Allenes and Alkynes:
Development of Cycloaddition Reactions and Application to Natural Product Synthesis

BY

ANH LE

B.S., University of Illinois at Chicago, USA, 2015

THESIS

Submitted as partial fulfillment of the requirements
for the degree of Doctor of Philosophy in Chemistry
in the Graduate College of the
University of Illinois at Chicago, 2021

Chicago, Illinois

Defense Committee: Daesung Lee, Advisor and Chair, Chemistry
Donald Wink, Chemistry
Andy Nguyen, Chemistry
Leslie Aldrich, Chemistry
Hyun-soon Chong, Illinois Institute of Technology

This thesis is dedicated to my beloved parents and brother.

ACKNOWLEDGEMENTS

I would like to take this opportunity to thank the people whose effort and support helped me complete the work presented in this thesis.

First of all, I would like to express my earnest gratitude to my academic advisor, Professor Daesung Lee, for his numerous insightful ideas, invaluable guidance, and endless encouragement to achieve several significant goals. I appreciate his passion for teaching, and I admire the way he presents organic chemistry both during the coursework as well as in the group meetings. He showed me how to work neatly and time-efficiently, and he inspired me throughout my PhD research at UIC. I am honored to have the privilege to work under his mentorship.

I want to thank my committee members, Professor Donald Wink, Professor Andy Nguyen, Professor Leslie Aldrich of UIC, and Professor Hyun-soon Chong of IIT for their time, helpful comments and suggestions to make this thesis better.

I would like to thank my excellent professors in our department, Prof. Daesung Lee, Prof. Vladimir Gevorgyan, Prof. Justin Mohr, Prof. Tom Driver, Prof. Neal Mankad, Prof. Leslie Aldrich and Prof. Duncan Wardrop for sharing their scientific knowledge during my PhD coursework.

I also want to thank Professor Xia and his group members in Wenzhou University for their computational study in several of my research projects. I also thank Professor Donald J. Wink of UIC for solving many X-ray structures of my compounds.

I also need to thank many former and current members of the Lee's group whom I had an opportunity to work with: Dr. Sang Young Yun, Dr. Matthew J. O'Connor, Dr. Venkata Sabbasani, Dr. Rajdip Karmakar, Dr. Hyunjin Lee, Dr. Sourav Ghorai, Dr. Fa-Jie Chen, Xinyu Guan, Saswata Gupta, Siyuan Su, and Erandi Liyanage Perera. I would like to give special thanks to Rajdip and Saswata who have worked with me in several collaborative projects. It was a great pleasure to work with all of them through the

years together, which will be the most memorable time in my life and I wish them the best in their future career. I also thank Prof. Mohr and his group members for sharing their ideas during our joint group meetings.

I am thankful to the staff members of Chemistry Department, including the late Ms. Rhonda Staudohar, Ms. Margaret Shortall, Ms. Silvia Solis, Ms. Jennifer Kazin, Ms. Gloria Torres Mares, and Ms Tanya Murry for the official works, Dr. Dan McElheny for helping me with NMR techniques, Dr. Randall Puchalski and Mr. Thomas Frueh for taking care of safety issues in the lab, Mr Brian Schwandt for making and fixing numerous glassware, and other staff members for their support in the past years.

Lastly but above all, I am grateful to my parents and brother for their love, caring, blessings, and support throughout these years. I appreciate the sacrifice that my parents have made, so I can focus on my study. I would like to express my deepest gratitude to Carrera family, who open their arms for me and take care of me as I am one of their children. Finally, I want to thank all my friends for keeping me company outside the laboratory and for the memorable time we spent together. Thank you all.

AL

2021, Chicago

CONTRIBUTION OF AUTHORS

I would like to acknowledge several people who have contributed to the projects presented in this thesis. Prof. Yuanzhi Xia and his group member carried out the computational study for chapter 3. Prof. Donald Wink solved all the X-ray structures for chapter 2.

TABLE OF CONTENTS

CHAPTER PAGE

PART I: REACTIONS OF ALLENES WITH ALKYNES

TABLE OF CONTENTS (continued)

CHAPTER PAGE

TABLE OF CONTENTS (continued)

CHAPTER PAGE

LIST OF SCHEMES

LIST OF SCHEMES (continued)

SCHEME PAGE

LIST OF SCHEMES (continued)

SCHEME PAGE

LIST OF TABLES

LIST OF ABBREVIATIONS

Ac	Acetyl
Ad	Adamantyl
Ar	Aryl
Boc	*t*-Butyloxycarbonyl
Bn	Benzyl
Bu (or *n*-Bu)	*n*-Butyl
t-Bu	*tert*-Butyl
c-Hex	Cyclohexyl
Cat.	Catalyst
Cp	Cyclopentadienyl
dppf	1,1′- Bis(diphenylphosphino)ferrocene
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*′-Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DFT	Density functional theory
DHP	3,4-Dihydropyran
DIBAL-H	Diisobutylaluminum hydride
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide

LIST OF ABBREVIATIONS (continued)

dr	Diastereomeric ratio
equiv	equivalent
E	Electrophile
EI	Electron impact
ESI	Electrospray ionization
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
FG	Functional group
HDDA	Hexadehydro Diels-Alder
Hex (or *n*-Hex)	*n*-Hexyl
HRMS	High resolution mass spectrometry
Hz	Hertz
i-Pr	Isopropyl
IN	Intermediate
IR	Infrared
Kcal	Kilocalorie
LA	Lewis acid
LAH	Lithium aluminum hydride
LG	Leaving group
MCR	Multicomponent reaction
MS	Molecular sieves
Ms	Methanesulfonyl (Mesyl)
mol	mole
Nu	Nucleophile

LIST OF ABBREVIATIONS (continued)

Naph	Naphthyl
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
NIS	*N*-Iodosuccinimide
Nm	Nanometer
NMR	Nuclear magnetic resonance
nOe	Nuclear Overhauser effect
o-DCB	*ortho*-Dichlorobenzene
Ph	Phenyl
Ph(4-Cl)	4-Chlorophenyl
PhH	Benzene
PhMe	Toluene
Ph(4-OMe)	4-Methoxyphenyl
ppm	Parts per million
PMB	*p*-Methoxybenzyl
Pr also (*n*-Pr)	*n*-Propyl
rt	Room temperature
sol	Solvent
TBAF	Tetra-*n*-butylammonium fluoride
TBAT	Tetrabutylammonium difluorotriphenylsilicate
TBS	*t*-Butyldimethylsilyl
TES	Triethylsilyl
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid

LIST OF ABBREVIATIONS (continued)

THF	Tetrahydrofuran
THP	Tetrahydropyran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMS	Trimethylsilyl
TMEDA	Tetramethylethylenediamine
Ts	*p*-Toluenesulfonyl (Tosyl)
TS	Transition state
t-Oc	1,1,3,3-Tetramethylbutyl

SUMMARY

This thesis consists of two main parts, Part I and Part II. The four chapters in Part I cover various reactions of allene. The special structure containing three consecutive unsaturated carbons allows allene to participate in various cycloaddition reactions with multiple reacting counterparts, furnishing diverse products including multicyclic carbon framework. Part II describes the applications of cycloaddition reactions of allene in total synthesis of natural product selaginpulvilin A. Below is the brief outline of each chapter.

Chapter 1 provides a brief overview of the discovery, developments, and synthetic applications of allene. Advancement in allene synthetic procedures in many cases has led to enantioselective syntheses of chiral molecules. In turn, the high reactivity of allenes is then utilized in synthetic steps to rapidly increase skeletal complexity. The effect of substituents on allenes is also briefly described.

Chapter 2 describes the selectivity of competing intramolecular reactions between a tethered allenes and arynes influenced by the substituent pattern of the allene moiety. Arynes generated from tri- and tetrayne precursors in general undergo a facile Alder-ene reaction with an allylic C–H bond with trisubstituted allenes whereas that of an allenic C–H bond becomes more favorable with monosubstituted and 1,3-disubstitued allenes. Alternatively, 1,1-disubstituted terminal allene induces [2 + 2] cycloaddition over an Alder-ene reaction.

In chapter 3, a new cycloaromatization process of allenyne–alkyne is described. The reaction proceeds via forming an α,3-dehydrotoluene intermediate, which formally behaves as a diradical to react with a hydrogen donor, whereas it behaves as a zwitterion to react with a nucleophile–proton donor. The efficiency and product distribution in this reaction mainly depends on the tether structure of the α,3-dehydrotoluene intermediate and the reacting counterparts. Most notable features of the reaction are the activating role of an extra alkyne in 1,3-diyne moiety that reacts with an allenyne moiety and the opposite mode of trapping with oxygen- and nitrogen-based nucleophiles. Oxygen-based nucleophiles such as

alcohol and carboxylic acid resulted in oxygen nucleophile incorporation at the benzylic position of the α,3-dehydrotoluene intermediate, whereas nitrogen nucleophiles were incorporated on the aromatic ring.

In chapter 4, an unprecedented Diels-Alder reaction between bis-allene and nitrile is described. Nitrile is known for its role as a dienophile in Diels-Alder reaction, but the cyclization requires both high temperature and special tether to promote the reaction. However, the reactions involving in situ generated bis-allene from alleneyne as a diene component proceeded at relatively mild condition with moderate to good yield.

In the final chapter 5, the prowess of the new cycloaromatization reaction described in chapter 3 is applied to synthesis of selaginpulvilin A, an alkynyl polyphenol natural product of *selaginella* family. The core fluorene skeleton of selaginpulvillin A can be directly constructed via cycloaromatization of diyne-allenyne. Sequential arylation of fluorenone adducts follow by demethylation furnished selaginpulvilin A in 6 steps.

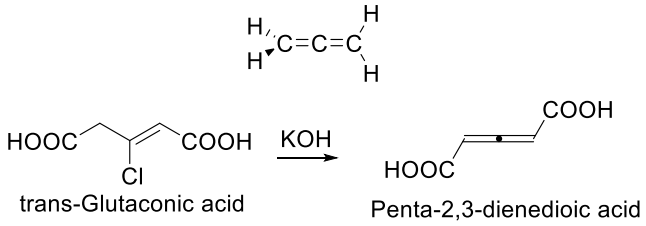
CHAPTER 1

Allenes and Their Transformations

1.1. Allene

1.1.1 First Documented Synthesis of Allene

Allene is a common name for 1,2-dienes. The central atom of the allene is *sp*-hybridized and two terminal carbons are sp^2-hybridized, therefore the molecular geometry is linear. Allenes contain two π-plane and these planes are twisted by 90° (perpendicular) from each other. For an allene molecule with four identical substituents, there are two twofold axes of rotation inclined at 45° with π planes. This molecule also has the third twofold axis of rotation passing through C=C=C bond and there are two mirror planes passing through both π planes. All these elements of symmetry indicate that the allene with four identical substituents belongs to a D_{2d} point group. Because of the symmetry, the allene molecule with four identical substituents have zero net dipole moment and for a long time allenes were considered highly unstable due to their unique structure. The structure of allene was first predict by Jacobus H. van't Hoff in 1874.[1] Not surprisingly, the first documented total synthesis of 2,3-pentadienoic by Burton and Pechmann in 1887[2] was an attempt to prove the nonexistence of the allene structure. Later in 1935,[3] an experiment conducted by Maitland and Mills proved the existence of the allene structure. When IR and Raman spectroscopy was introduced as a tool for studying molecular structures, the characteristic vibration at 1950 cm^{-1} of the allenic C=C bond suggested that Burton and Pechmann had indeed synthesized an allenic molecule.[4]

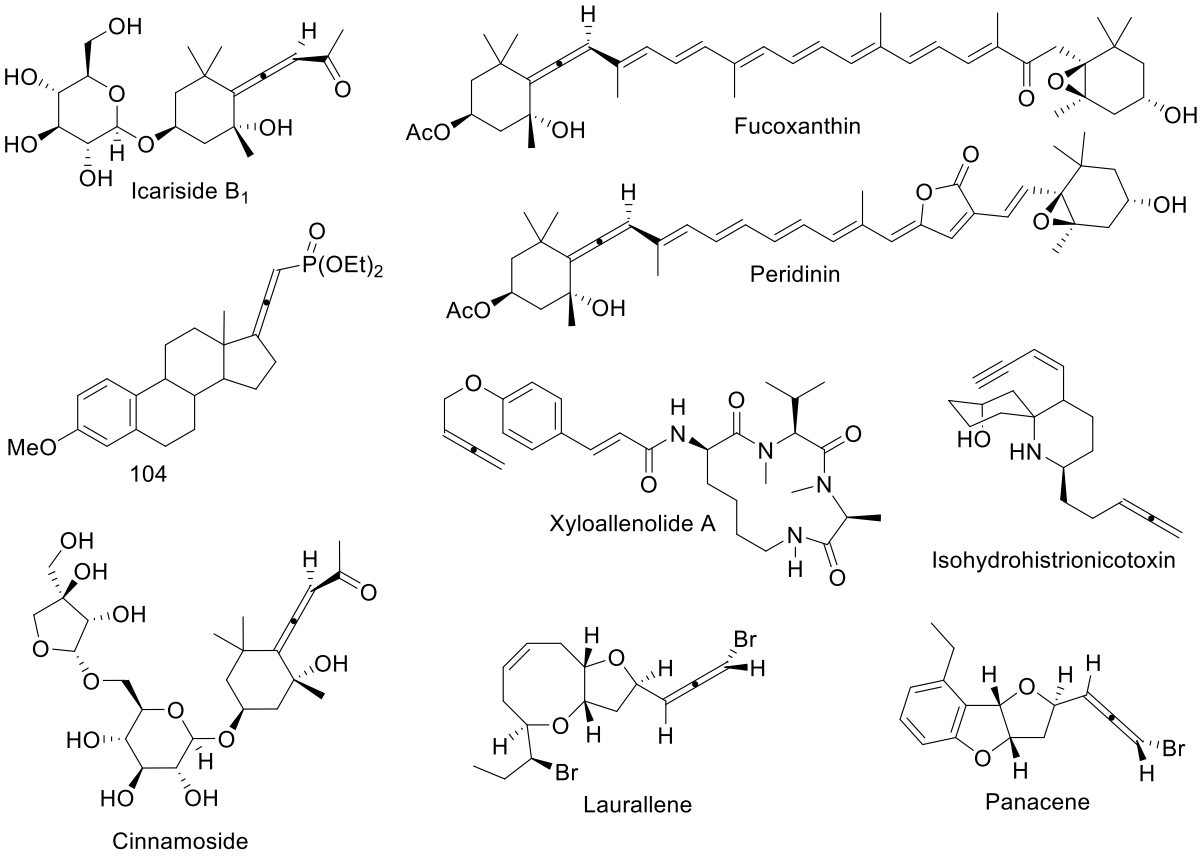


Scheme 1.1. Structure of Allene and the First Documented Synthesis of Allene

1.1.2. Allene-containing Natural Products

Because of the incorrect conception about the instability of the allene and limitation of analytical tools, the correct structural assignment of allenic natural products took place long after their isolation. For

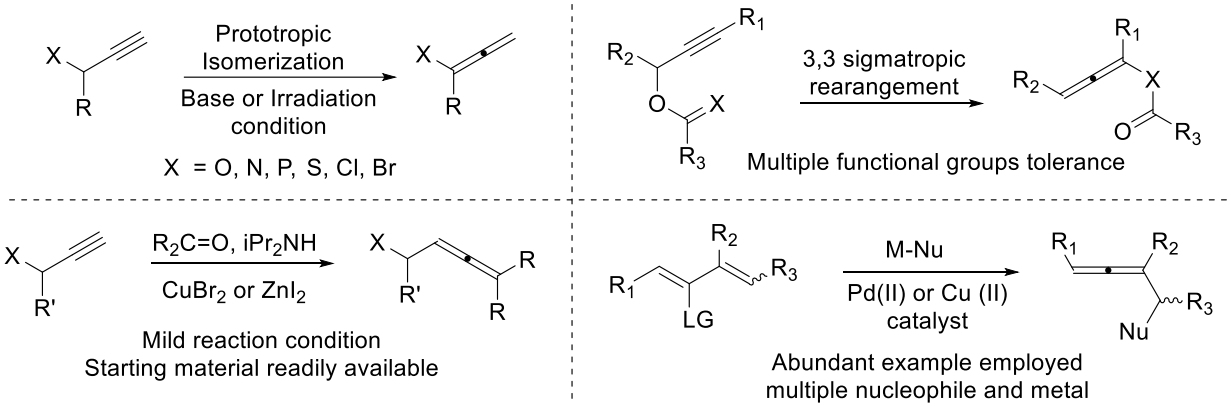
example, fucoxanthin, the most abundant of all carotenoids, was first isolated by Willstatter and Page in 1914,[5] but its correct structural assignment was realized fifty years later in 1964.[6] More surprisingly, peridinin, the carotenoid which plays an important role in photosystem of dinoflagellates, was first isolated in 1890,[7] but the full structure was not assigned until 1971.[8] Nowadays, about 150 natural products containing cumulenic structure are known. The allene moiety present in broad range of natural products, from glycosides to terpenoids and alkaloids. These increasing number of allene-containing natural products prove that allene is an important structural category for various classes of compounds. It has been described that allene-containing natural products display higher potency, increased metabolic stability, and enhanced bioactivity. For example, the allenic phosphonate 104 (**Scheme 1.2**) was found to inhibit the sterol biosynthesis of the pathogen responsible for *Pneumocystis-carinii* pneumonia (PCP), the most abundant AIDS-related disease.[9]



Scheme 1.2. Allene-containing Bioactive Compounds

1.2. Synthesis of Allenes

Allene, with their unique chemical and structure properties, becomes the integral parts of modern synthetic method of organic chemistry. The higher reactivity of allenic compounds compare to their alkyne and alkene counterparts allows the reactions to occur at mild conditions, resulting in higher selectivity. The π-systems of the allene are distributed over three-carbon atoms, which allow flexibility and opportunities to perform tandem or sequential reactions. The flexible reactivity of allenic compounds combines with their axial chirality make allene a versatile building block for synthetic method development. Allenes are typically synthesized by isomerization of alkyne and alkene,[10] Crabbe homologative allenylations[11] of terminal alkynes with aldehydes/ketones, sigmatropic rearrangement of propargyl alcohol derivatives[12] and metal-mediated S_N2' substitutions.[13]

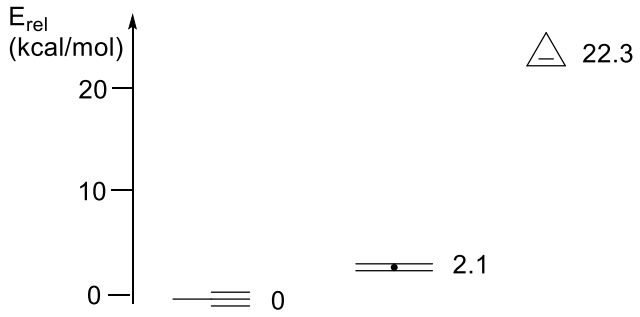


Scheme 1.3. Generation of Allenes with Various Conditions

1.2.1. Isomerization of Alkyne

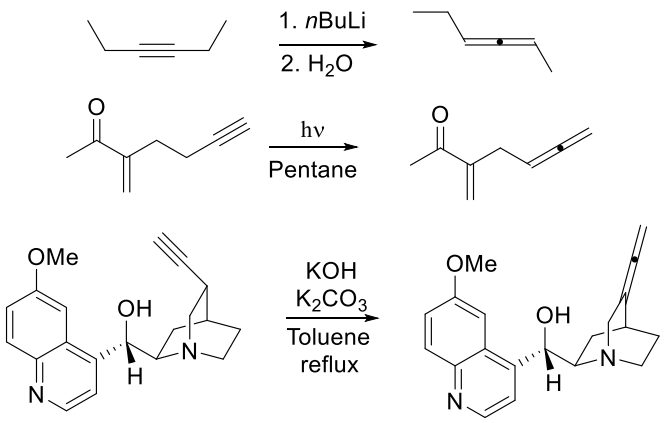
Isomerization is a chemical process associated with a change in either connectivity or spatial arrangement of atoms or functional groups in the molecule. However, the total degree of unsaturation in the molecule should be preserved during isomerization process. The simplest allene, 1,2-propadiene, can be generated from its two constitutional isomers, propyne and cyclopropene (**Scheme 1.4**). Thermodynamically, propyne is most stable, allene is 2.1 kJ higher in energy, and cyclopropene is least

stable with 22.3 kJ higher in energy. Therefore, isomerization among these isomers should be in favor of propyne. However, there are several elements that can alter the equilibrium in favor of allene. For example, the change in substituents can increase the thermodynamic stability of allene, which decreases the 2.1 kJ energy barriers between alkyne and allene. Another factor that can influence the equilibrium is a kinetically controlled environment, i.e., stoichiometric deprotonation followed by kinetic protonation. For a long time, thermodynamic stability controlled through altering substituents was the most popular method for the synthesis of allenes.



Scheme 1.4. Relative Energy of 1,2-Propadiene Isomers

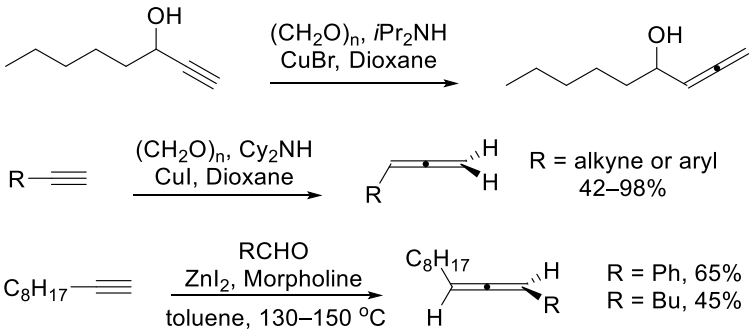
Most of the isomerization reactions require an initiator, either catalytic amount of base, heating or microwave irradiation. In some cases, a stoichiometric amount of base is required to initiate the isomerization process, for example, stoichiometric deprotonation using organolithium reagents followed by kinetic protonation. The isomerization approach is most popular to synthesize small allenic building blocks. The relatively high reactivity of allene is then utilized in the later stage of synthesis process. However, there are many situations where an allene moiety is installed at the late stage of total synthesis. In basic conditions, isomerization can take place via stoichiometric deprotonation of a propargyl proton followed by π-bond migration to generated allenyl anion, which can be kinetically protonated at an allenic carbon. As a result, alkyne can deliver 1,2-diene and the number of isomers depends on how many types of propargyl protons are available in the first deprotonation step. For the thermal isomerization, kinetic experiment data[13] suggest that at least 50% of 1,2-propadiene is formed via cyclopropene as an intermediate, contradicting the original proposal of a direct 1,3-H-shift from the precursor alkyne.[14]



Scheme 1.5. Formation of Allenes through Isomerization of Alkynes

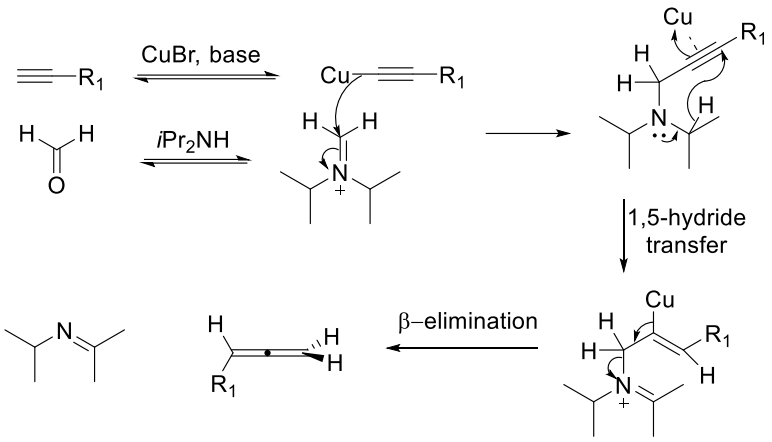
1.2.2. Crabbe Homologation

In 1979, Crabbe and coworker developed a method to synthesize allenes from terminal alkynes, using formaldehyde as a carbon source in the presence of a soft Lewis acid as a catalyst and diisopropylamine as a base (**Scheme 1.6**).[15] This method was the most convenient way to get access to allenes relying on mild reaction conditions and readily available starting materials. Later, Ma and coworker thoroughly investigated the scope of the reaction, and revealed the effect of the Lewis acid catalyst and identified the critical role of the base. The secondary amine serves not only as a Brønsted base but also as a hydride donor, generating imine as a side product.[16]



Scheme 1.6. Crabbe Homologation of Terminal Alkynes

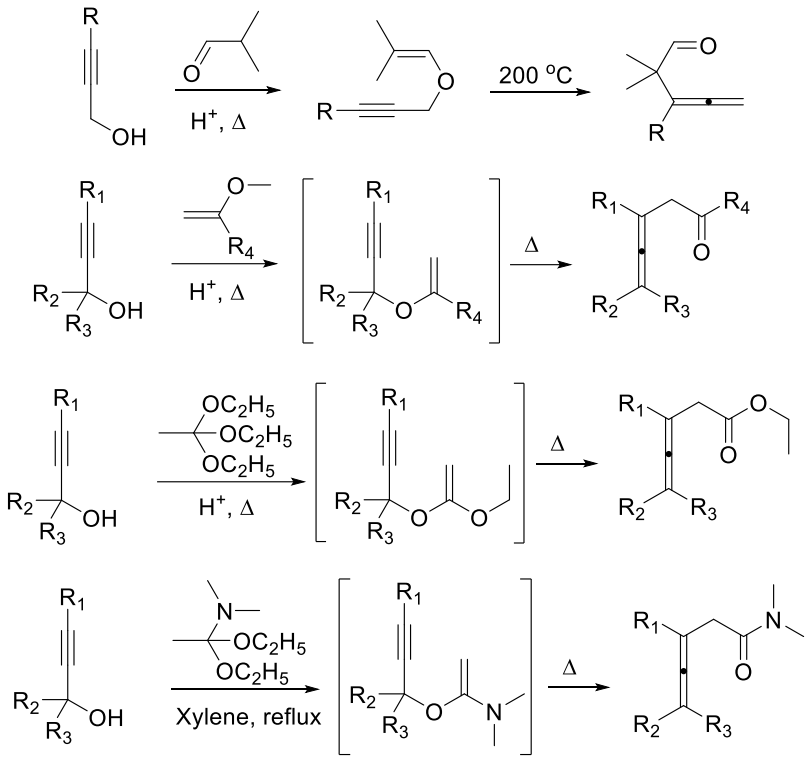
The mechanism was first invested by Searles and coworkers.[17] It is believed that the reaction is initiated by formation of an iminium ion between secondary amine and aldehyde follow by addition of alkynylmetal species into the iminium ion to produce propargyl amine as an intermediate. The alkyne moiety of the propargyl amine coordinated with a Lewis acid to delivery metal complex, which undergoes 1,5-hydride transfer followed by β-elimination to deliver allene as a product (**Scheme 1.7**). The mechanism is supported by an isotope-labelling experiment and an observed substituents effect.[17] The computational studies of this mechanism revealed that the hydride transfer step is a rate-determining step of the process.[18] Theoretical calculations also indicate a high activation barrier of the hydride transfer step in the absence of a Lewis acid catalyst.



Scheme 1.7. Proposed Mechanism of the Crabbe Homologation

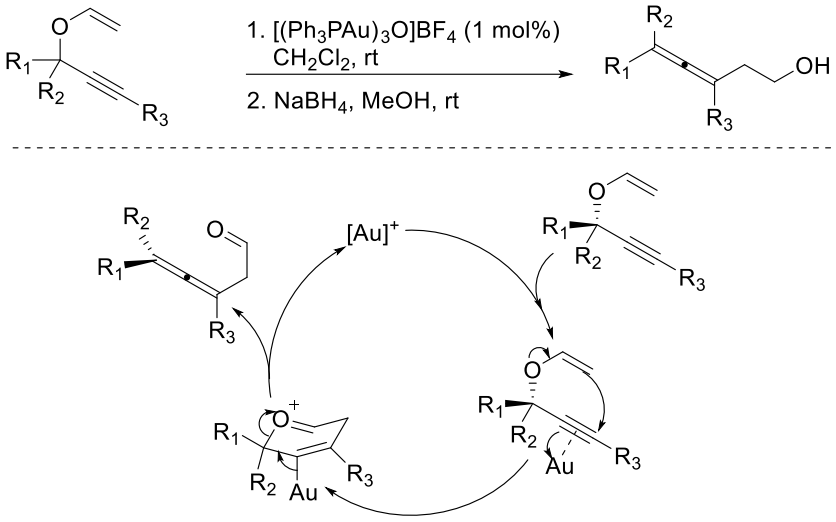
1.2.3. Allene Synthesis via Claisen Rearrangement

The [3,3] sigmatropic Claisen rearrangement of propargyl alcohols is a known protocol to gain access to functionalized allenes. The first Claisen rearrangement was discovered in 1912,[19] and in the next 50 years, there had been a common bias that alkyne cannot participated in this rearrangement due to a geometrical reason. This bias existed until early 1960s, when the first rearrangement of aryl propargyl ether was reported.[20] Since then, the thermal Claisen rearrangement was used for the generation of allenyl aldehyde,[21] ketone,[22] ester,[23] and amide[24] from their propargyl alcohol precursors (**Scheme 1.8**).



Scheme 1.8. Synthesis of Allenes through the Claisen Rearrangement

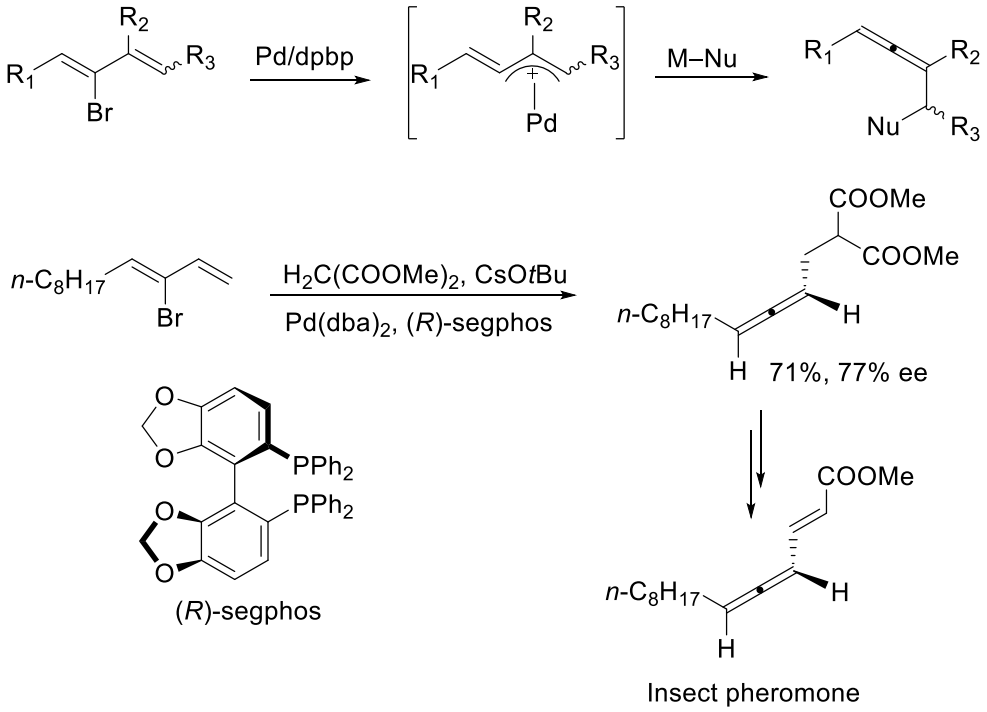
The Claisen rearrangement was conducted at high temperature, therefore the reaction conditions usually involved high boiling point solvent, or no solvent was employed. To improve the scope of the reaction, transition metal complexes were introduced to catalyze the process. In 2004, Toste and a coworker reported the Claisen rearrangement conducted at room temperature employing Au(I) complex as a catalyst.[25] It is believed that the reaction proceeds through a concerted mechanism, and it was found that the increased number of substituents has a minimum impact on the reaction rate, suggesting that steric hinderance is not an important factor. Further investigations revealed the effectiveness of Au(I) catalyst in transferring the chirality of starting materials into the chirality of allene product (**Scheme 1.9**).[25] The Claisen rearrangement is an excellent method to gain access to functionalized allenes with functional group tolerance.



Scheme 1.9. Au(I)-Catalyzed Claisen Rearrangement of Propargyl Ether

1.2.4. Allene Synthesis through Metal-mediated S_N2' Substitution

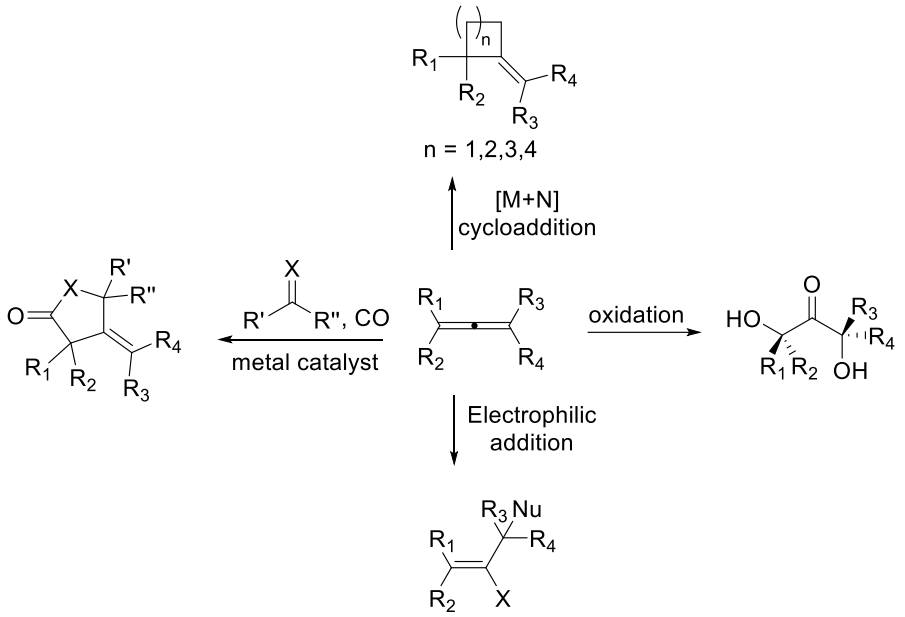
One of the traditional synthetic approaches to allenes relies on the S_N2' substitution reaction of propargylic compounds.[26] Unfortunately, the allene products formed by this method were usually contaminated with the corresponding S_N2 reaction product or 1,3-diene. These by-products often share similar physical properties such as retention factor, boiling point and melting point, thus making the purification process problematic. In the presence of a metal catalyst, allene products could be obtained with higher purity. The reaction occurred under mild conditions, and high enantioselectivity could be achieved in the presence of a chiral ligand.[27] The reaction proceeded through a π-allylmetal intermediate. Further investigation indicates that product distribution depends subtly on nucleophiles; hard nucleophiles tend to generate 1,3-diene while soft nucleophiles generate allene.[28] This method has several advantages: (1) the reactions proceed under mild conditions, (2) a wide variety of nucleophile can be used to construct functionalized allenic compounds, and (3) stereoselectivity can be achieved by using chiral ligands. The asymmetric protocol to form chiral allenes was applies to a total synthesis of methyl (*R*,*E*)-(–)-tetradeca-2,4,5-trienoate, a sex pheromone containing a chiral allene moiety found in a male dried bean beetle (**Scheme 1.10**).[29]



Scheme 1.10. Allene Synthesis by S_N2' Substitution

1.3. Allenes in Organic Synthesis

Preparation of allenes is an important task in organic chemistry. Cumulene compounds are interesting target for organic synthesis because of their synthetic challenge and their presence in natural products, and the relatively high reactivity of allenes make them a key intermediate en route to other functioning groups. The unsaturation of allene was distributed over 3 atoms, which has a unique feature for versatile synthetic manipulations. Allene can participated in [M+N] cycloaddition with a suitable reacting counterpart to generate cyclic compound with various ring sizes, and the unsaturation of allene allows its participation in oxidation reactions to generate compounds that contain a carbon chain of a high oxidation level. It is also found that allene can behave as either electrophile or nucleophile to react with both electron-rich and electron-deficient species. Moreover, the allene structure containing cumulated alkenes allows for forming unique metal complexes, which are useful intermediates for various functional group manipulations (**Scheme 1.11**).



