Enyne Metathesis (Part I)
and
Development of New Methods for Functionalized Arenes (Part II)

BY

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THESIS

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I dedicate this thesis to my lovely wife, Shao-Lun Hsu, for her endless love and constant support in each step of the way, to my parents for their understanding and unconditional love. Without whom none of my success will be possible.

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KPW

2013 in Chicago

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LIST Of ABBREVIATIONS

Ac	Acetyl ($CH_3C{=}O$)
bda	Benzylidene Acetone
bipy (bpy)	2,2'-bipyridyl
Boc	*t*-Butyloxycarbonyl [$COC(CH_3)_3$]
BOM	Benzyloxymethyl ($PhCH_2OCH_2$-alcohol protection)
Bz	Benzoyl (caution: sometimes used for benzyl)
Bn	Benzyl
Bu	Butyl
CAN	Ceric Ammonium Nitrate
Cbz	Carbobenzyloxy ($BnOC{=}O$)
cod	Cyclooctadiene
COT	Cyclooctatetraene
Cp	Cyclopentadienyl
Cp*	Pentamethylcyclopentadienyl
CSA	Camphorsulfonic Acid
DA	Diels-Alder Reaction
DAST	(Diethylamino)sulfur trifluoride Et_2NSF_3
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexyl Carbodiimide
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
de	Diastereomeric excess
DIBAL	Diisobutylaluminum Hydride
Dppe	1,2-Bis(diphenylphosphino)ethane
DMAP	4-Dimethylaminopyridine (base catalyst)

LIST Of ABBREVIATIONS (continued)

DMF	Dimethylformamide (solvent)
DMSO	Dimethyl Sulfoxide (solvent)
E	Entgegen (opposite, trans)
ee	Enantiomeric Excess
LAH	Lithium Aluminum Hydride ($LiAlH_4$)
LDA	Lithium Diisopropylamide
LHMDS	Lithium Hexamethyldisilazide ($LiN(SiMe_3)_2$)
MCPBA	*meta*-Chloroperoxybenzoic Acid
Ms	Methanesulfonyl (Mesyl, CH_3SO_2)
NBS, NCS	*N*-Bromo, N-Chlorosuccinimide
NIS	*N*-Iodosuccinimide
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
PMB	*p*-Methoxybenzyl
PPTS	Pyridinium *p*-Toluenesulfonate
Pv	Pivaloyl
Py	Pyridine; Solvent, base, catalyst
RT	Room Temperature
SEM	2-Trimethylsilylethoxymethoxy
SES	Trimethylsilylethylsulfonyl
TASF	Tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAF	Tetra-*n*-butylammonium fluoride
TBDMS	*t*-Butyldimethylsilyl
TBDPS	*t*-Butyldiphenylsilyl

LIST Of ABBREVIATIONS (continued)

TBHP	*t*-Butylhydroperoxide
TBS	*t*-Butyldimethylsilyl (also TBDMS)
TEA	Triethylamine
TES	Triethylsilyl
Tf	Triflate (CF_3SO_2)
TFA	Trifluoroacetic
THP	Tetrahydropyran
TIPS	Triisopropylsilyl
TMEDA	N,N,N',N'-Tetramethylethylenediamine
TMS	Tetramethylsilane, also Trimethylsilyl
Tol	*p*-Tolyl
Ts	Tosyl (p-CH3C6H4SO2)
Z	Zusammen (together, *cis*)

SUMMARY

This thesis has two main parts. Part I is composed of two chapters which describe the structure and reactivity of alkyne-chelated ruthenium alkylidene complexes and newly discovered non-metathetic activity of Grubbs catalysts. Part II consists of four chapters describing transition metal-catalyzed new synthetic methods for functionalized arenes via metal-complexed aryne intermediates generated in situ from multiynes.

Specifically, in chapter one, recent advances of olefin metathesis are briefly reviewed and the first well-defined alkyne-chelated ruthenium alkylidene is delineated. In chapter two, a brief summary of previously reported notable non-metathetic reactions using Grubbs-type ruthenium alkylidenes is presented and a new 1,4-hydrovinylative cyclization of various multiynes with ethylene using Grubbs type ruthenium alkylidene is discussed.

In chapter three, a brief survey for the progress of aryne chemistry and recent computational studies on regioselectivity of nucleophile addition to aryne intermediates is provided. In chapter four, a new paradigm of a catalytic hydrohalogenation to form structurally elaborated aryl halides using ruthenium alkylidene complex is described. In chapter five, a new C-H bond insertion reaction mediated by silver-stabilized arynes generated directly from alkyne building blocks is discussed. Preliminary mechanistic studies to elucidate the reaction mechanism are also presented. Finally, in chapter six a conceptually distinctive method capable of generating Ar-F, Ar-CF_3 and Ar-SCF_3 from non-aromatic precursors is described. Mechanistic novelty, broad substrate scope and excellent regioselectivity of this method allow an expeditious access to pharmaceutically important functionalized indoline and isoindoline derivatives.

Chapter 1. Structure and Reactivity of Alkyne-Chelated Ruthenium Alkylidene Complexes

1.1. Brief Overview of Olefin Metathesis

1.1.1. Historical Background

As highlighted by the Nobel Prize in chemistry in 2005, olefin metathesis is one of the most powerful tools to create molecular complexity in contemporary organic synthesis.[1] Historically, the first example of olefin metathesis, termed double bond scrambling reaction, was reported in the mid-1950s.[2] Olefin metathesis, a general term used nowadays, was subsequently coined in 1967 by Calderon and co-workers based on Greek words *meta* (change) and *thesis* (position), which refers the process involving controlled redistribution of carbon-carbon double bonds.[3] During the early period of olefin metathesis development, the mechanism of this process was not yet understood until Chauvin proposed a new mechanism in 1971.[4] Chauvin's mechanism relies on a metal carbene as a propagating species that reacts with an alkene via a [2+2]-cycloaddition to form metallacyclobutane intermediate. Inspired by Chauvin's innovative mechanistic proposal, considerable efforts have been devoted to the development of well-defined metal alkylidene catalysts. Major breakthroughs were made by Schrock and Grubbs. In 1990, Schrock reported the first well-defined molybdenum-based alkylidene complex.[5] Subsequently, in 1992, Grubbs developed a class of ruthenium-based alkylidene complexes exhibiting increased stability and functional group tolerance.[6] From the pioneering contributions of Schrock and Grubbs, molybdenum and ruthenium-based alkylidene complexes have continued to evolve over the past twenty years resulting in improved stability, reactivity and selectivity.[7] The broader scope of olefin metathesis reactions prompted by the use of Schrock's and Grubbs' catalysts has revolutionized the synthesis of a broad range of olefinic organic molecules from pharmaceuticals to advanced materials.

1.1.2. Classification of Metathesis

Olefin metathesis can be classified into three major categories depending on the types unsaturated systems: diene, enyne, and diyne metathesis (**Figure 1.1**).[8] Based on the structural change involved in the metathesis processes, different categorization has been made, and three most general classes are: cross metathesis (CM), ring-closing metathesis (RCM) and ring-opening metathesis (ROM).

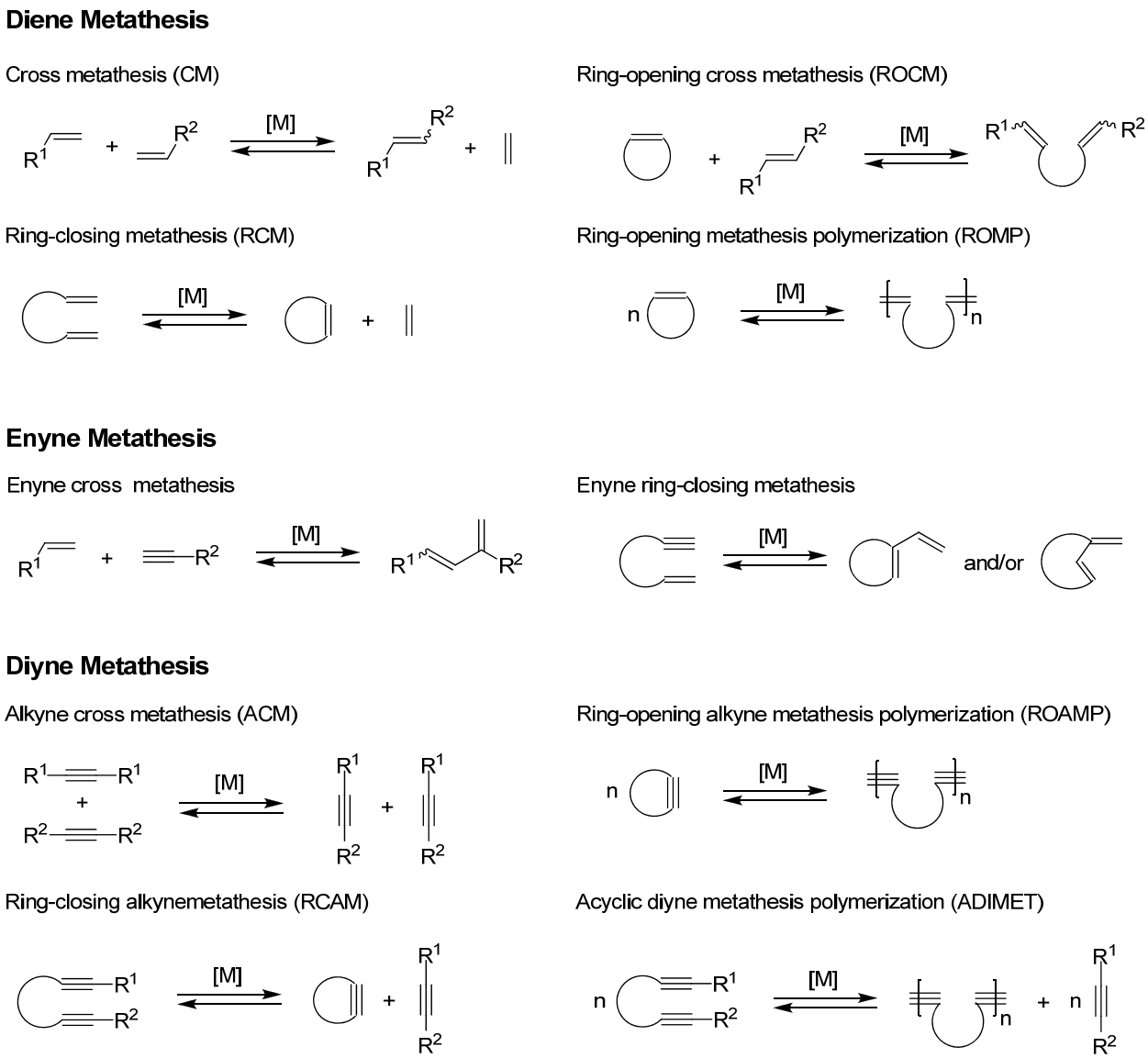


Figure 1.1. Classifications of metathesis reactions

Diene metathesis can be further divided into four categories: (1) cross metathesis (CM),[9] an intermolecular metathesis reaction between two alkenes to form a new alkene product and ethylene as the side product, (2) ring-closing metathesis (RCM),[10] a process in which a substrate containing two tethered alkene moieties is converted into a cyclic alkene product and ethylene, (3) ring-opening cross metathesis (ROCM),[8] an intermolecular metathesis reaction between a cyclic and an acyclic alkene to form an acyclic diene product, (4) ring-opening metathesis polymerization (ROMP),[11] a process by which polymeric compounds are generated from strained alkenes via ring-opening self-metathesis. On the other hand, enyne metathesis is a bond reorganization process between an alkene and an alkyne to generate 1,3-dienes.[12] This process has two main sub-categories, cross enyne metathesis[9c, 12] and ring-closing enyne metathesis.[12] Diyne metathesis is an exchange of alkylidyne units between a pair of alkynes. Analogous to alkene metathesis, diyne metathesis can be classified into four different types, including alkyne cross metathesis (ACM), ring-closing alkyne metathesis (RCAM), ring-opening alkyne metathesis polymerization (ROAMP) and acyclic diyne metathesis polymerization (ADIMET).[13]

1.1.3. Metathesis Catalysts

1.1.3.1. Schrock-Type Molybdenum and Tungsten Alkylidene Complexes

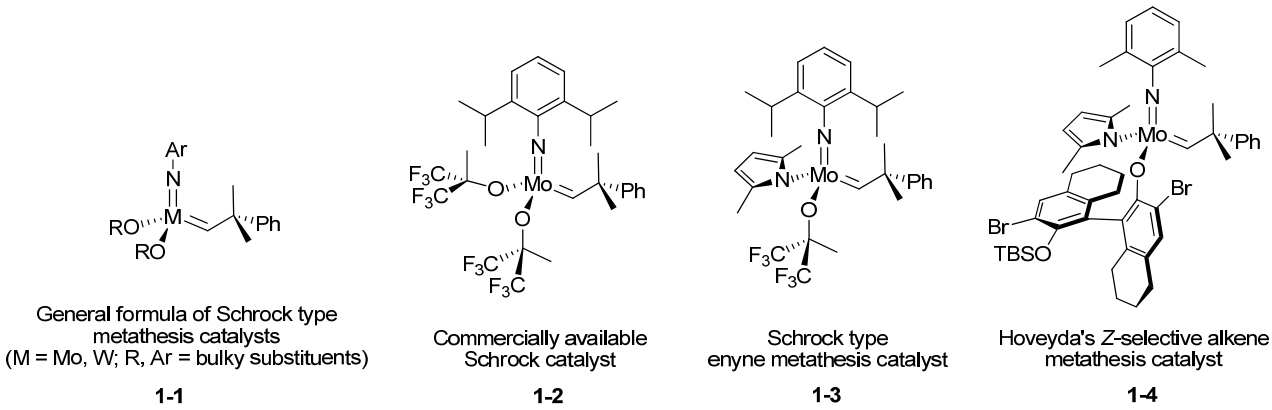
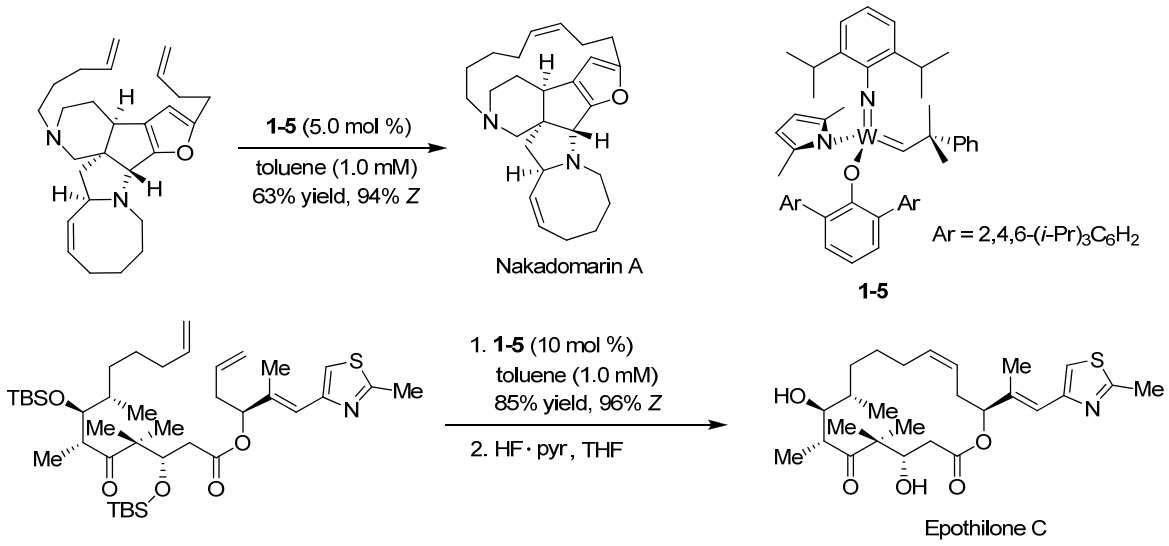


Figure 1.2. Schrock-type alkylidene complexes

To date, various molybdenum- and tungsten-based catalysts have been developed for metathesis purposes (**Figure 1.2**). Schrock developed well-defined molybdenum- and tungsten-based alkylidene

complexes **1-1** of the general formula [M(=CHMe$_2$Ph)(=N-Ar)(OR$_2$)] where M is Mo or W.[5, 14] Though these Schrock-type alkylidene complexes represent one of the most reactive catalysts for the alkene metathesis, these catalysts are extremely air and moisture sensitive due to their high oxophilicity. Even though Schrock-type molybdenum-based alkylidene complex **1-2** is now commercially available, it requires rigorously purified solvents and reagents, and even under these conditions, only a limited range of substrates can participate in the metathesis reaction due to limited functional group tolerance. Especially, Schrock-type molybdenum complex **1-3** bearing stereogenicity at Mo was exploited for *endo*-selective enyne RCM as demonstrated by Hoveyda.[15] By further extending this concept, Hoveyda and co-workers developed a *Z*-selective olefin metathesis catalyst **1-4** that possesses bulky and freely rotating monodentate alkoxide ligand.[16] It was demonstrated that this catalyst overcomes the inherent thermodynamic preference of the metathesis process to form *E*-alkene products, through a non-reversible reaction regime that selectively generates Z-alkenes. It is well known that RCM to form macrocycles generally provides product with low selectivity in alkene stereochemistry. Hoveyda and co-workers employed tungsten-based alkylidene complex **1-5** for the synthesis of macrocyclic natural products containing *Z*-alkene such as epothilone C and nakadomarin A (**Scheme 1.1**).[17]

Scheme 1.1. Late-stage tungsten-catalyzed RCM for synthesis of nakadomarin A and epothilone C.



Relying on this catalyst-controlled stereoselective *Z*-alkene formation as the key step performed at the late-stage ring-closing metathesis, these target natural products were synthesized in elegant manners.

1.1.3.2. Grubbs-Type Ruthenium Alkylidene Complexes

The first well-defined ruthenium-based alkylidene complex **1-6** of type [$RuCl_2(PPh_3)$(=CH-CH=CPh_2)][6] was reported in 1992 by Grubbs and co-workers (**Figure 1.3**). The triphenylphosphine (PPh_3) ligand was subsequently replaced with tricyclohexylphosphine (PCy_3) to improve the catalytic activity.[18] This PCy_3 analogue of **1-6** was shown to promote metathesis reactions as efficiently as the Schrock-type alkylidene complexes yet showed superior functional group tolerance and stability. In 1995, Grubbs reported a new ruthenium based alkylidene complex **G-I**, known as the Grubbs first generation catalyst, which has been widely used in olefin metatheses of a variety substrate classes.[19] In 1999, further ligand tuning of **G–I** by replacing one of the PCy_3 ligand with *N*-heterocyclic carbene (NHC) ligand resulted in **G-II,** known as the second generation Grubbs catalyst[20] which is currently the most widely used catalyst for a variety of metathesis reactions. The NHC ligand is a stronger σ-donor than PCy_3 and thus facilitates the dissociation of PCy_3 to activate the catalyst as a 14-electron species, necessary for the initiation of the catalytic cycle. Few years later, further improvement of thermal stability of the catalyst has been accomplished by switching PCy_3 ligand with a chelating isopropoxyl group on a benzylidene ligand on both **G-I** and **G-II** by Hoveyda and co-workers.[21] These new complexes called Hoveyda-Grubbs complexes (**HG-I** and **HG-II**), although similar to the parent complexes in their reactivity, sometimes show better performance in certain reactions.

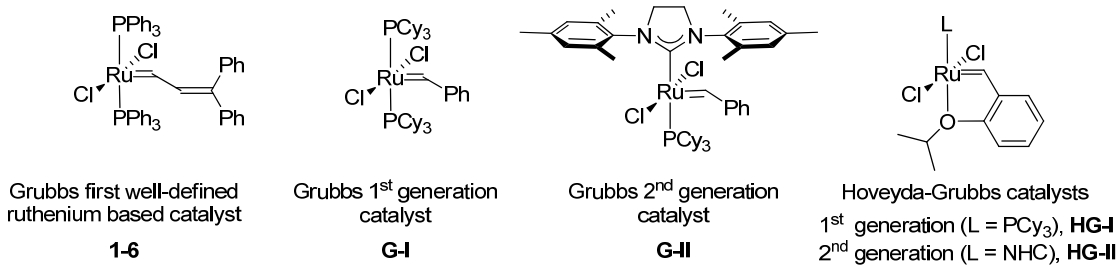


Figure 1.3. Grubbs-type ruthenium alkylidene complexes

More recently, a series of modified Grubbs-type ruthenium alkylidene complexes have been commercialized. These complexes provide broader reaction scope at lower initiation temperature even with sterically hindered alkene substrates (**Figure 1.4**).[22]

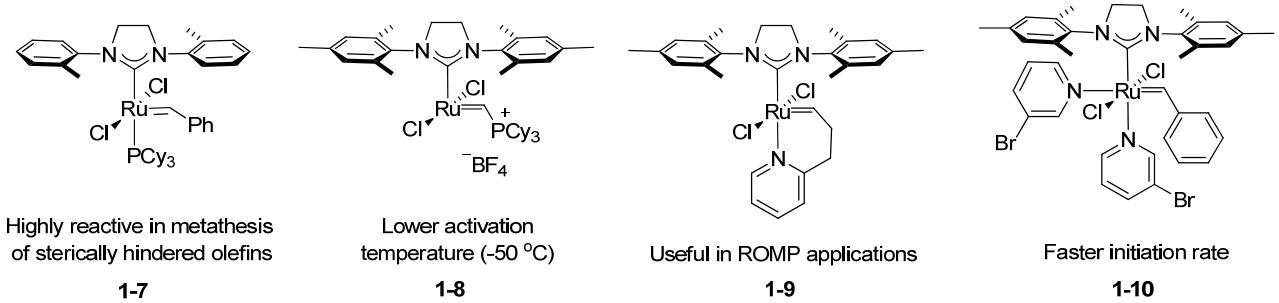


Figure 1.4. Other commercialized Grubbs-type ruthenium alkylidene complexes

1.1.3.3. Alkylidyne Complexes–Diyne Metathesis Catalysts

Catalysts for diyne metathesis known to date can be classified into two general categories: ill-defined (Mortreux's system) multi-component systems **1-11** and well-defined single-component systems **1-12** to **1-15** (**Figure 1.5**).[13, 23, 24] All well-defined single-component catalysts are represented by high oxidation state molybdenum- or tungsten-based Schrock-type alkylidyne complexes. Among these reagents, tungsten-based alkylidyne complex **1-12** is commercially available. Recently, Fürstner developed a series of molybdenum alkylidyne complexes possessing triphenylsilanoate ligands (**1-13**, **1-14** and **1-15**), and these complexes showed excellent reactivity and outstanding functional group compatibility compared to Schrock's catalyst **1-12**. The molybdenum benzylidyne complexes **1-13**, **1-14** and **1-15** can be prepared from commercially available $Mo(CO)_6$ with different additives under well-established reaction conditions.[24] Complexes **1-14** and **1-15** are air stable for several weeks and are capable of performing large scale reactions.

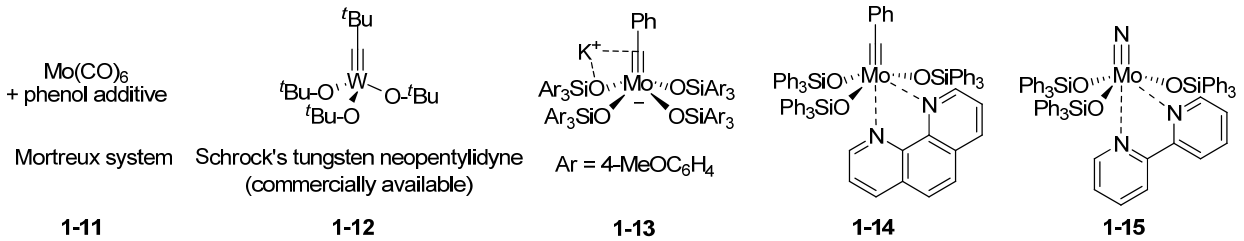


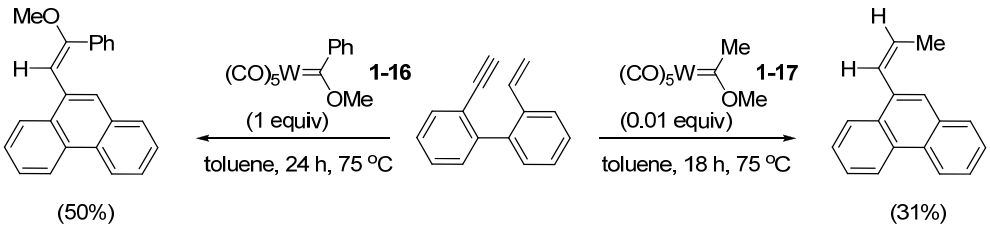
Figure 1.5. Diyne metathesis catalysts

1.1.4. Enyne Metathesis and Metallotropic [1,3]-Shift

1.1.4.1. Enyne Metathesis

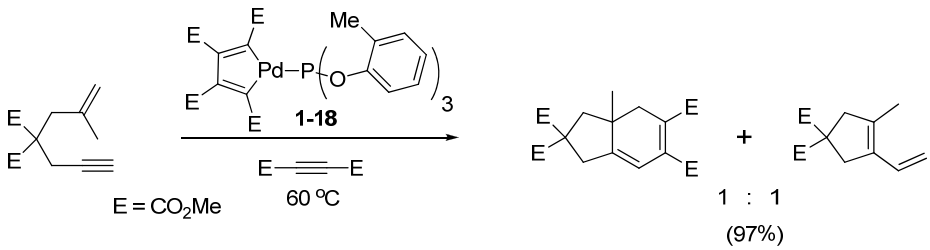
Among the three major types of metathesis processes, diene, enyne, and diyne metathesis, enyne metathesis possesses quit unique features whereby conjugated dienes are generated from an alkene and an alkyne in an atom economical manner.[12] Furthermore, the propagating alkylidene intermediate generated during the course of metathesis process allows for tandem reaction sequences, thereby enabling the formation of many bonds and rings in theory. The first example of intramolecular enyne metathesis reaction was reported by Katz and co-workers in 1985 wherein Fisher tungsten carbene complex **1-16** and **1-17** were used either as a stoichiometric reagent or a catalyst (**Scheme 1.2**).[25] At that time, the reaction was described as a methylene migration reaction in which the methylene group was shifted from one side to another after the reaction. Related reactions were subsequently reported by other research groups with molybdenum- and chromium-based Fisher carbene complexes.

Scheme 1.2. Examples of enyne metathesis by Katz



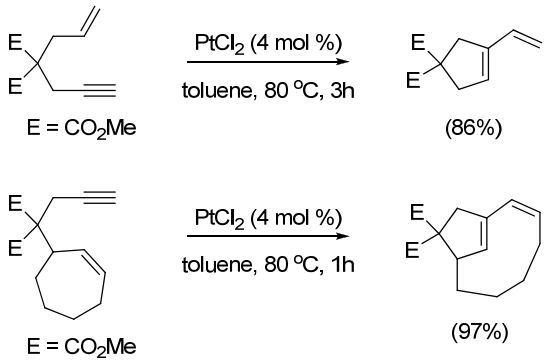
On the other hand, Trost and co-workers pioneered palladium-catalyzed enyne metathesis reactions. In their enyne cyclization with a low-valent metal complex **1-18**, generated from palladacyclopentadiene (TCPT) and tri-*o*-tolylphosphite in the presence of dimethyl acetylene dicarboxylate (**Scheme 1.3**), they obtained two products in a 1:1 ratio where the latter one is clearly the enyne metathesis product.[26]

Scheme 1.3. Trost's palladium catalyzed enyne metathesis/cyclization reaction



A simple platinum complex ($PtCl_2$) also found to be an efficient catalyst for enyne metathesis. The yield was comparable to that with **1-18** but the reaction rate was significantly higher.[27] In 1996, Murai and co-workers reported a platinum-catalyzed conversion of 1,6-enyne to the corresponding 1-vinylcycloalkene in high yields (**Scheme 1.4**).[28]

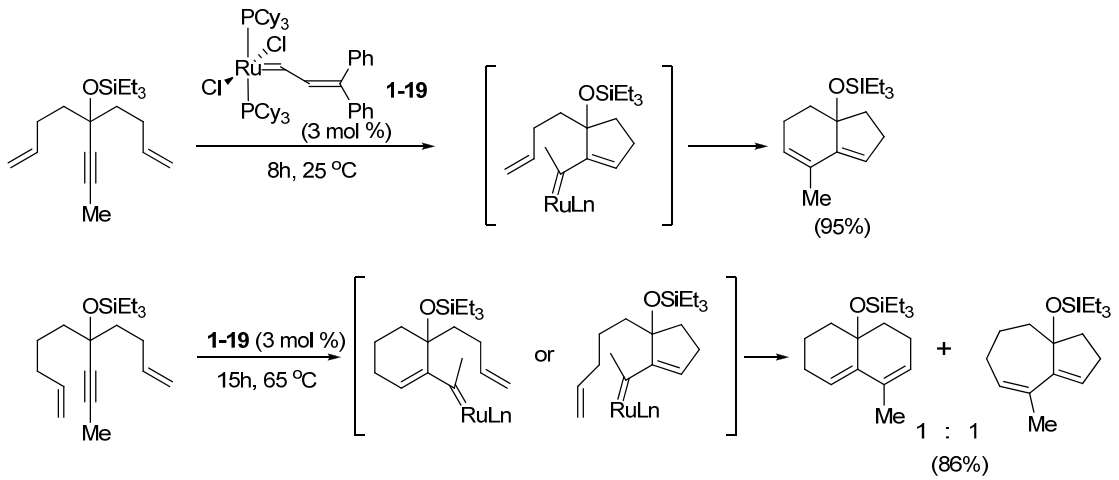
Scheme 1.4. Murai's platinum-catalyzed enyne metathesis reaction



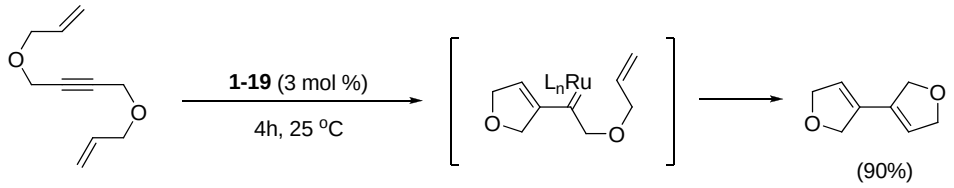
The recently developed efficient alkylidene complexes for olefin metathesis including Grubbs' and Schrock's catalysts facilitated the discovery of new enyne metathesis processes and their applications

to organic synthesis. The first enyne metathesis catalyzed by Grubbs-type ruthenium alkylidene **1-19** was reported by Mori in 1994 (**Scheme 1.5**),[29] and in the same year, Grubbs also reported an elegant dienyne metathesis reaction using the same complex (**Scheme 1.6**).[30] Since then, numerous synthetic applications of enyne metathesis were developed by using other Grubbs-type ruthenium alkylidene complexes.[31, 32]

Scheme 1.5. Enyne metathesis/ring closing metathesis reaction catalyzed by Grubbs-type complex **1-19**



Scheme 1.6. Dienyne metathesis reported by Grubbs



Although the mechanism of enyne metathesis was studied by many research groups, there are still some remaining uncertainties. The reaction pathways of enyne metathesis involve either an "ene-first" or "yne-first" mechanism depending on which π-system reacts first (**Figure 1.6**).[33] Mori observed *endo* RCM products when di-substituted alkenes were used.[34] Recently, Hoveyda demonstrated that tungsten- and molybdenum-based alkylidene complexes preferentially afforded *endo* products.[15] Theoretical calculations showed that neither the "ene-first" nor the "yne-first" mechanism have any energetic preference. The calculation, however, showed that the *exo* versus *endo* selectivity strongly depends on the substituent pattern and their nature.[31g]

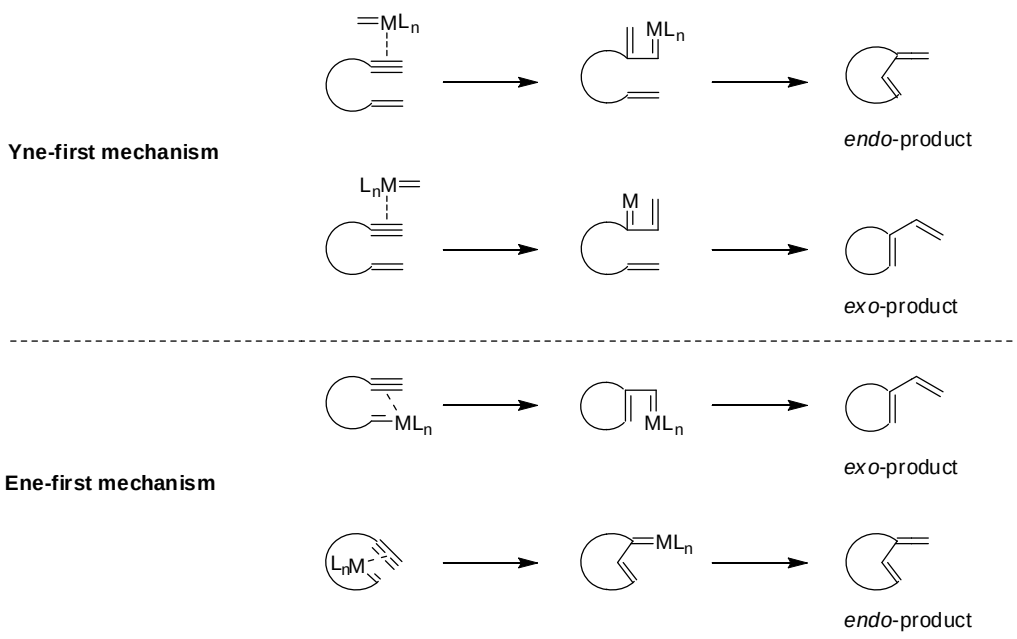


Figure 1.6. Possible reaction mechanisms for enyne metathesis

Lee and co-workers explored the mode selectivity and stereoselectivity of the ring-closing enyne metathesis of macrocyclic systems ranging from 10- to 15-membered rings.[35] These exo/endo products of ring-closing enyne metathesis with and without ethylene are shown in Figure 1.7.

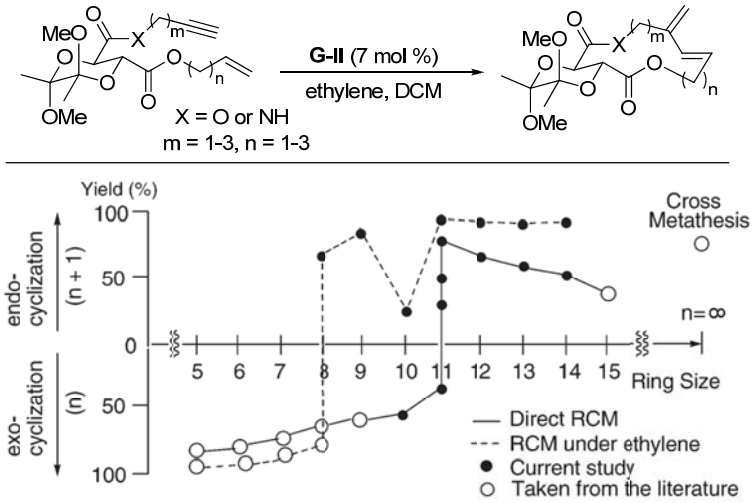


Figure 1.7. Exo/endo mode selectivity in ring-closing enyne metathesis

The exo/endo selectivity of the macrocyclization was found to be a function of ring size, whereby larger rings (12-15 membered rings) provided *endo*-products selectively, while smaller rings (5-11 membered rings) generated *exo*-products.

1.1.4.2. Metallotropic [1,3]-Shift

In 2005, Lee's group reported that the substrates containing 1,3-diyne and tethered alkene readily undergo metallotropic [1,3]-shift after ring-closing enyne metathesis.[36] From the mechanistic standpoint, it was surmised that the enyn RCM and metallotropic [1,3]-shift are conceptually identical processes but with the difference in tether size, and thus metallotropic [1,3]-shift, can be considered as a special case of enyne RCM where the tether size becomes zero (**Figure 1.8**).

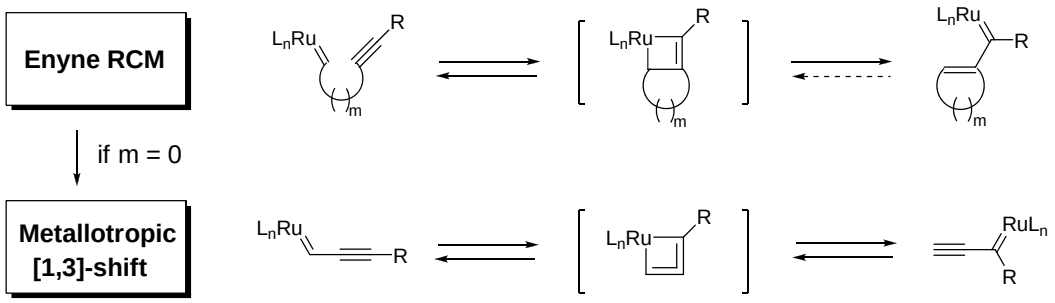
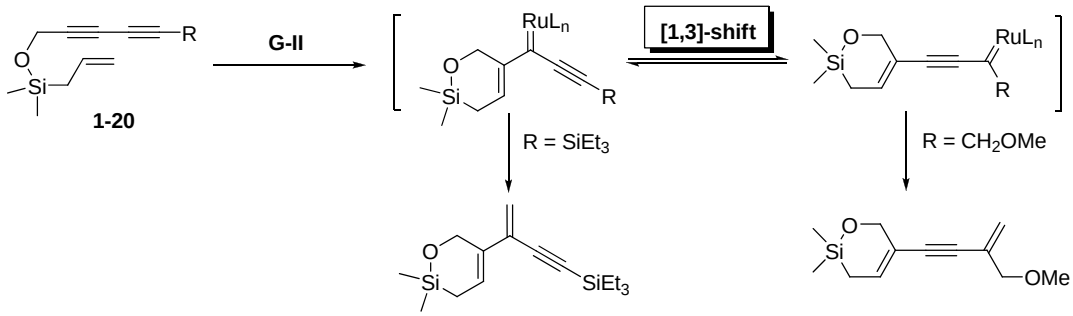


Figure 1.8. Enyne RCM and metallotropic [1,3]-shift

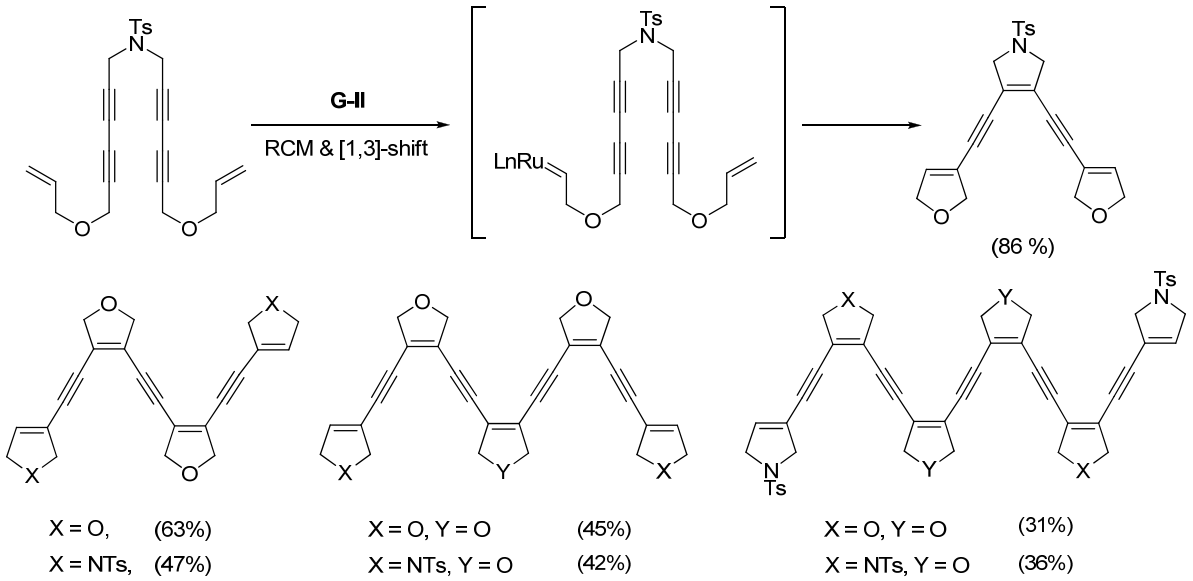
Recent theoretical investigation suggests that enyne RCM is not fully reversible, whereas metallotropic [1,3]-shift is expected to be reversible.[37] Therefore, it was hypothesized that the reaction of **1-20** with Grubbs second-generation catalyst **G-II** would generate a ruthenium alkynyl alkylidene which is in equilibrium with the corresponding 1,3-shifted ruthenium alkynyl alkylidene intermediate.[38] The fate of these two equilibrating ruthenium alkynyl alkylidene intermediates to select termination paths would largely depend on the nature of substituents (**Scheme 1.7**).

Scheme 1.7. Tandem enyne RCM and metallotropic [1,3]-shift reaction (M&M)



In order to exam the application of the tandem ring-closing metathesis and metallotropic [1,3]-shift (M&M), Lee and co-workers applied this M&M process to construct a series of enediynes and oligoenynes with highly conjugated enyne system, demonstrating the efficiency of the tandem metathesis and metallotropic [1,3]-shift (**Scheme 1.8**).[39]

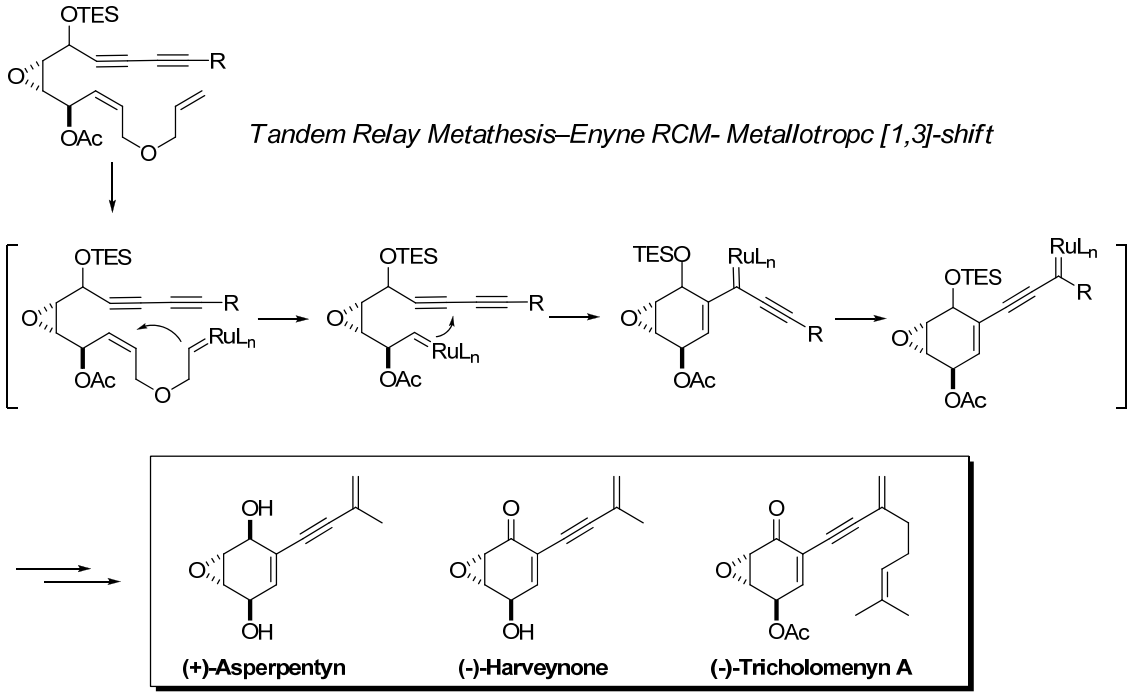
Scheme 1.8. Synthesis of enediynes and oligoenynes via tandem metathesis and metallotropic [1,3]-shift



The generality of tandem enyne RCM and metallotropic [1,3]-shift was demonstrated with various 1,3-diynes and 1,3,5-triynes carrying a tethered alkene.[40] Furthermore, in 2009, Lee and co-workers reported a total synthesis of epoxyquinoid natural products (+)-asperpentyne, (−)-harveynone and (−)-tricholomenyn.[41] In their synthesis, tandem sequences involving RCM and metallotropic [1,3]-shifts

were nicely utilized as the key step to efficiently construct the construction of the conjugated 1,5-diene-3-yne moiety in one step (**Scheme 1.9**).

Scheme 1.9. RCM and metallotropic [1,3]-shift for natural product synthesis



1.2. Results and Discussion

The initial coordination event of either an alkene or an alkyne to the coordinatively unsaturated ruthenium metal center is an important step for the metathesis process catalyzed by Grubbs-type ruthenium alkylidenes.[1, 31] Thus understanding the structure and dynamic properties of olefin-coordinated ruthenium alkylidene complexes should be crucial information for designing both metathesis substrates and new catalysts. In this regard, many research groups have studied how the metal-olefin bonding is influenced by the steric and electronic factors in the periphery of metal center and of the reacting olefins. In 1993, Grubbs and co-workers observed a transient alkene-chelated ruthenium alkylidene intermediate **1-21** during the ring-opening metathesis polymerization (ROMP) catalyzed by Grubbs type-catalyst **1-7** where the alkene was assigned *trans* to the triphenylphosphine (PPh_3) ligand (**Figure 1.9**).[42] Few years

later, Snapper and co-workers reported a stable alkene-chelated ruthenium alkylidene complex **1-22** captured during the ring-opening metathesis process.[43] The crystal structure of this complex shows that the alkylidene C–H bond is *syn*-periplanar to a tricyclohexylphosphine (PCy_3) ligand, and the alkene moiety is bound to the ruthenium in *trans* fashion to it. Grubbs reported a crystal structure of vinyl alkylidene complex **1-23** formed from **G-II** and diphenyl acetylene, and its crystal structure shows that the alkene bound is *cis* to the NHC ligand.[44] In 2006, Grubbs also reported the solution behavior of *cis* and *trans* alkene-chelated ruthenium alkylidene complexes **1-24** and **1-25** which undergo interconversion giving a 2:3 equilibrium ratio at 25 °C.[45]

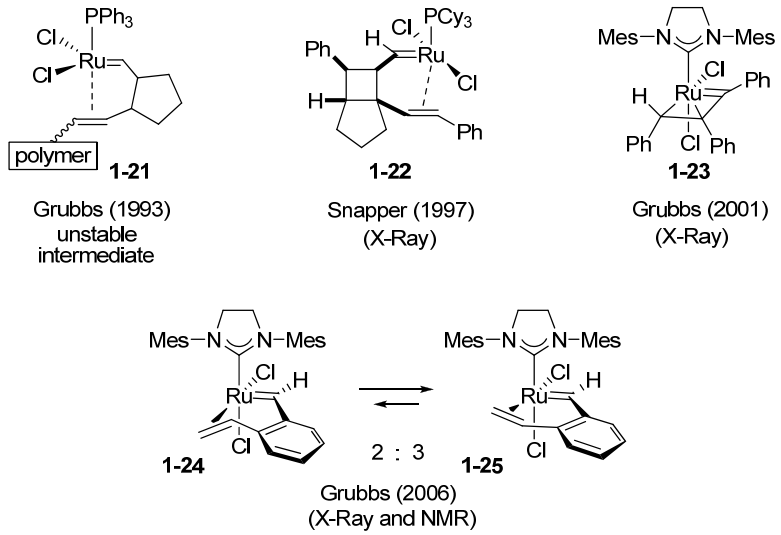
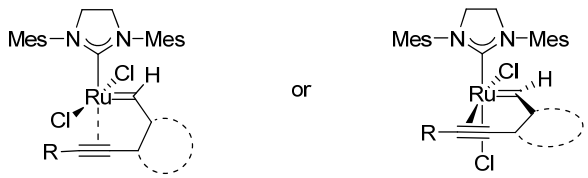


Figure 1.9. Alkene-chelated ruthenium alkylidene complexes

Although the structures and solution dynamics of alkene-coordinated ruthenium alkylidene complexes have been extensively studied, neither a crystal structure nor a spectroscopy-based structural characterization of an alkyne-chelated ruthenium alkylidene complex has been reported. To date, only a small number of computational studies on the mechanism of enyne metathesis have been reported based on the putative alkyne-bound ruthenium alkylidene intermediates. This discrepancy may be due to the lack of efficient methods to prepare the alkyne coordinated ruthenium alkylidene complexes of type **1-26** or **1-27** (**Figure 1.10**). It is thus expected that if this type of stable alkyne-chelated ruthenium alkylidene

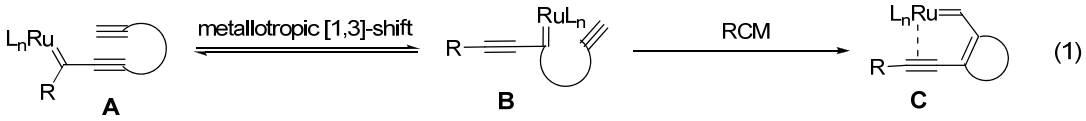
complex can be obtained, the structure and property of this complex will provide important insights into the mechanism of enyne metathesis. Furthermore, this structural information will also provide solutions to improve the problems associated with unproductive enyne metathesis reactions observed with sophisticated substrates containing multiple alkyne system.



1-26 **1-27**

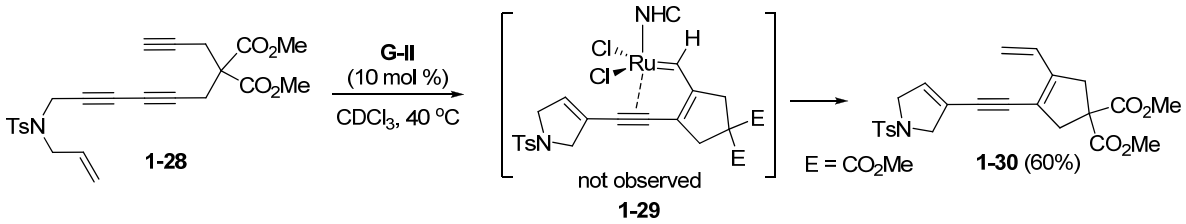
Figure 1.10. Possible ligand orientation of the alkyne-chelated ruthenium alkylidene complex

Previously, we reported the reaction of substrates possessing a conjugated diyne and tethered alkene with Grubbs-type ruthenium alkylidenes, which underwent facile metallotropic [1,3]-shift after ring-closing enyne metathesis.[36] On the basis of this observation, we envision that the tandem enyne metathesis and metallotropic [1,3]-shift sequence could be a useful tool to generate alkyne-chelated ruthenium alkylidene complexes. As shown in Eq. 1, an alkynyl ruthenium alkylidene intermediate **A**, formed via an initial enyne ring-closing metathesis (RCM) or cross metathesis (CM), would induce the metallotropic [1,3]-shift to provide a newly formed alkylidene **B**. The RCM of **B** is expected to provide a new alkylidene **C** where the proximity of the *cis*-orientated alkyne moiety and the metal center, we believe, would facilitate the formation of a chelated alkyne-ruthenium complex, which should be stable enough to be isolated if appropriate stabilizing elements exist.



To test our hypothesis, substrate **1-28** was synthesized and treated with 10 mol % of **G-II** in $CDCl_3$ at 40 ^oC, and the reaction was monitored by ^1H NMR. Unfortunately, no signal detected in ^1H

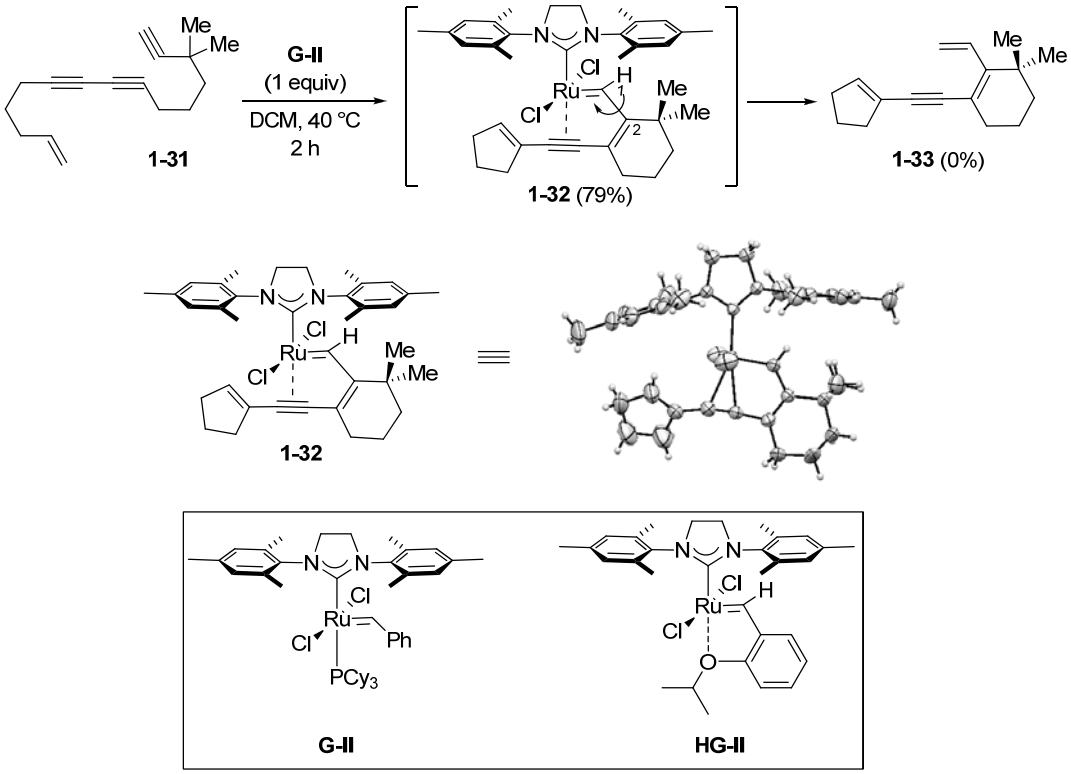
NMR could be assigned to the ruthenium alkylidene complex **1-29**, and clearly all the observed signals corresponded to the metathesis product **1-30**, which was isolated in 60% yield (Eq. 2).



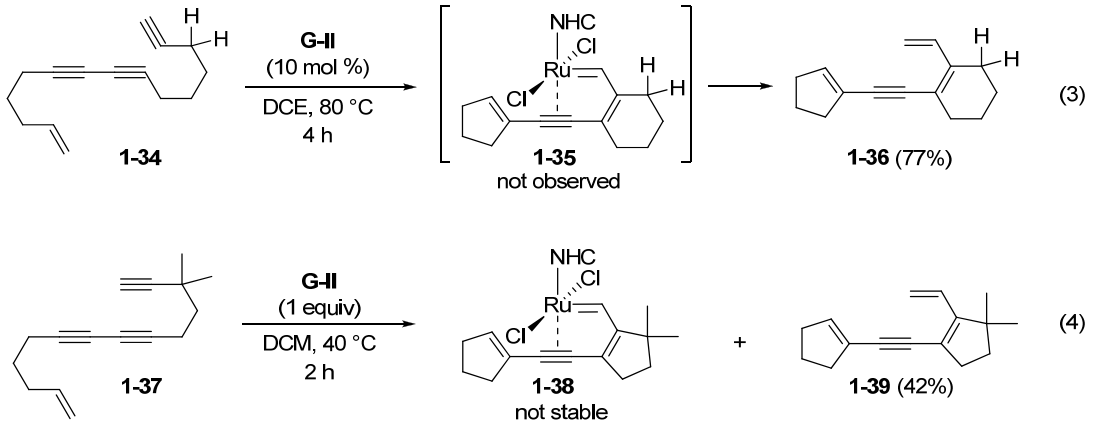
(2)

After several rounds of experiments with substrates of structural variations, to our gratification, we found that the substrate **1-31** containing *gem*-dimethyl group at the propargylic carbon displayed a new carbenic proton signal at 17.6 ppm upon treatment with 10 mol % of **G-II** with concomitant disappearance of its carbenic proton signal at 19.1 ppm. After all the added catalyst was consumed to form a new ruthenium alkylidene, which is assumed to be the desired alkyne-chelated ruthenium alkylidene complex **1-32**, no further conversion of the starting material was observed. Subsequently, by adding a stoichiometric amount of **G-II** to the reaction mixture, full conversion of the substrate was attained at 40 ^{o}C (**Scheme 1.10**), and a deep-green crystalline material was obtained after column chromatography devoid of metathesis product **1-33**. X-ray diffraction analysis of the crystalline compound confirms its identity of **1-32** where the alkyne moiety was chelated to the ruthenium center *trans* to the NHC ligand similar to Snapper's alkene-chelated ruthenium alkylidene **1-22**. The overall ligand arrangement of this new alkyne-chelated ruthenium alkylidene **1-32** is similar to that of Hoveyda-Grubbs second generation complex **HG-II**, where the alkyne moiety replaces the isopropoxyl group coordinated *trans* to the NHC ligand on the ruthenium center. To date, this is the first well-defined alkyne-chelated ruthenium alkylidene complex fully characterized.[46,47] We surmised that the key structural feature for this stable metal-complex might be the *gem*-dimethyl group and the 6-member ring skeleton, which hinders the rotation of the C1–C2 bond in metal complex **1-32**.

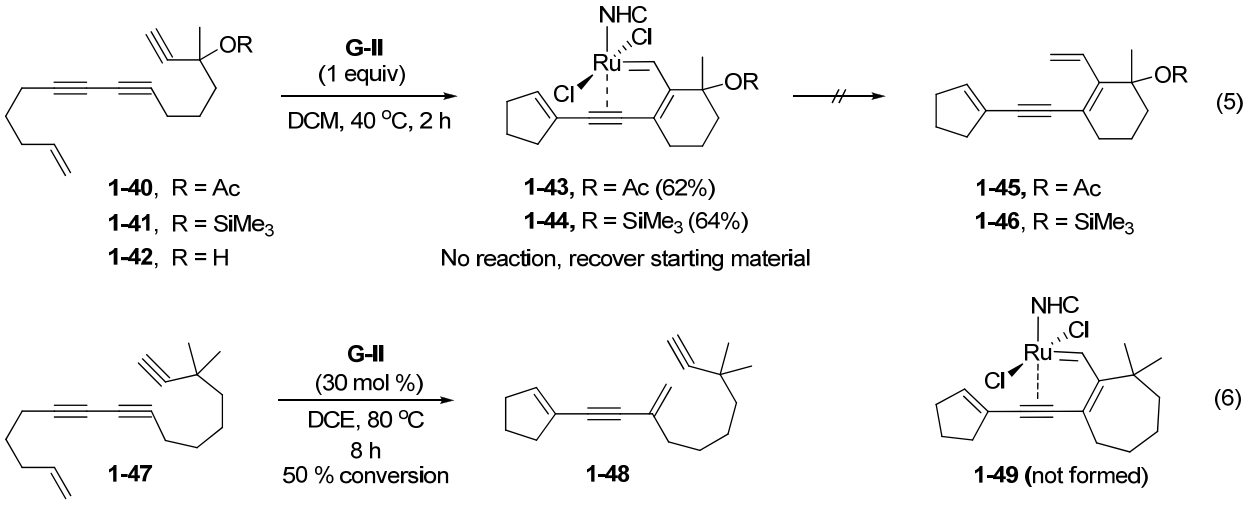
Scheme 1.10. First well-defined alkyne-chelated ruthenium alkylidene complex



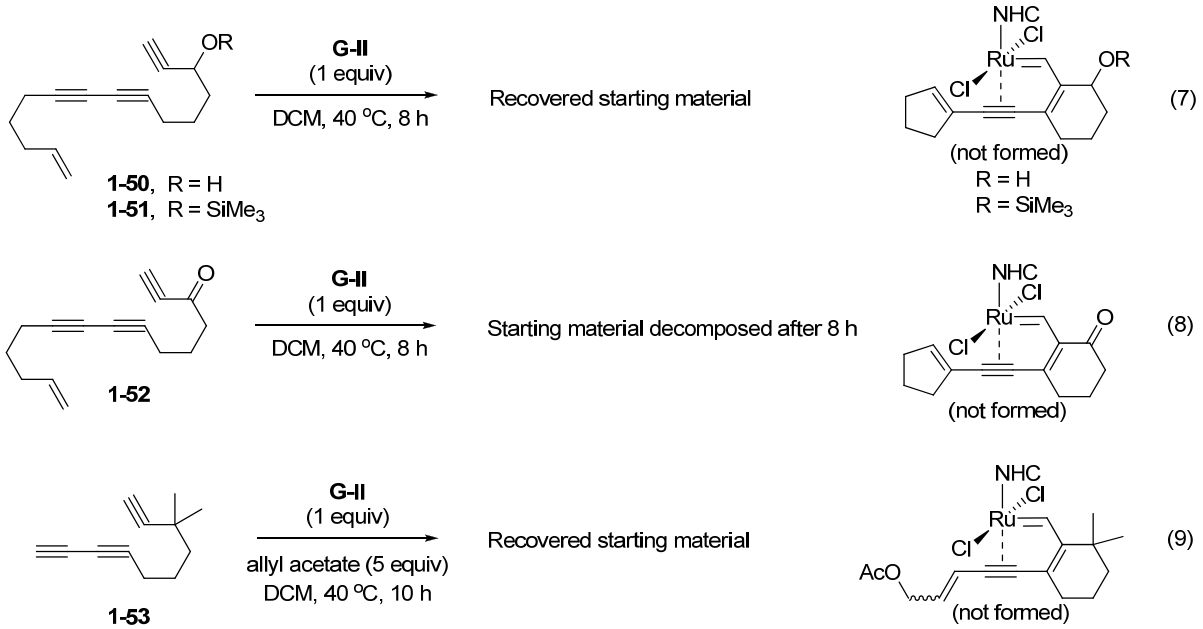
To confirm the role of the *gem*-dimethyl moiety, we synthesized several substrates with variations on the propargylic carbon and the size of the tether. Substrate **1-34** analogous to **1-31** but lacking *gem*-dimethyl group did not provide any detectable amount of the desired metal complex **1-35**, but afforded only metathesis product **1-36** in 77% yield after purification (Eq. 3). Substrate **1-37** containing *gem*-dimethyl group on propargylic carbon but with three-carbon unit between two alkynes was also prepared and examined its behavior. The reaction of **1-37** with one equivalent of **G-II** provided three products including alkyne-chelated ruthenium alkylidene **1-38**, **G-II**, and metathesis product **1-39** in a 1:2:3 ratio as indicated by ^{1}H NMR (Eq. 4). Attempt to isolate the desired alkynyl ruthenium complex **1-38** by column chromatography was failed and only the metathesis product **1-39** was isolated in 51% yield. These results clearly indicate that the substituent pattern and incipient ring size significantly affect the stability of the alkyne-chelated ruthenium alkylidene.



With these observations in hand, further variations were made in the substituents on the propargylic position and ring size. As expected, under identical reaction conditions, substrates **1-40** and **1-41** containing *gem*-disubstituents provided exclusively metal complexes **1-43** and **1-44** in 62 and 64% isolated yield, respectively, devoid of metathesis products **1-45** and **1-46**. Surprisingly, substrate **1-42** containing 3° hydroxyl group did not undergo metathesis reactions, but only the starting material was recovered intact (Eq. 5). Also, substrate **1-47** containing a five-carbon unit between two alkynes failed in generating either metal complex **1-49** or metathesis product most likely due to the difficulty in forming 7-member ring during the ring-closing metathesis process and thus led to a 1 : 1 mixture of **1-48** and starting material **1-47** (Eq. 6).

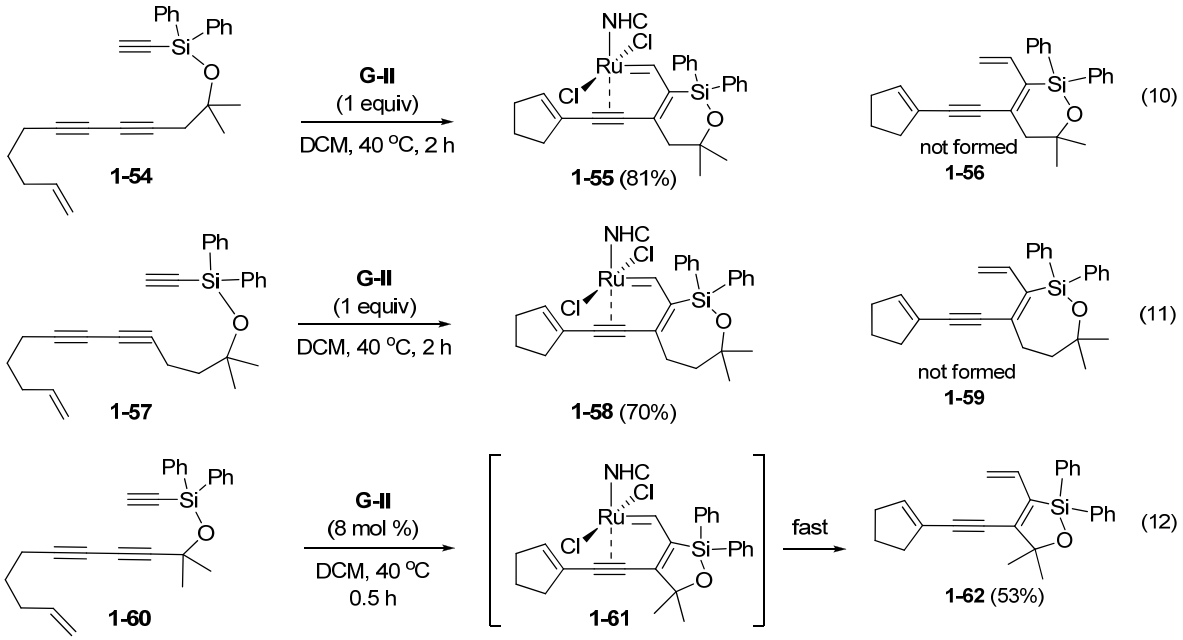


Further modifications were made with functional groups including a free 2° alcohol **1-50**, a 2° silyl ether **1-51**, and a carbonyl group **1-52**, but neither metal complexes nor metathesis products were obtained from these substrates, and these substrates were either recovered or decomposed during the reaction (Eq. 7–8). Attempt to utilize the enyne metathesis-metallotropic [1,3]-shift sequence initiated by enyne cross metathesis with the substrate **1-53** and allyl acetate failed to generate the desired ruthenium alkylidene complex, and only the homo metathesis product of allyl acetate was observed. The terminal diyne substrate **1-53** remained intact (Eq. 9).

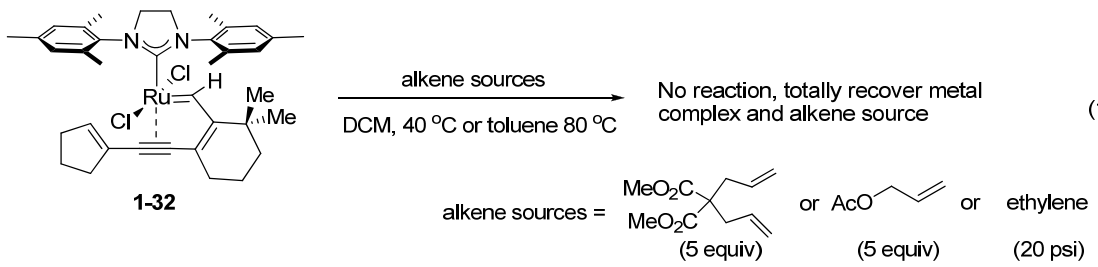


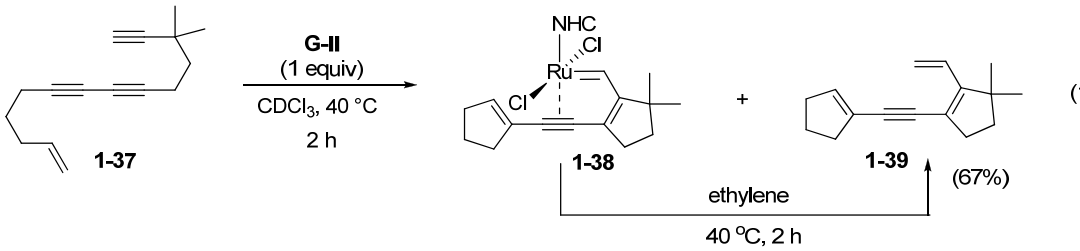
These results imply that the ring size affects the binding strength of the alkyne to the ruthenium center, which should be the consequence of different bond angles associated with the size of the ring. If true, replacement of the all-carbon tether with heteroatom-containing systems should show different reactivity and stability of the corresponding metal complexes. Thus, we synthesized a series of compounds containing silicon tether **1-54**, **1-57**, **1-60** where the propargylic positions of substrates **1-31**, **1-40** and **1-41** are replaced with the *gem*-diphenyl silyl moiety. The six- and seven-member ring complexes **1-55** and **1-58** are formed in 81 and 70% yield, respectively, without any trace amount of metathesis product **1-56** or **1-59** (Eq. 10–11). However, the substrate for five-membered ring-containing

metal complex **1-61** underwent even faster termination than that of carbon tethered metal complex **1-38**, exclusively affording metathesis product **1-62** in 53% yield (Eq. 12). These results are consistent with our hypothesis that the *gem*-disubstituents are the key for the stability of the chelated metal complexes and the internal bond angle of the product plays an important role as well.

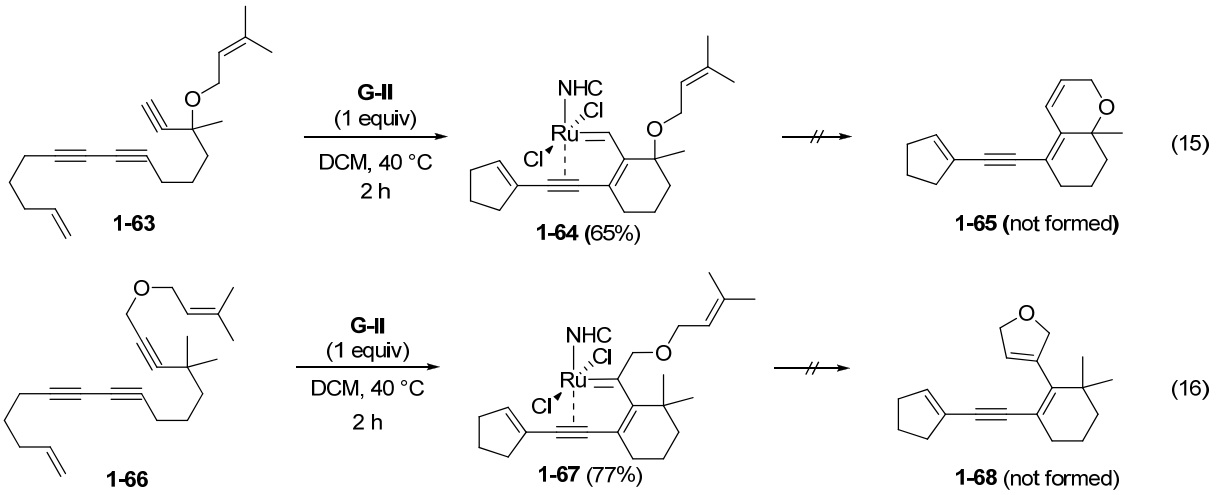


Next, we examined whether the alkyne-chelated ruthenium alkylidene complexes are viable catalysts for metathesis. Metal complex **1-32** was treated with high pressure ethylene (20 psi) or excess amount of allyl acetate (5 equiv) or dimethyl-2,2-diallyl malonate (5 equiv), which are known for their high reactivity in cross metathesis and ring-closing metathesis. However, the complex **1-32** did not show any reactivity towards metathesis even after prolonged heating at higher temperature (Eq. 13). On the other hand, metal complex **1-38** containing five-member ring was readily converted to the desired metathesis product **1-39** in 67% overall yield, and the process could be monitored by ^{1}H NMR (Eq. 14, **Figure 1.11** in page 30).





Having observed no metathesis activity of alkyne-chelated ruthenium alkylidene **1-32** with external alkenes, we installed an additional alkene tethered at an appropriate location so that once the alkyne-chelated ruthenium alkylidene complex has been generated, it can undergo metathesis reaction with this pre-installed alkene. Two substrates **1-63** and **1-66** were prepared and treated with **G-II**. Unfortunately, desired metathesis products **1-65** and **1-68** were not observed, and the ^{1}H NMR of the reaction mixture showed complete consumption of the starting material after introducing stoichiometric amount of **G-II**.

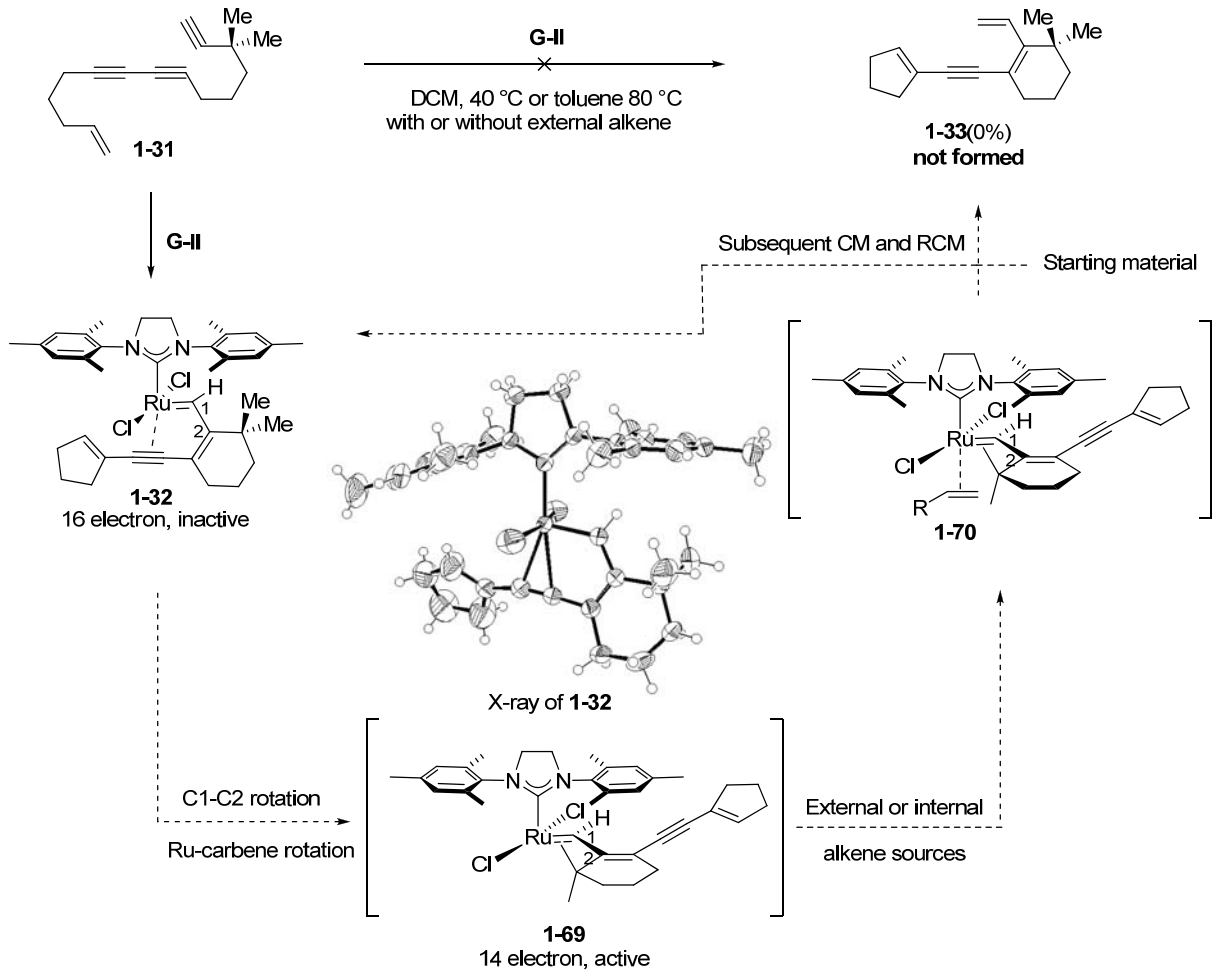


Yield was obtained by 1H NMR with inrernal standard (1,2,4,5-tetrabromobenzene)

Clearly, the signals from the ^{1}H NMR indicate the presence of alkyne-chelated ruthenium alkylidene complexes **1-64** and **1-67** (Eq. 15–16), however, attempt to isolate these two metal complexes led to the decomposition during flash column chromatography.

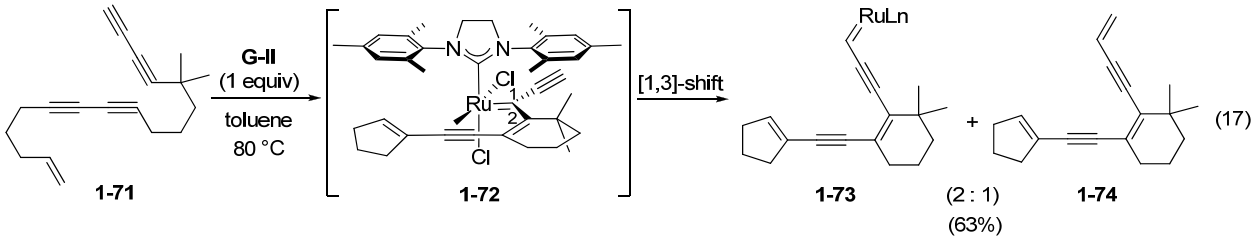
Based on these studies on the stability and reactivity of alkyne-chelated ruthenium alkylidene complexes with a variety of substrates containing structural variations, we conclude that the stability of the alkyne-chelated ruthenium alkylidene complexes is the consequence of the hindered rotation of the chelated alkyne moiety, which is caused by the steric interaction between the *gem*-dimethyl group and one of the mesityl groups on the NHC ligand.

Scheme 1.11. Rationale for the stability of alkyne-chelated ruthenium alkylidene complex **1-32**

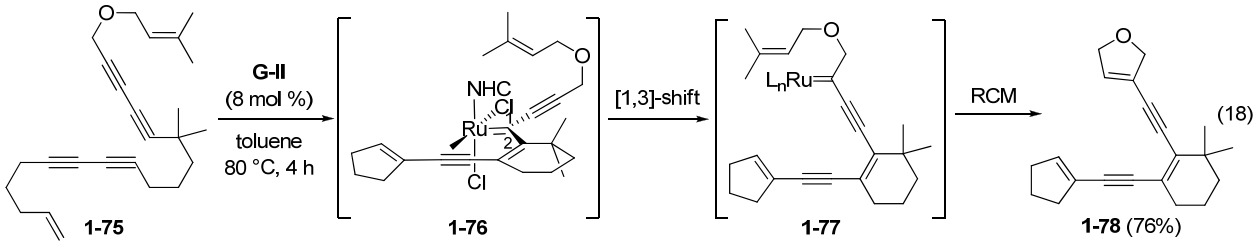


As shown in Scheme 1.11, after the formation of the metal complex **1-32**, the *gem*-dimethyl group on the propargylic position prohibits the rotation of the C1–C2 bond and the ruthenium carbene bond to form active intermediate **1-70** thereby the coordination site for the incoming alkene or alkyne is blocked by the coordinated alkyne and ultimately shuts down the catalytic cycle. At this juncture, we surmised that if an additional alkyne is attached to the carbenic carbon instead of hydrogen, ruthenium alkylidene would undergo facile metallotropic [1,3]-shift followed by termination, thus allowing catalytic turnovers.

This novel strategy of breaking the strong chelation by metallotropic [1,3]-shift was tested with substrate **1-71** where the simple terminal alkyne in **1-31** is replaced by a terminal 1,3-diyne moiety. We predict that once the alkyne-chelated ruthenium alkylidene **1-72** has been formed, it would undergo a subsequent metallotropic [1,3]-shift to generate thermodynamically most stable alkylidene **1-73**, which will ultimately lead to metathesis product **1-74** (Eq. 17).

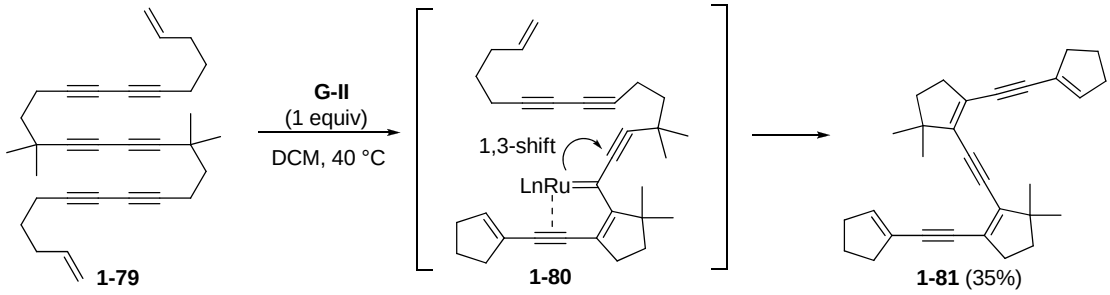


As expected, treatment of substrate **1-71** with a stoichiometric amount of **G-II** afforded two products, the final metathesis product **1-74** and the ruthenium alkylidene complex **1-73** in a 2:1 ratio. This experiment proved that although the sterically hindered environment imposed by the *gem*-dimethyl group is necessary for the stability of complex **1-32**, too severe steric congestion is detrimental like in **1-72** where the extra terminal alkyne directly pointing to the *gem*-dimethyl group destabilizes the chelation between the ruthenium center and the other alkyne moiety. This hypothesis was further tested with substrate **1-75** that contains an internal 1,3-diyne with a tethered prenyl group, which led to the formation of the metathesis product **1-78** in 76% yield (Eq. 18).

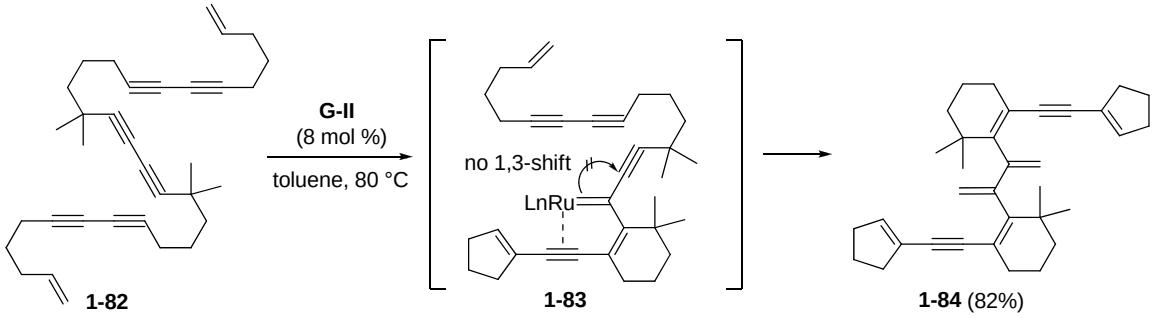


(18)

The ring size effects on the stability and reactivity of the ruthenium alkylidene complexes were examined with substrates **1-79** and **1-82**, which were synthesized via dimerization of **1-37** and **1-31** by the Hay coupling reaction.[48] As expected, five- and six-membered ring-forming substrates showed markedly different reactivity from each other. For five-member ring substrate **1-79**, ring-closing metathesis–metallotropic [1,3]-shift product **1-81** was formed exclusively in moderate yield, probably because of the low stability of the starting material (Eq. 19). A high loading of the catalyst is required to complete this reaction due to the putative chelation of the ruthenium alkylidene by the metathesis product bearing multi-enynes. On the other hand, for six-member ring substrate **1-82**, an alternative mode of metathesis resulted in product **1-84** in 82% yield (Eq. 20). This is the consequence of prohibited metallotropic [1,3]-shift on intermediate **1-83** as opposed to a facile [1,3]-shift in **1-80**, leading to two identical but independent ring-closing metathesis and metallotropic [1,3]-shift sequences.



(19)



(20)

1.3. Conclusion

In summary, for the first time, the well-define alkyne-chelated ruthenium alkylidene complex **1-32** was isolated and its structure was fully characterized by spectroscopic and crystallographic methods. Further investigation on stability and reactivity of alkyne-chelated ruthenium alkylidene complexes indicated that the substitution on the propargylic position is the key factor for the stability of these metal-alkyne chelated complex. We have also demonstrated that the nature of certain structural elements around the ruthenium alkylidene can effectively modulate their reactivity and stability in either of the alkyne-chelated ruthenium alkylidene complexes. This discovery will provide an effective way to generate a series of alkyne-chelated ruthenium alkylidenes, and will inspire the mechanistic study of enyne metathesis as well as future designs of more efficient and sophisticated tandem processes involving enyne metathesis.

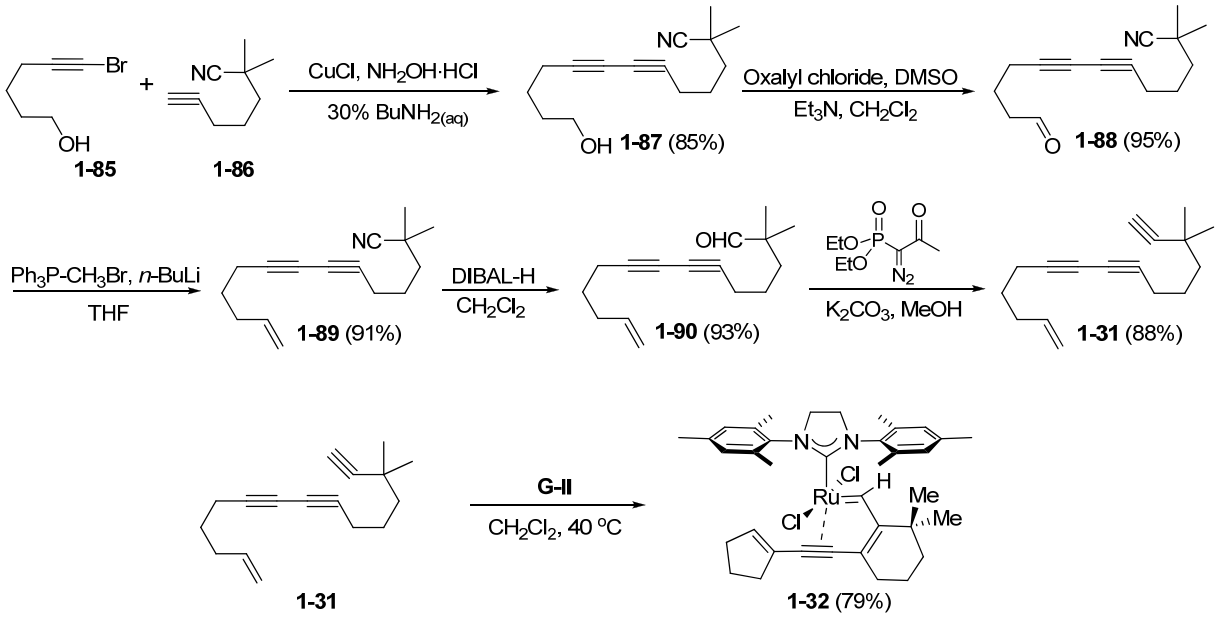
1.4. Experimental Details

1.4.1. General Information

All non-aqueous reactions were carried out under an inert nitrogen atmosphere, unless otherwise indicated. Reaction flasks were oven-dried overnight and cooled under a stream of nitrogen before use. Flash chromatography was performed using silica gel 60 Å (32–63 mesh) purchased from Sorbent Technologies or Silicycle Inc. Analytical thin layer chromatography (TLC) was performed on 0.25 mm E. Merck pre-coated silica gel 60 (particle size 0.040–0.063 mm). Visualization was accomplished by UV light, and TLC stains including potassium permanganate, *p*-anisaldehyde, vanillin and iodine. All reagents were purchased from Aldrich, TCI, Acros, Fisher, Alfa and used directly without further purification unless otherwise noted. Solvents including CH_2Cl_2, THF, Et_2O, Et_3N, $^iPr_2NH$, toluene *et al.* were purchased from Aldrich and were purified based on standard procedures. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AV-500 spectrometer at 501 MHz and 126 MHz respectively. ^{1}H and ^{13}C chemical shifts were referenced to internal solvent resonances; multiplicities are indicated by s

(singlet), d (doublet), t (triplet), q (quartet), qn (quintet), m (multiplet) and br (broad). Coupling constants, *J*, are reported in Hz (Hertz). Electrospray ionization (ESI) mass spectra were recorded on a Micromass LCT equipped with a time-of-flight analyzer in the University of Illinois at Urbana-Champaign. Electron impact (EI) mass spectra were obtained using a Micromass AutoSpecTM at the Mass Spectrometry Laboratory in the University of Illinois at Urbana-Champaign, using a Micromass 70-VS-4F and 70-VSE for HRFAB and LRFAB, respectively.

1.4.2. Representative Procedure for Substrate Preparation and Metal Complex Formation



Substrates **1-85** and **1-86** were coupled by using Cadiot–Chodkiewicz coupling conditions; cuprous chloride (0.01 equiv) was added to an aqueous solution of *n*-$BuNH_2$ at 0 °C. A few crystal of hydroxylamine hydrochloride were added to discharge the blue color. A solution of **1-86** (1 equiv) in CH_2Cl_2 was added to the solution, upon which the color of the solution became yellow. Bromoalkyne **1-85** (1.5 equiv) in CH_2Cl_2 was added dropwise to this solution for 30 min. During the addition, a small amount of hydroxylamine hydrochloride was added occasionally to keep the color of the reaction light yellow. After the addition of the bromoalkyne, the reaction was stirred while warming up to room temperature over 10 min and then quenched with water. The organic layer was separated and the aqueous

layer was further extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, hexanes : EtOAc = 4:1), affording alcohol **1-87** in 85% yield as pale yellow oil. **^{1}H NMR** (501 MHz, $CDCl_3$) δ 3.62 (t, *J* = 6.2 Hz, 2H), 2.33 – 2.25 (m, 4H), 1.82 (br, 1H), 1.72 – 1.63 (m, 4H), 1.63 – 1.55 (m, 4H), 1.32 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 124.7, 77.5, 76.0, 66.0, 65.3, 62.0, 39.2, 32.1, 31.6, 26.5, 24.5, 24.0, 19.1, 18.9; **HRMS** (EI) calcd for $C_{15}H_{21}NO$ $[M]^+$ 231.1623, found 231.1623; **HRMS (EI)** calcd for $C_{15}H_{21}NO$ $[M]^+$ 231.1623, found 231.1623.

Alcohol **1-87** was then oxidized using Swern conditions; to a stirred solution of DMSO (2 equiv) in CH_2Cl_2 at -78 ^oC, oxalyl chloride (1.5 equiv) was added dropwise and the resultant solution was stirred at -78 ^oC for 30 min. A solution of alcohol **1-87** (1 equiv) in CH_2Cl_2 was added slowly to the solution at the same temperature, and the mixture was stirred for 1 h. After adding Et_3N (3 equiv), the mixture was further stirred at -78 ^oC for 30 min then warmed up to room temperature over 1 h. The reaction was quenched with water, extracted with CH_2Cl_2 and dried over anhydrous $MgSO_4$. The filtrate was concentrated under reduced pressure and the crude product was purified by flash column chromatography (SiO_2, hexanes : EtOAc = 9:1), affording aldehyde **1-88** in 95% yield as pale yellow oil. ^{1}H NMR (501 MHz, $CDCl_3$) δ 9.74 (t, *J* = 1.1 Hz, 1H), 2.56 (dt, *J* = 7.2, 1.1 Hz, 2H), 2.32 – 2.26 (m, 4H), 1.80 (qn, *J* = 7.0 Hz, 2H), 1.69 – 1.62 (m, 2H), 1.61 – 1.55 (m, 2H), 1.31 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.3, 124.6, 76.4, 76.3, 66.0, 65.8, 42.4, 39.9, 32.0, 26.4, 23.9, 20.5, 19.0, 18.4; HRMS (EI) calcd for $C_{15}H_{19}NO$ $[M]^+$ 229.1467, found 229.1467; **HRMS (EI)** calcd for $C_{15}H_{19}NO$ $[M]^+$ 229.1467, found 229.1467.

Aldehyde **1-88** was converted to the corresponding alkene using an appropriate Wittig reagent in the presence of *n*-BuLi; to methyltriphenylphosphonium bromide (1.5 equiv) in THF was added *n*-BuLi (2.5 M in hexanes, 1.2 equiv) dropwise at 0 °C. After stirring for 30 min at 0 ^oC, the reaction mixture was cooled down to -78 ^oC, and aldehyde **1-88** (1 equiv) in THF was added. After being stirred at -78 ^oC for 30 min, the reaction was warmed to room temperature and kept for additional 12 h. The reaction was

quenched with water, extracted with Et_2O, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure and the crude product was purified by flash column chromatography (SiO_2, hexanes : EtOAc = 15:1), affording terminal alkene **1-89** in 91% yield as colorless oil. **^{1}H NMR** (501 MHz, $CDCl_3$) δ 5.74 (tdd, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.04 – 4.93 (m, 2H), 2.31 (t, *J* = 6.6 Hz, 2H), 2.24 (t, *J* = 7.1 Hz, 2H), 2.12 (dd, *J* = 14.5, 7.0 Hz, 2H), 1.72 – 1.64 (m, 2H), 1.63 – 1.55 (m, 4H), 1.32 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 137.3, 124.6, 115.3, 77.45, 75.9, 66.0, 65.2, 39.9, 32.6, 27.3, 26.5, 24.0, 19.1, 18.4; **HRMS** (EI) calcd For $C_{16}H_{20}N$ for $[M–H]^+$ 226.1596, found 226.1598; **HRMS (EI)** calcd For $C_{16}H_{20}N$ for $[M–H]^+$ 226.1596, found 226.1598.

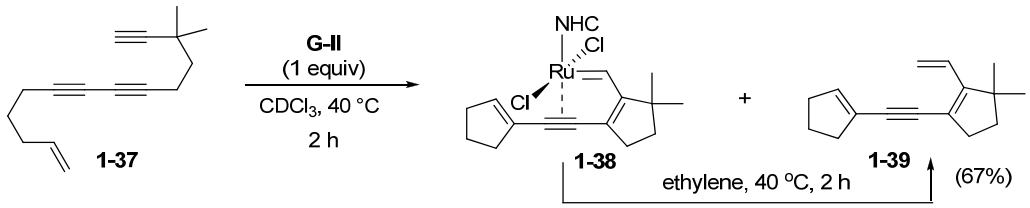
Alkene **1-89** (1 equiv) was dissolved in CH_2Cl_2 at -78 ^oC, and treated with DIBAL-H (1.0 M in hexanes, 1.1 equiv). The reaction mixture was stirred at -78 ^oC for 2 h, and quenched with few drops of MeOH. After the reaction mixture was warmed up to room temperature, and 2 N HCl was added. The mixture was extracted with Et_2O, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, hexanes: EtOAc = 10:1), affording aldehyde **1-90** in 93% yield as pale yellow oil; **^{1}H NMR** (501 MHz, $CDCl_3$) δ 9.41 (s, 1H), 5.73 (tdd, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.03 – 4.92 (m, 2H), 2.23 (t, *J* = 6.8 Hz, 4H), 2.11 (dd, *J* = 14.6, 6.9 Hz, 2H), 1.62 – 1.55 (m, 2H), 1.55 – 1.50 (m, 2H), 1.44 – 1.37 (m, 2H), 1.02 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 205.8, 137.4, 115.3, 77.3, 76.5, 65.8, 65.3, 45.5, 36.1, 32.6, 27.4, 23.2, 21.2, 19.1, 18.5; **HRMS** (EI) calcd for $C_{16}H_{21}O$ $[M–H]^+$ 229.1592, found 229.1593.

Aldehyde **1-90** was converted to the corresponding alkyne using the Bestmann-Ohira reagent and K_2CO_3 in MeOH; to a solution of the aldehyde **1-90** (1 equiv) in MeOH was added the Bestmann-Ohira reagent (1.5 equiv) and K_2CO_3 (2 equiv) at room temperature. The reaction mixture was stirred at the same temperature for 12 h, and the solvent was then removed under reduced pressure. After addition of water, the mixture was then extracted with Et_2O, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, hexanes), affording **1-31** in 88% yield as colorless oil; **^{1}H NMR** (501 MHz, $CDCl_3$) δ 5.75 (tdd, *J* = 17.0, 10.2, 6.7

Hz, 1H), 4.99 (dddd, J = 10.2, 4.2, 3.2, 1.4 Hz, 2H), 2.29 – 2.22 (m, 4H), 2.17 – 2.10 (m, 2H), 2.06 (s, 1H), 1.67 (dtd, J = 9.4, 7.1, 4.5 Hz, 2H), 1.60 (qn, J = 7.2 Hz, 2H), 1.50 – 1.44 (m, 2H), 1.19 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 137.5, 115.4, 91.3, 77.1, 77.1, 68.0, 65.5, 65.5, 42.2, 32.7, 30.7, 29.1, 27.4, 24.3, 19.5, 18.5; **HRMS** (EI) calcd for $C_{17}H_{21}$ $[M–H]^+$ 225.1643, found 225.1645.

A solution of **1-31** (1-equiv) and **G-II** (1.5 equiv) in CH_2Cl_2 was stirred at 40 °C in an air-free sealed tube for 2 h. After 2 h, the solvent was removed under reduced pressure and the dark green residue was subjected to flash column chromatography (SiO_2, hexanes : EtOAc = 5:1) to afford ruthenium complex **1-32** in 79% yield as green solid; **NMR** (501 MHz, $CDCl_3$) δ 17.6 (s, 1H), 7.01 (br, 4H), 5.54 – 5.52 (m, 1H), 4.04 (s, 4H), 2.57 (br, 6H), 2.46 – 2.36 (m, 8H), 2.33 (s, 6H), 2.06 (dtd, J = 10.2, 5.0, 2.5 Hz, 2H), 1.80 – 1.72 (m, 2H), 1.67 – 1.58 (m, 4H), 1.40 – 1.34 (m, 2H), 0.66 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 298.1, 211.6, 181.1, 140.2, 139.7, 138.7, 137.9, 137.3, 135.3, 130.4, 129.7, 127.0, 126.7, 125.6, 124.8, 99.5, 81.3, 53.5, 51.2, 38.3, 37.0, 34.5, 33.8, 32.6, 30.4, 29.8, 28.7, 25.3, 23.2, 22.8, 21.2, 20.4, 18.6, 18.4, 14.2; **HRMS** (ESI) calcd for $C_{37}H_{47}Cl_2N_2Ru$ $[M + H]^+$ 691.2160, found 691.2165.

1.4.3. Procedure of Monitoring the Formation of Product 1-39



A J. Young valve NMR tube containing substrate **1-37** (1 equiv) and **G-II** (1 equiv) in $CDCl_3$ solution was heated at 40 °C. The reaction was monitoring by ^{1}H NMR every 30 min and the signal of substrate **1-37** was totally disappeared after 2 h. At this point, a balloon containing ethylene gas was attached to the NMR tube and the NMR tube was heated at 40 °C for additional 2 h. After all metal complex **1-38** was converted to the final metathesis product **1-39**, the reaction mixture was concentrated under reduced pressure and the crude product was purified by flash column chromatography (SiO_2, pentane) to afford product **1-39** as colorless oil.

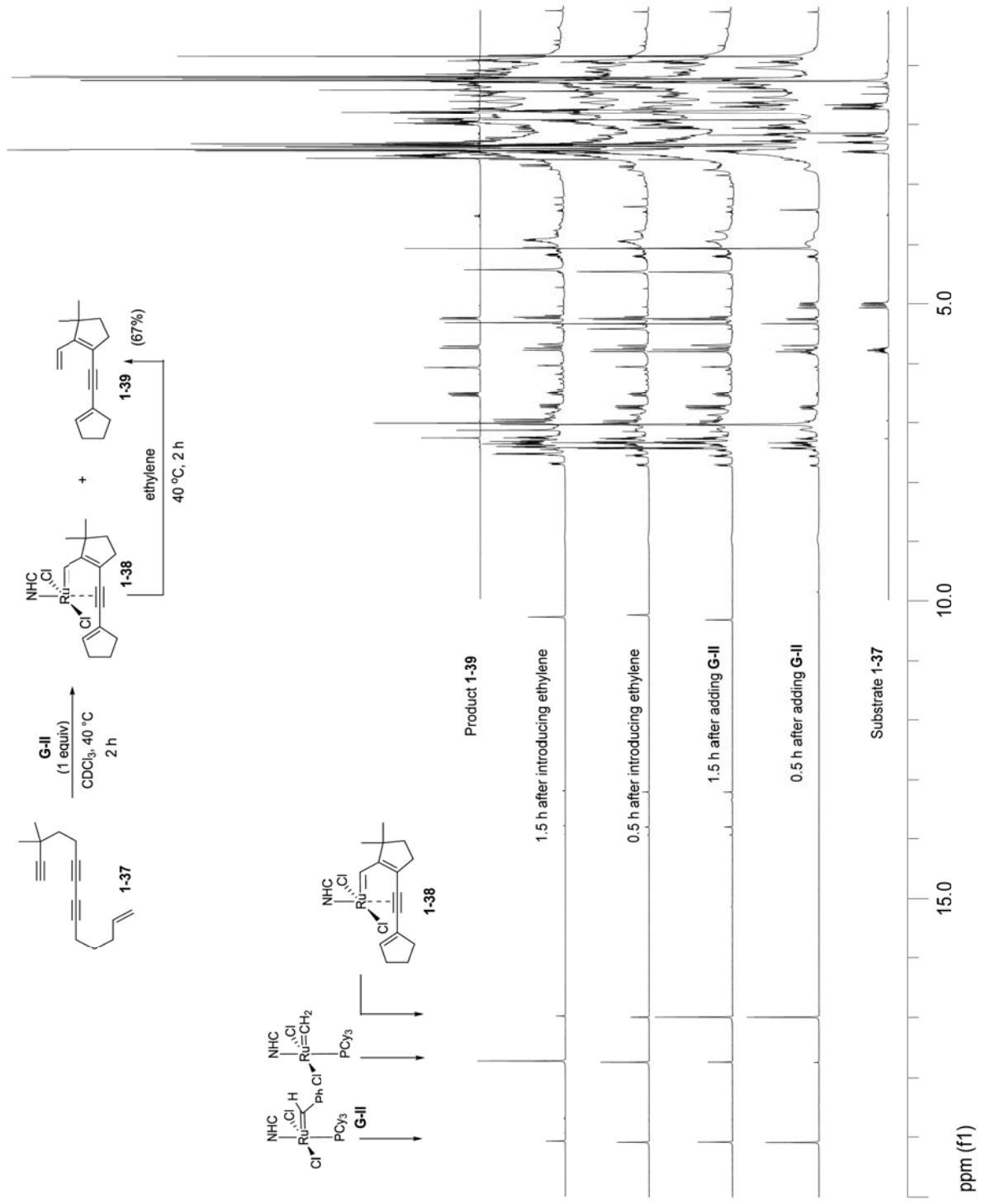
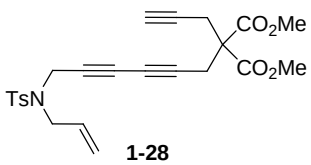
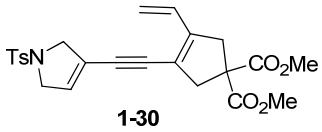


Figure 1.11. Formation of the metathesis product **1-39** monitored by ^{1}H NMR

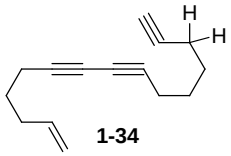
1.4.4. Selected Characterization Data



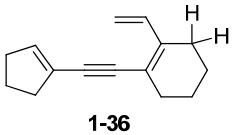
1-28: ^{1}**H NMR** (501 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 5.69 (tdd, *J* = 16.6, 10.1, 6.5 Hz, 1H), 5.24 (ddd, *J* = 13.6, 11.3, 1.3 Hz, 2H), 4.11 (s, 2H), 3.76 (s, 2H), 3.75 (s, 3H), 3.04 (s, 2H), 2.92 (d, *J* = 2.7 Hz, 2H), 2.44 (s, 3H), 2.05 (t, *J* = 2.7 Hz, 1H)); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 168.6, 143.8, 135.5, 131.7, 129.5, 127.7, 120.1, 78.0, 73.6, 72.1, 70.0, 69.9, 67.3, 56.3, 53.2, 49.3, 36.4, 23.4, 22.8, 21.5.



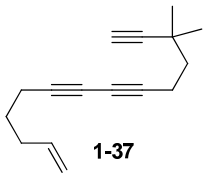
1-30 (60%): ^{1}**H NMR** (501 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 6.65 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.89 – 5.86 (m, 1H), 5.26 (dd, *J* = 14.1, 9.5 Hz, 2H), 4.21 (ddd, *J* = 5.8, 4.0, 1.7 Hz, 2H), 4.14 (ddd, *J* = 5.9, 3.6, 1.5 Hz, 2H), 3.75 (s, 6H), 3.22 (s, 2H), 3.20 (s, 2H), 2.43 (s, 3H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 171.7, 145.3, 143.8, 130.6, 130.3, 129.9, 127.5, 120.3, 118.06, 117.95, 88.4, 88.0, 57.5, 56.5, 55.3, 53.1, 43.8, 39.8, 21.6; **HRMS** (EI) calcd for $C_{24}H_{26}NO_6S$ $[M+H]^+$ 456.1481, found 456.1465.



1-34: ^{1}**H NMR** (501 MHz, $CDCl_3$) δ 5.76 (tdd, *J* = 17.0, 10.3, 6.8 Hz, 1H), 5.08 – 4.95 (m, 2H), 2.32 – 2.23 (m, 4H), 2.23 – 2.19 (m, 2H), 2.15 (q, *J* = 6.8 Hz, 2H), 1.95 (dd, *J* = 2.5, 1.7 Hz, 1H), 1.62 (m, 6H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 137.5, 115.4, 83.9, 76.9, 68.6, 65.6, 65.4, 32.7, 27.4, 27.4, 27.2, 18.7, 18.6, 17.9; **HRMS** (EI) calcd for $C_{15}H_{17}$ $[M–H]^+$ 197.1330, found 197.1334.

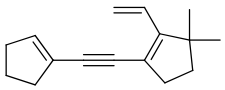


1-36 (77%): ^{1}**H NMR** (501 MHz, $CDCl_3$) δ 7.10 (dd, *J* = 17.6, 10.9 Hz, 1H), 6.05 – 6.01 (m, 1H), 5.24 (dd, *J* = 17.5, 0.9 Hz, 1H), 5.08 (dd, *J* = 11.0, 0.7 Hz, 1H), 2.50 (tdd, *J* = 10.0, 7.7, 2.3 Hz, 2H), 2.45 (dtd, *J* = 10.2, 5.1, 2.6 Hz, 2H), 2.29 (t, *J* = 5.9 Hz, 2H), 2.25 (t, *J* = 6.1 Hz, 2H), 1.92 (ddd, *J* = 18.8, 9.4, 5.5 Hz, 2H), 1.70 – 1.60 (m, 4H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 140.0, 137.0, 124.9, 120.2, 112.7, 91.7, 90.5, 36.6, 33.4, 30.9, 24.5, 23.4, 22.4, 22.0; **HRMS** (EI) calcd for $C_{15}H_{17}$ $[M–H]^+$ 197.1330, found 197.1331.



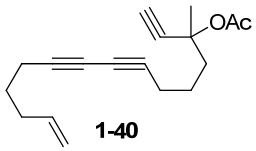
1-37: ^{1}**H NMR** (501 MHz, $CDCl_3$) δ 5.75 (tdd, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.05 – 4.94 (m, 2H), 2.42 – 2.38 (m, 2H), 2.24 (t, *J* = 7.1 Hz, 2H), 2.13 (dd, *J* = 14.5, 7.0 Hz, 2H), 2.09 (s, 1H), 1.68 – 1.63 (m, 2H), 1.63 – 1.57 (m, 2H), 1.19 (s, 6H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 137.5, 115.4, 90.1, 77.2, 77.1, 68.8, 65.5, 65.3, 41.5, 32.7, 30.9,

28.8, 27.4, 18.5, 15.6; **HRMS** (EI) calcd for $C_{16}H_{19}$ $[M–H]^+$ 211.1487, found 211.1490.



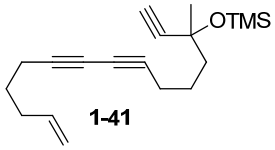
1-39

1-39 (67%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 6.52 (dd, *J* = 18.1, 11.7 Hz, 1H), 6.07 – 6.04 (m, 1H), 5.71 (d, *J* = 18.1 Hz, 1H), 5.23 (d, *J* = 11.7 Hz, 1H), 2.52 – 2.42 (m, 6H), 1.96 – 1.88 (m, 2H), 1.73 (t, *J* = 7.3 Hz, 2H), 1.19 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 152.8, 137.6, 130.4, 124.8, 121.1, 116.1, 93.3, 88.1, 46.3, 40.6, 36.5, 34.0, 33.4, 27.0, 23.4.



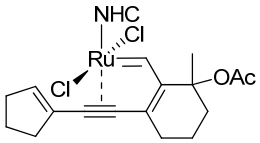
1-40

1-40: ^{1}H NMR (501 MHz, $CDCl_3$) δ 5.75 (tdd, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.06 – 4.93 (m, 2H), 2.55 (s, 1H), 2.30 (t, *J* = 6.7 Hz, 2H), 2.25 (t, *J* = 7.1 Hz, 2H), 2.14 (dd, *J* = 14.5, 7.0 Hz, 2H), 2.01 (s, 3H), 1.99 – 1.83 (m, 2H), 1.79 – 1.69 (m, 2H), 1.67 (s, 3H), 1.61 (m, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.2, 137.5, 115.4, 83.4, 77.4, 76.5, 74.3, 73.5, 65.8, 65.4, 40.6, 32.7, 27.4, 26.4, 23.1, 21.8, 19.1, 18.5; **HRMS** (EI) calcd for $C_{18}H_{21}O_2$ $[M–H]^+$ 269.1542, found 269.1540.



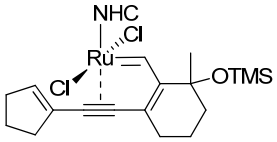
1-41

1-41: ^{1}H NMR (501 MHz, $CDCl_3$) δ 5.75 (tdd, *J* = 17.0, 10.2, 7.0 Hz, 1H), 5.06 – 4.94 (m, 2H), 2.43 (s, 1H), 2.31 – 2.22 (m, 4H), 2.14 (dd, *J* = 14.5, 7.0 Hz, 2H), 1.73 – 1.66 (m, 4H), 1.64 – 1.57 (m, 2H), 1.45 (s, 3H), 0.17 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 137.5, 115.4, 87.7, 77.2, 77.1, 72.5, 68.9, 65.6, 65.5, 44.1, 32.7, 31.1, 27.5, 23.6, 19.3, 18.5, 1.84; **HRMS** (EI) calcd for $C_{19}H_{28}OSi$ $[M]^+$ 300.1910, found 300.1910.



1-43

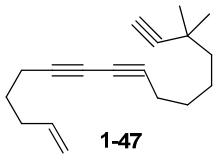
1-43 (62%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 17.4 (s, 1H), 7.00 (s, 4H), 5.67 – 5.53 (m, 1H), 4.05 (s, 4H), 2.51 (br , 9H), 2.44 – 2.38 (m, 3H), 2.33 (s, 6H), 2.17 (ddd, *J* = 15.2, 9.1, 4.3 Hz, 1H), 2.10 – 2.03 (m, 1H), 1.98 (ddd, *J* = 13.9, 8.4, 2.9 Hz, 1H), 1.94 (s, 3H), 1.81 – 1.74 (m, 2H), 1.69 – 1.63 (m, 2H), 1.33 – 1.22 (m, 4H), 1.16 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 295.1, 210.5, 173.9, 169.8, 141.3, 138.7, 129.6, 128.5, 126.3, 99.0, 84.0, 79.6, 53.6, 51.2, 36.9, 34.5, 33.4, 32.0, 31.6, 24.3, 23.2, 22.6, 21.1, 20.2, 19.1, 18.4, 14.1.



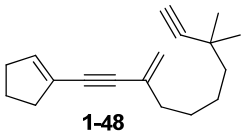
1-44

1-44 (64%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 17.6 (s, 1H), 7.03 (s, 2H), 6.97 (s, 2H), 5.59 – 5.56 (m, 1H), 4.06 – 3.98 (m, 4H), 2.55 (s, 9H), 2.50 – 2.37 (m, 3H), 2.34 (s, 6H), 2.07 – 2.00 (m, 2H), 1.88 – 1.69 (m, 6H), 1.64 – 1.52 (m, 4H), 1.25

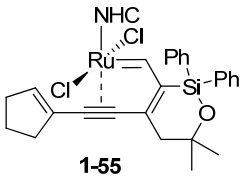
(s, 4H), 0.76 (s, 3H), -0.03 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 297.7, 211.0, 177.3, 140.8, 138.5, 130.5, 130.4, 130.1, 129.7, 128.3, 126.5, 99.8, 83.8, 71.5, 38.9, 37.0, 34.5, 32.4, 29.8, 29.0, 27.0, 26.9, 26.4, 26.2, 23.2, 21.2, 19.3, 2.6.


1-47

1-47: ^{1}H NMR (501 MHz, $CDCl_3$) δ 5.75 (tdd, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.05 – 4.93 (m, 2H), 2.27 – 2.22 (m, 4H), 2.16 – 2.10 (m, 2H), 2.05 (s, 1H), 1.63 – 1.56 (m, 2H), 1.54 – 1.49 (m, 4H), 1.39 – 1.34 (m, 2H), 1.18 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 137.5, 115.4, 91.6, 77.3, 77.0, 67.8, 65.6, 65.4, 42.5, 32.7, 30.9, 29.1, 28.7, 27.4, 24.5, 19.1, 18.5; **HRMS** (EI) calcd for $C_{18}H_{23}$ $[M–H]^+$ 239.1800, found 239.1799.

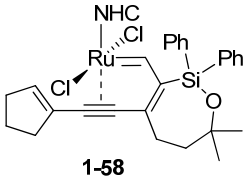

1-48

1-48: ^{1}H NMR (501 MHz, $CDCl_3$) δ 6.05 – 6.02 (m, 1H), 5.29 (d, *J* = 1.5 Hz, 1H), 5.21 (d, *J* = 1.2 Hz, 1H), 2.49 – 2.40 (m, 4H), 2.19 (t, *J* = 7.4 Hz, 2H), 2.07 (s, 1H), 1.94 – 1.87 (m, 2H), 1.57 – 1.51 (m, 2H), 1.50 – 1.43 (m, 2H), 1.20 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 137.7, 131.8, 124.5, 120.5, 92.0, 90.9, 86.4, 67.8, 42.9, 37.2, 36.4, 33.3, 30.9, 29.7, 29.1, 28.6, 23.3.



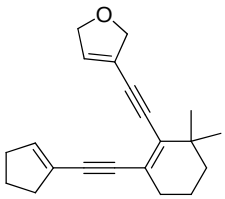
1-55

1-55 (81%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 17.4 (s, 1H), 7.46 (t, *J* = 7.4 Hz, 2H), 7.36 (t, *J* = 7.5 Hz, 4H), 7.30 (m, 4H), 7.00 (br, 2H), 6.21 (br, 2H), 5.67 (s, 1H), 4.00 (s, 4H), 2.58 (br, 4H), 2.49 (m, 3H), 2.45 – 2.12 (br, 9H), 2.10 (s, 2H), 2.07 (m, 3H), 1.82 (td, *J* = 15.1, 7.6 Hz, 3H), 1.74 (br, 2H), 1.25 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 297.2, 210.2, 169.4, 142.2, 137.7, 135.1, 134.4, 130.0, 129.7, 127.7, 126.7, 103.7, 86.2, 73.5, 53.2, 51.2, 47.5, 36.9, 34.7, 30.2, 23.2, 21.0.



1-58

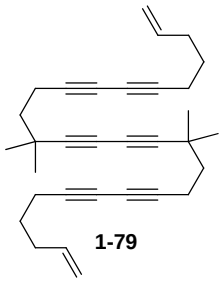
1-58 (70%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 17.2 (s, 1H), 7.45 (m, 2H), 7.40 – 7.32 (m, 8H), 6.99 (br, 2H), 5.81 (br, 2H), 5.63 (s, 1H), 3.93 (s, 4H), 2.52 (m, 6H), 2.41 (m, 4H), 2.06 (m, 4H), 1.84 (m, 5H), 1.58 (br, 6H), 1.25 (m, 3H), 1.02 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 300.6, 210.6, 170.9, 147.3, 141.8, 136.1, 135.4, 129.8, 127.7, 126.8, 104.6, 85.8, 75.0, 52.9, 51.4, 41.6, 36.9, 34.7, 32.8, 30.0, 29.7, 26.3, 23.3.



1-79

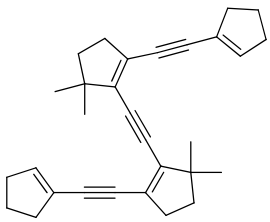
1-78 (76%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 6.09 (t, *J* = 2.0 Hz, 1H), 6.06 (t, *J* = 2.5 Hz, 1H), 4.77 (dt, *J* = 5.1, 4.9, 1.8 Hz, 2H), 4.65 (dt, *J* = 4.9, 4.8, 2.1 Hz, 2H), 2.46 (m, 4H), 2.25 (t, *J* = 6.2 Hz, 2H), 1.92 (td, *J* = 15.0, 7.6 Hz, 2H), 1.65 (m, 2H), 1.51 (m, 2H), 1.14 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 138.1, 134.5, 130.3, 127.2,

124.7, 121.9, 92.9, 91.5, 91.0, 86.9, 76.4, 37.0, 36.5, 34.6, 33.4, 30.8, 28.9, 23.4, 18.7.



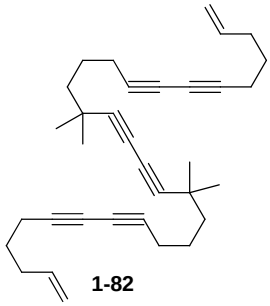
1-79

1-79: ^{1}**H NMR** (501 MHz, $CDCl_3$) δ 5.76 (tdd, *J* = 17.0, 10.2, 6.7 Hz, 2H), 5.02 (m, 4H), 2.40 (t, *J* = 8.0 Hz, 4H), 2.26 (t, *J* = 7.1 Hz, 4H), 2.15 (q, *J* = 7.1, Hz, 4H), 1.67 (m, 4H), 1.61 (qn, *J* = 7.2, 7.1 Hz, 4H), 1.20 (s, 12H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 137.5, 115.4, 83.8, 65.7, 65.5, 41.5, 32.7, 31.7, 28.6, 27.5, 18.6, 15.8.



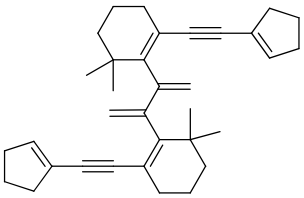
1-81

1-81 (35%): ^{1}**H NMR** (501 MHz, $CDCl_3$) δ 6.06 (t, *J* = 2.0 Hz, 2H), 2.57 (t, *J* = 7.1 Hz, 4H), 2.51 – 2.39 (m, 8H), 1.90 (td, *J* = 15.1, 7.6 Hz, 4H), 1.79 (t, *J* = 7.2 Hz, 4H), 1.19 (s, 12H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 139.6, 138.3, 127.6, 124.8, 93.5, 93.3, 87.9, 47.6, 38.7, 36.4, 34.7, 33.5, 27.1, 23.4.



1-82

1-82: ^{1}**H NMR** (501 MHz, $CDCl_3$) δ 5.75 (tdd, *J* = 13.6, 10.2, 6.7 Hz, 2H), 5.02 (d, *J* = 17.1 Hz, 2H), 4.97 (d, *J* = 10.2 Hz, 2H), 2.26 (q, *J* = 7.2, 7.0 Hz, 8H), 2.14 (q, *J* = 6.8 Hz, 4H), 1.70 – 1.56 (m, 8H), 1.47 (m, 4H), 1.19 (s, 12H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 137.4, 115.3, 84.6, 77.3, 65.5, 65.5, 65.2, 42.3, 42.2, 32.6, 31.5, 28.8, 27.4, 24.3, 19.5, 18.5.



1-84

1-84 (82%): ^{1}**H NMR** (501 MHz, $CDCl_3$) δ 7.26 (s, 2H), 6.05 (t, *J* = 2.0 Hz, 2H), 5.31 (d, *J* = 1.6 Hz, 2H), 5.22 (d, *J* = 1.0 Hz, 2H), 2.51 – 2.40 (m, 8H), 2.19 (t, *J* = 7.2 Hz, 4H), 1.91 (m, 4H), 1.69 (m, 4H), 1.41 (m, 4H), 1.21 (s, 12H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 137.8, 131.6, 124.6, 120.7, 90.7, 86.7, 85.0, 65.0, 42.2, 37.4, 36.4, 33.3, 31.7, 28.9, 23.7, 23.4.

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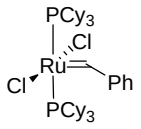
Chapter 2. Reactivity of Multiynes toward Olefin Metathesis and 1,4-Hydrovinylation Catalyzed by Grubbs-Type Ruthenium Alkylidenes

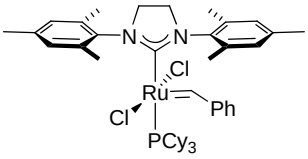
2.1. Overview of Non-Metathetic Reactivities of Grubbs-Type Ruthenium Alkylidenes

During the past decade, the chemistry of Grubbs-type ruthenium alkylidene complexes **G-I**, **G-II** and **HG-II** has witnessed explosive growth in olefin metathesis.[1] Despite their great synthetic potential, to date non-metathetic utility has been largely surpassed by the power of the olefin metathesis. Though several notable non-metathetic reactions of Grubbs-type pre-catalysts have been reported, in most cases, non-metathetic products are obtained as by-products, and they are supposed to be generated by ill-defined ruthenium complexes derived from the decomposition of the alkylidene complexes.[2] Consequently, the discovery of new non-methathetic reactions mediated by Grubbs-type pre-catalysts will broaden their utility in organic synthesis. Some non-metathetic reactions such as Kharasch addition, oxidation, hydrosilylation, hydrogenation, cyclopropanation and olefin isomerization have evolved as useful synthetic tools in organic chemistry.



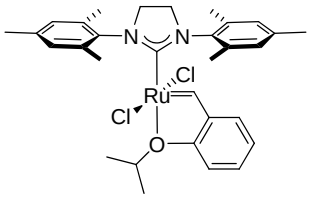
Grubbs 1st generation catalyst

G-I



Grubbs 2nd generation catalyst

G-II



Hoveyda-Grubbs 2nd generation catalyst

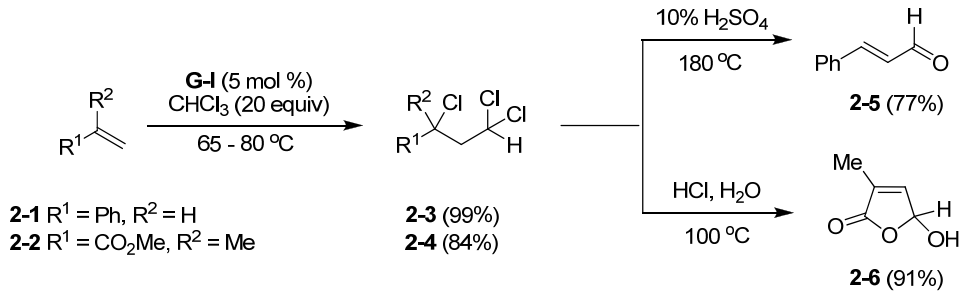
HG-II

2.1.1. Kharasch Addition and Tandem Metathesis–Dihydroxylation

Radical-based atom transfer is one of the characteristic reactivity of Grubbs-type alkylidene complexes.[3] In 1999, Snapper and co-workers discovered that ruthenium alkylidene **G-I** was an efficient catalyst for Kharasch addition of $CHCl_3$ to alkenes.[3a] For example, the reaction of styrenes **2-1** and **2-2** with 20 equivalents of $CHCl_3$ in the presence of **G-I** provided the corresponding trichloroalkane **2-3** and

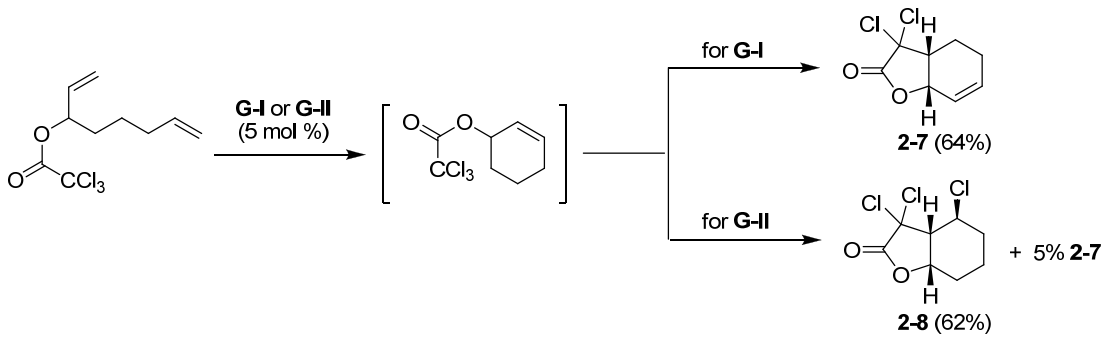
2-4, the Kharasch addition products quantitatively. In general, alkenes with low metathesis activity such as styrenes and acrylates serve as ideal substrates for Kharasch addition, especially with chloroform or 1,1,1-trichloroethane. This is a quite useful transformation because the products from the Kharasch addition can be easily converted to α,β-unsaturated aldehyde **2-5**, or γ-hydroxybutenolide **2-6** via hydrolysis under different conditions (**Scheme 2.1**).[3c]

Scheme 2.1 Kharasch addition catalyzed by Grubbs catalyst and subsequent hydrolysis



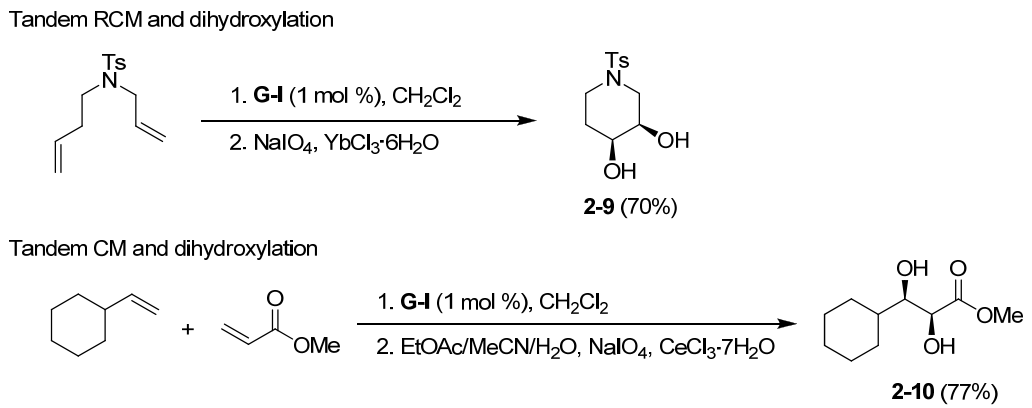
Tandem reactions involving RCM and intramolecular Kharasch addition were also examined with trichloroacetate derivative.[3d] Thus, 1,7-diene substrate containing trichlorocacetate at C-3 position would lead to metathesis product upon treatment with **G-I**, which is then further cyclized to form unsaturated bicyclic lactone **2-7**. The same reaction with **G-II** afforded saturated bicyclic lactone **2-8** together with small amount unsaturated bicyclic lactone **2-7** (5%). It's clear to see the product distribution for tandem RCM and intramolecular Kharasch addition is critically dependent on the catalyst used (**Scheme 2.2**).

Scheme 2.2. Tandem reactions involving RCM and intramolecular Kharasch addition



Blechert has reported a new tandem process involving RCM and dihydroxylation using **G-I**.[4] The ring-closing metathesis (RCM) of the substrate containing diene moiety provided the corresponding RCM product in the presence of **G-I**, which upon treating $NaIO_4$ and $YbCl_3{\cdot}6H_2O$ in MeCN/EtOAc/H_2O afforded *cis*-diol **2-9**. A similar sequence involving CM and dihydroxylation also provided diol **2-10** in good yield (**Scheme 2.3**).

Scheme 2.3. Tandem reaction involving metathesis and dihydroxlation

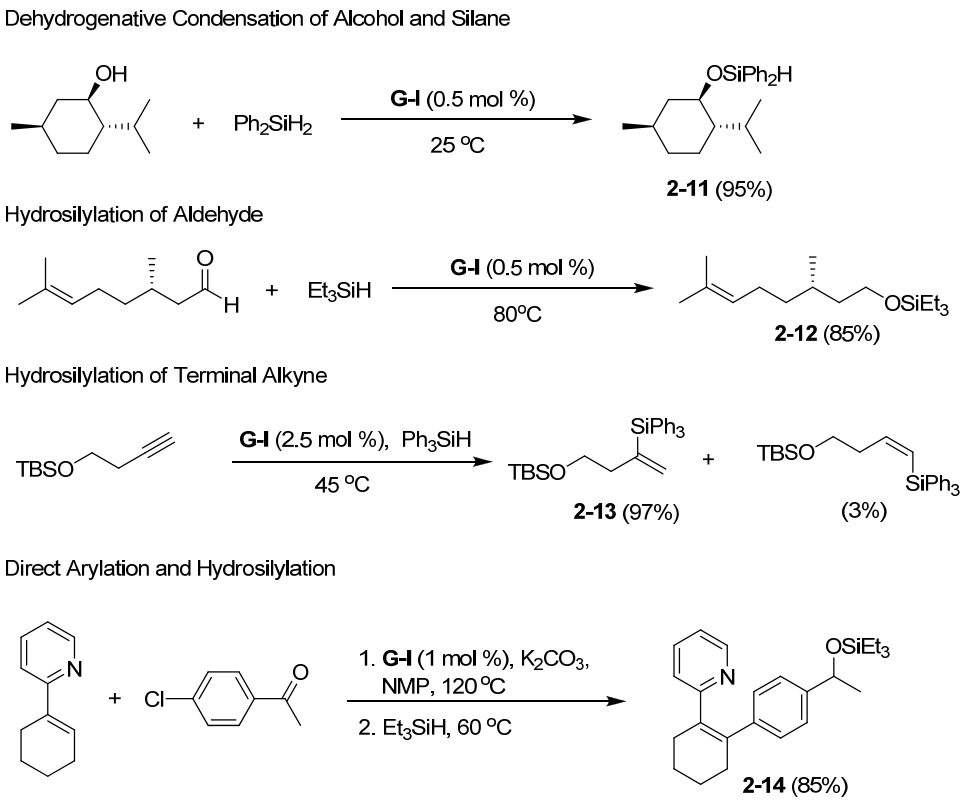


2.1.2. Hydrosilylation and Hydrogenation

Ruthenium-based alkylidene complexes have been shown to be an effective catalyst for a variety of hydrosilylation reactions (**Scheme 2.4**).[5] Lee and co-workers reported dehydrogenative condensation of alcohols with silanes using 0.5 mol % of **G-I** to form silylether **2-11**.[5a] Subsequently, the same group extended this method for hydrosilylation of aldehydes and ketones where 1 mol % of **G-I** promotes the reaction with various silanes under mild conditions to afford the corresponding silylether **2-12**. Hydrosilyation of terminal alkyne is a powerful method to generated vinylsilanes which are useful intermediates in organic synthesis.[6] Cossy reported hydrosilylation of terminal alkyne using **G-I** where α-vinylsilane **2-13** was obtained predominantly.[5b] Ackerman also developed a tandem arylation induced by directed C–H functionalization and hydrosilylation sequence catalyzed by **G-I** to provide **2-14** in 85%

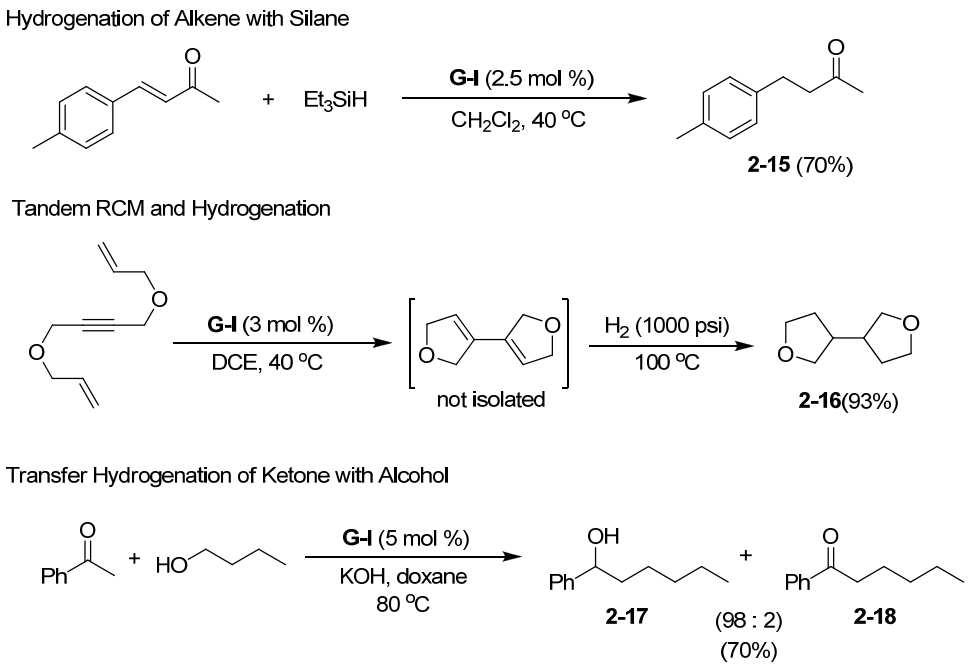
yield.[5c] 2-Pyridyl, pyrazolyl and oxazolinyl directing groups could be used and the change or removal of solvent was not required to obtain decent yields of the products.

Scheme 2.4. Activation of silanes



Cossy has demonstrated the selective reduction of α,β-unsaturated carbonyl compound with Et_3SiH using **G-I** at room temperature (**Scheme 2.5**).[7a] The corresponding saturated carbonyl compound **2-15** were obtained and the 1,2-reduction of ketone moiety was not observed. It is generally known that the addition of H_2 to **G-I** quantitatively generates a ruthenium hydride complex $RuHCl(H_2)(PCy_3)_2$ which is an effective catalyst for the hydrogenation of alkenes to generate saturated product such as **2-16** in good yield.[7b] Shim and Cho reported that the transfer hydrogenation of acetophenone with butanol catalyzed by **G-I** afforded unconventional alkylated products **2-17** and **2-18** rather than the expected direct transfer hydrogenation product, 1-phenylethanol.[7c]

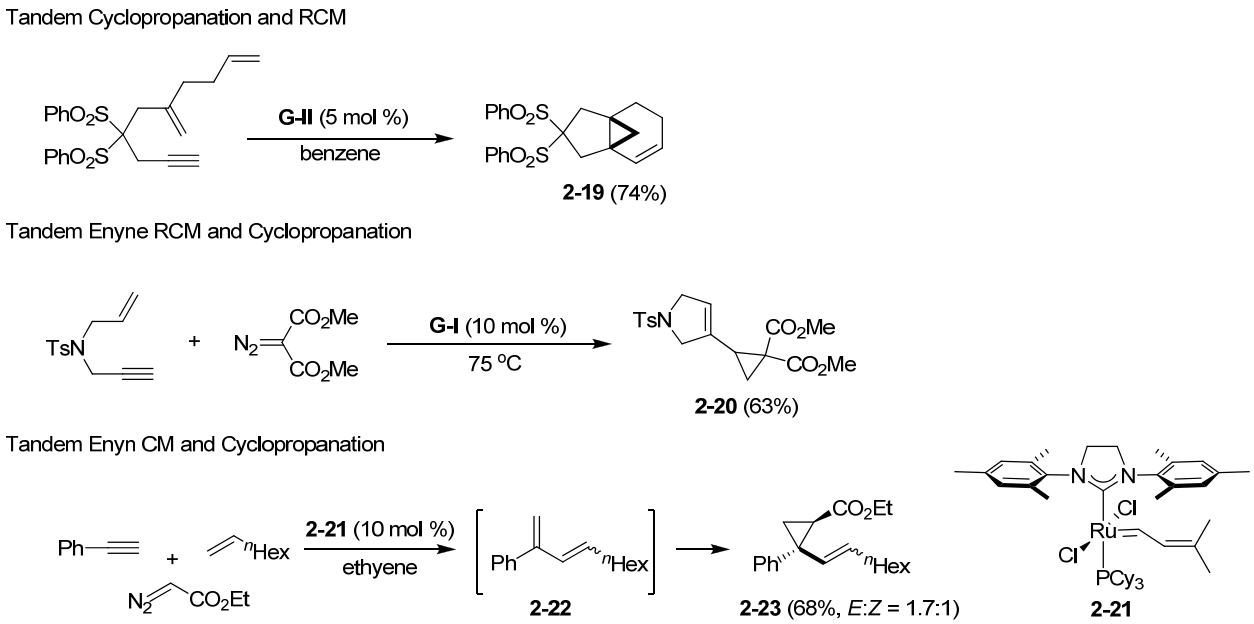
Scheme 2.5. Hydrogenation by ruthenium hydride complex



2.1.3. Cyclopropanation and Cycloaddition

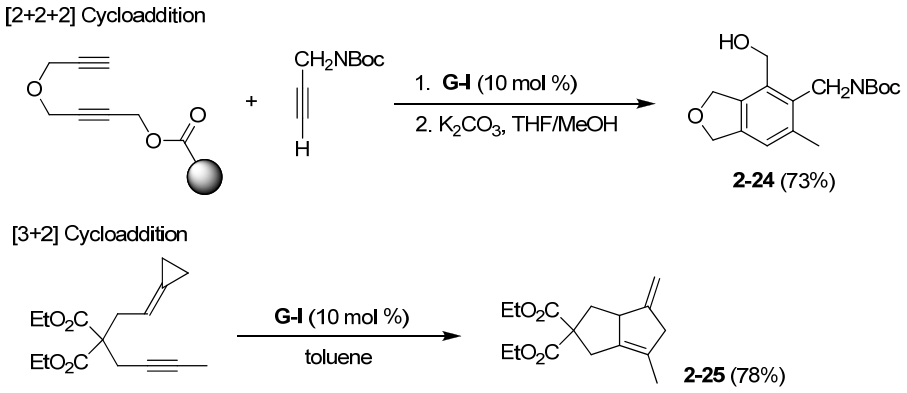
The ability of Grubbs-type ruthenium alkylidenes to promote cyclopropanation with alkenes combined with their similar mechanistic features of metathesis and cyclopropanation imply that a tandem cyclopropanation and olefin metathesis is feasible (**Scheme 2.6**).[8] Diver reported a tandem process involving cyclopropanation and RCM using **G-II** to generate tricyclic compound **2-19** in 74% yield.[9a] Snapper has developed an one-pot ring-closing enyne metathesis–cyclopropanation reaction. In his study, Grubbs first generation catalyst, **G-I** promoted the reaction of enynes with a variety of diazo compounds to form cyclopropane derivatives **2-20** at elevated temperatures, and the cyclopropanation occurred on a less-hindered double bond with high selectivity.[9b] The cyclopropanation could be combined with enyne cross metathesis such that the CM of terminal alkynes and alkenes in the presence of **2-21** under ethylene atmosphere generated enyne cross metathesis product **2-22**, which then followed by slow addition of diazoacetate to provide stereoselective cyclopropanation product **2-23**.[9c]

Scheme 2.6. Cyclopropanation



Deiters has reported a [2+2+2] cycloaddition of a solid-supported unsymmetrical diyne with internal alkyne from which high level of regioselectivity in the formation of product **2-24** was observed (**Scheme 2.7**).[10a] This method was subsequently used to assemble complex compound libraries. Interestingly, when the same reaction was performed with Wilkinson's catalyst, $RhCl(PPh_3)_3$, poor regioselectivity was observed regardless of the structure of internal alkynes. In the reaction of enyne substrate containing cyclopropane undergoes [3+2] cycloaddition with 10 mol % of **G-I** under high substrate concentration, unsaturated bicyclic product **2-25** was obtained in good yield.[10b]

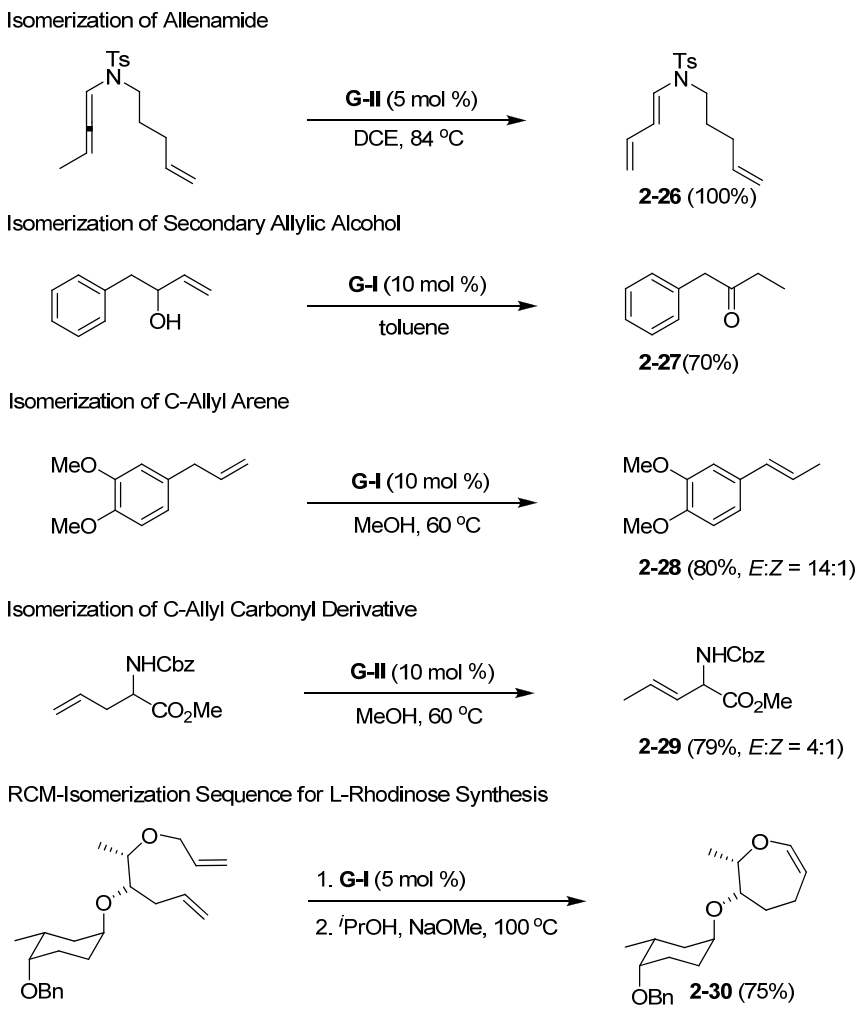
Scheme 2.7. Cycloaddition reactions



2.1.4. Double Bond Isomerization and Deprotection Reactions

Ruthenium alkylidene complexes are capable of isomerizing a variety of alkenes.[11] It was found that the treatment of a substrate possessing a methyl substituted allenamide moiety with **G-II** provided dieneamide **2-26** in quantitative yield (**Scheme 2.8**).[11a] A variety of secondary allylic alcohols can also undergo isomerization reaction upon treatment with **G-I** to give corresponding ketone **2-27**.[11b] Hanessian has reported a simple and efficient method for the isomerization of terminal alkenes into their 2-alkenyl counterparts, with minimal dimerization or cross metathesis products.[11c]

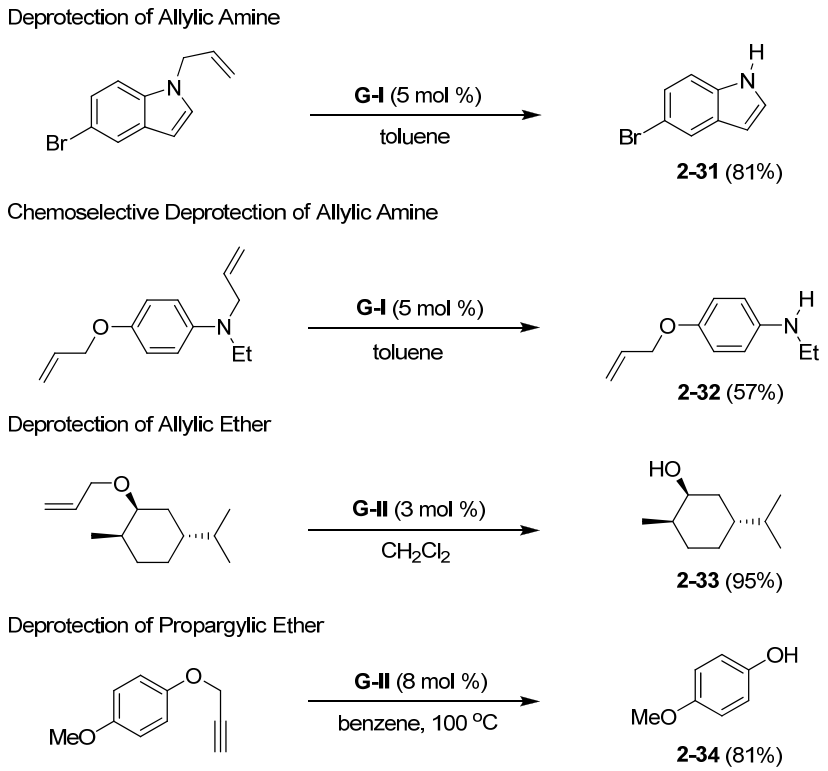
Scheme 2.8. Double bond isomerization reaction



For example, the reaction of simple allyl arenes with 10 mol % of **G-I** in MeOH at 60 °C gave 2-propenyl arenes **2-28**. The reaction of allyl substituted amino ester with **G-II** under the identical reaction conditions also provided the corresponding isomerization product **2-29** in good yield with moderate *E*/*Z* selectivity.[11d] This isomerization protocol using **G-II** could be combined with cross metathesis or ring-closing metathesis in tandem manner. The utility of which was demonstrated by several research groups for the synthesis of natural products. For example, glycoside containing one septanose unit and hexose unit was converted to disaccharide glycal **2-30** by using **G-I** in *i*-PrOH/NaOH.[11e]

It was also found that **G-I** could catalytically deallylate from *N*-allylindole to afford the corresponding indole **2-31** (**Scheme 2.9**).[12a] Both aromatic and aliphatic amines readily undergo deallylation at elevated temperature, thus in the presence of allyl ether, **G-I** can chemoselectively deprotect allyl amine to give aniline **2-32**.[12b,c]

Scheme 2.9. Deprotection reactions

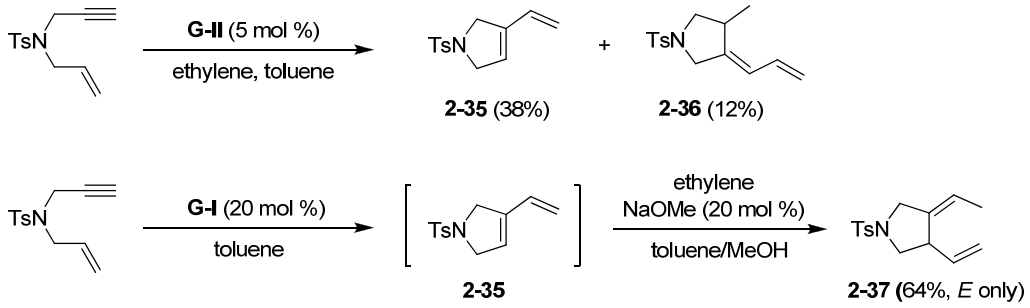


The reaction of allyl ether with a catalytic amount of **G-II** (3 mol%) followed by acidic treatment provided corresponding alcohols **2-33** in good yield.[12d] Deprotection of propargyl group from phenyl propargyl ether generating phenol **2-34** was also achieved by using **G-II** at 100 °C.[12e]

2.1.5. Hydrovinylation

In 2003, Mori reported an unusual reactivity of ruthenium alkylidene complexes in the enyne metathesis of 1,6-enynes, hydrovinylatied product **2-36** was obtained in 12% yield in addition to the expected enyne metathesis product **2-35** (**Scheme 2.10**).[13a,b] Recently, Snapper reported a tandem process involving enyne RCM and hydrovinylation using **G-I**.[13c] After metathesis reaction, Grubbs catalyst was subsequently converted to a ruthenium hydride complex *in situ* by adding NaOMe in toluene/MeOH under ethylene, which provided 1,4-hydrovinylation product **2-37** in a stereoselective manner.

Scheme 2.10. Hydrovilylation with Grubbs-type catalysts



2.2. Results and Discussion

2.2.1. Tandem Enyne CM–Metallotropic [1,3]-Shift

Control of regio- and steroselectivity in enyne cross metathesis is a fundamentally challenging problem.[18] Blechert has demonstrated that diyne-alkene cross metathesis (CM) using Ru-based Grubbs catalyst allowed only α-insertion leading to products of type **F**.[19] On the other hand, Hoveyda and Schrock reported that Mo-based alkylidene complexes prefer β-insertion pathway to give **H**.[20] Especially,

in cyclopolymerization of 1,6-diyne of type **A**, the ring size of the repeating unit affects many key polymer properties, rendering this regioselectivity a critical issue (**Figure 2.1**).[21]

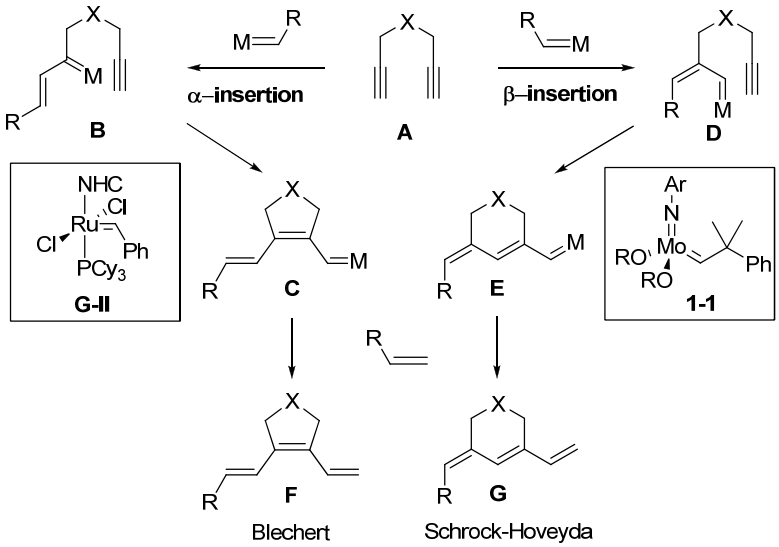
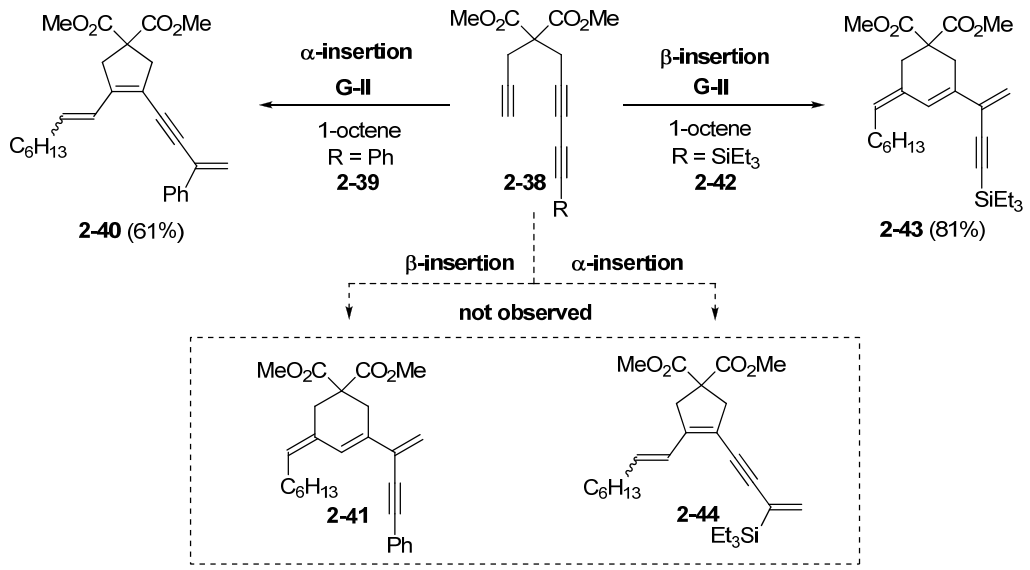


Figure 2.1. Two different modes of enyne metathesis

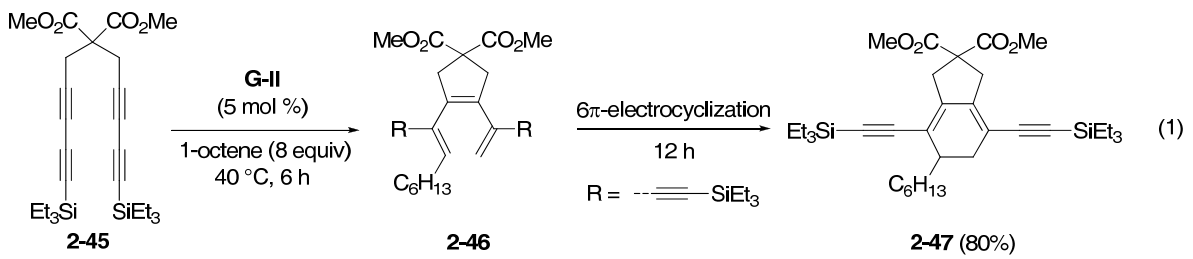
In conjunction with our early studies on divergent metallotropic [1,3]-shift[22] behavior of conjugated multiynes,[23] we envision that the tandem enyne CM of triyne **2-38** with an alkene followed by RCM–metallotropic [1,3]-shift would provide novel molecular structures with multiple conjugations in a straightforward fashion. Initial studies demonstrated that the regio- and stereochemical outcome of the products could be controlled, but critically depends on the nature of the substituent at the terminating end.[24] For example, the reaction of triyne **2-39** bearing phenyl group with 1-octene in the presence of the **G-II** exclusively afforded **2-40** as a mixture of *E/Z*-isomers. In contrast, triyne **2-42** bearing triethylsilyl functionality proceeded with excellent regioselctivity of β-insertion to produce **2-43** as a single product, where termination occurred prior to metallotropic [1,3]-shift. The bifurcated reaction pathways were controlled so precisely that no detectable amount of the β-insertion product **2-41** from substrate **2-39** or the α-insertion product **2-44** from substrate **2-42** was observed in these reactions (**Scheme 2.11**).

Scheme 2.11. Controllable initiation/termination of enyne CM and metallotropic [1,3]-shift

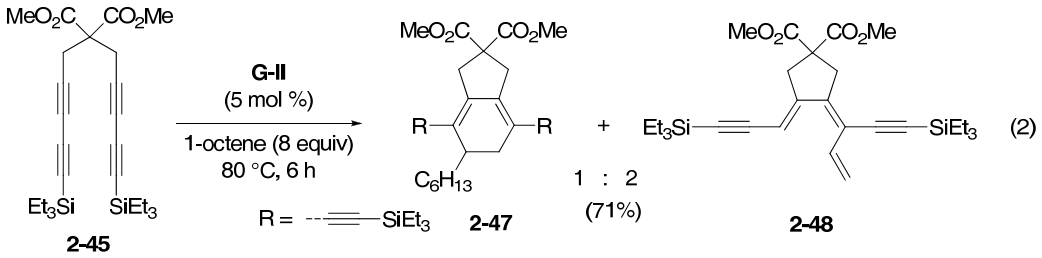


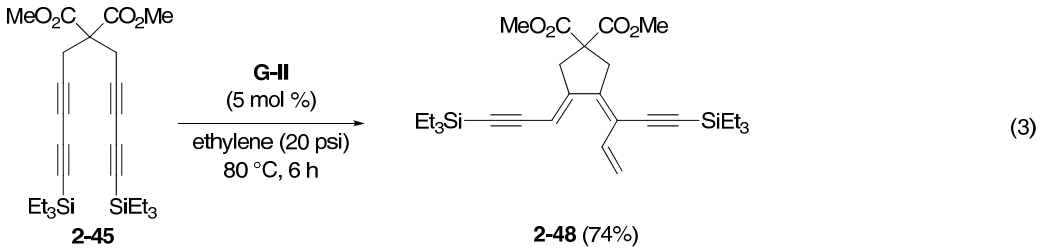
It's quite interesting to note from these reactions that the substituent remote from the initiation site can control the mode of insertion. Moreover, the metallotropic [1-3]-shift seems to be directly coupled with the mode of initiation; the intermediate formed from an α-insertion leads a product with metallotropic [1-3]-shift, but that of β-insertion provides a product without metallotropic [1-3]-shift. Having the above results in hand, we expanded the reaction scope by adding an additional alkyne to the triyne moiety to generate a new class of substrates, and investigated their reactivity and initiation and termination behavior.

A symmetrical *bis*-1,3-diyne substrate **2-45** bearing triethylsilyl groups was prepared and treated under the identical reaction conditions as before. Unexpectedly, only α-insertion product **2-46** was obtained along with bicyclic product **2-47** without observing any β-insertion product. This selectivity is in stark contrast to that of triynes. At 40 ^{o}C, the highly conjugated triene product **2-46** slowly cyclized to form bicyclic product **2-47** via a thermal 6π-electrocyclization (Eq. 1).[25] We assume that at higher temperature, a tandem CM–RCM–6π-electrocyclization would occur spontaneously to generate product **2-47** in one step from an acyclic building block.



Different from our expectation, however, the reaction of tetrayne **2-45** at 80 °C under otherwise identical reaction conditions provided an inseparable mixture of **2-47** and hydrovinylation product **2-48** in 1:2 ratio with 71% combined yield (Eq. 2).[25, 26] We inferred that the 1,4-hydrovinylative cyclization occurred between *bis*-1,3-diyne **2-45** and ethylene that was generated in situ by homometathesis of 1-octene. Indeed, exposure of **2-45** to ethylene atmosphere in CH_2Cl_2 in the presence of a catalytic amount of **G-II** at 40 °C afforded the 1,4-hydrovinylation product **2-48** exclusively as the single isomer in 74% yield (Eq. 3). It is quite surprising that Grubbs catalyst promotes completely different catalytic processes simply by exposing to a different alkene reacting counterparts.





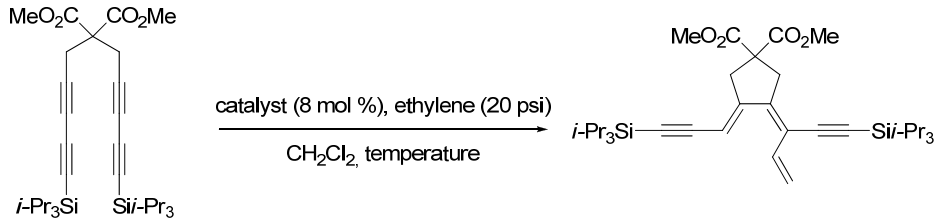
2.2.2. Hydrovinylative Cyclization

2.2.2.1. Initial Discovery

To further investigate the factors that promote 1,4-hydrovinylative cyclization instead of metathesis, we screened different ruthenium alkylidene complexes **G-I**, **G-II** and **HG-II** and other ruthenium-based complexes such as $RuCl_3$, $RuCl_2(PPh_3)_2$, $Ru_3(CO)_{12}$, and $[RuCp(CH_3CN)_3]PF_6$ at 40 ^oC and 80 ^oC, respectively (**Table 2.1**).

From these screening, we found that the catalytic activity of Grubbs-type ruthenium alkylidenes, regardless of their structural variations, is general toward the 1,4-hydrovinylative cyclization. Reactions with other ruthenium-based complexes, however, did not provide any hydrovinylative cyclization product at either 40 ^oC or 80 ^oC, instead, only returned the starting material intact. Among these three Grubbs-type catalysts examined, **G-II** was the most effective catalyst compared to the other two.

Table 2.1. Optimization for 1,4-hydrovinylative cyclization



entry	catalyst	temperature (^oC)	time (h)	yield of **2-50** (%)[a]
1	**G-I**	40	6	54
2	**G-II**	40	6	98
3	**HG-II**	40	6	0
4	**G-I**	80	1	95
5	**G-II**[b]	80	1	98
6	**HG-II**	80	1	72[c]

[a] Isolated yield. [b] Running reaction with 5 mol % of catalyst gave only 80% conversion of the starting material after 1 hour, reaction completed after 4 hours with slightly diminished yield (89%). [c] 25% of the starting material was recovered after 1 hour reaction time.

Treating *bis*-1,3-diyne **2-49** with **G-II** at 40 °C for 6 hours led to a quantitative conversion, providing **2-50** as a single product in 98% yield. **G-I** showed moderate efficiency towards to the hydrovinylative cyclization, providing the same product in 54% yield. On the other hand, **HG-II** showed no catalytic activity at 40 °C, providing only recovered starting material, but at 80 °C under otherwise identical reaction conditions afforded 72% yield of the product. The identity of product **2-50** was further confirmed by X-Ray crystallography (**Figure 2.2**).

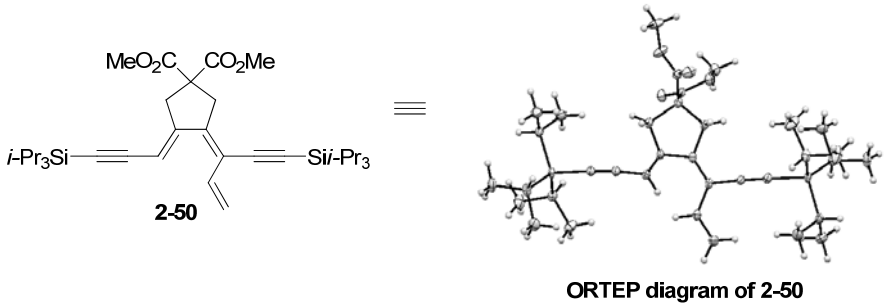


Figure 2.2. X-Ray structure of 1,4-hydrovinylative product **2-50**

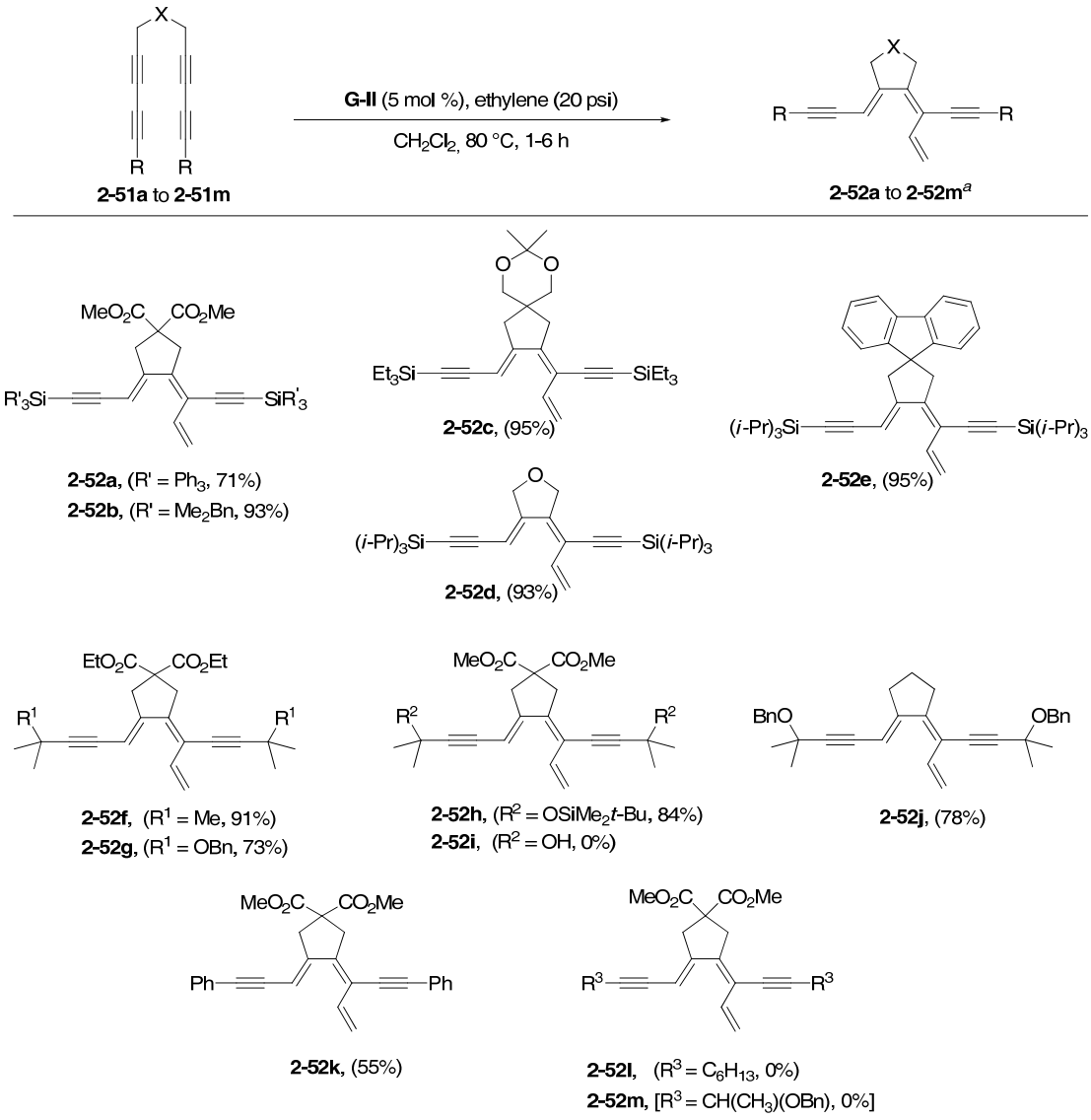
2.2.2.2. Reaction Scope

Having established the optimal reaction conditions, we next explored the generality and reaction scope of this 1,4-hydrovinylative cyclization using a verity of tetrayne substrates (**Table 2.2**). Substrates bearing different silyl groups such as triphenylsilyl group (**2-51a**), benzyldimethylsilyl group (**2-51b**), triethylsilyl group (**2-51c)** and triisopropylsilyl groups (**2-51d** and **2-51e**) all afforded 1,4-hydrovinylative cyclization products **2-52a**–**2-52e** in good yields regardless of the tether.

A substrate containing *tert*-butyl group also provided product **2-52f** in 91% yield. Similarly, substrates bearing silyl- or benzyl-protected tertiary alcohol provide products **2-52g**, **2-52h** and **2-52j** in good to excellent yields. However, substrate **2-51i** containing free alcohol failed to yield the desired product **2-52i**, but only the starting material was recovered intact. The reaction of substrate bearing phenyl group was found to be less efficient, providing product **2-52k** in moderate yield (55%). To our

surprise, however, neither primary nor secondary alkyl group-containing substrates gave the corresponding cyclized product **2-52l** or **2-52m**, but the starting material remained untouched. We suspect that chelation of ruthenium alkylidene with distal alkyne moieties might prohibiting the cyclization event.

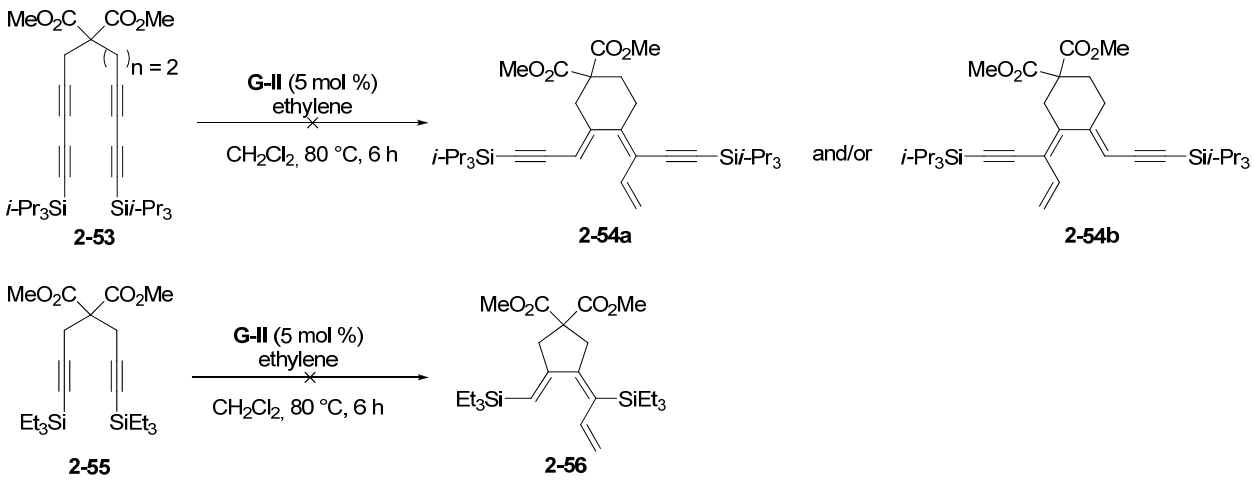
Table 2.2. Substrate scope of 1,4-Hydrovilylative cyclization of tetraynes



[a] Isolated yield.

Next, we examined the 1,4-hydrovinylative cyclization of substrate **2-53** containing a longer tether and 1,3-diyne substrate **2-55** (**Scheme 2.12**). These substrates, however, did not provide **2-54a**, **2-54b** or **2-56**, instead, the starting materials were recovered intact even without forming metathesis product.

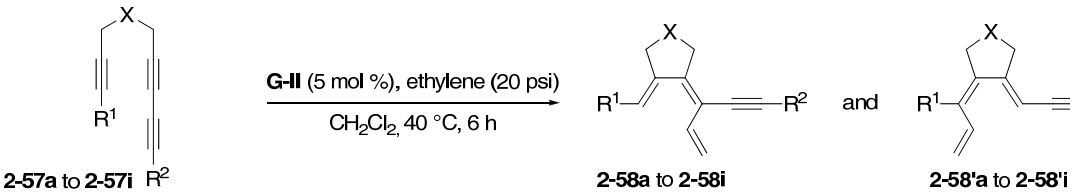
Scheme 2.12. 1,4-Hydrovinylative cyclization with longer tethered *bis*-1,3-diyne and 1,6-diyne

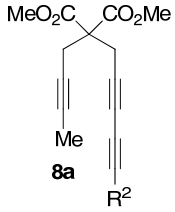
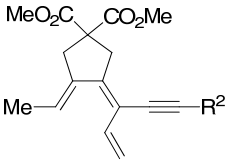
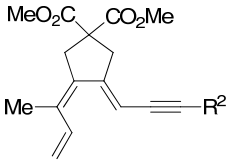
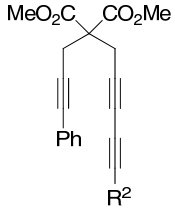
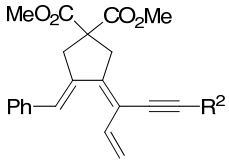
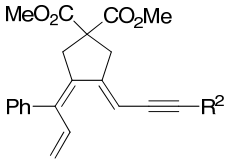
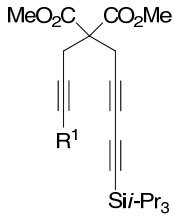
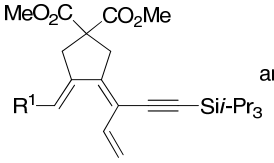
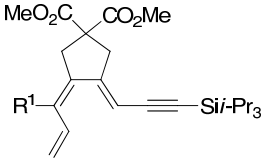
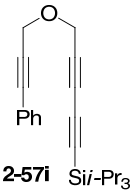
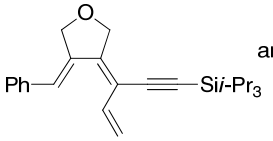
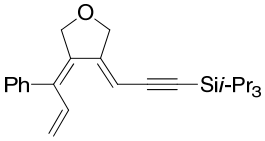


To further expand the reaction scope of the 1,4-hydrovinylative cyclization, we examined the reactivity of unsymmetrical triyne substrates (**Table 2.3**). We surmised substrates of inherently less reactive nature toward metathesis reaction should have better chance to participate in non-metathetic reaction such as 1,4-hydrovinylative cyclization. In this regard, triynes **2-57** containing all internal triple bonds should be a good substrate because of its sluggish metathesis rate. Gratifyingly, the delicate balance between the metathesis and the hydrovinylation reaction still favored the latter, providing 1,4-hydrovinylative cyclization products in excellent yields.

Under the optimized reaction conditions, substrates **2-57a** and **2-57b** containing a methyl group afforded products **2-58a/2-58a'** and **2-58b/2-58b'** in 82 and 77% yields with 1:1.5 and 1.8:1 ratios (entries 1–2). For the substrates containing phenyl group at the unconjugated alkyne **2-57c**–**2-57f**, the regioselectivity increased progressively depending on the size of the substituents, providing regioisomers **2-58c**–**2-58f** over **2-58c'**–**2-58f'** up to a 9:1 ratio (entries 3–6). While substrate **2-57g** with a combination of *p*-methoxyphenyl and triisopropylsilyl substituents provided **2-58g** and **2-58g'** in a 10:1 ratio (entry 7), both substrates **2-57h** and **2-57i** containing phenyl and triisopropylsilyl groups afforded virtually single regioisomers **2-58h** and **2-58i** (>20:1 ratio) with 85 and 69% yields, respectively (entries 8–9).

Table 2.3. 1,4-Hydrovilylative cyclization of triaynes

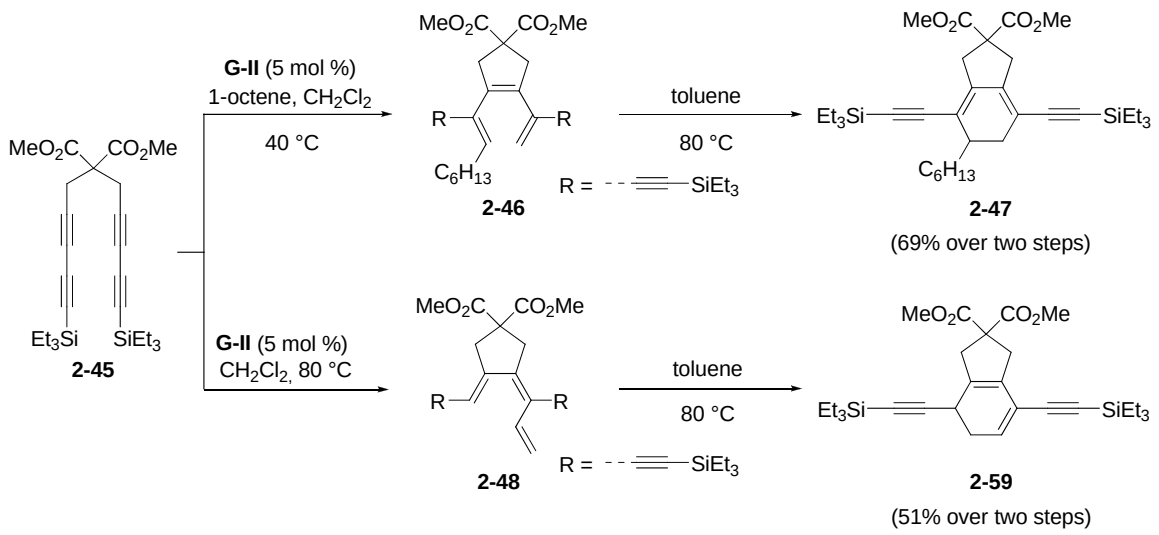


entry	substrate	products and ratio			yield
			and		
1	**2-57a**, R^2 = $SiEt_3$	**2-58a**	1 : 1.5	**2-58a'**	82
2	**2-57b**, R^2 = CMe_2OH	**2-58b**	1.8 : 1	**2-58b'**	77
			and		
3	**2-57c**, R^2 = CMe_2OBn	**2-58c**	3 : 1	**2-58c'**	87
4	**2-57d**, R^2 = *t*-Bu	**2-58d**	5 : 1	**2-58d'**	91
5	**2-57e**, R^2 = $SiEt_3$	**2-58e**	9 : 1	**2-58e'**	85
6	**2-57f**, R^2 = $SiMe_2$*t*-Bu	**2-58f**	9 : 1	**2-58f'**	80
			and		
7	**2-57g**, R^1 = (4-OMe)-Ph	**2-58g**	10 : 1	**2-58g'**	82
8	**2-57h**, R^1 = Ph	**2-58h**	>20 : 1	**2-58h'**	85
9	 **2-57i**	 **2-58i**	and >20 : 1	 **2-58i'**	69[b]

[a] Combined yields of two isomers. [b] Contaminated with a product of ethylene cross metathesis on the 1,3-

This newly developed 1,4-hydrovinylative cyclization, which generates conjugated trienes with the unique connectivity different from that of the product from metathesis process, should have significant synthetic utility (**Scheme 2.13**). For example, triene **2-46** generated via tandem enyne RCM could be converted to a highly conjugated enyne **2-47** via 6π-electrocyclization. On the other hand, compound **2-59** containing a different conjugation system can be obtained by a 1,4-hydrovinylative cyclization–6π-electrocyclization sequence. It is noteworthy that compounds with similar molecular frameworks but different conjugated system can be selectively formed from the same starting material by different reaction sequences. This tunable reactivity will provide a convenient method for the synthesis of a series of conjugated compounds of important applications.

Scheme 2.13. Formation of different bicyclic systems via tandem processes

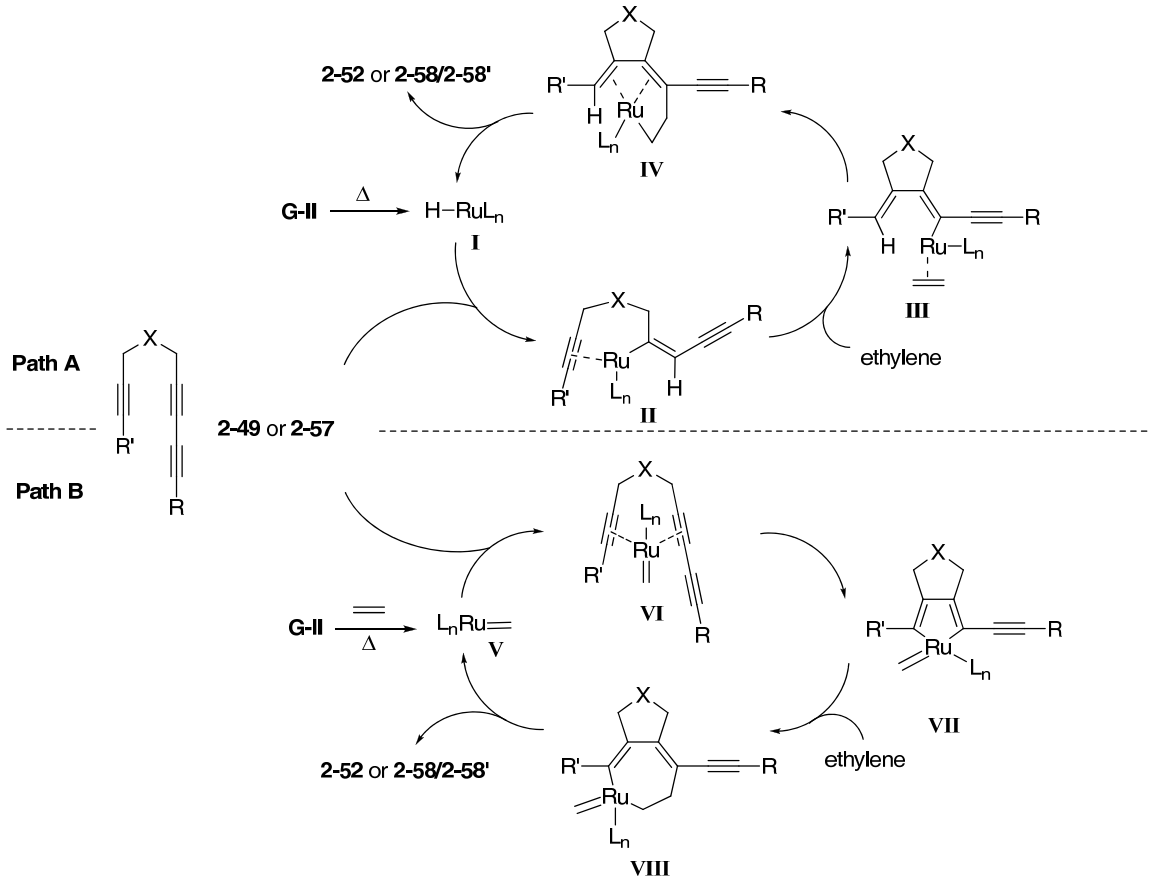


2.2.2.3. Mechanistic Study

Having demonstrated the generality of the reaction, we became interested in the reaction mechanism of this novel 1,4-hydrovinylative cyclization, where two possible reaction pathways are considered for (**Scheme 2.14**). In path A, a ruthenium hydride **I** derived from the decomposition of ruthenium alkylidene complex would be able to serve as a catalyst. Initial hydroruthenation on one of the proximal triple bond followed by migratory insertion onto the other proximal alkyne moiety would

generate vinyl ruthenium intermediate **III**. Subsequent ethylene insertion by **III** to form a penultimate intermediate **IV**, which then undergo β-hydride elimination to deliver product **2-52** or **2-58**/**2-58′** and the regenerated ruthenium hydride catalyst.

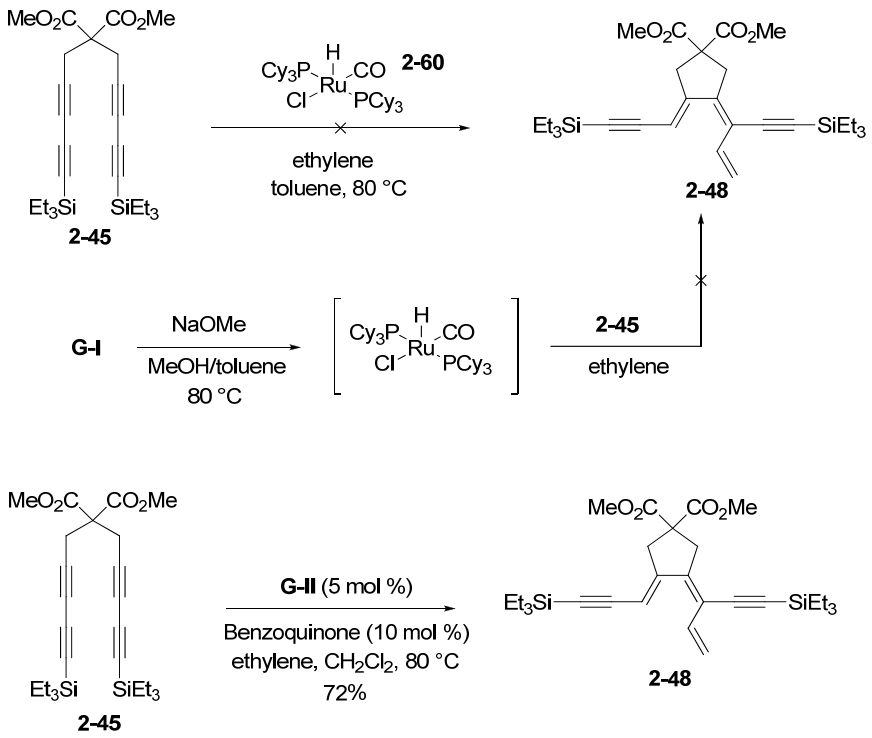
Scheme 2.14. Possible reaction mechanism for 1,4-hydrovinylative cyclization



To gain more insight into these proposed mechanisms, we treated compound **2-45** with ruthenium hydride complex $[(PCy_3)_2COClRuH]$ **2-60**,[27] which is well-known for its reactivity in hydrovinylation reaction (**Scheme 2.15**). However, the expected product **2-48** was not observed under this condition. The hydrovinylation protocol developed by Snapper, where the ruthenium alkylidene complex **G-I** was treated with NaOMe in MeOH/toluene,[13c] did not give any 1,4-hydrovinylative cyclization product instead substrate **2-45** was recovered intact. To further disprove the involvement of ruthenium hydride in the 1,4-hydrovinylative cyclization, we ran the reaction with 5 mol % of the **G-II** and 10 mol % of

benzoquinone.[28] Because Grubbs reported that benzoquinone suppressed the formation of ruthenium hydride species from ruthenium alkylidene. 1,4-Hydrovinylative cyclization should not occur under this condition if the ruthenium hydride is the catalytically active species. We found that reactions with and without benzoquinone were equally efficient for the formation of 1,4-hydrovinylative cyclization product. We consider these control experiments are strong evidences that can disprove the hydroruthenation pathway catalyzed by the ruthenium hydride **I** (path A).

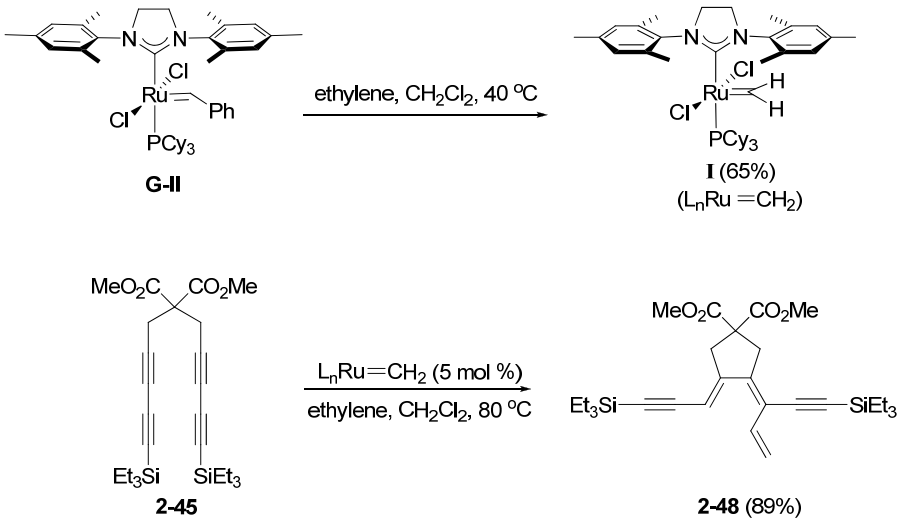
Scheme 2.15. Control experiments for 1,4-hydrovinylative cyclization



Next we turned our attention to path B where the intact ruthenium methylidene **V** is supposed to be the catalytically active species or at least its precursor (**Scheme 2.16**). Therefore, we assumed that an independently prepared ruthenium methylidene **V** should show identical reactivity profile as that of the in situ generated catalyst under ethylene, and indeed that was found to be the case. Base on this discovery, we conclude that the most probable mechanism for the 1,4-hydrovinylative cyclization involves the in situ generated ruthenium methylidene species **V**, where the catalytically active species is either the ruthenium

methylidene itself or its tricyclohexylphosphine-dissoicated form. This observation is quite unusual because without exception that the known examples of non-metathetic activity of Grubbs-type alkylidene complexes are the consequence of ruthenium hydride species such as **I**.

Scheme 2.16. Ruthenium methylidene-catalyzed Hydrovinylation



2.3. Conclusion

In summary, we have demonstrated that the reactivity of multiynes with Grubbs catalysts can be switched from metathesis to non-metathetic mode by changing the reacting alkene counterpart. Using this new non-metathetic reactivity of Grubbs complexes, we have developed an efficient 1,4-hydrovinylative cyclization of multiynes with ethylene under mild conditions. For unsymmetrical triyne substrates, the regioselectivity of 1,4-hydrovinylative cyclization could be controlled by incorporating appropriate substituents on the alkyne and 1,3-diyne moieties. This study adds a new entry to the list of non-metathetic reactivity of Grubbs-type ruthenium alkylidene complexes, and we believe more interesting reactivity of Grubbs-type alkylidene complexes are yet to be discovered.

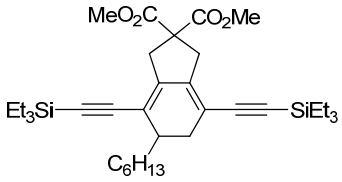
2.4. Experimental Details

2.4.1. General Information (See Chapter 1.4.1)

2.4.2. Procedure for Tandem CM–RCM–Thermal 6π-Electrocyclization: Substrate **2-45**, 1-octene (8 equiv) and **G-II** (5 mol %) were dissolved in CH_2Cl_2 in a thick-walled Schlenk tube equipped with a magnetic stir bar. The reaction mixture was degassed under vacuum at -78 ^oC. The tube was stirred in an oil bath at 40 °C for 18 h. The tube was then opened to air at room temperature and the solvent was removed under reduced pressure. Purification of the crude product by flash column chromatography (SiO_2, hexanes: EtOAc = 5:1) provided desired organic product **2-47** in 68% over two steps

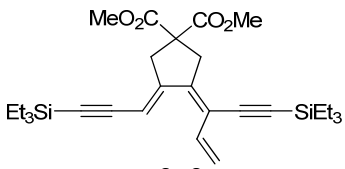
2.4.3. General Procedure for 1,4-Hydrovinylation: A substrate and **G-II** (8 mol %) were dissolved in CH_2Cl_2 (0.02 M) in a thick-walled Schlenk tube equipped with a magnetic stir bar. The reaction mixture was degassed under vacuum at -78 ^oC. The tube was pressurized with ethylene (20 psi) and then stirred in an oil bath at 80 ^oC (40 ^oC for triyne) for 1-6 h. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography on silica gel to give the 1,4-hydrovinylation products.

2.4.4. Selected Characterization Data



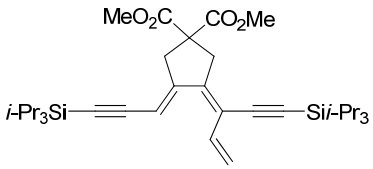
2-47

2-47 (68% from **2-45**): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 3.74 (s, 6H), 3.17 – 3.14 (m, 4H), 2.45 (dd, *J* = 16.6, 8.3 Hz, 1H), 2.41–2.30 (m, 1H), 2.16 (dd, *J* = 16.6, 8.6 Hz, 1H), 1.71 – 1.60 (m, 1H), 1.42 – 1.33 (m, 2H), 1.33 – 1.22 (m, 7H), 1.01 (t, *J* = 7.9 Hz, 18H), 0.87 (t, *J* = 6.6 Hz, 3H), 0.63 (q, *J* = 7.9 Hz, 12H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.8, 171.7, 143.4, 142.9, 117.6, 111.3, 106.3, 105.6, 100.8, 99.6, 58.3, 52.9, 39.4, 39.1, 36.8, 33.0, 32.8, 31.8, 29.4, 26.7, 22.7, 14.1, 7.53, 4.54, 4.50; **HRMS** (ESI) calcd for $C_{35}H_{57}O_4Si_2$ $[M+H]^+$ 597.3795, found 597.3799.



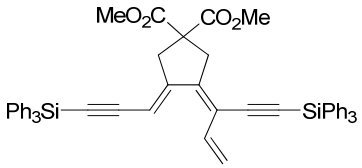
2-48

2-48 (74%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 6.79 (dd, *J* = 16.8, 10.5 Hz, 1H), 5.84 (s, 1H), 5.79 (d, *J* = 16.8 Hz, 1H), 5.30 (d, *J* = 10.5 Hz, 1H), 3.74 (s, 6H), 3.36 (s, 2H), 3.30 (d, *J* = 2.2 Hz, 2H), 1.06 – 0.98 (m, 18H), 0.68 – 0.62 (m, 12H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.5, 149.5, 144.0, 132.1, 119.9, 119.3, 109.2, 104.4, 103.4, 102.5, 101.8, 56.3, 53.0, 42.7, 41.4, 7.53, 7.49, 4.48, 4.43; **HRMS** (EI) calcd for $C_{29}H_{44}O_4Si_2$ $[M]^+$ 512.2778, found 512.2761.



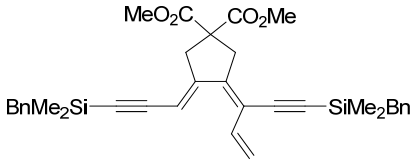
2-50

2-50 (98%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 6.80 (dd, *J* = 16.8, 10.4 Hz, 1H), 5.86 (s, 1H), 5.81 (d, *J* = 16.8 Hz, 1H), 5.30 (d, *J* = 10.4 Hz, 1H), 3.73 (s, 6H), 3.38 (s, 2H), 3.32 (d, *J* = 1.0 Hz, 2H), 1.11 (s, 21H), 1.10 (s, 21H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.5, 149.3, 143.9, 132.3, 120.0, 119.3, 110.0, 109.3, 105.2, 104.2, 101.3, 100.6, 56.2, 52.9, 42.8, 41.5, 18.7, 11.3; **HRMS** (EI) calcd for $C_{35}H_{56}O_4Si_2$ $[M]^+$ 596.3717, found 596.3707.



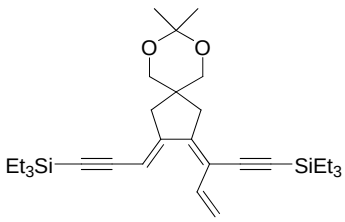
2-52a

2-52a (71%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.73 – 7.68 (m, 12H), 7.48 – 7.39 (m, 18H), 6.86 (dd, *J* = 16.9, 10.5 Hz, 1H), 6.05 (t, *J* = 2.5 Hz, 1H), 5.90 (d, *J* = 16.9 Hz, 1H), 5.39 (d, *J* = 10.5 Hz, 1H), 3.75 (s, 6H), 3.49 (s, 2H), 3.45 (d, *J* = 2.0 Hz, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.2, 150.9, 145.1, 135.6, 133.4, 133.3, 131.8, 130.0, 128.0, 120.3, 120.1, 109.2, 107.5, 106.6, 99.8, 99.2, 56.3, 53.0, 42.7, 41.6; **HRMS** (ESI) calcd for $C_{53}H_{45}O_4Si_2$ $[M+H]^+$ 801.2856, found 801.2856.



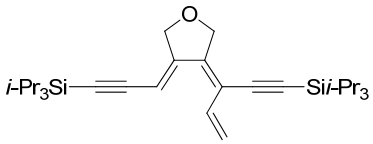
2-52b

2-52b (93%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.26 – 7.22 (m, 4H), 7.11 – 7.08 (m, 6H), 6.75 (dd, *J* = 16.8, 10.0 Hz, 1H), 5.83 (s, 1H), 5.72 (d, *J* = 16.8 Hz, 1H), 5.30 (d, *J* = 10.4 Hz, 1H), 3.78 (s, 6H), 3.33 (s, 2H), 3.28 (d, *J* = 2.2 Hz, 2H), 2.26 (s, 2H), 2.24 (s, 2H), 0.20 (s, 6H), 0.18 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.5, 149.8, 144.2, 138.8, 131.9, 128.4, 128.2, 124.4, 119.8, 119.7, 109.0, 104.4, 103.5, 103.4, 102.7, 56.3, 53.0, 42.6, 41.4, 26.2, -1.90, -2.02; **HRMS** (EI) calcd for $C_{35}H_{40}O_4Si_2$ $[M]^+$ 580.2465, found 580.2448.



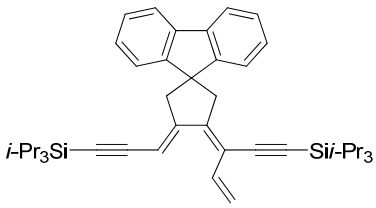
2-52c

2-52c (95%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 6.82 (dd, *J* = 16.9, 10.4 Hz, 1H), 5.86 (s, 1H), 5.78 (d, *J* = 16.9 Hz, 1H), 5.27 (d, *J* = 10.4 Hz, 1H), 3.62 (s, 4H), 2.69 (s, 2H), 2.65 (d, *J* = 2.0 Hz, 2H), 1.42 (s, 6H), 1.03 (q, *J* = 7.8 Hz, 18H), 0.65 (q, *J* = 7.8, 12H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 151.6, 146.2, 132.3, 120.1, 118.7, 109.3, 104.9, 103.8, 101.8, 101.2, 97.9, 68.4, 42.3, 40.9, 38.1, 23.9, 23.7, 7.59, 7.53, 4.50, 4.46; **HRMS** (EI) calcd for $C_{30}H_{48}O_2Si_2$ $[M]^+$ 496.3193, found 496.3177.



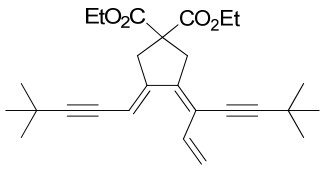
2-52d

2-52d (92%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 6.84 (dd, *J* = 16.8, 10.33 Hz, 1H), 5.98 (s, 1H), 5.89 (d, *J* = 16.8 Hz, 1H), 5.39 (d, *J* = 10.3 Hz, 1H), 4.79 (s, 2H), 4.77 (d, *J* = 2.4 Hz, 2H), 1.10 (s, 21H), 1.09 (s, 21H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.9, 142.4, 131.3, 120.4, 117.7, 106.1, 104.6, 103.1, 101.7, 75.7, 75.0, 18.68, 18.65, 11.2; **HRMS** (EI) calcd for $C_{30}H_{50}O_2Si_2$ $[M]^+$ 482.3400, found 482.3413.



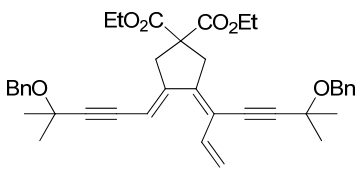
2-52e

2-52e (95%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.5 Hz, 2H), 7.43 (d, *J* = 7.5 Hz, 2H), 7.37 (t, *J* = 8.1 Hz, 2H), 7.31 (m, 2H), 7.11 (dd, *J* = 16.8, 10.4 Hz, 1H), 6.14 (s, 1H), 5.93 (d, *J* = 16.8 Hz, 1H), 5.42 (d, *J* = 10.4 Hz, 1H) 3.23 (s, 2H), 3.15 (s, 2H), 1.05 – 0.96 (m, 38H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 152.5, 151.7, 147.3, 139.5, 132.8, 127.6, 127.2, 122.6, 119.8, 119.6, 119.0, 109.3, 105.5, 104.4, 100.9, 100.3, 53.0, 47.5, 46.4, 18.6, 18.5, 11.1.



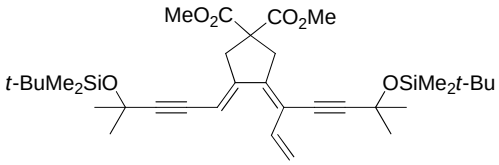
2-52f

2-52f (91%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 6.82 (dd, *J* = 16.8, 10.5 Hz, 1H), 5.75 (t, *J* = 2.3 Hz, 1H), 5.69 (d, *J* = 16.8 Hz, 1H), 5.21 (d, *J* = 10.5 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 4H), 3.28 (s, 2H), 3.23 (d, *J* = 2.2 Hz, 2H), 1.30 (s, 9H), 1.27 (s, 9H), 1.25 (t, *J* = 16.0 Hz, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.3, 147.1, 142.6, 132.9, 119.2, 118.0, 108.9, 108.1, 108.0, 77.9, 61.7, 56.4, 42.3, 41.0, 31.2, 31.1, 30.5, 28.5, 28.4, 14.0; **HRMS** (EI) calcd for $C_{27}H_{36}O_4$ $[M]^+$ 424.2614, found 424.2600.



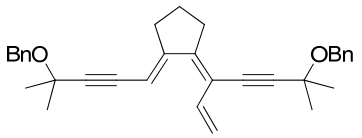
2-52g

2-52g (73%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.37 (d, *J* = 7.1 Hz, 5H), 7.33 (dd, *J* = 7.6, 6.9 Hz, 5H), 6.83 (dd, *J* = 16.9, 10.4 Hz, 1H), 5.86 (s, 1H), 5.73 (d, *J* = 16.9 Hz, 1H), 5.29 (d, *J* = 10.4 Hz, 1H), 4.67 (s, 2H), 4.65 (s, 2H), 4.18 (dd, *J* = 14.2, 7.1 Hz, 4H), 3.34 (s, 2H), 3.28 (d, *J* = 1.7 Hz, 2H), 1.63 (s, 6H), 1.59 (s, 6H), 1.21 (t, *J* = 7.1 Hz, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.0, 149.0, 143.4, 139.0, 138.9, 132.4, 128.3, 127.8, 127.7, 127.4, 127.4, 127.3, 119.1, 119.0, 108.4, 101.1, 100.8, 82.8, 81.9, 71.4, 66.8, 66.7, 61.8, 56.4, 42.4, 41.2, 29.2, 29.0, 14.0; **HRMS** (EI) calcd for $C_{39}H_{44}O_6$ $[M]^+$ 608.3138, found 608.3152.



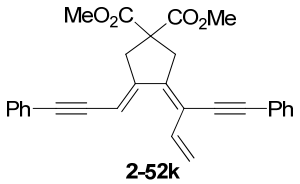
2-52h

2-52h (84%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 6.80 (dd, *J* = 16.9, 10.6 Hz, 1H), 5.82 (t, *J* = 2.3 Hz, 1H), 5.73 (d, *J* = 16.9 Hz, 1H), 5.29 (d, *J* = 10.6 Hz, 1H), 3.75 (s, 6H), 3.33 (s, 2H), 3.27 (d, *J* = 2.2 Hz, 2H), 1.55 (s, 6H), 1.51 (s, 6H), 0.87 (s, 18H), 0.16 (s, 6H), 0.16 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.5, 148.0, 143.0, 132.5, 119.2, 118.9, 108.6, 104.5, 104.1, 81.1, 80.2, 67.0, 56.3, 53.0, 42.5, 41.3, 33.2, 33.0, 32.6, 25.7, 17.9, -2.93; **HRMS** (ESI) calcd for $C_{35}H_{56}O_6Si_2Na$ $[M+Na]^+$ 651.3513, found 651.3517.



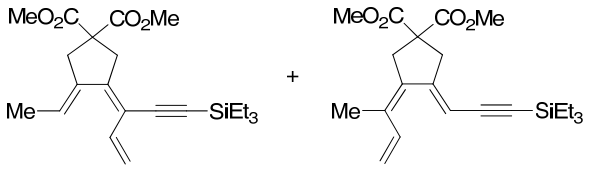
2-52j

2-52j (78%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.6 Hz, 4H), 7.34 (t, *J* = 7.5 Hz, 4H), 7.29 – 7.24 (m, 2H), 6.90 (dd, *J* = 16.9, 10.4 Hz, 1H), 5.85 (s, 1H), 5.72 (d, *J* = 16.9 Hz, 1H), 5.27 (d, *J* = 10.4 Hz, 1H), 4.69 (s, 2H), 4.67 (s, 2H), 2.73 (t, *J* = 7.5 Hz, 2H), 2.67 (dt, *J* = 7.5, 1.9 Hz, 2H), 1.77 (t, *J* = 7.5 Hz, 2H), 1.64 (s, 6H), 1.60 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 153.2, 148.4, 139.2, 139.1, 132.9, 128.3, 127.8, 127.8, 127.4, 117.9, 107.2, 100.0, 99.9, 83.6, 82.7, 71.4, 66.8, 66.7, 35.7, 34.3, 29.3, 29.2, 22.3; **HRMS** (EI) calcd for $C_{33}H_{36}O_2$ $[M]^+$ 464.2715, found 464.2705.



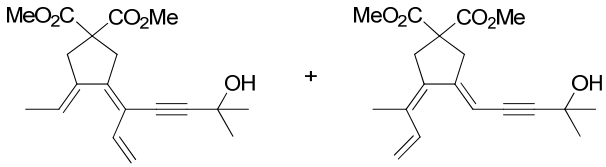
2-52k

2-52k (55%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 6.4, 3.1 Hz, 2H), 7.47 (dd, *J* = 7.0, 2.5 Hz, 2H), 7.36 – 7.32 (m, 6H), 6.93 (dd, *J* = 16.9, 10.4 Hz, 1H), 6.11 (s, 1H), 5.89 (d, *J* = 16.9 Hz, 1H), 5.39 (d, *J* = 10.4 Hz, 1H), 3.78 (s, 6H), 3.49 (s, 2H), 3.44 (d, *J* = 2.0 Hz, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.6, 148.3, 143.3, 132.4, 131.5, 131.5, 128.5, 128.5, 128.4, 128.2, 123.3, 123.2, 119.7, 119.3, 109.0, 99.4, 98.9, 88.3, 87.3, 56.4, 53.1, 42.7, 41.5; **HRMS** (EI) calcd for $C_{29}H_{24}O_4$ $[M]^+$ 436.1675, found 436.1666.



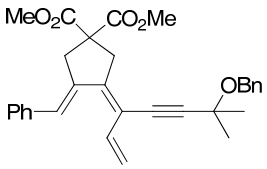
2-58a **2-58a'**

(82% combined yield): **^{1}H NMR** (501 MHz, $CDCl_3$) **2-58a:** δ 6.82 (dd, *J* = 16.5, 10.4 Hz, 1H), 5.89 (q, *J* = 7.0 Hz, 1H), 5.70 (d, *J* = 16.5 Hz, 1H), 5.20 (d, *J* = 10.4 Hz, 1H), 3.73 (s, 6H), 3.33 (s, 2H), 3.02 (s, 2H), 1.79 (d, *J* = 7.1 Hz, 3H), 1.03 (t, *J* = 7.8 Hz, 9H), 0.65 (dd, *J* = 16.4, 8.4 Hz, 6H), **2-58a′:** 6.91 (dd, *J* = 17.4, 11.0 Hz, 1H), 5.70 (s, 1H), 5.33 (d, *J* = 17.4 Hz, 1H), 5.13 (d, *J* = 11.0 Hz, 1H), 3.74 (s, 6H), 3.27 (d, *J* = 1.9 Hz, 2H), 3.11 (s, 2H), 1.89 (s, 3H), 1.02 (t, *J* = 7.8 Hz, 9H), 0.63 (dd, *J* = 16.4, 8.4 Hz, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) **2-58a+2-58a′:** δ 171.8, 171.8, 150.5, 146.2, 140.9, 137.1, 136.3, 135.1, 132.7, 132.5, 131.8, 126.9, 125.6, 117.1, 116.5, 115.3, 112.3, 107.1, 105.3, 104.8, 103.8, 99.4, 99.1, 65.9, 56.5, 52.9, 42.2, 40.9, 40.0, 17.2, 7.57, 7.52, 4.57, 4.51; **HRMS** (EI) calcd for $C_{22}H_{32}O_4Si$ $[M]^+$ 388.2070, found 388.2058.



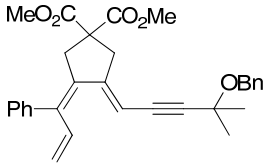
2-58b **2-58b'**

(77% combined yield): **^{1}H NMR** (501 MHz, $CDCl_3$) **2-58b:** δ 6.82 (dd, *J* = 16.9, 10.5 Hz, 1H), 5.88 (td, *J* = 9.2, 7.0 Hz, 1H), 5.62 (d, *J* = 16.9 Hz, 1H), 5.18 (d, *J* = 10.5 Hz, 1H), 3.75 (s, 6H), 3.27 (s, 2H), 3.02 (s, 2H), 2.09 (br, 1H), 1.79 (d, *J* = 7.1 Hz, 3H), 1.60 (s, 6H), **2-58b′:** 6.89 (dd, *J* = 17.4, 11.0 Hz, 1H), 5.65 (s, 1H), 5.32 (d, *J* = 17.4 Hz, 1H), , 5.13 (d, *J* = 11.0 Hz, 1H), 3.74 (s, 6H), 3.21 (d, *J* = 2.1 Hz, 1H), 3.11 (s, 1H), 2.07 (br, 1H), 1.88 (s, 3H), 1.57 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) **2-58b+2-58b′:** δ 171.8, 171.8, 149.4, 145.4, 137.0, 136.3, 135.0, 132.9, 132.3, 126.8, 116.8, 115.7, 115.3, 106.3, 101.4, 101.1, 80.7, 79.8, 65.8, 56.6, 56.5, 53.0, 41.9, 40.6, 40.0, 38.2, 31.7, 31.6, 30.4, 17.2, 15.7; **HRMS** (EI) calcd for $C_{19}H_{24}O_5$ $[M]^+$ 322.1624, found 322.1604.



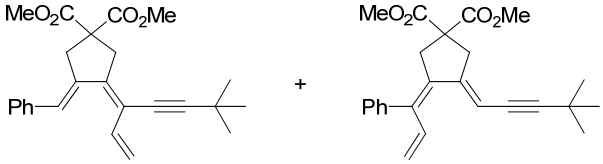
2-58c

2-58c (65%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.49 – 7.33 (m, 8H), 7.30 – 7.26 (m, 2H), 6.98 (dd, *J* = 16.8, 10.3 Hz, 1H), 6.79 (s, 1H), 5.74 (d, *J* = 16.8 Hz, 1H), 5.27 (d, *J* = 10.3 Hz, 1H), 4.72 (s, 2H), 3.69 (s, 6H), 3.37 (s, 2H), 3.35 (s, 2H), 1.66 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.6, 146.6, 139.0, 137.2, 137.0, 133.2, 131.0, 129.2, 128.4, 128.3, 128.2, 127.8, 127.7, 127.6, 127.4, 117.4, 117.4, 100.0, 82.1, 71.4, 66.8, 57.0, 53.0, 40.8, 40.0, 29.3; **HRMS** (EI) calcd for $C_{31}H_{32}O_5$ $[M]^+$ 484.2250, found 484.2231.



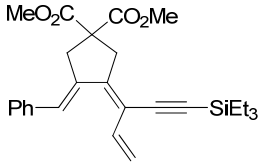
2-58c'

2-58c′ (22%)**:** **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.45 – 7.27 (m, 8H), 7.15 – 7.12 (m, 3H), 5.93 (s, 1H), 5.24 (d, *J* = 10.9 Hz, 1H), 4.88 (d, *J* = 17.2 Hz, 1H), 4.68 (s, 2H), 3.66 (s, 6H), 3.29 (d, *J* = 2.3 Hz, 2H), 2.84 (s, 2H), 1.62 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.5, 149.4, 140.3, 139.1, 138.9, 136.3, 135.8, 129.6, 128.3, 128.2, 127.9, 127.8, 127.6, 127.4, 127.3, 119.8, 107.1, 99.9, 82.8, 71.4, 66.7, 56.7, 52.8, 41.5, 40.5, 29.2; **HRMS** (EI) calcd for $C_{31}H_{32}O_5$ $[M]^+$ 484.2250, found 484.2230.



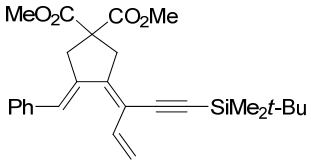
2-58d **2-58d'**

(91% combined yield): **^{1}H NMR** (501 MHz, $CDCl_3$) **2-58d:** δ 7.35 (d, *J* = 7.3 Hz, 2H), 7.33 – 7.23 (m, 3H), 6.97 (dd, *J* = 16.8, 10.6 Hz, 1H), 6.73 (s, 1H), 5.73 (d, *J* = 16.8 Hz, 1H), 5.22 (d, *J* = 10.6 Hz, 1H), 3.71 (s, 6H), 3.35 (d, *J* = 2.0 Hz, 2H), 3.31 (s, 2H), 1.34 (s, 9H); **2-58d′:** 7.38 – 7.23 (m, 5H), 7.09 (dd, *J* = 16.7, 10.3 Hz, 1H), 5.88 (s, 1H), 5.19 (d, *J* = 10.3 Hz, 1H), 4.84 (d, *J* = 16.7 Hz, 1H), 3.68 (s, 6H), 3.26 (d, *J* = 2.3 Hz, 2H), 2.82 (s, 2H), 1.30 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) **2-58d+2-58d′:** δ 171.8, 171.7, 147.7, 145.2, 140.4, 138.0, 137.4, 137.2, 136.5, 136.1, 133.5, 130.2, 129.7, 129.1, 128.5, 128.3, 128.1, 127.7, 127.3, 127.2, 119.1, 118.3, 117.1, 108.4, 107.6, 57.0, 56.8, 52.9, 52.7, 41.5, 40.6, 40.2, 40.0, 31.2, 31.11, 31.06, 30.5, 28.5, 28.4; **HRMS** (ESI) calcd for $C_{25}H_{29}O_4$ $[M+H]^+$ 393.2079, found 393.2077.



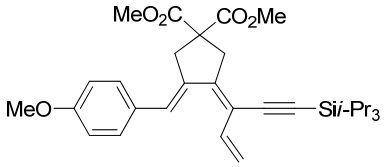
2-58e

2-58e (77%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.39 – 7.30 (m, 3H), 7.29 – 7.24 (m, 2H), 6.94 (dd, *J* = 16.9, 10.4 Hz, 1H), 6.77 (s, 1H), 5.79 (d, *J* = 16.9 Hz, 1H), 5.27 (d, *J* = 10.4 Hz, 1H), 3.71 (s, 6H), 3.37 (s, 2H), 3.35 (d, *J* = 2.1 Hz, 2H), 1.05 (t, *J* = 7.9 Hz, 9H), 0.68 (q, *J* = 7.9 Hz, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.7, 147.5, 137.3, 137.0, 132.9, 131.0, 129.3, 128.4, 127.6, 118.0, 117.7, 103.7, 100.3, 57.0, 53.6, 53.0, 52.4, 40.9, 40.0, 7.57, 4.53; **HRMS** (EI) calcd for $C_{27}H_{34}O_4Si$ $[M]^+$ 450.2226, found 450.2216.



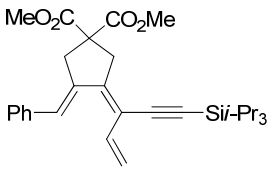
2-58f

2-58f (72%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.39 – 7.30 (m, 4H), 7.27 (dd, *J* = 8.8, 5.5 Hz, 1H), 6.94 (dd, *J* = 16.9, 10.4 Hz, 1H), 6.77 (s, 1H), 5.78 (d, *J* = 16.9 Hz, 1H), 5.27 (d, *J* = 10.4 Hz, 1H), 3.71 (s, 6H), 3.38 – 3.35 (m, 4H), 1.00 (s, 9H), 0.20 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.7, 147.5, 137.3, 137.0, 132.9, 131.1, 129.2, 128.4, 128.2, 127.6, 117.9, 117.7, 103.2, 101.2, 57.0, 52.9, 40.9, 39.9, 26.2, 26.0, 16.6, -4.42; **HRMS** (ESI) calcd for $C_{27}H_{35}O_4Si$ $[M+H]^+$ 451.2305, found 451.2308.



2-58g

2-58g (75%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.6 Hz, 2H), 6.94 (dd, *J* = 17.1, 10.6 Hz, 1H), 6.90 (d, *J* = 8.7 Hz, 2H), 6.72 (s, 1H), 5.79 (d, *J* = 17.1 Hz, 1H), 5.25 (d, *J* = 10.6 Hz, 1H), 3.83 (s, 3H), 3.71 (s, 6H), 3.38 (s, 2H), 3.34 (d, *J* = 1.9 Hz, 2H), 1.14 (s, 21H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.7, 159.1, 147.7, 135.2, 133.1, 130.7, 130.7, 130.6, 129.8, 117.4, 117.3, 113.9, 104.7, 98.7, 57.0, 55.3, 52.9, 41.2, 40.0, 18.7, 11.3; **HRMS** (ESI) calcd for $C_{31}H_{43}O_5Si$ $[M+H]^+$ 523.2880, found 523.2879.



