UNIVERSITY OF CALIFORNIA, MERCED

Brønsted Acid Catalyzed Intramolecular Hydroarylation of Alkenes to Access Benzylic Quaternary Center Containing Benzocarbocycles

A dissertation submitted in partial fulfillment of the requirements for the degree

Doctor of Philosophy

in

Chemistry and Biochemistry

by

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University of California, Merced

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To Uyghurs who are going through GENOCIDE

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LIST OF ABBREVIATIONS AND ACRONYMS

Å	Angstrom
α	alpha
β	beta
°C	degrees Celsius
Ac	acetyl
aq.	aqueous
Ar	aryl
br.	broad
Bu	butyl
C–C	carbon–carbon
cat.	catalyst or catalytic amount
$CHCl_3$	chloroform
$CDCl_3$	deuterated chloroform
CSA	camphorsulfonic acid
d	doublet
DCE	1,2-dichloroethane
DCM	dichloromethane
dd	doublet of doublet
DMF	N, N-dimethylformamide
dr	diastereomeric ratio
Et	ethyl
EtOAc	ethyl acetate
Et_2O	diethyl ether
EAS	Electrophilic aromatic substitution
Equiv.	molar equivalent
g	gram(s)
h	hour(s)
Hz	hertz
HCl	hydrochloric acid
J	coupling constant
$LiAlH_4$	lithium aluminum hydride

M	molarity
m	multiplet
$MaSO_4$	magnesium sulfate
Me	methyl
mg	milligram(s)
mmol	millimole
mol	mole
min	minute(s)
NaH	sodium hydride
NaCl	sodium chloride
$NaHCO_3$	sodium bicarbonate
$NaSO_4$	sodium sulfate
NMR	Nuclear magnetic resonance
NEt_3	triethylamine
PCC	pyridinium chlorochromate
Ph	phenyl
$PhSO_3H$	benzenesulfonic acid
$Pd(dba)_2$	bis(dibenzylideneacetone)palladium (0)
ppm	parts per million
P*(t*-Bu)$_3$	tri-*tert*-butylphosphine
q	quartet
R_f	retention factor
rt	room temperature
s	singlet
t	triplet
t-BuOK	potassium *tert*-butoxide
TfOH	triflic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMSCl	chlorotrimethylsilane
ZnF_2	zinc fluoride

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VITA

Education

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Publications

1) X. Cai, A. Tohti, C. Ramirez, H. Harb, F. James, H. P. Hratchian, and B. J. Stokes. Regioselective acid-catalyzed cyclization of cis-methindolylstyrenes affords tetrahydrobenzo[*cd*]indoles. *Org. Lett.*, **2019**, *21*, 1574-1577.
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3) K. Ablajan and A. Tuoheti. Fragmentation characteristics and isomeric differentiation of flavonol O-rhamnosides using negative ion electrospray ionization tandem mass spectrometry. *Rapid Commun. Mass Spectrom.*, **2013**, *27*, 451-460.
4) K. Ablajan, L. Wang, and A. Tuoheti. An efficient synthesis of some new hydrazone derivatives containing 1,2,3-triazole and thiazole. *Lett. Org. Chem*. **2013**, *10*, 715–721.
5) K. Ablajan, W. Kamil, A. Tuoheti, and W.-Fu. Sun. An efficient three component one-pot synthesis of 5-amino-7-aryl-7,8-dihydro-[1,2,4] triazolo[4,3-a]-pyrimidine-6-carbonitriles. Molecules, **2012**, *17*, 1860-1869.
6) K. Ablajan, L. Wang, A. Tuoheti, and Y. Kelimu. An efficient four-component, one-pot synthesis of 6-amino-4-aryl-3- methyl-2,4-ihydropyrano[2,3-c]pyrazole-5-carbonitriles under phase-transfer catalyst. *Lett. Org. Chem*. **2012**, *9*, 639-643.
7) A. Tuoheti, K. Ablajan, L. Wang, and W. Kamil. Three component one-pot synthesis of 4-arylmethylidene-1-(4'-carboxyphenyl)-3-methyl-pyrazole-5-ones. *Chemical Research and Application* (Chinese edition), **2012**, *24*.
8) K. Ablajan, A. Tuoheti, and F. Liu. Synthesis of 1-[3'-(4"-methoxyphenyl)-5'-methylisoxazole-4'-formyl]-4-arylthiosemicarbazides and its derivatives. *Chinese Journal of Synthetic Chemistry* (Chinese edition), **2012**, 20.
9) A. Tuoheti and K. Ablajan. Extraction and separation of total flavonoids from morusalba L. *Chinese Archives of Traditional Chinese Medicine* (Chinese edition), **2012**, 4.
10) A. Tuoheti and K. Ablajan. Synthesis of novel phenyl-hydrazonyl pyrazolone and aromatic azonly pyrazolone derivatives containing isoxazole ring. *Chinese Journal of Synthetic Chemistry* (Chinese edition), **2011**.

Manuscripts in progress

1) A. Tohti, R. Baxter, and B. J. Stokes. Acid catalyzed intramolecular alkene hydroarylation reactions to access benzylic quaternary center containing carbocycles, **2021**.
2) A. Tohti, V. Lerda, and B. J. Stokes. Dearomative spirocyclization of benzothiophene alkenes to access vicinal quaternary centers, **2021**.

ABSTRACT

Construction of the alkylarenes with benzylic all-carbon quaternary center is an attractive topic within synthetic community due to the synthetic challenge it possesses and the presence of the benzylic quaternary center in natural and synthetic molecules with remarkable chemical as well as pharmaceutical properties. Brønsted acid catalyzed intramolecular hydroarylation of unactivated alkenes is an atom-economic and environmentally friendly straightforward method to obtain benzylic quaternary centers. This research has focused on acid catalyzed intramolecular functionalization of unactivated congested alkenes in which the heteroaromatic ring is linked to the styrene moiety via a quaternary benzylic geminal dimethyl group. The Brønsted acid catalyzed intramolecular reactions of the designed alkenes of this kind produce a variety of synthetically challenging spiroheterocycles bearing vicinal quaternary centers through dearomative spirocyclization at ambient temperature. The seven-membered-ring compounds with benzylic quaternary center are also obtained.

CHAPTER 1

A Literature Review of Brønsted Acid Catalyzed Intramolecular Hydroarylation of Unactivated Alkenes to Benzylic Quaternary Center Containing Carbocycles

1. Introduction

The construction of all-carbon quaternary center bearing alkylarenes is an area of intense research interest by the synthetic community because of their ubiquitous presence in scaffolds of natural and bioactive molecules.[1] Installing the quaternary carbon at the benzylic position can improve the physicochemical and pharmacokinetic properties of the target drug molecules.[2] Many natural products and small molecule pharmaceuticals with benzylic quaternary center have shown anticancer, antimicrobial, anti-Alzheimer and other important biological activities (Figure 1.1, 1.2).[3] Despite their importance, there has limited methods to access benzylic quaternary centers due to the steric congestion at the quaternary carbon.[4]

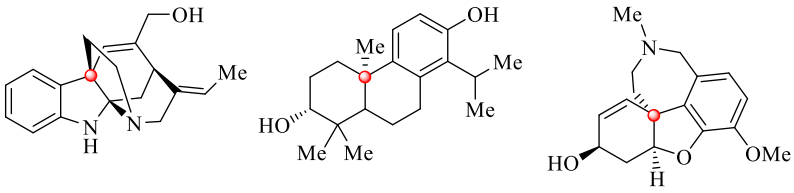


Figure 1.1. Representative natural products containing benzylic quaternary centers[3h, 3i]

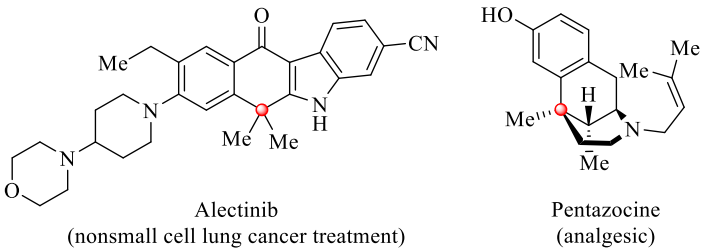


Figure 1.2. Representative marketed drugs containing benzylic quaternary centers[3g]

Since the pioneering study by Charles Friedel and James Crafts in 1877,[5] Friedel-Crafts reaction has been widely applied in industry and in academic laboratory as a powerful tool to derivatize aromatic compounds by adding new carbon functionalities to the ring.[6] Friedel–Crafts type intramolecular hydroarylation reactions of alkenes tethered with diverse functional groups is a direct, atom-efficient way to synthesis complex benzocyclic compounds.[7] The alkylarenes can be achieved through acid or metal

catalyzed hydroarylation of electronically activated and/or unactivated, electronically neutral alkenes. In contrast to intramolecular hydroarylation of activated alkenes, the reaction of unactivated alkenes can avoid further functionalization of the target molecule to remove the activating group. Despite metal catalysis having been widely used in carbon-carbon bond forming reactions, few factors such as the toxicity, oxygen and water sensitiveness, need of stoichiometric catalyst due to the product inhibition and rareness of many metal catalysis limit their application in industry.[8] On the other hand, Brønsted acids, a new class of catalyst in carbon-carbon-bond forming reactions, have gained increased attention in organic synthesis in recent years.[9] While the conventional procedures applied stoichiometric amounts of Brønsted acids, catalytic acids, including chiral/achiral single or dual catalysis, have been emerging as an effective catalyst in synthesis. Compared with metal catalysis, Brønsted acids are cheap, relatively easy to handle and can be stored for long period of time.[9a] Also, the reactions can be run under aerobic conditions. The metal-free nature of Brønsted acids makes them an attractive alternative to metal catalyst in chemical and pharmaceutical industry, as it is challenging to remove the traces of metal impurities from the target compound.[9b] Furthermore, the Brønsted acids are more effective in the reactions of highly substituted alkenes where metal catalysts are less favored.[10]

Numerous Friedel-Crafts type intramolecular hydroarylation protocols have been reported over the decades. However, limited number of them are Brønsted acid catalyzed reactions of unactivated alkenes. In this chapter, we will cover the scarce examples reported until now focused on the Brønsted acid catalyzed intramolecular hydroarylation reactions of unactivated alkenes to alkylarenes with benzylic all-carbon quaternary centers. As indicated in Figure 1.3, the benzylic quaternary center could be achieved from the hydroarylation of di-and/or tri-substituted alkenes or from the alkenes which have a preinstalled benzylic quaternary center. In those Friedel-Crafts-type reactions, the alkene can function as electrophile in which the double bond is activated by the Brønsted acid and subsequently attacked by the arene nucleophile. Intramolecular rearomatization of the intermediate would then afford the desired product. Those approaches have used in the synthesis of various small molecules, natural products, and polymers.

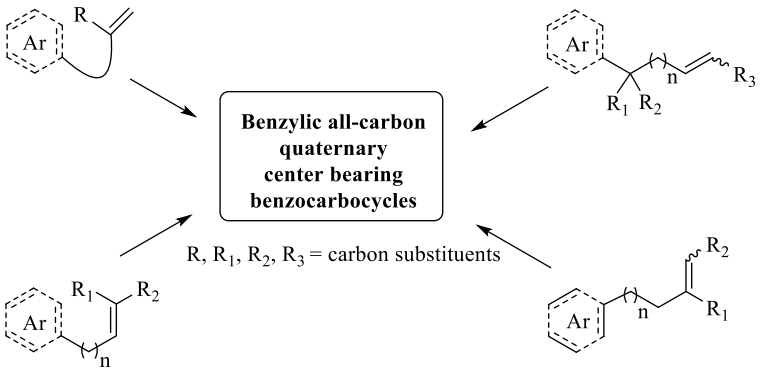


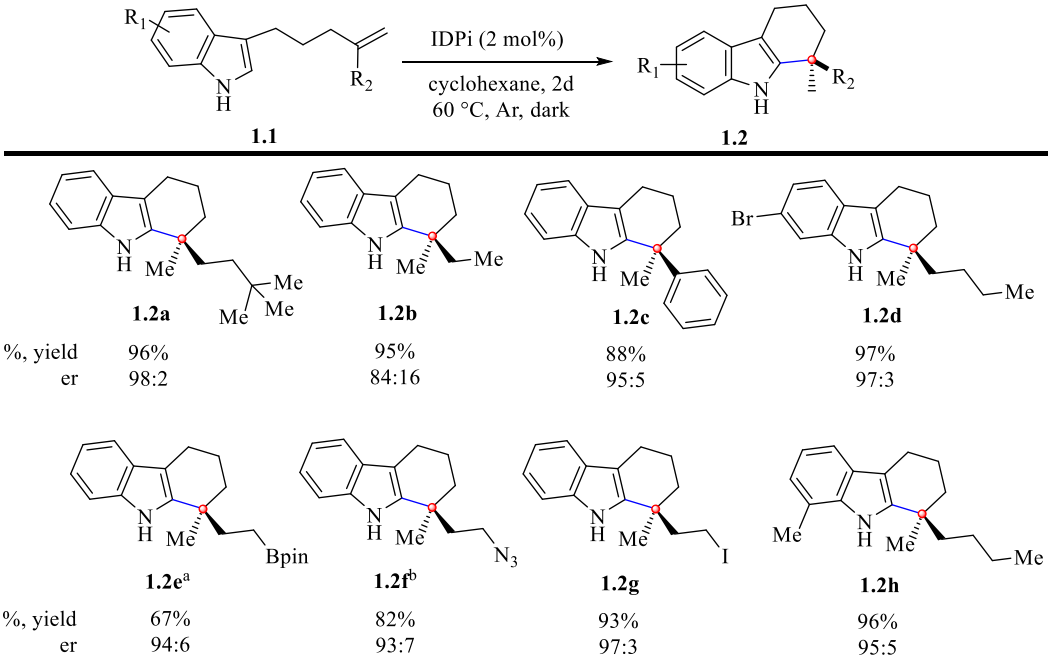
Figure 1.3. Approaches to access benzylic quaternary center bearing benzocarbocycles via intramolecular hydroarylation of unactivated alkenes

2. Synthesis of Polycyclic Nitrogen Heterocycles

Nitrogen heterocycles are important structural motifs which are widely present in biologically active natural or synthetic molecules, pharmaceuticals, agrochemicals, and functional materials.[11] More than half of the recent FDA approved drugs are constituted from nitrogen heterocycles.[12] Considering their importance, the synthesis of N-heterocyclic scaffolds has been a hot topic in synthetic chemistry.[13] Over the past decades, much efforts have been made in Brønsted acid catalyzed reactions along with other novel and efficient methods for their preparation.

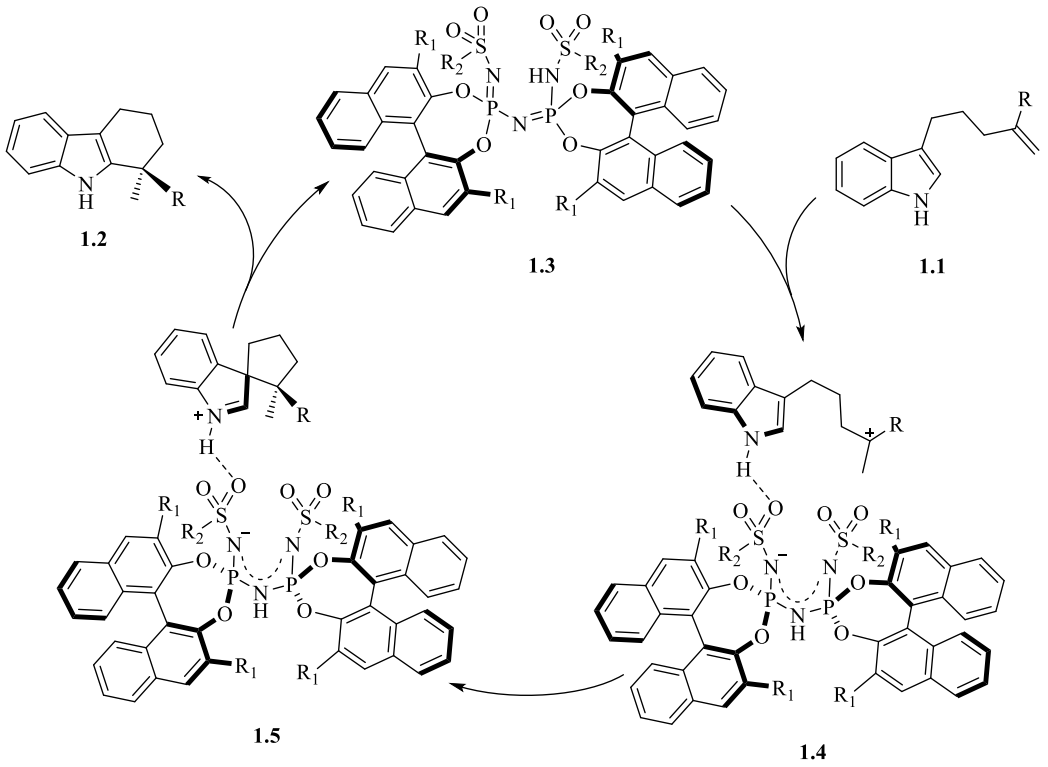
2.1. Synthesis of Indole Derivatives

Since the first report of chiral Brønsted acid catalyzed enantioselective Strecker reaction in 1998,[14] chiral Brønsted acids have been widely used in asymmetric synthesis.[9h-j] However, the activation of unactivated alkenes with Chiral Brønsted acid catalyst has remained elusive due to the low basicity of alkenes.[15]



Scheme 1.1 Chiral Brønsted acid catalyzed intramolecular hydroarylation of unactivated alkenes with indole.

Very recently, inspired by their previous work on catalytic asymmetric intramolecular hydroalkoxylation of unbiased olefins,[16a] List and co-workers have reported intramolecular hydroheteroarylation of unactivated indole alkenes in the presence of a Brønsted acidic chiral catalyst (Scheme 1.1).[16b] The electronic nature of the catalyst was found to be important for product formation. The result was obtained with most electron rich catalyst. 1,1-disubstituted aliphatic and aromatic alkenes **1.1** catalyzed with 2 mol% highly acidic and confined imidodiphosphorimidates (IDPi) Brønsted acid catalyst to a range of tetrahydrocarbazoles **1.2** with excellent yield and enantioselectivity, up to 96% and 98:2 er, at 60 °C in cyclohexane. The scope of the reaction was broad. A wide range of aliphatic/phenyl substituted olefins with different steric and electronic properties, as well as sensitive functional groups were tolerated. Further functional group manipulation of the bromo-, boronate- and azido-substituted tetrahydrocarbazoles did not affect the enantiopurity.



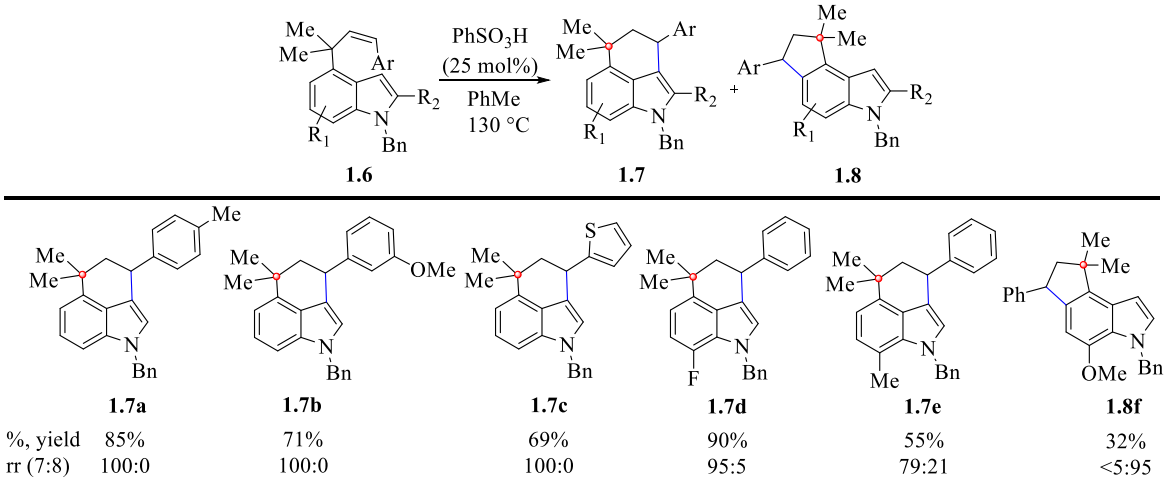
Scheme 1.2. Proposed mechanism for chiral Brønsted acid catalyzed hydroarylation

Several control experiments including hydroarylation of N-methylated indole, terminal alkene and two more alkenes in which the length of the alkyl chain between the indole and olefine is modulated, were performed to gain insight into the mechanism of this transformation. Based on the observations, the authors proposed the mechanism to involve the generation of tertiary carbocation intermediate **1.4** through olefin protonation with the chiral catalyst (Scheme 1.2). The IDPi catalyst **1.3**,[17] a BINOL-derived chiral phosphoric acid derivative, acts as a bifunctional catalyst in which the acidic proton of the catalyst activates the alkene double bond to form the carbocation, whereas the S=O interacts with

the NH of the indole ring. Due to the confined nature of the catalyst, the counterion orients olefin to intramolecular hydroarylation mainly on one face after protonation. Nucleophilic attack of the indole which complexed with the catalyst counterion through hydrogen bonding produces the spirocyclized intermediate **1.5.** Alkyl migration followed by deprotonation affords the tetrahydrocarbazole product and regenerates the catalyst.

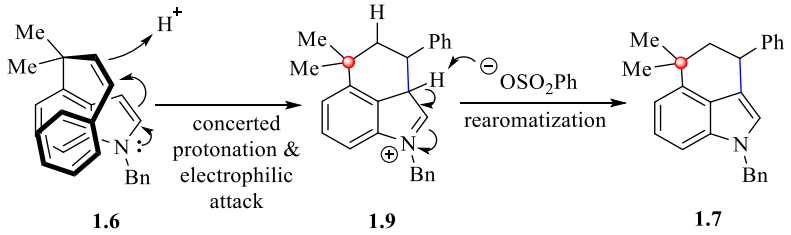
Intramolecular hydroarylation of alkenes with a pre-installed benzylic quaternary center is a direct way to form benzylic quaternary center containing benzocycloalkanes. In 2019, Stokes group reported the dispersion-controlled catalytic regioselective intramolecular hydroarylation of indoles in which the indole and styrene rings are linked by a benzylic geminal dialkyl carbon atom (Scheme 1.3).[18] The hydroarylation was found to depend on the isomeric identity of the starting alkene, while the regioselectivity was dictated by the dispersive interactions between styrene and indole. *Cis*-configured benzyl protected indole alkenes **1.6** were converted into **1.7** in moderate to excellent yield with 25 mol% of benzenesulfonic acid in toluene at 130 °C, whereas *trans* isomers tent to oligomerize under the identical condition.

A variety of 3-aryl-5,5-dimethyl-1,3,4,5-tetrahydrobenzo[*cd*]indoles **1.7** were obtained from **1.6** with different electron-donating and electron-withdrawing functional groups and thiophene heterocycle with good regioselectivity, ranging from 80:20 to >95:5. However, diminished regioselectivity was observed when electron-donating groups were installed at C7 of the indole core. In particular, regioselectivity was completely eroded when methoxy substituted substrate was used. In this case, **1.8f** was mainly obtained. The hydroarylation was also evaluated on benzothiophene and benzofuran analogue. Under identical conditions, c*is* and *trans* benzothiophene cyclized with similar regioselectivity with indoles, whereas alkene isomerization, *cis* to *trans*, along with small amount of C-5 cyclized product was observed with benzofuran analogue.



Scheme 1.3. Dispersion controlled intramolecular hydroindolation of *cis*-methindolylstyrenes

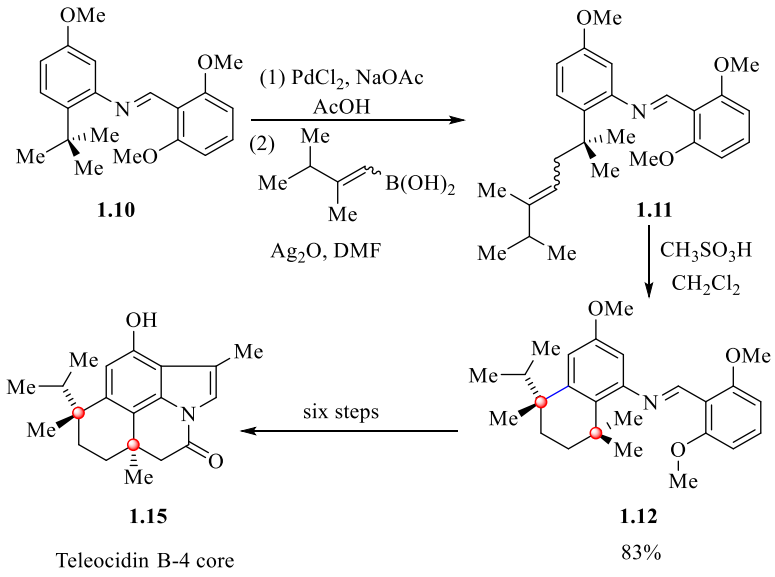
To gain insight into the reaction mechanism, DFT calculations were performed on the two rotamers of 7-substituted *cis* indole substrates. The enthalpic calculations indicated that electronic dispersion adds an additional 6 kcal/mol of substrate stabilization. According to the experimental and computational investigations, the authors proposed that the hydroindolation happened through a concerted protonation and carbon-carbon bond formation (Scheme 1.4). Geminal dimethyl group-imposed stabilizing stacking of the *cis*-isomers *via* the dispersive interactions between indole and styrene π systems facilitates concerted protonation and electrophilic attack to afford **1.9.** In next step, **1.9** is transformed into **1.7** after regaining aromaticity. The oligomerization of *trans* alkenes under identical condition and the resistance of *cis*-configured alkene to isomerization under acidic conditions at 80 °C further assist the proposed mechanism.



Scheme 1.4. Proposed mechanism for concerted hydroindolation

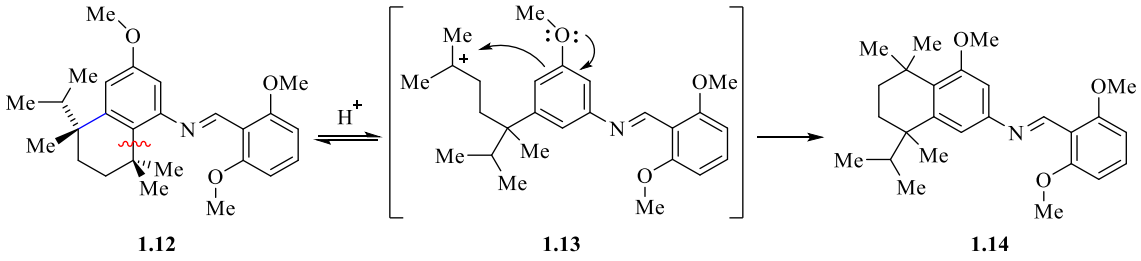
The tetrahydro[*cd*]indole is the core structure of the important natural products including ambiguine and hapalindole family. Various methods to access tetrahydrobenzo[*cd*]indoles have been reported. The recent intramolecular methods include the palladium catalyzed multi-step synthesis and stoichiometric TMS-OTf catalyzed cyclization in which methoxy group was introduced at C7 of the indole ring to get selective ring formation by increasing the nucleophilicity of C4.[19] The above synthetic protocol is advantageous not only because it has larger substrate scope, but also the transformation was achieved in fewer reaction steps with catalytic Brønsted acid. In this work, the tetrahydro[*cd*]indole derivatives were obtained in four steps from commercially available 4-bromoindole via enolate cross-coupling, N-H protection, Wittig olefination and acid catalyzed cyclization reactions. Benzyl cleavage was easily achieved with potassium *tert*-butoxide in DMSO under oxygen in 91% yield.

The construction of another polycyclic indole derivative which is the core fragment of the well-known naturally occurring tumor promotor teleocidin B4, was reported by Sames group (Scheme 1.5).[20] In this work, the key intermediate **1.12** with two benzylic quaternary center was constructed via an acid-promoted intramolecular Friedel–Crafts type hydroarylation reaction. The alkene was prepared from **1.10** (Schiff base) through $PdCl_2$ catalyzed selective sp^3 C-H bond activation and subsequent trans metalation with vinyl boronic acid (*cis*:*trans*=3:1).



Scheme 1.5. Synthesis of Teleocidin B-4 core

When the 3:1 mixture of *cis* and *trans* alkenes **1.11** was exposed to the stoichiometric amount of $MeSO_3H$ (50 equivalent) in CH_2Cl_2, the tetrahydronaphthalene **1.12** was produced in 83% as a racemic mixture. It was proposed that the presence of the methoxy group meta to the amine/Schiff base facilitated the Friedel-Crafts reaction and contributed to the formation of the racemic mixture.[21] The teleocidin B4 core **1.15** was obtained further functionalization of **1.12** in six steps. The regioisomer **1.14** was observed when **1.12** was exposed to the strong acid for prolonged time (Scheme 1.6).



Scheme 1.6. Acid promoted isomerization

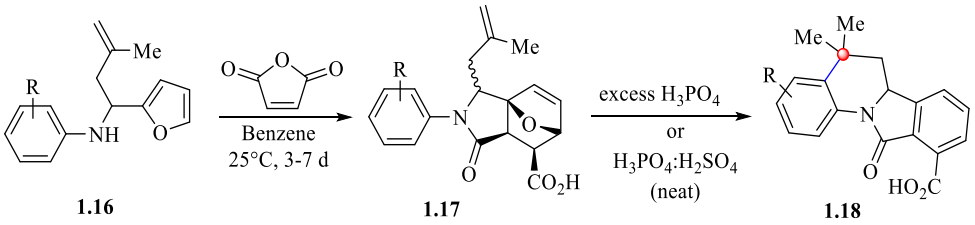
2.2. Synthesis of Quinoline

The phosphoric acid promoted formation of a polycyclic nitrogen heterocycle, isoindolo[2,1-a]quinolines which has important biological properties, was reported by Zubkov group (Table 1.1).[22] The starting alkenes **1.17** were derived from furfurylamine and maleic anhydride in benzene via N-acelation, intramolecular Diels-Alder reaction sequence within 3-7 days in 83-96% yield. The isoindolo[2,1-a]quinoline products **1.18**

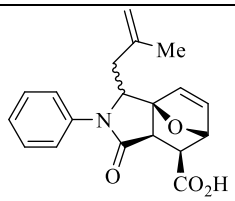
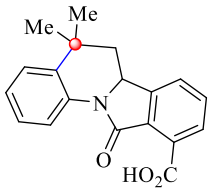
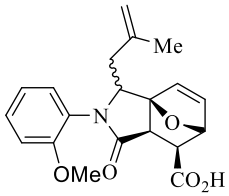
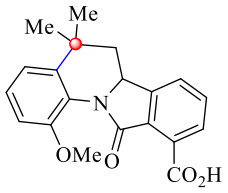
were obtained through the cyclic ether opening/aromatization of the oxabicyclo[2.2.1]-heptene fragment[23] and subsequent intramolecular electrophilic cyclization of the terminal alkene in excess phosphoric acid at 65 °C. Seven examples were reported in range of yields from 31% to 68%. For selected examples, see Table 1.1, entry 1-3.

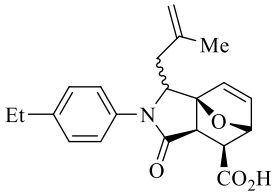
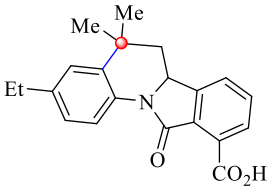
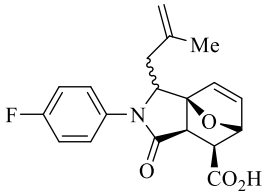
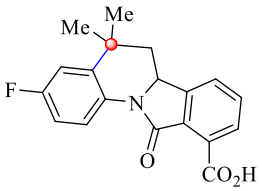
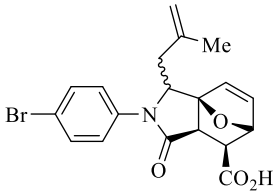
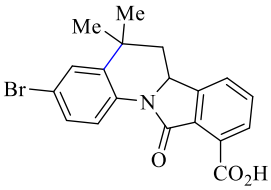
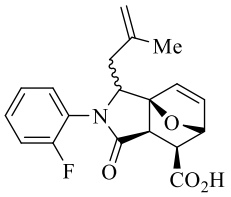
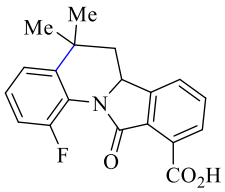
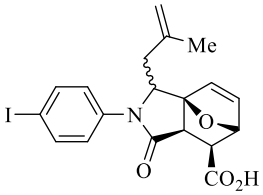
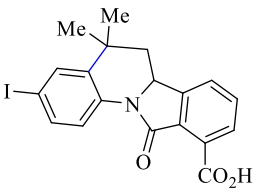
In 2005, this protocol was extended to the formation of isoindolo[2,1-a]quinolines possessing halogen substituents in the quinoline moiety (Table 1.1, entry 4-7).[24] The electron-withdrawing halogen substituents did not affect product formation. Isoindolo[2,1-a]quinoline **1.18** were obtained in 21-92% yields in neat 3:1 H_3PO_4:H_2SO_4 from the substrates in which halogens are positioned *ortho* or *para* to the nitrogen. *Para*-substituents afforded better yield than *ortho* substituents. Compared with the substrates in their previous work of 2003, in this work, the intramolecular ring formation required higher temperatures, 110-155 °C, to form isoindolo[2,1-a]quinolines.

Table 1.1. Synthesis of oxoisoindolo[2,1-a]quinoline derivatives.



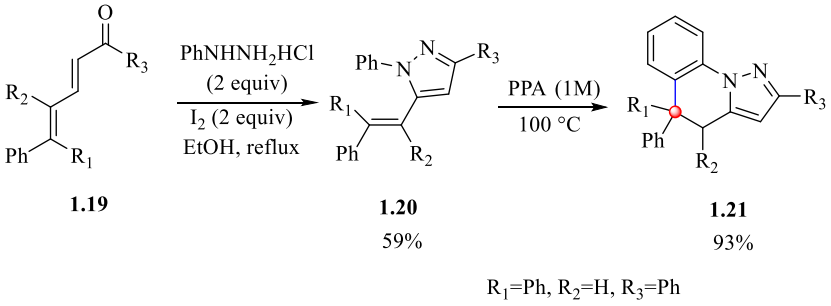
1.16 **1.17** **1.18**

Entry	Substrate	Product	Yield (%)
1	 **1.17a**	 **1.18a**	68
2	 **1.17b**	 **1.18b**	40

3	 **1.17c**	 **1.18c**	61
4	 **1.17d**	 **1.18d**	92
5	 **1.17e**	 **1.18e**	62
6	 **1.17f**	 **1.18f**	85
7	 **1.17g**	 **1.18g**	83

During the preparation of pyrazolo[1,5-*a*]quinoline derivatives **1.21**, the intramolecular Friedel-Crafts reaction of pyrazole alkenes was carried out in polyphosphoric acid (PPA).[25] The 5-styrylpyrazoles **1.20** were derived from phenylhydrazine hydrochloride and corresponding conjugated dienones in range of yields

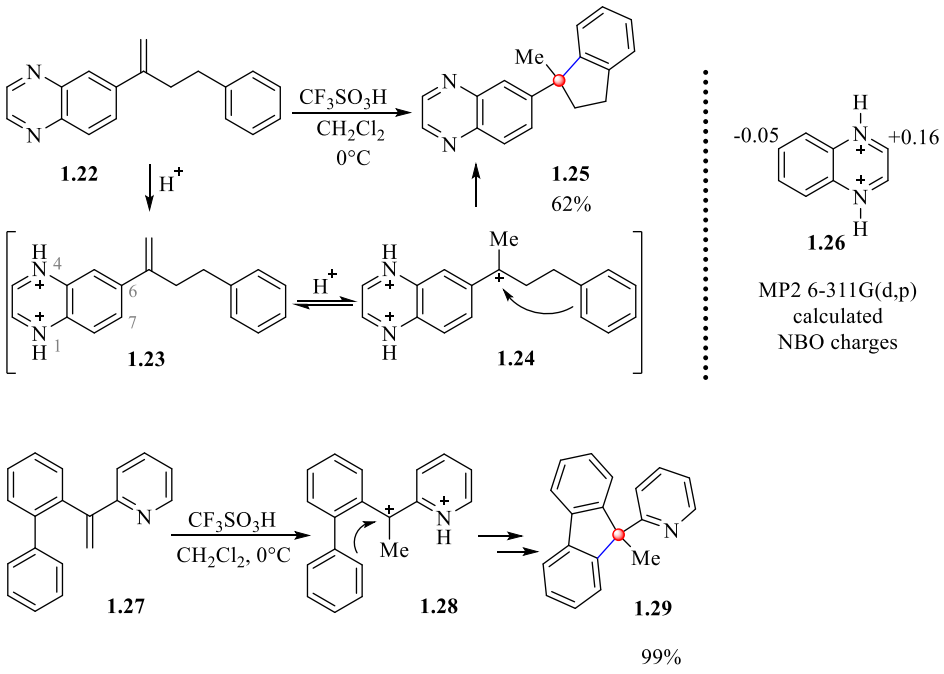
40-71%. Polyphosphoric acid and sulfuric acid (10 equivalent) were able to transform 5-styrylpyrazoles to dihydropyrazolo[1,5-*a*]quinolines. However, the hydroarylation was carried out in neat polyphosphoric acid (1M) due to the lower yield, 62%, and side product formation with H_2SO_4. The reaction scope included 11 examples (87-93% yields) in which only one example which is shown in Scheme 1.7 has benzylic quaternary center.



Scheme 1.7. Synthesis of pyrazolo[1,5-a]quinolines.

2.3. Synthesis of other N-Heterocycles

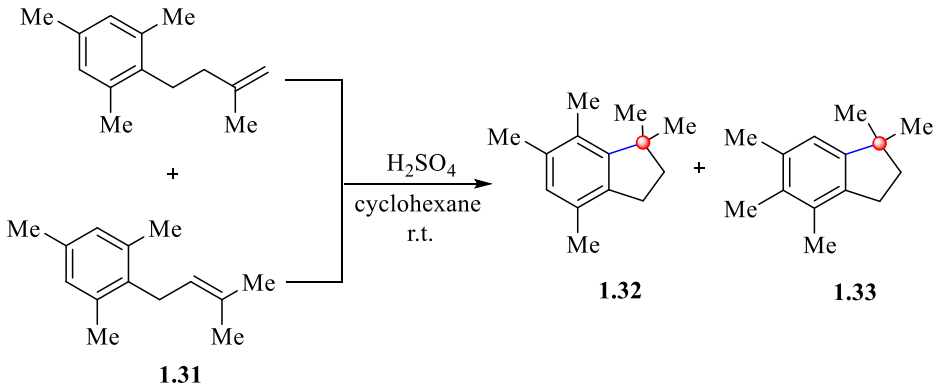
Superacids, acids which are stronger than 100% sulfuric acid, can generate different types of superelectrophilic intermediates which include di-, tri, tetra-cationic species with enhanced reactivity than that of their monocationic electrophiles.[26] Klumpp and co-workers used superacidic TfOH to produce superelectrophilic di- and tricationic intermediates during the cyclization of alkenyl-substituted N-heterocycles (Scheme 1.8).[27] 5-membered rings with benzylic quaternary center were obtained from pyridine **1.22** and 5-quinoxaline-based olefins **1.27** with stoichiometric triflic acid in 99% and 62% yields respectively in dichloromethane, whereas pyrazine, 2-pyrimidine, and 2-quinoxaline analogues provided tetralin derivatives without benzylic quaternary center under identical condition. The authors asserted that the product formation is determined by the charge distribution in the fully protonated heterocyclic system. According to the NBO calculations, in **1.23**, the charge separation and high electron density at C6 allows the protonation of alkene double bond to form the benzylic carbocation as in **1.24** and leads to the 5-membered ring formation. This method demonstrated the first example of vinyl substituted N-heterocycles with weak aryl nucleophiles.



Scheme 1.8. Intramolecular cyclization of vinyl-substituted N-heterocycles.

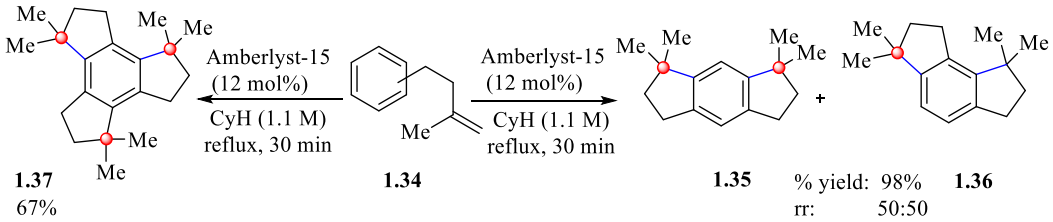
3. Synthesis of Indane

Indanes are important carbocyclic scaffolds in medicine and material science.[28] One of the earliest examples of intramolecular Brønsted acid catalyzed indane formation was the hydroarylation of polysubstituted butenylbenzenes with stoichiometric sulfuric acid (Scheme 1.9).[29] The isomers **1.31**, 1,3,5-trimethyl-2-(3-methylbut-3-en-1-yl)benzene and 1,3,5-trimethyl-2-(3-methylbut-2-en-1yl)benzene were prepared from the intermolecular hydroarylation of mesitylene with isoprene. The indane products **1.32** and **1.33** were obtained in 62% yield when the mixture of isomers **1.31** (50:1) was treated with 97% sulfuric acid in cyclohexane at ambient temperature. Catalyst concentration had large effect on reaction outcome. With 93% sulfuric acid, product yield was increased by 16%, whereas the reduced yield, 57%, was reported with 85% sulfuric acid. In 75% sulfuric acid, isomerization of internal alkene to terminal alkene was observed. The authors proposed that 1,2-methyl shift resulted in the formation of product **1.32**, while product **1.33** was the result of Jacobsen rearrangement.[30]



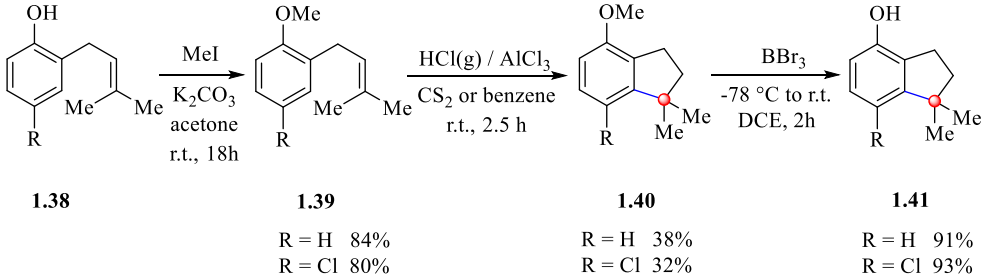
Scheme 1.9. Synthesis of polysubstituted indane nucleus.

In 1977, the same group reported the synthesis of tetramethylhydrindacene and hexamethyltrindan (Scheme 1.10).[31] Amberlyst-15, a sulfonic acid resin, was used as an effective catalyst in cyclohexane. Intramolecular hydroarylation of 1,3-bis(3-methyl-3-butenyl)benzene afforded **1.35** and **1.36** as a 1:1 mixture, whereas **1.37** was obtained from 1,3,5-tris(3-methyl-3-butenyl)benzene.



Scheme 1.10. Synthesis of polysubstituted indanes

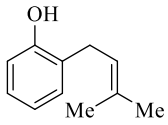
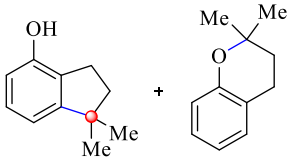
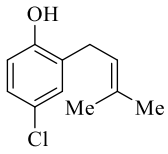
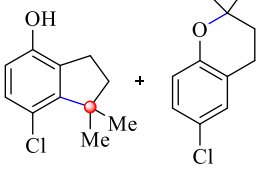
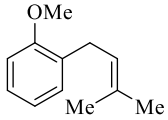
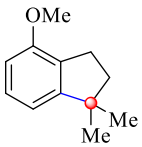
In 1981, Okogun and Fatope realized the intramolecular hydroarylation of ortho-prenylated anisole to 1,1-dimethyl-4-methoxyindane.[32] The mixture of hydrogen chloride and $AlCl_3$ initiated the transformation in 60% yield in Benzene. Later, Xia's group used this methodology during their synthesis of 1,1-dimethyl-4-indanol **1.41** which is a possible precursor of anti-HIV agents (Scheme 1.11).[33]

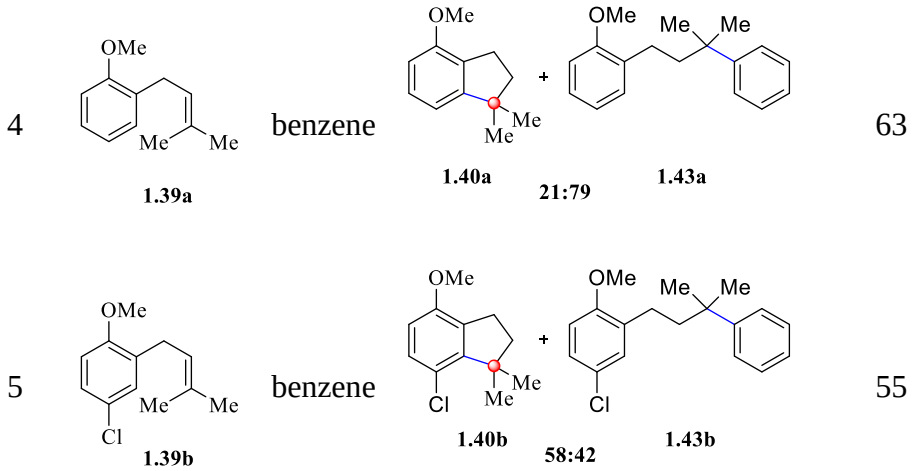


Scheme 1.11. Synthesis of 1,1-dimethyl-4-indanol.

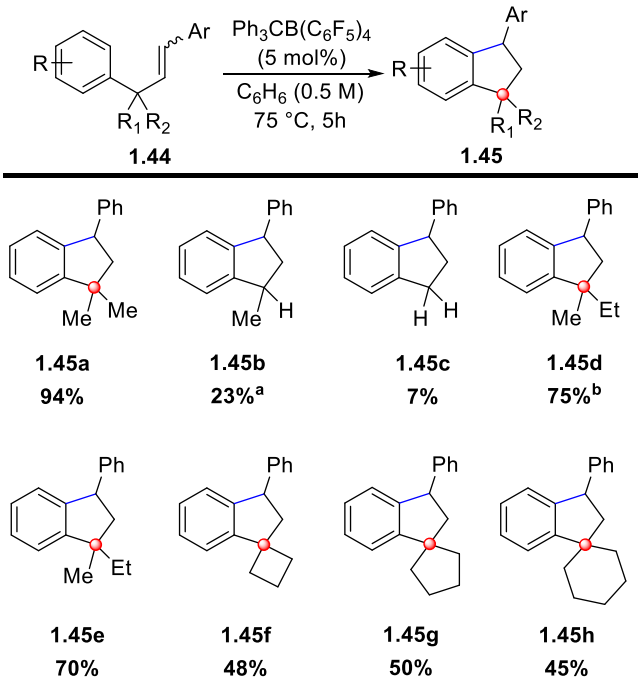
With unprotected phenol substrate **1.38**, alkoxylated product was formed as the major isomer in 73% along with 13% indane product (entry 1, Table 1.2). To improve the chemoselectivity of the hydroarylation in the cyclization step, the phenol hydroxyl group was then protected by methyl group. It was found that solvent is crucial to avoid the intermolecular reaction in addition to the low concertation and quick workup after the reaction. When treated with stoichiometric acid, the intramolecular hydroarylation of **1.39a** afforded the 1,1-dimethyl-4-methoxyindane **1.40a** with the best yield of the study in carbon disulfide as the only product (entry 3, Table 1.2). However, in benzene, solvated product **1.43a** was obtained as the major isomer in 79:21 regioisomeric ratio (solvated product : indane) (entry 4, Table 1.2). The hydroarylation of chlorine substituted substrate afforded the indane product **1.40b** in 32% with 58:42 regioisomeric ratio (indane : solvated product) in benzene (entry 5, Table 1.2). No further substrate scope was reported. The target compound **1.41** was then obtained by subsequent demethylation of **1.40** with BBr_3 in DCE within 2 hours. The authors didn't investigate the hydroarylation with single catalyst, either HCl or $AlCl_3$.