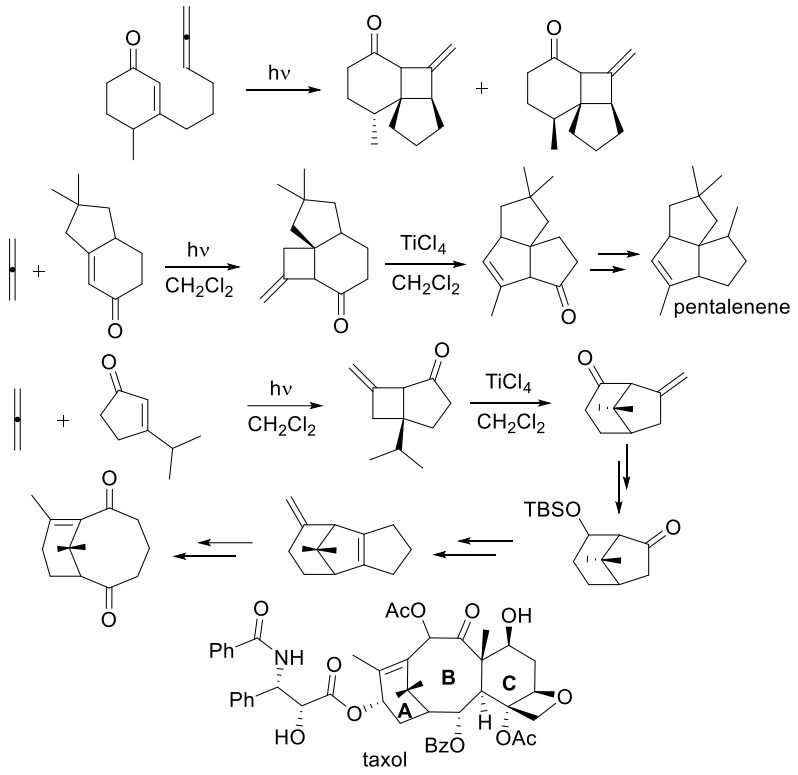
Scheme 1.11. Different Modes of Transformation of Allene

1.4. Cycloaddition Reactions

The π-system of allene is distributed over three atoms and the central atom is *sp*-hybridized, therefore allene can participate in various cycloaddition reaction ranging from [2+2] cycloaddition to [4+3] cycloaddition to generate cyclobutanes to cycloheptanes.

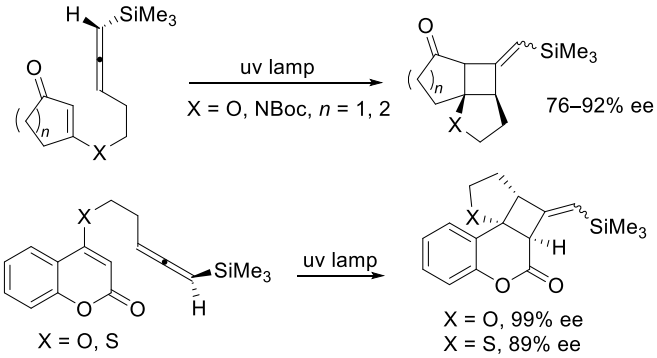
1.4.1. [2+2] Cycloaddition

In mid 1970s, , Becker and coworkers studies the intramolecular [2+2] cycloaddition reaction of allene-tethered cyclohexenone, an electron-deficient α,β-unsaturated ketone, which produced cyclobutane-containing tricyclic product.[30a, 30b] This type of bicyclic compounds containing an α-keto methylenecyclobutane can undergo a Cargrill rearrangement[30d] in the presence of acid to generate triquinane.[30c, 31] In 2004, Kaikiuchi and coworkers applied intermolecular [2+2] cycloaddition reaction between propadiene and cyclo-enone to the total synthesis of (±)-pentalenene[31] and to the construction of the AB ring core of taxol (**Scheme 1.12**).[32]



Scheme 1.12. Cycloaddition of Allene and Its Applications to Synthesis of Pentalene and Taxol

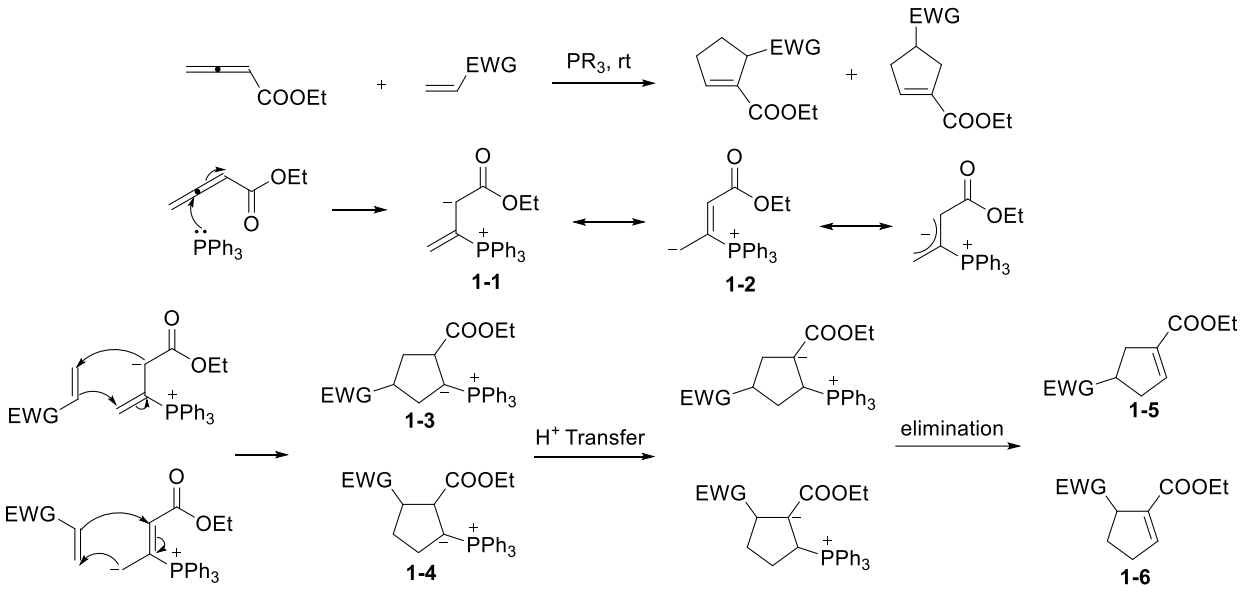
[2+2] Cycloaddition was promoted with irradiation under high pressure and temperature. It is also found that the axial chirality of allene could be efficiently translated into the central chirality in the products. Carreira and a coworker reported an enantioselective intramolecular [2+2] reaction between chiral allenyl silane and α,β-unsaturated ketone.[33] In this case, only the non-silyl substituted C=C bond participated in the [2+2] cycloaddition reaction with high enantioselectivity (**Scheme 1.13**).



Scheme 1.13. Intramolecular [2+2] Cycloaddition of Chiral Allene with Tethered Enone

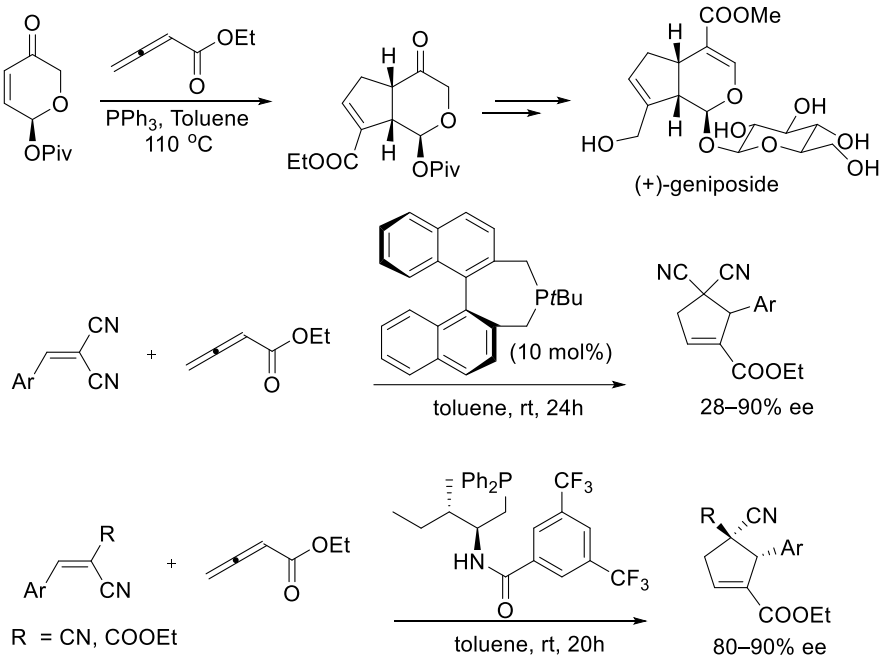
1.4.2. [3+2] Cycloaddition

In 1995, Lu and a coworker reported a phosphine-catalyzed [3+2] reaction between 2,3-butadienoate and electron-deficient alkene to afford cyclopentene derivatives.[34] The reaction was initiated by nucleophilic addition of phosphine to 2,3-butadienoate to generate zwitterion **1-1** or its resonance form **1-2**. Subsequent Michael addition occurs between the allylic carbanion and the electron-deficient alkene to afford cyclopentane anion **1-3** and **1-4**. The cyclic intermediates undergo intramolecular proton transfer followed by elimination of phosphine to afford cyclopentene derivative **1-5** and **1-6**, respectively (**Scheme 1.14**).



Scheme 1.14. [3+2] Cycloaddition of Allene with a Nucleophilic Initiator

[3+2] Cycloaddition of allene and alkene is novel and reliable method to construct cyclopentene derivatives under mild reaction condition from readily available starting materials. In 2009, Krische and a coworker successfully applied the [3+2] cycloaddition to a total synthesis of (+)-geniposide.[35] Around the same time, Marinetti[36] and Zhao[37] independently reported an enantioselective [3+2] cycloaddition employing chiral phosphine as a nucleophilic initiator (**Scheme 1.15**).

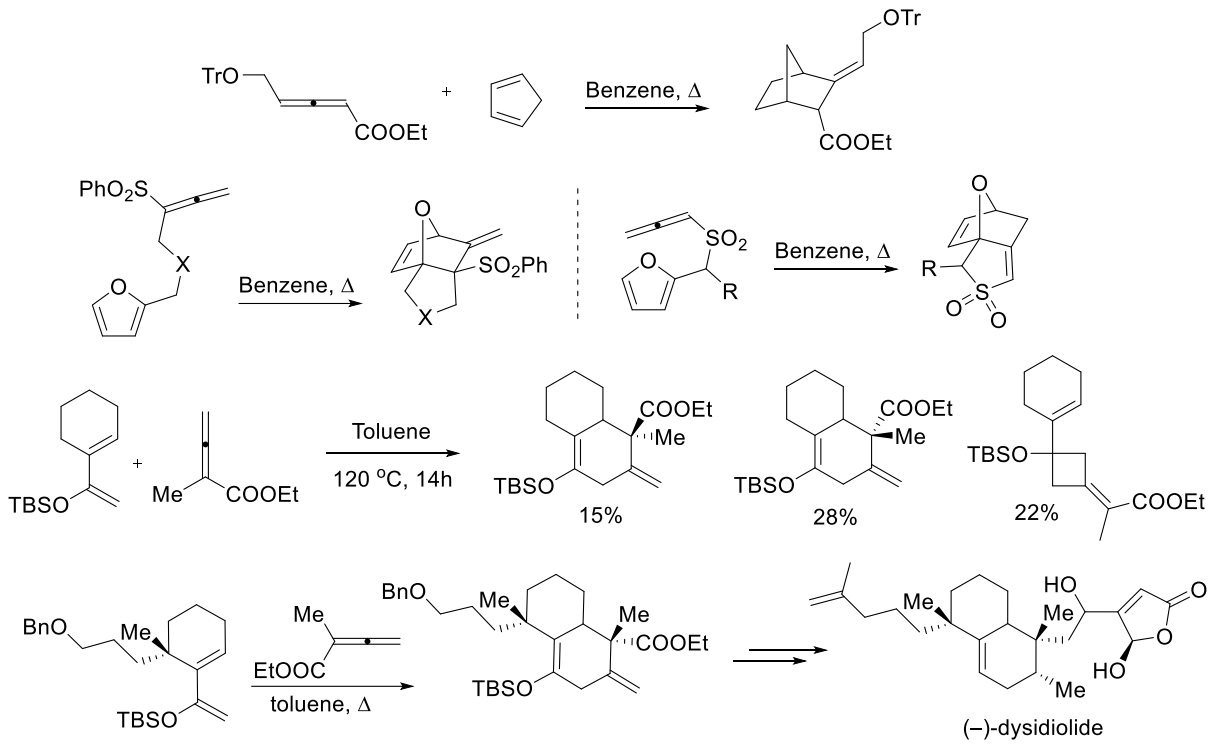


Scheme 1.15. Enantioselective [3+2] Cycloaddition between Allenyl Carboxylate and Alkene

1.4.3. [4+2] Cycloaddition

[4+2] Cycloaddition, Diels-Alder reactions, is a transformation of a diene and a dienophile to generate a cyclohexene derivative. There are many examples where allene serves as a dienophile in [4+2] cycloaddition. The main concern of the [4+2] cycloaddition is the selectivity between two C=C bonds of the allene, which is expected to depend on the substituent patterns and their electronic nature. The more electron-deficient C=C bond is more reactive as a dienophile,[38] whereas the length of the tether between diene and allene will determine which π-system will engage as a dienophile in intramolecular reactions (**Scheme 1.16**).[39]

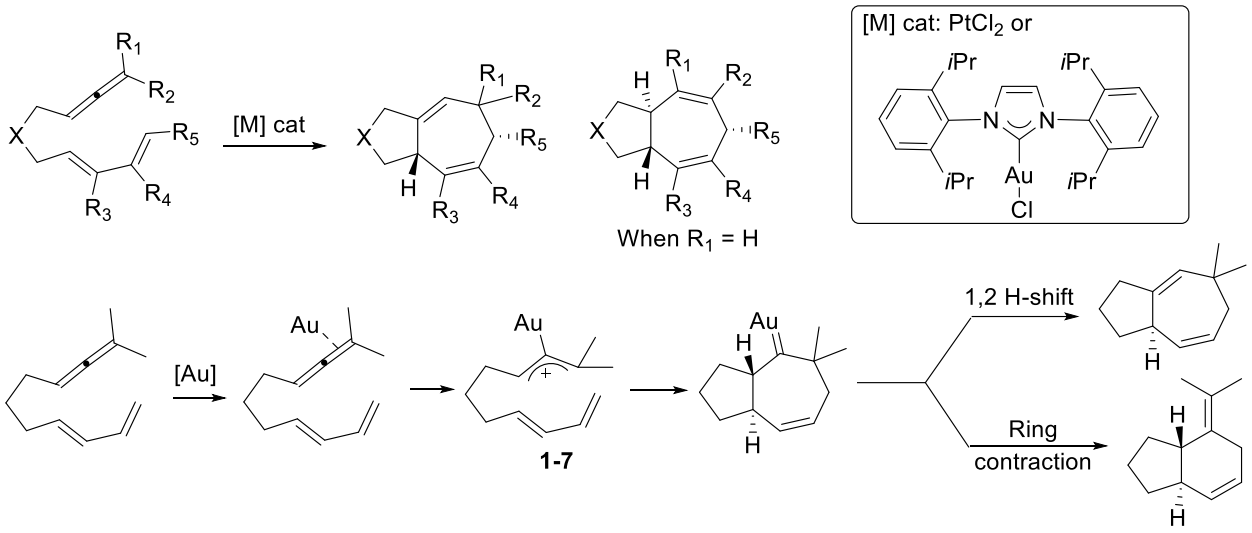
The similarity between [4+2] and [2+2] cycloadditions often led to competition between them, affording both cyclohexene and cyclobutane adducts.[40] The intermolecular [4+2] reaction between a diene and an allene ester was successfully applied to a total synthesis of natural product (−)-dysidiolide,[41a] which inhibited the growth of the A-549 human lung carcinoma and P388 murine leukemia cell lines (**Scheme 1.16**).[41b]



Scheme 1.16. Selectivity in [4+2] and [2+2] Cycloadditions

1.4.4. [4+3] Cycloaddition

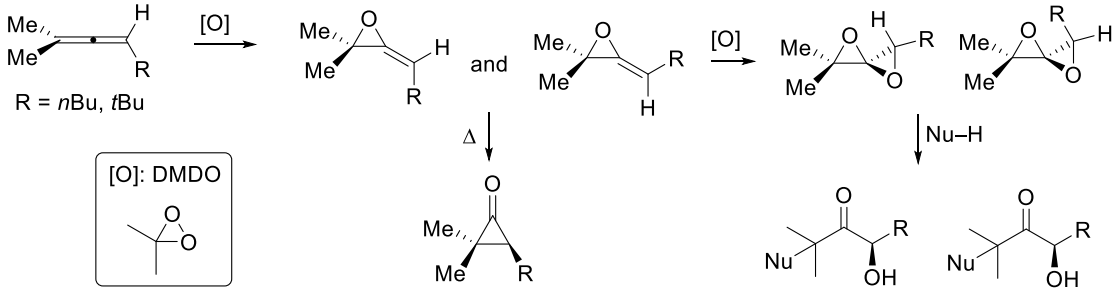
Cycloheptanoid systems are attractive synthetic targets because of their abundant existence in a wide range of biologically active natural products. Among different methods of constructing seven-membered rings, [4+3] is one of the most attractive methods because of its potential to rapidly increase the skeletal complexity.[42] In [4+3] cycloaddition reactions, 1,3-diene was employed as a four-atom component and allene was employed as a three-atom component. The reaction was initiated by activation of allene with a π-philic Lewis acid to generate allylic cation–Lewis acid adduct **1-7**, which reacts with 1,3-diene. In this reaction, the allylic cation generated from allene serves as a reacting counterpart with the 1,3-diene similar to the dienophile in Diels-Alder reaction, while the π-system is distributed over three-carbon unit (**Scheme 1.17**).[43]



Scheme 1.17. Metal-catalyzed [4+3] Cycloaddition

1.5. Oxidation Reactions

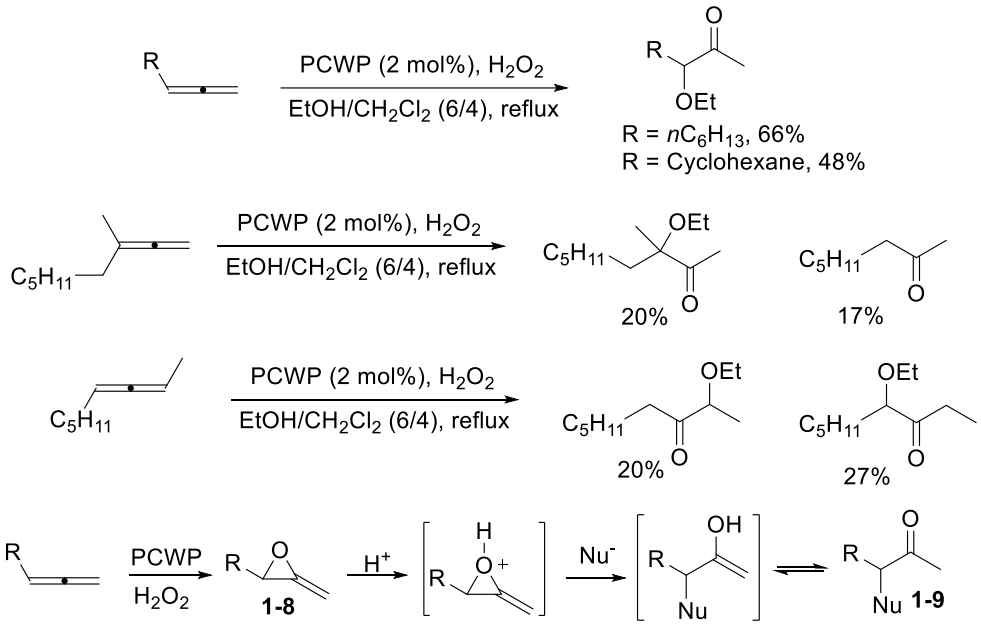
Allene can behave as either a nucleophilic species or an electrophilic species depending mostly on the reacting counterpart. In the presence of oxidizing reagents, allene usually serves as an electron-donor component. In 1991, Crandall and coworkers studied stoichiometric oxidation of allene, and they observed the tautomerization between allene monoxide and cyclopropenone.[44]



Scheme 1.18. Stoichiometry-controlled Epoxidation of Allene

Crandal also demonstrated the bis-epoxidation reaction of allene with dimethyldioxirane (DMDO) as an oxidizing reagent to afford two diastereomeric products. The first epoxidation selectively occurred at the more substituted π-bond of the allene (**Scheme 1.18**).

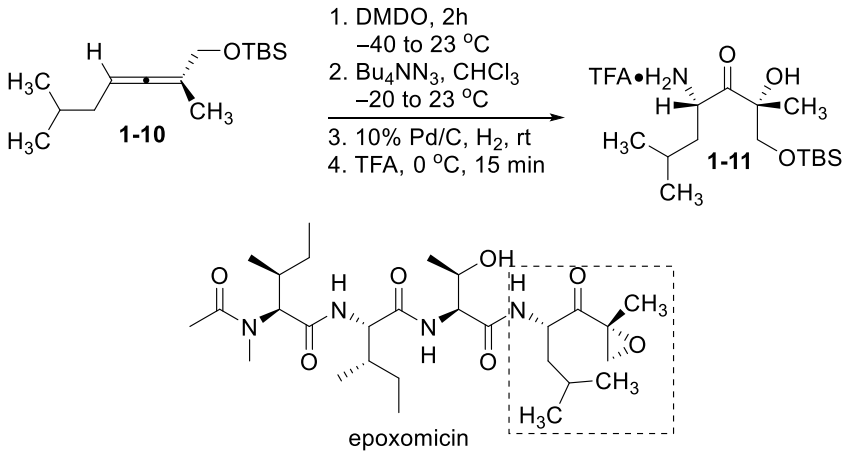
In 1994, Ishii and coworkers described the oxidation reaction of allene employing hydrogen peroxide as an oxidizing reagent in the presence of a catalytic amount of cetylpyridinium peroxotungstophosphate (PCWP), which afforded α-ethoxy ketone as a product.[45] The reaction initiated with mono-epoxidation of the allene to afford allene oxide **1-8**, which underwent protonation under acidic condition to afford an oxonium ion intermediate follow by nucleophilic attack and tautomerization of α-ethoxy enol formed α-ethoxy ketone **1-9** (**Scheme 1.19**). In this reaction, terminal allene provided the highest regioselectivity with epoxidation selectively occurring at the more substituted π-bond of the allene while 1,3-disubtituted allene afforded a mixture of both regioisomers (**Scheme 1.19**).



Scheme 1.19. Oxidation of Allenes with Hydrogen Peroxide Catalyzed by Cetylpyridinium Peroxotungstophosphate (PCWP)

The oxidation of allene has a potential to be applied to prepare compounds with multiple oxygen functional groups. The stoichiometry-controlled oxidation can form either allene oxide or spirodiepoxides.[46] Both allene oxide and spirodiepoxide can react with various nucleophiles, both in intra- and intermolecular manners, to afford ketones bearing incorporated nucleophile as an α-substituent.[47] The spirodiepoxide formation followed by stereoselective nucleophilic ring-opening was successfully applied

to a total synthesis of proteasome inhibitor epoxomicin.[48] The chiral allene **1-10** derived from isovaleraldehyde was subjected to epoxidation conditions with an excess amount of DMDO to afford spirodiepoxide. Treatment of the spiroepoxide with azide followed by reduction of the azide furnished α-amino-α'-hydroxyl ketone **1-11**, which was used as a building block for synthesis of epoxomicin (**Scheme 1.20**).

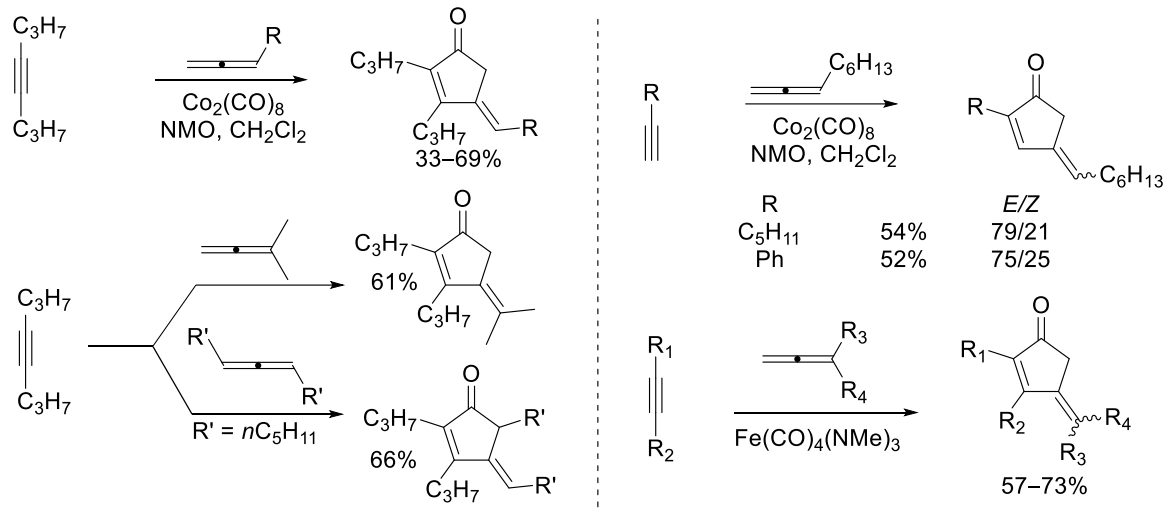


Scheme 1.20. Application of Spirodiepoxide to a Total Synthesis of Natural Products

1.6. Transition Metal-catalyzed Reaction of Allenes

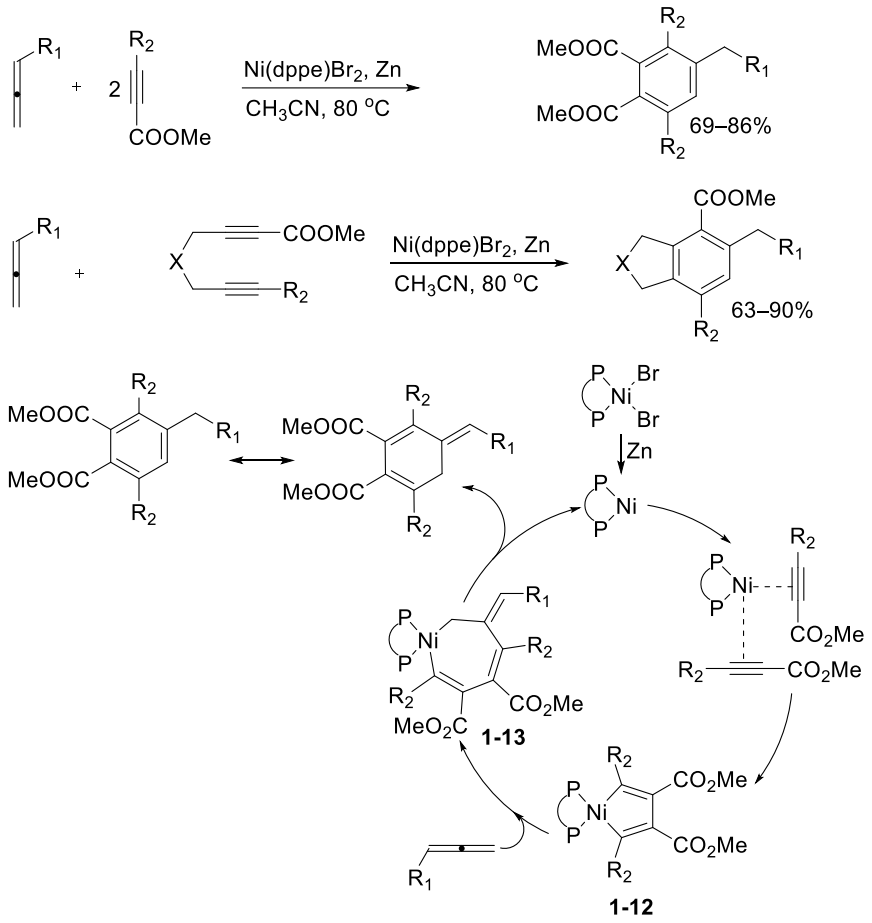
1.6.1. Cyclometallation of Allenes with Alkyne

The Pauson-Khand reaction is a [2+2+1] cycloaddition of alkyne with alkene and carbon monoxide to afford 2-cyclopentenone derivative.[49] In 1995, Cazes and coworkers reported a new Pauson-Khand protocol employing allene as an unsaturated reacting counterpart instead of alkene.[50] The octacarbonyldicobalt-mediated Paulson-Khand reaction was promoted by *N*-methylmorpholine *N*-oxide (NMO) and the regioselectivity of the reaction proved to be dependent on the substituent pattern on both alkyne and allene. Later, it was found that the same type of reaction can be mediated by $Fe(CO)_4(NMe_3)$ under photo-irradiation conditions (**Scheme 1.21**).[51]



Scheme 1.21. Cobalt- and Iron-mediated Paulson-Khand Reaction of Allene and Alkyne

In 2001, Cheng and coworkers developed nickel-catalyzed cyclotrimerization of two electron-deficient alkynes with an allene to afford polysubstituted benzene derivatives.[52] The reaction was initiated by generation of electron-rich Ni(0) from Ni(II) and Zn, and the catalytic cycle proceeds through the coordination of the electron-deficient alkynoates to the Ni-center followed by regioselective oxidative cyclometallation to afford nikelacyclopentadiene **1-12**. Allene was then coordinated with **1-12** follow by regioselective insertion of the sterically less hinderance C=C bond of the allene into the Ni(II)–C bond to afford nikkelacycloheptadiene **1-13**. The catalytic cycle was concluded by reductive elimination and tautomerization to afford polysubtituted benzene derivatives (**Scheme 1.22**). The same pattern of the reaction was expanded to cyclotrimerization of arynes. Because of the electrophilic nature of arynes,[53] the more electron rich C=C bond of the allene engaged in [2+2+2] cyclotrimerization to afford 10-methylene-9,10-dihydrophenanthrenes.[54]

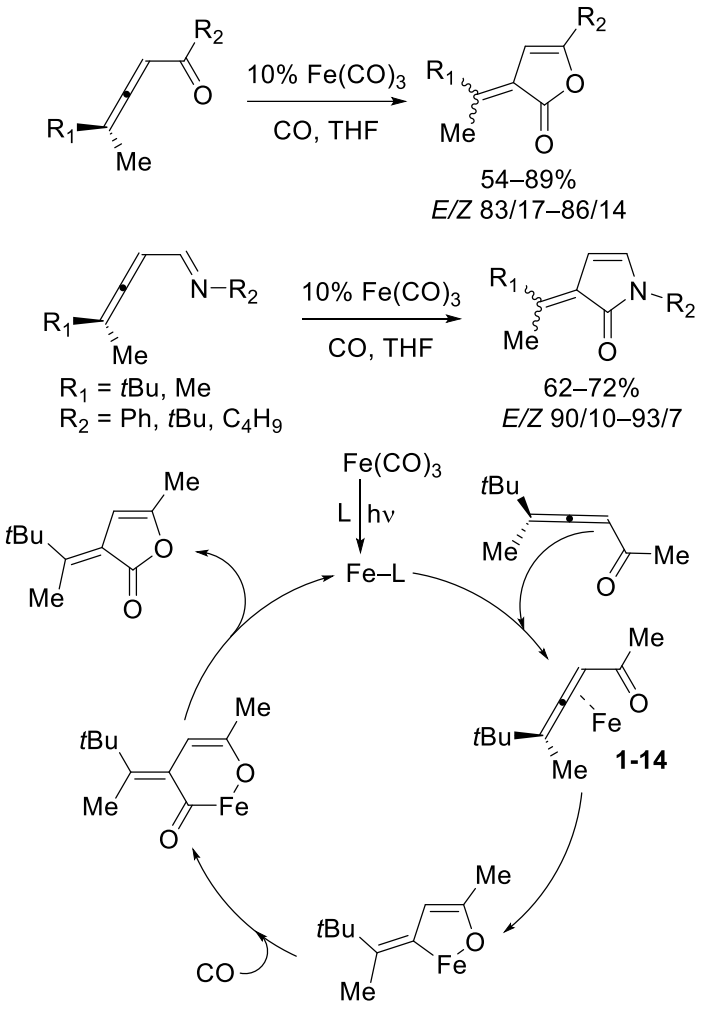


Scheme 1.22. Nickel-catalyzed Cyclotrimerization of Allene and Alkynes

1.6.2. Cyclometallation of Allenes

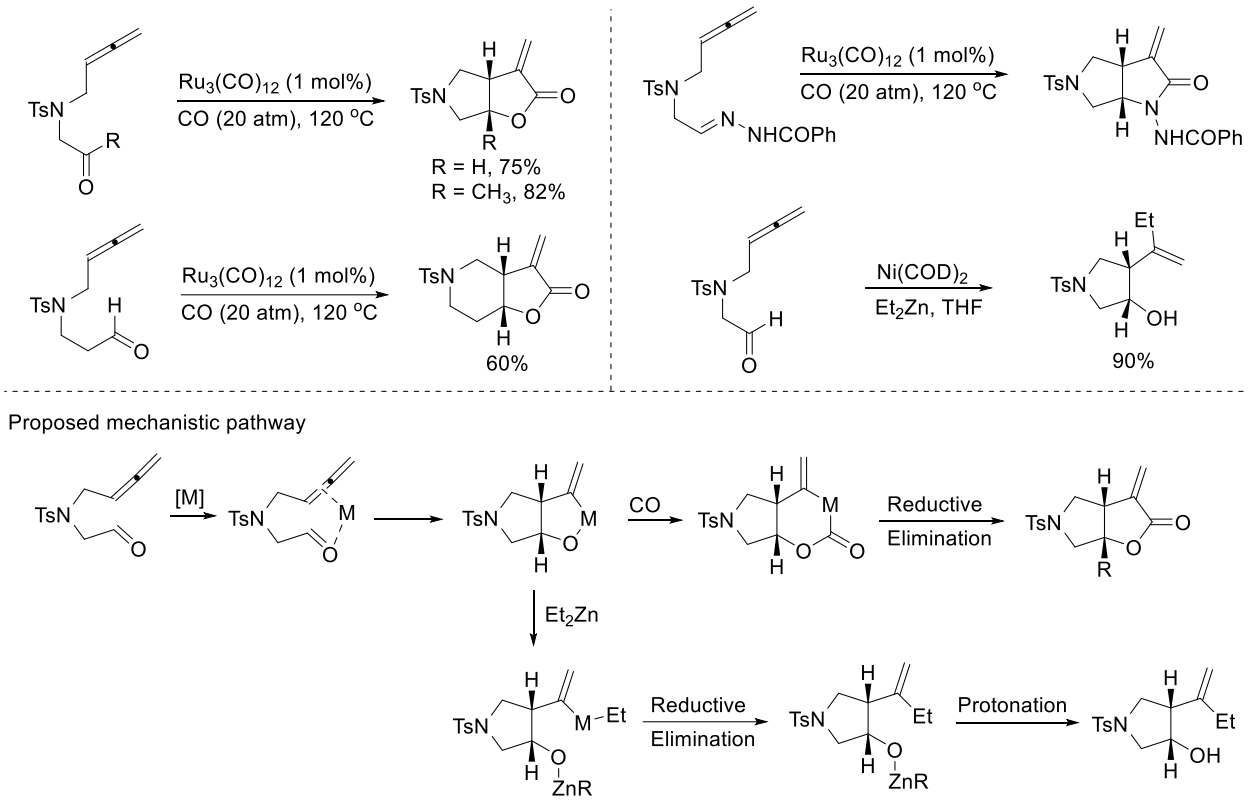
There are many cases where allenes were employed as unsaturated coupling partners in various cyclization processes. In 1993, Eaton and coworkers reported the first intramolecular iron-mediated [4+1] reaction between 1,2-allenyl ketone and carbon monoxide under photoirradiation conditions to afford a five-membered lactone.[55] This reaction concept was later extended to imines, affording lactams as the product.[56] The reaction was initiated by activation of the metal catalyst under photoirradiation conditions followed by the coordination between the electron-rich Fe(0) and the electron-deficient α,β-unsaturated ketone to afford metal complex **1-14**. Subsequent oxidative cyclometallation followed by insertion of

carbon monoxide into Fe(II)–C bond and reductive elimination furnished the five-membered ring lactone (**Scheme 1.23**).



