 1.39 (d, *J* = 7.6 Hz, 1H), 1.16 (d, *J* = 9.5 Hz, 4H), 1.03 (dd, *J* = 12.0, 7.1 Hz, 1H), 0.87 (s, 3H), 0.78 (t, *J* = 6.8 Hz, 3H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 145.0, 144.9, 134.6, 131.5, 128.64, 128.57, 125.53, 125.46, 119.64, 119.58, 92.1, 61.66, 61.55, 57.9, 56.6, 39.2, 31.9, 27.9, 23.4, 22.1, 21.9, 21.1, 14.1.; ^{11}B NMR (160 MHz, $CDCl_3$) δ 35.5.; IR (neat): ν_{max}, 2956.71 (m), 2929.81 (m), 2870.72 (m), 2367.40 (br), 1459.80 (m), 1116.51 (s), 1077.45 (s), 783.15 (s) cm^{-1}. HRMS (DART) for $C_{26}H_{36}BNO_3$ $[M+H]^+$: Calc'd: 422.28610, found: 422.28687. $[\alpha]^{20}_D$: 10.998 (c = 1.0 g/mL, $CHCl_3$, *l* = 50 mm).

2.4.7 Synthesis of (+)-Adalinine



(R)-3-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-1-morpholino-3-pentyloct-7-en-1-one (2.131). To an oven-dried 25 ml round bottom flask equipped with a magnetic stir bar in an argon-filled glovebox was added 6bR,9aS)-8-(hepta-1,6-dien-2-yl)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (**2.129**) (632.2 mg, 2.0 mmol, 1.0 equiv.) and THF (4.0 mL). This flask was sealed with a septum, and then removed from the glovebox. The flask was placed under a nitrogen atmosphere and cooled to 0 ˚C using an ice bath. To a separate oven-dried 25.0 ml round bottom flask equipped with a magnetic stir bar was added n-pentyl chloride (532.97 mg, 5.0 mmol) and diethyl ether (10.0 ml) under argon. Lithium metal (154.10 mg, 20.0 mmol) was added at room temperature. Reaction was cooled down to 0 ˚C and sonicated at this temperature for 2 hours. Concentration of n-pentyllithium solution was determined to be 0.44 M (88% conversion from n-pentyl chloride) by using BHT titration and 1,10-phenathroline as indicator. Suitable amount of this n-pentyllithium solution (4.54 mL, 2.0 mmol, 1 equiv.) was added into boronic ester solution via syringe at 0 ˚C. Reaction was allowed to warm up to room temperature and stirred for 30 min. Then, deionized water (0.216 mL, 12.0 mmol, 6 equiv.) was added via syringe and allowed to stir for an additional 5 minutes. The solvent was carefully removed under reduced pressure and was brought back into the glovebox. To a separate oven-dried 2-dram vial equipped with a magnetic stir bar in the glovebox was added $Pd(OAc)_2$ (13.5 mg, 0.06 mmol, 0.03 equiv.), (R_p,R_p)-**2.52** (75.8 mg, 0.072 mmol, 0.036 equiv.), and 2 mL THF. This palladium solution was allowed to stir for 15 minutes at room temperature. Cesium fluoride (911.3 mg, 6.0 mmol, 3 equiv.) was added to the “ate” flask, followed by

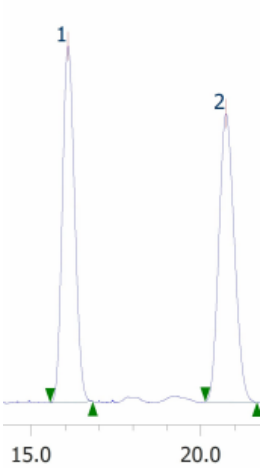
palladium solution, then 10 mL THF, and finally carbamoyl chloride (593.3 mg, 4.0 mmol, 2 equiv.) by mass. The reaction flask was sealed with a rubber septum, taped, and brought out of the glovebox. The reaction was stirred at room temperature for 3 days. The resulting mixture was filtered through a silica plug eluted with diethyl ether and concentrated under reduced pressure. The crude mixture was purified by silica gel chromatography (eluted with 40% diethyl ether: toluene) to isolate the title compound (693.0 mg, 1.37 mmol, 68.5% yield) as a white solid. Product Rf = 0.60 in 50% diethyl ether: 50% toluene (UV active and stains pale yellow with potassium permanganate stain).; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.0 Hz, 2H), 7.52 (dd, *J* = 16.4, 7.3 Hz, 4H), 5.51 (ddt, *J* = 16.9, 10.3, 6.6 Hz, 1H), 4.84 – 4.73 (m, 2H), 3.59 (dt, *J* = 32.3, 4.8 Hz, 4H), 3.38 (t, *J* = 4.9 Hz, 4H), 2.29 (d, *J* = 1.8 Hz, 2H), 1.75 (d, *J* = 1.3 Hz, 8H), 1.33 – 1.18 (m, 4H), 1.05 – 0.86 (m, 7H), 0.78 (ddq, *J* = 11.4, 7.0, 4.4 Hz, 1H), 0.68 (t, *J* = 7.0 Hz, 3H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.8, 146.9, 139.4, 135.1, 131.2, 128.3, 124.4, 118.91, 118.89, 113.8, 90.6, 66.8, 66.5, 45.9, 42.8, 41.11, 41.10, 34.5, 33.5, 33.1, 32.6, 23.8, 23.6, 22.6, 22.32, 22.31, 14.03.; ^{11}B NMR (160 MHz, $CDCl_3$) δ 29.6.; IR (neat): ν_{max}, 2968.22 (m), 2926.03 (m), 2855.75 (m), 1633.18 (s), 1457.99 (m), 1114.54 (s), 1081.15 (s), 781.28 (s) cm^{-1}. HRMS (DART) for $C_{31}H_{42}BNO_4$ $[M+H]^+$: Calc'd: 504.32797, found: 504.32885. $[\alpha]^{20}_D$: 12.789 (c = 1.0 g/mL, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Racemic compound was prepared according to the procedure described above with $Pd(OAc)_2$ (3 mol%) and BrettPhos (3.6 mol%) as the catalyst. Crude material was used for SFC without purification.

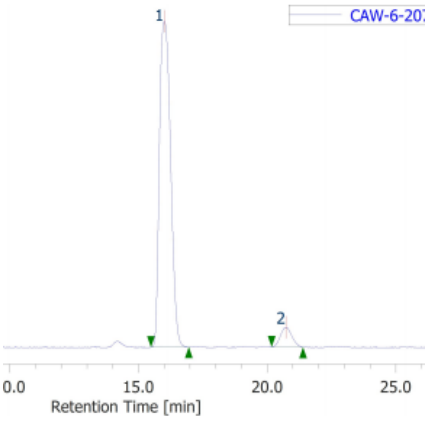
Chiral SFC (Chiralcel AD-H, 10% IPA, 1.0 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (R)-3-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho-[1,2-d][1,3,2]dioxaborol-8-yl)-1-morpholino-3-pentyl

Racemic

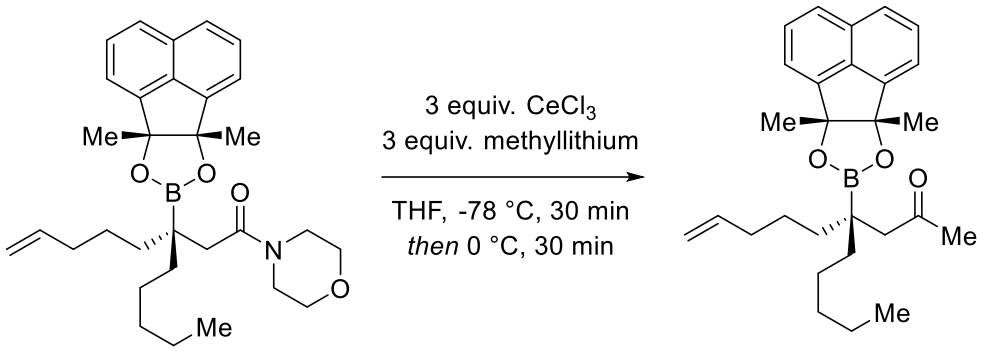


#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%
1	Unknown	11	16.080	4680576	186078	49.549
2	Unknown	11	20.733	4765772	150720	50.451

Enriched

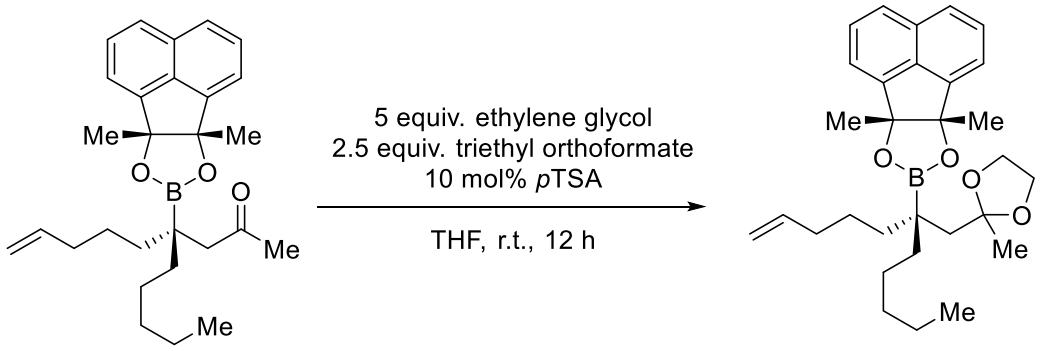


#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%
1	Unknown	11	15.997	46973169	1560917	94.126
2	Unknown	11	20.720	2931329	94493	5.874



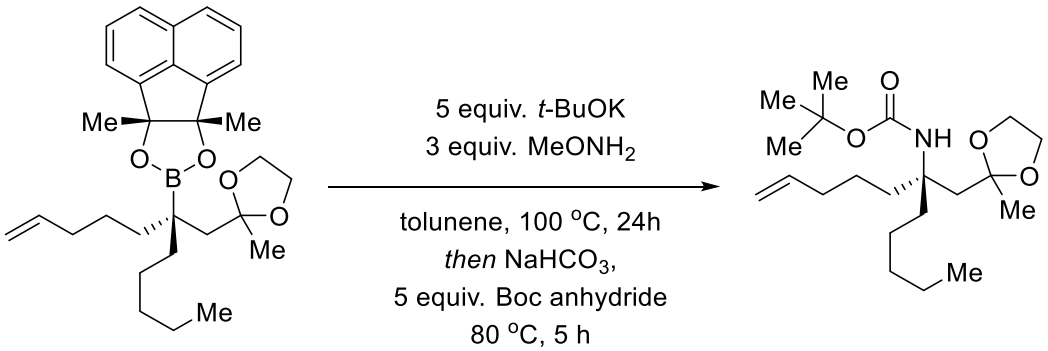
(R)-3-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-1-morpholino-3-pentyloct-7-en-1-one (2.132) To an oven-dried 25 ml round bottom flask equipped with a magnetic stir bar in an argon-filled glovebox was added $CeCl_3$ (1.21 g, 4.85 mol) and 20.0 mL THF. This flask was sealed with a septum, and then removed from the glovebox. The flask was placed under a nitrogen atmosphere and cooled to -78 ˚C using an acetone-dry ice bath. Commercial methyllithium solution (1.6 M in ether, 3 mL, 4.8 mol) was added dropwise via syringe. Reaction was stirred at -78 ˚C for 15 min and then at 0 ˚C for 10 min. Then, reaction was cooled to and kept at -78 ˚C without stirring. Supernatant of this solution was deemed as a 0.2 M methylcerium solution. To a separate 50 mL round bottom flask was added (R)-3-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-1-morpholino-3-pentyloct-7-en-1-one (**2.131**) (700.0 mg, 1.39 mmol, 1.0 equiv.) and 4.0 mL THF under argon. Reaction was cooled down to -78 ˚C. Then, the freshly prepared methylcerium solution was added (20.8 mL, 4.2 mmol, 3 equiv.) while stirring. Reaction was stirred at -78 ˚C for 30 min and then at 0 ˚C for another 30 min. The reaction was then quenched using 1.0 mL methanol and filtered through a silica plug eluted with diethyl ether and concentrated under reduced pressure. The resulting crude mixture was purified by silica gel chromatography (eluted with 3% ethyl acetate: hexane) to isolate the title compound (402.0 mg, 0.930 mmol, 66.2% yield) as a white solid. Product Rf = 0.50 in 10% ethyl acetate: 90% hexane (UV active and stains yellow with potassium

permanganate stain).; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.1 Hz, 2H), 7.59 – 7.50 (m, 4H), 5.46 (ddt, *J* = 17.1, 11.2, 6.7 Hz, 1H), 4.80 – 4.70 (m, 2H), 2.50 (s, 2H), 2.04 (s, 3H), 1.78 (d, *J* = 4.3 Hz, 6H), 1.72 (dd, *J* = 15.0, 7.2 Hz, 2H), 1.27 – 1.17 (m, 4H), 1.02 (dd, *J* = 13.3, 6.3 Hz, 1H), 0.93 (ddd, *J* = 28.4, 8.0, 4.1 Hz, 5H), 0.84 (dt, *J* = 12.6, 6.8 Hz, 1H), 0.73 – 0.68 (m, 1H), 0.63 (t, *J* = 6.9 Hz, 3H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 209.3, 145.6, 139.1, 134.9, 131.4, 128.4, 125.0, 119.3, 114.0, 91.68, 91.67, 51.2, 34.3, 33.7, 33.1, 32.42, 32.41, 30.2, 23.9, 23.7, 22.5, 21.9, 13.9.; ^{11}B NMR (160 MHz, $CDCl_3$) δ 35.4.; IR (neat): ν_{max}, 2927.75 (m), 2857.64 (m), 1710.57 (s), 1458.53 (m), 1116.96 (s), 1078.96 (s), 825.10 (s), 781.07 (s) cm^{-1}. HRMS (DART) for $C_{28}H_{37}BO_3$ $[M+H]^+$: Calc'd: 433.29085, found: 433.29090. $[\alpha]^{20}_D$: 9.299 (c = 1.0 g/mL, $CHCl_3$, *l* = 50 mm).



((6bR,9aS)-6b,9a-dimethyl-8-((R)-6-((2-methyl-1,3-dioxolan-2-yl)methyl)undec-1-en-6-yl)-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (2.133). To an oven dried 2-dram vial and stir bar was charged with (R)-3-((6bR,9aS)-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborol-8-yl)-1-morpholino-3-pentyloct-7-en-1-one (**2.132**) (370 mg, 0.856 mmol, 1.0 equiv.), 2 ml dry toluene, 4-methylbenzenesulfonic acid monohydrate (16.28 mg, 0.0856 μmol, 10 mmol%), triethyl orthoformate (317.03 mg, 2.14 mmol, 2.5 equiv.) and then lastly ethylene glycol (265.56 mg, 4.28 mmol, 5.0 equiv.). Reaction was allowed to stir for 12 hours. The resulting mixture was filtered through a silica plug eluted with diethyl ether and concentrated under reduced pressure. The resulting crude mixture was purified by silica gel chromatography (eluted with 3%

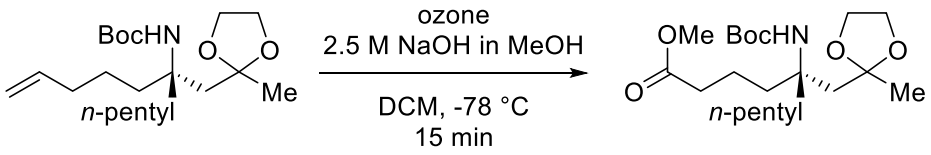
ethyl acetate: hexane) to isolate the title compound (370.0 mg, 0.776 mmol, 90.7% yield) as a white solid. Product Rf = 0.45 in 10% ethyl acetate: 90% hexane (UV active and stains yellow with potassium permanganate stain).; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.7 Hz, 2H), 7.61 – 7.50 (m, 4H), 5.74 – 5.61 (m, 1H), 4.95 – 4.79 (m, 2H), 3.26 (dt, *J* = 14.2, 8.1 Hz, 4H), 1.88 (q, *J* = 7.1 Hz, 2H), 1.75 (d, *J* = 14.2 Hz, 8H), 1.30 (dd, *J* = 18.7, 7.9 Hz, 6H), 1.13 (dt, *J* = 12.4, 7.7 Hz, 5H), 1.00 (s, 4H), 0.77 (t, *J* = 6.9 Hz, 3H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 145.93, 145.90, 139.5, 135.2, 131.2, 128.39, 128.37, 124.77, 124.76, 119.3, 113.9, 109.8, 91.3, 63.45, 63.41, 44.7, 34.6, 33.0, 32.7, 32.2, 25.2, 23.2, 22.9, 22.7, 22.5, 22.25, 22.23, 14.19, 14.15.; ^{11}B NMR (160 MHz, $CDCl_3$) δ 34.2.; IR (neat): ν_{max}, 2928.24 (m),1377.94 (m), 1293.32 (s), 1263.54 (m), 1115.86 (s), 1079.16 (s), 825.56 (s), 780.51 (s) cm^{-1}. HRMS (DART) for $C_{30}H_{41}BO_4$ $[M+H]^+$: Calc'd: 477.31707, found: 477.31931. $[\alpha]^{20}_D$: 11.998 (c = 1.0 g/mL, $CHCl_3$, *l* = 50 mm).



tert-butyl (S)-(6-((2-methyl-1,3-dioxolan-2-yl)methyl)undec-1-en-6-yl)carbamate (2.134). The title compound was prepared according to a literature procedure with slight modification.[140] In the glovebox, an oven dried 4-dram vial was added *t*-BuOK (280.52 mg, 2.50 mmol, 5 equiv.), ((6bR,9aS)-6b,9a-dimethyl-8-((R)-6-((2-methyl-1,3-dioxolan-2-yl)methyl)undec-1-en-6-yl)-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (**2.133**) (238.23 mg, 0.5 mmol) and THF (5.0

[140] Edelstein, E. K.; Grote, A. C.; Palkowitz, M. D.; Morken, J. P. *Synlett*, **2018**, *29*, 1749-1752

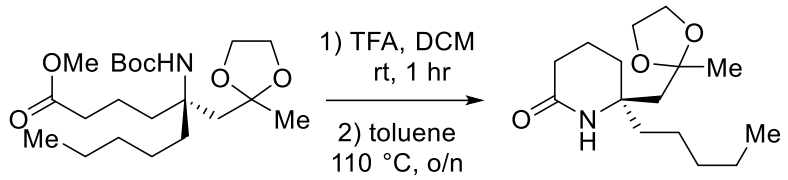
mL). Vial was sealed by a septum cap and removed out of glovebox. Previously prepared $MeONH_2$ solution (2.0 M, 0.750 mL, 3 equiv.) was taken out of the freezer and allowed to warm to room temperature before adding to the reaction mixture via syringe. Reaction was slowly heated to 100 ˚C and allowed to stir at that temperature for 24 hours. Then, reaction was allowed to cool to 80 ˚C. Then, Boc anhydride (545.62 mg, 2.5 mmol, 5.0 equiv.) was added, followed by 1 mL saturated $NaHCO_3$ water solution. Reaction was stirred at 80 ˚C for 5 hours. Then reaction was quenched with water and extracted three times with ether. The collected organics were washed with brine, dried with magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting crude mixture was purified by silica gel chromatography (eluted with 10% ethyl acetate: hexane) to isolate the title compound (145.5 mg, 0.394 mmol, 78.5% yield) as a white solid. Product Rf = 0.6 in 20% ethyl acetate: 80% toluene (UV inactive but stains yellow with potassium permanganate stain).; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.80 (ddt, *J* = 17.0, 10.2, 6.6 Hz, 1H), 5.11 – 4.91 (m, 3H), 3.93 (s, 4H), 2.07 – 1.97 (m, 4H), 1.71 (s, 4H), 1.41 (s, 9H), 1.34 (s, 4H), 1.30 – 1.20 (m, 7H), 0.87 (t, *J* = 7.1 Hz, 3H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 156.9, 139.0, 114.4, 110.3, 81.6, 64.4, 64.09, 64.08, 56.8, 34.1, 32.2, 28.5, 28.3, 26.3, 25.6, 23.1, 23.0, 22.7, 14.1.; IR (neat): ν_{max}, 3393.87 (br), 2931.02 (m), 1717.78 (s), 1498.95 (s), 1365,20 (s), 1116.74 (s), 1082.15 (s), 908.98 (s), 779.91 (s) cm^{-1}. HRMS (DART) for $C_{21}H_{39}NO_4$ $[M+H]^+$: Calc'd: 370.29519, found: 370.29484. $[\alpha]^{20}_D$: 11 (c = 1.0 g/mL, $CHCl_3$, *l* = 50 mm).



methyl (S)-5-((tert-butoxycarbonyl)amino)-5-((2-methyl-1,3-dioxolan-2-yl)methyl)decanoate (2.135). The title compound was prepared according to a literature procedure with slight modification.[141] A 2.5 M methanolic NaOH was freshly prepared by mixing pulverized solid NaOH and dry methanol under a nitrogen in an oven dry vial equipped with a magnetic stir bar. Mixture was allowed to stir for 1 hour at room temperature. A solution tert-butyl (S)-(6-((2-methyl-1,3-dioxolan-2-yl)methyl)undec-1-en-6-yl)carbamate (**2.134**) (115 mg, 311.20 μmol, 1 equiv.) in 15 mL dry dichloromethane and 2.5 M methanolic NaOH (0.622 mL, 1.56 mmol, 5 equiv.) was stirred at -78 ˚C using dry an ice/acetone bath. Ozone was passed through the solution. Clear solution changed to an orange color and an orange precipitate formed. After about 10 minutes, orange solution changed to a blue color, indicating reaction completion. The reaction mixture was diluted with diethyl ether and water and allowed to warm to room temperature. The aqueous layer was extracted three times with ether and collect organic layers were dried over magnesium sulfate, filtered, and concentrated under vacuum. The crude mixture was purified by silica gel chromatography with deactivated silica (2% triethylamine:98% hexanes) and eluted with 10% ethyl acetate:hexanes to isolate the title compound (65.3 mg, 0.163 mmol, 52.3% yield) as a clear oil. Product Rf = 0.4 in 20% ethyl acetate: 80% hexanes (not UV active and stains blue with *para*-anisaldehyde stain).; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.15 (s, 1H), 3.93 (s, 3H), 3.66 (s, 3H), 2.29 (t, *J* = 7.5 Hz, 2H), 1.99 (s, 2H), 1.82 – 1.51 (m, 6H), 1.41 (s, 10H), 1.35 – 1.17 (m, 9H), 0.88 (t, *J* = 7.3 Hz, 2H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.3, 110.4, 64.19, 64.18, 56.9, 51.6, 41.3, 34.5, 34.1, 32.3, 32.1, 28.6, 28.5, 25.7, 23.3, 22.8, 19.4, 19.0, 14.22. IR (neat): ν_{max}, 3381.54 (bm), 2952.02 (m), 2928.94 (m), 2869.76 (m), 1736.51 (s), 1715.18 (s), 1501.05 (m), 1364.00 (m),

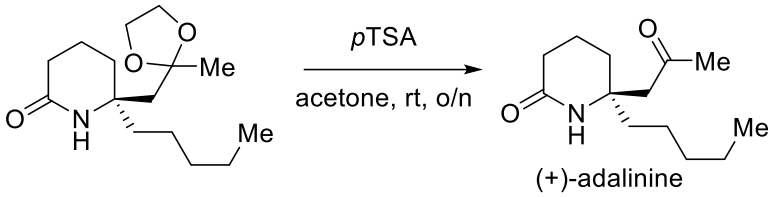
[141] Marshall, J. A.; Garofalo, A. W. *J. Org. Chem.* **1993**, *58*, 3675-3680

1166.11 (s) cm^{-1}. HRMS (DART) for $C_{21}H_{40}NO_6$ $[M+H]^+$: Calc'd: 402.28501, found: 402.28522. $[\alpha]^{20}_D$: 5.5 (c = 1.0 g/ 100 mL, $CHCl_3$, *l* = 50 mm).



(S)-6-((2-methyl-1,3-dioxolan-2-yl)methyl)-6-pentylpiperidin-2-one (2.136). To an oven-dried vial equipped with a magnetic stir bar and septum under nitrogen was charged with methyl 5-(tert-butoxycarbonylamino)-5-[(2-methyl-1,3-dioxolan-2-yl)methyl]decanoate (120.6 mg, 300.35 μmol, 1 equiv.) (**2.135**) and 5 mL dry dichloromethane. Trifluoroacetic acid (0.440 mL, 5.7 mmol, 20 equiv.) was added via syringe dropwise at room temperature. Reaction was allowed stir at that temperature for 1 hour. Reaction was quenched with saturated sodium bicarbonate (aqueous). Aqueous layer was extracted 3 times with ethyl ether. Collected organics were washed with brine, dried with magnesium sulfate, filtered, and concentrated under vacuum to yield a clear oil. The resulting oil was dissolved in 5 mL dry toluene in an oven-dried vial equipped with a magnetic stir bar and enclosed with a Teflon lined hard cap and sealed with electrical tape. Solution was heated to 110 ˚C and allowed to stir overnight at that temperature. The resulting solution was allowed to cool to room temperature and concentrated under vacuum. The crude mixture was purified with neutral alumina chromatography eluted with 100% ethyl acetate to isolate the title compound (25.9 mg, 0.096 mmol, 32% yield) as a clear oil. Product Rf is 0.4 in 10% methanol:ethyl acetate (silica TLC plate) (not UV active, stains red with *para*-anisaldehyde stain).; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.71 (s, 1H), 4.07 – 3.90 (m, 4H), 2.35 – 2.24 (m, 2H), 2.03 (d, *J* = 15.2 Hz, 1H), 1.89 (d, *J* = 15.3 Hz, 1H), 1.83 – 1.49 (m, 6H), 1.37 – 1.17 (m, 9H), 0.89 (t, *J* = 7.2 Hz, 3H).; ^{13}C NMR (151

MHz, $CDCl_3$) δ 171.8, 110.1, 64.1, 63.7, 57.0, 45.9, 40.1, 32.5, 32.4, 30.9, 25.9, 24.0, 22.7, 17.0, 14.2.; IR (neat): ν_{max} 2950.64 (m), 2929.16 (m), 2869.37 (m), 1656.60 (s), 1457.11 (m), 1401.74 (m), 1374.53 (m), 1040.84 (m) cm^{-1}. HRMS (DART) for $C_{15}H_{28}NO_3$ $[M+H]^+$: Calc'd: 270.20637, found: 270.20688. $[\alpha]^{20}_D$: 14 (c = 0.2 g/ 100 mL, $CHCl_3$, *l* = 50 mm)



(S)-6-(2-oxopropyl)-6-pentylpiperidin-2-one (2.137). A vial equipped with a magnetic stir bar was charged with 6-[(2-methyl-1,3-dioxolan-2-yl)methyl]-6-pentyl-piperidin-2-one (20.6 mg, 76.47 μmol, 1 equiv.) (**2.136**) and 10 mL of wet acetone. 4-methylbenzenesulfonic acid monohydrate (145.46 mg, 764.72 μmol, 10 equiv.) was added directly at room temperature and reaction was allowed to stir for 8 hours. Reaction was quenched with 1 mL saturated sodium carbonate (aqueous). The aqueous layer was extracted ethyl acetate three times. The collected organics were washed with brine, dried with magnesium sulfate, filtered, and concentrated to yield a clear oil. The crude mixture was purified using neutral alumina chromatography by eluting with 100% ethyl acetate and then 5% methanol:95% ethyl acetate. Product Rf is 0.3 in 10% methanol:ethyl acetate (silica TLC plate) (not UV active, stains red with *para*-anisaldehyde stain).; ^1H NMR (600 MHz, $CDCl_3$) δ 6.57 (s, 1H), 2.69 (d, *J* = 17.8 Hz, 1H), 2.63 (d, *J* = 17.8 Hz, 1H), 2.36 – 2.23 (m, 2H), 2.13 (s, 3H), 1.85 – 1.67 (m, 4H), 1.67 – 1.52 (m, 2H), 1.34 – 1.08 (m, 6H), 0.87 (t, *J* = 7.0 Hz, 3H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 207.3, 171.6, 56.3, 51.4, 39.4, 32.1, 32.0, 31.5, 31.4, 24.0, 22.6, 17.4, 14.1.; IR (neat): ν_{max} 2950.70 (m), 2928.58 (m), 2858.05 (m), 1704.60

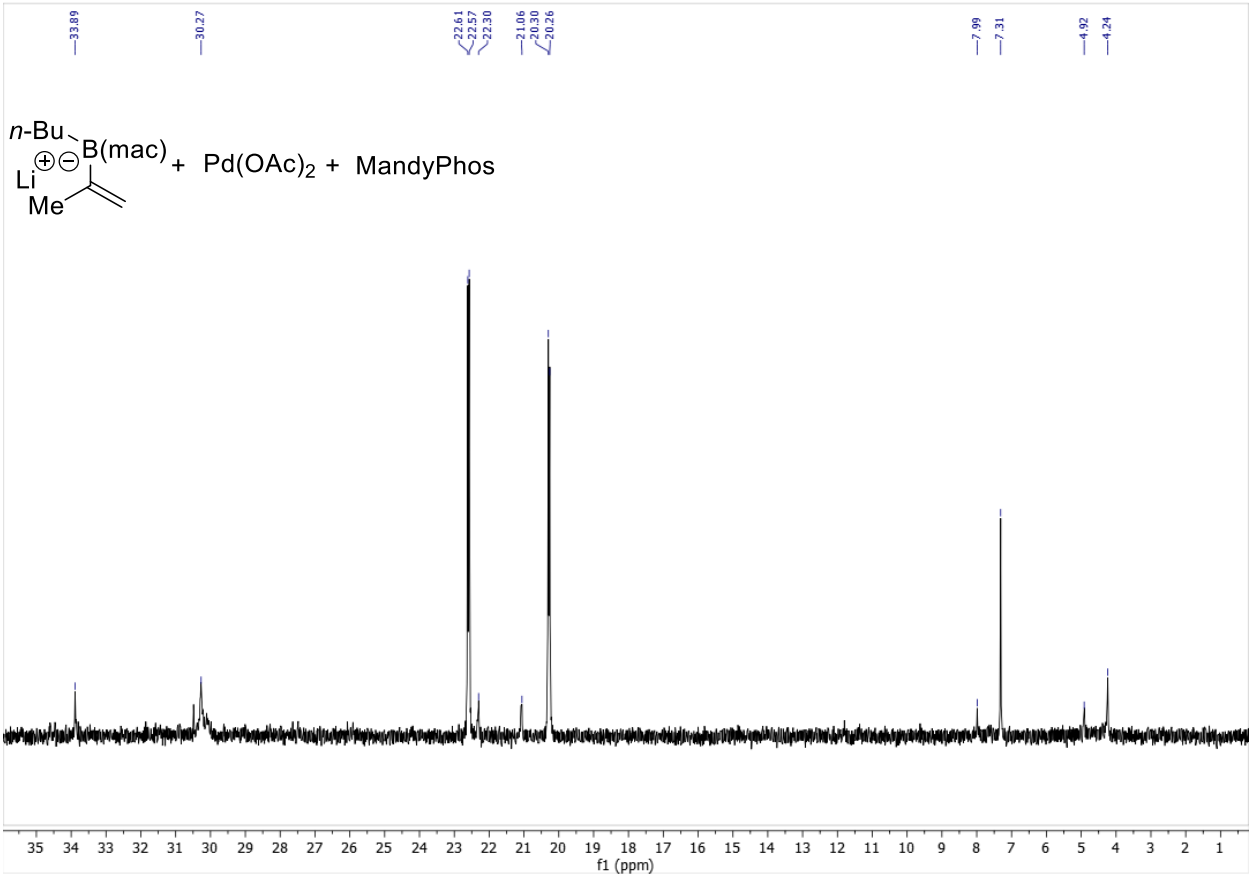
(m), 1656.58 (s), 1455.59 (m), 1401.68 (m), 1361.75 (m) cm^{-1}. HRMS (DART) for $C_{13}H_{24}NO_2$ $[M+H]^+$: Calc'd: 226.18016, found: 226.17989 $[\alpha]^{20}_D$: 21 (c = 0.2 g/100 mL, $CHCl_3$, *l* = 50 mm)

2.4.8 ^{31}P NMR Studies

(Figure 2.3.2)

Preparation of Equation "A"

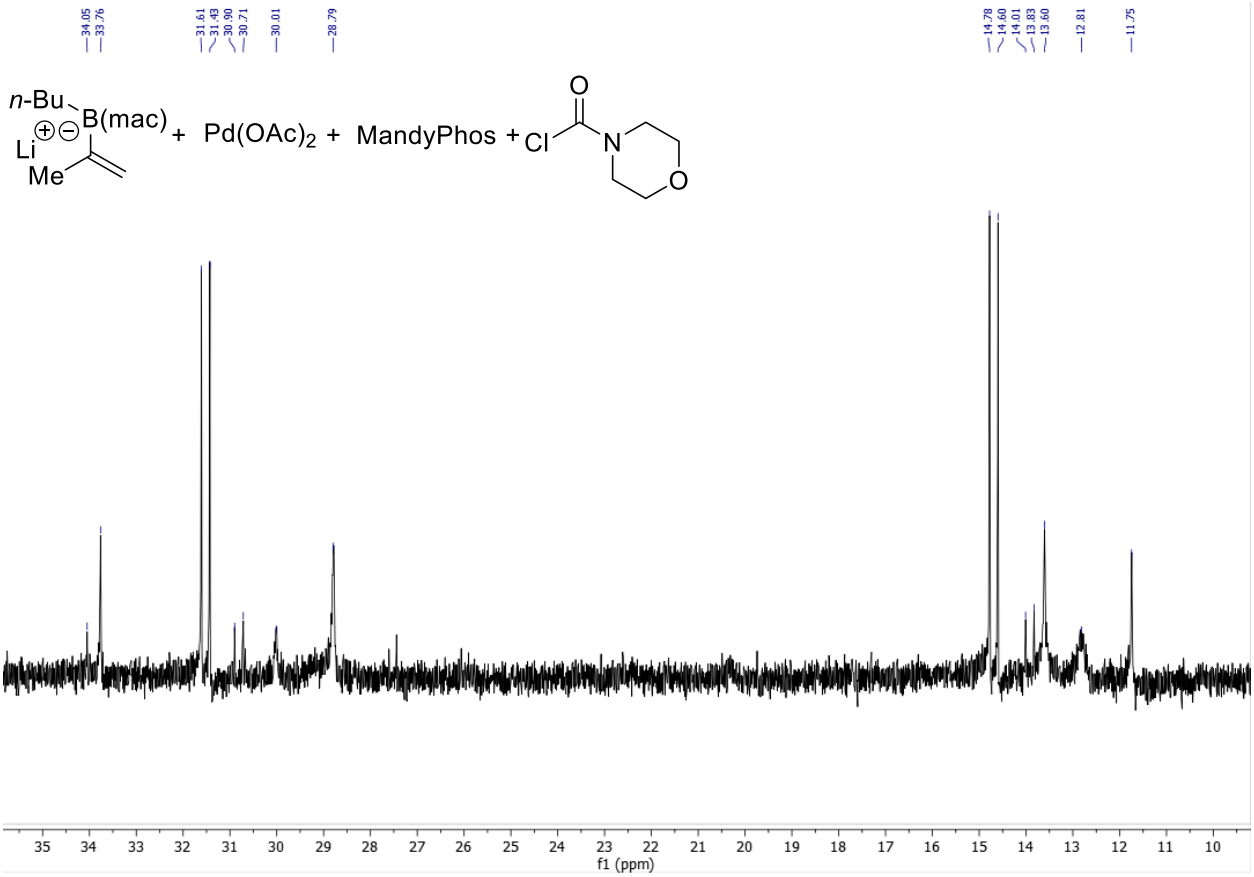
To an oven-dried 2-dram vial equipped with a magnetic stir bar in an argon-filled glovebox was added isopropenyl boronic acid "mac" ester (53 mg, 0.2 mmol, 1.0 equiv.) and THF (0.4 mL). This vial was sealed with a septum cap, and then removed from the glovebox. The vial was placed under a nitrogen atmosphere and cooled to 0 ˚C using an ice bath. Butyllithium solution (80.0 µL, 2.5 M, 0.2 mmol, 1.0 equiv.) was added dropwise to the stirring solution. Upon completion of addition, reaction was allowed to warm to room temperature and stirred for 30 minutes at that temperature. The solvent was carefully removed under reduced pressure to yield a white solid and was brought back into the glovebox. To a separate oven-dried 2-dram vial equipped with a magnetic stir bar in the glovebox was added $Pd(OAc)_2$ (0.01 mmol, 0.05 equiv.), (R_p,R_p)-**2.52** (0.012 mmol, 0.06 equiv.), and 0.2 mL THF-*d8*. This palladium solution was allowed to stir for 15 minutes at room temperature. 0.3 mL THF-*d8* was used to quantitatively transfer the "ate" complex and palladium solution to an NMR tube. ^{31}P NMR (243 MHz, THF-*d8*) δ 33.89, 30.27, 22.59 (d, *J* = 9.5 Hz), 22.30, 21.06, 20.28 (d, *J* = 9.4 Hz), 7.99, 7.31, 4.92, 4.24.



Preparation of Equation "B"

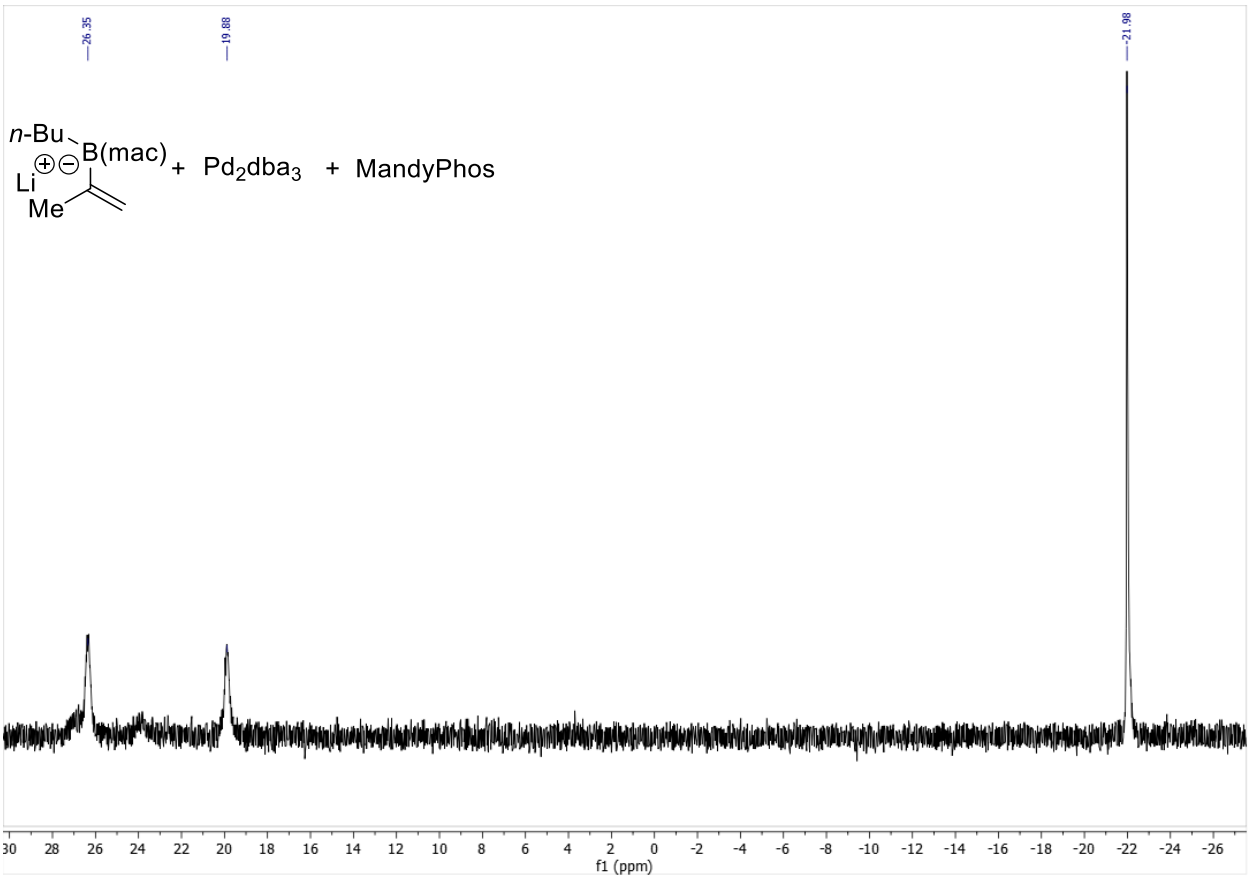
To an oven-dried 2-dram vial equipped with a magnetic stir bar in an argon-filled glovebox was added isopropenyl boronic acid "mac" ester (53 mg, 0.2 mmol, 1.0 equiv.) and THF (0.4 mL). This vial was sealed with a septum cap, and then removed from the glovebox. The vial was placed under a nitrogen atmosphere and cooled to 0 ˚C using an ice bath. Butyllithium solution (80.0 µL, 2.5 M, 0.2 mmol, 1.0 equiv.) was added dropwise to the stirring solution. Upon completion of addition, reaction was allowed to warm to room temperature and stirred for 30 minutes at that temperature. The solvent was carefully removed under reduced pressure to yield a white solid and was brought back into the glovebox. To a separate oven-dried 2-dram vial equipped with a magnetic stir bar in the glovebox was added $Pd(OAc)_2$ (0.01 mmol, 0.05 equiv.), (R_p,R_p)-**2.52**

(0.012 mmol, 0.06 equiv.), and 0.2 mL THF-*d8*. This palladium solution was allowed to stir for 15 minutes at room temperature. 0.3 mL THF-*d8* was used to quantitatively transfer the "ate" complex and palladium solution to an NMR tube. Morphine carbamoyl chloride (**2.74**) (60 mg, 0.4 mmol, 2 equiv.) was added via syringe directly to the NMR tube. ^{31}P NMR (243 MHz, THF-*d8*) δ 34.05, 33.76, 31.52 (d, J = 43.5 Hz), 30.81 (d, J = 45.0 Hz), 30.01, 28.79, 14.69 (d, J = 43.5 Hz), 13.92 (d, J = 44.1 Hz), 13.60, 12.81, 11.75.



Preparation of Equation "C"

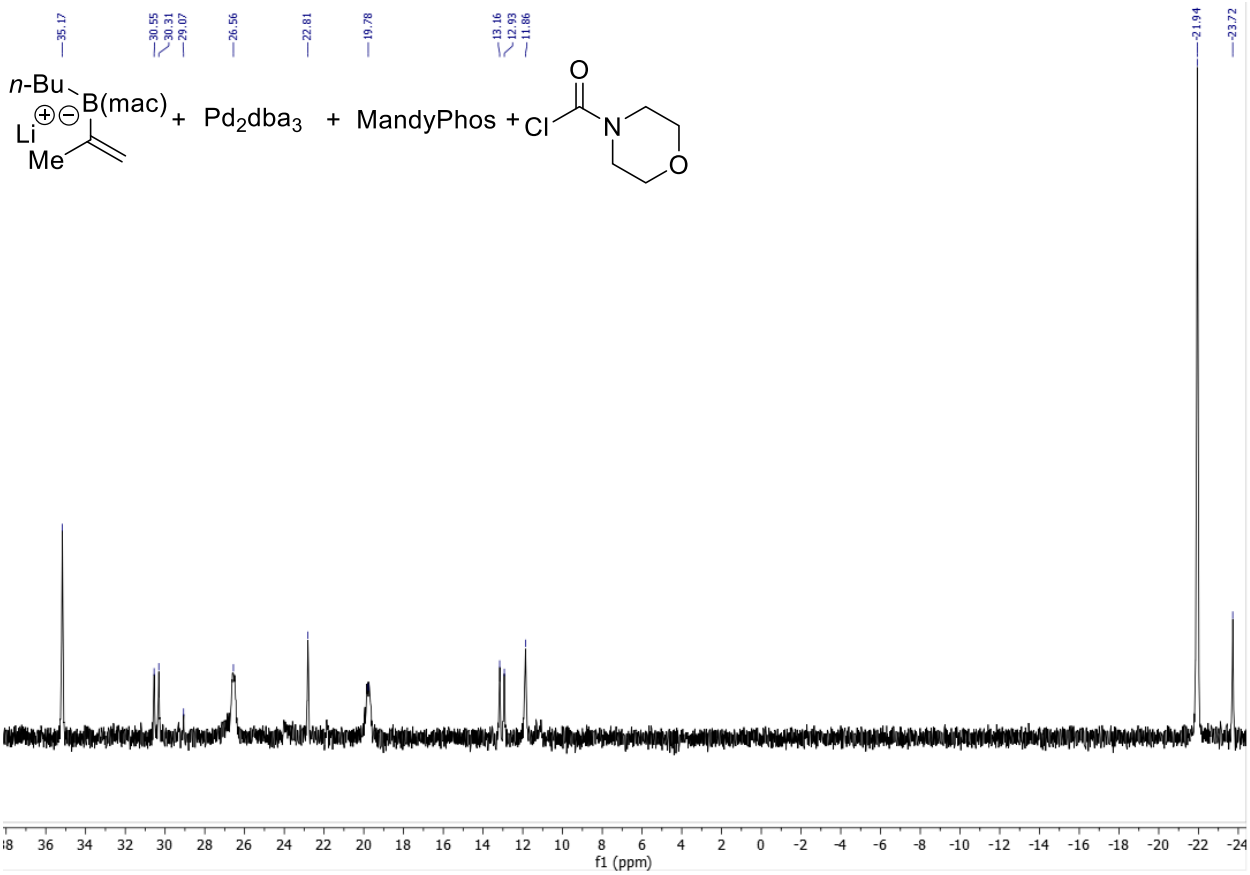
To an oven-dried 2-dram vial equipped with a magnetic stir bar in an argon-filled glovebox was added isopropenyl boronic acid "mac" ester (53 mg, 0.2 mmol, 1.0 equiv.) and THF (0.4 mL). This vial was sealed with a septum cap, and then removed from the glovebox. The vial was placed under a nitrogen atmosphere and cooled to 0 ˚C using an ice bath. Butyllithium solution (80.0 µL, 2.5 M, 0.2 mmol, 1.0 equiv.) was added dropwise to the stirring solution. Upon completion of addition, reaction was allowed to warm to room temperature and stirred for 30 minutes at that temperature. The solvent was carefully removed under reduced pressure to yield a white solid and was brought back into the glovebox. To a separate oven-dried 2-dram vial equipped with a magnetic stir bar in the glovebox was added $Pd_2(dba)_3$ (0.005 mmol, 0.025 equiv.), (R_p,R_p)-**2.52** (0.012 mmol, 0.06 equiv.), and 0.2 mL THF-*d8*. This palladium solution was allowed to stir for 1 hour at room temperature. 0.3 mL THF-*d8* was used to quantitatively transfer the "ate" complex and palladium solution to an NMR tube. Morphine carbamoyl chloride (**2.74**) (60 mg, 0.4 mmol, 2 equiv.) was added via syringe directly to the NMR tube. ^{31}P NMR (202 MHz, THF-*d8*) δ 26.35 (not resolved), 19.88 (not resolved), -21.98 (free MandyPhos).



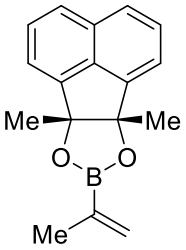
Preparation of Equation "D"

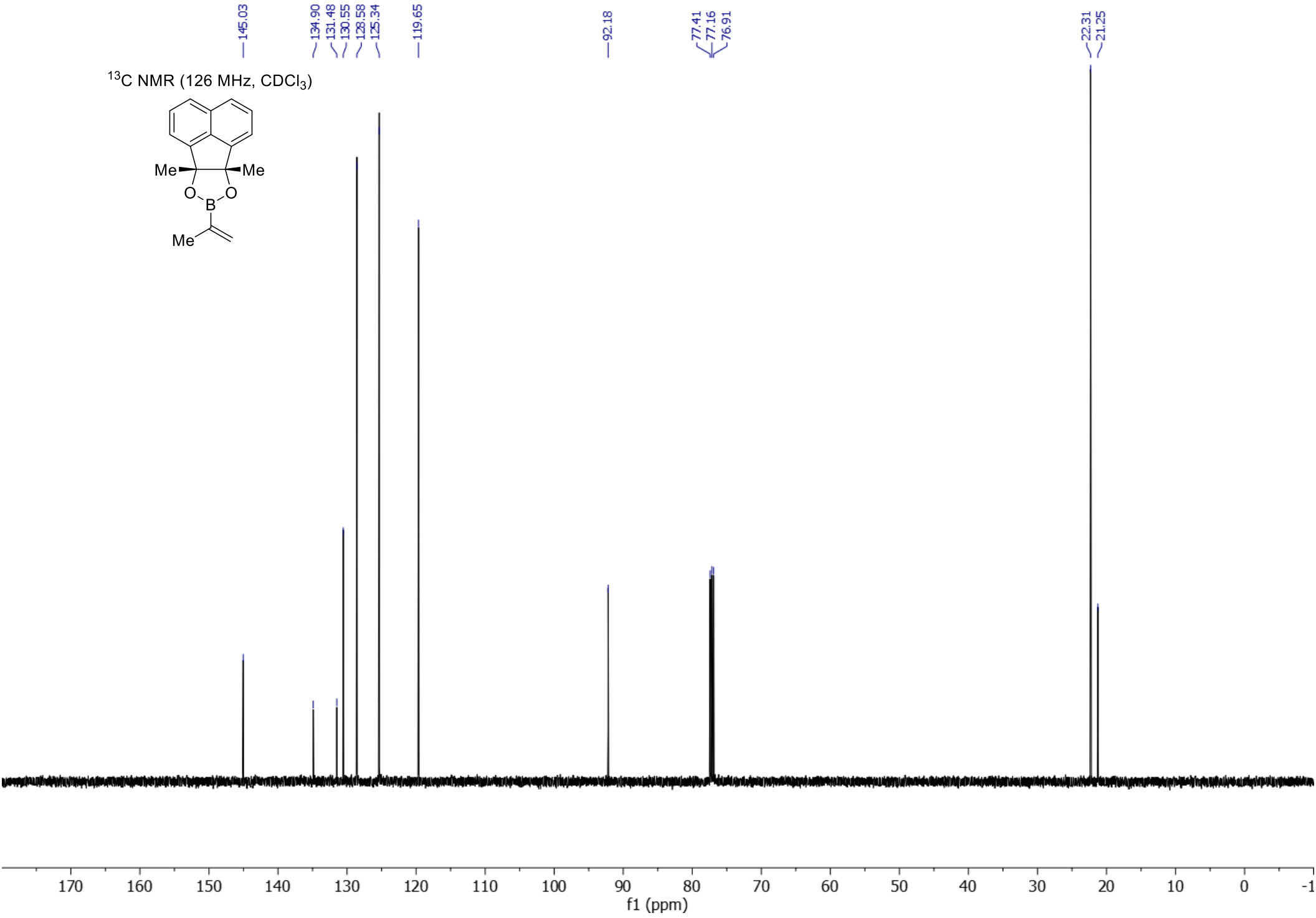
To an oven-dried 2-dram vial equipped with a magnetic stir bar in an argon-filled glovebox was added isopropenyl boronic acid "mac" ester (53 mg, 0.2 mmol, 1.0 equiv.) and THF (0.4 mL). This vial was sealed with a septum cap, and then removed from the glovebox. The vial was placed under a nitrogen atmosphere and cooled to 0 ˚C using an ice bath. Butyllithium solution (80.0 µL, 2.5 M, 0.2 mmol, 1.0 equiv.) was added dropwise to the stirring solution. Upon completion of addition, reaction was allowed to warm to room temperature and stirred for 30 minutes at that temperature. The solvent was carefully removed under reduced pressure to yield a white solid and was brought back into the glovebox. To a separate oven-dried 2-dram vial equipped with a magnetic stir bar in the glovebox was added $Pd_2(dba)_3$ (0.005 mmol, 0.025 equiv.), (R_p,R_p)-**2.52** (0.012 mmol, 0.06 equiv.), and 0.2 mL THF-*d8*. This palladium solution was allowed to stir for 1

hour at room temperature. 0.3 mL THF-*d8* was used to quantitatively transfer the "ate" complex and palladium solution to an NMR tube. Morphine carbamoyl chloride (**2.74**) (60 mg, 0.4 mmol, 2 equiv.) was added via syringe directly to the NMR tube and allowed to sit at room under an inert atmosphere for 18 hours. ^{31}P NMR (202 MHz, THF-*d8*) δ 35.17, 30.43 (d, J = 48.0 Hz), 29.07, 26.56, 22.81, 19.78, 13.05 (d, J = 47.2 Hz), 11.86, -21.94, -23.72.



^{1}H NMR (500 MHz, $CDCl_3$)




145.03
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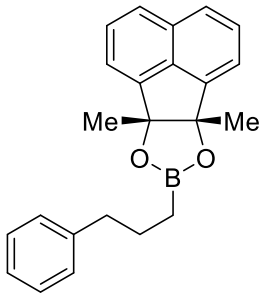
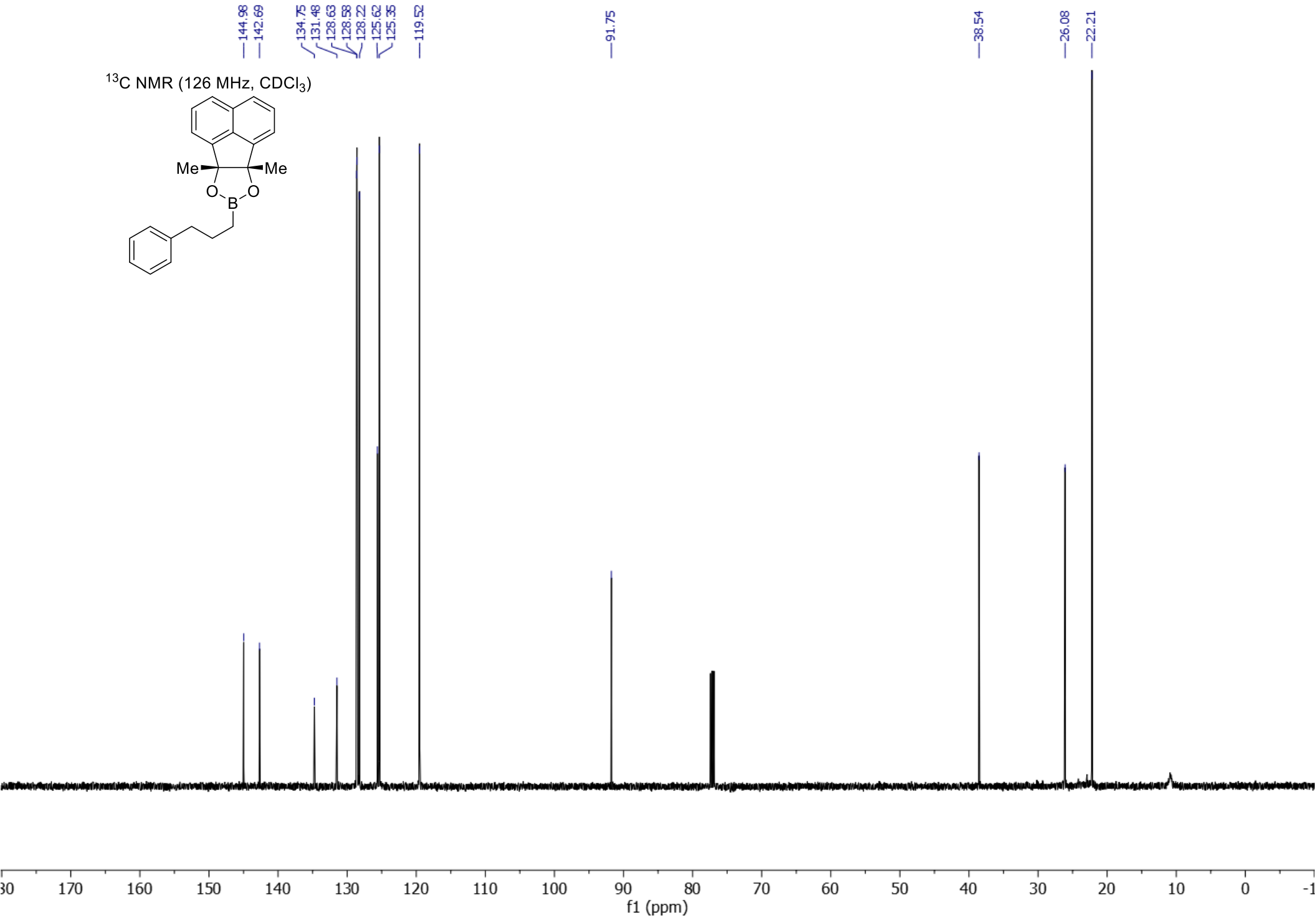
131.48
130.55
128.58
125.34
119.65
92.18
77.41
77.16
76.91
22.31
21.25
^{13}C NMR (126 MHz, $CDCl_3$)
Me
Me
O
O
B
Me
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
f1 (ppm)

^{1}H NMR (400 MHz, $CDCl_3$)

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128.63
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128.22
125.62
125.35
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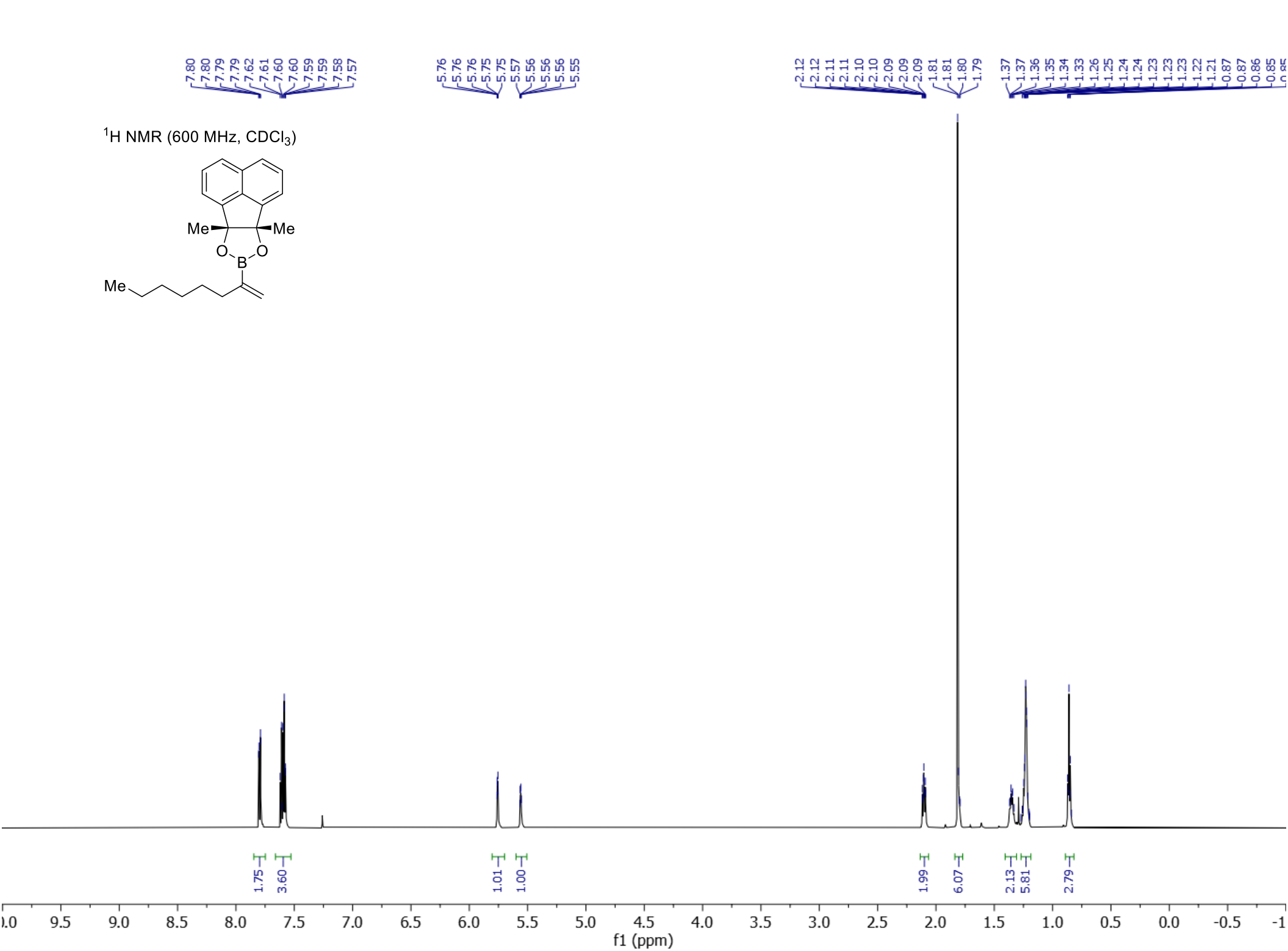
Me
O
B
O
f1 (ppm)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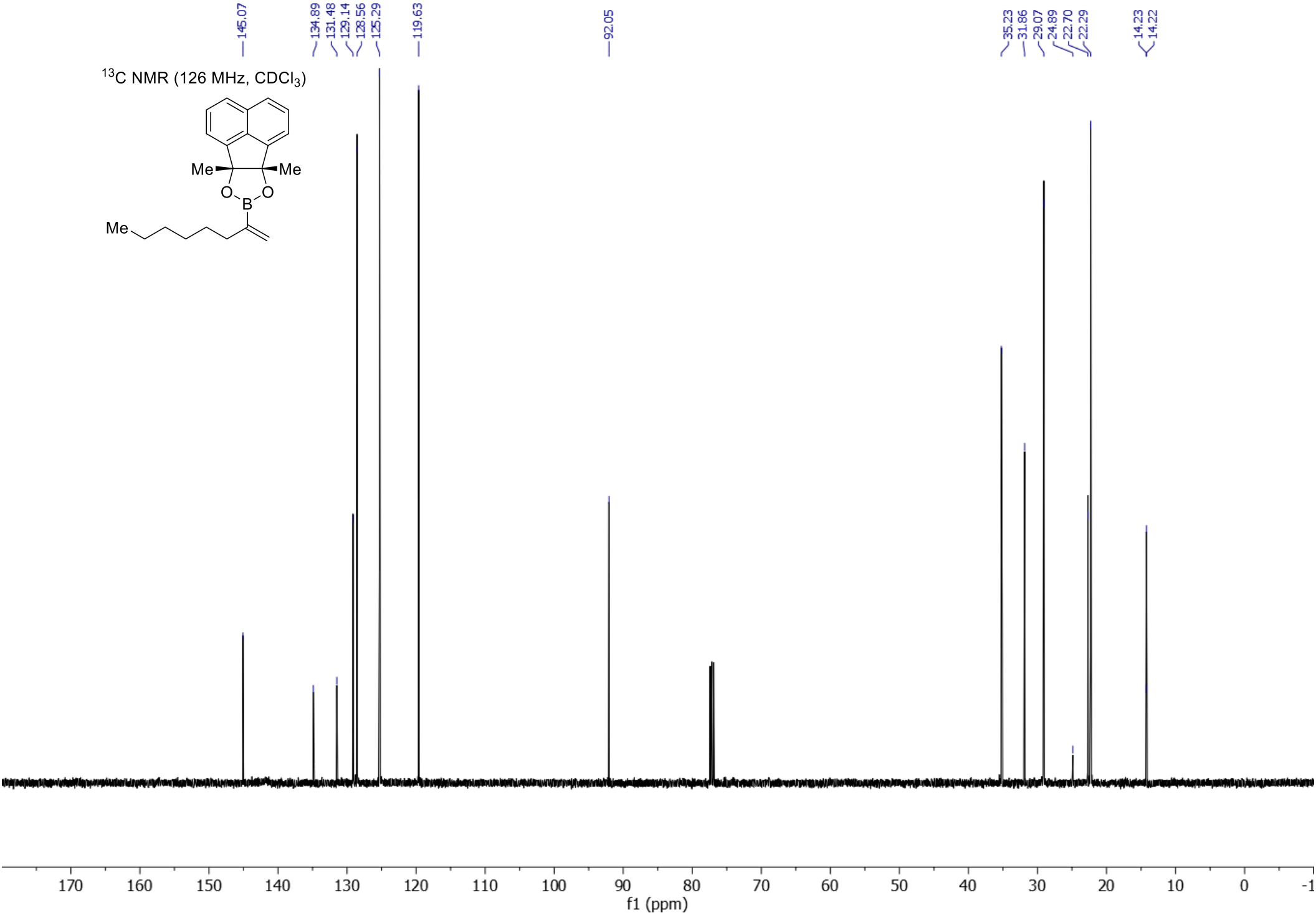
2.12 2.12 2.11 2.11 2.10 2.10 2.09 2.09 2.09 1.81 1.81 1.80 1.79
1.37 1.37 1.36 1.35 1.34 1.33 1.26 1.25 1.24 1.24 1.23 1.23 1.23 1.22 1.21 0.87 0.87 0.86 0.85
1H NMR (600 MHz, CDCl3)
Me
Me
O
O
B
Me
1.75
3.60
1.01
1.00
1.99
6.07
2.13
5.81
2.79
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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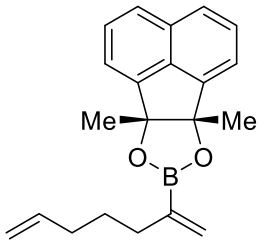
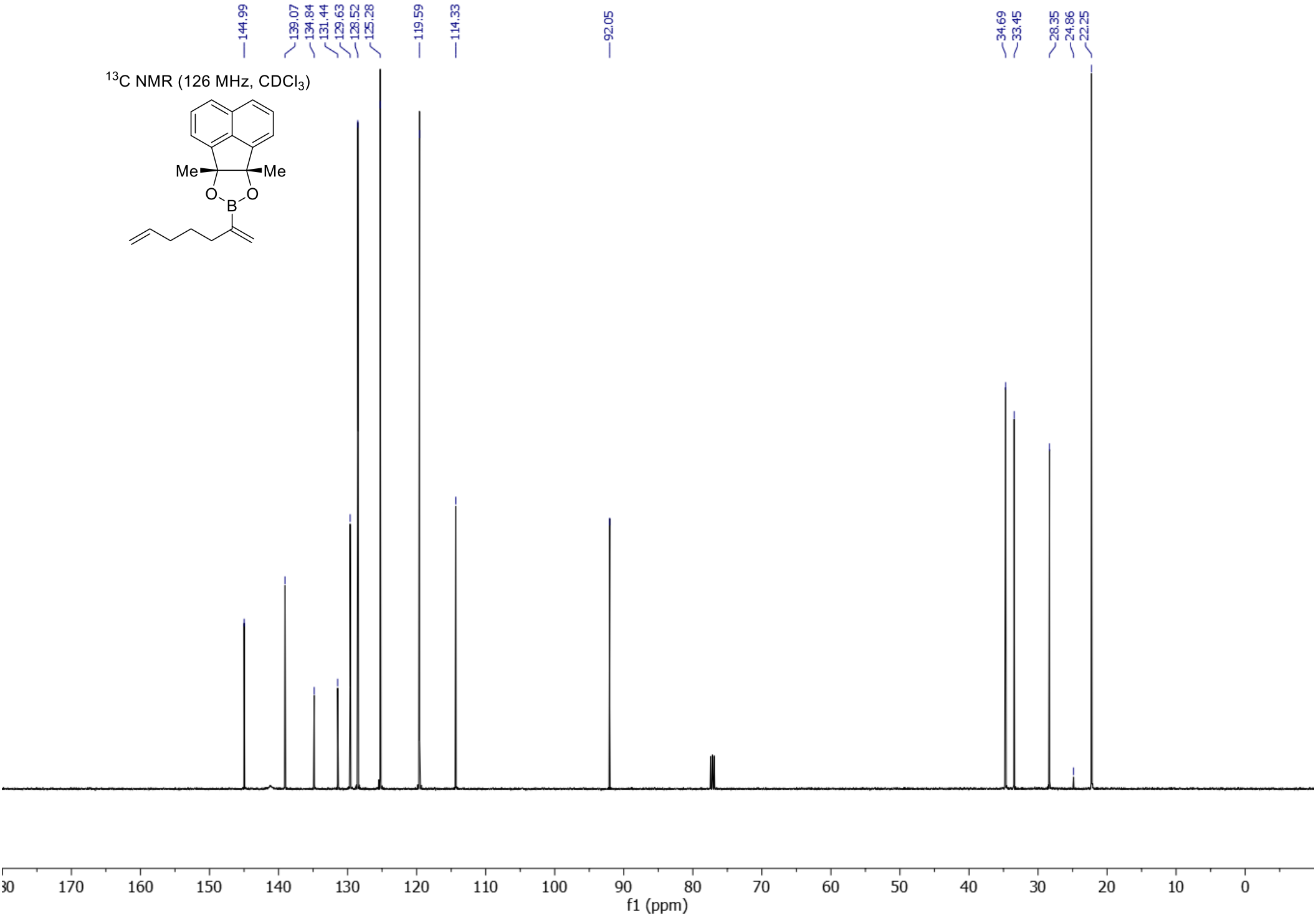
22.70
22.29
14.23
14.22
13C NMR (126 MHz, CDCl3)
Me
Me
O
B
O
Me
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
f1 (ppm)

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

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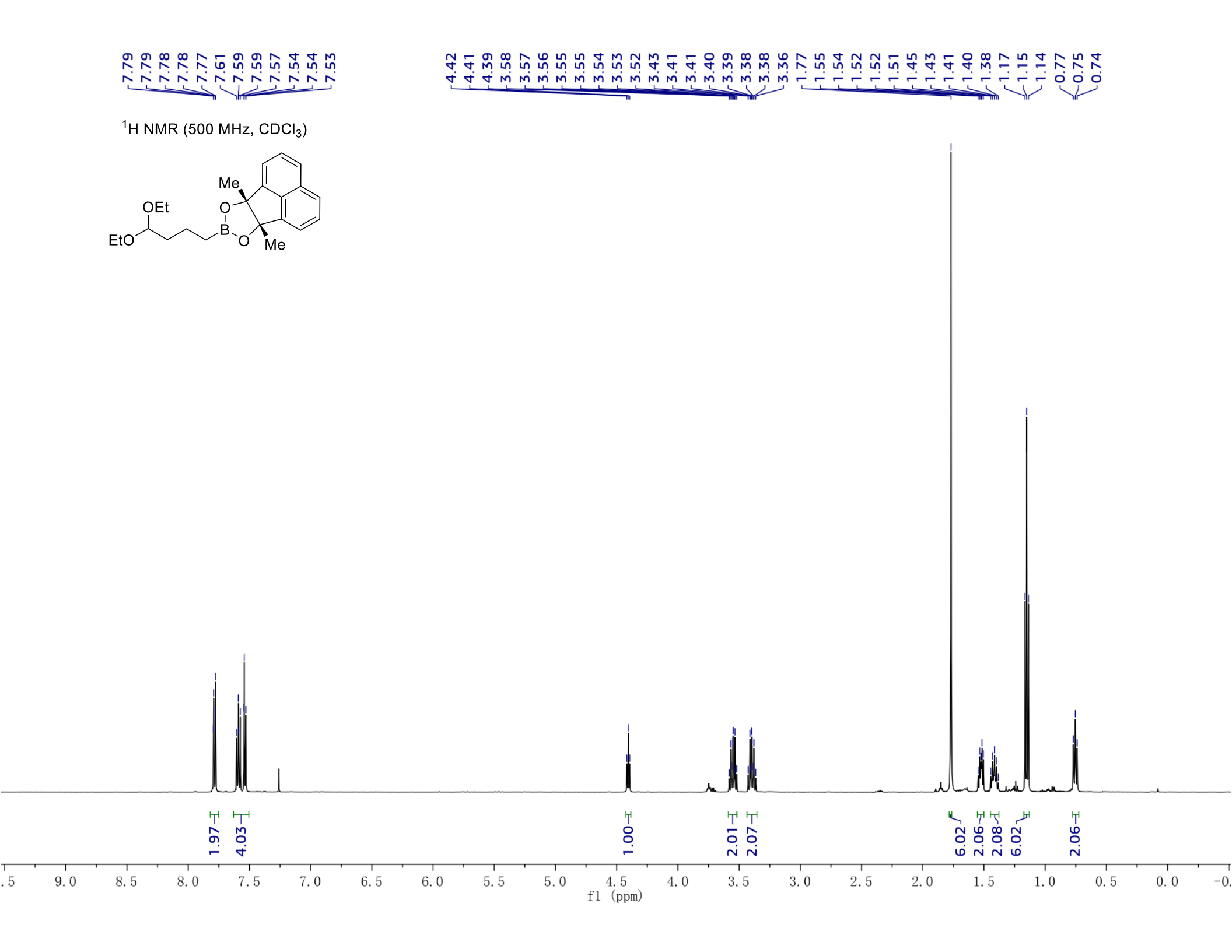
134.84
131.44
129.63
128.52
125.28
119.59
114.33
92.05
34.69
33.45
28.35
24.86
22.25
^{13}C NMR (126 MHz, $CDCl_3$)
Me
Me
O
B
O
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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7.78
7.78
7.77
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7.59
7.59
7.57
7.54
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4.41
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3.56
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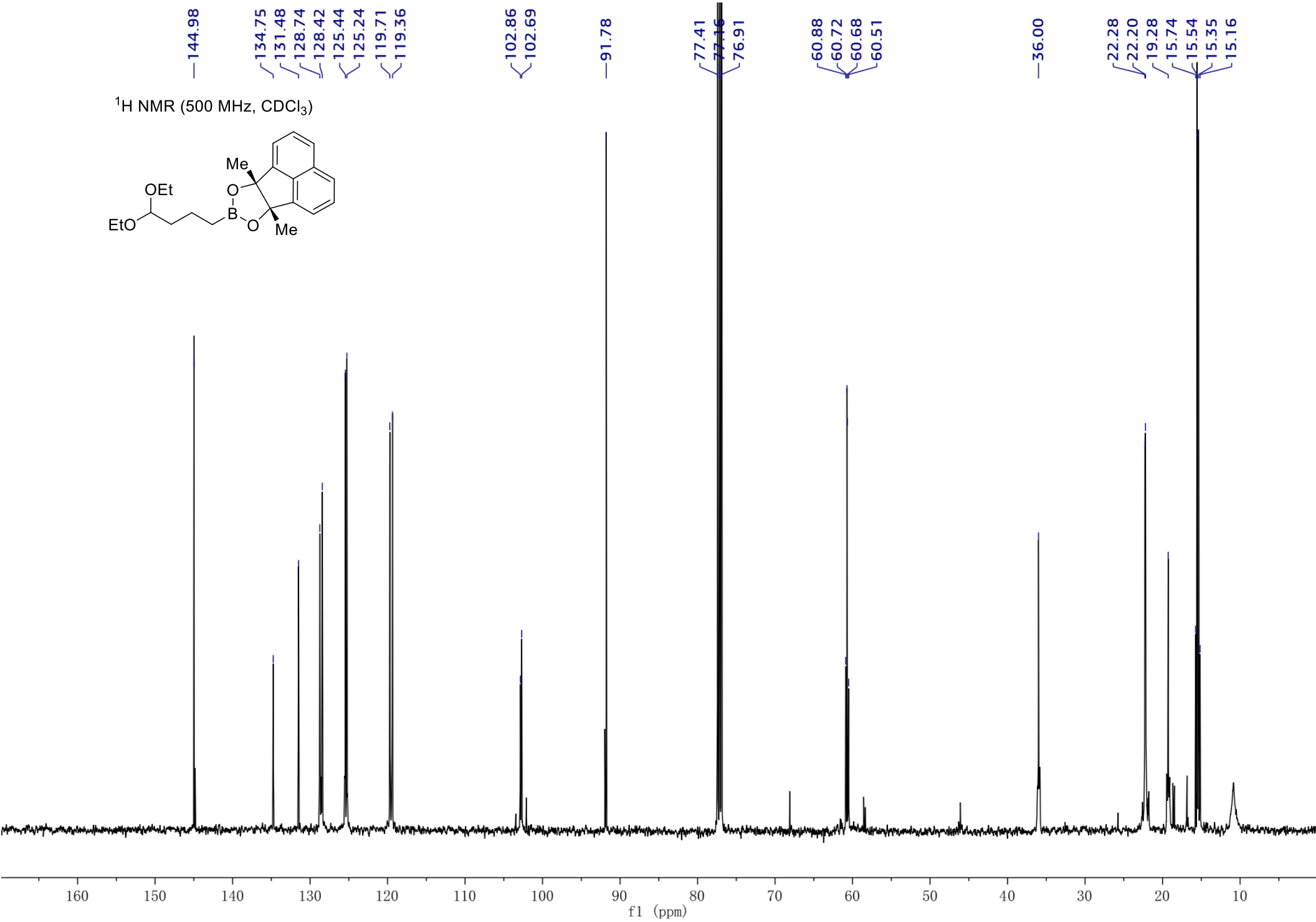
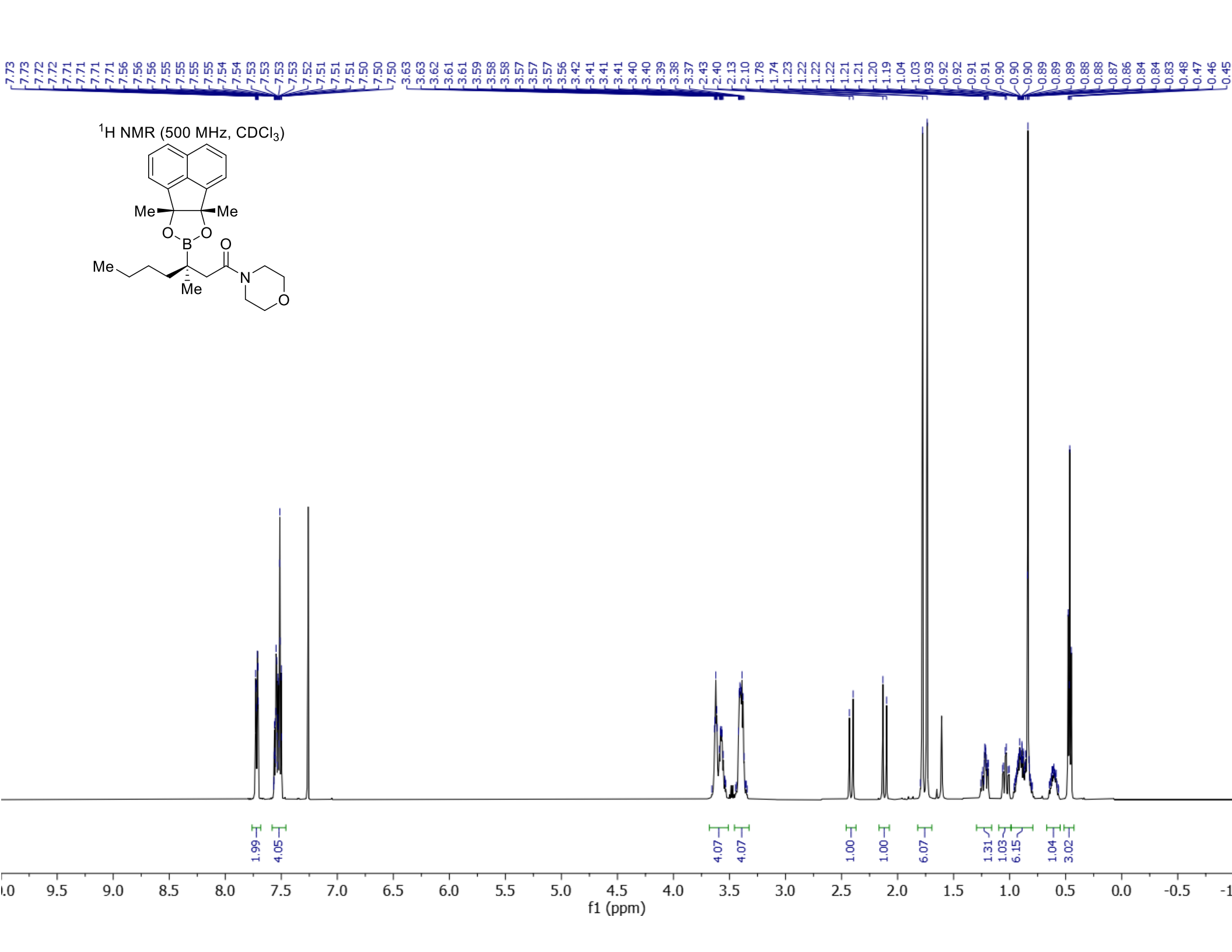
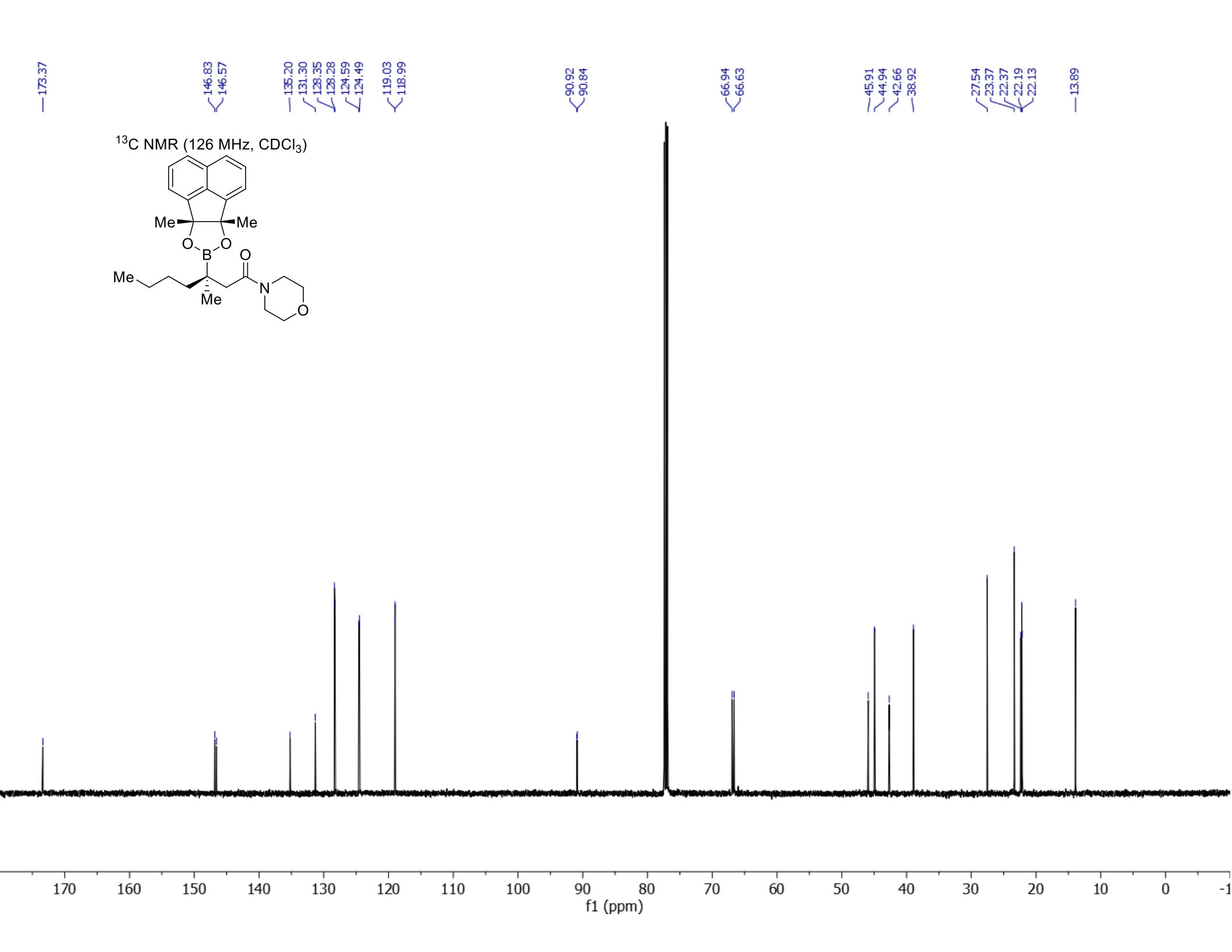
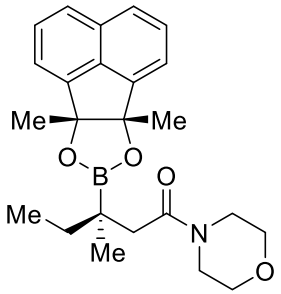
1.54
1.52
1.52
1.51
1.45
1.43
1.41
1.40
1.38
1.17
1.15
1.14
0.77
0.75
0.74
1H NMR (500 MHz, CDCl3)
Me
OEt
O
EtO
B
O
Me
1.97
4.03
1.00
2.01
2.07
6.02
2.06
2.08
6.02
2.06
f1 (ppm)

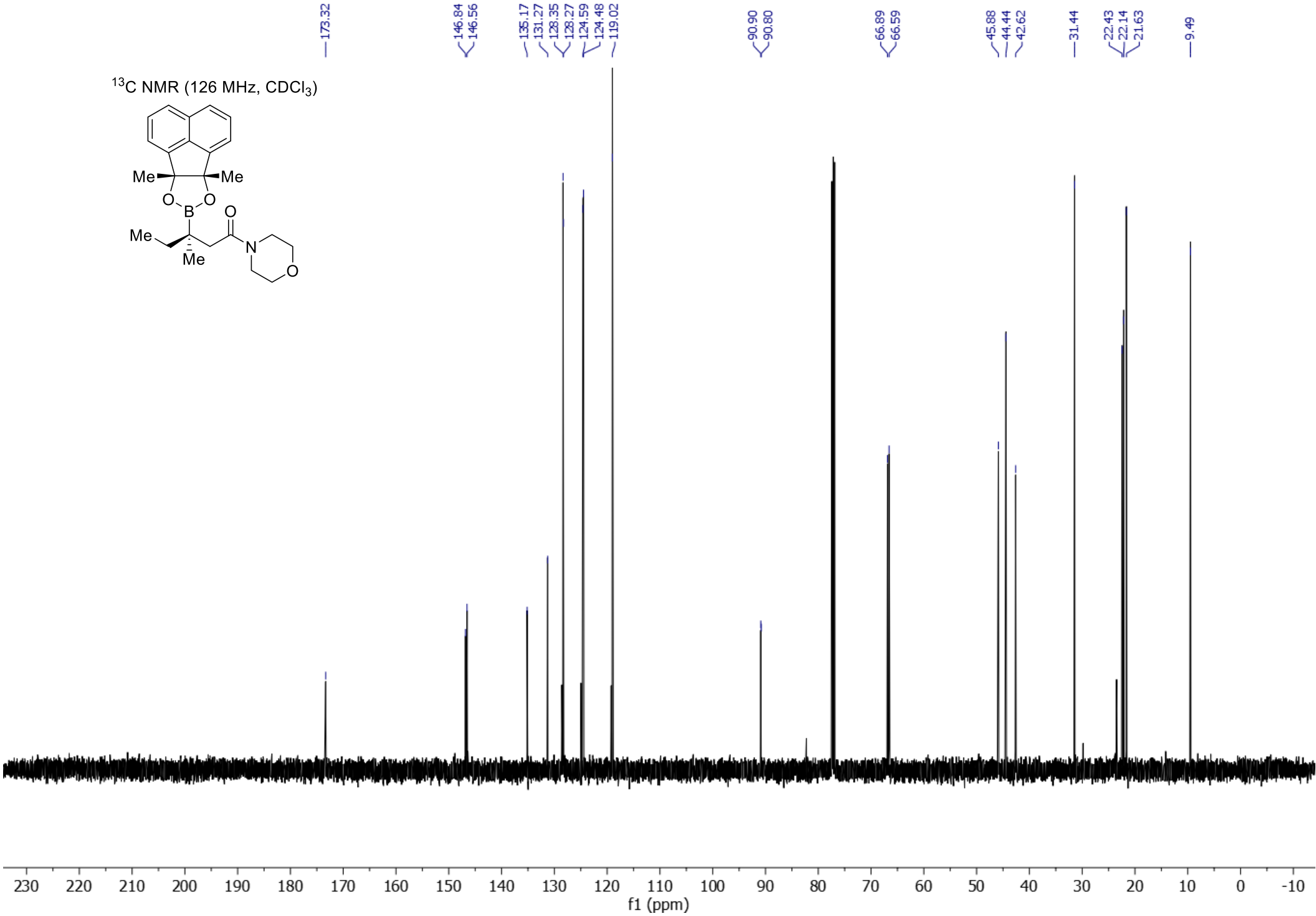

144.98
134.75
131.48
128.74
128.42
125.44
125.24
119.71
119.36
102.86
102.69
91.78
77.41
77.16
76.91
60.88
60.72
60.68
60.51
36.00
22.28
22.20
19.28
15.74
15.54
15.35
15.16
1H NMR (500 MHz, CDCl3)
Me
OEt
O
EtO
B
O
Me
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

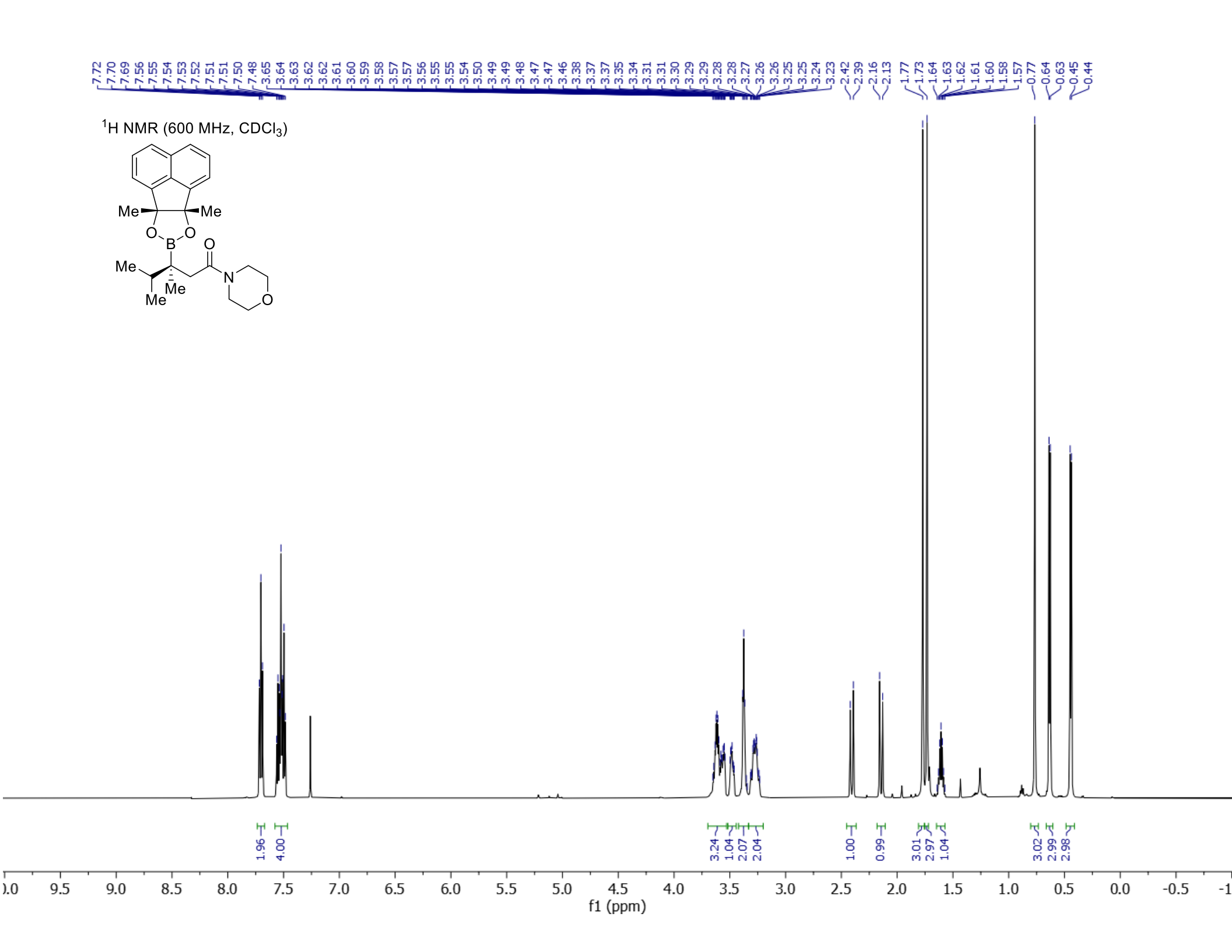

^{1}H NMR (500 MHz, $CDCl_3$)
Me
Me
O
B
O
O
Me
Me
N
O
1.99
4.05
4.07
4.07
1.00
1.00
6.07
1.31
1.03
6.15
1.04
3.02
f1 (ppm)

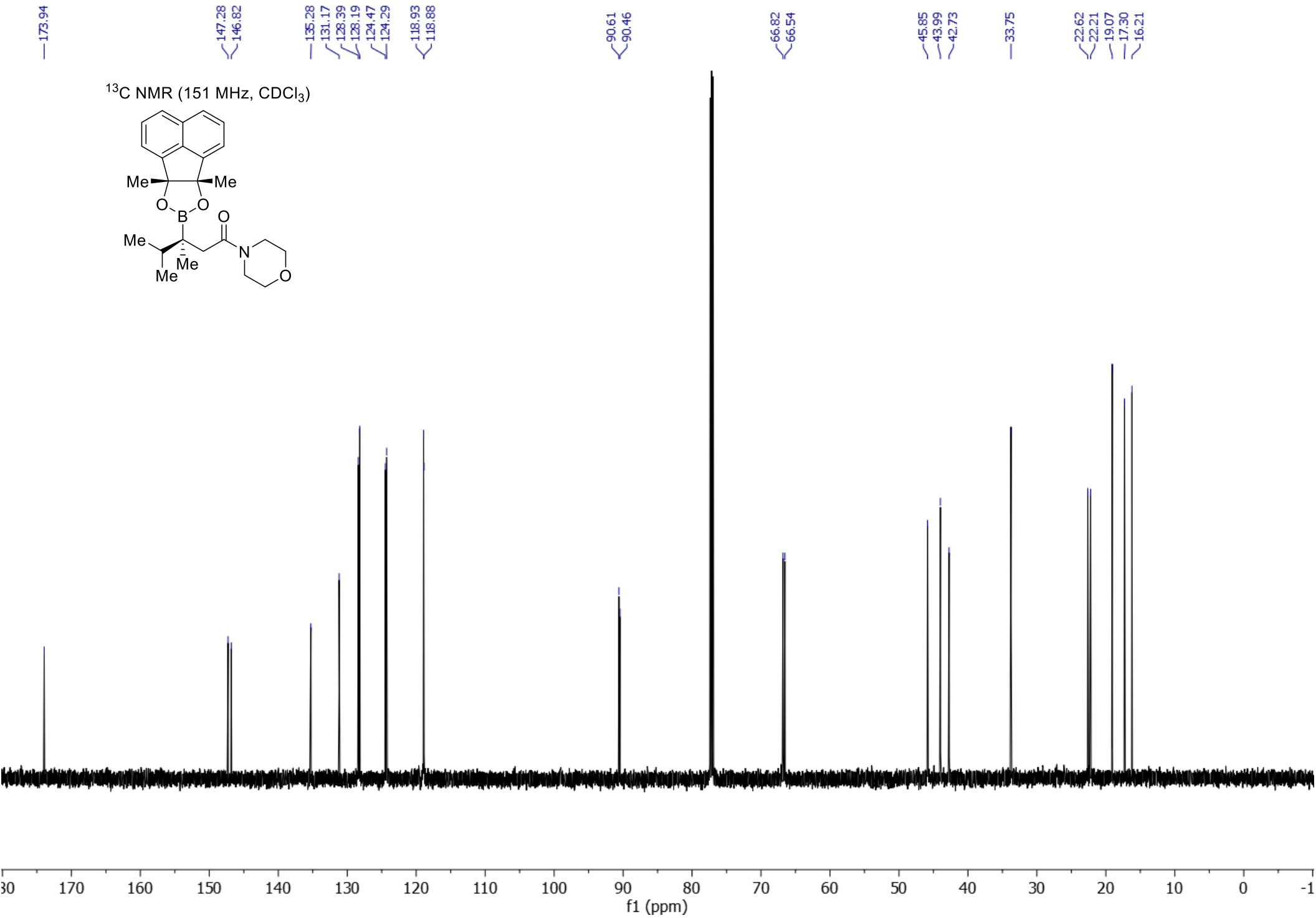

173.37
146.83
146.57
135.20
131.30
128.35
128.28
124.59
124.49
119.03
118.99
90.92
90.84
66.94
66.63
45.91
44.94
42.66
38.92
27.54
23.37
22.37
22.19
22.13
13.89
13C NMR (126 MHz, CDCl3)
Me
Me
O
B
O
O
Me
Me
N
O
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

^{1}H NMR (500 MHz, $CDCl_3$)

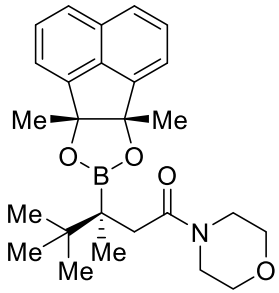



173.32
146.84
146.56
135.17
131.27
128.35
128.27
124.59
124.48
119.02
90.90
90.80
66.89
66.59
45.88
44.44
42.62
31.44
22.43
22.14
21.63
9.49
13C NMR (126 MHz, CDCl3)
Me
Me
O
B
O
O
Me
Me
N
O
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.72 7.70 7.69 7.56 7.55 7.54 7.53 7.52 7.51 7.51 7.50 7.48 3.65 3.64 3.63 3.62 3.62 3.61 3.60 3.59 3.58 3.57 3.57 3.56 3.55 3.55 3.54 3.50 3.49 3.49 3.48 3.47 3.47 3.46 3.38 3.37 3.37 3.35 3.34 3.31 3.31 3.30 3.29 3.29 3.28 3.28 3.27 3.26 3.26 3.25 3.24 3.23 2.42 2.39 2.16 2.13 1.77 1.73 1.64 1.63 1.62 1.61 1.60 1.58 1.57 0.77 0.64 0.63 0.45 0.44
^{1}H NMR (600 MHz, $CDCl_3$)
Me
Me
O
B
O
O
Me
Me
Me
N
O
1.96
4.00
3.24
1.04
2.07
2.04
1.00
0.99
3.01
2.97
1.04
3.02
2.99
2.98
f1 (ppm)


173.94
147.28
146.82
135.28
131.17
128.39
128.19
124.47
124.29
118.93
118.88
90.61
90.46
66.82
66.54
45.85
43.99
42.73
33.75
22.62
22.21
19.07
17.30
16.21
13C NMR (151 MHz, CDCl3)
Me
Me
O
B
O
O
Me
Me
Me
N
O
f1 (ppm)

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



7.73 7.72 7.71 7.56 7.55 7.55 7.55 7.54 7.53 7.52 7.51 7.50

3.67 3.66 3.65 3.63 3.62 3.60 3.59 3.59 3.48 3.47 3.46 3.45 3.44 3.43 3.42 3.41 3.40 3.40 3.39 3.38 3.37 3.36 2.66 2.63