2-58h

2-58h (85%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.35 (td, *J* = 15.0, 7.5 Hz, 4H), 7.27 (dd, *J* = 8.7, 5.4 Hz, 1H), 6.96 (dd, *J* = 16.9, 10.4 Hz, 1H), 6.78 (s, 1H), 5.82 (d, *J* = 16.9 Hz, 1H), 5.28 (d, *J* = 10.4 Hz, 1H), 3.71 (s, 6H), 3.39 (s, 2H), 3.37 (d, *J* = 1.9 Hz, 2H), 1.14 (s, 21H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.7, 147.4, 137.3, 137.0, 133.0, 130.9, 129.2, 128.4, 128.23, 128.18, 127.5, 118.1, 117.7, 104.5, 99.1, 57.0, 52.9, 41.1, 39.9, 18.7, 18.5, 11.3; **HRMS** (ESI) calcd for $C_{30}H_{41}O_4Si$ $[M+H]^+$ 493.2774, found 493.2771

2.5. References

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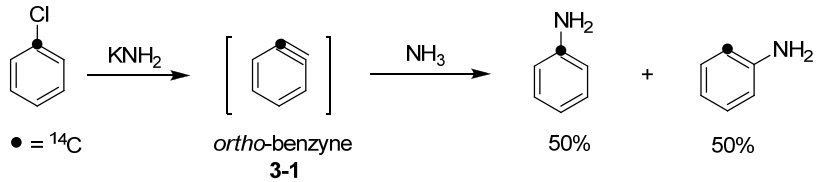
Chapter 3. An Overview of Aryne Chemistry

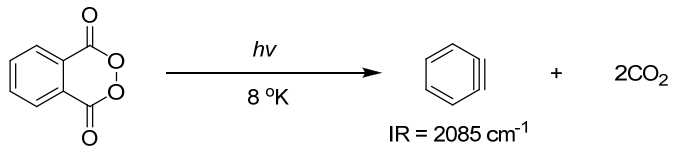
3.1. Historical Background

Arynes are highly reactive intermediates widely used in organic synthesis to create diverse array of molecular architectures. Thus, arynes have been of considerable theoretical and experimental interest to chemical community for the past century.[1,2] The existence of *ortho*-benzyne **3-1** was first proposed in 1927 by Bachman and Clarke,[3] and convincing evidences of its existence were reported in 1953 by Roberts.[4] Roberts demonstrated that the reaction of ^{14}C-labeled chlorobenzene with potassium amide generated a putative intermediate **3-1,** which was responsible for nucleophilic aromatic substitution with ammonia (Eq. 1).

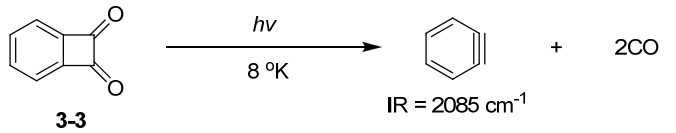


(1)

In 1963, Fisher and co-worker studied the pyrolysis of diiodobenzene, and detected benzyne intermediate by using mass spectrometry.[5] Berry and co-workers investigated the photo-initiated decomposition of benzendiazonium carboxylate in the gas phase and characterized benzyne intermediate by using UV and mass spectrometry.[6] Chapman reported the first IR spectroscopic evidence for *ortho*-benzyne in 1973.[7] He used phthaloyl peroxide **3-2** and benzocyclobutenedione **3-3** to generate *ortho*-benzyne and confirmed its identity by using matrix isolation spectroscopy at low temperature and a peak at 2085 cm^{-1} was assigned to be C≡C (Eq. 2–3). While the formal triple bond in benzyne is significantly weaker than unstrained alkyne (ν = 2120 cm^{-1}), *ortho*-benzyne is more closely resembles cyclic alkyne than biradical considering the fact that its reactivity is similar to that of alkynes.



(2)



(3)

In 1997 Warmuth isolated *ortho*-benzyne generated by photolysis of benzocyclobutenedione in a hemicarcerand as a molecular container and its NMR spectrum was measured in solution.[8] The experimental ^{1}H and ^{13}C NMR chemical shifts of *ortho*-benzyne could be reproduced by *ab initio* calculations using B3LYP/6-311G**.[9]

3.2. Traditional Aryne Generation

3.2.1. 1,2-Elimination

Classical methods[10-14] to generate arynes relying on 1,2-elimination of haloarenes[10] typically require strong bases or reactive organometallic reagents, which fundamentally limit the applications due to the functional group compatibility (**Figure 3.1**). While oxidation of aminobenzotriazoles **3-4**[11] and thermal decomposition of arenedizonium carboxylates **3-5**[12] have emerged as complementary methods, the synthesis of aminobenzotriazoles requires multi-step sequences and arenedizonium carboxylates are difficult to handle. Even the improved modern protocols have only a limited scope. For example, the most popular Kobayashi's method involving the 1,2-elimination of 1-trimethylsilyl-2-trifluoro-methanesulfonyl arenes **3-6** with various fluoride sources is remarkably effective in its own right but the installation of prerequisite functionalities is tedious and can be achieved only via a multi-step process.[13]

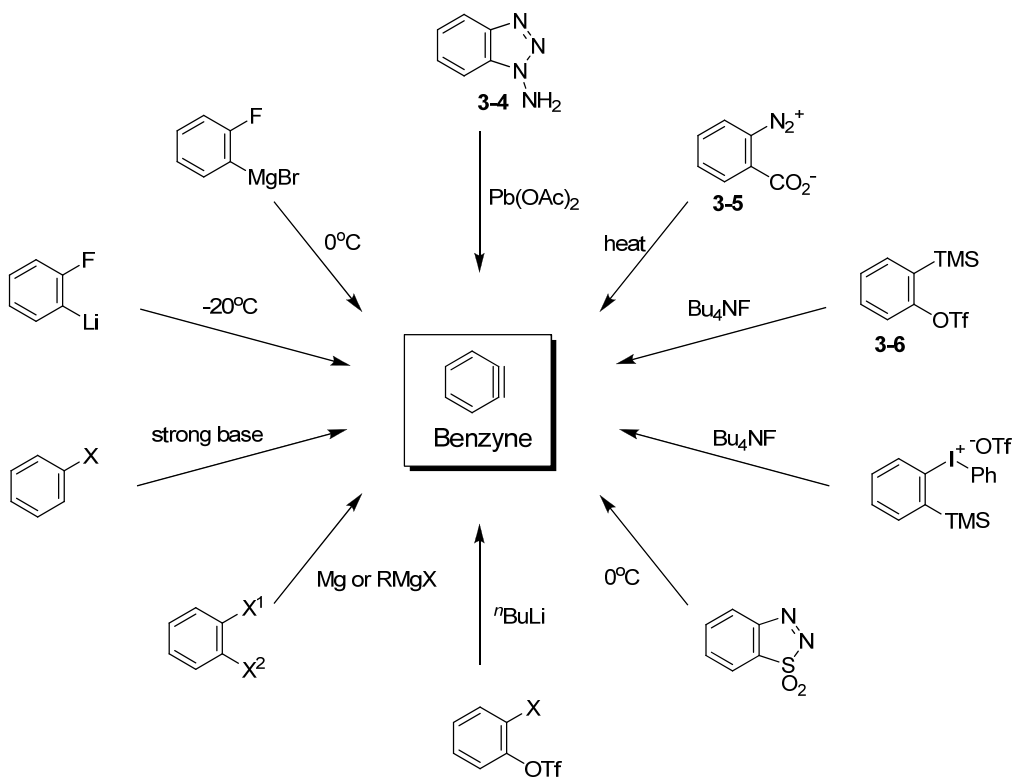
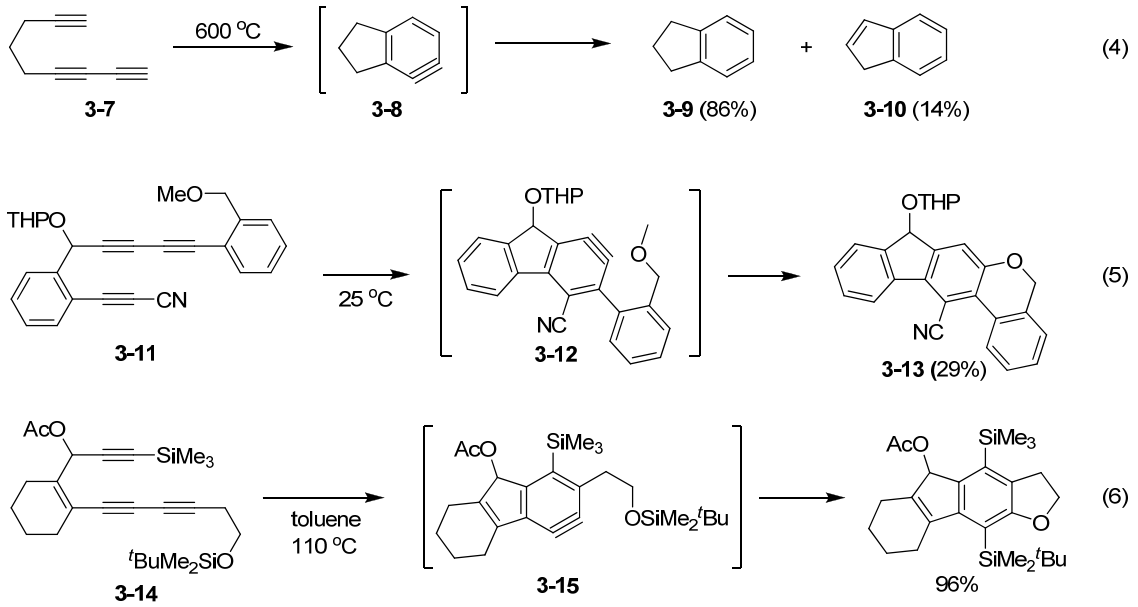


Figure 3.1. Traditional aryne formation via 1,2-elimination

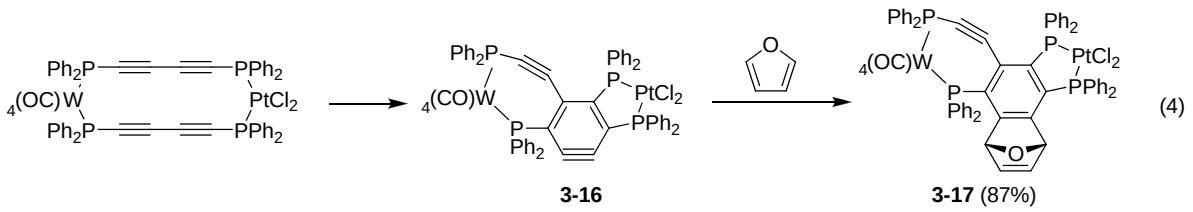
3.2.2. Hexadehydro-Diels-Alder Reaction

Though hexadehydro-Diels-Alder reaction[15-19] has been the subject of theoretical and experimental studies, developments of practical methods and their applications still remain to be explored. It has been shown by Johnson and co-workers that flash vacuum thermolysis of 1,3,8-nonatriyne **3-7** at 600 °C at low pressure (10^{-2} torr) provided two products **3-9** and **3-10**, which was assumed to be the result of disproportionation of initially formed aryne **3-8** via hydrogenation and dehydrogenation (Eq. 4).[15] Although the formation of *ortho*-benzyne has a strong thermodynamic driving force (ca. -40 kcal/mol) from 1,3-butadiyne and acetylene, this process requires a high activation barrier (ca. 42 kcal/mol). Ueda demonstrated that the thermal cyclization of nonconjugated ene-diyne-nitriles **3-11** provided cyanofluorenol derivatives **3-13** via aryne intermediate **3-12** (Eq. 5).[16] Recently, Hoye reported the

hexadehydro-Diels-Alder reaction of 1,3-diynes **3-14** and trapped the aryne intermediate **3-15** with pendant nucleophiles (Eq. 6).[17]



Sterenberg reported a metal-templated [4+2] cycloaddition approach to generate aryne at room temperature.[18] Coordination of *bis*-phosphinodiyne substrates to mixed platinum and tungsten metal templates resulted in a templated [4+2] alkyne-diyne cycloaddition to form aryne intermediate **3-16**, which was trapped with furan to give the corresponding Diels-Alder reaction product **3-17**.



3.3. Reactions of Aryne

Arynes readily undergo [4+2]-cycloaddition[20,21] with strained or electron-rich cyclic dienes such as furans to form product **3-18**. Depending on the substituent patterns of arynes and dienes, [4+2]-cycloaddition can be proceeded in either concerted or stepwise manners. On the other hand, arynes are

known to undergo [2+2]-cycloaddition[22] with alkenes to form a bicyclic compound **3-19**, typically electron-rich alkenes because of the low-lying LUMO. The [2+2]-cycloaddition of aryne, however, is less developed area of research compared to analogous [4+2]-cycloaddition because of significant byproducts formation. Arynes can also undergo [3+2]-cycloaddition[23] with stable 1,3-dipoles such as diazo compound **3-20** and azides, as well as aminothiazadiene and lithium trimethylsilyldiazomethane (**Figure 3.2**).

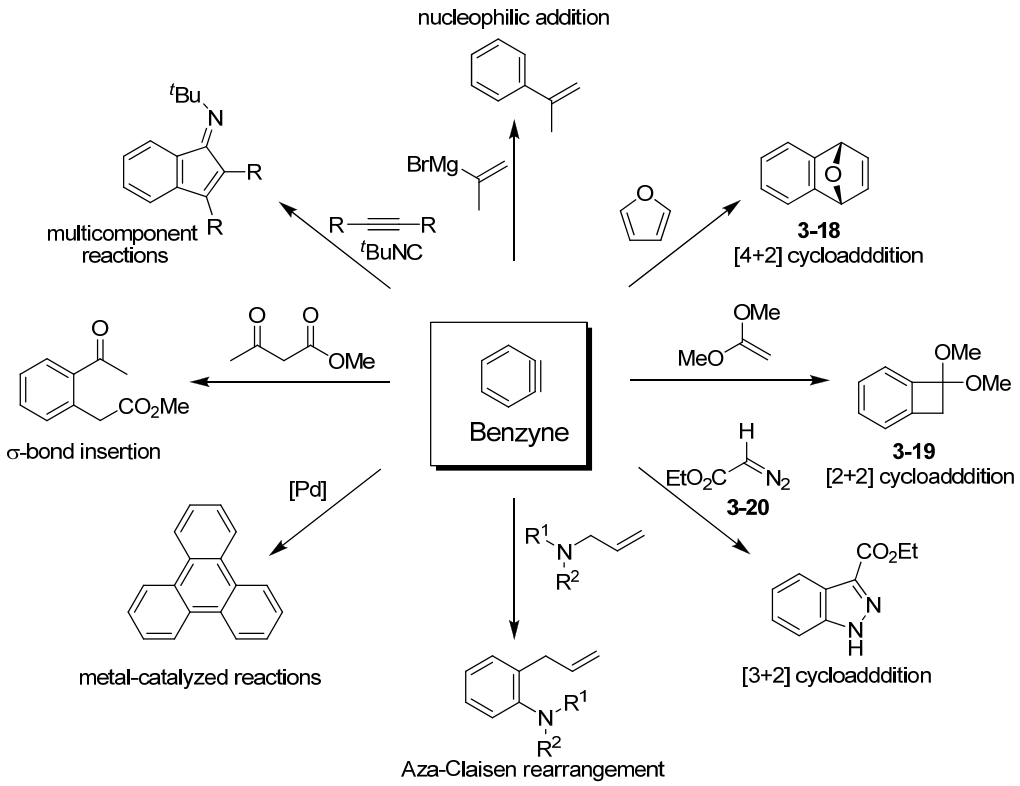


Figure 3.2. Current reports for the trapping of aryne

Because of their electrophilic characteristics, arynes can undergo nucleophilic addition reactions with a variety of nucleophiles.[24] The addition of a nucleophile to aryne generated an aryl carbanion or a zwitterion, depending on the nature of nucleophile (anionic or neutral) and the intermediate is subsequently trapped with an electrophile such as a proton.

To date a variety of transition metal-catalyzed reactions of arynes have been developed to provide a useful entry into the synthesis of substituted arenes that are difficult to access by conventional methods.[25,26] The effectiveness of transition metal-catalyzed reactions of arynes depends on the choice of metal catalysts as well as the method to generate arynes. It is well known that the formal triple bond of arynes can be inserted into a variety of σ bonds such as P–P, O–C, O–B, Cl–Sn, I–I, Se–Se, C–C, C–Si and S–S bonds (**Figure 3.3**).[27] In the early stage of the development of aryne chemistry, aryne insertion into σ-bonds gained less attention due largely to harsh reaction conditions, difficulties associated with aryne generation and low yield due to self-polymerizations. These problems could be resolved by the use of transition metal catalysts, which facilitated the development of efficient methods for the σ-bond insertion of arynes. In 2001, Hiyama reported that iminophosphine-palladium complex promoted the insertion of aryne into C–Sn bonds to give *ortho*-substituted arylstannanes **3-21**.[28a] Hiyama also reported the insertion of benzyne into N–CO bond of ureas to form 1-amino-2-(aminocarbonyl)-arenes **3-22**.[28b]

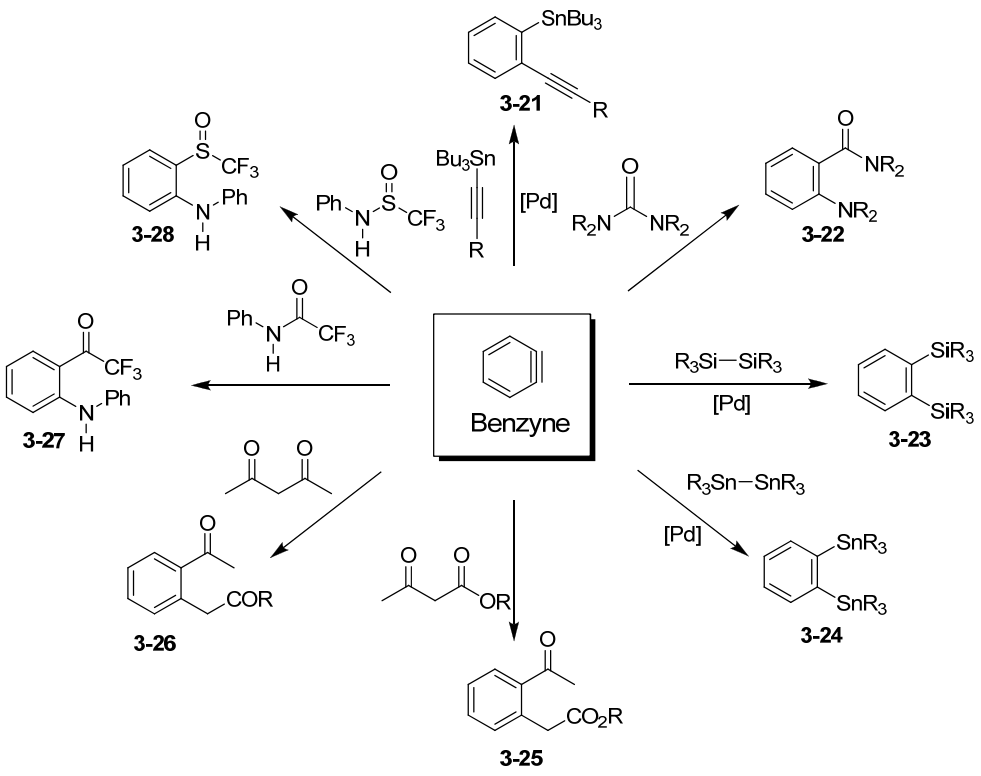


Figure 3.3. σ-Bond insertion reactions with benzyne

The nucleophilicity of nitrogen of urea is sufficient to attack benzyne and thereby induces the cleaveage of the σ-bond without metal catalysts. Subsequently, palladium-catalyzed aryne insertions into Si–Si[28c,d] and Sn–Sn[28e,f] bonds were reported by Kunai (**3-23**, **3-24**). Stoltz reported an efficient protocol for the acyl-alkylation of arynes by insertion of aryne into α,β-bond of β-ketoesters.[28g] This reaction, although has some precedents, is especially novel and useful for the synthesis of *ortho*-disubstituted arenes **3-25** because of its mildness and effectiveness to form two new C–C bonds on arenes. Other examples of aryne insertion into σ-bond include the insertion into C–C bonds of β-dicarbonyl **3-26**[28h] and α-cyanocarbonyl[28i] compounds, the insertion into the N–C bonds of amides **3-27**, and the N–S bonds of sulfonamides **3-28**,[28j] and the carbophosphinylation of arynes with cyanomethyldiphenylphosphine oxide.[28k]

3.4. Metal Complexes of Arynes

3.4.1. Early Transition Metal–Aryne Complexes

Arynes can be stabilized by coordination to electron rich transition metals, and this metal-stabilized arynes are known to undergo various transformation[29] with different molecules containing C=O, C=C, C≡C, and C≡N functionalities (**Figure 3.4**). Buchwald and Erker pioneered group IV–metal stabilized aryne mediated chemical transformations as shown in Scheme 3.4.[30] Erker discovered that zirconocene–benzyne complex **3-30** was formed upon heating the diphenylzirconocene complex **3-29** via a concerted elimination of benzene.[30a] The reactivity of this zirconocene–benzyne complex was examined by Erker and Buchwald, and this complex could be further stabilized by forming PMe_3 adduct **3-31** that was characterized by X-ray crystallography.[30b] The reaction of **3-30** with ethylene afforded ethylene insertion product **3-32**.[30c] The reaction with substituted alkene such as *cis*- and *trans*-stilbene gave the corresponding insertion product **3-33** and **3-34** in a stereospecific manner.[30d] Dimeric azazirconacy-clopentenes **3-35** was formed with cyanides and it was hydrolyzed to the corresponding ketones.[30e] Zirconocene–benzyne complex also reacts with $W(CO)_6$ to form the zirconaoxycarbene complex **3-36**.[30f]

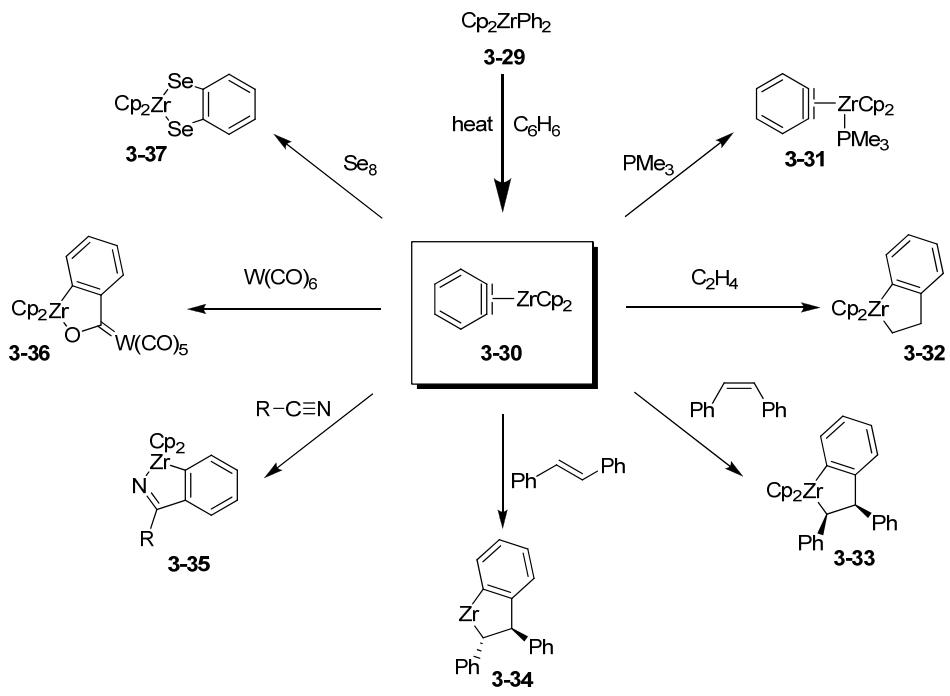


Figure 3.4. Reactivity of zirconocene–benzyne complex

The strategy to generate metal–aryne complex via a formal elimination of hydride from phenyl ligands was also utilized to the synthesis of benzyne complexes of niobium, tantalum, molybdenum, tungsten, and rhenium. However, the synthetic utility of these complexes still remains to be further explored (**Figure 3.5**).[31]

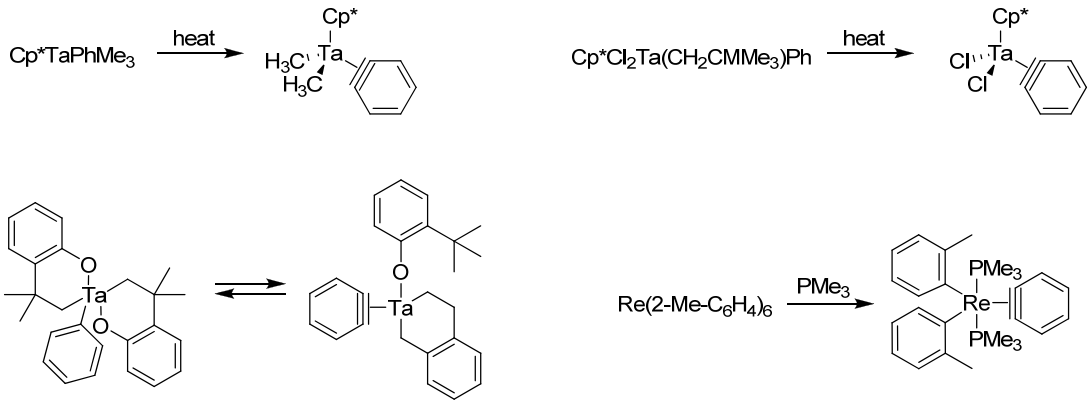
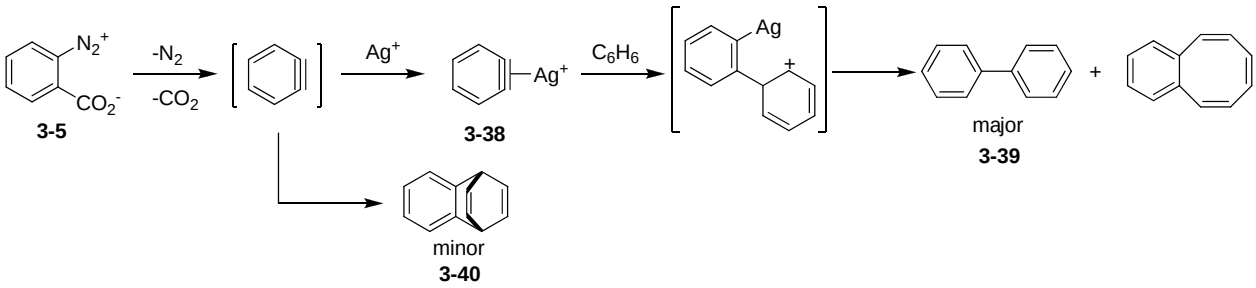


Figure 3.5. Early transition metal–benzyne complexes

3.4.2. Late Transition Metal–Aryne Complexes

In 1967, Friedman reported that silver–benzyne complex **3-38** was formed upon treatment of benzyne generated by decomposition of benzenediazonium-2-carboxylate **3-5** with $AgClO_4$ (**Scheme 3.1**). This silver–benzyne complex was found to be more electrophilic than free benzyne and reacted with benzene to give biphenyl **3-39** as a major product and the formation of [4+2]-cycloaddition product **3-40** was significantly suppressed.[33]

Scheme 3.1 Silver-stabilized benzyne



The first well-defined mononuclear nickel–benzyne complex **3-42** was reported in 1992. It was found that the reduction of 2-bromophenyl-chloronickel complex **3-41** with 1% sodium amalgam provided a yellow crystalline solid, the structure of which was confirmed by X-ray crystallography.[33] The nickel-benzyne complexes readily react with electrophiles such as CH_3I and I_2 to give products **3-43** and **3-44**.[33] While the reaction with CO_2, ethylene, and dimethyl acetylenedicarboxylate provided corresponding insertion products **3-45**, **3-46** and **3-47** respectively, the reaction with acetonitrile afforded **3-48** by deprotonation. Gin has shown that conjugated 1,3-diynes react regioselectively with nickel–benzyne complex **3-42** via a formal [2+2+2] cycloaddition to produce highly substituted dialkynyl naphthalenes **3-49**.

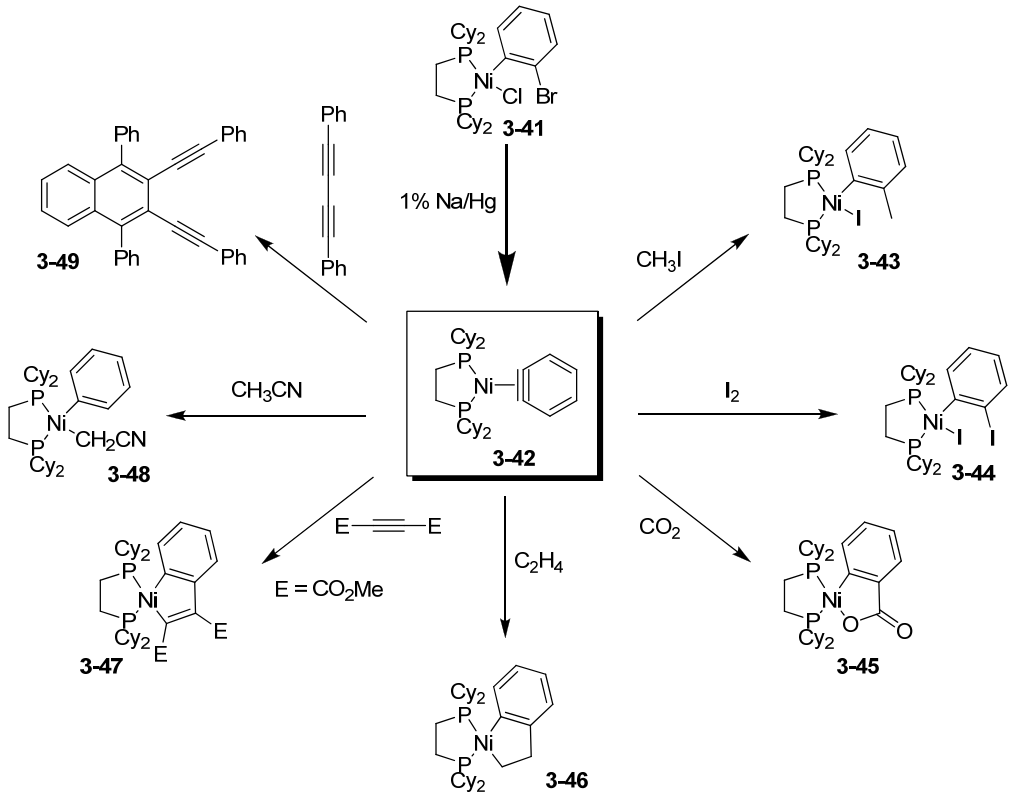


Figure 3.6. Nickel stabilized benzyne complex

3.5. Theoretical Studies

Houk and Garg have developed an efficient computational approach for the evaluation of the synthetic potential of heterocyclic arynes such as indolynes.[34] They demonstrated that DFT or *ab initio* calculations could be utilized to predict the likelihood that a given heterocyclic aryne can be generated. Also the degree of regioselectivity of nucleophilic trapping can be gauged. Moreover, geometry optimization of several known heterocyclic aryne derivatives and the corresponding parent arynes was performed using DFT (B3LYP/6-31G*) and *ab initio* methods (MP2/6-311^{+}G**). The computed atomic charges at the triple bond termini are related to the asymmetric distortion of indolynes (**Figure 3.7**). The unsymmetrical biases direct nuclepohilic attack to the flatter, more electropositive end of the aryne, leading to an energetically favorable decrease in ring distortion. On the basis of the distortion model, they also found that by comparing computed internal bond angles of indolynes, a predictable

regioselectivity could be obtained (**Table 3.2**). In all cases, the terminus of the aryne that is flatter, correlates to the experimentally favored site of the nycleophilic attack. The difference in the internal bond angle also relates to the degree of the regioselecitivity; the larger the difference between the two bond angles, the higher the regioselectivity.

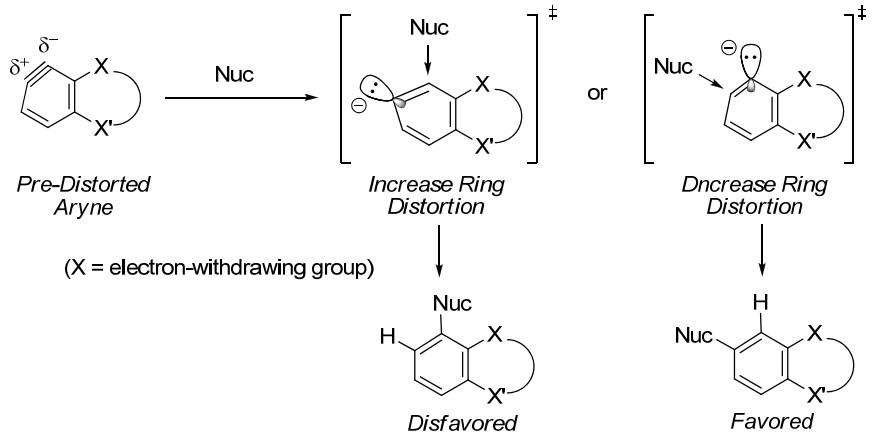
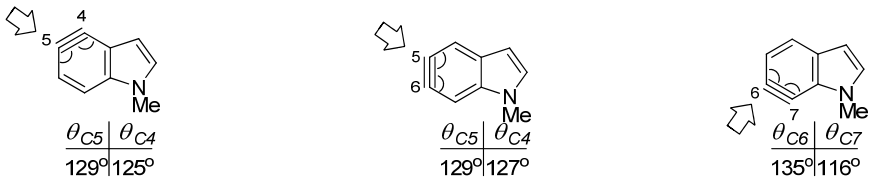
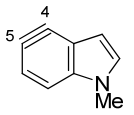
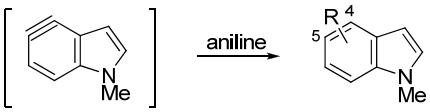
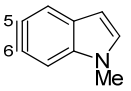
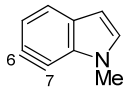


Figure 3.7. Distortion model for regioselective nucleophilic addition to fused aryne.

Table 3.2. Predictable site attack based on calculation



	Predicted site attack[a] B3LYP	MP2	Experimental data	Ratio of regioisomers
 4,5-indolyne	C5	C5		C5 : C4 = 13 : 1
 5,6-indolyne	C5	C5		C5 : C 6 = 3 : 1
 6,-indolyne	C6	C6		C6 only

[a] Predicted regioselectivity for indolynes based on aryne distortion model.

3.6. Conclusion

Aryne chemistry evolved through more than a century, and various approaches for the generation of arynes and their applications have been developed. Yet, because of the high reactivity of arynes towards nucleophilic addition or self-polymerization, their generation in a controlled manner under mild conditions has become a key factor for the application of arynes in organic synthesis.

3.7. References

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Chapter 4. Ruthenium-Catalyzed Hydrohalogenation of Arynes with Halogenated Hydrocarbons

4.1. Introduction

Halogenated arenes **4-1** constitute an important class of molecules because they can serve as versatile building blocks in organic synthesis (**Figure 4.1**).[1] Classically, these halogenated arenes have been used as the precursors for organolithium and Grignard reagents via metal-halogen exchange.[2] Also, halogenated arenes were used for aryne formation[3] as well as for electrophilic or nucleophilic aromatic substitutions relying on the directing effect of halogen.[4] Over the past few decades, aryl halides have also found widespread utility as counterparts for metal-catalyzed cross-coupling reactions for C-C, C–N, C–O and C–S bond formations.[5] Moreover, due to their highly conjugated electronic characters, haloarenes are often used in polymer and semiconductor materials as the repeating unit.[6] In addition, aryl chlorides, bromides and iodides play an important role in a variety of biologically active natural products and drug candidates.[7]

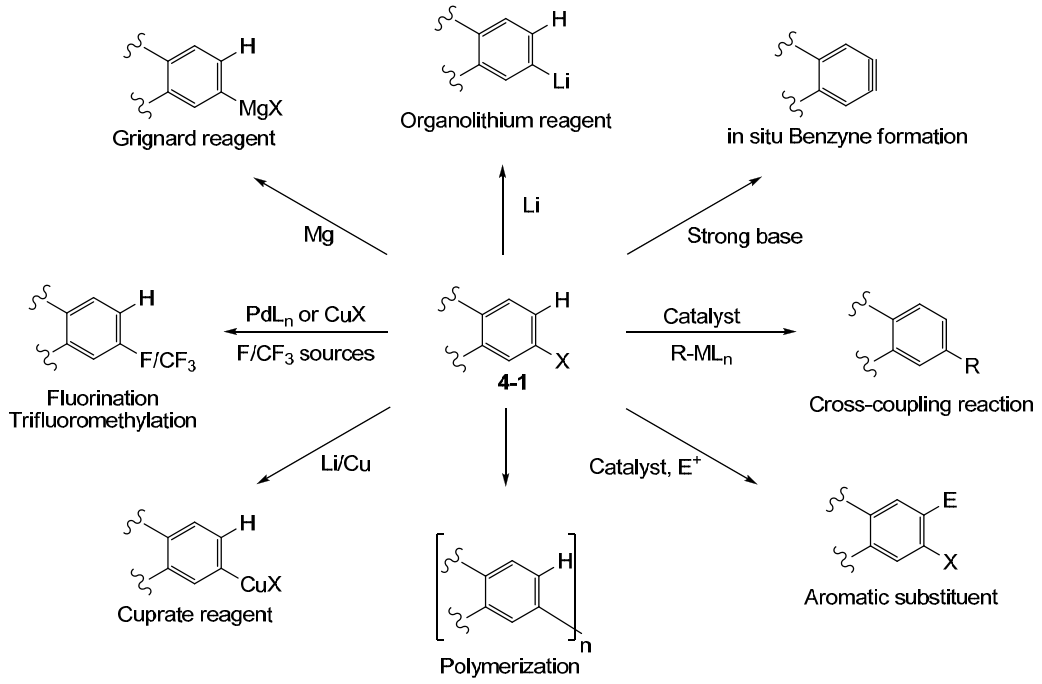


Figure 4.1. Representative applications of halogenated arenes

4.1.1. Recent Synthetic Approaches to Halogenated arene

Although many elegant methods to introduce halogen atoms onto the aromatic system have been developed over the years, the formation of the halogenated arenes in regioselective manners under mild conditions still remains as a challenging problem. To date, one of the most common approaches to halogenated arenes is the electrophilic aromatic substitution with electrophilic halogen sources such as *N*-halosuccinimides, X_2, or hypervalent iodine reagents/MX (M = Li, Na, K, or TMS) (**Figure 4.2**).[8] Another common method for regioselective halogenation of arenes involves directed *ortho*-metalation followed by quenching with selected halogen sources.[9] Recently, transition metal-catalyzed direct halogenation draws extensive attention from many research groups, and various approaches have been reported in the literature.[10-20]

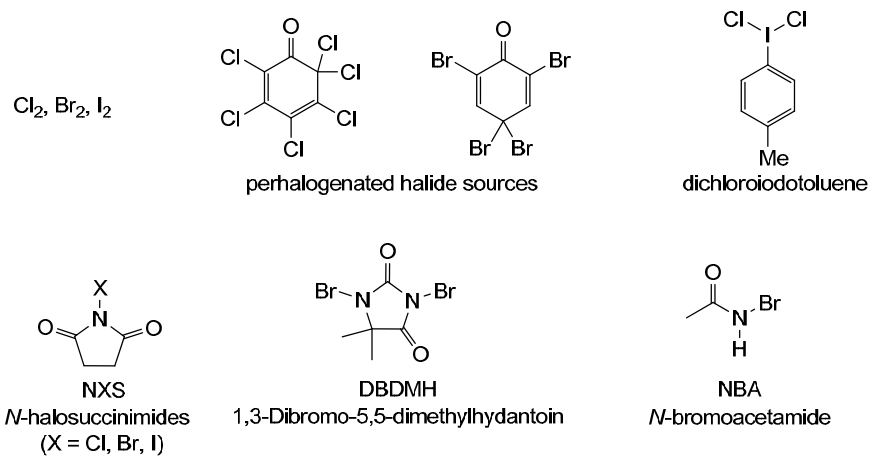
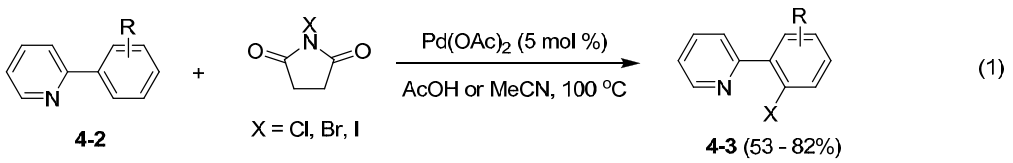


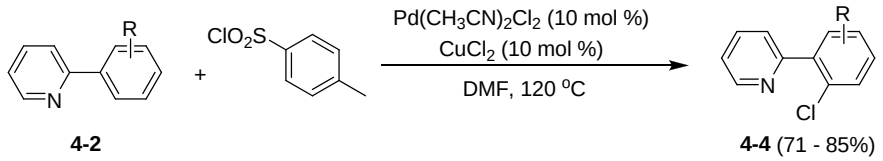
Figure 4.2. Representative electrophilic halogenating agents

For example, Sanford developed palladium-catalyzed regioselective chlorination, bromination and iodination of arene C–H bonds using pyridinyl moiety as the directing group and *N*-halosuccinimides as oxidants, and this transformation has been applied to a wide range of substrates (Eq. 1).[15b]



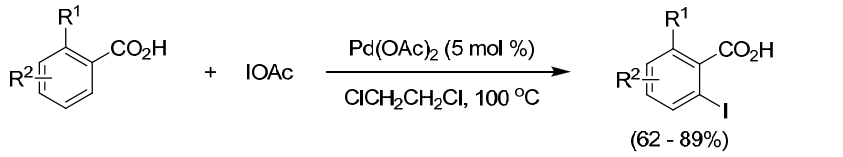
(1)

Dong and co-workers also utilized a variety of phenylpyridine derivatives **4-2** for regioselective chlorination by using arylsulfonyl chloride as the chlorine source in the presence of palladium catalyst to form chlorinated phenylpyridine derivatives **4-4**. It was found that the use of $CuCl_2$ as the co-catalyst and DMF as solvent was critical to achieve decent yield (Eq. 2).[15e]

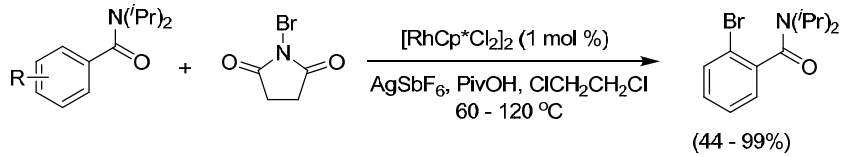


(2)

In 2008, Yu and co-workers reported a palladium-catalyzed *ortho*-selective iodination of benzoic acid derivatives by using in situ generated IOAc as the iodine source, and this method was further expanded to bromination as well (Eq. 3).[16] Recently, Glorius developed a rhodium-catalyzed bromination of benzamide derivatives with *N*-bromosuccinimide in the presence of $AgSbF_6$ to achieve *ortho*-selective bromination in moderate to good yields (Eq. 4).[17]

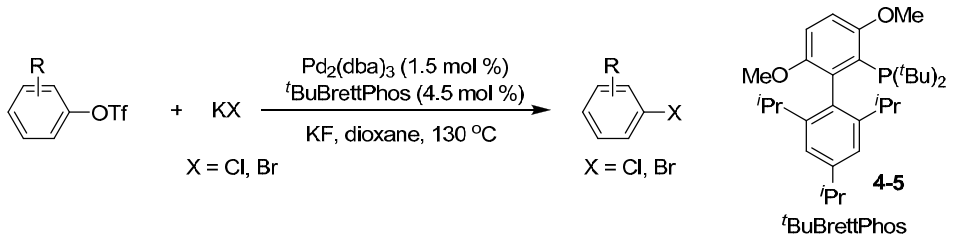


(3)



(4)

Buchwald developed a palladium-catalyzed conversion of aryl triflates to aryl chlorides and aryl bromides.[19] Though this method allows convenient access to a variety aryl and hetroaryl halides, the usage of an expensive ligand ^{t}BuBrettPhos **4-5**[21] is required to ensure the reactivity.

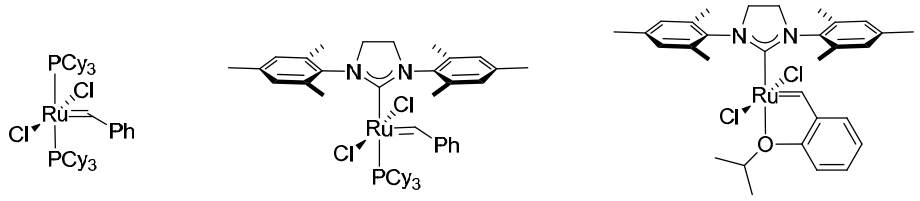


(5)

Classical halogenation methods for arene formations suffer from several limitations including low regioselectivity, multistep sequence and over-halogenation.[22,23] As described above, the directing group-assisted methods have been developed to address these limitations. Although attractive, the requirement for a suitable pre-installed directing group and strong bases or excess amount of specialized oxidants are yet to be improved. Especially, the requirement of specific additives/ligands for transition metal-catalyzed direct-halogenation also limits their broad utilities. Thus, more efficient and green methods are still in high demand for the synthesis of halogenated arenes.

4.2. Results and Discussion

In previous chapter, we described an efficient 1,4-hydrovinylative cyclization of multiynes with ethylene catalyzed by the ruthenium alkylidene complex **G-II**.[24] Inspired by this unusual non-metathetic reactivity of the Grubbs type catalysts toward multiynes, we continued our exploration by introducing variations in the tether of these multiynes.

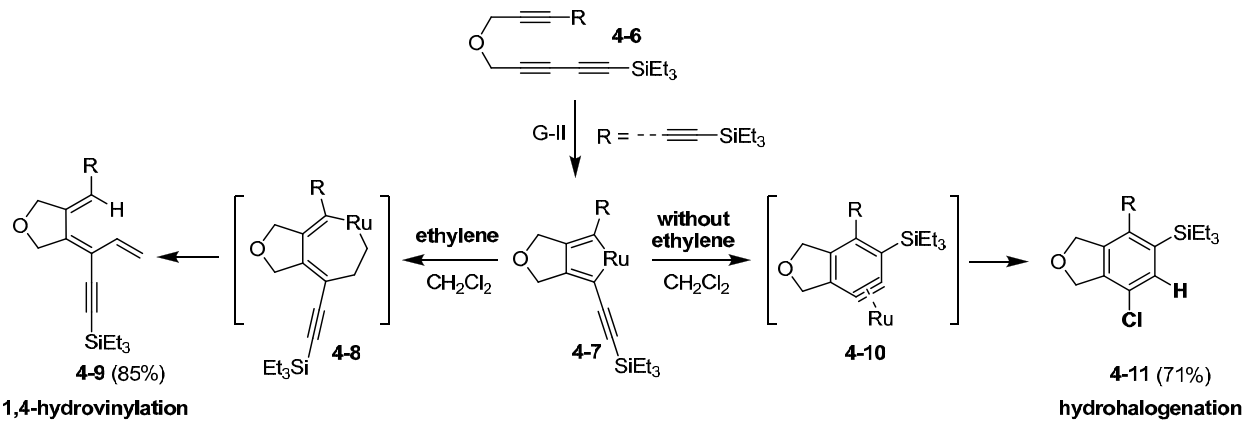


G-I **G-II** **HG-II**

In these efforts, we recognized that in certain occasions when the tether contained either nitrogen or oxygen, completely different product structures were realized without any formation of the 1,4-hydrovinylative cyclization product. After extensive characterization, we found that a new arene moiety was created at the expense of consuming three triple bonds, and one molecule of hydrochloride was incorporated in the newly formed arene moiety. For example, when *bis*-1,3-diyne **4-6** was treated with **G-II** in CH_2Cl_2 at 80 ^oC under ethylene atmosphere, 1,4-hydrovinylative cyclization product **4-9** was obtained in high yield. On the other hand, in the absence of the ethylene, halogenated arene product **4-11** was produced exclusively. Based on these observations, we hypothesized that the common intermediate

4-7 is bifurcated into **4-8** with ethylene and **4-10** without ethylene. As proposed before, **4-8** would provide 1,4-hydrovinylative cyclization products after β-hydride elimination.[25] Alternatively, in the absence of ethylene, the pendant alkyne moiety on the ruthenacyclopentadiene **4-7** would interact with the ruthenium metal center and eventually generates the ruthenium-stabilized aryne **4-10**. This ruthenium-stabilized aryne intermediate then abstracts hydrogen and halogen atoms from halogenated solvents to yield the observed haloarene **4-11**.[26-30]

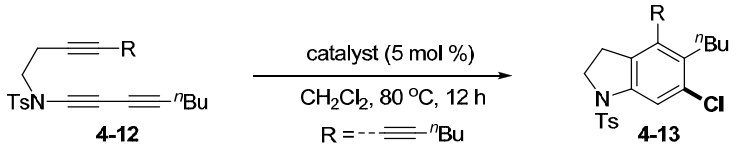
Scheme 4.1. Discovery of ruthenium alkylidene catalyzed hydrohalogenation



4.2.1. Catalysts Screen for Hydrohalogenation

To define the novel catalytic role of the ruthenium alkylidene complex **G-II** for this unexpected hydrohalogenation of putative aryne species, we further screened the reaction efficacy of Grubbs-type ruthenium alkylidene complexes **G-I**, **G-II**, and **HG-II** as well as other transition metal complexes using substrate **4-12** in CH_2Cl_2 at 80 ^oC (**Table 4.1**). Among these three Grubbs-type ruthenium complexes, we found that **G-II** showed the highest efficiency, yielding chlorinated isoindoline **4-13** in 76% yield (entry 1). Cyclization reaction of this unsymmetrical substrate occurs to form a single aryne regioisomer. The observed regioselectivity of chloride incorporation is consistent with the inherent regioselectivity trend of nucleophile addition to indolynes reported by Garg and Houk.[31]

Table 4.1. Catalyst screening of hydrohalogenation



Entry	Catalyst	Yield (%)	Entry	Catalyst	Yield (%)
1	**G-I**	43[a]	8	$RhCl(PPh_3)_3$	15[b]
2	**G-II**	76[a]	9	$Rh_2(O_2CCH_3)_4$	<3[b]
3	**HG-II**	66[a]	10	$Rh(O_2C_5H_7)_3$	<3[b]
4	$Ru_3(CO)_{12}$	10[b]	11	$Pd(OAc)_2$	0
5	[Cp*RuCl (COD)]	0	12	$PtCl_2$	0
6	$[CpRu(CH_3CN)_3]PF_6$	0	13	PPh_3AuCl	0
7	$[RuCl_2(p\text{-cymene})]_2$	0	14	none	0

[a] Isolated yield. [b] Yield was determined by ^{1}H NMR with internal standard.

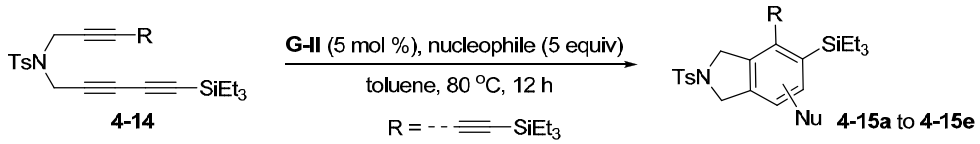
Grubbs first-generation complex **G-I** and Hoveyda-Grubbs second-generation complex **HG-II** gave slightly diminished yields, providing product **4-13** in 43 and 66% yield, respectively (entries 2–3). Although $Ru_3(CO)_{12}$ provided product **4-13**, the yield was significantly lower than that with ruthenium alkylidenes (entry 4). Other ruthenium complexes such as [Cp*RuCl(COD)], $[CpRu(CH_3CN)_3]PF_6$, and $[RuCl_2(p\text{-cymene})]_2$ did not exhibit any catalytic activity for this reaction (entries 5–7), and the starting material decomposed over 12 hours of the reaction time. While Wilkinson's catalyst $RhClPPh_3$ gave 15% yield of the product, other rhodium complexes like $Rh_2(O_2CCH_3)_4$ or $Rh(O_2C_5H_7)_3$ generated only trace amount of the product **4-13** (entries 8–10). $Pd(OAc)_2$ was completely inactive for this transformation and other metal complexes known for their high affinity for alkynes such as $PtCl_2$ and PPh_3AuCl generated only intractable material (entries 11–13). Running the reaction under thermal conditions without adding catalyst did not provide any desired product after 12 hours (entry 14).

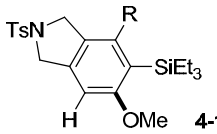
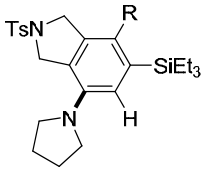
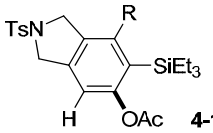
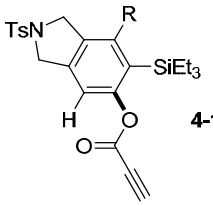
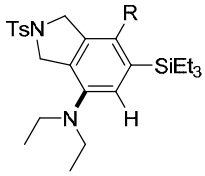
4.2.2. Identity of Aryne Intermediate for Hydrohalogenation

Having identified the effective catalyst and the optimized reaction conditions, we became interested in identifying a putative intermediate, which might provide more insight into designing better substrates for hydrohalogenation. In Scheme 4.1, we proposed the reaction mechanism involving a

ruthenium-complexed aryne intermediate generated in situ from diyne and tethered alkyne. A subsequent HCl abstraction from halogenated solvent will deliver the hydrohalogenation product. If an aryne species is the real intermediate involved in this process, this highly electrophilic aryne should be trapped with even a weak nucleophile. With this assumption, we performed the reaction of substrate **4-14** with various external nucleophiles (**Table 4.2**).

Table 4.2. Trapping the reaction intermediate by using external nucleophiles



External nuleophile	Product	Yield[a]	External nuleophile	Product	Yield[a]
MeOH	 **4-15a**	84%	Pyrrolidine	 **4-15d**	71%
HOAc	 **4-15b**	86%			
Propiolic acid	 **4-15c**	65%	Et_3N	 **4-15e**	80%
				By excluding ethylene during the reaction	

[a] Isolated yield

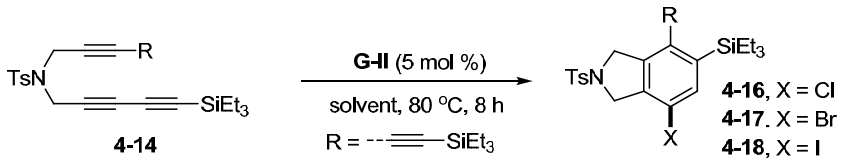
Indeed, in the presence of a super-stioichiometric amount of external nucleophiles, products **4-15a–e** were obtained in good yields. Without external nucleophilic additives, mostly polymerized materials (based on broad ^{1}H NMR signals) were obtained. The formation of these products is in line with the typical aryne reactivity. The high selectivity for single regioisomer is noteworthy in these reactions. When the external nucleophile is sterically unhindered (MeOH, HOAc and propiolic acid), nucleophile was added exclusively at the *ortho*-position to triethylsilyl group, providing functionalized isoindolines in 65 to 84% yields. On the other hand, when pyrrolidine and triethylamine were used as nucleophiles, only

meta-addition products were observed. Especially, when triethylamine was used, diethylamino group adduct **4-15d** was obtained, which is the consequence of triethylamine addition followed by β-elimination with one of the ethyl group to extrude ethylene. These nucleophilic trapping experiments suggest that the hydrohalogenation process most likely involves an in situ generated aryne intermediate even though it's not clear how the aryne intermediate reacts with methylene chloride and other halogenated hydrocarbons in the presence of ruthenium alkylidene complexes.

4.2.3. Hydrogen Halide Source

Next, we investigated the reactivity of various haloalkanes with symmetrical *bis*-1,3-diyne **4-14** in the presence of catalytic amount of **G-II** (**Table 4.3**). This screening revealed that hydrogen chloride, hydrogen bromide, and hydrogen iodide could be incorporated into the putative aryne intermediates to generate halogenated arenes from conventional halogenated hydrocarbons including CH_2Cl_2, $CHCl_3$, $ClCH_2CH_2Cl$, CH_2Br_2, $BrCH_2CH_2Br$, and CH_2I_2.

Table 4.3. Screening of hydrogen halide source for hydrohalogenaion



Entry	Halogen source	Product	X	Yield (%)[a]
1	CH_2Cl_2	**4-16**	Cl	92
2	$CHCl_3$	**4-16**	Cl	90
3	$ClCH_2CH_2Cl$	**4-16**	Cl	85
4	CCl_4	**4-16**	Cl	0
5	CH_2Br_2	**4-17**	Br	76
6	$BrCH_2CH_2Br$	**4-17**	Br	74
7	CH_2I_2	**4-18**	I	45

[a]Isolation yield.

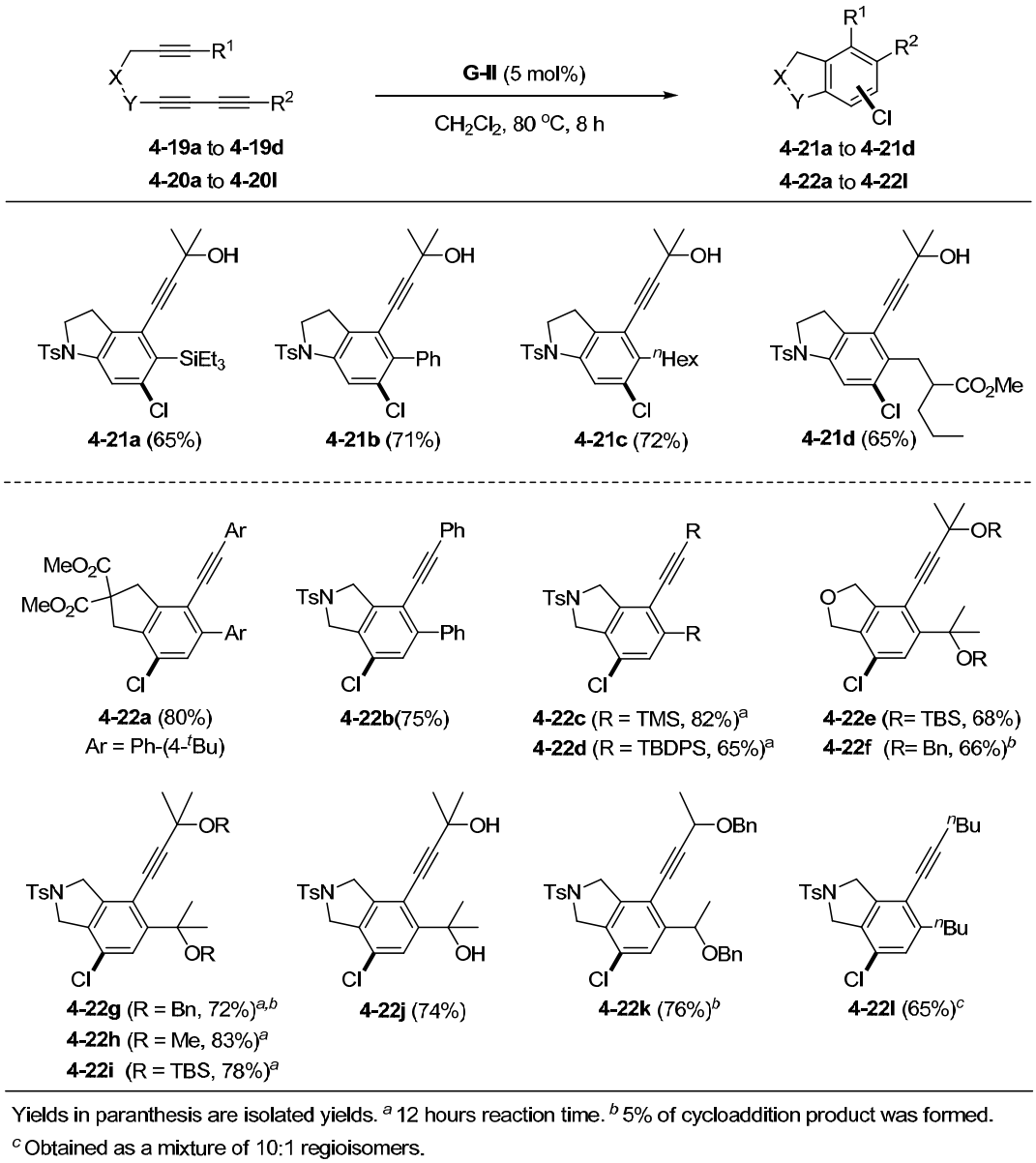
When CH_2Cl_2 and $CHCl_3$ were used as the solvent, the corresponding hydrochlorination product **4-16** was formed in 92 and 90% yields respectively; $ClCH_2CH_2Cl$ gave slightly diminished yield,

providing the same product in 85% yield. The same reaction in halogenated solvent lacking proton such as CCl_4 did not produce any hydrochlorination product even though the starting material was completely consumed. Similarly, reactions with CH_2Br_2 and $BrCH_2CH_2Br$ gave brominated product **4-17** in 76 and 74% yields without the formation of a notable amount of the competing chlorination product resulting from the chloride transfer from the chloride-containing **G-II** complex. Under the typical hydrohalogenation conditions, the use of CH_2I_2 as the hydrogen iodide source afforded iodoisoindoline **4-18** in moderate yield.

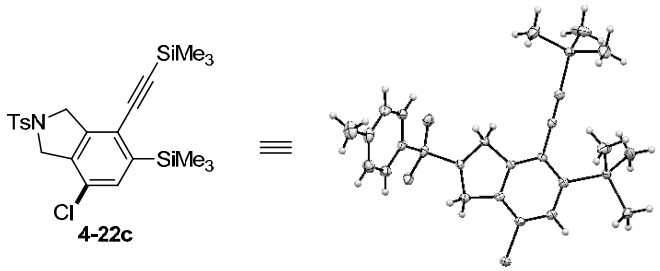
4.2.4. Reaction Scope of Hydrohalogenation

Having established the reactivity profile of hydrohalogenation of *bis*-1,3-diyne substrate **4-14** with various haloalkanes, we then explored the reaction scope with a variety of unsymmetrical and symmetrical *bis*-1,3-diyne substrates (**Table 4.4**). For unsymmetrical *bis*-1,3-diyne systems containing ynamide tether, complete regioselectivity of hydrochlorination was observed. The substituents on the incipient arenes such as silyl group **4-21a**, phenyl group **4-21b**, alkyl group **4-21c** and alkyl group possessing ester moiety **4-21d** did not affect the selectivity, provide chlorinated indolines in 65 to 72% yields. It is noteworthy that this reaction tolerates free alcohol and carbonyl functionalities. On the other hand, the substituents on the symmetrical substrates play more significant roles for regioselectivity. In general, symmetrical *bis*-1,3-diyne containing aryl substituents delivered single regioisomer regardless the nature of tether. Specifically, *bis*-1,3-diyne substrates carrying 4-*tert*-butyphenyl group and simple phenyl group provided chlorinated products **4-22a** and **4-22b** in good yields. Trimethylsily and *tert*-butyldiphenylsilyl group-substituted chloroisoindolines **4-22c** and **4-22d** were obtained in 82 and 65% yields, respectively, with complete regioselectivity. The regiochemistry of these products was established by nOe experiments and further confirmed by a single crystal X-ray crystallographic analysis of **4-22c**.

Table 4.4. Reaction scope of hydrochlorination



Yields in paranthesis are isolated yields. [a] 12 hours reaction time. [b] 5% of cycloaddition product was formed. [c] Obtained as a mixture of 10:1 regioisomers.



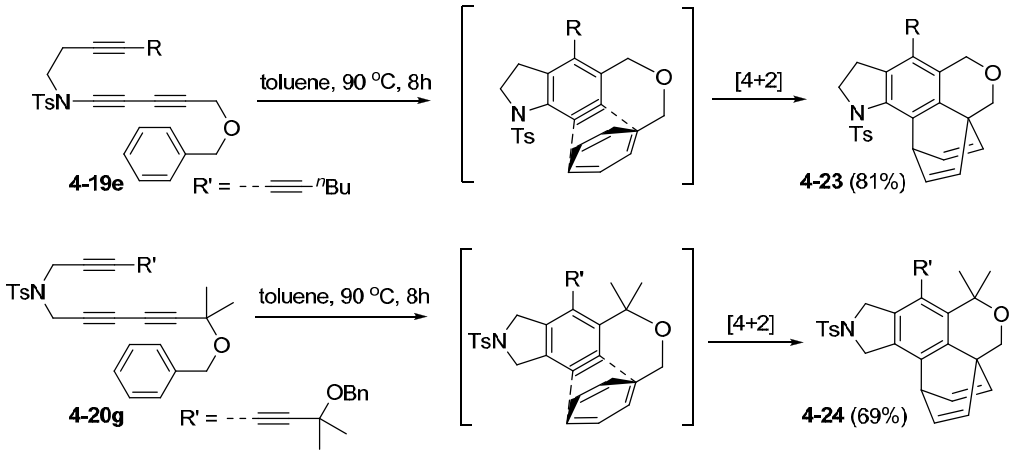
ORTEP diagram of 4-22c

Oxygen-tethered *bis*-1,3-diynes containing protected tertiary alcohol also produced chlorinated 1,3-dihydroisobenzofuran **4-22e** and **4-22f** in 68 and 66% yield. Furthermore, secondary and tertiary alkyl

group as well as free tertiary alcohol substituted substrates generated the corresponding hydrochlorination products **4-22g** to **4-22k** as a single regioisomer in good yields. A symmetrical *bis*-1,3-diyne substrate containing a butyl group afforded a 10:1 mixture of regioisomers **4-22l**, and the regiochemistry of the major isomer is consistent with the product formed from other symmetrical *bis*-1,3-diyne substrates.

When substrate **4-19a** carrying a benzyl group was used, a small amount of intramolecular [4+2] cycloadduct **4-23** was obtained, but its formation was maximized by changing the solvent form halogenated hydrocarbon to toluene. As shown in Scheme 4.2, the [4+2] cycloaddition products from both symmetrical and unsymmetrical *bis*-1,3-diyne substrates could be obtained in good yield.

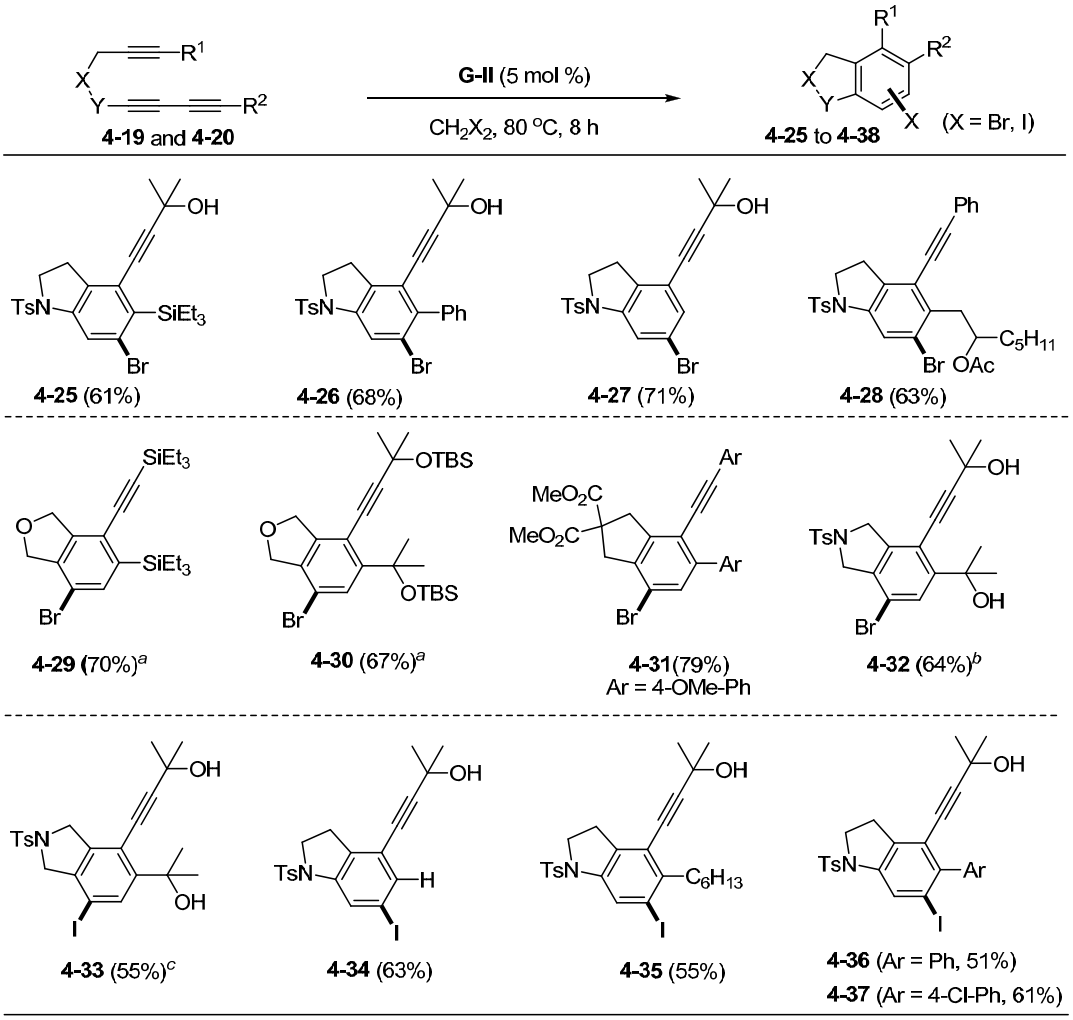
Scheme 4.2. Tandem aryne formation–[4+2] cycloaddition



Next, we examined the reaction scope of hydrobromination and hydroiodination with various symmetrical and unsymmetrical *bis*-1,3-diyne substrates using CH_2Br_2 and CH_2I_2 as the hydrogen halide source. In general, unsymmetrical *bis*-1,3-diyne substrates provided functionalized bromoarenes **4-25** to **4-32** in good yields and regioselectivity. The overall reaction profile is very similar to that of hydrochlorination regardless of the tether and the substituents on the 1,3-diyne. On the other hand, the hydroiodination of selected substrates using CH_2I_2 as the hydrogen iodide source provided corresponding aryl iodides **4-33** to **4-37** in slightly lower yields albeit the sense of regioselectivity is the same as that of hydrobromination. However, in symmetrical *bis*-1,3-diyne cases, a small amount of competing

hydrochlorination products were observed in both hydrobromination and hydroiodination reaction where the chloride source must be the catalyst (**Table 4.5**).

Table 4.5. Reaction scope of hydrobromination and hydroiodination

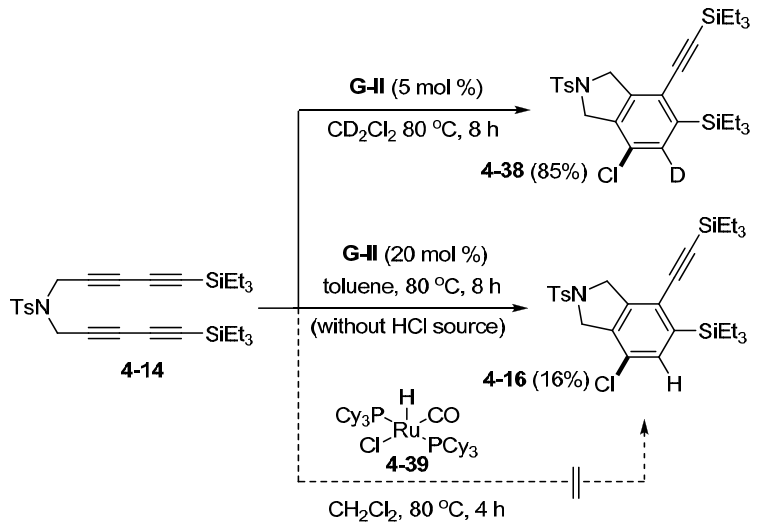


Yields in paranthesis are isolated yields.[a] Bromination : chlorination = 12 : 1. [b] Bromination : chlorination = 18:1, [c] Iodination : chlorination = 13:1

4.2.5. Mechanistic Study

In order to gain insight into the mechanism of this novel hydrohalogenation, substrate **4-14** was subjected to the optimal reaction conditions in the presence of CD_2Cl_2 as the halogen and deuterium source. From this reaction, the deuterated chloroisoindoline **4-38** with nearly complete deuterium

Scheme 4.3. Control experiments for the mechanistic study

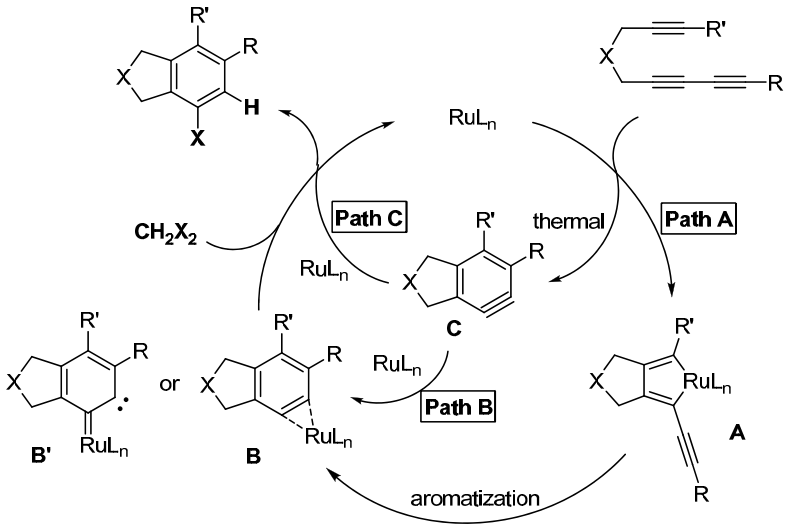


incorporation at the carbon *ortho* to the silyl group was obtained. This experiment clearly indicates that the halogen-containing solvent indeed was the source for both Cl and H for the hydrohalogenation. Moreover, when the reaction was performed with 20 mol % of **G-II** in non-halogenated solvent such as toluene, product **4-16** was obtained in 16% yield. This result also suggests that the chloride ligand on the ruthenium alkylidene complex could be transferred from ruthenium center to the aryne intermediate. When ruthenium hydride **4-39**, a well-known decomposition product of **G-I**, was used as the catalyst, no hydrochlorination product was found after 4 hours of reaction.

While more evidences are yet to be obtained for a meaningful reaction mechanism, we purpose a working hypothesis based on the preliminary mechanistic studies (**Scheme 4.4**). In this mechanistic scenario, ruthenium alkylidene complex can be involved in two distinctive modes of direct interaction with aryne intermediate. First, in Path A, a ruthenium alkylidene complex (RuL_n) forms a ruthenacyclopentadiene intermediate **A** which then rearranges to the ruthenium-aryne complex **B** or **B'** followed by halogen abstraction and proton transfer from the halogenated solvent would deliver the observed product and a regenerated catalyst. In an alternative mechanism, a thermal cycloaddition of the *bis*-1,3-diyne substrate to form an aryne intermediate **C**, which undergoes complexation with a ruthenium

alkylidene (**Path B**), leading to the same ruthenium-aryne complex **B** or **B′**. Another possible pathway (**Path C**) involves the free aryne intermediate **C**, which undergoes hydrohalogenation where the role of the ruthenium alkylidene is just to activate halogenated hydrocarbons without its contact with the aryne **C**.

Scheme 4.4. Possible reaction mechanisms for hydrohalogenation



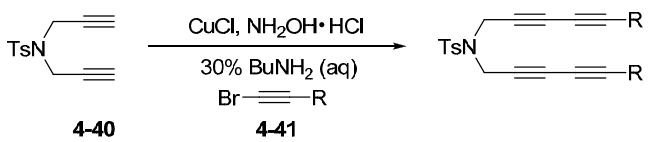
4.3. Conclusion

In summary, we discovered an unusual non-metathetic activity of Grubbs-type ruthenium alkylidene complexes whereby a variety of halogenated arenes were synthesized directly from *bis*-1,3-diynes in the presence of halogenated hydrocarbons as the source of halogen atoms. Several mechanistic considerations suggest that this transformation occurs through the formation of a free aryne species or its ruthenium-complexed form as the critical intermediate followed by incorporation of hydrogen halide from halogenated hydrocarbons. This novel hydrohalogenation reaction of arynes allows the preparation of a variety of halogenated indolines, isoindolines and related structures in an effective and regioselective manner. We believe that the unique catalytic activity of Grubbs-type ruthenium complexes discovered herein would further broaden the utility of these complexes in organic synthesis.

4.4. Experimental Details

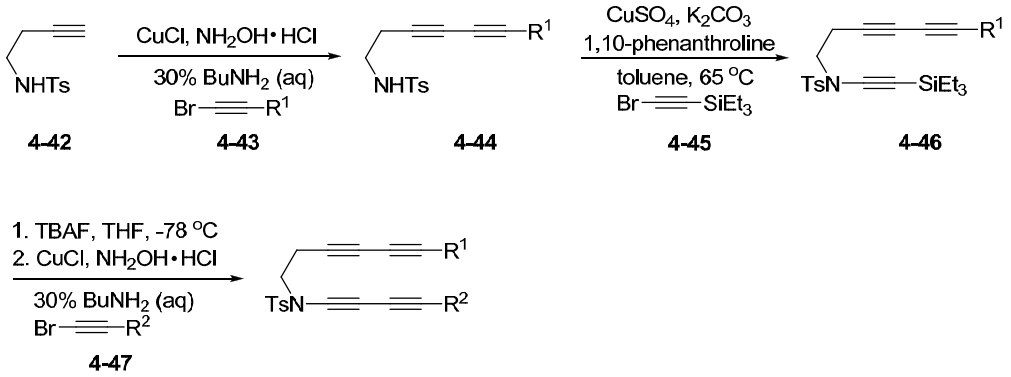
4.4.1. General Information (See Chapter 1.4.1)

4.4.2. General Procedure for the Symmetric *bis*-1,3-Diyne Synthesis



Symmetrical *bis*-1,3-diyne substrates can be prepared in one step using Cadiot-Chodkiewicz coupling reaction. To a 30% *n*-$BuNH_2$ (3 mL/1 mmol of substrate) aqueous solution containing CuCl (2 equiv), and $NH_2OH{\cdot}HCl$ (0.1 equiv) was added diyne **4-40** at 0 ^oC. Bromoalkyne **4-41** (3 – 4 equiv) was then added dropwise over 5 min and the reaction mixture was stirred at 0 ^oC for additional 5 min. After aqueous work up, the crude product was purified by column chromatography on silica gel to afford *bis*-1,3-diynes in moderate to good yields.

4.4.3. General Procedure for the Unsymmetric *bis*-1,3-Diyne Synthesis



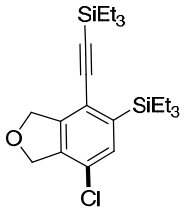
Unsymmetrical *bis*-1,3-diyne substrates can be synthesized in four steps involving Cadiot-Chodkiewicz coupling reaction, *N*-alkynalation of tosylamide, desilylation and another Cadiot-Chodtiewicz coupling reaction sequence. Tosylamide **4-42** was coupled with bromoalkyne **4-43** (1.5 equiv) under the typical Cadiot-Chodkiewicz reaction conditions described above gave diyne **4-44**. *N*-alkynylation of **4-44** with bromoalkyne **4-45** (1.1 equiv) in the presence of catalytic amount of $CuSO_4 \cdot 5H_2O$ (0.1 equiv), 1,10-phenanthroline (0.2 equiv) and K_2CO_3 (2 equiv) in toluene at 65 ^oC for 8 h

afforded triyne **4-46**. Desilylaton of **4-46** using TBAF (1.1 equiv) at -78 ^{o}C and a subsequent coupling reaction with bromoalkyne **4-47** (1.5 equiv) generated unsymmetrical *bis*-1,3-diyne in moderate to good yields.

4.4.4. General Procedure for the Hydrohalogenation Reaction

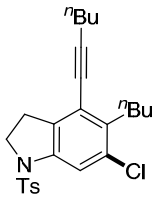
Grubbs second generation catalyst **G-II** (5 mol %) and *bis*-1,3-diyne (0.1 mmol) were dissolved in 5 mL of selected halogen-contained solvent (CH_2Cl_2, CH_2Br_2, or CH_2I_2) in a thick-walled 25 mL Schlenk tube equipped with a magnetic stirring bar. The reaction tube was degased under vacuum and refilled with argon. The reaction tube was stirred in an oil bath at 80 °C for 8 h. The solvent was removed under reduced pressure and the organic product was isolated by column chromatography on silica gel (hexanes/EtOAc as eluting solvent).

4.4.5. Selected Characterization Data



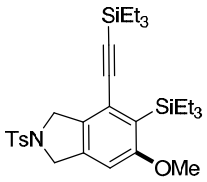
4-11

4-11 (71%)**: ^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.25 (s, 1H), 5.20 (s, 2H), 5.15 (s, 2H), 1.03 (t, *J* = 7.9 Hz, 9H), 0.95 (s, 15H), 0.68 (q, *J* = 7.9 Hz, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 145.2, 141.5, 138.1, 134.0, 127.5, 120.5, 103.6, 100.0, 75.2, 74.1, 7.41, 4.28, 3.10; **HRMS** (ESI) calcd for $C_{22}H_{34}ClOSi_2$ $[M-H]^+$: 405.1837, found 405.1837.



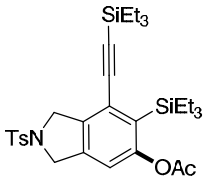
4-13

4-13 (76%)**: ^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.1 Hz, 2H), 7.57 (s, 1H), 7.26 (d, *J* = 8.1 Hz, 2H), 3.88 (t, *J* = 8.5 Hz, 2H), 2.90 (t, *J* = 8.5 Hz, 2H), 2.81 (m, 2H), 2.42 (t, *J* = 6.9 Hz, 2H), 2.39 (s, 3H), 1.58 – 1.34 (m, 8H), 0.94 (t, *J* = 6.0 Hz, 3H), 0.92 (t, *J* = 6.2 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 144.3, 140.1, 137.2, 133.7, 133.1, 133.1, 129.8, 127.4, 122.0, 114.8, 98.6, 76.4, 49.9, 31.5, 31.4, 30.8, 27.9, 22.8, 21.9, 21.6, 19.2, 13.9, 13.6; **HRMS** (ESI) calcd for $C_{25}H_{31}ClNO_2S$ $[M+H]^+$: 444.1764, found 444.1773.



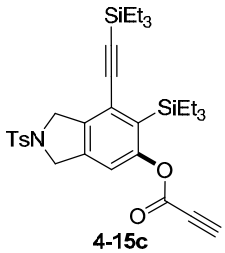
4-15a

4-15a (84%)**: ^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 6.58 (s, 1H), 4.64 (s, 2H), 4.55 (s, 2H), 3.70 (s, 3H), 2.40 (s, 3H), 1.06 (t, *J* = 7.9 Hz, 9H), 0.97 – 0.87 (m, 15H), 0.69 (q, *J* = 7.9 Hz, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.1, 143.5, 137.8, 133.9, 133.0, 129.7, 127.6, 126.6, 125.2, 104.28, 104.22, 100.3, 55.2, 54.8, 54.2, 21.5, 7.74, 7.42, 4.85, 4.26.



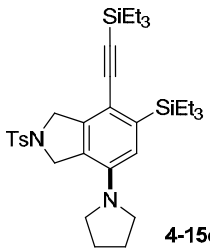
4-15b

4-15b (86%)**: ^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 6.76 (s, 1H), 4.63 (s, 2H), 4.58 (s, 2H), 2.41 (s, 3H), 2.27 (s, 3H), 1.05 (t, *J* = 7.9 Hz, 9H), 0.97 – 0.87 (m, 15H), 0.70 (q, *J* = 7.9 Hz, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.7, 155.8, 143.8, 138.8, 137.9, 133.6, 130.0, 127.6, 125.3, 117.0, 103.5, 102.3, 54.3, 54.2, 21.5, 7.51, 7.40, 4.30, 4.21.



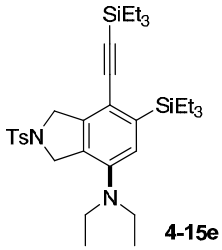
4-15c

4-15c (65%)**: ^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 2H), 6.82 (s, 1H), 4.63 (s, 2H), 4.59 (s, 2H), 3.10 (s, 1H), 2.41 (s, 3H), 1.05 (t, *J* = 7.9 Hz, 9H), 0.98 (m, 6H), 0.90 (t, *J* = 7.5 Hz, 9H), 0.70 (q, *J* = 7.9 Hz, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.7, 151.3, 143.8, 139.6, 138.2, 133.6, 130.3, 129.9, 127.6, 125.7, 116.6, 103.2, 102.8, 77.4, 74.2, 54.3, 54.2, 21.5, 7.54, 7.42, 7.27, 4.30, 4.21.



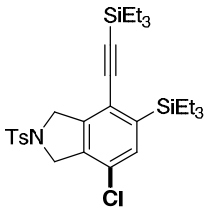
4-15d

4-15d (71%)**: ^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 6.47 (s, 1H), 4.87 (s, 2H), 4.56 (s, 2H), 3.37 (t, *J* = 6.2 Hz, 4H), 2.41 (s, 3H), 1.95 (t, *J* = 6.2 Hz, 4H), 1.04 (t, *J* = 7.9 Hz, 9H), 0.95 – 0.87 (m, 15H), 0.66 (q, *J* = 7.9 Hz, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 143.5, 143.4, 142.2, 140.3, 133.9, 130.0, 127.6, 120.0, 118.7, 110.9, 105.3, 96.6, 55.1, 54.0, 49.1, 25.4, 21.5, 7.55, 7.48, 4.50, 3.25.



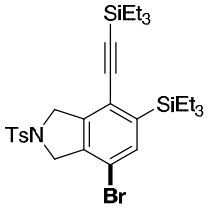
4-15e

4-15e (80%)**: ^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.9 Hz, 2H), 7.29 (d, *J* = 7.9 Hz, 2H), 6.77 (s, 1H), 4.61 (q, *J* = 6.7 Hz, 4H), 3.12 (q, *J* = 6.7 Hz, 4H), 2.39 (s, 3H), 1.04 (m, 15H), 0.91 (m, 15H), 0.68 (q, *J* = 7.8 Hz, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 144.8, 143.5, 142.2, 139.7, 133.9, 129.7, 127.6, 127.2, 123.8, 114.5, 104.8, 97.6, 54.4, 54.3, 45.6, 21.4, 12.8, 7.45, 4.42, 3.21.



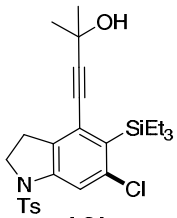
4-16

4-16 (92%)**:** ^{1}**H NMR** (501 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 7.22 (s, 1H), 4.67 (s, 2H), 4.65 (s, 2H), 2.41 (s, 3H), 1.05 (t, *J* = 7.9 Hz, 6H), 0.91 (s, 15H), 0.70 (t, *J* = 7.9 Hz, 6H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 143.8, 142.0, 135.2, 134.2, 133.8, 129.9, 128.4, 127.5, 122.0, 103.0, 101.1, 54.9, 54.0, 21.5, 7.39, 7.33, 4.23, 2.95; **HRMS** (ESI) calcd for $C_{29}H_{42}ClNO_2SSi_2$ $[M]^+$: 559.2163, found 559.2164.



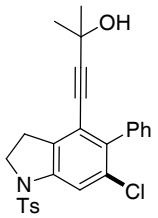
4-17

4-17 (76%)**:** ^{1}**H NMR** (501 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.2 Hz, 2H), 7.37 (s, 1H), 7.33 (d, *J* = 8.2 Hz, 2H), 4.70 (s, 2H), 4.61 (s, 2H), 2.41 (s, 3H), 1.65 (t, *J* = 7.9 Hz, 6H), 0.90 (s, 15H), 0.69 (t, *J* = 7.9 Hz, 6H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 143.8, 142.1, 141.6, 137.3, 137.1, 133.6, 129.9, 127.6, 122.6, 117.2, 103.0, 101.3, 55.7, 55.1, 21.5, 7.42, 7.36, 4.20, 2.93; **HRMS** (ESI) calcd for $C_{29}H_{42}ClNO_2SSi_2$ $[M]^+$: 559.2163, found 559.2164.



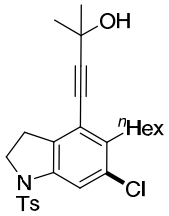
4-21a

4-21a (65%)**:** ^{1}**H NMR** (501 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.2 Hz, 2H), 7.56 (s, 1H), 7.28 (d, *J* = 8.2 Hz, 2H), 3.89 (t, *J* = 8.6 Hz, 2H), 2.96 (t, *J* = 8.6 Hz, 2H), 2.40 (s, 3H), 1.92 (br, 1H), 1.56 (s, 6H); 1.04 (m, 6H), 0.94 (m, 9H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 144.5, 143.0, 141.5, 134.3, 133.8, 130.7, 129.9, 127.3, 127.1, 115.5, 101.8, 80.9, 65.7, 49.5, 31.1, 28.2, 21.6, 7.78, 5.39; **HRMS** (ESI) calcd for $C_{26}H_{35}ClNO_3SSi$ $[M+H]^+$: 504.1795, found 504.1790.



4-21b

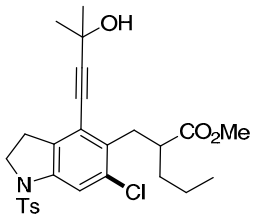
4-21b (71%)**:** ^{1}**H NMR** (501 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.2 Hz, 2H), 7.72 (s, 1H), 7.38 (m, 3H), 7.31 (d, *J* = 8.2 Hz, 2H), 7.26 (d, *J* = 8.2 Hz, 2H), 3.94 (t, *J* = 8.5 Hz, 2H), 2.98 (t, *J* = 8.5 Hz, 2H), 2.41 (s, 3H), 1.82 (br, 1H), 1.27 (s, 6H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 144.6, 141.6, 137.6, 133.6, 132.9, 132.6, 129.9, 129.9, 127.7, 127.6, 127.3, 121.1, 115.0, 78.3, 65.3, 49.9, 30.8, 27.7, 21.5; **HRMS** (ESI) calcd for $C_{26}H_{25}ClNO_3S$ $[M+H]^+$: 466.1244, found 466.1243.



4-21c

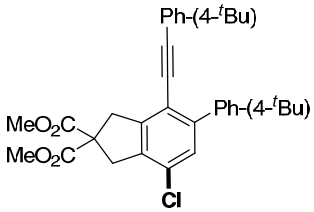
4-21c (72%)**:** ^{1}**H NMR** (501 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.2 Hz, 2H), 7.60 (s, 1H), 7.26 (d, *J* = 8.2 Hz, 2H), 3.88 (t, *J* = 8.5 Hz, 2H), 2.91 (d, *J* = 8.5 Hz, 2H), 2.79 (m, 2H), 2.39 (s, 3H), 1.97 (br, 1H), 1.58 (s, 6H), 1.51 (td, *J* = 15.3, 7.5 Hz, 2H), 1.36 (m, 2H), 1.31 (m, 4H), 0.88 (t, *J* = 6.3 Hz, 3H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 144.4, 140.3, 137.3, 133.6,

133.3, 133.2, 129.8, 129.3, 120.6, 115.5, 101.7, 77.8, 65.7, 49.8, 31.8, 31.7, 31.5, 29.4, 29.1, 27.8, 22.6, 21.5, 14.0.



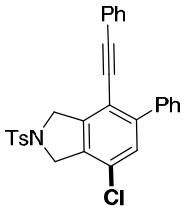
4-21d

4-21d (65%)**:** ^{1}**H NMR** (501 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.2 Hz, 2H), 7.61 (s, 1H), 7.27 (d, *J* = 8.2 Hz, 2H), 3.93 (m, 2H), 3.60 (s, 3H), 3.18 (br, 1H), 3.13 (dd, *J* = 13.5, 7.7 Hz, 1H), 3.00 (dd, *J* = 13.5, 6.8 Hz, 1H), 2.91 (t, *J* = 8.5 Hz, 2H), 2.76 (m, 1H), 2.39 (s, 3H), 1.73 (m, 1H), 1.57 (s, 3H), 1.55 (s, 3H), 1.40 (m, 1H), 1.27 (m, 2H), 0.87 (t, *J* = 87.3 Hz, 3H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 176.8, 144.5, 141.0, 134.0, 133.8, 133.7, 133.0, 129.8, 127.3, 121.3, 115.3, 103.1, 77.4, 65.2, 51.8, 49.8, 45.3, 34.5, 34.0, 31.4, 31.0, 27.7, 21.5, 20.7, 13.9; **HRMS** (ESI) calcd for $C_{27}H_{33}ClNO_5S$ $[M+H]^+$: 518.1768, found 518.1778.



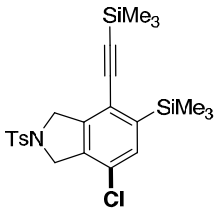
4-22a

4-22a (80%)**:** ^{1}**H NMR** (501 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.3 Hz, 2H), 7.46 (d, *J* = 8.3 Hz, 2H), 7.34 – 7.25 (m, 5H), 3.87 (s, 2H), 3.81 (s, 6H), 3.74 (s, 2H), 1.39 (s, 9H), 1.31 (s, 9H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 171.8, 151.7, 150.7, 144.8, 144.2, 136.6, 136.3, 131.1, 129.9, 128.9, 128.3, 125.3, 124.9, 120.2, 116.8, 96.8, 86.0, 58.8, 53.2, 41.8, 40.3, 34.8, 34.6, 31.4, 31.1; **HRMS** (ESI) calcd for $C_{35}H_{37}ClO_4$ $[M]^+$: 556.2380, found 556.2381.



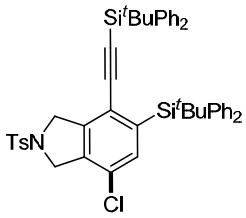
4-22b

4-22b (75%)**:** ^{1}**H NMR** (501 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.1 Hz, 2H), 7.57 (d, *J* = 7.0 Hz, 2H) 7.47 – 7.40 (m, 3H), 7.37 (d, *J* = 8.1 Hz, 2H), 7.33 (m, 5H), 7.30 (s, 1H), 4.87 (s, 2H), 4.72 (s, 2H), 2.43 (s, 3H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 1452, 143.9, 141.1, 138.5, 133.7, 133.6, 131.5, 130.0, 129.1, 129.0, 128.8, 128.5, 128.4, 128.2, 128.1, 127.6, 122.5, 115.4, 97.5, 84.9, 55.1, 53.9, 21.5; **HRMS** (ESI) calcd for $C_{29}H_{23}ClNO_2S$ $[M+H]^+$: 484.1138, found 484.1129.



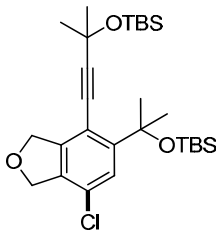
4-22c

4-22c (82%)**:** ^{1}**H NMR** (501 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.5 Hz, 2H), 7.34 (d, *J* = 8.5 Hz, 2H), 7.25 (s, 1H), 4.70 (s, 2H), 4.61 (s, 2H), 2.41 (s, 3H), 0.32 (s, 9H), 0.25 (s, 9H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 145.1, 143.8, 141.3, 135.3, 133.8, 133.2, 129.9, 128.6, 127.6, 121.5, 103.6, 102.0, 54.7, 53.9, 21.5, -0.34, -1.35; **HRMS** (ESI) calcd for $C_{23}H_{30}ClNO_2SSi_2$ $[M]^+$: 475.1224, found 475.1229.



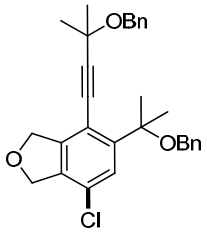
4-22d

4-22d (65%)**:** ^{1}**H NMR** (501 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.2 Hz, 2H), 7.63 (s, 1H), 7.51 (d, *J* = 8.0, 1.2 Hz, 4H), 7.39 (m, 2H), 7.33 – 7.21 (m, 16H), 4.73 (s, 2H), 4.66 (s, 2H), 2.43 (s, 3H), 1.11 (s, 9H), 0.84 (s, 9H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 144.1, 143.8, 139.1, 136.7, 136.2, 136.0, 135.6, 133.8, 133.6, 132.6, 129.9, 129.3, 128.6, 127.7, 127.61, 127.58, 123.6, 105.5, 102.1, 55.6, 54.1, 29.0, 27.1, 21.5, 19.0, 18.2; **HRMS** (ESI) calcd for $C_{49}H_{51}ClNO_2SSi_2$ $[M+H]^+$: 800.2868, found 800.2867.



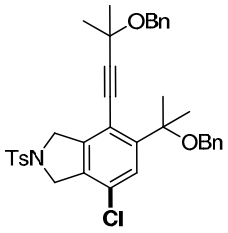
4-22e

4-22e (68%)**:** ^{1}**H NMR** (501 MHz, $CDCl_3$) δ 7.79 (s, 1H), 5.20 (s, 2H), 5.15 (s, 2H), 1.77 (s, 6H), 1.57 (s, 6H), 0.99 (s, 9H), 0.88 (s, 9H), 0.19 (s, 6H), 0.17 (s, 6H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 153.3, 145.7, 135.3, 127.5, 125.5, 100.9, 104.5, 79.0, 75.9, 75.4, 73.9, 67.1, 32.7, 30.1, 26.0, 25.6, 18.4, 17.9, -1.80, -2.79; **HRMS** (ESI) calcd for $C_{28}H_{47}ClO_3Si_2$ $[M+H]^+$: 522.2752, found 522.2758.



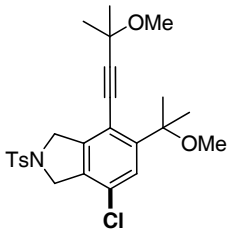
4-22f

4-22f (66%)**:** ^{1}**H NMR** (501 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.38 (m, 2H), 7.33 (m, 2H), 7.27 (m, 2H), 5.21 (s, 2H), 5.18 (s, 2H), 4.61 (s, 1H), 4.34 (s, 2H), 1.79 (s, 6H), 1.56 (s, 6H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 148.9, 146.3, 139.1, 138.9. 136.2, 128.3, 128.2, 127.64, 127.60, 127.4, 127.31, 127.26, 126.2, 101.7, 81.0, 77.4, 75.4, 74.0, 71.3, 66.8, 65.2, 28.7, 27.2.



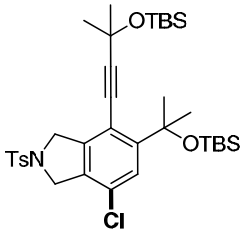
4-22g

4-22g (72%)**:** ^{1}**H NMR** (501 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.2 Hz, 2H), 7.42 (s, 1H), 7.37 – 7.23 (m, 12H), 4.71 (s, 2H), 4.66 (s, 2H), 4.62 (s, 2H), 4.28 (s, 2H), 2.39 (s, 3H), 1.73 (s, 6H), 1.57 (s, 6H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 149.4, 143.8, 142.8, 138.9, 138.7, 133.7, 133.4, 129.9, 128.4, 128.2, 127.6, 127.5, 127.4, 127.3, 126.4, 114.4, 102.8, 80.5, 71.3, 66.9, 65.1, 55.2, 53.8, 28.6, 27.0, 21.5.



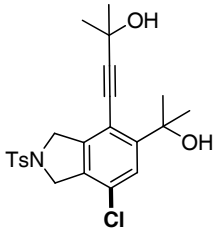
4-22h

4-22h (83%)**:** ^{1}**H NMR** (501 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 7.33 (s, 1H), 4.68 (s, 2H), 4.64 (s, 2H), 3.42 (s, 3H), 3.13 (s, 3H), 2.42 (s, 3H), 1.60 (s, 6H), 1.55 (s, 6H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 148.6, 143.9, 142.6, 133.8, 133.2, 129.9, 128.4, 127.7, 127.6, 126.9, 126.3, 125.6, 114.1, 100.0, 80.2, 77.1, 71.2, 55.1, 53.8, 52.0, 50.5, 28.1, 26.3, 21.5; **HRMS** (ESI) calcd for $C_{25}H_{31}ClNO_4S$ $[M+H]^+$: 476.1662, found 476.166.



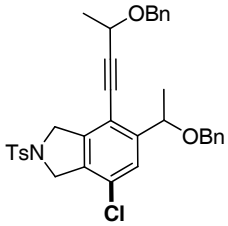
4-22i

4-22i (78%)**: ^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.0 Hz, 2H), 7.77 (s, 1H), 7.33 (d, *J* = 8.0 Hz, 2H), 4.68 (s, 2H), 4.64 (s, 2H), 2.42 (s, 3H), 1.72 (s, 6H), 1.59 (s, 6H), 0.97 (s, 9H), 0.90 (s, 9H), 0.17 (s, 6H), 0.16 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 153.6, 143.8, 142.2, 133.7, 132.5, 129.9, 128.6, 127.6, 125.8, 112.3, 105.5, 78.5, 75.8, 67.1, 55.2, 53.8, 32.6, 29.9, 26.0, 25.6, 21.5, 18.4, 17.9, -1.85, -2.72.



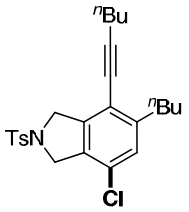
4-22j

4-22j (74%)**: ^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.2 Hz, 2H), 7.49 (s, 1H), 7.34 (d, *J* = 8.2 Hz, 2H), 4.68 (s, 2H), 4.60 (s, 2H), 2.69 (br, 1H), 2.42 (s, 3H), 2.36 (br, 1H), 1.67 (s, 6H), 1.63 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 152.0, 143.9, 142.3, 133.7, 133.1, 130.0, 128.8, 127.5, 125.0, 112.7, 105.5, 78.0, 65.7, 54.9, 53.7, 31.1, 29.7, 21.5; **HRMS** (ESI) calcd for $C_{23}H_{27}ClNO_4S$ $[M+H]^+$: 448.1349, found 448.1349.



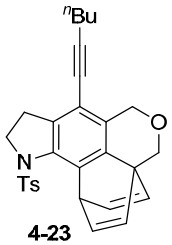
4-22k

4-22k (76%)**: ^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.0 Hz, 2H), 7.45 (s, 1H), 7.42 – 7.22 (m, 12H), 4.91 (q, *J* = 6.3 Hz, 1H), 4.78 – 4.71 (m, 3H), 4.66 (s, 2H), 4.49 (dd, *J* = 2.1, 11.6 Hz, 2H), 4.47 – 4.42 (m, 2H), 4.30 (d, *J* = 8.0 Hz, 1H), 2.42 (s, 3H), 1.53 (t, *J* = 6.0 Hz, 3H), 1.43 (d, *J* = 6.3 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 147.9, 143.9, 140.7, 137.9, 137.6, 133.7, 129.9, 129.5, 128.5, 128.4, 127.9, 127.7, 127.6, 125.2, 114.5, 99.4, 78.6, 74.2, 70.9, 70.8, 64.9, 54.6, 53.7, 23.1, 22.1, 21.5; **HRMS** (ESI) calcd for $C_{35}H_{35}ClNO_4S$ $[M+H]^+$: 600.1975, found 600.1971.



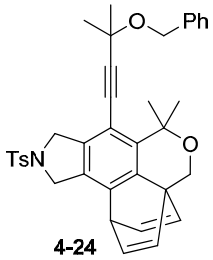
4-22l

4-22l (65%)**: ^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 7.01 (s, 1H), 4.67 (s, 2H), 4.60 (s, 2H), 2.66 (m, 3H), 2.45 (t, *J* = 7.0 Hz, 2H), 2.41 (s, 3H), 1.63 – 1.44 (m, 6H), 1.33 (m, 2H), 0.97 (t, *J* = 7.3 Hz, 3H), 0.91 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 146.4, 143.8, 140.5, 133.8, 131.8, 129.9, 128.0, 127.6, 127.3, 117.1, 99.6, 75.4, 55.0, 53.5, 33.5, 32.7, 30.8, 22.4, 22.0, 21.5, 19.3, 13.9, 13.6; **HRMS** (ESI) calcd for $C_{25}H_{31}ClNO_2S$ $[M+H]^+$: 444.1764, found 444.1773.



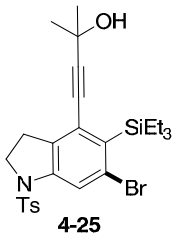
4-23

4-23 (81%)**:** ^{1}**H NMR** (501 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.2 Hz, 2H), 7.13 (d, *J* = 8.2 Hz, 2H), 7.00 (t, *J* = 6.2 Hz, 2H), 6.71 (dd, *J* = 6.6, 1.2 Hz, 2H), 5.78 (tt, *J* = 5.8, 1.4 Hz, 1H), 4.71 (s, 2H), 4.57 (s, 2H), 3.93 (t, *J* = 7.5 Hz, 2H), 2.37 (s, 3H), 2.33 (t, *J* = 6.9 Hz, 2H), 2.14 (t, *J* = 7.5 Hz, 2H), 1.48 (m, 2H), 1.39 (m, 2H), 0.88 (t, *J* = 7.3 Hz, 2H; ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 144.0, 143.9, 141.9, 141.2, 139.4, 134.6, 134.4, 134.2, 129.8, 129.5, 127.6, 111.6, 97.2, 75.2, 71.4, 66.7, 52.1, 51.0, 46.2, 30.8, 28.3, 21.8, 21.6, 19.1, 13.5.



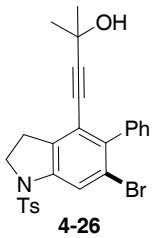
4-24

4-24 (69%)**:** ^{1}**H NMR** (501 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.2 Hz, 2H), 7.34 (m, 4H), 7.30 (m, 1H), 7.24 (d, *J* = 8.2 Hz, 2H), 6.85 (t, *J* = 6.2 Hz, 1H), 6.68 (d, *J* = 6.6 Hz, 1H), 4.78 (t, *J* = 5.7 Hz, 1H), 4.67 (s, 2H), 4.66 (s, 2H), 4.57 (s, 2H), 4.55 (s, 2H), 2.38 (s, 3H), 1.71 (s, 6H), 1.64 (s, 6H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 143.6, 142.5, 142.3, 139.9, 139.4, 138.7, 136.5, 133.6, 129.8, 128.4, 127.6, 127.5, 127.1, 108.3, 100.2, 81.2, 74.5, 71.3, 66.9, 64.1, 54.2, 52.6, 51.4, 46.1, 28.8, 26.0, 21.5.



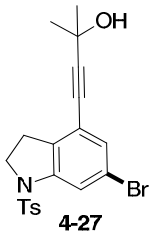
4-25

4-25 (61%)**:** ^{1}**H NMR** (501 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.71 (d, *J* = 8.1 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 3.88 (t, *J* = 8.5 Hz, 2H), 2.93 (t, *J* = 8.5 Hz, 2H), 2.40 (s, 3H), 1.92 (br, 1H), 1.56 (s, 6H); 1.06 (m, 6H), 0.94 (m, 9H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 144.5, 143.0, 135.0, 133.7, 132.9, 130.4, 129.9, 129.6, 127.6, 127.3, 119.1, 115.5, 102.0, 80.9, 65.7, 49.4, 31.1, 28.4, 28.2, 21.6, 7.85, 7.79, 5.65, 5.39; **HRMS** (ESI) calcd for $C_{26}H_{35}BrNO_3SSi$ $[M+H]^+$: 540.1290, found 540.1294.



4-26

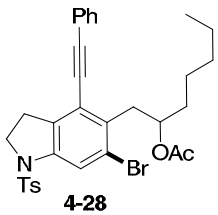
4-26 (68%)**:** ^{1}**H NMR** (501 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.75 (d, *J* = 7.9 Hz, 2H), 7.42 – 7.34 (m, 3H), 7.32 (d, *J* = 7.9 Hz, 2H), 7.23 (d, *J* = 7.3 Hz, 2H), 3.95 (t, *J* = 8.5 Hz, 2H), 2.96 (t, *J* = 8.5 Hz, 2H), 2.43 (s, 3H), 1.60 (br, 1H), 1.25 (s, 6H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 144.6, 141.9, 139.7, 133.6, 133.5, 130.0, 129.8, 127.8, 127.7, 127.4, 122.2, 121.0, 118.1, 102.1, 78.5, 65.4, 49.9, 30.9, 27.8, 21.6.



4-27

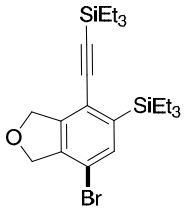
4-27 (71%)**:** ^{1}**H NMR** (501 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.68 (d, *J* = 8.1 Hz, 2H), 7.27 (d, *J* = 8.1 Hz, 2H), 7.14 (s, 1H), 3.90 (t, *J* = 8.6 Hz, 2H), 2.90 (t, *J* = 8.6 Hz, 2H), 2.39 (s, 3H), 2.02 (br, 1H), 1.56 (s, 6H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 144.6, 143.2, 133.6, 133.2, 129.9, 128.8, 127.2, 121.2, 120.9, 117.6, 99.1, 78.1, 65.5, 49.8, 31.4, 27.2, 21.6; **HRMS**

(ESI) calcd for $C_{20}H_{21}BrNO_3S$ $[M+H]^+$: 434.0426, found 434.0418.



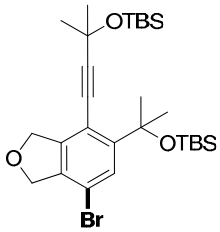
4-28

4-28 (63%)**:** ^{1}**H NMR** (501 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.68 (d, *J* = 8.0 Hz, 2H), 7.47 (m, 2H), 7.35 (m, 3H), 7.28 (d, *J* = 8.0 Hz, 2H), 5.29 (m, 1H), 3.93 (t, *J* = 8.5 Hz, 2H), 3.27 (dd, *J* = 13.5, 9.0 Hz, 1H), 3.16 (dd, *J* = 13.5, 4.0 Hz, 1H), 2.98 (m, 2H), 2.39 (s, 3H), 1.90 (s, 3H), 1.65 (m, 2H), 1.44 – 1.16 (m, 6H), 0.84 (t, *J* = 6.4 Hz, 3H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 170.3, 144.5, 141.3, 134.4, 134.2, 133.7, 131.5, 129.9, 128.9, 128.5, 127.3, 124.2, 122.6, 122.0, 118.8, 97.8, 85.1, 73.8, 49.9, 38.9, 34.7, 31.7, 28.0, 25.1, 22.5, 21.6, 21.1, 14.0; **HRMS** (ESI) calcd for $C_{32}H_{35}BrNO_4S$ $[M+H]^+$: 608.1470, found 608.1468.



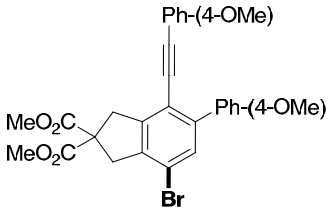
4-29

4-29 (70%)**:** ^{1}**H NMR** (501 MHz, $CDCl_3$) δ 7.40 (s, 1H), 5.23 (s, 2H), 5.11 (s, 2H), 1.03 (t, *J* = 7.9 Hz, 9H), 0.95 (s, 15H), 0.67 (q, *J* = 7.9 Hz, 6H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 144.9, 141.7, 140.2, 136.8, 121.1, 115.9, 103.6, 100.2, 75.6, 75.4, 7.42, 4.27, 3.10; **HRMS** (ESI) calcd for $C_{22}H_{36}BrOSi_2$ $[M+H]^+$: 451.1488, found 451.1493.



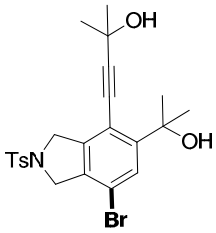
4-30

4-30 (67%)**:** ^{1}**H NMR** (501 MHz, $CDCl_3$) δ 7.96 (s, 1H), 5.23 (s, 2H), 5.10 (s, 2H), 1.77 (s, 6H), 1.57 (s, 6H), 2.41 (s, 6H), 1.00 (s, 9H), 0.87 (s, 9H), 0.19 (s, 6H), 0.15 (s, 6H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 153.1, 145.4, 137.3, 128.4, 115.6, 111.4, 104.7, 79.1, 75.81, 75.6, 75.3, 67.1, 32.6, 30.1, 26.0, 25.6, 18.4, 17.9, -1.80, -2.78; **HRMS** (ESI) calcd for $C_{28}H_{46}BrO_3Si_2$ $[M-H]^+$: 525.2169, found 525.2181.



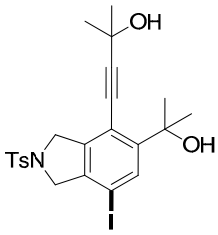
4-31

4-31 (79%)**:** ^{1}**H NMR** (501 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.7 Hz, 2H), 7.41 (s, 1H), 7.31 (d, *J* = 8.8 Hz, 2H), 6.97 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 3.90 (s, 2H), 3.86 (s, 3H), 3.80 (s, 9H), 3.70 (s, 2H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 171.7, 159.8, 159.3, 144.2, 143.7, 138.5, 134.2, 132.9, 131.7, 131.1, 130.4, 118.6, 117.3, 115.3, 114.1, 114.0, 113.4, 96.9, 85.3, 58.5, 55.3, 53.2, 42.22, 42.20; **HRMS** (ESI) calcd for $C_{29}H_{25}BrO_6$ $[M]^+$: 548.0835, found 548.0843.



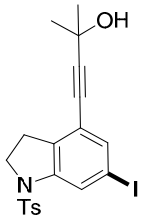
4-32

4-32 (64%)**: ^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.0 Hz, 2H), 7.64 (s, 1H), 7.33 (d, *J* = 8.0 Hz, 2H), 4.69 (s, 2H), 4.54 (s, 2H), 2.84 (br, 1H), 2.71 (br, 1H), 2.41 (s, 3H), 1.67 (s, 6H), 1.63 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 151.8, 143.9, 141.9, 135.3, 133.6, 130.0, 127.9, 127.5, 117.2, 113.3, 105.7, 78.0, 72.8, 65.7, 55.3, 55.0, 31.1, 29.7, 21.5; **HRMS** (ESI) calcd for $C_{23}H_{27}BrNO_4S$ $[M+H]^+$: 492.0844, found 492.0847



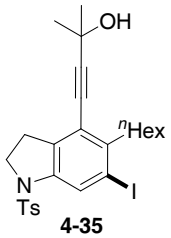
4-33

4-33 (55%)**: ^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.78 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 7.26 (s, 1H), 4.74 (s, 2H), 4.49 (s, 2H), 2.73 (br, 1s), 2.51 (br, 1H), 2.41 (s, 3H), 1.67 (s, 6H), 1.63 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 151.3, 143.9, 140.8, 139.4, 133.8, 133.7, 130.0, 127.5, 114.2, 106.0, 89.8, 78.1, 72.7, 65.7, 58.6, 55.4, 31.1, 29.7, 21.5; **HRMS** (ESI) calcd for $C_{23}H_{27}INO_4S$ $[M+H]^+$: 540.0706, found 540.0701.



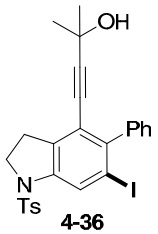
4-34

4-34 (63%)**: ^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.67 (d, *J* = 8.2 Hz, 2H), 7.35 (s, 1H), 7.28 (d, *J* = 8.2 Hz, 2H), 3.89 (t, *J* = 8.6 Hz, 2H), 2.90 (d, *J* = 8.6 Hz, 2H), 2.40 (s, 3H), 1.98 (br, 1H), 1.55 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 144.6, 143.1, 134.8, 134.0, 133.6, 129.9, 127.2, 123.2, 121.6, 99.1, 91.6, 77.8, 65.6, 49.7, 31.4, 27.3, 21.6; **HRMS** (ESI) calcd for $C_{20}H_{21}INO_3S$ $[M+H]^+$: 482.0287, found 482.0287.



4-35

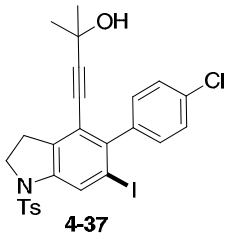
4-35 (55%)**: ^{1}H NMR** (501 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.67 (d, *J* = 8.2 Hz, 2H), 7.27 (d, *J* = 8.2 Hz, 2H), 3.87 (t, *J* = 8.5 Hz, 2H), 2.89 (d, *J* = 8.5 Hz, 2H), 2.83 (m, 2H), 2.39 (s, 3H), 1.94 (br, 1H), 1.58 (s, 6H), 1.49 (m, 2H), 1.40 (m, 2H), 1.31 (m, 4H), 0.89 (m, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 144.4, 141.9, 140.5, 135.3, 133.6, 129.8, 129.6, 127.3, 124.9, 119.2, 115.5, 101.6, 97.9, 78.1, 65.7, 49.8, 39.2, 31.8, 31.6, 31.5, 29.5, 29.3, 29.1, 27.9, 22.6, 21.5, 14.1; **HRMS** (ESI) calcd for $C_{26}H_{33}INO_3S$ $[M+H]^+$: 566.1226, found 566.1229.



4-36

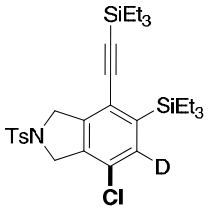
4-36 (51%)**: ^{1}H NMR** (501 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.74 (d, *J* = 8.2 Hz, 2H), 7.38 (m, 3H), 7.32 (d, *J* = 8.2 Hz, 2H), 7.17 (d, *J* = 8.2 Hz, 2H), 3.94 (t, *J* = 8.5 Hz, 2H), 2.96 (t, *J* = 8.5 Hz, 2H), 2.43 (s, 3H), 1.59 (br, 1H), 1.23 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 144.5, 143.0, 135.0, 133.7, 132.9, 130.4, 129.9, 129.6, 127.6, 127.2, 119.1, 115.5, 102.0, 80.9, 65.7, 49.4, 31.1, 28.4, 28.2, 21.6, 7.85, 7.79, 5.65, 5.39; **HRMS** (ESI) calcd for

$C_{26}H_{25}INO_3S$ $[M+H]^+$: 558.0600, found 558.0589.



4-37

4-37 (61%)**:** **^{1}H NMR** (501 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.73 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.2 Hz, 2H), 3.93 (t, *J* = 8.5 Hz, 2H), 2.96 (t, *J* = 8.5 Hz, 2H), 2.42 (s, 3H), 1.67 (br, 1H), 1.27 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 144.6, 142.1, 141.4, 134.7, 133.7, 133.6, 131.2, 129.9, 128.0, 127.3, 124.0, 119.9, 102.4, 97.1, 78.3, 65.3, 49.8, 49.8, 30.9, 27.8, 21.6; **HRMS** (ESI) calcd for $C_{26}H_{24}ClINO_3S$ $[M+H]^+$: 592.0210, found 592.0209.



4-38

4-39 (85%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.1 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 4.67 (s, 2H), 4.65 (s, 2H), 2.41 (s, 3H), 1.05 (t, *J* = 7.9 Hz, 9H) 0.92 (s, 15H), 0.69 (q, *J* = 7.9 Hz, 6H) ; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 143.8, 142.0, 141.9, 135.2, 133.8, 129.9, 128.4, 127.6, 122.0, 103.0, 101.1, 55.0, 54.0, 21.5, 7.44, 7.38, 4.26, 2.98; **HRMS** (ESI) calcd for $C_{29}H_{41}DClNO_2SSi_2$ $[M]^+$: 561.2304, found 561.2314.

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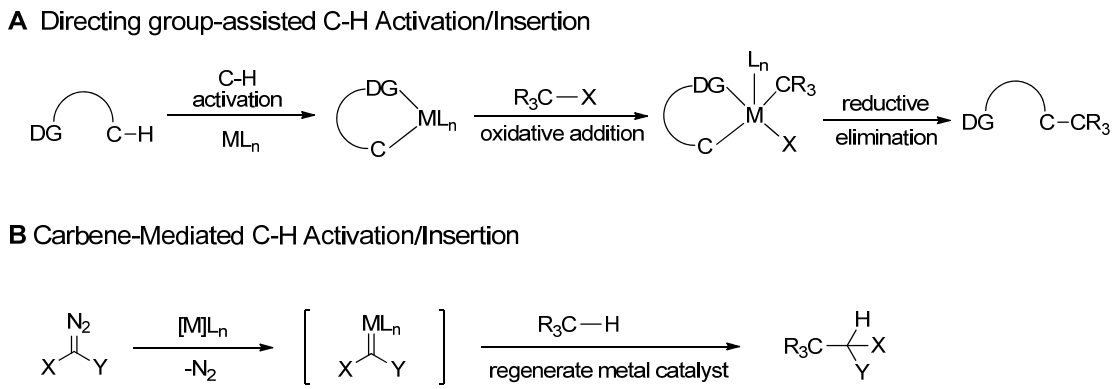
Chapter 5. Alkane C–H Insertion by Aryne Intermediates with a Silver Catalyst

5.1. Introduction

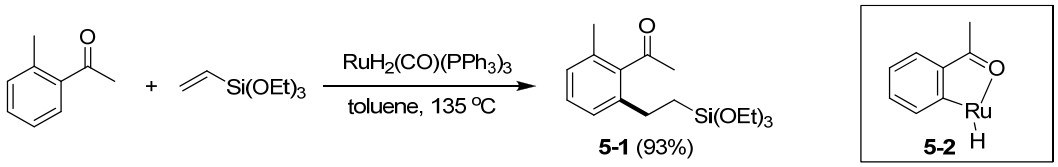
Alkane C–H bond is one of the most abundant chemical bonds in organic compounds. However, activation of the alkane C–H bond still remains as one of the most challenging problems because of its low reactivity associated with the large kinetic barrier to cleave the C–H bond and the difficulty in controlling the chemio- and regioselectivity.[1-6] To engage the inert alkane C–H bonds in typical chemical transformations, availability of highly reactive species that can interact with the stable electron pairs of alkane C–H bonds is required. Toward this goal, many research groups have focused on developing C–H bond activation strategies relying on highly electrophilic metal complexes that can activate C–H bonds in the presence of heteroatom directing groups (**Scheme 5.1**, **A**).[3-4] In alternative approaches, metal-carbenoide or nitrenoid-based direct insertion into C(sp^3)–H bonds were developed, which have witnessed significant growth in the past decades especially for stereo- and enantioselective processes (**Scheme 5.1**, **B**).[7]

Scheme 5.1. Traditional-based C–H bond functionalization strategies



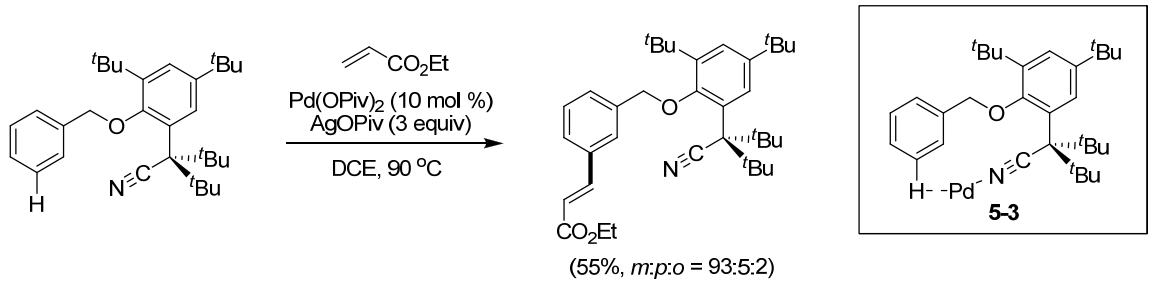
Murai reported the first example of a chelation-assisted regioselective C–H bond activation of arene followed by its addition with alkenes.[8] For example, acetophenone is regioselectively added onto vinyl silane to form an *ortho*-alkylated product **5-1** in the presence of a catalytic amount of

$RuH_2(CO)(PPh_3)_3$ (Eq. 1). It was proposed that the reaction involved the coordination of the carbonyl group to the ruthenium metal center, which is placed in a favorable position for the activation of the *ortho* C–H bond to form ruthenium hydride complex **5-2**. Since this seminal report by Murai on the ruthenium-catalyzed activation of aromatic C–H bonds, the directing group-assisted approach has significantly improved such that it can be used as a standard transformation in the synthesis of even complex natural products.



(1)

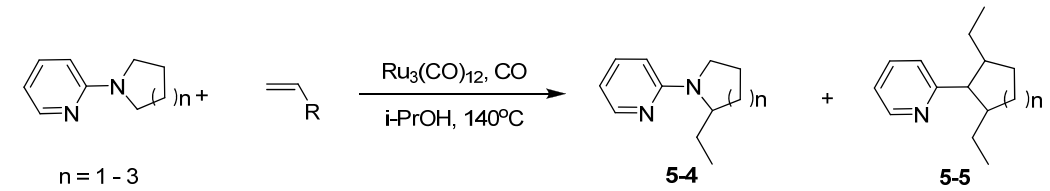
Although the potential synthetic utility of this strategy has been demonstrated by many research groups, the concept of chelating group-promoted reactivity has fundamental limitation to perform the reaction only at the *ortho*-C–H bonds to the directing group. To overcome this limitation, Yu and co-workers developed a new template to selectively activate *meta*-C–H bonds where the nitrile group coordinates in an end-on mode to assemble a cyclophane-like transition state **5-3** there by activating only *meta*-C–H bonds (Eq. 2).[9]



(2)

This new strategy for directed *meta*-C–H activation provides a useful route for the synthesis of functionalized arenes including hydrocinnamic acids, 2-biphenylcarboxylic acids, unnatural amino acids, and pharmaceuticals with complex substitution patterns that are difficult to access by using conventional C–H activation protocols.

Heteroatom-directed metallation is a powerful method for regioselective functionalization of unreactive arene C–H bonds. This chelation-assisted approach was successfully applied to a member of alkane C–H activation events.



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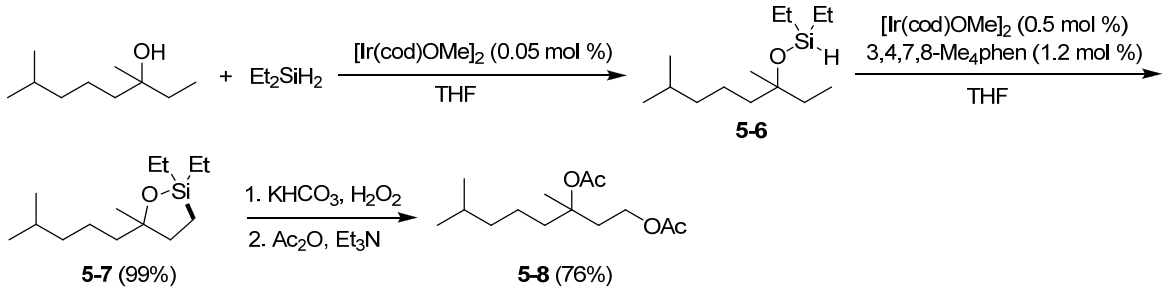


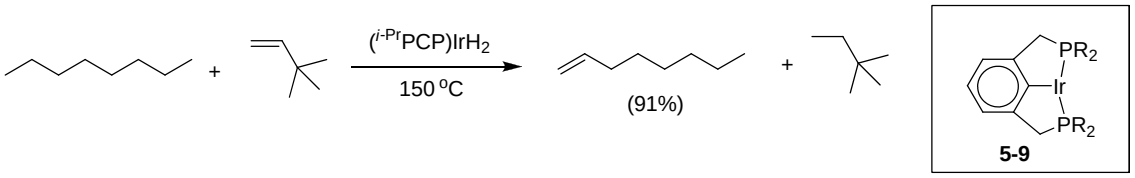
(4)

For example, Murai reported catalytic reactions that involve the cleavage of the sp^3 C-H bond adjacent to the nitrogen atom in *N*-2-pyridynyl alkylamines.[10] The use of $Ru_3(CO)_{12}$ as the catalyst resulted in the insertion of alkenes to sp^3 C-H bond of amine to give the coupling products **5-4** and **5-5**. The presence of a pyridine ring on the nitrogen of cyclic amines is essential for the reaction to proceed, suggesting the importance of the coordination of the pyridine nitrogen to the ruthenium. Recently, Hartwig developed a catalytic functionalization of unactivated primary C–H bonds directed by a hydroxyl group (Eq. 4).[11] Iridium catalyzed dihydrogenative coupling of an alcohol with dihydrosilane provided hydridosilyl ether **5-6** from which the Si–H moiety undergoes site-selective γ-functionalization of primary C–H bond to form oxasilacyclopentane **5-7**. Subsequent Tamao-Fleming oxidation and acetate protection of the resulting diol affords final product **5-8**. The scope of this new C–H bond functionalization protocol encompasses alcohols and ketones possessing diverse substituent patterns and auxiliary functionalities.

Although heteroatom-directed C–H activation is a powerful method for facilitating the activation of inert C–H bonds in regioselective manner, the directing group needs to be removed after all when it is

not a part of the target molecules, which is a significant limitation of this approach. In addition, the necessity of stoichiometric amount of activators such as oxidants and bases or other additives significantly compromise the practicality of the current metal-catalyzed C–H functionalization approaches.

As opposed to the directing group-based approach, direct and site selective alkane C–H bond functionalization without directing group is rare. Jensen and Goldman developed a selective catalytic system for the dehydrogenation of linear alkanes to give α-olefins using iridium "pincer" complexes ($^{i\text{-}Pr}$PCP)IrH_2 ($^{i\text{-}Pr}$PCP = 2,6-*bis*-[di(*i*-propyl)phosphinomethyl]phenyl) (Eq. 5). However, non-selective isomerization of the newly formed double bond limits the yield of the α-olefin products obtained under these reaction conditions.[12] Preliminary mechanistic study suggests that the highly reactive 14-electron iridium intermediate **5-9** is responsible for the C–H bond cleavage. Hartwig and co-workers reported a rhodium complex $Cp^*Rh(\eta^4\text{-}C_6Me_6)$ catalyzed regiospecific functionalization of linear alkanes with borane reagents to form primary alkylboranes **5-10** (Eq. 6).[13] These borylated products are useful synthetic intermediates, since they can be easily converted to amines, alcohols, alkenes, and other classes of functionalized molecules.



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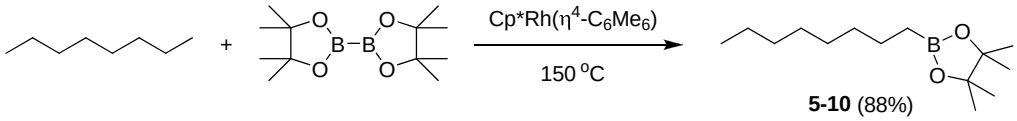
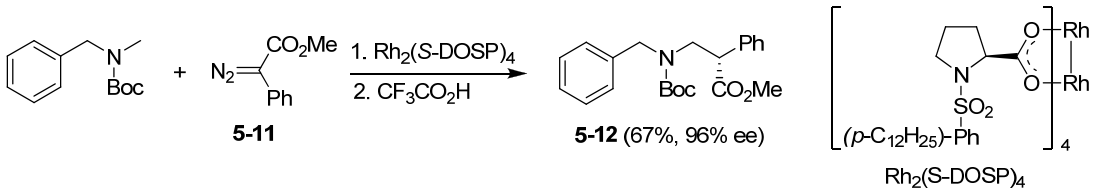
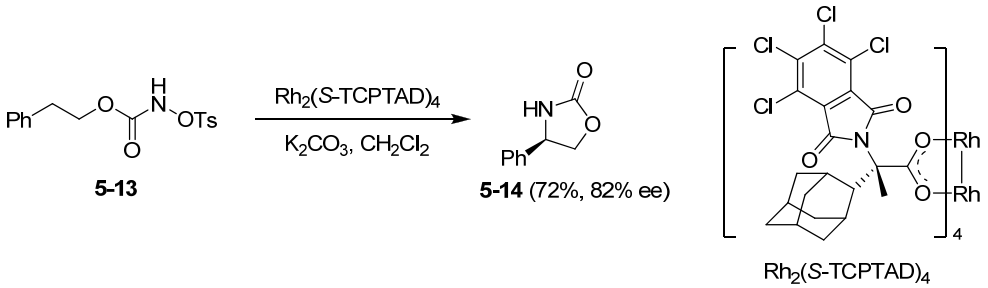


(6)

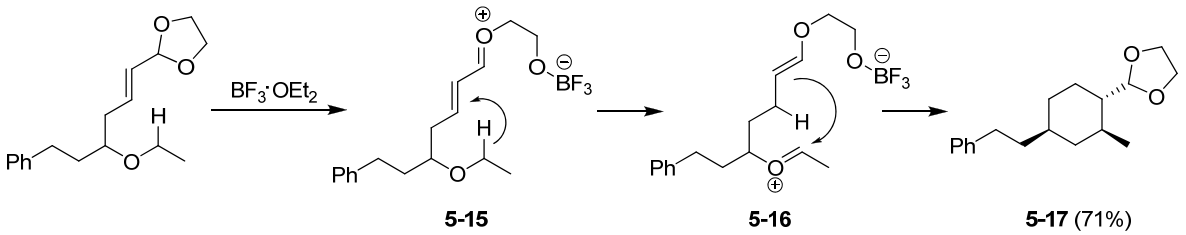
Alternatively, the metal-carbenoides or nitrenoids-based direct insertion into C(sp^3)–H bonds constitutes another site selective C–H activation method, which has witnessed significant growth in the past decades especially for stereo- and enantioselective processes.[7] Davies and co-workers reported the intermolecular C–H insertion of carbenoids derived from aryldiazoacetates **5-11** catalyzed by [Rh_2(S-DOSP)$_4$] (Eq. 7).[14] This method allowed for the asymmetric synthesis of substituted-amino acids **5-12**

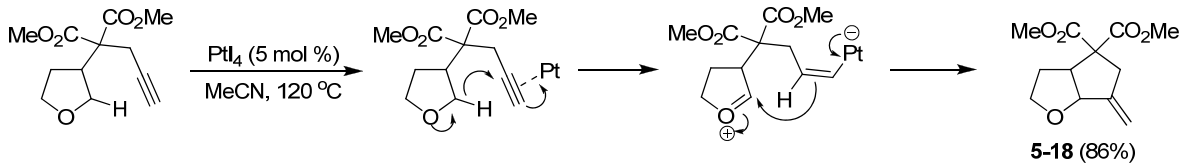
with good chemo- and enantioselectivity. This example illustrates the important controlling influences in steric factors, because the electronically most activated site in the compound, the benzylic carbon, is sterically inaccessible and selective functionalization occurs at the *N*-methyl group.[15,16] Label and co-workers reported an enantioselective C–H amination catalyzed by chiral rhodium catalyst [Rh_2(S-TCPTAD)$_4$] using *N*-tosyloxyamide **5-13** as metal nitrenoide precursor (Eq. 8).[17] The site selectivity for C–H amination is controlled by the size of the tether and the formation of five-membered ring **5-14** is generally favored.





Recently, Lewis acid-catalyzed remote C–H bond activation has been described as a new paradigm of C–H activation, where the pivotal step is the hydride transfer from a tethered carbon center to the Lewis acid-activated carbon–heteroatom multiple bond to form a carbocationic intermediate.[18,19]

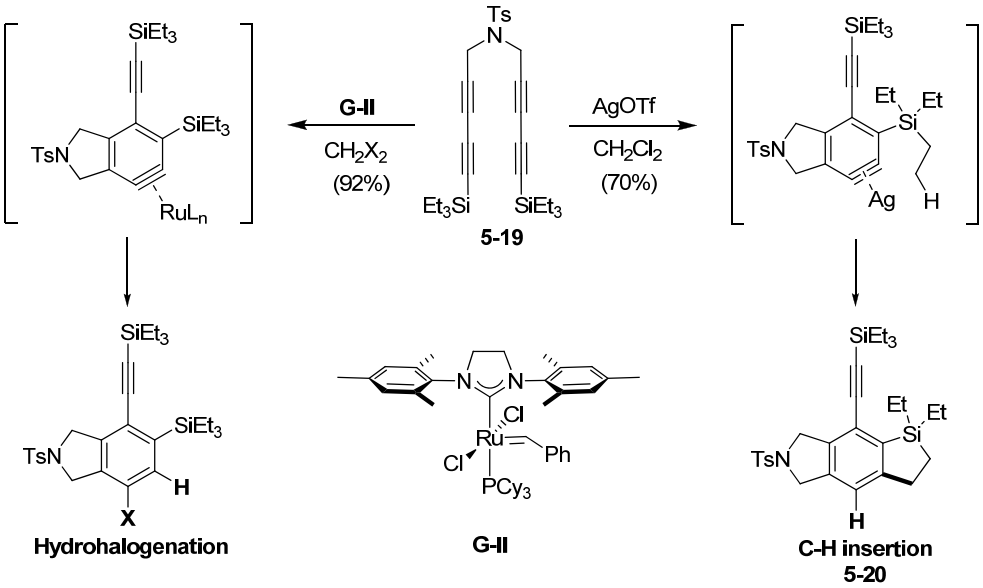




Sames and co-workers developed a Lewis acid catalyzed alkylation by direct intramolecular coupling of C–H bond and reactive alkenyl oxocarbenium intermediates (Eq. 9).[18a] Lewis acid, $BF_3{\cdot}OEt_2$ opens the cyclic acetal, forming the alkenyl oxocarbenium intermediate **5-15**, which promotes hydride transfer aided by the lone pair electrons of the oxygen substituent to form oxocarbenium-enol ether intermediate **5-16**. After C–C bond formation occurs between the oxocarbenium and enol ether, the original acetal formation completes the process, producing the product **5-17** in 71% yield. Similarly, the direct coupling reaction of unactivated alkyne and C–H bond catalyzed by platinum tetraiodide (Eq. 10) was achieved.[18e] The unactivated terminal alkyne serves as the hydride acceptor via the formation of a vinyl cation, which allows a rapid access to heteroatom-containing bicyclic products **5-18**.

5.2. Results and Discussion

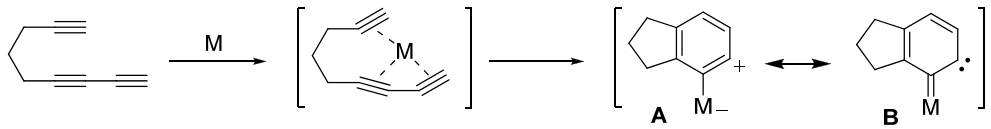
Scheme 5.2. Initial discovery of sp^3 C–H insertion by aryne



Inspired by the successful development of ruthenium alkylidene-catalyzed hydrohalogenation of aryne generated in situ from *bis*-1,3-diyne in the presence of haloalkanes, we explored the reactivity of *bis*-1,3-diynes with numbers of different metal complexes. While we were screening the reactivity of the *bis*-1,3-diyne substrate **5-19** with various transition metal complexes, we discovered a facile C–H

insertion of an aryne intermediate to generate product **5-20** when catalytic amount of AgOTf (10 mol %) was employed in CH_2Cl_2, where hydrohalogenation product was not detected.[20] The salient feature of this transformation is the direct conversion of an acyclic precursor to a complex multiple ring product through a selective C–H bond activation at the β-position to the silicon (**Scheme 5.2**).

Even though arynes have been employed in organic synthesis for more than a century, alkane C–H bond functionalization by arynes has not been reported in the literature except for that with electron-rich aromatic C–H bonds.[21,22]



(11)

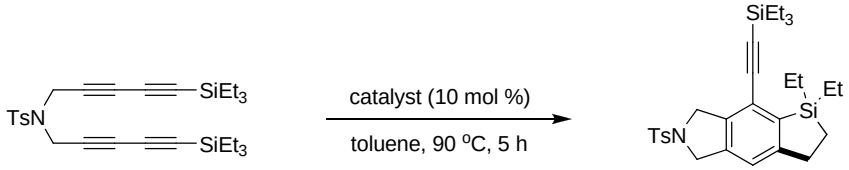
We surmised that the effective C–H bond functionalization should be the consequence of the presence of a suitable metal catalyst that would generate an unusually reactive intermediate such as a metal-stabilized aryl cation (**A** in Eq. 11) or a 1,2-*bis*-carbene-carbenoid (**B** in Eq. 11). Different from free arynes, these metal-complexed arynes[23] have a subtle balance for its stability and reactivity such that even the least nucleophilic C–H bonds can be activated.

5.2.1. Catalyst Screen and Reaction Scope of the C–H Insertion Reaction of Silicon-Containing Substrates

Encouraged by this initial discovery on C–H insertion, the reaction parameters were subsequently optimized including the solvent, which clearly indicated that the C–H insertion was best achieved in non-polar solvent such as toluene wherein the C–H insertion products were obtained almost quantitatively. We then evaluated the catalytic activity of other metal complexes with symmetric *bis*-1,3-diyne substrate **5-19** (**Table 5-1**). Various silver salts including $AgSbF_6$, $AgNO_3$, AgOAc and AgO were tested. However, only AgOTf and $AgSbF_6$ provided reasonable yields (95% and 68%, entries 1–2). Other silver salts, such as $AgNO_3$, AgOAc and AgO showed significantly low reactivity, affording 8 to 16% yields of the desired

C–H insertion products (entries 3–5). Running the C–H insertion reaction at 60 °C with AgOTf did not show any C-H insertion activity and some starting material was recovered. A combination of ruthenium carbonyl $Ru_3(CO)_{12}$ and $HBF_4{\cdot}OEt_2$, known to catalyze hydroamination and C–H activation, also promoted the reaction smoothly, providing 89% yield of the C–H insertion product, but $Ru_3(CO)_{12}$ alone didn't show any catalytic activity (entry 6). Other metal triflates such as $Sm(OTf)_3$, $In(OTf)_3$, $Sc(OTf)_3$, $Cu(OTf)_2$ and $Zn(OTf)_2$ were completely ineffective in this case (entries 7–11). Moreover, other metal complexes known for their high affinity toward alkynes such as PPh_3AuCl and $PtCl_2$ did not exhibit any reactivity for this aryne C–H insertion (entries 12–13).[24] Without catalyst under otherwise identical conditions, the substrate decomposed and no desired C–H insertion product was observed (entry 14).

Table 5.1. Catalyst screening for the C–H insertion of *bis*-1,3-diyne containing triethylsilyl group



5-19 **5-20**

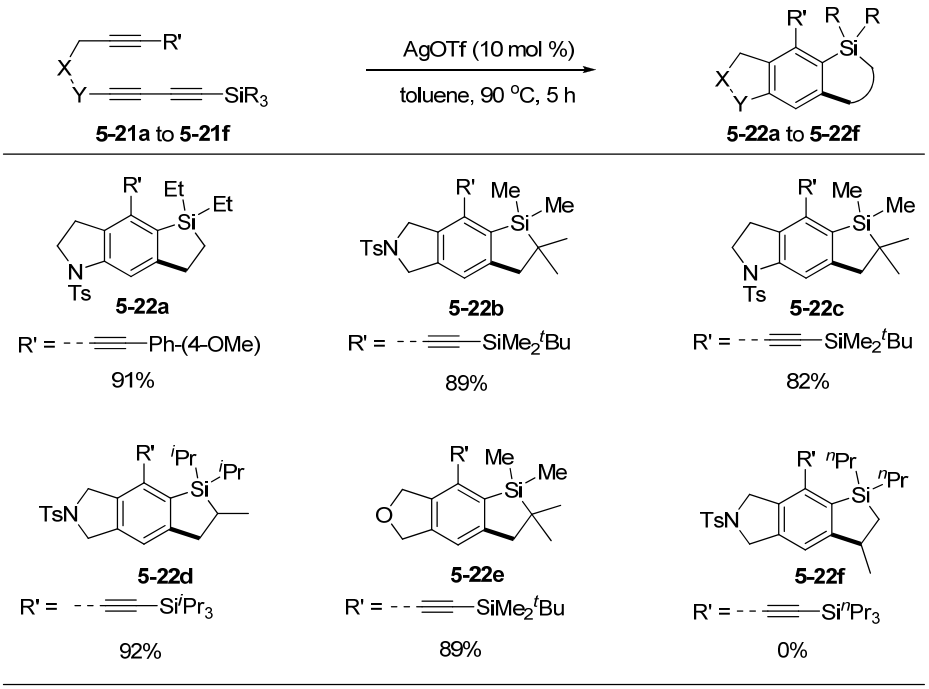
entry	catalyst	yield (%)[a]	entry	catalyst	yield (%)[a]
1	AgOTf	95[b]	8	$In(OTf)_3$	0
2	$AgSbF_6$	68	9	$Sc(OTf)_3$	0
3	$AgNO_3$	8	10	$Cu(OTf)_2$	0
4	AgOAc	16	11	$Zn(OTf)_2$	0
5	AgO	13	12	PPh_3AuCl	0
6	$Ru_3(CO)_{12}$	89[c,d]	13	$PtCl_2$	0
7	$Sm(OTf)_3$	0	14	none	0

[a] Yield was determined by ^{1}H NMR. [b] No conversion at 60 °C.

Having optimized the reaction conditions for the C–H insertion with an appropriate silver salt, we examined the reaction scope with various silicon-containing substrates. As shown in Table 5-2, regardless of the tether, symmetrical and unsymmetrical *bis*-1,3-diyne substrates **5-21a–e** bearing triethylsilyl, *tert*-butyldimethylsilyl (TBS) and triisopropylsilyl (TIPS) groups, afforded the corresponding C–H insertion product **5-22a–e** in excellent yields (82–92%) via primary C(sp^3)–H bond insertion by arynes. On the

other hand, substrate with tri-^{n}propylsilyl group that contains only secondary C(sp^3)–H bond at the β-carbon to silicon did not provide the expected product **5-22f**. A salient structural feature of these substrates is the strong activating role of the germinal dialkyl substituents that provides the well-known Thorpe-Ingold effect for ring closing reactions.[25]

Table 5.2. Reaction scope of the C–H insertion of *bis*-1,3-diynes containing silyl groups

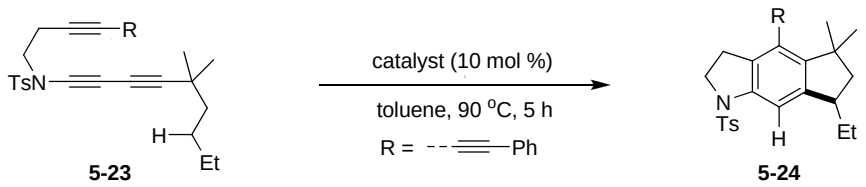


5.2.2. Catalyst Screen and Reaction Scope of the C–H Insertion Reaction of All Carbon-Tethered Substrates

Inspired by the favorable C–H insertion behavior of the trialkylsilyl-containing *bis*-1,3-diynes, we surmised the replacement of the silyl group with an appropriate *gem*-dimethyl containing alkyl group should be tolerant. So we prepared the *bis*-1,3-diyne substrate **5-22** containing ynamide moiety with alkyl substituents possessing *gem*-dimethyl group on propargylic carbon and explored its C–H insertion behavior with various metal complexes (**Table 5-3**). To our surprised, different from the silicon-containing substrates where only AgOTf displayed decent catalytic activity, substrate **5-22** showed similar range of reactivity with AgOTf, $AgSbF_6$, $AgNO_3$ and AgOAc, affording 82–91% yields of the C–

H insertion product **5-23** (entries 1–4). But AgO was not as efficient as other silver complexes, giving 23% yield of the desired product (entry 5). The C–H insertion reaction at lower temperature (60 ^{o}C) did not produce insertion product and some starting material was recovered. Other metal triflates such as $Sm(OTf)_3$, $In(OTf)_3$, $Sc(OTf)_3$, $Cu(OTf)_2$ and $Zn(OTf)_2$ were also found to promote the C–H insertion to generate the product in slightly diminished yields (62–86%, entries 6–10). The cationic ruthenium carbonyl complex generated in suit from $Ru_3(CO)_{12}$ and $HBF_4{\cdot}OEt_2$ showed moderate reactivity, affording 53% yield of the C–H insertion product (entry 11). Au- and Pt- complexes showed no reactivity for substrate **5-23**, and the reaction under thermal condition without catalyst led to the decomposition of the substrate with no vestige of the product **5-24** (entries 12–14).

Table 5.3. Catalyst screening for the C–H insertion of a *bis*-1,3-diyne containing *gem*-dimethyl substituted alkyl group on propargylic carbon



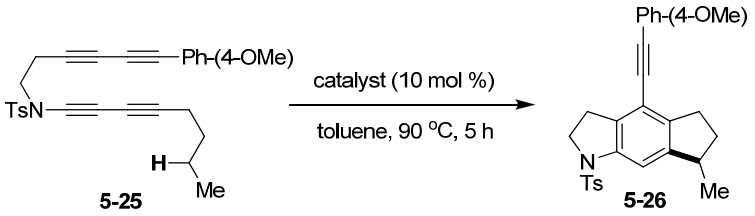
entry	catalyst	yield (%)[a]	entry	catalyst	yield (%)[a]
1	AgOTf	91[b]	8	$Sm(OTf)_3$	62
2	$AgSbF_6$	88	9	$In(OTf)_3$	78
3	$AgNO_3$	82	10	$Sc(OTf)_3$	63
4	AgOAc	85	11	$Ru_3(CO)_{12}$	53[c,d]
5	AgO	23	12	PPh_3AuCl	0
6	$Cu(OTf)_2$	86	13	$PtCl_2$	0
7	$Zn(OTf)_2$	73	14	none	0

[a] Determined by ^{1}H NMR. [b] No conversion at 60 ^{o}C.
[c] $HBF_4{\cdot}OEt_2$ (15 mol%) was used. [d] No conversion without $HBF_4{\cdot}OEt_2$

Next, we prepared the *bis*-1,3-diyne substrate **5-25** lacking *gem*-dimethyl group on propargylic carbon and examined its C–H insertion reactivity with various metal complexes (**Table 5-4**). The reaction of **5-25** with AgOTf under otherwise identical conditions provided only 30% of the desired C–H insertion product together with a small amount of the OTf-addition product. The low efficiency of the C–H

insertion for this substrate compare to **5-23** containing *gem*-dimethyl group can be explained by the known beneficial effect of the germinal dialkly group on ring closure reactions. When we switched the catalyst to $AgSbF_6$, the yield was increased from 30 to 62%. Further optimization by changing the solvent to iodobenzene produced tricyclic product **5-26** in 78% yield. Other metal complexes, which have been shown promising results in C–H insertion reaction with substrate **5-23** were inefficient in this case.

Table 5.4. C–H insertion of substrate containing alkyl substituent without *gem*-dimethyl group

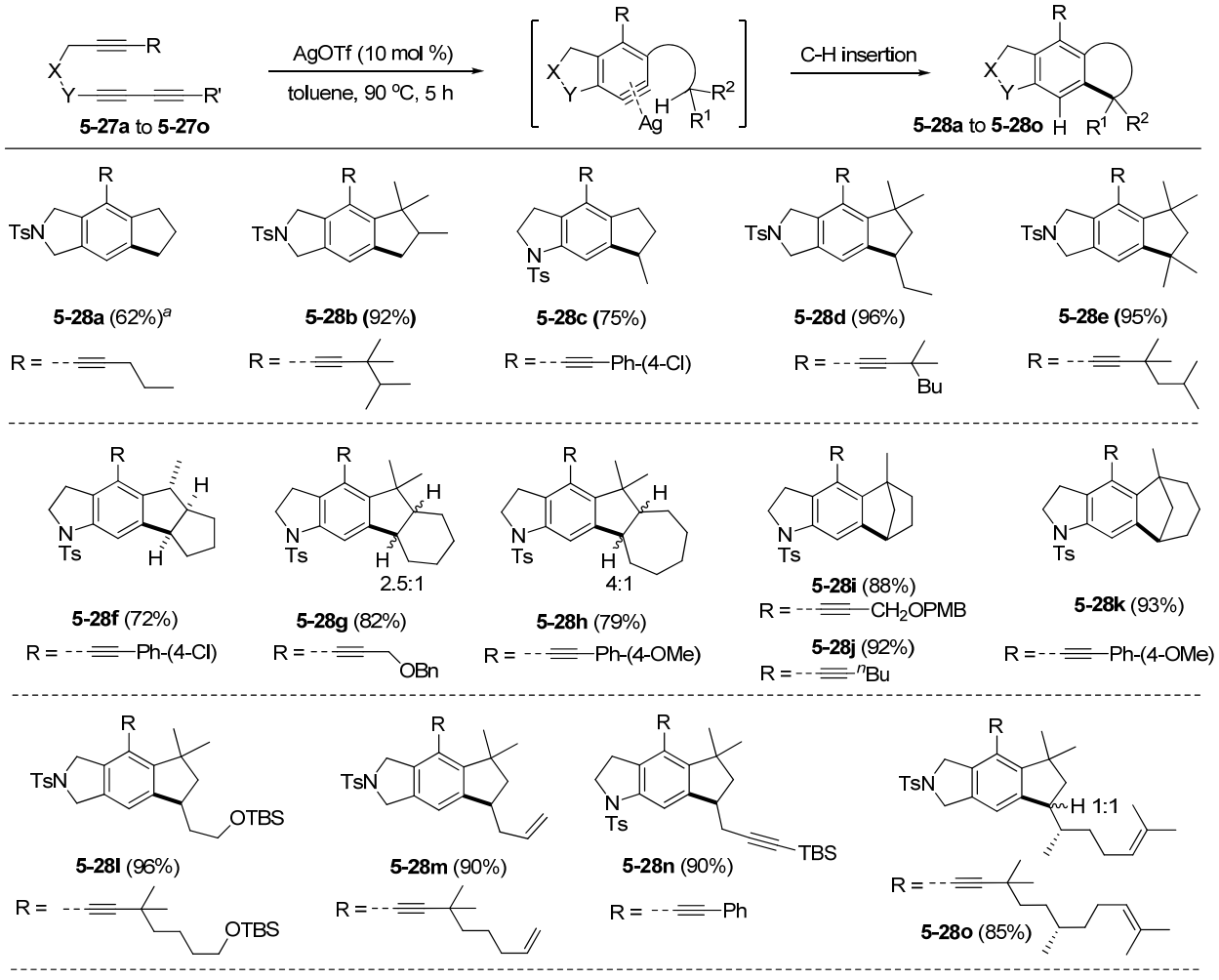


entry	catalyst	yield (%)[a]
1	AgOTf	30
2	$AgSbF_6$	62 (78)[b]
3	$AgNO_3$	<10
4	$Cu(OTf)_2$	0
5	$Cu(CH_3CN)_4PF_6$	0
6	$Cu(OAc)_2$	0

[a]Yield was determined by ^{1}H NMR. [b]Iodobenzene was used as solvent.

The scope of the C–H insertion reaction was then explored with various symmetrical and unsymmetrical *bis*-1,3-diynes (**Table 5-5**). In general, 1°, 2°, and 3° C–H bonds were efficiently inserted into aryne intermediate to afford five-member ring products. The C–H insertion of substrate **5-27a** containing primary C–H bond without *gem*-dimethyl group at propargylic position was best achieved by treating the substrate with $AgSbF_6$ (10 mol %) in iodobenzene to form product **5-28a** in 62% yield. C–H insertion of substrate **5-27b** containing primary C–H bond with *gem*-dimethyl group was much more efficient even under standard reaction conditions (AgOTf, toluene), providing tricyclic product **5-28b** in 92 % yield.

Table 5.5. Reaction scope of the C–H insertion reaction of *bis*-1,3-diynes

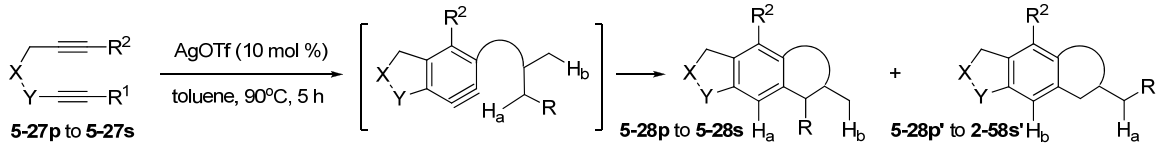


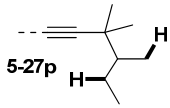
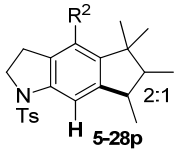
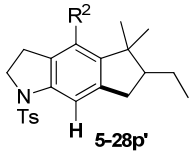
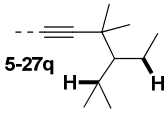
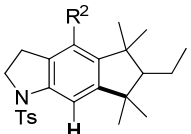
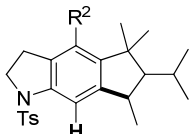
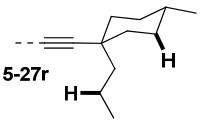
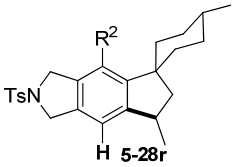
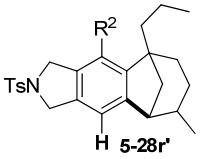
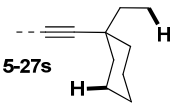
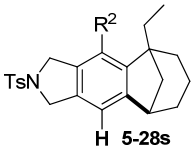
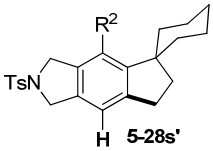
Isolated yields are indicated below each entry. [a] Reactions were performed with $AgSbF_6$ (10 mol %) in iodobenzene and the reported yield was measured by ^{1}H NMR with an internal standard.

The reaction of **5-27c** without *gem*-dimethyl group was also performed with $AgSbF_6$ in iodobenzene, affording secondary C–H bond insertion product **5-28c** in good yield (75%). Substrates **5-27d** and **5-27e** bearing 2° and 3° C–H bond, respectively, afforded tricyclic products **5-28d** and **5-28e** with nearly quantitative yields. For substrate **5-27f** containing mono-methyl group, the 2° C–H bond on the cyclopentyl moiety was inserted to give **5-28f** in 72% yield as a single diastereomer. On the other hand, when the reaction was performed with substrates **5-27g** and **5-27h** carrying *gem*-dimethyl groups, the C–H insertion of the 2° C–H bonds on the cyclohexyl and cycloheptyl moieties generated diastereomeric mixtures **5-28g** and **5-28h**. Interestingly, bridged bicycle frameworks, such as

bicyclo[2,2,1]heptanes **5-28i** and **5-28j** as well as bicyclo[3,2,1]octane **5-28k**, were created in high yields. Substrates **5-28l–n** containing silyl ether, alkene, and alkyne functionalities were tolerant under these reaction conditions. The existing stereogenic center on *bis*-1,3-diyne **5-27o** did not impose any stereochemical bias for the diastereotopic C–H insertion event, affording **5-28o** as a 1:1 diastereomeric mixture in 85% yield.

Table 5.6. Chemoselectivity of the C–H insertion



Entry	R^1	R^2	Selectivity	Products (Yields & Ratio)[c,d]		
1[a]	 5-27p	Ph-(4-OMe)	2° >> 1°	 2:1 5-28p	13 : 1 80%	 5-28p'
2[a]	 5-27q	Ph	3° > 2°	 5-28q	3 : 2 84%	 5-28q'
3[b]	 5-27r	$R^1 = R^2$	2° acyclic > 2° cyclic	 5-28r	4 : 1 93%	 5-28r'
4[b]	 5-27s	$R^1 = R^2$	2° cyclic >> 1° acyclic	 5-28s	10 : 1 88%	 5-28s'

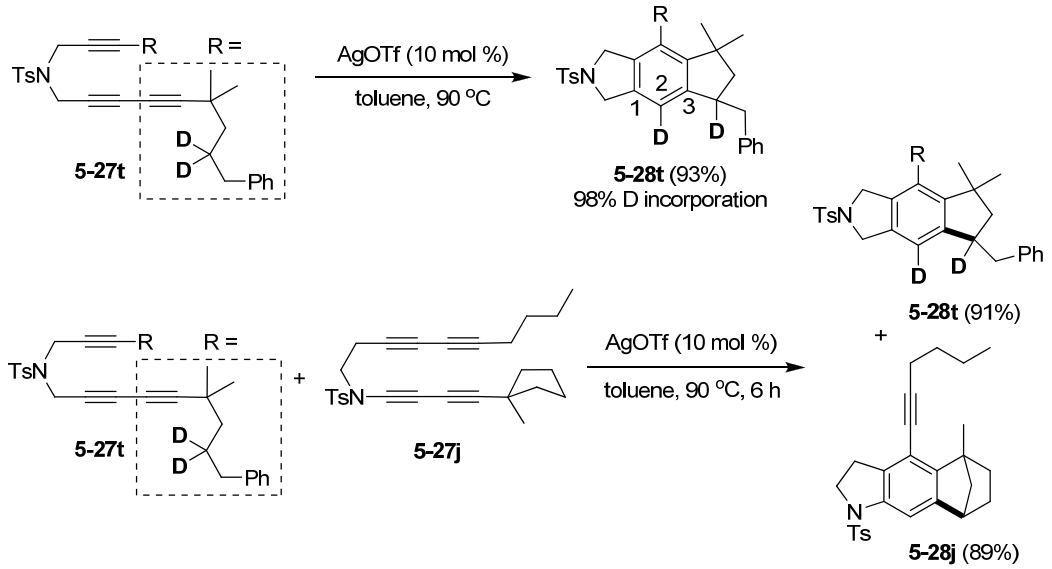
[a] X=NTs, Y=CH_2. [b] X=CH_2, Y=NTs. [c] Isolated yield. [d] Ratio was determined by ^{1}H NMR.

Next, we examined the chemoselectivity of C–H insertion by using substrates **5-27p–s**. When two different C–H bonds are available for the insertion, both electronic and steric factors needed to be considered for their selectivity (**Table 5-6**). A general trend is that the more substituted C–H bond is more reactive toward C–H insertion, and when C–H bonds are on both an acyclic and a cyclic system, the

acyclic C–H bond seems to react preferentially. The secondary C–H bond on substrate **5-27p** was significantly more reactive then primary C–H bond, providing a mixture of **5-28p** and **5-28p′** in 80% yield with a 13:1 ratio (entry 1). For the selectivity between 2° and 3° C–H bonds in substrate **5-27q**, insertion into 3° C–H is slightly more favorable, affording 84% yield with a mixture of **5-28q** and **5-28q′** in 3:2 ratio (entry 2). Substrate **5-27r** carrying both 2° acyclic and cyclic C–H bonds showed insertion preference to acyclic C–H bond probably due to a conformational flexibility that allow an optimal geometry of the transition state for C–H insertion (entry 3). Substrate **5-27s** containing 2° cyclic and 1° acyclic C–H bonds afforded products **5-28s** and **5-28s′** in 10:1 ratio (entry 4), which indicates that the insertion into the electronically favored 2° C–H bond outcompetes that of the conformationally favorable 1° C–H bond.

5.2.3. Mechanistic Study of the C–H Insertion

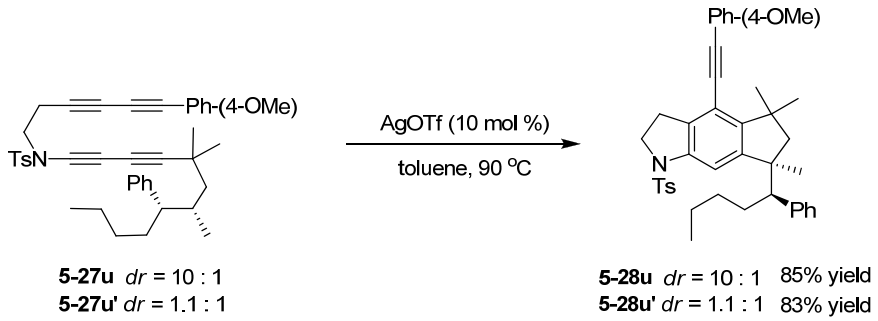
Scheme 5.3. Control experiments with deuterium-labeled substrates



To gain more mechanistic insight into the C–H insertion, a reaction with a deuterium-labeled substrate **5-27t** was carried out, which showed nearly complete deuterium incorporation (>98%) occurred at the C2 position of the arene product **5-28t** (**Scheme 5.3**). When a competition experiment was

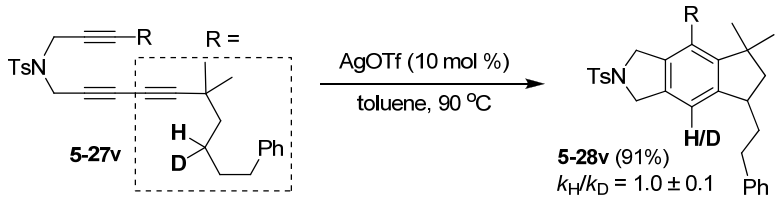
performed with an equimolar mixture of a deuterium-labeled substrate **5-27t** and unlabeled **5-27j**, no crossover products were detected. These results taken together imply that C(sp^3)–H bond-breaking and C(sp^2)–H bond-forming events take place in a concerted rather than a stepwise manner.

To examine the possibility of a radical- or a cation-mediated C–H bond cleavage, diastereomerically-enriched substrate **5-27u** (*dr* = 10:1) and **5-27u'** (*dr* = 1.1:1) were subjected to the standard conditions (10 mol % of AgOTf in toluene at 90 °C), which provided product **5-28u** and **5-28u'** with unchanged diasteromeric ratios (Eq. 12). These results, in combination with the lack of stereochemistry-inducing effect of the substituent at the vicinal stereogenic carbon center as demonstrated in **5-28o** in Table 5.5, further bolster the concerted C–H insertion mechanism, and repudiate a stepwise process via radical or cationic intermediate.



(12)

Finally, a negligible magnitude of deuterium kinetic isotope effect (k_H/k_D = 1.0 ± 0.1) measured during the conversion of mono-deuterated substrate **5-27v** to the observed insertion product **5-28v** suggests that the C(sp^3)–H bond-breaking event is not the rate-limiting step (Eq. 13).[27]



(13)

Although a complete picture of the reaction mechanism remains to be established, a tentative mechanism is formulated (**Figure 5.1**). In this proposed mechanistic scenario, a sequence of bond-

forming events induced by the complexation of silver cation to the diyne moiety would lead to a silver-stabilized aryne intermediate **A** or its resonance form **B**, which then activates an appropriate C–H bond through **C** in a concerted manner or generate another intermediate **D**. Once **D** is formed, a 1,2-hydride shift should deliver the final product and regenerate the catalyst.

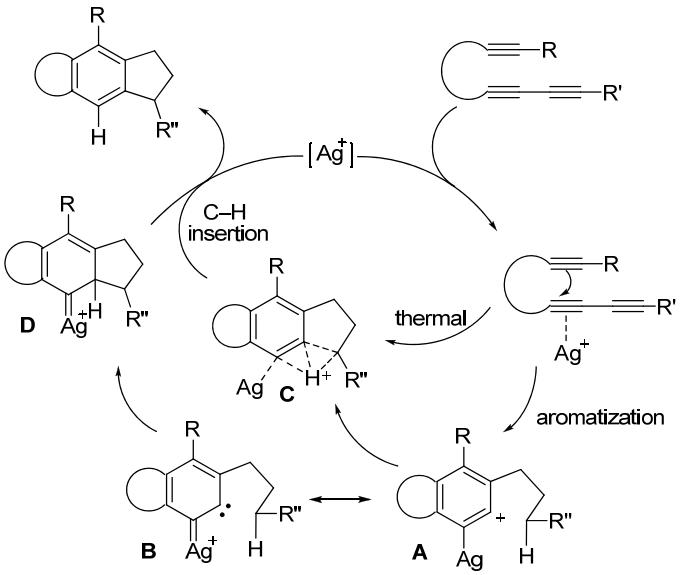


Figure 5.1. Plausible reaction mechanism for the C–H insertion

5.3. Conclusion

In summary, we have developed an efficient method for alkane C–H bond insertion into the aryne intermediate. Requiring only a catalytic amount of silver complex, this aryne-based C–H insertion has evolved as a novel alkane C–H activation to form carbon-carbon bonds. The simplicity of operation, broad substrate scope, and excellent site-selectivity of this unprecedented C–H activation method would inspire the synthesis of natural products, new drug candidates and pharmaceutical agents in green and atom-economical manners.

5.4. Experimental Details

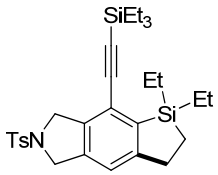
5.4.1. General Information (See Chapter 1.4.1)

5.4.2. General Procedure for the Synthesis of Symmetrical and Unsymmetrical *bis*-I,3-Diynes (Same Procedures in Chapter 4.4.2 and 4.4.3)

5.4.3. General Procedure for the C–H Insertion Reaction: In a glove box, *bis*-1,3-diyne substrate **5-27** (0.1 mmol) and AgOTf (0.01 mmol) were dissolved in 5 mL of toluene in a thick-walled 25 mL Schlenk tube equipped with a magnetic stirring bar. The reaction tube was brought out of the box, and was stirred in an oil bath at 90 °C for 5 h. The tube was opened to air at room temperature and solvent was removed from a rotary aspirator. Crude product was purified by flash column chromatography (SiO_2, hexanes/EtOAc as eluting solvents) to afford the desired C–H insertion product.

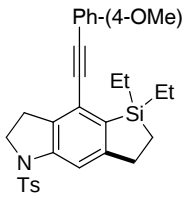
5.4.4. Crossover Experiment: In a glove box, **5-27u** (0.1 mmol), **5-27k** (0.1 mmol) and AgOTf (0.02 mmol) were dissolved in 5 mL of toluene in a thick-walled 25 mL Schlenk tube equipped with a magnetic stirring bar. The reaction tube was brought out of the box, and was stirred in an oil bath at 90 °C for 5 h. The tube was opened to air at room temperature and solvent was removed from a rotary aspirator. ^{1}H NMR of crude reaction mixture shows only two products of **5-28u** and **5-28k**. No crossover product was detected.

5.4.5. Selected Characterization Data



5-20

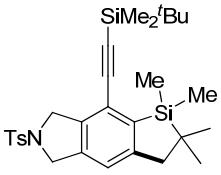
5-20 (95%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.5 Hz, 2H) 7.32 (d, *J* = 8.5 Hz, 2H), 6.95 (s, 1H), 4.62 (s, 2H), 4.59 (s, 2H), 2.97 (t, *J* = 7.5 Hz, 2H), 2.40 (s, 3H), 1.07 (t, *J* = 7.5 Hz, 9H), 0.98 (t, *J* = 7.5 Hz, 2H), 0.92 (t, *J* = 4.0 Hz, 6H), 0.87 (q, *J* = 8.0 Hz, 4H), 0.24 (q, *J* = 7.5 Hz, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.3, 143.5, 140.2, 137.7, 136.7, 133.8, 129.7, 127.5, 121.9, 119.5, 103.9, 96.7, 54.0, 53.4, 31.6, 21.4, 7.5, 7.4, 6.9, 4.7, 4.3; **HRMS** (ESI) calcd for $C_{29}H_{42}NO_2SSi_2$ $[M+H]^+$: 524.2475, found 524.2479.



5-22a

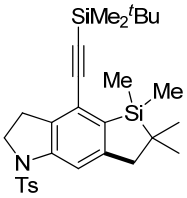
5-22a (91%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.3 Hz, 2H), 7.45 (s, 1H), 7.38 (d, *J* = 8.8 Hz, 2H), 7.25 (d, *J* = 8.3 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 3.95 (t, *J* = 8.4 Hz, 2H), 3.82 (s, 3H), 3.04 (m, 4H), 1.03 – 0.81 (m, 12H); **^{13}C NMR** (126 MHz, $CDCl_3$)

δ 159.7, 155.0, 144.0, 143.6, 134.8, 134.3, 132.8, 131.7, 129.7, 127.3, 123.9, 115.3, 114.1, 111.4, 93.1, 87.0, 55.3, 50.1, 32.2, 27.3, 21.5, 7.71, 7.11, 5.18.



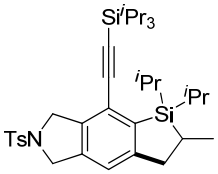
5-22b

5-22b (89%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.5 Hz, 2H) 7.30 (d, *J* = 8.5 Hz, 2H), 6.90 (s, 1H), 4.62 (s, 2H), 4.58 (s, 2H), 2.64 (s, 2H), 2.40 (s, 3H), 1.02 (s, 6H). 1.00 (s, 9H), 0.25 (s, 6H), 0.20 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 151.3, 143.5, 141.8, 137.7, 136.5, 133.8, 129.7, 127.5, 122.1, 120.0, 103.1, 97.8, 54.1, 53.4, 49.5, 26.1, 25.0, 23.7, 21.4, 16.6; **HRMS** (ESI) calcd for $C_{29}H_{42}NO_2SSi_2$ $[M+H]^+$: 524.2475, found 524.2473.



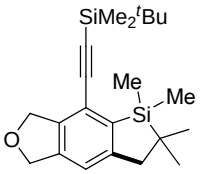
5-22c

5-22c (82%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.2 Hz, 2H), 7.41 (s, 1H), 7.24 (d, *J* = 8.2 Hz, 2H), 3.91 (t, *J* = 8.4 Hz, 2H), 2.96 (t, *J* = 8.4 Hz, 2H), 2.70 (s, 2H), 2.39 (s, 3H), 1.05 (s, 6H), 0.96 (s, 9H), 0.24 (s, 6H), 0.15 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 152.0, 144.1, 143.5, 136.2, 134.1, 132.4, 129.7, 127.3, 112.2, 103.9, 96.9, 50.1, 49.9, 27.3, 26.1, 25.2, 23.9, 21.5, 16.5, -4.6, -5.2; **HRMS** (ESI) calcd for $C_{29}H_{42}NO_2SSi_2$ $[M+H]^+$: 524.2475, found 524.2467.



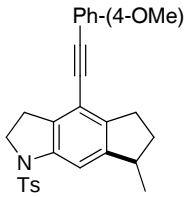
5-22d

5-22d (92%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.5 Hz, 2H) 7.31 (d, *J* = 8.5 Hz, 2H), 6.94 (s, 1H), 4.65 (m, 4H), 3.31 (dd, *J* = 16.5, 9 Hz, 1H), 2.61 (dd, *J* = 16.5, 10 Hz, 1H), 2.40 (s, 3H), 1.59 (m, 1H), 1.52 (m, 1H), 1.33 (m, 1H), 1.24 (d, *J* = 7.5 Hz, 3H), 1.14 (s, 18H), 1.14 (m, 3H), 1.12 (d, *J* = 7.5 Hz, 3H), 1.09 (d, *J* = 7.5 Hz, 3H), 0.94 (d, *J* = 7.5 Hz, 3H), 0.92 (d, *J* = 7.5 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 153.4, 143.5, 129.3, 137.7, 137.4, 133.8, 129.7, 127.5, 122.5, 119.4, 105.4, 95.8, 54.2, 53.9, 42.2, 21.4, 18.9, 18.5, 18.4, 17.6, 17.5, 15.7, 11.6, 11.3, 10.6; **HRMS** (ESI) calcd for $C_{35}H_{54}NO_2SSi_2$ $[M+H]^+$: 608.3414, found 608.3418.



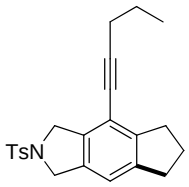
5-22e

5-22e (89%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 6.98 (s, 1H), 5.13 (s, 2H), 5.08 (s, 2H), 2.71 (s, 2H), 1.07 (s, 6H), 1.00 (s, 9H), 0.30 (s, 6H), 0.20 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 151.0, 141.2, 141.1, 139.9, 120.5, 118.5, 103.8, 96.8, 74.0, 73.4, 49.6, 26.1, 25.2, 23.9, 16.6, -4.5, -5.2; **HRMS** (ESI) calcd for $C_{22}H_{33}OSi_2$ $[M-1]^+$: 369.2070, found 369.2058.



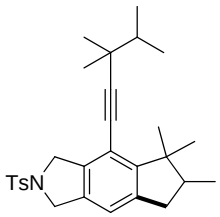
5-26

5-26 (78%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.2 Hz, 2H), 7.45 (s, 1H), 7.38 (d, *J* = 8.7 Hz, 2H), 7.22 (d, *J* = 8.2 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 3.95 (m, 2H), 3.82 (s, 3H), 3.21 (m, 1H), 3.01 – 2.92 (m, 3H), 2.84 (td, *J* = 16.3, 8.2 Hz, 1H), 2.37 (s, 3H), 2.35 (m, 1H), 1.64 (qd, *J* = 12.5, 8.3 Hz, 1H), 1.30 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.8, 148.9, 144.0, 141.4, 140.7, 134.0, 133.0, 132.0, 129.6, 127.3, 116.4, 115.2, 114.0, 110.5, 95.6, 84.1, 55.3, 50.4, 40.0, 34.4, 30.4, 27.5, 21.5, 20.2; **HRMS** (ESI) calcd for $C_{28}H_{28}NO_3S$ $[M+H]^+$: 458.1795, found 458.1790.



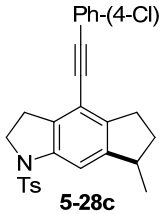
5-28a

5-28a (62%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 6.90 (s, 1H), 4.61 (s, 2H), 4.57 (s, 2H), 2.89 (t, *J* = 7.4 Hz, 2H), 2.84 (t, *J* = 7.4 Hz, 2H), 2.42 (t, *J* = 7.0 Hz, 2H), 2.40 (s, 3H), 2.04 (qn, *J* = 7.5 Hz, 2H), 1.63 (m, 2H), 1.06 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 146.1, 144.2, 143.5, 136.0, 133.9, 133.8, 129.8, 127.6, 117.5, 115.2, 97.6, 76.4, 54.1, 53.7, 33.0, 32.1, 25.1, 22.3, 21.6, 21.5, 13.5; **HRMS** (ESI) calcd for $C_{23}H_{25}NO_2S$ $[M+H]^+$: 380.1684, found 380.1677.



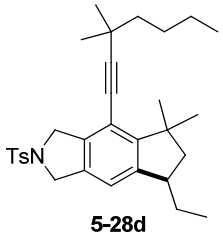
5-28b

5-28b (92%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 6.86 (s, 1H), 4.59 (m, 4H), 2.82 (dd, *J* = 15.6, 7.6 Hz, 1H), 2.40 (s, 3H), 2.38 (dd, *J* = 15.6, 7.6 Hz, 1H), 2.06 (m, 1H), 1.66 (sept, *J* = 6.7, 1H), 1.45 (s, 3H), 1.28 (s, 6H), 1.04 (d, *J* = 6.7 Hz, 6H), 1.03 (s, 3H), 1.01 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 152.2, 143.6, 142.7, 137.5, 133.8, 133.7, 129.7, 127.5, 117.5, 114.6, 106.0, 76.3, 54.2, 53.9, 46.3, 45.6, 37.8, 37.6, 36.1, 26.9, 25.8, 21.4, 20.2, 18.4, 13.6; **HRMS** (ESI) calcd for $C_{29}H_{38}NO_2S$ $[M+H]^+$: 464.2623, found 464.2628.



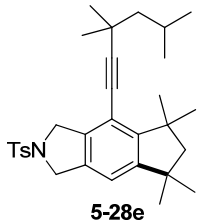
5-28c

5-28c (75%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.3 Hz, 2H), 7.48 (s, 1H), 7.37 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.3 Hz, 2H), 7.23 (d, *J* = 8.3 Hz, 2H), 3.95 (m, 2H), 3.22 (sext., *J* = 7.0 Hz, 1H)), 3.01 – 2.91 (m, 3H), 2.83 (td, *J* = 16.4, 8.4 Hz, 1H), 2.37 (s, 3H), 2.34 (m, 1H), 1.65 (qd, *J* = 12.5, 8.4 Hz, 1H), 1.31 (d, *J* = 7.0, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 149.0, 144.0, 141.6, 140.8, 134.4, 133.9, 132.7, 132.2, 129.6, 128.7, 127.3, 121.6, 115.7, 111.0, 94.3, 86.4, 50.3, 39.9, 34.4, 30.4, 27.5, 21.5, 20.2; **HRMS** (ESI) calcd for $C_{27}H_{25}ClNO_2S$ $[M+H]^+$: 462.1295, found 462.1307.



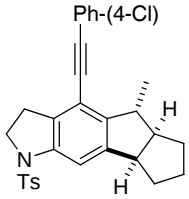
5-28d

5-28d (96%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 6.84 (s, 1H), 4.59 (m, 4H), 2.91 (m, 1H), 2.41 (s, 3H), 2.12 (dd, *J* = 12.6, 7.8 Hz, 1H), 1.95 (dqd, *J* = 14.8, 7.4, 4.3, 1H), 1.53 (dd, *J* = 12.6, 7.8 Hz, 1H), 1.51 (s, 3H), 1.49 (m, 1H), 1.43 (s, 3H), 1.36 (m, 3H), 1.29 (s, 6H), 1.27 (s, 3H), 0.97 (t, *J* = 7.0 Hz, 3H), 0.95 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 151.6, 147.2, 143.5, 137.7, 134.0, 133.9, 129.7, 127.6, 116.7, 114.5, 106.7, 75.6, 54.3, 53.8, 48.6, 43.7, 43.0, 42.5, 32.2, 29.1, 28.3, 27.8, 27.7, 26.9, 23.2, 21.4, 14.1, 11.7; **HRMS** (ESI) calcd for $C_{31}H_{42}NO_2S$ $[M+H]^+$: 492.2936, found 492.2936.



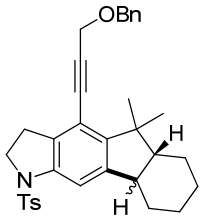
5-28e

5-28e (95%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 6.79 (s, 1H), 4.59 (s, 2H), 4.58 (s, 2H), 2.41 (s, 3H), 1.89 (s, 2H), 1.44 (s, 6H), 1.42 (d, *J* = 6.5 Hz, 2H), 1.31 (s, 6H), 1.21 (s, 6H), 1.02 (d, *J* = 6.5 Hz, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 152.5, 150.3, 143.5, 138.0, 134.6, 133.9, 129.7, 127.6, 115.9, 114.5, 106.9, 76.1, 57.7, 54.2, 53.9, 51.7, 43.4, 41.5, 32.0, 31.6, 30.0, 29.2, 25.8, 24.7, 21.5; **HRMS** (ESI) calcd for $C_{31}H_{42}NO_2S$ $[M+H]^+$: 492.2936, found 492.2939.



5-28f

5-28f (72%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.2 Hz, 2H), 7.44 (s, 1H), 7.38 (d, *J* = 8.5 Hz, 2H), 7.30 (d, *J* = 8.5 Hz, 2H), 7.23 (d, *J* = 8.2 Hz, 2H), 3.95 (t, *J* = 8.4 Hz, 2H), 3.71 (t, *J* = 7.4 Hz, 1H), 3.07 (q, *J* = 6.6 Hz, 1H), 2.97 (t, *J* = 8.4 Hz, 2H), 2.45 (td, *J* = 7.9, 6.5 Hz, 1H), 2.37 (s, 3H), 2.04 (m, 1H), 1.88 (m, 1H), 1.76 (m, 1H), 1.55 (m, 1H), 1.39 (m, 2H), 1.33 (d, *J* = 7.1 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 147.6, 145.7, 144.0, 141.2, 134.4, 133.8, 132.9, 132.5, 129.6, 128.7, 127.3, 121.6, 115.4, 111.7, 94.6, 86.4, 51.9, 50.3, 48.6, 46.1, 34.0, 33.6, 27.5, 25.7, 21.5, 21.4; **HRMS** (ESI) calcd for $C_{30}H_{29}ClNO_2S$ $[M+H]^+$: 502.1608, found 502.1615.

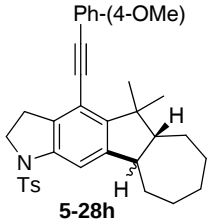


2.5:1 ratio of two diastereomers

5-28g

5-28g (82%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.0 Hz, 2H), 7.38 (s, 1H), 7.34 (s, 3H), 7.31 (m, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 4.64, (s, 2H), 4.20 (s, 2H), 3.95 (m, 2H), 3.98 (m, 1H), 3.95 (m, 2H), 2.44 (m, 2H), 2.38 (s, 3H), 1.91 (m, 2H), 1.78 (m, 2H), 1.49 (s, 3H), 1.4 – 1.2 (m, 3H), 1.05 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.7, 147.5, 146.4, 145.9, 144.1, 144.0, 140.4, 140.2, 137.4, 134.1, 133.8, 133.5, 133.3, 129.7, 129.6, 128.4, 128.0, 127.9, 127.4, 127.3, 115.4, 114.8, 110.4, 109.3, 92.8, 82.5, 82.4, 71.5, 59.5, 57.9, 51.2, 50.1, 46.6, 46.0, 44.5,

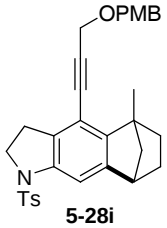
40.7, 29.4, 27.8, 26.7, 26.6, 26.4, 26.3, 25.8, 25.3, 24.8, 23.1, 22.4, 21.5, 19.7; **HRMS** (ESI) calcd for $C_{34}H_{38}NO_3S$ $[M+H]^+$: 540.2572, found 540.2563.



5-28h

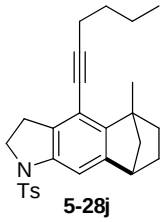
4:1 ratio of two diastereomers

5-28h (79%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.7 Hz, 2H), 7.39 (d, *J* = 8.3 Hz, 2H), 7.38 (s, 1H), 7.24 (d, *J* = 7.7 Hz, 2H), 6.87 (d, *J* = 8.3 Hz, 2H), 3.93 (m, 2H), 3.82 (s, 3H), 2.99 (m, 2H), 2.76 (m, 1H), 2.51 (m, 1H), 2.38 (s, 3H), 1.90 – 1.64 (m, 6H), 1.56 (m, 2H), 1.53 (s, 3H), 1.40 (m, 2H), 1.06 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.8, 147.8, 147.3, 144.0, 140.4, 134.0, 133.1, 132.6, 129.7, 127.4, 115.5, 115.4, 114.1, 110.1, 97.2, 84.3, 57.8, 55.4, 50.2, 46.7, 46.0, 33.1, 28.3, 27.8, 27.7, 27.3, 26.7, 26.4, 21.9, 21.6; **HRMS** (ESI) calcd for $C_{34}H_{38}NO_3S$ $[M+H]^+$: 540.2572, found 540.2573.



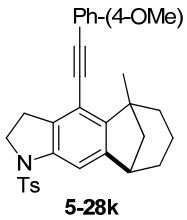
5-28i

5-28i (88%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.2 Hz, 2H), 7.47 (s, 1H), 7.27 (d, *J* = 6.9 Hz, 2H), 7.22 (d, *J* = 8.2 Hz, 2H), 6.88 (d, *J* = 6.9 Hz, 2H), 4.55 (s, 2H), 4.34 (s, 2H), 3.90 (m, 2H), 3.80 (s, 3H), 3.25 (s, 1H), 2.89 (m, 2H), 2.38 (s, 3H), 2.03 (m, 1H), 1.76 (s, 3H), 1.66 (m, 2H), 1.44 (d, *J* = 8.7 Hz, 1H), 1.23 (m, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.4, 149.9, 145.5, 143.9, 139.4, 134.0, 132.0, 129.7, 129.6, 129.4, 127.3, 113.8, 112.2, 108.9, 91.7, 82.4, 71.2, 57.5, 55.8, 55.3, 50.8, 50.0, 43.5, 34.1, 29.5, 27.9, 21.5, 18.8; **HRMS** (ESI) calcd for $C_{32}H_{34}NO_4S$ $[M+H]^+$: 528.2209, found 528.2214.



5-28j

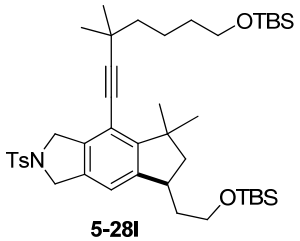
5-28j (92%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.2 Hz, 2H), 7.42 (s, 1H), 7.21 (d, *J* = 8.2 Hz, 2H), 3.88 (m, 2H), 3.22 (s, 1H), 2.85 (m, 2H), 2.39 (t, *J* = 7.0 Hz, 2H), 2.37 (s, 3H), 2.01 (m, 1H), 1.73 (s, 3H), 1.63 (m, 2H), 1.54 (m, 2H), 1.44 (m, 3H), 1.18 (m, 2H), 0.91 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 149.7, 144.9, 143.8, 139.2, 134.7, 131.7, 129.5, 127.3, 113.6, 107.9, 97.0, 55.7, 50.7, 49.9, 43.4, 34.1, 30.7, 29.5, 27.8, 21.9, 21.4, 19.2, 18.7, 13.5; **HRMS** (ESI) calcd for $C_{27}H_{32}NO_2S$ $[M+H]^+$: 434.2154, found 434.2153.



5-28k

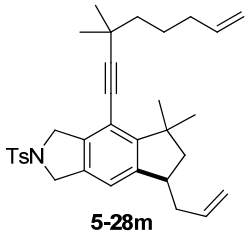
5-28k (93%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.0 Hz, 2H), 7.44 (s, 1H), 7.37 (d, *J* = 8.9 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 6.89 (d, *J* = 8.9 Hz, 2H), 3.94 (m, 2H), 3.82 (s, 3H), 3.09 (m, 1H), 2.97 (m, 2H), 2.38 (s, 3H), 2.08 (m, 1H), 1.64 – 1.40 (m, 7H), 1.57 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.7, 147.6, 144.3, 144.0, 140.3,

133.9, 132.9, 132.6, 129.6, 127.3, 115.4, 114.6, 114.0, 110.1, 96.2, 84.3, 55.3, 52.0, 50.2, 45.5, 40.2, 35.9, 28.8, 27.9, 24.6, 21.5, 19.8; **HRMS** (ESI) calcd for $C_{31}H_{32}NO_3S$ $[M+H]^+$: 498.2103, found 498.2102.



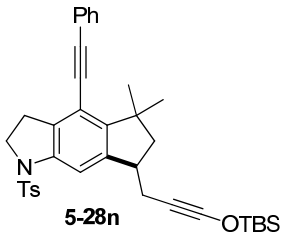
5-28l

5-28l (96%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 6.85 (s, 1H), 4.60 (m, 4H), 3.73 (m, 2H), 3.64 (t, *J* = 7.0 Hz, 2H), 3.10 (m, 1H), 2.40 (s, 3H), 2.12 (m, 2H), 1.56 (m, 8H), 1.49 (s, 3H), 1.28 (s, 6H), 1.25 (s, 3H), 0.89 (s, 9H), 0.87 (s, 9H), 0.05 (s, 6H), 0.04 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 151.3, 147.1, 143.4, 137.8, 134.1, 133.9, 129.7, 127.6, 111.6, 114.4, 106.6, 74.5, 63.1, 61.4, 54.2, 53.8, 49.3, 43.9, 43.1, 38.5, 37.8, 33.3, 32.2, 29.0, 28.3, 26.8, 25.9, 21.8, 21.4, 18.3, -5.2; **HRMS** (ESI) calcd for $C_{43}H_{70}NO_4SSi_2$ $[M+H]^+$: 752.4564, found 752.4562.



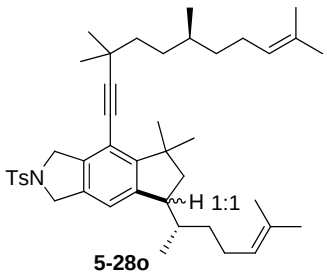
5-28m

5-28m (90%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 6.89 (s, 1H), 5.83 (m, 2H), 5.05 (m, 4H), 4.59 (m, 4H), 3.09 (m, 1H), 2.57 (m, 1H), 2.40 (s, 3H), 2.11 (m, 4H), 1.62 (m, 3H), 1.52 (m, 2H), 1.50 (s, 3H), 1.30 (s, 6H), 1.27 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 151.6, 146.4, 143.5, 138.7, 137.9, 136.6, 134.1, 133.9, 129.7, 127.6, 116.9, 116.2, 114.6, 114.5, 106.5, 75.7, 54.2, 53.8, 48.7, 43.6, 42.7, 40.5, 39.4, 34.1, 32.2, 29.0, 28.2, 27.0, 24.9, 21.4; **HRMS** (ESI) calcd for $C_{33}H_{42}NO_2S$ $[M+H]^+$: 516.2936, found 516.2928.

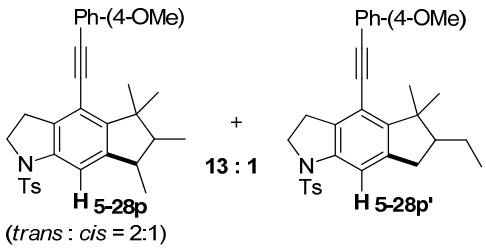


5-28n

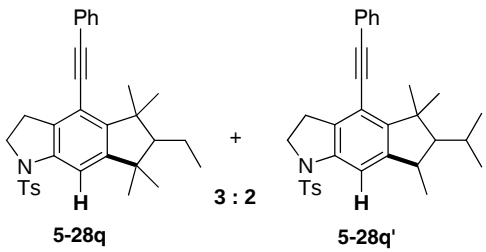
5-28n (90%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.3 Hz, 2H), 7.51 (s, 1H), 7.46 (m, 2H), 7.34 (m, 3H), 7.25 (d, *J* = 8.3 Hz, 2H), 3.95 (m, 2H), 3.33 (m, 1H), 3.01 (t, *J* = 8.4 Hz, 2H), 2.76 (dd, *J* = 16.8, 5.3 Hz, 1H), 2.46 (dd, *J* = 16.8, 8.2 Hz, 1 H), 2.39 (s, 3H), 2.27 (dd, *J* = 12.9, 8.0 Hz, 1 H), 1.84 (dd, *J* = 12.9, 8.5 Hz, 1 H), 1.58 (s, 3H), 1.36 (s, 3H), 0.93 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 147.6, 145.2, 144.0, 140.8, 134.2, 134.0, 131.1, 129.6, 128.5, 128.4, 127.4, 123.2, 115.4, 110.5, 106.0, 97.2, 85.2, 83.9, 50.2, 48.7, 43.6, 41.0, 28.6, 27.7, 27.6, 26.1, 26.0, 21.5, 16.5, -4.48; **HRMS** (ESI) calcd for $C_{37}H_{44}NO_2SSi_2$ $[M+H]^+$: 594.2862, found 594.2853.



5-28o (85%): **^{1}H NMR** (501 MHz, $CDCl_3$) (mixture of diastereomers) δ 7.78 (d, *J* = 8.2 Hz, 2H), 7.77 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 6.79 (s, 1H), 6.78 (s, 1H), 5.18 – 5.10 (m, 3H), 5.01 (t, *J* = 7.1 Hz, 1H), 4.60 (m, 8H), 3.18 (m, 1H), 3.09 (m, 1H), 2.41 (s, 6H), 2.13 – 1.92 (m, 10H), 1.92 – 1.77 (m, 3H), 1.71 (s, 3H), 1.70 – 1.65 (m, 1H), 1.69 (s, 6H), 1.67 (s, 3H), 1.63 (s, 3H), 1.61 (s, 6H), 1.56 (s, 3H), 1.55 – 1.49 (m, 2H), 1.52 (s, 3H), 1.51 (s, 3H), 1.49 – 1.33 (m, 12H), 1.30 (s, 12H), 1.26 (s, 3H), 1.25 (s, 3H), 1.24 – 1.09 (m, 4H), 0.99 (d, *J* = 6.5 Hz, 3H), 0.94 (d, *J* = 6.3 Hz, 6H), 0.64 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 152.9, 151.9, 145.9, 145.6, 143.3, 137.6, 134.0, 133.96, 133.93, 131.37, 131.34, 130.9, 129.7, 127.5, 124.9, 124.7, 124.5, 117.0, 116.8, 114.45, 114.40, 106.5, 75.7, 54.2, 53.7, 47.0, 44.9, 43.5, 43.3, 43.2, 42.1, 40.6, 37.0, 35.6, 33.5, 32.9, 32.79, 32.70, 32.2, 31.4, 29.1, 29.0, 28.07, 28.03, 27.07, 27.02, 26.2, 26.0, 25.6, 25.5, 21.4, 19.6; **HRMS** (ESI) calcd for $C_{43}H_{62}NO_2S$ $[M+H]^+$: 656.4501, found 656.4496.

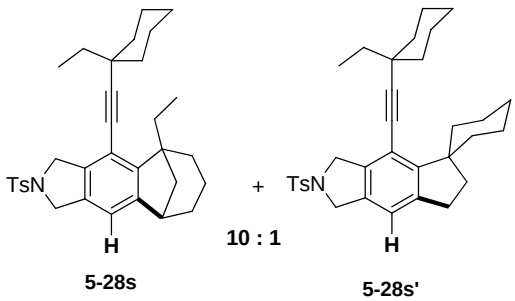


(80% combined yield)**: ^{1}H NMR** (501 MHz, $CDCl_3$): **5-28p (*trans*)** δ 7.69 (d, *J* = 8.1 Hz, 2H), 7.40 (d, *J* = 8.5 Hz, 2H), 7.39 (s, 1H), 7.24 (d, *J* = 8.1 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 3.94 (m, 2H), 3.82 (s, 3H), 3.00 (m, 2H), 2.59 (m, 1H), 2.38 (s, 3H), 1.60 (m, 1H), 1.53 (s, 3H), 1.34 (d, *J* = 6.7 Hz, 3H), 1.07 (s, 3H), 1.06 (d, *J* = 6.7 Hz, 3H); **5-28p (*cis*)** δ 7.69 (d, *J* = 8.1 Hz, 2H), 7.40 (d, *J* = 8.5 Hz, 2H), 7.45 (s, 3H), 7.24 (d, *J* = 8.1 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 3.94 (m, 2H), 3.82 (s, 3H), 3.17 (qn, *J* = 7.4 Hz, 1H), 2.38 (s, 3H), 2.25 (qn, *J* = 7.4 Hz, 1H), 1.47 (s, 3H), 1.27 (s, 3H), 1.16 (d, *J* = 7.4 Hz, 3H), 0.99 (d, *J* = 7.4 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) **5-28p + 5-28p′** δ 159.8, 148.6, 147.8, 147.3, 147.0, 144.0, 142.5, 140.5, 134.1, 134.1, 133.4, 133.2, 132.6, 132.3, 129.6, 129.5, 129.4, 127.6, 127.4, 115.9, 115.5, 115.5, 114.1, 111.1, 110.9, 109.8, 97.2, 84.3, 84.2, 55.3, 54.3, 53.4, 50.3, 50.2, 47.5, 46.3, 46.3, 45.5, 42.9, 41.3, 36.2, 34.7, 31.5, 29.6, 27.8, 27.5, 26.5, 26.3, 25.3, 24.1, 22.7, 22.2, 21.5, 21.1, 21.0, 17.5, 17.2, 13.3, 11.6, 10.1; **HRMS** (ESI) calcd for $C_{31}H_{34}NO_3S$ $[M+H]^+$: 500.2259, found 500.2257.

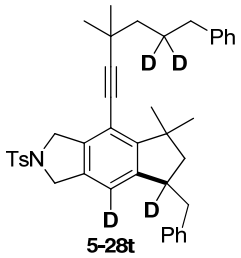


(84% combined yield): **^{1}H NMR** (501 MHz, $CDCl_3$): **5-28q** + **5-28q′** δ 7.70 (d, *J* = 8.0 Hz, 4H), 7.49 – 7.45 (m, 4H), 7.43 (**5-28q′**, s, 1H), 7.42 (**5-28q**, s, 1H), 7.37 – 7.31 (m, 4H), 7.26 – 7.21 (m, 4H), 4.02 – 3.87 (m, 4H), 3.06 – 2.98 (m, 4H), 2.97 (**5-28q′**, m, 1H), 2.38 (s, 6H), 1.99 (m, 1H), 1.75 (**5-28q**, t, *J* =

7.3 Hz, 1H), 1.59 (s, 3H), 1.58 (s, 3H), 1.41 (**5-28q′**, d, *J* = 6.8 Hz, 3H), 1.40 (s, 3H), 1.26 (s, 3H), 1.21 (s, 3H), 1.16 – 1.12 (m, 5H), 1.11 (s, 3H), 1.05 (**5-28q′**, d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$): **5-28q + 5-28q′** δ 152.6, 147.6, 147.4, 146.5, 144.1, 144.1, 140.7, 140.5, 134.02, 133.98, 133.8, 133.6, 131.2, 129.69, 129.66, 128.5, 127.5, 127.4, 123.4, 115.3, 115.0, 110.3, 109.7, 97.41, 97.37, 85.7, 85.6, 64.8, 61.9, 50.3, 50.2, 46.9, 46.1, 44.8, 38.4, 30.5, 29.2, 27.8, 26.5, 26.0, 25.7, 23.0, 22.2, 21.6, 20.8, 20.3, 19.2, 14.7; **HRMS** (ESI) calcd for $C_{32}H_{36}NO_2S$ $[M+H]^+$: 498.2467, found 498.2473.

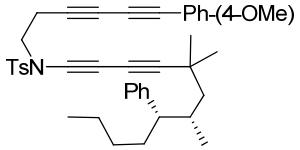


(88% combined yield): **^{1}H NMR** (501 MHz, $CDCl_3$): **5-28** δ 7.76 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 6.87 (s, 1H), 6.80 (s, 1H), 4.70 – 4.50 (m, 4H), 3.02 (s, 1H), 2.76 (t, *J* = 7.3, 1H), 2.40 (s, 3H), 2.21 – 2.10 (m, 1H), 2.32 – 2.20 (m, 1H), 2.00 (t, *J* = 7.6 Hz, 1H), 1.88 – 1.13 (m, 19H), 1.03 (t, *J* = 7.4 Hz, 3H), 0.85 (t, *J* = 7.5 Hz, 3H), 0.77 – 0.56 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) **5-28** δ 148.3, 146.6, 143.5, 137.7, 134.1, 133.8, 129.8, 127.6, 115.7, 113.8, 103.1,78.1, 54.4, 54.2, 50.0, 46.9, 39.7, 38.1, 37.4, 37.3, 35.8, 34.9, 29.4, 29.1, 26.3, 23.3, 21.5, 19.7, 8.9, 8.7; **HRMS** (ESI) calcd for $C_{33}H_{42}NO_2S$ $[M+H]^+$: 516.2936, found 516.2943.



5-28t
98% D incorporation

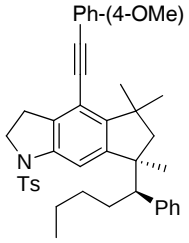
5-28t (93%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.2 Hz, 2H), 7.38 – 7.29 (m, 6H), 7.29 – 7.21 (m, 6H), 4.65 (m, 4H), 3.24 (d, *J* = 13.5 Hz, 1H), 2.71 (s, 2H), 2.61 (d, *J* = 13.5 Hz, 1H), 2.44 (s, 3H), 2.00 (d, *J* = 12.8 Hz, 1H), 1.68 (d, *J* = 12.8 Hz, 1H), 1.60 (s, 2H), 1.55 (s, 3H), 1.35 (s, 6H), 1.29 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 151.6, 146.3, 143.4, 142.2, 140.3, 138.0, 134.0, 133.9, 129.7, 128.8, 128.3, 127.5, 126.0, 125.7, 114.5, 106.4, 75.7, 54.1, 53.7, 48.9, 43.6, 42.6, 41.7, 36.1, 29.0, 28.3, 27.0, 21.4; **HRMS** (ESI) calcd for $C_{41}H_{42}D_4NO_2S$ $[M+H]^+$: 620.3500, found 620.3492.



5-27u

5-27u (dr = 10 : 1): ^{1}H NMR (501 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.2 Hz, 2H), 7.42 (d, *J* = 8.8 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 7.28 (m, 2H), 7.22 – 7.12 (m, 3H), 6.84 (d, *J* = 8.8 Hz, 2H), 3.82 (s, 3H), 3.55 (t, *J* = 7.6 Hz, 2H), 2.69 (t, *J* = 7.6 Hz, 2H), 2.46 (ddd, *J* = 4.5, 5.8, 10.4 Hz, 1H), 2.43 (s, 3H)1.89 (ddd, *J* = 2.6, 6.9, 13.7 Hz, 1H), 1.75 (m, 1H), 1.68 – 1.61 (m, 2H), 1.34 – 1.23 (m, 2H), 1.22 (s, 3H), 1.18 (s, 3H), 1.16 – 1.08 (3H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.83 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 160.3, 145.1, 143.8, 134.4, 134.2, 130.0, 129.0, 127.9, 127.6, 125.8, 114.1, 113.5, 91.4, 78.3,

76.1, 72.6, 67.6, 67.3, 64.5, 59.2, 55.3, 52.1, 49.8, 47.5, 35.6, 32.5, 31.9, 30.2, 30.0, 29.1, 22.8, 21.7, 19.6, 19.4, 14.0; **HRMS** (ESI) calcd for $C_{41}H_{46}NO_3S$ $[M+H]^+$: 632.3198, found 632.3198.



5-28u

5-28u: ^{1}**H NMR** (501 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.3 Hz, 2H), 7.48 (s, 1H), 7.35 (d, *J* = 8.5 Hz, 2H), 7.20 (d, *J* = 8.3 Hz, 2H), 7.18 (m, 5H), 6.85 (d, *J* = 8.5 Hz, 2H), 3.96 (d, *J* = 9.5 Hz, 2H), 3.80 (s, 3H), 2.97 – 2.81 (m, 2H), 2.93 (t, *J* = 8.0 Hz, 1H), 2.41 (s, 3H), 1.97 (m, 1H), 1.76 (m, 1H), 1.68(d, *J* = 14.0 Hz, 1H), 1.44 (d, *J* = 14.0 Hz, 1H), 1.42 (s, 3H), 1.38 (s, 3H), 1.23 – 1.22 (m, 4H), 1.27 (s, 3H), 0.84 (t, *J* = 7.0 Hz, 3H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 159.7, 150.9, 147.0, 143.9, 142.2, 140.3, 134.3, 134.1, 132.5, 130.3, 129.6, 127.5, 127.4, 125.8, 115.5, 115.3, 114.1, 111.9, 97.1, 84.3, 55.3, 54.3, 52.2, 50.3, 49.9, 42.9, 30.5, 30.3, 29.7, 29.4, 28.6, 27.8, 22.8, 21.5, 14.0; **HRMS** (ESI) calcd for $C_{41}H_{46}NO_3S$ $[M+H]^+$: 632.3198, found 632.3195.

Characteristic signals from the other diastereomer: ^{1}**H NMR** (501 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.2 Hz, 2H), 4.03 (m, 1H), 3.82 (s, 3H), 3.08 – 2.97 (m, 2H), 2.53 (d, *J* = 13.5 Hz, 2H), 2.37 (s, 3H), 1.44 (s, 3H), 1.07 (s, 3H), 0.78 (t, *J* = 7.0 Hz, 3H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ (mixture of diastereomers) 159.9, 159.8, 151.3, 150.9, 147.0, 146.9, 144.1, 144.0, 143.0, 142.3, 141.1, 140.4, 134.3, 134.2, 134.0, 132.6, 132.5, 132.5, 130.3, 129.7, 129.6, 129.4, 128.0, 127.8, 127.6, 127.4, 127.4, 126.3, 125.9, 115.8, 115.5, 115.4, 114.2, 114.1, 111.9, 109.4, 97.5, 97.2, 84.4, 84.3, 55.4, 55.2, 54.4, 52.2, 50.9, 50.3, 50.2, 49.9, 43.3, 43.0, 32.0, 31.6, 30.7, 30.5, 30.4, 29.9, 29.7, 29.5, 28.7, 27.8, 27.8, 23.1, 22.9, 21.6, 14.1.

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Chapter 6. Unified Approach for Fluorination, Trifluoromethylation, and Trifluoromethyl-thiolation via Aryne Intermediates

6.1. Introduction of Ar-F, Ar-CF_3 and Ar-SCF_3

6.1.1. Fluorinated Compounds in Nature

Fluorine is the most electronegative atom (Pauling electronegativity: 3.98, Mulliken electronegativity: 4.42) in the periodic table, and has the highest reduction potential (E^o = 2.866 V; $F_2 + 2e^- = 2F^-$) to accept electron from other electron sources.[1] This special character of fluorine dramatically affects properties of organic molecules through strong polar interactions. For example, in medicinal chemistry, the introduction of fluorine into drugs makes them no longer susceptible to metabolic alternation, and increases their lipophilicity. In addition, the decreased metabolic susceptibility increases bioavailability and thus lowers the dose of the administered drug. Therefore, a large number of drug candidates containing fluorinated arenes are routinely evaluated in modern drug discovery.[2] To date, more than 80 drugs containing at least one fluorine atom have been approved and released to the market (**Figure 6.1**).

For example, the amount of the retail sales for Pfizer's Lipitor in US reaches to 7,688 million dollars. In 2011, 7 out of 35 new drugs approved contain fluorine,[3] and 25 out of the 200 best selling drugs contain fluorine as well.[4] Moreover, ^{18}F-labeled arenes are widely used as tracers for positron emission tomography (PET) imaging in oncology.[5] Millions of PET scans using 2-[^{18}F]-fluoro-2-deoxyglucose([^{18}F]FDG) are performed every year.[6] Despite fluorine being the thirteenth most abundant element in the Earth's crust, only 21 biosynthesized natural molecules containing fluorine (**Figure 6.2**) are known to date due to nature's poor ability to incorporate fluorine into organic molecules. There are only a few specialized organisms capable of activating inorganic fluoride to build up fluorinated organic

molecules.[7] Accordingly recent years have witnessed explosive interests in developing facile chemical methods to incorporate fluorine into organic compounds.

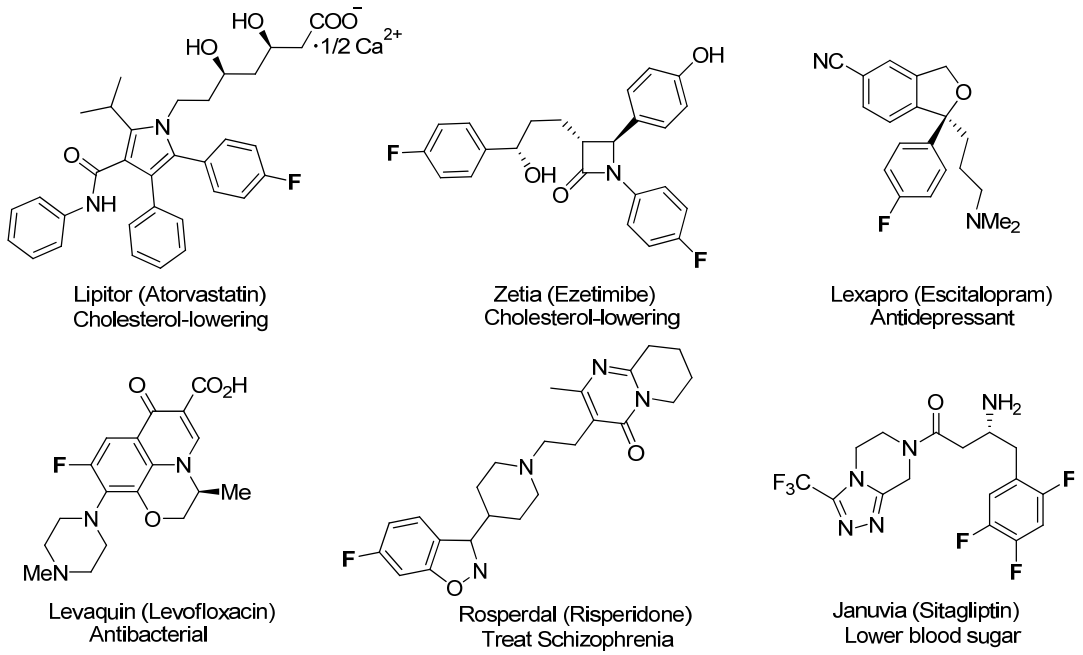


Figure 6.1. Representative fluorinated pharmaceuticals

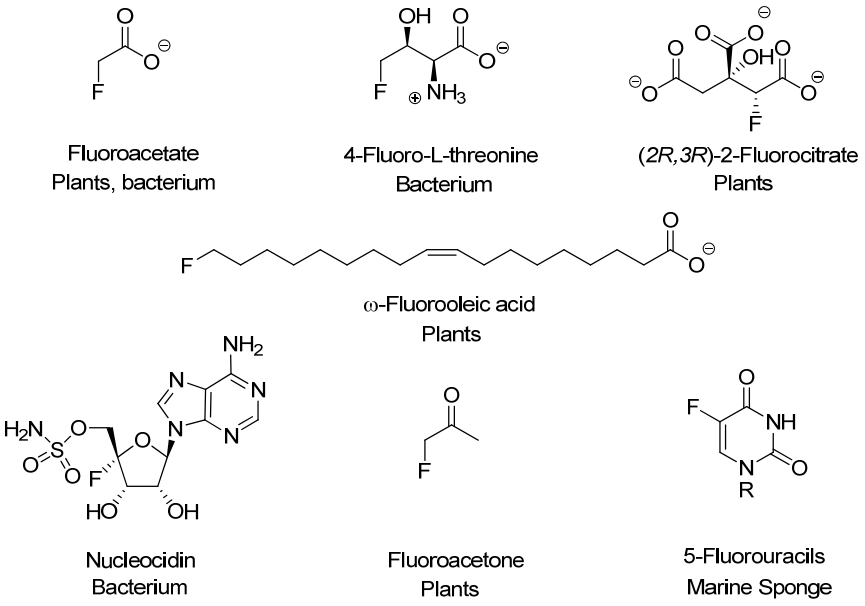
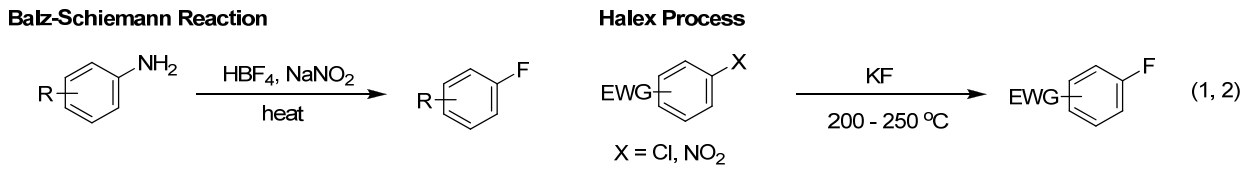


Figure 6.2. Selected examples of fluorinated natural products

6.1.2. Reported Synthetic Approaches for Fluorinated Arenes



Conventional fluorination methods to generate aryl fluorides such as the Balz-Schiemann reaction[8] and the Halex process[9] (Eq. 1 and 2) generally require harsh conditions and consequently exhibit narrow substrate scopes. Therefore, during the past five years, transition metal catalyzed reactions using various nucleophilic or electrophilic fluorinating reagents[10] (**Figure 6.3**) have revolutionized synthetic methods to forge Ar–F linkage. These methodologies can be classified into two general categories: directed electrophilic fluorination and cross-coupling reaction.