Scheme 1.23. Iron-catalyzed Lactonization of 1,2-Allenyl Ketone

Later in early 2000s, Kang and coworkers reported a ruthenium-mediated [2+2+1] cyclization of γ-allenyl aldehyde or ketone and carbon monoxide to afford α-methylene γ-butyrolactone.[57] The reaction proceeded with high stereoselectivity, generating only cis-butyrolactone as the product. In the identical reaction conditions, δ-allenyl aldehyde and γ-allenyl imine afforded γ-butyrolactone and γ-butyrolactam, respectively. With the absence of CO, the metallacyclopentene intermediate can be captured by organozinc reagent to afford cis-fused homoallylic cyclopentanol (**Scheme 1.24**).[58]



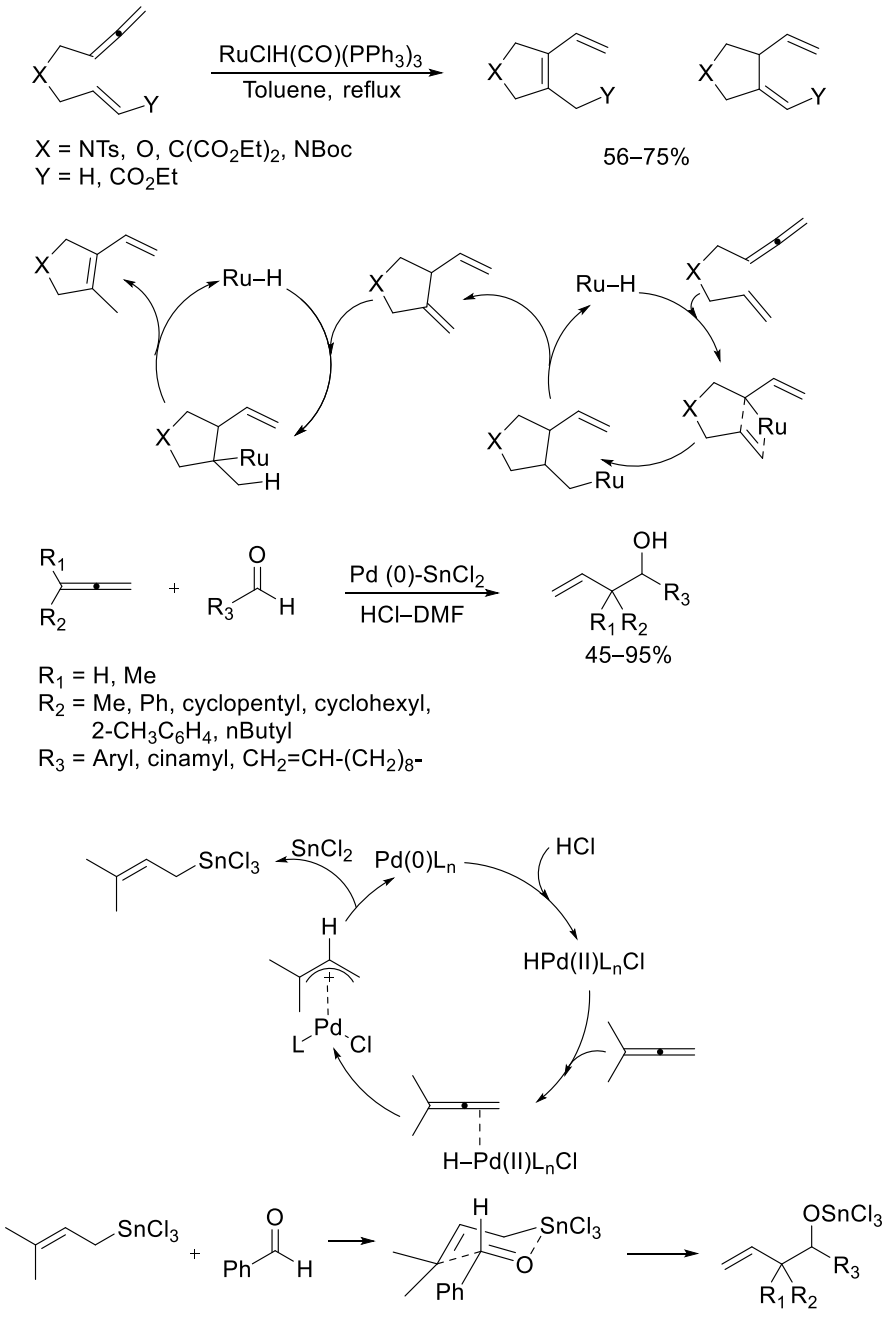
Scheme 1.24. Ru(0)-catalyzed Cyclization of Allenyl Aldehyde

1.6.3. Hydrometallation of Allenes

Kang and coworkers reported an intramolecular ruthenium-catalyzed cycloisomerization of γ-enallenes that afforded vinyl cyclopentene derivative.[59] The reaction is initiated by regioselective hydroruthenation of the more electron-rich C=C bond of the allene to generate an allyl ruthenium complex. Subsequent intramolecular olefin addition followed by β-hydride elimination affords 1-methylene-2-vinyl cyclopentane. The hydroruthenation and β-hydride elimination sequence occurs one more time to furnish vinyl cyclopentene as the product (**Scheme 1.25**).

At the same time, Cheng and coworkers reported the stereoselective allylation reaction of aldehyde by allene to afford homoallylic secondary alcohol.[60] The reaction was catalyzed by a Pd(II) catalyst via regioselective hydropalladation of allene to generate an allyl palladium intermediate. Nucleophilic attack

of in situ generated $SnCl_3^-$ to allyl palladium complex affords an allylstannane intermediate, which reacts with aldehyde through a six-membered ring transition state to generate the final product (**Scheme 1.25**).

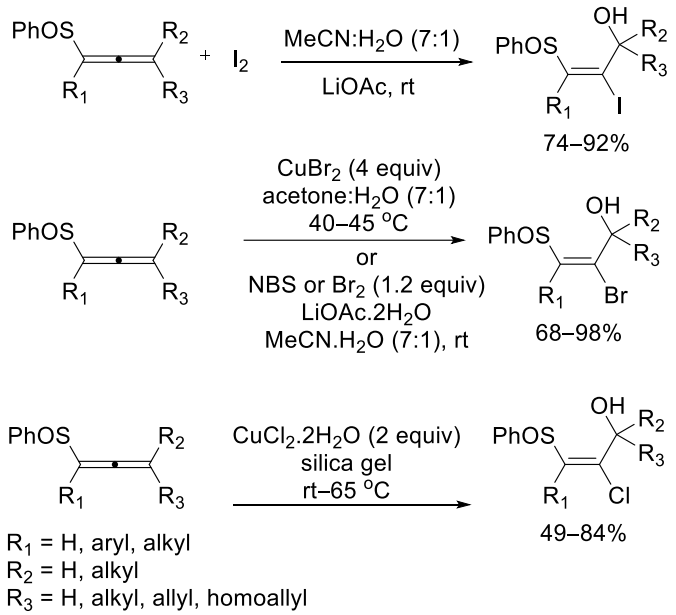


Scheme 1.25. Hydrometallation Reaction of Allene

1.7. Electrophilic Reactions of Allenes

1.7.1. Addition to Electron-deficient Allenes

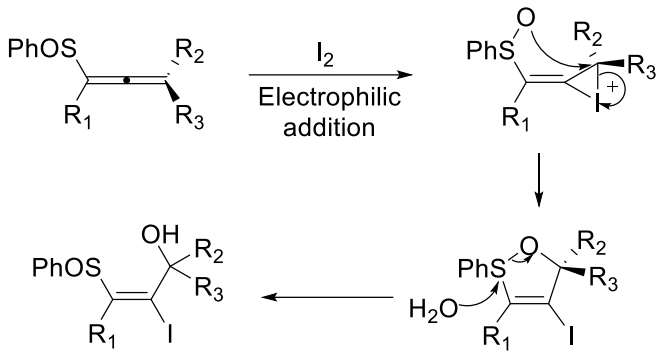
The wide varieties of examples of electrophilic addition and cyclization reactions of alkynes and alkenes[61] bode for allenes to display similar reactivity. The main concern of the addition reaction with allene is the regioselectivity between two π-bonds of allene, which is expected to mainly depend on substituents. Ma and a coworker reported regio- and *E*-stereoselectivity nucleophilic addition of inorganic halides to 1,2-allenyl sulfoxide.[62] The reaction between 1,2-propadienyl sulfoxide with I_2 in the presence of water afforded 3-hydroxy-2-iodo-1(*E*)-propenyl phenyl sulfide. The reaction displayed high chemo- and regioselectivity such that the allene moiety reacted exclusively even in the presence of another unsaturated functional group in the molecule, and only at the less electron-deficient C=C of the allene. The addition reaction affords only the *E*-stereoisomer with high selectivity. The same reaction protocol can be applied to bromo- and chlorohydrin formation[63] to afford 3-hydroxy-2-halog-1(*E*)-propenyl phenyl sulfide (**Scheme 1.26**).



Scheme 1.26. Selectivity of Halohydrin Reaction of Electron-deficient Allene

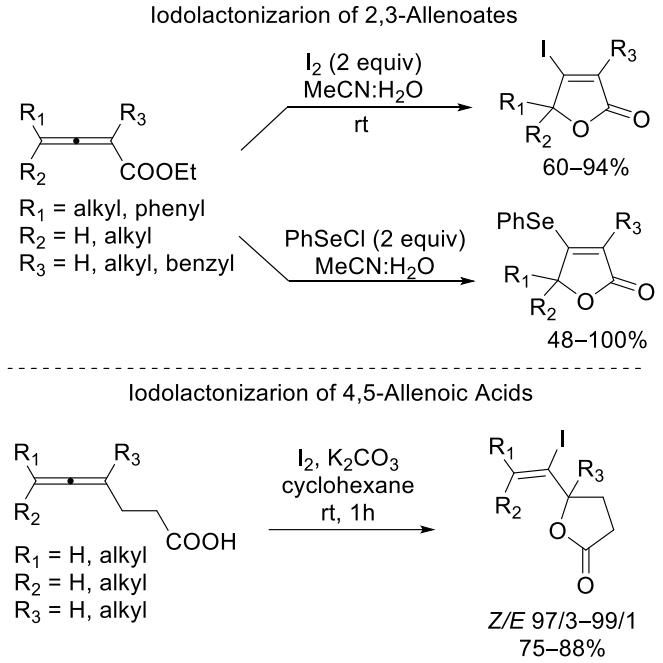
The reaction was proposed to start with interaction of I_2 to the less electron-deficient C=C of 1,2-allenyl sulfoxide to afford an iodinonium intermediate. An intramolecular by the sulfoxide oxygen to form

a five-membered ring intermediate, with which a water molecule reacts at the sulfur to furnish the iodo-hydroxylation product (**Scheme 1.27**).



Scheme 1.27. Mechanism for Iodohydroxylation of 1,2-Allenyl Sulfoxides

1.7.2. Intramolecular Cyclization



Scheme 1.28. Electrophilic Lactonization of Allenyl Carboxylate

Similar to the I_2-promoted addition reactions with allene, the iodinonium intermediate can be captured by an internal nucleophile to generate lactones. In the intramolecular reactions, the regioselectivity

depends mainly on the relative electron density of the two C=C bonds and the length of the tether connecting the internal nucleophile and the allene. In most of the cases, the more electron-rich π-bond participates in the reaction more favorably to form five membered lactone.[64]

1.8. Summary

In this chapter, the recent developments in allene chemistry are summarized. The establishment of efficient synthetic procedures opens the opportunity to use allenes as a key building block in organic synthesis. The capability of allenes to undergo a wide range of reactions including isomerization, cycloaddition, transition metal-catalyzed couplings, electrophilic additions have been successfully applied to synthesis of natural products with high regio- and stereoselectivity. There are many cases that the reactivity of allenes depends on the number and nature of substituents, which dictate the products distribution of allene reactions. Moreover, the *sp*-hybridization of the central carbon of allene can be used to generate high strain energy intermediates, leading to rapid construction of skeletons that exist in many natural products.

1.9. References

(1) Van't Hoff, J. H. *La Chimie dans L'Espace*, Bazendijk, Rotterdam, **1875**.

(2) Burton, B. S.; Pechmann, H. V. *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 145.

(3) Maitland, P.; Mills, W. H. *Nature* **1935**, *135*, 994.

(4) Jones, E. R. H.; Mansfield, G. H.; Whiting, M. L. H. *J. Chem. Soc.* **1954**, 3208.

(5) Willstatter, R.; Page, H. J. *Justus Liebigs Ann. Chem.* **1914**, *404*, 237.

(6) Bonnett, R.; Spark, A. A.; Tee, J. L.; Weedon, B. C. L. *Proc. Chem. Soc. London* **1964**, 419.

(7) Schutt, F. *Ber. Dtsch. Bot. Ges.* **1890**, *8*, 9.

(8) Strain, H. H.; Svec, W. A.; AitzetmSller, K.; Grandolfo, M. C.; Katz, J. J.; Kjøsen, H.; Norgard, S.; Liaaen-Jensen, S.; Haxo, F. T.; Wegfahrt, P.; Rapoport, H. *J. Am. Chem. Soc.* **1971**, *93*, 1823.

(9) Beach, D. H.; Chen, F.; Cushion, M. T.; Macomber, R. S.; Krudy, G. A.; Wyder, M. A.; Kaneshiro, E. S.; *Antimicrob. Agents Chemother*. **1997**, *41*, 162.

(10) Krause, N.; Hashmi, A. S. K. In *Modern Allene Chemistry*; Wiley-VCH, **2004**; 3.

(11) Huang, X.; Ma, S. *Acc. Chem. Res.* **2019**, *52*, 1301.

(12) Black, D. K.; Landor, S. R. *J. Chem. Soc.* **1965**, 6784.

(13) Taylor, D. R. *Chem. Rev.* **1967**, *67*, 317.

(14) (a) Lifshitz, A.; Frenklach, M.; Burcat, A.; *J. Phys. Chem.* **1975**, *79*, 1148. (b) Hopf, H.; Priebe, H.; Walsh, R. *J. Am. Chem. Soc.* **1980**, *102*, 1210.

(15) Crabbé, P.; Fillion, H.; André, D.; Luche, J. L. *J. Chem. Soc., Chem. Commun.* **1979**, *19*, 859.

(16) (a) Kuang, J.; Ma, S. *J. Org. Chem.* **2009**, *74*, 1763. (b) Kuang, J.; Ma, S. *J. Am. Chem. Soc.* **2010**, *132*, 1786.

(17) Crabbé, P.; Tran, P. T.; Lopes, M.-T. R.; Nassim, B.; Li, Y.; Searles, S. *J. Chem. Soc., Perkin Trans. 1* **1984**, 747.

(18) Gonzalez, M.; Alvarez-Rodrıguez, R.; Cid, M. M.; Silva Lopez, C. *J.Computational Chem.* **2012**, *33*, 1236.

(19) Claisen, L. *Chem. Ber.* **1912**, *45*, 3157.

(20) Thyagarajan, B. S.; Balasubramanian, K. K.; Rao, R. B. *Tetrahedron Lett*. **1963**, *21*, 1393.

(21) Nonoshita, K.; Banno, H.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1990**, *112*, 316.

(22) Saucy, G.; Marbet, R. *Helv. Chim. Acta* **1967**, *50*, 1158.

(23) Johnson, W. S.; Werthermann, L.; Bartlett, W. R.; Brockson, T. J.; Li, T.-T.; Faulkner, D. J.;

Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741.

(24) Trost, B. M.; Pinkerton, A. B.; Seidel, M. *J. Am. Chem. Soc.* **2001**, *123*, 12466.

(25) Sherry, B. D.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 15978.

(26) Pasto, D. J. *Tetrahedron* **1984**, *40*, 2805.

(27) Ogasawara, M.; Ikeda, H.; Nagano, T.; Hayashi, T. *J. Am. Chem. Soc.* **2001**, *123*, 2089.

(28) Ogasawara, M.; Ikeda, H.; Hayashi, T. *Angew. Chem. Int. Ed.* **2000**, *39*, 1042.

(29) Ogasawara, M.; Nagano, T.; Hayashi, T. *J. Org. Chem.* **2005**, *70*, 5764.

(30) (a) Becker, D.; Harel, Z.; Birnbaum, D. *J. Chem. Soc., Chem. Commun.* **1975**, 377. (b) Becker, D.; Harel, Z.; Nagler, M.; Gillon, A. *J. Org. Chem.* **1982**, *47*, 3297. (c) Kakiuchi, K.; Ue, M.; Tsukahara, H.; Shimizu, T.; Miyao, T.; Tobe, Y.; Odaira, Y.; Yasuda, M.; Shima, K. *J. Am. Chem. Soc.* **1989**, *111*, 3707. (d) Cargill, R. L.; Jackson, T. E.; Peet, N. P.; Pond, D. M. *Acc. Chem.Res.* **1974**, *7*, 106. For application of α-keto methylenecyclobutane to total synthesis, see: (e) Schreiber, S. L.; Santini, C. *J. Am. Chem. Soc.* **1984**, *106*, 4038.

(31) Morimoto, T.; Horiguchi, T.; Yamada, K.; Tsutsumi, K.; Kurosawa, H.; Kakiuchi, K. *Synthesis.* **2004**, 753.

(32) Shimada, Y.; Nakamura, M.; Suzuka, T.; Matsui, J.; Tatsumi, R.; Tsutsumi, K.; Morimoto, T.; Kurosawa, H.; Kakiuchi, K. *Tetrahedron Lett.* **2003**, *44*, 1401.

(33) Shepard, M. S.; Carreira, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 2597.

(34) Zhang, C.; Lu, X. *J. Org. Chem.* **1995**, *60*, 2906.

(35) Jones, R. A.; Krische, M. J. *Org. Lett.* **2009**, *11*, 1849.

(36) Schuler, M.; Voituriez, A.; Marinetti, A.; *Tetrahedron: Asymmetry* **2010**, *21*, 1569.

(37) Xiao, H.; Chai, Z.; Zheng, C.-W.; Yang, Y.-Q.; Liu, W.; Zhang, J.-K.; Zhao, G. *Angew. Chem. Int.*

Ed. **2010**, *49*, 4467.

(38) Yasukouchi, T.; Kanematsu, K. *Tetrahedron Lett.* **1989**, *30*, 6559.

(39) (a) Padwa, A.; Filipkowski, M. A.; Meske, M.; Watterson, S. H.; Ni, Z. *J. Am. Chem. Soc.* **1993**, *115*, 3776. (b) Kanematsu, K.; Kinoyama, I. *Chem. Commun.* **1992**, 735.

(40) Jung, M. E.; Nishimura, N. *J. Am. Chem. Soc.* **1999**, *121*, 3529.

(41) (a) Jung, M. E.; Nishimura, N. *Org. Lett.* **2001**, *3*, 2113. (b) Gunasekera, S. P.; McCarthy, P. J.; Kelly-Borges, M.; Lobkovsky, E.; Clardy, J. *J. Am. Chem. Soc.* **1996**, *118*, 8759.

(42) (a) Harmata, M. *Chem. Commun.* **2010**, *46*, 8904. (b) Lohse, A. G.; Hsung, R. P. *Chem. Eur. J.* **2011**, *17*, 3812.

(43) Alonso, I.; Faustino, H.; Lopez, F.; Mascarenas J. L. *Angew. Chem. Int. Ed.* **2011**, *50*, 11496.

(44) Crandall, J. K.; Batal, D. J.; Sebesta, D. P.; Lin, F. *J. Org. Chem.* **1991**, *56*, 1153.

(45) Sakaguchi, S.; Watase, S.; Katayama, Y.; Sakata, Y.; Nishiyama, Y.; Ishii, Y. *J. Org. Chem.* **1994**, *59*, 5681.

(46) Crandall, J. K.; Conover, W. W.; Komin, J. B.; Machleder, W. H.; *J. Org. Chem.* **1974**, *39*, 1723.

(47) Crandall, J. K.; Rambo, E.; *Tetrahedron Lett.* **1994**, *35*, 1489.

(48) Katukojvala, S.; Barlett, K. N.; Lotesta, S. D.; Williams, L. J. *J. Am. Chem. Soc.* **2004**, *126*, 15348.

(49) Pauson, P. L.; Khand, I. U. *Ann. N. Y. Acad. Sci.* **1997**, 295.

(50) Ahmar, M.; Antras, F.; Cazes, B. *Tetrahedron Lett.* **1995**, *36*, 4417.

(51) Shibata, T.; Koga, Y.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 911.

(52) Shanmugasundaram, M.; Wu, M.-S.; Cheng, C.-H. *Org. Lett.* **2001**, *3*, 4233.

(53) Rondan, N. G.; Domelsmith, L. N.; Houk, K. N.; Bowne, A. T.; Levin, R. H. *Tetrahedron Lett.* **1979**, *20*, 3237.

(54) Hsieh, J.-C.; Rayabarapu, D. K.; Cheng, C.-H. *Chem. Commun.* **2004**, 532.

(55) Sigman, M. S.; Kerr, C. E.; Eaton, B. E. *J. Am. Chem. Soc.* **1993**, 115, 7545.

(56) Sigman, M. S.; Eaton, B. E. *J. Org. Chem.* **1994**, *59*, 7488.

(57) Kang, S.-K.; Kim, K.-J.; Hong, Y.-T. *Angew. Chem., Int. Ed.* **2002**, *41*, 1584.

(58) Kang, S.-K.; Yoon, S.-K. *Chem. Commun.* **2002**, 2634.

(59) Kang, S.-K.; Ko, B.-S.; Lee, D.-M. *Tetrahedron Lett.* **2000**, *43*, 6693.

(60) Chong, H.-M.; Cheng, C.-H. *Org. Lett.* **2000**, *2*, 3439.

(61) (a) Smit, W. A.; Caple, R.; Smoliakova, I. P. *Chem. Rev.* **1994**, *94*, 2359. (b) French, A. N.; Bissmire, S.; Wirth, T. *Chem. Soc. Rev.* **2004**, *33*, 354.

(62) Ma, S.; Wei, Q.; Wang, H. *Org. Lett.* **2000**, *2*, 3893.

(63) Ma, S.; Ren, H.; Wei, Q. *J. Am. Chem. Soc.* **2003**, *125*, 4817.

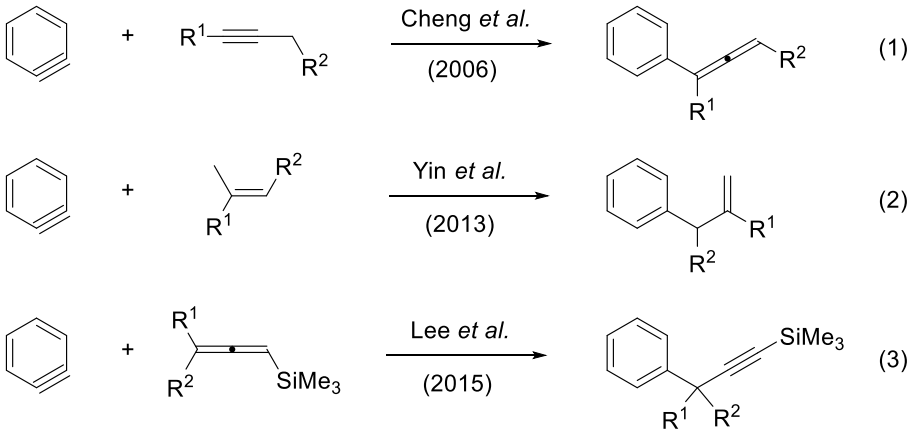
(64) (a) Jiang, X.; Fu, C.; Ma, S. *Chem. Eur. J.* **2008**, *14*, 9656. (b) Fu, C.; Ma, S. *Eur. J. Org. Chem.* **2005**, 3942.

CHAPTER 2

Intramolecular Reactions of Allene with Arynes

2.1. Introduction*

A wide variety of electron-deficient π-systems have been employed as an ene-acceptor either in thermal or Lewis acid-catalyzed conditions.[1] Arynes, as a form of transient electrophilic intermediate,[2] can behave as an efficient ene-acceptor[3] to react with ene-donors containing π-systems such as alkynes, alkenes, and allenes (**Scheme 2.1**). In 2006, Cheng reported intermolecular Alder-ene reactions between benzyne and terminal and internal alkynes (Eq 1),[4] and in 2013, Yin also reported the corresponding reaction of benzyne with alkenes (Eq 2),[5] which was further extended to alkenes containing a polar functional group[6] in the reaction of arynes generated from tetraynes via hexadehydro Diels-Alder reaction.[7] Recently, Lee and coworkers also explored the Alder-ene reaction between benzyne and a silylated allene (Eq 3).[8]

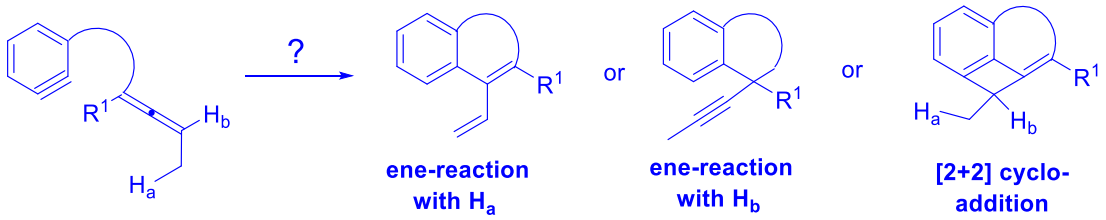


Scheme 2.1. Alder-ene Reactions of Arynes

In 2011, Lautens and coworkers reported intramolecular Alder-ene reactions of arynes generated via a strong based-mediated elimination of aryl bromides.[9] Recently, Hoye[10] and Lee[11] reported the intramolecular Alder-ene reactions of arynes generated from tri- and tetraynes under thermal conditions. At this juncture, the scope and selectivity of the intramolecular Alder-ene reactions was further explored by accommodating an allene as the ene-donor (**Scheme 2.2**).[12] The main concern in this intramolecular Alder-

* Some parts of this chapter have been reproduced (adapted) partially with permission from Le, A.; Lee, D. "Selectivity between an Alder–ene reaction and a [2 + 2] cycloaddition in the intramolecular reactions of allene-tethered arynes" *Org. Chem. Front*. **2021**, DOI: 10.1039/D1QO00459J with permission from The Royal Society of Chemistry.

ene reaction is the selectivity between the allylic and allenic C–H bonds, which is expected to mainly depend on the substituent pattern of the allene moiety. In this chapter, we describe the reactivity and selectivity trend of intramolecular Alder-ene reactions that also compete with [2+2] cycloaddition of the terminal π-system of the allene.[13]

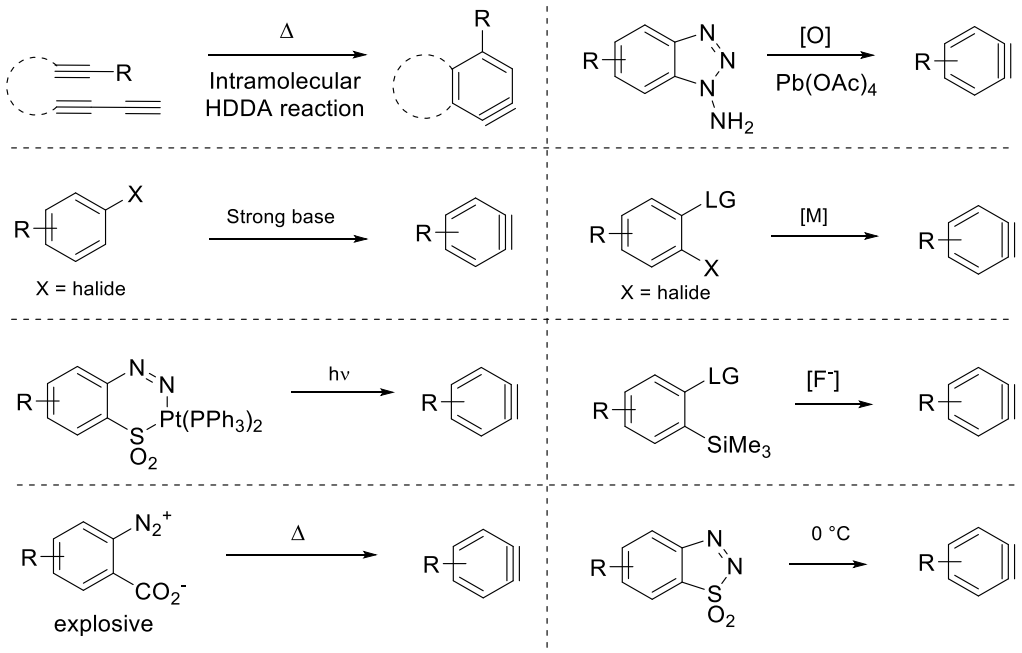


Scheme 2.2. Possible Reaction Pathways of Aryne Tethered with an Allene Moiety

2.2. Hexadehydo Diels-Alder Reactions

Aryne (benzyne), a highly strained six-membered ring consisting of two C=C bonds and one C≡C bonds, has been widely used as a reactive intermediate in construction of aromatic skeleton-containing compound. First evidence of the existence of benzyne emerged more than 100 years ago, when Stoermer and Kahlert observed the formation of 2-ethoxybenzofuran upon treatment of 3-bromobenzofuran with base in ethanol solvent.[14] The result was justified by the generation of the first aryne intermediate (known as 2,3-dehydrobenzofuran) through β-elimination of aryl bromide. Despite the versatility, the effectiveness of forming benzyne combined with the unusually high reactivity posed a great barrier to the application of benzyne in synthesis of complex molecules. A benzyne intermediate must be generated in situ from its precursor and immediately be trapped by suitable reactants to avoid facile self-decomposition due to extreme reactivity. Since the discovery of benzyne, various methods concerning the generation of aryne have been developed. Traditional methods to produce benzyne include base- or metal-promoted β-elimination of aryl halide,[15] fluoride-promoted desilylation of aryl trimethylsilanes with concomitant elimination of *ortho*-leaving group,[16] thermal decomposition of benzenediazonium-2-carboxylate,[17] and thermal,[18] photochemical[19] and oxidative[20] elimination of molecular nitrogen from various precursors

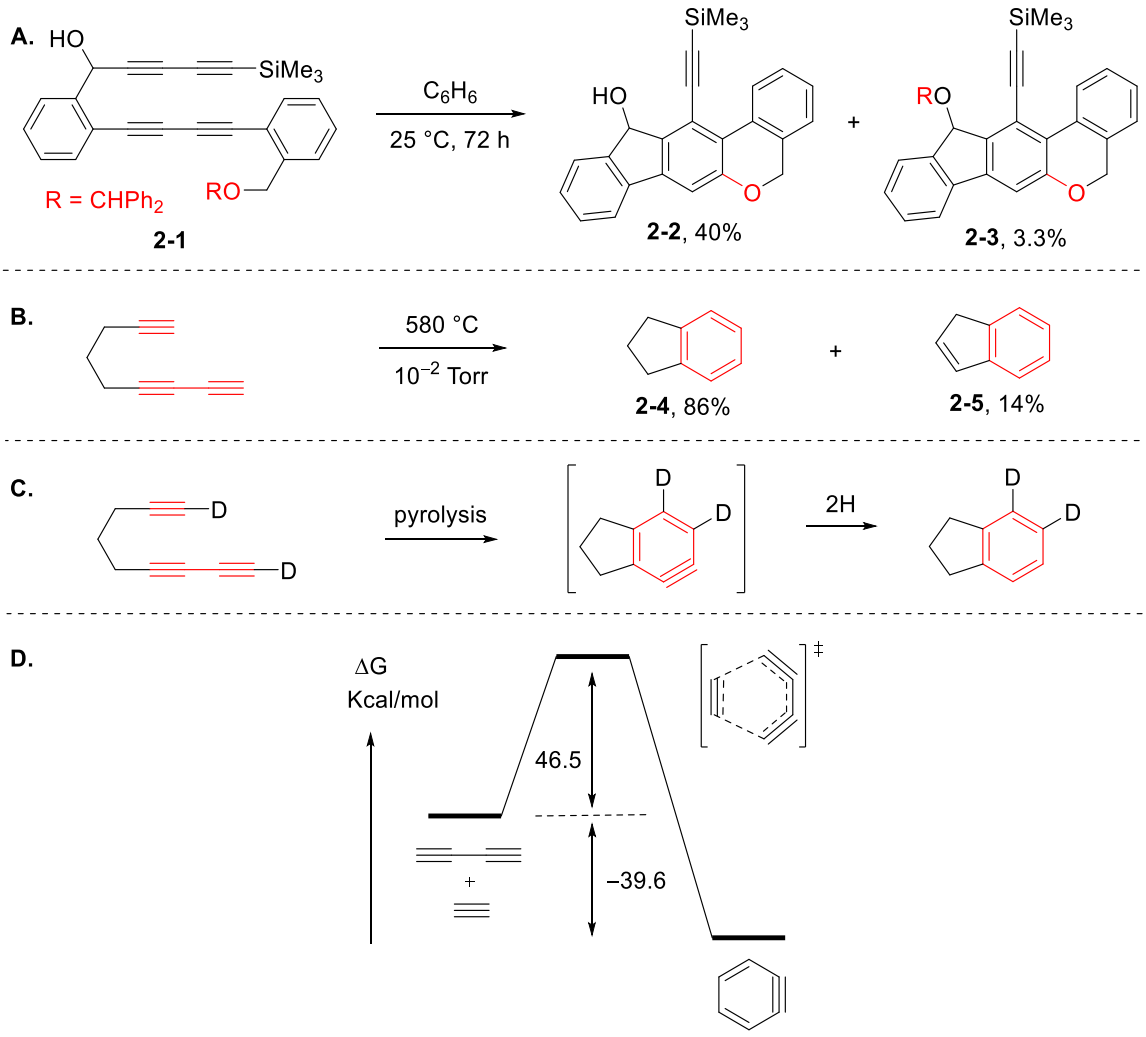
(**Scheme 2.3**). A unique method has been recently developed by employing thermal intramolecular hexadehydro Diels-Alder (HDDA) reaction of triynes and tetraynes. Compare with the existing methods, the hexadehydro Diels-Alder (HDDA) reaction may eliminate some potential complications of other methods but high temperature for typical substrates is considered to be a barrier of this method.