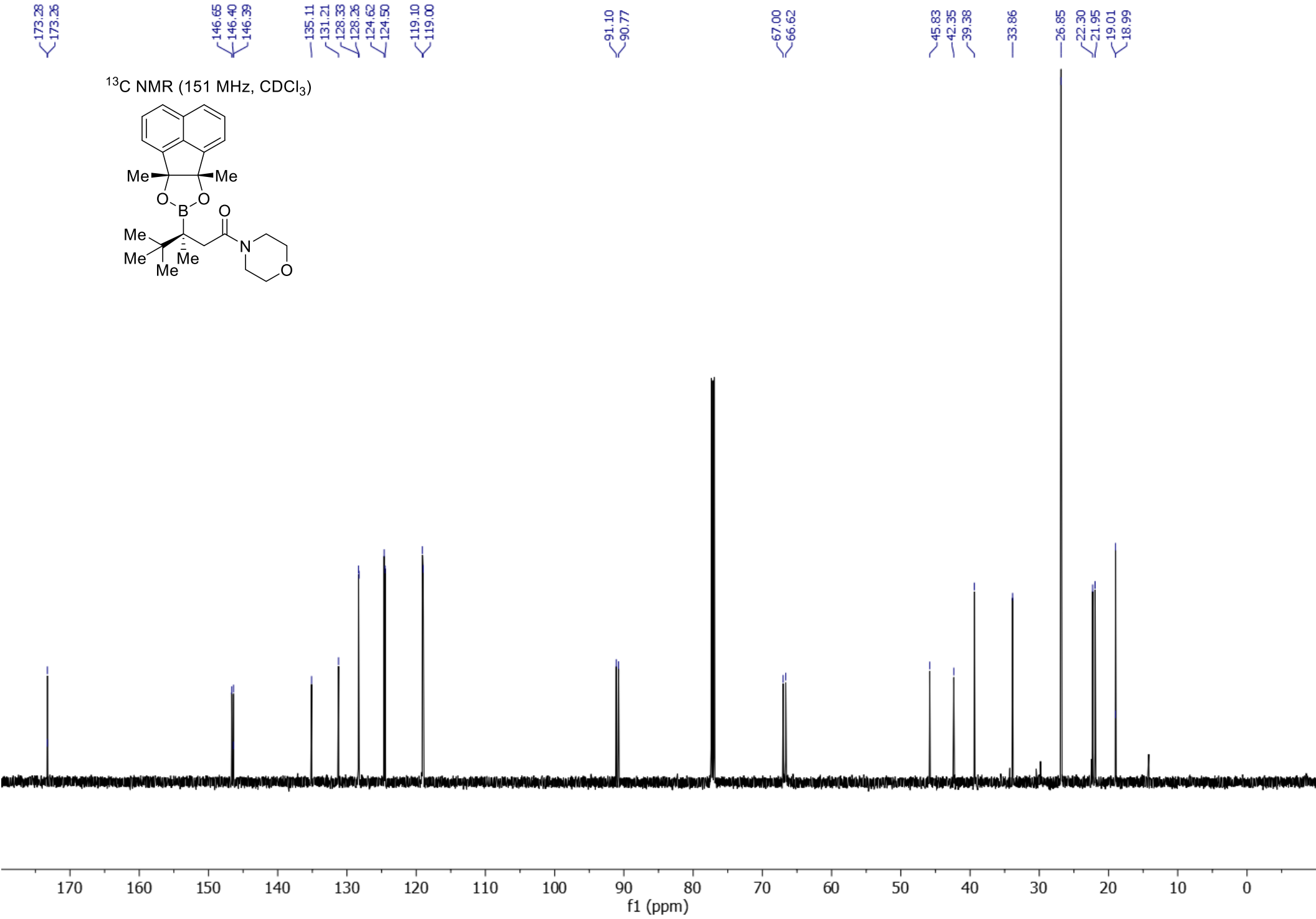
2.05 2.02 1.80 1.73

0.91 0.90 0.61

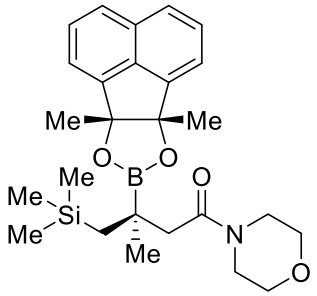
1.95 3.99 4.23 4.14 1.00 1.03 6.36 3.16 8.97

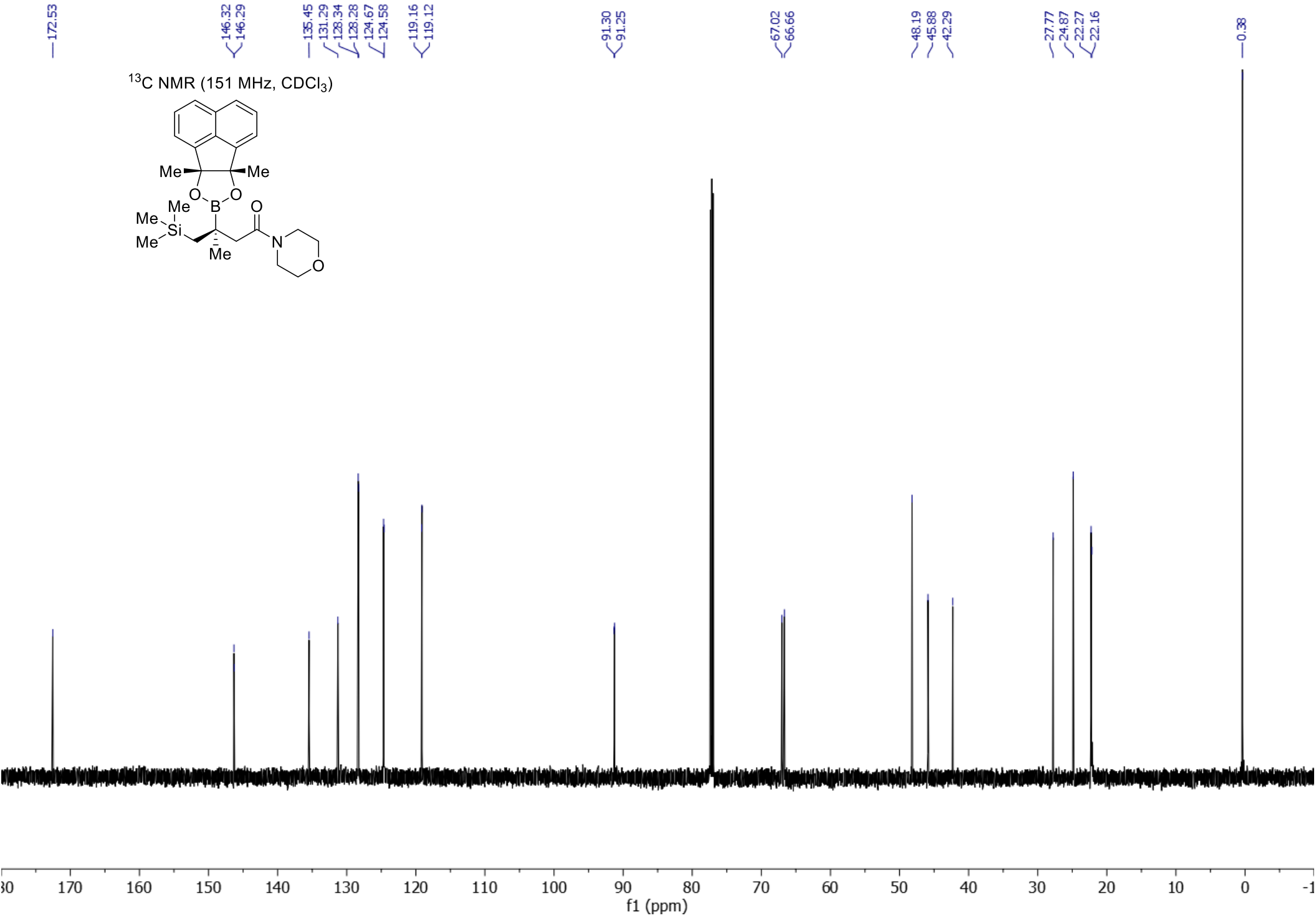
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1

f1 (ppm)

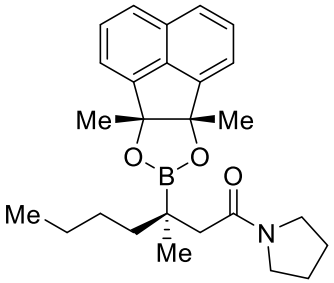

173.28
173.26
146.65
146.40
146.39
135.11
131.21
128.33
128.26
124.62
124.50
119.10
119.00
91.10
90.77
67.00
66.62
45.83
42.35
39.38
33.86
26.85
22.30
21.95
19.01
18.99
13C NMR (151 MHz, CDCl3)
Me
Me
O
B
O
O
Me
Me
Me
Me
N
O
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

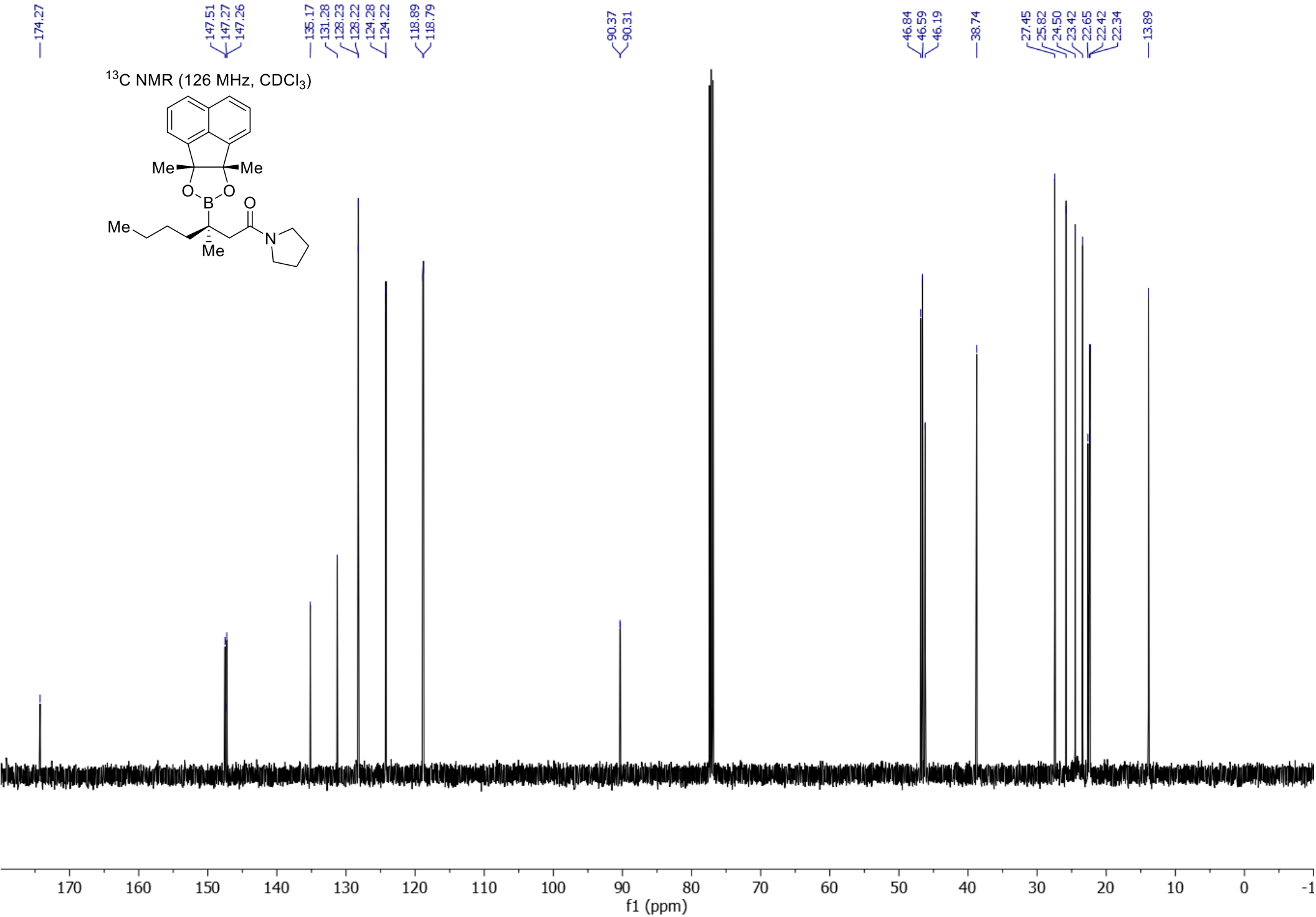
^{1}H NMR (600 MHz, $CDCl_3$)



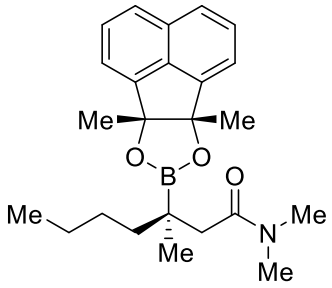

172.53
146.32
146.29
135.45
131.29
128.34
128.28
124.67
124.58
119.16
119.12
91.30
91.25
67.02
66.66
48.19
45.88
42.29
27.77
24.87
22.27
22.16
0.38
13C NMR (151 MHz, CDCl3)
Me
Me
O
O
B
Me
O
Me
Si
Me
Me
N
O
f1 (ppm)

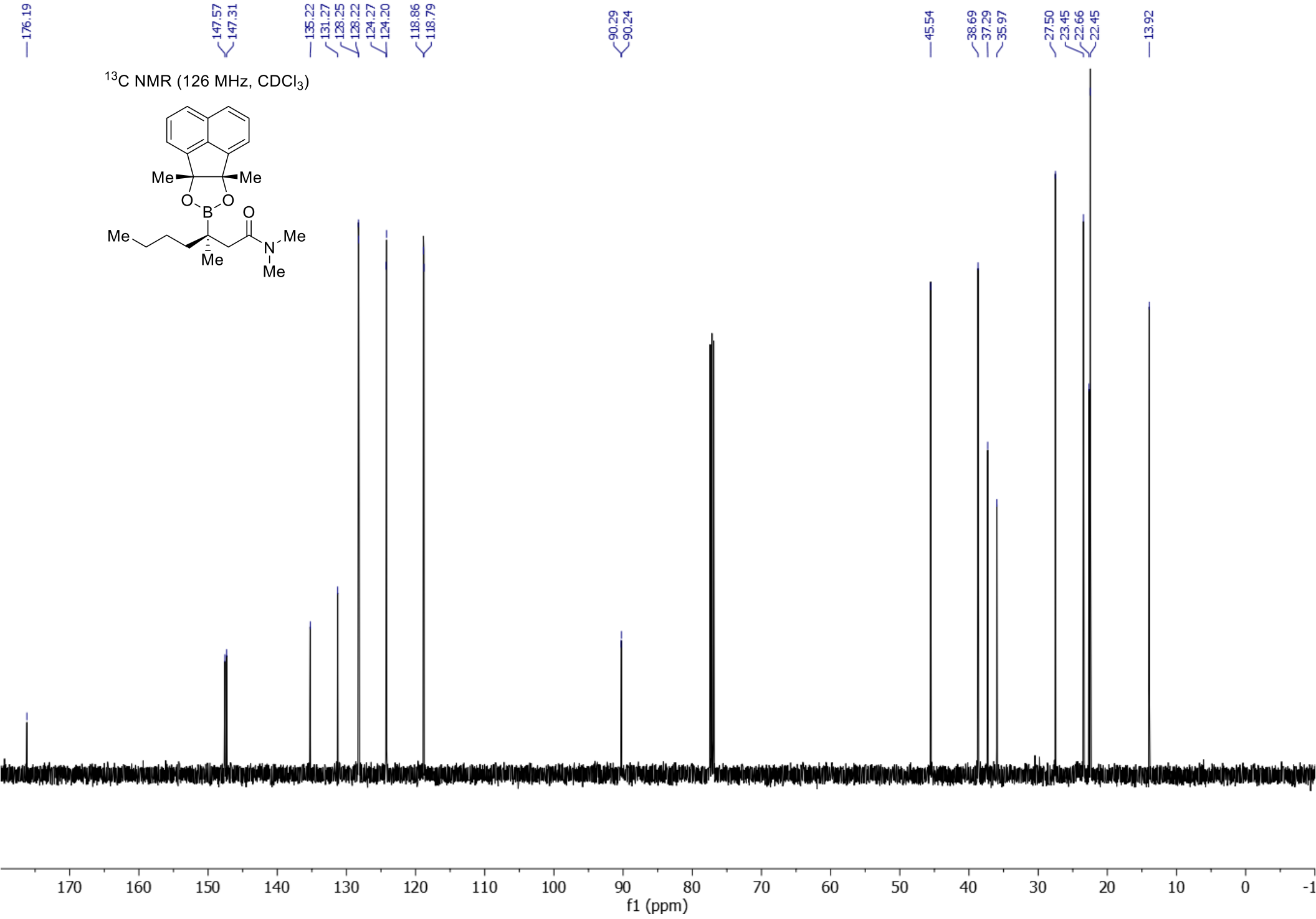
^{1}H NMR (500 MHz, $CDCl_3$)



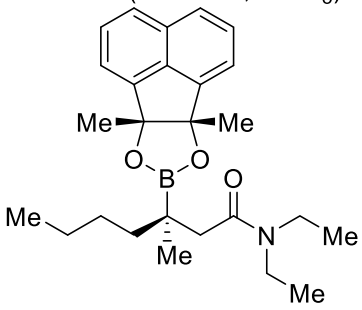

174.27
147.51
147.27
147.26
135.17
131.28
128.23
128.22
124.28
124.22
118.89
118.79
90.37
90.31
46.84
46.59
46.19
38.74
27.45
25.82
24.50
23.42
22.65
22.42
22.34
13.89
13C NMR (126 MHz, CDCl3)
Me
Me
O
B
O
O
Me
N
Me
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
f1 (ppm)

^{1}H NMR (500 MHz, $CDCl_3$)

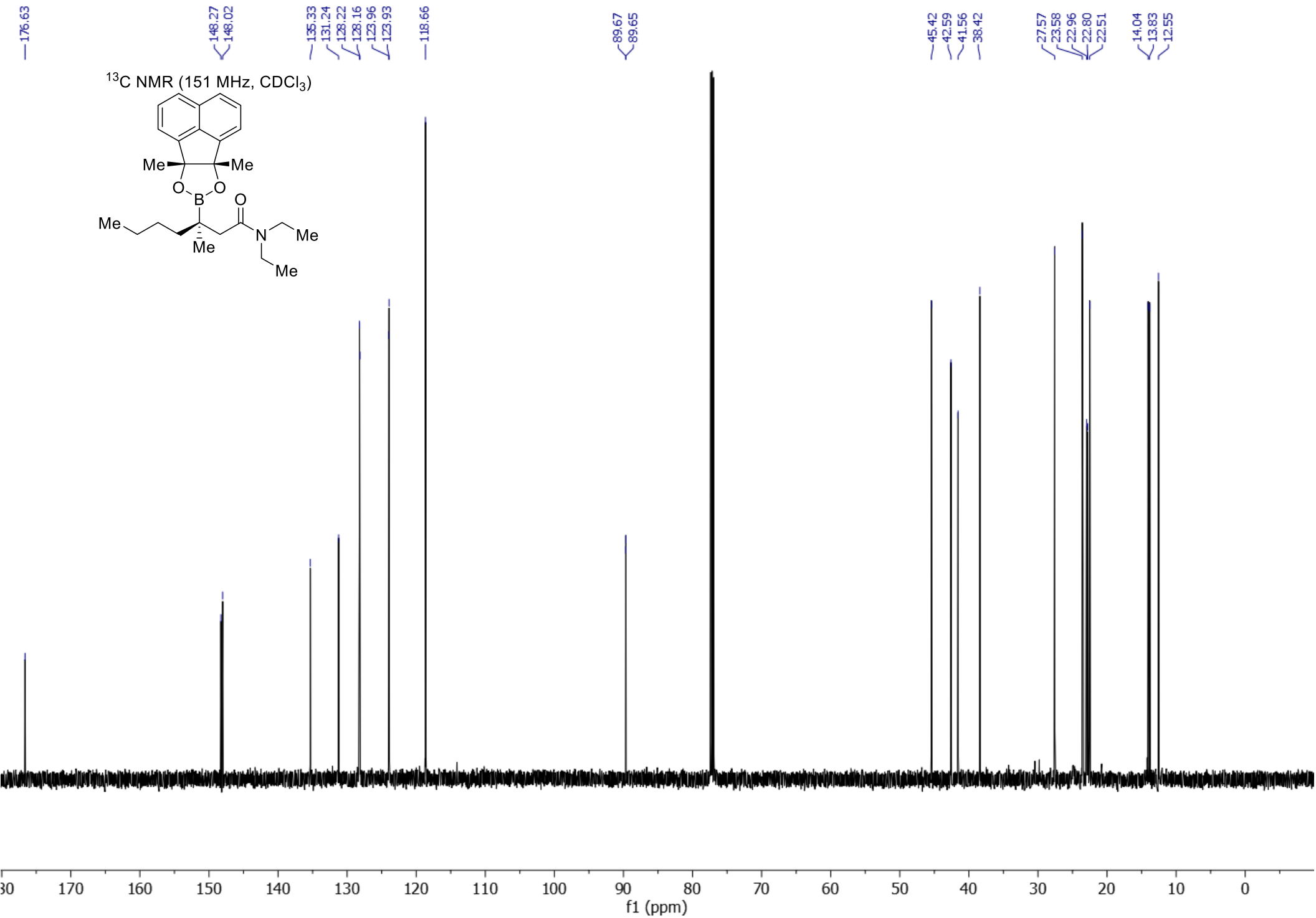


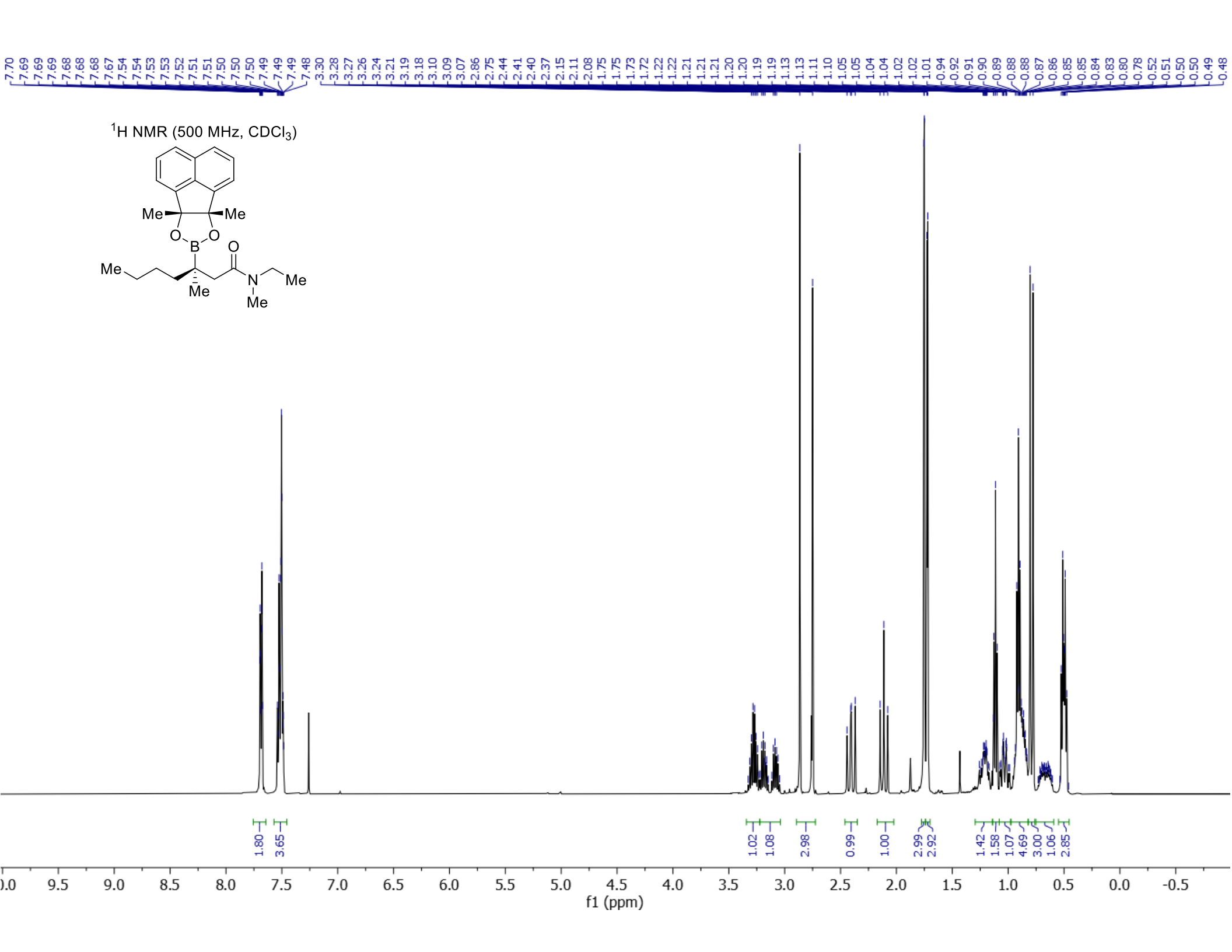

176.19
147.57
147.31
135.22
131.27
128.25
128.22
124.27
124.20
118.86
118.79
90.29
90.24
45.54
38.69
37.29
35.97
27.50
23.45
22.66
22.45
13.92
13C NMR (126 MHz, CDCl3)
Me
Me
O
B
O
O
Me
N
Me
Me
Me
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
f1 (ppm)

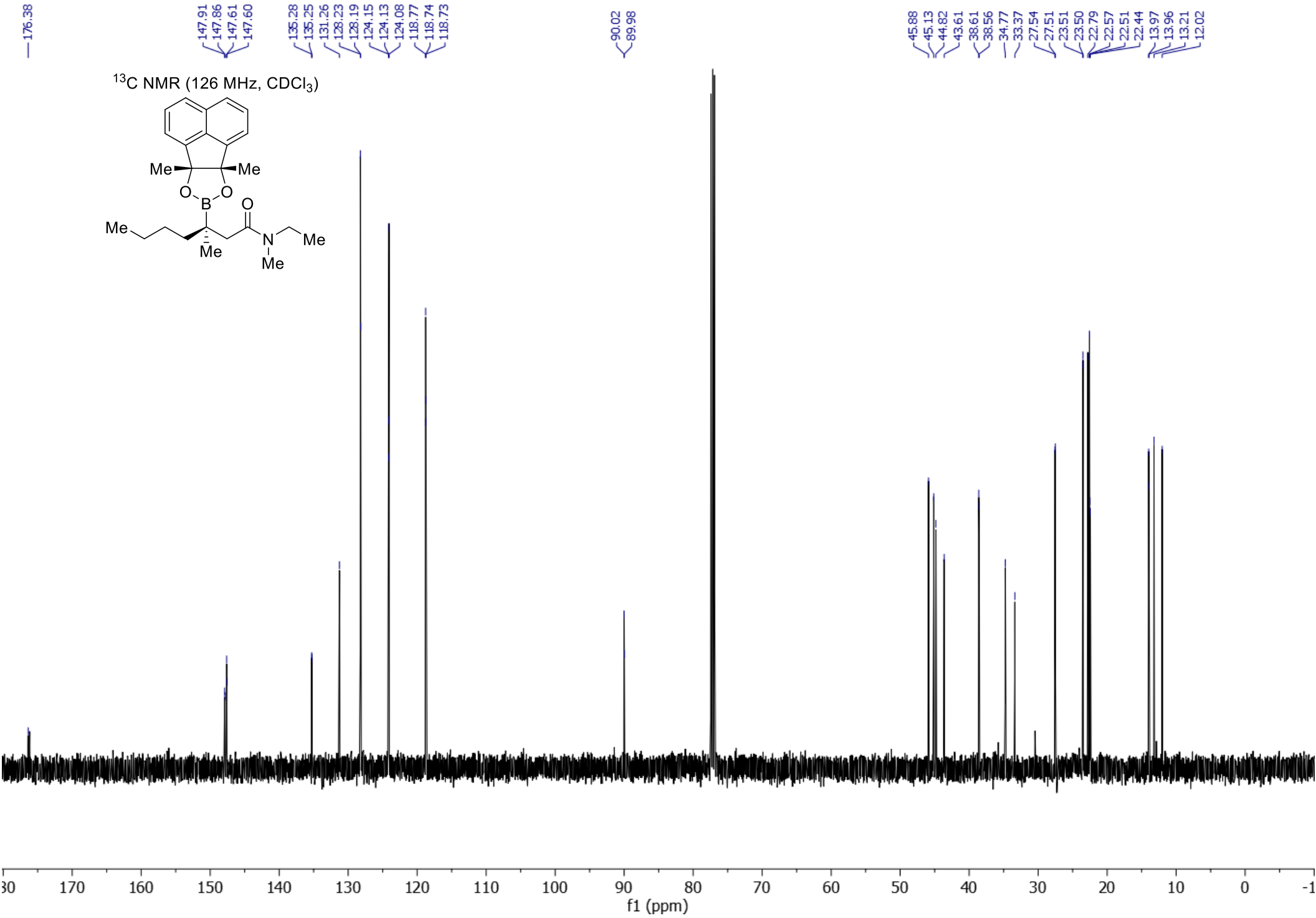
^{1}H NMR (600 MHz, $CDCl_3$)



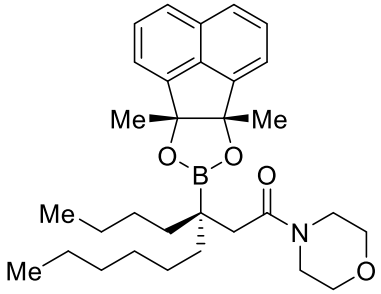
f1 (ppm)

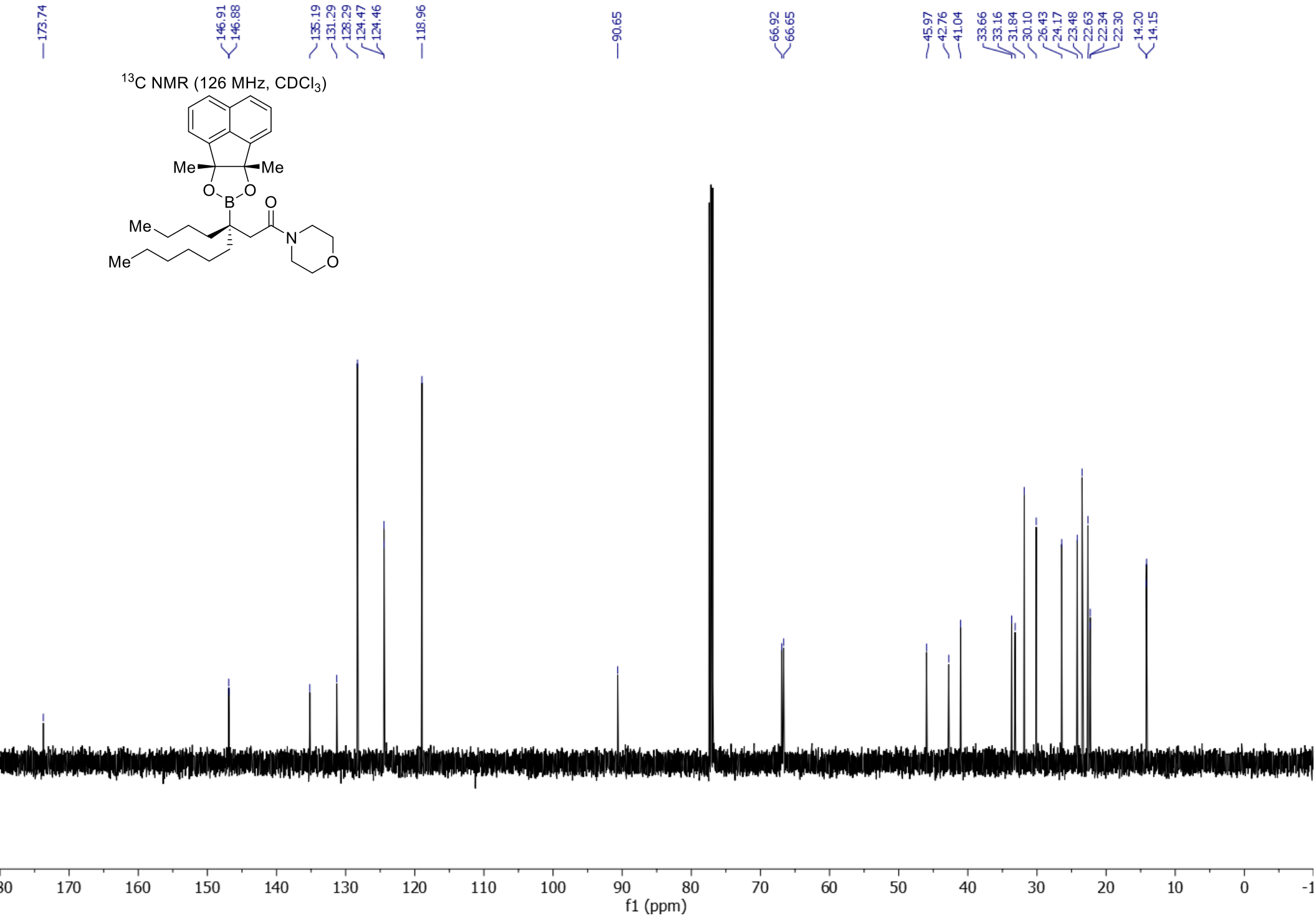

176.63
148.27
148.02
135.33
131.24
128.22
128.16
123.96
123.93
118.66
89.67
89.65
45.42
42.59
41.56
38.42
27.57
23.58
22.96
22.80
22.51
14.04
13.83
12.55
13C NMR (151 MHz, CDCl3)
Me
Me
O
B
O
O
Me
N
Me
Me
Me
f1 (ppm)


^{1}H NMR (500 MHz, $CDCl_3$)
Me
Me
O
B
O
O
Me
Me
N
Me
Me
f1 (ppm)

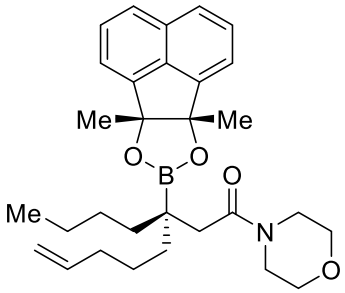

176.38
147.91
147.86
147.61
147.60
135.28
135.25
131.26
128.23
128.19
124.15
124.13
124.08
118.77
118.74
118.73
90.02
89.98
45.88
45.13
44.82
43.61
38.61
38.56
34.77
33.37
27.54
27.51
23.51
23.50
22.79
22.57
22.51
22.44
13.97
13.96
13.21
12.02
^{13}C NMR (126 MHz, CDCl$_3$)
Me
Me
O
B
O
O
Me
Me
N
Me
Me
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

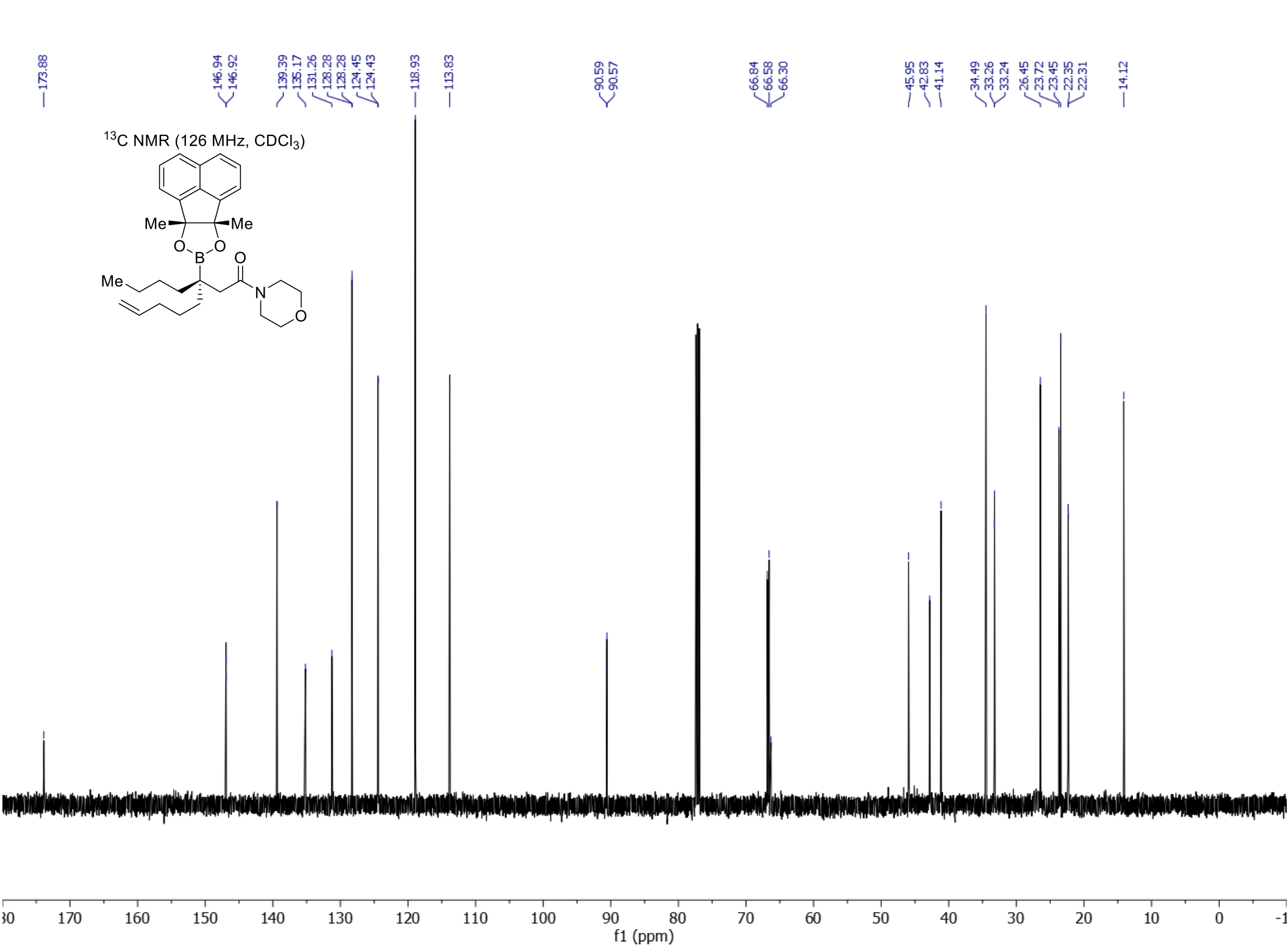
^{1}H NMR (500 MHz, $CDCl_3$)



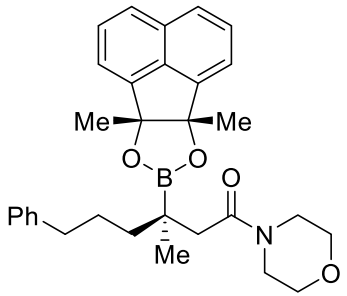

173.74
146.91
146.88
135.19
131.29
128.29
124.47
124.46
118.96
90.65
66.92
66.65
45.97
42.76
41.04
33.66
33.16
31.84
30.10
26.43
24.17
23.48
22.63
22.34
22.30
14.20
14.15
13C NMR (126 MHz, CDCl3)
Me
Me
O
B
O
O
Me
N
Me
O
f1 (ppm)

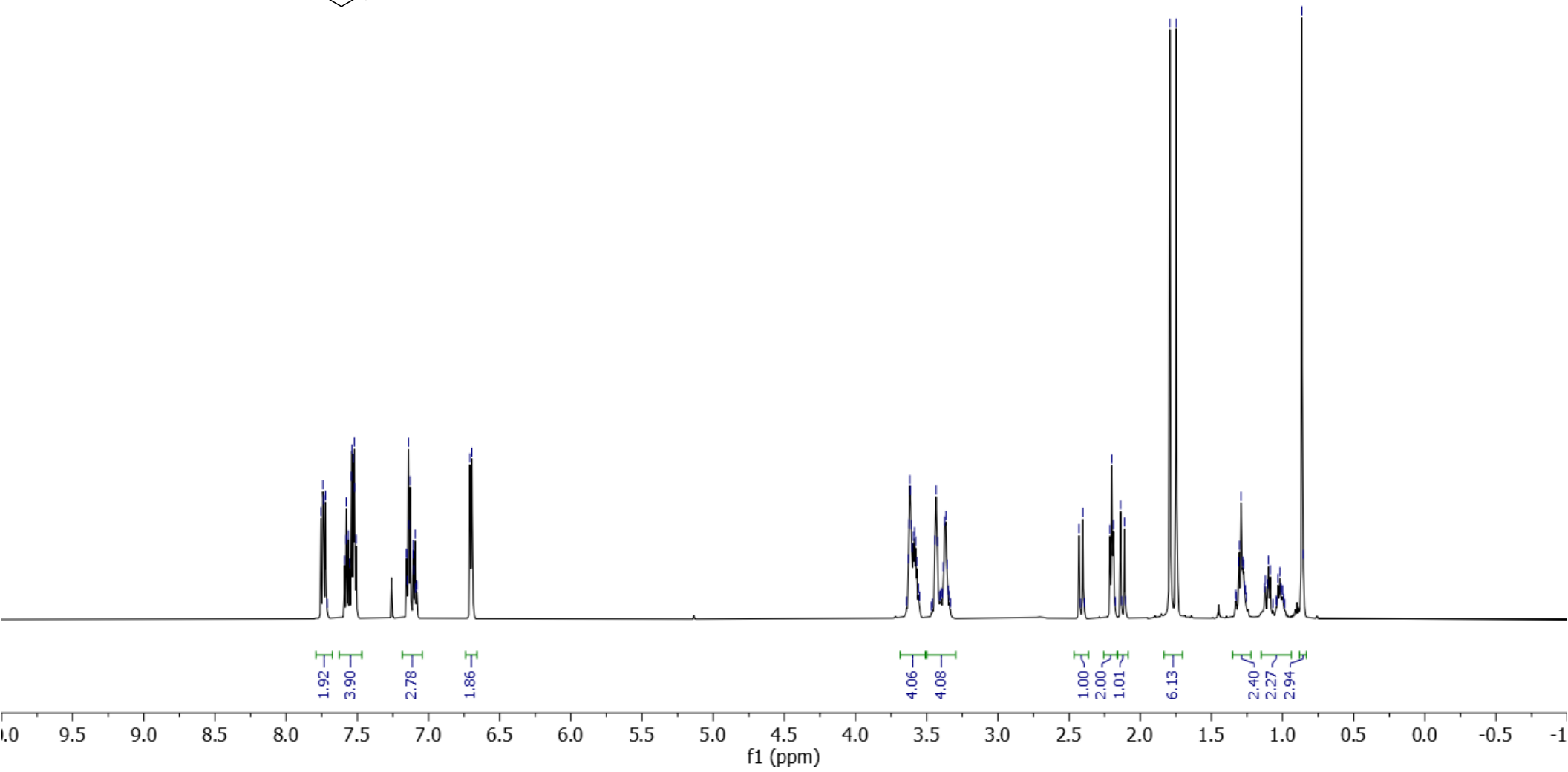
^{1}H NMR (500 MHz, $CDCl_3$)

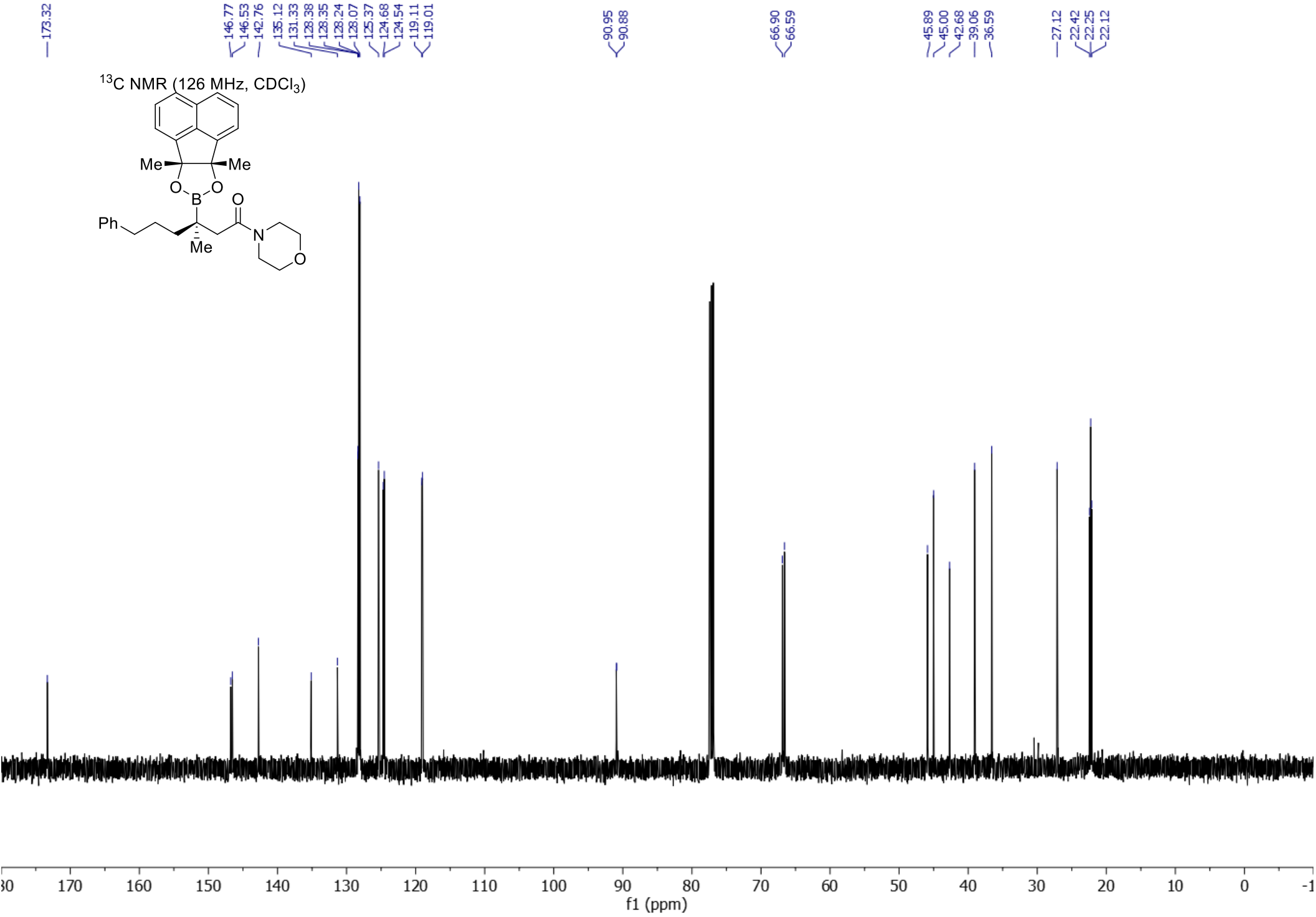


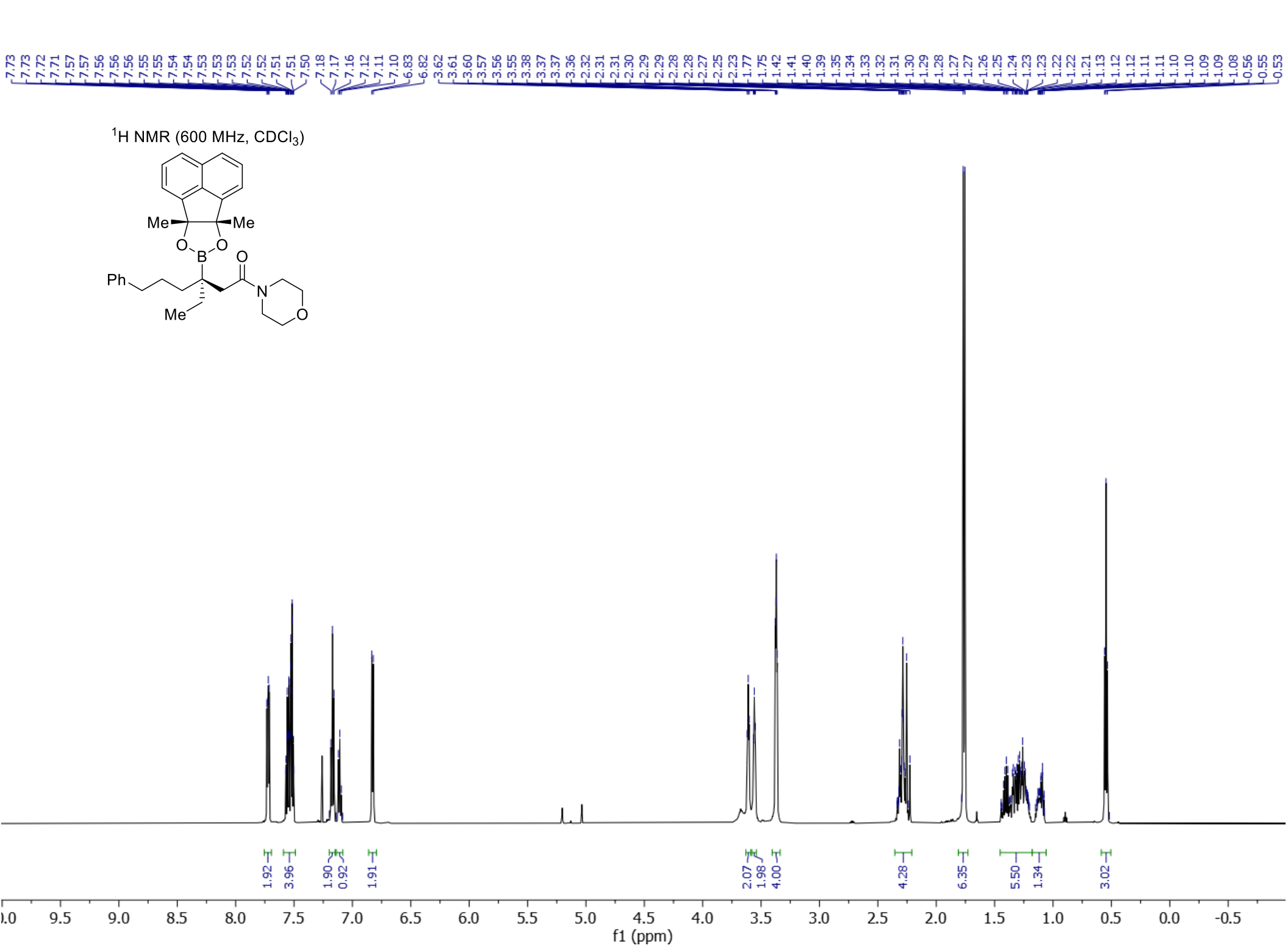

173.88
146.94
146.92
139.39
135.17
131.26
128.28
128.28
124.45
124.43
118.93
113.83
90.59
90.57
66.84
66.58
66.30
45.95
42.83
41.14
34.49
33.26
33.24
26.45
23.72
23.45
22.35
22.31
14.12
13C NMR (126 MHz, CDCl3)
Me
Me
O
B
O
O
Me
N
O
f1 (ppm)

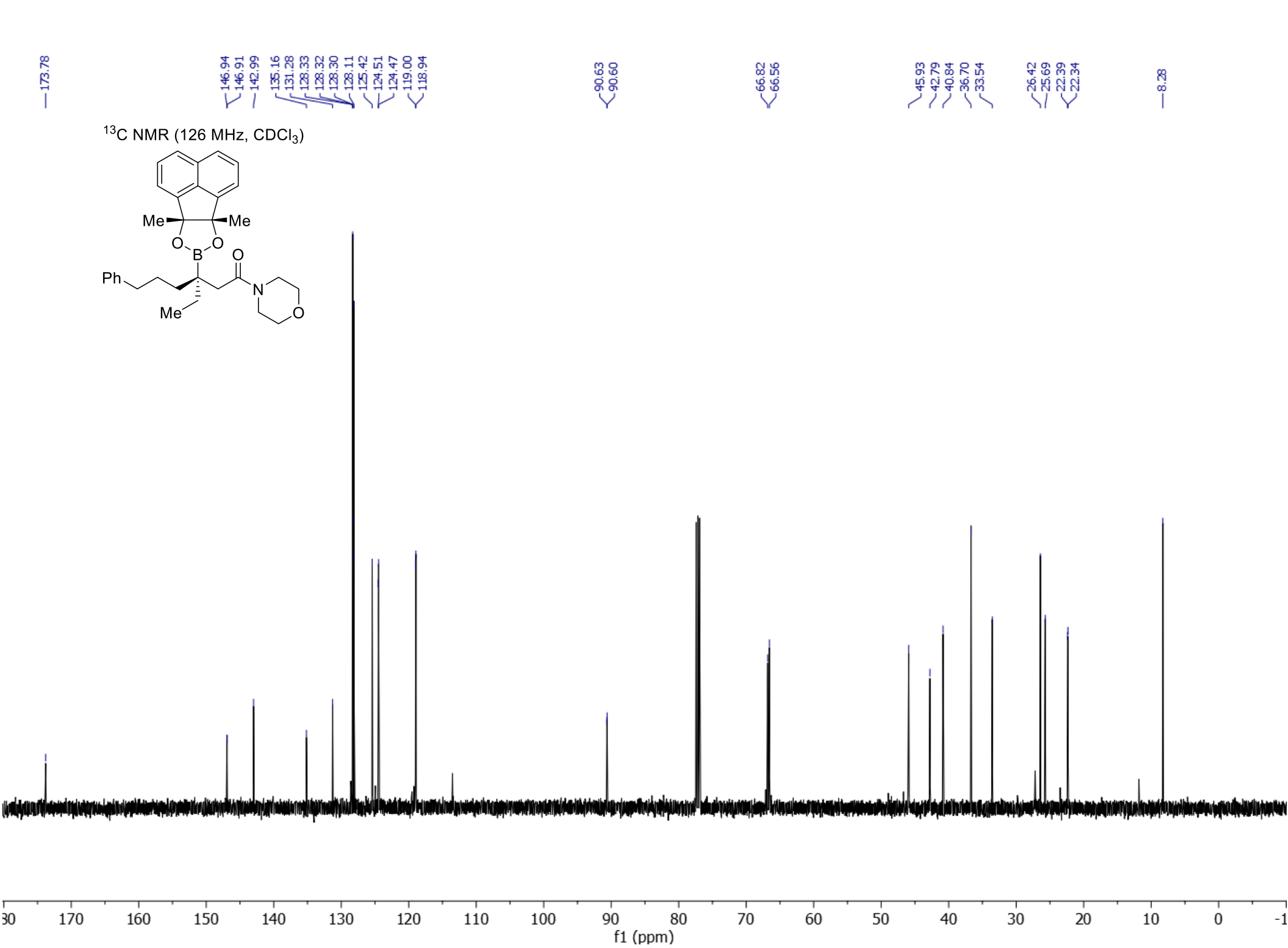
^{1}H NMR (600 MHz, $CDCl_3$)

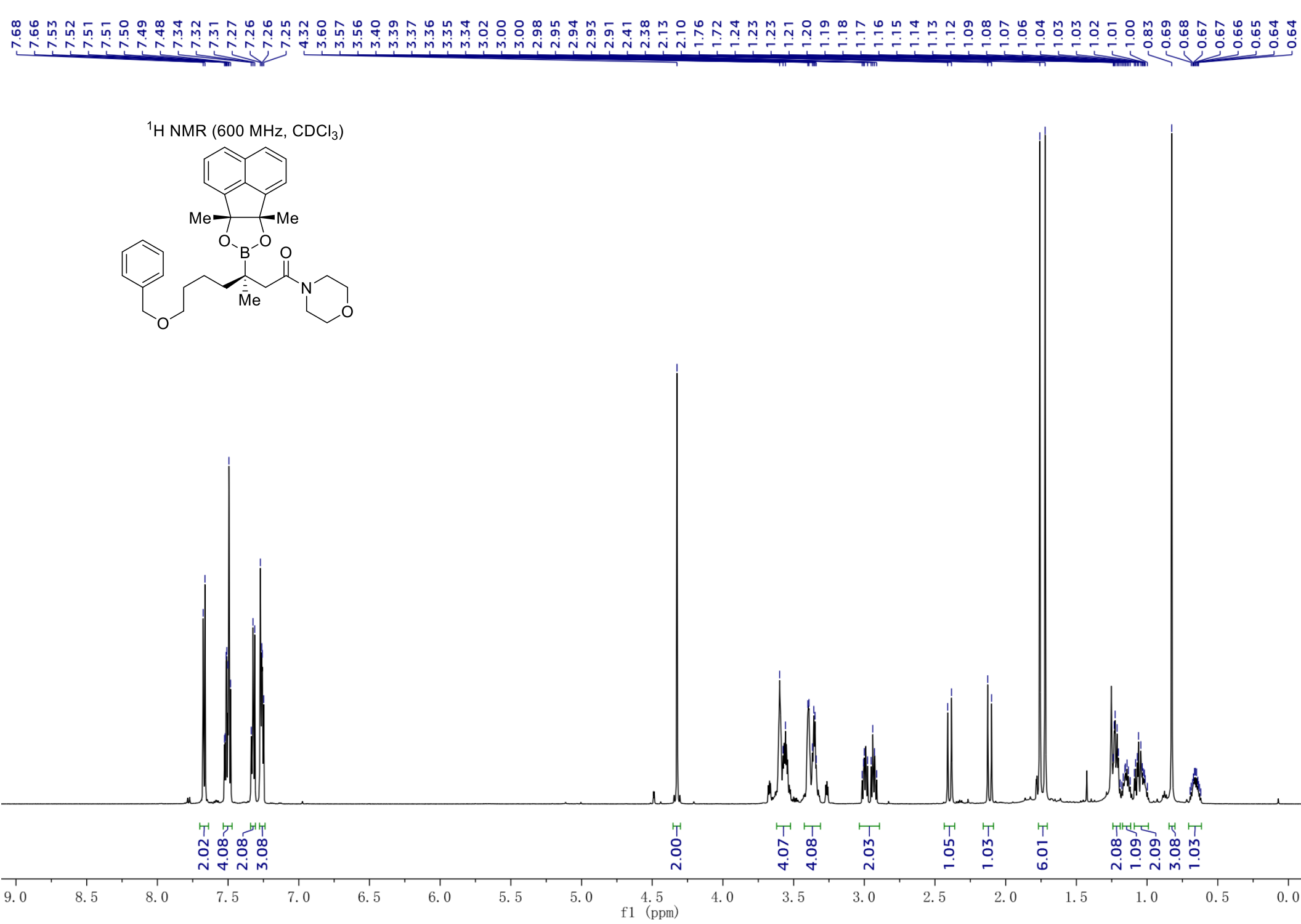


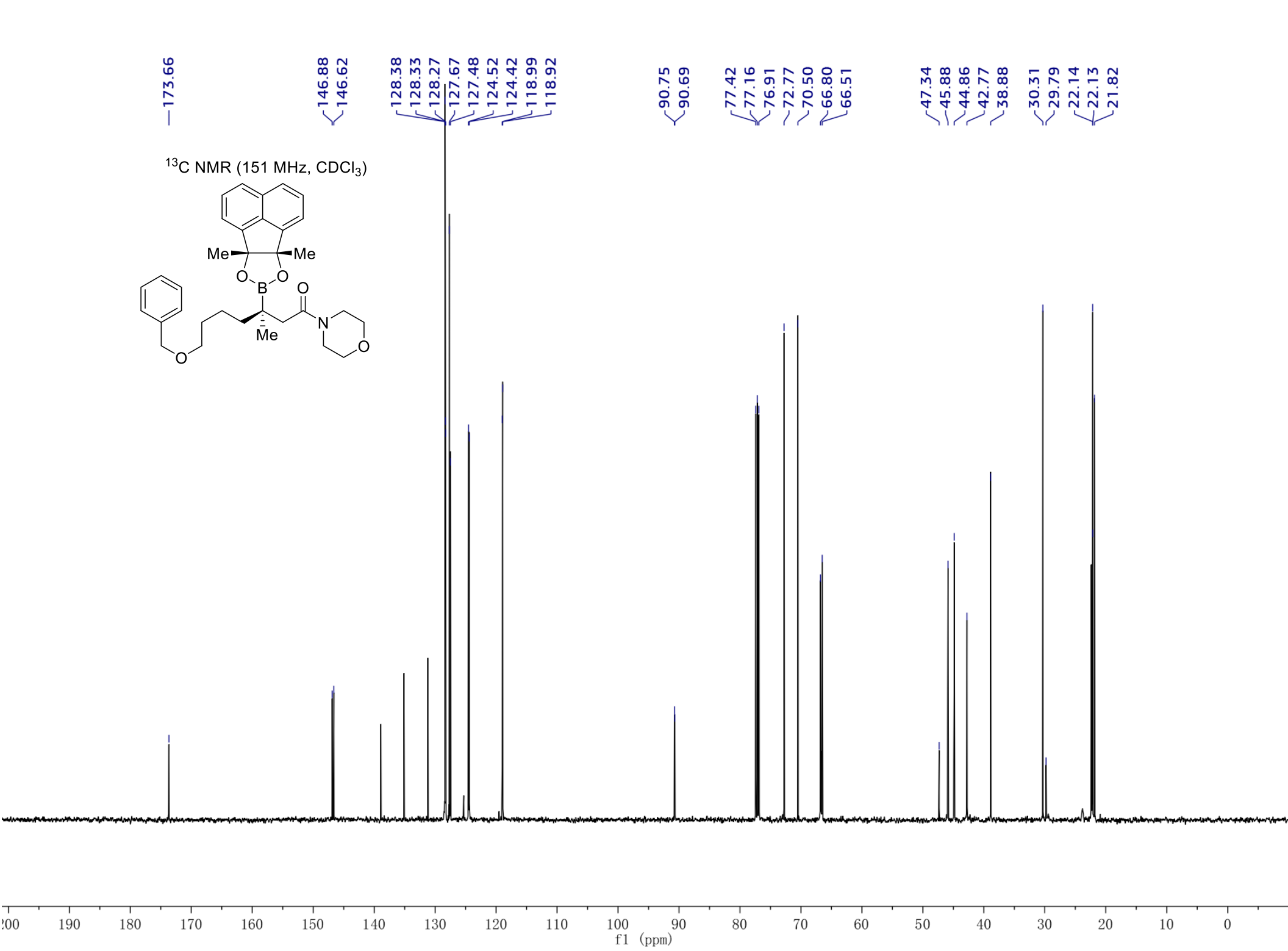



173.32
146.77
146.53
142.76
135.12
131.33
128.38
128.35
128.24
128.07
125.37
124.68
124.54
119.11
119.01
90.95
90.88
66.90
66.59
45.89
45.00
42.68
39.06
36.59
27.12
22.42
22.25
22.12
13C NMR (126 MHz, CDCl3)
Me
Me
O
B
O
O
Ph
Me
N
O
f1 (ppm)

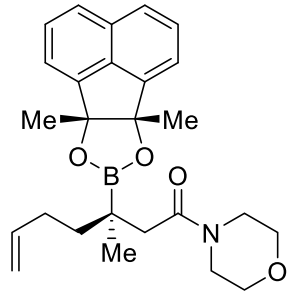

7.73 7.73 7.72 7.71 7.57 7.57 7.56 7.56 7.56 7.55 7.55 7.54 7.54 7.53 7.53 7.53 7.52 7.52 7.51 7.51 7.50 7.18 7.17 7.16 7.12 7.11 7.10 6.83 6.82 3.62 3.61 3.60 3.57 3.56 3.55 3.38 3.37 3.37 3.36 2.32 2.31 2.31 2.30 2.29 2.29 2.28 2.28 2.27 2.25 2.23 1.77 1.75 1.42 1.41 1.40 1.39 1.35 1.34 1.33 1.32 1.31 1.30 1.29 1.28 1.27 1.27 1.26 1.25 1.24 1.23 1.23 1.22 1.22 1.21 1.13 1.12 1.12 1.11 1.11 1.10 1.10 1.09 1.09 1.08 0.56 0.55 0.53
^{1}H NMR (600 MHz, $CDCl_3$)
Me
Me
O
B
O
O
Ph
N
Me
O
1.92
3.96
1.90
0.92
1.91
2.07
1.98
4.00
4.28
6.35
5.50
1.34
3.02
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
f1 (ppm)


173.78
146.94
146.91
142.99
135.16
131.28
128.33
128.32
128.30
128.11
125.42
124.51
124.47
119.00
118.94
90.63
90.60
66.82
66.56
45.93
42.79
40.84
36.70
33.54
26.42
25.69
22.39
22.34
8.28
13C NMR (126 MHz, CDCl3)
Me
Me
O
B
O
O
Ph
N
Me
O
f1 (ppm)


7.68 7.66 7.53 7.52 7.51 7.51 7.50 7.49 7.48 7.34 7.32 7.31 7.27 7.26 7.26 7.25
4.32 3.60 3.57 3.56 3.40 3.39 3.37 3.36 3.35 3.34 3.02 3.00 3.00 2.98 2.95 2.94 2.93 2.91 2.41 2.38 2.13 2.10 1.76 1.72 1.24 1.23 1.23 1.21 1.20 1.19 1.18 1.17 1.16 1.15 1.14 1.13 1.12 1.09 1.08 1.07 1.06 1.04 1.03 1.03 1.02 1.01 1.00 0.83 0.69 0.68 0.67 0.67 0.66 0.65 0.64 0.64
1H NMR (600 MHz, CDCl3)
Me
Me
O
O
B
O
N
Me
O
O
2.02
4.08
2.08
3.08
2.00
4.07
4.08
2.03
1.05
1.03
6.01
2.08
1.09
2.09
3.08
1.03
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
f1 (ppm)


173.66
146.88
146.62
128.38
128.33
128.27
127.67
127.48
124.52
124.42
118.99
118.92
90.75
90.69
77.42
77.16
76.91
72.77
70.50
66.80
66.51
47.34
45.88
44.86
42.77
38.88
30.31
29.79
22.14
22.13
21.82
13C NMR (151 MHz, CDCl3)
Me
Me
O
B
O
O
N
Me
O
O
f1 (ppm)

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



7.73 7.72 7.72 7.71 7.56 7.55 7.54 7.54 7.53 7.52 7.51 7.50 7.50

5.52 5.51 5.50 5.50 5.49 5.48 5.48 5.47 5.46 5.45 4.61 4.59 4.54 4.51

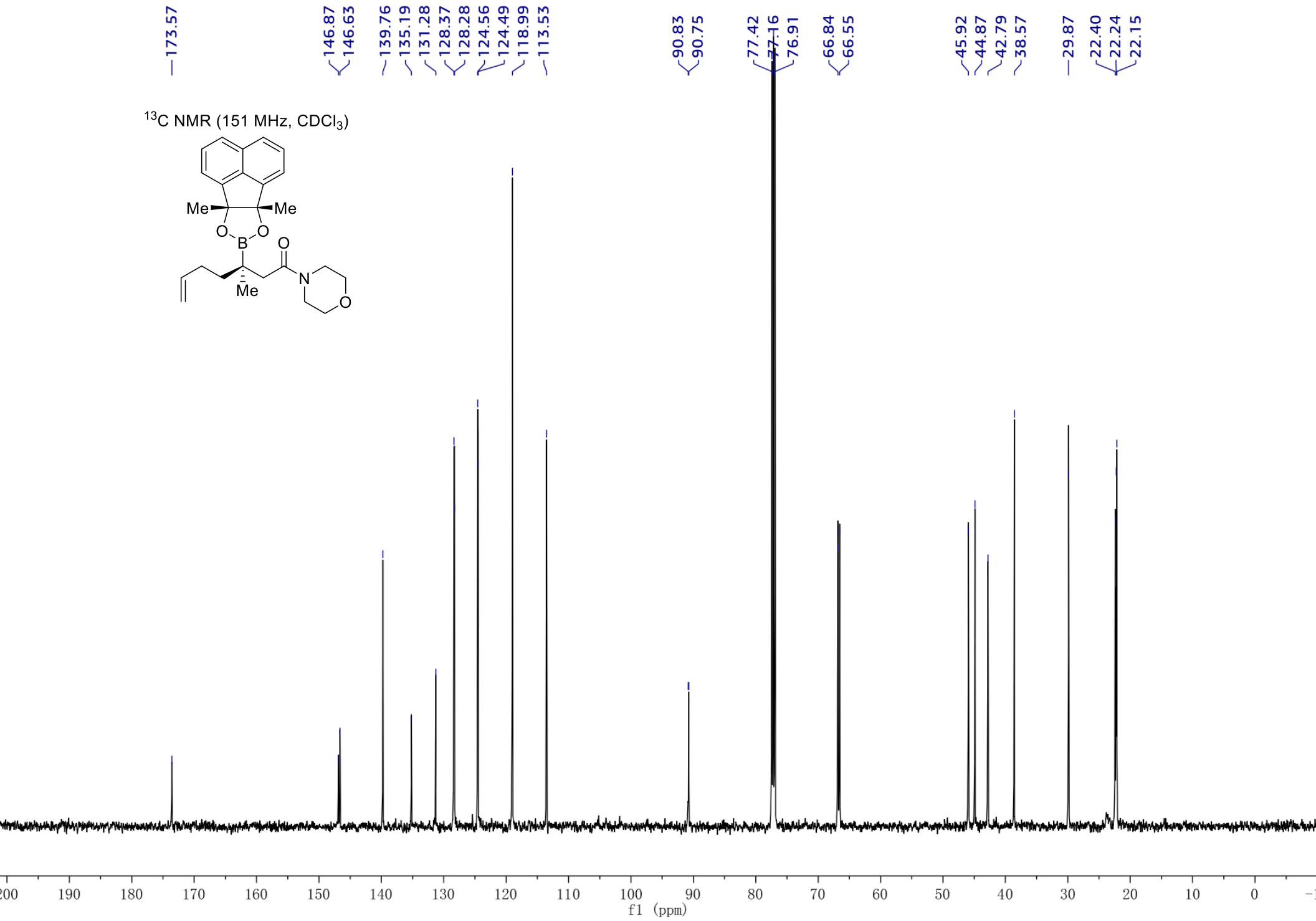
3.62 3.56 3.38 3.37

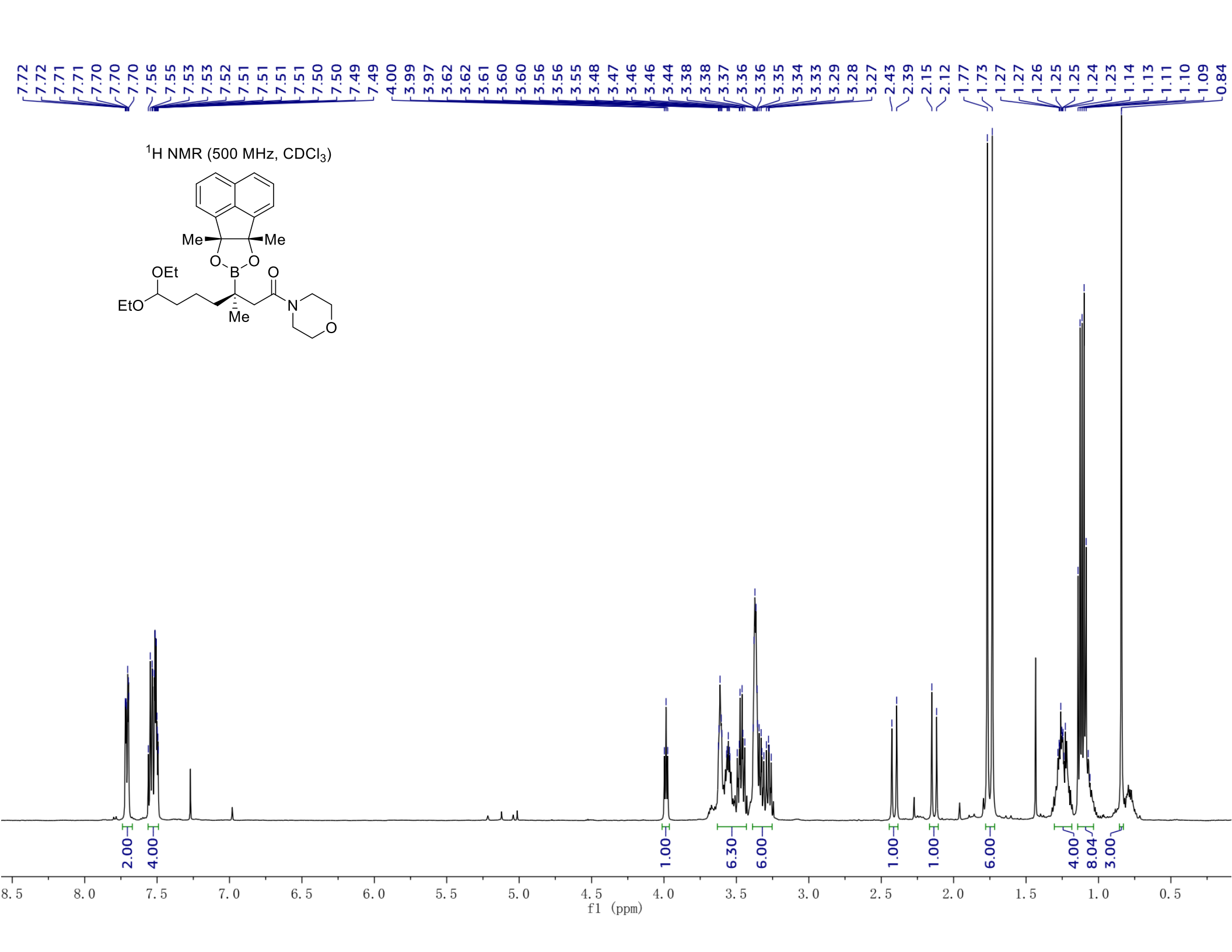
2.43 2.41 2.16 2.13 1.77 1.73 1.50 1.36 1.35 1.34 1.33 1.32 1.31 1.18 1.17 1.16 1.15 1.14 1.13 0.86

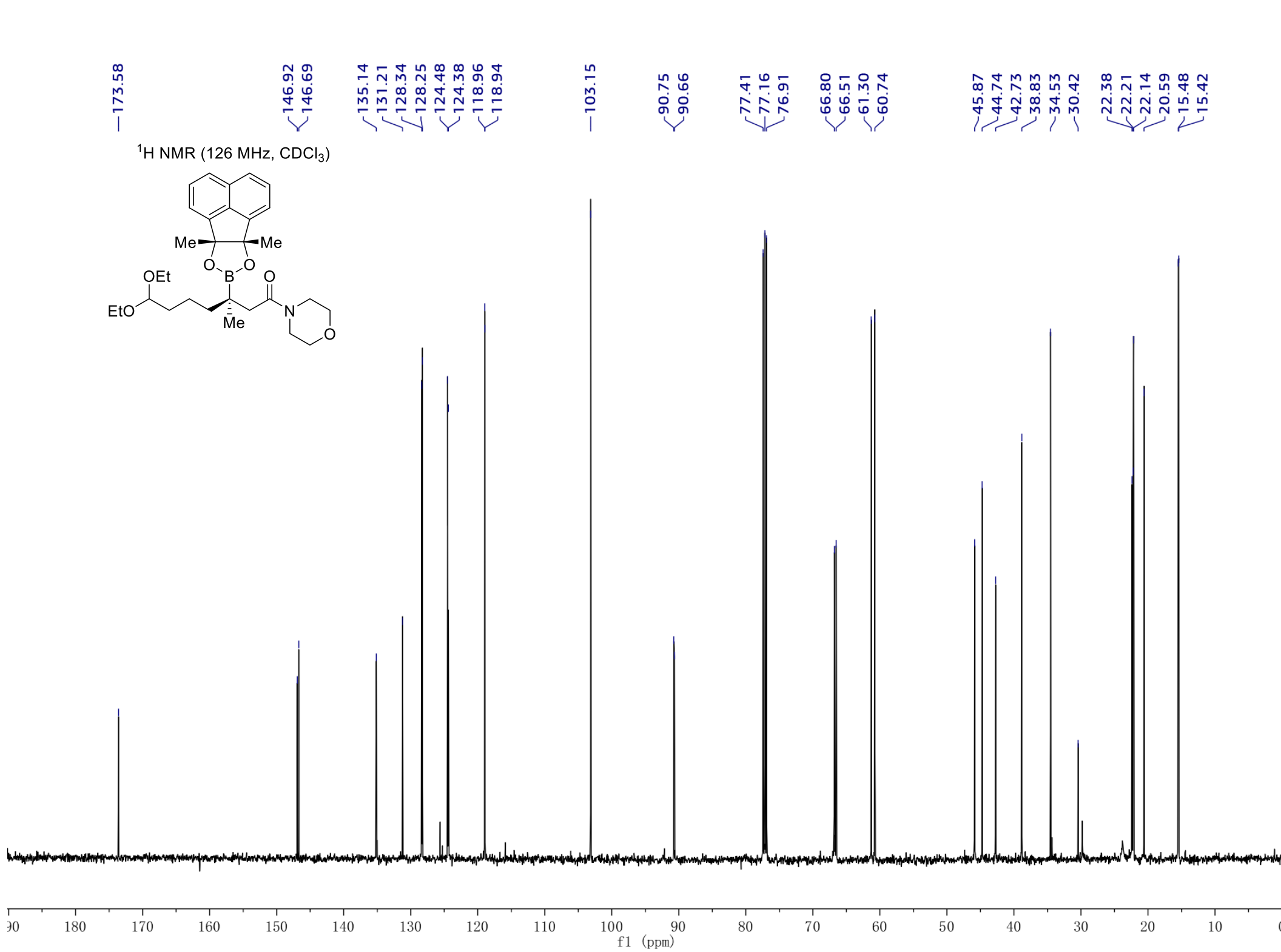
1.96 4.00 0.97 1.98 4.07 4.01 1.03 1.01 7.06 1.06 1.10 1.06 3.06

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

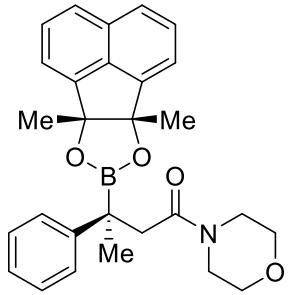
f1 (ppm)


173.57
146.87
146.63
139.76
135.19
131.28
128.37
128.28
124.56
124.49
118.99
113.53
90.83
90.75
77.42
77.16
76.91
66.84
66.55
45.92
44.87
42.79
38.57
29.87
22.40
22.24
22.15
13C NMR (151 MHz, CDCl3)
Me
Me
O
B
O
O
N
Me
O
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.72 7.72 7.71 7.71 7.70 7.70 7.70 7.56 7.55 7.53 7.53 7.52 7.51 7.51 7.51 7.51 7.50 7.50 7.49 7.49
4.00 3.99 3.97 3.62 3.62 3.61 3.60 3.60 3.56 3.56 3.55 3.48 3.47 3.46 3.46 3.44 3.38 3.38 3.37 3.36 3.36 3.35 3.34 3.33 3.29 3.28 3.27
2.43 2.39 2.15 2.12 1.77 1.73 1.27 1.27 1.26 1.25 1.25 1.24 1.23 1.14 1.13 1.11 1.10 1.09 0.84
1H NMR (500 MHz, CDCl3)
Me
Me
O
B
O
OEt
O
EtO
N
Me
O
2.00
4.00
1.00
6.30
6.00
1.00
1.00
6.00
4.00
8.04
3.00
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
f1 (ppm)


173.58
146.92
146.69
135.14
131.21
128.34
128.25
124.48
124.38
118.96
118.94
103.15
90.75
90.66
77.41
77.16
76.91
66.80
66.51
61.30
60.74
45.87
44.74
42.73
38.83
34.53
30.42
22.38
22.21
22.14
20.59
15.48
15.42
1H NMR (126 MHz, CDCl3)
Me
Me
O
B
O
OEt
O
EtO
N
Me
O
f1 (ppm)

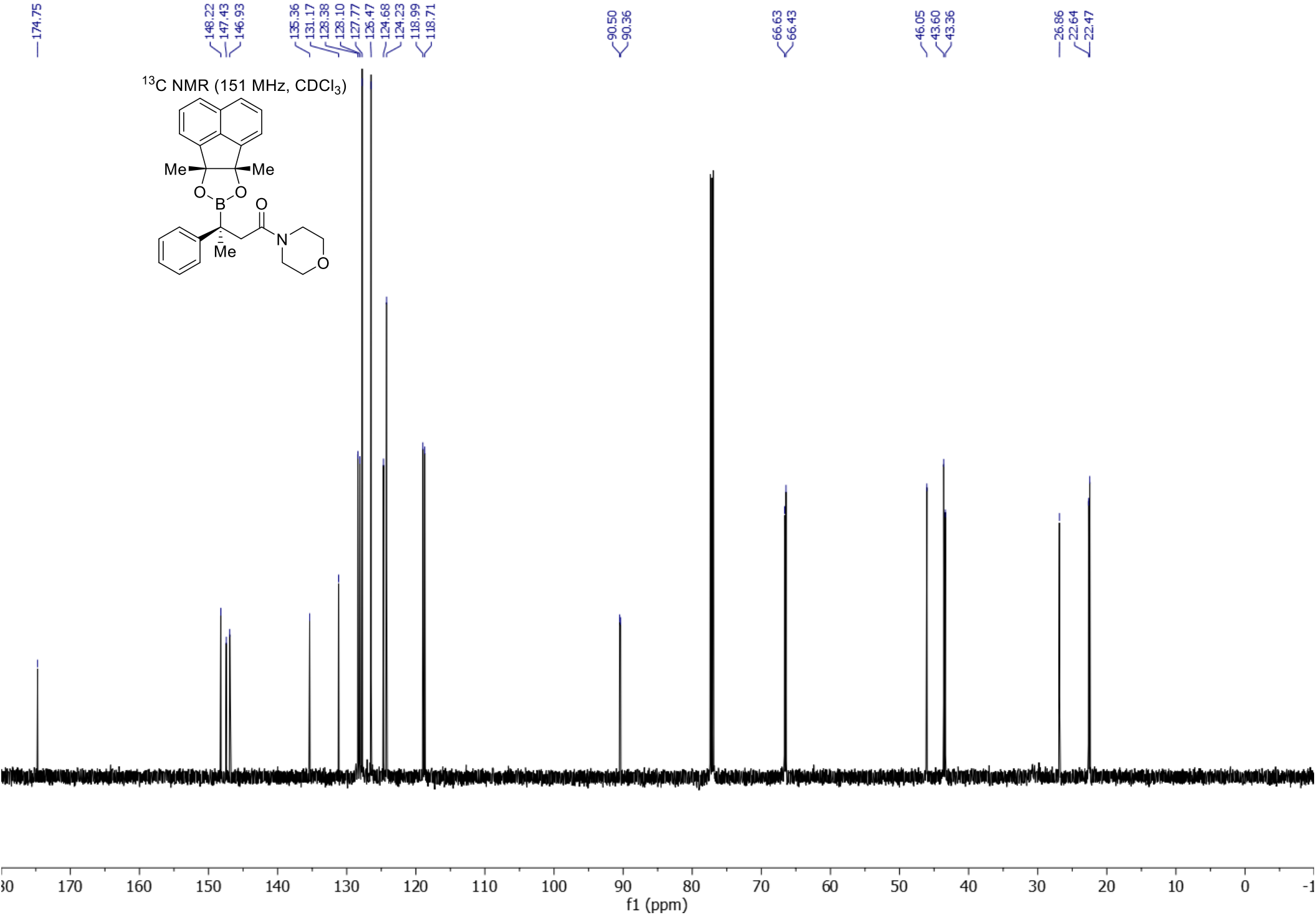
^{1}H NMR (500 MHz, $CDCl_3$)

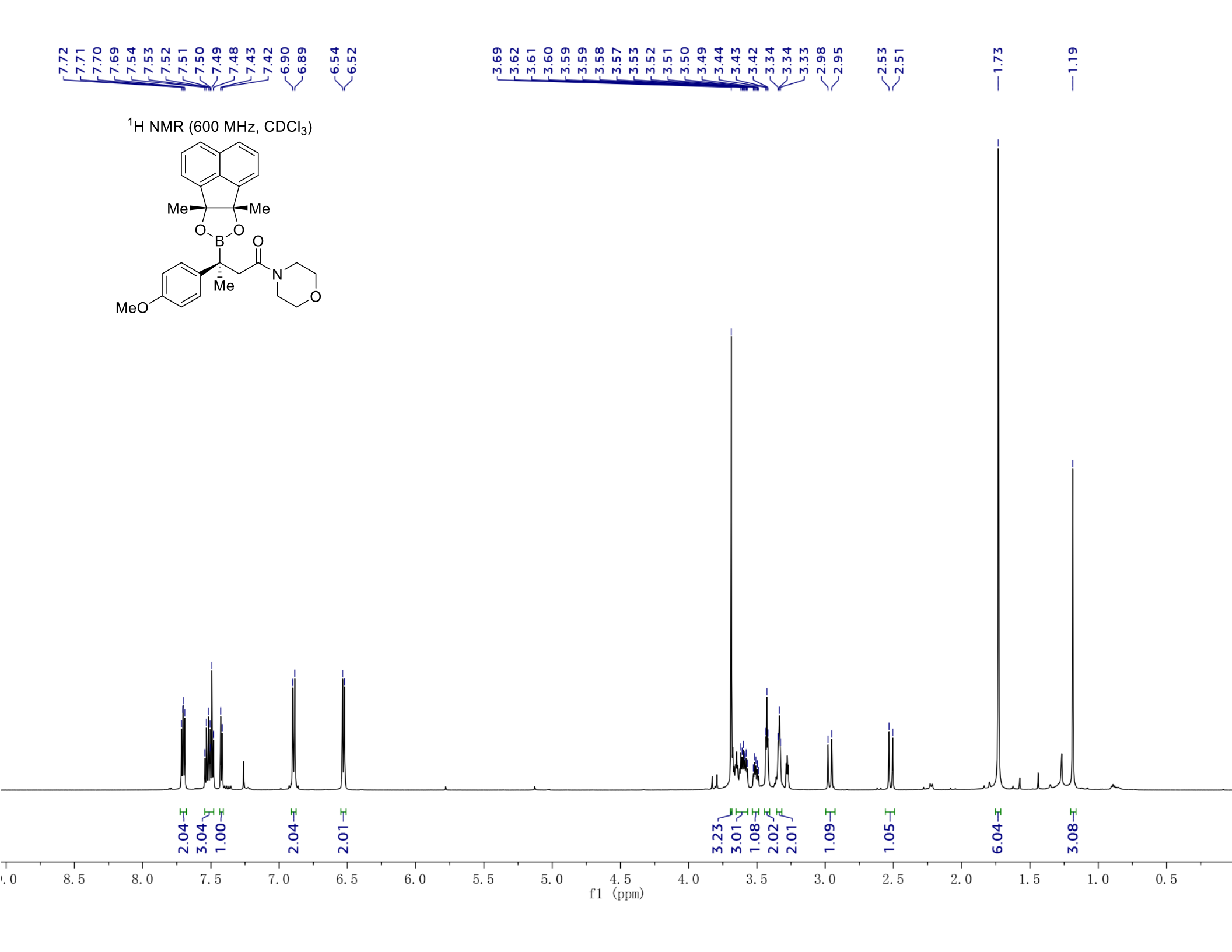


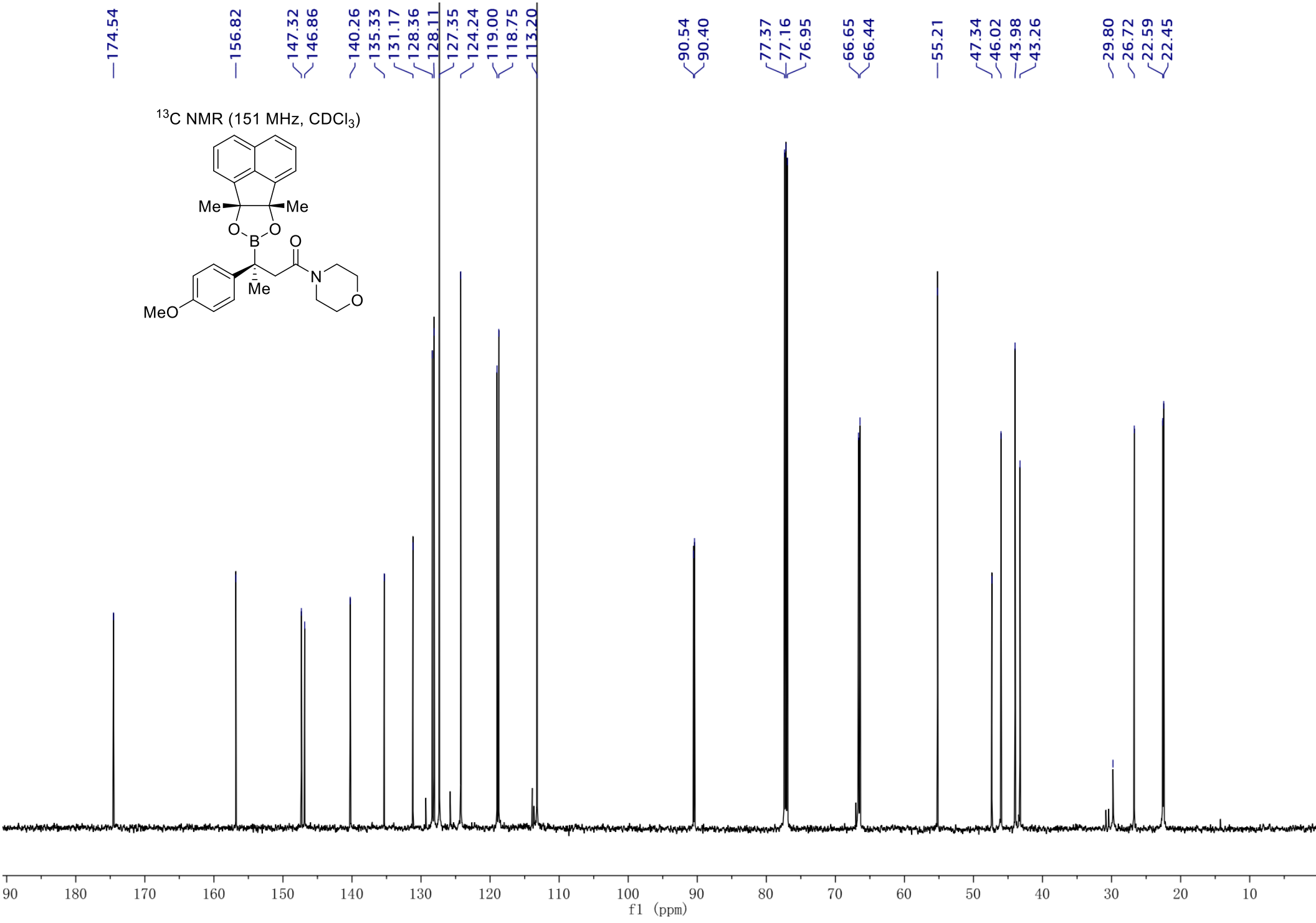
7.72 7.71 7.70 7.55 7.54 7.52 7.52 7.51 7.49 7.48 7.43 7.42 7.01 6.99 6.99 6.98 6.97 6.97 6.96 6.95 6.95 3.69 3.68 3.67 3.66 3.65 3.63 3.62 3.62 3.60 3.60 3.59 3.59 3.58 3.57 3.52 3.51 3.50 3.49 3.48 3.45 3.44 3.43 3.33 3.32 3.32 3.04 3.02 2.57 2.54 1.74 1.72 1.22

1.96 2.99 1.07 4.91 3.25 1.15 2.00 2.07 0.98 1.00 6.18 3.02

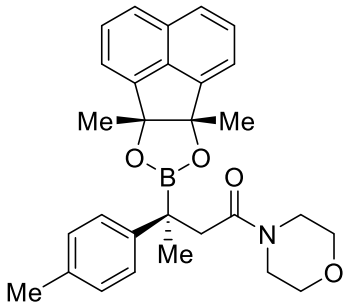
f1 (ppm)


174.75
148.22
147.43
146.93
135.36
131.17
128.38
128.10
127.77
126.47
124.68
124.23
118.99
118.71
90.50
90.36
66.63
66.43
46.05
43.60
43.36
26.86
22.64
22.47
13C NMR (151 MHz, CDCl3)
Me
Me
O
B
O
O
N
O
Me
f1 (ppm)


7.72
7.71
7.70
7.69
7.54
7.53
7.52
7.51
7.50
7.49
7.48
7.43
7.42
6.90
6.89
6.54
6.52
3.69
3.62
3.61
3.60
3.59
3.59
3.58
3.57
3.53
3.52
3.51
3.50
3.49
3.44
3.43
3.42
3.34
3.34
3.33
2.98
2.95
2.53
2.51
1.73
1.19
1H NMR (600 MHz, CDCl3)
Me
Me
O
B
O
O
N
O
Me
MeO
2.04
3.04
1.00
2.04
2.01
3.23
3.01
1.08
2.02
2.01
1.09
1.05
6.04
3.08
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
f1 (ppm)


174.54
156.82
147.32
146.86
140.26
135.33
131.17
128.36
128.11
127.35
124.24
119.00
118.75
113.20
90.54
90.40
77.37
77.16
76.95
66.65
66.44
55.21
47.34
46.02
43.98
43.26
29.80
26.72
22.59
22.45
13C NMR (151 MHz, CDCl3)
Me
Me
O
B
O
O
N
O
Me
MeO
90
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

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

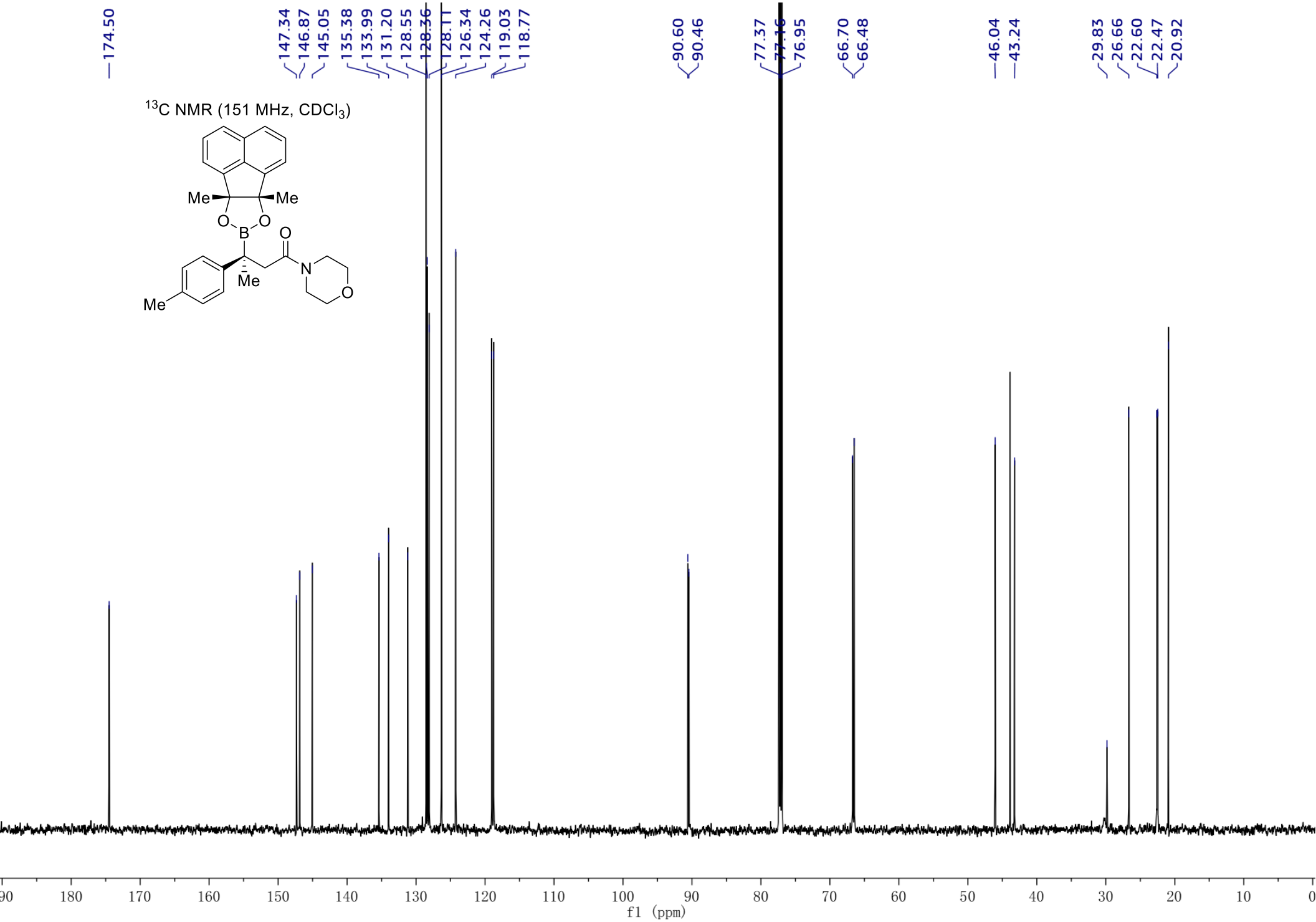


7.72 7.71 7.70 7.70 7.54 7.53 7.52 7.51 7.49 7.49 7.48 7.43 7.42 6.89 6.88 6.81 6.80 3.68 3.67 3.66 3.65 3.65 3.64 3.63 3.62 3.62 3.61 3.61 3.60 3.60 3.59 3.59 3.58 3.58 3.57 3.52 3.52 3.51 3.51 3.50 3.49 3.49 3.45 3.44 3.43 3.34 3.33 3.32 3.31 3.00 2.97 2.54 2.51 2.20 1.73 1.72 1.20

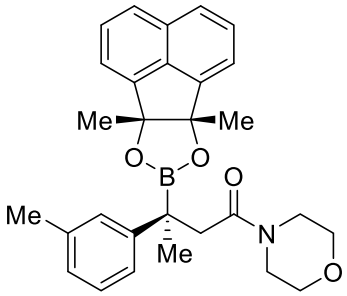
2.01 3.09 1.00 2.02 2.02 3.02 1.07 2.04 2.03 1.06 1.03 3.08 6.08 3.09

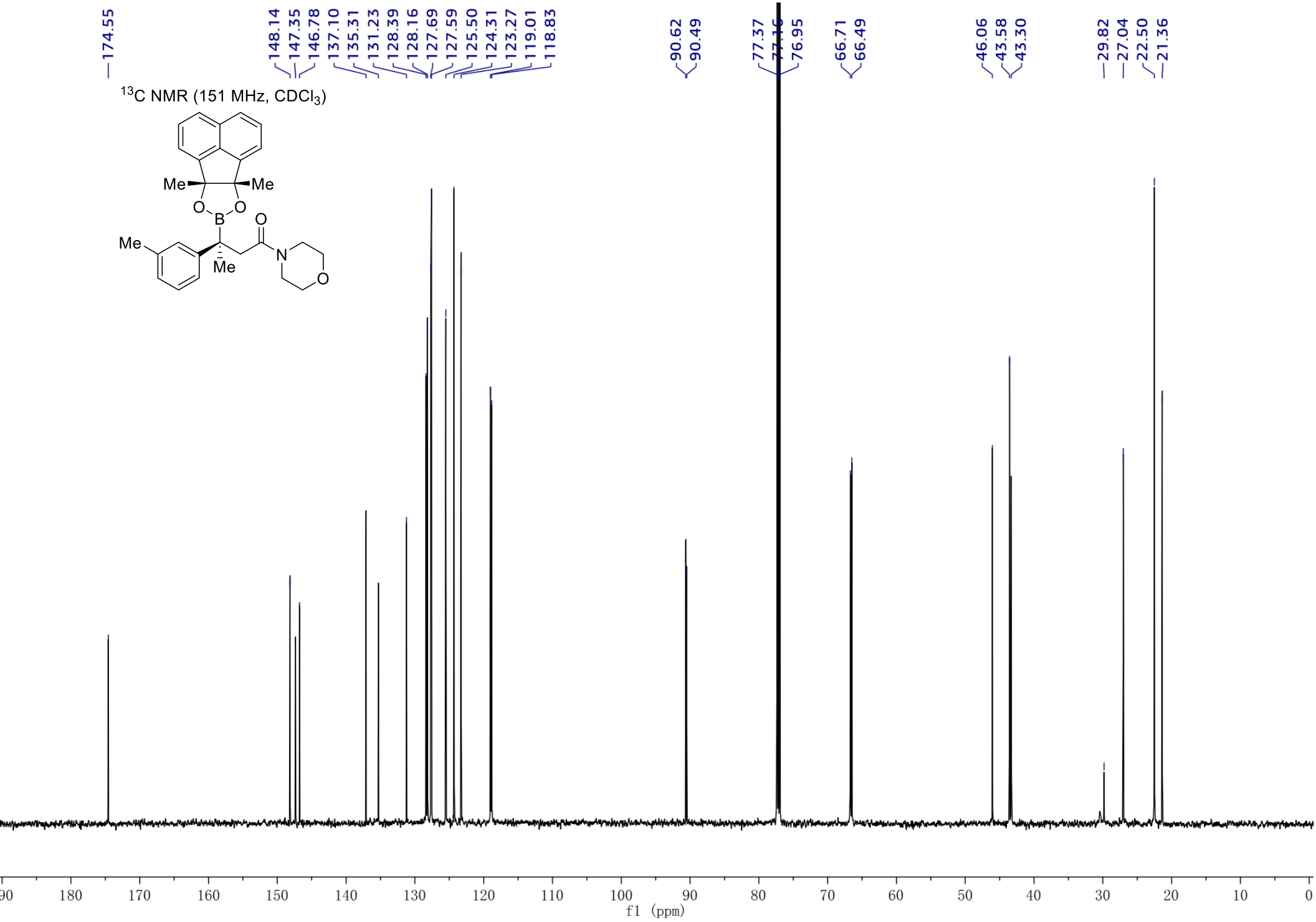
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5