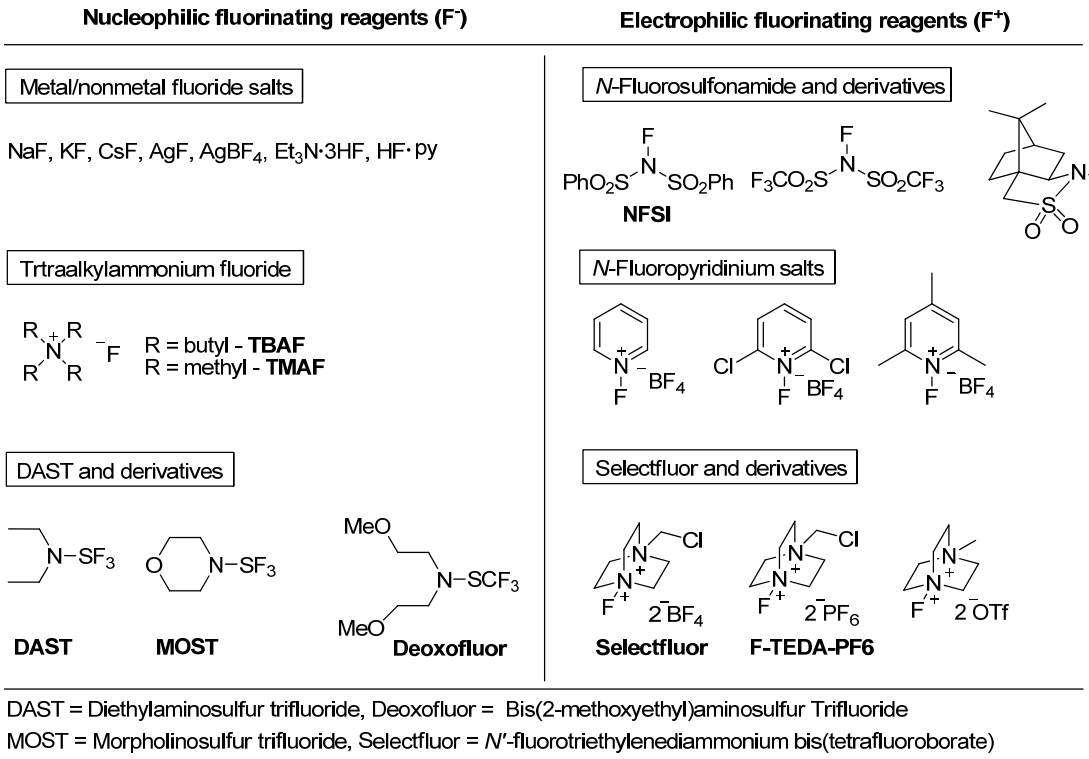
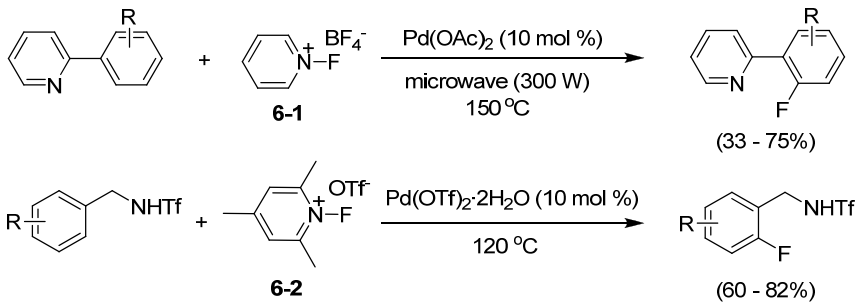
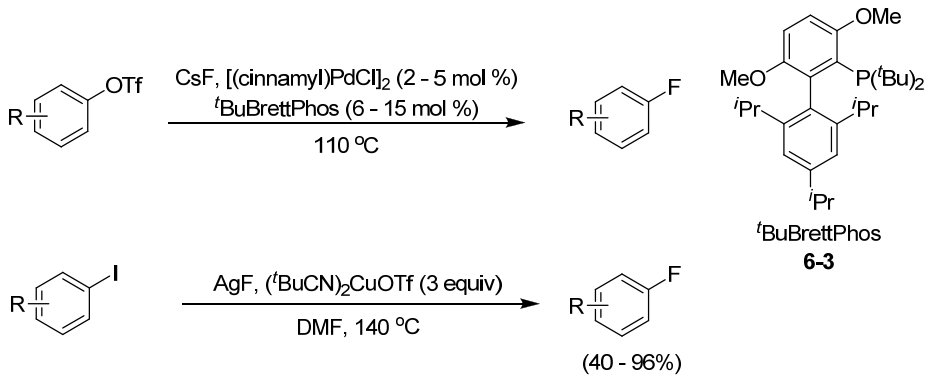


Figure 6.3. Some common fluorinating reagents

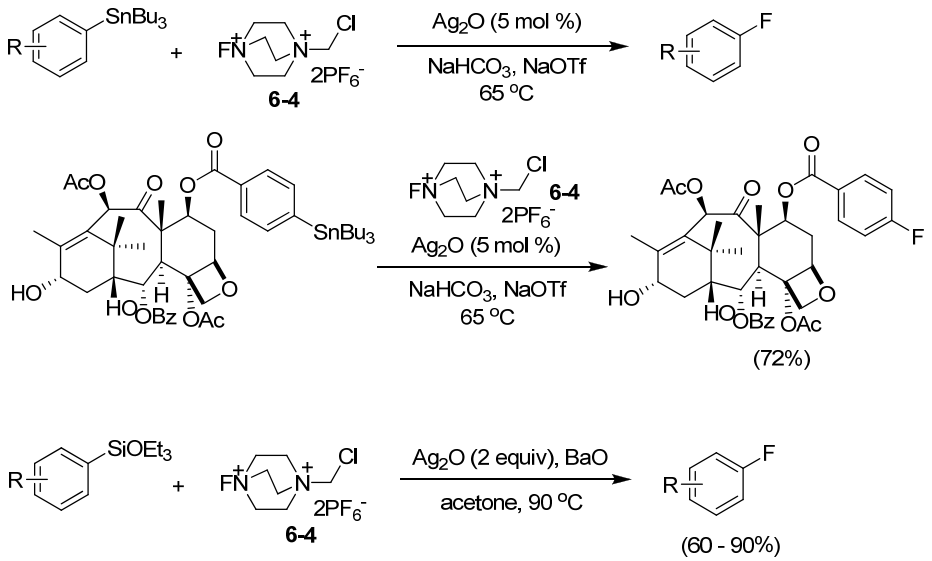
The directing group-assisted strategy allows regioselective introduction of fluorine by positioning the metal in proximity to specific C–H bonds. For example, Sanford reported the first Pd(II)--catalyzed *ortho*-fluorination of 2-phenylpyridines in 2006 using *N*-fluoropyridium tetrafluoroborate **6-1** as the electrophilic fluorine source (Eq. 3).[11] Few years later, Yu and coworkers demonstrated a similar *ortho*-fluorination catalyzed by $Pd(OTf)_2{\cdot}2H_2O$ using trifloromethanesulfonamide (NHTf) as a directing group (Eq. 4) with a new fluorinating reagent, *N*-fluoro-2,4,6-trimethylpyridinium triflate **6-2**.[12] The advantage of these methods is the capability of converting an unreactive C–H bond directly to C–F bond.



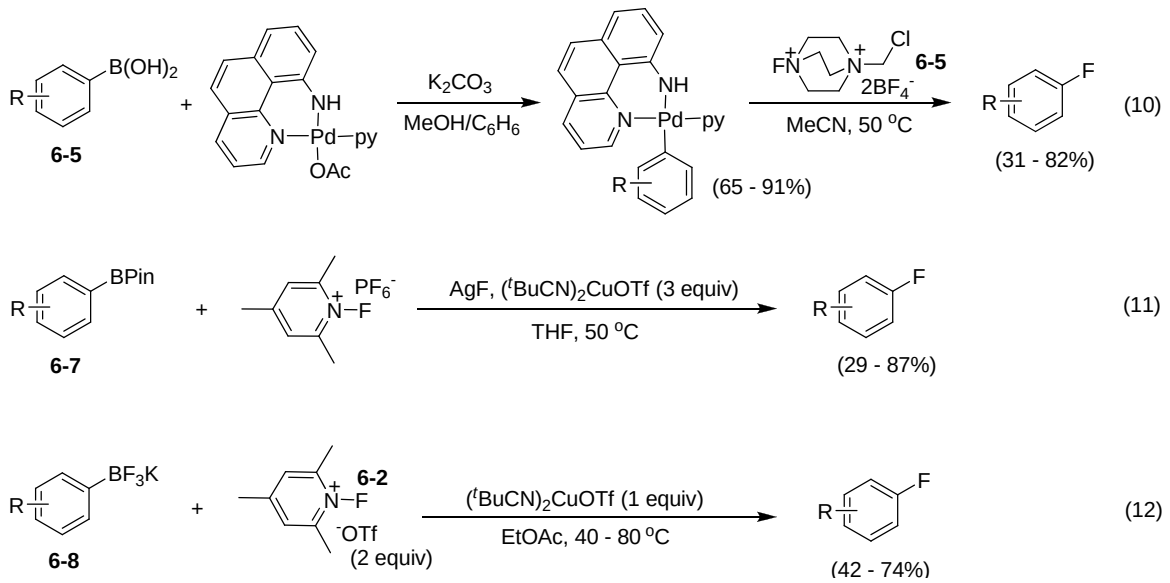
In 2009, Buchwald pioneered a cross-coupling strategy to form Ar–F bonds between aryl trifluoromethanesulfonate (ArOTf) and cesium fluoride (CsF) (Eq. 5).[13] The key aspect of this coupling is the facilitation of a challenging C–F reductive elimination from a three-coordinate arylpalladium(II) fluoride complex by the critical role of a bulky monodendate phosphine ligand (*t*-BuBrettphos, **6-3**). In 2012, Hartwig developed a fluorination protocol of aryl iodides relying on a relatively effective reductive elimination from arylcopper(III) fluoride (Eq. 6).[14]



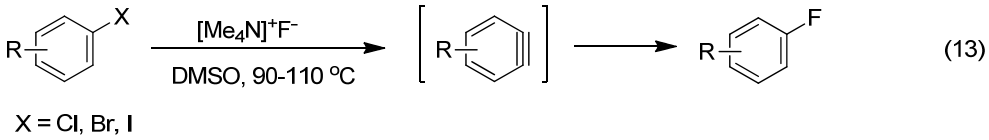
Recently, Ritter *et al.* have developed an efficient silver-catalyzed electrophilic fluorination of aryl stannanes using F-TEDA-PF_6 **6-4** as the fluorine cation source and demonstrated a late-stage fluorination of complex molecules including taxol (Eq. 7 and 8).[15] On the other hand, he used stoichiometric amount of Ag_2O to achieve fluorination of aryl silane substrates in the presence of BaO as an additive (Eq. 9).[16]



In 2011, Ritter also reported a palladium-mediated fluorination of allyl boronic acids **6-5** with electrophilic fluorine source (selectfluor, **6-6**) (Eq. 10).[6c] A copper-mediated direct conversion of alylboronate ester **6-7** to aryl fluoride was reported by Hartwig and co-workers in 2013 (Eq. 11).[17] Preliminary mechanistic study showed that fluorination proceeds through facile oxidation of Cu(I) to Cu(III), followed by transmetalation. Fast C−F reductive elimination was suggested to occur from an Ar−Cu(III)−F complex. They also generated Cu(III) intermediates independently and characterized by NMR and ESI-MS. More recently, Sanford reported a new copper-mediated fluorination of aryl trifluoroborates **6-8** with *N*-fluoro-2,4,6-trimethylpyridinium triflate **6-2** (Eq. 12).[18] It is also proposed that the reaction occurs through an arylcopper (III) fluoride intermediate. Though significant progress has been made to date in the realm of fluorination of arenes, all current approaches require the installation of either a directing group on or pre-functionalization of substrates.



To date only one example of aryne-mediated fluorination has been reported.[19] In 2008, Grushin discovered that the reaction of halogenated arenes with tetramethylammoniumfluoride (Me_4NF) at high temperature produced fluorinated arenes (Eq. 13). Mechanistic considerations suggest that 3 equivalents of Me_4NF are required for the introduction of one fluorine atom into the aromatic ring via the aryne intermediate. In the first step of the reaction, a C–H bond *ortho* to the halogen is deprotonated by the first equivalent of fluoride that is highly basic, despite its high solvation energy in DMSO. As a result, HF formed by deprotonation consumes the second equivalent of F^- to form stable FHF^-. Indeed, large quantities of FHF^- are always produced as detected by ^{19}F NMR. The third equivalent of fluoride is needed for nucleophilic addition to the aryne in the C–F bond forming step.



6.1.3. Ar-CF_3 and Ar-SCF_3 in Modern World

Trifluoromethyl group has distinct electronic and steric properties compared to methyl (CH_3) group. CF_3 group has a significant electronegativity that is often described as being intermediate between

the electronegativities of fluorine and chlorine,[20] and is similar in size to that of isopropyl (*i*-Pr) group (van der Waals radius 2.2A°).[21] Therefore, the trifluoromethyl group should be considered more appropriately as an individual functional group rather than just a substituted methyl group. Trifluoromethylated arenes also represent intriguing structural motif in the fields of pharmaceuticals, agrochemicals, and material science due to their unique physical and biological properties.[2a,c,f] In medicinal chemistry, the introduction of strongly electron-withdrawing trifluoromethyl group into drug candidates often improves their metabolic stability and lipophilicity. Among the top 200 best-selling medicines in 2011, six of them contain Ar-CF_3 group[4] as shown in Figure 6.4. CF_3 group also presents in many agrochemicals such as fungicides, pesticides and insecticides which are currently used worldwide (**Figure 6.5**). Trifluoromethylthio group shares similar characteristics to those of CF_3 group but has significant smaller size compared to that of CF_3. In addition, aryl trifluoromethylthio ethers (Ar-SCF_3) are key intermediates for the synthesis of trifluoromethyl sulfoxides ($ArSOCF_3$) and sulfones ($ArSO_2CF_3$).

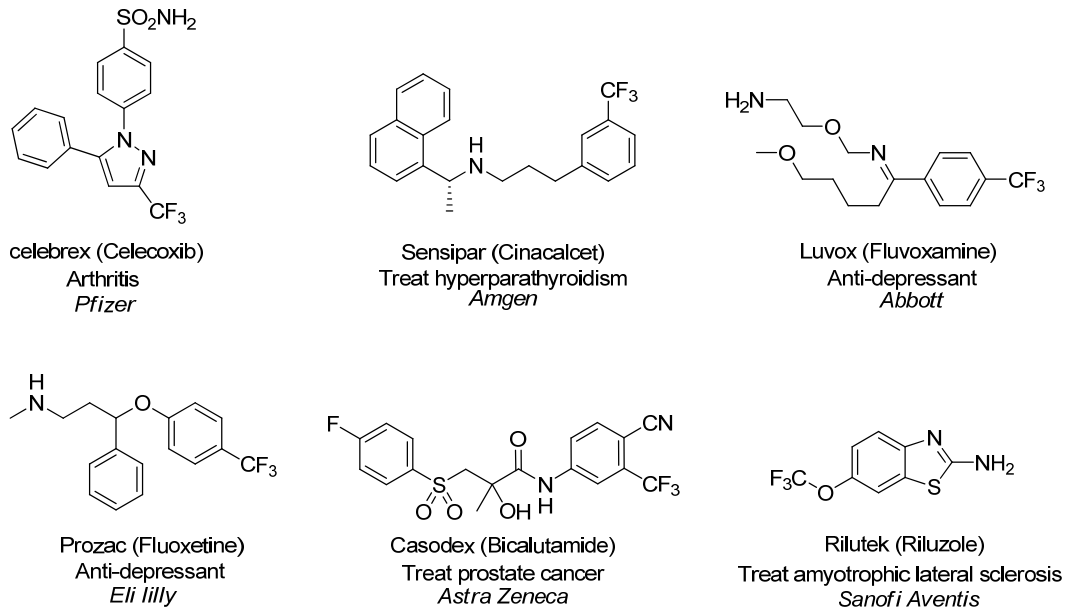


Figure 6.4. Pharmaceutical products contain trifluoromethylated arenes.

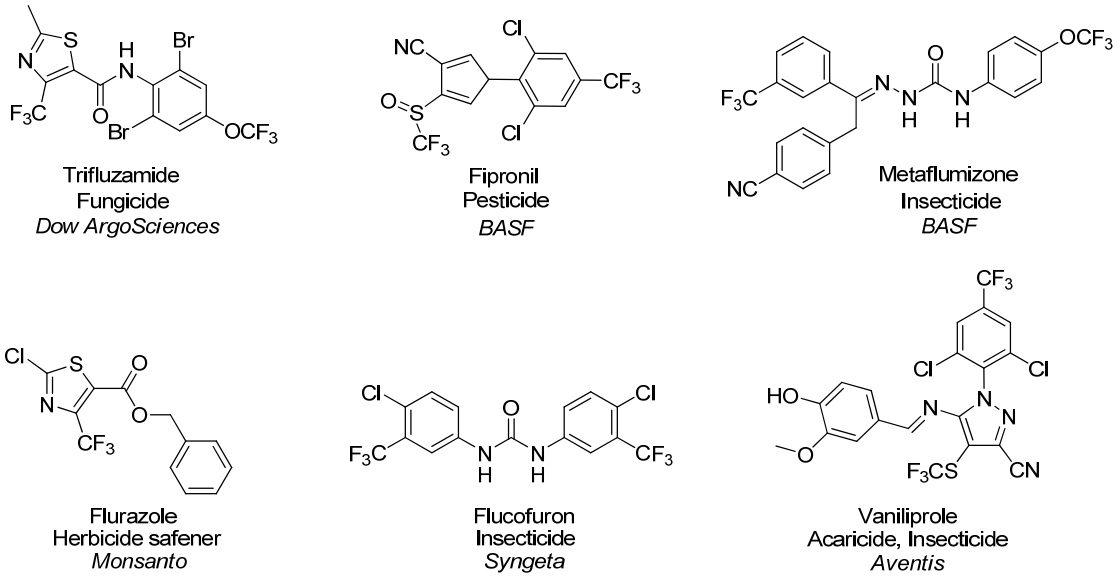
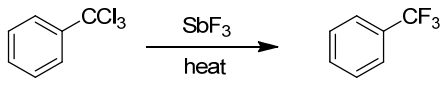


Figure 6.5. Agrochemicals contain CF_3 functional groups

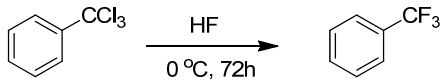
It is generally known that perfluorocarbons have a high propensity in dissolving gases such as molecular oxygen or carbon dioxide.[22] Because of the inertness of perfluorocarbons, they are often considered to be the ideal oxygen carriers[23] in living organisms when applied as aqueous emulsions. Currently, perfluorocarbon-based oxygen carriers as blood substitutes are in clinical trials in the U.S. for FDA approval. The advantages of such an approach over blood transfusions are numerous. Not only the blood group related shortages, storage and hygienic issues of the donated blood, but most importantly the dormant risk of passing on diseases could be ruled out by applying artificial blood substitutes.

6.1.4. Synthetic Approaches of Trifluoromethylated Arenes (Ar-CF_3)

In late 19th century, Swarts found that benzotrifluoride **6-10**, the simplest trifluoromethylated aromatic compound, can be prepared by treating benzotrichloride **6-9** with excess amount of antimony fluoride (SbF_3) (Eq. 14).[24] In 1938, Simons and Lewis found the Swarts reaction occurs under much more drastic conditions with the same substrates **6-9** employing anhydrous hydrogen fluoride (HF) alone, which provides the scalable manufacturing method for the preparation of trifluoromethylated aromatic compounds (Eq. 15).[25]



6-9 **6-10** (14)



6-9 **6-10** (75 - 95%) (15)

However, the Swarts reaction is nonetheless neither atom-economical nor environmentally benign due to the production of stoichiometric amount of hazardous chemicals as well as large amount of chlorine by-products. Moreover, the forcing reaction conditions significantly limit its utility in complex organic molecule synthesis. Accordingly recent years have witnessed explosive interests in developing facile chemical methods to incorporate CF_3 group into aromatic compounds. With the development of new trifluoromethylation reagents (**Figure 6.6**) and methods, in the last five years, transition metal catalyzed cross coupling strategy has facilitated the synthesis of a range of trifluoromethylated arenes[26] and has become one of the most useful methods for the preparation of trifluoromethylated arenes.

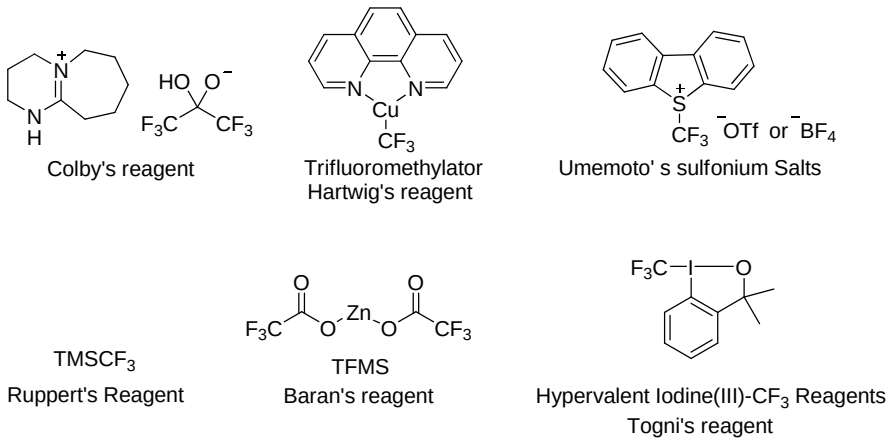
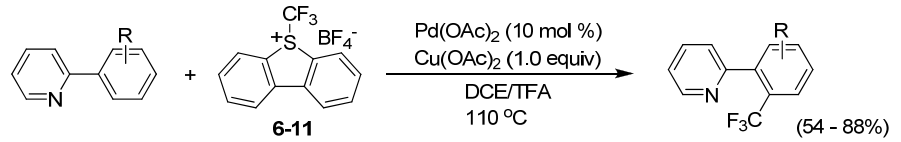


Figure 6.6. Common CF_3 sources

Specifically, Yu and co-workers developed a Pd(II)-catalyzed *ortho*-trifluoromethylation of arenes directed by pendant pyridine moiety using electrophilic trifluoromethylating reagent **6-11** through C–H functionalization (Eq. 16).[27] In this method the use of TFA (trifluoroacetic acid) is essential to

achieve Ar-CF_3 bond formation and stoichiometric amount of $Cu(OAc)_2$ is required for decent catalytic turnover. Yu also reported a Pd(II)-catalyzed trifluoromethylation of *N*-arylbenzamides in the presence of *N*-methylformamide as promoter with the same reagent **6-11** for Ar-CF_3 bond formation (Eq. 17).[28] Bräse reported an *ortho*-selective trifluoromethylation of aromatic triazenes using $AgCF_3$ generated in situ form AgF and Ruppert's reagent ($TMSCF_3$) (Eq. 18).[29] Triazenes are useful equivalent of protected diazonium salts and thus can be converted to a variety of functional groups.



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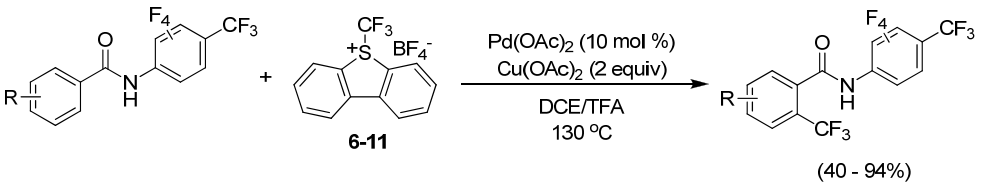

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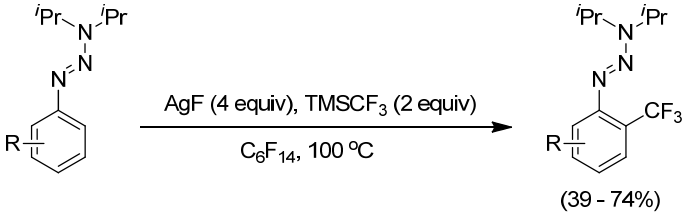
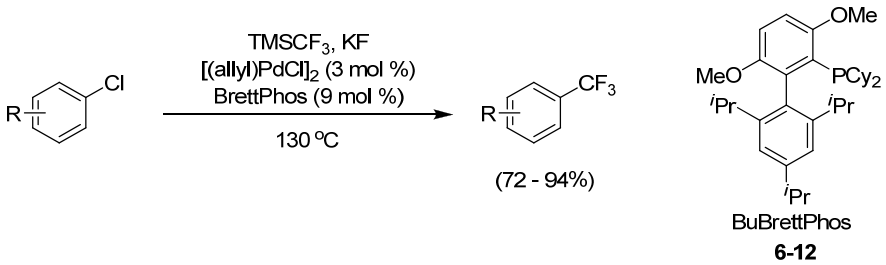


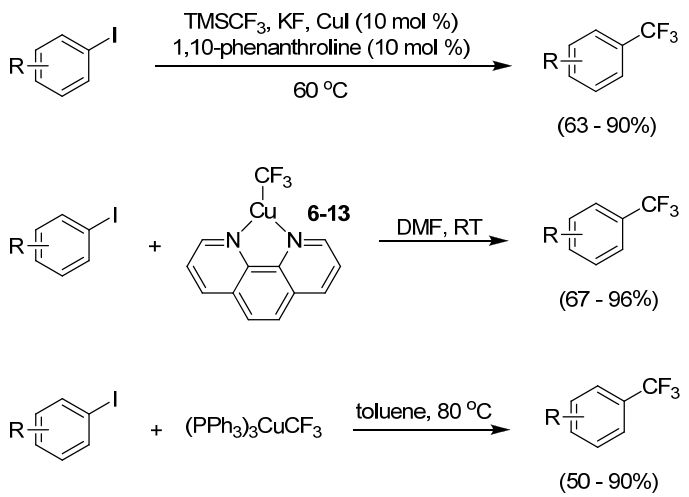
(18)

Buchwald reported the first palladium-catalyzed trifluoromethylation of aryl chlorides using $TESCF_3$ as the CF_3 source. This process tolerates range of functional groups including esters, amides, ethers, acetals, nitriles, and tertiary amines. The use of the bulky monodendate phosphine ligand (BuBrettphos, **6-12**) is crucial to form Ar-CF_3 linkage (Eq. 19).[30]



(19)

Copper-catalyzed trifluoromethylation of electron-deficient aryl iodides using $TESCF_3$ as the trifluoromethylating regent was reported in 2009 by Amii and co-workers.[31] The reaction is assumed to occur through the generation of Cu(I)-CF_3 complex followed by oxidative addition to form arylcopper (III) intermediate (Eq. 20). Hartwig further utilized the well-defined trifluoromethyl copper reagent **6-13** ligated by 1,10-phenanthroline and employed this reagent for trifluoromethylation of aryl iodides under mild conditions (Eq. 21).[32] Grushin also developed a stable and well-defined copper-based trifluoromethylating regent and the utility of this reagent toward trifluoromethylation was demonstrated with various *para*-substituted aryl iodides (Eq. 22).[33]

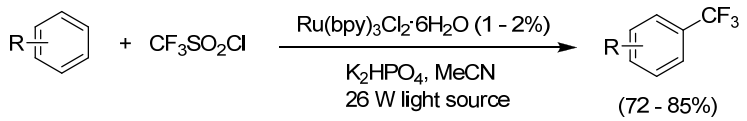


(20)

(21)

(22)

While these strategies can selectively introduce CF_3 group into the positions that are not naturally reactive, pre-functionalization of aromatic compounds or installation of directing groups is typically required. To address such limitations, radical-mediated innate trifluoromethylations have emerged as complementary methods.

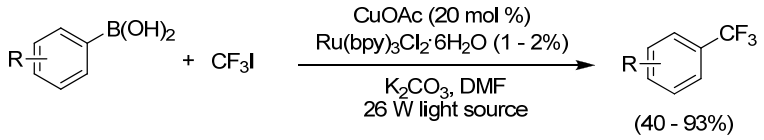


(23)

In 2011, MacMillan and co-workers reported the radical-mediated direct trifluoromethylation of unactivated arenes and heteroarenes using photo-redox catalyst and a household light bulb as the light

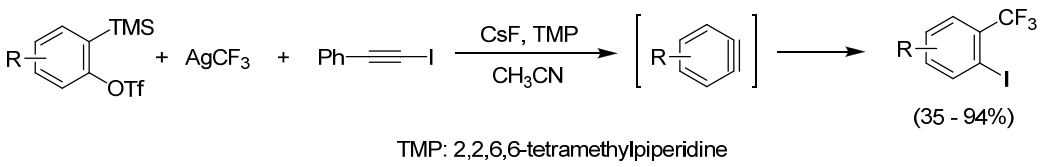
source (Eq. 23).[34] In this reaction, CF_3SO_2Cl was employed as the CF_3 radical source. It was demonstrated that this radical-mediated approach was successfully applied to the trifluoromethylation of biologically active molecules such as vitamin P, ibuprofen and the cholesterol-lowering drug, Lipitor. Although these methods preclude the necessity of pre-functionalization, a mixture of regioisomers is often generated. Thus regioselective incorporation of CF_3 group into arenes without pre-functionalization and directing group still remains a challenge.

Recently, Sanford reported a trifluoromethylation of aryl boronic acids with CF_3I via the merge of photo redox and copper catalysis. This protocol was applied to trifluoromethylation of electronically diverse arenes and heteroarenes (Eq. 24).[35]



(24)

The first example of trifluoromethylation-iodonation via aryne intermediate has been reported by Hu in 2013.[36] It was found that arynes generated from 1,2-elimination of 1-trimethylsilyl-2-aryl triflate can be simultaneously captured by both CF_3^- and I^+ to give trifluoromethyliodoarenes (Eq. 25).

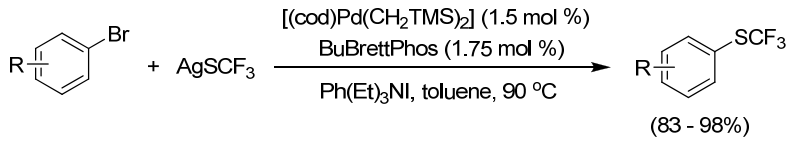


(25)

6.1.5. Synthetic Approaches for Trifluoromethylthiolated Arenes (Ar-SCF_3)

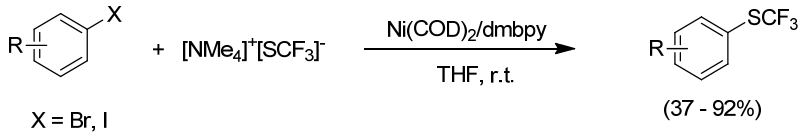
While significant progress has been made in trifluoromethylation of arenes, analogous triflouromethylthiolation has started gaining interests but less developed due to instability of SCF_3 salts under the standard metal-catalyzed cross-coupling conditions.[37] Buchwald reported a Pd-catalyzed triflouromethylthiolation of aryl bromides using $AgSCF_3$ as a triflouromethylthiolating agent. Optimal

combination of $AgSCF_3$ and $Ph(Et)_3NI$ with the incorporation of a bulky monodendate phosphine ligand (BuBrettPhos, **6-12**) are found to be critical to achieve a decent range of product yields.[38]



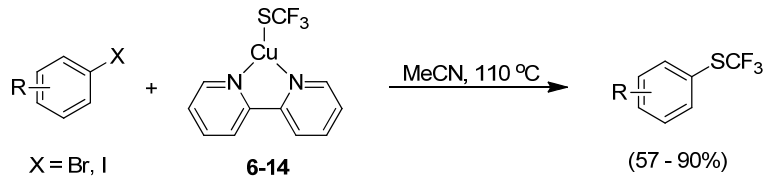
(26)

Vicic discovered an inexpensive nickel-bipyridine complexes were found to be active for the trifluoromethylthiolation of aryl iodides and aryl bromides at room temperature using the convenient $[NMe_4][SCF_3]$ reagent.[39]



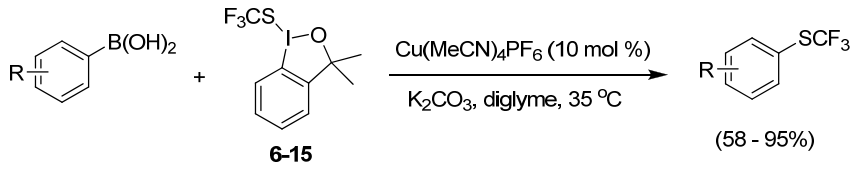
(27)

Huang developed an air-stable, copper-based triflouromethylthiolating agent **6-14** ligated by bipyridine ligand (Eq. 28) similar to that of Hartwig's reagent **6-13** in trifluoromethylation. This triflouromethylthiolating agent was found to react with a wide range of aryl halides to afford triflouromethylthiolated arenes.[40]



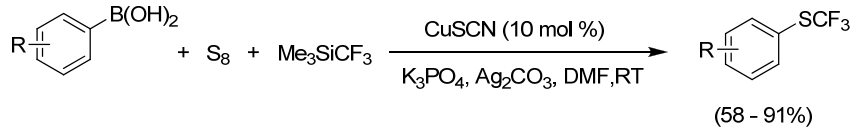
(28)

Shen has developed an electrophilic hypervalent iodine reagent **6-15** based on the well-defined Togni's reagent which utilized the 1,2-benziodoxol for triflouromethylthiolation with aryl boronic acids (Eq. 29).[41] Qing also reported a copper-catalyzed oxidative triflouromethylthiolation of aryl boronic acids using $TMSCF_3$ and elemental sulfur in the presence of Ag_2CO_3 at room temperature (Eq. 30).[42]



(29)

(58 - 95%)



(30)

(58 - 91%)

6.2. Results and Discussion

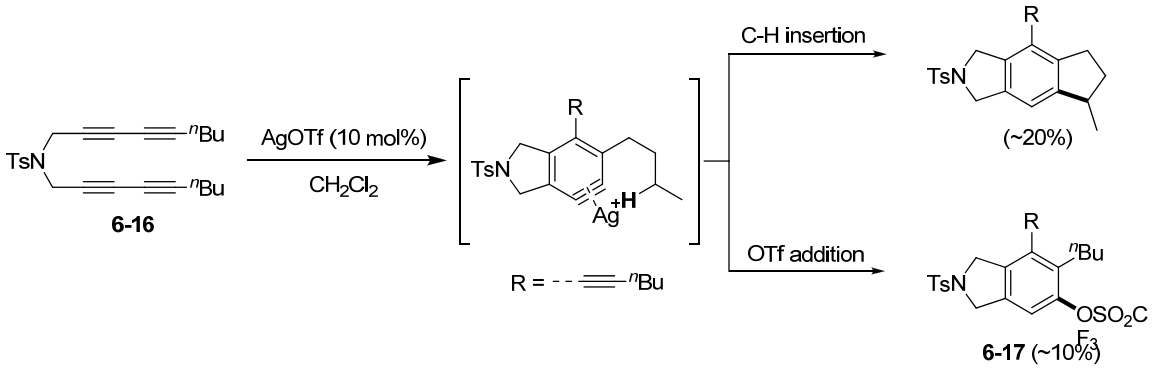
6.2.1. Fluorination

6.2.1.1. Initial Discovery of Silver-Mediated Fluorination

While we were exploring the reaction scope of the hydrohalogenation using *bis*-1,3-diynes with different metal complexes, we found that the reaction of *bis*-1,3-diyne substrate **6-16** containing butyl group with 10 mol % of silvertrifluoromethanesulfonate (AgOTf) in CH_2Cl_2 generated C–H insertion product along with aryl triflate **6-17** (**Scheme 6.1**). The formation of C–H insertion product can be maximized by switching the solvent from CH_2Cl_2 to non-polar solvent such as toluene and the details are discussed in the previous chapter. Inspired by the observed reactivity of arynes where even a weak nucleophile such as triflate (OTf) can serve as a nucleophile add to the π-bond of arynes in the presence of silver salt, we became interested in intercepting the putative silver-complexed aryne intermediate with unconventional nucleophiles such as fluorine anion (F^-). On the basis of the observed product outcome and the study of the C–H insertion in the previous chapter, we surmised that when the structure has prone to C–H insertion, the intramolecular C–H insertion is favored over the intermolecular nucleophilic addition of OTf anion. On the other hand, the nucleophilic addition reaction with even a weakly coordinating anionic ligand of silver such as OTf will become the major or the sole reaction pathway if C–H insertion is slow or the required C–H bond is not available. Based on this observed reactivity, we

became interested in intercepting putative silver aryne intermediate with fluoride sources to form aryl fluoride which is of much current interest.

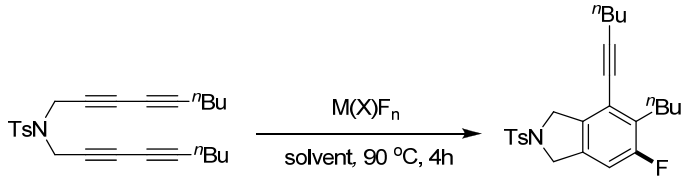
Scheme 6.1. Initial discovery of C–H insertion and triflate incorporation



6.2.1.2. Optimal Reaction Conditions

To test this concept, we searched for a suitable fluorinating reagent (**Table 6.1**) with symmetrical *bis*-1,3-diyne substrate **6-16**, which is known to have low reactivity toward C–H insertion. Silver fluoride (AgF)[43] was first used as the reagent which contains all required elements including the silver cation for the formation of the silver-coordinated aryne intermediate as well as the fluorine anion for the nucleophilic addition. Unfortunately, initial result indicated the starting material was totally consumed after 4 hours of reaction time but the desired fluoroarene **6-18** was not formed. We rationalized that the inefficiency of the transformation was due to the poor solubility of AgF in non-polar solvent like toluene. Switching the solvent to acetonitrile (MeCN) under otherwise identical reaction conditions resulted in the formation of fluoroarene product **6-18** in 20% yield and a large amount of polymers as indicated by broad ^{1}H NMR signals (entries 1–2). We then used $AgBF_4$ (silver tetrafluoroborate),[44] another common fluorine anion source but has higher solubility in organic solvent than AgF. Thus the reaction of substrate **6-17** with 1.5 equivalent of $AgBF_4$ in toluene was performed for 4 hours. The crude NMR indicated full conversion of the starting material and the fluorinated isolidoline product was formed in 96% yield (See **Chapter 6.4, Figure 6.7**).

Table 6.1. Fluoride source screen



6-16 **6-18**

entry	$M(X)F_n$	solvent	yield (%)[a]
1	AgF	toluene	0
2	AgF	MeCN	20
3	$AgBF_4$	toluene	96
4	$AgBF_4$	MeCN	0
5	$AgSbF_6$	toluene	0
6	$AgSbF_6$	MeCN	0
7	CuF_2	MeCN	0
8	$Cu(MeCN)_4PF_6$	MeCN	0
9	$Cu(MeCN)_4BF_4$	toluene	0
10	$[(Au_3O)(PPh_3)_3]BF_4$	MeCN	0
11	$[(Au_3O)(PPh_3)_3]BF_4$	toluene	0

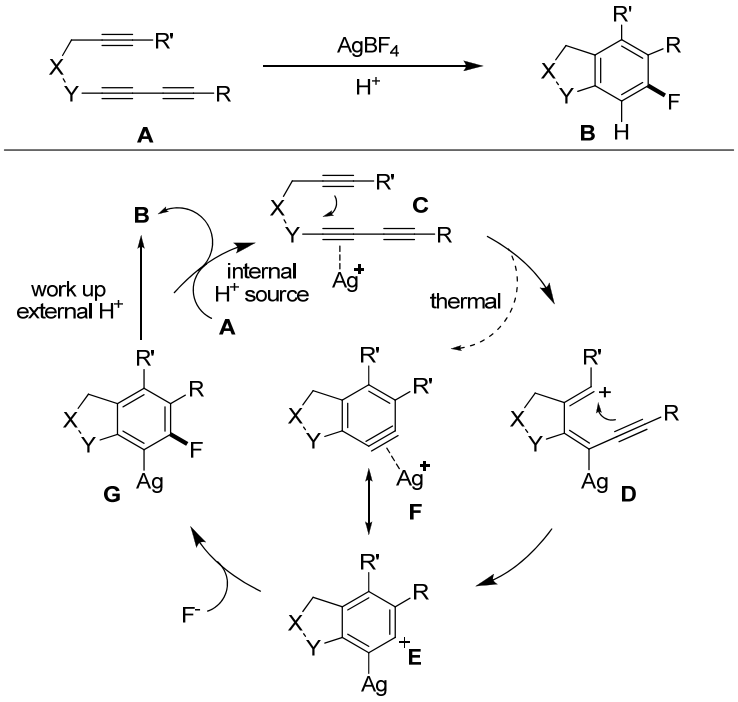
[a] Yield was determined by ^{1}H NMR with internal standard.

The same reaction run in MeCN under otherwise identical conditions failed to give fluorinated isolidoline product **6-18** and only polymers of the aryne (entries 3–4) were observed. Another silver salt containing fluoride source such as $AgSbF_6$ was tested in both toluene and MeCN, however no detectable amount of the product was observed (entries 5–6). Various fluorine-containing copper and gold complexes did not give any fluorinated product (entries 7–11) in both toluene and MeCN.

6.2.1.3. Mechanistic Study and Catalytic Fluorination

The thermal reactions of three alkynes to form an aryne, hexadehydro Diels-Alder reaction were reported as the pyrolysis (600 °C, 10^{-2} torr) of triyne by Johnson[45] and a radical-mediated stepwise ring-closure by Ueda.[46] Recently, Hoye and co-workers reported the expanded scope of this thermal hexadehydro Diels-Alder reaction.[47] As opposed to these thermal processes, we propose a mechanism that involves organosilver intermediate **G** (**Scheme 6.2**).

Scheme 6.2. Possible operating reaction mechanism

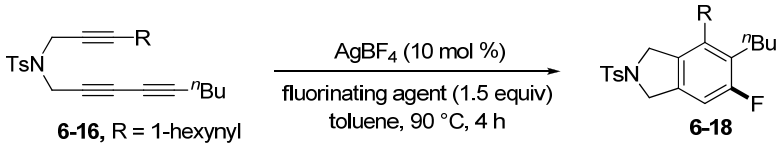


In this mechanistic scenario, although a concerted thermal Diels-Alder reaction is equally possible, a silver-coordinated 1,3-diyne **C** would undergo an intramolecular attack by the alkyne moiety in another side of the tethered 1,3-diyne to form a vinyl cation **D**. The highly active vinyl cation will then accept the electron from alkyne moiety to form an aryl cation **E** or its silver-stabilized aryne **F**.[48] The nucleophilic fluorine anion then participated in the reaction and added into the aryne intermediate to generate the organosilver species **G**. When a superstoichiometric amount of the $AgBF_4$ was used, the starting material **C** will exclusively convert to the organosilver intermediate **G** waiting for the subsequent protonolysis of which will then produce fluorinated product **B**. In the absence of the proton source, the proton-silver exchange occurred while work-up or exposed to moisture.

We postulated that this fluorination method could be performed in a catalytic manner because only catalytic amount of silver cation is needed as long as an efficient protonation of the silver–aryne complex **G** occurs during the reaction process, which will reduce the amount of the required silver salt for

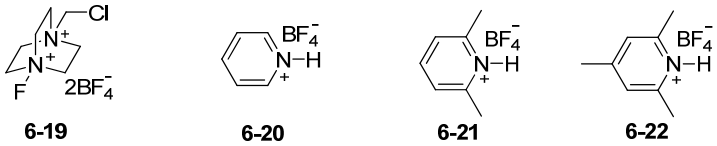
the reaction. To test the feasibility of this catalytic fluorination, $AgBF_4$ was chosen as the catalyst on the basis of its effectiveness in the stoichiometric reaction, and a variety of fluorinating agents were evaluated (**Table 6.2**).

Table 6.2. Catalytic fluorination by $AgBF_4$ and pyridinium salts



entry	fluorinating agent	yield (%)[a]
1	CsF	<10
2	**6-19**	<10
3	**6-20**	89
4	**6-21**	81
5	**6-22**	82
6	**6-20** without $AgBF_4$	0

[a] Yield was determined by ^{1}H NMR with internal standard.



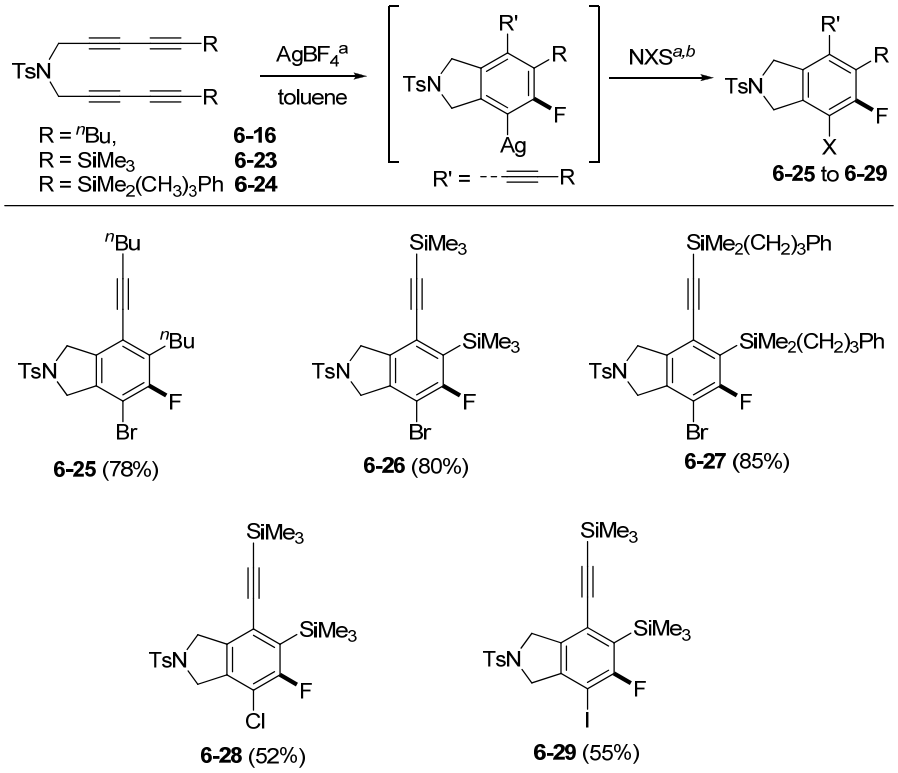
6-19 **6-20** **6-21** **6-22**

The reaction of substrate **6-16** with $AgBF_4$ (10 mol %) and a common fluorinating agent lacking proton such as cesium fluoride (CsF) or selectfluor **6-19**,[49] did not show any catalytic turnover, yielding less than 10% of aryl fluoride which should be derived from the added 10 mol % of $AgBF_4$ (entries 1–2). On the other hand, performing the reaction with pyridinium salts **6-20**, **6-21** and **6-20** under otherwise identical conditions, reached complete conversion within 4 hours. Among these pyridinium salts screened, **6-20** was found to be most efficient, providing the fluorinated arene in 89% yield with only 10 mol % of $AgBF_4$ used (entry 3). More sterically hindered pyridinium salts **6-21** and **6-22** showed slightly lower yield than that of **6-20**. As expected, the reaction of substrate **6-16** with fluorinating reagent **6-20** alone without adding sliver catalyst did not give any desired product (entry 6), which indicates that the silver

cation plays an important role for this transformation, and thus the fluorination is not the result of a simple nucleophilic trapping of a free aryne species by fluorine anion (See **Chapter 6.4**, **Figure 6.7**).

With this proposed mechanism, we surmised that the organosilver intermediate **G**, if exists, could be trapped by an appropriate electrophile. In order to test this possibility, substrate **6-16** was treated with $AgBF_4$ (1.5 equiv) and 2 equivalent of *N*-bromosuccimide under typical reaction conditions (toluene, 90 ^oC, 4 hours). Gratifyingly, a 1,2-fluorobromo-, *bis*-halogenated product **6-25** was isolated in 78% yield. (**Table 6.3**)

Table 6.3. Stoichiometric *bis*-Halogenation under fluorination conditions with halosuccinimide



[a] Reaction was performed by mixing *bis*-1,3-diyne with $AgBF_4$ (1.5 equiv) and NXS (2 equiv) in toluene at 90 ^oC for 4 h. [b] NXS = *N*-Halosuccinimide (X = Cl, Br, I).

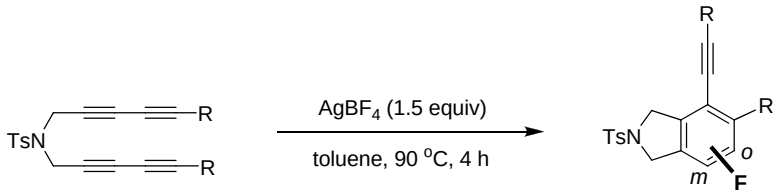
Similarly, exposure of substrate **6-23** and **6-24** to the same conditions but with *N*-chloro and *N*-iodosuccinamide afforded corresponding *bis*-halogenated arenes **6-26** (80%), **6-27** (85%), **6-28** (52%) and **6-29** (55%), respectively. The formation of these *bis*-halogenated arene products is a strong evidence for

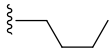
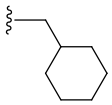
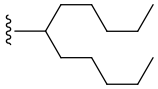
the existence of the proposed organosilver species **G** in Scheme 6.2 and further strength our proposed reaction mechanism based on the formation of organosilver intermediate.

6.2.1.4. Reaction Profile of Fluorination

Next, we examined how the substituents on the *bis*-1,3-diyne will affect the regioselectivity of fluoride addition (**Table 6.4**). Fluorination of substrate **6-17** containing a butyl group in the *bis*-1,3-diyne provided only *ortho*-regioisomer **6-18** in 93% isolated yield (entry 1), whereas a similar substrate **6-30** containing slightly larger cyclohexylmethylene group produced a mixture of *ortho*- and *meta*-isomers **6-33** and **6-33′** in 85% combined yield with a ratio of 88:12 (entry 2).

Table 6.4. Steric effect of fluorination



entry	substrate	R	ratio (*o*-F: *m*-F)	yield (%)[a]
1	**6-16**		**6-18 : 6-18'** (100 : 0)	93
2	**6-30**		**6-33 : 6-33'** (88 : 12)	85
3	**6-31**		**6-34 : 6-34'** (55 : 45)	86
4	**6-32**		**6-35 : 6-35'** (7 : 93)	91
5	**6-23**		**6-36 : 6-36'** (100 : 0)	91

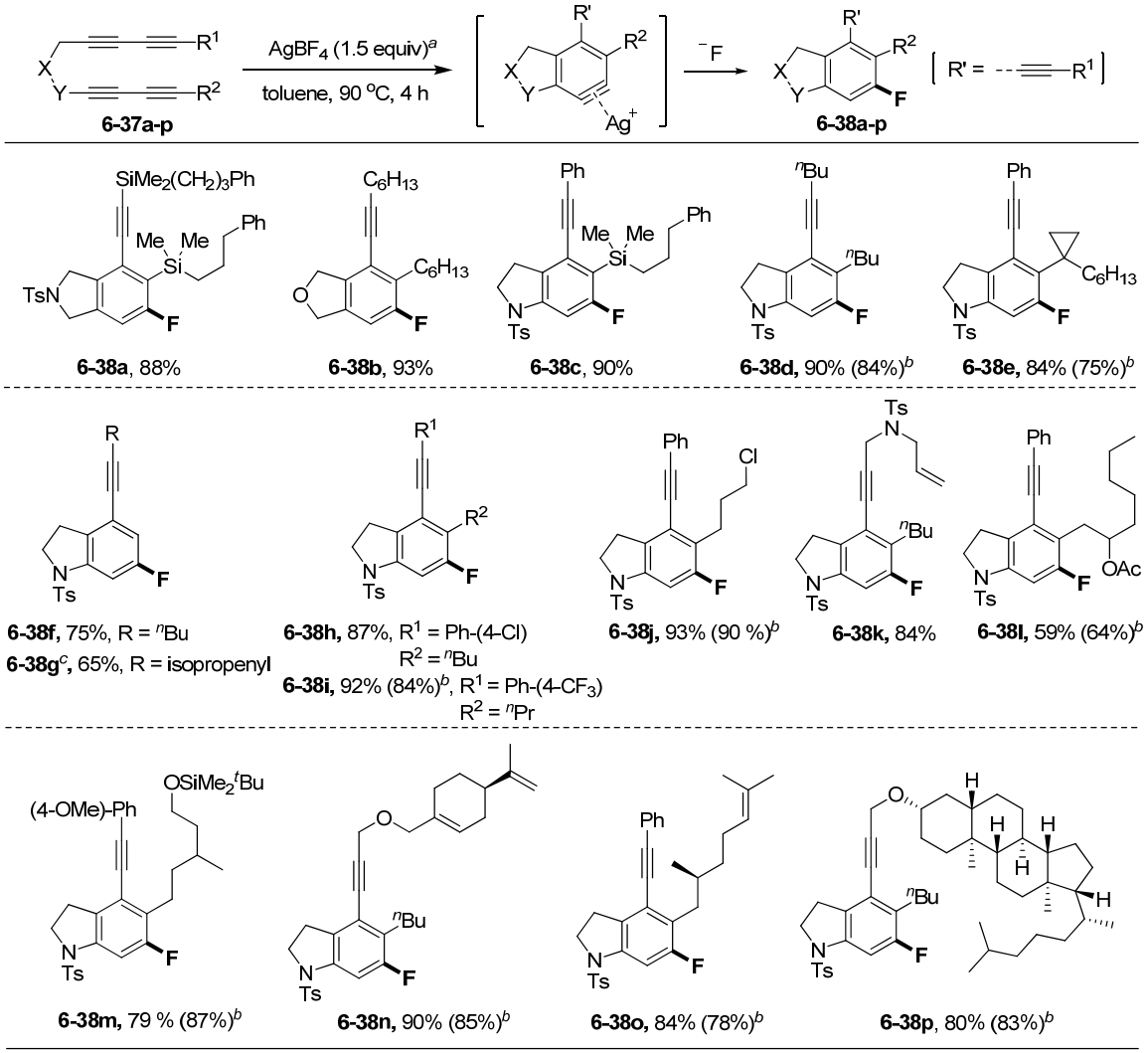
[a] Isolated yield

Furthermore, when the fluorination was run with the substrate **6-31** having secondary alkyl group, *ortho*-fluorination product **6-34** was still slightly preferred, giving a 55:45 ratio of two isomers in 86% combined yield (entry 3). While the fluorination of substrate **6-32** possessing a bukyl *t*-butyl group

afforded predominantly *meta*-isomer **6-35′** in a 7:93 ratio with 91% combined yield (entry 4). However, substrate **6-23** containing trimethylsilyl group gave exclusively *ortho*-isomer **6-36** in 91% yield despite the large size of the trimethylsilyl group (entry 5). This *ortho*-directing effect of silyl group is consistent with the reaction outcome previously reported by Akia and co-workers for the nucleophilic addition of primary amines to silylbenzynes.[50]

Because the conventional fluorination methods such as Halex process require relatively severe conditions to forge the Ar-F bond, early-stage installation of the fluorine atom is generally required. In the development of an effective new tool for the late-stage fluorination, the compatibility of existing functional groups with fluorination conditions is considered to be one of the most important issues.[15b] Under the established optimal reaction conditions for the in situ aryne formation and subsequent nucleophilic fluorine addition, various *bis*-1,3-diyne substrates **6-37a–p** containing a range of functional groups were examined (**Table 6.5**). All substrates efficiently provided fluoroarene products with high regio- and chemoselectivity. As we previously described silyl-substituted *bis*-1,3-diyne **6-37a** gave the fluorinated isoindoline derivative **6-38a** in 88% yield as a single regioisomer where the regioselectivity was controlled by the directing effect of sliyl group. *Bis*-1,3-diyne substrate **6-37b** having an oxygen tether afforded fluorinated dihydroisobenzene **6-38b** with complete *ortho*-addition in 90% yield. Moreover, *bis*-1,3-diyne substrates **6-37c–p** containing an ynamide moiety,[51] which can be easily accessed in few steps, provided corresponding fluorinated indoline derivatives **6-38c–p** in moderate to excellent yields.

Table 6.5. Reaction scope of fluorination



[a] All yields are reported as isolated yields.
[b] Numbers in paranthesis are the yield for catalytic reactions with $AgBF_4$ (10 mol%) and fluorinating reagent(II) (1.5 equiv).
[c] Reaction starts with R = $C(CH_3)_2OBn$ undergo E-1 elimination in the presence of $AgBF_4$ to generate isopropenyl group.

On the basis of the inherent regioselectivity trend of the nucleophilic addition to indolynes reported by Garg and Houk,[52] the nucleophile addition to arynes generated from ynamide-containing *bis*-1,3-diynes is anticipated to be regioselective. As expected, regardless of the steric and electronic nature of the substituent that attached to ynamide, fluorinated indolines were obtained as a single regioisomer where the fluorine is attached to the *meta*-carbon to the indoline nitrogen.

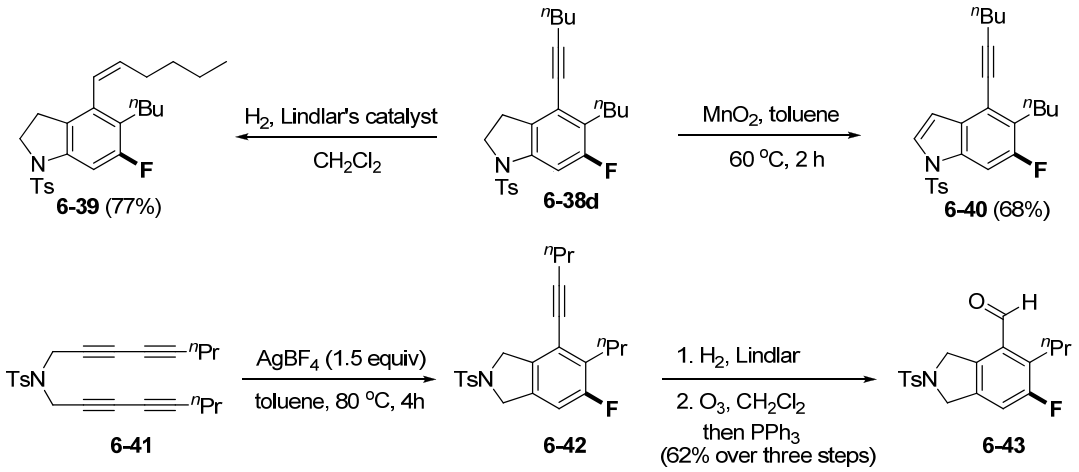
Specifically, silyl, primary and tertiary alkyl group-substituted *bis*-1,3-diynes **6-37c–e** provided fluorinated products **6-38c** (93%), **6-38d** (90%) and **6-38e** (84%) as a single product with complete regioselectivity. Fluorination of arynes derived from terminal *bis*-1,3-diyne **6-37f** and **6-37g** also afforded fluoroarenes **6-38f** and **6-38g** but with diminished yields due to the instability of the terminal 1,3-diyne at high temperature. It is worth to mention that for the formation of product **6-38g** from the substrate bearing benzyl-protected tertiary alcohol, a subsequent E1 elimination was promoted by the Lewis acidity of the silver cation and boron trifluoride (BF_3) to generate isopropenyl group during the fluorination process.

In this fluorination, a high level of functional group tolerance was recognized such that halogen, nitrogen, and alkene functional groups did not interfere with fluorination, affording products **6-38h–k** in good yields. Various oxygen functionalities including acetate, methoxy, and other silyl ether moieties, which are sensitive to the strong Lewis acidic environment, remained untouched under these conditions, providing products **6-38l** and **6-38m** in 59% and 79% yield respectively. Fluorination of *bis*-1,3-diyne substrates **6-37n–p** containing natural product-derived functional groups such as perillyloxymethyl, citronelly, and dihydrochloesterol groups, provided structurally diversified fluorinated indolines **6-38n–p** in 80–90% yields. The individual yield for each substrate under catalytic version of fluorination was also shown in parenthesis in Table 6.5.

While we were exploring the reactivity of the multiyne system, we found that *bis*-1,3-diyne substituent is necessary for the efficient formation of the aryne intermediate[53] although the extra alkyne group does not directly participate in the aryne formation. In order to take advantage of this extra alkyne, we performed alkyne functional group transformation after fluorination (**Scheme 6.3**). Fluorinated indoline **6-38d** could be either semi-hydrogenated by using Lindlar's conditions[54] (H_2, Pd/$CaCO_3$, quinoline) to give Z-alkenyl substituted indoline product **6-39** in 77% yield or oxidized by MnO_2[55] in toluene at 60 ^oC to afford the corresponding fluorinated indole derivative **6-40** in 68% yield. Fluorinated isoindoline carboxaldehyde **6-43** could be generated in 62% overall yield from *bis*-1,3-diyne substrate **6-**

41 via a stoichiometric fluorination to form **6-42** followed by semi-hydrogenation and ozonolysis sequence.

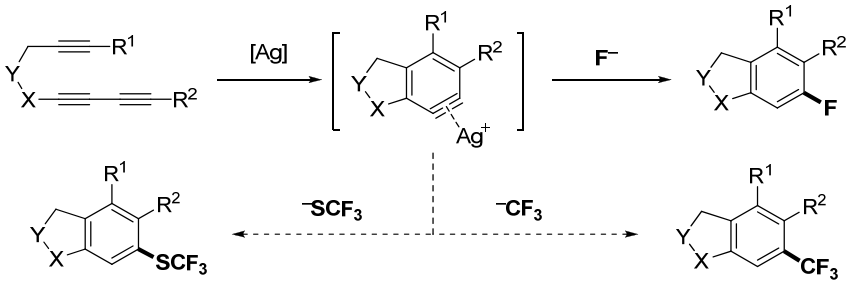
Scheme 6.3. Functionalization of the extra alkyne moiety in fluorinated indoline and isoindoline



6.2.2. Trifluoromethylation and Trifluoromethylthiolation

In the context of silver-mediated fluorination of *bis*-1,3-diynes, high level of regioselectivity was achieved by tailoring steric and electronic nature of substituents on *bis*-1,3-diynes. To expand the synthetic utility of this unique transformation of *bis*-1,3-diynes, we became interested in intercepting the putative silver stabilized aryne species with nucleophilic CF_3 or SCF_3 sources (**Scheme 6.4**).

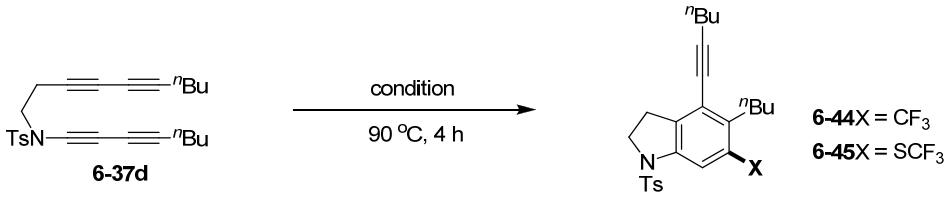
Scheme 6.4. Purposed approaches for Ar-F, Ar-CF_3 and Ar-SCF_3 formations



6.2.2.1. Optimal Reaction Conditions for Ar-CF_3 and Ar-SCF_3 Formations

First, we used the conventional method to generate CF_3 anion for the nucleophilic trifluoromethylation (**Table 6.6**). Classically, CF_3 anion can be generated in situ by mixing Ruppert's reagent ($TMSCF_3$)[56] with fluoride source such as CsF in a 1:1 mixture of toluene and CH_3CN (entry 1). However, the reagent generated by this method when applied to *bis*-1,3-diyne substrate **6-37d** under thermal conditions did not produce any trifluoromethylation product **6-44** and the starting material decomposed. Changing fluoride sources and catalysts still failed to provide any trifluoromethylated product (entries 2-6).

Table 6.6 Optimal conditions for trifluoromethylation and trifluoromethylthiolation



Entry	Reagents	Catalyst (10 mol %)	Solvent	Product	Yield (%)[b]
1	$TMSCF_3$ (2 equiv), CsF (2 equiv)	none	toluene/CH_3CN	**6-44**	0
2	$TMSCF_3$ (2 equiv), CsF (2 equiv)	AgOTf	toluene/CH_3CN	**6-44**	0
3	$TMSCF_3$ (2 equiv), KF (2 equiv)	AgOTf	toluene/CH_3CN	**6-44**	0
4	$TMSCF_3$ (2 equiv), CsF (2 equiv)	$AgNO_3$	toluene/CH_3CN	**6-44**	0
5	$TMSCF_3$ (2 equiv), CsF (2 equiv)	$AgSbF_6$	toluene/CH_3CN	**6-44**	0
6	$TMSCF_3$ (2 equiv), NH_4F (2 equiv)	$AgSbF_6$	toluene/CH_3CN	**6-44**	0
7[a]	$AgCF_3$ (1.5 equiv)	none	CH_3CN	**6-44**	75
8[a]	$AgCF_3$ (1.5 equiv)	none	toluene	**6-44**	<10
9	$AgSCF_3$ (1.5 equiv)	none	CH_3CN	**6-45**	69[c]
10	$AgSCF_3$ (1.5 equiv)	none	toluene	**6-45**	85

[a] The $AgCF_3$ was generated in situ by mixing AgF (1.5 equiv) with $TMSCF_3$ (2 equiv) at room temperature for 30 mins. [b] Isolated yield. [c] 7% of starting material was recovered.

At this juncture, we envision that the incorporation of stoichiometric amount of trifluoromethylsilver ($AgCF_3$)[57] would generate the silver-stabilized aryne intermediate as well as the required CF_3 anion. Subsequent protonation of this organosilver intermediate during the work up process

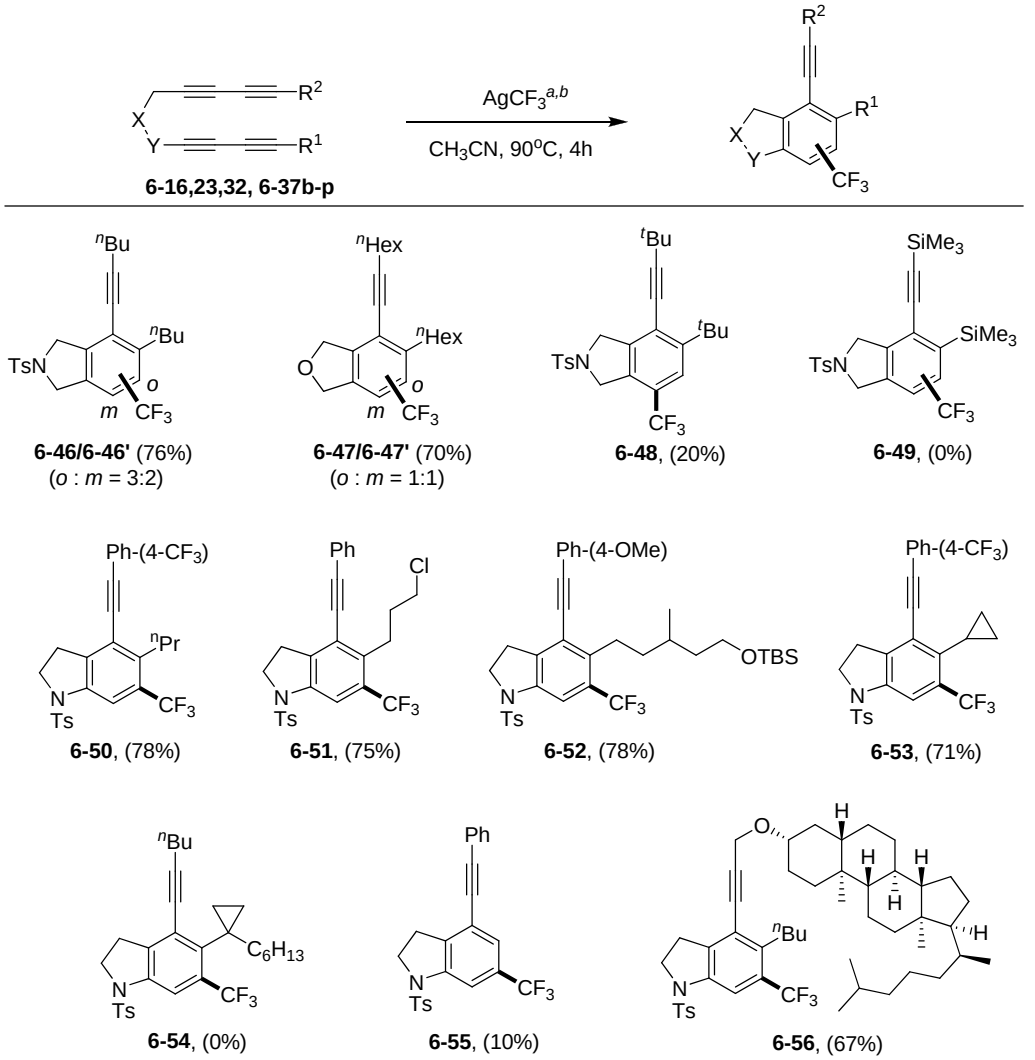
should deliver the corresponding trifluoromethylated arene without extra additives. Indeed, addition of the tetrayne substrate **6-37d** into CH_3CN solution containing $AgCF_3$ generated in situ from mixing AgF (1.5 equiv) and $TMSCF_3$ (2 equiv) in CH_3CN (excess amount of the $TMSCF_3$ was used to exclude the free fluoride anion in the possible fluorination reaction) gave trifluoromethylated product **6-44** in 75 % isolated yield (entry 7). However, the reaction in toluene provided less than 10% of the product **6-44**.

With this successful result in hand, we applied the similar reaction conditions but replaced $AgCF_3$ with $AgSCF_3$,[58] trifluoromethylthiolated product **6-45** was obtained in 69% yield with 7% of the recovered starting material. Raising the temperature up to 100 ^{o}C and longer reaction time led to full conversion but no improvement in yield. Running the reaction in toluene, however, a full conversion of the starting material was observed and the trifluoromethylthiolated product **6-45** was obtained in higher yield (85%) after purification.

6.2.2.2. Reaction Scope of Trifluoromethylation

Securing the optimal reaction conditions, we then explored the reaction scope of the trifluoromethylation with various symmetrical and unsymmetrical *bis*-1,3-diyne substrates (**Table 6.7**). Regardless of the nature of tether, primary alkyl substituted symmetrical *bis*-1,3-diynes **6-17** and **6-37b** bearing NTs or oxygen in the tether produced a mixture of regioisomers **6-46**/**6-46′** (**6-46** : **6-46′** = 3:2) for NTs tether substrate in 76% yield and **6-47**/**6-47′** (**6-47** : **6-47′** = 1:1) for oxygen tether substrate in 70% yield. In case of sterically hindered *t*-butyl-substituted symmetrical *bis*-1,3-diyne **6-32**, single regioisomer **6-48**, which has the CF_3 group at *meta*-position to the butyl *t*-butyl group, was obtained with significantly diminished yield. For the *bis*-1,3-diyne substrate carrying trimethylsilyl group **6-23**, trifluoromethylation was not viable, giving no desired product **6-49**.

Table 6.7. Reaction scope of trifluoromethylation



[a] Isolated yield. [b] $AgCF_3$ was generated in situ by mixing AgF (1.5 equiv) and $TMSCF_3$ (2 equiv) in CH_3CN for 30 min.

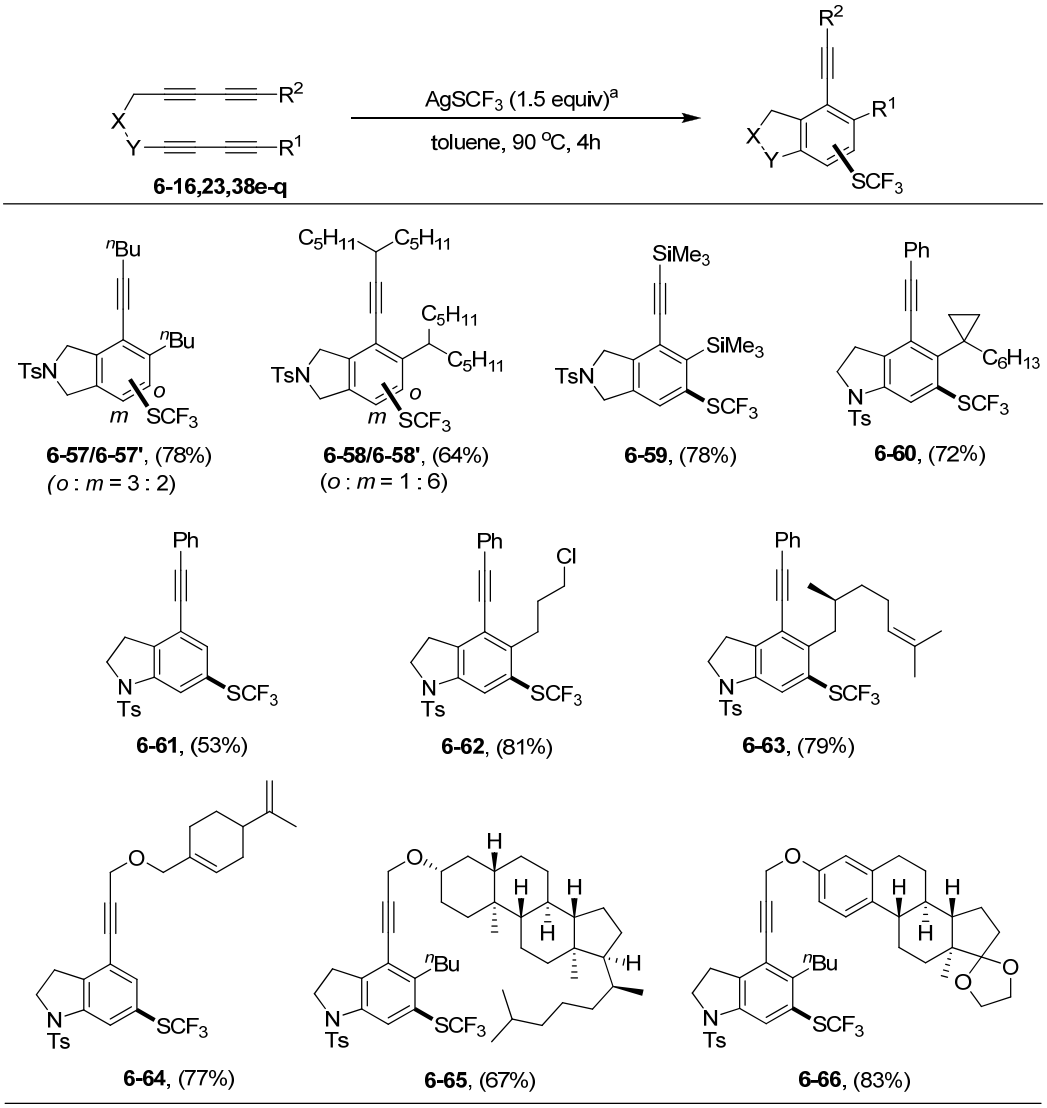
Considering the fact that the similar fluorinated isoindoline **6-36** can be obtained in higher yield with complete *ortho*-selectivity, it is reasonable to infer that the size of the CF_3 group is not compatible with the sterically bulky trimethylsilyl group. In general, ynamide-derived unsymmetrical *bis*-1,3-diyne substrates afforded a single regioisomer, where the regiochemical sense of nucleophile addition is consistent with Garg and Houk's calculation of indolynes. Relying on this trifluoromethylation protocol, various trifluoromethylated indolines were obtained. This trifluoromethylation showed high level of functional group tolerance, and the corresponding trifluoromethylated indoines containing CF_3 (**6-50**),

chloride (**6-51**), methoxy and silylether functionalities (**6-52)** can be obtained without interference. The reaction also works smoothly with sterically hindered 2° alkyl substituent, and thus trifluoromethylation product **6-53** bearing cyclopropyl group can be obtained in 71% yield. However, more steric hindered 3° alkyl group on the diynes completely prohibit the reaction, thus indoline product **6-54** was not observed. The reaction with substrate containing terminal diyne was not efficient, providing only 10% of the desired trifluoromethylated product **6-55**. Running the reaction with *bis*-1,3-diyne bearing dihydrochloesterol substituent provided structurally elaborated trifluoromethylated indoline derivative **6-56** in 67% yield.

6.2.2.3. Apply Optimal Reaction Conditions for Trifluoromethylthiolation

Next, we performed trifluoromethylthiolation with various symmetrical and unsymmetrical *bis*-1,3-diynes using $AgSCF_3$ as a nucleophilic SCF_3 source (**Table 6.8**). Under optimal reaction conditions, the trifluoromethylthiolation with 1° and 2° alkyl substituted symmetrical *bis*-1,3-diynes in the presence of $AgSCF_3$ still produce mixture of regioisomers. For the 1° alkyl substituted *bis*-1,3-diynes **6-16**, a 3:2 ratio of *ortho*- and *meta*-regioisomers **6-57**/**6-57′** were obtained, and this regioisomeric ratio is similar to that of trifluoromethylation products **6-46**/**6-46′**. When more sterically hindered 2° alkyl group substituted *bis*-1,3-diyne **6-36q** was used, the nucleophilic trifluoromethylthiolation prefers to attack the less steric hindered *meta*-position to give a 1:6 ratio of regioisomers **6-58**/**6-58′** in favor of *meta*-addition. In case of trimethylsilyl substituted symmetrical *bis*-1,3-diyne **6-23**, 78% of trifluoromethylthiolation product **6-59** was obtained with complete *ortho*-selectivity probably because of the smaller size of trifluoromethylthio group compared to trifluoromethyl group and the *ortho*-directing effect of the silyl group. Ynamide-containing unsymmetrical *bis*-1,3-diynes generally afford single regioisomers regardless of the substituent patterns on both side of the diyne. More specifically, substrate bearing 3° alkyl group **6-38e** provided trifluoromethylthiolated indoline **6-60** smoothly in 72% yield with complete *ortho*-regioselectivity as opposed to trifluoromethylation that failed to generate any desired product.

Table 6.8. Reaction scope of trifluoromethylthiolation



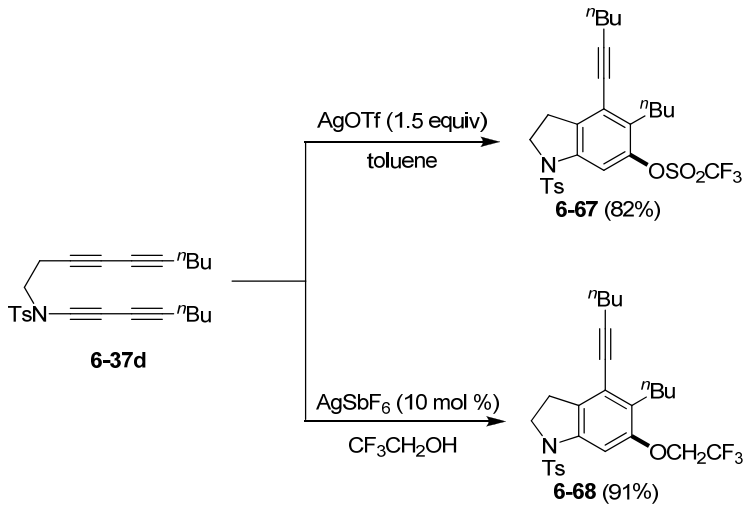
[a] Isolated yield.

Trifluoromethylthiolation of unsymmetrical *bis*-1,3-diyne substrate bearing a terminal diyne provide 4,6-disubstituted indoline compound **6-61** in 53% yield. Substituted indoline **6-62** containing alkyl halide could also be prepared under these conditions. For the purpose of late-stage trifluoromethylthiolation, substrates containing natural product derivatives are examined, and trifluoromethylthiolated indolines containing citronelly **6-63**, perillyloxymethyl **6-64**, dihydrochloesterol **6-65** and 1,3-dioxolane estrone **6-66** groups could be obtained in 79, 77, 67 and 83% yield, respectively.

6.2.3. Forming Other CF_3 Containing Moieties via Aryne Intermediate

Based on the unique reactivity of aryne intermediate in the presence of silver cation and the predominant regioselectivity of nucleophilic addition to indolynes generated from ynamide-containing unsymmetrical *bis*-1,3-siynes, we could introduce trifluoromethanesulfonate (OTf) and 2,2,2-trifluoroethoxyl groups to the newly formed aryne moiety generated from *bis*-1,3-diyne substrate **6-37d** to form indoline products **6-67** and **6-68** with high yields and complete regioselectivity (**Scheme 6.5**).

Scheme 6.5. Nucleophilic addition of other CF_3 containing moieties



6.3. Conclusion

In summary, a new unified approach to generate Ar-F, Ar-CF_3 and Ar-SCF_3 is developed via a regioselective nucleophilic addition to a silver-complexed aryne intermediate generated in situ from non-aromatic building blocks. These unique transformations highlight simplicity of operation, broad substrate scope, and excellent regioselectivity. Mechanistically, the formation of the organosilver intermediate was validated by *bis*-halogenation experiments with halosuccinamides in fluorination process. It is worth to mention that our method can generate Ar-F, Ar-CF_3, and Ar-SCF_3 products in one step from non-aromatic building blocks, which is a truly unique feature compared to other reported methods that use aromatic

building blocks. These merits would find many applications especially in the field of drug discovery and pharmaceuticals.

6.4. Experimental Details

6.4.1. General Information

All reactions were run under an atmosphere of nitrogen, unless otherwise indicated. Flasks were oven-dried overnight and cooled under a stream of nitrogen. Compounds were purchased from Aldrich unless otherwise noted. CH_2Cl_2, THF, Et_2O, MeCN and toluene were purified based on standard procedures. AgF was purchased from Oakwood Product Inc, and $TMSCF_3$ was purchased from Matrix Scientific. $AgSCF_3$ was made followed the literature procedure[56] and stored at -20 ^oC in the glove box. Flash chromatography was performed using silica gel 60 Å (32-63 mesh) purchased from Silicycle Inc. Analytical thin layer chromatography (TLC) was performed on 0.25 mm E. Merck pre-coated silica gel 60 (particle size 0.040-0.063 mm). ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AV-500 spectrometer at 501 MHz and 126 MHz respectively, ^{19}F NMR spectra was recorded on Bruker Avance 400 MHz (at 375 MHz) or Varian Mercury 300 MHz (at 283 MHz) spectrometer using CF_3COOH (-76.6 ppm) as a reference standard; multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), qn (quintet), m (multiplet) and br (broad). Coupling constants, *J*, are reported in Hertz. Electrospray ionization (ESI) mass spectra were recorded on a Micromass LCT equipped with a time-of-flight analyzer at the Mass Spectrometry Laboratory at the University of Illinois at Urbana-Champaign.

6.4.2. General Procedure for the Synthesis of Symmetrical and Unsymmetrical *bis*-1,3-Diynes (Same Procedures in Chapter 4.4.2 and 4.4.3)

6.4.3. General Procedure for the Stoichiometric Fluorination: In a glove box, *bis*-1,3-diyne (0.1 mmol) and $AgBF_4$ (0.15 mmol) were dissolved in 5 mL of toluene in a thick-walled 25 mL Schlenk tube equipped with a magnetic stirring bar. The reaction tube was brought out of the box, and was stirred in an

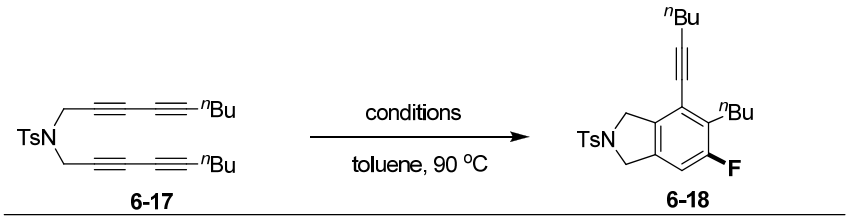
oil bath at 90 °C for 2 h. The tube was opened to air at room temperature and the crude reaction mixture was filtered through a small pipet column packed with silica gel. The solvent was removed under reduce pressure and the organic product was isolated by column chromatography on silica gel.

6.4.4. General Procedure for the Catalytic Fluorination Reaction: In a glove box, *bis*-1,3-diyne (0.1 mmol), pyridinium salt (0.15 mmol, generated in situ by mixing 1:1 ratio of selected base and $HBF_4 \cdot OEt_2$) and $AgBF_4$ (0.01 mmol) were dissolved in 5 mL of toluene in a thick-walled 25 mL Schlenk tube equipped with a magnetic stirring bar. The reaction tube was brought out of the box, and was stirred in an oil bath at 90 °C for 4 h. The tube was opened to air at room temperature and the crude reaction mixture was filtered through a small pipet column packed with silica gel. The solvent was removed under reduce pressure and the organic product was isolated by column chromatography on silica gel.

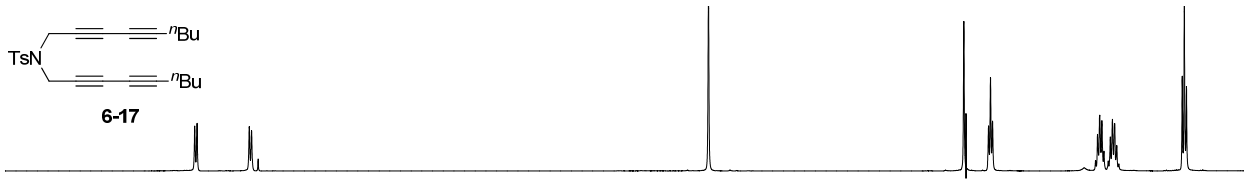
6.4.5 General Procedure for Trapping of a Putative Organosilver Intermediate by Using Different Halosuccinimides: In a glove box, *bis*-1,3-diyne (0.1 mmol), $AgBF_4$ (0.15 mmol) and halosuccinimide (0.2 mmol) were dissolved in 5 mL of toluene in a thick-walled 25 mL Schlenk tube equipped with a magnetic stirring bar. The reaction tube was brought out of the box and stirred in an oil bath at 90 ^{o}C for 4 h. The tube was opened to air at room temperature and the crude reaction mixture was filtered through a small pipet column packed with silica gel. The solvent was removed under reduce pressure and desired 1,2-halofluoroarenes were isolated by column chromatography on silica gel.

6.4.6 General Procedure for the Trifluoromethylation: In a glove box, AgF (0.15 mmol) was added into a solution of $TMSCF_3$ (0.2 mmol) in 3 mL of MeCN in a thick-walled 25 mL Schlenk tube equipped with a magnetic stirring bar. The reaction tube was stirred at room temperature for 30 min, then the *bis*-1,3-diyne (0.1mmol) in 2 mL of MeCN was added. The reaction tube was brought out of the box, and was stirred in an oil bath at 90 °C for 4 h. The tube was opened to air at room temperature and solvent was removed under reduce pressure. The organic product was isolated by column chromatography on silica gel.

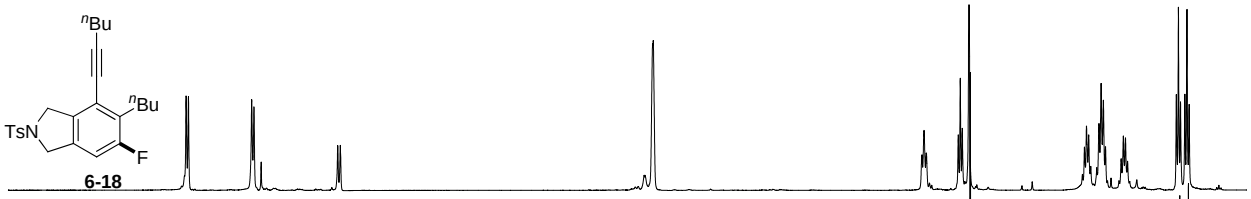
6.4.7 General Procedure for the Trifluoromethylthiolation: In a glove box, *bis*-1,3-diyne (0.1 mmol), and $AgSCF_3$ (0.15 mmol) were dissolved in 5 mL of toluene in a thick-walled 25 mL Schlenk tube equipped with a magnetic stirring bar. The reaction tube was brought out of the box, and was stirred in an oil bath at 90 °C for 4 h. The tube was opened to air at room temperature and solvent was removed under reduce pressure. The organic product was isolated by column chromatography on silica gel.



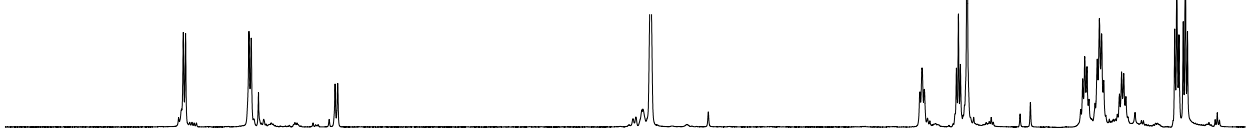
A ^{1}H NMR of substrate **6-17**



B Crude ^{1}H NMR of **6-18** (stoichiometric fluorination, Table 6.1, entry 3)



C Crude ^{1}H NMR of **6-18** (catalytic fluorination, Table 6.2, entry 3)



D Crude ^{1}H NMR of reaction with only pyridinium salt **6-20** (Table 6.2, entry 6)

E ^{1}H NMR of **6-18** after purification

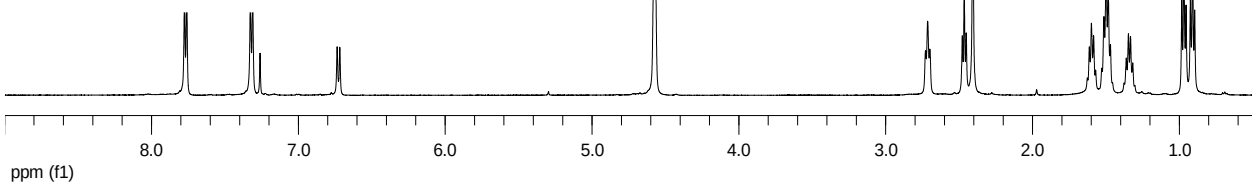
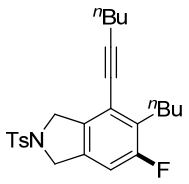


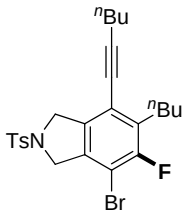
Figure 6.7. Efficiency of fluorination reaction under specified conditions

6.4.8. Selected Characterization Data



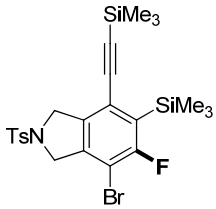
6-18

6-18 (93%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.5 Hz, 2H), 7.32 (d, *J* = 8.5 Hz, 2H), 6.73 (d, *J* = 9 Hz, 1H), 4.57 (s, 4H), 2.72 (t, *J* = 7 Hz, 2H), 2.47 (t, *J* = 7 Hz, 2H), 2.40 (s, 3H), 1.61 (qn, *J* = 7 Hz, 2H), 1.52 (m, 4H), 1.36 (m, 2H), 0.98 (t, *J* = 7 Hz, 3H), 0.92 (t, *J* = 7 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 161.7 (d, *J* = 242.1 Hz), 143.7, 134.3, 134.2, 133.9, 131.2 (d, *J* = 17.5 Hz), 129.9, 127.6, 120.3 (d, *J* = 6.3 Hz), 108.9 (d, *J* = 26.2 Hz), 99.5, 75.5 (d, *J* = 2.9 Hz), 54.1, 53.8, 31.8, 30.7, 27.0, 22.6, 22.0, 21.5, 19.3, 13.9, 13.6; **^{19}F NMR** (375 MHz, $CDCl_3$) δ -118.5 (d, *J* = 8.3 Hz); **HRMS** (ESI) calcd for $C_{25}H_{31}FNO_2S$ $[M+H]^+$: 428.2060, found 428.2068.



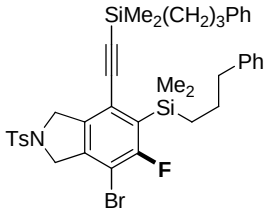
6-25

6-25 (78%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8 Hz, 2H), 7.34 (d, *J* = 8 Hz, 2H), 4.67 (s, 2H), 4.56 (s, 2H), 2.75 (t, *J* = 7 Hz, 2H), 2.46 (t, *J* = 7 Hz, 2H), 2.44 (s, 3H), 1.62 (m, 2H), 1.50 (m, 2H), 1.35 (m, 2H), 0.98 (t, *J* = 7 Hz, 3H), 0.92 (t, *J* = 7 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 157.7 (d, *J* = 242.5 Hz), 143.8, 135.3, 134.7, 133.7, 132.6 (d, *J* = 20 Hz), 129.9, 127.6, 127.5, 119.2 (d, *J* = 6.2Hz), 103.4 (d, *J* = 26.2 Hz), 100.3, 74.9, 55.4, 54.8, 31.6, 30.6, 27.6, 21.9, 21.5, 19.3, 13.8, 13.7, 13.5; **^{19}F NMR** (375 MHz, $CDCl_3$) δ -113.9; **HRMS** (ESI) calcd for $C_{25}H_{29}BrFNO_2S$ $[M]^+$ 506.1165, found 506.1164.



6-26

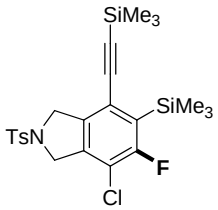
6-26 (80%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 4.68 (s, 2H), 4.59 (s, 2H), 2.42 (s, 3H), 0.39 (s, 9H), 0.25 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.8 (d, *J* = 239.8 Hz), 143.9, 139.7, 136.8, 133.6, 130.0 128.7 (d, *J* = 33.2 Hz), 127.5, 123.1 (d, *J* = 13.0 Hz), 105.0 (d, *J* = 33.7 Hz), 101.4, 77.0, 55.7, 54.8, 21.5, 0.4, -0.3; **^{19}F NMR** (375 MHz, $CDCl_3$) δ -96.0; **HRMS** (ESI) calcd for $C_{23}H_{29}BrFNO_2S$ $[M]^+$ 538.0703, found 538.0709.



6-27

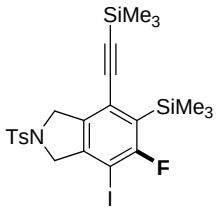
6-27 (85%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.0 Hz, 2H), 7.32 – 7.14 (m, 10H), 7.12 (d, *J* = 8.0 Hz, 2H), 4.67 (s, 2H), 4.60 (s, 2H), 2.73 (t, *J* = 8.5 Hz, 2H), 2.61 (t, *J* = 8.5 Hz, 2H), 2.41 (s, 3H), 1.78 (m, 2H), 1.61 (m, 2H), 0.98 (m, 2H), 0.78 (m, 2H), 0.39 (s, 3H), 0.38 (s, 3H), 0.24 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 163.0 (d, *J* = 240 Hz), 143.9, 142.3 (d, *J* = 18.7 Hz), 139.8, 137.1, 133.7, 130.0, 128.5, 128.4, 128.3, 128.2, 127.5, 125.8 (d, *J* = 12.5 Hz), 105.2 (d, *J* = 30 Hz), 104.4, 102,

55.7, 54.8, 39.7, 39.5, 25.94, 25.91, 21.5, 15.9, 15.6, -1.1, -2.0; **^{19}F NMR** (375 MHz, $CDCl_3$) δ -99.2; **HRMS** (ESI) calcd for $C_{39}H_{46}BrFNO_2SSi_2$ $[M+H]^+$ 746.1955, found 746.1950.



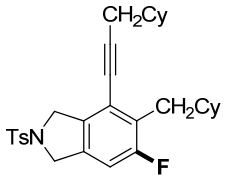
6-28

6-28 (52%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.79 (d, *J* = 10 Hz, 2H), 7.35 (d, *J* = 10 Hz, 2H), 4.64 (s, 2H), 4.62 (s, 2H), 2.42 (s, 3H), 0.39 (s, 9H), 0.25 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.0 (d, *J* = 255 Hz), 143.9, 137.5, 137.0, 133.7, 129.9, 129.0 (d, *J* = 31.2), 127.5, 22.2 (d, *J* = 12.5), 116.6 (d, *J* = 26.2), 104.8, 101.4, 54.6, 53.9, 21.5, 0.3, -0.3; **^{19}F NMR** (375 MHz, $CDCl_3$) δ -104.1; **HRMS** (ESI) calcd for $C_{23}H_{30}ClFNO_2SSi_2$ $[M+H]^+$ 494.1208, found 494.1204.



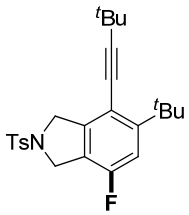
6-29

6-29 (55%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8 Hz, 2H), 7.35 (d, *J* = 8 Hz, 2H), 4.71 (s, 2H), 4.53 (s, 2H), 2.41 (s, 3H), 0.38 (s, 9H), 0.25 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.4 (d, *J* = 237.5 Hz), 143.9, 143.8 (d, *J* = 12.5 Hz), 136.1, 133.7, 129.9, 127.6, 127.5, 127.3, 124.3 (d, *J* = 12.5 Hz), 105.3, 101.4, 78.4 (d, *J* = 36.2 Hz), 59.0, 55.0, 21.5, 0.4, -0.38; **^{19}F NMR** (375 MHz, $CDCl_3$) δ -82.2; **HRMS** (ESI) calcd for $C_{23}H_{30}FINO_2SSi_2$ $[M+H]^+$ 586.0565, found 586.0570.



6-33

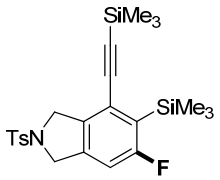
6-33 (75%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.5 Hz, 2H), 7.32 (d, *J* = 8.5 Hz, 2H), 6.73 (d, *J* = 9 Hz, 1H), 4.57 (s, 4H), 2.61 (d, *J* = 5.5 Hz, 2H), 2.43 (s, 3H), 2.37 (d, *J* = 5.5 Hz, 2H), 1.86 (d, *J* = 12 Hz, 2H), 1.78 (d, *J* = 12 Hz, 2H), 1.75 – 1.54 (m, 8H), 1.39 – 1.03 (m, 10H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 161.9 (d, *J* = 241.9 Hz), 143.6, 134.3, 134.2, 133.8, 129.9, 129.8, 129.7, 127.5, 120.9 (d, *J* = 13.7 Hz), 108.7 (d, *J* = 26.2 Hz), 98.6, 76.7, 54.2, 53.8, 38.5, 37.5, 34.8, 33.1, 32.7, 32.6, 27.4, 26.4, 26.39, 26.30, 26.2, 26.1, 21.5; **^{19}F NMR** (375 MHz, $CDCl_3$) δ -116.7 (d, *J* = 8.0 Hz); **HRMS** (ESI) calcd for $C_{31}H_{39}FNO_2S$ $[M+H]^+$ 508.2686, found 508.2687.



6-35'

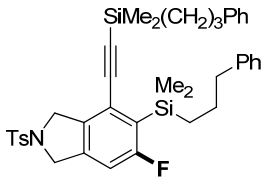
6-35′ (85%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 6.92 (d, *J* = 11 Hz, 1H), 4.64 (s, 2H), 4.63 (s, 2H), 2.41(s, 3H), 1.46 (s, 9H), 1.36 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 163.0 (d, *J* = 240 Hz), 154.2 (d, *J* = 5.3 Hz), 143.8 (d, *J* = 12.5 Hz), 133.8, 129.8, 127.5, 119.6 (d, *J* = 17.5 Hz), 113.4, 112.5 (d, *J* = 21 Hz), 108.9, 76.3, 54.7, 51.4, 35.9, 30.6, 29.6, 28.5, 21.5; **^{19}F NMR** (375 MHz, $CDCl_3$) δ -117.4 (d, *J* = 11.4 Hz); **HRMS** (ESI) calcd for $C_{25}H_{31}FNO_2S$ $[M+H]^+$

428.2060, found 428.2050.



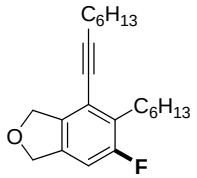
6-36

6-36 (91%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8 Hz, 2H), 7.32 (d, *J* = 8 Hz, 2H), 6.74 (d, *J* = 8.5 Hz, 1H), 4.5 (s. 4H), 2.40 (s, 3H), 0.37 (s, 9H), 0.25 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.7 (d, *J* = 238.7 Hz), 143.7, 138.8 (d, *J* = 10 Hz), 136.0, 133.7, 129.9, 127.5, 127.1(d, *J* = 31.2 Hz), 124.5 (d, *J* = 13.7 Hz), 110.1 (d, *J* = 30 Hz), 104.0, 102.1, 54.1, 53.6, 21.5, 0.4, -0.3; **^{19}F NMR** (375 MHz, $CDCl_3$) δ -99.4; **HRMS** (ESI) calcd for $C_{24}H_{30}FNO_2SSi_2$ $[M]^+$ 494.1208, found 494.1204.



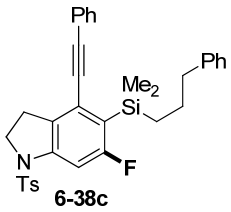
6-38a

6-38a (88%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.0 Hz, 2H), 7.32 – 7.14 (m, 10H), 7.12 (d, *J* = 8.0 Hz, 2H), 6.75 (d, *J* = 9.0 Hz, 1H), 4.60 (s, 2H), 4.58 (s, 2H), 2.73 (t, *J* = 8.0 Hz, 2H), 2.61 (t, *J* = 8.0 Hz, 2H), 2.40 (s, 3H), 1.80 (m, 2H), 1.63 (m, 2H), 0.98 (t, *J* = 9.5 Hz, 2H), 0.77 (t, *J* = 9.5 Hz, 2H), 0.38 (s, 6H), 0.24 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.6 (d, *J* = 240 Hz), 143.7, 142.5 (d, *J* = 31 Hz), 138.9 (d, *J* = 10 Hz), 51.4, 53.7, 39.8, 39.5, 26.0, 25.9, 21.5, 16.0, 15.6, -1.0, -1.9; **^{19}F NMR** (375 MHz, $CDCl_3$) δ -99.2; **HRMS** (ESI) calcd for $C_{39}H_{47}FNO_2SSi_2$ $[M+H]^+$ 668.2852, found 668.2850.



6-38b

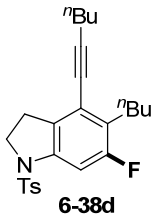
6-38b (93%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 6.80 (d, *J* = 9.0 Hz, 2H), 2.78 (t, *J* = 8.5 Hz, 2H), 2.46 (t, *J* = 8.5 Hz, 2H), 1.63 (m, 4H), 1.48 (m, 2H), 1.37 (m, 10H), 0.92 (m, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 161.7 (d, *J* = 241.2 Hz), 137.4 (d, *J* = 8.7 Hz), 137.0, 130.6 (d, *J* = 18.7 Hz), 118.6 (d, *J* = 7.5 Hz), 107.5 (d, *J* = 25 Hz), 98.4, 75.9, 74.0, 73.8, 31.6, 31.3, 29.7, 29.2, 28.5, 27.2, 22.5, 19.5, 14.08, 14.06; **^{19}F NMR** (375 MHz, $CDCl_3$) δ -119.9 (d, *J* = 8.4 Hz); **HRMS** (ESI) calcd for $C_{22}H_{32}FO$ $[M+H]^+$ 331.2437, found 331.2452.



6-38c

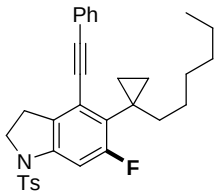
6-38c (90%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8 Hz, 2H), 7.42 (m, 2H), 7.35 (m, 3H), 7.24 (m, 3H), 7.22 (m, 2H), 7.16 (d, *J* = 8 Hz, 2H), 3.97 (t, *J* = 8 Hz, 2H), 3.08 (t, *J* = 8 Hz, 2H), 2.61 (t, *J* = 7.5 Hz, 2H), 2.39 (s, 3H), 1.67 (m, 2H), 1.02 (t, *J* = 8 Hz, 2H), 0.43 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.4 (d, *J* = 237.3 Hz), 144.6, 144.1 (d, *J* = 14.4 Hz), 142.6, 133.8, 131.7. 131.2, 130.9, 129.9, 128.8, 128.5, (d, *J* = 12.0 Hz), 128.2, 127.3, 125.6, 119.7 (d, *J* = 32.4 Hz), 102.3 (d, *J* = 36.3 Hz), 97.1, 50.0,

39.6, 27.6, 26.1, 21.6, 16.4, -0.89, -0.92; **^{19}F NMR** (375 MHz, $CDCl_3$) δ -97.8 (d, *J* = 6.0 Hz); **HRMS** (ESI) calcd for $C_{34}H_{35}FNO_2SSi$ $[M+H]^+$ 568.2142, found 568.2131.



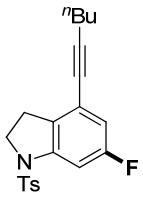
6-38d

6-38d (90%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 10.5 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 2H), 3.90 (d, *J* = 8.5 Hz, 2H), 2.91 (d, *J* = 8.0 Hz, 2H), 2.68 (d, *J* = 7.5 Hz, 2H), 2.42 (d, *J* = 7.5 Hz, 2H), 2.38 (s, 3H), 1.53 – 1.44 (m, 6H), 1.36 (m, 2H), 0.93 (d, *J* = 7.5 Hz, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 161.5 (d, *J* = 238.7 Hz), 144.2, 140.2 (d, *J* = 13.7 Hz), 133.7, 129.7, 129.4, 127.3, 126.3 (d, *J* = 18.7 Hz), 121.8 (d, *J* = 7.5 Hz), 102.4 (d, *J* = 31.2 Hz), 98.6, 76.0, 50.0, 31.9, 30.7, 27.6, 26.8, 22.5, 21.9, 21.5, 19.1, 13.9, 13.5; **^{19}F NMR** (375 MHz, $CDCl_3$) δ -117.6 (d, *J* = 10.1 Hz); **HRMS** (ESI) calcd for $C_{25}H_{31}FNO_2S$ $[M+H]^+$ 428.2060, found 428.2065.



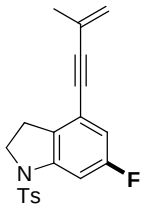
6-38e

6-38e (84%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.5 Hz, 2H), 7.47 (m, 2H), 7.35 (m, 3H), 7.32 (d, *J* = 10.5 Hz, 1H), 7.28 (d, *J* = 7.5 Hz, 2H), 3.96 (t, *J* = 8.5 Hz, 2H), 3.05 (t, *J* = 8.5 Hz, 2H), 2.39 (s, 3H), 1.32 (t, *J* = 4.6 Hz, 2H), 1.23 (m, 6H), 0.84 – 0.88 (m, 7H);); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 161.4 (d, *J* = 242 Hz), 144.4, 140.9 (d, *J* = 13 Hz), 133.7, 131.3, 125.9, 129.8, 129.6, 128.6, 128.4, 128.3 (d, *J* = 17.5 Hz), 127.3, 123.1, 122.7(d, *J* = 7.5 Hz),102.9 (d, *J* = 31.3 Hz), 98.1, 85.6, 50.0, 39.9, 29.5, 27.6, 27.1, 22.6, 21.5, 19.4, 14.0, 13.7; **^{19}F NMR** (375 MHz, $CDCl_3$) δ -113.2 (d, *J* = 10.6 Hz); **HRMS** (ESI) calcd for $C_{30}H_{30}FNO_2S$ $[M]^+$ 487.1981, found 487.1987.



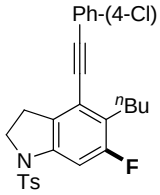
6-38f

6-38f (75%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 10.0 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 2H), 6.68 (d, *J* = 10.0 Hz, 1H), 3.94 (t, *J* = 8.5 Hz, 2H), 2.93 (t, *J* = 8.5 Hz, 2H), 2.39 (s, 3H), 2.37 (t, *J* = 7.0 Hz, 2H), 1.54 (qn, *J* = 7.5 Hz, 2H), 1.45 (qn, *J* = 7.5 Hz, 2H), 0.93 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 163.3 (d, *J* = 240 Hz), 144.5, 143.1 (d, *J* = 12.5 Hz), 133.7, 129.7, 127.3, 121.8 (d, *J* = 11.2 Hz), 112.6 (d, *J* = 23.7 Hz), 102.5 (d, *J* = 28.7 Hz), 95.6, 76.7, 50.2, 30.6, 27.0, 21.9, 21.5, 19.0, 13.5; **^{19}F NMR** (375 MHz, $CDCl_3$) δ -114.2 (t, *J* = 9.4 Hz) **HRMS** (ESI) calcd for $C_{21}H_{23}FNO_2S$ $[M+H]^+$ 372.1434, found 372.1442.



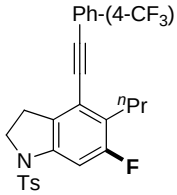
6-38g

6-38g (65%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.0 Hz, 2H), 7.36 (dd, *J* = 9.5, 2 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 2H), 6.73 (d, *J* = 9.5, 2 Hz, 1H), 5.35 (s, 1H), 5.30 (s, 1H), 3.95 (t, *J* = 8.5 Hz, 2H), 2.96 (t, *J* = 8.5 Hz, 2H), 2.39 (s, 3H), 1.92 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 163.3 (d, *J* = 241.2 Hz), 144.5, 143.2 (d, *J* = 13.7 Hz), 133.6, 129.8, 129.7 (d, *J* = 21.2 Hz), 127.3, 126.2, 123.0, 120.9 (d, *J* = 11.2 Hz), 112.5 (d, *J* = 25 Hz), 103.1 (d, *J* = 28.7 Hz), 95.2, 84.5, 50.2, 27.0, 23.3, 21.5; **^{19}F NMR** (375 MHz, $CDCl_3$) δ -111.8 (t, *J* = 9.2 Hz); **HRMS** (ESI) calcd for $C_{20}H_{19}FNO_2S[M+H]^+$ 356.1121, found 356.1131.



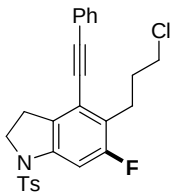
6-38h

6-38h (87%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.5 Hz, 2H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.36 (d, d, *J* = 10.5 Hz, 2H), 7.32 (d, *J* = 8.5 Hz, 2H), 7.27 (d, *J* = 8.5 Hz, 2H), 3.95 (t, *J* = 8.5 Hz, 2H), 3.02 (t, *J* = 8.5 Hz, 2H), 2.77 (t, *J* = 7.5 Hz, 2H), 2.39 (s, 3H), 1.59 (m, 2H), 1.40 (m, 2H), 0.94 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.0 (d, *J* = 240 Hz), 144.4, 140.6 (d, *J* = 13.7 Hz), 134.8, 133.6, 132.6, 129.8, 129.6, 128.8, 127.3, 126.5 (d, *J* = 18.7 Hz), 121.2, 120.6 (d, *J* = 8.7 Hz), 103.3 (d, *J* = 30 Hz), 95.8, 85.6, 50.0, 32.0, 27.6, 26.9, 22.5, 21.5, 13.9; **^{19}F NMR** (375 MHz, $CDCl_3$) δ -117.0 (d, *J* = 10.0 Hz); **HRMS** (ESI) calcd for $C_{27}H_{26}ClFNO_2S$ $[M+H]^+$ 482.1357, found 482.1348.



6-38i

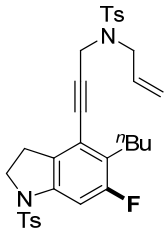
6-38i (92%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.72 (d, *J* = 10 Hz, 2H), 7.61 (d, *J* = 10 Hz, 2H), 7.55 (d, *J* = 10 Hz, 2H), 7.39 (d, *J* = 10.5 Hz, 2H), 7.28 (d, *J* = 10 Hz, 2H), 3.97 (t, *J* = 8.5 Hz, 2H), 3.04 (t, *J* = 8.5 Hz, 2H), 2.77 (t, *J* = 8 Hz, 2H), 2.39 (s, 3H), 1.66 (m, 2H), 0.98 (t, *J* = 8 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 161.5 (d, *J* = 237.5 Hz), 144.4, 140.6 (d, *J* = 12.5 Hz), 133.6, 131.7, 130.4 (q, *J* = 32.5), 129.8, 127.3 126.6, 126.4, 123.8 (q, *J* = 271.2), 120.2 (d, *J* = 7.5 Hz), 103.6 (d, *J* = 31.5), 95.3, 87.0, 50.0, 29.1, 27.6, 23.1, 21.5, 13.9; **^{19}F NMR** (375 MHz, $CDCl_3$) δ -63.3, -116.8 (d, *J* = 9.9 Hz); **HRMS** (ESI) calcd for $C_{27}H_{24}FNO_2S$ $[M+H]^+$ 502.1464, found 502.1454.



6-38j

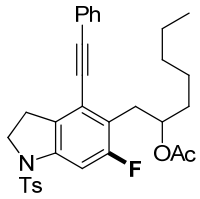
6-38j (93%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.5 Hz, 2H), 7.52 (m, 2H), 7.41 (d, *J* = 10.5 Hz, 1H), 7.39 (m, 3H), 7.33 (d, *J* = 8.5 Hz, 2H), 4.01 (t, *J* = 7.5 Hz, 2H), 3.63 (t, *J* = 7.5 Hz, 2H), 3.09 (t, *J* = 8.5 Hz, 2H),3.00 (t, *J* = 8.5 Hz, 2H), 2.43 (s, 3H), 2.15 (qn, *J* = 8.5 Hz, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 161.6 (d, *J* = 240 Hz), 144.5, 141.1 (d, *J* = 12.5), 133.6, 131.6, 129.9, 128.9, 128.5, 127.3, 124.2 (d, *J* = 18.7), 122.5, 121.2 (d, *J* = 7.5), 103.1 (d, *J* = 31.2), 97.7, 84.2, 50.1, 44.6, 32.6, 27.6, 24.8, 21.6; **^{19}F NMR** (375 MHz,

$CDCl_3$) δ -116.8 (d, *J* = 10.1 Hz); **HRMS** (ESI) calcd for $C_{26}H_{24}ClFNO_2S$ $[M+H]^+$ 468.1200, found 468.1194.



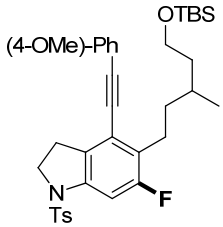
6-38k

6-38k (84%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.0 Hz, 2H), 7.68 (d, *J* = 8.5Hz, 2H), 7.30 (d, *J* = 11 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 8.5 Hz, 2H), 5.76 (m, 1H), 5.26 (m, 2H), 4.30 (m, 2H), 4.30 (m, 4H), 2.67 (t, *J* = 8.0 Hz, 2H), 2.45 (d, *J* = 5.0 Hz, 2H), 2.39 (s, 3H), 2.20 (s, 3H), 1.39 (m, 2H), 1.28 (m, 2H), 0.89 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 161.4 (d, *J* = 240 Hz), 144.4, 143.6, 140.3 (d, *J* = 13.7 Hz), 136.1, 133.6, 131.9, 129.8, 129.7, 127.6, 127.3, 126.2 (d, *J* = 18.7 Hz), 119.9, 103.1 (d, *J* = 30 Hz), 89.8, 80.9, 49.9, 49.2, 36.5, 32.0, 27.4, 26.7, 22.4, 21.5, 21.3, 13.9; **^{19}F NMR** (375 MHz, $CDCl_3$) δ -116.9 (d, *J* = 10.1 Hz); **HRMS** (ESI) calcd for $C_{32}H_{36}FN_2O_4S_2$ $[M+H]^+$ 595.2101, found 595.2109.



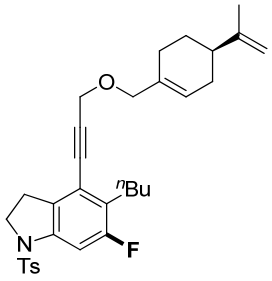
6-38l

6-38l (64%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.0 Hz, 2H), 7.48 (m, 2H), 7.46 (d, *J* = 11 Hz, 1H), 7.34 (br s, 3H), 7.26 (d, *J* = 8.0Hz, 2H), 5.18 (qn, *J* = 6.5Hz, 1H), 3.96 (d, *J* = 9 Hz, 2H), 3.04 (m, 4H), 2.39 (s, 3H), 1.92 (s, 3H), 1.60 (m, 2H), 1.41 – 1.24 (m, 6H), 0.85 (t, *J* = 6.5Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.4, 161.4 (d, *J* = 240 Hz), 144.4, 141.4 (d, *J* = 12.5 Hz), 133.6, 131.5, 129.9, 128.8, 128.4, 127.3, 122.5, (d, *J* = 7.5 Hz), 121.4 (d, *J* = 17.5 Hz), 103.1 (d, *J* = 31.2 Hz), 97.5, 84.6, 73.6, 50.0, 34.0, 31.9, 31.6, 27.6, 25.1, 22.5, 21.5, 21.1, 13.9; **^{19}F NMR** (375 MHz, $CDCl_3$) δ -114.9 (d, *J* = 10.1 Hz); **HRMS** (ESI) calcd for $C_{32}H_{35}FNO_4S$ $[M+H]^+$ 548.2271, found 548.2266.



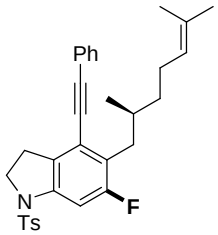
6-38m

6-38m (87%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 9.0 Hz, 2H), 7.33 (d, *J* = 10.5 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 2H), 6.86 (d, *J* = 9 Hz, 2H), 3.94 (t, *J* = 8.5 Hz, 2H), 3.81 (s, 3H), 3.66 (m, 2H), 3.01 (t, *J* = 8.5 Hz, 2H), 2.86 (m, 2H), 2.39 (m, 3H), 1.61 – 1.56 (m, 4H), 1.43 – 1.25 (m, 3H), 0.99 (d, *J* = 6.0 Hz, 2H), 0.84 (s, 9H), 0.02 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 161.4 (d, *J* = 240 Hz), 160.0, 144.3, 140.4 (d, *J* = 13.7 Hz), 133.7, 132.9, 132.8, 129.8, 129.6, 127.3, 126.3 (d, *J* = 18.7 Hz), 121.2 (d, *J* = 8.75 Hz), 114.8, 114.1, 102.9, 102.9 (d, *J* = 31.2 Hz), 97.2, 83.4, 63.1, 59.0, 50.0, 39.8, 35.3, 29.7, 27.6, 25.9, 24.8, 23.9, 21.5, 19.6, 18.3, -5.2; **^{19}F NMR** (375 MHz, $CDCl_3$) δ -117.5 (d, *J* = 10 Hz); **HRMS** (ESI) calcd for $C_{36}H_{47}FNO_4SSi$ $[M]^+$ 636.2979, found 636.2968.



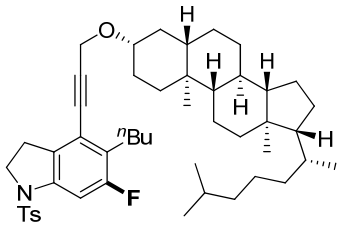
6-38n

6-38n (90%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 10.5 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 2H), 5.73 (s, 1H), 4.72 (d, *J* = 12.5 Hz, 2H), 4.31 (s, 2H), 3.95 (s, 2H), 3.92 (t, *J* = 10.5 Hz, 2H), 2.94 (t, *J* = 10.5 Hz, 2H), 2.71 (t, *J* = 6.5 Hz, 2H), 2.39 (s, 3H), 2.16 (m, 4H), 2.12 – 1.83 (m, 2H), 1.72 (s, 3H), 1.54 – 1.36 (m, 5H), 0.92 (t, *J* = 7.0 Hz, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 161.4 (d, *J* = 240 Hz), 149.6, 144.3, 140.5 (d, *J* = 13.7 Hz), 133.8 (d, *J* = 23.7 Hz), 129.8, 127.3, 126.7 (d, *J* = 18.7 Hz), 125.7, 120.4, (d, *J* = 7.5 Hz), 108.7, 103.3 (d, *J* = 31.2 Hz), 93.2, 81.3, 73.9, 57.2, 50.0, 40.9, 32.0, 30.5, 27.6, 27.4, 26.9, 26.4, 22.5, 21.5, 20.7, 13.9; **^{19}F NMR** (375 MHz, $CDCl_3$) δ -117.1 (d, *J* = 10.1 Hz); **HRMS** (ESI) calcd for $C_{32}H_{39}FNO_3S$ $[M+H]^+$ 536.2635, found 536.2629.



6-38o

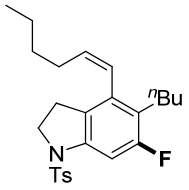
6-38o (84%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.5 Hz, 2H), 7.45 (m, 2H), 7.37 (d, obscured by Ph resonance, 1H), 7.35 (m, 3H), 7.27 (d, *J* = 8.5 Hz, 2H), 5.09 (t, *J* = 7 Hz, 1H), 3.96 (t, *J* = 9 Hz, 2H), 3.03 (t, *J* = 9 Hz, 2H), 2.80 (ABX, *J* = 13, 5.5 Hz, 1H), 2.61 (ABX, *J* = 12, 8.5 Hz, 1H), 2.36 (s, 3H), 2.06 (m, 1H), 2.00 (m, 1H), 1.88 (m, 1H), 1.64 (s, 3H), 1.56 (s, 3H), 1.43 (m, 1H), 1.29 (m, 1H), 0.89 (d, *J* = 8.5 Hz, 6.5H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 161.7 (d, *J* = 238.7 Hz), 144.4, 140.6 (d, *J* = 12.5 Hz), 133.7, 131.4, 131.1, 129.8, 129.7, 128.7, 128.4, 127.3, 125.5 (d, *J* = 18.7 Hz), 124.7, 122.7, 121.4 (d, *J* = 7.5 Hz), 103.1(d, *J* = 31.2 Hz), 97.3, 85.0, 50.1, 37.2, 34.6, 33.7, 27.6, 25.7, 25.6, 21.5, 19.2, 17.6; **^{19}F NMR** (375 MHz, $CDCl_3$) δ -115.6 (d, *J* = 9.9 Hz); **HRMS** (ESI) calcd for $C_{32}H_{35}FNO_2S$ $[M+H]^+$ 516.2373, found 516.2372.



6-38p

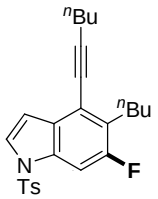
6-38p (83%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.0 Hz, 2H), 7.32(d, *J* = 10 Hz, 1H), 7.26 (d, *J* = 8 Hz, 2H), 4.40 (s, 2H), 3.90 (t, *J* = 8.4 Hz, 2H), 3.50 (m, 1H), 2.91 (t, *J* = 8.4 Hz, 2H), 2.69 (t, *J* = 7.2 Hz, 2H), 2.39 (s, 3H), 1.96 (d, *J* = 13 Hz, 1H), 1.86 (d, *J* = 14 Hz, 1H), 1.81 (m, 1H), 1.73 (d, *J* = 13 Hz, 1H), 1.64 (m, 2H), 1.51 (m, 4H), 1.33 (m, 8H), 1.25 (m, 6H), 1.09 (m, 8H), 0.98 (m, 2H), 0.91 (m, 6H), 0.86 (d, *J* = 1.4 Hz, 3H), 0.85 (d, *J* = 1.4 Hz, 3H), 0.79 (s, 3H), 0.64 (s, 3H), 0.60 (t, *J* = 9.1 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 160.5 (d, *J* = 240.2 Hz), 144.4, 140.4 (d, *J* = 13.0 Hz), 133.7, 129.9, 129.8, 127.4, 126.6 (d, *J* = 19.2 Hz), 120.5 (d, *J* = 8.10 Hz), 103.2 (d, *J* = 30.6 Hz), 93.9, 80.8 (d, *J* = 3.40 Hz), 77.5, 56.3, 55.5, 54.4, 50.1, 44.9, 42.6, 40.1, 39.5, 37.0, 36.2, 35.8, 35.7, 35.5, 34.5, 32.1, 32.0, 28.9, 28.3, 28.0, 27.6, 26.9, 24.2, 23.8,

22.8, 22.6, 21.6, 21.3, 18.7, 14.0, 12.3, 12.1; **^{19}F NMR** (283 MHz, $CDCl_3$) δ -117.1 (d, *J* = 10.2 Hz); **HRMS** (ESI) calcd for $C_{49}H_{70}FNO_3S$ $[M+H]^+$: 772.5139, found 772.5145.



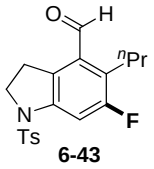
6-39

6-39 (77%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8 Hz, 2H), 7.27 (d, *J* = 10 Hz, 1H), 7.24 (d, *J* = 8 Hz, 2H), 6.13 (d, *J* = 11Hz, 1H), 5.69 (dt, *J* = 10, 7.5 Hz, 1H), 3.88 (d, *J* = 8.5 Hz, 2H), 2.58 (d, *J* = 8 Hz, 2H), 2.47 (d, *J* = 7 Hz, 2H), 2.37 (s, 3H), 1.62 (q, *J* = 7.5 Hz, 2H), 1.38 – 1.18 (m, 6H), 0.89 (t, *J* = 8 Hz, 3H), 0.79 (t, *J* = 8 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 161.6 (d, *J* = 240 Hz), 144.0, 140.0 (d, *J* = 13 Hz), 135.5 (d, *J* = 6 Hz), 134.8, 134.0, 129.6, 127.3, 125.9, 124.4, 123.4 (d, *J* = 16.7 Hz), 102.0 (d, *J* = 30.2 Hz), 50.3, 31.9, 31.1, 28.5, 27.3, 25.8, 22.6, 22.3, 21.5, 13.9, 13.8; **^{19}F NMR** (375 MHz, $CDCl_3$) δ -117.9 (d, *J* = 10.1 Hz); **HRMS** (ESI) calcd for $C_{25}H_{33}FNO_2S$ $[M+H]^+$ 430.2216, found 430.2212.



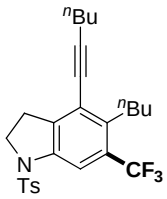
6-40

6-40 (68%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8 Hz, 2H), 7.61(d, *J* = 10 Hz, 1H), 7.49 (d, *J* = 3.5 Hz, 1H), 7.23 (d, *J* = 8 Hz, 2H), 6.73 (d, *J* = 3.5 Hz, 1H), 2.84 (t, *J* = 8 Hz, 2H), 2.52 (t, *J* = 7 Hz, 2H), 2.34 (s, 3H), 1.63 (qn, *J* = 8 Hz, 2H), 1.55 (m, 4H), 1.39 (qn, *J* = 8 Hz, 2H), 0.97 (t, *J* = 8 Hz, 3H), 0.94 (t, *J* = 8 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.3 (d, *J* = 238.8 Hz), 145.1, 135.1, 132.5 (d, *J* = 14.6 Hz), 130.0, 129.0, 128.3 (d, *J* = 19.3 Hz), 126.8, 126.2 (d, *J* = 2.5 Hz), 117.1, 108.7, 100.6 (d, *J* = 30.4 Hz), 98.2, 76.1 (d, *J* = 3.2 Hz), 32.2, 30.9, 27.3, 22.6, 22.0, 21.6, 19.3, 13.9, 13.6; **^{19}F NMR** (375 MHz, $CDCl_3$) δ -120.0 (d, *J* = 9.7 Hz); **HRMS** (ESI) calcd for $C_{25}H_{29}FNO_2S$ $[M+H]^+$ 426.1903, found 426.1902.



6-43

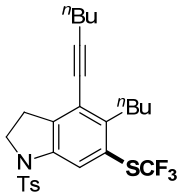
6-43 (62% from **6-41**): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 10.4 (s, 1H), 7.77(d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 7.09 (d, *J* = 8.8 Hz, 1H), 4.84 (s, 2H), 4.56 (s, 2H), 2.96 (t, *J* = 7.3 Hz, 2H), 2.39 (s, 3H), 1.61 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 190.0 (d, *J* = 2 Hz), 160.9 (d, *J* = 245 Hz), 143.8, 136.8 (d, *J* = 8.9 Hz), 133.7 (d, *J* = 19.7 Hz), 132.7 (d, *J* = 16.9 Hz), 129.9, 129.7, 127.6, 127.5, 115.0 (d, *J* = 25.9 Hz), 54.5, 52.3, 25.5, 25.4, 25.3, 21.5, 13.7; **^{19}F NMR** (375 MHz, $CDCl_3$) δ -117.8 (d, *J* = 8.7 Hz); **GC-Ms** $[M]^+$ = 361.1.



6-44

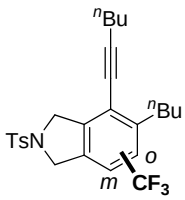
6-44 (75%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.67 (d, *J* = 8.2 Hz, 2H), 7.26 (d, *J* = 8.2 Hz, 2H), 3.93 (t, *J* = 8.6 Hz, 2H), 2.98 (t, *J* = 8.5 Hz, 2H), 2.80 (m, 2H), 2.43 (t, *J* = 6.9 Hz, 2H), 2.39 (s, 3H), 1.59 – 1.39 (m, 8H), 0.94 (t, *J* = 7.3 Hz, 3H), 0.93 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 144.4, 139.6, 139.1, 138.7, 133.7, 128.2 (d,

J = 29.9 Hz), 127.3, 124.3 (q, J = 274.2 Hz), 123.2, 110.9 (d, J = 6.3 Hz), 99.6, 75.8, 49.7, 32.9, 30.9, 30.7, 28.3, 23.2, 21.9, 21.5, 19.2, 13.7, 13.5; **^{19}F NMR** (283 MHz, $CDCl_3$) δ -59.7; **HRMS** (ESI) calcd for $C_{26}H_{31}F_3NO_2S$ $[M+H]^+$: 478.2028, found 478.2024.



6-45

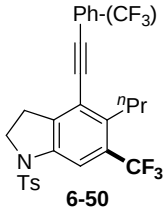
6-45 (85%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.69 (d, J = 8.2 Hz, 2H) 7.24 (d, J = 8.3 Hz, 2H), 3.91 (t, J = 8.5 Hz, 2H), 2.97 (m, 4H), 2.42 (t, J = 6.9 Hz, 2H), 2.38 (s, 3H), 1.54 (m, 2H), 1.46 (m, 4H), 1.38 (m, 2H), 0.93 (m, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 145.4, 144.5, 140.0, 138.2, 133.2, 129.78, 129.73 (q, J = 309.1 Hz), 127.4, 122.8, 122.4, 122.1, 99.2, 76.3, 49.7, 32.8, 32.4, 30.8, 28.3, 22.9, 22.0, 21.6, 19.2, 13.9, 13.6; **^{19}F NMR** (283 MHz, $CDCl_3$) δ -42.8; **HRMS** (ESI) calcd for $C_{26}H_{31}F_3NO_2S_2$ $[M+H]^+$: 510.1748, found 510.1746.



6-46/6-46'

6-46 (46%): ***Ortho*-CF$_3$ isoindoline: ^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.77 (d, J = 8.1 Hz, 2H), 7.32 (d, J = 8.1 Hz, 2H), 7.30 (s, 1H), 4.65 (s, 2H), 4.62 (s, 2H), 2.84 (m, 2H), 2.49 (t, J = 7.0 Hz, 2H), 2.41 (s, 3H), 1.61 (m, 2H), 1.51 (m, 4H), 1.43 (m, 2H), 0.97 (t, J = 7.3 Hz, 3H), 0.94 (t, J = 7.3 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 143.9, 143.6, 142.8, 133.7, 133.4, 129.9, 128.6 (d, J = 30.0 Hz), 127.6, 124.2 (q, J = 274.7 Hz), 121.3, 119.0 (dd, J = 11.3, 5.5 Hz), 100.7, 75.3, 54.3, 54.1, 32.8, 31.2, 30.7, 23.3, 22.0, 21.5, 19.3, 13.8, 13.7, 13.6; **^{19}F NMR** (283 MHz, $CDCl_3$) δ -60.0; **HRMS** (ESI) calcd for $C_{26}H_{31}F_3NO_2S$ $[M+H]^+$: 478.2028, found 478.2029;

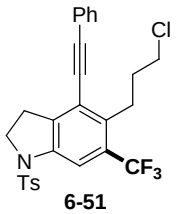
6-46′ (30%): ***Meta*-CF$_3$ isoindoline: ^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.78 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.27 (s, 1H), 4.72 (s, 2H), 4.64 (s, 2H), 2.72 (m, 2H), 2.49 (t, J = 6.9 Hz, 2H), 2.41 (s, 3H), 1.61 (m, 2H), 1.52 (m, 4H), 1.34 (m, 2H), 0.98 (t, J = 7.3 Hz, 3H), 0.92 (t, J = 7.3 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 145.1, 143.8, 140.7, 133.7, 130.9, 129.9, 127.6, 125.01 (d, J = 4.1 Hz), 123.7 (q, J = 272.7 Hz), 123.5 (d, J = 32.6 Hz), 122.3, 101.6, 75.4, 53.8, 53.3, 33.8, 32.6, 30.7, 22.47, 22.0, 21.5, 19.4, 13.8, 13.6; **^{19}F NMR** (283 MHz, $CDCl_3$) δ -62.6.



6-50

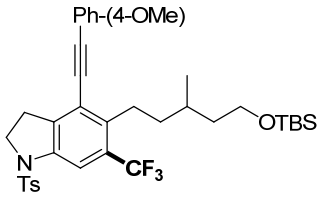
6-50 (78%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.70 (d, J = 8.3 Hz, 2H) 7.62 (d, J = 8.2 Hz, 2H), 7.55 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 8.3 Hz, 2H), 3.99 (t, J = 8.5 Hz, 2H), 3.11 (t, J = 8.5 Hz, 2H), 2.88 (m, 2H), 2.40 (s, 3H), 1.05 (t, J = 7.3 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 144.6, 140.1, 139.3, 138.4, 133.6, 131.7, 130.6 (d, J = 33.0

Hz), 129.9, 128.7 (d, *J* = 29.9 Hz), 127.8, 126.3, 125.54, 125.52, 124.2 (q, *J* = 274.4 Hz), 123.8 (q, *J* = 272.9 Hz), 121.8, 112.1 (d, *J* = 6.2 Hz), 96.3, 86.6, 49.7, 33.4, 28.3, 24.4, 21.6, 14.7; **^{19}F NMR** (283 MHz, $CDCl_3$) δ -59.8, -63.3; **HRMS** (ESI) calcd for $C_{28}H_{24}F_6NO_2S$ $[M+H]^+$: 552.1432, found 552.1432.



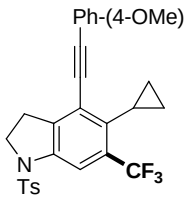
6-51

6-51 (75%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.49 (m, 2H), 7.36 (m, 3H), 7.29 (d, *J* = 8.2 Hz, 2H), 3.99 (t, *J* = 8.6 Hz, 2H), 3.66 (t, *J* = 6.4 Hz, 2H), 3.12 (t, *J* = 8.6 Hz, 2H), 3.08 (m, 2H), 2.40 (s, 3H), 2.11 (m, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 144.7, 140.4, 138.4, 136.9, 131.6, 130.0, 129.1, 128.8 (d, *J* = 30.6 Hz), 128.6, 128.3, 124.2 (q, *J* = 275.0 Hz), 122.7, 122.3, 111.6 (dd, *J* = 12.0, 5.8 Hz), 98.7, 83.9, 49.8, 45.1, 33.4, 29.0, 28.3, 21.6; **^{19}F NMR** (283 MHz, $CDCl_3$) δ -59.7; **HRMS** (ESI) calcd for $C_{27}H_{24}ClF_3NO_2S$ $[M+H]^+$: 518.1168, found 518.1174.



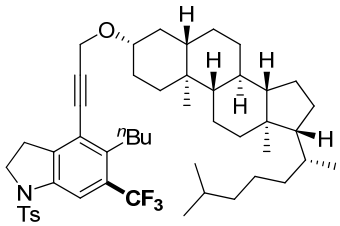
6-52

6-52 (78%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.69 (d, *J* = 8.3 Hz, 2H), 7.39 (d, *J* = 8.7 Hz, 2H), 7.27 (d, *J* = 8.3 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 3.97 (t, *J* = 8.5 Hz, 2H), 3.64 (m, 2H), 3.09 (t, *J* = 8.5 Hz, 2H), 2.90 (m, 2H), 2.39 (s, 3H), 1.65 (m, 3H), 1.42 (m, 2H), 0.99 (d, *J* = 6.6 Hz, 3H), 0.87 (s, 9H), 0.02 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 160.12, 144.54, 139.81, 138.94, 138.04, 133.54, 132.99, 129.92, 128.37 (d, *J* = 30.2 Hz), 127.34, 123.34 (q, *J* = 274.3 Hz), 122.79, 114.59, 114.21, 111.33 (d, *J* = 5.8 Hz), 98.29, 83.20, 61.44, 55.36, 49.78, 39.80, 38.17, 30.48, 30.34, 29.05, 28.31, 25.97, 21.59, 19.55, 18.33, -5.28; **^{19}F NMR** (283 MHz, $CDCl_3$) δ -59.7; **HRMS** (ESI) calcd for $C_{37}H_{47}F_3NO_4SSi$ $[M+1]^+$: 686.2947, found 686.2942.



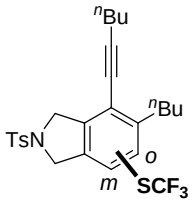
6-53

6-53 (71%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.69 (d, *J* = 8.2 Hz, 2H) 7.40 (d, *J* = 8.7 Hz, 2H), 7.27 (d, *J* = 8.2 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 3.96 (t, *J* = 8.5 Hz, 2H), 3.83 (s, 3H), 3.08 (t, *J* = 8.5 Hz, 2H), 2.39 (s, 3H), 1.99 (m, 1H), 1.07 (q, *J* = 6.0, 5.7 Hz, 2H), 0.94 (q, *J* = 5.9, 5.6 Hz, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 160.09, 144.54, 140.10, 137.92, 137.62, 133.57, 132.32, 131.33 (d, *J* = 30.3 Hz), 129.91, 127.35, 124.30 (q, *J* = 274.2 Hz), 124.08, 114.99, 114.19, 111.60 (d, *J* = 5.8 Hz), 99.54, 84.23, 55.38, 49.73, 28.34, 21.57, 12.74, 8.13; **^{19}F NMR** (283 MHz, $CDCl_3$) δ -58.7; **HRMS** (ESI) calcd for $C_{28}H_{25}F_3NO_3S$ $[M+1]^+$: 512.1507, found 512.1507.



6-56

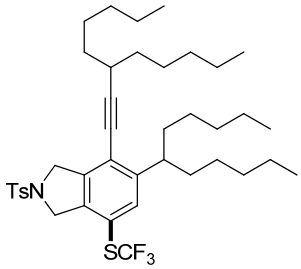
6-56 (67%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 4.41 (s, 2H), 3.94 (t, *J* = 8.5 Hz, 2H), 3.49 (m, 1H), 3.00 (t, *J* = 8.5 Hz, 2H), 2.81 (m, 2H), 2.39 (s, 3H), 1.96 (d, *J* = 12.6 Hz, 1H), 1.89 –1.77 (m, 2H), 1.73 (d, *J* = 13.3 Hz, 1H), 1.64 (t, *J* = 11.8 Hz, 2H), 1.58 – 1.47 (m, 4H), 1.47 – 1.39 (m, 4H), 1.39 – 1.21 (m, 11H), 1.19 – 0.97 (m, 10H), 0.94 (t, *J* = 7.2 Hz, 3H), 0.90 (d, *J* = 6.3 Hz, 3H), 0.86 (d, *J* = 6.4 Hz, 6H), 0.79 (s, 3H), 0.64 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 144.5, 139.8, 139.5, 138.6, 133.6, 129.9, 128.4 (d, *J* = 29.8 Hz), 127.3, 124.2 (q, *J* = 247.4 Hz), 122.1, 111.8 (d, *J* = 6.1 Hz), 94.9, 80.5, 77.6, 56.5, 56.3, 55.4, 54.4, 49.7, 44.9, 42.6, 40.1, 39.5, 37.0, 36.2, 35.8, 35.5, 34.5, 33.0, 32.1, 30.9, 28.9, 28.3, 28.0, 24.2, 23.8, 23.2, 22.8, 22.6, 21.6, 21.3, 18.7, 13.8, 12.3, 12.1; **^{19}F NMR** (283 MHz, $CDCl_3$) δ -59.7; **HRMS** (ESI) calcd for $C_{50}H_{71}F_3NO_3S$ $[M+H]^+$: 822.5107, found 822.5115.



6-57/6-57'

6-57 (47%): ***Ortho*-SCF$_3$ isoindoline: ^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.1 Hz, 2H) 7.36 (s, 1H), 7.32 (d, *J* = 8.1 Hz, 2H), 4.64 (s, 2H), 4.61 (s, 2H), 3.02 (m, 2H), 2.48 (t, *J* = 6.9 Hz, 2H), 2.40 (s, 3H), 1.61 (m, 2H), 1.48 (m, 4H), 1.41 (m, 2H) 0.97 (t, *J* = 7.3 Hz, 3H), 0.94 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 149.6, 143.9, 142.6, 134.4, 133.7, 130.7, 129.9, 129.3 (q, *J* = 309.5 Hz), 127.6, 123.4, 120.6, 75.7, 54.2, 53.8, 32.7, 32.6, 30.7, 22.9, 22.0, 21.5, 19.3, 13.6, 13.5; **^{19}F NMR** (283 MHz, $CDCl_3$) δ -42.8; **HRMS** (ESI) calcd for $C_{26}H_{31}F_3NO_2S_2$ $[M+H]^+$: 510.1748, found 510.1749.

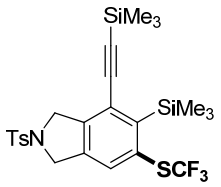
6-57′ (31%): ***Meta*-SCF$_3$ isoindoline: ^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.2 Hz, 2H) 7.33 (d, *J* = 8.2 Hz, 2H), 7.31 (s, 1H), 4.73 (s, 2H), 4.69 (s, 2H), 2.71 (m, 2H), 2.49 (t, *J* = 7.0 Hz, 2H), 2.41 (s, 3H), 1.55 (m, 6H), 1.32 (td, *J* = 14.7, 7.4 Hz, 2H), 0.97 (t, *J* = 7.3 Hz, 2H), 0.92 (t, *J* = 7.3 Hz, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 145.8, 143.8, 140.3, 139.5, 136.8, 133.7, 129.9, 129.3 (q, *J* = 310.0 Hz), 127.6, 122.0. 116.7, 101.9, 75.5, 54.9, 54.5, 33.6, 32.6, 30.7, 29.7, 22.4, 22.0, 21.5, 19.4, 13.8, 13.6; **^{19}F NMR** (283 MHz, $CDCl_3$) δ -42.3.



6-58'

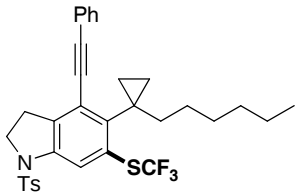
6-58′ (55%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.2 Hz, 2H) 7.32 (d, *J* = 8.2 Hz, 2H), 7.29 (s, 1H), 4.75 (s, 2H), 4.68 (s, 2H), 3.16 (m, 1H), 2.60 (m, 1H), 2.41 (s, 3H), 1.63 – 1.45 (m, 12H), 1.40 – 1.27 (m, 10H), 1.25 – 1.10 (m, 10H), 0.93 (t, *J* = 6.9 Hz, 6H), 0.82 (t, *J* = 6.8 Hz, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 149.3, 143.8, 140.1, 139.2, 134.8, 134.0, 133.1, 133.0, 129.9, 129.4 (q, *J* = 309.1 Hz), 127.6, 122.8, 116.9, 129.4, 55.0, 54.5, 42.2, 36.2, 35.2, 32.9,

31.9, 31.8, 27.4, 27.0, 22.7, 22.5, 21.5, 14.1, 14.0; **^{19}F NMR** (283 MHz, $CDCl_3$) δ -42.5.



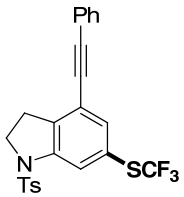
6-59

6-59 (78%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.6 Hz, 2H), 7.42 (s, 1H), 7.33 (d, *J* = 8.6 Hz, 2H), 4.64 (s, 4H), 2.41 (s, 3H), 0.48 (s, 9H), 0.27 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 149.2, 143.9, 143.6, 137.6, 133.7, 132.3, 130.5, 129.9, 129.5 (q, *J* = 308.3 Hz), 127.6, 125.9, 106.4, 102.2, 54.3, 54.0, 21.5, 2.90, -0.41; **^{19}F NMR** (283 MHz, $CDCl_3$) δ -43.1; **HRMS** (ESI) calcd for $C_{24}H_{31}F_3NO_2S_2Si_2$ $[M+H]^+$: 542.1287, found 542.1281.



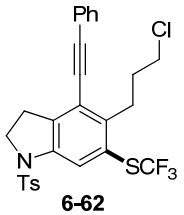
6-60

6-60 (72%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.73 (d, *J* = 8.2 Hz, 2H), 7.47 (m, 2H), 4.36 (m, 3H), 7.27 (d, *J* = 8.2 Hz, 2H), 3.98 (m, 2H), 3.10 (m, 2H), 2.39 (s, 3H), 1.82 (td, *J* = 12.6 Hz, 4.1 1H), 1.39 (m, 2H), 1.23 (m, 7H), 1.07 (m, 1H), 0.94 (m, 2H), 0.81 (t, *J* = 6.8 Hz, 3H) 0.78 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 144.5, 144.3, 140.7, 137.0, 133.4, 131.3, 129.82, 129.80 (q, *J* = 309.2 Hz), 129.7, 128.8, 128.52, 128.45, 127.4, 123.8, 123.1, 119.5, 99.0, 85.7, 49.8, 40.3, 31.8, 29.6, 28.2, 26.9, 23.8, 22.6, 21.6, 16.6, 14.8, 14.0; **^{19}F NMR** (283 MHz, $CDCl_3$) δ -40.6; **HRMS** (ESI) calcd for $C_{33}H_{35}F_3NO_2S_2$ $[M+1]^+$:598.2061, found 598.2067.



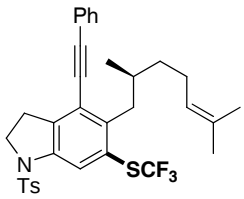
6-61

6-61 (53%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.71 (d, *J* = 8.3 Hz, 2H), 7.47 (m, 2H), 7.41 (s, 1H), 7.35 (m, 2H), 7.27 (d, *J* = 8.3 Hz, 2H), 4.00 (t, *J* = 8.6 Hz, 2H), 3.11 (t, *J* = 8.6 Hz, 2H), 2.39 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 144.8, 143.1, 137.3, 134.0, 133.2, 131.7, 129.9, 129.6 (q, *J* = 309.0 Hz), 129.0, 128.4, 127.4, 124.0, 122.3, 121.6, 121.5, 94.8, 85.1, 49.9, 27.7.; **^{19}F NMR** (283 MHz, $CDCl_3$) δ -43.1; **HRMS** (ESI) calcd for $C_{24}H_{19}F_3NO_2S_2$ $[M+1]^+$: 474.0809, found 474.0807.



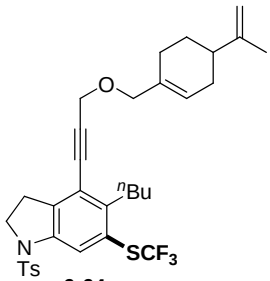
6-62

6-62 (81%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.94, (s, 1H), 7.72 (d, *J* = 8.2 Hz, 2H) 7.48 (m, 2H), 7.36 (m, 3H), 7.27 (d, *J* = 8.2 Hz, 2H), 3.98 (t, *J* = 8.5 Hz, 2H), 3.63 (t, *J* = 6.4 Hz, 2H), 3.24 (m, 2H), 3.12 (t, *J* = 8.5 Hz, 2H), 2.39 (s, 3H), 2.06 (m, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 144.7, 143.3, 140.8, 138.5, 133.2, 131.6, 129.9, 129.6 (q, *J* = 309.3 Hz), 129.1, 128.6, 127.4, 123.4, 122.9, 122.4, 121.9, 98.2, 84.3, 49.7, 44.8, 33.2, 30.4, 28.3, 21.6; **^{19}F NMR** (283 MHz, $CDCl_3$) δ -42.7; **HRMS** (ESI) calcd for $C_{27}H_{24}ClF_3NO_2S_2$ $[M+H]^+$: 550.0889, found 550.0884.



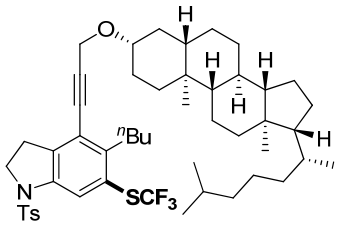
6-63

6-63 (79%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.72 (d, *J* = 8.2 Hz, 2H), 7.45 (m, 2H), 7.35 (m, 3H), 7.26 (d, *J* = 8.2 Hz, 2H), 5.05 (t, *J* = 6.9 Hz, 1H), 3.98 (t, *J* = 8.6 Hz, 2H), 3.11 (t, *J* = 8.6 Hz, 2H), 3.09 (dd, *J* = 13.2, 8.8 Hz, 1H), 2.96 (dd, *J* = 13.2, 8.8 Hz, 1H), 2.39 (s, 3H), 2.06 (m, 1H), 1.98 (m, 1H), 1.89 (m, 1H), 1.64 (s, 3H), 1.56 (s, 3H), 1.41 (m, 1H), 1.31 (m, 1H), 0.87 (d, *J* = 7.4 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 144.6, 144.1, 140.3, 138.2, 133.4, 131.4, 131.3, 131.0, 129.8, 129.7 (q, *J* = 309.8 Hz), 129.6, 128.9, 128.5, 127.4, 124.6, 124.1, 122.7, 122.6, 122.3, 98.0, 85.3, 49.8, 39.6, 37.2, 34.9, 28.4; **^{19}F NMR** (283 MHz, $CDCl_3$) δ -42.7; **HRMS** (ESI) calcd for $C_{33}H_{35}F_3NO_2S_2$ $[M+H]^+$: 598.2061, found 598.2046.



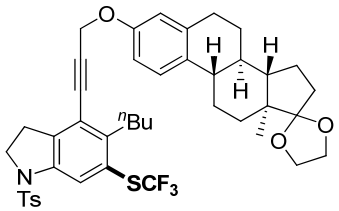
6-64

6-64 (77%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.69 (d, *J* = 8.3 Hz, 2H), 7.24 (d, *J* = 8.3 Hz, 2H), 5.74 (s, 1H), 4.73 (s, 1H), 4.70 (s, 1H), 4.32 (s, 2H), 3.95 (s, 2H), 3.93 (t, *J* = 8.7 Hz, 2H), 3.08 (t, *J* = 8.7 Hz, 2H), 2.98 (m, 2H), 2.39 (s, 3H), 2.12 (m, 4H), 1.88 (m, 1H), 1.84 (m, 1H), 1.73 (s, 3H), 1.48 (m, 3H), 1.40 (td, *J* = 14.7, 7.2 Hz, 2H), 0.93 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 149.6, 145.6, 144.6, 140.2, 138.6, 133.8, 133.2, 129.8, 129.7 (q, *J* = 309.2 Hz), 127.4, 125.8, 123.1, 123.0, 121.1, 108.8, 93.8, 81.4, 74.1, 57.2, 49.7, 41.0, 32.9, 32.4, 30.5, 28.3, 27.4, 26.4, 22.8, 21.6, 20.8, 13.9; **^{19}F NMR** (283 MHz, $CDCl_3$) δ -42.7; **HRMS** (ESI) calcd for $C_{33}H_{39}F_3NO_3S_2$ $[M+H]^+$: 618.2323, found 618.2319.



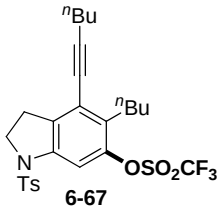
6-65

6-65 (67%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.69 (d, *J* = 8.1 Hz, 2H), 7.25 (d, *J* = 8.1 Hz, 2H), 4.41 (s, 2H), 3.92 (t, *J* = 8.5 Hz, 2H), 3.49 (m, 1H), 2.99 (m, 4H), 2.39 (s, 3H), 1.93 (d, *J* = 12.5 Hz, 1H), 1.89 – 1.77 (m, 2H), 1.73 (d, *J* = 13.3 Hz, 1H), 1.64 (t, *J* = 13.9 Hz, 2H), 1.59 – 1.43 (m, 6H), 1.42 – 1.19 (m, 12H), 1.18 – 0.97 (m, 10H), 0.93 (t, *J* = 7.2 Hz, 3H), 0.90 (d, *J* = 6.4 Hz, 3H), 0.864 (d, *J* = 6.6 Hz, 3H), 0.860 (d, *J* = 6.6 Hz, 3H), 0.79 (s, 3H), 0.65 (s, 3H), 0.60 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 145.6, 144.5, 140.2, 138.6, 133.2, 129.8, 129.7 (q, *J* = 309.2 Hz), 127.4, 123.0, 122.9, 121.2, 94.5, 80.9, 77.5, 56.5, 56.3, 55.4, 54.4, 49.7, 44.9, 42.6, 40.1, 39.5, 37.0, 36.2, 35.8, 35.5, 34.5, 32.9, 32.4, 32.1, 28.9, 28.3, 28.0, 24.2, 23.8, 22.8, 22.6, 21.6, 21.3, 18.7, 14.0, 12.3, 12.1; **^{19}F NMR** (283 MHz, $CDCl_3$) δ -42.7; **HRMS** (ESI) calcd for $C_{50}H_{71}F_3NO_3S_2$ $[M+H]^+$: 854.4827, found 854.4810.



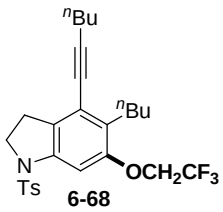
6-66

6-66 (83%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.68 (d, *J* = 8.2 Hz, 2H), 7.24 (d, *J* = 8.2 Hz, 2H), 7.20 (d, *J* = 8.6 Hz, 1H), 6.76 (dd, *J* = 8.6, 2.5 Hz, 1H), 6.69 (d, *J* = 2.5 Hz, 1H), 4.88 (s, 2H), 3.95 – 3.86 (m, 7H), 2.93 (t, *J* = 8.1 Hz, 2H), 2.83 (s, 3H), 2.31 (m, 1H), 2.22 (m, 1H), 2.04 (m, 1H), 1.94 – 1.73 (m, 4H), 1.68 – 1.51 (m, 2H), 1.50 – 1.24 (m, 8H), 0.89 (s, 3H), 0.88 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.3, 145.7, 144.6, 140.3, 138.8, 138.1, 133.8, 133.2, 129.8, 129.6 (q, *J* = 309.2 Hz), 127.4, 126.4, 123.1, 120.7, 119.4, 115.0, 112.3, 92.6, 82.4, 65.3, 64.6, 56.2, 49.7, 49.4, 46.1, 43.7, 39.1, 34.3, 32.9, 32.3, 30.7, 29.9, 28.2, 27.0, 26.2, 22.7, 22.4, 21.6, 14.3, 13.9; **^{19}F NMR** (283 MHz, $CDCl_3$) δ -42.7; **HRMS** (ESI) calcd for $C_{43}H_{49}F_3NO_5S_2$ $[M+H]^+$: 780.3004, found 780.3000.



6-67

6-67 (82%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.2 Hz, 2H), 7.47 (s, 1H), 7.26 (d, *J* = 8.2 Hz, 2H), 3.92 (t, *J* = 8.5 Hz, 2H), 2.96 (t, *J* = 8.5 Hz, 2H), 2.73 (m, 2H), 2.43 (t, *J* = 6.9 Hz, 2H), 2.39 (s, 3H), 1.53 (m, 4H), 1.46 (m, 2H), 1.38 (m, 2H), 0.929 (t, *J* = 7.3 Hz, 3H), 0.926 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 147.0, 144.6, 140.6, 134.4, 133.0, 132.2, 129.9, 127.5, 122.8, 118.6 (q, *J* = 319.2 Hz), 107.3, 100.1, 75.6, 49.9, 31.6, 30.6, 28.4, 27.8, 22.7, 21.9, 21.5, 19.2, 13.7, 13.5; **^{19}F NMR** (283 MHz, $CDCl_3$) δ -74.4; **HRMS** (ESI) calcd for $C_{26}H_{31}F_3NO_5S_2$ $[M+H]^+$: 558.1596, found 558.1602.



6-68

6-68 (91%): **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.14 (s, 1H), 4.39 (q, *J* = 8.0 Hz, 2H), 3.88 (t, *J* = 8.4 Hz, 2H), 2.86 (t, *J* = 8.4 Hz, 2H), 2.72 (m, 2H), 2.41 (t, *J* = 6.9 Hz, 2H), 2.39 (s, 1H), 1.55 (m, 2H), 1.46 (m, 4H), 1.35 (m, 2H), 0.92 (t, *J* = 7.1 Hz, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.9, 144.3, 140.1, 133.9, 129.8, 129.7, 127.9, 127.3, 123.4, (q, *J* = 278.6 Hz), 121.8, 99.8, 98.2, 76.4, 66.9, 66.6, 66.3, 66.1, 50.1, 31.8, 30.8, 27.70, 27.65, 22.7, 21.9, 21.5, 19.2, 13.9, 13.5; **^{19}F NMR** (283 MHz, $CDCl_3$) δ -74.4 (t, *J* = 7.9 Hz); **HRMS** (ESI) calcd for $C_{27}H_{33}F_3NO_3S$ $[M+H]^+$: 508.2133, found 508.2130.

6.5. References

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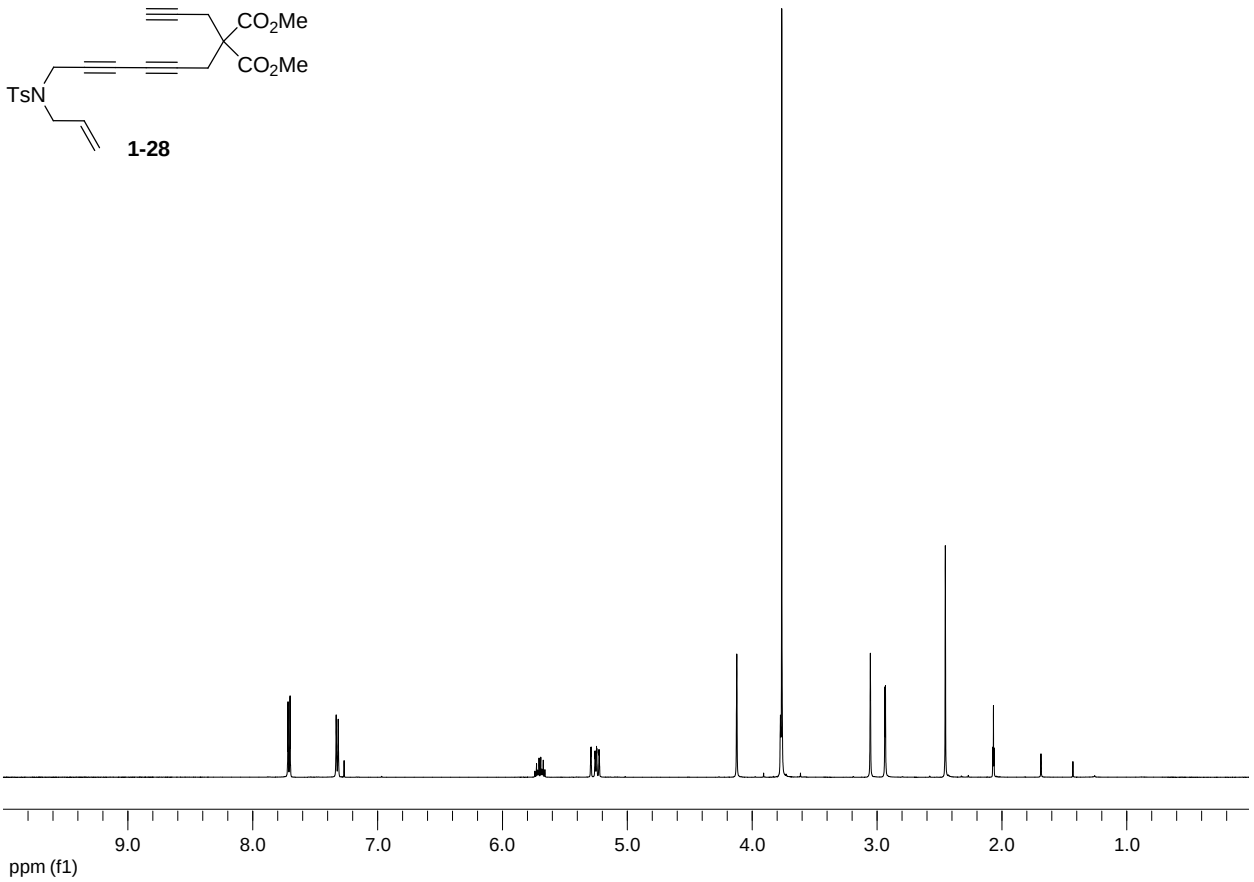
Appendix A

(Selected NMR spectra)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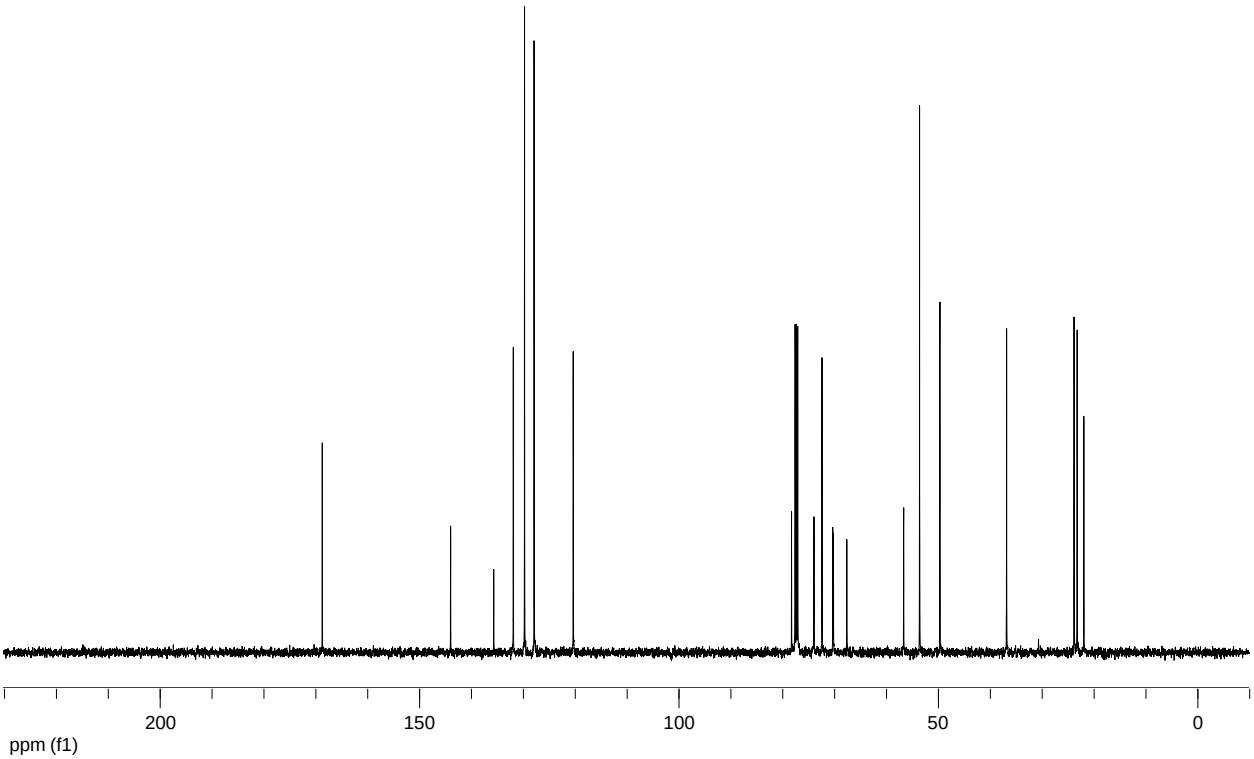
1.0
ppm (f1)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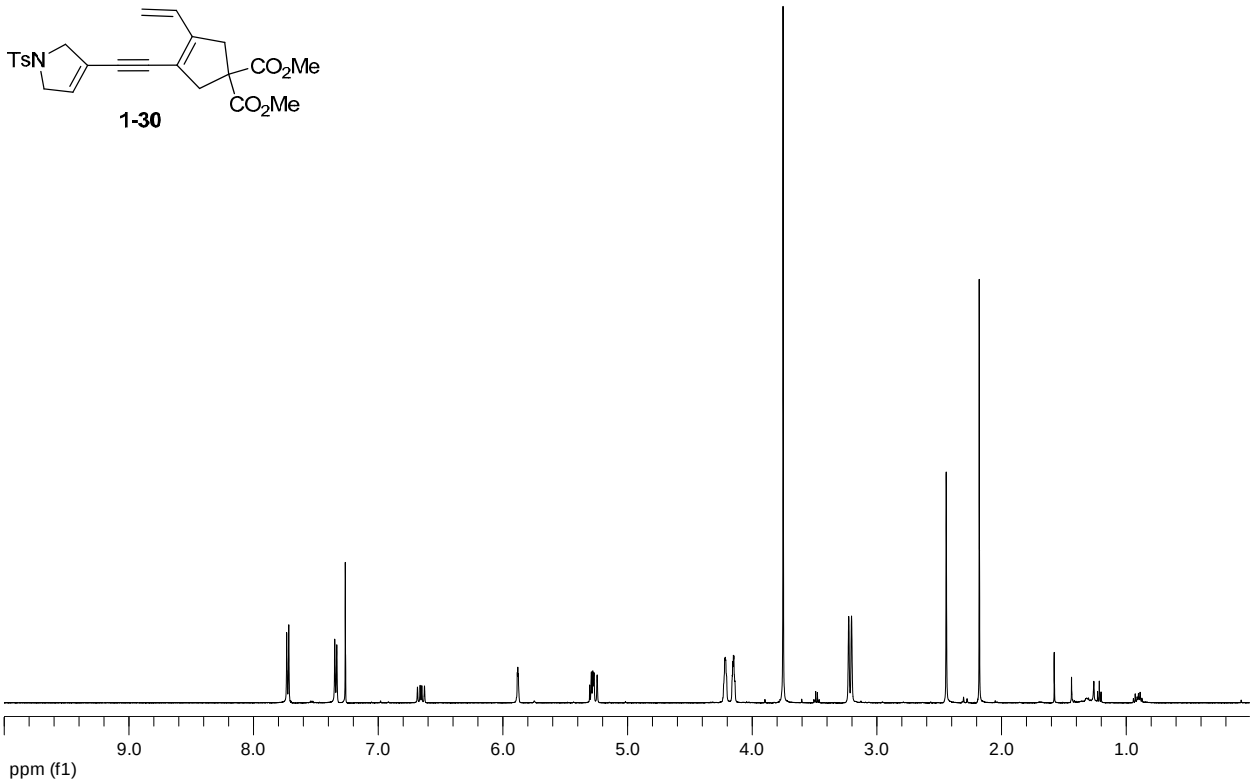
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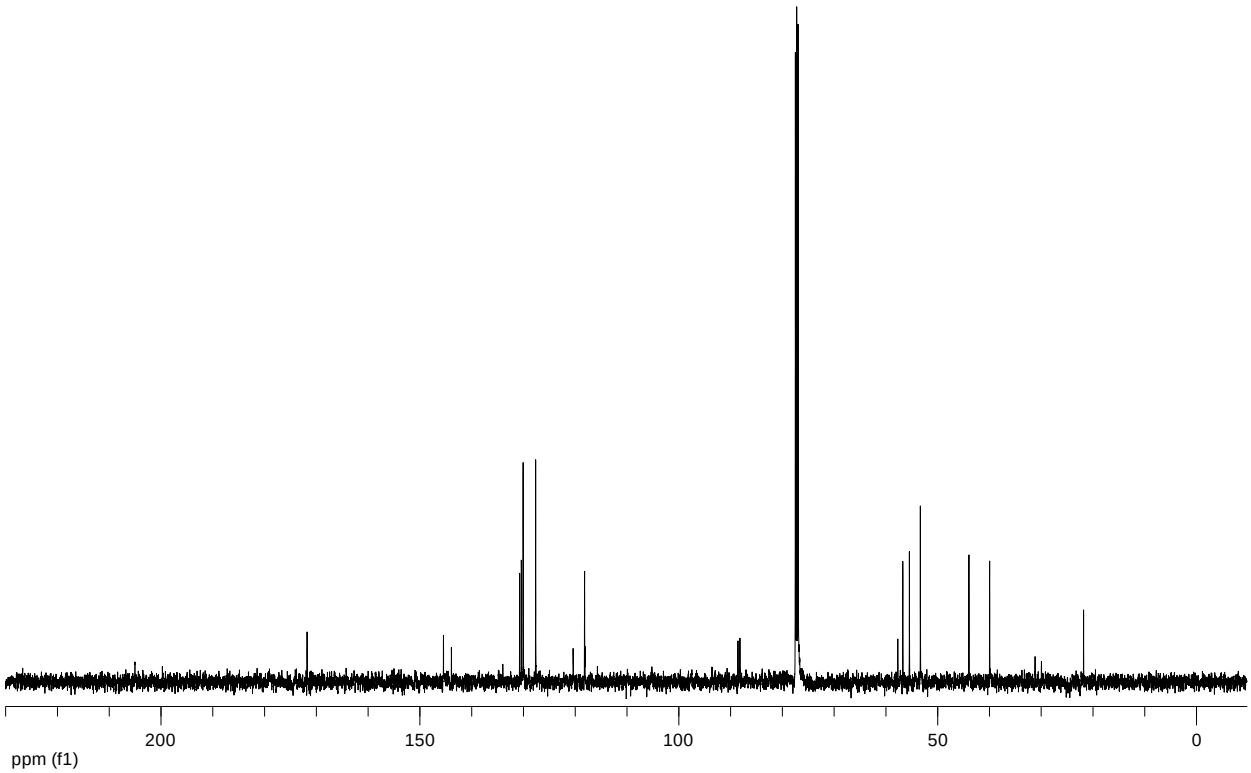
ppm (f1)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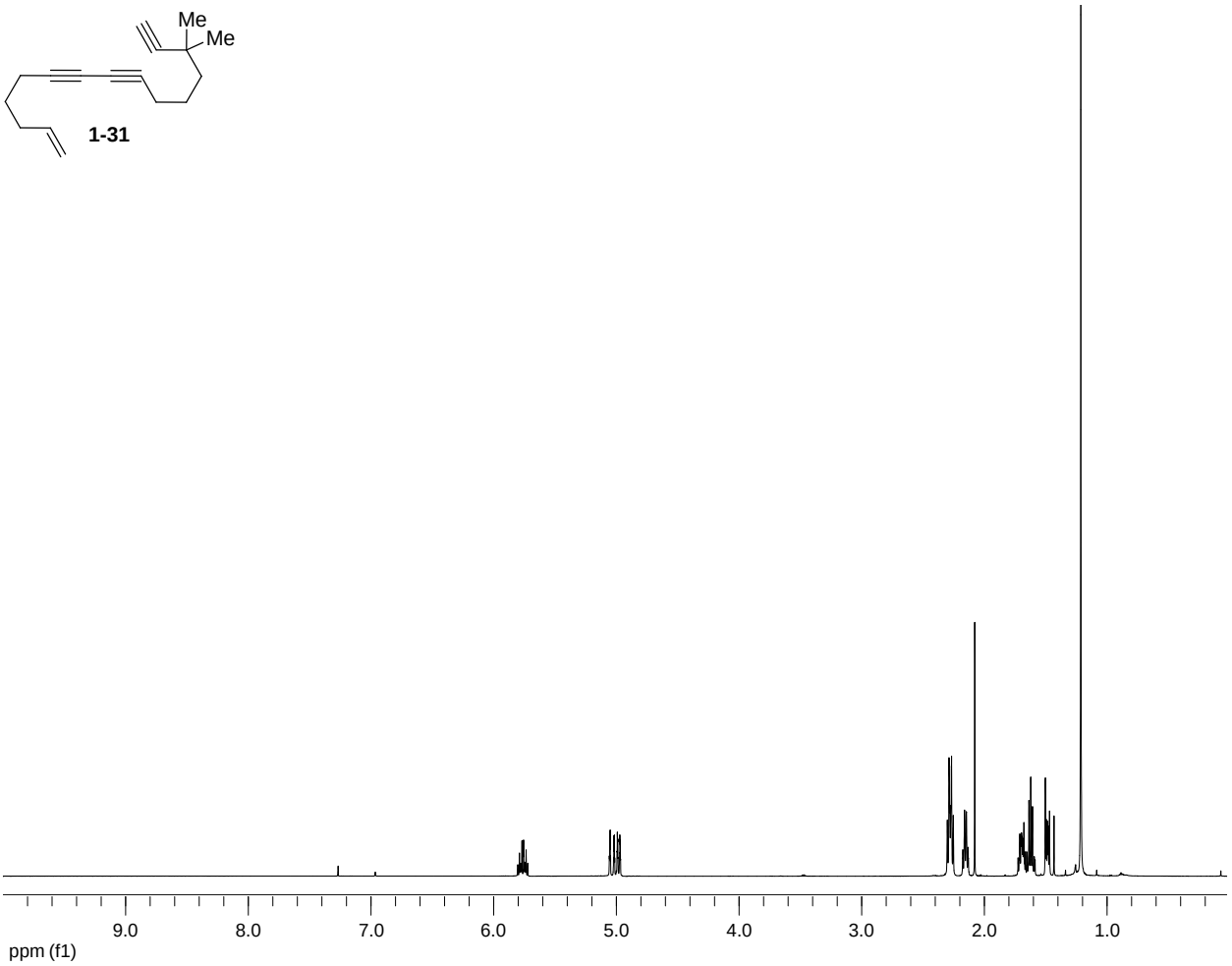
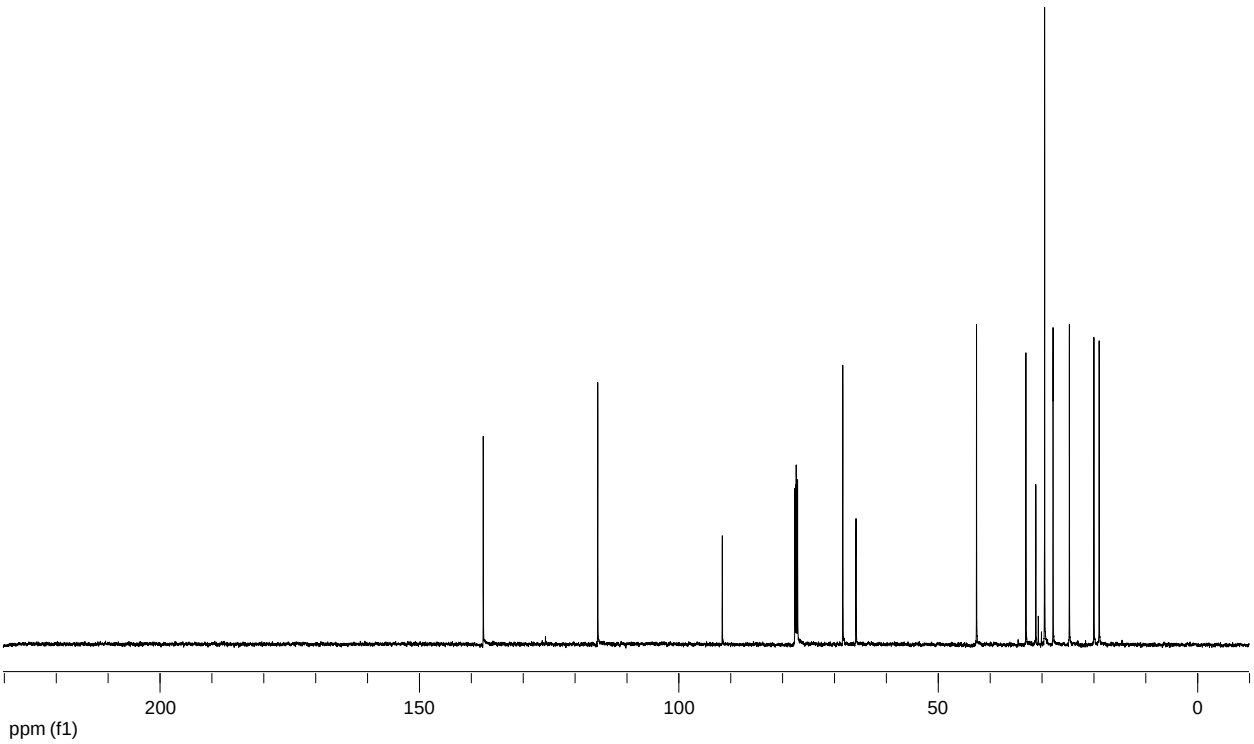
ppm (f1)

1-31





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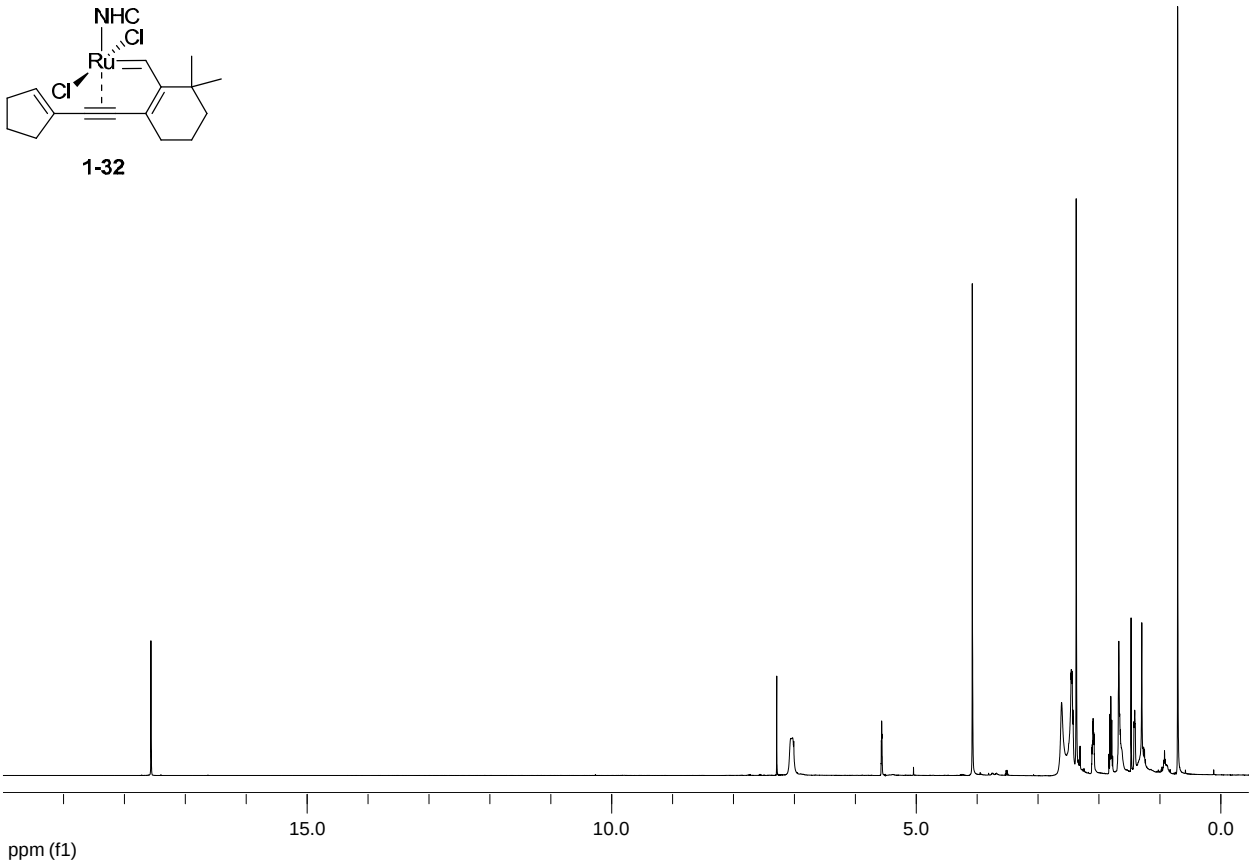

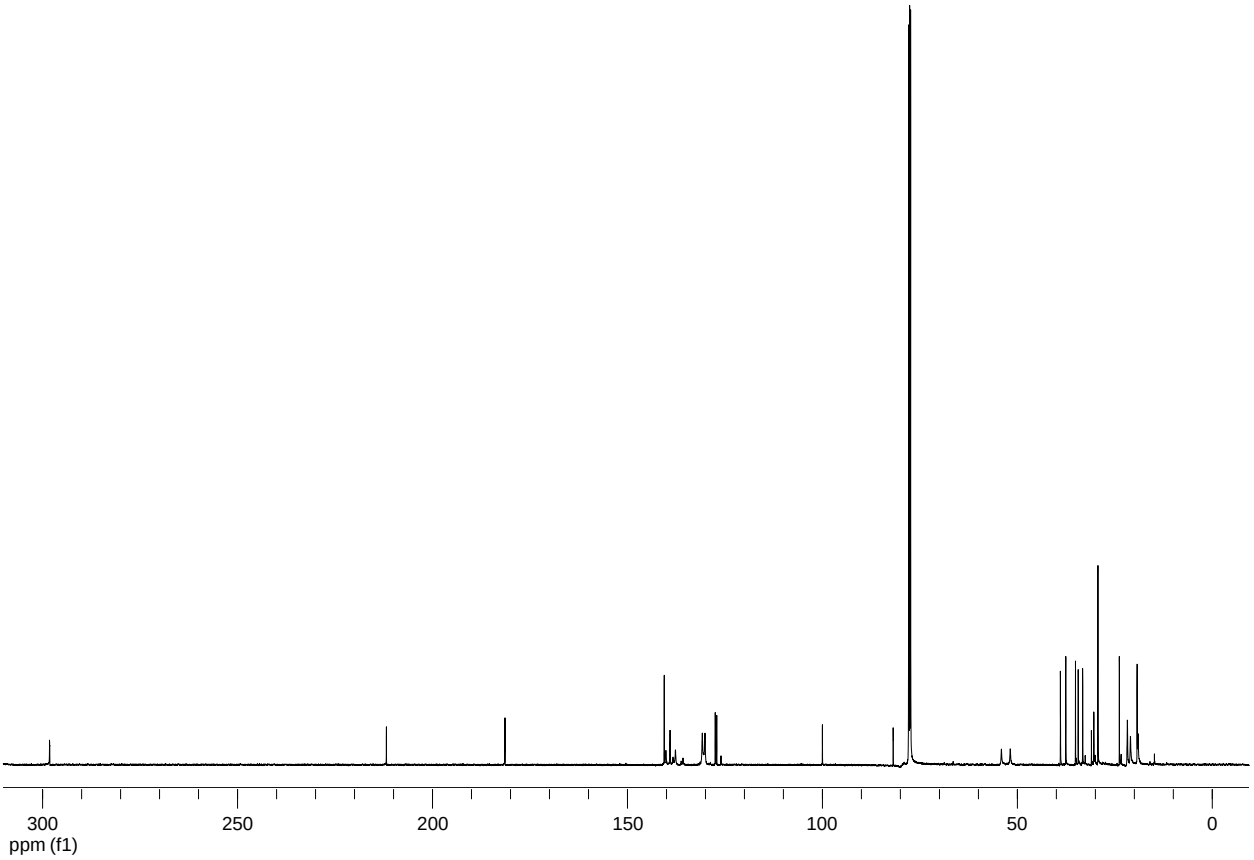

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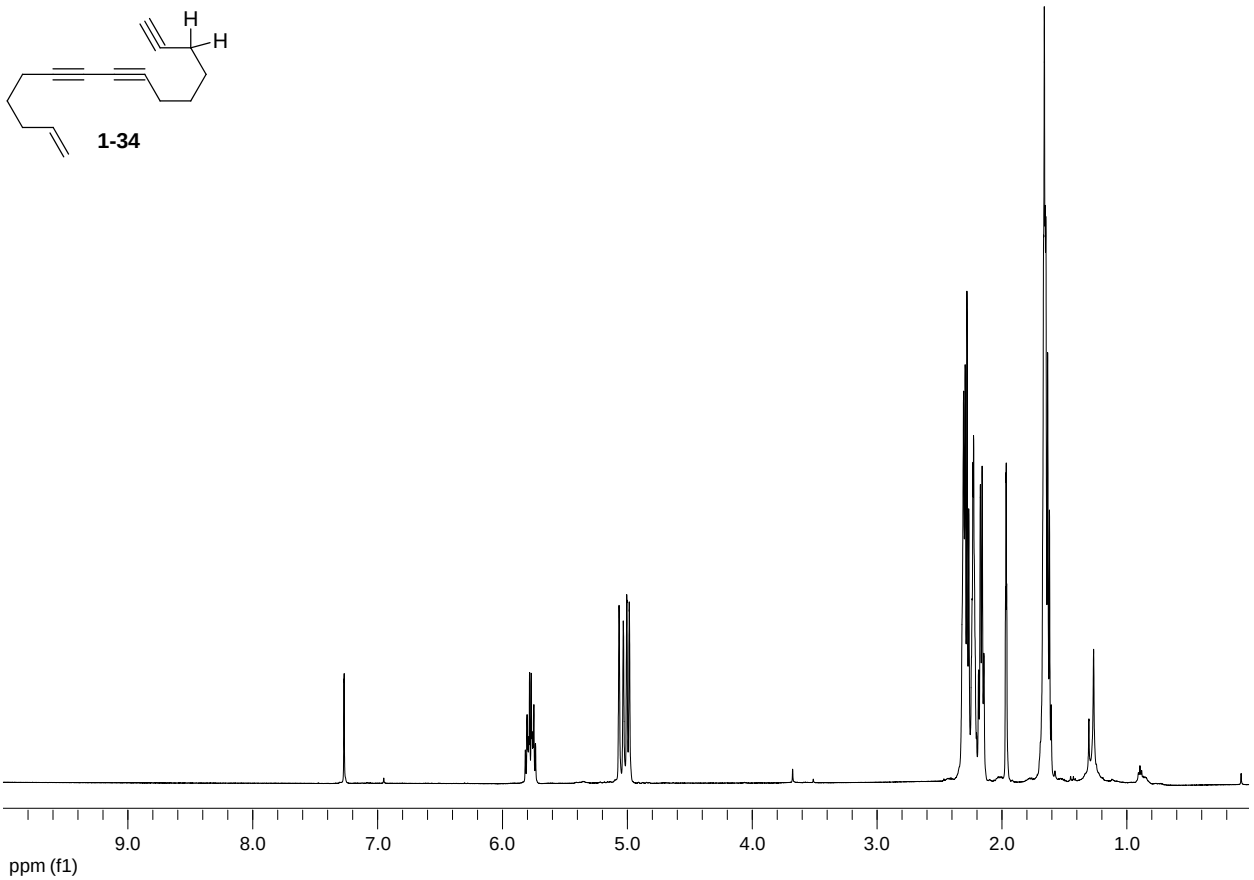

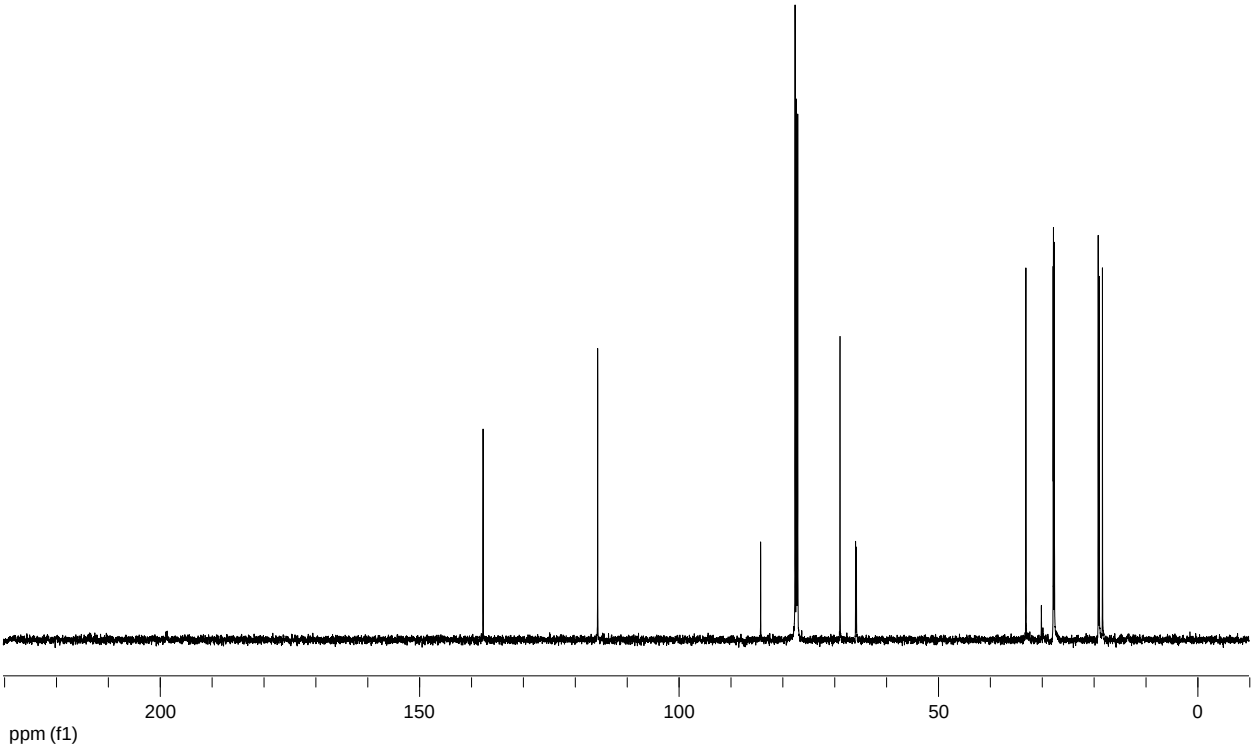

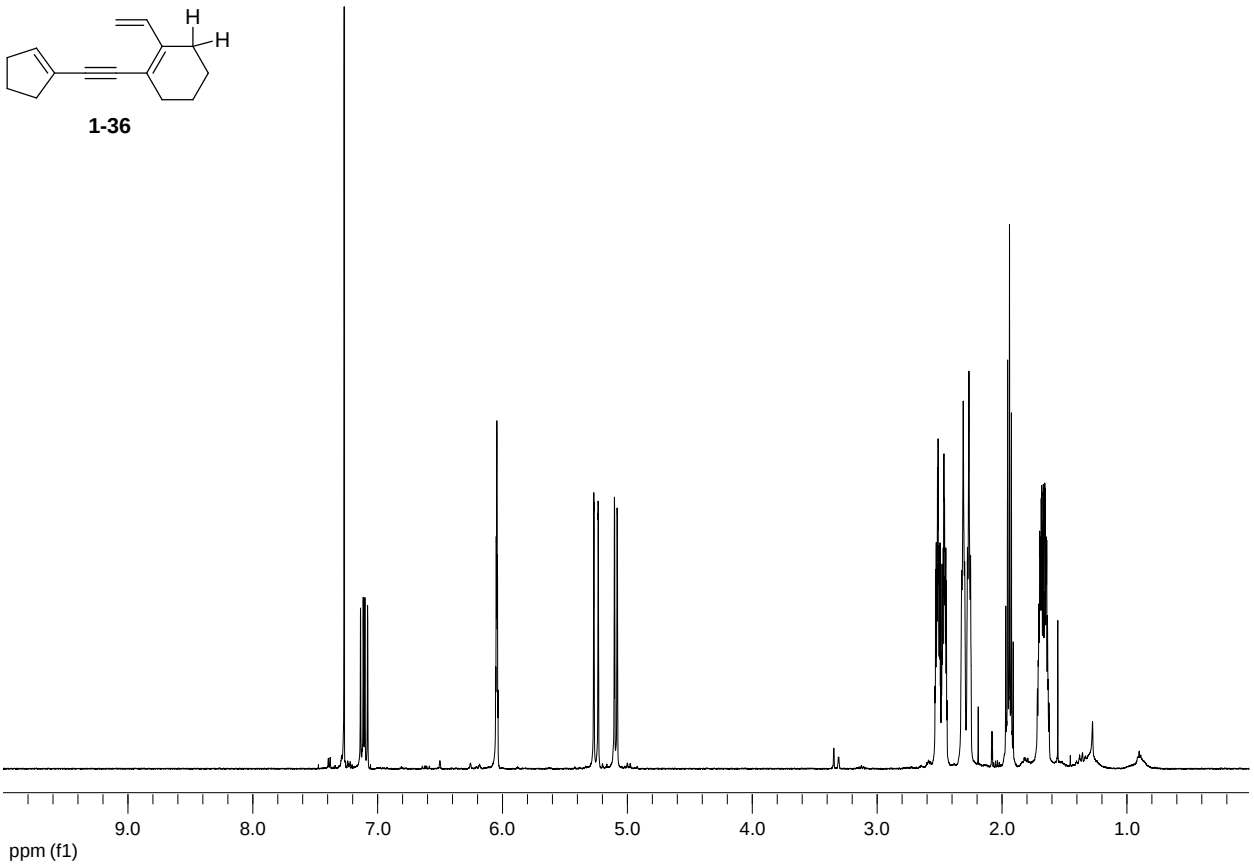
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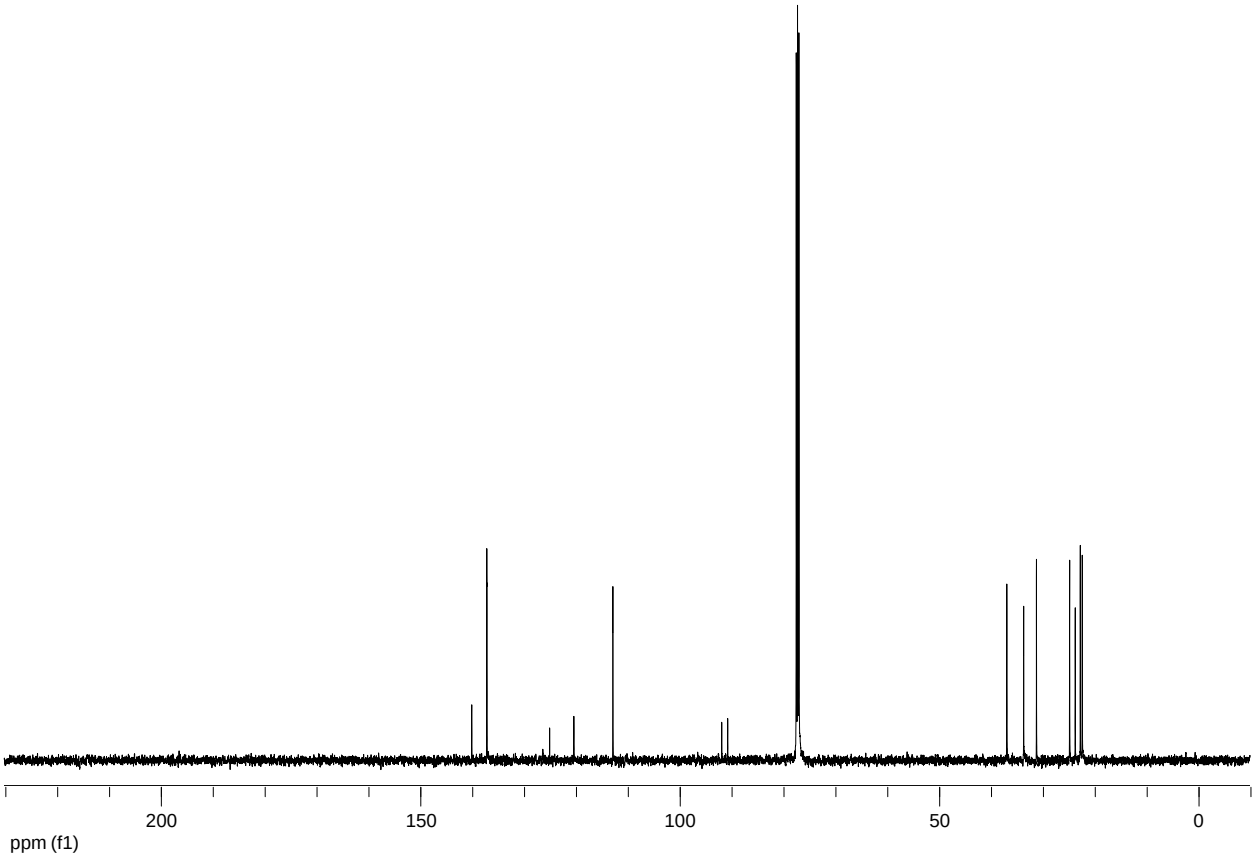
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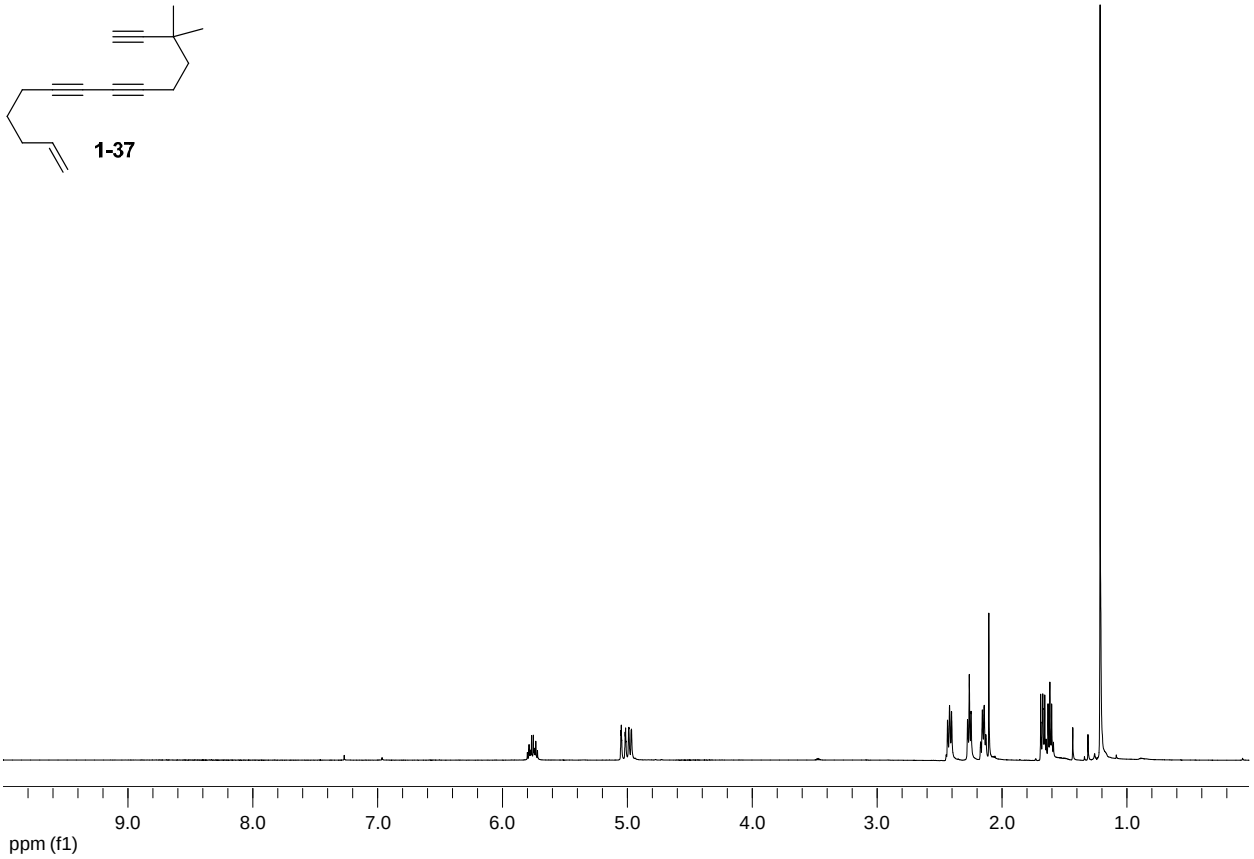
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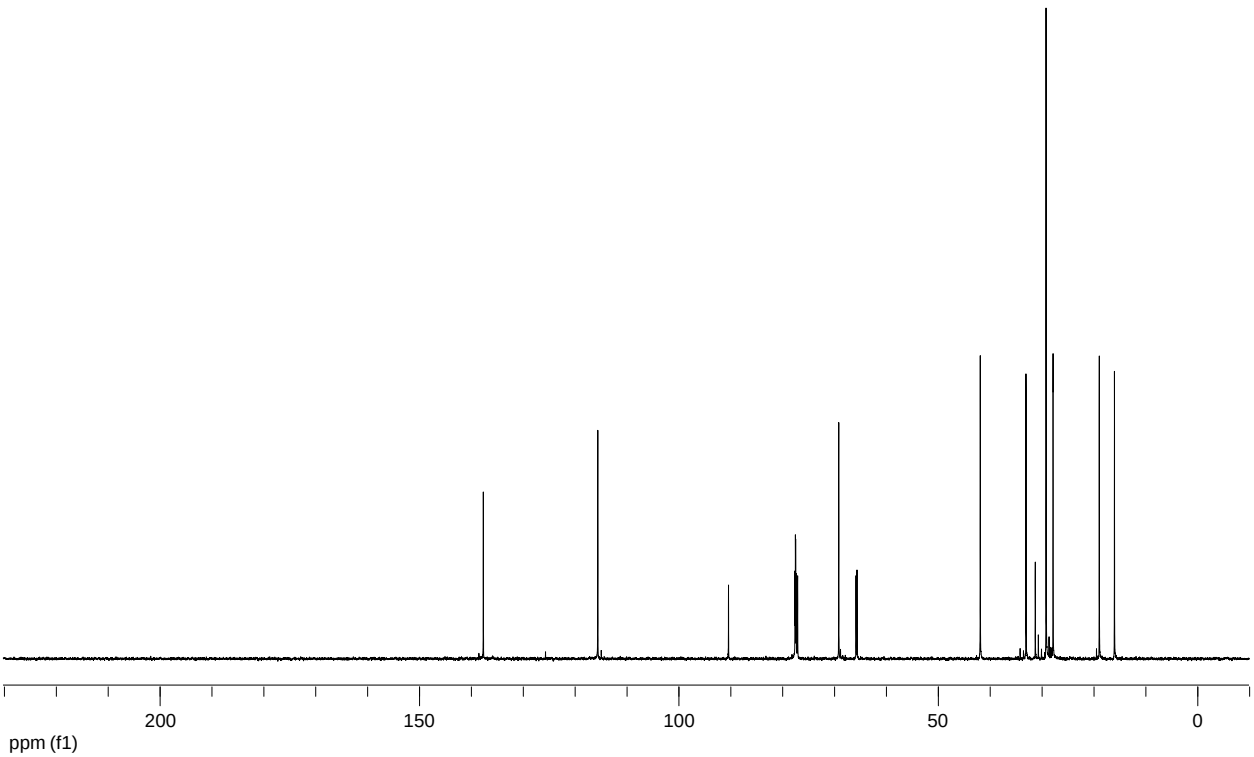
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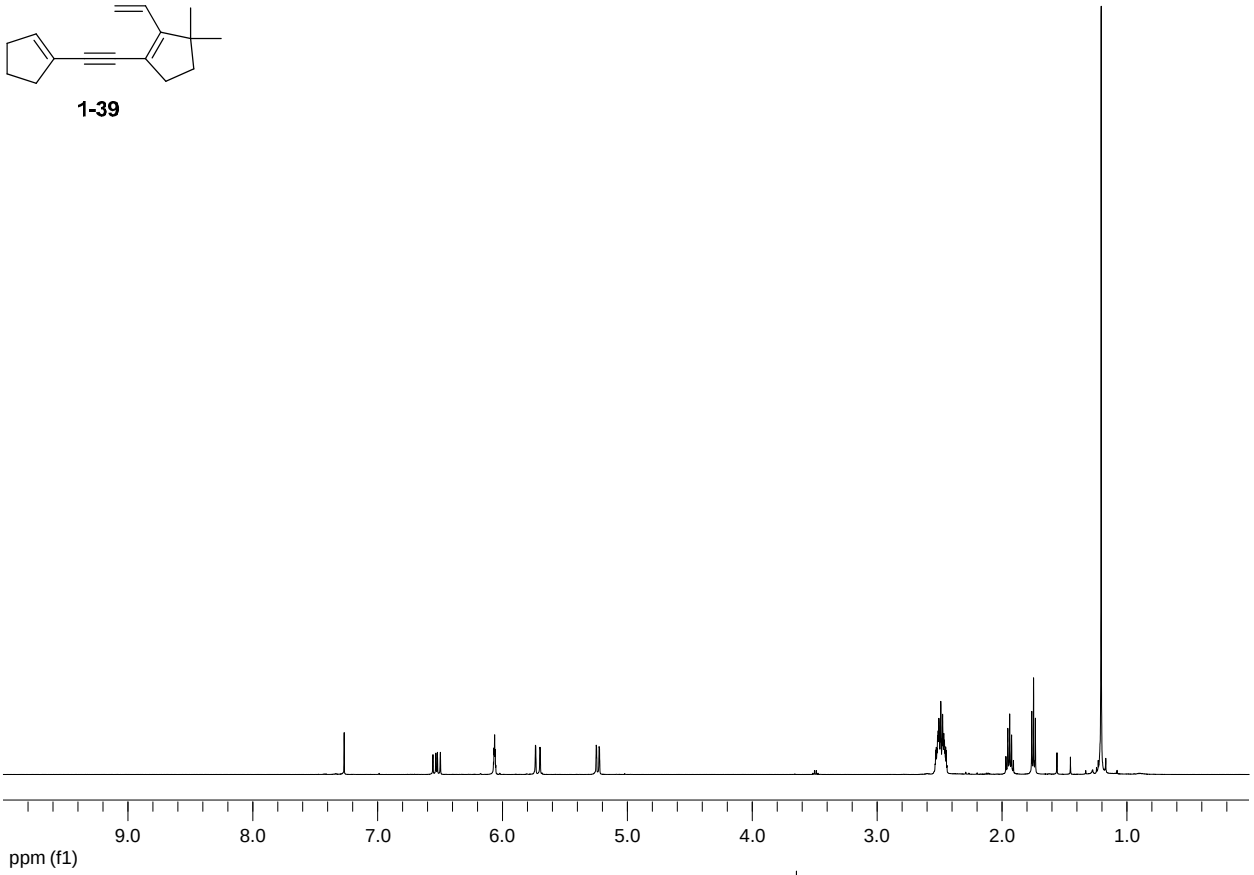

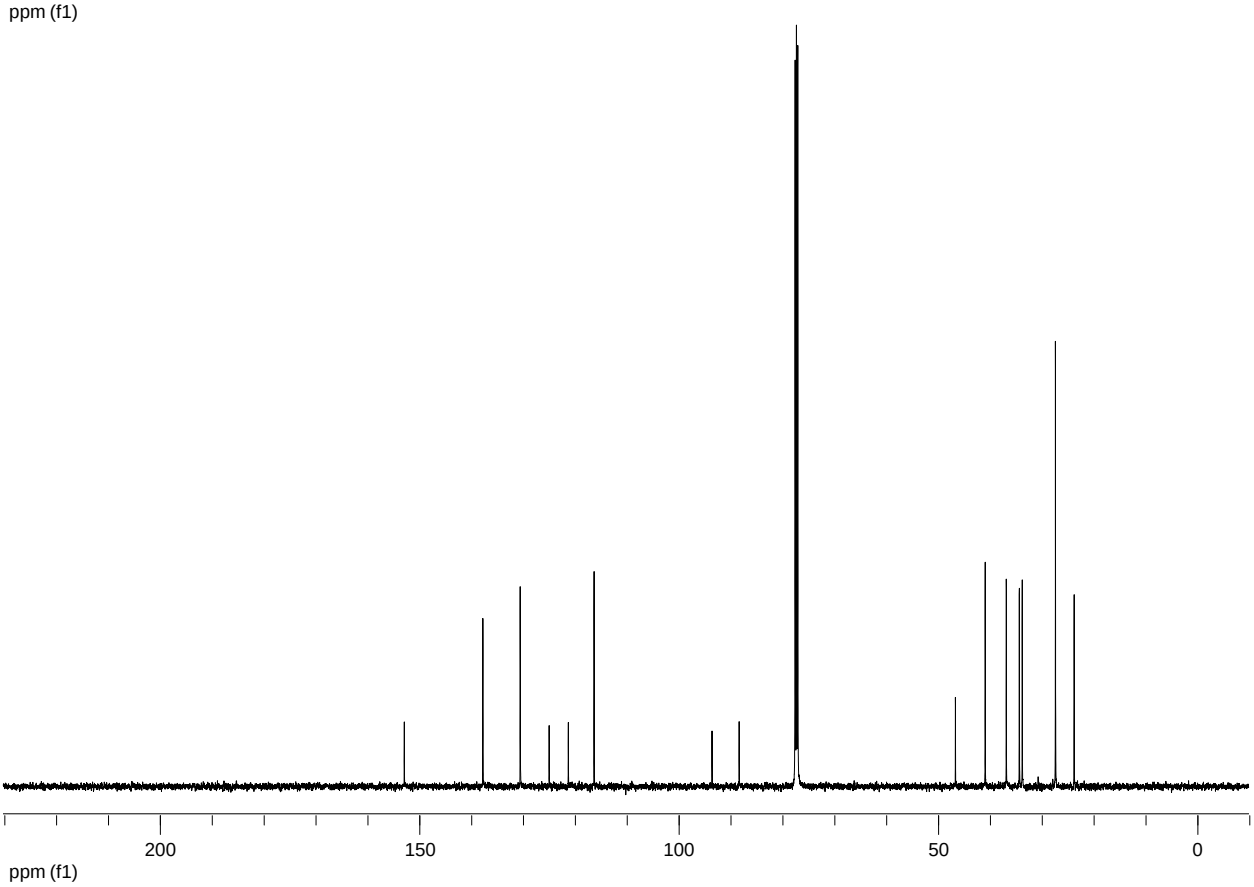

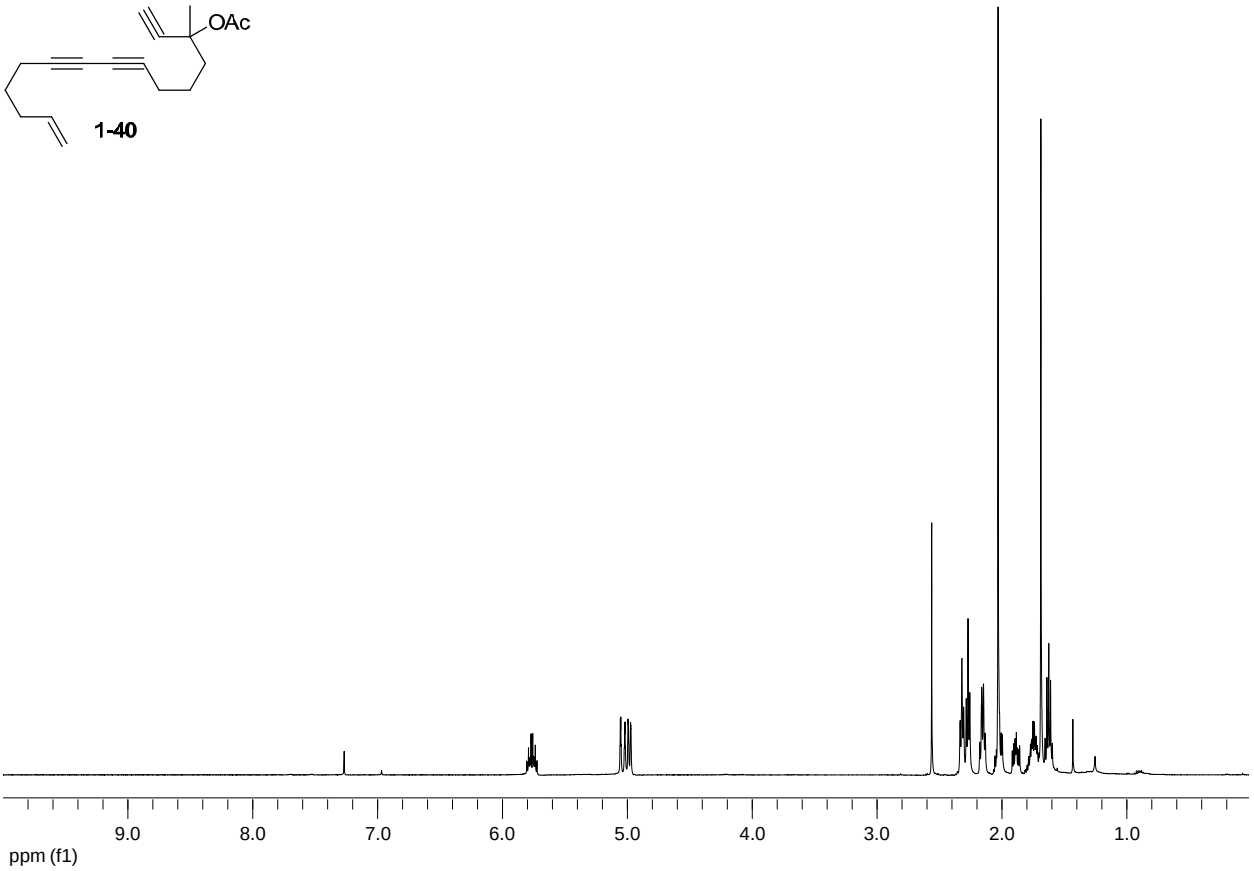
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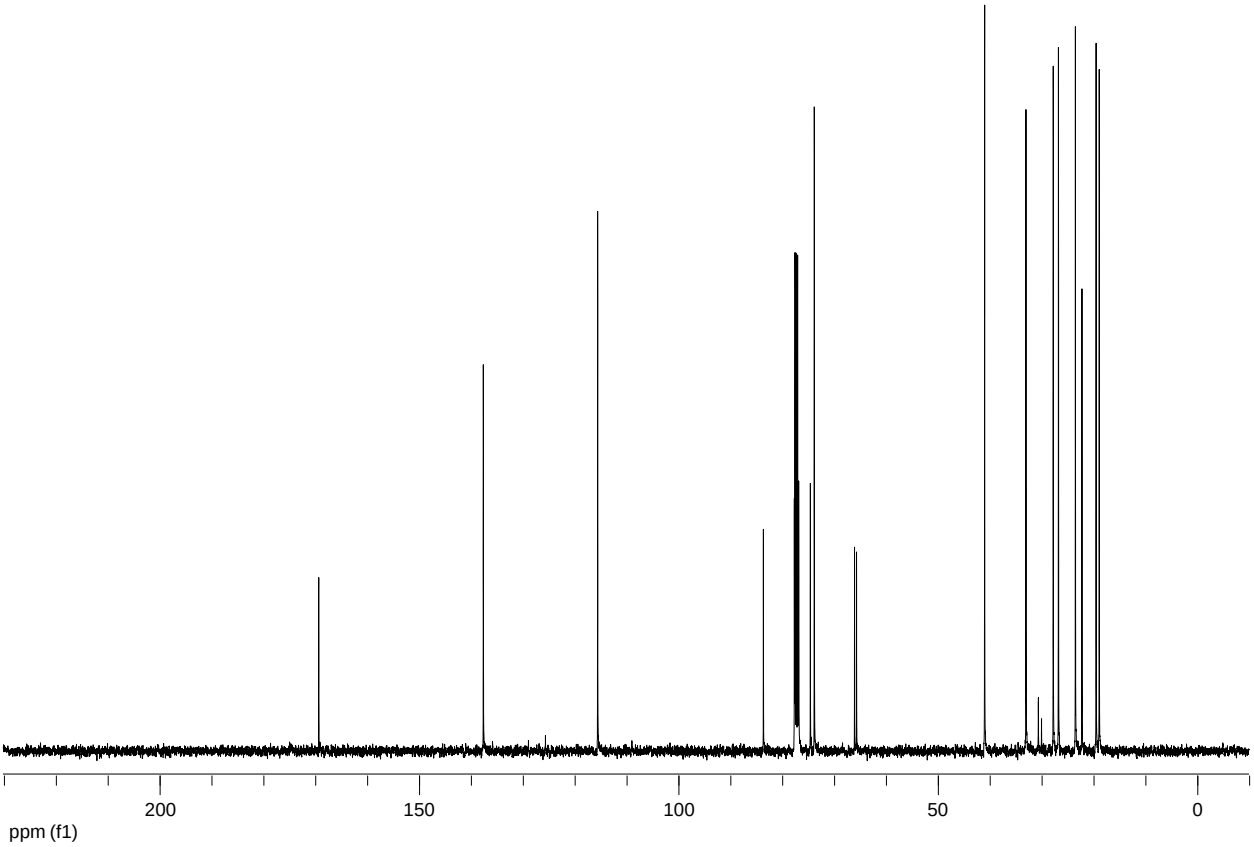
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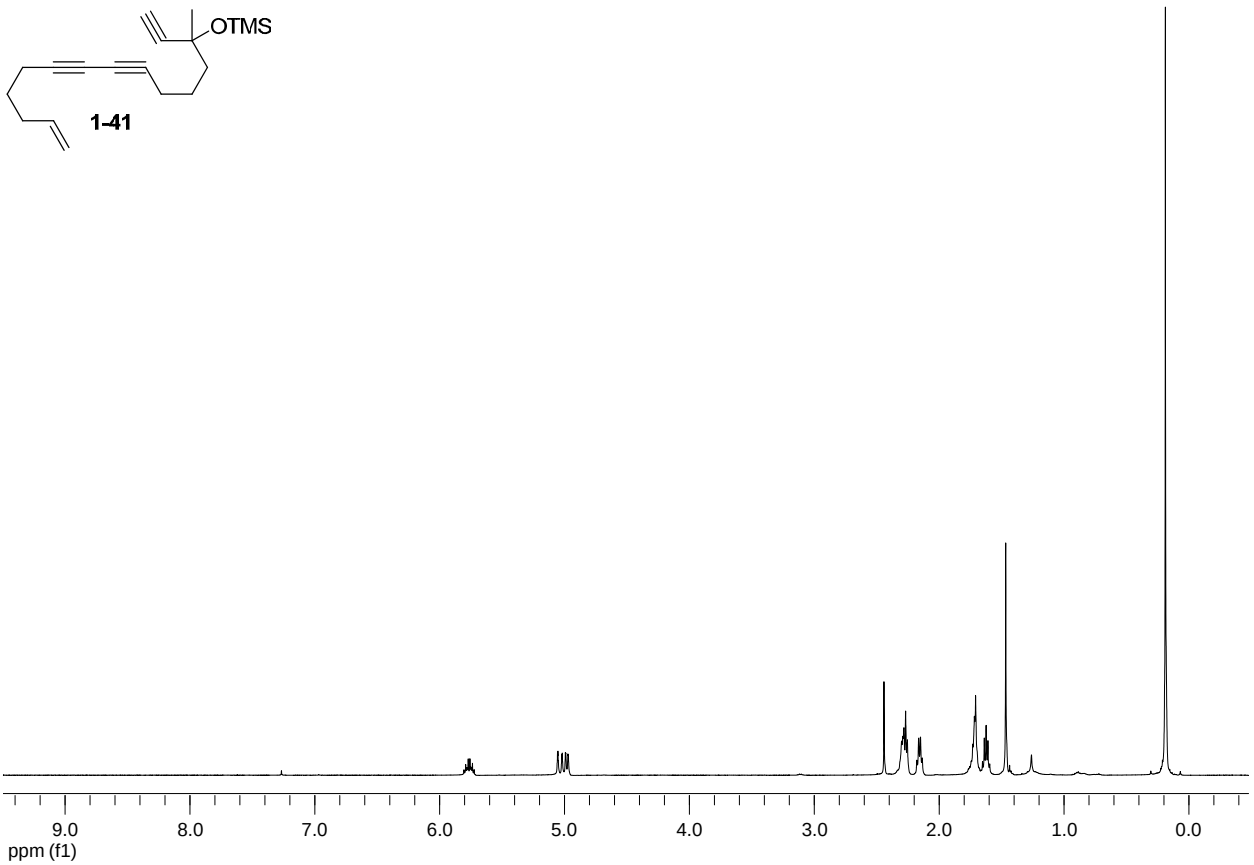