Scheme 2.3. Various Route for Generation of Arynes

Hexadehydro Diels-Alder (HDDA) reaction is a unique process that forms aryne frameworks from non-aromatic precursors. Appropriate triyne and tetrayne precursors can undergo HDDA reaction at various temperatures, ranging from 25 °C to as high as 580 °C depending on their structures. This reaction was pioneered by by Ueda[26b] and Johnson[26a] in 1997. Ueda reported a tandem thermal cyclization of non-conjugated tetraynes **2-1** follow by intramolecular nucleophilic trapping to afforded **2-2** and **2-3** (**Scheme 2.4 A**).[26a] At the same time, Johnson reported the cycloaromatization of 1,3,8-nonatriye under flash vacuum thermolysis conditions to generate a mixture of indane **2-4** and indene **2-5** (**Scheme 2.4 B**).[26b] Deuterium isotope labelling experiment revealed that cycloaromatization reaction should proceed through a classical mode of [4+2] cycloaddtion between alkyne and diyne to afford an aryne intermediate followed by

hydrogen transfer to furnish the observed products (**Scheme 2.4 C**). Ab initio calculation was also conducted to prove the feasibility of cycloaddition reaction between 1,3-butadiyne acetylene. The results reveal that even though high activation energy and dramatic molecular distortion is required, the [4+2] cycloaddition between diyne and alkyne is associated with large exothermicity due to the formation of aromatic system (**Scheme 2.4 D**). In this chapter, our investigations of the selectivity in the intramolecular reaction between allenes and arynes are described wherein ynamide-tethered tetraynes and benzene-tethered triynes are employed as the aryne precursors.

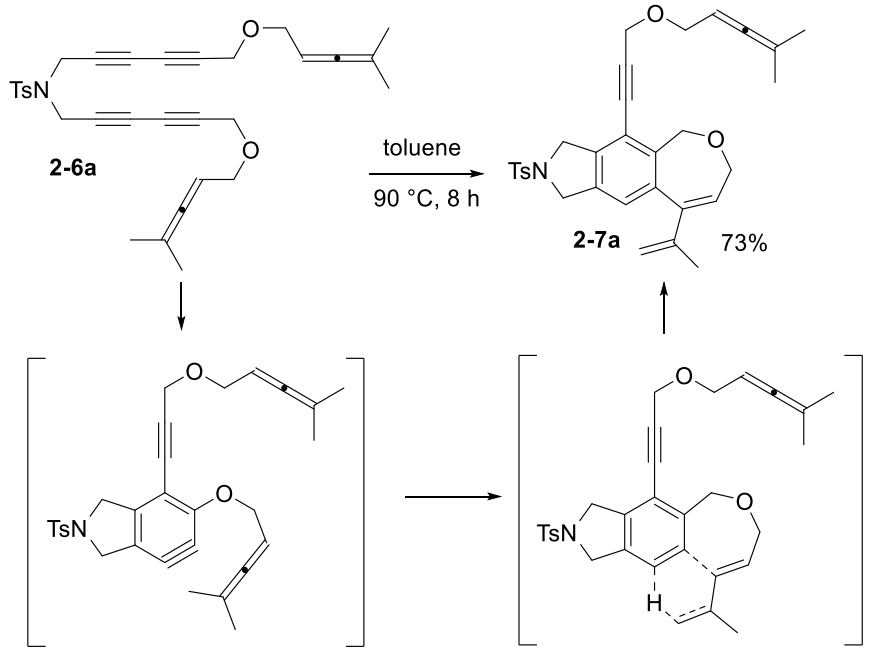


Free energy diagram (Kcal/mol, 25 °C and MP2/6-31G* transition state structure for the cycloaddition of acetylene with 1,3-butadiyne.

Scheme 2.4. Cycloaromatization of Tetrayne and Triyne and the Calculated Energy

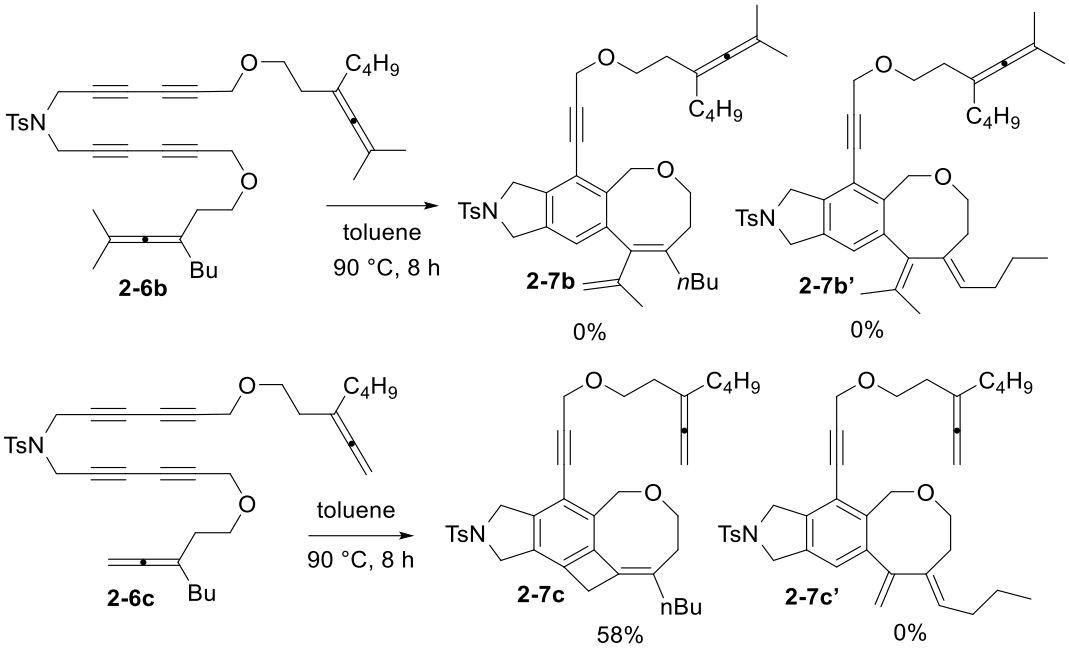
2.3. Initial Observation

Inspired by the recent report of the intermolecular Alder-ene reactions of arynes generated from tri- and tetraynes under thermal conditions, we explored the reactivity of intramolecular reaction of aryne-tethered allene. First, we examined the Alder-ene reaction by using symmetrical tetraynes **2-6a** (**Scheme 2.5**). The reaction of tetrayne **2-6a** that contains a three-atom tether with a *gem*-dimethylated allene[21] moiety (toluene, 90 °C, 8 h) afforded 7-membered ring Alder-ene product **2-7a** in 73% yield.



Scheme 2.5. Reaction of Symmetrical Tetraynes Containing a Three-atom Tethered Allene Moiety

On the other hand, tetrayne **2-6b** containing a four-atom tether with a tetrasubstituted allene moiety did not provide either Type-I or Type-II ene reaction product **2-7b**/**2-7b′ (Scheme 2.6)**. Under the identical conditions, however, substrate **2-6c** containing a terminal allene[22] moiety afforded only the [2+2] cycloadduct of the terminal π-bond of the allene to generate **2-7c** in 58% yield, and type-II ene product **2-7c′** was not observed. Despite the availability of allenic proton in **2-6c**, no Alder-ene product with the allenic proton was observed.



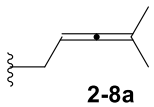
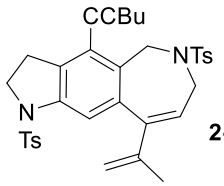
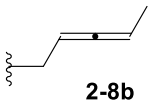
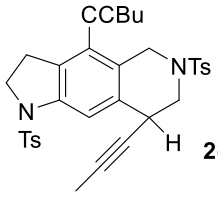
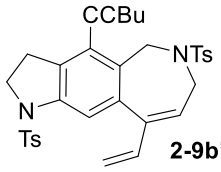
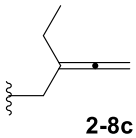
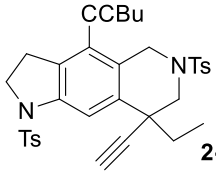
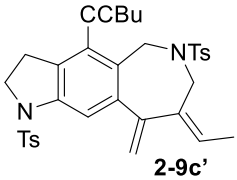
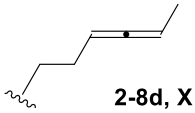
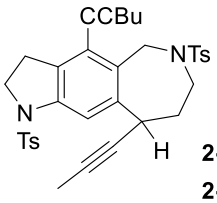
Scheme 2.6. Reactions of Symmetrical Tetraynes Containing a Four-atom Tethered Allene Moiety

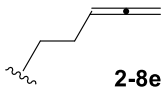
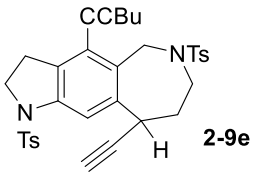
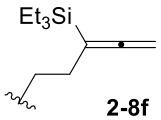
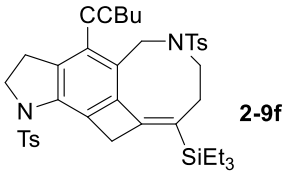
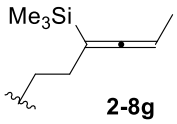
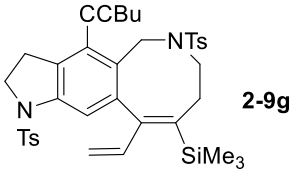
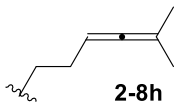
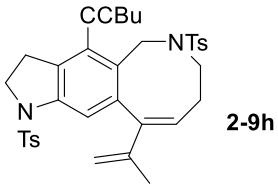
2.4. Results and Discussion

2.4.1. Reactions of Ynamide-tethered Tetraynes

On the basis of the drastic change of the reaction modes depending on the substituent pattern in allenes, the general trend of the reactivity of unsymmetrical tetraynes **2-8a**–**2-8h** that contain structurally different allene moieties was further explored (**Table 2.1**). As expected, tetrayne **2-8a** bearing a three-atom tether with a *gem*-dimethyl allene moiety exclusively formed 7-membered Alder-ene product **2-9a** in 63% yield (entry 1). In stark contrast, tetrayne **2-8b** containing a 1,3-disubtituted allene[23] moiety results in decomposition of the starting material and neither Alder-ene product **2-9b** nor **2-9b′** of the allenic or allylic C–H bond was observed (entry 2). Substrate **3c** containing a 1,1-disubstituted terminal allene also decomposed without providing either Type-I or Type-II ene product **2-9c** or **2-9c′** (entry 3). Surprisingly, however, substrates **2-8d** and **2-8d′** containing a 1,3-disubtituted allene with an extra methylene exclusively engaged in the Alder-ene reaction with an allenic C–H bond[8] to afford **2-9d** and **2-9d′** in 64 and 60% yield,

respectively (entries 4 and 5), and the Type-1 ene product of the corresponding allylic C–H bond was not observed. The reaction of the mono-substituted allene in **2-8e** induced the Type-I ene reaction of an allenic C–H bond to provide a terminal alkyne-containing product **2-9e** in 55% yield (entry 6). Substrate **2-8f** containing a 1,1-disubstituted terminal allene, which is identical with **2-8e** but containing a triethylsilyl group at the internal position of the allene, afford [2 + 2] cycloadduct **2-9f** in 62% yield and no Alder-ene product was observed (entry 7). Both substrates **2-8g** and **2-8h** containing a 1,1,3- or 1,3,3-trisubstituted allene[24] moiety, respectively, afforded the corresponding Type-I Alder-ene products **2-9g** and **2-9h** in 34 and 58% yield, respectively (entries 4 and 5).

entries	R	product	yield (%)[a]
1	 **2-8a**	 **2-9a**	63
2	 **2-8b**	 **2-9b**  **2-9b'**	0[b]
3	 **2-8c**	 **2-9c**  **2-9c'**	0[b]
4	 **2-8d, X = NTs**	 **2-9d**	64
5	**2-8d', X = O**	**2-9d'**	60

6	 **2-8e**	 **2-9e**	55
7	 **2-8f**	 **2-9f**	62
8	 **2-8g**	 **2-9g**	34
9	 **2-8h**	 **2-9h**	58

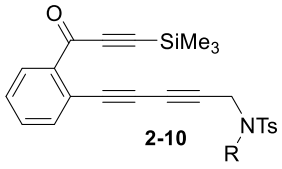
[a]Isolated Yield. [b]Decomposition of starting material

Table 2.1. Reactions of Ynamide-tethered Tetraynes Containing Different Allene Moieties

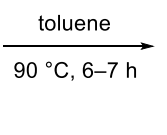
These examples suggest that the preference for the formation of different modes of Alder-ene or [2+2] cycloaddition depends subtly on the substituents on the allene moiety and the length of the tether between the allene and the aryne. In general, Alder-ene reaction of an allylic C–H bond is most favorable with trisubstituted allenes (entries 1, 8 and 9) whereas that of an allenic C–H bond becomes more favorable with monosubstituted and 1,3-disubstitued allenes (entries 4–6). Alternatively, 1,1-disubstituted terminal allene induces [2 + 2] cycloaddition over an Alder-ene reaction (entry 7).

2.4.2. Reactions of Benzo-tethered Triynes

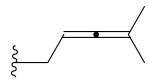
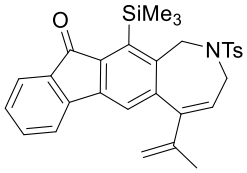
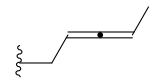
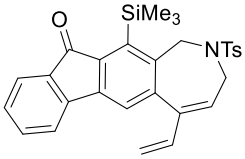
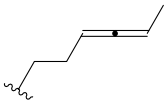
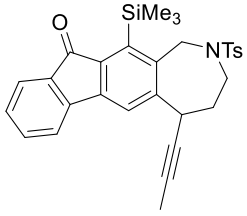
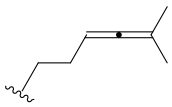
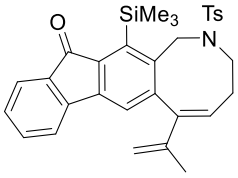
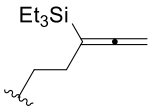
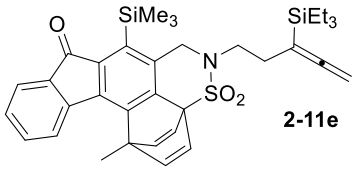
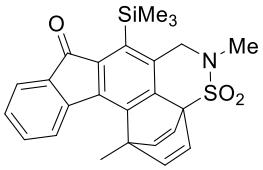
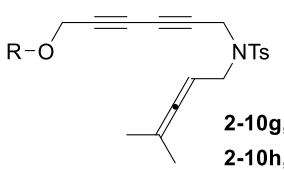
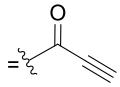
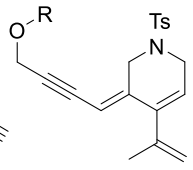
Next, the reactivity of arynes generated from triynes **2-10a**–**2-10f** containing different allene moieties was explored (Table 2.2). The reaction of triynes **2-10**a and **2-10b** bearing a *gem*-dimethyl-containing trisubstituted allene or a 1,3-disubstituted allene moiety led to only decomposition without



2-10



Alder-ene product or [4 + 2] cycloadduct

entries	R		product		yield (%)[a]
1		**2-10a**		**2-11a**	0[b]
2		**2-10b**		**2-11b**	0[b]
3		**2-10c**		**2-11c**	72
4		**2-10d**		**2-11d**	50
5		**2-10e**		**2-11e**	34
6	—Me	**2-10f**		**2-11f**	58
7		**2-10g,** R = 		**2-11g**	32[c]
8		**2-10h,** R = H		**2-11h**	62[c]

[a]Isolated yield. [b]Decomposition of starting material. [c]Reaction at 150 °C for 12 h.

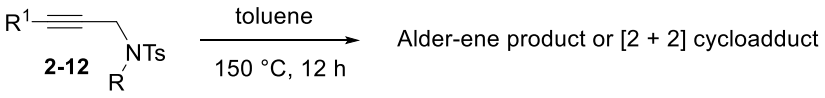
Table 2.2. Reactions of Benzo-tethered Triynes Containing Different Allene Moieties

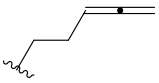
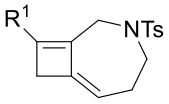
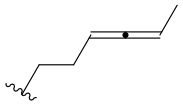
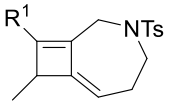
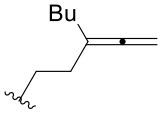
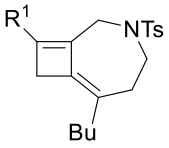
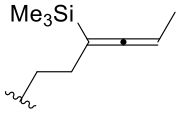
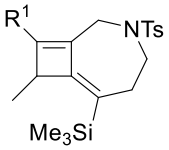
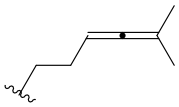
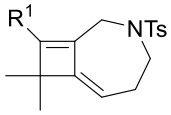
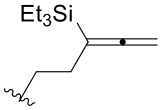
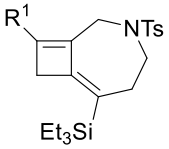
generating the expected 7-membered ring Type-I Alder-ene product **2-11a** and **2-11b** (entries 1 and 2). On the other hand, triynes **2-10c** with a longer tether bearing a 1,3-disubstituted allene moiety provided Type-I ene product **2-11c** in 72% yield, where only an allenic C–H bond participated in the reaction (entry 3). Unexpectedly, substrate **2-10d** bearing a *gem*-dimethyl-containing trisubstituted allene provided an 8-membered ring Type-I Alder-ene product **2-11d** in 50% yield (entry 4). It is quite surprising to find that **2-10e** containing a 1,1-disubstituted terminal allene moiety did not participate in the expected [2+2] cycloaddition between the allene and aryne, instead the toluene moiety of NTs group participated in a Diels-Alder reaction to generate benzobarrelene[25] **2-11e**, where the allene moiety remains intact (entry 5). The preference of a Diels-Alder reaction is further demonstrated with triyne **2-10f** devoid of the allene moiety, which provided benzobarrelene **2-11f** in 58% yield (entry 6). Despite the identical allene moieties in tetraynes **2-8f** and triynes **2-10e**, their reaction outcomes are quite different, which strongly suggests that the reactivity of the putative aryne intermediates are intricately affected by multiple factors including the substituents on the aryne core moiety. In comparison, a *gem*-dimethyl allene-containing propiolated triynes **2-10g** exclusively provided Alder-ene reaction product **2-11g** in marginal yields (entry 7). The formation of product **2-11g** suggests that the HDDA reaction of **2-10g** require higher activation barrier than the Alder-ene reaction between the alkyne moiety and the tethered allene segment. It was surmised that the low yield from this reaction is the consequence of the instability of the propiolate ester functionality at the elevated temperature. Indeed, when 1,3-diynyl propargyl alcohol **2-10h** was subjected to the identical conditions, the corresponding Alder-ene product **2-11h** was obtained in 62% yield (entry 8).

2.4.3. [2+2] Cycloadditions of Alkynes with Allenes

Having recognized the significant impact of the structure of the tether, alkynes and allene moiety, various substrates that contain a 1,3-diyne (**2-12a–2-12f**) and monoynes (**2-12ga–2-12gd**) tethered with differently substituted allene moieties were further examined to define the selectivity between the Alder-ene and a [2+2] cycloaddition (Table 3). Upon heating (150 °C, toluene, 12 h), all 1,3-diyne-tethered allenes **2-12a–2-12f** provided [2+2] cycloadducts **2-13a–2-13f** in good yields (entries 1–6), whereas

monoynes **7ga–7gd** only led to decomposition under the identical conditions (entries 7–10) and none of the expected [2+2] cycloadducts **8ga–8gd** were observed. It is worthy of note the activating role of the extra alkynyl substituent at the terminal position of the alkyne in these [2+2] cycloadditions.[26]



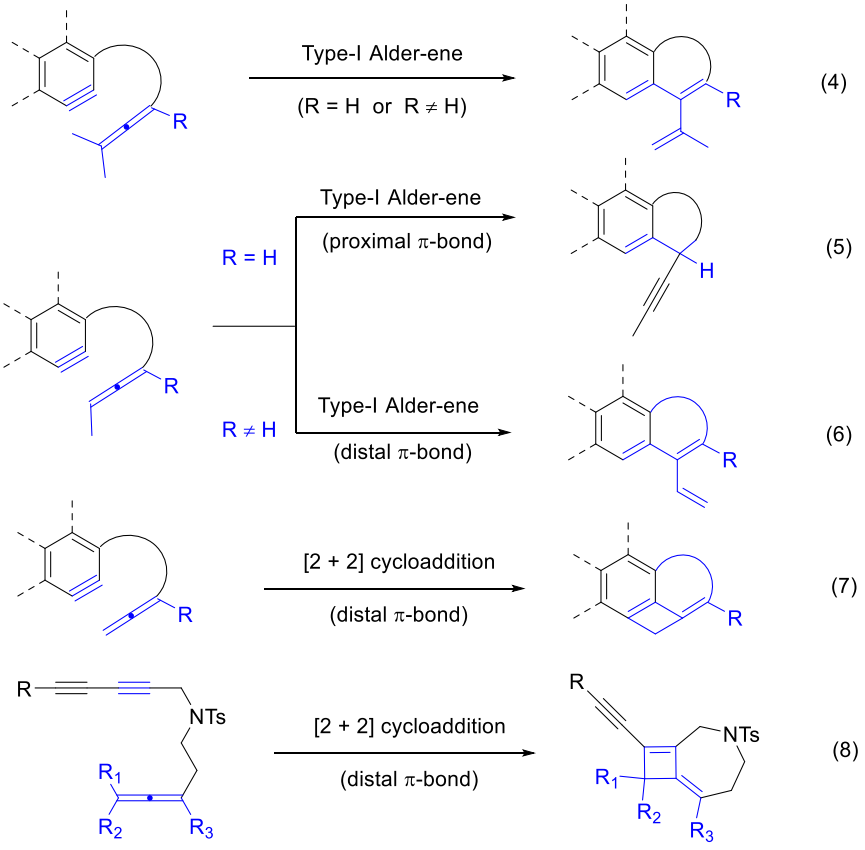
entries	R	R^1	product	yield (%)[a]
1		**2-12a,** R^1 = $CCSiEt_3$		**2-13a** 82
2		**2-12b,** R^1 = $CCSiEt_3$		**2-13b** 85
3		**2-12c,** R^1 = $CCSiEt_3$		**2-13c** 80
4		**2-12d,** R^1 = $CCSiEt_3$		**2-13d** 78
5		**2-12e,** R^1 = $CCSiEt_3$		**2-13e** 65
6		**2-12f,** R^1 = $CCSiEt_3$		**2-13f** 78
7		**2-12ga,** R^1 = H		**2-13ga** 0[b]
8		**2-12gb,** R^1 = Br		**2-13gb** 0[b]
9		**2-12gc,** R^1 = Bu		**2-13gc** 0[b]
10		**2-12gd,** R^1 = Ph		**2-13gd** 0[b]

[a]Isolated yield. [b]Decomposition of starting material.

Table 2.3. Reactivity of Sulfonamide-tethered Alkyne Containing Different Allene Moieties

2.5. Conclusion

In summary, the intramolecular reactions between allenes and arynes were systematically investigated by employing allene-tethered tetraynes and triynes as the aryne precursors. From the data accumulated in **Scheme 2.5–2.6** and **Tables 2.1–2.3**, a general reactivity and selectivity trend has emerged (**Scheme 2.7**). Allenes containing a *gem*-dimethyl group at the distal carbon exclusively participates in the Type-I ene reaction regardless of the substituent at the proximal carbon (Eq 4). 1,3-Disubstituted allenes favorably participate in the Alder-ene reaction with an allenic C–H bond (Eq 5), whereas 1,1,3-trisubstituted allenes prefers to generate the Alder-ene product with an allylic–H bond (Eq 6). The reaction of aryne with a 1,1-disubstituted terminal allene favors for a [2+2] cycloaddition (Eq 7). On the other hand, the reaction between 1,3-diynes and an allene moiety provides [2+2] cycloaddition products irrespective of the substituent pattern of the allene (Eq 8).



Scheme 2.7. General Selectivity Trend in the Intramolecular Reactions of Allenes with an Aryne

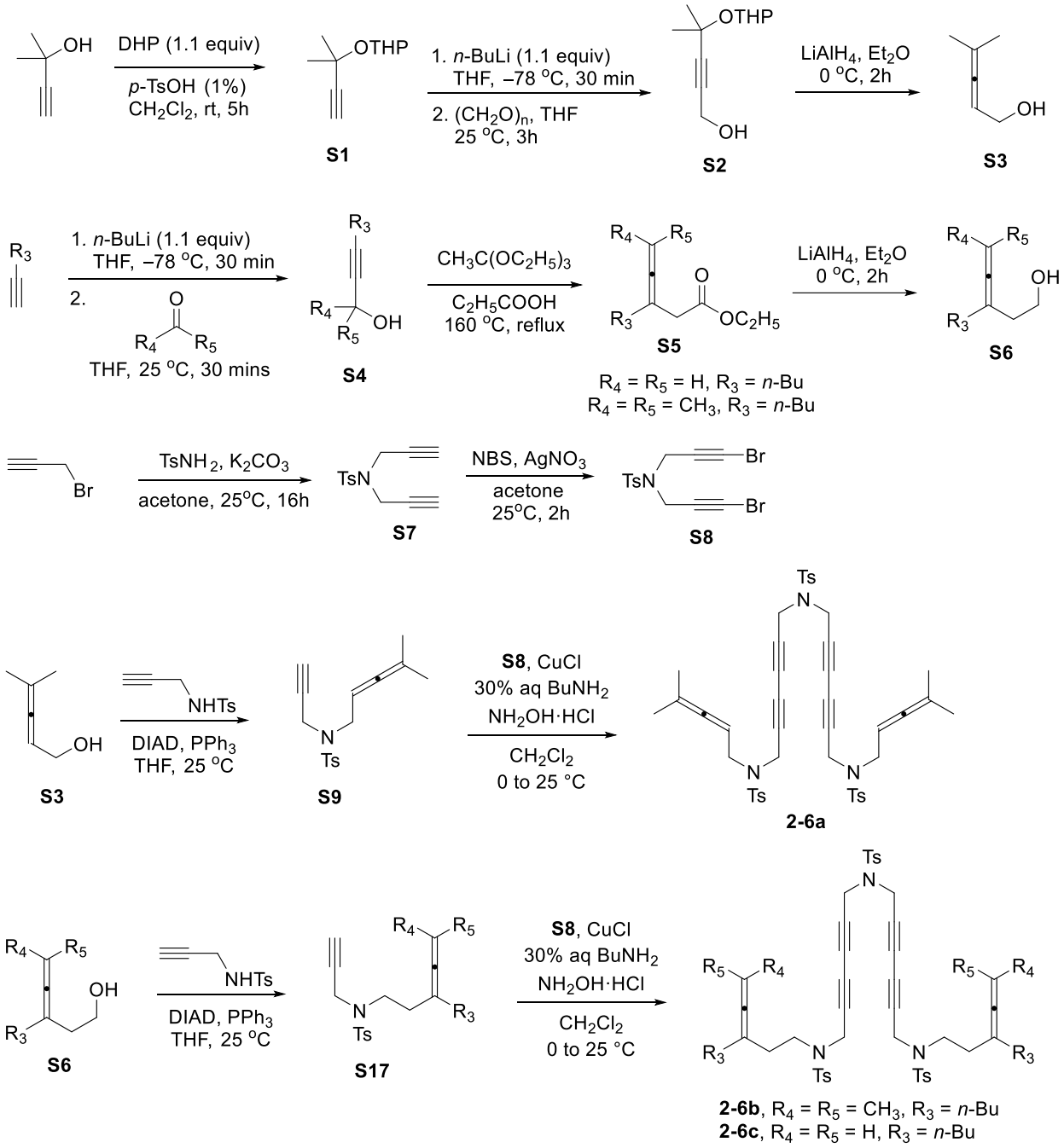
2.6. Experimental Details

2.6.1. General Information

Reactions were carried out in oven-dried glassware unless otherwise noted. Compounds were purchased from Aldrich or Acros or TCI America or Oakwood Chemicals unless otherwise noted. Toluene, acetonitrile, dichloromethane and α,α,α-trifluorotoluene were distilled over calcium hydride (CaH_2) under nitrogen atmosphere. THF was distilled over sodium-benzophenone ketyl under nitrogen atmosphere. Column 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 precoated silica gel 60 (particle size 0.040−0.063 mm). Yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AV-500 spectrometer. 19F NMR spectrum was recorded in Varian Mercury-Vx-300 spectrometer. ^{1}H NMR chemical shifts (δ) are reported in parts per million (ppm) downfield of TMS and are referenced relative to the residual proteated solvent peak ($CDCl_3$ (7.26 ppm)). ^{13}C chemical shifts (δ) are reported in parts per million downfield of TMS and are referenced to the carbon resonance of the solvent ($CDCl_3$ (77.2 ppm)). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sext (sextet) or m (multiplet). 1H NMR signals that fall within a ca. 0.3 ppm range are generally reported as a multiplet, with a range of chemical shift values corresponding to the peak or center of the peak. Coupling constants, J, are reported in Hz (Hertz). Electrospray ionization (ESI) mass spectra were recorded on a Waters Micromass Q-Tof Ultima in the University of Illinois at Urbana-Champaign. Electron impact (EI) mass spectra and Chemical Ionization (CI) mass spectra were obtained using a Micromass 70-VSE in the University of Illinois at Urbana–Champaign.

2.6.2 Experimental Procedures

Synthesis of Symmetrical Tetraynes (2-6a-c)



To a solution of 2-methyl-3-butyn-2-ol (2 g, 35.7 mmol) in CH_2Cl_2 (30 mL) was added PTSA (0.5 g, 2.5 mmol) at 0 °C and the mixture was stirred for 5 min at 0 °C before addition of 3,4-dehydropyran (3.3

g, 39.2 mmol). The resulting solution was warmed to room temperature and stirred for 5 h. The reaction solution was quenched with sat. $NaHCO_3$ (50 mL) solution and the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (x2). The combined organic layers were dried with $MgSO_4$ and concentrated under vacuum to afford compound **S1** (4.5 g, 32 mmol, 90%) as a light-yellow oil. The crude product was used for the next step without any further purification.

In a dried round-bottomed flask, **S1** was dissolved in dry THF at –78 °C under nitrogen and *n*-BuLi (2.5 M in hexane, 1.1 equiv) was added slowly and the mixture was stirred at –78 °C for 30 minutes. A solution of carbonyl compound (1.1 equiv) in THF was added slowly to the mixture and the mixture was allowed to warm up to room temperature over 2 hours, and the progression of the reaction was monitor by TLC. The mixture was then cooled to 0 °C with an ice bath and Et_2O (20 mL) and saturated NH_4Cl were added. The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated in vacuo, and the crude product was purified by silica gel column chromatography (SiO_2, hexanes:EtOAc = 10:1 to 3:1) to obtain desired products **S2** (82%) and **S4** (68−75%)**.**

A dry round-bottomed flask was equipped with a Dean-Stark trap. Propargyl alcohol (1 equiv), triethyl orthoacetate (3 equiv), and propanoic acid (0.2 equiv) were added sequentially. The mixture was heated to 150 °C until complete consumption of the starting material (monitor by TLC). The mixture was then cooled to 0 °C with an ice bath. Et_2O (20 mL) and dilute HCl (1 M, 20 mL) were added. The organic layer was separated, and the aqueous layer was extracted with Et_2O (x2). The combined organic layers were dried over Na_2SO_4, filtered, concentrated in vacuo, and purified by silica gel column chromatography (SiO_2, hexanes:EtOAc = 10:1) to afford a desired product **S5** (43−60%).

In a 100 mL round-bottomed flask, $LiAlH_4$ (2 equiv) was suspended in anhydrous Et_2O (30 mL) and it was cooled to –78 °C. A solution of an ester substrate (1 equiv) in anhydrous Et_2O (10 mL) was added dropwise and the reaction mixture was warmed up slowly to room temperature over 1.5 h. The reaction was quenched with MeOH, then with a saturated aqueous solution of potassium sodium tartrate

and extracted with Et_2O (x3). The combined organic extracts were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure (rotary evaporator bath at 19 ºC, ≥ 100 mbar) and the crude residue was purified by silica gel column chromatography (SiO_2, hexanes:EtOAc = 10:1 to 5:1) to afford a pure alcohol **S3** (57%) and **S6** (42%).