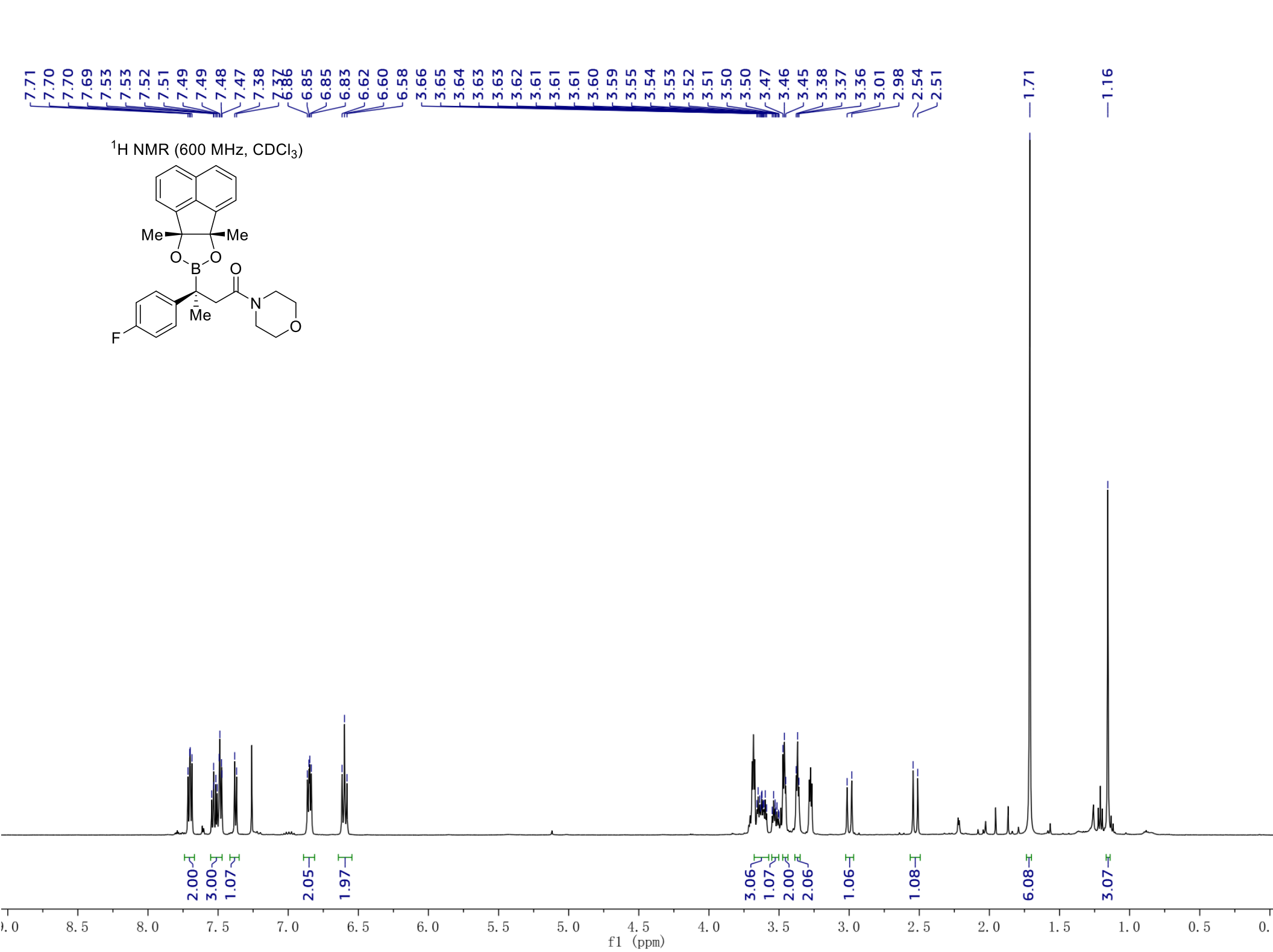
f1 (ppm)

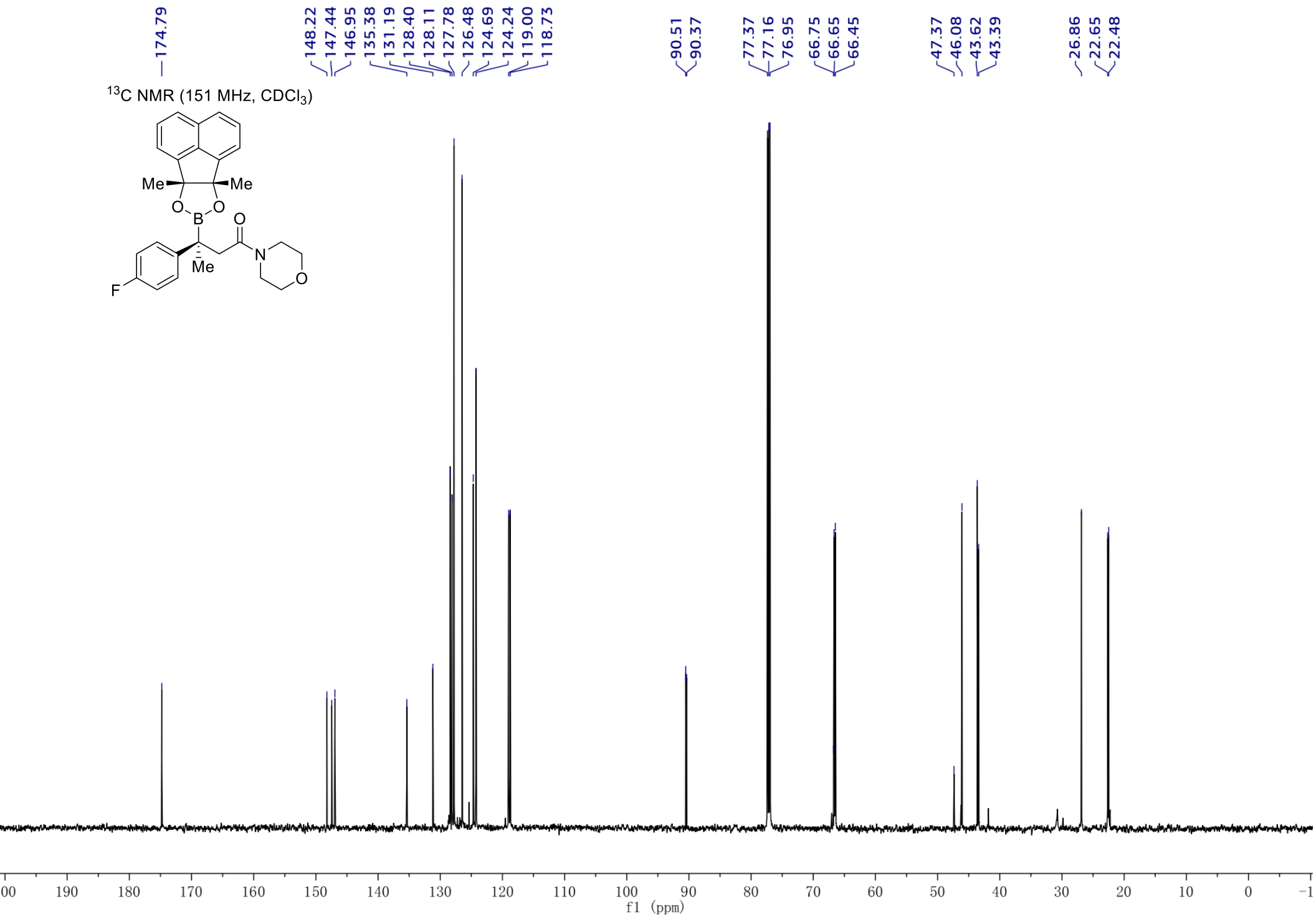

174.50
147.34
146.87
145.05
135.38
133.99
131.20
128.55
128.36
128.11
126.34
124.26
119.03
118.77
90.60
90.46
77.37
77.16
76.95
66.70
66.48
46.04
43.24
29.83
26.66
22.60
22.47
20.92
13C NMR (151 MHz, CDCl3)
Me
Me
O
B
O
O
N
O
Me
Me
f1 (ppm)

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

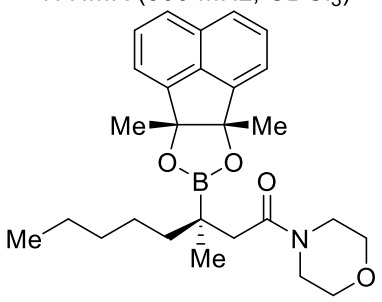


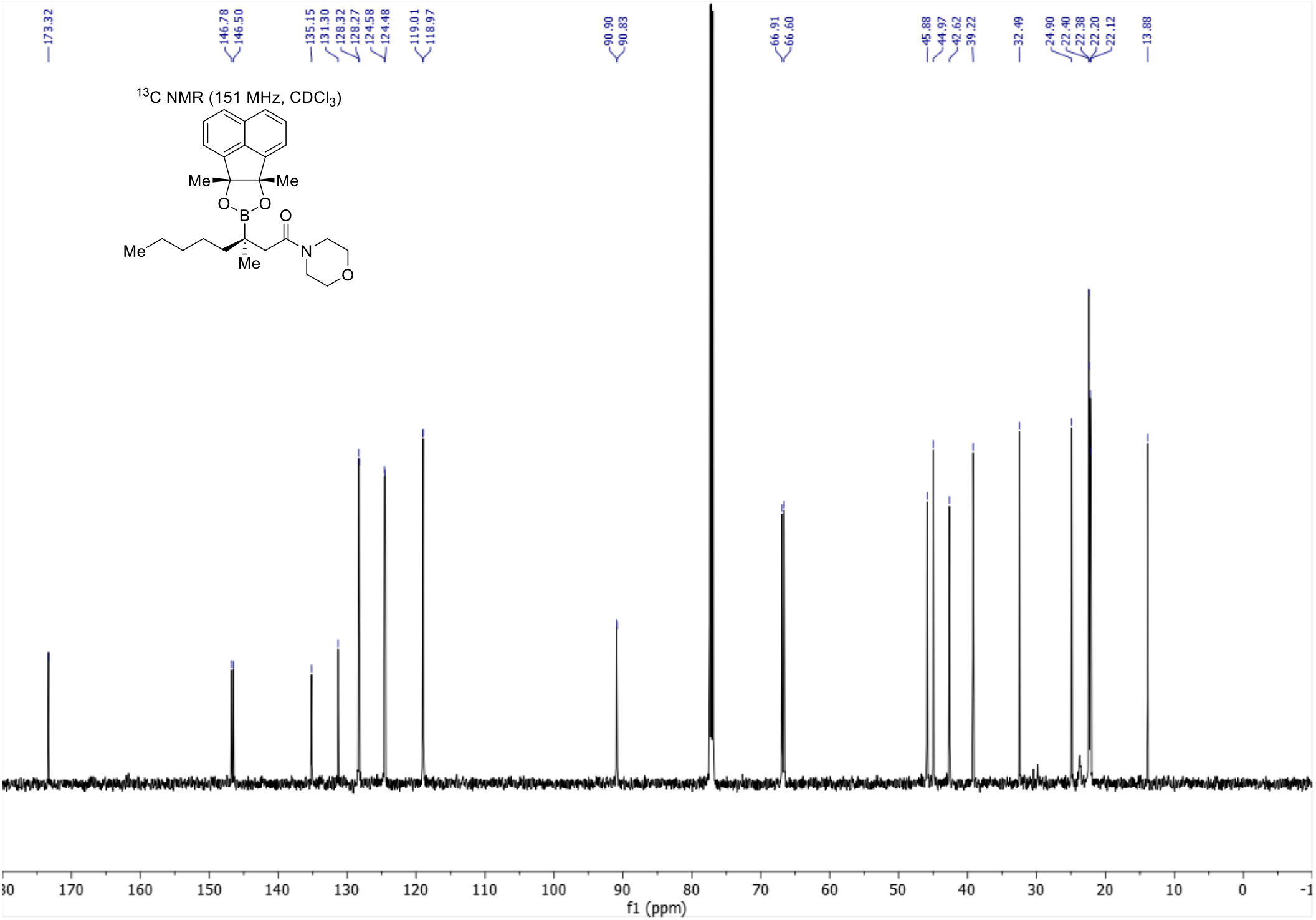

174.55
148.14
147.35
146.78
137.10
135.31
131.23
128.39
128.16
127.69
127.59
125.50
124.31
123.27
119.01
118.83
90.62
90.49
77.37
77.16
76.95
66.71
66.49
46.06
43.58
43.30
29.82
27.04
22.50
21.36
13C NMR (151 MHz, CDCl3)
Me
Me
O
B
O
O
Me
Me
N
O
f1 (ppm)


7.71
7.70
7.70
7.69
7.53
7.53
7.52
7.51
7.49
7.49
7.48
7.47
7.38
6.86
6.85
6.85
6.83
6.62
6.60
6.58
3.66
3.65
3.64
3.63
3.63
3.62
3.61
3.61
3.61
3.60
3.59
3.55
3.54
3.53
3.52
3.51
3.50
3.50
3.47
3.46
3.45
3.38
3.37
3.36
3.01
2.98
2.54
2.51
1.71
1.16
1H NMR (600 MHz, CDCl3)
Me
Me
O
B
O
O
Me
N
O
F
2.00
3.00
1.07
2.05
1.97
3.06
1.07
2.00
2.06
1.06
1.08
6.08
3.07
f1 (ppm)

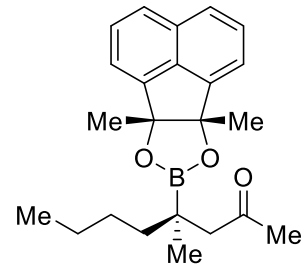

174.79
148.22
147.44
146.95
135.38
131.19
128.40
128.11
127.78
126.48
124.69
124.24
119.00
118.73
90.51
90.37
77.37
77.16
76.95
66.75
66.65
66.45
47.37
46.08
43.62
43.39
26.86
22.65
22.48
13C NMR (151 MHz, CDCl3)
Me
Me
O
O
B
O
N
O
Me
F
f1 (ppm)

^{1}H NMR (500 MHz, $CDCl_3$)



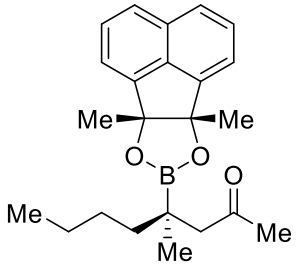

173.32
146.78
146.50
135.15
131.30
128.32
128.27
124.58
124.48
119.01
118.97
90.90
90.83
66.91
66.60
45.88
44.97
42.62
39.22
32.49
24.90
22.40
22.38
22.20
22.12
13.88
13C NMR (151 MHz, CDCl3)
Me
Me
O
B
O
O
Me
Me
N
O
f1 (ppm)

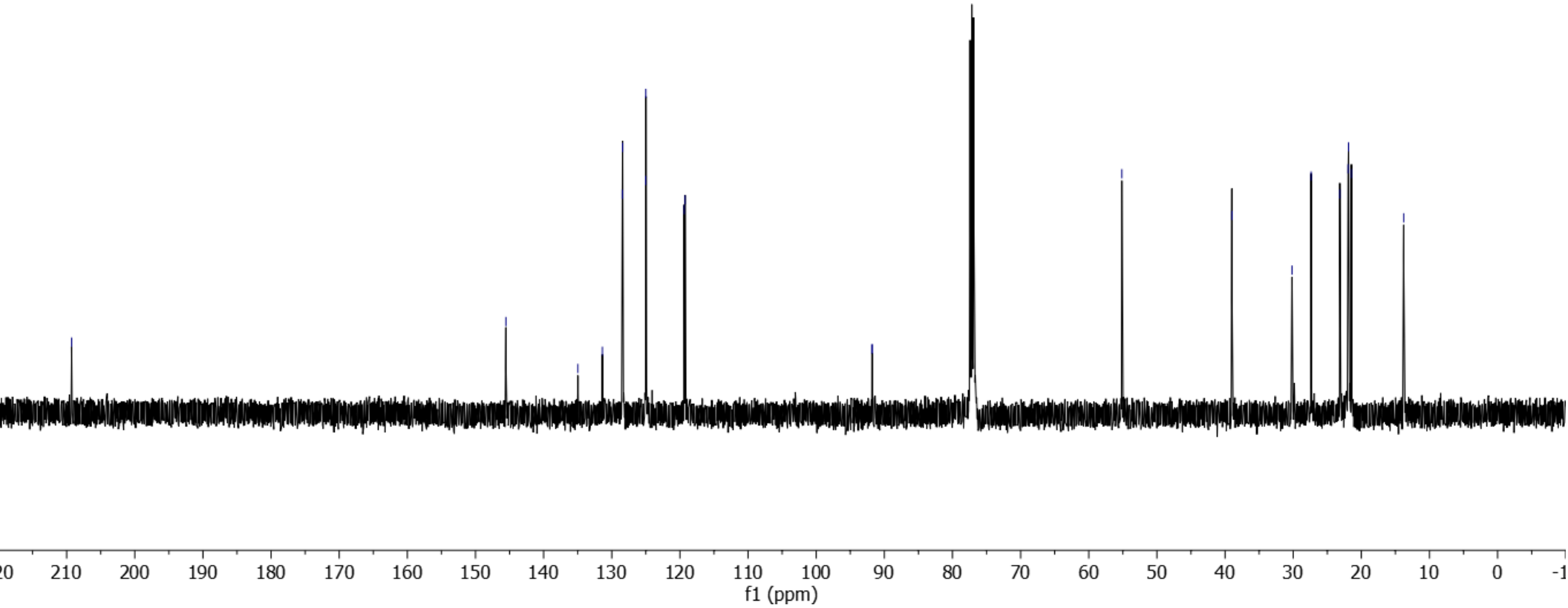
^{1}H NMR (500 MHz, $CDCl_3$)



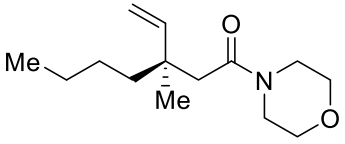
209.27
145.53
134.98
131.37
128.45
128.41
125.02
125.00
119.38
119.25
91.82
91.77
55.15
38.99
30.18
27.37
23.17
21.94
21.88
21.45
13.78

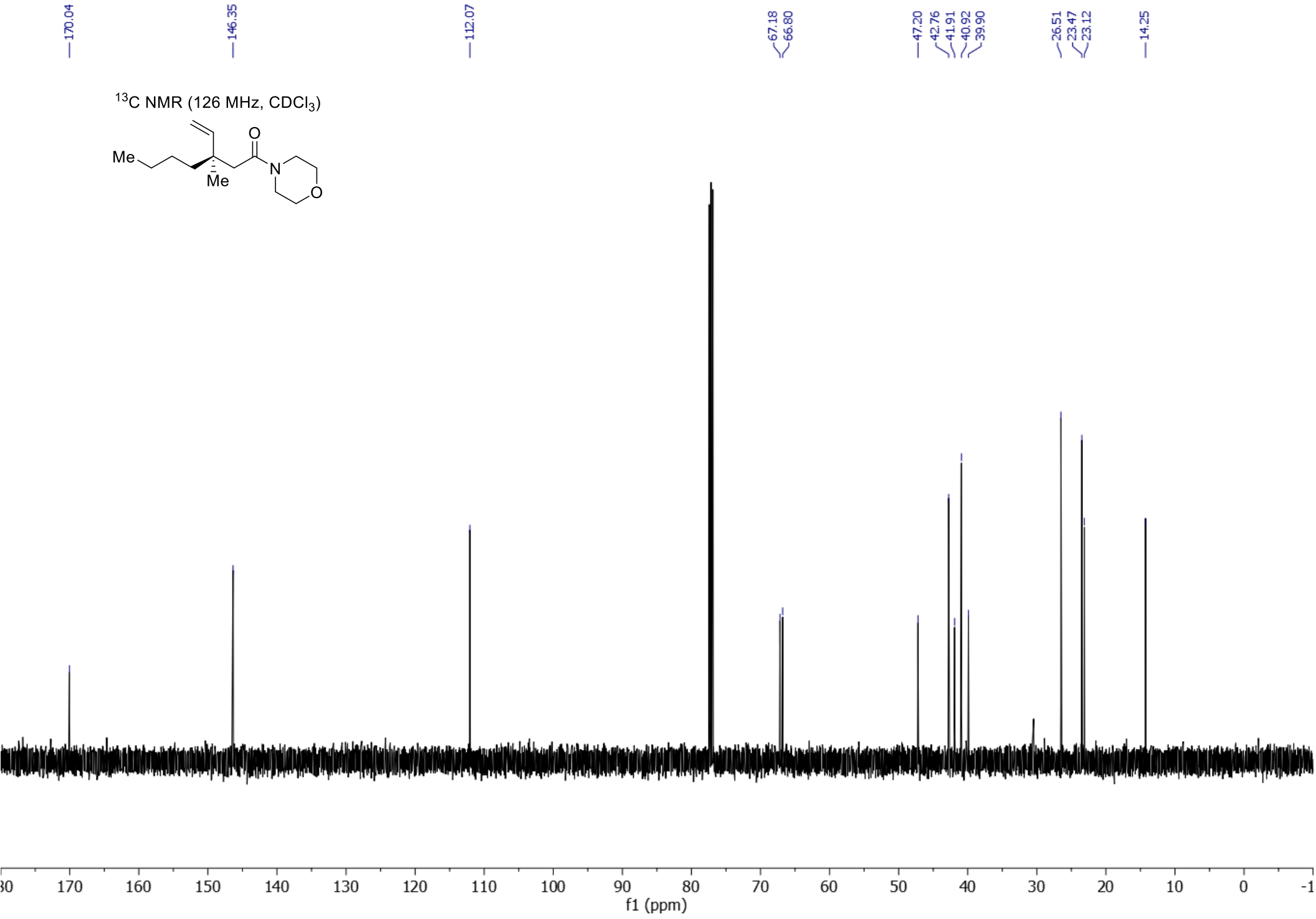
^{13}C NMR (126 MHz, $CDCl_3$)



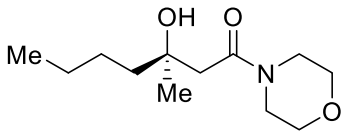


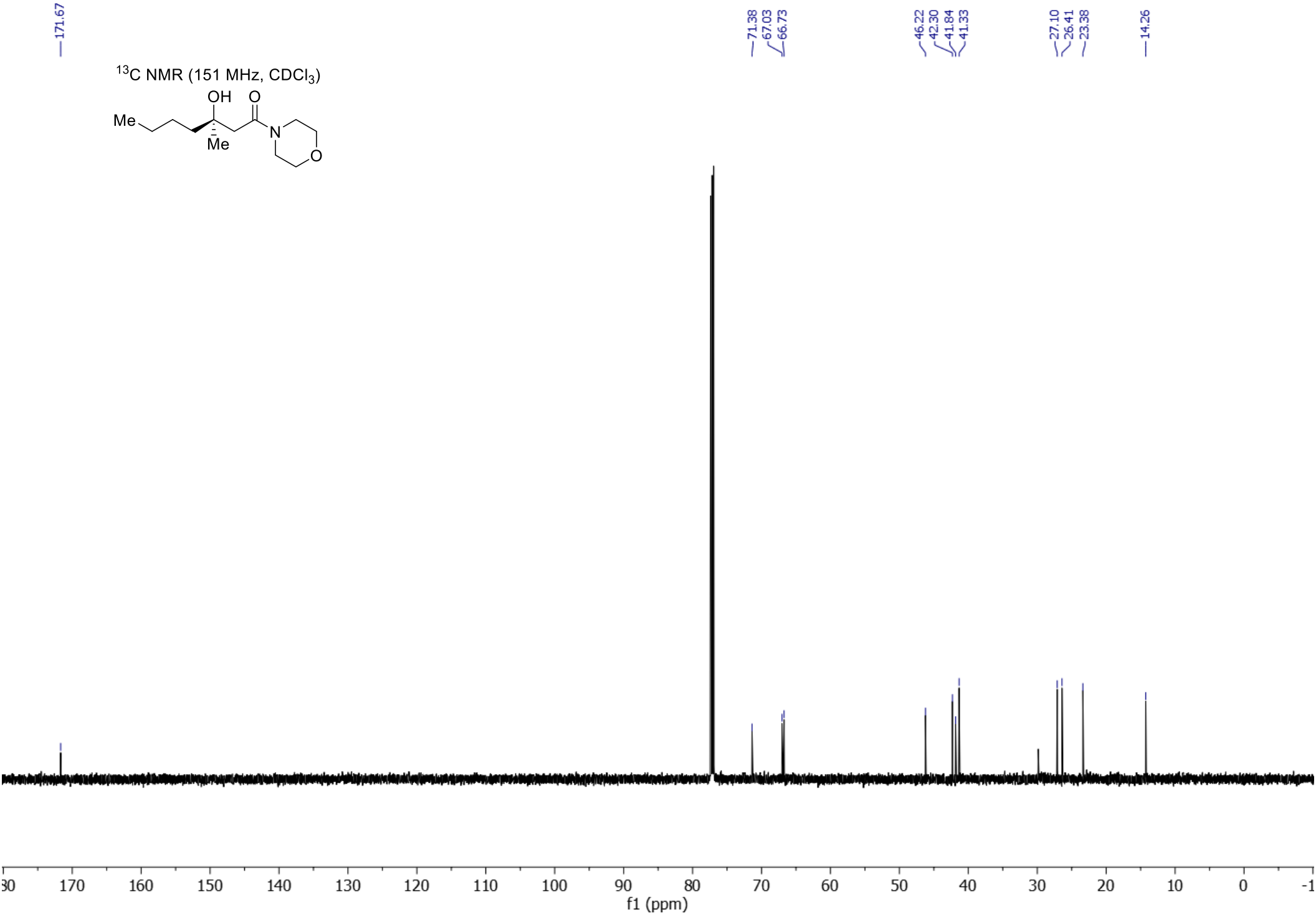
^{1}H NMR (400 MHz, $CDCl_3$)

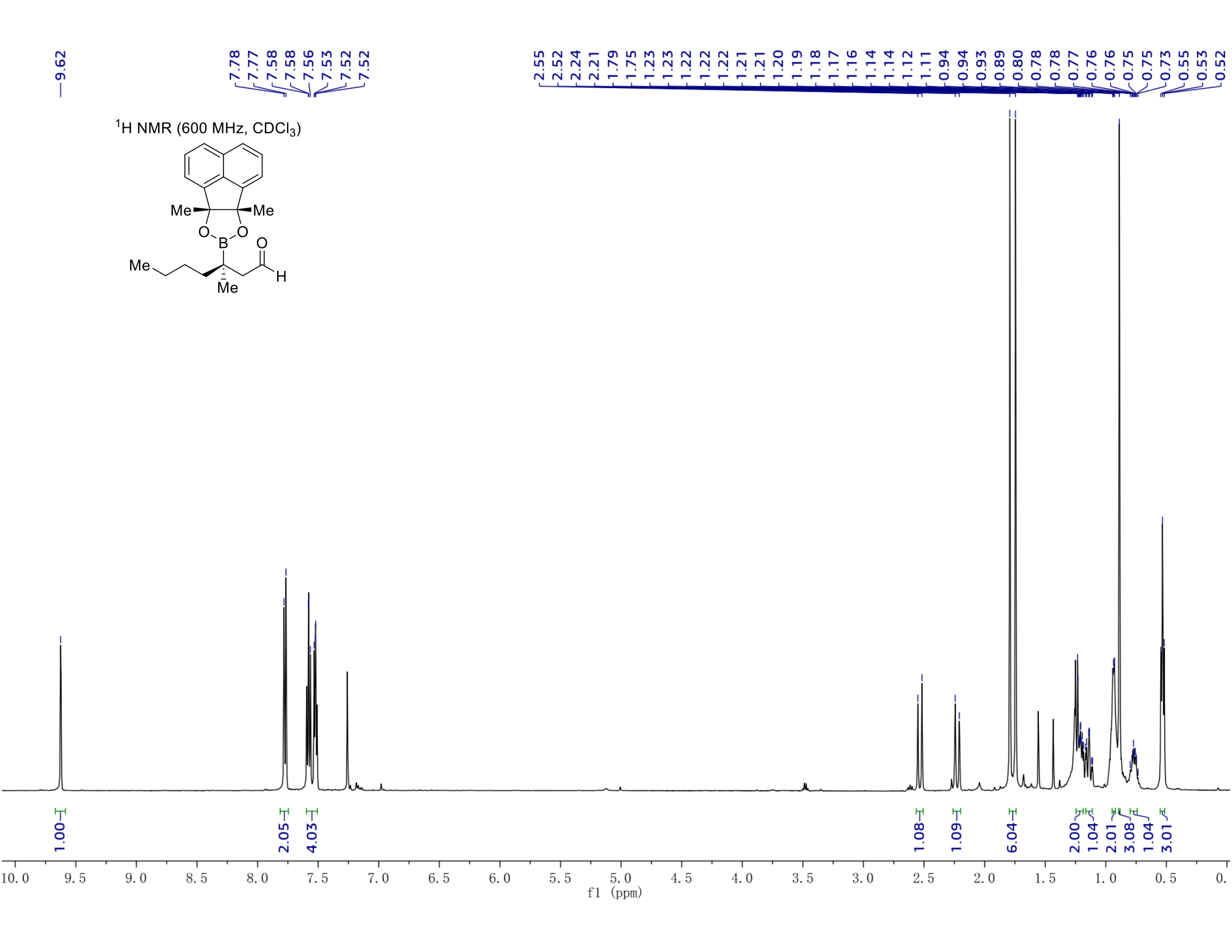


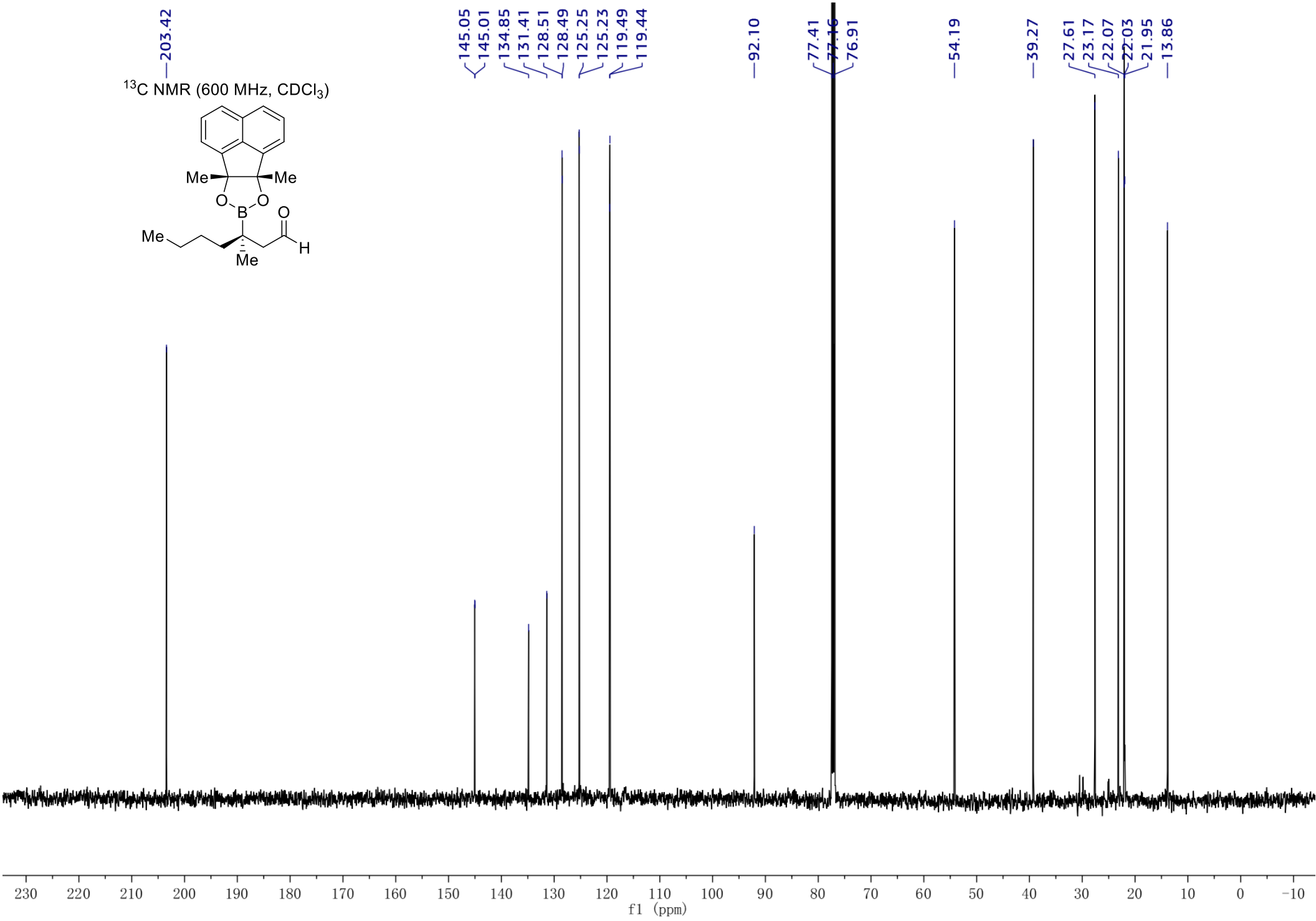

170.04
146.35
112.07
67.18
66.80
47.20
42.76
41.91
40.92
39.90
26.51
23.47
23.12
14.25
^{13}C NMR (126 MHz, $CDCl_3$)
Me
Me
O
N
O
f1 (ppm)

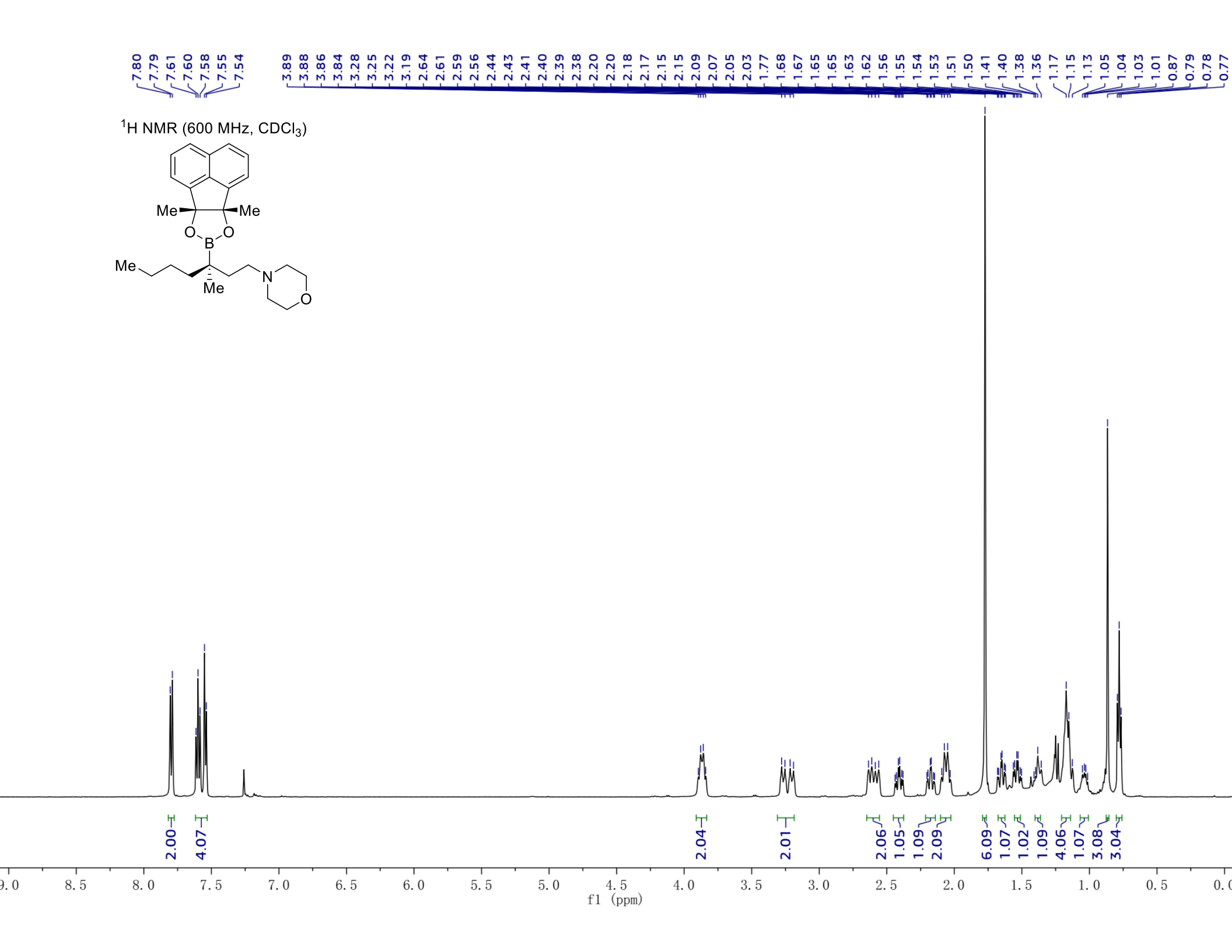
^{1}H NMR (600 MHz, $CDCl_3$)

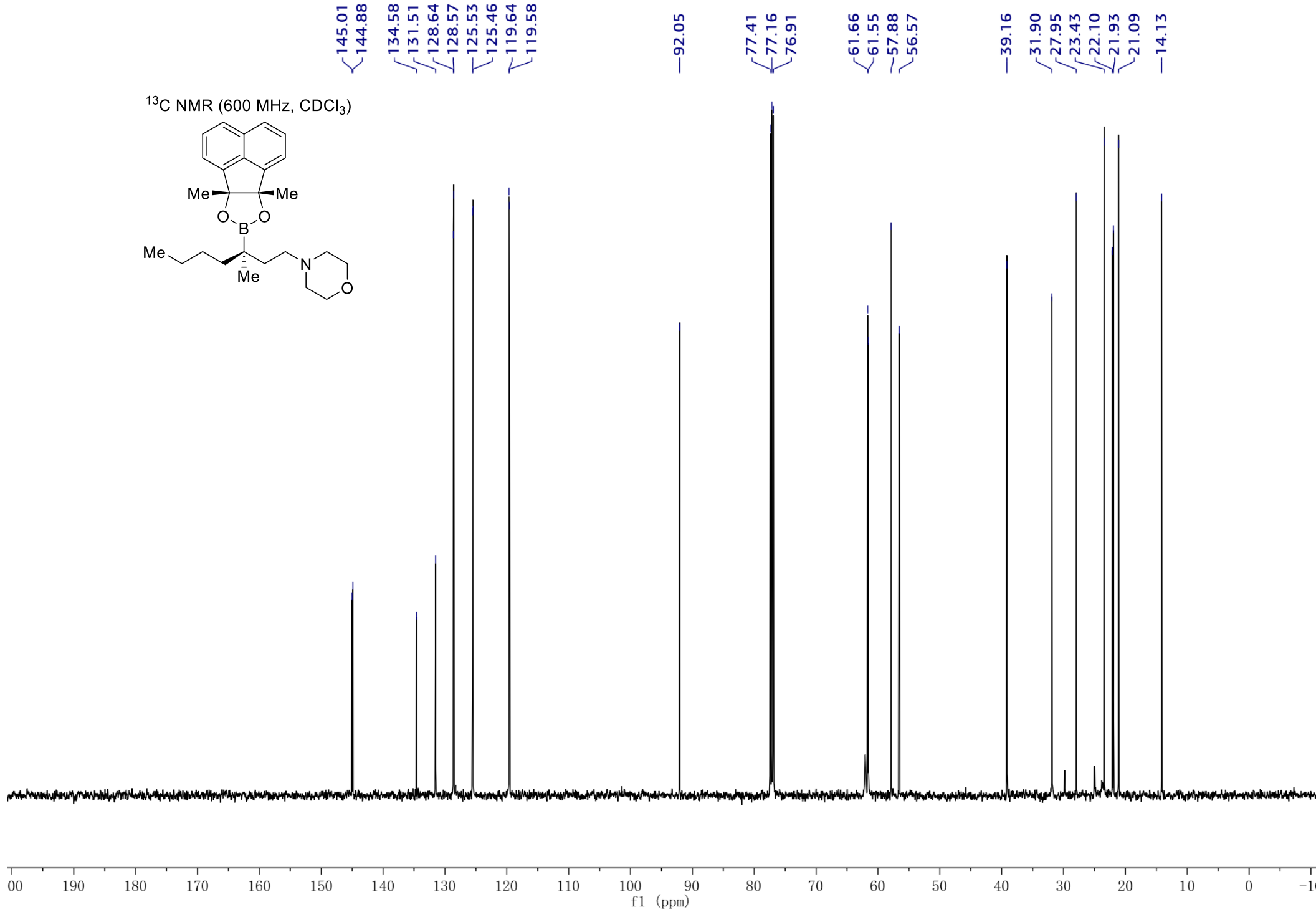



171.67
71.38
67.03
66.73
46.22
42.30
41.84
41.33
27.10
26.41
23.38
14.26
13C NMR (151 MHz, CDCl3)
OH
O
Me
Me
N
O
f1 (ppm)

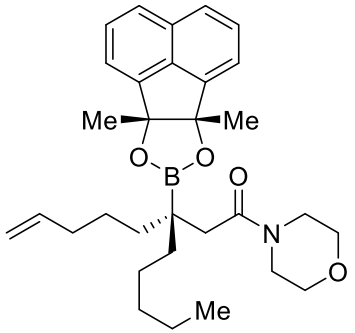

9.62
7.78
7.77
7.58
7.58
7.56
7.53
7.52
7.52
2.55
2.52
2.24
2.21
1.79
1.75
1.23
1.23
1.22
1.22
1.22
1.21
1.21
1.20
1.19
1.18
1.17
1.16
1.14
1.14
1.12
1.11
0.94
0.94
0.93
0.89
0.80
0.78
0.78
0.77
0.76
0.76
0.75
0.75
0.73
0.55
0.53
0.52
1H NMR (600 MHz, CDCl3)
Me
Me
O
B
O
O
Me
H
Me
1.00
2.05
4.03
1.08
1.09
6.04
2.00
1.04
2.01
3.08
1.04
3.01
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
f1 (ppm)

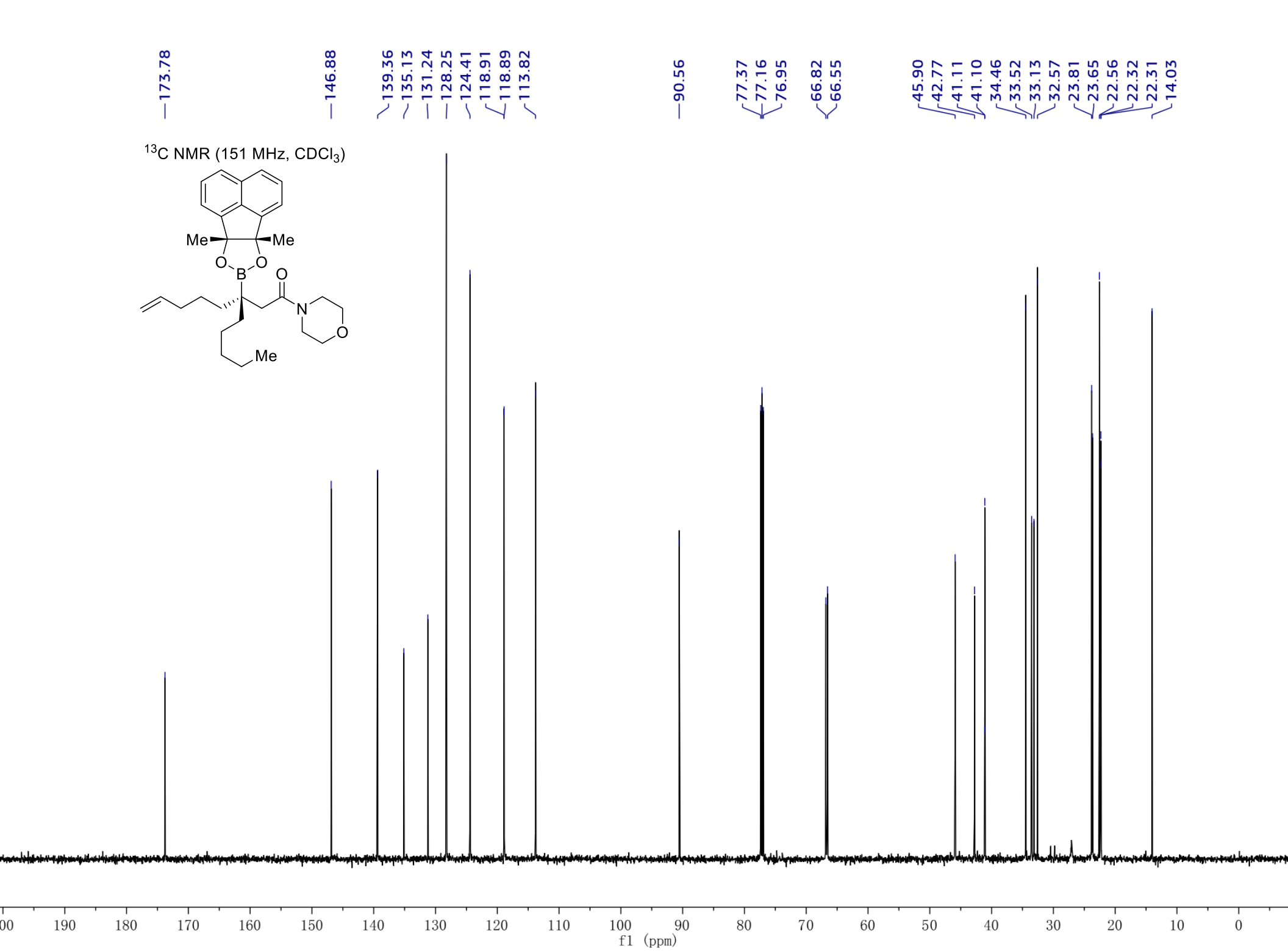

203.42
145.05
145.01
134.85
131.41
128.51
128.49
125.25
125.23
119.49
119.44
92.10
77.41
77.16
76.91
54.19
39.27
27.61
23.17
22.07
22.03
21.95
13.86
13C NMR (600 MHz, CDCl3)
Me
Me
O
B
O
O
Me
Me
H
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)


7.80 7.79 7.61 7.60 7.58 7.55 7.54
3.89 3.88 3.86 3.84 3.28 3.25 3.22 3.19 2.64 2.61 2.59 2.56 2.44 2.43 2.41 2.40 2.39 2.38 2.20 2.20 2.18 2.17 2.15 2.15 2.09 2.07 2.05 2.03 1.77 1.68 1.67 1.65 1.65 1.63 1.62 1.56 1.55 1.54 1.53 1.51 1.50 1.41 1.40 1.38 1.36 1.17 1.15 1.13 1.05 1.04 1.03 1.01 0.87 0.79 0.78 0.77
1H NMR (600 MHz, CDCl3)
Me
Me
O
B
O
Me
Me
N
O
2.00 4.07 2.04 2.01 2.06 1.05 1.09 2.09 6.09 1.07 1.02 1.09 4.06 1.07 3.08 3.04
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
f1 (ppm)

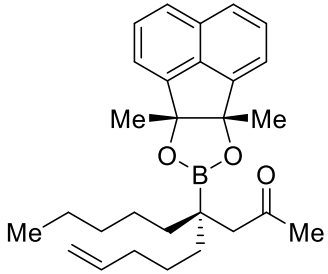

145.01
144.88
134.58
131.51
128.64
128.57
125.53
125.46
119.64
119.58
92.05
77.41
77.16
76.91
61.66
61.55
57.88
56.57
39.16
31.90
27.95
23.43
22.10
21.93
21.09
14.13
13C NMR (600 MHz, CDCl3)
Me
Me
O
B
O
Me
Me
N
O
f1 (ppm)

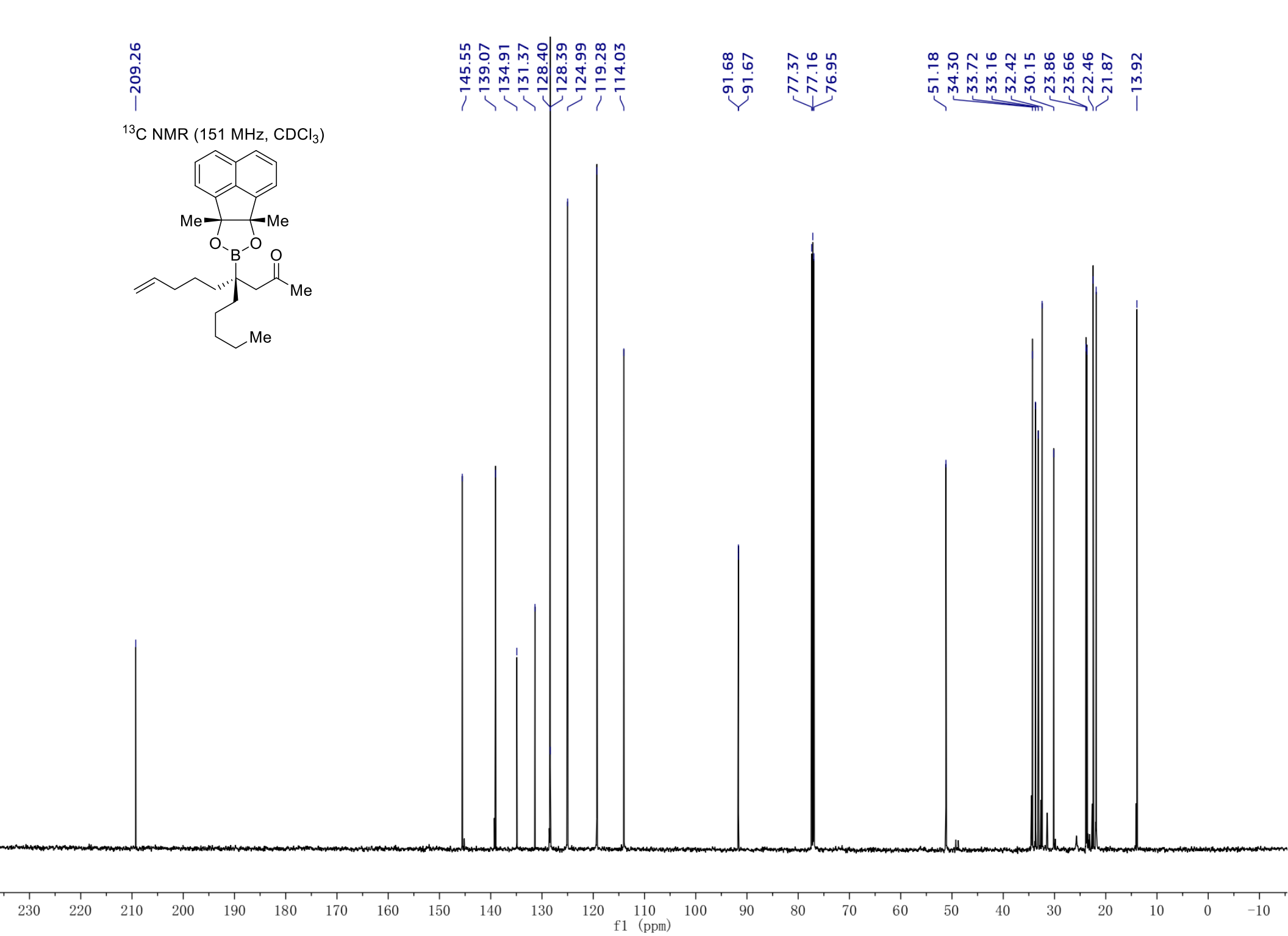
^{1}H NMR (600 MHz, $CDCl_3$)



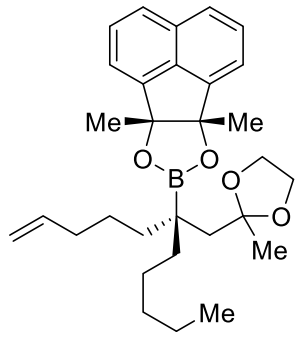

173.78
146.88
139.36
135.13
131.24
128.25
124.41
118.91
118.89
113.82
90.56
77.37
77.16
76.95
66.82
66.55
45.90
42.77
41.11
41.10
34.46
33.52
33.13
32.57
23.81
23.65
22.56
22.32
22.31
14.03
13C NMR (151 MHz, CDCl3)
Me
Me
O
B
O
O
N
O
Me
f1 (ppm)

^{1}H NMR (400 MHz, $CDCl_3$)




209.26
145.55
139.07
134.91
131.37
128.40
128.39
124.99
119.28
114.03
91.68
91.67
77.37
77.16
76.95
51.18
34.30
33.72
33.16
32.42
30.15
23.86
23.66
22.46
21.87
13.92
13C NMR (151 MHz, CDCl3)
Me
Me
O
B
O
O
Me
Me
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
f1 (ppm)

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

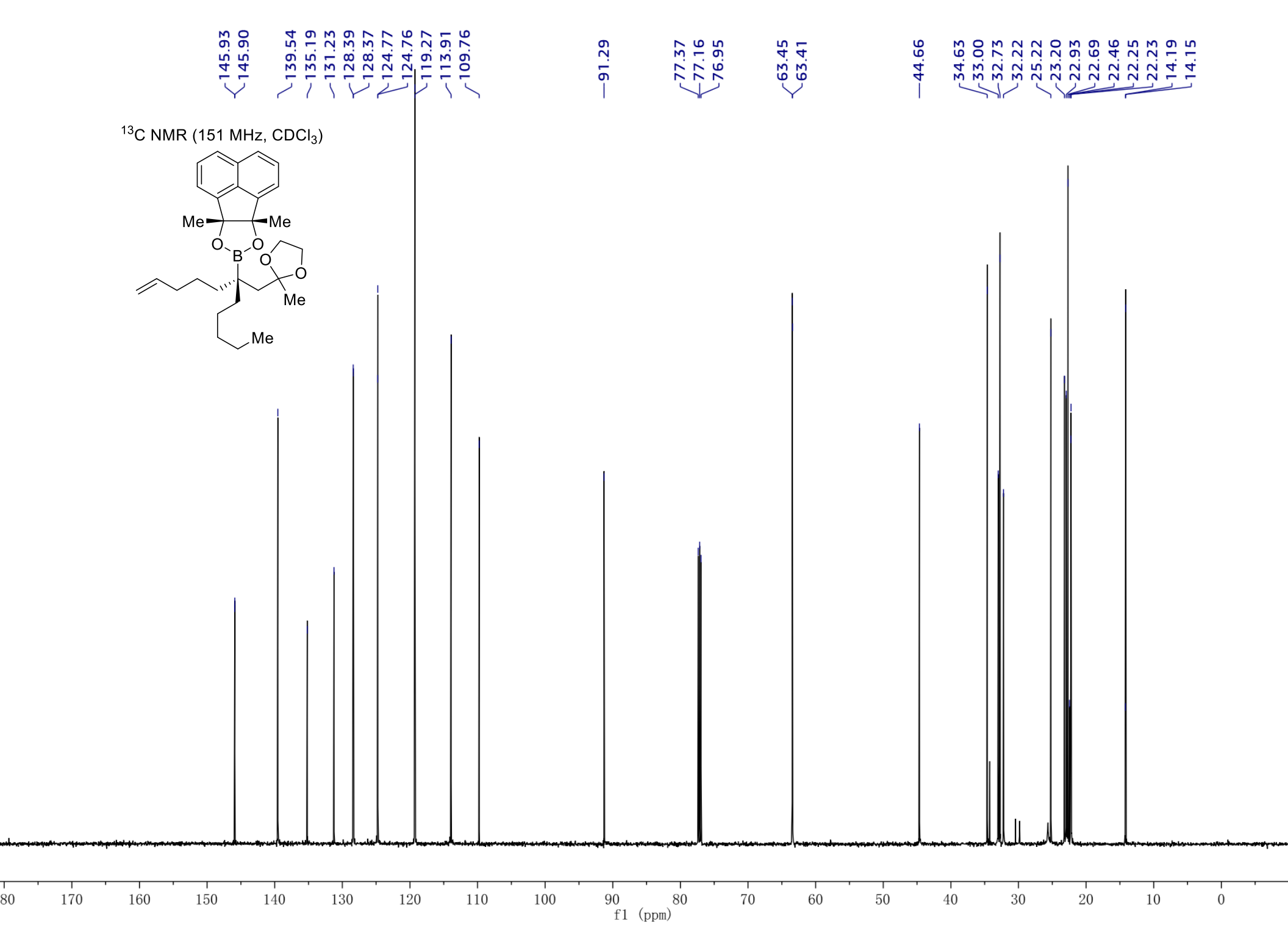


7.75 7.73 7.58 7.56 7.55 7.54 7.53 5.70 5.69 5.69 5.68 5.67 5.66 5.65 5.65 4.91 4.91 4.88 4.88 4.86 4.84 3.29 3.28 3.27 3.26 3.25 3.24 3.23 1.91 1.89 1.88 1.86 1.76 1.73 1.32 1.31 1.29 1.27 1.16 1.14 1.13 1.12 1.11 1.10 1.00 0.79 0.77 0.76

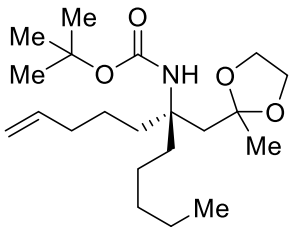
2.00 4.02 0.91 1.91 4.02 2.05 8.04 6.08 5.02 4.07 3.08

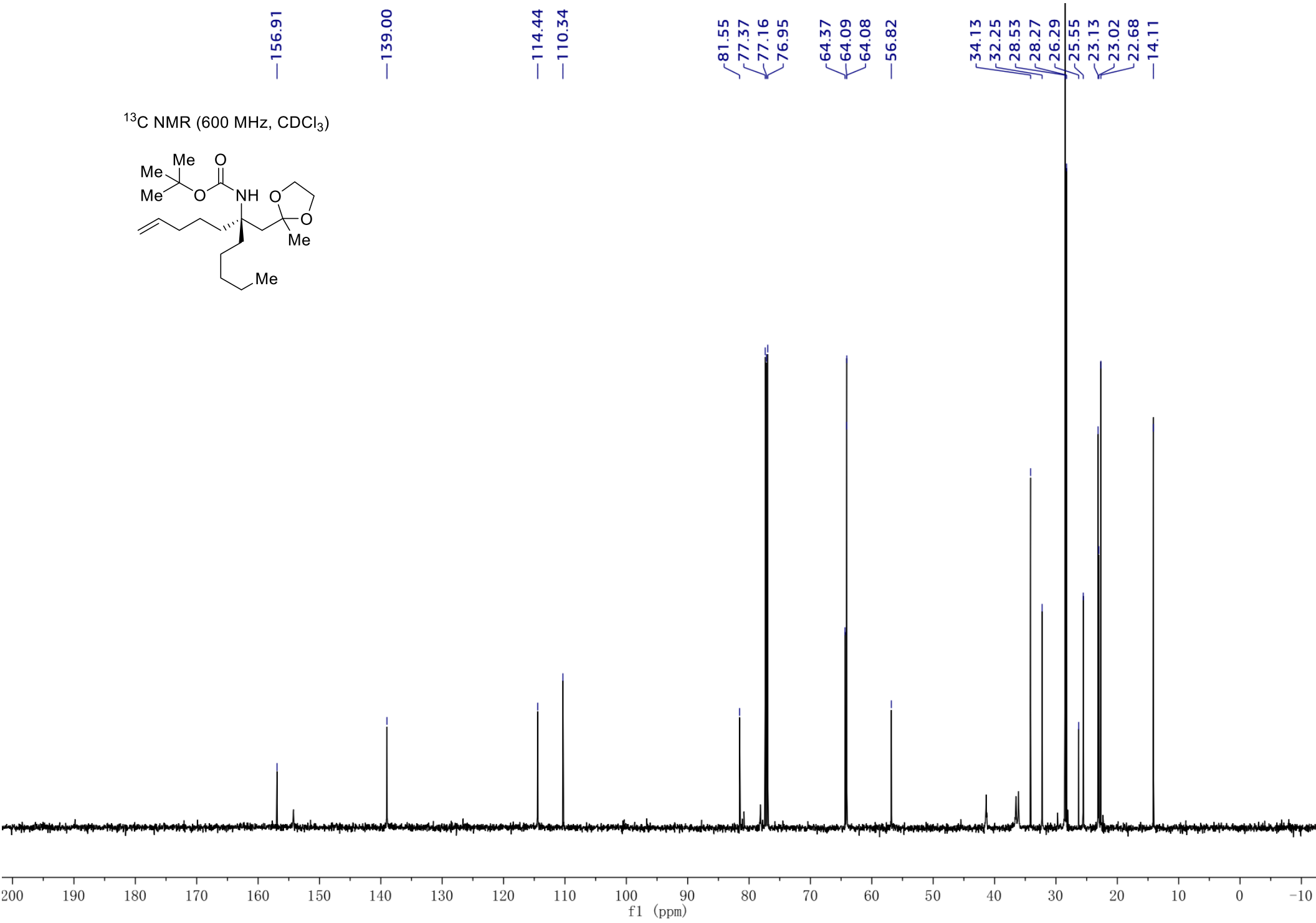
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

f1 (ppm)

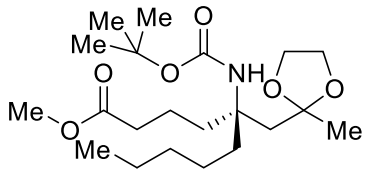

145.93
145.90
139.54
135.19
131.23
128.39
128.37
124.77
124.76
119.27
113.91
109.76
91.29
77.37
77.16
76.95
63.45
63.41
44.66
34.63
33.00
32.73
32.22
25.22
23.20
22.93
22.69
22.46
22.25
22.23
14.19
14.15
13C NMR (151 MHz, CDCl3)
Me
Me
O
B
O
O
O
Me
Me
f1 (ppm)

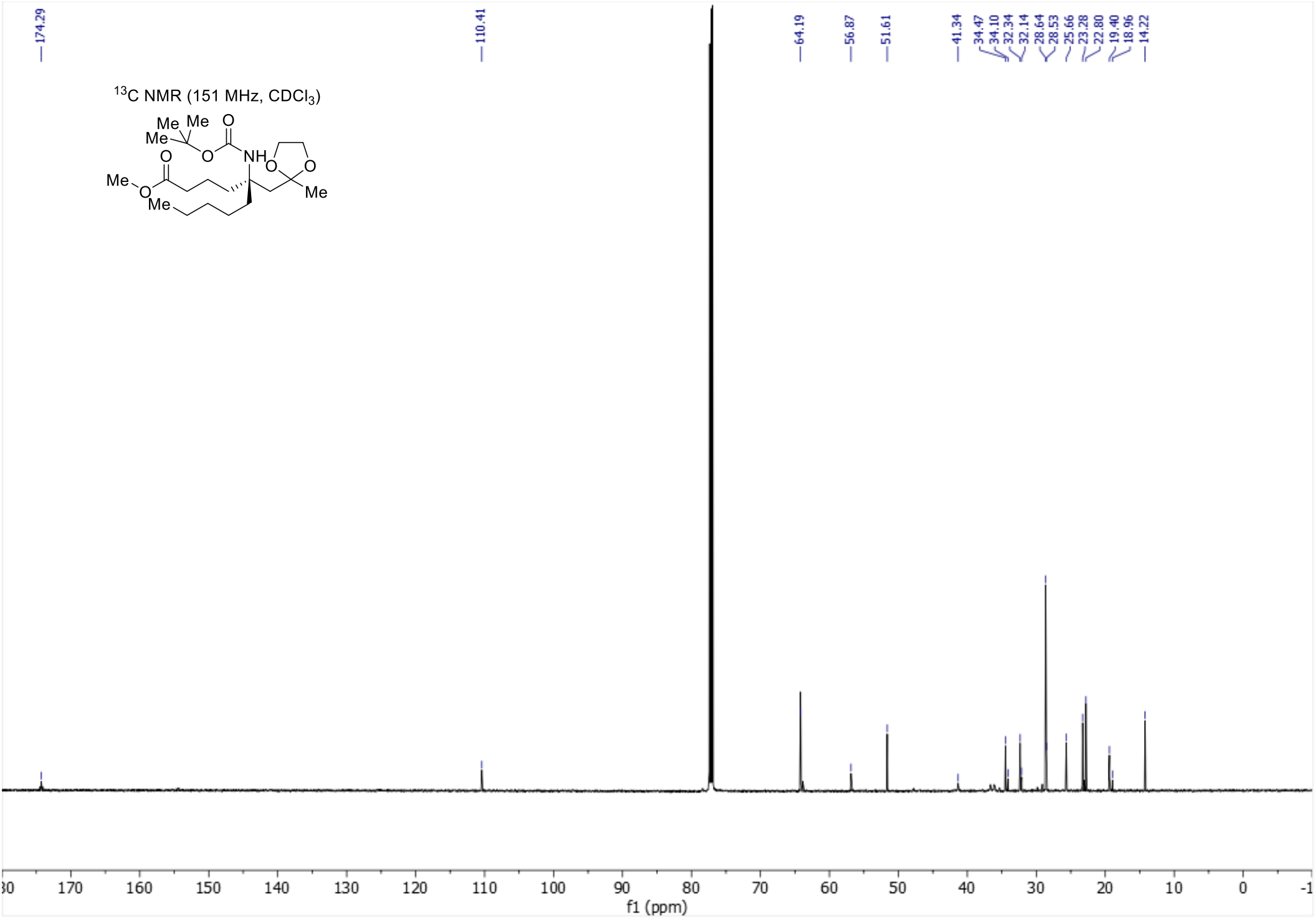
^{1}H NMR (600 MHz, $CDCl_3$)



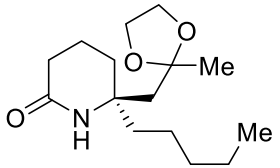

156.91
139.00
114.44
110.34
81.55
77.37
77.16
76.95
64.37
64.09
64.08
56.82
34.13
32.25
28.53
28.27
26.29
25.55
23.13
23.02
22.68
14.11
13C NMR (600 MHz, CDCl3)
Me
Me
Me
O
O
NH
O
O
Me
Me
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

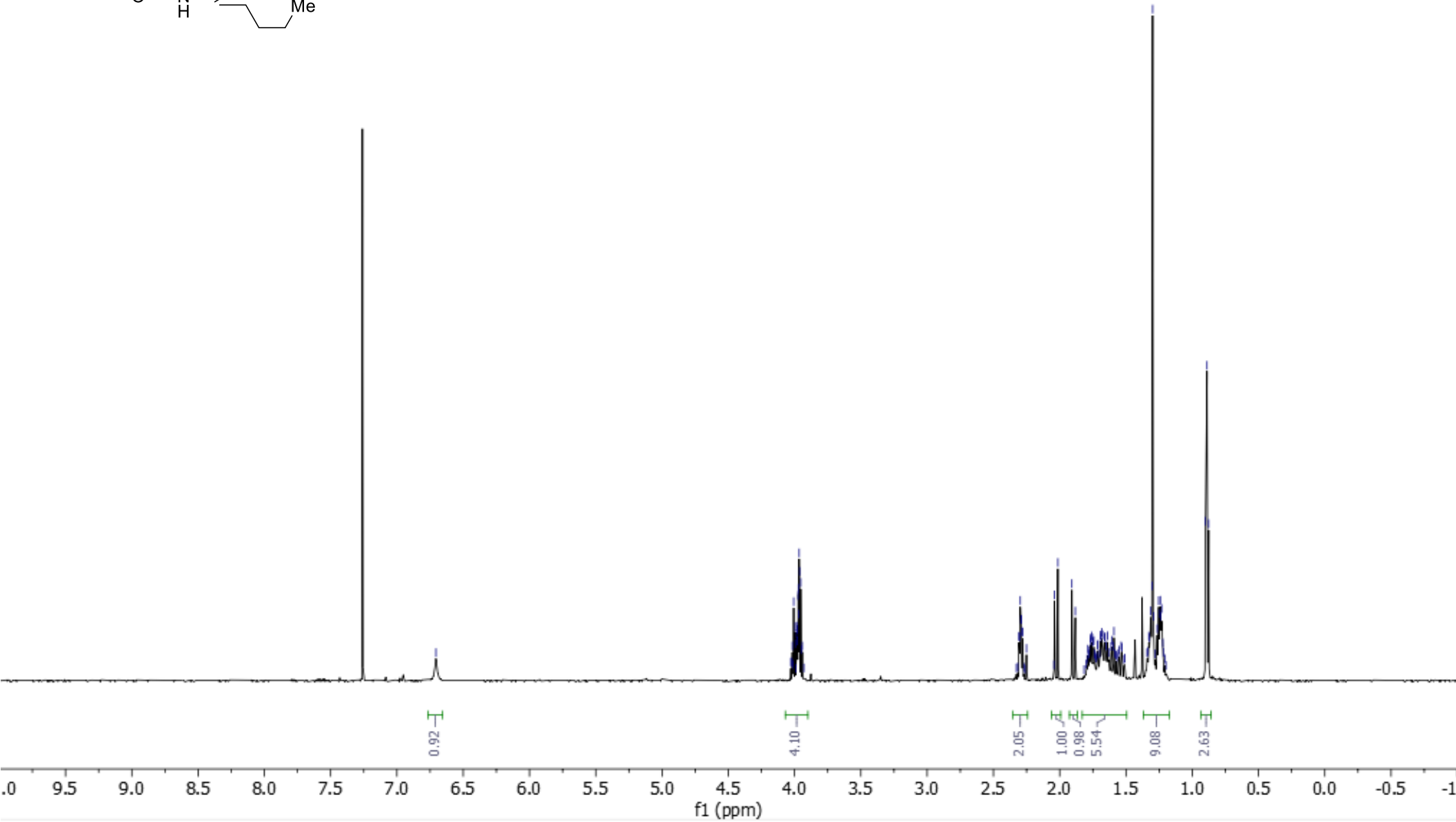
^{1}H NMR (500 MHz, $CDCl_3$)

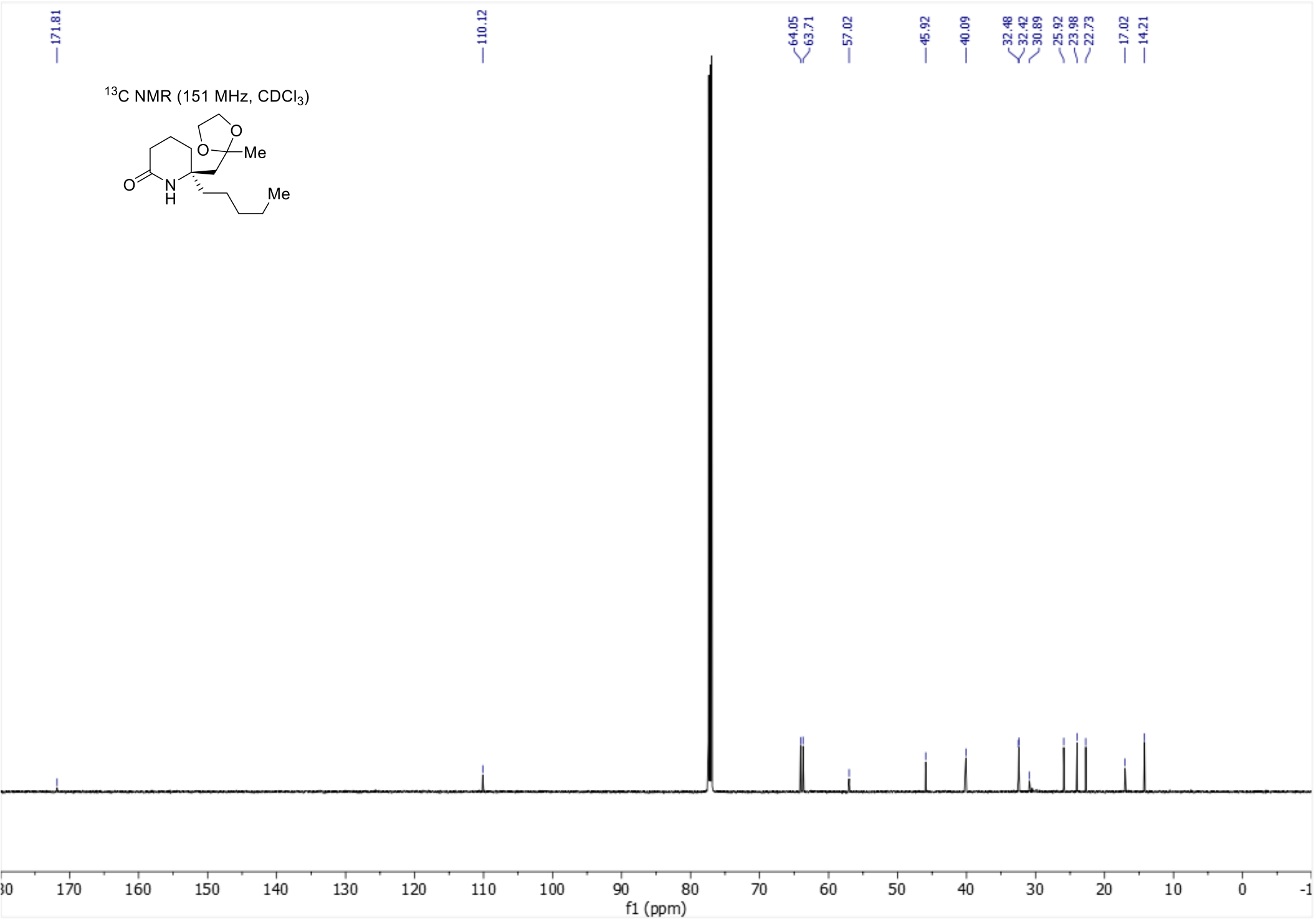



174.29
110.41
64.19
56.87
51.61
41.34
34.47
34.10
32.34
32.14
28.64
28.53
25.66
23.28
22.80
19.40
18.96
14.22
^{13}C NMR (151 MHz, $CDCl_3$)
Me
Me
Me
O
O
NH
O
O
Me
O
Me
Me
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

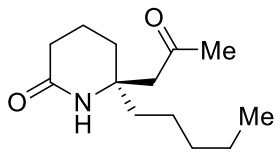
^{1}H NMR (600 MHz, $CDCl_3$)



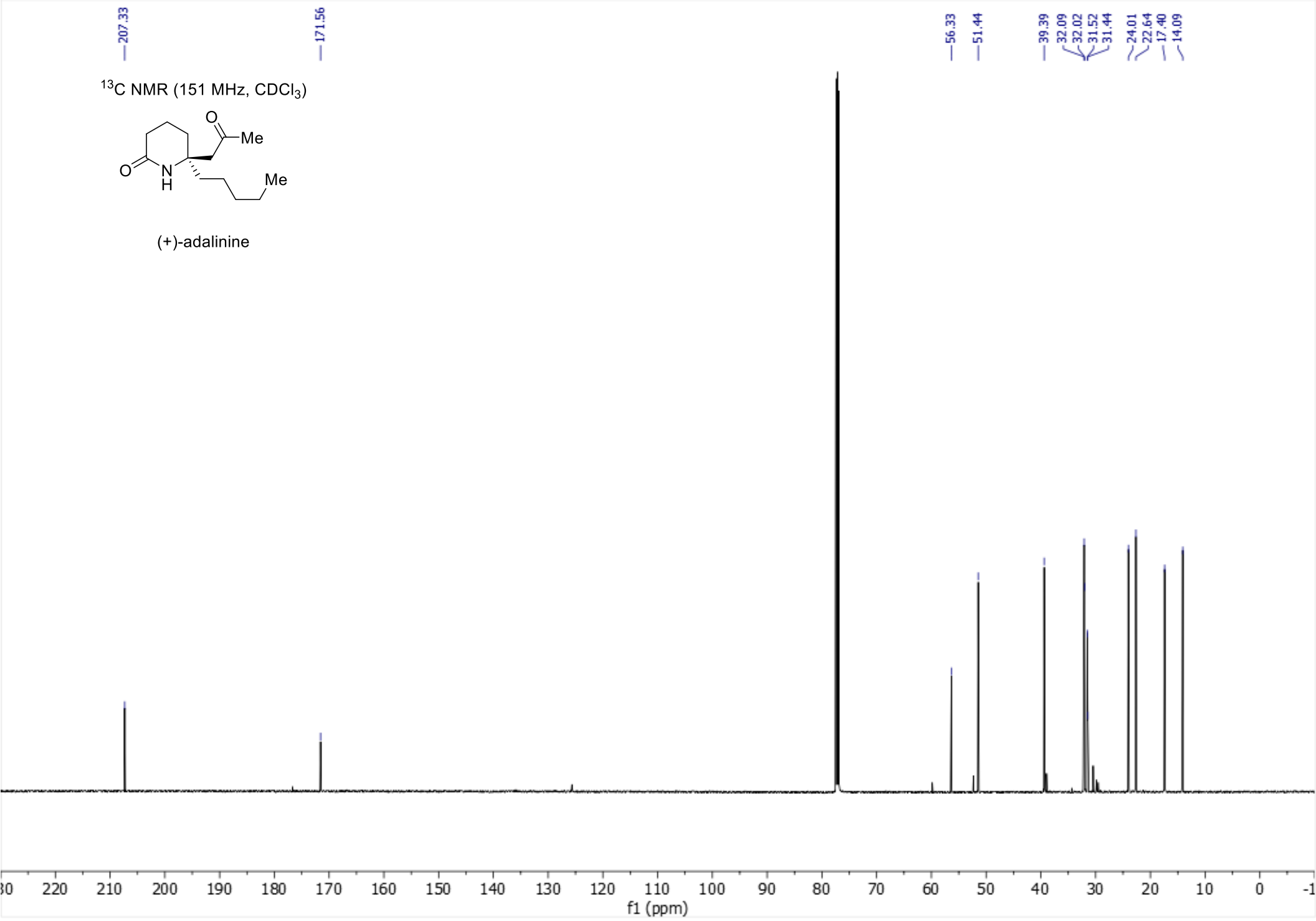



171.81
110.12
64.05
63.71
57.02
45.92
40.09
32.48
32.42
30.89
25.92
23.98
22.73
17.02
14.21
13C NMR (151 MHz, CDCl3)
O
O
Me
O
N
H
Me
f1 (ppm)

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

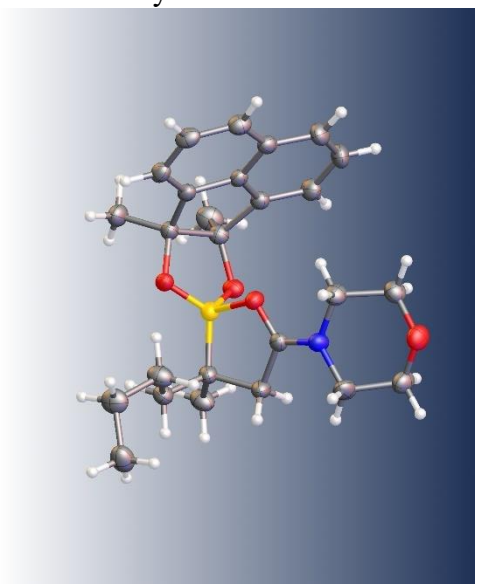


(+)-adalinine


207.33
171.56
56.33
51.44
39.39
32.09
32.02
31.52
31.44
24.01
22.64
17.40
14.09
13C NMR (151 MHz, CDCl3)
O
Me
O
N
H
Me
(+)-adalinine
f1 (ppm)

2.4.9 Crystal Structure Data

Table 1. Crystal data and structure refinement for C26H34BNO4 (**2.76**).



Identification code	C26H34BNO4
Empirical formula	C26 H34 B N O4
Formula weight	435.35
Temperature	173(2) K
Wavelength	1.54178 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 9.4672(7) Å α= 90°.
	b = 13.2370(9) Å β= 90°.
	c = 18.5559(13) Å γ = 90°.
Volume	2325.4(3) $Å^3$
Z	4
Density (Calc'd)	1.244 Mg/m^3
Absorption coefficient	0.652 mm^{-1}
F(000)	936
Crystal size	0.360 x 0.180 x 0.120 mm^3
Theta range for data collection	4.102 to 66.465°.
Index ranges	-11<=h<=11, -15<=k<=15, -22<=l<=21
Reflections collected	55923
Independent reflections	4073 [R(int) = 0.0394]
Completeness to theta = 66.465°	99.3 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7528 and 0.6825
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4073 / 0 / 289
Goodness-of-fit on F^2	1.054

Final R indices [I>2sigma(I)] R1 = 0.0292, wR2 = 0.0756
R indices (all data) R1 = 0.0315, wR2 = 0.0790
Absolute structure parameter -0.01(4)
Extinction coefficient n/a
Largest diff. peak and hole 0.120 and -0.166 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for C26H34BNO4. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	4071(1)	5266(1)	6404(1)	29(1)
O(2)	1140(2)	3000(1)	4972(1)	41(1)
O(3)	5458(1)	6614(1)	7048(1)	28(1)
O(4)	5864(1)	4949(1)	7358(1)	30(1)
N(1)	3227(2)	4341(1)	5486(1)	32(1)
B(1)	5660(2)	5628(2)	6768(1)	27(1)
C(1)	6506(3)	7693(2)	4173(1)	48(1)
C(2)	5878(3)	7935(2)	4904(1)	46(1)
C(3)	5519(2)	6995(2)	5353(1)	40(1)
C(4)	6824(2)	6449(1)	5621(1)	32(1)
C(5)	6625(2)	5471(1)	6058(1)	28(1)
C(6)	5808(2)	4689(2)	5606(1)	35(1)
C(7)	4287(2)	4778(1)	5832(1)	28(1)
C(8)	1776(2)	4411(2)	5747(1)	36(1)
C(9)	1078(2)	3383(2)	5689(1)	35(1)
C(10)	2570(2)	2878(2)	4760(1)	40(1)
C(11)	3361(2)	3865(2)	4773(1)	39(1)
C(12)	8100(2)	5070(2)	6245(1)	40(1)
C(13)	5183(2)	5370(1)	7975(1)	28(1)
C(14)	3677(2)	4974(1)	8055(1)	26(1)
C(15)	3176(2)	4025(1)	8202(1)	33(1)
C(16)	1695(2)	3885(2)	8237(1)	39(1)
C(17)	744(2)	4655(2)	8130(1)	36(1)
C(18)	1239(2)	5645(1)	7981(1)	29(1)
C(19)	425(2)	6530(2)	7876(1)	34(1)
C(20)	1084(2)	7443(2)	7753(1)	35(1)
C(21)	2569(2)	7539(1)	7708(1)	31(1)
C(22)	3380(2)	6692(1)	7803(1)	25(1)
C(23)	2715(2)	5767(1)	7948(1)	25(1)
C(24)	4965(2)	6537(1)	7776(1)	27(1)
C(25)	6070(2)	5149(2)	8637(1)	42(1)
C(26)	5764(2)	7299(2)	8230(1)	38(1)

Table 3. Bond lengths [Å] and angles [°] for C26H34BNO4.

O(1)-C(7)	1.260(2)
O(1)-B(1)	1.717(2)
O(2)-C(10)	1.419(3)
O(2)-C(9)	1.425(3)
O(3)-B(1)	1.419(2)
O(3)-C(24)	1.432(2)
O(4)-C(13)	1.427(2)
O(4)-B(1)	1.430(3)
N(1)-C(7)	1.324(3)
N(1)-C(8)	1.461(3)
N(1)-C(11)	1.470(3)
B(1)-C(5)	1.616(3)
C(1)-C(2)	1.516(3)
C(1)-H(1A)	0.9800
C(1)-H(1B)	0.9800
C(1)-H(1C)	0.9800
C(2)-C(3)	1.535(3)
C(2)-H(2A)	0.9900
C(2)-H(2B)	0.9900
C(3)-C(4)	1.515(3)
C(3)-H(3A)	0.9900
C(3)-H(3B)	0.9900
C(4)-C(5)	1.538(3)
C(4)-H(4A)	0.9900
C(4)-H(4B)	0.9900
C(5)-C(12)	1.533(3)
C(5)-C(6)	1.541(3)
C(6)-C(7)	1.505(3)
C(6)-H(6A)	0.9900
C(6)-H(6B)	0.9900
C(8)-C(9)	1.516(3)
C(8)-H(8A)	0.9900
C(8)-H(8B)	0.9900
C(9)-H(9A)	0.9900
C(9)-H(9B)	0.9900
C(10)-C(11)	1.506(3)
C(10)-H(10A)	0.9900
C(10)-H(10B)	0.9900
C(11)-H(11A)	0.9900
C(11)-H(11B)	0.9900
C(12)-H(12A)	0.9800
C(12)-H(12B)	0.9800
C(12)-H(12C)	0.9800
C(13)-C(25)	1.516(3)

C(13)-C(14)	1.527(3)
C(13)-C(24)	1.602(3)
C(14)-C(15)	1.370(3)
C(14)-C(23)	1.404(3)
C(15)-C(16)	1.416(3)
C(15)-H(15A)	0.9500
C(16)-C(17)	1.374(3)
C(16)-H(16A)	0.9500
C(17)-C(18)	1.419(3)
C(17)-H(17A)	0.9500
C(18)-C(23)	1.408(3)
C(18)-C(19)	1.416(3)
C(19)-C(20)	1.379(3)
C(19)-H(19A)	0.9500
C(20)-C(21)	1.414(3)
C(20)-H(20A)	0.9500
C(21)-C(22)	1.370(3)
C(21)-H(21A)	0.9500
C(22)-C(23)	1.403(2)
C(22)-C(24)	1.516(3)
C(24)-C(26)	1.517(3)
C(25)-H(25A)	0.9800
C(25)-H(25B)	0.9800
C(25)-H(25C)	0.9800
C(26)-H(26A)	0.9800
C(26)-H(26B)	0.9800
C(26)-H(26C)	0.9800

C(7)-O(1)-B(1)	109.38(13)
C(10)-O(2)-C(9)	109.79(15)
B(1)-O(3)-C(24)	108.90(13)
C(13)-O(4)-B(1)	107.95(14)
C(7)-N(1)-C(8)	121.59(16)
C(7)-N(1)-C(11)	123.95(17)
C(8)-N(1)-C(11)	114.02(16)
O(3)-B(1)-O(4)	108.41(16)
O(3)-B(1)-C(5)	119.55(15)
O(4)-B(1)-C(5)	117.84(15)
O(3)-B(1)-O(1)	106.43(14)
O(4)-B(1)-O(1)	104.11(14)
C(5)-B(1)-O(1)	98.03(13)
C(2)-C(1)-H(1A)	109.5
C(2)-C(1)-H(1B)	109.5
H(1A)-C(1)-H(1B)	109.5
C(2)-C(1)-H(1C)	109.5
H(1A)-C(1)-H(1C)	109.5

H(1B)-C(1)-H(1C)	109.5
C(1)-C(2)-C(3)	113.6(2)
C(1)-C(2)-H(2A)	108.8
C(3)-C(2)-H(2A)	108.8
C(1)-C(2)-H(2B)	108.8
C(3)-C(2)-H(2B)	108.8
H(2A)-C(2)-H(2B)	107.7
C(4)-C(3)-C(2)	112.62(18)
C(4)-C(3)-H(3A)	109.1
C(2)-C(3)-H(3A)	109.1
C(4)-C(3)-H(3B)	109.1
C(2)-C(3)-H(3B)	109.1
H(3A)-C(3)-H(3B)	107.8
C(3)-C(4)-C(5)	118.34(17)
C(3)-C(4)-H(4A)	107.7
C(5)-C(4)-H(4A)	107.7
C(3)-C(4)-H(4B)	107.7
C(5)-C(4)-H(4B)	107.7
H(4A)-C(4)-H(4B)	107.1
C(12)-C(5)-C(4)	107.37(16)
C(12)-C(5)-C(6)	110.32(16)
C(4)-C(5)-C(6)	109.82(17)
C(12)-C(5)-B(1)	112.04(16)
C(4)-C(5)-B(1)	113.00(15)
C(6)-C(5)-B(1)	104.29(14)
C(7)-C(6)-C(5)	106.00(15)
C(7)-C(6)-H(6A)	110.5
C(5)-C(6)-H(6A)	110.5
C(7)-C(6)-H(6B)	110.5
C(5)-C(6)-H(6B)	110.5
H(6A)-C(6)-H(6B)	108.7
O(1)-C(7)-N(1)	120.68(17)
O(1)-C(7)-C(6)	115.50(16)
N(1)-C(7)-C(6)	123.74(16)
N(1)-C(8)-C(9)	109.23(16)
N(1)-C(8)-H(8A)	109.8
C(9)-C(8)-H(8A)	109.8
N(1)-C(8)-H(8B)	109.8
C(9)-C(8)-H(8B)	109.8
H(8A)-C(8)-H(8B)	108.3
O(2)-C(9)-C(8)	111.59(17)
O(2)-C(9)-H(9A)	109.3
C(8)-C(9)-H(9A)	109.3
O(2)-C(9)-H(9B)	109.3
C(8)-C(9)-H(9B)	109.3
H(9A)-C(9)-H(9B)	108.0

O(2)-C(10)-C(11) 111.79(18)
O(2)-C(10)-H(10A) 109.3
C(11)-C(10)-H(10A) 109.3
O(2)-C(10)-H(10B) 109.3
C(11)-C(10)-H(10B) 109.3
H(10A)-C(10)-H(10B) 107.9
N(1)-C(11)-C(10) 110.07(17)
N(1)-C(11)-H(11A) 109.6
C(10)-C(11)-H(11A) 109.6
N(1)-C(11)-H(11B) 109.6
C(10)-C(11)-H(11B) 109.6
H(11A)-C(11)-H(11B) 108.2
C(5)-C(12)-H(12A) 109.5
C(5)-C(12)-H(12B) 109.5
H(12A)-C(12)-H(12B) 109.5
C(5)-C(12)-H(12C) 109.5
H(12A)-C(12)-H(12C) 109.5
H(12B)-C(12)-H(12C) 109.5
O(4)-C(13)-C(25) 108.96(16)
O(4)-C(13)-C(14) 111.45(15)
C(25)-C(13)-C(14) 111.81(16)
O(4)-C(13)-C(24) 104.46(14)
C(25)-C(13)-C(24) 116.38(16)
C(14)-C(13)-C(24) 103.50(14)
C(15)-C(14)-C(23) 119.32(17)
C(15)-C(14)-C(13) 131.13(17)
C(23)-C(14)-C(13) 109.55(15)
C(14)-C(15)-C(16) 118.13(18)
C(14)-C(15)-H(15A) 120.9
C(16)-C(15)-H(15A) 120.9
C(17)-C(16)-C(15) 123.06(19)
C(17)-C(16)-H(16A) 118.5
C(15)-C(16)-H(16A) 118.5
C(16)-C(17)-C(18) 119.78(18)
C(16)-C(17)-H(17A) 120.1
C(18)-C(17)-H(17A) 120.1
C(23)-C(18)-C(19) 116.06(17)
C(23)-C(18)-C(17) 116.24(17)
C(19)-C(18)-C(17) 127.68(18)
C(20)-C(19)-C(18) 120.10(18)
C(20)-C(19)-H(19A) 119.9
C(18)-C(19)-H(19A) 119.9
C(19)-C(20)-C(21) 122.61(18)
C(19)-C(20)-H(20A) 118.7
C(21)-C(20)-H(20A) 118.7
C(22)-C(21)-C(20) 118.41(17)

C(22)-C(21)-H(21A)	120.8
C(20)-C(21)-H(21A)	120.8
C(21)-C(22)-C(23)	119.18(17)
C(21)-C(22)-C(24)	131.42(17)
C(23)-C(22)-C(24)	109.39(15)
C(14)-C(23)-C(22)	112.92(16)
C(14)-C(23)-C(18)	123.47(17)
C(22)-C(23)-C(18)	123.60(17)
O(3)-C(24)-C(22)	110.16(15)
O(3)-C(24)-C(26)	108.31(15)
C(22)-C(24)-C(26)	112.61(16)
O(3)-C(24)-C(13)	104.16(14)
C(22)-C(24)-C(13)	104.52(14)
C(26)-C(24)-C(13)	116.68(16)
C(13)-C(25)-H(25A)	109.5
C(13)-C(25)-H(25B)	109.5
H(25A)-C(25)-H(25B)	109.5
C(13)-C(25)-H(25C)	109.5
H(25A)-C(25)-H(25C)	109.5
H(25B)-C(25)-H(25C)	109.5
C(24)-C(26)-H(26A)	109.5
C(24)-C(26)-H(26B)	109.5
H(26A)-C(26)-H(26B)	109.5
C(24)-C(26)-H(26C)	109.5
H(26A)-C(26)-H(26C)	109.5
H(26B)-C(26)-H(26C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for C26H34BNO4. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	28(1)	28(1)	30(1)	-7(1)	4(1)	-1(1)
O(2)	34(1)	42(1)	45(1)	-8(1)	-7(1)	-3(1)
O(3)	34(1)	24(1)	26(1)	-1(1)	5(1)	-3(1)
O(4)	30(1)	27(1)	33(1)	2(1)	6(1)	4(1)
N(1)	32(1)	37(1)	28(1)	-6(1)	4(1)	-5(1)
B(1)	25(1)	24(1)	32(1)	-2(1)	2(1)	-1(1)
C(1)	56(2)	50(1)	38(1)	6(1)	-2(1)	-13(1)
C(2)	50(1)	44(1)	43(1)	9(1)	1(1)	7(1)
C(3)	35(1)	46(1)	40(1)	7(1)	5(1)	6(1)
C(4)	30(1)	31(1)	34(1)	-1(1)	4(1)	-2(1)
C(5)	27(1)	25(1)	33(1)	-3(1)	6(1)	-1(1)
C(6)	33(1)	32(1)	39(1)	-9(1)	10(1)	-4(1)
C(7)	32(1)	25(1)	27(1)	-1(1)	4(1)	-3(1)
C(8)	29(1)	38(1)	40(1)	-5(1)	1(1)	1(1)
C(9)	30(1)	37(1)	39(1)	1(1)	0(1)	-2(1)
C(10)	38(1)	43(1)	38(1)	-12(1)	-1(1)	-4(1)
C(11)	45(1)	48(1)	25(1)	-9(1)	3(1)	-9(1)
C(12)	31(1)	38(1)	49(1)	7(1)	7(1)	5(1)
C(13)	27(1)	29(1)	29(1)	1(1)	0(1)	2(1)
C(14)	30(1)	26(1)	23(1)	-1(1)	2(1)	0(1)
C(15)	37(1)	26(1)	36(1)	3(1)	2(1)	2(1)
C(16)	43(1)	27(1)	46(1)	0(1)	4(1)	-9(1)
C(17)	31(1)	36(1)	41(1)	-3(1)	1(1)	-8(1)
C(18)	29(1)	32(1)	25(1)	-5(1)	1(1)	-2(1)
C(19)	30(1)	38(1)	33(1)	-3(1)	-2(1)	6(1)
C(20)	40(1)	34(1)	31(1)	0(1)	0(1)	13(1)
C(21)	41(1)	24(1)	29(1)	-1(1)	2(1)	2(1)
C(22)	31(1)	24(1)	21(1)	-2(1)	2(1)	0(1)
C(23)	31(1)	24(1)	20(1)	-3(1)	1(1)	-1(1)
C(24)	31(1)	25(1)	26(1)	-2(1)	2(1)	-4(1)
C(25)	38(1)	53(1)	37(1)	8(1)	-6(1)	3(1)
C(26)	38(1)	39(1)	35(1)	-9(1)	0(1)	-8(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for C26H34BNO4.

	x	y	z	U(eq)
H(1A)	6710	8323	3916	73
H(1B)	7383	7309	4236	73
H(1C)	5832	7290	3893	73
H(2A)	5008	8337	4835	55
H(2B)	6556	8356	5178	55
H(3A)	4937	7199	5771	48
H(3B)	4951	6525	5055	48
H(4A)	7368	6927	5923	38
H(4B)	7416	6285	5197	38
H(6A)	5911	4837	5085	42
H(6B)	6168	4000	5700	42
H(8A)	1245	4910	5457	43
H(8B)	1772	4639	6255	43
H(9A)	1557	2905	6019	43
H(9B)	79	3438	5841	43
H(10A)	2603	2592	4267	47
H(10B)	3038	2393	5089	47
H(11A)	4371	3744	4664	47
H(11B)	2976	4322	4399	47
H(12A)	8010	4445	6524	59
H(12B)	8622	4933	5799	59
H(12C)	8609	5576	6530	59
H(15A)	3805	3476	8279	40
H(16A)	1342	3229	8340	46
H(17A)	-242	4525	8157	43
H(19A)	-577	6495	7891	40
H(20A)	518	8030	7697	42
H(21A)	2993	8175	7613	38
H(25A)	5610	5436	9063	64
H(25B)	6166	4417	8696	64
H(25C)	7008	5452	8578	64
H(26A)	5440	7257	8731	56
H(26B)	6777	7152	8209	56
H(26C)	5590	7981	8044	56

Table 6. Torsion angles [°] for C26H34BNO4.

C(24)-O(3)-B(1)-O(4)	-23.2(2)
C(24)-O(3)-B(1)-C(5)	-162.14(16)
C(24)-O(3)-B(1)-O(1)	88.31(16)
C(13)-O(4)-B(1)-O(3)	25.90(19)
C(13)-O(4)-B(1)-C(5)	165.69(16)
C(13)-O(4)-B(1)-O(1)	-87.11(15)
C(7)-O(1)-B(1)-O(3)	141.66(15)
C(7)-O(1)-B(1)-O(4)	-103.92(16)
C(7)-O(1)-B(1)-C(5)	17.54(17)
C(1)-C(2)-C(3)-C(4)	70.6(3)
C(2)-C(3)-C(4)-C(5)	-178.03(18)
C(3)-C(4)-C(5)-C(12)	178.82(18)
C(3)-C(4)-C(5)-C(6)	58.8(2)
C(3)-C(4)-C(5)-B(1)	-57.1(2)
O(3)-B(1)-C(5)-C(12)	102.4(2)
O(4)-B(1)-C(5)-C(12)	-32.8(2)
O(1)-B(1)-C(5)-C(12)	-143.48(14)
O(3)-B(1)-C(5)-C(4)	-19.0(2)
O(4)-B(1)-C(5)-C(4)	-154.27(17)
O(1)-B(1)-C(5)-C(4)	95.07(16)
O(3)-B(1)-C(5)-C(6)	-138.26(18)
O(4)-B(1)-C(5)-C(6)	86.5(2)
O(1)-B(1)-C(5)-C(6)	-24.16(17)
C(12)-C(5)-C(6)-C(7)	145.12(17)
C(4)-C(5)-C(6)-C(7)	-96.73(18)
B(1)-C(5)-C(6)-C(7)	24.6(2)
B(1)-O(1)-C(7)-N(1)	174.03(16)
B(1)-O(1)-C(7)-C(6)	-3.0(2)
C(8)-N(1)-C(7)-O(1)	0.4(3)
C(11)-N(1)-C(7)-O(1)	172.28(18)
C(8)-N(1)-C(7)-C(6)	177.09(19)
C(11)-N(1)-C(7)-C(6)	-11.0(3)
C(5)-C(6)-C(7)-O(1)	-14.1(2)
C(5)-C(6)-C(7)-N(1)	169.02(18)
C(7)-N(1)-C(8)-C(9)	-136.51(19)
C(11)-N(1)-C(8)-C(9)	50.8(2)
C(10)-O(2)-C(9)-C(8)	61.5(2)
N(1)-C(8)-C(9)-O(2)	-55.9(2)
C(9)-O(2)-C(10)-C(11)	-60.6(2)
C(7)-N(1)-C(11)-C(10)	137.2(2)
C(8)-N(1)-C(11)-C(10)	-50.4(2)
O(2)-C(10)-C(11)-N(1)	54.4(2)
B(1)-O(4)-C(13)-C(25)	-142.76(16)
B(1)-O(4)-C(13)-C(14)	93.37(17)

B(1)-O(4)-C(13)-C(24)	-17.75(18)
O(4)-C(13)-C(14)-C(15)	66.2(3)
C(25)-C(13)-C(14)-C(15)	-56.0(3)
C(24)-C(13)-C(14)-C(15)	177.98(19)
O(4)-C(13)-C(14)-C(23)	-113.39(16)
C(25)-C(13)-C(14)-C(23)	124.37(17)
C(24)-C(13)-C(14)-C(23)	-1.66(19)
C(23)-C(14)-C(15)-C(16)	0.2(3)
C(13)-C(14)-C(15)-C(16)	-179.39(19)
C(14)-C(15)-C(16)-C(17)	0.0(3)
C(15)-C(16)-C(17)-C(18)	-0.3(3)
C(16)-C(17)-C(18)-C(23)	0.4(3)
C(16)-C(17)-C(18)-C(19)	-178.1(2)
C(23)-C(18)-C(19)-C(20)	-0.1(3)
C(17)-C(18)-C(19)-C(20)	178.27(19)
C(18)-C(19)-C(20)-C(21)	1.5(3)
C(19)-C(20)-C(21)-C(22)	-1.2(3)
C(20)-C(21)-C(22)-C(23)	-0.5(3)
C(20)-C(21)-C(22)-C(24)	178.75(18)
C(15)-C(14)-C(23)-C(22)	179.91(17)
C(13)-C(14)-C(23)-C(22)	-0.4(2)
C(15)-C(14)-C(23)-C(18)	-0.2(3)
C(13)-C(14)-C(23)-C(18)	179.50(17)
C(21)-C(22)-C(23)-C(14)	-178.12(16)
C(24)-C(22)-C(23)-C(14)	2.5(2)
C(21)-C(22)-C(23)-C(18)	2.0(3)
C(24)-C(22)-C(23)-C(18)	-177.45(16)
C(19)-C(18)-C(23)-C(14)	178.49(16)
C(17)-C(18)-C(23)-C(14)	-0.1(3)
C(19)-C(18)-C(23)-C(22)	-1.6(3)
C(17)-C(18)-C(23)-C(22)	179.79(17)
B(1)-O(3)-C(24)-C(22)	-100.31(17)
B(1)-O(3)-C(24)-C(26)	136.12(17)
B(1)-O(3)-C(24)-C(13)	11.28(19)
C(21)-C(22)-C(24)-O(3)	-71.3(2)
C(23)-C(22)-C(24)-O(3)	108.05(16)
C(21)-C(22)-C(24)-C(26)	49.7(3)
C(23)-C(22)-C(24)-C(26)	-130.93(17)
C(21)-C(22)-C(24)-C(13)	177.36(19)
C(23)-C(22)-C(24)-C(13)	-3.31(19)
O(4)-C(13)-C(24)-O(3)	4.07(18)
C(25)-C(13)-C(24)-O(3)	124.23(17)
C(14)-C(13)-C(24)-O(3)	-112.70(15)
O(4)-C(13)-C(24)-C(22)	119.69(15)
C(25)-C(13)-C(24)-C(22)	-120.15(18)
C(14)-C(13)-C(24)-C(22)	2.92(18)

O(4)-C(13)-C(24)-C(26)	-115.24(17)
C(25)-C(13)-C(24)-C(26)	4.9(3)
C(14)-C(13)-C(24)-C(26)	128.00(17)

Symmetry transformations used to generate equivalent atoms:

Chapter 3

Enantioselective Palladium-Catalyzed Conjunctive Cross-Coupling with a PHOX Palladium Ligand

3.1 Background

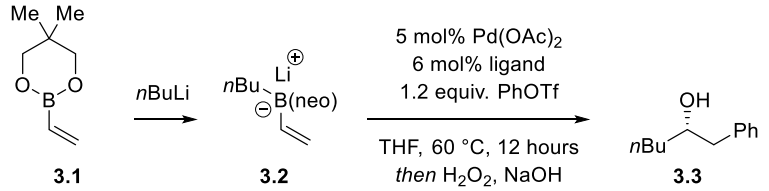
3.1.1 Ligands Used in Palladium-Mediated 1,2-Metallate Shifts

So far, MandyPhos (**3.18**), has been the optimal ligand in every palladium-catalyzed asymmetric conjunctive cross-coupling reaction. The expansion of substrate scope has been largely accomplished by the logical implementation of additives. We considered examining other ligand classes in order to address synthetic challenges within conjunctive cross-coupling.