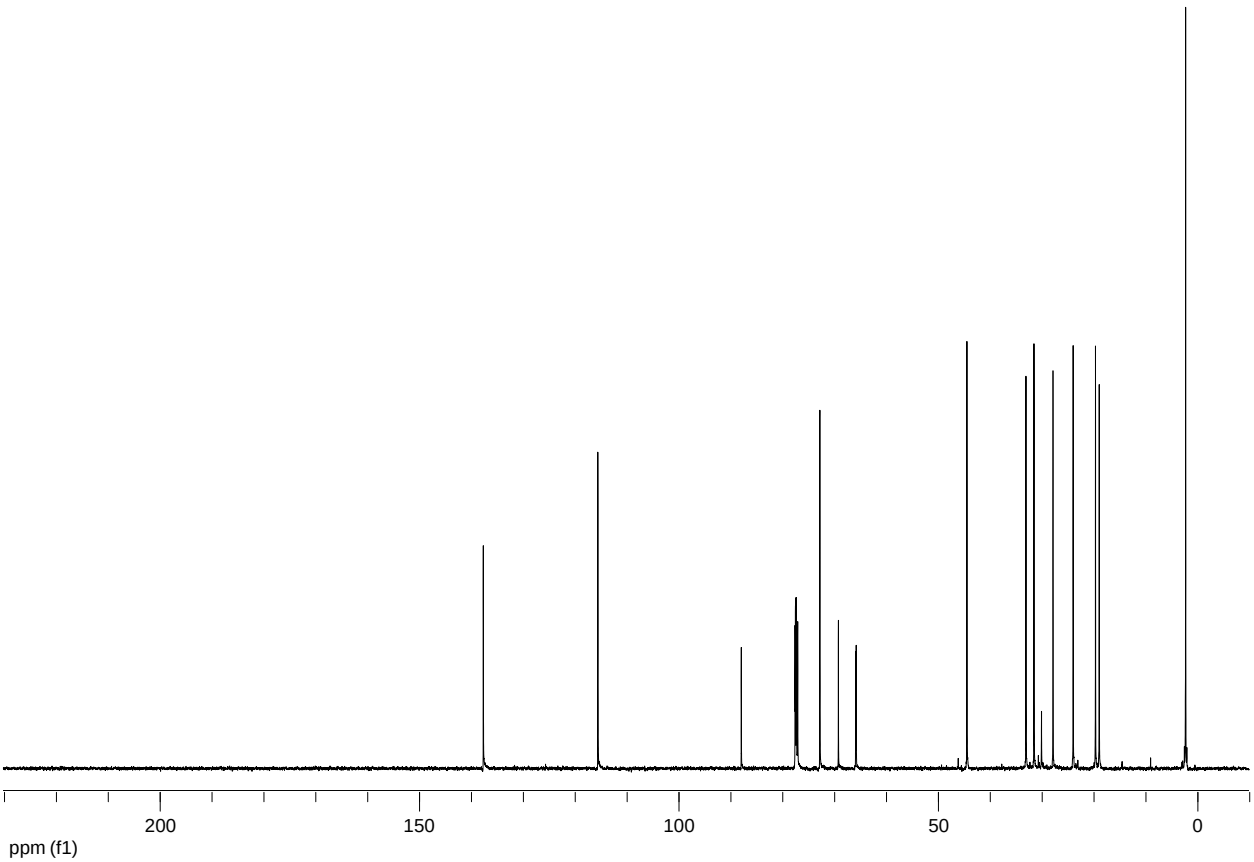

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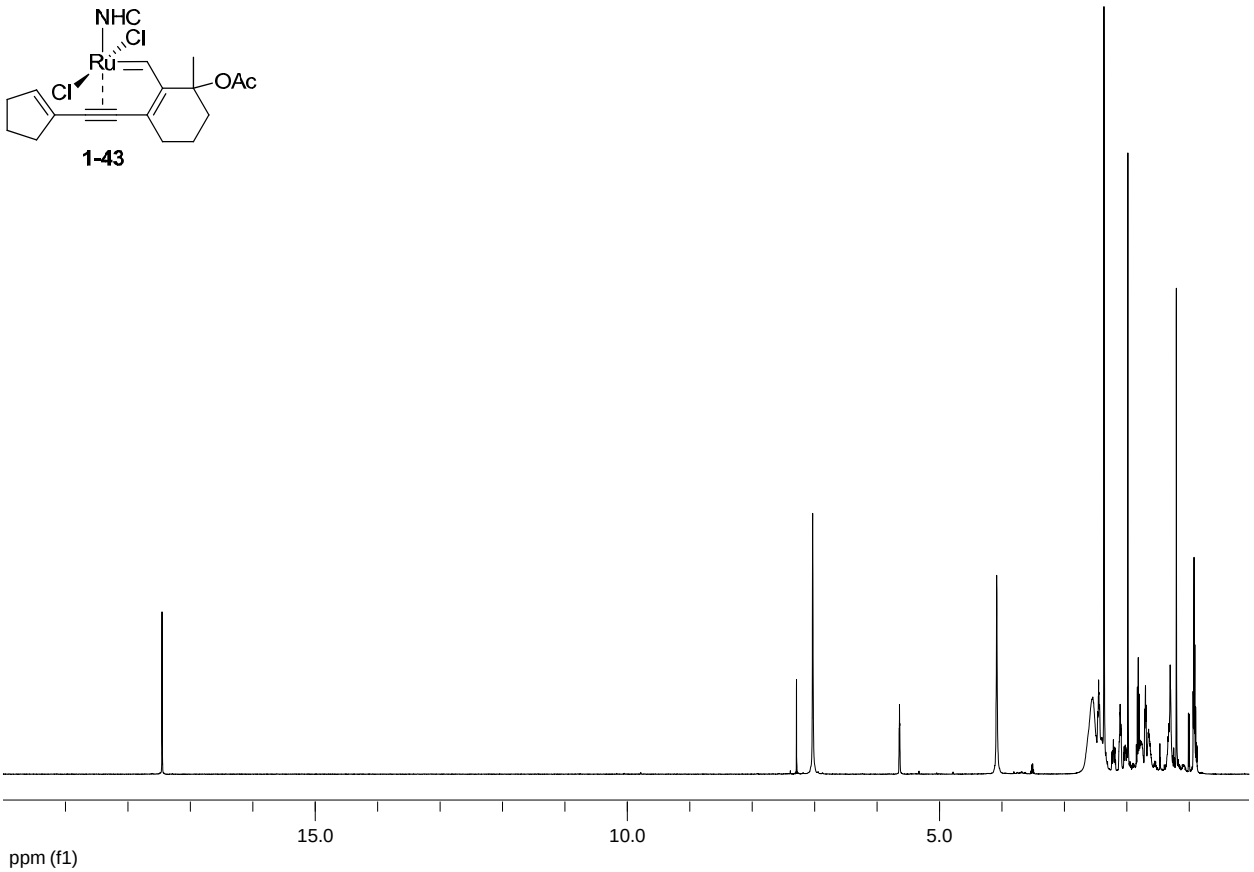

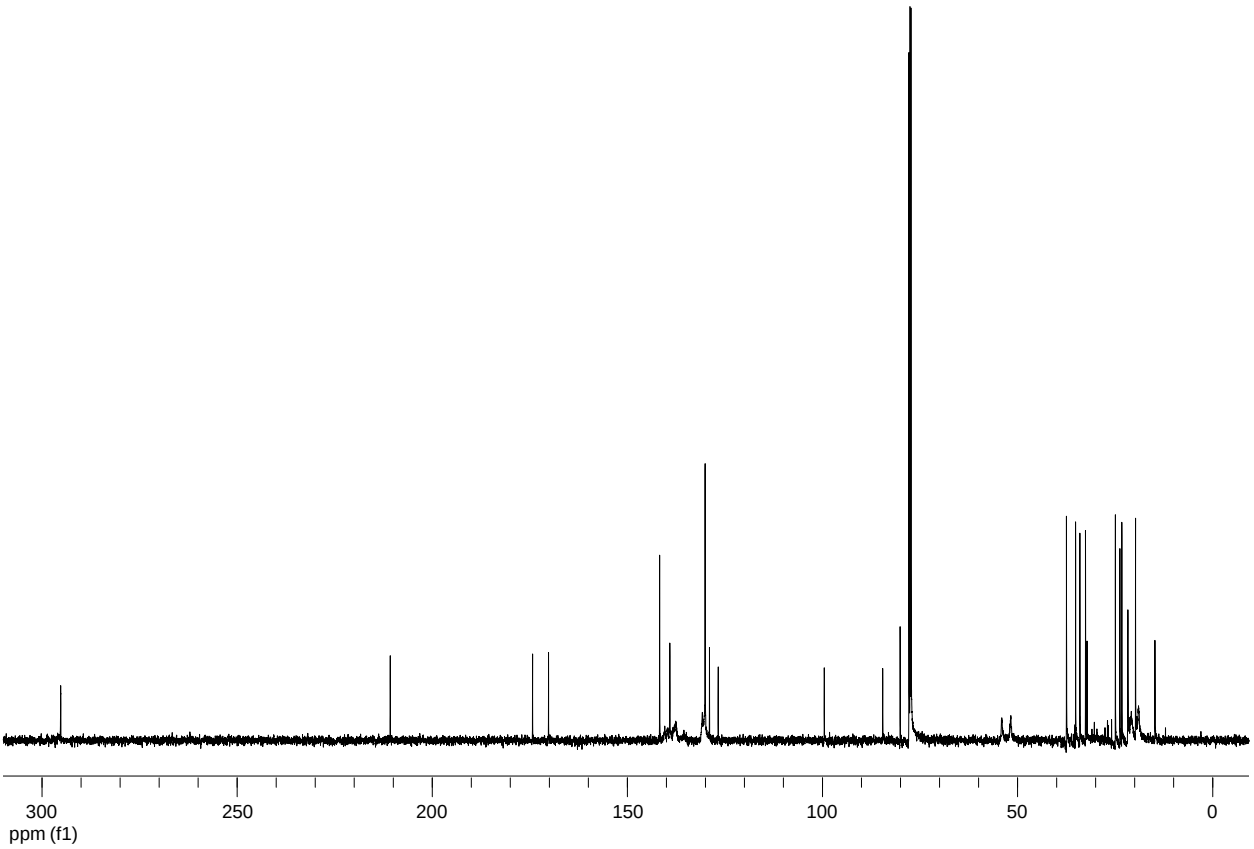

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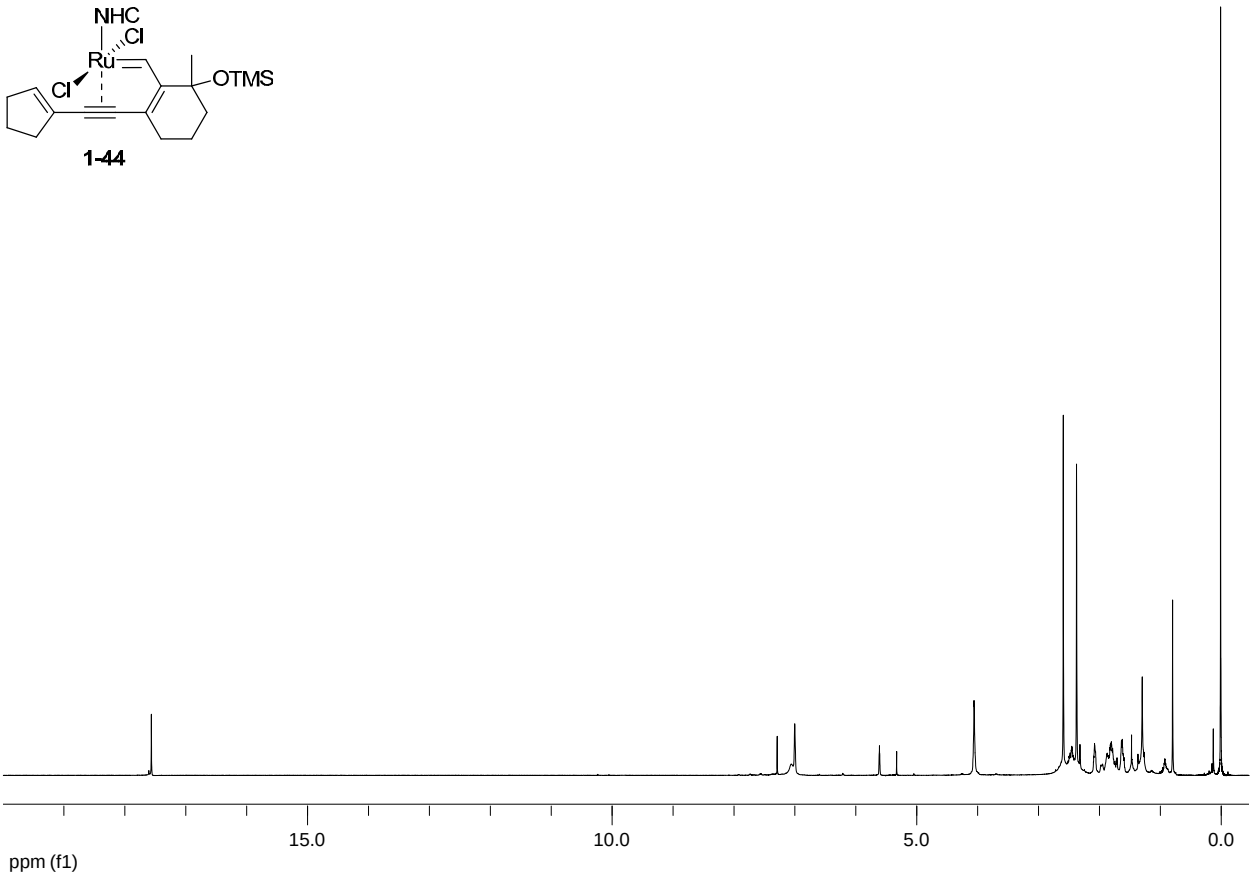
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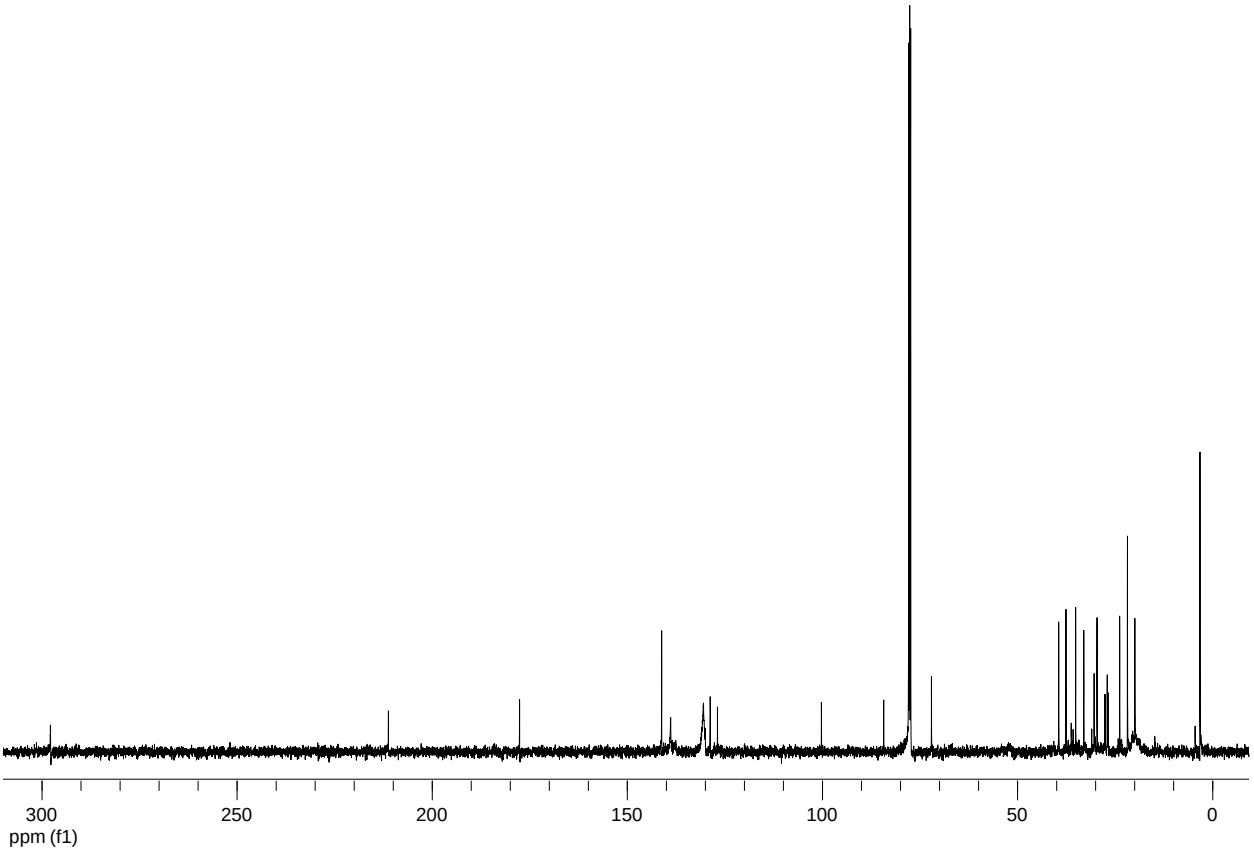
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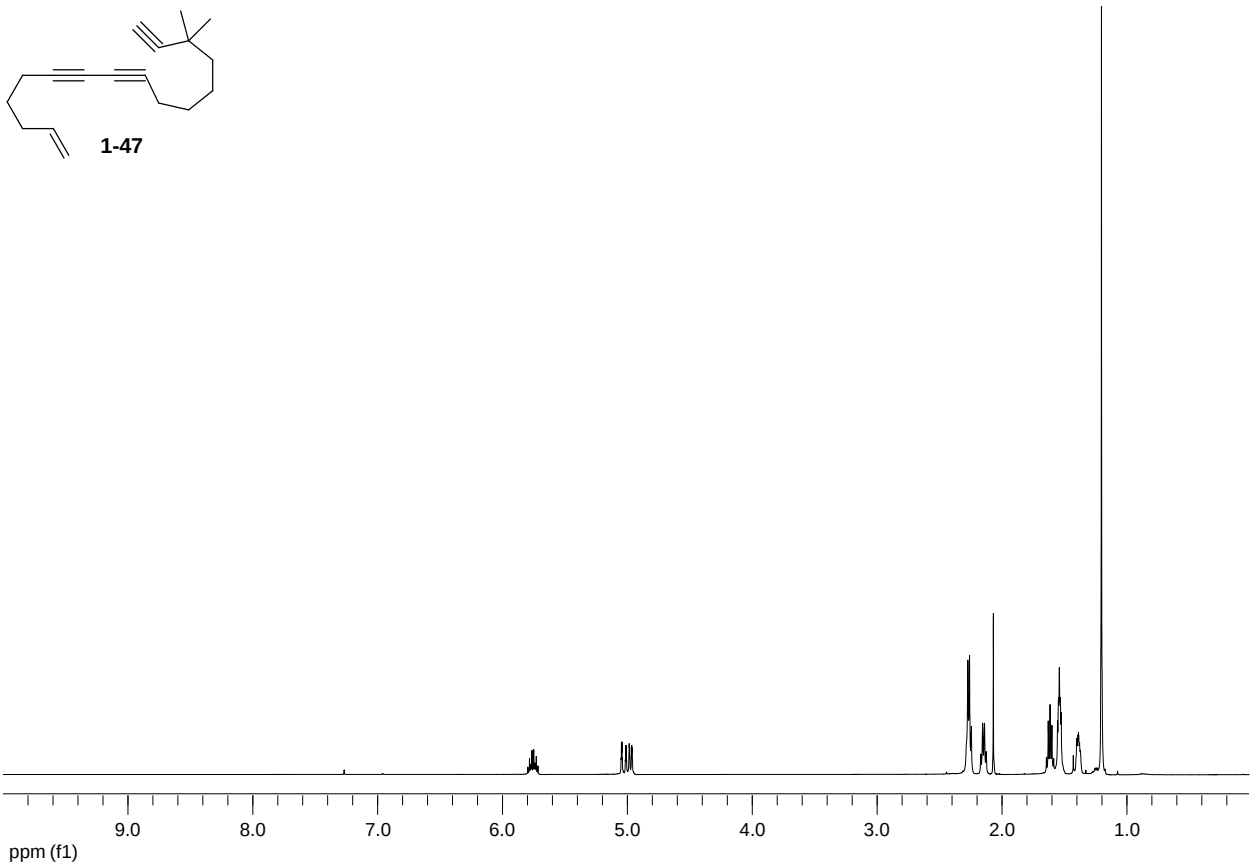

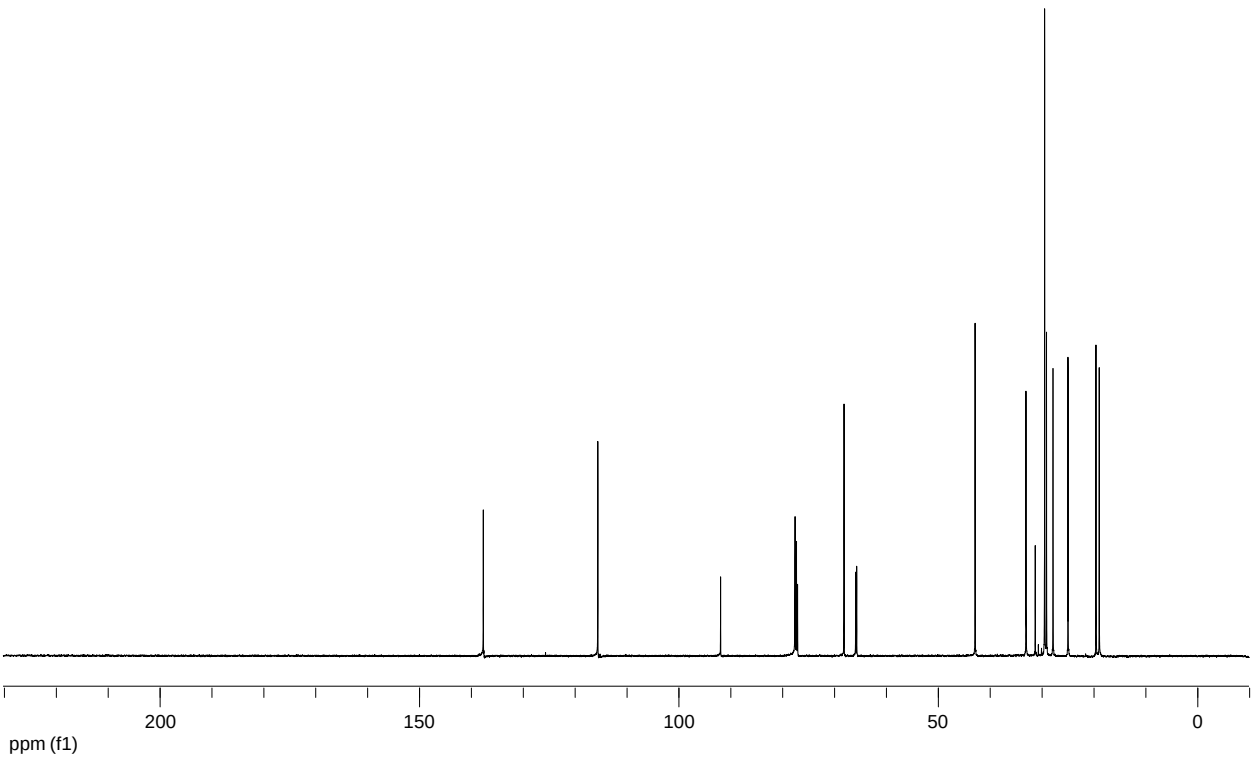

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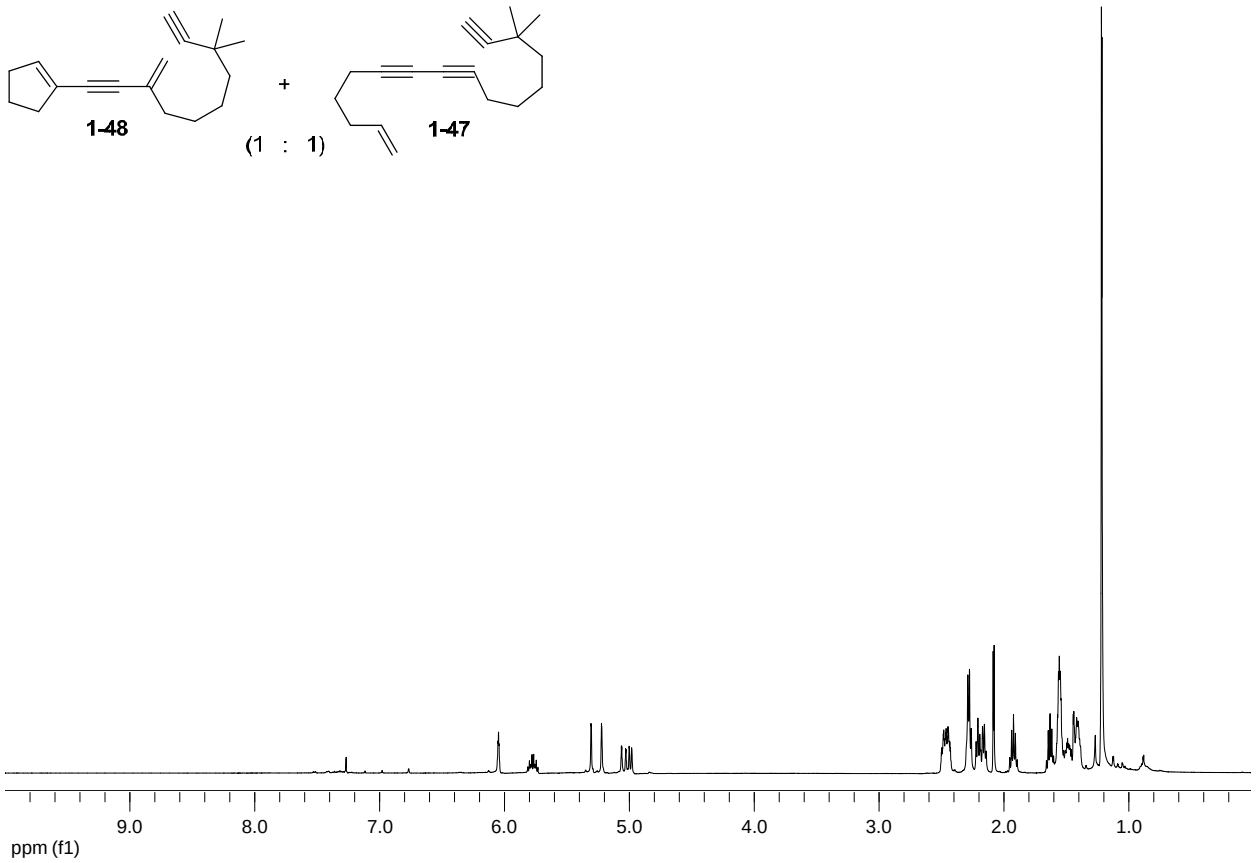
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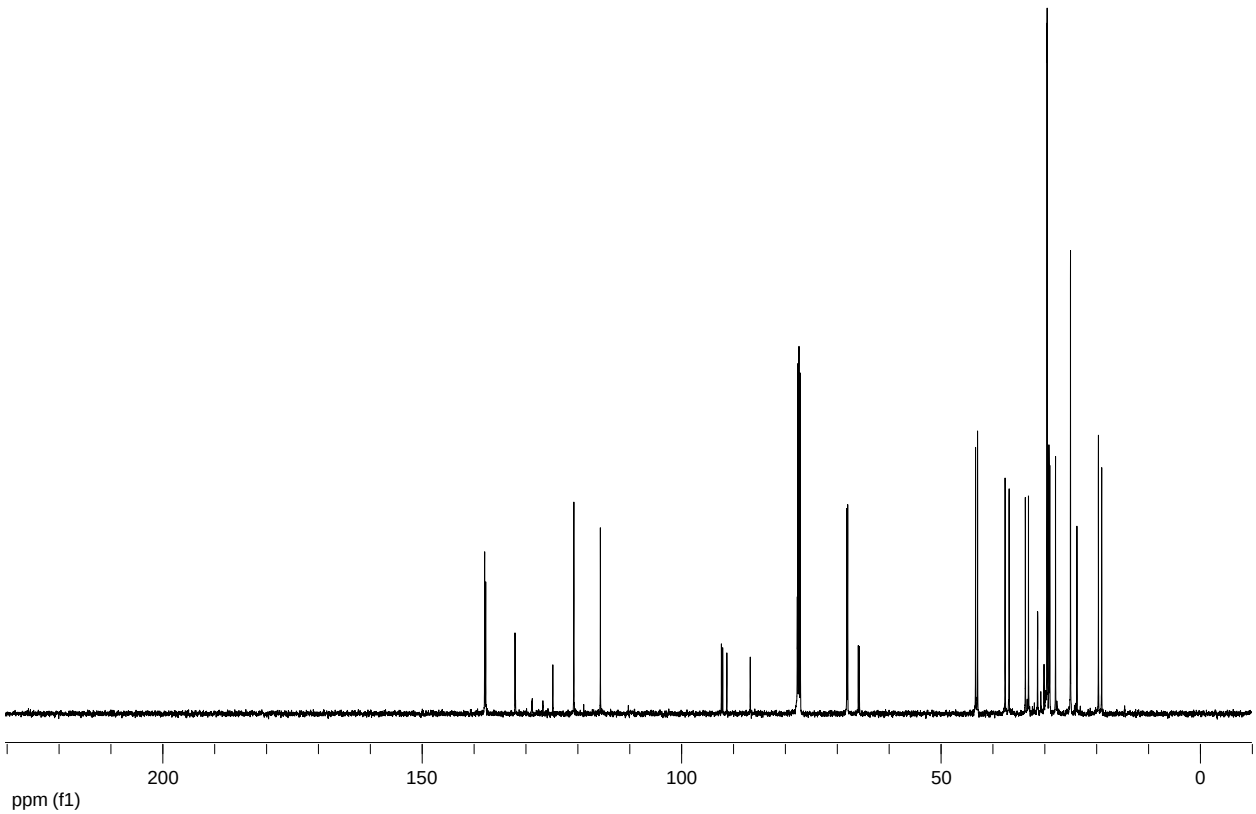
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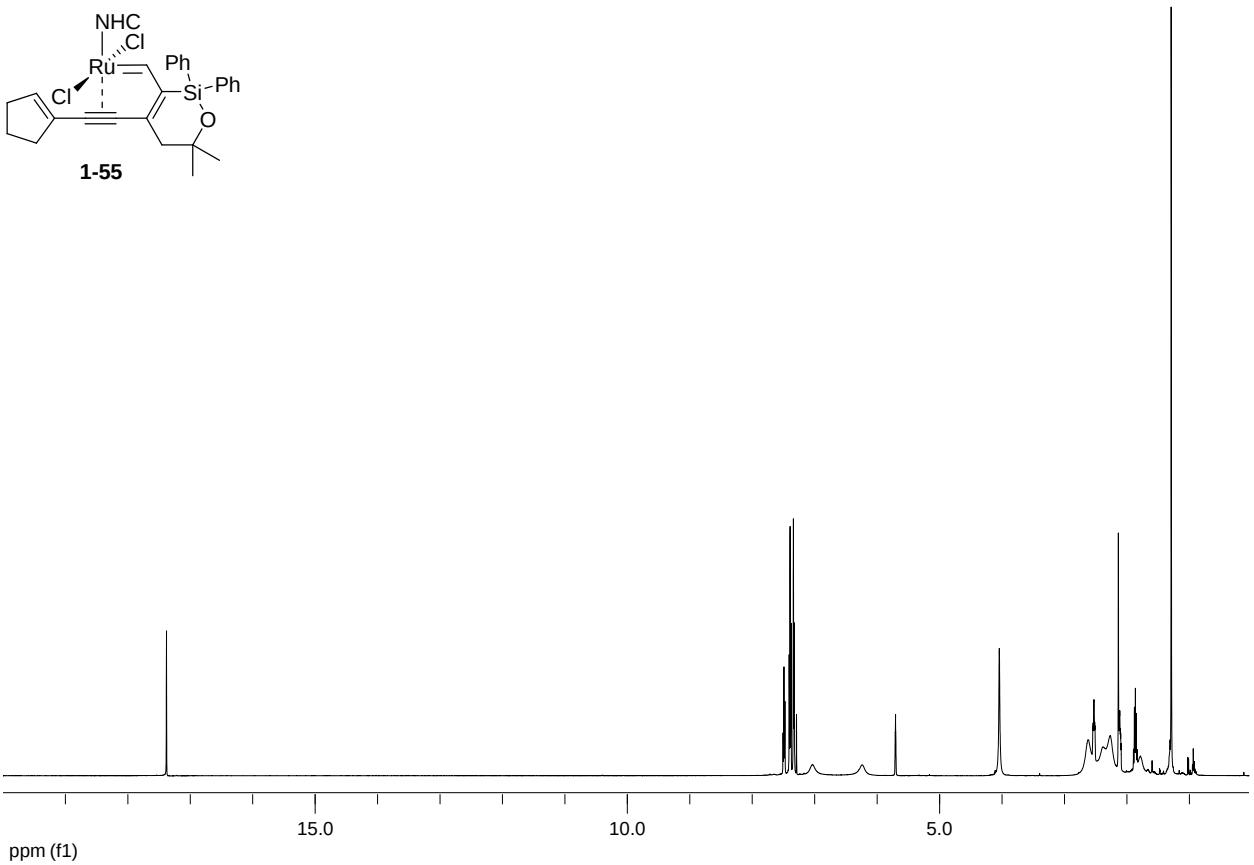
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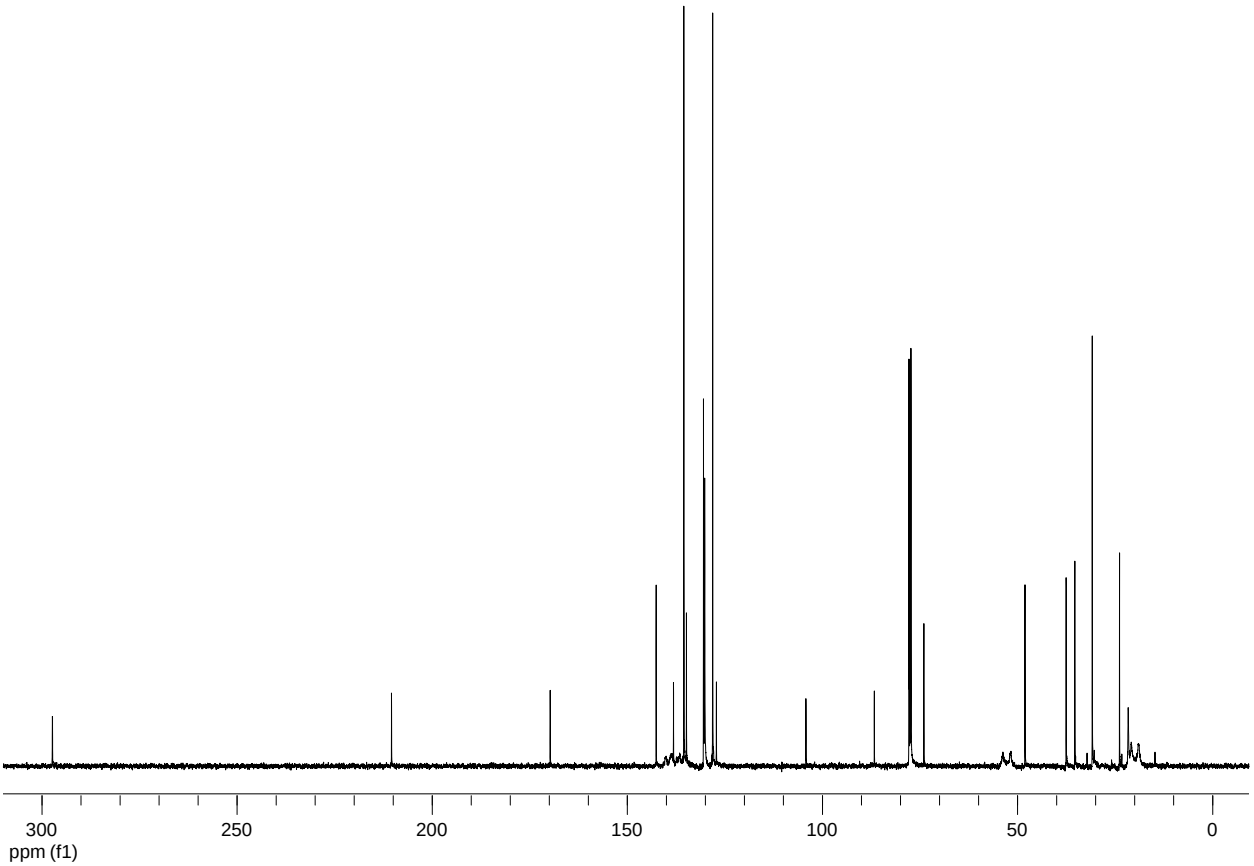
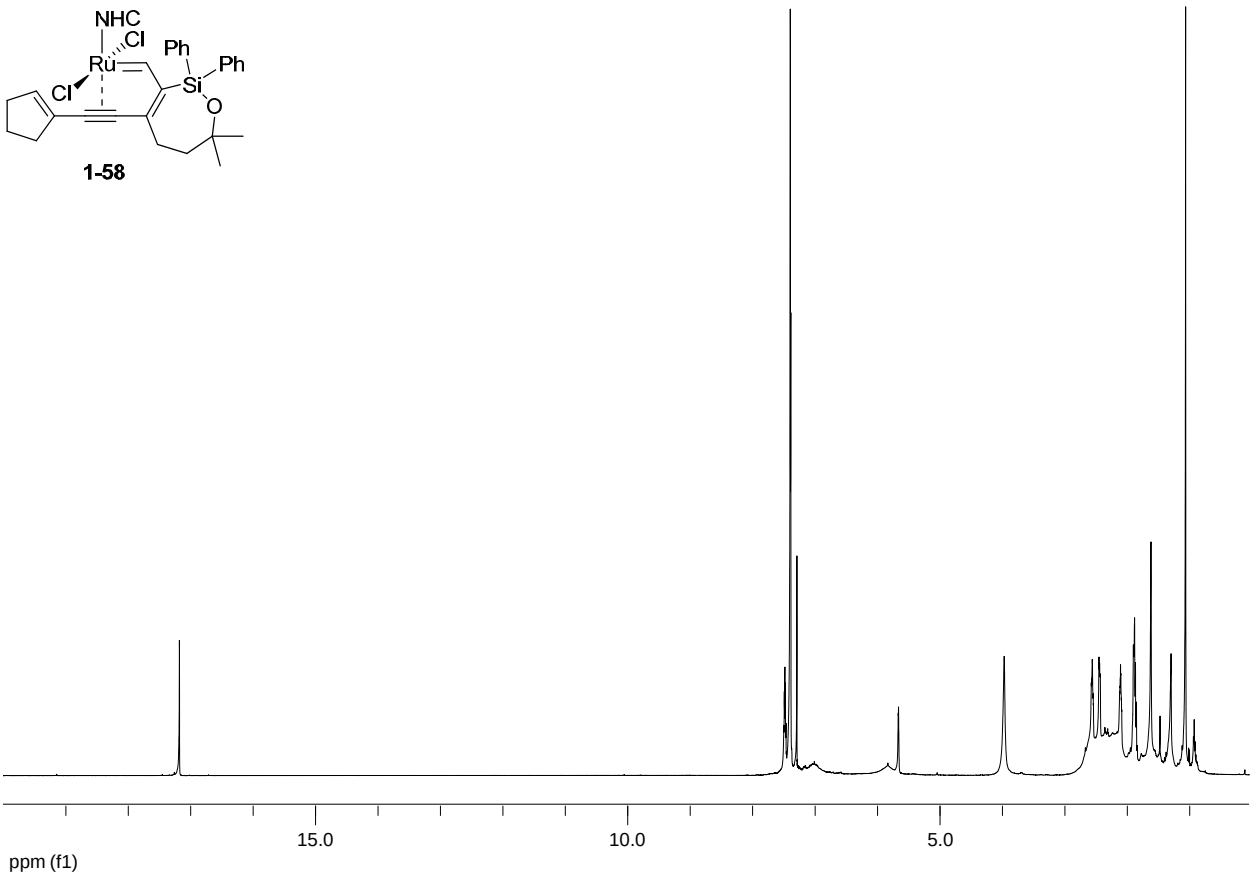
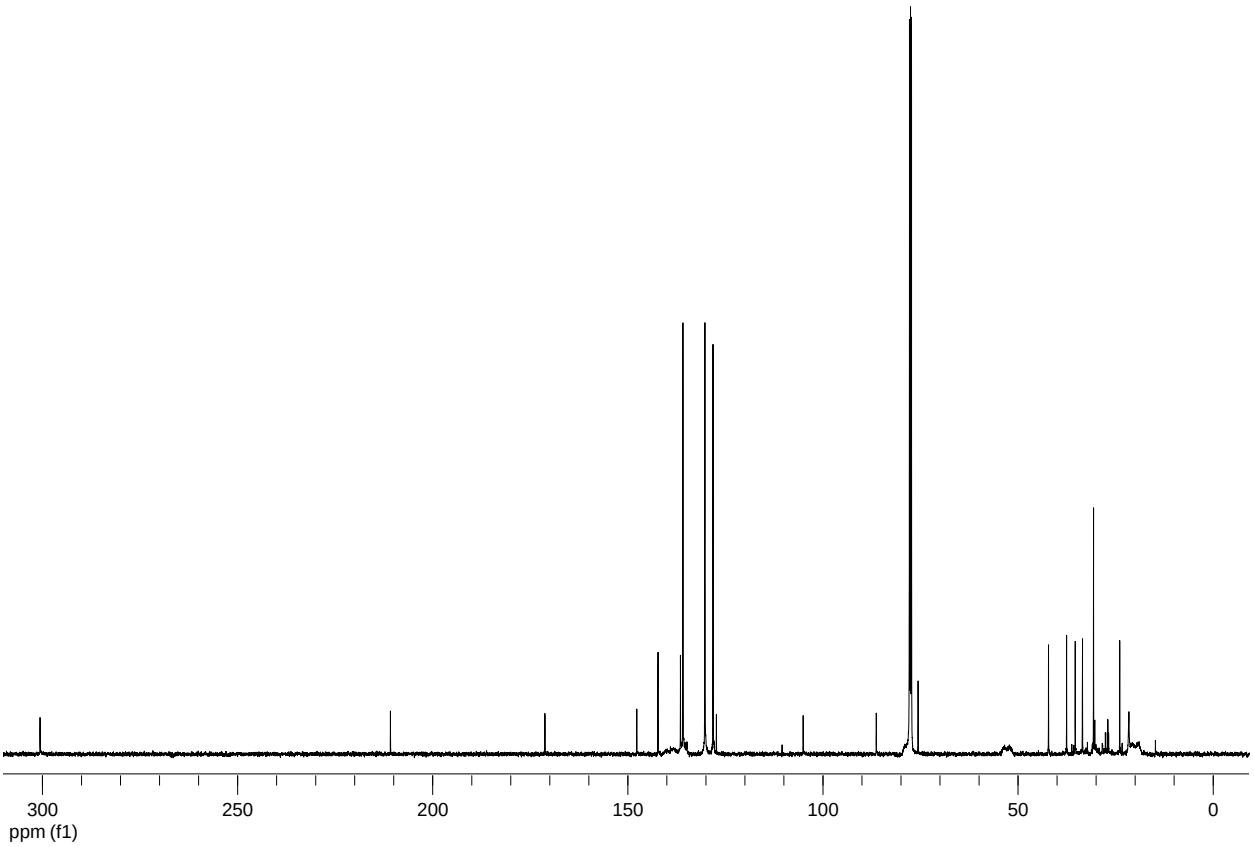
10.0
5.0
ppm (f1)


300
250
200
150
100
50
0
ppm (f1)

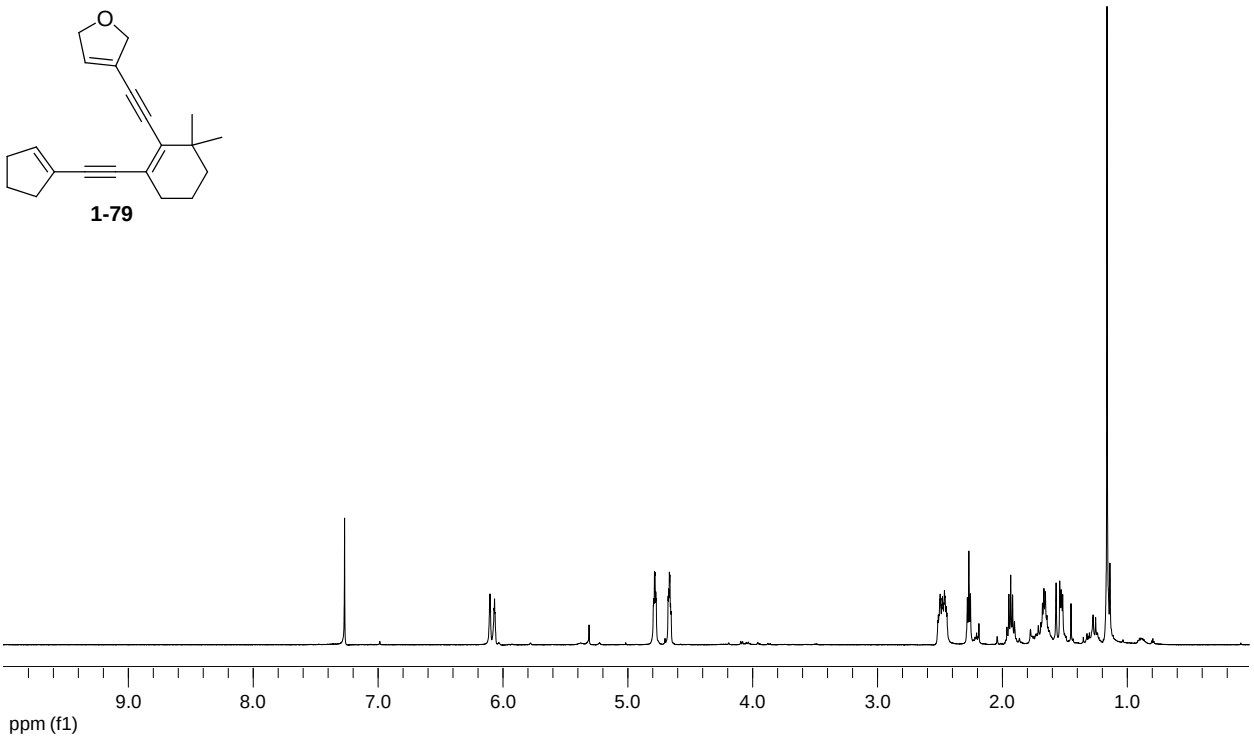
NHC
Cl
Ru
Cl
Ph
Ph
Si
O

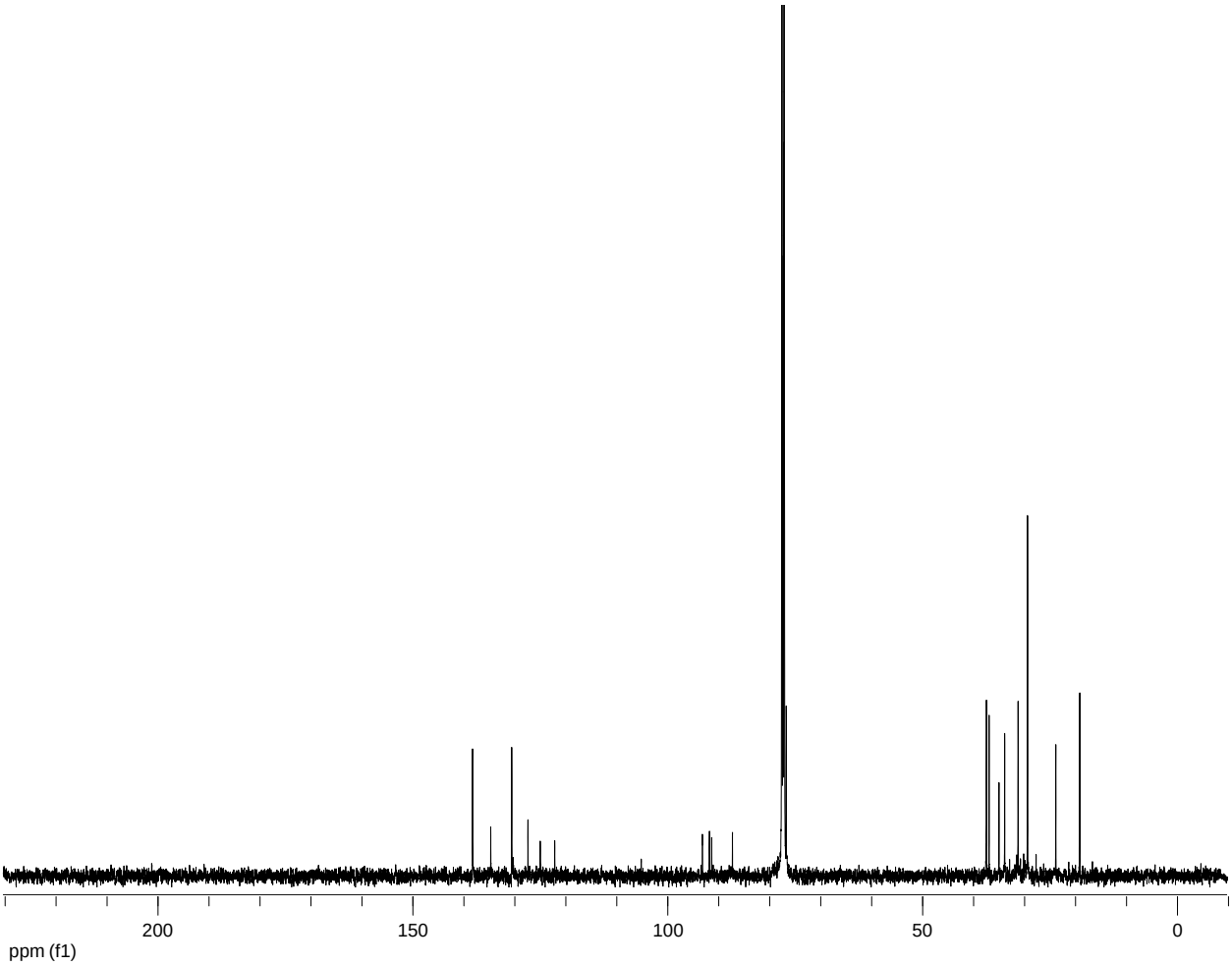
1-58


15.0
10.0
5.0
ppm (f1)

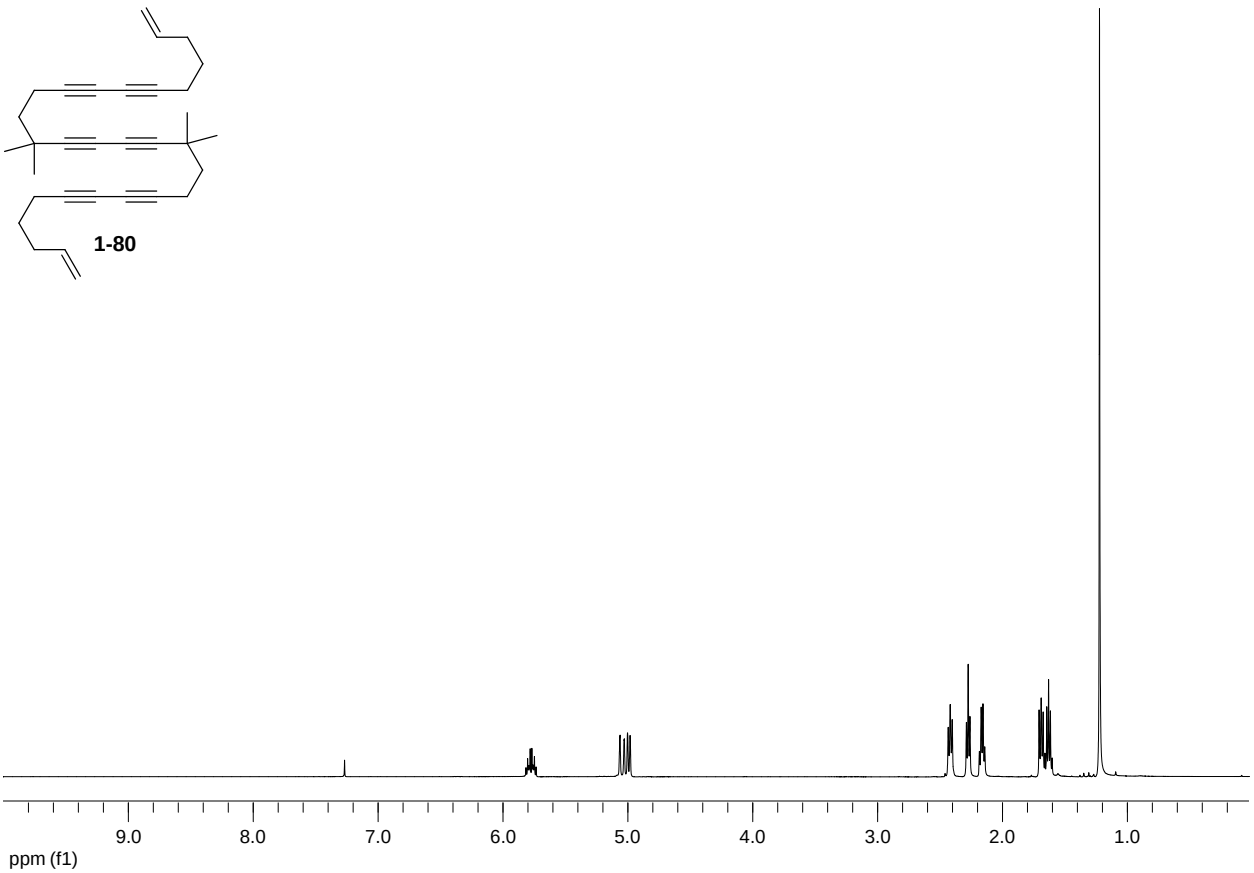

300
250
200
150
100
50
0
ppm (f1)

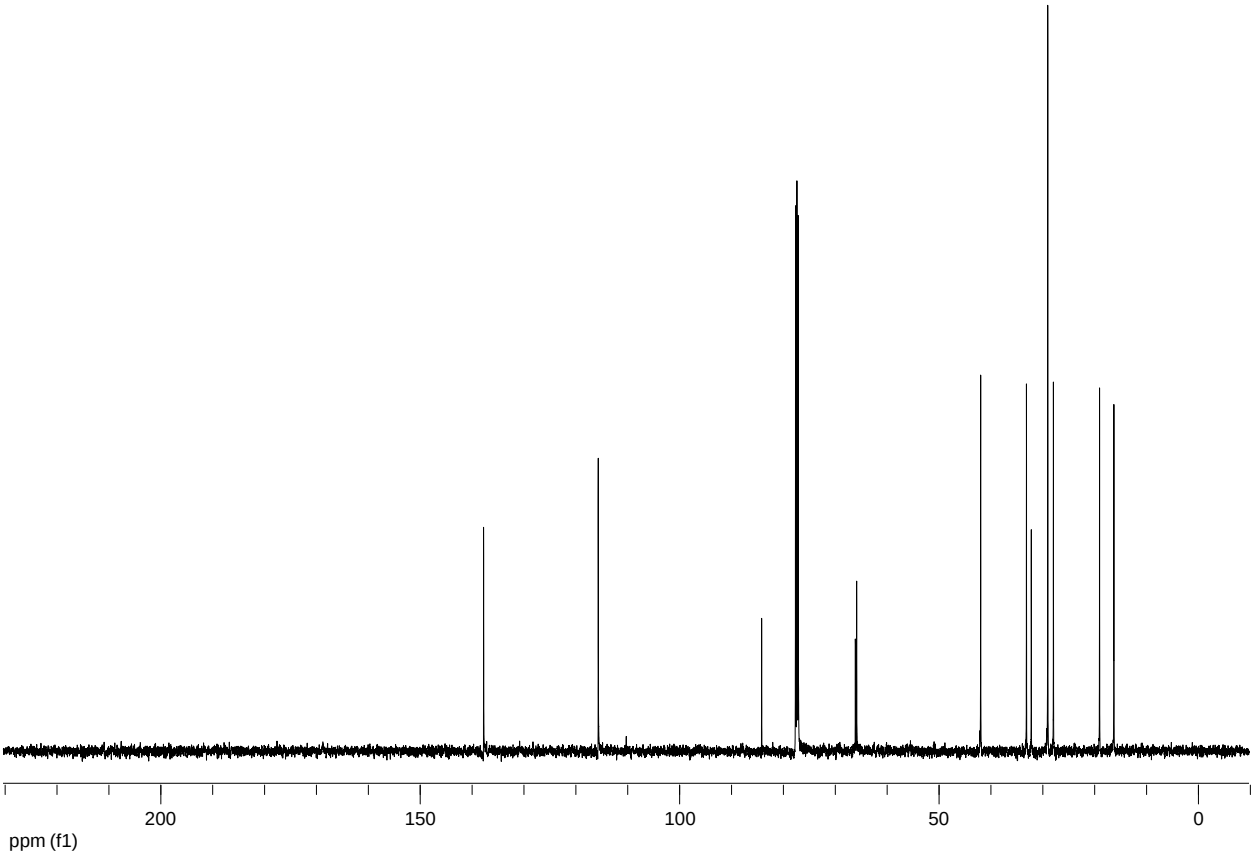
1-79



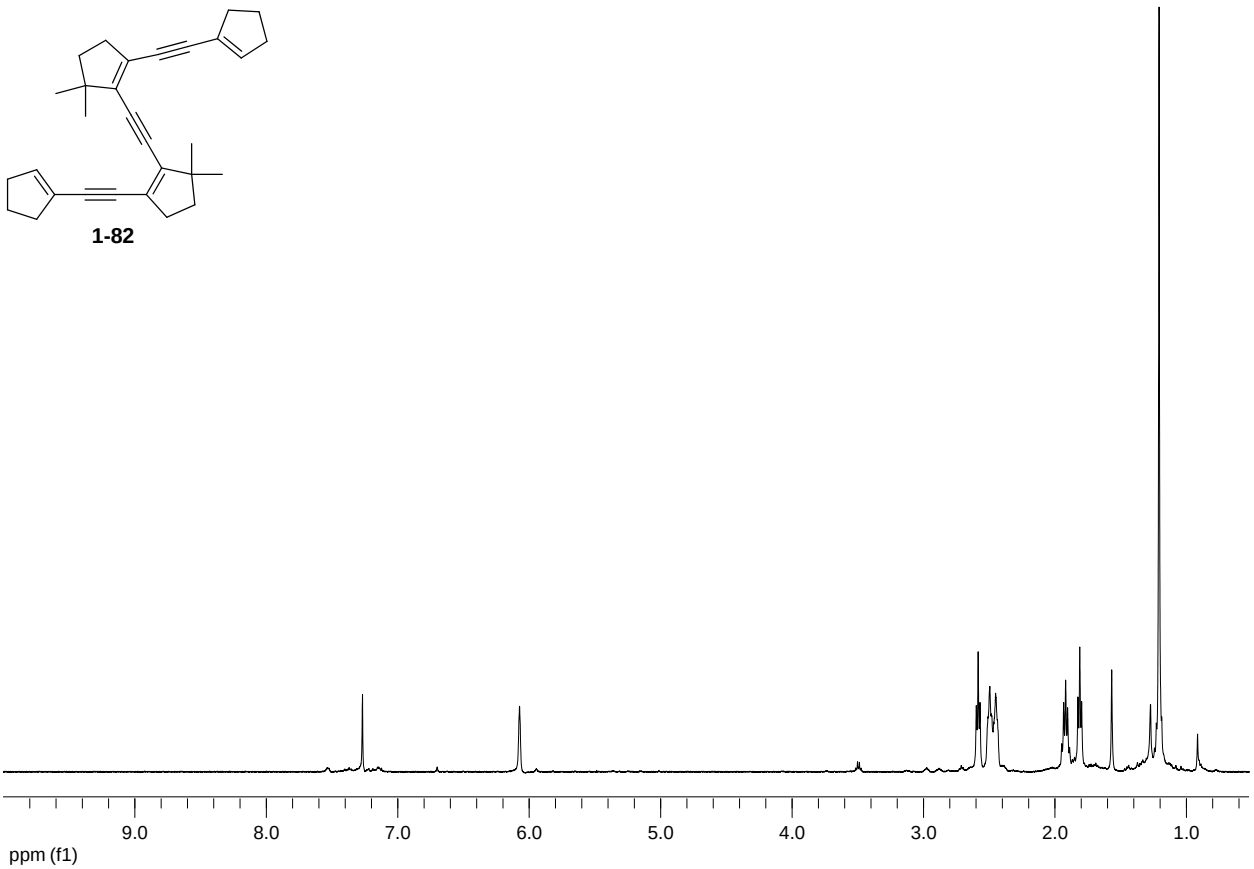


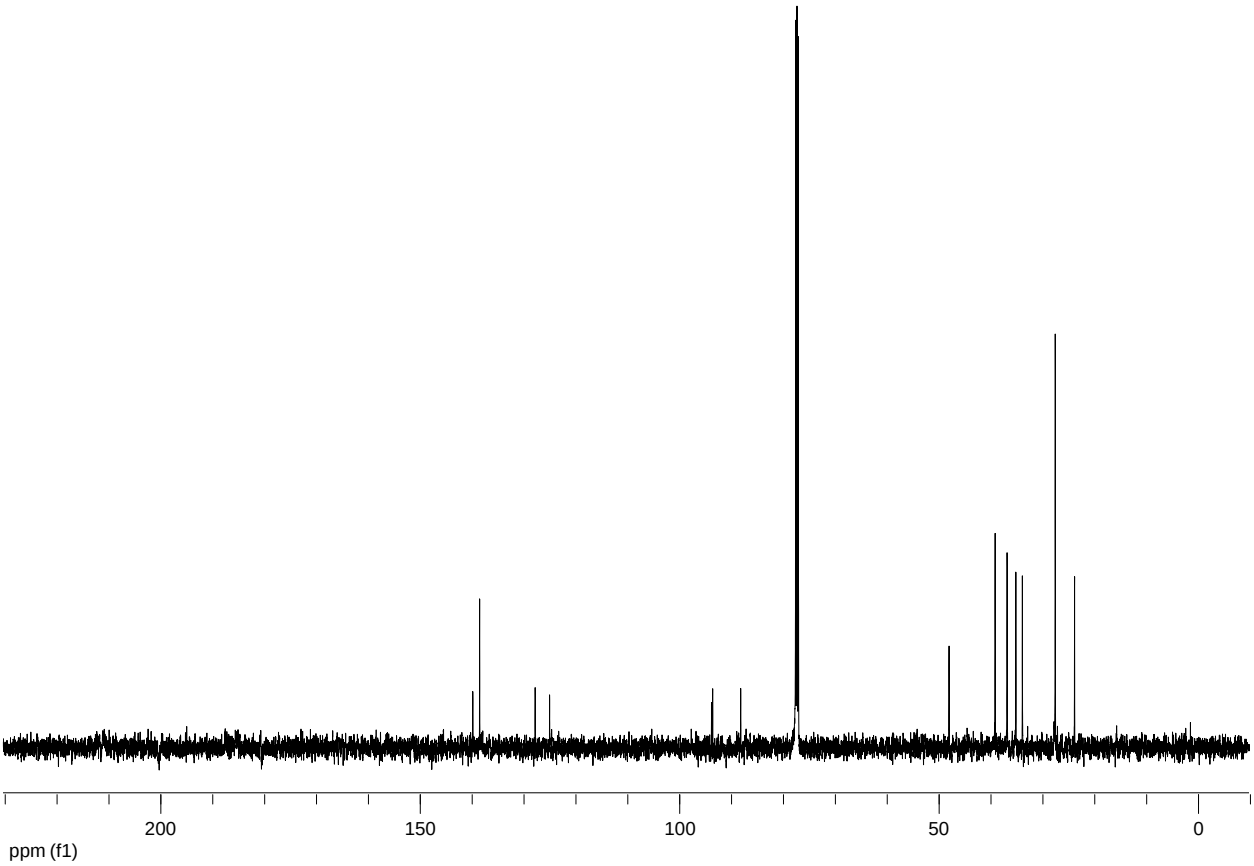
1-80



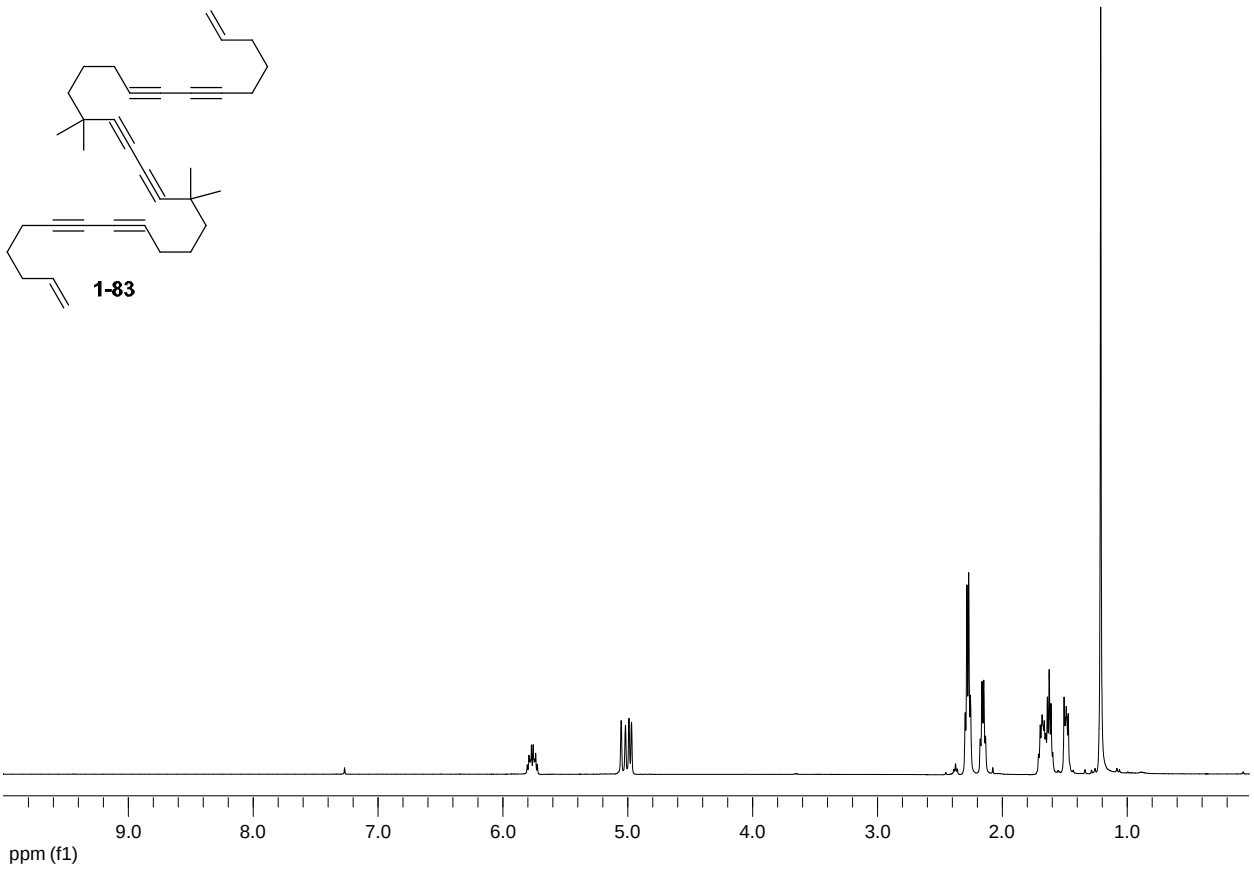


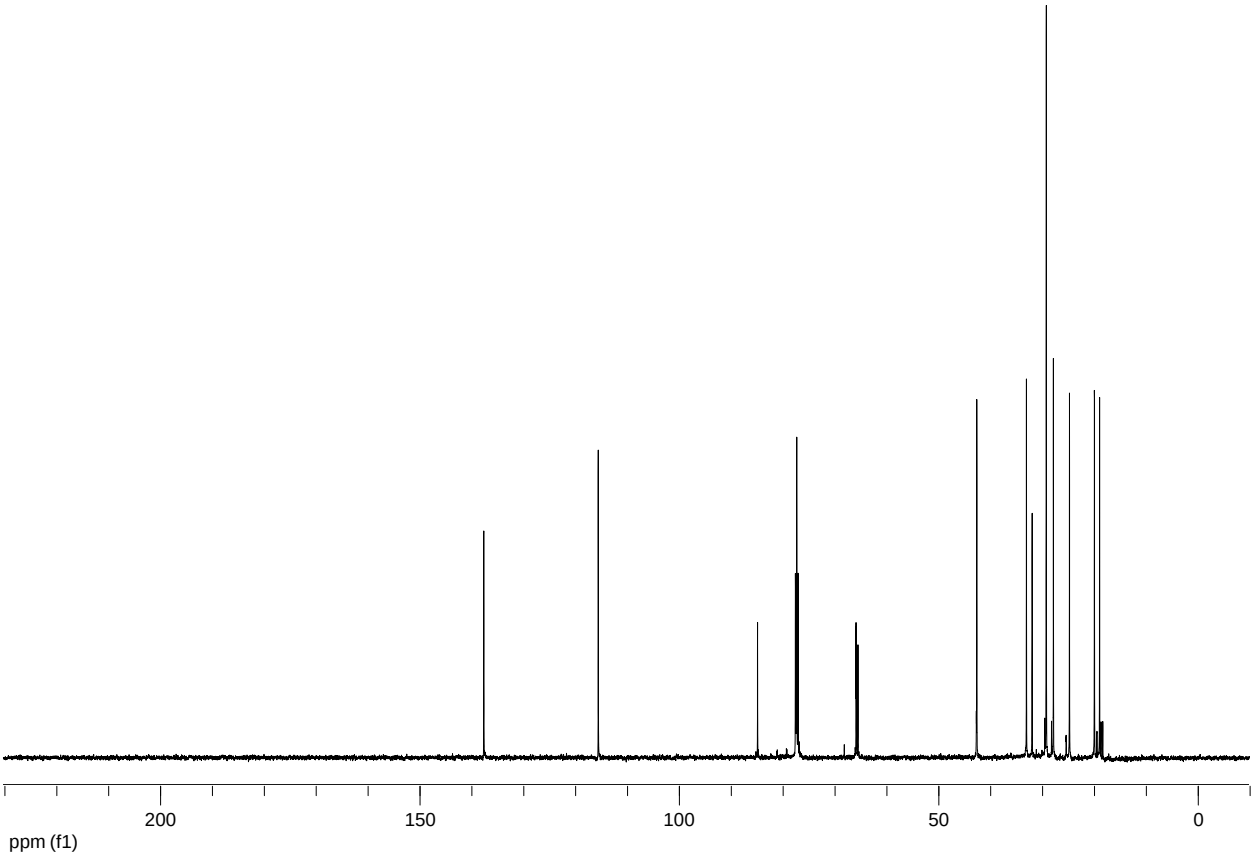
1-82



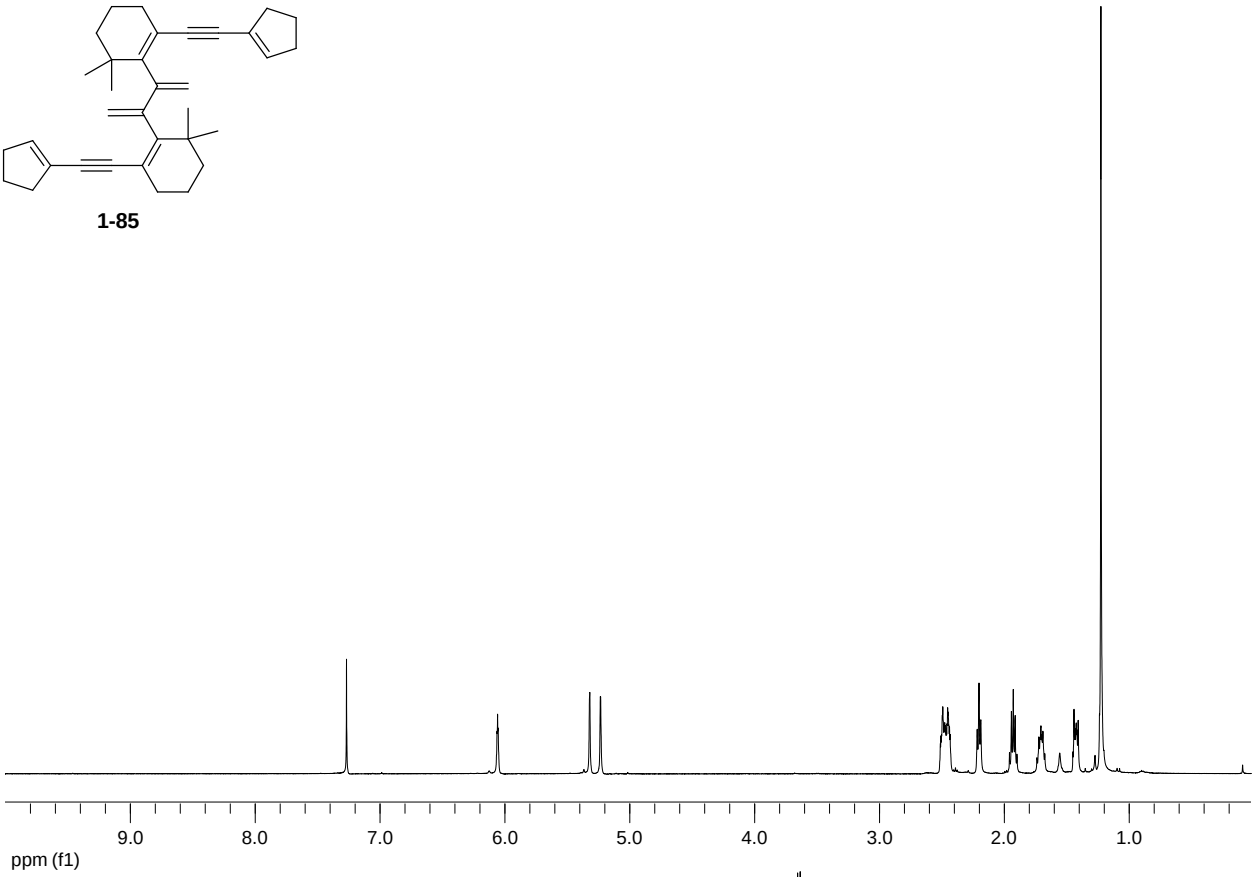


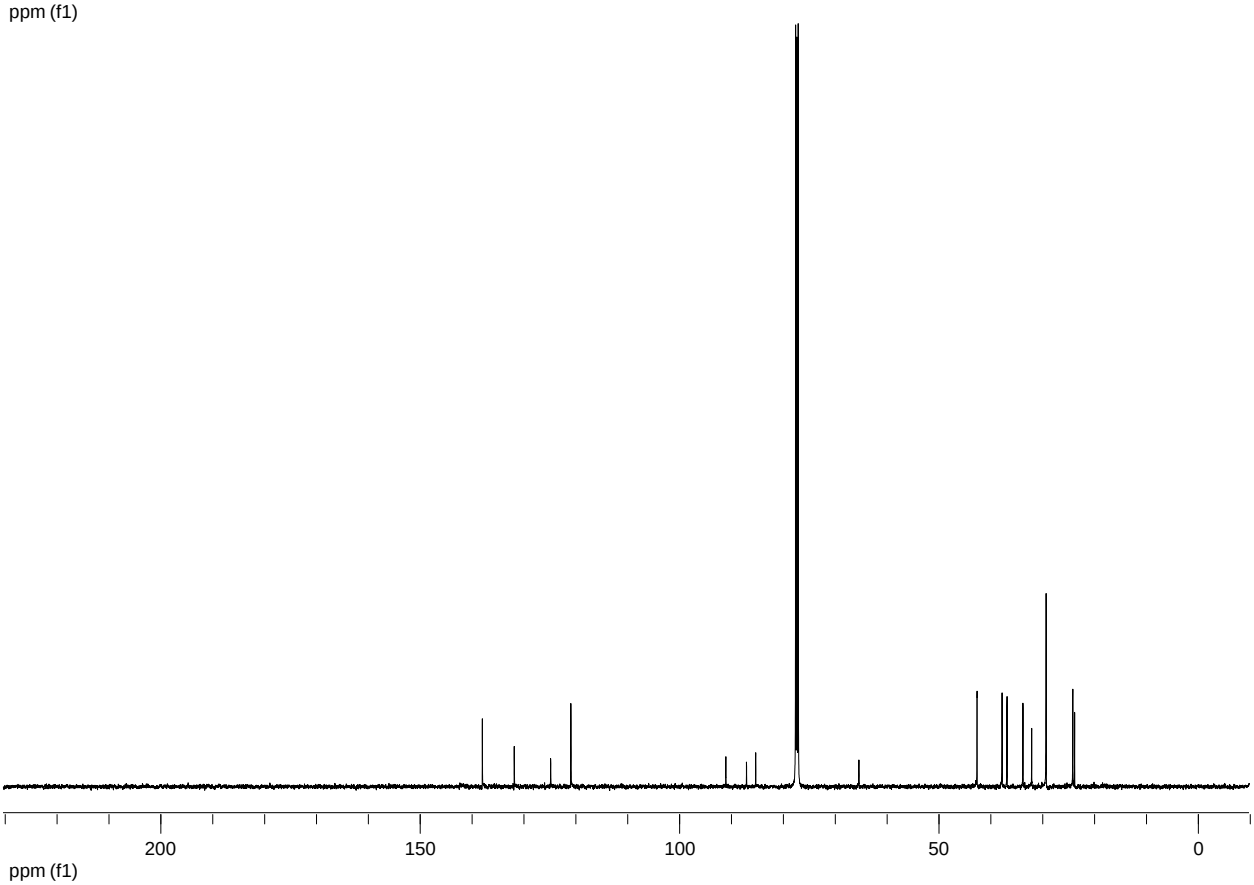
1-83



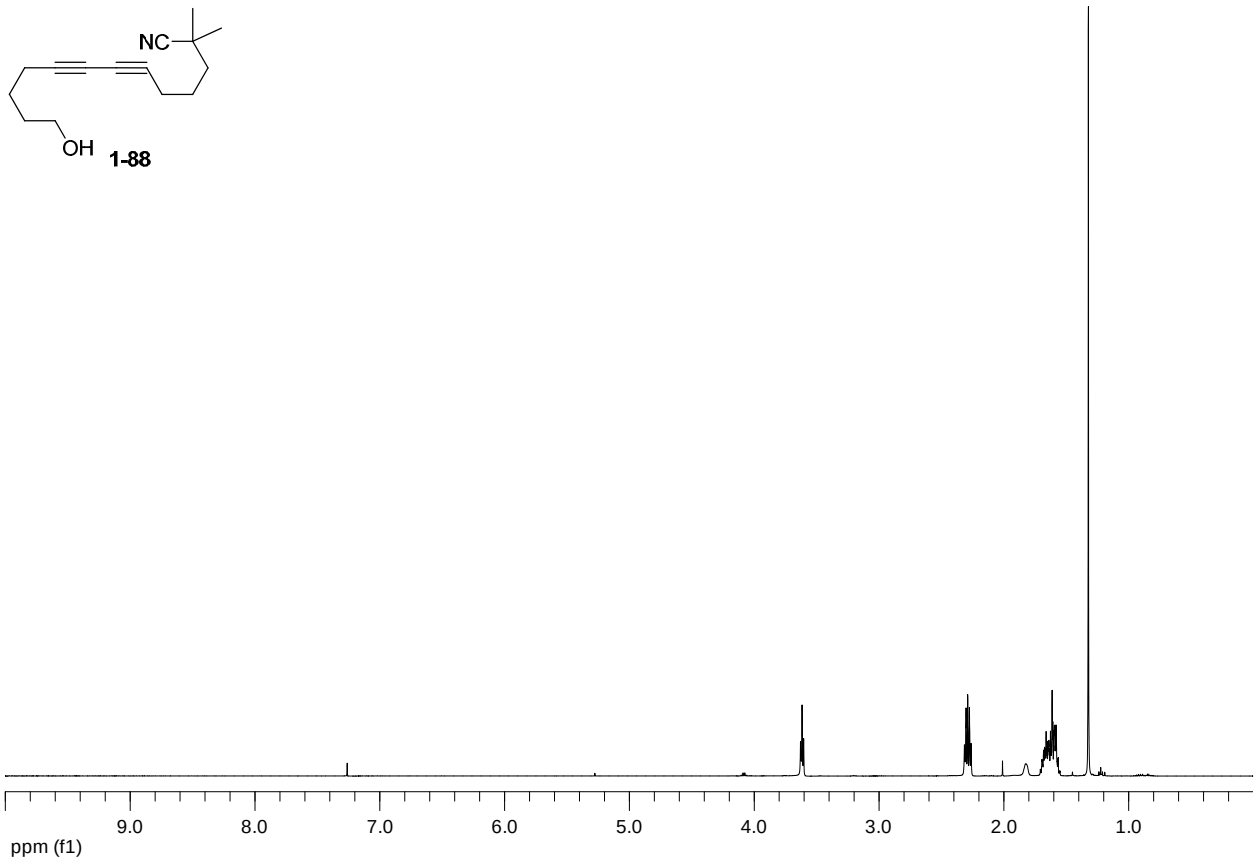


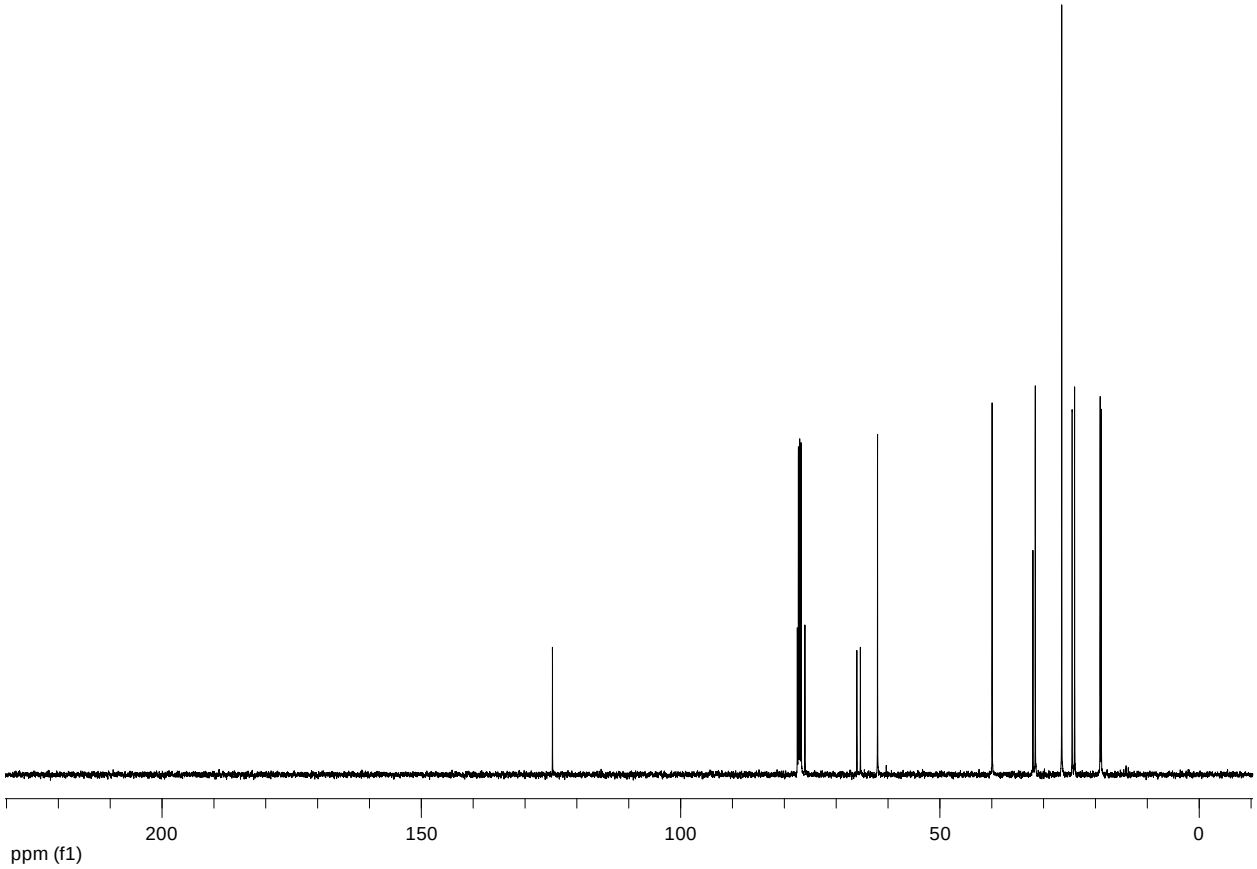
1-85

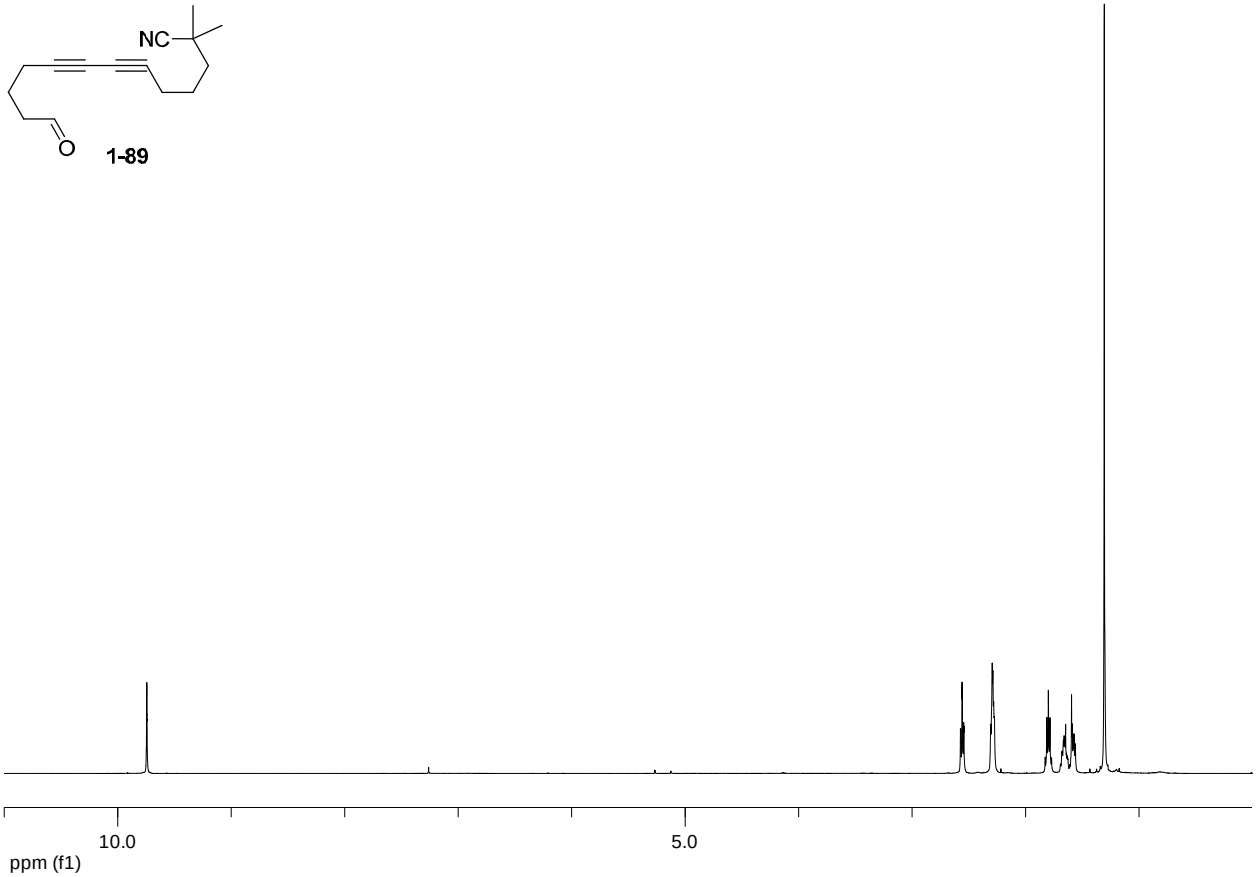


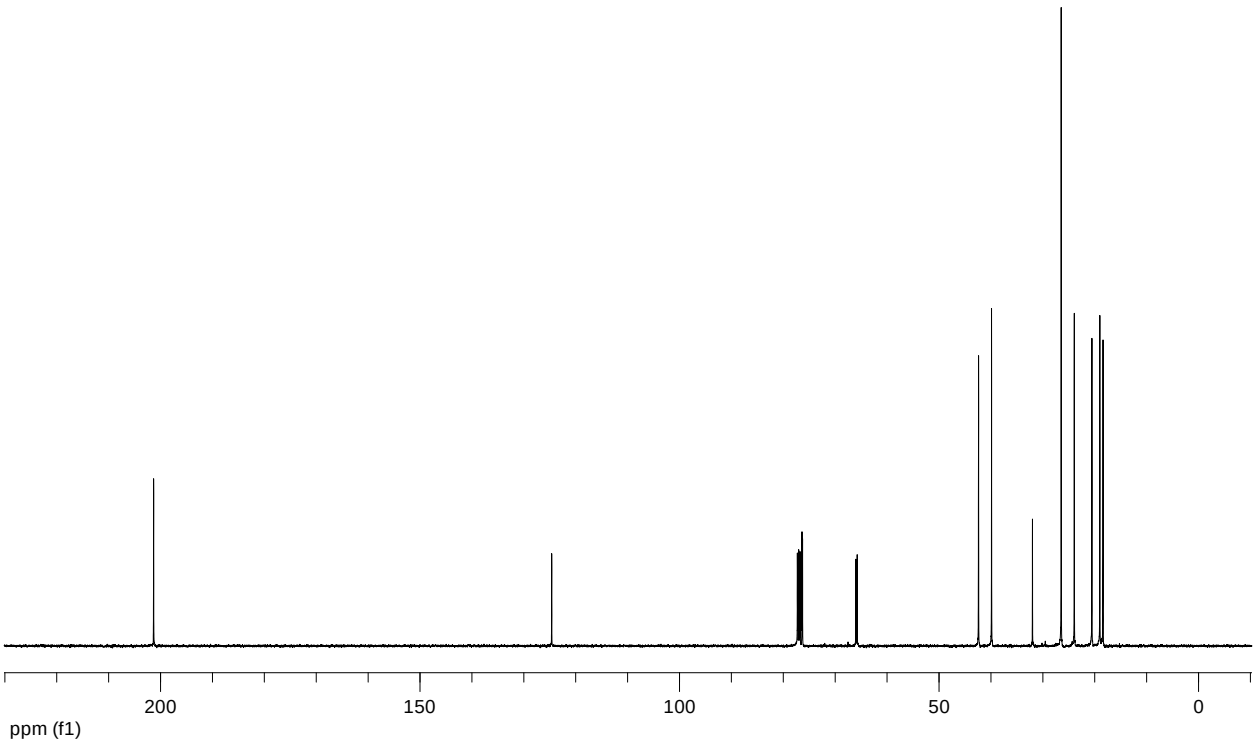


1-88

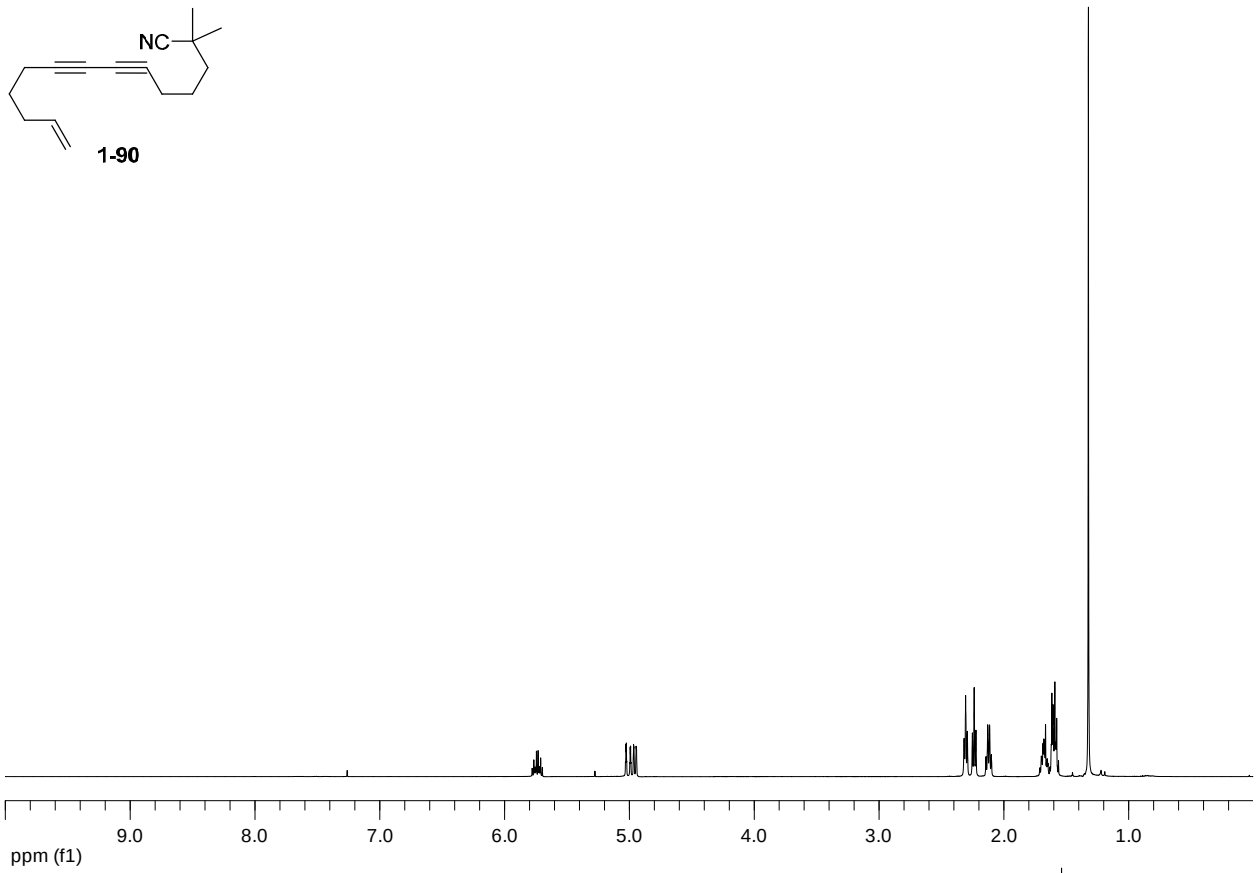


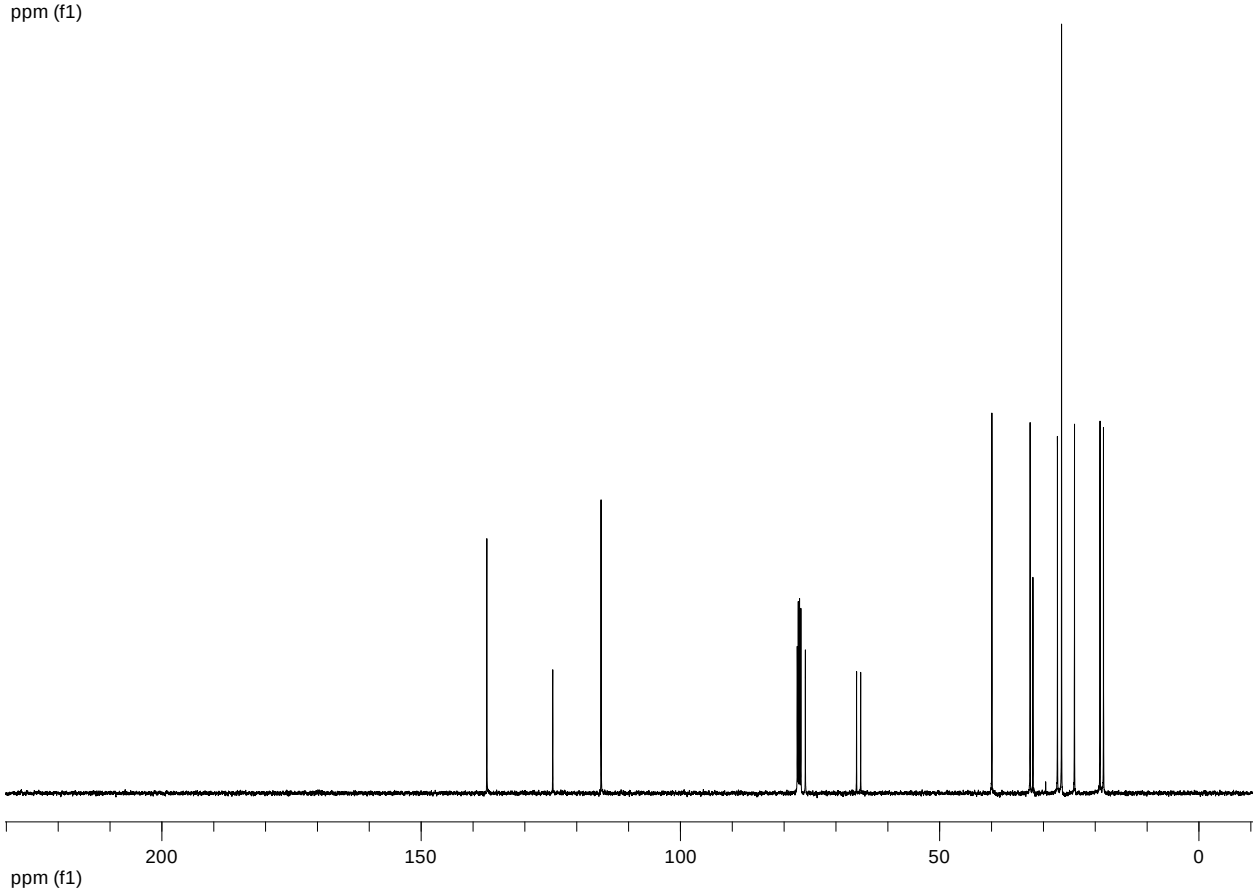


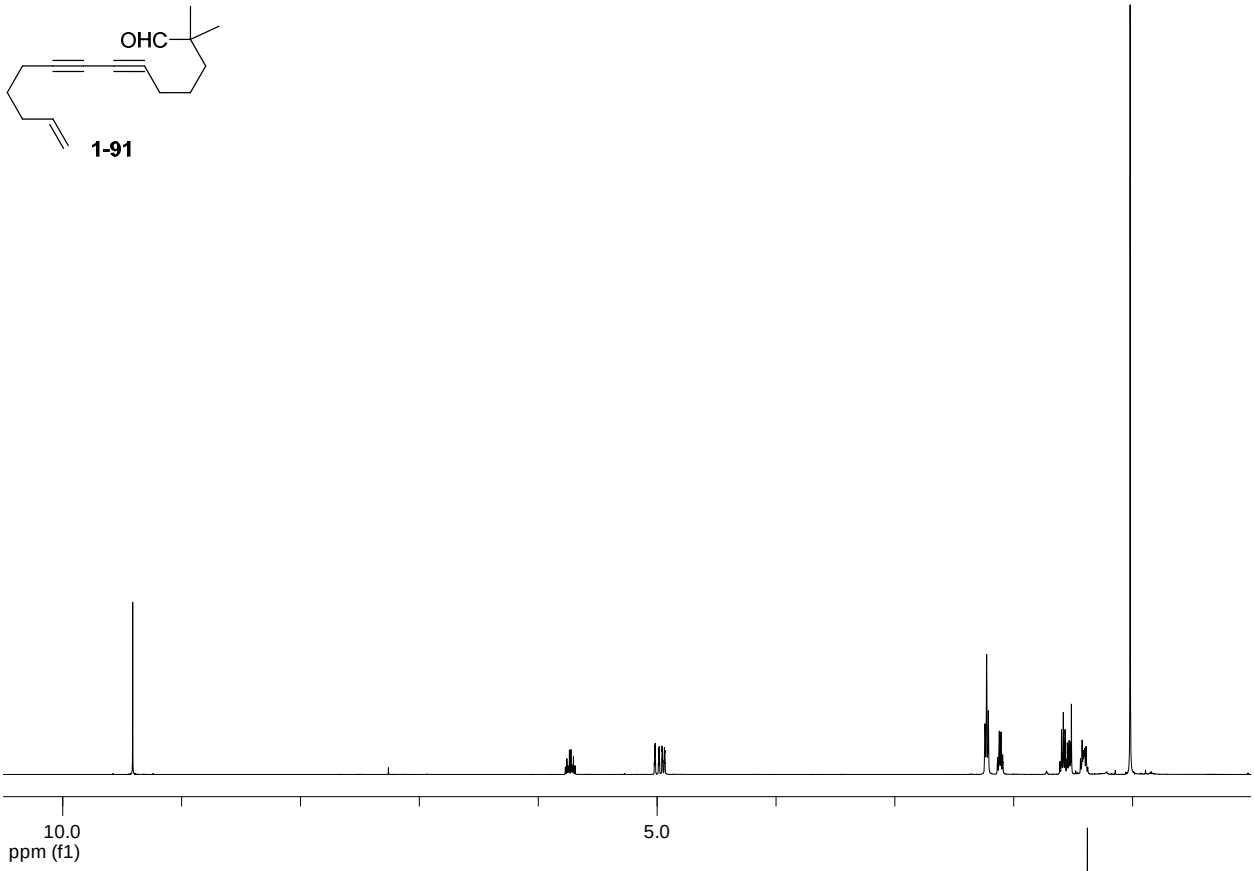

NC
O
1-89
10.0
5.0
ppm (f1)

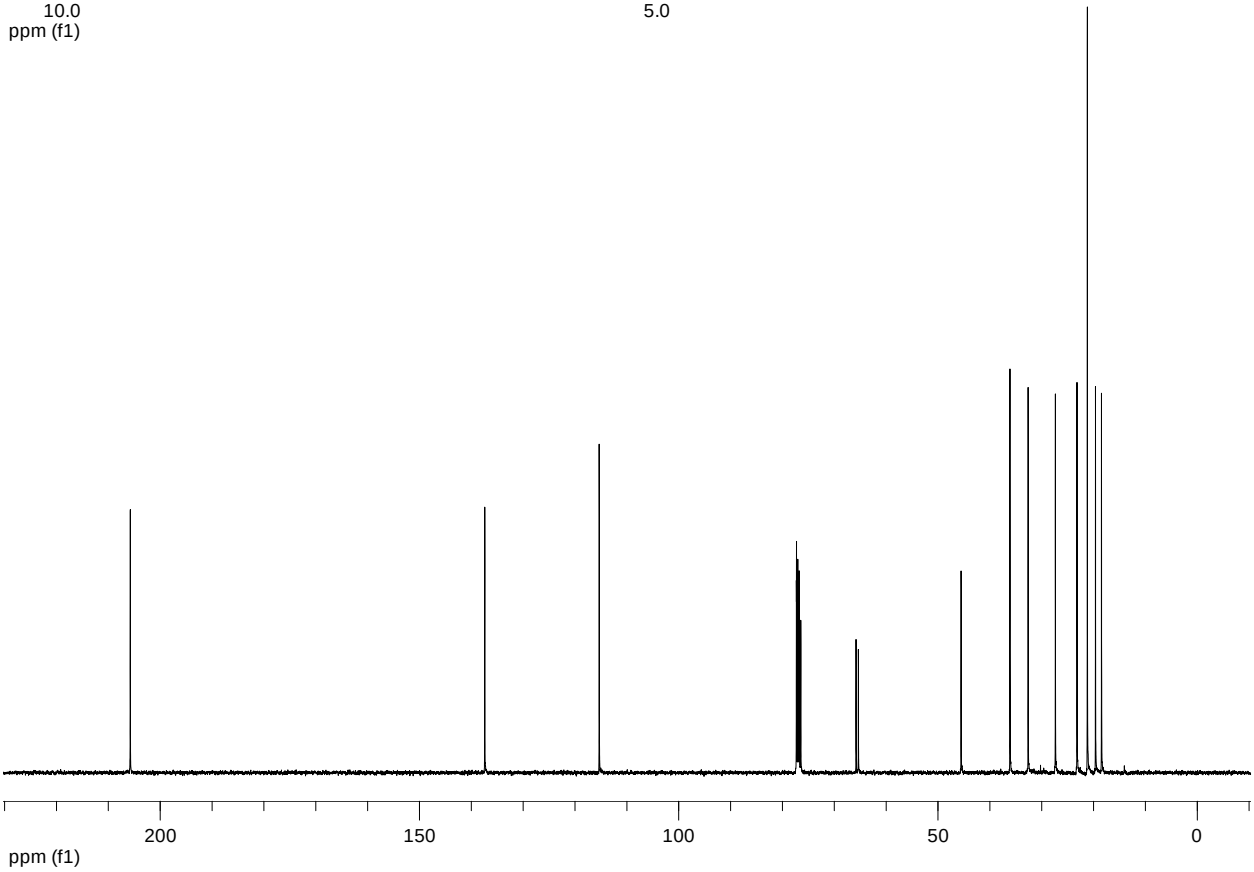

200
150
100
50
0
ppm (f1)

1-90



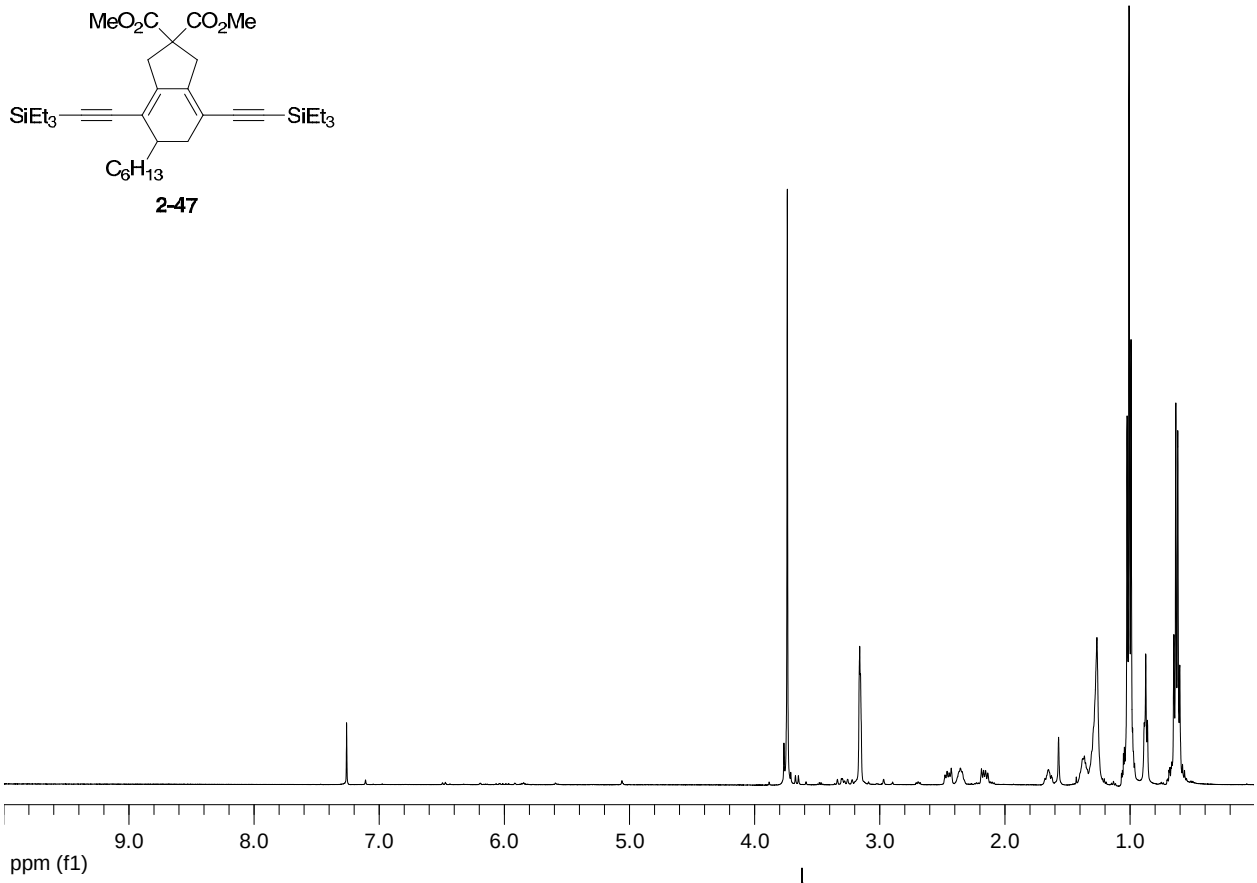


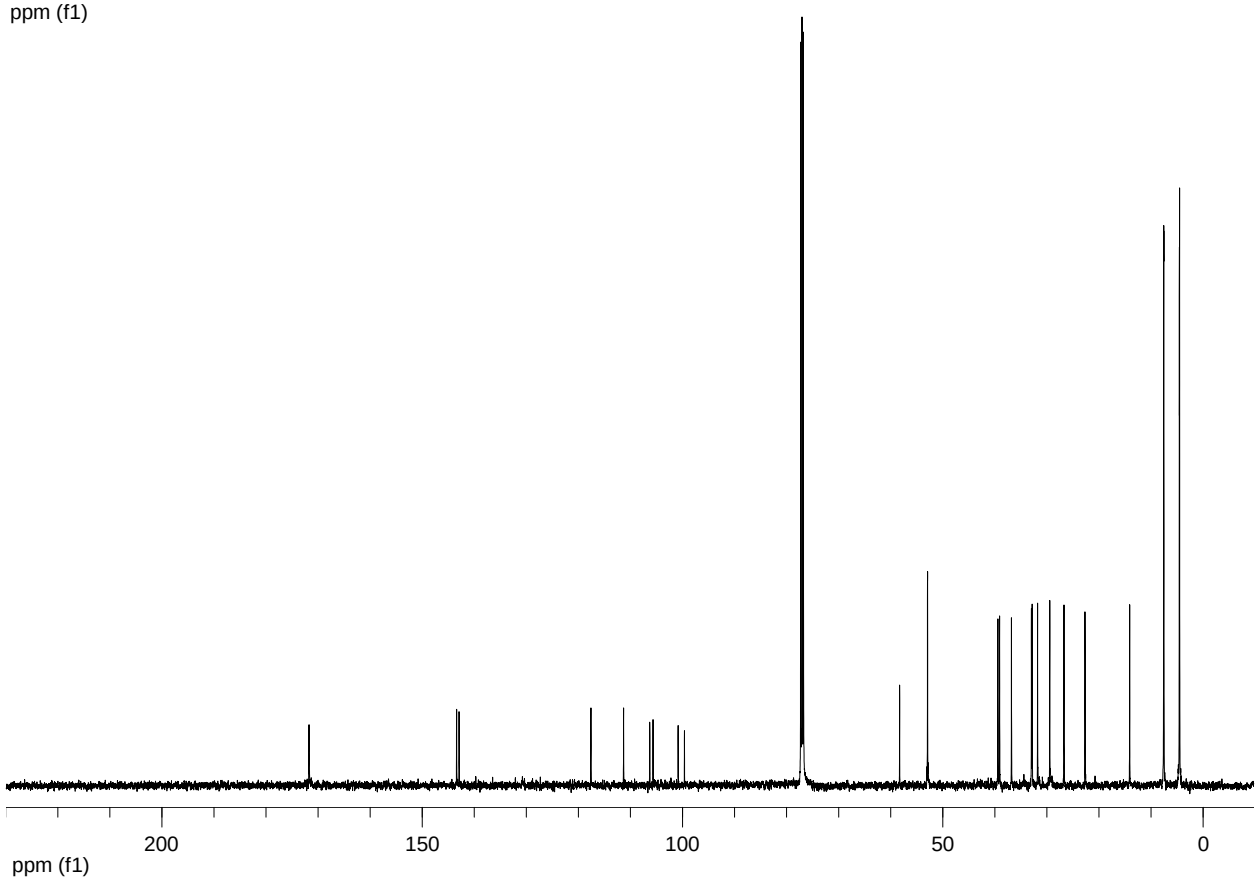

OHC
1-91
10.0
5.0
ppm (f1)


200
150
100
50
0
ppm (f1)

MeO2C
CO2Me
SiEt3
SiEt3
C6H13

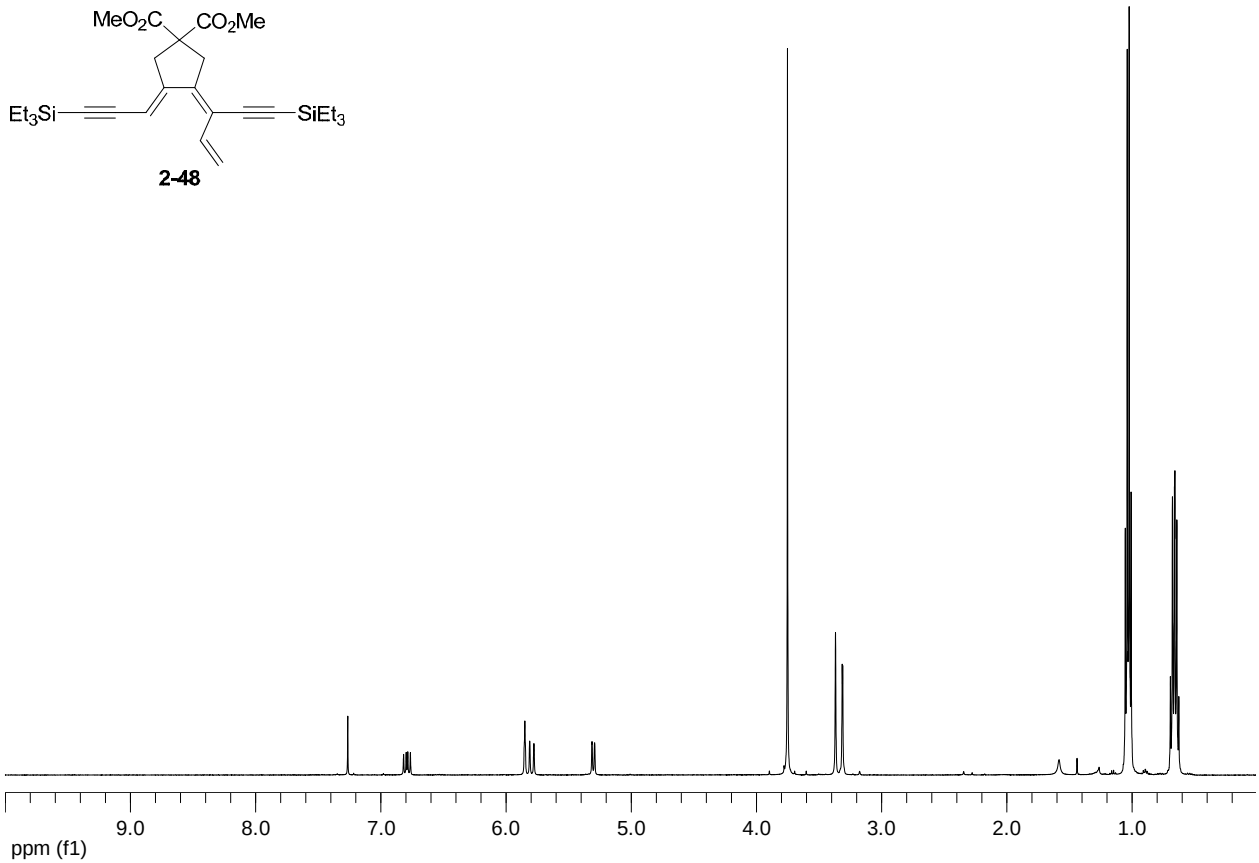
2-47

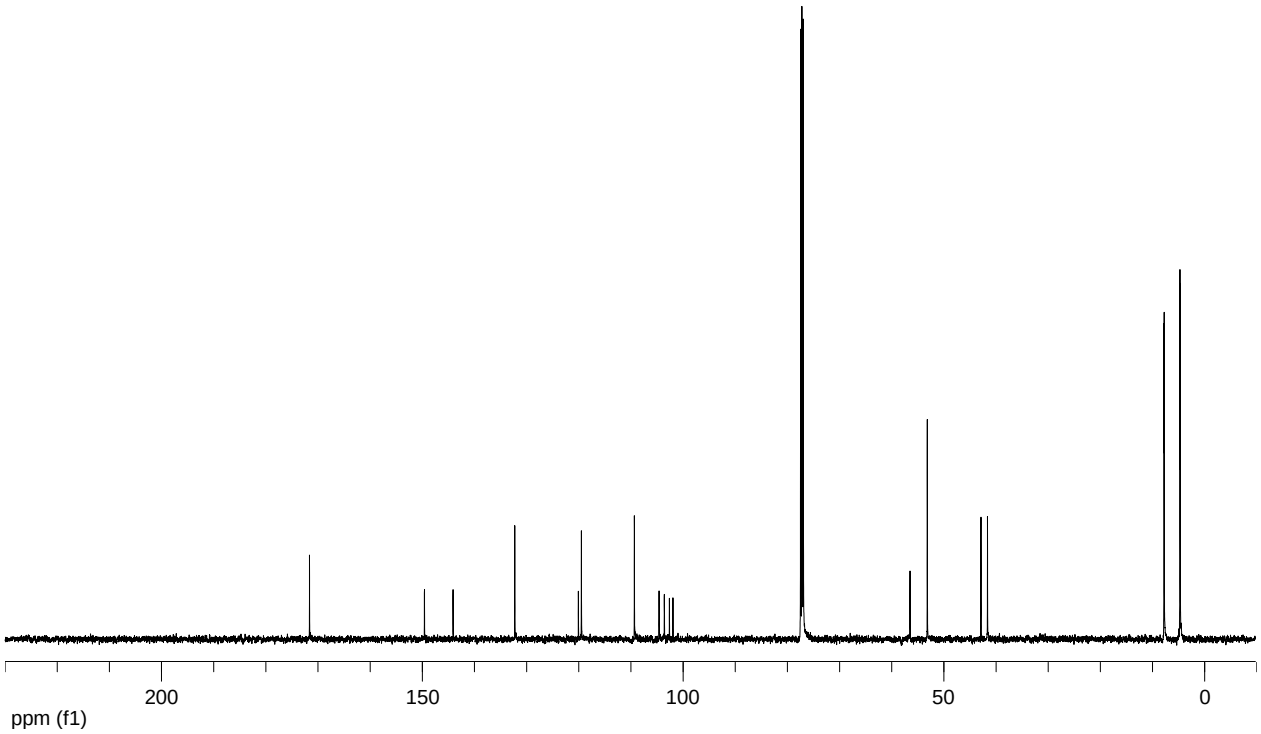

9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)


200
150
100
50
0
ppm (f1)

MeO2C
CO2Me
Et3Si
SiEt3

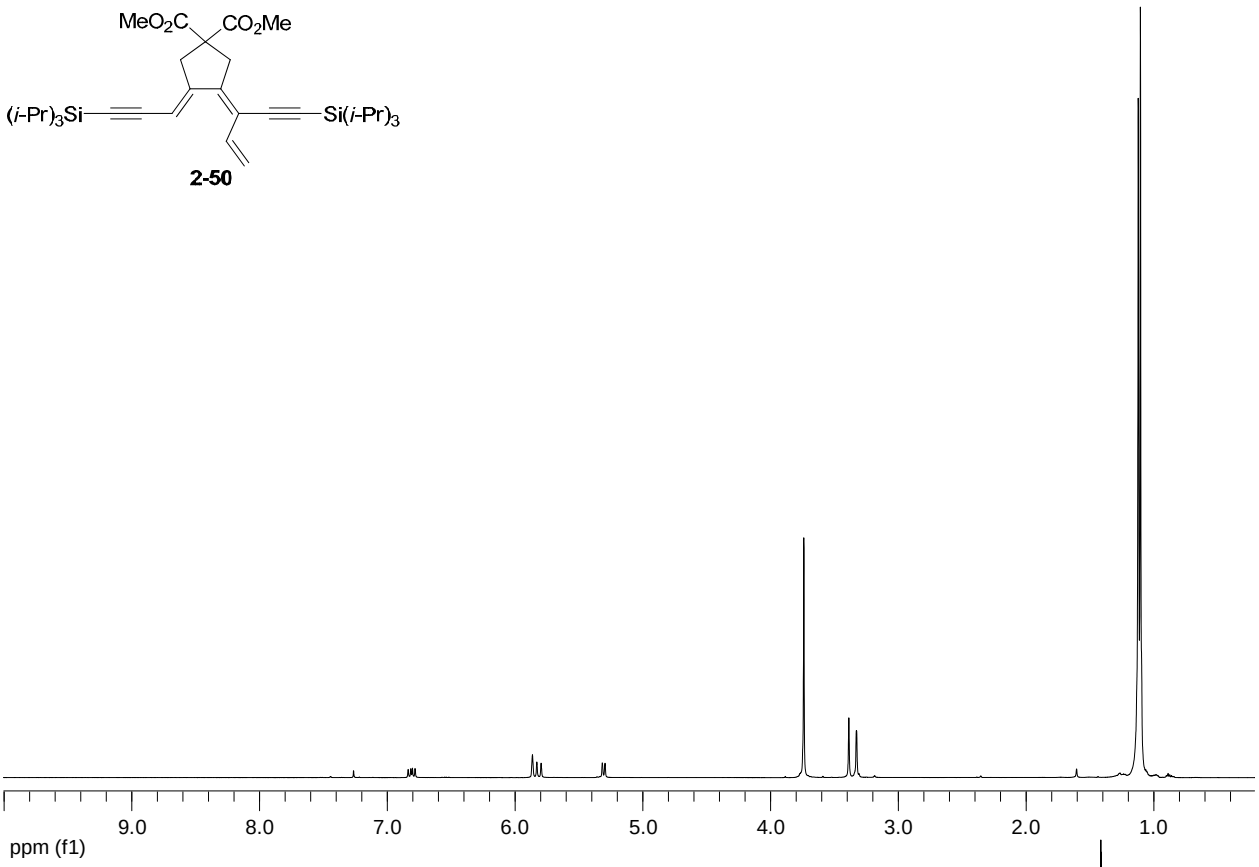
2-48

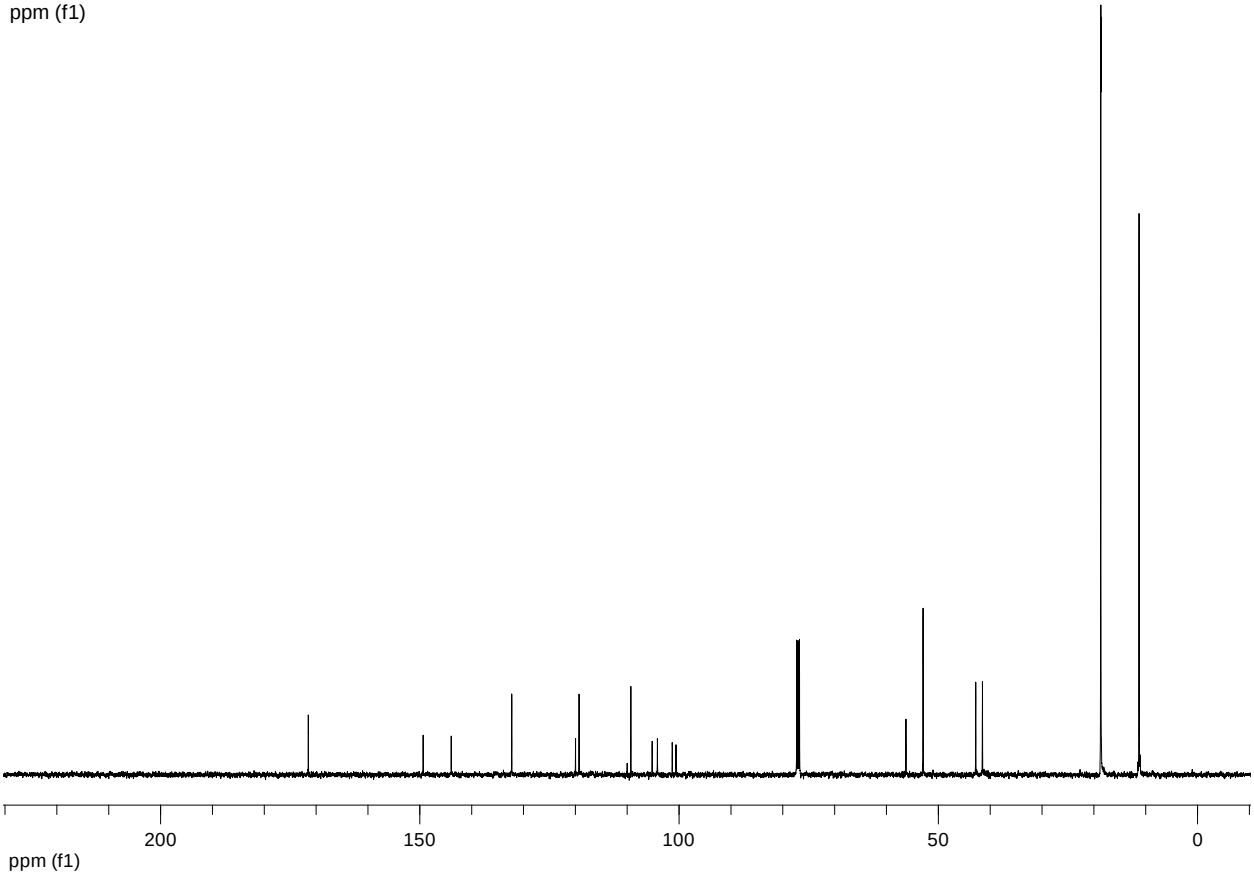

9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

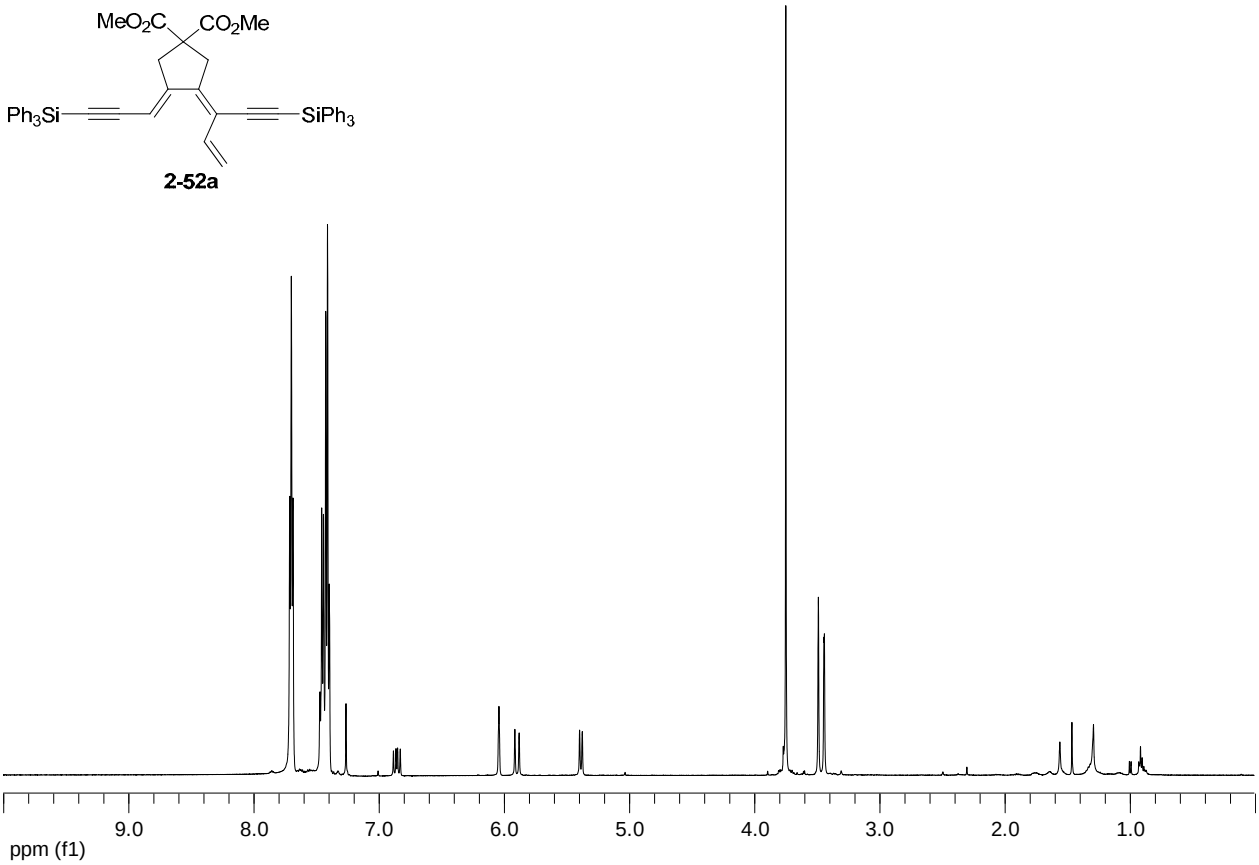

200
150
100
50
0
ppm (f1)

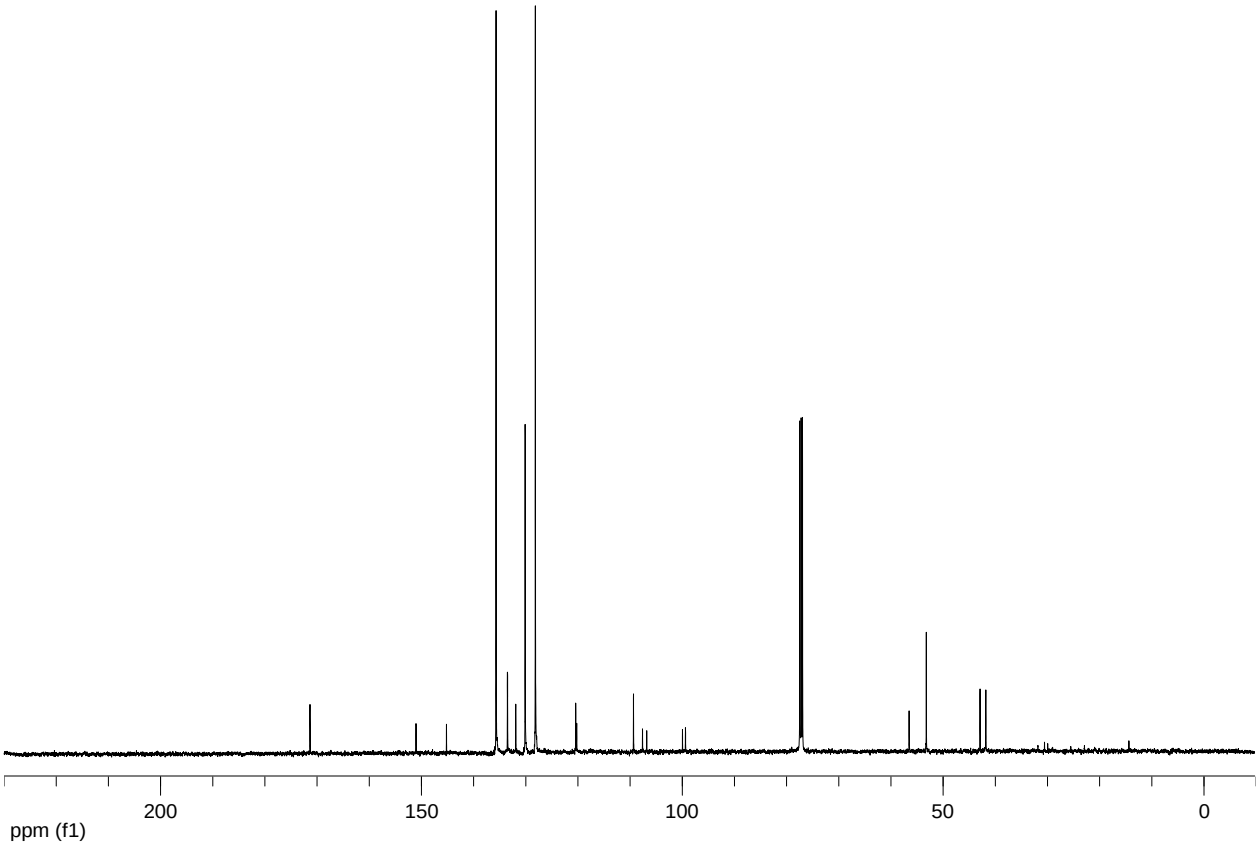
MeO2C
CO2Me
(i-Pr)3Si
Si(i-Pr)3

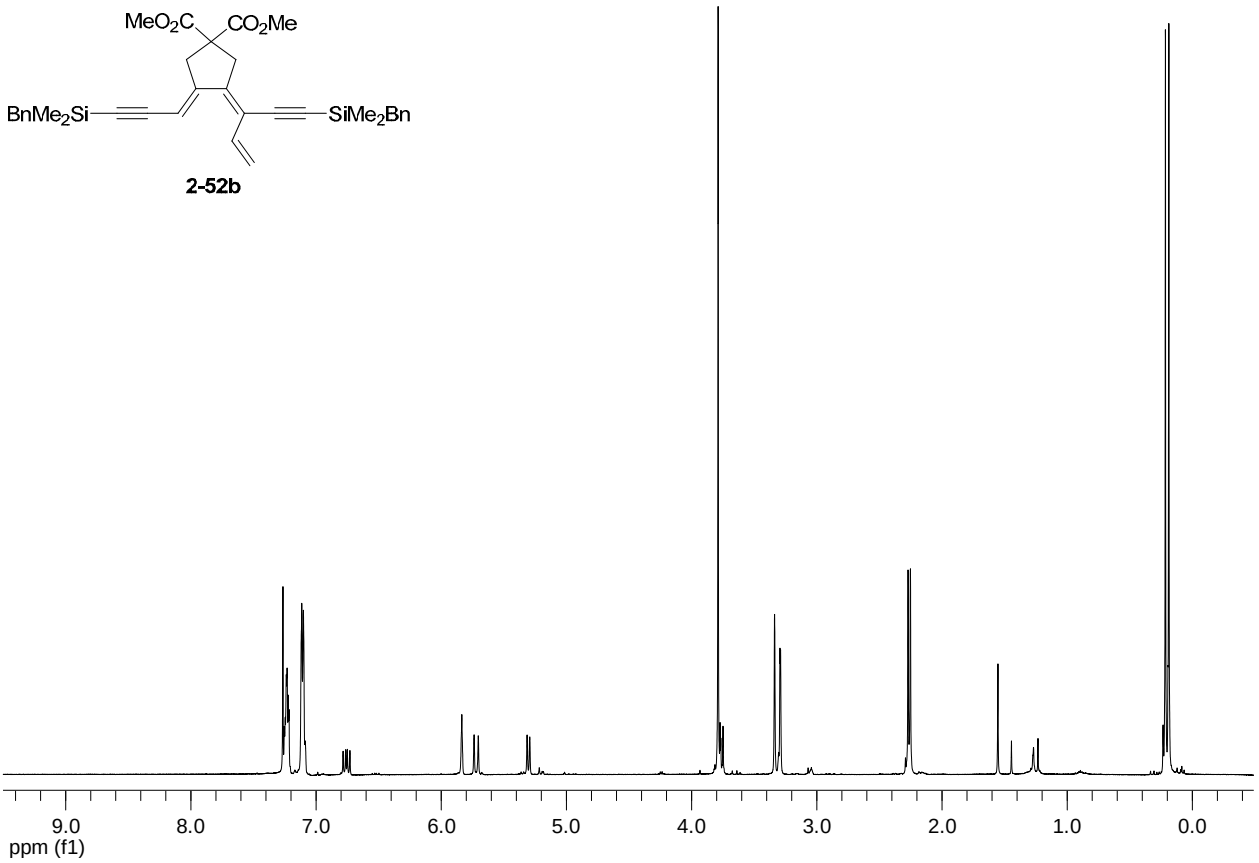
2-50

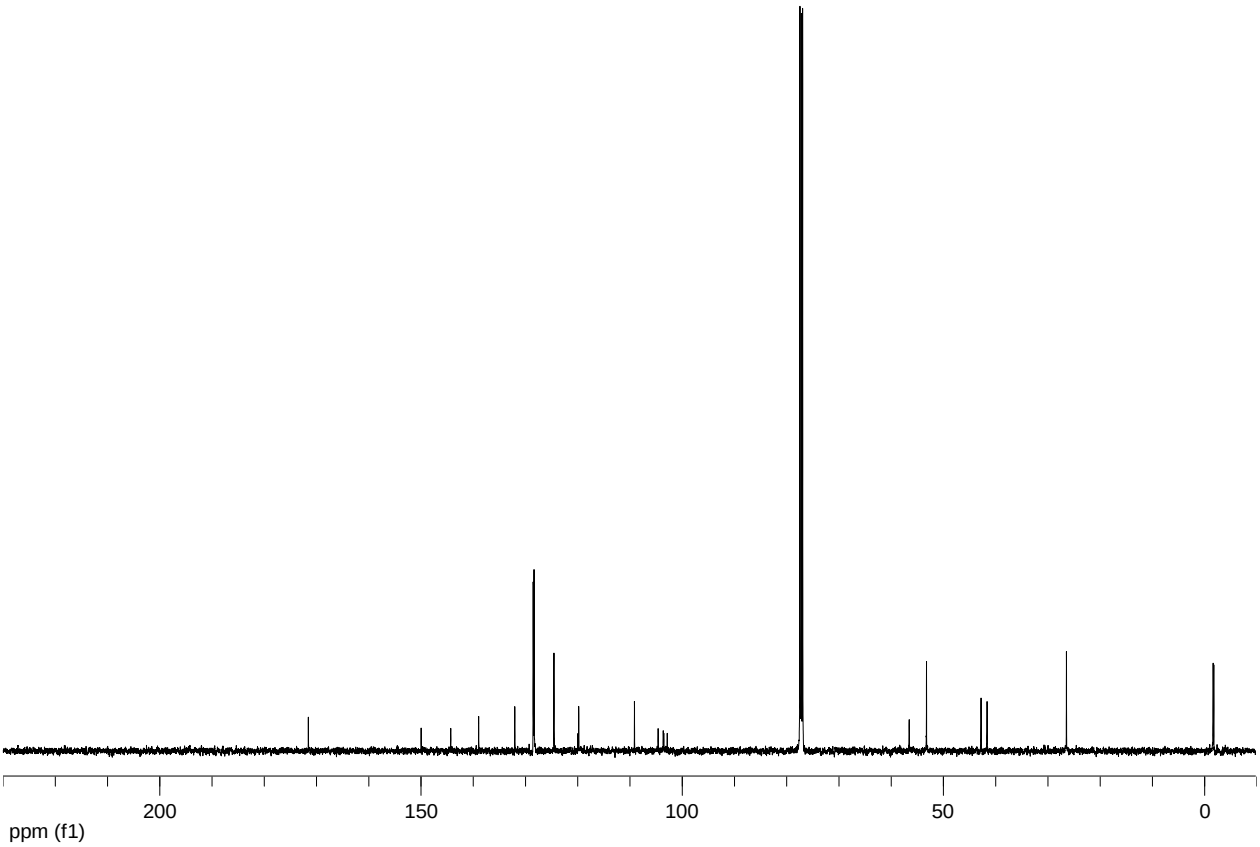

9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

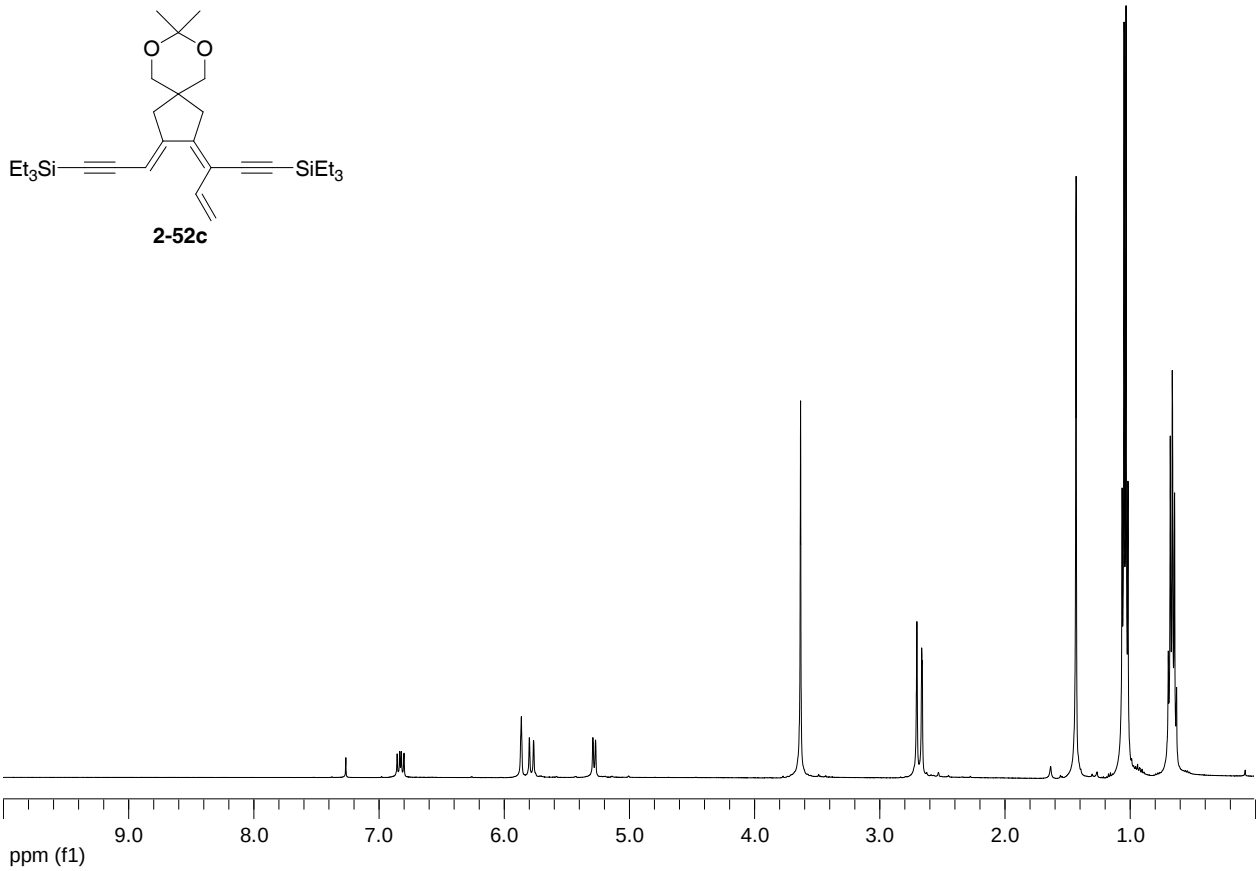

200
150
100
50
0
ppm (f1)

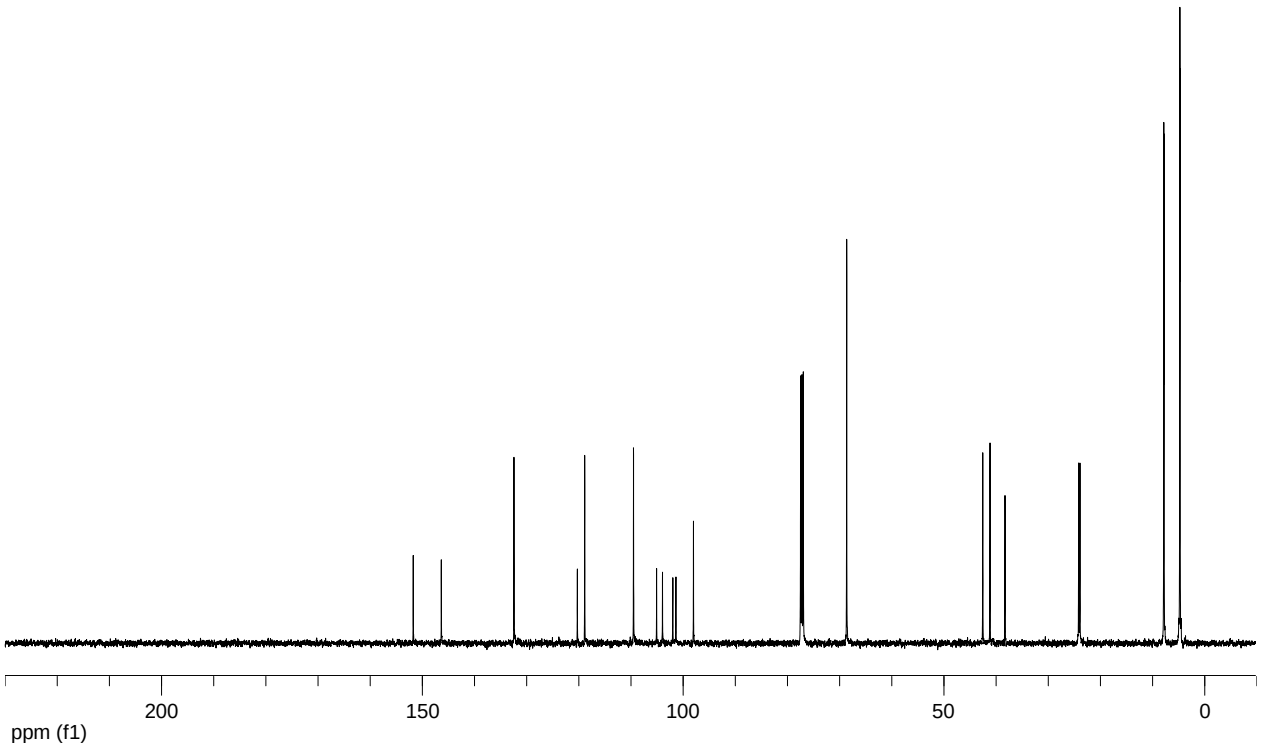

MeO2C
CO2Me
Ph3Si
SiPh3
2-52a
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)


200
150
100
50
0
ppm (f1)


MeO2C
CO2Me
BnMe2Si
SiMe2Bn
2-52b
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

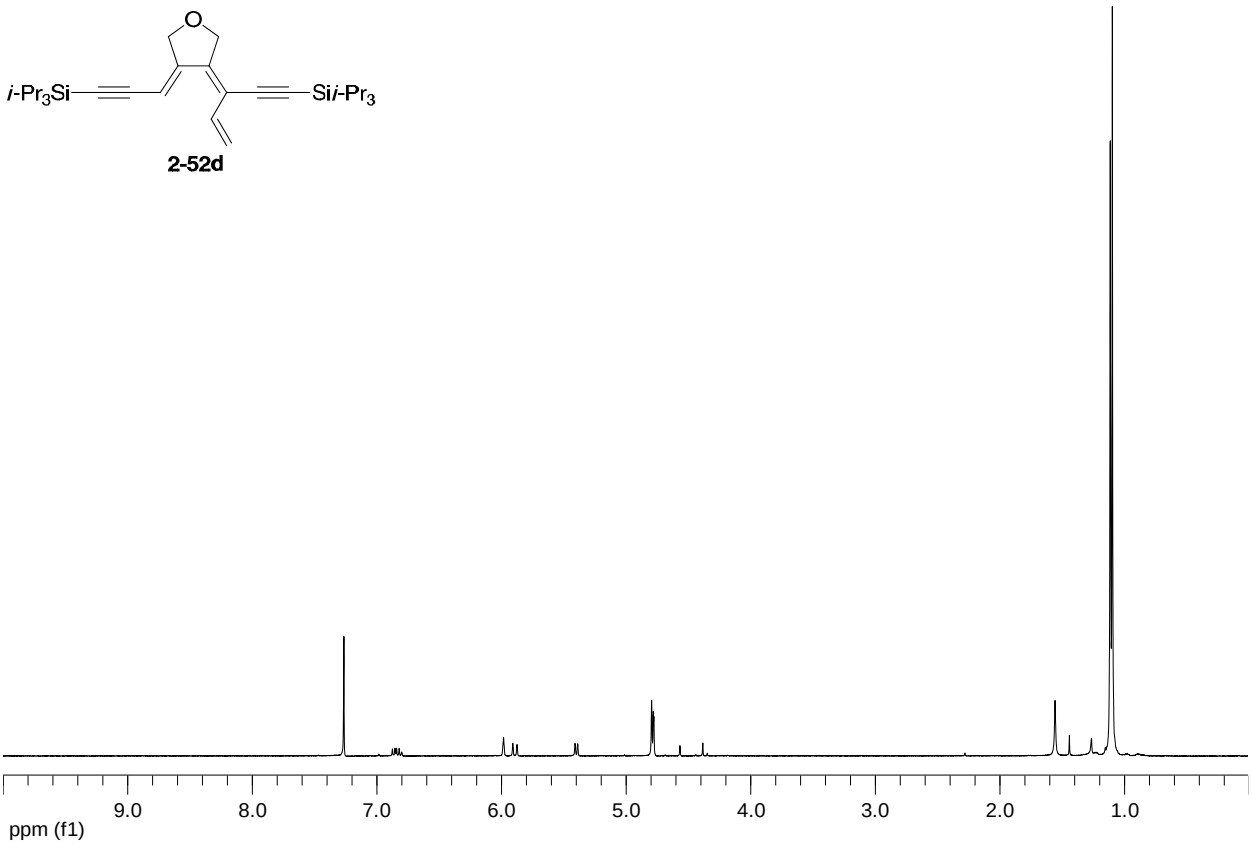

200
150
100
50
0
ppm (f1)

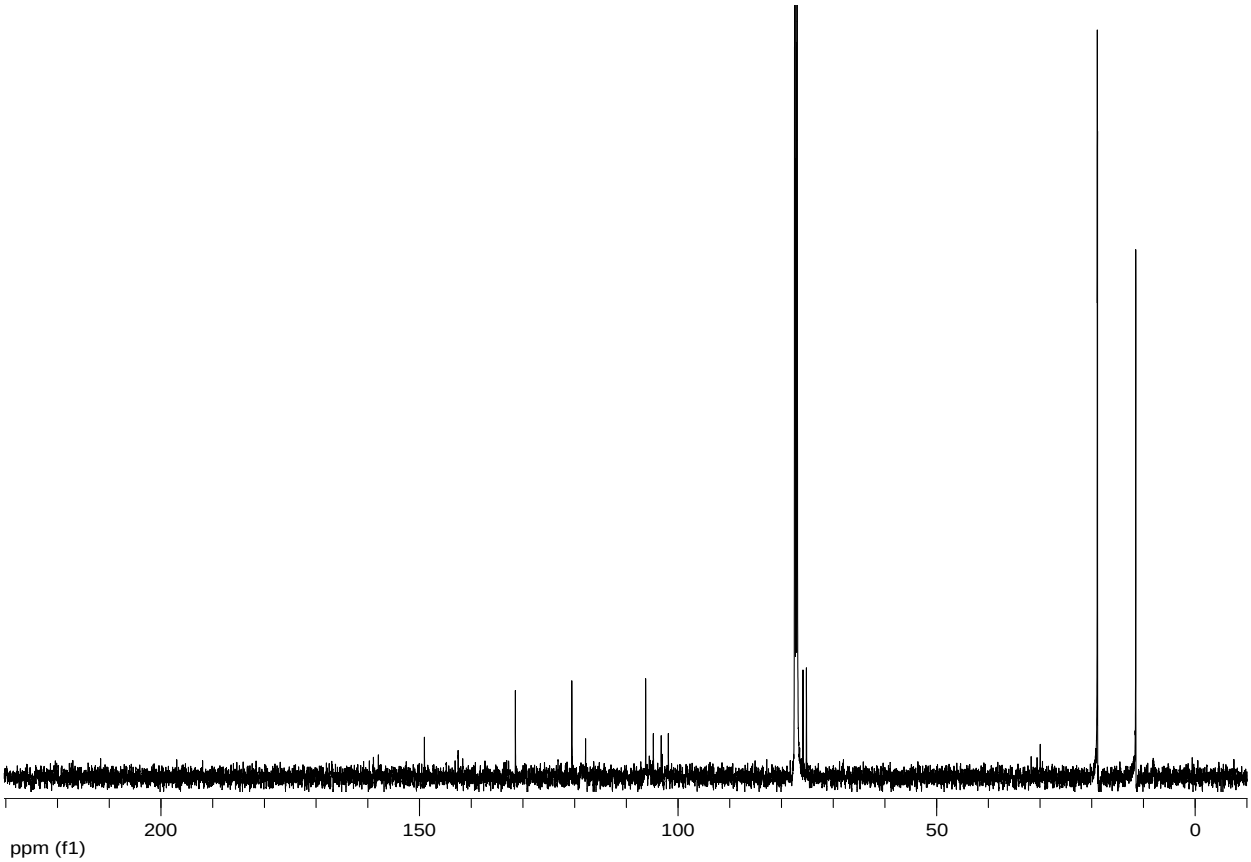

O
O
Et3Si
SiEt3
2-52c
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)


200
150
100
50
0
ppm (f1)

O
i-Pr3Si
Sii-Pr3

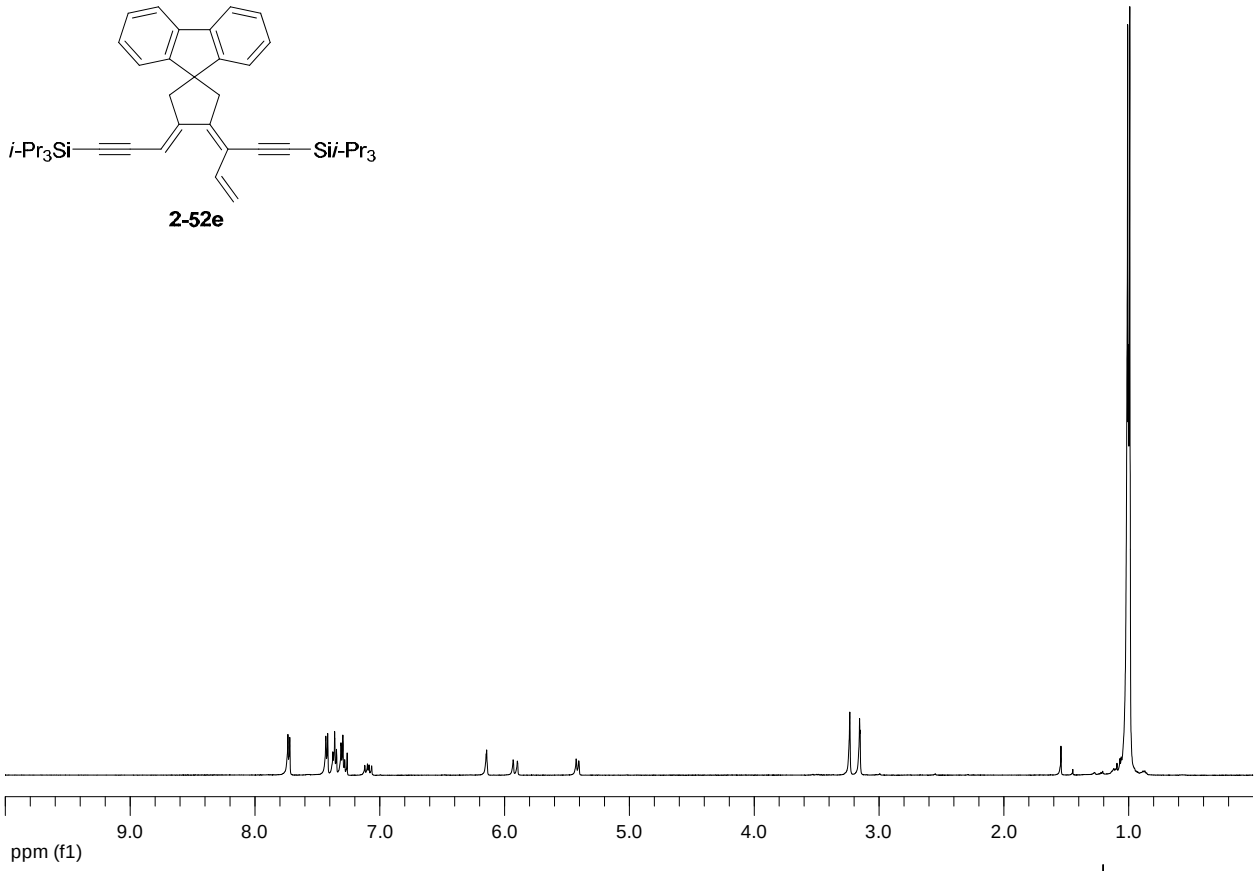
2-52d

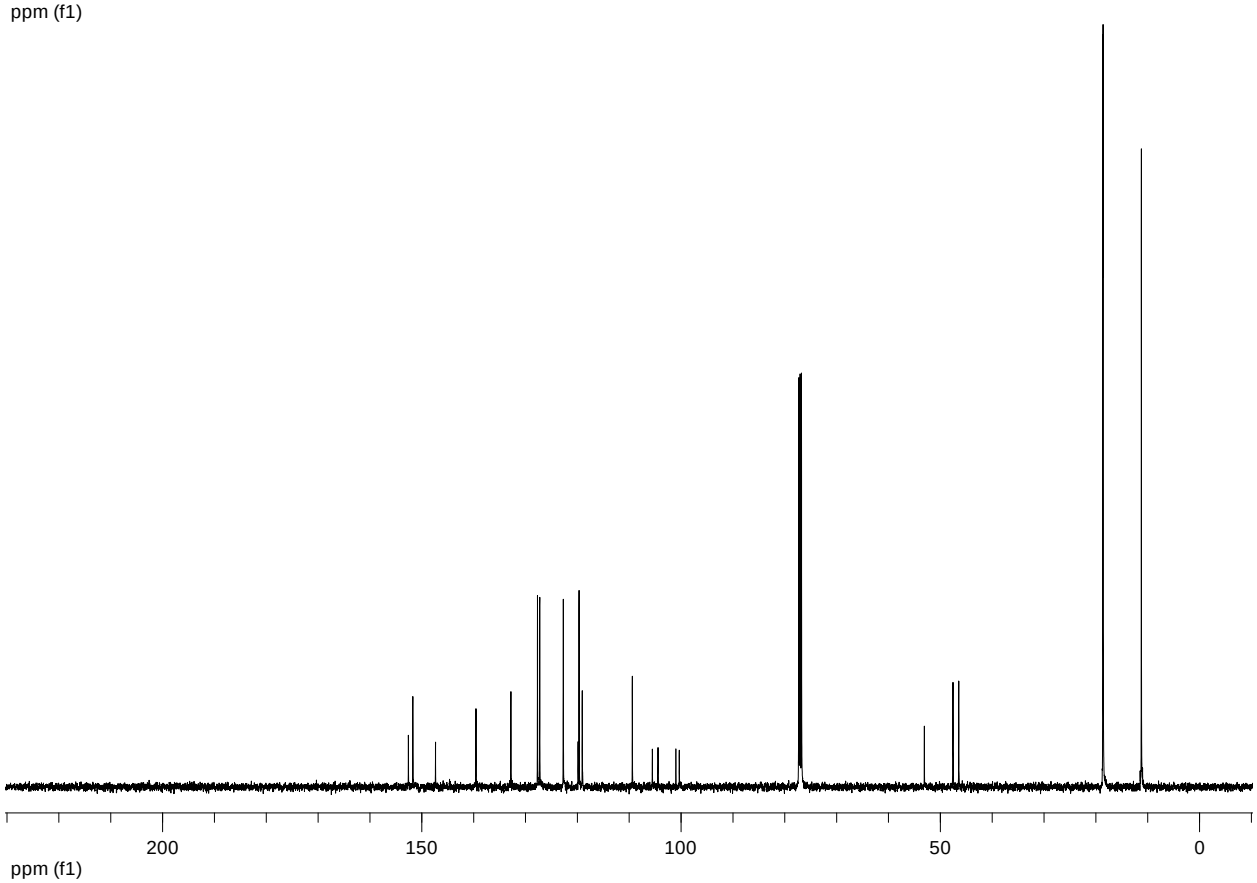

9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)


200
150
100
50
0
ppm (f1)

i-Pr3Si
Sii-Pr3

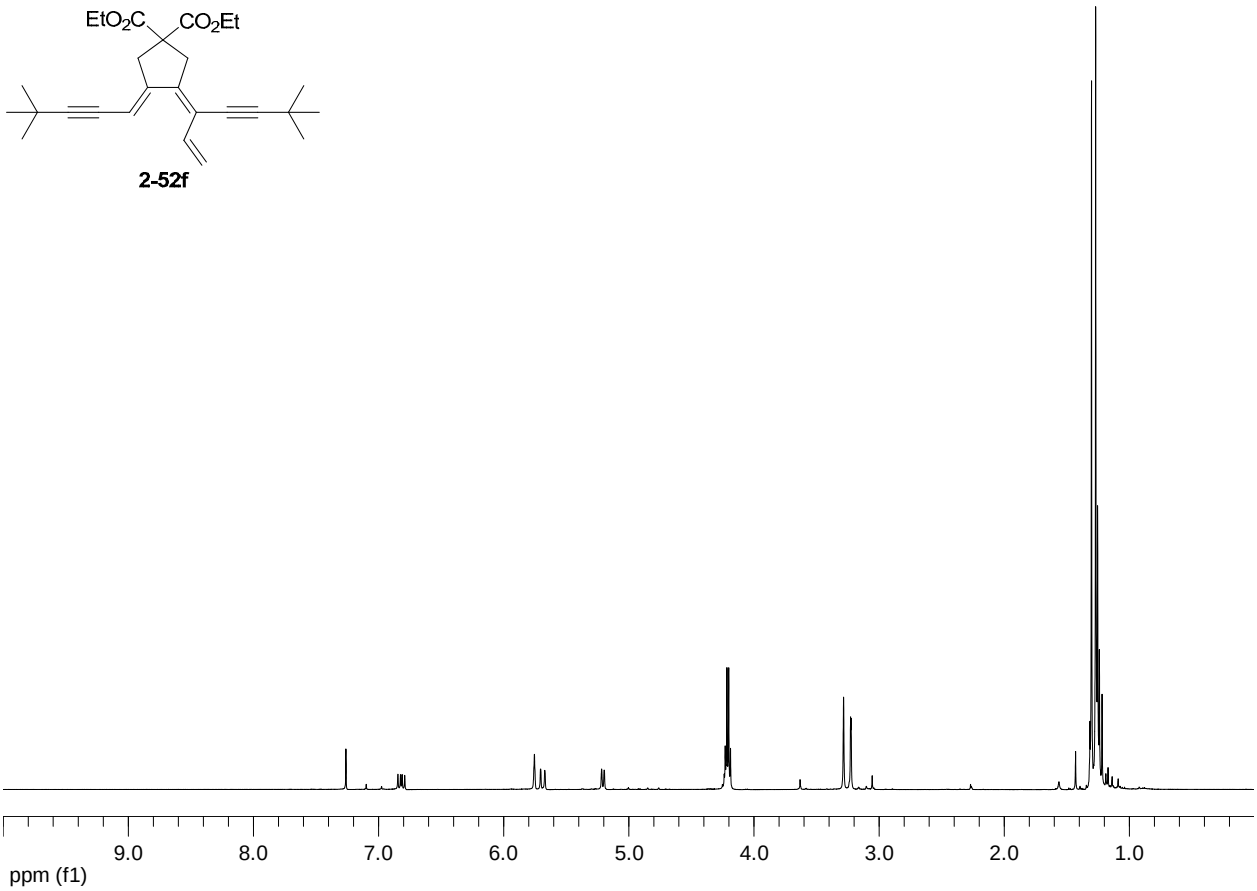
2-52e

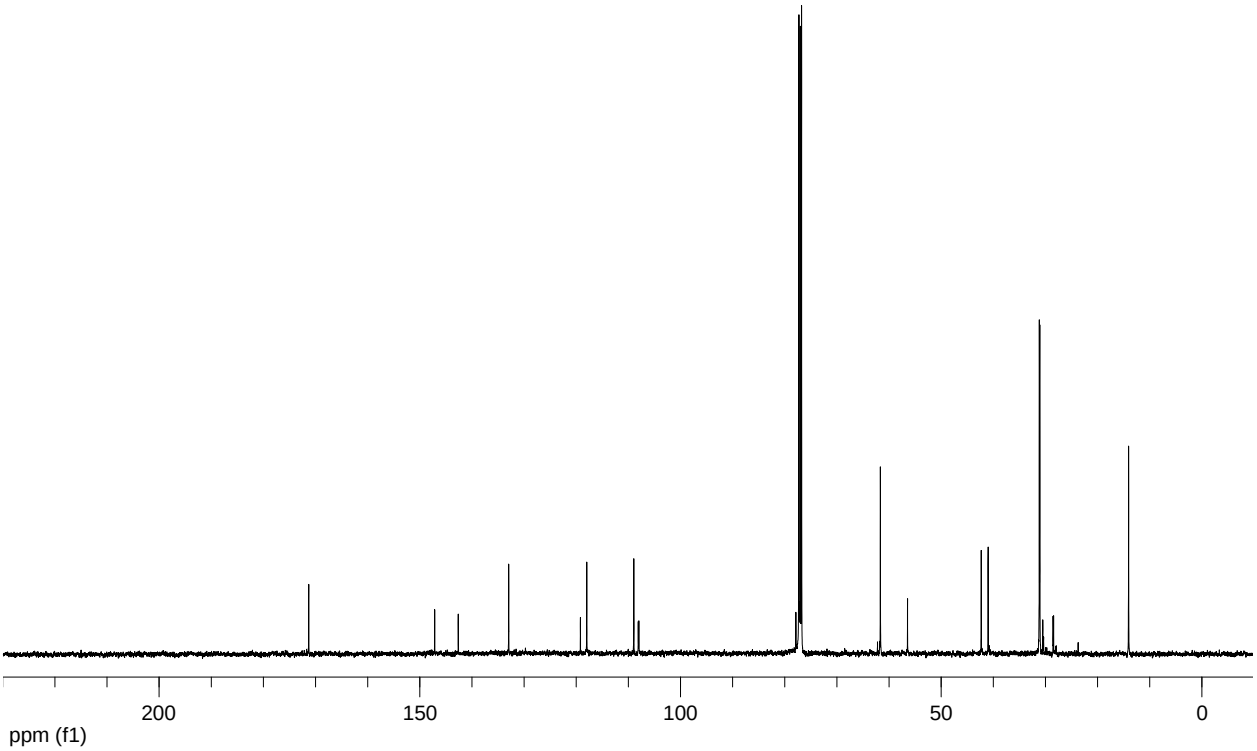

9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

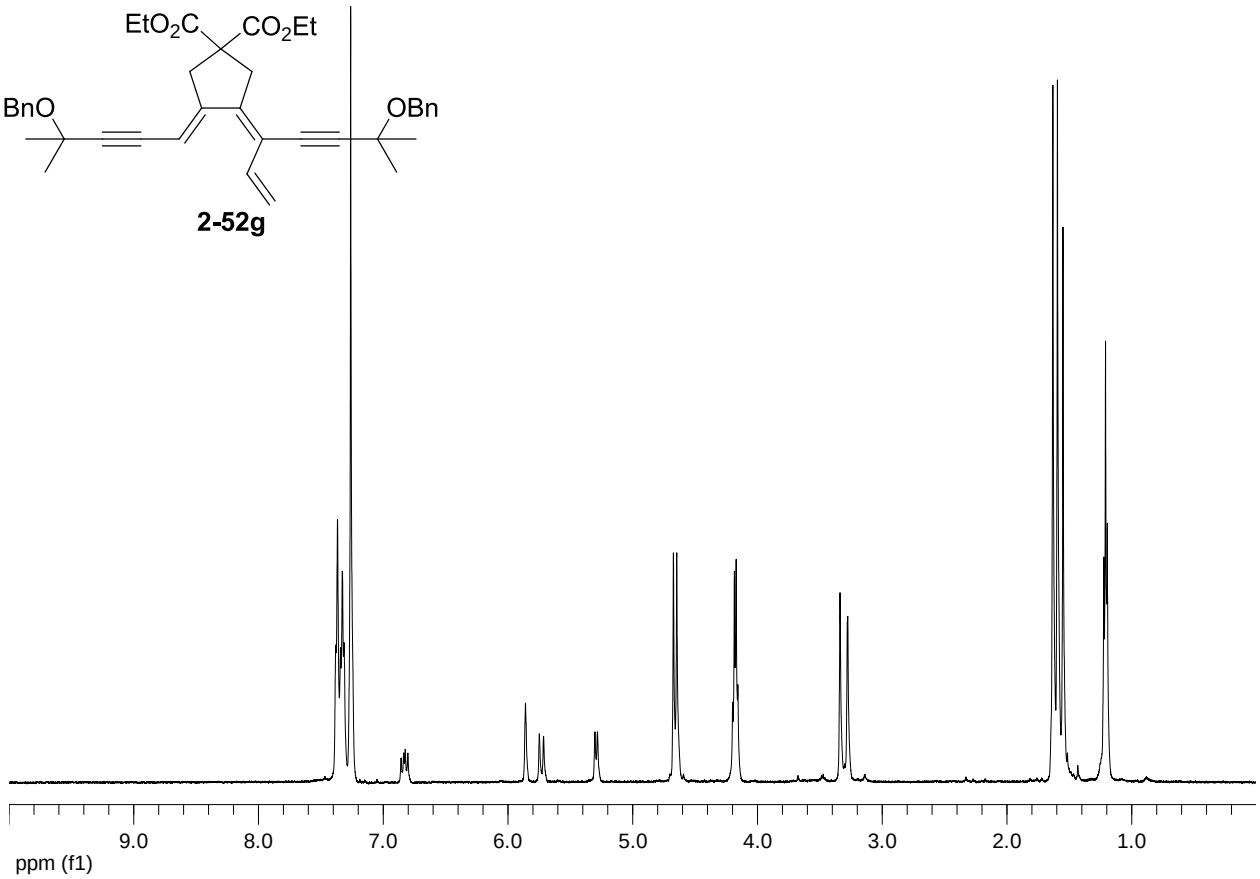

200
150
100
50
0
ppm (f1)

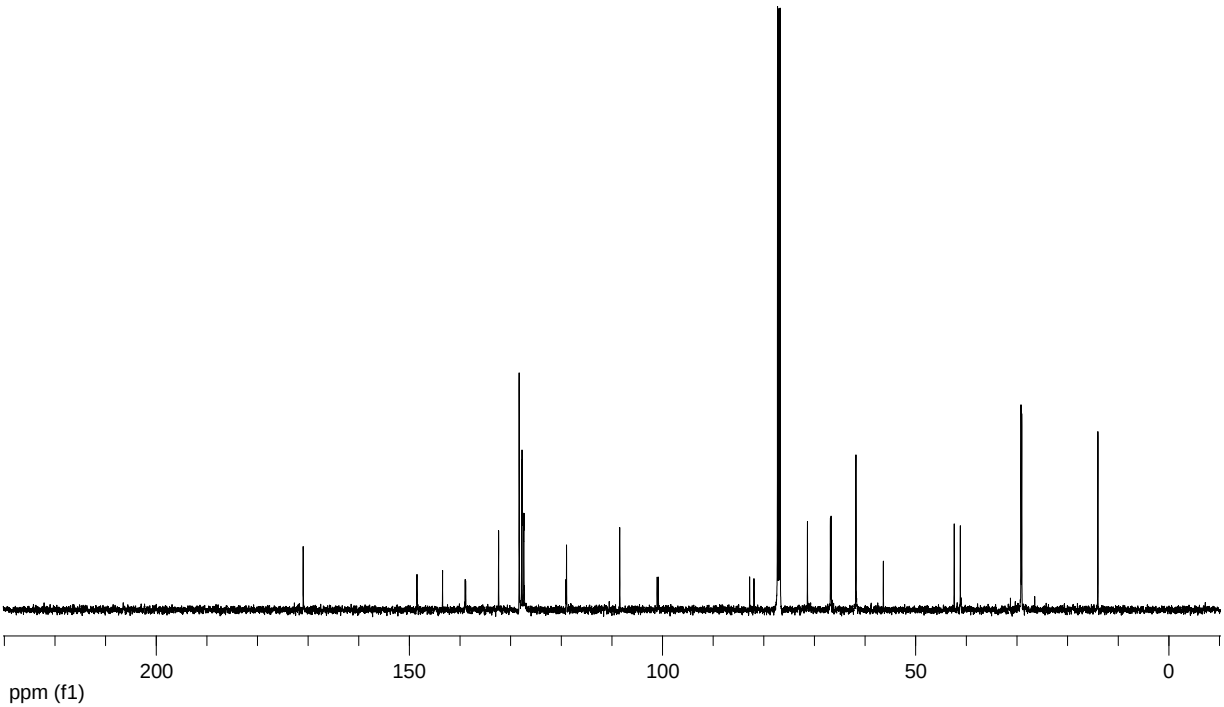
EtO2C
CO2Et

2-52f


9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

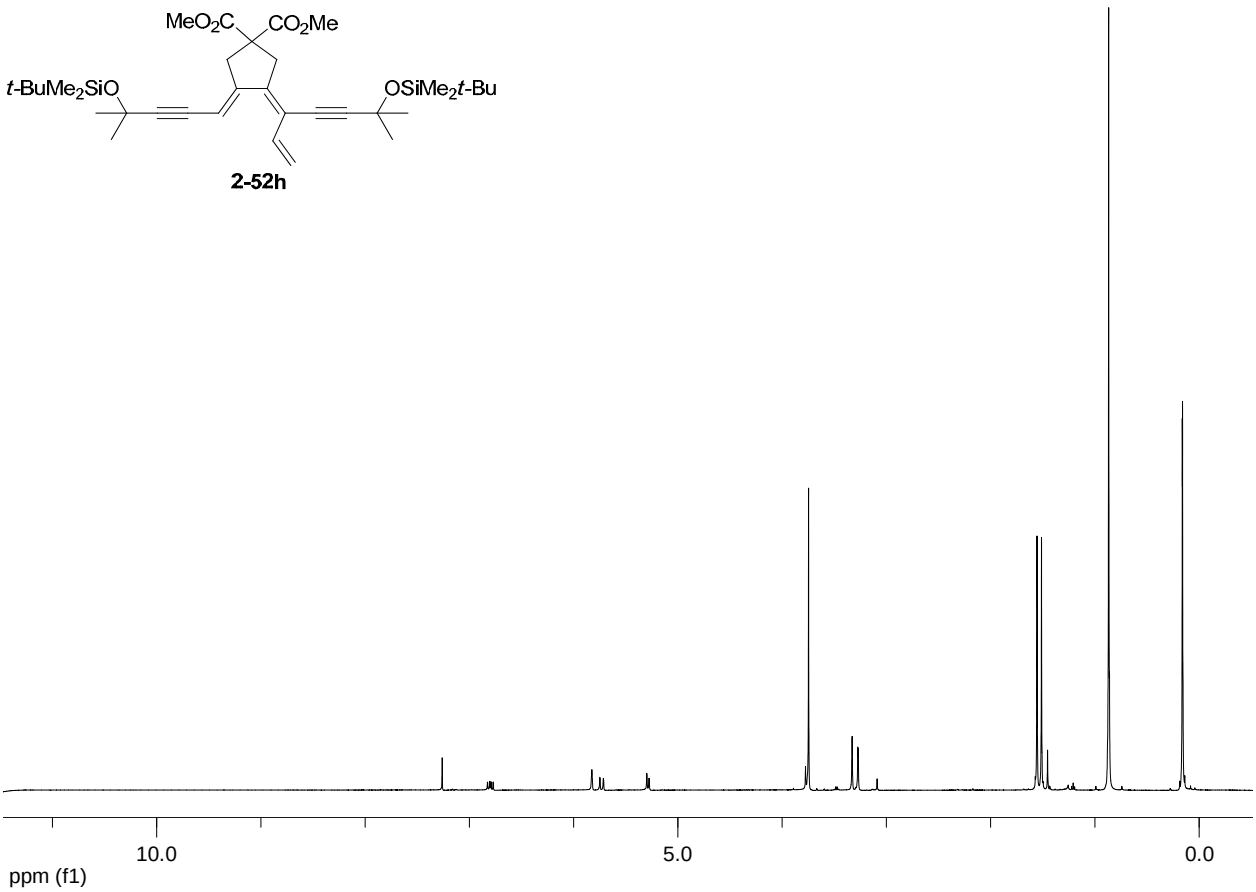

200
150
100
50
0
ppm (f1)

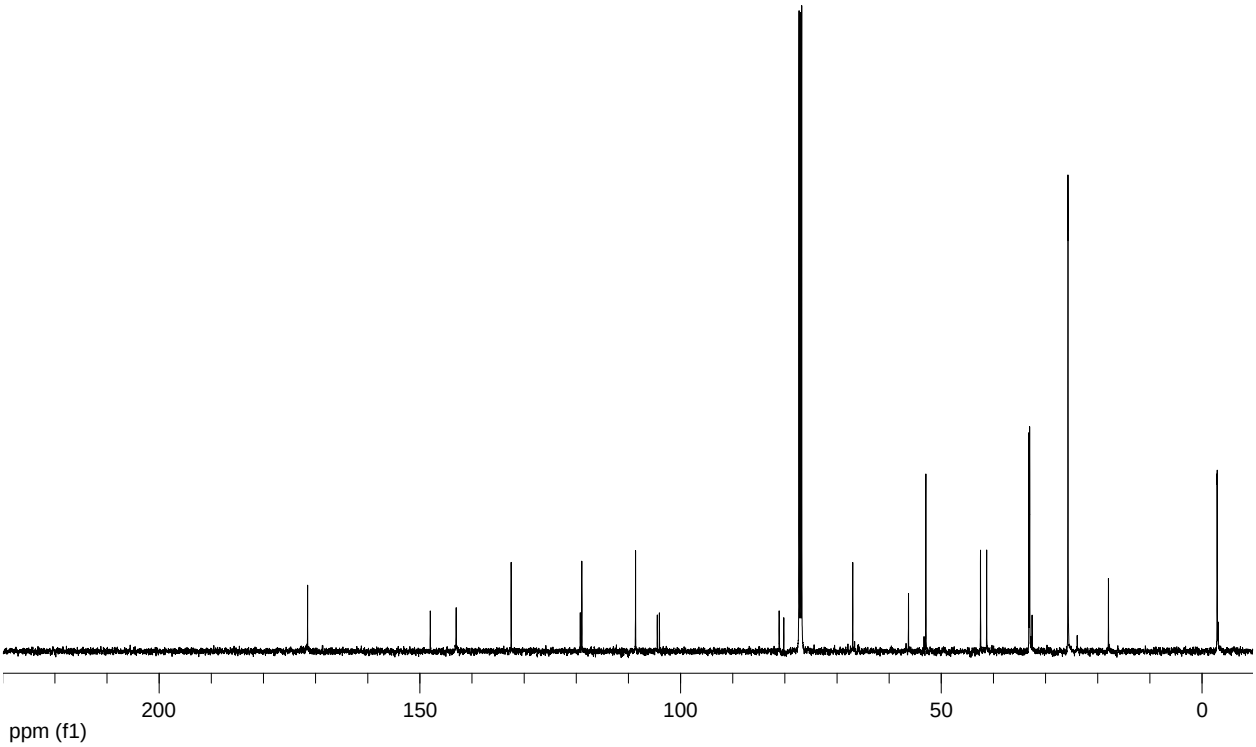

EtO2C
CO2Et
BnO
OBn
2-52g
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)


200
150
100
50
0
ppm (f1)

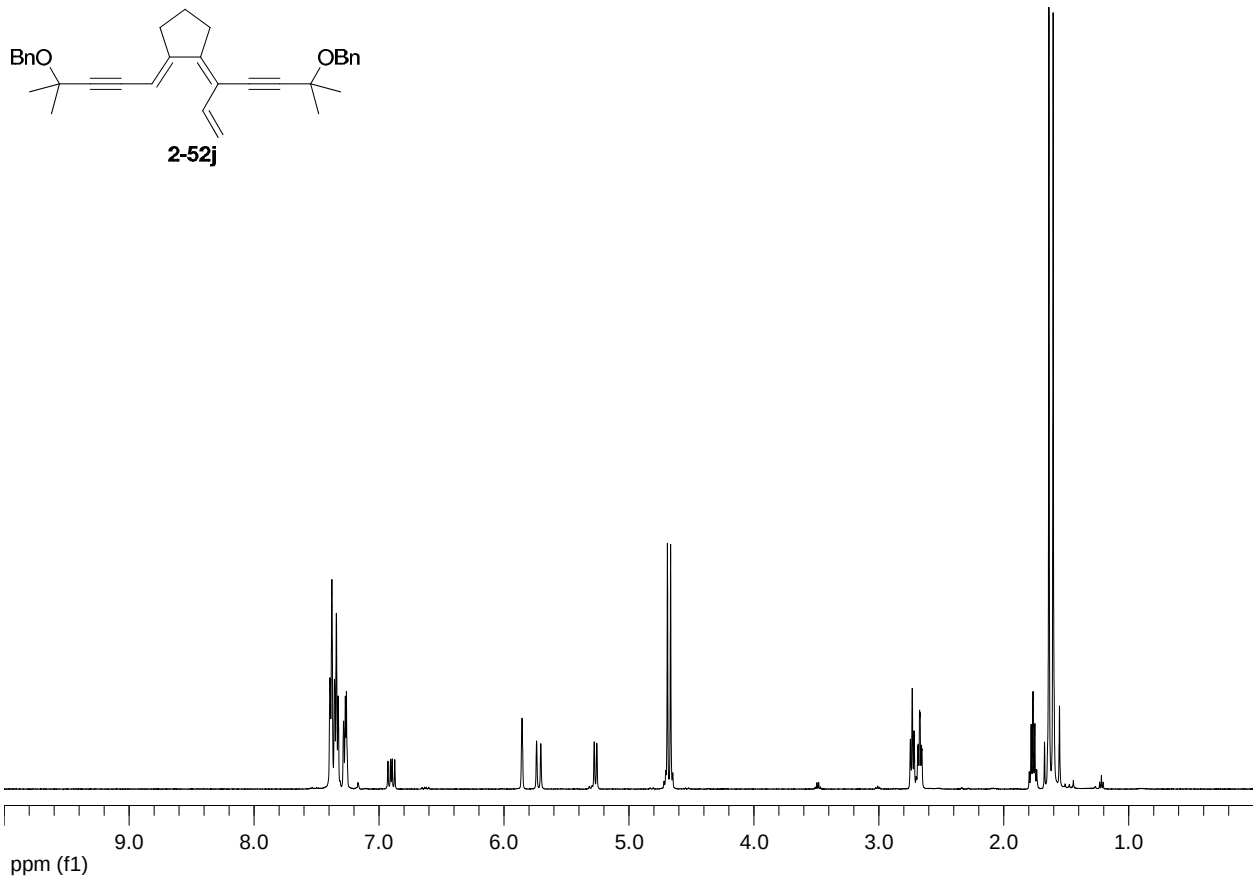
MeO2C
CO2Me
t-BuMe2SiO
OSiMe2t-Bu

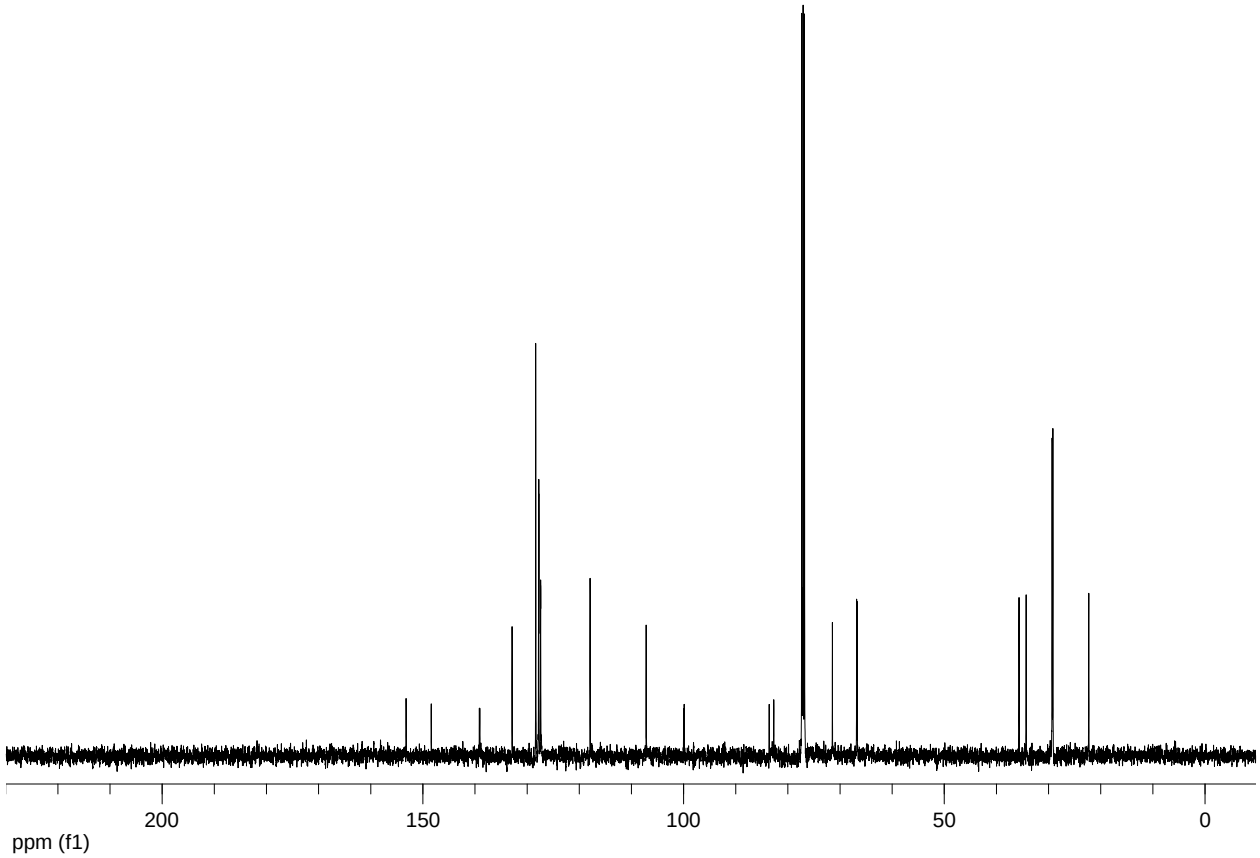
2-52h


10.0
5.0
0.0
ppm (f1)


200
150
100
50
0
ppm (f1)

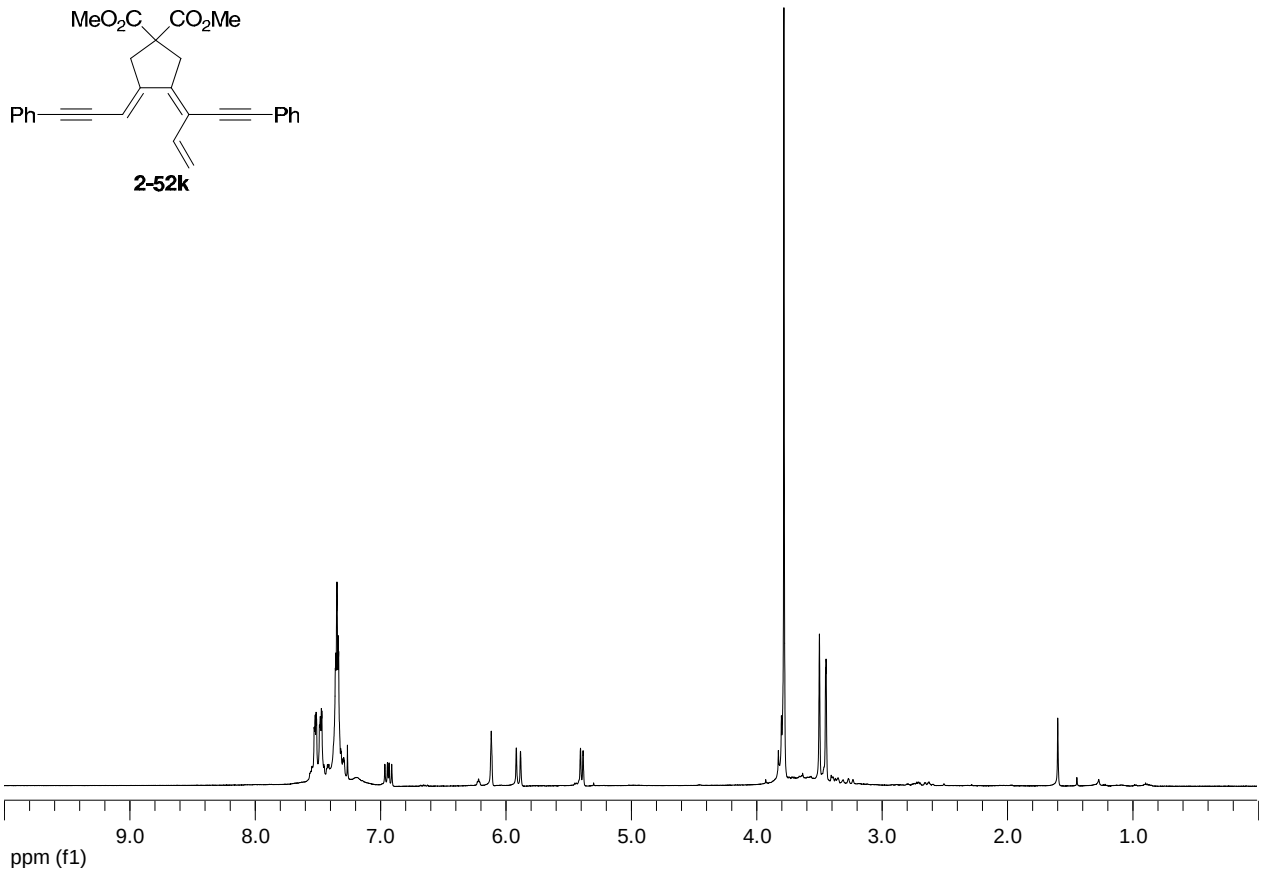
2-52j

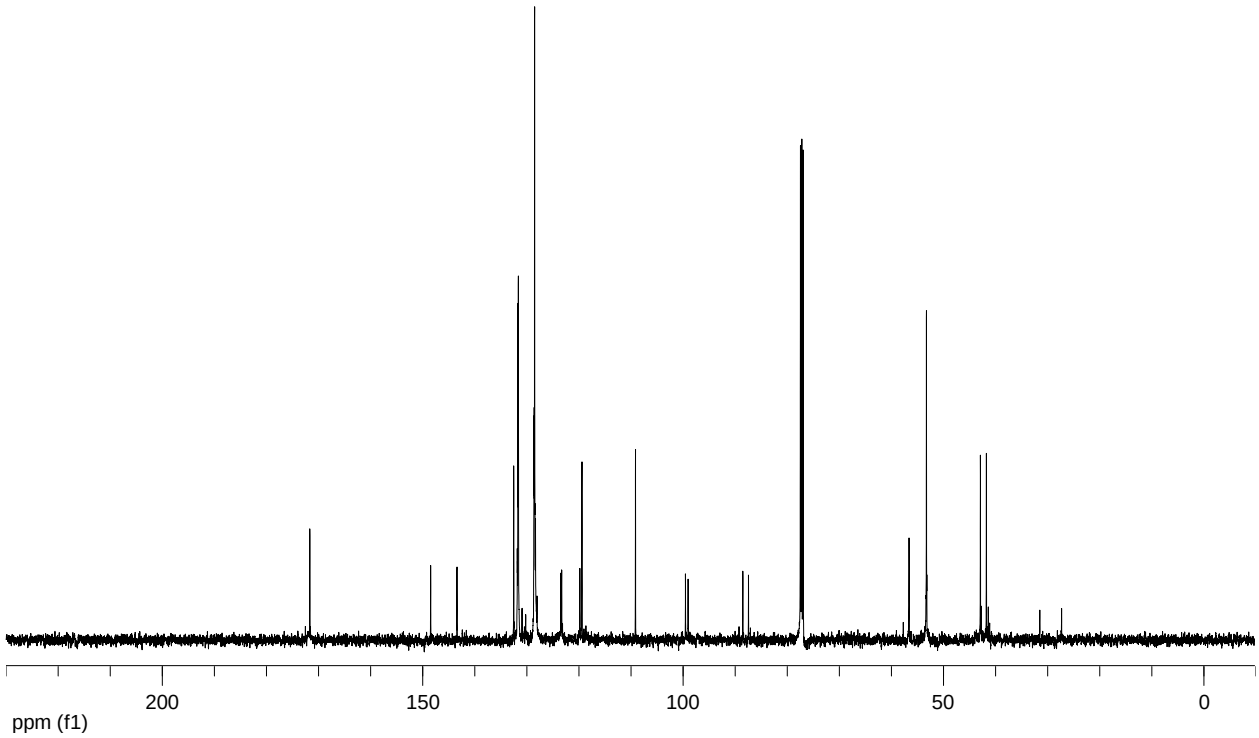


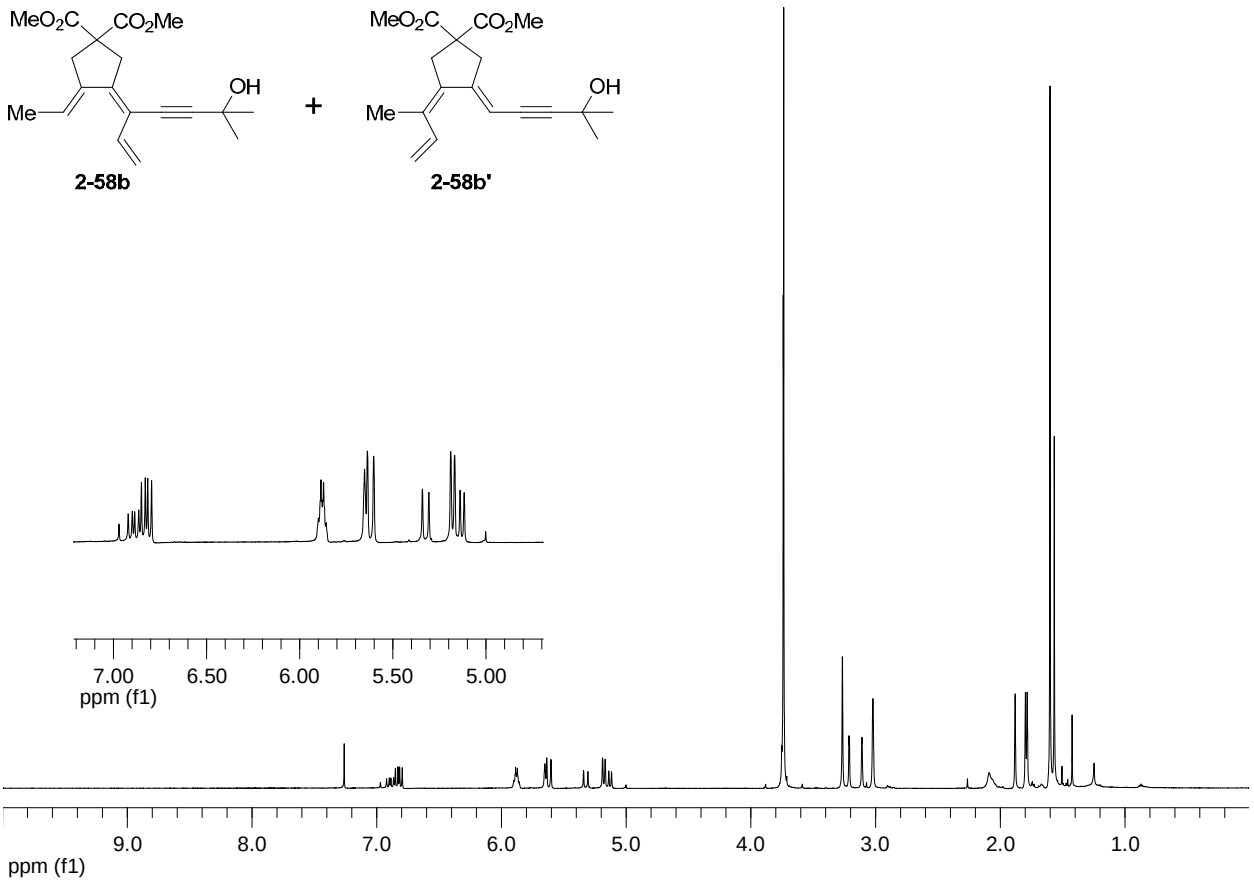


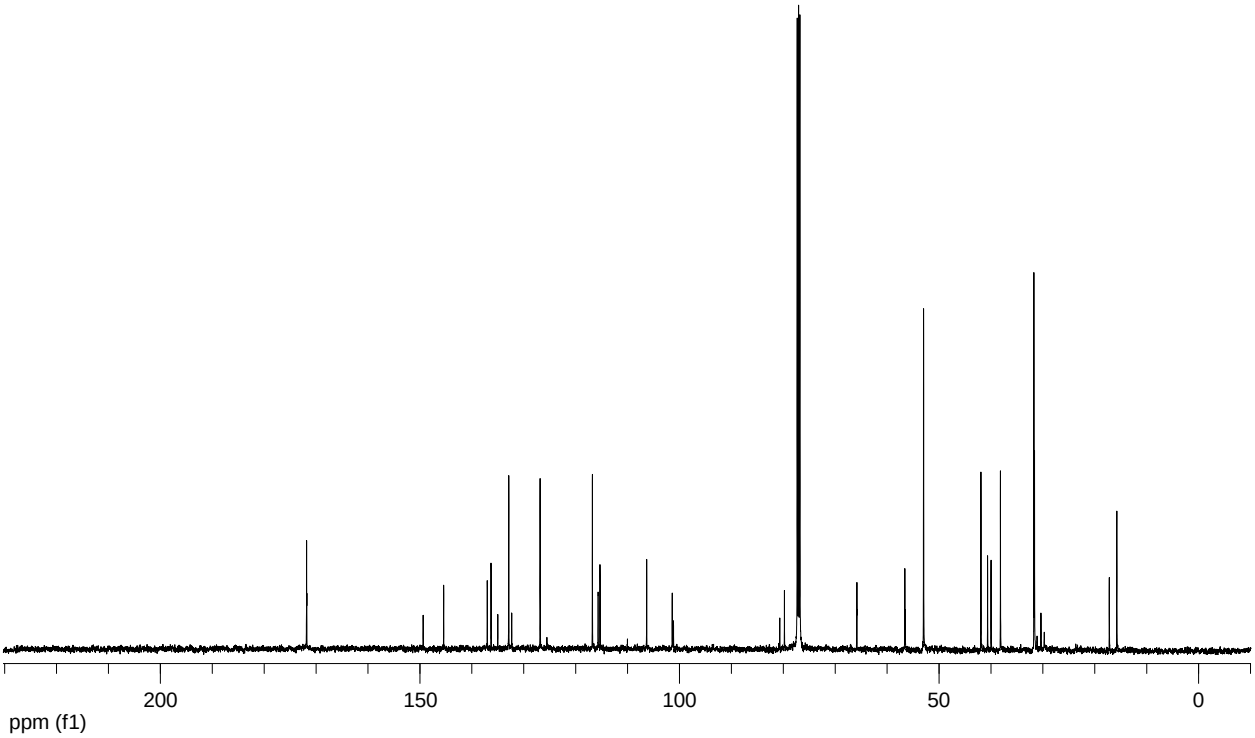
MeO2C
CO2Me
Ph
Ph

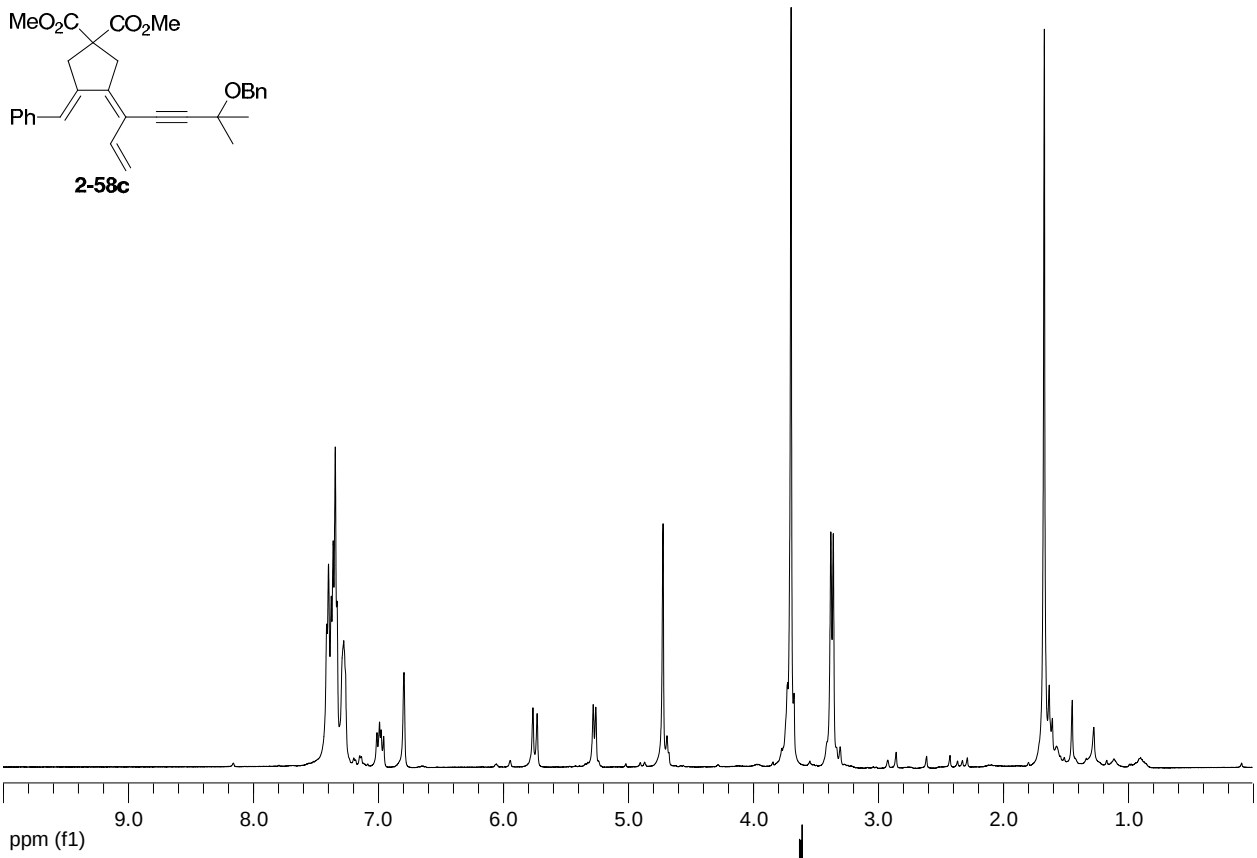
2-52k

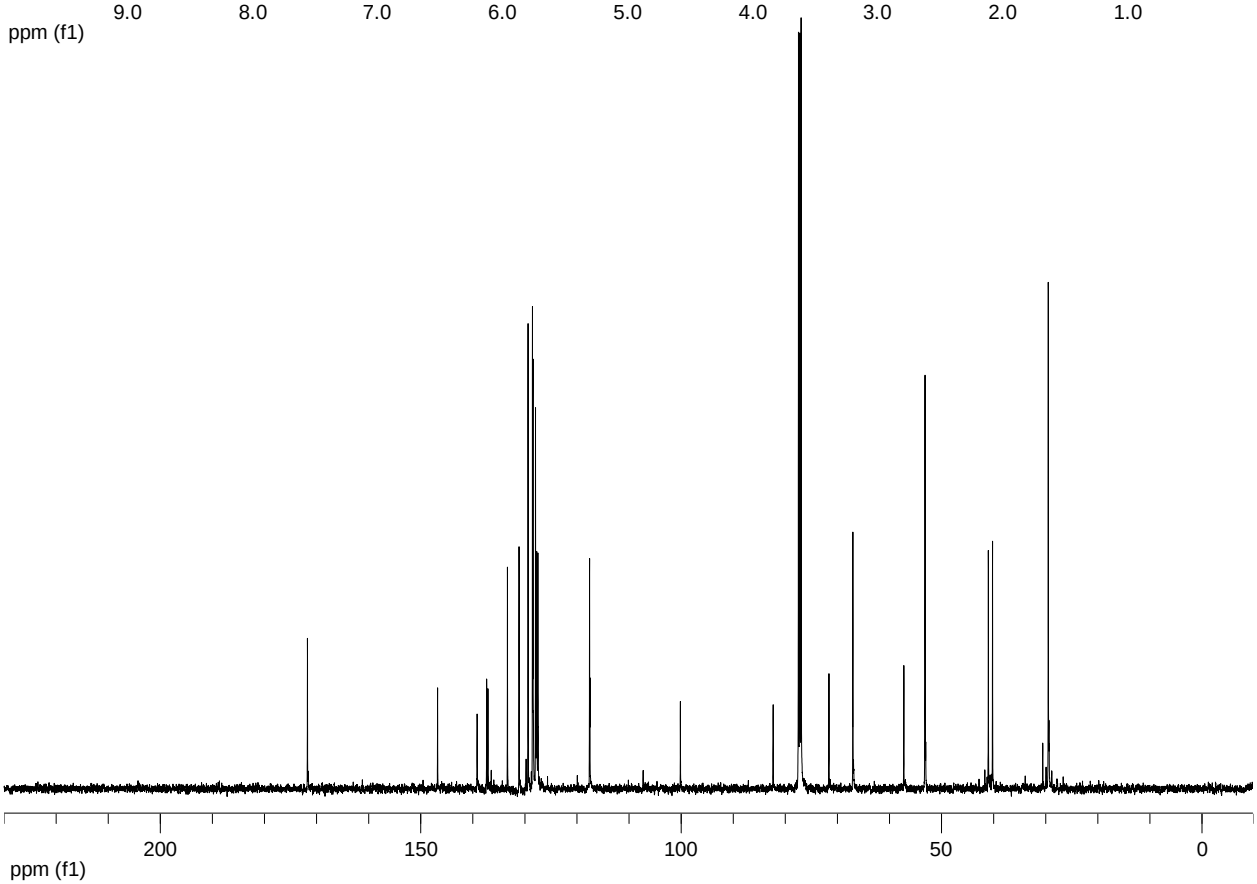

9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

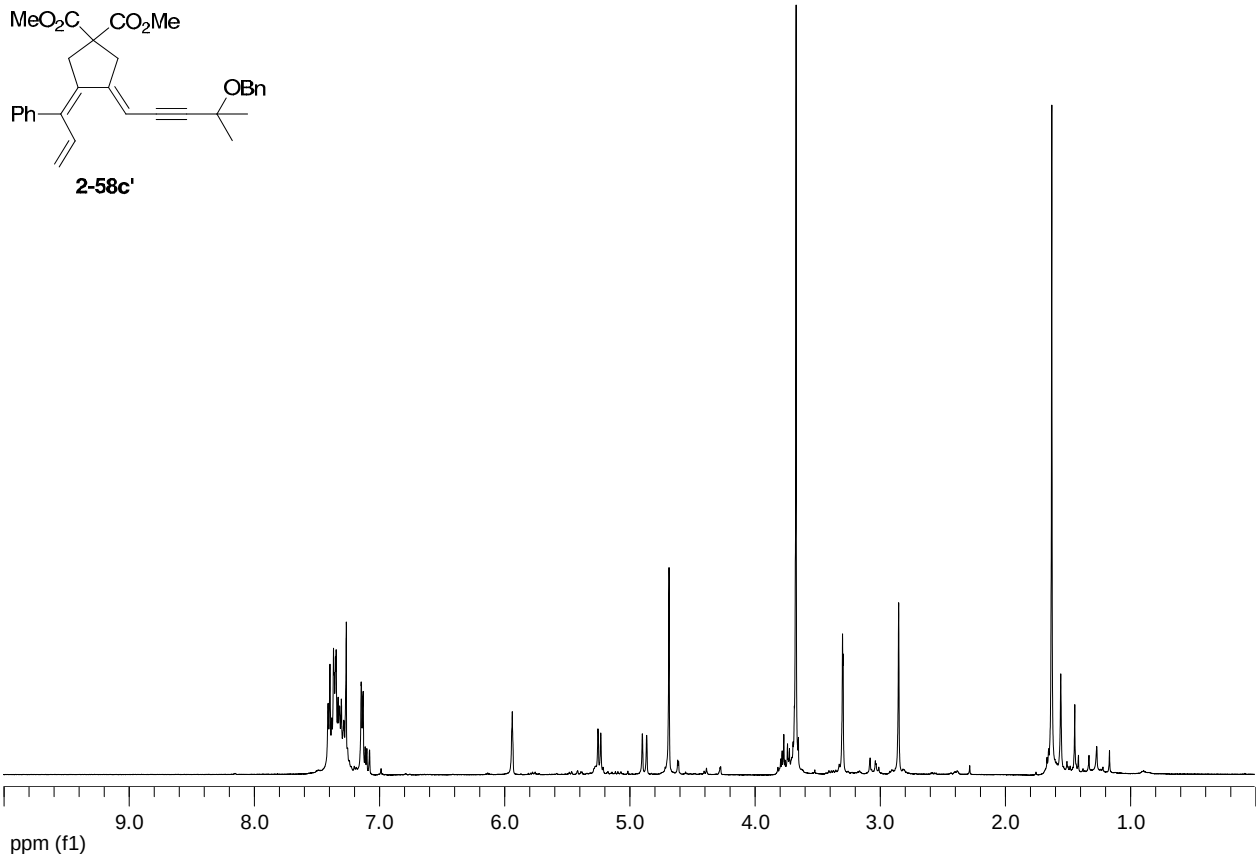

200
150
100
50
0
ppm (f1)

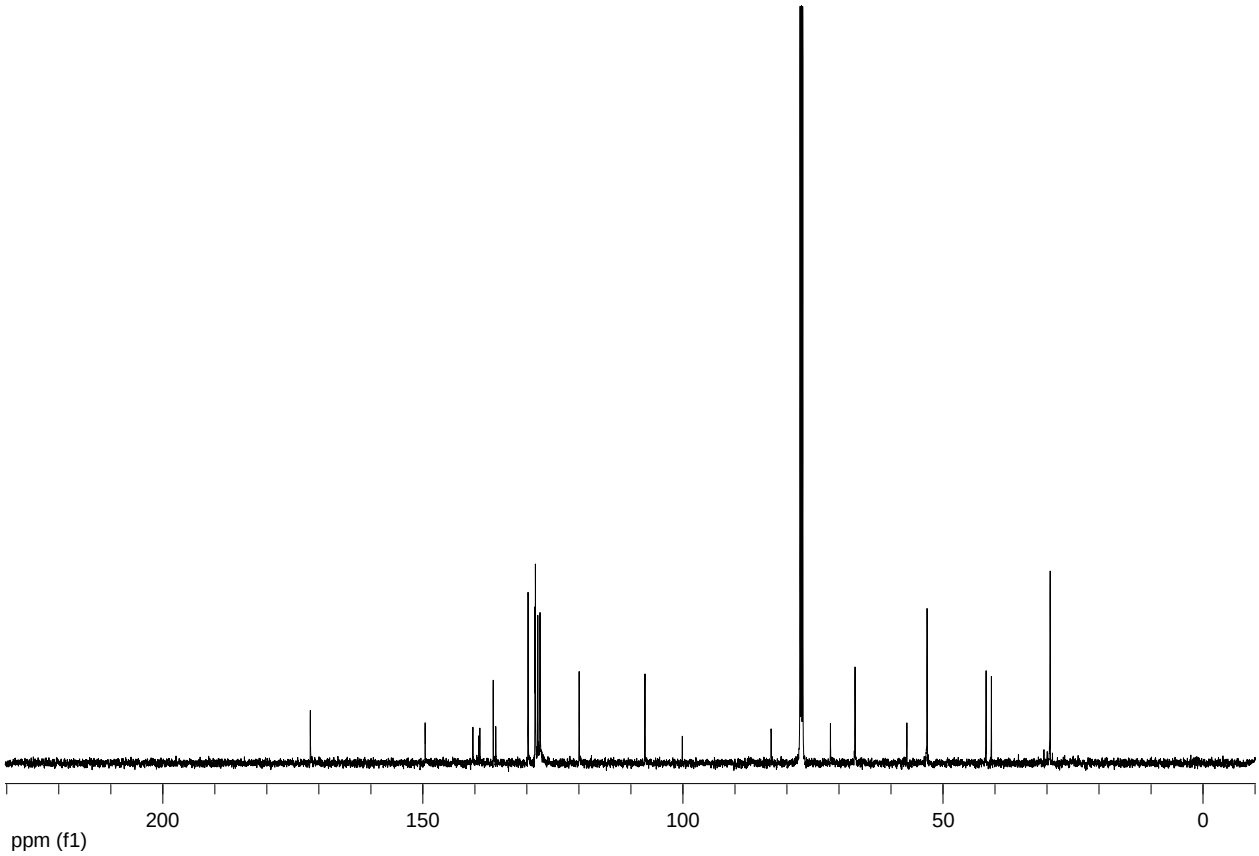

MeO2C
CO2Me
OH
Me
2-58b
+
MeO2C
CO2Me
OH
Me
2-58b'
7.00
6.50
6.00
5.50
5.00
ppm (f1)
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

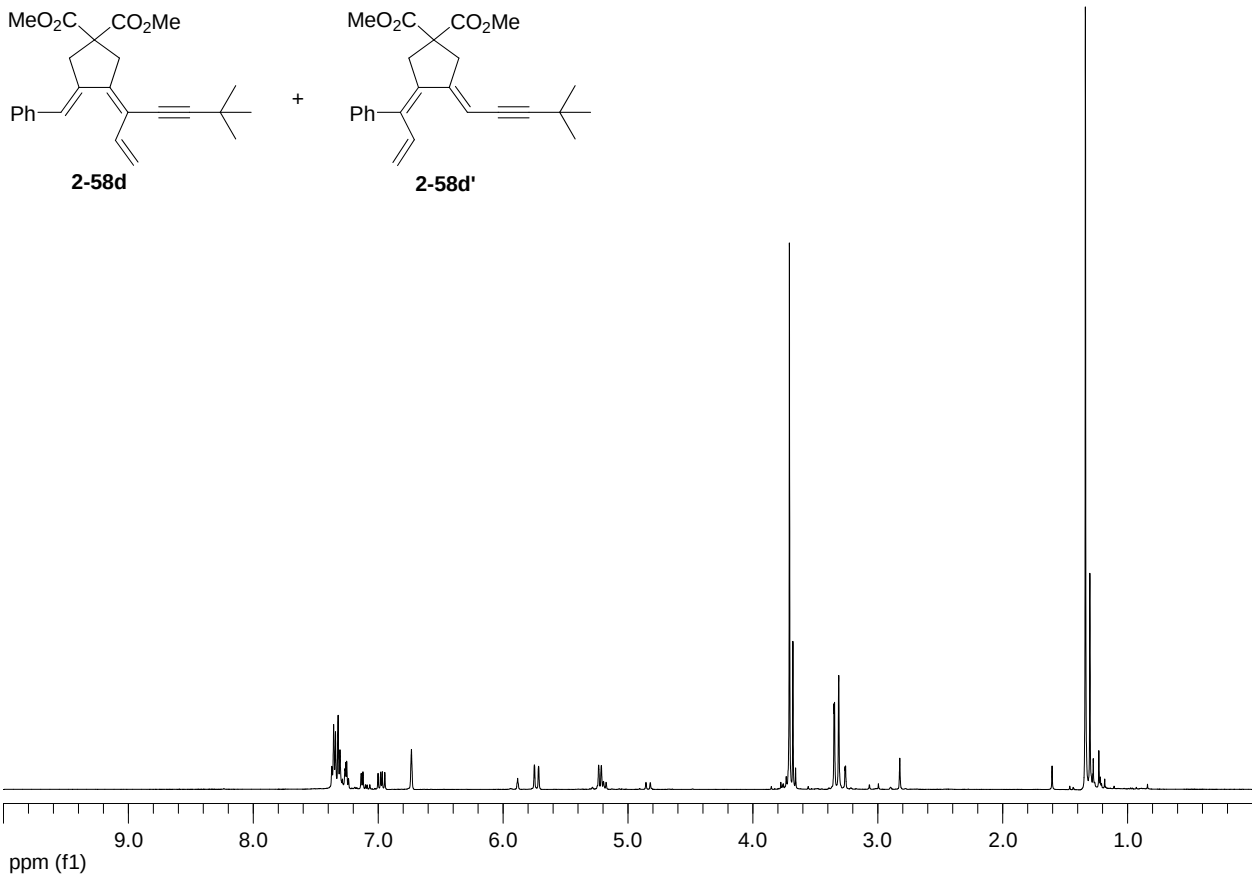

200
150
100
50
0
ppm (f1)