To a mixture of *p*-toluenesulfonamide (100 mg, 0.58 mmol) and K_2CO_3 (241 mg, 1.75 mmol) in acetone (6 mL) was added propargyl bromide (0.125 mL, 1.46 mmol), and the reaction mixture was stir at room temperature overnight. The mixture was concentrated under reduced pressure, diluted with Et_2O (30 mL), washed with brine (5 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (SiO_2, hexanes:EtOAc = 5:1) to give **S7** (118 mg, 0.48 mmol, 82%).

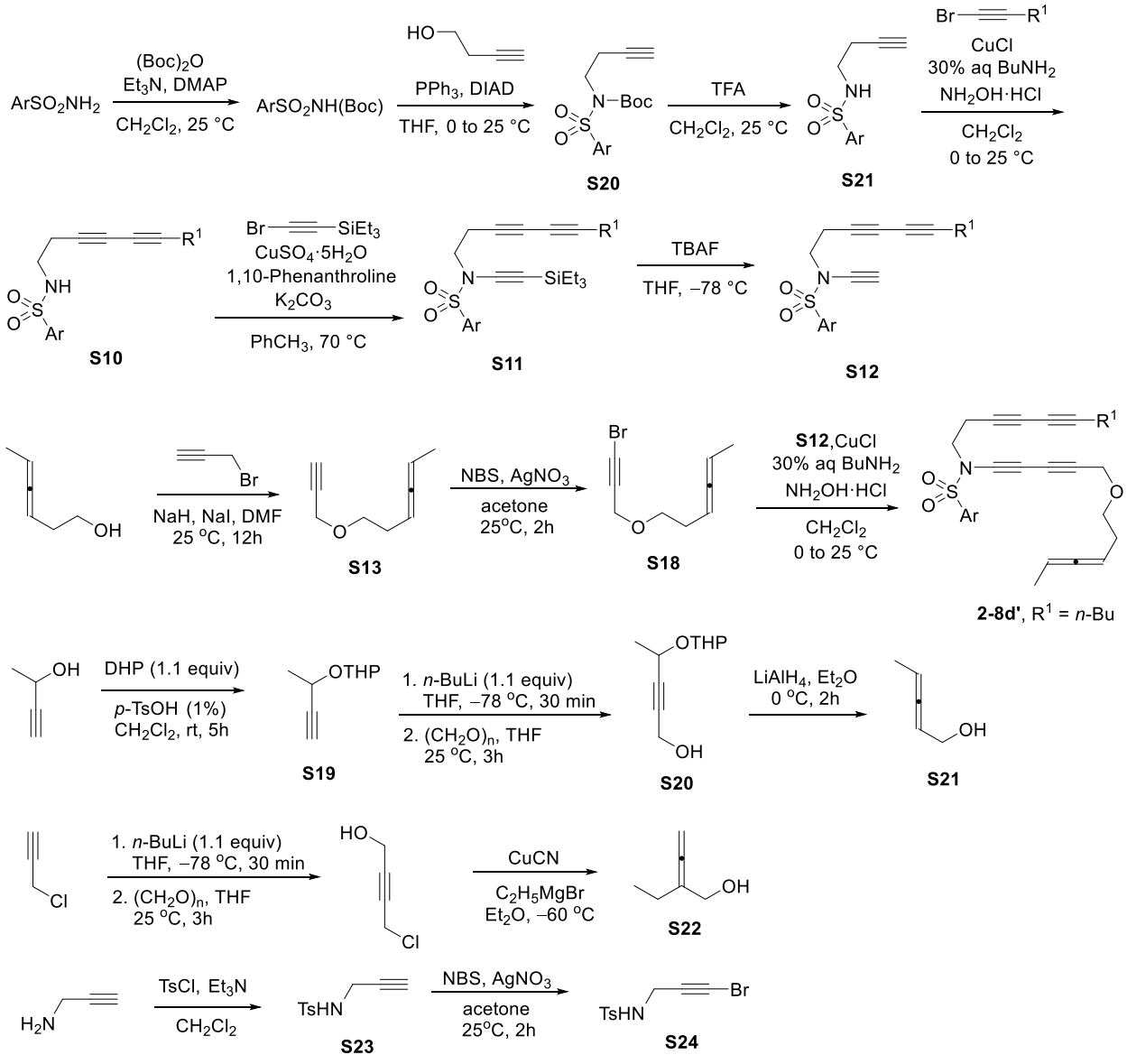
To a stirred solution of diyne (1.0 mmol) in acetone at 25 °C, *N*-bromosuccinimide (2.5 mmol) and $AgNO_3$ (0.1 mmol) were added sequentially under N_2 atmosphere in the dark. After addition, the reaction was allowed to warm up to room temperature over 3 h. Upon complete consumption of alkyne, the reaction mixture was concentrated under reduced pressure and filtered through silica gel. Purification by flash column chromatography (SiO_2, hexanes:EtOAc = 10:1 to 5:1) provided dibromide **S8** (316 mg, 0.78 mmol, 78%).

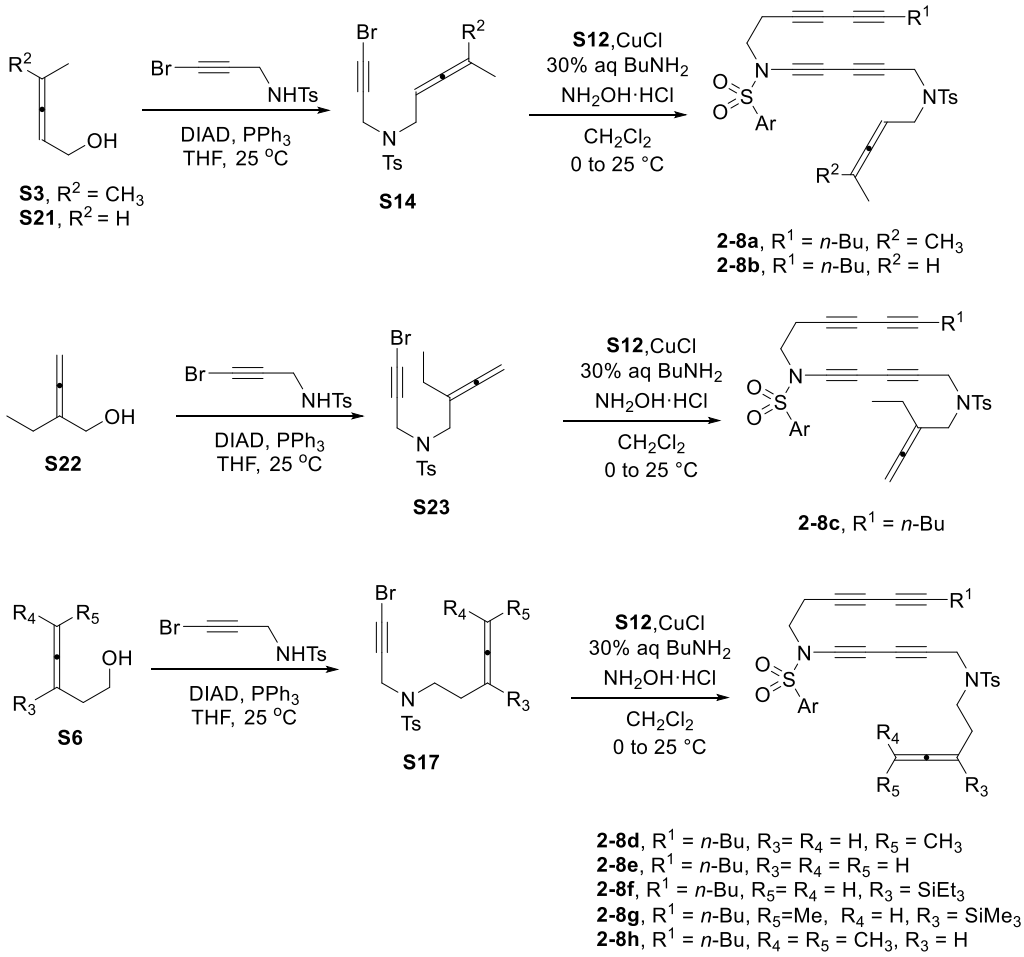
Diisopropyl azodicarboxylate (1.2 equiv) was added dropwise to a solution of sulfoamide (1.0 equiv), PPh_3 (1.2 equiv), and a substrate alcohol (1.0 equiv) in dry THF at 0 °C under nitrogen. The reaction mixture was warmed up to room temperature and further stirred overnight. After completion, the reaction mixture was concentrated and purified by silica gel column chromatography (SiO_2, hexanes:EtOAc = 10:1 to 5:1) to get a pure product **S9** (62%)**.** Exact procedures were repeated to obtain **S17** (58%).

In a two-necked round bottomed flask containing CuCl (0.3 equiv) in CH_2Cl_2 was added 30% aqueous $BuNH_2$ solution under nitrogen flow. A pinch of $NH_2OH{\bullet}HCl$ was added until the blue color disappeared. A solution of terminal alkyne **S9** (1.1 equiv) in CH_2Cl_2 was added at 0 °C to the flask and the

solution became yellow. A dilute solution of dibromoalkyne (0.5 equiv) in CH_2Cl_2 was added drop wise at 0 °C and the reaction mixture was stirred for 5 minutes at room temperature. The progression of the reaction was monitored by TLC and after complete consumption of the starting materials, the nitrogen flow was removed, and the biphasic reaction mixture was transferred to a separatory funnel. The CH_2Cl_2 layer was separated and dried over anhydrous Na_2SO_4. After filtration, the organic layer was concentrated, and the crude material was purified by silica gel column chromatography (SiO_2, hexanes:EtOAc = 10:1 to 5:1) to get a pure product **2-6a** (57%). Exact procedures were repeated with terminal alkyne **S17** to obtain **2-6b** (45%) and **2-6c** (53%).

Synthesis of Unsymmetrical Tetraynes (2-8a-h)





To a solution of arylsulfonamide (1.0 equiv) in CH_2Cl_2 were added trimethylamine (1.5 equiv) and DMAP (0.1 equiv). A solution of $(Boc)_2O$ (1.05 equiv) in CH_2Cl_2 was added slowly to the reaction mixture at room temperature, which was stirred until complete consumption of the starting materials (monitored by TLC). After completion, the reaction mixture was transferred to a separatory funnel diluted with CH_2Cl_2 and washed with water (x2) and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure and the crude product was used for the next reaction without further purification.

Diisopropyl azodicarboxylate (1.2 equiv) was added dropwise to a solution of $ArSO_2NH(Boc)$ (1.0 equiv), PPh_3 (1.2 equiv), and 3-butyne-1-ol (1.0 equiv) in dry THF at 0 °C under nitrogen. The reaction mixture was warmed up to room temperature and further stirred overnight. After completion, the reaction

mixture was concentrated and purified by silica gel column chromatography (SiO_2, hexanes:EtOAc = 10:1 to 5:1) to get pure product **S20** (65%).

Trifluoroacetic acid (5.0 equiv) was added to a solution of Boc-protected sulfonamide (1.0 equiv) in CH_2Cl_2 at room temperature and the mixture was stirred until complete consumption of the starting materials (monitored by TLC). After completion, the reaction mixture was transferred to a separatory funnel diluted with CH_2Cl_2 and washed with water (x2) and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure and the crude product was purified by silica gel column chromatography (SiO_2, hexanes:EtOAc = 10:1 to 5:1) to obtain pure product **S21** (56%).

In a two-necked round bottomed flask containing CuCl (0.3 equiv) was added 30% aqueous $BuNH_2$ solution under nitrogen flow. A pinch of NH_2OH•HCl was added until the blue color disappeared. A solution of terminal alkyne (1.0 equiv) in CH_2Cl_2 was added at 0 °C to the flask and the solution became yellow. A dilute solution of bromoalkyne (1.2 equiv) in CH_2Cl_2 was added drop wise at 0 °C and the reaction mixture was stirred for 5 minutes at room temperature. The progression of the reaction was monitored by TLC and after complete consumption of the starting materials, the nitrogen flow was removed, and the biphasic reaction mixture was transferred to a separatory funnel. The CH_2Cl_2 layer was separated and dried over anhydrous Na_2SO_4. After filtration, the organic layer was concentrated, and the crude material was purified by silica gel column chromatography (SiO_2, hexanes:EtOAc = 5:1 to 3:1)to get a pure product **S10** (62%).

$CuSO_4$•$5H_2O$ (10 mol %), 1,10-phenanthroline (20 mol %), K_2CO_3 (2.0 equiv) and bromoalkyne (2.0 equiv) were added to a solution of sulfonamide **S10** (1.0 equiv) in dry toluene. The reaction mixture was stirred at 70 °C overnight. After complete consumption of the starting materials, the reaction mixture was filtered through a small pad of celite. The filtrate was concentrated to get a crude product which was purified by silica gel column chromatography (SiO_2, hexanes:EtOAc = 10:1 to 5:1) to isolate a pure product **S11** (43%).

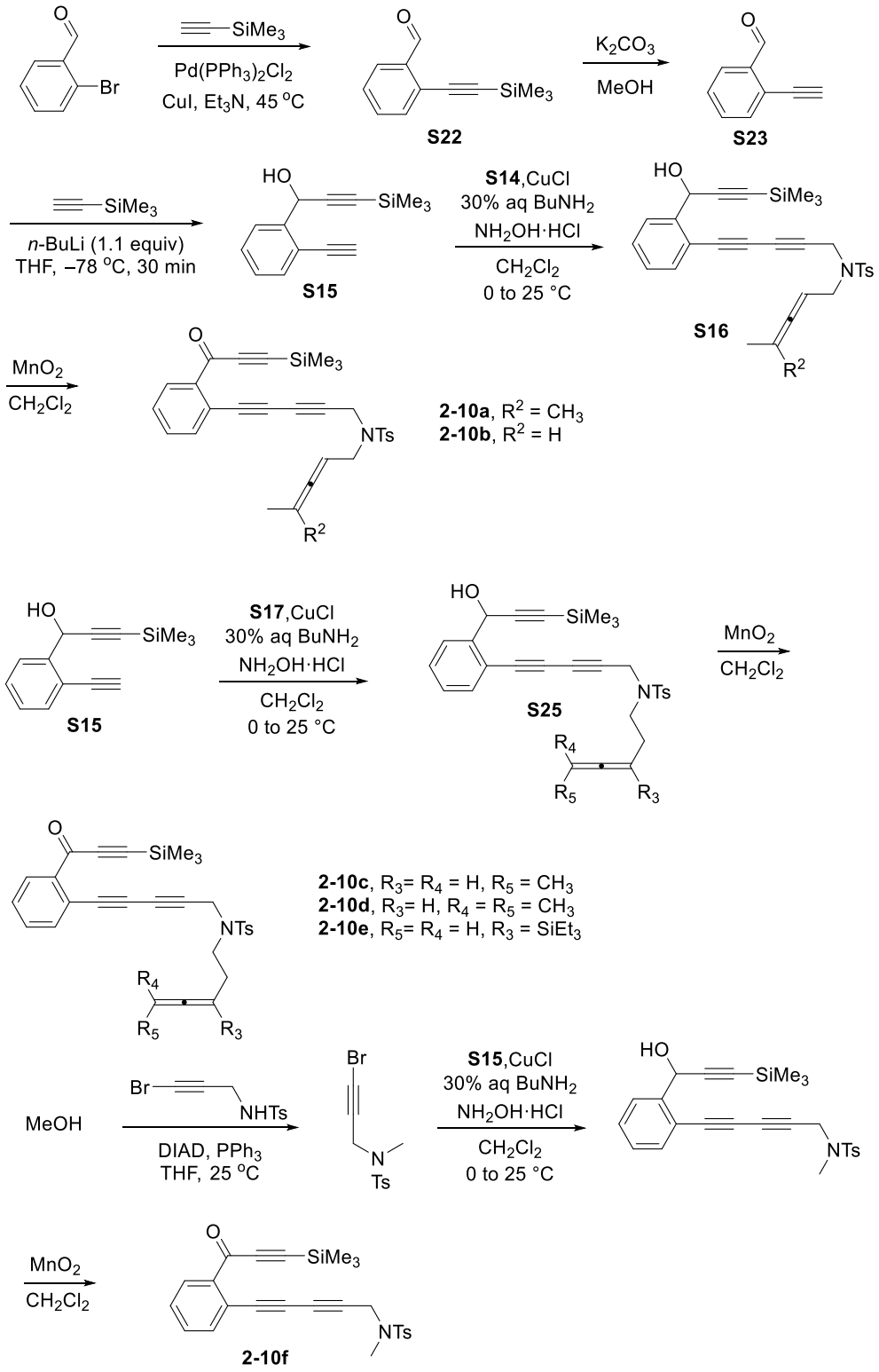
Tetrabutylammonium fluoride (1.1 equiv) was added to a solution of alkynyl trialkylsilane (1.0 equiv) in dry THF at –78 °C under nitrogen and progression of the reaction was checked by TLC. Upon completion, the reaction mixture was transferred to a separatory funnel, diluted with EtOAc, washed with water (x2) and then brine. The organic layer was separated, drier over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product **S12** was directly used for the next reaction without further purification.

To a stirred solution of alkyne (**S13**, **S23**, 1.0 mmol) in acetone at 25 °C, *N*-bromosuccinimide (2.5 mmol) and $AgNO_3$ (0.1 mmol) were added sequentially under N_2 atmosphere in the dark. After addition, the reaction was allowed to stir at room temperature for 3h. Upon complete consumption of alkyne, the reaction mixture was concentrated under reduced pressure and filtered through silica gel. Purification by flash column chromatography (SiO_2, hexanes:EtOAc, 1:5 to 1:3) provided bromide **S18** (78%) and **S24** (75%).

In a two-necked round bottomed flask containing CuCl (0.3 equiv) was added 30% aqueous $BuNH_2$ solution under nitrogen flow. A pinch of $NH_2OH{\bullet}HCl$ was added until the blue color disappeared. A solution of terminal alkyne **S12** (1.0 equiv) in CH_2Cl_2 was added at 0 °C to the flask and the solution became yellow. A dilute solution of bromoalkyne **S14** (1.2 equiv) in CH_2Cl_2 was added drop wise at 0 °C and the reaction mixture was stirred for 5 minutes at room temperature. The progression of the reaction was monitored by TLC and after complete consumption of the starting materials, the nitrogen flow was removed, and the biphasic reaction mixture was transferred to a separatory funnel. The CH_2Cl_2 layer was separated and dried over anhydrous Na_2SO_4. After filtration, the organic layer was concentrated, and the crude material was purified by silica gel column chromatography (SiO_2, hexanes:EtOAc = 10:1 to 5:1) to get pure products **2-8a** (65%) and **2-8b** (58%). Exact procedures were repeat three more time with **S17**, **S18** and **S23** as bromo alkyne to afford **2-8c**–**2-8h** (53–68%).

S22 was produce following the established procedure in literature.[27] Please see reference for more information.

Synthesis of Benzo-tethered Triynes



To a solution of aryl bromide (1 equiv) in Et_3N (20 mL) was added $(Ph_3P)_2PdCl_2$ (0.5 mol%) and CuI (1.0 mol%) at room temperature under nitrogen. Terminal alkyne (1.2 equiv) was added dropwise to the above solution with continuous stirring. After 15 minutes, the reaction mixture was warmed up to 40 °C and stirred until complete consumption of the alkenyl bromide (monitored by thin layer chromatography). Upon completion, the reaction mixture was filtered through Celite pad, concentrated and directly loaded on a silica gel column and eluted (hexanes:EtOAc, 20:1 to 5:1) to obtain pure product **S22** (quantitative yield).

Potassium carbonate (5 mol%) was added to a solution of alkynyltrialkylsilane **S22** (1.0 equiv) in methanol at room temperature under nitrogen and progress of the reaction was checked by TLC. Upon completion, the reaction mixture was filtered through silica gel and concentrated under reduced pressure. The crude product was loaded on a silica gel column and eluted (hexanes:EtOAc, 20:1 to 5:1) to obtain the pure product **S23** (95%).

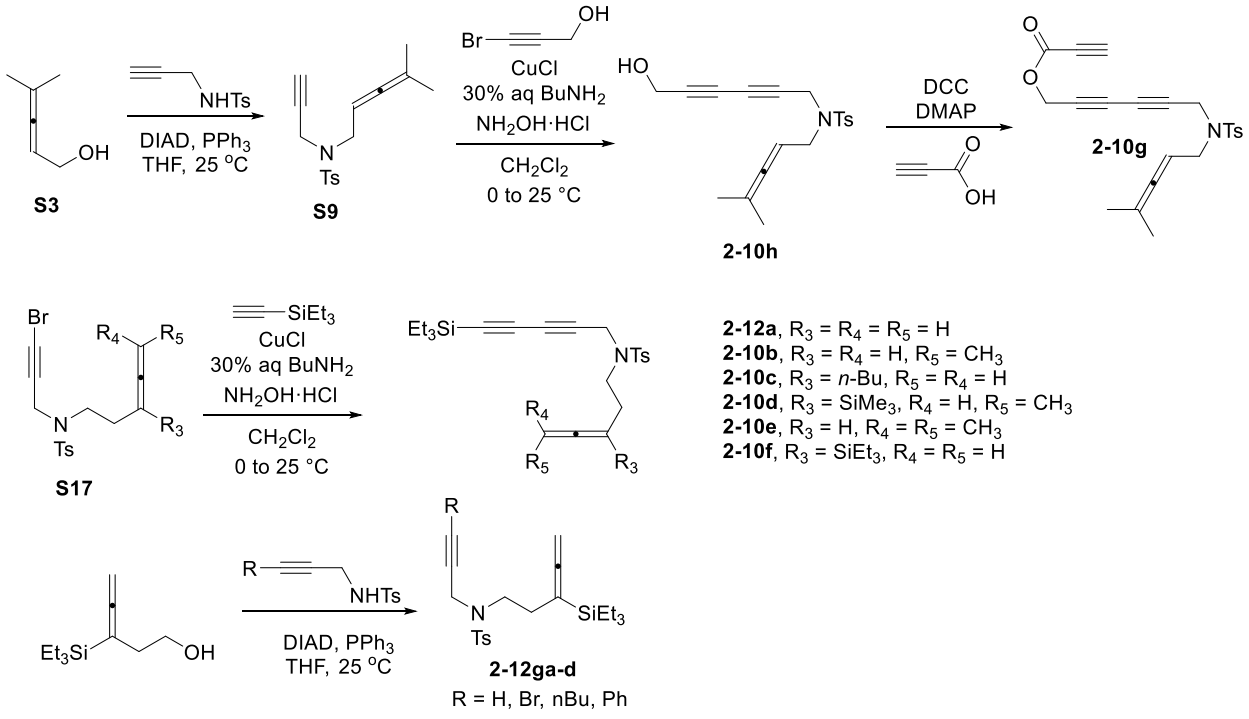
In a dried round-bottomed flask, a precursor alkyne was dissolved in dry THF at –78 °C under nitrogen and *n*-BuLi (2.5 M in hexane, 1.1 equiv) was added slowly and the mixture was stirred at –78 °C for 30 minutes. A solution of carbonyl compound (1.1 equiv) in THF was added slowly to the mixture and the mixture was allowed to warm up to room temperature over 2 hours, and the progression of the reaction was monitor by TLC. The mixture was then cooled to 0 °C with an ice bath and Et_2O (20 mL) and saturated NH_4Cl were added. The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated in vacuo, and the crude product was purified by silica gel column chromatography (SiO_2, hexanes:EtOAc = 10:1 to 5:1) to obtain desired products **S15** (86%).

In a two-necked round bottomed flask containing CuCl (0.3 equiv) was added 30% aqueous $BuNH_2$ solution under nitrogen flow. A pinch of $NH_2OH{\bullet}HCl$ was added until the blue color disappeared. A solution of terminal alkyne **S15** (1.0 equiv) in CH_2Cl_2 was added at 0 °C to the flask and the solution became yellow. A dilute solution of bromoalkyne **S14** (1.2 equiv) in CH_2Cl_2 was added drop wise at 0 °C and the

reaction mixture was stirred for 5 minutes at room temperature. The progression of the reaction was monitored by TLC and after complete consumption of the starting materials, the nitrogen flow was removed, and the biphasic reaction mixture was transferred to a separatory funnel. The CH_2Cl_2 layer was separated and dried over anhydrous Na_2SO_4. After filtration, the organic layer was concentrated, and the crude material was purified by silica gel column chromatography (SiO_2, hexanes:EtOAc = 10:1 to 5:1) to get a pure product **S16** (62%). An exact procedure was repeat one more time to obtain product **S25** (57%).

Manganese (IV) oxide (5 equiv) was added to a solution of benzylic alcohol **S16** (1 equiv) in CH_2Cl_2 at room temperature. The reaction progress was monitored by TLC. Upon completion, the reaction mixture was filtered through Celite and the solid was washed with CH_2Cl_2. The combine organic solution was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (SiO_2, hexanes:EtOAc = 15:1 to 10:1) to obtain pure product **2-10a**–**2-10f** (65–82%).

Synthesis of Diyne and Monoyne-tethered Allenes



Diisopropyl azodicarboxylate (1.2 equiv) was added dropwise to a solution of sulfoamide (1.0 equiv), PPh_3 (1.2 equiv), and a substrate alcohol (1.0 equiv) in dry THF at 0 °C under nitrogen. The reaction mixture was warmed up to room temperature and further stirred overnight. After completion, the reaction mixture was concentrated and purified by silica gel column chromatography (SiO_2, hexanes:EtOAc = 10:1 to 5:1) to get a pure product **S9** (65%).

In a two-necked round bottomed flask containing CuCl (0.3 equiv) was added 30% aqueous $BuNH_2$ solution under nitrogen flow. A pinch of NH_2OH•HCl was added until the blue color disappeared. A solution of terminal alkyne (1.0 equiv) in CH_2Cl_2 was added at 0 °C to the flask and the solution became yellow. A dilute solution of bromoalkyne (1.2 equiv) in CH_2Cl_2 was added drop wise at 0 °C and the reaction mixture was stirred for 5 minutes at room temperature. The progression of the reaction was monitored by TLC and after complete consumption of the starting materials, the nitrogen flow was removed, and the biphasic reaction mixture was transferred to a separatory funnel. The CH_2Cl_2 layer was separated and dried over anhydrous Na_2SO_4. After filtration, the organic layer was concentrated, and the crude material was purified by silica gel column chromatography (SiO_2, hexanes:EtOAc = 10:1 to 5:1) to get a pure product **2-10h** (62%).

4-Dimethylaminopyridine (0.1 equiv) was add slowly to the solution of propargryl alcohol **2-10h** (1 equiv), propionic acid (1 equiv), and *N,N'*-Dicyclohexylcarbodiimide (1.2 equiv). The reaction was allowed to stir at room temperature for 1h. The process was monitor by TLC. After completion, the reaction mixture was concentrated and purified by silica gel column chromatography (SiO_2, hexanes:EtOAc = 10:1 to 5:1) to get a pure product **2-10g** (72%).

In a two-necked round bottomed flask containing CuCl (0.3 equiv) was added 30% aqueous $BuNH_2$ solution under nitrogen flow. A pinch of NH_2OH•HCl was added until the blue color disappeared. A solution of (Triethylsilyl)acetylene (1.0 equiv) in CH_2Cl_2 was added at 0 °C to the flask and the solution became yellow. A dilute solution of bromoalkyne **S17** (1.2 equiv) in CH_2Cl_2 was added drop wise at 0 °C and the reaction mixture was stirred for 5 minutes at room temperature. The progression of the reaction was

monitored by TLC and after complete consumption of the starting materials, the nitrogen flow was removed, and the biphasic reaction mixture was transferred to a separatory funnel. The CH_2Cl_2 layer was separated and dried over anhydrous Na_2SO_4. After filtration, the organic layer was concentrated, and the crude material was purified by silica gel column chromatography (SiO_2, hexanes:EtOAc = 10:1 to 5:1)to get a pure product **2-12a-f** (65–78%).

General procedures for the intramolecular reaction of alkynes with allenes

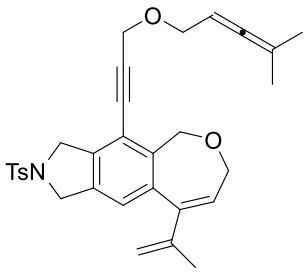
General Procedure A (GPA)

A solution of a substrate in toluene (10–15 mM) in a Schlenk tube was flushed with nitrogen. The mixture was stirred for 6 h at 90 °C unless otherwise noted. After completion, the reaction mixture was transferred to a round-bottomed flask, concentrated, and purified by column chromatography eluted (hexanes:EtOAc = 15:1 to 5:1) to get pure products.

General Procedure B (GPB)

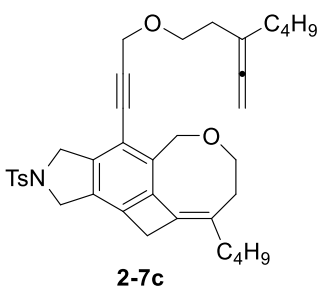
A solution of a substrate in toluene (10–15 mM) in a Schlenk tube was flushed with nitrogen. The mixture was stirred for 12 h at 150 °C unless otherwise noted. After completion, the reaction mixture was transferred to a round-bottomed flask, concentrated, and purified by column chromatography eluted (hexanes:EtOAc = 15:1 to 5:1) to get pure products.

2.6.3. Characterization Data



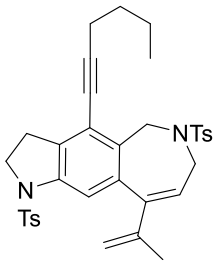
2-7a

2-7a, yellow oil, 73% yield, 18 mg (using GPA). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.79–7.78 (m, 2H), 7.33–7.32 (m, 2H), 7.10 (s, 1H), 6.19 (t, 1H, *J* = 6.8 Hz), 5.16 (s, 1H), 5.11–5.07 (m, 1H), 4.89 (s, 1H), 4.70 (s, 2H), 4.64 (s, 2H), 4.58 (s, 2H), 4.44 (s, 2H), 4.11 (d, 2H, *J* = 6.9 Hz), 3.74 (d, 2H, *J* = 6.9 Hz), 2.41 (s, 3H), 1.96 (s, 3H), 1.74 (d, 6H, *J* = 2.8 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 203.6, 147.2, 143.8, 142.8, 139.8, 139.1, 138.4, 135.5, 133.8, 129.9, 127.6, 123.7, 122.9, 117.8, 96.4, 93.7, 85.4, 80.7, 68.8, 64.1, 62.4, 57.1, 54.1, 54.1, 29.7, 21.5, 20.4. HRMS (ESI) calcd for $C_{31}H_{34}NO_4S$ $[M + H]^+$ 516.2208 , found 516.2206.



2-7c

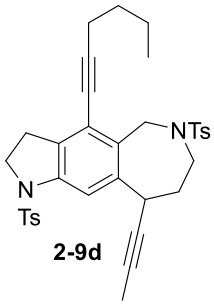
2-7c, yellow oil, 58% yield, 11 mg (using GPA). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.78–7.76 (m, 2H), 7.33–7.31 (m, 2H), 4.76 (s, 2H), 4.71 (t, 2H, *J* = 3.1 Hz), 4.62 (s, 2H), 4.55 (s, 2H), 4.40 (s, 2H), 3.89 (t, 2H, *J* = 4.6 Hz), 3.66 (t, 2H, *J* = 2.0 Hz), 3.49 (s, 2H), 2.42–2.40 (m, 5H, mixed peaks), 2.29–2.26 (m, 2H), 2.11 (t, 2H, *J* = 7.5 Hz), 1.99–1.97 (m, 2H), 1.48–1.41 (m, 4H, mixed peaks), 1.36–1.31 (m, 4H, mixed peaks), 0.92–0.88 (m, 6H, mixed peaks); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 205.6, 143.7, 140.6, 139.2, 138.1, 135.1, 133.8, 132.7, 129.9, 128.5, 128.4, 127.6, 112.8, 100.0, 94.3, 80.5, 76.1, 70.0, 69.4, 68.5, 58.8, 53.9, 52.1, 36.5, 34.2, 33.9, 32.1, 31.9, 30.6, 29.7, 29.6, 22.6, 22.4, 21.5, 14.0. HRMS (ESI) calcd for $C_{37}H_{46}NO_4S$ $[M + H]^+$ 600.3145, found 600.3147.



2-9a

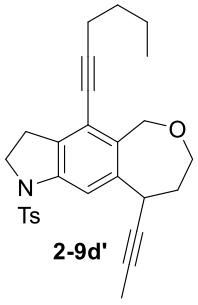
2-9a, yellow oil, 63% yield, 12 mg (using GPA). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.76–7.74 (m, 2H), 7.64–7.63 (m, 2H), 7.36 (s, 1H), 7.28–7.27 (m, 2H), 7.23–7.21 (m, 2H), 5.72 (t, 1H, *J* = 7.5 Hz), 5.16 (s, 1H), 4.80 (s, 1H), 4.27 (s, 2H), 3.94 (t, 2H, *J* = 8.5 Hz), 3.52 (d, 2H, *J* = 7.5 Hz), 2.99 (t, 2H, *J* = 8.5 Hz), 2.44–2.42 (m, 5H, mixed peaks), 2.38 (s, 3H), 1.84 (s, 3H), 1.60–1.56 (m, 2H), 1.49–1.41 (m, 2H), 0.94 (t, 3H, *J* = 7.3

Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 147.3, 144.4, 143.2, 142.0, 141.0, 139.0, 136.6, 134.4, 133.6, 130.2, 129.7, 129.5, 127.6, 127.4, 121.6, 119.8, 118.0, 114.1, 99.6, 75.7, 49.9, 45.9, 43.0, 30.7, 28.1, 22.1, 21.5, 21.5, 21.0, 19.3, 13.6. HRMS (ESI) calcd for $C_{35}H_{39}N_2O_4S_2$ $[M + H]^+$ 615.2349 , found 615.2047.



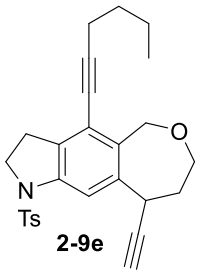
2-9d

2-9d, yellow oil, 64% yield, 14 mg (using GPA). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.68–7.67 (m, 2H), 7.63–7.61 (m, 2H), 7.56 (s, 1H), 7.26–7.24 (m, 2H), 7.21–7.19 (m, 2H), 4.78–4.68 (m, 1H), 3.91–3.85 (m, 3H, mixed peaks), 3.71 (brs, 1H), 3.58 (t, 1H, *J* = 10.5 Hz), 2.92 (t, 2H, *J* = 8.6 Hz), 2.47 (t, 2H, *J* = 7.0 Hz), 2.39 (brs, 6H, mixed peaks), 1.98 (t, 1H, *J* = 10.5 Hz), 1.84 (s, 3H), 1.64–1.58 (m, 4H, mixed peaks), 1.51–1.45 (m, 2H), 0.93 (t, 3H, *J* = 7.3 Hz) ; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 144.3, 142.9, 141.2, 141.1, 136.8, 133.7, 132.6, 129.8, 129.4, 127.3, 127.2, 121.6, 114.1, 99.5, 81.4, 78.0, 76.0, 49.9, 48.5, 48.1, 37.1, 33.7, 30.8, 28.0, 22.1, 21.6, 21.5, 19.4, 13.6, 3.6. HRMS (ESI) calcd for $C_{35}H_{39}N_2O_4S_2$ $[M + H]^+$ 615.2347 , found 615.2346.