Table 1.2. Reaction scope of 1,1-dimethyl-4-indanol synthesis

entry	substrate	solvent	products	Combined yield (%)
1	 **1.38a**	CyH	 **1.41a** + **1.42a** **17:83**	88
2	 **1.38b**	CyH	 **1.41b** + **1.42b** **24:76**	51
3	 **1.39a**	CS_2	 **1.40a**	38

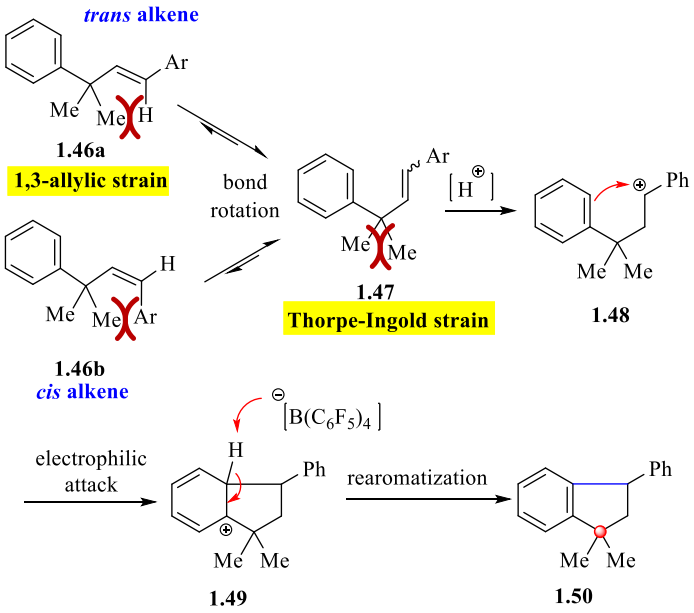


Geminal-dialkyl group has important applications in organic synthesis and medicine. It is reported that, replacing the hydrogen atoms with geminal dialkyl group could improve the biological activity and metabolic stability of the target drug molecule.[2a] In organic synthesis, geminal dialkyl effect has been using to overcome energetic barriers during the cyclization reactions.[34] In 2017, Stokes group reported geminal dialkyl group assisted hydroarylation of β-benzylstyrenes to benzylic quaternary center containing indanes (Scheme 1.12).[35] The β-(α,α-dimethylbenzyl)styrene **1.44** was transformed into the indane **1.45** with a range of different catalysts including *p*-toluenesulfonic acid monohydrate, sulfuric acid, triflic acid, tritylium tetrakis(pentafluorophenyl)borate (TPFPB), trimethylsilyltriflate (TMSOTf) and $Pd(OAc)_2$. The best yields were obtained with catalytic triflic acid and tritylium TPFPB. Due to the less toxicity and convenience, 5mol% $Ph_3CB(C_6F_5)_4$ was used as the optimum catalyst in benzene at 75 °C, except from a few cases where the reaction was carried out with triflic acid. In tritylium tetrakis(pentafluorophenyl)borate catalyzed reaction, the control experiment indicated that the reaction is catalyzed by *in-situ* generated Brønsted acid H-TPFPB. The reaction scope was broad. A wide range of indanes functionalized with electron-donating and electron-withdrawing functional groups were obtained. The substituents at the benzylic position found to be crucial in product formation. With geminal dimethyl substituted alkene the indane product **1.45a** was obtained with the highest yield. Diminished yields were observed when the geminal dimethyl group was replaced with mono methyl, mono/di-ethyl and cycloalkyl groups. In the absence of the geminal dialkyl group, only 7% of the indane product **1.45C** was observed. The scope of this hydroarylation has also evaluated on benzothiophene and naphthalene analogues of β-(α,α-dimethylbenzyl)styrene and the corresponding indane products were formed at the more sterically hindered position in 63% and 91% yield respectively. The authors also investigated the regioselectivity of the reaction. It was revealed that the product formation was affected by the electronic and steric properties of the nucleophilic arene ring.



a: diastereomeric ratio *cis*:*trans* is 61:39; b: diastereomeric ratio *cis*:*trans* is 55:45

Scheme 1.12. The influence of alkyl substitution at the benzylic position of β-benzylstyrenes



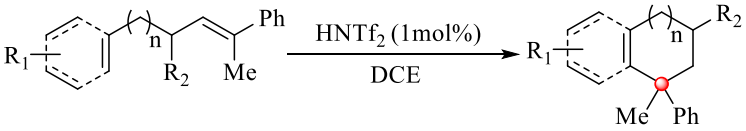
Scheme 1.13. Proposed mechanism for geminal dialkyl group assisted hydroarylation of β-benzylstyrenes.

As it is obvious from the reaction results, the geminal dialkyl group was crucial in this hydroarylation. The authors asserted that the 1,3-allylic strain and Thorpe–Ingold strain, both ultimately the result of the presence of the benzylic quaternary dialkyl group, induced conformational activation of the substrate **1.47** (Scheme 1.13). As a result, the proximity of the two reactive sites in **1.48** enabled the electrophilic aromatic attack to construct the synthetically challenging benzocyclopentane ring **1.50** after rearomatization of **1.49**.

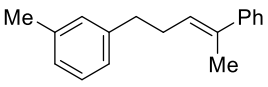
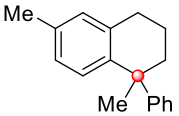
4. Synthesis of Tetralin

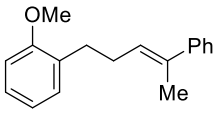
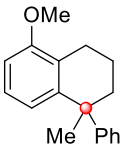
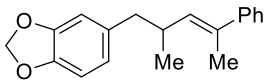
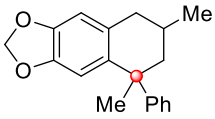
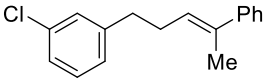
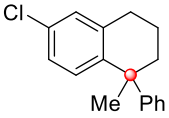
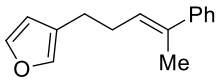
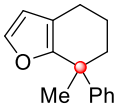
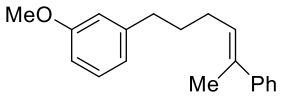
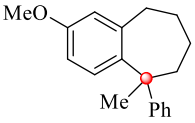
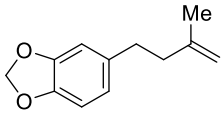
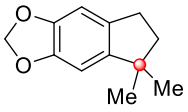
Tetralin motifs attract continuing interest from organic chemists due to their presence in many biologically active molecules, natural products, and medicine.[36] A few examples of Brønsted acid catalyzed intramolecular alkene hydroarylation reactions leading to benzylic quaternary center containing tetralin moieties were reported by West and Chein separately.[10, 37] In 2012, West and co-workers reported that trifluoromethanesulfonimide catalyzed the hydroarylation of unactivated alkenes **1.51** into tetralin, indane and 7-membered carbocycles under reflux or microwave heating conditions (Table 1.3).[10] While as much as 0.5-1mol% $HNTf_2$ was effective to catalyze this reaction, other Brønsted acids including *p*-toluenesulfonic acid monohydrate, methanesulfonic acid and camphorsulfonic acid (CSA), were found inefficient, with the exception of triflic acid in 38% yield. The carbocycles were obtained in good to excellent yields, 56-94%, from the electron-rich and electron-poor arenes as well as furan analogue. Different substrates required different catalyst loading, 0.5 or 1 mol%, reaction time or reflux/microwave heating to complete the reaction. The products were formed at the sterically more accessible position and product identity relayed upon the length of carbon tethers in alkenes. Tetralin derivatives were obtained from pentenyl arenes, whereas extension of carbon tether afforded benzocycloheptene **1.52f**. The hydroarylation of the 2-methyl-4-(3,4-methylenedioxyphenyl)-1-butene afforded indane **1.52g**.

Table 1.3. Super acid catalyzed intramolecular hydroarylation of unactivated alkenes



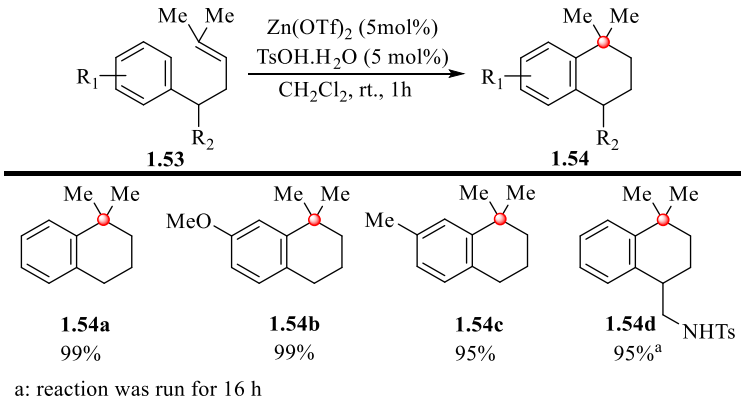
1.51 **1.52**

Entry	Substrate	Condition	Time	Yield (%)[a]	Product
1[b,c]	 **1.51a**	reflux	2 h	92	 **1.52a**

2	 **1.51b**	microwave heating (180 °C)	20 min	80	 **1.52b**
3[d]	 **1.51c**	microwave heating (180 °C)	15 min	90	 **1.52c**
4	 **1.51d**	microwave heating (180 °C)	2 h	87	 **1.52d**
5	 **1.51e**	microwave heating (180 °C)	5 min	56	 **1.52e**
6[c]	 **1.51f**	reflux	20 h	60	 **1.52f**
7	 **1.51g**	microwave heating (180 °C)	15 min	74	 **1.52g**

[a] Isolated yield. [b] 0.5 mol % catalyst is used. [c] Solvent is DCM. [d] Diastereomeric ratio is 2.8:1.

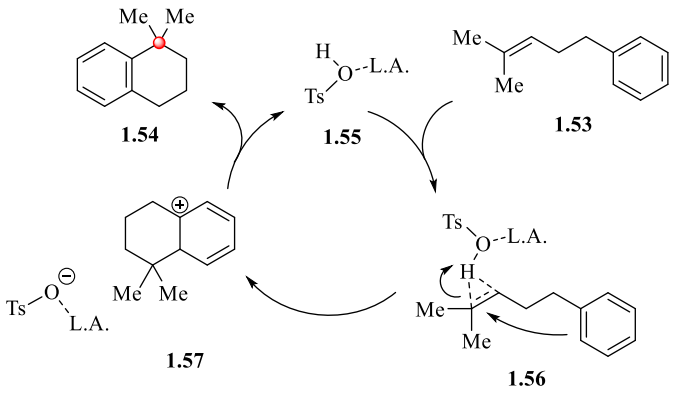
Combined acids, which include Brønsted acid assisted Lewis acid (BLA), Lewis acid assisted Lewis acid (LLA), Lewis acid assisted Brønsted acid (LBA), and Brønsted acid assisted Brønsted acid (BBA), have been widely used in organic synthesis due to their high catalytic activity.[9d] Chein and his group exploited the intramolecular cyclization of unactivated alkenes in Lewis acid-assisted Brønsted acid (LBA) system, [ZnI_2/$Zn(OTf)_2$ and *p*-TsOH].[37a]



Scheme 1.14 LBA catalyzed tetralin synthesis.

Good functional group tolerance was observed: tetralin derivatives, polycycles, five- and six-membered saturated lactones, piperidine, pyrrolidine, tetrahydrofuran, pyran derivatives and chroman nucleus with benzylic quaternary centers were formed smoothly. The intramolecular hydroarylation of the corresponding (4-methylpent-3-en-1-yl)benzene derivatives **1.53** with the combined acid, 5mol% $Zn(OTf)_2$ and 5mol% $TsOH.H_2O$, afforded benzylic quaternary center bearing tetralin derivatives **1.54** with excellent yield, 95-99% at ambient temperature in dichloromethane (Scheme 1.14).

The direct cross-comparison of this work with previously published reports[38] indicated that the acidity of this combined acid is stronger than that of *para*-toluene sulfonic acid. Based on experimental results and NMR, MS, ESI-MS spectral analysis, the authors proposed the reaction mechanism to involve the formation of the LBA system by the coordination of the Lewis acid with the heteroatom of the $TsOH.H_2O$. This coordination could increase the catalytic activity of Brønsted acid (Scheme 1.15). The nucleophilic attack to the π-hydrogen complex generates the intermediate **1.57**, then the following deprotonation affords the final product and regenerates the catalyst.



Scheme 1.15. Proposed mechanism for LBA catalyzed tetralin synthesis .

Conclusion

A few successful methodologies have been developed to access various types of benzylic quaternary center containing compounds with Brønsted acid catalyst. Despite few in number, those methods have demonstrated the effectiveness of intramolecular hydroarylation reactions for the construction of synthetically challenging molecules and the suitability of Brønsted acids to activate electronically inert, unbiased alkenes. Moreover, the asymmetric synthesis was also achieved with chiral Brønsted acid catalyst. Despite such progress, the development of catalytic, more efficient, and eco-friendly synthetic methodologies is still very important. In the next future, much efforts will be necessary to improve the selectivity of the synthesis. Although, chemoselectivity of the hydroarylation is better controlled, the investigation on regioselectivity is not fully developed yet. Moreover, from our knowledge, only one example of asymmetric process has been reported, while the study on diasteroselectivity is remain untouched despite the biological and pharmacological importance of benzylic quaternary center containing compounds. In addition, while many methods afford five- and six-membered rings, the synthesis of seven-membered rings remains rare.

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CHAPTER 2

Acid-Catalyzed Dearomative Spirocyclization of Benzothiophenyl Analogues of β-(α′,α′-Dimethyl)-4′-methindolylstyrenes Affords Vicinal Quaternary Centers

1. Introduction and Background

Spirocycles, bicyclic organic compounds in which the quaternary carbon is shared by the two fused rings, are well-presented in biologically active natural products and pharmaceuticals (Figure 2.1).[1] In addition, they have been used as a ligand and catalyst in asymmetric synthesis (Figure 2.2).[2] Taking advantage of their inherent rigidity and structural novelty, spiro molecules have demonstrated improved pharmaceutical properties compared to analogues cyclic or flat aromatic molecules.[3] In this regard, they are considering as privileged structural motifs in drug discovery.[4]

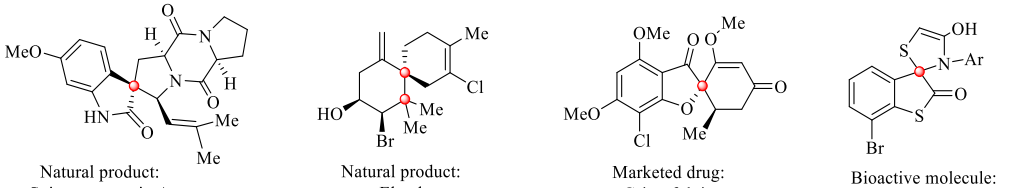


Figure 2.1. Selected natural products, marketed drugs and bioactive molecules featuring spirocycles

Significant efforts have been made to develop effective synthetic methods to prepare spirocyclic compounds, with dearomatization approaches among the most popular.[5] Over the years, various dearomatization approaches to construct different spiro molecules are reported.[6] However, Brønsted acid catalyzed intramolecular approaches are less encountered.[7] In particular, dearomative formation of spirocycles incorporating vicinal all-carbon quaternary centers with Brønsted acid catalyst has been rarely explored.

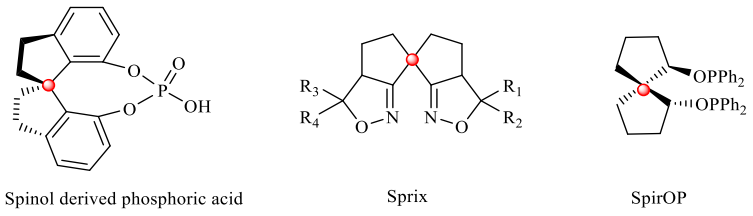
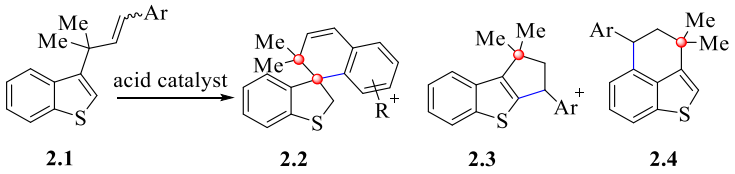


Figure 2.2. Selected chiral catalyst and ligands containing spirocycles

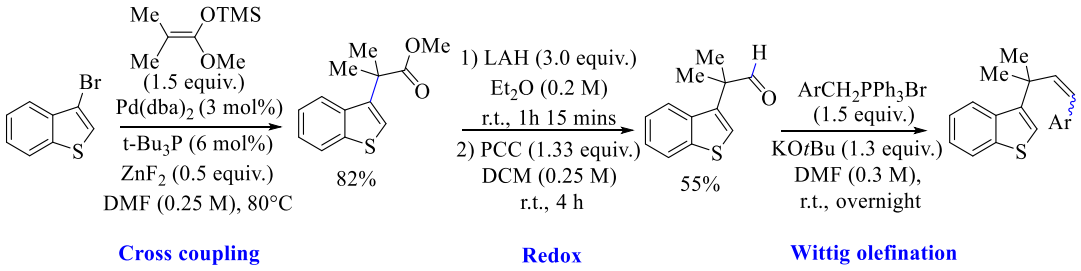
One research interest of Stokes Group was developing new catalytic reactions to functionalize unactivated congested alkenes in which the styrene moiety is attached to a benzylic geminal dialkyl group. The acid catalyzed intramolecular hydroarylation reactions of those alkenes provides benzocycloalkanes with benzylic all carbon quaternary center. See chapter one for the previously published group papers,[8] as well as the importance of benzylic quaternary center containing alkylarenes and geminal dialkyl group in synthesis. During our continuing interest in this type of reactions, we envisioned that the corresponding benzo[*b*]thiophene analogue of β-benzylstyrene in which C3-position of the heteroaromatic ring is linked to the β-position of styrene with a geminal dialkyl carbon atom could undergo intramolecular hydroarylation under acidic condition. We assumed that three regioisomers, **2.2**, **2.3** and **2.4** could be formed via dearomative spirocyclization or general Friedel-Crafts type electrophilic aromatic substitution of **2.1** with catalytic Brønsted acid (Scheme 2.1). The spirocycle with vicinal quaternary centers and the dearomatization under metal-free condition warranted further investigation. We believed that the regioselectivity of the hydroarylation could be controlled by changing the reaction conditions and/or the substrates.



Scheme 2.1. Envisioned hydroarylation of C3 substituted benzothiophene alkenes

2. Results and Discussion

The alkene substrates were prepared by sequential enolate cross-coupling, redox, and Wittig olefination reactions as it is shown in Scheme 2.2. The general procedure for each step can be found in experimental section.

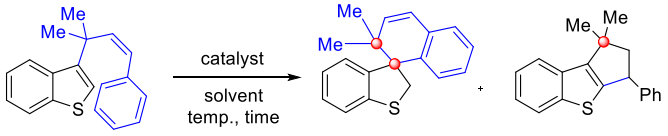


Scheme 2.2. Reaction sequence for preparing alkene substrates

After purifying the alkene with flash column chromatography, we began our investigation using *cis* alkene **2.1a** as a model substrate and evaluated the effect of different parameters on the intramolecular hydroarylation (Table 2.1). Initially, we found that no reaction happened with 25 mol% of benzenesulfonic acid at room temperature in dichloroethane (entry 1). Under otherwise identical conditions, 100 mol% benzenesulfonic

acid provided the two regioisomers 2a:3a in 93:07 ratio, but substrate **2.1a** wasn't consumed efficiently (entry 2). This indicated the necessity of stronger acid to activate the alkene double bond. The increase of temperature resulted in increasing of conversion and yields in toluene, dichloroethane, and dichloromethane; However, the regioselectivity of the reactions decreased along with the temperature increase (entries 3-5). No conversion was observed when the tritylium tetrakis(pentafluorophenyl)borate used as a catalyst (entry 6). Then we evaluated a strong Brønsted acid, trifluoromethanesulfonic acid, for this hydroarylation (entries 7-12). The results revealed that *cis*-configured analogues could be cyclized with good regioselectivity favoring **2.2a** by using triflic acid as catalyst at room temperature. Increasing of concentration and reaction time increased the conversion and yield. The best yield and regioselectivity of the spirocyclic product **2.2a** were obtained after stirring for 12 h at 25 °C in the presence of 5 mol % of triflic acid in dichloromethane (entry 10). However, *trans*-configured alkene did not produce the spirocycle, instead **2.3a** was formed as the major product (entry 11).

Table 2.1. Optimization of reaction conditions[a]



2.1a **2.2a** **2.3a**

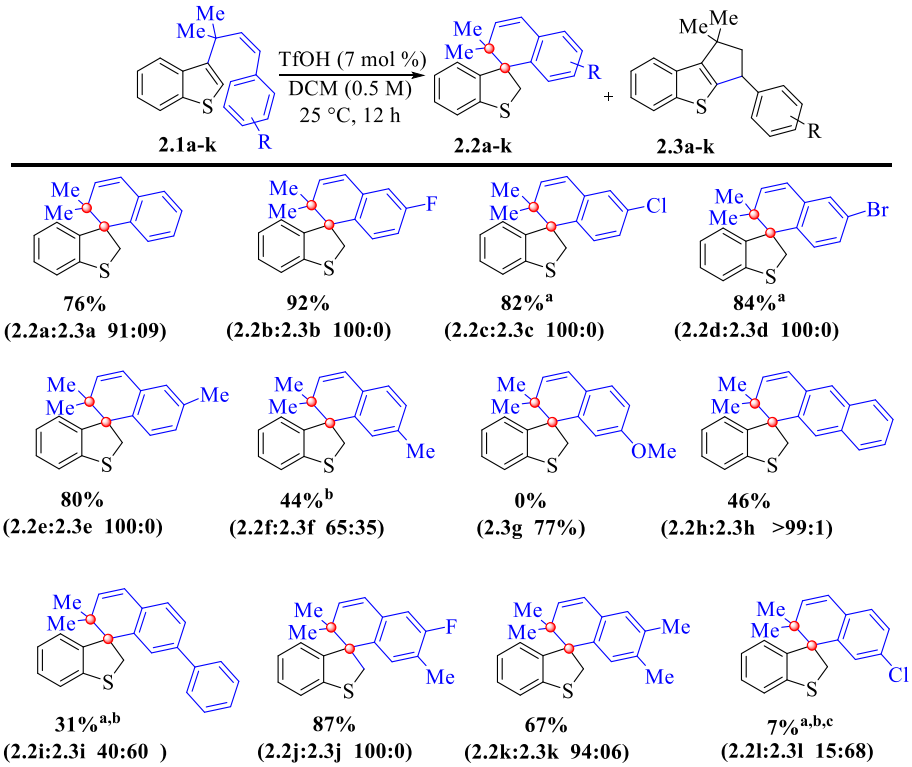
No.	Catalyst	Loading (mol%)	Solvent	Concent. (M)	Temp. (°C)	Time (h)	Conv. (%)[b]	Yield (%)[b]	rr[b] (2a:3a)
1	$PhSO_3H$	25	DCE	0.1	rt	21	-	-	-
2	$PhSO_3H$	100	DCE	0.1	rt	21	46	28	93:07
3	$PhSO_3H$	100	DCE	0.1	50	21	95	59	78:22
4	$PhSO_3H$	100	PhMe	0.1	50	21	50	45	56:44
5	$PhSO_3H$	100	DCM	0.1	50	21	97	61	79:21
6	$Ph_3CB(C_6F_5)_4$	30	DCM	0.1	rt	21	-	-	-
7	TfOH	10	DCM	0.1	rt	6	87	70	91:09
8	TfOH	10	DCM	0.5	rt	6	95	77	92:08
9	TfOH	5	DCM	0.5	rt	6	93	80	93:07
10	TfOH	5	DCM	0.5	rt	12	>99	83	93:07
11[c]	TfOH	5	PhMe	0.1	rt	6	29	17	00:100
12	TfOH	2	DCM	0.5	rt	12	90	79	92:08

a: reactions were conducted on 0.3 mmol cis alkene. 2-methoxynaphthalen was used as internal standard. Yield refers to the combined NMR yield of the regioisomers
b: determined by 1H NMR of crude reaction mixture
c: trans alkene

With the optimized reaction conditions in hand, we next investigated the scope of this dearomative spirocyclization (Table 2.2). In general, triflic acid catalyst fully converted substrates containing variety of functional groups to the dearomative spirocyclized isomer in good or excellent yield. *Meta*-substituents on the styrene moiety, including F, Cl, Br and Me (**2.1b-2.1e**), selectively afforded dearomative spirocyclized single isomers (**2.2b-2.2e**) in high yield at the more nucleophilic and less sterically hindered position. The *m*-F

substrate afforded the best yield and regioselectivity that we observed in this study. This observation consistent with the result of previously published paper.[9]

Table 2.2. Scope of the dearomative spirocyclization

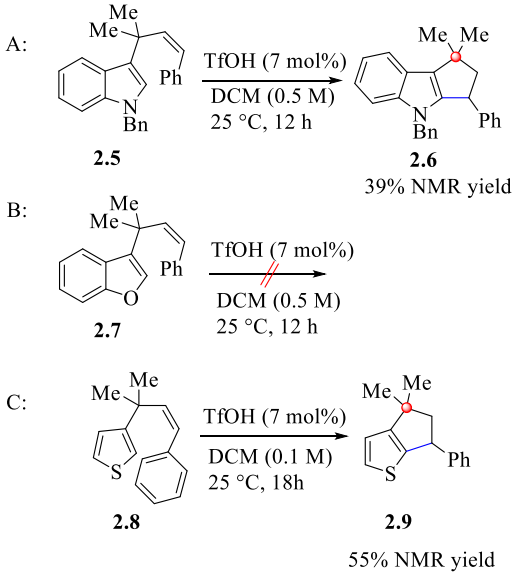


Reactions employed pure cis-alkenyl starting materials and were conducted on a 0.3 mmol scale in a closed vial. The substrates were fully consumed unless otherwise noted. Yields refer to the isolated indicated major product unless otherwise noted. Regioisomeric ratio (2.2:2.3 indicated in parentheses) were determined by ^{1}H NMR analysis of the crude reaction using 2-methoxynaphthalen as an internal standard. [a]conversion is >97 %. [b]NMR yield. [c]C4 cyclized isomer was also observed.

p-Methyl substrate **2.1f** produced the 65:35 mixture of two regioisomers, **2.2f:2.3f**, in 68% overall yield, whereas the *p*-methoxy substrate selectively formed the cyclopentane isomer 3g in 77% yield. Beyond substituted benzenes, 2-naphthyl analogue **2.1h** gave 46% yield of **2.2h** at the less sterically hindered position and 4-biphenyl analogue **2.1i** gave 31% yield of **2.2i**, respectively. We next evaluated the influence of di-substituents on the styrene moiety on the dearomative spirocyclization. 3-F, 4-Me substrate **2.1j** formed the dearomative spirocyclized isomer **2.2j** at para to the F group. Whereas the 3,4-dimethyl analogue **2.1k** gave 67% yield of **2.2k** at the less sterically hindered position. The *p*-Cl substrate **2.1l** failed to afford the cyclized products our reaction condition.

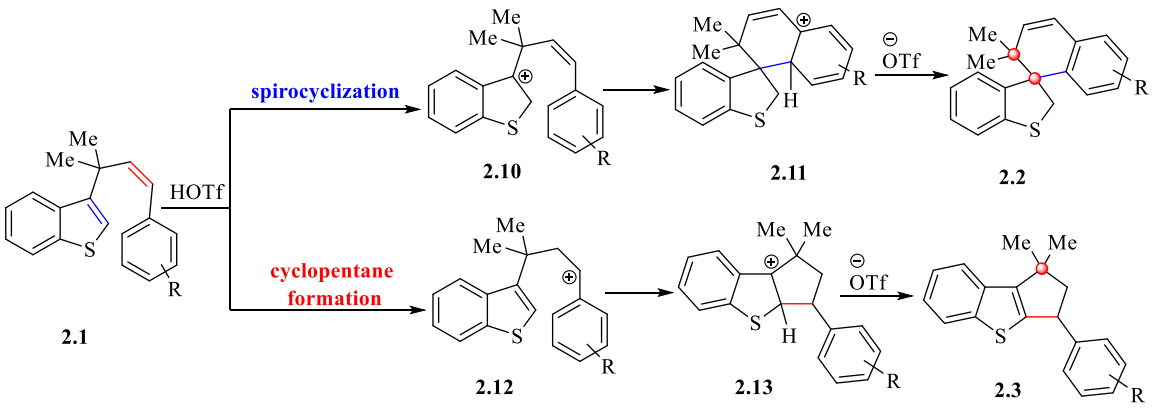
Along with benzothiophene derivatives, the hydroarylation of the corresponding indole, benzofuran and thiophene analogues were also investigated (Scheme 2.3). With indole and thiophene substrates, C2 cyclized five-membered ring products **2.6** and **2.9** were

observed in 39 % and 55% yield respectively (Scheme 2.3A, C), whereas the benzofuran analogue **2.7** wasn't tolerated under superacidic condition (Scheme 2.3B).



Scheme 2.3. Acid catalyzed hydroarylation of indole, benzofuran and thiophene analogues

Based on our results, we proposed a possible reaction mechanism for the formation of **2.2** and **2.3** (Scheme 2.4). The carbocation might be formed on the C3 position of benzothiophene ring as in **2.10** through the protic activation of the C2=C3 bond or on the styrene benzylic position as in **2.12**. The following electrophilic attacks to the corresponding aromatic rings would then generate **2.11** or **2.13** which then afford **2.2** or **2.3** after intramolecular rearomatization. In general, dearomative spirocyclization to form **2.2** was favored at room temperature. However, when the styrene moiety has a substituent on the *para* position such as methoxy group, the regioselectivity of the dearomative spirocyclization was eroded.



Scheme 2.4. Proposed mechanism

During our previous projects, the geminal dimethyl group was found important in overall yield and regioselectivity of the hydroarylation.[8] According to those findings, we hypothesized that the geminal dialkyl effect may resulted in the discrepancy in the hydroarylation of *cis* and *trans* configured alkenes. In *cis* alkene, the formation of spiro compound may enabled by the close proximity of the styrenyl and benzothiophene rings which is enforced by the steric repulsion between the geminal dimethyl groups via Thorpe–Ingold effect. However, in *trans* isomer, the two rings don't have the same proximity as in *cis* isomer which may then led to the formation of cyclopentane product via the activation of styrenyl double bond.

3. Conclusion

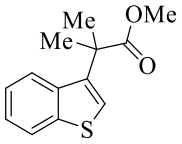
In conclusion, we have developed a method to access contiguous quaternary center containing spiroheterocycles under metal free condition. The alkene configuration was found essential in product formation. Spiro compounds were obtained from *cis* alkenes, whereas *trans* isomer afforded cyclopentane product. The dearomative spirocyclization was favored at ambient temperature. In addition, the substituents on the styrene ring played important role on regioselectivity of the spirocyclization. *Meta*-substituents on the styrene moiety selectively afforded dearomative spirocyclized single isomers up to 92%. However, with *para*-substituted substrates or with the substrates in which the nucleophilic position was blocked the regioselectivity was eroded.

Our work demonstrates the first example for the dearomative formation of the spirocycles with vicinal quaternary centers from unactivated hindered alkenes under Brønsted acid-catalyzed mild conditions. The reserved alkene double bond and the halogens in the spirocycle leaves a room for further manipulation of the final product.

4. Experimental

4.1 Preparation of α-Quaternary Aldehydes

A. Preparation of α-Quaternary Ester via Cross-Coupling Reaction

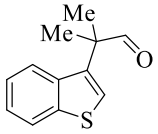


S1

Methyl 2-(benzo[*b*]thiophen-3-yl)-2-methylpropanoate S1. The cross-coupling procedure previously reported by Hartwig and coworkers[10] was followed with slight modification. To an oven dried 100 mL round bottom flask charged with PTFE coated magnetic stir bar, 520 mg of zinc fluoride (5 mmol, 0.5 equiv), 172.5 mg of bis(dibenzylideneacetone) palladium (0) (0.3 mmol, 0.03 equiv), and 2243 mg 3-bromobenzo[*b*]thiophene (with 95% purity) (10 mmol, 1.0 equiv) were added. The reaction

flask was then sealed with a rubber septum, degassed, and backfilled with nitrogen. Then 0.6 mL of a 1.0 M solution of tri-*tert*-butylphosphine in toluene (0.6 mmol, 0.06 equiv) and 3.02 mL *tert*-butyl trimethylsilyl methyl ketene acetal (14.9 mmol, 1.49 equiv) were added followed by 40 mL of DMF (0.25 M) at room temperature. The reaction mixture was then allowed to stir at 80 °C for 18 hours under nitrogen. The crude reaction was allowed to cool to room temperature and diluted with Et_2O (200 mL). The resulting solution was washed with H_2O (5×50 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated at reduced pressure. The crude product was then purified by chromatography (hexanes:ethyl acetate = 95:5) to afford **S1** (1912 mg, 82%) as a light-yellow oil. R_f=0.53 (hexanes:ethyl acetate = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89–7.82 (m, 1 H), 7.63–7.70 (m, 1H), 7.34–7.32 (m, 2H), 7.27 (s, 1H), 3.61 (s, 3H), 1.70 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.3 (C=O), 141.0 (C), 139.9 (C), 137.5 (C), 124.1 (CH), 123.2 (CH), 122.5 (CH), 121.1 (CH), 52.5 (CH_3), 44.4 (C), 26.3 (CH_3).

B. Preparation of α-Quaternary Aldehyde via Sequential Reduction-Oxidation of C3 Benzo[*b*]thiophenyl Methyl Ester



S2

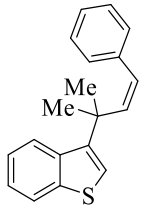
2-(Benzo[*b*]thiophen-3-yl)-2-methylpropanal S2. The procedure previously reported by Stokes and coworkers[8a] was followed with slight modification. Lithium aluminum hydride (930 mg, 24.51 mmol, 3 equiv) was added to a stirred, cooled solution of methyl 2-(benzo[*b*]thiophen-3-yl)-2-methylpropanoate **S1** (1912 mg, 8.17 mmol, 1.00 equiv) in diethyl ether (33 mL, 0.25 M) in four portions over 10 minutes at 0°C. After 10 minuts, the reaction was allowed to warm to room temperature and stir for an additional 1 hour 15 minutes. After TLC monitoring showed complete consumption of the methyl ester, the flask was returned to an ice bath and quenched with aqueous NH_4Cl. The primary alcohol product was extracted with diethyl ether (3×50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was then dissolved in 33 mL of DCM. To this solution were added 2340 mg of pyridinium chlorochromate (10.87 mmol, 1.33 equiv) at ambient temperature. The oxidation was monitored by TLC and was complete after four hours. The reaction mixture was then diluted with 50 mL of EtOAc, filtered through a packed Celite® cake and concentrated *in vacuo*. The crude product was then purified by chromatography (hexanes:benzene = 85:15) to afford **S2** as off white solid (921 mg, 55% over 2 steps). m.p. = 35-37 °C. R_f = 0.51 (hexanes:ethyl acetate = 10:1, visualized by 254 nm UV light and **2,4-Dinitrophenyl-hydrazine** stain). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.54 (s, 1 H), 7.91–7.85 (m, 1H), 7.71–7.62 (m, 1H), 7.40–7.3 (m, 3H), 1.61 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.4 (C=O), 141.1 (C), 137.2 (C), 136.5 (C), 124.3 (CH), 124.2 (CH), 123.4 (CH), 123.2 (CH), 123.0 (CH), 49.3 (C), 22.1 (CH_3).

4.2 Preparation of Alkenyl Substrates

A. General Wittig-Olefination Procedure

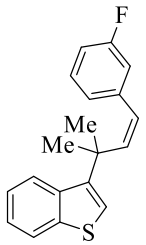
In an oven-dried 25 mL round bottom flask charged with PTFE coated magnetic stir bar, benzyl triphenylphosphonium bromide (1.5 equiv) was dissolved in 2.8 mL DMF. The reaction flask was then sealed with a rubber septum before 0.76 ml of a 1.7 M potassium *tert*-butoxide solution in THF (1.3 equiv) was syringed into the mixture at room temperature. The reaction mixture was continuously being stirred for an additional 20-30 minutes before it was chilled to 0 °C. A solution of 2-(benzo[*b*]thiophen-3-yl)-2-methylpropanal **S2** (1 mmol, 1 equiv) in 0.5 mL DMF was then added to the ylides drop-wise through syringe. The reaction was then brought to room temperature and allowed to stir for 18–24 hours. The reaction was quenched with saturated aqueous NH_4Cl solution and the alkene was extracted with ethyl acetate (3×10 mL). The combined organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to afford crude alkene product as a mixture of *E* and *Z* isomers. Purification by silica gel chromatography using gradient elution afforded analytically pure Z alkenes unless otherwise noted.

B. Synthesis and Characterization of Alkenyl Substrates



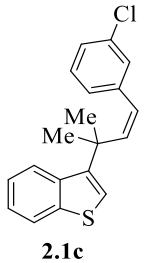
2.1a

(Z)-3-(2-methyl-4-phenylbut-3-en-2-yl)benzo[*b*]thiophene 2.1a. The general Wittig-Olefination procedure was followed using 204 mg of **S2** (1.0 mmol), 648 mg of triphenyl phosphonium bromide (1.5 mmol) and 0.76 mL of a 1.7 M solution of *t*-BuOK in THF. Purification by flash column chromatography with hexanes afforded *Z* stereoisomer **2.1a** (132.8 mg, 47% yield) as a white solid (total yield for *cis* and *trans* alkene was 91%). m.p. = 49-51 °C. R_f = 0.34 (hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (d, *J* = 8.2 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.30 (t, *J* = 7.5 Hz, 1H), 7.24 (t, *J* = 7.5 Hz, 1H), 6.96 – 6.88 (m, 4 H), 6.65 (d, *J* = 6.5 Hz, 2H), 6.50 (d, *J* = 12.5 Hz, 1H), 6.08 (d, *J* = 12.5 Hz, 1H), 1.59 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.3 (C), 141.1 (C), 139.8 (CH), 137.8 (C), 137.2 (C), 129.8 (CH), 128.0 (CH), 126.8 (CH), 126.0 (CH), 124.7 (CH), 123.5 (CH), 123.0 (CH), 122.7 (CH), 1201.1 (CH), 39.3 (C), 30.4 (CH_3).



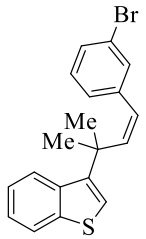
2.1b

(Z)-3-(4-(3-fluorophenyl)-2-methylbut-3-en-2-yl)benzo[*b*]thiophene 2.1b. The general Wittig-olefination procedure was followed using 204 mg of **S2** (1.0 mmol), 677 mg of (3-fluorobenzyl)triphenylphosphonium bromide (1.5 mmol) and 0.76 mL of a 1.7 M solution of *t*-BuOK in THF. Purification by flash column chromatography with hexanes afforded *Z* stereoisomer **2.1b** (121.4 mg, 41% yield) as a colorless oil (total yield for *cis* and *trans* alkene was 93%). R_f = 0.32 (hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (d, *J* = 8.1 Hz, 1H), 7.75 (d, *J* = 7.9 Hz, 1H), 7.37 – 7.26 (m, 2H), 7.00 (s, 1H), 6.86 (td, *J* = 7.9, 6.2 Hz, 1H), 6.66 (td, *J* = 8.6, 2.5 Hz, 1H), 6.47 (d, *J* = 12.5 Hz, 1H), 6.40 (d, *J* = 7.6 Hz, 1H), 6.34 (d, *J* = 10.2 Hz, 1H), 6.14 (d, *J* = 12.5 Hz, 1H), 1.65 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.6 (d, *J* = 244.7 Hz, C-F), 143.8 (C), 141.1 (C), 140.6 (CH), 139.1 (d, *J* = 7.8 Hz, C), 137.6 (C), 128.5 (CH), 127.9 (d, *J* = 8.3 Hz, CH), 124.5 (CH), 123.7 (CH), 123.5 (CH), 123.1 (CH), 122.8 (CH), 120.3 (CH), 114.8 (d, *J* = 21.4 Hz, CH), 112.8 (d, *J* = 21.1 Hz, CH), 39.2 (C), 30.4 (CH_3). ^{19} F NMR (470 MHz, $CDCl_3$): δ -115.0.



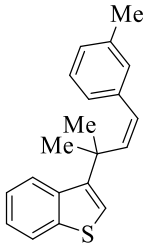
2.1c

(Z)-3-(4-(3-chlorophenyl)-2-methylbut-3-en-2-yl)benzo[*b*]thiophene 2.1c. The general Wittig-olefination procedure was followed using 204 mg of **S2** (1.0 mmol), 701 mg of (3-chlorobenzyl)triphenylphosphonium bromide (1.5 mmol) and 0.76 mL of a 1.7 M solution of *t*-BuOK in THF. Purification by flash column chromatography with hexanes afforded *Z* stereoisomer **2.1c** (135.2 mg, 43% yield) as a colorless oil (total yield for *cis* and *trans* alkene was 84%). R_f = 0.34 (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, *J* = 8.1 Hz, 1H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.33 – 7.20 (m, 2H), 6.95 (s, 1H), 6.88 – 6.83 (m, 1H), 6.76 (t, *J* = 7.8 Hz, 1H), 6.52 (s, 1H), 6.45 – 6.36 (m, 2H), 6.10 (d, *J* = 12.4 Hz, 1H), 1.60 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.7 (C), 141.2 (C), 140.9 (CH), 138.7 (C), 137.6 (C), 132.6 (C), 128.4 (CH), 128.0 (CH), 128.7 (CH), 126.1 (2CH), 124.6 (CH), 123.6 (CH), 123.1 (CH), 122.8 (CH), 120.5 (CH), 39.3 (C), 30.6 (CH_3).



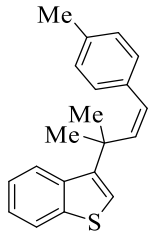
2.1d

(Z)-3-(4-(3-bromophenyl)-2-methylbut-3-en-2-yl)benzo[*b*]thiophene 2.1d. The general Wittig-olefination procedure was followed using 204 mg of **S2** (1.0 mmol), 768 mg of (3-bromobenzyl)triphenylphosphonium bromide (1.5 mmol) and 0.76 mL of a 1.7 M solution of *t*-BuOK in THF. Purification by flash column chromatography with hexanes afforded *Z* stereoisomer **2.1d** (167 mg, 47% yield) as a colorless oil (total yield for *cis* and *trans* alkene was 88%). R_f = 0.35 (hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90 (d, *J* = 8.2 Hz, 1H), 7.72 (d, *J* = 7.9 Hz, 1H), 7.34 – 7.24 (m, 2H), 7.03 (m, 1H), 6.98 (s, 1H), 6.76 – 6.67 (m, 2H), 6.49 (dd, *J* = 7.6, 0.7 Hz, 1H), 6.40 (d, *J* = 12.5 Hz, 1H), 6.12 (d, *J* = 12.5 Hz, 1H), 1.62 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.5 (C), 141.1 (C), 140.8 (CH), 138.8 (C), 137.5 (C), 130.8 (CH), 128.8 (CH), 128.2 (CH), 127.9 (CH), 126.4 (CH), 124.4 (CH), 123.5 (CH), 123.0 (CH), 122.8 (CH), 120.8 (C), 120.4 (CH), 39.2 (C), 30.5 (CH_3).



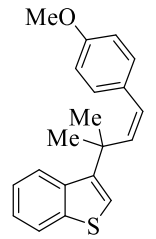
2.1e

(Z)-3-(2-methyl-4-(*m*-tolyl)but-3-en-2-yl)benzo[*b*]thiophene 2.1e. The general Wittig-olefination procedure was followed using 204 mg of **S2** (1.0 mmol), 671 mg of (3-methylbenzyl)triphenylphosphonium bromide (1.5 mmol) and 0.76 mL of a 1.7 M solution of *t*-BuOK in THF. Purification by flash column chromatography with hexanes afforded *Z* stereoisomer **2.1e** (160 mg, 55% yield) as a light-yellow oil (total yield for *cis* and *trans* alkene was 97%). R_f = 0.31 (hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.05 (d, *J* = 8.1 Hz, 1H), 7.80 (d, *J* = 7.9 Hz, 1H), 7.42–7.36 (m, 1H), 7.35–7.29 (m, 1H), 6.99 (s, 1H), 6.92 (t, *J* = 7.5 Hz, 1H), 6.83 (d, *J* = 7.6 Hz, 1H), 6.59 (d, *J* = 7.6 Hz, 1H), 6.55 (d, *J* = 12.4 Hz, 1H), 6.41 (s, 1H), 6.14 (d, *J* = 12.4 Hz, 1H), 2.15 (s, 3H), 1.66 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.6 (C), 141.2 (C), 139.6 (CH), 137.9 (C), 137.1 (C), 136.4 (C), 130.1 (CH), 128.8 (CH), 126.8 (CH), 126.7 (CH), 125.2 (CH), 124.8 (CH), 123.5 (CH), 123.1 (CH), 122.7 (CH), 119.9 (CH), 39.2 (C), 30.5 (CH_3), 21.4 (CH_3).



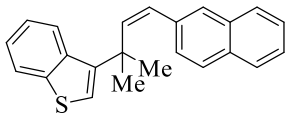
2.1f

(Z)-3-(2-methyl-4-(*p*-tolyl)but-3-en-2-yl)benzo[*b*]thiophene 2.1f. The general Wittig-olefination procedure was followed using 204 mg of **S2** (1.0 mmol), 671 mg of (4-methylbenzyl)triphenylphosphonium bromide (1.5 mmol) and 0.76 mL of a 1.7 M solution of *t*-BuOK in THF. Purification by flash column chromatography with hexanes afforded *Z* stereoisomer **2.1f** (137.5 mg, 47% yield) as a colorless oil (total yield for *cis* and *trans* alkene was 81%). R_f = 0.31 (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.0 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 7.9 Hz, 1H), 7.36–7.24 (m, 2H), 6.98 (d, *J* = 1.7 Hz, 1H), 6.77 (d, *J* = 7.2 Hz, 2H), 6.60 (d, *J* = 7.0 Hz, 2H), 6.50 (d, *J* = 12.4 Hz, 1H), 6.07 (dd, *J* = 12.4, 1.8 Hz, 1H), 2.21 (s, 3H), 1.60 (d, *J* = 1.9 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.8 (C), 141.2 (C), 139.6 (CH), 137.9 (C), 135.6 (C), 134.4 (C), 129.9 (CH), 128.1 (CH), 127.6 (CH), 124.8 (CH), 123.5 (CH), 123.1 (CH), 122.8 (CH), 120.0 (CH), 39.3 (C), 30.4 (CH_3), 21.1 (CH_3).