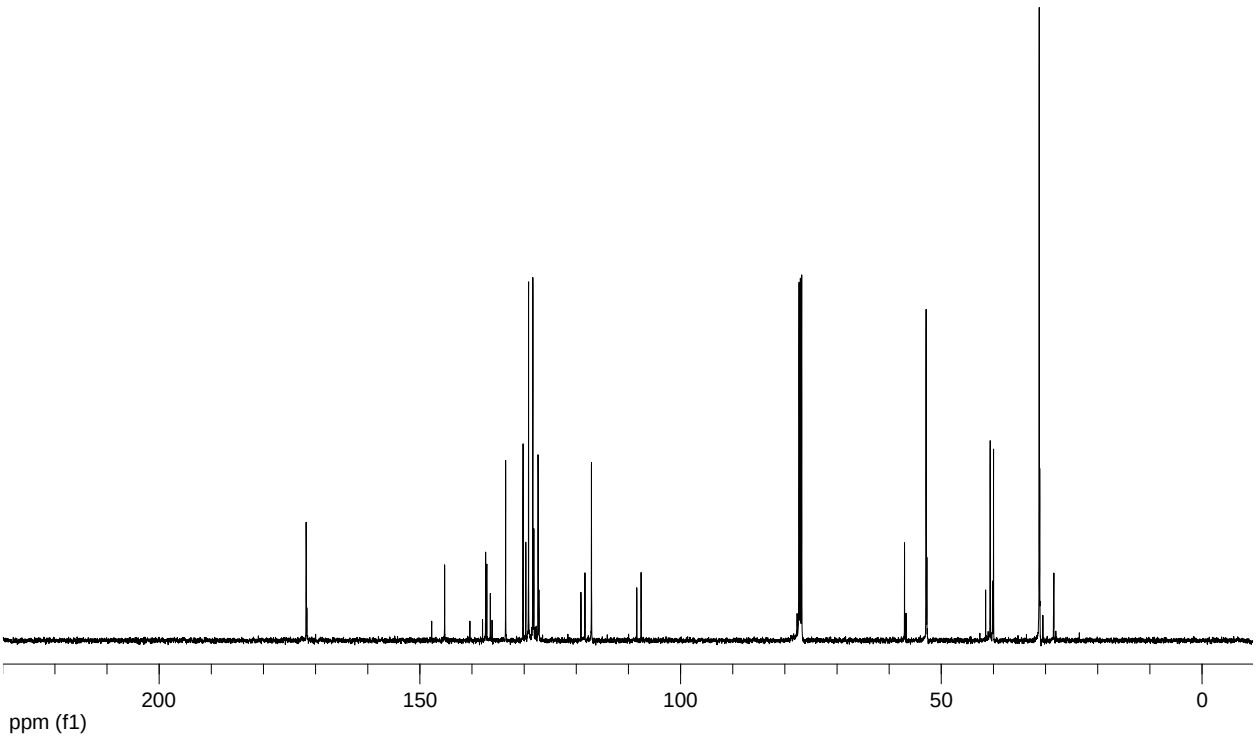

MeO2C
CO2Me
OBn
Ph
2-58c
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

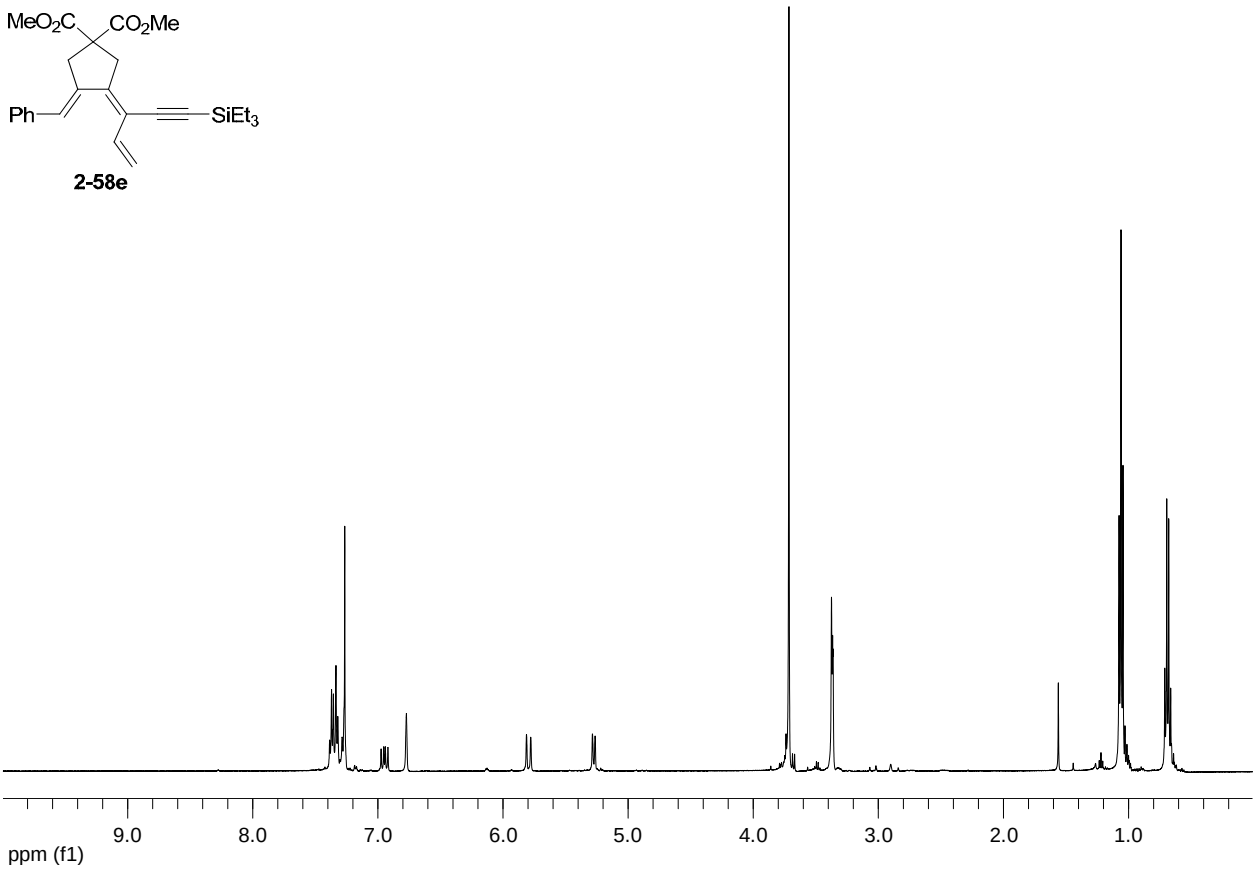

200
150
100
50
0
ppm (f1)

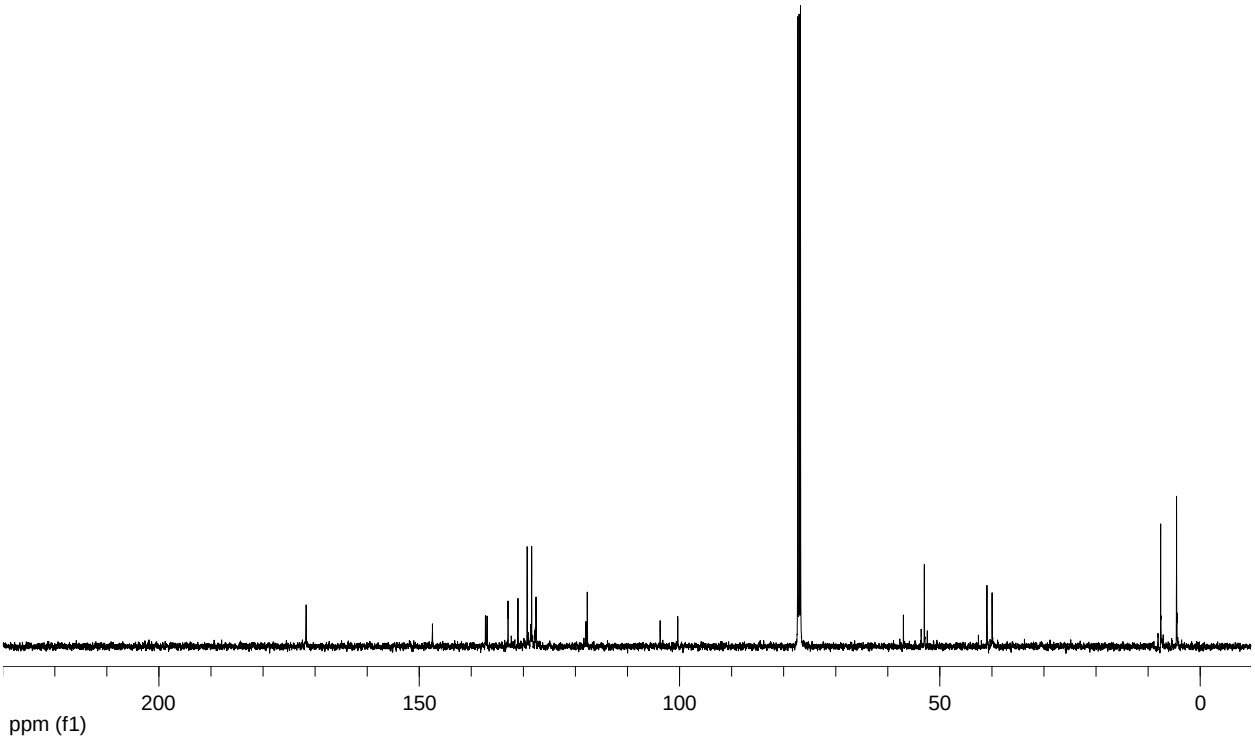

MeO2C
CO2Me
OBn
Ph
2-58c'
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)


200
150
100
50
0
ppm (f1)


MeO2C
CO2Me
Ph
+
MeO2C
CO2Me
Ph
2-58d
2-58d'
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

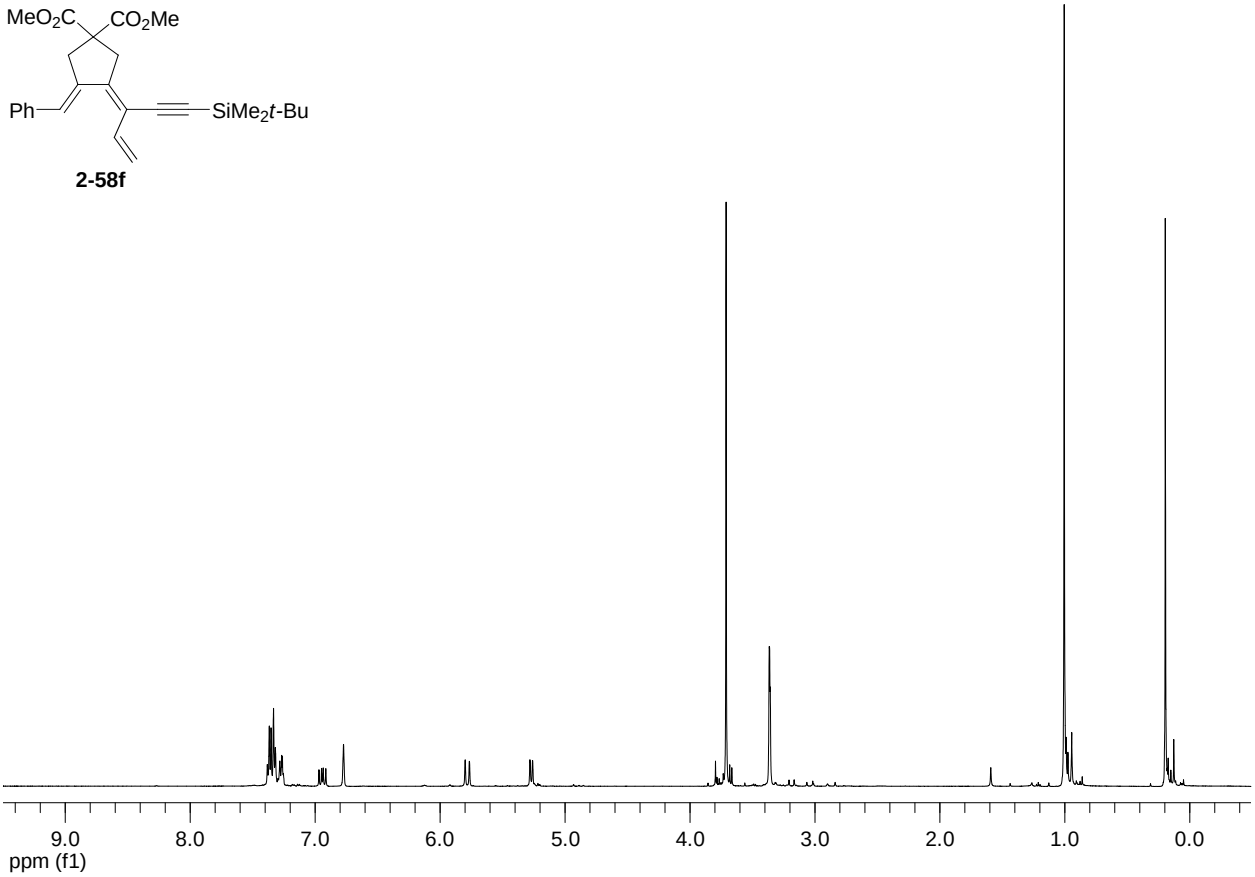

200
150
100
50
0
ppm (f1)

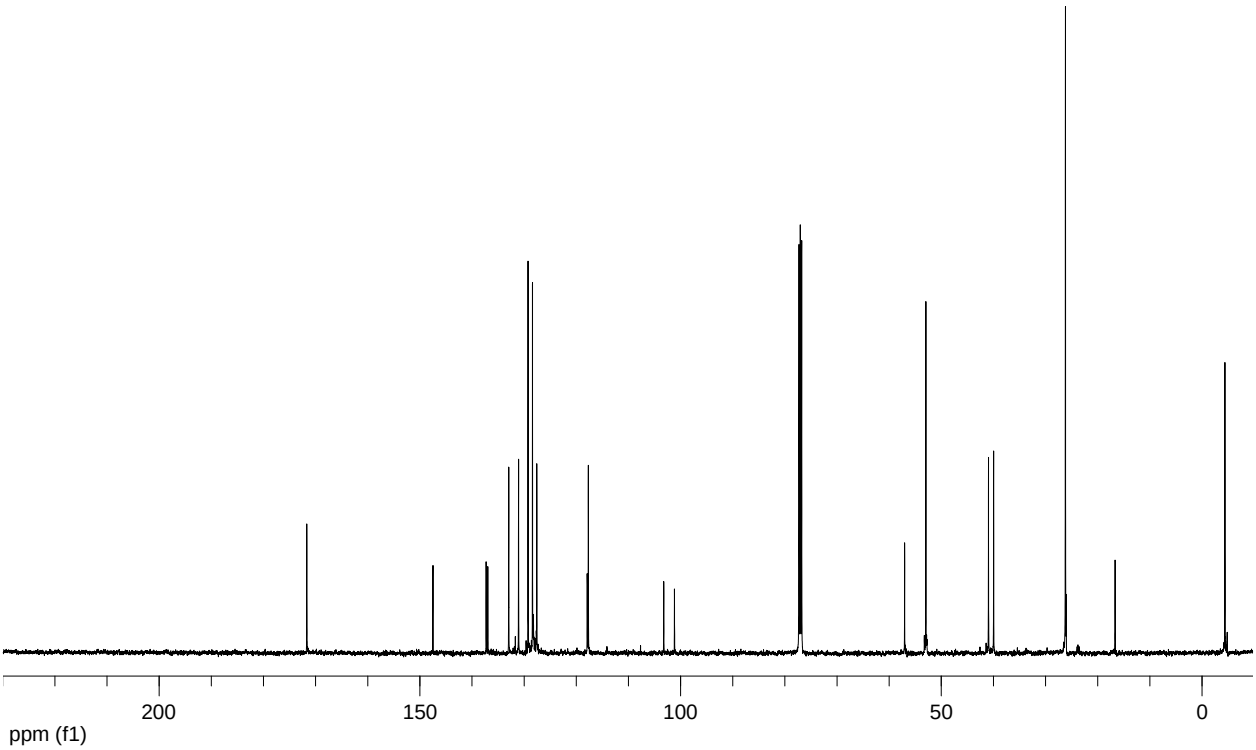

MeO2C
CO2Me
Ph
SiEt3
2-58e
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)


200
150
100
50
0
ppm (f1)

MeO2C
CO2Me
Ph
SiMe2t-Bu

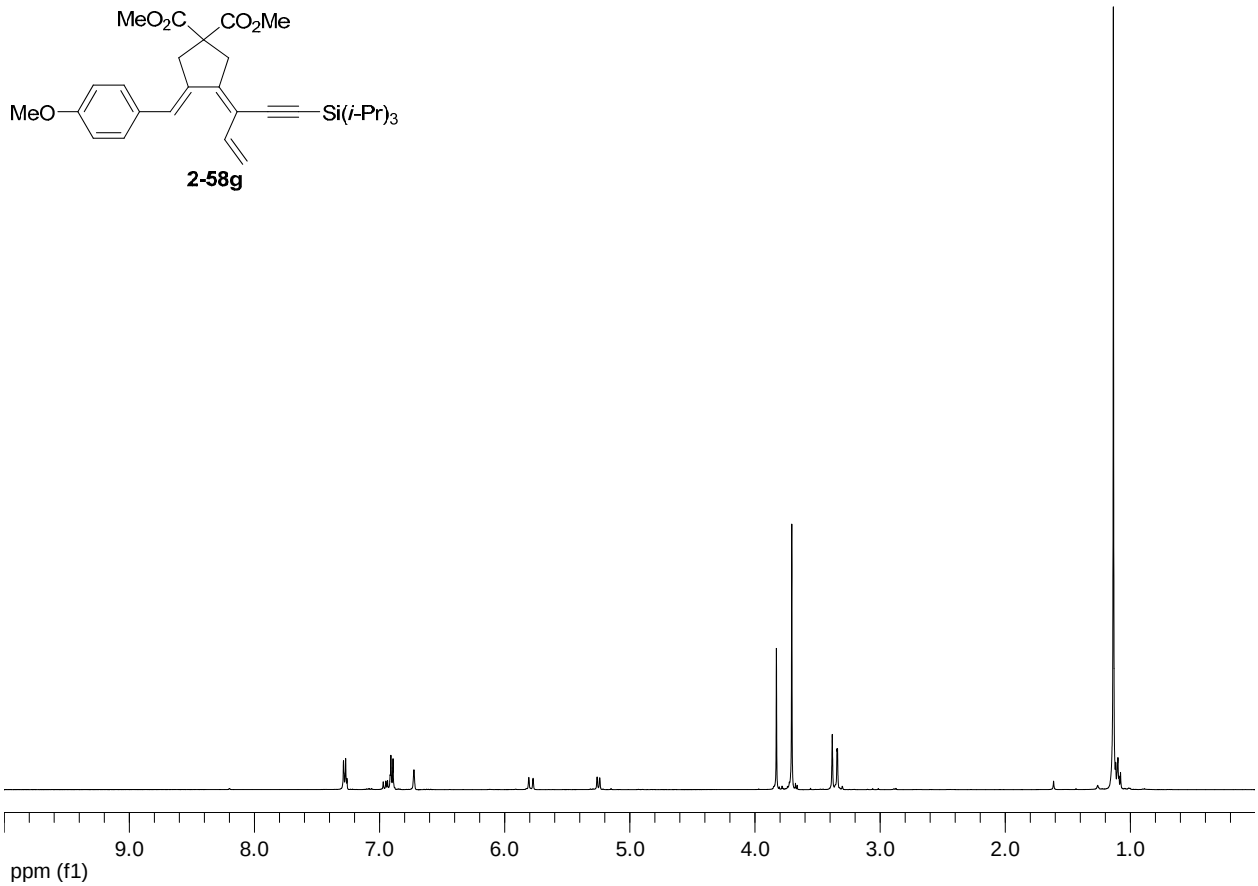
2-58f

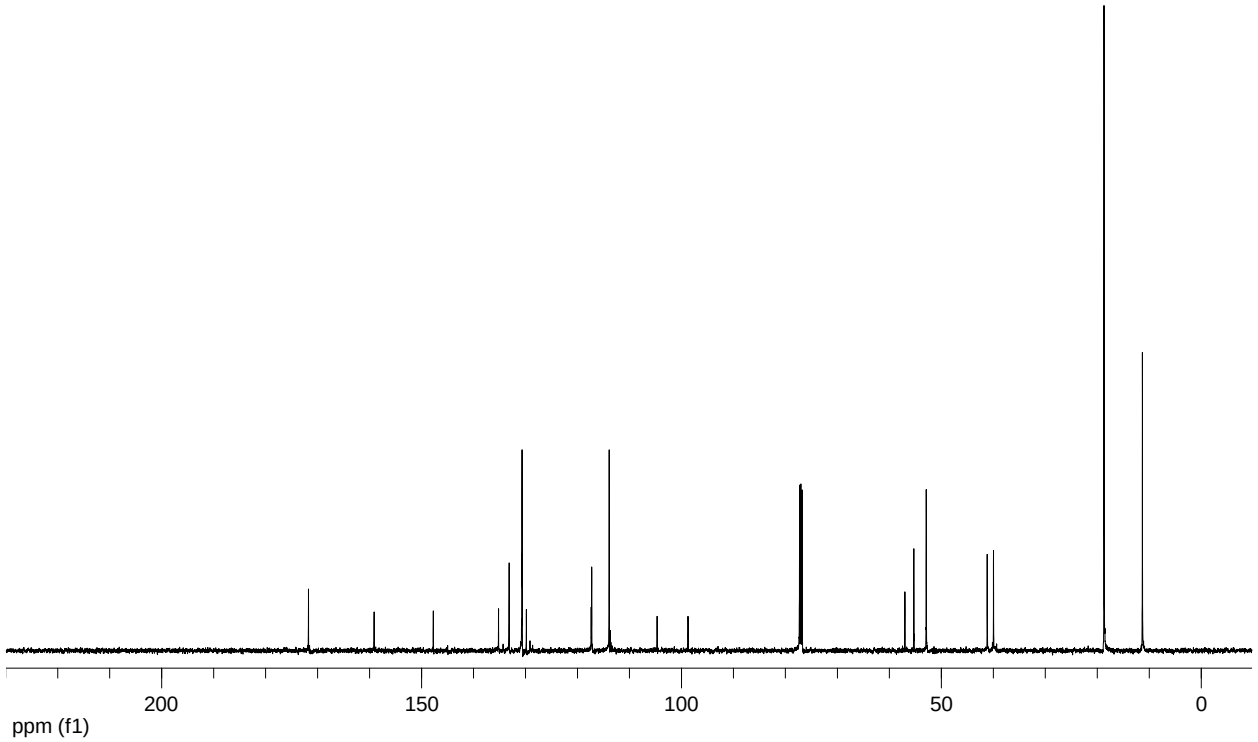

9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

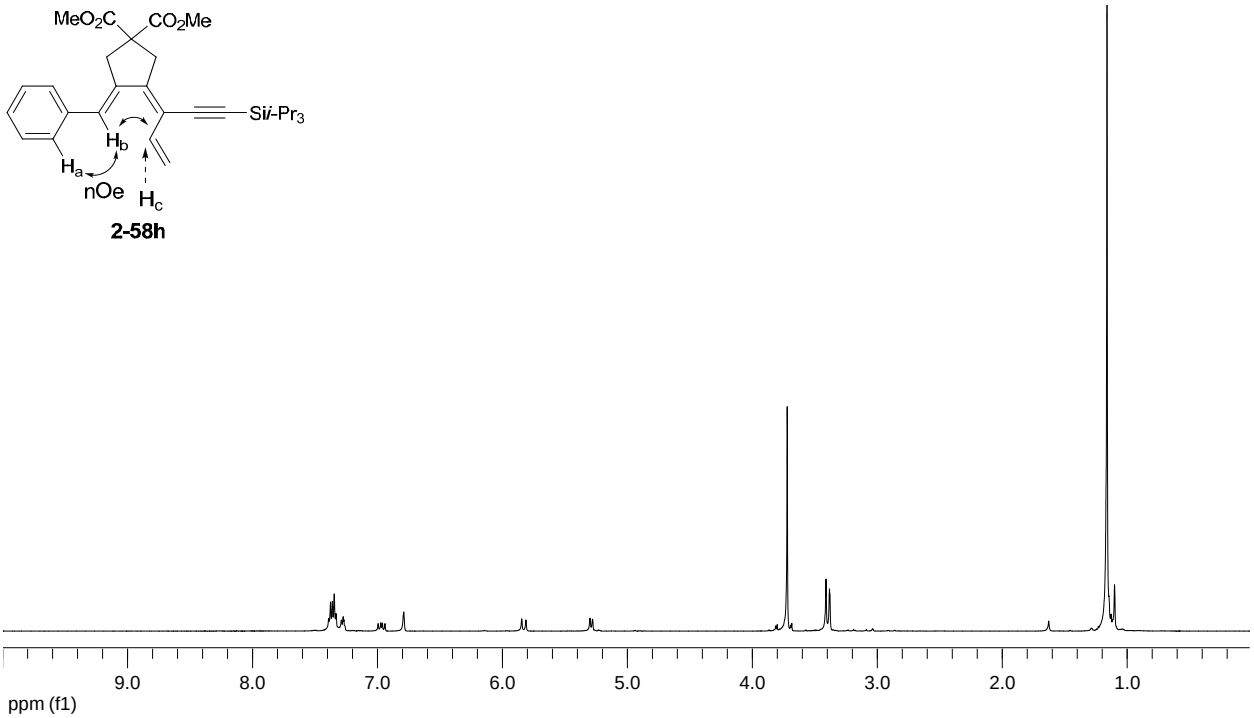

200
150
100
50
0
ppm (f1)

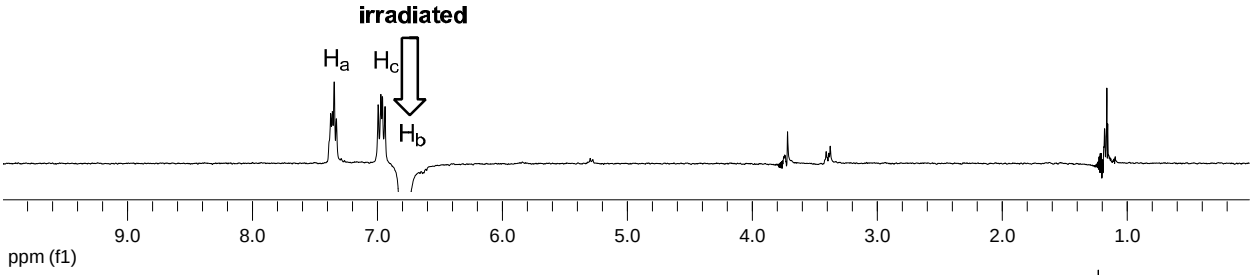
MeO2C
CO2Me
MeO
Si(i-Pr)3

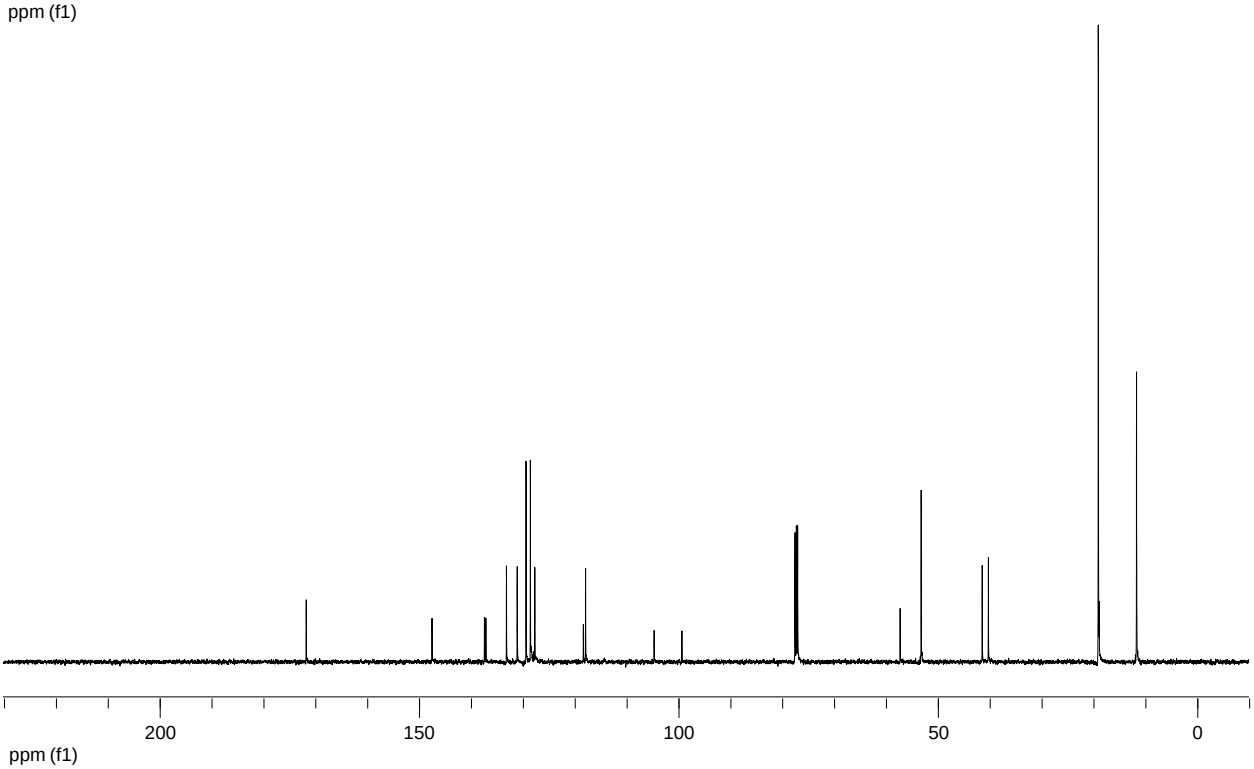
2-58g


9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)


200
150
100
50
0
ppm (f1)

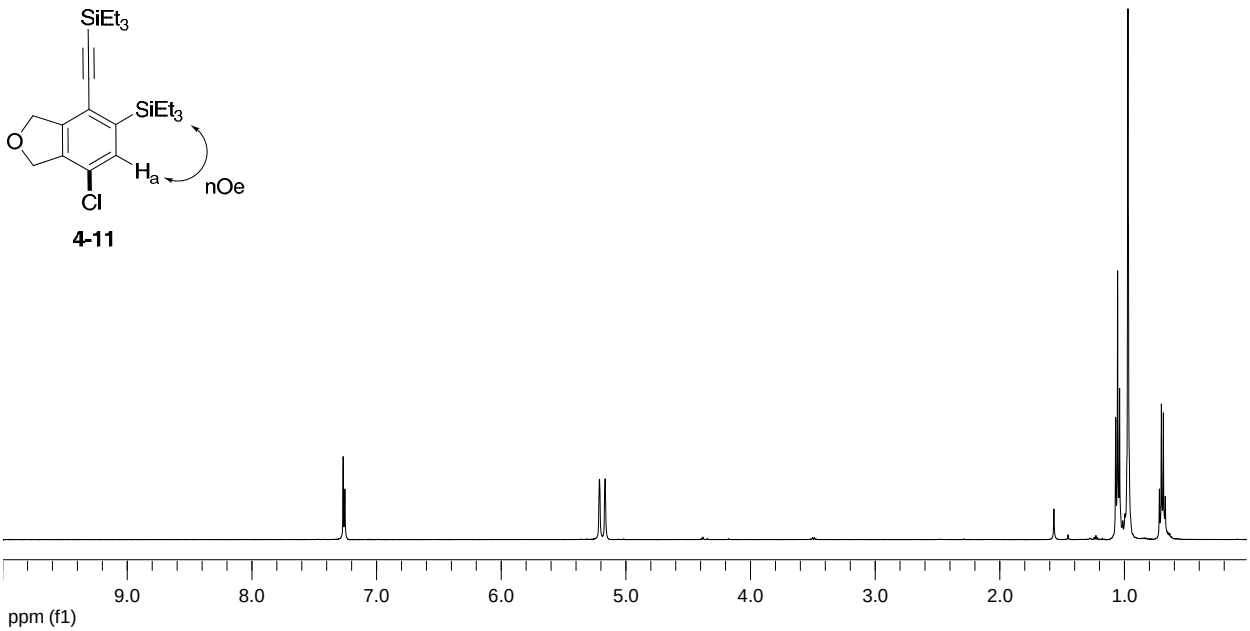

MeO2C
CO2Me
Si-Pr3
Hb
Ha
nOe
Hc
2-58h
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

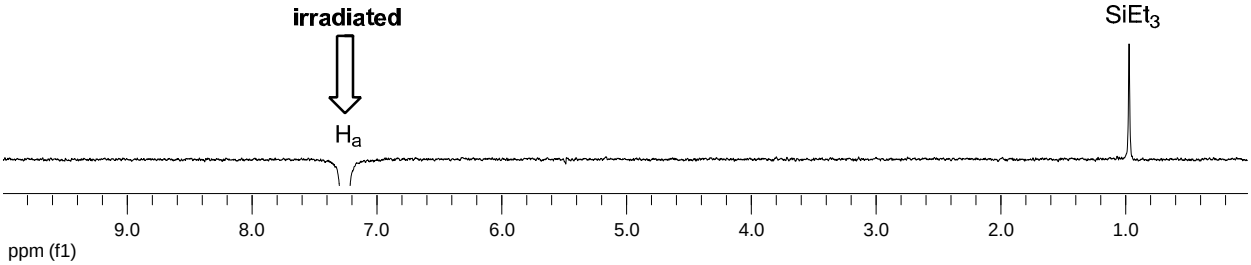

irradiated
Ha
Hc
Hb
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

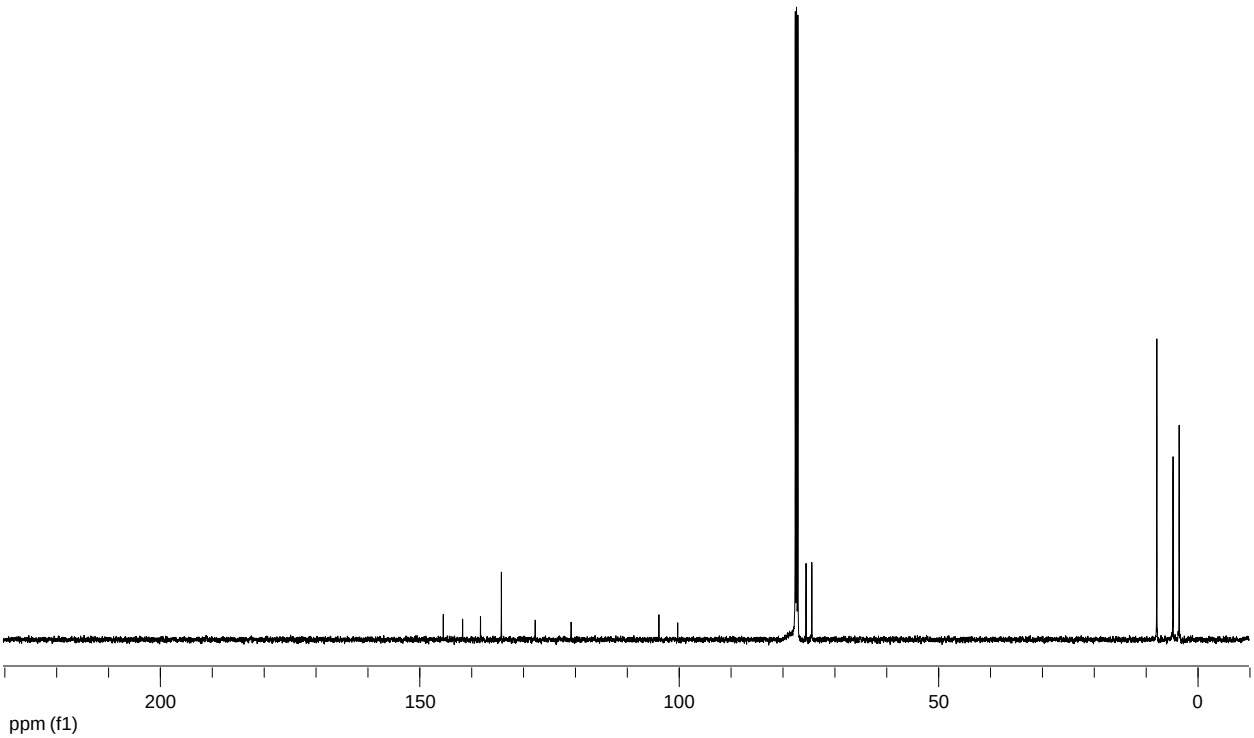

200
150
100
50
0
ppm (f1)

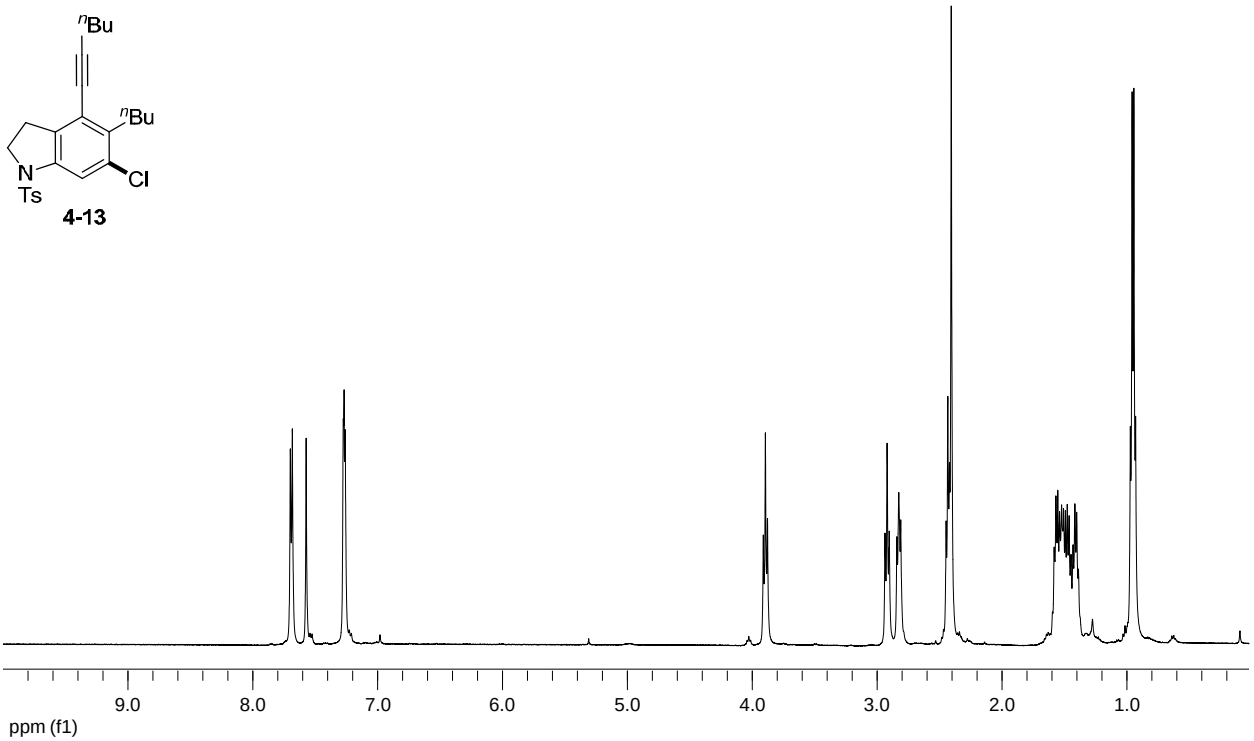
SiEt3
SiEt3
O
Ha
nOe
Cl

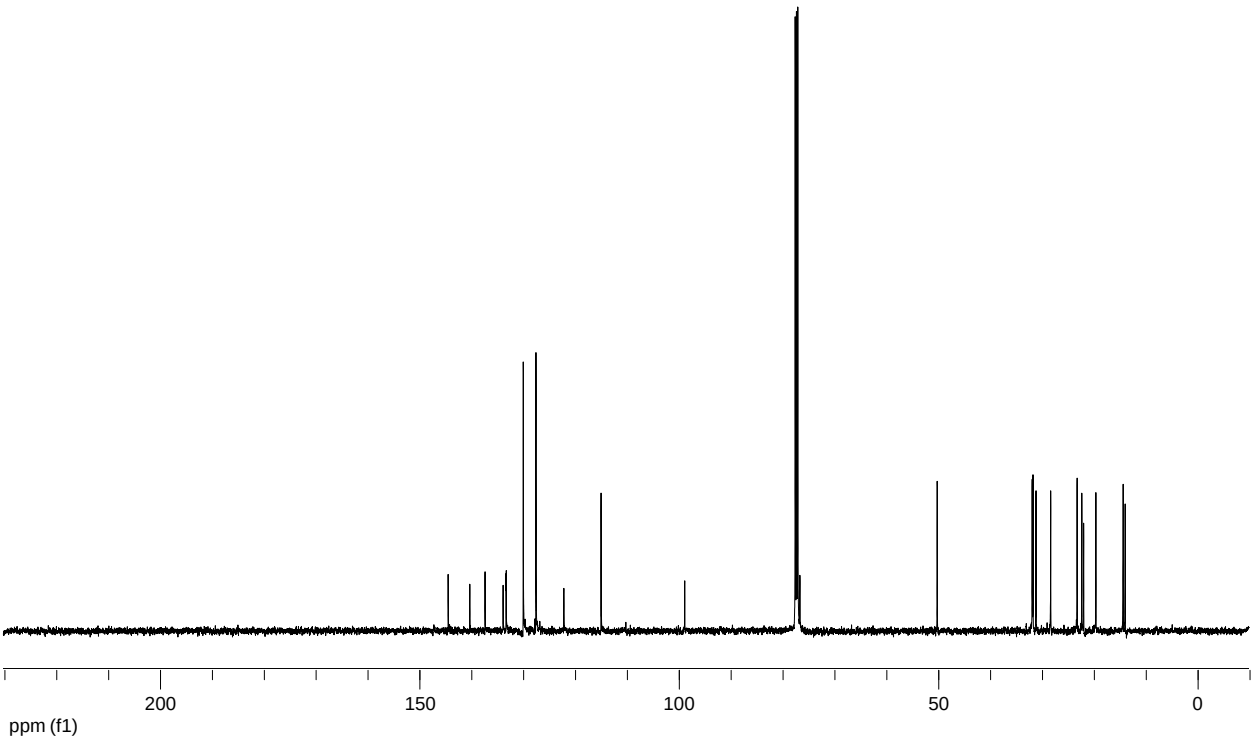
4-11

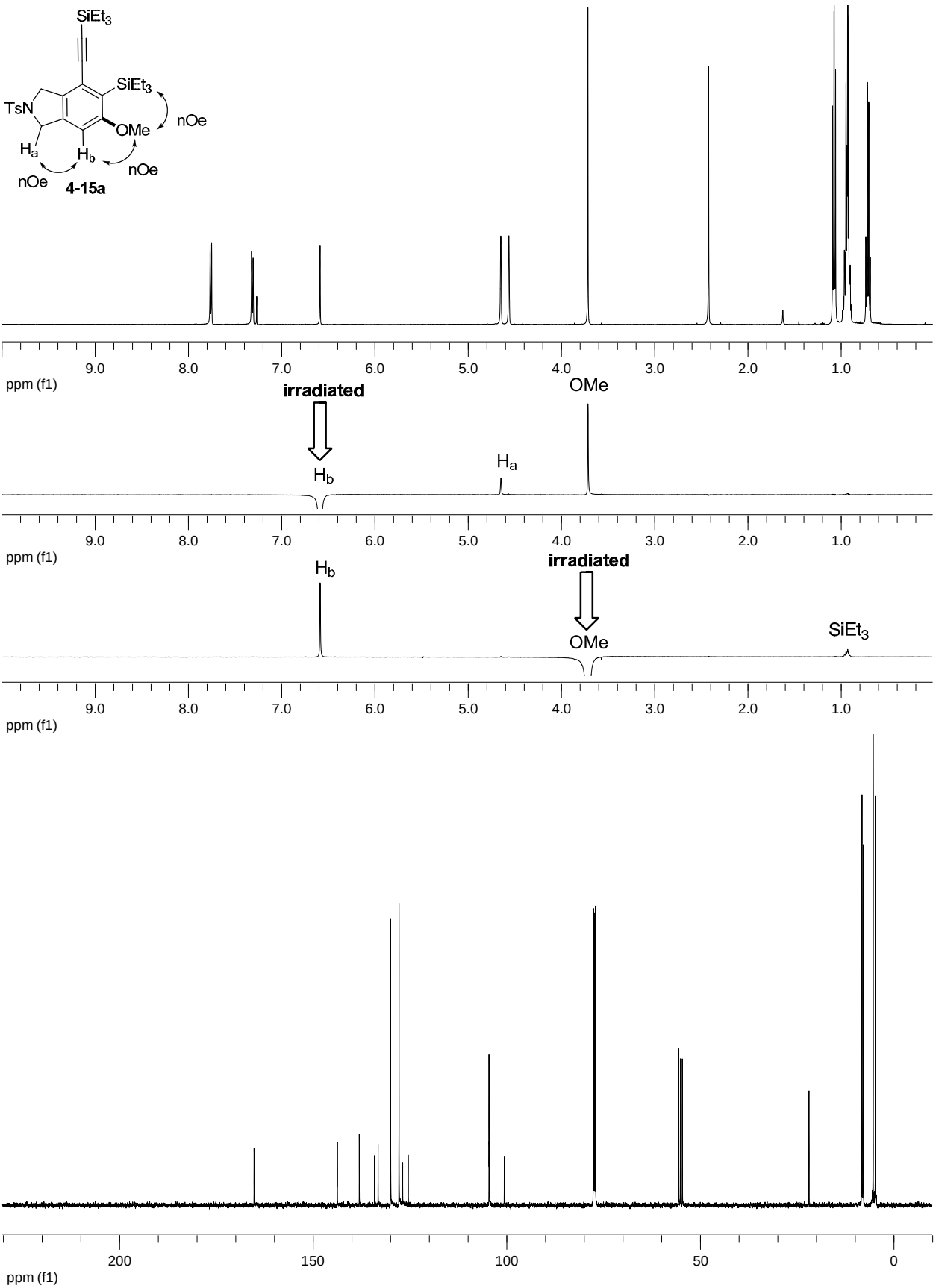

9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

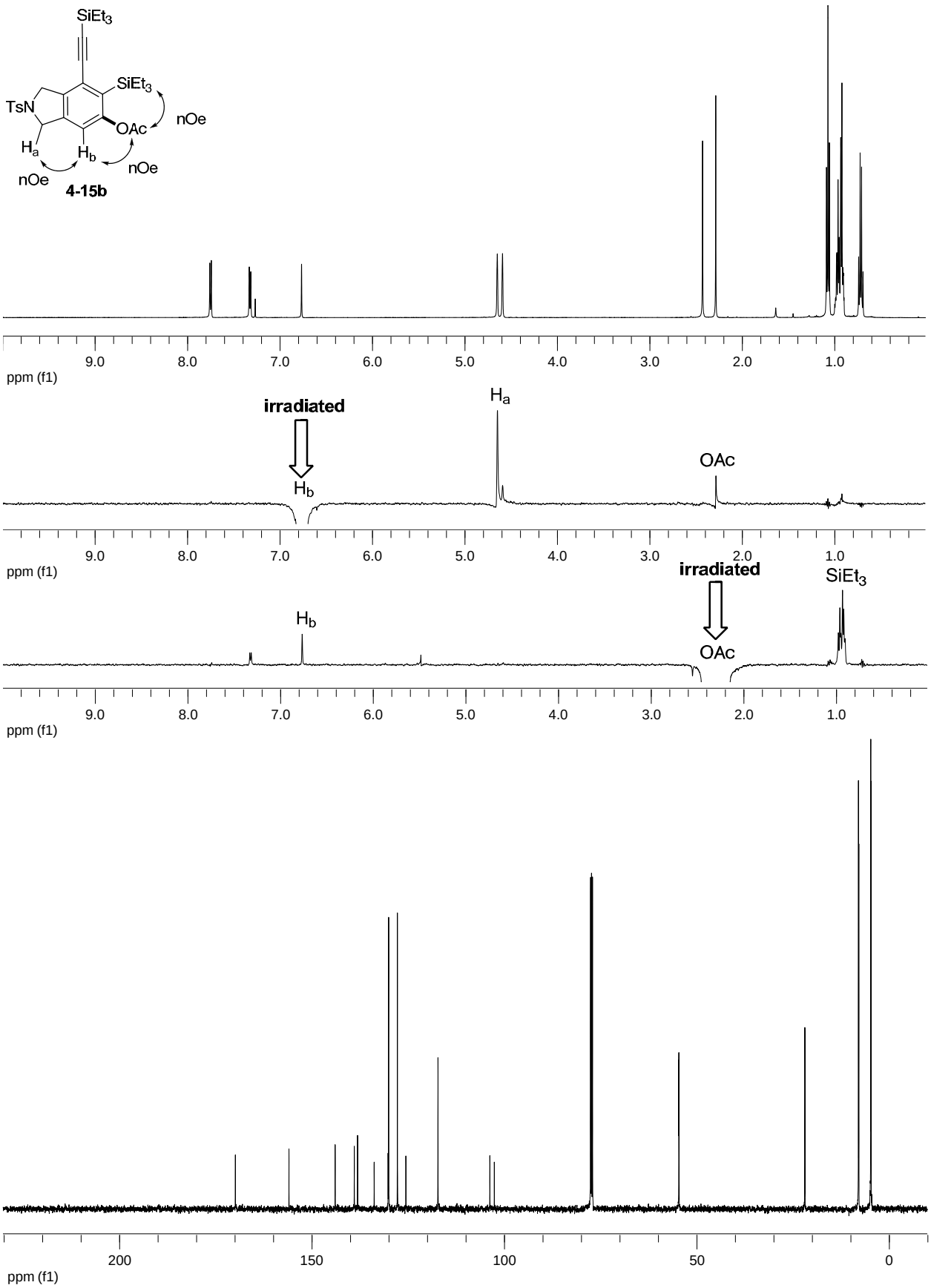

irradiated
Ha
SiEt3
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

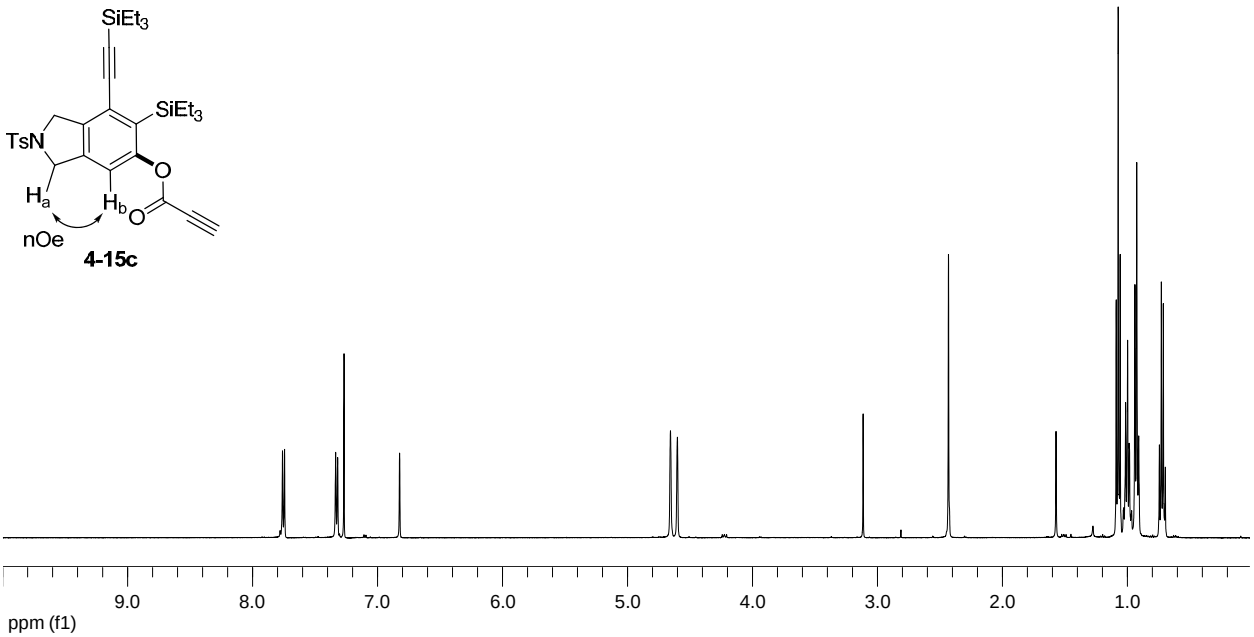

200
150
100
50
0
ppm (f1)

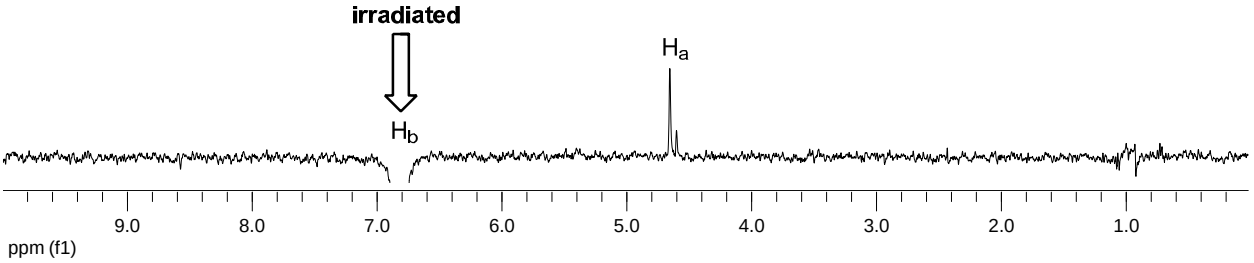

nBu
nBu
N
Ts
Cl
4-13
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

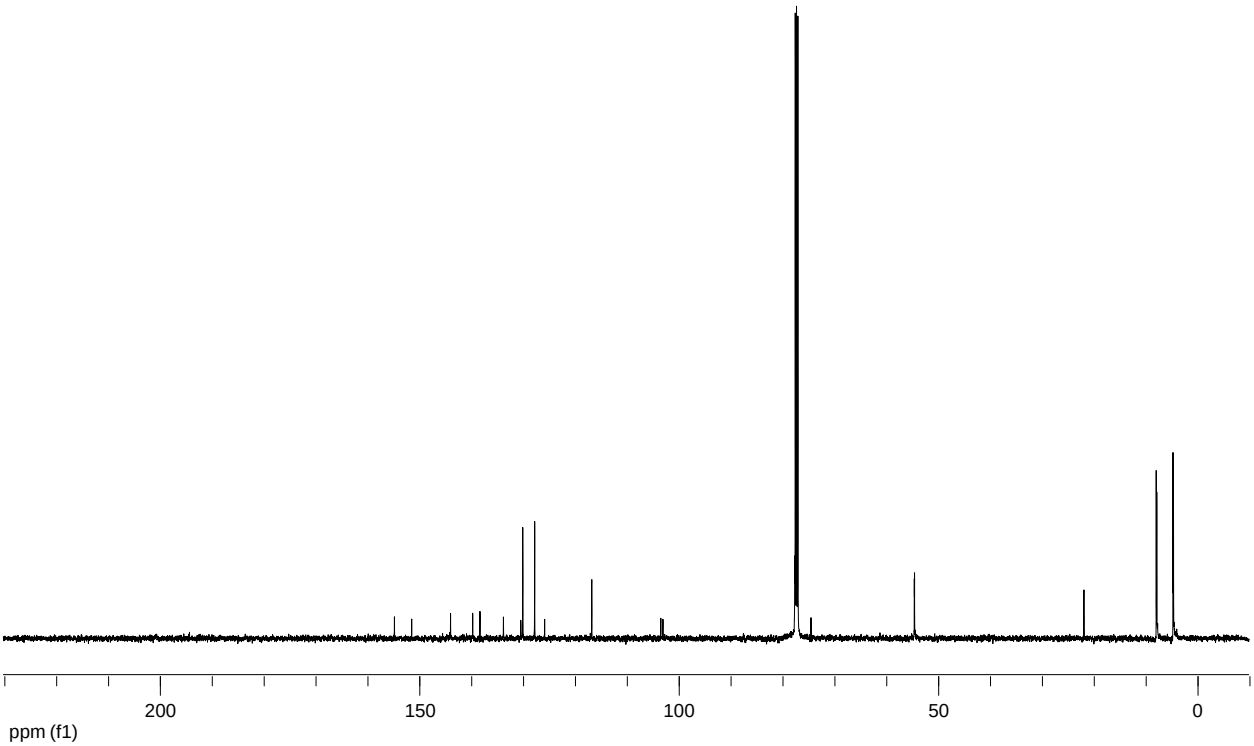

200
150
100
50
0
ppm (f1)

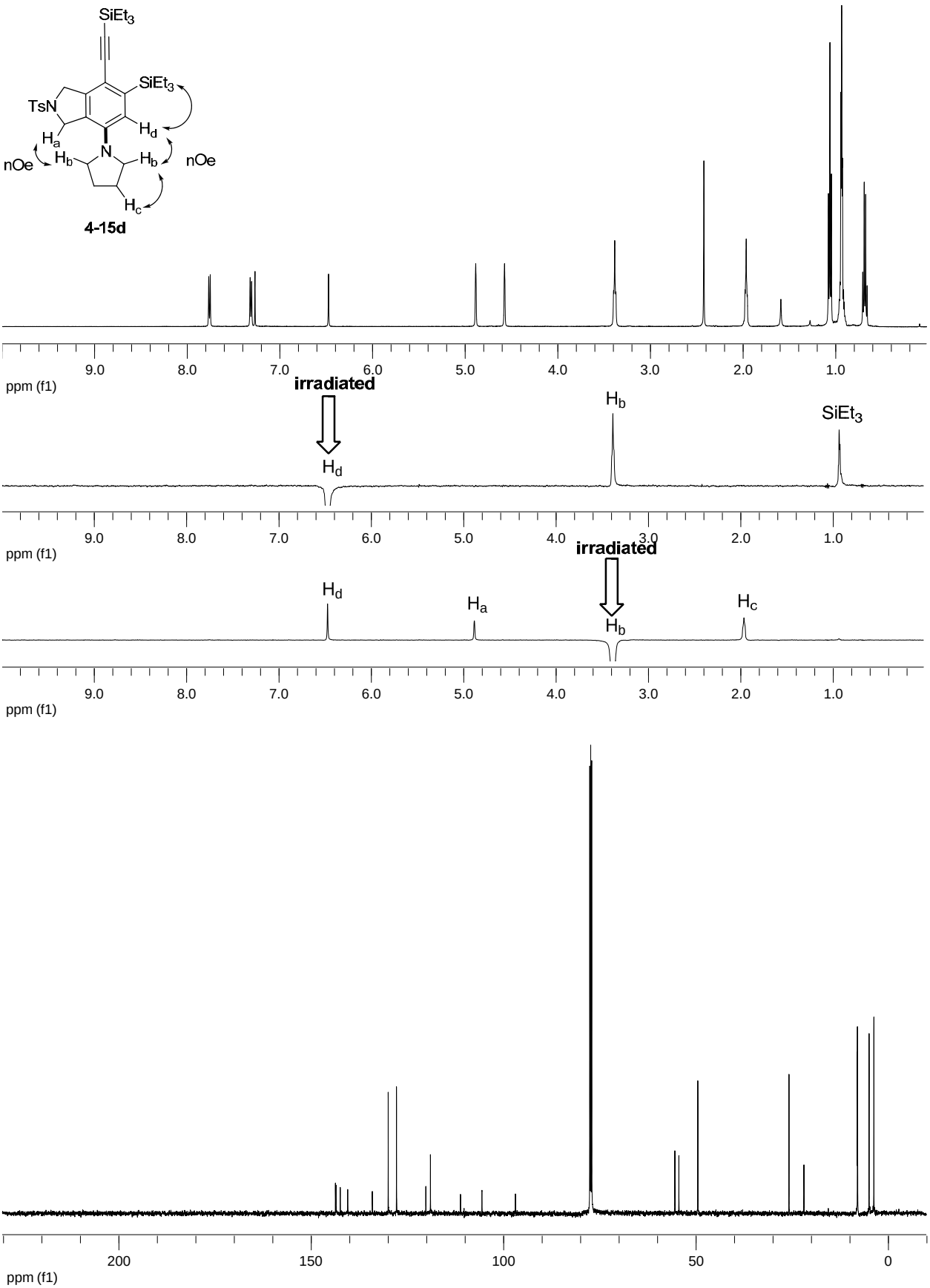

SiEt3
SiEt3
TsN
OMe
nOe
Ha
Hb
nOe
nOe
4-15a
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)
irradiated
OMe
Hb
Ha
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)
Hb
irradiated
OMe
SiEt3
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)
200
150
100
50
0
ppm (f1)

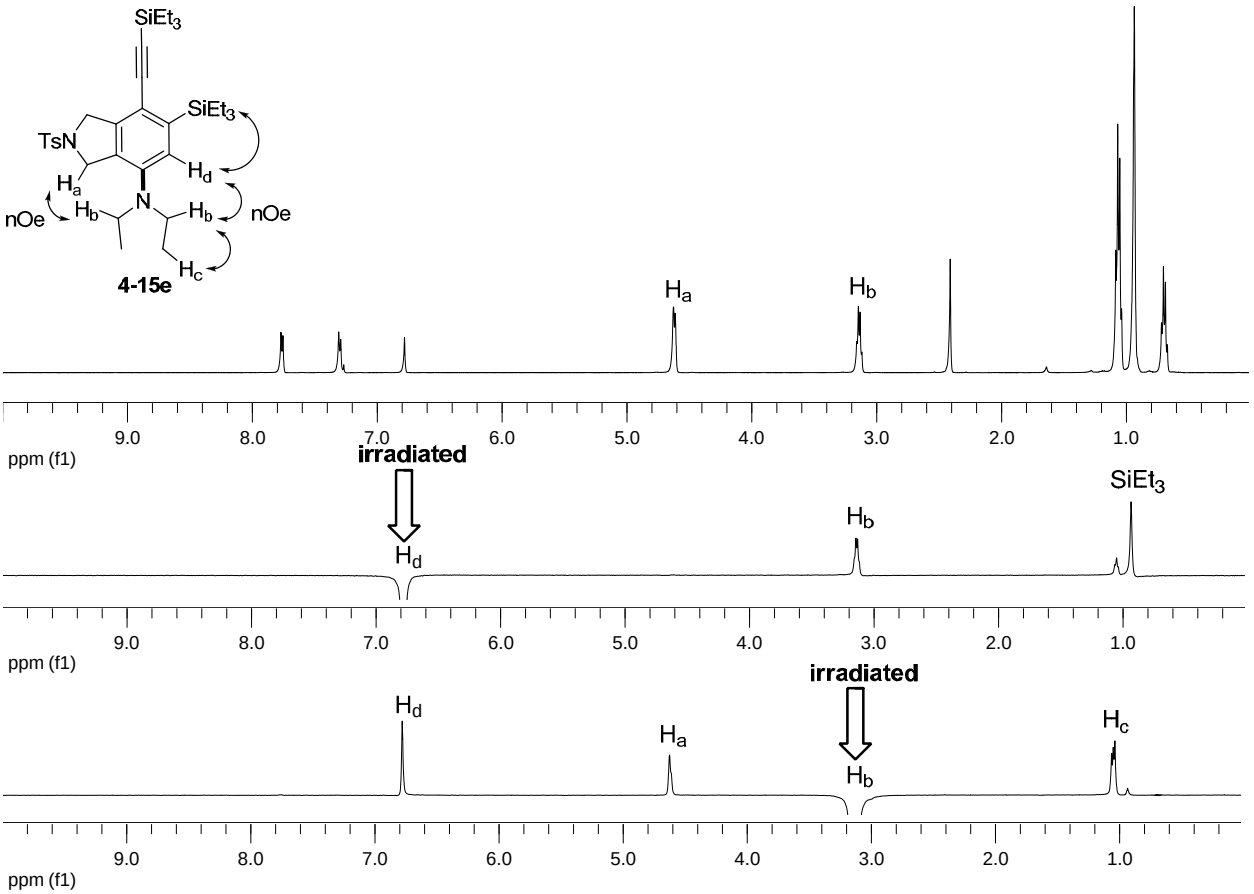

SiEt3
SiEt3
TsN
OAc
nOe
Ha
Hb
nOe
nOe
4-15b
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)
irradiated
Hb
Ha
OAc
irradiated
OAc
SiEt3
Hb
200
150
100
50
0

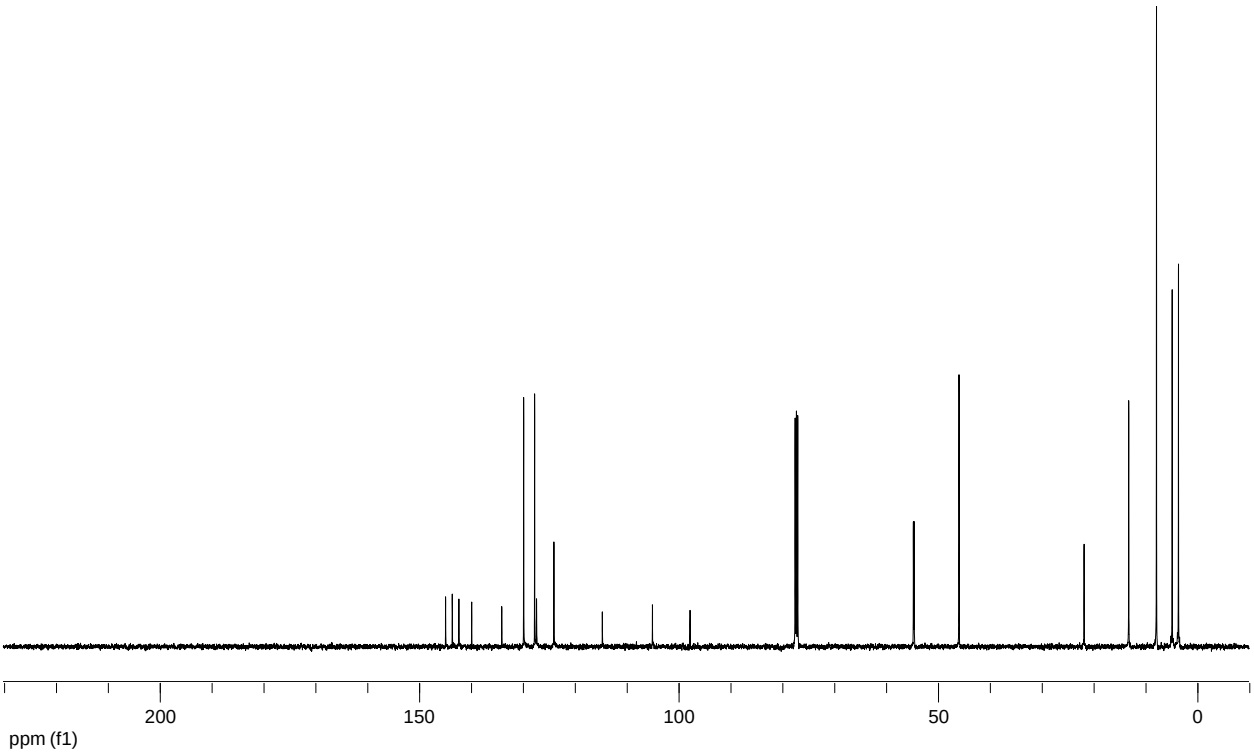

SiEt3
SiEt3
TsN
O
Ha
Hb
O
nOe
4-15c
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

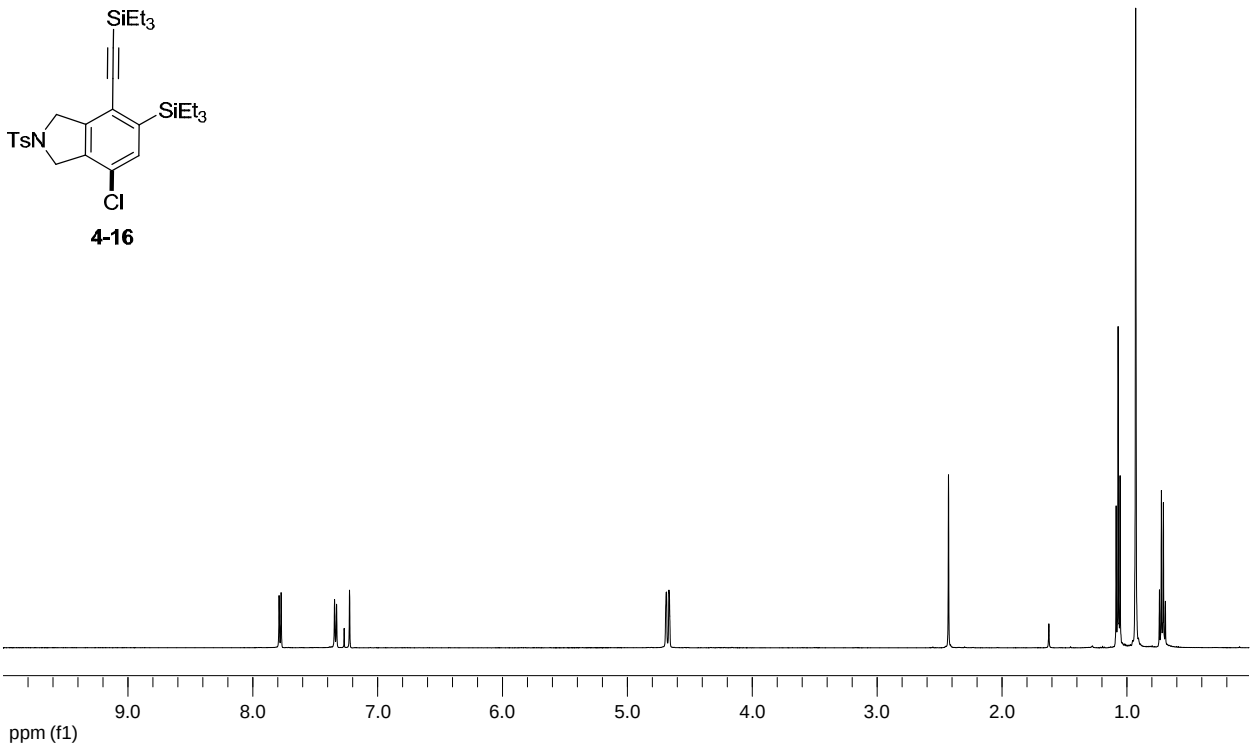

irradiated
Ha
Hb
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

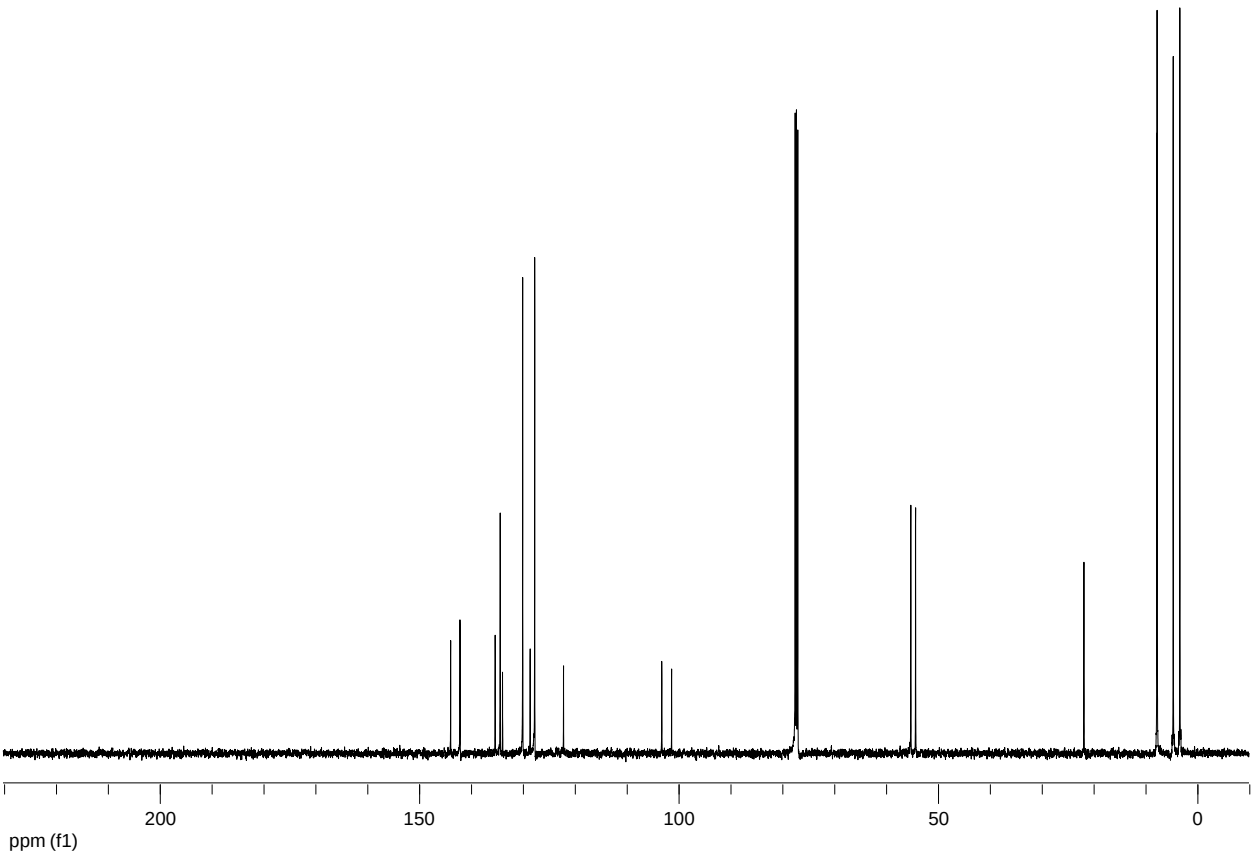

200
150
100
50
0
ppm (f1)


SiEt3
SiEt3
TsN
Ha
Hd
N
Hb
Hb
nOe
nOe
Hc
4-15d
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)
irradiated
Hd
Hb
SiEt3
irradiated
Hd
Ha
Hb
Hc
200
150
100
50
0

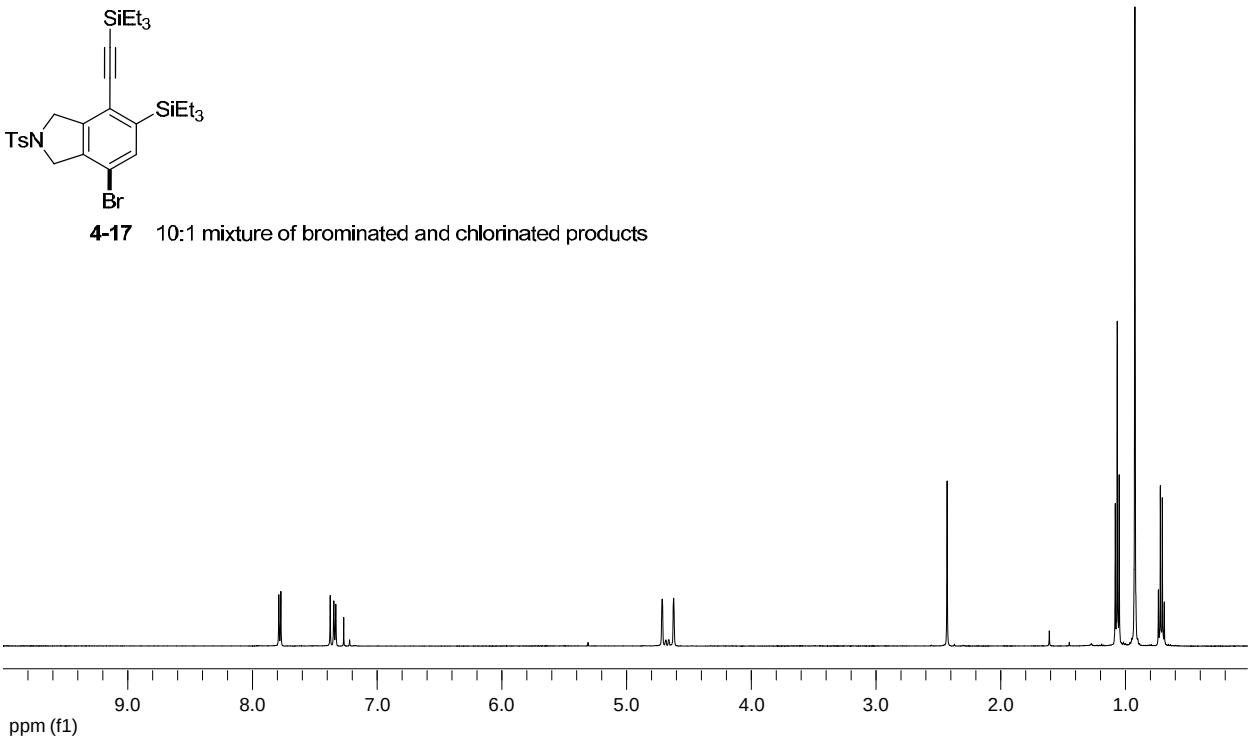

SiEt3
SiEt3
TsN
Ha
Hd
N
Hb
Hb
nOe
nOe
Hc
4-15e
Ha
Hb
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)
irradiated
Hd
Hb
SiEt3
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)
irradiated
Hd
Ha
Hb
Hc
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

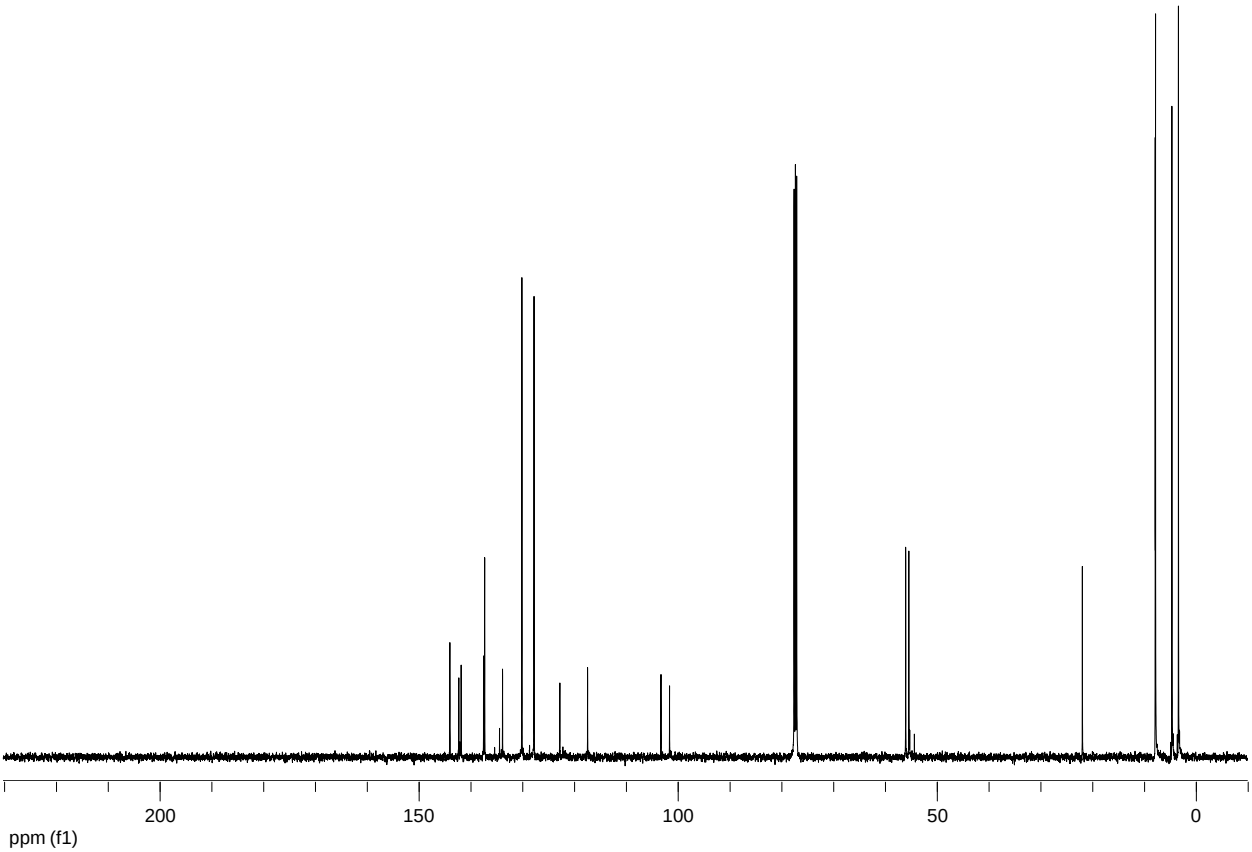

200
150
100
50
0
ppm (f1)

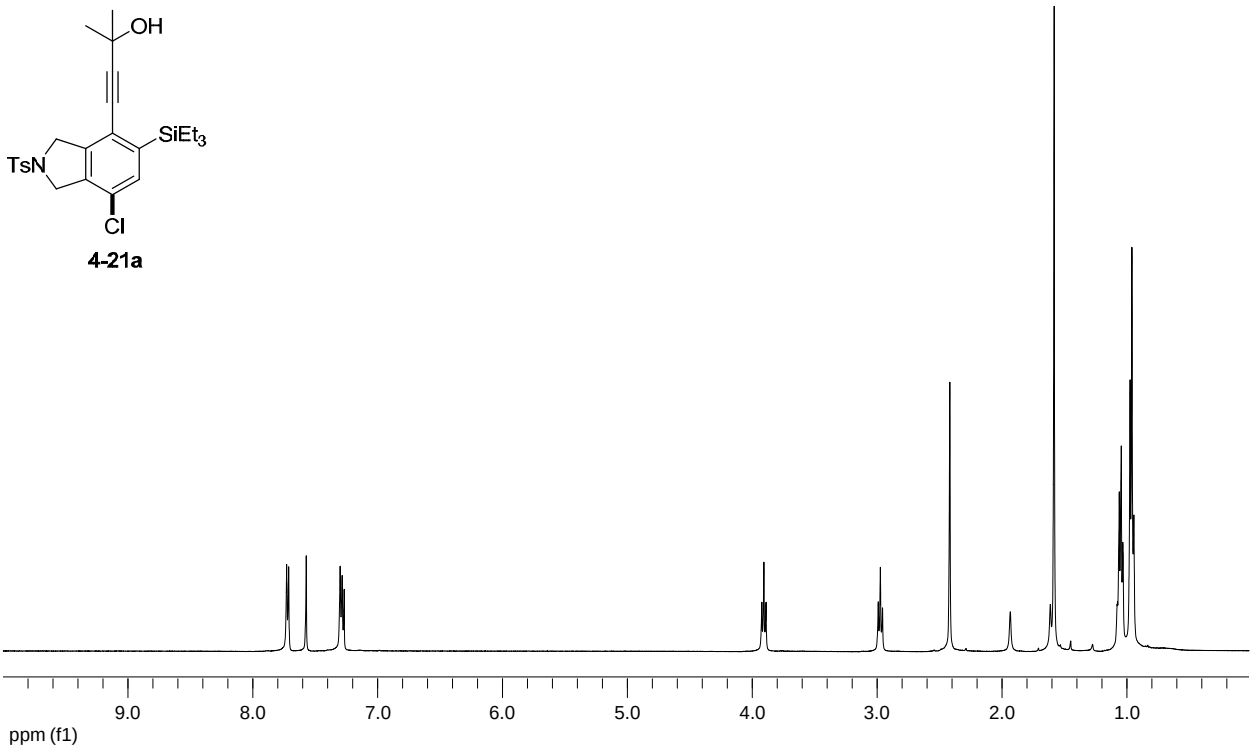

SiEt3
SiEt3
TsN
Cl
4-16
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

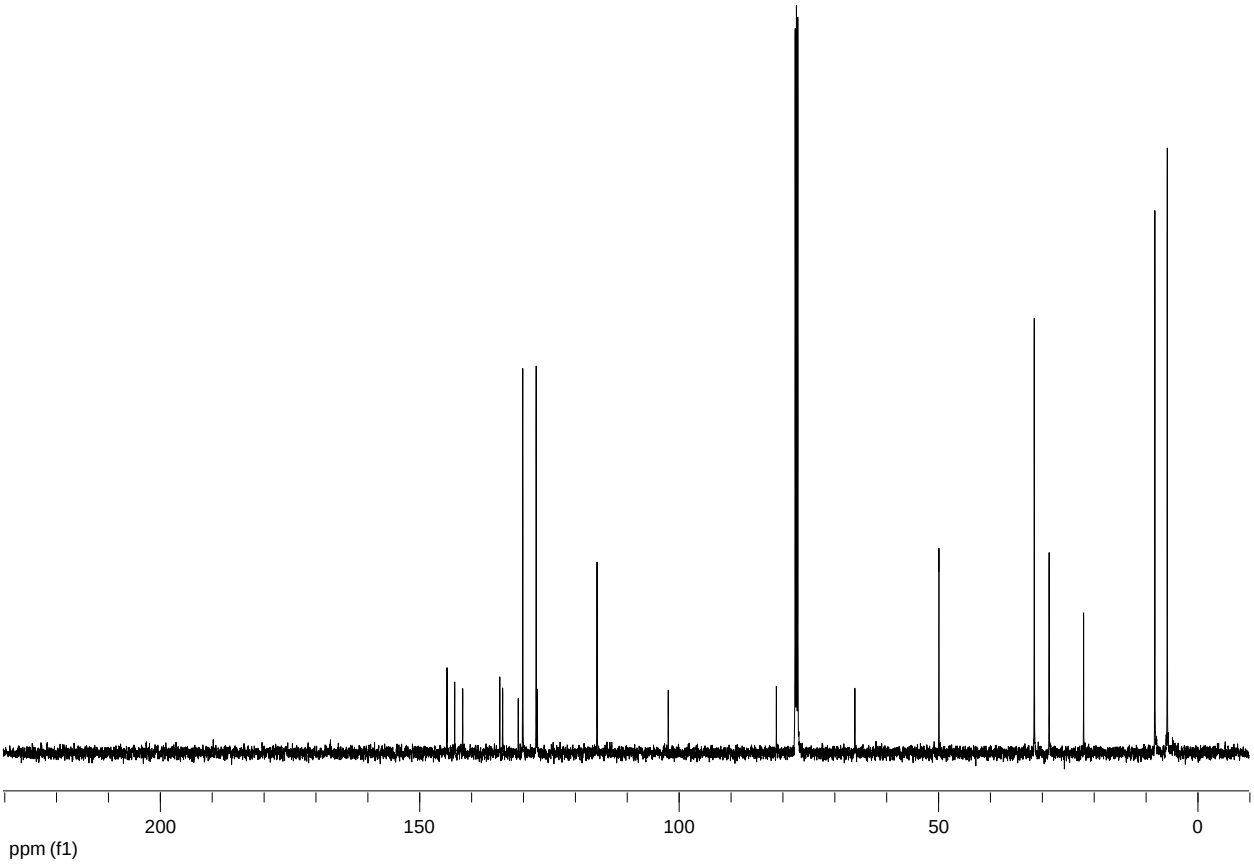

200
150
100
50
0
ppm (f1)

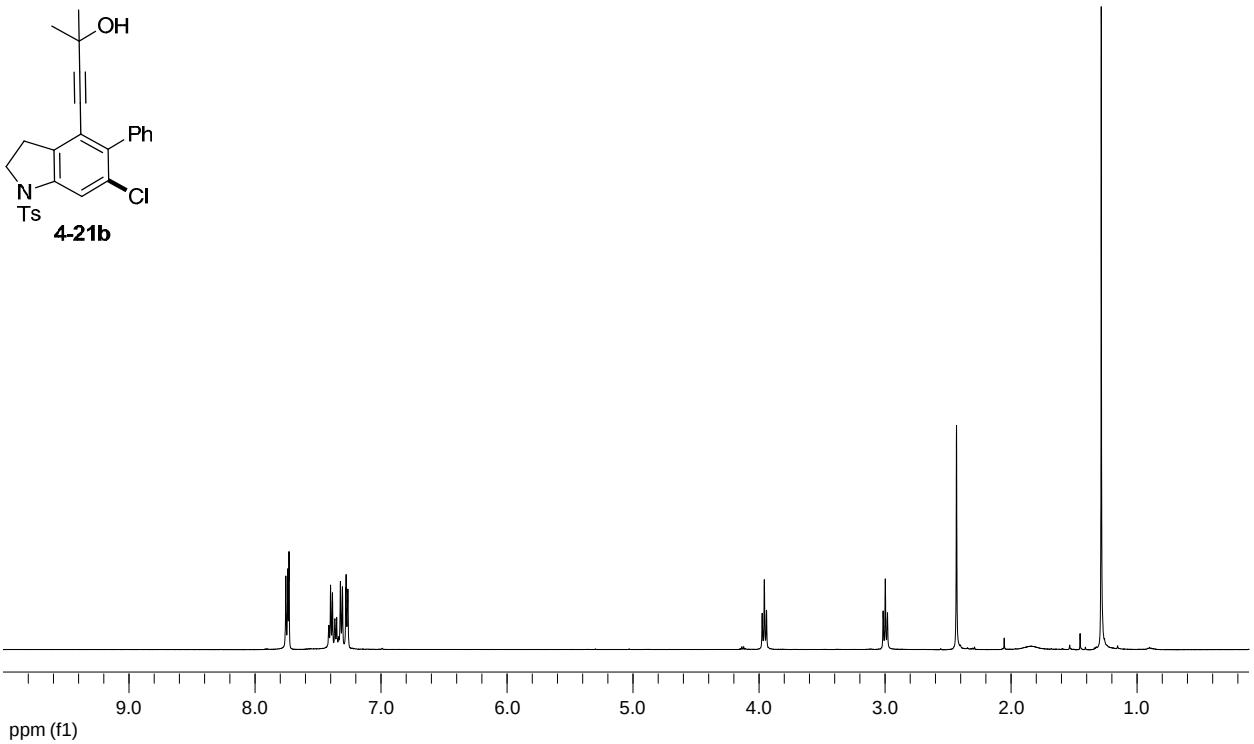
4-17 10:1 mixture of brominated and chlorinated products

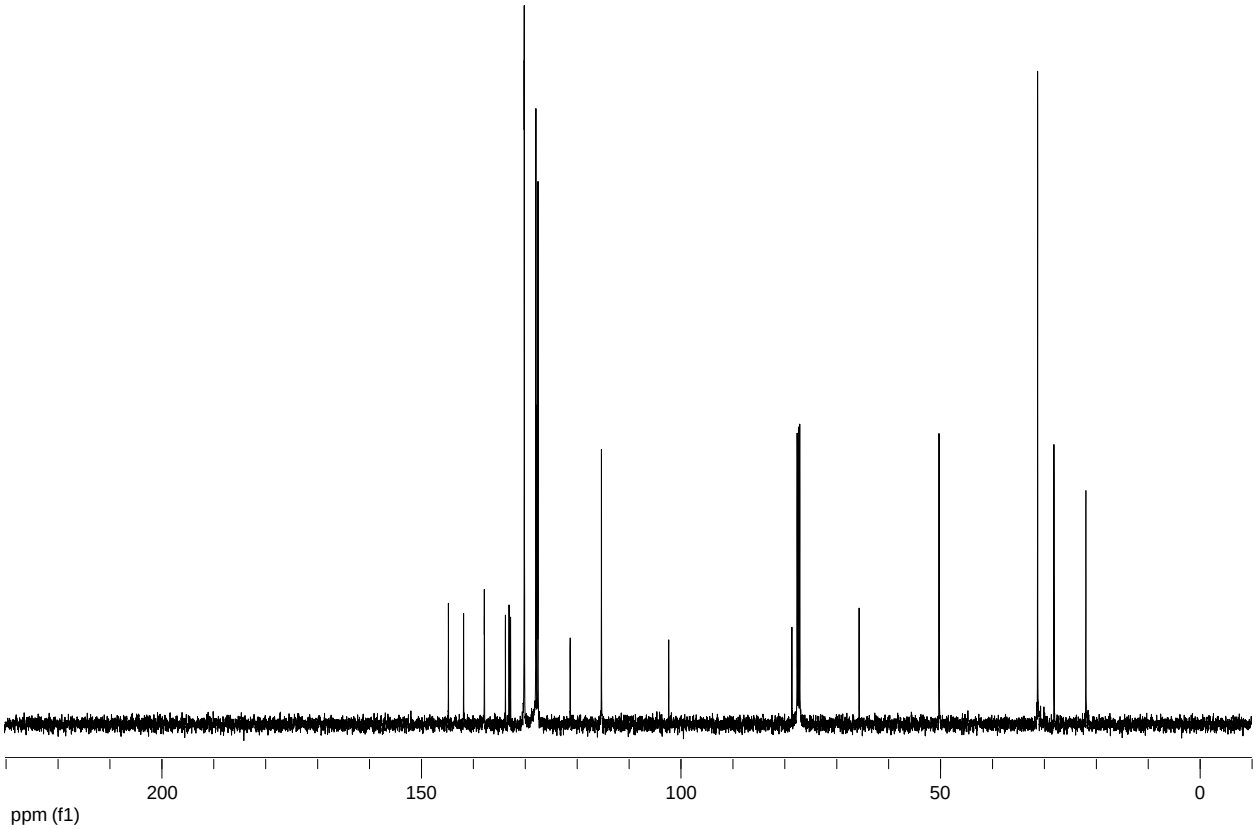


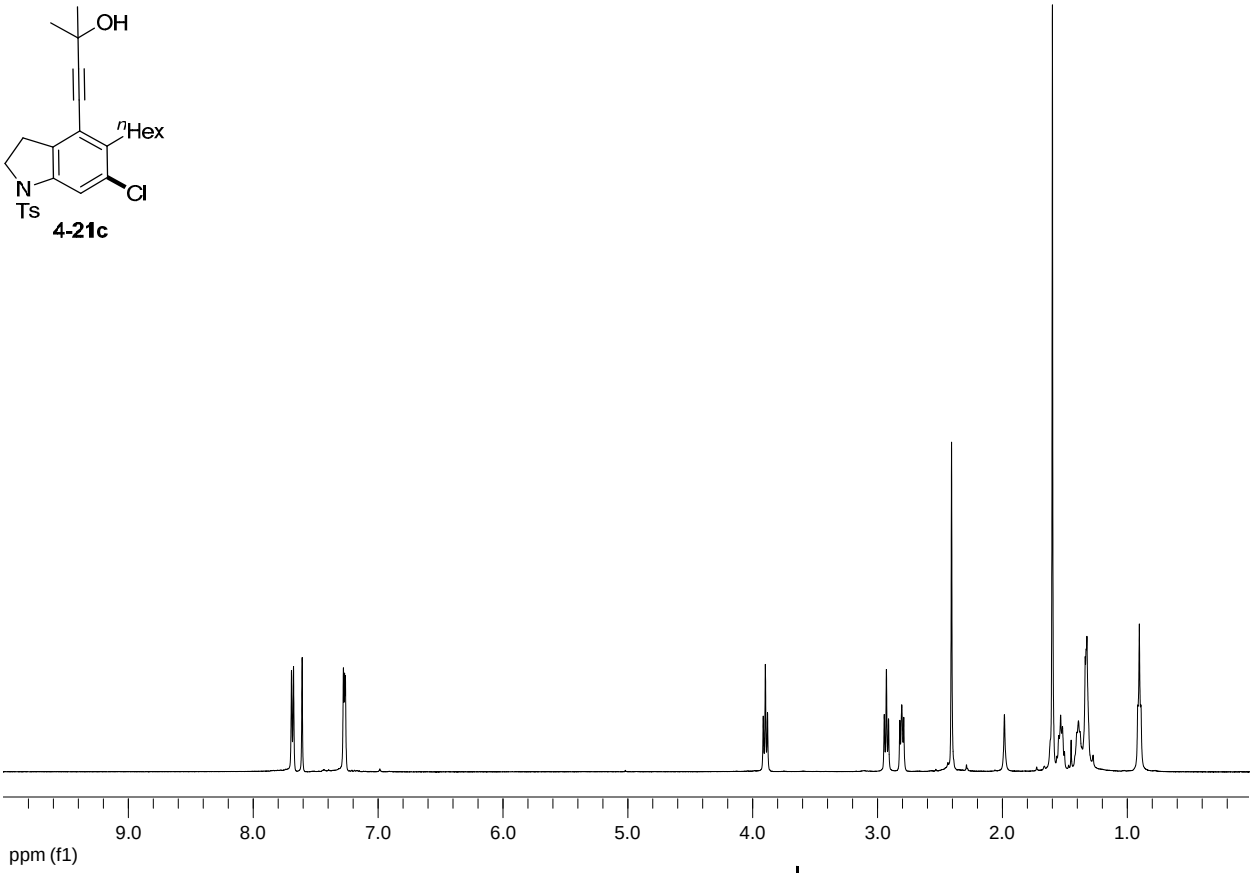


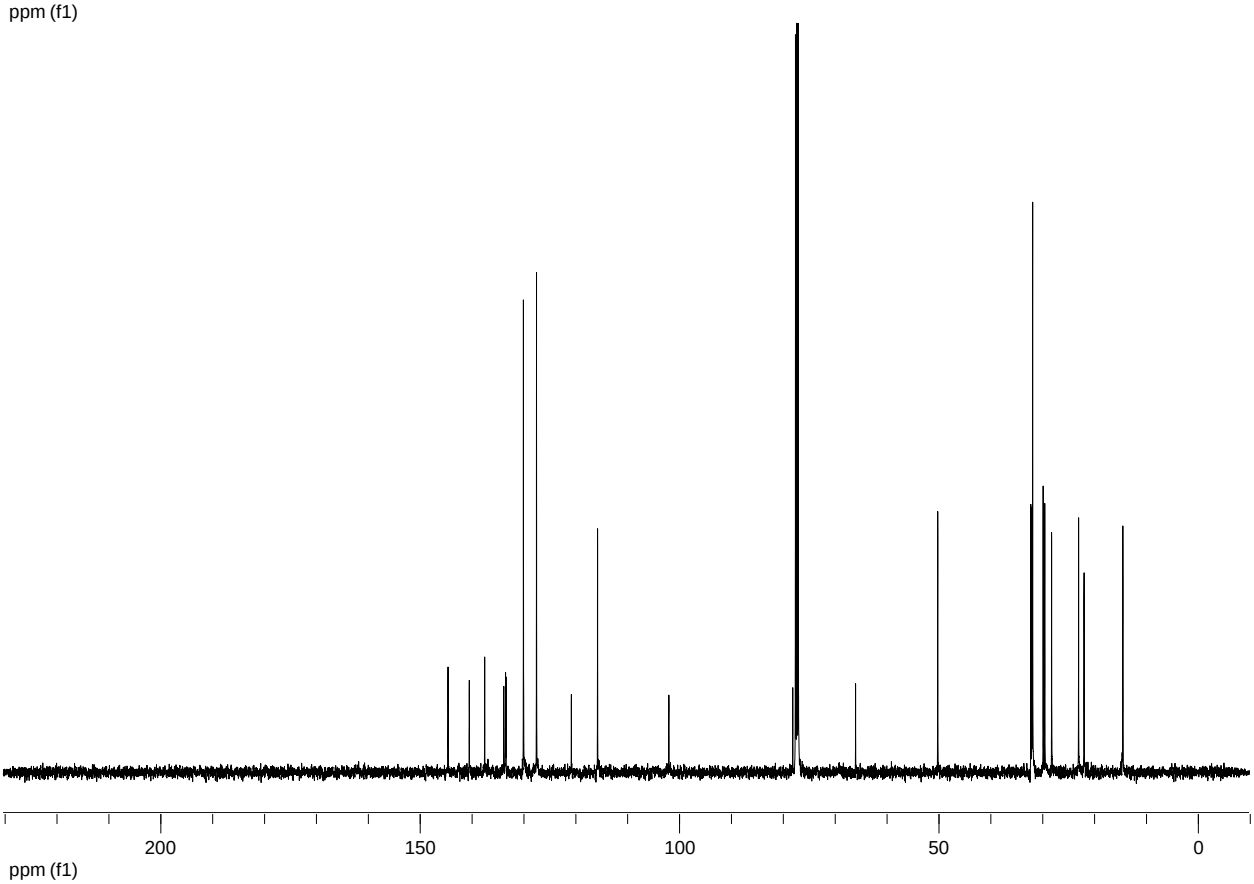

OH
SiEt3
TsN
Cl
4-21a
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

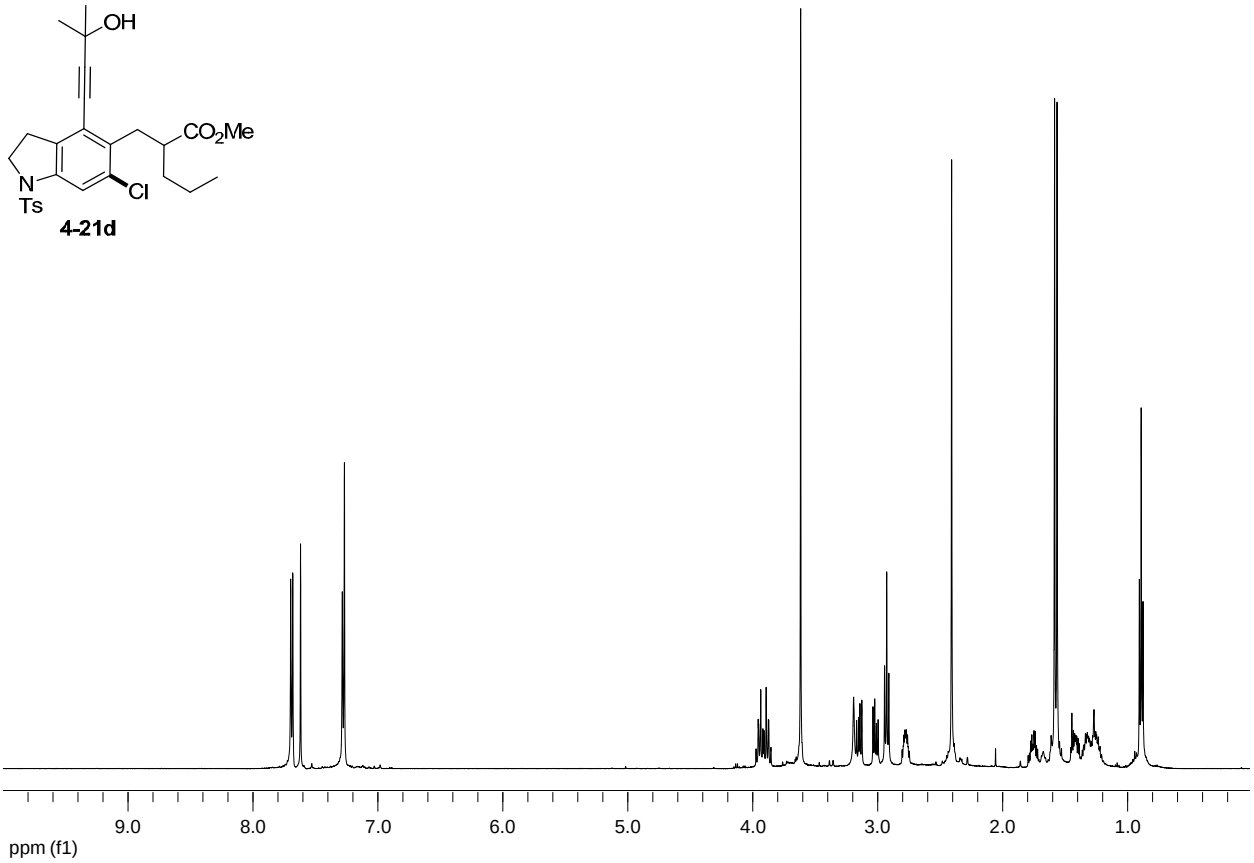

200
150
100
50
0
ppm (f1)

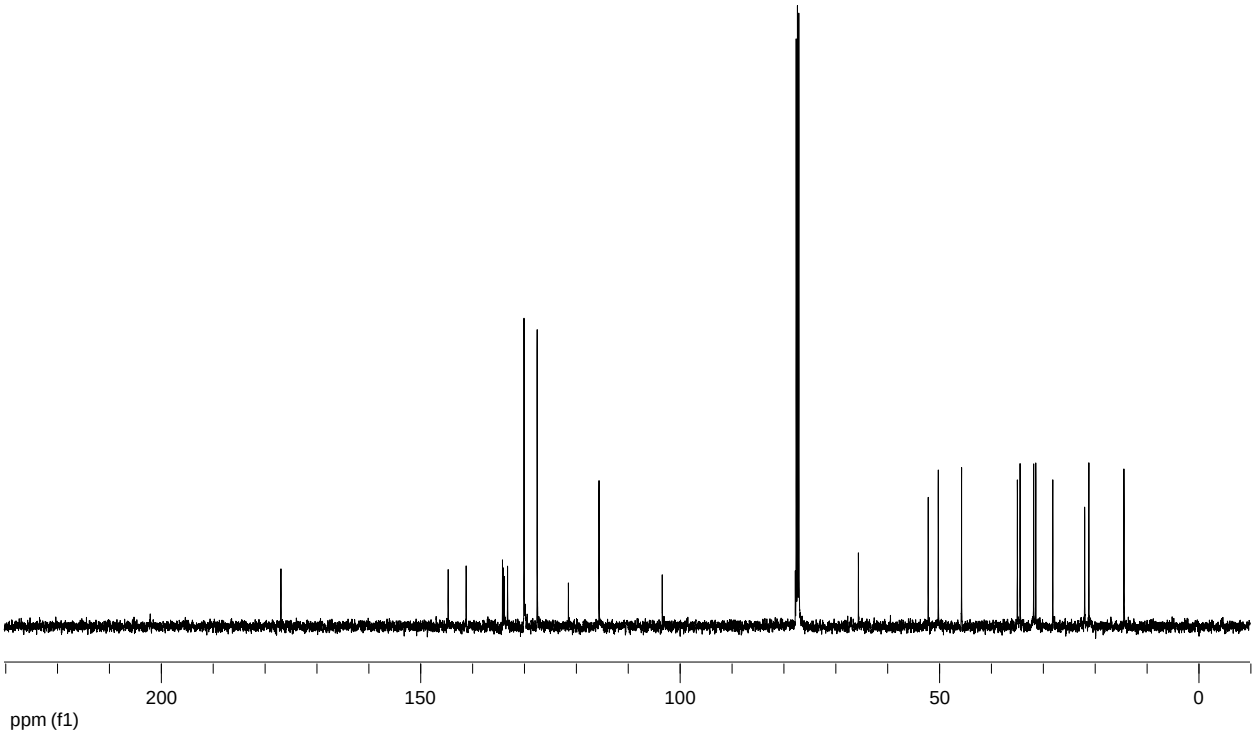

OH
Ph
N
Ts
Cl
4-21b
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

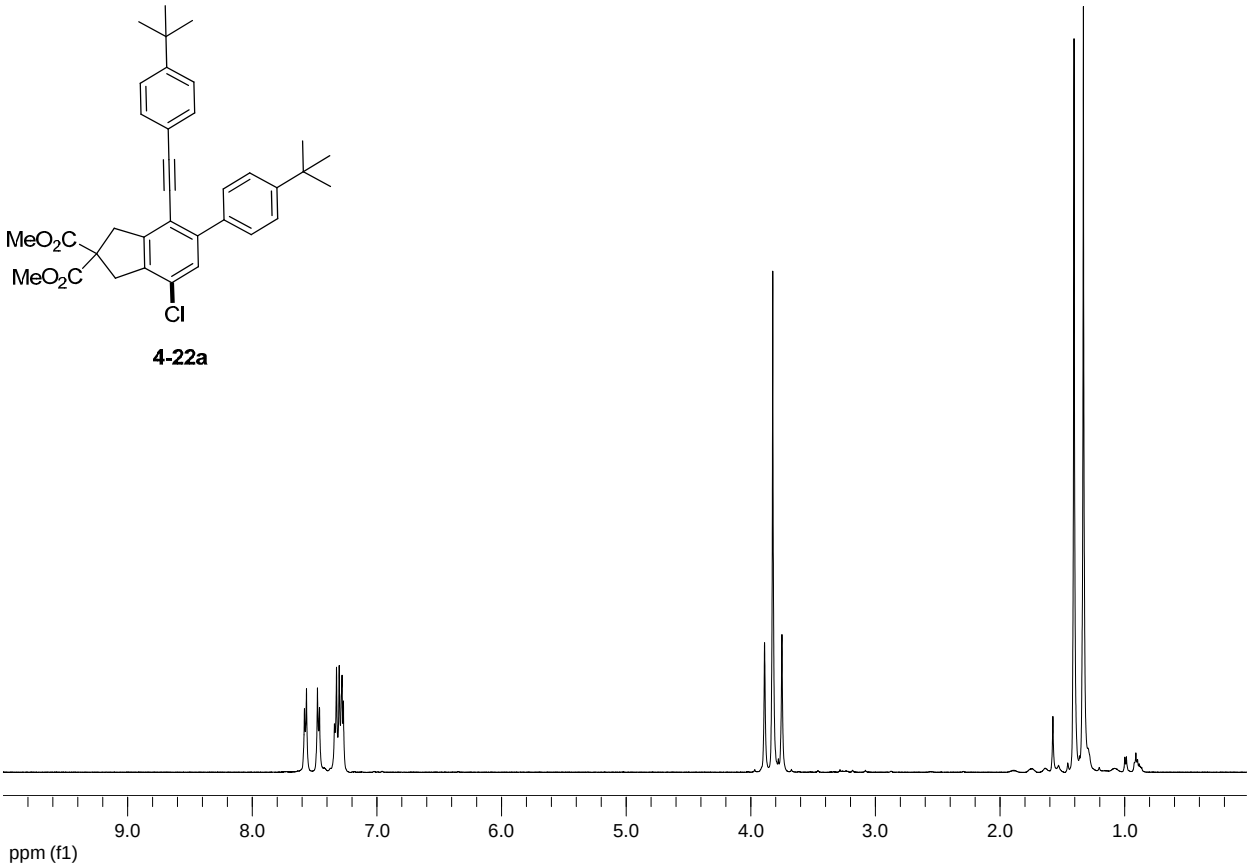

200
150
100
50
0
ppm (f1)

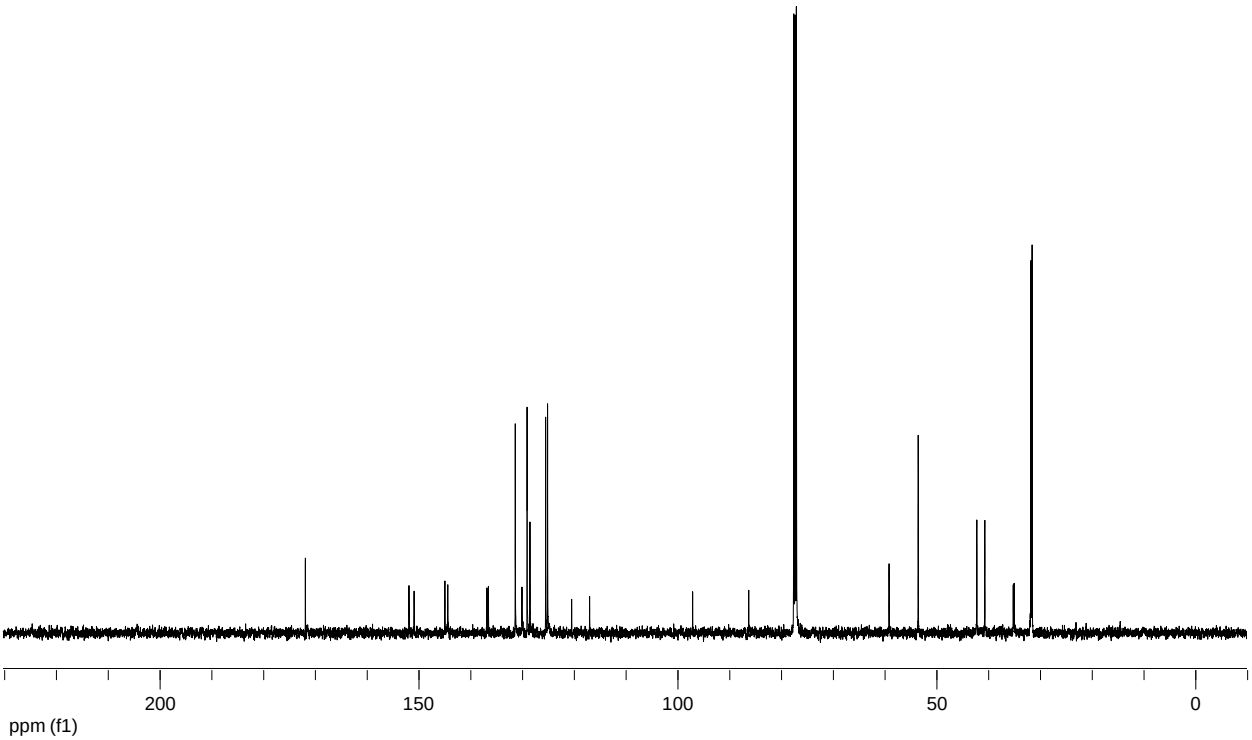

OH
nHex
N
Ts
Cl
4-21c
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

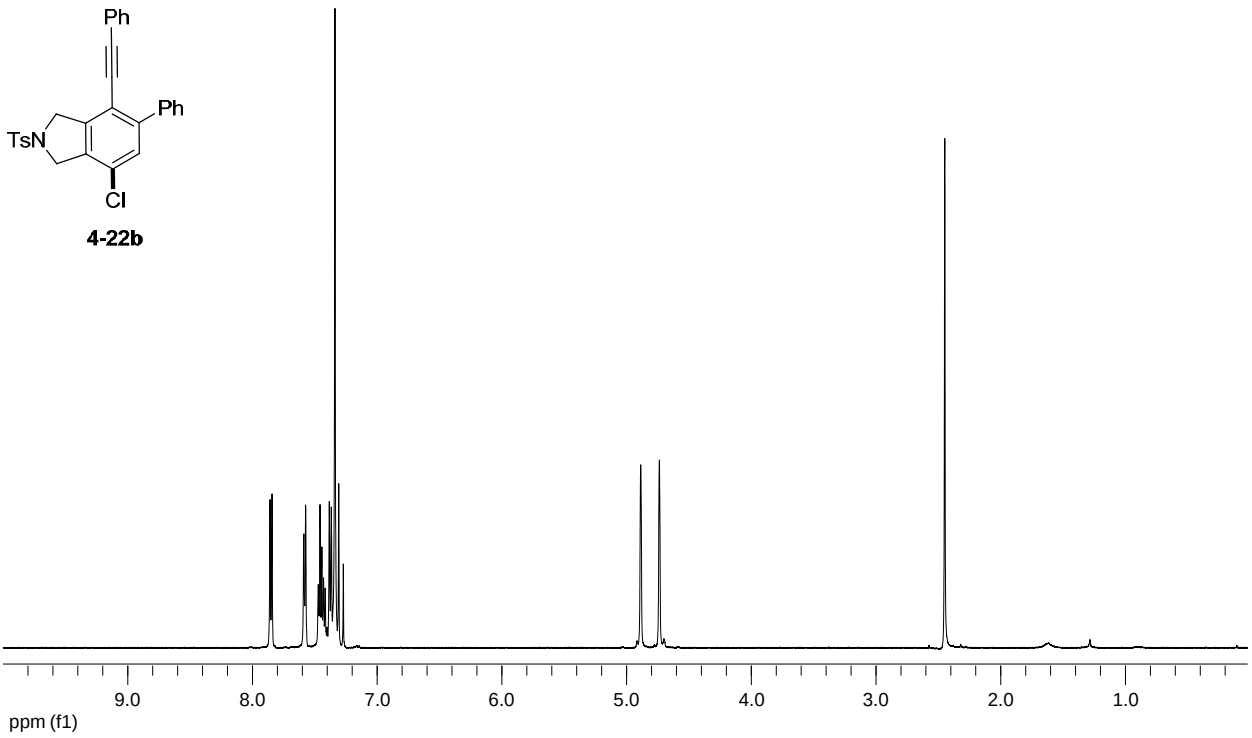

200
150
100
50
0
ppm (f1)

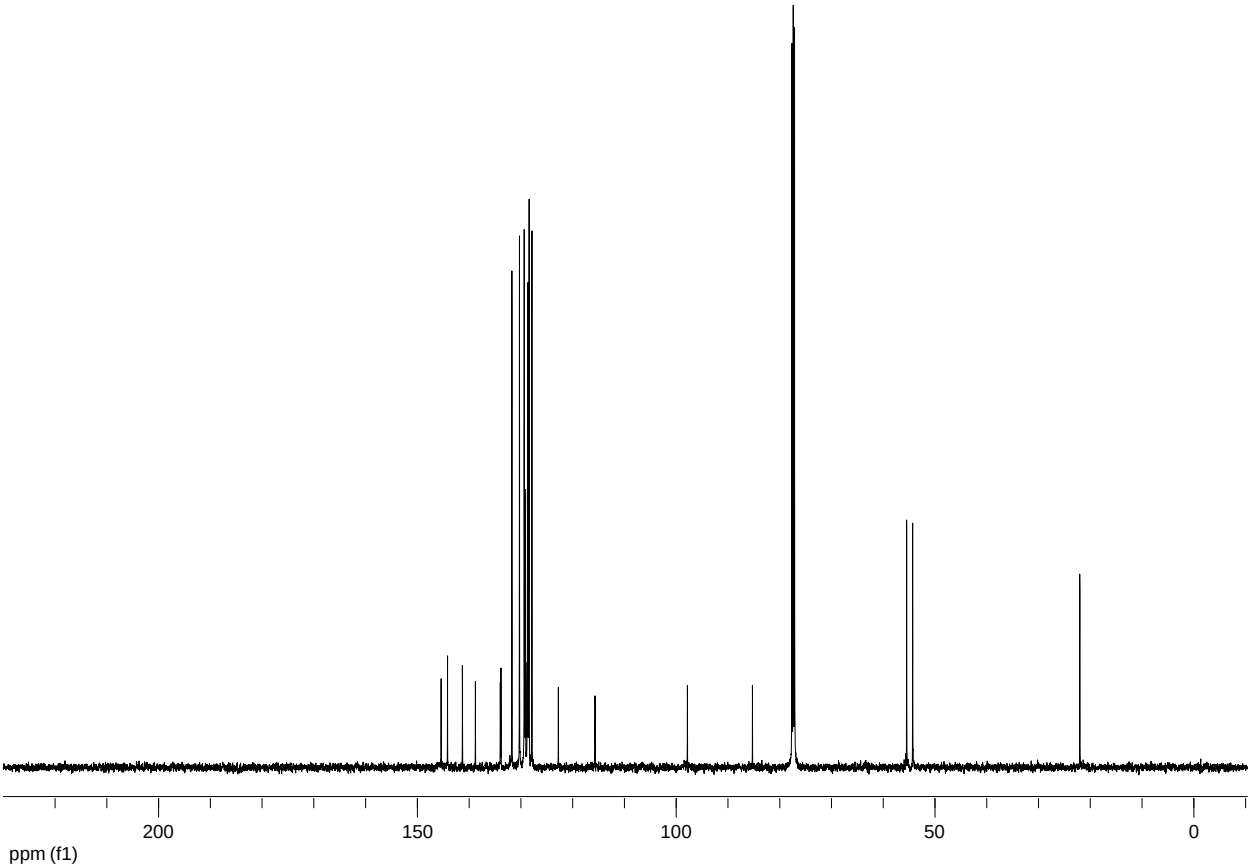

OH
CO2Me
N
Ts
Cl
4-21d
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)


200
150
100
50
0
ppm (f1)


MeO2C
MeO2C
Cl
4-22a
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

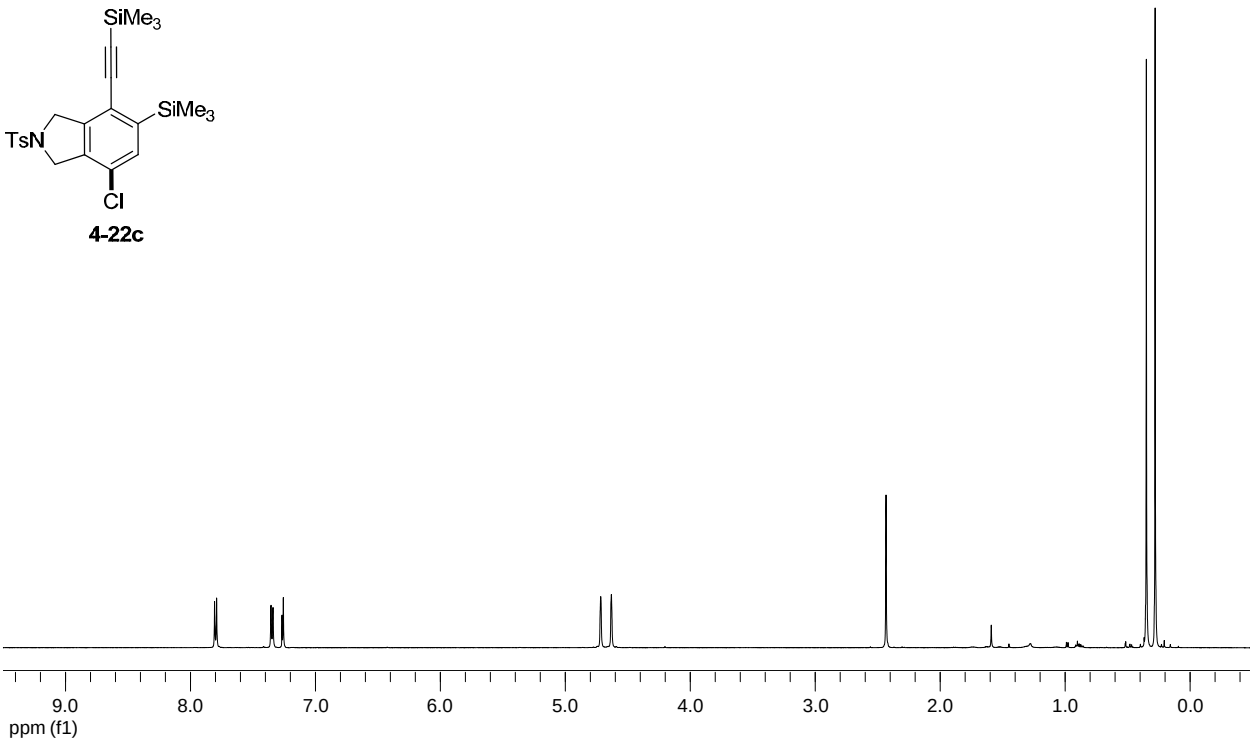

200
150
100
50
0
ppm (f1)

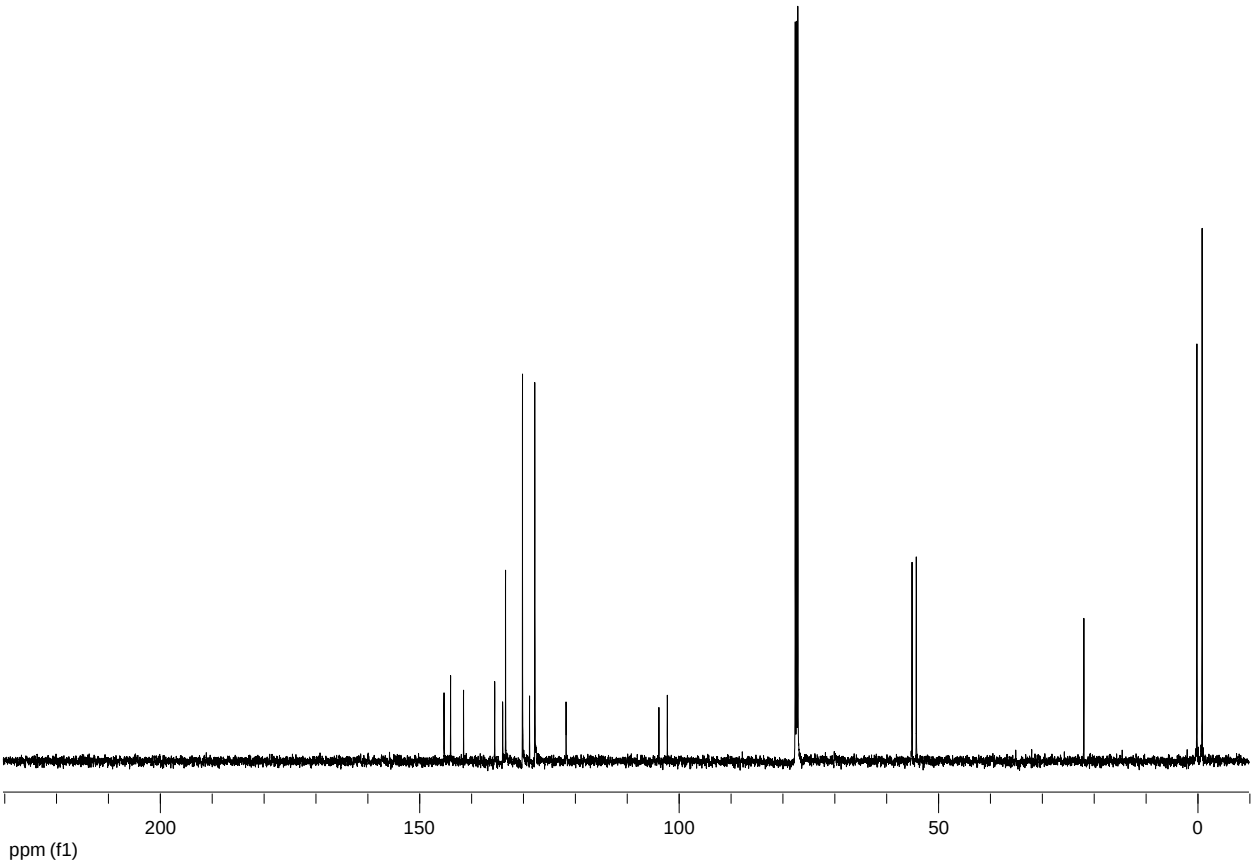

Ph
Ph
TsN
Cl
4-22b
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)


200
150
100
50
0
ppm (f1)

SiMe3
SiMe3
TsN
Cl

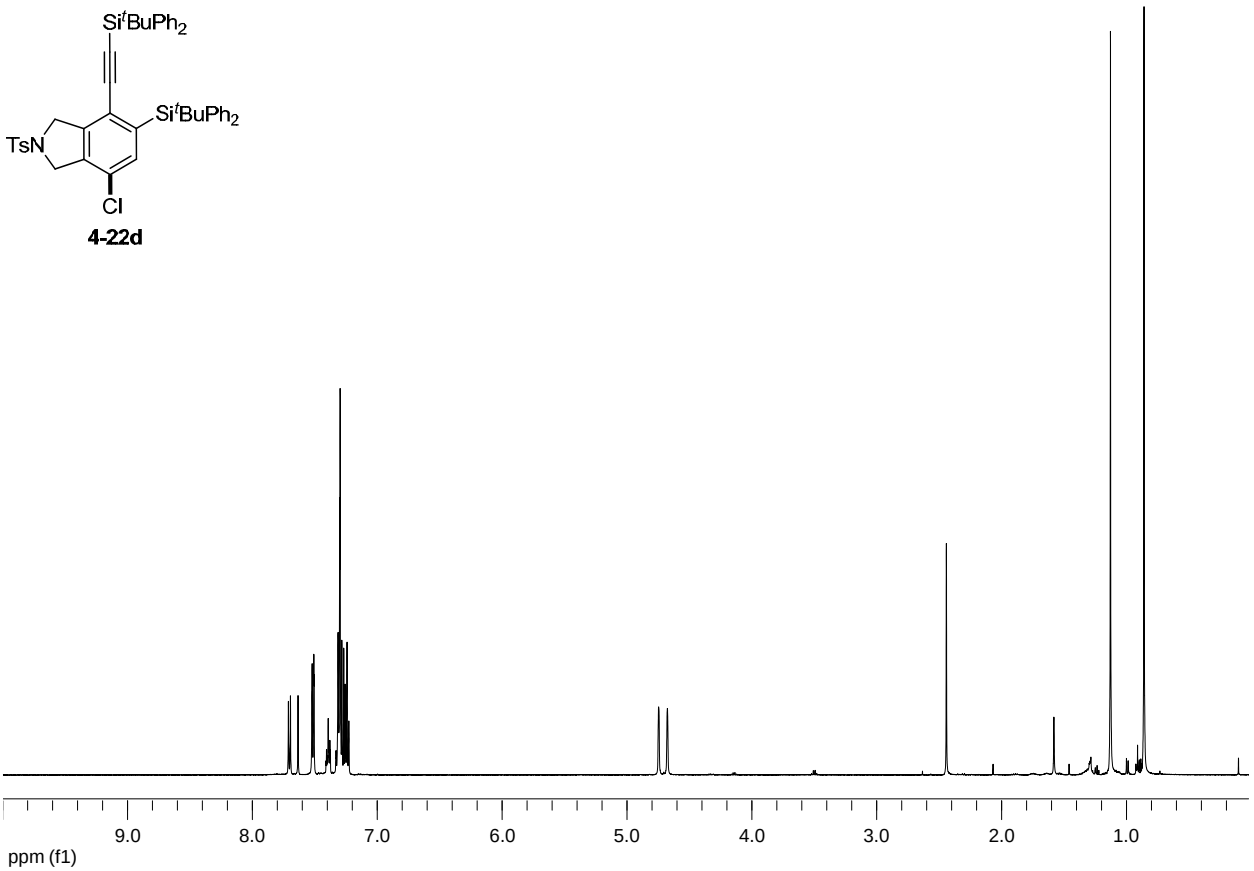
4-22c

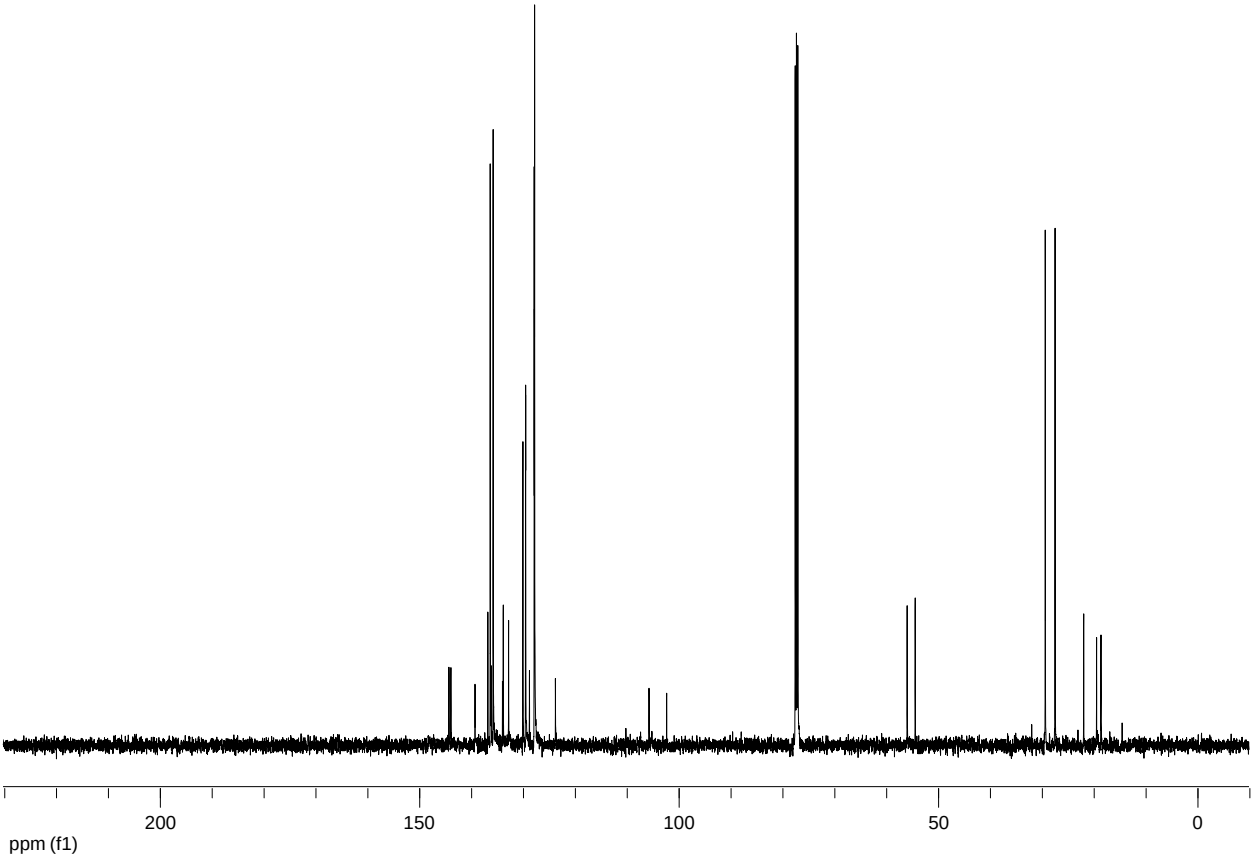

9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

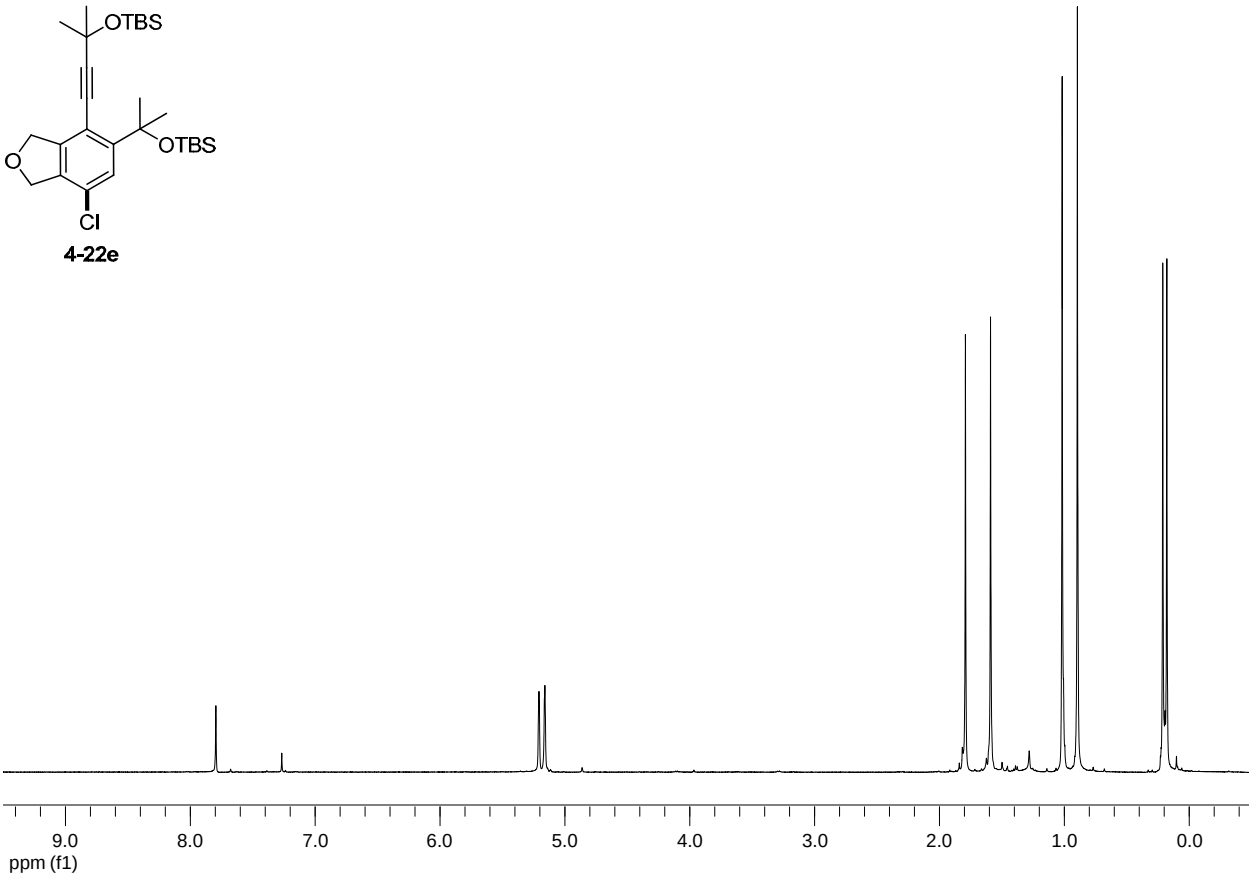

200
150
100
50
0
ppm (f1)

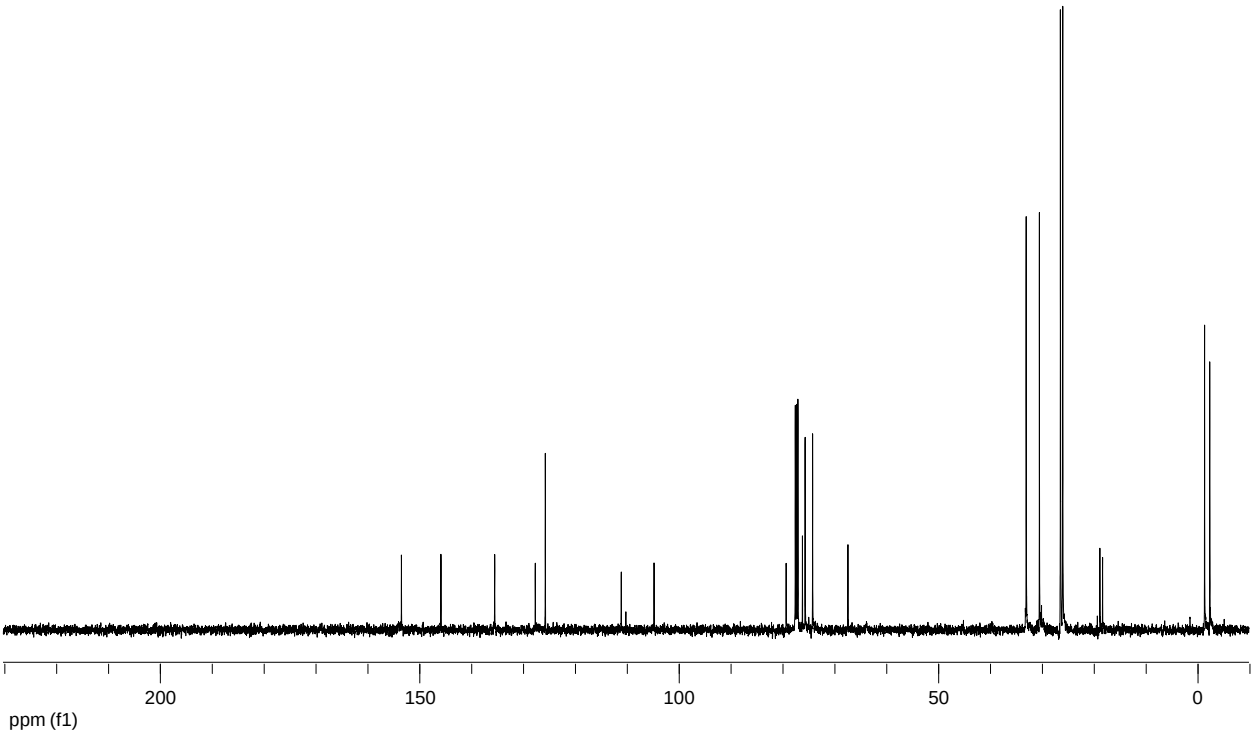
Si^{t}BuPh$_2$
Si^{t}BuPh$_2$
TsN
Cl

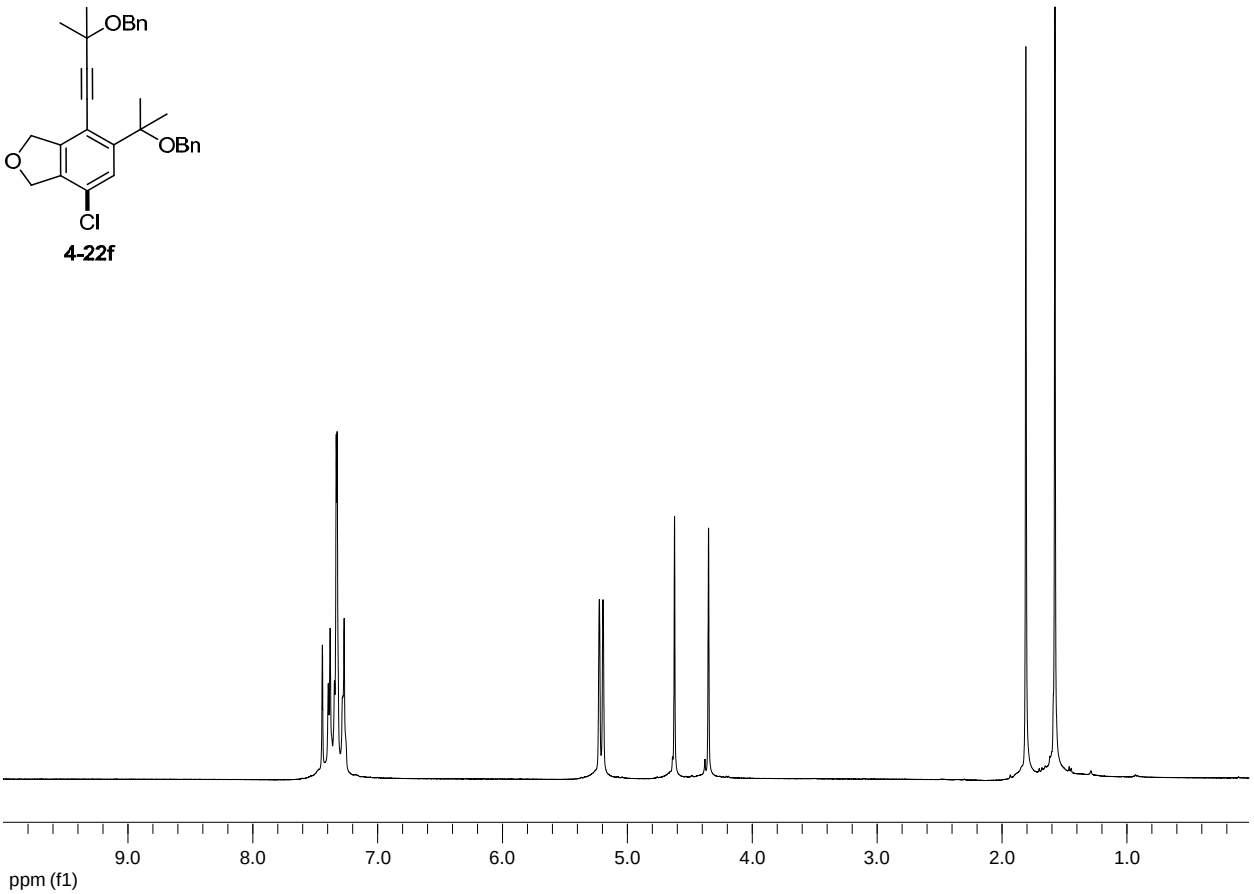
4-22d

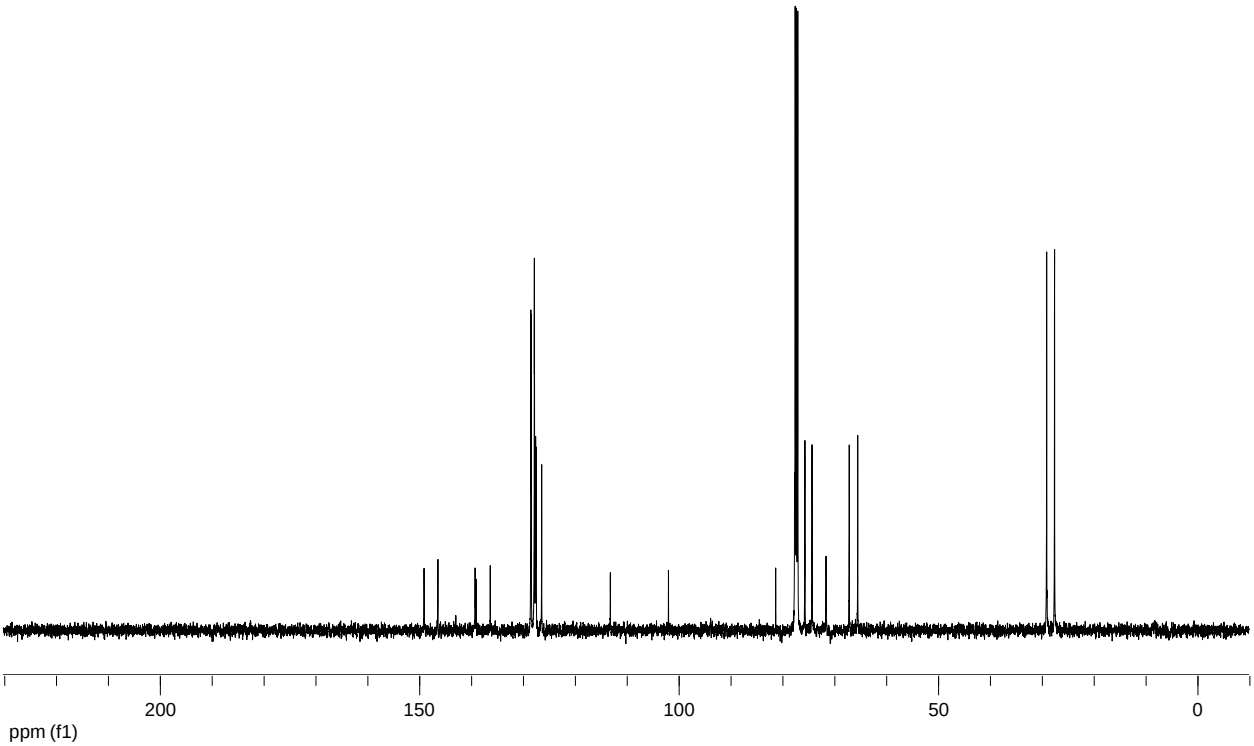

9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)


200
150
100
50
0
ppm (f1)


OTBS
OTBS
O
Cl
4-22e
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

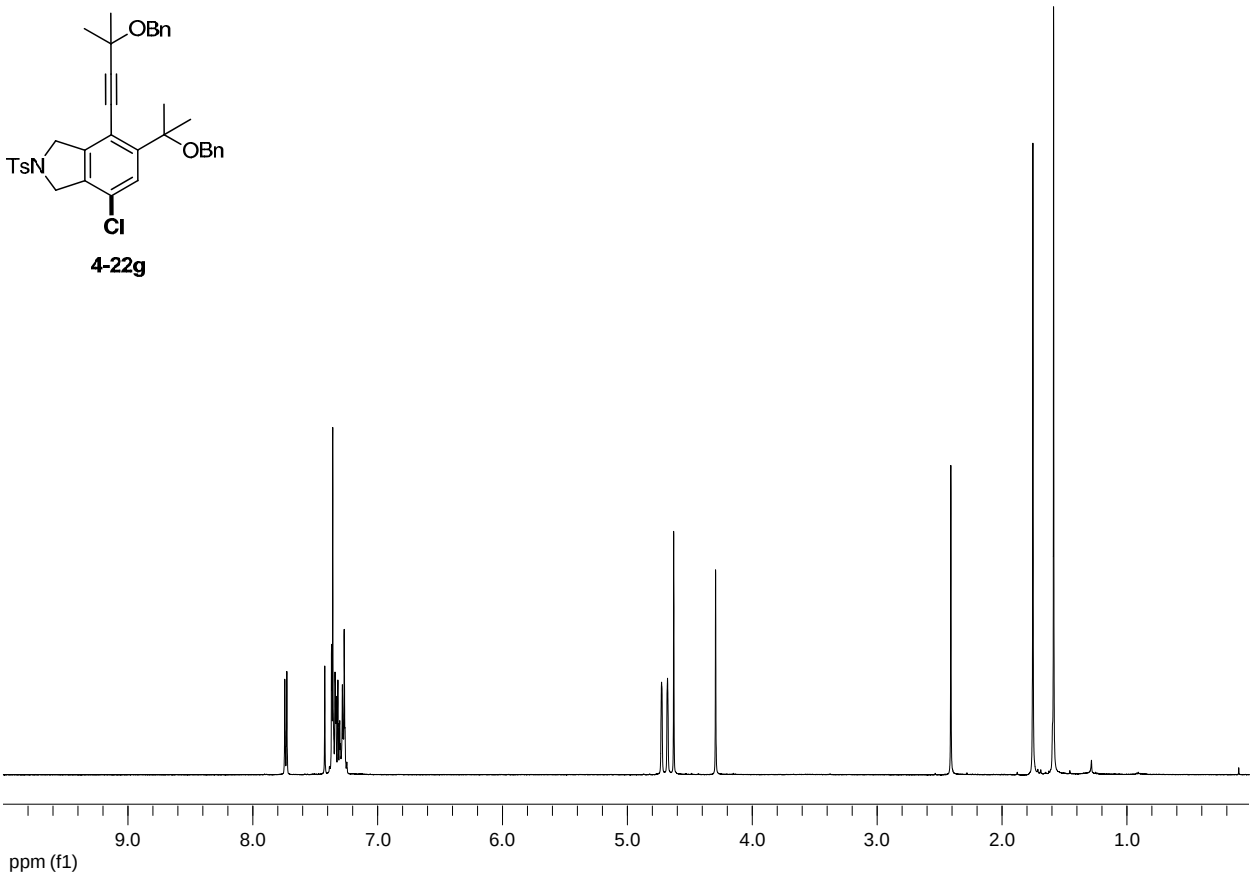

200
150
100
50
0
ppm (f1)

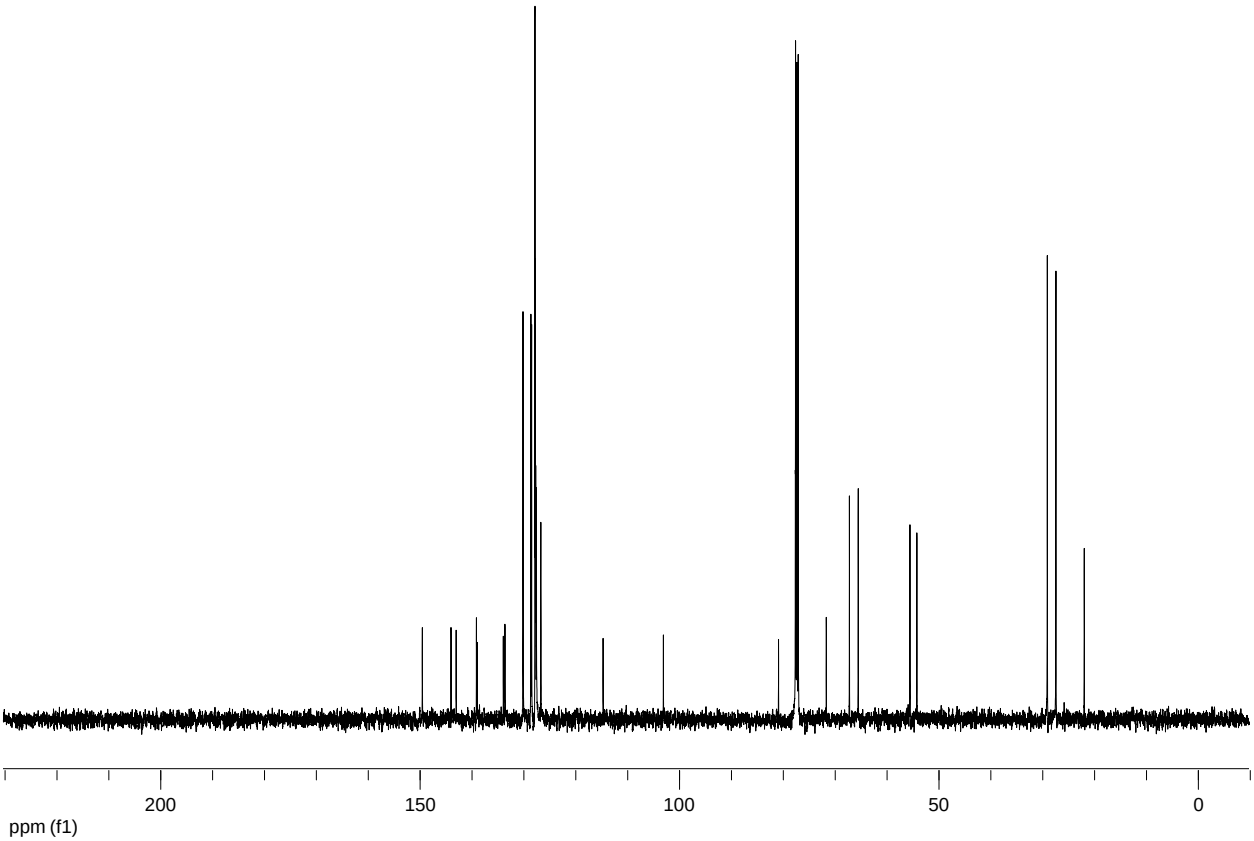

OBn
OBn
O
Cl
4-22f
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

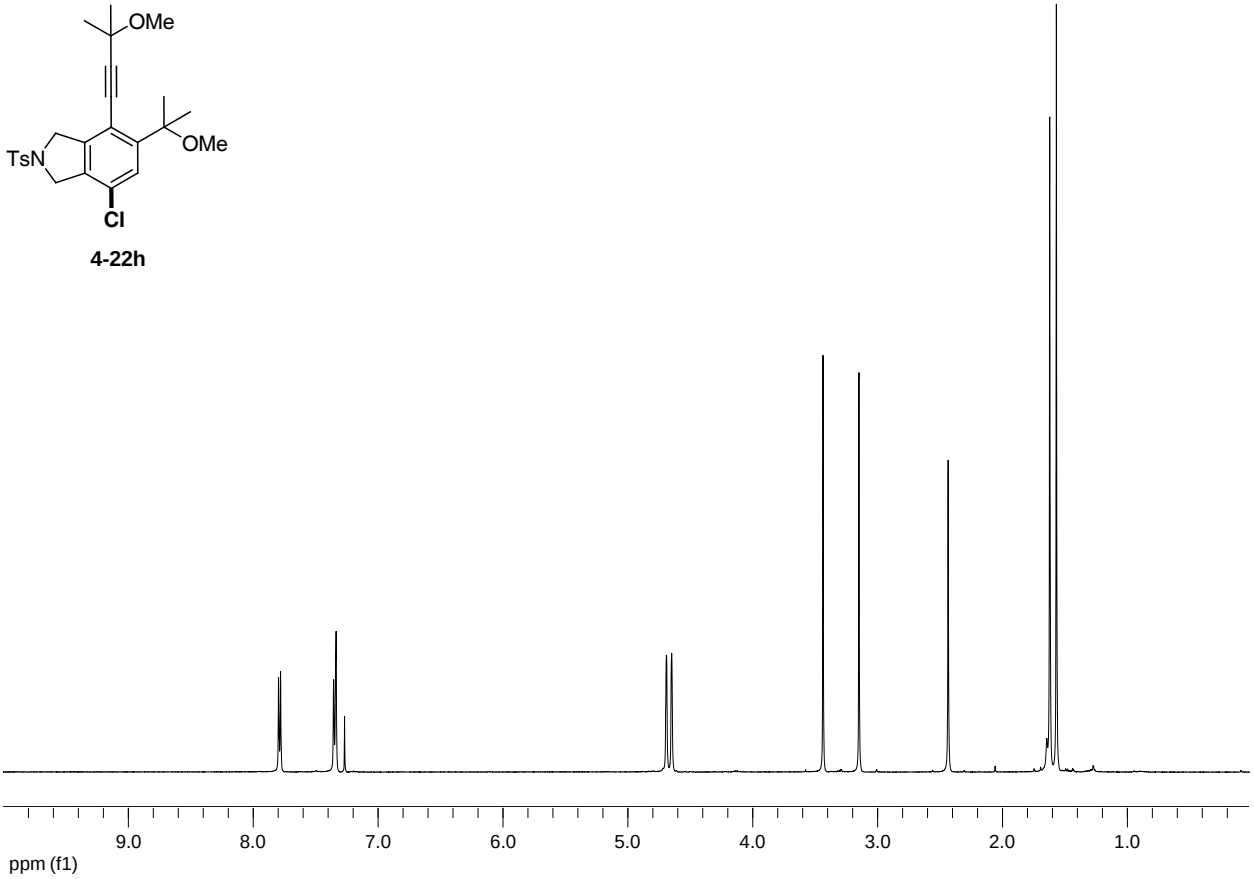

200
150
100
50
0
ppm (f1)

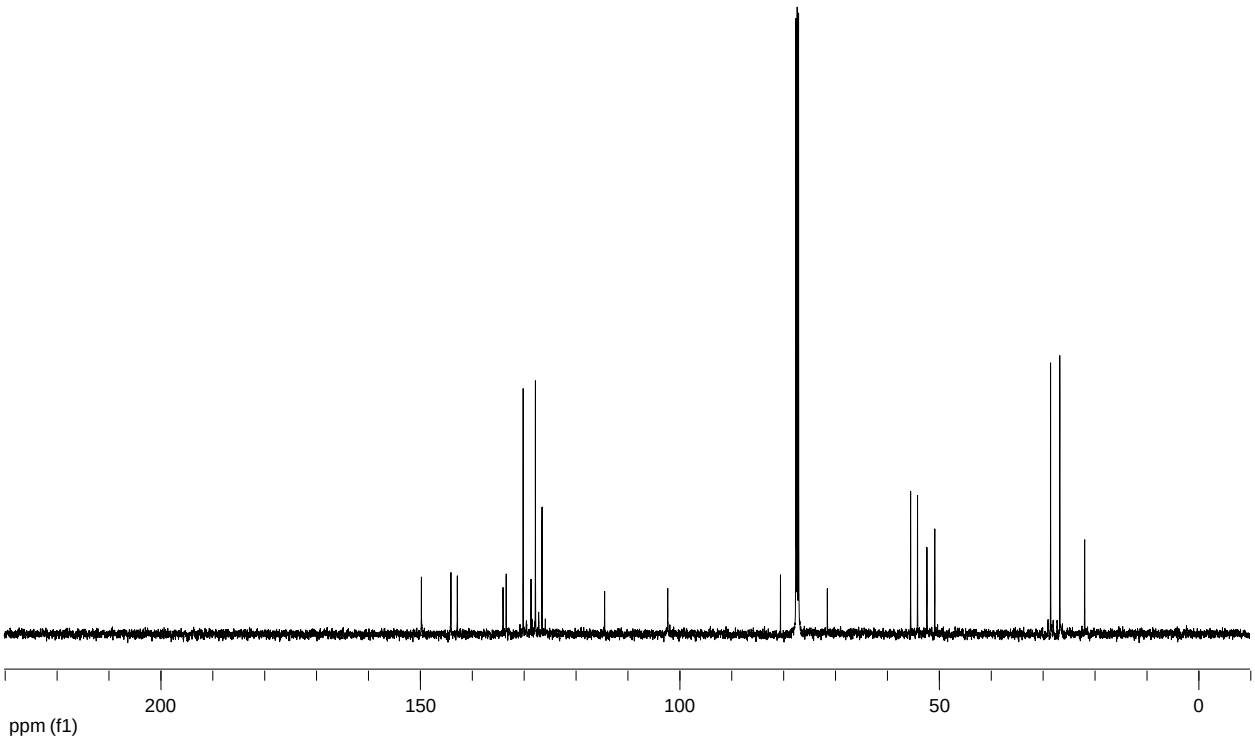
OBn
OBn
TsN
Cl

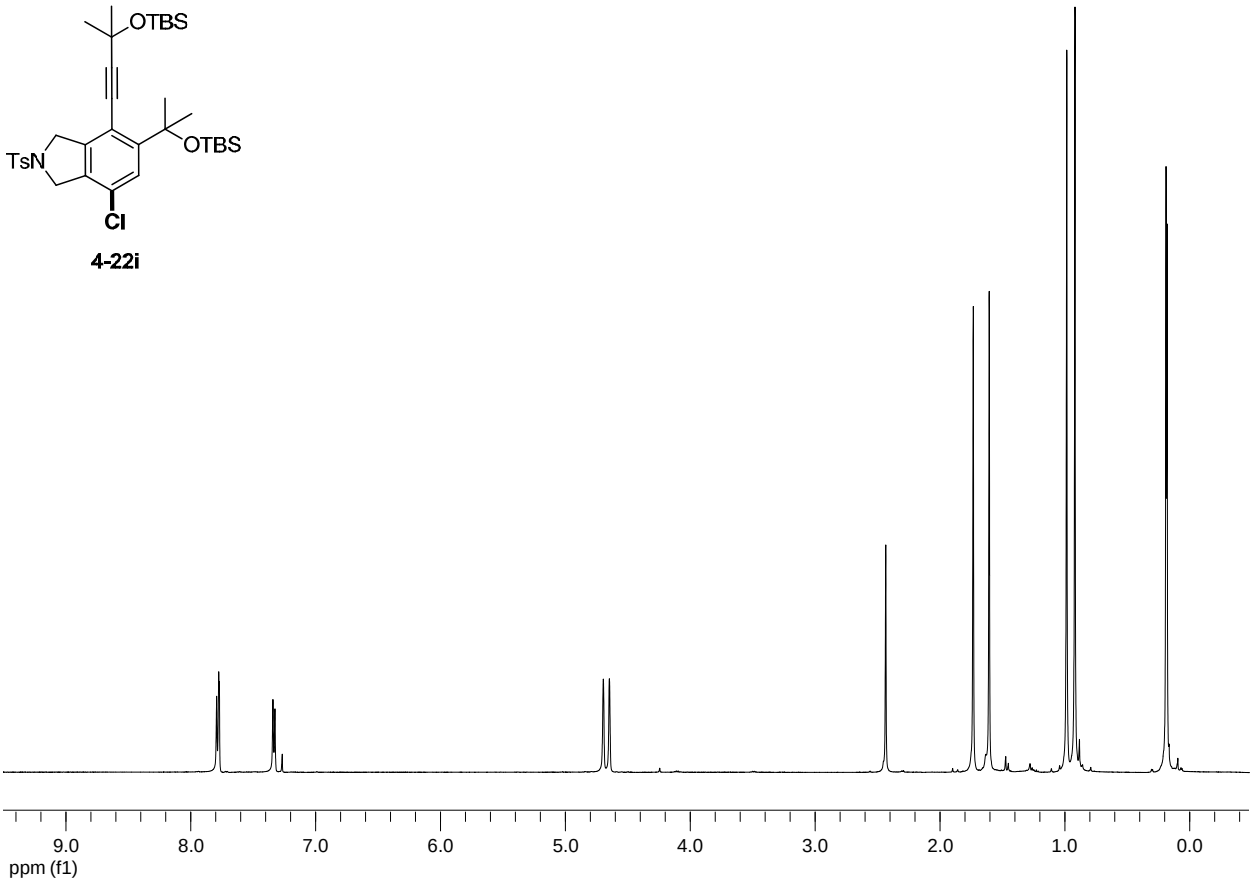
4-22g

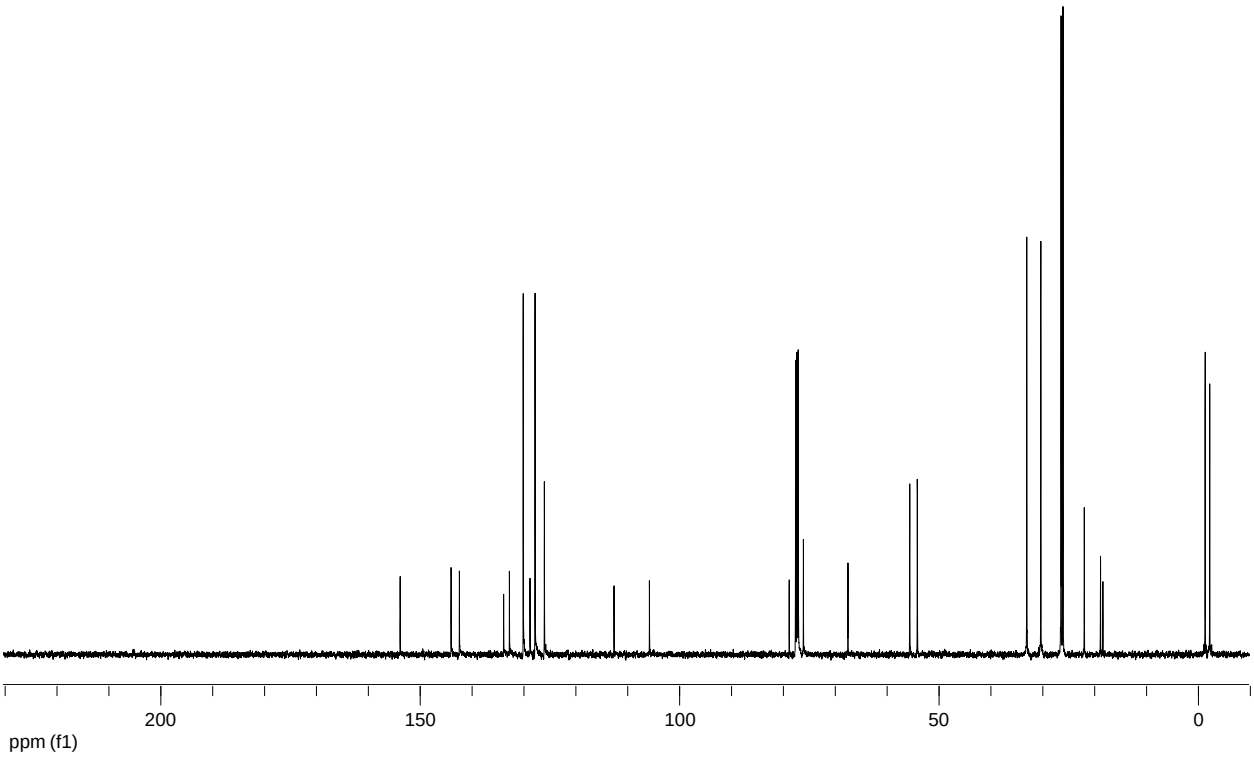

9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)


200
150
100
50
0
ppm (f1)

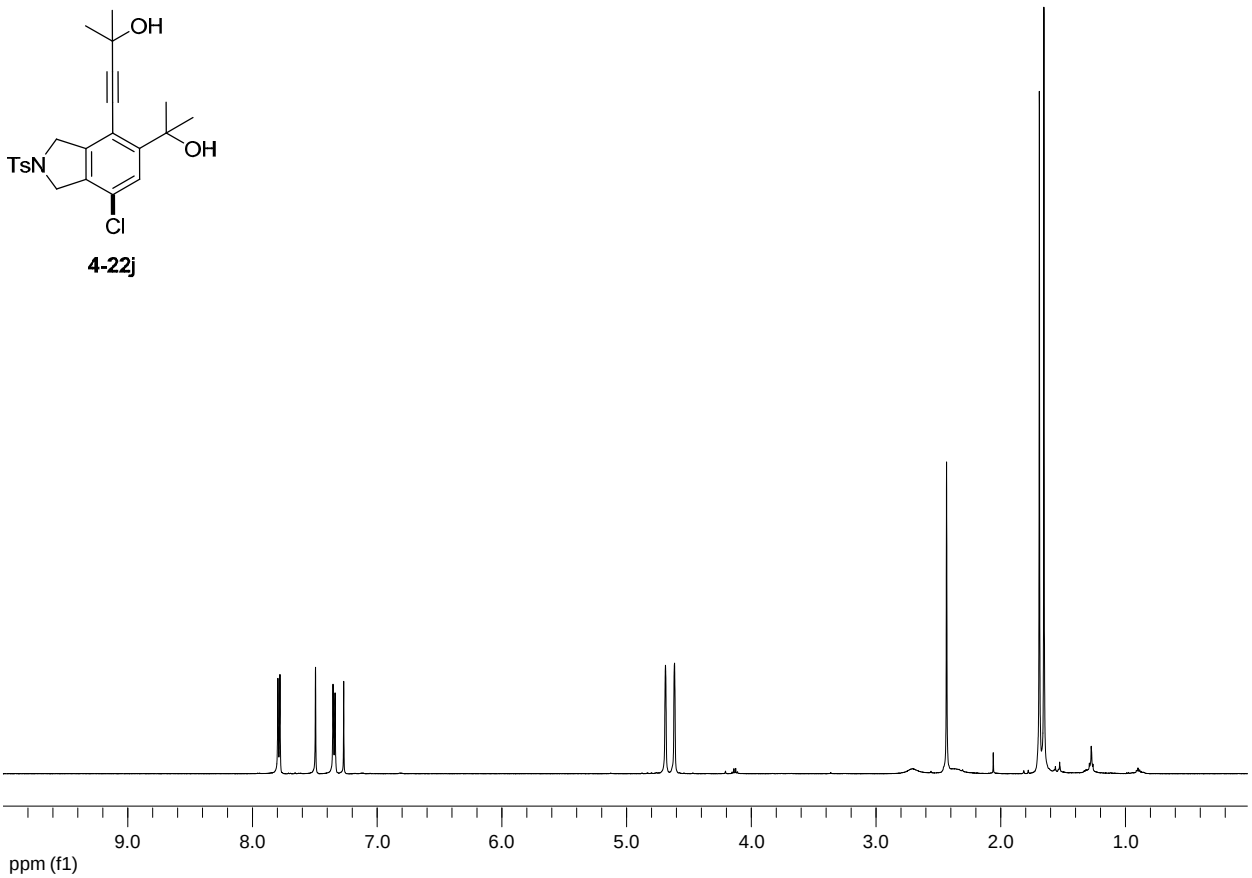

OMe
OMe
TsN
Cl
4-22h
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

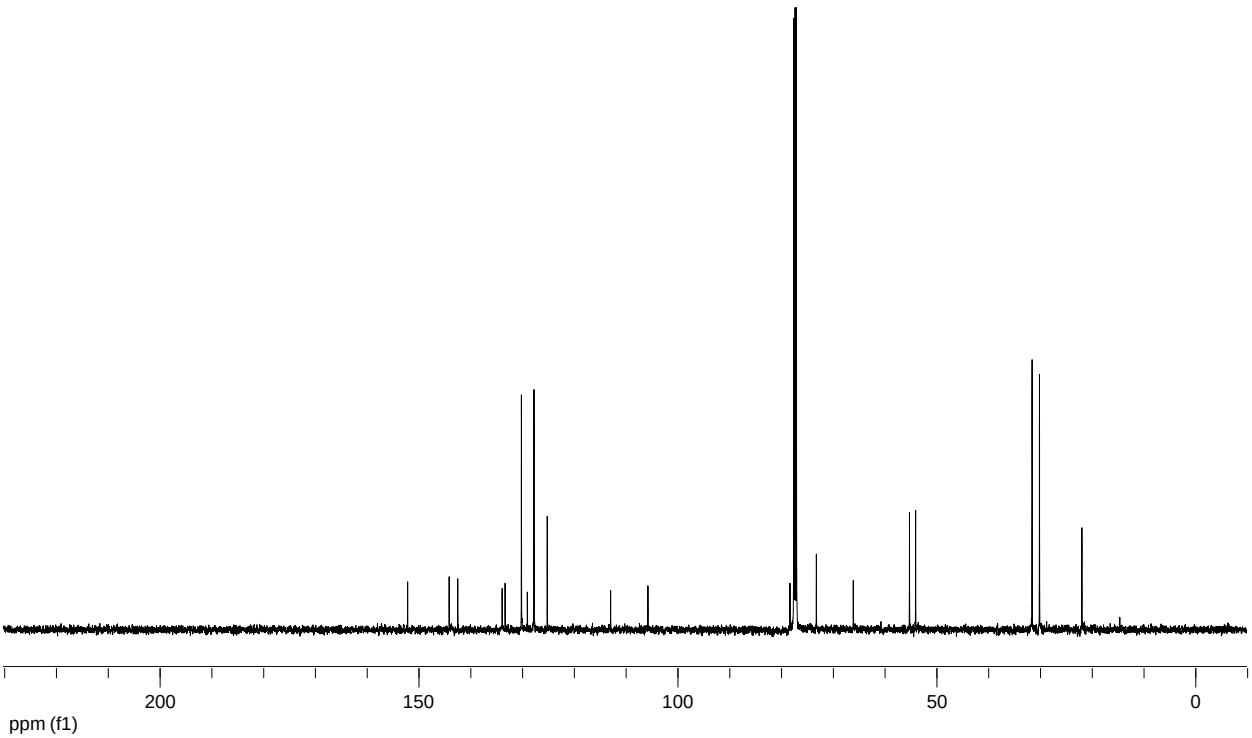

200
150
100
50
0
ppm (f1)

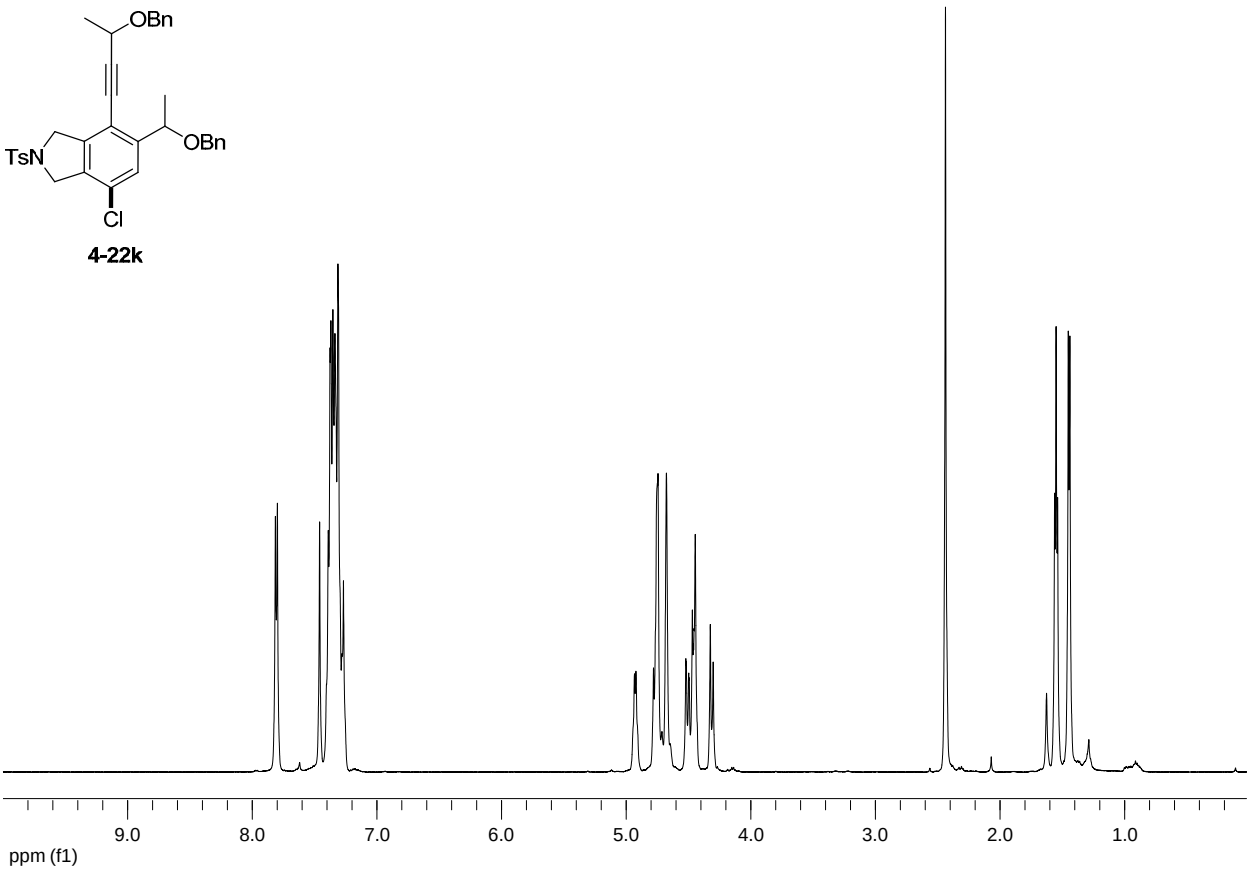

OTBS
OTBS
TsN
Cl
4-22i
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

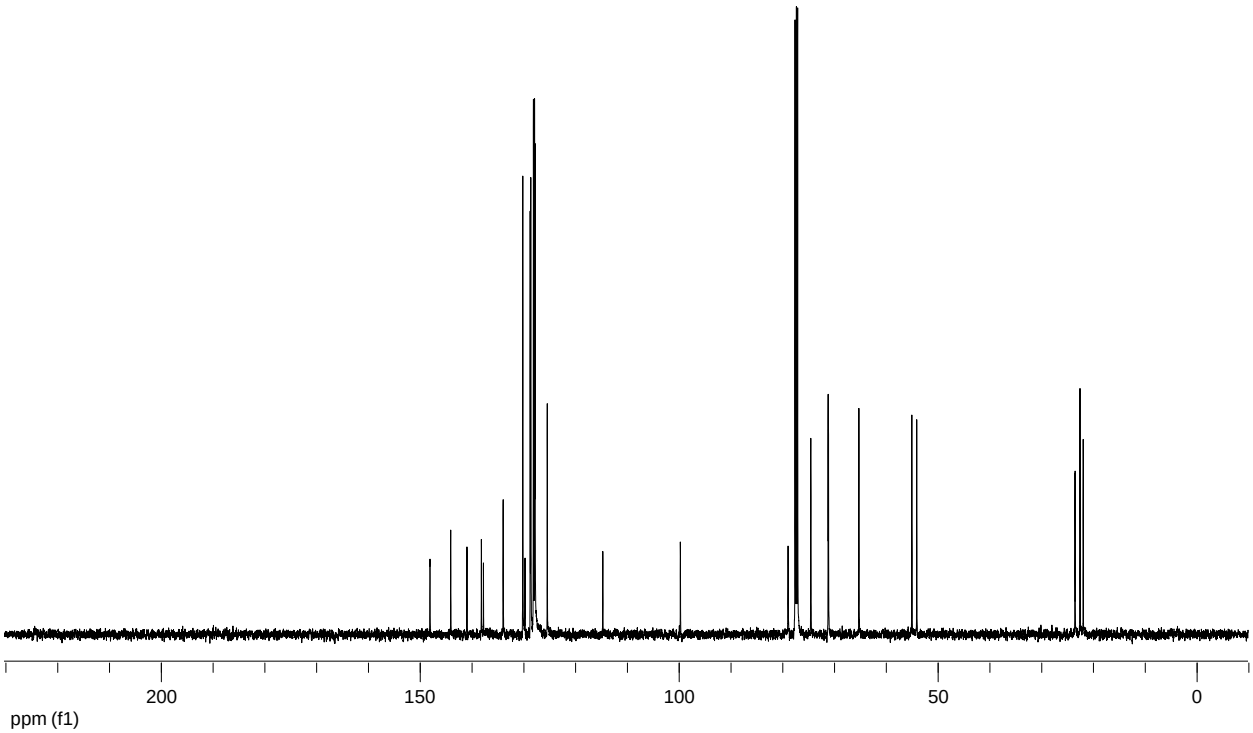

200
150
100
50
0
ppm (f1)

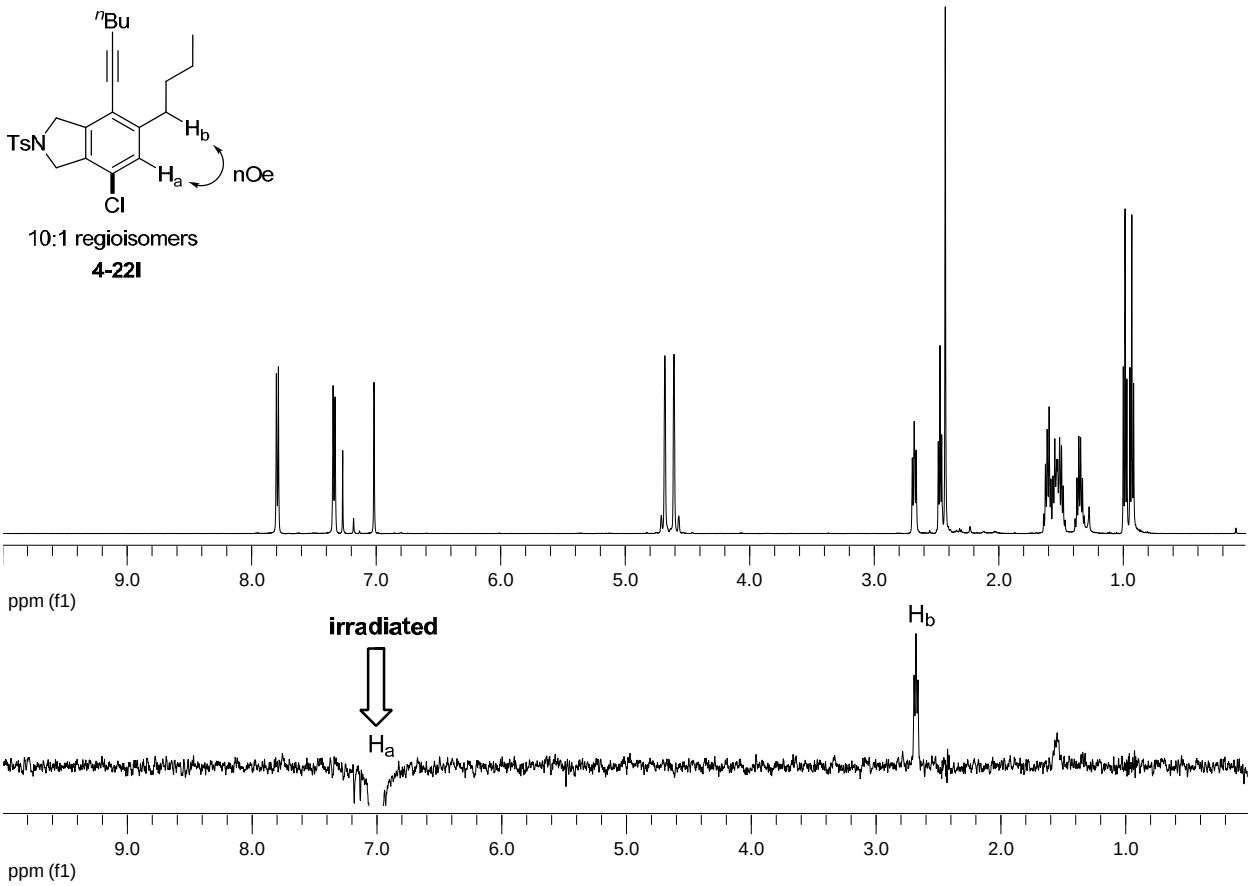
4-22j

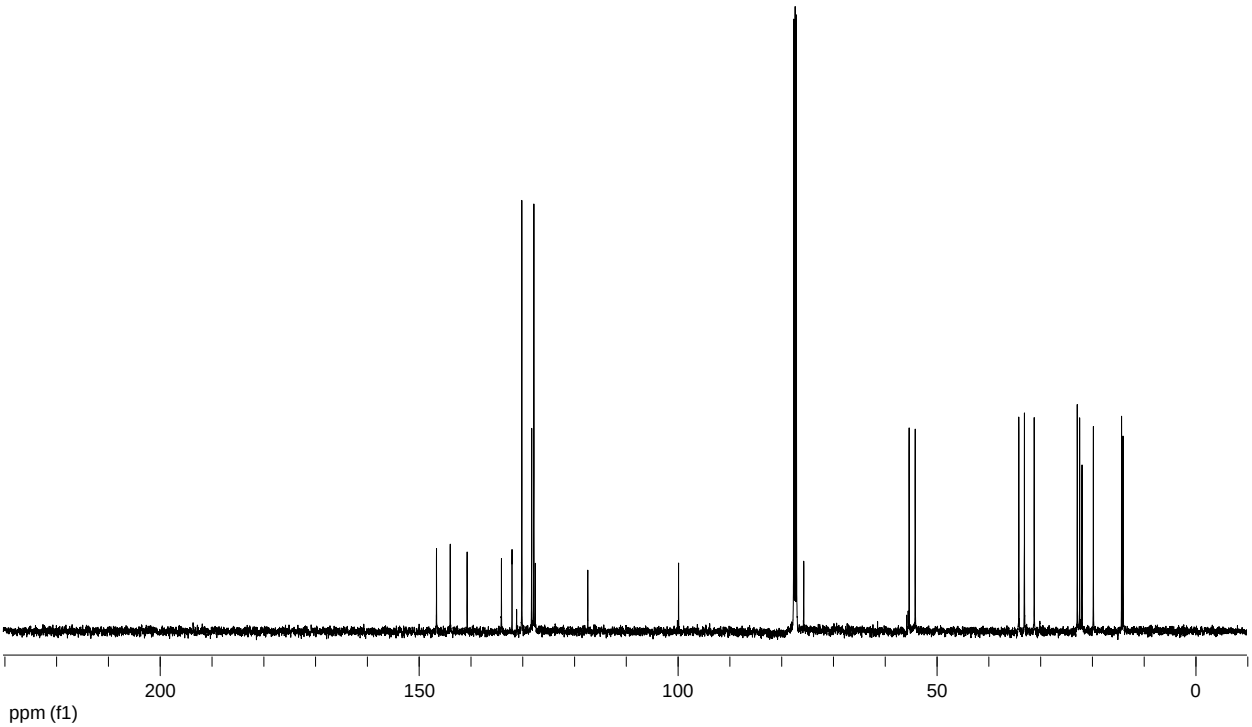


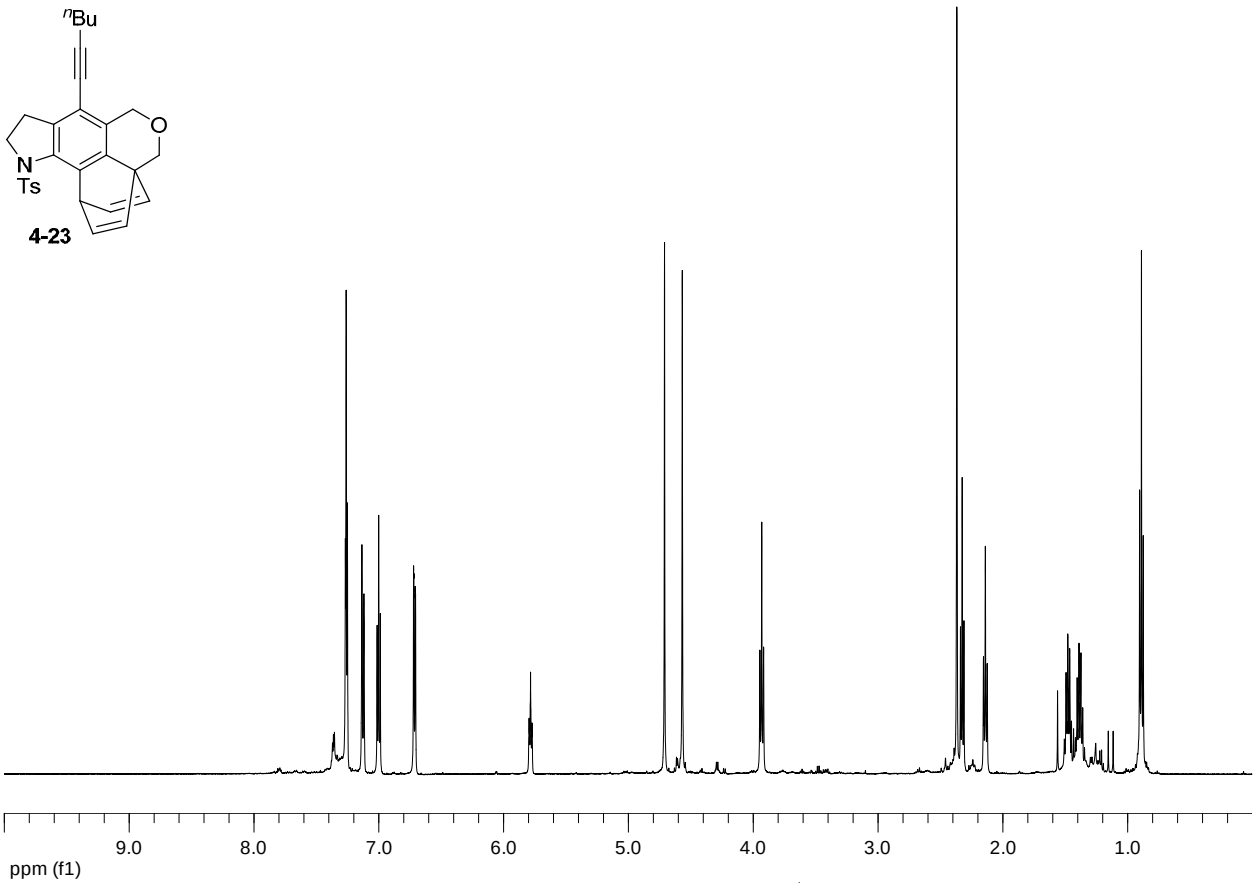


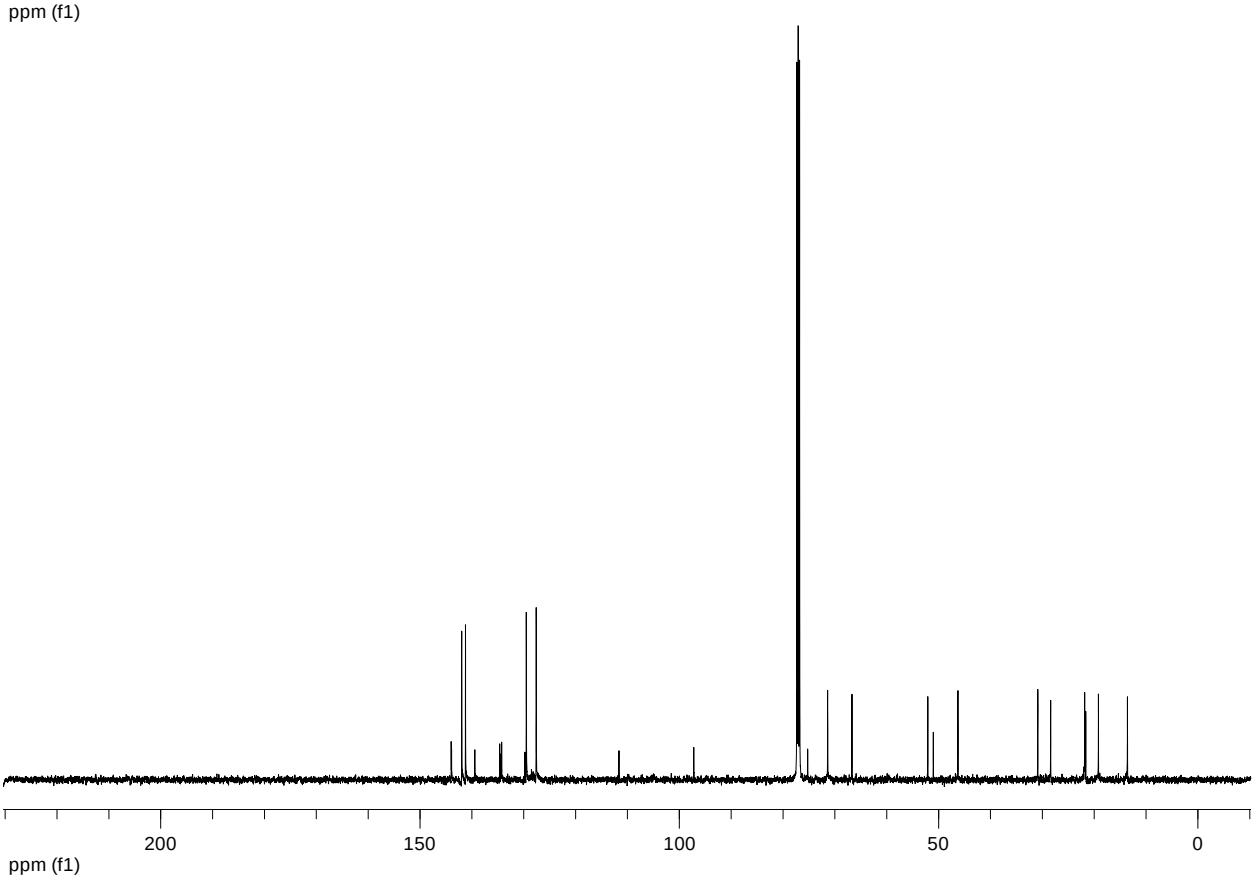

OBn
TsN
OBn
Cl
4-22k
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

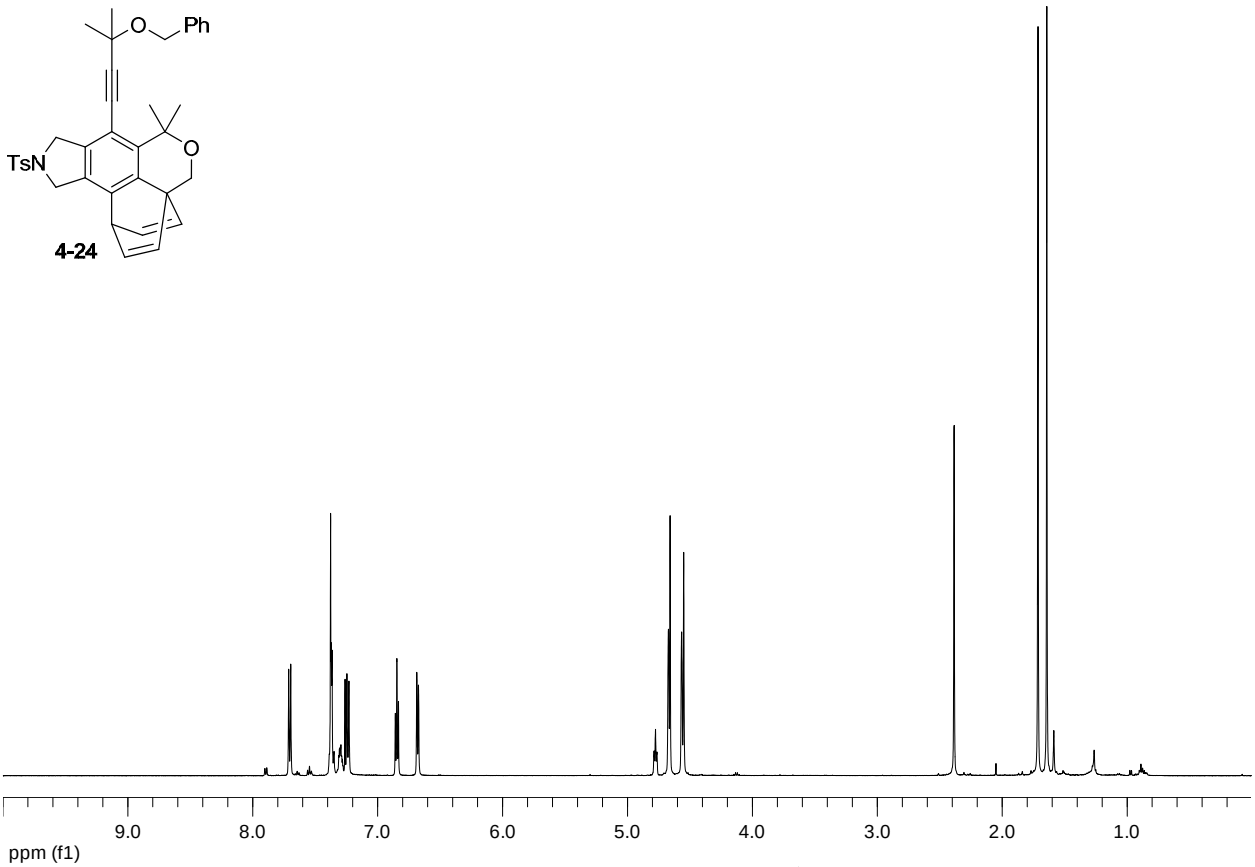

200
150
100
50
0
ppm (f1)

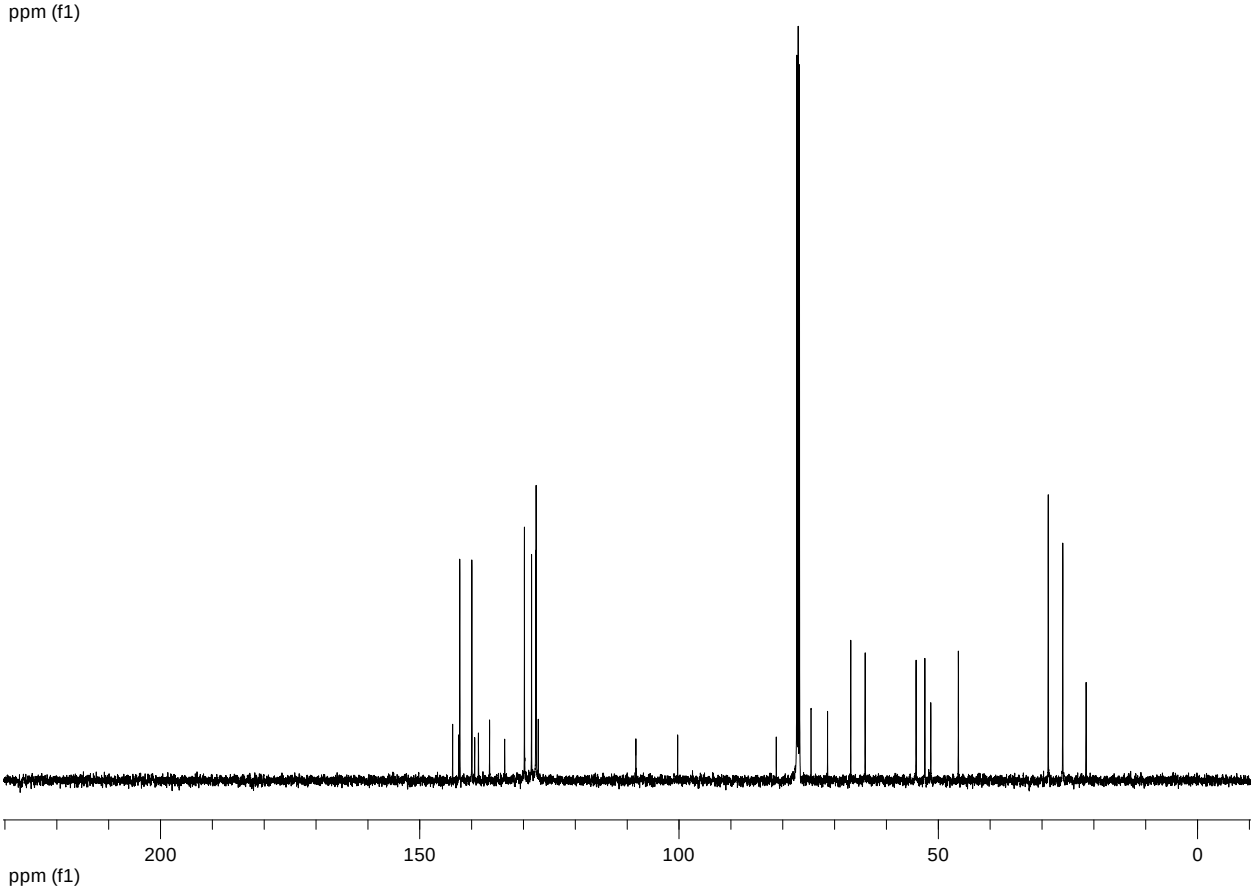

nBu
TsN
Hb
Ha
nOe
Cl
10:1 regioisomers
4-22l
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)
irradiated
Hb
Ha
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

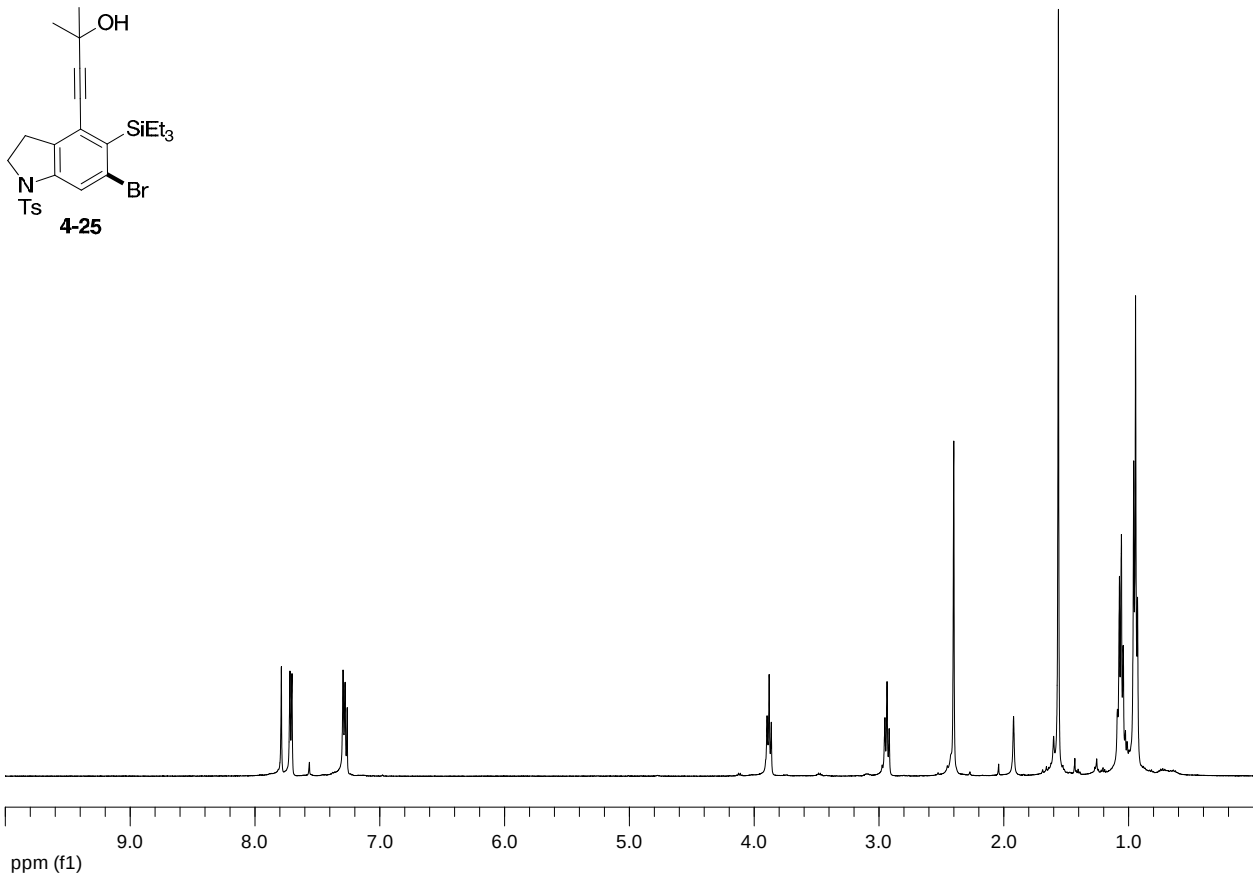

200
150
100
50
0
ppm (f1)

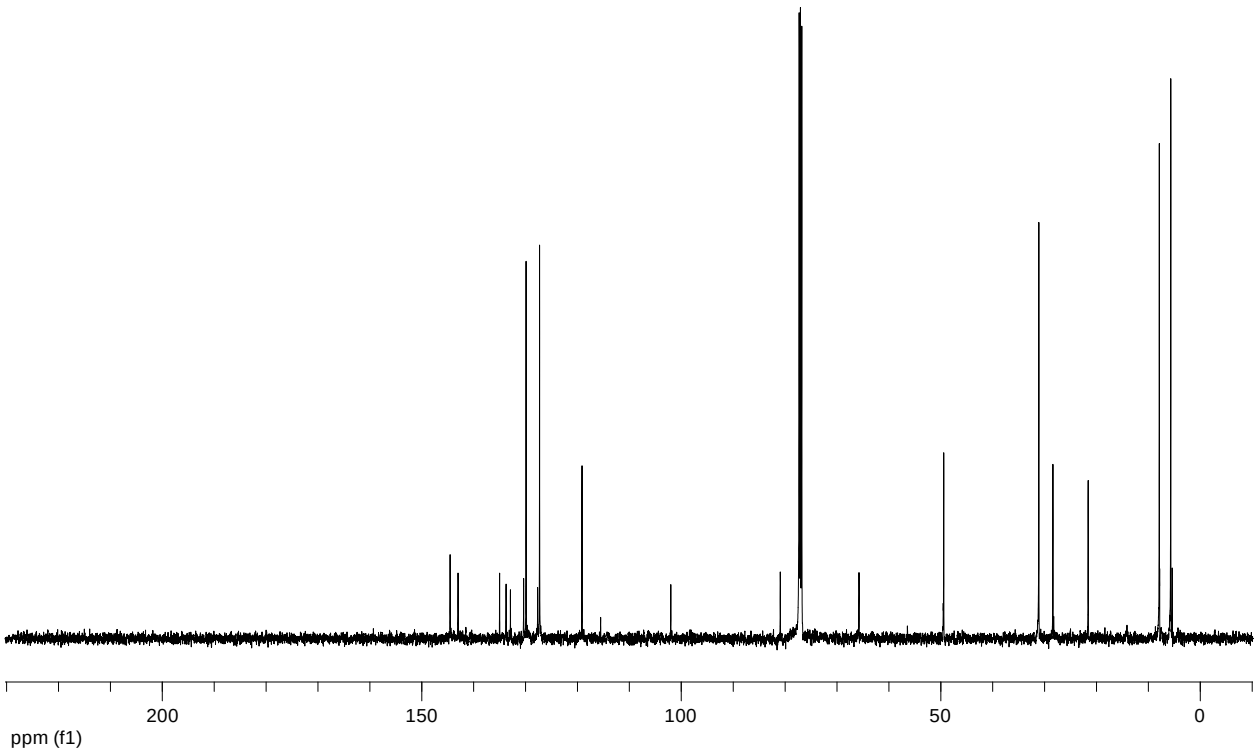

nBu
O
N
Ts
4-23
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

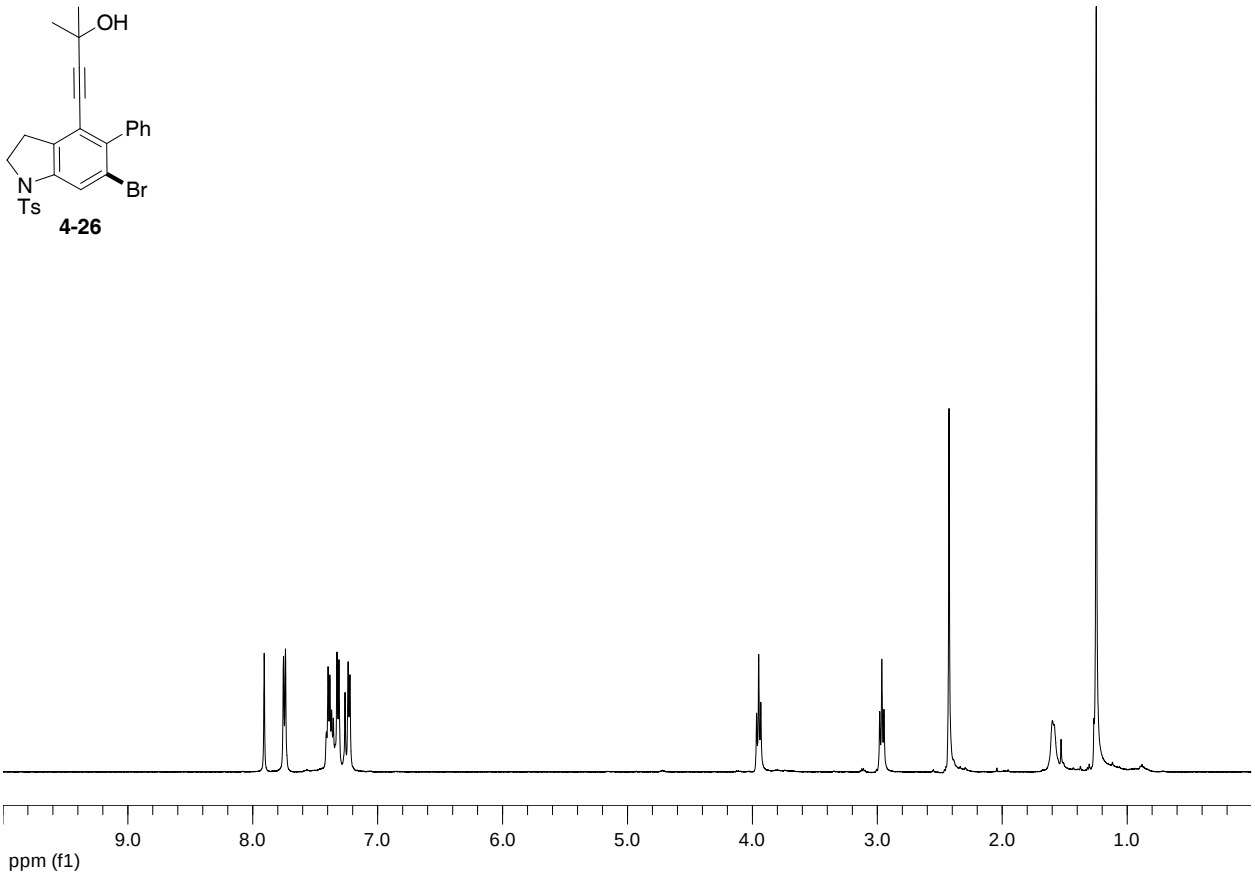

200
150
100
50
0
ppm (f1)

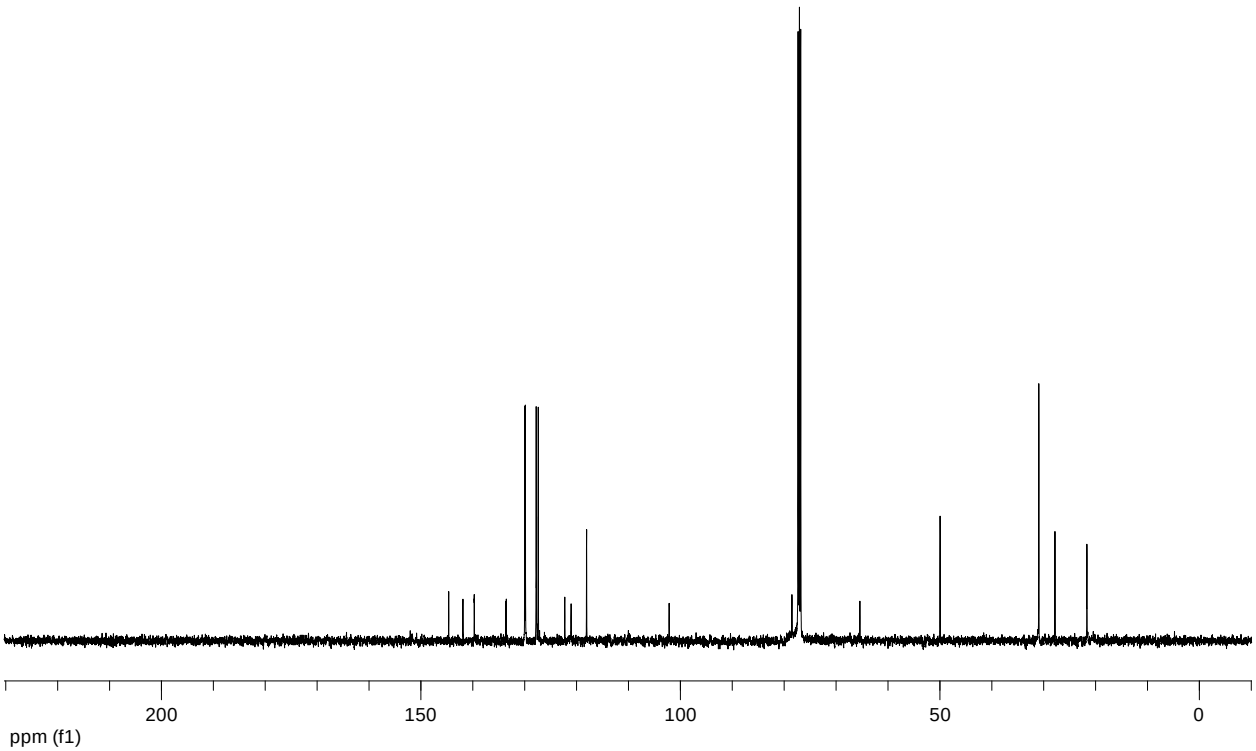

O
Ph
TsN
O
4-24
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

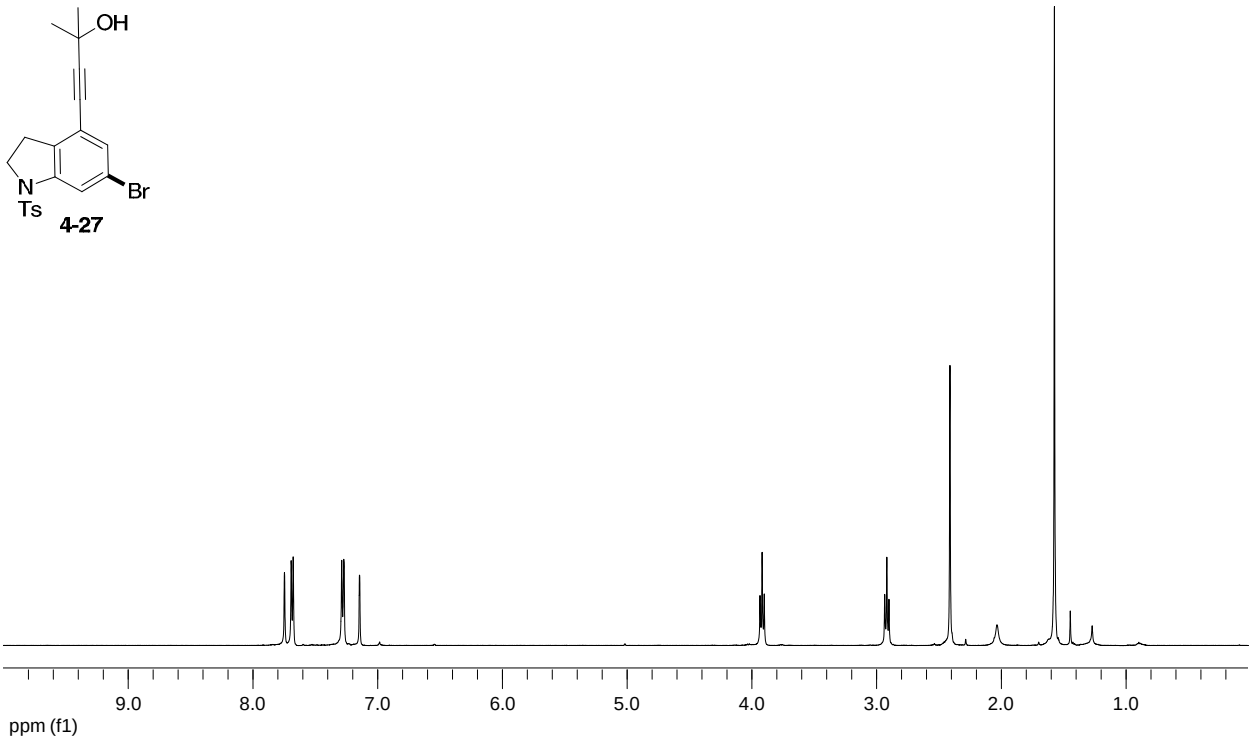

200
150
100
50
0
ppm (f1)