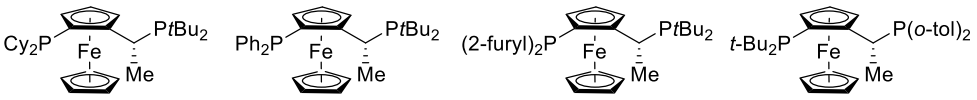
In 2016, a ligand screening determined the best ligand class for palladium-catalyzed conjunctive cross-coupling.[142] As seen in Table 3.1.1.1, many chiral bisphosphines did not enable efficient conversion or high enantioselectivity. The ligand class JosiPhos (**3.4-3.7**) only furnished moderate levels of conversion or enantioselectivity. However, despite testing numerous JosiPhos derivatives, none were able to garner satisfactory results. Only a few derivatives of MandyPhos (**3.18**, **3.21-3.25**) enabled the desired high level of conversion and enantioselectivity. Interestingly, high levels of conversion and enantioselectivity were observed using neopentyl glycol derived boron "ate" complexes. Whereas, the products of pinacol derived boron "ate" complexes exhibited lower levels of conversion and enantioselectivity when using any derivative of MandyPhos (Table 3.1.1.2).

[142] (a) Zhang, L.; Lovinger, G. J.; Edelstein, E. K.; Szymaniak, A. A.; Chierchia, M. P.; Morken, J. P. *Science* **2016**, *351*, 70-74 (b) Zhang, L 2017, *Catalytic Conjunctive Cross-Coupling and Catalytic Diboration Reactions*, Boston College, Chestnut Hill

Table 3.1.1.1: *Ligand Survey of Palladium-Catalyzed Conjunctive Cross-Coupling*



3.1 **3.2** **3.3**

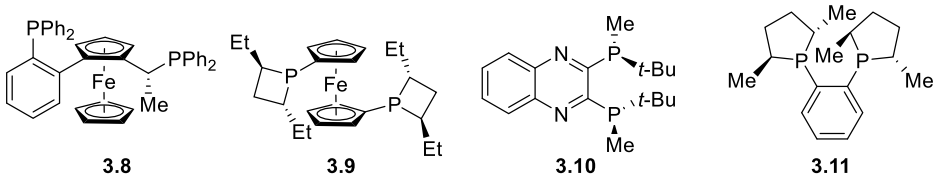


3.4 39%, 18:82 er

3.5 24%, 34:66 er

3.6 39%, 65:35 er

3.7 84%, 47:53 er

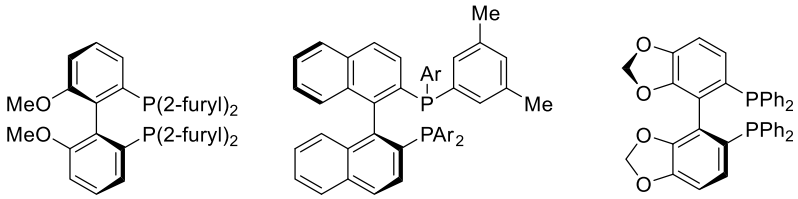


3.8 <5%, N.D. er

3.9 15%, 49:51 er

3.10 <5%, N.D. er

3.11 <5%, N.D. er



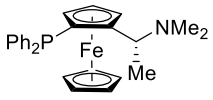
3.12 30%, 72:28 er

3.13 32%, 51:49 er

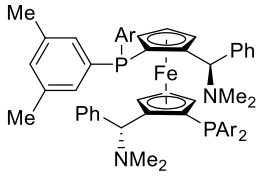
3.14 <5%, N.D. er

Di-PrPF
3.15
19% yield

DCyPF
3.16
31% yield

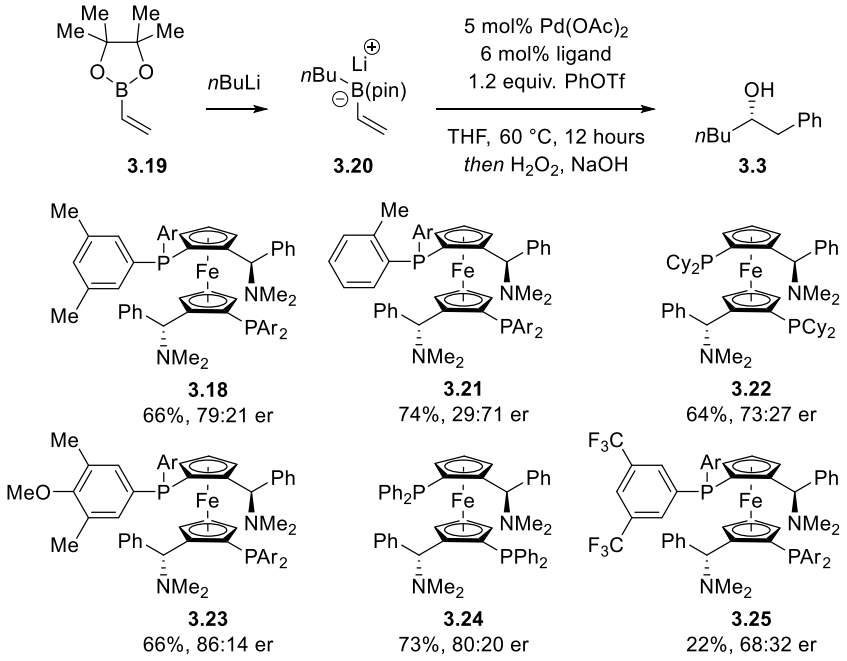


3.17 <5%, N.D. er



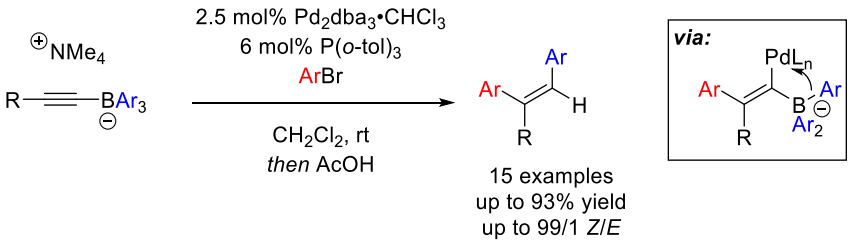
3.18 77%, 96:4 er

Table 3.1.1.2: *MandyPhos Survey Using Pinacol as a Ligand for Boron*



In studying the literature for ligands used in palladium-induced 1,2-metallate shift methods, there have been non-enantioselective reports worth noting. Among the few examples of a palladium-induced metallate shift by an inner-sphere mechanism include a publication in 2007.[143] Murakami and coworkers reported a highly selective *cis*-diarylation of an alkynyl boron "ate" complex via a 1,2-migratory insertion with a subsequent 1,3-metallate shift. In this study, the resulting borane was protodeborylated to generate trisubstituted alkenes in high yield and diastereoselectivity (Scheme 3.1.1.1).

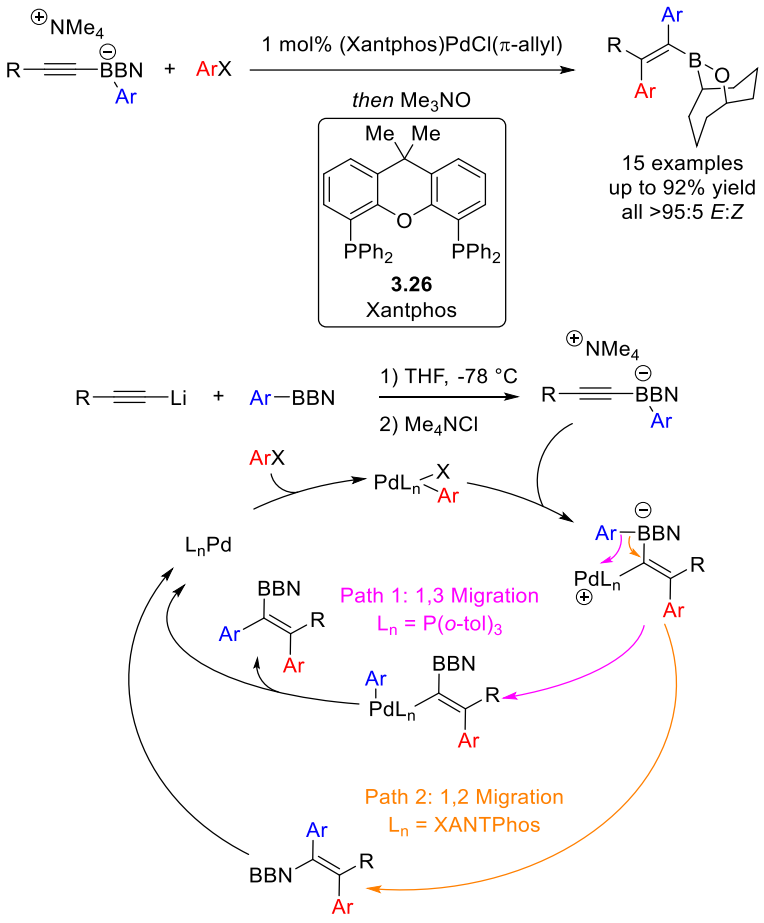
Scheme 3.1.1.1: *Murakami's Palladium-Catalyzed Metal-Induced Metallate Shift of Alkynyl Boron "Ate" Complexes*



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

In 2009, Murakami and coworkers described a stereoselective synthesis of trisubstituted alkenyl borinic esters by cross-coupling 9-BBN alkynyl boron "ate" complexes and aryl halides using a palladium catalyst.[144]

Scheme 3.1.1.2: *Murakami's Palladium-Catalyzed Metallate of Alkynyl Boron "Ate" Complexes*



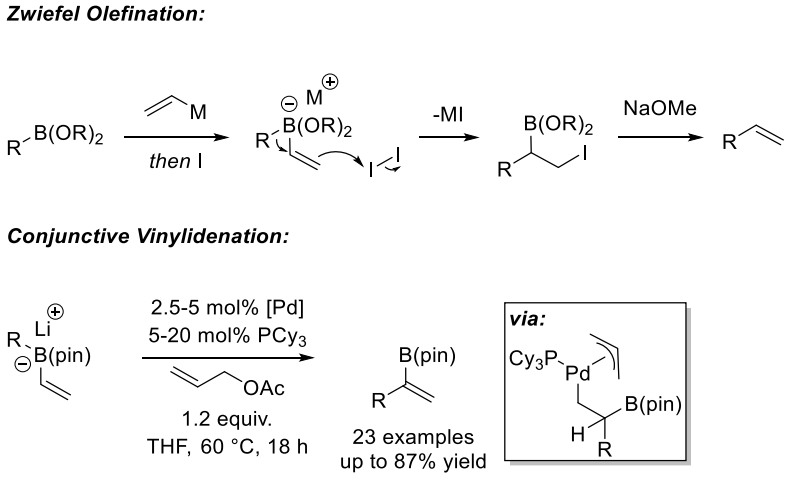
The authors noted an interesting divergence in reactivity depending on the ligand on palladium. In the proposed catalytic cycle, a palladium (0) species underwent oxidative addition with an aryl halide. A 1,2-migratory insertion with the alkyne of the "ate" complex occurred as described in Scheme 3.1.1.2. The reaction diverged depending on the ligated phosphine. If tri(*ortho*-tolyl)phosphine was used, a 1,3-migration was proposed to occur where the aryl migrating group

[144] Ishida, N.; Shimamoto, Y.; Murakami, M. *Org. Lett.* **2009**, *11*, 5434-5437

transmetallated to palladium. A subsequent reductive elimination yielded the *Z*-olefin as the major product (up 97:3 *Z*:*E*). If XantPhos was used, a 1,2-migration was proposed to occur where the aryl migrating group reductively displaced palladium with inversion of stereochemistry of the carbon stereocenter to synthesize the *E*-olefin as the major product (up 99:1 *E*:*Z*).[145]

In 2019, our group reported a vinylidenation of organoboronates facilitated by a palladium-induced 1,2-metallate shift.[146] This process is similar to a Zweifel olefination, where treatment of an olefin-containing boron "ate" complex with iodine promotes a 1,2-metallate shift to form a new carbon-carbon bond and a new carbon-iodine bond;[147] subsequent elimination is enabled under basic conditions to generate the olefin product (Scheme 3.1.1.3). In the catalytic vinylidenation, palladium-induced 1,2-metallate shift with a vinyl-containing boron "ate" complex and subsequent β-hydride elimination furnished the alkenyl boronic ester moiety.

Scheme 3.1.1.3: *Palladium-Catalyzed Conjunctive Vinylidenation Reaction*



[145] For reports a palladium π-allyl species inducting a 1,2-metallate shift by an outer-sphere mechanism: (a) Chan, Y.; Li, N. S.; Deng, M. Z. *Tetrahedron Lett.* **1990**, *31*, 2405-2406 (b) Ishikura, M.; Terashima, M.; Okamura, K.; Date, T. *J. Chem. Soc. Chem. Commun.* **1991**, 1219-1221 (c) Ishikura, M.; Matsuzaki, Y.; Agata, I.; Katagiri, N. *Tetrahedron* **1998**, *54*, 13929-13942 (d) Ishikura, M.; Kato, H. *Tetrahedron* **2002**, *58*, 9827-9838 (e) Panda, S.; Ready, J. M. *J. Am. Chem. Soc.* **2017**, *139*, 6038-6041 (f) Panda, S.; Ready, J. M. *J. Am. Chem. Soc.* **2018**, *140*, 13242-13252

[146] Aparece, M. D.; Gao, C.; Lovinger, G. J.; Morken, J. P. *Angew. Chem. Int. Ed.* **2019**, *58*, 592-595

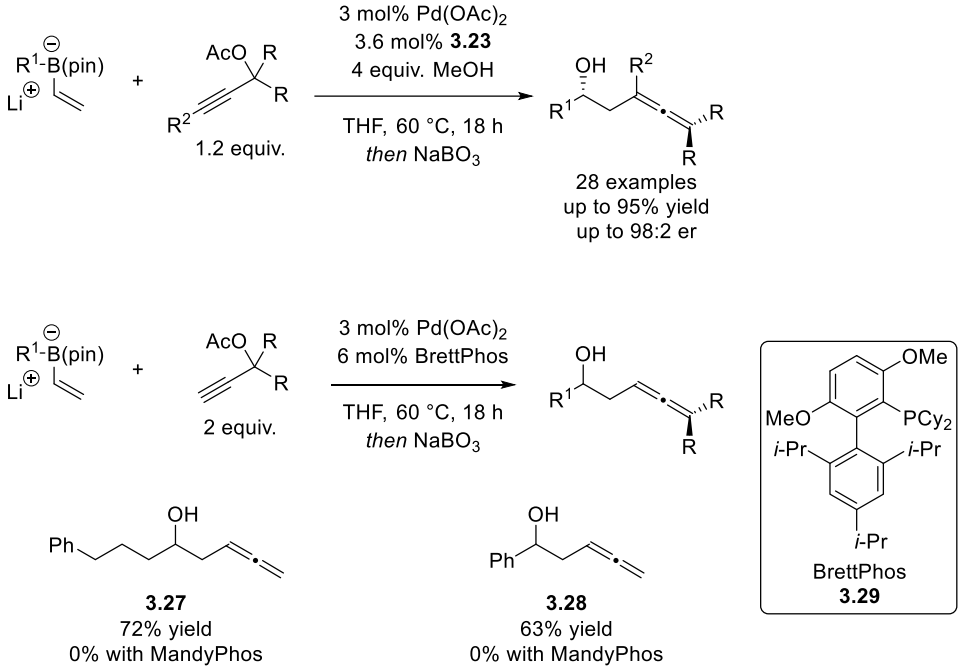
[147] (a) Zweifel, G.; Polston, N. L.; Whitney, C. C. *J. Am. Chem. Soc.* **1968**, *90*, 6243-6245 (b) Armstrong, R. J.; Aggarwal, V. K. *Synthesis* **2017**, *49*, 3323-3336

In this study, MandyPhos (**3.23**) and XantPhos (not shown) were originally chosen as ligands in an attempt to catalyze a conjunctive cross-coupling with allyl electrophiles. This process would enable sp^3-carbon functionalization of the β-carbon of alkenyl boron "ate" complexes. However, minimal desired conjunctive cross-coupling occurred. In contrast, use of a monodentate ligand, tricyclohexyl phosphine, facilitated an efficient inner-sphere palladium-induced 1,2 metallate shift with a palladium π-allyl intermediate (Scheme 3.1.1.3).

In 2019, an enantioselective palladium-catalyzed conjunctive cross-coupling with propargyl carbonates was described.[148] In this method, β-boryl allenes were synthesized from achiral tertiary propargylic carbonates and vinyl-derived boron "ate" complexes. High yields and enantioselectivities were achieved by using an alcohol additive as seen in Scheme 3.1.1.4. However, there were notable challenges described with the electrophile scope. For example, low yields were observed when using terminal and simple aliphatic internal alkynes. Interestingly, R^2 substituents were mostly limited to sp^2-carbons or carbinol substrates. Additionally, it was mandatory that the electrophile was tertiary propargylic, otherwise, decomposition of the "ate" complex was observed with no desired product. Though not reported in the peer-reviewed article, BrettPhos enabled the transformation of some of these challenging electrophiles. High yields were obtained for these racemic products where MandyPhos previously failed.[149]

[148] Aparece, M. D.; Hu, W.; Morken, J. P. *ACS Catal.* **2019**, *9*, 11381-11385
[149] Aparece, M 2020, *Synthesis of Organoboron Compounds via a Palladium-Induced 1,2-Metallate Shift Mechanism*, Boston College, Chestnut Hill

Scheme 3.1.1.4: *Palladium-Catalyzed Conjunctive Cross-Coupling of Propargyl Electrophiles*



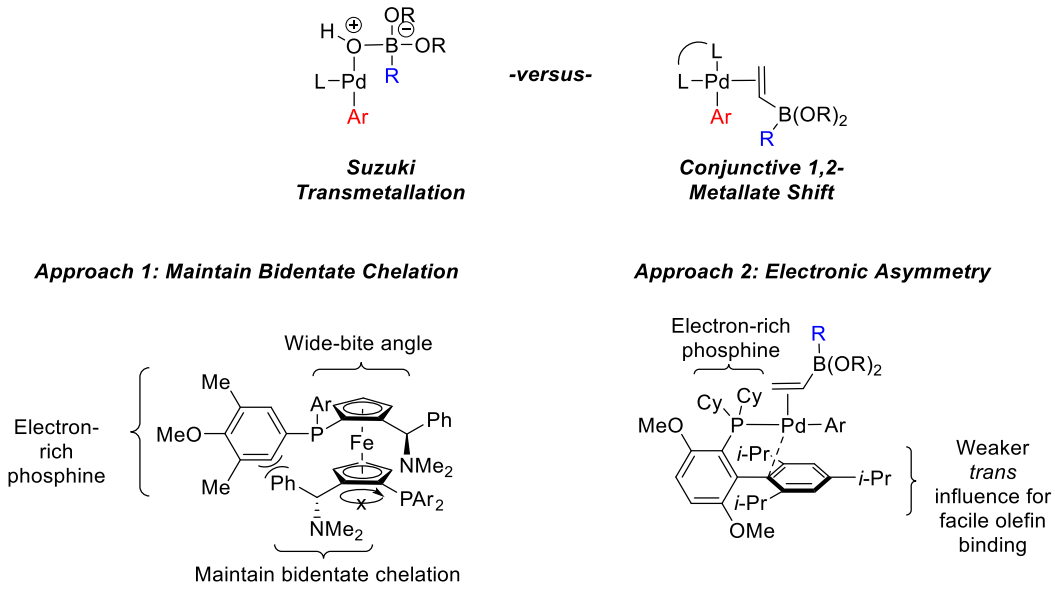
The difficulty associated with synthesizing racemic samples of organoboronate products using conjunctive cross-coupling deserves comment. Ligands usually included DPPF and DPPP. These wide bite angle bisphosphines were used to mimic the hypothetical beneficial properties of MandyPhos, However, due to the poor reactivity rendered with these ligands, increased catalyst loading and reaction scale were necessary in order to isolate a sufficient amount of material for analysis. Unfortunately, in many cases, it was necessary to use mixtures of (R_p,R_p) and (S_p,S_p) MandyPhos to obtain racemic samples. BrettPhos, however, is now often used for efficient racemic cross-coupling reactions. This was an interesting observation considering palladium-alkyls ligated with monodentate ligands have a propensity to undergo β-hydride elimination like in the previously mentioned vinylidenation reaction.

It was hypothesized that wide-bite angle, electron-rich, bisphosphines such as MandyPhos would facilitate palladium-catalyzed conjunctive cross-coupling. An electron donating group would enable more facile oxidative addition, and a wide-bite angle ligand would enable rapid

reductive elimination in order to minimize β-hydride elimination byproducts.[150] Although the precise reason MandyPhos was more able than DPPF to chemoselectively transform a boron "ate" complexes to the desired conjunctive product instead of the Suzuki-Miyaura byproduct is not clear. The mechanism for transmetallation could provide an explanation (Scheme 3.1.1.5): after oxidative addition, in the Suzuki-Miyaura reaction, requires two open coordination sites. One site is for the oxygen atom to bridge palladium and boron, and the second is to form the new carbon palladium bond. This mechanism is operative for three-coordinate boronate transmetallating to a palladium-hydroxyl species, or an oxygen atom of a four-coordinate boron "ate" complex functioning as the bridging oxygen to palladium. Whereas in conjunctive cross-coupling, only a single open coordination is necessary for palladium to bind to the alkene and induce a 1,2-metallate shift. For bisphosphines, dissociation of one of the phosphine from the metal center may to be necessary for productive direct-transmetallation.[151] Perhaps MandyPhos is uniquely suited to maintain bidentate chelation to a palladium center (Figure 3.1.1.1). In addition, a unique structural feature of MandyPhos compared to other previously studied phosphine ligands is the adjacent, appended tertiary amines. Perhaps this functional group minimizes the generation of arm-off intermediates as the torsional rotation of the ferrocenyl backbone would force the benzyl amines to closer proximity to each other. Thus, MandyPhos maybe an exceptionally rigid ligand and any dissociated phosphine intermediates would be relatively high energy.

[150] Van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Reek, J. N. H.; Dierkes, P. *Chem. Rev.* **2000**, *100*, 2741-2769
[151] Tymonko, S. A.; Smith, R. C.; Ambrosi, A.; Ober, M. H.; Wang, H.; Denmark, S. E. *J. Am. Chem. Soc.* **2015**, *137*, 6200-6218

Figure 3.1.1.1: *Possible Requirements for Suzuki Transmetallation and Conjunctive 1,2-Metallate Shift. Possible Ligand Design Approaches for Efficient Conjunctive Cross-Coupling*



In conclusion, though MandyPhos provided excellent reactivity in conjunctive coupling by an asymmetric palladium-induced 1,2 metallate shift, there might be other ligands that can be utilized in conjunctive cross-coupling. Indeed, there are some ligands that enable unique reactivity that MandyPhos cannot provide (i.e., BrettPhos). We considered this an opportunity to discover alternative approaches for effective catalysis and study alternative ligand classes for conjunctive cross-coupling. In this connection, BrettPhos may be an effective ligand in conjunctive cross-coupling because of its pseudo-bidentate nature.[152] The phosphine with the biaryl motif enables the ligand to partially occupy two coordination sites for a palladium (II) intermediate (Figure 3.1.1.1). The weak coordination of the biaryl functionality results in a more electron deficient palladium (II) intermediate, and its weaker *trans*-influence may provide more facile alkene binding.

[152] (a) Ingoglia, B. T.; Wagen, C. C.; Buchwald, S. L. *Tetrahedron.* **2019**, *75*, 4199-4211 (b) Surry, D. S.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 6338-6361 (c) Martin, R.; Buchwald, S. L. *Acc. of Chem. Res.* **2008**, *41*, 1461-1473

3.1.2 Mechanistic Investigations into Palladium-Catalyzed Alkene Functionalizations Using Electronically Asymmetric Ligands

There are numerous palladium-catalyzed alkene functionalizations such as nucleo-palladation[153], Heck reactions[154], polymerization[155], and conjunctive cross-coupling.[156] All share a common metal-olefin complex as a key intermediate in the catalytic cycle. In many of these examples, electronically asymmetric ligands (except for conjunctive cross-coupling) are used for efficient catalysis.

Of the methods for alkene functionalization, asymmetric Heck reactions share many common intermediates and limitations with conjunctive cross-coupling. For example, the catalytic cycle for asymmetric Heck reactions typically started with palladium (0) undergoing oxidative addition with an aryl triflate to generate a cationic palladium (II) intermediate. Like in conjunctive cross-coupling, if the electrophile was not an aryl triflate, additives are required to generate a cationic palladium species.[157] Next, olefin binding occurs and the reaction either proceeds through olefin insertion (Heck) or metallate-shift (conjunctive cross-coupling). Due the to the similarities

[153] For selected examples using electronically asymmetric ligands: (a) White, D. R.; Hutt, J. T.; Wolfe, J. P. *J. Am. Chem. Soc.* **2015**, *137*, 11246-11249 (b) Ross, S. P.; Rahman, A. A.; Sigman, M. S. *J. Am. Chem. Soc.* **2020**, *142*, 10516-10525 (c) Allen, J. R.; Bahamonde, A.; Furukawa, Y.; Sigman, M. S. *J. Am. Chem. Soc.* **2019**, *141*, 8670-8674 (c) Saha, S.; Yadav, S.; Reshi, N. U. D.; Dutta, I.; Kunnikuruvan, S.; Bera, J. K. *ACS Catal*. **2020**, *10*, 11385-11393;

[154] For selected examples using electronically asymmetric ligands: (a) McCartney, D.; Guiry, P. J. *Chem. Soc. Rev.* **2011**, *40*, 5122-5150 (b) Shibasaki, M.; Vogl, E. M.; Ohshima, T. *Adv. Synth. Catal.* **2004**, *346*, 1533-1552 (c) Werner, E. W.; Mei, T. -S.; Burckle, A. J.; Sigman, M. S. *Science* **2012**, *338*, 1455-1458 (d) Zhang, Z. -M.; Xu, B.; Qian, Y.; Wu, L.; Wu, Y.; Zhou, L.; Liu, Y.; Zhang, J. *Angew. Chem. Int. Ed.* **2018**, *57*, 10373-10377 (e) Diéguez, M.; Pàmies, O. *Isr. J. Chem.* **2012**, *52*, 572-581

[155] For selected examples using electronically asymmetric ligands and the references therein: (a) Sediel, F. W.; Tomizawa, I.; Nozaki, K. *Angew. Chem. Int. Ed.* **2020**, *59*, 22591-22601 (b) Nozaki, K. *The Chemical Record* **2005**, *5*, 376-384

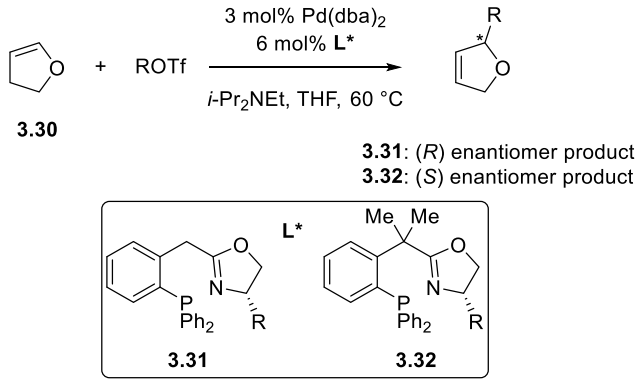
[156] (a) Law, C. Kativhu, E.; Wang, J.; Morken, J. P. *Angew. Chem. Int. Ed.* **2020**, *59*, 10311-10315 (b) Meng, Y.; Kong, Z.; Morken, J. P. *Angew. Chem. Int. Ed.* **2020**, *59*, 8456-8459 (c) Apraece, M. D.; Hu, W.; Morken, J. P. *ACS Catal.* **2019**, *9*, 11381-11385 (d) Myhill, J. A.; Wilhelmsen, C. A.; Zhang, L.; Morken, J. P. *J. Am. Chem. Soc.* **2018**, *140*, 15181-15185 (e) Myhill, J. A.; Zhang, L.; Lovinger, G. J.; Morken, J. P. *Angew. Chem. Int. Ed.* **2018**, *57*, 12799-12803 (f) Edelstein, E. K.; Namirembe, S.; Morken, J. P. *J. Am. Chem. Soc.* **2017**, *139*, 5027-5030 (g) Lovinger, G. J.; Aparece, M. D.; Morken, J. P. *J. Am. Chem. Soc.* **2017**, *139*, 3153-3160 (h) Zhang, L.; Lovinger, G. J.; Edelstein, E. K.; Szymaniak, A. A.; Chierchia, M. P.; Morken, J. P. *Science*, **2016**, *351*, 70-74

[157] (a) A Heck reaction example: Wu, C.; Zhou, J. *J. Am. Chem. Soc.* **2014**, *136*, 650-652 (b) a conjunctive example: Lovinger, G. J.; Aparece, M. D.; Morken, J. P. *J. Am. Chem. Soc*. **2017**, *139*, 3153-3160

between Heck and conjunctive coupling reactions and the abundance of studies on Heck reactions using electronically asymmetric ligands, studying asymmetric Heck reactions and their mechanistic investigations is an ideal starting point to inspire new directions in conjunctive cross-coupling.

In 2008, Wu and coworkers reported an interesting switch in enantioselectivity in an asymmetric Heck reaction when including benzylic substituents on the backbone of a PHOX-like ligand (Scheme 3.1.2.1).[158]

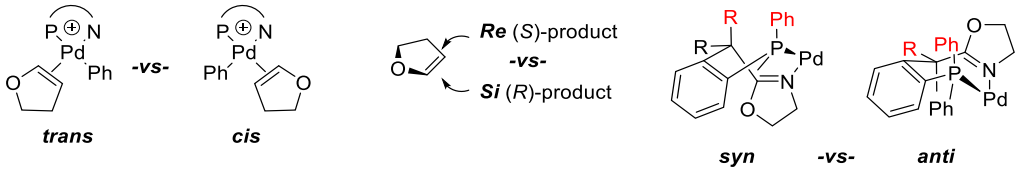
Scheme 3.2.2.1: *Wu's Unexpected Switch in Enantioselectivity in an Asymmetric Heck Reaction*



To address this interesting observation, three different stereochemical elements were investigated (Figure 3.1.2.1). Firstly, the authors considered whether the olefin binds *trans* or *cis* from the phosphine (binding mode) during the enantio-determining step of the reaction. Secondly, they probed if the pseudo axial or equatorial positioning of the phenyl groups on phosphorus is determined by the benzyl substitution of the ligand backbone. Lastly, they considered if the olefin binds from the ***Re*** or the ***Si*** face.

[158] Wu, W. -Q.; Peng, Q.; Dong, D. -X.; Hou, X. -L.; Wu, Y. -D. *J. Am. Chem. Soc.* **2008**, *130*, 9717-9725

Figure 3.1.2.1: *Stereochemical Elements Investigated by Wu*



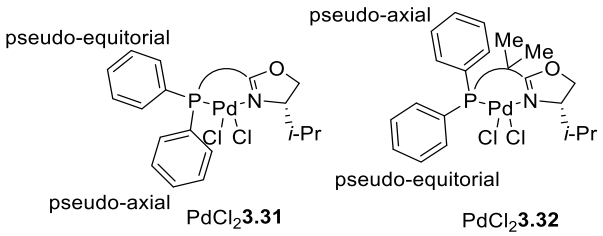
Regarding ***cis*** versus ***trans*** binding modes, the authors used calculations to determine the relative energies of the two binding modes and the transition state energies for a 1,2-migratory insertion. The ***cis*** mode was calculated to be more stable than the ***trans*** mode, but the ***trans*** transition state was determined to be a lower in energy than the ***cis*** transition state. This result arises since the phosphine is a better σ-donor and π-acceptor than nitrogen (phosphorus exhibited a greater *trans*-influence).[159] This effect lengthens the carbon-palladium bond and activates phenyl group for the 1,2 migratory insertion. Additionally, the carbon-carbon double bond of the olefin is lengthened when *trans* to the oxazoline. This signifies better back bonding from palladium to the olefin and indicate a more reactive olefin for 1,2-migratory insertion. In summary, calculations designated the ***trans*** binding mode and the subsequent 1,2 migratory insertion transition state as the likely pathway for this Heck reaction.

Next, calculations and crystal structures were used to determine whether the palladium catalyst has a ***syn*** or ***anti*** configuration. The notable difference between these two configurations is the positioning of the R group relative to the phenyl group of the phosphine. For the ***syn*** configuration, both the R group and the phenyl group are axial and *cis* to each other. For the ***anti*** configuration, the groups are still *cis* to each other, but the R group is pseudo-equatorial. For **3.31**, where R was a hydrogen, the ***syn*** configuration was the most stable and this stability was also exhibited in the transition-state compared to ***anti***. However, for **3.32**, where R was methyl, the ***anti*** configuration

[159] Coe, B. J.; Glenwright, S. J. *Coord. Chem. Rev.* **2000**, *203*, 5-80

was the most stable for the ground-state and the transition-state. Crystal structures of palladium (II) dichloride with **3.31** and **3.32** were solved and indicated a switch in the pseudo-axial and pseudo-equatorial positioning of the phenyl groups on phosphorus relative to the substituent positioning on the chiral oxazoline as seen in Figure 3.1.2.1. This computational and crystal structure evidence is suggestive that the olefin likely approaches *cis* to the phosphine and that the diastereoselective formation of the olefin-palladium complexation is determined by the pseudo-axial and pseudo-equatorial orientation of the aryl groups on phosphine.

Figure 3.1.2.1: *Simplified Crystal Structure of Both Ligands with Palladium (II) Dichloride*



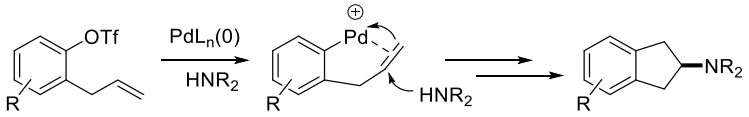
With the binding mode and the configuration of the palladium catalyst determined, the stereochemical model was predicted using calculations. Calculations supported the ***Re*** or ***Si*** facial selectivity of the olefin in 1,2-migratory insertion-step as compared to the absolute configuration of the product from catalysis. Ultimately, the pseudo-axial and the pseudo-equatorial orientation of the phenyl groups on phosphorus determined the ***Re*** and ***Si*** facial selectivity, and calculations supported the experimentally determined configuration of the products.

Another reaction class that shares many of the same fundamental elementary transformations as conjunctive cross-coupling is the nucleopalladation reaction. In this reaction, following oxidative addition, olefin binding of an aryl-palladium (II) intermediate activates the alkene for either an outer-sphere or inner-sphere nucleopalladation reaction. Subsequent reductive elimination furnishes the product and turns over the catalytic cycle. Though palladium-catalyzed nucleopalladation reactions did not often use oxidative addition palladium (II) adducts from aryl

electrophiles to activate olefins for nucleophilic attack, there were some non-enantioselective methods reported.[160]

An enantioselective method of a nucleopalladation using an aryl electrophile as an oxidant is worth discussing in detail.[161] In 2015, Wolfe and coworkers described an enantioselective intermolecular anti-aminopalladation (Scheme 3.1.2.2).

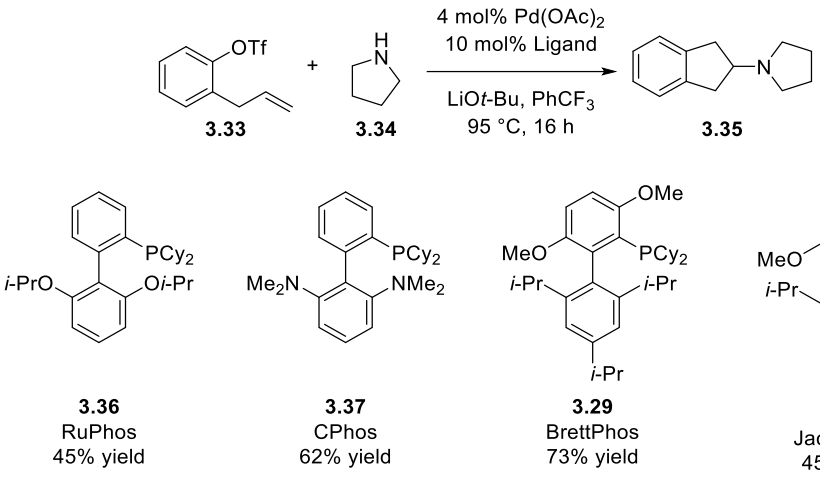
Scheme 3.1.2.2: *Wolfe's Asymmetric Palladium-Catalyzed Intermolecular Anti-Aminopalladation*



With this reaction's resemblance to palladium-catalyzed conjunctive cross-coupling, it was interesting to note the choice of ligands. Initially, a variety of the Buchwald-type ligands were surveyed to obtain a carboamination product (Table 3.1.2.1). These ligands were previously surveyed in an intramolecular variant of this reaction by the same group.[162] The authors did not speculate as to why BrettPhos (**3.29**) was a superior ligand to others. However, simply increasing the equivalents of amine nucleophile from 1 to 1.2 enabled quantitative conversion to product.

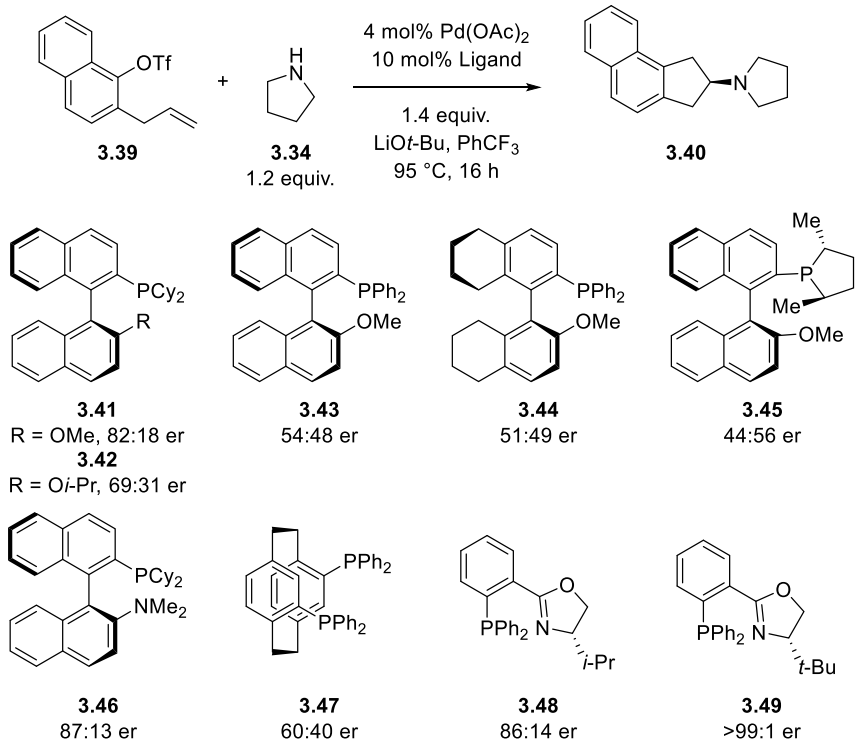
[160] (a) Bruyère, D.; Bouyssi, D.; Balme, G. *Tetrahedron* **2004**, *60*, 4007-4017 (b) Nakhla, J. S.; Kampf, J. W.; Wolfe, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 2893-2901
[161] White, D. R.; Hutt, J. T.; Wolfe, J. P. *J. Am. Chem. Soc.* **2015**, *137*, 11246-11249
[162] Fornwald, R. M.; Fritz, J. A.; Wolfe, J. P. *Chem. Eur. J.* **2014**, *20*, 8782-8790

Table 3.1.2.1: *Ligand Survey of Buchwald Ligands in Nucleopalladation Reaction*



With conditions for efficient generation of racemic products in hand, Wolfe set out to survey chiral ligands that exhibited steric and electronic features that may be similar to BrettPhos (Table 3.1.2.2). MOP (monodentate phosphine) ligands were selected for these reasons. Initial results suggested that MOP ligands (**3.41-3.45**) with electron-rich, alkyl substituents on the phosphorus facilitated good reactivity and enantioselectivity for the desired product. However, racemic product was obtained when switching to less electron-rich aryl substituents on the phosphorus. A combination of a P-chiral ligand (**3.45**) with an axially chiral backbone furnished near racemic product. Trading the ethereal component of the MOP ligand for a tertiary amine yielded similar enantioselectivity for an otherwise identical ligand (**3.46**). Switching to a PHOX ligand with an isopropyl substituent (**3.48**) on the oxazoline provided good enantioselectivities, but using a *tert*-butyl group (**3.49**) enabled excellent enantioselectivity and yield for ten examples.

Table 3.1.2.2: *Chiral Ligands Survey of Asymmetric Palladium-Catalyzed Nucleopalladation Reaction*

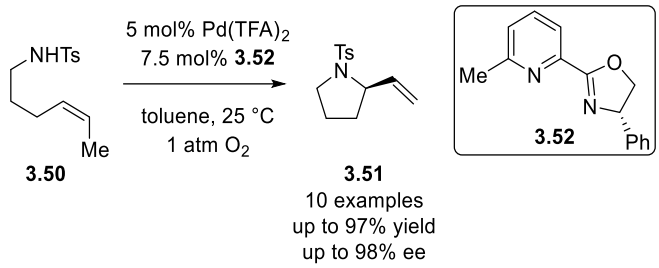


The authors proposed a stereochemical model for the original of selectivity based on the lowest energy orientation of the oxazoline substituent *cis* to the substrate olefin. However, Wolfe did not provide a rationale for the positioning of the olefin *cis* to the oxazoline.

In 2011, Stahl and coworkers studied the electronic effects of an electronically asymmetric ligand in an enantioselective palladium-catalyzed Wacker-type intramolecular amination of olefins using molecular oxygen as the oxidant.[163] The combination of palladium (II) trifluoroacetate and a chiral PyrOx (**3.52**) ligand enabled high conversion and enantioselectivity (Scheme 3.1.2.3).

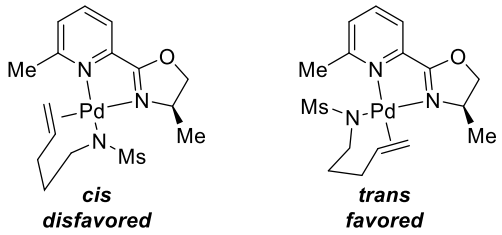
[163] McDonald, R. I.; White, P. B.; Weinstein, A. B.; Tam, C. P.; Stahl, S. S. *Org. Lett.* **2011**, *13*, 2830-2833

Scheme 3.1.2.3: *Stahl's Enantioselective Palladium-Catalyzed Oxidative Amination of Alkenes*



Calculations were performed to suggest the nature of the transition-state and the role of electronic asymmetry in PyrOx ligands. Ground-state calculations were performed on various orientations (*re* versus *si* orientations) and binding modes between the palladium-catalyst and the substrate. In general, the lower energy ground states were found to have the amido group *trans* to the oxazoline and the olefin *trans* to the pyridine. The authors claimed the preference in binding modes was because the more basic oxazoline has a stronger *trans* influence compared to the pyridine (Figure 3.1.2.2)

Figure 3.1.2.2: *Two Ground-State Binding Modes*



Moreover, the hypothesis that the binding mode is ***trans*** was given more credence when the catalytically relevant diastereomeric transition states were calculated, and the $\Delta\Delta G^{\neq}$ matched well with the product's experimentally determined % ee. Though the authors do not propose that the electronic properties of the ligand enable more facile catalysis, the stereocenter of the oxazoline is proposed to greatly influence the *re* and *si* facial selectivity of the *Z*-olefin of the substrate.

In conclusion, electronic asymmetric ligands have beneficial properties for efficient catalysis of alkene functionalization. Given the opportunities that come with a new ligand class to address

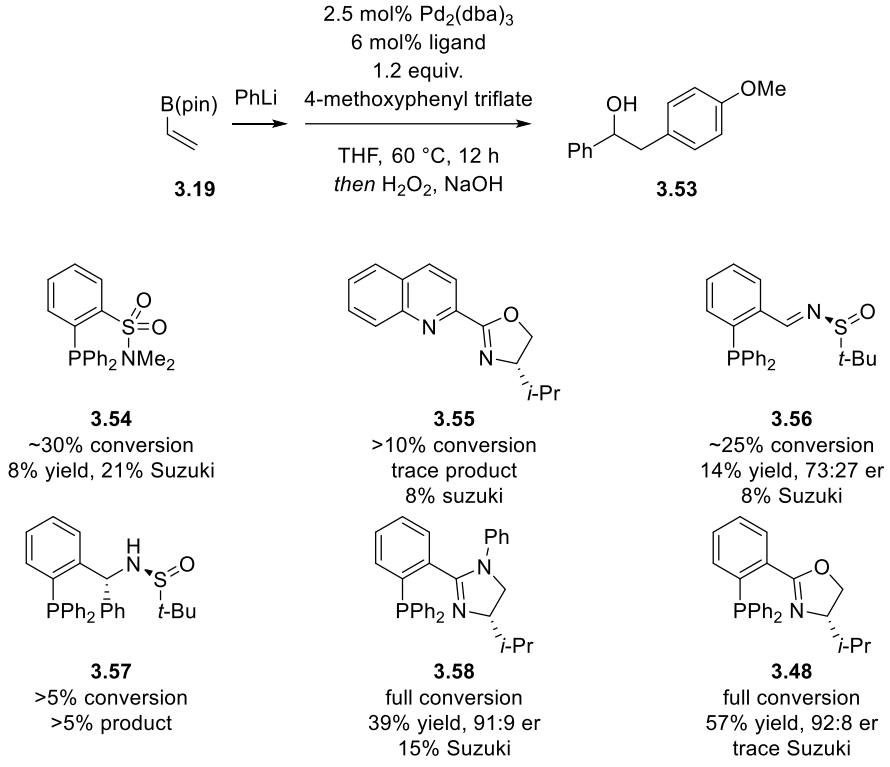
challenging reactivity, a ligand survey centered around a hypothesis that electronically asymmetric ligands could enable effective palladium-catalyzed conjunctive cross-coupling is worthwhile.

3.2 Enantioselective PHOX-ligated Palladium-Catalyzed Conjunctive Cross-Coupling

There were several criteria of ligand design that were implemented for the ligand survey. The general design features included electronic asymmetry in the ligand scaffold. Specifically, one component of the ligand would be electron rich enough to facilitate oxidative addition. The other component of the ligand would block or occupy a second coordination site and would be significantly electron deficient to enable 1,2-metallate shift to occur and minimize direct-transmetallation. Additionally, ligand design should have practical considerations. Firstly, ligands would ideally be inexpensive or easily synthesized from inexpensive starting materials. Secondly, in order to systematically study their effects in catalysis, the ligand's components must be tunable and easily incorporated in synthesis. Lastly, we aimed for new reactivity in conjunctive cross-coupling without the assistance of special additives.

The preparation of ligands was prioritized based on their utility in related Heck or nucleopalladation reactions, similar electronic properties as BrettPhos (**3.29**), along with their ease of synthesis (Table 3.2.1).

Table 3.2.1: *Ligand Survey of Electronically Asymmetric Ligands for Palladium-Catalyzed Conjunctive Cross-Coupling*



3.54 is a phosphine-sulfonamide ligand that has previously used in cationic palladium-catalyzed ethylene oligomerization reactions.[164] The authors obtained a crystal structure of a cationic palladium with this ligand, and noted the P,O binding mode. Additionally, the authors suggested that the ligand's strong σ-donating phosphine and the weaking σ-donating sulfonamide oxygen facilitated effective ethylene oligomerization catalysis, and such ligand properties are hypothetically beneficial for effective conjunctive cross-coupling like BrettPhos (**3.29**). **3.54** was easily synthesized from a directed lithiation of phenyl sulfonylamide and trapping with chlorodiphenylphosphine. Though not a chiral ligand, this ligand exhibited some selectivity for the desired product with the major side reaction being Suzuki-Miyaura cross-coupling. Quinox, **3.55**, is a commercially available N,N ligand that was previously used in an enantioselective

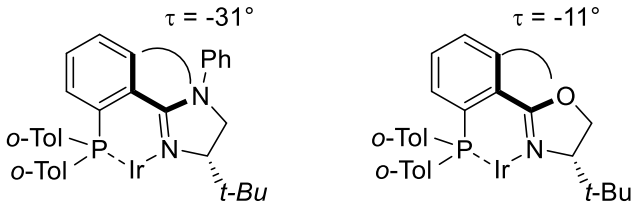
[164] Zhang, Y.; Cao, Y.; Leng, X.; Chen, C.; Huang, Z. *Organometallics*. **2014**, *33*, 3738-3745

palladium-catalyzed nucleopalladation reaction.[165] Using a commercially available electronically asymmetric ligand that contained stereocenter would be an excellent starting place to study the enantioinduction and reactivity of ligands in conjunctive cross-coupling reaction. Unfortunately, Quinox exhibited poor conversion of the starting "ate" complex and electrophile. Based on previously performed kinetic studies in conjunctive cross-coupling, the turnover-limiting step is the dissociation of the olefin bound "ate" complex from palladium (0) and subsequent oxidation addition.[166] Perhaps Quinox was not electron rich enough to facilitate an "ate" complex dissociation and oxidative addition mechanism. Comparing the results obtained from **3.54** and **3.55**, a least one phosphine maybe necessary to provide a suitable σ-donor to facilitate the desired mechanism. **3.56** is a P,N sulfinyl imine ligand that was previously used in palladium-catalyzed asymmetric allylic alkylation reactions.[167] There were design features that make this ligand desirable to study. It is prepared from a commercially available and inexpensive phosphino aldehyde and the chiral Ellman sulfinyl amine. Additionally, this ligand contained the desired phosphine functionality to facilitate oxidative addition and catalysis like in **3.54**, but it also contained a nitrogen σ-donor. This nitrogen chelate may reduce the availability of an open coordination site for undesirable transmetallation compared to an oxygen σ-donor, but still facilitate 1,2-metallate shift. Similar levels of conversion were obtained with **3.56** compared to **3.54**, but with better selectivity. Gratifyingly, the ligand was able to provide some enantioinduction during catalysis. A diastereoselective phenyl magnesium bromide addition to **3.56** furnished **3.57** as a single diastereomer. **3.57** is a P,O-ligand that was previously used in an enantioselective palladium-catalyzed cross-coupling of secondary phosphine oxides and aryl bromides to obtain P-

[165] Jensen, K. H.; Pathak, T. P.; Zhang, Y.; Sigman, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 17074-17075
[166] Myhill, J. A.; Zhang, L.; Lovinger, G. L.; Morken, J. P. *Angew. Chem. Int. Ed.* **2018**, *57*, 12799-12803
[167] Schenkel, L. B.; Ellman, J. A. *Org. Lett.* **2003**, *5*, 545-548

chiral phosphine oxides.[168] The main inspiration for using this ligand is the multiple sites that could be employed for fine-tuning. In addition, there could several advantages to using a wide bite-angle (facile reductive elimination to minimize unwanted β-hydride elimination), phosphine/sulfoxide (electron asymmetry) ligand for conjunctive cross-coupling. However, low conversion was observed when using **3.57**. Though there are several variables that changed compared to previously used ligands, perhaps the wide bite-angle in conjunction with a relatively less rigid ligand backbone provides poor bischelation and is not electron rich enough for productive catalysis. With these current results in mind, imine derived P,N-ligands could be a productive direction develop alternative ligand classes for palladium-catalyzed conjunctive cross-coupling. A more electron rich variant of **3.56** was envisioned in **3.58**, and full conversion of the "ate" complex was observed. Additionally, the product was furnished in modest yields and good enantioselectivity but with a significant amount of the Suzuki-Miyaura product. These phosphino-imidazoline (PHIM) ligands have been previously used in the Pfaltz laboratory for enantioselective hydrogenation reactions.[169] The authors noted the difference in torsion angle between PHIM (**3.58**) and PHOX (**3.48**) Ir complexes in crystal structures as seen in Figure 3.2.1.

Figure 3.2.1: *Simplified Crystal Structures of PHIM and PHOX Ir Complexes*



3.59 **3.60**

Severe torsional strain maybe a relevant concern in the conjunctive cross-coupling reaction because of arm-off mechanisms that promote Suzuki-Miyaura reactions may occur. With this

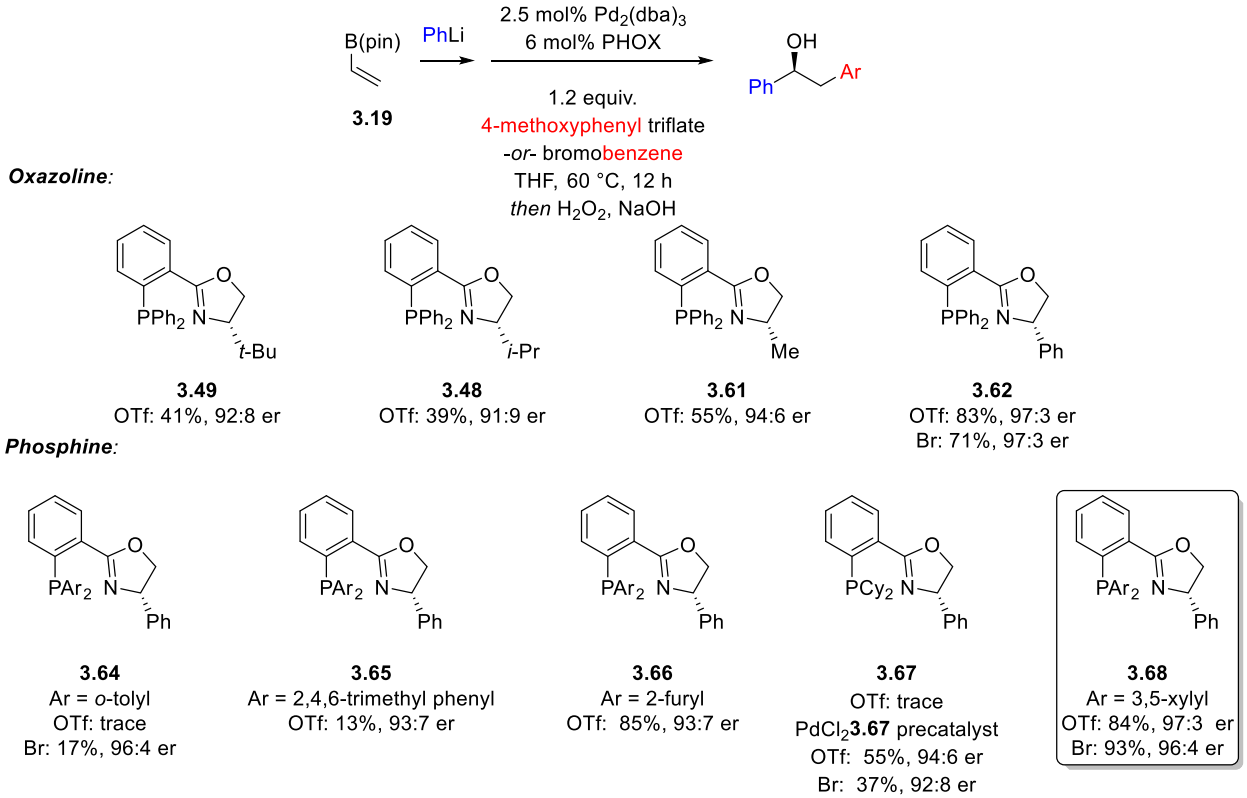
[168] Dai, Q.; Li, W.; Li, Z.; Zhang, J. *J. Am. Chem. Soc.* **2019**, *141*, 20556-20564
[169] Menges, F.; Neuburger, M.; Pfaltz, A. *Org. Lett.* **2002**, *4*, 4713-4716

hypothesis in mind, phosphinooxazoline ligands (**3.48**) are electronically and sterically similar to **3.58** without the built-in torsional strain. Indeed, **3.48** provided full conversion of the "ate" complex with good yield and enantioselectivity of the desired product and notably low selectivity for the undesired Suzuki-Miyaura product. In particular, PHOX ligands are thought to be an excellent ligand class to study because of the enormous breath of prior literature and the ease of synthesis.

With an effective ligand class in hand, fine tuning of the ligand was conducted (Table 3.2.2). The chiral oxazoline portion of the ligand was derived from amino alcohols, which were commercially available or easily synthesized. The phosphine portion of the ligand was installed by lithium-halogen exchange of the corresponding bromide, followed by reaction with bisarylphosphine chlorides. Keeping the phosphorus portion of the molecule constant, the effect of substituent on the oxazoline stereocenter was studied. Minimal differences in yield and enantioselectivity were observed with *t*-Bu (**3.49**) and *i*-Pr (**3.48**) substituents. Interestingly, the smaller methyl substituent (**3.61**) facilitated the highest conversion to product and the highest enantioinduction among the aliphatic groups. Interestingly, using a phenyl substituent enabled superior conversion to product and enantioselectivity. The results of the oxazoline survey suggest that the size of the substituent may play a small role in conversion and enantioselectivity of the reaction. Instead, subtle electronic features may be a more important factor for conversion and enantioselectivity as the phenyl group is more inductively withdrawing than the aliphatic groups. With this optimal oxazoline component, the phosphine portion of the ligand was surveyed. In general, enantioinduction was good with most ligands, but adding *ortho* substituents to the aryl phosphines (**3.64** and **3.65**) resulted in the sluggish catalysis. Perhaps the palladium center is too hindered for effective catalysis under these reaction conditions. 2-furyl phosphine (**3.66**) might

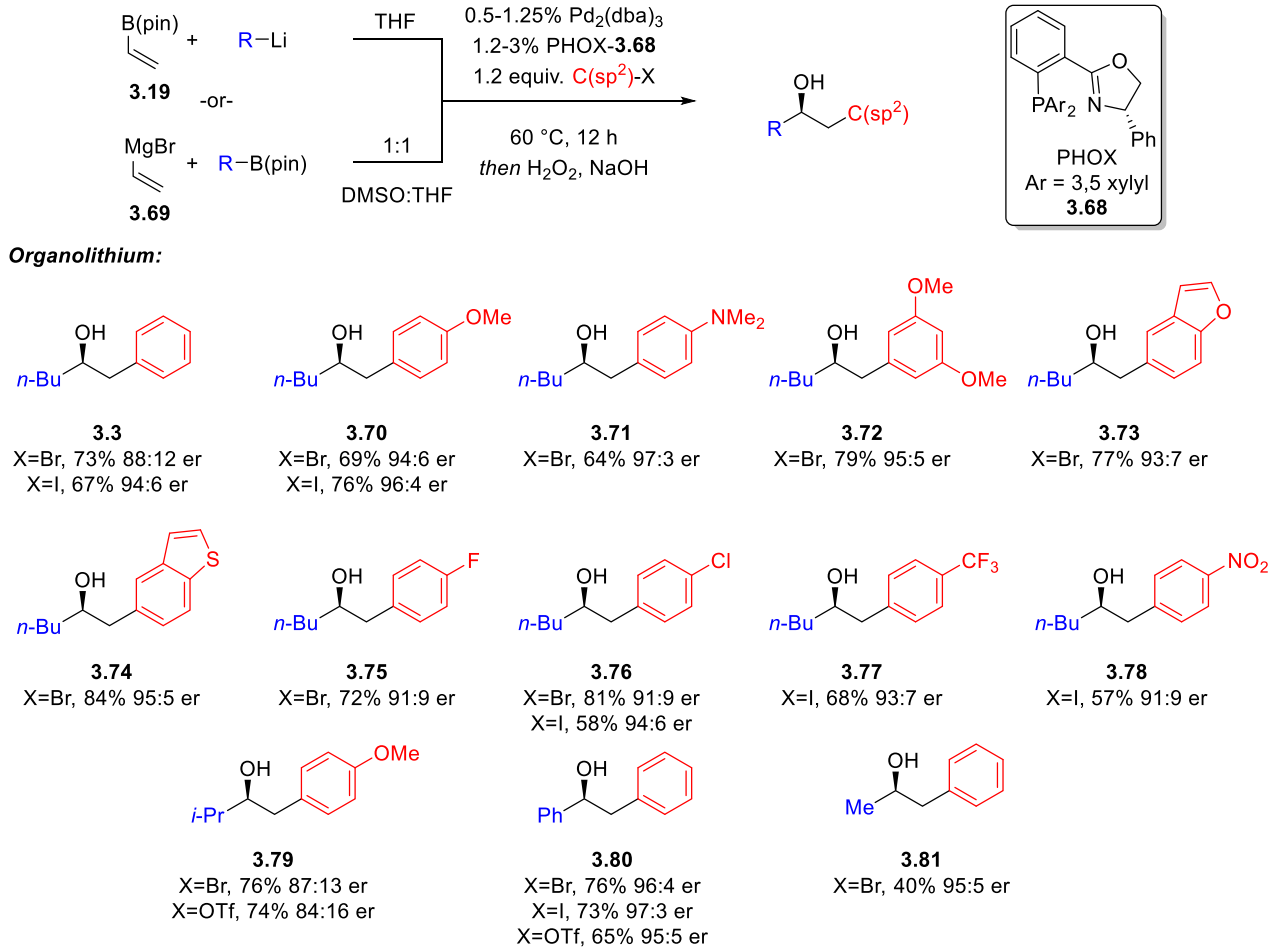
provide beneficial reactivity due to the aryl groups smaller size and greater electron donation. Electron rich ligands may enable greater selectivity for conjunctive cross-coupling because direct transmetallation is slowed. Moreover, electron rich ligands may provide productive conjunctive cross-coupling because the higher energy d-orbitals may more favorably back bond to olefins of "ate" complexes. Ligand **3.66** provided excellent conversion to product with slightly reduced enantioselectivity. Using a more electron rich alkyl phosphine **3.67** resulted in slow conversion to product. It was hypothesized that dba may competitively binding to palladium and inhibit reactivity. Switching to a **3.67**$PdCl_2$, where dba was no longer in the reaction, restored reactivity. However, conversion to product and enantioselectivity was modest. Ultimately, 3,5 xylyl (**3.68**), a ligand that appears to have the appropriate electron donation and sterics in the appropriate positions, was the optimal ligand for catalysis.

Table 3.2.2: *Fine-Tuning Ligand Optimization for the Synthesis of B(pin) Derived Secondary Organoboronates*



We studied the generality of catalysis with **3.68**. "Ate" complexes derived from commercially available vinyl B(pin) and organolithium were good coupling partners with electron rich and deficient aryl electrophiles (Table 3.2.3). Along with bromides and triflates, aryl iodides and aryl chloride electrophiles can participate in the reaction without special additives. This ligand also enabled the first palladium-catalyzed conjuctive cross-coupling with an "ate" complex derived from methyllithium, which had been a poor migrating group. As seen by compound **3.111**, it was furnished in a synthetically useful yield and enantioselectivity.

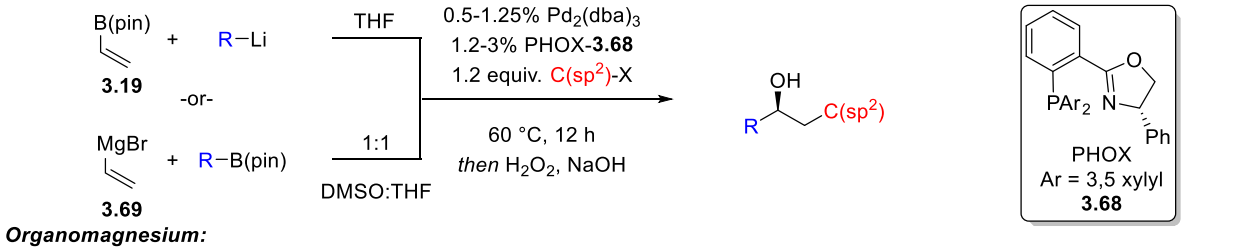
Table 3.2.3: *Substrate Scope of Organolithium-Derived "Ate" Complexes*



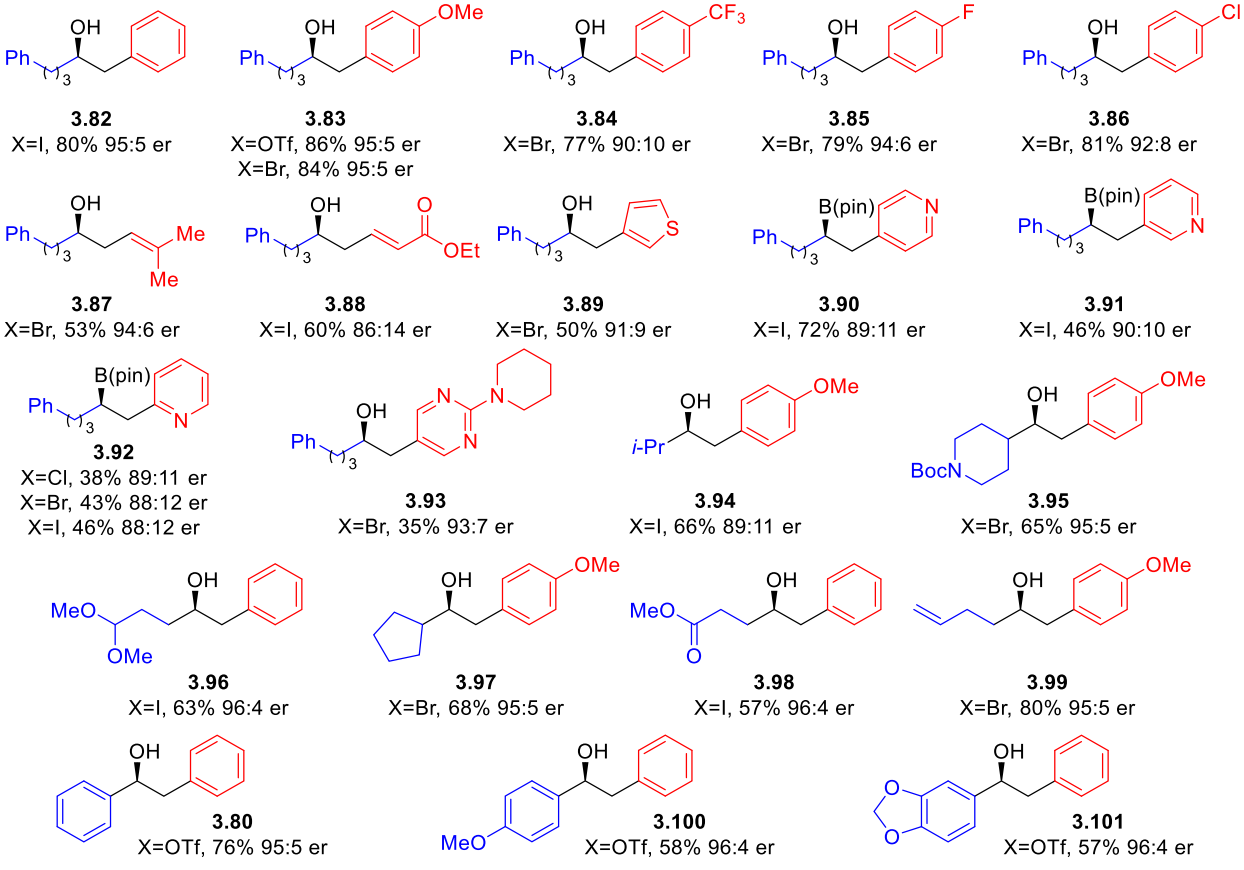
Yields are isolated yields of purified material and represent an average yield of two separate experiments. Enantiomeric ratios were determined by SFC analysis on a chiral stationary phased and are in comparison to authentic racemic materials.

Efficient cross-coupling of organomagnesium derived "ate" complexes with aryl and alkenyl electrophiles furnished products in high yield and enantioselectivity (Table 3.2.4). Both electron rich and deficient aryl electrophiles underwent catalysis with similar efficiency, and often products were obtained in greater yield and enantioselectivity than with equivalent lithium "ate" complexes.

Table 3.2.4: *Substrate Scope of Organomagnesium Derived "Ate" Complexes*



Organomagnesium:

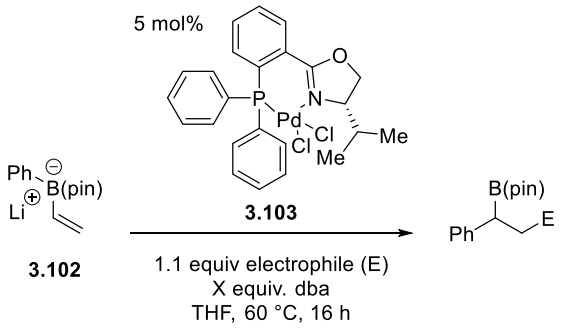


Yields are isolated yields of purified material and represent an average yield of two separate experiments. Enantiomeric ratios were determined by SFC analysis on a chiral stationary phased and are in comparison to authentic racemic materials.

Heterocycle electrophiles participated in the reaction in synthetically useful yields and enantioselectivities. A myriad of organomagnesium derived "ate" complexes including esters, acetals, olefins, and carbamates functionality were competent cross-coupling partners. It is worth noting that some nitrogen-containing heterocycle electrophiles were challenging cross-coupling partners (**3.91-3.93**)

There are some notable differences between this palladium-catalyzed conjunctive cross-coupling method and other methods. Aside from the obvious difference in the ligand, the palladium pre-catalyst choice is optimized for $Pd_2(dba)_3$. In Heck literature, the benefit of a $Pd_2(dba)_3$ pre-catalyst has been attributed to extended catalyst life time when using similar electronically asymmetric ligands.[170] The role of dba was studied and results were summarized in Table 3.2.5. Various amounts of dba were added to conjuctive cross-coupling reactions catalyzed by a $PHOXPdCl_2$ pre-catalyst **3.103** and using bromide and triflate electrophiles.

Table 3.3.5: *Dibenzylideneacetone Studies in Conjunctive Cross-Coupling*



Entry	electrophile	Equiv. dba	NMR Yield	Suzuki Yield
1	4-methoxyphenyl triflate	0.0	65%	10%
2	4-methoxyphenyl triflate	0.075	74%	6%
3	phenyl bromide	0.0	37%	17%
4	phenyl bromide	0.05	43%	3%
5	phenyl bromide	0.075	56%	14%
6	phenyl bromide	0.15	50%	15%

[170] Mazloomi, Z.; Magre, M.; Del Valle, E.; Pericàs, M. A.; Pàmies, O.; van Leeuwen, P. W. N. M.; Diéguez, M. *Adv. Synth. Catal.* **2018**, *360*, 1650-1664

When using a triflate electrophile with only the PHOX pre-catalyst, good yield of the desired product was obtained with some Suzuki-Miyaura products were observed (entry 1). Adding dba to resemble the number of equivalents of used in reactions with $Pd_2(dba)_3$, a notable increase of the desired product was observed with reduced amounts of Suzuki products (entry 2). From these observations, dba may provide higher catalyst fidelity and perhaps occupies coordination sites to minimize Suzuki products. The effects observed when dba is applied to conjunctive cross-coupling reaction with bromide electrophiles is interesting. Without dba, the precatalyst performed relatively poorly with modest amounts of desired product obtained and proportionally higher amounts of Suzuki products (entry 3). It is worth mentioning that the main Suzuki-Miyaura product observed is styrene, and biphenyl is observed in only trace amounts. Some styrene may evaporate during work up, and Suzuki yields vary. Conjunctive cross-coupling with equimolar amounts of dba and pd catalyst furnished slightly higher amounts of desired product and "reduced" Suzuki products. This trend peaked when using the same amount of dba as using a $Pd_2(dba)_3$ pre-catalyst (entry 5), but too much dba rendered less product (entry 6). Dba is a non-innocent ligand in catalysis, but its beneficial role in cross-coupling with halide electrophiles is noteworthy. The inhibitory nature of halide salts in MandyPhos-ligated palladium catalyzed conjunctive cross-coupling reactions has been well studied.[171] Iodide and bromide electrophiles yielded less than 10% product; where triflate electrophiles would furnish products in high yield. It is interesting to observe that the combination of PHOX ligands and dba reduce the inhibitory effects of halide anions. Further studies are necessary to access the reason for this observation, but perhaps dba may promote solvation of a palladium-bromide intermediate and open a coordination site for conjunctive cross-coupling to occur.

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

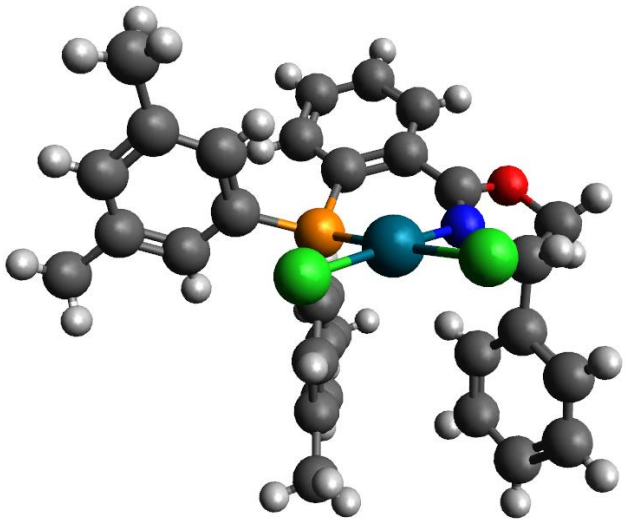
Using an electronically asymmetric ligand, an opportunity was presented to study the enantiodetermining step of the reaction. Regardless as to whether alkene binding or 1,2 metallate shift was the enantiodetermining step of the reaction, understanding the nature of catalyst-substrate interactions could be of use in future ligand design. First, whether the olefin binds *trans* to phosphorus or to nitrogen must be determined.

A crystal structure of the optimal palladium complex could provide insights in catalysis. Unfortunately, an oxidative addition adduct was not obtained from PHOX ligated palladium sources (Pd_2dba_3 and $Pd(COD)TMS_2$) reacting with phenyl bromide. However, a crystal structure was obtained by complexing palladium dichloride bis(acetonitrile) with ligand **3.68** in methylene chloride (Figure 3.2.2). A longer palladium-chloride bond (2.368 Å) *trans* to phosphorus indicates that the phosphine ligand exhibits a greater *trans* influence than the oxazoline (Pd-Cl 2.286 Å). The difference in *trans* influence will determine positioning of the aryl group and the "ate" complex prior to 1,2-metallate shift. If the aryl moiety exhibits greater *trans*-influence than the "ate" complex, then it will likely reside *trans* to the oxazoline. Thus, the "ate" complex may bind *trans* to the phosphine. However, a higher energy intermediate (aryl group *trans* to phosphine) may have a lower energy barrier for 1,2-metallate shift, a scenario previously described by Wu and others.[172] Additionally, the stereocenter of the oxazoline influences the pseudoaxial and pseudoequatorial positioning of the aryl groups on phosphine as seen in our crystal structure and others.[173] Therefore, an enantioselective trajectory for olefin binding is possible from both sides of the palladium center.

[172] Mazloomi, Z.; Magre, M.; Del Valle, E.; Pericàs, M. A.; Pàmies, O.; van Leeuwen, P. W. N. M.; Diéguez, M. *Adv. Synth. Catal.* **2018**, *360*, 1650-1664

[173] (a) Blacker, A. J.; Clarke, M. L.; Loft, M. S.; Mahon, M. F.; Humphries, M. E.; Williams, J. M. J. *Chem. Eur. J.* **2000**, *6*, 353-360 (b) Cabrera, A.; Sharma, P.; Pérez-Flores, F. J.; Velasco, L.; Arias, J. L.; Rubio-Pérez, L. *Catal. Sci. Technol.* **2014**, *4*, 2626-2630

Figure 3.2.2: *Crystal Structure of $PdCl_2$3.68(CH_2Cl_2) (Methylene Chloride Omitted)*



An empirical argument can be made through analysis of different ligands (Table 3.2.6). To investigate the binding mode of the olefin of the "ate", we can systematically replace portions of the PHOX ligand with non-asymmetric functional groups with similar steric and electronic properties and then evaluate the new ligand's performance in conjunctive cross-coupling. To replace the phosphine, a sulfide-ligated palladium **(3.107)** could function as a pseudo phosphine by exhibiting similar *trans* influence,[174] but it is difficult to maintain a single conformer for enantioinduction.[175] This ligand did not furnish an enriched chiral product. This outcome suggests that the olefin of the "ate" complex binds *trans* to the oxazoline (away from the stereocenter on the oxazoline) because if the stereocenter on the oxazoline governed the diastereoselective transition state of a 1,2-metallate shift (like in perhaps with a PHOX ligand) then an enantioenriched product would be expected. However, in this case, a racemic product was furnished.

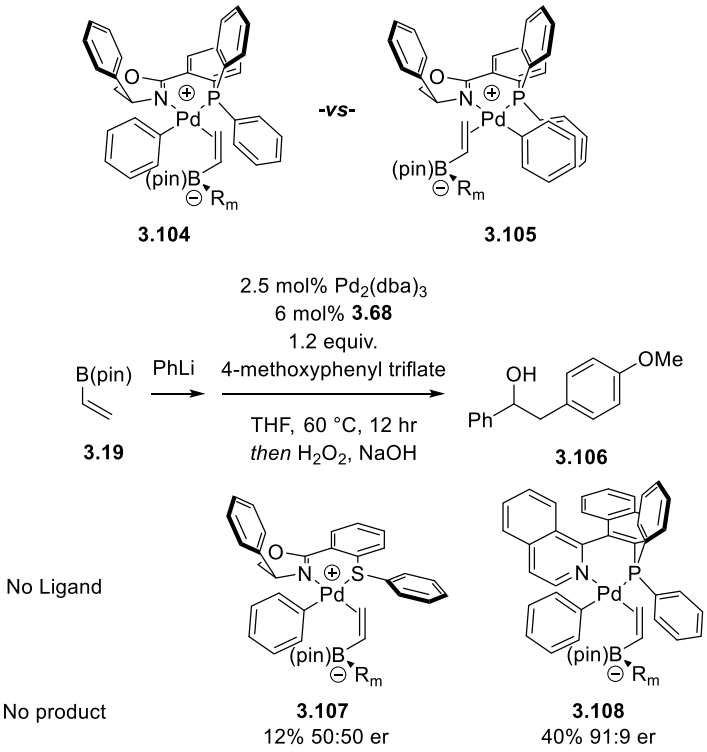
[174] Allen, J. V.; Coote, S. J.; Dawson, G. J.; Frost, C. G.; Martin, C. J.; Williams, J. M. J. *J. Chem. Soc. Perkin. Trans. 1* **1994**, 2065-2072
[175] Evans, D. A.; Campos, K. R.; Tedrow, J. S.; Michael, F. E.; Gagné, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 7905-7920

Alternatively, the oxazoline could be replaced with an electronically similar isoquinoline. For a PHOX ligand, the chiral information induced by the stereocenter of oxazoline that could influence the stereochemical outcome of a 1,2-metallate shift. For Quinap-ligated palladium species (**3.108**), the only chiral information exhibited was the axial chirality of the ligand backbone, which influenced the pseudoaxial and pseudoequatorial orientation of the aryl groups on phosphine.[176] Interestingly, a Quinap-ligated palladium furnished the product in a 91:9 enantiometric ratio. This result suggests that the gearing of the aryls groups on phosphine determine diastereoselective transition state of a 1,2-metallate shift.

If these results are directly translatable to PHOX ligands, this suggests the "ate" olefin may approach *trans* to the oxazoline. Future experiments could include using the PHOX ligands designed by Wu and co-workers (as described in Scheme 3.1.2). These ligands use the same enantiomer of the oxazoline and are, nearly, electronically identical, but the Heck products were obtained as opposite configurations for the major enantiomer. If the olefin approaches *trans* to the oxazoline under these reaction conditions, then the opposite configuration of the major enantiomer would be expected for the conjunctive product when using **3.31** and **3.32** because of the opposite configuration of the phenyl groups at phosphorus. Likewise, if the olefin approaches *trans* to the phosphine, then the same configuration of the major enantiomer would be expected because of the same configuration of the oxazoline stereocenter in **3.31** and **3.32**. This experiment may provide better evidence of the nature of olefin binding during the 1,2-metallate shift.

[176] For an x-ray structure of a Pd-Quinap complex: Alcock, N. W.; Brown, J. M.; Hulmes, D. L. *Tetrahedron Asymmetry*. **1993**, *4*, 743-756

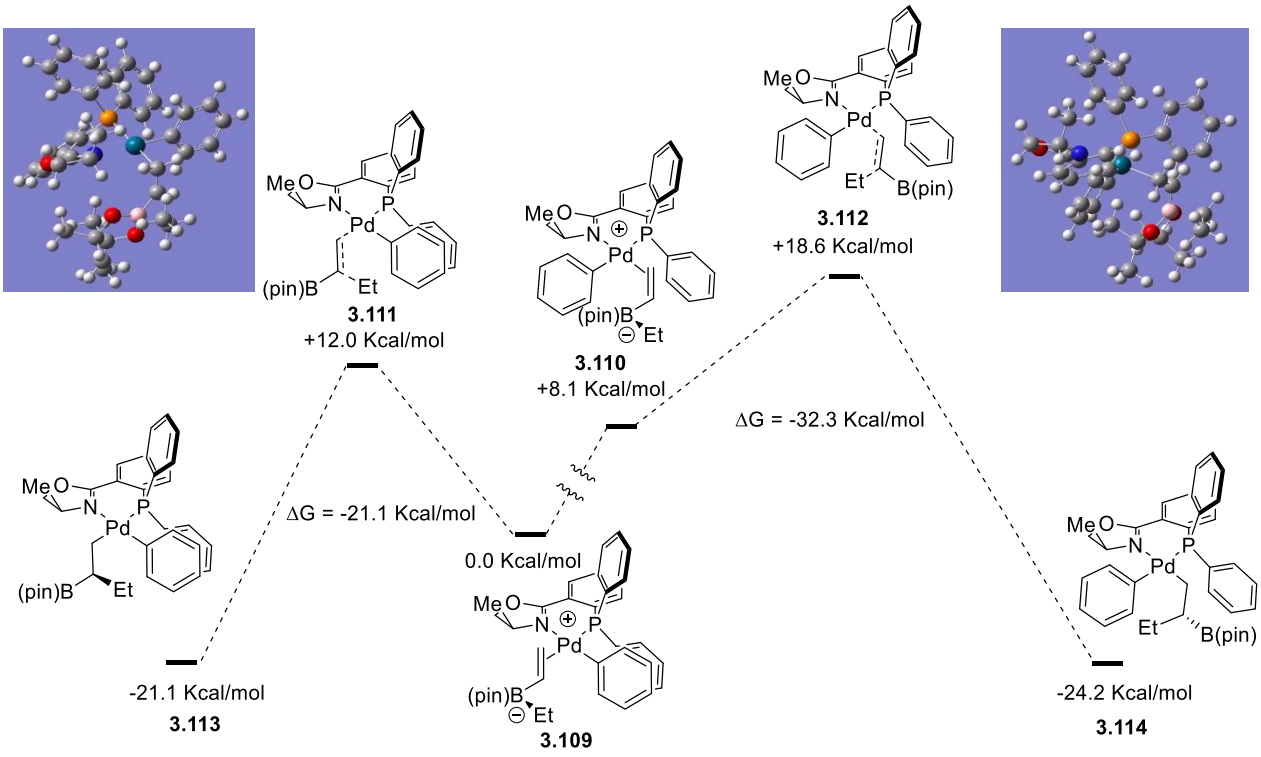
Table 3.2.6: *Empirical Approach to Determine the Binding Mode for Conjunctive Transmetallation*



To further investigate the preferred binding for 1,2-metallate shift, calculations were performed to explore the approach of the "ate" complex to the catalyst center (Figure 3.3.3). A simplified ligand system was implemented using a methyl substituent on the oxazoline ring and phenyl substituents on the phosphine. The "ate" was derived from vinyl B(pin) and ethyllithium. The facial selectivity of the "ate" complex for each path was determined by the known absolute configuration of product resulting from the known configuration of the ligand. Alternative orientations of the "ate" complex, where the boron, alkene plane was rotated 180 degrees about an orthogonal axis, were determined to give higher energy intermediates because of steric clashing with the ligand. Starting from a cationic palladium (II) phenyl PHOX species, there was a large difference between the energies of an "ate" complex *trans* to phosphorus and *trans* to nitrogen. Assuming an equilibrium process takes place, the equilibrium greatly favors the phenyl from the electrophile placed *trans* to the oxazoline by 8.1 Kcal/mol. This may be due to the phenyl group

being placed *trans* to the weaker *trans*-influencing ligand. From these two starting intermediates, the barrier for palladium-induced 1,2-metallate shift was calculated. The transition-state barrier with the "ate" complex *trans* to the oxazoline was lower than *trans* to the phosphine from their respective starting materials (10.5 Kcal/mol vs 12.0 Kcal/mol). However, the overall pathway was lower when the "ate" complex was *trans* to the phosphine. As expected, the transformation from starting materials to products was an exergonic process as seen in other calculations.[177]

Figure 3.2.3: *Transition-State Calculations for Palladium-Mediated 1,2-Metallate Shift. Final Energies Calculated Using DFT (ωB9XD/LANL2DZ)*



In conclusion, calculations suggested that 1,2-metallate shift was likely to occur *trans* to the phosphine. Though not an expected outcome based on the current hypothesis and experiments, continued synthesis of next generation ligands and using computational models could build a greater understanding of palladium-catalyzed conjunctive cross-coupling. Given the ease of

[177] Myhill, J. A.; Zhang, L.; Lovinger, G. J.; Morken, J. P. *Angew. Chem. Int. Ed.* **2018**, 57, 12799-12803

synthesis and the many permutations of PHOX derivatives, developing second generation ligands with new conjunctive cross-coupling methods is a low energy barrier process.

3.3 Experimental Section

3.3.1 General information

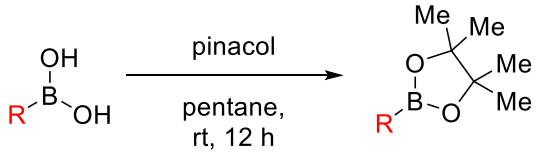
^{1}H NMR spectra were recorded on either a Varian Gemini-500 (500 MHz), Varian Gemini-600 (600 MHz), or Varian Inova-500 (500 MHz) spectrometer. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 7.26 ppm). Data are reported as follows: chemical shift, 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 (126 MHz), Varian Gemini-600 (151 MHz) or a Varian Inova-500 (126 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 77.2 ppm). ^{11}B NMR spectra were recorded on a Varian Gemini-500 (128 MHz) or Varian Gemini-600 (160 MHz) spectrometer. ^{19}F NMR spectra were recorded on a Varian Gemini-500 (470 MHz) spectrometer. Infrared (IR) spectra were recorded on a Bruker alpha-P Spectrometer using compounds neat. 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) 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. 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 (magic stain). 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. X-ray crystal structure determination was performed using a Bruker Kappa Apex Duo automated single crystal diffractometer.

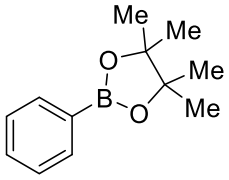
All reactions were conducted in oven- or flame-dried glassware under an inert atmosphere of nitrogen or argon. Tetrahydrofuran (THF), diethyl ether (Et_2O), dichloromethane (DCM) and toluene were purified using Pure Solv MD-4 solvent purification system, from Innovative Technology, Inc., by passing the solvent through two activated alumina columns after purging with nitrogen. Vinylboronic acid pinacol ester was purchased from Combi Blocks and distilled using a short path distillation apparatus. Vinyl magnesium bromide, phenyllithium, *n*-butyllithium and iso-butyllithium were purchased from Sigma Aldrich. All organohalides, other pinacol esters and all other reagents were purchased from Aldrich, Alfa Aesar, Acros, Combi Blocks, TCI Chemicals or Oakwood Chemicals and used without further purification.

3.3.2 Procedures for Preparation of Boronic Esters

Aryl Boronic Ester Synthesis

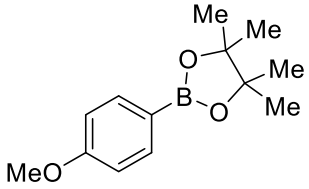


To an oven-dried round bottom flask with magnetic stir bar was added boronic acid (1.0 equiv.) and pentane. 2,3-dimethylbutane-2,3-diol (pinacol) (1.05 equiv.) was added into the suspension. Then the reaction solution was allowed to stir at room temperature for 12 hours. Upon completion, to the resulting mixture was filtered through a silica plug and washed with three times with dichloromethane. The solvent was removed under reduced pressure and the resulting residue was subsequently purified via silica gel column chromatography.



4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (S-1)

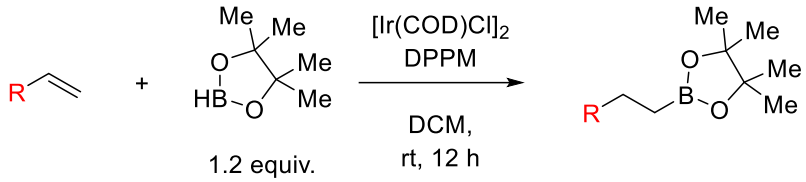
Prepared according to the general procedure above phenylboronic acid to afford a white solid. All spectral data were in accordance with the literature.[178]



2-(4-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (S-2)

Prepared according to the general procedure above (4-methoxyphenyl)boronic acid to afford a white solid. All spectral data were in accordance with the literature.[173]

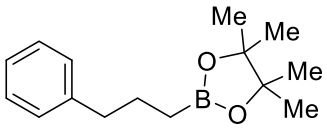
Alkyl Boronic Ester Synthesis



The following general protocol is derived from a modified literature procedure.[179] In a glovebox under argon, bis(1,5-cyclooctadiene)diiridium(I) dichloride (0.01 equiv.) and bis(diphenylphosphino)methane (0.02 equiv.) were added directly as solids to an oven-dried round bottom flask with magnetic stir bar. The solids were dissolved in dichloromethane and allowed to

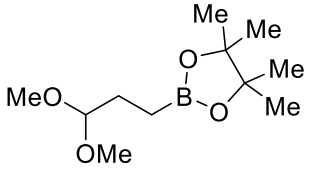
[178] Clary, J. W.; Rettenmaier, T. J.; Snelling, R.; Bryks, W.; Banwell, J.; Wipke, W. T.; Singaram, B. *J. Org. Chem.* **2011**, *76*, 9602-9610
[179] Yamamoto, Y.; Fujikawa, R.; Umemoto, T.; Miyaura, N. *Tetrahedron* **2004**, *60*, 10695-10700

stir for five minutes. Then the corresponding alkene (1.0 equiv.) was added to the mixture followed by the dropwise addition of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.2 equiv.). The reaction vessel was then sealed and removed from the glove box and was allowed to stir for 12 hours at room temperature. Upon completion, the reaction was quenched with methanol and water and then partitioned between saturated sodium chloride solution and dichloromethane. The aqueous layer was extracted with dichloromethane. The combined organics were dried over sodium sulfate and concentrated under reduced pressure to afford a cloudy orange oil. The crude oil was subsequently purified via silica gel column chromatography to afford the desired organoboronate ester.



4,4,5,5-tetramethyl-2-(3-phenylpropyl)-1,3,2-dioxaborolane (S-3)

Prepared according to the general procedure above with allyl benzene. Following extraction, drying and concentrating *in vacuo*, the crude product was purified by automated flash column chromatography (Biotage 2% → 10% ethyl acetate in *n*-hexane, stained in CAM) to afford a colorless oil. All spectral data were in accordance with the literature.[180]



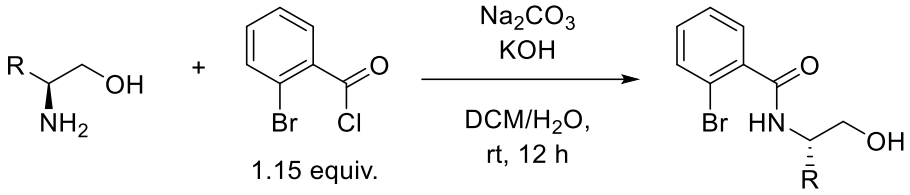
2-(3,3-dimethoxypropyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (S-4)

[180] Bose, S. K.; Brand, S.; Omoregie, H. O.; Haehnel, M.; Maier, J.; Bringmann, G.; Marder, T. B. *ACS Catal.* **2016**, *6*, 8332-8335

Prepared according to the general procedure above with 3,3-dimethoxyprop-1-ene. Following extraction, drying and concentrating *in vacuo*, the crude product was passed through a silica gel plug, which was washed with dichloromethane, to afford an orange oil. All spectral data were in accordance with the literature.[181]

3.3.3 Procedures for Preparation of Phosphinooxazolines (PHOX)

Amide Synthesis

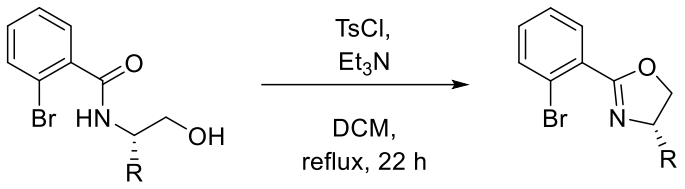


The following general protocol was derived from a modified literature procedure.[182] To a solution of the corresponding amino alcohol (1.0 equiv.) in dichloromethane (0.3 M) was added a solution of sodium carbonate (3.0 equiv.) in deionized water (1.2 M). To the vigorously stirred biphasic mixture was added 2-bromobenzoyl chloride (1.15 equiv.) in a dropwise manner. After 12 hours at ambient temperature, the layers were separated, and the aqueous layer was extracted with dichloromethane. The combined organics were treated with 1M potassium hydroxide (0.5 equiv.) for 15 minutes, then neutralized with 3 M HCl, and water was added. The layers were separated, and the aqueous layer extracted with dichloromethane. The combined organic layers were dried over sodium sulfate and concentrated to afford the corresponding amide. The crude product could be purified by silica gel chromatography (acetone in *n*-hexane), or by recrystallization in

[181] Kalinin, A. V.; Scherer, S.; Snieckus, V. *Angew. Chem. Int. Ed.* **2003**, *42*, 3399-3404
[182] Tani, K.; Behenna, D. C.; McFadden, R. M.; Stoltz, B. M. *Org. Lett.* **2007**, *9*, 2529-2531

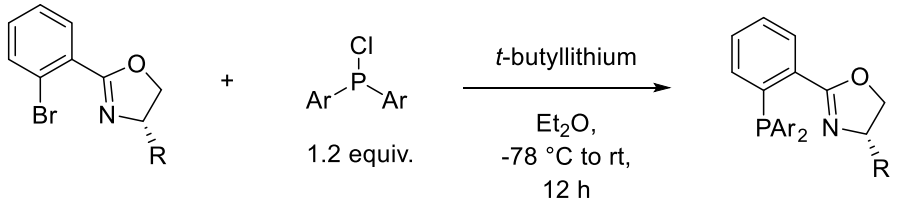
dichloromethane. For the ease of ligand synthesis, the amide was directly used in the next step without further purification.

Oxazoline Synthesis



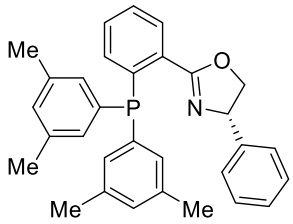
The following general protocol was derived from a modified literature procedure.[177] To an oven-dried round bottom flask equipped with a reflux condenser, a solution of the corresponding amide (1.0 equiv.), p-toluenesulfonyl chloride (1.3 equiv.), triethylamine (5.0 equiv.) in dichloromethane (0.3 M) was heated at 55 °C for 22 hours. Upon completion, water was added and heating continued at 75 °C for 2 hours. Then the reaction mixture was cooled, the layers separated, and the aqueous layers were extracted with dichloromethane. The combined organics were dried over sodium sulfate, concentrated, and the residue was purified by silica gel chromatography (10% EtOAc in *n*-hexanes) to give the desired phenyloxazoline.

Phosphine Synthesis



To an oven-dried round bottom flask, the corresponding phenyloxazoline (1.0 equiv.) was dissolved in diethyl ether (0.2 M). The flask was then flushed by nitrogen and was cooled down at -78 °C. Under positive nitrogen pressure, *t*-butyllithium (2.0 equiv.) was added in a dropwise

manner. The mixture was stirred at -78 °C for an hour, and the corresponding chlorophosphine (1.2 equiv.) was added. The reaction was allowed to warm to room temperature and was allowed to stir for 12 hours. Upon completion, the reaction was quenched by saturated ammonium chloride solution and layers were separated. The aqueous layers were extracted with diethyl ether and the combined organic layers were dried over magnesium sulfate. The solution was then filtered and concentrated to afford the crude residue, which was subsequently purified by silica gel chromatography to yield the desired phosphinooxazoline.

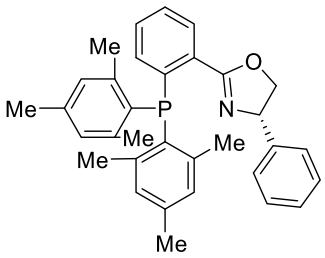


(S)-2-(2-(bis(3,5-dimethylphenyl)phosphaneyl)phenyl)-4-phenyl-4,5-dihydrooxazole (3.68)

The reaction was performed according to the general procedure using (4S)-2-(2-bromophenyl)-4-phenyl-4,5-dihydrooxazole (993 mg, 3.28 mmol, 1 equiv.), *tert*-butyllithium (4.11 mL, 1.6 M in pentane, 6.57 mmol, 2 equiv.), and chloro-bis(3,5-dimethylphenyl)phosphane (1 g, 3.61 mmol, 1.1 equiv.). Crude was subject to silica gel chromatography. Silica was loaded onto a column with 2% triethylamine and toluene. Crude sample was transferred to the column with a minimal amount of dichloromethane and eluted with 2% ethyl acetate: toluene to yield a white solid (1.52 grams, 44.5%). Rf = 0.6 in 5% ethyl acetate: 1% triethylamine: toluene.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.00 – 7.95 (m, 1H), 7.39 – 7.29 (m, 2H), 7.24 – 7.18 (m, 3H), 7.00 – 6.89 (m, 9H), 5.25 – 5.14 (m, 1H), 4.56 – 4.50 (m, 1H), 3.95 – 3.86 (m, 1H), 2.24 (d, *J* = 7.0 Hz, 12H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.20, 142.30, 139.85, 139.68, 138.01, 137.96, 137.92, 137.86, 137.76, 137.68, 137.47, 137.41, 133.98, 132.27, 132.13, 131.93, 131.79, 131.73, 131.61, 130.74, 130.72, 130.55, 130.45, 130.43, 128.51, 127.94, 127.31, 126.90, 74.61, 70.23, 21.49.; ^{31}P

NMR (162 MHz, $CDCl_3$) δ -4.92.; IR (neat) ν_{max} 3055.35 (m), 3022.21 (m), 2952.31 (m), 2916.42 (m), 2855.90 (m), 1646.51 (s), 1597.36 (m), 1581.03 (m), 1467.74 (m), 1452.43 (m), 1033.03 (s), 694.56 (s) cm^{-1}.; HRMS (DART) for $C_{31}H_{30}NOP$ $[M+H]^+$: calculated: 464.21378, found: 464.21428.; $[\alpha]^{20}_D$: -23.171 (c = 0.05 g/100 mL, $CHCl_3$, *l* = 50 mm)

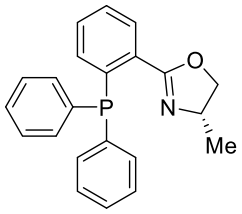


(S)-2-(2-(dimesitylphosphaneyl)phenyl)-4-phenyl-4,5-dihydrooxazole (3.65)

The reaction was performed according to the general procedure using (4S)-2-(2-bromophenyl)-4-phenyl-4,5-dihydrooxazole (302 mg, 1 mmol, 1 equiv.), *tert*-butyllithium (0.647 mL, 1.7 M in pentane, 1.1 mmol, 1.1 equiv.), and chloro-bis(2,4,6-trimethylphenyl)phosphane (335 mg, 1.1 mmol, 1.1 equiv.). Crude was subject to silica gel chromatography. Silica was loaded onto a column with 2% triethylamine and toluene. Crude sample was transferred to the column with a minimal amount of dichloromethane and eluted with 2% ethyl acetate: toluene to yield a white solid (200 mg, 40.7%). Rf = 0.5 in 5% ethyl acetate: 1% triethylamine: toluene.