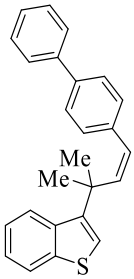
2.1g

(Z)-3-(4-(4-methoxyphenyl)-2-methylbut-3-en-2-yl)benzo[*b*]thiophene 2.1g. The general Wittig-olefination procedure was followed using 204 mg of **S2** (1.0 mmol), 694 mg of (4-methoxybenzyl)triphenylphosphonium bromide (1.5 mmol) and 0.76 mL of a 1.7 M solution of *t*-BuOK in THF. Purification by flash column chromatography twice (hexanes:benzene = 95:5) afforded *Z* stereoisomer **2.1g** (91.2 mg, 30% yield) as a light-yellow oil (total yield for *cis* and *trans* alkene was 50%). R_f = 0.19 (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, *J* = 8.1 Hz, 1H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.33–7.21 (m, 2H), 6.98 (s, 1H), 6.59 (d, *J* = 8.5 Hz, 2H), 6.51–6.41 (m, 3H), 6.03 (d, *J* = 12.4 Hz, 1H), 3.69 (s, 3H), 1.58 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.8 (C), 144.6 (C), 141.2 (C), 139.3 (CH), 137.9 (C), 129.7 (C), 129.5 (CH), 129.3 (CH), 124.7 (CH), 123.5 (CH), 123.1 (CH), 122.8 (CH), 120.0 (CH), 112.4 (CH), 55.3 (OCH_3), 39.2 (C), 30.5 (CH_3).



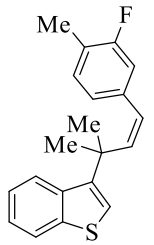
2.1h

(Z)-3-(2-methyl-4-(naphthalen-2-yl)but-3-en-2-yl)benzo[*b*]thiophene 2.1h. The general Wittig-olefination procedure was followed using 204 mg of **S2** (1.0 mmol), 725 mg of (2-naphthylmethyl)triphenylphosphonium bromide (1.5 mmol) and 0.76 mL of a 1.7 M solution of *t*-BuOK in THF. Purification by flash column chromatography (hexanes:benzene = 90:10) afforded *Z* stereoisomer **2.1h** (120 mg, 37% yield) as a light-yellow oil (total yield for *cis* and *trans* alkene was 84%). R_f = 0.25 (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, *J* = 8.2 Hz, 1H), 7.73–7.64 (m, 2H), 7.55–7.33 (m, 5H), 7.27 (t, *J* = 7.1 Hz, 1H),7.03 (s, 1H), 6.93 (s, 1H), 6.85 (d, *J* = 8.3 Hz, 1H), 6.66 (d, *J* = 12.4 Hz, 1H), 6.24 (d, *J* = 12.4 Hz, 1H), 1.62 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.0 (C), 141.2 (C), 140.4 (CH), 137.9 (C), 134.9 (C), 132.6 (C), 131.9 (C), 130.1 (CH), 128.0 (CH), 127.4 (CH), 127.1 (CH), 126.6 (CH), 126.3 (CH), 125.6 (CH), 125.5 (CH), 124.7 (CH), 123.6 (CH), 123.2 (CH), 122.9 (CH), 120.0 (CH), 39.3 (C), 30.5 (CH_3).



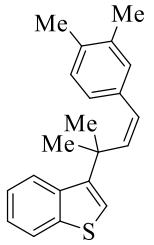
2.1i

(Z)-3-(4-([1,1'-biphenyl]-4-yl)-2-methylbut-3-en-2-yl)benzo[*b*]thiophene 1i. The general Wittig-olefination procedure was followed using 204 mg of **S2** (1.0 mmol), 764 mg of ([1,1'-biphenyl]-4-ylmethyl)triphenylphosphonium bromide (1.5 mmol) and 0.76 mL of a 1.7 M solution of *t*-BuOK in THF. Purification by flash column chromatography (hexanes:benzene = 90:10) afforded *Z* stereoisomer **1i** (105.8 mg, 30% yield) as an off-white oil. R_f = 0.47 (hexanes:benzene=10:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, *J* = 8.1 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.53–7.41 (m, 4H), 7.40–7.22 (m, 3H), 7.13 (d, *J* = 7.3 Hz, 2H), 7.00 (s, 1H), 6.72 (d, *J* = 7.7 Hz, 2H), 6.57 (d, *J* = 12.4 Hz, 1H), 6.14 (d, *J* = 12.4 Hz, 1H), 1.67 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.2 (C), 141.3 (C), 141.2 (C), 140.2 (CH), 137.8 (C), 137.8 (C), 136.1 (C), 129.4 (CH), 128.7 (CH), 128.3 (CH), 127.1 (CH), 127.0 (CH), 125.4 (CH), 124.7 (CH), 123.5 (CH), 123.1 (CH), 122.7 (CH), 120.3 (CH), 39.4 (C), 30.6 (CH_3).



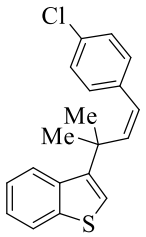
2.1j

(Z)-3-(4-(3-fluoro-4-methylphenyl)-2-methylbut-3-en-2-yl)benzo[*b*]thiophene 2.1j. The general Wittig-olefination procedure was followed using 204 mg of **S2** (1.0 mmol), 698 mg of (3-fluoro-4-methylbenzyl)triphenylphosphonium bromide (1.5 mmol) and 0.76 mL of a 1.7 M solution of *t*-BuOK in THF. Purification by flash column chromatography (hexanes) afforded *Z* stereoisomer **2.1j** (113.6 mg, 37% yield) as a colorless oil. R_f = 0.25 (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.36–7.23 (m, 2H), 6.98 (d, *J* = 1.8 Hz, 1H), 6.70 (t, *J* = 7.7 Hz, 1H), 6.42 (d, *J* = 12.4 Hz, 1H), 6.29 (m, 2H), 6.09 (dd, *J* = 12.4, 1.8 Hz, 1H), 2.11 (s, 3H), 1.61 (d, *J* = 1.9 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.1 (d, *J* = 243.4 Hz, C-F), 144.2 (C), 141.2 (C), 140.4 (CH), 137.8 (C), 136.6 (d, *J* = 7.9 Hz, C), 129.6 (d, *J* = 5.6 Hz, CH), 128.7 (d, *J* = 1.8 Hz, CH), 124.6 (CH), 123.7 (d, *J* = 3.2 Hz, CH), 123.6 (CH), 123.1 (CH), 122.8 (CH), 122.3 (d, *J* = 17.2 Hz, C), 120.2 (CH), 114.6 (d, *J* = 22.5 Hz, CH), 39.3 (C), 30.4 (CH_3), 14.2 (d, *J* = 3.5 Hz, CH_3). ^{19} F NMR (376 MHz, $CDCl_3$): δ -119.5 (dd, *J* = 10.3, 8.9 Hz).



2.1k

(Z)-3-(4-(3,4-dimethylphenyl)-2-methylbut-3-en-2-yl)benzo[*b*]thiophene 2.1k. The general Wittig-olefination procedure was followed using 204 mg of **S2** (1.0 mmol), 692 mg of (3,4-dimethylbenzyl)triphenylphosphonium bromide (1.5 mmol) and 0.76 mL of a 1.7 M solution of *t*-BuOK in THF. Purification by flash column chromatography (hexanes) afforded *Z* stereoisomer **2.1k** (94.3 mg, 31% yield) as a colorless oil. R_f = 0.20 (hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00 (d, *J* = 8.1 Hz, 1H), 7.75 (d, *J* = 7.9 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.27 (dd, *J* = 8.6, 6.1 Hz, 1H), 6.95 (s, 1H), 6.74 (d, *J* = 7.6 Hz, 1H), 6.51–6.44 (m, 2H), 6.33 (s, 1H), 6.06 (d, *J* = 12.4 Hz, 1H), 2.11 (s, 3H), 1.99 (s, 3H), 1.59 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.0 (C), 141.2 (C), 139.5 (CH), 138.0 (C), 135.0 (C), 134.9 (C), 134.3 (C), 130.1 (CH), 129.5 (CH), 128.2 (CH), 125.8 (CH), 124.8 (CH), 123.5 (CH), 123.1 (CH), 122.7 (CH), 119.8 (CH), 39.3 (C), 30.5 (CH_3), 19.7 (CH_3), 19.4 (CH_3).



2.1l

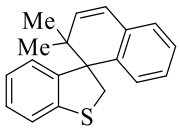
The general Wittig-olefination procedure was followed using 204 mg of **S2** (1.0 mmol), 635 mg of (4-chlorobenzyl)triphenylphosphonium chloride (1.5 mmol) and 0.76 mL of a 1.7 M solution of *t*-BuOK in THF. Purification by flash column chromatography (hexanes) afforded *Z* stereoisomer **2.1l** (98.4 mg, 32% yield) as a colorless oil (total yield for *cis* and *trans* alkene was 64%). R_f = 0.34 (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, *J* = 7.8 Hz, 1H), 7.73 (d, *J* = 7.9 Hz, 1H), 7.34-7.22 (m, 2H), 6.94 (s, 1H), 6.84 (dd, *J* = 8.3, 1.5 Hz, 2H), 6.51 (d, *J* = 7.5 Hz, 2H), 6.43 (d, *J* = 12.4 Hz, 1H), 6.11 (dd, *J* = 12.3, 1.6 Hz, 1H), 1.61 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.9 (C), 141.2 (C), 140.7 (CH), 137.7 (C), 135.4 (C), 131.7 (C), 129.2 (CH), 128.6 (CH), 126.7 (CH), 124.6 (CH), 123.6 (CH), 123.2 (CH), 122.8 (CH), 120.4 (CH), 39.3 (C), 30.6 (CH_3).

4.3 Synthesis of Spirocycles Bearing Vicinal Quat Centers *via* Dearomative spirocyclization

A. General Cyclization Procedure

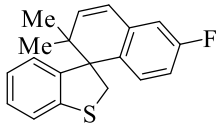
In a dry 4 mL glass vial charged with PTFE coated magnetic stir bar, the *cis* alkene (0.3 mmol, 1.0 equiv) was dissolved in 0.5 M of anhydrous dichloromethane and the solution is cooled to 0 °C. After 10 mins, triflic acid (7 mol%) was slowly added to the solution and let it stir for another 5 minuts at 0 °C. Then the reaction mixture was allowed to stir for 12 hours at 25 °C. The reaction solution was quenched by saturated $NaHCO_3$ and extracted with DCM (3×1.0 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford the crude product. Purification by silica gel chromatography using gradient elution afforded corresponding pure cyclized product.

B. Synthesis and Characterization of Spirocycles



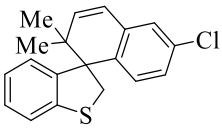
2.2a

2',2'-dimethyl-2H,2'H-spiro[benzo[*b*]thiophene-3,1'-naphthalene] 2.2a. The general cyclization procedure was followed using 83.5 mg of alkene **2.1a** (0.3 mmol), 1.85 uL of triflic acid (0.07 mmol) and 0.6 mL of anhydrous DCM (0.5 M) in a 4 mL glass vial. Purification by flash column chromatography with hexanes afforded the major spiro product **2.2a** (63.1 mg, 76% yield) as a white solid. m.p. = 106-109 °C. R_f = 0.33 (hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31-7.17 (m, 5H), 7.15-7.01 (m, 3H), 6.46 (d, *J* = 9.6 Hz, 1H), 5.81 (d, *J* = 9.6 Hz, 1H), 4.00 (d, *J* = 12.1 Hz, 1H), 3.33 (d, *J* = 12.1 Hz, 1H), 1.16 (s, 3H), 1.02 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.2 (C), 142.6 (C), 139.8 (C), 139.2 (CH), 132.3 (C), 128.6 (CH), 128.4 (CH), 128.1 (CH), 127.2 (CH), 126.9 (CH), 126.6 (CH), 126.0 (CH), 123.1 (CH), 122.3 (CH), 63.5 (C), 41.4 (C), 40.6 (CH_2), 23.8 (CH_3), 23.5 (CH_3).



2.2b

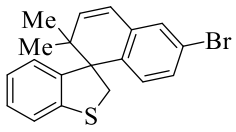
6'-fluoro-2',2'-dimethyl-2H,2'H-spiro[benzo[*b*]thiophene-3,1'-naphthalene] 2.2b. The general cyclization procedure was followed using 88.8 mg of alkene **2.1b** (0.3 mmol), 1.85 uL of triflic acid (0.07 mmol) and 0.6 mL of anhydrous DCM (0.5 M) in a 4 mL glass vial. Purification by flash column chromatography with hexanes afforded the major spiro product **2.2b** (81.5 mg, 92% yield) as a colorless oil. R_f = 0.30 (hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30–7.15 (m, 5H), 7.05 (ddd, *J* = 8.3, 6.9, 1.7 Hz, 1H), 7.01–6.83 (m, 2H), 6.41 (d, *J* = 9.6 Hz, 1H), 5.89 (d, *J* = 9.6 Hz, 1H), 3.98 (d, *J* = 12.1 Hz, 1H), 3.30 (d, *J* = 12.1 Hz, 1H), 1.17 (s, 3H), 1.03 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.0 (d, *J* = 245.0 Hz, C-F), 144.1 (C), 140.8 (CH), 139.6 (C), 138.2 (d, *J* = 3.3 Hz, C), 134.2 (d, *J* = 7.9 Hz, C), 128.5 (CH), 128.3 (CH), 128.2 (d, *J* = 8.0 Hz, CH), 125.2 (d, *J* = 2.2 Hz, CH), 123.2 (CH), 122.4 (CH), 114.2 (d, *J* = 21.0 Hz, CH), 113.4 (d, *J* = 21.8 Hz, CH), 63.0 (C), 41.5 (C), 40.6 (d, *J* = 1.3 Hz, CH_2), 23.7 (CH_3), 23.4 (CH_3). ^{19} F NMR (470 MHz, $CDCl_3$): δ -116.3 (td, *J* = 8.8, 5.7 Hz).



2.2c

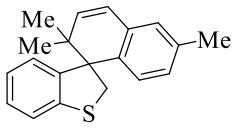
6'-chloro-2',2'-dimethyl-2H,2'H-spiro[benzo[*b*]thiophene-3,1'-naphthalene] 2.2c. The general cyclization procedure was followed using 94.2 mg of alkene **2.1c** (0.3 mmol), 1.86 uL of triflic acid (0.07 mmol) and 0.6 mL of anhydrous DCM (0.5 M) in a 4 mL glass vial. Purification by flash column chromatography with hexanes afforded the major spiro product **2.2c** (77.2 mg, 82% yield) as a colorless oil. R_f = 0.33 (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27–6.99 (m, 7H), 6.38 (d, *J* = 9.6 Hz, 1H), 5.86 (d, *J* = 9.6 Hz, 1H), 3.96 (d, *J* = 12.1 Hz, 1H), 3.28 (d, *J* = 12.1 Hz, 1H), 1.14 (s, 3H), 1.00 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.1 (C), 141.0 (C), 140.8 (CH), 139.4 (C), 134.0 (C), 132.9 (C), 128.6

(CH), 128.3 (CH), 128.0 (CH), 127.7 (CH), 126.6 (CH), 125.0 (CH), 123.2 (CH), 122.4 (CH), 63.0 (C), 41.4 (C), 40.5 (CH_2), 23.8 (CH_3), 23.4 (CH_3).



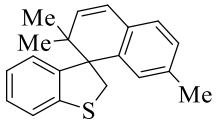
2.2d

6'-bromo-2',2'-dimethyl-2H,2'H-spiro[benzo[*b*]thiophene-3,1'-naphthalene] 2.2d. The general cyclization procedure was followed using 107.7 mg of alkene **2.1d** (0.3 mmol), 1.86 uL of triflic acid (0.07 mmol) and 0.6 mL of anhydrous DCM (0.5 M) in a 4 mL glass vial. Purification by flash column chromatography with hexanes afforded the major spiro product **2.2d** (90.5 mg, 84% yield) as a colorless oil. R_f = 0.34 (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27–7.18 (m, 5H), 7.09 (d, *J* = 8.2 Hz, 1H), 7.05-7.00 (m, 1H), 6.38 (d, *J* = 9.6 Hz, 1H), 5.86 (d, *J* = 9.6 Hz, 1H), 3.96 (d, *J* = 12.1 Hz, 1H), 3.28 (d, *J* = 12.1 Hz, 1H), 1.14 (s, 3H), 1.0 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.1 (C), 141.5 (C), 140.8 (CH), 139.3 (C), 134.3 (C), 130.7 (CH), 129.5 (CH), 128.6 (CH), 128.4 (CH), 128.2 (CH), 124.9 (CH), 123.2 (CH), 122.4 (CH), 121.0 (C), 63.1 (C), 41.3 (C), 40.4 (CH_2), 23.7 (CH_3), 23.4 (CH_3).

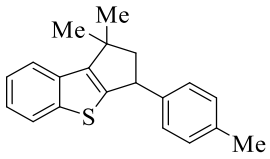


2.2e

2',2',6'-trimethyl-2H,2'H-spiro[benzo[*b*]thiophene-3,1'-naphthalene] 2.2e. The general cyclization procedure was followed using 87.9 mg of alkene **2.1e** (0.3 mmol), 1.86 uL of triflic acid (0.07 mmol) and 0.6 mL of anhydrous DCM (0.5 M) in a 4 mL glass vial. Purification by flash column chromatography with hexanes afforded the major spiro product **2.2e** (70.5 mg, 80% yield) as a colorless oil. R_f = 0.24 (hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (d, *J* = 7.7 Hz, 1H), 7.28–7.20 (m, 2H), 7.10 (d, *J* = 7.8 Hz, 1H), 7.05–7.02 (m, 1H), 6.98–6.92 (m, 2H), 6.44 (d, *J* = 9.6 Hz, 1H), 5.81 (d, *J* = 9.6 Hz, 1H), 4.0 (d, *J* = 12.1 Hz, 1H), 3.33 (d, *J* = 12.1 Hz, 1H), 2.37 (s, 3H), 1.17 (s, 3H), 1.03 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.2 (C), 140.0 (C), 139.7 (C), 139.2 (CH), 136.7 (C), 132.1 (C), 128.6 (CH), 128.5 (CH), 128.3 (CH), 127.6 (CH), 126.5 (CH), 126.0 (CH), 123.0 (CH), 122.2 (CH), 63.2 (C), 41.4 (C), 40.7 (CH_2), 23.8 (CH_3), 23.6 (CH_3), 21.1 (CH_3).



2.2f

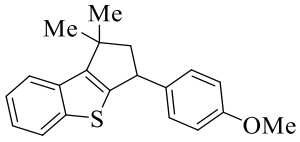


2.3f

2',2',7'-trimethyl-2H,2'H-spiro[benzo[*b*]thiophene-3,1'-naphthalene] 2.2f and 1,1-dimethyl-3-(p-tolyl)-2,3-dihydro-1H-benzo[*b*]cyclopenta[*d*]thiophene 2.3f. The general cyclization procedure was followed using 87.8 mg of alkene **2.1f** (0.3 mmol), 1.86 uL of triflic acid (0.07 mmol) and 0.6 mL of anhydrous DCM (0.5 M) in a 4 mL glass vial. Purification by flash column chromatography with hexanes afforded the mixture of regioisomers **2.2f + 2.3f** (70.5 mg, 80% yield) as yellow oil. R_f = 0.29 (hexanes).

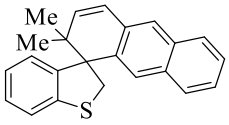
Selected spectral data for **2.2f:** ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.44 (d, *J* = 9.6 Hz, 1H), 5.75 (d, *J* = 9.5 Hz, 1H), 4.0 (d, *J* = 12.0 Hz, 1H), 3.33 (d, *J* = 12.0 Hz, 1H), 2.26 (s, 3H), 1.15 (s, 3H), 1.02 (s, 3H). Other peaks in aromatic region were obscured by **2.3f.** ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.1 (CH), 125.9 (CH), 63.6 (C), 41.5 (C), 40.6 (CH_2), 23.8 (CH_3), 23.6 (CH_3), 21.8 (CH_3). Other peaks in aromatic region were obscured by **2.3f.**

Selected spectral data for **1,1-dimethyl-3-(p-tolyl)-2,3-dihydro-1H-benzo[*b*]cyclopenta[*d*]thiophene 2.3f.** ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.59 (t, *J* = 8.0 Hz, 1H), 2.83 (dd, *J* = 12.7, 8.2 Hz, 1H), 2.37 (s, 3H), 2.32 (dd, *J* = 12.7, 7.8 Hz, 1H), 1.61 (s, 3H), 1.47 (s, 3H). Other peaks in aromatic region were obscured by **2.2f.** ^{13}C NMR (100 MHz, $CDCl_3$): δ 57.2 (CH_2), 47.1 (CH), 42.7 (C), 29.0 (CH_3), 27.8 (CH_3), 21.2 (CH_3). Other peaks in aromatic region were obscured by **2.2f.**



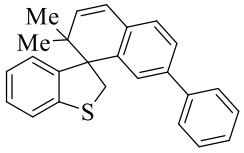
2.3g

3-(4-methoxyphenyl)-1,1-dimethyl-2,3-dihydro-1H-benzo[*b*]cyclopenta[*d*]thiophene 2.3g. The general cyclization procedure was followed using 85.7 mg of alkene **2.1g** (0.28 mmol), 1.72 uL of triflic acid (0.07 mmol) and 0.56 mL of anhydrous DCM (0.5 M) in a 4 mL glass vial. Purification by flash column chromatography with hexanes afforded the cyclopentane product **2.3g** (65.8 mg, 77% yield) as a yellow solid. m.p. = 88-90 °C. R_f = 0.19 (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, *J* = 8.2 Hz, 2H), 7.38–7.18 (m, 4H), 6.86 (d, *J* = 8.6 Hz, 2H), 4.55 (t, *J* = 8.0 Hz, 1H), 3.80 (s, 3H), 2.79 (dd, *J* = 12.7, 7.8 Hz, 1H), 2.28 (dd, *J* = 12.7, 7.8 Hz, 1H), 1.59 (s, 3H), 1.43 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.5 (C), 148.3 (C), 146.0 (C), 145.0 (C), 136.9 (C), 134.5 (C), 128.6 (CH), 124.1 (CH), 123.9 (CH), 123.3 (CH), 121.4 (CH), 114.1 (CH), 57.3 (CH_2), 55.4 (OCH_3), 46.6 (CH), 42.7 (C), 28.9 (CH_3), 27.8 (CH_3).

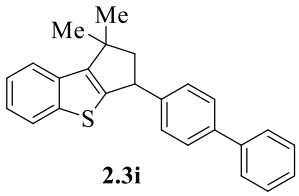


2.2h

2,2-dimethyl-2H,2'H-spiro[anthracene-1,3'-benzo[*b*]thiophene] 2.2h. The general cyclization procedure was followed using 100.1 mg of alkene **2.1h** (0.3 mmol), 1.86 uL of triflic acid (0.07 mmol) and 0.6 mL of anhydrous DCM (0.5 M) in a 4 mL glass vial. Purification by flash column chromatography with hexanes afforded the major spiro product **2.2h** (46 mg, 46% yield) as an off white solid. R_f = 0.23 (hexanes).^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 7.8 Hz, 1H), 7.64 (d, *J* = 6.9 Hz, 2H), 7.52 (s, 1H), 7.46–7.31 (m, 3H), 7.30–7.19 (m, 2H), 7.07 (t, *J* = 7.1 Hz, 1H), 6.64 (d, *J* = 9.6 Hz, 1H), 5.93 (d, *J* = 9.6 Hz, 1H), 4.02 (d, *J* = 12.1 Hz, 1H), 3.39 (d, *J* = 12.1 Hz, 1H), 1.17 (s, 3H), 1.04 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.4 (C), 141.5 (C), 140.2 (CH), 139.8 (C), 133.5 (C), 132.9 (C), 130.0 (C), 128.7 (CH), 128.5 (CH), 128.0 (CH), 127.5 (CH), 126.3 (CH), 126.2 (CH), 125.9 (CH), 125.5 (CH), 125.4 (CH), 123.2 (CH), 122.3 (CH), 63.9 (C), 41.8 (C), 41.7 (CH_2), 24.4 (CH_3), 23.7 (CH_3).



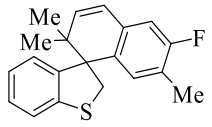
2.2i



2.3i

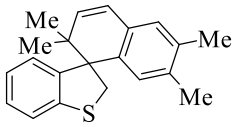
2',2'-dimethyl-7'-phenyl-2H,2'H-spiro[benzo[*b*]thiophene-3,1'-naphthalene] 2.2i and **3-([1,1'-biphenyl]-4-yl)-1,1-dimethyl-2,3-dihydro-1H-benzo[*b*]cyclopenta[*d*] thiophene 2.3i.** The general cyclization procedure was followed using 105.8 mg of alkene **2.1i** (0.3 mmol), 1.84 uL of triflic acid (0.07 mmol) and 0.6 mL of anhydrous DCM (0.5 M) in a 4 mL glass vial. Purification by flash column chromatography with hexanes afforded the regioisomers **2.2i** and **2.3i** as an inseparable mixture (78 mg, 74% yield) as a yellow oil. R_f = 0.23 (hexanes). Selected spectral data for **2.2i**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.51 (d, *J* = 9.5 Hz, 1H), 5.85 (d, *J* = 9.5 Hz, 1H), 4.03 (d, *J* = 12.1 Hz, 1H), 3.4 (d, *J* = 12.1 Hz, 1H), 1.19 (s, 3H), 1.06 (s, 3H). Other peaks in aromatic region were obscured by **2.2i.** ^{13}C NMR (120 MHz, $CDCl_3$): δ 139.4 (CH), 125.6 (CH), 63.5 (C), 41.4 (C), 40.5 (CH_2), 23.7 (CH_3), 23.5 (CH_3).

Selected spectral data for **2.3i**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.66 (t, *J* = 8.0 Hz, 1H), 2.87 (dd, *J* = 12.7, 8.2 Hz, 1H), 2.38 (dd, *J* = 12.7, 7.8 Hz, 1H), 1.63 (s, 3H), 1.49 (s, 3H). Other peaks in aromatic region were obscured by **2.2i.** ^{13}C NMR (120 MHz, $CDCl_3$): δ 57.0 (CH_2), 47.0 (CH), 42.7 (C), 28.8 (CH_3), 27.7 (CH_3). Other peaks in aromatic region were obscured by **2.2i.**



2.2j

6'-fluoro-2',2',7'-trimethyl-2H,2'H-spiro[benzo[*b*]thiophene-3,1'-naphthalene] 2.2j. The general cyclization procedure was followed using 93.5 mg of alkene **2.1i** (0.3 mmol), 1.86 uL of triflic acid (0.07 mmol) and 0.6 mL of anhydrous DCM (0.5 M) in a 4 mL glass vial. Purification by flash column chromatography with hexanes afforded the major spiro product **2.2j** (81.1 mg, 87% yield) as a white solid. m.p. = 108-111 °C. R_f = 0.23 (hexanes).^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31–7.20 (m, 3H), 7.08–6.99 (m, 2H), 6.74 (d, *J* = 9.8 Hz, 1H), 6.37 (d, *J* = 9.6 Hz, 1H), 5.81 (d, *J* = 9.6 Hz, 1H), 3.97 (d, *J* = 12.1 Hz, 1H), 3.29 (d, *J* = 12.1 Hz, 1H), 2.17 (d, *J* = 1.6 Hz, 3H), 1.14 (s, 3H), 1.01 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.4 (d, *J* = 243.7 Hz, C-F), 144.1 (C), 139.9 (C), 139.6 (CH), 138.0 (d, *J* = 3.6 Hz, C), 131.8 (d, *J* = 7.9 Hz, C), 129.7 (d, *J* = 5.2 Hz, CH), 128.4 (2CH), 125.1 (d, *J* = 2.0 Hz, CH), 123.8 (d, *J* = 17.1 Hz, C), 123.2 (CH), 122.3 (CH), 113.1 (d, *J* = 22.7 Hz, CH), 63.0 (C), 41.5 (C), 40.6 (d, *J* = 1.1 Hz, CH_2), 23.7 (CH_3), 23.5 (CH_3), 14.8 (d, *J* = 3.3 Hz, CH_3). ^{19} F NMR (470 MHz, $CDCl_3$): δ -120.9 (m).



2.2k

2',2',6',7'-tetramethyl-2H,2'H-spiro[benzo[*b*]thiophene-3,1'-naphthalene] 2.2k. The general cyclization procedure was followed using 92.3 mg of alkene **2.1k** (0.3 mmol), 1.86 uL of triflic acid (0.07 mmol) and 0.6 mL of anhydrous DCM (0.5 M) in a 4 mL glass vial. Purification by flash column chromatography with hexanes afforded the major spiro product **2.2k** (61.5 mg, 67% yield) as a white solid. m.p. = 136-138 °C . R_f = 0.17 (hexanes).^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (d, *J* = 7.8 Hz, 1H), 7.27–7.18 (m, 2H), 7.03 (t, *J* = 7.3 Hz, 1H), 6.96 (s, 1H), 6.87 (s, 1H), 6.40 (d, *J* = 9.6 Hz, 1H), 5.73 (d, *J* = 9.6 Hz, 1H), 3.97 (d, *J* = 12.1 Hz, 1H), 3.32 (d, *J* = 12.1 Hz, 1H), 2.23 (s, 3H), 2.17 (s, 3H), 1.14 (s, 3H), 1.0 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.1 (C), 140.2 (C), 140.1 (C), 138.2 (CH), 136.3 (C), 135.2 (C), 130.0 (C), 128.6 (CH), 128.3 (CH), 128.2 (CH), 127.9 (CH), 125.8 (CH), 123.0 (CH), 122.2 (CH), 63.2 (C), 41.4 (C), 40.7 (CH_2), 23.8 (CH_3), 23.6 (CH_3), 20.0 (CH_3), 19.4 (CH_3).

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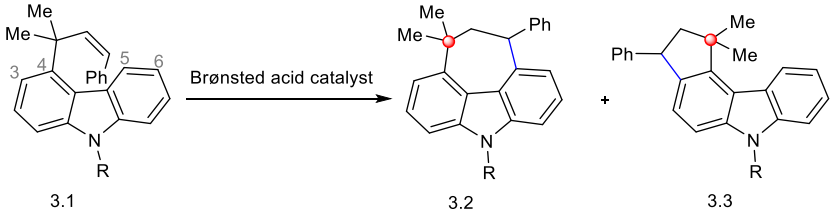
CHAPTER 3

Brønsted Acid Catalyzed Intramolecular Hydroarylation of Unactivated Alkenes to Access Cyclohepta[*def*]carbazoles

1. Introduction and Background

During our continuing interest in catalytic Brønsted acid catalyzed functionalization of unactivated alkenes, we envisioned that the hydroarylation of corresponding carbazole analogue of β-benzylstyrene would form the seven-membered-ring containing cyclohepta[*def*]carbazole **3.2** (Scheme 3.1).



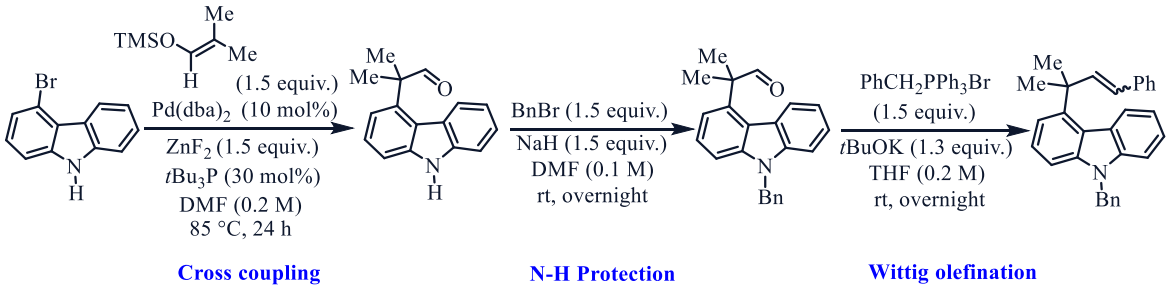
3.1 3.2 3.3

Scheme 3.1. Envisioned hydroarylation of Carbazole alkenes

However, accessing cyclohepta[*def*]carbazole **3.2** will be synthetically challenging due to the preferential five-membered-ring formation in the cyclisation step due to the following factors: First, in general, due to the entropic factors and the development of nonbonded interactions in the transition state, seven-membered rings are more difficult to access than five-, or six-membered rings.[27] Secondly, in electrophilic substitution reaction, C3 of the carbazole is more reactive than C5.[24] Thus, formation of tetrahydrocyclopenta[*c*]carbazole **3.3** at C3 is more favored unless C3 is blocked in advance. Due to the synthetic challenge and absence of general methods for the construction of cyclohepta[*def*]carbazole derivatives, we were interested to further investigate this hydroarylation.

2. Results and Discussion

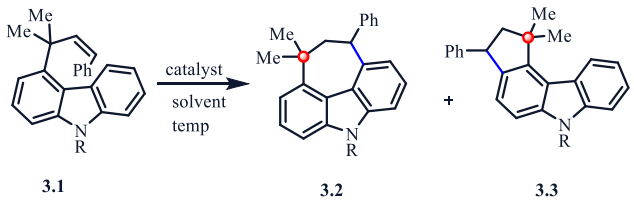
The alkene substrates were prepared by sequential enolate cross-coupling, N-H protection, and Wittig olefination reactions from commercially available 4-Bromo-9H-carbazole as it is shown in Scheme 3.2. The general procedure for each step can be found in experimental section. The alkene substrate was purified by flash column chromatography before we began our investigation on the regioselectivity of this Brønsted-acid catalyzed intramolecular hydroarylation.



Scheme 3.2. Synthetic route to prepare carbazole alkenes

We conducted our optimization by evaluating the effect of different parameters including catalyst, catalyst loading, temperature, solvent, and concentration on the intramolecular hydroarylation (Table 3.1). We began our investigation by treating the pure *cis* and *trans* alkenes with 25 mol% $PhSO_3H$ in DCE at 130 °C separately (entry 1-2). Both alkenes were fully consumed with moderate to good yield. However, with *cis* alkene, no regioselectivity was found, whereas the reaction of *trans* alkene favored the five-membered-ring product **3.3** over **3.2** (entry 2). For this reason, we used *cis* alkene for our further optimizations to get better selectivity for seven-membered-ring product formation. At 50 °C, the regioselectivity was improved to 66:34, but only 6% of the substrate was consumed (entry 3). This result indicated temperature has effect on regioselectivity**.** At lower temperature, the trityl salt, sulfuric acid, and hydrochloric acid were all failed to convert the substrate effectively (entry 4-6). The evaluation of the super acid, triflic acid, was more fruitful, affording the mixture of **3.2** and **3.3** in 57% with 78:22 regioisomeric ratio (entry 7). Despite the moderate yield and conversion, the hydroarylation of N-H unprotected alkene with $PhSO_3H$ also didn't show selectivity at 110 °C (entry 8). With TfOH, low conversion and product yield were obtained with 68:32 ratio. Next, we evaluated the effect of catalyst loading on the reaction. 15 mol%, 10 mol% and 5 mol% triflic acids were all produced similar yield and selectivity, but the substrates weren't fully consumed with 10 mol% and 5 mol% catalyst (entry 10-12). With the toluene and dichloromethane, improved regioselectivity was observed in DCM (entry 13-14). The effect of concentration was also examined (entry 15-18) and best yield was achieved in a 0.05 M solution (entry 16). Finally, further decreasing the temperature to -78 °C didn't improve the reaction outcome.

Table 3.1. Optimization of the reaction conditions.



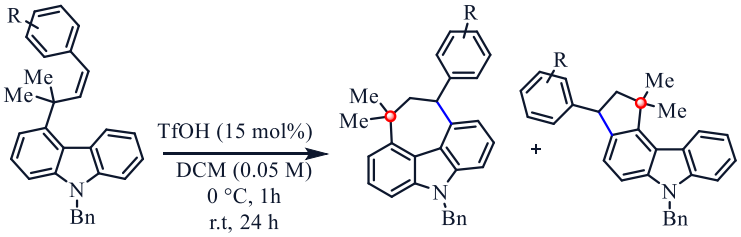
3.1 3.2 3.3

Entry	Catalyst	Loading (mol%)	Concent. (M)	Solvent	Temp. (°C)	Conv. (%)[a]	Yield (%)[a]	rr[b]
1	$PhSO_3H$	25	0.1	DCE	130	100	70	52:48
2[d]	$PhSO_3H$	25	0.1	DCE	130	100	52	30:70
3	$PhSO_3H$	25	0.1	DCE	50	6	3	66:34
4	$Ph_3CB(C_6F_5)_4$	25	0.1	DCE	50	88	< 2	n.d.
5	H_2SO_4	25	0.1	DCE	r.t	45	3	66:34
6	HCl	50	0.1	DCE	r.t.	14	-	-
7	TfOH	25	0.1	DCE	r.t	100	57	78:22
8[c]	$PhSO_3H$	25	0.1	DCE	110	80	41	50:50
9[c]	TfOH	25	0.1	DCE	r.t	50	12	68:32
10	TfOH	15	0.1	DCE	r.t	100	59	79:21
11	TfOH	10	0.1	DCE	r.t	95	59	79:21
12	TfOH	5	0.1	DCE	r.t	95	59	79:21
13	TfOH	15	0.1	PhMe	r.t	100	54	70:30
14	TfOH	15	0.1	DCM	r.t	100	57	81:19
15	TfOH	15	0.2	DCM	r.t	100	46	81:19
16	TfOH	15	0.05	DCM	r.t	100	77	82:18
17	TfOH	15	0.02	DCM	r.t	40	25	80:20
18	TfOH	15	0.08	DCM	r.t	100	63	82:18
19[e]	TfOH	15	0.05	DCM	r.t	100	76	82:18

Reactions were conducted on 0.1 mmol scale. a: by NMR. NMR yield refers to the combined yield of two regioisomers. b: determined by ^{1}H NMR of crude reaction mixture. c: R=H. d: trans alkene, R=Bn, 0.05 mmol. e: at -78 °C 1h, at r.t. 23 h.

With the optimized reaction conditions in hand, we next investigated the scope of this hydroarylation (Table 3.2). In general, 15 mol% triflic acid fully converted substrates, with the exception of *meta*-Br substituted substrate. Electron-donating m*eta*-substituents on the styrene moiety, including methyl and methoxy (entry 2-3), afforded the corresponding cyclohepta[*def*]carbazole in 67% and 43% yield respectively with good regioselectivity. However, *meta*-bromo-substituted substrate failed to go full conversion within 24 hours and cyclized with only a modest preference for the seven-membered ring product (entry 4). Similarly, the *m*-Me substrate afforded the cyclohepta[*def*]carbazole product with a modest preference over 5-membered-ring product despite the 74% combined yield (entry 5). Cyclization favored the seven-membered-ring isomer in 79:21 regioisomeric ratio for *m*-F substituted substrate which was a 71:29 mixture of *cis* and *trans* alkene (entry 6). Finally, 2-naphthyl analogue cyclized with moderate yield and regioselectivity (entry 7).

Table 3.2. Scope of the intramolecular hydroarylation of unactivated carbazole alkenes

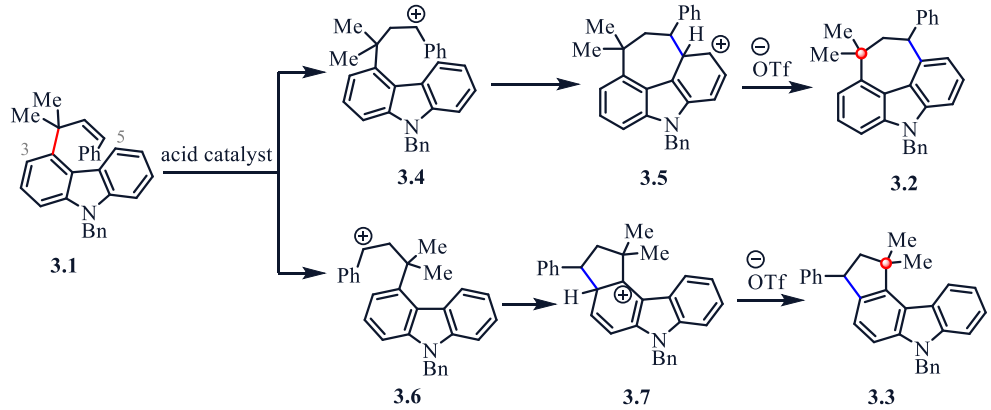


3.1 3.2 3.3

Entry	R	Yield %[a]	$rr_{(3.2:3.3)}$[b]
1[c]	H	77	82:18
2	*m*-Me	84	80:20
3	*m*-OMe	55	78:22
4	*m*-Br	9	60:40
5	*p*-Me	74	61:39
6[d]	*p*-F	86	79:21
7	Ph	51	69:31

Reactions were conducted on 0.2 mmol scale. a: by NMR. NMR yield refers to the combined yield of two regioisomers. b: determined by ^{1}H NMR of crude reaction mixture. c: 0.1 mmol. d: mixture of *cis*:*trans* = 71:29.

According to experimental results we proposed that this transformation is enabled by carbocation formation. The electronic nature of the styrene ring dictates the regioselectivity of the reaction by changing the stability/reactivity of the electrophile which is generated by the protonation of the alkene double bond. The super acid, triflic acid, activates the alkene **3.1** to generate benzylic carbocation. As the single bond in red color can freely rotate, the carbocation can be exit as in **3.4** or **3.6**. The following electrophilic attack at C5 or C3 and subsequent rearomatization affords the final product **3.2** or **3.3** through Friedel-Crafts type electrophilic aromatic substitution reaction.



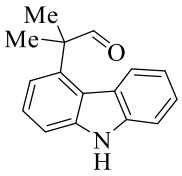
Scheme 3.3 Proposed mechanism

3. Conclusion

In conclusion, we have developed a method to access seven-membered-ring containing benzocycloalkanes in which the seven-membered-ring flanked to the aromatic moiety. The formation of seven-membered-ring was favored at ambient temperature in dilute reaction system. Isomerization of *cis*-configured alkene and the lower product yield with *trans* alkene indicated that the hydroarylation might happened through a stepwise mechanism. The cyclohepta[*def*]carbazole derivatives were obtained from benzyl protected *cis* alkenes, whereas *trans* isomer didn't show regioselectivity. The regioselectivity of the reaction was affected by the electronics of the styrene ring. Electron donating *para*-substituents on the styrene moiety eroded regioselectivity probably *via* changing the stability of the benzylic carbocation. Seven examples with different *meta*- and *para* substituted substrates were prepared. Even though the substrate scope is small on number, our work demonstrates the first general method for the synthesis of 8,8-dimethyl-tetrahydrocyclohepta[*def*]carbazoles.

4. Experimental

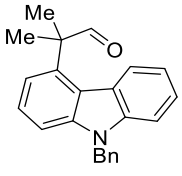
4.1. Preparation of α-Quaternary Aldehyde via Cross-Coupling reaction



S1

2-(9H-carbazol-4-yl)-2-methylpropanal S1. The cross-coupling procedure previously reported by Stokes group[3] was followed with slight modification. To an oven dried 50 mL round bottom flask charged with PTFE coated magnetic stir bar, 390 mg of zinc fluoride (3.75 mmol, 1.5 equivalents), 143.8 mg of bis(dibenzylideneacetone) palladium (0) (0.25 mmol, 0.1 equivalents), and 648 mg 4-bromo-9H-carbazole (with 95% purity) (2.5 mmol, 1.0 equivalents) were added. The reaction flask was then sealed with a rubber septum, degassed and backfilled with nitrogen. Then 0.36 mL of a 2.1 M solution of tri-*tert*-butylphosphine in toluene (0.75 mmol, 0.3 equivalents) and 0.7 mL trimethyl((2-methylprop-1-en-1-yl)oxy)silane (3.75 mmol, 1.5 equivalents) were added followed by 12.5 mL of DMF (0.2 M) at room temperature. The reaction mixture was then allowed to stir at 80 °C for 24 hours under nitrogen. The crude reaction was allowed to cool to room temperature before passed through a pad of Celite. Then the Celite cake was washed with ethyl acetate and the filtrate was concentrated under reduced pressure. Purification by flash chromatography (hexane: ethyl acetate = 90:10) afforded the aldehyde **S1** (308 mg, 52%) as a light-yellow oil. R_f = (hexanes:ethyl acetate = 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.82 (s, 1H), 8.35 (s, 1H), 7.88 (d, *J* = 8.2 Hz, 1H), 7.51 – 7.39 (m, 4H), 7.29 – 7.26 (m, 1H), 7.23 – 7.19 (m, 1H), 1.74 (s, 6H).

4.2. N-H Protection of α-Quaternary Aldehyde



S2

2-(9-benzyl-9H-carbazol-4-yl)-2-methylpropanal S2. To a well stirred solution of the aldehyde from procedure A, 308 mg (1.3 mmol, 1 equivalent), in 13 mL DMF (0.1 M) at 0 °C was added 78 mg of sodium hydride (1.95 mmol, 1.5 equivalents, 60% in mineral oil) in three portions. The reaction was warmed to room temperature and allowed to stir for half hour. After 30 min, the reaction flask was cooled again to 0 °C and 0.23 mL of benzyl bromide (1.95 mmol, 1.5 equivalents) was added dropwise. Then the mixture was warmed to ambient temperature and was allowed to stir overnight. After TLC monitoring showed complete consumption of the starting unprotected aldehyde, the flask was returned to ice bath and quenched with saturated ammonium chloride. The product was extracted with EtOAc and the combined organic layer dried over anhydrous Na_2SO_4. After removing the solvent under reduced pressure, the crude mixture was loaded on a packed silica column. Purification by flash chromatography (hexane: ethyl acetate = 95:5) afforded the N-

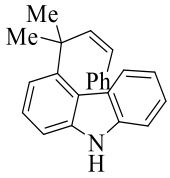
benzylated aldehyde **S2** (395 mg, 93%) as an off white solid. m.p.= 119-120 °C. R_f = 0.48 (hexanes:ethyl acetate = 10:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.89 (s, 1H), 8.0 (d, *J* = 8.2 Hz, 1H), 7.54 – 7.44 (m, 4H), 7.35 (d, *J* = 7.4 Hz, 1H), 7.32 – 7.27 (m, 4H), 7.18 (d, *J* = 6.7 Hz, 2H), 5.58 (s, 2H), 1.80 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.2 (C=O), 141.7 (C), 140.9 (C), 138.1 (C), 137.0 (C), 129.0 (CH), 127.7 (CH), 126.5 (CH), 126.0 (CH), 125.7 (CH), 124.7 (CH), 121.0 (C), 120.9 (C), 119.5 (CH), 117.9 (CH), 109.0 (CH), 108.9 (CH), 51. 2 (C), 46.7 (CH_2), 23.1 (CH_3).