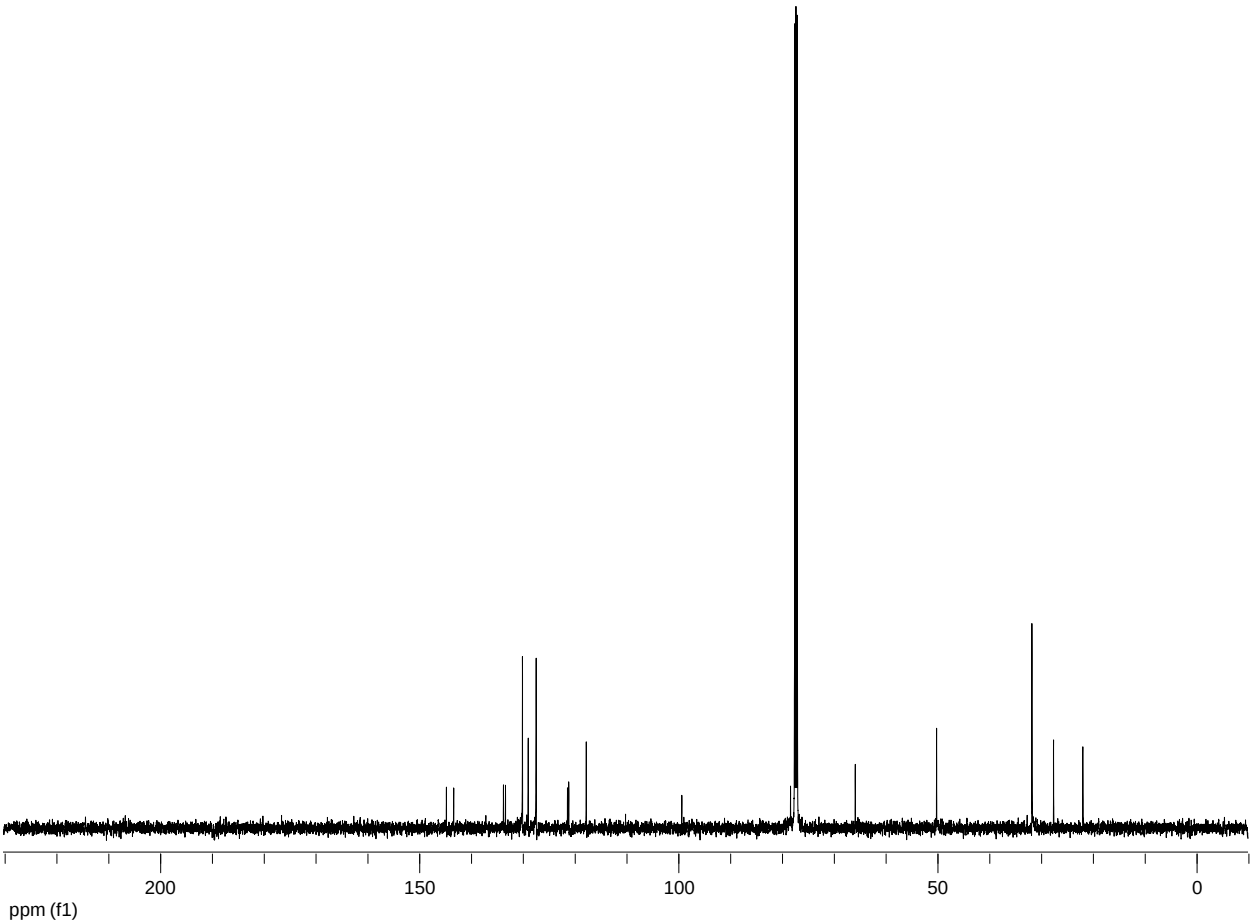

OH
SiEt3
N
Ts
Br
4-25
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

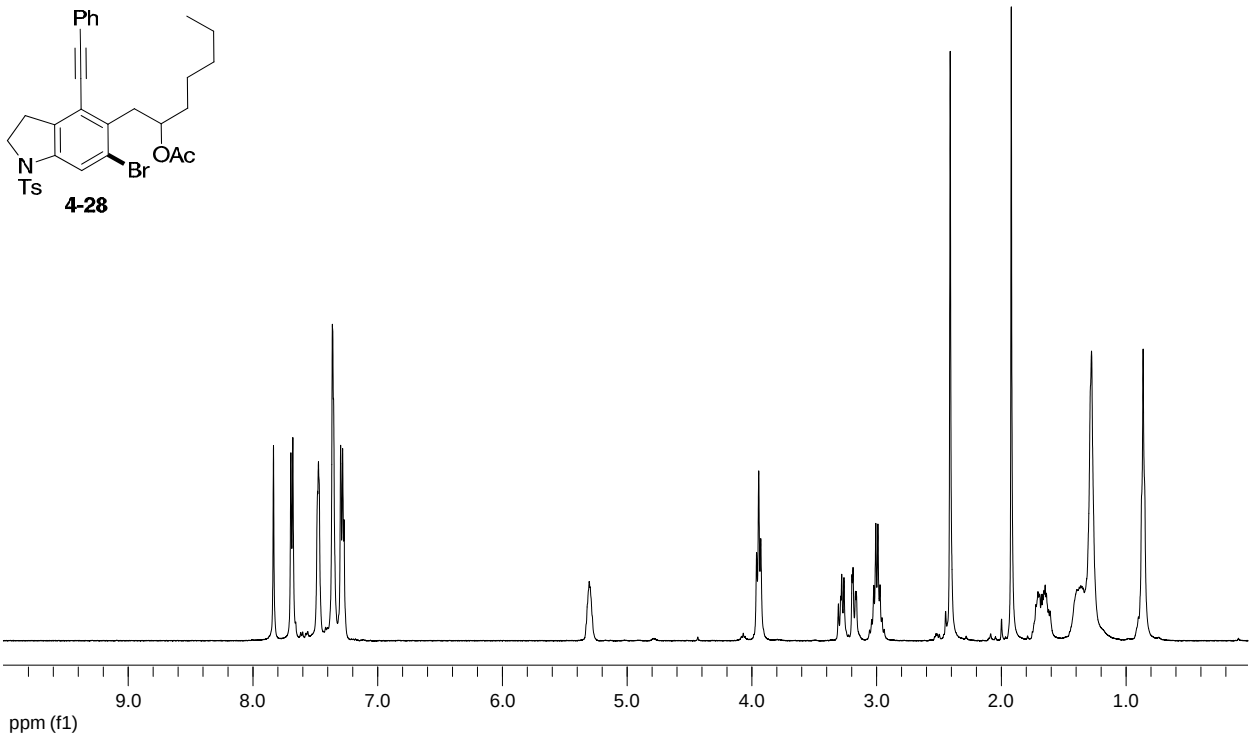

200
150
100
50
0
ppm (f1)

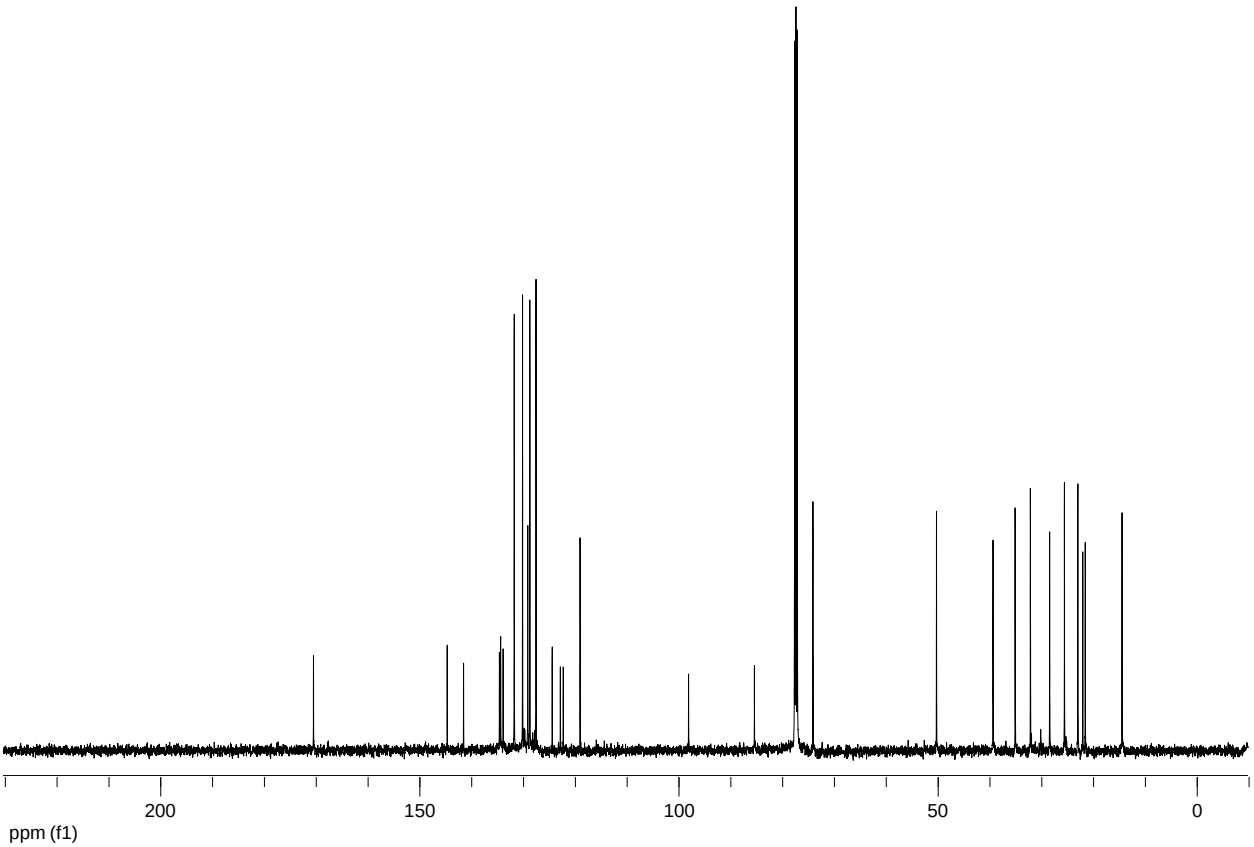

OH
Ph
Br
N
Ts
4-26
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)


200
150
100
50
0
ppm (f1)

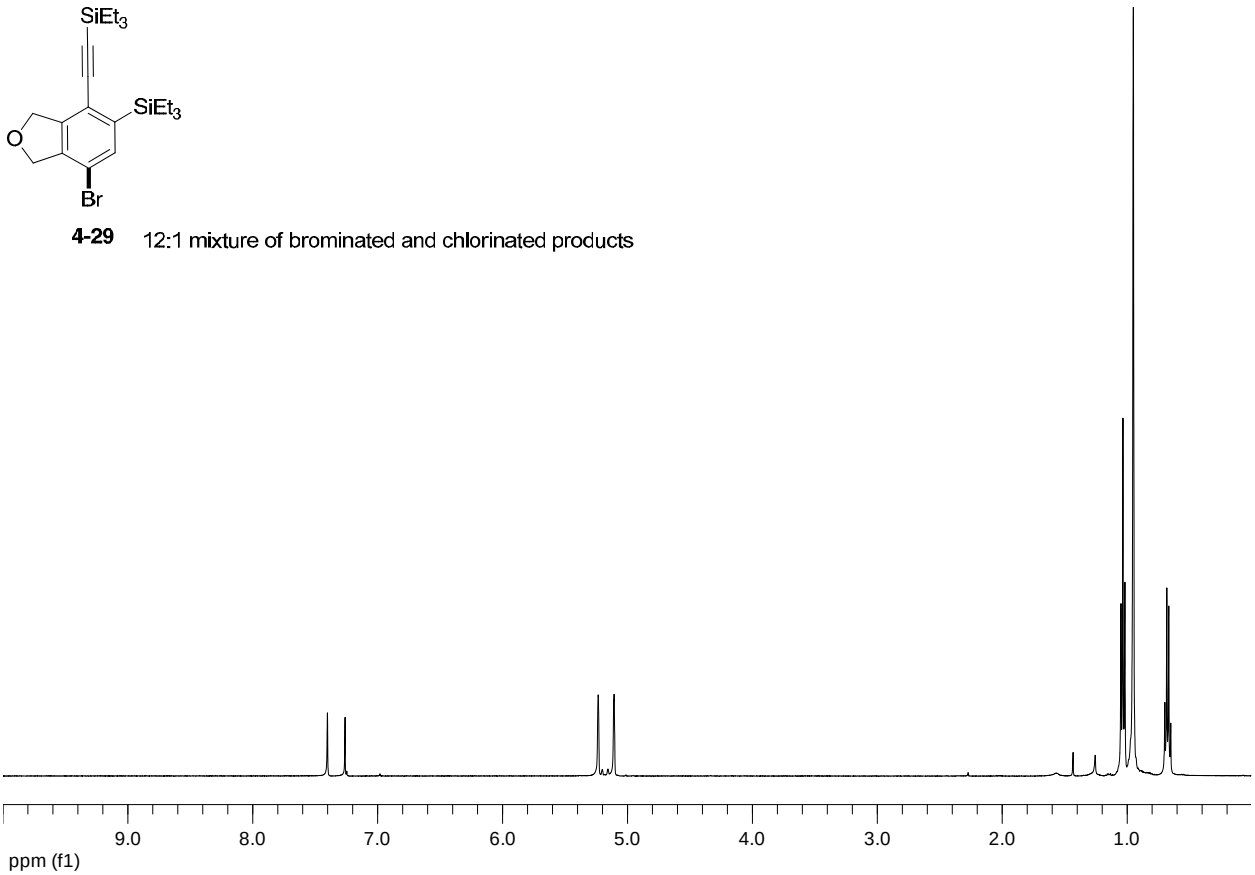

OH
N
Ts
Br
4-27
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

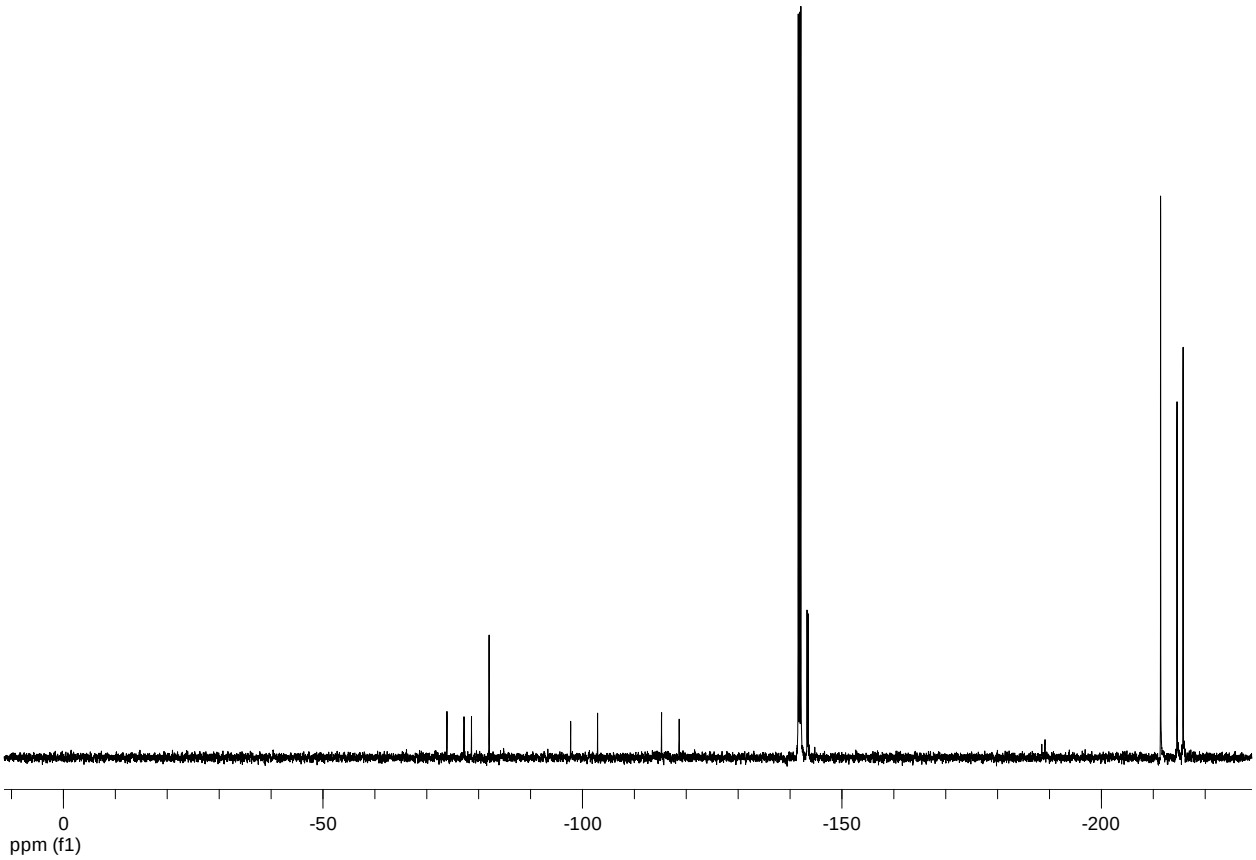

200
150
100
50
0
ppm (f1)


Ph
N
Ts
Br
OAc
4-28
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

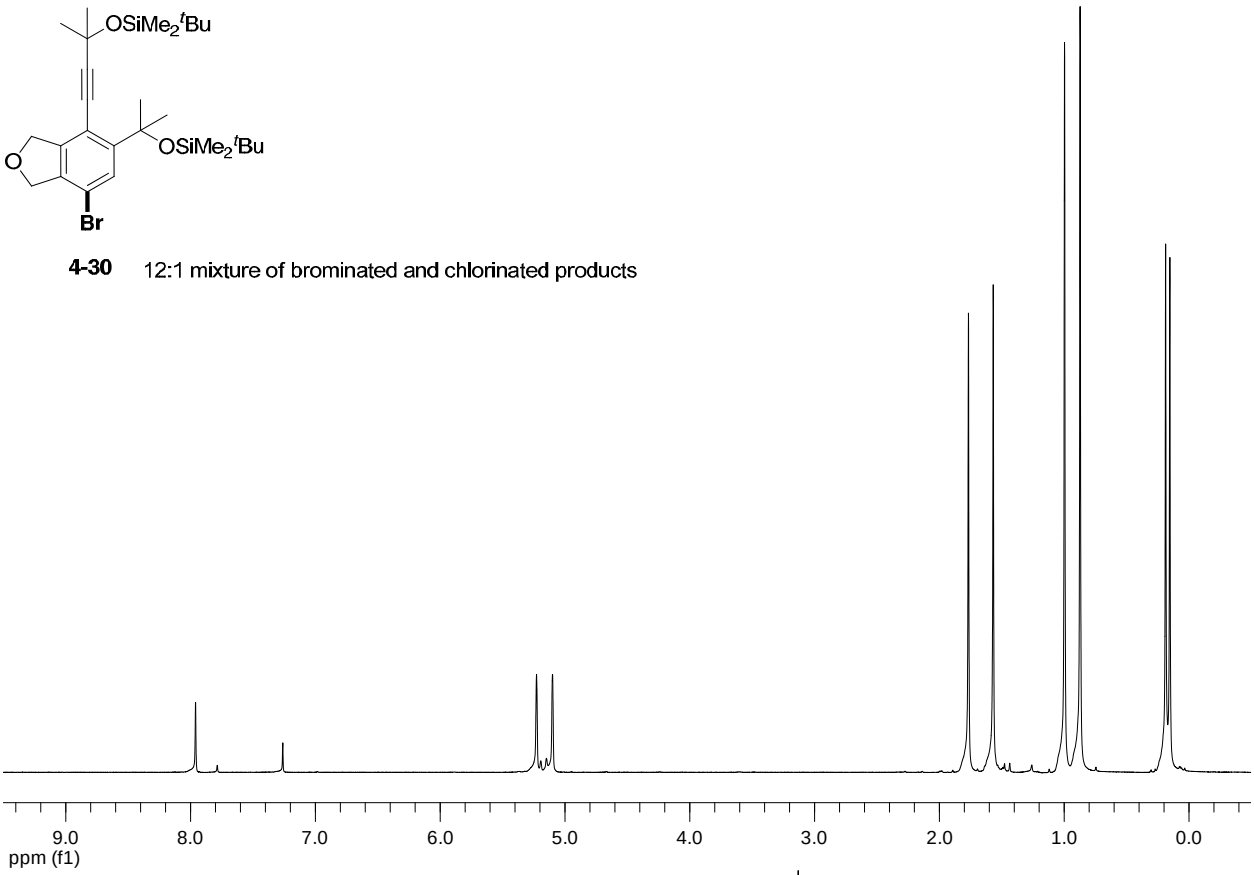

200
150
100
50
0
ppm (f1)

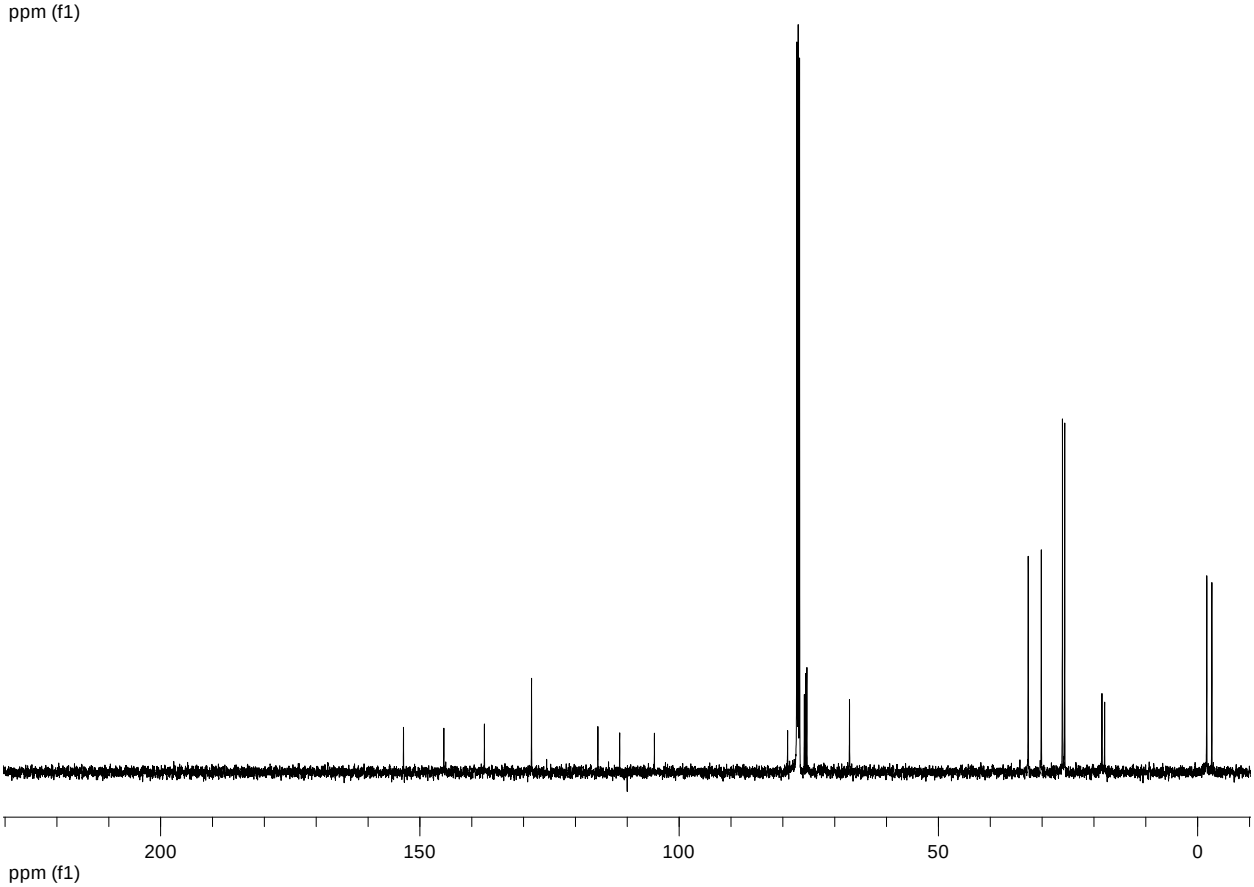
4-29 12:1 mixture of brominated and chlorinated products

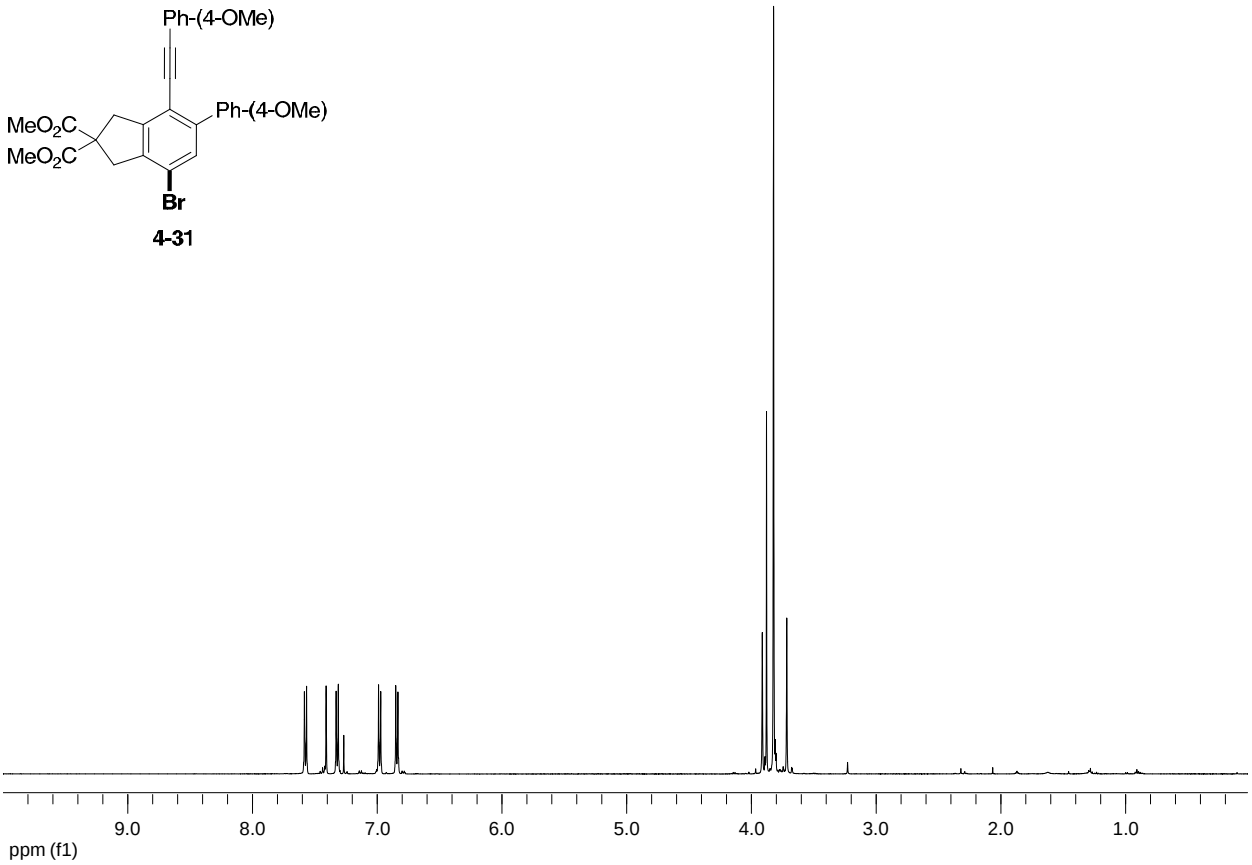


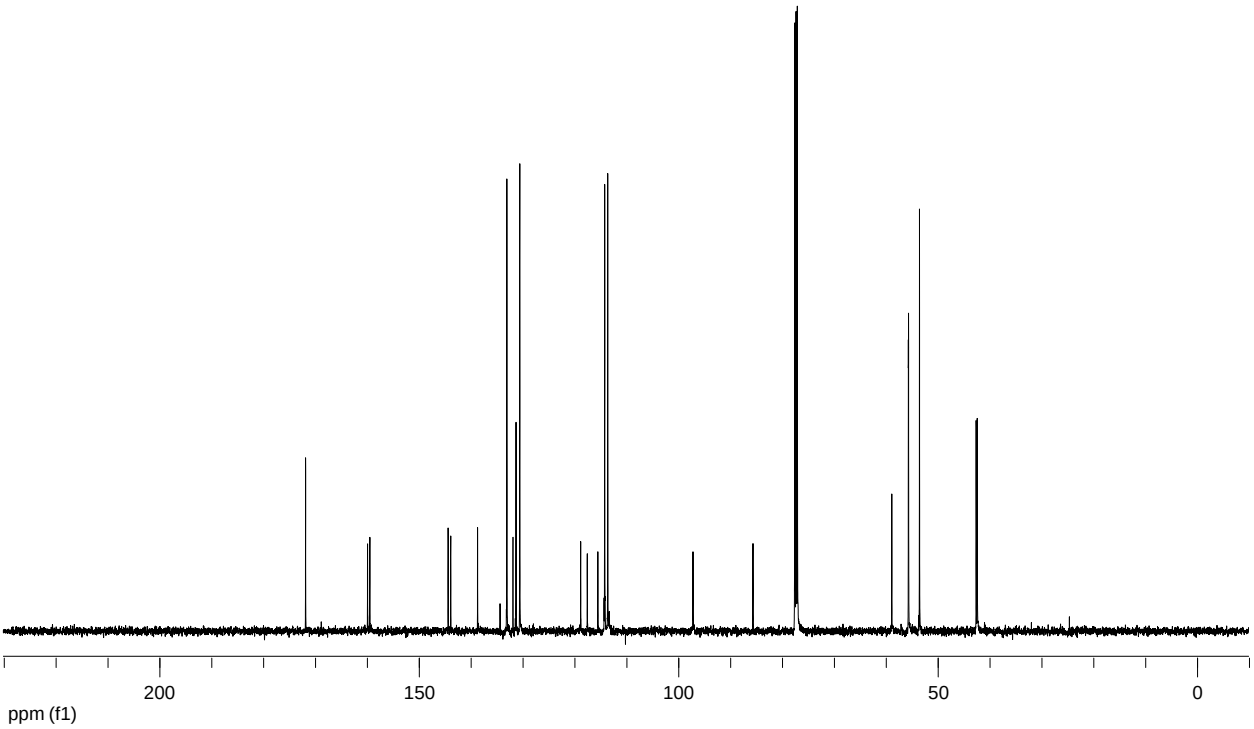


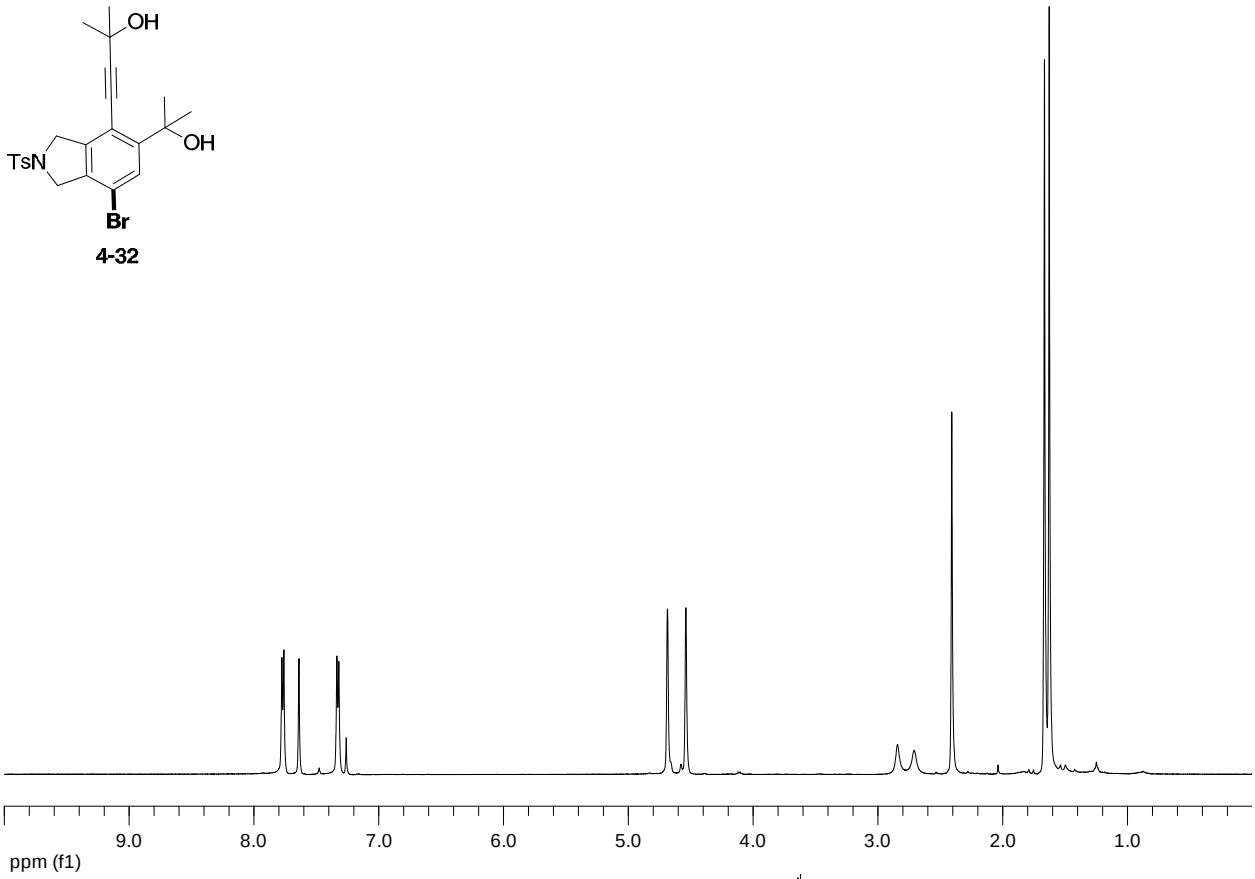
4-30 12:1 mixture of brominated and chlorinated products

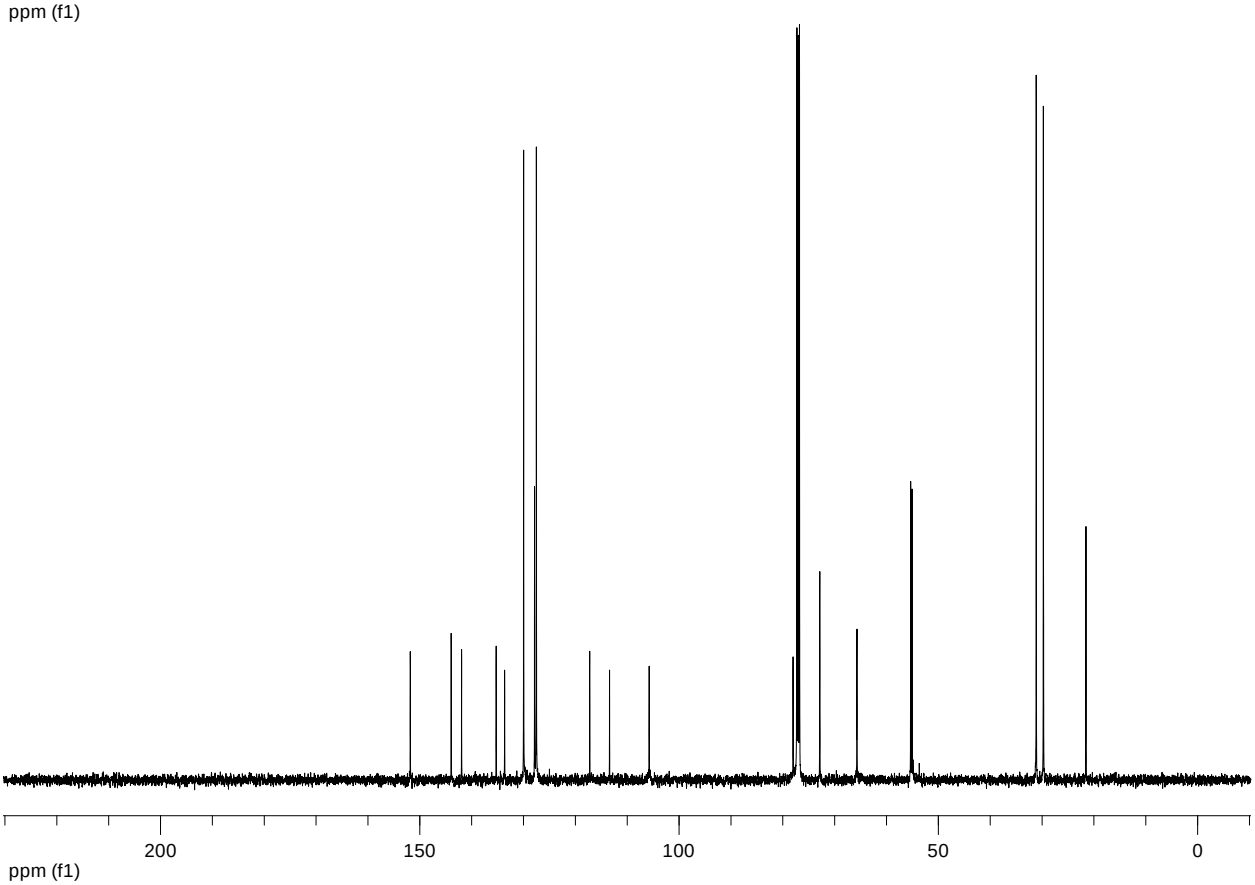


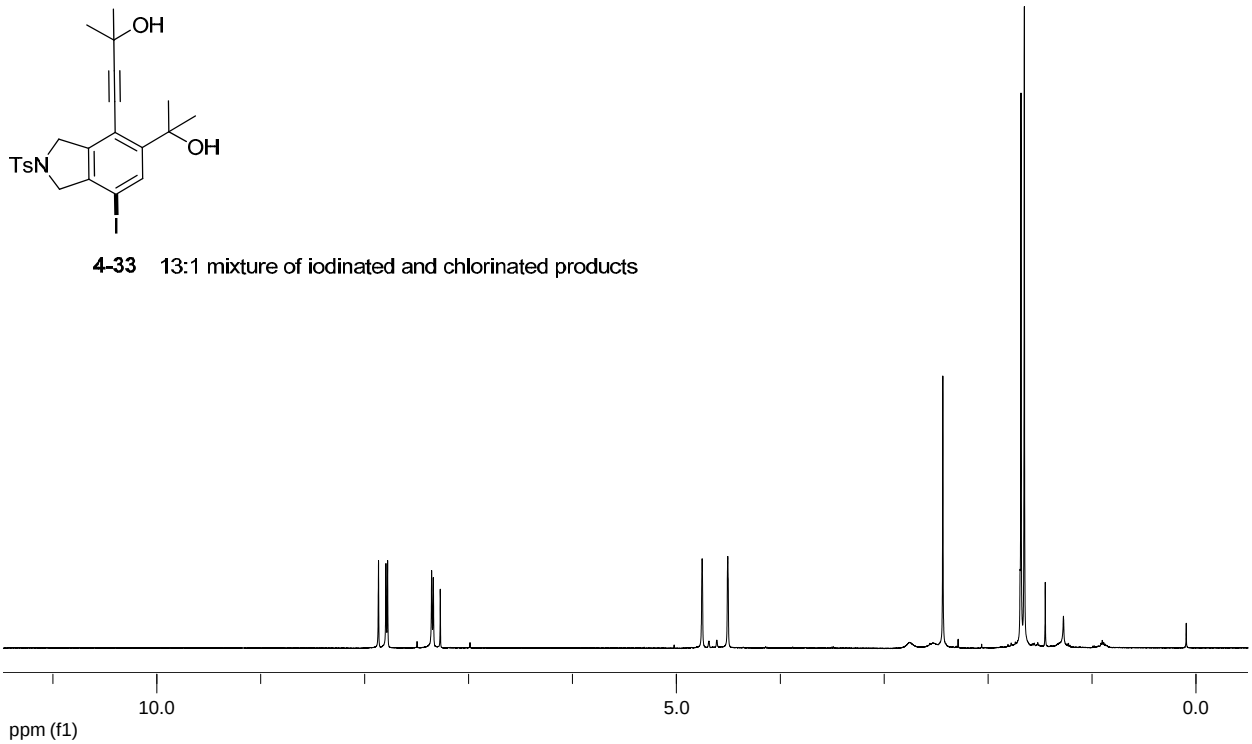



Ph-(4-OMe)
Ph-(4-OMe)
MeO2C
MeO2C
Br
4-31
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

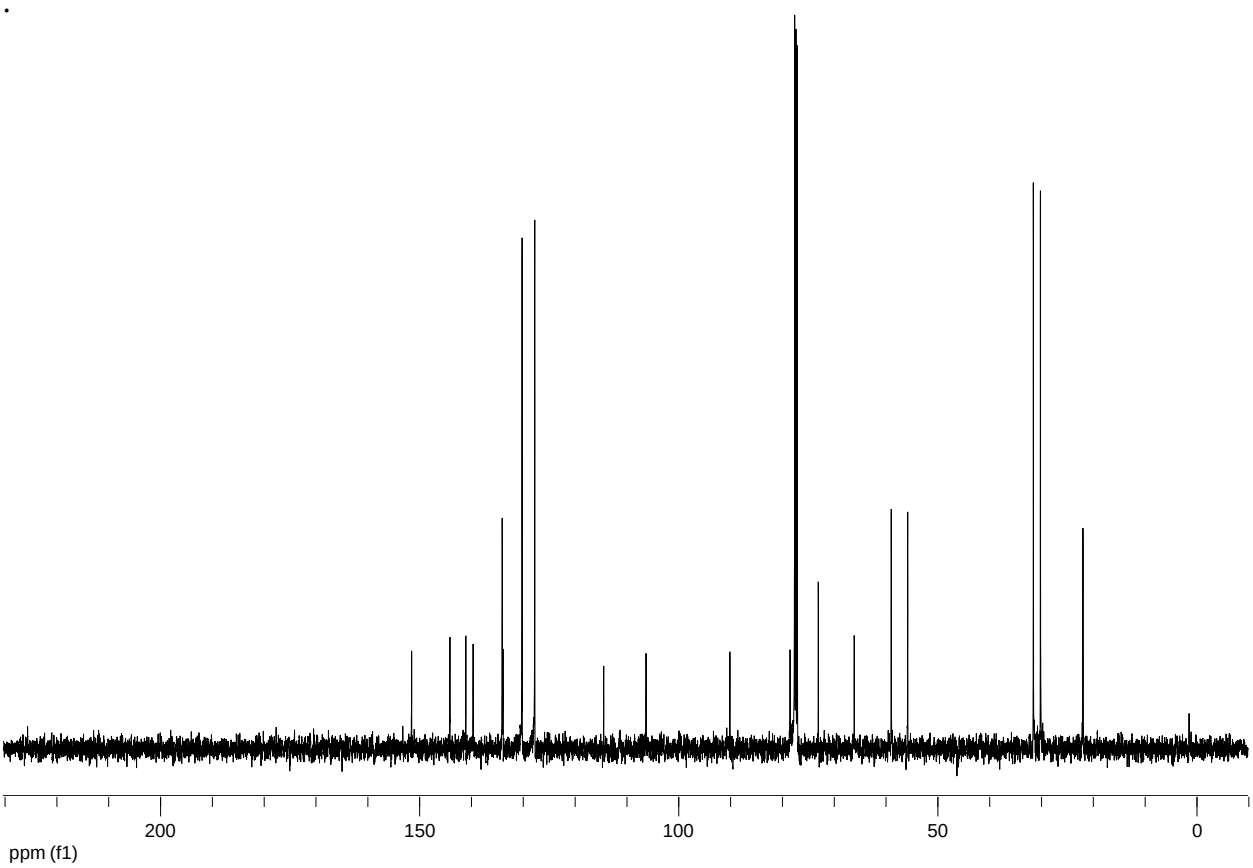

200
150
100
50
0
ppm (f1)

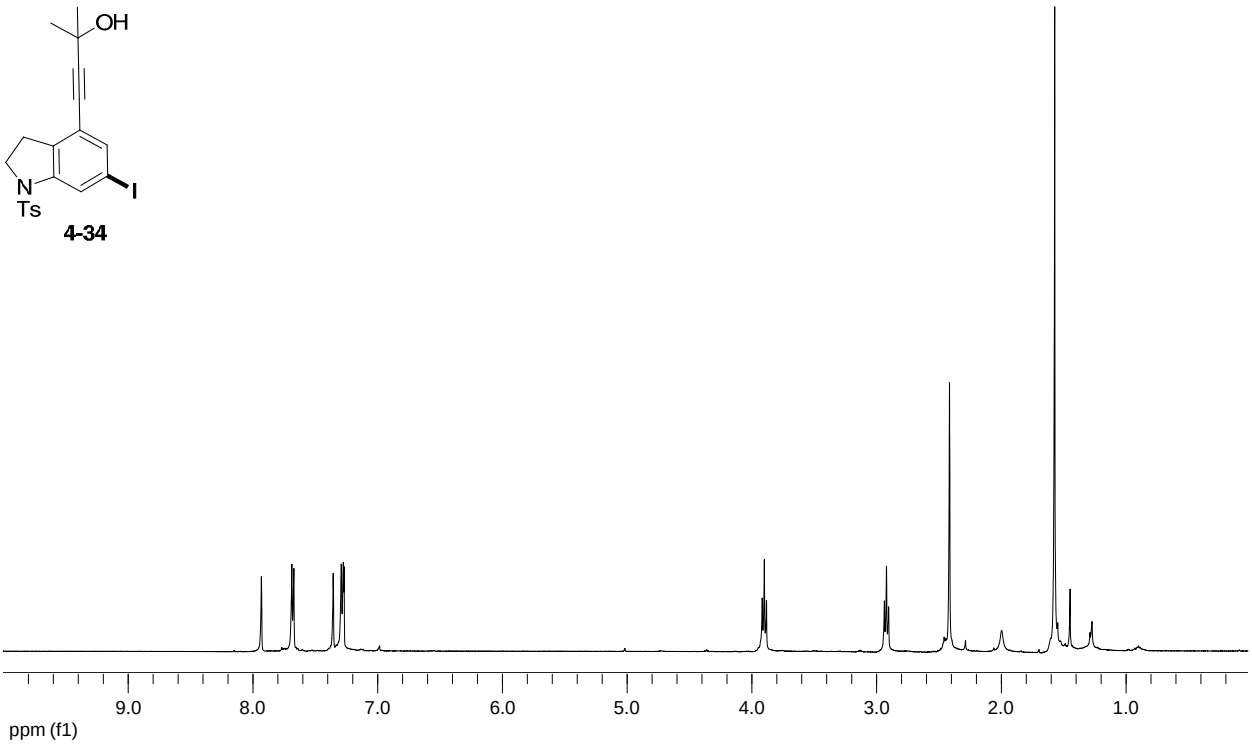

OH
OH
TsN
Br
4-32
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

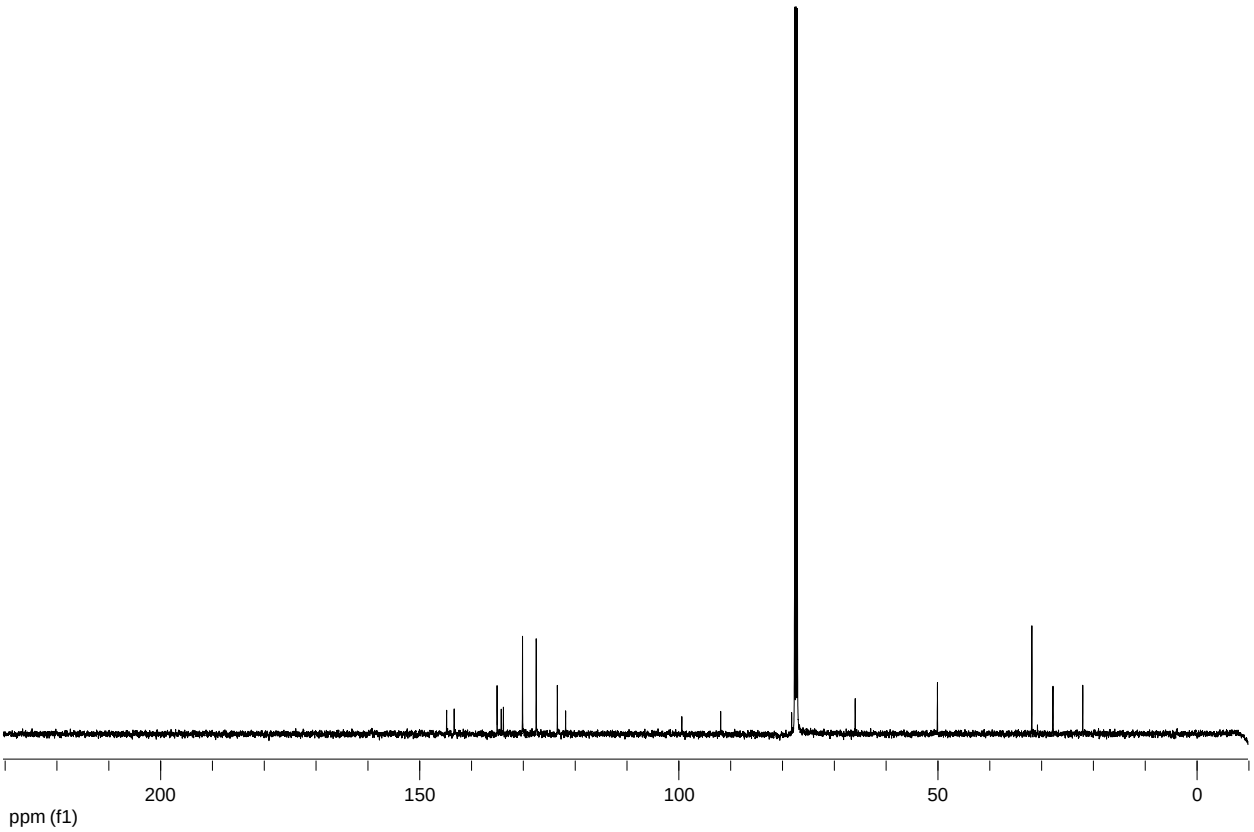

200
150
100
50
0
ppm (f1)



4-33 13:1 mixture of iodinated and chlorinated products

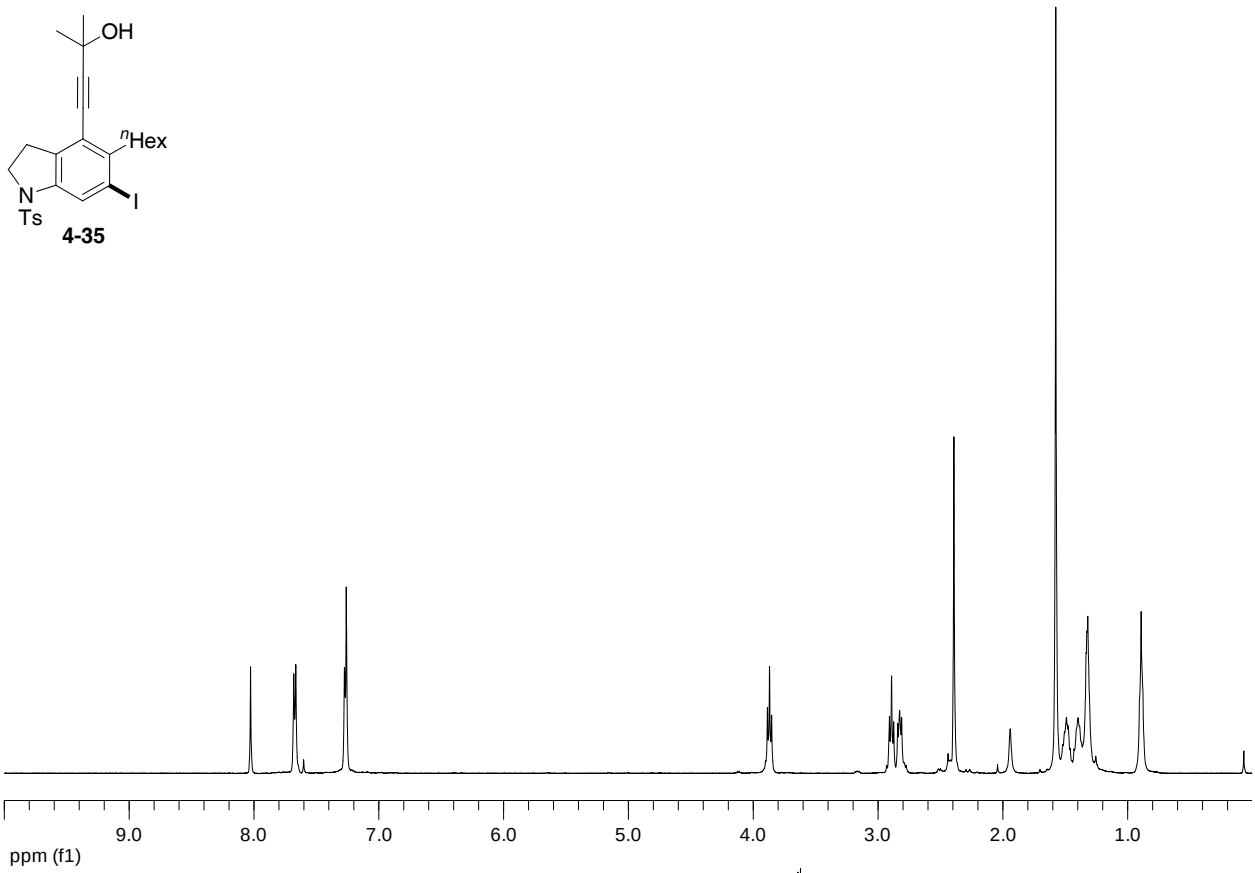


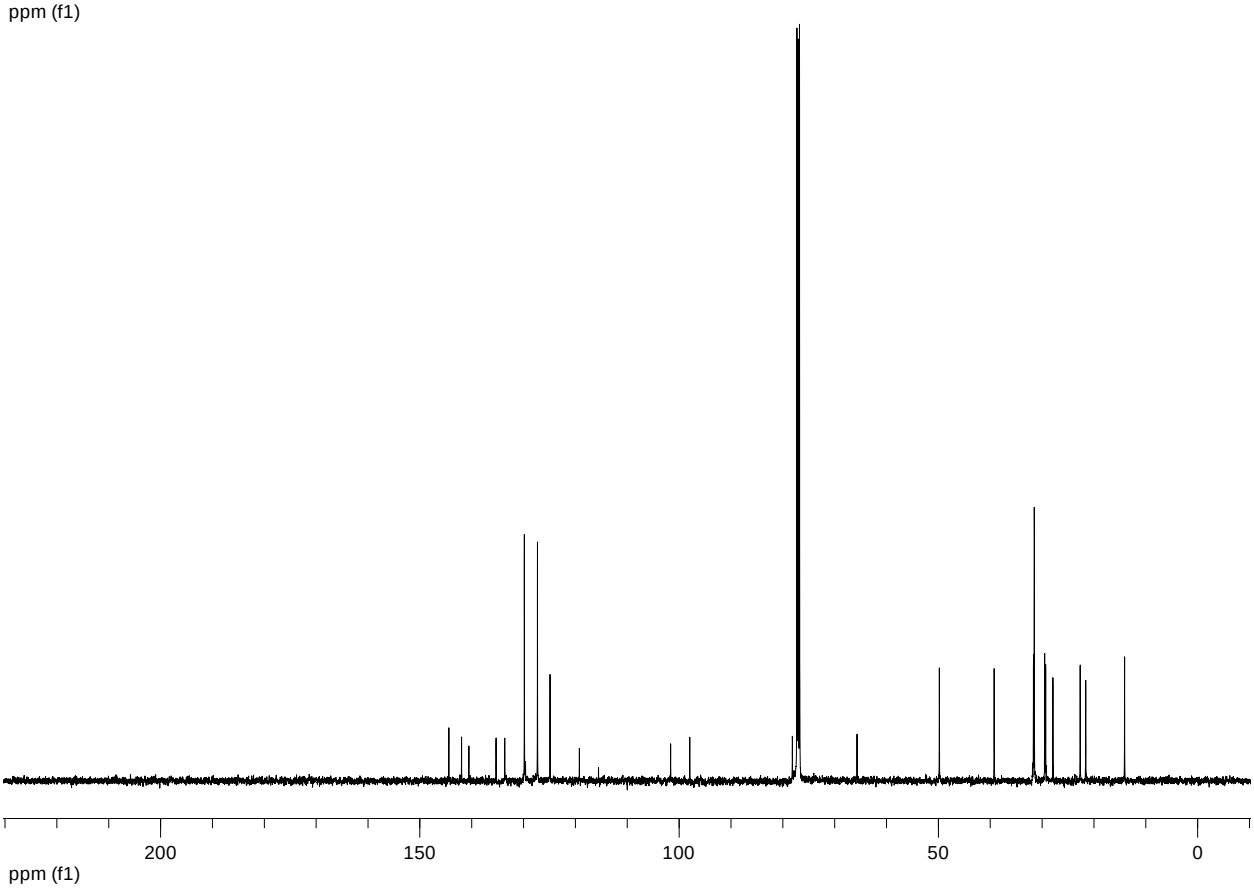

OH
N
Ts
I
4-34
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

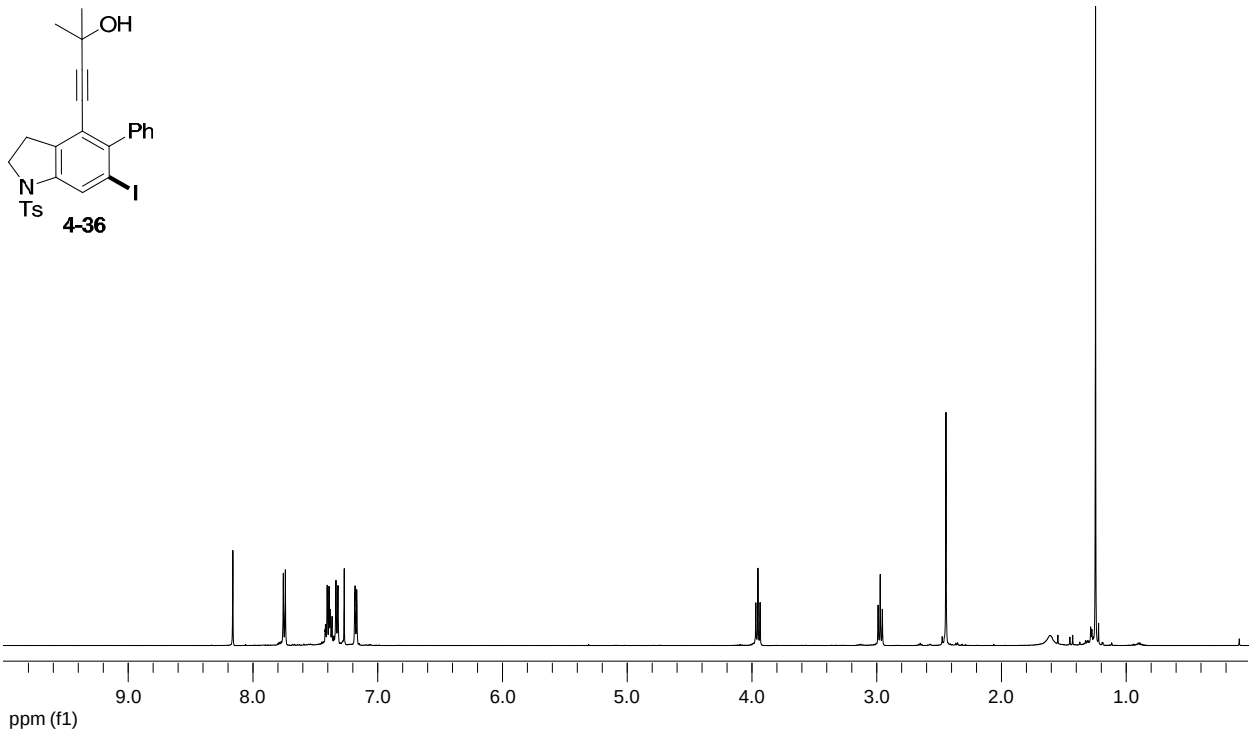

200
150
100
50
0
ppm (f1)

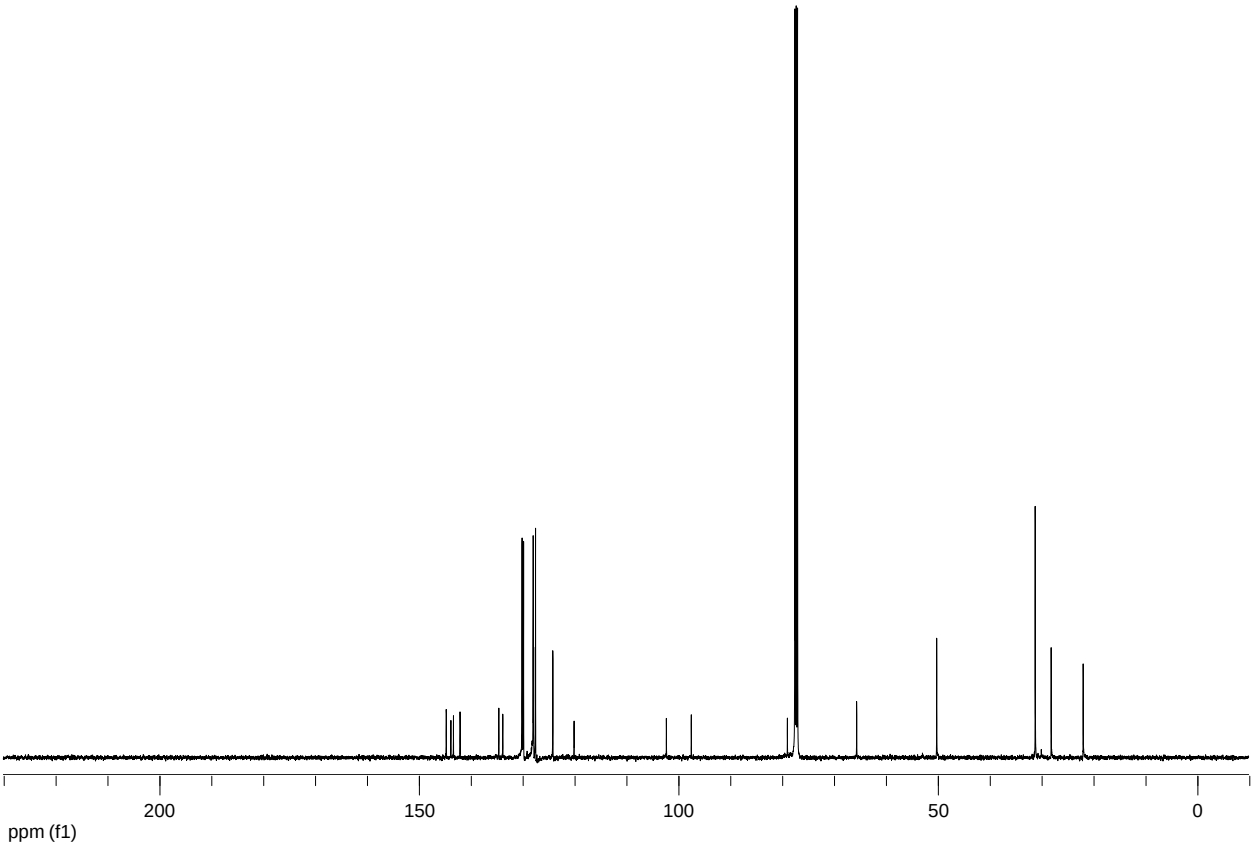
OH
nHex
N
Ts
I

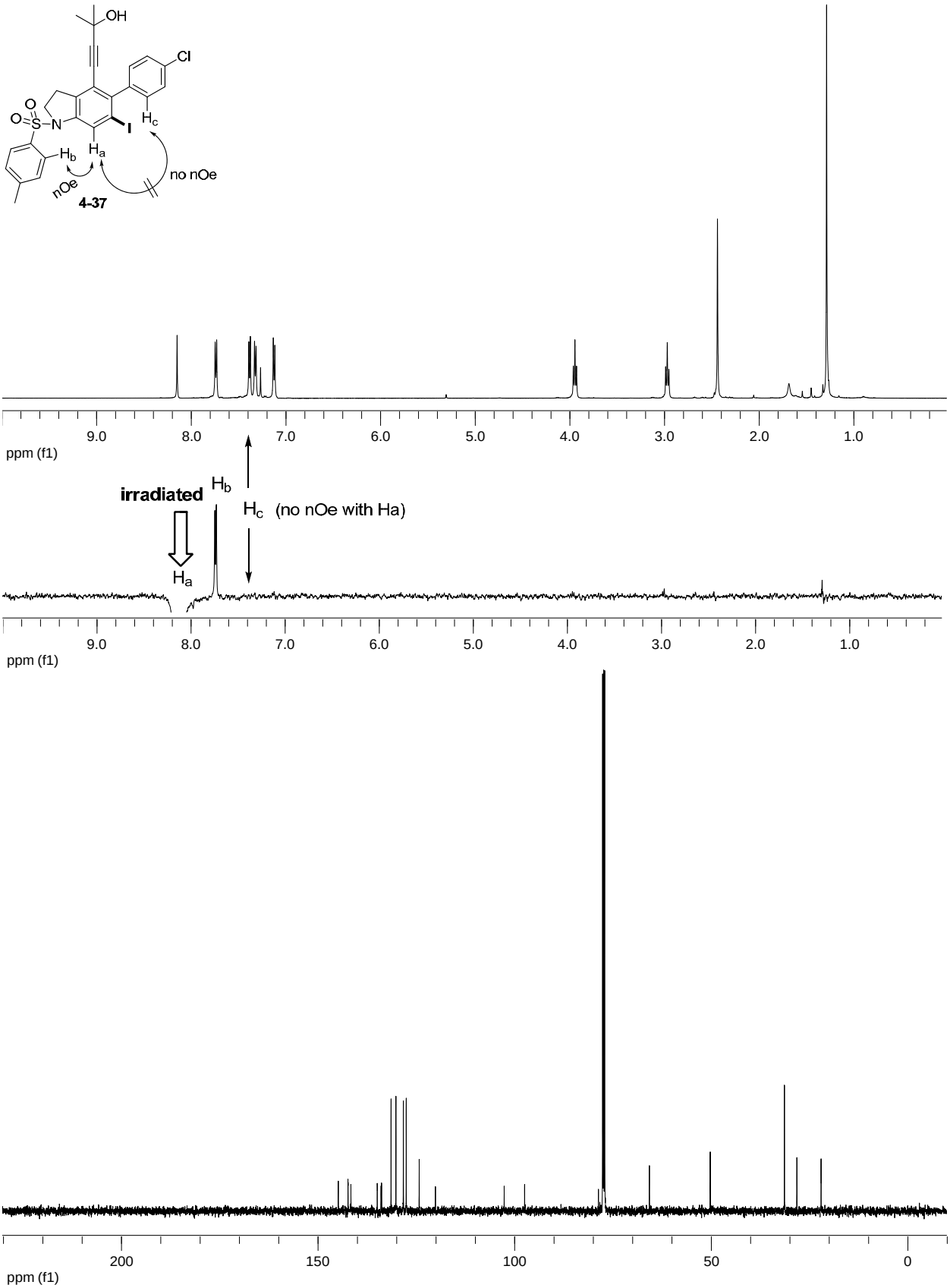
4-35


9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)


200
150
100
50
0
ppm (f1)

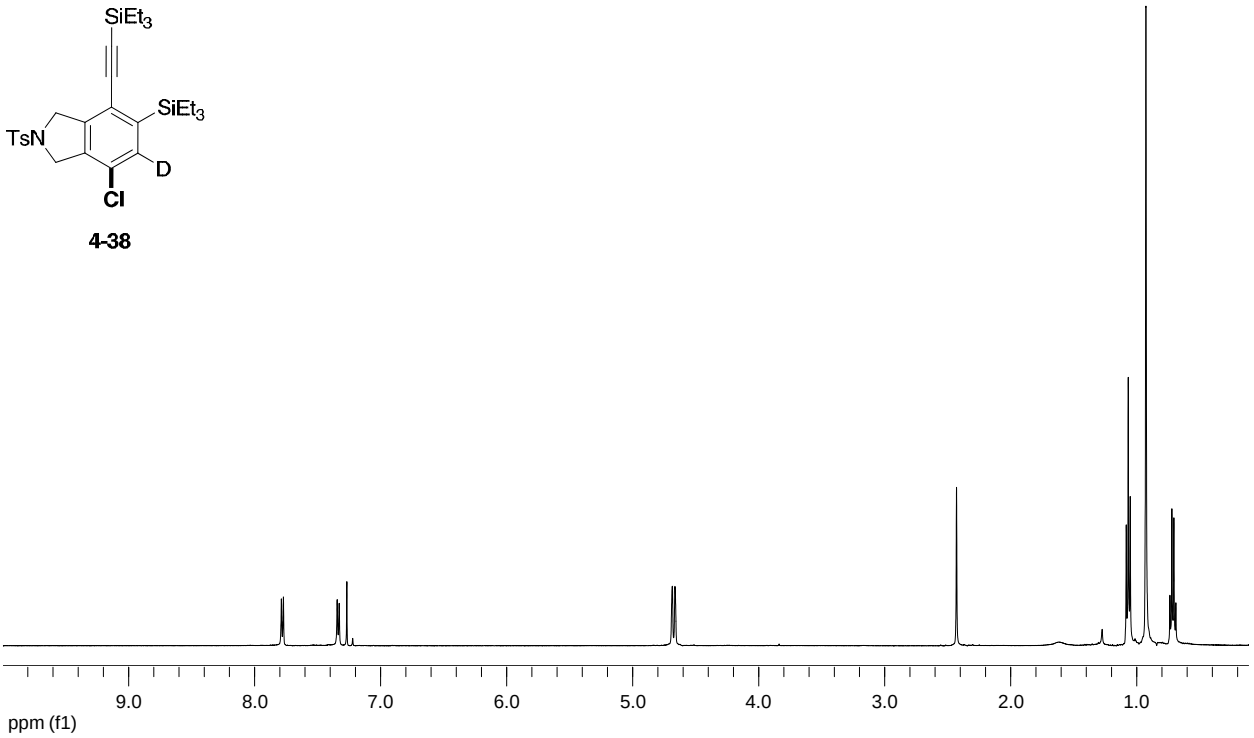

OH
Ph
N
Ts
I
4-36
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

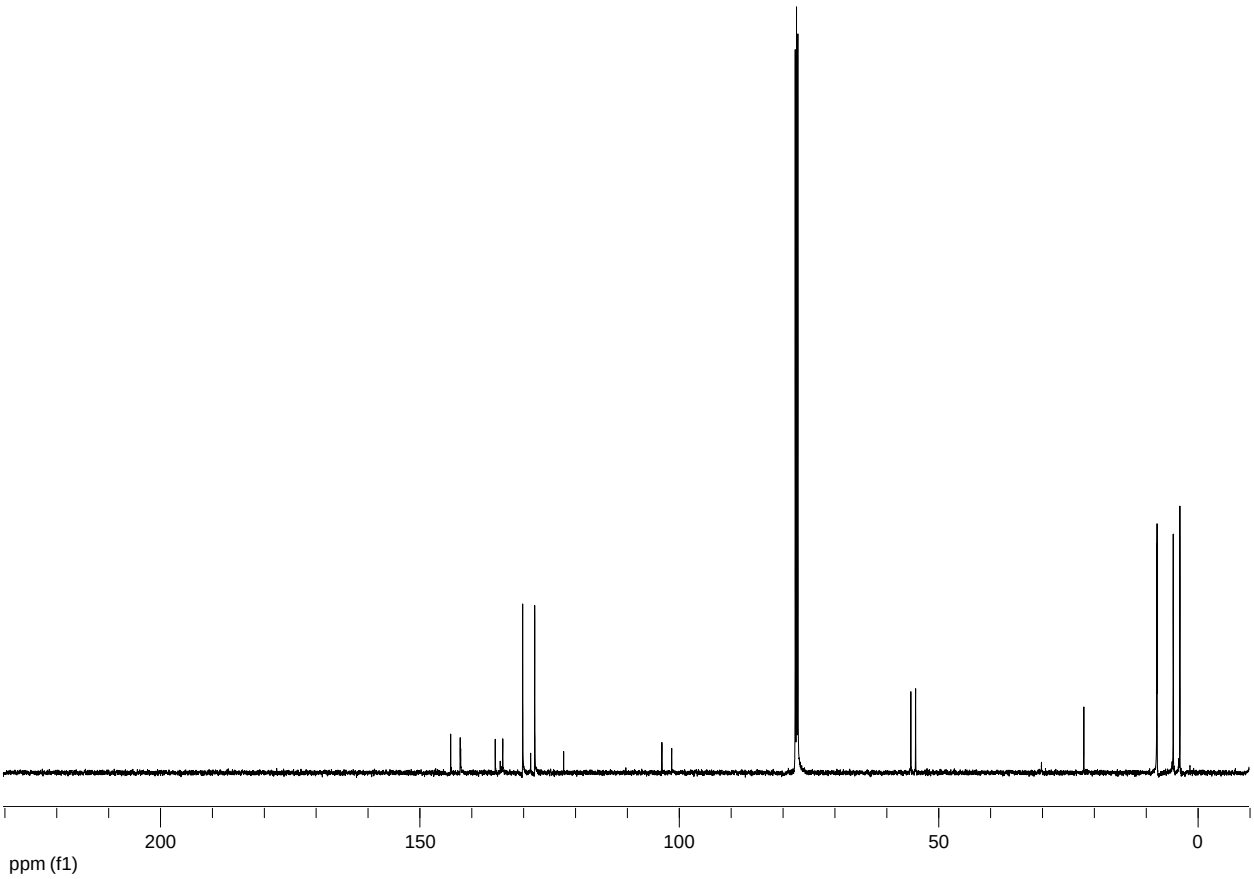

200
150
100
50
0
ppm (f1)

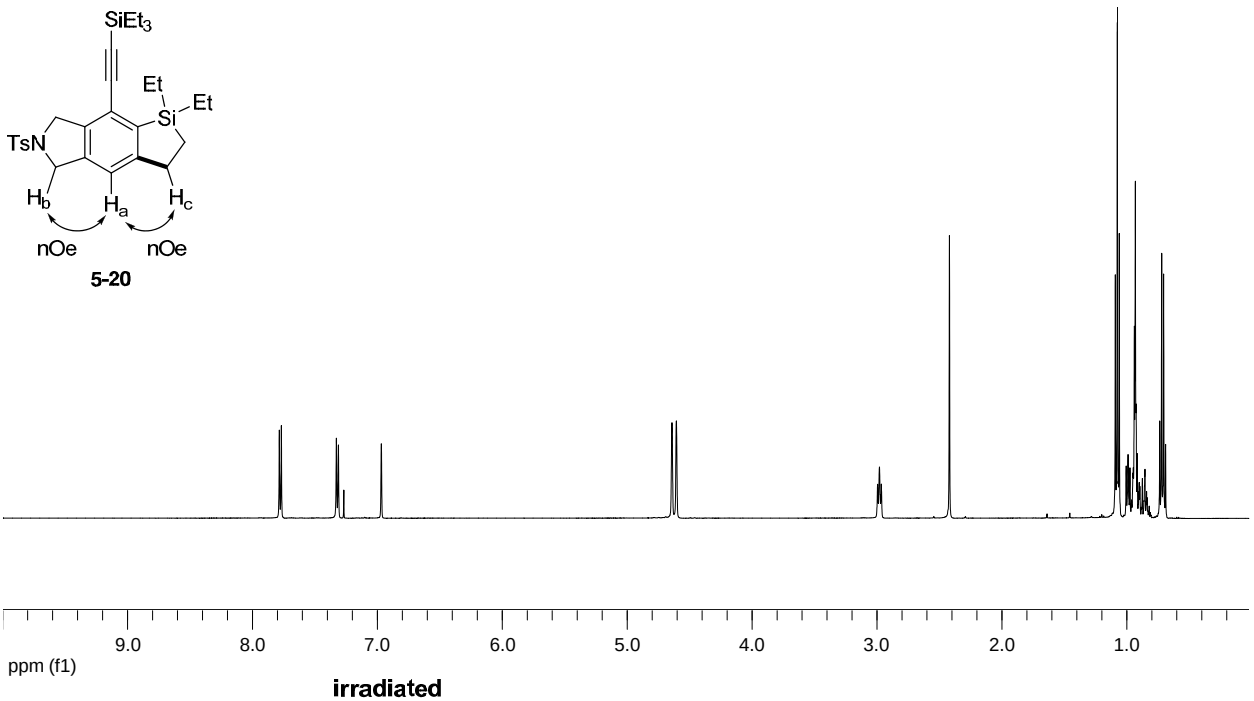

OH
Cl
O
O
S
N
I
Hc
Hb
Ha
nOe
no nOe
4-37
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)
irradiated
Hb
Hc (no nOe with Ha)
Ha
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)
200
150
100
50
0
ppm (f1)

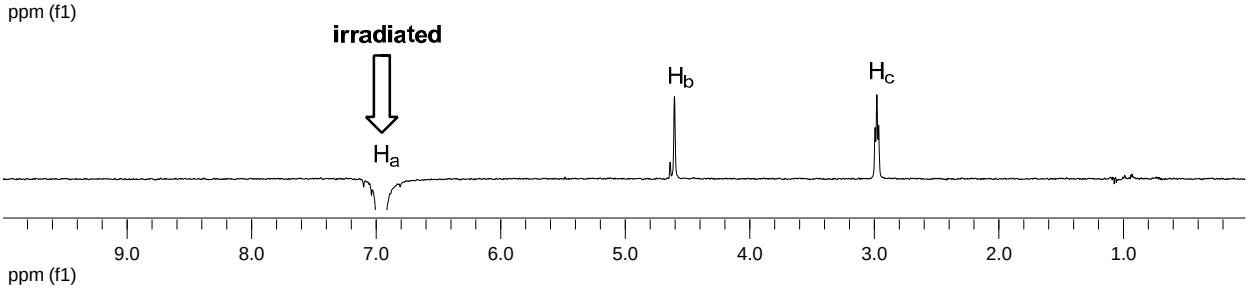
SiEt3
SiEt3
TsN
D
Cl

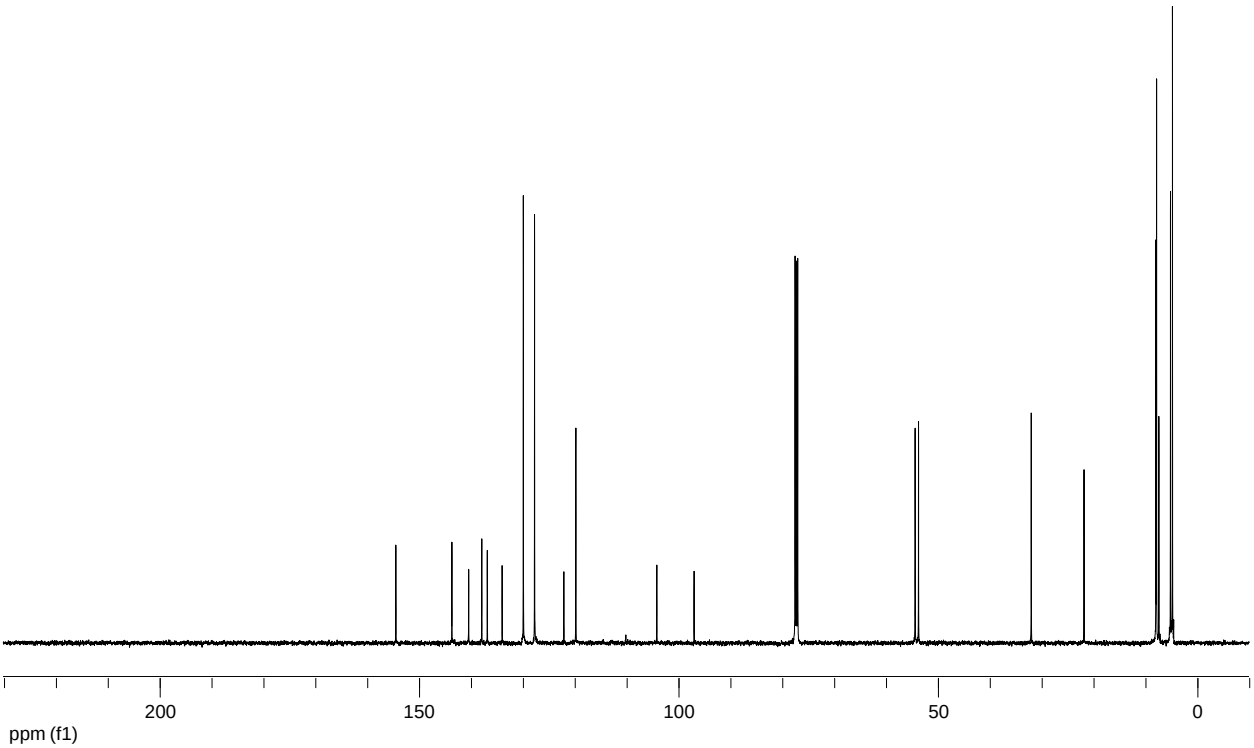
4-38

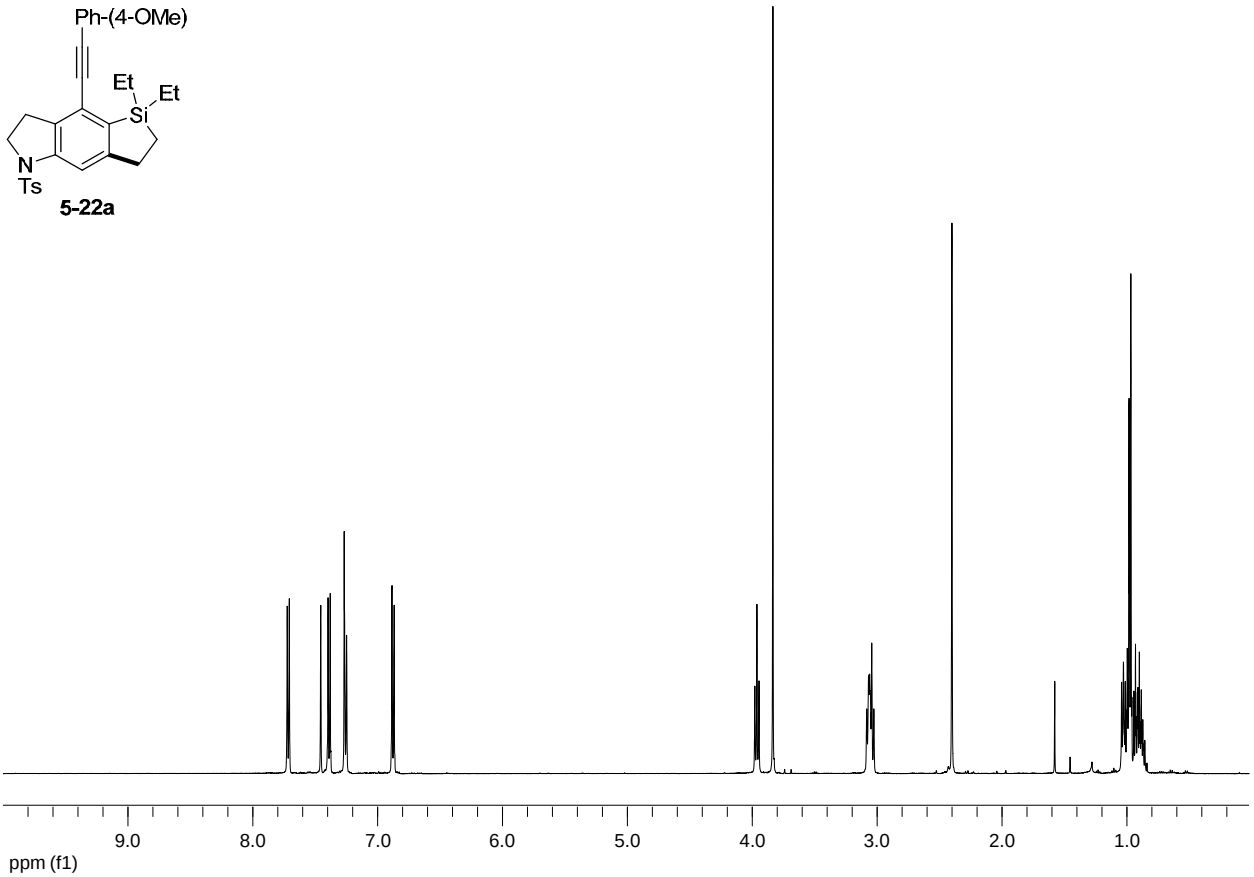

9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

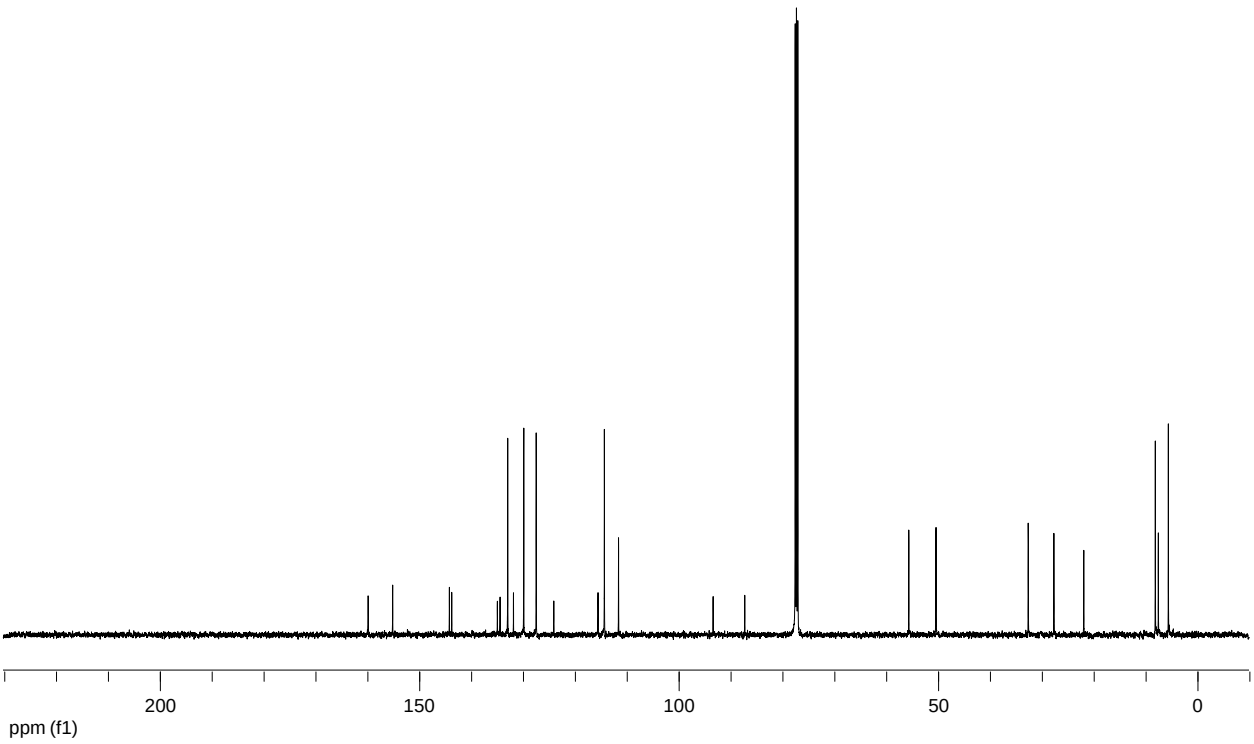

200
150
100
50
0
ppm (f1)

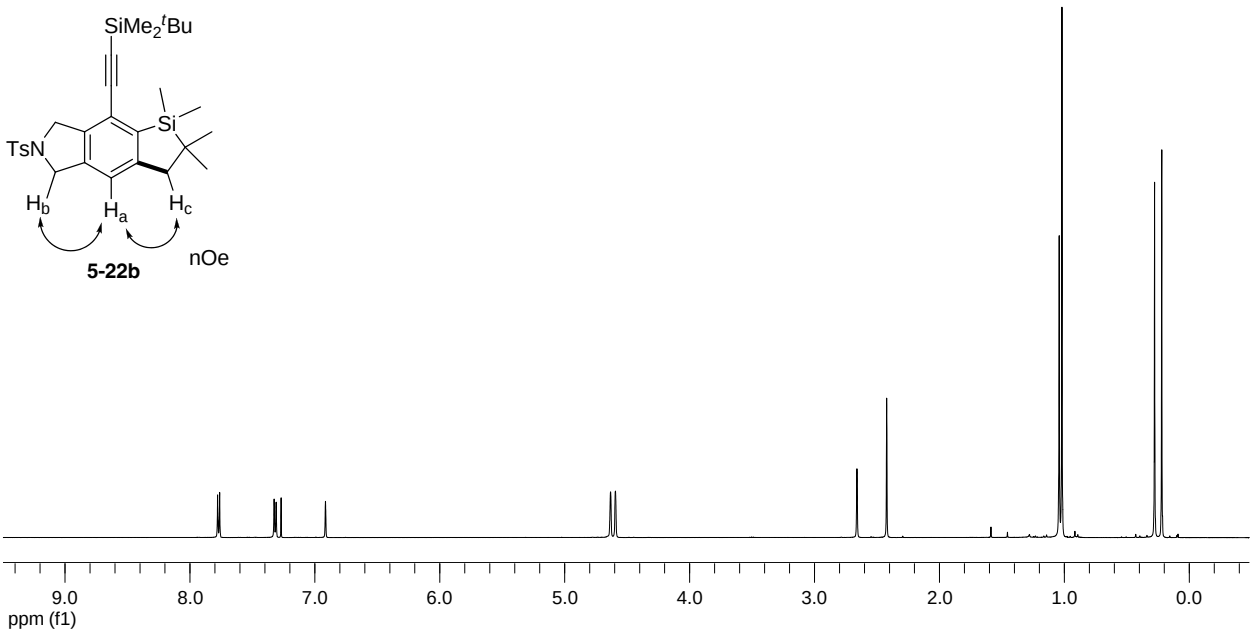

SiEt3
Et
Si
Et
TsN
Hb
Ha
Hc
nOe
nOe
5-20
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

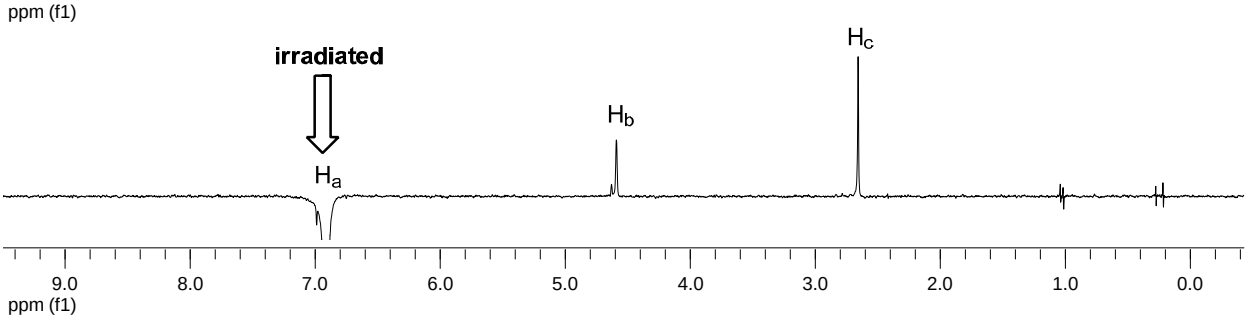

irradiated
Ha
Hb
Hc
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

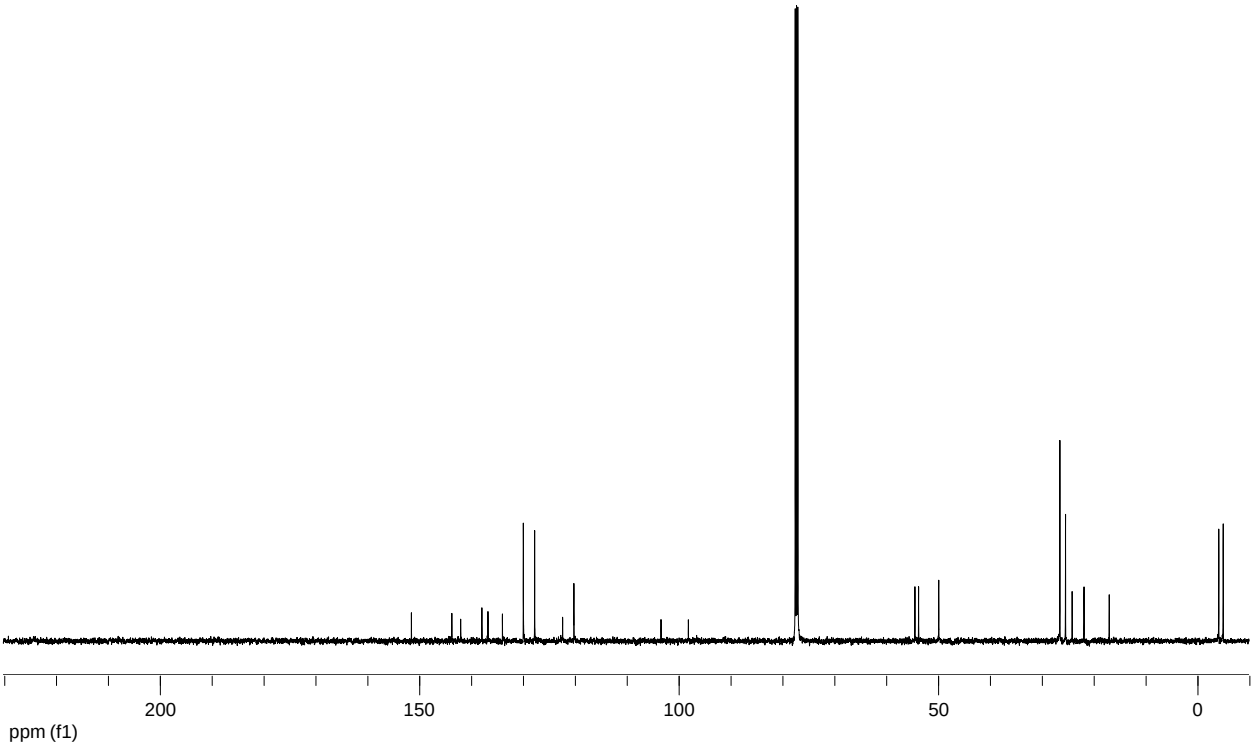

200
150
100
50
0
ppm (f1)

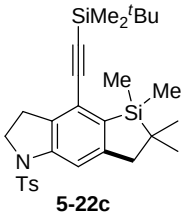

Ph-(4-OMe)
Et
Et
Si
N
Ts
5-22a
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)


200
150
100
50
0
ppm (f1)

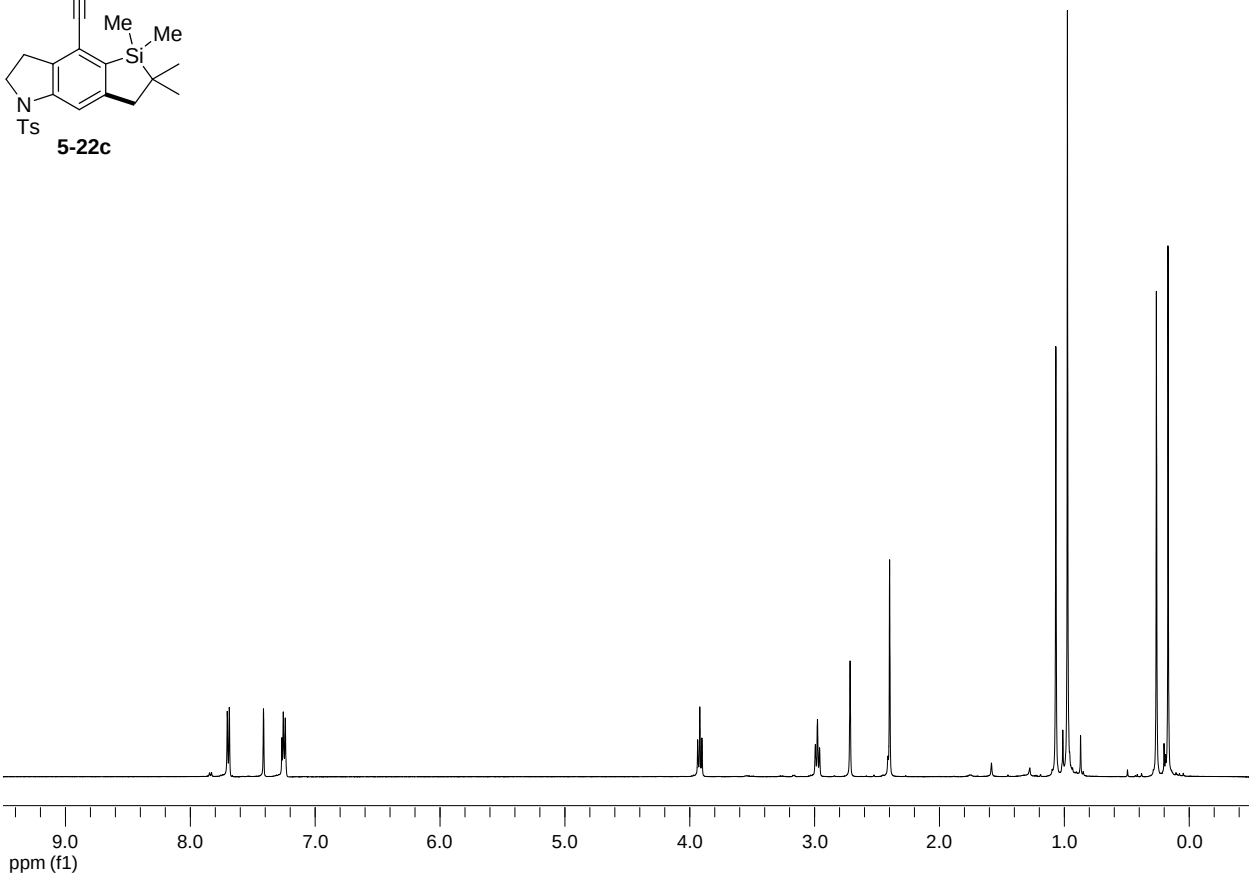

SiMe2tBu
TsN
Si
Hb
Ha
Hc
nOe
5-22b
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

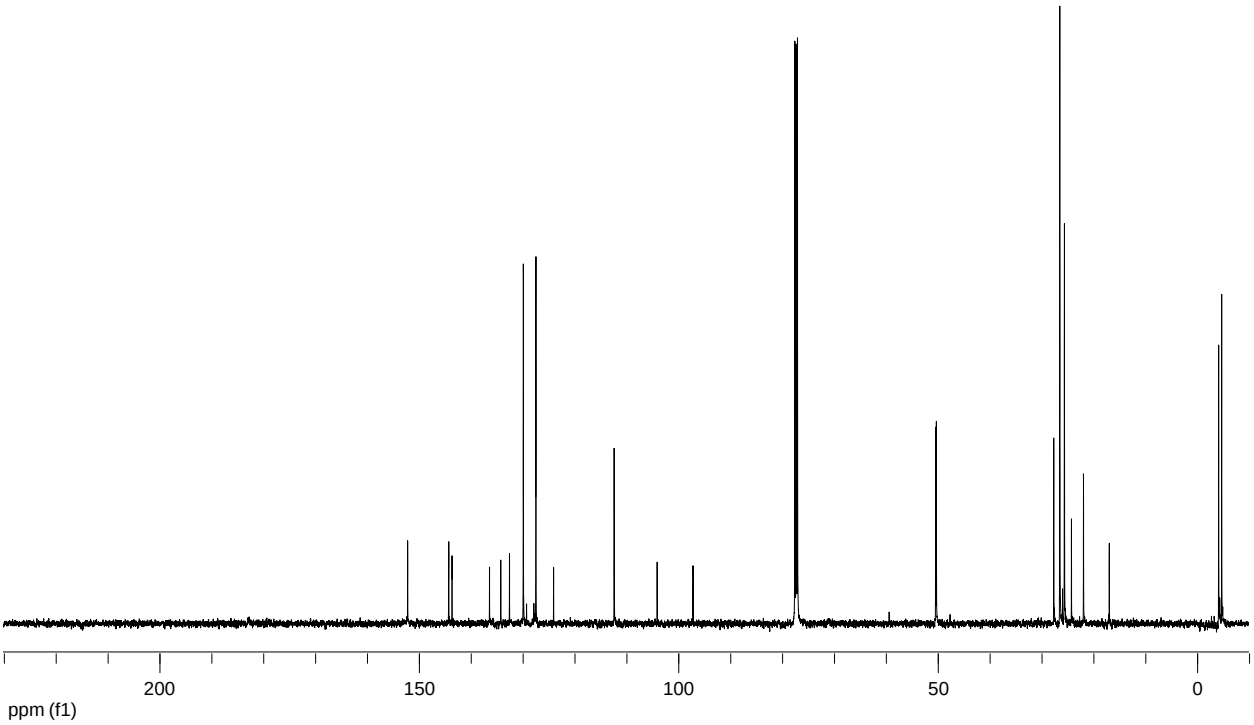

irradiated
Ha
Hb
Hc
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)


200
150
100
50
0
ppm (f1)


SiMe2tBu
Me
Me
Si
N
Ts

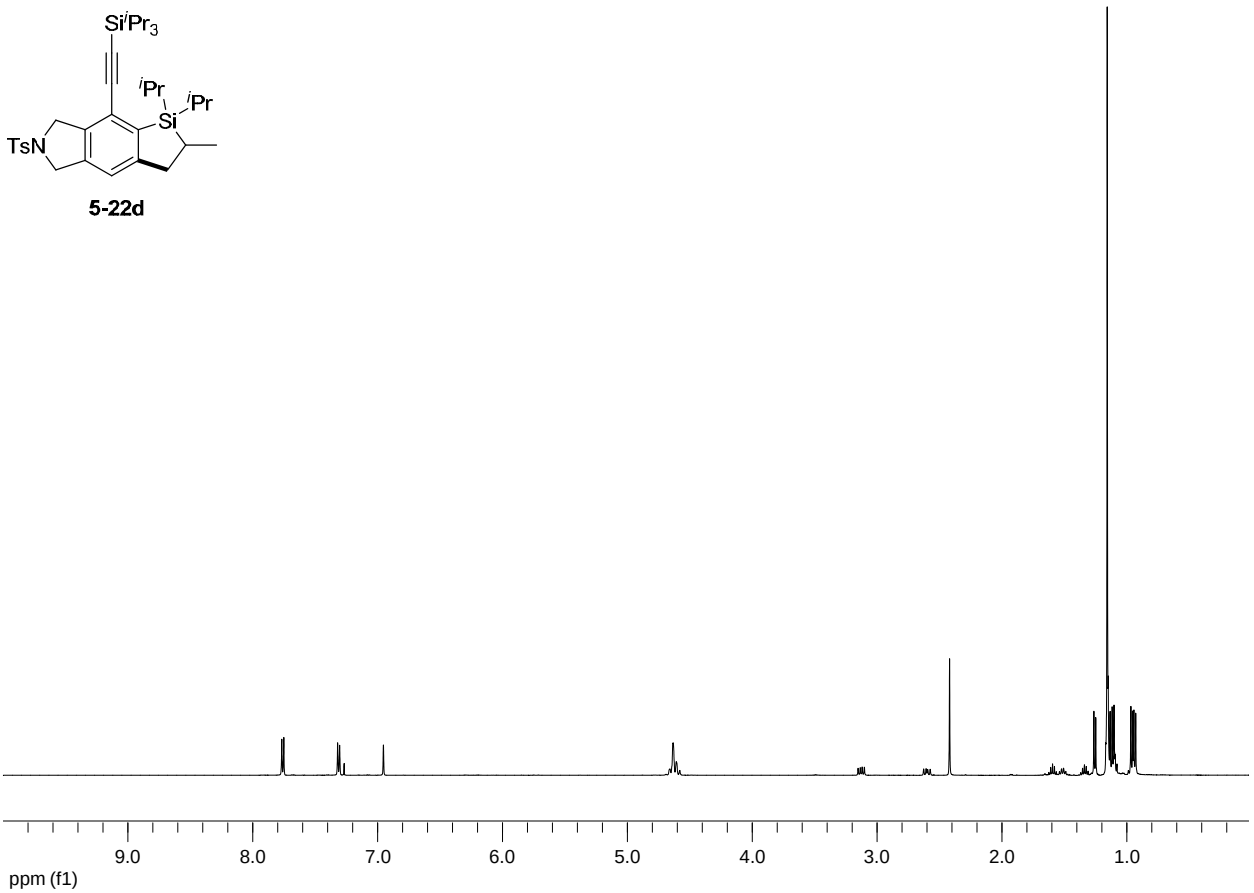
5-22c

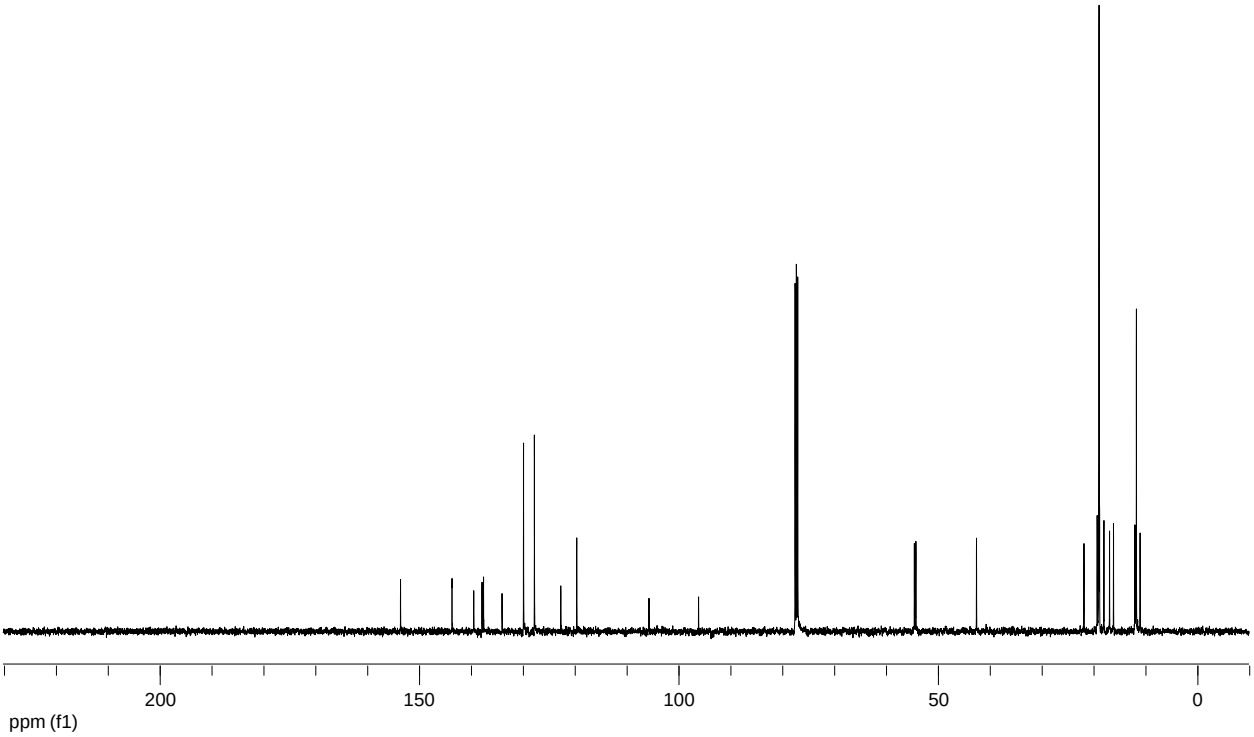

9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)


200
150
100
50
0
ppm (f1)

Si^{i}Pr$_3$
^{i}Pr
^{i}Pr
Si
TsN

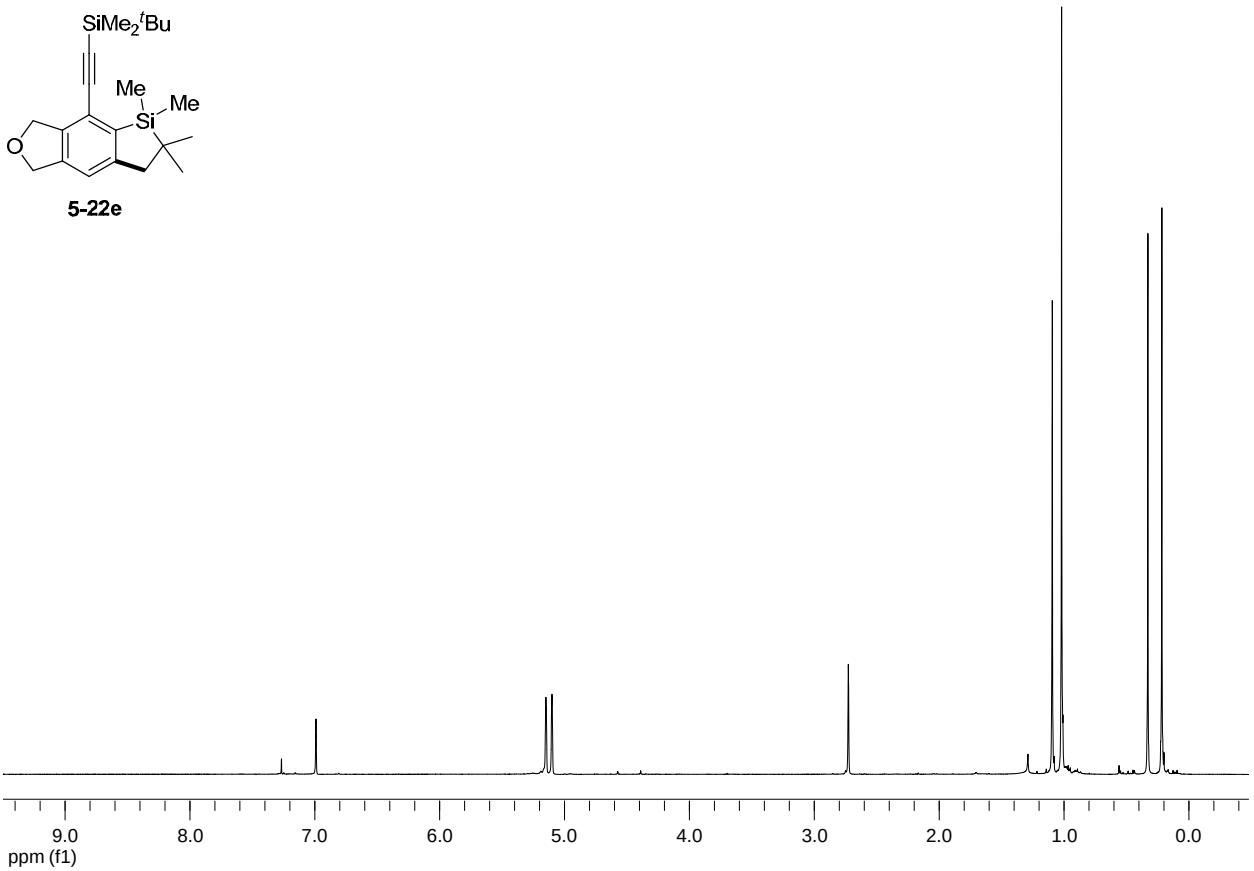
5-22d

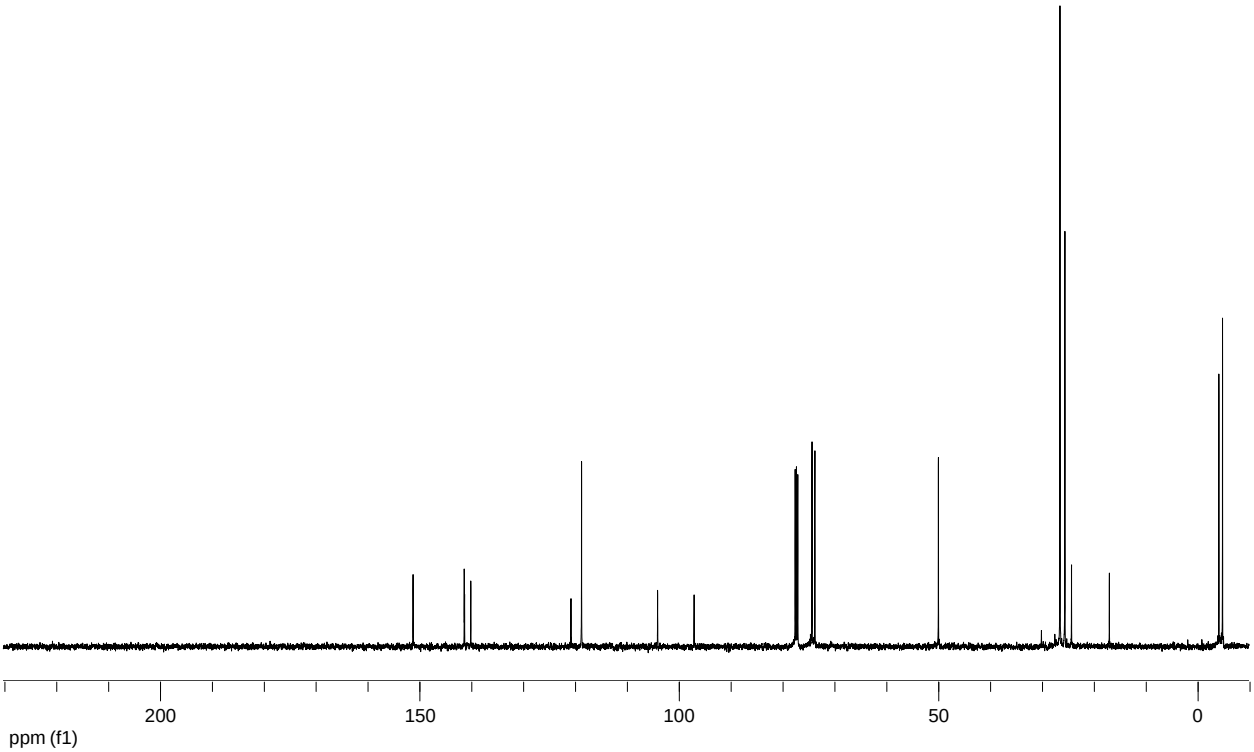

9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

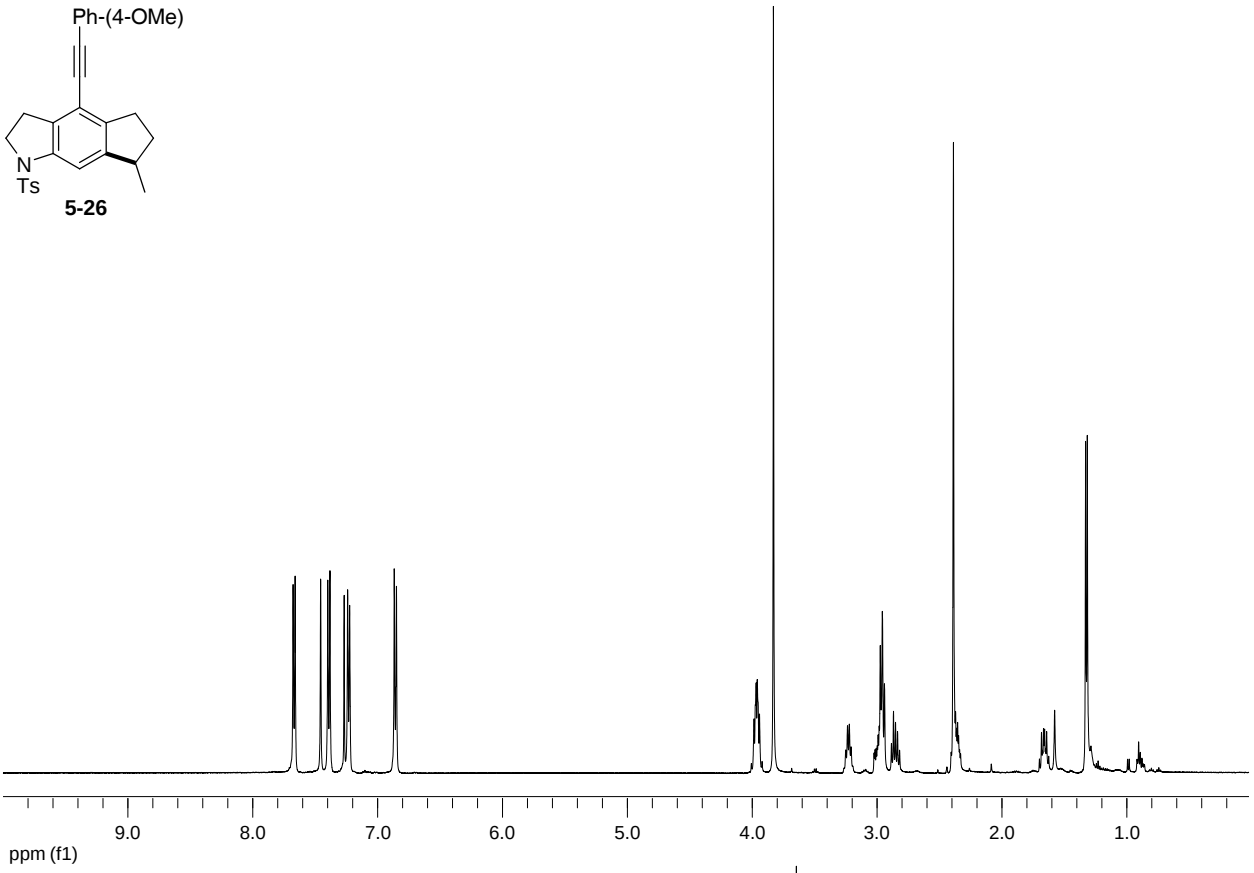

200
150
100
50
0
ppm (f1)

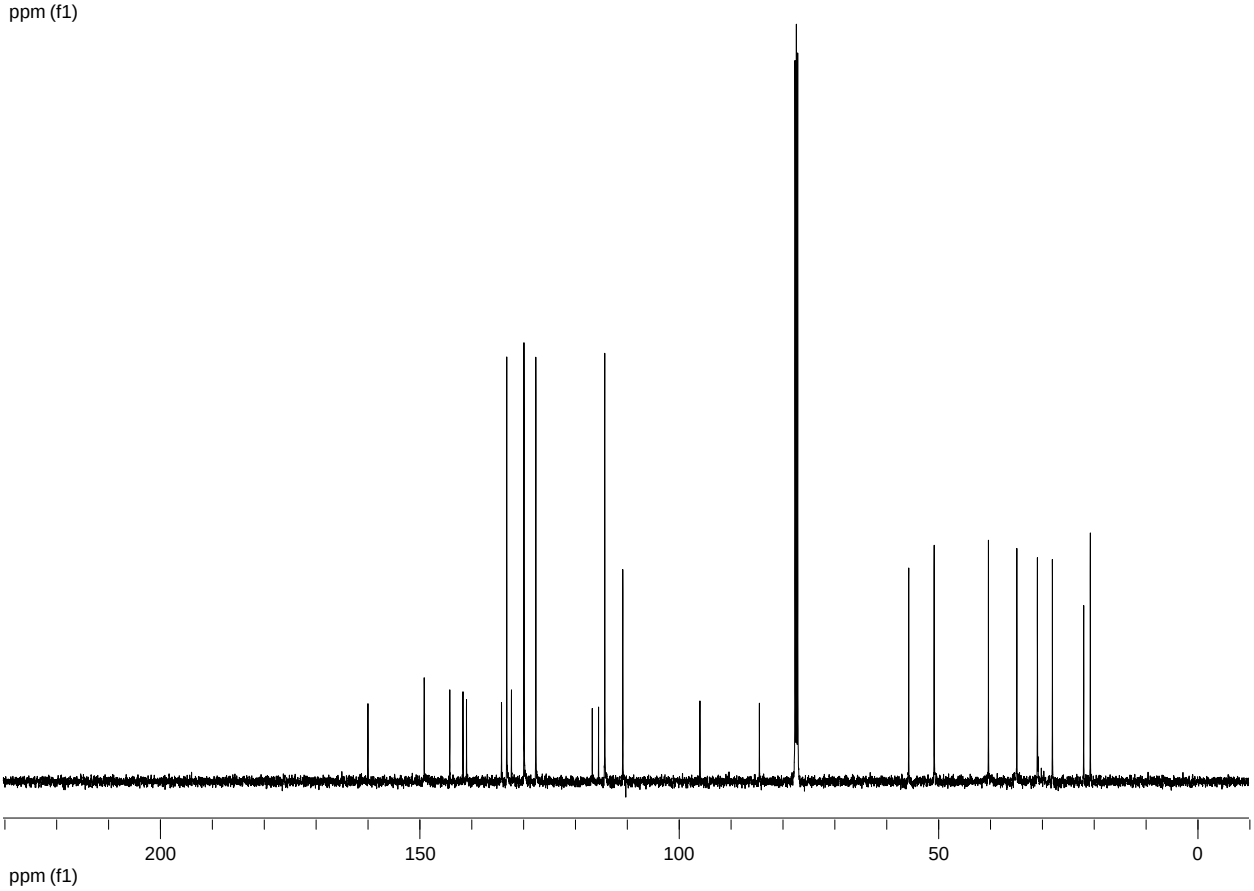
SiMe2tBu
Me
Me
Si
O

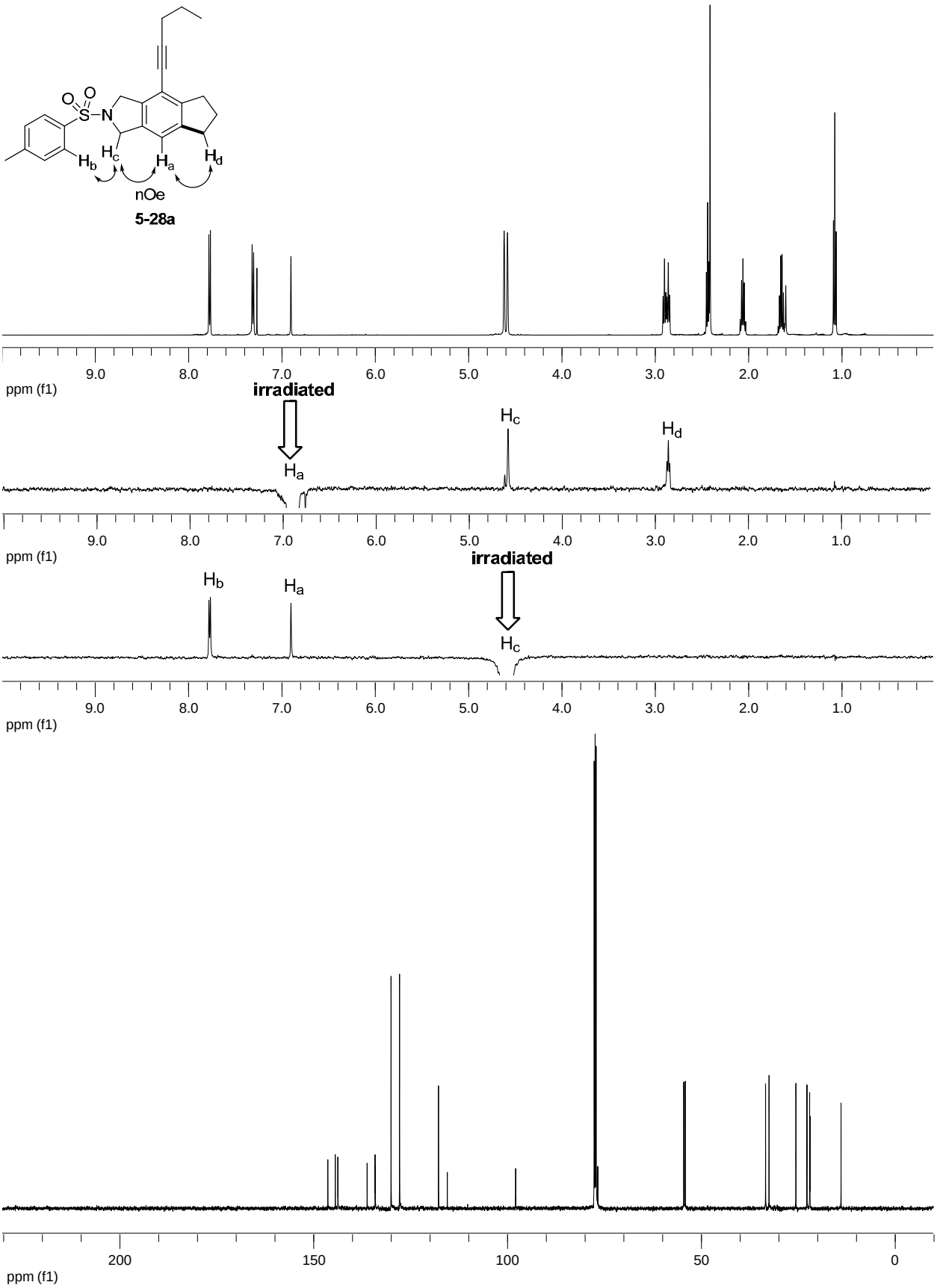
5-22e


9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

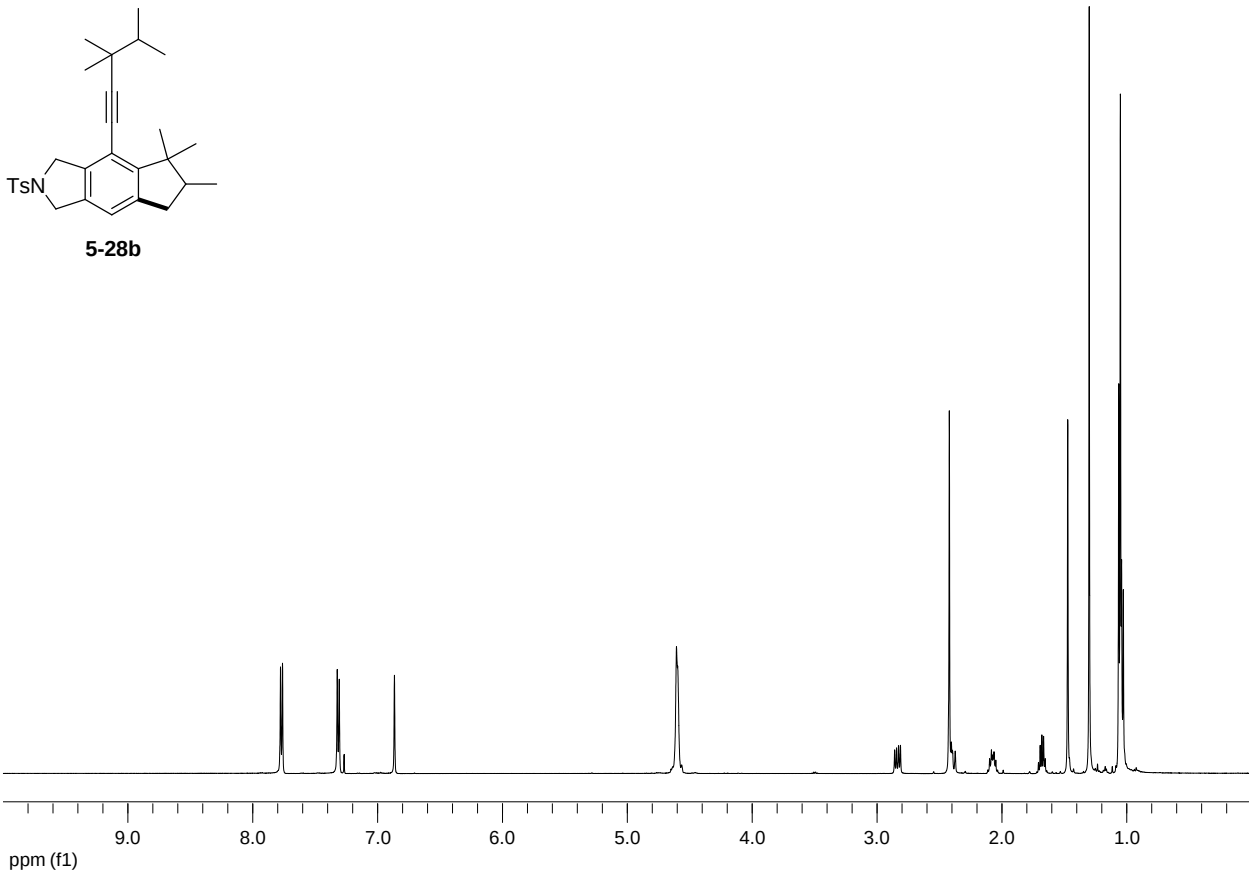

200
150
100
50
0
ppm (f1)

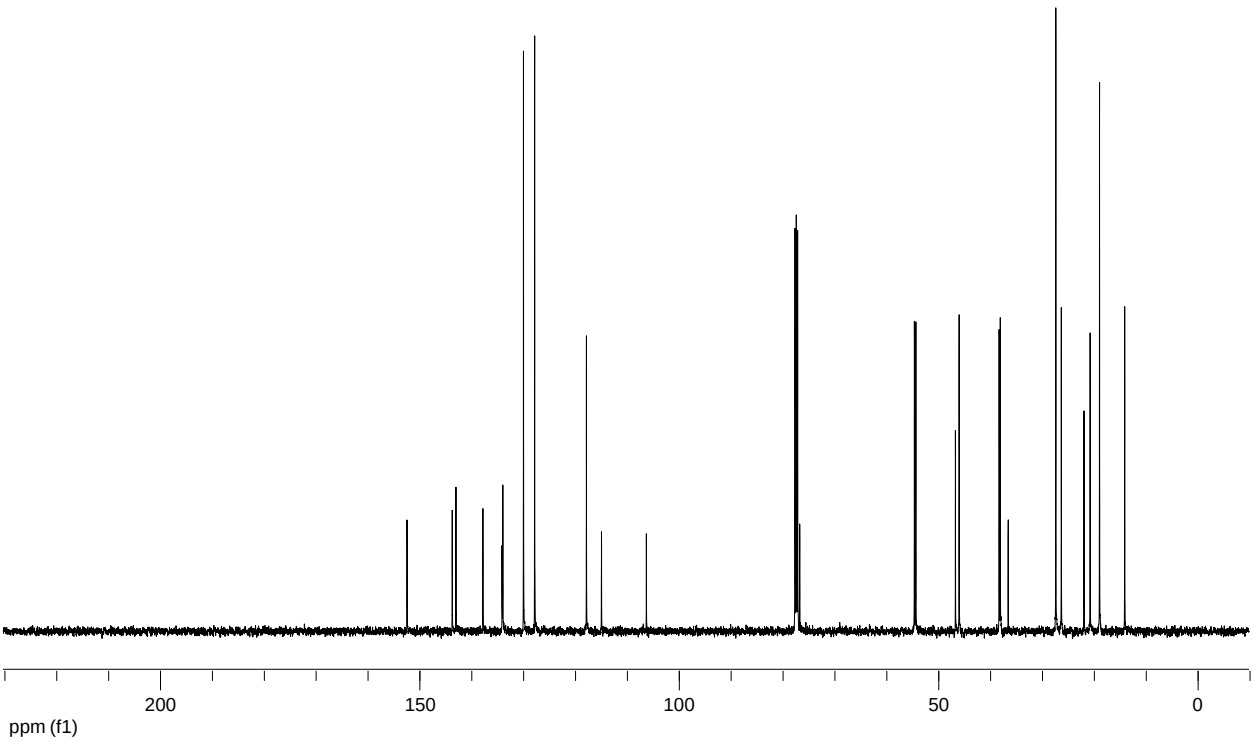

Ph-(4-OMe)
N
Ts
5-26
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

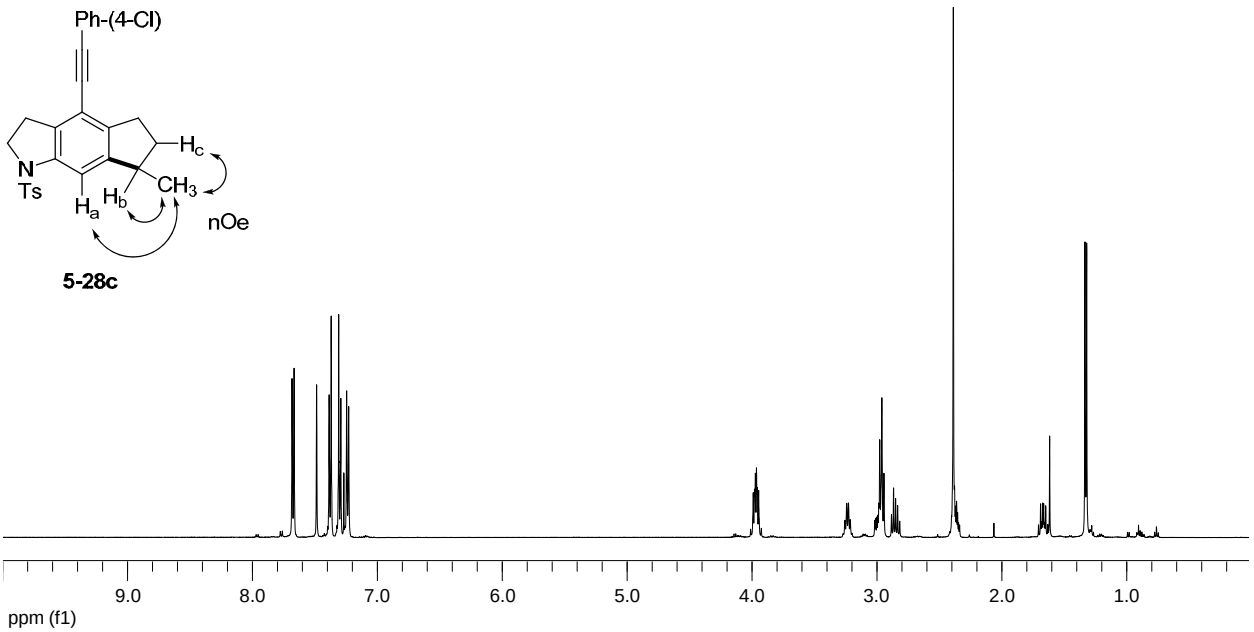

200
150
100
50
0
ppm (f1)

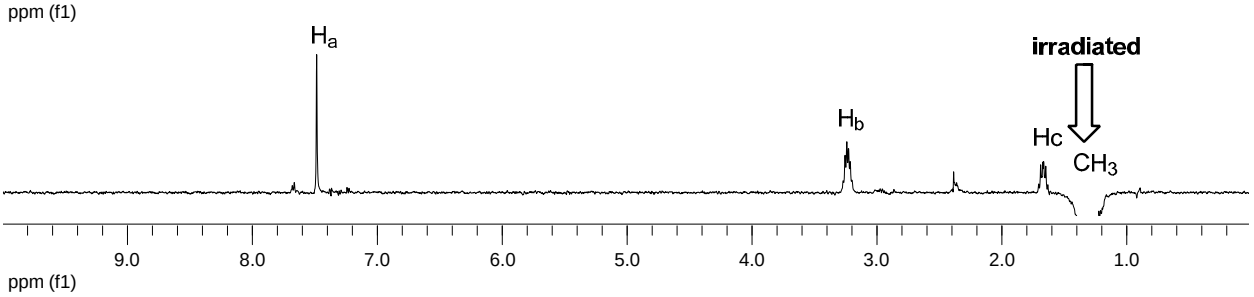

O
O
S
N
H_b
H_c
H_a
H_d
nOe
5-28a
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)
irradiated
H_a
H_c
H_d
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)
H_b
H_a
irradiated
H_c
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)
200
150
100
50
0
ppm (f1)

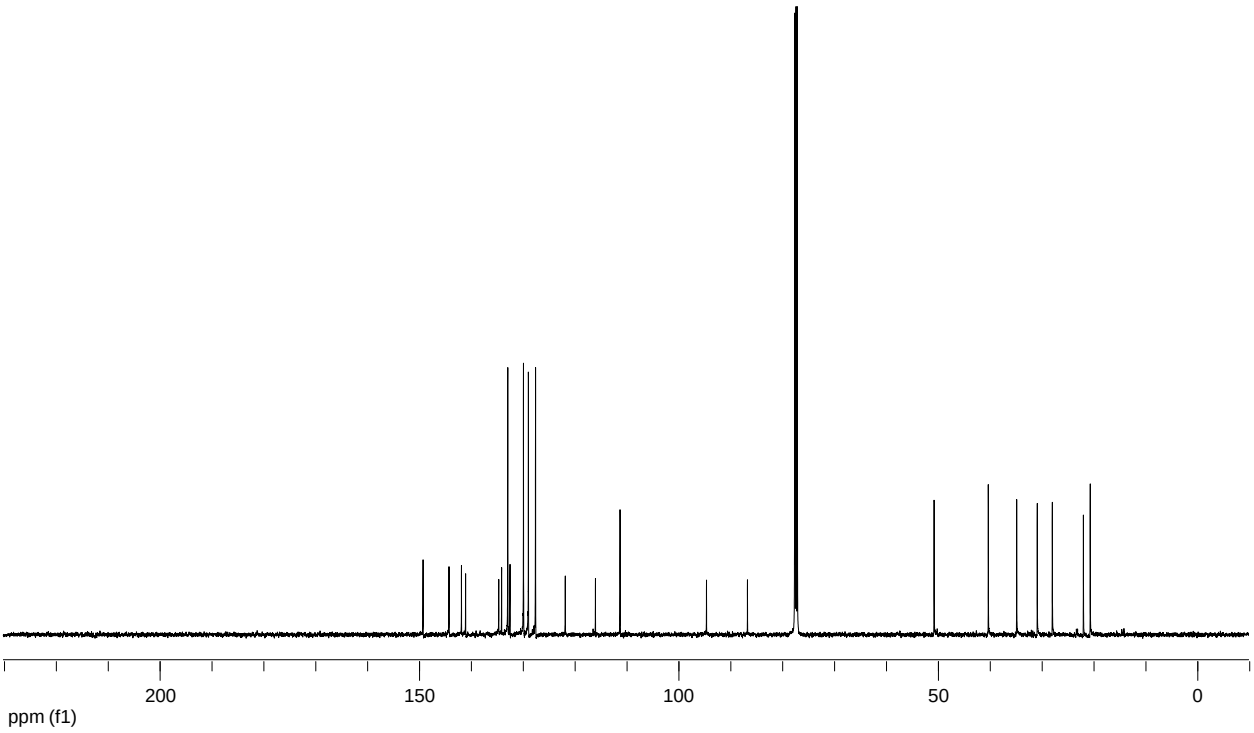
5-28b

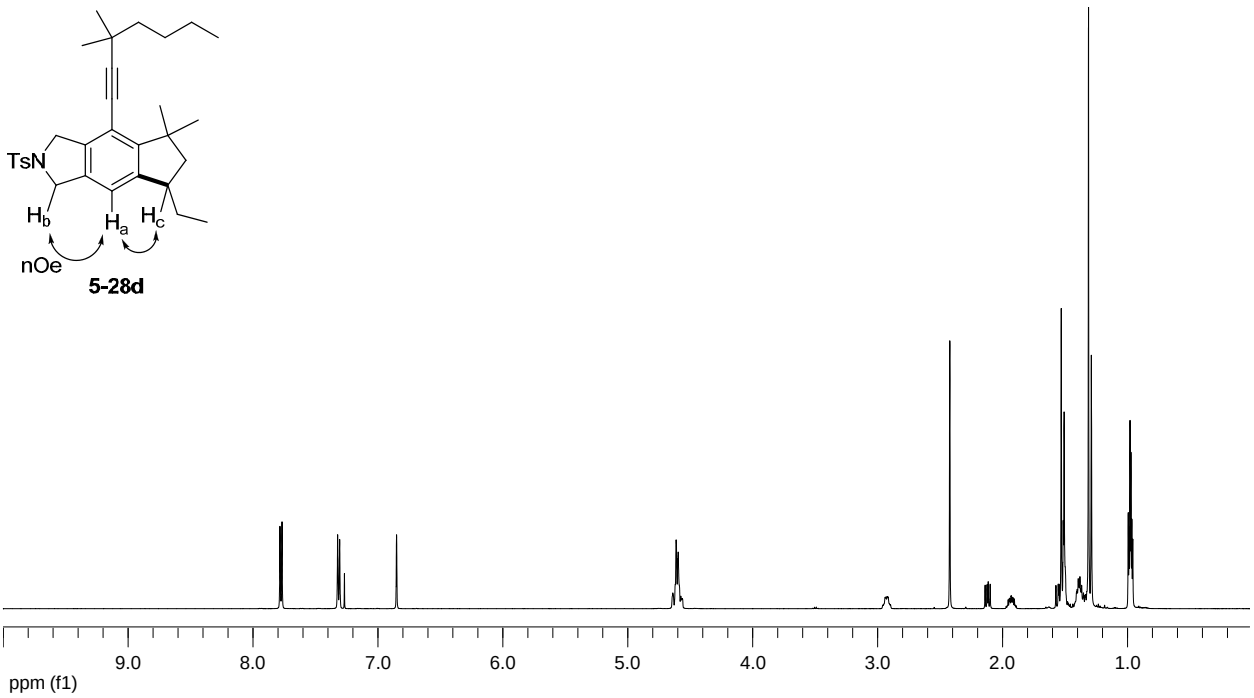


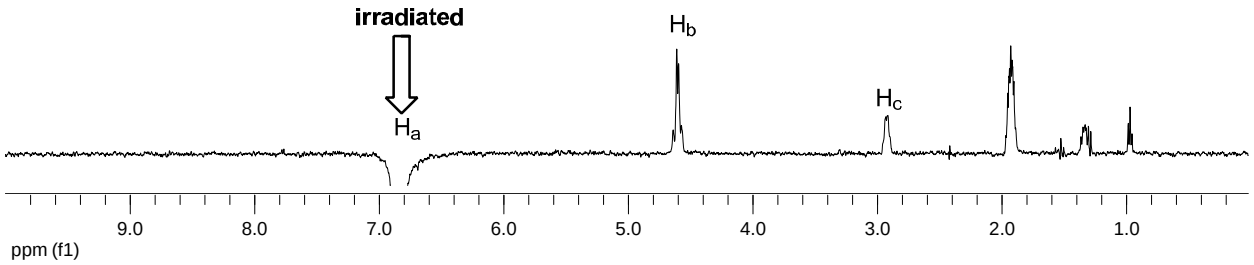


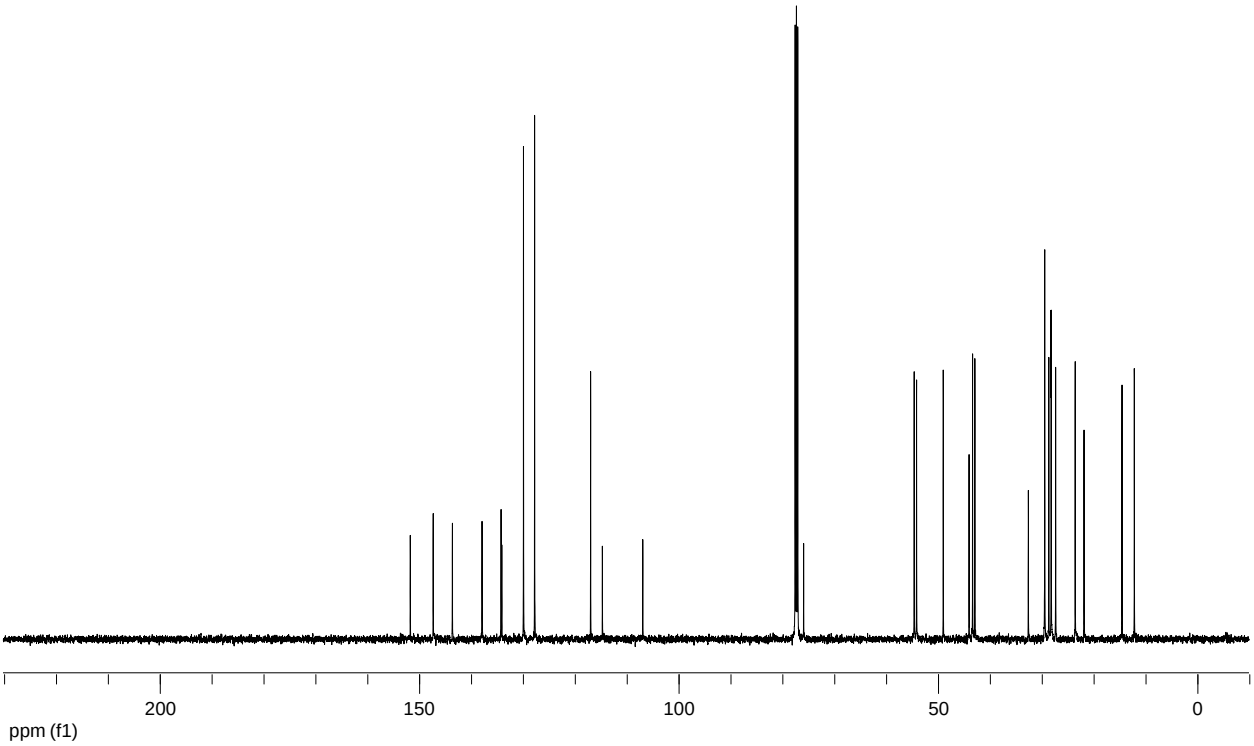

Ph-(4-Cl)
N
Ts
Ha
Hb
Hc
CH3
nOe
5-28c
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)


Ha
Hb
irradiated
Hc
CH3
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

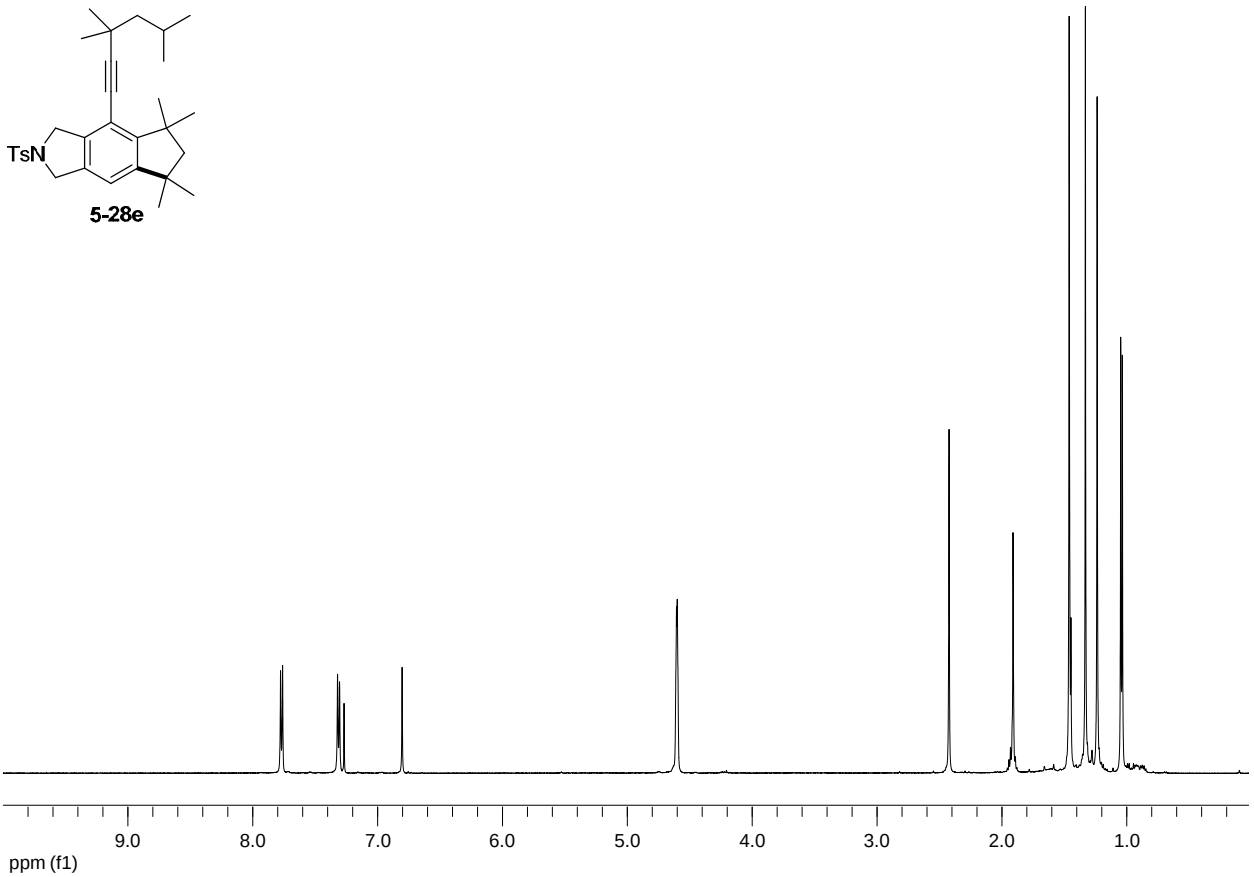

200
150
100
50
0
ppm (f1)

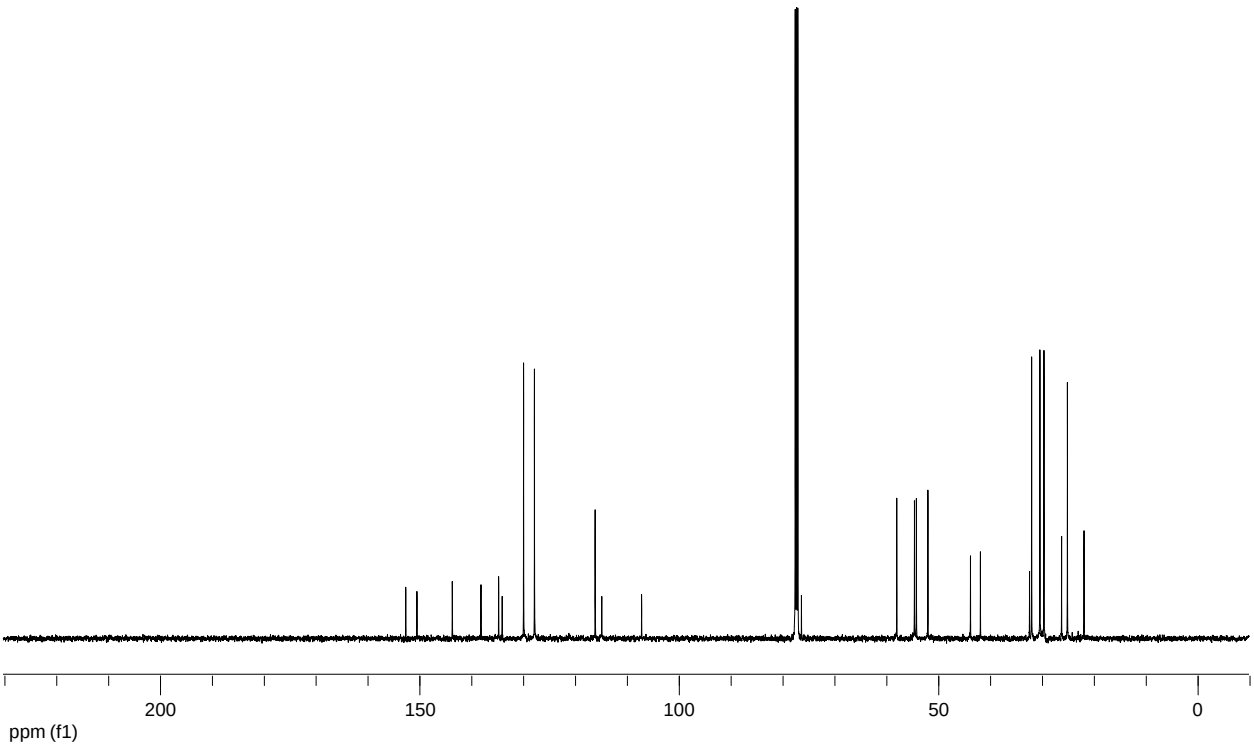

TsN
Hb
Ha
Hc
nOe
5-28d
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

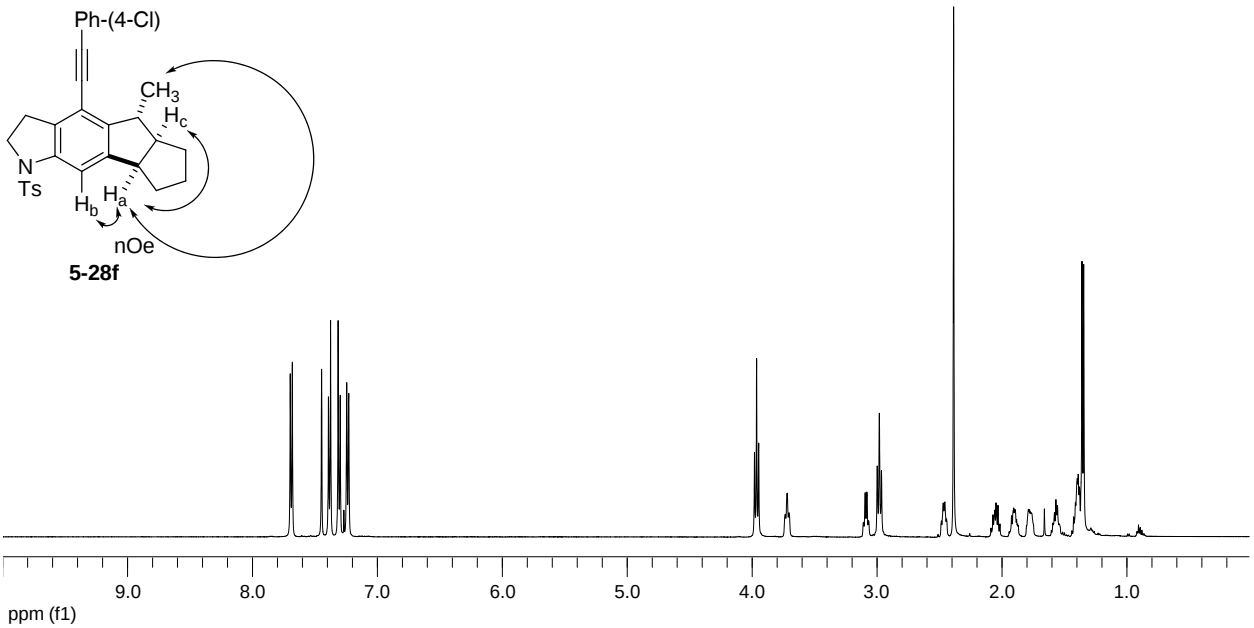

irradiated
Ha
Hb
Hc
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

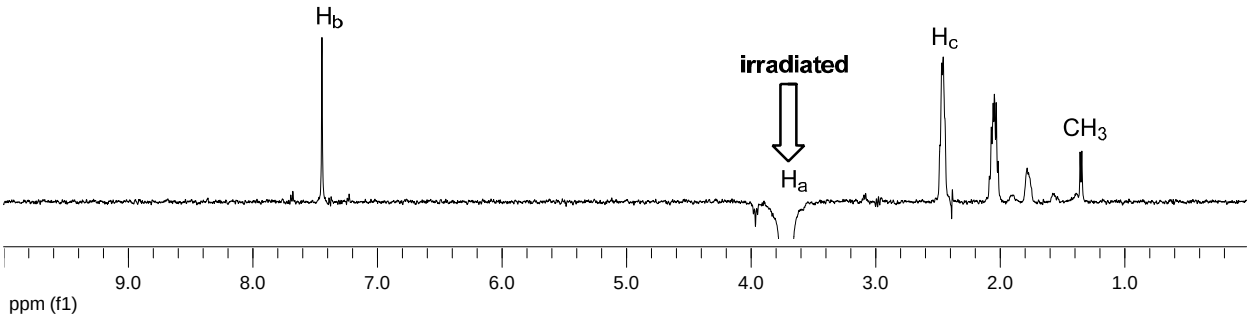

200
150
100
50
0
ppm (f1)

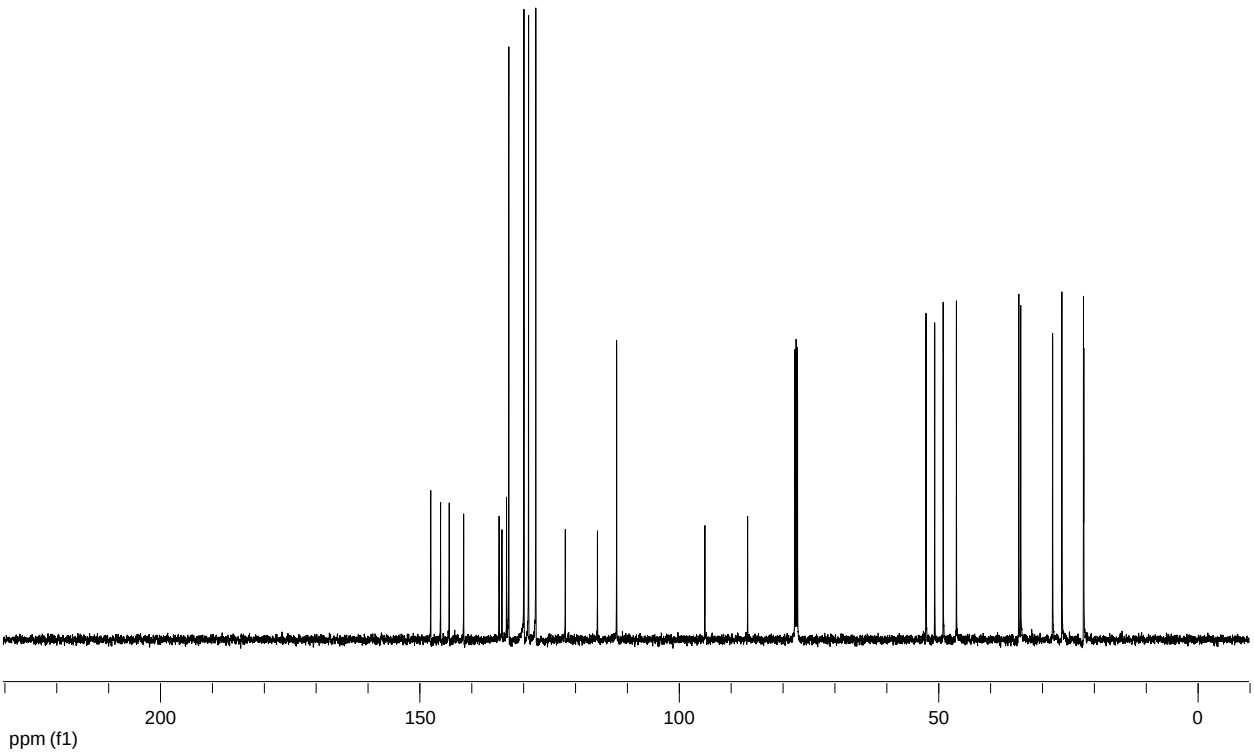
5-28e

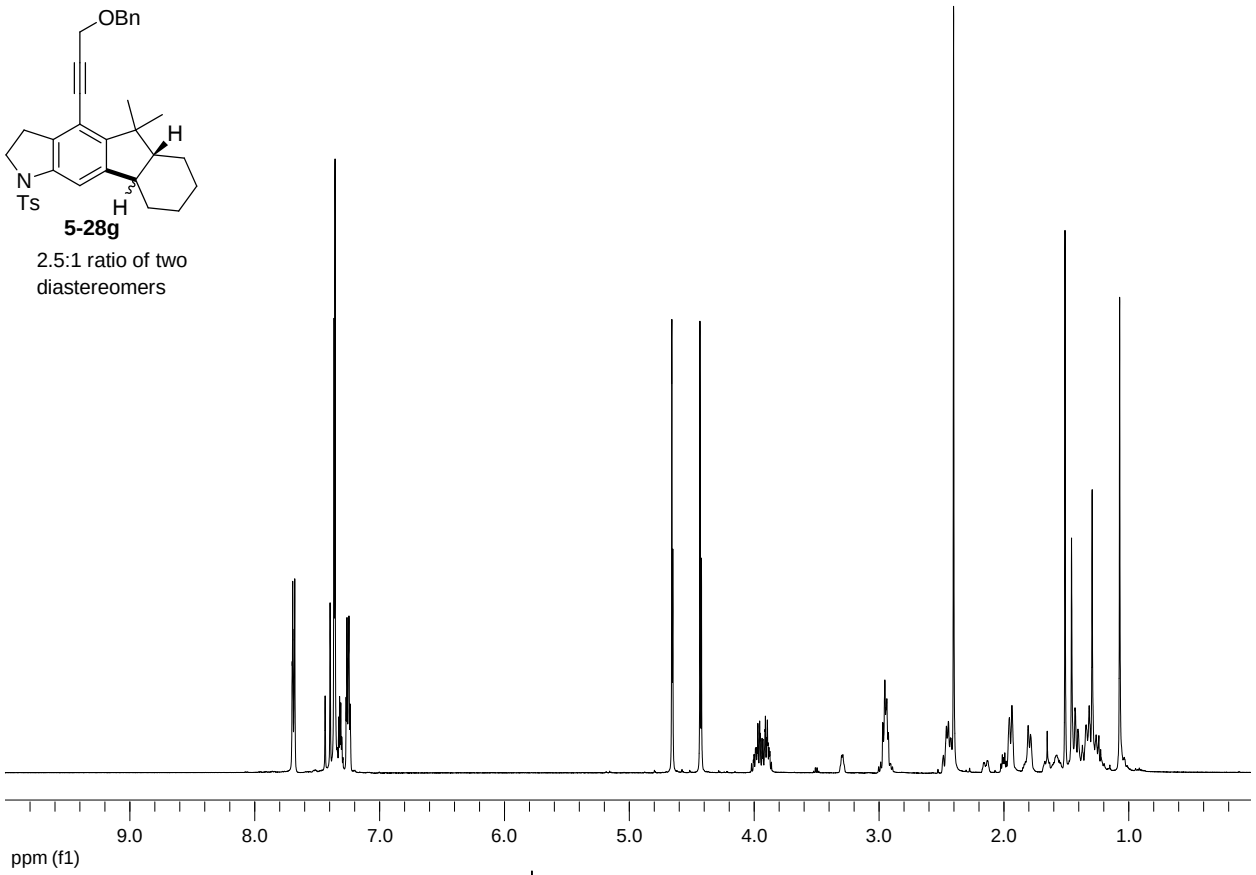


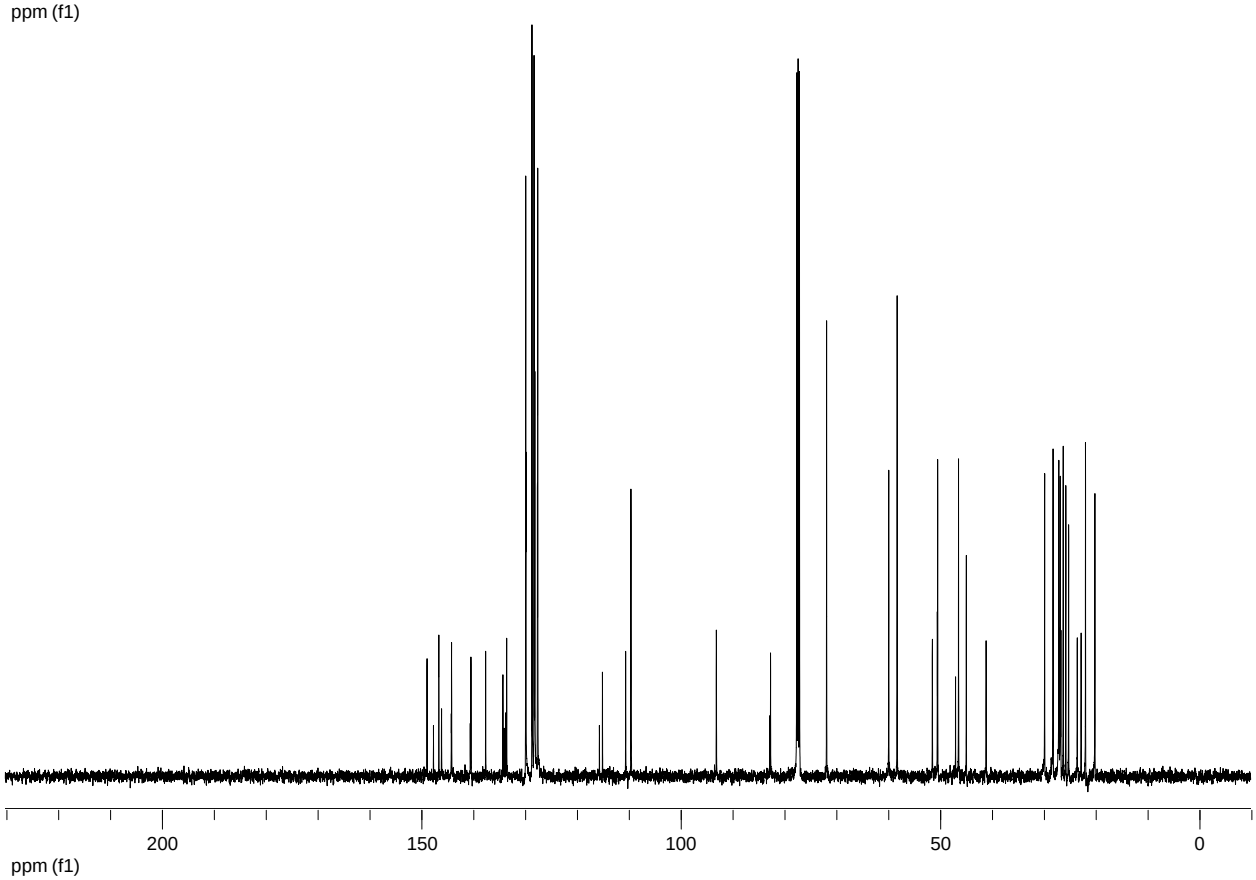


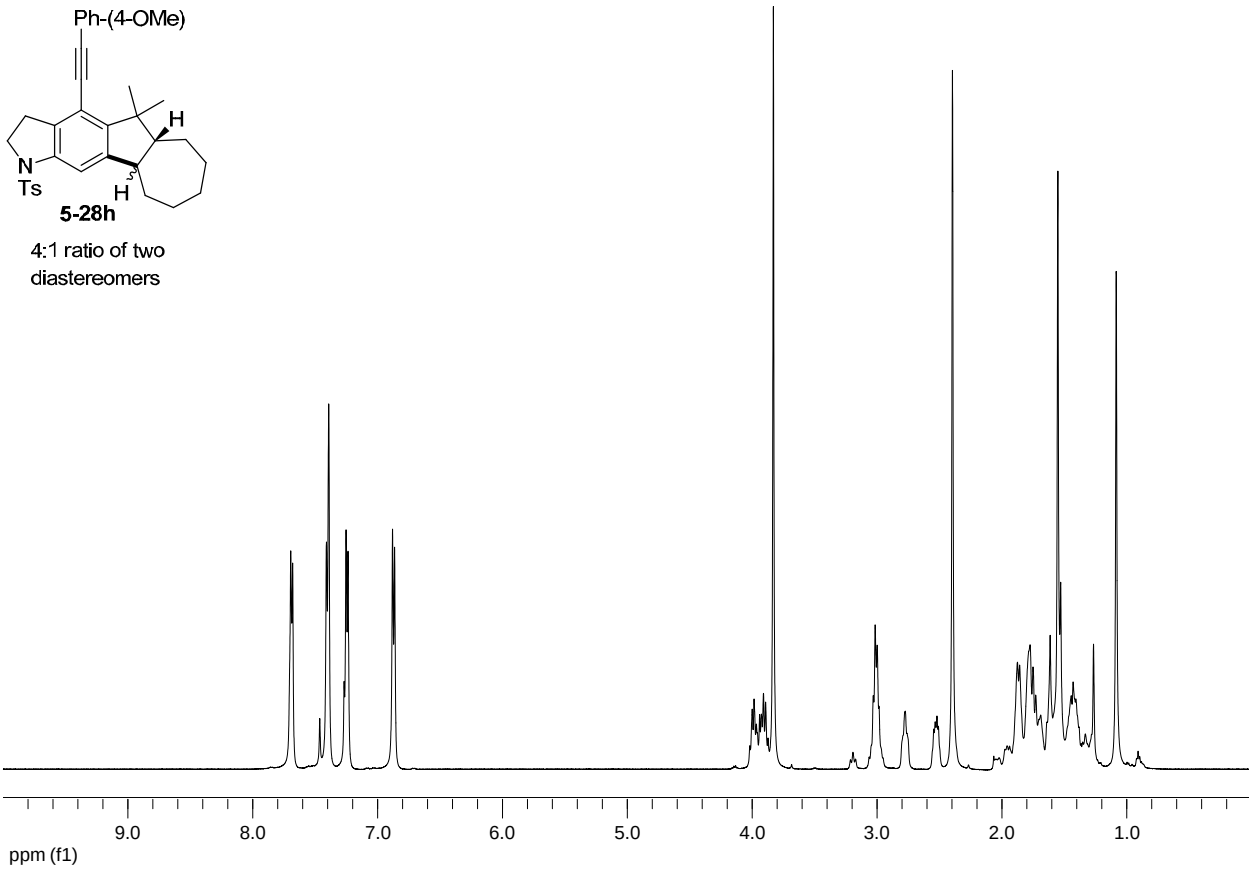

Ph-(4-Cl)
CH3
Hc
N
Ts
Hb
Ha
nOe
5-28f
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

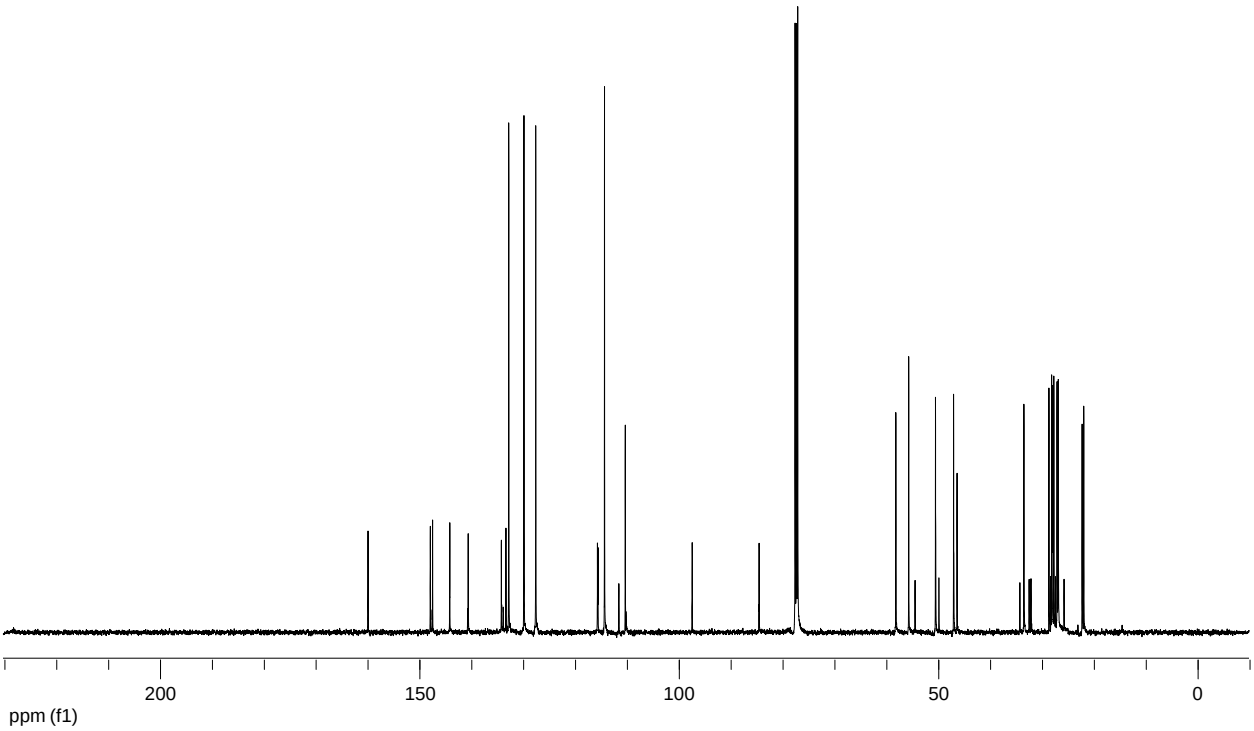

Hb
irradiated
Hc
CH3
Ha
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

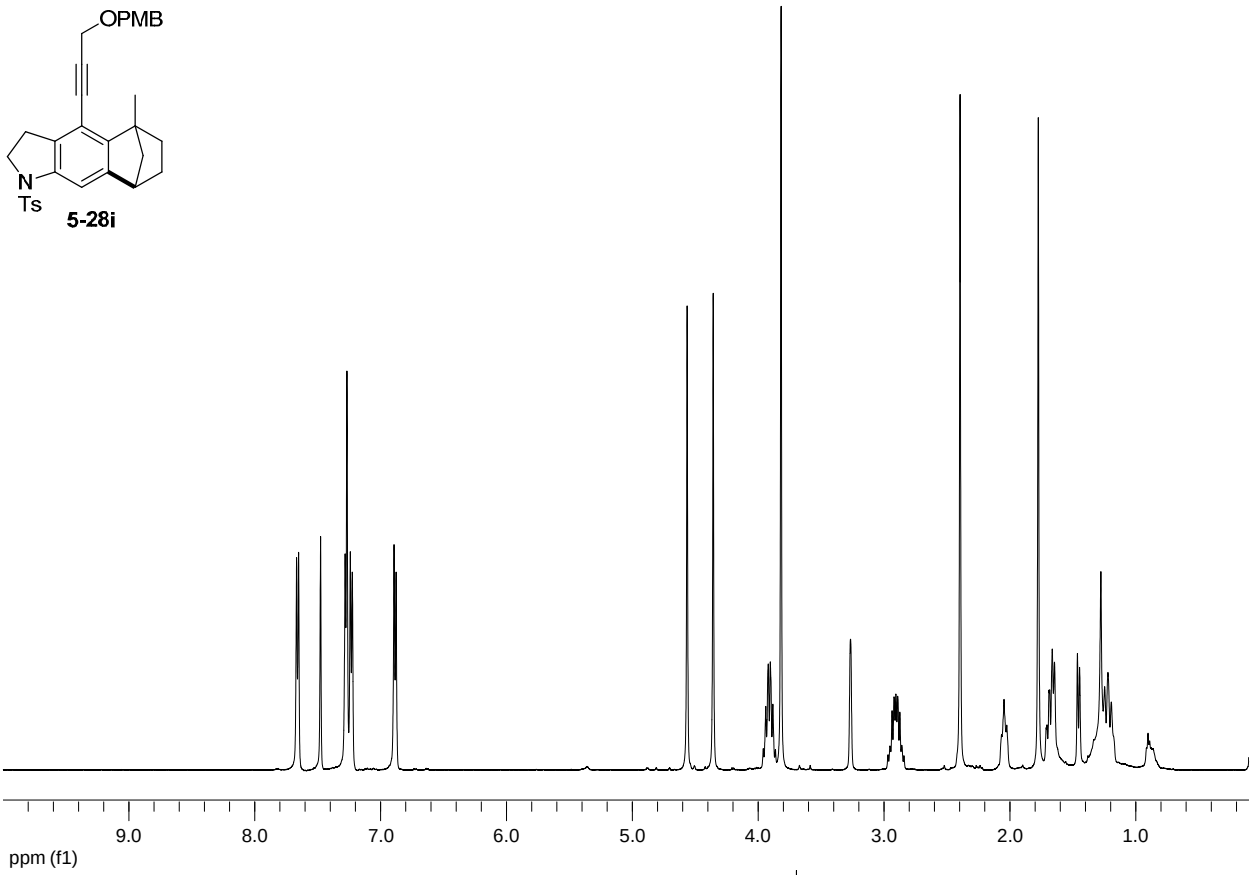

200
150
100
50
0
ppm (f1)

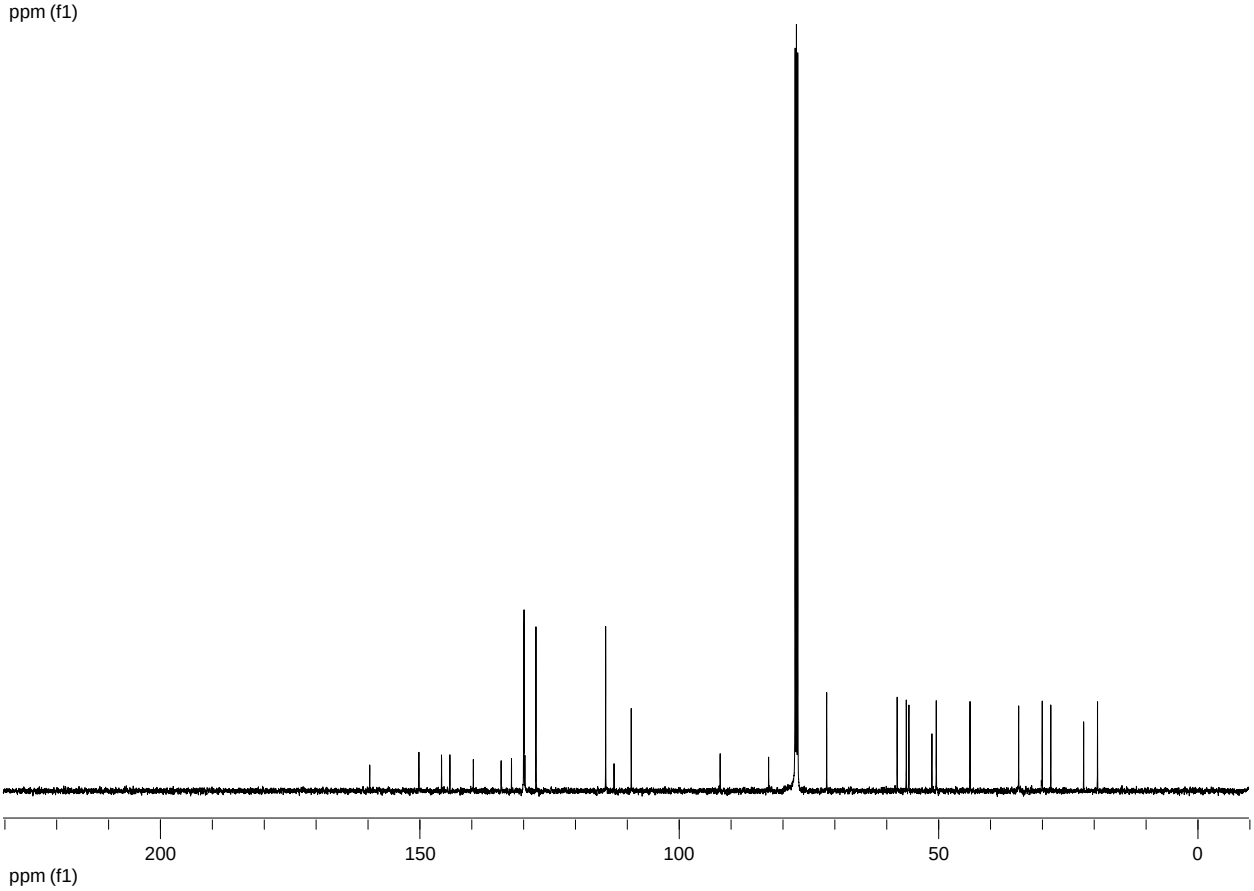

OBn
H
N
Ts
H
5-28g
2.5:1 ratio of two
diastereomers
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

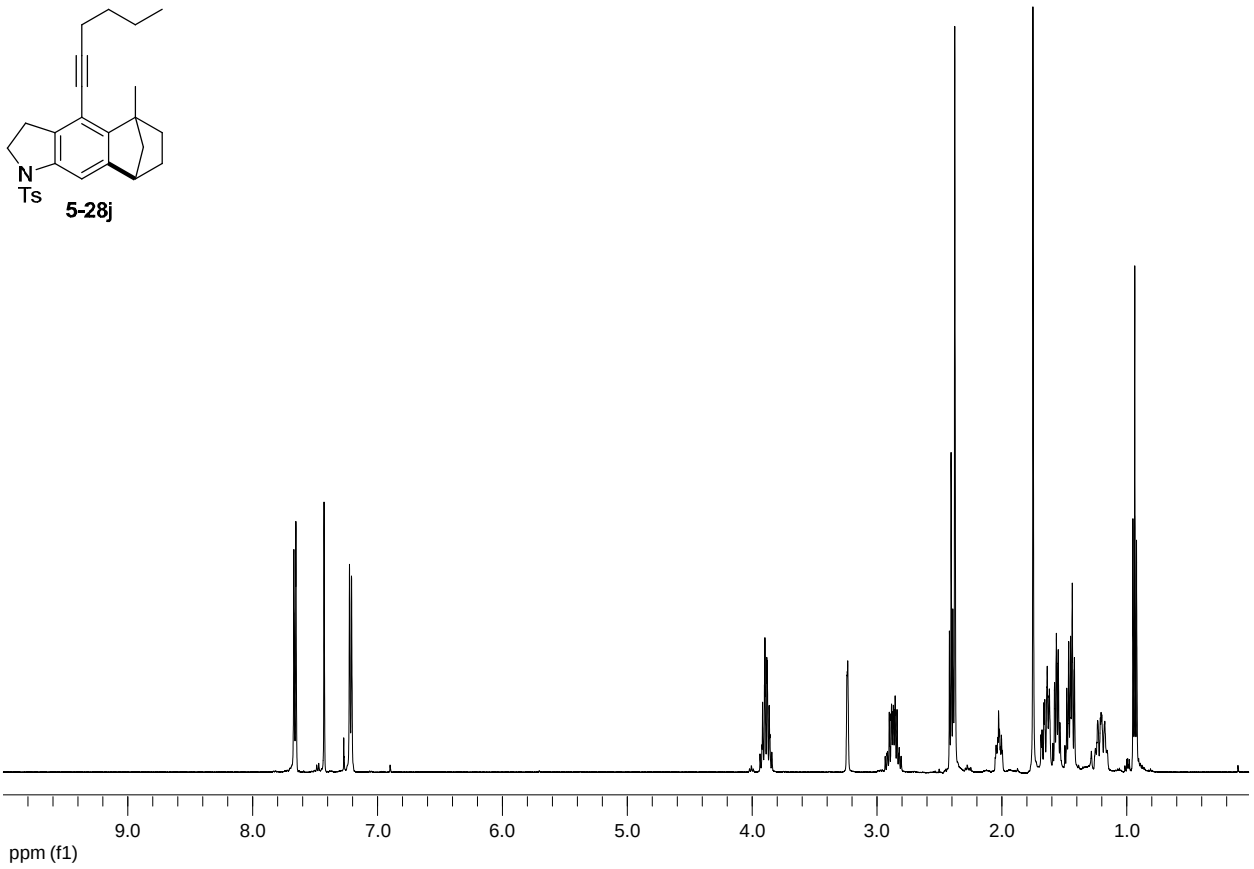

200
150
100
50
0
ppm (f1)

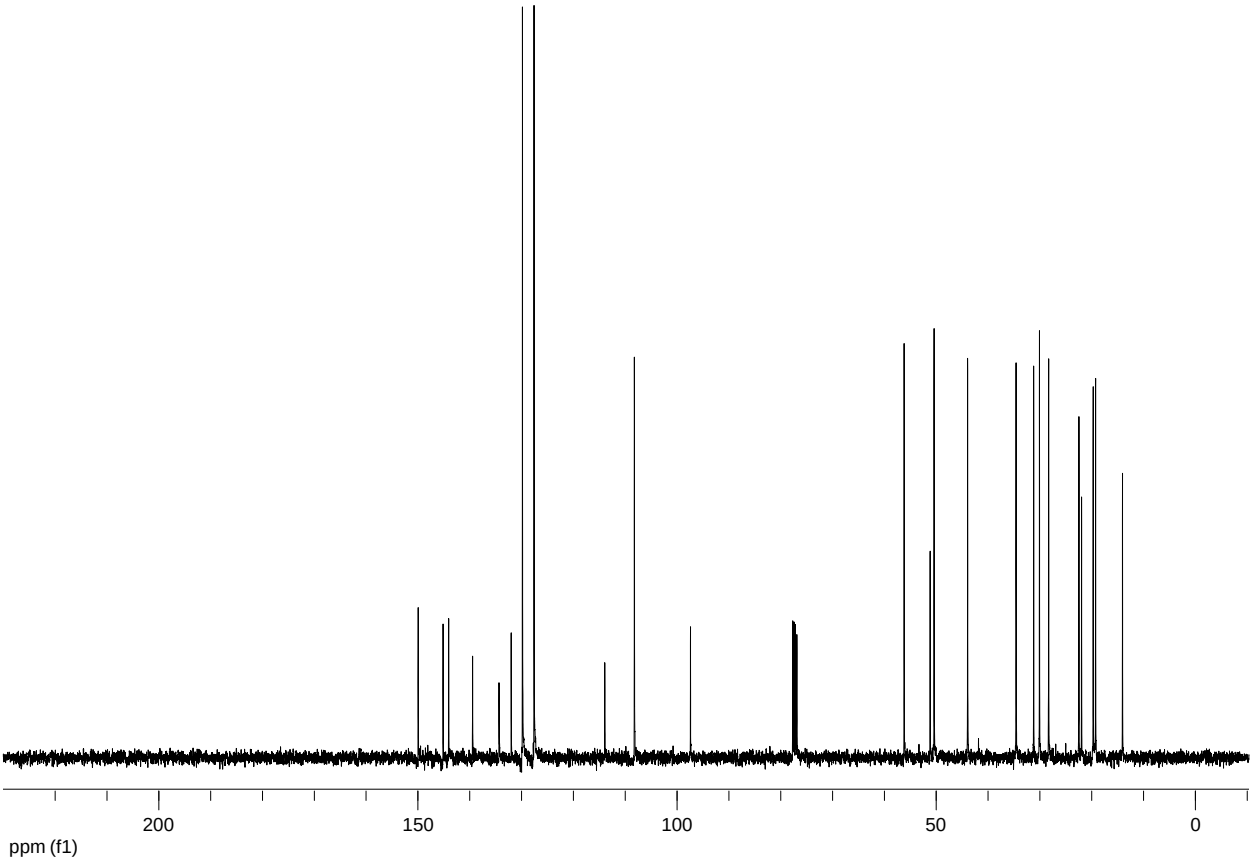

Ph-(4-OMe)
H
N
Ts
H
5-28h
4:1 ratio of two
diastereomers
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

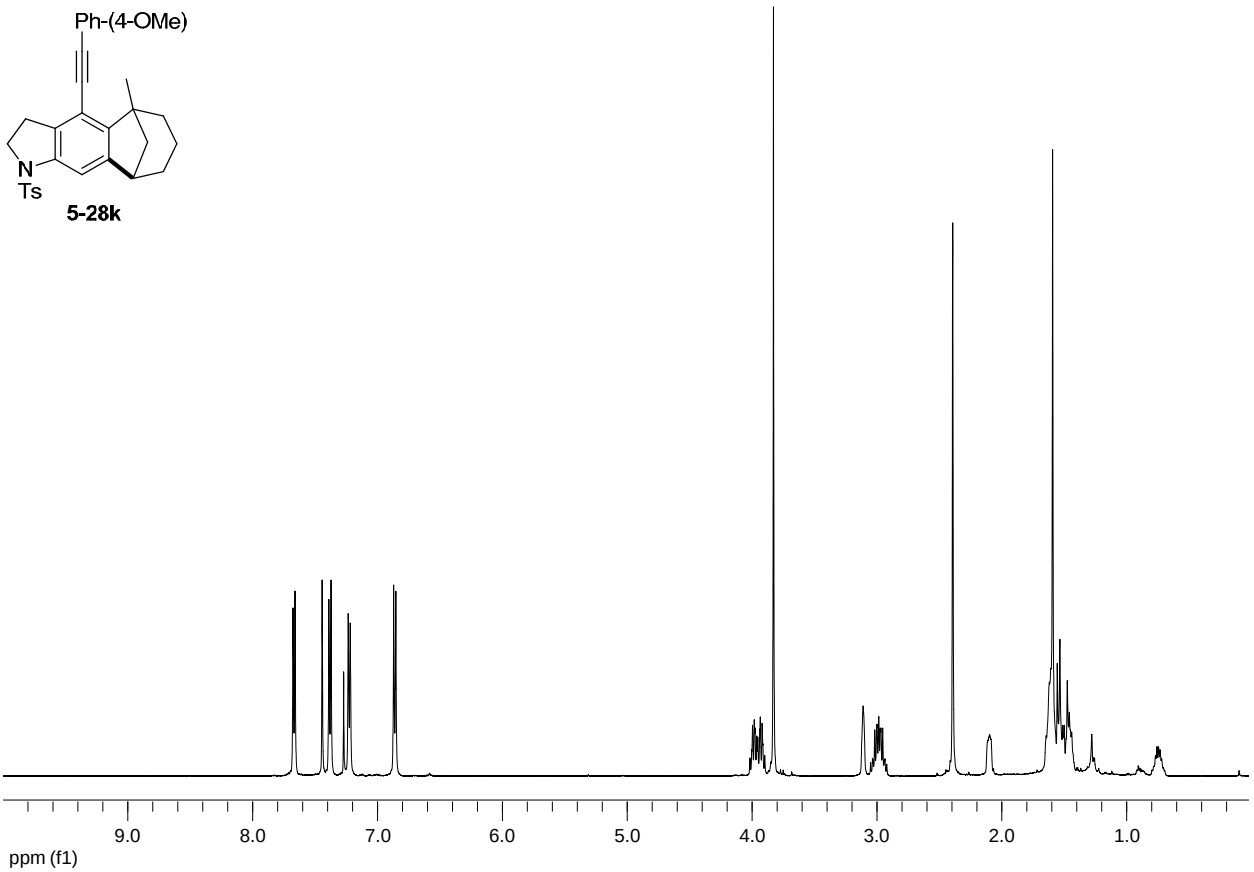

200
150
100
50
0
ppm (f1)

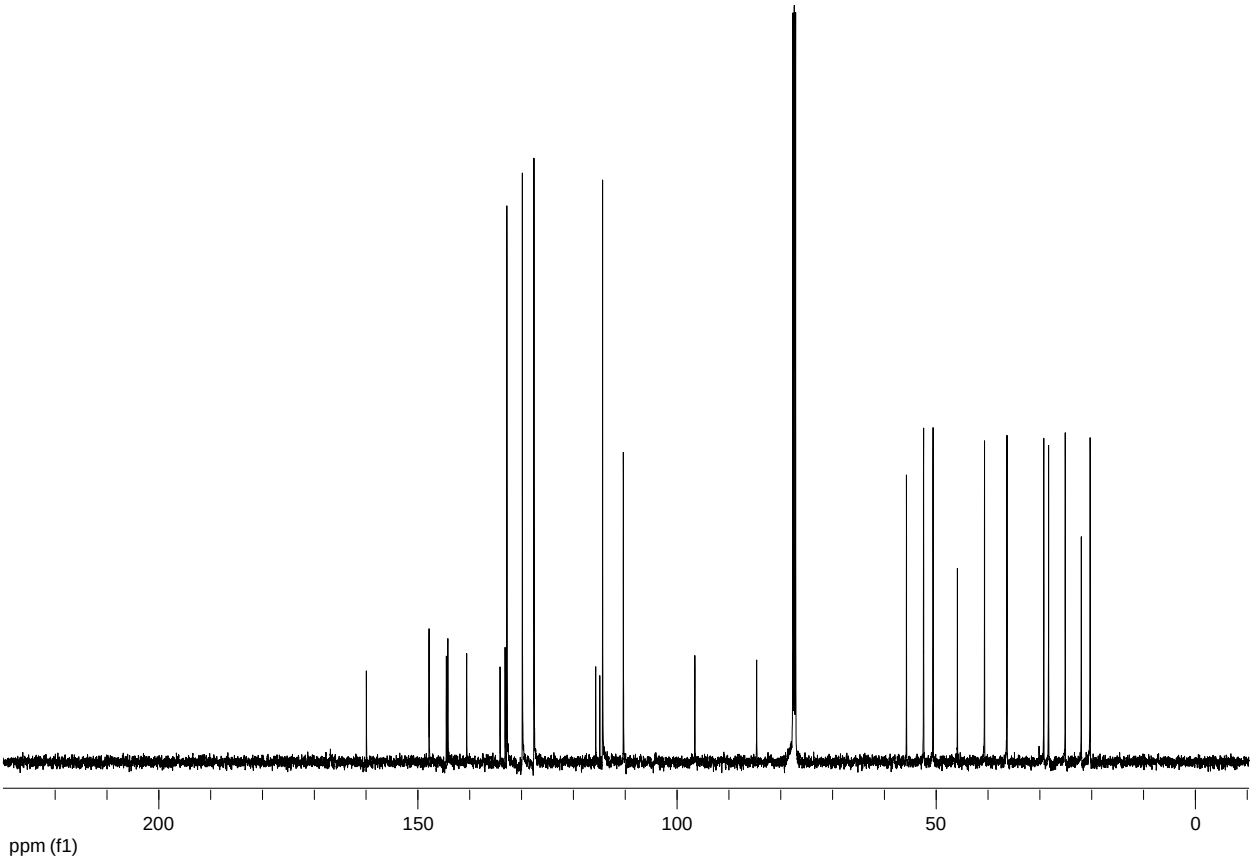

OPMB
N
Ts
5-28i
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

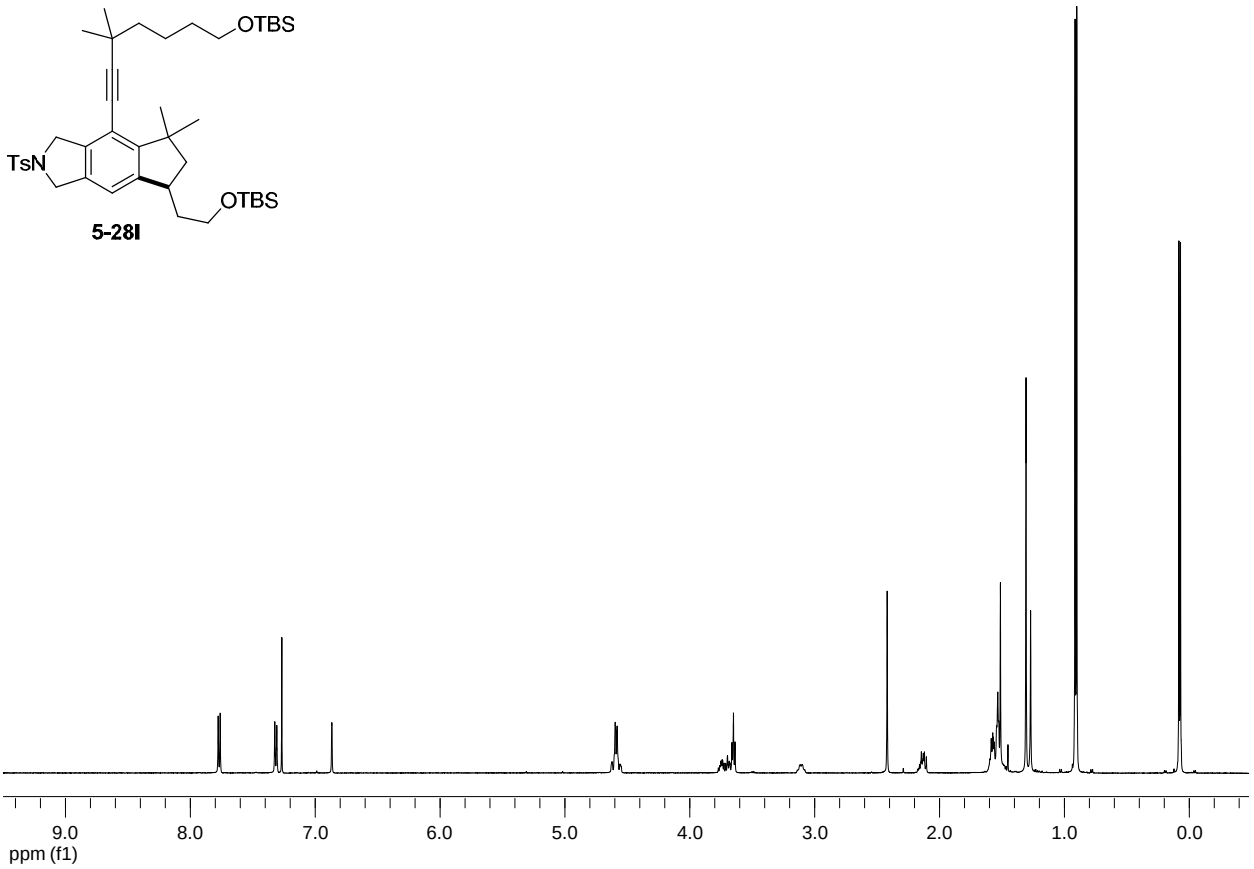

200
150
100
50
0
ppm (f1)

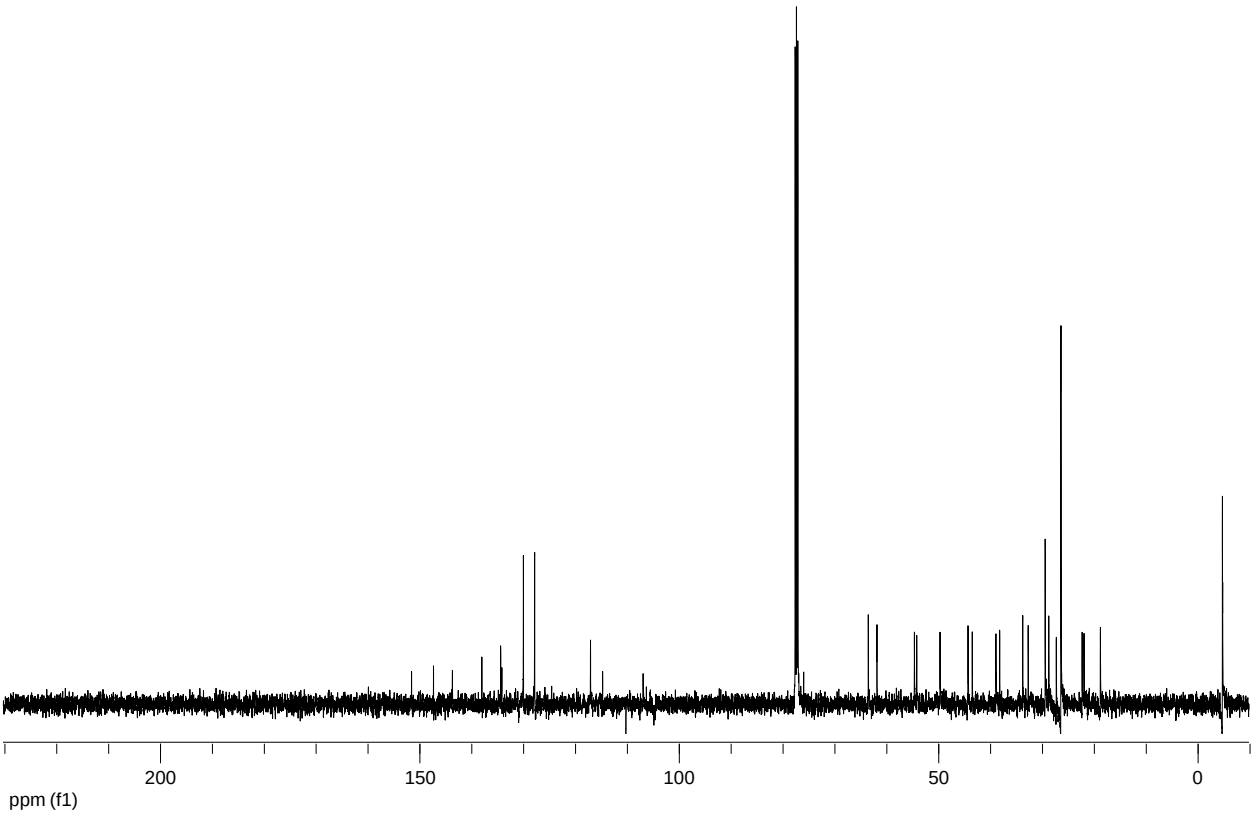

N
Ts
5-28j
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)


200
150
100
50
0
ppm (f1)

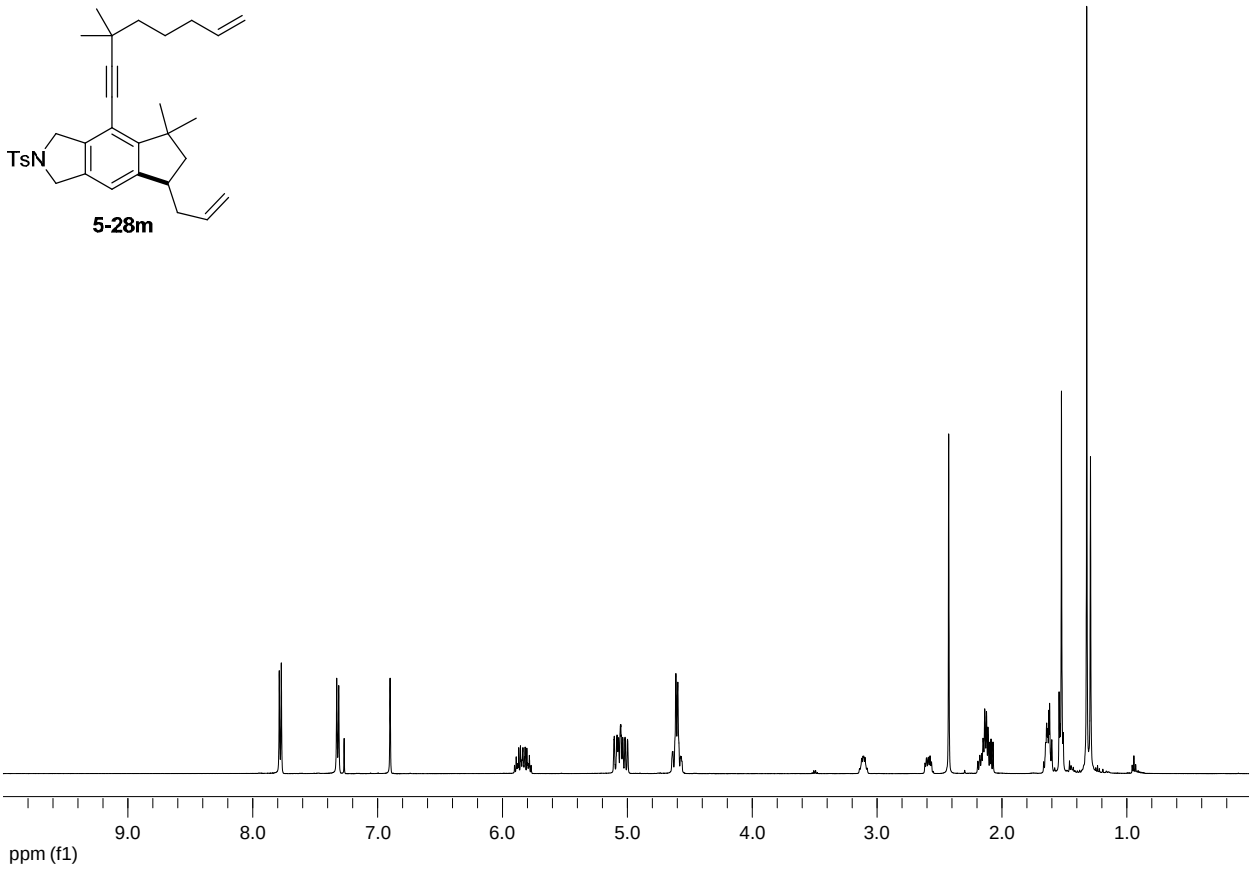

Ph-(4-OMe)
N
Ts
5-28k
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

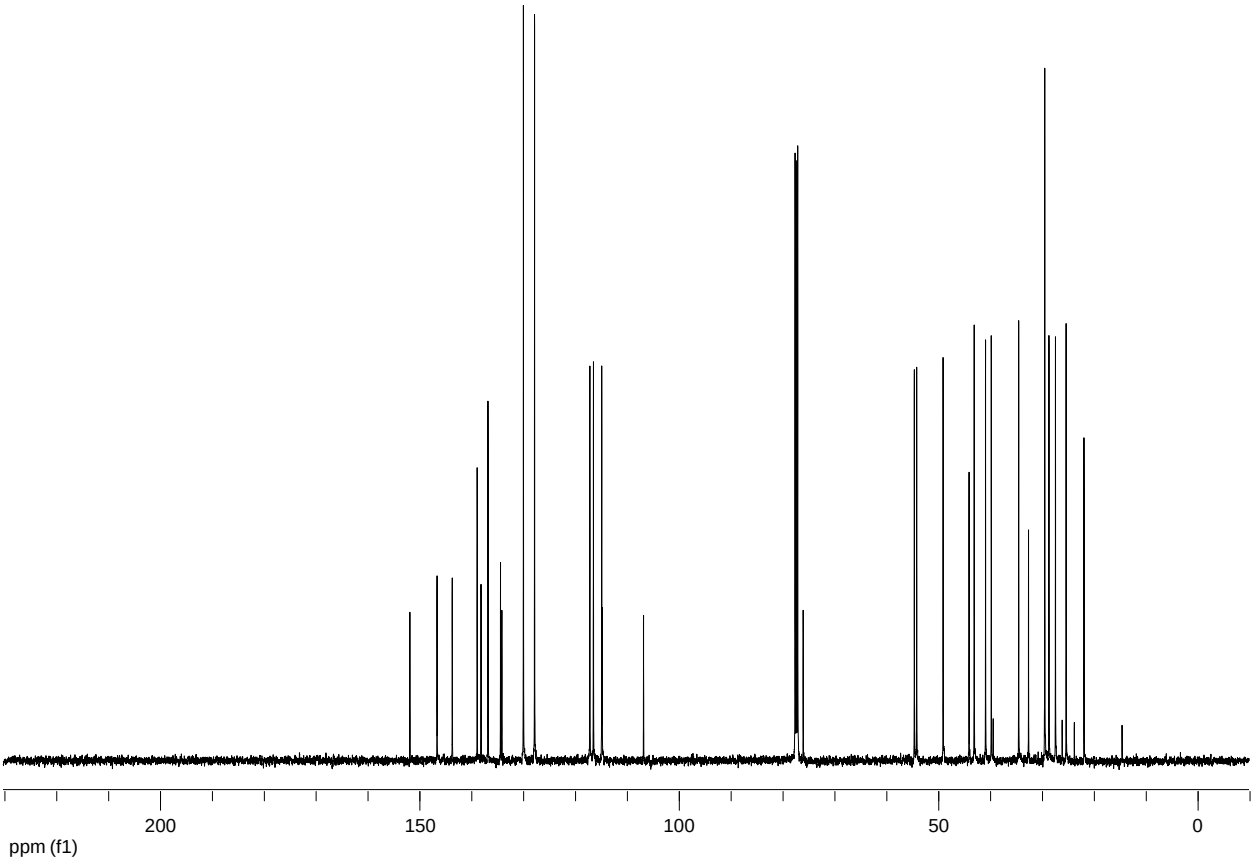

200
150
100
50
0
ppm (f1)


OTBS
TsN
OTBS
5-28l
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)


200
150
100
50
0
ppm (f1)

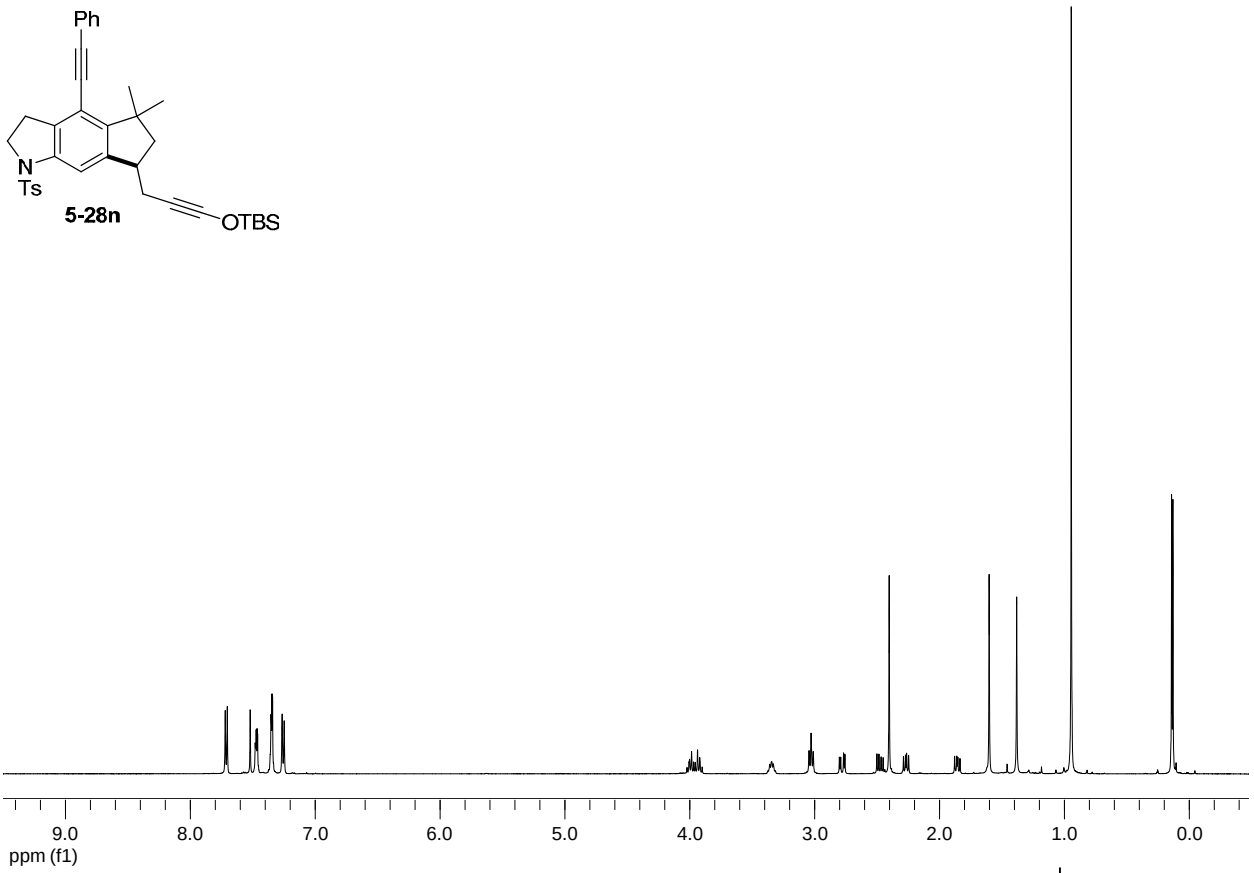
5-28m

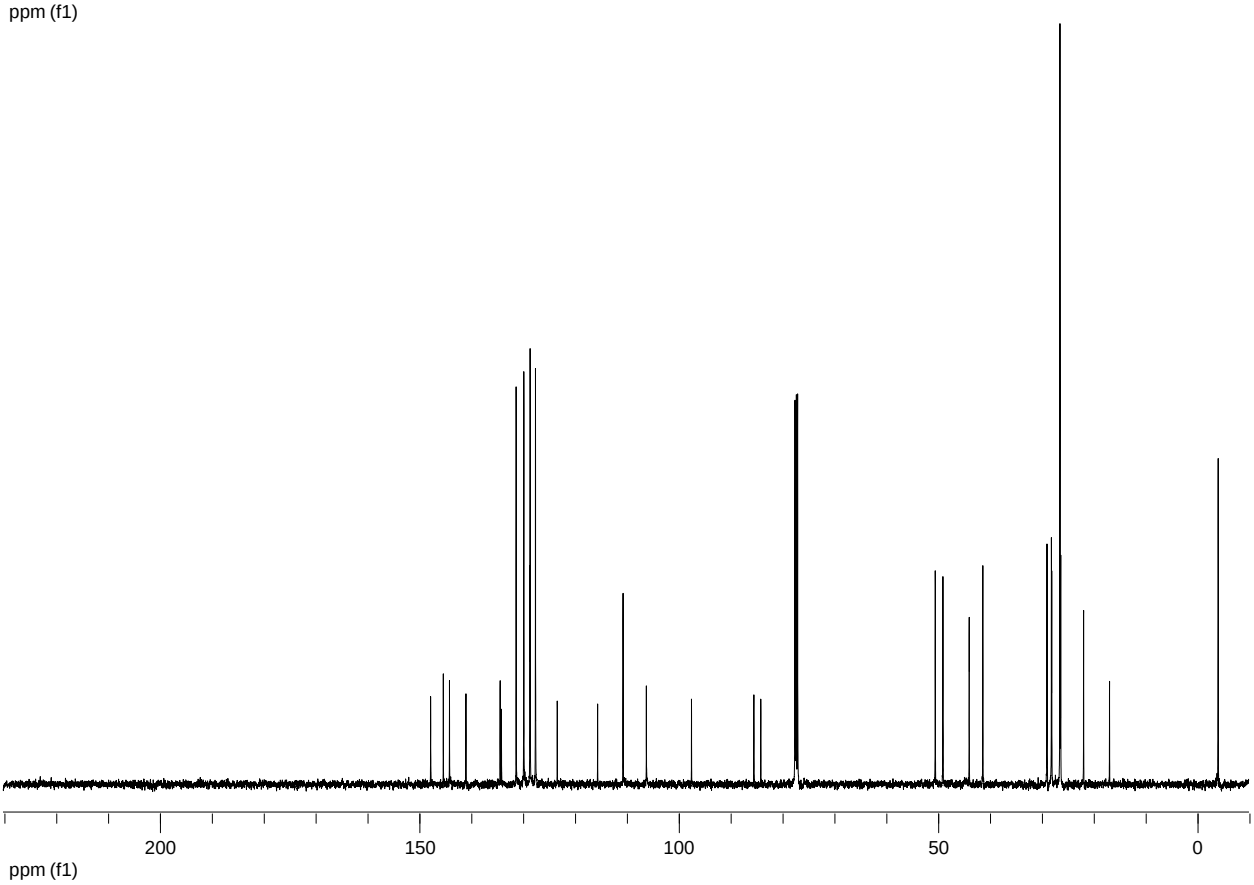




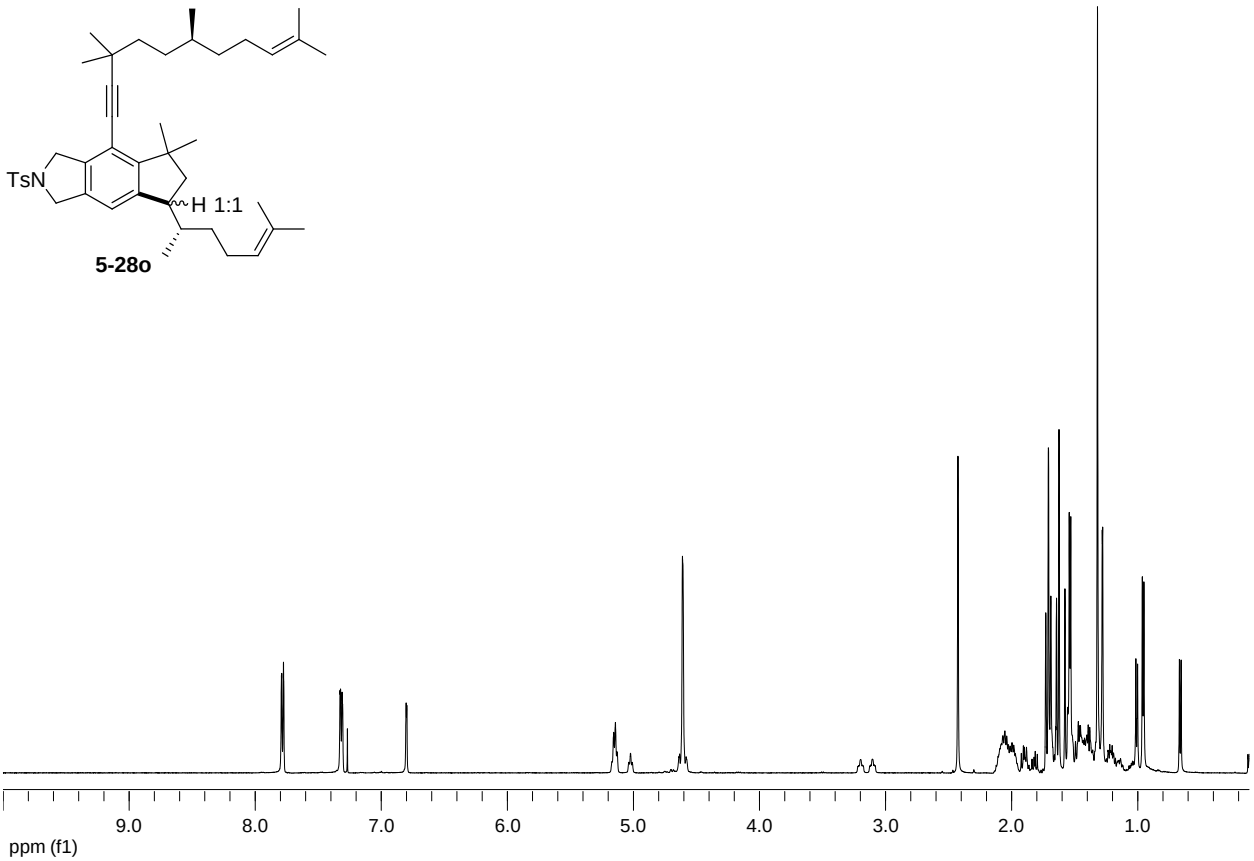
Ph
N
Ts
OTBS

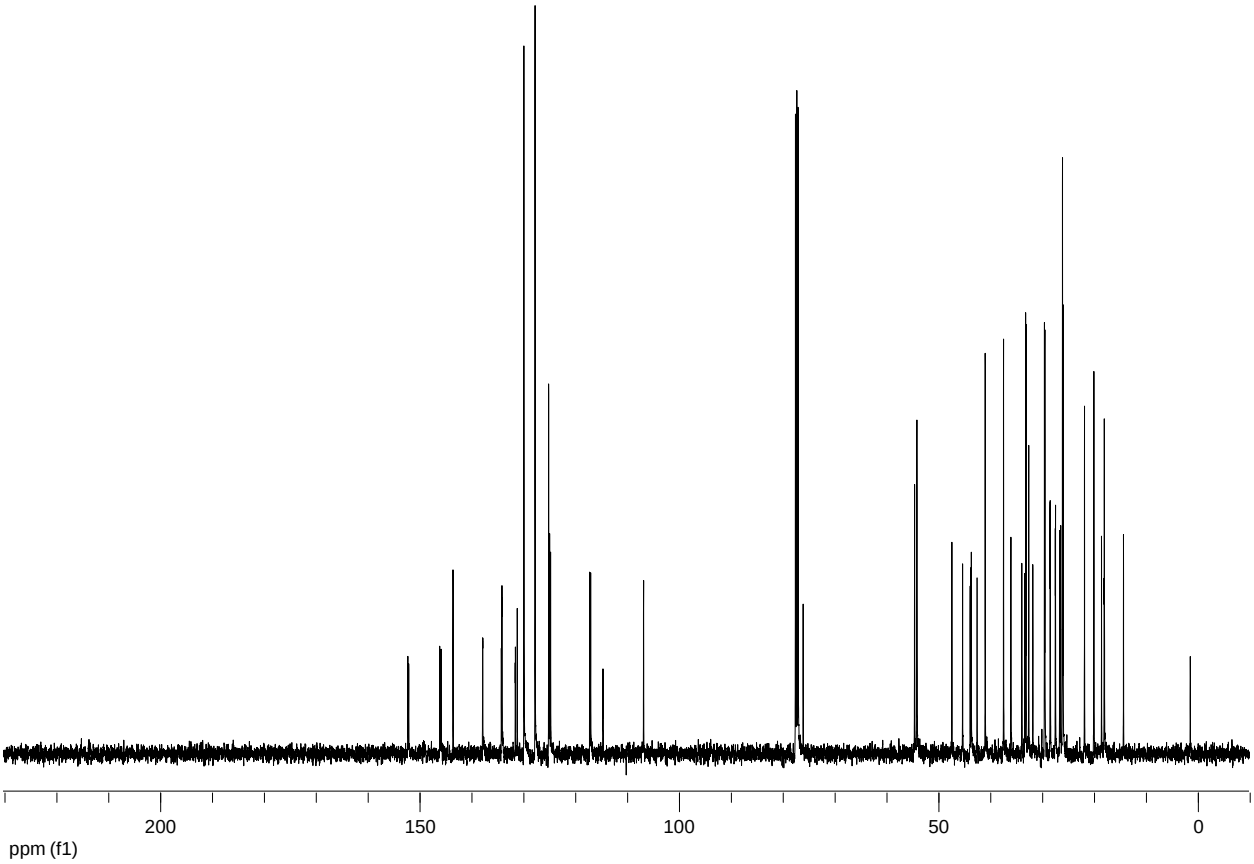
5-28n

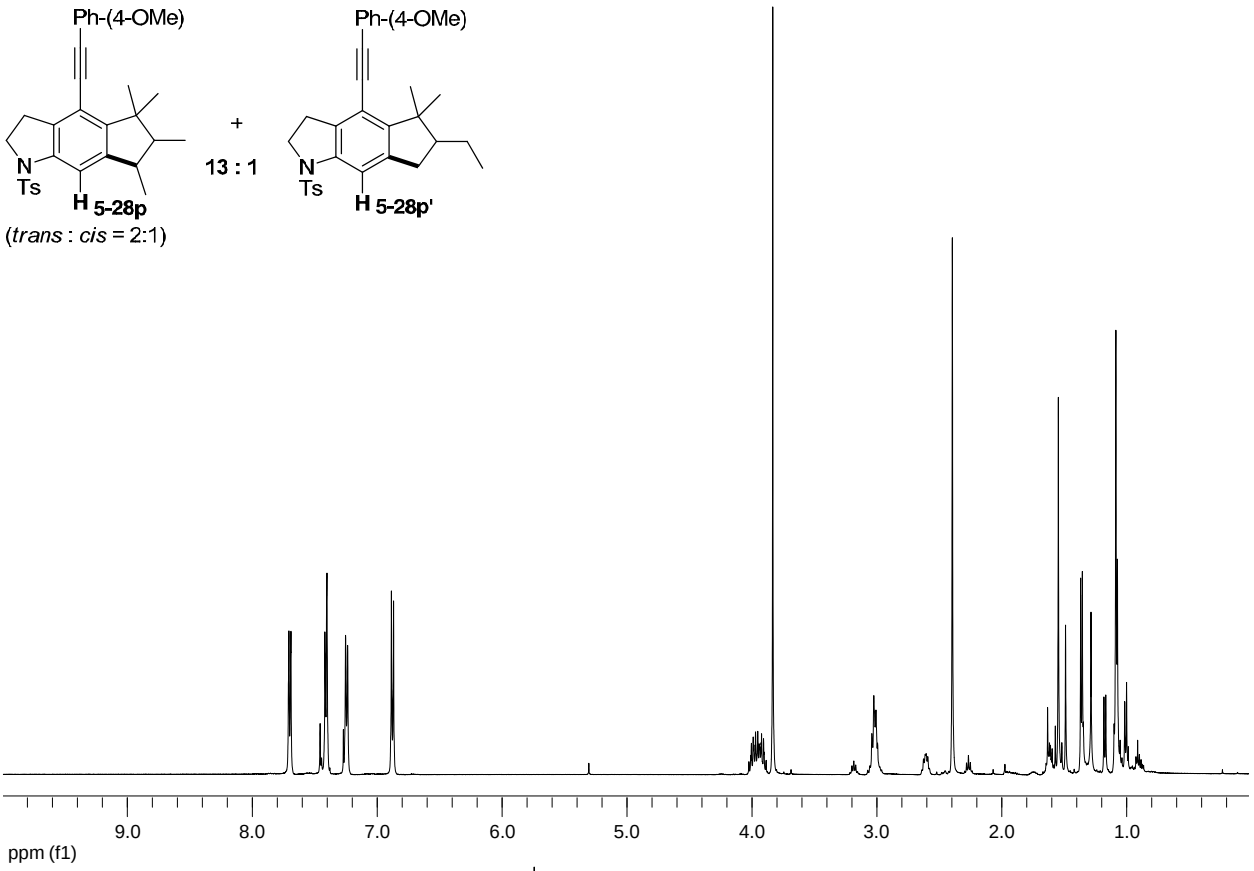

9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

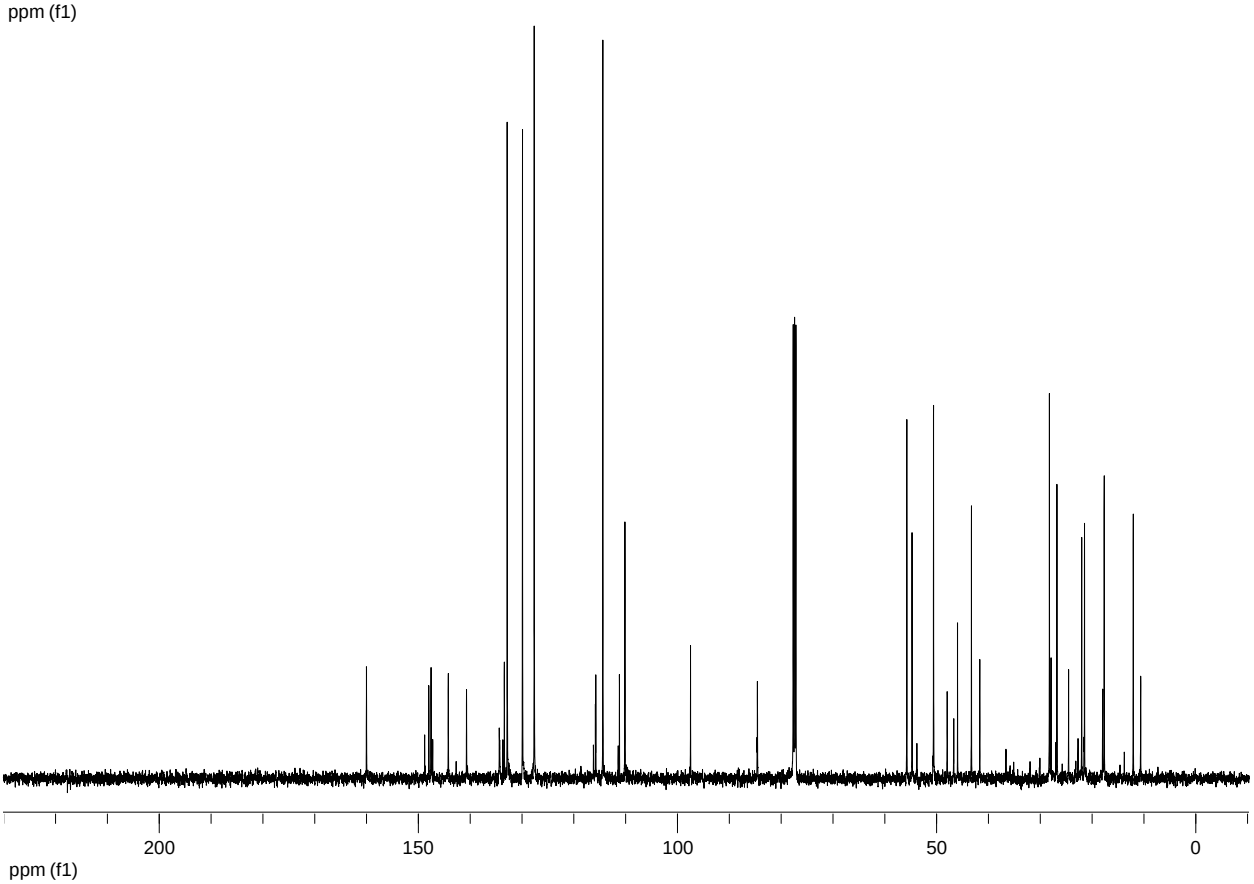

200
150
100
50
0
ppm (f1)