^1H NMR (600 MHz, $CDCl_3$) δ 8.02 – 7.82 (m, 1H), 7.31 (t, *J* = 7.4 Hz, 1H), 7.29 – 7.25 (m, 1H), 7.25 – 7.20 (m, 4H), 7.13 – 7.08 (m, 2H), 6.81 – 6.77 (m, 4H), 5.29 (t, *J* = 9.6 Hz, 1H), 4.60 (dd, *J* = 10.1, 8.2 Hz, 1H), 3.98 (t, *J* = 8.7 Hz, 1H), 2.25 (d, *J* = 13.7 Hz, 6H), 2.11 (d, *J* = 11.0 Hz, 12H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.93, 143.31, 143.20, 143.14, 143.03, 142.45, 140.07, 139.88, 137.86, 137.66, 133.42, 133.09, 132.91, 131.89, 131.85, 131.77, 131.73, 130.25, 130.20, 130.17, 129.89, 129.87, 128.41, 128.39, 127.49, 127.12, 126.83, 126.82, 74.35, 70.38, 23.17, 23.15, 23.06, 23.04, 21.06.; ^{31}P NMR (243 MHz, $CDCl_3$) δ -23.91.; IR (neat) ν_{max} 3055.63 (m), 3020.20 (m), 2959.85 (m), 2918.59 (m), 2918.59 (m), 2856.72 (m), 1645.73 (s), 1601.21 (m),

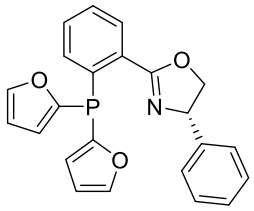
1464.12 (s), 1450.04 (s), 1031.85 (s), 754.51 (s), 698.529 (m) cm^{-1}.; HRMS (DART) for $C_{33}H_{34}NOP$ $[M+H]^+$: calculated: 492.24508, found: 492.24343.; $[\alpha]^{20}_D$: -692 (c = 0.032 g/100 mL, CH_2Cl_2, *l* = 50 mm)



(S)-2-(2-(diphenylphosphaneyl)phenyl)-4-methyl-4,5-dihydrooxazole (3.61)

The reaction was performed according to the general procedure using (4S)-2-(2-bromophenyl)-4-methyl-4,5-dihydrooxazole (500 mg, 2.08 mmol, 1 equiv.), *tert*-butyllithium (2.6 mL, 1.6 M in pentane, 4.16 mmol, 2 equiv.), and chloro(diphenyl)phosphane (505 mg, 2.29 mmol, 1.1 equiv.). Crude was subject to silica gel chromatography. Silica was loaded onto a column with 2% triethylamine and toluene, Crude sample was transferred to the column with a minimal amount of dichloromethane and eluted with 2% ethyl acetate: toluene to yield a white solid (310 mg, 43.1%). Rf = 0.4 in 5% ethyl acetate: 1% triethyl amine and toluene.

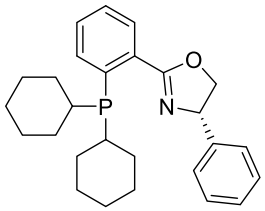
^1H NMR (600 MHz, $CDCl_3$) δ 7.91 – 7.83 (m, 1H), 7.40 – 7.24 (m, 12H), 6.88 – 6.84 (m, 1H), 4.20 (dd, *J* = 9.3, 7.8 Hz, 1H), 4.17 – 4.08 (m, 1H), 3.56 (t, *J* = 7.8 Hz, 1H), 0.96 (d, *J* = 6.6 Hz, 3H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.45, 163.43, 139.04, 138.88, 138.01, 138.00, 137.94, 137.92, 134.47, 134.33, 134.04, 133.90, 133.52, 133.51, 131.80, 131.68, 130.47, 130.00, 129.98, 128.77, 128.62, 128.55, 128.51, 128.47, 128.42, 127.97, 73.68, 62.03, 20.85.; ^{31}P NMR (243 MHz, $CDCl_3$) δ -4.60.; IR (neat) ν_{max} 3063.66 (m), 3049.84 (m), 2962.91 (m), 2920.89 (m), 2890.23 (m), 1648.14 (s), 1432.40 (s), 1032.87 (s), 741.27 (s), 695.23 (s), 502.82 (m) cm^{-1}.; HRMS (DART) for $C_{22}H_{20}NOP$ $[M+H]^+$: calculated: 346.13553, found: 346.13510.; $[\alpha]^{20}_D$: -136.48 (c = 0.1 g/100 mL, $CHCl_3$, *l* = 50 mm)



(S)-2-(2-(di(furan-2-yl)phosphaneyl)phenyl)-4-phenyl-4,5-dihydrooxazole (3.66)

The reaction was performed according to the general procedure using (4S)-2-(2-bromophenyl)-4-phenyl-4,5-dihydrooxazole (151 mg, 0.5 mmol, 1 equiv.), *tert*-butyllithium (0.323 mL, 1.7 M in pentane, 0.55 mmol, 1.1 equiv.), and chloro-bis(2-furyl)phosphane (110 mg, 0.55 mmol, 1.1 equiv.). Crude was subject to silica gel chromatography. Silica was loaded onto a column with 2% triethylamine and toluene, Crude sample was transferred to the column with a minimal amount of dichloromethane and eluted with 2% ethyl acetate: toluene to yield a white solid (105 mg, 54.2%). Rf = 0.5 in 5% ethyl acetate: 1% triethyl amine and toluene.

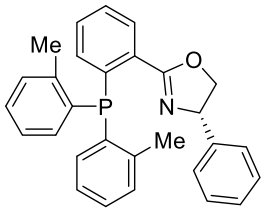
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (dt, *J* = 5.9, 3.8 Hz, 1H), 7.63 (dd, *J* = 13.8, 1.7 Hz, 2H), 7.40 (dd, *J* = 5.8, 3.4 Hz, 2H), 7.36 – 7.22 (m, 3H), 7.20 – 7.16 (m, 2H), 7.14 (td, *J* = 5.1, 3.2 Hz, 1H), 6.65 (ddd, *J* = 32.2, 3.5, 1.5 Hz, 2H), 6.41 (ddt, *J* = 10.3, 3.2, 1.6 Hz, 2H), 5.32 (t, *J* = 9.5 Hz, 1H), 4.67 (dd, *J* = 10.2, 8.2 Hz, 1H), 4.10 (t, *J* = 8.6 Hz, 1H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.57, 152.03, 151.94, 151.82, 151.77, 147.21, 147.19, 147.05, 147.03, 142.15, 137.10, 136.97, 133.30, 130.90, 130.80, 130.65, 130.31, 130.28, 128.68, 128.59, 127.48, 126.89, 121.28, 121.09, 120.92, 110.97, 110.92, 110.90, 110.86, 74.64, 70.31.; ^{31}P NMR (243 MHz, $CDCl_3$) δ 194.13.; IR (neat) ν_{max} 2957.26 (m), 2921.91 (m), 2898.08 (m), 2850.75 (m), 1647.07 (s), 1452.90 (m), 1354.21(m), 1005.55 (s), 742.84 (s), 699.55 (m) cm^{-1}.; HRMS (DART) for $C_{23}H_{18}NO_3P$ $[M+H]^+$: calculated: 388.10971, found: 388.11131.; $[\alpha]^{20}_D$: 119.89 (c = 0.1 g/100 mL, $CHCl_3$, *l* = 50 mm)



(S)-2-(2-(dicyclohexylphosphaneyl)phenyl)-4-phenyl-4,5-dihydrooxazole (3.67)

The reaction was performed according to the general procedure using (4S)-2-(2-bromophenyl)-4-phenyl-4,5-dihydrooxazole (500 mg, 1.65 mmol, 1 equiv.), *tert*-butyllithium (2.1 mL, 1.6 M in pentane, 3.3 mmol, 2 equiv.), and chloro(dicyclohexyl)phosphane (424 mg, 1.82 mmol, 1.1 equiv.). Crude was subject to silica gel chromatography. Silica was loaded onto a column with 2% triethylamine and toluene, Crude sample was transferred to the column with a minimal amount of dichloromethane and eluted with 4% ethyl acetate: toluene to yield a thick, clear solid (191 mg, 27.5%). Rf = 0.3 in 5% ethyl acetate: 1% triethyl amine and toluene.

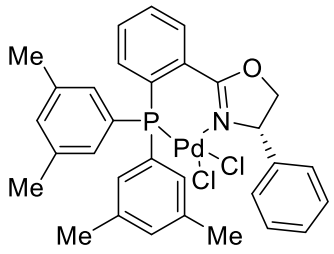
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71 (ddd, *J* = 7.7, 3.2, 1.5 Hz, 1H), 7.59 (dt, *J* = 7.8, 1.7 Hz, 1H), 7.47 – 7.42 (m, 3H), 7.40 – 7.34 (m, 3H), 7.30 (dt, *J* = 14.7, 7.1 Hz, 1H), 5.43 (dd, *J* = 10.1, 8.5 Hz, 1H), 4.81 (dd, *J* = 10.1, 8.3 Hz, 1H), 4.29 (t, *J* = 8.4 Hz, 1H), 1.93 (ddt, *J* = 25.7, 17.2, 8.1 Hz, 4H), 1.83 – 1.75 (m, 2H), 1.71 – 1.61 (m, 4H), 1.60 – 1.52 (m, 2H), 1.36 – 1.09 (m, 10H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.63, 166.62, 142.71, 137.08, 136.90, 136.74, 136.54, 132.79, 132.77, 129.81, 129.77, 129.45, 128.63, 128.39, 127.48, 127.14, 127.13, 74.80, 70.54, 34.93, 34.84, 34.59, 34.50, 30.48, 30.36, 30.26, 30.15, 29.91, 29.84, 27.42, 27.38, 27.35, 27.32, 27.28, 27.24, 27.21, 27.18, 26.54, 26.48.; ^{31}P NMR (243 MHz, $CDCl_3$) δ -5.48.; IR (neat) ν_{max} 2920.63 (s), 2846.37 (m), 1650.29 (m), 1446.13 (m), 1349.29 (w), 1029.10 (m), 756.88 (m), 698.46 (m) cm^{-1}.; HRMS (DART) for $C_{27}H_{34}NOP$ $[M+H]^+$: calculated: 420.24508, found: 420.24551.; $[\alpha]^{20}_D$: -93.441 (c = 0.1 g/100 mL, $CHCl_3$, *l* = 50 mm)



(S)-2-(2-(di-o-tolylphosphaneyl)phenyl)-4-phenyl-4,5-dihydrooxazole (3.64)

The reaction was performed according to the general procedure using (4S)-2-(2-bromophenyl)-4-phenyl-4,5-dihydrooxazole (151 mg, 0.5 mmol, 1 equiv.), *tert*-butyllithium (0.323 mL, 1.7 M in pentane, 0.55 mmol, 1.1 equiv.), and chloro(bis-o-tolyl)phosphane (137 mg, 0.55 mmol, 1.1 equiv.). Crude was subject to silica gel chromatography. Silica was loaded onto a column with 2% triethylamine and toluene, Crude sample was transferred to the column with a minimal amount of dichloromethane and eluted with 2% ethyl acetate: toluene to yield a white solid (218 mg, 27.6%). Rf = 0.5 in 5% ethyl acetate: 1% triethyl amine and toluene.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.03 – 7.99 (m, 1H), 7.40 (td, *J* = 7.5, 1.3 Hz, 1H), 7.34 (td, *J* = 7.6, 1.5 Hz, 1H), 7.29 – 7.24 (m, 2H), 7.24 – 7.16 (m, 5H), 7.09 (t, *J* = 7.6, 1.9 Hz, 2H), 6.99 – 6.92 (m, 3H), 6.81 (td, *J* = 8.3, 3.9 Hz, 2H), 5.29 (t, *J* = 9.5 Hz, 1H), 4.60 (dd, *J* = 10.2, 8.2 Hz, 1H), 3.97 (t, *J* = 8.6 Hz, 1H), 2.41 (s, 3H), 2.38 (s, 3H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.84, 143.00, 142.89, 142.82, 142.71, 142.32, 138.17, 138.01, 136.35, 136.28, 136.19, 134.10, 133.63, 133.23, 132.28, 132.14, 130.91, 130.59, 130.57, 130.22, 130.19, 130.16, 130.13, 129.72, 128.73, 128.66, 128.55, 128.54, 128.28, 127.26, 127.19, 126.81, 126.35, 126.23, 74.60, 70.39, 21.50, 21.48, 21.35, 21.33.; ^{31}P NMR (243 MHz, $CDCl_3$) δ -22.41.; IR (neat) ν_{max} 3052.47 (m), 3001.54 (m), 2963.92 (m), 2914.24 (m), 1645.29 (s), 1466.41 (s), 1450.35 (s), 1032.78 (s), 748.94 (s), 698.85 (s) cm^{-1}.; HRMS (DART) for $C_{29}H_{26}NOP$ $[M+H]^+$: calculated: 436.18248, found: 436.18179.; $[\alpha]^{20}_D$: -86.862 (c = 0.049 g/100 mL, $CHCl_3$, *l* = 50 mm)



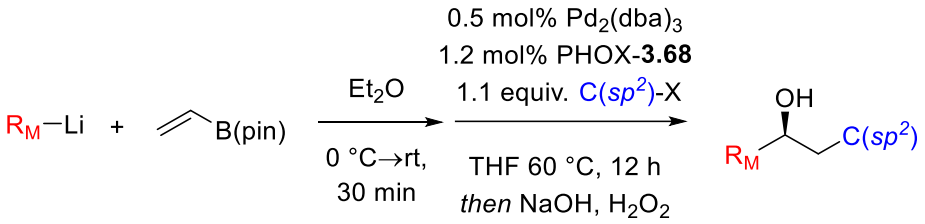
Palladium dichloride PHOX ($PdCl_2$(*S*)-3.68)

The title compound was prepared by mixing (S)-2-(2-(bis(3,5-dimethylphenyl)phosphaneyl)phenyl)-4-phenyl-4,5-dihydrooxazole (92.7 mg, 0.2 mmol, 1 equiv.) and bis(acetonitrile) palladium dichloride (51.9 mg, 0.2 mmol, 1 equiv.) in dichloromethane (5 mL, 0.04 M). Reaction was allowed to stir overnight at room temperature. Solvent was removed under vacuum and the mixture was recrystallized using a mixture of dichloromethane and hexanes to yield yellow crystals.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (dd, *J* = 7.7, 3.5 Hz, 1H), 7.74 (t, *J* = 7.7 Hz, 1H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.20 – 7.15 (m, 1H), 7.15 – 7.05 (m, 2H), 6.98 (d, *J* = 4.3 Hz, 4H), 6.96 – 6.91 (m, 1H), 6.88 (dt, *J* = 13.4, 2.4 Hz, 4H), 6.69 (dd, *J* = 10.1, 4.5 Hz, 1H), 4.91 (t, *J* = 10.1, 9.0 Hz, 1H), 4.63 (dd, *J* = 9.0, 4.6 Hz, 1H), 2.22 (d, *J* = 12.6 Hz, 12H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 162.05, 161.98, 139.10, 139.02, 138.06, 137.97, 135.08, 135.06, 134.27, 134.25, 133.97, 133.95, 133.72, 133.66, 132.41, 132.39, 132.24, 132.16, 132.11, 132.06, 131.13, 131.05, 128.89, 128.53, 128.46, 128.30, 127.99, 127.68, 127.51, 126.56, 126.20, 125.73, 125.30, 76.10, 69.42, 21.58, 21.48.; ^{31}P NMR (202 MHz, $CDCl_3$) δ 26.11.; IR (neat) ν_{max} 3061.36 (m), 3028.66 (m), 3000.81 (m), 2980.06 (m), 2948.84 (m), 2915.35 (m), 2858.93 (m), 2224.46 (m), 1622.70 (s), 1378.69 (s), 1231.81 (s), 1124.18 (s), 910.79 (s), 847.80 (s)727.91 (s), 686.52 (s) cm^{-1}.; HRMS (DART) for $C_{31}H_{30}NOPClPd$ $[M+H]^+$: calculated: 604.07829, found: 604.08064.; $[\alpha]^{20}_D$: 40 (c = 0.01 g/100 mL, acetone, *l* = 50 mm)

3.3.4 General Procedures for Conjunctive Cross-Coupling

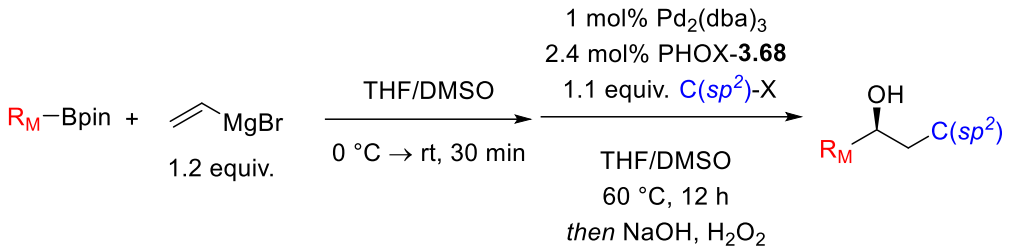
Method A: (using organolithium-derived boron "ate" complexes)



In a glovebox under argon, an oven-dried 2-dram vial equipped with a magnetic stir bar was charged with 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (0.20 mmol, 1.0 equiv.) and diethyl ether (0.3 mL), sealed with a septum cap and removed from glovebox. Under positive nitrogen pressure, the reaction vial was cooled to 0 °C, and phenyllithium solution in dibutyl ether or alkyllithium solution in diethyl ether (0.20 mmol, 1.0 equiv.) was added dropwise. Upon completion of the addition, the reaction was allowed to warm to room temperature and stir for 30 minutes. Then solvent was carefully removed under reduced pressure to yield a white solid and was brought back into the glovebox. In the glovebox, a second oven-dried 2-dram vial equipped with a magnetic stir bar was charged with $Pd_2(dba)_3$ (1.00 μmol, 0.005 equiv.), Phosphinooxazolines ligand (2.40 μmol, 0.012 equiv.) and tetrahydrofuran (0.06 mL). The $Pd_2(dba)_3$/**3.68** solution was allowed to stir for 3 hours at room temperature. The $Pd_2(dba)_3$/**3.68** solution was then transferred into the reaction vial, followed by tetrahydrofuran (0.54 mL) (used to rinse the $Pd_2(dba)_3$/**3.68** vial), and aryl/vinyl halide (0.22 mmol. 1.1 equiv.). The reaction vial was sealed with a polypropylene cap, taped and brought out of the glovebox where it was allowed to stir at 60 °C for 12 hours. To the resulting mixture was filtered through a silica plug with diethyl ether, re-concentrated, and diluted with tetrahydrofuran (1 mL). The crude mixture was cooled to 0 °C and 3 M sodium hydroxide solution (0.8 mL) was added, followed by 30% hydrogen peroxide

(0.4 mL), dropwise. The reaction mixture was allowed to warm to room temperature, and was allowed to stir at room temperature for 3 hours. Upon completion, the reaction mixture was cooled to 0 °C and saturated aqueous sodium thiosulfate (2 mL) was added dropwise. After warming to room temperature, the aqueous layer was extracted with diethyl ether (8 x 2 mL). The combined organic layers were dried over sodium sulfate, concentrated under reduced pressure and subsequently purified via silica gel column chromatography to provide the desired products.

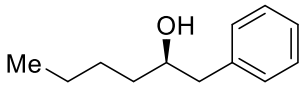
Method B: (using Grignard-derived boron "ate" complexes)



In a glovebox under argon, an oven-dried 2-dram vial equipped with a magnetic stir bar was charged with boronate (0.20 mmol, 1.0 equiv.), tetrahydrofuran (0.1 mL) , and dimethyl sulfoxide (0.1 mL), sealed with a septum cap, and removed from the glovebox. Under positive nitrogen pressure, the reaction vial was cooled to 0 °C, and vinyl magnesium bromide solution in tetrahydrofuran (0.24 mmol, 1.2 equiv.), was added dropwise. The reaction vial was allowed to warm to room temperature and stir for 30 minutes before being brought back into the glovebox. In the glovebox, a second oven-dried 2-dram vial equipped with a magnetic stir bar was charged with $Pd_2(dba)_3$ (2.0 µmol, 0.01 equiv.), Phosphinooxazolines ligand (4.80 µmol, 0.024 equiv.) and tetrahydrofuran (0.06 mL). The $Pd_2(dba)_3$/**3.68** solution was allowed to stir for 3 hours at room temperature. The $Pd_2(dba)_3$/**3.68** solution was then transferred into the reaction vial, followed by dimethyl sulfoxide (0.2 mL) (used to rinse the $Pd_2(dba)_3$/**3.68** vial), and aryl/vinyl halide (0.22

mmol. 1.1 equiv.). The reaction vial was sealed with a polypropylene cap, taped and brought out of the glovebox where it was allowed to stir at 60 °C for 12 hours. To the resulting mixture was added saturated ammonium chloride solution and the aqueous layer was extracted with diethyl ether. The combined organic layers were filtered through a silica plug with, re-concentrated, and diluted with tetrahydrofuran (1 mL). The crude mixture was cooled to 0 °C and 3 M sodium hydroxide solution (0.8 mL) was added, followed by 30% hydrogen peroxide (0.4 mL), dropwise. The reaction mixture was allowed to warm to room temperature, and was allowed to stir at room temperature for 3 hours. Upon completion, the reaction mixture was cooled to 0 °C and saturated aq. sodium thiosulfate (2 mL) was added dropwise. After warming to room temperature, the aqueous layer was extracted with diethyl ether (8 x 2 mL). The combined organic layers were dried over sodium sulfate, concentrated under reduced pressure and subsequently purified via silica gel column chromatography to provide the desired products.

3.3.5 Characterization of Conjunctive Cross-Coupling Products



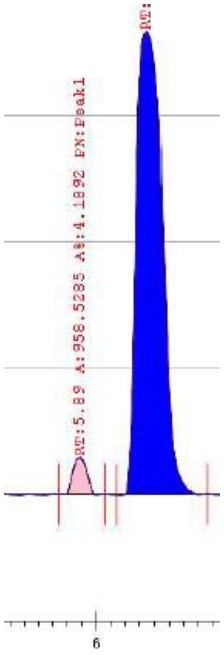
(R)-1-phenylhexan-2-ol (3.3)

The reaction was performed according to general procedure *Method A* using 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (30.8 mg, 0.2 mmol, 1.0 equiv.), *n*-butyllithium (2.5 M in diethyl ether, 0.08 mL, 0.20 mmol, 1.0 equiv.), iodobenzene (44.9 mg, 0.22 mmol, 1.1 equiv.), tris(dibenzylideneacetone)-dipalladium (0) (0.82 mg, 1.00 μmol, 0.005 equiv.), phosphinooxazoline **3.68** (1.11 mg, 2.40 μmol, 0.012 equiv.). The crude product was purified by automated flash column chromatography (Biotage 2% → 24% ethyl acetate in *n*-hexane, stained in CAM) to afford a colorless oil (23.9 mg, 67% yield). All spectral data were in accordance with the literature.[183]

Analysis of Stereochemistry: Racemic compound was prepared in a previous publication. This enriched sample was subject to the same chiral SFC conditions and similar retention times were observed.[178]

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

Chiral SFC (OD-H, 5% IPA, 3ml/min, 100 bar, 35 °C, 210-270 nm) -analysis of **(R)-1-phenylhexan-2-ol**



Peak No	% Area	Area	RT (min)
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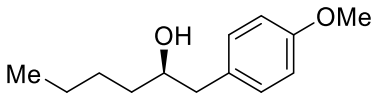
2	95.8108	21922.2711	6.35
Total:	100	22880.7996	



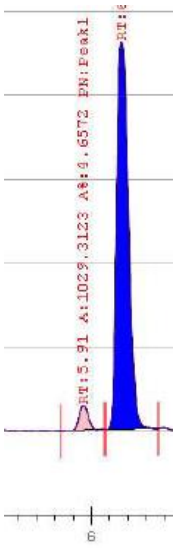
(R)-1-(4-methoxyphenyl)hexan-2-ol (3.70)

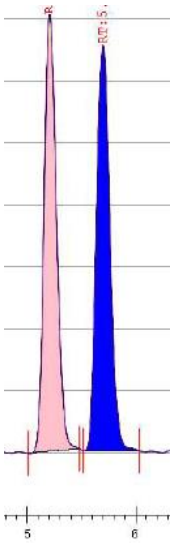
The reaction was performed according to general procedure *Method A* using 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (30.8 mg, 0.2 mmol, 1.0 equiv.), *n*-butyllithium (2.5 M in diethyl ether, 0.08 mL, 0.20 mmol, 1.0 equiv.), 1-iodo-4-methoxy-benzene (54.2 mg, 0.22 mmol, 1.1 equiv.), tris(dibenzylideneacetone)-dipalladium(0) (0.82 mg, 1.00 μmol, 0.005 equiv.), phosphinooxazoline **3.68** (1.11 mg, 2.40 μmol, 0.012 equiv.). The crude product was purified by automated flash column chromatography (Biotage 2% → 28% ethyl acetate in *n*-hexane, stained in CAM) to afford a colorless oil (31.7 mg, 76% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.13 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 3.80 (s, 3H), 3.77 (tt, J = 8.8, 4.5 Hz, 1H), 2.78 (dd, J = 13.6, 4.3 Hz, 1H), 2.58 (dd, J = 13.7, 8.4 Hz, 1H), 1.58 – 1.42 (m, 4H), 1.43 – 1.28 (m, 3H), 0.92 (t, J = 7.2 Hz, 3H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.4, 130.7, 130.5, 114.1, 72.9, 55.4, 43.2, 36.6, 28.1, 22.9, 14.2.; IR (neat) ν_{max} 3392.03 (br), 2994.09 (m), 2955.14 (m), 2859.05 (w), 1612.32 (m), 1512.04 (s), 1464.93 (m), 1246.46 (s), 1036.09 (m), 816.88 (m), 523.03 (w) cm^{-1}.; HRMS (DART) for $C_{13}H_{19}O$ $[M+H-H_2O]^+$: calculated: 191.14304, found: 191.14366.; $[\alpha]^{20}_D$: -12.0 (c = 1.0 g/100 mL, $CHCl_3$, *l* = 50 mm)

Analysis of Stereochemistry: Racemic compound was prepared according to the procedure described above with $Pd_2(dba)_3$ (1 mol%) and 2-(2-(diphenylphosphino)phenyl)-4,4-dimethyl-4,5-dihydrooxazole (1.2 mol%) as the catalyst.

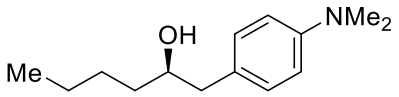
Chiral SFC (OJ-H, 5% IPA, 3ml/min, 100 bar, 35 °C, 210-270 nm) -analysis of **(R)-1-(4-methoxyphenyl)hexan-2-ol**





Peak No	% Area	Area	RT (min)
1	4.6572	1029.3123	5.91
2	95.3428	21072.1104	6.33
Total:	100	22101.4227	

Peak No	% Area	Area	RT (min)
1	49.6071	5544.1592	5.2
2	50.3929	5631.9845	5.7
Total:	100	11176.1437	



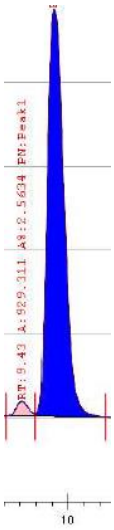
(R)-1-(4-(dimethylamino)phenyl)hexan-2-ol (3.71)

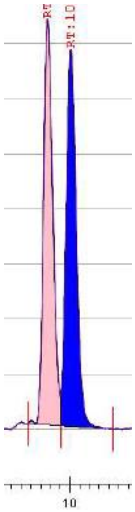
The reaction was performed according to general procedure *Method A* using 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (30.8 mg, 0.2 mmol, 1.0 equiv.), *n*-butyllithium (2.5 M in diethyl ether, 0.08 mL, 0.20 mmol, 1.0 equiv.), 4-bromo-N,N-dimethyl-aniline (44.9 mg, 0.22 mmol, 1.1 equiv.), tris(dibenzylideneacetone)-dipalladium(0) (0.82 mg, 1.00 μmol, 0.005 equiv.), phosphinooxazoline **3.68** (1.11 mg, 2.40 μmol, 0.012 equiv.). The crude product was purified by automated flash column chromatography (Biotage 2% → 30% ethyl acetate in *n*-*n*-hexane, stained in CAM) to afford a faint yellow solid (28.3 mg, 64% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.7 Hz, 2H), 6.73 (d, *J* = 8.1 Hz, 2H), 3.75 (tt, *J* = 8.5, 4.3 Hz, 1H), 2.93 (s, 6H), 2.76 (dd, *J* = 13.7, 4.2 Hz, 1H), 2.54 (dd, *J* = 13.7, 8.5 Hz, 1H), 1.57 (s, 1H), 1.55 – 1.44 (m, 3H), 1.42 – 1.31 (m, 3H), 0.92 (t, *J* = 7.3 Hz, 3H).; ^{13}C NMR (151 MHz, CDCl3) δ 130.2, 113.2, 72.9, 43.1, 41.0, 36.5, 28.1, 22.9, 14.2.; IR (neat) ν_{max} 3385.26 (br), 2954.34 (m), 2929.06 (s), 2798.62 (m), 1615.42 (m), 1521.40 (s), 1445.29 (w), 1345.24 (m), 1227.99 (w), 947.43 (w), 805.64 (m), 560.69 (w) cm^{-1}.; HRMS (DART) for $C_{14}H_{24}NO$ $[M+H]^+$: calculated: 222.18524, found: 222.18667.; $[\alpha]^{20}_D$: -7.96 (c = 1.0 g/100 mL, $CHCl_3$, *l* = 50 mm)

Analysis of Stereochemistry: Racemic compound was prepared according to the procedure described above with $Pd_2(dba)_3$ (1 mol%) and 2-(2-(diphenylphosphino)phenyl)-4,4-dimethyl-4,5-dihydrooxazole (1.2 mol%) as the catalyst.

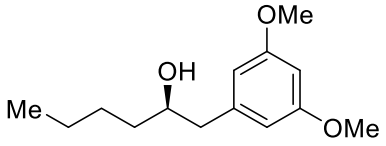
Chiral SFC (OD-H, 5% IPA, 3ml/min, 100 bar, 35 °C, 210-270 nm) -analysis of **(R)-1-(4-(dimethylamino)phenyl)hexan-2-ol**





Peak No	% Area	Area	RT (min)
1	2.5634	929.311	9.43
2	97.4366	35323.675	9.82
Total:	100	36252.986	

Peak No	% Area	Area	RT (min)
1	49.9725	19628.6356	9.54
2	50.0275	19650.2164	10.02
Total:	100	39278.852	



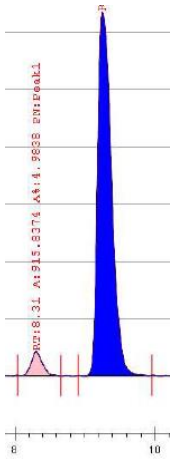
(R)-1-(3,5-dimethoxyphenyl)hexan-2-ol (3.72)

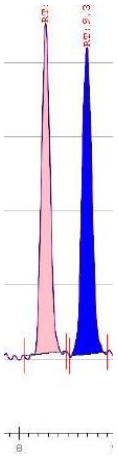
The reaction was performed according to general procedure *Method A* (with the modification: the reaction was run with 2 % catalyst loading instead of 1 %) using 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (30.8 mg, 0.2 mmol, 1.0 equiv.), *n*-butyllithium (2.5 M in diethyl ether, 0.08 mL, 0.20 mmol, 1.0 equiv.), 1-bromo-3,5-dimethoxy-benzene (48.7 mg, 0.22 mmol, 1.1 equiv.), tris(dibenzylideneacetone)-dipalladium(0) (1.83 mg, 2.0 μmol, 0.01 equiv.), phosphinooxazoline **3.68** (2.23 mg, 4.80 μmol, 0.024 equiv.). The crude product was purified by automated flash column chromatography (Biotage 4% → 32% ethyl acetate in *n*-hexane, stained in CAM) to afford a colorless oil (37.7 mg, 79% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.37 (d, *J* = 2.2 Hz, 2H), 6.34 (t, *J* = 2.3 Hz, 1H), 3.83 – 3.79 (m, 1H), 3.78 (s, 6H), 2.77 (dd, *J* = 13.5, 4.0 Hz, 1H), 2.57 (dd, *J* = 13.5, 8.6 Hz, 1H), 1.61 (d, *J* = 3.4 Hz, 1H), 1.56 – 1.44 (m, 3H), 1.41 – 1.30 (m, 3H), 0.92 (t, *J* = 7.2 Hz, 3H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 160.9, 141.0, 107.3, 98.4, 72.5, 55.3, 44.4, 36.5, 27.9, 22.7, 14.1.; IR (neat) ν_{max} 3400.24 (br), 2954.75 (m), 2954.75 (m), 2859.23 (w), 1596.11 (s), 1462.54 (s), 1342.77 (w), 1322.13 (w), 1205.33 (s), 1150.47 (s), 1066.72 (m), 829.39 (w) cm^{-1}.; HRMS (DART) for $C_{14}H_{23}O_3$ $[M+H]^+$: calculated: 239.16417, found: 239.16427.; $[\alpha]^{20}_D$: -11.4 (c = 1.0 g/100 mL, $CHCl_3$, *l* = 50 mm)

Analysis of Stereochemistry: Racemic compound was prepared according to the procedure described above with $Pd_2(dba)_3$ (1 mol%) and 2-(2-(diphenylphosphino)phenyl)-4,4-dimethyl-4,5-dihydrooxazole (1.2 mol%) as the catalyst.

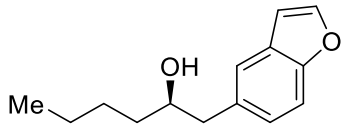
Chiral SFC (OD-H, 5% IPA, 3ml/min, 100 bar, 35 °C, 210-270 nm) -analysis of **(R)-1-(3,5-dimethoxyphenyl)hexan-2-ol**





Peak No	% Area	Area	RT (min)
1	4.9838	915.8374	8.31
2	95.0162	17460.6226	9.26
Total:	100	18376.46	

Peak No	% Area	Area	RT (min)
1	48.3857	2749.0661	8.54
2	51.6143	2932.4981	9.39
Total:	100	5681.5642	



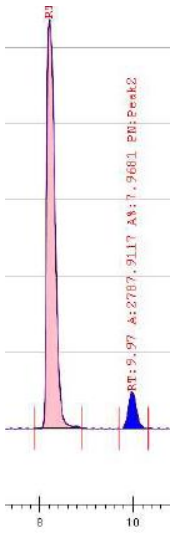
(R)-1-(benzofuran-5-yl)hexan-2-ol (3.73)

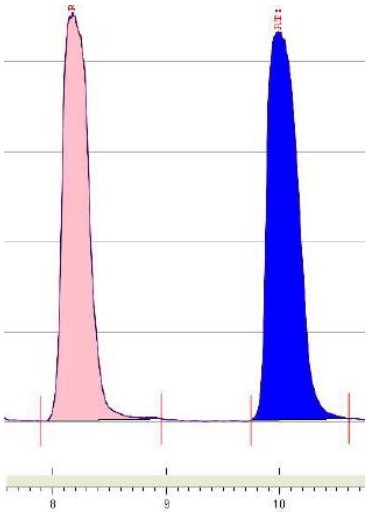
The reaction was performed according to general procedure *Method A* using 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (30.8 mg, 0.2 mmol, 1.0 equiv.), *n*-butyllithium (2.5 M in diethyl ether, 0.08 mL, 0.20 mmol, 1.0 equiv.), 5-bromobenzofuran (44.2 mg, 0.22 mmol, 1.1 equiv.), tris(dibenzylideneacetone)-dipalladium(0) (0.82 mg, 1.00 μmol, 0.005 equiv.), phosphinooxazoline **3.68** (1.11 mg, 2.40 μmol, 0.012 equiv.). The crude product was purified by automated flash column chromatography (Biotage 2% → 30% ethyl acetate in *n*-hexane, stained in CAM) to afford a colorless oil (33.6 mg, 77% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.61 (d, *J* = 2.2 Hz, 1H), 7.49 – 7.43 (m, 2H), 7.15 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.73 (d, *J* = 2.2 Hz, 1H), 3.83 (ddt, *J* = 12.6, 8.5, 4.5 Hz, 1H), 2.93 (dd, *J* = 13.7, 4.2 Hz, 1H), 2.73 (dd, *J* = 13.7, 8.5 Hz, 1H), 1.62 – 1.44 (m, 4H), 1.43 – 1.31 (m, 3H), 0.93 (t, *J* = 7.1 Hz, 3H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 154.0, 145.4, 133.1, 127.8, 125.8, 121.8, 111.4, 106.5, 73.1, 44.0, 36.6, 28.1, 22.9, 14.2.; IR (neat) ν_{max} 3389.28 (br), 2955.25 (m), 2930.48 (s), 2858.88 (m), 1538.76 (w), 1488.77 (s), 1261.81 (s), 1110.47 (m), 1030.97 (s), 735.00 (s), 425.50 (m) cm^{-1}.; HRMS (DART) for $C_{14}H_{17}O$ $[M+H-H_2O]^+$: calculated: 201.12739, found: 201.12788.; $[\alpha]^{20}_D$: -7.16 (c = 1.0 g/100 mL, $CHCl_3$, *l* = 50 mm)

Analysis of Stereochemistry: Racemic compound was prepared according to the procedure described above with $Pd_2(dba)_3$ (1 mol%) and 2-(2-(diphenylphosphino)phenyl)-4,4-dimethyl-4,5-dihydrooxazole (1.2 mol%) as the catalyst.

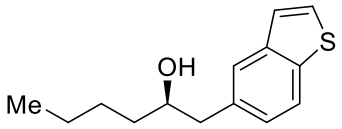
Chiral SFC (OJ-H, 5% IPA, 3ml/min, 100 bar, 35 °C, 210-270 nm) -analysis of **(R)-1-(benzofuran-5-yl)hexan-2-ol**





Peak No	% Area	Area	RT (min)
1	92.0319	32200.4984	8.2
2	7.9681	2787.9117	9.97
Total:	100	34988.4101	

Peak No	% Area	Area	RT (min)
1	47.3813	35971.2056	8.17
2	52.6187	39947.359	9.98
Total:	100	75918.5646	



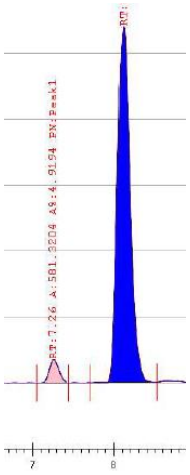
(R)-1-(benzo[b]thiophen-5-yl)hexan-2-ol (3.74)

The reaction was performed according to general procedure *Method A* (with the modification: the reaction was run with 2 % catalyst loading instead of 1 %) using 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (30.8 mg, 0.2 mmol, 1.0 equiv.), *n*-butyllithium (2.5 M in diethyl ether, 0.08 mL, 0.20 mmol, 1.0 equiv.), 5-bromobenzothiophene (45.7 mg, 0.21 mmol, 1.05 equiv.), tris(dibenzylideneacetone)-dipalladium(0) (0.82 mg, 1.00 μmol, 0.005 equiv.), phosphinooxazoline **3.68** (1.11 mg, 2.40 μmol, 0.012 equiv.). The crude product was purified by automated flash column chromatography (Biotage 4% → 30% ethyl acetate in *n*-hexane, stained in CAM) to afford a colorless oil (39.4 mg, 84% yield).

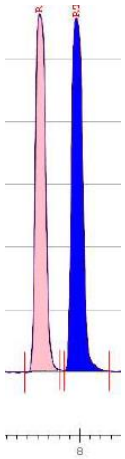
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.2 Hz, 1H), 7.67 (s, 1H), 7.43 (d, *J* = 5.4 Hz, 1H), 7.29 (dd, *J* = 5.4, 0.8 Hz, 1H), 7.20 (dd, *J* = 8.2, 1.7 Hz, 1H), 3.88 – 3.83 (m, 1H), 2.95 (dd, *J* = 13.6, 4.2 Hz, 1H), 2.75 (dd, *J* = 13.6, 8.4 Hz, 1H), 1.61 – 1.44 (m, 4H), 1.42 – 1.25 (m, 3H), 0.92 (t, *J* = 7.3 Hz, 3H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 140.1, 138.1, 134.8, 126.9, 126.1, 124.3, 123.8, 122.6, 73.0, 44.1, 36.7, 28.1, 22.9, 14.2.; IR (neat) ν_{max} 3394.91 (br), 2954.12 (s), 2929.22 (s), 2858.07 (m), 1464.89 (w), 1455.93(s), 1260.35 (w), 1050.95 (m), 1031.38 (m), 703.15 (s), 690.37 (s), 478.29 (m) cm^{-1}.; HRMS (DART) for $C_{14}H_{17}S$ $[M+H-H_2O]^+$: calculated: 217.10455, found: 217.10429.; $[\alpha]^{20}_D$: -7.80 (c = 1.0 g/100 mL, $CHCl_3$, *l* = 50 mm)

Analysis of Stereochemistry: Racemic compound was prepared according to the procedure described above with $Pd_2(dba)_3$ (1 mol%) and 2-(2-(diphenylphosphino)phenyl)-4,4-dimethyl-4,5-dihydrooxazole (1.2 mol%) as the catalyst.

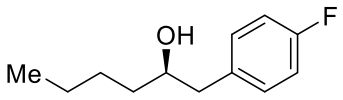
Chiral SFC (OD-H, 10% IPA, 3ml/min, 100 bar, 35 °C, 210-270 nm) -analysis of **(R)-1-(benzo[b]thiophen-5-yl)hexan-2-ol**



Peak No	% Area	Area	RT (min)
1	4.9194	581.3204	7.26
2	95.0806	11235.6493	8.12
Total:	100	11816.9697	



Peak No	% Area	Area	RT (min)
1	48.2408	37721.6787	7.23
2	51.7592	40472.9422	7.94
Total:	100	78194.6209	



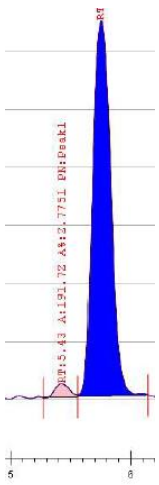
(R)-1-(4-fluorophenyl)hexan-2-ol (3.75)

The reaction was performed according to general procedure *Method A* using 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (30.8 mg, 0.2 mmol, 1.0 equiv.), *n*-butyllithium (2.5 M in diethyl ether, 0.08 mL, 0.20 mmol, 1.0 equiv.), 1-bromo-4-fluorobenzene (38.5 mg, 0.22 mmol, 1.1 equiv.), tris(dibenzylideneacetone)-dipalladium(0) (0.82 mg, 1.00 μmol, 0.005 equiv.), phosphinooxazoline **3.68** (1.11 mg, 2.40 μmol, 0.012 equiv.). The crude product was purified by automated flash column chromatography (Biotage 2% → 26% ethyl acetate in *n*-hexane, stained in CAM) to afford a white solid (28.3 mg, 72% yield).

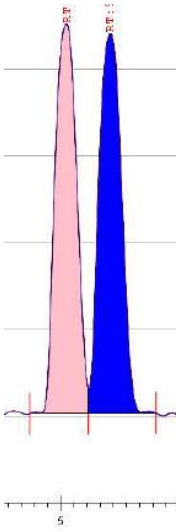
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.20 – 7.15 (m, 2H), 6.99 (t, J = 8.6 Hz, 2H), 3.77 (ddt, J = 8.4, 8.4, 4.4 Hz, 1H), 2.79 (dd, J = 13.8, 4.2 Hz, 1H), 2.62 (dd, J = 13.7, 8.3 Hz, 1H), 1.55 – 1.44 (m, 4H), 1.40 – 1.29 (m, 3H), 0.91 (t, J = 7.2 Hz, 1H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 161.8 (d, $^{1}J_{C\text{-}F}$ = 244.3 Hz), 134.5 (d, $^{4}J_{C\text{-}F}$ = 3.4 Hz), 130.9 (d, $^{3}J_{C\text{-}F}$ = 7.7 Hz), 115.4 (d, $^{2}J_{C\text{-}F}$ = 20.9 Hz), 72.80, 43.3, 36.7, 28.0, 22.8, 14.2.; ^{19}F NMR (564 MHz, $CDCl_3$) δ -116.85.; IR (neat) ν_{max} 3365.47 (br), 2956.56 (m), 2931.97 (s), 2859.60 (m), 1509.39 (s), 1222.28 (s), 1029.82 (m), 851.37 (m) cm^{-1}.; HRMS (DART) for $C_{12}H_{16}F$ $[M+H-H_2O]^+$: calculated: 179.12273, found: 179.12306.; $[\alpha]^{20}_{D}$: -13.1 (c = 1.0 g/100 mL, $CHCl_3$, l = 50 mm)

Analysis of Stereochemistry: Racemic compound was prepared according to the procedure described above with $Pd_2(dba)_3$ (1 mol%) and 2-(2-(diphenylphosphino)phenyl)-4,4-dimethyl-4,5-dihydrooxazole (1.2 mol%) as the catalyst.

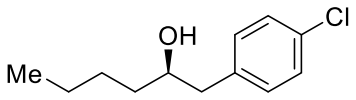
Chiral SFC (OJ-H, 3% IPA, 3ml/min, 100 bar, 35 °C, 210-270 nm) -analysis of **(R)-1-(4-fluorophenyl)hexan-2-ol**



Peak No	% Area	Area	RT (min)
1	2.7751	191.72	5.43
2	97.2249	6716.777	5.75
Total:	100	6908.497	



Peak No	% Area	Area	RT (min)
1	49.5327	5146.7451	5.05
2	50.4673	5243.846	5.38
Total:	100	10390.5911	



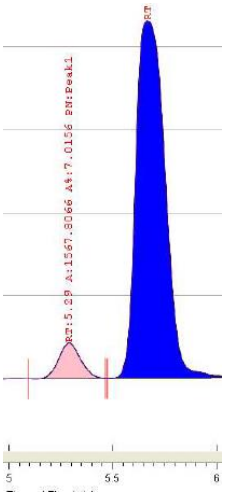
(R)-1-(4-chlorophenyl)hexan-2-ol (3.76)

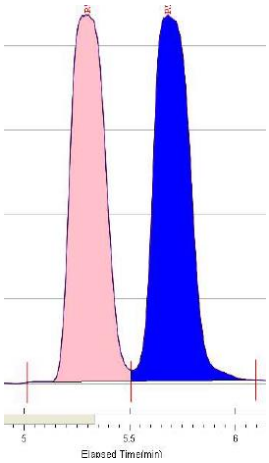
The reaction was performed according to general procedure *Method A* using 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (30.8 mg, 0.2 mmol, 1.0 equiv.), *n*-butyllithium (2.5 M in diethyl ether, 0.08 mL, 0.20 mmol, 1.0 equiv.), 1-chloro-4-iodobenzene (52.5 mg, 0.22 mmol, 1.1 equiv.), tris(dibenzylideneacetone)-dipalladium(0) (0.82 mg, 1.00 μmol, 0.005 equiv.), phosphinooxazoline **3.68** (1.11 mg, 2.40 μmol, 0.012 equiv.). The crude product was purified by automated flash column chromatography (Biotage 2% → 28% ethyl acetate in *n*-hexane, stained in CAM) to afford a white solid (37.0 mg, 58% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28 – 7.25 (m, 2H), 7.15 (d, *J* = 8.3 Hz, 2H), 3.78 (ddt, *J* = 12.0, 8.3, 4.6 Hz, 1H), 2.78 (dd, *J* = 13.8, 4.3 Hz, 1H), 2.62 (dd, *J* = 13.8, 8.3 Hz, 1H), 1.53 (s, 1H), 1.52 – 1.44 (m, 3H), 1.39 – 1.29 (m, 3H), 0.91 (t, *J* = 7.2 Hz, 3H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 137.3, 132.3, 130.9, 128.7, 72.7, 43.4, 36.7, 28.0, 22.8, 14.2.; IR (neat) ν_{max} 3356.08 (m), 3300.74 (br), 2955.07 (s), 2929.81 (s), 2857.15 (m), 1491.02 (s), 1468.67 (m), 1127.22 (m), 1017.28 (m), 803.66 (s), 649.80 (w), 477.25 (w) cm^{-1}.; HRMS (DART) for $C_{12}H_{16}Cl$ $[M+H-H_2O]^+$: calculated: 195.09350, found: 195.09368.; $[\alpha]^{20}_D$: -12.0 (c = 1.0 g/100 mL, $CHCl_3$, *l* = 50 mm)

Analysis of Stereochemistry: Racemic compound was prepared according to the procedure described above with $Pd_2(dba)_3$ (1 mol%) and 2-(2-(diphenylphosphino)phenyl)-4,4-dimethyl-4,5-dihydrooxazole (1.2 mol%) as the catalyst.

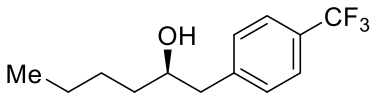
Chiral SFC (OJ-H, 5% IPA, 3ml/min, 100 bar, 35 °C, 210-270 nm) -analysis of **(R)-1-(4-chlorophenyl)hexan-2-ol**





Peak No	% Area	Area	RT (min)
1	7.0156	1567.8066	5.29
2	92.9844	20779.6736	5.67
Total:	100	22347.4802	

Peak No	% Area	Area	RT (min)
1	48.9687	24695.3745	5.3
2	51.0313	25735.5567	5.68
Total:	100	50430.9312	



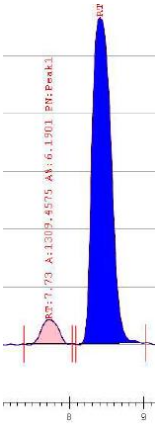
(R)-1-(4-(trifluoromethyl)phenyl)hexan-2-ol (3.77)

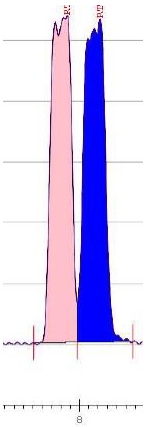
The reaction was performed according to general procedure *Method A* using 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (30.8 mg, 0.2 mmol, 1.0 equiv.), *n*-butyllithium (2.5 M in diethyl ether, 0.08 mL, 0.20 mmol, 1.0 equiv.), 1-iodo-4-(trifluoromethyl)benzene (63.0 mg, 0.22 mmol, 1.1 equiv.), tris(dibenzylideneacetone)-dipalladium(0) (0.82 mg, 1.00 μmol, 0.005 equiv.), phosphinooxazoline **3.68** (1.11 mg, 2.40 μmol, 0.012 equiv.). The crude product was purified by automated flash column chromatography (Biotage 2% → 25% ethyl acetate in *n*-hexane, stained in CAM) to afford a white solid (33.5 mg, 68% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 7.9 Hz, 2H), 3.84 (ddt, *J* = 8.7, 7.3, 4.4 Hz, 1H), 2.87 (dd, *J* = 13.6, 4.2 Hz, 1H), 2.72 (dd, *J* = 13.7, 8.3 Hz, 1H), 1.58 – 1.43 (m, 4H), 1.41 – 1.30 (m, 3H), 0.92 (t, *J* = 7.2 Hz, 3H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 143.2, 129.9, 128.9 (q, $^{2}J_{C\text{-}F}$ = 32.6 Hz), 125.5 (q, $^{3}J_{C\text{-}F}$ = 3.6 Hz), 124.4 (q, $^{1}J_{C\text{-}F}$ = 271.7 Hz), 72.6, 43.9, 36.9, 28.0, 22.8, 14.2.; ^{19}F NMR (564 MHz, $CDCl_3$) δ -62.76.; IR (neat) ν_{max} 3355.39 (w), 3287.02 (br), 2960.82 (w), 2929.69 (m), 2857.31 (m), 1327.31 (s), 1160.46 (m), 1107.42 (s), 1067.53 (m), 819.55 (m), 641.69 (w) cm^{-1}.; HRMS (DART) for $C_{13}H_{21}NOF_3$ $[M+NH_4]^+$: calculated: 264.15698, found: 264.15685.; $[\alpha]^{20}_D$: -12.1 (c = 1.0 g/100 mL, $CHCl_3$, *l* = 50 mm)

Analysis of Stereochemistry: Racemic compound was prepared according to the procedure described above with $Pd_2(dba)_3$ (1 mol%) and 2-(2-(diphenylphosphino)phenyl)-4,4-dimethyl-4,5-dihydrooxazole (1.2 mol%) as the catalyst.

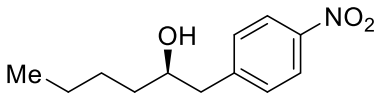
Chiral SFC (OJ-H, 1% IPA, 3ml/min, 100 bar, 35 °C, 210-270 nm) -analysis of **(R)-1-(4-(trifluoromethyl)phenyl)hexan-2-ol**





Peak No	% Area	Area	RT (min)
1	6.1901	1309.4575	7.73
2	93.8099	19844.5698	8.41
Total:	100	21154.0273	

Peak No	% Area	Area	RT (min)
1	49.4523	16116.8765	7.74
2	50.5477	16473.8533	8.44
Total:	100	32590.7298	



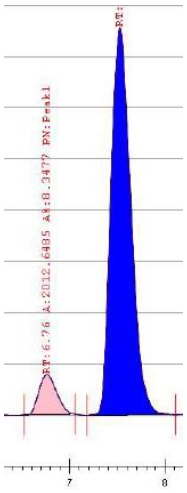
(R)-1-(4-nitrophenyl)hexan-2-ol (3.78)

The reaction was performed according to general procedure *Method A* using 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (30.8 mg, 0.2 mmol, 1.0 equiv.), *n*-butyllithium (2.5 M in diethyl ether, 0.08 mL, 0.20 mmol, 1.0 equiv.), 1-iodo-4-nitro-benzene (57.7 mg, 0.22 mmol, 1.1 equiv.), tris(dibenzylideneacetone)-dipalladium(0) (0.82 mg, 1.00 μmol, 0.005 equiv.), phosphinooxazoline **3.68** (1.11 mg, 2.40 μmol, 0.012 equiv.). The crude product was purified by automated flash column chromatography (Biotage 2% → 28% ethyl acetate in *n*-hexane, stained in CAM) to afford an orange solid (38.2 mg, 57% yield).

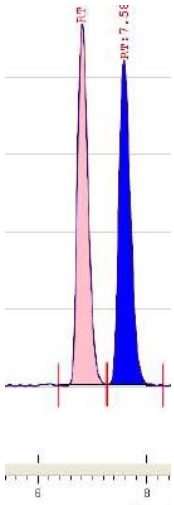
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.6 Hz, 2H), 7.39 (d, *J* = 8.6 Hz, 2H), 3.87 (ddt, J = 8.3, 8.3, 4.5 Hz, 1H), 2.91 (dd, *J* = 13.7, 4.2 Hz, 1H), 2.78 (dd, *J* = 13.7, 8.3 Hz, 1H), 1.60 – 1.42 (m, 4H), 1.39 – 1.28 (m, 3H), 0.91 (t, *J* = 7.2 Hz, 3H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 147.0, 146.8, 130.4, 123.7, 72.5, 43.8, 37.0, 27.9, 22.8, 14.2.; IR (neat) ν_{max} 3332.23 (br), 2931.78 (m), 2858.33 (w), 1605.60 (w), 1517.05 (s), 1344.12 (s), 1106.83 (m), 840.82 (m), 651.51 (w) cm^{-1}.; HRMS (DART) for $C_{12}H_{18}NO_3$ $[M+H]^+$: calculated: 224.12812, found: 224.12872.; $[\alpha]^{20}_D$: -16.4 (c = 1.0 g/100 mL, $CHCl_3$, *l* = 50 mm)

Analysis of Stereochemistry: Racemic compound was prepared according to the procedure described above with $Pd_2(dba)_3$ (1 mol%) and 2-(2-(diphenylphosphino)phenyl)-4,4-dimethyl-4,5-dihydrooxazole (1.2 mol%) as the catalyst.

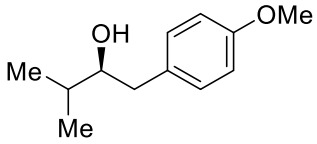
Chiral SFC (AD-H, 10% IPA, 3ml/min, 100 bar, 35 °C, 210-270 nm) -analysis of **(R)-1-(4-nitrophenyl)hexan-2-ol**



Peak No	% Area	Area	RT (min)
1	8.3477	2012.6485	6.76
2	91.6523	22097.5416	7.52
Total:	100	24110.1901	



Peak No	% Area	Area	RT (min)
1	50.326	12763.1538	6.8
2	49.674	12597.8197	7.58
Total:	100	25360.9735	



(S)-1-(4-methoxyphenyl)-3-methylbutan-2-ol (3.79)

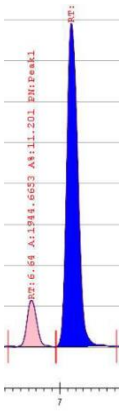
The reaction was performed according to general procedure *Method A* using 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (30.8 mg, 0.2 mmol, 1.0 equiv.), *iso*-propyl lithium (0.7 M in pentane, 0.28 mL, 0.20 mmol, 1.0 equiv.), 4-bromoanisole (41.2 mg, 0.22 mmol, 1.1 equiv.), tris(dibenzylideneacetone)-dipalladium(0) (0.82 mg, 1.00 μmol, 0.005 equiv.), phosphinooxazoline **3.68** (1.11 mg, 2.40 μmol, 0.012 equiv.). The crude product was purified by automated flash column chromatography (Biotage 2% → 30% ethyl acetate in *n*-hexane, stained in CAM) to afford a colorless oil (29.5 mg, 76% yield).

Method B using 2-isopropyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (34.0 mg, 0.2 mmol, 1.0 equiv.), vinyl magnesium bromide (1.0 M in tetrahydrofuran, 0.24 mL, 0.24 mmol, 1.2 equiv.), 4-bromoanisole (41.2 mg, 0.22 mmol, 1.1 equiv.), tris(dibenzylideneacetone)-dipalladium(0) (1.83 mg, 2.0 μmol, 0.01 equiv.), phosphinooxazoline **3.68** (2.23 mg, 4.80 μmol, 0.024 equiv.). The crude product was purified by automated flash column chromatography (Biotage 2% → 30% ethyl acetate in *n*-hexane, stained in CAM) to afford a colorless oil (25.6 mg, 66% yield).

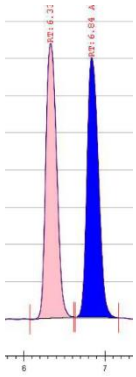
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.13 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 3.78 (s, 3H), 3.53 (ddd, J = 9.2, 5.2, 3.6 Hz, 1H), 2.79 (dd, J = 13.8, 3.6 Hz, 1H), 2.53 (dd, J = 13.8, 9.4 Hz, 1H), 1.73 (pd, J = 6.9, 5.3 Hz, 1H), 1.45 (s, 1H), 0.98 (d, J = 6.8 Hz, 3H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.4, 131.2, 130.4, 114.2, 77.7, 55.4, 40.0, 33.2, 19.1, 17.6.; IR (neat) ν_{max} 3482.50 (br), 2957.92 (m), 2835.71 (w), 1612.31 (w), 1540.53 (s), 1512.52 (m), 1300.43 (s), 1109.62 (m), 820.53 (w) cm^{-1}.; HRMS (DART) for $C_{12}H_{17}O$ $[M+H-H_2O]^+$: calculated: 177.12739, found: 177.12685.; $[\alpha]^{20}_D$: -23.4 (c = 1.0 g/100 mL, $CHCl_3$, *l* = 50 mm)

Analysis of Stereochemistry: Racemic compound was prepared according to the procedure described above with $Pd_2(dba)_3$ (1 mol%) and 2-(2-(diphenylphosphino)phenyl)-4,4-dimethyl-4,5-dihydrooxazole (1.2 mol%) as the catalyst.

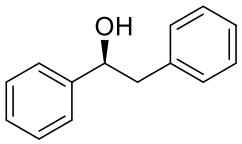
Chiral SFC (OJ-H, 5% IPA, 3ml/min, 100 bar, 35 °C, 210-270 nm) -analysis of **(S)-1-(4-methoxyphenyl)-3-methylbutan-2-ol**



Peak No	% Area	Area	RT (min)
1	11.201	1944.6653	6.64
2	88.799	15416.9076	7.15
Total:	100	17361.5729	



Peak No	% Area	Area	RT (min)
1	50.1997	13691.9722	6.33
2	49.8003	13583.0483	6.84
Total:	100	27275.0205	



(S)-1,2-diphenylethan-1-ol (3.80)

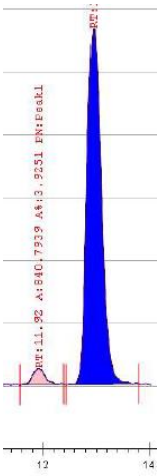
The reaction was performed according to general procedure *Method A* (with the modification: the reaction was run with 5 % catalyst loading instead of 1 %) using 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (30.8 mg, 0.2 mmol, 1.0 equiv.), phenyllithium (1.9 M in dibutyl ether, 0.28 mL, 0.11 mmol, 1.0 equiv.), 1-bromo-4-methoxy-benzene (41.2 mg, 0.22 mmol, 1.1 equiv.), tris(dibenzylideneacetone)-dipalladium(0) (4.1 mg, 5 μmol, 0.025 equiv.), phosphinooxazoline **3.68** (5.55 mg, 0.012 mmol, 0.06 equiv.). The crude product was purified by automated flash column chromatography (Biotage 2% → 28% ethyl acetate in *n*-hexane, stained in CAM) to afford a white solid (30.1 mg, 76% yield). All spectral data were in accordance with the literature.[184]

Method B using 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (40.8 mg, 0.2 mmol, 1.0 equiv.), vinyl magnesium bromide (1.0 M in tetrahydrofuran, 0.24 mL, 0.24 mmol, 1.2 equiv.), phenyl trifluoromethanesulfonate (49.8 mg, 0.22 mmol, 1.1 equiv.) tris(dibenzylideneacetone)-dipalladium(0) (1.83 mg, 2.0 μmol, 0.01 equiv.), phosphinooxazoline **3.68** (2.23 mg, 4.80 μmol, 0.024 equiv.). The crude product was purified by automated flash column chromatography (Biotage 2% → 28% ethyl acetate in *n*-hexane, stained in CAM) to afford a white solid (30.1 mg, 76% yield). All spectral data were in accordance with the literature.[179]

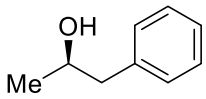
Analysis of Stereochemistry: Racemic compound was prepared in a previous publication. This enriched sample was subject to the same chiral SFC conditions and similar retention times were observed.[179]

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

Chiral SFC (OD-H, 5% IPA, 3ml/min, 100 bar, 35 °C, 210-270 nm) -analysis of **(S)-1,2-diphenylethan-1-ol**



Peak No	% Area	Area	RT (min)
1	3.9251	840.7939	11.92
2	96.0749	20579.9959	12.95
Total:	100	21420.7898	

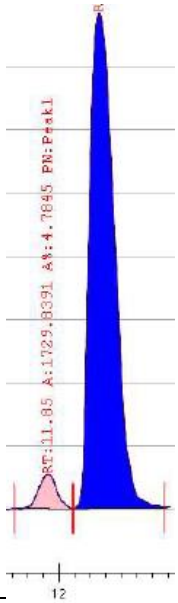


(R)-1-phenylpropan-2-ol (3.81)

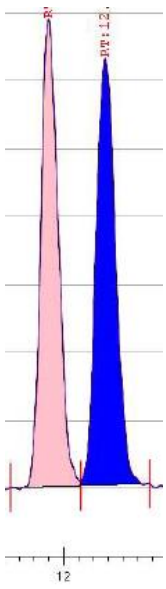
The reaction was performed according to general procedure *Method A* using 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (30.8 mg, 0.2 mmol, 1.0 equiv.), methyl lithium (1.6 M in diethyl ether, 0.125 mL, 0.20 mmol, 1.0 equiv.), bromobenzene (34.5 mg, 0.22 mmol, 1.1 equiv.), tris(dibenzylideneacetone)-dipalladium(0) (0.82 mg, 1.00 µmol, 0.005 equiv.), phosphinooxazoline **3.3** (1.11 mg, 2.40 µmol, 0.012 equiv.). The crude product was purified by automated flash column chromatography (Biotage 2% → 20% ethyl acetate in *n*-hexane, stained in CAM) to afford a colorless oil (10.9 mg, 40% yield). All spectral data were in accordance with the literature.[185]

Analysis of Stereochemistry: Racemic compound was purchased from Sigma Aldrich (CAS: [14898-87-4]).

Chiral SFC (OJ-H, 1% IPA, 3ml/min, 100 bar, 35 °C, 210-270 nm) -analysis of **(R)-1-phenylpropan-2-ol**

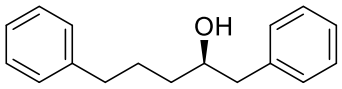


Peak No	% Area	Area	RT (min)
1	4.7845	1729.8391	11.85
2	95.2155	34425.3013	12.52
Total:	100	36155.1404	



Peak No	% Area	Area	RT (min)
1	49.5046	11280.6927	11.79
2	50.4954	11506.4487	12.56
Total:	100	22787.1414	

[1] 2413.



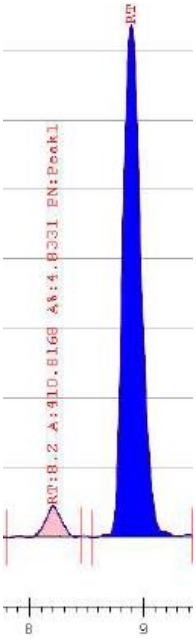
(R)-1,5-diphenylpentan-2-ol (3.82)

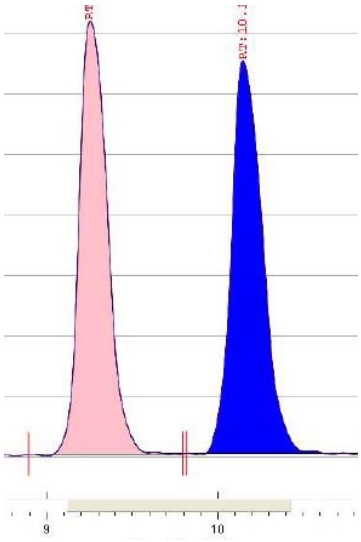
The reaction was performed according to general procedure *Method B* using 4,4,5,5-tetramethyl-2-(3-phenylpropyl)-1,3,2-dioxaborolane (49.2 mg, 0.2 mmol, 1.0 equiv.), vinyl magnesium bromide (1.0 M in tetrahydrofuran, 0.24 mL, 0.24 mmol, 1.2 equiv.), iodobenzene (44.9 mg, 0.22 mmol, 1.1 equiv.), tris(dibenzylideneacetone)-dipalladium(0) (1.83 mg, 2.0 μmol, 0.01 equiv.), phosphinooxazoline **3.68** (2.23 mg, 4.80 μmol, 0.024 equiv.). The crude product was purified by automated flash column chromatography (Biotage 2% → 28% ethyl acetate in *n*-hexane, stained in CAM) to afford a colorless oil (38.5 mg, 80% yield). All spectral data were in accordance with the literature.[186]

Analysis of Stereochemistry: Racemic compound was prepared according to the procedure described above with $Pd_2(dba)_3$ (1 mol%) and 2-(2-(diphenylphosphino)phenyl)-4,4-dimethyl-4,5-dihydrooxazole (1.2 mol%) as the catalyst.

Chiral SFC (OJ-H, 9% IPA, 3ml/min, 100 bar, 35 °C, 210-270 nm) -analysis of **(R)-1,5-diphenylpentan-2-ol**

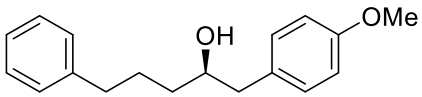
[186] Chierchia, M.; Law, C.; Morken, J. P.; *Angew. Chem. Int. Ed.* **2017**, *56*, 11870





Peak No	% Area	Area	RT (min)
1	4.8331	410.8168	8.2
2	95.1669	8089.2752	8.89
Total:	100	8500.092	

Peak No	% Area	Area	RT (min)
1	49.9923	8174.1298	9.25
2	50.0077	8176.6332	10.15
Total:	100	16350.763	



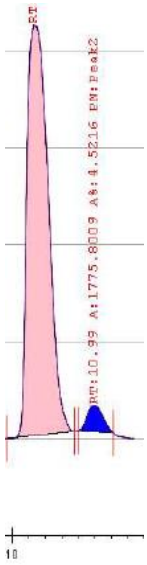
(R)-1-(4-methoxyphenyl)-5-phenylpentan-2-ol (3.83)

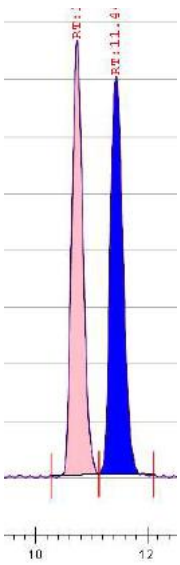
The reaction was performed according to general procedure *Method B* using 4,4,5,5-tetramethyl-2-(3-phenylpropyl)-1,3,2-dioxaborolane (49.2 mg, 0.2 mmol, 1.0 equiv.), vinyl magnesium bromide (1.0 M in tetrahydrofuran, 0.24 mL, 0.24 mmol, 1.2 equiv.), 4-bromoanisole (41.2 mg, 0.22 mmol, 1.1 equiv.), tris(dibenzylideneacetone)-dipalladium(0) (1.83 mg, 2.0 μmol, 0.01 equiv.), phosphinooxazoline **3.68** (2.23 mg, 4.80 μmol, 0.024 equiv.). The crude product was purified by automated flash column chromatography (Biotage 2% → 30% ethyl acetate in *n*-hexane, stained in CAM) to afford a colorless oil (45.4 mg, 84% yield).

Analysis of Stereochemistry: Racemic compound was prepared according to the procedure described above with $Pd_2(dba)_3$ (1 mol%) and 2-(2-(diphenylphosphino)phenyl)-4,4-dimethyl-4,5-dihydrooxazole (1.2 mol%) as the catalyst.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 2H), 7.23 – 7.18 (m, 3H), 7.13 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 3.81 (s, 3H), 3.80 – 3.77 (m, 1H), 2.78 (dd, *J* = 13.7, 4.2 Hz, 1H), 2.66 (ddd, *J* = 8.3, 6.7, 3.3 Hz, 2H), 2.59 (dd, *J* = 13.7, 8.4 Hz, 1H), 1.91 – 1.82 (m, 1H), 1.78 – 1.68 (m, 1H), 1.63 – 1.51 (m, 3H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.4, 142.5, 130.5, 130.5, 128.5, 128.4, 125.8, 114.1, 72.7, 55.4, 43.2, 36.4, 36.0, 27.7.; IR (neat) ν_{max} 3415.05 (br), 2934.10 (s), 1611.55 (m), 1511.43 (s), 1246.08 (s), 1178.04 (m), 1035.04 (m), 818.38 (br), 699.82 (s) cm^{-1}.; HRMS (DART) for $C_{18}H_{26}NO_2$ $[M+NH_4]^+$: calculated: 288.19581, found: 288.19610.; $[\alpha]^{20}_D$: -4.10 (c = 1.0 g/100 mL, $CHCl_3$, *l* = 50 mm)

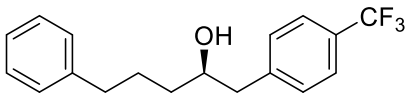
Chiral SFC (OD-H, 10% IPA, 3ml/min, 100 bar, 35 °C, 210-270 nm) -analysis of **(R)-1-(4-methoxyphenyl)-5-phenylpentan-2-ol**





Peak No	% Area	Area	RT (min)
1	95.4784	37497.7287	10.26
2	4.5216	1775.8009	10.99
Total:	100	39273.5296	

Peak No	% Area	Area	RT (min)
1	49.1915	10739.772	10.74
2	50.8085	11092.8179	11.44
Total:	100	21832.5899	



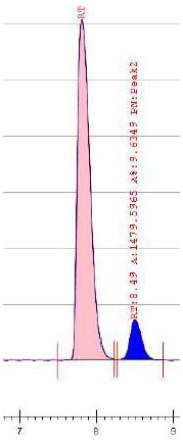
(R)-5-phenyl-1-(4-(trifluoromethyl)phenyl)pentan-2-ol (3.84)

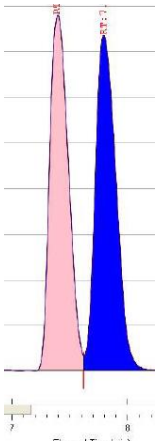
The reaction was performed according to general procedure *Method B* using 4,4,5,5-tetramethyl-2-(3-phenylpropyl)-1,3,2-dioxaborolane (49.2 mg, 0.2 mmol, 1.0 equiv.), vinyl magnesium bromide (1.0 M in tetrahydrofuran, 0.24 mL, 0.24 mmol, 1.2 equiv.), 1-bromo-4-(trifluoromethyl)benzene (50.5 mg, 0.22 mmol, 1.1 equiv.), tris(dibenzylideneacetone)-dipalladium(0) (1.83 mg, 2.0 μmol, 0.01 equiv.), phosphinooxazoline **3.68** (2.23 mg, 4.80 μmol, 0.024 equiv.). The crude product was purified by automated flash column chromatography (Biotage 2% → 25% ethyl acetate in *n*-hexane, stained in CAM) to afford a white solid (47.5 mg, 77% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.0 Hz, 2H), 7.31 (dd, *J* = 15.3, 7.8 Hz, 4H), 7.23 – 7.17 (m, 3H), 3.90 – 3.80 (m, 1H), 2.86 (dd, *J* = 13.6, 4.3 Hz, 1H), 2.73 (dd, *J* = 13.7, 8.3 Hz, 1H), 2.72 – 2.61 (m, 2H), 1.93 – 1.82 (m, 1H), 1.77 – 1.68 (m, 1H), 1.65 – 1.50 (m, 3H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 143.0, 142.3, 129.9, 128.9 (q, $^{2}J_{C\text{-}F}$ = 32.4 Hz), 128.53, 128.48, 126.0, 125.5 (q, $^{3}J_{C\text{-}F}$ = 4.0 Hz), 124.4 (q, $^{1}J_{C\text{-}F}$ = 271.7 Hz), 72.4, 43.9, 36.6, 35.9, 27.6.; ^{19}F NMR (564 MHz, $CDCl_3$) δ -62.38.; IR (neat) ν_{max} 3380.72 (br), 3063.31 (w), 2937.75 (m), 2859.70 (m), 1418.06 (w), 1325.00 (s), 1122.25 (s), 1019.51 (s), 749.77 (w), 699.65 (m) cm^{-1}.; HRMS (DART) for $C_{18}H_{18}F_3$ $[M+H-H_2O]^+$: calculated: 291.13551, found: 291.13644.; $[\alpha]^{20}_D$: -3.10 (c = 1.0 g/100 mL, $CHCl_3$, *l* = 50 mm)

Analysis of Stereochemistry: Racemic compound was prepared according to the procedure described above with $Pd_2(dba)_3$ (1 mol%) and 2-(2-(diphenylphosphino)phenyl)-4,4-dimethyl-4,5-dihydrooxazole (1.2 mol%) as the catalyst.

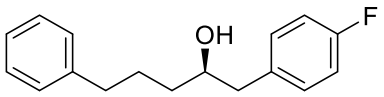
Chiral SFC (OJ-H, 7% IPA, 3ml/min, 100 bar, 35 °C, 210-270 nm) -analysis of **(R)-5-phenyl-1-(4-(trifluoromethyl)phenyl)pentan-2-ol**





Peak No	% Area	Area	RT (min)
1	90.3651	13876.9727	7.81
2	9.6349	1479.5965	8.49
Total:	100	15356.5692	

Peak No	% Area	Area	RT (min)
1	48.9591	17462.7338	7.39
2	51.0409	18205.2436	7.79
Total:	100	35667.9774	



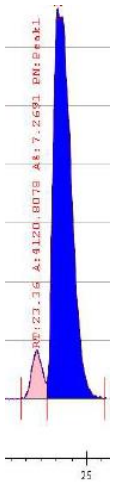
(R)-1-(4-fluorophenyl)-5-phenylpentan-2-ol (3.85)

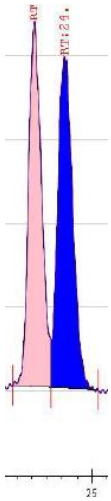
The reaction was performed according to general procedure *Method B* using 4,4,5,5-tetramethyl-2-(3-phenylpropyl)-1,3,2-dioxaborolane (49.2 mg, 0.2 mmol, 1.0 equiv.), vinyl magnesium bromide (1.0 M in tetrahydrofuran, 0.24 mL, 0.24 mmol, 1.2 equiv.), 1-bromo-4-fluorobenzene (38.5 mg, 0.22 mmol, 1.1 equiv.), tris(dibenzylideneacetone)-dipalladium(0) (1.83 mg, 2.0 μmol, 0.01 equiv.), phosphinooxazoline **3.68** (2.23 mg, 4.80 μmol, 0.024 equiv.). The crude product was purified by automated flash column chromatography (Biotage 2% → 25% ethyl acetate in *n*-hexane, stained in CAM) to afford a white solid (40.8 mg, 79% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30 (t, J = 7.5 Hz, 2H), 7.21 (t, J = 8.1 Hz, 3H), 7.16 (dd, J = 8.4, 5.5 Hz, 2H), 7.01 (t, J = 8.6 Hz, 2H), 3.81 (ddt, J = 8.2, 4.1, 3.9 Hz, 1H), 2.79 (dd, J = 13.8, 4.3 Hz, 1H), 2.71 – 2.61 (m, 1H), 1.91 – 1.82 (m, 1H), 1.77 – 1.68 (m, 1H), 1.62 – 1.51 (m, 3H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 161.8 (d, $^{1}J_{C\text{-}F}$ = 244.5 Hz), 142.4, 134.3 (d, $^{4}J_{C\text{-}F}$ = 3.1 Hz), 130.9 (d, $^{3}J_{C\text{-}F}$ = 7.7 Hz), 128.53, 128.45, 125.9, 115.4 (d, $^{2}J_{C\text{-}F}$ = 21.1 Hz), 72.6, 43.2, 36.4, 35.9, 27.7.; ^{19}F NMR (564 MHz, CDCl3) δ -116.77.; IR (neat) ν_{max} 3350.47 (m), 3280.51 (br), 3027.74 (w), 2941.00 (m), 2858.49 (m), 1601.97 (w), 1509.43 (s), 1217.95 (s), 1090.40 (m), 851.56 (m), 764.43 (s), 697.70 (s), 567.38 (m) cm^{-1}.; HRMS (DART) for $C_{17}H_{18}F$ $[M+H-H_2O]^+$: calculated: 241.13871, found: 241.13931.; $[\alpha]^{20}_{D}$: -3.47 (c = 1.0 g/100 mL, $CHCl_3$, l = 50 mm)

Analysis of Stereochemistry: Racemic compound was prepared according to the procedure described above with $Pd_2(dba)_3$ (1 mol%) and 2-(2-(diphenylphosphino)phenyl)-4,4-dimethyl-4,5-dihydrooxazole (1.2 mol%) as the catalyst.

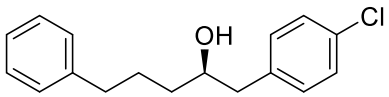
Chiral SFC (OD-H, 4% IPA, 3ml/min, 100 bar, 35 °C, 210-270 nm) -analysis of **(R)-1-(4-fluorophenyl)-5-phenylpentan-2-ol**





Peak No	% Area	Area	RT (min)
1	7.2691	4120.8078	23.36
2	92.7309	52568.4952	24.06
Total:	100	56689.303	

Peak No	% Area	Area	RT (min)
1	50.3712	13241.8986	23.08
2	49.6288	13046.7373	24.09
Total:	100	26288.6359	

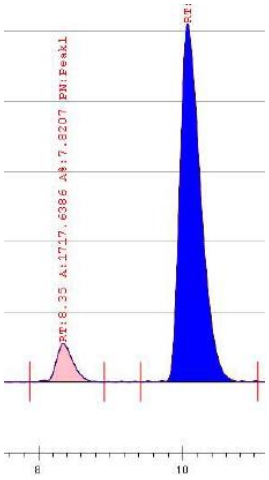


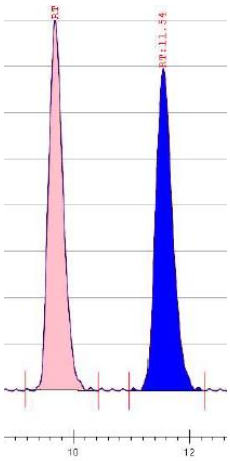
(R)-1-(4-chlorophenyl)-5-phenylpentan-2-ol (3.86)

The reaction was performed according to general procedure *Method B* using 4,4,5,5-tetramethyl-2-(3-phenylpropyl)-1,3,2-dioxaborolane (49.2 mg, 0.2 mmol, 1.0 equiv.), vinyl magnesium bromide (1.0 M in tetrahydrofuran, 0.24 mL, 0.24 mmol, 1.2 equiv.), 1-bromo-4-chlorobenzene (42.1 mg, 0.22 mmol, 1.1 equiv.), tris(dibenzylideneacetone)-dipalladium(0) (1.83 mg, 2.0 μmol, 0.01 equiv.), phosphinooxazoline **3.68** (2.23 mg, 4.80 μmol, 0.024 equiv.). The crude product was purified by automated flash column chromatography (Biotage 2% → 28% ethyl acetate in *n*-hexane, stained in CAM) to afford a white solid (44.5 mg, 81% yield).

Analysis of Stereochemistry: Racemic compound was prepared according to the procedure described above with $Pd_2(dba)_3$ (1 mol%) and 2-(2-(diphenylphosphino)phenyl)-4,4-dimethyl-4,5-dihydrooxazole (1.2 mol%) as the catalyst.

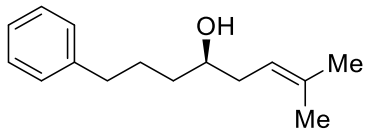
Chiral SFC (AD-H, 10% IPA, 3ml/min, 100 bar, 35 °C, 210-270 nm) -analysis of **(R)-1-(4-chlorophenyl)-5-phenylpentan-2-ol**





Peak No	% Area	Area	RT (min)
1	7.8207	1717.6386	8.35
2	92.1793	20245.1548	10.07
Total:	100	21962.7934	

Peak No	% Area	Area	RT (min)
1	49.8937	7070.5625	9.68
2	50.1063	7100.6955	11.54
Total:	100	14171.258	



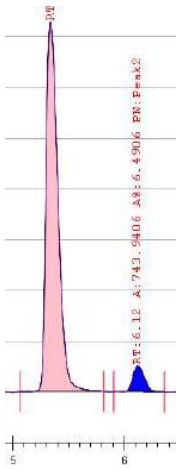
(R)-7-methyl-1-phenyloct-6-en-4-ol (3.87)

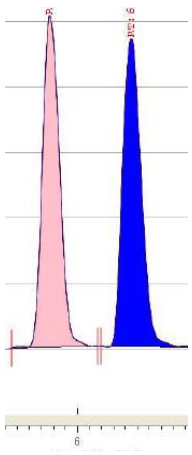
The reaction was performed according to general procedure *Method B* using 4,4,5,5-tetramethyl-2-(3-phenylpropyl)-1,3,2-dioxaborolane (49.2 mg, 0.2 mmol, 1.0 equiv.), vinyl magnesium bromide (1.0 M in tetrahydrofuran, 0.24 mL, 0.24 mmol, 1.2 equiv.), 1-bromo-2-methylprop-1-ene (29.7 mg, 0.22 mmol, 1.1 equiv.), tris(dibenzylideneacetone)-dipalladium(0) (1.83 mg, 2.0 μmol, 0.01 equiv.), phosphinooxazoline **3.68** (2.23 mg, 4.80 μmol, 0.024 equiv.). The crude product was purified by automated flash column chromatography (Biotage 2% → 24% ethyl acetate in *n*-hexane, stained in CAM) to afford a colorless oil (23.1 mg, 53% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28 (t, *J* = 7.6 Hz, 2H), 7.21 – 7.15 (m, 3H), 5.19 – 5.13 (m, 1H), 3.62 (ddt, *J* = 12.2, 7.4, 4.8 Hz, 1H), 2.70 – 2.59 (m, 2H), 2.22 – 2.09 (m, 2H), 1.86 – 1.77 (m, 1H), 1.74 (s, 3H), 1.72 – 1.65 (m, 1H), 1.64 (s, 3H), 1.56 (d, *J* = 4.1 Hz, 1H), 1.55 – 1.47 (m, 2H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 142.6, 135.4, 128.6, 128.4, 125.8, 120.2, 71.7, 36.5, 36.4, 36.1, 27.8, 26.1, 18.1.; IR (neat) ν_{max} 3362.01 (br), 3062.38 (m), 3026.21 (m), 2965.80 (s), 2857.97 (s),1496.15 (m), 1472.67 (s), 1453.26 (m), 1375.69 (m), 1083.03 (m), 875.17 (w), 748.24 (s), 698.52 (s) cm^{-1}.; HRMS (DART) for $C_{15}H_{21}$ $[M+H-H_2O]^+$: calculated: 201.16335, found: 201.16378.; $[\alpha]^{20}_D$: -5.00 (c = 1.0 g/100 mL, $CHCl_3$, *l* = 50 mm

Analysis of Stereochemistry: Racemic compound was prepared according to the procedure described above with $Pd_2(dba)_3$ (1 mol%) and 2-(2-(diphenylphosphino)phenyl)-4,4-dimethyl-4,5-dihydrooxazole (1.2 mol%) as the catalyst.

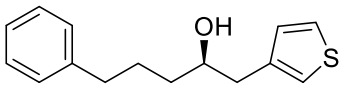
Chiral SFC (OJ-H, 5% IPA, 3ml/min, 100 bar, 35 °C, 210-270 nm) -analysis of **(R)-7-methyl-1-phenyloct-6-en-4-ol**





Peak No	% Area	Area	RT (min)
1	93.5094	10717.9072	5.34
2	6.4906	743.9406	6.12
Total:	100	11461.8478	

Peak No	% Area	Area	RT (min)
1	49.7127	9957.2566	5.77
2	50.2873	10072.3468	6.45
Total:	100	20029.6034	



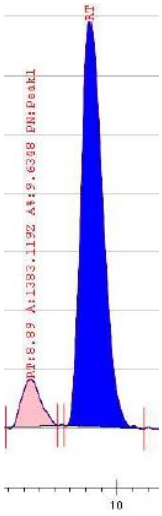
(R)-5-phenyl-1-(thiophen-3-yl)pentan-2-ol (3.89)

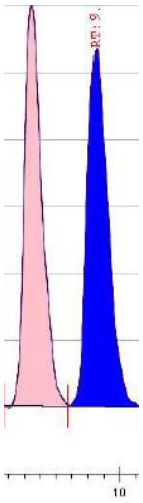
The reaction was performed according to general procedure *Method B* using 4,4,5,5-tetramethyl-2-(3-phenylpropyl)-1,3,2-dioxaborolane (49.2 mg, 0.2 mmol, 1.0 equiv.), vinyl magnesium bromide (1.0 M in tetrahydrofuran, 0.24 mL, 0.24 mmol, 1.2 equiv.), 3-bromothiophene (35.9 mg, 0.22 mmol, 1.1 equiv.), tris(dibenzylideneacetone)-dipalladium(0) (1.83 mg, 2.0 μmol, 0.01 equiv.), phosphinooxazoline **3.68** (2.23 mg, 4.80 μmol, 0.024 equiv.). The crude product was purified by automated flash column chromatography (Biotage 2% → 30% ethyl acetate in *n*-hexane, stained in CAM) to afford a colorless oil (24.6 mg, 50% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29 (t, *J* = 7.6 Hz, 3H), 7.21 – 7.17 (m, 3H), 7.03 – 7.02 (m, 1H), 6.96 (d, *J* = 4.9 Hz, 1H), 3.83 (ddt, *J* = 8.2, 8.2, 4.2 Hz, 1H), 2.84 (dd, *J* = 14.2, 4.1 Hz, 1H), 2.71 (dd, *J* = 14.2, 8.4 Hz, 1H), 2.65 (t, *J* = 7.6 Hz, 2H), 1.89 – 1.79 (m, 1H), 1.76 – 1.67 (m, 1H), 1.61 – 1.50 (m, 3H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 142.5, 138.8, 128.8, 128.6, 128.5, 126.0, 125.9, 122.2, 71.9, 38.5, 36.4, 36.0, 27.7.; IR (neat) ν_{max} 3547.09 (w), 3383.94 (br), 3025.39 (m), 2935.19 (s), 2858.21 (m), 1495.17 (m), 1453.00 (s), 1082.07 (m), 774.95 (s), 749.63 (s), 699.17 (s), 636.39 (m), 478.05 (w) cm^{-1}.; HRMS (DART) for $C_{15}H_{17}S$ $[M+H-H_2O]^+$: calculated: 229.10455, found: 229.10563.; $[\alpha]^{20}_D$: -2.75 (c = 1.0 g/100 mL, $CHCl_3$, *l* = 50 mm)

Analysis of Stereochemistry: Racemic compound was prepared according to the procedure described above with $Pd_2(dba)_3$ (1 mol%) and 2-(2-(diphenylphosphino)phenyl)-4,4-dimethyl-4,5-dihydrooxazole (1.2 mol%) as the catalyst.

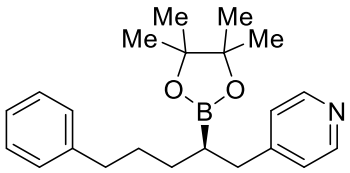
Chiral SFC (AD-H, 10% IPA, 3ml/min, 100 bar, 35 °C, 210-270 nm) -analysis of **(R)-5-phenyl-1-(thiophen-3-yl)pentan-2-ol**





Peak No	% Area	Area	RT (min)
1	9.6348	1383.1192	8.89
2	90.3652	12972.293	9.65
Total:	100	14355.4122	

Peak No	% Area	Area	RT (min)
1	49.3139	9325.338	8.89
2	50.6861	9584.8151	9.71
Total:	100	18910.1531	



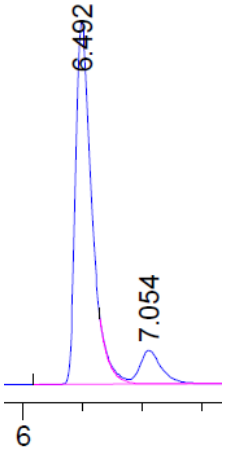
(R)-4-(5-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentyl)pyridine (3.90)

The reaction was performed according to general procedure *Method B* (with the modification: the boronate ester product was directly isolated without further oxidation) using 4,4,5,5-tetramethyl-2-(3-phenylpropyl)-1,3,2-dioxaborolane (49.2 mg, 0.2 mmol, 1.0 equiv.), vinyl magnesium bromide (1.0 M in tetrahydrofuran, 0.24 mL, 0.24 mmol, 1.2 equiv.), 4-iodopyridine (45.1 mg, 0.22 mmol, 1.1 equiv.), tris(dibenzylideneacetone)-dipalladium(0) (1.83 mg, 2.0 μmol, 0.01 equiv.), phosphinooxazoline **3.68** (2.23 mg, 4.80 μmol, 0.024 equiv.). The crude product was purified by automated flash column chromatography (Biotage 10% → 65% ethyl acetate in *n*-hexane, stained in CAM) to afford an orange solid (50.6 mg, 72% yield).

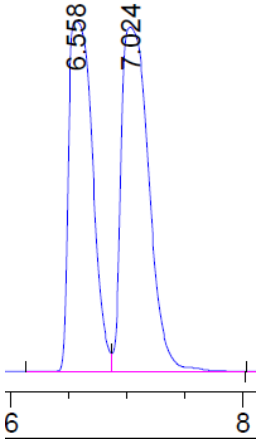
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (d, 2H), 7.29 – 7.22 (m, 2H), 7.20 – 7.12 (m, 2H), 7.10 (d, J = 6.1 Hz, 3H), 2.77 – 2.51 (m, 4H), 1.73 – 1.59 (m, 2H), 1.56 – 1.35 (m, 3H), 1.15 (s, 6H), 1.13 (s, 6H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 151.4, 149.6, 142.6, 128.5, 128.4, 125.8, 124.4, 83.4, 36.6, 36.1, 30.9, 30.8, 24.9, 24.8.; ^{11}B NMR (160 MHz, $CDCl_3$) δ 35.63.; HRMS (DART) for $C_{22}H_{31}BNO_2$ $[M+H]^+$: calculated: 352.24424, found: 352.24360.; $[\alpha]^{20}_D$: 31.4 (c = 1.0 g/100 mL, $CHCl_3$, l = 50 mm)

Analysis of Stereochemistry: Racemic compound was prepared according to the procedure described above with $Pd_2(dba)_3$ (1 mol%) and 2-(2-(diphenylphosphino)phenyl)-4,4-dimethyl-4,5-dihydrooxazole (1.2 mol%) as the catalyst.

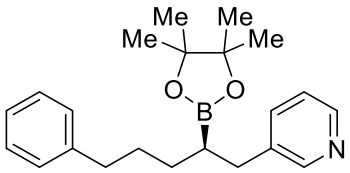
Chiral HPLC (AD-H, 5% IPA, 1ml/min, 70 bar, 35 °C, 210-270 nm) -analysis of **(R)-4-(5-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentyl)pyridine**



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.492	BV R	0.1429	1.01941e4	1072.20313	88.4448
2	7.054	VB E	0.1991	1331.85010	98.91973	11.5552



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.558	BV	0.1570	4536.02100	437.41650	49.3564
2	7.024	VB	0.1906	4654.31885	370.43768	50.6436



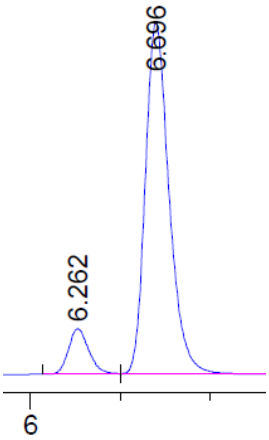
(R)-3-(5-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentyl)pyridine (3.91)

The reaction was performed according to general procedure *Method B* (with the modification: the boronate ester product was directly isolated without further oxidation) using 4,4,5,5-tetramethyl-2-(3-phenylpropyl)-1,3,2-dioxaborolane (49.2 mg, 0.2 mmol, 1.0 equiv.), vinyl magnesium bromide (1.0 M in tetrahydrofuran, 0.24 mL, 0.24 mmol, 1.2 equiv.), 3-iodopyridine (45.1 mg, 0.22 mmol, 1.1 equiv.), tris(dibenzylideneacetone)-dipalladium(0) (1.83 mg, 2.0 μmol, 0.01 equiv.), phosphinooxazoline **3.68** (2.23 mg, 4.80 μmol, 0.024 equiv.). The crude product was purified by automated flash column chromatography (Biotage 10% → 65% ethyl acetate in *n*-hexane, stained in CAM) to afford a colorless oil (32.3 mg, 46% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (s, 1H), 8.40 (dd, *J* = 4.8, 1.7 Hz, 1H), 7.49 (d, *J* = 7.8 Hz, 1H), 7.30 – 7.21 (m, 2H), 7.21 – 7.12 (m, 4H), 2.75 – 2.52 (m, 4H), 1.65 (d, *J* = 11.8 Hz, 2H), 1.57 – 1.43 (m, 2H), 1.42 – 1.32 (m, 1H), 1.15 (s, 6H), 1.12 (s, 6H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 150.5, 147.3, 142.7, 137.6, 136.3, 128.5, 128.4, 125.7, 123.2, 83.3, 36.2, 34.5, 31.0, 30.9, 24.88, 24.85.; ^{11}B NMR (160 MHz, $CDCl_3$) δ 35.58.; IR (neat) ν_{max} 3061.59 (w), 3025.93 (m), 2977.37 (s), 2855.55 (m), 1386.84 (s), 1326.09 (m), 1256.11 (w), 1143.00 (s), 749.69 (m), 699.74 (w) cm^{-1}.; HRMS (DART) for $C_{22}H_{31}BNO_2$ $[M+H]^+$: calculated: 352.24424, found: 352.24366.; $[\alpha]^{20}_D$: 7.13 (c = 1.0 g/100 mL, $CHCl_3$, *l* = 50 mm)

Analysis of Stereochemistry: Racemic compound was prepared according to the procedure described above with $Pd_2(dba)_3$ (1 mol%) and 2-(2-(diphenylphosphino)phenyl)-4,4-dimethyl-4,5-dihydrooxazole (1.2 mol%) as the catalyst.

Chiral HPLC (AD-H, 5% IPA, 1ml/min, 70 bar, 35 °C, 210-270 nm) -analysis of **(R)-3-(5-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentyl)pyridine**



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
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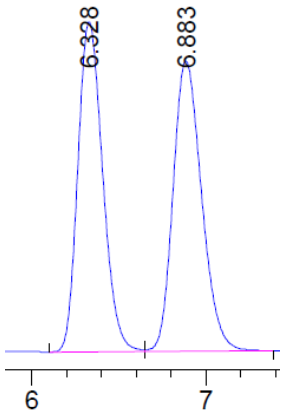
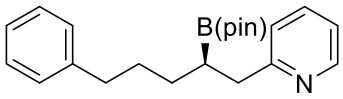
2	6.696	VB	0.1412	1118.74829	121.72294	89.9432



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.328	BV	0.1553	2576.13281	260.68866	49.7064
2	6.883	VB	0.1765	2606.56592	229.57101	50.2936



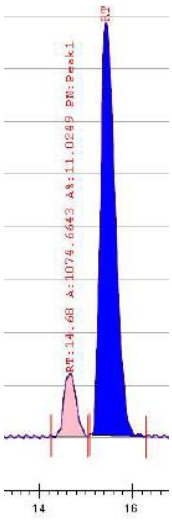
(R)-5-phenyl-1-(pyridin-2-yl)pentan-2-ol (3.92)

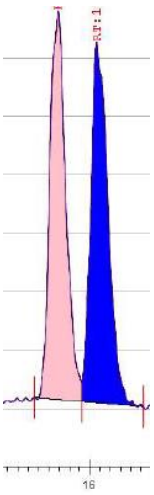
The reaction was performed according to general procedure *Method B* using 4,4,5,5-tetramethyl-2-(3-phenylpropyl)-1,3,2-dioxaborolane (49.2 mg, 0.2 mmol, 1.0 equiv.), vinyl magnesium bromide (1.0 M in tetrahydrofuran, 0.24 mL, 0.24 mmol, 1.2 equiv.), 2-iodopyridine (45.1 mg, 0.22 mmol, 1.1 equiv.), tris(dibenzylideneacetone)-dipalladium(0) (1.83 mg, 2.0 μmol, 0.01 equiv.), phosphinooxazoline **3.68** (2.23 mg, 4.80 μmol, 0.024 equiv.). The crude product was purified by automated flash column chromatography (Biotage 10% → 75% ethyl acetate in *n*-hexane, stained in CAM) to afford a colorless oil (22.2 mg, 46% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.49 (d, *J* = 4.5 Hz, 1H), 7.61 (td, *J* = 7.7, 2.0 Hz, 1H), 7.30 – 7.26 (m, 2H), 7.22 – 7.08 (m, 5H), 5.12 (s, 1H), 4.11 – 4.03 (m, 1H), 2.90 (dd, *J* = 15.0, 2.7 Hz, 1H), 2.83 (dd, *J* = 15.0, 8.8 Hz, 1H), 2.66 (t, *J* = 7.7 Hz, 2H), 1.93 – 1.82 (m, 1H), 1.81 – 1.70 (m, 1H), 1.68 – 1.60 (m, 1H), 1.59 – 1.51 (m, 1H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.5, 148.7, 142.7, 136.9, 128.6, 128.4, 125.8, 123.8, 121.6, 70.9, 43.4, 36.8, 36.0, 27.6.; IR (neat) ν_{max} 3403.34 (br), 3026.30 (m), 2930.68 (s), 2857.58 (s), 1595.22 (s), 1436.83 (s), 1089.23 (m), 749.34 (s), 699.72 (s) cm^{-1}.; HRMS (DART) for $C_{16}H_{20}NO$ $[M+H]^+$: calculated: 242.15394, found: 242.15445.; $[\alpha]^{20}_D$: 7.37 (c = 1.0 g/100 mL, $CHCl_3$, *l* = 50 mm)

Analysis of Stereochemistry: Racemic compound was prepared according to the procedure described above with $Pd_2(dba)_3$ (1 mol%) and 2-(2-(diphenylphosphino)phenyl)-4,4-dimethyl-4,5-dihydrooxazole (1.2 mol%) as the catalyst.