4.3. Preparation of Alkenyl Substrates

A. General Wittig-Olefination Procedure

In an oven-dried 25 mL round bottom flask charged with PTFE coated magnetic stir bar, benzyltriphenylphosphonium bromide (1.5 equivalents) was dissolved in 0.3 M dry solvent. Then 1.7 M potassium *tert*-butoxide solution in THF (1.5 equivalents) or anhydrous potassium *tert*-butoxide was added to the mixture at room temperature. The reaction mixture was continuously being stirred for an additional 20-30 minutes before it was chilled to 0 °C. A solution of aldehyde (1 equivalent) dissolved in minimal amount of dry solvent was slowly added to the ylides drop-wise through syringe. The reaction was then allowed to stir for 24 - 48 hours. Then the reaction was quenched with saturated aqueous NH_4Cl solution and the alkene was extracted with ethyl acetate (3 x 10 mL). The combined organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to afford crude alkene product as a mixture of *E* and *Z* isomers. Purification by silica gel chromatography using gradient elution afforded analytically pure Z alkenes unless otherwise noted.

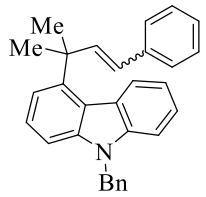
B. Synthesis and characterization of alkenes



S3

(Z)-4-(2-methyl-4-phenylbut-3-en-2-yl)-9H-carbazole S3. General Wittig olefination procedure was followed using 556 mg of 2-(9H-carbazol-4-yl)-2-methylpropanal **S1** (2.34 mmol), 1521 mg of benzyltriphenylphosphonium bromide (3.51 mmol), 7.8 mL of dry DMF and 2 mL of a 1.7 M potassium *tert*-butoxide solution in THF. The reaction was run at room temperature 24 hours. Purification by flash column chromatography (hexanes:ethyl acetate = 10:1) afforded the *cis*-configured alkene **S3** (390 mg, 54%) as an

off white solid. R_f = 0.29 (hexanes:ethyl acetate = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.41 (d, *J* = 8.2 Hz, 1H), 7.92 (s, 1H), 7.44 – 7.31 (m, 2H), 7.28 – 7.09 (m, 3H), 7.06 (dd, J = 7.7, 1.2 Hz, 1H), 6.73 (app. t, *J* = 7.3 Hz, 1H), 6.65 (app. t, *J* = 7.4 Hz, 2H), 6.39 (d, *J* = 12.4 Hz, 1H), 6.30 (d, *J* = 7.8 Hz, 2H), 6.21 (d, *J* = 12.4 Hz, 1H), 1.77 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.1 (C), 140.3 (C), 140.2 (CH), 139.5 (C), 137.2 (C), 128.9 (CH), 127.6 (CH), 126.5 (CH), 126.3 (CH), 125.4 (2CH), 124.8 (CH), 122.6 (C), 121.2 (C), 118.0 (CH), 117.3 (CH), 110.0 (CH), 109.0 (CH), 41.5 (C), 30.6 (CH_3).

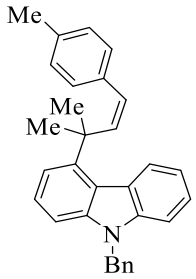


3.1a

(Z)- and (E)-9-benzyl-4-(2-methyl-4-phenylbut-3-en-2-yl)-9H-carbazole 3.1a. General Wittig olefination procedure was followed using 142 mg of 2-(9-benzyl-9H-carbazol-4-yl)-2-methylpropanal **S2** (0.43 mmol), 279 mg of benzyltriphenylphosphonium bromide (0.65 mmol), 2.15 mL of dry THF and 0.33 mL of a 1.7 M potassium *tert*-butoxide solution in THF (1.3 equivalent). The reaction was run at room temperature for 24 hours. Purification by flash column chromatography (hexanes:ethyl acetate = 10:1) afforded the *cis*-configured alkene **3.1a** (104 mg, 60%) as an off white solid. R_f = 0.51 (hexanes:ethyl acetate = 10:1). *Trans* alkene was isolated as a white solid (45 mg, 16%). R_f = 0.49 (hexanes:ethyl acetate = 10:1).

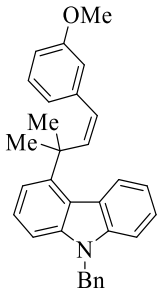
Spectral data for **(Z)-9-benzyl-4-(2-methyl-4-phenylbut-3-en-2-yl)-9H-carbazole 3.1a.** ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.53 (d, *J* = 8.1 Hz, 1H), 7.48 – 7.41 (m, 1H), 7.34 – 7.20 (m, 7H), 7.10 – 7.02 (m, 3H), 6.76 (t, *J* = 7.3 Hz, 1H), 6.66 (t, *J* = 7.6 Hz, 2H), 6.47 (d, *J* = 12.4 Hz, 1H), 6.36 (d, *J* = 7.5 Hz, 2H), 6.29 (d, *J* = 12.4 Hz, 1H), 5.44 (s, 2H), 1.86 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.9 (C), 141.5 (C), 140.6 (C), 140.2 (CH), 137.4 (C), 137.0 (C), 128.8 (CH), 127.6 (CH), 127.4 (CH), 126.7 (CH), 126.4 (CH), 126.3 (CH), 125.4 (CH), 125.3 (CH), 124.8 (CH), 122.1 (C), 120.8 (C), 117.8 (CH), 117.4 (CH), 108.2 (CH), 107.1 (CH), 46.4 (CH_2), 41.5 (C), 30.7 (CH_3).

Spectral data for **(E)-9-benzyl-4-(2-methyl-4-phenylbut-3-en-2-yl)-9H-carbazol**e **3.1a**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (d, *J* = 8.2 Hz, 1H), 7.37 – 7.01 (m, 17H), 6.71 (d, *J* = 16.3 Hz, 1H), 6.13 (d, *J* = 16.3 Hz, 1H), 5.43 (s, 2H), 1.72 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.8 (C), 141.9 (C), 140.9 (C), 140.3 (CH), 138.3 (C), 137.4 (C), 128.9 (CH), 128.5 (d, *J* = 1 Hz, CH), 128.3 (CH), 127.6 (CH), 127.0 (CH), 126.9 (CH), 126.5 (CH), 126.2 (CH), 125.7 (CH), 125.0 (CH), 121.9 (C), 120.7 (C), 118.8 (CH), 117.6 (CH), 108.5 (CH), 108.0 (CH), 46.7 (CH_2), 42.0 (C), 30.1 (CH_3).



3.1b

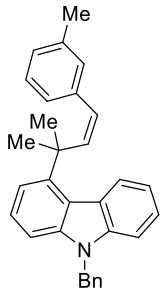
(Z)-9-benzyl-4-(2-methyl-4-(p-tolyl)but-3-en-2-yl)-9H-carbazole 3.1b. General Wittig olefination procedure was followed using 165 mg of 2-(9-benzyl-9H-carbazol-4-yl)-2-methylpropanal **S2** (0.5 mmol), 336 mg of (4-methylbenzyl)triphenylphosphonium bromide (0.75 mmol), 1.7 mL of dry THF and 0.38 mL of a 1.7 M potassium *tert*-butoxide solution in THF (1.3 equivalent). The reaction was run at room temperature for 24 hours. Purification by flash column chromatography (hexanes:benzene = 20:1) afforded the *cis*-configured alkene as a white solid (125 mg, 60%). R_f = 0.16 (hexanes:benzene = 9:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.57 (d, *J* = 8.1 Hz, 1H), 7.50 – 7.43 (m, 1H), 7.36 – 7.24 (m, 7H), 7.12 (app. t, *J* = 6.9 Hz, 3H), 6.55 (d, *J* = 7.6 Hz, 2H), 6.47 (d, *J* = 12.4 Hz, 1H), 6.35 (d, *J* = 7.5 Hz, 2H), 6.29 (d, *J* = 12.4 Hz, 1H), 5.46 (s, 2H), 2.13(s, 3H), 1.88 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.4 (C), 141.6 (C), 140.7 (C), 140.1 (CH), 137.5 (C), 134.7 (C), 134.3 (C), 128.9 (CH), 128.8 (CH), 127.7 (CH), 127.4 (CH), 127.1 (CH), 126.7 (CH), 126.4 (CH), 125.4 (CH), 124.8 (CH), 122.2 (C), 120.8 (C), 117.9 (CH), 117.3 (CH), 108.3 (CH), 107.0 (CH), 46.5 (CH_2), 41.5 (C), 30.6 (CH_3), 21.1 (CH_3).



3.1c

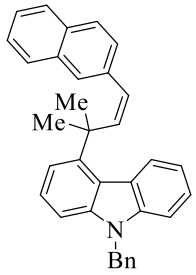
(Z)-9-benzyl-4-(4-(3-methoxyphenyl)-2-methylbut-3-en-2-yl)-9H-carbazole 3.1c. General Wittig olefination procedure was followed using 227 mg of 2-(9-benzyl-9H-carbazol-4-yl)-2-methylpropanal **S2** (0.7 mmol), 440 mg of (3-methoxybenzyl)triphenylphosphonium bromide (1.05 mmol), 2.3 mL of dry DMF and 118 mg of potassium *tert*-butoxide (1.05 equivalent). The reaction was run at 80 °C for 24 hours. Purification by flash column chromatography (hexane:benzene = 10:1) afforded *cis* isomer (198 mg, 65%) as colorless oil (total yield of the mixture is 87%). R_f = 0.35 (hexane:benzene = 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52 (d, *J* = 8.1 Hz, 1H), 7.45 – 7.41 (m, 1H), 7.33 – 7.23 (m, 7H), 7.09 – 7.05 (m, 3H), 6.56 (t, *J* = 7.9 Hz, 1H), 6.44 (d,

J = 12.4 Hz, 1H), 6.33 (dd, *J* = 8.2, 2.5 Hz, 1H), 6.26 (d, *J* = 12.4 Hz, 1H), 5.96 (d, *J* = 7.5 Hz, 1H), 5.86 (s, 1H), 5.42 (s, 2H), 3.38 (s, 3H), 1.86 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.8 (C), 142.9 (C), 141.6 (C), 140.7 (C), 140.2 (CH), 138.4 (C), 137.4 (C), 128.9 (CH), 128.7 (CH), 127.5 (CH), 127.3 (CH), 126.6 (CH), 126.5 (CH), 125.4 (CH), 124.8 (CH), 122.4 (C), 120.8 (C), 120.5 (CH), 117.9 (CH), 117.5 (CH), 112.2 (CH), 112.1 (CH), 108.2 (CH), 107.2 (CH), 54.8 (OCH_3), 46.5 (CH_2), 41.6 (C), 30.8 (CH_3).



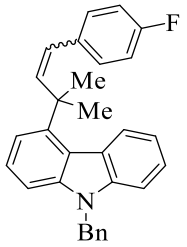
3.1d

(Z)-9-benzyl-4-(2-methyl-4-(m-tolyl)but-3-en-2-yl)-9H-carbazole 3.1d. General Wittig olefination procedure was followed using 327 mg of 2-(9-benzyl-9H-carbazol-4-yl)-2-methylpropanal **S2** (1 mmol), 604 mg of (3-methylbenzyl)triphenylphosphonium chloride (1.5 mmol), 3.3 mL of dry DMF and 168 mg of potassium *tert*-butoxide (1.5 equivalent). The reaction was run at 50 °C for 24 hours. Purification by flash column chromatography (hexanes:benzene = 10:1) afforded cis isomer (108 mg, 37%) as white solid (total yield of the mixture is 71%). m.p.= 104-107 °C. R_f = 0.44 (hexanes:benzene = 4:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.56 (d, *J* = 8.1 Hz, 1H), 7.49 – 7.45 (m, 1H), 7.36 – 7.26 (m, 7H), 7.10 (d, *J* = 7.2 Hz, 3H), 6.63– 6.59 (m, 2H), 6.46 (d, *J* = 12.4 Hz, 1H), 6.29 (d, *J* = 12.4 Hz, 1H), 6.18 (app. s, 2H), 5.45 (s, 2H), 1.96 (s, 3H), 1.89 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.2 (C), 141.5 (C), 140.6 (C), 140.0 (CH), 137.4 (C), 136.8 (C), 135.6 (C), 128.9 (CH), 128.8 (CH), 128.7 (CH), 127.4 (CH), 126.6 (CH), 126.4 (CH), 126.2 (CH), 126.0 (CH), 125.3 (CH), 122.3 (C), 120.8 (C), 117.8 (CH), 117.3 (CH), 108.1 (CH), 107.1 (CH), 46.4 (CH_2), 41.5 (C), 30.7 (CH_3), 21.2 (CH_3).



3.1e

(Z)-9-benzyl-4-(2-methyl-4-(naphthalen-2-yl)but-3-en-2-yl)-9H-carbazole 3.1e. General Wittig olefination procedure was followed using 327 mg of 2-(9-benzyl-9H-carbazol-4-yl)-2-methylpropanal **S2** (1 mmol), 725 mg of (Naphthalen-2-ylmethyl)triphenyl-phosphonium bromide (1.5 mmol), 3.3 mL of dry THF and 168 mg of potassium *tert*-butoxide (1.5 equivalent). The reaction was run at 50 °C for 24 hours and didn't go to completion. Purification by flash column chromatography (hexanes:ethyl acetate = 95:5) afforded *cis* isomer (135 mg, 30%) as off white solid (total isolated yield of the mixture is 50%). R_f = 0.3 (hexanes:ethyl acetate = 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53 (d, *J* = 8.1 Hz, 1H), 7.57 – 7.52 (m, 1H), 7.44 (m, 1H), 7.34 – 7.25 (m, 5H), 7.25 – 7.18 (m, 4H), 7.10 – 7.04 (m, 2H), 6.99 – 6.93 (m, 2H), 6.78 (d, *J* = 7.8 Hz, 1H), 6.66 (s, 1H), 6.54 (d, *J* = 12.4 Hz, 1H), 6.40 (dd, *J* = 8.4, 1.5 Hz, 1H), 6.35 (d, *J* = 12.4 Hz, 1H), 5.53 (s, 2H), 1.88 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.0 (C), 141.4 (C), 140.7 (C), 140.7 (CH), 137.4 (C), 134.6 (C), 132.1 (CH), 131.4 (CH), 128.8 (CH), 128.7 (CH), 127.9 (CH), 127.3 (CH), 127.2 (CH), 126.5 (CH), 126.4 (CH), 126.3 (CH), 126.1 (CH), 125.4 (CH), 125.3 (CH), 125.1 (CH), 125.0 (CH), 124.9 (CH), 122.3 (C), 120.8 (C), 117.8 (CH), 117.3 (CH), 108.2 (CH), 107.1 (CH), 46.2 (CH_2), 41.6 (C), 30.8 (CH_3).

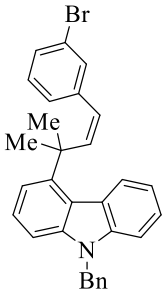


3.1f

(Z)- and (E)-9-benzyl-4-(4-(4-fluorophenyl)-2-methylbut-3-en-2-yl)-9H-carbazole 3.1f. General Wittig olefination procedure was followed using 231 mg of 2-(9-benzyl-9H-carbazol-4-yl)-2-methylpropanal **S2** (0.7 mmol), 480 mg of (4-Fluorobenzyl)triphenylphosphonium bromide (1.05 mmol), 2.3 mL of dry DMF and 0.54 mL of a 1.7 M potassium *tert*-butoxide solution in THF (1.3 equivalent). The reaction was run at 80 °C for 48 hours and didn't go to completion**.** Purification by flash column chromatography (hexanes:ethyl acetate = 97:3) afforded inseparable Z and E stereoisomers (Z:E = 71:29, 155 mg, 52%) as colorless oil. R_f = 0.48 (hexane:EtOAc = 10:1). Selected spectral data for Z isomer: ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.45 (d, *J* = 8.1 Hz, 1H), 7.08

(dd, *J* = 7.9, 0.9 Hz, 1H), 7.05 (d, *J* = 7.1 Hz, 2H), 6.36 (d, *J* = 12.3 Hz, 1H), 5.42 (s, 2H), 1.84 (s, 6H). Other peaks in aromatic region were obscured by E isomer.[13]C NMR (125 MHz, $CDCl_3$): δ 160.6 (d, *J* = 243.8 Hz, C-F), 142.4 (C), 141.5 (C), 140.6 (C), 140.4 (CH), 137.4 (C), 132.7 (d, *J* = 3.3 Hz, C), 129.0 (d, *J* = 1.2 Hz, CH), 128.9 (CH), 127.6 (CH), 127.5 (CH), 126.7 (d, *J* = 1.7 Hz, CH), 126.4 (CH), 125.5 (CH), 124.9 (CH), 122.1 (C), 120.8 (C), 117.8 (CH), 117.5 (CH), 112.7 (d, *J* = 21.2 Hz, CH), 108.2 (CH), 107.2(CH), 46.3 (CH_2), 41.5 (C), 30.8 (CH_3). [19] F NMR (470 MHz, $CDCl_3$): δ -117.3 (m).

Selected spectral data for E isomer: [1]H NMR (500 MHz, $CDCl_3$): δ 8.33 (d, *J* = 8.2 Hz, 1H), 6.93 (t, *J* = 8.7 Hz, 2H), 6.76 (d, *J* = 16.3 Hz, 1H), 5.58 (s, 2H), 1.85 (s, 6H). other peaks in aromatic region were obscured by Z isomer. [13]C NMR (125 MHz, $CDCl_3$): δ 162.0 (d, *J* = 245.4 Hz, C-F), 143.7 (C), 141.9 (C), 140.9 (C), 140.1 (d, J = 2.0 Hz, C), 137.4 (C), 134.4 (d, J = 7.0 Hz, C), 127.7 (CH), 127.2 (CH), 127.0 (CH), 125.7 (CH), 125.1 (CH), 121.9 (C), 120.7 (C), 118.7 (CH), 117.6 (CH), 115.4 (d, *J* = 21.5 Hz, CH), 108.6 (CH), 108.1 (CH), 46.7 (CH_2), 41.9 (C), 30.1 (CH_3). [19] F NMR (470 MHz, $CDCl_3$): δ -115.9 (tt, *J* = 8.7, 5.5 Hz).



3.1g

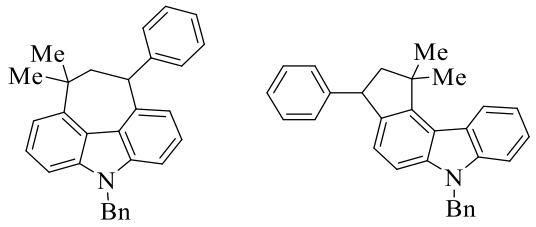
(Z)-9-benzyl-4-(4-(3-bromophenyl)-2-methylbut-3-en-2-yl)-9H-carbazole 3.1g. General Wittig olefination procedure was followed using 260 mg of 2-(9-benzyl-9H-carbazol-4-yl)-2-methylpropanal **S2** (0.8 mmol), 610 mg of (3-bromobenzyl)triphenylphosphonium bromide (1.2 mmol), 2.7 mL of dry DMF and 134 mg of potassium *tert*-butoxide (1.2 equivalent). The reaction was run at 80 °C for 48 hours and didn't go to completion. Purification by flash column chromatography (hexane:benzene = 4:1) afforded *cis* isomer (68 mg, 17%) as white solid (total isolated yield of the mixture is 55%). m.p.= 137-139 °C. R_f = 0.47 (hexane:benzene = 10:1). [1]H NMR (500 MHz, $CDCl_3$): δ 8.41 (d, *J* = 8.1 Hz, 1H), 7.41– 7.47 (m, 1H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.34 – 7.25 (m, 5H), 7.21 (d, *J* = 7.4 Hz, 1H), 7.11 (d, *J* = 7.1 Hz, 2H), 7.05 (d, *J* = 7.9 Hz, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 6.41 (t, *J* = 7.8 Hz, 1H), 6.32 (d, *J* = 12.4 Hz, 1H), 6.27 (m, 2H), 6.13 (d, *J* = 7.6 Hz, 1H), 5.43 (s, 2H), 1.86 (s, 6H). [13]C NMR (125 MHz, $CDCl_3$): δ 142.0 (C), 141.4 (C), 141.2 (CH), 140.7 (C), 138.8 (C), 137.5 (C), 130.3 (CH), 128.8 (CH), 128.1 (CH), 127.5 (d, *J* = 1.9 Hz, CH), 127.1 (CH), 126.5 (CH), 126.4 (CH), 125.9 (CH), 125.6 (CH), 122.1 (C), 120.6 (C), 120.1 (C), 117.8 (CH), 117.5 (CH), 108.4 (CH), 107.4 (CH), 46.6 (CH_2), 41.6 (C), 30.8 (CH_3).

4.4. Brønsted acid catalyzed hydroarylation of carbazole alkenes

A. General procedure

In a dry 5 mL round bottom flask charged with PTFE coated magnetic stir bar, the *cis* alkene (0.2 mmol, 1.0 equivalent) was dissolved in 0.05 M of anhydrous dichloromethane and the solution is cooled to 0 °C. After 10 mins, triflic acid (15 mol%) was slowly added to the solution and let it stir for one hour at 0 °C. After one hour, the reaction mixture was removed from ice bath and let it stir for 24 hours at room temperature. The reaction solution was quenched by saturated $NaHCO_3$ and extracted with DCM three times. The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford the crude product. Purification by silica gel chromatography using gradient elution afforded corresponding cyclized product.

B. Hydroarylation and characterization of the products

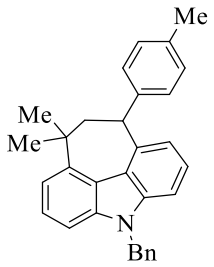


3.2a **3.3a**

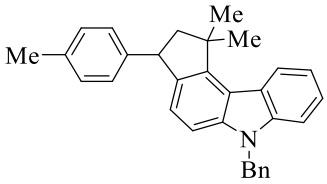
The general cyclization procedure was followed using 40.5 mg of alkene **3.1a** (0.1 mmol), 1.34 uL of TfOH (15 mol%) and 2 mL of anhydrous DCM (0.05 M) in a 4 mL vial. The crude NMR yield of the mixture **3.2a** and **3.3a** was 77% (rr = 82:18). The regioisomers were purified by flash column chromatography with hexanes:benzene = 4:1.

4-benzyl-8,8-dimethyl-10-phenyl-4,8,9,10-tetrahydrocyclohepta[*def*]carbazole 3.2a. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 – 7.17 (m, 15H), 6.51 – 6.46 (m, 1H), 5.53 (s, 2H), 4.73 (apt. d, *J* = 11.6 Hz, 1H), 2.89 (dd, *J* = 14.2, 11.9 Hz, 1H), 2.16 (dd, *J* = 14.3, 2.1 Hz, 1H), 1.62 (s, 3H), 1.51 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.9 (C), 146.6 (C), 141.4 (C), 141.1 (C), 140.8 (C), 137.4 (C), 128.9 (CH), 128.8 (CH), 127.6 (CH), 126.7 (CH), 126.5 (CH), 125.6 (CH), 125.1 (CH), 120.2 (CH), 122.3 (C), 121.1 (C), 116.4 (CH), 106.3 (CH), 106.1 (CH), 49.1 (CH_2), 47.6 (CH), 46.9 (CH_2), 39.5 (C), 32.0 (CH_3), 30.9 (CH_3).

6-benzyl-1,1-dimethyl-3-phenyl-1,2,3,6-tetrahydrocyclopenta[*c*]carbazole 3.3a. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (d, *J* = 8.0 Hz, 1H), 7.48 – 7.12 (m, 14H), 6.94 (d, *J* = 8.3 Hz, 1H), 5.52 (s, 2H), 4.57 (apt. t, *J* = 8.9 Hz, 1H), 2.65 (dd, *J* = 12.7, 8.3 Hz, 1H), 2.20 (dd, *J* = 9.3, 3.3 Hz, 1H), 1.86 (s, 3H), 1.72 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.7 (C), 146.6 (C), 141.4 (C), 141.3 (C), 137.4 (C), 137.3 (C), 128.9 (CH), 128.6 (CH), 127.6 (CH), 126.6 (CH), 126.3 (CH), 125.3 (CH), 124.9 (CH), 123.2 (CH), 119.0 (CH), 121.7 (C), 118.5 (C), 109.0 (CH), 107.8 (CH), 55.0 (CH_2), 49.8 (CH), 46.9 (CH_2), 44.9 (C), 29.1 (CH_3), 26.4 (CH_3).



3.2b

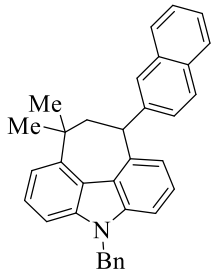


3.3b

The general cyclization procedure was followed using 83.8 mg of alkene **3.1b** (0.2 mmol), 2.67 uL of TfOH (15 mol%) and 4 mL of anhydrous DCM (0.05 M) in a 5 mL round bottom flask. The crude NMR yield of the mixture of **3.2b** and **3.3b** was 74% (rr = 61:39). The regioisomers were obtained by flash column chromatography with hexanes:benzene = 6:1 as an inseparable mixture. R_f = 0.31 (hexanes:benzene = 4:1).

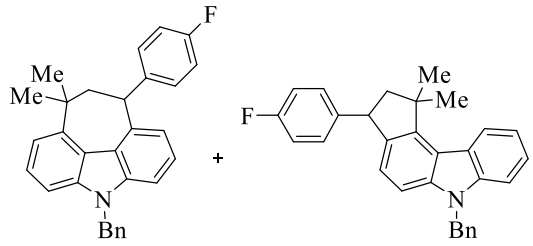
Selected spectral date for **4-benzyl-8,8-dimethyl-10-(p-tolyl)-4,8,9,10-tetrahydrocyclohepta[*def*]carbazole 3.2b.** ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.54 – 6.48 (m, 1H), 5.53 (s, 2H), 4.70 (apt. d, *J* = 11.7 Hz, 1H), 2.88 (dd, *J* = 14.2, 11.9 Hz, 1H), 2.40 (s, 3H), 2.13 (dd, *J* = 14.3, 2.1 Hz, 1H), 1.61 (s, 3H), 1.50 (s, 3H). Other peaks in aromatic region were obscured by **3.3b**. ^{13}C NMR (500 MHz, $CDCl_3$): δ 146.6 (C), 145.0 (C), 141.6 (C), 141.1 (C), 140.8 (C), 137.5 (C), 136.0 (C), 128.9 (CH), 127.6 (CH), 126.7 (CH), 126.6 (CH), 125.6 (CH), 125.1 (CH), 120.2 (CH), 116.4 (CH), 106.3 (CH), 106.0 (CH), 49.3 (CH_2), 47.2 (CH), 46.9 (CH_2), 44.8 (C), 32.1 (CH_3), 30.9 (CH_3), 21.3 (CH_3).

Selected spectral date for **6-benzyl-1,1-dimethyl-3-(*p*-tolyl)-1,2,3,6-tetrahydrocyclopenta[*c*]carbazole 3.3b.** ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.38 (d, *J* = 8.0 Hz, 1H), 6.95 (dd, *J* = 8.3 Hz, 1H), 5.53 (s, 2H), 4.53 (apt. t, *J* = 8.9 Hz, 1H), 2.64 (dd, *J* = 12.7, 8.3 Hz, 1H), 2.36 (s, 3H), 2.17 (dd, *J* = 12.6, 9.6 Hz, 1H), 1.86 (s, 3H), 1.71 (s, 3H). Other peaks in aromatic region were obscured by **3.2b.** ^{13}C NMR (500 MHz, $CDCl_3$): δ 141.6 (C), 141.3 (C), 137.4 (C), 135.8 (C), 125.2 (CH), 124.9 (CH), 123.2 (CH), 118.5 (CH), 109.0 (CH), 107.8 (CH), 55.1 (CH_2), 49.4 (CH), 29.1 (CH_3), 26.4 (CH_3), 21.3 (CH_3).



3.2e

4-benzyl-8,8-dimethyl-10-(naphthalen-2-yl)-4,8,9,10-tetrahydrocyclohepta[*def*] carbazole 3.2e. The general cyclization procedure was followed using 90.5 mg of alkene **3.1e** (0.2 mmol), 2.68 uL of TfOH (15 mol%) and 4 mL of anhydrous DCM (0.05 M) in a 5 mL round bottom flask. The crude NMR yield of the mixture of **3.2e** and **3.3e** was 51% (rr = 69:31). The regioisomers were isolated by flash column chromatography with hexanes:benzene = 6:1. R_f = 0.26 (hexanes:benzene = 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (m, 4H), 7.43-7.28 (m, 3H), 7.21 – 7.02 (m, 10H), 6.39 (d, *J* = 7.2 Hz, 1H), 5.43 (s, 2H), 4.80 (apt. d, *J* = 11.6 Hz, 1H), 2.87 (dd, *J* = 14.1, 12.0 Hz, 1H), 2.09 (d, *J* = 14.3 Hz, 1H), 1.52 (s, 3H), 1.44 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.6 (C), 141.1 (C), 140.8 (C), 137.4 (C), 132.5 (C), 127.9 (CH), 127.8 (C), 127.6 (CH), 127.3 (C), 126.2 (C), 129.0 (CH), 128.5 (CH), 127.9 (CH), 127.6 (CH), 126.7 (CH), 125.7 (CH), 125.6 (CH), 125.1 (CH), 122.4 (C), 121.1 (C), 120.4 (CH), 116.5 (CH), 106.4 (CH), 106.2 (CH), 49.1 (CH_2), 47.7 (CH), 46.9 (CH_2), 39.6 (C), 32.1 (CH_3), 31.0 (CH_3).



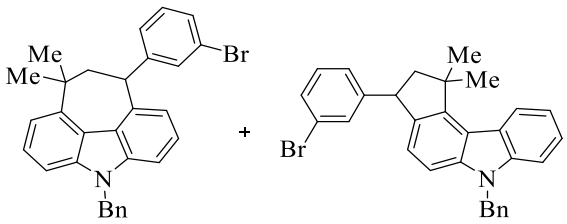
3.2f **3.3f**

The general cyclization procedure was followed using 84 mg of 71:29 mixture of cis:trans alkene **3.1f** (0.2 mmol), 2.67 uL of TfOH (15 mol%) and 4 mL of anhydrous DCM (0.05 M) in a 5 mL round bottom flask. The crude NMR yield of the mixture of **3.2f** and **3.3f** was 86% (rr = 79:21). The regioisomers **3.2f** and **3.3f** were isolated by flash column chromatography with hexanes:benzene = 6:1. R_f = 0.23 (pentane:dichloromethane = 10:1).

Selected spectral data for **4-benzyl-10-(4-fluorophenyl)-8,8-dimethyl-4,8,9,10-tetrahydrocyclohepta[def] carbazole 3.2f.** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 – 7.41 (m, 2H), 7.30 – 7.21 (m, 10H), 7.08 (t, *J* = 8.8 Hz, 2H), 6.49 – 6.43 (m, 1H), 5.54 (s, 2H), 4.73 (apt. d, *J* = 11.6 Hz, 1H), 2.86 (dd, *J* = 14.2, 11.9 Hz, 1H), 2.12 (dd, *J* = 14.3, 2.1 Hz, 1H), 1.63 (s, 3H), 1.50 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.6 (d, *J* = 244.1 Hz, C-F), 146.4 (C), 143.7 (d, *J* = 3.4 Hz, CH), 141.1(C), 141.0 (C), 140.8 (C), 137.4 (C), 129.0 (CH), 127.6 (CH), 126.7 (CH),

125.7 (CH), 125.1 (CH), 122.3 (C), 121.0 (C), 120.1 (CH), 116.4 (CH), 106.3 (d, J = 19.5 Hz, CH), 49.3 (CH_2), 46.9 (CH_2), 46.8 (CH), 39.5 (C), 32.0 (CH_3), 30.9 (CH_3). ^{19} F NMR (376 MHz, $CDCl_3$): δ -117 (tt, J = 8.8, 5.5 Hz).

Selected spectral data for **6-benzyl-3-(4-fluorophenyl)-1,1-dimethyl-1,2,3,6-tetrahydrocyclopenta[c]carbazole 3.3f.** ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.39 (d, J = 8.0 Hz, 1H), 6.92 (d, J = 8.3 Hz, 1H), 5.54 (s, 2H), 4.56 (apt. t, J = 8.8 Hz, 1H), 2.65 (dd, J = 12.7, 8.2 Hz, 1H), 2.16 (dd, J = 12.6, 9.6 Hz, 1H), 1.86 (s, 3H), 1.72 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 125.3 (CH), 124.9 (CH), 123.0 (CH), 119.1 (CH), 115.2 (CH), 109.1 (CH), 107.9 (CH), 55.2 (CH_2), 48.9 (CH), 46.9 (CH_2), 44.9 (C), 29.1 (CH_3), 26.4 (CH_3). ^{19} F NMR (376 MHz, $CDCl_3$): δ -117.4 (tt, J = 8.8, 5.5 Hz).



3.2g **3.3g**

The general cyclization procedure was followed using 48 mg of alkene **3.1g** (0.1 mmol), 1.32 uL of TfOH (15 mol%) and 2 mL of anhydrous DCM (0.05 M) in a 4 mL round bottom flask. The crude NMR yield of the mixture of **3.2g** and **3.3g** was 9% (rr = 60:40). This compound isn't purified due to the low product yield.

References

[1] T. V. Nguyen, J. M. Hartmann, D. Enders, *Synthesis*, **2013**, *45*, 845-873.

[2] V. Ji Ram, A. Sethi, M. Nath, R. Pratap, Five-Membered Heterocycles. In *The Chemistry of Heterocycles*; Elsevier, 2019; pp 149–478.

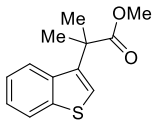
[3] X. Cai, A. Keshavarz, J. D. Omaque, B. J. Stokes, *Org. Lett.* **2017**, *19*, 2626-2629.

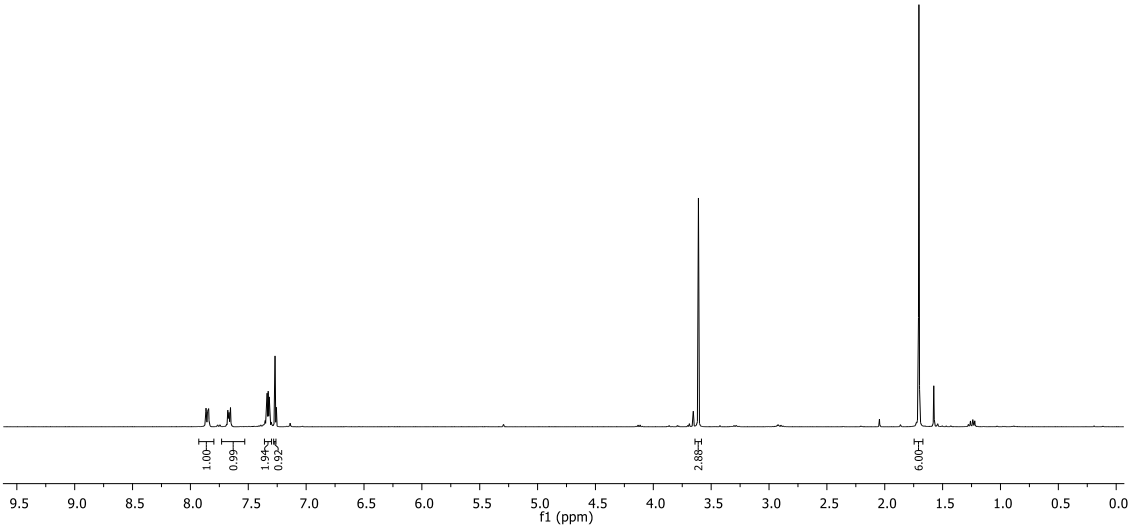
CONCLUSION

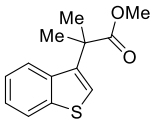
Brønsted acid catalyzed intramolecular alkene hydroarylation reactions are a direct and environmentally friendly way to access various types of benzocycloalkanes. We have developed methods to access the synthetically challenging and medicinally interesting vicinal quaternary center containing spirocycles and seven-membered-ring incorporated benzocycloalkanes from unactivated alkenes. I have studied the catalytic BA catalyzed functionalization of C3 substituted benzothiophene and C4 substituted carbazole alkenes in which styrene and heteroaromatic rings are linked by a benzylic geminal dialkyl group. In both systems, the target compounds were obtained from *cis*-configured alkenes at ambient temperature. In addition, electronics of styrene ring was found crucial in regioselectivity of the hydroarylation. The dearomative spirocyclization of C3 substituted benzothiophene alkenes afforded various vicinal quaternary center containing spirocycles with triflic acid. The dearomatization happened on the benzothiophene ring and the styrenyl double bond reserved under super acidic condition. With C4 substituted carbazole alkenes, formation of seven-membered-ring products favored over five-membered.

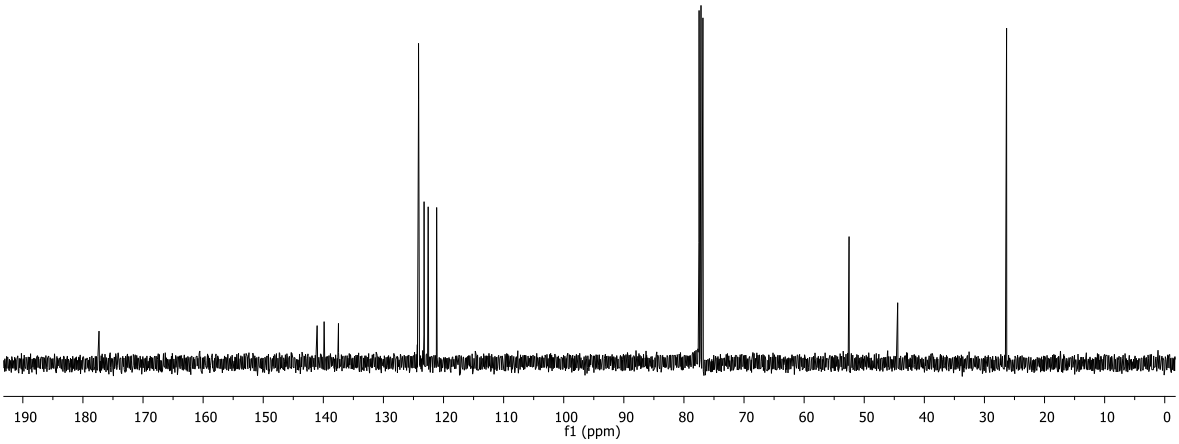
Our studies provide the first general method for the Brønsted acid catalyzed dearomative spirocyclization to access vicinal quaternary centers and first general method for tetrahydrocyclohepta[*def*]carbazole synthesis.