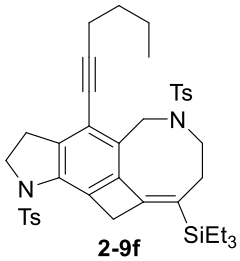
2-9d'

2-9d', yellow oil, 60% yield, 12 mg (using GPA). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.69–7.67 (m, 3H, mixed peaks), 7.24–7.23 (m, 2H), 5.09 (d, 1H, *J* = 13.7 Hz), 4.90 (brs, 1H), 4.26 (t, 1H, *J* = 9.6 Hz), 4.05–3.99 (m, 2H), 3.89 (t, 1H, *J* = 8.0 Hz), 2.90 (t, 2H, *J* = 8.5 Hz), 2.39–2.35 (m, 5H, mixed peaks), 2.17 (s, 2H), 2.04 (t, 1H, *J* = 11.2 Hz), 1.92 (s, 3H), 1.54–1.49 (m, 2H), 1.45–1.38 (m, 2H), 0.90 (t, 3H, *J* = 7.3 Hz) ; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 144.2, 142.3, 141.0, 133.8, 132.5, 130.0, 129.7, 127.5, 127.4, 114.2, 98.8, 81.3, 76.0, 71.6, 69.7, 49.9, 45.0, 37.5, 35.9, 30.8, 28.0, 21.9, 21.5, 19.2, 13.6, 3.7. HRMS (ESI) calcd for $C_{28}H_{32}NO_3S$ $[M + H]^+$ 462.2103 , found 462.2101.



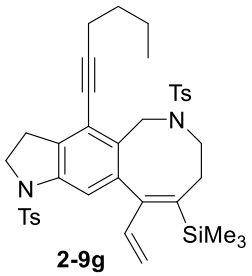
2-9e

2-9e, yellow oil, 55% yield, 12 mg (using GPA). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.72–7.68 (m, 3H, mixed peaks), 7.24–7.22 (m, 2H), 5.09 (d, 1H, *J* = 13.8 Hz), 4.89 (brs, 1H), 4.26 (t, 1H, *J* = 9.4 Hz), 4.11 (d, 1H, *J* = 7.4 Hz), 4.03–4.00 (m, 1H), 3.89 (t, 2H, *J* = 8.5 Hz), 2.90 (t, 2H, *J* = 8.5 Hz), 2.50 (s, 1H), 2.40–2.37 (m, 5H, mixed peaks), 2.11–2.07 (m, 1H), 1.97–1.93 (m, 1H), 1.54–1.49 (m, 2H), 1.44–1.40 (m, 2H), 0.90 (t, 3H, *J* = 7.3 Hz) ; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 144.2, 141.1, 140.9, 135.5, 133.7, 132.9, 129.7, 127.4, 121.3, 114.1. 99.0, 83.6, 75.9, 73.7, 71.4, 69.7, 49.9, 37.1, 35.5, 30.7, 28.0, 21.9, 21.5, 19.2, 13.6. HRMS (ESI) calcd for $C_{28}H_{32}NO_3S$ $[M + H]^+$ 448.1946, found 448.1944.



2-9f

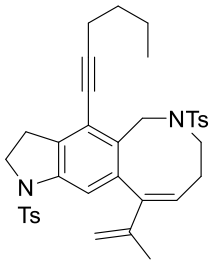
2-9f, yellow oil, 62% yield, 15 mg (using GPA). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.64–7.62 (m, 2H), 7.55–7.53 (m, 2H), 7.28–7.26 (m, 2H), 7.19–7.17 (m, 2H), 4.48 (s, 2H), 3.87 (t, 2H, *J* = 8.3 Hz), 3.68 (s, 2H), 3.53 (t, 2H, *J* = 6.0 Hz), 2.93 (t, 2H, *J* = 8.3 Hz), 2.62 (t, 2H, *J* = 6.0 Hz), 2.43 (t, 2H, *J* = 6.0 Hz), 2.40 (s, 3H), 2.39 (s, 3H), 1.59–1.55 (m, 2H), 1.50–1.45 (m, 2H), 0.98–0.95 (m, 12H, mixed peaks), 0.67 (q, 6H, *J* = 8.3 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 146.0, 144.4, 144.1, 143.1, 136.1, 134.9, 134.6, 134.2, 129.8, 129.1, 127.4, 126.6, 118.7, 99.5, 75.7, 50.1, 49.7, 48.1, 42.0, 32.0, 30.9, 29.7, 28.7, 22.0, 21.5, 21.5, 19.3, 13.6, 7.6, 3.5. HRMS (ESI) calcd for $C_{40}H_{50}N_2O_4S_2Si$ $[M + H]^+$ 715.3059, found 715.3057.



2-9g

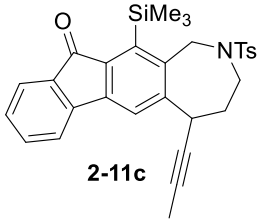
2-9g, yellow oil, 34% yield, 11 mg (using GPA). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.67–7.64 (m, 4H, mixed peaks), 7.30–7.21 (m, 5H, mixed peaks), 6.85 (dd, 1H, *J* = 16.8, 10.9 Hz), 5.24–5.17 (m, 2H, mixed peaks), 4.64 (d, 1H, *J* = 16.7 Hz), 4.05–3.99 (m, 1H), 3.89–3.83 (m, 1H), 3.63–3.60 (m, 1H), 3.18 (d, 1H, *J* = 16.7 Hz), 3.02 (t, 2H, *J* = 8.3 Hz), 2.51 (t, 2H, *J* = 8.4 Hz), 2.41–2.28 (m, 7H, mixed peaks), 2.04–1.91 (m, 1H), 1.60–1.56 (m, 2H), 1.48–1.42 (m, 2H), 0.91 (t, 2H, *J* = 8.3 Hz), 0.09 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 149.0, 144.3, 143.2, 142.7, 140.6, 140.0, 137.8, 134.6, 131.9, 129.6, 129.4, 127.8,

127.4, 122.6, 118.6, 113.9, 102.0, 75.7, 50.0, 47.3, 46.7, 30.7, 30.6, 28.1, 22.1, 21.5, 21.4, 19.7, 13.7, 0.5. HRMS (ESI) calcd for $C_{38}H_{47}N_2O_4S_2Si$ $[M + H]^+$ 678.2746 , found 687.2745.



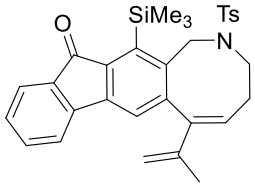
2-9h

2-9h, yellow oil, 58% yield, 11 mg (using GPA). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.70–7.68 (m, 2H), 7.65–7.63 (m, 2H), 7.29–7.28 (m, 3H, mixed peaks), 7.22–7.20 (m, 2H), 5.80 (t, 1H, *J* = 8.5 Hz), 5.25 (d, 1H, *J* = 12.0 Hz), 5.07 (s, 1H), 4.50 (s, 1H), 4.04–3.98 (m, 1H), 3.88–3.83 (m, 1H), 3.57–3.53 (m, 1H), 3.38 (d, 1H, *J* = 12.5 Hz), 3.02 (t, 2H, *J* = 8.3 Hz), 2.51 (t, 2H, *J* = 8.4 Hz), 2.42 (s, 3H), 2.38 (s, 3H), 1.94 (s, 3H), 1.60–1.54 (m, 2H), 1.47–1.40 (m, 2H), 0.91 (t, 2H, *J* = 8.3 Hz), 0.09 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 144.4, 143.6, 143.1, 142.7, 140.7, 139.3, 135.2, 134.9, 133.3, 131.8, 129.6, 129.5, 127.8, 127.5, 126.9, 122.6, 116.8, 114.5, 101.8, 75.9, 49.9, 47.4, 45.6, 30.6, 28.1, 27.4, 22.1, 21.5, 20.8, 19.7, 13.7. HRMS (ESI) calcd for $C_{36}H_{41}N_2O_4S_2$ $[M + H]^+$ 629.8538, found 629.8536.



2-11c

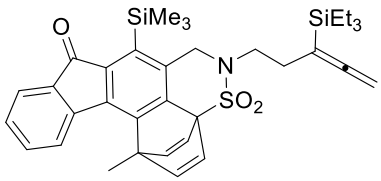
2-11c, yellow oil, 72% yield, 11 mg (using GPA). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.61 (d, 1H, *J* = 7.4 Hz), 7.48–7.44 (m, 5H, mixed peaks), 7.31–7.28 (m, 1H), 7.09–7.07 (m, 2H), 5.01–4.90 (m, 1H), 4.85–4.71 (m, 1H), 3.95–3.93 (m, 1H), 3.70–3.68 (m, 2H, mixed peaks), 2.24 (s, 3H), 1.93 (brs, 1H), 1.88 (d, 3H, *J* = 3.2 Hz), 1.75–1.70 (m, 1H), 1.63–1.56 (m, 2H), 0.89–0.84 (m, 1H), 0.49 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 194.8, 146.8, 144.8, 143.3, 142.9, 138.9, 134.4, 134.0, 129.4, 129.1, 127.0, 124.0, 121.5, 119.6, 81.2, 51.1, 47.8, 29.7, 21.3, 3.7, 2.5. HRMS (ESI) calcd for $C_{30}H_{32}NO_3SSi$ $[M + H]^+$ 514.1872, found 514.1870.



2-11d

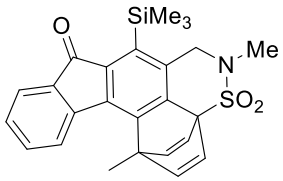
2-11d, yellow oil, 50% yield, 11 mg (using GPA). ^{1}H NMR ($CDCl_3$, 500 MHz): 7.77–7.75 (m, 2H), 7.63–7.61 (m, 1H), 7.47–7.43 (m, 2H), 7.32–7.29 (m, 3H, mixed peaks), 7.22 (s, 1H), 5.30 (t, 1H, *J* = 6.8 Hz), 4.90 (s, 2H), 4.38 (s, 1H), 4.19 (d, 1H, *J* = 10.6 Hz), 3.56 (brs, 1H), 3.03 (brs, 1H), 2.45–2.39 (m, 4H, mixed peaks), 1.95–1.92 (m, 1H), 1.71 (s, 3H), 0.47 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 194.6, 148.3, 145.0, 144.4,

143.4, 143.4, 143.2, 143.1, 139.8, 137.3, 134.5, 134.1, 129.5, 129.3, 127.5, 126.9, 124.1, 122.8, 119.9, 116.0, 49.7, 43.0, 27.3, 21.5, 20.2, 2.2. HRMS (ESI) calcd for $C_{31}H_{34}NO_3SSi$ $[M + H]^+$ 528.2028 , found 528.2026.



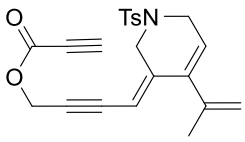
2-11e

2-11e, yellow oil, 34% yield, 11 mg (using GPA). ^{1}H NMR ($CDCl_3$, 500 MHz): 8.12 (d, 1H, *J* = 7.4 Hz), 7.67 (d, 1H, *J* = 7.4 Hz), 7.50 (t, 1H, *J* = 7.4 Hz), 7.30 (t, 1H, *J* = 7.4 Hz), 7.14–7.12 (m, 2H), 6.67–6.66 (m, 2H), 4.66 (s, 2H), 4.35 (s, 2H), 3.37 (t, 2H, *J* = 6.1 Hz), 2.42 (s, 3H), 2.25–2.22 (m, 2H), 0.92 (t, 9H, *J* = 7.4 Hz), 0.60 (q, 6H, *J* = 7.4 Hz), 0.40 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 209.0, 193.7, 148.9, 146.5, 145.9, 144.0, 137.5, 136.5, 134.2, 132.1, 128.5, 126.9, 126.5, 124.2, 121.3, 88.2, 69.9, 53.9, 52.0, 51.1, 47.5, 28.0, 25.1, 7.3, 3.2, 3.0. HRMS (ESI) calcd for $C_{35}H_{44}NO_3SSi_2$ $[M + H]^+$ 614.2580 , found 614.2578.



2-11f

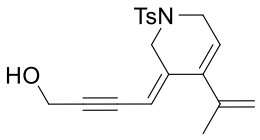
2-11f, yellow oil, 58% yield, 11 mg (using GPA). ^{1}H NMR ($CDCl_3$, 500 MHz): 8.12 (d, 1H, *J* = 7.4 Hz), 7.67 (d, 1H, *J* = 7.4 Hz), 7.52–7.48 (m, 1H), 7.31 (t, 1H, *J* = 7.4 Hz), 7.16–7.15 (m, 2H), 6.68–6.67 (m, 2H), 4.62 (s, 2H), 2.93 (s, 3H), 2.44 (s, 3H), 0.40 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 193.7, 148.5, 146.4, 145.9, 143.9, 137.7, 137.6, 136.5, 135.0, 134.3, 131.4, 128.5, 126.5, 124.2, 56.9, 52.0, 35.5, 29.7, 25.1, 3.2. HRMS (ESI) calcd for $C_{25}H_{26}NO_3SSi$ $[M + H]^+$ 448.1402, found 448.1401.



2-11g

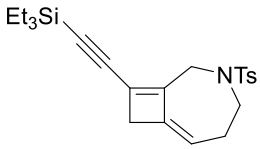
2-11g, yellow oil, 32% yield, 12 mg (using GPB). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.70–7.68 (m, 2H), 7.30–7.28 (m, 2H), 5.57 (t, 1H, *J* = 3.8 Hz), 5.45 (s, 1H), 5.01 (d, 2H, *J* = 2.0 Hz), 4.95 (t, 1H, *J* = 1.7 Hz), 4.57 (s, 1H), 4.15 (s, 2H), 3.90 (d, 2H, *J* = 4.0 Hz), 2.96 (s, 1H), 2.41 (s, 3H), 1.68 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 143.6, 141.9, 141.2,

140.4, 134.2, 129.6, 127.8, 123.4, 116.1, 105.5, 90.8, 84.0, 75.8, 54.5, 46.0, 45.3, 22.9, 21.5. HRMS (ESI) calcd for $C_{22}H_{22}NO_4S$ $[M + H]^+$ 396.1269, found 396.1262.



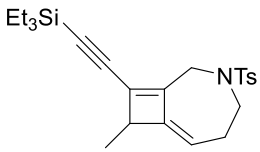
2-11h

2-11h, yellow oil, 62% yield, 18 mg (using GPB). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.69–7.67 (m, 2H), 7.28–7.26 (m, 2H), 5.52 (t, 1H, *J* = 3.8 Hz), 5.46 (s, 1H), 4.95 (s, 1H), 4.56 (s, 1H), 4.50 (s, 2H), 4.18 (s, 2H), 3.90 (d, 2H, *J* = 3.8 Hz), 2.40 (s, 3H), 1.67 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ143.7, 142.0, 140.6, 139.7, 134.3, 129.6, 127.8, 122.6, 116.0, 106.4, 96.8, 82.1, 51.8, 46.0, 45.3, 22.9, 21.5. HRMS (ESI) calcd for $C_{19}H_{22}NO_3S$ $[M + H]^+$ 344.1320, found 344.1318.



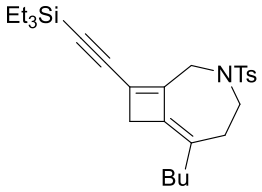
2-13a

2-13a, yellow oil, 82% yield, 25 mg (using GPB). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.68–7.67 (m, 2H), 7.30–7.28 (m, 2H), 5.09 (t, 1H, *J* = 4.1 Hz), 4.06 (s, 2H), 3.38 (t, 2H, *J* = 5.7 Hz), 2.90 (s, 2H), 2.46 (q, 2H, *J* = 5.0 Hz), 2.41 (s, 3H), 1.00 (t, 9H, *J* = 8.0 Hz), 0.64 (q, 6H, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ149.4, 143.3, 137.1, 136.1, 129.7, 127.1, 122.3, 116.2, 103.4, 100.0, 50.0, 48.9, 38.5, 32.9, 21.5, 7.5, 4.3. HRMS (ESI) calcd for $C_{23}H_{32}NO_2SSi$ $[M + H]^+$ 414.1923, found 414.1910.



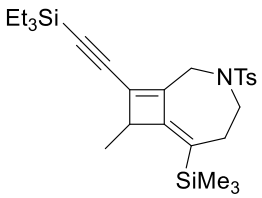
2-13b

2-13b, yellow oil, 85% yield, 22 mg (using GPB). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.69–7.67 (m, 2H), 7.30–7.28 (m, 2H), 5.10 (t, 1H, *J* = 4.0 Hz), 4.16 (d, 1H, *J* = 17.4 Hz), 3.99 (dd, 1H, *J* = 17.4, 3.2 Hz), 3.49–3.46 (m, 1H), 3.31–3.27 (m, 1H), 3.16–3.14 (m, 1H), 2.48–2.41 (m, 5H, mixed peaks), 1.11 (d, 3H, *J* = 6.4 Hz), 1.01 (t, 9H, *J* = 7.7 Hz), 0.65 (q, 6H, *J* = 7.7 Hz) ; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 147.4, 143.8, 143.3, 136.2, 129.7, 128.7, 127.1, 113.9, 104.5, 98.9, 50.0, 48.9, 45.8, 32.7, 21.5, 15.5, 7.5, 4.3. HRMS (ESI) calcd for $C_{24}H_{34}NO_2SSi$ $[M + H]^+$ 428.2080, found 428.2078.



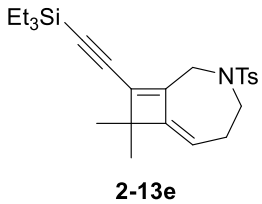
2-13c

2-13c, yellow oil, 80% yield, 20 mg (using GPB). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.69–7.65 (m, 2H), 7.28–7.27 (m, 2H), 4.06 (s, 2H), 3.36 (t, 2H, *J* = 4.0 Hz), 2.87 (s, 2H), 2.40–2.38 (m, 5H, mixed peaks), 1.89 (t, 2H, *J* = 6.5 Hz), 1.26–1.17 (m, 4H, mixed peaks), 1.00 (t, 9H, *J* = 7.7 Hz), 0.85 (t, 3H, *J* = 7.1 Hz), 0.63 (q, 6H, *J* = 7.7 Hz) ; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 148.7, 143.3, 136.1, 132.0, 129.7, 128.7, 127.1, 119.1, 102.3, 100.5, 49.3, 49.2, 37.5, 35.8, 32.6, 30.4, 22.4, 21.5, 14.0, 7.5, 4.4. HRMS (ESI) calcd for $C_{27}H_{40}NO_2SSi$ $[M + H]^+$ 470.2549, found 470.2544.



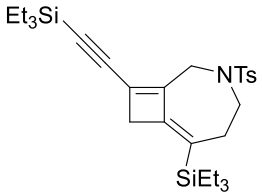
2-13d

2-13d, yellow oil, 78% yield, 22 mg (using GPB). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.70–7.65 (m, 2H), 7.28–7.26 (m, 2H), 4.22 (d, 1H, *J* = 17.2 Hz), 3.87 (d, 1H, *J* = 17.4 Hz), 3.54–3.51 (m, 1H), 3.22–3.20 (m, 2H), 2.56–2.51 (m, 1H), 2.43–2.36 (m, 4H, mixed peaks), 1.18 (d, 3H, *J* = 7.0 Hz), 1.00 (t, 9H, *J* = 7.9 Hz), 0.64 (q, 6H, *J* = 7.9 Hz), 0.06 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 150.5, 148.2, 143.3, 136.0, 130.2, 129.6, 127.4, 127.2, 105.9, 98.8, 50.5, 48.8, 47.1, 36.2, 21.5, 17.0, 7.5, 4.4, -0.5. HRMS (ESI) calcd for $C_{27}H_{42}NO_2SSi_2$ $[M + H]^+$ 500.2475, found 500.2476.



2-13e

2-13e, yellow oil, 65% yield, 16 mg (using GPB). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.69–7.67 (m, 2H), 7.29–7.27 (m, 2H), 5.10 (t, 1H, *J* = 4.2 Hz), 4.07 (s, 2H), 3.38 (t, 2H, *J* = 5.2 Hz), 2.44 (q, 2H, *J* = 4.4 Hz), 2.40 (s, 3H), 1.15 (s, 6H), 1.01 (t, 9H, *J* = 8.0 Hz), 0.64 (q, 6H, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 149.1, 145.1, 143.2, 136.3, 133.6, 129.7, 127.1, 111.5, 105.5, 97.7, 51.5, 50.0, 48.9, 32.5, 22.8, 21.5, 7.5, 4.4. HRMS (ESI) calcd for $C_{25}H_{36}NO_2SSi$ $[M + H]^+$ 442.2236, found 442.2242.



2-13f

2-13f, yellow oil, 78% yield, 22 mg (using GPB). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.68–7.66 (m, 2H), 7.30–7.28 (m, 2H), 4.06 (s, 2H), 3.36 (t, 3H, *J* = 5.0 Hz), 2.99 (s, 2H), 2.45 (t, 2H, *J* = 5.0 Hz), 2.40 (s, 3H), 1.15 (s, 6H), 1.01 (t, 9H, *J* = 8.2 Hz), 0.87 (t, 9H, *J* = 7.9 Hz), 0.64 (q, 6H, *J* = 7.9 Hz), 0.55 (q, 6H, *J* = 8.2 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 150.4, 144.9, 143.3, 136.0, 129.7, 127.9, 127.8, 127.1, 123.9, 104.9, 99.9, 50.7, 48.8, 40.8, 36.4, 21.5, 7.5, 7.4, 4.3, 3.4. HRMS (ESI) calcd for $C_{29}H_{46}NO_2SSi_2$ $[M + H]^+$ 528.2788, found 528.2776.

2.7. References

(1) For general reviews on Alder-ene reactions: (a) Hoffmann, H. M. R. *Angew. Chem., Int. Ed.* **1969**, *8*, 556. (b) Snider, B. B. *Acc. Chem. Res*. **1980**, *13*, 426. (c) Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021. (d) Dias, L. C. *Curr. Org. Chem.* **2000**, *4*, 30. (e) Adam, W.; Krebs, O. *Chem. Rev.* **2003**, *103*, 4131. For a review on transition metal-catalyzed Alder-ene reactions: (f) Trost, B. M.; Frederiksen, M. U.; Rudd, M. T. *Angew. Chem., Int. Ed.* **2005**, *44*, 6630.

(2) Rondan, N. G.; Domelsmith, L. N.; Houk, K. N.; Bowne, A. T.; Levin, R. H. *Tetrahedron Lett.* **1979**, *20*, 3237.

(3) Alder-ene reactions of arynes: (a) Tabushi, I.; Okazaki, K.; Oda, R. *Tetrahedron* **1969**, *25*, 4401. (b) Ahlgren, G.; Akermark, B. *Tetrahedron Lett.* **1970**, *11*, 3047. (c) Garsky, V.; Koster, D. F.; Arnold, R. T. *J. Am. Chem. Soc*. **1974**, *96*, 4207. (c) Nakayama, J.; Yoshimura, K. *Tetrahedron Lett*. **1994**, *35*, 2709. (d) Aly, A. A.; Mohamed, N. K.; Hassan, A. A.; Mourad, A.-F. E. *Tetrahedron* **1999**, *55*, 1111. (e) Aly, A. A.; Shaker, R. M. *Tetrahedron Lett*. **2005**, *46*, 2679.

(4) Jayanth, T. T.; Jeganmohan, M.; Cheng, M.-J.; Chu, S.-Y.; Cheng, C.-H. *J. Am. Chem. Soc.* **2006**, *128*, 2232.

(5) (a) Chen, Z.; Liang, J.; Yin, J.; Yu, G. A.; Liu, S. H. *Tetrahedron Lett.* **2013**, *54*, 5785. (b) Pérez, P.; Domingo, L. R. *Eur. J. Org. Chem.* **2015**, 2826.

(6) Gupta, S.; Xie, P.; Xia, Y.; Lee, D. *Org. Lett.* **2017**, *19*, 5162.

(7) (a) Hoye, T. R.; Baire, B.; Niu, D.; Willoughby, P. H.; Woods, B. P. *Nature* **2012**, *490*, 208. (b) Baire, B.; Niu, D.; Willoughby, P. H.; Woods, B. P.; Hoye, T. R. *Nature Protocols* **2013**, *8*, 501. (c) Niu, D.; Willoughby, P. H.; Baire, B.; Woods, B. P.; Hoye, T. R. *Nature* **2013**, *501*, 53. (d) Karmakar, R.; Ghorai, S.; Xia, Y.; Lee, D. *Molecules* **2015**, *20*, 15862. (e) Wang, T.; Hoye, T. R. *J. Am. Chem. Soc.* **2016**, *138*, 13870. (f) Xu, F.; Xiao, X.; Hoye, T. R. *Org. Lett.* **2016**, *18*, 5636. (g) Chen, J.; Palani, V.; Hoye, T. R. *J. Am. Chem. Soc.* **2016**, *138*, 4318. (h) Palani, V.; Chen, J.; Hoye, T. R. *Org. Lett.* **2016**, *18*, 6312. (i) Karmakar, R.; Mamidipalli, P.; Salzman, R. M.; Hong, S.; Yun, S. Y.; Xia, Y.; Lee, D. *Org. Lett.* **2016**, *18*, 3530. (j) Ross, S. P.; Hoye, T. R. *Nature Chem.* **2017**, *9*, 523. (k) Ghorai, S.; Lee, D. *Tetrahedron Lett.* **2017**, *73*, 4062. (l) Hu, Q.; Li, L.; Yin, F.; Zhang, H.; Hu, Y.; Liu, B.; Hu, Y. *RSC. Adv.* **2017**, *7*, 49810. (m) Meng, X.; Lv, S.; Cheng, D.; Hu, Q.; Ma, J.; Liu, B.; Hu, Y. *Chem.–Eur. J.* **2017**, *23*, 6264. (n) Hu, Y.; Ma, J.; Li, L.; Hu, Q.; Lv, S.; Liu, B.; Wang, S. *Chem. Commun.* **2017**, *53*, 1542. A review: (o) Diamond, O. J.; Marder, T. B. *Org. Chem. Front.* **2017**, *4*, 891. (p) Karmakar, R.; Le, A.; Xie, P.; Xia, Y.; Lee, D. *Org. Lett*. **2018**, *20*, 4168. (q) Ghorai, S.; Lee, D. *Org. Lett.* **2019**, *21*, 7390. (r) Ghorai, S.; Lin, Y.; Xia, Y.; Wink, J. D.; Lee, D. *Org. Lett*. **2020**, *22*, 642. (s) Ghorai, S.; Lin, Y.; Xia, Y.; Wink, J. D.; Lee, D. *Org. Lett.* **2020**, *22*, 626. (t) Ghorai, S.; Lin, Y.; Xia, Y.; Wink, D.; Lee, D. *Org. Lett*. **2020**, *22*, 626. Mechanistic and theoretical studies of HDDA reaction: (u) Ajaz, A.; Bradley, A. Z.; Burrell, R. C.; Li, W. H. H.; Daoust, K. J.; Bovee, L. B.; DiRico, K. J.; Johnson, R. P. *J. Org. Chem.* **2011**, *76*, 9320. (v) Willoughby, P. H.; Niu, D.; Wang, T.; Haj, M. K.; Cramer, C. J.; Hoye, T. R. *J. Am. Chem. Soc.* **2014**, *136*, 13657. (w) Baire, B.; Wang, T.; Hoye, T. R. *Chem.*

Sci. **2014**, *5*, 545. (x) Liaung, Y.; Hong, X.; Yu, P.; Houk, K. N. *Org. Lett*. **2014**, *16*, 5702. (y) Marell, D. J.; Furan, L. R.; Woods, B. P.; Lei, X.; Bendelsmith, A. J.; Cramer, C. J.; Hoye, T. R.; Kuwata, K. T. *J. Org. Chem.* **2015**, *80*, 11744. (z) Marell, D. J.; Furan, L. R.; Woods, B. P.; Lei, X.; Bendelsmith, A. J.; Cramer, C. J.; Hoye, T. R.; Kuwata, K. T. *J. Org. Chem.* **2015**, *80*, 11744. (aa) Wang, T.; Niu, D.; Hoye, T. R. *J. Am. Chem. Soc*. **2016**, *138*, 7832.

(8) Sabbasani, V.R.; Huang, G.; Xia, Y.; Lee, D. *Chem.–Eur. J*. **2015**, *21*, 17210.

(9) a) Candito, D. A.; Panteleev, J.; Lautens, M. *J. Am. Chem. Soc*. **2011**, *133*, 14200. (b) Candito, D. A.; Dobrovolsky, D.; Lautens, M. *J. Am. Chem. Soc.* **2012**, *134*, 15572.

(10) (a) Niu, D.; Hoye, T. R. *Nature Chem.* **2014**, *6*, 34. (b) Zhang, J.; Niu, D.; Brinker, V. A.; Hoye, T. R. *Org. Lett.* **2016**, *18*, 5596.

(11) (a) Karmakar, R.; Mamidipalli, P.; Yun, S. Y.; Lee, D.; *Org. lett.* **2013**, *15*, 1938. (b) Karmakar, R.; Yun, S. Y.; Chen, Y.; Xia, Y.; Lee, D. *Angew. Chem., Int. Ed*. **2015**, *54*, 6582. (c) Gupta, S.; Xie, P.; Xia, Y.; Lee, D. *Org. Lett.* **2017**, *19*, 5162, (d) Gupta, S.; Xie, P.; Xia, Y.; Lee, D. *Org. Chem. Front.* **2018**, *5*, 2208. (e) Gupta, S.; Lin, Y.; Xia, Y.; Wink, J. D.; Lee, D. *Chem. Sci.* **2019**, *10*, 2212.

(12) Alder-ene reaction of allenes: (a) Dal, S.-H.; Dolber Jr, W. R.; *J. Am. Chem. Soc*. **1972**, *94*, 3953. (b) Lee, C. B.; Taylor, D. R.; *J. Chem. Soc. Perkin Trans. 1* **1977**, 1463. (c) Brummond, K. M.; Chen, H.; Sill, P.; You, L. *J. Am. Chem. Soc*. **2002**, *124*, 15186. (d) Cheong, P. H.-Y.; Morganelli, P.; Luzung, M. R.; Houk, K. N.; Toste, F. D. *J. Am. Chem. Soc.* **2008**, *130*, 4517.

(13) For examples of thermal [2+2] cycloadditions of allenes with alkynes, see: (a) Brummond, K. M.; Chen, D. *Org. Lett.* **2005**, *7*, 3473. (b) Mukai, C.; Hara, Y.; Miyashita, Y.; Inagaki, F. *J. Org. Chem.* **2007**, *72*, 4454. (c) Jiang, X.; Ma, S. *Tetrahedron Lett.* **2007**, *63*, 7589. (d) Ovaska, T. V.; Kyne, R. E. *Tetrahedron Lett.* **2008**, *49*, 376. (e) Siebert, M. R.; Osbourn, J. M.; Brummond, K. M.;

Tantillo, D. J. *J. Am. Chem. Soc.* **2010**, *132*, 11952. (f) Ding, W.; Yoshikai, N. *Angew. Chem. Int. Ed.* **2019**, *58*, 2500.

(14) Stoermer, R.; Kahlert, B. *Berichte der Dtsch. Chem. Gesellschaft* **1902**, *35*, 1633.

(15) Matsumoto, T.; Hosoya, T.; Katsuki, M.; Suzuki, K. *Tetrahedron Lett.* **1991**, *32*, 6735.

(16) Yoshio, H.; Takaaki, S.; Hiroshi, K. *Chem. Lett.* **1983**, *12*, 1211.

(17) Stiles, M.; Miller, R. G. *J. Am. Chem. Soc.* **1960**, *82*, 3802.

(18) Wittig, G.; Hoffmann, R. W. *Org. Synth.* **1967**, *47*, 4.

(19) Gilchrist, T. L.; Graveling, F. J.; Rees, C. W. *Chem. Commun.* **1968**, 821.

(20) Campbell, C. D.; Rees, C. W. *J. Chem. Soc. C* **1969**, 742.

(21) For preparation of *gem*-dimethyl allenes, see: (a) Wright, M. W.; Smalley Jr., T. L.; Welker, M. E.; Rheingold, A. L. *J. Am. Chem. Soc.* **1994**, *116*, 6777. (b) Murakami, M.; Kadowaki, S.; Matsuda, T. *Org. Lett.* **2005**, *7*, 3953. (c) Boutier, A.; Kammerer-Pentier, C.; Krause, N.; Prestat, G.; Poli, G. *Chem.–Eur. J.* **2012**, *18*, 3840. (d) Kulandai Raj, A. S.; Kale, B. S.; Mokar, B. D.; Liu, R.-S. *Org. Lett.* **2017**, *19*, 5340.

(22) For the preparation of this terminal allene, see: (a) Maynard, D. F.; Okamura, W. H. *J. Org. Chem.* **1995**, *60*, 1763. (b) Ma, S.; Gao, W. *J. Org. Chem.* **2002**, *67*, 6104.

(23) For the preparation of this 1,3-disubstituted allene, see: Lippincott, D. J.; Linstadt, R. T. H.; Maser, M. R.; Lipshutz, B. H. *Angew. Chem., Int. Ed.* **2017**, *56*, 847

(24) For the preparation of this tetrasubstituted allene, see: Posevins, D.; Qiu, Y.; Backvall, J.-E. *J. Am. Chem. Soc.* **2018**, *140*, 3210.

(25) For the Diels-Alder reaction of arynes with benzene or other aromatics to form benzobarrelenes, see: (a)Wittig, G.; Pohmer, L. *Angew. Chem.* **1955**, *67*, 348. (b)Tabushi, I.; Yamada, H.; Yoshida,

Z.; Oda, R. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 285. (c) Chen, J.; Baire, B.; Hoye, T. R. *Heterocycles* **2014**, *88*, 1191. (d) Niu, D.; Wang, T.; Woods, B. P.; Hoye, T. R. *Org. Lett.* **2014**, *16*, 254. (e) Pogula, V. D.; Wang, T.; Hoye, T. R. *Org. Lett*. **2015**, *17*, 856. (f) Wang, Y.; Hoye, T. R. *Org. Lett.* **2018**, *20*, 88.

(26) The reactivity difference between triynes and tetraynes in hexadehydro Diels-Alder reaction, see: (a) Miyawaki, K.; Suzuki, R.; Kawano, T.; Ueda, I. *Tetrahedron Lett.* **1997**, *38*, 3943. (b) Bradley, A. Z.; Johnson, R. P. *J. Am. Chem. Soc.* **1997**, *119*, 9917. (a) Miyawaki, K.; Suzuki, R.; Kawano, T.; Ueda, I. *Tetrahedron Lett.* **1997**, *38*, 3943.