Chiral SFC (OD-H, 4% IPA, 3ml/min, 100 bar, 35 °C, 210-270 nm) -analysis of **(R)-2-(5-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentyl)pyridine**





Peak No	% Area	Area	RT (min)
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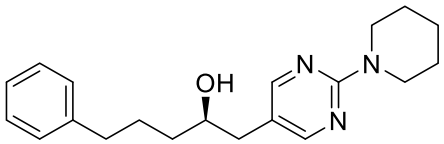
2	88.9751	8672.9475	15.44
Total:	100	9747.6118	

Peak No	% Area	Area	RT (min)
1	49.9616	7245.8995	15.38
2	50.0384	7257.0309	16.14
Total:	100	14502.9304	



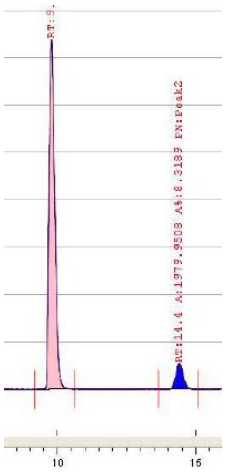
(R)-5-phenyl-1-(2-(piperidin-1-yl)pyrimidin-5-yl)pentan-2-ol (3.93)

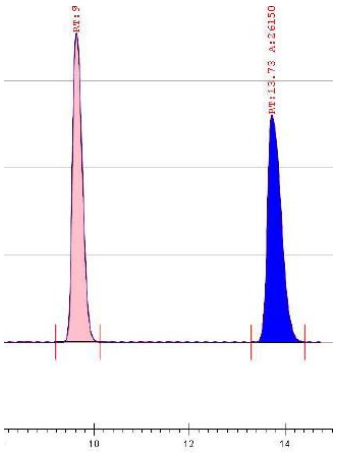
The reaction was performed according to general procedure *Method B* (with the modification: the reaction was run with 5 % catalyst loading instead of 2 %) using 4,4,5,5-tetramethyl-2-(3-phenylpropyl)-1,3,2-dioxaborolane (49.2 mg, 0.2 mmol, 1.0 equiv.), vinyl magnesium bromide (1.0 M in tetrahydrofuran, 0.24 mL, 0.24 mmol, 1.2 equiv.), 5-bromo-2-(1-piperidinyl)pyrimidine (41.2 mg, 0.22 mmol, 1.1 equiv.), tris(dibenzylideneacetone)-dipalladium(0) (4.58 mg, 5.0 μmol, 0.025 equiv.), phosphinooxazoline **3.68** (5.58 mg, 0.012 mmol, 0.06 equiv.). The crude product was purified by automated flash column chromatography (Biotage 5% → 45% ethyl acetate in *n*-hexane, stained in CAM) to afford a white solid (22.8 mg, 35% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.13 (s, 2H), 7.29 – 7.27 (m, 2H), 7.20 – 7.16 (m, 3H), 3.79 – 3.70 (m, 4H), 3.71 – 3.67 (m, 1H), 2.63 (ddd, *J* = 8.2, 6.8, 3.1 Hz, 2H), 2.57 (dd, *J* = 14.2, 4.2 Hz, 1H), 2.44 (dd, *J* = 14.3, 8.0 Hz, 1H), 1.93 – 1.76 (m, 2H), 1.72 – 1.46 (m, 9H).; ^{13}C NMR (151 MHz, CDCl3) δ 161.1, 158.5, 142.3, 128.51, 128.46, 125.9, 118.5, 72.3, 45.0, 37.7, 36.4, 35.9, 27.8, 25.8, 25.0.; IR (neat) ν_{max} 3385.66 (br), 2932.09 (s), 2853.26 (m), 1605.40 (s), 1500.11 (s), 1461.99 (m), 1304.54 (m), 1025.88 (m), 749.20 (m) cm^{-1}.; HRMS (DART) for $C_{20}H_{28}N_3O$ $[M+H]^+$: calculated: 326.22269, found: 326.22164.; $[\alpha]^{20}_D$: -7.10 (c = 1.0 g/100 mL, $CHCl_3$, *l* = 50 mm)

Analysis of Stereochemistry: Racemic compound was prepared according to the procedure described above with $Pd_2(dba)_3$ (1 mol%) and 2-(2-(diphenylphosphino)phenyl)-4,4-dimethyl-4,5-dihydrooxazole (1.2 mol%) as the catalyst.

Chiral SFC (OJ-H, 15% IPA, 3ml/min, 100 bar, 35 °C, 210-270 nm) -analysis of **(R)-5-phenyl-1-(2-(piperidin-1-yl)pyrimidin-5-yl)pentan-2-ol**





Peak No	% Area	Area	RT (min)
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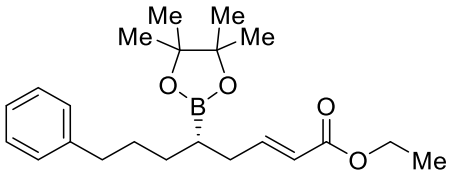
Total:	100	23800.5095	

Peak No	% Area	Area	RT (min)
1	49.7601	25900.2866	9.63
2	50.2399	26150.0175	13.73
Total:	100	52050.3041	



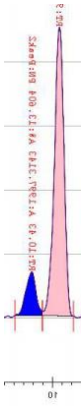
ethyl (R,E)-8-phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oct-2-enoate (3.88)

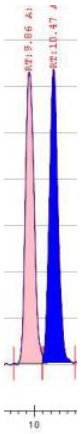
The reaction was performed according to general procedure *Method B* (with the modification: the boronate ester product was directly isolated without further oxidation) using 4,4,5,5-tetramethyl-2-(3-phenylpropyl)-1,3,2-dioxaborolane (49.2 mg, 0.2 mmol, 1.0 equiv.), vinyl magnesium bromide (1.0 M in tetrahydrofuran, 0.24 mL, 0.24 mmol, 1.2 equiv.), ethyl (E)-3-iodoacrylate (49.7 mg, 0.22 mmol, 1.1 equiv.), tris(dibenzylideneacetone)-dipalladium(0) (1.83 mg, 2.0 μmol, 0.01 equiv.), phosphinooxazoline **ent-3.68** (2.23 mg, 4.80 μmol, 0.024 equiv.). The crude product was purified by automated flash column chromatography (Biotage 2% → 10% ethyl acetate in *n*-hexane, stained in CAM) to afford a clear oil (48.0 mg, 64%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 – 7.24 (m, 2H), 7.20 – 7.13 (m, 3H), 7.03 – 6.87 (m, 1H), 5.80 (d, J = 15.6 Hz, 1H), 4.17 (q, J = 7.1 Hz, 2H), 2.66 – 2.53 (m, 2H), 2.35 – 2.18 (m, 2H), 1.69 – 1.57 (m, 2H), 1.54 – 1.39 (m, 2H), 1.27 (t, J = 7.1 Hz, 3H), 1.22 (s, 12H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.64, 149.12, 142.59, 128.34, 128.23, 125.59, 121.73, 83.24, 60.01, 36.06, 33.71, 30.77, 30.52, 24.79, 24.76, 14.27.; ^{11}B NMR (160 MHz, $CDCl_3$) δ 34.06.; IR (neat) ν_{max} 2975.37 (w), 2925.84 (w), 1717.16 (m), 1651.73 (w), 1380.63 (w), 1368.84 (m), 1141.68 (s) cm^{-1}.; HRMS (DART) for $C_{22}H_{34}BO_4$ $[M+H]^+$: calculated: 373.25447, found: 373.25355.; $[\alpha]^{20}_D$: (c = 1.0 g/100 mL, $CHCl_3$, l = 50 mm)

Analysis of Stereochemistry: Racemic compound was prepared according to the procedure described above with $Pd_2(dba)_3$ (1 mol%) and 2-(2-(diphenylphosphino)phenyl)-4,4-dimethyl-4,5-dihydrooxazole (1.2 mol%) as the catalyst.

Chiral SFC (OD-H, 3% IPA, 3ml/min, 100 bar, 35 °C, 210-270 nm) -analysis of **ethyl (R,E)-8-phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oct-2-enoate**





Peak No	% Area	Area	RT (min)
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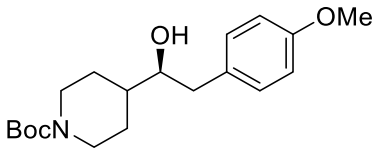
Total:	100	14681.7798	

Peak No	% Area	Area	RT (min)
1	49.6284	9311.9943	9.86
2	50.3716	9451.4489	10.47
Total:	100	18763.4432	



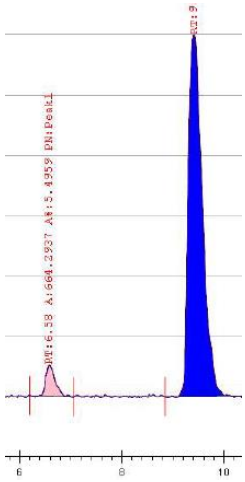
tert-butyl (S)-4-(1-hydroxy-2-(4-methoxyphenyl)ethyl)piperidine-1-carboxylate (3.95)

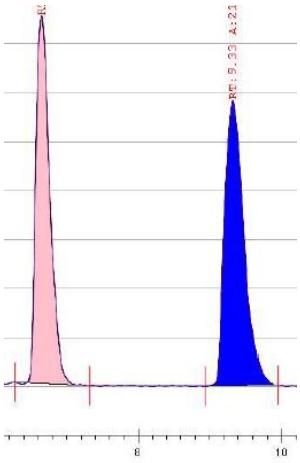
The reaction was performed according to general procedure *Method B* using tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)piperidine-1-carboxylate (62.2 mg, 0.2 mmol, 1.0 equiv.), vinyl magnesium bromide (1.0 M in tetrahydrofuran, 0.24 mL, 0.24 mmol, 1.2 equiv.), 4-bromoanisole (41.2 mg, 0.22 mmol, 1.1 equiv.), tris(dibenzylideneacetone)-dipalladium(0) (1.83 mg, 2.0 μmol, 0.01 equiv.), phosphinooxazoline **3.68** (2.23 mg, 4.80 μmol, 0.024 equiv.). The crude product was purified by automated flash column chromatography (Biotage 2% → 45% ethyl acetate in *n*-hexane, stained in CAM) to afford a white solid (43.6 mg, 65% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.11 (d, *J* = 8.2 Hz, 2H), 6.84 (d, *J* = 8.1 Hz, 2H), 4.15 (s, 2H), 3.77 (s, 3H), 3.53 (s, 1H), 2.81 (dd, *J* = 13.8, 3.4 Hz, 1H), 2.66 (s, 2H), 2.52 (dd, *J* = 13.7, 9.5 Hz, 1H), 1.84 (d, *J* = 12.8 Hz, 1H), 1.75 – 1.61 (m, 2H), 1.56 – 1.49 (m, 1H), 1.45 (s, 9H), 1.37 – 1.22 (m, 2H).; ^{13}C NMR (151 MHz, CDCl3) δ 158.4, 154.9, 130.5, 130.4, 114.2, 79.4, 76.0, 55.3, 43.6, 41.6, 39.9, 28.6.; IR (neat) ν_{max} 3439.19 (br), 2974.28 (m), 2933.93 (m), 2857.28 (m), 1689.32 (s), 1670.79 (s), 1512.55 (s), 1426.16 (s), 1246.23 (s), 1169.66 (s), 1082.57 (m), 865.14 (w) cm^{-1}.; HRMS (DART) for $C_{19}H_{30}NO_4$ $[M+H]^+$: calculated: 336.21693, found: 336.21712.; $[\alpha]^{20}_D$: -7.36 (c = 1.0 g/100 mL, $CHCl_3$, *l* = 50 mm)

Analysis of Stereochemistry: Racemic compound was prepared according to the procedure described above with $Pd_2(dba)_3$ (1 mol%) and 2-(2-(diphenylphosphino)phenyl)-4,4-dimethyl-4,5-dihydrooxazole (1.2 mol%) as the catalyst.

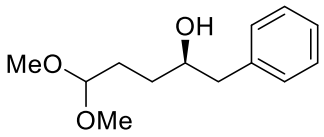
Chiral SFC (AD-H, 10% IPA, 3ml/min, 100 bar, 35 °C, 210-270 nm) -analysis of **tert-butyl (S)-4-(1-hydroxy-2-(4-methoxyphenyl)ethyl)piperidine-1-carboxylate**





Peak No	% Area	Area	RT (min)
1	5.4959	664.2937	6.58
2	94.5041	11422.8686	9.41
Total:	100	12087.1623	

Peak No	% Area	Area	RT (min)
1	48.3889	20402.7902	6.65
2	51.6111	21761.4055	9.33
Total:	100	42164.1957	

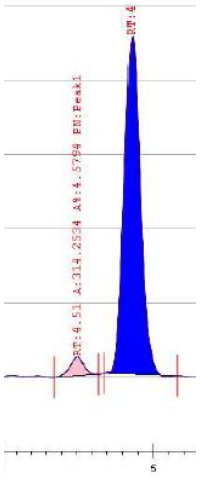


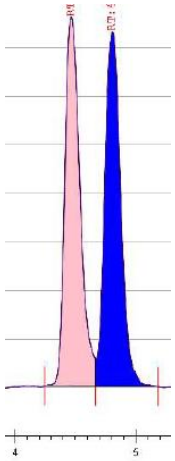
(R)-5,5-dimethoxy-1-phenylpentan-2-ol (3.96)

The reaction was performed according to general procedure *Method B* using 2-(3,3-dimethoxypropyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (46.0 mg, 0.2 mmol, 1.0 equiv.), vinyl magnesium bromide (1.0 M in tetrahydrofuran, 0.24 mL, 0.24 mmol, 1.2 equiv.), 4-bromoanisole (41.2 mg, 0.22 mmol, 1.1 equiv.), tris(dibenzylideneacetone)-dipalladium(0) (1.83 mg, 2.0 μmol, 0.01 equiv.), phosphinooxazoline **3.68** (2.23 mg, 4.80 μmol, 0.024 equiv.). The crude product was purified by automated flash column chromatography (Biotage 6% → 50% ethyl acetate in *n*-hexane, stained in CAM) to afford a colorless oil (28.2 mg, 63% yield). All spectral data were in accordance with the literature.[178]

Analysis of Stereochemistry: Racemic compound was prepared according to the procedure described above with $Pd_2(dba)_3$ (1 mol%) and 2-(2-(diphenylphosphino)phenyl)-4,4-dimethyl-4,5-dihydrooxazole (1.2 mol%) as the catalyst.

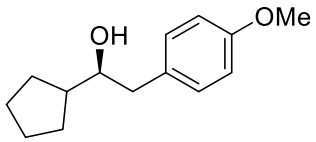
Chiral SFC (OD-H, 10% IPA, 3ml/min, 100 bar, 35 °C, 210-270 nm) -analysis of **(R)-5,5-dimethoxy-1-phenylpentan-2-ol**





Peak No	% Area	Area	RT (min)
1	4.5794	314.2534	4.51
2	95.4206	6548.146	4.86
Total:	100	6862.3994	

Peak No	% Area	Area	RT (min)
1	49.7755	13263.0378	4.46
2	50.2245	13382.6518	4.8
Total:	100	26645.6896	



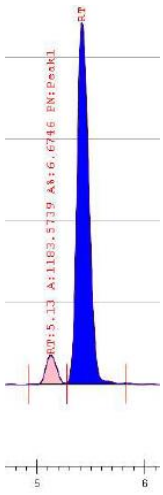
(S)-1-cyclopentyl-2-(4-methoxyphenyl)ethan-1-ol (3.97)

The reaction was performed according to general procedure *Method B* using 2-cyclopentyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (39.2 mg, 0.2 mmol, 1.0 equiv.), vinyl magnesium bromide (1.0 M in tetrahydrofuran, 0.24 mL, 0.24 mmol, 1.2 equiv.), 4-bromoanisole (41.2 mg, 0.22 mmol, 1.1 equiv.), tris(dibenzylideneacetone)-dipalladium(0) (1.83 mg, 2.0 μmol, 0.01 equiv.), phosphinooxazoline **3.68** (2.23 mg, 4.80 μmol, 0.024 equiv.). The crude product was purified by automated flash column chromatography (Biotage 2% → 28% ethyl acetate in *n*-hexane, stained in CAM) to afford a colorless oil (30.0 mg, 68% yield).

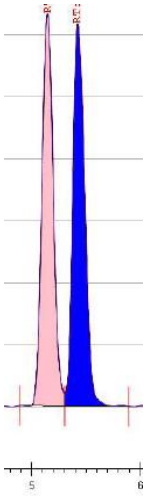
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.15 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 3.79 (s, 3H), 3.62 – 3.54 (m, 1H), 2.85 (dd, *J* = 13.8, 3.5 Hz, 1H), 2.55 (dd, *J* = 13.8, 8.9 Hz, 1H), 1.92 (dtt, *J* = 8.2, 8.2, 8.2 Hz, 1H), 1.86 – 1.72 (m, 2H), 1.69 – 1.61 (m, 2H), 1.60 – 1.52 (m, 3H), 1.49 – 1.39 (m, 1H), 1.37 – 1.28 (m, 1H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.3, 130.9, 130.5, 114.1, 76.8, 55.4, 45.7, 41.9, 29.5, 28.7, 25.9, 25.8.; IR (neat) ν_{max} 3421.97 (br), 2948.36 (m), 2865.52 (m), 2835.15 (m), 1611.81 (m), 1511.56 (s), 1300.18 (m), 1245.39 (s), 1177.69 (m), 1036.95 (m), 817.91 (m), 530.04 (s) cm^{-1}.; HRMS (DART) for $C_{14}H_{19}O$ $[M+H-H_2O]^+$: calculated: 203.14304, found: 203.14292.; $[\alpha]^{20}_D$: -8.76 (c = 1.0 g/100 mL, $CHCl_3$, *l* = 50 mm)

Analysis of Stereochemistry: Racemic compound was prepared according to the procedure described above with $Pd_2(dba)_3$ (1 mol%) and 2-(2-(diphenylphosphino)phenyl)-4,4-dimethyl-4,5-dihydrooxazole (1.2 mol%) as the catalyst.

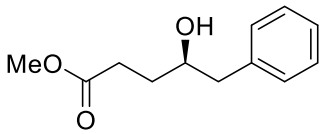
Chiral SFC (OJ-H, 10% IPA, 3ml/min, 100 bar, 35 °C, 210-270 nm) -analysis of **(S)-1-cyclopentyl-2-(4-methoxyphenyl)ethan-1-ol**



Peak No	% Area	Area	RT (min)
1	6.6746	1183.5739	5.13
2	93.3254	16548.953	5.42
Total:	100	17732.5269	



Peak No	% Area	Area	RT (min)
1	49.2959	9113.2049	5.15
2	50.7041	9373.5418	5.42
Total:	100	18486.7467	



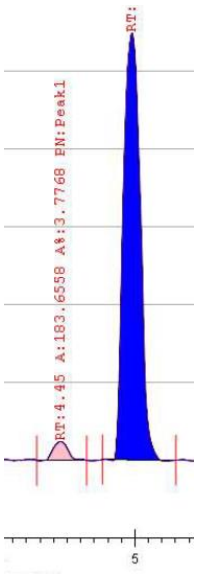
methyl (R)-4-hydroxy-5-phenylpentanoate (3.98)

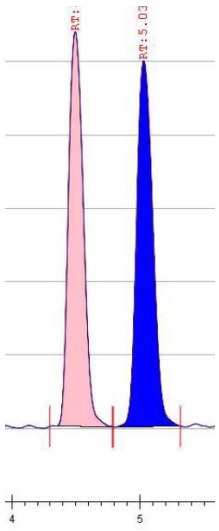
The reaction was performed according to general procedure *Method B* using methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoate (42.8 mg, 0.2 mmol, 1.0 equiv.), vinyl magnesium bromide (1.0 M in tetrahydrofuran, 0.24 mL, 0.24 mmol, 1.2 equiv.), iodobenzene (44.9 mg, 0.22 mmol, 1.1 equiv.), tris(dibenzylideneacetone)-dipalladium(0) (1.83 mg, 2.0 μmol, 0.01 equiv.), phosphinooxazoline **3.68** (2.23 mg, 4.80 μmol, 0.024 equiv.). The crude product was purified by automated flash column chromatography (Biotage 4% → 55% ethyl acetate in *n*-hexane, stained in CAM) to afford a colorless oil (23.7 mg, 57% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.28 (m, 2H), 7.26 – 7.17 (m, 4H), 3.89 – 3.81 (m, 1H), 3.67 (s, 3H), 2.82 (dd, *J* = 13.6, 4.6 Hz, 1H), 2.70 (dd, *J* = 13.5, 8.2 Hz, 1H), 2.57 – 2.42 (m, 2H), 1.91 (ddt, *J* = 14.3, 7.2, 3.6 Hz, 1H), 1.83 (s, 1H), 1.80 – 1.71 (m, 1H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.6, 138.3, 129.5, 128.7, 126.7, 72.1, 51.8, 44.3, 31.7, 30.7.; IR (neat) ν_{max} 3460.01 (br), 3027.91 (w), 2949.68 (m), 1773.03 (m), 1734.32 (s), 1520.72 (w), 1257.85 (m), 1176.73 (m), 747.69 (m), 701.66 (s) cm^{-1}.; HRMS (DART) for $C_{12}H_{17}O_3$ $[M+H]^+$: calculated: 209.11722, found: 209.11741.; $[\alpha]^{20}_D$: -7.10 (c = 1.0 g/100 mL, $CHCl_3$, *l* = 50 mm)

Analysis of Stereochemistry: Racemic compound was prepared according to the procedure described above with $Pd_2(dba)_3$ (1 mol%) and 2-(2-(diphenylphosphino)phenyl)-4,4-dimethyl-4,5-dihydrooxazole (1.2 mol%) as the catalyst.

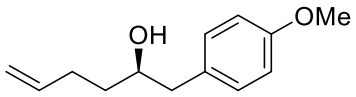
Chiral SFC (OD-H, 10% IPA, 3ml/min, 100 bar, 35 °C, 210-270 nm) -analysis of **methyl (R)-4-hydroxy-5-phenylpentanoate**





Peak No	% Area	Area	RT (min)
1	3.7768	183.6558	4.45
2	96.2232	4679.0992	4.98
Total:	100	4862.755	

Peak No	% Area	Area	RT (min)
1	49.8003	4294.5434	4.5
2	50.1997	4328.9786	5.03
Total:	100	8623.522	



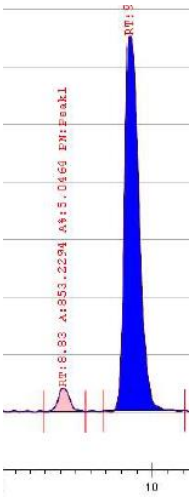
(R)-1-(4-methoxyphenyl)hex-5-en-2-ol (3.99)

The reaction was performed according to general procedure *Method B* using 2-(but-3-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (36.4 mg, 0.2 mmol, 1.0 equiv.), vinyl magnesium bromide (1.0 M in tetrahydrofuran, 0.24 mL, 0.24 mmol, 1.2 equiv.), 4-bromoanisole (41.2 mg, 0.22 mmol, 1.1 equiv.), tris(dibenzylideneacetone)-dipalladium(0) (1.83 mg, 2.0 μmol, 0.01 equiv.), phosphinooxazoline **3.68** (2.23 mg, 4.80 μmol, 0.024 equiv.). The crude product was purified by automated flash column chromatography (Biotage 2% → 25% ethyl acetate in *n*-hexane, stained in CAM) to afford a colorless oil (33.2 mg, 80% yield).

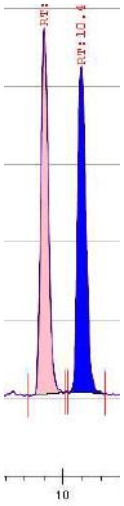
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.18 – 7.08 (m, 2H), 6.90 – 6.79 (m, 2H), 5.84 (ddt, *J* = 16.9, 10.0, 6.7 Hz, 1H), 5.05 (dd, *J* = 17.1, 1.7 Hz, 1H), 4.98 (dd, *J* = 10.2, 1.2 Hz, 1H), 3.90 – 3.68 (m, 4H), 2.77 (dd, *J* = 13.7, 4.4 Hz, 1H), 2.61 (dd, *J* = 13.7, 8.3 Hz, 1H), 2.32 – 2.11 (m, 2H), 1.67 – 1.53 (m, 3H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.4, 138.6, 130.52, 130.48, 114.9, 114.1, 72.3, 55.4, 43.2, 35.9, 30.3.; IR (neat) ν_{max} 3429.00 (br), 2996.41 (m), 2934.28 (m), 2836.04 (w), 1640.00 (w), 1512.44 (s), 1246.88 (s), 1178.16 (m), 1036.63 (m), 818.86 (w) cm^{-1}.; HRMS (DART) for $C_{14}H_{19}O$ $[M+H-H_2O]^+$: calculated: 189.12739, found: 189.12748.; $[\alpha]^{20}_D$: -9.03 (c = 1.0 g/100 mL, $CHCl_3$, *l* = 50 mm)

Analysis of Stereochemistry: Racemic compound was prepared according to the procedure described above with $Pd_2(dba)_3$ (1 mol%) and 2-(2-(diphenylphosphino)phenyl)-4,4-dimethyl-4,5-dihydrooxazole (1.2 mol%) as the catalyst.

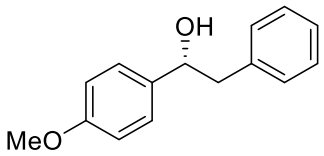
Chiral SFC (OJ-H, 3% IPA, 3ml/min, 100 bar, 35 °C, 210-270 nm) -analysis of **(R)-1-(4-methoxyphenyl)hex-5-en-2-ol**



Peak No	% Area	Area	RT (min)
1	5.0464	853.2294	8.83
2	94.9536	16054.4798	9.71
Total:	100	16907.7092	



Peak No	% Area	Area	RT (min)
1	50.2788	12965.7387	9.5
2	49.7212	12821.966	10.47
Total:	100	25787.7047	

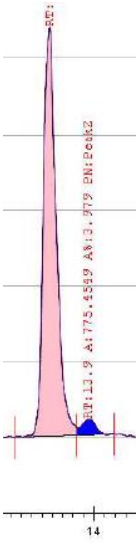


(R)-1-(4-methoxyphenyl)-2-phenylethan-1-ol (3.100)

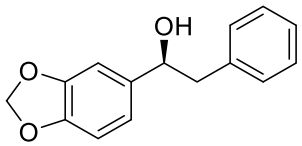
The reaction was performed according to general procedure *Method B* using 2-(4-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (46.8 mg, 0.2 mmol, 1.0 equiv.), vinyl magnesium bromide (1.0 M in tetrahydrofuran, 0.24 mL, 0.24 mmol, 1.2 equiv.), phenyl trifluoromethanesulfonate (49.8 mg, 0.22 mmol, 1.1 equiv.), tris(dibenzylideneacetone)-dipalladium(0) (1.83 mg, 2.0 µmol, 0.01 equiv.), phosphinooxazoline **ent-3.68** (2.23 mg, 4.80 µmol, 0.024 equiv.). The crude product was purified by automated flash column chromatography (Biotage 2% → 25% ethyl acetate in *n*-hexane, stained in CAM) to afford a white solid (26.5 mg, 58% yield). All spectral data were in accordance with the literature.[178]

Analysis of Stereochemistry: Racemic compound was prepared in a previous publication. This enriched sample was subject to the same chiral SFC conditions and similar retention times were observed.[178]

Chiral SFC (OD-H, 8% IPA, 3ml/min, 100 bar, 35 °C, 210-270 nm) -analysis of **(R)-1-(4-methoxyphenyl)-2-phenylethan-1-ol**



Peak No	% Area	Area	RT (min)
1	96.021	18713.3168	13.15
2	3.979	775.4549	13.9
Total:	100	19488.7717	



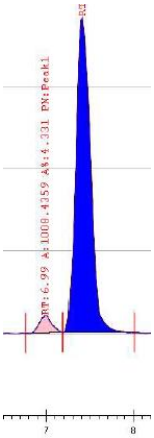
(S)-1-(benzo[d][1,3]dioxol-5-yl)-2-phenylethan-1-ol (3.101)

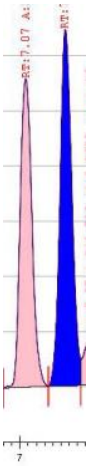
The reaction was performed according to general procedure *Method B* using 2-(benzo[d][1,3]dioxol-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (49.6 mg, 0.2 mmol, 1.0 equiv.), vinyl magnesium bromide (1.0 M in tetrahydrofuran, 0.24 mL, 0.24 mmol, 1.2 equiv.), phenyl trifluoromethanesulfonate (49.8 mg, 0.22 mmol, 1.1 equiv.), tris(dibenzylideneacetone)-dipalladium(0) (1.83 mg, 2.0 μmol, 0.01 equiv.), phosphinooxazoline **3.68** (2.23 mg, 4.80 μmol, 0.024 equiv.). The crude product was purified by automated flash column chromatography (Biotage 2% → 25% ethyl acetate in *n*-hexane, stained in CAM) to afford a white solid (27.5 mg, 57% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30 (t, *J* = 7.4 Hz, 2H), 7.24 (t, *J* = 7.4 Hz, 1H), 7.19 (d, *J* = 6.9 Hz, 2H), 6.90 (d, *J* = 1.6 Hz, 1H), 6.80 – 6.74 (m, 2H), 5.95 (d, *J* = 1.3 Hz, 2H), 5.01 – 4.66 (m, 1H), 3.19 – 2.74 (m, 2H), 1.94 (d, *J* = 2.8 Hz, 1H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 147.88, 147.09, 138.11, 138.04, 129.61, 128.65, 126.76, 108.17, 106.60, 101.13, 75.35, 46.22.; IR (neat) ν_{max} 3385.63 (br), 3027.47 (w), 2893.96 (w), 1502.21 (s), 1487.62 (m), 1442.01 (s), 1244.46 (s), 1038.25 (s), 932.82 (m), 811.43 (m), 700.11 (m), 513.96 (w) cm^{-1}.; HRMS (DART) for $C_{15}H_{13}O_2$ $[M+H-H_2O]^+$: calculated: 225.09101, found: 225.09043.; $[\alpha]^{20}_D$: 12.4(c = 1.0 g/100 mL, $CHCl_3$, *l* = 50 mm)

Analysis of Stereochemistry: Racemic compound was prepared according to the procedure described above with $Pd_2(dba)_3$ (1 mol%) and 2-(2-(diphenylphosphino)phenyl)-4,4-dimethyl-4,5-dihydrooxazole (1.2 mol%) as the catalyst.

Chiral SFC (OD-H, 10% IPA, 3ml/min, 100 bar, 35 °C, 210-270 nm) -analysis of **(S)-1-(benzo[d][1,3]dioxol-5-yl)-2-phenylethan-1-ol**

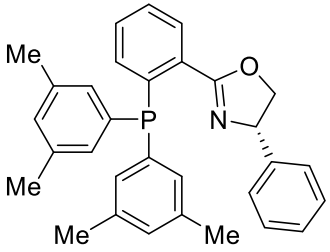


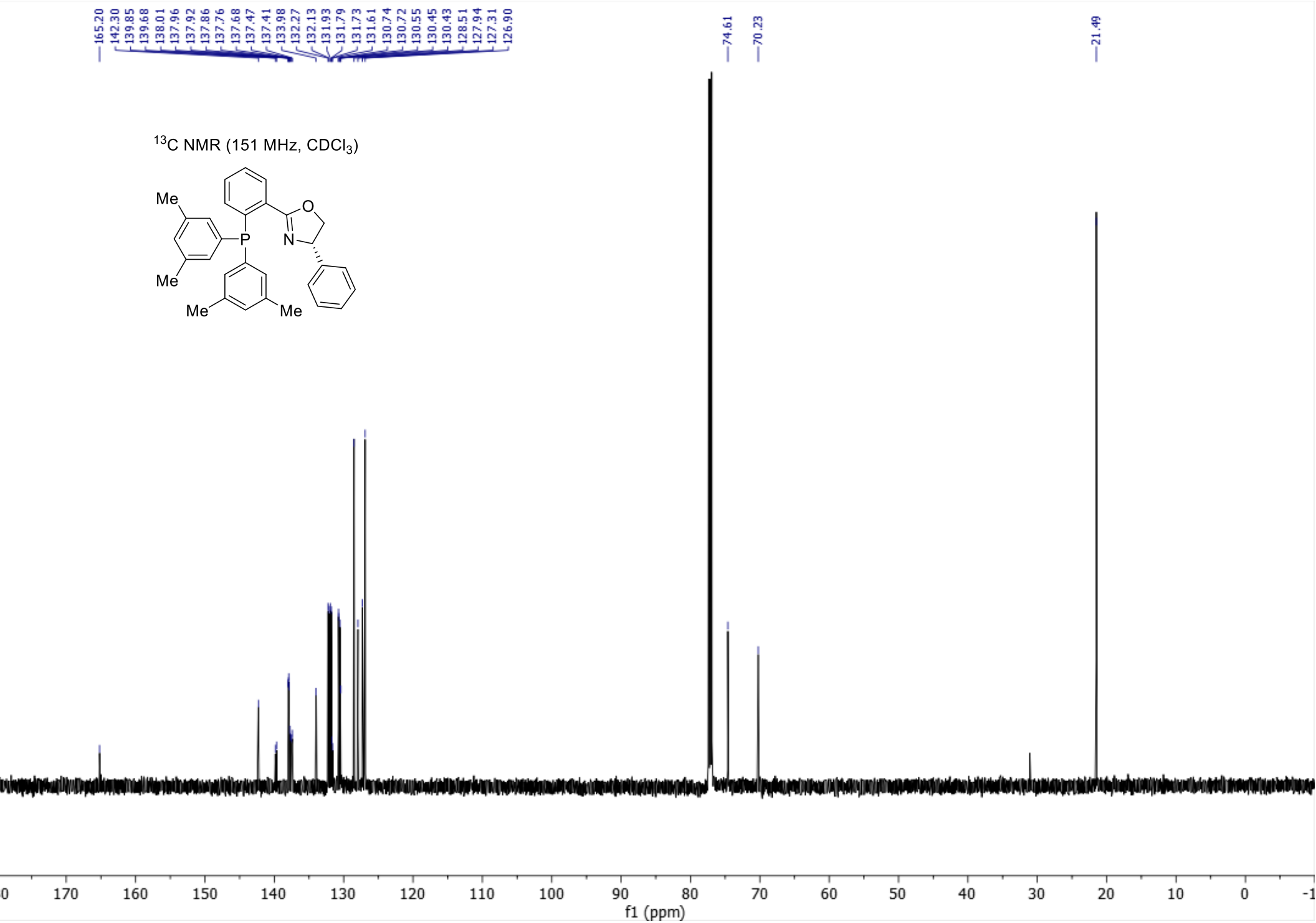


Peak No	% Area	Area	RT (min)
1	4.331	1008.4359	6.99
2	95.669	22275.7901	7.41
Total:	100	23284.226	

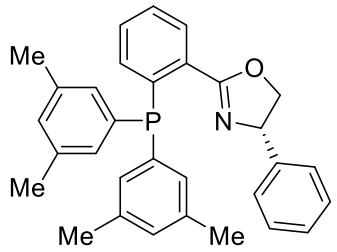
Peak No	% Area	Area	RT (min)
1	42.4416	2777.3719	7.07
2	49.2678	3224.0768	7.55

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

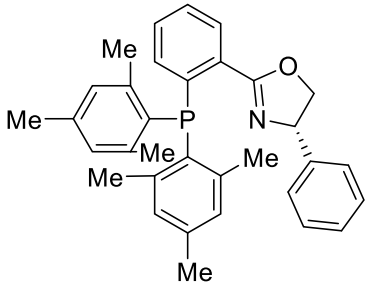


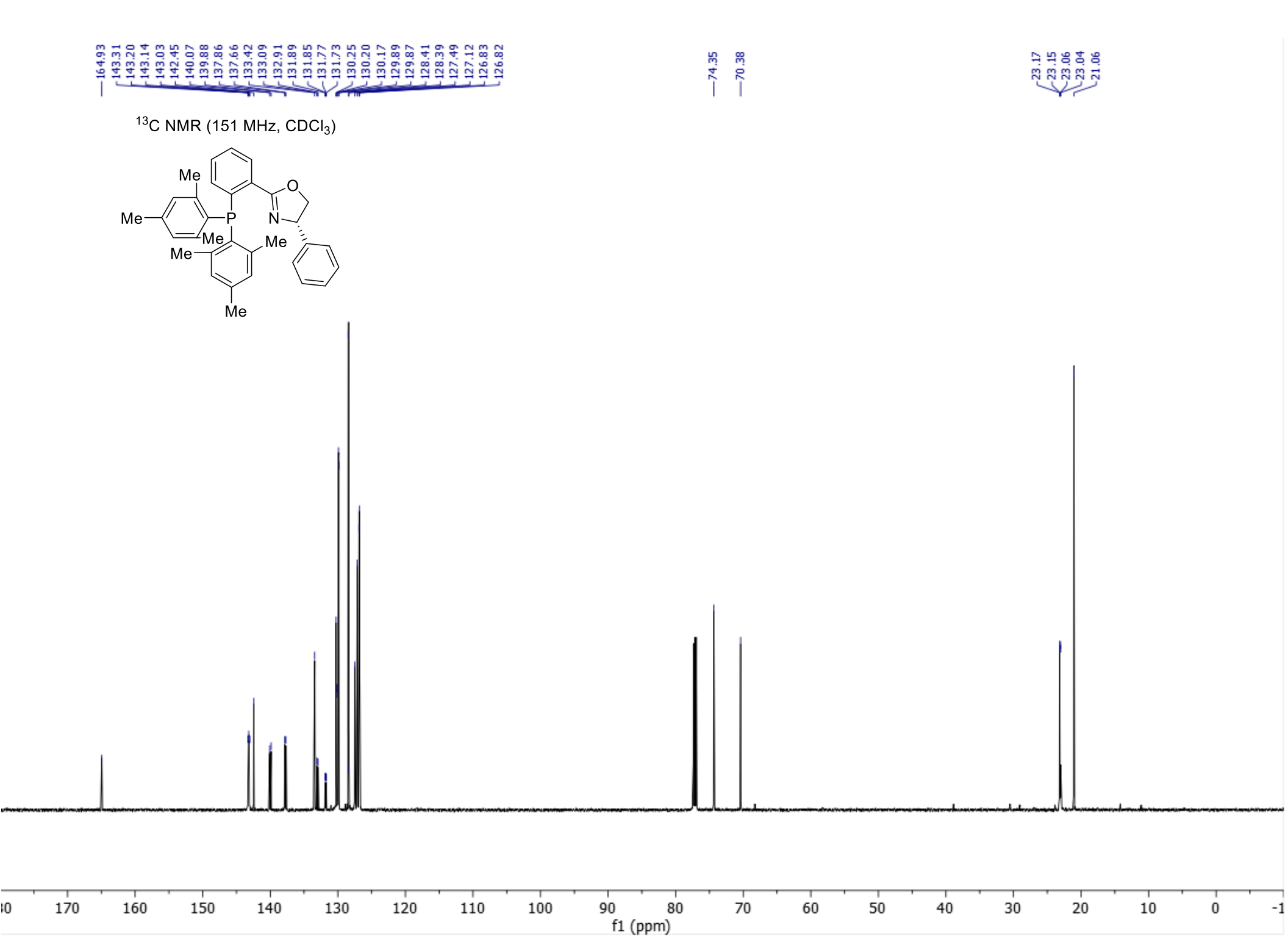

165.20
142.30
139.85
139.68
138.01
137.96
137.92
137.86
137.76
137.68
137.47
137.41
133.98
132.27
132.13
131.93
131.79
131.73
131.61
130.74
130.72
130.55
130.45
130.43
128.51
127.94
127.31
126.90
74.61
70.23
21.49
13C NMR (151 MHz, CDCl3)
Me
Me
Me
Me
P
O
N
f1 (ppm)

^{31}P NMR (162 MHz, $CDCl_3$)

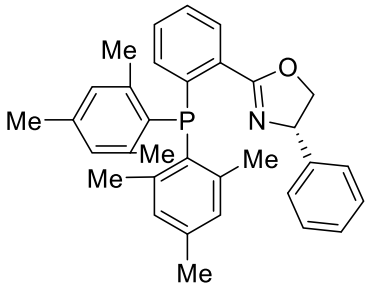


^{1}H NMR (600 MHz, $CDCl_3$)

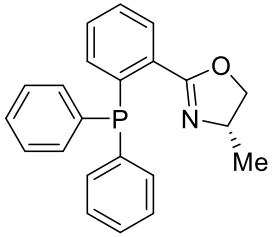


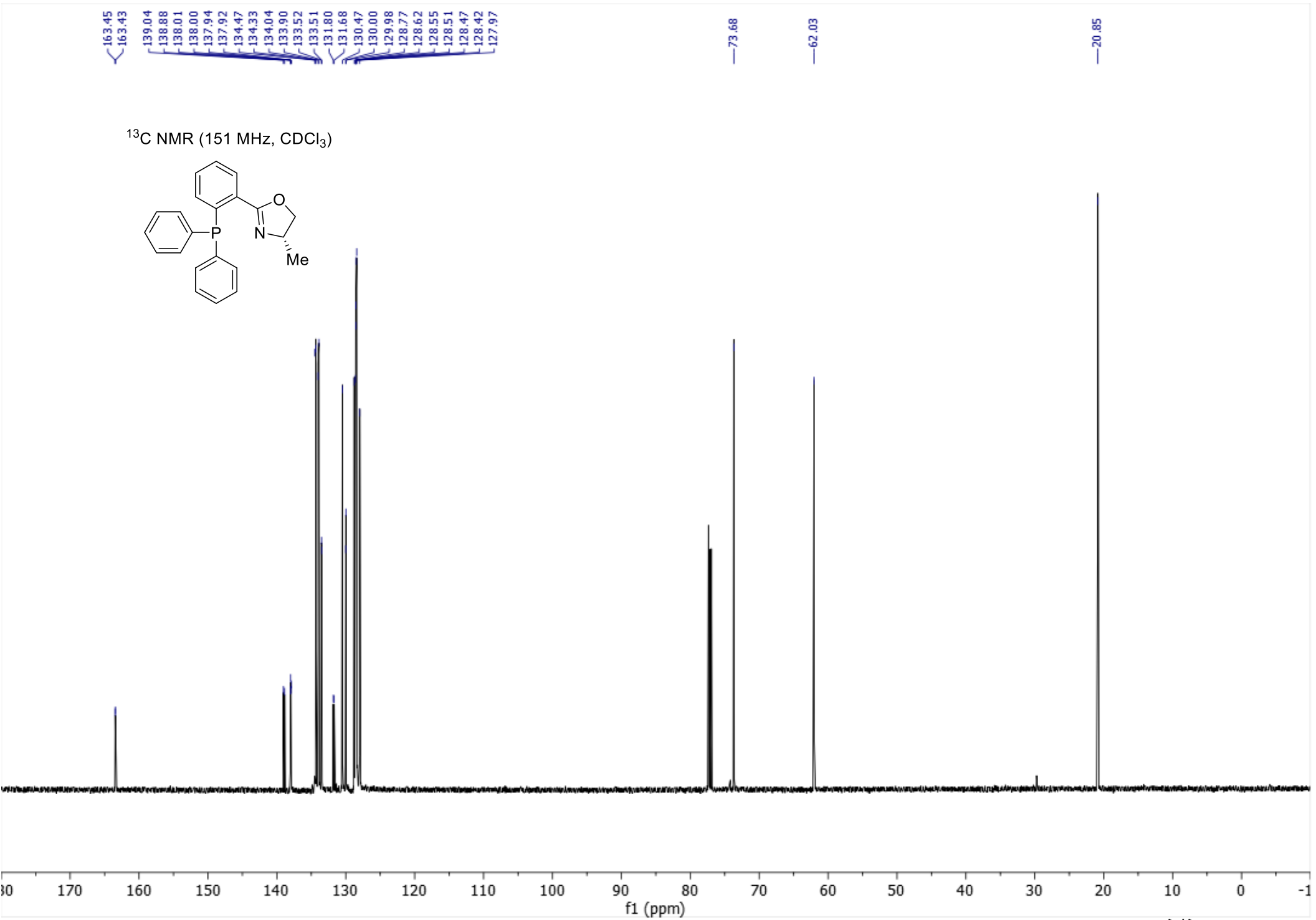

164.93
143.31
143.20
143.14
143.03
142.45
140.07
139.88
137.86
137.66
133.42
133.09
132.91
131.89
131.85
131.77
131.73
130.25
130.20
130.17
129.89
129.87
128.41
128.39
127.49
127.12
126.83
126.82
74.35
70.38
23.17
23.15
23.06
23.04
21.06
13C NMR (151 MHz, CDCl3)
Me
Me
P
O
N
Me
Me
Me
Me
f1 (ppm)

^{31}P NMR (243 MHz, $CDCl_3$)

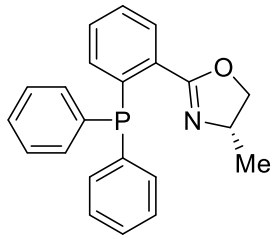


^{1}H NMR (600 MHz, $CDCl_3$)

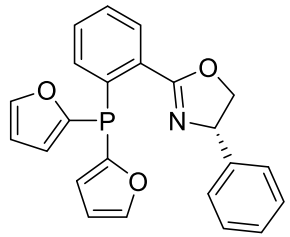


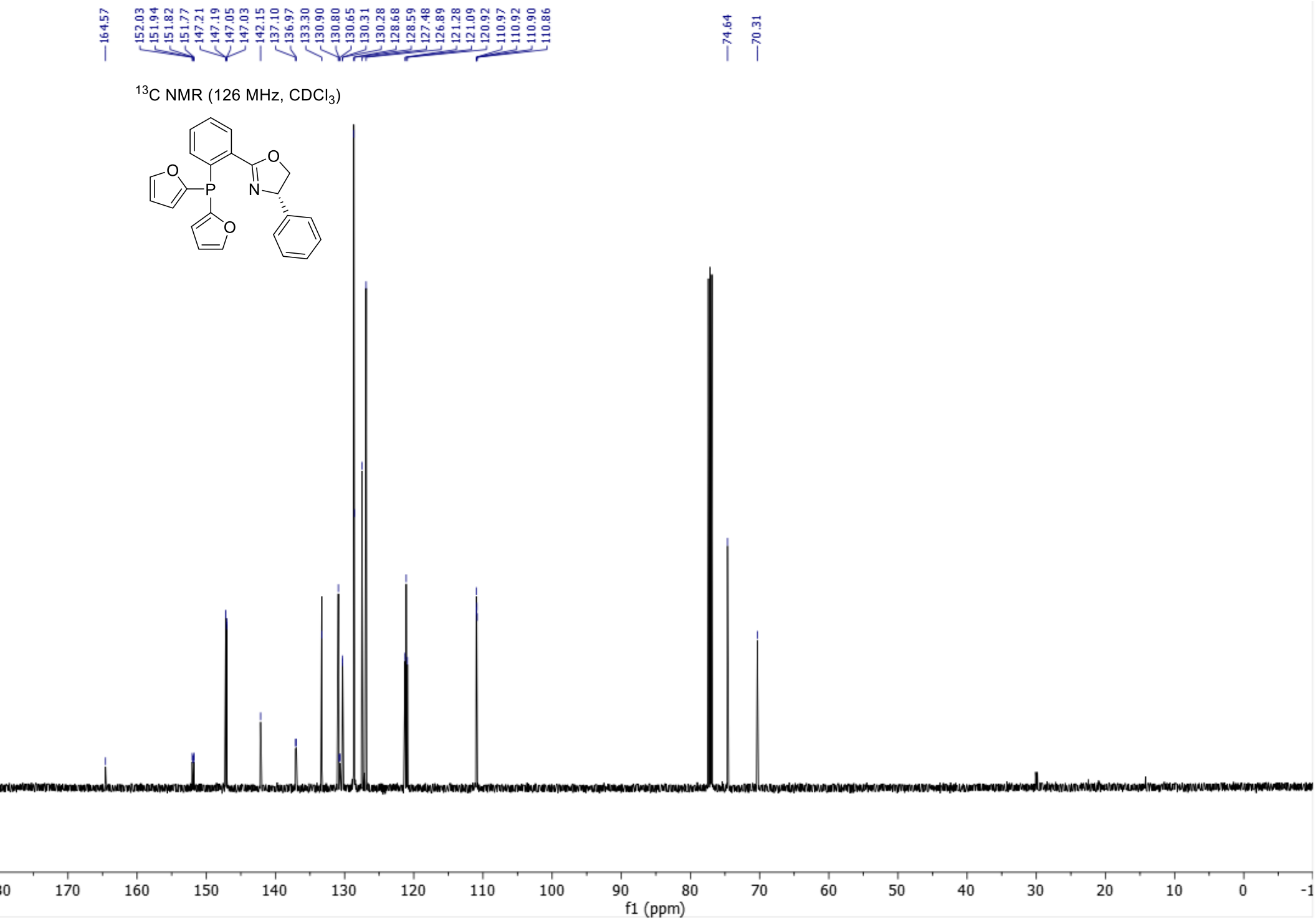

163.45
163.43
139.04
138.88
138.01
138.00
137.94
137.92
134.47
134.33
134.04
133.90
133.52
133.51
131.80
131.68
130.47
130.00
129.98
128.77
128.62
128.55
128.51
128.47
128.42
127.97
73.68
62.03
20.85
13C NMR (151 MHz, CDCl3)
O
N
P
Me
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

^{31}P NMR (243 MHz, $CDCl_3$)



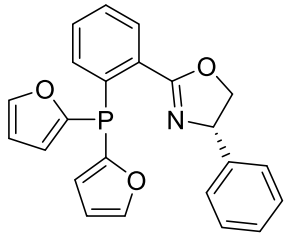
^{1}H NMR (500 MHz, $CDCl_3$)

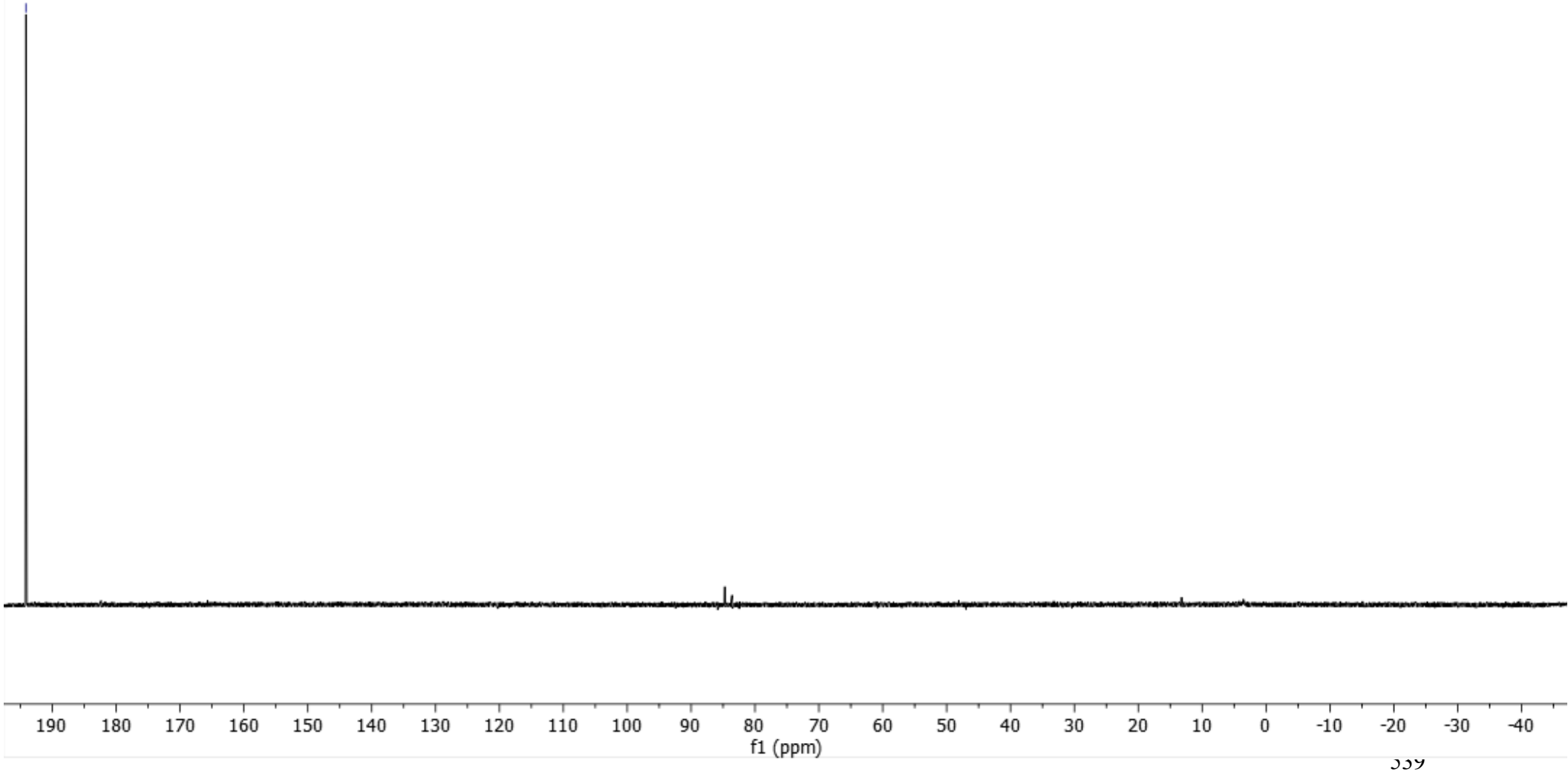



164.57
152.03
151.94
151.82
151.77
147.21
147.19
147.05
147.03
142.15
137.10
136.97
133.30
130.90
130.80
130.65
130.31
130.28
128.68
128.59
127.48
126.89
121.28
121.09
120.92
110.97
110.92
110.90
110.86
74.64
70.31
13C NMR (126 MHz, CDCl3)
O
O
P
O
N
O
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

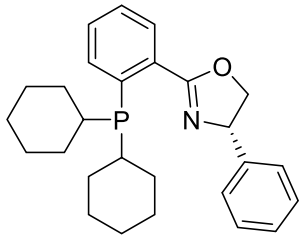
194.13

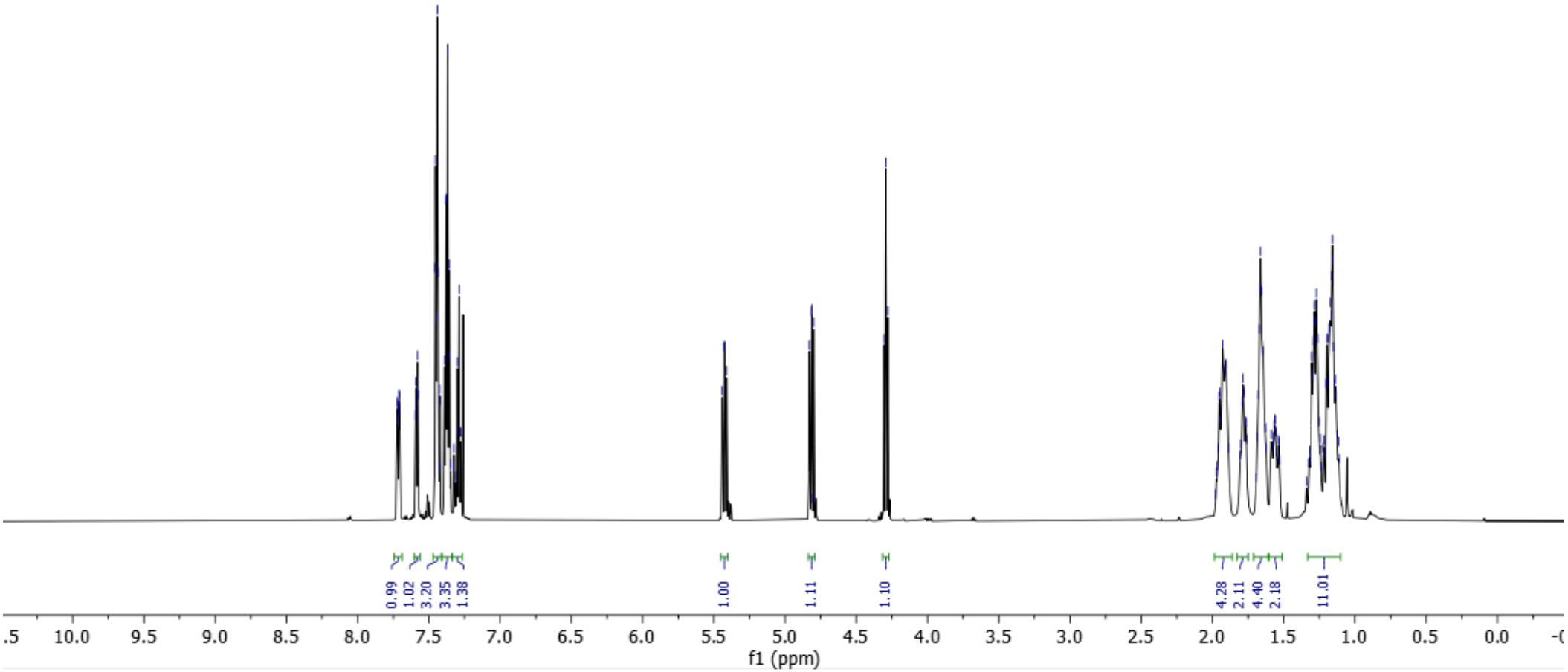
^{31}P NMR (243 MHz, $CDCl_3$)

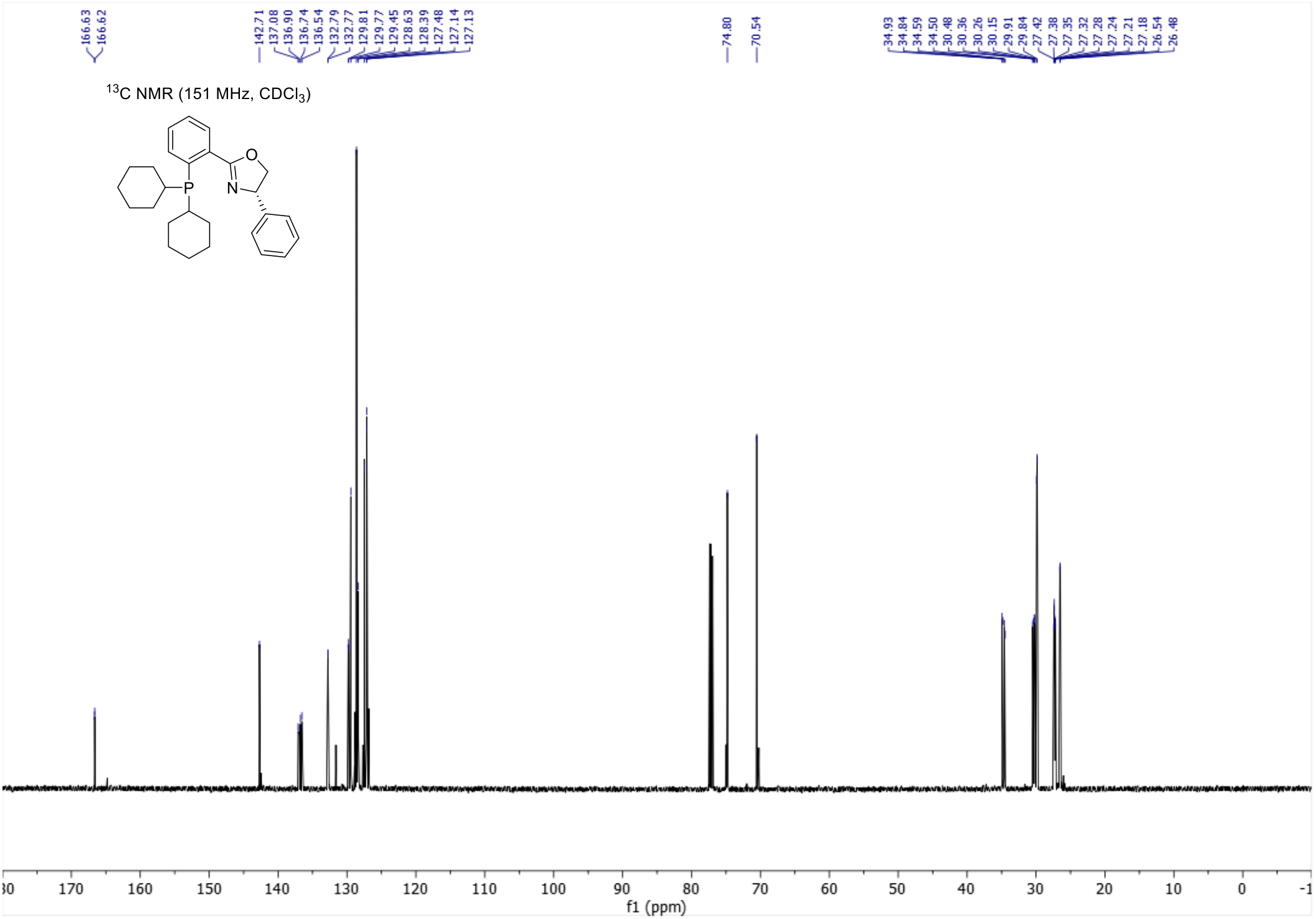




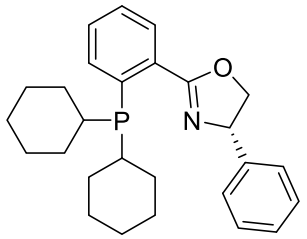
^{1}H NMR (600 MHz, $CDCl_3$)



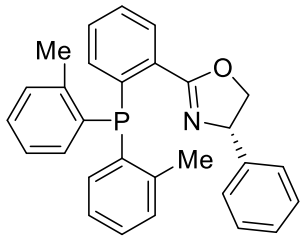


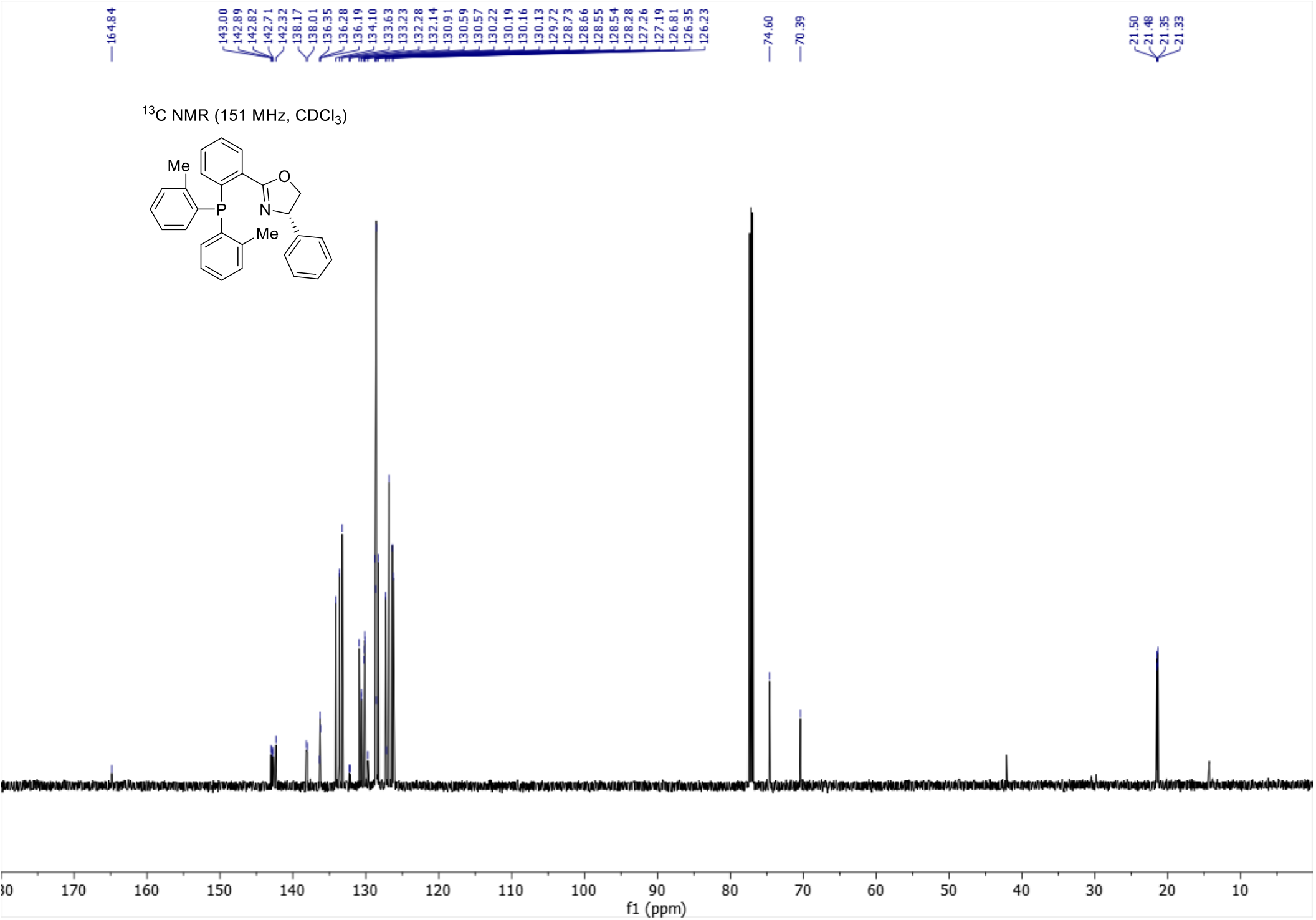

166.63
166.62
142.71
137.08
136.90
136.74
136.54
132.79
132.77
129.81
129.77
129.45
128.63
128.39
127.48
127.14
127.13
74.80
70.54
34.93
34.84
34.59
34.50
30.48
30.36
30.26
30.15
29.91
29.84
27.42
27.38
27.35
27.32
27.28
27.24
27.21
27.18
26.54
26.48
13C NMR (151 MHz, CDCl3)
O
N
P
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

^{31}P NMR (243 MHz, $CDCl_3$)

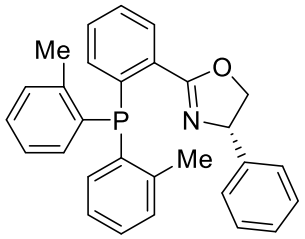


^{1}H NMR (600 MHz, $CDCl_3$)

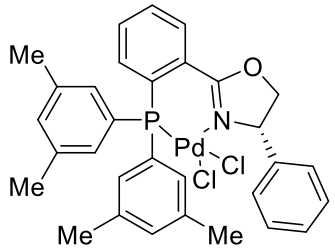


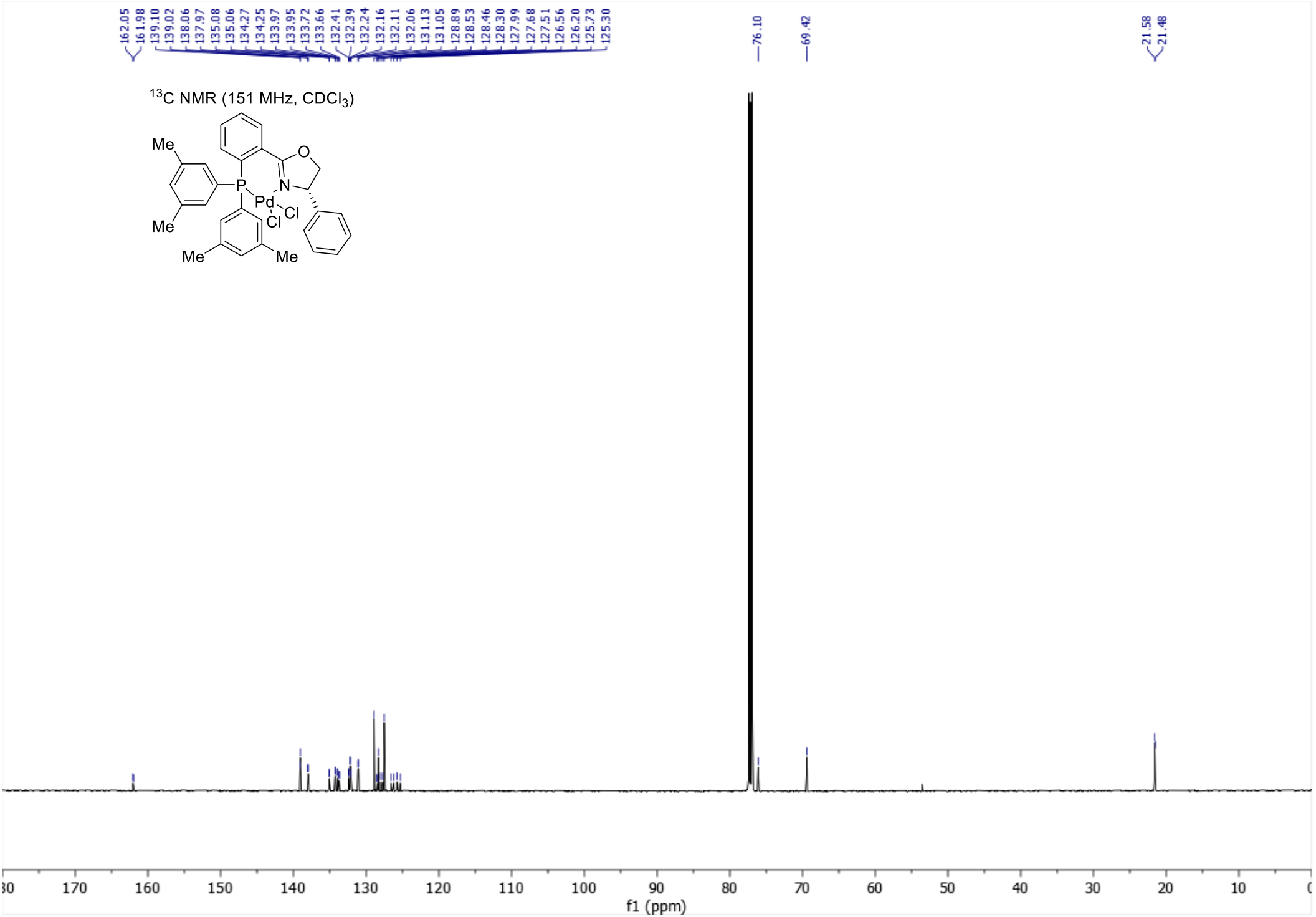

164.84
143.00
142.89
142.82
142.71
142.32
138.17
138.01
136.35
136.28
136.19
134.10
133.63
133.23
132.28
132.14
130.91
130.59
130.57
130.22
130.19
130.16
130.13
129.72
128.73
128.66
128.55
128.54
128.28
127.26
127.19
126.81
126.35
126.23
74.60
70.39
21.50
21.48
21.35
21.33
13C NMR (151 MHz, CDCl3)
Me
P
O
N
Me
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

^{31}P NMR (243 MHz, $CDCl_3$)

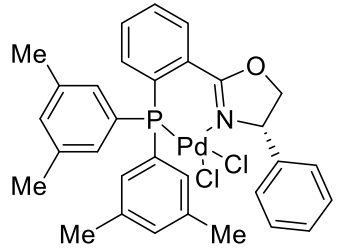


^{1}H NMR (500 MHz, $CDCl_3$)

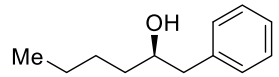


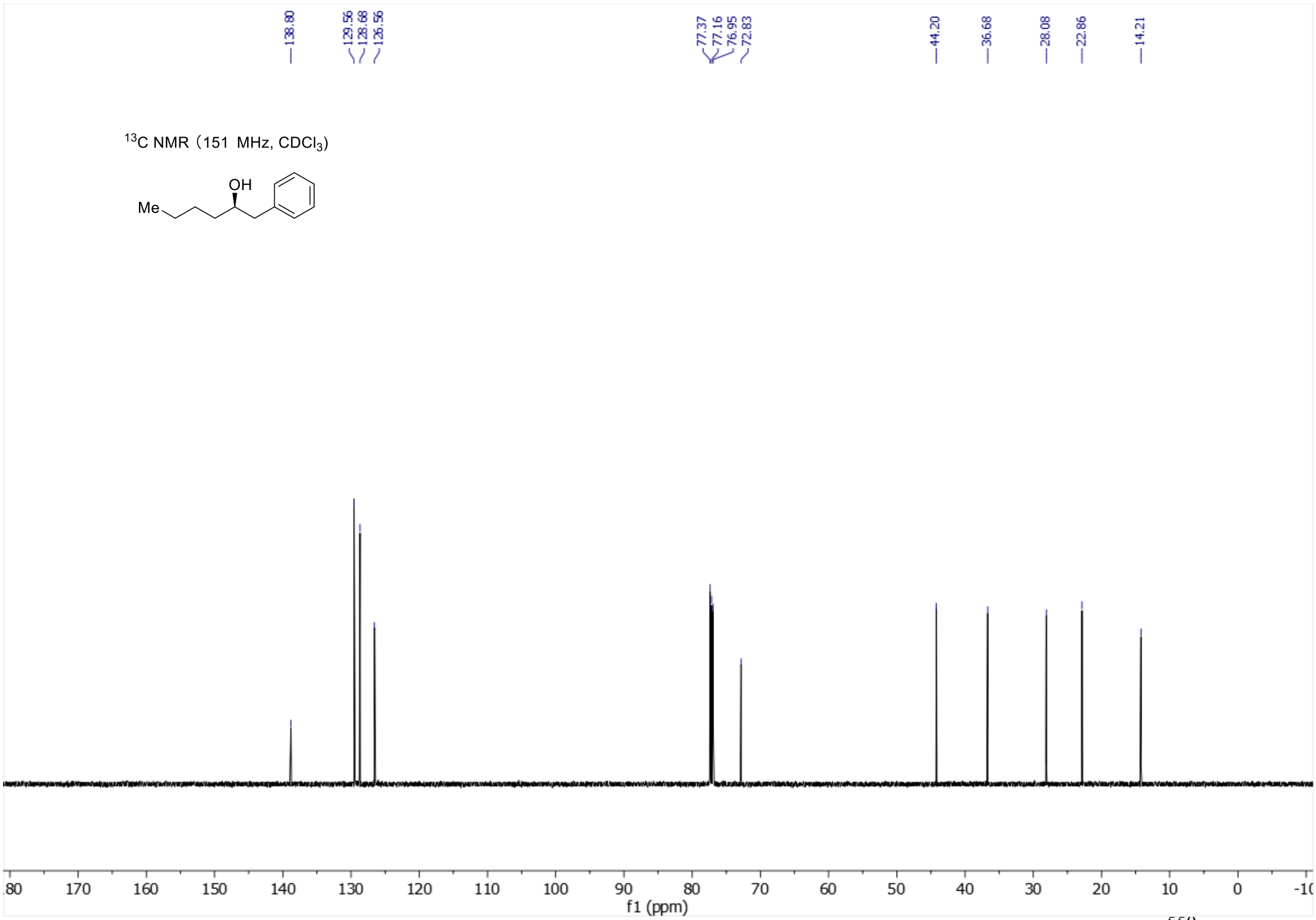

162.05
161.98
139.10
139.02
138.06
137.97
135.08
135.06
134.27
134.25
133.97
133.95
133.72
133.66
132.41
132.39
132.24
132.16
132.11
132.06
131.13
131.05
128.89
128.53
128.46
128.30
127.99
127.68
127.51
126.56
126.20
125.73
125.30
76.10
69.42
21.58
21.48
13C NMR (151 MHz, CDCl3)
Me
Me
Me
Me
P
Pd
Cl
Cl
O
N
f1 (ppm)

^{31}P NMR (202 MHz, $CDCl_3$)

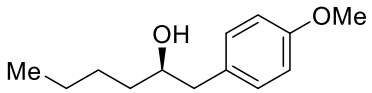


^{1}H NMR (600 MHz, $CDCl_3$)



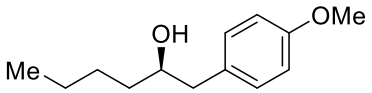

138.80
129.56
128.68
126.56
77.37
77.16
76.95
72.83
44.20
36.68
28.08
22.86
14.21
^{13}C NMR（151 MHz, $CDCl_3$）
OH
Me
f1 (ppm)

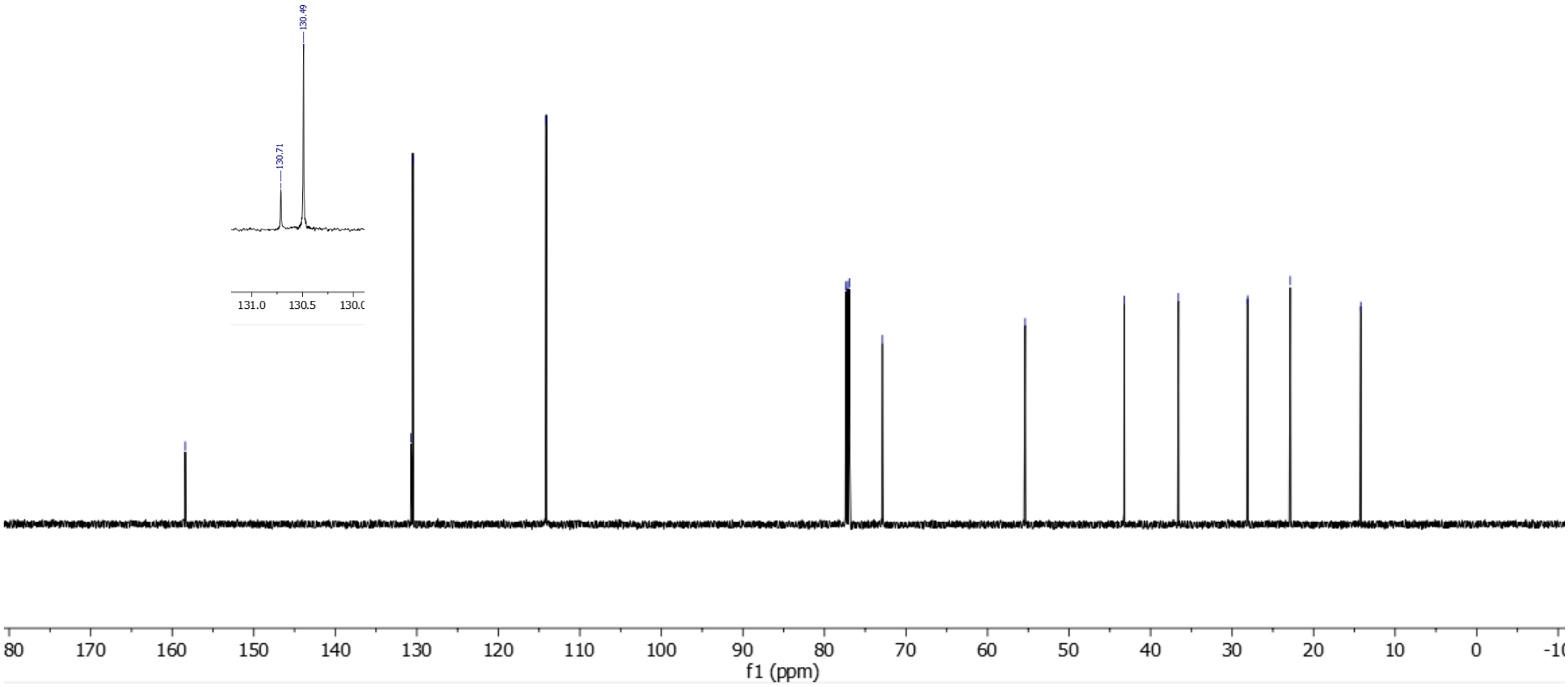
^{1}H NMR (600 MHz, $CDCl_3$)

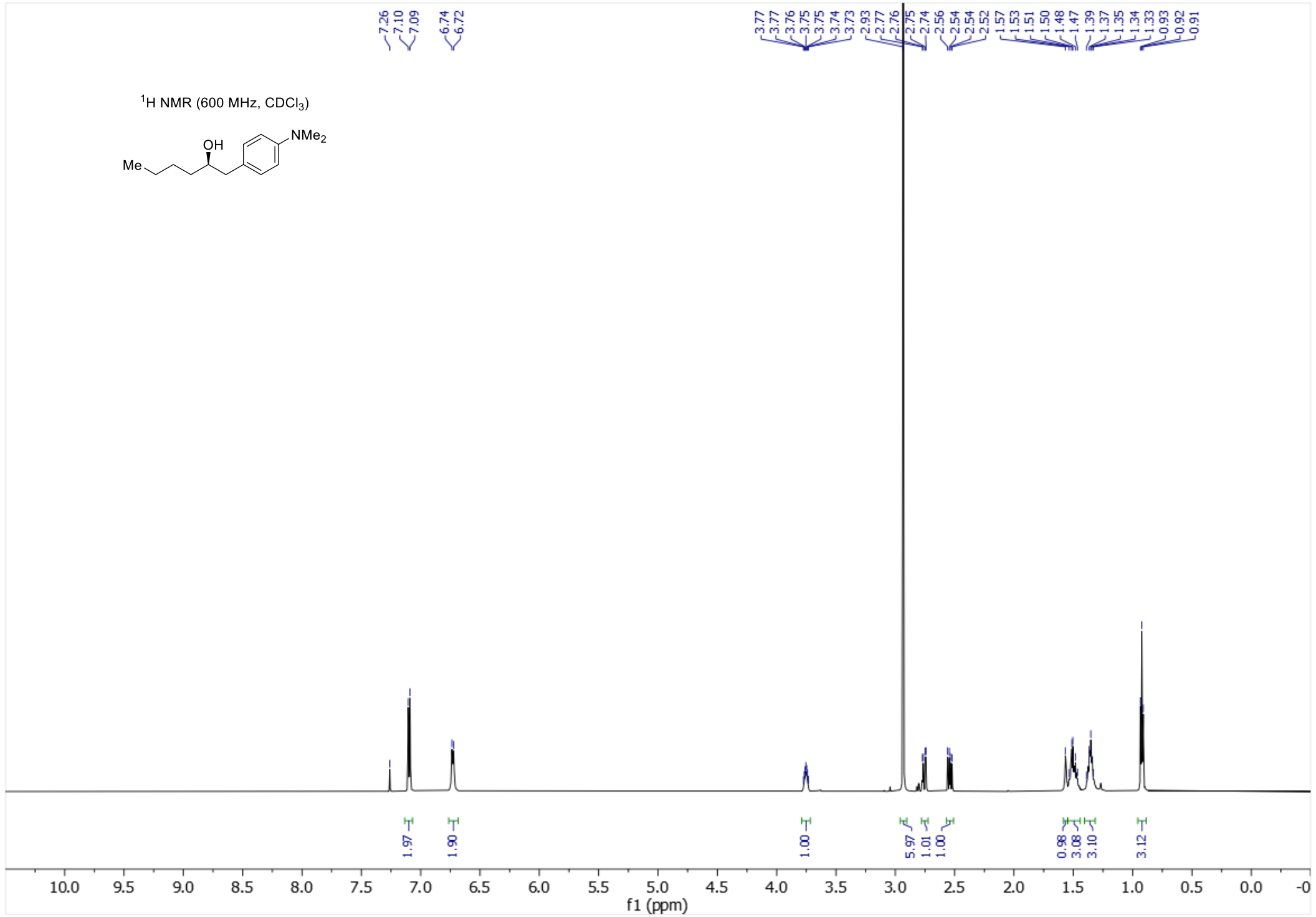


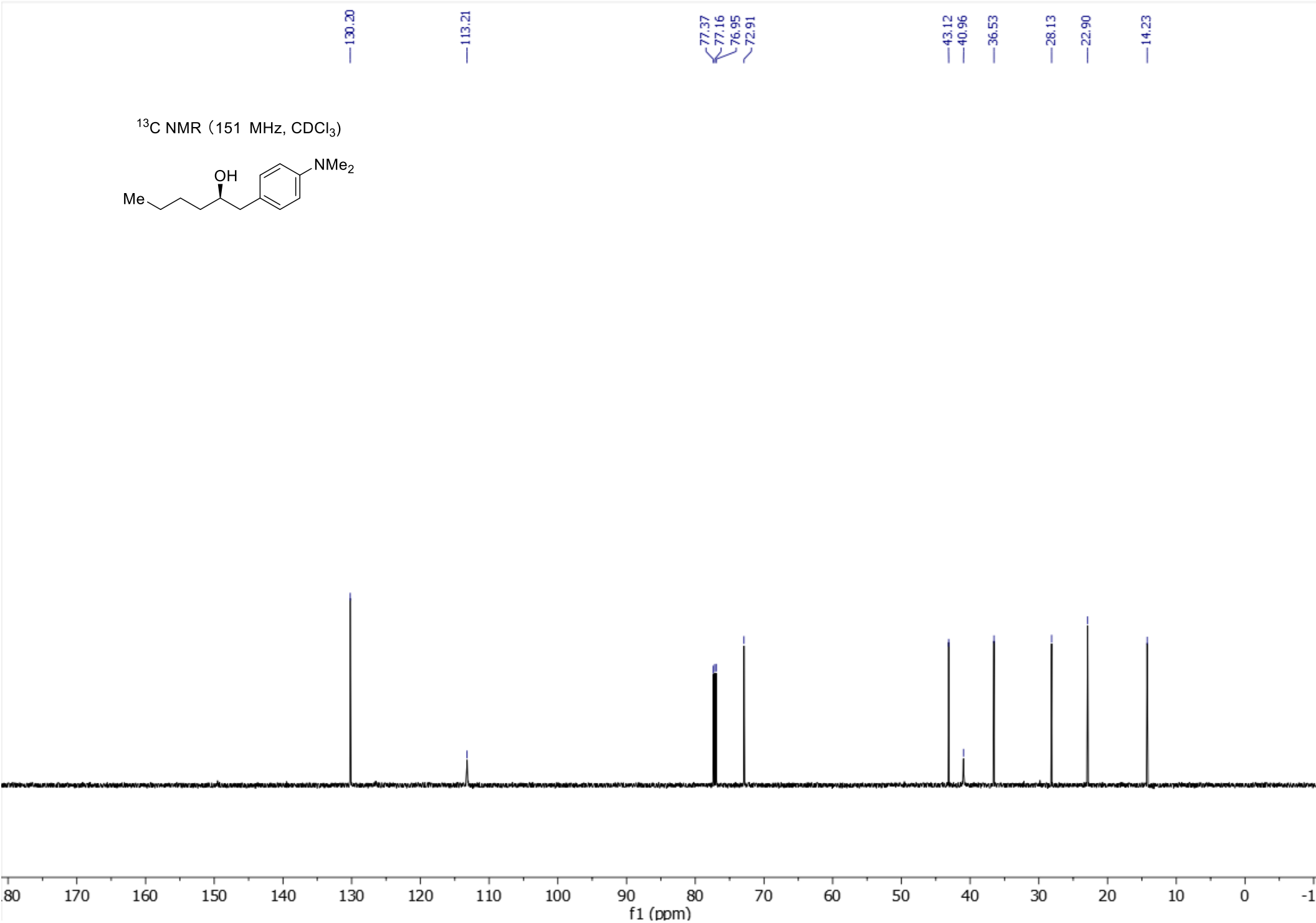
158.40
130.71
130.49
114.12
77.37
77.16
76.95
72.89
55.39
43.23
36.58
28.09
22.87
14.21

^{13}C NMR（151 MHz, $CDCl_3$）

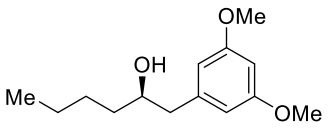


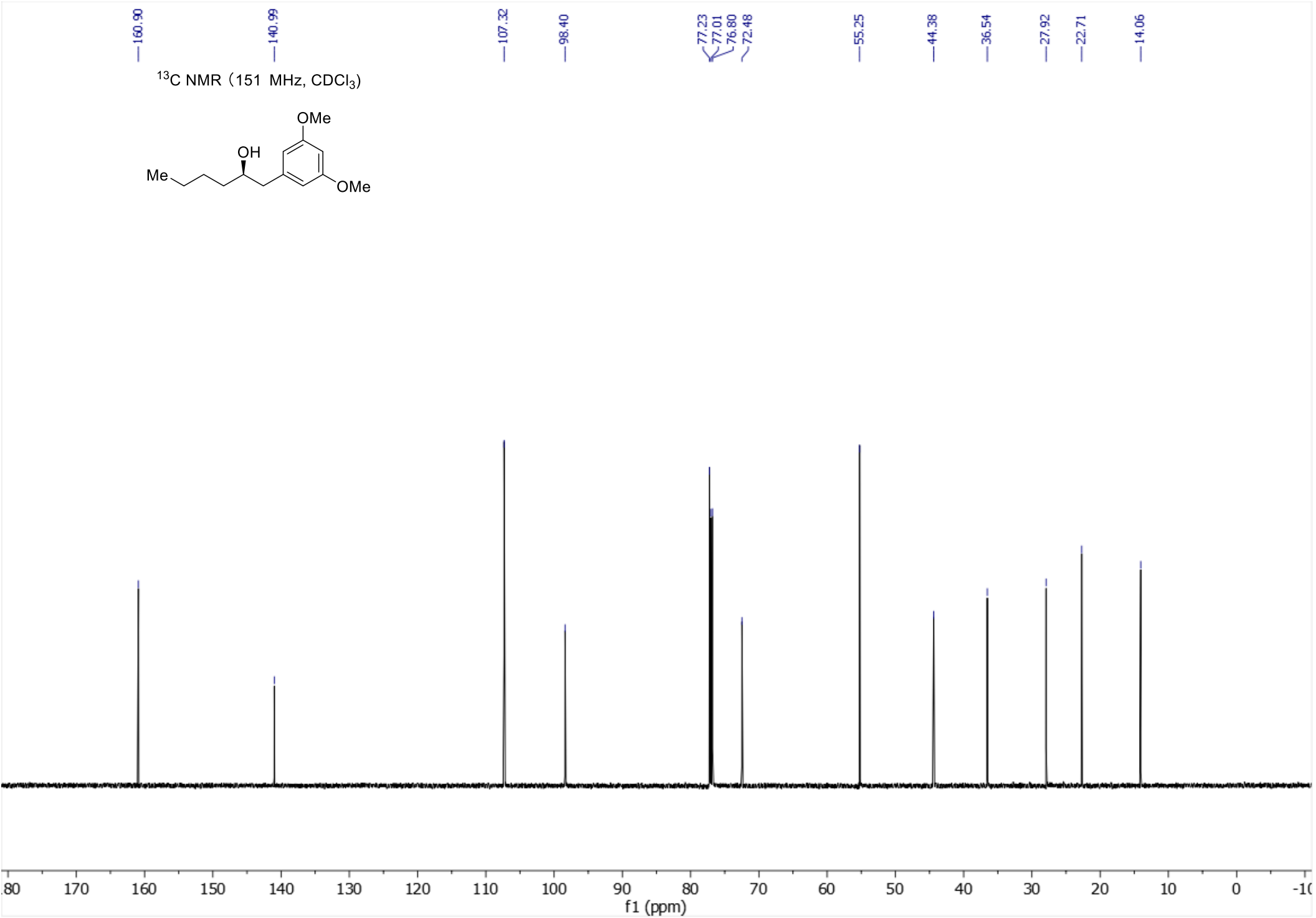



7.26
7.10
7.09
6.74
6.72
3.77
3.77
3.76
3.75
3.75
3.74
3.73
2.93
2.77
2.76
2.75
2.74
2.56
2.54
2.54
2.52
1.57
1.53
1.51
1.50
1.48
1.47
1.39
1.37
1.35
1.34
1.33
0.93
0.92
0.91
1H NMR (600 MHz, CDCl3)
OH
NMe2
Me
1.97
1.90
1.00
5.97
1.01
1.00
0.98
3.08
3.10
3.12
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0
f1 (ppm)

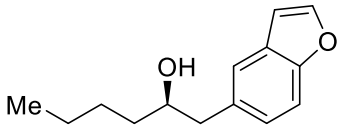

130.20
113.21
77.37
77.16
76.95
72.91
43.12
40.96
36.53
28.13
22.90
14.23
^{13}C NMR（151 MHz, $CDCl_3$）
OH
NMe$_2$
Me
f1 (ppm)

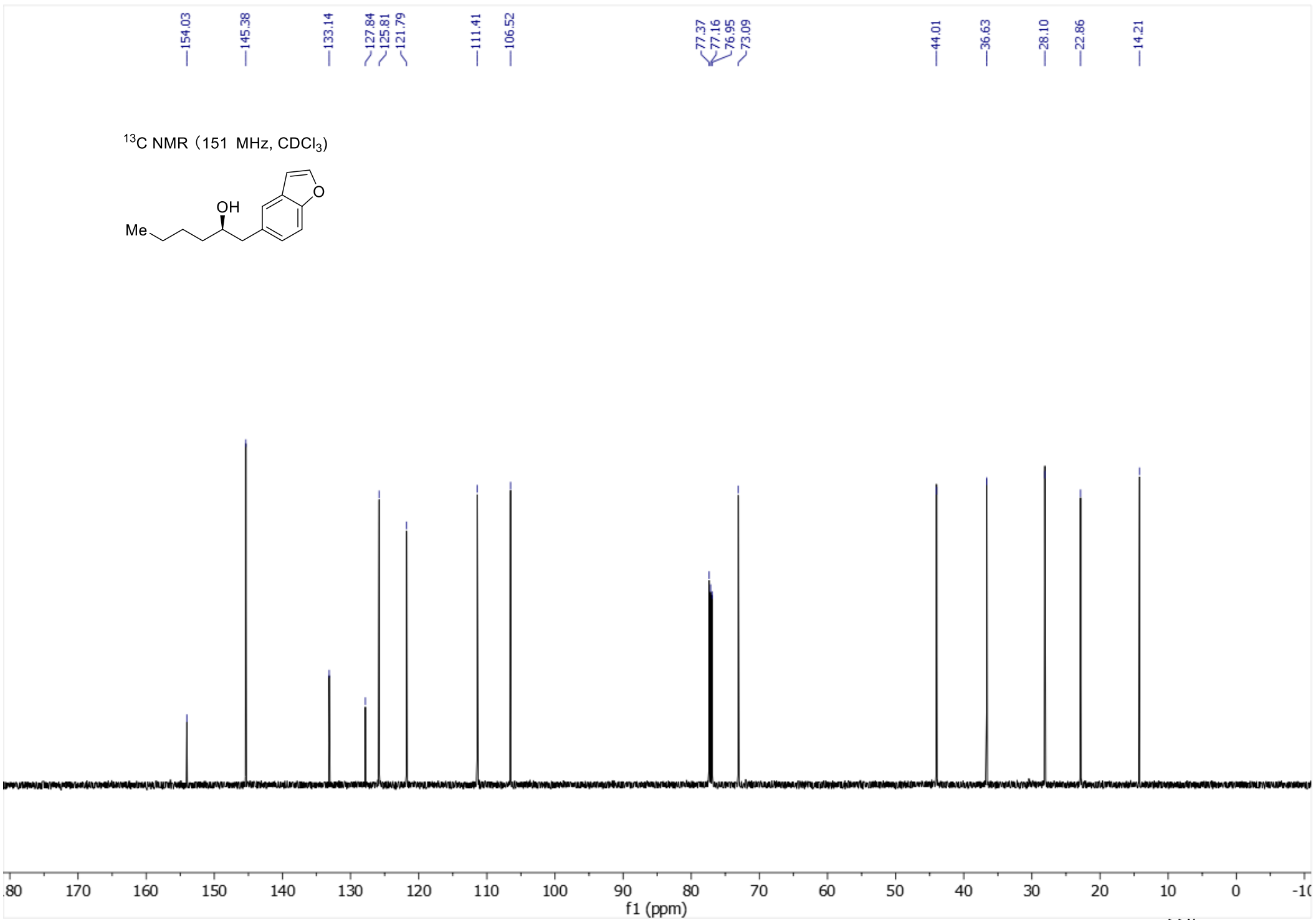
^{1}H NMR (600 MHz, $CDCl_3$)



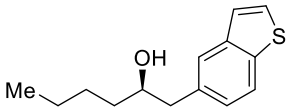

160.90
140.99
107.32
98.40
77.23
77.01
76.80
72.48
55.25
44.38
36.54
27.92
22.71
14.06
^{13}C NMR（151 MHz, $CDCl_3$）
OMe
OH
Me
OMe
f1 (ppm)

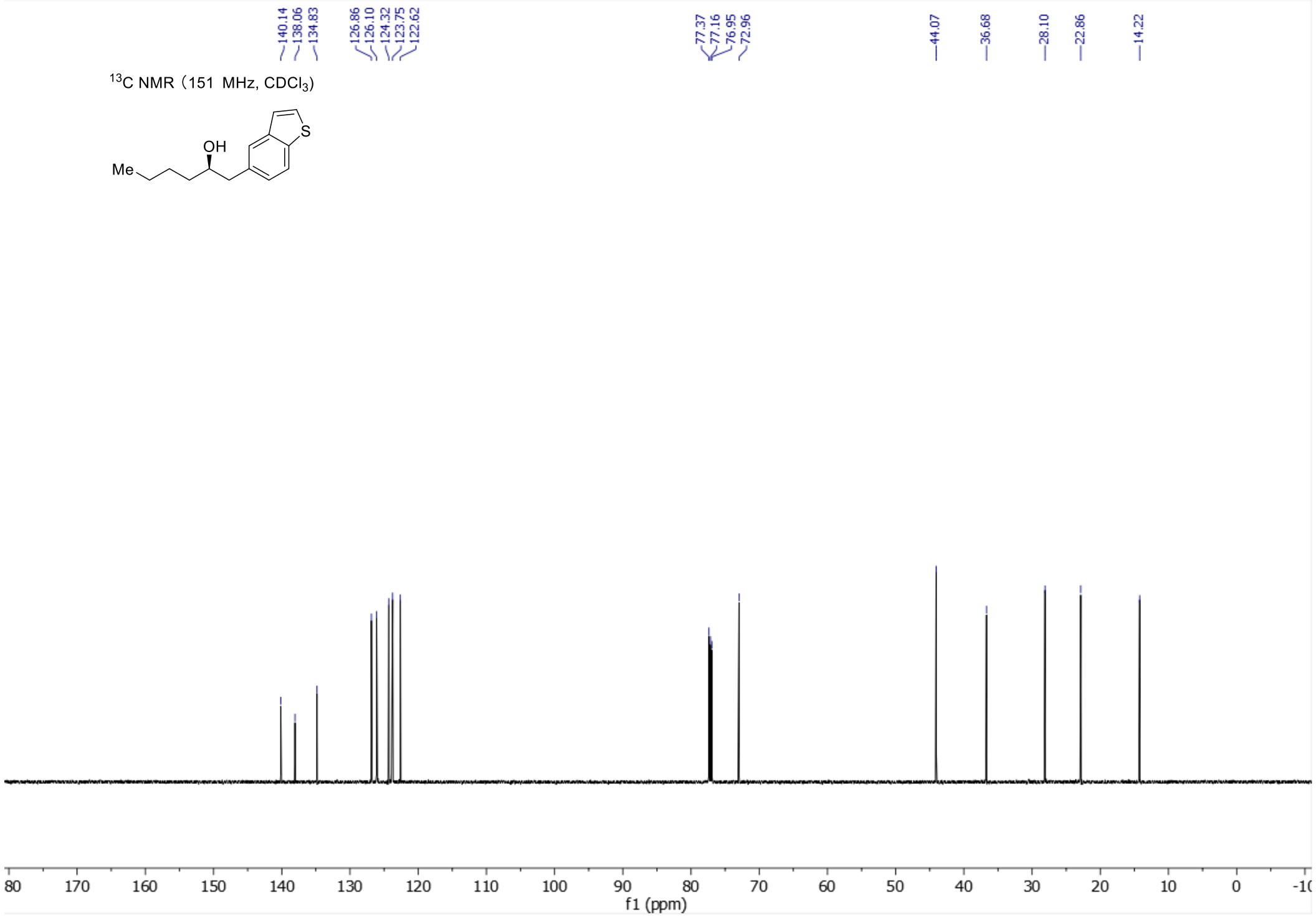
^{1}H NMR (600 MHz, $CDCl_3$)



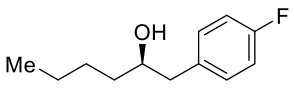

154.03
145.38
133.14
127.84
125.81
121.79
111.41
106.52
77.37
77.16
76.95
73.09
44.01
36.63
28.10
22.86
14.21
13C NMR（151 MHz, CDCl3）
OH
Me
O
f1 (ppm)