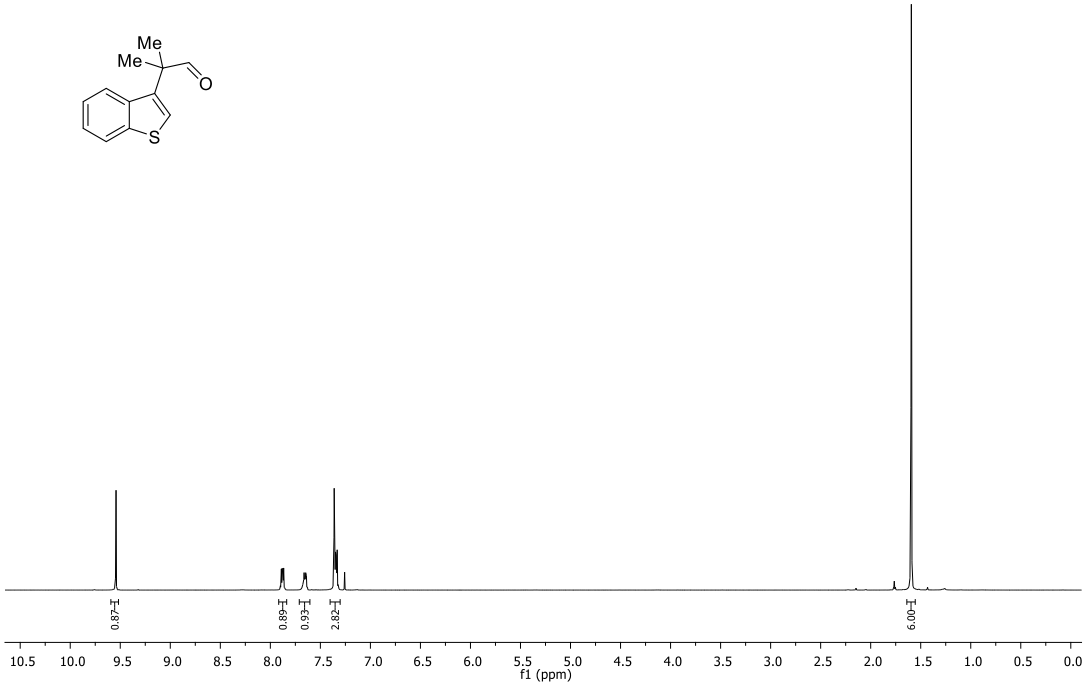
Appendix A: NMR Spectra







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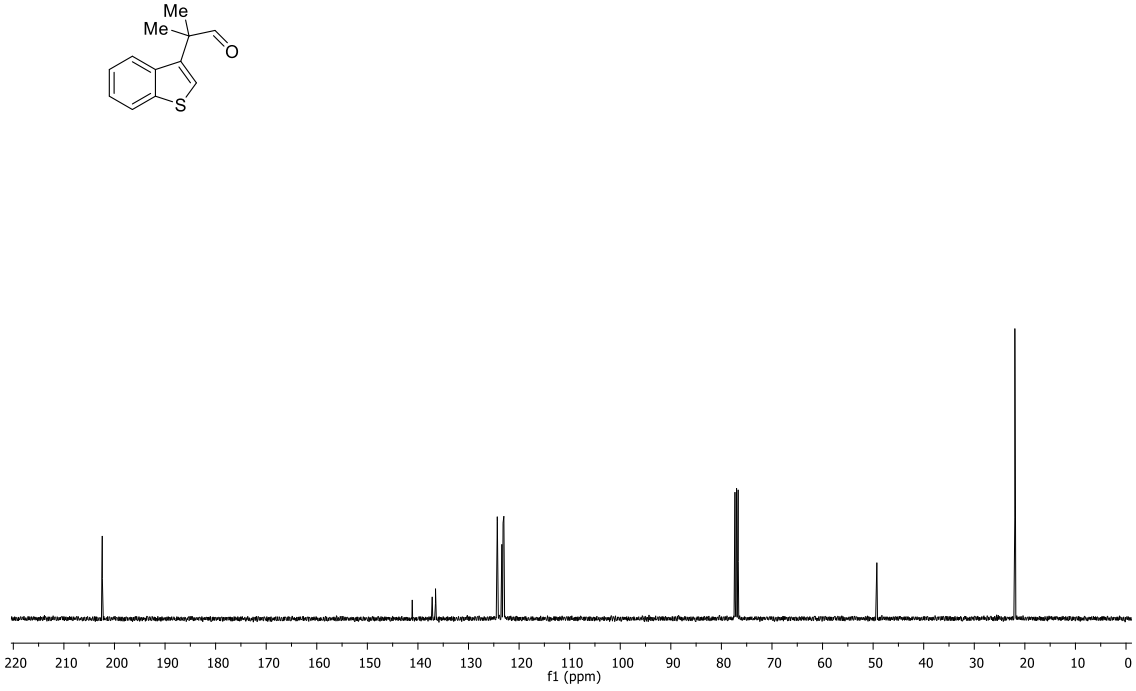
Me
O
S
0.87
0.89
0.93
2.82
6.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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Me
O
S
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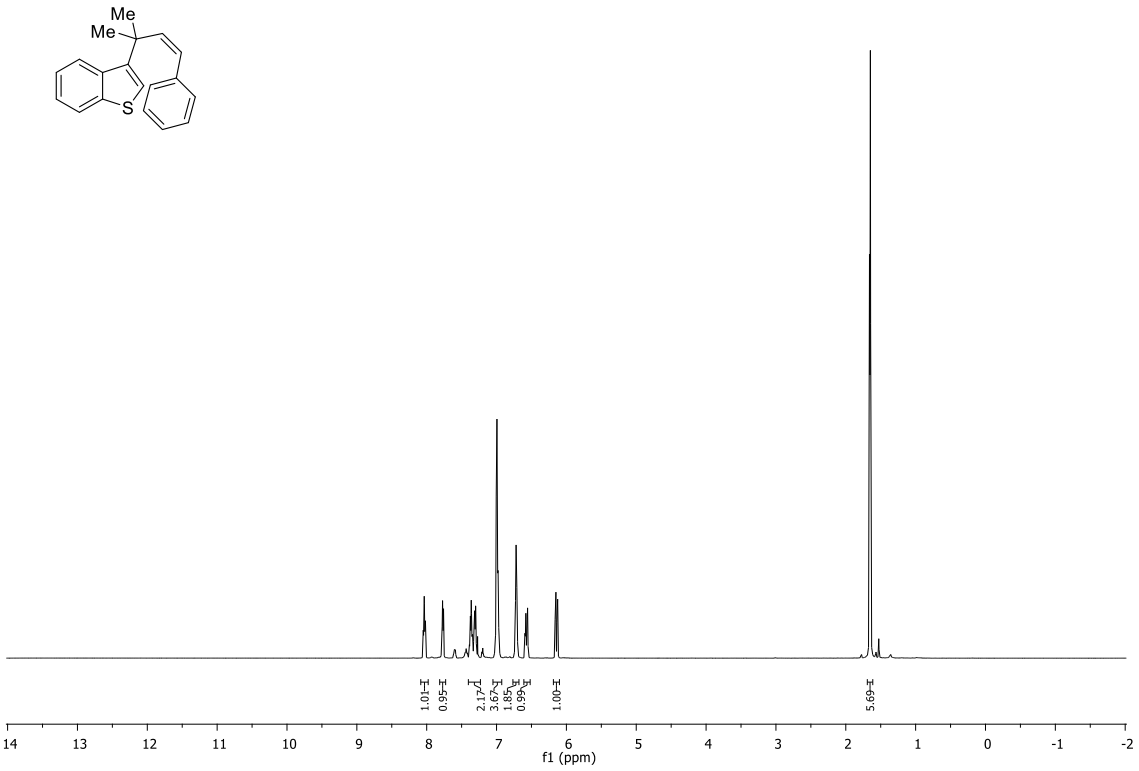
f1 (ppm)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5.69
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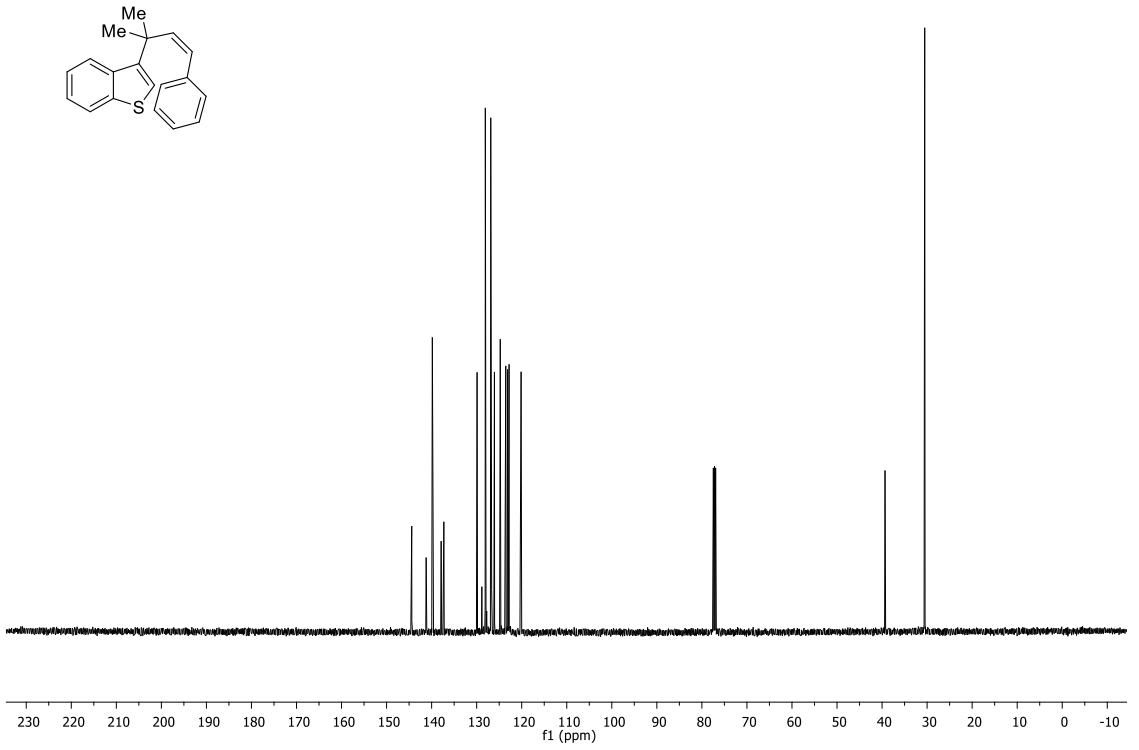
f1 (ppm)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Me
S
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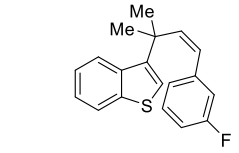
f1 (ppm)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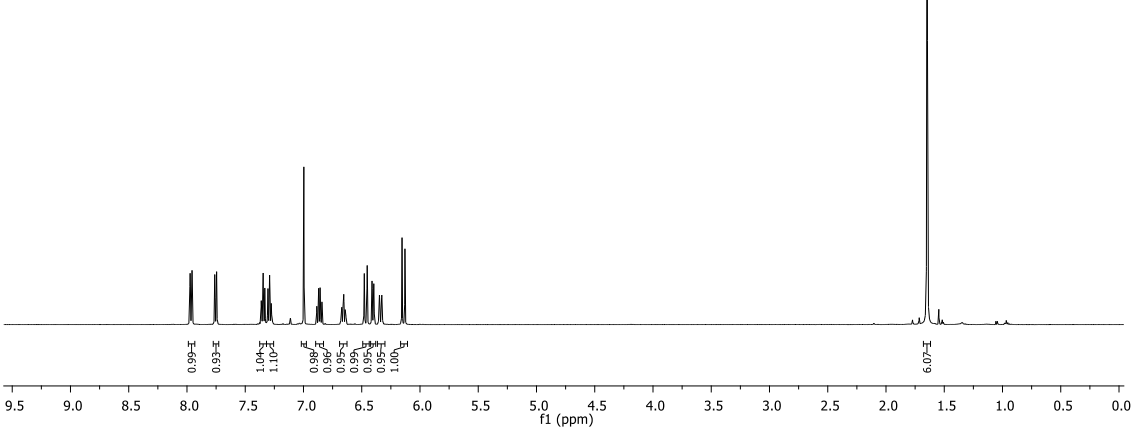
Me
S
F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0.93
1.04
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0.96
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0.95
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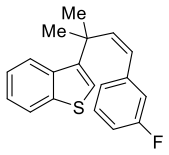
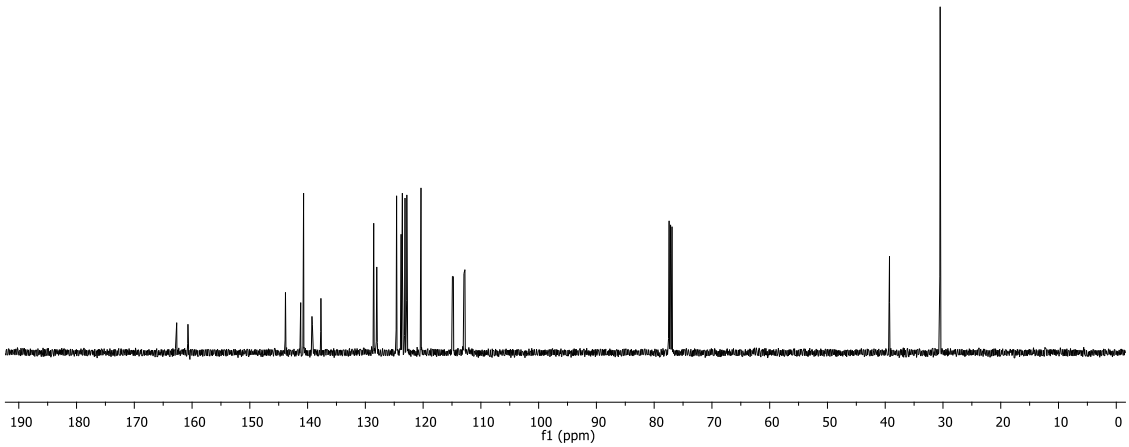
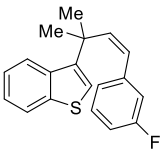
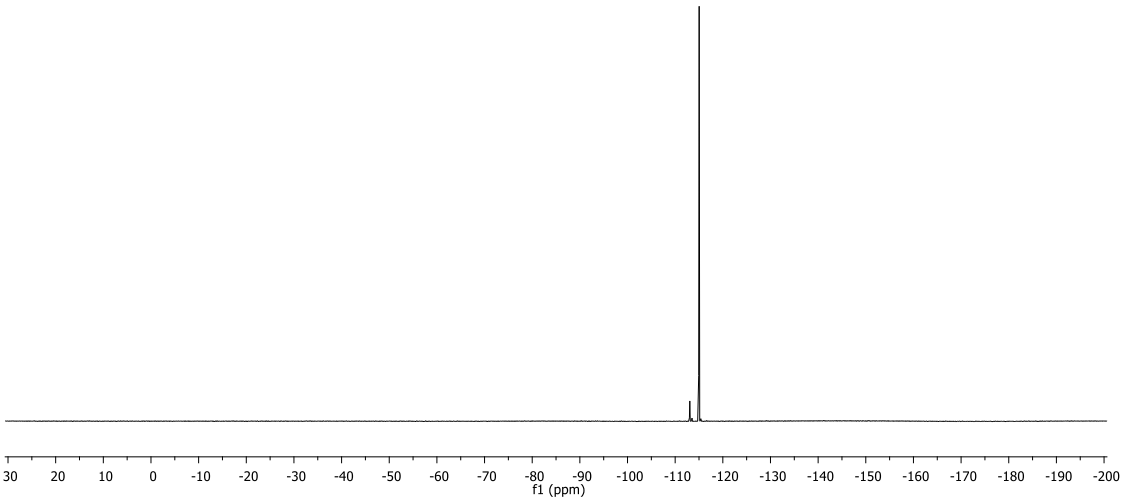
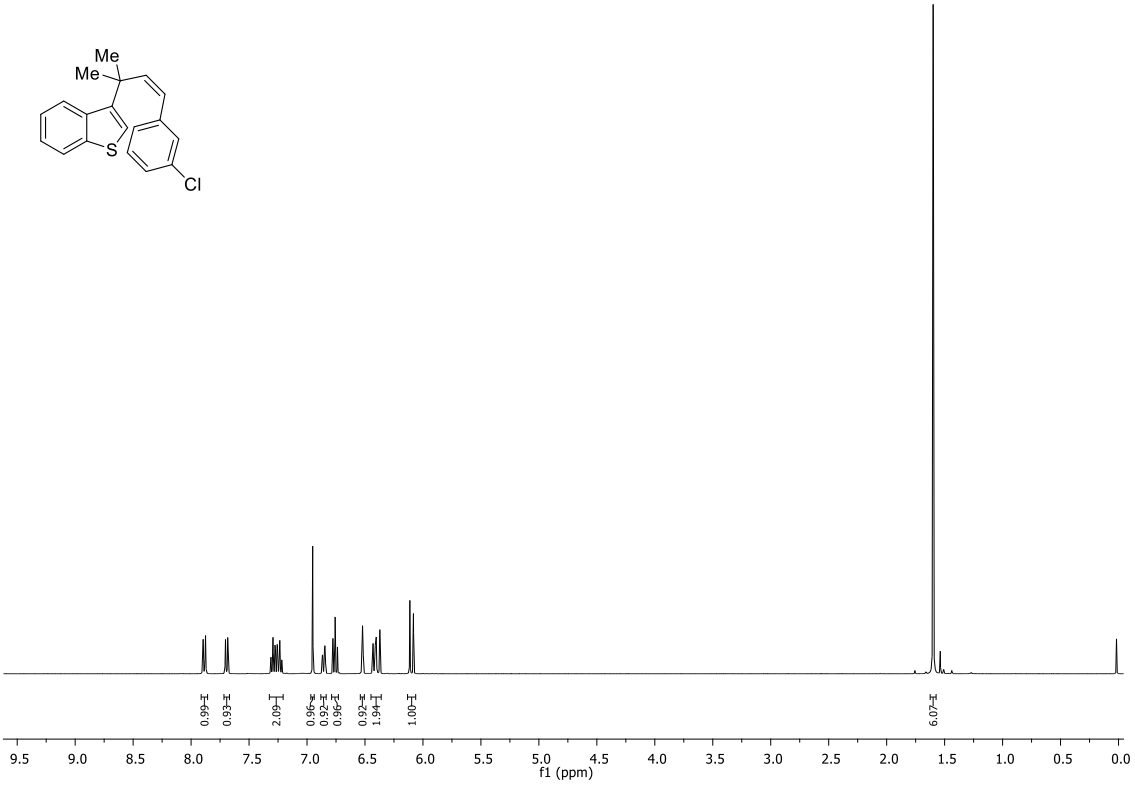
1.00
6.07
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

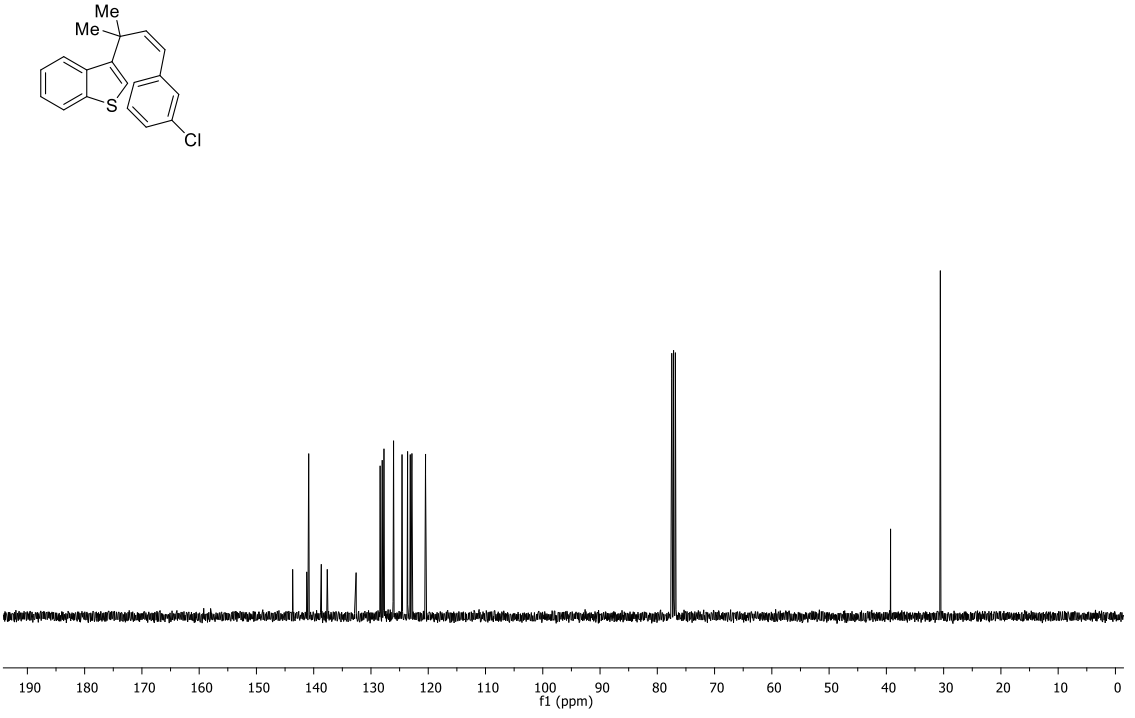

Me
Me
S
F

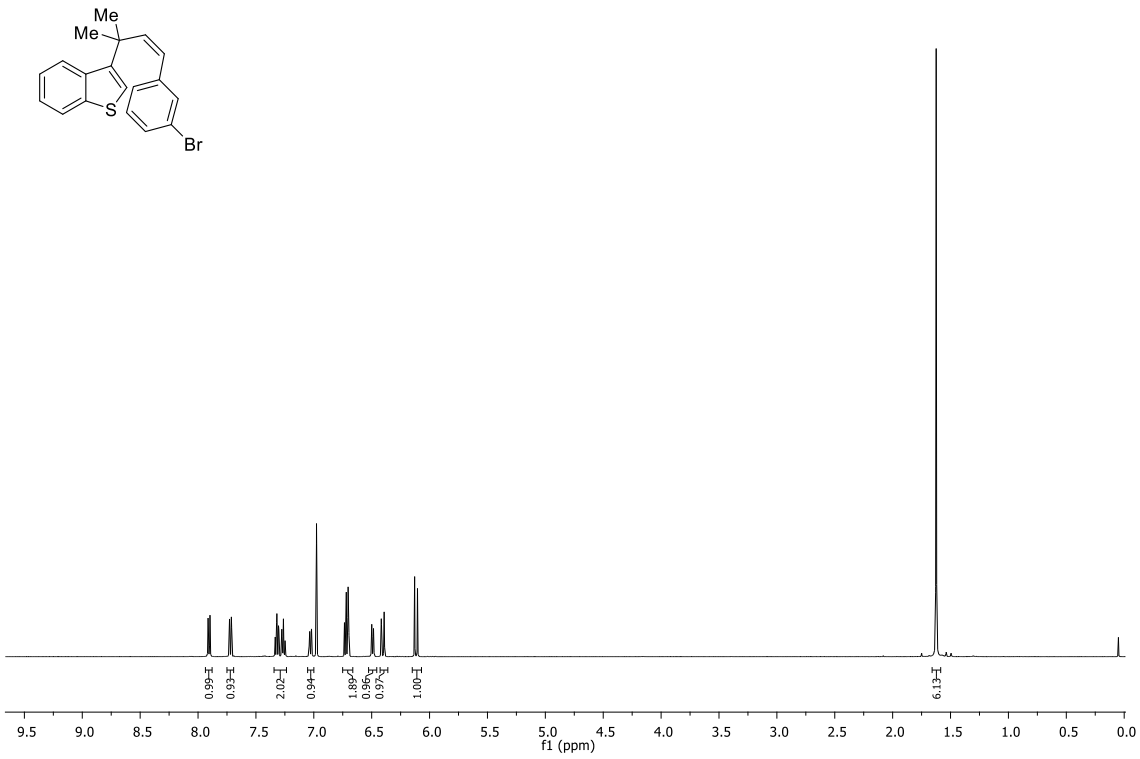

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

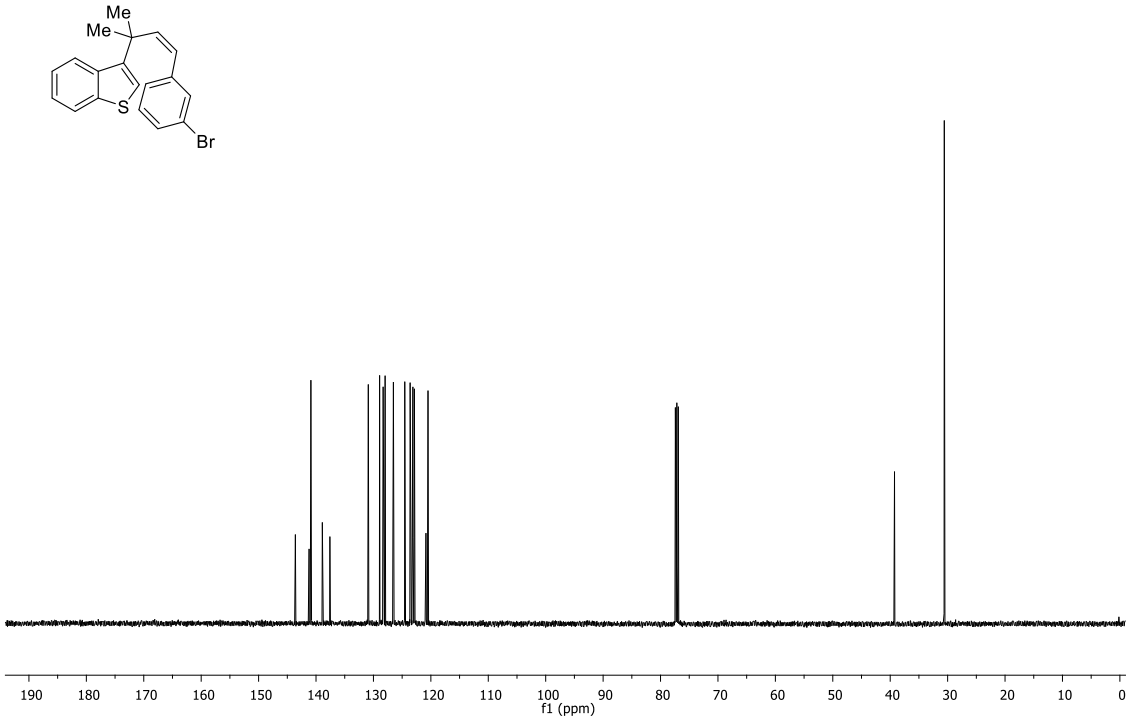

Me
Me
S
F

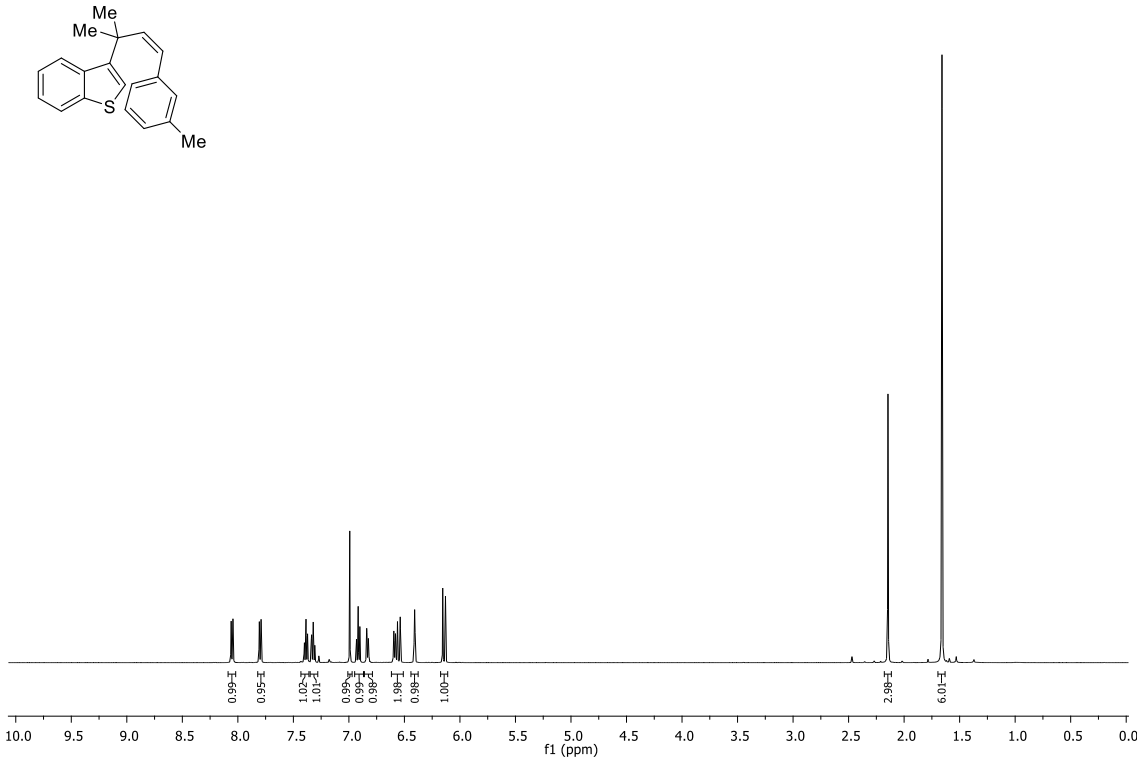

30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

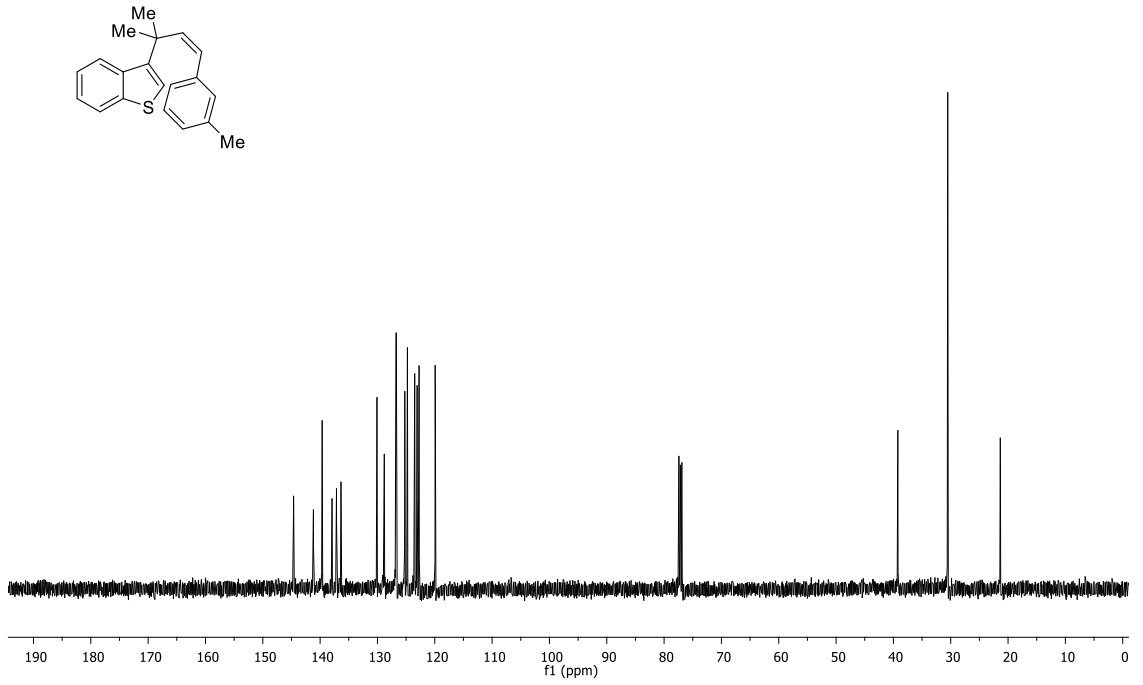

Me
Me
S
Cl
0.99
0.93
2.09
0.96
0.92
0.96
0.92
1.94
1.00
6.07
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

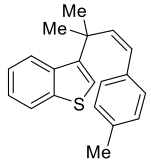

Me
Me
S
Cl
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


Me
Me
S
Br
0.99
0.93
2.02
0.94
1.89
0.96
0.97
1.00
6.13
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)

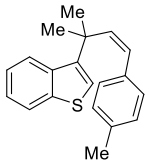

Me
Me
S
Br
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


Me
Me
S
Me
0.99
0.95
1.02
1.01
0.99
0.99
0.98
1.90
0.98
1.00
2.98
6.01
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)

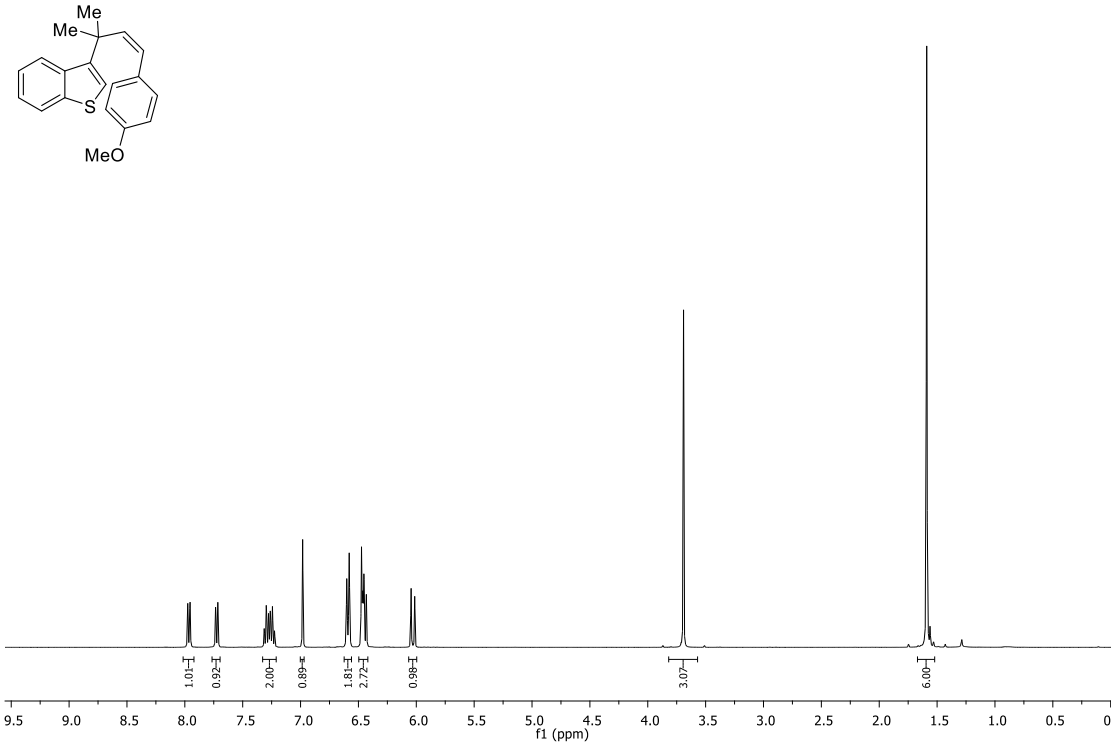

Me
Me
S
Me
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

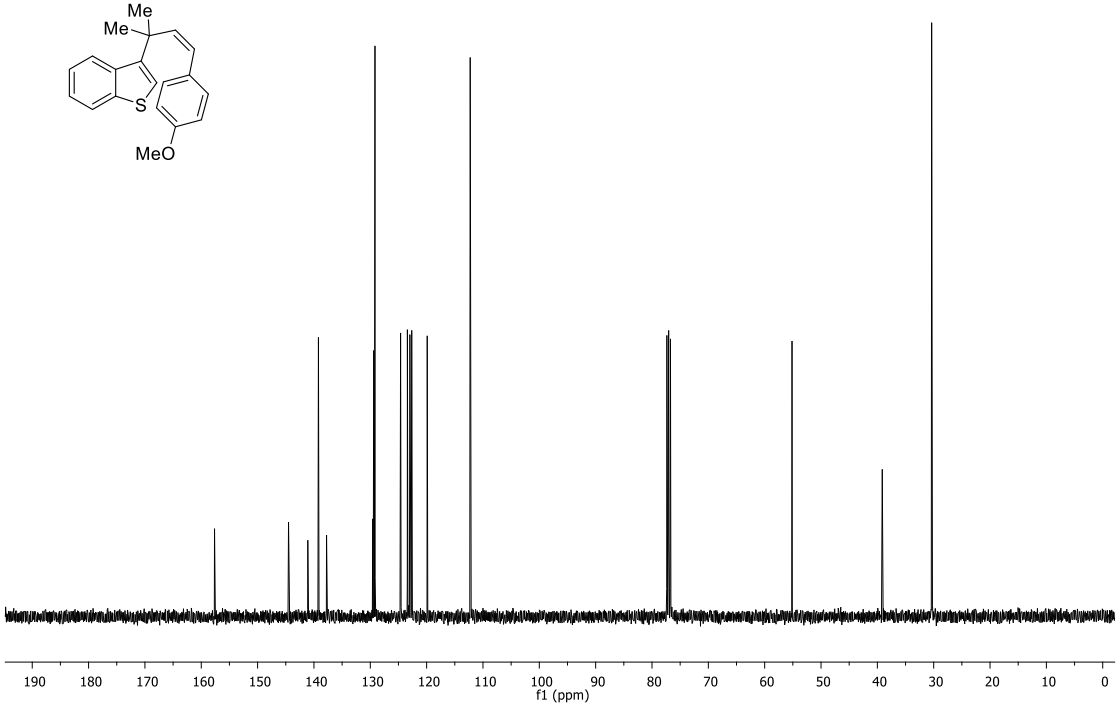

Me
Me
S
Me

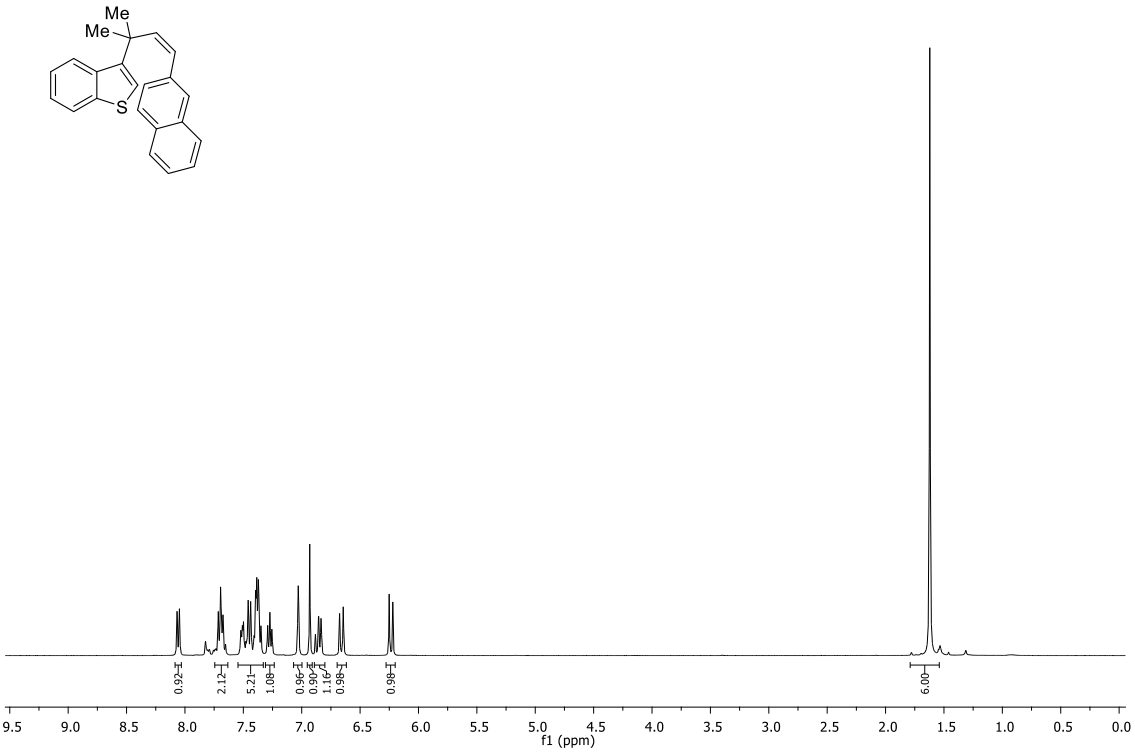
1.01
0.95
2.14
1.03
1.96
1.95
1.04
1.04
2.99
6.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

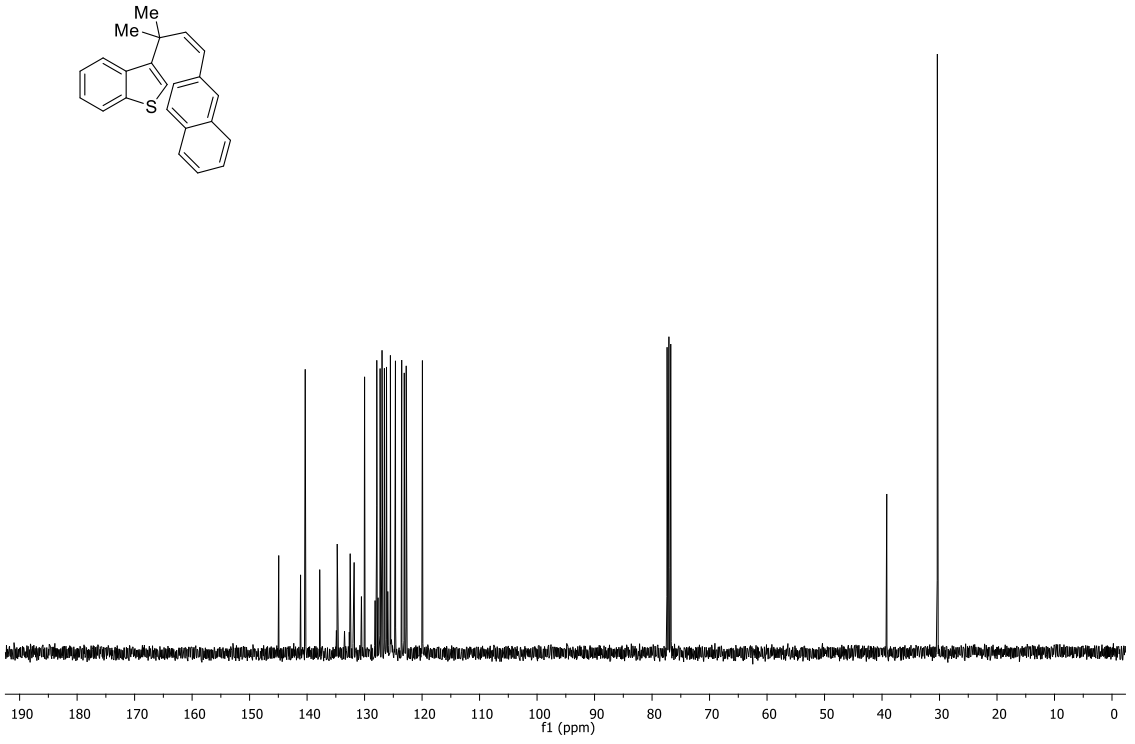

Me
Me
S
Me

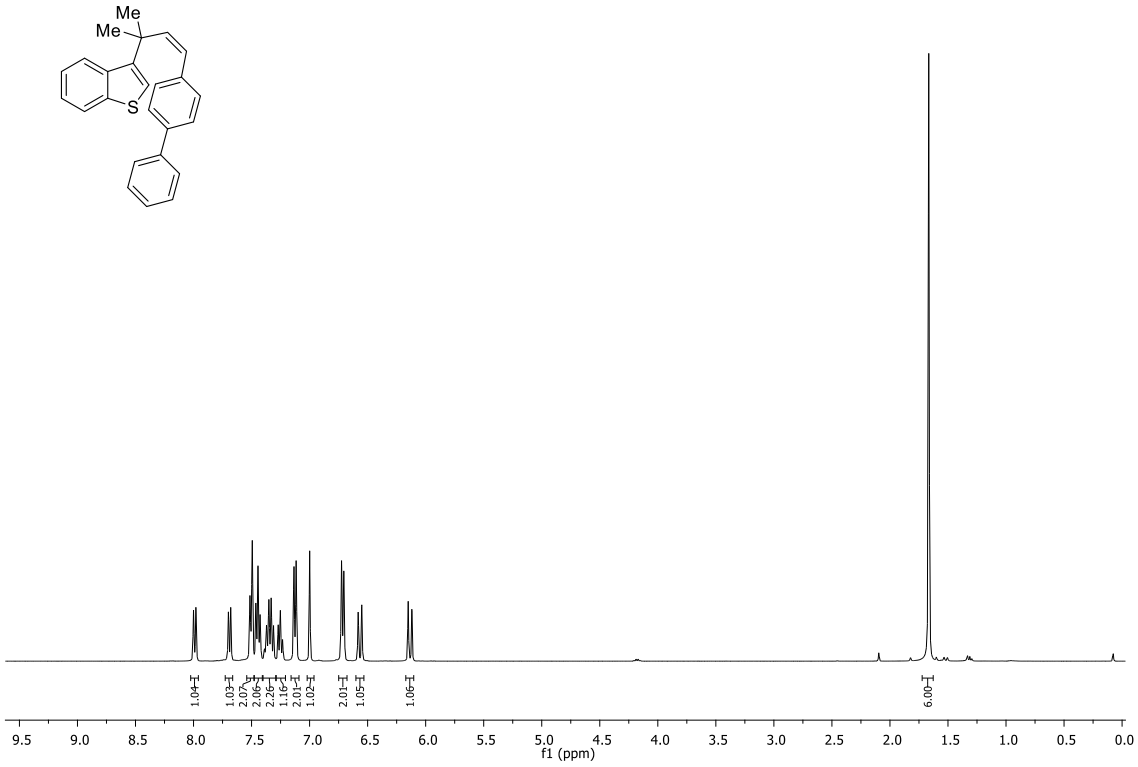
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

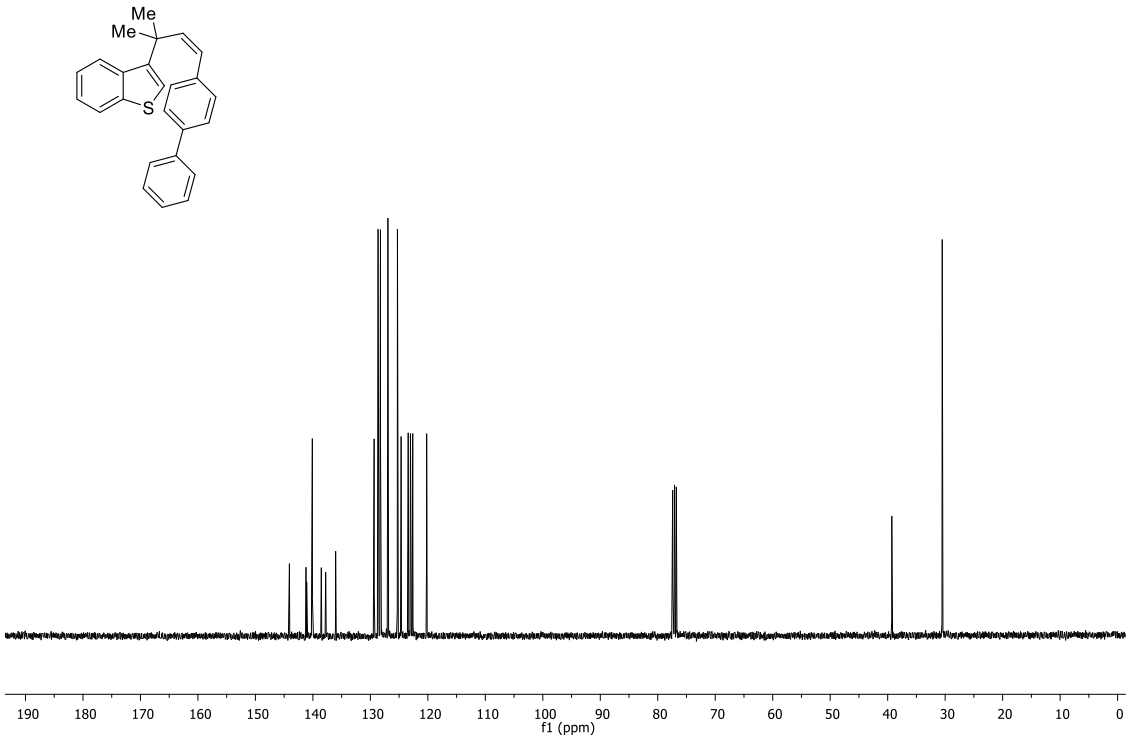

Me
Me
S
MeO
1.01
0.92
2.00
0.89
1.81
2.72
0.98
3.07
6.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
f1 (ppm)

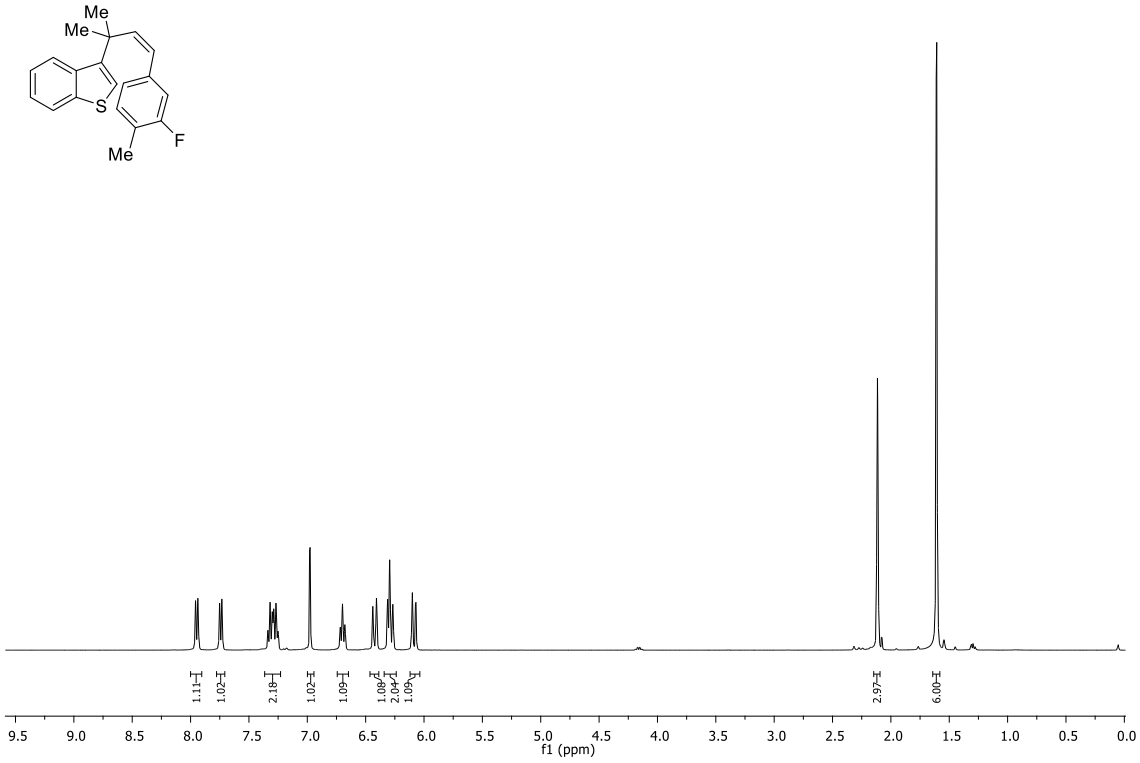

Me
Me
S
MeO
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

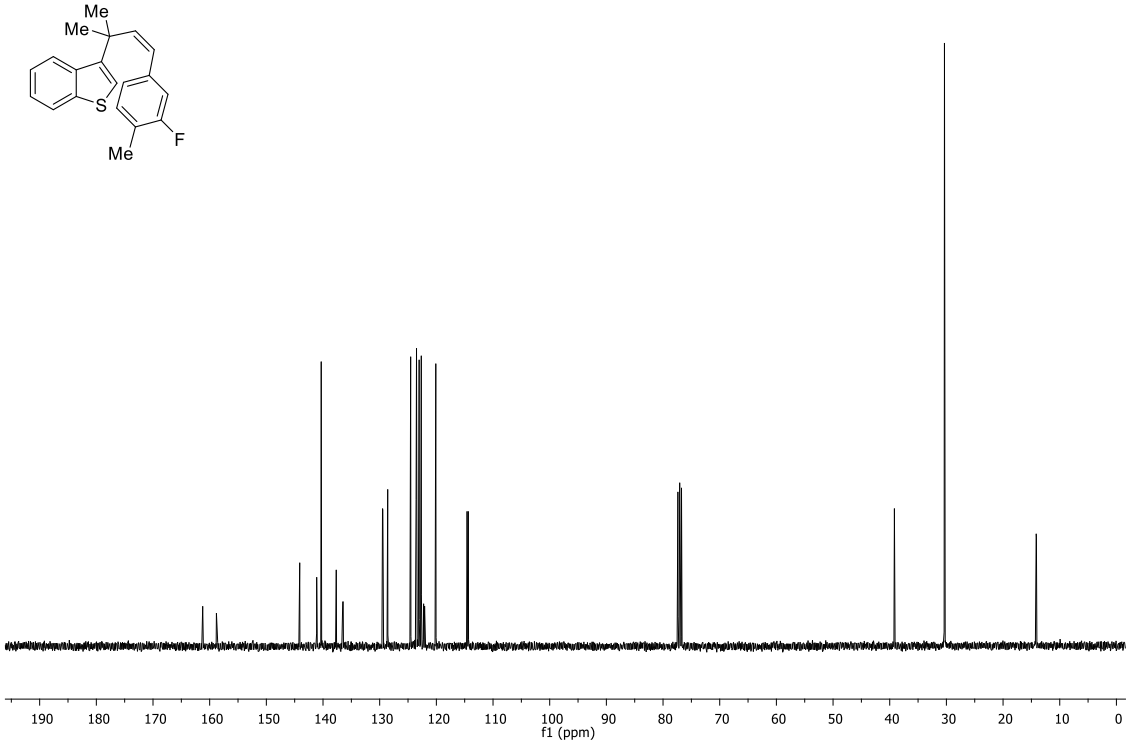

Me
Me
S
0.92
2.12
5.21
1.08
0.96
0.90
1.16
0.98
0.98
6.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

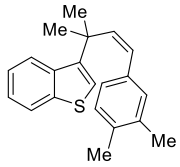

Me
Me
S
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

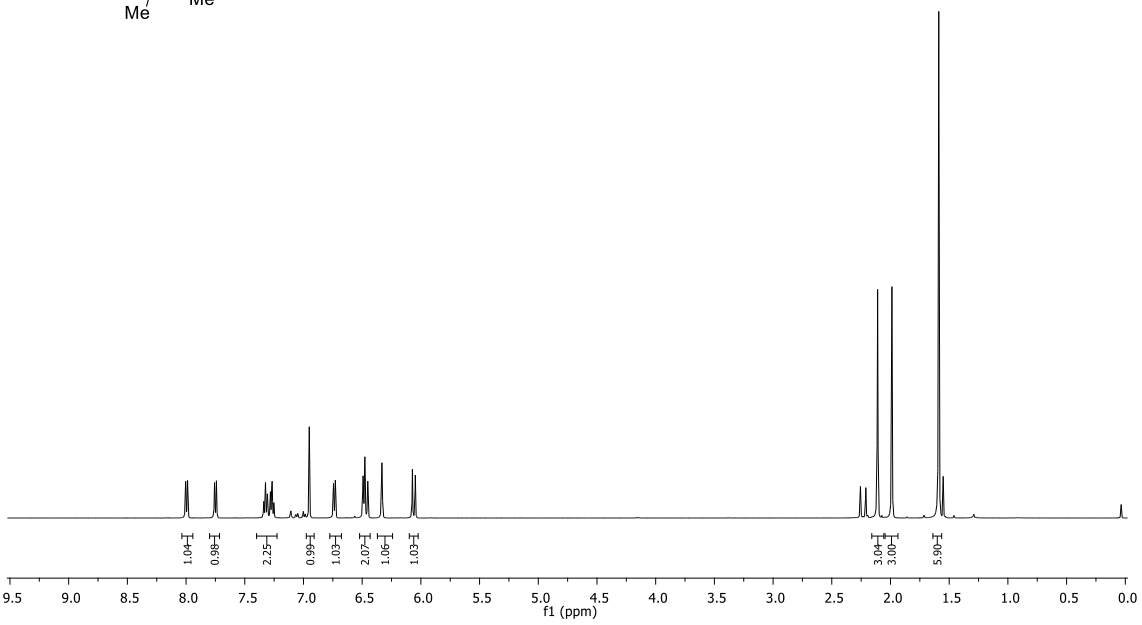

Me
Me
S
1.04
1.03
2.07
2.06
2.26
1.16
2.01
1.02
2.01
1.05
1.06
6.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