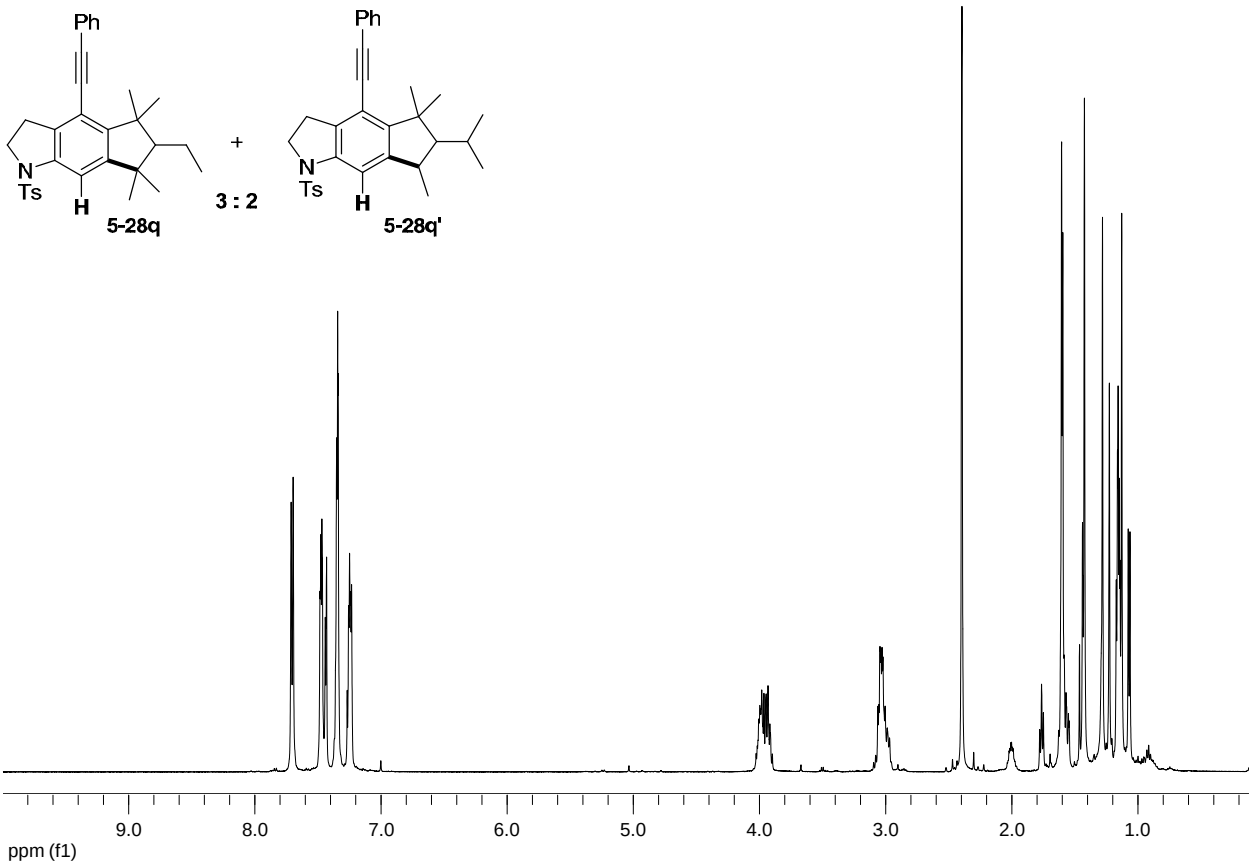
5-28o

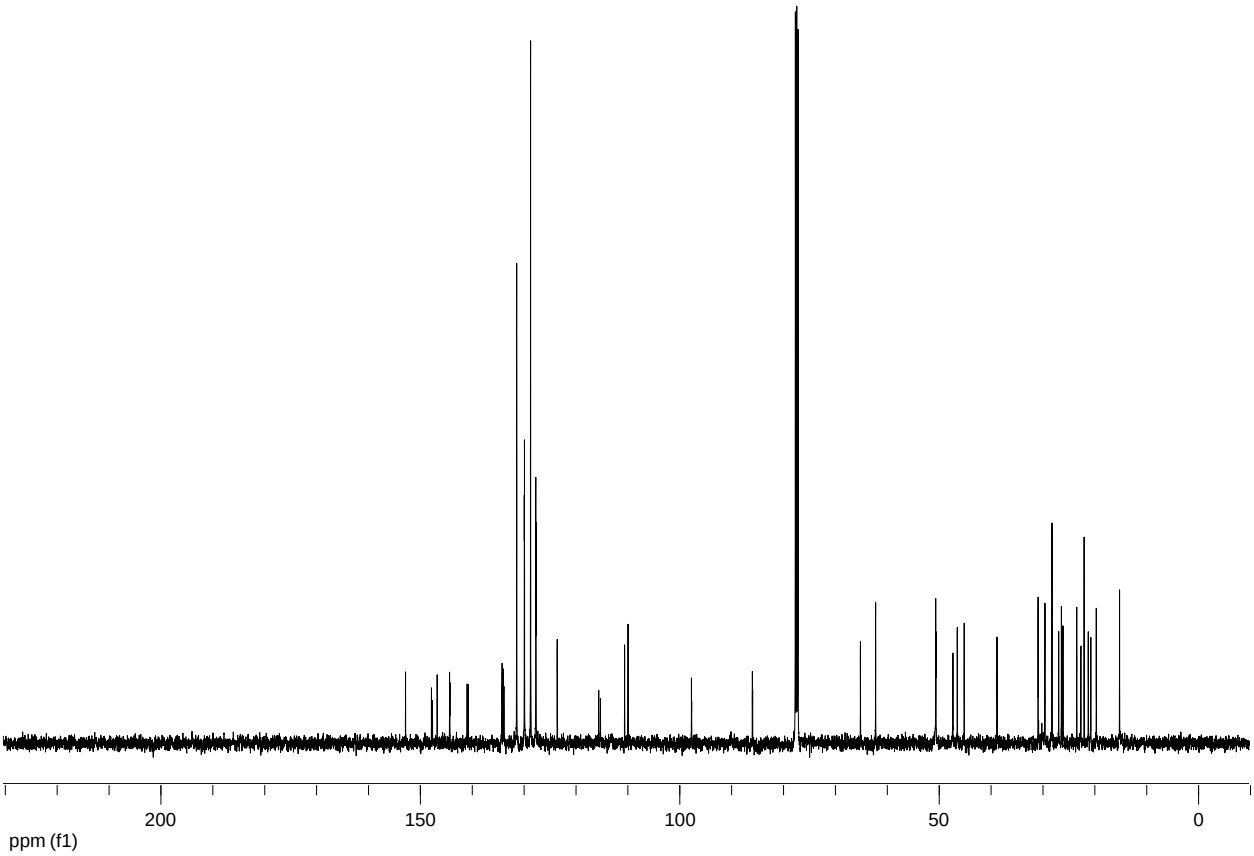


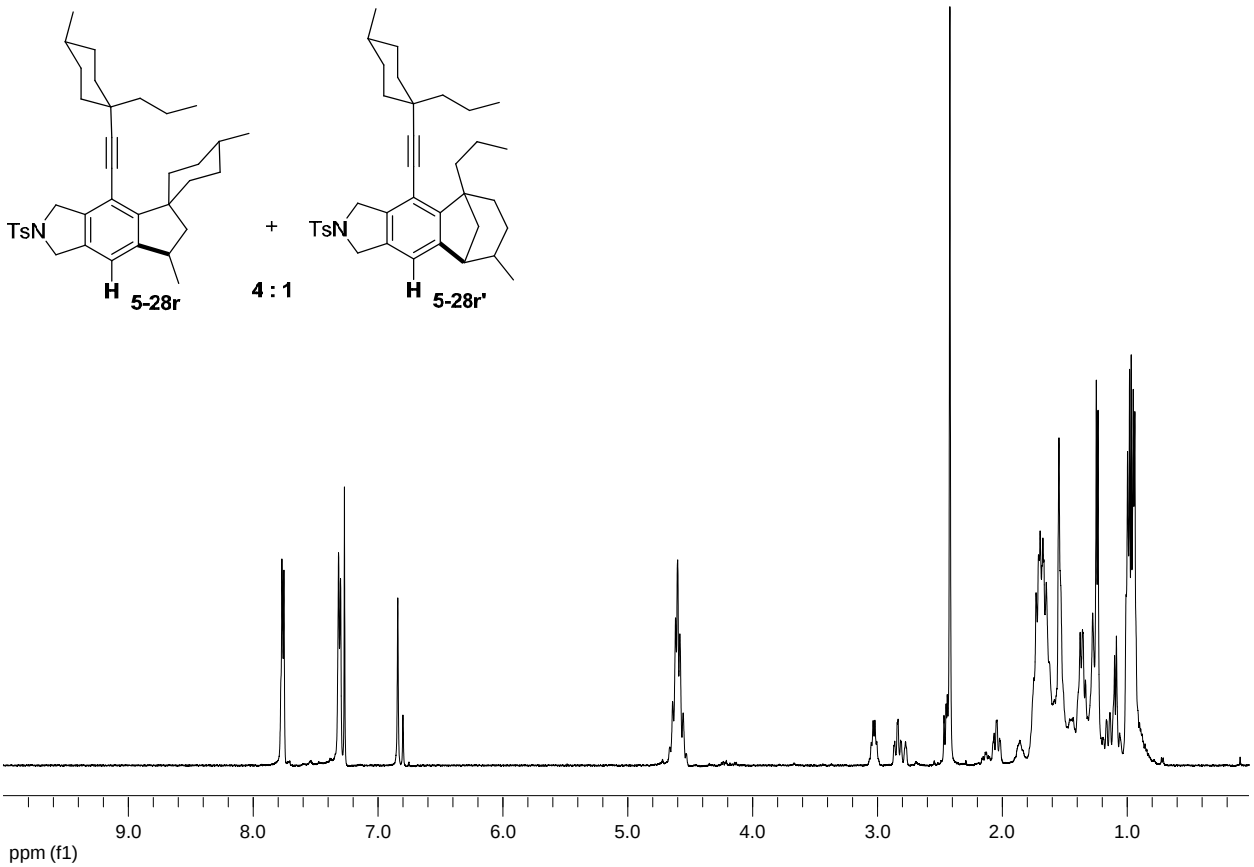


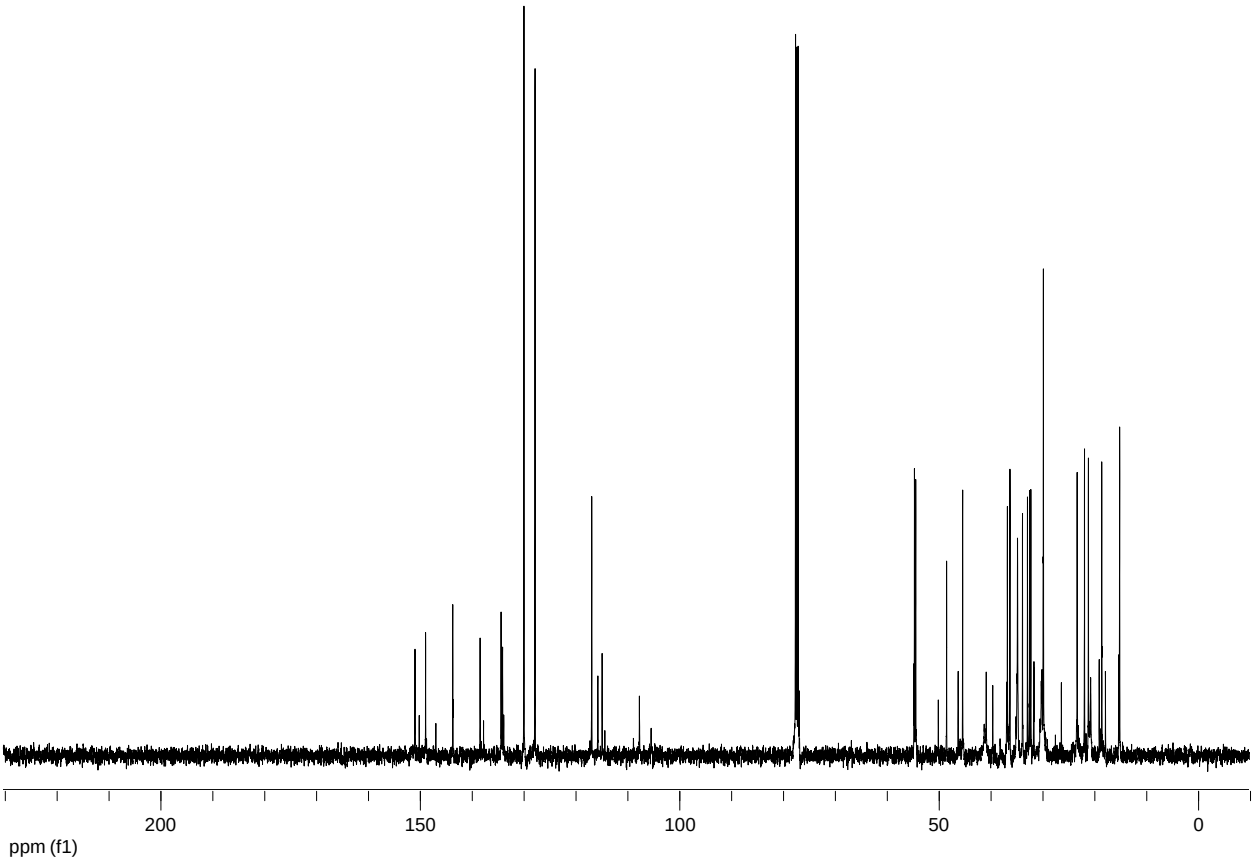

Ph-(4-OMe)
N
Ts
H
5-28p
(trans : cis = 2:1)
+
13 : 1
Ph-(4-OMe)
N
Ts
H
5-28p'
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

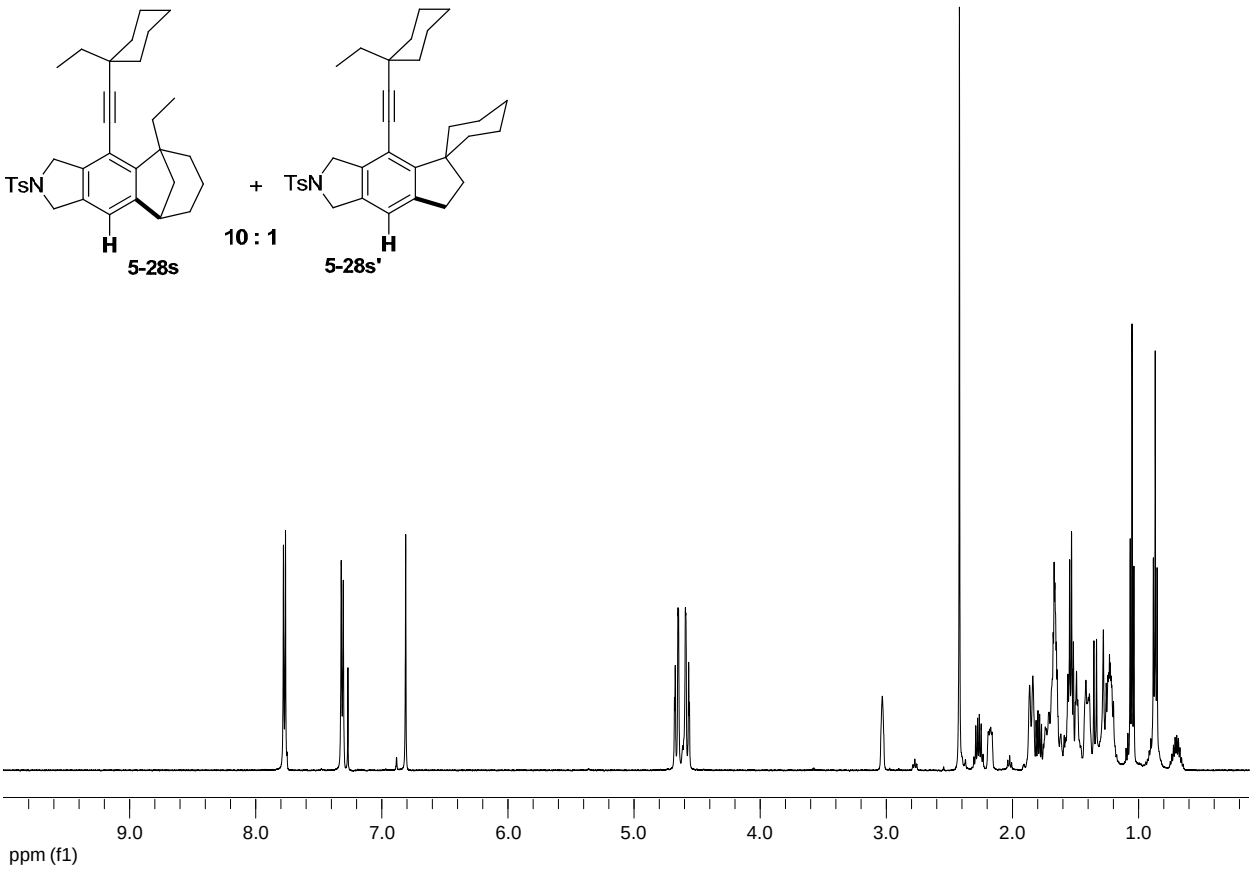

200
150
100
50
0
ppm (f1)

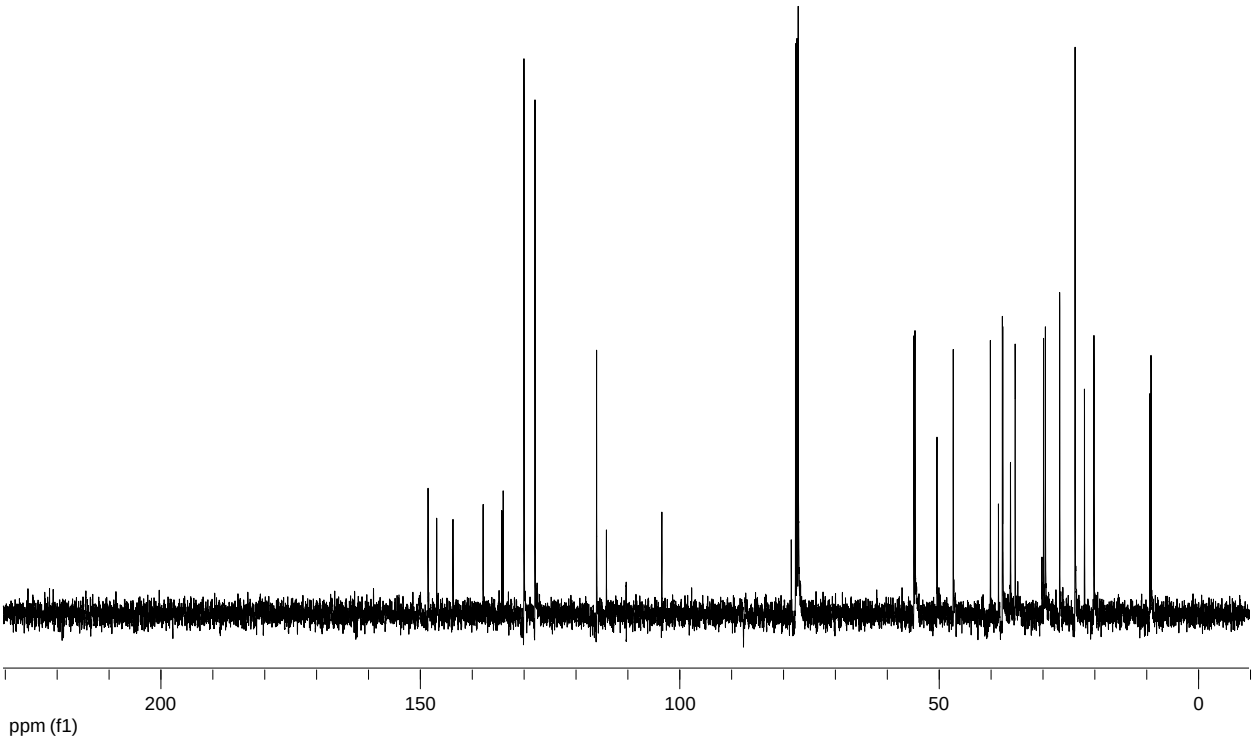

Ph
N
Ts
H
5-28q
+
3 : 2
Ph
N
Ts
H
5-28q'
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

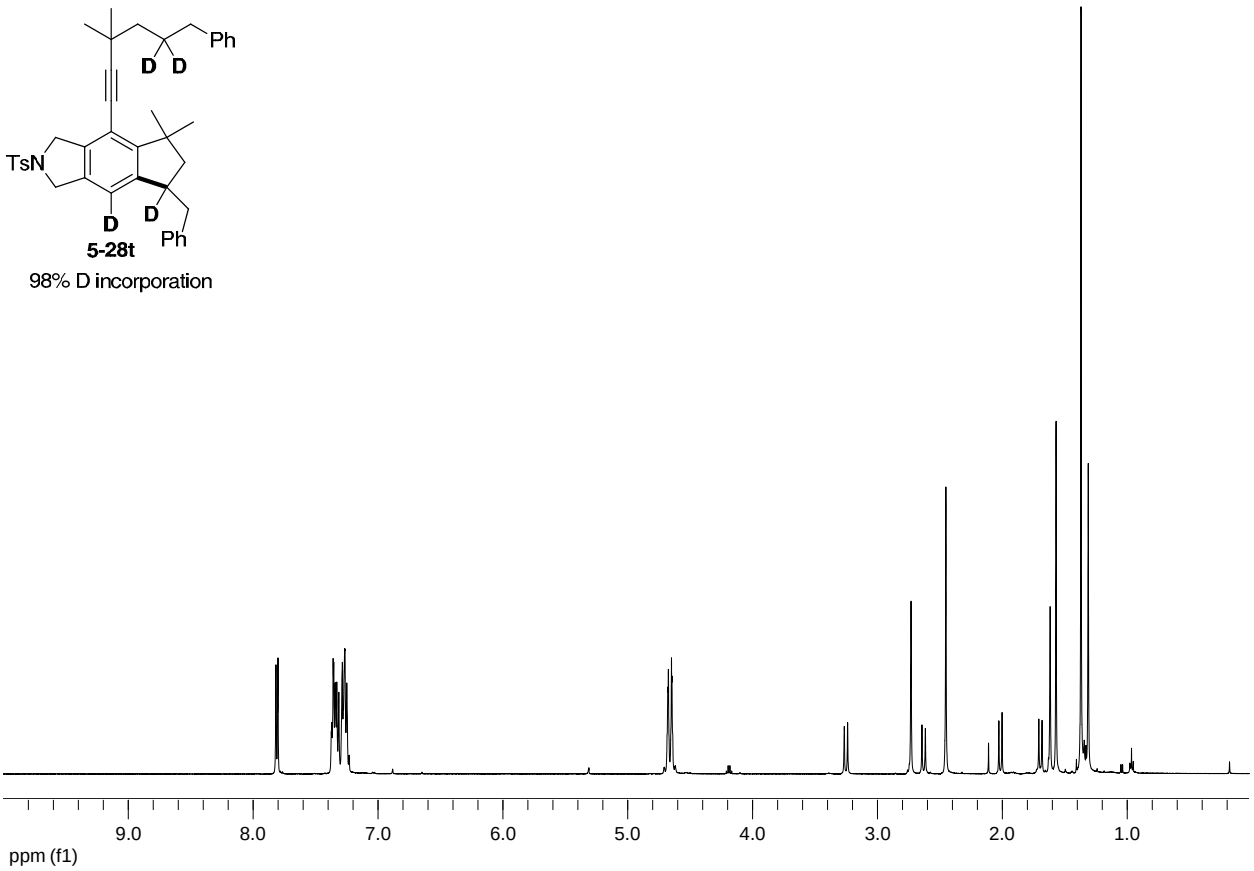

200
150
100
50
0
ppm (f1)

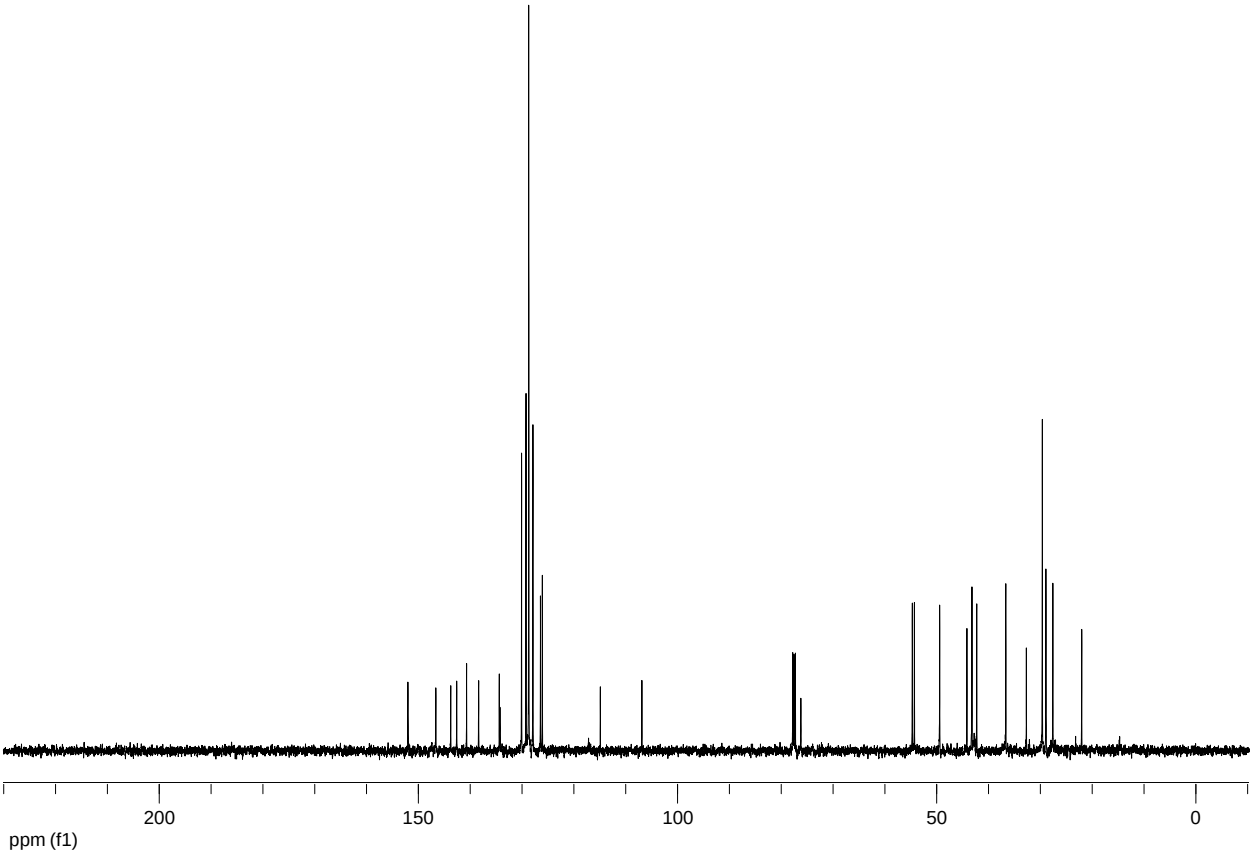

TsN
H
5-28r
+
4 : 1
TsN
H
5-28r'
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)


200
150
100
50
0
ppm (f1)


TsN
H
5-28s
+
10 : 1
TsN
H
5-28s'
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

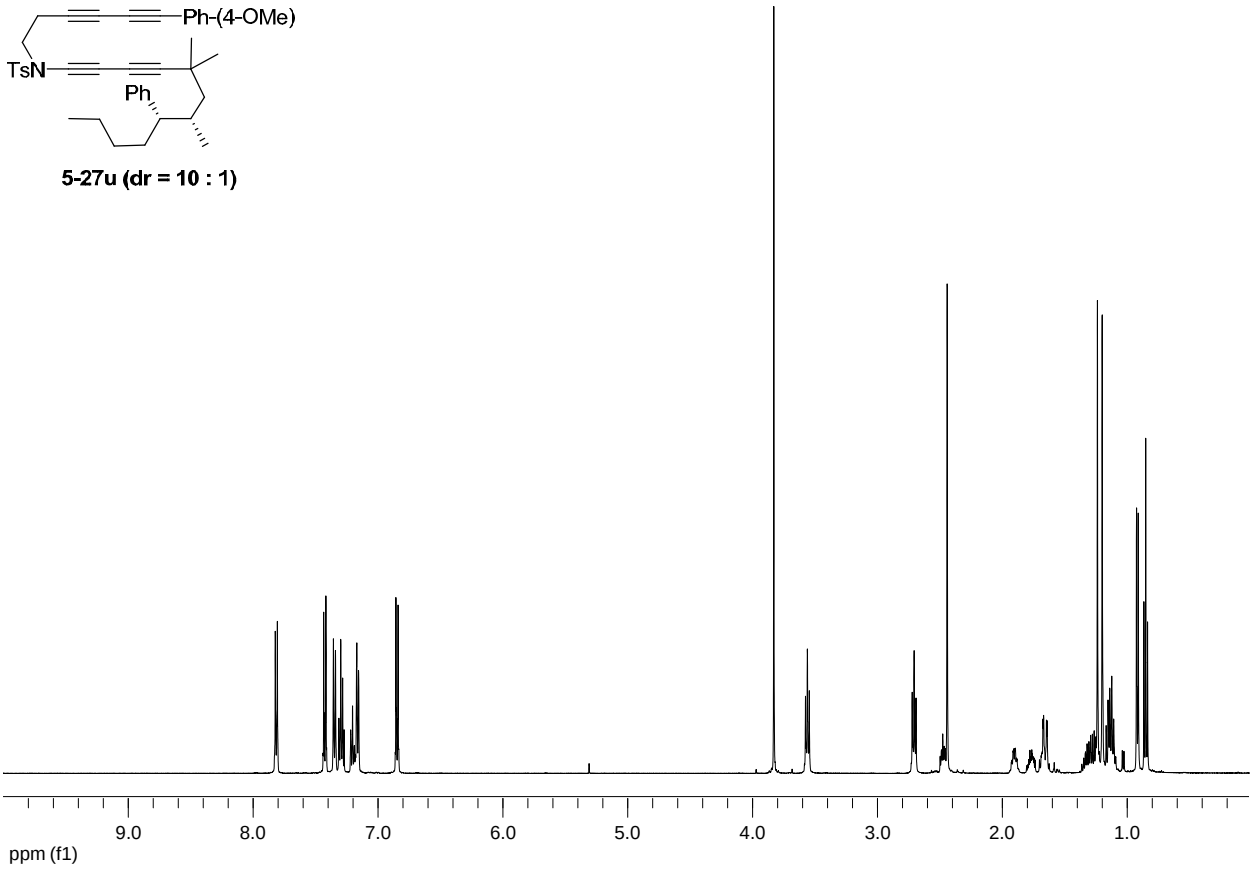

200
150
100
50
0
ppm (f1)

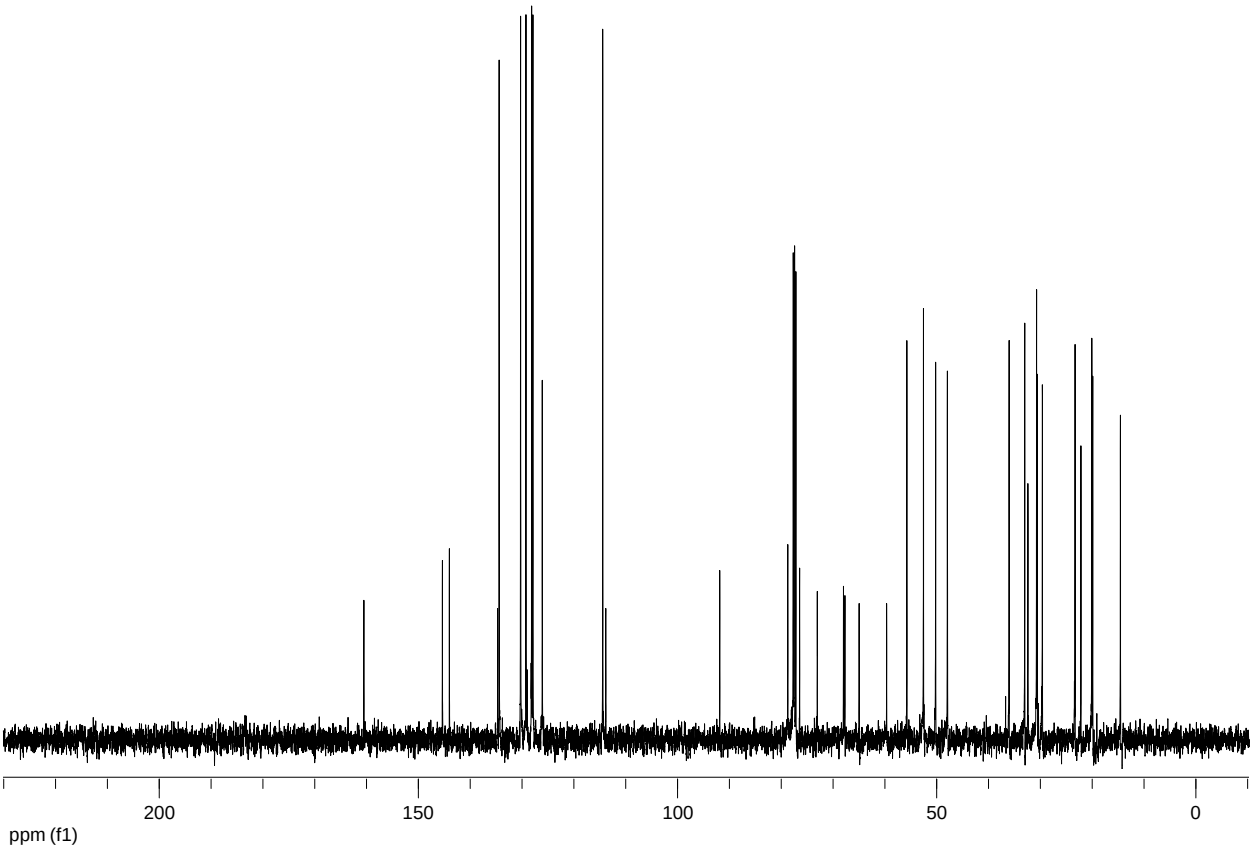

Ph
D D
TsN
D
D
Ph
5-28t
98% D incorporation
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)


200
150
100
50
0
ppm (f1)

Ph-(4-OMe)
TsN
Ph

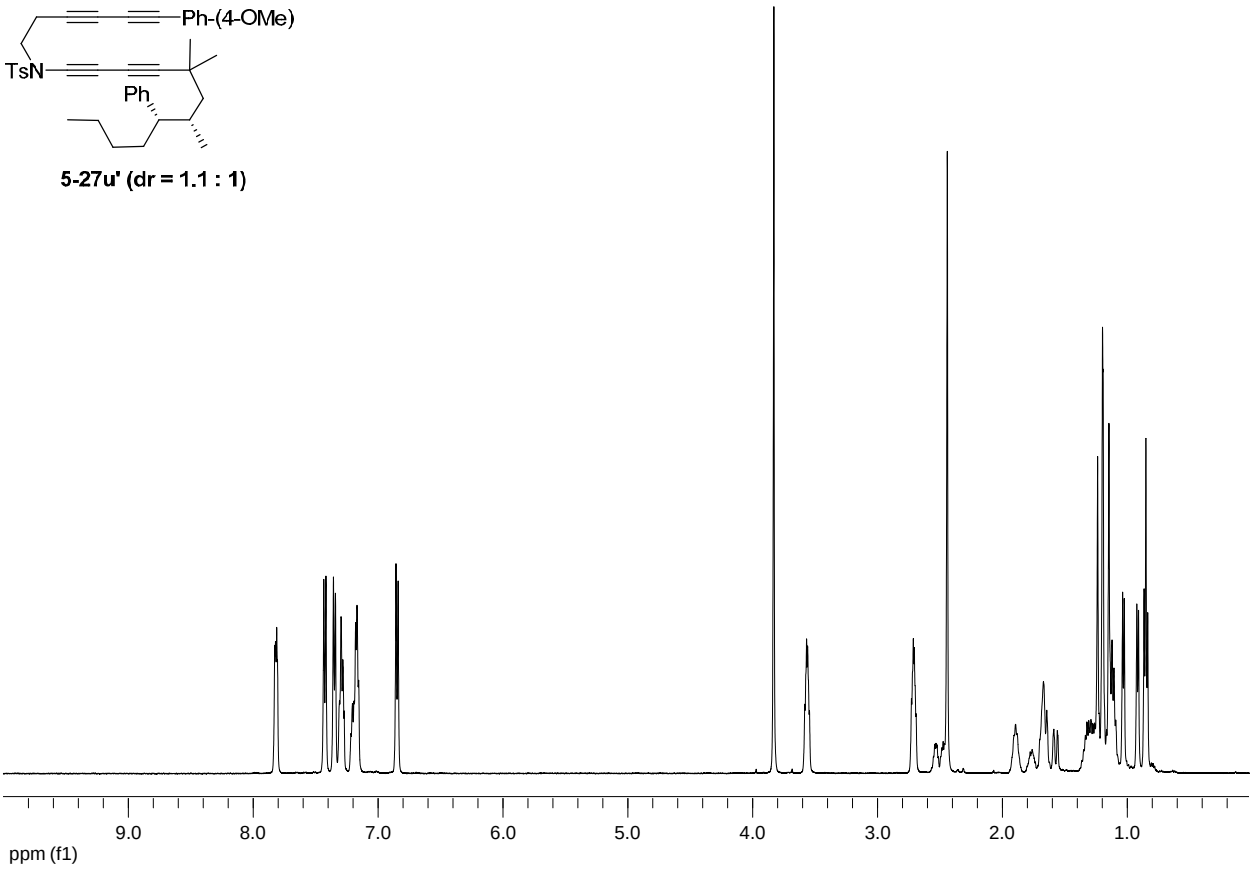
5-27u (dr = 10 : 1)

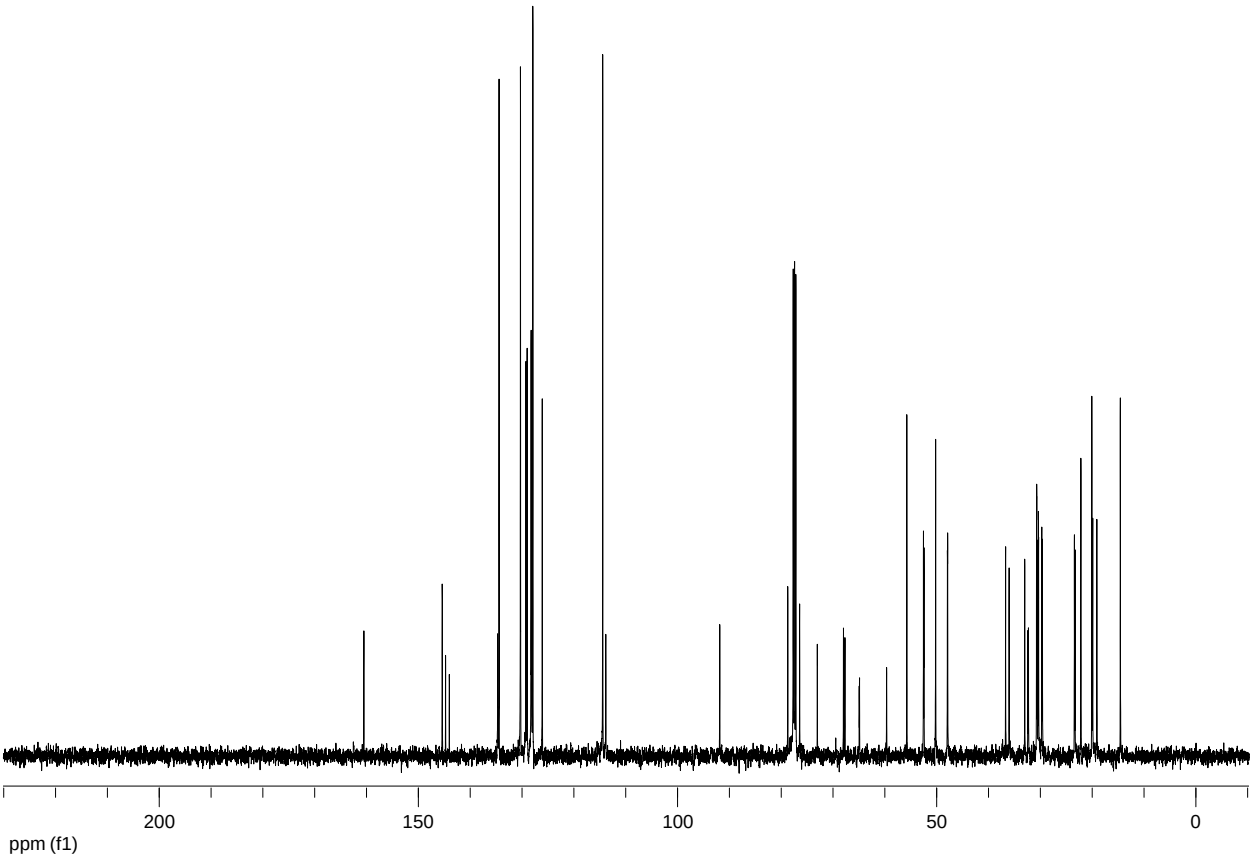

9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

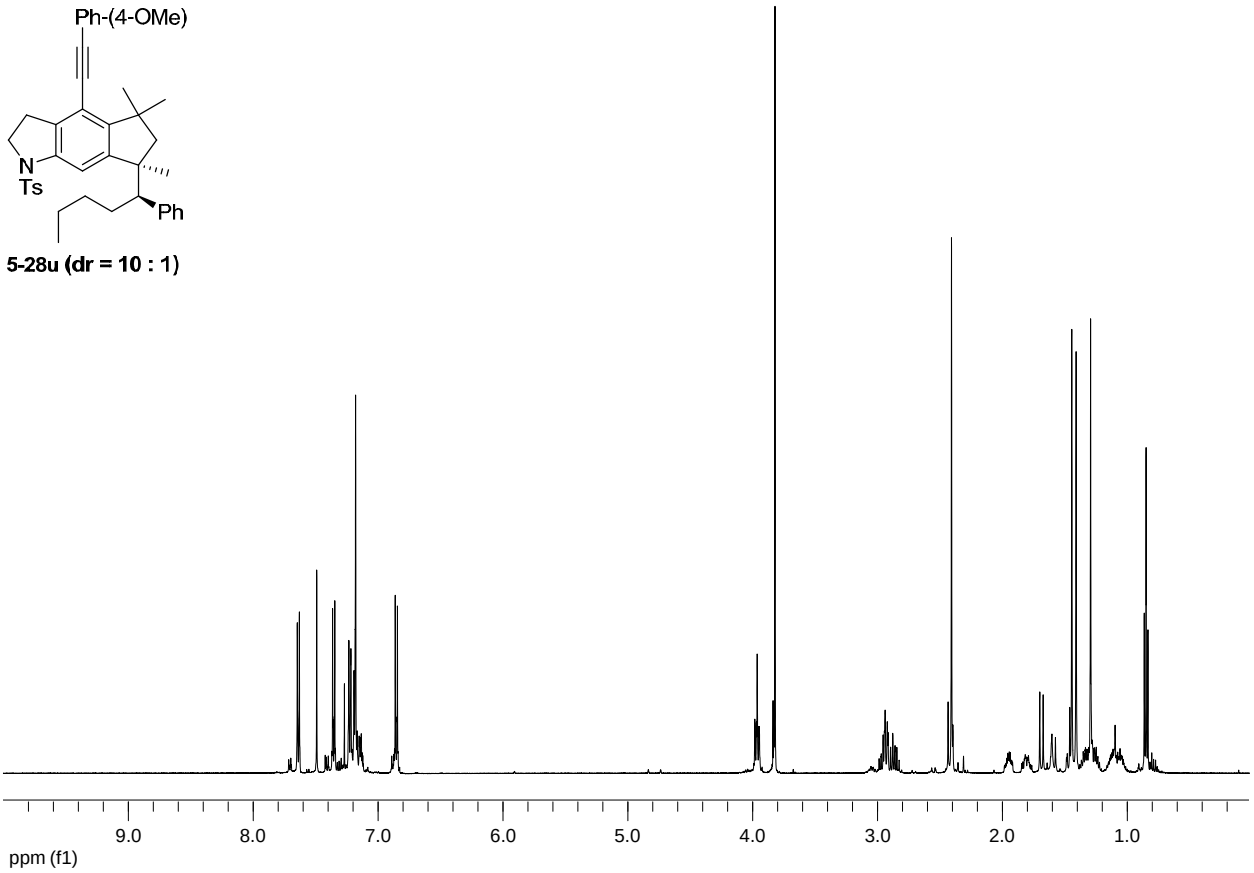

200
150
100
50
0
ppm (f1)

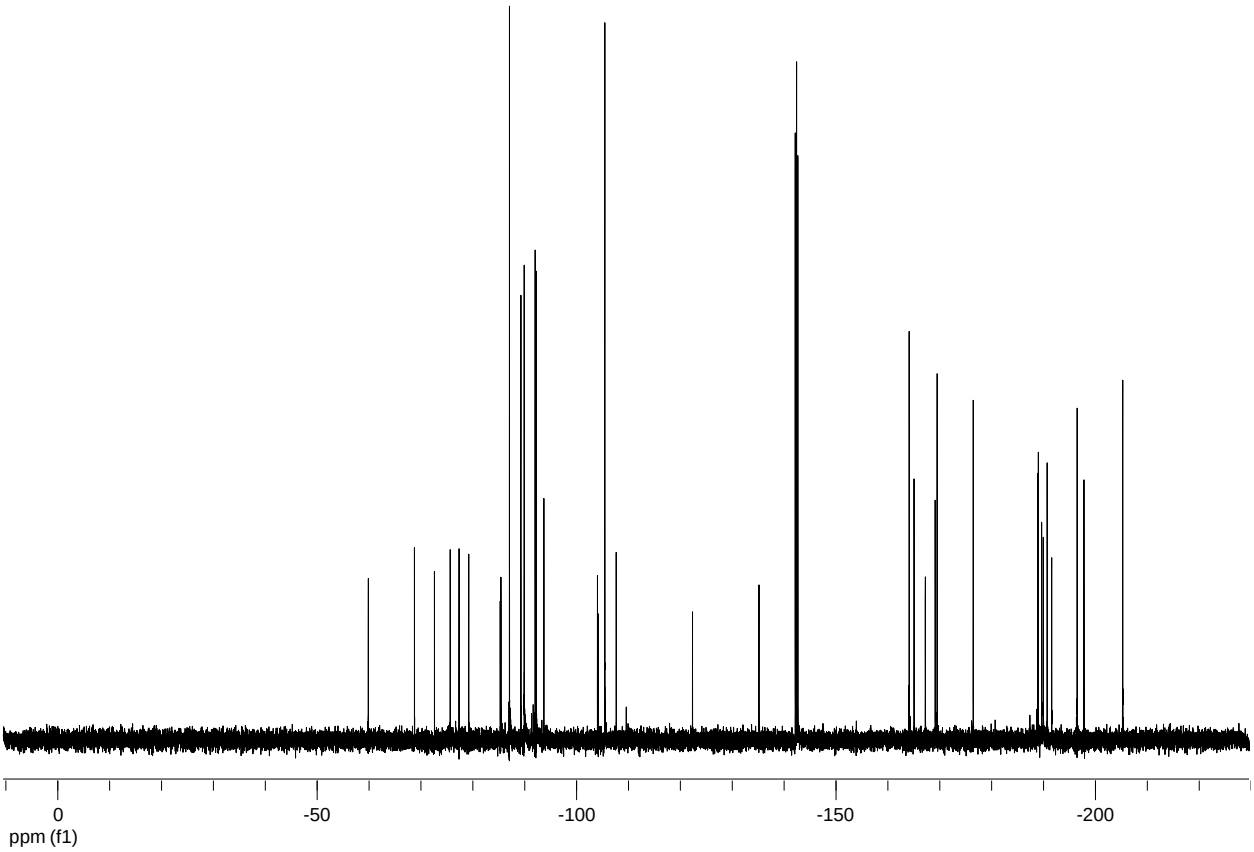
Ph-(4-OMe)
TsN
Ph

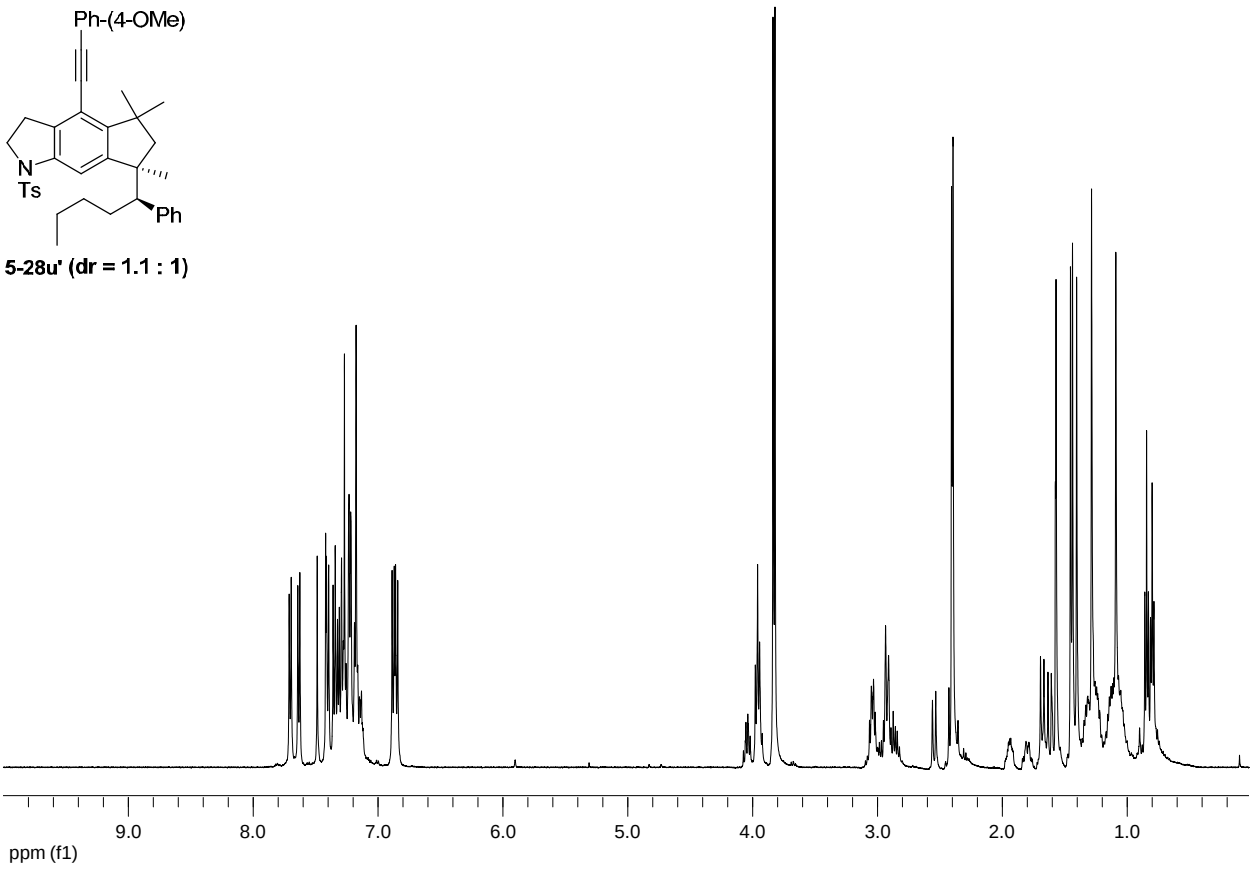
5-27u' (dr = 1.1 : 1)

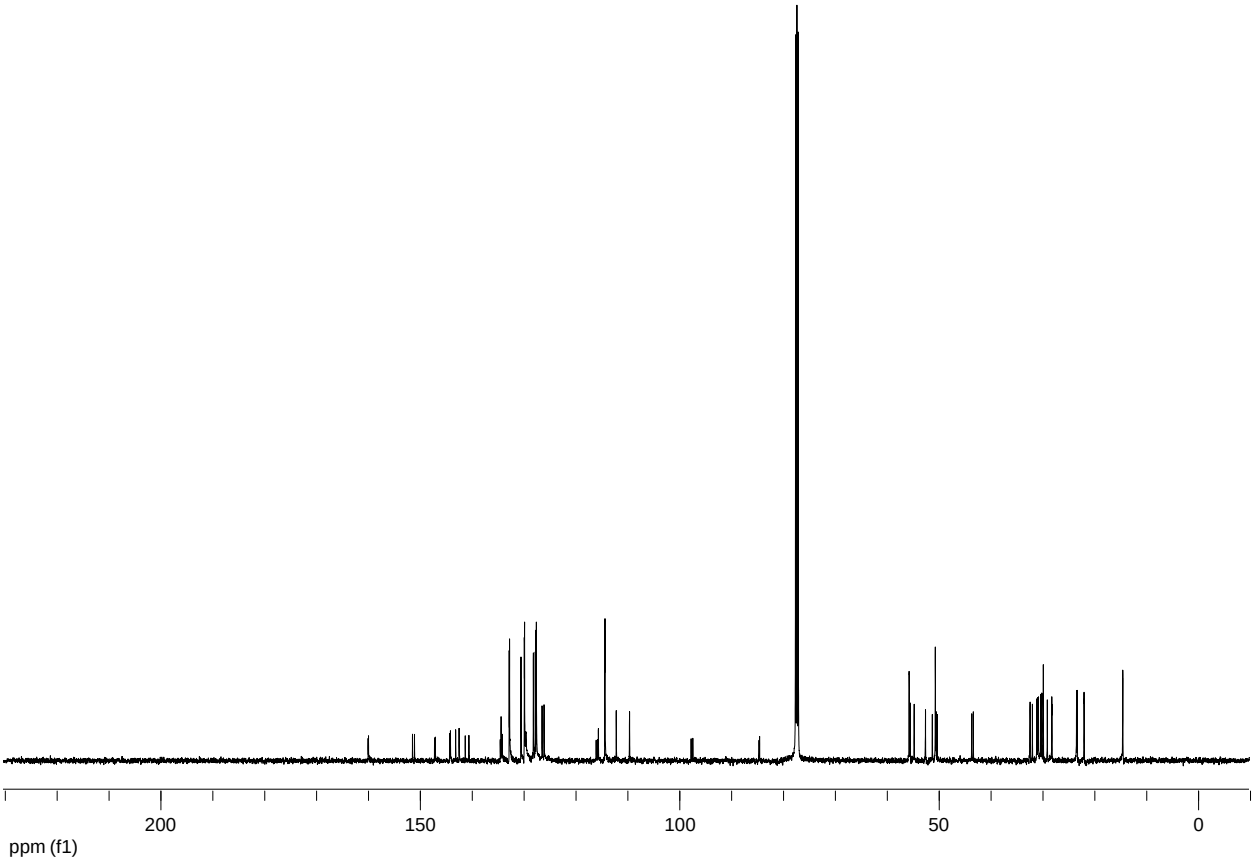

9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

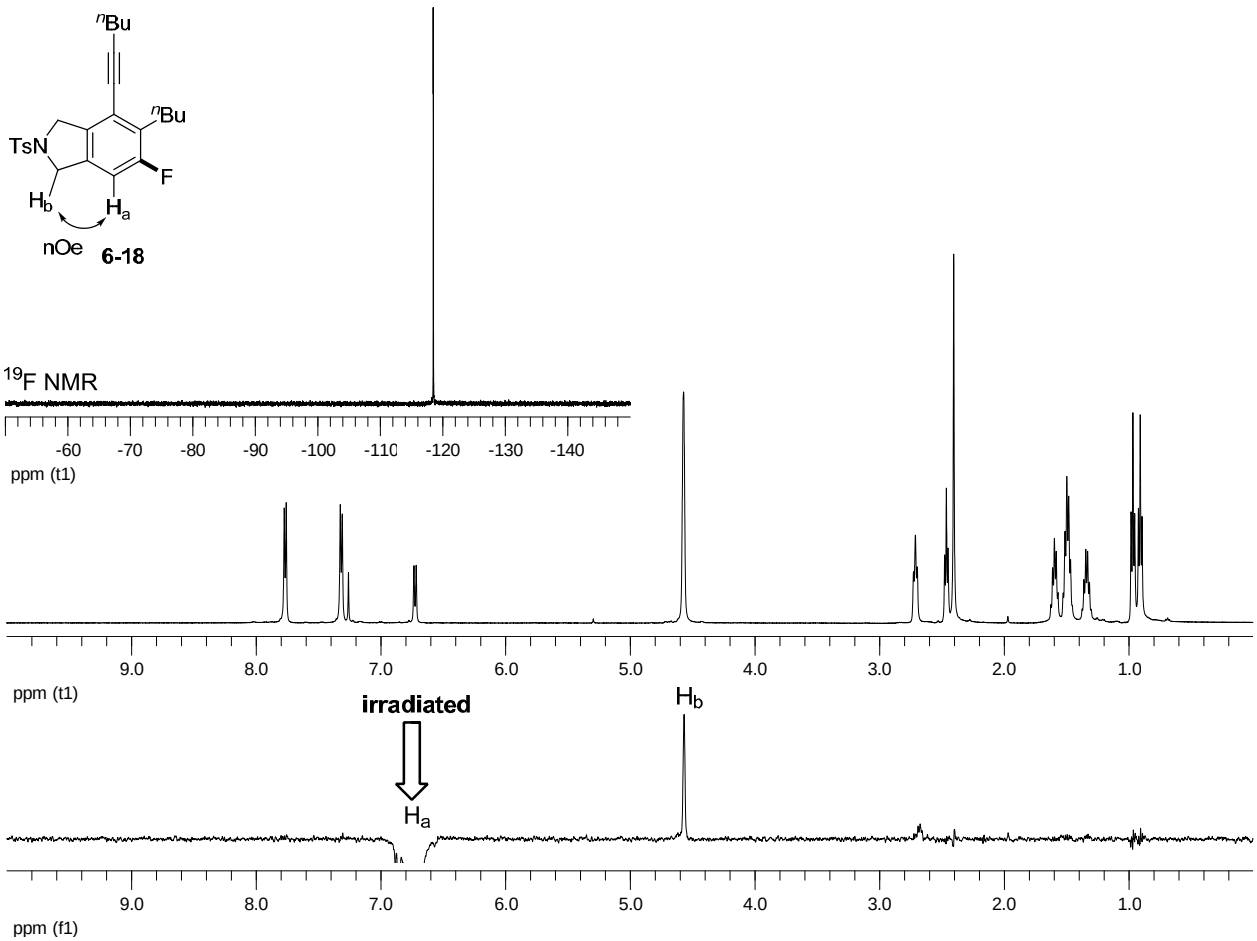

200
150
100
50
0
ppm (f1)

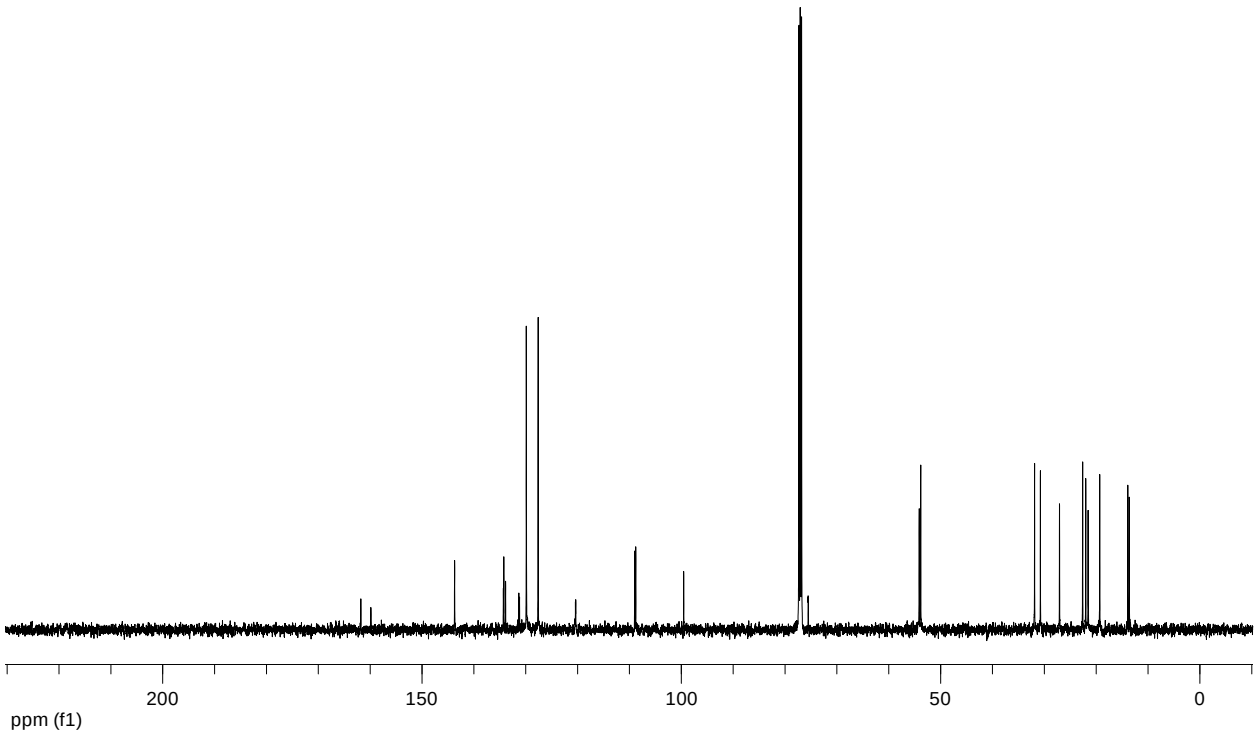

Ph-(4-OMe)
N
Ts
Ph
5-28u (dr = 10 : 1)
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

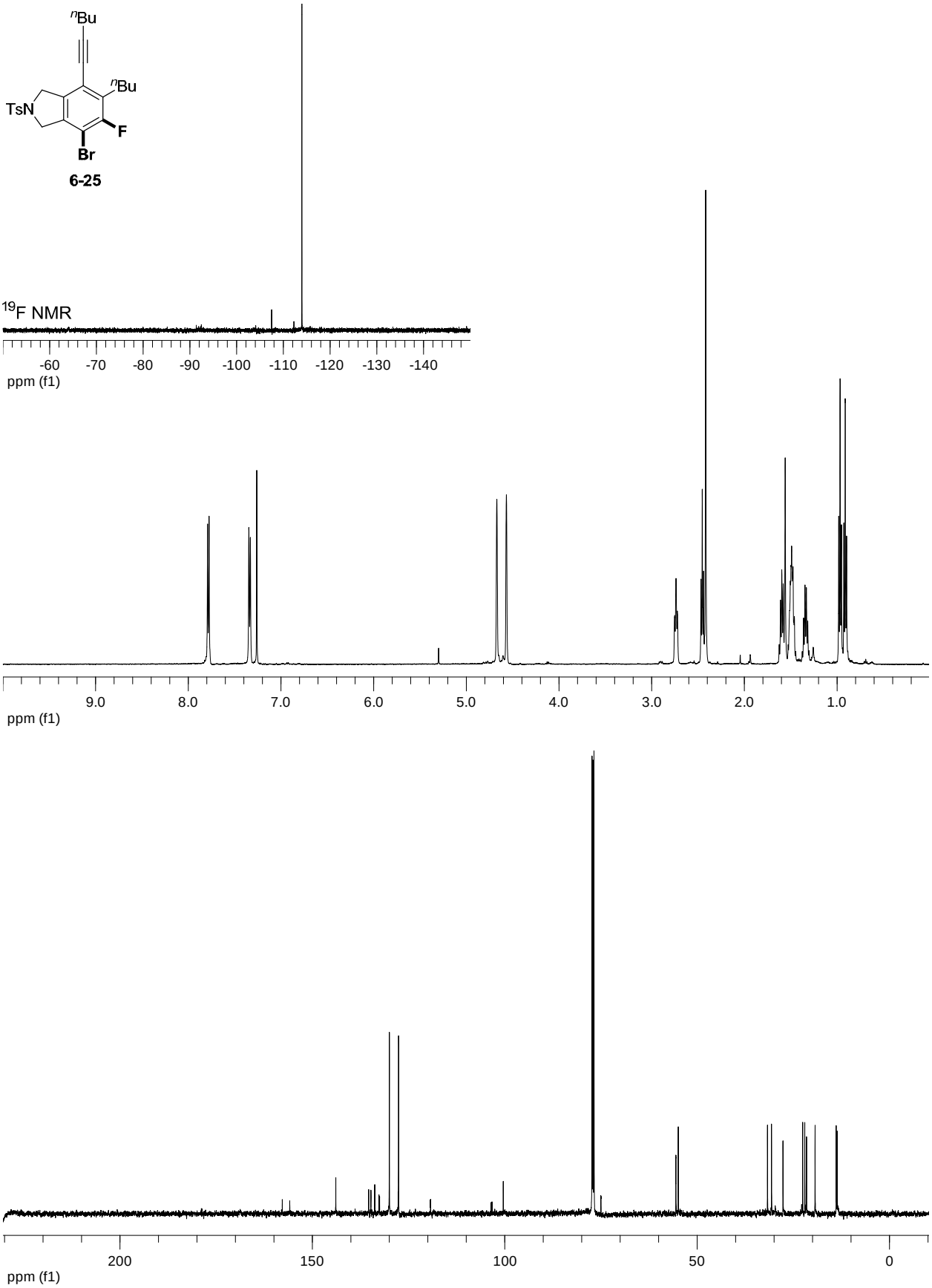

0
-50
-100
-150
-200
ppm (f1)

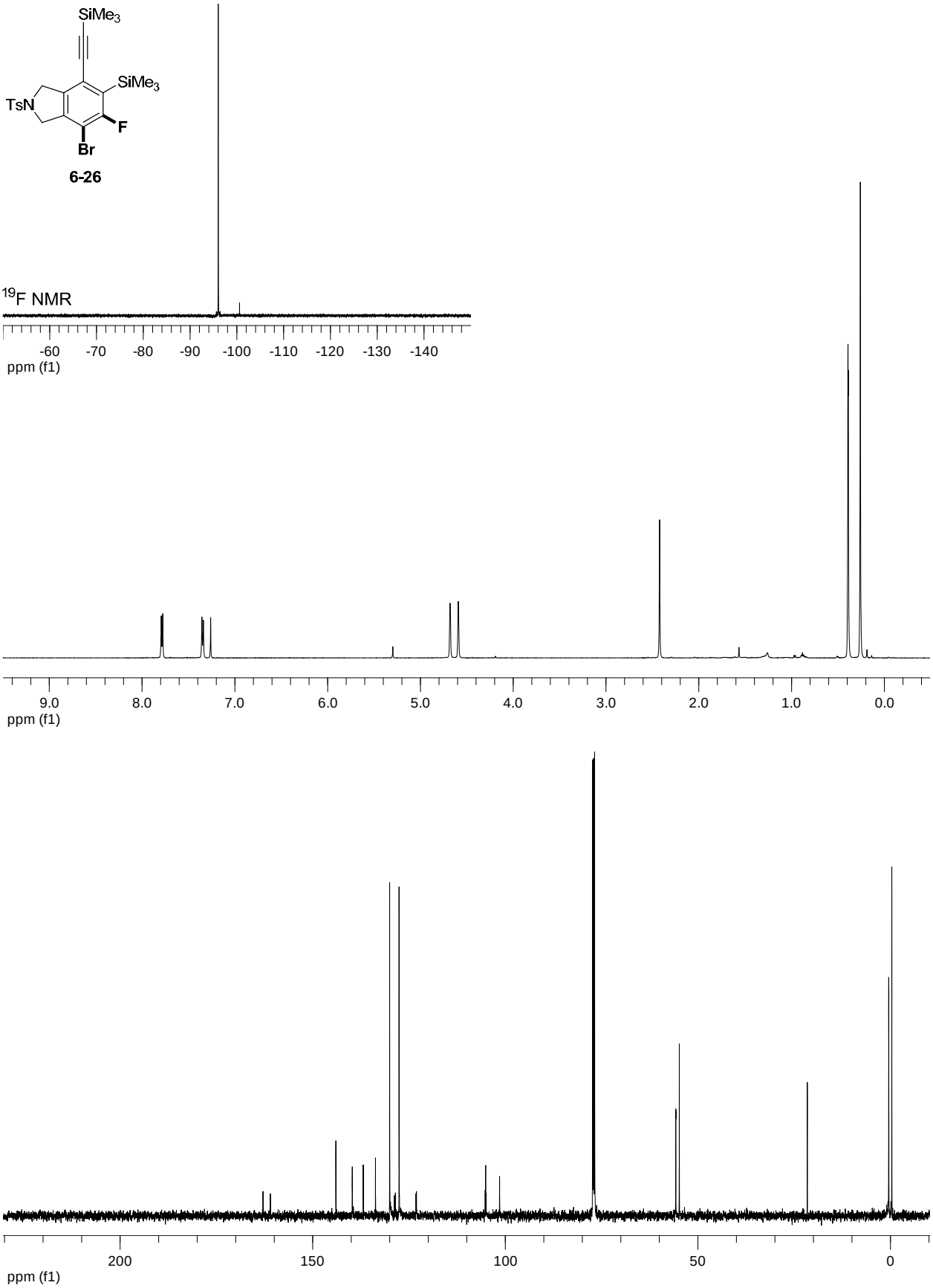

Ph-(4-OMe)
N
Ts
Ph
5-28u' (dr = 1.1 : 1)
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

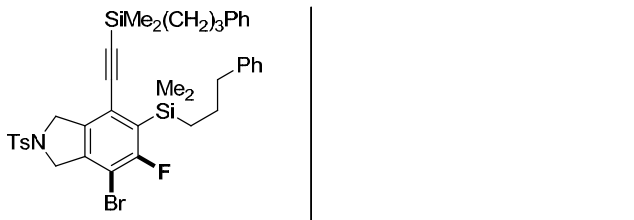

200
150
100
50
0
ppm (f1)


nBu
nBu
TsN
F
Hb
Ha
nOe
6-18
19F NMR
-60 -70 -80 -90 -100 -110 -120 -130 -140
ppm (t1)
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0
ppm (t1)
irradiated
Hb
Ha
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0
ppm (f1)


200 150 100 50 0
ppm (f1)


nBu
nBu
TsN
F
Br
6-25
19F NMR
-60 -70 -80 -90 -100 -110 -120 -130 -140
ppm (f1)
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0
ppm (f1)
200 150 100 50 0
ppm (f1)

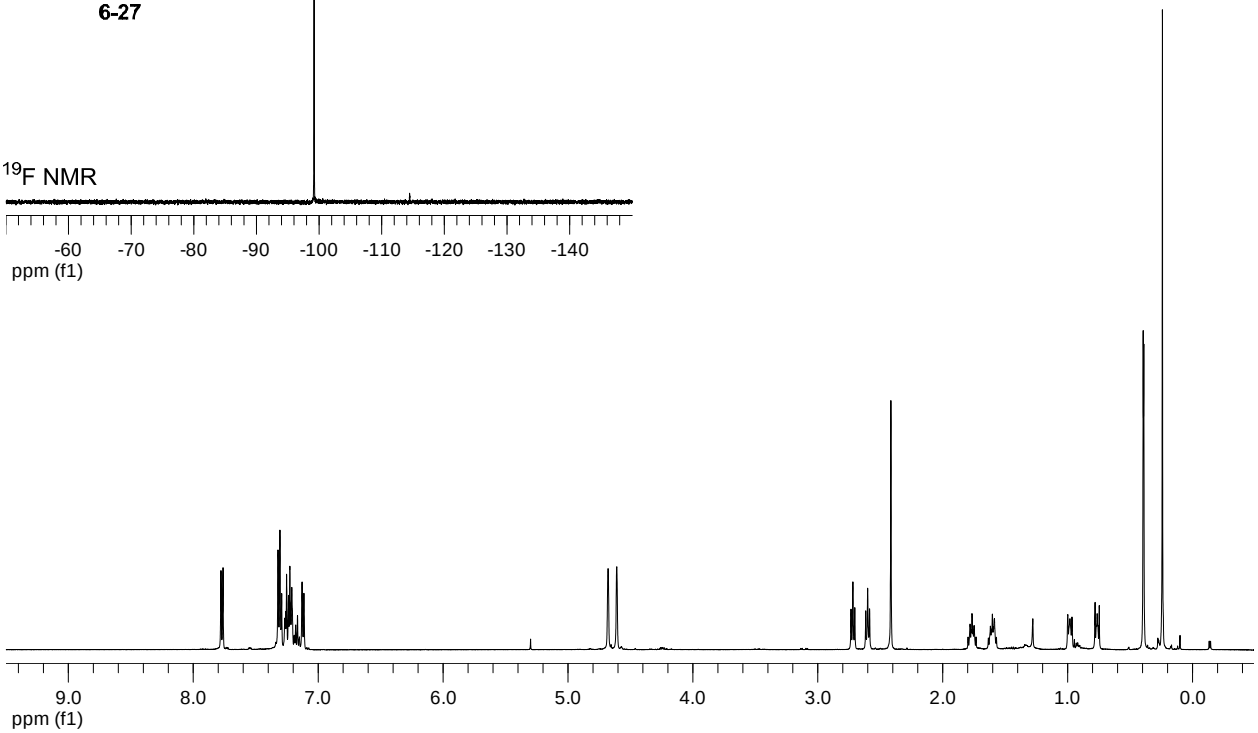

SiMe3
SiMe3
TsN
F
Br
6-26
19F NMR
-60 -70 -80 -90 -100 -110 -120 -130 -140
ppm (f1)
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0
ppm (f1)
200 150 100 50 0
ppm (f1)

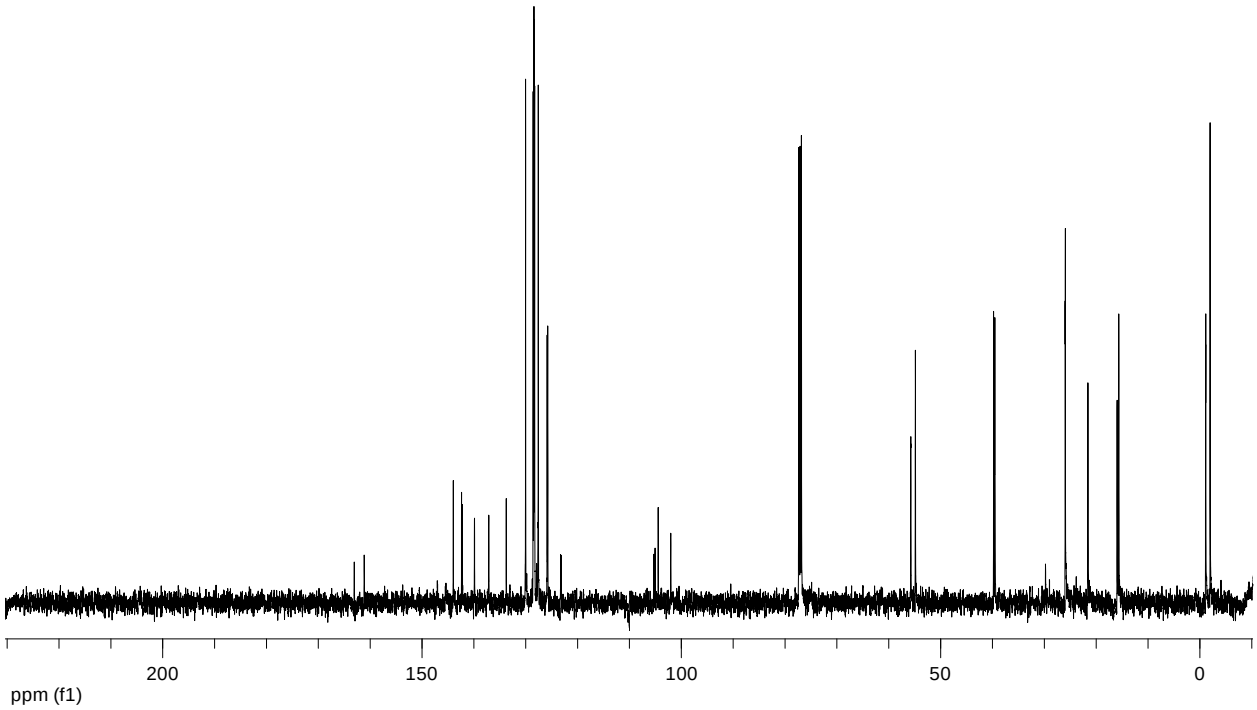

SiMe2(CH2)3Ph
Ph
Me2
Si
TsN
F
Br

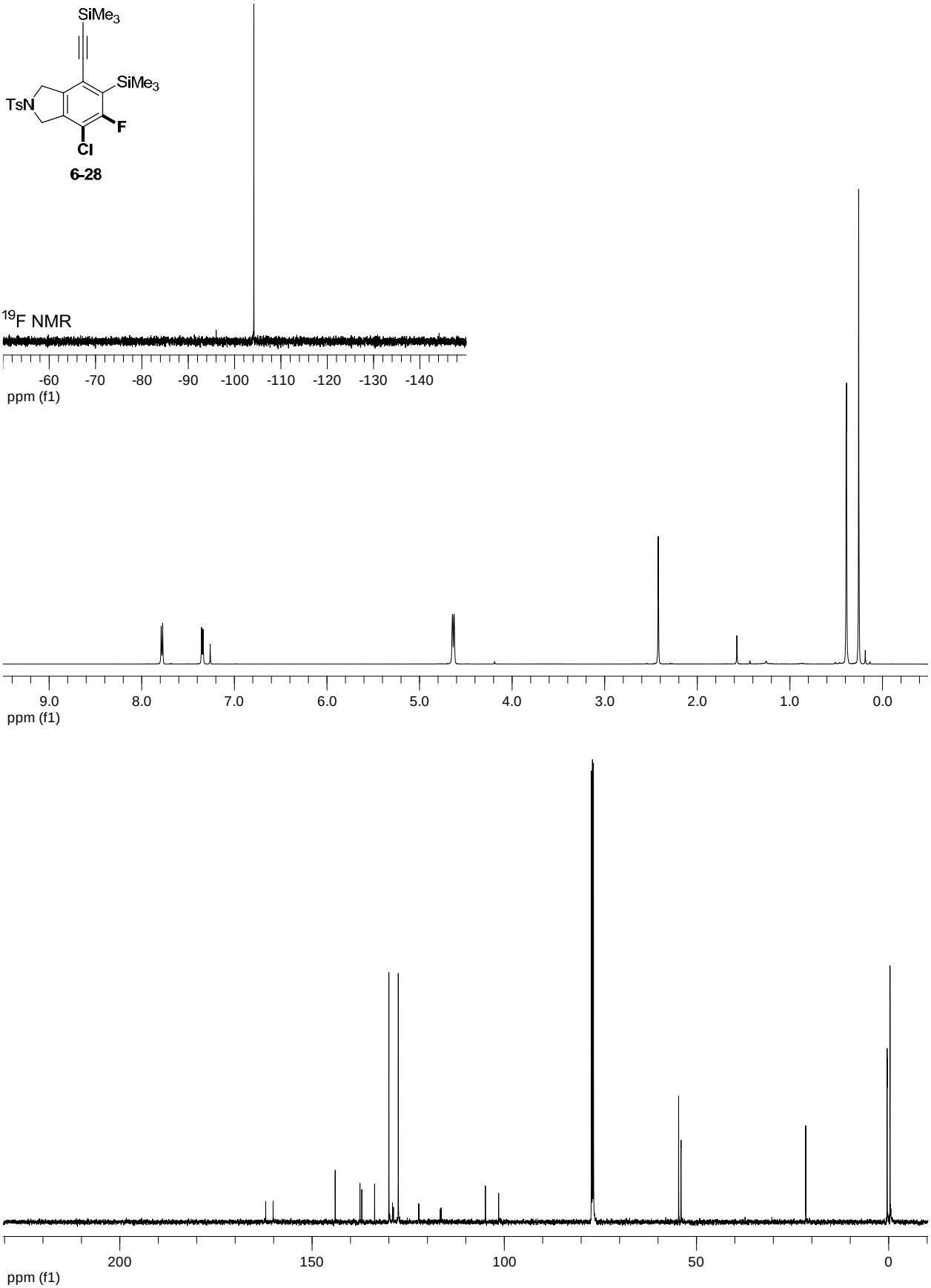
6-27

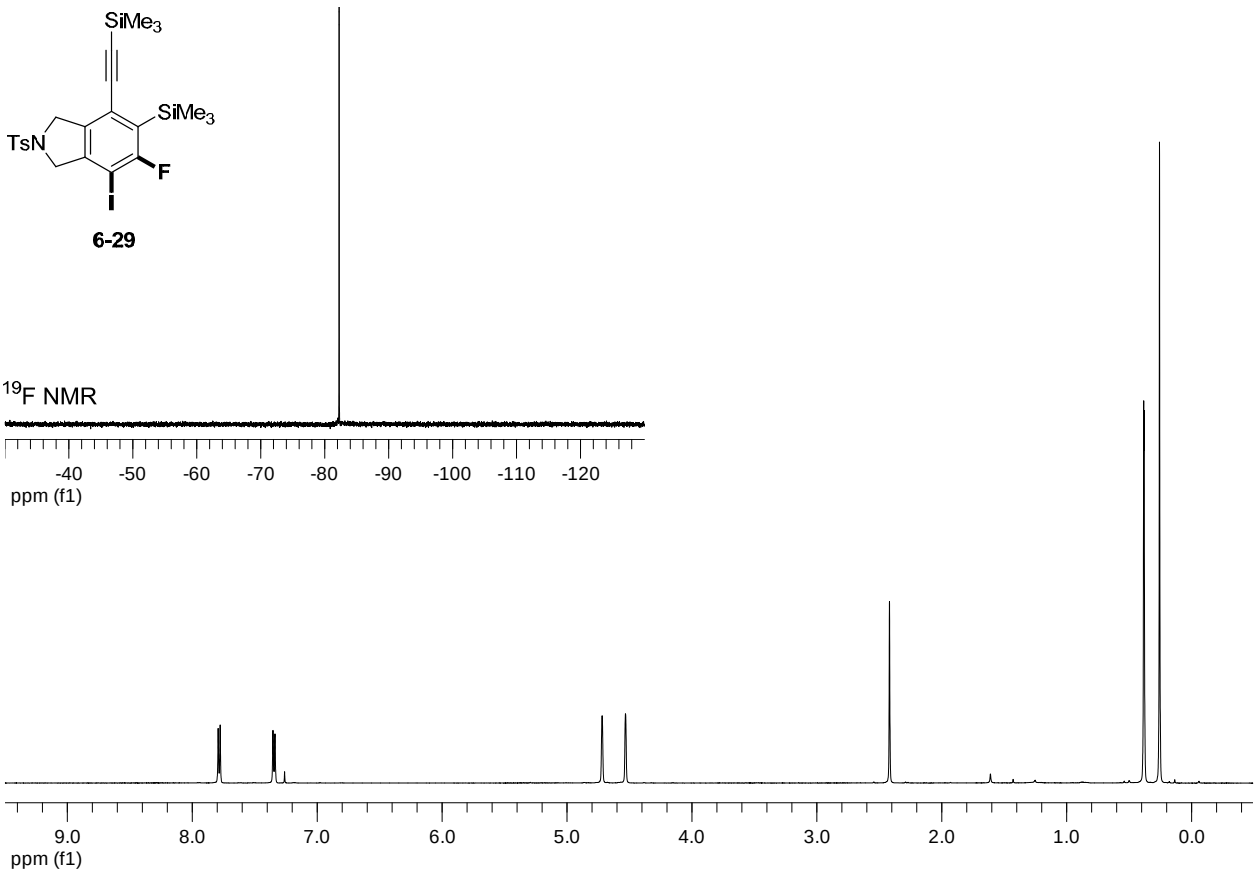
^{19}F NMR

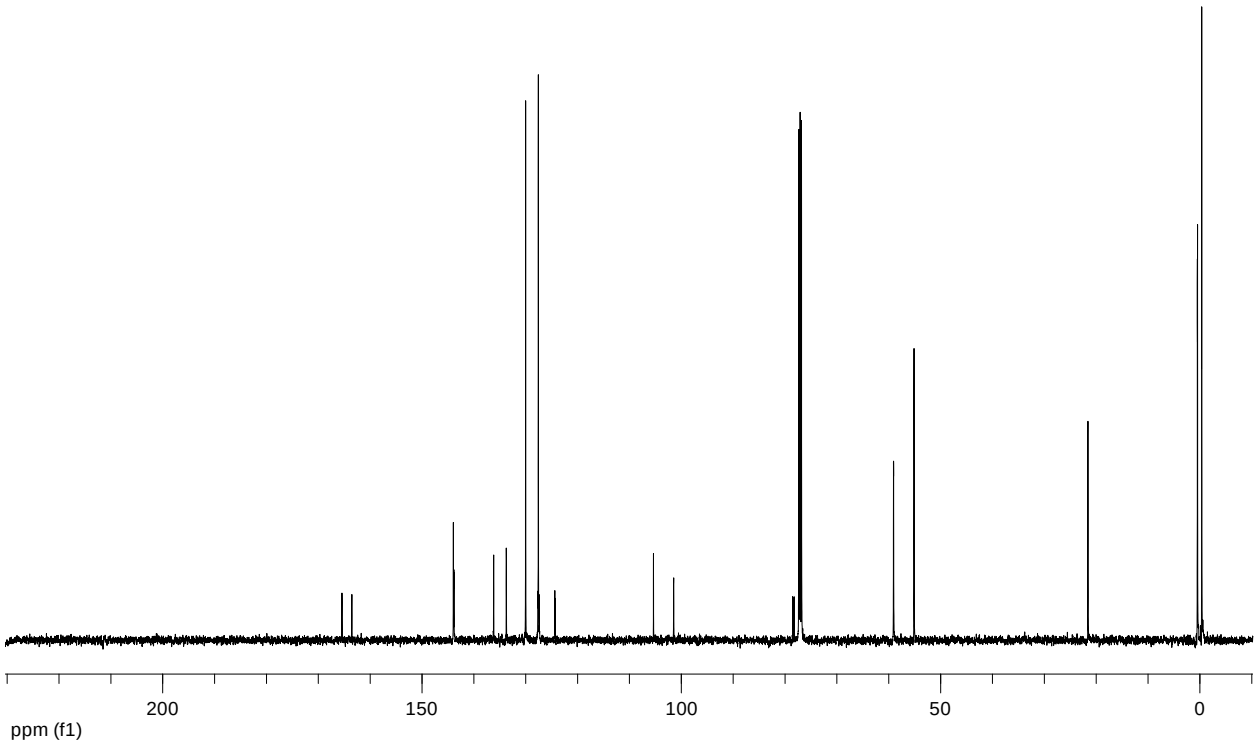
-60
-70
-80
-90
-100
-110
-120
-130
-140
ppm (f1)

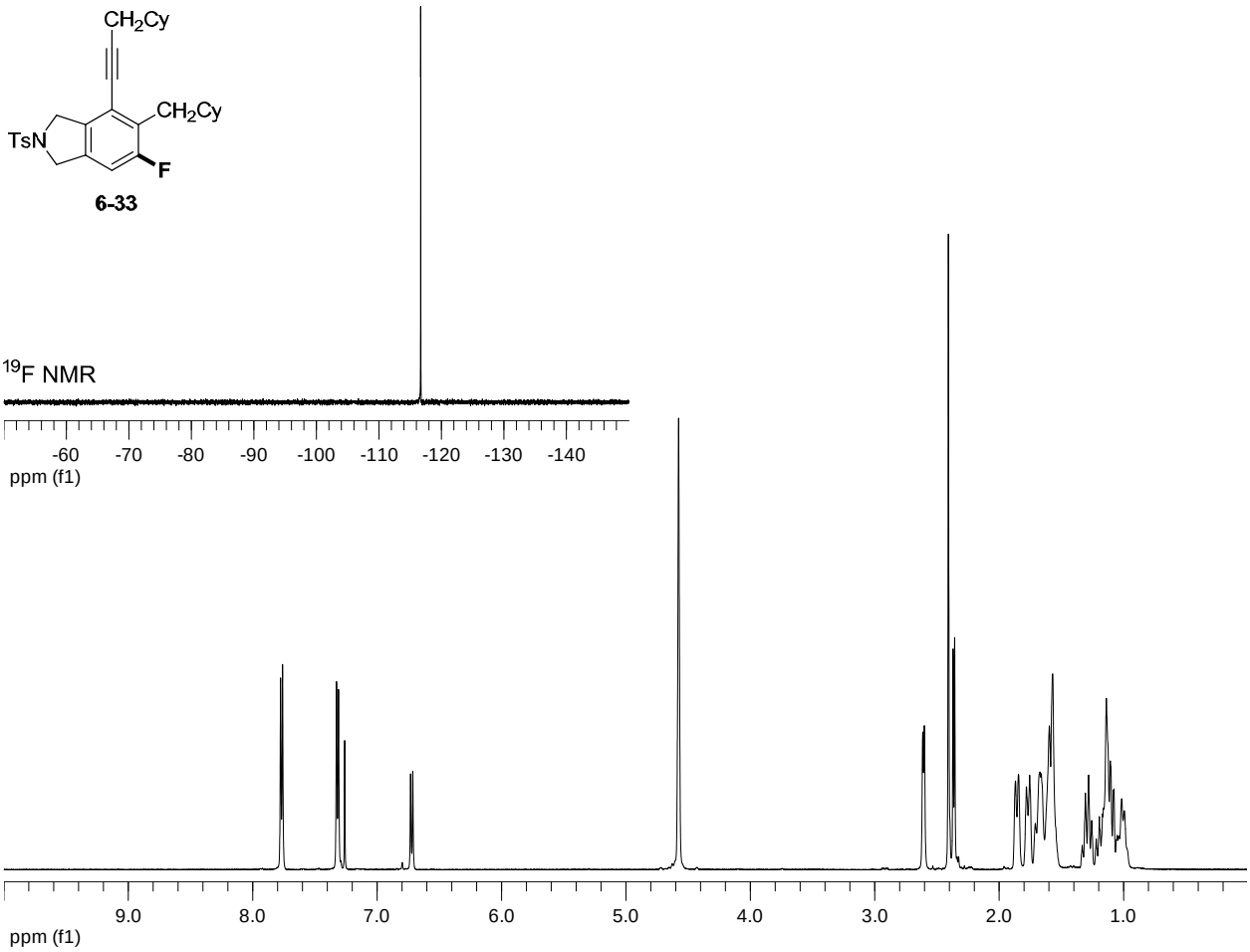

9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

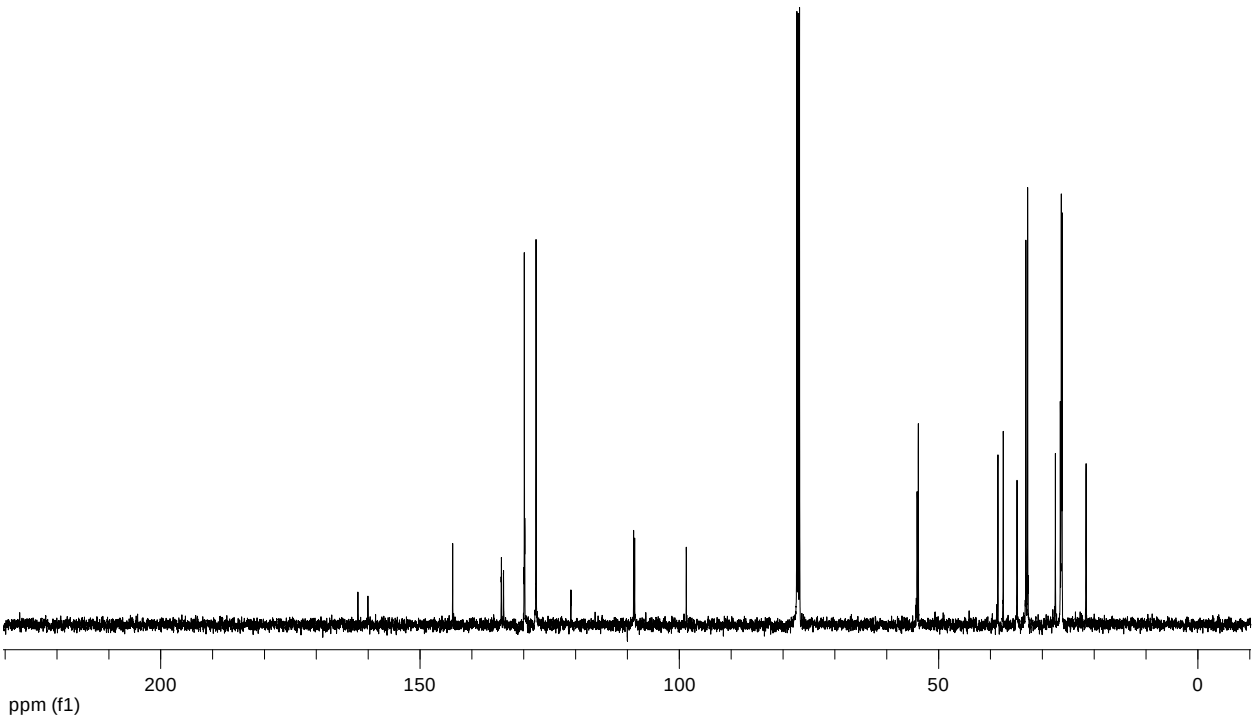

200
150
100
50
0
ppm (f1)

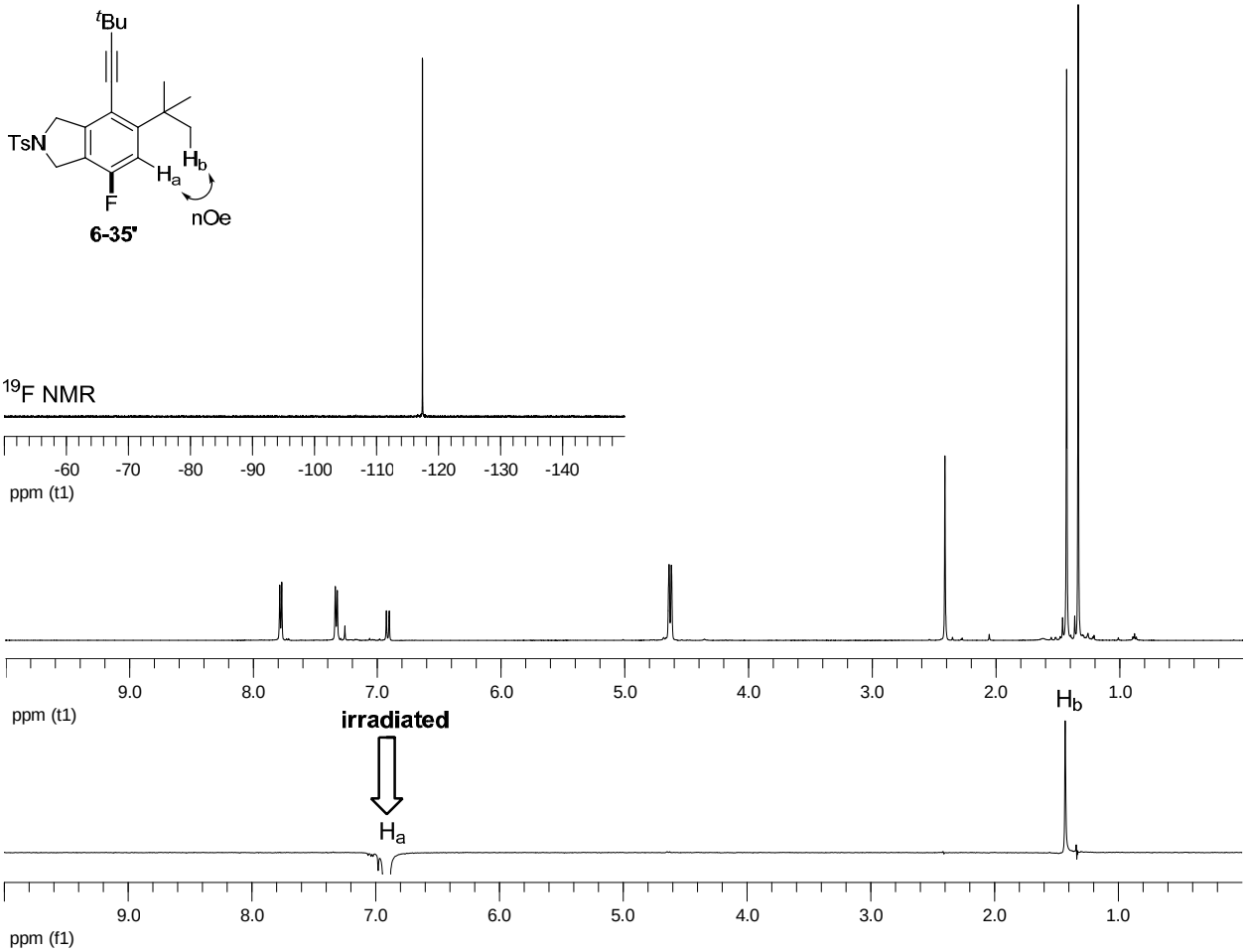

SiMe3
SiMe3
TsN
F
Cl
6-28
19F NMR
-60 -70 -80 -90 -100 -110 -120 -130 -140
ppm (f1)
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0
ppm (f1)
200 150 100 50 0
ppm (f1)

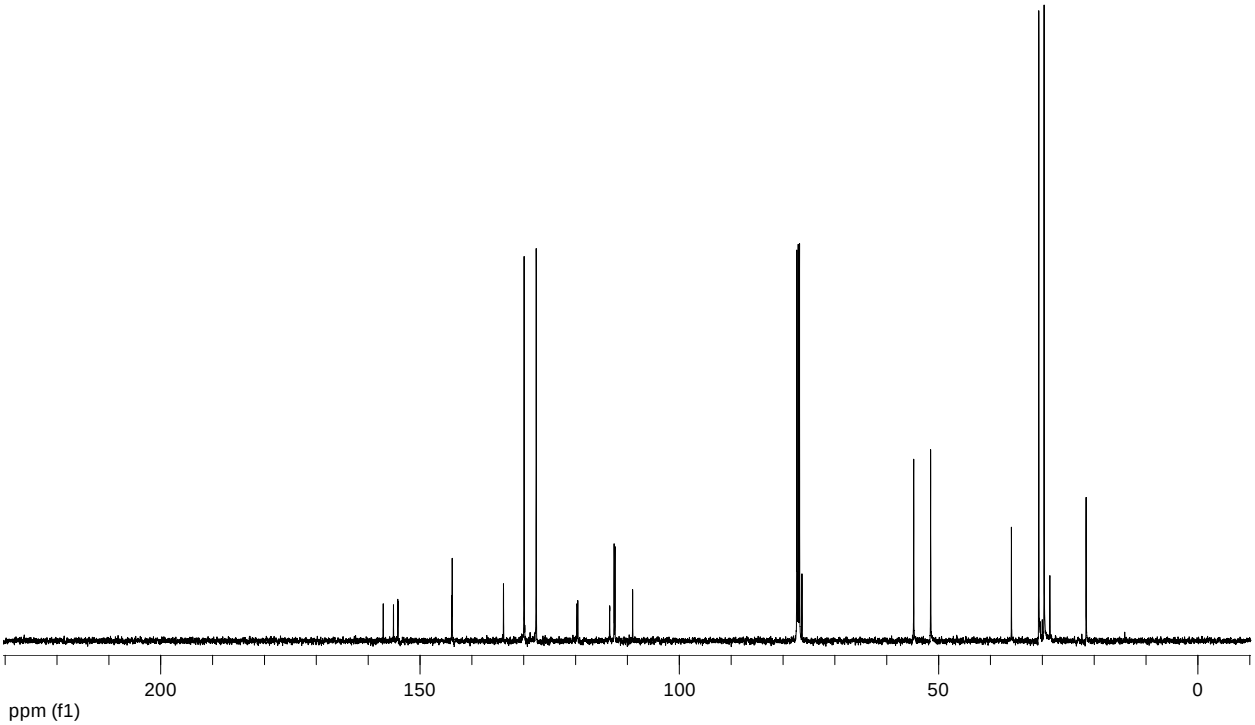

SiMe3
SiMe3
TsN
F
I
6-29
19F NMR
-40 -50 -60 -70 -80 -90 -100 -110 -120
ppm (f1)
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0
ppm (f1)

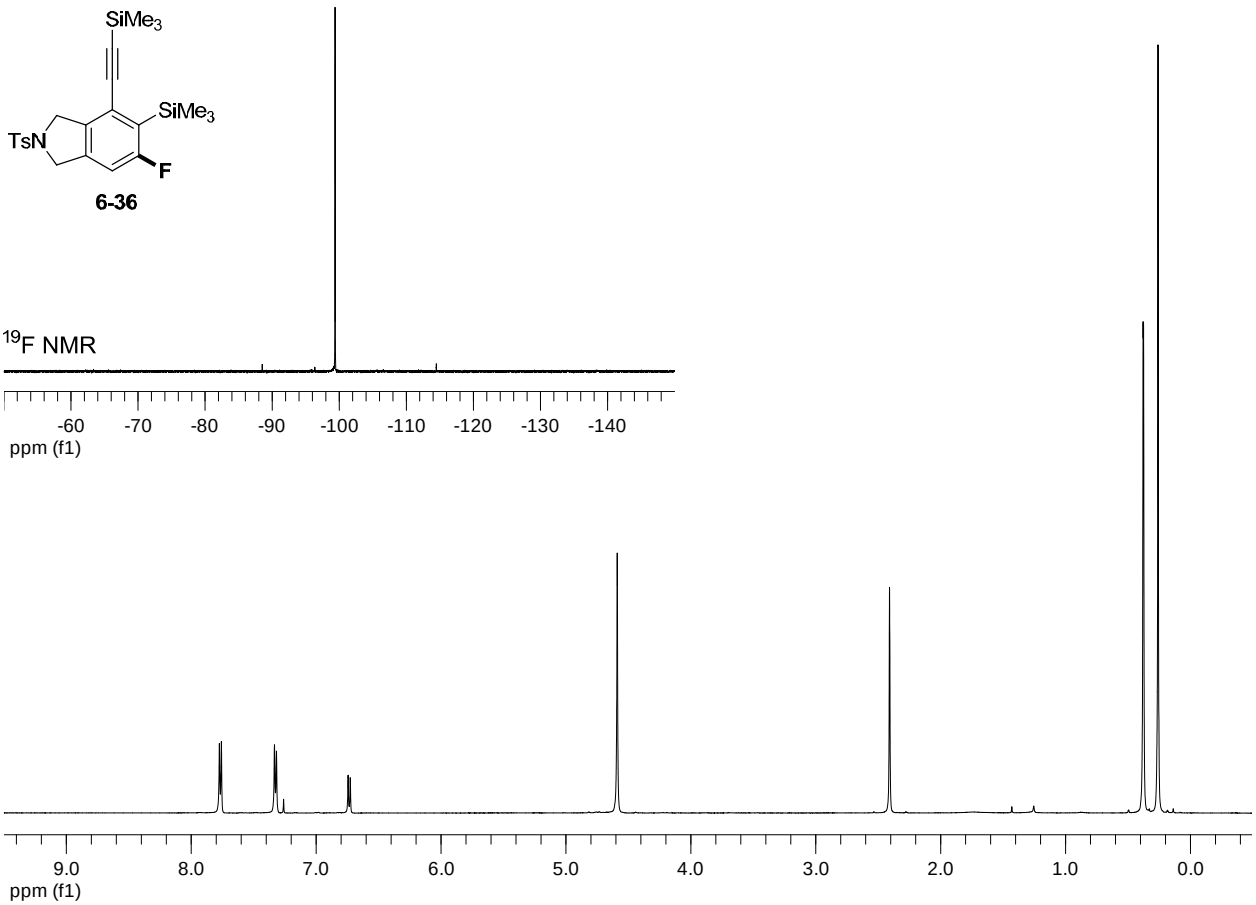

200 150 100 50 0
ppm (f1)

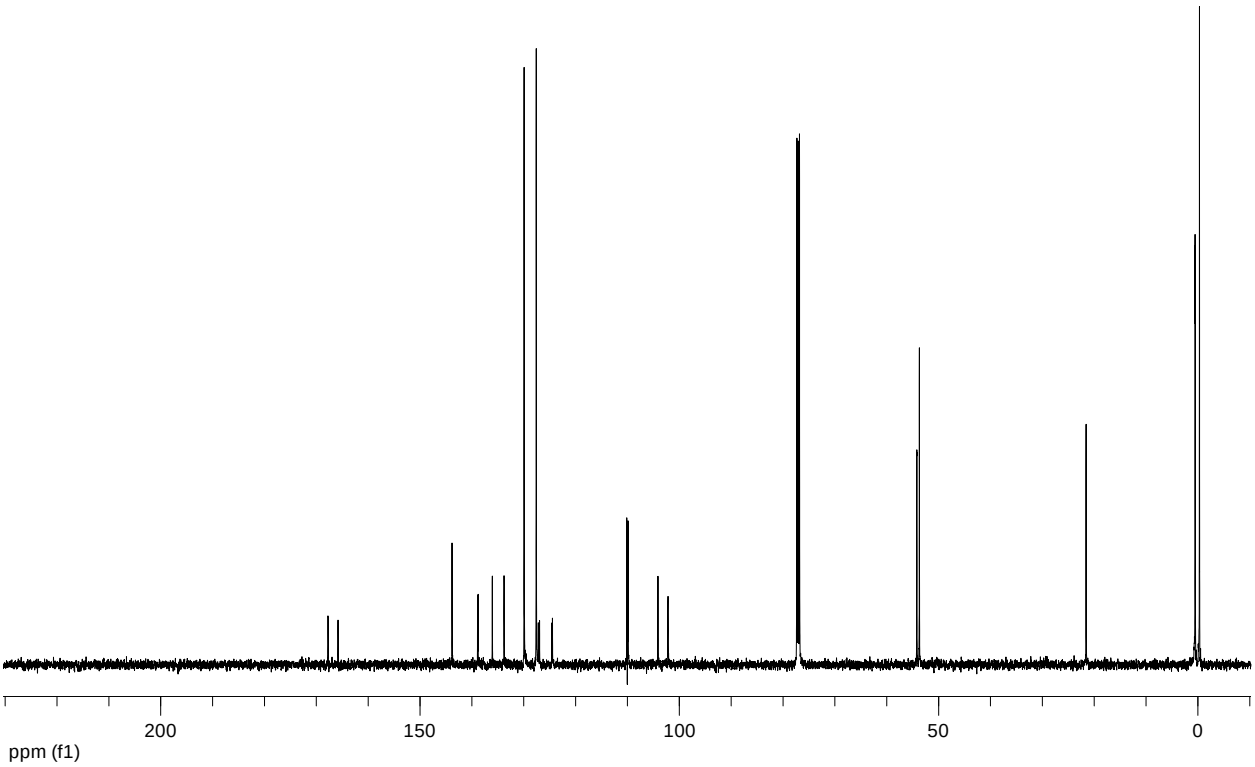

CH2Cy
CH2Cy
TsN
F
6-33
19F NMR
-60 -70 -80 -90 -100 -110 -120 -130 -140
ppm (f1)
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0
ppm (f1)

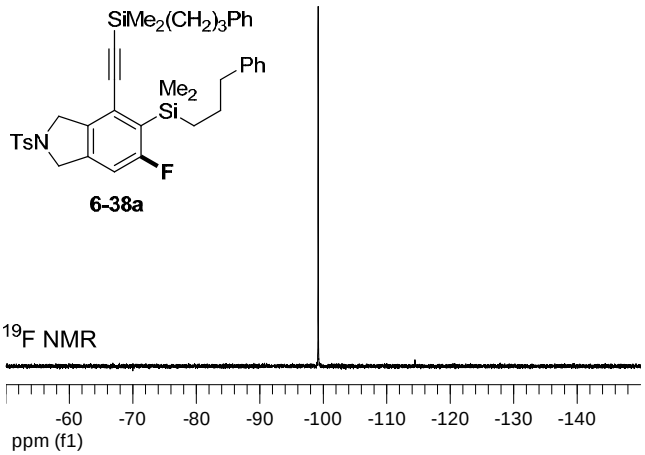

200 150 100 50 0
ppm (f1)

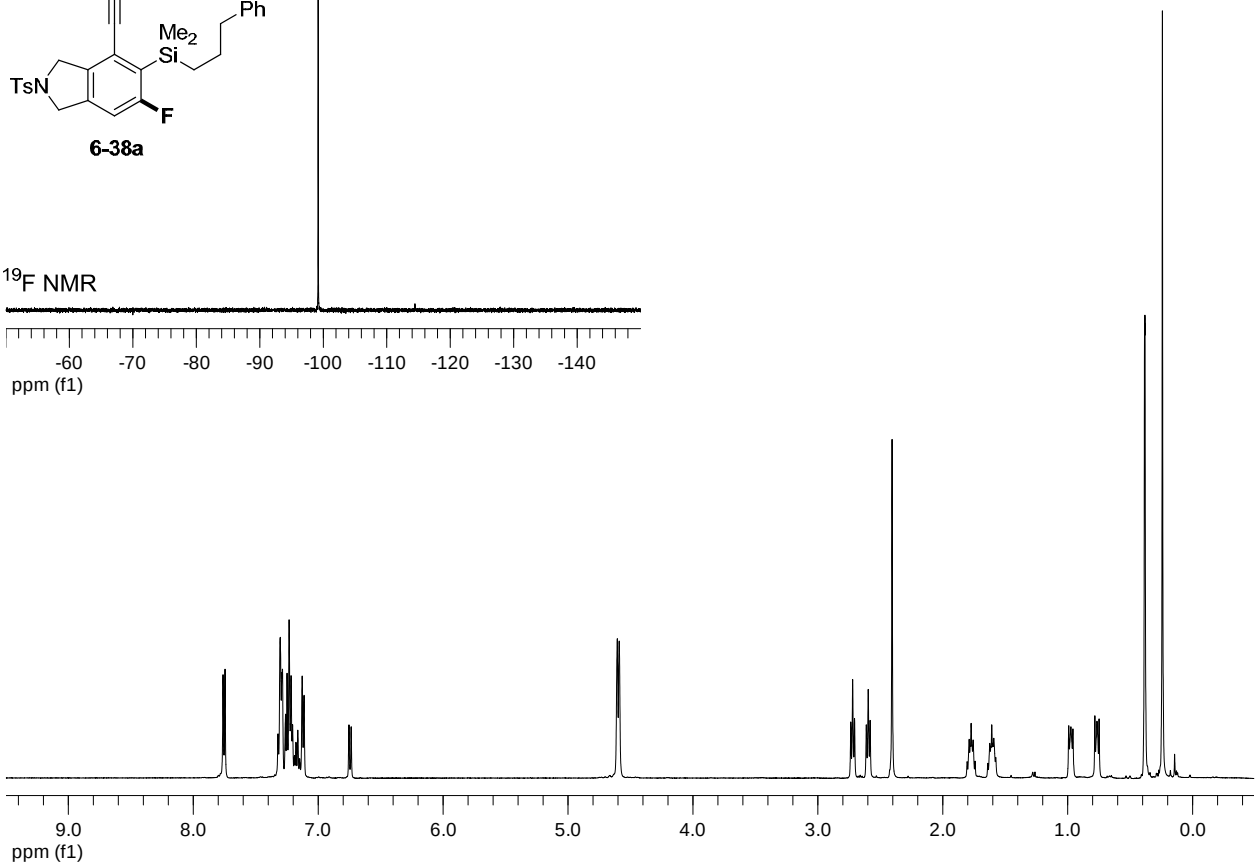

tBu
TsN
Ha
Hb
F
nOe
6-35"
19F NMR
-60 -70 -80 -90 -100 -110 -120 -130 -140
ppm (t1)
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0
ppm (t1)
irradiated
Ha
Hb
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0
ppm (f1)

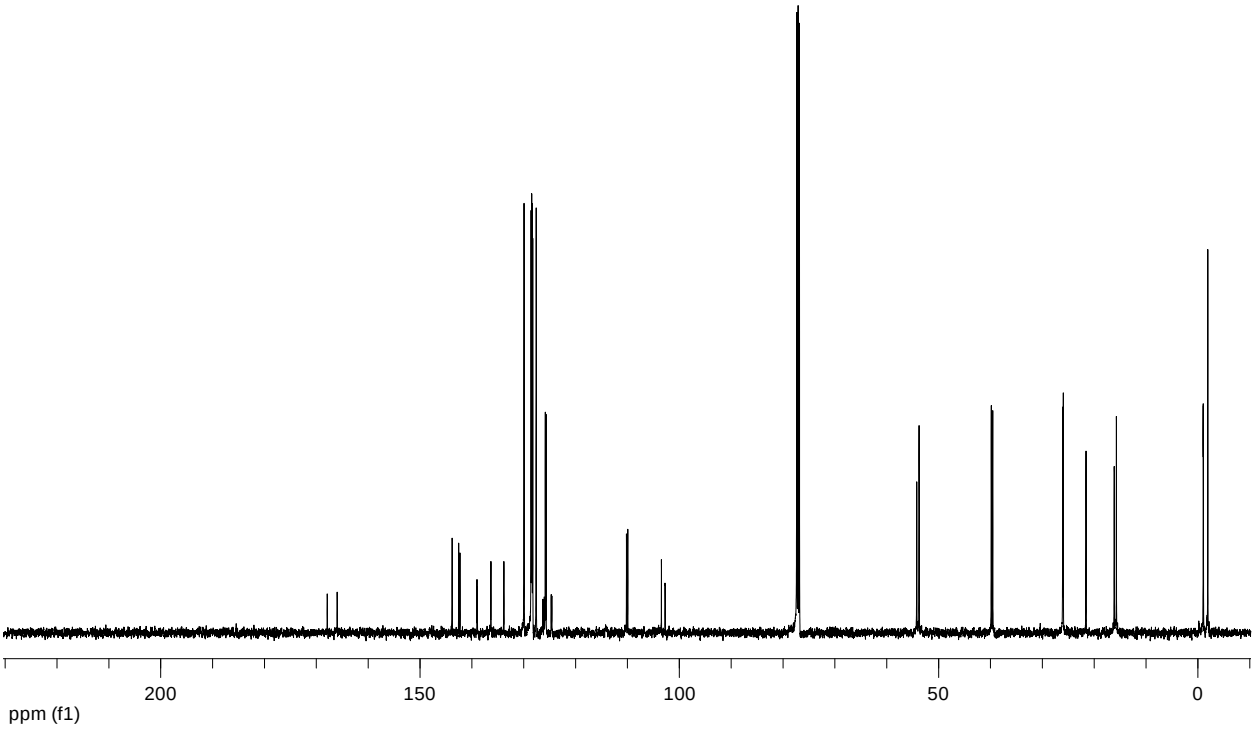

200 150 100 50 0
ppm (f1)

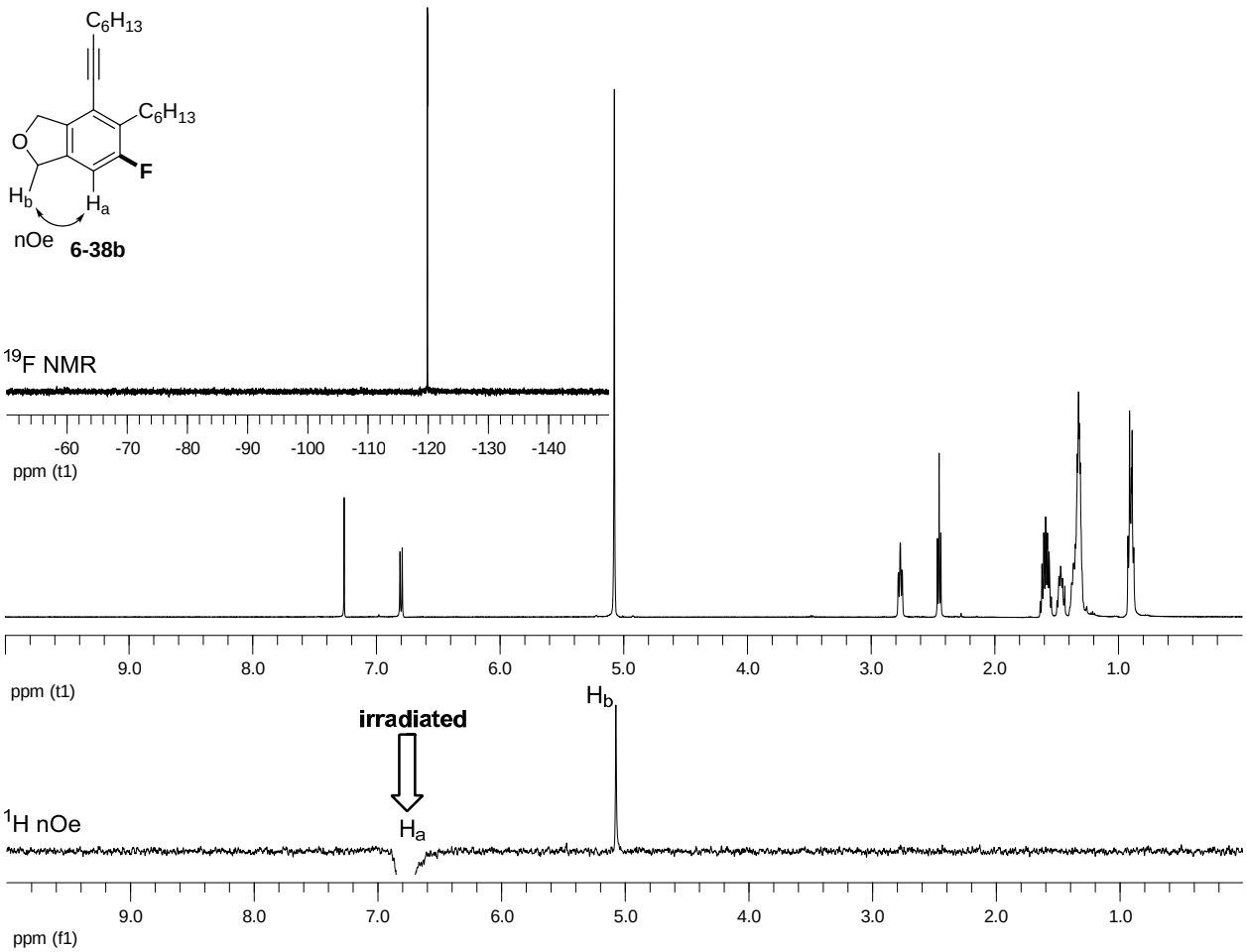

SiMe3
SiMe3
TsN
F
6-36
19F NMR
-60 -70 -80 -90 -100 -110 -120 -130 -140
ppm (f1)
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0
ppm (f1)

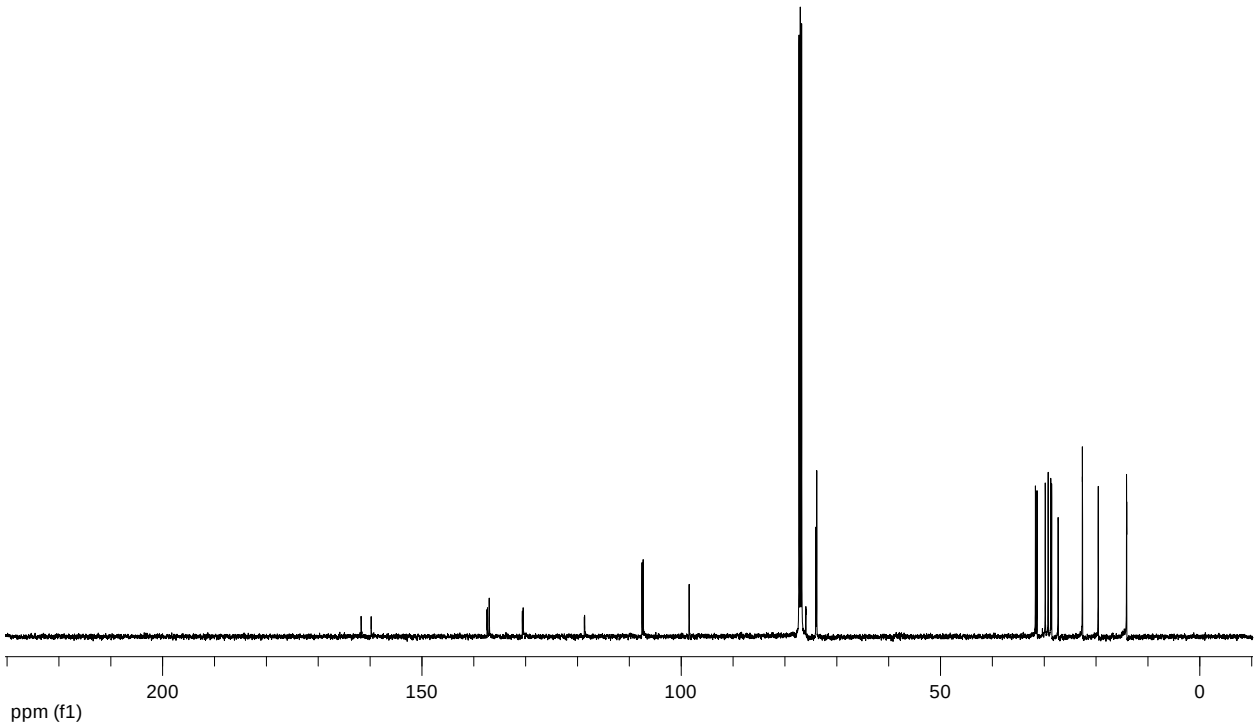

200 150 100 50 0
ppm (f1)

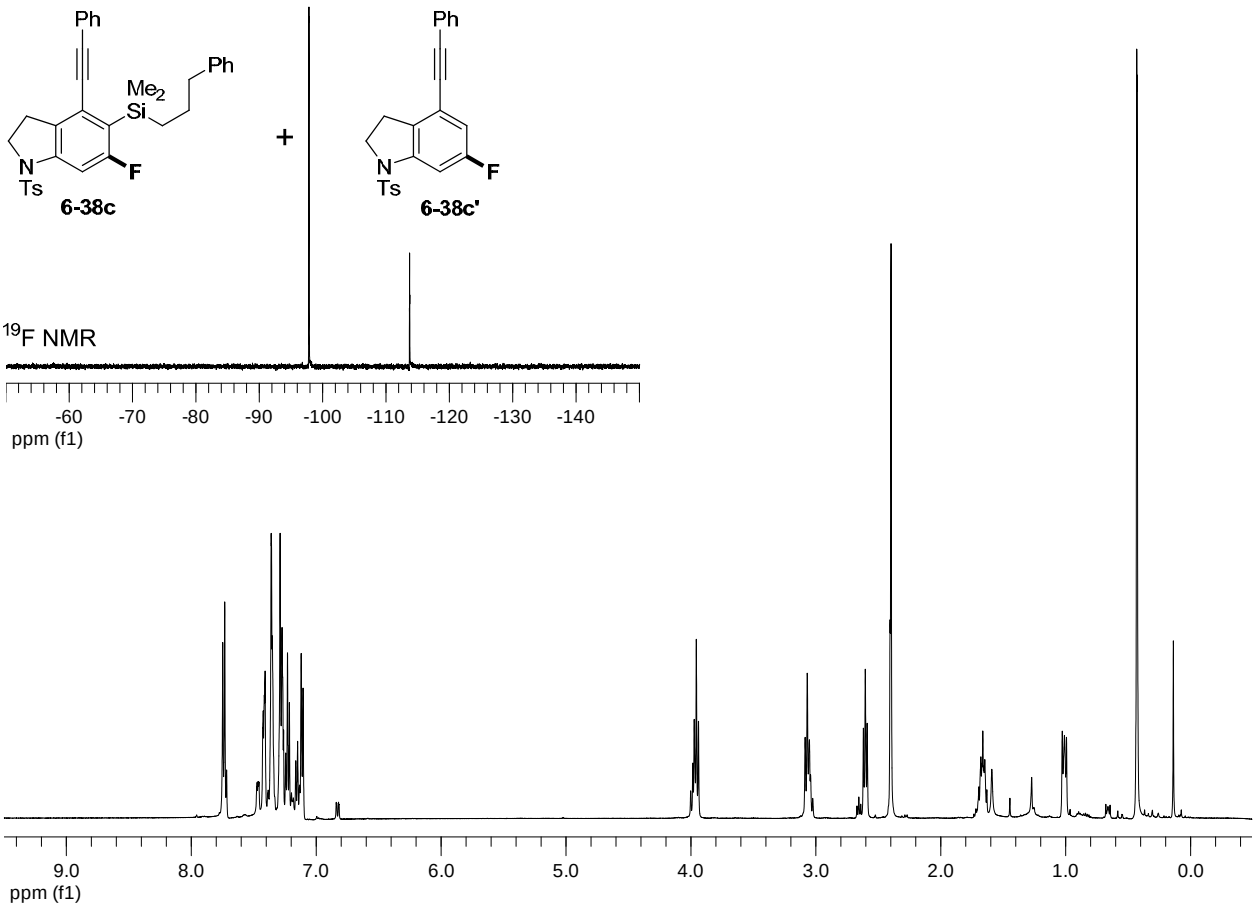

SiMe2(CH2)3Ph
Ph
Me2
Si
TsN
F
6-38a
19F NMR
-60 -70 -80 -90 -100 -110 -120 -130 -140
ppm (f1)

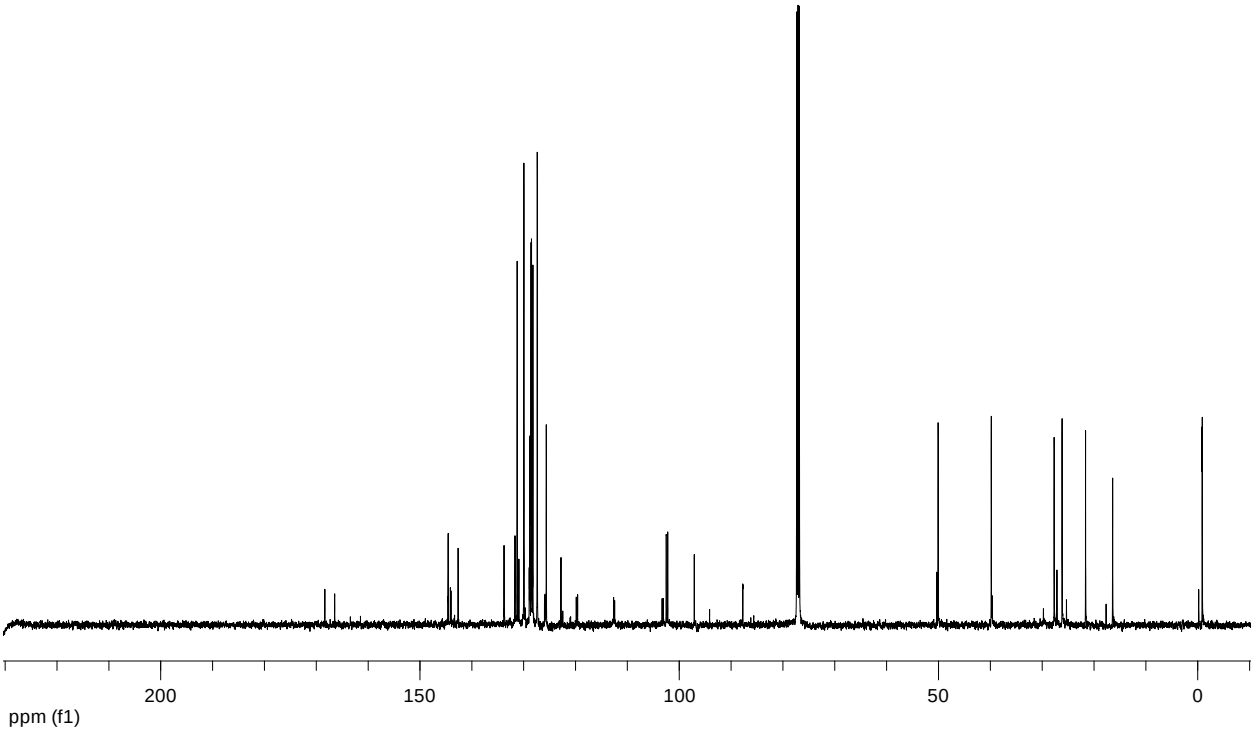

9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0
ppm (f1)

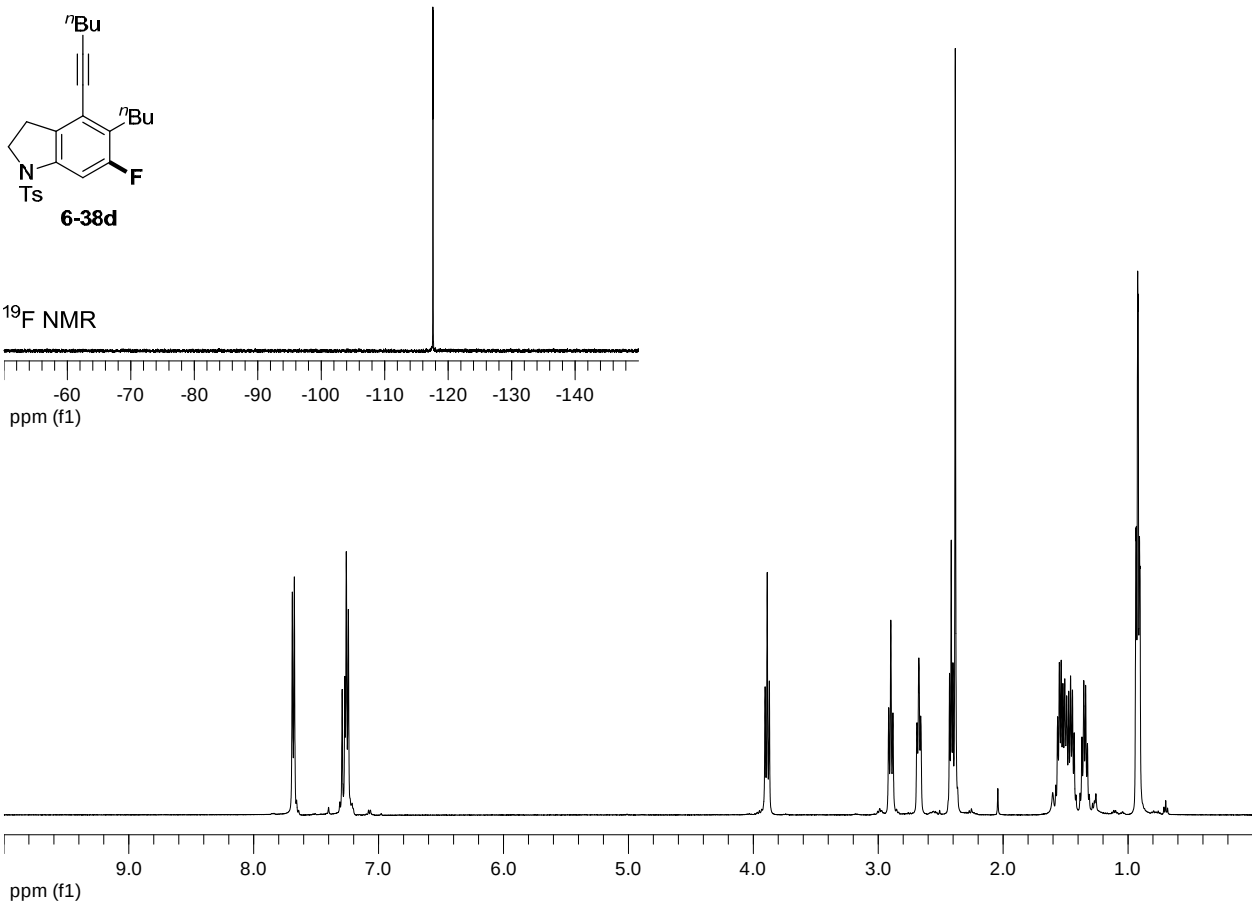

200 150 100 50 0
ppm (f1)

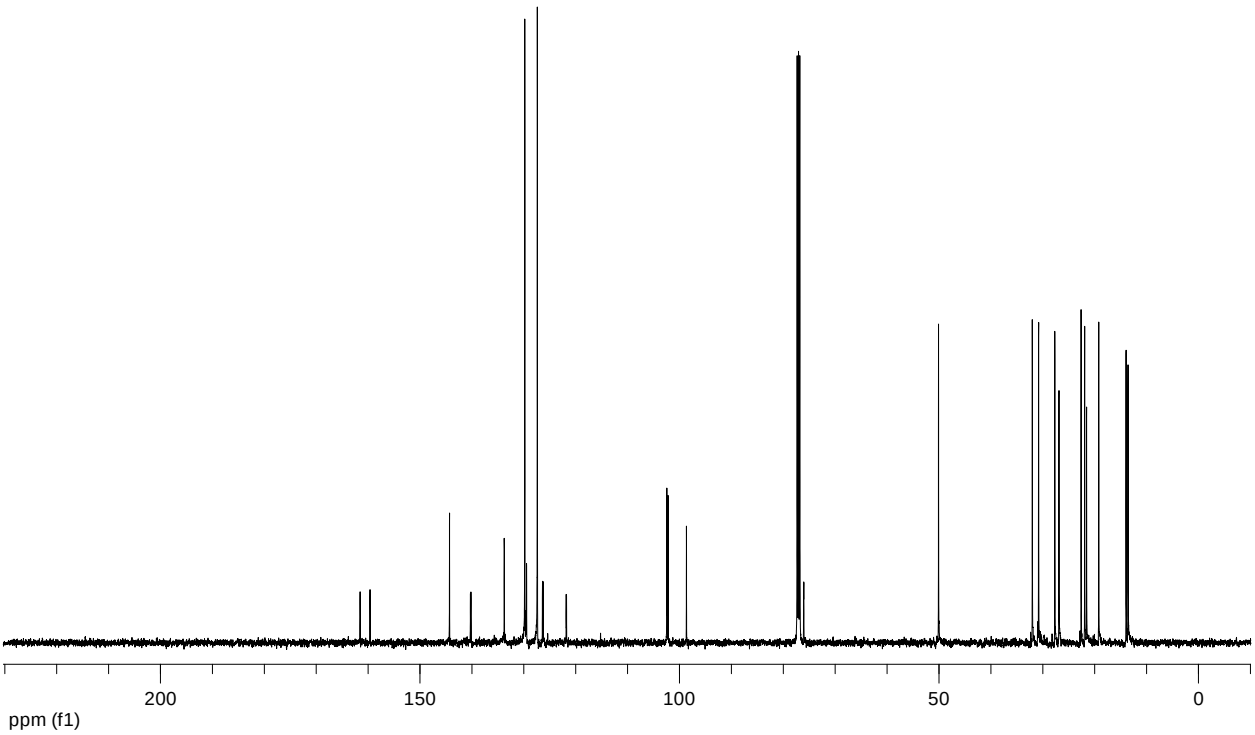

C6H13
C6H13
O
F
Hb
Ha
nOe
6-38b
19F NMR
-60 -70 -80 -90 -100 -110 -120 -130 -140
ppm (t1)
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0
ppm (t1)
irradiated
Hb
Ha
1H nOe
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0
ppm (f1)

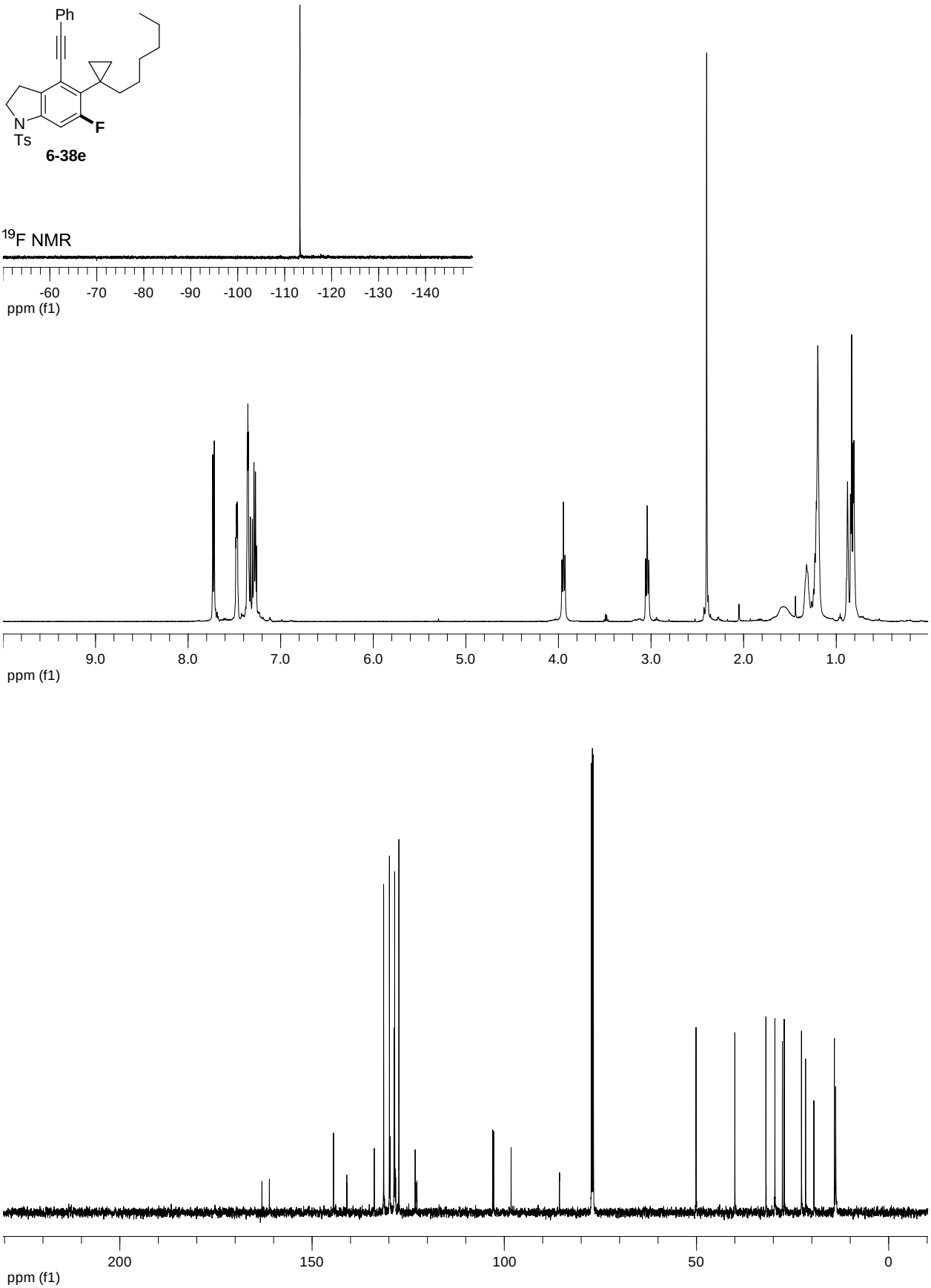

200 150 100 50 0
ppm (f1)

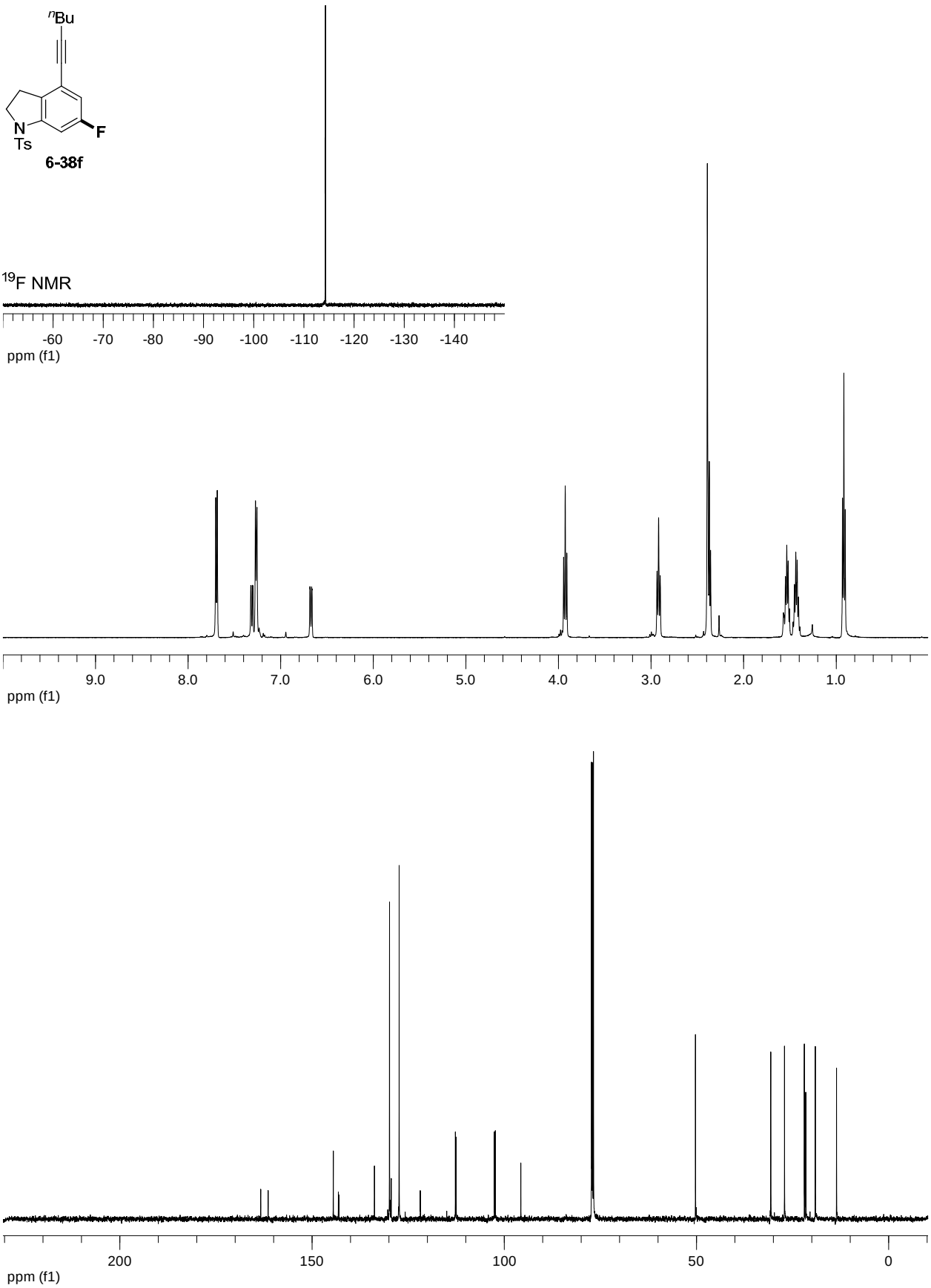

Ph
Ph
Me2
Si
N
Ts
F
6-38c
+
Ph
N
Ts
F
6-38c'
19F NMR
-60 -70 -80 -90 -100 -110 -120 -130 -140
ppm (f1)
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0
ppm (f1)

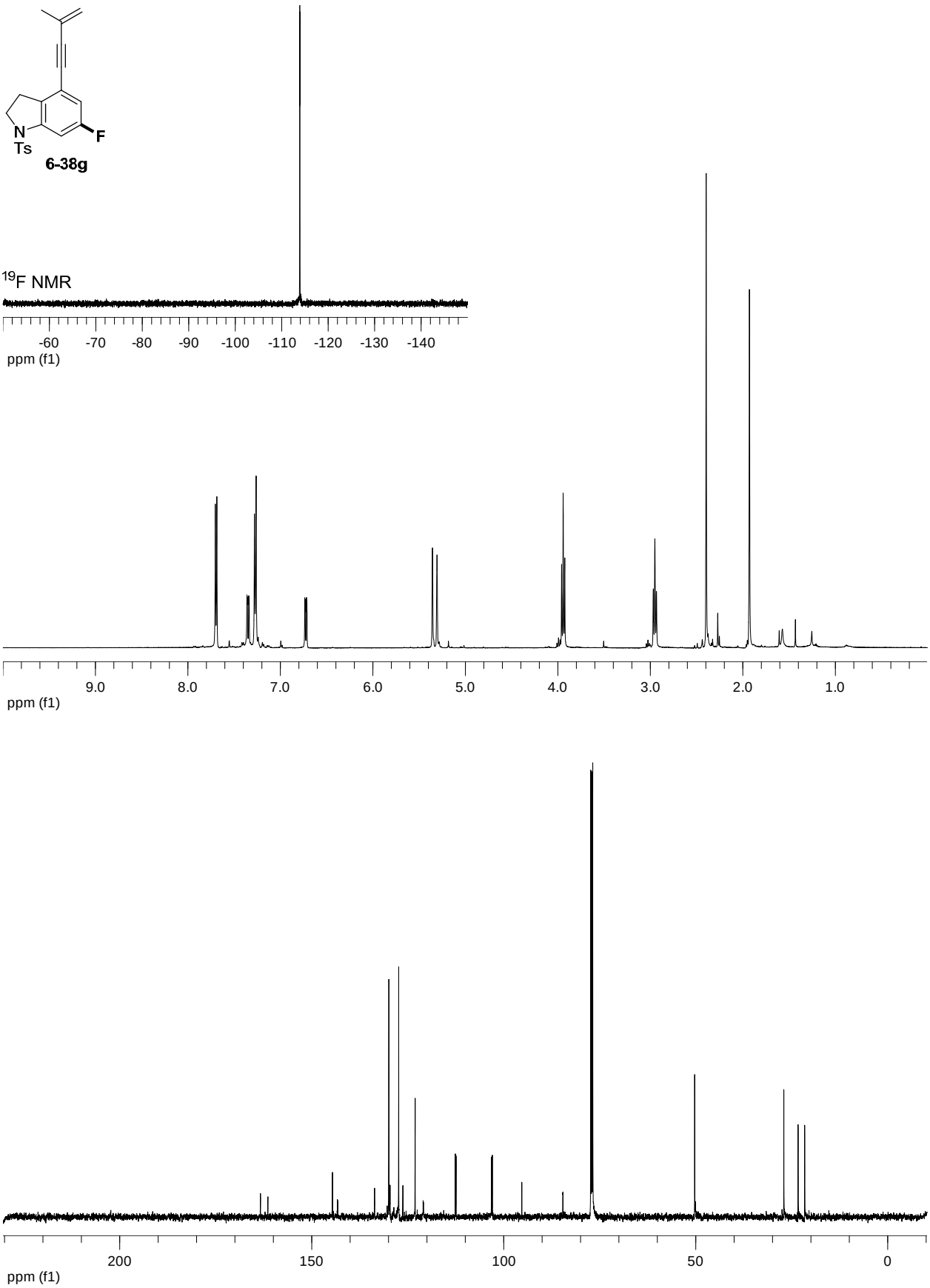

200 150 100 50 0
ppm (f1)

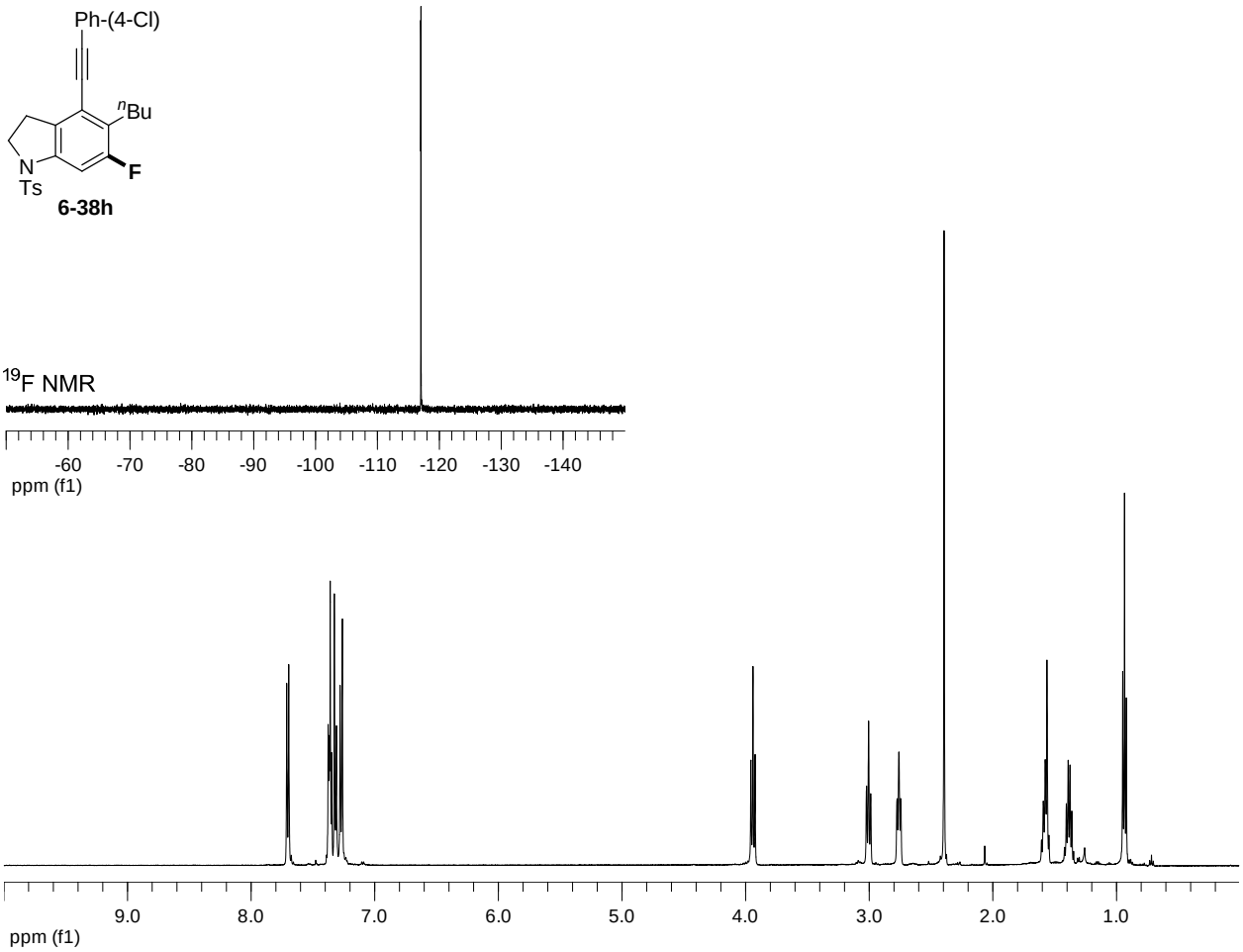

nBu
nBu
N
Ts
F
6-38d
19F NMR
-60 -70 -80 -90 -100 -110 -120 -130 -140
ppm (f1)
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0
ppm (f1)

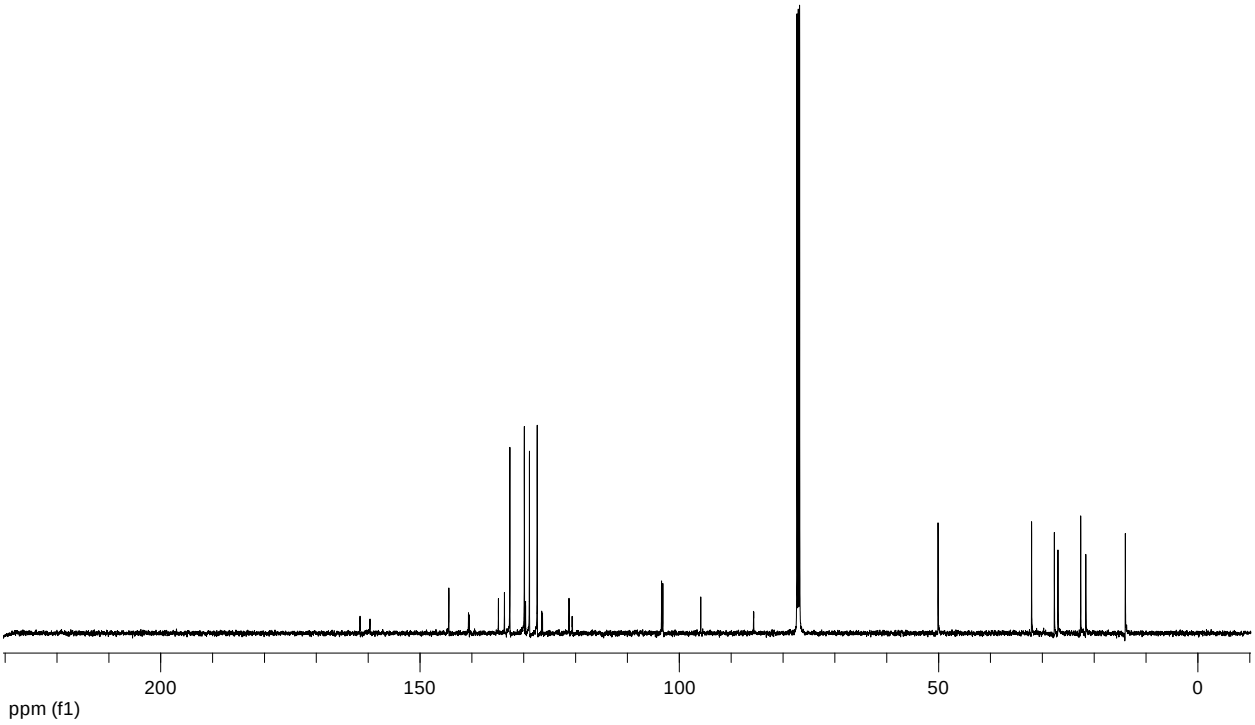

200 150 100 50 0
ppm (f1)

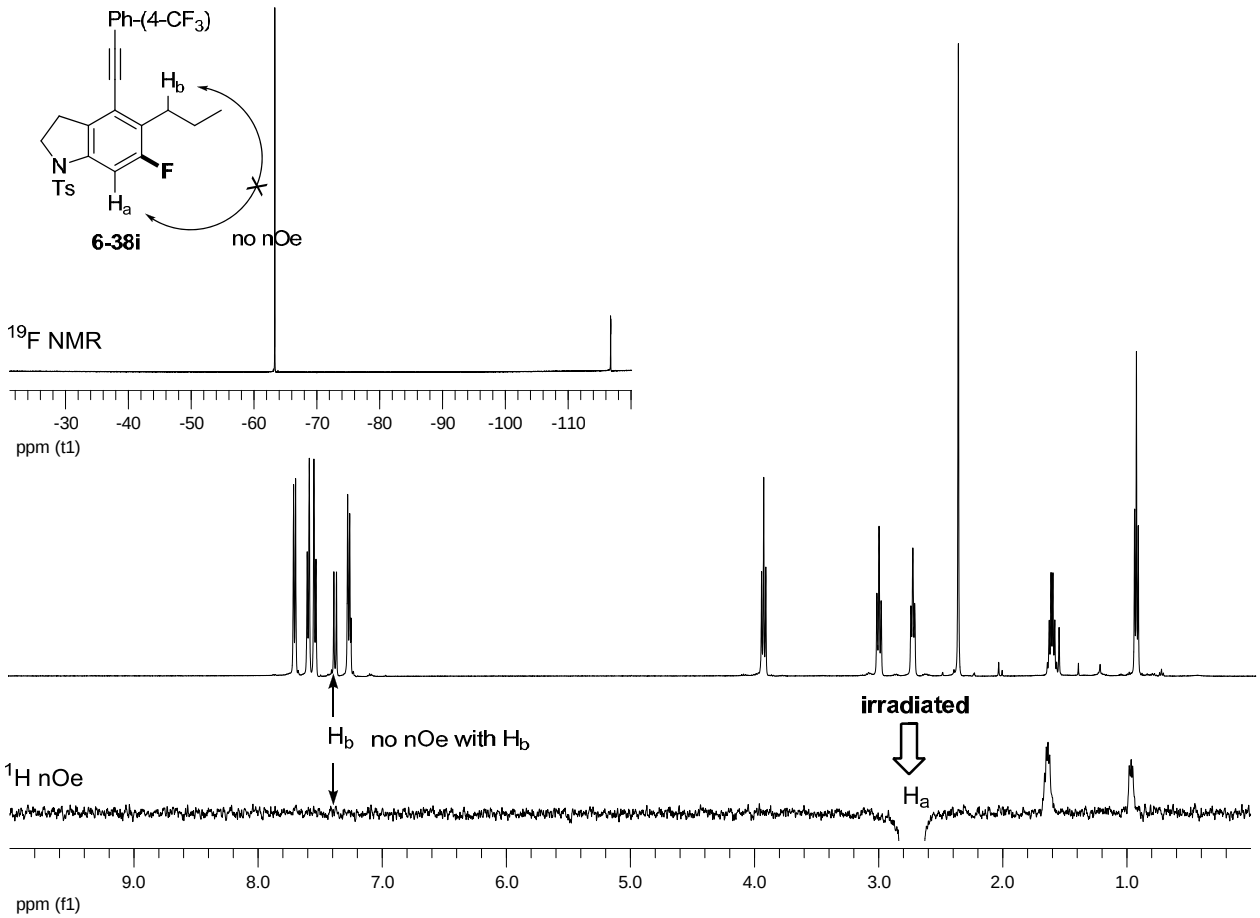

Ph
N
Ts
F
6-38e
19F NMR
-60 -70 -80 -90 -100 -110 -120 -130 -140
ppm (f1)
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0
ppm (f1)
200 150 100 50 0
ppm (f1)

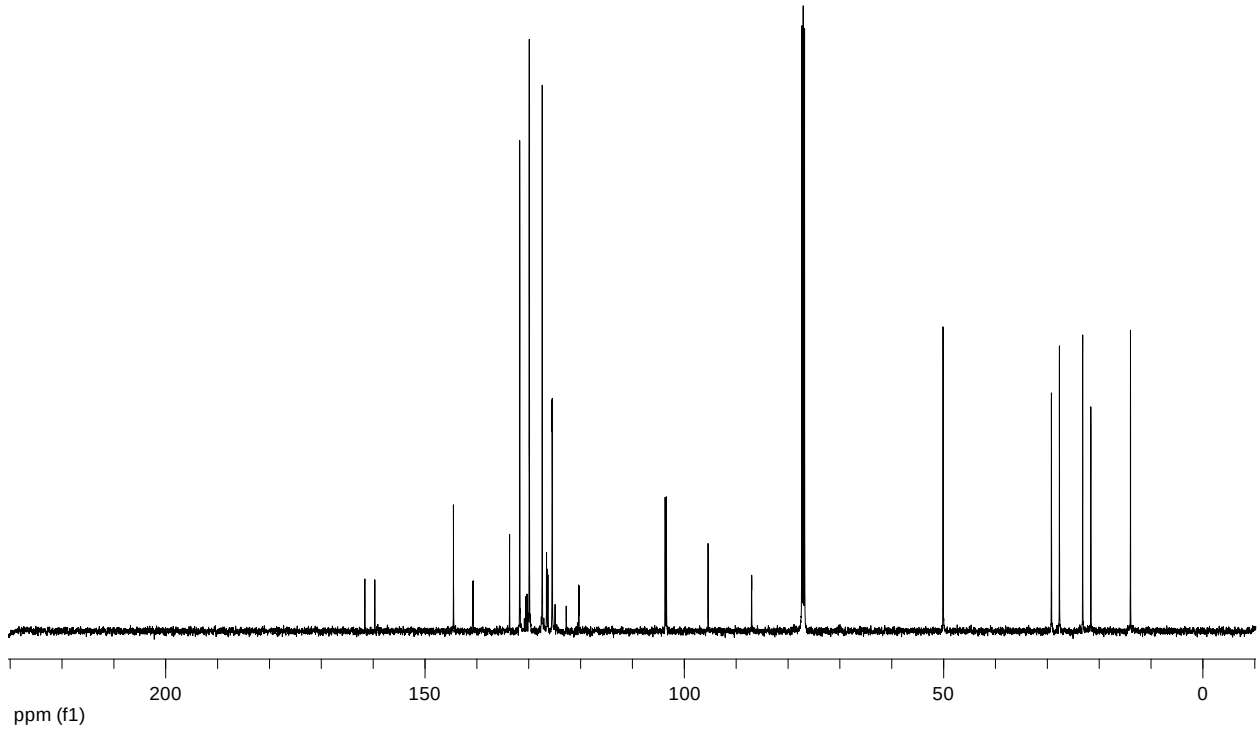

nBu
N
Ts
F
6-38f
19F NMR
-60 -70 -80 -90 -100 -110 -120 -130 -140
ppm (f1)
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0
ppm (f1)
200 150 100 50 0
ppm (f1)

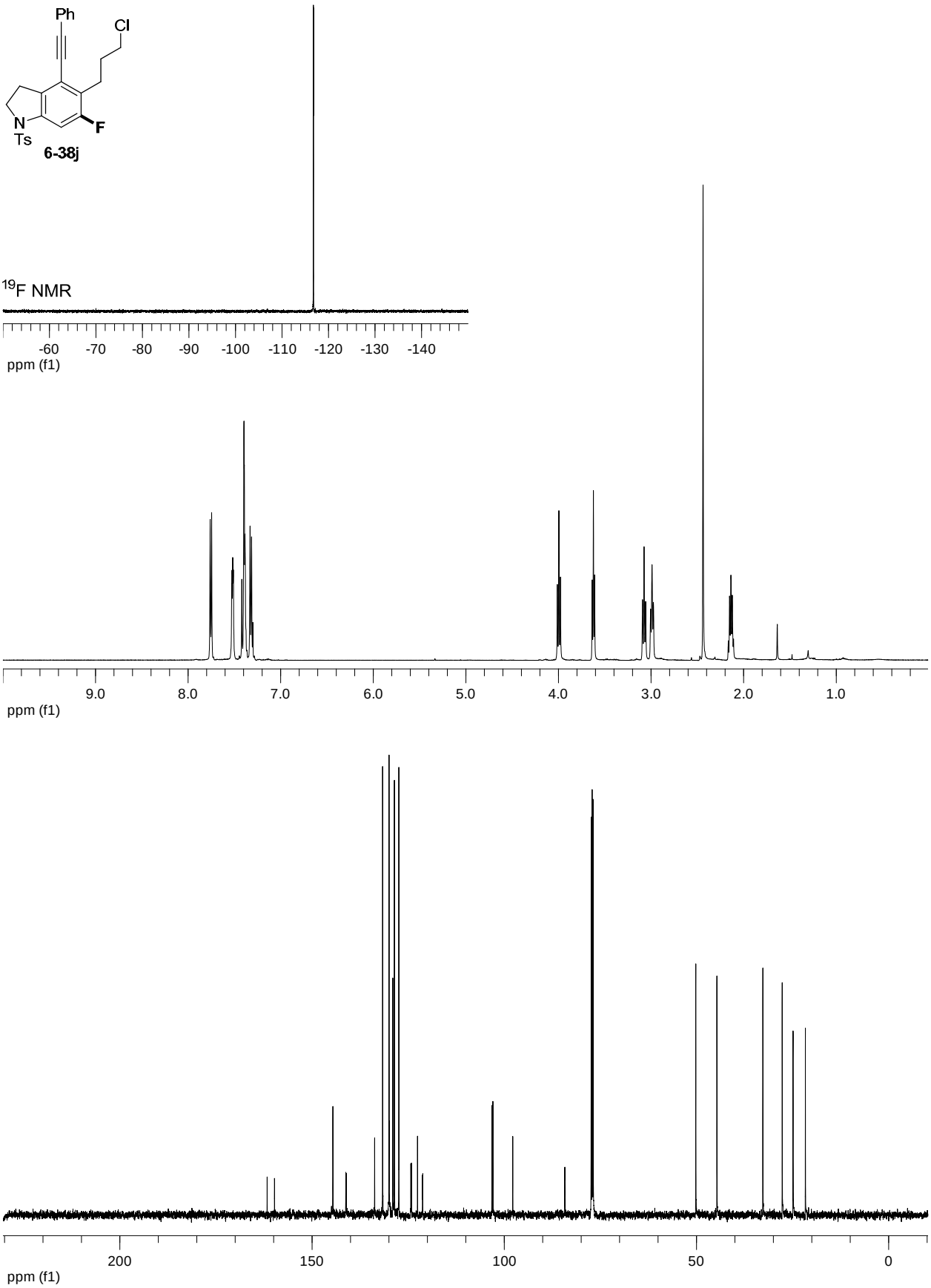

N
Ts
F
6-38g
19F NMR
-60 -70 -80 -90 -100 -110 -120 -130 -140
ppm (f1)
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0
ppm (f1)
200 150 100 50 0
ppm (f1)

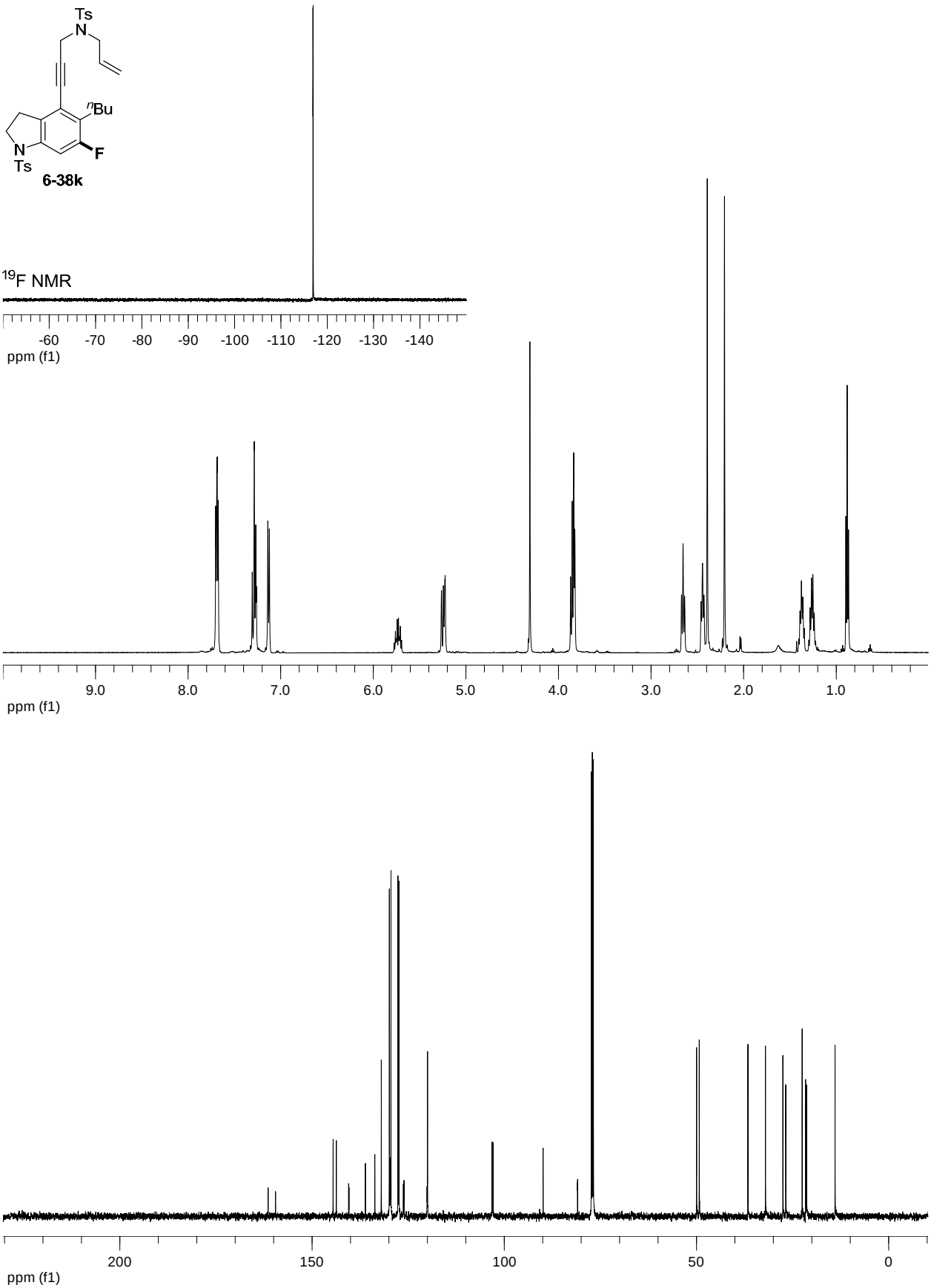

Ph-(4-Cl)
nBu
N
Ts
F
6-38h
19F NMR
-60 -70 -80 -90 -100 -110 -120 -130 -140
ppm (f1)
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0
ppm (f1)

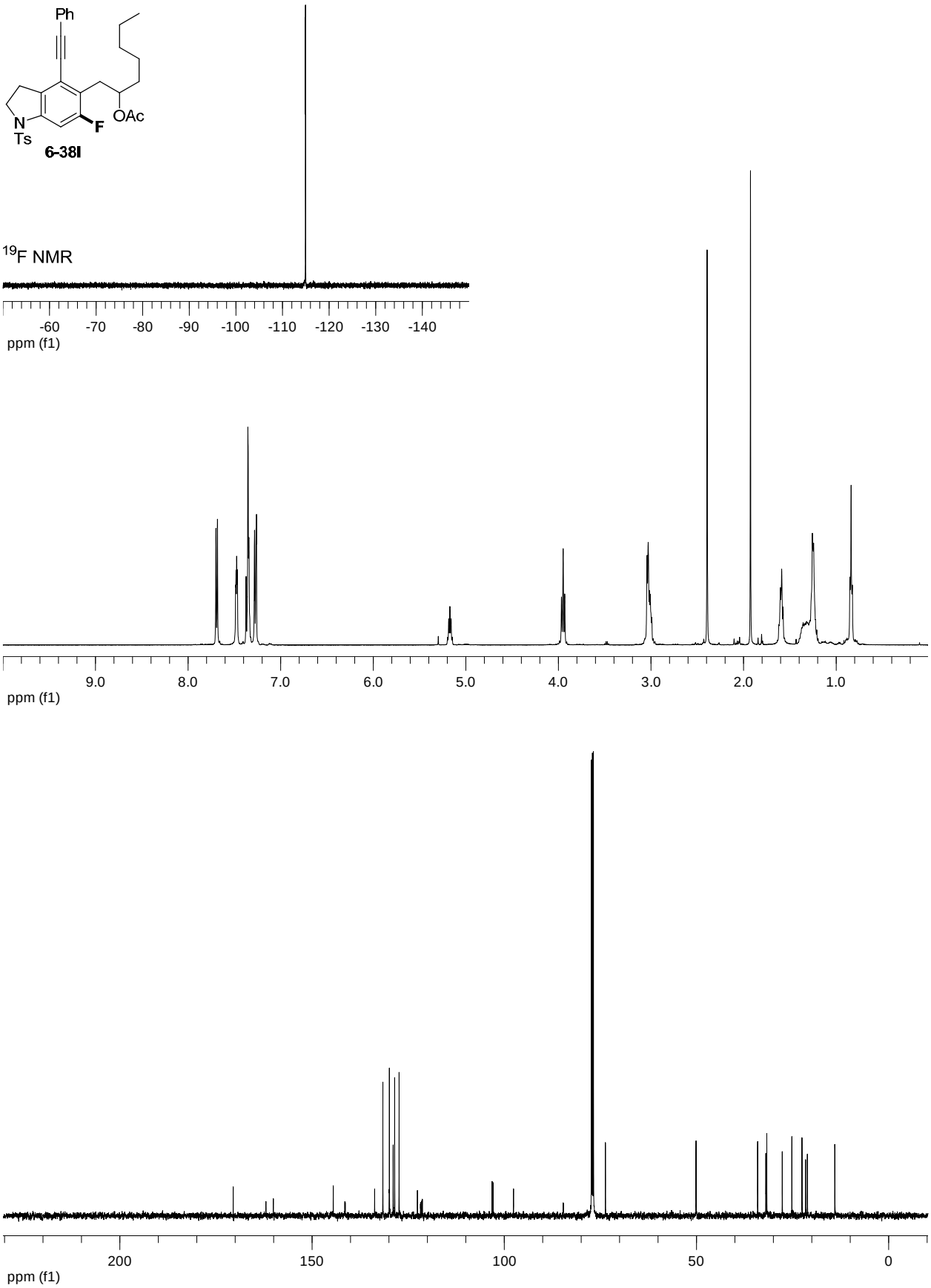

200 150 100 50 0
ppm (f1)

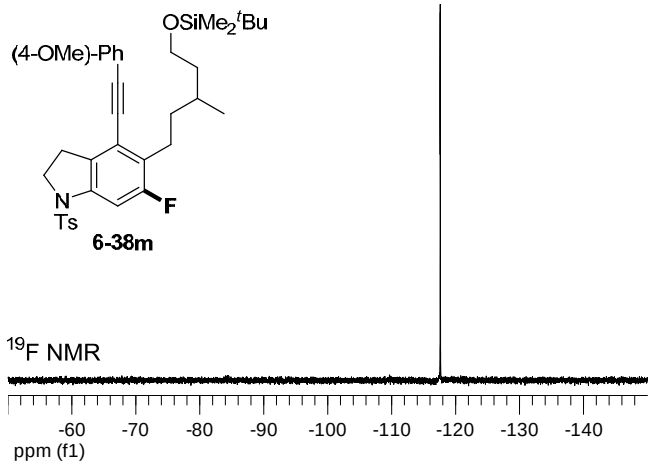

Ph-(4-CF3)
Hb
N
Ts
F
Ha
6-38i
no nOe
19F NMR
-30 -40 -50 -60 -70 -80 -90 -100 -110
ppm (t1)
irradiated
Hb no nOe with Hb
1H nOe
Ha
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0
ppm (f1)

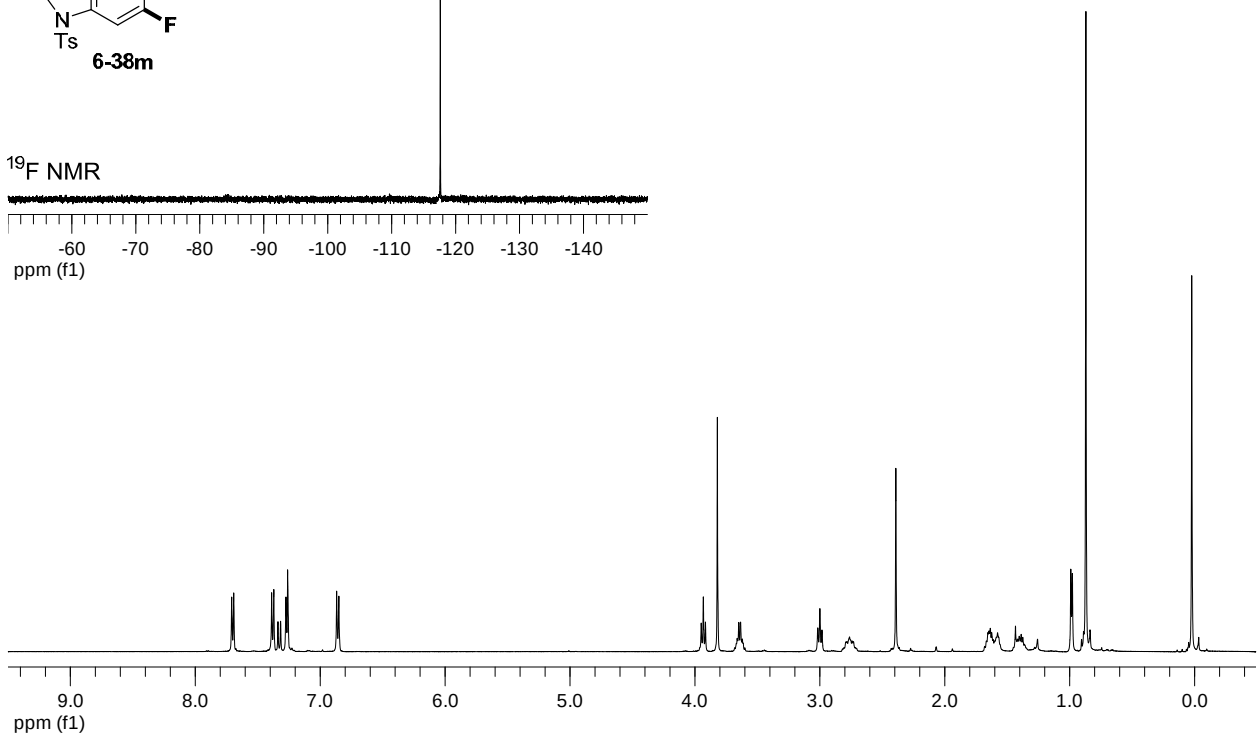

200 150 100 50 0
ppm (f1)

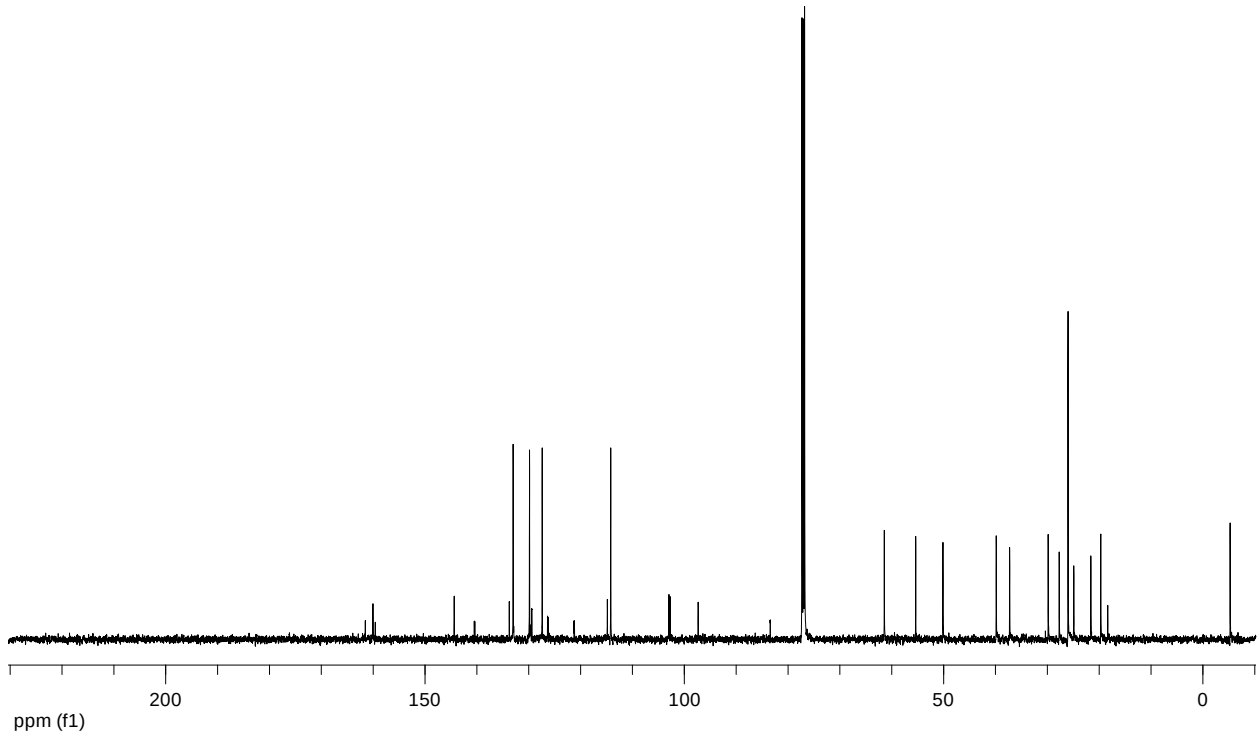

Ph
Cl
N
Ts
F
6-38j
19F NMR
-60 -70 -80 -90 -100 -110 -120 -130 -140
ppm (f1)
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0
ppm (f1)
200 150 100 50 0
ppm (f1)

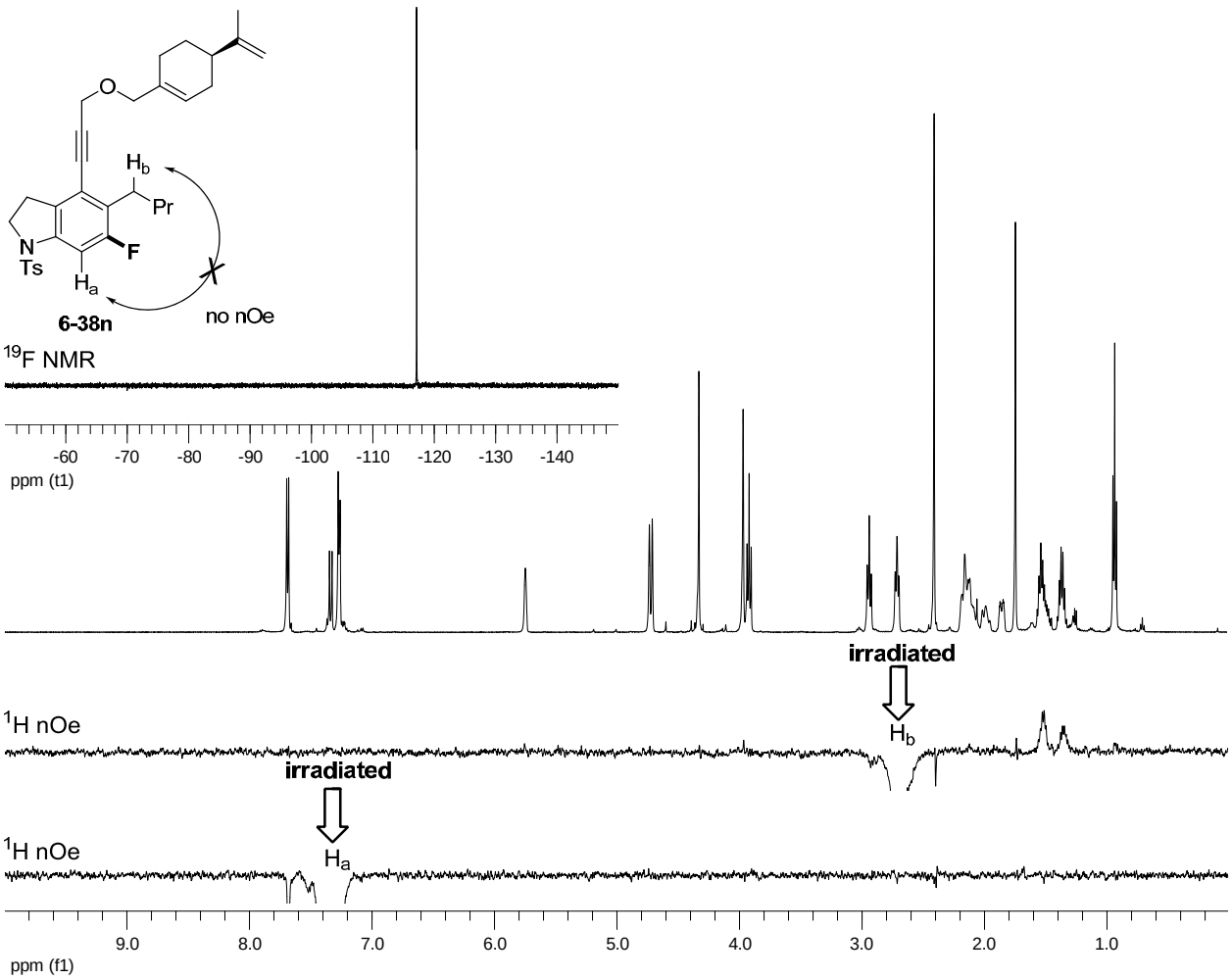

Ts
N
nBu
N
Ts
F
6-38k
19F NMR
-60 -70 -80 -90 -100 -110 -120 -130 -140
ppm (f1)
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0
ppm (f1)
200 150 100 50 0
ppm (f1)

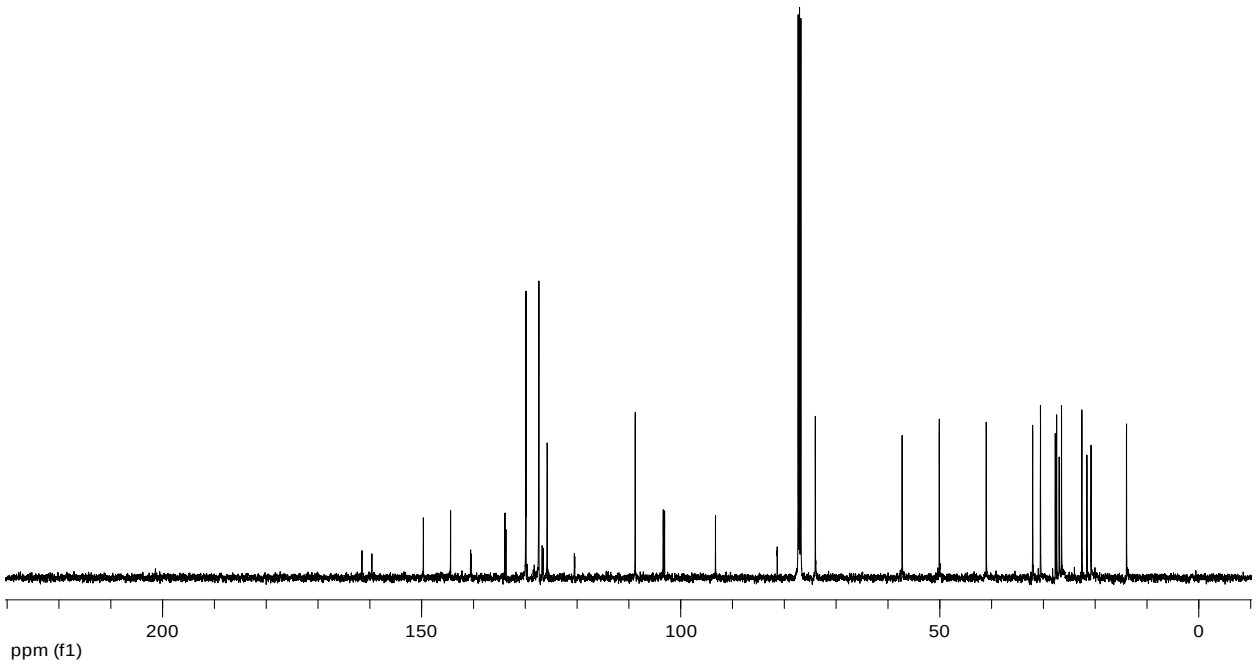

Ph
N
Ts
F
OAc
6-38l
19F NMR
-60 -70 -80 -90 -100 -110 -120 -130 -140
ppm (f1)
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0
ppm (f1)
200 150 100 50 0
ppm (f1)

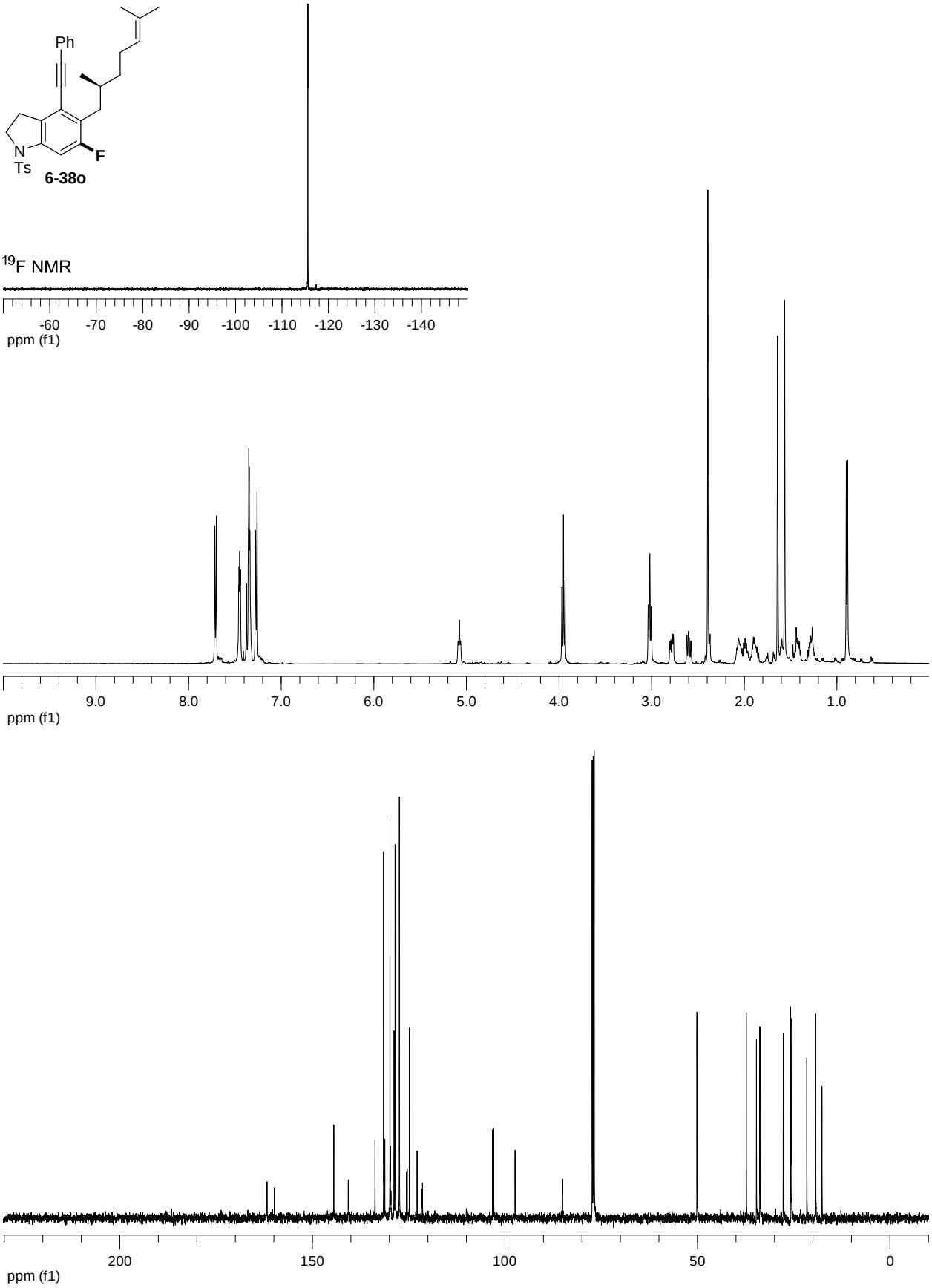

OSiMe2tBu
(4-OMe)-Ph
N
Ts
F
6-38m
19F NMR
-60 -70 -80 -90 -100 -110 -120 -130 -140
ppm (f1)

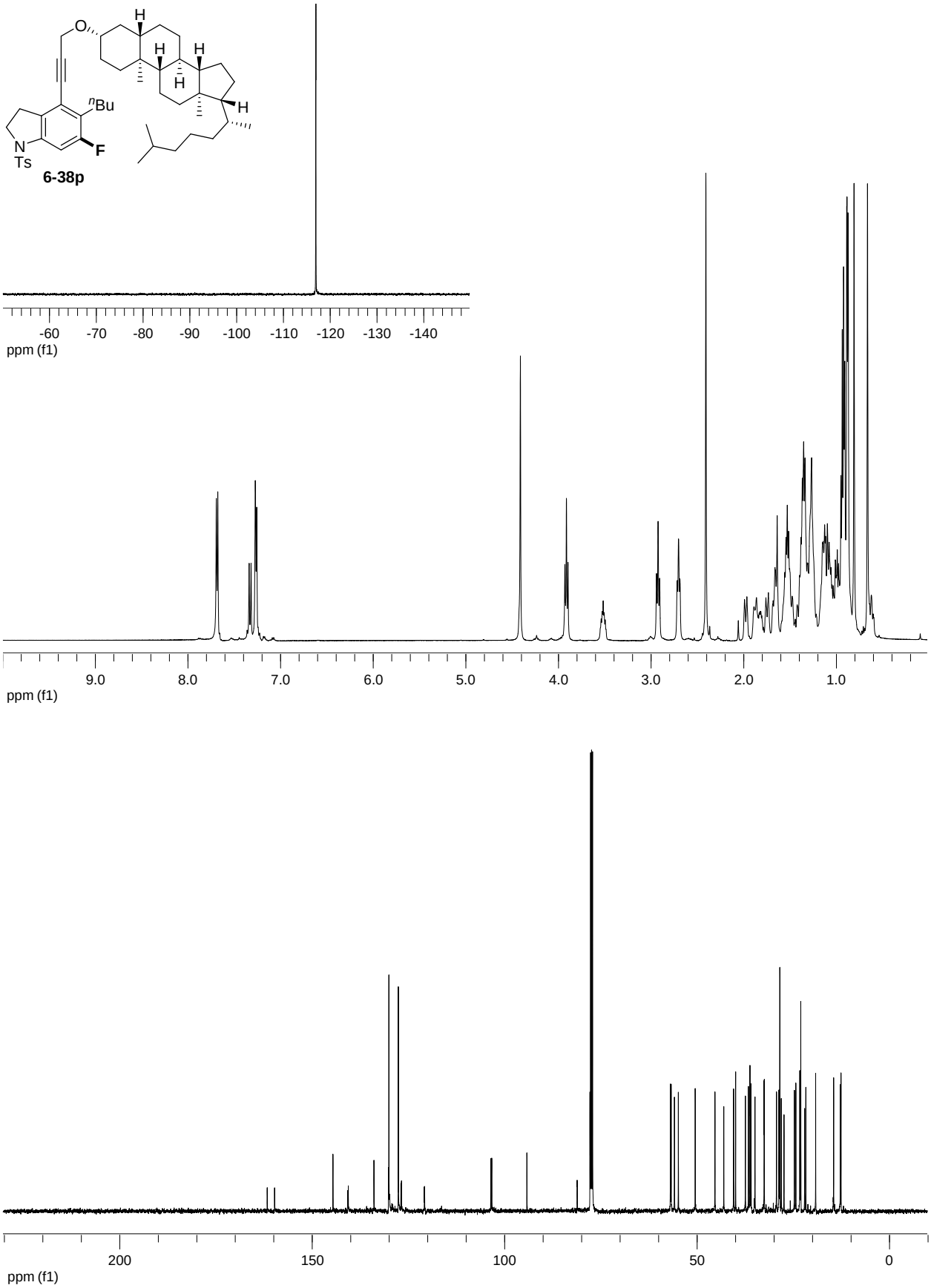

9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0
ppm (f1)

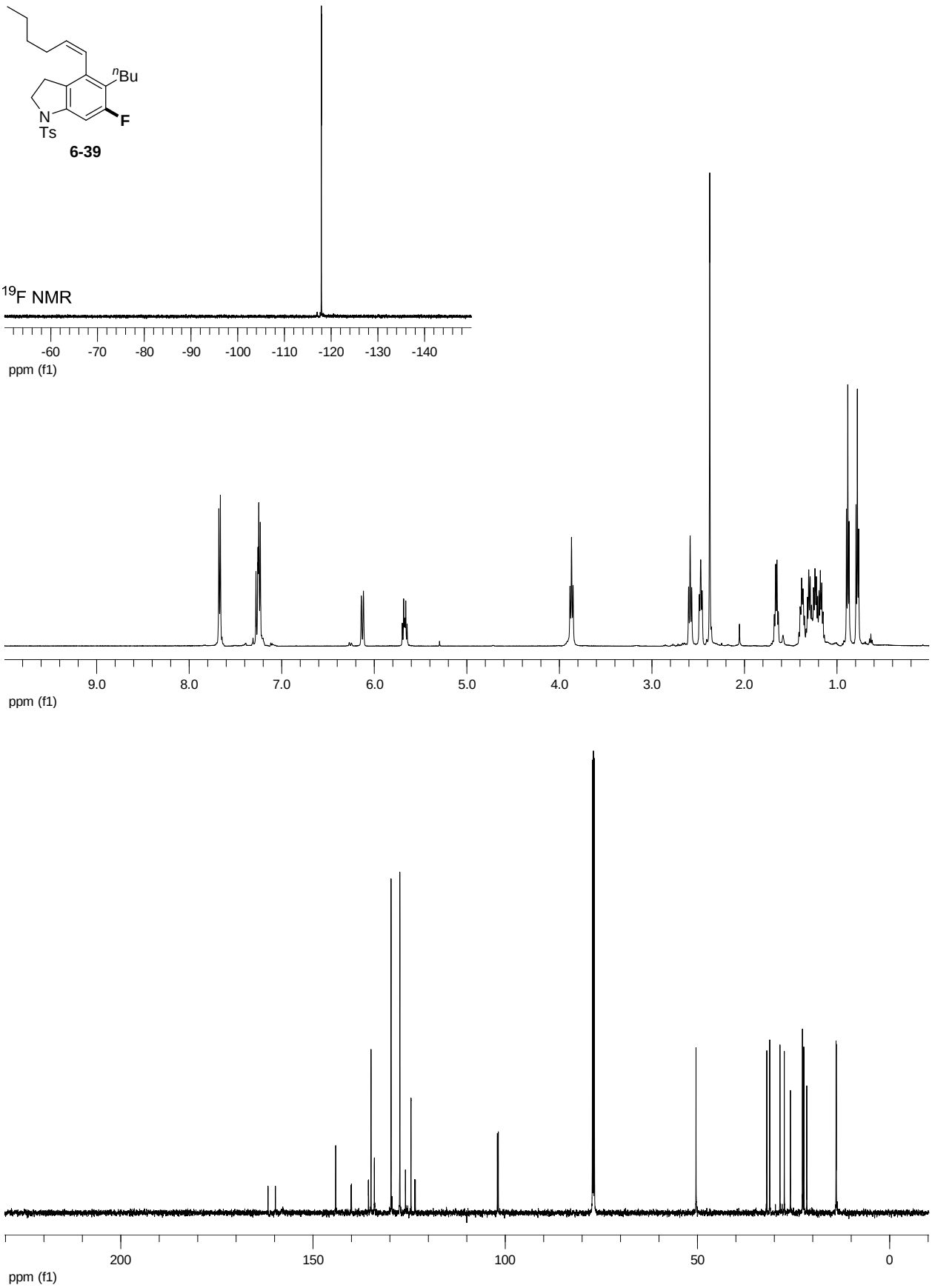

200 150 100 50 0
ppm (f1)

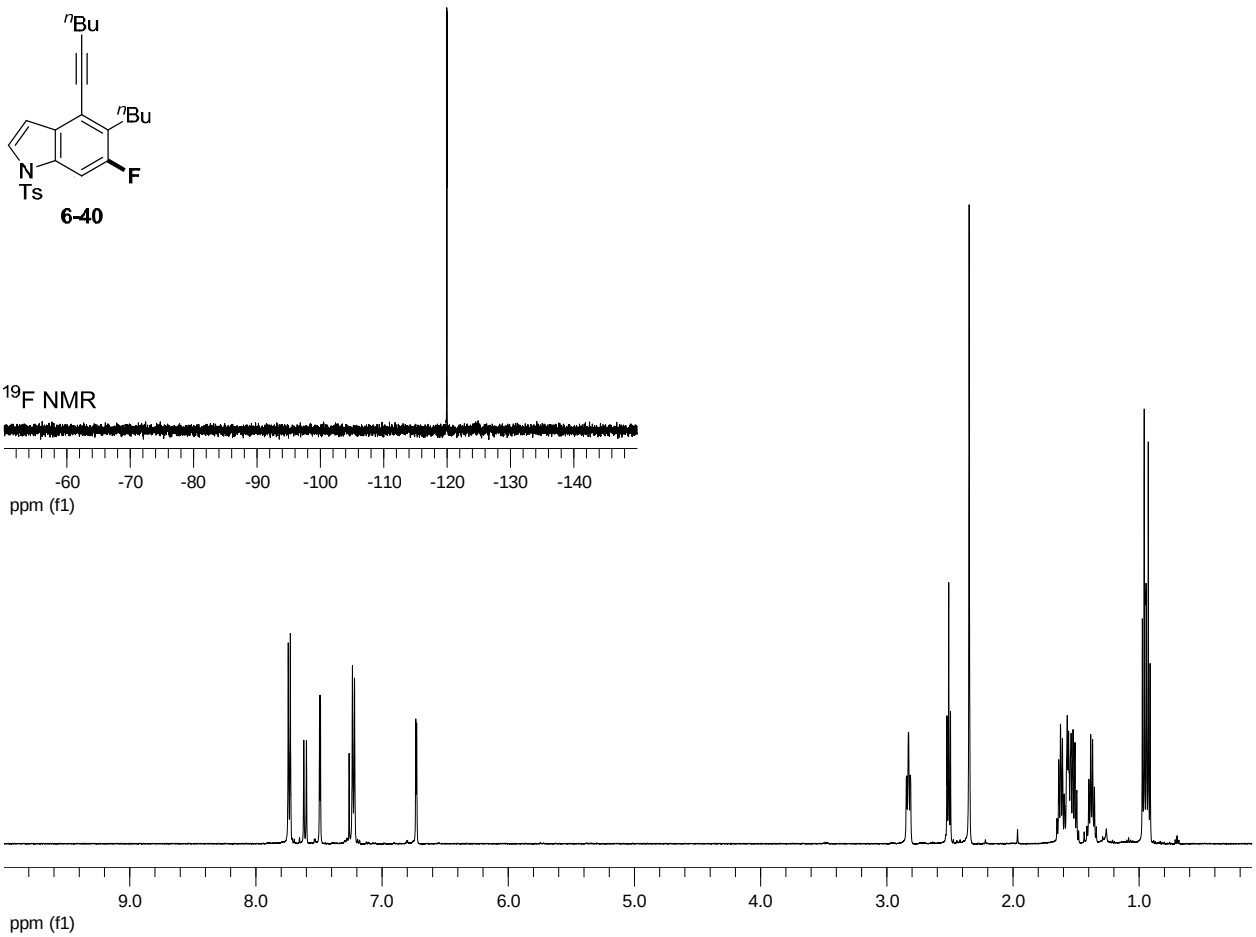

O
H_b
Pr
N
Ts
F
H_a
6-38n
no nOe
^{19}F NMR
-60 -70 -80 -90 -100 -110 -120 -130 -140
ppm (t1)
irradiated
H_b
^{1}H nOe
irradiated
H_a
^{1}H nOe
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0
ppm (f1)

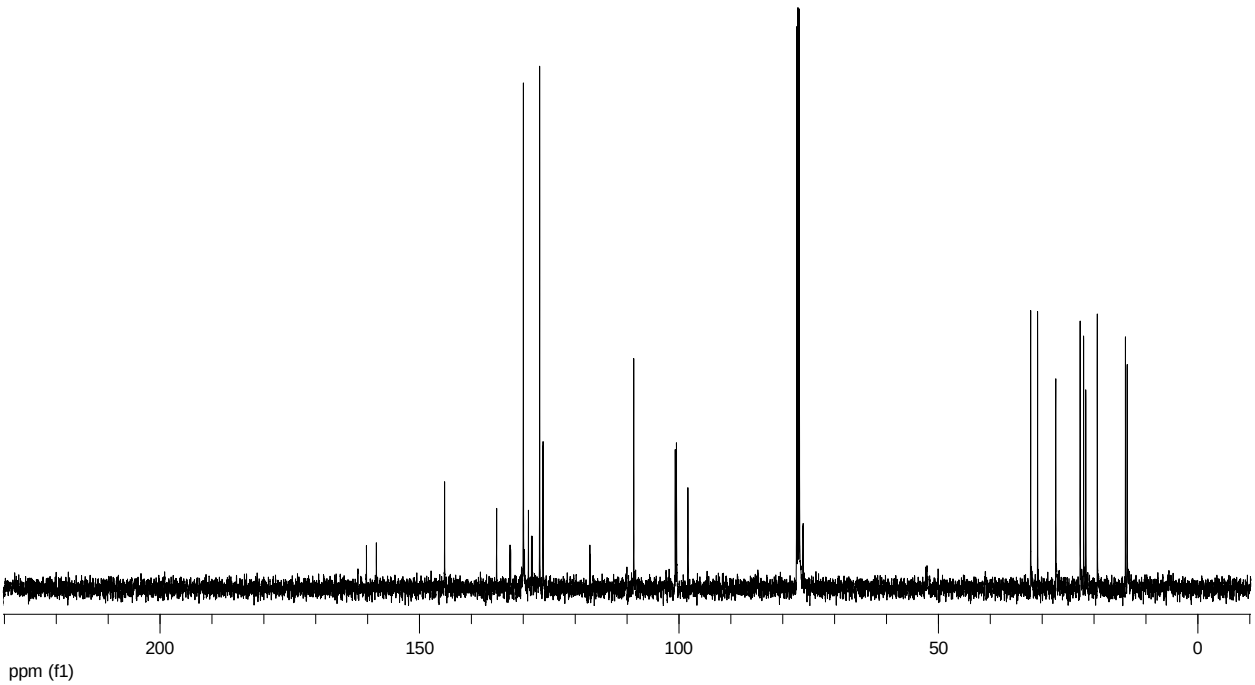

200 150 100 50 0
ppm (f1)