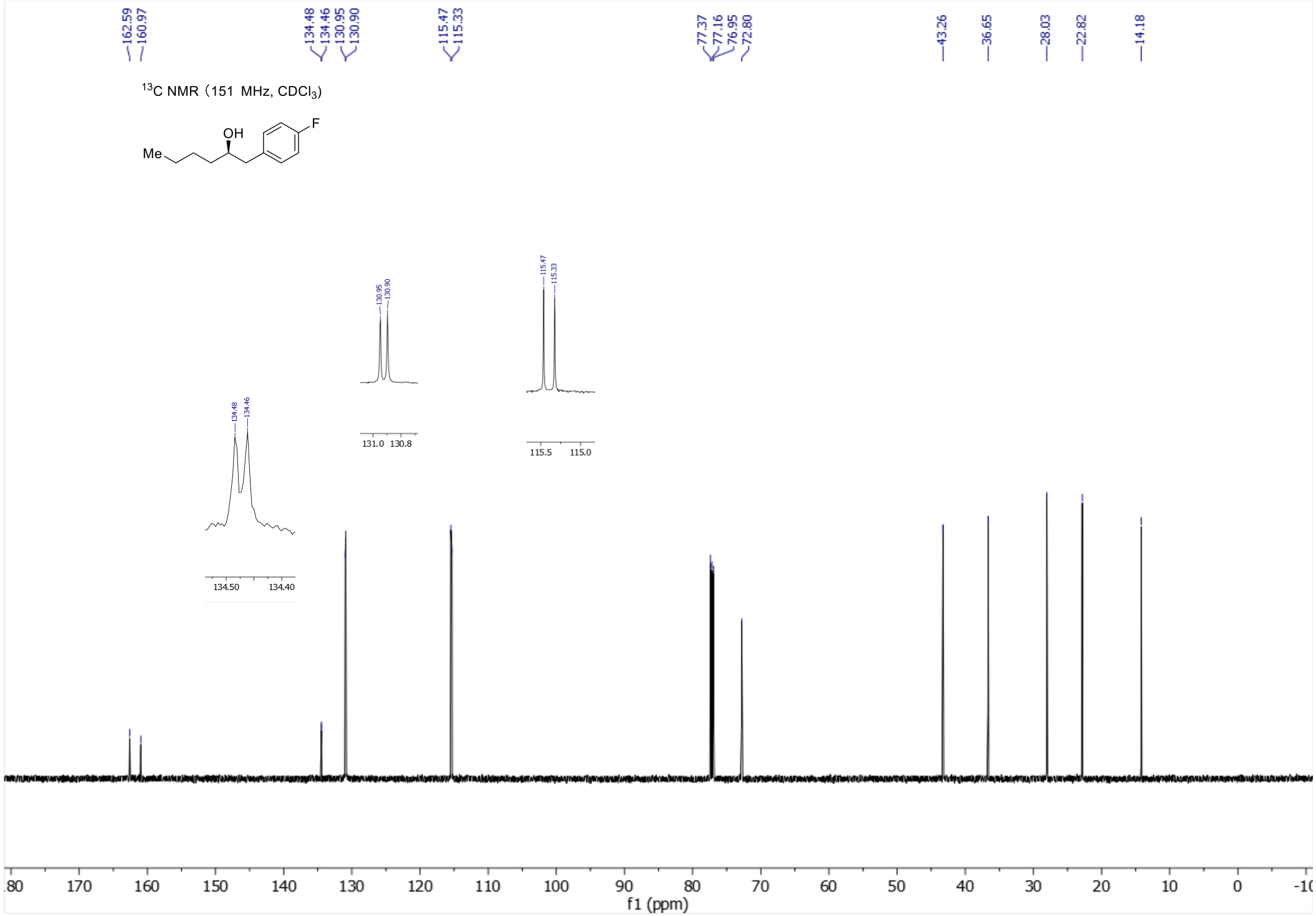
^{1}H NMR (600 MHz, $CDCl_3$)



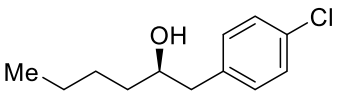

140.14
138.06
134.83
126.86
126.10
124.32
123.75
122.62
77.37
77.16
76.95
72.96
44.07
36.68
28.10
22.86
14.22
13C NMR（151 MHz, CDCl3）
OH
Me
S
f1 (ppm)

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

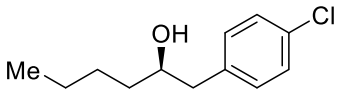



162.59
160.97
134.48
134.46
130.95
130.90
115.47
115.33
77.37
77.16
76.95
72.80
43.26
36.65
28.03
22.82
14.18
^{13}C NMR（151 MHz, $CDCl_3$）
OH
F
Me
130.95
130.90
131.0
130.8
115.47
115.33
115.5
115.0
134.48
134.46
134.50
134.40
f1 (ppm)

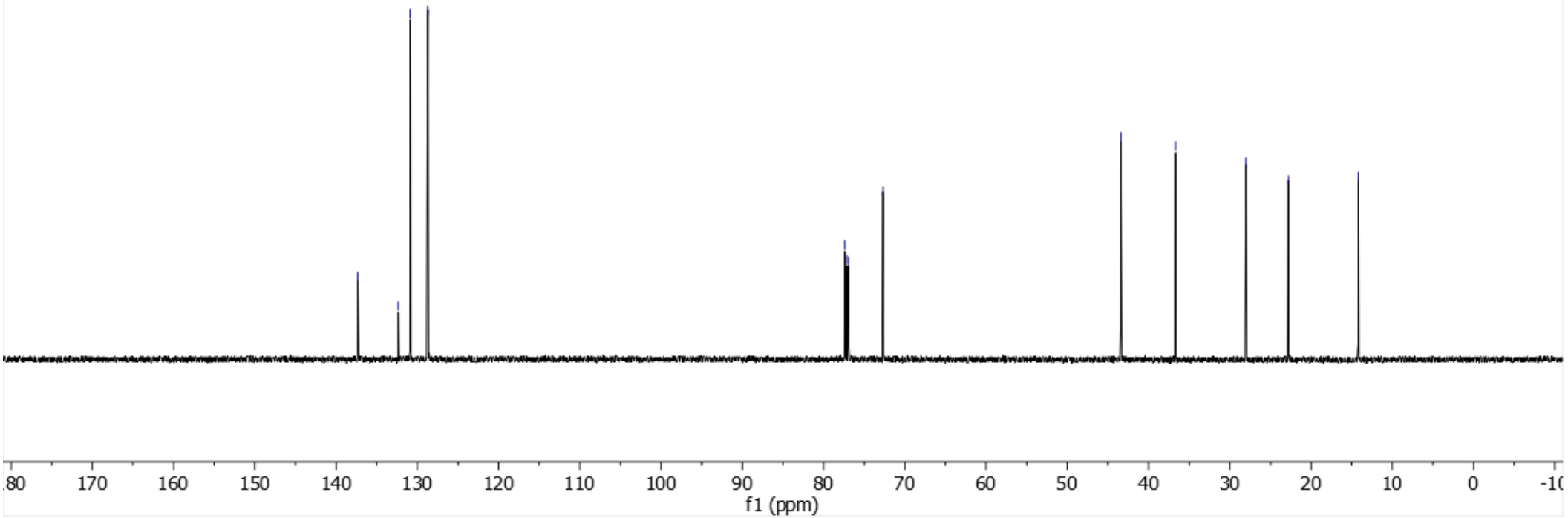
^{1}H NMR (600 MHz, $CDCl_3$)

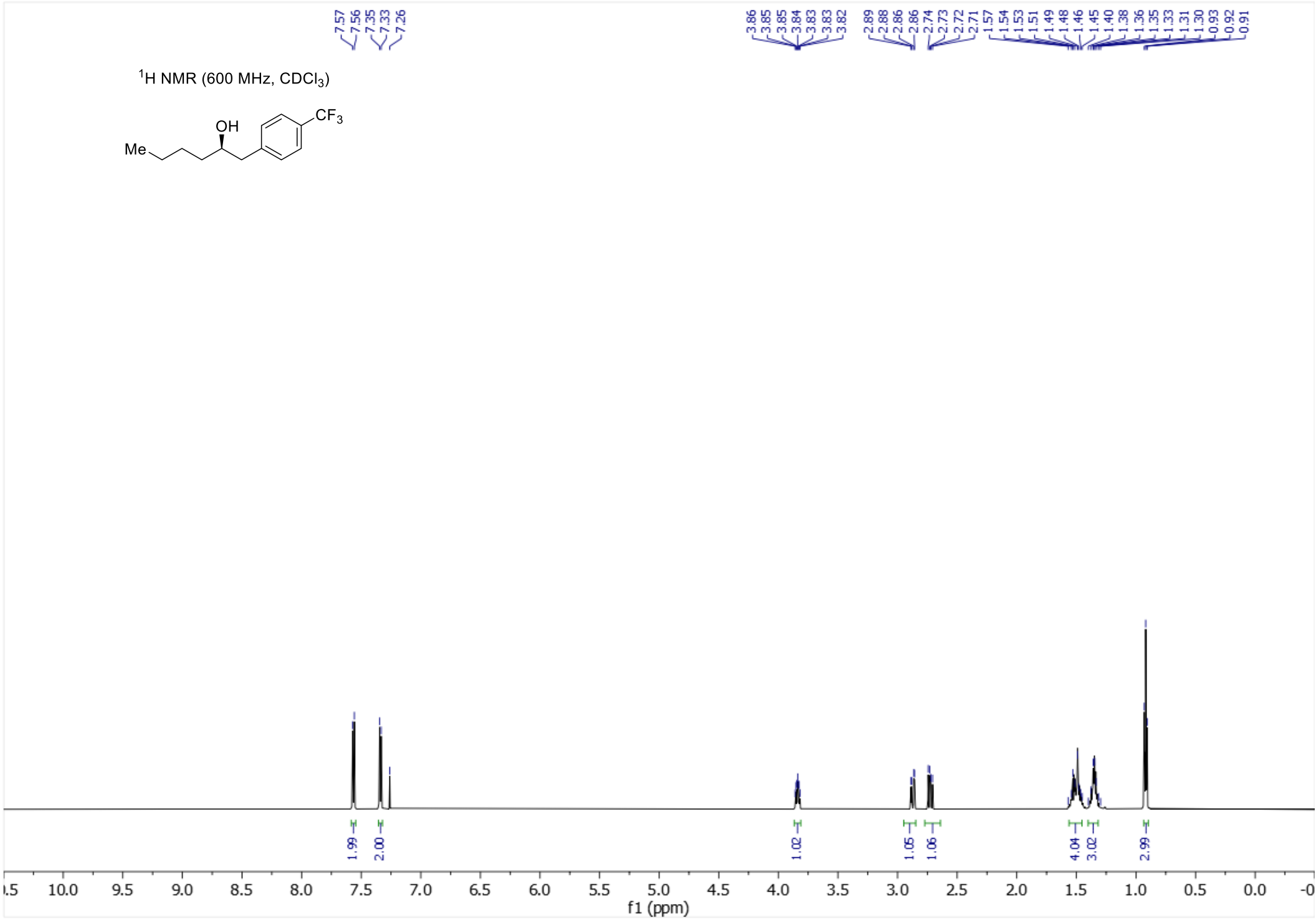


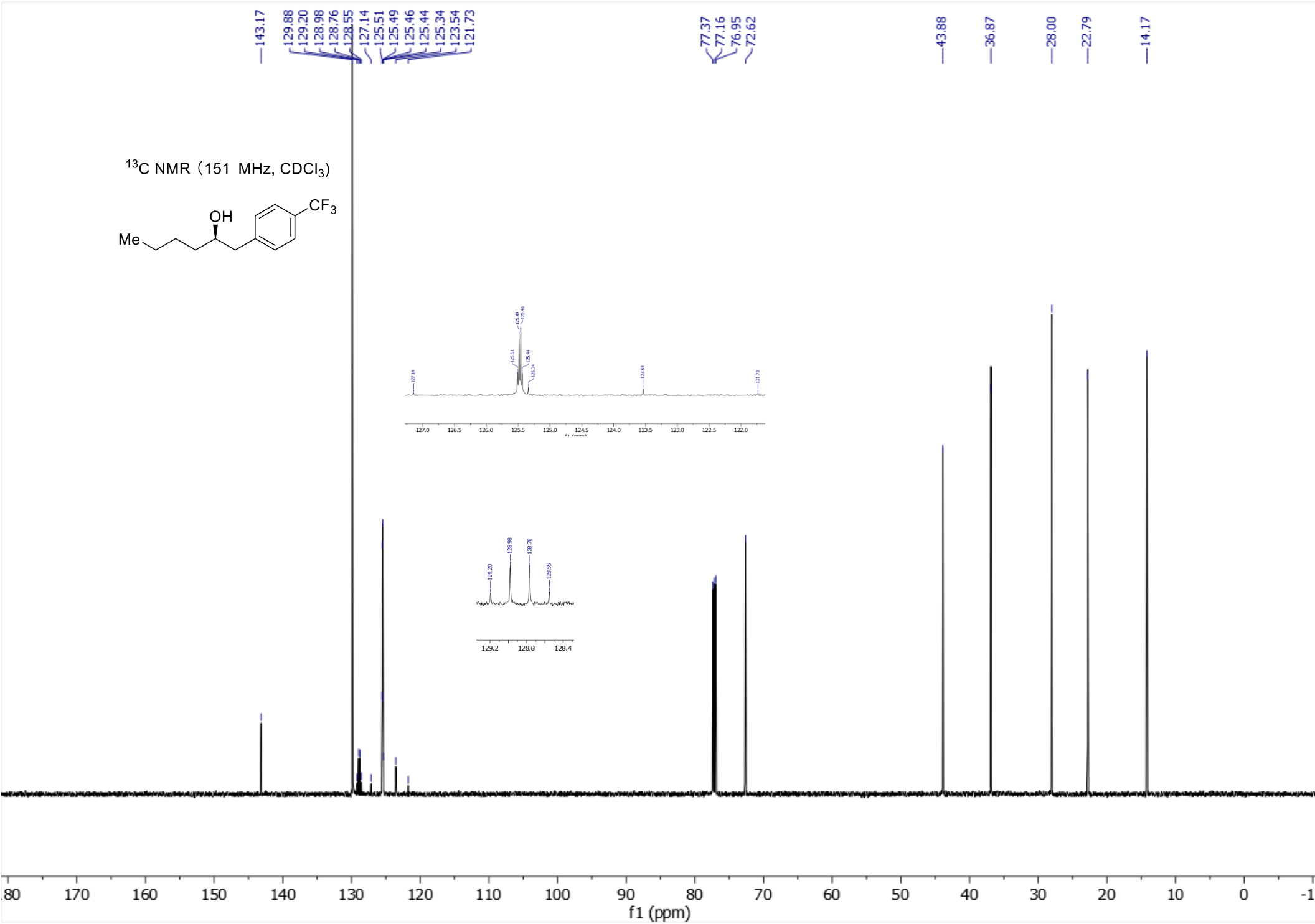
^{13}C NMR（151 MHz, $CDCl_3$）

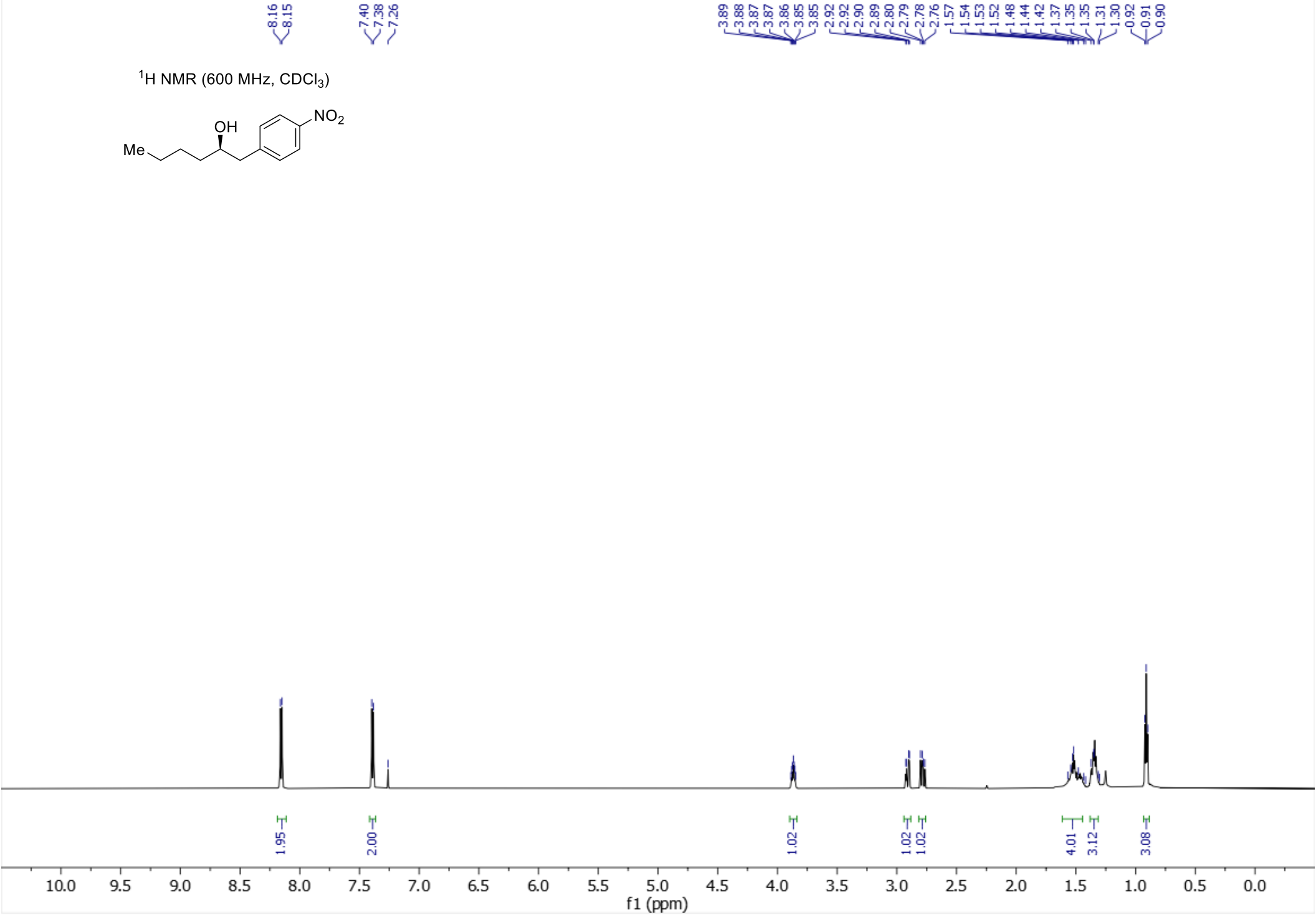


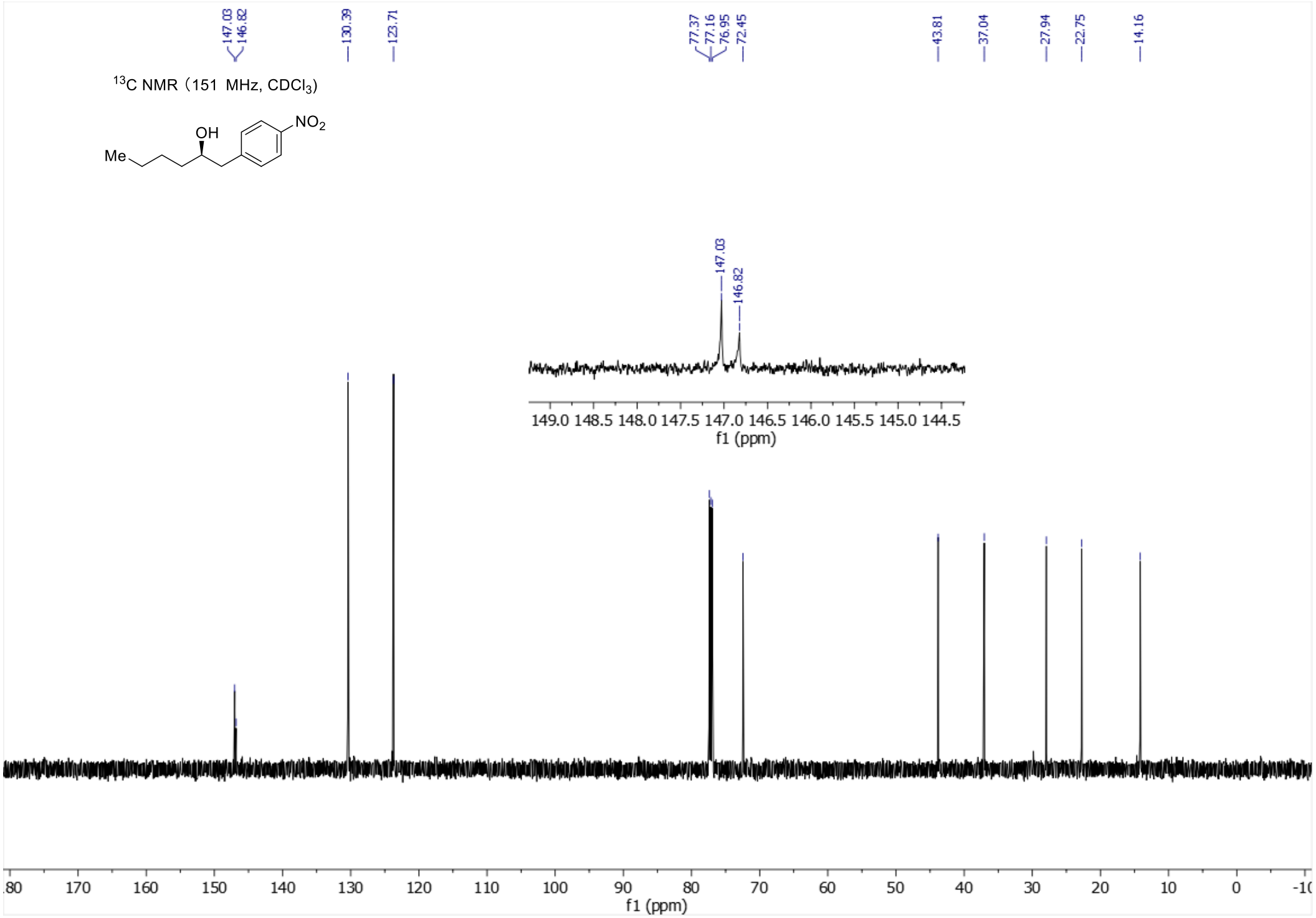
137.33
132.34
130.88
128.70
77.37
77.16
76.95
72.68
43.41
36.69
28.01
22.81
14.18



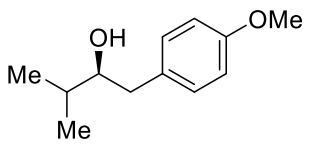

7.57
7.56
7.35
7.33
7.26
3.86
3.85
3.85
3.84
3.83
3.83
3.82
2.89
2.88
2.86
2.86
2.74
2.73
2.72
2.71
1.57
1.54
1.53
1.51
1.49
1.48
1.46
1.45
1.40
1.38
1.36
1.35
1.33
1.31
1.30
0.93
0.92
0.91
^{1}H NMR (600 MHz, $CDCl_3$)
OH
Me
CF_3
1.99
2.00
1.02
1.05
1.06
4.04
3.02
2.99
f1 (ppm)

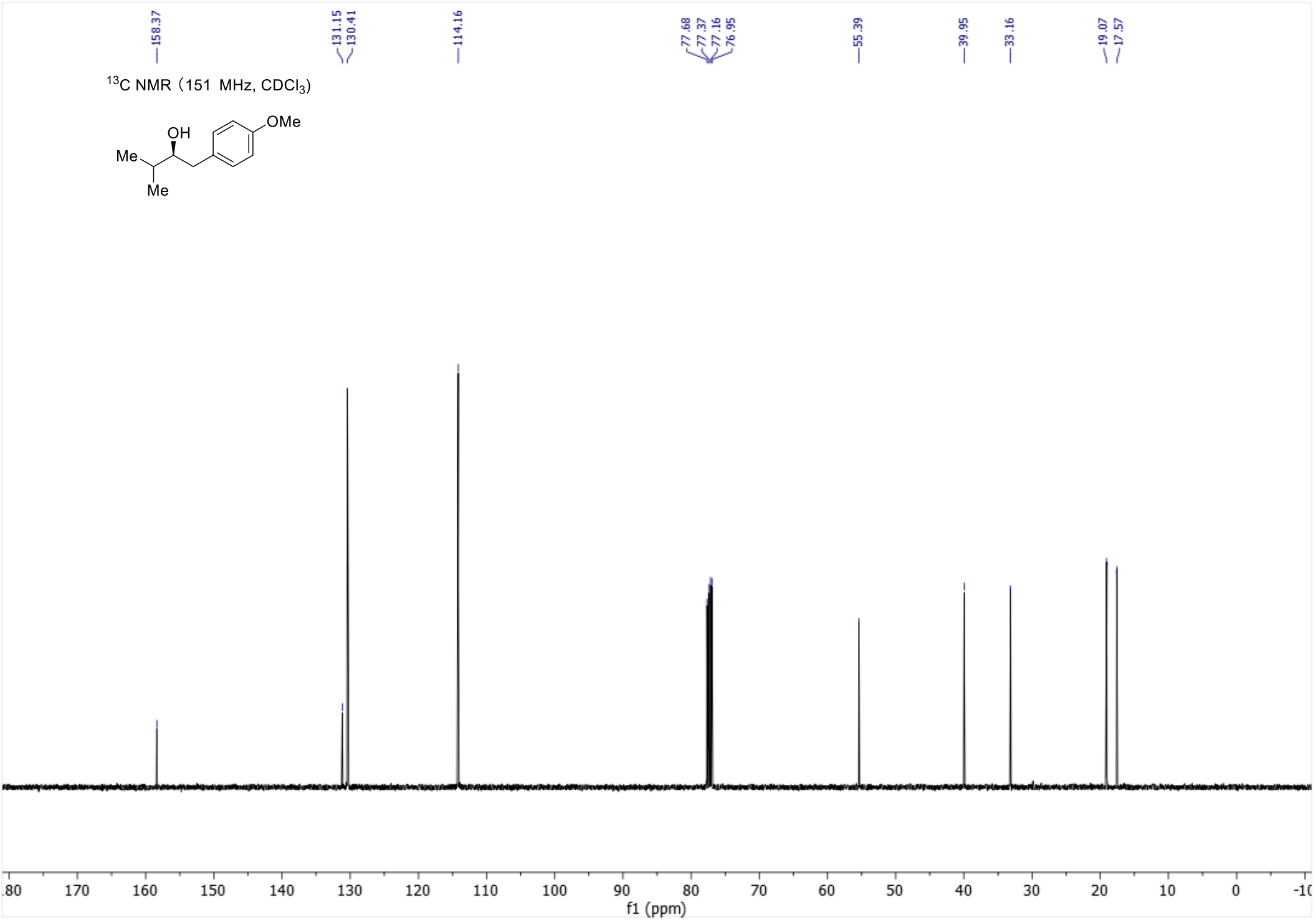

143.17
129.88
129.20
128.98
128.76
128.55
127.14
125.51
125.49
125.46
125.44
125.34
123.54
121.73
77.37
77.16
76.95
72.62
43.88
36.87
28.00
22.79
14.17
13C NMR (151 MHz, CDCl3)
OH
CF3
Me
f1 (ppm)


8.16
8.15
7.40
7.38
7.26
3.89
3.88
3.87
3.87
3.86
3.85
3.85
2.92
2.92
2.90
2.89
2.80
2.79
2.78
2.76
1.57
1.54
1.53
1.52
1.48
1.44
1.42
1.37
1.35
1.35
1.31
1.30
0.92
0.91
0.90
^{1}H NMR (600 MHz, $CDCl_3$)
OH
NO_2
Me
1.95
2.00
1.02
1.02
1.02
4.01
3.12
3.08
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
f1 (ppm)

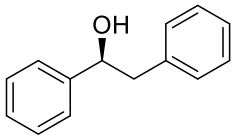

147.03
146.82
130.39
123.71
77.37
77.16
76.95
72.45
43.81
37.04
27.94
22.75
14.16
^{13}C NMR（151 MHz, $CDCl_3$）
OH
NO_2
Me
147.03
146.82
149.0 148.5 148.0 147.5 147.0 146.5 146.0 145.5 145.0 144.5
f1 (ppm)
f1 (ppm)

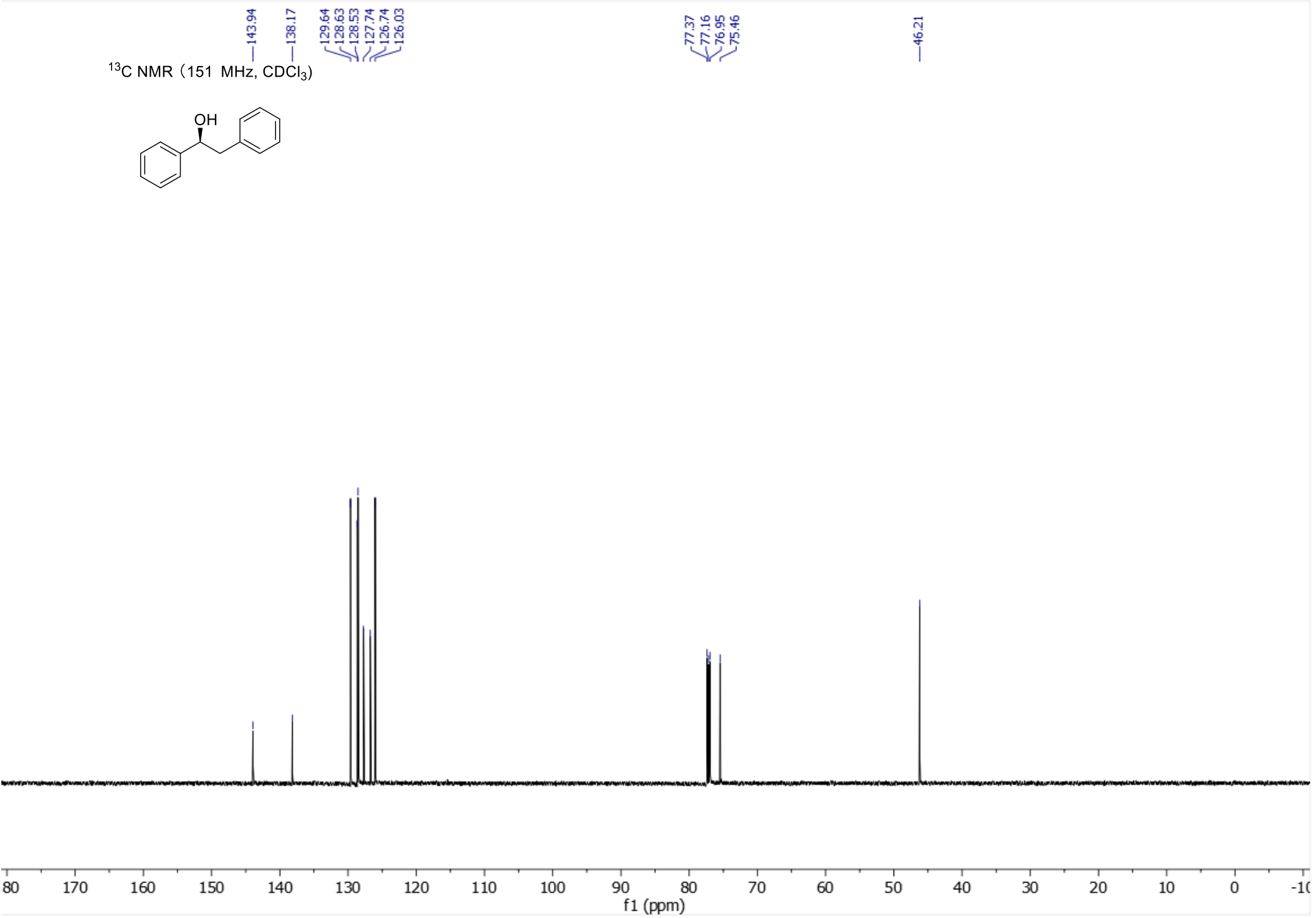
^{1}H NMR (500 MHz, $CDCl_3$)




158.37
131.15
130.41
114.16
77.68
77.37
77.16
76.95
55.39
39.95
33.16
19.07
17.57
^{13}C NMR（151 MHz, $CDCl_3$）
OH
OMe
Me
Me
f1 (ppm)

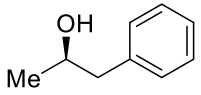
^{1}H NMR (600 MHz, $CDCl_3$)

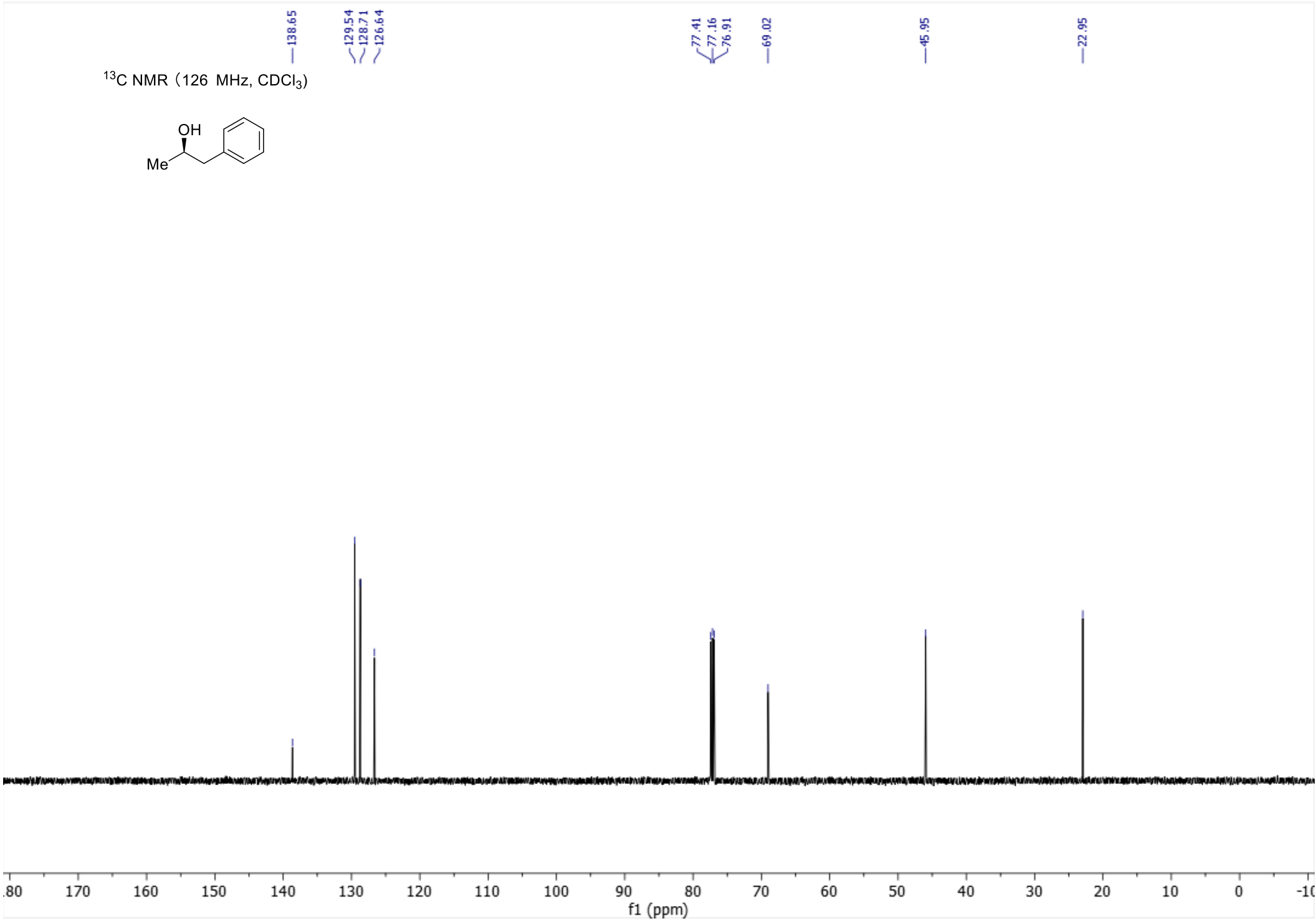




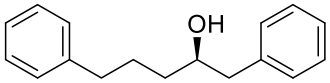
^{13}C NMR（151 MHz, $CDCl_3$）

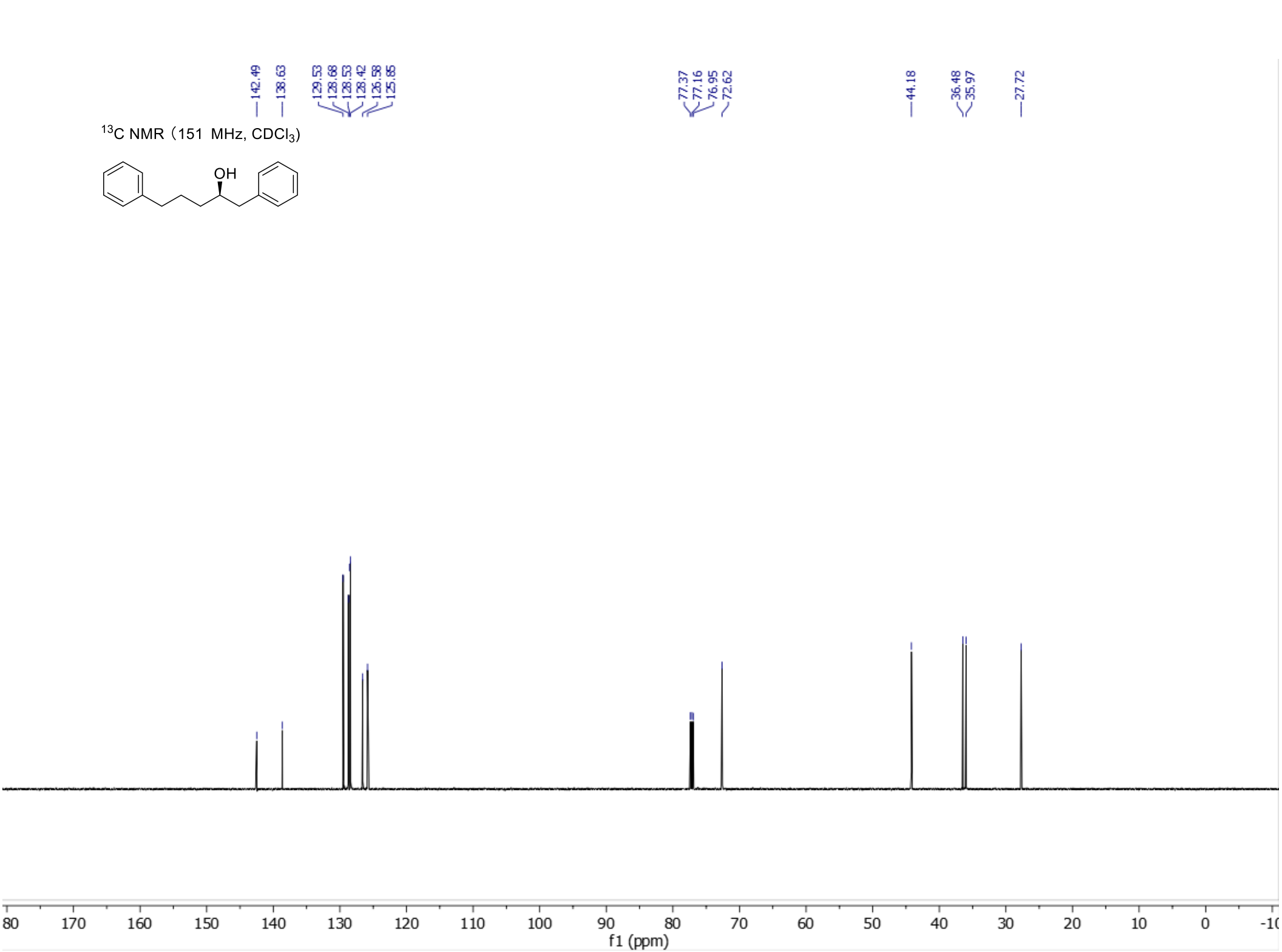
^{1}H NMR (500 MHz, $CDCl_3$)




138.65
129.54
128.71
126.64
77.41
77.16
76.91
69.02
45.95
22.95
^{13}C NMR（126 MHz, $CDCl_3$）
OH
Me
f1 (ppm)

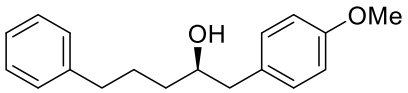
^{1}H NMR (600 MHz, $CDCl_3$)





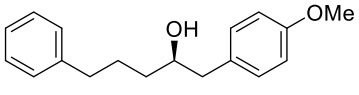
^{13}C NMR（151 MHz, $CDCl_3$）

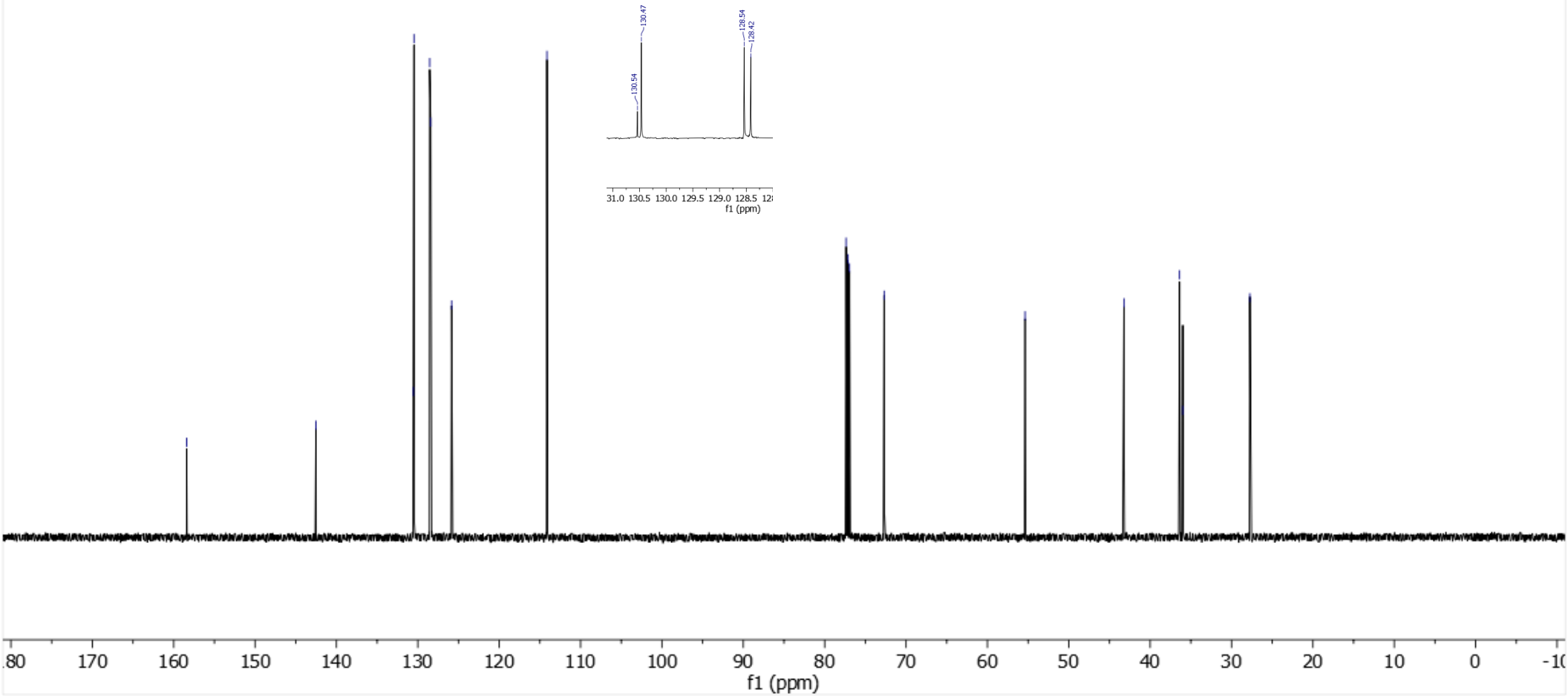
^{1}H NMR (600 MHz, $CDCl_3$)

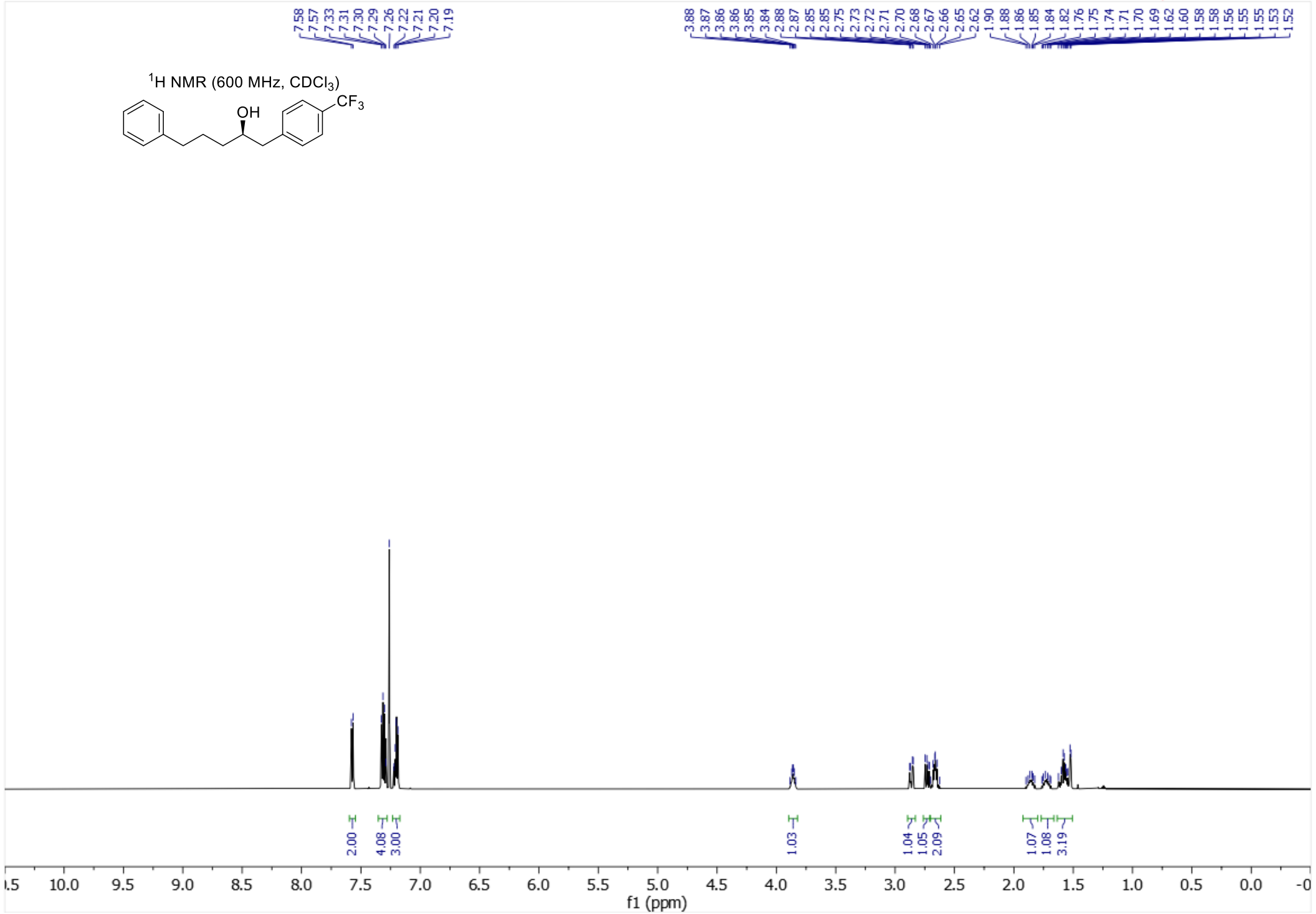


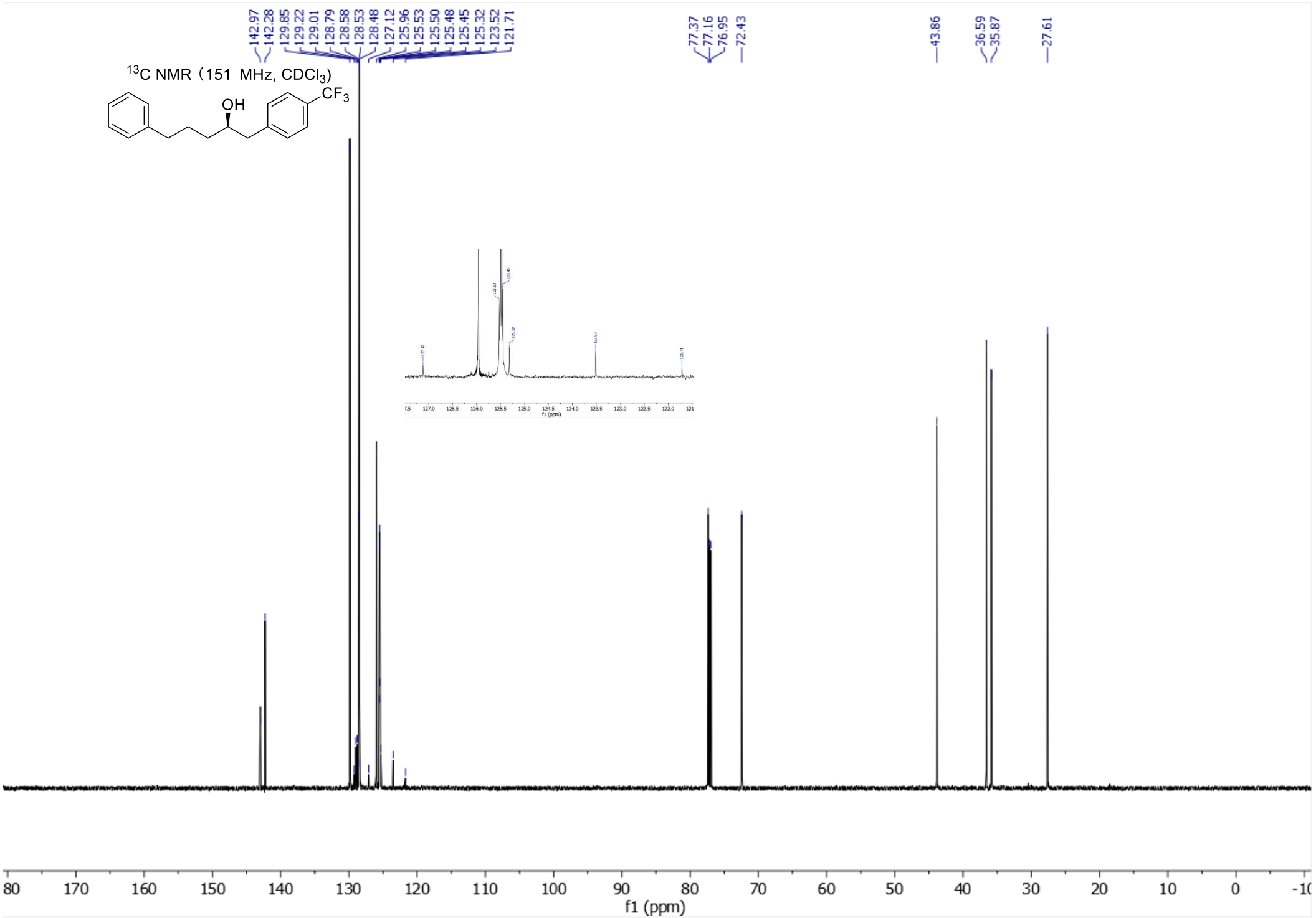
158.41
142.51
130.54
130.47
128.54
128.42
125.84
114.13
77.37
77.16
76.95
72.69
55.37
43.22
36.39
35.99
27.74

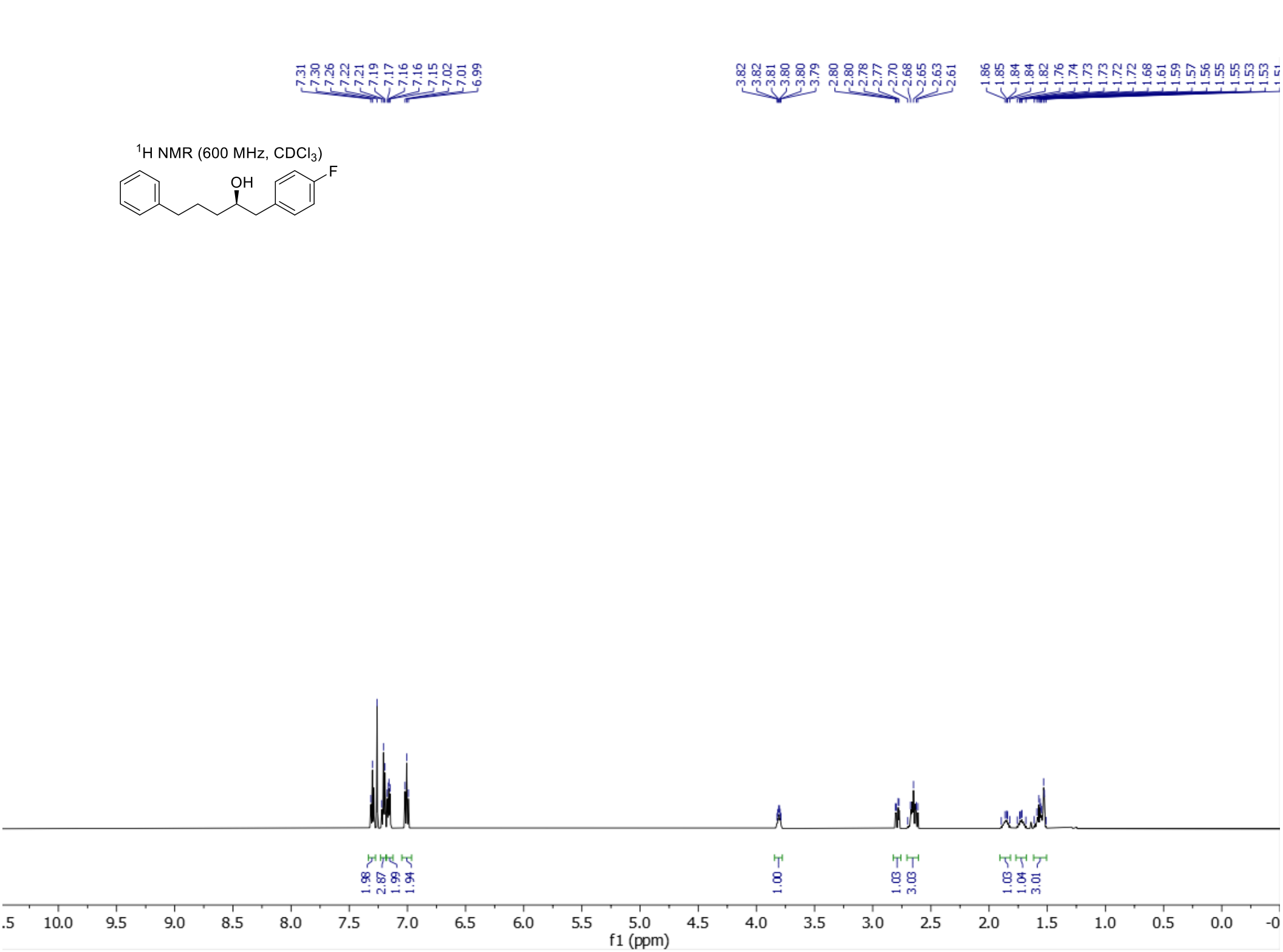
^{13}C NMR（151 MHz, $CDCl_3$）

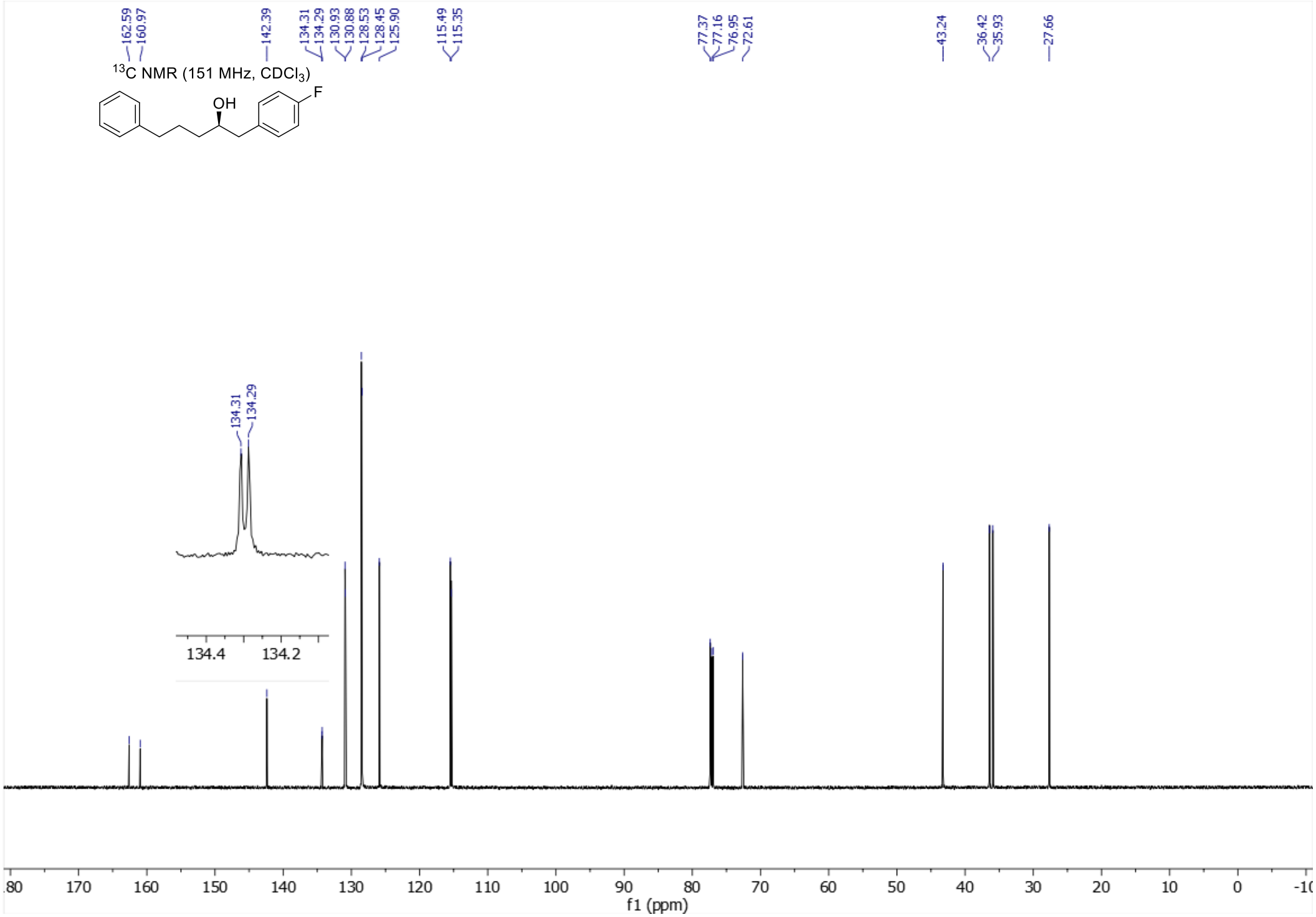


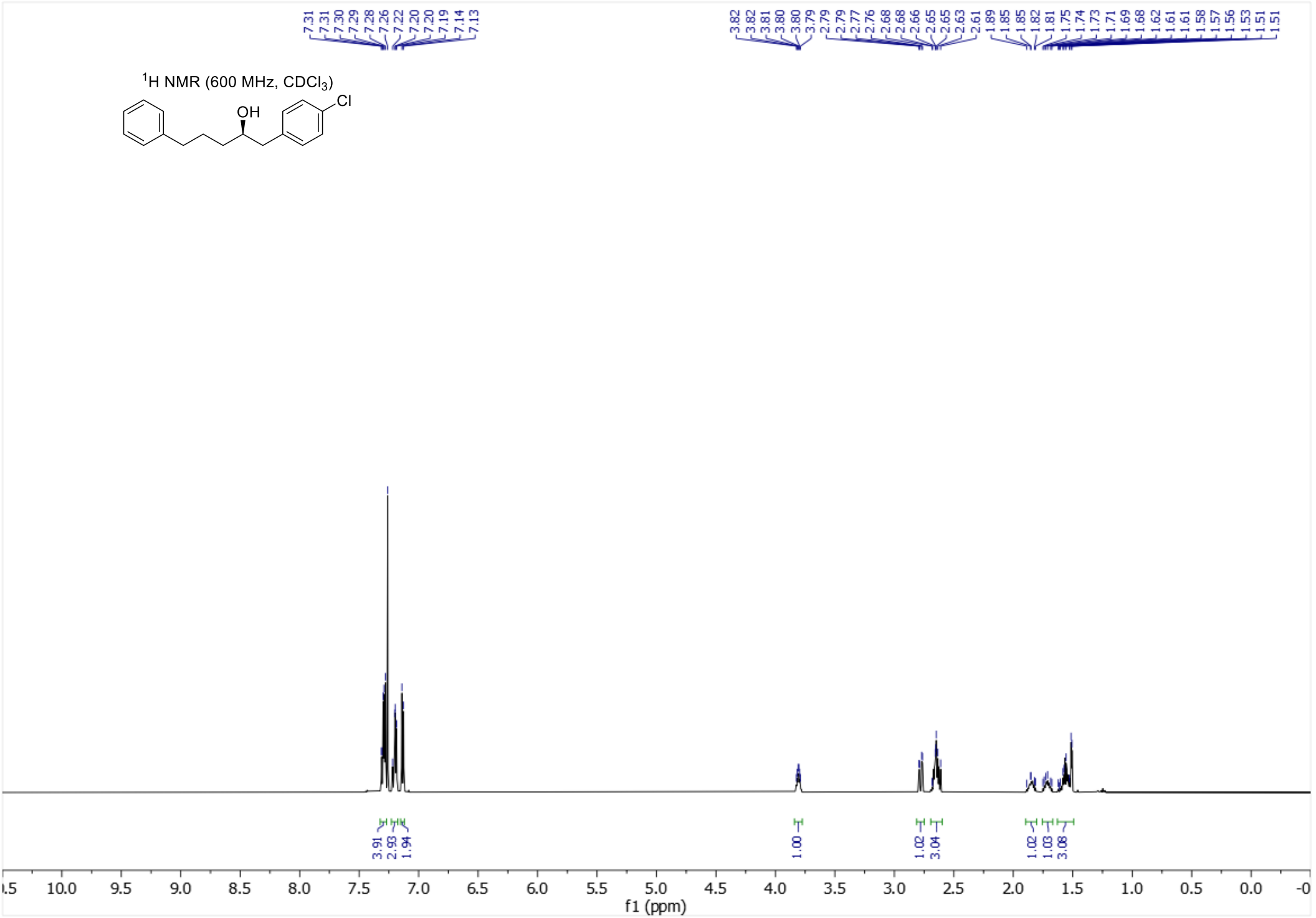


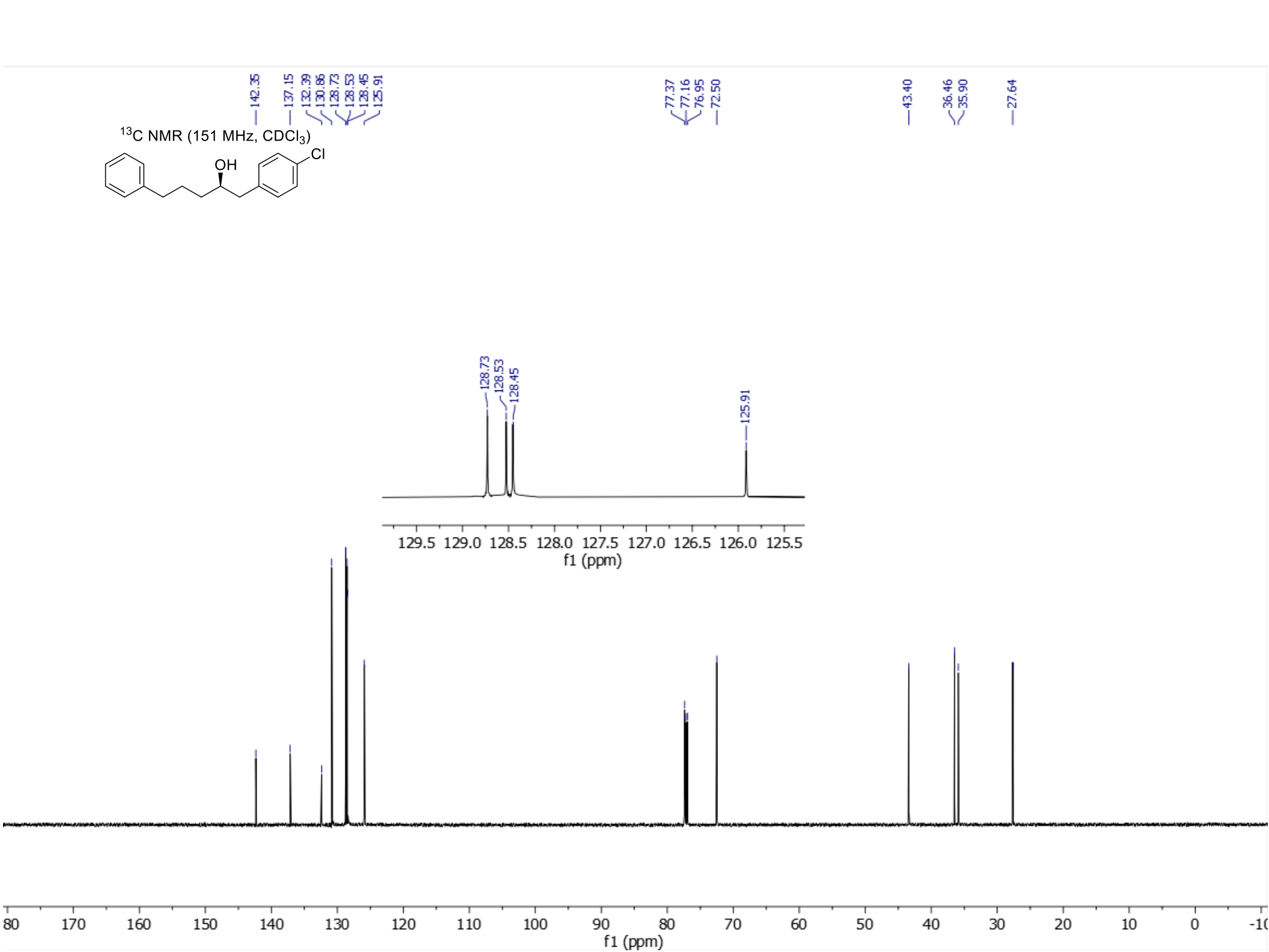

7.58
7.57
7.33
7.31
7.30
7.29
7.26
7.22
7.21
7.20
7.19
3.88
3.87
3.86
3.86
3.85
3.84
2.88
2.87
2.85
2.85
2.75
2.73
2.72
2.71
2.70
2.68
2.67
2.66
2.65
2.62
1.90
1.88
1.86
1.85
1.84
1.82
1.76
1.75
1.74
1.71
1.70
1.69
1.62
1.60
1.58
1.58
1.56
1.55
1.55
1.53
1.52
1H NMR (600 MHz, CDCl3)
OH
CF3
2.00
4.08
3.00
1.03
1.04
1.05
2.09
1.07
1.08
3.19
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
f1 (ppm)


142.97
142.28
129.85
129.22
129.01
128.79
128.58
128.53
128.48
127.12
125.96
125.53
125.50
125.48
125.45
125.32
123.52
121.71
77.37
77.16
76.95
72.43
43.86
36.59
35.87
27.61
^{13}C NMR (151 MHz, $CDCl_3$)
OH
CF_3
f1 (ppm)

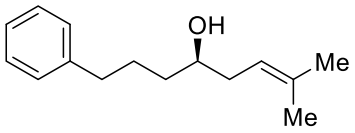

7.31
7.30
7.26
7.22
7.21
7.19
7.17
7.16
7.16
7.15
7.02
7.01
6.99
3.82
3.82
3.81
3.80
3.80
3.79
2.80
2.80
2.78
2.77
2.70
2.68
2.65
2.63
2.61
1.86
1.85
1.84
1.84
1.82
1.76
1.74
1.73
1.73
1.72
1.72
1.68
1.61
1.59
1.57
1.56
1.55
1.55
1.53
1.53
^{1}H NMR (600 MHz, $CDCl_3$)
OH
F
1.98
2.87
1.99
1.94
1.00
1.03
3.03
1.03
1.04
3.01
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
f1 (ppm)

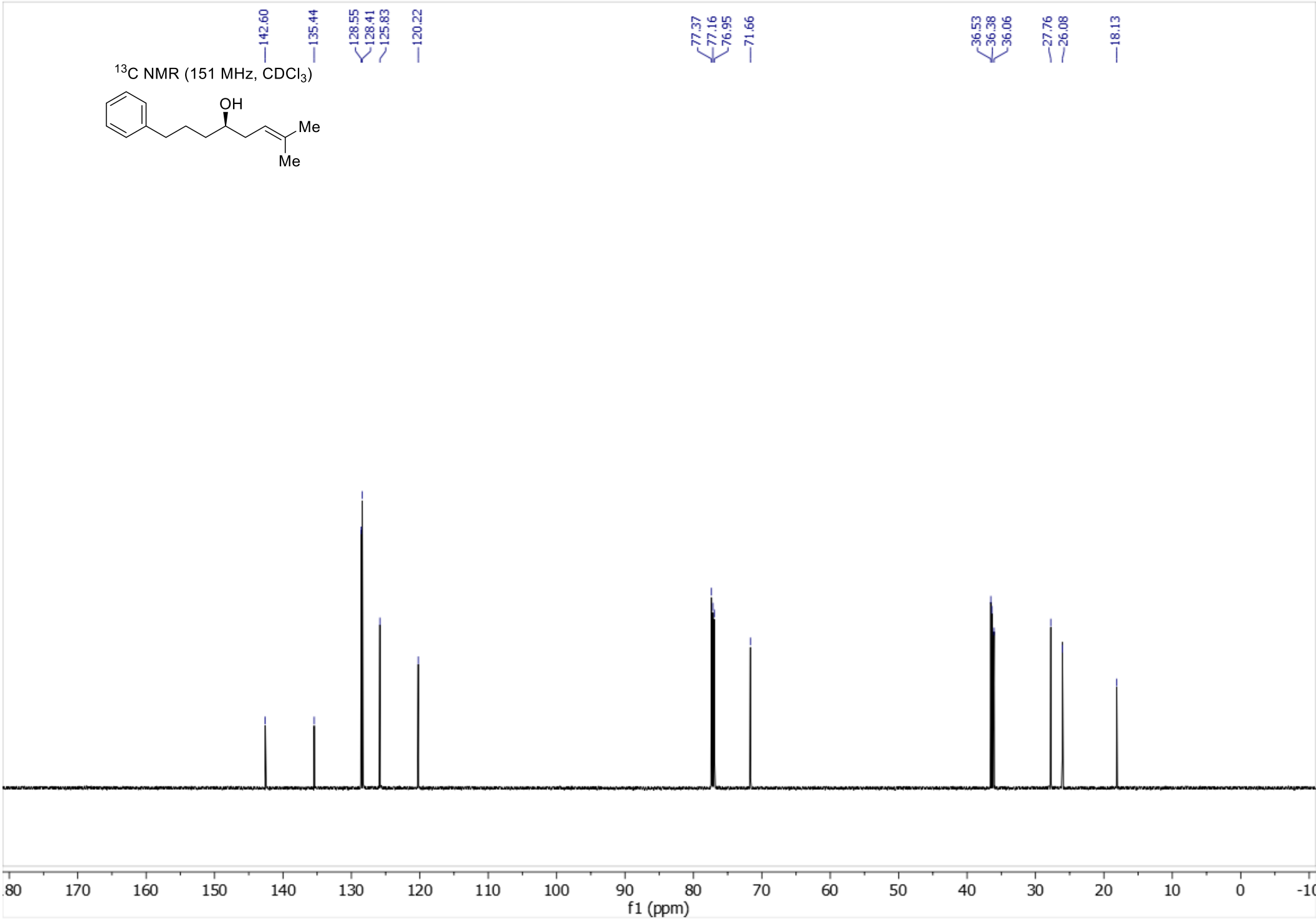

162.59
160.97
142.39
134.31
134.29
130.93
130.88
128.53
128.45
125.90
115.49
115.35
77.37
77.16
76.95
72.61
43.24
36.42
35.93
27.66
13C NMR (151 MHz, CDCl3)
OH
F
134.31
134.29
134.4
134.2
f1 (ppm)


7.31
7.31
7.30
7.29
7.28
7.26
7.22
7.20
7.20
7.19
7.14
7.13
3.82
3.82
3.81
3.80
3.80
3.79
2.79
2.79
2.77
2.76
2.68
2.68
2.66
2.65
2.65
2.63
2.61
1.89
1.85
1.85
1.82
1.81
1.75
1.74
1.73
1.71
1.69
1.68
1.62
1.61
1.61
1.58
1.57
1.56
1.53
1.51
1.51
^{1}H NMR (600 MHz, $CDCl_3$)
OH
Cl
3.91
2.93
1.94
1.00
1.02
3.04
1.02
1.03
3.08
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
f1 (ppm)

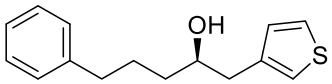

142.35
137.15
132.39
130.86
128.73
128.53
128.45
125.91
77.37
77.16
76.95
72.50
43.40
36.46
35.90
27.64
^{13}C NMR (151 MHz, $CDCl_3$)
OH
Cl
128.73
128.53
128.45
125.91
129.5 129.0 128.5 128.0 127.5 127.0 126.5 126.0 125.5
f1 (ppm)
80 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

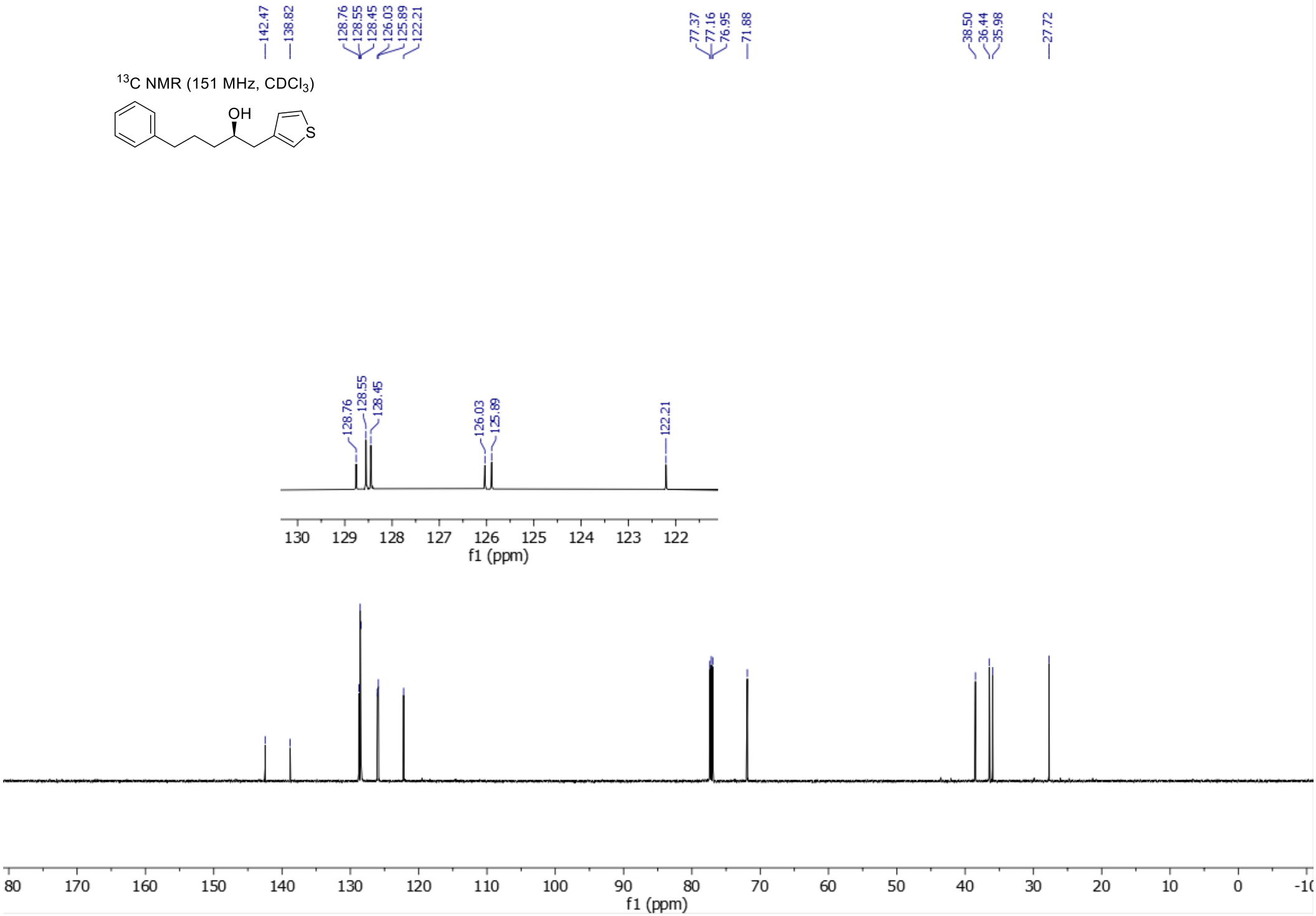
^{1}H NMR (600 MHz, $CDCl_3$)

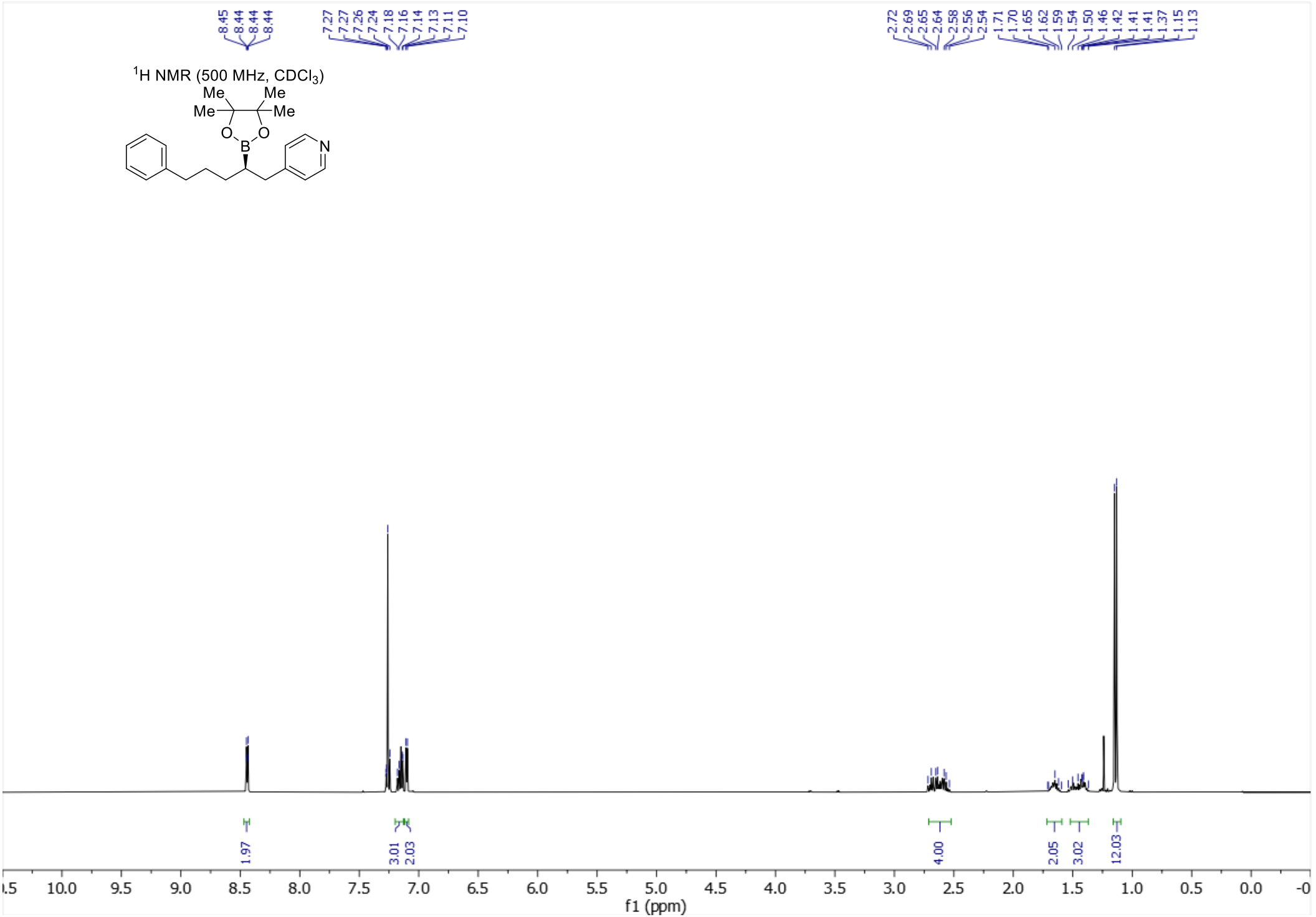


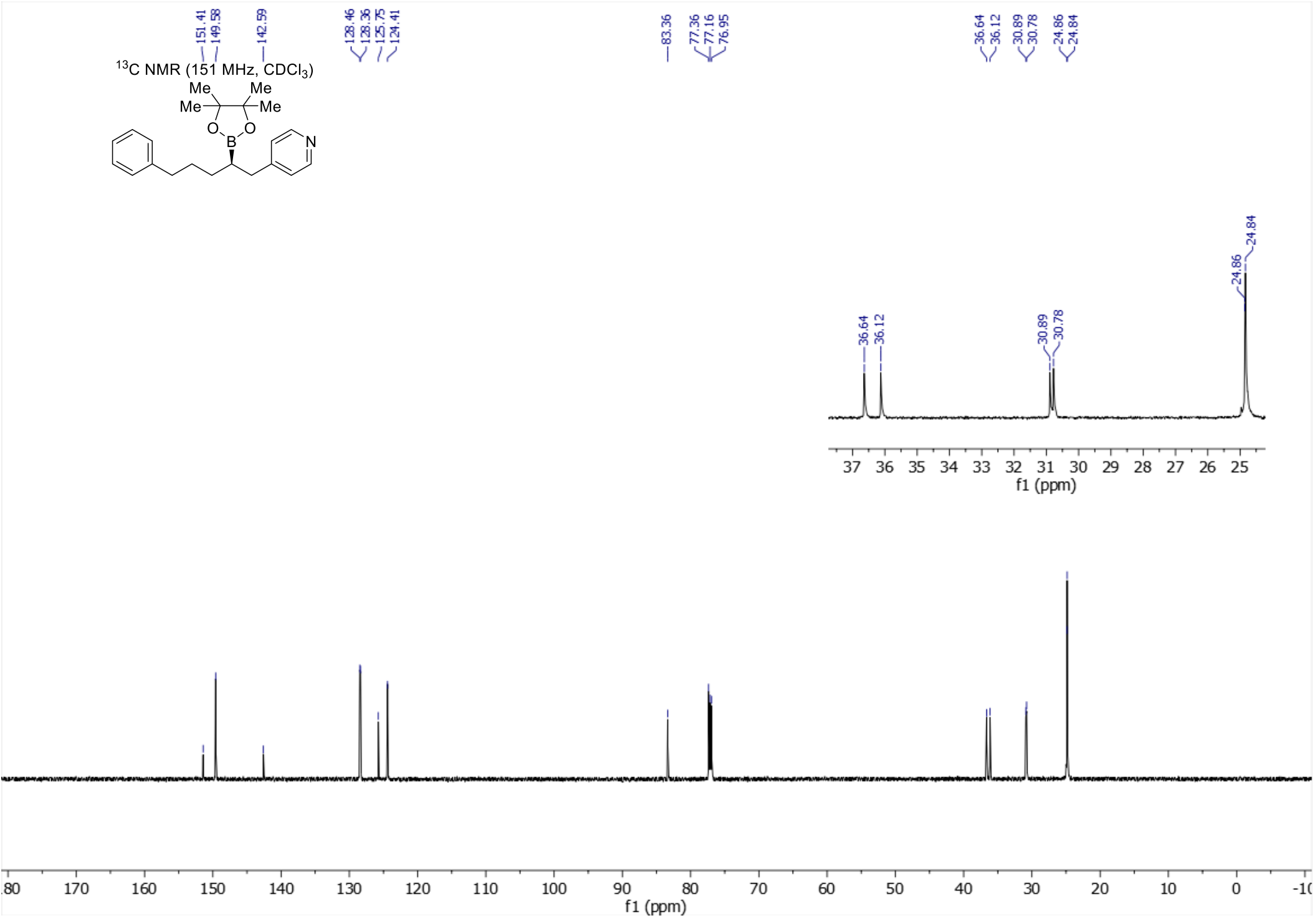

142.60
135.44
128.55
128.41
125.83
120.22
77.37
77.16
76.95
71.66
36.53
36.38
36.06
27.76
26.08
18.13
^{13}C NMR (151 MHz, $CDCl_3$)
OH
Me
Me
f1 (ppm)

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

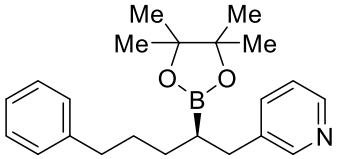


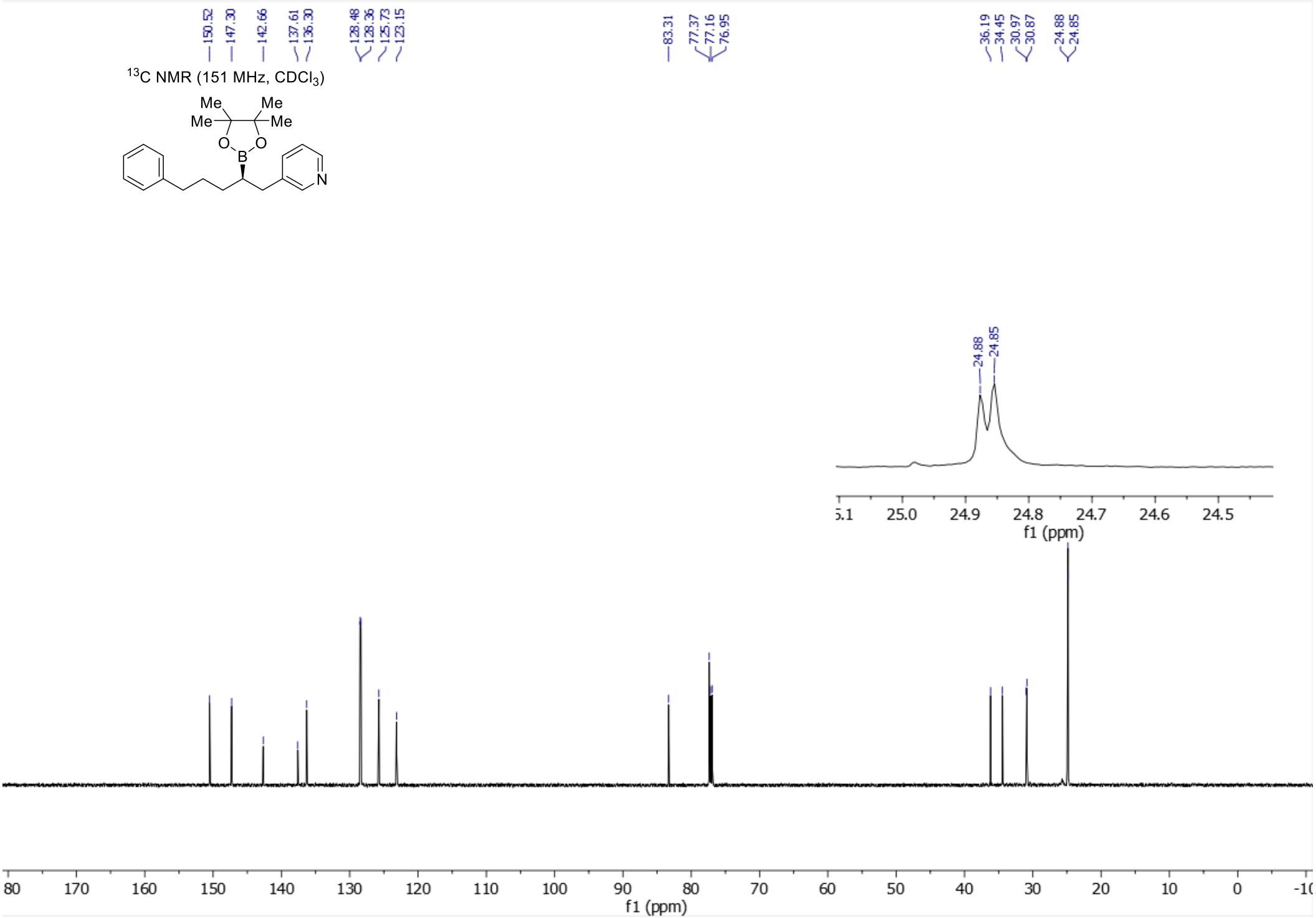

142.47
138.82
128.76
128.55
128.45
126.03
125.89
122.21
77.37
77.16
76.95
71.88
38.50
36.44
35.98
27.72
^{13}C NMR (151 MHz, $CDCl_3$)
OH
S
f1 (ppm)
f1 (ppm)

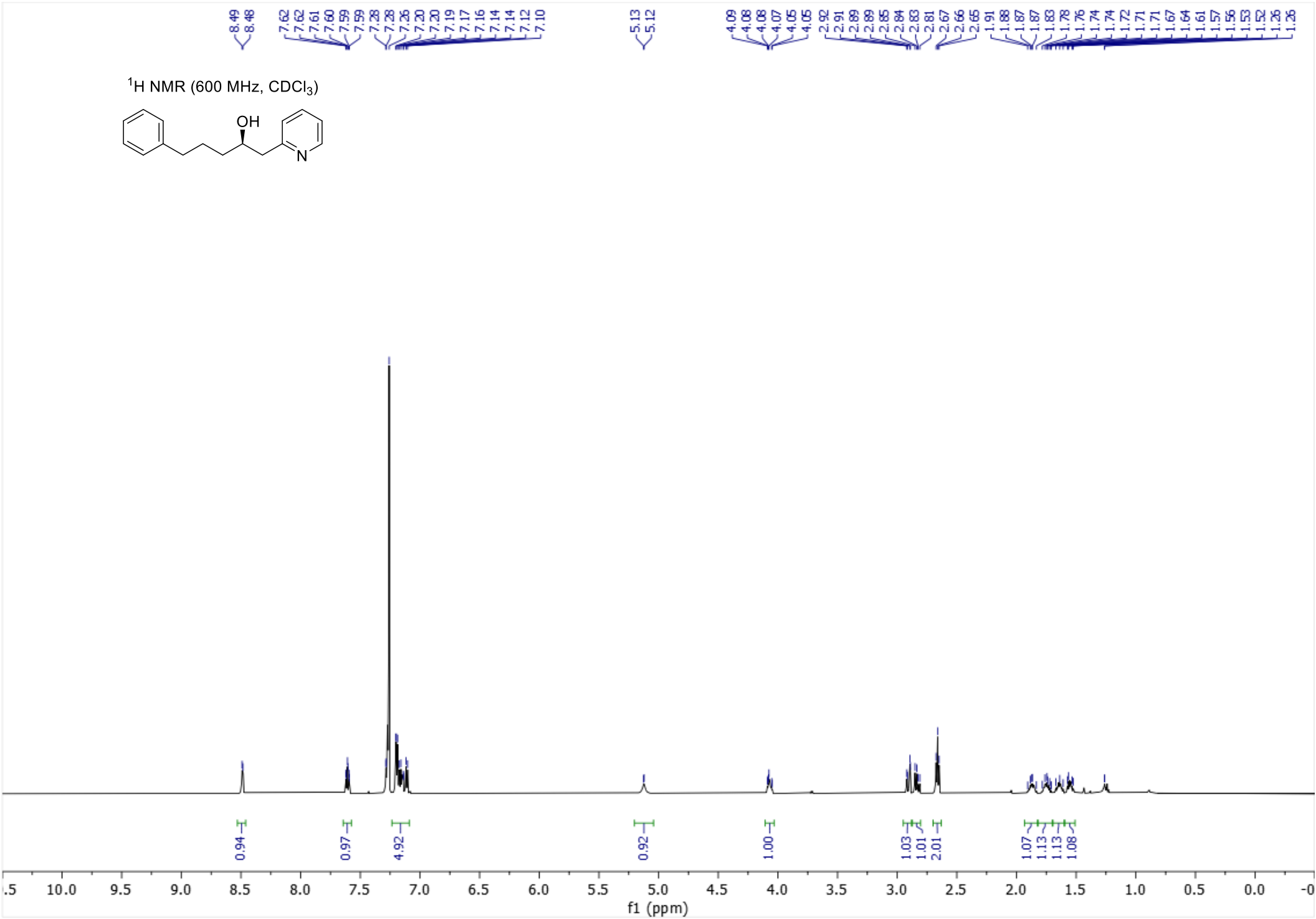

8.45
8.44
8.44
8.44
7.27
7.27
7.26
7.24
7.18
7.16
7.14
7.13
7.11
7.10
2.72
2.69
2.65
2.64
2.58
2.56
2.54
1.71
1.70
1.65
1.62
1.59
1.54
1.50
1.46
1.42
1.41
1.41
1.37
1.15
1.13
1H NMR (500 MHz, CDCl3)
Me
Me
Me
Me
O
O
B
N
1.97
3.01
2.03
4.00
2.05
3.02
12.03
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

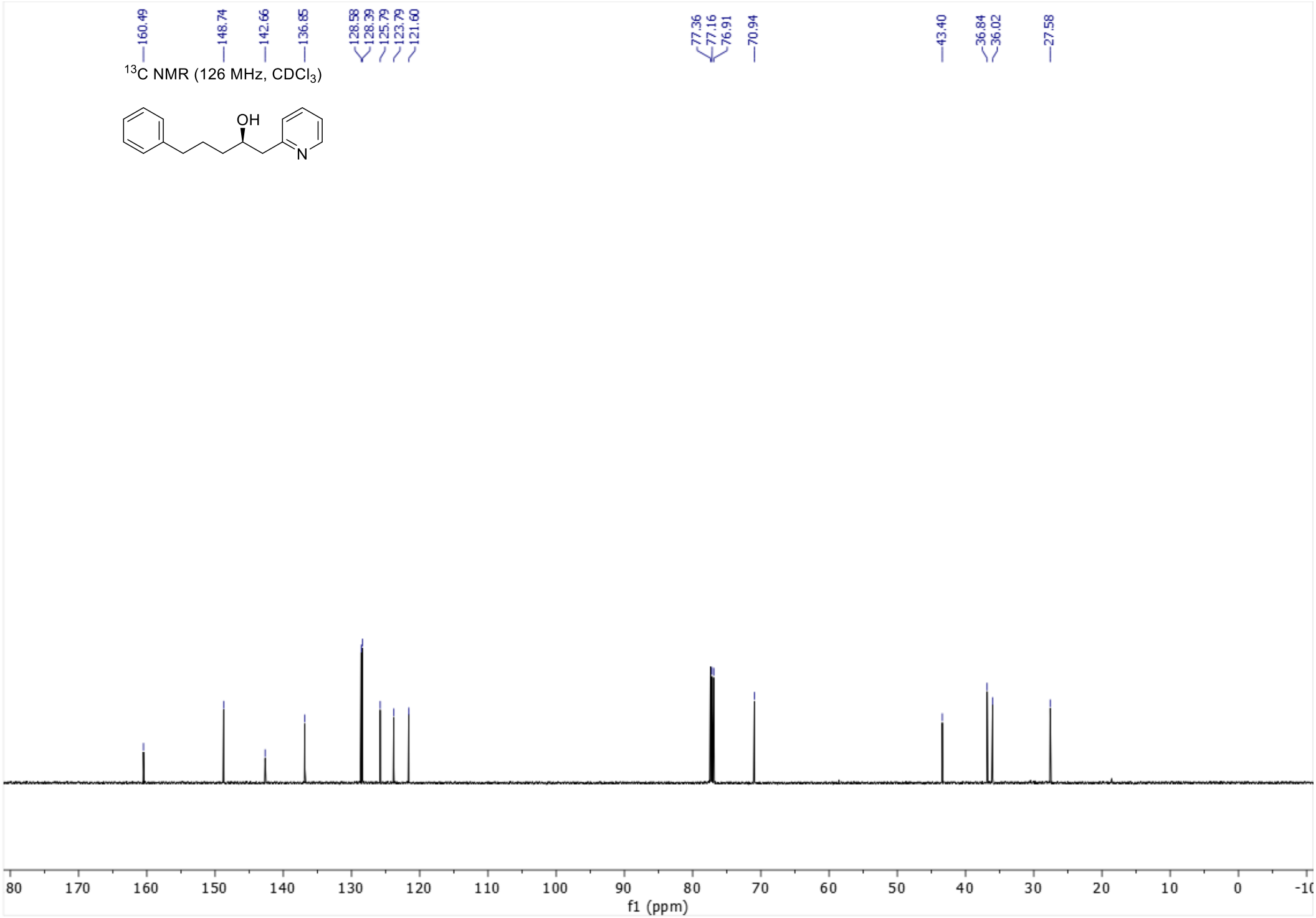

151.41
149.58
142.59
128.46
128.36
125.75
124.41
83.36
77.36
77.16
76.95
36.64
36.12
30.89
30.78
24.86
24.84
^{13}C NMR (151 MHz, $CDCl_3$)
Me
Me
Me
Me
O
B
O
N
f1 (ppm)

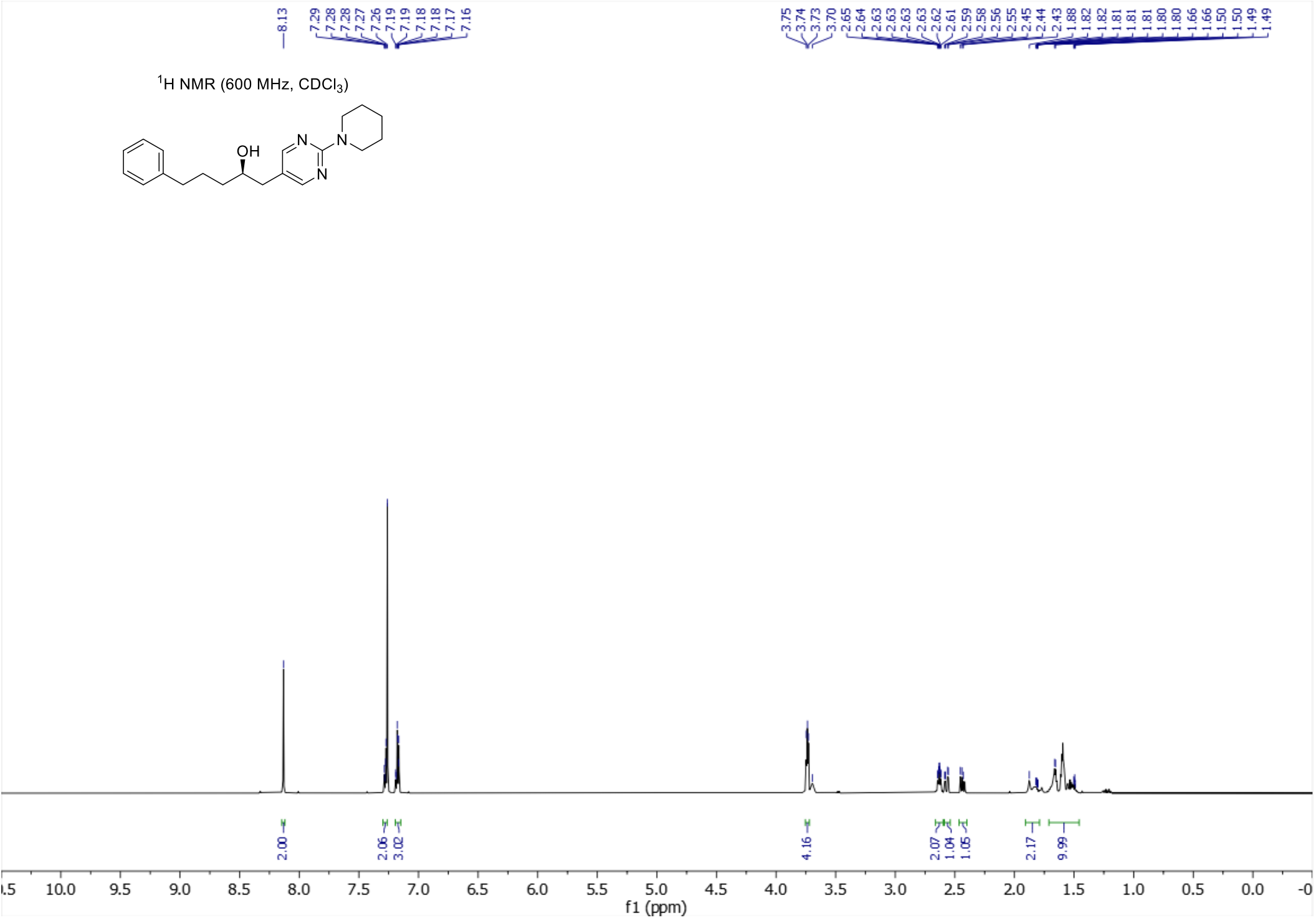
^{1}H NMR (500 MHz, $CDCl_3$)