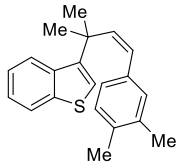

Me
Me
S
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


Me
Me
S
F
Me
1.11
1.02
2.18
1.02
1.09
1.08
2.04
1.09
2.97
6.00
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)

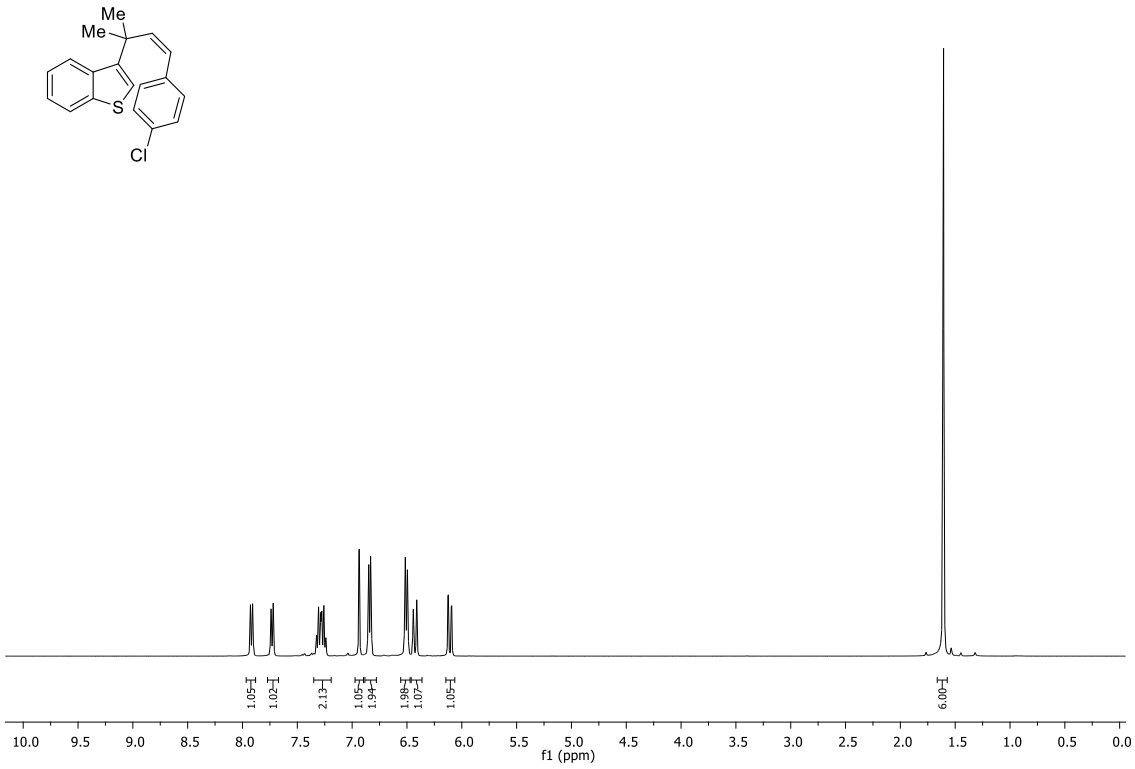

Me
Me
S
F
Me
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

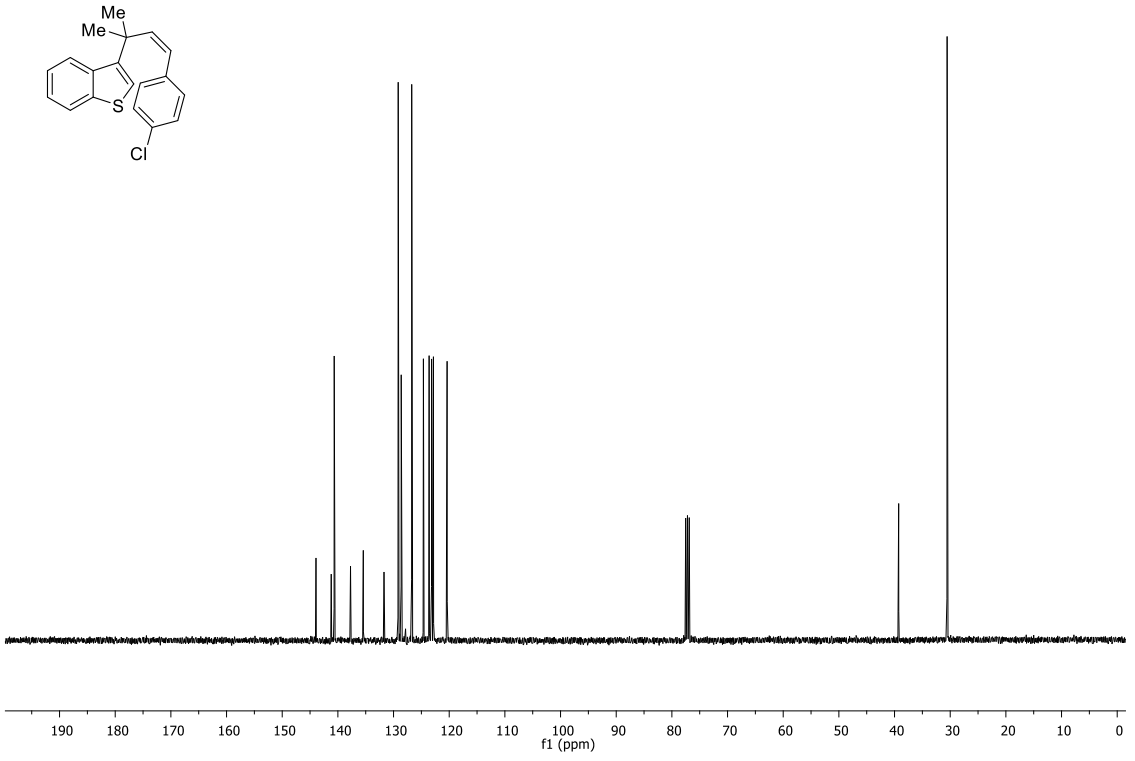

Me
Me
S
Me
Me

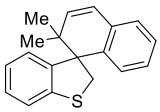

1.04
0.98
2.25
0.99
1.03
2.07
1.06
1.03
3.04
3.00
5.90
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

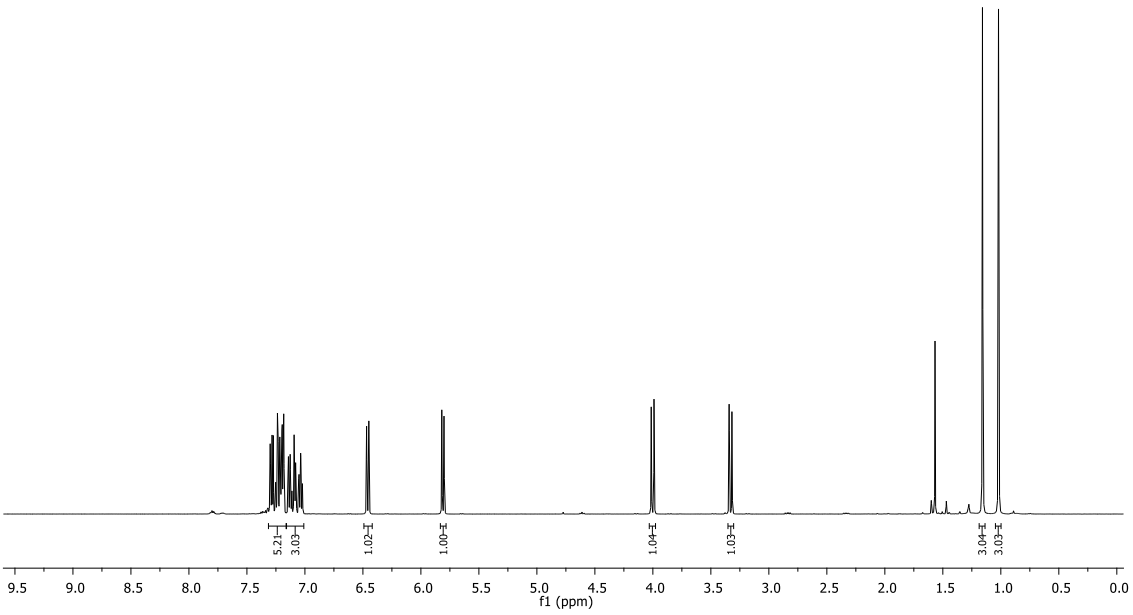

Me
Me
S
Me
Me

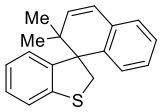
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

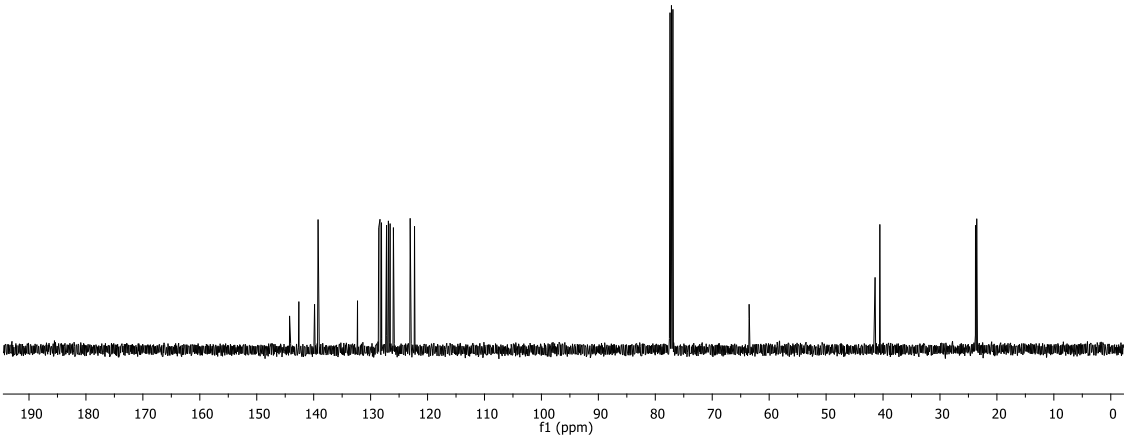

Me
Me
S
Cl
1.05
1.02
2.13
1.05
1.94
1.98
1.07
1.05
6.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

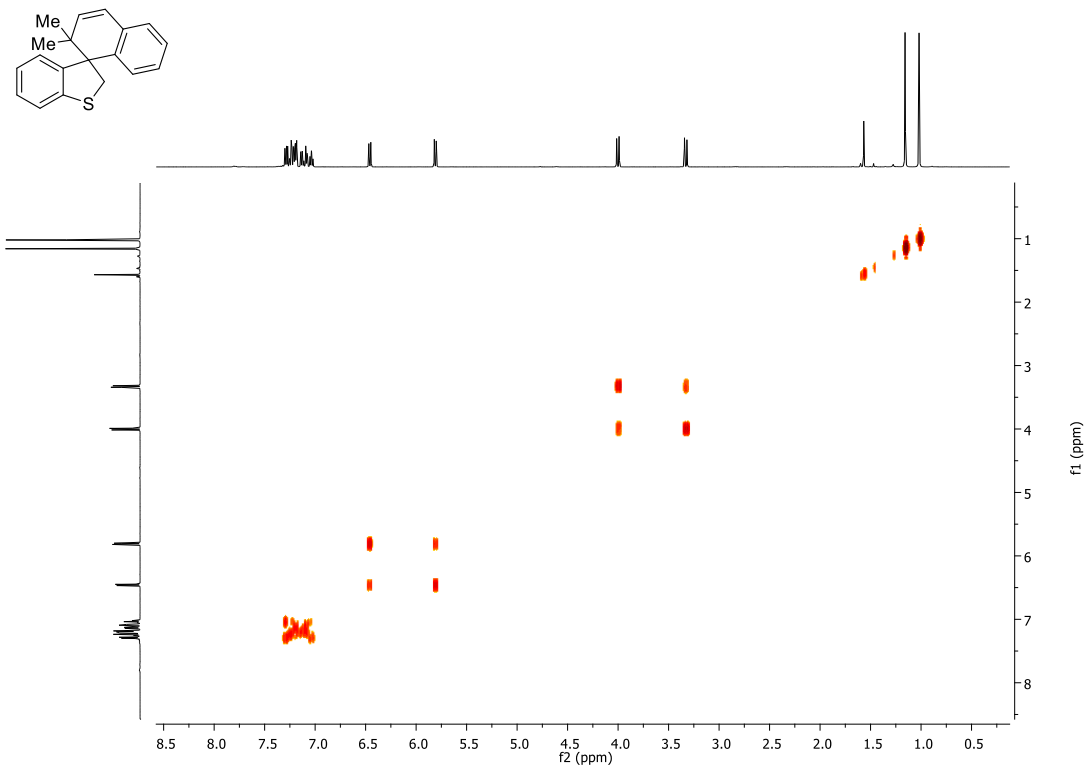

Me
Me
S
Cl
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

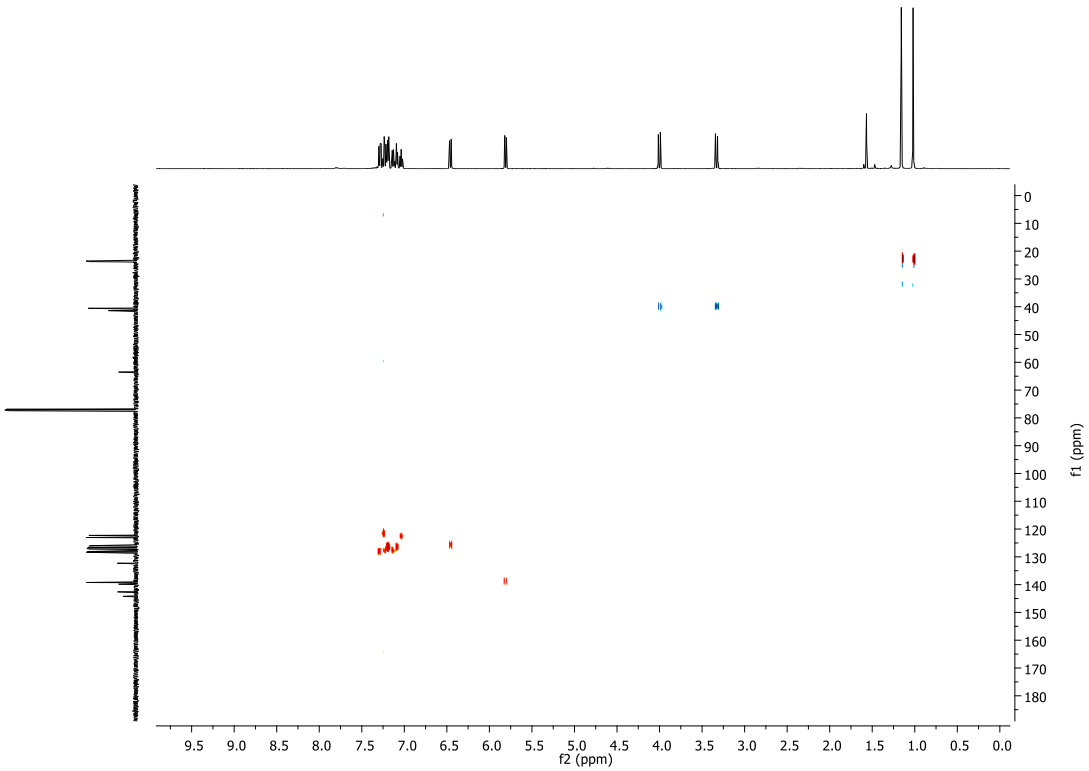

Me
Me
S

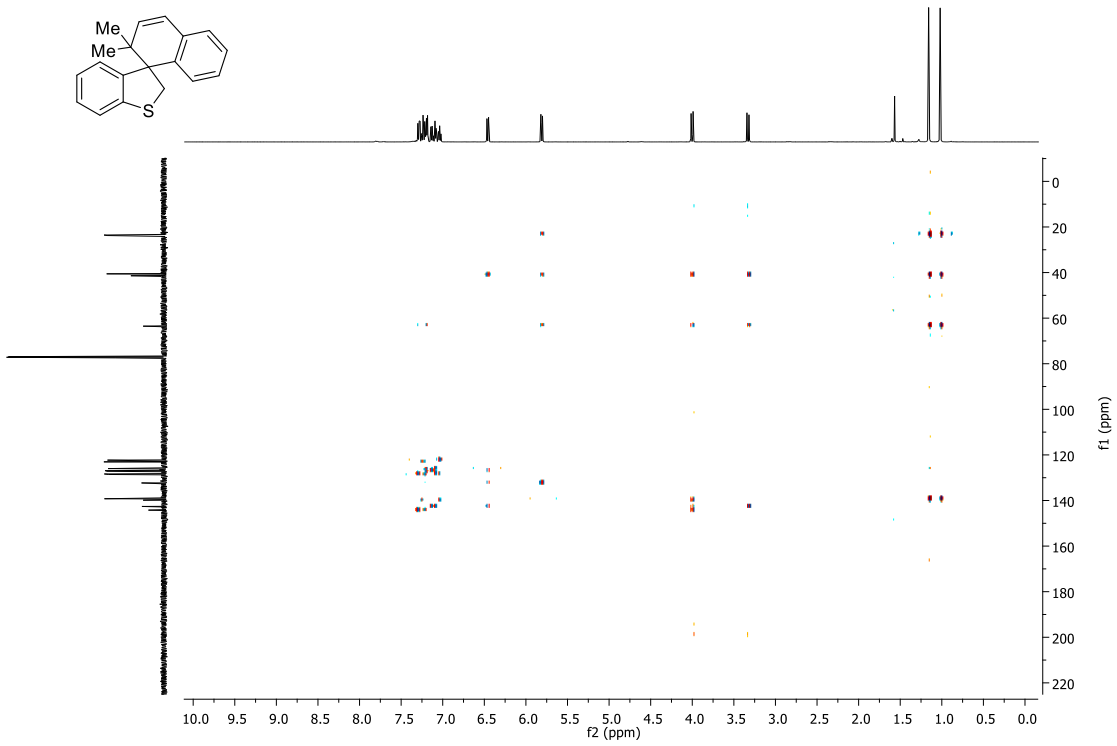

5.21
3.03
1.02
1.00
1.04
1.03
3.04
3.03
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

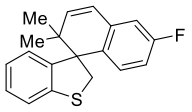

Me
Me
S

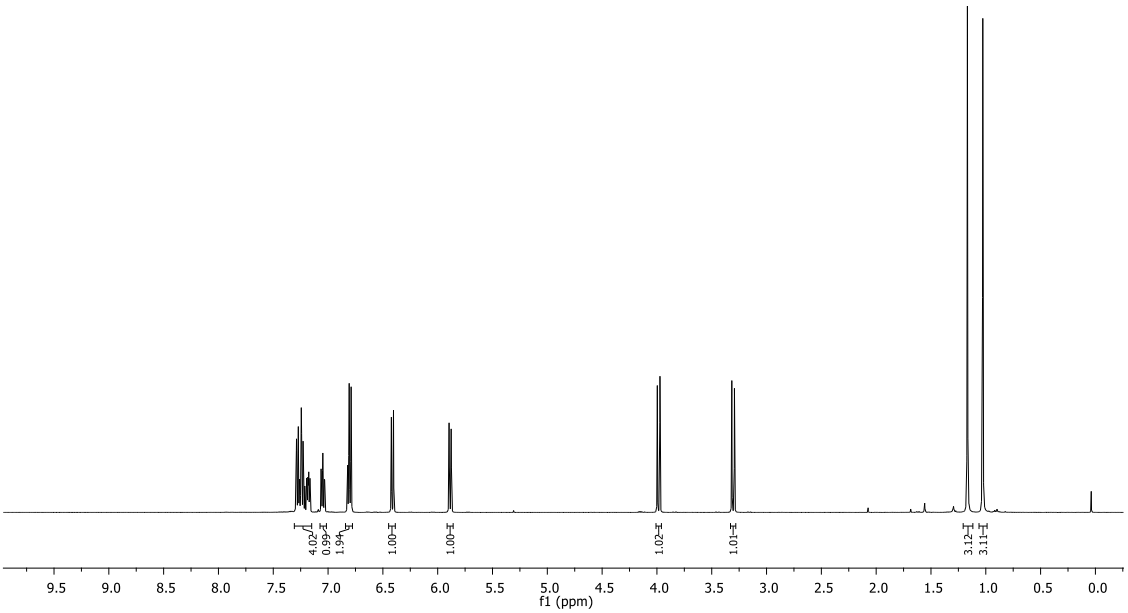

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

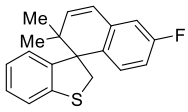

Me
Me
S
f1 (ppm)
f2 (ppm)

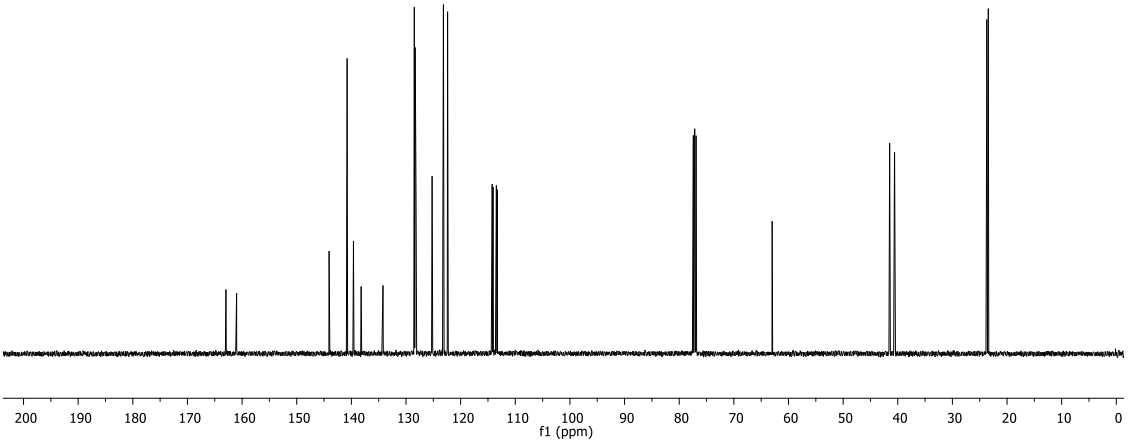

f1 (ppm)
f2 (ppm)

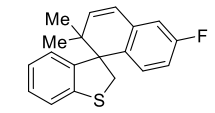

Me
Me
S
0
20
40
60
80
100
120
140
160
180
200
220
f1 (ppm)
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f2 (ppm)

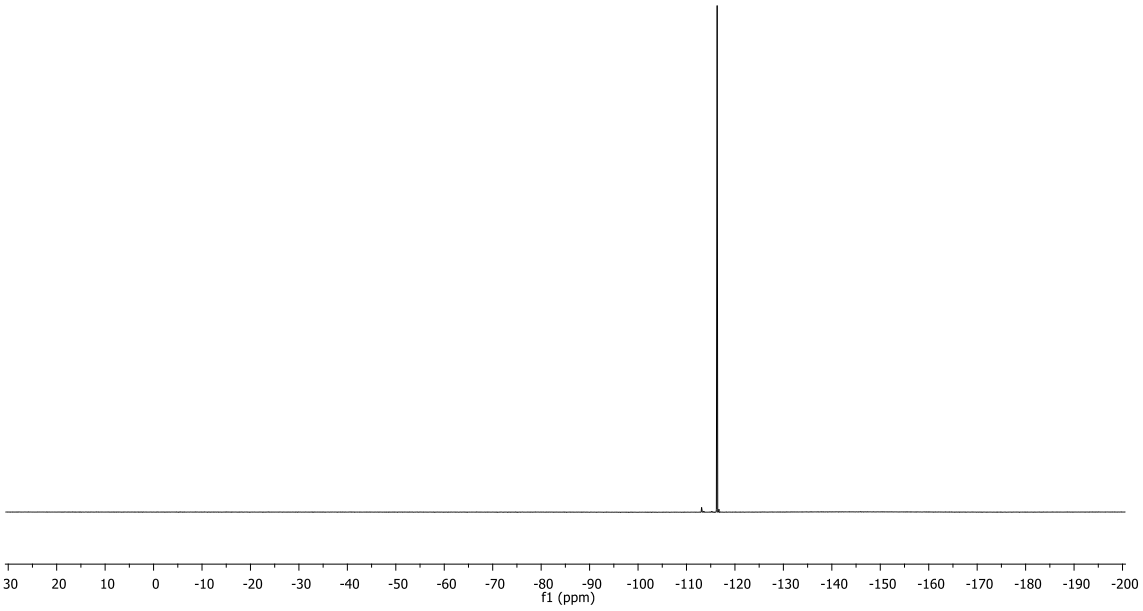

Me
Me
F
S

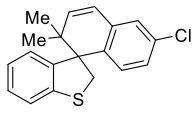

4.02
0.99
1.94
1.00
1.00
1.02
1.01
3.12
3.11
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

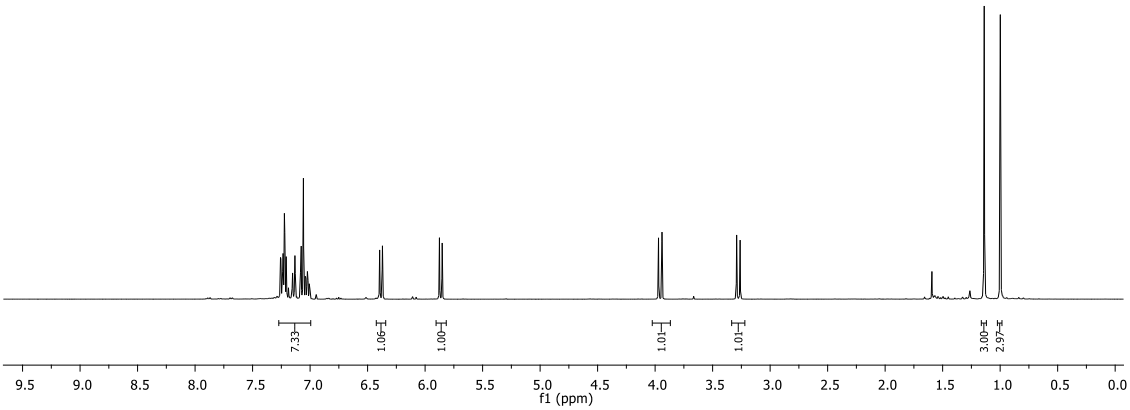

Me
Me
F
S

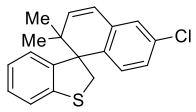

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

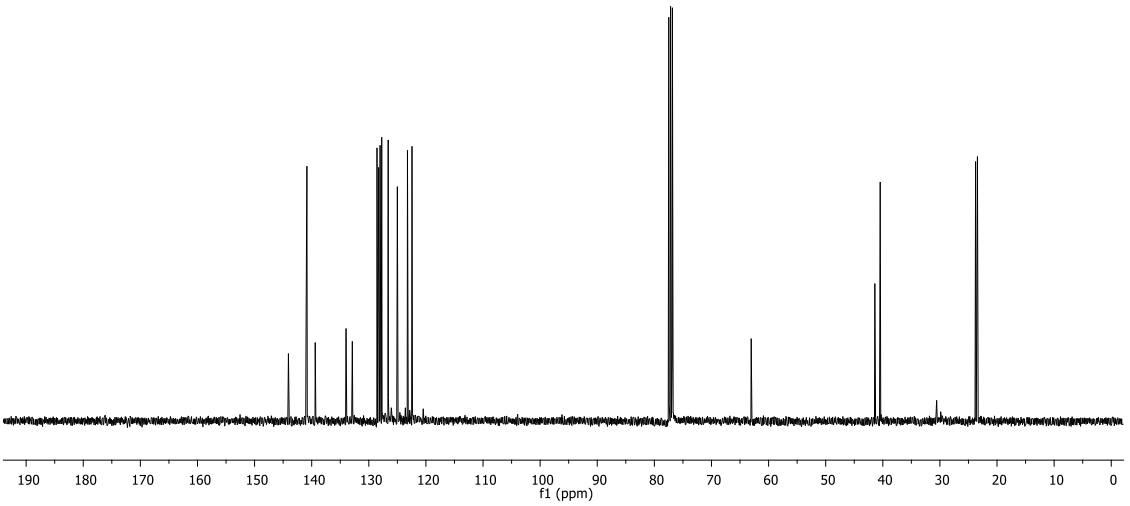

Me
Me
F
S

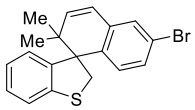

30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

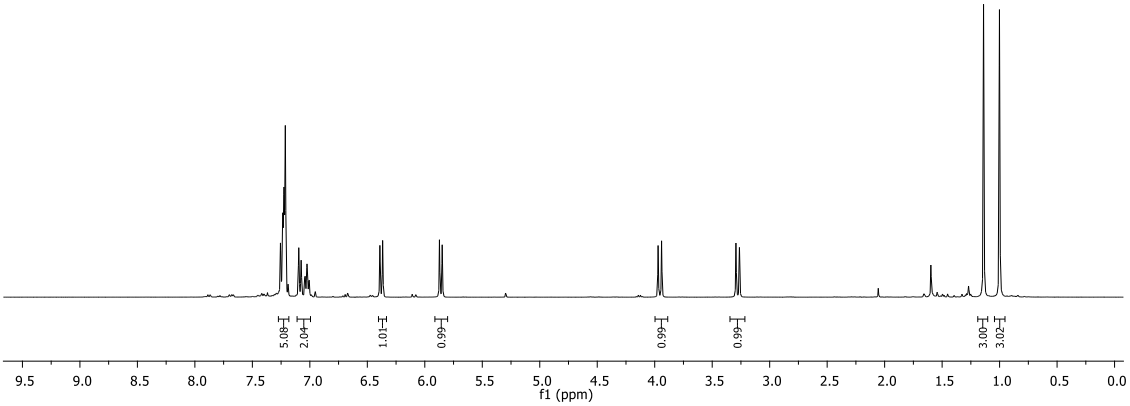

Me
Me
Cl
S

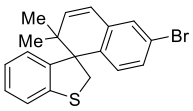

7.33
1.06
1.00
1.01
1.01
3.00
2.97
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

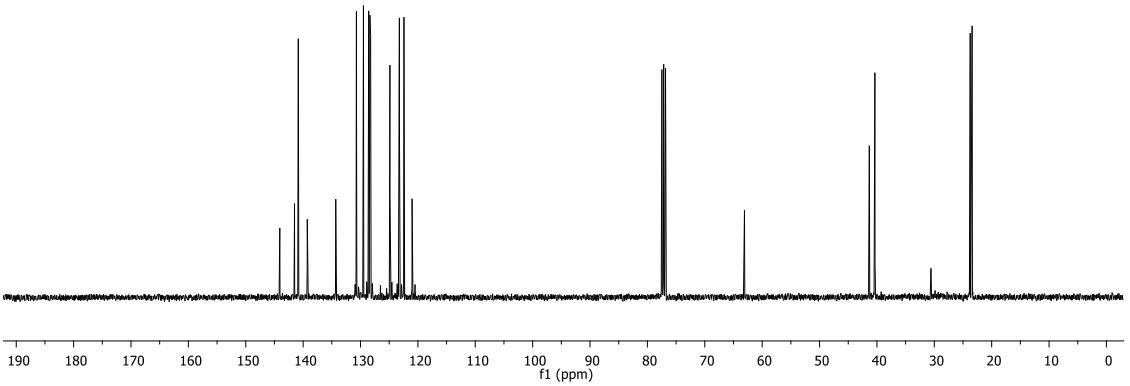

Me
Me
Cl
S

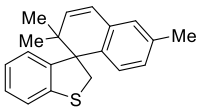

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

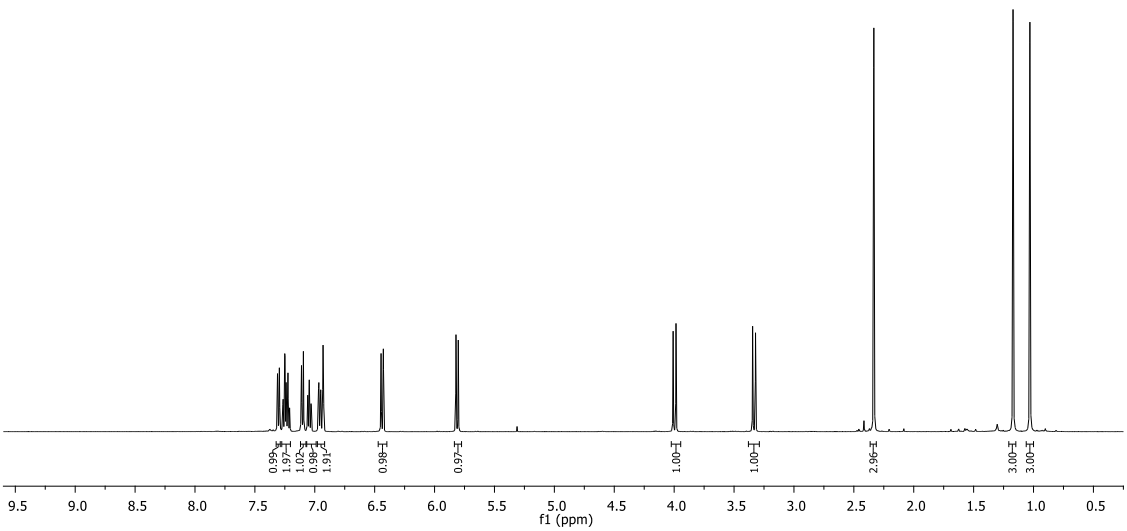

Me
Me
Br
S

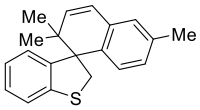

5.08
2.04
1.01
0.99
0.99
0.99
3.00
3.02
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

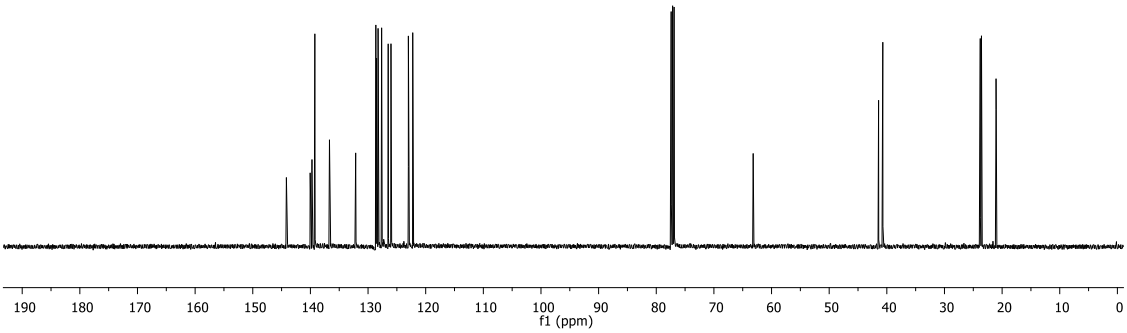

Me
Me
Br
S

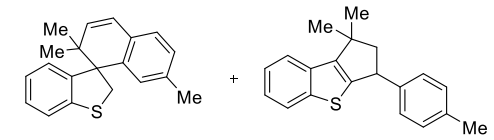

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

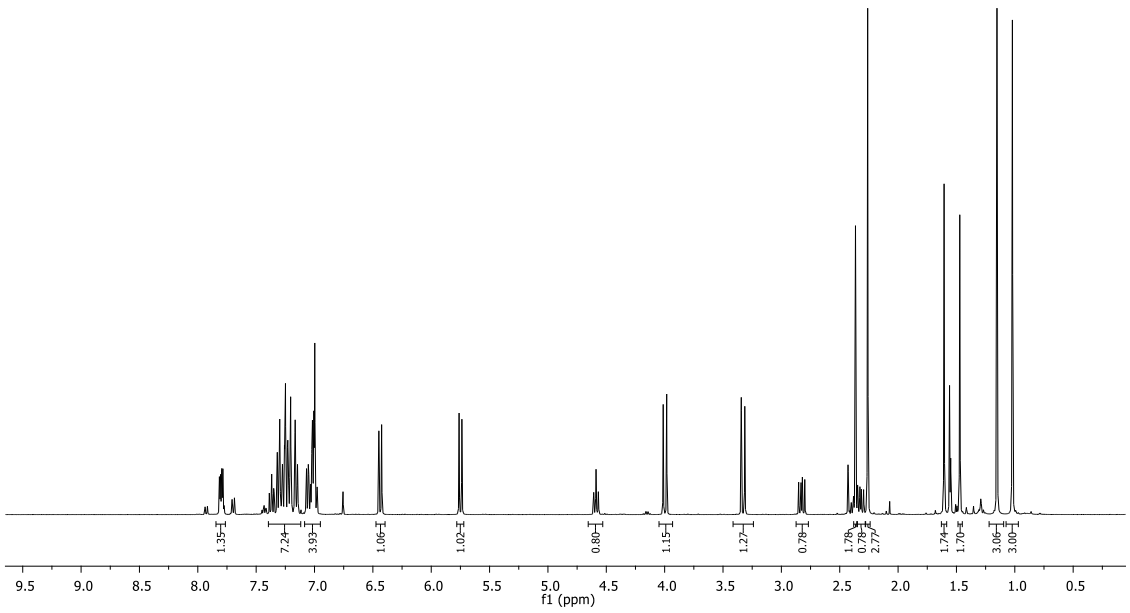

Me
Me
Me
S

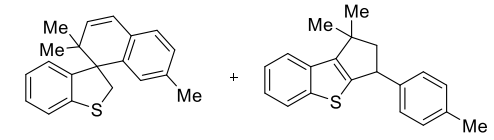

0.99
1.97
1.02
0.98
1.91
0.98
0.97
1.00
1.00
2.96
3.00
3.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

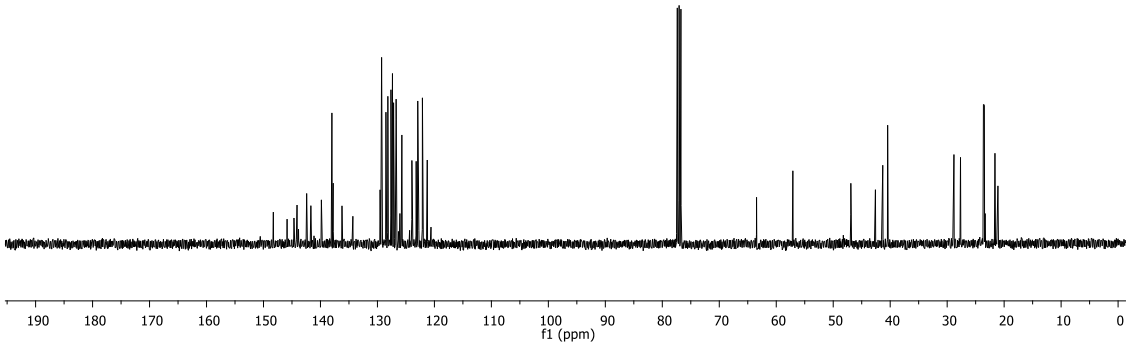

Me
Me
Me
S

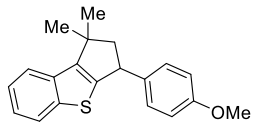

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

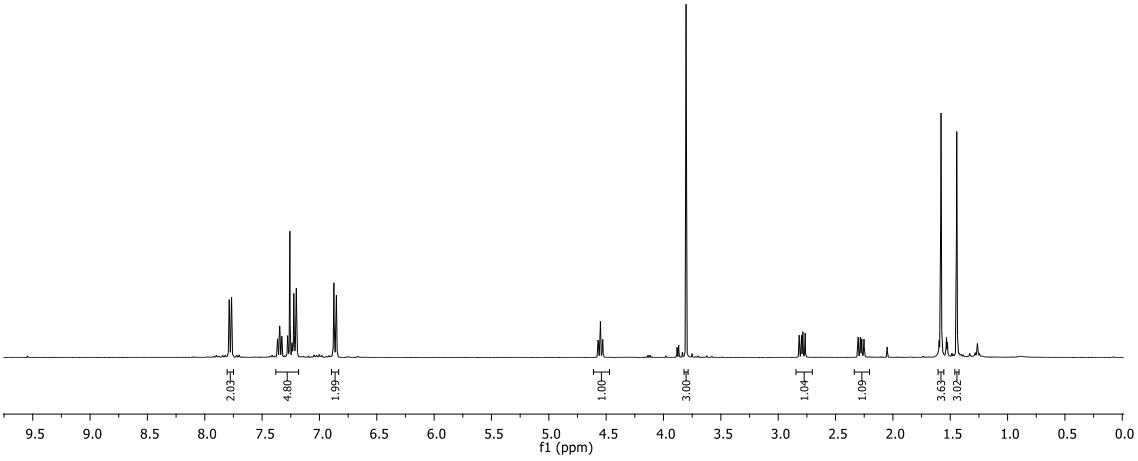

Me
Me
Me
S
+
Me
Me
S
Me

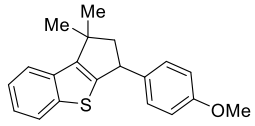

1.35
7.24
3.93
1.06
1.02
0.80
1.15
1.27
0.78
1.78
0.78
2.77
1.74
1.70
3.06
3.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

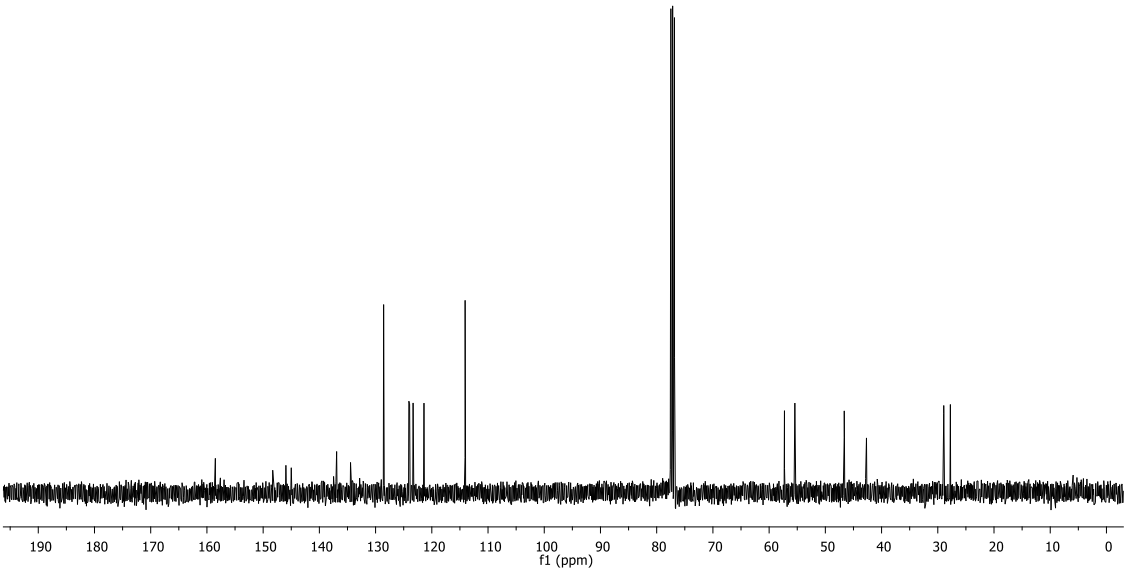

Me
Me
Me
S
+
Me
Me
S
Me

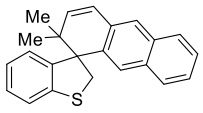

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

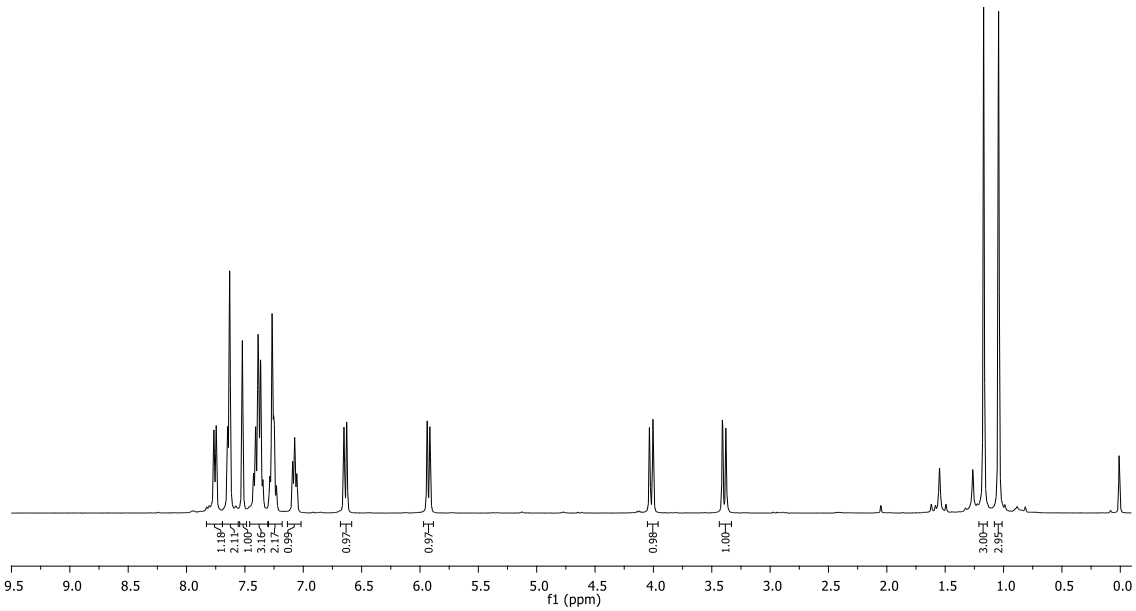

Me
Me
S
OMe

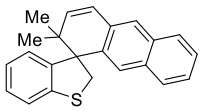

2.03
4.80
1.99
1.00
3.00
1.04
1.09
3.63
3.02
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