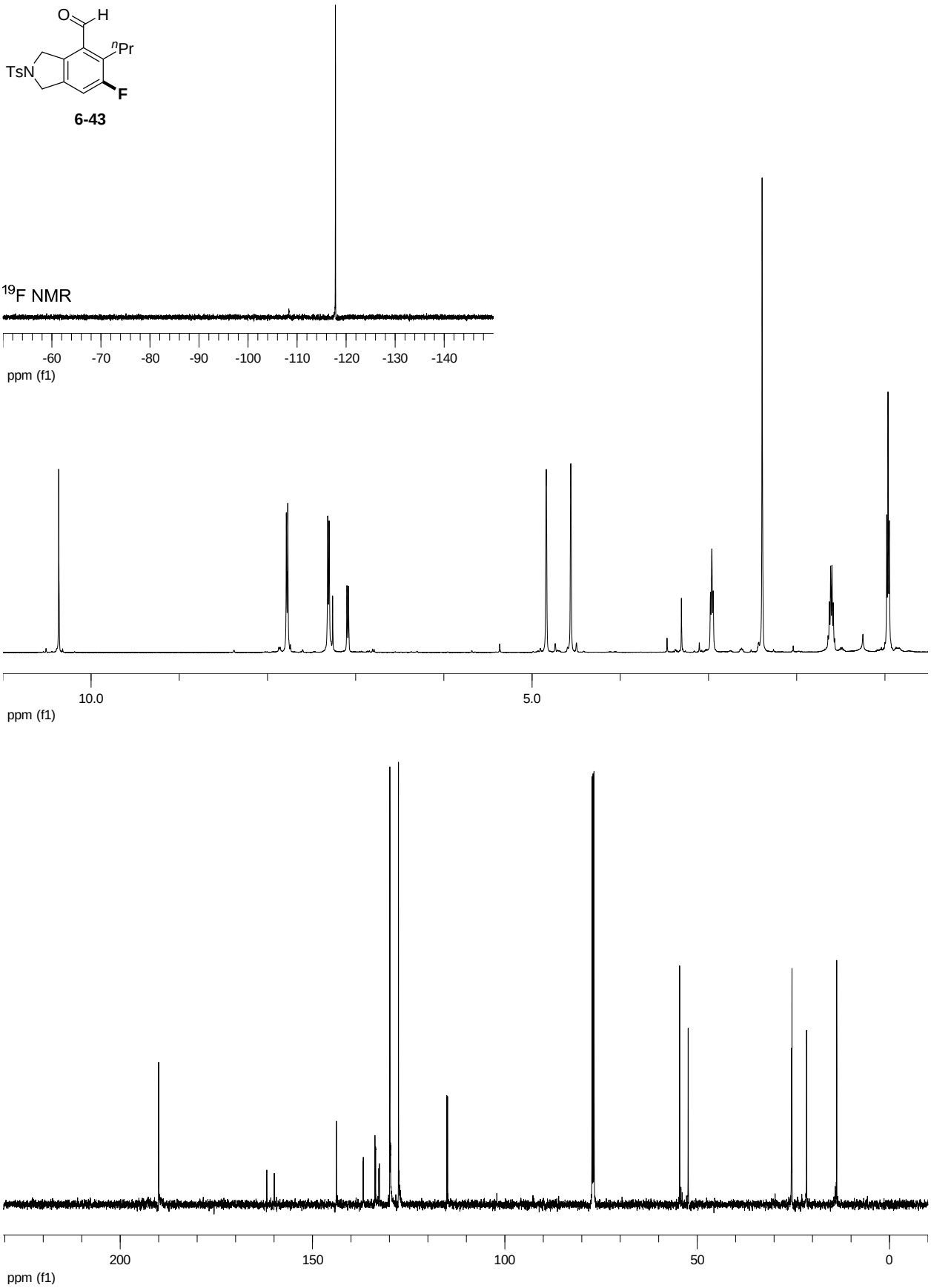

Ph
N
Ts
F
6-38o
19F NMR
-60 -70 -80 -90 -100 -110 -120 -130 -140
ppm (f1)
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0
ppm (f1)
200 150 100 50 0
ppm (f1)

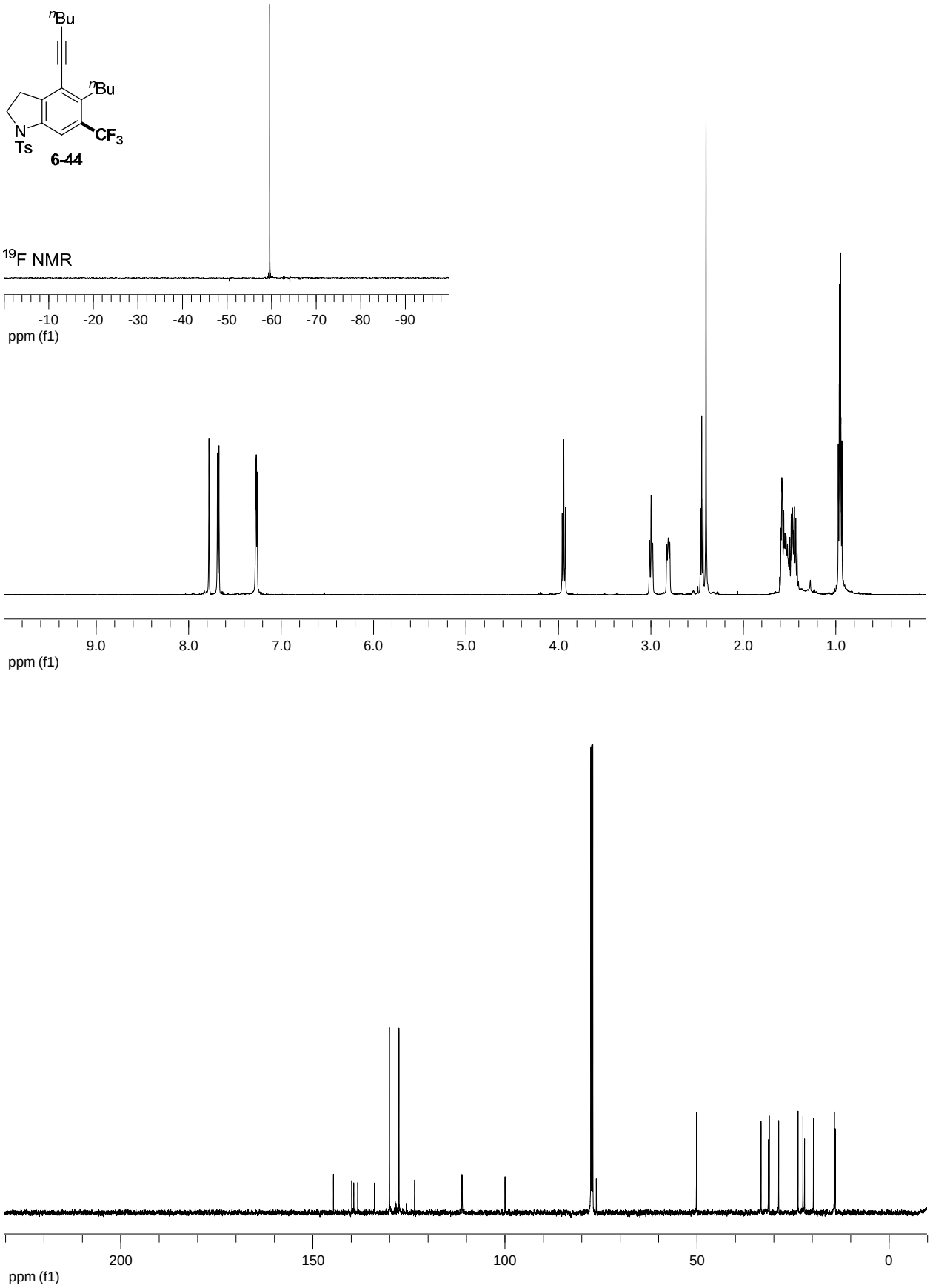

O
H
H
H
H
H
nBu
N
Ts
F
6-38p
-60 -70 -80 -90 -100 -110 -120 -130 -140
ppm (f1)
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0
ppm (f1)
200 150 100 50 0
ppm (f1)

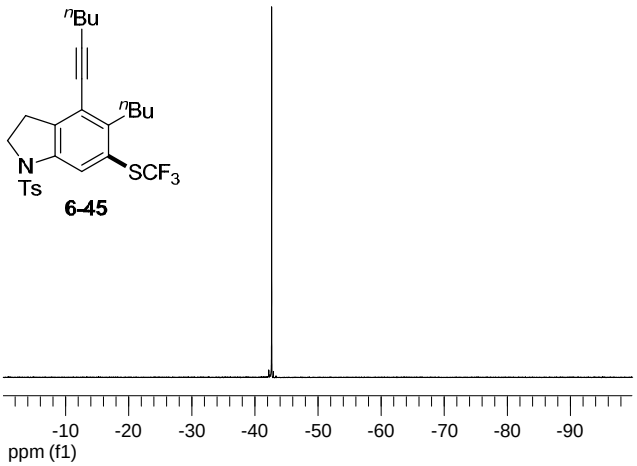

nBu
N
Ts
F
6-39
19F NMR
-60 -70 -80 -90 -100 -110 -120 -130 -140
ppm (f1)
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0
ppm (f1)
200 150 100 50 0
ppm (f1)

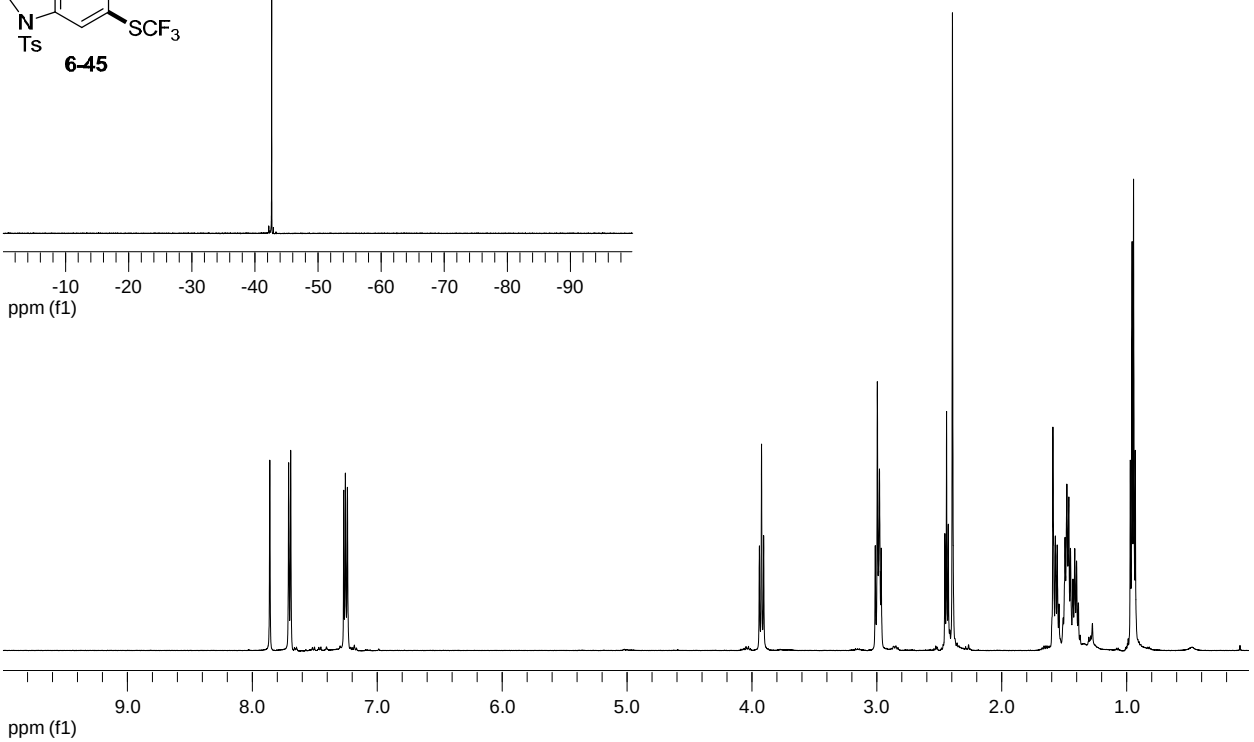

nBu
nBu
N
Ts
F
6-40
19F NMR
-60 -70 -80 -90 -100 -110 -120 -130 -140
ppm (f1)
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0
ppm (f1)

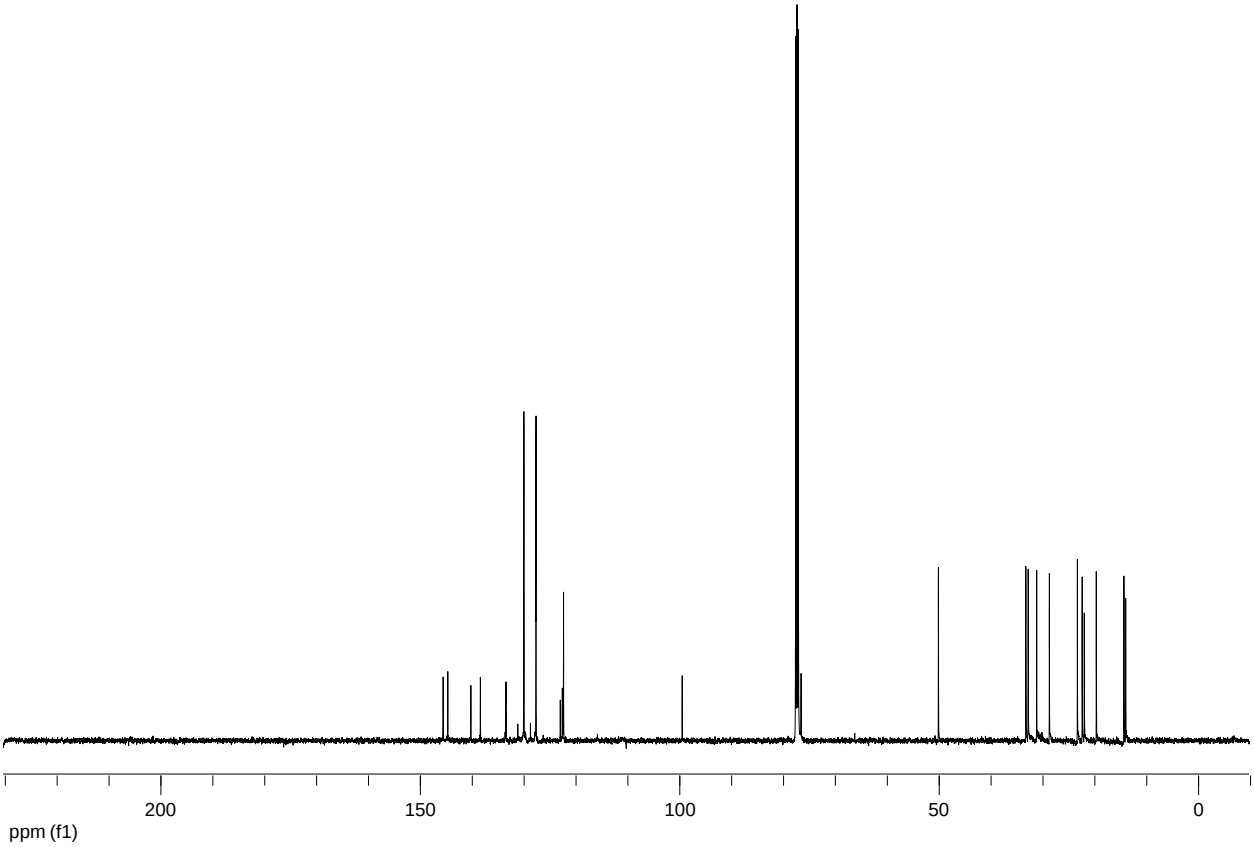

200 150 100 50 0
ppm (f1)

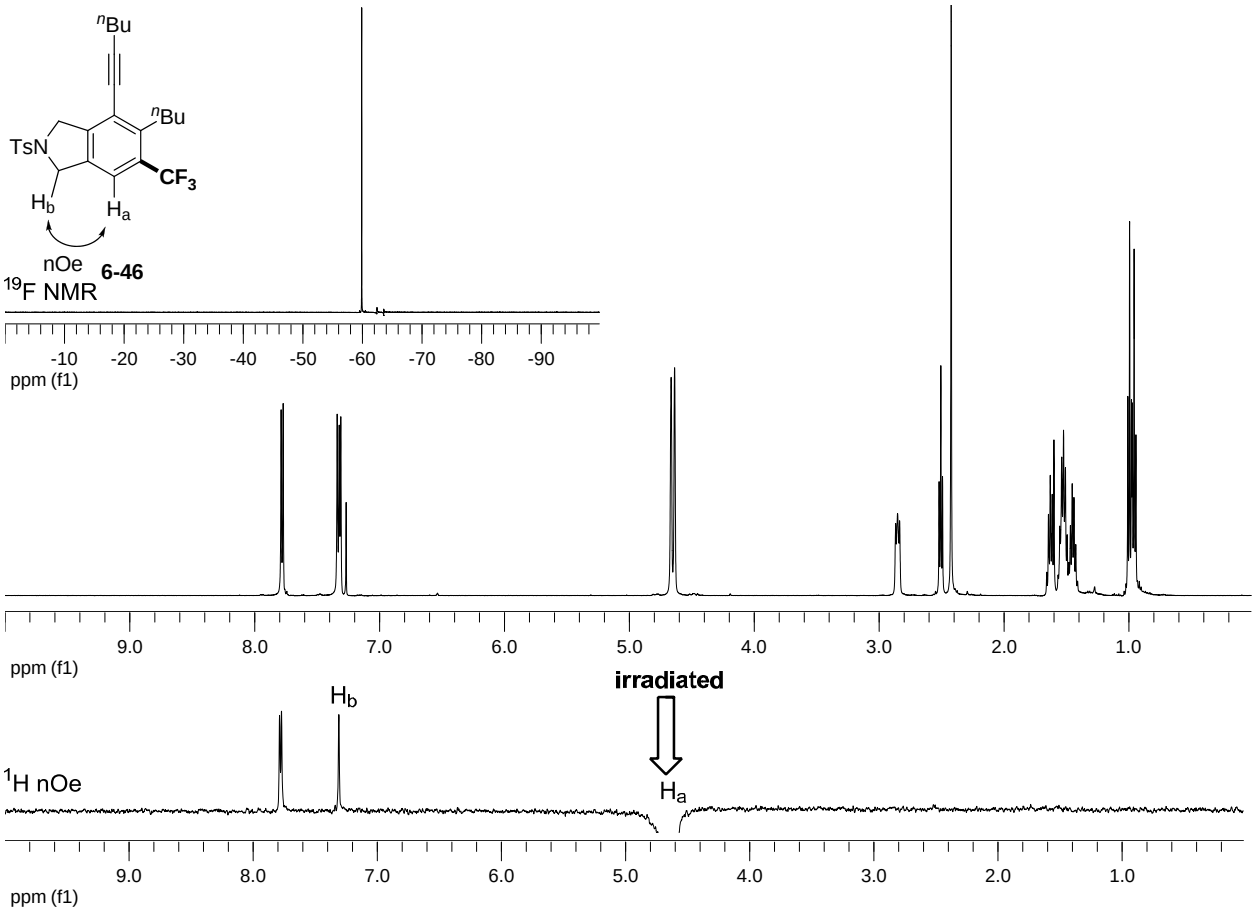

O
H
nPr
TsN
F
6-43
19F NMR
-60
-70
-80
-90
-100
-110
-120
-130
-140
ppm (f1)
10.0
5.0
ppm (f1)
200
150
100
50
0
ppm (f1)

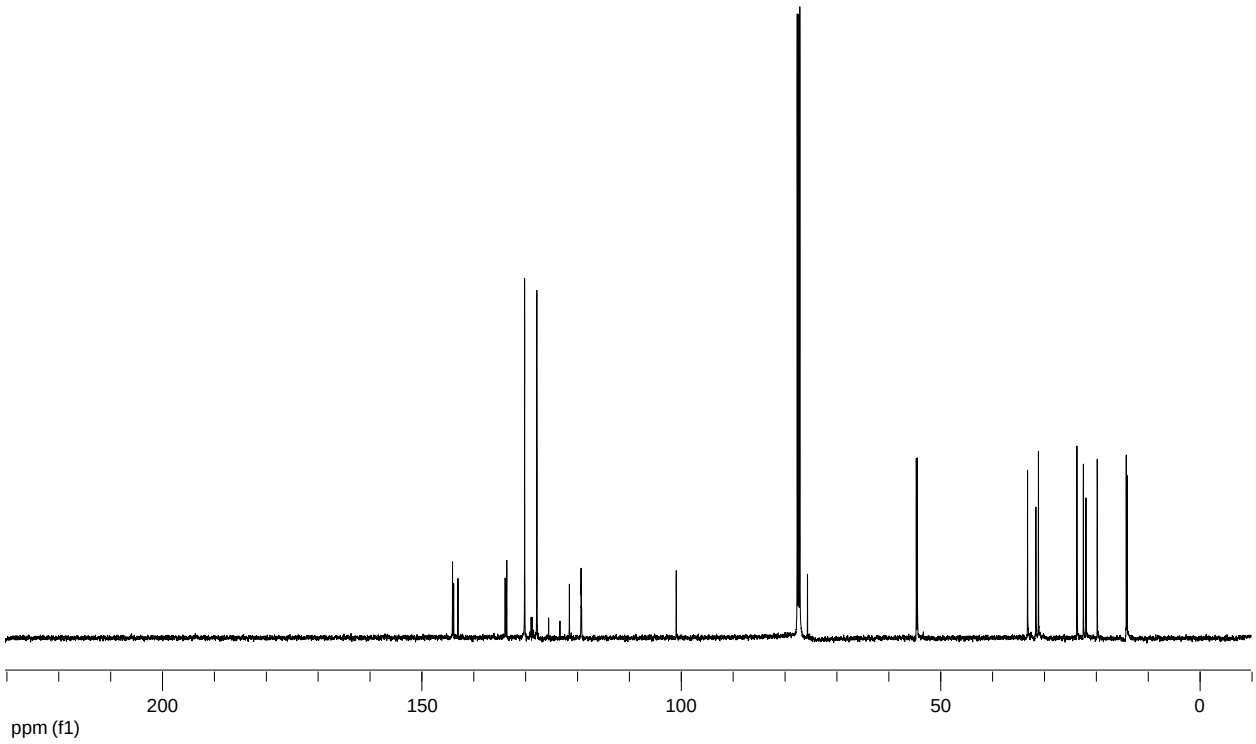

nBu
nBu
N
Ts
CF3
6-44
19F NMR
-10 -20 -30 -40 -50 -60 -70 -80 -90
ppm (f1)
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0
ppm (f1)
200 150 100 50 0
ppm (f1)

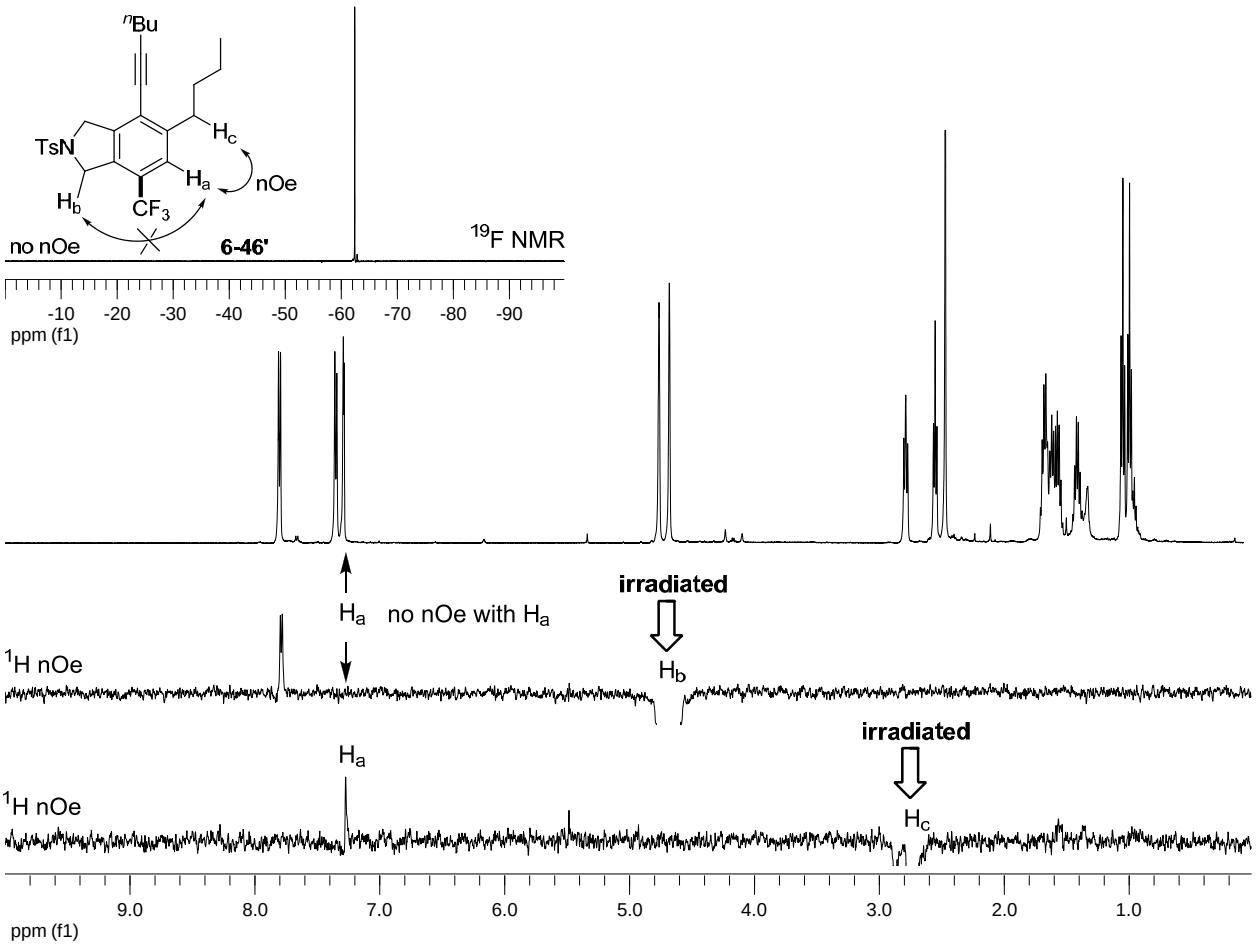

nBu
nBu
N
Ts
SCF3
6-45
-10
-20
-30
-40
-50
-60
-70
-80
-90
ppm (f1)

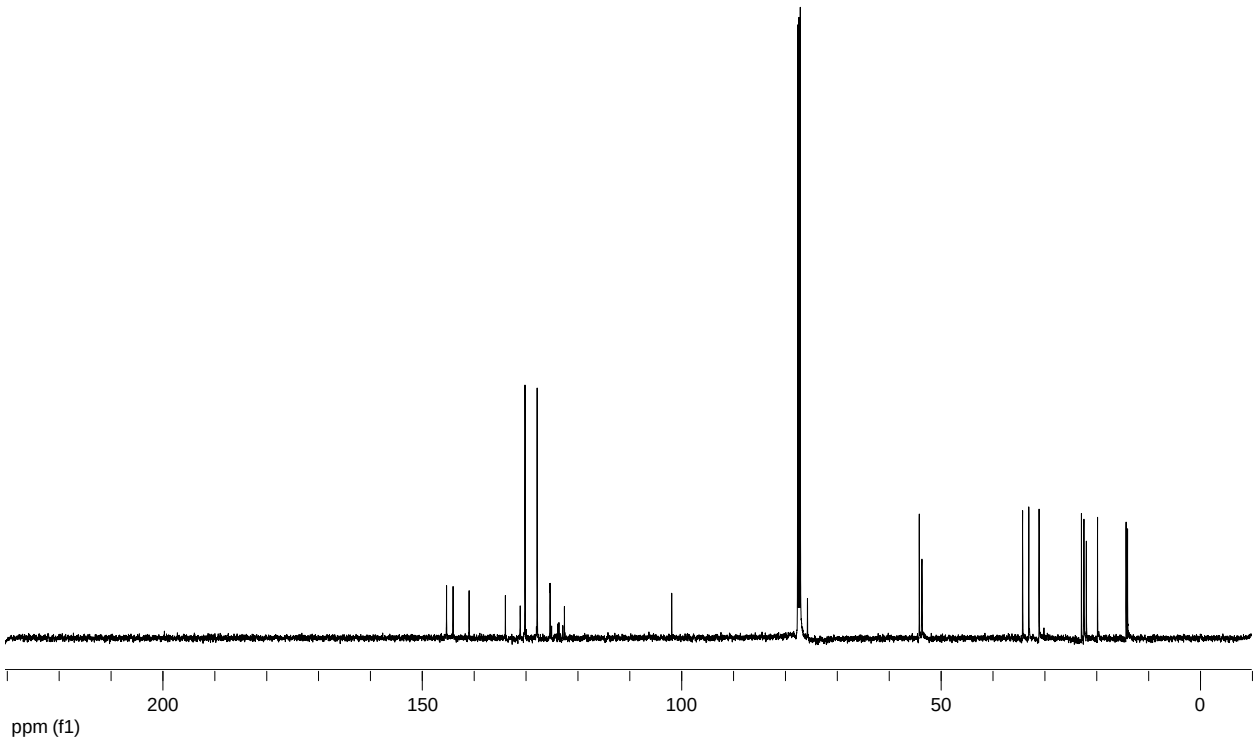

9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

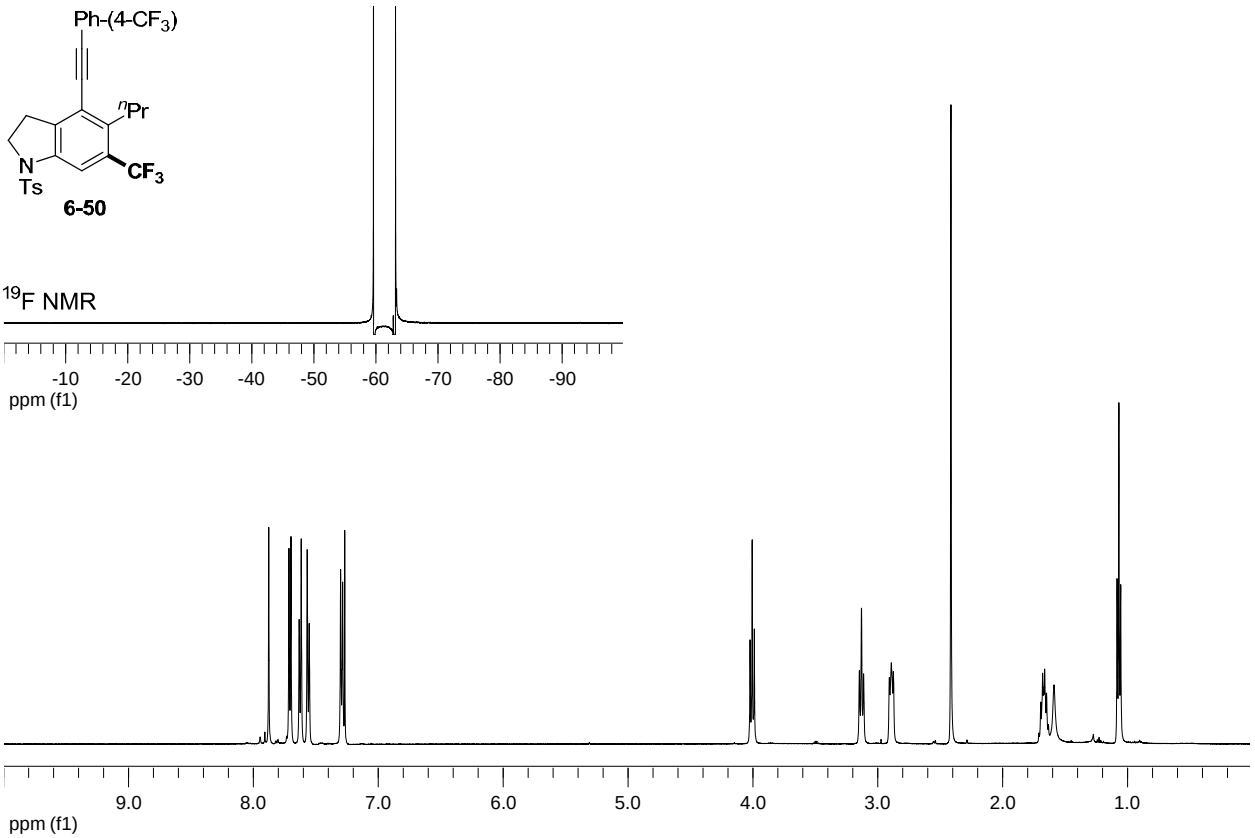

200
150
100
50
0
ppm (f1)

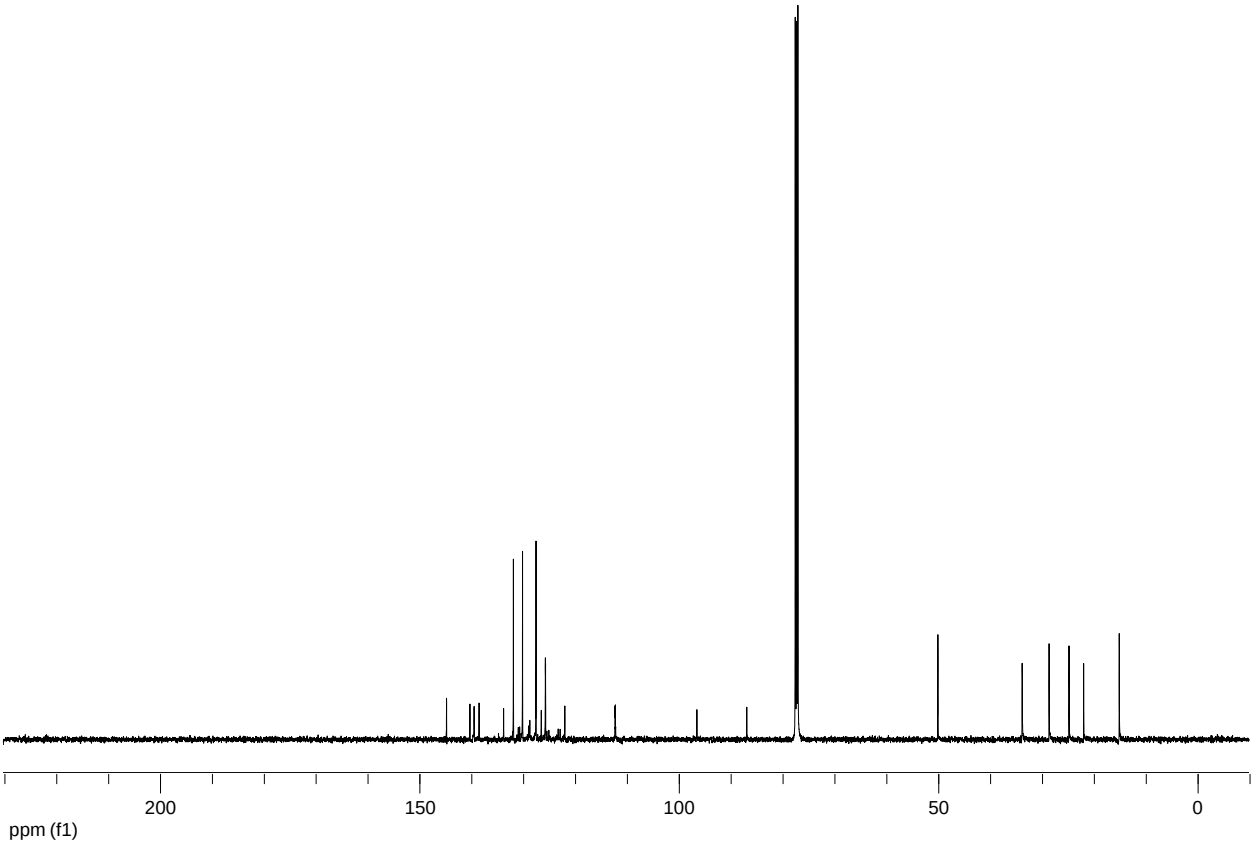

nBu
nBu
TsN
CF3
Hb
Ha
nOe
6-46
19F NMR
-10 -20 -30 -40 -50 -60 -70 -80 -90
ppm (f1)
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0
ppm (f1)
irradiated
Hb
Ha
1H nOe
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0
ppm (f1)

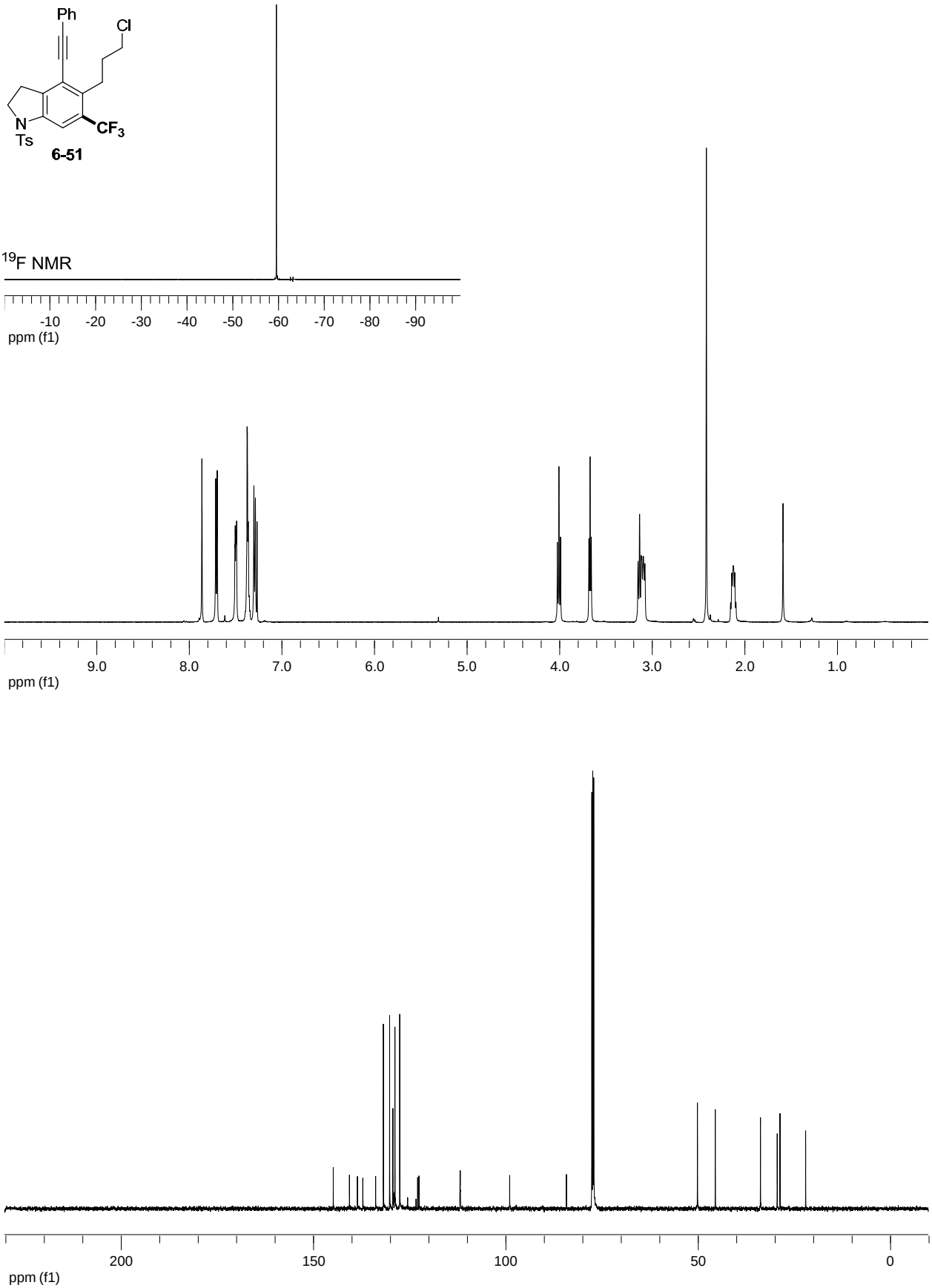

200 150 100 50 0
ppm (f1)

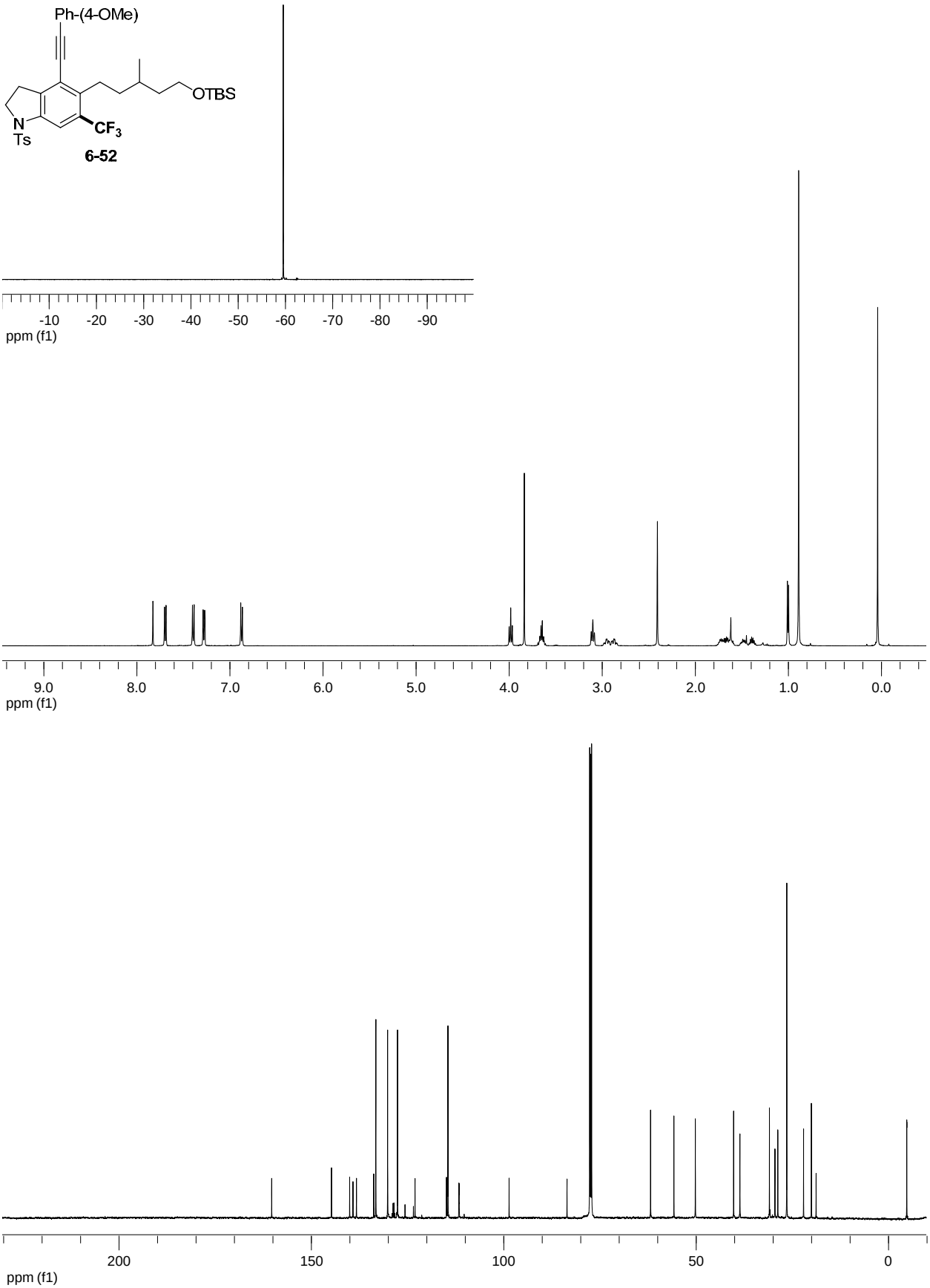

nBu
TsN
Hc
Ha
nOe
Hb
CF3
no nOe
6-46'
19F NMR
-10 -20 -30 -40 -50 -60 -70 -80 -90
ppm (f1)
Ha
no nOe with Ha
irradiated
Hb
1H nOe
irradiated
Ha
1H nOe
Hc
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0
ppm (f1)

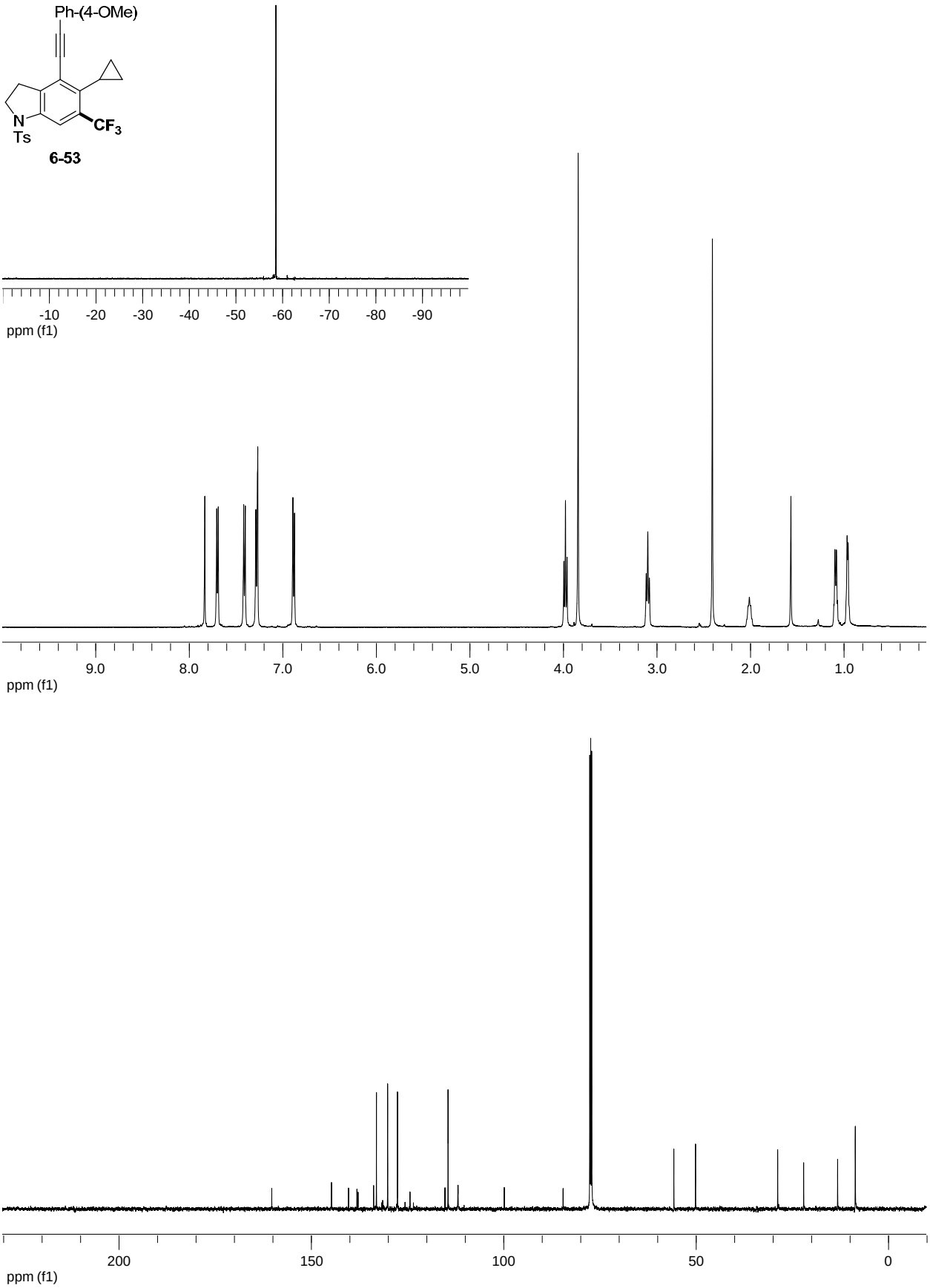

200 150 100 50 0
ppm (f1)

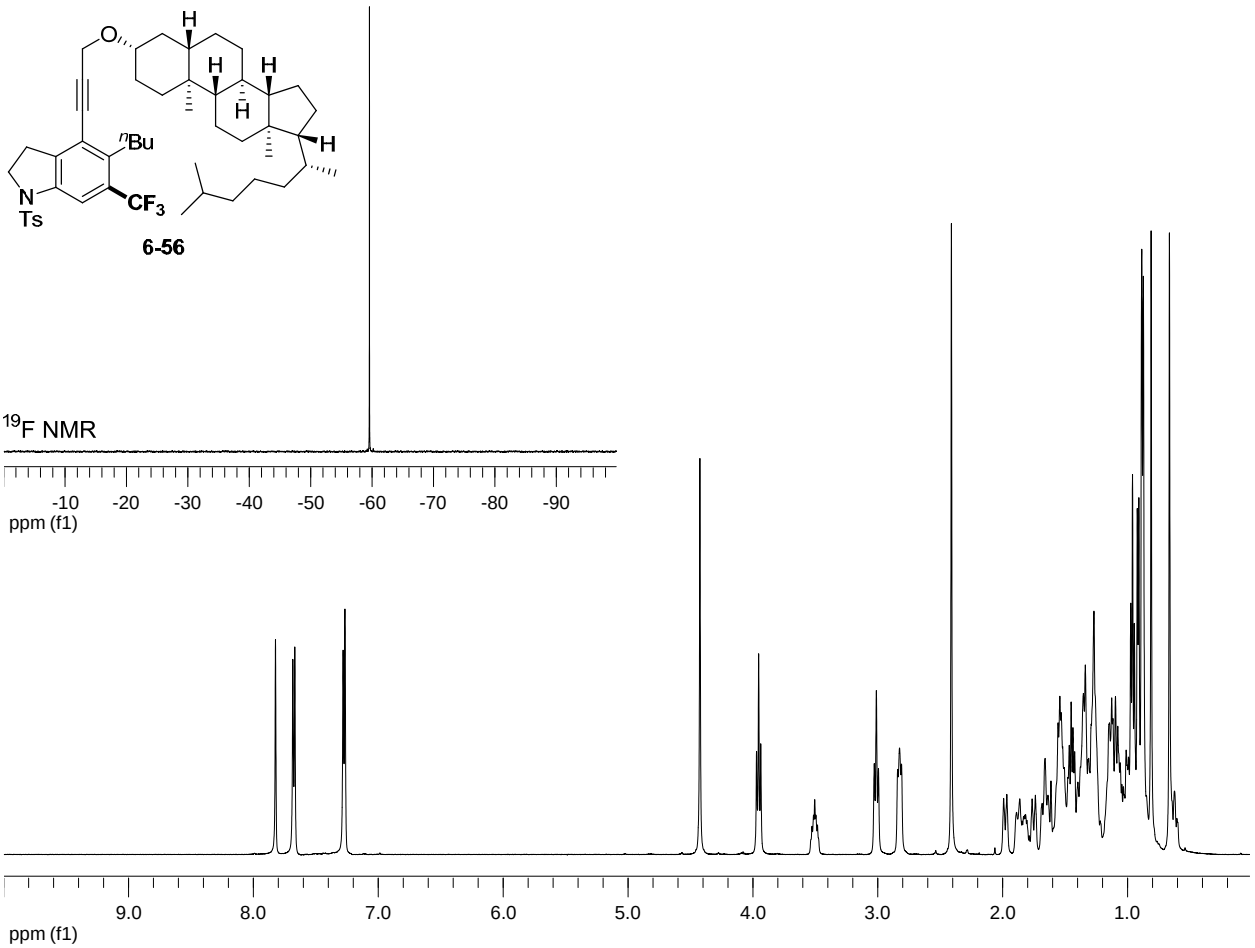

Ph-(4-CF3)
nPr
N
Ts
CF3
6-50
19F NMR
-10 -20 -30 -40 -50 -60 -70 -80 -90
ppm (f1)
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0
ppm (f1)

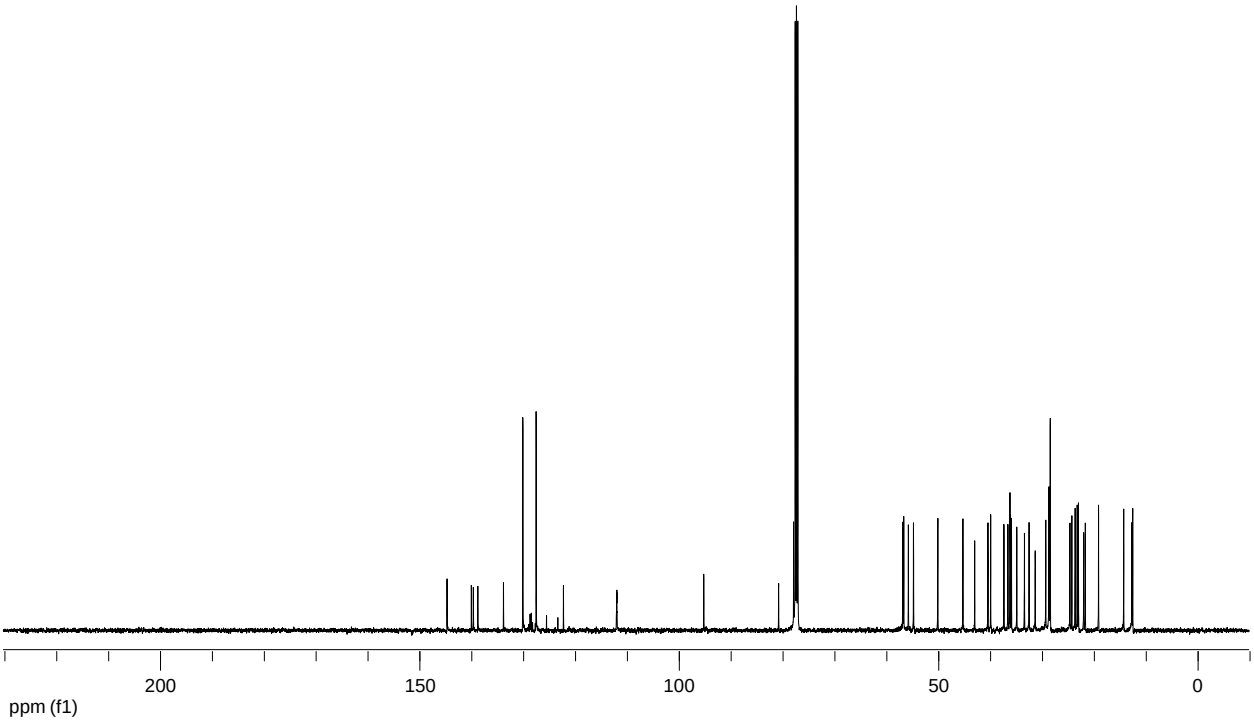

200 150 100 50 0
ppm (f1)

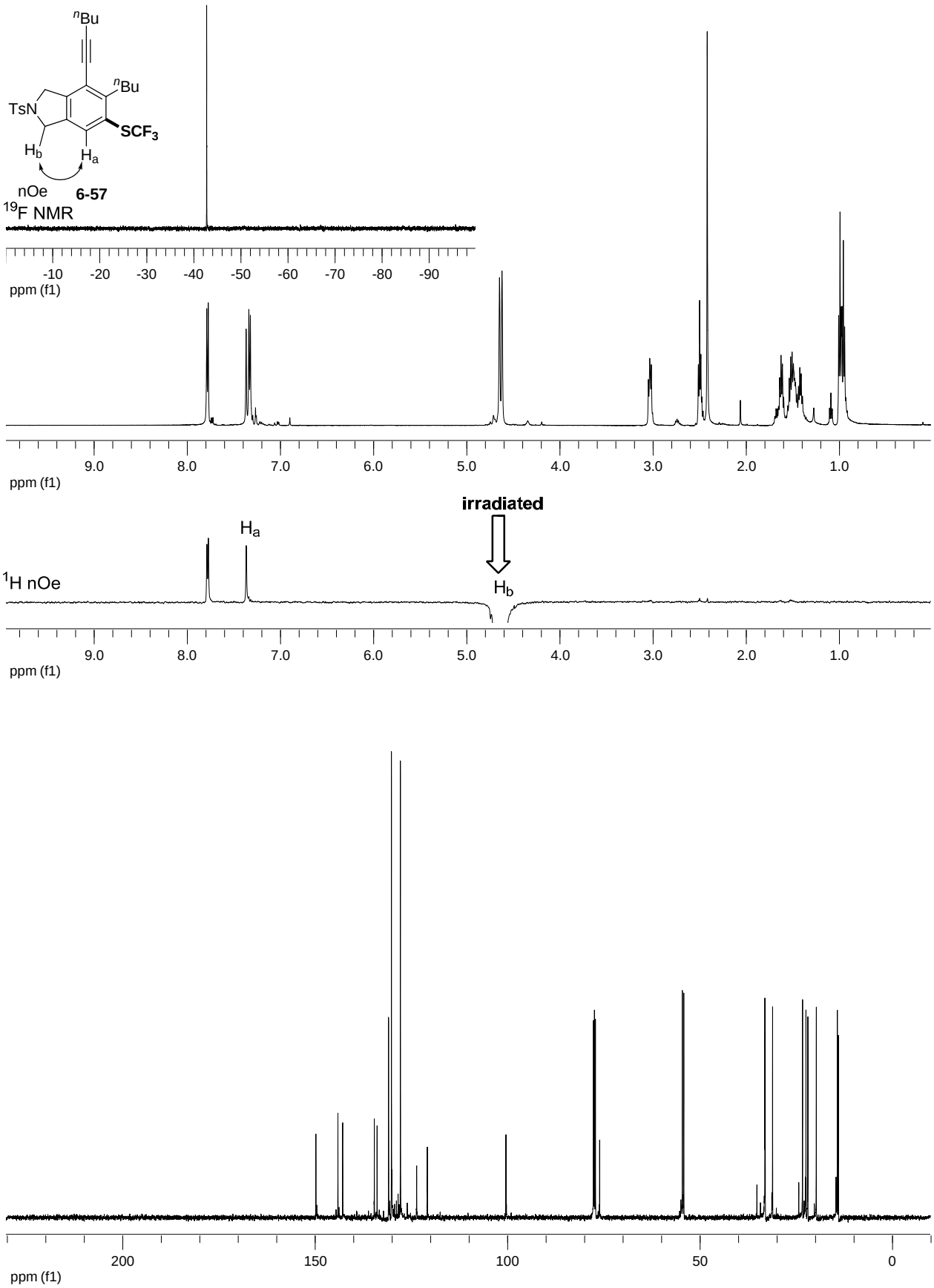

Ph
Cl
N
Ts
CF3
6-51
19F NMR
-10 -20 -30 -40 -50 -60 -70 -80 -90
ppm (f1)
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0
ppm (f1)
200 150 100 50 0
ppm (f1)

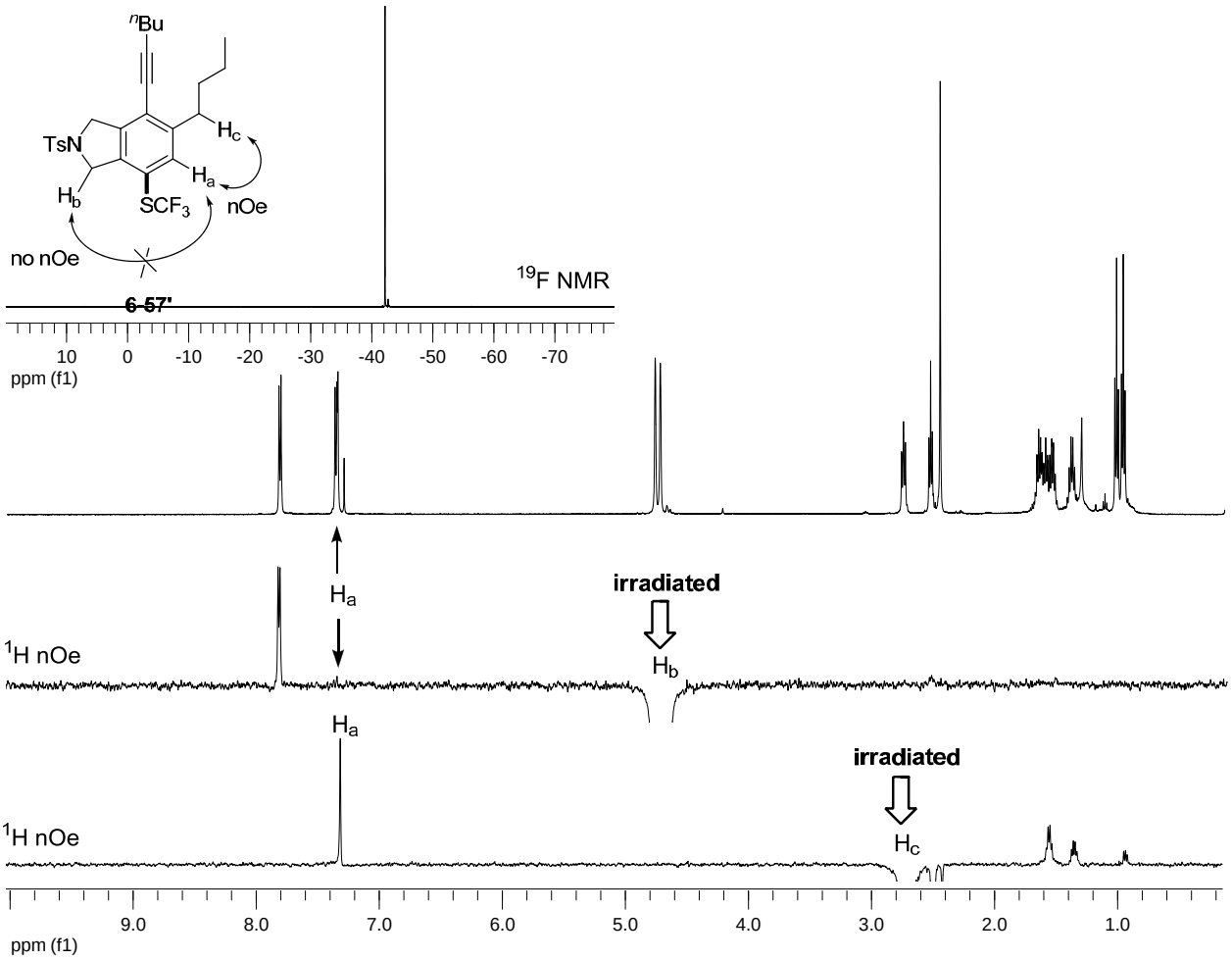

Ph-(4-OMe)
OTBS
N
Ts
CF3
6-52
-10 -20 -30 -40 -50 -60 -70 -80 -90
ppm (f1)
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0
ppm (f1)
200 150 100 50 0
ppm (f1)

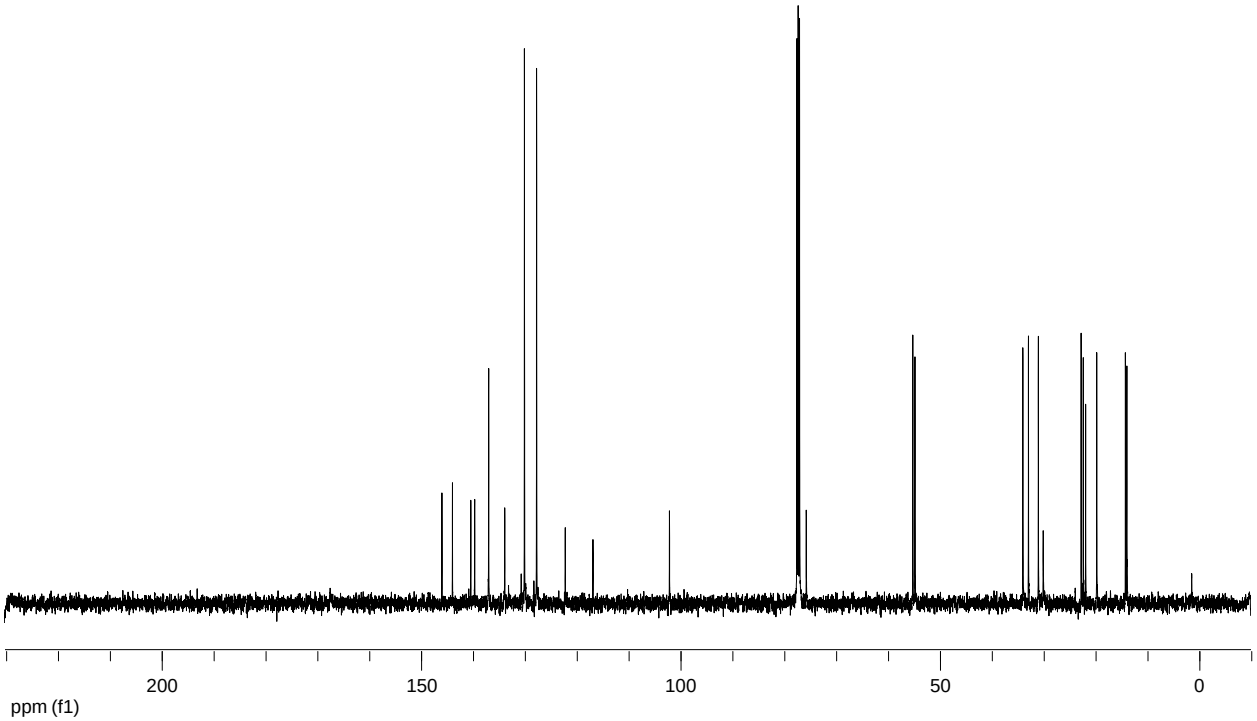

Ph-(4-OMe)
N
Ts
CF3
6-53
-10 -20 -30 -40 -50 -60 -70 -80 -90
ppm (f1)
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0
ppm (f1)
200 150 100 50 0
ppm (f1)

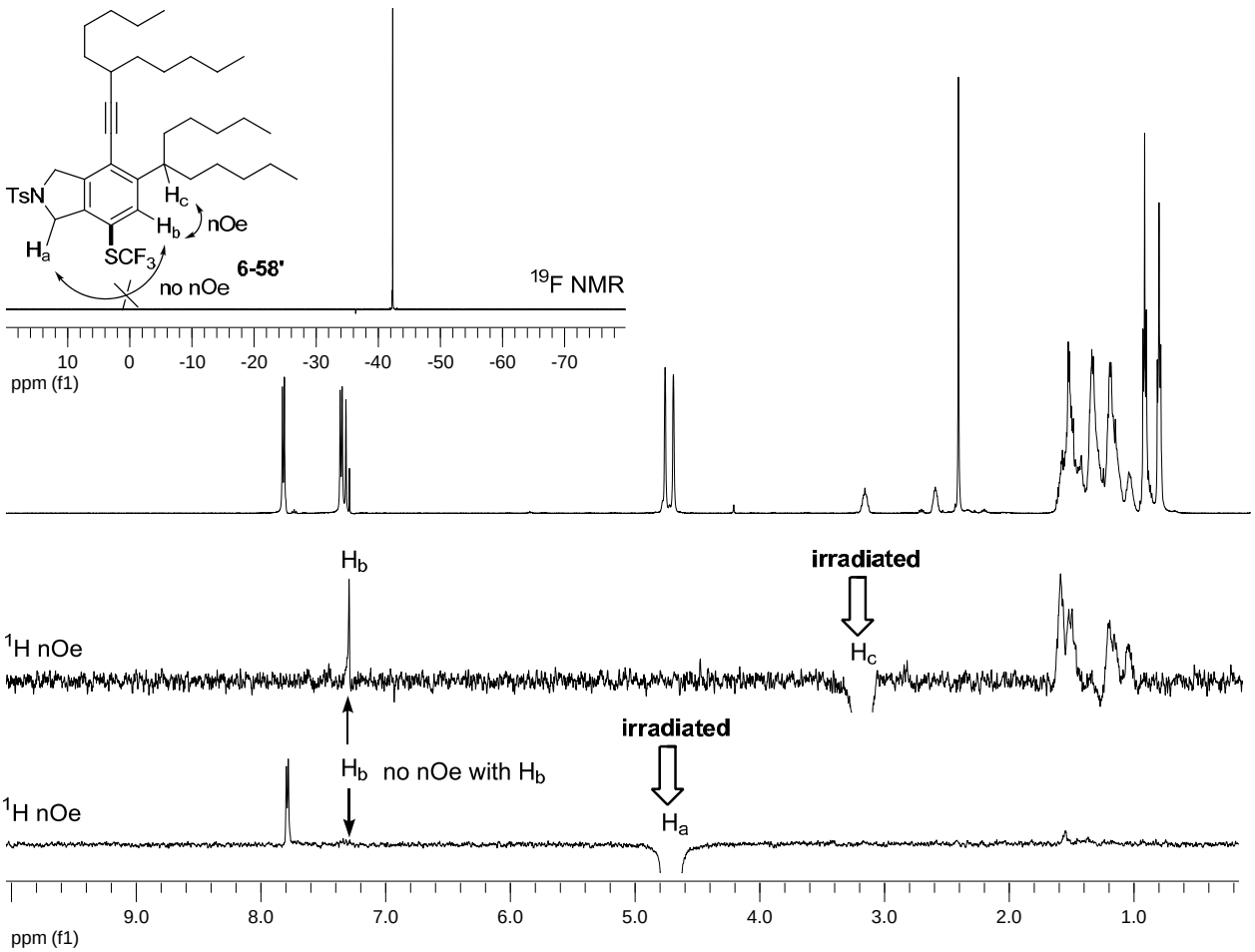

O
H
H
H
H
H
nBu
N
Ts
CF3
6-56
19F NMR
-10 -20 -30 -40 -50 -60 -70 -80 -90
ppm (f1)
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0
ppm (f1)

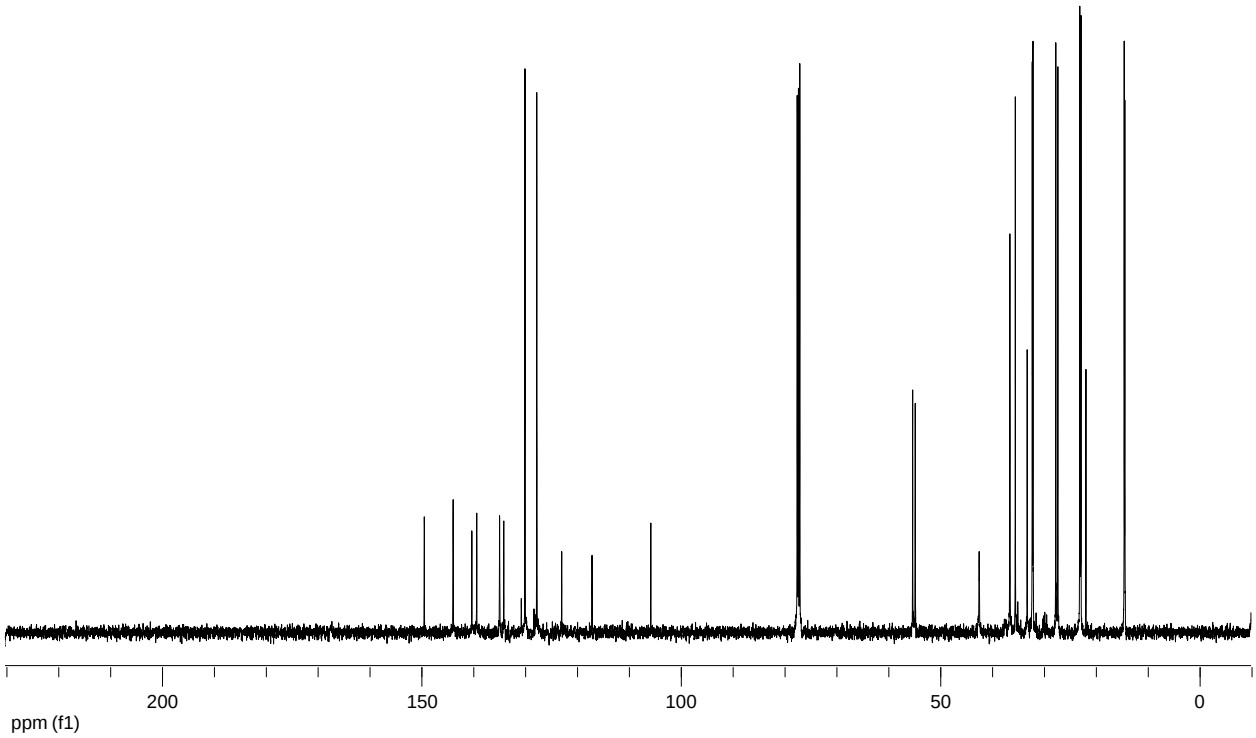

200 150 100 50 0
ppm (f1)

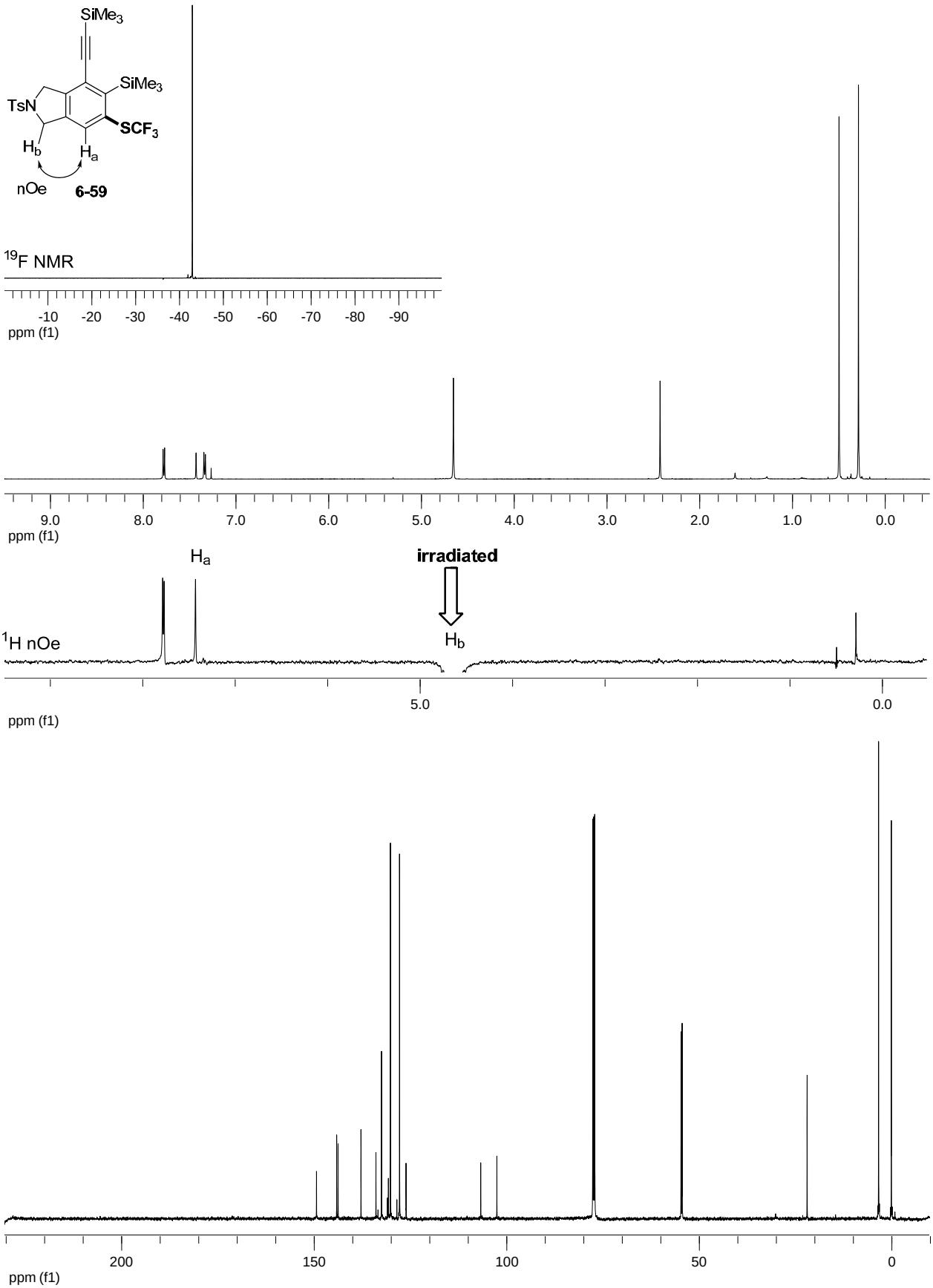

nBu
nBu
TsN
SCF3
Hb
Ha
nOe
6-57
19F NMR
-10 -20 -30 -40 -50 -60 -70 -80 -90
ppm (f1)
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0
ppm (f1)
irradiated
Ha
1H nOe
Hb
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0
ppm (f1)
200 150 100 50 0
ppm (f1)

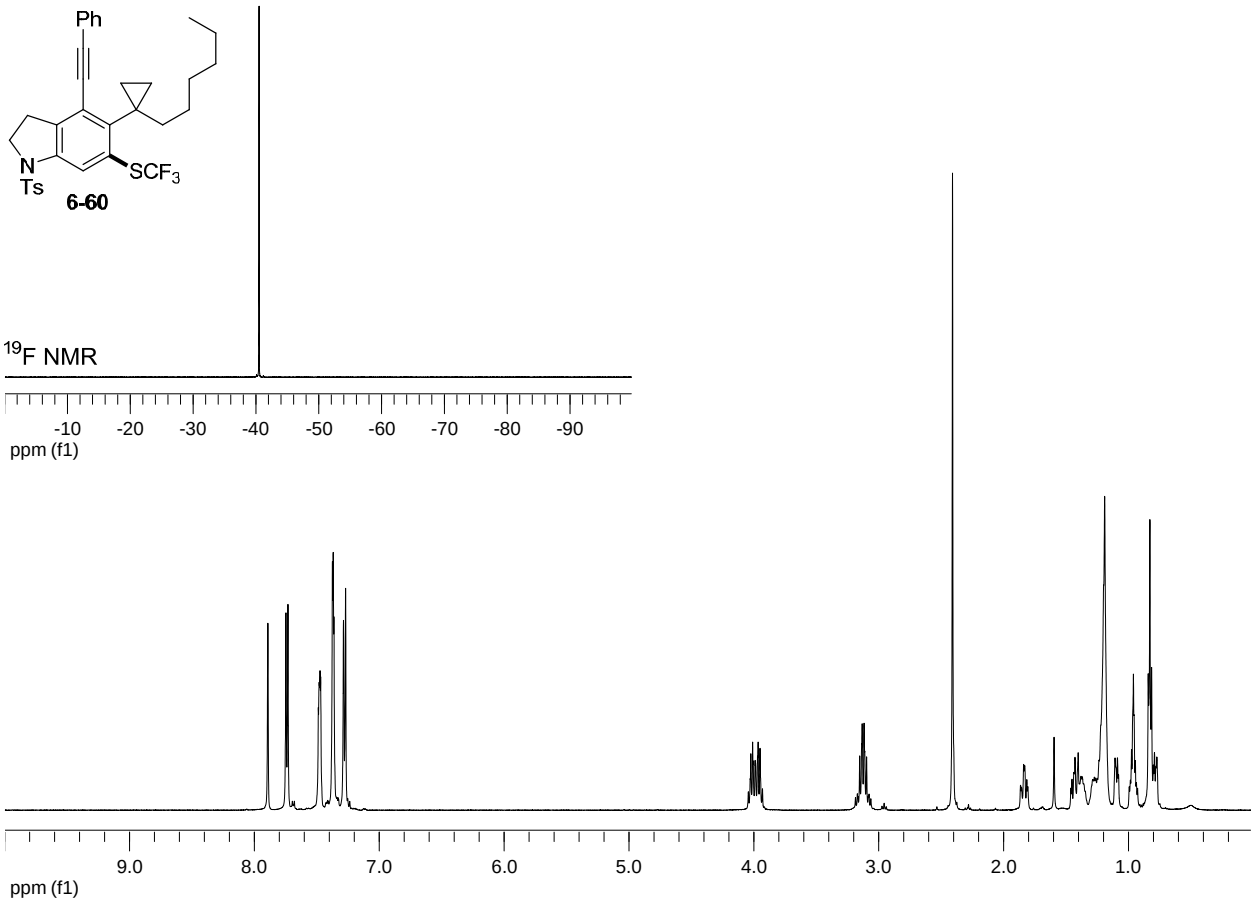

nBu
TsN
Hc
Ha
Hb
SCF3
nOe
no nOe
6-57'
19F NMR
10 0 -10 -20 -30 -40 -50 -60 -70
ppm (f1)
Ha
irradiated
Hb
1H nOe
Ha
irradiated
Hc
1H nOe
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0
ppm (f1)

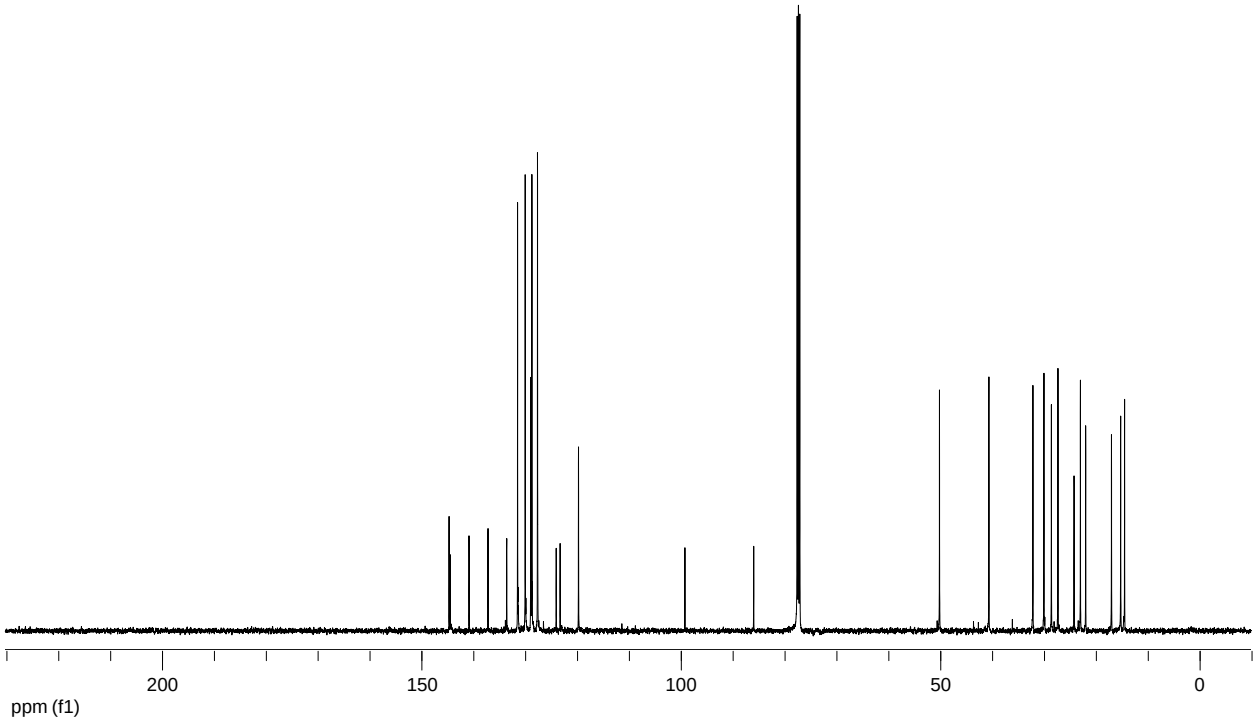

200 150 100 50 0
ppm (f1)

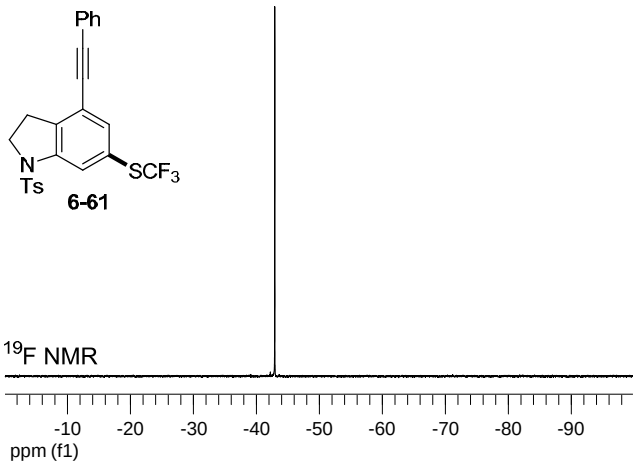

TsN
H_c
H_b
nOe
H_a
SCF_3
no nOe
6-58'
^{19}F NMR
10 0 -10 -20 -30 -40 -50 -60 -70
ppm (f1)
H_b
irradiated
H_c
^{1}H nOe
irradiated
H_b no nOe with H_b
H_a
^{1}H nOe
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0
ppm (f1)

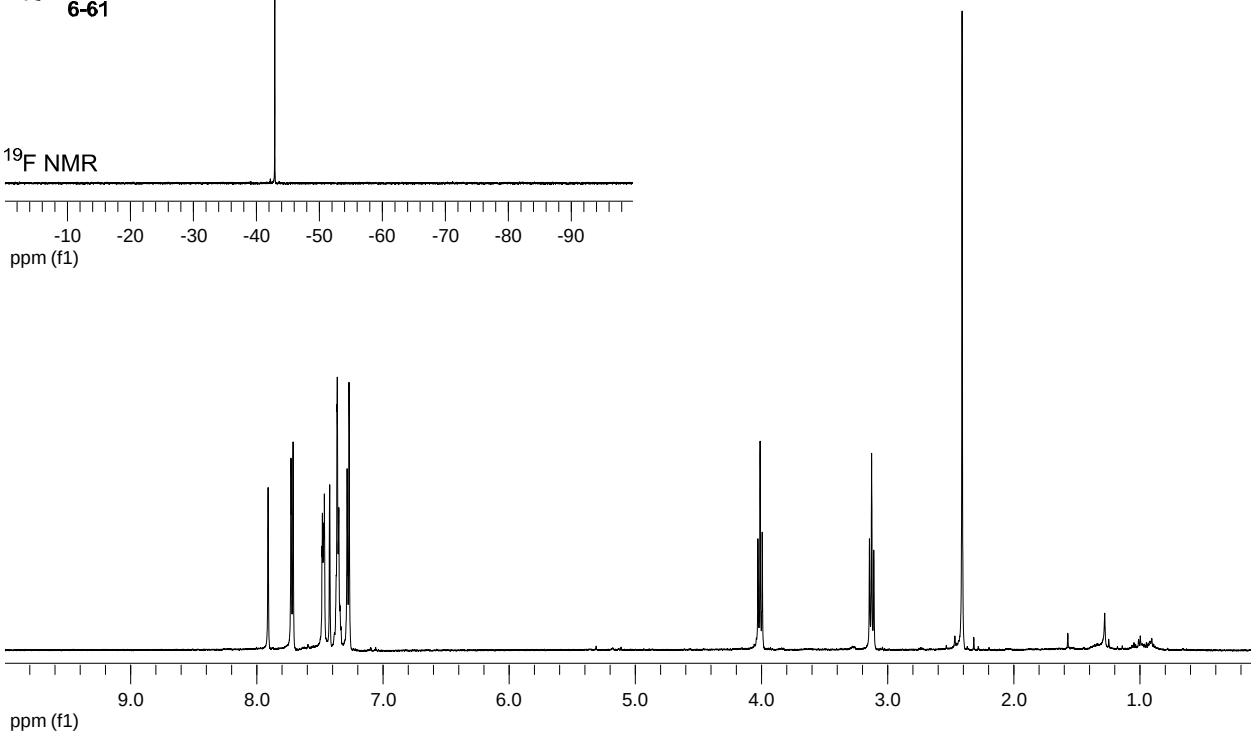

200 150 100 50 0
ppm (f1)

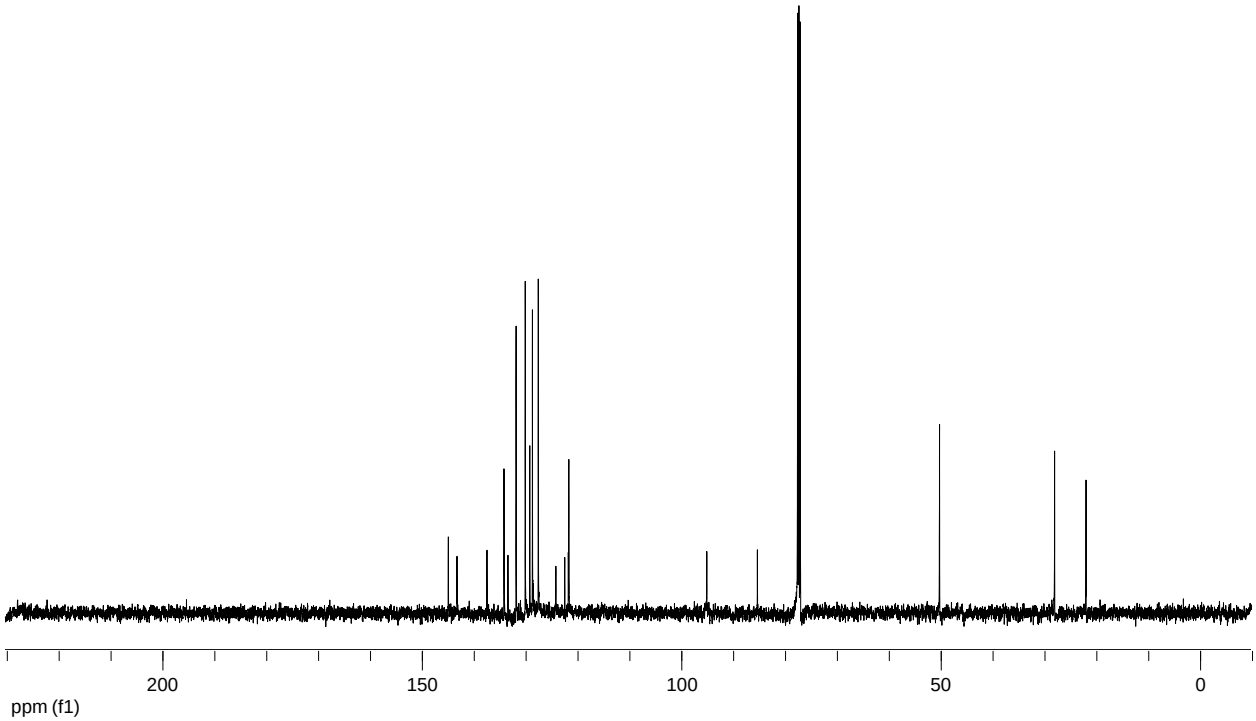

SiMe3
SiMe3
TsN
SCF3
Hb
Ha
nOe
6-59
19F NMR
-10 -20 -30 -40 -50 -60 -70 -80 -90
ppm (f1)
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0
ppm (f1)
Ha
irradiated
Hb
1H nOe
5.0
0.0
ppm (f1)
200 150 100 50 0
ppm (f1)

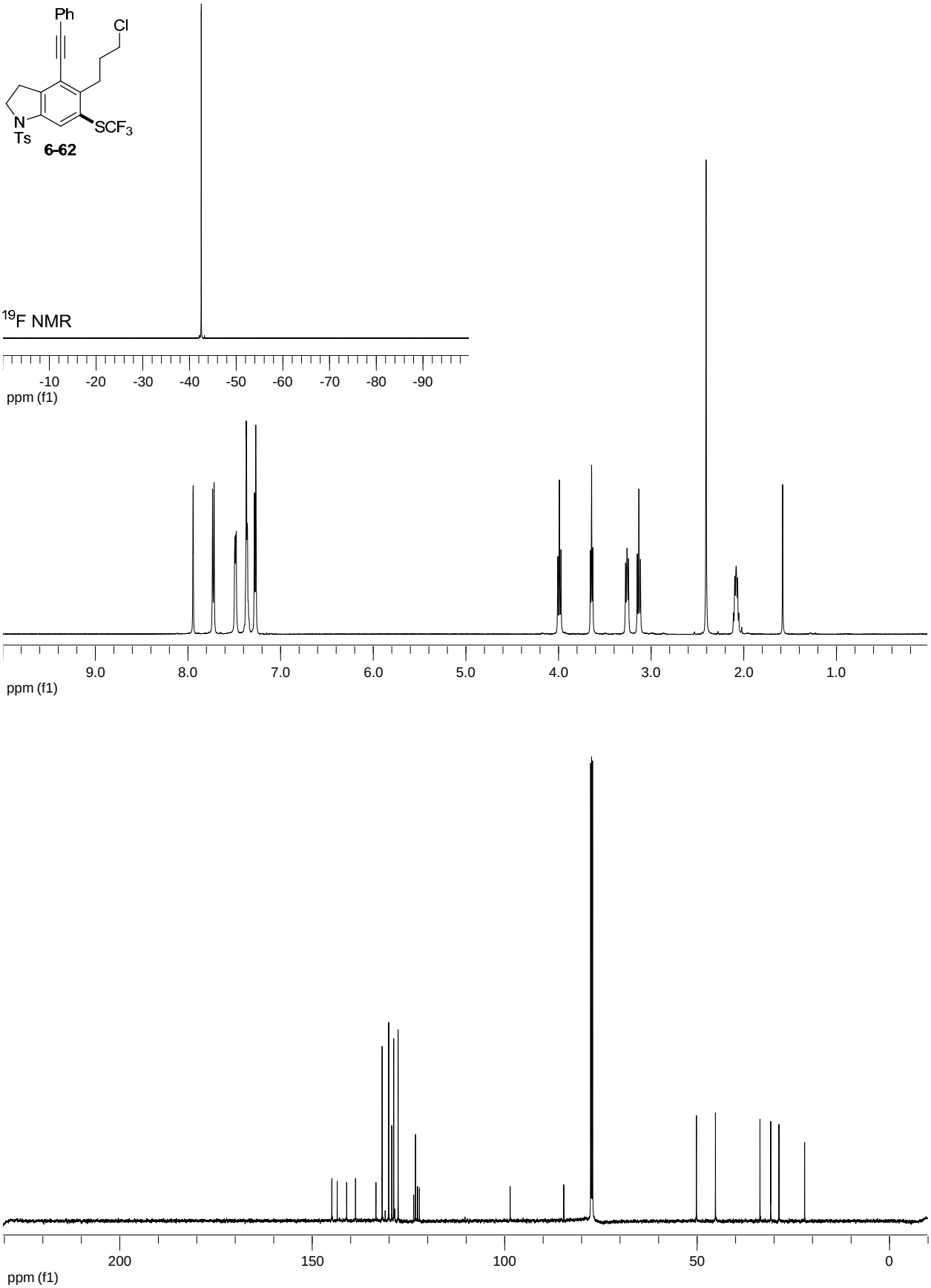

Ph
N
Ts
SCF3
6-60
19F NMR
-10 -20 -30 -40 -50 -60 -70 -80 -90
ppm (f1)
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0
ppm (f1)

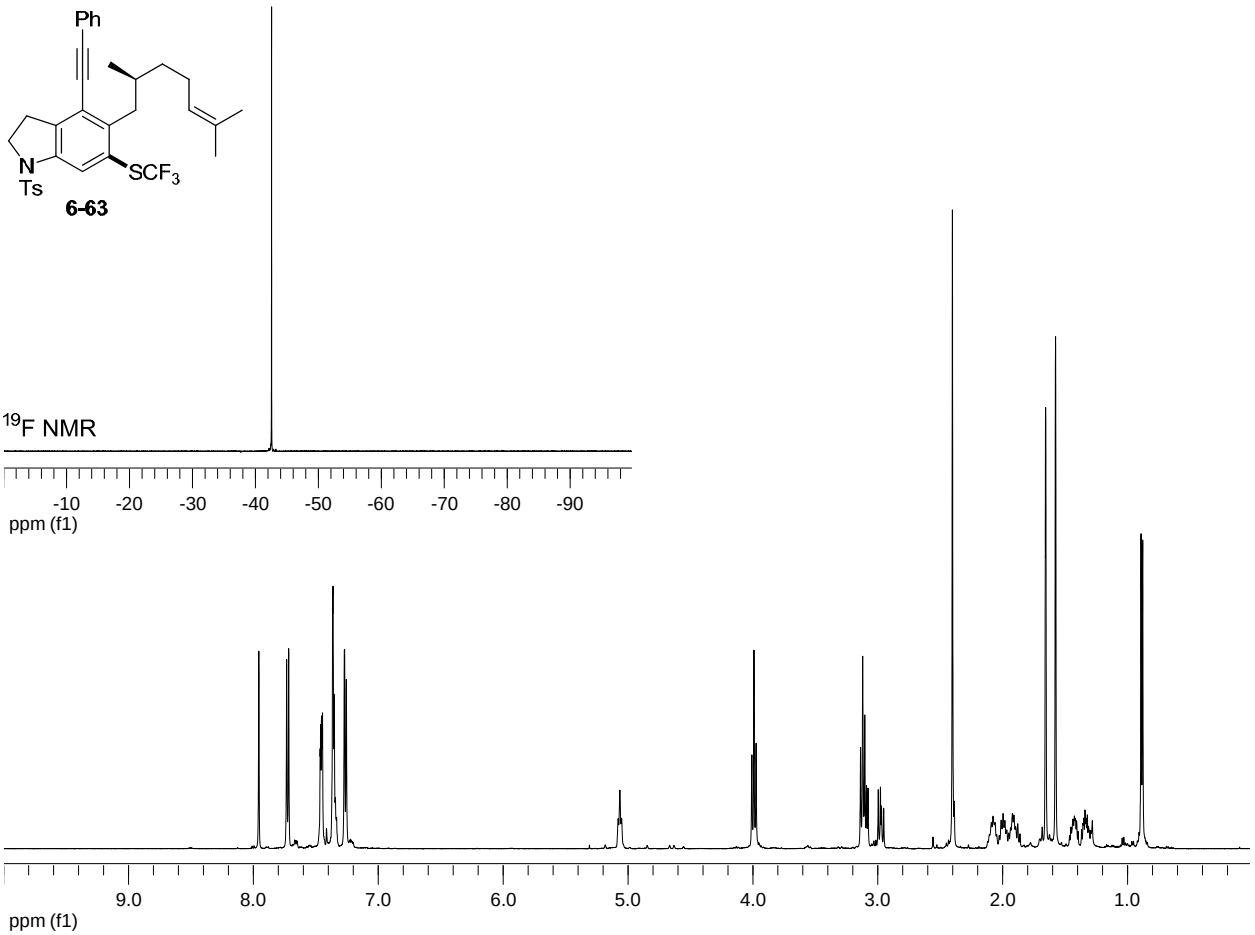

200 150 100 50 0
ppm (f1)

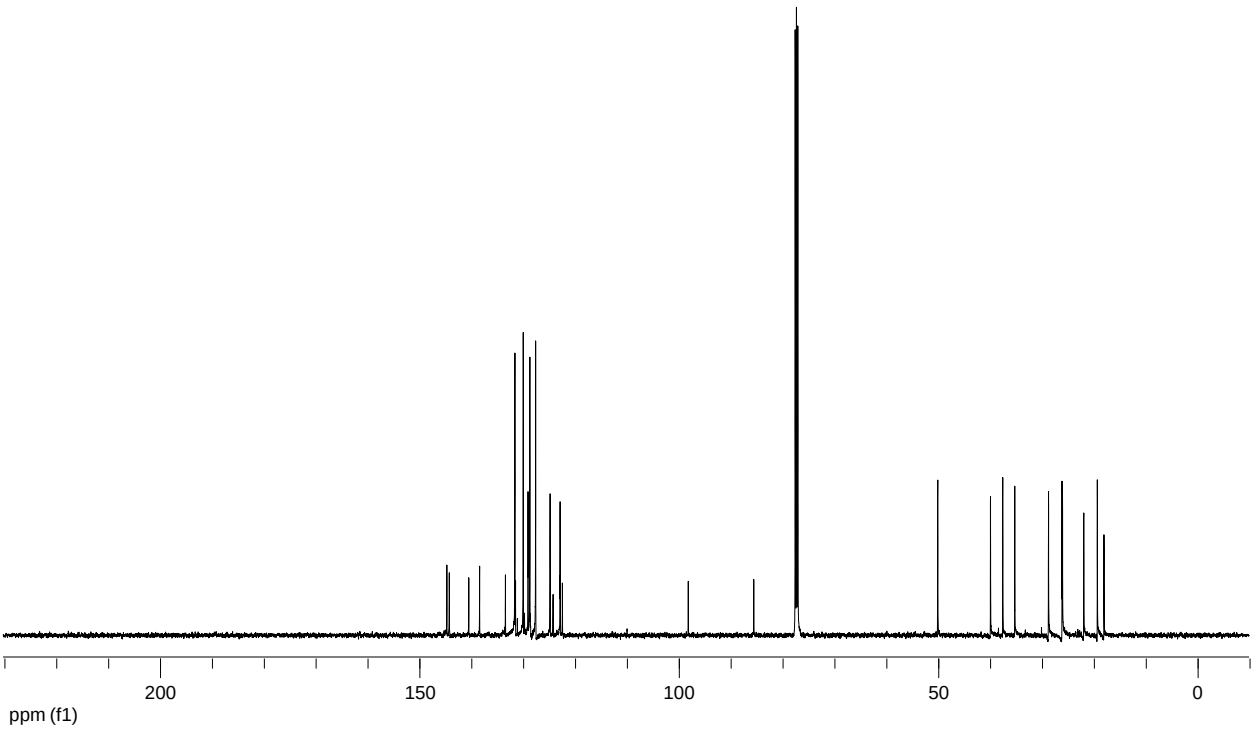

Ph
N
Ts
SCF3
6-61
19F NMR
-10 -20 -30 -40 -50 -60 -70 -80 -90
ppm (f1)

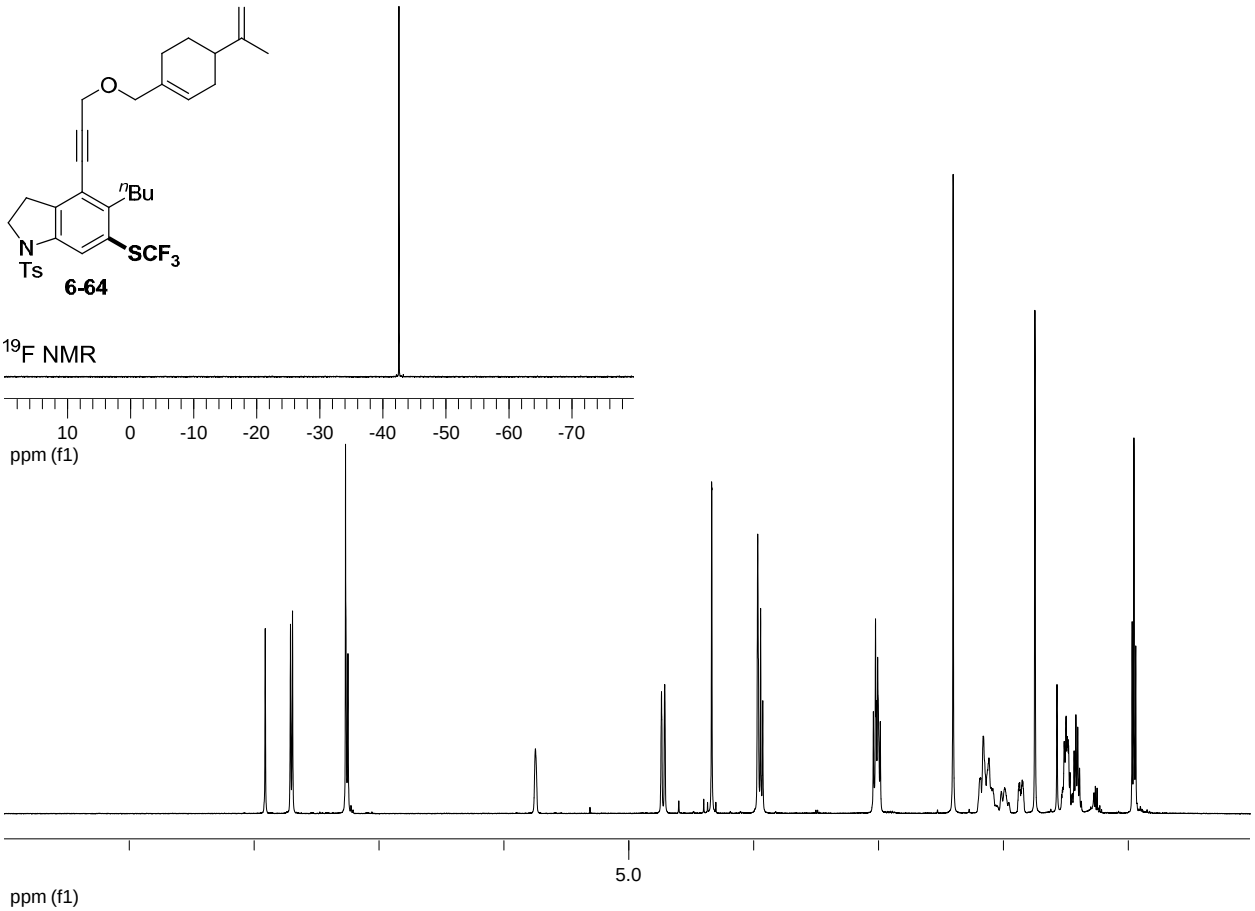

9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0
ppm (f1)

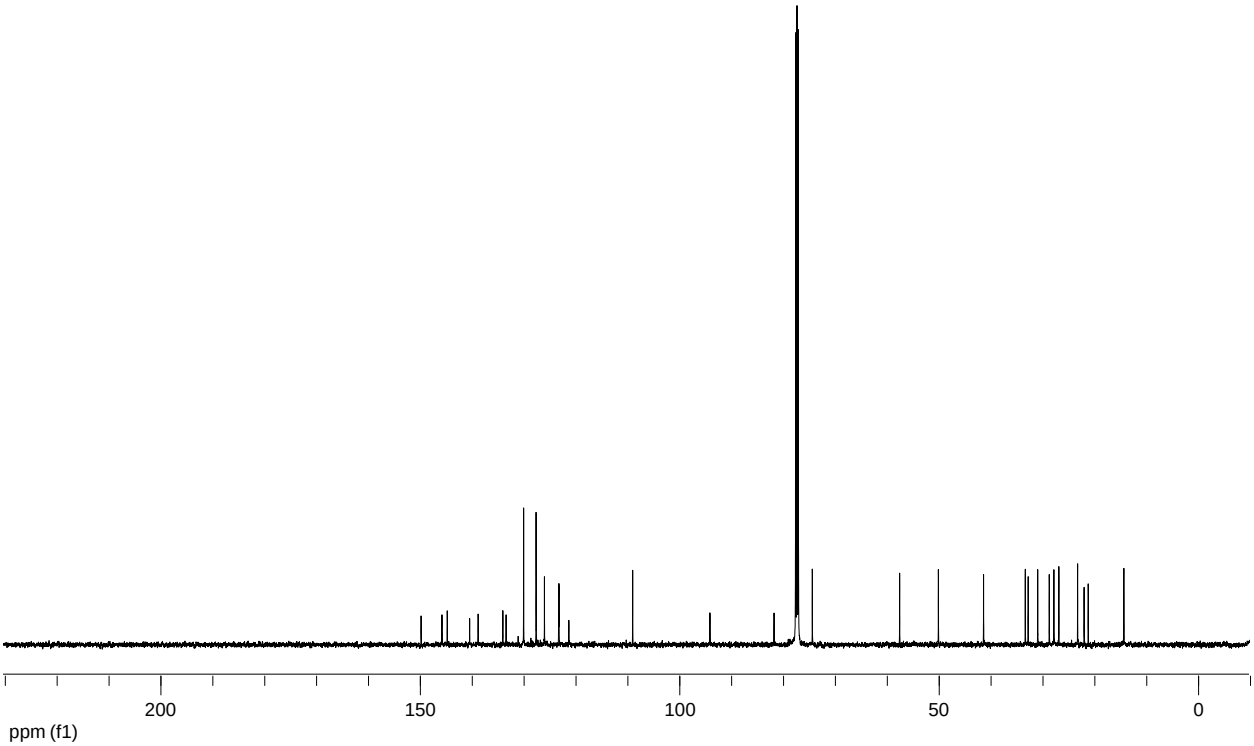

200 150 100 50 0
ppm (f1)

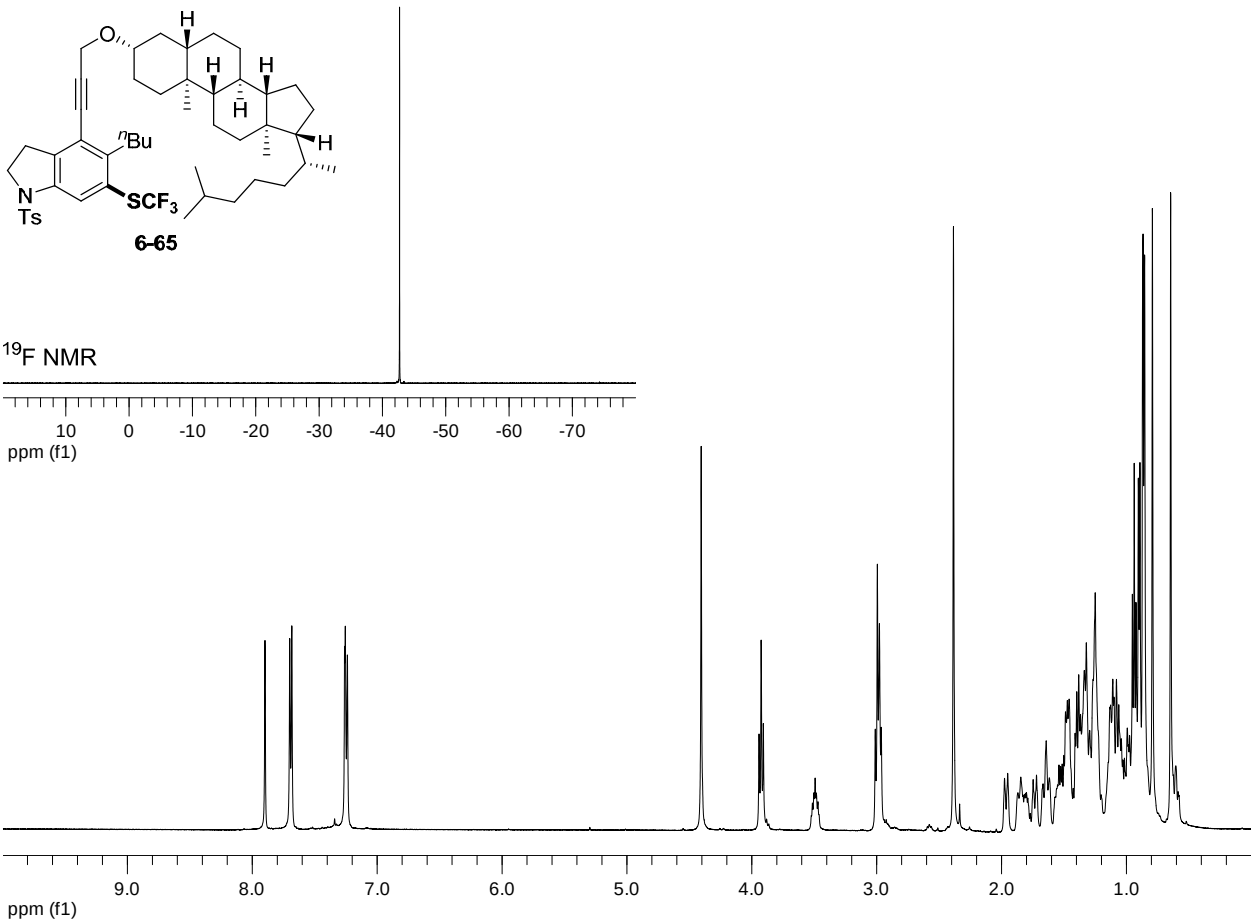

Ph
Cl
N
Ts
SCF3
6-62
19F NMR
-10 -20 -30 -40 -50 -60 -70 -80 -90
ppm (f1)
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0
ppm (f1)
200 150 100 50 0
ppm (f1)

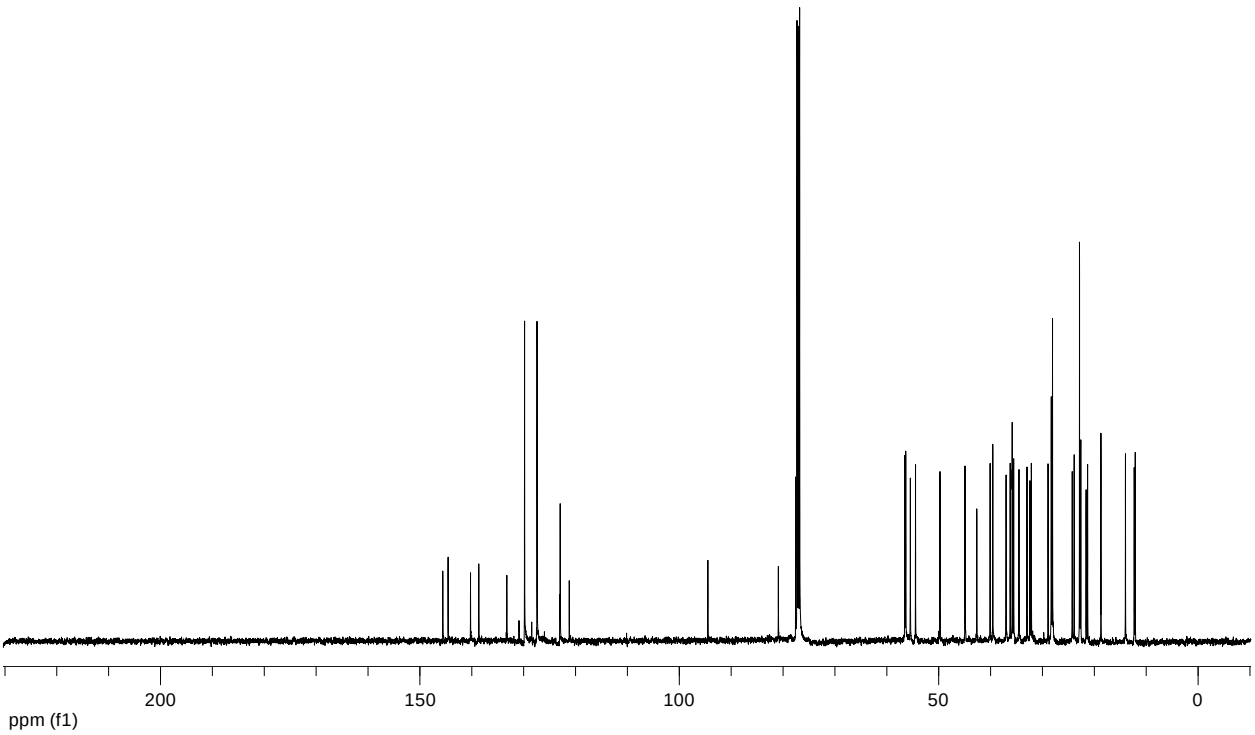

Ph
N
Ts
SCF3
6-63
19F NMR
-10 -20 -30 -40 -50 -60 -70 -80 -90
ppm (f1)
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0
ppm (f1)

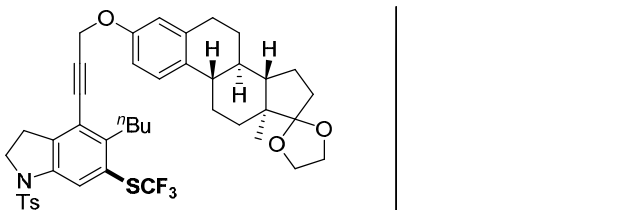

200 150 100 50 0
ppm (f1)


O
nBu
N
Ts
SCF3
6-64
19F NMR
10
0
-10
-20
-30
-40
-50
-60
-70
ppm (f1)
5.0
ppm (f1)


200
150
100
50
0
ppm (f1)

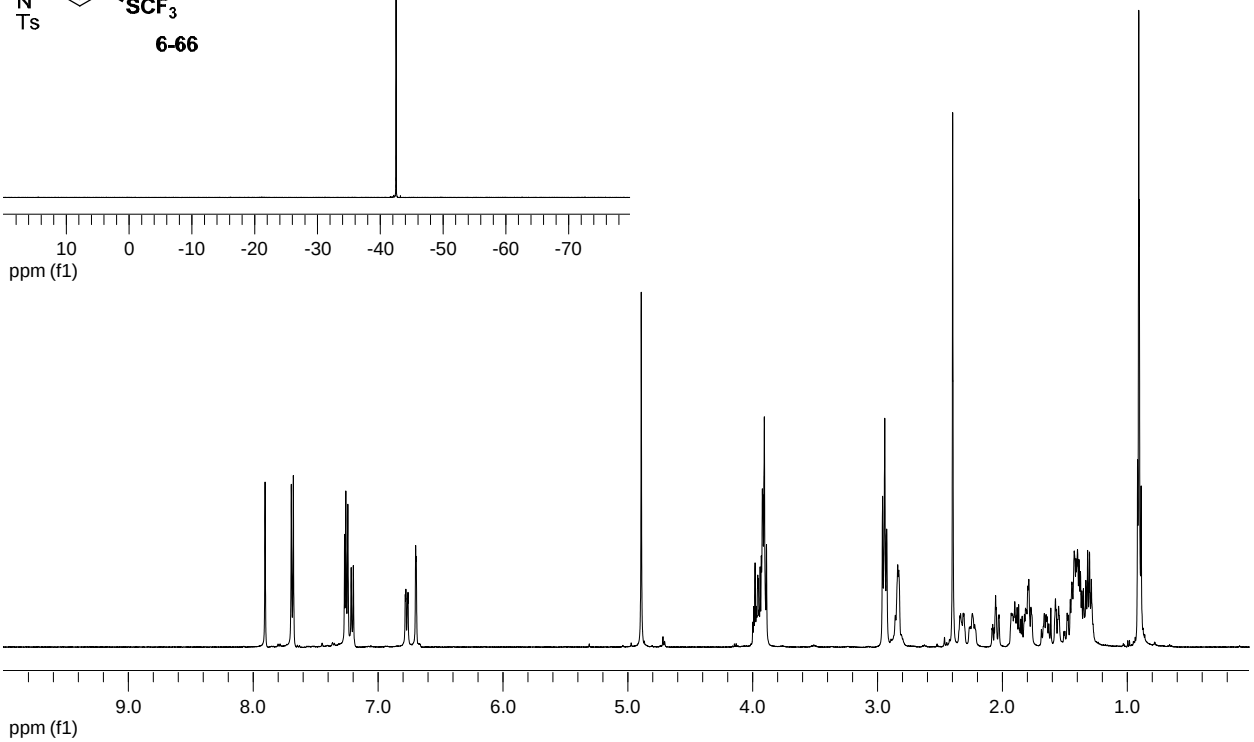

O
H
H
H
H
H
^{n}Bu
N
Ts
SCF$_3$
6-65
^{19}F NMR
10
0
-10
-20
-30
-40
-50
-60
-70
ppm (f1)
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

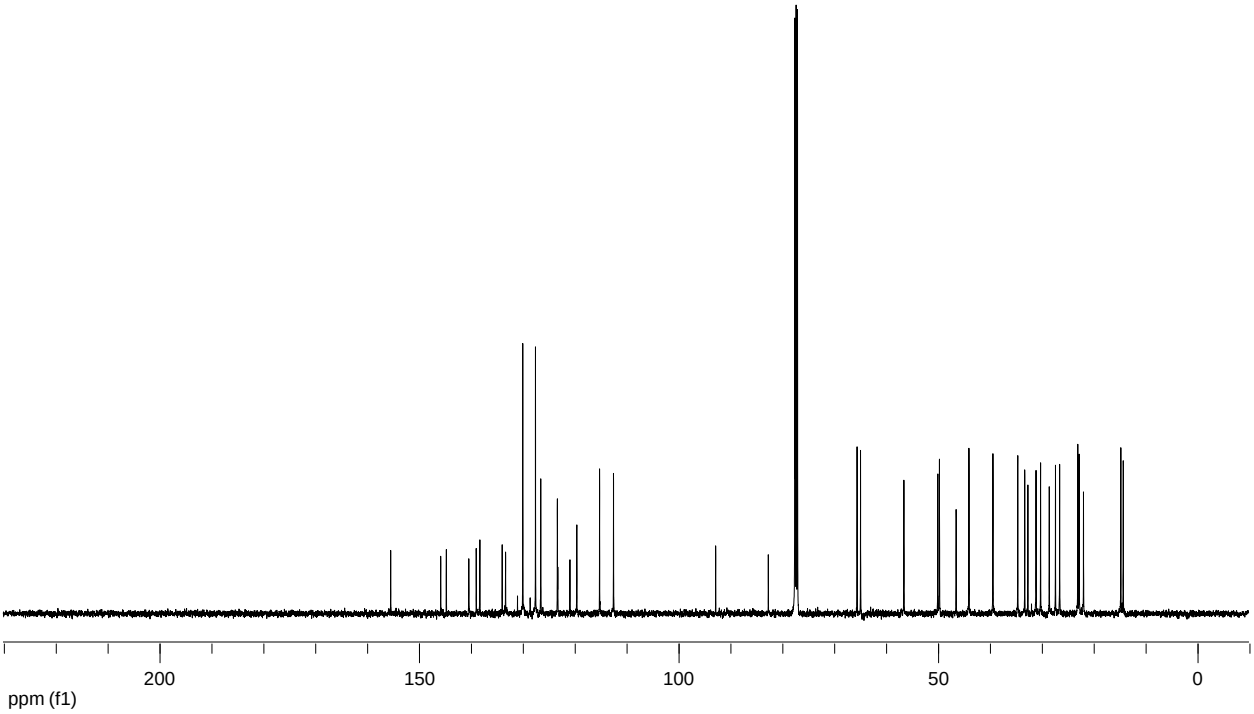

200
150
100
50
0
ppm (f1)

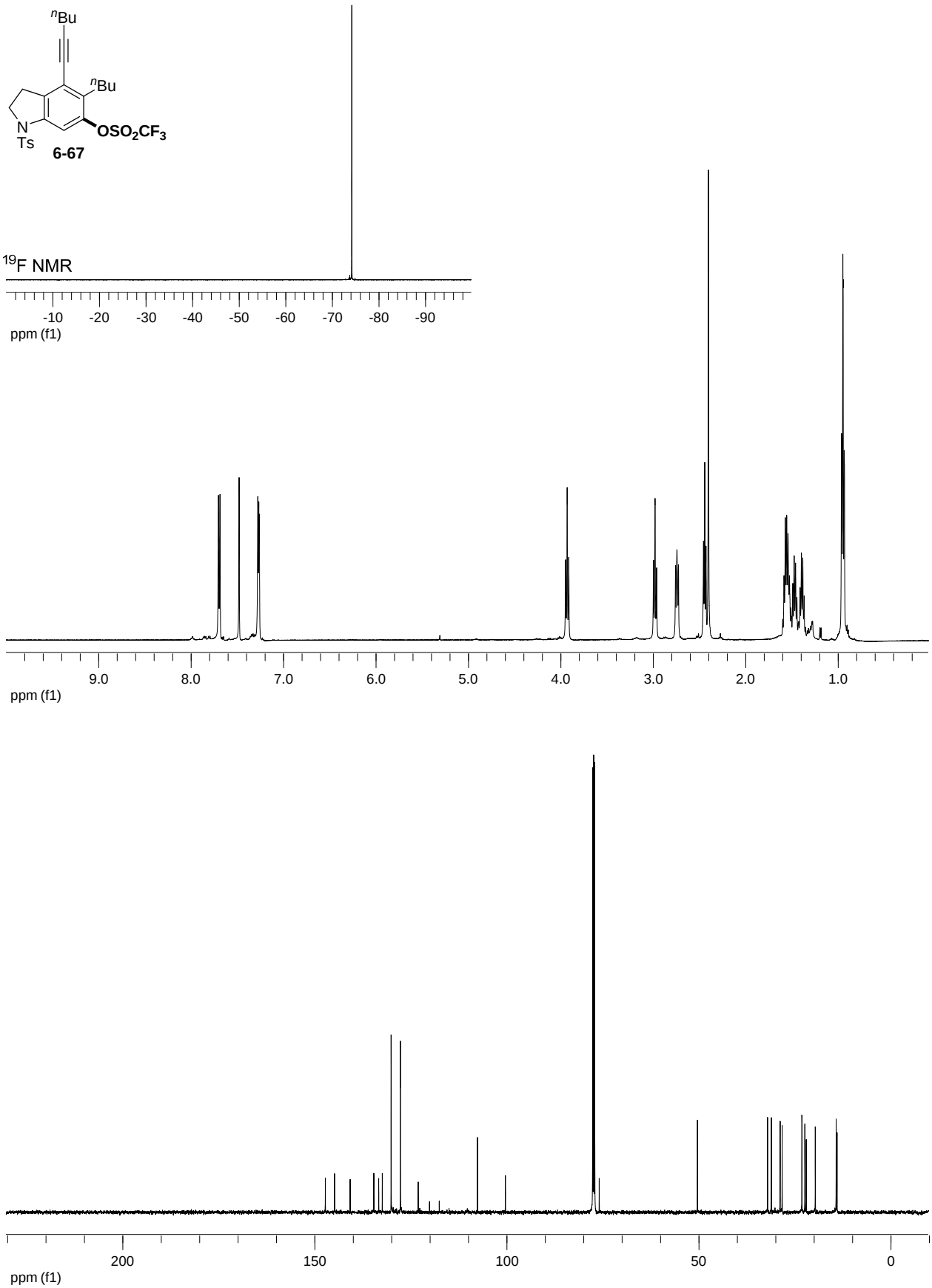

O
H
H
H
O
O
^{n}Bu
N
Ts
SCF$_3$

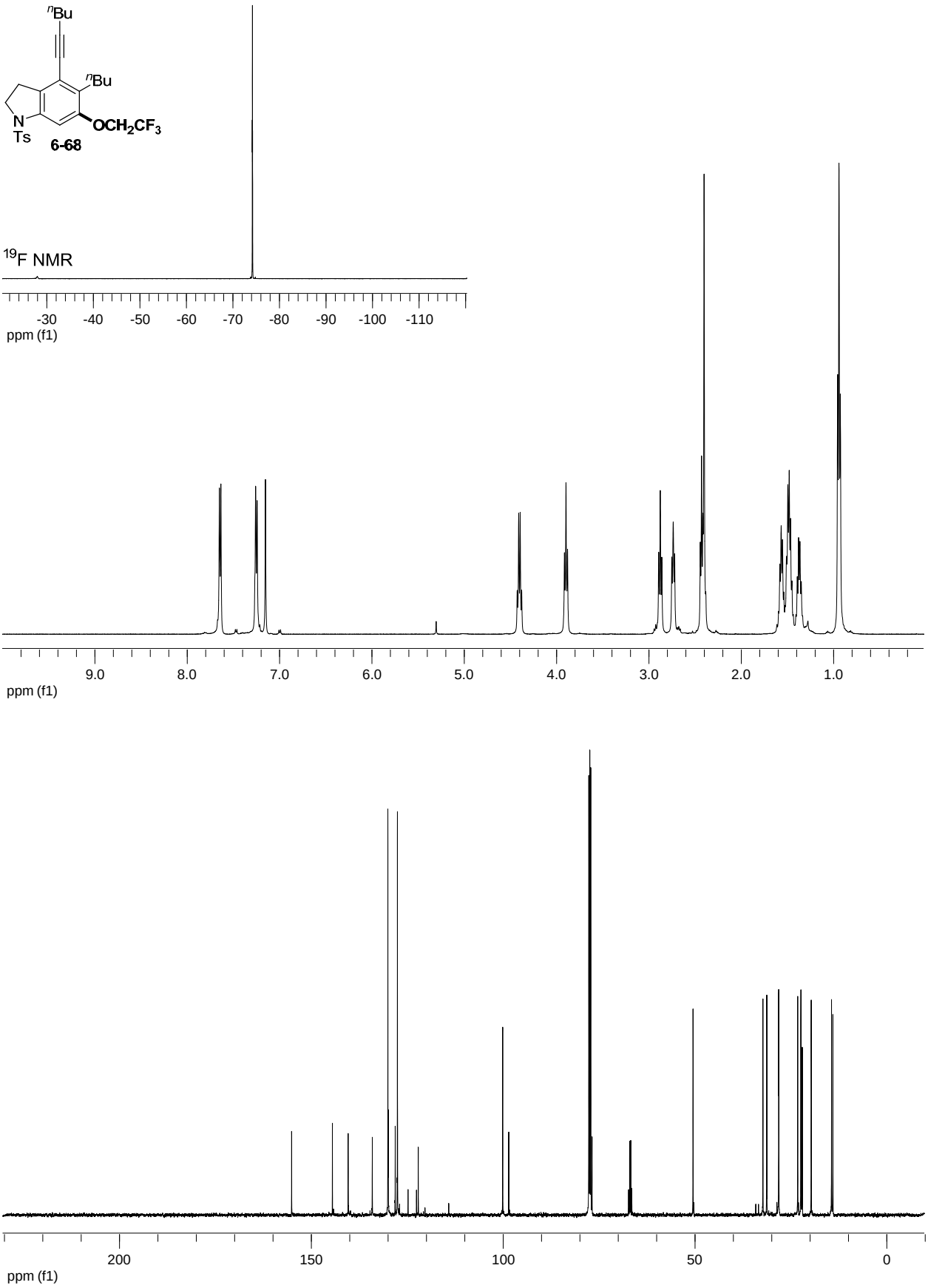
6-66

10
0
-10
-20
-30
-40
-50
-60
-70
ppm (f1)


9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)


200
150
100
50
0
ppm (f1)


nBu
nBu
N
Ts
OSO2CF3
6-67
19F NMR
-10 -20 -30 -40 -50 -60 -70 -80 -90
ppm (f1)
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0
ppm (f1)
200 150 100 50 0
ppm (f1)


nBu
nBu
N
Ts
OCH2CF3
6-68
19F NMR
-30 -40 -50 -60 -70 -80 -90 -100 -110
ppm (f1)
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0
ppm (f1)
200 150 100 50 0
ppm (f1)

Appendix B

(Full X-Ray Data for Compound 1-32, 2-50 and 4-22c)

X-Ray Structural Report of Compound 1-32

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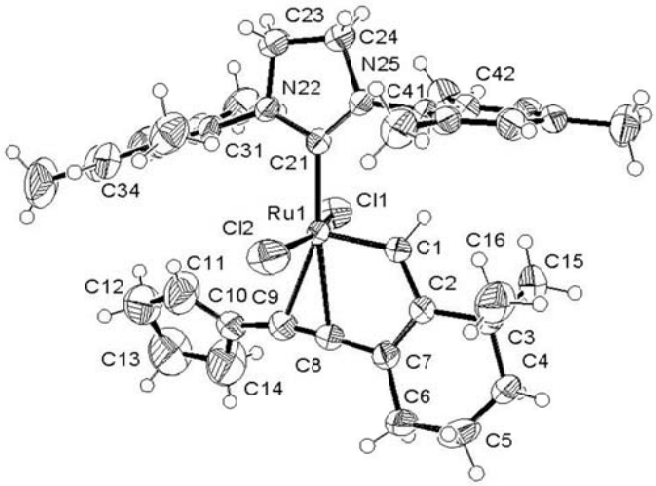


Data Collection

A dark green plate crystal with approximate dimensions 0.54 mm × 0.23 mm × 0.03 mm was selected and mounted on a glass fiber using epoxy glue. The crystal was evaluated and data collected in air at ambient temperature. The crystal evaluation and data collection were performed on a Bruker AXS diffractometer with Mo K_α (λ = 0.71073 Å) radiation and the diffractometer to crystal distance of 6.0 cm.

The initial cell constants were obtained from three series of ω scans at different starting angles. A total of 132reflections were obtained. The reflections were successfully indexed by an automated indexing routine built in the SMART program. The final cell constants were calculated from reflections from the actual data collection. The data were collected by using the multiscan data collection routine. A total of 16348 data were collected. These highly redundant datasets were corrected for Lorentz and polarization effects [1]. These were corrected for absorption using semi-empirical methods (SADABS). Of these data, 7688 unique reflections were available, with an R_{int} of 3.05%. There were 3522 reflections with $I > 2$.

Structure Solution and Refinement

The systematic absences in the diffraction data were consistent for the space group $P2_1$ and successful solution in this space group was accomplished by direct methods, which yielded all of the non-hydrogen atoms from the *E*-map. All non-hydrogen atoms were refined with anisotropic displacement coefficients. All hydrogen atoms were included in the structure factor calculation at idealized positions and were allowed to ride on the neighboring atoms with relative isotropic displacement coefficients.

The final least-squares refinement of 387 parameters against 7688 data resulted in residuals R (based on F^2 for $I \geq 2\sigma$) and wR (based on F^2 for all data) of 0.0488 and 0.0863 respectively with a final goodness of fit of 1.009. The final difference Fourier map had peaks around the ruthenium atom of up to 0.92 electrons $Å^{-3}$, which were determined to be noise.

The molecular diagrams are drawn with 30% probability ellipsoids.

References

[1] Bruker-AXS. (2000-2003) SADABS V.2.05, SAINT V.6.22, SHELXTL V.6.10 & SMART 5.622 Software Reference Manuals. Bruker-AXS, Madison, Wisconsin, USA.

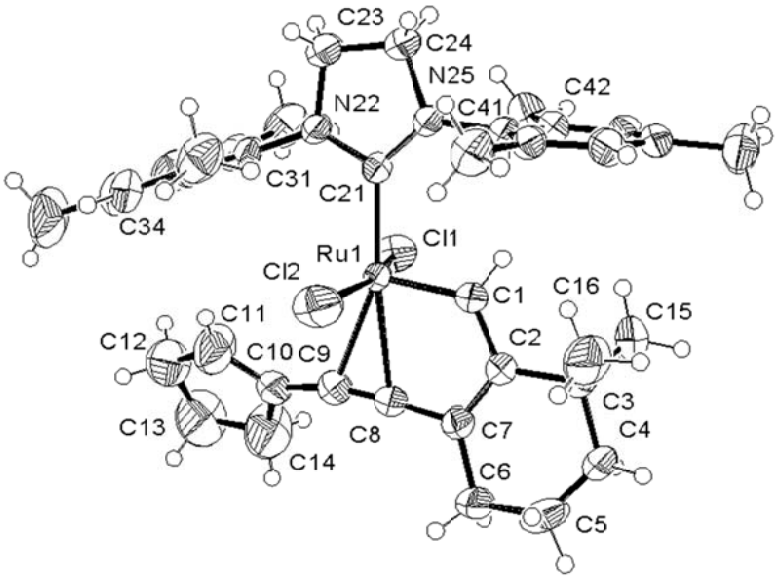


Figure 1. ORTEP drawing of **1-32**, with thermal parameters drawn at 30% probability.

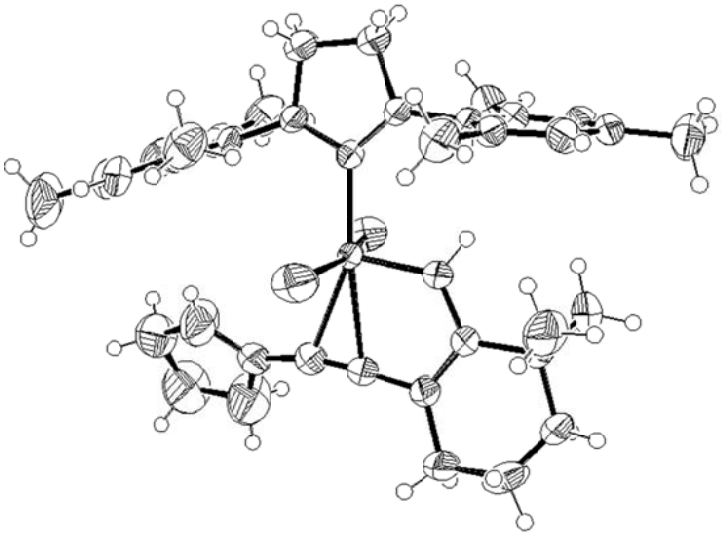


Figure 2. ORTEP drawing of **1-32**, with thermal parameters drawn at 30% probability. Atom names omitted

Table 1. Crystal data and structure refinement for **1-32**.

Crystal data		
Identification code	cdwdl6	
Empirical formula	$C_{37}H_{46}Cl_2N_2Ru$	
Formula weight	690.71	
Temperature	298(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 12.0154(13) Å	= 90°.
	b = 10.6506(11) Å	= 94.059(2)°.
	c = 13.5976(14) Å	= 90°.
Volume	1735.7(3) $Å^3$	
Z	2	
Density (calculated)	1.318 Mg/m^3	
Absorption coefficient	0.632 mm^{-1}	
F(000)	716	
Crystal size	0.54 x 0.21 x 0.03 mm	
Theta range for data collection	1.70 to 28.27°.	
Index ranges	-15<=h<=16, -13<=k<=13, -17<=l<=18	
Reflections collected	16348	
Independent reflections	7688 [R(int) = 0.0305]	
Completeness to theta = 28.27°	94.8 %	
Max. and min. transmission	0.9813 and 0.7264	

Structure solution and refinement

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	7688 / 1 / 387
Goodness-of-fit on F^2	1.005
Final R indices [I>2sigma(I)]	R1 = 0.0379, wR2 = 0.0762
R indices (all data)	R1 = 0.0475, wR2 = 0.0799
Absolute structure parameter	0.00
a, b (for weights)	0.0398, 0
Largest diff. peak and hole	0.945 and -0.305 e.Å^{-3}

$wR2 = \sqrt{\sum w(F_o^2 - F_c^2)^2 / \sum w\left(w(F_o^2)^2\right)}$; $R1 = \sum\left(|F_o| - |Fc|\right) \sum |F_o|$; $w = 1/\left[\sigma^2\left(F_o^2\right) + (aP)^2 + bP\right]$;
$P = \left[F_o^2 + 2F_c^2\right]/3$ and Goodness of Fit is: $GoF = S = \left[\sum w\left(F_o^2 - F_c^2\right)^2\right] / (n-p)^{1/2}$ with n = number of reflections and p = number of parameters refined.

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for cdwdl6. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Ru(1)	9373(1)	8180(1)	7376(1)	33(1)
Cl(1)	8303(1)	7780(1)	8712(1)	59(1)
Cl(2)	9871(1)	8825(1)	5844(1)	71(1)
C(1)	10779(2)	8138(5)	8027(2)	46(1)
C(2)	11429(3)	9215(3)	8331(2)	38(1)
C(3)	12646(3)	9088(3)	8748(3)	49(1)
C(4)	13056(4)	10360(4)	9147(4)	88(2)
C(5)	12690(5)	11430(6)	8623(7)	123(3)
C(6)	11433(4)	11596(4)	8481(4)	63(1)
C(7)	10913(3)	10321(3)	8241(3)	42(1)
C(8)	9776(3)	10268(3)	7887(3)	45(1)
C(9)	8796(3)	10309(4)	7626(3)	51(1)
C(10)	7651(3)	10634(4)	7450(3)	53(1)
C(11)	6914(4)	10187(6)	6724(5)	97(2)
C(12)	5783(4)	10719(6)	6835(5)	102(2)
C(13)	5938(5)	11648(7)	7642(5)	112(2)
C(14)	7126(5)	11525(7)	8041(5)	108(2)
C(15)	12725(3)	8185(7)	9605(3)	76(1)
C(16)	13336(3)	8628(5)	7937(4)	81(2)
C(21)	9261(3)	6335(3)	6953(2)	34(1)
N(22)	8351(2)	5918(3)	6411(2)	40(1)
C(23)	8385(3)	4563(4)	6174(3)	55(1)
C(24)	9472(3)	4166(3)	6668(3)	51(1)

N(25)	9933(2)	5342(3)	7105(2)	38(1)
C(31)	7381(3)	6619(3)	6042(3)	43(1)
C(32)	6448(3)	6652(4)	6607(3)	52(1)
C(33)	5512(3)	7283(5)	6214(4)	73(1)
C(34)	5460(4)	7856(5)	5309(4)	77(2)
C(35)	6365(4)	7743(4)	4754(3)	69(1)
C(36)	7336(3)	7099(4)	5090(3)	50(1)
C(37)	6397(4)	5956(5)	7560(3)	71(1)

Table 2 (continued)

	x	y	z	U(eq)
C(38)	4426(5)	8577(7)	4922(5)	124(3)
C(39)	8244(4)	6878(5)	4421(3)	72(1)
C(41)	10994(3)	5228(3)	7653(2)	35(1)
C(42)	11031(3)	4915(4)	8645(3)	39(1)
C(43)	12057(3)	4732(3)	9140(3)	47(1)
C(44)	13040(3)	4810(4)	8660(3)	46(1)
C(45)	12974(3)	5139(4)	7682(3)	49(1)
C(46)	11969(3)	5355(3)	7153(3)	40(1)
C(47)	9977(3)	4764(4)	9179(3)	60(1)
C(48)	14154(4)	4621(5)	9248(4)	82(2)
C(49)	11929(4)	5752(4)	6099(3)	59(1)

Table 3a. Bond lengths [Å] for cdwdl11.

Ru(1)-C(1)	1.851(3)	N(22)-C(31)	1.444(4)
Ru(1)-C(21)	2.049(3)	N(22)-C(23)	1.480(5)
Ru(1)-Cl(2)	2.3128(10)	C(23)-C(24)	1.488(5)
Ru(1)-Cl(1)	2.3378(9)	C(24)-N(25)	1.478(4)
Ru(1)-C(8)	2.370(4)	N(25)-C(41)	1.435(4)
Ru(1)-C(9)	2.402(4)	C(31)-C(36)	1.389(5)
C(1)-C(2)	1.433(6)	C(31)-C(32)	1.403(5)
C(2)-C(7)	1.333(5)	C(32)-C(33)	1.385(6)
C(2)-C(3)	1.536(5)	C(32)-C(37)	1.498(6)
C(3)-C(16)	1.507(6)	C(33)-C(34)	1.371(7)
C(3)-C(15)	1.508(6)	C(34)-C(35)	1.371(7)
C(3)-C(4)	1.529(6)	C(34)-C(38)	1.522(6)
C(4)-C(5)	1.398(8)	C(35)-C(36)	1.402(6)
C(5)-C(6)	1.519(7)	C(36)-C(39)	1.487(6)
C(6)-C(7)	1.520(6)	C(41)-C(42)	1.387(5)
C(7)-C(8)	1.417(5)	C(41)-C(46)	1.402(5)
C(8)-C(9)	1.206(5)	C(42)-C(43)	1.376(5)
C(9)-C(10)	1.423(5)	C(42)-C(47)	1.513(5)
C(10)-C(11)	1.364(7)	C(43)-C(44)	1.392(5)
C(10)-C(14)	1.421(7)	C(44)-C(45)	1.373(6)
C(11)-C(12)	1.490(7)	C(44)-C(48)	1.523(5)
C(12)-C(13)	1.479(9)	C(45)-C(46)	1.381(5)
C(13)-C(14)	1.497(8)	C(46)-C(49)	1.493(5)
C(21)-N(25)	1.338(4)		
C(21)-N(22)	1.350(4)		

Table 3b. Bond angles [°] for cdwdl11.

C(1)-Ru(1)-C(21)	98.67(19)	C(2)-C(7)-C(8)	115.3(3)	C(36)-C(31)-N(22)	119.4(3)
C(1)-Ru(1)-Cl(2)	98.75(11)	C(2)-C(7)-C(6)	126.0(3)	C(32)-C(31)-N(22)	118.6(3)
C(21)-Ru(1)-Cl(2)	92.75(10)	C(8)-C(7)-C(6)	118.7(3)	C(33)-C(32)-C(31)	117.3(4)
C(1)-Ru(1)-Cl(1)	99.07(11)	C(9)-C(8)-C(7)	174.9(4)	C(33)-C(32)-C(37)	119.5(4)
C(21)-Ru(1)-Cl(1)	90.85(9)	C(9)-C(8)-Ru(1)	76.8(3)	C(31)-C(32)-C(37)	123.0(4)
Cl(2)-Ru(1)-Cl(1)	161.06(4)	C(7)-C(8)-Ru(1)	108.0(2)	C(34)-C(33)-C(32)	123.1(4)
C(1)-Ru(1)-C(8)	73.87(19)	C(8)-C(9)-C(10)	166.0(4)	C(33)-C(34)-C(35)	117.8(4)
C(21)-Ru(1)-C(8)	172.00(12)	C(8)-C(9)-Ru(1)	73.9(2)	C(33)-C(34)-C(38)	121.2(5)
Cl(2)-Ru(1)-C(8)	85.68(10)	C(10)-C(9)-Ru(1)	119.4(3)	C(35)-C(34)-C(38)	121.0(5)
Cl(1)-Ru(1)-C(8)	93.17(9)	C(11)-C(10)-C(14)	110.6(4)	C(34)-C(35)-C(36)	122.6(4)
C(1)-Ru(1)-C(9)	102.60(19)	C(11)-C(10)-C(9)	127.4(4)	C(31)-C(36)-C(35)	117.3(4)
C(21)-Ru(1)-C(9)	158.56(13)	C(14)-C(10)-C(9)	122.0(4)	C(31)-C(36)-C(39)	122.0(4)
Cl(2)-Ru(1)-C(9)	86.70(10)	C(10)-C(11)-C(12)	110.1(5)	C(35)-C(36)-C(39)	120.6(4)
Cl(1)-Ru(1)-C(9)	83.22(10)	C(13)-C(12)-C(11)	105.2(5)	C(42)-C(41)-C(46)	121.6(3)
C(8)-Ru(1)-C(9)	29.28(12)	C(12)-C(13)-C(14)	106.1(5)	C(42)-C(41)-N(25)	119.5(3)
C(2)-C(1)-Ru(1)	125.4(3)	C(10)-C(14)-C(13)	107.7(5)	C(46)-C(41)-N(25)	118.8(3)
C(7)-C(2)-C(1)	116.2(3)	N(25)-C(21)-N(22)	106.3(3)	C(43)-C(42)-C(41)	118.5(3)
C(7)-C(2)-C(3)	122.5(3)	N(25)-C(21)-Ru(1)	133.4(2)	C(43)-C(42)-C(47)	120.1(4)
C(1)-C(2)-C(3)	121.4(3)	N(22)-C(21)-Ru(1)	120.2(2)	C(41)-C(42)-C(47)	121.4(4)
C(16)-C(3)-C(15)	110.5(4)	C(21)-N(22)-C(31)	128.5(3)	C(42)-C(43)-C(44)	121.5(4)
C(16)-C(3)-C(4)	111.5(4)	C(21)-N(22)-C(23)	113.9(3)	C(45)-C(44)-C(43)	118.5(4)
C(15)-C(3)-C(4)	106.8(4)	C(31)-N(22)-C(23)	117.6(3)	C(45)-C(44)-C(48)	122.1(4)
C(16)-C(3)-C(2)	108.5(3)	N(22)-C(23)-C(24)	102.5(3)	C(43)-C(44)-C(48)	119.3(4)
C(15)-C(3)-C(2)	110.4(3)	N(25)-C(24)-C(23)	103.4(3)	C(44)-C(45)-C(46)	122.4(3)
C(4)-C(3)-C(2)	109.1(3)	C(21)-N(25)-C(41)	130.7(3)	C(45)-C(46)-C(41)	117.5(3)
C(5)-C(4)-C(3)	117.3(4)	C(21)-N(25)-C(24)	113.8(3)	C(45)-C(46)-C(49)	120.9(3)
C(4)-C(5)-C(6)	115.7(6)	C(41)-N(25)-C(24)	115.5(3)	C(41)-C(46)-C(49)	121.5(3)
C(5)-C(6)-C(7)	108.3(4)	C(36)-C(31)-C(32)	121.4(3)		

Table 4. Anisotropic displacement parameters ($Å^2 x 10^3$) for cdwdl11. The anisotropic displacement factor exponent takes the form: $-2 \quad {}^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Ru(1)	32(1)	33(1)	34(1)	-3(1)	-2(1)	0(1)
Cl(1)	70(1)	60(1)	50(1)	-11(1)	22(1)	-7(1)
Cl(2)	106(1)	64(1)	44(1)	8(1)	13(1)	-20(1)
C(1)	45(2)	33(2)	57(2)	-1(3)	-12(1)	1(3)
C(2)	38(2)	36(2)	39(2)	-1(1)	-1(1)	-1(2)
C(3)	37(2)	36(2)	73(3)	-6(2)	-14(2)	-2(2)
C(4)	63(3)	45(3)	148(5)	-10(3)	-54(3)	-4(2)
C(5)	63(4)	50(4)	248(9)	-14(4)	-52(5)	-15(3)
C(6)	54(3)	35(2)	98(4)	-6(2)	-15(3)	1(2)
C(7)	43(2)	40(2)	43(2)	-4(2)	-1(2)	1(2)
C(8)	48(2)	33(2)	53(2)	-4(2)	-7(2)	3(2)
C(9)	48(2)	43(2)	61(3)	-3(2)	-5(2)	5(2)
C(10)	50(2)	42(2)	65(3)	3(2)	-4(2)	4(2)
C(11)	65(3)	97(5)	123(5)	-32(4)	-26(3)	27(3)
C(12)	48(3)	88(4)	166(6)	10(4)	-20(3)	5(3)
C(13)	69(4)	124(6)	144(6)	-14(5)	15(4)	38(4)
C(14)	86(4)	121(5)	116(5)	-32(4)	-3(4)	32(4)
C(15)	70(2)	68(2)	84(3)	5(4)	-32(2)	8(4)
C(16)	41(2)	84(4)	118(4)	-9(3)	8(2)	-3(2)
C(21)	32(2)	36(2)	33(2)	-3(1)	2(1)	-1(1)
N(22)	34(2)	37(2)	46(2)	-8(1)	-7(1)	1(1)
C(23)	49(2)	44(2)	70(3)	-14(2)	-11(2)	-1(2)
C(24)	49(2)	41(2)	60(2)	-8(2)	-7(2)	-4(2)

N(25)	34(2)	36(2)	42(2)	-6(1)	-6(1)	1(1)
C(31)	32(2)	45(2)	49(2)	-9(2)	-11(2)	0(2)
C(32)	39(2)	58(3)	57(3)	-15(2)	-4(2)	-3(2)
C(33)	35(2)	89(3)	93(4)	-29(3)	-6(2)	10(2)
C(34)	57(3)	75(4)	94(3)	-15(3)	-32(2)	15(2)
C(35)	77(3)	68(3)	58(3)	4(2)	-28(2)	-2(2)
C(36)	50(2)	54(2)	45(2)	-6(2)	-11(2)	-9(2)
C(37)	50(3)	92(4)	72(3)	-13(3)	13(2)	-16(2)

Table 4 (continued). Anisotropic displacement parameters ($Å^2 x 10^3$) for cdwdl11. The anisotropic displacement factor exponent takes the form: $-2 \quad ^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(38)	83(4)	136(7)	144(5)	-28(4)	-54(4)	49(4)
C(39)	82(3)	90(4)	44(2)	-4(2)	5(2)	-17(3)
C(41)	33(2)	30(2)	41(2)	-6(1)	-3(1)	4(1)
C(42)	41(2)	33(2)	44(2)	1(2)	-1(2)	3(2)
C(43)	59(2)	38(2)	44(2)	9(2)	-4(2)	1(2)
C(44)	39(2)	37(2)	59(2)	4(2)	-6(2)	-1(2)
C(45)	36(2)	46(2)	66(3)	5(2)	5(2)	-2(2)
C(46)	38(2)	38(2)	43(2)	-2(2)	2(2)	-1(2)
C(47)	55(2)	70(3)	57(3)	12(2)	11(2)	6(2)
C(48)	58(3)	82(4)	99(4)	16(3)	-28(3)	-8(3)
C(49)	59(3)	73(3)	46(2)	-1(2)	8(2)	-6(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for cdwdl11.

	x	y	z	U(eq)
H(1)	11089	7352	8168	55
H(4A)	12834	10441	9816	106
H(4B)	13865	10354	9182	106
H(5A)	12988	11404	7978	148
H(5B)	13003	12163	8964	148
H(6A)	11249	12180	7947	76
H(6B)	11149	11929	9078	76
H(11)	7092	9631	6232	116
H(12A)	5496	11121	6229	122
H(12B)	5267	10065	7004	122
H(13A)	5435	11473	8152	134
H(13B)	5793	12490	7394	134
H(14A)	7501	12329	8018	130
H(14B)	7157	11244	8721	130
H(15A)	12499	7364	9380	114
H(15B)	12246	8464	10097	114
H(15C)	13482	8154	9883	114
H(16A)	14078	8440	8206	121
H(16B)	13368	9268	7443	121
H(16C)	13003	7885	7647	121
H(23A)	8366	4426	5468	66
H(23B)	7769	4117	6438	66
H(24A)	9367	3542	7173	61

H(24B)	9959	3823	6196	61
H(33)	4889	7321	6582	87
H(35)	6333	8108	4132	83
H(37A)	5957	6424	7994	107
H(37B)	7139	5850	7861	107
H(37C)	6063	5147	7435	107

Table 5 (continued).

	x	y	z	U(eq)
H(38A)	3999	8072	4448	186
H(38B)	4647	9340	4616	186
H(38C)	3979	8772	5460	186
H(39A)	8951	6880	4798	108
H(39B)	8235	7531	3934	108
H(39C)	8134	6080	4101	108
H(43)	12095	4551	9811	57
H(45)	13630	5218	7363	59
H(47A)	10163	4457	9834	90
H(47B)	9488	4179	8828	90
H(47C)	9610	5562	9214	90
H(48A)	14605	4046	8904	122
H(48B)	14027	4284	9885	122
H(48C)	14533	5412	9325	122
H(49A)	12674	5896	5911	89
H(49B)	11503	6511	6014	89
H(49C)	11586	5103	5692	89

Table 6. Torsion angles [°] for cdwdl11.

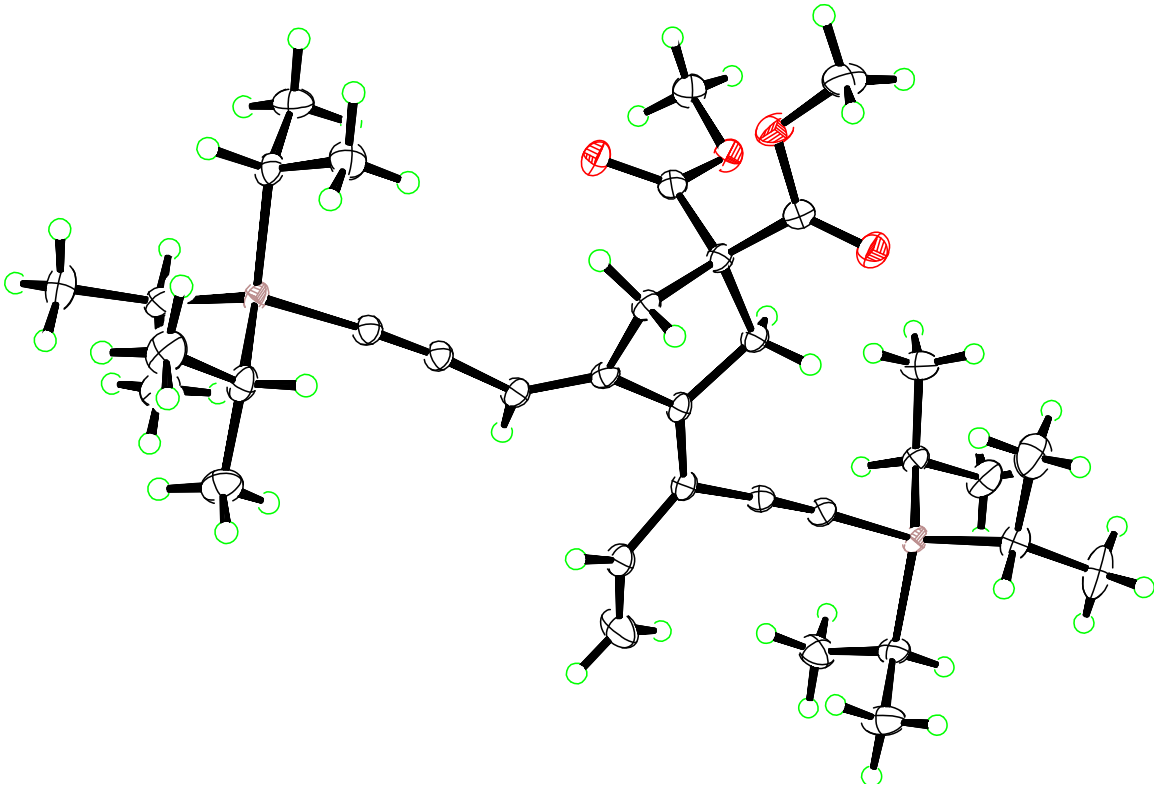
C(21)-Ru(1)-C(1)-C(2)	167.1(3)	C(6)-C(7)-C(8)-Ru(1)	171.5(3)
Cl(2)-Ru(1)-C(1)-C(2)	72.9(3)	C(1)-Ru(1)-C(8)-C(9)	-168.6(3)
Cl(1)-Ru(1)-C(1)-C(2)	-100.7(3)	C(21)-Ru(1)-C(8)-C(9)	169.9(9)
C(8)-Ru(1)-C(1)-C(2)	-10.0(3)	Cl(2)-Ru(1)-C(8)-C(9)	91.0(3)
C(9)-Ru(1)-C(1)-C(2)	-15.6(3)	Cl(1)-Ru(1)-C(8)-C(9)	-70.1(3)
Ru(1)-C(1)-C(2)-C(7)	8.6(5)	C(1)-Ru(1)-C(8)-C(7)	9.7(2)
Ru(1)-C(1)-C(2)-C(3)	-172.1(3)	C(21)-Ru(1)-C(8)-C(7)	-11.8(11)
C(7)-C(2)-C(3)-C(16)	-114.0(4)	Cl(2)-Ru(1)-C(8)-C(7)	-90.7(2)
C(1)-C(2)-C(3)-C(16)	66.8(5)	Cl(1)-Ru(1)-C(8)-C(7)	108.2(2)
C(7)-C(2)-C(3)-C(15)	124.8(4)	C(9)-Ru(1)-C(8)-C(7)	178.3(4)
C(1)-C(2)-C(3)-C(15)	-54.5(5)	C(7)-C(8)-C(9)-C(10)	2(6)
C(7)-C(2)-C(3)-C(4)	7.7(6)	Ru(1)-C(8)-C(9)-C(10)	163.5(18)
C(1)-C(2)-C(3)-C(4)	-171.5(4)	C(7)-C(8)-C(9)-Ru(1)	-162(5)
C(16)-C(3)-C(4)-C(5)	82.5(7)	C(1)-Ru(1)-C(9)-C(8)	11.2(3)
C(15)-C(3)-C(4)-C(5)	-156.7(6)	C(21)-Ru(1)-C(9)-C(8)	-176.2(3)
C(2)-C(3)-C(4)-C(5)	-37.4(7)	Table 6 (continued)	
C(3)-C(4)-C(5)-C(6)	57.2(9)	Cl(2)-Ru(1)-C(9)-C(8)	-87.0(3)
C(4)-C(5)-C(6)-C(7)	-41.2(8)	Cl(1)-Ru(1)-C(9)-C(8)	109.0(3)
C(1)-C(2)-C(7)-C(8)	2.2(5)	C(1)-Ru(1)-C(9)-C(10)	-164.3(3)
C(3)-C(2)-C(7)-C(8)	-177.1(3)	C(21)-Ru(1)-C(9)-C(10)	8.3(6)
C(1)-C(2)-C(7)-C(6)	-177.9(4)	Cl(2)-Ru(1)-C(9)-C(10)	97.5(3)
C(3)-C(2)-C(7)-C(6)	2.8(6)	Cl(1)-Ru(1)-C(9)-C(10)	-66.5(3)
C(5)-C(6)-C(7)-C(2)	12.3(7)	C(8)-Ru(1)-C(9)-C(10)	-175.5(5)
C(5)-C(6)-C(7)-C(8)	-167.7(5)	C(8)-C(9)-C(10)-C(11)	161.1(16)
C(2)-C(7)-C(8)-C(9)	152(5)	Ru(1)-C(9)-C(10)-C(11)	-37.2(7)
C(6)-C(7)-C(8)-C(9)	-27(5)	C(8)-C(9)-C(10)-C(14)	-18(2)
C(2)-C(7)-C(8)-Ru(1)	-8.6(4)	Ru(1)-C(9)-C(10)-C(14)	143.6(5)

C(14)-C(10)-C(11)-C(12)	-3.8(7)
C(9)-C(10)-C(11)-C(12)	176.9(5)
C(10)-C(11)-C(12)-C(13)	6.1(8)
C(11)-C(12)-C(13)-C(14)	-5.8(8)
C(11)-C(10)-C(14)-C(13)	-0.1(8)
C(9)-C(10)-C(14)-C(13)	179.2(5)
C(12)-C(13)-C(14)-C(10)	3.9(8)
C(1)-Ru(1)-C(21)-N(25)	2.6(3)
Cl(2)-Ru(1)-C(21)-N(25)	101.9(3)
Cl(1)-Ru(1)-C(21)-N(25)	-96.7(3)
C(8)-Ru(1)-C(21)-N(25)	23.4(12)
C(9)-Ru(1)-C(21)-N(25)	-170.1(3)
C(1)-Ru(1)-C(21)-N(22)	-178.1(3)
Cl(2)-Ru(1)-C(21)-N(22)	-78.8(3)
Cl(1)-Ru(1)-C(21)-N(22)	82.6(3)

C(8)-Ru(1)-C(21)-N(22)	-157.3(9)
C(9)-Ru(1)-C(21)-N(22)	9.2(6)
N(25)-C(21)-N(22)-C(31)	-179.4(3)
Ru(1)-C(21)-N(22)-C(31)	1.1(5)
N(25)-C(21)-N(22)-C(23)	0.2(4)
Ru(1)-C(21)-N(22)-C(23)	-179.3(3)
C(21)-N(22)-C(23)-C(24)	0.7(4)
C(31)-N(22)-C(23)-C(24)	-179.6(3)
N(22)-C(23)-C(24)-N(25)	-1.2(4)
N(22)-C(21)-N(25)-C(41)	-178.1(3)
Ru(1)-C(21)-N(25)-C(41)	1.3(5)
N(22)-C(21)-N(25)-C(24)	-1.1(4)
Ru(1)-C(21)-N(25)-C(24)	178.3(3)
C(23)-C(24)-N(25)-C(21)	1.5(4)
C(23)-C(24)-N(25)-C(41)	179.0(3)
C(21)-N(22)-C(31)-C(36)	95.0(4)
C(23)-N(22)-C(31)-C(36)	-84.7(4)
C(21)-N(22)-C(31)-C(32)	-93.5(5)
C(23)-N(22)-C(31)-C(32)	86.9(4)
C(36)-C(31)-C(32)-C(33)	-5.8(6)
N(22)-C(31)-C(32)-C(33)	-177.1(4)
C(36)-C(31)-C(32)-C(37)	169.2(4)
N(22)-C(31)-C(32)-C(37)	-2.2(6)
C(31)-C(32)-C(33)-C(34)	0.6(7)
C(37)-C(32)-C(33)-C(34)	-174.5(4)
C(32)-C(33)-C(34)-C(35)	3.0(7)
C(32)-C(33)-C(34)-C(38)	-177.9(5)
C(33)-C(34)-C(35)-C(36)	-1.7(7)
C(38)-C(34)-C(35)-C(36)	179.2(5)

C(32)-C(31)-C(36)-C(35)	7.0(6)
N(22)-C(31)-C(36)-C(35)	178.3(3)
C(32)-C(31)-C(36)-C(39)	-169.3(4)
N(22)-C(31)-C(36)-C(39)	2.0(5)
C(34)-C(35)-C(36)-C(31)	-3.2(6)
C(34)-C(35)-C(36)-C(39)	173.1(4)
C(21)-N(25)-C(41)-C(42)	89.8(5)
C(24)-N(25)-C(41)-C(42)	-87.2(4)
C(21)-N(25)-C(41)-C(46)	-94.4(4)
C(24)-N(25)-C(41)-C(46)	88.6(4)
C(46)-C(41)-C(42)-C(43)	0.2(6)
N(25)-C(41)-C(42)-C(43)	175.9(3)
C(46)-C(41)-C(42)-C(47)	-179.3(4)
N(25)-C(41)-C(42)-C(47)	-3.6(5)
C(41)-C(42)-C(43)-C(44)	-2.3(6)
C(47)-C(42)-C(43)-C(44)	177.2(4)
C(42)-C(43)-C(44)-C(45)	3.2(6)
C(42)-C(43)-C(44)-C(48)	179.0(4)
C(43)-C(44)-C(45)-C(46)	-2.0(6)
C(48)-C(44)-C(45)-C(46)	-177.7(4)
C(44)-C(45)-C(46)-C(41)	0.0(6)
C(44)-C(45)-C(46)-C(49)	178.0(4)
C(42)-C(41)-C(46)-C(45)	0.9(5)
N(25)-C(41)-C(46)-C(45)	-174.8(3)
C(42)-C(41)-C(46)-C(49)	-177.0(4)
N(25)-C(41)-C(46)-C(49)	7.3(5)

X-ray Structure Report of Compound 2-50



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Oct 5 2011

Experimental

Data Collection

A colorless parallelapiped crystal of $C_{35}H_{56}Si_2O_4$ was mounted on a mitigen polymer mount. All measurements were made on a Bruker diffractometer equiped with an APEX2 CCD area detector with graphite monochromated MoK_α radiation.

Cell constants and an orientation matrix for data collection corresponded to amonoclinic cell with dimensions:

a = 8.1624(13) Å
b = 13.199(2) Å
c = 17.708(3) Å
α = 108.260(2) Å
β = 92.017(2) Å
γ = 93.497(2) Å
V = 1805.4(5) $Å^3$

For Z = 2 and F.W. = 596.98, the calculated density is 1.098 g/cm^3. The space group was determine the to be:

P-1 (#2)

The data were collected in a stream of cold nitrogen gas to a maximum 2θ value of 55.16^o.

Data Reduction

Of the 20866 reflections which were collected, 8169 were unique (R_{int} = 0.058); equivalent reflections were merged.

The linear absorption coefficient, μ, for MoK_α radiation is 0.132 cm^{-1}. The data were corrected for Lorentz and polarization effects.

Structure Solution and Refinement

The structure was solved by direct methods[1] and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined.

[1] SHELXTL: BrukerAXS, Madison WI (2004)

The final cycle of full-matrix least-squares refinement was based on 8169 observed reflections ($I > 2.00\sigma(I)$) and 384 variable parameters and converged (largest parameter shift was 0.009 times its esd) with unweighted and weighted agreement factors of:

$$R = \Sigma \, ||Fo| - |Fc|| \, / \, \Sigma \, |Fo| = 0.0543$$

$$R_w = [(\Sigma \, w \, (|Fo| - |Fc|)^2 \, / \, \Sigma \, w \, Fo^2)]^{1/2} = 0.1297$$

The standard deviation of an observation of unit weight was 0.781. The weighting scheme was based on counting statistics. Plots of $\Sigma \, w \, (|Fo| - |Fc|)^2$ versus $|Fo|$, reflection order in data collection, $\sin \theta/\lambda$ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.521 and -0.251 $e^-/Å^3$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber[2]. The values for the mass attenuation coefficients are those of Creagh and Hubbel[3].

References

[2] Cromer, D. T. & Waber, J. T.; "International Tables for X-ray Crystallography", Vol. IV, The Kynoch Press, Birmingham, England, Table 2.2 A (1974).

[3] Creagh, D. C. & Hubbell, J.H..; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.4.3, pages 200-206 (1992).

EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula	$C_{35}H_{56}Si_2O_4$
Formula Weight	596.98
Crystal System	triclinic
Lattice Type	Primitive
Lattice Parameters	a = 8.1624(13) Å
	b = 13.199(2) Å
	c = 17.708(3) Å
	α = 108.260(2)°
	β = 92.017(2)°
	γ = 93.497(2)°
	V = 1805.4(5) Å^3
Space Group	P-1 (#2)
Z value	1
D_{calc}	1.098 g/cm^3
F_{000}	652.00
μ(MoKα)	0.132 cm^{-1}

B. Intensity Measurements

Diffractometer	Bruker APEX2 CCD
Radiation	MoKα (λ = 0.71069 Å)
	graphite monochromated
Crystal to Detector Distance	60.0 mm
Data Images	1464 exposures @ 30.0 seconds
Scan Type	ω
$2\theta_{max}$	55.16^o
No. of Reflections Measured	Total: 20866
	Unique: 8169 (R_{int}=0.0578)
Corrections	Lorentz-polarization

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SHELXS87)
Refinement	Full-matrix least-squares
Function Minimized	Σ w (|Fo| - |Fc|)^2

Least Squares Weights	$1/\sigma^2(Fo) = 4Fo^2/\sigma^2(Fo^2)$
No. Observations (I>2.00σ(I))	8169
No. Variables	384
Reflection/Parameter Ratio	21.3
Residuals: R; Rw	0.0543 ; 0.1297
Goodness of Fit Indicator	0.781
Max Shift/Error in Final Cycle	0.009
Maximum peak in Final Diff. Map	0.521 $e^-/Å^3$
Minimum peak in Final Diff. Map	-0.251 $e^-/Å^3$

Table 1 Atom Coordinates

Atom	x	y	z	Biso
Si1	0.66616(5)	0.72238(3)	0.36742(2)	0.01614(11)
Si2	1.01435(5)	0.82486(3)	-0.26063(2)	0.01615(11)
O1	0.46480(14)	0.85114(8)	-0.05381(6)	0.0246(2)
O2	0.31365(13)	0.84203(8)	0.04780(6)	0.0212(2)
O3	0.29565(15)	0.54066(9)	-0.00878(7)	0.0306(3)
O4	0.23448(15)	0.62790(9)	-0.09437(7)	0.0286(3)
C1	0.9577(2)	0.83784(15)	0.45135(10)	0.0320(4)
H1A	1.0559	0.8375	0.4827	0.048
H1B	0.8913	0.8924	0.4813	0.048
H1C	0.9866	0.8521	0.4034	0.048
C2	0.86078(19)	0.72868(13)	0.43004(9)	0.0226(3)
H2	0.8286	0.7181	0.4800	0.027
C3	0.9701(2)	0.63873(16)	0.38953(10)	0.0343(4)
H3A	0.9977	0.6440	0.3386	0.051
H3B	0.9120	0.5706	0.3824	0.051
H3C	1.0689	0.6453	0.4223	0.051
C4	0.4077(3)	0.56371(15)	0.28336(11)	0.0394(5)
H4A	0.3712	0.4892	0.2679	0.059
H4B	0.4414	0.5816	0.2374	0.059
H4C	0.3193	0.6059	0.3062	0.059
C5	0.5534(2)	0.58691(12)	0.34511(9)	0.0242(3)
H5	0.6332	0.5356	0.3206	0.029
C6	0.5046(3)	0.55954(15)	0.41948(10)	0.0401(5)
H6A	0.4136	0.5994	0.4418	0.060
H6B	0.5962	0.5777	0.4580	0.060

H6C	0.4734	0.4843	0.4053	0.060
C7	0.4000(2)	0.85290(14)	0.36366(10)	0.0300(4)
H7A	0.3195	0.7942	0.3571	0.045
H7B	0.4353	0.8526	0.3125	0.045
H7C	0.3524	0.9190	0.3890	0.045
C8	0.54762(19)	0.84173(12)	0.41529(8)	0.0185(3)
H8	0.6232	0.9051	0.4224	0.022
C9	0.4959(2)	0.84634(14)	0.49869(9)	0.0306(4)
H9A	0.4501	0.9133	0.5234	0.046
H9B	0.5901	0.8400	0.5304	0.046
H9C	0.4150	0.7886	0.4944	0.046
C10	0.72957(19)	0.73097(11)	0.27072(8)	0.0188(3)
C11	0.77646(18)	0.73139(11)	0.20699(8)	0.0174(3)
C12	0.83875(18)	0.73203(11)	0.13211(8)	0.0171(3)
C13	1.0174(2)	0.73655(13)	0.12765(9)	0.0234(3)
H13	1.0592	0.7219	0.0775	0.028
C14	1.1239(2)	0.75997(17)	0.18981(10)	0.0387(5)
H14A	1.0865	0.7751	0.2409	0.046
H14B	1.2362	0.7613	0.1824	0.046
C15	0.72914(18)	0.72203(11)	0.07011(8)	0.0164(3)
C16	0.54654(18)	0.69987(12)	0.07358(8)	0.0183(3)
H16A	0.5026	0.7565	0.1155	0.022
H16B	0.5230	0.6324	0.0836	0.022
C17	0.47119(18)	0.69516(11)	-0.00909(8)	0.0174(3)
C18	0.61590(18)	0.66524(11)	-0.06449(8)	0.0177(3)
H18A	0.6263	0.5887	-0.0823	0.021
H18B	0.6029	0.6896	-0.1105	0.021
C19	0.76104(18)	0.72468(11)	-0.01022(8)	0.0168(3)

C20	0.88445(19)	0.78397(12)	-0.02819(8)	0.0197(3)
H20	0.9594	0.8217	0.0134	0.024
C21	0.91223(19)	0.79493(12)	-0.10450(8)	0.0191(3)
C22	0.94868(19)	0.80932(12)	-0.16584(8)	0.0193(3)
C23	0.7243(2)	0.71264(13)	-0.34662(10)	0.0282(4)
H23A	0.6931	0.6978	-0.2992	0.042
H23B	0.7910	0.6581	-0.3763	0.042
H23C	0.6274	0.7137	-0.3786	0.042
C24	0.82229(19)	0.82173(12)	-0.32391(8)	0.0204(3)
H24	0.8558	0.8338	-0.3732	0.024
C25	0.7119(2)	0.91062(13)	-0.28245(10)	0.0279(4)
H25A	0.6163	0.9071	-0.3166	0.042
H25B	0.7718	0.9791	-0.2714	0.042
H25C	0.6788	0.9012	-0.2334	0.042
C26	1.2980(2)	0.70886(13)	-0.26142(10)	0.0291(4)
H26A	1.3454	0.6414	-0.2813	0.044
H26B	1.2802	0.7235	-0.2058	0.044
H26C	1.3714	0.7645	-0.2684	0.044
C27	1.1331(2)	0.70434(12)	-0.30736(9)	0.0217(3)
H27	1.0669	0.6422	-0.3028	0.026
C28	1.1580(2)	0.68176(14)	-0.39678(9)	0.0307(4)
H28A	1.2273	0.7389	-0.4042	0.046
H28B	1.0533	0.6767	-0.4248	0.046
H28C	1.2088	0.6156	-0.4171	0.046
C29	1.2653(2)	0.98553(13)	-0.16960(10)	0.0302(4)
H29A	1.3465	0.9340	-0.1819	0.045
H29B	1.2138	0.9838	-0.1221	0.045
H29C	1.3170	1.0557	-0.1615	0.045

C30	1.13486(19)	0.95843(11)	-0.23899(8)	0.0195(3)
H30	1.0553	1.0130	-0.2239	0.023
C31	1.2121(2)	0.96988(14)	-0.31408(10)	0.0319(4)
H31A	1.2615	1.0413	-0.3029	0.048
H31B	1.1285	0.9557	-0.3563	0.048
H31C	1.2947	0.9197	-0.3299	0.048
C32	0.41845(18)	0.80460(11)	-0.00949(8)	0.0180(3)
C33	0.2602(2)	0.94733(12)	0.05450(10)	0.0252(3)
H33A	0.3543	0.9981	0.0650	0.038
H33B	0.1879	0.9684	0.0974	0.038
H33C	0.2032	0.9451	0.0056	0.038
C34	0.32485(19)	0.61194(11)	-0.03544(8)	0.0191(3)
C35	0.0965(2)	0.55024(13)	-0.12746(11)	0.0330(4)
H35A	0.1364	0.4822	-0.1549	0.050
H35B	0.0313	0.5736	-0.1642	0.050
H35C	0.0304	0.5435	-0.0853	0.050

Table 2 Atomic Displacement Parameters

Atom	U11	U22	U33	U23	U13	U12
Si1	0.0217(2)	0.0175(2)	0.00963(18)	0.00461(14)	0.00232(15)	0.00223(16)
Si2	0.0212(2)	0.0175(2)	0.01088(19)	0.00564(15)	0.00345(15)	0.00227(16)
O1	0.0301(6)	0.0240(6)	0.0232(6)	0.0121(5)	0.0050(5)	0.0024(5)
O2	0.0262(6)	0.0185(5)	0.0200(5)	0.0065(4)	0.0058(4)	0.0045(4)
O3	0.0310(7)	0.0295(6)	0.0354(7)	0.0188(5)	-0.0072(5)	-0.0066(5)
O4	0.0328(7)	0.0222(6)	0.0302(6)	0.0109(5)	-0.0149(5)	-0.0066(5)
C1	0.0254(9)	0.0434(10)	0.0253(8)	0.0094(7)	-0.0042(7)	-0.0012(8)
C2	0.0232(8)	0.0334(8)	0.0134(7)	0.0095(6)	0.0019(6)	0.0082(7)
C3	0.0338(10)	0.0457(10)	0.0253(9)	0.0107(8)	0.0036(7)	0.0199(8)
C4	0.0478(12)	0.0311(9)	0.0355(10)	0.0097(8)	-0.0105(9)	-0.0145(8)
C5	0.0345(9)	0.0188(7)	0.0181(7)	0.0046(6)	0.0041(6)	-0.0003(6)
C6	0.0663(14)	0.0281(9)	0.0254(9)	0.0102(7)	0.0068(9)	-0.0130(9)
C7	0.0285(9)	0.0342(9)	0.0273(8)	0.0088(7)	-0.0017(7)	0.0093(7)
C8	0.0229(8)	0.0188(7)	0.0141(7)	0.0053(5)	0.0018(6)	0.0030(6)
C9	0.0461(11)	0.0288(8)	0.0197(8)	0.0080(6)	0.0144(7)	0.0151(8)
C10	0.0219(8)	0.0199(7)	0.0142(7)	0.0049(5)	-0.0004(6)	0.0021(6)
C11	0.0183(7)	0.0186(7)	0.0144(7)	0.0042(5)	-0.0012(5)	0.0016(5)
C12	0.0212(8)	0.0181(7)	0.0119(6)	0.0046(5)	0.0026(5)	0.0011(6)
C13	0.0234(8)	0.0334(8)	0.0156(7)	0.0107(6)	0.0037(6)	0.0024(7)
C14	0.0229(9)	0.0725(14)	0.0228(9)	0.0186(9)	0.0018(7)	-0.0001(9)
C15	0.0207(8)	0.0164(7)	0.0128(6)	0.0049(5)	0.0037(5)	0.0018(6)
C16	0.0200(8)	0.0238(7)	0.0124(6)	0.0074(5)	0.0016(5)	0.0024(6)
C17	0.0201(8)	0.0186(7)	0.0137(7)	0.0058(5)	0.0003(5)	0.0010(6)
C18	0.0220(8)	0.0194(7)	0.0115(6)	0.0043(5)	0.0014(5)	0.0022(6)
C19	0.0208(8)	0.0191(7)	0.0110(6)	0.0048(5)	0.0017(5)	0.0050(6)
C20	0.0213(8)	0.0255(7)	0.0128(7)	0.0068(6)	0.0008(6)	0.0021(6)
C21	0.0205(8)	0.0203(7)	0.0165(7)	0.0059(6)	0.0015(6)	0.0019(6)
C22	0.0206(8)	0.0208(7)	0.0169(7)	0.0063(6)	0.0021(6)	0.0034(6)
C23	0.0281(9)	0.0296(8)	0.0248(8)	0.0070(7)	-0.0018(7)	-0.0035(7)
C24	0.0245(8)	0.0245(7)	0.0128(7)	0.0069(6)	0.0012(6)	0.0007(6)

C25	0.0264(9)	0.0321(9)	0.0241(8)	0.0073(7)	-0.0042(7)	0.0068(7)
C26	0.0330(10)	0.0253(8)	0.0290(8)	0.0068(7)	0.0031(7)	0.0112(7)
C27	0.0291(9)	0.0194(7)	0.0178(7)	0.0064(6)	0.0071(6)	0.0043(6)
C28	0.0422(11)	0.0302(9)	0.0190(8)	0.0046(6)	0.0095(7)	0.0109(8)
C29	0.0363(10)	0.0238(8)	0.0280(9)	0.0065(7)	-0.0075(7)	-0.0026(7)
C30	0.0237(8)	0.0176(7)	0.0178(7)	0.0060(5)	0.0017(6)	0.0034(6)
C31	0.0422(11)	0.0274(8)	0.0269(9)	0.0110(7)	0.0058(8)	-0.0076(7)
C32	0.0197(8)	0.0197(7)	0.0134(7)	0.0037(5)	-0.0010(5)	-0.0002(6)
C33	0.0282(9)	0.0192(7)	0.0274(8)	0.0053(6)	0.0038(7)	0.0051(6)
C34	0.0213(8)	0.0178(7)	0.0174(7)	0.0043(5)	0.0005(6)	0.0032(6)
C35	0.0329(10)	0.0217(8)	0.0401(10)	0.0067(7)	-0.0175(8)	-0.0049(7)

Table 3 Bond Lengths

Atom 1	Atom 2	Distance	Atom 1	Atom 2	Distance
Si1	C10	1.8413(15)	C15	C19	1.4659(19)
Si1	C5	1.8790(16)	C15	C16	1.508(2)
Si1	C8	1.8822(15)	C16	C17	1.5492(19)
Si1	C2	1.8874(16)	C16	H16A	0.9700
Si2	C22	1.8472(15)	C16	H16B	0.9700
Si2	C24	1.8854(16)	C17	C34	1.527(2)
Si2	C30	1.8871(16)	C17	C32	1.534(2)
Si2	C27	1.8904(15)	C17	C18	1.552(2)
O1	C32	1.1963(18)	C18	C19	1.509(2)
O2	C32	1.3430(17)	C15	C19	1.4659(19)
O2	C33	1.4526(17)	C18	H18A	0.9700
O3	C34	1.1932(18)	C18	H18B	0.9700
O4	C34	1.3342(17)	C19	C20	1.346(2)
O4	C35	1.449(2)	C20	C21	1.4278(19)
C1	C2	1.531(2)	C20	H20	0.9300
C1	H1A	0.9600	C21	C22	1.204(2)
C1	H1B	0.9600	C23	C24	1.533(2)
C1	H1C	0.9600	C23	H23A	0.9600
C2	C3	1.537(2)	C23	H23B	0.9600
C2	H2	0.9800	C23	H23C	0.9600
C3	H3A	0.9600	C24	C25	1.537(2)
C3	H3B	0.9600	C24	H24	0.9800
C3	H3C	0.9600	C25	H25A	0.9600
C4	C5	1.536(2)	C25	H25B	0.9600
C4	H4A	0.9600	C25	H25C	0.9600
C4	H4B	0.9600	C26	C27	1.536(2)

C4	H4C	0.9600	C26	H26A	0.9600
C5	C6	1.530(2)	C26	H26B	0.9600
C5	H5	0.9800	C26	H26C	0.9600
C6	H6A	0.9600	C27	C28	1.540(2)
C6	H6B	0.9600	C27	H27	0.9800
C6	H6C	0.9600	C28	H28A	0.9600
C7	C8	1.529(2)	C28	H28B	0.9600
C7	H7A	0.9600	C28	H28C	0.9600
C7	H7B	0.9600	C29	C30	1.535(2)
C7	H7C	0.9600	C29	H29A	0.9600
C8	C9	1.534(2)	C29	H29B	0.9600
C8	H8	0.9800	C29	H29C	0.9600
C9	H9A	0.9600	C30	C31	1.537(2)
C9	H9B	0.9600	C30	H30	0.9800
C9	H9C	0.9600	C31	H31A	0.9600
C10	C11	1.206(2)	C31	H31B	0.9600
C11	C12	1.4391(19)	C31	H31C	0.9600
C12	C15	1.360(2)	C33	H33A	0.9600
C12	C13	1.462(2)	C33	H33B	0.9600
C13	C14	1.323(2)	C33	H33C	0.9600
C13	H13	0.9300	C35	H35A	0.9600
C14	H14A	0.9300	C35	H35B	0.9600
C14	H14B	0.9300	C35	H35C	0.9600

Table 4 Bond Angles

Atom 1	Atom 2	Atom 3	Angle	Atom 1	Atom 2	Atom 3	Angle
C10	Si1	C5	105.65(7)	C32	C17	C16	111.67(11)
C10	Si1	C8	108.08(6)	C34	C17	C18	111.96(11)
C5	Si1	C8	116.79(7)	C32	C17	C18	108.55(12)
C10	Si1	C2	106.73(7)	C16	C17	C18	103.55(11)
C5	Si1	C2	109.45(7)	C19	C18	C17	101.82(11)
C8	Si1	C2	109.62(7)	C19	C18	H18A	111.4
C22	Si2	C24	107.24(7)	C17	C18	H18A	111.4
C22	Si2	C30	108.90(7)	C19	C18	H18B	111.4
C24	Si2	C30	109.53(7)	C17	C18	H18B	111.4
C22	Si2	C27	105.13(7)	H18A	C18	H18B	109.3
C24	Si2	C27	110.57(7)	C20	C19	C15	125.07(13)
C30	Si2	C27	115.10(7)	C20	C19	C18	126.88(13)
C32	O2	C33	115.01(12)	C15	C19	C18	107.27(12)
C34	O4	C35	115.81(12)	C19	C20	C21	126.69(14)
C2	C1	H1A	109.5	C19	C20	H20	116.7
C2	C1	H1B	109.5	C21	C20	H20	116.7
H1A	C1	H1B	109.5	C22	C21	C20	174.13(16)
C2	C1	H1C	109.5	C21	C22	Si2	176.31(13)
H1A	C1	H1C	109.5	C24	C23	H23A	109.5
H1B	C1	H1C	109.5	C24	C23	H23B	109.5
C1	C2	C3	110.51(14)	H23A	C23	H23B	109.5
C1	C2	Si1	112.14(11)	C24	C23	H23C	109.5
C3	C2	Si1	111.66(11)	H23A	C23	H23C	109.5
C1	C2	H2	107.4	H23B	C23	H23C	109.5
C3	C2	H2	107.4	C23	C24	C25	109.82(13)
Si1	C2	H2	107.4	C23	C24	Si2	111.52(10)

C2	C3	H3A	109.5	C25	C24	Si2	111.82(10)
C2	C3	H3B	109.5	C23	C24	H24	107.8
H3A	C3	H3B	109.5	C25	C24	H24	107.8
C2	C3	H3C	109.5	Si2	C24	H24	107.8
H3A	C3	H3C	109.5	C24	C25	H25A	109.5
H3B	C3	H3C	109.5	C24	C25	H25B	109.5
C5	C4	H4A	109.5	H25A	C25	H25B	109.5
C5	C4	H4B	109.5	C24	C25	H25C	109.5
H4A	C4	H4B	109.5	H25A	C25	H25C	109.5
C5	C4	H4C	109.5	H25B	C25	H25C	109.5
H4A	C4	H4C	109.5	C27	C26	H26A	109.5
H4B	C4	H4C	109.5	C27	C26	H26B	109.5
C6	C5	C4	111.11(15)	H26A	C26	H26B	109.5
C6	C5	Si1	113.76(11)	C27	C26	H26C	109.5
C4	C5	Si1	115.12(11)	H26A	C26	H26C	109.5
C6	C5	H5	105.3	H26B	C26	H26C	109.5
C4	C5	H5	105.3	C26	C27	C28	110.64(14)
Si1	C5	H5	105.3	C26	C27	Si2	112.17(10)
C5	C6	H6A	109.5	C28	C27	Si2	114.60(11)
C5	C6	H6B	109.5	C26	C27	H27	106.3
H6A	C6	H6B	109.5	C28	C27	H27	106.3
C5	C6	H6C	109.5	Si2	C27	H27	106.3
H6A	C6	H6C	109.5	C27	C28	H28A	109.5
H6B	C6	H6C	109.5	C27	C28	H28B	109.5
C8	C7	H7A	109.5	H28A	C28	H28B	109.5
C8	C7	H7B	109.5	C27	C28	H28C	109.5
H7A	C7	H7B	109.5	H28A	C28	H28C	109.5
C8	C7	H7C	109.5	H28B	C28	H28C	109.5

H7A	C7	H7C	109.5	C30	C29	H29A	109.5
H7B	C7	H7C	109.5	C30	C29	H29B	109.5
C7	C8	C9	110.61(14)	H29A	C29	H29B	109.5
C7	C8	Si1	113.87(10)	C30	C29	H29C	109.5
C9	C8	Si1	112.79(10)	H29A	C29	H29C	109.5
C7	C8	H8	106.3	H29B	C29	H29C	109.5
C9	C8	H8	106.3	C29	C30	C31	110.31(14)
Si1	C8	H8	106.3	C29	C30	Si2	115.21(10)
C8	C9	H9A	109.5	C31	C30	Si2	111.32(10)
C8	C9	H9B	109.5	C29	C30	H30	106.5
H9A	C9	H9B	109.5	C31	C30	H30	106.5
C8	C9	H9C	109.5	Si2	C30	H30	106.5
H9A	C9	H9C	109.5	C30	C31	H31A	109.5
H9B	C9	H9C	109.5	C30	C31	H31B	109.5
C11	C10	Si1	176.09(13)	H31A	C31	H31B	109.5
C10	C11	C12	177.82(16)	C30	C31	H31C	109.5
C15	C12	C11	118.39(13)	H31A	C31	H31C	109.5
C15	C12	C13	124.99(13)	H31B	C31	H31C	109.5
C11	C12	C13	116.49(12)	O1	C32	O2	124.35(13)
C14	C13	C12	124.74(15)	O1	C32	C17	125.19(13)
C14	C13	H13	117.6	O2	C32	C17	110.46(12)
C12	C13	H13	117.6	O2	C33	H33A	109.5
C13	C14	H14A	120.0	O2	C33	H33B	109.5
C13	C14	H14B	120.0	H33A	C33	H33B	109.5
H14A	C14	H14B	120.0	O2	C33	H33C	109.5
C12	C15	C19	128.72(14)	H33A	C33	H33C	109.5
C12	C15	C16	123.20(12)	H33B	C33	H33C	109.5
C19	C15	C16	108.02(12)	O3	C34	O4	123.97(14)

C15	C16	C17	105.39(11)	O3	C34	C17	125.36(14)
C15	C16	H16A	110.7	O4	C34	C17	110.65(12)
C17	C16	H16A	110.7	O4	C35	H35A	109.5
C15	C16	H16B	110.7	O4	C35	H35B	109.5
C17	C16	H16B	110.7	H35A	C35	H35B	109.5
H16A	C16	H16B	108.8	O4	C35	H35C	109.5
C34	C17	C32	109.75(12)	H35A	C35	H35C	109.5
C34	C17	C16	111.21(12)	H35B	C35	H35C	109.5

Table 5. Torsion Angles

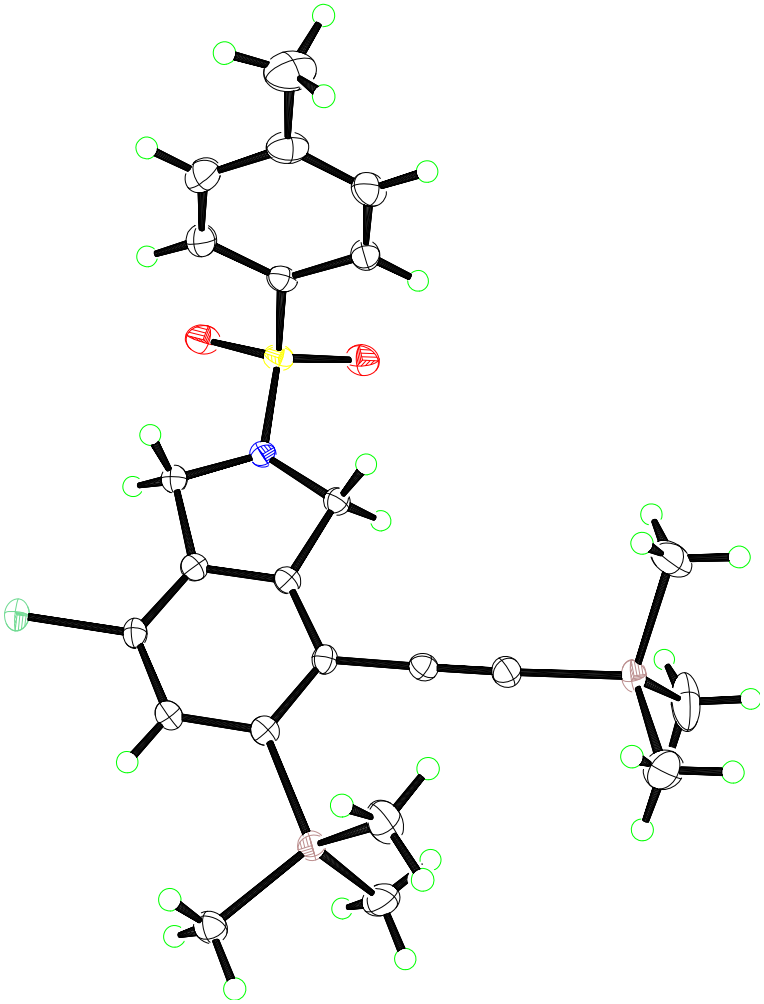
Atom 1	Atom 2	Atom 3	Atom 4	Angle
C10	Si1	C2	C1	66.87(12)
C5	Si1	C2	C1	-179.25(11)
C8	Si1	C2	C1	-49.94(13)
C10	Si1	C2	C3	-57.77(13)
C5	Si1	C2	C3	56.10(14)
C8	Si1	C2	C3	-174.59(11)
C10	Si1	C5	C6	174.34(13)
C8	Si1	C5	C6	-65.50(15)
C2	Si1	C5	C6	59.76(15)
C10	Si1	C5	C4	-55.79(14)
C8	Si1	C5	C4	64.37(14)
C2	Si1	C5	C4	-170.36(12)
C10	Si1	C8	C7	55.92(13)
C5	Si1	C8	C7	-62.94(13)
C2	Si1	C8	C7	171.88(11)
C10	Si1	C8	C9	-176.97(12)
C5	Si1	C8	C9	64.17(14)
C2	Si1	C8	C9	-61.01(14)
C5	Si1	C10	C11	-61(2)
C8	Si1	C10	C11	174(2)
C2	Si1	C10	C11	56(2)
Si1	C10	C11	C12	-54(5)
C10	C11	C12	C15	176(100)
C10	C11	C12	C13	0(4)
C15	C12	C13	C14	170.85(17)
C11	C12	C13	C14	-13.3(2)

C11	C12	C15	C19	177.31(13)
C13	C12	C15	C19	-6.9(2)
C11	C12	C15	C16	-6.0(2)
C13	C12	C15	C16	169.81(14)
C12	C15	C16	C17	179.95(13)
C19	C15	C16	C17	-2.74(15)
C15	C16	C17	C34	144.60(12)
C15	C16	C17	C32	-92.42(14)
C15	C16	C17	C18	24.19(14)
C34	C17	C18	C19	-155.78(11)
C32	C17	C18	C19	82.91(13)
C16	C17	C18	C19	-35.88(13)
C12	C15	C19	C20	-33.3(2)
C16	C15	C19	C20	149.63(14)
C12	C15	C19	C18	156.30(14)
C16	C15	C19	C18	-20.81(15)
C17	C18	C19	C20	-134.85(15)
C17	C18	C19	C15	35.36(14)
C15	C19	C20	C21	-174.91(14)
C18	C19	C20	C21	-6.3(2)
C19	C20	C21	C22	-173.7(15)
C20	C21	C22	Si2	75(3)
C24	Si2	C22	C21	133(2)
C30	Si2	C22	C21	-109(2)
C27	Si2	C22	C21	15(2)
C22	Si2	C24	C23	-64.80(12)
C30	Si2	C24	C23	177.17(10)
C27	Si2	C24	C23	49.30(13)

C22	Si2	C24	C25	58.60(12)
C30	Si2	C24	C25	-59.43(13)
C27	Si2	C24	C25	172.70(11)
C22	Si2	C27	C26	-69.54(13)
C24	Si2	C27	C26	175.03(11)
C30	Si2	C27	C26	50.27(13)
C22	Si2	C27	C28	163.22(12)
C24	Si2	C27	C28	47.79(14)
C30	Si2	C27	C28	-76.96(14)
C22	Si2	C30	C29	46.00(13)
C24	Si2	C30	C29	162.99(11)
C27	Si2	C30	C29	-71.71(13)
C22	Si2	C30	C31	172.55(11)
C24	Si2	C30	C31	-70.47(13)
C27	Si2	C30	C31	54.83(13)
C33	O2	C32	O1	-1.4(2)
C33	O2	C32	C17	177.95(12)
C34	C17	C32	O1	-112.69(17)
C16	C17	C32	O1	123.51(16)
C18	C17	C32	O1	10.0(2)
C34	C17	C32	O2	68.02(15)
C16	C17	C32	O2	-55.78(16)
C18	C17	C32	O2	-169.32(11)
C35	O4	C34	O3	-1.7(2)
C35	O4	C34	C17	176.83(13)
C32	C17	C34	O3	-142.46(15)
C16	C17	C34	O3	-18.4(2)
C18	C17	C34	O3	96.93(17)

C32	C17	C34	O4	39.04(16)
C16	C17	C34	O4	163.11(12)
C18	C17	C34	O4	-81.58(15)

X-ray Structure Report of compound 4-22c



Experimental

Data Collection

A colorless parallelapiped crystal of $C_{23}H_{30}Si_2O_2NS$ was mounted on a mitigen polymer mount. All measurements were made on a Bruker diffractometer equiped with an APEX2 CCD area detector with graphite monochromated MoK_α radiation.

Cell constants and an orientation matrix for data collection corresponded to amonoclinic cell with dimensions:

a = 11.592(2) Å
b = 11.7363(13) Å
c = 11.7880(13) Å
α = 118.7280(10) Å
β = 104.041(2) Å
γ = 100.602(2) Å
V = 1276.3(3) $Å^3$

For Z = 2 and F.W. = 476.17, the calculated density is 1.239 g/cm^3. The space group was determine the to be:

P-1 (#2)

The data were collected in a stream of cold nitrogen gas to a maximum 2θ value of 55.02

Data Reduction

Of the 14633 reflections which were collected, 5746 were unique (R_{int} = 0.047); equivalent reflections were merged.

The linear absorption coefficient, μ, for MoK_α radiation is 0.344 cm^{-1}. The data were corrected for Lorentz and polarization effects.

Structure Solution and Refinement

The structure was solved by direct methods[1] and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement was based on 5746 observed reflections ($I > 2.00\sigma(I)$) and 278 variable parameters and converged (largest parameter shift was

0.063 times its esd) with unweighted and weighted agreement factors of:

$$R = \Sigma \, ||Fo| - |Fc|| \, / \, \Sigma \, |Fo| = 0.0346$$

$$R_w = [(\Sigma \, w \, (|Fo| - |Fc|)^2 \, / \, \Sigma \, w \, Fo^2)]^{1/2} = 0.1314$$

The standard deviation of an observation of unit weight was 1.072. The weighting scheme was based on counting statistics. Plots of $\Sigma \, w \, (|Fo| - |Fc|)^2$ versus |Fo|,reflection order in data collection, sin θ/λ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.377 and -0.573 $e^-/Å^3$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber[2]. The values for the mass attenuation coefficients are those of Creagh and Hubbel[3].

References

EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula	$C_{23}H_{30}Si_2O_2NS$
Formula Weight	476.17
Crystal System	triclinic
Lattice Type	Primitive
Lattice Parameters	a = 11.592(2) Å
	b = 11.7363(13) Å
	c = 11.7880(13) Å
	α = 118.7280(10)°
	β = 104.041(2)°
	γ = 100.602(2)°
	V = 1276.3(3) $Å^3$
Space Group	P-1 (#2)
Z value	1
D_{calc}	1.239 g/cm^3
F_{000}	504.00
μ(MoKα)	0.344 cm^{-1}

B. Intensity Measurements

Diffractometer	Bruker APEX2 CCD
Radiation	MoKα (λ = 0.71069 Å)
	graphite monochromated
Crystal to Detector Distance	60.0 mm
Data Images	1464 exposures @ 30.0 seconds
Scan Type	ω
$2\theta_{max}$	55.02°
No. of Reflections Measured	Total: 14633
	Unique: 5746 (R_{int}=0.0471)
Corrections	Lorentz-polarization

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SHELXS87)
Refinement	Full-matrix least-squares
Function Minimized	Σ w (|Fo| - |Fc|)^2

Least Squares Weights	$1/\sigma^2(Fo) = 4Fo^2/\sigma^2(Fo^2)$
No. Observations (I>2.00σ(I))	5746
No. Variables	278
Reflection/Parameter Ratio	20.7
Residuals: R; Rw	0.0346 ; 0.1314
Goodness of Fit Indicator	1.072
Max Shift/Error in Final Cycle	0.063
Maximum peak in Final Diff. Map	0.377 $e^-/Å^3$
Minimum peak in Final Diff. Map	-0.573 $e^-/Å^3$

Table 6 Atom Coordinates

Atom	x	y	z	Biso
Cl1	-0.21757(3)	0.22292(3)	0.35973(3)	0.02246(12)
S1	-0.13237(3)	0.81990(3)	0.68741(4)	0.01897(12)
Si1	0.33782(4)	0.80621(4)	1.25406(4)	0.02288(13)
Si2	0.17533(4)	0.30367(4)	0.80317(4)	0.01917(12)
O1	-0.19173(10)	0.78611(11)	0.54802(11)	0.0251(2)
O2	-0.02870(10)	0.94750(10)	0.79233(11)	0.0252(2)
N1	-0.07935(11)	0.69655(12)	0.67151(12)	0.0180(2)
C1	0.23966(18)	0.89981(18)	1.33569(19)	0.0358(4)
H1A	0.2181	0.9523	1.2970	0.054
H1B	0.2865	0.9616	1.4350	0.054
H1C	0.1633	0.8342	1.3175	0.054
C2	0.48587(18)	0.9297(2)	1.28560(19)	0.0503(6)
H2A	0.5372	0.8794	1.2457	0.076
H2B	0.5323	0.9947	1.3846	0.076
H2C	0.4648	0.9790	1.2428	0.076
C3	0.3736(2)	0.6942(2)	1.31759(19)	0.0471(5)
H3A	0.2955	0.6286	1.2961	0.071
H3B	0.4204	0.7509	1.4171	0.071
H3C	0.4233	0.6454	1.2724	0.071
C4	0.24252(14)	0.69229(14)	1.06403(15)	0.0208(3)
C5	0.17186(13)	0.61240(14)	0.94291(14)	0.0175(3)
C6	0.08401(12)	0.51657(13)	0.79983(13)	0.0159(3)
C7	0.07243(13)	0.37508(14)	0.72372(14)	0.0169(3)
C8	0.14340(19)	0.32652(17)	0.95899(16)	0.0328(4)

H8A	0.2071	0.3101	1.0123	0.049
H8B	0.0611	0.2617	0.9286	0.049
H8C	0.1455	0.4195	1.0163	0.049
C9	0.34442(15)	0.39573(17)	0.8480(2)	0.0351(4)
H9A	0.3977	0.3600	0.8878	0.053
H9B	0.3670	0.4933	0.9146	0.053
H9C	0.3558	0.3814	0.7647	0.053
C10	0.13448(15)	0.11539(14)	0.67367(16)	0.0234(3)
H10A	0.1479	0.1025	0.5917	0.035
H10B	0.0469	0.0664	0.6482	0.035
H10C	0.1875	0.0800	0.7143	0.035
C11	-0.01987(13)	0.28757(14)	0.58673(14)	0.0178(3)
H11	-0.0283	0.1946	0.5346	0.021
C12	-0.09900(13)	0.33658(14)	0.52708(14)	0.0170(3)
C13	-0.08481(13)	0.47550(14)	0.60050(14)	0.0165(3)
C14	-0.15732(13)	0.55114(14)	0.55788(14)	0.0192(3)
H14A	-0.1610	0.5327	0.4673	0.023
H14B	-0.2430	0.5270	0.5554	0.023
C15	0.00410(13)	0.70944(14)	0.79755(14)	0.0182(3)
H15A	-0.0319	0.7342	0.8686	0.022
H15B	0.0885	0.7771	0.8373	0.022
C16	0.00609(12)	0.56411(13)	0.73577(14)	0.0159(3)
C17	-0.25251(13)	0.81161(14)	0.75381(14)	0.0187(3)
C18	-0.37696(15)	0.72454(16)	0.66092(16)	0.0261(3)
H18	-0.3972	0.6731	0.5648	0.031
C19	-0.47024(15)	0.71597(17)	0.71432(17)	0.0304(4)

H19	-0.5534	0.6574	0.6529	0.036
C20	-0.44190(15)	0.79332(17)	0.85801(17)	0.0279(3)
C21	-0.31708(16)	0.88003(17)	0.94793(16)	0.0268(3)
H21	-0.2970	0.9327	1.0440	0.032
C22	-0.22183(14)	0.88983(15)	0.89759(15)	0.0226(3)
H22	-0.1386	0.9479	0.9591	0.027
C23	-0.54466(18)	0.7821(2)	0.9140(2)	0.0409(4)
H23A	-0.6227	0.7119	0.8381	0.061
H23B	-0.5566	0.8697	0.9589	0.061
H23C	-0.5200	0.7574	0.9806	0.061

Table 7 Atomic Displacement Parameters

Atom	U11	U22	U33	U23	U13	U12
Cl1	0.02102(19)	0.01980(19)	0.01565(19)	0.00561(15)	0.00108(14)	0.00531(14)
S1	0.0230(2)	0.0196(2)	0.0209(2)	0.01364(16)	0.01071(16)	0.01058(15)
Si1	0.0231(2)	0.0240(2)	0.0133(2)	0.00577(18)	0.00450(17)	0.00825(17)
Si2	0.0232(2)	0.0162(2)	0.0165(2)	0.00920(17)	0.00454(17)	0.00744(16)
O1	0.0340(6)	0.0312(6)	0.0235(6)	0.0200(5)	0.0151(5)	0.0191(5)
O2	0.0268(6)	0.0189(5)	0.0317(6)	0.0150(5)	0.0119(5)	0.0077(4)
N1	0.0206(6)	0.0177(6)	0.0159(6)	0.0093(5)	0.0055(5)	0.0089(5)
C1	0.0474(10)	0.0324(9)	0.0323(9)	0.0149(8)	0.0228(8)	0.0223(8)
C2	0.0327(10)	0.0538(12)	0.0224(9)	0.0027(8)	0.0048(7)	-0.0085(9)
C3	0.0651(13)	0.0567(12)	0.0261(9)	0.0231(9)	0.0133(9)	0.0396(11)
C4	0.0227(7)	0.0192(7)	0.0195(7)	0.0102(6)	0.0076(6)	0.0072(6)
C5	0.0200(7)	0.0168(6)	0.0183(7)	0.0107(5)	0.0085(6)	0.0076(5)
C6	0.0164(6)	0.0176(6)	0.0134(6)	0.0087(5)	0.0059(5)	0.0045(5)
C7	0.0192(6)	0.0176(6)	0.0167(6)	0.0105(5)	0.0088(5)	0.0063(5)
C8	0.0546(11)	0.0263(8)	0.0210(8)	0.0155(7)	0.0131(8)	0.0160(8)
C9	0.0220(8)	0.0253(8)	0.0446(10)	0.0150(8)	0.0023(7)	0.0077(6)
C10	0.0298(8)	0.0192(7)	0.0228(7)	0.0125(6)	0.0091(6)	0.0101(6)
C11	0.0205(7)	0.0154(6)	0.0164(6)	0.0077(5)	0.0078(6)	0.0061(5)
C12	0.0165(6)	0.0173(6)	0.0128(6)	0.0065(5)	0.0047(5)	0.0035(5)
C13	0.0173(6)	0.0188(6)	0.0157(6)	0.0102(5)	0.0081(5)	0.0067(5)
C14	0.0199(7)	0.0190(6)	0.0158(6)	0.0081(6)	0.0052(5)	0.0074(5)
C15	0.0225(7)	0.0179(7)	0.0150(6)	0.0092(6)	0.0065(5)	0.0089(5)
C16	0.0176(6)	0.0159(6)	0.0155(6)	0.0090(5)	0.0079(5)	0.0060(5)
C17	0.0226(7)	0.0193(7)	0.0193(7)	0.0119(6)	0.0104(6)	0.0112(5)
C18	0.0254(8)	0.0304(8)	0.0192(7)	0.0112(6)	0.0074(6)	0.0114(6)
C19	0.0208(7)	0.0355(9)	0.0299(8)	0.0157(7)	0.0080(6)	0.0093(6)
C20	0.0307(8)	0.0371(9)	0.0325(8)	0.0249(7)	0.0191(7)	0.0195(7)
C21	0.0348(8)	0.0331(8)	0.0197(7)	0.0159(7)	0.0140(7)	0.0181(7)
C22	0.0252(7)	0.0206(7)	0.0190(7)	0.0095(6)	0.0061(6)	0.0094(6)

C23	0.0388(10)	0.0607(12)	0.0466(11)	0.0376(10)	0.0282(9)	0.0256(9)

Table 8 Bond Lengths

Atom 1	Atom 2	Distance	Atom 1	Atom 2	Distance
Cl1	C12	1.7437(14)	C8	H8C	0.9600
S1	O2	1.4327(11)	C9	H9A	0.9600
S1	O1	1.4337(11)	C9	H9B	0.9600
S1	N1	1.6220(12)	C9	H9C	0.9600
S1	C17	1.7646(14)	C10	H10A	0.9600
Si1	C1	1.8445(16)	C10	H10B	0.9600
Si1	C4	1.8446(15)	C10	H10C	0.9600
Si1	C2	1.855(2)	C11	C12	1.3917(19)
Si1	C3	1.859(2)	C11	H11	0.9300
Si2	C9	1.8595(17)	C12	C13	1.3821(19)
Si2	C10	1.8599(15)	C13	C16	1.3863(18)
Si2	C8	1.8643(16)	C13	C14	1.4984(18)
Si2	C7	1.8929(14)	C14	H14A	0.9700
N1	C14	1.4735(17)	C14	H14B	0.9700
N1	C15	1.4829(17)	C15	C16	1.5062(18)
C1	H1A	0.9600	C15	H15A	0.9700
C1	H1B	0.9600	C15	H15B	0.9700
C1	H1C	0.9600	C17	C22	1.3905(19)
C2	H2A	0.9600	C17	C18	1.393(2)
C2	H2B	0.9600	C18	C19	1.388(2)
C2	H2C	0.9600	C18	H18	0.9300
C3	H3A	0.9600	C19	C20	1.394(2)
C3	H3B	0.9600	C19	H19	0.9300
C3	H3C	0.9600	C20	C21	1.389(2)
C4	C5	1.205(2)	C20	C23	1.510(2)

C5	C6	1.4381(19)	C21	C22	1.386(2)
C6	C16	1.3989(18)	C21	H21	0.9300
C6	C7	1.4169(18)	C22	H22	0.9300
C7	C11	1.4036(19)	C23	H23A	0.9600
C8	H8A	0.9600	C23	H23B	0.9600
C8	H8B	0.9600	C23	H23C	0.9600

Table 9 Bond Angles

Atom 1	Atom 2	Atom 3	Angle	Atom 1	Atom 2	Atom 3	Angle
O2	S1	O1	121.45(7)	H9A	C9	H9C	109.5
O2	S1	N1	106.11(6)	H9B	C9	H9C	109.5
O1	S1	N1	106.09(6)	Si2	C10	H10A	109.5
O2	S1	C17	107.54(7)	Si2	C10	H10B	109.5
O1	S1	C17	107.37(7)	H10A	C10	H10B	109.5
N1	S1	C17	107.61(6)	Si2	C10	H10C	109.5
C1	Si1	C4	106.80(8)	H10A	C10	H10C	109.5
C1	Si1	C2	110.73(10)	H10B	C10	H10C	109.5
C4	Si1	C2	109.07(8)	C12	C11	C7	121.60(12)
C1	Si1	C3	111.04(9)	C12	C11	H11	119.2
C4	Si1	C3	107.85(8)	C7	C11	H11	119.2
C2	Si1	C3	111.20(11)	C13	C12	C11	120.24(13)
C9	Si2	C10	108.38(7)	C13	C12	Cl1	119.52(11)
C9	Si2	C8	112.68(9)	C11	C12	Cl1	120.24(10)
C10	Si2	C8	108.97(7)	C12	C13	C16	119.18(12)
C9	Si2	C7	108.57(7)	C12	C13	C14	129.62(13)
C10	Si2	C7	109.90(7)	C16	C13	C14	111.18(12)
C8	Si2	C7	108.33(7)	N1	C14	C13	101.03(11)
C14	N1	C15	112.54(10)	N1	C14	H14A	111.6
C14	N1	S1	119.90(9)	C13	C14	H14A	111.6
C15	N1	S1	120.13(9)	N1	C14	H14B	111.6
Si1	C1	H1A	109.5	C13	C14	H14B	111.6
Si1	C1	H1B	109.5	H14A	C14	H14B	109.4
H1A	C1	H1B	109.5	N1	C15	C16	100.81(10)
Si1	C1	H1C	109.5	N1	C15	H15A	111.6

H1A	C1	H1C	109.5	C16	C15	H15A	111.6
H1B	C1	H1C	109.5	N1	C15	H15B	111.6
Si1	C2	H2A	109.5	C16	C15	H15B	111.6
Si1	C2	H2B	109.5	H15A	C15	H15B	109.4
H2A	C2	H2B	109.5	C13	C16	C6	121.69(12)
Si1	C2	H2C	109.5	C13	C16	C15	110.64(12)
H2A	C2	H2C	109.5	C6	C16	C15	127.67(12)
H2B	C2	H2C	109.5	C22	C17	C18	120.85(13)
Si1	C3	H3A	109.5	C22	C17	S1	119.88(11)
Si1	C3	H3B	109.5	C18	C17	S1	119.26(11)
H3A	C3	H3B	109.5	C19	C18	C17	118.85(14)
Si1	C3	H3C	109.5	C19	C18	H18	120.6
H3A	C3	H3C	109.5	C17	C18	H18	120.6
H3B	C3	H3C	109.5	C18	C19	C20	121.39(15)
C5	C4	Si1	173.90(13)	C18	C19	H19	119.3
C4	C5	C6	178.07(15)	C20	C19	H19	119.3
C16	C6	C7	119.40(12)	C21	C20	C19	118.41(14)
C16	C6	C5	118.87(12)	C21	C20	C23	121.03(15)
C7	C6	C5	121.71(12)	C19	C20	C23	120.57(16)
C11	C7	C6	117.83(12)	C22	C21	C20	121.44(14)
C11	C7	Si2	120.42(10)	C22	C21	H21	119.3
C6	C7	Si2	121.74(10)	C20	C21	H21	119.3
Si2	C8	H8A	109.5	C21	C22	C17	119.06(14)
Si2	C8	H8B	109.5	C21	C22	H22	120.5
H8A	C8	H8B	109.5	C17	C22	H22	120.5
Si2	C8	H8C	109.5	C20	C23	H23A	109.5

H8A	C8	H8C	109.5	C20	C23	H23B	109.5
H8B	C8	H8C	109.5	H23A	C23	H23B	109.5
Si2	C9	H9A	109.5	C20	C23	H23C	109.5
Si2	C9	H9B	109.5	H23A	C23	H23C	109.5
H9A	C9	H9B	109.5	H23B	C23	H23C	109.5
Si2	C9	H9C	109.5	.	.	?	

Table 10. Torsion Angles

Atom 1	Atom 2	Atom 3	Atom 4	Angle	Atom 1	Atom 2	Atom 3	Atom 4	Angle
O2	S1	N1	C14	-171.71(10)	S1	N1	C14	C13	-169.40(9)
O1	S1	N1	C14	-41.28(12)	C12	C13	C14	N1	-169.99(14)
C17	S1	N1	C14	73.41(11)	C16	C13	C14	N1	11.67(14)
O2	S1	N1	C15	40.63(12)	C14	N1	C15	C16	19.25(14)
O1	S1	N1	C15	171.06(10)	S1	N1	C15	C16	169.11(9)
C17	S1	N1	C15	-74.26(12)	C12	C13	C16	C6	0.1(2)
C1	Si1	C4	C5	-57.7(12)	C14	C13	C16	C6	178.65(12)
C2	Si1	C4	C5	-177.4(12)	C12	C13	C16	C15	-178.89(12)
C3	Si1	C4	C5	61.7(12)	C14	C13	C16	C15	-0.35(15)
Si1	C4	C5	C6	21(5)	C7	C6	C16	C13	1.7(2)
C4	C5	C6	C16	78(4)	C5	C6	C16	C13	-176.82(12)
C4	C5	C6	C7	-101(4)	C7	C6	C16	C15	-179.51(12)
C16	C6	C7	C11	-1.32(19)	C5	C6	C16	C15	2.0(2)
C5	C6	C7	C11	177.12(12)	N1	C15	C16	C13	-11.05(14)
C16	C6	C7	Si2	179.61(9)	N1	C15	C16	C6	170.02(13)
C5	C6	C7	Si2	-1.94(18)	O2	S1	C17	C22	-21.72(13)
C9	Si2	C7	C11	119.53(12)	O1	S1	C17	C22	-153.96(11)
C10	Si2	C7	C11	1.14(13)	N1	S1	C17	C22	92.21(12)
C8	Si2	C7	C11	-117.81(12)	O2	S1	C17	C18	159.33(12)
C9	Si2	C7	C6	-61.43(13)	O1	S1	C17	C18	27.09(14)
C10	Si2	C7	C6	-179.82(11)	N1	S1	C17	C18	-86.74(13)
C8	Si2	C7	C6	61.23(13)	C22	C17	C18	C19	-0.6(2)
C6	C7	C11	C12	-0.8(2)	S1	C17	C18	C19	178.34(12)
Si2	C7	C11	C12	178.32(10)	C17	C18	C19	C20	0.6(2)
C7	C11	C12	C13	2.6(2)	C18	C19	C20	C21	-0.1(2)
C7	C11	C12	Cl1	-176.92(10)	C18	C19	C20	C23	-179.75(16)
C11	C12	C13	C16	-2.2(2)	C19	C20	C21	C22	-0.4(2)
Cl1	C12	C13	C16	177.28(10)	C23	C20	C21	C22	179.24(15)

C11	C12	C13	C14	179.55(13)	C20	C21	C22	C17	0.4(2)
Cl1	C12	C13	C14	-1.0(2)	C18	C17	C22	C21	0.1(2)
C15	N1	C14	C13	-19.45(14)	S1	C17	C22	C21	-178.83(11)

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