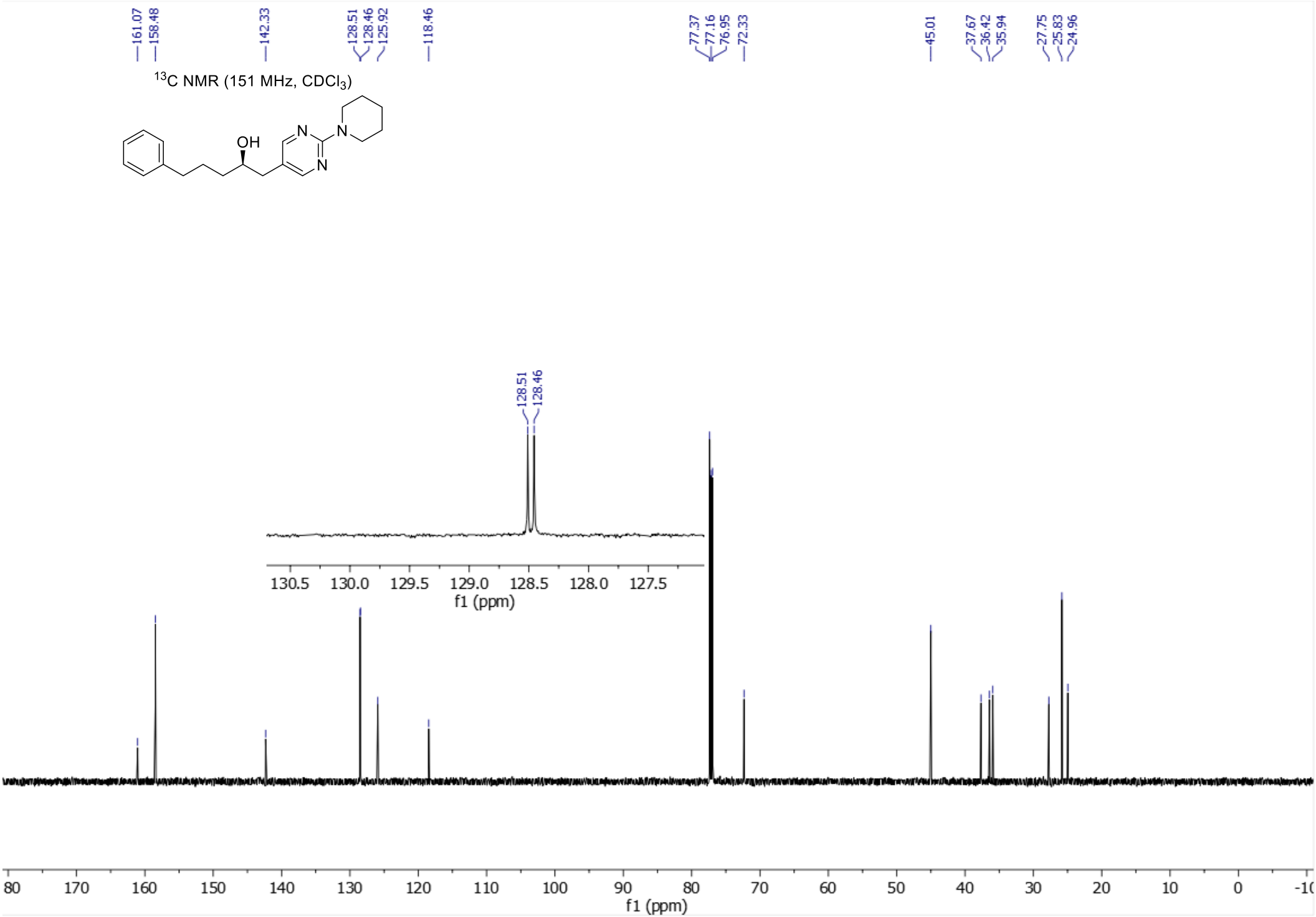


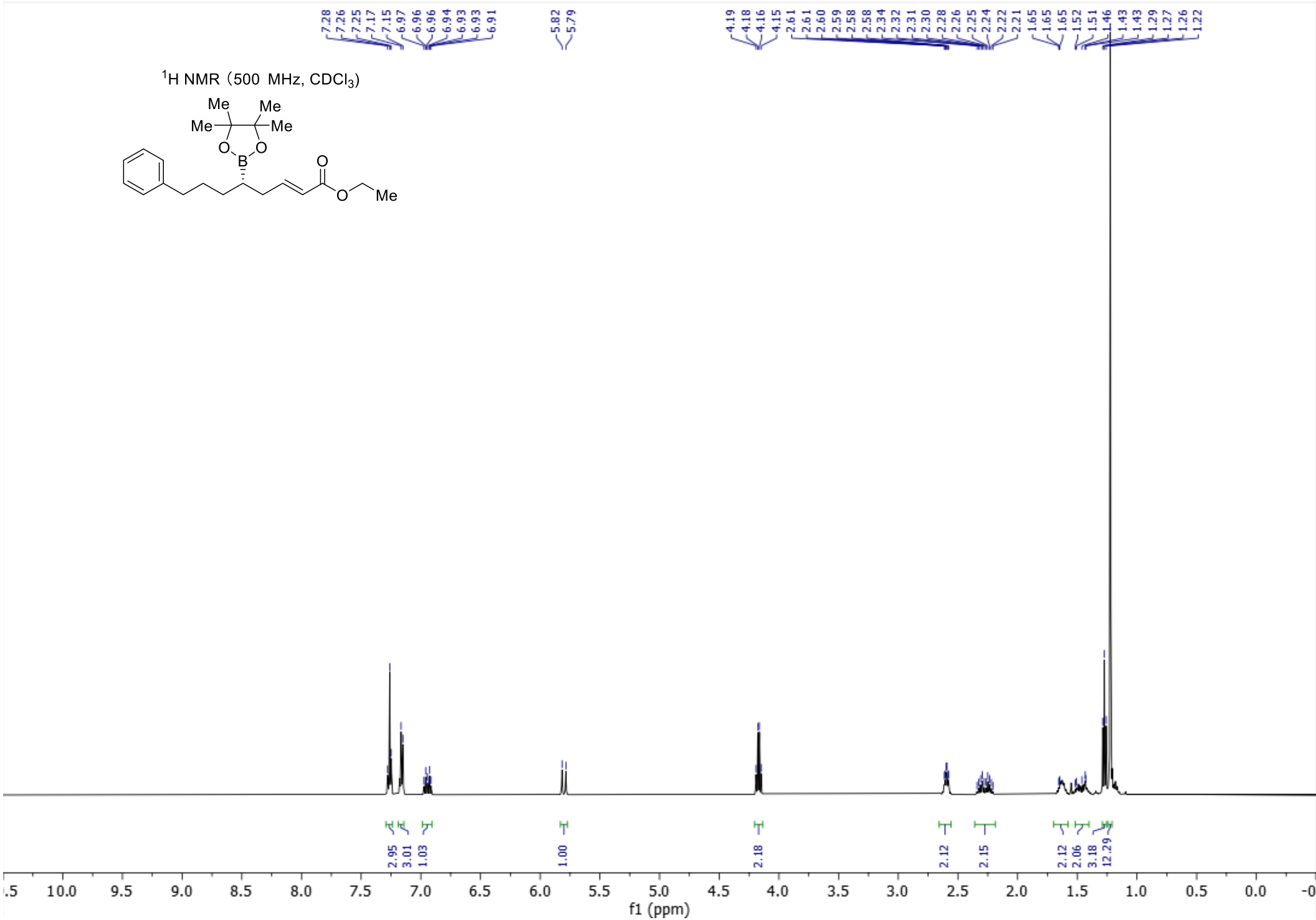

150.52
147.30
142.66
137.61
136.30
128.48
128.36
125.73
123.15
83.31
77.37
77.16
76.95
36.19
34.45
30.97
30.87
24.88
24.85
13C NMR (151 MHz, CDCl3)
Me
Me
Me
Me
O
O
B
N
24.88
24.85
5.1
25.0
24.9
24.8
24.7
24.6
24.5
f1 (ppm)
80
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

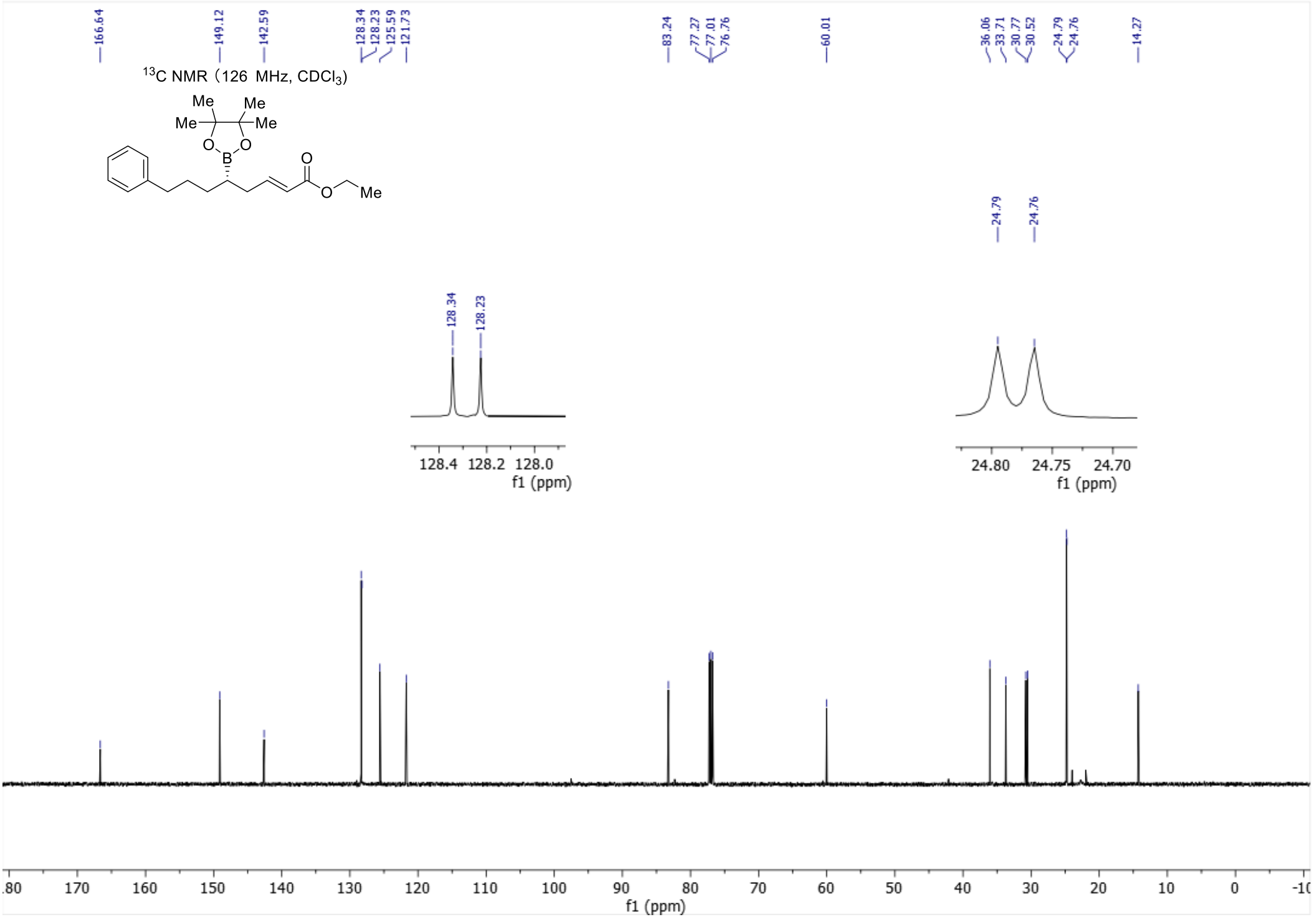

8.49
8.48
7.62
7.62
7.61
7.60
7.59
7.59
7.28
7.28
7.26
7.20
7.20
7.19
7.17
7.16
7.14
7.12
7.10
5.13
5.12
4.09
4.08
4.08
4.07
4.05
4.05
2.92
2.91
2.89
2.89
2.85
2.84
2.83
2.81
2.67
2.66
2.65
1.91
1.88
1.87
1.87
1.83
1.78
1.76
1.74
1.74
1.72
1.71
1.71
1.67
1.64
1.61
1.57
1.56
1.53
1.52
1.26
1.26
^{1}H NMR (600 MHz, $CDCl_3$)
OH
N
0.94
0.97
4.92
0.92
1.00
1.03
1.01
2.01
1.07
1.13
1.13
1.08
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
f1 (ppm)


160.49
148.74
142.66
136.85
128.58
128.39
125.79
123.79
121.60
77.36
77.16
76.91
70.94
43.40
36.84
36.02
27.58
^{13}C NMR (126 MHz, $CDCl_3$)
OH
N
f1 (ppm)

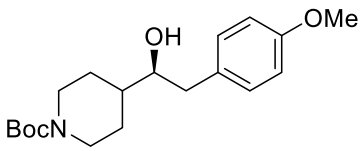

8.13
7.29
7.28
7.28
7.27
7.26
7.19
7.19
7.18
7.18
7.17
7.16
3.75
3.74
3.73
3.70
2.65
2.64
2.63
2.63
2.63
2.63
2.62
2.61
2.59
2.58
2.56
2.55
2.45
2.44
2.43
1.88
1.82
1.82
1.81
1.81
1.81
1.80
1.80
1.66
1.66
1.50
1.50
1.49
1.49
^{1}H NMR (600 MHz, $CDCl_3$)
OH
N
N
N
2.00
2.06
3.02
4.16
2.07
1.04
1.05
2.17
9.99
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
f1 (ppm)

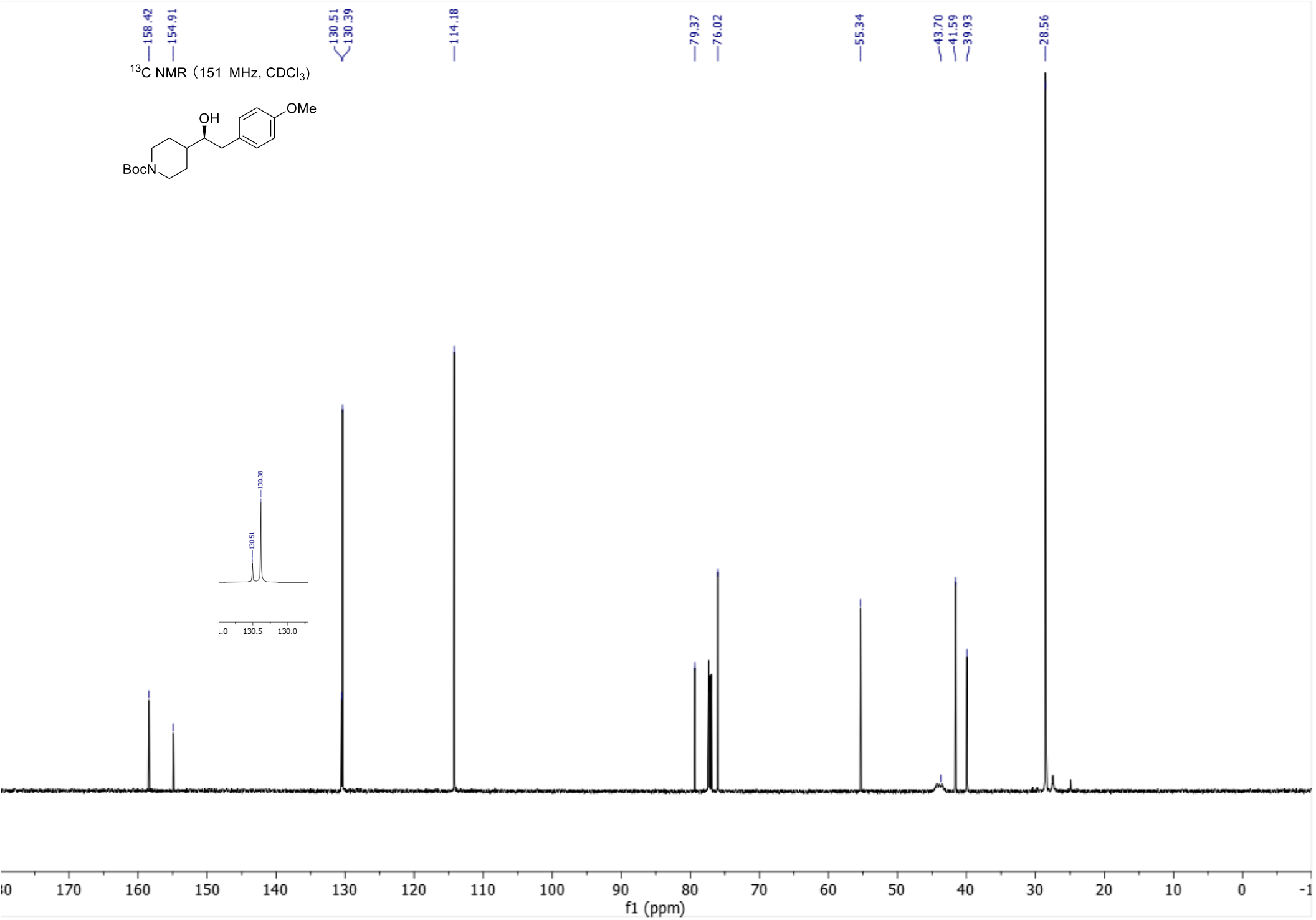

161.07
158.48
142.33
128.51
128.46
125.92
118.46
77.37
77.16
76.95
72.33
45.01
37.67
36.42
35.94
27.75
25.83
24.96
^{13}C NMR (151 MHz, $CDCl_3$)
OH
N
N
N
128.51
128.46
130.5
130.0
129.5
129.0
128.5
128.0
127.5
f1 (ppm)
80
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


7.28
7.26
7.25
7.17
7.15
6.97
6.96
6.96
6.94
6.93
6.93
6.91
5.82
5.79
4.19
4.18
4.16
4.15
2.61
2.61
2.60
2.59
2.58
2.58
2.34
2.32
2.31
2.30
2.28
2.26
2.25
2.24
2.22
2.21
1.65
1.65
1.65
1.52
1.51
1.46
1.43
1.43
1.29
1.27
1.26
1.22
^{1}H NMR (500 MHz, $CDCl_3$)
Me
Me
Me
Me
O
O
B
O
O
Me
2.95
3.01
1.03
1.00
2.18
2.12
2.15
2.12
2.06
3.18
12.29
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
f1 (ppm)

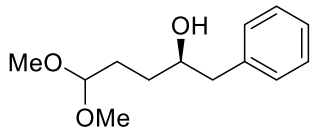

166.64
149.12
142.59
128.34
128.23
125.59
121.73
83.24
77.27
77.01
76.76
60.01
36.06
33.71
30.77
30.52
24.79
24.76
14.27
13C NMR (126 MHz, CDCl3)
Me
Me
Me
Me
O
O
B
O
O
Me
128.34
128.23
128.4 128.2 128.0
f1 (ppm)
24.79
24.76
24.80 24.75 24.70
f1 (ppm)
f1 (ppm)

^{1}H NMR（600 MHz, $CDCl_3$）

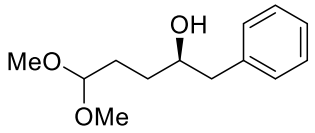



158.42
154.91
130.51
130.39
114.18
79.37
76.02
55.34
43.70
41.59
39.93
28.56
13C NMR (151 MHz, CDCl3)
OH
OMe
BocN
130.38
130.51
130.5
130.0
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

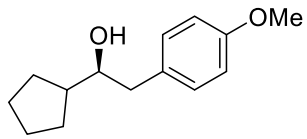
^{1}H NMR（600 MHz, $CDCl_3$）

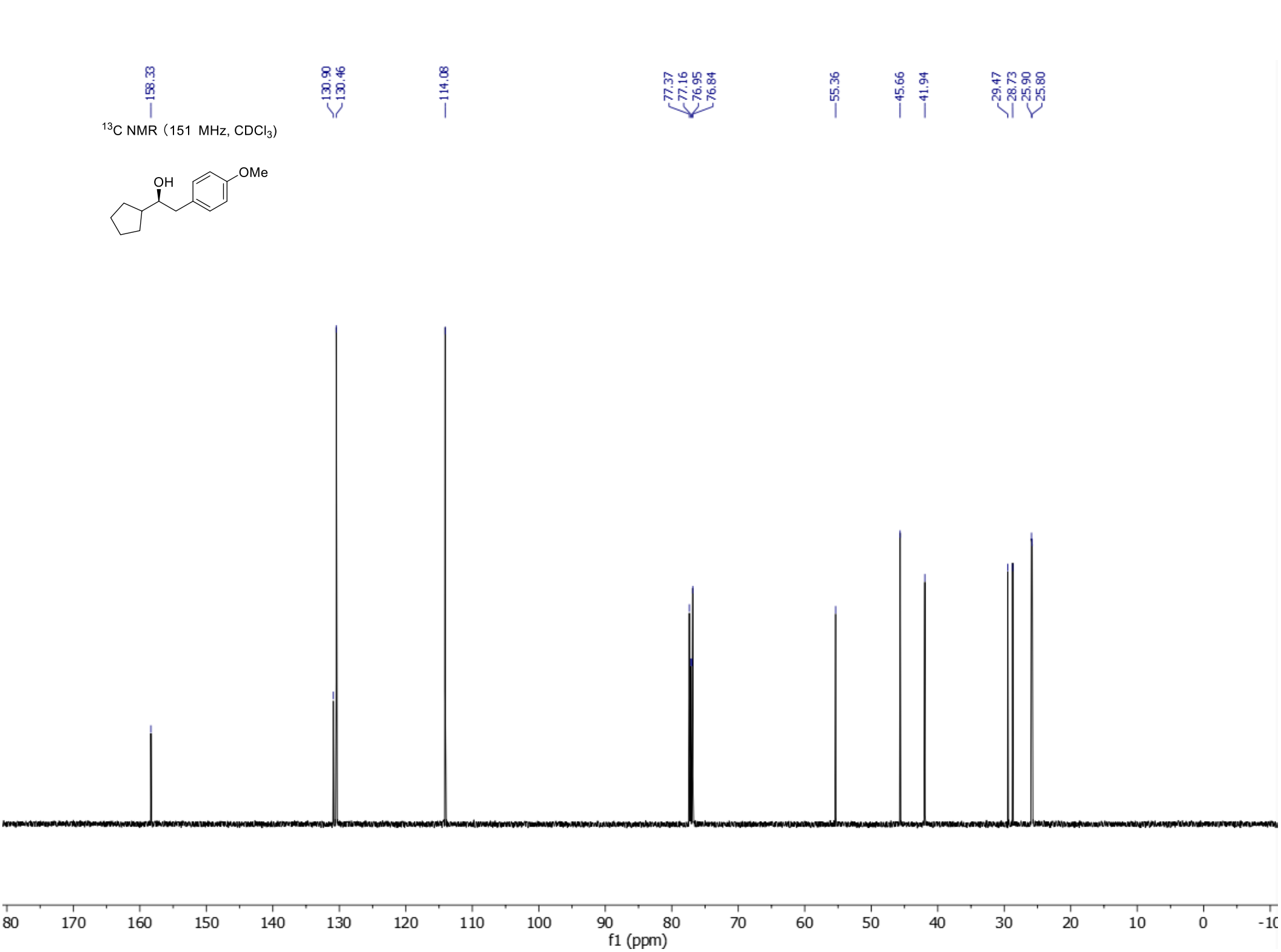


^{13}C NMR（151 MHz, $CDCl_3$）

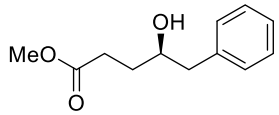


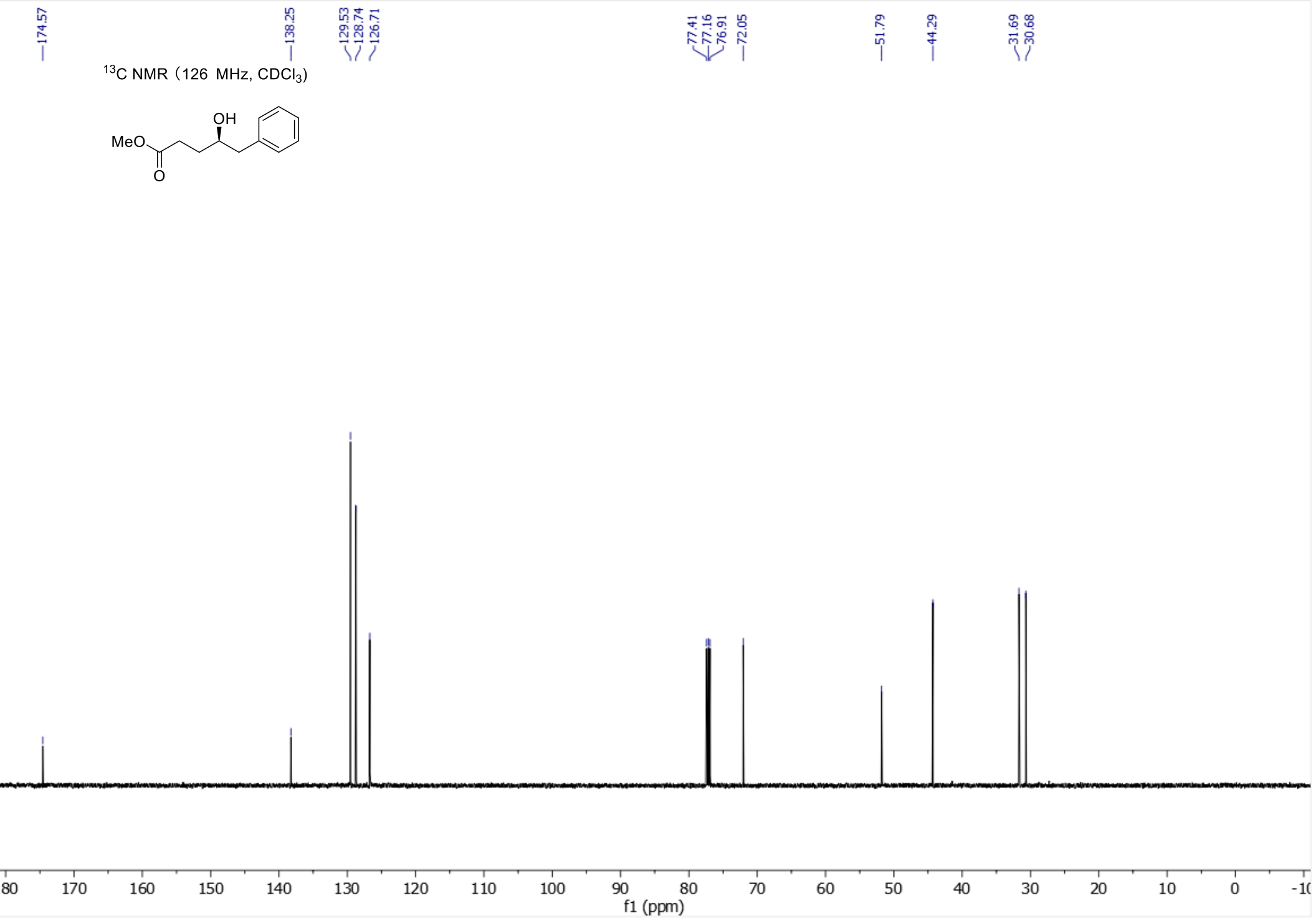
^{1}H NMR（600 MHz, $CDCl_3$）



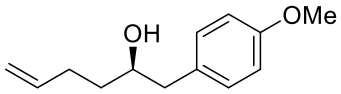

158.33
130.90
130.46
114.08
77.37
77.16
76.95
76.84
55.36
45.66
41.94
29.47
28.73
25.90
25.80
^{13}C NMR (151 MHz, $CDCl_3$)
OH
OMe
f1 (ppm)

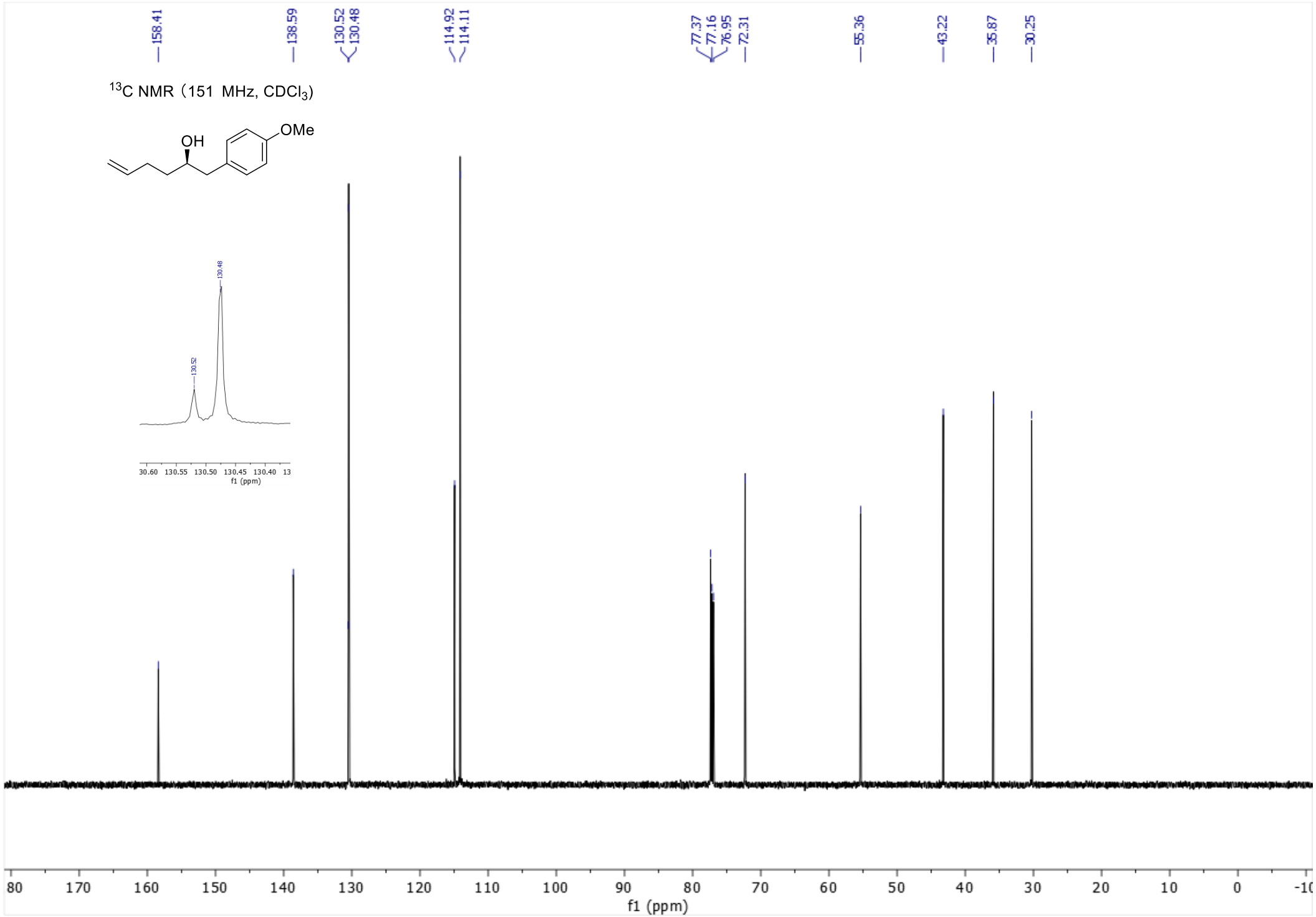
^{1}H NMR（500 MHz, $CDCl_3$）



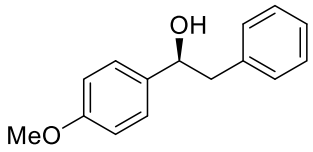

174.57
138.25
129.53
128.74
126.71
77.41
77.16
76.91
72.05
51.79
44.29
31.69
30.68
^{13}C NMR（126 MHz, $CDCl_3$）
OH
MeO
O
f1 (ppm)

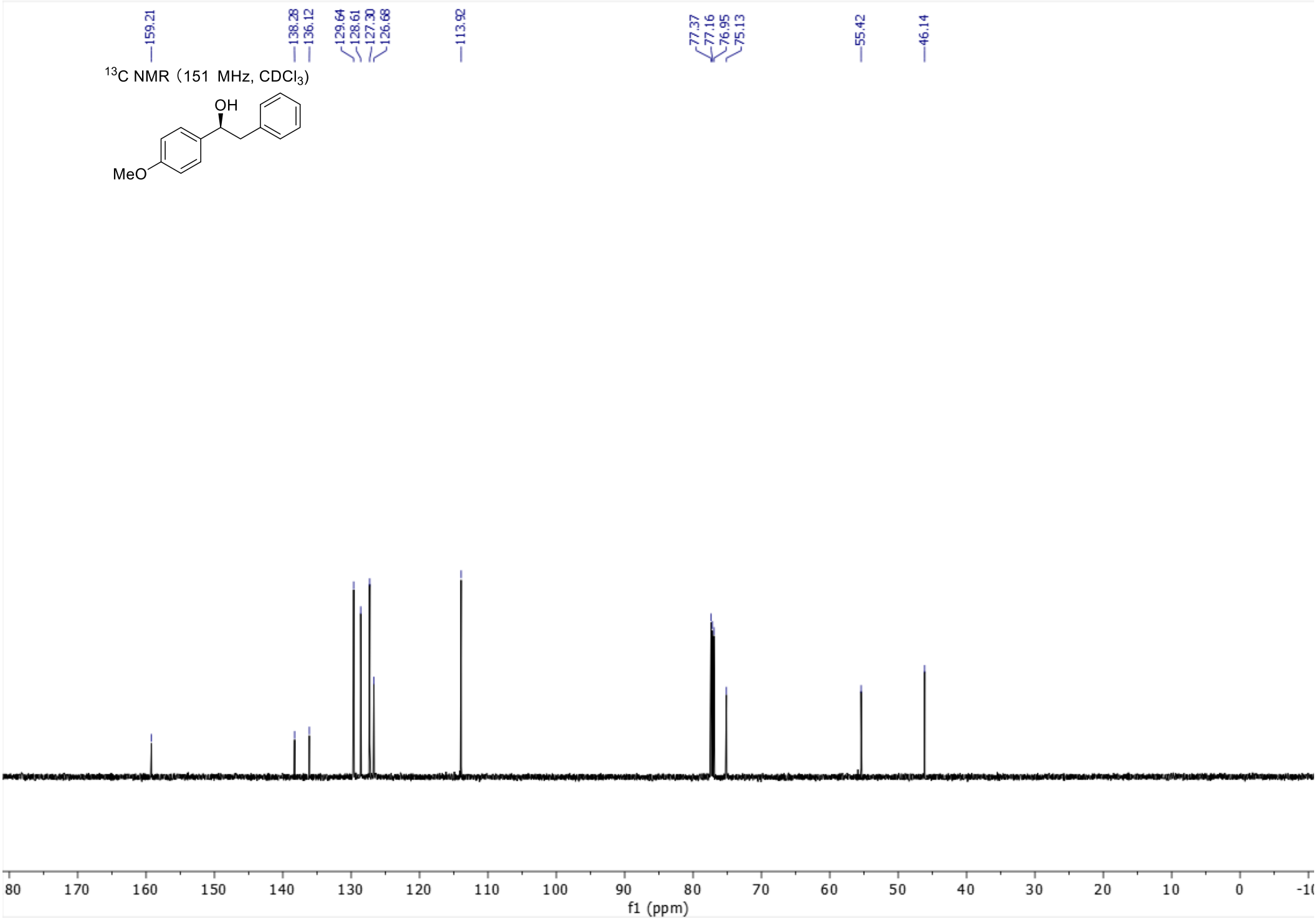
^{1}H NMR（600 MHz, $CDCl_3$）



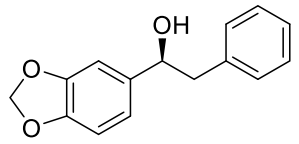

158.41
138.59
130.52
130.48
114.92
114.11
77.37
77.16
76.95
72.31
55.36
43.22
35.87
30.25
13C NMR (151 MHz, CDCl3)
OH
OMe
130.48
130.52
30.60 130.55 130.50 130.45 130.40 13
f1 (ppm)
80 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

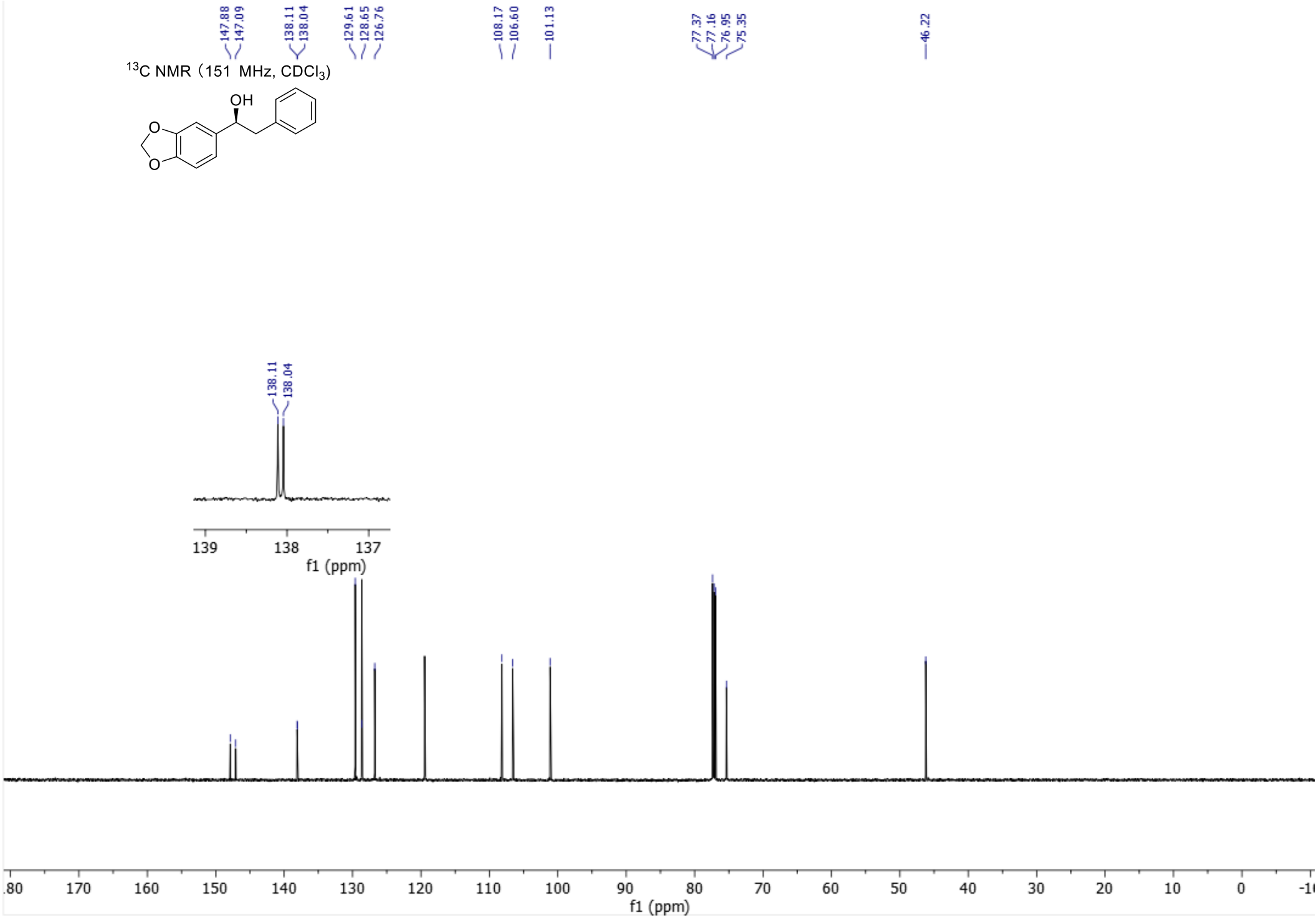
^{1}H NMR (600 MHz, $CDCl_3$)




159.21
138.28
136.12
129.64
128.61
127.30
126.68
113.92
77.37
77.16
76.95
75.13
55.42
46.14
^{13}C NMR（151 MHz, $CDCl_3$）
OH
MeO
80
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

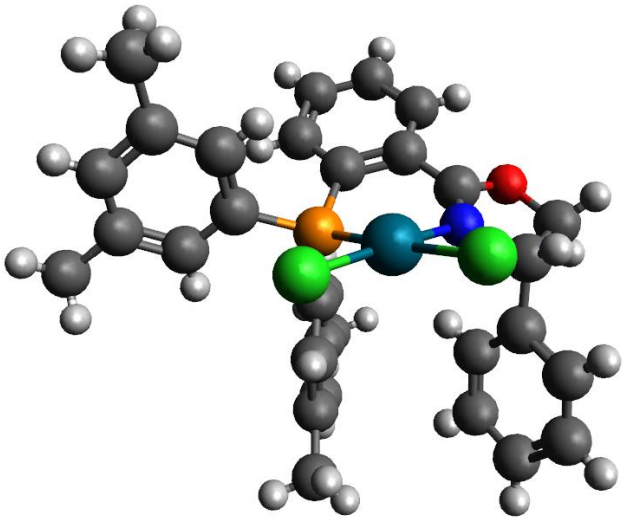
^{1}H NMR (600 MHz, $CDCl_3$)




147.88
147.09
138.11
138.04
129.61
128.65
126.76
108.17
106.60
101.13
77.37
77.16
76.95
75.35
46.22
^{13}C NMR（151 MHz, $CDCl_3$）
OH
O
O
138.11
138.04
139
138
137
f1 (ppm)
f1 (ppm)

3.3.7 Crystal Structure Data

Table 1. Crystal data and structure refinement for C31H30Cl2NOPPd(CH2Cl2).



Identification code	C31H30Cl2NOPPd(CH2Cl2)	
Empirical formula	C32 H32 Cl4 N O P Pd	
Formula weight	725.75	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Hexagonal	
Space group	$P6_5$	
Unit cell dimensions	a = 13.3864(10) Å	a= 90°.
	b = 13.3864(10) Å	b= 90°.
	c = 31.008(4) Å	g = 120°.
Volume	4812.0(9) $Å^3$	
Z	6	
Density (calculated)	1.503 Mg/m^3	

Absorption coefficient	0.988 mm^{-1}
F(000)	2208
Crystal size	0.240 x 0.200 x 0.180 mm^3
Theta range for data collection	1.757 to 28.277°.
Index ranges	-17<=h<=17, -17<=k<=17, -41<=l<=41
Reflections collected	279880
Independent reflections	7951 [R(int) = 0.0989]
Completeness to theta = 25.242°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7457 and 0.6650
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	7951 / 4 / 363
Goodness-of-fit on F^2	1.060
Final R indices [I>2sigma(I)]	R1 = 0.0400, wR2 = 0.0948
R indices (all data)	R1 = 0.0583, wR2 = 0.1084
Absolute structure parameter	-0.013(10)
Extinction coefficient	n/a
Largest diff. peak and hole	0.639 and -0.926 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)

for C31H30Cl2NOPPd(CH2Cl2). U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Pd(1)	6751(1)	3315(1)	4618(1)	33(1)
P(1)	6716(1)	1754(1)	4886(1)	29(1)
Cl(1)	8047(1)	3478(2)	4104(1)	46(1)
Cl(2)	6808(2)	5006(2)	4358(1)	57(1)
O(1)	4550(4)	2721(5)	5683(2)	53(1)
N(1)	5525(5)	3076(5)	5065(2)	41(1)
C(1)	6601(5)	1745(5)	5472(2)	33(1)
C(2)	7082(6)	1234(6)	5716(2)	43(2)
C(3)	7055(7)	1239(7)	6167(2)	52(2)
C(4)	6526(7)	1756(7)	6373(2)	53(2)
C(5)	6002(6)	2246(6)	6135(2)	45(2)
C(6)	6032(5)	2243(5)	5689(2)	36(1)
C(7)	5398(5)	2712(5)	5452(2)	40(1)
C(8)	4018(8)	3209(9)	5401(3)	65(2)

C(9)	4602(6)	3361(6)	4965(3)	49(2)
C(10)	3798(5)	2605(6)	4615(3)	44(2)
C(11)	3393(7)	3080(8)	4313(3)	57(2)
C(12)	2615(8)	2425(10)	4008(3)	70(3)
C(13)	2222(8)	1234(10)	3986(3)	73(3)
C(14)	2607(7)	755(8)	4287(3)	65(2)
C(15)	3399(6)	1437(6)	4591(3)	52(2)
C(16)	7980(5)	1614(5)	4799(2)	32(1)
C(17)	9029(5)	2494(5)	4945(2)	35(1)
C(18)	10037(5)	2443(6)	4895(2)	39(1)
C(19)	9948(5)	1484(6)	4678(3)	46(2)
C(20)	8916(6)	600(6)	4527(3)	48(2)
C(21)	7912(5)	667(6)	4587(2)	41(1)
C(22)	11182(6)	3385(7)	5066(3)	55(2)
C(23)	8863(7)	-411(7)	4289(4)	69(3)
C(24)	5462(5)	444(5)	4691(2)	32(1)
C(25)	4740(5)	-444(5)	4965(2)	35(1)
C(26)	3749(6)	-1393(5)	4800(3)	41(2)
C(27)	3533(6)	-1440(6)	4366(3)	44(2)
C(28)	4250(6)	-558(6)	4080(2)	43(2)
C(29)	5226(5)	405(5)	4253(2)	37(1)
C(30)	2927(7)	-2351(6)	5098(3)	56(2)
C(31)	3958(7)	-589(7)	3610(2)	52(2)

C(32S)	6546(15)	6708(17)	5858(6)	86(5)
Cl(3S)	6723(5)	6061(5)	5422(2)	75(1)
Cl(4S)	7796(4)	7541(4)	6180(2)	86(2)
C(32T)	6950(30)	7440(20)	5767(9)	87(8)
Cl(3T)	7526(13)	8581(12)	5427(5)	165(6)
Cl(4T)	7135(13)	6502(12)	5410(4)	135(5)

Table 3. Bond lengths [Å] and angles [°] for C31H30Cl2NOPPd(CH2Cl2).

Pd(1)-N(1)	2.047(6)
Pd(1)-P(1)	2.2280(16)
Pd(1)-Cl(1)	2.2858(19)
Pd(1)-Cl(2)	2.3675(18)
P(1)-C(16)	1.814(6)
P(1)-C(24)	1.821(6)
P(1)-C(1)	1.822(7)
O(1)-C(7)	1.347(7)
O(1)-C(8)	1.472(10)
N(1)-C(7)	1.274(9)
N(1)-C(9)	1.497(8)
C(1)-C(2)	1.376(9)
C(1)-C(6)	1.410(8)
C(2)-C(3)	1.400(10)
C(2)-H(2)	0.9500
C(3)-C(4)	1.370(11)
C(3)-H(3)	0.9500
C(4)-C(5)	1.388(11)
C(4)-H(4)	0.9500
C(5)-C(6)	1.382(9)
C(5)-H(5)	0.9500

C(6)-C(7)	1.479(9)
C(8)-C(9)	1.525(11)
C(8)-H(8A)	0.9900
C(8)-H(8B)	0.9900
C(9)-C(10)	1.507(11)
C(9)-H(9)	1.0000
C(10)-C(15)	1.378(9)
C(10)-C(11)	1.386(10)
C(11)-C(12)	1.354(13)
C(11)-H(11)	0.9500
C(12)-C(13)	1.409(15)
C(12)-H(12)	0.9500
C(13)-C(14)	1.369(13)
C(13)-H(13)	0.9500
C(14)-C(15)	1.372(12)
C(14)-H(14)	0.9500
C(15)-H(15)	0.9500
C(16)-C(17)	1.383(9)
C(16)-C(21)	1.390(9)
C(17)-C(18)	1.394(8)
C(17)-H(17)	0.9500
C(18)-C(19)	1.400(10)
C(18)-C(22)	1.513(9)

C(19)-C(20)	1.377(10)
C(19)-H(19)	0.9500
C(20)-C(21)	1.403(8)
C(20)-C(23)	1.511(10)
C(21)-H(21)	0.9500
C(22)-H(22A)	0.9800
C(22)-H(22B)	0.9800
C(22)-H(22C)	0.9800
C(23)-H(23A)	0.9800
C(23)-H(23B)	0.9800
C(23)-H(23C)	0.9800
C(24)-C(25)	1.385(8)
C(24)-C(29)	1.392(9)
C(25)-C(26)	1.396(9)
C(25)-H(25)	0.9500
C(26)-C(27)	1.372(10)
C(26)-C(30)	1.516(10)
C(27)-C(28)	1.404(10)
C(27)-H(27)	0.9500
C(28)-C(29)	1.404(9)
C(28)-C(31)	1.502(10)
C(29)-H(29)	0.9500
C(30)-H(30A)	0.9800

C(30)-H(30B)	0.9800
C(30)-H(30C)	0.9800
C(31)-H(31A)	0.9800
C(31)-H(31B)	0.9800
C(31)-H(31C)	0.9800
C(32S)-Cl(3S)	1.684(17)
C(32S)-Cl(4S)	1.781(17)
C(32S)-H(32A)	0.9900
C(32S)-H(32B)	0.9900

N(1)-Pd(1)-P(1)	87.78(15)
N(1)-Pd(1)-Cl(1)	176.68(17)
P(1)-Pd(1)-Cl(1)	90.49(6)
N(1)-Pd(1)-Cl(2)	91.20(16)
P(1)-Pd(1)-Cl(2)	177.95(9)
Cl(1)-Pd(1)-Cl(2)	90.62(8)
C(16)-P(1)-C(24)	108.0(3)
C(16)-P(1)-C(1)	103.3(3)
C(24)-P(1)-C(1)	106.9(3)
C(16)-P(1)-Pd(1)	117.23(19)
C(24)-P(1)-Pd(1)	110.86(19)
C(1)-P(1)-Pd(1)	109.9(2)
C(7)-O(1)-C(8)	106.6(6)

C(7)-N(1)-C(9)	108.9(6)
C(7)-N(1)-Pd(1)	129.9(4)
C(9)-N(1)-Pd(1)	121.2(5)
C(2)-C(1)-C(6)	118.1(6)
C(2)-C(1)-P(1)	119.4(5)
C(6)-C(1)-P(1)	122.4(5)
C(1)-C(2)-C(3)	121.8(6)
C(1)-C(2)-H(2)	119.1
C(3)-C(2)-H(2)	119.1
C(4)-C(3)-C(2)	119.3(7)
C(4)-C(3)-H(3)	120.4
C(2)-C(3)-H(3)	120.4
C(3)-C(4)-C(5)	120.2(7)
C(3)-C(4)-H(4)	119.9
C(5)-C(4)-H(4)	119.9
C(6)-C(5)-C(4)	120.5(6)
C(6)-C(5)-H(5)	119.7
C(4)-C(5)-H(5)	119.7
C(5)-C(6)-C(1)	120.1(6)
C(5)-C(6)-C(7)	118.2(6)
C(1)-C(6)-C(7)	121.6(6)
N(1)-C(7)-O(1)	116.7(6)
N(1)-C(7)-C(6)	129.4(6)

O(1)-C(7)-C(6)	113.9(6)
O(1)-C(8)-C(9)	104.9(5)
O(1)-C(8)-H(8A)	110.8
C(9)-C(8)-H(8A)	110.8
O(1)-C(8)-H(8B)	110.8
C(9)-C(8)-H(8B)	110.8
H(8A)-C(8)-H(8B)	108.8
N(1)-C(9)-C(10)	112.4(5)
N(1)-C(9)-C(8)	102.4(6)
C(10)-C(9)-C(8)	113.8(7)
N(1)-C(9)-H(9)	109.3
C(10)-C(9)-H(9)	109.3
C(8)-C(9)-H(9)	109.3
C(15)-C(10)-C(11)	117.8(8)
C(15)-C(10)-C(9)	122.8(7)
C(11)-C(10)-C(9)	119.3(7)
C(12)-C(11)-C(10)	121.7(8)
C(12)-C(11)-H(11)	119.2
C(10)-C(11)-H(11)	119.2
C(11)-C(12)-C(13)	119.8(8)
C(11)-C(12)-H(12)	120.1
C(13)-C(12)-H(12)	120.1
C(14)-C(13)-C(12)	118.8(9)

C(14)-C(13)-H(13)	120.6
C(12)-C(13)-H(13)	120.6
C(13)-C(14)-C(15)	120.2(9)
C(13)-C(14)-H(14)	119.9
C(15)-C(14)-H(14)	119.9
C(14)-C(15)-C(10)	121.6(8)
C(14)-C(15)-H(15)	119.2
C(10)-C(15)-H(15)	119.2
C(17)-C(16)-C(21)	120.5(5)
C(17)-C(16)-P(1)	117.7(5)
C(21)-C(16)-P(1)	121.8(5)
C(16)-C(17)-C(18)	121.1(6)
C(16)-C(17)-H(17)	119.4
C(18)-C(17)-H(17)	119.4
C(17)-C(18)-C(19)	117.3(6)
C(17)-C(18)-C(22)	121.5(6)
C(19)-C(18)-C(22)	121.2(6)
C(20)-C(19)-C(18)	122.7(6)
C(20)-C(19)-H(19)	118.7
C(18)-C(19)-H(19)	118.7
C(19)-C(20)-C(21)	118.8(6)
C(19)-C(20)-C(23)	120.9(6)
C(21)-C(20)-C(23)	120.3(6)

C(16)-C(21)-C(20)	119.6(6)
C(16)-C(21)-H(21)	120.2
C(20)-C(21)-H(21)	120.2
C(18)-C(22)-H(22A)	109.5
C(18)-C(22)-H(22B)	109.5
H(22A)-C(22)-H(22B)	109.5
C(18)-C(22)-H(22C)	109.5
H(22A)-C(22)-H(22C)	109.5
H(22B)-C(22)-H(22C)	109.5
C(20)-C(23)-H(23A)	109.5
C(20)-C(23)-H(23B)	109.5
H(23A)-C(23)-H(23B)	109.5
C(20)-C(23)-H(23C)	109.5
H(23A)-C(23)-H(23C)	109.5
H(23B)-C(23)-H(23C)	109.5
C(25)-C(24)-C(29)	121.3(6)
C(25)-C(24)-P(1)	122.3(5)
C(29)-C(24)-P(1)	116.3(4)
C(24)-C(25)-C(26)	119.6(6)
C(24)-C(25)-H(25)	120.2
C(26)-C(25)-H(25)	120.2
C(27)-C(26)-C(25)	119.0(6)
C(27)-C(26)-C(30)	120.7(7)

C(25)-C(26)-C(30)	120.3(7)
C(26)-C(27)-C(28)	122.8(6)
C(26)-C(27)-H(27)	118.6
C(28)-C(27)-H(27)	118.6
C(27)-C(28)-C(29)	117.5(7)
C(27)-C(28)-C(31)	122.0(6)
C(29)-C(28)-C(31)	120.4(7)
C(24)-C(29)-C(28)	119.9(6)
C(24)-C(29)-H(29)	120.1
C(28)-C(29)-H(29)	120.1
C(26)-C(30)-H(30A)	109.5
C(26)-C(30)-H(30B)	109.5
H(30A)-C(30)-H(30B)	109.5
C(26)-C(30)-H(30C)	109.5
H(30A)-C(30)-H(30C)	109.5
H(30B)-C(30)-H(30C)	109.5
C(28)-C(31)-H(31A)	109.5
C(28)-C(31)-H(31B)	109.5
H(31A)-C(31)-H(31B)	109.5
C(28)-C(31)-H(31C)	109.5
H(31A)-C(31)-H(31C)	109.5
H(31B)-C(31)-H(31C)	109.5
Cl(3S)-C(32S)-Cl(4S)	116.2(10)

Cl(3S)-C(32S)-H(32A) 108.2

Cl(4S)-C(32S)-H(32A) 108.2

Cl(3S)-C(32S)-H(32B) 108.2

Cl(4S)-C(32S)-H(32B) 108.2

H(32A)-C(32S)-H(32B) 107.4

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for C31H30Cl2NOPPd(CH2Cl2).

The anisotropic

displacement factor exponent takes the form: $-2p^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Pd(1)	29(1)	27(1)	43(1)	2(1)	0(1)	14(1)
P(1)	26(1)	27(1)	35(1)	0(1)	2(1)	13(1)
Cl(1)	40(1)	54(1)	47(1)	16(1)	11(1)	25(1)
Cl(2)	56(1)	37(1)	81(1)	14(1)	-1(1)	25(1)
O(1)	50(3)	66(3)	58(3)	-6(3)	7(2)	39(3)
N(1)	40(3)	36(3)	57(4)	-3(2)	3(3)	27(2)
C(1)	27(3)	31(3)	38(3)	-2(2)	1(2)	13(2)
C(2)	47(4)	53(4)	37(3)	6(3)	8(3)	32(3)
C(3)	54(4)	71(5)	39(4)	7(3)	1(3)	36(4)
C(4)	48(4)	67(5)	34(4)	-7(3)	5(3)	20(4)
C(5)	35(3)	52(4)	43(4)	-10(3)	6(3)	17(3)
C(6)	30(3)	33(3)	41(3)	-6(2)	-1(2)	13(2)
C(7)	36(3)	33(3)	52(4)	-8(3)	5(3)	18(3)
C(8)	74(6)	87(6)	68(5)	0(5)	8(4)	66(5)
C(9)	50(4)	46(4)	69(5)	0(3)	3(3)	37(3)
C(10)	38(3)	47(4)	60(4)	9(3)	10(3)	29(3)
C(11)	62(5)	64(5)	64(5)	5(4)	2(4)	46(4)

C(12)	65(5)	101(7)	64(5)	14(5)	1(4)	56(6)
C(13)	52(5)	106(8)	72(6)	-13(5)	2(4)	48(5)
C(14)	41(4)	66(5)	99(7)	-14(5)	2(4)	34(4)
C(15)	49(4)	49(4)	71(5)	9(4)	9(4)	34(3)
C(16)	28(3)	31(3)	38(3)	4(2)	4(2)	16(2)
C(17)	32(3)	37(3)	39(3)	0(3)	3(2)	19(3)
C(18)	27(3)	47(4)	41(4)	-1(3)	0(2)	16(3)
C(19)	31(3)	57(4)	58(4)	0(3)	5(3)	27(3)
C(20)	40(3)	42(4)	68(5)	-3(3)	6(3)	25(3)
C(21)	35(3)	41(3)	49(4)	-5(3)	-3(3)	21(3)
C(22)	29(3)	63(5)	62(5)	-13(4)	-1(3)	15(3)
C(23)	39(4)	57(5)	118(8)	-26(5)	1(4)	30(4)
C(24)	26(2)	30(3)	43(4)	-1(2)	1(2)	16(2)
C(25)	28(3)	29(3)	46(4)	4(2)	3(2)	13(2)
C(26)	32(3)	31(3)	63(4)	-2(3)	-2(3)	17(3)
C(27)	35(3)	34(3)	62(5)	-8(3)	-7(3)	17(3)
C(28)	37(3)	42(3)	54(4)	-11(3)	-6(3)	22(3)
C(29)	31(3)	34(3)	49(4)	-2(3)	1(3)	18(3)
C(30)	44(4)	31(3)	84(6)	6(4)	11(4)	12(3)
C(31)	53(4)	58(5)	49(4)	-15(3)	-11(3)	31(4)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for C31H30Cl2NOPPd(CH2Cl2).

	x	y	z	U(eq)
H(2)	7443	869	5574	51
H(3)	7400	888	6329	63
H(4)	6518	1779	6679	64
H(5)	5619	2585	6279	55
H(8A)	4156	3960	5514	78
H(8B)	3176	2678	5378	78
H(9)	4967	4187	4874	59
H(11)	3668	3886	4320	68
H(12)	2336	2768	3809	85
H(13)	1698	771	3767	87
H(14)	2325	-52	4284	78
H(15)	3679	1096	4791	63
H(17)	9063	3146	5082	42
H(19)	10628	1441	4634	55
H(21)	7191	70	4483	49

H(22A)	11231	3271	5376	83
H(22B)	11245	4137	5017	83
H(22C)	11811	3356	4916	83
H(23A)	9641	-213	4197	104
H(23B)	8364	-593	4036	104
H(23C)	8551	-1083	4481	104
H(25)	4919	-407	5263	42
H(27)	2870	-2099	4254	52
H(29)	5724	1027	4071	45
H(30A)	2539	-2064	5287	84
H(30B)	3360	-2614	5274	84
H(30C)	2351	-2997	4926	84
H(31A)	4173	-1091	3455	78
H(31B)	4382	192	3491	78
H(31C)	3127	-889	3579	78
H(32A)	5944	6106	6043	104
H(32B)	6253	7218	5760	104
H(32C)	6129	7169	5833	105
H(32D)	7397	7595	6037	105

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Table 6. Torsion angles [°] for C31H30Cl2NOPPd(CH2Cl2).

C(16)-P(1)-C(1)-C(2)	-24.0(6)
C(24)-P(1)-C(1)-C(2)	89.8(5)
Pd(1)-P(1)-C(1)-C(2)	-149.8(5)
C(16)-P(1)-C(1)-C(6)	156.0(5)
C(24)-P(1)-C(1)-C(6)	-90.2(5)
Pd(1)-P(1)-C(1)-C(6)	30.2(5)
C(6)-C(1)-C(2)-C(3)	-2.4(10)
P(1)-C(1)-C(2)-C(3)	177.7(6)
C(1)-C(2)-C(3)-C(4)	0.6(12)
C(2)-C(3)-C(4)-C(5)	1.4(12)
C(3)-C(4)-C(5)-C(6)	-1.6(11)
C(4)-C(5)-C(6)-C(1)	-0.2(10)
C(4)-C(5)-C(6)-C(7)	176.3(6)
C(2)-C(1)-C(6)-C(5)	2.2(9)
P(1)-C(1)-C(6)-C(5)	-177.9(5)
C(2)-C(1)-C(6)-C(7)	-174.2(6)
P(1)-C(1)-C(6)-C(7)	5.7(8)
C(9)-N(1)-C(7)-O(1)	-3.4(8)
Pd(1)-N(1)-C(7)-O(1)	175.4(4)
C(9)-N(1)-C(7)-C(6)	174.8(6)
Pd(1)-N(1)-C(7)-C(6)	-6.4(10)

C(8)-O(1)-C(7)-N(1)	-1.5(9)
C(8)-O(1)-C(7)-C(6)	180.0(6)
C(5)-C(6)-C(7)-N(1)	159.8(7)
C(1)-C(6)-C(7)-N(1)	-23.7(10)
C(5)-C(6)-C(7)-O(1)	-21.9(8)
C(1)-C(6)-C(7)-O(1)	154.6(6)
C(7)-O(1)-C(8)-C(9)	5.5(9)
C(7)-N(1)-C(9)-C(10)	-116.0(7)
Pd(1)-N(1)-C(9)-C(10)	65.1(7)
C(7)-N(1)-C(9)-C(8)	6.5(8)
Pd(1)-N(1)-C(9)-C(8)	-172.4(5)
O(1)-C(8)-C(9)-N(1)	-7.0(8)
O(1)-C(8)-C(9)-C(10)	114.6(7)
N(1)-C(9)-C(10)-C(15)	41.3(10)
C(8)-C(9)-C(10)-C(15)	-74.6(8)
N(1)-C(9)-C(10)-C(11)	-141.8(7)
C(8)-C(9)-C(10)-C(11)	102.4(8)
C(15)-C(10)-C(11)-C(12)	1.2(12)
C(9)-C(10)-C(11)-C(12)	-175.9(7)
C(10)-C(11)-C(12)-C(13)	-1.7(13)
C(11)-C(12)-C(13)-C(14)	2.4(13)
C(12)-C(13)-C(14)-C(15)	-2.7(13)
C(13)-C(14)-C(15)-C(10)	2.3(12)

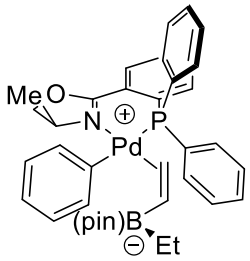
C(11)-C(10)-C(15)-C(14)	-1.5(11)
C(9)-C(10)-C(15)-C(14)	175.5(7)
C(24)-P(1)-C(16)-C(17)	-176.7(5)
C(1)-P(1)-C(16)-C(17)	-63.7(5)
Pd(1)-P(1)-C(16)-C(17)	57.3(5)
C(24)-P(1)-C(16)-C(21)	4.2(6)
C(1)-P(1)-C(16)-C(21)	117.1(6)
Pd(1)-P(1)-C(16)-C(21)	-121.9(5)
C(21)-C(16)-C(17)-C(18)	-1.8(10)
P(1)-C(16)-C(17)-C(18)	179.1(5)
C(16)-C(17)-C(18)-C(19)	2.1(10)
C(16)-C(17)-C(18)-C(22)	-178.1(7)
C(17)-C(18)-C(19)-C(20)	-1.6(11)
C(22)-C(18)-C(19)-C(20)	178.6(7)
C(18)-C(19)-C(20)-C(21)	0.8(12)
C(18)-C(19)-C(20)-C(23)	179.1(8)
C(17)-C(16)-C(21)-C(20)	0.9(10)
P(1)-C(16)-C(21)-C(20)	180.0(5)
C(19)-C(20)-C(21)-C(16)	-0.4(11)
C(23)-C(20)-C(21)-C(16)	-178.8(7)
C(16)-P(1)-C(24)-C(25)	98.9(5)
C(1)-P(1)-C(24)-C(25)	-11.6(5)
Pd(1)-P(1)-C(24)-C(25)	-131.4(4)

C(16)-P(1)-C(24)-C(29)	-84.4(5)
C(1)-P(1)-C(24)-C(29)	165.0(4)
Pd(1)-P(1)-C(24)-C(29)	45.3(5)
C(29)-C(24)-C(25)-C(26)	-0.7(9)
P(1)-C(24)-C(25)-C(26)	175.7(5)
C(24)-C(25)-C(26)-C(27)	2.1(9)
C(24)-C(25)-C(26)-C(30)	-177.8(6)
C(25)-C(26)-C(27)-C(28)	-1.9(10)
C(30)-C(26)-C(27)-C(28)	178.0(6)
C(26)-C(27)-C(28)-C(29)	0.2(10)
C(26)-C(27)-C(28)-C(31)	-175.9(7)
C(25)-C(24)-C(29)-C(28)	-1.0(9)
P(1)-C(24)-C(29)-C(28)	-177.7(5)
C(27)-C(28)-C(29)-C(24)	1.2(9)
C(31)-C(28)-C(29)-C(24)	177.4(6)

Symmetry transformations used to generate equivalent atoms:

3.3.8 Density Functional Theory Calculations (DFT)

All calculations were performed using the Gaussian09 package of programs. Optimized geometries were calculated using DFT (ωB9XD/LANL2DZ; PCM solvent model with THF) under standard conditions (298.15 K, 1 atm). Intrinsic Reaction Coordinate (IRC) calculations were performed followed by optimization of the end points.



3.110

Single Point Calculation

Electronic Energy + Thermal Free Energy Correction: -1912.2781779 Hartree

C -1.0111210000 -2.2329330000 -2.0066380000

C 0.0690050000 -1.6114190000 -1.3569760000

C 1.0365860000 -0.9026710000 -2.1070790000

C 0.8872900000 -0.8261150000 -3.4976650000

C -0.1853590000 -1.4592070000 -4.1448420000

C -1.1331260000 -2.1703730000 -3.3998720000

H -1.7486420000 -2.7642630000 -1.4177020000

H 1.6114260000 -0.2791200000 -4.0897080000

H -0.2733680000 -1.3940410000 -5.2232430000

H -1.9613870000 -2.6649590000 -3.8933650000

C 0.1034240000 -1.6905530000 0.1161820000

C 0.5774890000 -1.5956730000 2.3431400000

C -0.9164490000 -1.9428510000 2.1637000000

H 1.0847180000 -2.3395250000 2.9537610000

H -1.5902850000 -1.2651830000 2.6843920000

H -1.1503860000 -2.9816230000 2.3987620000

Pd 3.2130490000 -1.7547590000 0.5233000000

P 2.5190990000 -0.1463110000 -1.2544760000

C 0.8174400000 -0.1885370000 2.8993270000

H 0.4785860000 -0.1356030000 3.9385280000

H 1.8809130000 0.0604750000 2.8640610000

H 0.2776380000 0.5612270000 2.3095420000

O -1.1365230000 -1.7574140000 0.7068400000

C 3.4979510000 0.6039430000 -2.6474700000

C 3.4820840000 1.9884570000 -2.8907600000

C 4.2531290000 -0.2506460000 -3.4745380000

C 4.2213590000 2.5210820000 -3.9581390000

H 2.9004050000 2.6528300000 -2.2601560000

C 4.9833060000 0.2895800000 -4.5434990000

H 4.2892170000 -1.3288660000 -3.2977660000

C 4.9719280000 1.6726510000 -4.7873220000

H 4.2078960000 3.5901960000 -4.1403800000

H 5.5640550000 -0.3721720000 -5.1768780000

H 5.5428070000 2.0856480000 -5.6123080000

C 1.8160340000 1.3121600000 -0.3349730000

C 0.5267770000 1.8152820000 -0.5707740000

C 2.6264250000 1.9038130000 0.6512150000

C 0.0472590000 2.8984410000 0.1827820000

H -0.1065400000 1.3731650000 -1.3335120000

C 2.1528020000 2.9935400000 1.3934530000

H 3.6193090000 1.5087690000 0.8480070000

C 0.8585360000 3.4891410000 1.1640240000

H -0.9516930000 3.2790970000 0.0007260000

H 2.7832310000 3.4449690000 2.1513720000

H 0.4866270000 4.3264890000 1.7443410000

N 1.1094150000 -1.6818140000 0.9397830000

C 3.4837080000 -2.9768410000 2.1161110000

C 3.5765490000 -4.3685460000 1.9339940000

C 3.5317890000 -2.4467570000 3.4202880000

C 3.6515540000 -5.2204900000 3.0512030000

H 3.6550530000 -4.7683420000 0.9262890000

C 3.6160400000 -3.3011870000 4.5341320000

H 3.5140590000 -1.3723600000 3.5810150000

C 3.6619330000 -4.6937010000 4.3537360000

H 3.7196050000 -6.2940760000 2.8999140000

H 3.6507180000 -2.8792610000 5.5343800000

H 3.7253930000 -5.3547020000 5.2123930000

C 5.2308210000 -2.0893670000 -0.6437670000

C 5.4484570000 -1.7900220000 0.7014460000

B 5.3843250000 -3.4939060000 -1.4704210000

O 4.8454530000 -3.2386360000 -2.8803310000

C 4.0943820000 -4.3967520000 -3.3402850000

C 3.5130220000 -4.9844150000 -1.9979650000

O 4.5617080000 -4.6904000000 -1.0286790000

C 3.2725300000 -6.4971650000 -2.0162890000

C 2.2212080000 -4.2654040000 -1.5759510000

C 3.0305820000 -3.9189010000 -4.3355000000

C 5.0428580000 -5.3829930000 -4.0491980000

H 5.7679940000 -5.8076780000 -3.3501720000

H 5.5921590000 -4.8433210000 -4.8280410000

H 4.4887250000 -6.2041190000 -4.5192200000

H 2.4324600000 -3.1078440000 -3.9128970000

H 2.3599630000 -4.7394510000 -4.6192460000

H 3.5190820000 -3.5444720000 -5.2424770000

H 2.8553330000 -6.8139270000 -1.0535240000

H 2.5609750000 -6.7700410000 -2.8056620000

H 4.2051630000 -7.0425690000 -2.1782080000

H 2.3869420000 -3.1853190000 -1.5700550000

H 1.9429180000 -4.5737300000 -0.5628220000

H 1.3859050000 -4.4864530000 -2.2502160000

C 6.9819520000 -3.8567310000 -1.4636010000

C 7.5025680000 -4.3922350000 -0.1133980000

H 7.5765700000 -2.9802150000 -1.7717010000

H 7.1394190000 -4.6224200000 -2.2379850000

H 7.5499740000 -3.5971630000 0.6413350000

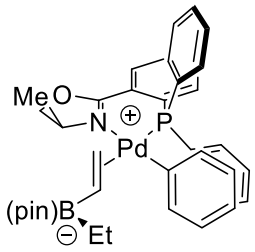
H 8.5113250000 -4.8206470000 -0.1951640000

H 6.8308410000 -5.1722010000 0.2670720000

H 5.2507130000 -1.2128570000 -1.2991560000

H 5.7041030000 -2.5690030000 1.4078400000

H 5.6653090000 -0.7713540000 1.0279760000



3.109

Single Point Calculation

Electronic Energy + Thermal Free Energy Correction: -1912.291513 Hartree

C -1.4842400000 -1.1048100000 -2.5563700000

C -0.3897000000 -0.7216700000 -1.7604300000

C 0.5369070000 0.2236620000 -2.2608600000

C 0.3552770000 0.7496160000 -3.5470500000

C -0.7303700000 0.3488700000 -4.3406700000

C -1.6535400000 -0.5779700000 -3.8420500000

H -2.1934400000 -1.8217000000 -2.1628000000

H 1.0566180000 1.4788560000 -3.9369400000

H -0.8523100000 0.7643900000 -5.3343300000

H -2.4973300000 -0.8903900000 -4.4460300000

C -0.2846700000 -1.3297000000 -0.4157100000

C 0.3052450000 -2.0482400000 1.6611530000

C -1.1051100000 -2.5818300000 1.3278270000

H 0.9696330000 -2.8851700000 1.8615590000

H -1.8675300000 -2.3187700000 2.0596960000

H -1.0916300000 -3.6502400000 1.1156550000

Pd 2.8243030000 -1.0901400000 -0.0475700000

P 1.9675160000 0.7855100000 -1.2054700000

C 0.3442370000 -1.0113500000 2.7878290000

H 0.0586830000 -1.4767000000 3.7365390000

H 1.3529450000 -0.5991200000 2.8918290000

H -0.3409000000 -0.1818500000 2.5798650000

O -1.4492300000 -1.8862600000 0.0601710000

C 3.0282600000 1.8294500000 -2.3070700000

C 3.1360890000 3.2169870000 -2.1268000000

C 3.7781010000 1.1910950000 -3.3119700000

C 3.9918240000 3.9648200000 -2.9512900000

H 2.5681350000 3.7182760000 -1.3499600000

C 4.6259040000 1.9397110000 -4.1364100000

H 3.7126280000 0.1157880000 -3.4434700000

C 4.7362160000 3.3289530000 -3.9556400000

H 4.0761350000 5.0360620000 -2.8058100000

H 5.2045540000 1.4415560000 -4.9060600000

H 5.3997370000 3.9077770000 -4.5889100000

C 1.1770580000 1.9543730000 0.0042170000

C 0.0518610000 2.7192960000 -0.3474000000

C 1.7241080000 2.0652140000 1.2934800000

C -0.5211000000 3.5927950000 0.5883560000

H -0.3835400000 2.6343370000 -1.3383800000

C 1.1541620000 2.9425160000 2.2263130000

H 2.5789400000 1.4583110000 1.5756510000

C 0.0302970000 3.7068920000 1.8748510000

H -1.3916800000 4.1784480000 0.3150490000

H 1.5783350000 3.0212020000 3.2209860000

H -0.4149700000 4.3816140000 2.5977820000

N 0.7356480000 -1.4201300000 0.3757770000

C 4.7012690000 -0.6041100000 -0.5779800000

C 5.3731560000 -1.3191900000 -1.5889300000

C 5.3585070000 0.4880860000 0.0237650000

C 6.6663720000 -0.9465500000 -1.9942300000

H 4.8936870000 -2.1641000000 -2.0737500000

C 6.6518320000 0.8618840000 -0.3804800000

H 4.8682800000 1.0622650000 0.8055000000

C 7.3106550000 0.1470080000 -1.3940600000

H 7.1661460000 -1.5098200000 -2.7768100000

H 7.1388580000 1.7097080000 0.0921140000

H 8.3078480000 0.4365580000 -1.7094100000

C 3.6400870000 -3.2777100000 0.6314550000

C 3.7233620000 -2.3387600000 1.6458310000

B 2.6249620000 -4.5708800000 0.5045200000

O 3.1823220000 -5.5258200000 -0.5425500000

C 2.4145280000 -5.3820700000 -1.7707900000

C 0.9761140000 -5.0487500000 -1.2292900000

O 1.2586140000 -4.2105600000 -0.0742800000

C 2.9978930000 -4.2194100000 -2.6001400000

C 2.5056900000 -6.6832100000 -2.5714600000

H 2.2452650000 -7.5431800000 -1.9490800000

H 3.5299210000 -6.8235900000 -2.9349000000

H 1.8334900000 -6.6575900000 -3.4383300000

C 0.0988130000 -4.2622900000 -2.2066300000

C 0.2224590000 -6.3082800000 -0.7593100000

H 4.5121280000 -3.3166000000 -0.0301400000

H 2.9979390000 -2.3278400000 2.4575020000

H 4.6245310000 -1.7523300000 1.8194980000

C 2.5117580000 -5.3142900000 1.9499880000

C 3.8566740000 -5.8334700000 2.5004450000

H 1.8132700000 -6.1582000000 1.8378870000

H 2.0578390000 -4.6293500000 2.6886510000

H 4.3262980000 -6.5056400000 1.7722920000

H 3.7447110000 -6.3828300000 3.4457660000

H 4.5529950000 -5.0032600000 2.6799280000

H 2.8572250000 -3.2655400000 -2.0793200000

H 2.5299530000 -4.1496300000 -3.5890500000

H 4.0723520000 -4.3893700000 -2.7331100000

H 0.8551250000 -6.9144400000 -0.1045400000

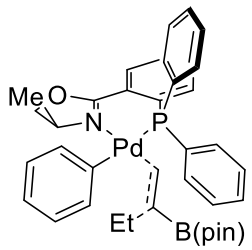
H -0.1081400000 -6.9252800000 -1.6034100000

H -0.6611400000 -5.9948800000 -0.1913100000

H 0.5636610000 -3.3102700000 -2.4737000000

H -0.8692800000 -4.0483000000 -1.7387800000

H -0.0795300000 -4.8360100000 -3.1246000000



3.112

Single Point Calculation

Electronic Energy + Thermal Free Energy Correction: -1912.261990 Hartree

C -0.9376200000 -2.2930100000 -1.8602300000

C 0.1073400000 -1.6069600000 -1.2173300000

C 1.1059930000 -0.9505500000 -1.9778900000

C 1.0192470000 -1.0027100000 -3.3763000000

C -0.0139500000 -1.7053600000 -4.0151900000

C -0.9938500000 -2.3568400000 -3.2573000000

H -1.6992300000 -2.7764800000 -1.2602600000

H 1.7593930000 -0.4960500000 -3.9833500000

H -0.0489200000 -1.7363400000 -5.0983400000

H -1.7950200000 -2.9008100000 -3.7437700000

C 0.0851020000 -1.5828400000 0.2579370000

C 0.5439820000 -1.4429900000 2.4874310000

C -0.9822800000 -1.6477500000 2.2994050000

H 0.9839850000 -2.2542400000 3.0679270000

H -1.5817400000 -0.8434200000 2.7242880000

H -1.3359400000 -2.6179400000 2.6477090000

Pd 3.1957950000 -1.6815000000 0.7173050000

P 2.5525070000 -0.1046500000 -1.1263600000

C 0.9161780000 -0.0950200000 3.1084390000

H 0.5452440000 -0.0431800000 4.1370980000

H 2.0030810000 0.0233620000 3.1210210000

H 0.4857980000 0.7310370000 2.5316230000

O -1.1707600000 -1.6088500000 0.8263030000

C 3.4767080000 0.7067760000 -2.5353700000

C 3.4700370000 2.1020180000 -2.7100700000

C 4.2038670000 -0.1024400000 -3.4303600000

C 4.1879060000 2.6851850000 -3.7664200000

H 2.9114440000 2.7401810000 -2.0340000000

C 4.9126630000 0.4847690000 -4.4880900000

H 4.2229040000 -1.1867900000 -3.3276700000

C 4.9109510000 1.8787970000 -4.6584100000

H 4.1781480000 3.7627520000 -3.8904900000

H 5.4664390000 -0.1495400000 -5.1719900000

H 5.4645940000 2.3304560000 -5.4748400000

C 1.7648460000 1.3458630000 -0.2562800000

C 0.4720140000 1.8081930000 -0.5490000000

C 2.5239880000 1.9878490000 0.7387760000

C -0.0619500000 2.8987500000 0.1558740000

H -0.1219200000 1.3285190000 -1.3207800000

C 1.9985310000 3.0876430000 1.4302910000

H 3.5176600000 1.6223610000 0.9817020000

C 0.7005640000 3.5417250000 1.1437030000

H -1.0642600000 3.2459620000 -0.0702200000

H 2.5914920000 3.5777240000 2.1945610000

H 0.2879810000 4.3863690000 1.6848470000

N 1.0753200000 -1.5379100000 1.0897150000

C 3.3883470000 -2.8753800000 2.3294150000

C 2.9557920000 -4.2190300000 2.2765710000

C 3.8468750000 -2.3759200000 3.5679730000

C 2.9551620000 -5.0271100000 3.4278740000

H 2.6169100000 -4.6422400000 1.3354280000

C 3.8438580000 -3.1796900000 4.7225490000

H 4.2092840000 -1.3534000000 3.6385770000

C 3.3938480000 -4.5092700000 4.6585980000

H 2.6173510000 -6.0578000000 3.3627880000

H 4.1949790000 -2.7703200000 5.6658840000

H 3.3933320000 -5.1320600000 5.5477800000

C 5.3600810000 -2.0504400000 -0.8910200000

C 5.2759420000 -2.0486100000 0.5583860000

B 5.2087490000 -3.2616100000 -1.7803900000

O 4.7804320000 -3.1399900000 -3.1775900000

C 4.2585560000 -4.4414900000 -3.6182500000

C 3.7446310000 -5.0546100000 -2.2630800000

O 4.7422240000 -4.5570000000 -1.3044100000

C 3.7309790000 -6.5811300000 -2.2146800000

C 2.3723860000 -4.4897200000 -1.8579000000

C 3.1698440000 -4.1979900000 -4.6628300000

C 5.4164850000 -5.2498000000 -4.2270900000

H 6.1721710000 -5.4865400000 -3.4711800000

H 5.8886470000 -4.6535100000 -5.0145400000

H 5.0601660000 -6.1874800000 -4.6675400000

H 2.4229650000 -3.4902800000 -4.2942600000

H 2.6679730000 -5.1369900000 -4.9243600000

H 3.6170240000 -3.7826500000 -5.5722200000

H 3.3534840000 -6.9138200000 -1.2421700000

H 3.0760350000 -6.9857100000 -2.9952600000

H 4.7349770000 -6.9909800000 -2.3484200000

H 2.3700620000 -3.3966100000 -1.9109400000

H 2.1603110000 -4.7781800000 -0.8237800000

H 1.5706710000 -4.8743400000 -2.4979300000

C 7.0490110000 -3.1247200000 -1.5964800000

C 7.6090960000 -4.0636200000 -0.5281000000

H 7.5608670000 -2.1570800000 -1.5875100000

H 7.1743260000 -3.5276000000 -2.6101600000

H 7.5539350000 -3.6081700000 0.4672330000

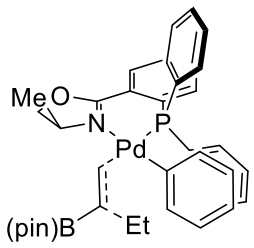
H 8.6632270000 -4.2991600000 -0.7248400000

H 7.0411360000 -4.9985300000 -0.5035700000

H 5.5594920000 -1.0897600000 -1.3672800000

H 5.4385370000 -3.0200700000 1.0205410000

H 5.8060650000 -1.2493900000 1.0876260000



3.111

Single Point Calculation

Electronic Energy + Thermal Free Energy Correction: -1912.272407 Hartree

C -0.8386500000 -1.3344400000 -3.1428300000

C 0.1060640000 -0.8401600000 -2.2266200000

C 0.9903170000 0.1942640000 -2.6141400000

C 0.9189880000 0.6952280000 -3.9209300000

C -0.0106400000 0.1822830000 -4.8390600000

C -0.8938900000 -0.8319500000 -4.4483200000

H -1.5200000000 -2.1163100000 -2.8296200000

H 1.5859850000 1.4923650000 -4.2302300000

H -0.0459400000 0.5799200000 -5.8470100000

H -1.6181400000 -1.2289200000 -5.1501000000

C 0.1136210000 -1.4364700000 -0.8731800000

C 0.5981330000 -2.2536900000 1.2000920000

C -0.9112700000 -2.4713400000 0.9142900000

H 1.1127080000 -3.2148300000 1.2596730000

H -1.5616800000 -1.9076600000 1.5843800000

H -1.1990900000 -3.5206100000 0.8902670000

Pd 3.1967610000 -1.0362500000 -0.2522500000

P 2.2337880000 0.8603070000 -1.3866600000

C 0.8618540000 -1.3840500000 2.4310140000

H 0.4983690000 -1.8898500000 3.3314030000

H 1.9329320000 -1.1938900000 2.5454870000

H 0.3512330000 -0.4192200000 2.3363740000

O -1.1060300000 -1.9237000000 -0.4506600000

C 3.1961700000 2.1324110000 -2.3344800000

C 2.9129310000 3.5056880000 -2.2501900000

C 4.2546860000 1.6859930000 -3.1468900000

C 3.6833620000 4.4270090000 -2.9768000000

H 2.1040540000 3.8624800000 -1.6208700000

C 5.0188730000 2.6063490000 -3.8762200000

H 4.4894780000 0.6283390000 -3.2003900000

C 4.7351880000 3.9794670000 -3.7912500000

H 3.4631580000 5.4865270000 -2.9050400000

H 5.8353760000 2.2546880000 -4.4970200000

H 5.3312270000 4.6932440000 -4.3497400000

C 1.1671590000 1.8345970000 -0.2113200000

C -0.0823200000 2.3580090000 -0.5841600000

C 1.6441480000 2.0343650000 1.0962410000

C -0.8494400000 3.0765730000 0.3455860000

H -0.4634600000 2.2053160000 -1.5893200000

C 0.8818770000 2.7597280000 2.0225250000

H 2.5989920000 1.6114350000 1.3937370000

C -0.3677200000 3.2804100000 1.6485870000

H -1.8150700000 3.4746080000 0.0536420000

H 1.2555310000 2.9086510000 3.0295420000

H -0.9616500000 3.8360170000 2.3662530000

N 1.0957780000 -1.5864700000 -0.0440900000

C 5.1008490000 -0.4412600000 -0.4733900000

C 5.9128810000 -0.9338400000 -1.5202700000

C 5.6573560000 0.5403140000 0.3778230000

C 7.2214780000 -0.4588600000 -1.7168800000

H 5.5213610000 -1.6837800000 -2.2030100000

C 6.9650940000 1.0202260000 0.1842070000

H 5.0696490000 0.9426440000 1.1993250000

C 7.7548390000 0.5235140000 -0.8663000000

H 7.8200770000 -0.8538200000 -2.5332100000

H 7.3641140000 1.7799580000 0.8507720000

H 8.7639460000 0.8937750000 -1.0180200000

C 4.1006540000 -3.5886200000 -0.2447300000

C 3.9547930000 -2.6783200000 0.8745090000

B 3.1785340000 -4.6879100000 -0.7104000000

O 3.2541010000 -5.2621000000 -2.0582700000

C 1.8789080000 -5.4436200000 -2.5394600000

C 1.0984360000 -5.7188900000 -1.2012700000

O 1.8070770000 -4.8482900000 -0.2509500000

C 1.4489820000 -4.1265200000 -3.2081400000

C 1.8449540000 -6.5943300000 -3.5430500000

H 2.2932000000 -7.4984700000 -3.1242100000

H 2.4083850000 -6.3175900000 -4.4401400000

H 0.8132580000 -6.8167500000 -3.8402400000

C -0.3747300000 -5.3171800000 -1.2388600000

C 1.2389590000 -7.1723100000 -0.7187600000

H 5.0145010000 -3.4700900000 -0.8284200000

H 3.1614250000 -2.9217200000 1.5814900000

H 4.8755370000 -2.3731000000 1.3779510000

C 4.4146060000 -5.5733400000 0.3867230000

C 3.8761710000 -5.7922900000 1.7999440000

H 5.4799120000 -5.3234100000 0.4008140000

H 4.3114510000 -6.4671700000 -0.2422000000

H 4.4115400000 -6.6064600000 2.3055720000

H 2.8108040000 -6.0406900000 1.7728690000

H 3.9988270000 -4.8892800000 2.4101340000

H 1.4894350000 -3.3027400000 -2.4881600000

H 0.4369030000 -4.1856400000 -3.6229200000

H 2.1445920000 -3.9005400000 -4.0226600000

H 2.2844710000 -7.4954500000 -0.7367100000

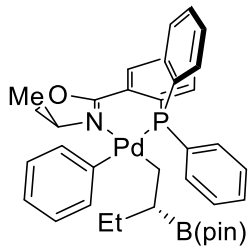
H 0.6499990000 -7.8582500000 -1.3372900000

H 0.8771560000 -7.2374300000 0.3125580000

H -0.4884300000 -4.2433100000 -1.4048800000

H -0.8542300000 -5.5748400000 -0.2881700000

H -0.8986000000 -5.8525700000 -2.0390900000



3.114

Single Point Calculation

Electronic Energy + Thermal Free Energy Correction: -1912.330194 Hartree

C -0.0952900000 -2.1739600000 -2.9358900000

C 0.7183870000 -1.5205000000 -1.9930000000

C 1.7151620000 -0.6087100000 -2.4189800000

C 1.8646060000 -0.3838800000 -3.7954200000

C 1.0674810000 -1.0552800000 -4.7350400000

C 0.0843290000 -1.9552900000 -4.3063300000

H -0.8614600000 -2.8561300000 -2.5876400000

H 2.6051080000 0.3218510000 -4.1506700000

H 1.2129300000 -0.8661700000 -5.7926500000

H -0.5384500000 -2.4746600000 -5.0253200000

C 0.4646100000 -1.8213200000 -0.5709000000

C 0.5420820000 -2.1092600000 1.6860480000

C -0.8755900000 -2.4854200000 1.1813010000

H 1.0212310000 -2.9485200000 2.1904290000

H -1.6699600000 -1.9022600000 1.6456200000

H -1.0902500000 -3.5522000000 1.2496190000

Pd 3.4638920000 -1.4742100000 0.5166210000

P 2.8388550000 0.2339940000 -1.1678100000

C 0.5702070000 -0.8731000000 2.5889270000

H 0.0332440000 -1.0788800000 3.5206370000

H 1.6047660000 -0.6113800000 2.8281180000

H 0.1036260000 -0.0164100000 2.0897250000

O -0.8472200000 -2.1286100000 -0.2599800000

C 3.8698130000 1.3865910000 -2.2185500000

C 3.7242250000 2.7821400000 -2.1420400000

C 4.8358980000 0.8364920000 -3.0850100000

C 4.5382880000 3.6217650000 -2.9198300000

H 2.9834570000 3.2227550000 -1.4833200000

C 5.6395400000 1.6769700000 -3.8667000000

H 4.9587410000 -0.2420300000 -3.1473100000

C 5.4965130000 3.0722300000 -3.7843500000

H 4.4202130000 4.6977820000 -2.8500200000

H 6.3780710000 1.2427860000 -4.5321400000

H 6.1239320000 3.7216540000 -4.3856800000

C 1.6756620000 1.3992500000 -0.2865900000

C 0.4251050000 1.7745040000 -0.8035100000

C 2.0923250000 1.9061180000 0.9577930000

C -0.4059800000 2.6425640000 -0.0776700000

H 0.0921520000 1.3957200000 -1.7648400000

C 1.2705530000 2.7856380000 1.6756470000

H 3.0491150000 1.6008500000 1.3715700000

C 0.0159200000 3.1514300000 1.1609200000

H -1.3739200000 2.9217700000 -0.4797100000

H 1.6006460000 3.1713530000 2.6339450000

H -0.6263800000 3.8237630000 1.7195770000

N 1.2964450000 -1.8418000000 0.4183950000

C 3.6918150000 -2.9076800000 1.9340790000

C 3.2837450000 -4.2355400000 1.6560360000

C 4.1411830000 -2.6415600000 3.2492050000

C 3.3243580000 -5.2452200000 2.6344370000

H 2.9146150000 -4.4893600000 0.6644360000

C 4.1689230000 -3.6401000000 4.2396860000

H 4.4817870000 -1.6411100000 3.5062950000

C 3.7634070000 -4.9510500000 3.9365030000

H 3.0129690000 -6.2556300000 2.3817400000

H 4.5112110000 -3.3970400000 5.2423610000

H 3.7924080000 -5.7262900000 4.6962850000

C 6.3080780000 -1.0544400000 -0.5270300000

C 5.4676350000 -1.0575100000 0.7782710000

B 5.9197930000 -2.3171400000 -1.3564300000

O 5.2405590000 -2.2923400000 -2.5838800000

C 4.8463050000 -3.6822300000 -2.9463800000

C 5.8861670000 -4.5403000000 -2.1216600000

O 6.2292530000 -3.6286600000 -0.9973400000

C 3.3963700000 -3.8602800000 -2.4806600000

C 4.9431430000 -3.8340700000 -4.4620300000

C 5.3264830000 -5.8345500000 -1.5387300000

C 7.1950620000 -4.8016100000 -2.8792400000

H 6.0419030000 -0.1615100000 -1.1054800000

H 5.9112370000 -1.7652400000 1.4879240000

H 5.4692360000 -0.0594000000 1.2473790000

H 3.2978310000 -3.6429200000 -1.4114400000

H 3.0377460000 -4.8751300000 -2.6777100000

H 2.7620150000 -3.1557000000 -3.0256200000

H 4.2072830000 -3.1799000000 -4.9400300000

H 5.9341390000 -3.5650800000 -4.8335000000

H 4.7258330000 -4.8673600000 -4.7539200000

H 4.5044060000 -5.6340400000 -0.8485800000

H 6.1129580000 -6.3574700000 -0.9870700000

H 4.9690670000 -6.4921000000 -2.3388900000

H 7.6128830000 -3.8729800000 -3.2814600000

H 7.0417970000 -5.5043200000 -3.7042100000

H 7.9244930000 -5.2317600000 -2.1868000000

C 7.8341760000 -0.9973200000 -0.2443600000

C 8.2665670000 0.3001310000 0.4609700000

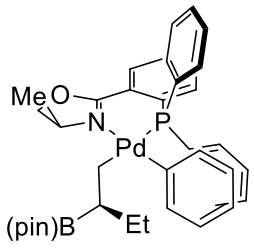
H 8.3876940000 -1.0865900000 -1.1912200000

H 8.1167480000 -1.8634500000 0.3696660000

H 7.9730110000 1.1758560000 -0.1322100000

H 9.3535740000 0.3330850000 0.6011150000

H 7.7964280000 0.3889430000 1.4463560000



3.113

Single Point Calculation

Electronic Energy + Thermal Free Energy Correction: -1912.325152 Hartree

C -1.2257000000 -1.4870500000 -2.3664100000

C -0.0768800000 -1.0367800000 -1.6891500000

C 0.6342000000 0.0864510000 -2.1776000000

C 0.1773470000 0.7221190000 -3.3413700000

C -0.9594000000 0.2591620000 -4.0214100000

C -1.6635200000 -0.8484600000 -3.5327900000

H -1.7683600000 -2.3388400000 -1.9750200000

H 0.7088640000 1.5856850000 -3.7255300000

H -1.2910600000 0.7649850000 -4.9212600000

H -2.5439500000 -1.2113500000 -4.0504000000

C 0.3046440000 -1.7629800000 -0.4573500000

C 1.2838770000 -2.6373200000 1.4003910000

C -0.1773400000 -3.1425800000 1.3242120000

H 1.9843800000 -3.4717500000 1.4334880000

H -0.7633900000 -2.9176500000 2.2139650000

H -0.2570900000 -4.1991800000 1.0653900000

Pd 3.4535020000 -1.2596100000 -0.5599400000

P 2.1735740000 0.6798770000 -1.2926400000

C 1.5391560000 -1.6680900000 2.5606240000

H 1.4687620000 -2.2005700000 3.5151920000

H 2.5341310000 -1.2213500000 2.4768850000

H 0.8003350000 -0.8587700000 2.5510710000

O -0.7539100000 -2.3637800000 0.2012510000

C 2.8609780000 1.9815340000 -2.4261200000

C 2.6728170000 3.3570040000 -2.2197000000

C 3.6372250000 1.5400410000 -3.5144100000

C 3.2516060000 4.2863520000 -3.0997900000

H 2.0881900000 3.7108610000 -1.3766000000

C 4.2045950000 2.4660890000 -4.3982100000

H 3.8169680000 0.4783890000 -3.6545500000

C 4.0139230000 3.8430350000 -4.1912600000

H 3.1074010000 5.3482350000 -2.9317300000

H 4.8045170000 2.1171200000 -5.2314300000

H 4.4617040000 4.5618520000 -4.8693400000

C 1.4852710000 1.6057460000 0.1695950000

C 0.2580540000 2.2900170000 0.1252600000

C 2.2356170000 1.5902200000 1.3596660000

C -0.2139600000 2.9641620000 1.2612780000

H -0.3338000000 2.2922030000 -0.7856200000

C 1.7642890000 2.2703500000 2.4925250000

H 3.1631290000 1.0238380000 1.4171460000

C 0.5415700000 2.9584420000 2.4456650000

H -1.1629800000 3.4879290000 1.2230770000

H 2.3404100000 2.2497380000 3.4118110000

H 0.1760860000 3.4785380000 3.3248440000

N 1.4668640000 -1.9233800000 0.0950860000

C 5.2201060000 -0.5817600000 -1.2566700000

C 5.9979690000 -1.2737500000 -2.2159100000

C 5.6596130000 0.7191590000 -0.9075500000

C 7.1386470000 -0.6957300000 -2.8044400000

H 5.7102280000 -2.2779000000 -2.5180200000

C 6.8012900000 1.3012880000 -1.4803300000

H 5.0890160000 1.2975900000 -0.1855700000

C 7.5491560000 0.5972540000 -2.4389700000

H 7.7045300000 -1.2552300000 -3.5450500000

H 7.1021820000 2.3029630000 -1.1835500000

H 8.4294980000 1.0450890000 -2.8902100000

C 4.7680800000 -3.0005600000 1.6460710000

C 4.4416720000 -2.9506700000 0.1253130000

B 5.5281410000 -1.7347600000 2.1691090000

O 4.9638170000 -0.4698200000 2.3759480000

C 5.8751410000 0.3328810000 3.2377570000

C 7.2651180000 -0.3892300000 3.0260750000

O 6.8436270000 -1.7629300000 2.6391060000

C 5.3273880000 0.2000170000 4.6661530000

C 5.8423810000 1.7890680000 2.7839730000

H 6.5479210000 2.3833340000 3.3750480000

H 4.8400970000 2.2020490000 2.9334180000

H 6.1012130000 1.8857270000 1.7285990000

C 8.0763780000 0.1630120000 1.8483320000

C 8.1311870000 -0.4812400000 4.2807430000

H 3.8156250000 -3.0098300000 2.1967590000

H 5.3708910000 -3.1041300000 -0.4383800000

H 3.7549840000 -3.7756600000 -0.1309800000

C 5.5189860000 -4.3065200000 2.0314360000

C 4.6956310000 -5.5838100000 1.7865870000

H 5.7992100000 -4.2665600000 3.0933490000

H 6.4581640000 -4.3590000000 1.4647230000

H 3.7315530000 -5.5278500000 2.3103610000

H 5.2265700000 -6.4704400000 2.1529170000

H 4.4910180000 -5.7319900000 0.7209720000

H 5.3292510000 -0.8436300000 4.9970460000

H 4.2939940000 0.5599750000 4.6820930000

H 5.9135260000 0.7938220000 5.3741610000

H 7.6262480000 -1.0243400000 5.0825480000

H 8.3845820000 0.5223030000 4.6400520000

H 9.0615580000 -1.0058100000 4.0443760000

H 7.4762590000 0.1988020000 0.9350150000

H 8.9313920000 -0.4959800000 1.6700370000

H 8.4527390000 1.1683900000 2.0636540000