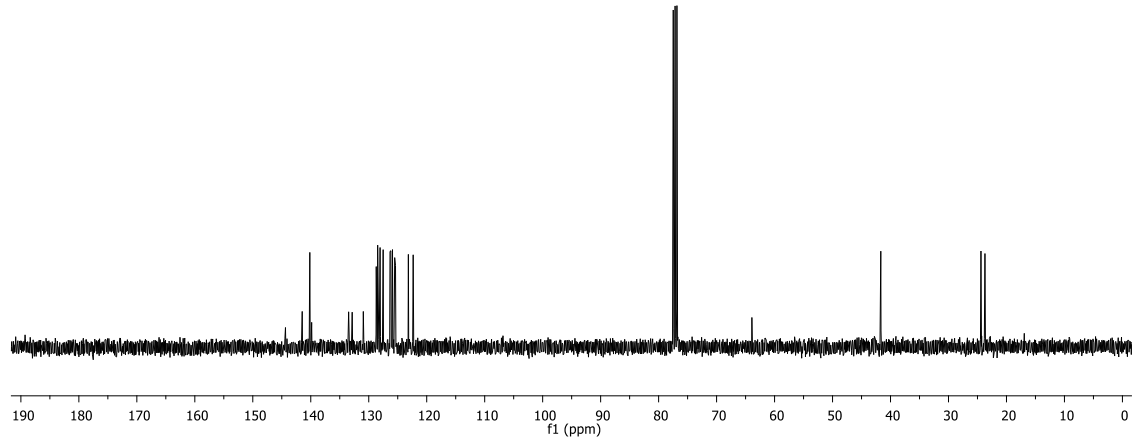

Me
Me
S
OMe

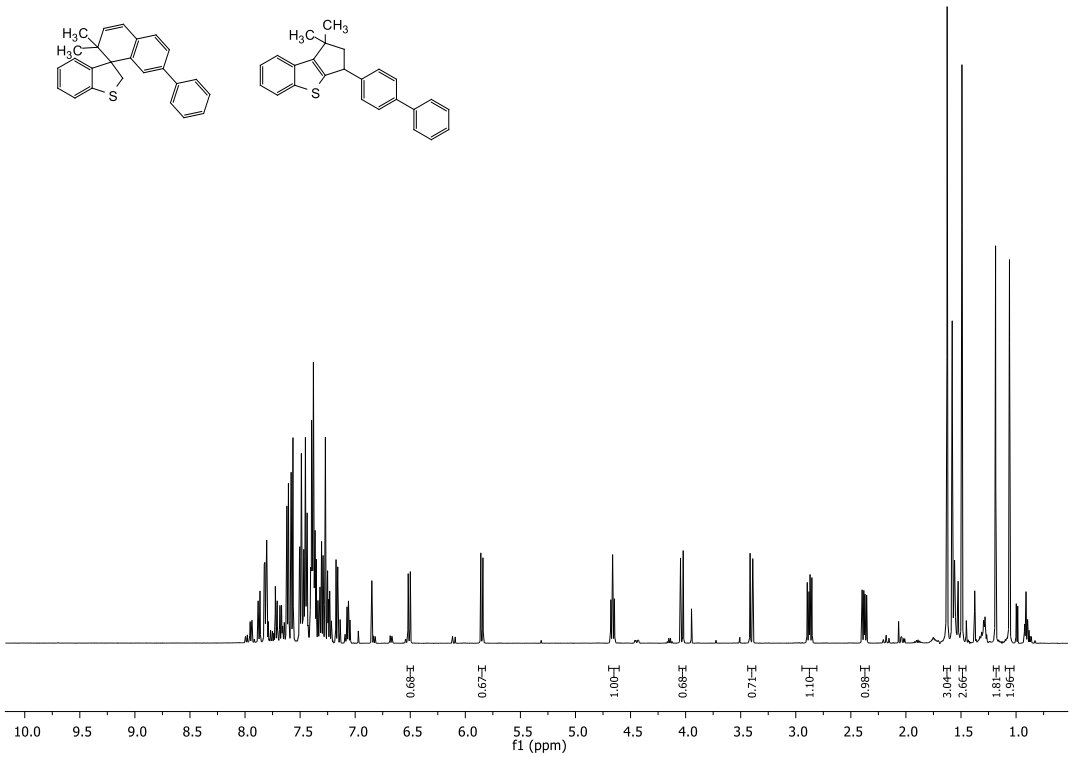

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

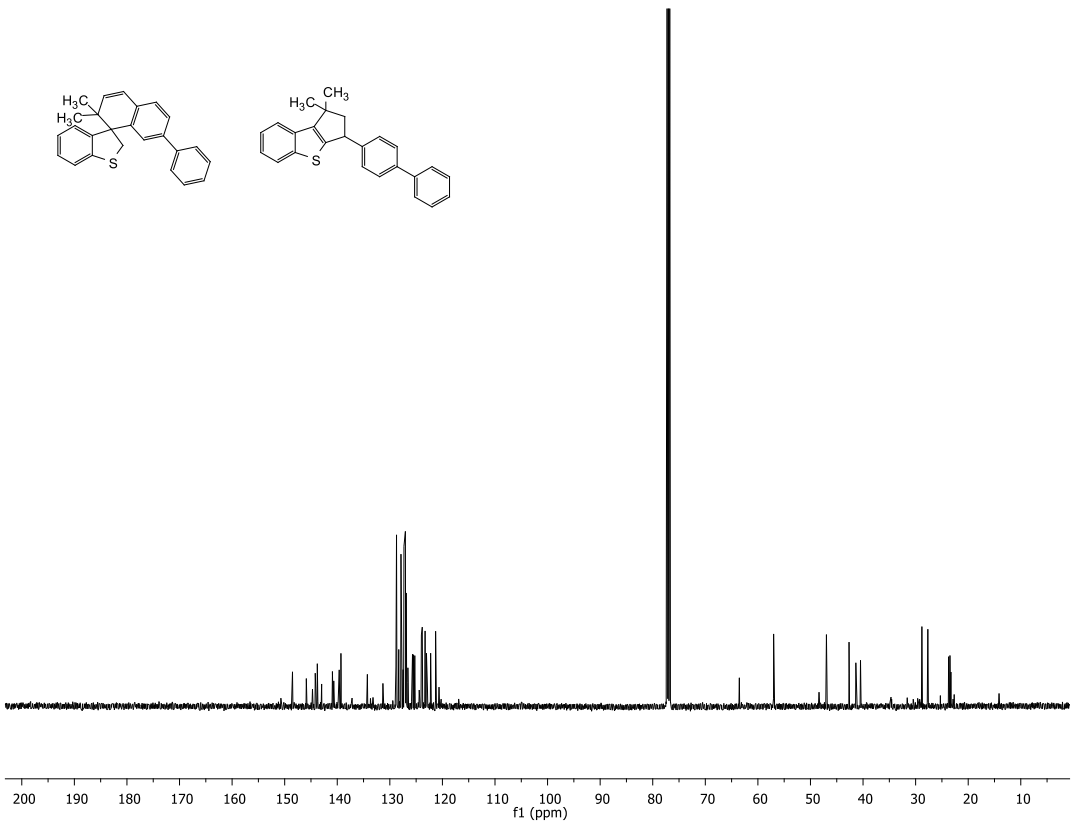

Me
Me
S

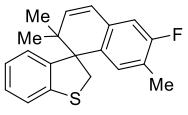

1.18
2.11
1.00
3.16
2.17
0.99
0.97
0.97
0.98
1.00
3.00
2.95
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

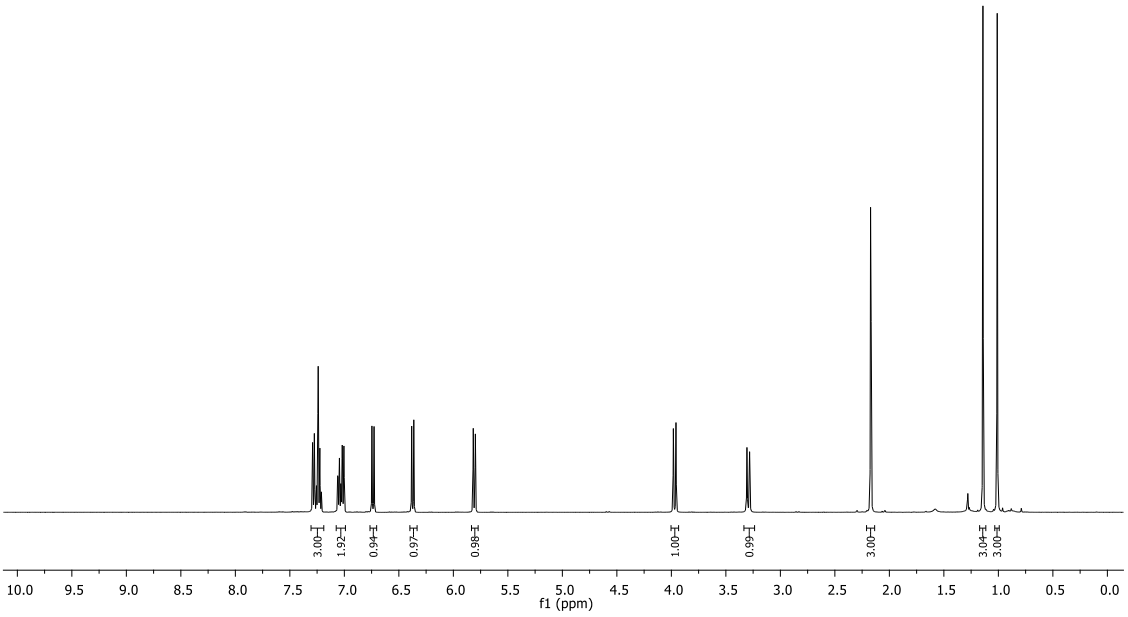

Me
Me
S

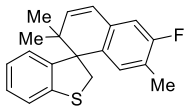

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

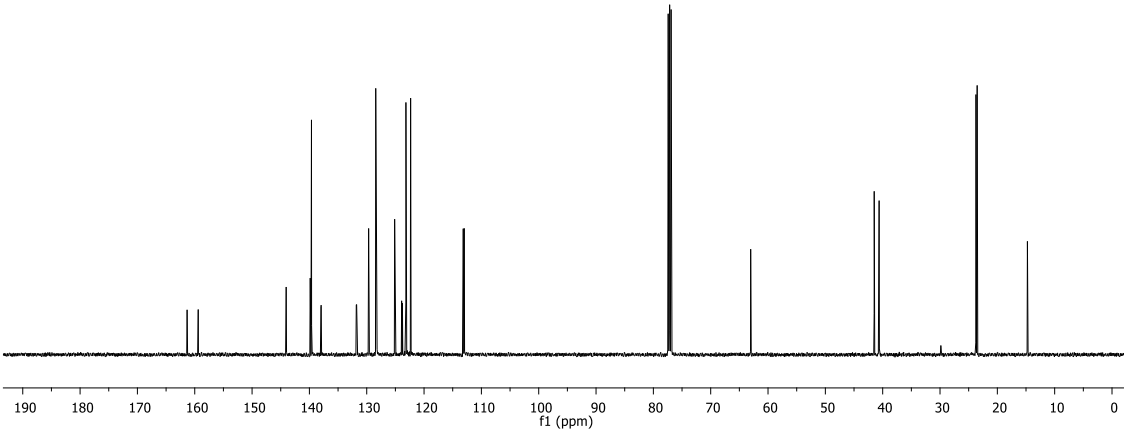

H3C
H3C
S
H3C
CH3
S
0.69
0.67
1.00
0.69
0.71
1.10
0.98
3.04
2.66
1.81
1.96
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
f1 (ppm)

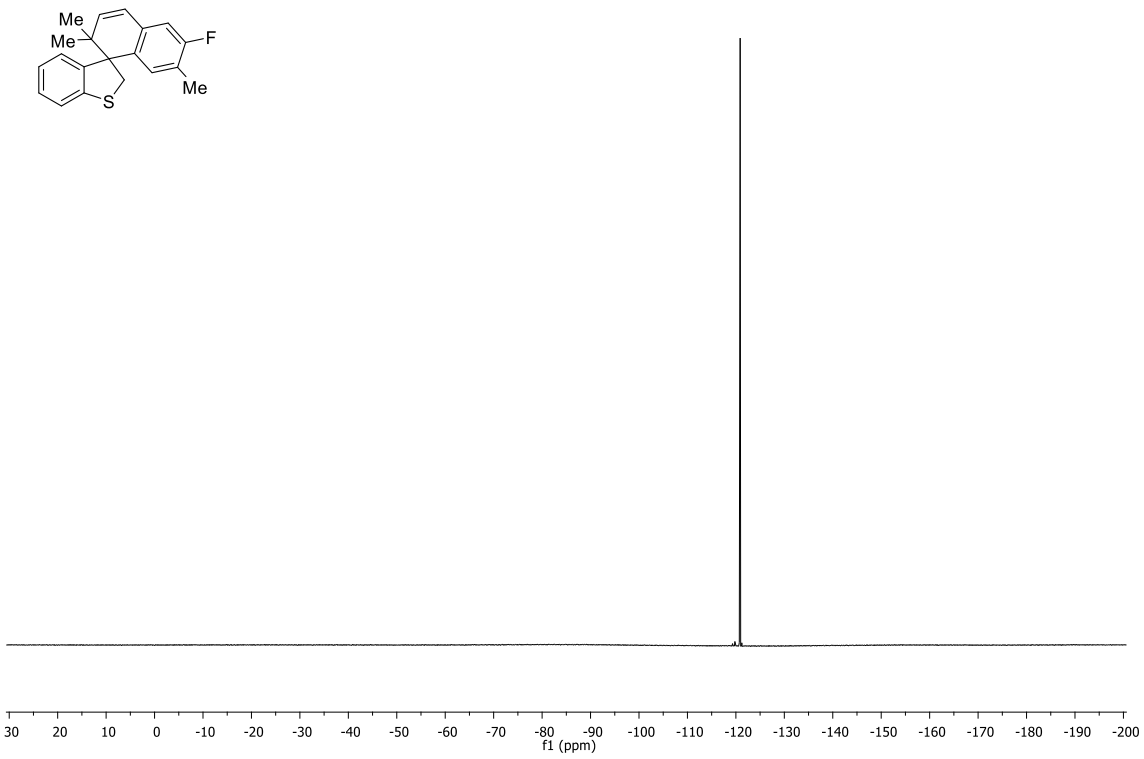

H3C
H3C
S
H3C
CH3
S
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

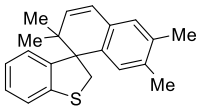

Me
Me
F
Me
S

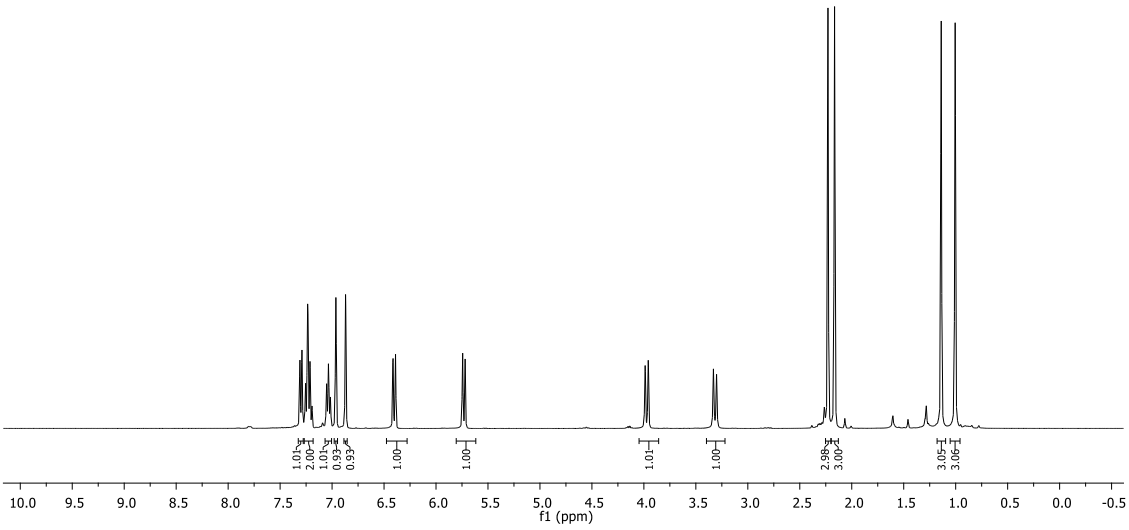

3.00
1.92
0.94
0.97
0.98
1.00
0.99
3.00
3.04
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

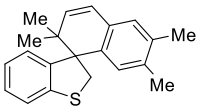

Me
Me
F
Me
S

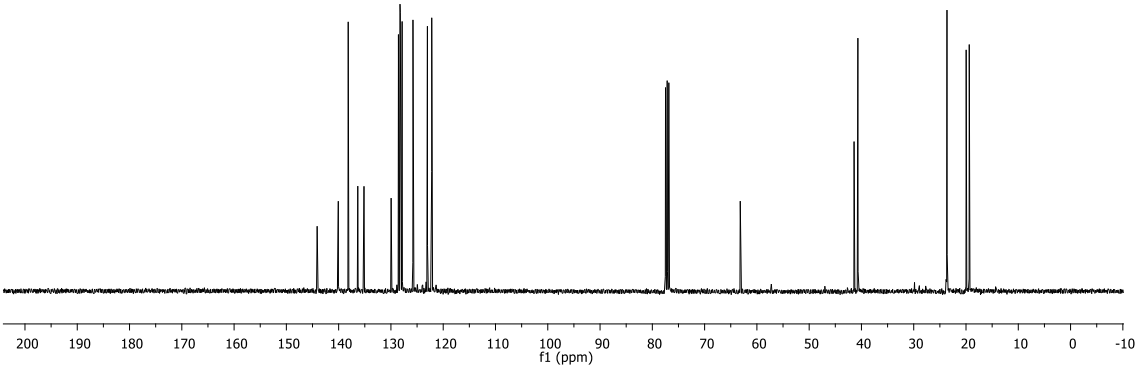

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

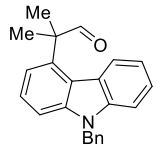

Me
Me
F
Me
S
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

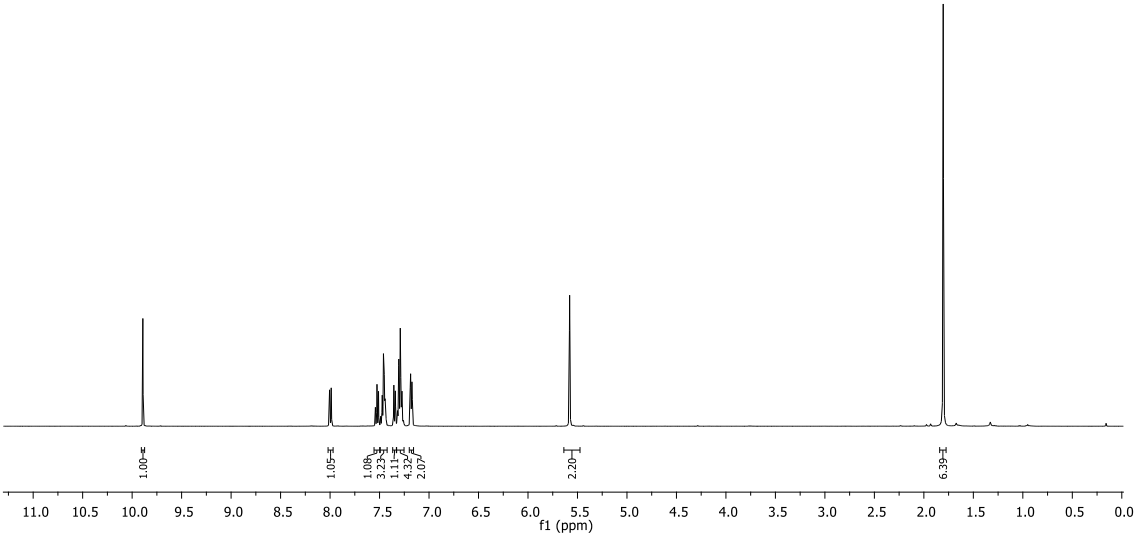

Me
Me
Me
Me
S

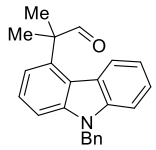

1.01
2.00
1.01
0.93
0.93
1.00
1.00
1.01
1.00
2.98
3.00
3.05
3.06
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

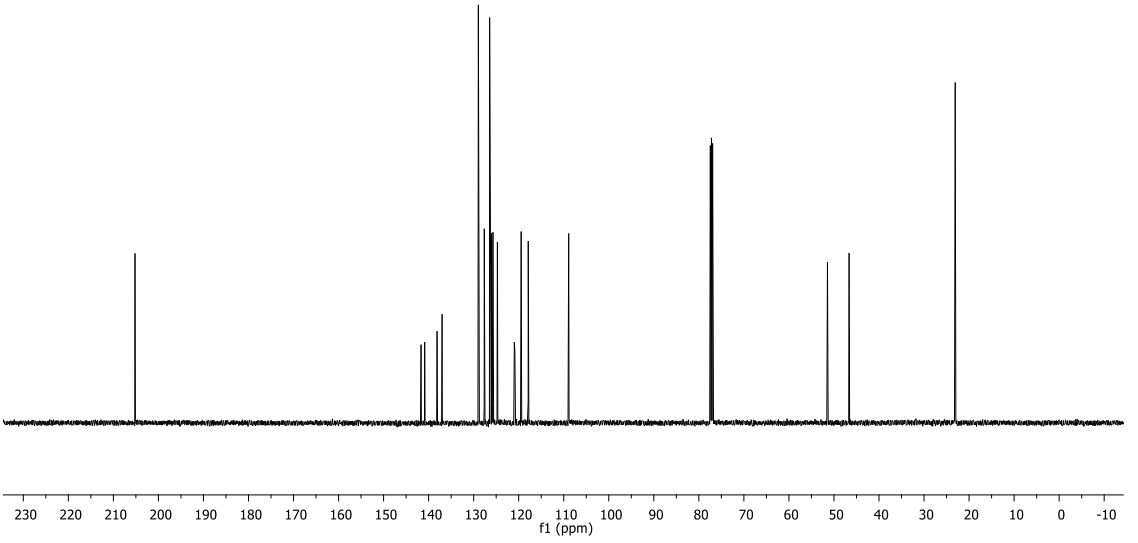

Me
Me
Me
Me
S

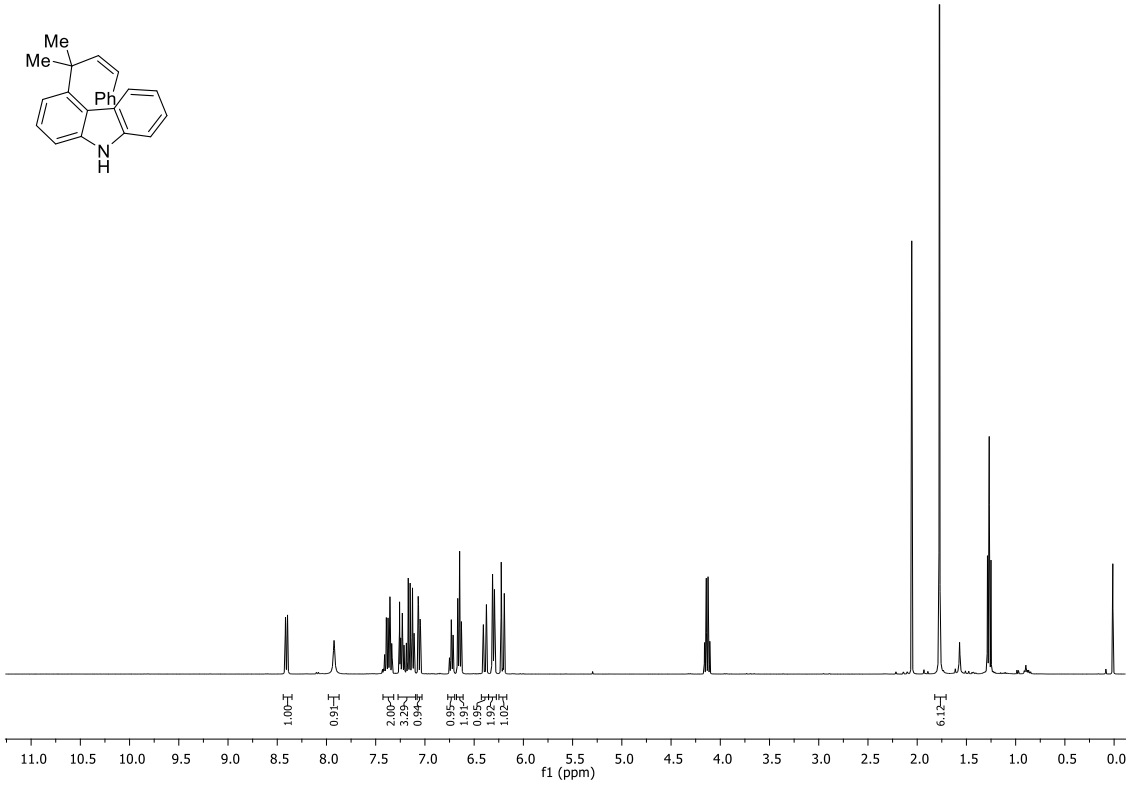

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

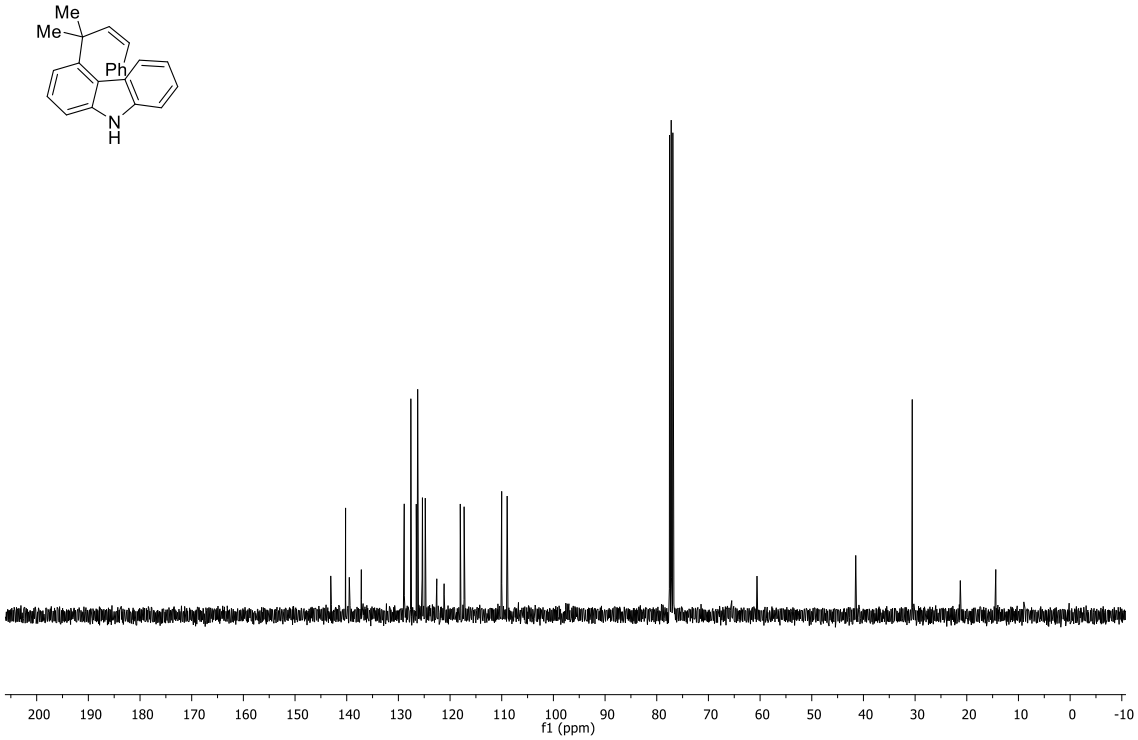

Me
Me
O
N
Bn

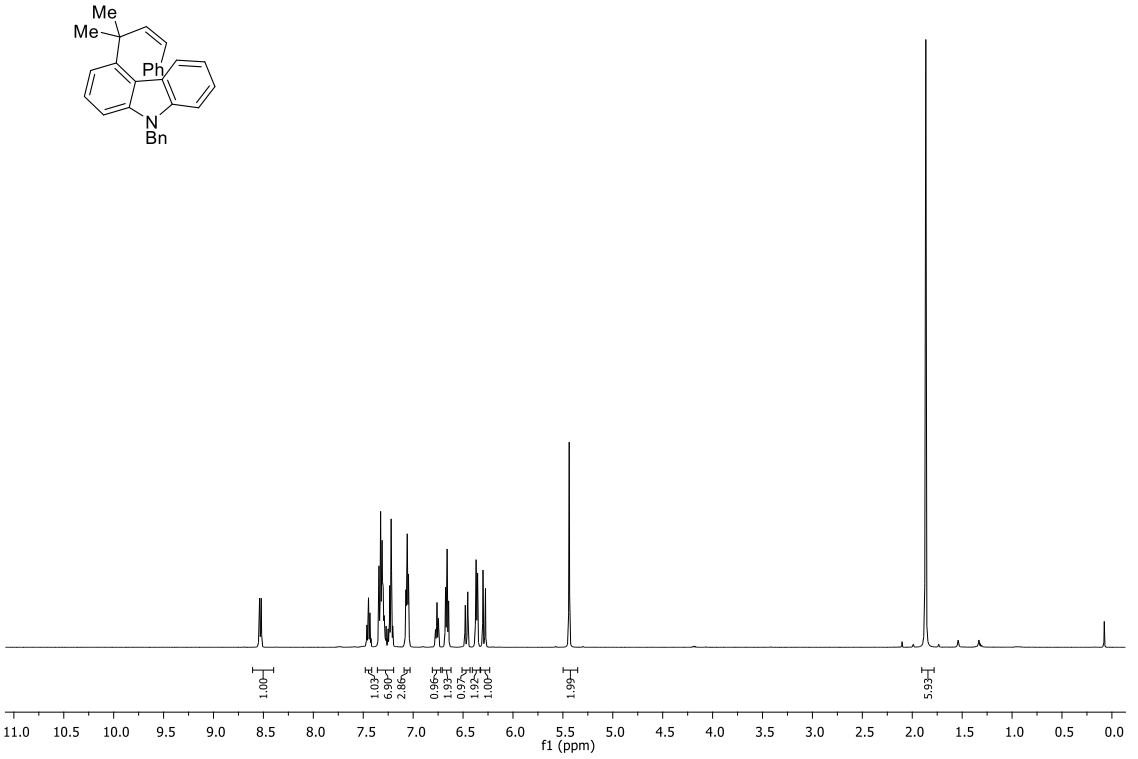

1.00
1.05
1.08
3.23
1.11
4.32
2.07
2.20
6.39
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

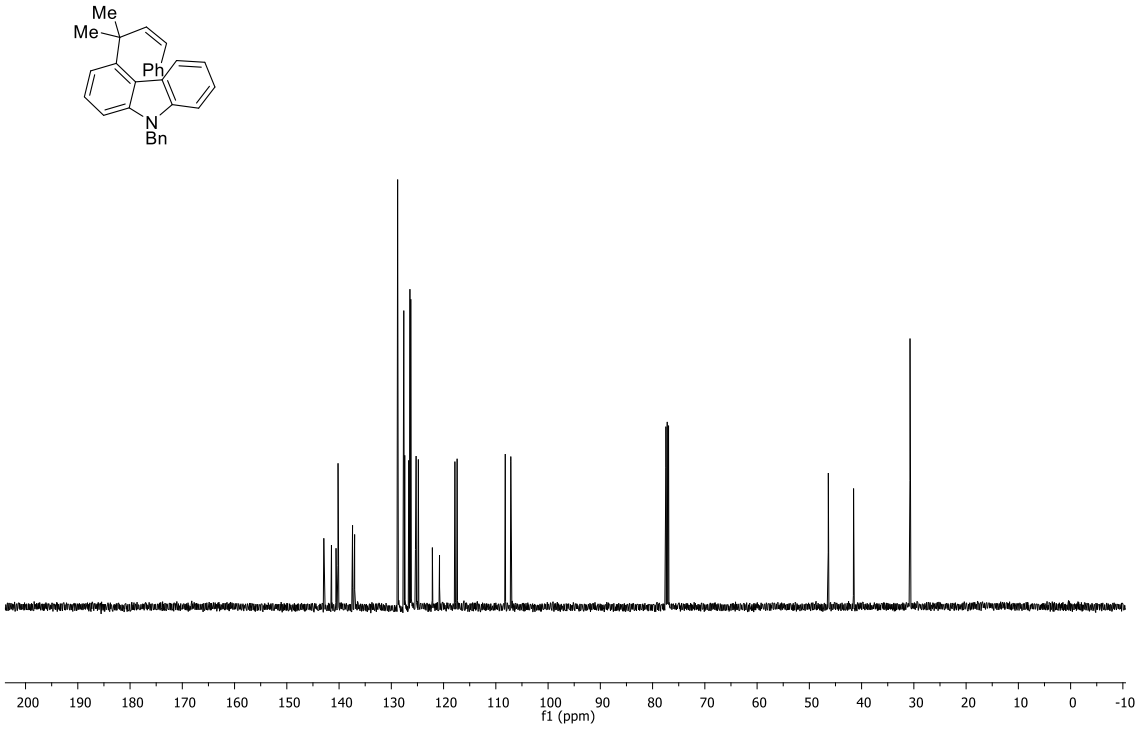

Me
Me
O
N
Bn

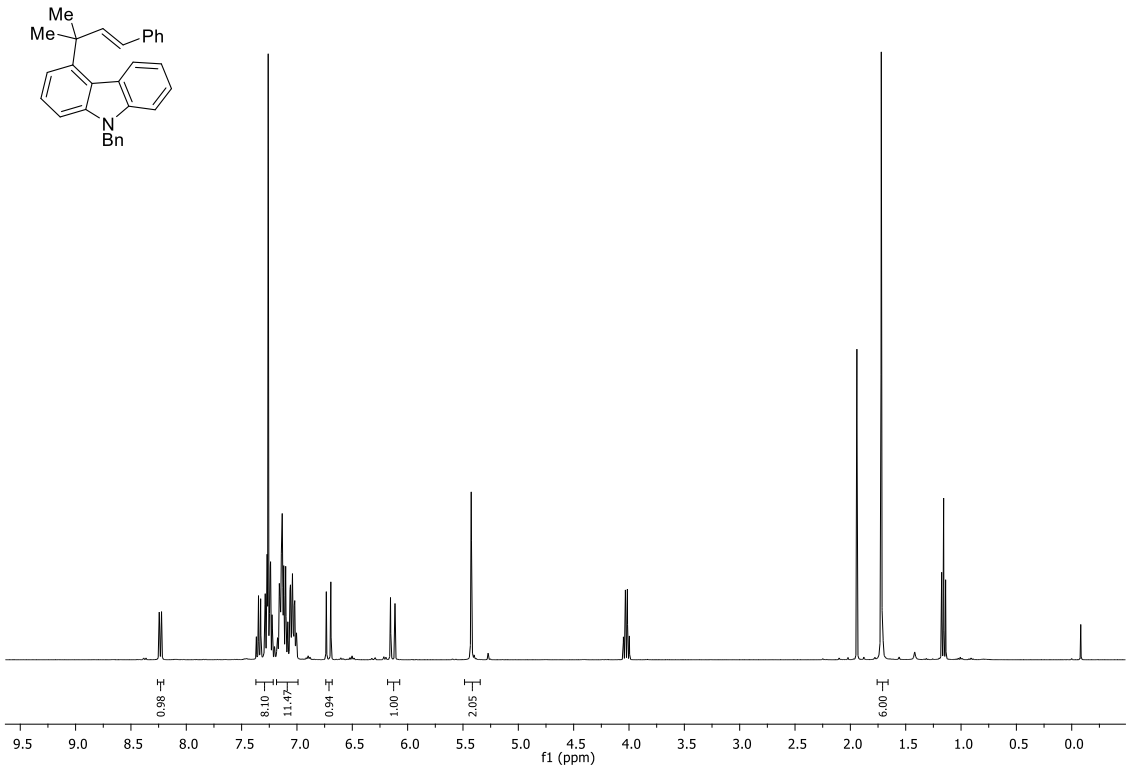

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

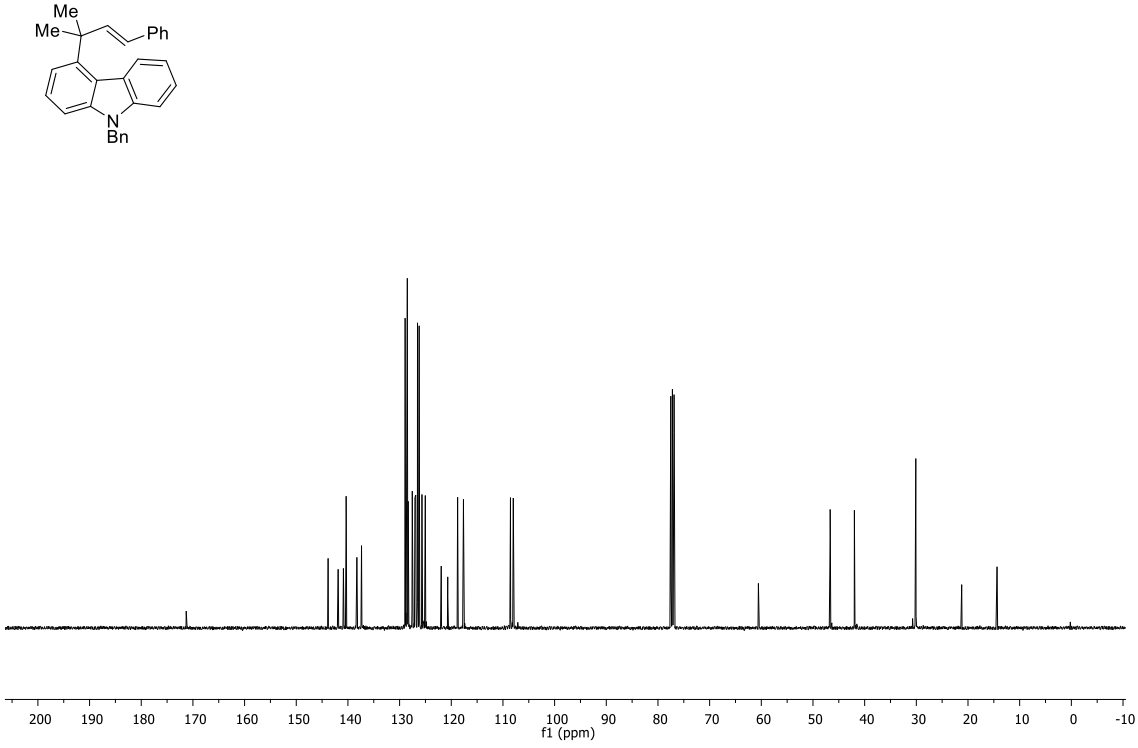

Me
Me
Ph
N
H
1.00
0.91
2.00
3.29
0.94
0.95
1.91
0.95
1.92
1.02
6.12
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

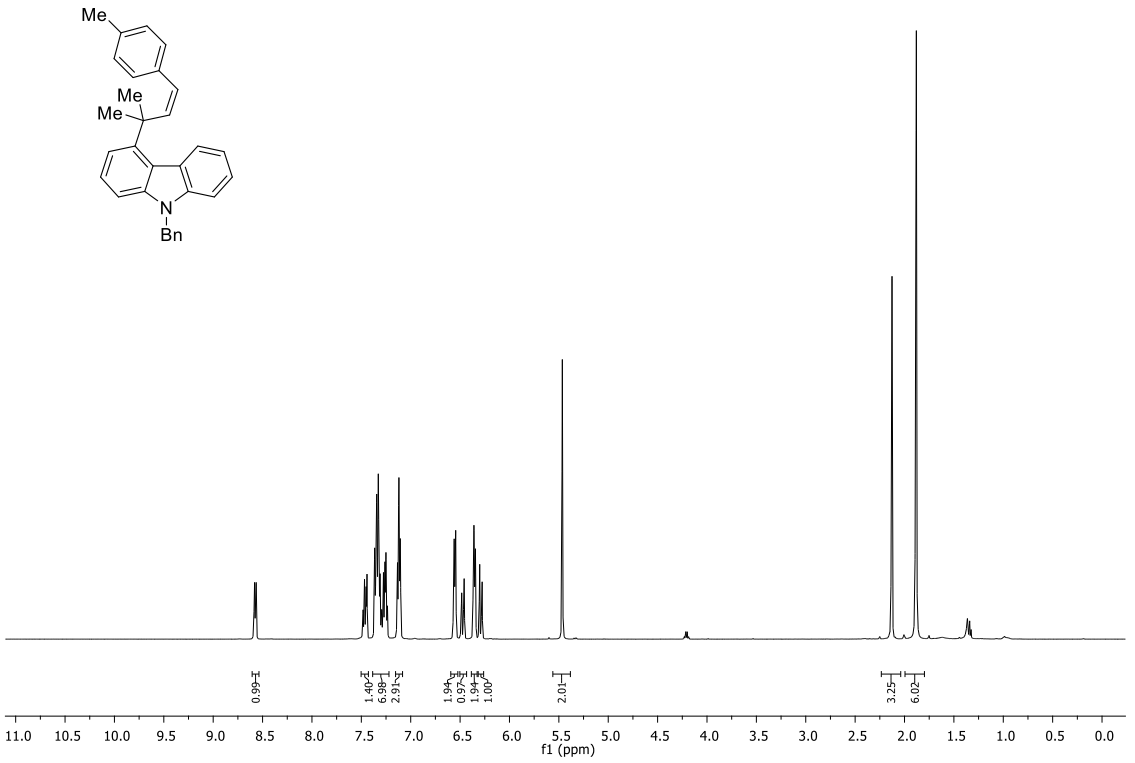

Me
Me
Ph
N
H
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

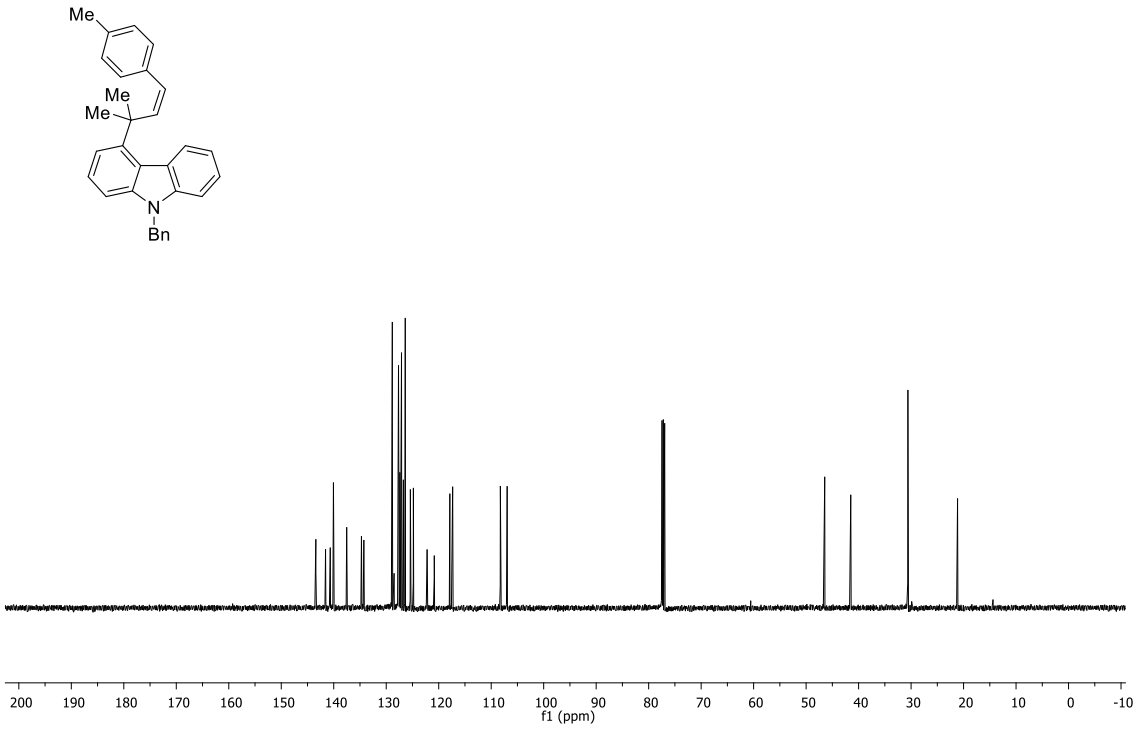

Me
Me
Ph
N
Bn
1.00
1.03
6.90
2.86
0.96
1.93
0.97
1.92
1.00
1.99
5.93
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

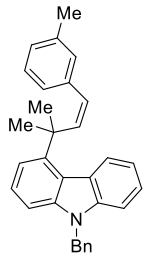

Me
Me
Ph
N
Bn
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

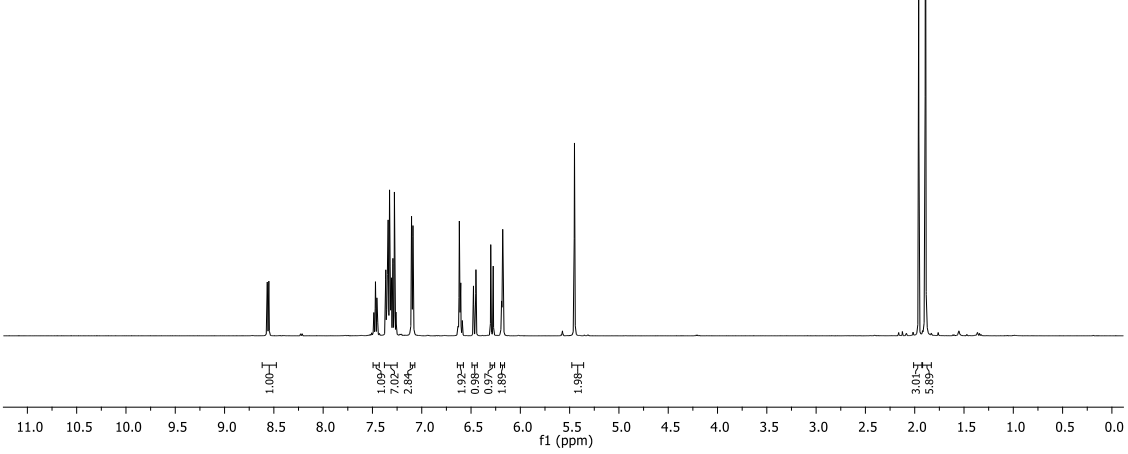

Me
Me
Ph
N
Bn
0.98
8.10
11.47
0.94
1.00
2.05
6.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

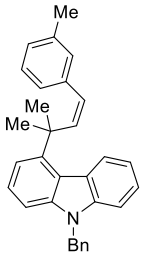

Me
Me
Ph
N
Bn
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

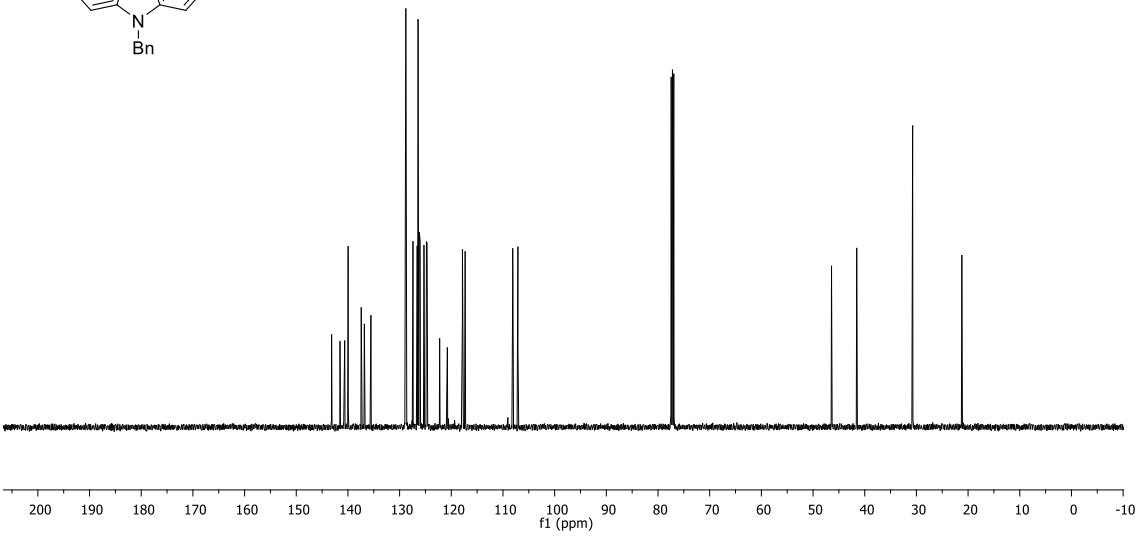

Me
Me
Me
N
Bn
0.99
1.40
6.98
2.91
1.94
0.97
1.94
1.00
2.01
3.25
6.02
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