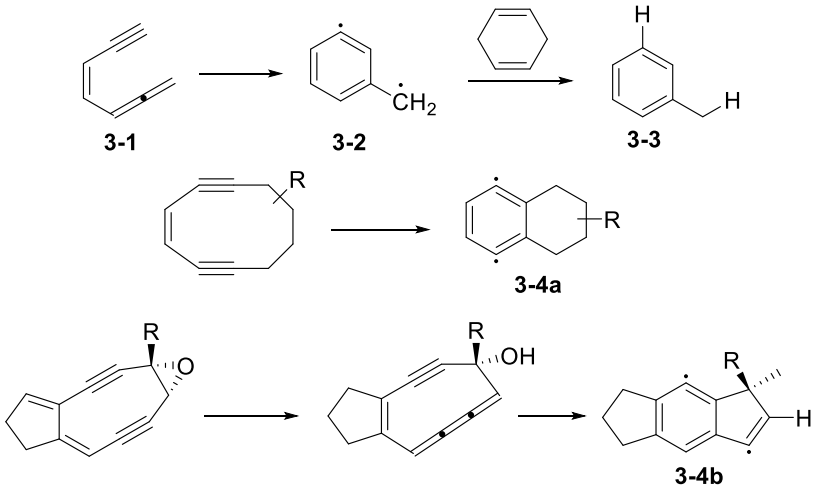
(27) Li, J.; Kong, W.; Fu, C.; Ma, S. *J. Org. Chem.* **2009**, *74*, 5104.

CHAPTER 3

[Allenyne + Alkyne] Cycloaddition to Generate α,3-Dehydrotoluene and Their Reactivity

3.1. Introduction

The Myers-Saito cyclization refers to the aromatization of enallene–alkyne such as **3-1** to form a 1,4-diradical intermediate **3-2**, which reacts with a hydrogen donor to generate arene product **3-3**.[1] There are abundant evidences revealing the intermediacy of 1,4-diradical for the DNA-clevage mechanism of natural antitumor antibiotic including neocarzinostatin,[2] calichemicin, esperamicin, and dynemicin. In case of calichemicin, esperamicin and dynemicin, the 1,4-diradical **3-4a** arise from electrocyclization of (*Z*)-ene-diyne, the process known as Bergman cyclization.[3] But in neocarzinostatin, the isomerization of (Z)-ene-diyne occur to afford (*Z*)-cumulene-ene-yne followed by cyclization to generate 1,4-dehydro toluene **3-4b (Scheme 3.1)**, which is accountable for DNA strand scission.[4]

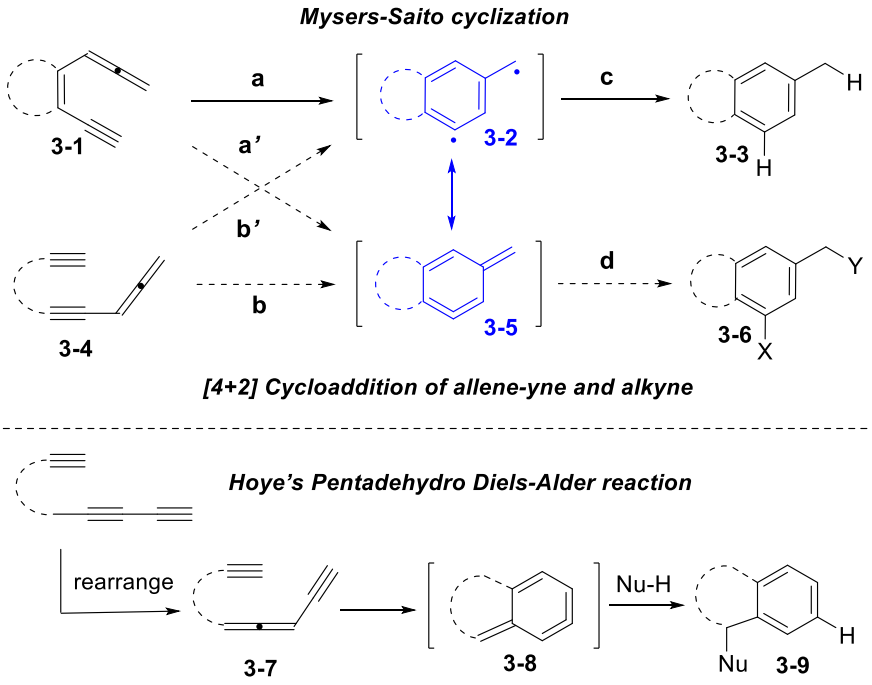


Scheme 3.1. 1,4-Diradical as a Key Intermediate in DNA-cleavage

Because of the relevancy of this aromatization process for the biological mode of action of anticancer natural products including neocarzinostatin[2] chromophore, extensive synthetic[5] and mechanistic[1] studies on Myers-Saito reaction have been reported. Although diradical **3-2** reacts with hydrogen donor to generate final product **3-3**, in the presence of nucleophile–proton donor, the reactivity of **3-2** might be revealed by its resonance form, α,3-dehydrotoluene **3-5**, leading to functionalized arene **3-6** (path a–d). We surmised this hypothesis can be tested by using allenyne–alkyne **3-4** that may undergo a concerted [4+2] cycloaddition to directly generate **3-5**. If this hypothesis is correct **3-5** should provide not only arene **3-3**

(via path b–c) in the presence of a hydrogen donor but also **3-6** (via path b–d) by reacting with nucleophile–proton donor. Altenatively, allenyne–alkyne **3-4** can undergo a stepwise cyclization (path b') to form diradical **3-2** leading to the same arene **3-3** or **3-6**. This reactivity crossing between diradical[6] and zwitterion[5] depending on the reacting counterparts was also observed in the Bergman cyclization.[3,5g]

In 2016, Hoye and coworkers reported[8] cycloaddition of an in situ generated ynallene–alkyne **3-7**, which afford product **3-9** via an intermediate **3-8** followed by trapping with a nucleophile–proton, and this process was termed as a pentadehydro Diels-Alder (PDDA) reaction. Considering the structural characteristics and the mechanism of these two processes, the cycloaddition of allenyne–alkyne to generate **3-5** followed by trapping to yield **3-6** should be considered as a pentadehydro Diels-Alder reaction. On the same token, the aromatization process of **3-4** to form **3-3** or **3-6** can be considered as a pseudo-Myers-Saito cyclization[9] because of it similarity to the conversion of **3-1** to **3-3**.



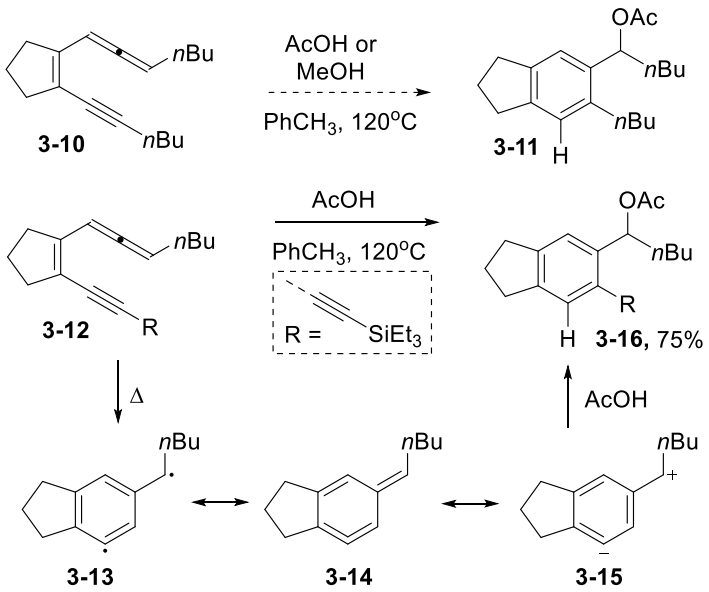
Scheme 3.2. Development of a New Cycloaromatization Related to Other Aromatization Processes

In this chapter is described new aromatization processes to form functionalized arenes by introducing structural variations on the parent yne–allene–alkyne system **3-4** in combination with a variety

of hydrogen and nucleophile–proton donors. Since this thermal process to generate α,3-dehydrotoluene **3-5** occurs under base-free conditions, the intrinsic reactivity of this reactive intermediate could be examined with a diverse variation of structural elements on the parent allenyne–alkyne and the reacting counterparts.

3.2. Initial Observation

To experiment the feasibility of tautomerization between **3-2** and **3-5** eventually leads to formation of functionalized arene through nucleophilic capture of **3-5** in presence of nucleophile-proton sources, we subjected (*Z*)-ene-alkyne-allene **3-10** to thermal condition (toluene, 120 °C) with presence of excess amount of acetic acid, an excellent source of nucleophile. To our surprised, **3-10** remained intact after 48h under heating without any sight of forming desired product **3-11**. More aggressive heating at higher temperature only leads to complete decomposition of **3-10** without even a trace of **3-11** (**Scheme 3.3**). We hypothesize that the low reactivity of **3-10** is the result of high activation barrier[1b] (22.5 kcal/mol) of Myers-Saito cyclization. As expected, under identical condition, (Z)-ene-diyne-allene **3-12** undergoes cyclization



Scheme 3.3. Reactivity of 1,4-Diradical with Nucleophile–Proton Donor

followed by nucleophilic trapping with AcOH to afford arene **3-16** at 75% yield. The successfully capture of intermediate **3-15** in nucleophile-proton condition indicates that the reactivity of **3-13** manifests through its resonance form.

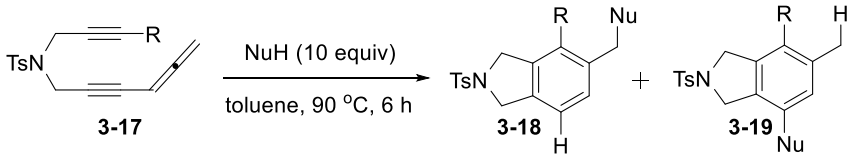
3.3. Results and Discussions

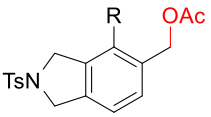
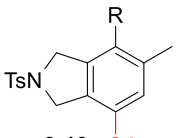
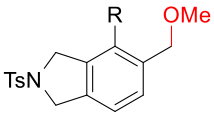
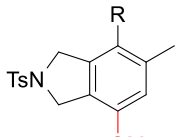
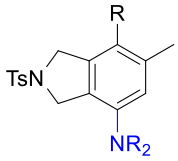
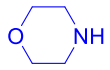
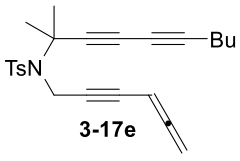
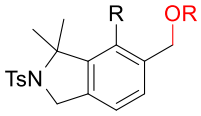
3.3.1. α,3-Dehydrotoluens Generated from Monosubstituted Allenes

Our investigation was commenced with sulfonamide-tethered allenyne–alkyne **1a** containing a monosubstituted allene (Table 1). When **1a** was heated at 90 °C in toluene in presence of AcOH (10 equiv) as trapping reagent, **3-17a** remained intact but led to decomposition on prolonged heating at higher temperature and there was no sign of forming **3-18a** or **3-19a** (entry 1). One particular structural element that was found to play a significant activating role for the initial cyclization of **3-12** to form α,3-dehydrotoluene **3-13** is an alkynyl substituent at the terminal alkyne. We envisioned that introducing an extra alkynyl substituent on the terminal alkyne of **3-17a** would increase its reactivity based on the significant activating role of an extra alkyne in hexadehydro Diels-Alder reaction.[10] Gratifyingly, under the same conditions, **3-17b** containing an extra alkynyl substituent provided the desired AcOH-trapped product **3-18b** (76%), devoid of its regioisomer **3-19b** (entry 2). The same reaction with **3-17c** containing a TMS substituent instead of a butyl group afforded a mixture of **3-18c**/**3-19c** with a 3:1 ratio in 66% yield (entry 3). Next, MeOH was used as a trapping agent, which improved the regioselectivity, affording a mixture of regioisomers **3-18d**/**3-19d** (10:1) and **3-18e**/**3-19e** (8:1) in 79 and 68% yield, respectively (entries 4 and 5). It is worth noting that the regioisomeric ratio depends significantly on the substituent on the pendant alkyne (butyl vs. trimethyl or triethylsilyl), which is assumed to be mainly a steric effect.

Next, nitrogen-based nucleophiles including butylamine, diethylamine, piperidine and morpholine were employed as a trapping agent (entries 6–10). These reactions provided single regioisomers **3-19f**–**3-19j** wherein the sense of regioselectivity is the opposite to that of oxygen-based nucleophile trapped products. Also, it was found that the yields of these nitrogen-based nucleophile-trapped products increased

drastically when the reaction was performed at higher temperature (120 °C vs 90 °C).[11] The effect of a *gem*-dimethyl substituent was also examined with **3-17e**, which provided the expected product **3-18f** and **3-18g** in 52 and 65% yield respectively (entries 11 and 12). However, contrary to the typical benefits of the *gem*-dimethyl substituent effect for ring closure reaction,[12] **3-17e** took longer time (12 h) than **3-17b** (6 h).



Entries		R	NuH	Product			Yield (%)[a]
							
1	**a**	--H	AcOH	**3-18a**		**3-19a** OAc	0
2	**b**	--≡—Bu	AcOH	**3-18b**	1 : 0	**3-19b**	76
3	**c**	--≡—$SiMe_3$	AcOH	**3-18c**	3 : 1	**3-19c**	66
							
4	**b**	--≡—Bu	MeOH	**3-18d**	10 : 1	**3-19d** OMe	79
5	**d**	--≡—$SiEt_3$	MeOH	**3-18e**	8 : 1	**3-19e**	68
6	**b**	--≡—Bu	$BuNH_2$			**3-19f**	45^b (20)
7	**b**	--≡—Bu	Et_2NH			**3-19g**	62^b (30)
8	**b**	--≡—Bu				**3-19h**	55^b (27)
9	**b**	--≡—Bu				**3-19i**	55^b
10	**d**	--≡—$SiEt_3$				**3-19j**	32
11			AcOH			**3-18f**, R = Ac	52^c
12		**3-17e**	MeOH			**3-18g**, R = Me	65^c

[a] Isolated Yield. [b] Yield at 120 °C for 2 h (yields in the parenthesis are obtained at 90 °C for 4 h). [c] Reaction for 12 h.

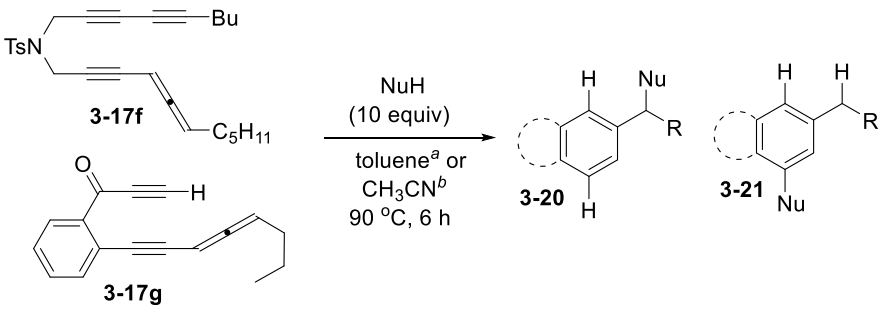
Table 3.1. Reaction Profiles of Monosubstituted Allenes

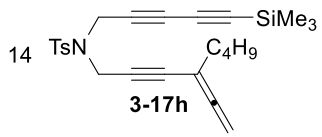
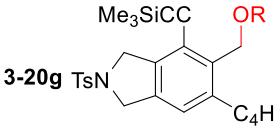
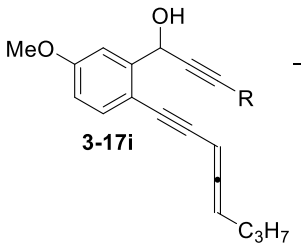
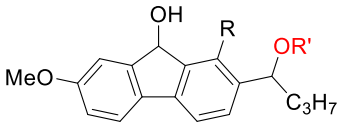
The regioselectivity of the trapping with different nucleophiles seems to have an intimate relationship with the acidity (pK_a values) of the trapping agents. Because of the relatively higher acidity of the oxygen-based nucleophiles (H_2O, MeOH, AcOH), the initial protonation would preferentially occur with the α,3-dehydrotoluene on the endocyclic carbon to generate a benzylic cation intermediate, which subsequently reacts with the oxygen nucleophiles to generate complete the reaction. On the other hand, nitrogen-based nucleophiles behave mainly as a nucleophile to react with the α,3-dehydrotoluene on the endocyclic carbon to generate a benzylic anion, which upon protonation leads to the observed regioisomer.[13]

3.3.2. α,3-Dehydrotoluens Generated from Disubstituted Allenes

Next was examined the reactivity of allenyne–alkyne **3-17f** and **3-17g** containing a disubstituted allenyl moiety (Table 2). Under the standard conditions (90 °C in toluene, 6 h, 10 equiv nucleophile), **3-17f** reacted with H_2O and MeOH to provide **3-20a** (48%) and **4-20b** (50%) as a single isomer (entries 1 and 2). Under the same condition, reaction of **3-17f** with AcOH also provided adduct 3-20c in 45% yield. Similar to **3-17f**, under the identical condition, **3-17g** reacted with H_2O, MeOH and AcOH to provide **3-20d–3-20f** (entry 7-9).

Much to our surprise, the reactions with nitrogen-based nucleophiles such as diethylamine, piperidine and morpholine failed in producing the expected products (**3-21a–g**), resulting in only decomposition (entries 4–6 and 10–13). In addition, allenyne–alkyne **3-17h** contining the butyl group on the internal carbon of the allene also failed in providing the corresponding **3-21g** even reacting with oxygen-based nucleophiles (entry 14). At this points, the origins of these unsuccessful reaction are not clear.[14] Desprite the similarity between **3-17b** and **3-17f**, their results when subjected to identical condition (entry 7, **table 3.1** vs entry 4, **table 3.2**) are very much diffrent, suggesting that the reactivity of 1,4 diradical intermediate depends subtly on the subtituents pattern of the allene moiety.



Entries	Substrate	NuH	Product	Yield (%)[c]
1	**3-17f**	H_2O[b]	**3-20a**, R = H	48
2	**3-17f**	MeOH[a]	**3-20b**, R = Me	50
3	**3-17f**	AcOH[a]	**3-20c**, R = Ac	45
4	**3-17f**	Et_2NH[a]	**3-21a**	0[d]
5	**3-17f**	NH[a]	**3-21b**	0[d]
6	**3-17f**	O NH[a]	**3-21c**	0[d]
7	**3-17g**	H_2O[b]	**3-20d**, R = H	61
8	**3-17g**	MeOH[a]	**3-20e**, R = Me	62
9	**3-17g**	AcOH[a]	**3-20f**, R = Ac	66
10	**3-17g**	Et_2NH[a]	**3-21d**	0[d]
11	**3-17g**	NH[a]	**3-21e**	0[d]
12	**3-17g**	O NH[a]	**3-21f**	0[d]
13	**3-17g**	$BuNH_2$[a]	**3-21g**	0[d]
14		H_2O MeOH AcOH	 **3-20g**	0[d]
15		AcOH[a] MeOH[a]	 **3-20h**, R' = Ac	58
16		R = OMe	**3-20i**, R' = Me	62

[a] Toluene is the solvent. [b] CH_3CN is the solvent. [c] Isolated Yield.
[d] No reaction at 90 °C and decomposition on prolonged heating at 150 °C.

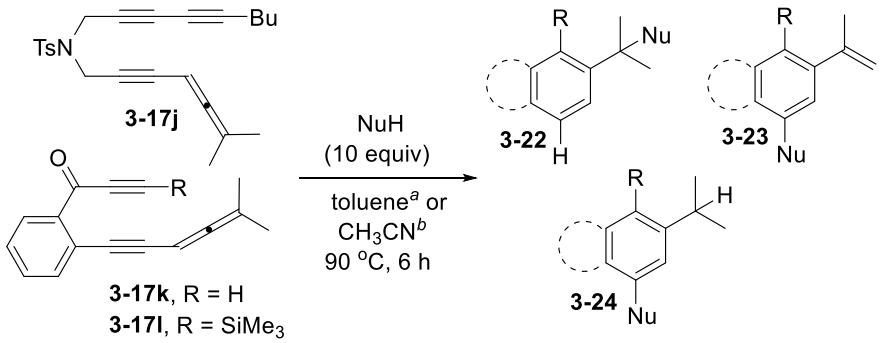
Table 3.2. Reaction Profiles of Disubstituted Allenes

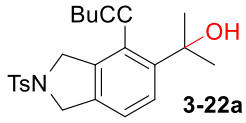
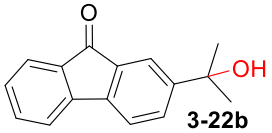
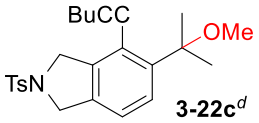
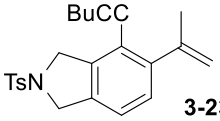
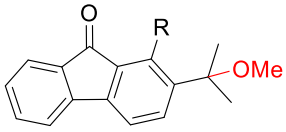
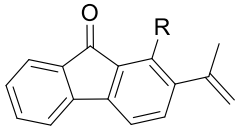
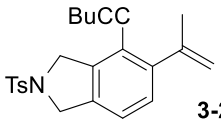
Moreover, the extra alkynyl substituent on the terminal alkyne proves to have the same activating effect as a carbonyl group in Diels-Alder reactions.[10] Under standard conditions, substrate **3-17i** reacts with AcOH and MeOH to provide adducts **3-21h** (58%) and **3-21i** (62%) respectively as a single regioisomer (entries 15 and 16).

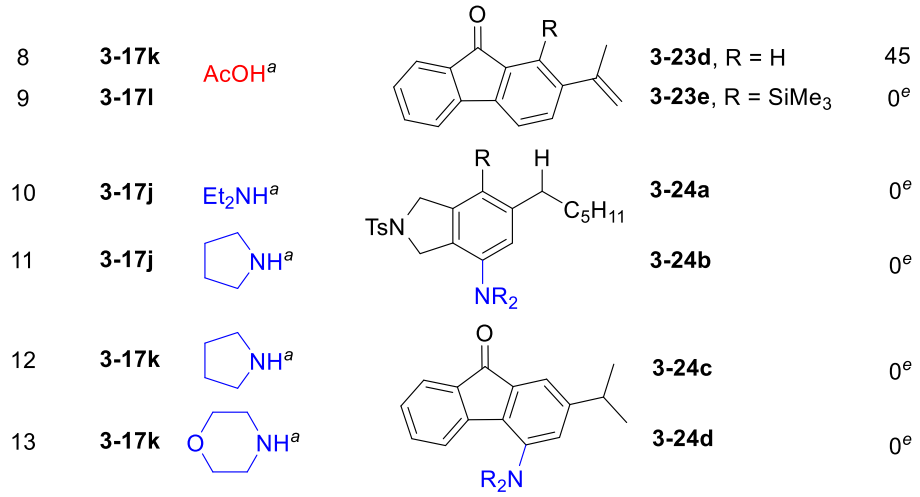
3.3.3. α,3-Dehydrotoluens Generated from Trisubstituted Allenes

The effect of the substituents on the allene moiety was further examined with allenyne–alkynes **3-17j**–**3-17l** containing a trisubstituted allenyl group (**Table 3.3**). The reaction of **3-17j** and **3-17k** with H_2O (10 equiv) in toluene or CH_3CN provided cycloaromatization products **3-22a** (80%) and **3-22b** (62%) as a single regioisomer (entries 1 and 2). On the other hand, under identical conditions the reactions with MeOH generated a mixture of **3-22c**/**3-23c** (3:1) and **3-22d**/**3-23d** (5.5:1) in 78 and 65% yield, respectively (entries 3 and 4). The reaction of **3-17l** with MeOH, however, failed in producing **3-22e**/**3-23e** (entry 5). We believe the trimethylsilyl alkynyl group interferes with the initial formation of α,3-dehydrotoluene intermediate due to the steric hindrance, not interfering with the nucleophile trapping. Both the reactions of **3-17j** with *i*-PrOH and this AcOH yielded only alkene product **3-23c** (entries 6 and 7). In case, *i*-PrOH did not play a role as a hydrogen donor.[15] While the reaction of **3-17k** with AcOH resulted in alkene product **3-23d** (entry 8), the same reaction of **3-17l** containing a trimethylsilyl group failed in generating **3-23e** (entry 9). The formation of alkene **3-23c** and **3-23d** can be justified by the formation of benzylic cation intermediate. In case of nucleophile-proton donor (H_2O, CH_3OH and AcOH), the initial protonation would preferentially occur with the α,3-dehydrotoluene on the endocyclic carbon to generate a benzylic cation intermediate. In turn, the benzylic cation intermediate can either react with oxygen nucleophile to generate oxygen-containing adducts (**3-22a–d**) or undergo E_1 elimination of β-hydrogen to afford alkene (**3-23c–d**). We hypothesis that the preference of which process occurs depends on the nucleophile. For the primary benzylic cation generating from terminal allenes (**Table 3.1**), the elimination process is impossible due to the absence of β-hydrogen, therefore only oxygen-containing adducts were observed in previous table**.** On the other hand, despite the similarity between **3-17k** and **3-17l**, their experiment outcomes are quite different

suggesting that the substituents on alkyne moiety have tremendous impact on the cyclization process of alkyne-allenyne. Similar to the reactivity of disubstituted allene-containing substrate **3-17f**, the reactions of **3-17j** and **3-17k** containing a trisubstituted allenyl moiety did not provide nitrogen nucleophile adducts **3-24a–3-24d** (entries 10–13). Because amine behave mainly as a nucleophile to react with the α,3-dehydrotoluene on the endocyclic carbon to generate a benzylic anion, the transition state can be destabilized by the present of extra substituents on the allene, which ultimately develops an incipient benzylic carbon-centered anion.



Entries	Substrate	NuH	Product	Yield (%)[c]
1	**3-17j**	H_2O^b	 **3-22a**	80
2	**3-17l**	H_2O^b	 **3-22b**	62
3	**3-17j**	CH_3OH^a	 **3-22c**[d]  **3-23c**	78 (3:1)
4	**3-17l**	CH_3OH^a	 **3-22d**, R = H  **3-23d**, R = H	65 (5.5:1)
5	**3-17k**		**3-22e**, R = $SiMe_3$ **3-23e**, R = $SiMe_3$	0[d]
6	**3-17j**	*i*-PrOH[a]	 **3-23c**	65
7	**3-17j**	AcOH[a]		75

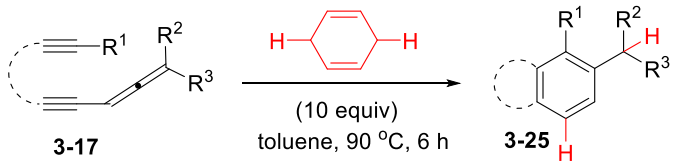


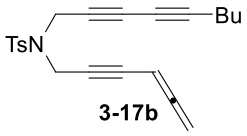
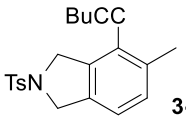
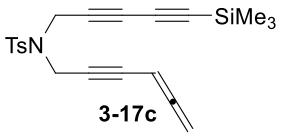
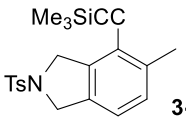
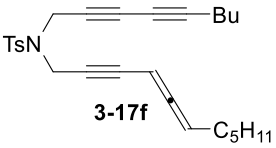
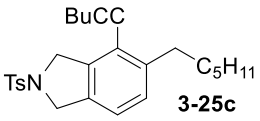
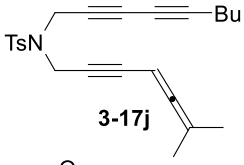
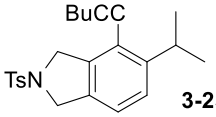
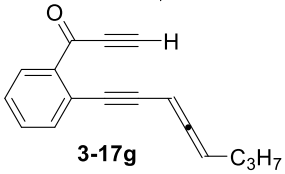
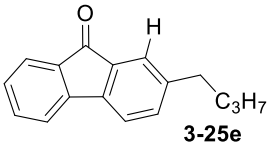
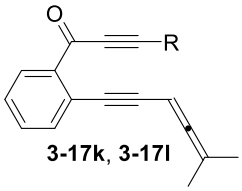
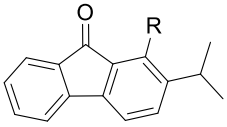
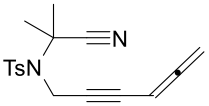
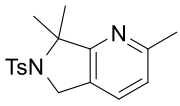
[a] Toluene is the solvent. [b] CH_3CN is the solvent. [c] Isolated Yield.
[d] Contaminated with 6% of the regioisomer.
[e] No reaction at 90 °C and decomposition on prolonged heating at 150 °C.

Table 3.3. Reaction Profiles of Trisubstituted Allenes

3.3.4. Trapping α,3-Dehydrotoluenes with a Hydrogen Donor

To test the hypothesis that α,3-dehydrotoluene **3-5** in Scheme 1 might reveal its reactivity through a diradical **3-2** in the presence of a hydrogen donor, various allenyne–alkynes **3-17b**, **3-17c**, **3-17f**, **3-17g** and **3-17j–l** were subjected to the standard reaction conditions but with a 1,4-cyclohexadiene instead of a nucleophlie-proton donor (Table 3.4). While substrates containing a mono, di, and trisubstituted allene **3-17b**, **3-17c**, **3-17f**, and **3-17j** provided the expected dihydrogen adduct **3-25a**, **3-25b**, **3-25c** and **3-25d** (entries 1–4), the reaction of **3-17g** failed in producing **3-25e** (entry 5). Similar to **3-17g**, trisubstituted allene-containing substrate **3-17k** and **3-17l** also failed to produce corresponding product **3-25e** and **3-25f**. Under the indentical conditions, substrate **3-17m** containing a nitrile instead of a 1,3-diyne[16] also failed in producing the corresponding pyridine derivative **3-25h** (entry 7). For now, failure to generate dihydrogen adduct of **3-17g**, **3-17k** and **3-17l** was unclear. We hypothesis that the linkage-containing alkyne-allenyne (sulfonamide vs benzene) might have different effects on stability of α,3-dehydro toluene intermediate, untimately manifesting in different reactivity.



Entries	Susbstrate	Product	Yield (%)[a]
1	 **3-17b**	 **3-25a**	66[c]
2	 **3-17c**	 **3-25b**	66[c]
3	 **3-17f**	 **3-25c**	61[c]
4	 **3-17j**	 **3-25d**	59[c]
5	 **3-17g**	 **3-25e**	0[b]
6	 **3-17k**, **3-17l**	 **3-25f, 3-25g** (R = H, $SiMe_3$)	0[b]
7	 **3-17m**	 **3-25h**	0[b]

[a]Isolated Yield. [b]Decomposition of starting materials. [c]Contaminated with 15% of side product.[16]

Table 3.4. Trapping α,3-Dehydrotoluene Containing a Differently Substituted Allene Moieties with Hydrogen Source

3.4. Conclusion

In conclusion, a new cycloaromatization reaction of allenyne–alkynes has been developed, which is a new variation of pentadehydro Diels-Alder reaction. The reaction proceeds via forming α,3-dehydrotoluene intermediates, which formally behaves as a diradical to react with a hydrogen donor, whereas it behaves as a zwitterion to react with a nucleophile–proton donor. The efficiency and product distribution of the reaction mainly depend on the tether structure of the α,3-dehydrotoluene intermediate and the reacting counterpart. Most notable features of the reaction are the activating role of an extra alkyne in 1,3-diyne that reacts with an allenyne moiety and the opposite mode of trapping with oxygen- and nitrogen-based nucleophiles. In general, oxygen-based nucleophiles such as alcohols and carboxylic acids resulted in oxygen nucleophile incorporation at the benzylic position, whereas nitrogen nucleophiles were incorporated on the aromatic ring.

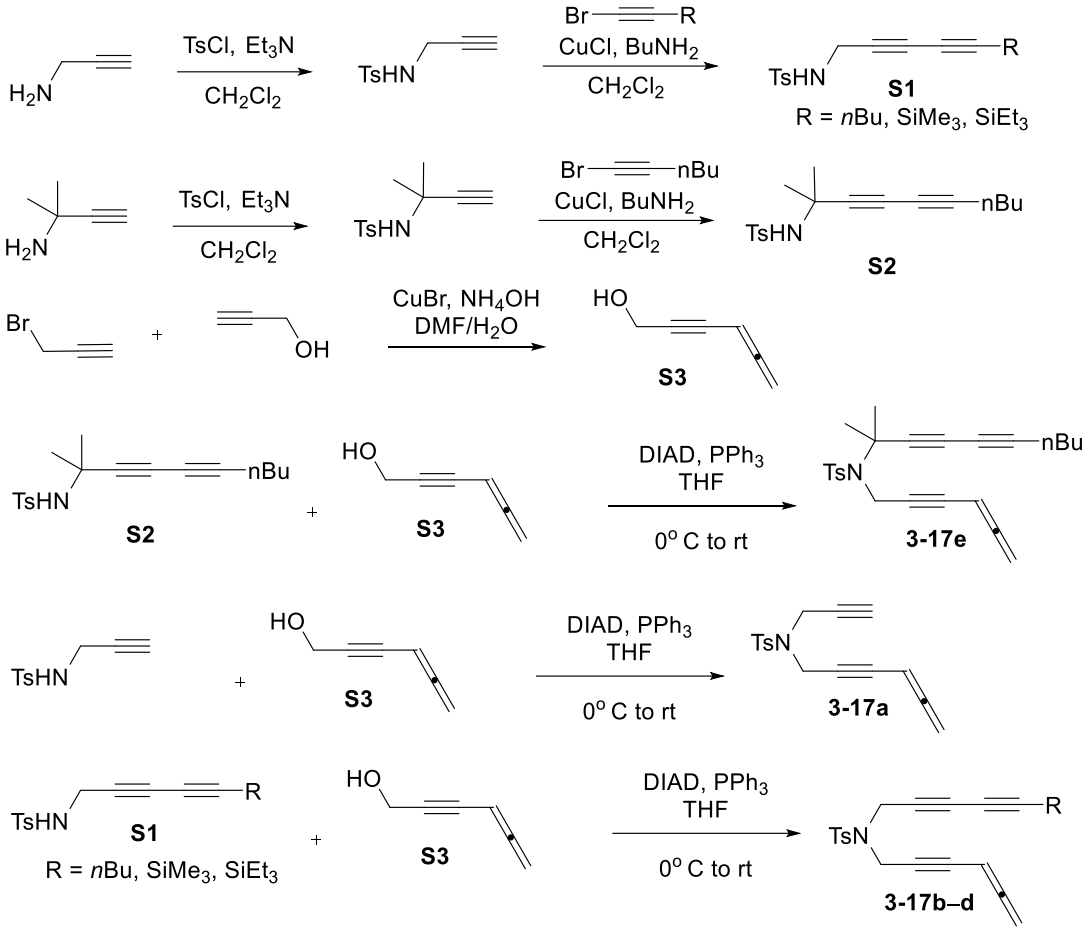
3.5. Experimental details

3.5.1. General Information

Reactions were carried out in oven-dried glassware unless otherwise noted. Compounds were purchased from Sigma-Aldrich or TCI America or Oakwood Chemicals unless otherwise noted. Toluene, acetonitrile, dichloromethane and triethyl amine were distilled over calcium hydride (CaH_2) under nitrogen atmosphere. THF was distilled over sodium-benzophenone ketyl under nitrogen atmosphere. Column chromatography was performed using silica gel 60 Å (32−63 mesh) purchased from Silicycle Inc. Thin layer chromatography (TLC) was performed on 0.25 mm E. Merck precoated silica gel 60 (particle size 0.040−0.063 mm). Yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AV-500 spectrometer. ^{1}H NMR chemical shifts (δ) are reported in parts per million (ppm) downfield of TMS and are referenced relative to the residual proteated solvent peak ($CDCl_3$ (7.26 ppm)). ^{13}C chemical shifts (δ) are reported in parts per million downfield of TMS and are referenced to the carbon resonance of the solvent ($CDCl_3$ (77.2 ppm)). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sext (sextet) or m (multiplet). ^{1}H NMR signals that fall within a ca. 0.3 ppm range are generally reported as a multiplet, with a range of chemical shift values corresponding to the peak or center of the peak. Coupling constants, *J*, are reported in Hz (Hertz). Electrospray ionization (ESI) mass spectra were recorded on a Waters Micromass Q-Tof Ultima in the University of Illinois at Urbana-Champaign. Electron impact (EI) mass spectra and Chemical Ionization (CI) mass spectra were obtained using a Micromass 70-VSE in the University of Illinois at Urbana–Champaign.