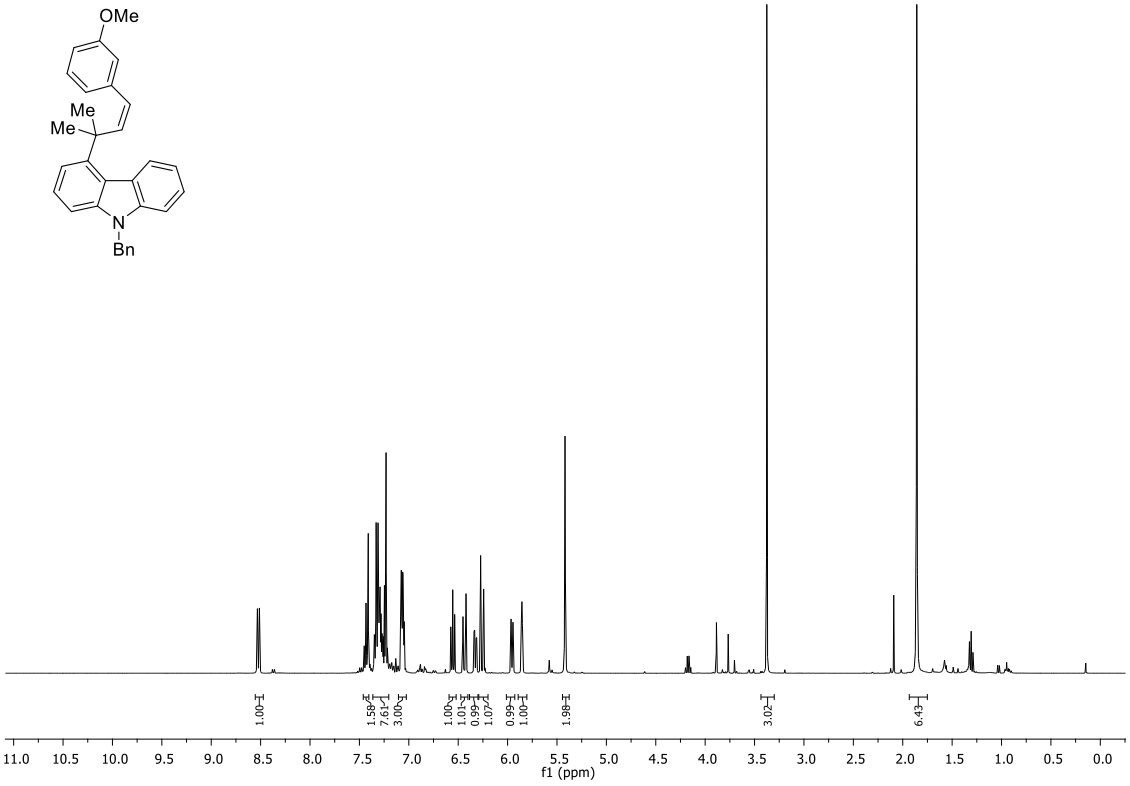

Me
Me
Me
N
Bn
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

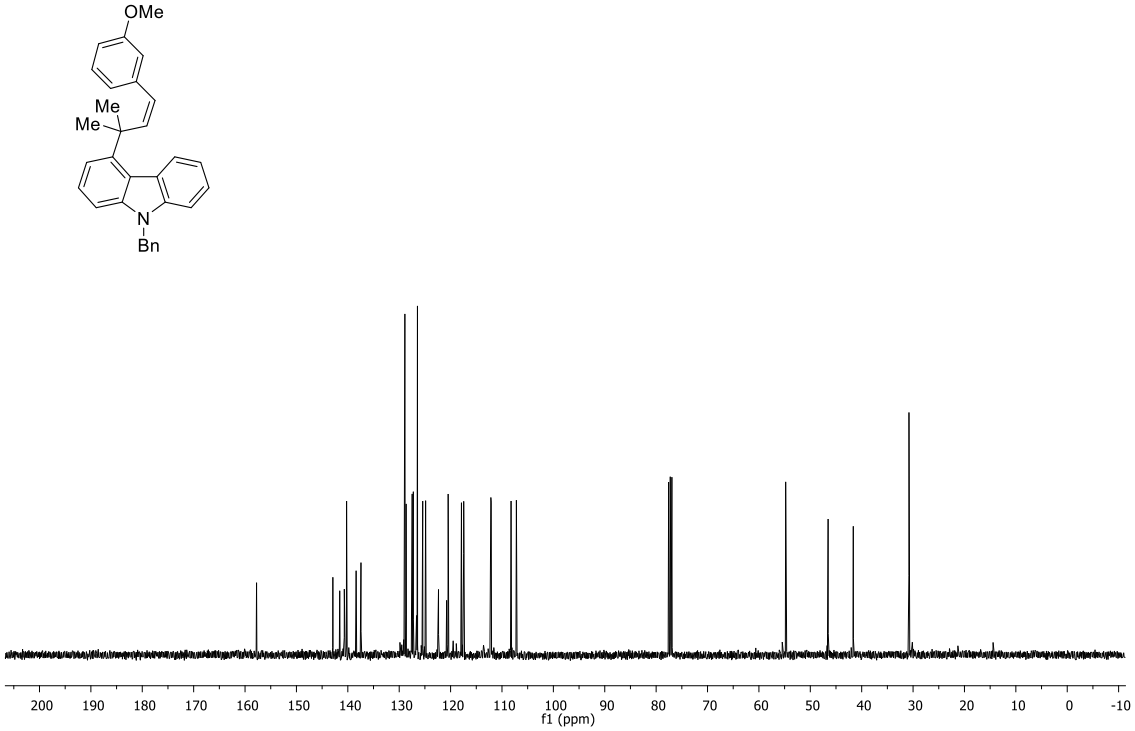

Me
Me
Me
N
Bn

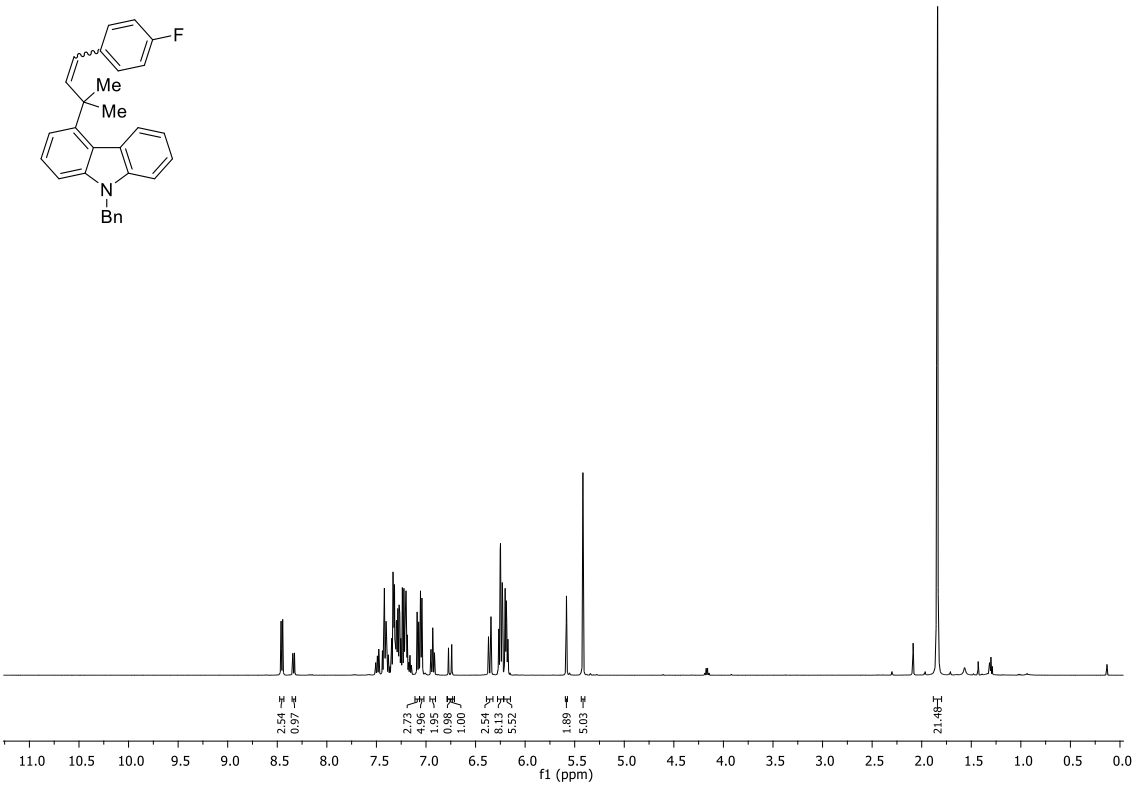

1.00
1.09
7.02
2.84
1.92
0.98
0.97
1.89
1.98
3.01
5.89
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

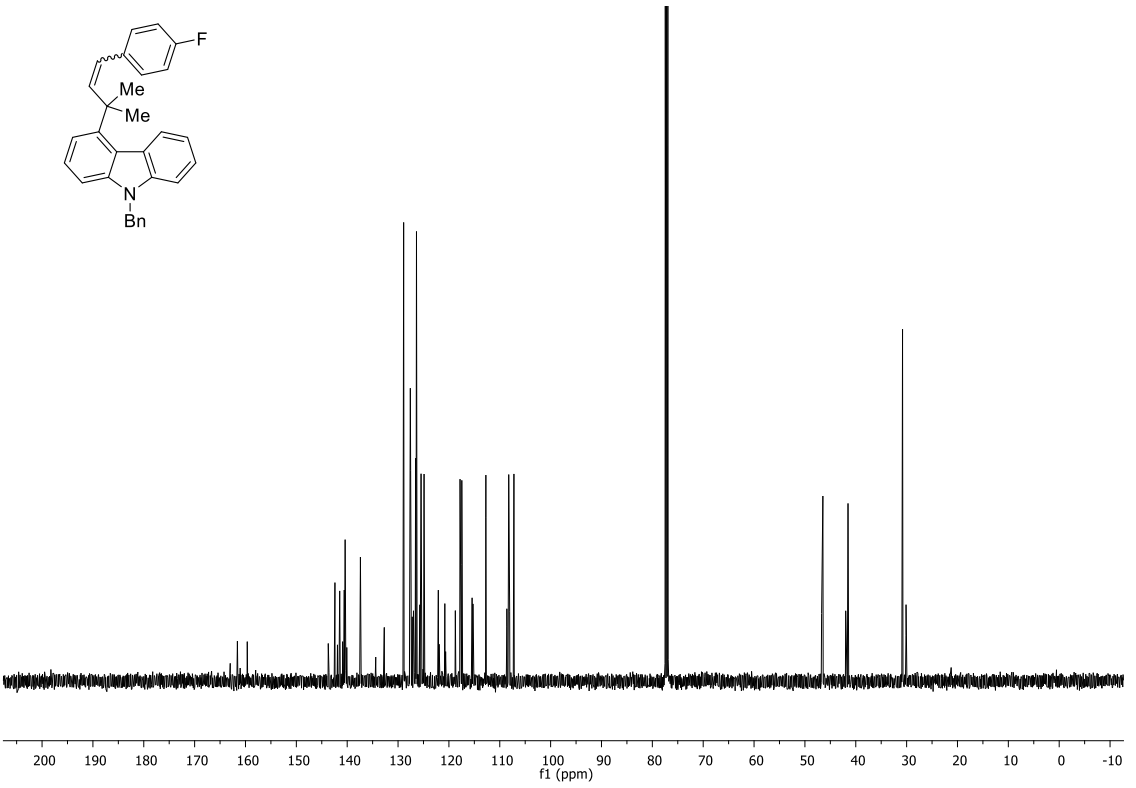

Me
Me
Me
N
Bn

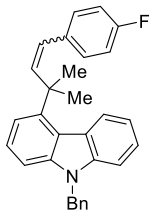

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

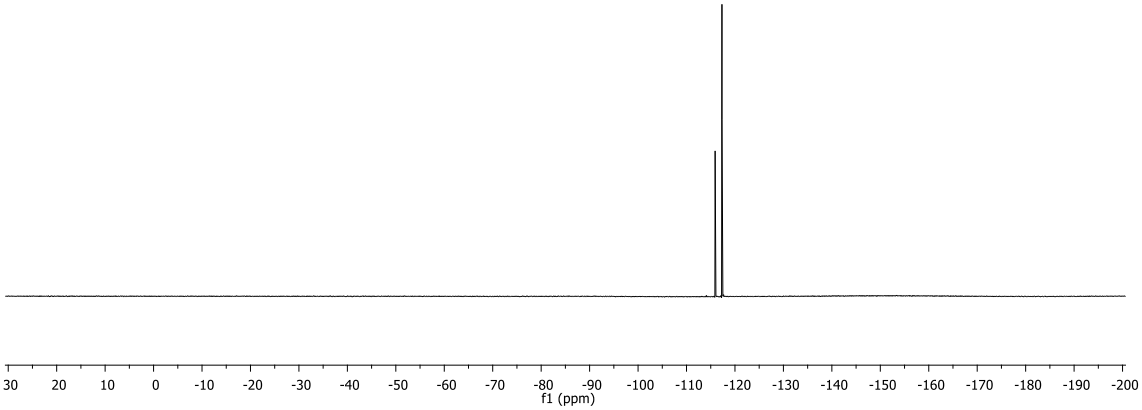

OMe
Me
Me
N
Bn
1.00
1.58
7.61
3.00
1.00
1.01
0.99
1.07
0.99
1.00
1.98
3.02
6.43
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

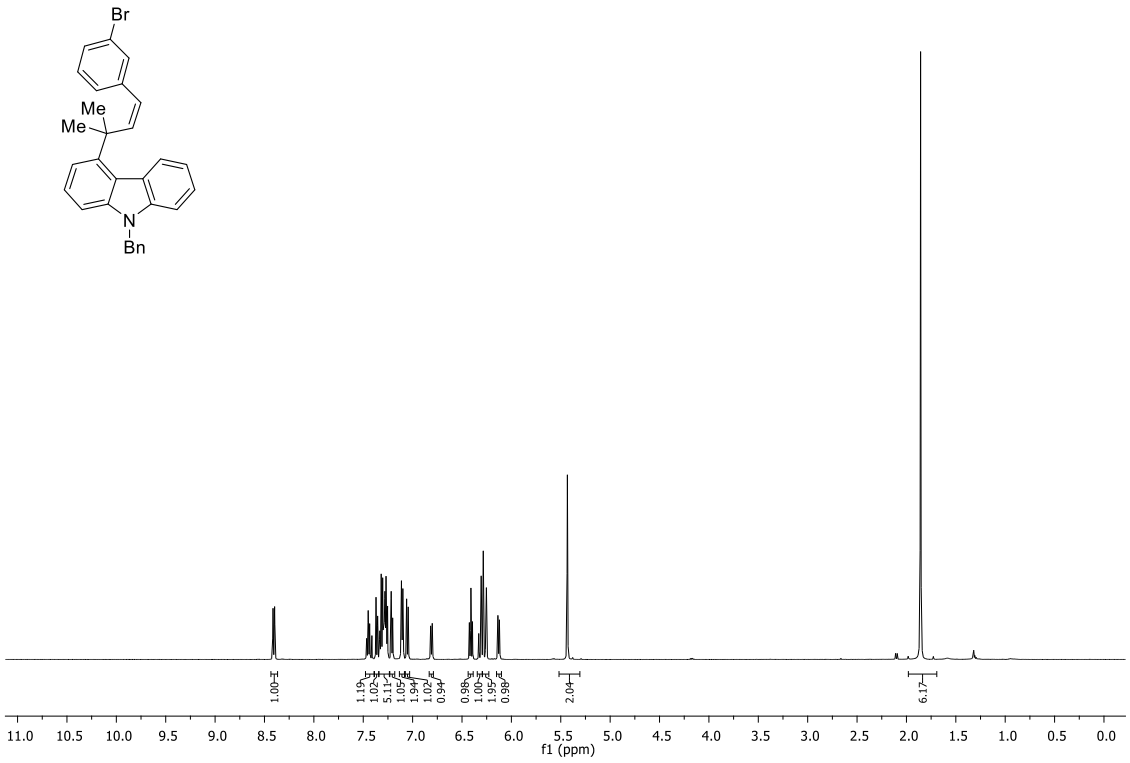

OMe
Me
Me
N
Bn
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

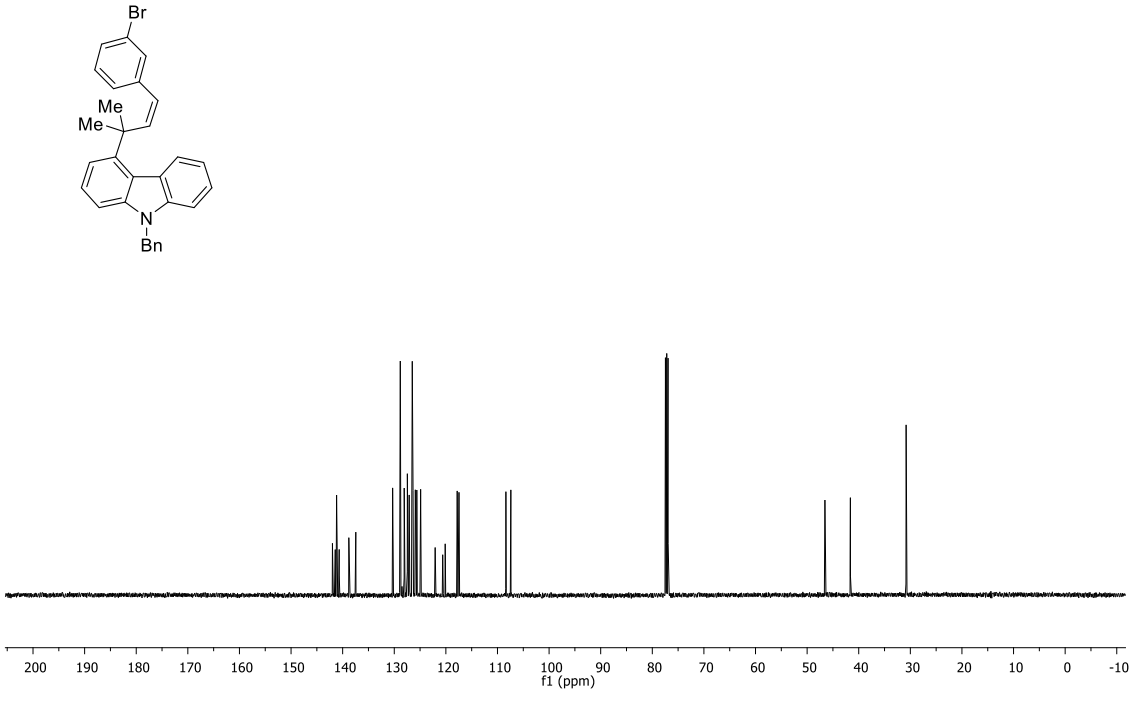

F
Me
Me
N
Bn
2.54
0.97
2.73
4.96
1.95
0.98
1.00
2.54
8.13
5.52
1.89
5.03
21.48
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

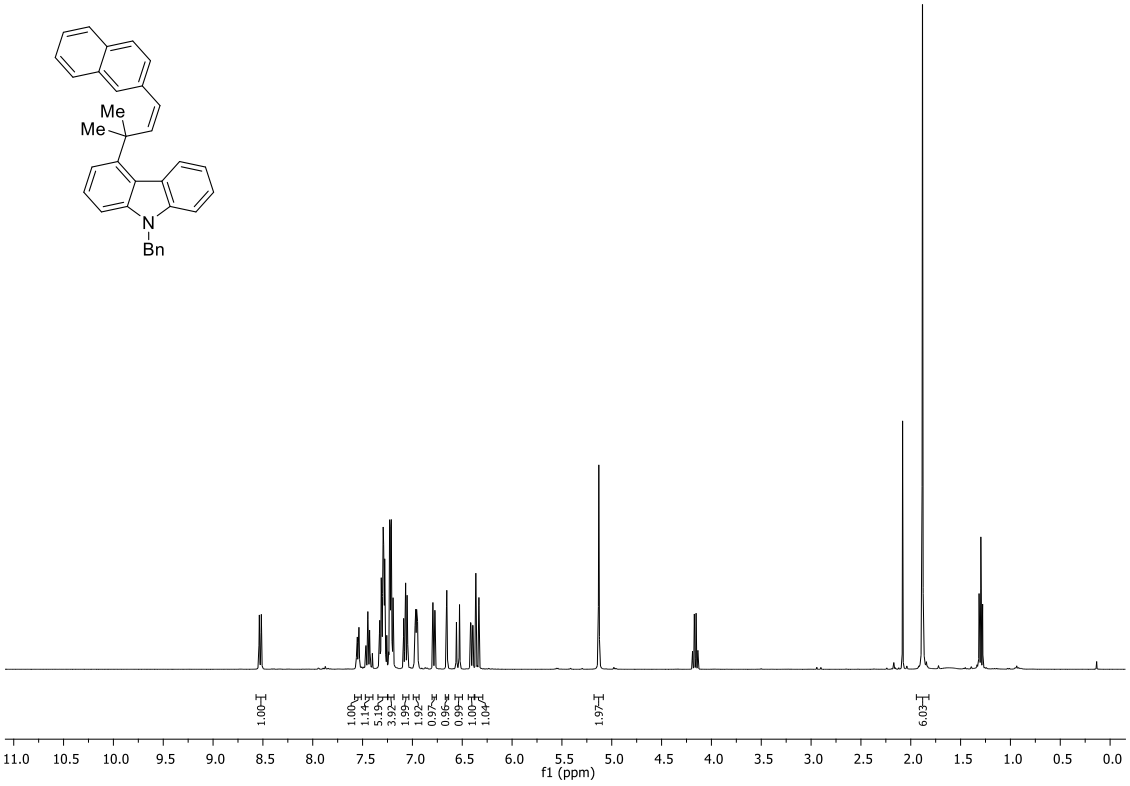

F
Me
Me
N
Bn
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

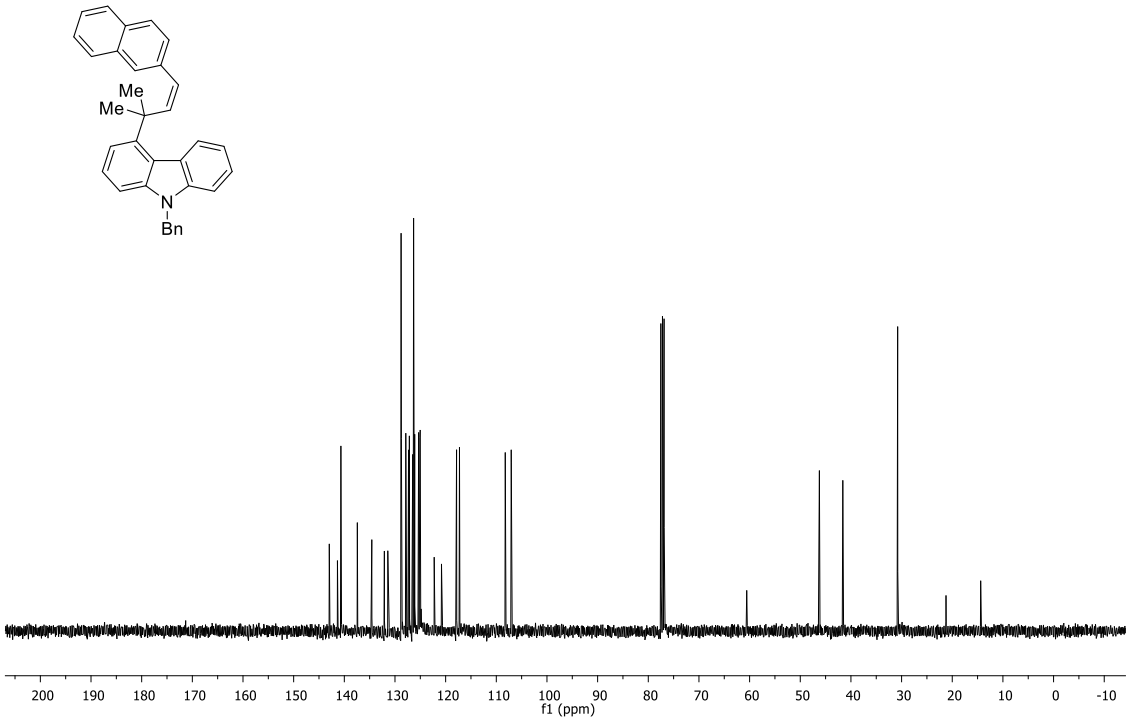

F
Me
Me
N
Bn

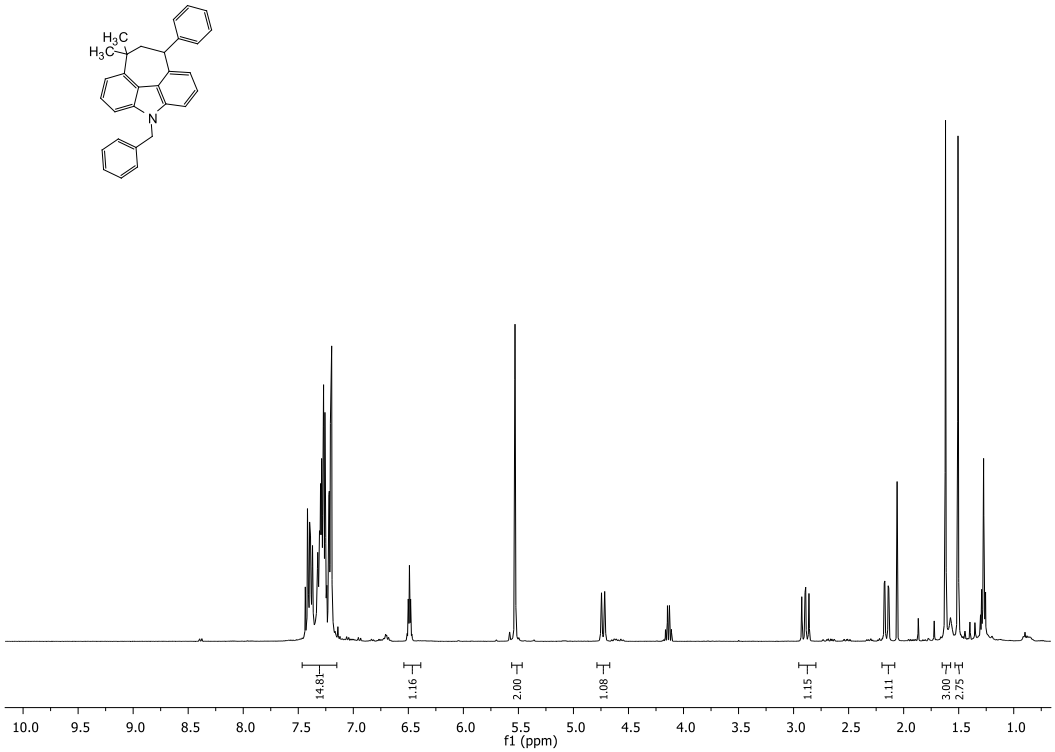

30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

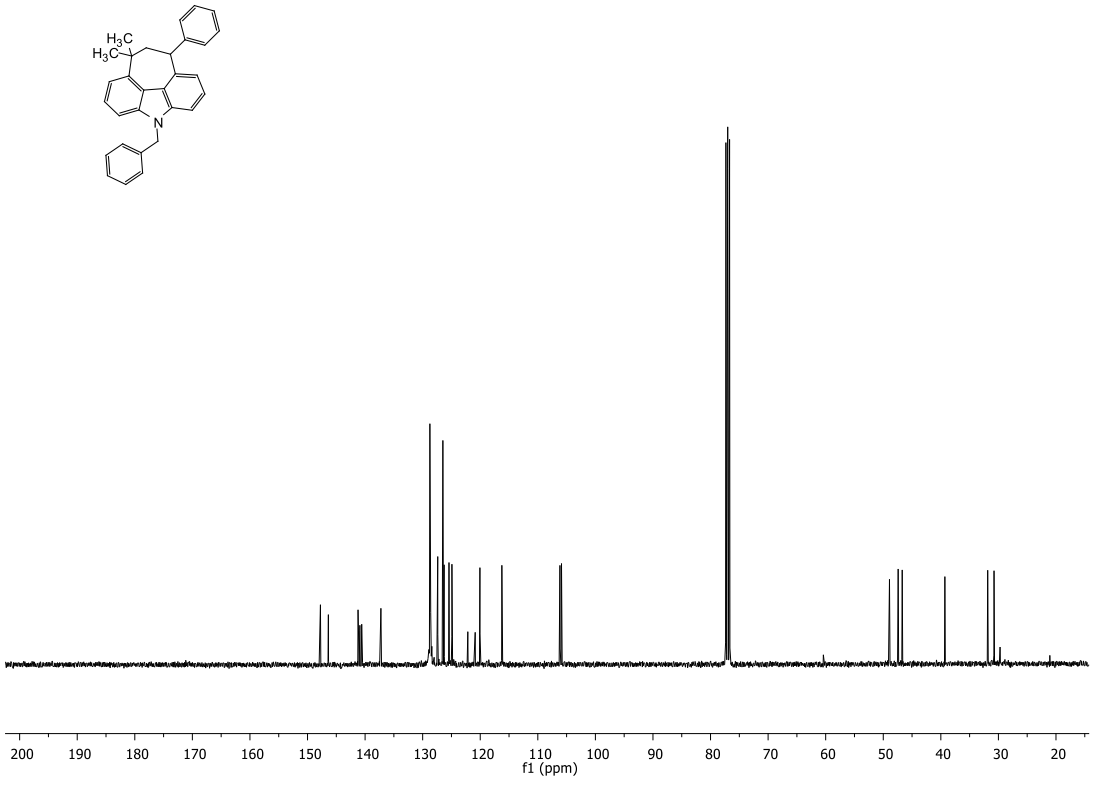

Br
Me
Me
N
Bn
1.00
1.19
1.02
5.11
1.05
1.94
1.02
0.94
0.98
1.00
1.95
0.98
2.04
6.17
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

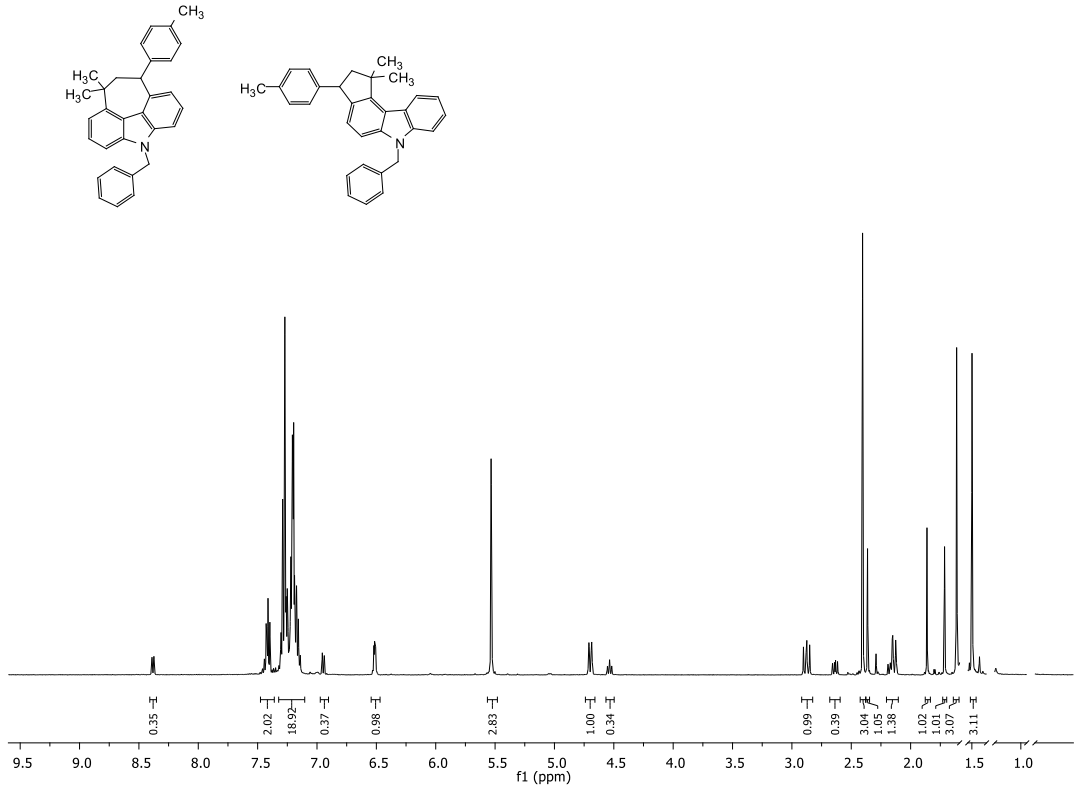

Br
Me
Me
N
Bn
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

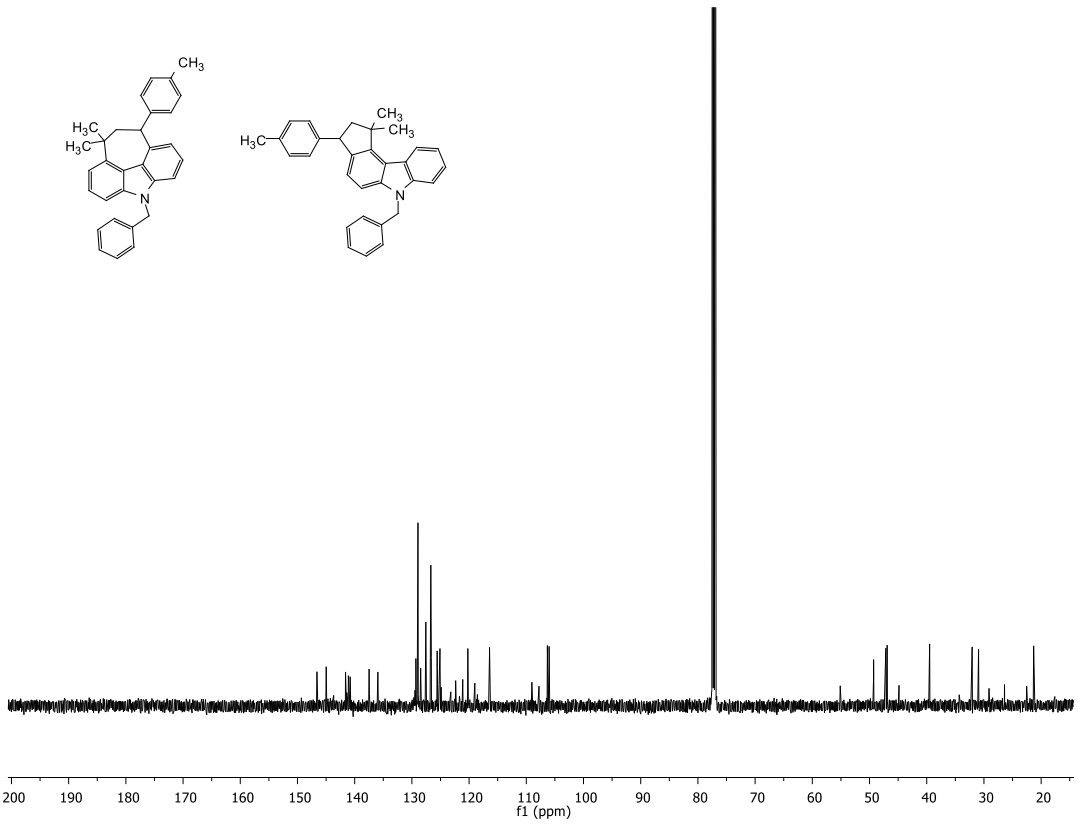

Me
Me
N
Bn
1.00
1.04
1.14
5.19
3.93
1.99
1.92
0.97
0.96
0.99
1.00
1.04
1.97
6.03
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

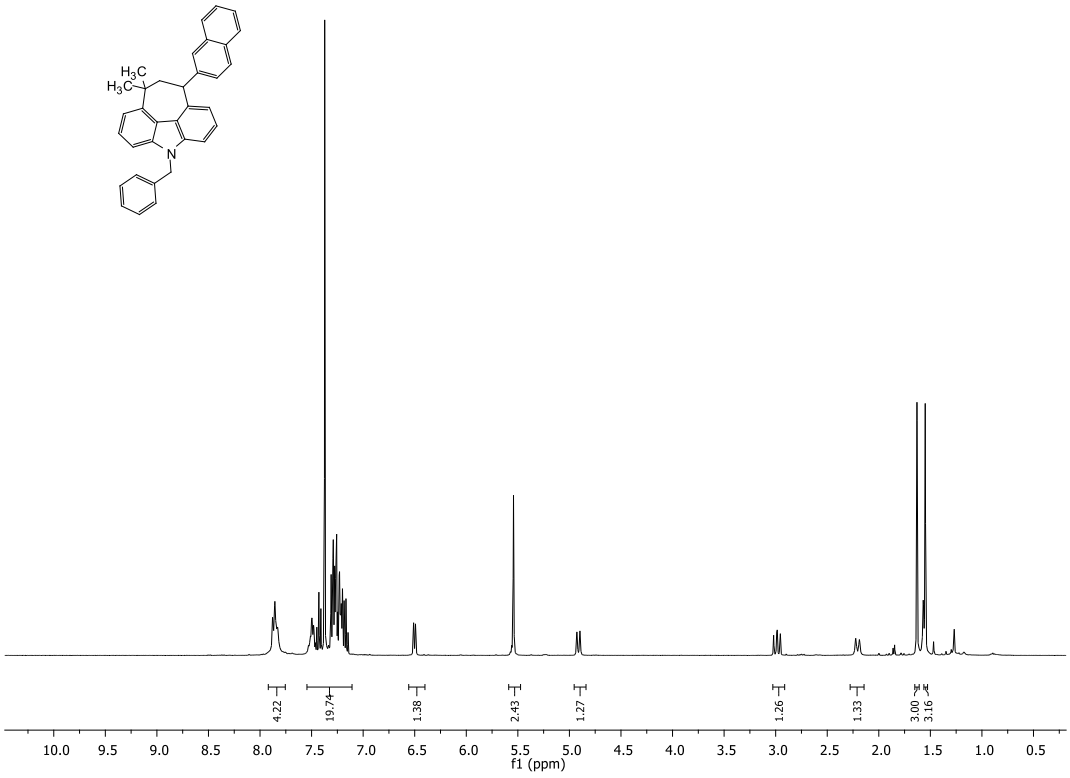

Me
Me
N
Bn
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

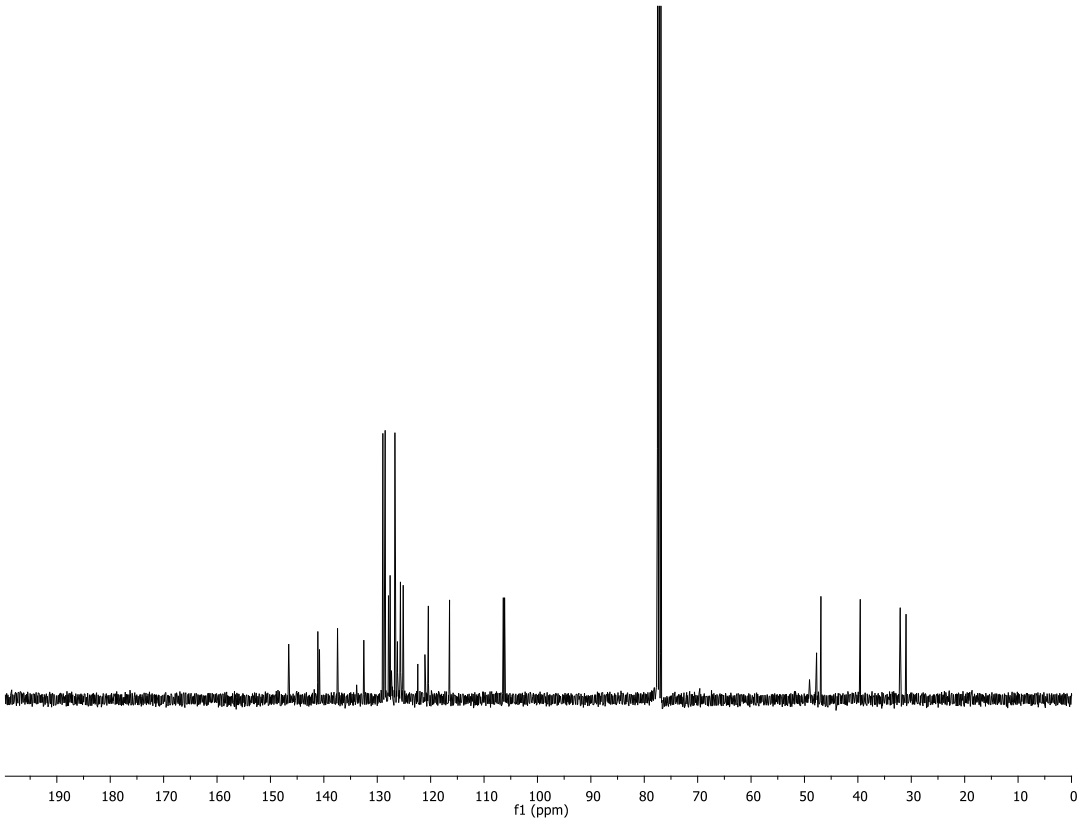

H3C
H3C
N
14.81
1.16
2.00
1.08
1.15
1.11
3.00
2.75
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
f1 (ppm)

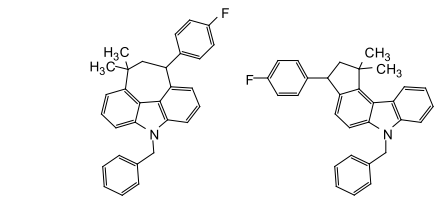

H3C
H3C
N
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
f1 (ppm)

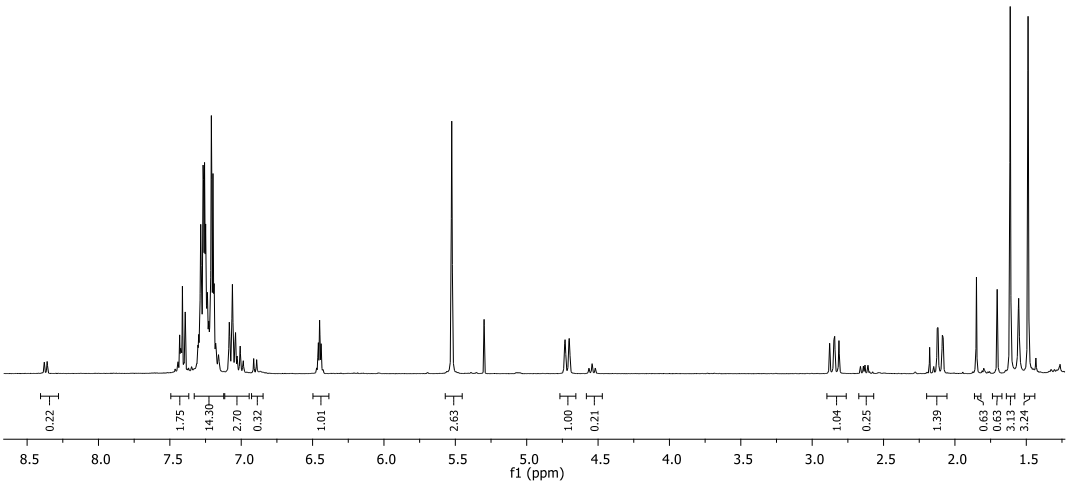

CH3
H3C
H3C
N
CH3
CH3
H3C
N
0.35
2.02
18.92
0.37
0.98
2.83
1.00
0.34
0.99
0.39
3.04
1.05
1.38
1.02
1.01
3.07
3.11
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
f1 (ppm)

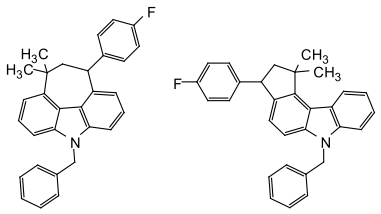

CH3
H3C
H3C
N
CH3
CH3
H3C
N
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
f1 (ppm)


H3C
H3C
N
4.22
19.74
1.38
2.43
1.27
1.26
1.33
3.00
3.16
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)

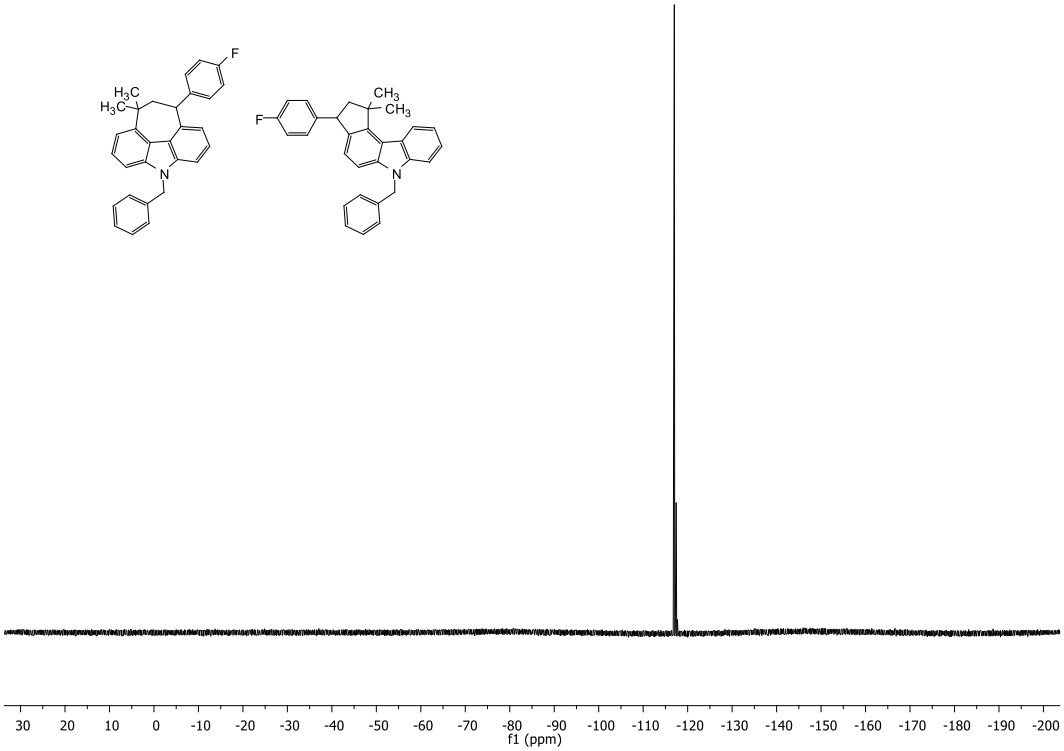

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


F
H3C
H3C
N
CH3
CH3
F
N


0.22
1.75
14.30
2.70
0.32
1.01
2.63
1.00
0.21
1.04
0.25
1.39
0.63
0.63
3.13
3.24
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
f1 (ppm)


F
H3C
H3C
N
CH3
CH3
F
N

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


F
H3C
H3C
N
CH3
CH3
F
N
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)