3.5.2. Experimental Procedures

Synthesis of Sulfonamide Tether-containing Monosubstituted Allene



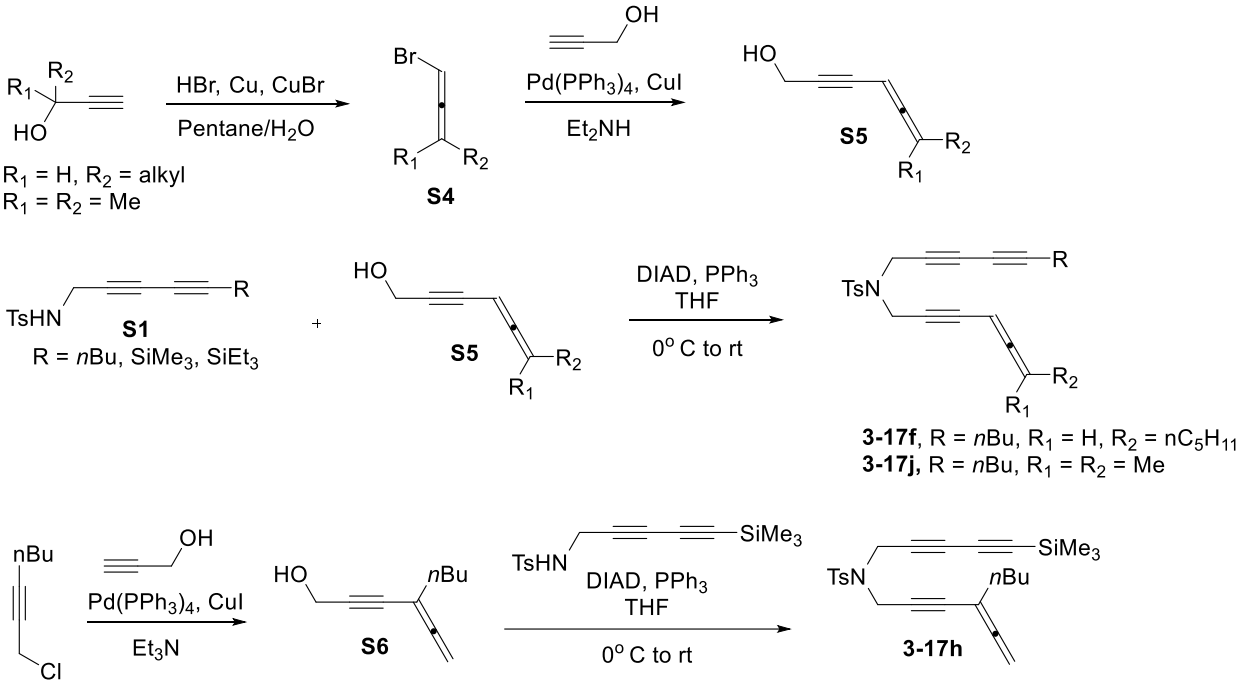
To a solution of propargylamine (2 ml, 31 mmol) in CH_2Cl_2 (30 mL) at 0 °C were added Et_3N (1.5 equiv) and 4-toluenesulfonylchloride (1.1 equiv). The reaction mixture was stirred until complete consumption of starting material (monitored by TLC). After completion, the reaction mixture was transferred to a separatory funnel, diluted with diethyl ether (100mL) and washed with aqueous HCl (1 N, 200 mL), water (x2) and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get the crude which was used for the next reaction without further purification. The exact procedure was repeated with 2-methyl-3-butyn-2-amine to afford 4-methyl-*N*-(2-methylbut-3-yn-2-yl) benzenesulfonamide.

In a two-neck round–bottom flask containing CuCl (0.3 equiv) was added 30% aqueous $BuNH_2$ solution under nitrogen flow. A pinch of NH_2OH•HCl was added until a blue color disappeared. A solution of terminal alkyne (1.0 equiv) in CH_2Cl_2 was added at 0 °C to the flask and the solution became yellow. A dilute solution of bromoalkyne (1.2 equiv) in CH_2Cl_2 was added drop wise at 0 °C. The reaction mixture was stirred for 5 minutes at room temperature. The progress of the reaction was monitored by TLC. The nitrogen flow was removed, and the biphasic reaction mixture was transferred to a separatory funnel. Organic layer was separated and dried over anhydrous Na_2SO_4. After filtration, the organic layer was concentrated, and the crude material was purified by silica gel column chromatography (SiO_2, hexanes:EtOAc = 5:1 to 3:1) to get pure diyne **S1** at 82% yield. The same procedure was repeated with 4-methyl-*N*-(2-methylbut-3-yn-2-yl) benzenesulfonamide to afford **S2** at 78% yield.

Propargyl alcohol (1 equiv) was added to a solution of CuBr (0.5 equiv) in NH_4OH (25% in water)/DMF (1:1). The resulting yellow green solution was cooled to 0 °C and added slowly propargyl bromide (1.3 equiv, 80% in toluene). The deep blue suspension allowed to warm up slowly to room temperature during 2h. Then water was added and filtered through Celite pad. The solid was washed with diethyl ether. The filtrate was extracted by diethyl ether. The combine organic layer was washed with water, brine and dried over Na_2SO_4. After filtration, the organic layer was concentrated, and the crude material was purified by silica gel column chromatography (SiO_2, hexanes:EtOAc = 4:1) to get pure hexa-4,5-dien-2-yn-1-ol as yellow liquid at 75% yield.

DIAD (1.2 equiv) was added dropwise to a solution of sulfonamide (1.0 equiv), PPh_3 (1.2 equiv), and alcohol (1.0 equiv) in dry THF at 0 °C under nitrogen balloon. The reaction mixture was warmed up to room temperature and further stirred overnight. After completion, the reaction mixture was concentrated and purified by silica gel column chromatography (SiO_2, hexanes:EtOAc = 10:1 to 5:1) to get pure product **3-17a–e** (62–75% yield).

Synthesis of Sulfonamide Tether Containing Mono- and Disubstituted Allenes



A 100 mL round-bottom flask was charged with copper (I) bromide (20 mol%), copper metal powder (5 mol %), and hydrobromic acid (48%, 25 mL). To this mixture was added dropwise corresponding propargyl alcohol (1 equiv) dissolved in 30 mL of pentane over 30 minutes. The reaction was then stirred for 3 hours at 40 °C. The biphasic mixture was transferred to a separatory funnel and the organic layer was collected. The aqueous layer was extracted with pentane (3 x 50 mL). The combined organic phases were washed with aqueous concentrated hydrobromic acid (3 x 5 mL) and water (2 x 10 mL), dried over $MgSO_4$, and eluated through a plug of silica (hexanes:EtOAc = 20:1), which afforded allenyl bromide **S4** (80% yield) after gentle evaporation of volatiles. Spectra data are in accordance with those previously reported.

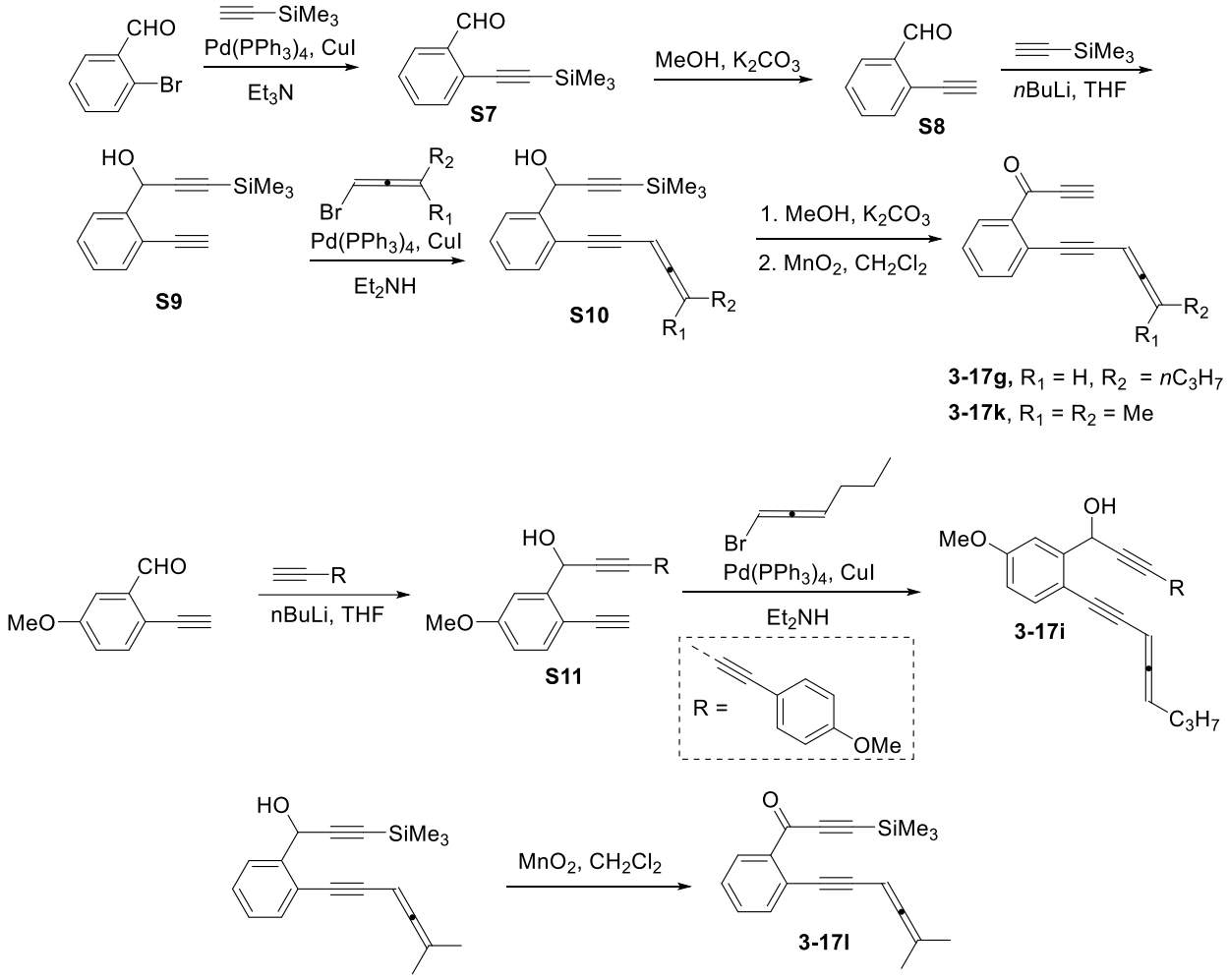
To a solution of allenyl bromide (1 equiv) in Et_3N (20 mL) was added $(Ph_3P)_4Pd$ (0.5 mol %) and CuI (1.0 mol %) at room temperature under nitrogen. Propargyl alcohol (1.2 equiv) was added dropwise to the above solution with continuous stirring. After 15 minutes, the reaction mixture was warmed up to 40 °C and stirred until complete consumption of the alkenyl bromide (monitored by thin layer chromatography). Upon completion, the reaction mixture was filtered through Celite pad, concentrated, and

purified by silica gel column chromatography (SiO_2, hexanes:EtOAc = 5:1 to 3:1) to obtain pure allene-yne **S5** (92% yield).

To a solution of 1-chloro-2-heptyne (1 equiv) in Et_3N (20 mL) was added $(Ph_3P)_4Pd$ (0.5 mol %) and CuI (1.0 mol %) at room temperature under nitrogen. Propargyl alcohol (1.2 equiv) was added dropwise to the above solution with continuous stirring. After 15 minutes, the reaction mixture was warmed up to 40 °C and stirred until complete consumption of the alkenyl bromide (monitored by thin layer chromatography). Upon completion, the reaction mixture was filtered through Celite pad, concentrated, and purified by silica gel column chromatography (SiO_2, hexanes:EtOAc = 5:1 to 3:1) to obtain pure allene-yne **S6** (73% yield)**.**

DIAD (1.2 equiv) was added dropwise to a solution of sulfonamide (1.0 equiv), PPh_3 (1.2 equiv), and alcohol (1.0 equiv) in dry THF at 0 °C under nitrogen balloon. The reaction mixture was warmed up to room temperature and further stirred overnight. After completion, the reaction mixture was concentrated and purified by silica gel column chromatography (SiO_2, hexanes:EtOAc = 15:1 to 5:1) to get pure product **3-17f** (55% yield), **3-17j** (64% yield) and **3-17h** (73% yield)**.**

Synthesis of Benzo Tether-containing Allene



To a solution of arene bromide (1 equiv) in Et_3N (20 mL) was added $(Ph_3P)_4Pd$ (0.5 mol %) and CuI (1.0 mol %) at room temperature under nitrogen. Terminal alkyne (1.2 equiv) was added dropwise to the above solution with continuous stirring. After 15 minutes, the reaction mixture was warmed up to 40 °C and stirred until complete consumption of the alkenyl bromide (monitored by thin layer chromatography). Upon completion, the reaction mixture was filtered through Celite pad, concentrated and directly loaded on a silica gel column and eluted (hexanes:EtOAc, 20:1 to 5:1) to obtain pure product **S7** (92% yield).

Potassium carbonate (5 mol%) was added to a solution of alkynyltrialkylsilane S7 (1.0 equiv) in methanol at room temperature under nitrogen and progress of the reaction was checked by TLC. Upon completion, the reaction mixture was filtered through silicagel and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (SiO_2, hexanes:EtOAc = 10:1 to 5:1) to obtain pure terminal alkyne **S8** (85% yield).

To a solution of terminal alkyne (1.1 equiv) in dry THF (30 mL) was added *n*-butyllithium (2.5 M in hexanes, 2.2 mL, 1.05 equiv) slowly at –78 °C under nitrogen atmosphere. After stirring for 1 h at the same temperature, benzaldehyde **S8** (1.0 equiv) was dissolved in dry THF (6 mL) and added dropwise to the reaction flask. The stirring was continued for 30 min at –78 °C before gradually warming up to room temperature. The progress of the reaction was monitored by TLC, and upon completion, ice-water was added to quench the reaction. Ethyl acetate was added and the organic layer was separated. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude was further purified by silica gel column chromatography (SiO_2, hexanes:EtOAc = 10:1 to 5:1) to afford diyne **S9** at 82% yield. The exact procedure was repeated once more time to afford triyne **S11** at 78% yield.

To a solution of allenyl bromide (1 equiv) in Et_3N (20 mL) was added $(Ph_3P)_4Pd$ (0.5 mol %) and CuI (1.0 mol %) at room temperature under nitrogen. Terminal alkyne dissolve in 3mL Et_3N (1.2 equiv) was added dropwise to the above solution with continuous stirring. After 15 minutes, the reaction mixture was warmed up to 40 °C and stirred until complete consumption of the allenyl bromide (monitored by thin layer chromatography). Upon completion, the reaction mixture was filtered through Celite pad, concentrated, and directly loaded on a silica gel column and eluted (hexanes:EtOAc, 20:1 to 5:1) to obtain pure alkyne-allenyne **S10** at 63% yield**.** The same procedure was repeated once more time to synthesize **3-17i** (58% yield) from triyne **S11** and 1-bromo-1,2-hexadiene.

Manganese (IV) oxide (5 equiv) was added to a solution of benzylic alcohol (1 equiv) in CH_2Cl_2 at room temperature. The reaction progress was monitored by TLC. Upon completion, the reaction mixture

was filtered through Celite and the solid was washed with CH_2Cl_2. The combine organic solution was concentrated under reduced pressure. The crude product was loaded on a silica gel column and eluted (hexanes:EtOAc, 10:1 to 5:1) to obtain pure product **3-17g** (76%), **3-17k** (65%) and **3-17l** (69%)**.**

General Procedure for Cyclization Between Alkyne and Allenyne

General Procedure A (GPA)

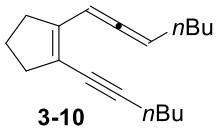
A solution of a substrate and nucleophile (10 equiv) in toluene in a Schlenk tube was flushed with nitrogen. The mixture was stirred for 6 h at 90 °C unless otherwise noted. After completion (monitored by TLC), the reaction mixture was transferred to a round-bottom flask, concentrated, and purified by silica gel column chromatography (SiO_2, hexanes:EtOAc = 10:1 to 5:1) to obtain pure product.

General Procedure (GPB)

A solution of a substrate and water (10 equiv) in dry CH_3CN in a Schlenk tube was flushed with nitrogen. The mixture was stirred for 6 h at 90 °C unless otherwise noted. After completion, the reaction mixture was transferred to a round-bottom flask, concentrated, and subjected to column chromatography (SiO_2, hexanes:EtOAc = 10:1 to 5:1) to get pure products.

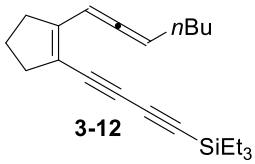
3.5.3 Characterization Data

Characterization Data of Substrates



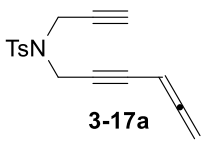
3-10

3-10: 215 mg, light yellow liquid, purify by flash column chromatography (SiO_2, EtOAc–Hexanes, 1:20). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.30 (m, 1H), 5.38 (d, 1H, *J* = 7.8 Hz), 2.51 (t, 2H, *J* = 6.2 Hz), 2.41–2.38 (m, 4H), 2.04–2.03 (m, 2H), 1.87–1.84 (m, 2H), 1.56–1.52 (m, 2H), 1.47–1.35 (m, 6H), 0.94–0.89 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 207.5, 142.6, 120.1, 96.7, 93.1, 90.6, 76.9, 37.4, 33.3, 31.4, 31.1, 28.6, 22.3, 19.5, 13.9, 13.6; HRMS (ESI) calcd for $C_{18}H_{27}$ $[M+H]^+$ 243.2113, found 243.2110.



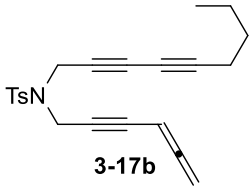
3-12

3-12: 157 mg, light yellow liquid, purify by flash column chromatography (SiO_2, EtOAc–Hexanes, 1:20). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.33 (m, 1H), 5.41 (d, 1H, *J* = 6.5 Hz), 2.55 (t, 2H, *J* = 6.2 Hz), 2.46–2.44 (m, 2H), 2.05–2.04 (m, 2H), 1.90–1.87 (m, 2H), 1.40–1.34 (m, 4H), 1.01 (t, 9H, *J* = 7.00 Hz), 0.90 (t, 3H, *J* = 6.1 Hz), 0.63 (q, 6H, *J* = 7.00 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 208.3, 150.4, 117.4, 93.5, 90.8, 89.7, 89.2, 80.5, 73.1, 36.7, 33.8, 31.3, 28.4, 22.5, 22.2, 13.9, 7.4, 4.3; HRMS (ESI) calcd for $C_{22}H_{33}Si$ $[M+H]^+$ 325.2352, found 325.2350.

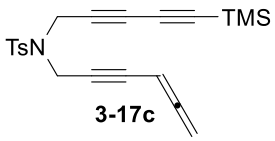


3-17a

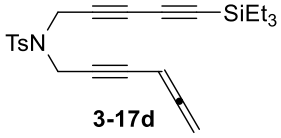
3-17a: 196 mg, light yellow liquid, purify by flash column chromatography (SiO_2, EtOAc–Hexanes, 1:10). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.70–7.68 (m, 2H), 7.28–7.27 (m, 2H), 5.17 (m, 1H), 4.95 (d, 2H, *J* = 6.9 Hz), 4.17 (s, 2H), 4.10 (d, 2H, *J* = 2.1 Hz), 2.40 (s, 3H), 2.15 (t, 1H, *J* = 2.2 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 216.7, 143.9, 135.2, 129.5, 127.9, 83.1, 78.0, 77.3, 76.4, 74.5, 74.0, 37.1, 36.3, 21.6; HRMS (ESI) calcd for $C_{16}H_{16}NO_2S$ $[M+H]^+$ 286.0901, found 286.0899.



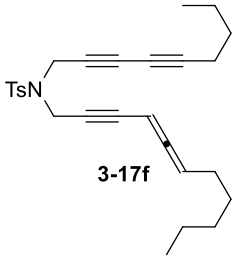
3-17b: 534mg, pale yellow liquid, purify by flash column chromatography (SiO_2, EtOAc–Hexanes, 1:10). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.65–7.64 (m, 2H), 7.26–7.24 (m, 2H), 5.15 (m, 1H), 4.91 (d, 2H, *J* = 6.7 Hz), 4.17 (s, 2H), 4.12 (s, 2H), 2.37 (s, 3H), 2.19 (t, 2H, *J* = 6.3 Hz), 1.44–1.40 (m, 2H), 1.36–1.32 (m, 2H), 0.86 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 216.7, 143.9, 134.9, 129.6, 127.9, 83.0, 80.8, 78.2, 77.3, 74.5, 70.8, 68.2, 64.4, 37.4, 37.2, 30.1, 21.9, 21.5, 18.8, 13.5; HRMS (ESI) calcd for $C_{22}H_{24}NO_2S$ $[M+H]^+$ 366.1577, found 366.1572.



3-17c: 213mg, pale yellow oil, purify by flash column chromatography (SiO_2, EtOAc–Hexanes, 1:10). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.66–7.65 (m, 2H), 7.27–7.26 (m, 2H), 5.17 (m, 1H), 4.92 (d, 2H, *J* = 6.7 Hz), 4.17 (s, 2H), 4.15 (s, 2H), 2.37 (s, 3H), 0.14 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 216.7, 144.0, 134.8, 129.6, 127.9, 87.1, 86.6, 82.9, 78.4, 77.3, 74.5, 70.6 (2 peaks), 37.6, 37.1, 21.6, -0.5; HRMS (ESI) calcd for $C_{21}H_{24}NO_2SSi$ $[M+H]^+$ 382.1297, found 382.1295.

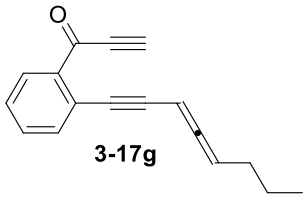


3-17d: 110 mg, yellow oil, purify by flash column chromatography (SiO_2, EtOAc–Hexanes, 1:10). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, 2H, *J* = 8.0 Hz), 7.30 (d, 2H, *J* = 8.1 Hz), 5.21 (tt, 1H, *J* = 7.1, 2.4 Hz), 4.97 (d, 2H, *J* = 6.9 Hz), 4.25 – 4.18 (m, 4H), 2.41 (s, 3H), 0.98 (t, 9H, *J* = 7.9 Hz), 0.60 (q, 6H, *J* = 7.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.76, 143.95, 134.93, 129.71, 129.59, 127.95, 127.88, 88.03, 84.78, 82.95, 78.34, 74.52, 70.81, 69.91, 37.63, 37.13, 21.58, 7.33, 4.11; HRMS (ESI) calcd for $C_{24}H_{30}NO_2SiS$ $[M+H]^+$ 424.1767, found 424.1756.



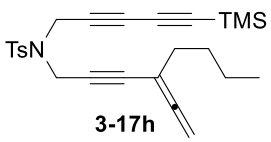
3-17f

3-17f: 352 mg, pale yellow liquid, purify by flash column chromatography (SiO_2, EtOAc–Hexanes, 1:10). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.67–7.66 (m, 2H), 7.27–7.26 (m, 2H), 5.33–5.30 (m, 1H), 5.13–5.09 (m, 1H), 4.18 (s, 2H), 4.15 (s, 2H), 2.38 (s, 3H), 2.20 (t, 2H, *J* = 6.5 Hz), 1.99 (t, 2H, *J* = 5.5 Hz), 1.46–1.20 (m, 12H), 0.89–0.86 (m, 6H; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 212.5, 143.8, 135.1, 129.5, 127.9, 93.4, 81.7, 80.7, 79.5, 74.6, 70.8, 68.2, 64.4, 37.5, 37.0, 31.2, 30.1, 28.4, 28.0, 22.4, 21.9, 21.5, 18.8, 14.0, 13.5; HRMS (ESI) calcd for $C_{27}H_{34}NO_2S$ $[M+H]^+$ 436.2310, found 436.2304.



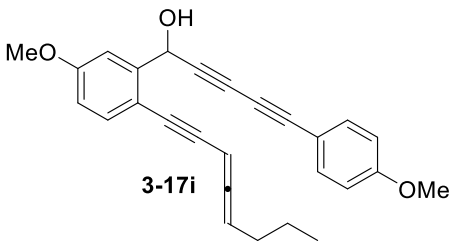
3-17g

3-17g: 296 mg, pale yellow liquid, purify by flash column chromatography (SiO_2, EtOAc–Hexanes, 1:10). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.11 (d, 1H, *J* = 7.8 Hz), 7.53 (d, 1H, *J* = 7.5 Hz), 7.48 (t, 1H, *J* = 7.5 Hz), 7.38 (t, 1H, *J* = 7.6 Hz), 5.64–5.62 (m, 1H), 5.49–5.45 (m, 1H), 3.44 (s, 1H), 2.07–2.05 (m, 2H), 1.50–1.46 (m, 2H), 0.94 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 213.1, 176.5, 136.8, 134.4, 132.9, 132.1, 127.7, 123.5, 93.3, 89.4, 88.3, 81.1, 80.9, 76.1, 30.2, 22.1, 13.6; HRMS (ESI) calcd for $C_{17}H_{15}O$ $[M+H]^+$ 235.1123, found 235.1118.

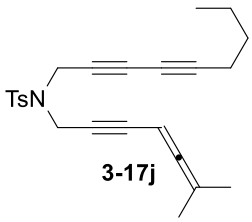


3-17h

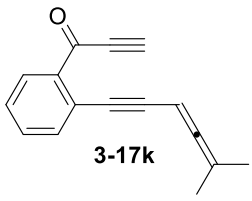
3-17h: 315 mg, pale yellow liquid, purify by flash column chromatography (SiO_2, EtOAc–Hexanes, 1:10). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.67–7.66 (m, 2H), 7.27–7.26 (m, 2H), 4.83 (s, 2H), 4.22 (s, 2H), 4.17 (s, 2H), 2.38 (s, 3H), 1.91 (t, 2H, *J* = 3.3 Hz), 1.34–1.20 (m, 4H, mix peak), 0.85 (t, 3H, *J* = 7.1 Hz), 0.15 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ213.7, 143.9, 134.9, 129.6, 127.9, 88.7, 87.1, 86.5, 83.2, 81.6, 76.8, 70.7, 70.5, 37.7, 37.0, 32.6, 29.7, 21.9, 21.6, 13.8, -0.5; HRMS (ESI) calcd for $C_{25}H_{32}NO_2SSi$ $[M+H]^+$ 438.1924, found 438.1921.



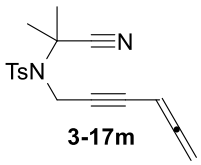
3-17i: 152 mg, dark brown liquid, purify by flash column chromatography (SiO_2, EtOAc–Hexanes, 1:6). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.42–7.36 (m, 3H, mix peak), 7.20 (s, 1H), 6.83–6.80 (m, 3H, mix peak), 5.92 (d, 1H, *J* = 3.6 Hz), 5.61–5.59 (m, 1H), 5.50–5.46 (m, 1H), 3.83 (s, 2H), 3.79 (s, 2H), 2.11–2.06 (m, 2H), 1.52–1.47 (m, 2H) 0.96 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 212.5, 160.4, 159.9, 143.0, 134.2, 133.7, 114.3, 114.2, 113.9, 113.4, 112.2, 93.3, 87.2, 86.6, 80.7, 79.4, 75.8, 72.3, 71.2, 63.72, 63.67, 55.5, 55.3, 30.2, 22.1, 13.6; HRMS (ESI) calcd for $C_{27}H_{29}O_3$ $[M+H]^+$ 397.1805, found 397.1803.



3-17j: 495 mg, pale yellow liquid, purify by flash column chromatography (SiO_2, EtOAc–Hexanes, 1:10). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.65–7.63 (m, 2H), 7.25–7.23 (m, 2H), 4.97 (m, 1H), 4.14 (s, 2H), 4.12 (s, 2H), 2.35 (s, 3H), 2.17 (t, 2H, *J* = 6.5 Hz), 1.64 (d, 6H, *J* = 2.5 Hz), 1.43–1.39 (m, 2H), 1.35–1.30 (m, 2H), 0.84 (t, 3H, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 210.4, 143.8, 135.1, 129.5, 127.9, 97.8, 80.64, 80.63, 80.1, 72.4, 70.7, 68.3, 64.4, 37.5, 37.0, 30.1, 21.8. 21.5, 19.8, 18.8, 13.4; HRMS (ESI) calcd for $C_{22}H_{24}NO_2S$ $[M+H]^+$ 394.1841, found 394.1839.

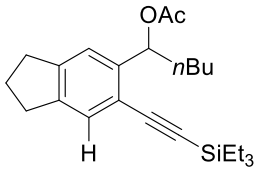


1h: 357 mg, pale yellow liquid, purify by flash column chromatography (SiO_2, EtOAc–Hexanes, 1:10). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.09 (d, 1H, *J* = 7.8 Hz), 7.52 (d, 1H, *J* = 7.6 Hz), 7.47 (t, 1H, *J* = 7.4 Hz), 7.36 (t, 1H, *J* = 7.6 Hz), 5.50 (s, 1H), 3.45 (s, 1H), 1.74 (d, 6H, *J* = 2.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 211.0, 176.5, 136.8, 134.4, 132.9, 132.1, 127.6, 123.6, 97.9, 90.3, 87.3, 81.1, 81.0, 74.0, 19.9; HRMS (ESI) calcd for $C_{16}H_{13}O$ $[M+H]^+$ 221.0967, found 221.0972.



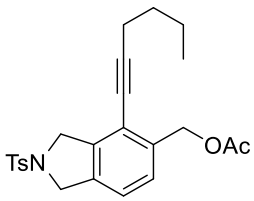
1m: 246 mg, pale yellow liquid, purify by flash column chromatography (SiO_2, EtOAc–Hexanes, 1:10). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.79–7.77 (m, 2H), 7.26–7.24 (m, 2H), 5.32–5.23 (m, 1H), 4.94 (d, 2H, J = 6.6 Hz), 4.24 (s, 2H), 2.36 (s, 3H), 1.80 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 216.7, 144.2, 137.4, 129.7, 127.7, 120.6, 85.7, 77.8, 77.4, 74.5, 36.7, 28.6, 21.9, 21.5; HRMS (ESI) calcd for $C_{17}H_{19}N_2O_2$ $[M+H]^+$ 315.1168, found 315.1162.

Characterization Data of Products



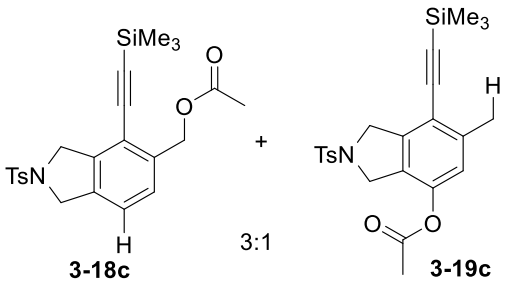
3-16

3-16, yellow oil, 75% yield (using GPA), 27 mg obtained. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.32(s, 1H), 7.20 (s, 1H), 6.21 (t, 1H, *J* = 6.2 Hz), 2.90–2.83 (m, 4H), 2.09–2.04 (m, 5H, mix peak), 1.85–1.83 (m, 2H), 1.34–1.27 (m, 4H), 1.06 (t, 9H, *J* = 7.00 Hz), 0.88 (t, 3H, *J* = 6.1 Hz), 0.68 (q, 6H, *J* = 7.00 Hz) ; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.4, 145.4, 143.3, 141.7, 128.5, 121.2, 119.0, 104.4, 95.6, 74.5, 36.0, 33.0, 32.3, 27.9, 25.4, 22.6, 21.3, 14.0, 7.5, 4.5. HRMS (ESI) calcd for $C_{24}H_{37}O_2Si$ $[M+H]^+$ 385.2563, found 385.2560.



3-18b

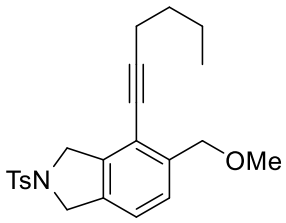
3-18b, colorless oil, 76% yield (using GPA), 25 mg obtained. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.78–7.76 (m, 2H), 7.64 (s, 1H), 7.32–7.30 (m, 2H), 7.24 (d, 2H, *J* = 7.8 Hz), 7.05 (d, 2H, *J* = 7.8 Hz), 5.18 (s, 2H), 4.64 (s, 2H), 4.62 (s, 2H), 2.45 (t, 2H, *J* = 6.8 Hz), 2.41 (s, 3H), 2.08 (s, 3H), 1.62–1.58 (m, 2H), 1.49–1.45 (m, 2H), 0.96 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.8, 143.8, 139.2, 136.7, 135.9, 133.7, 129.9, 128.1, 127.6, 121.5, 100.7, 74.7, 64.4, 54.2, 54.0, 30.7, 22.0, 21.5, 20.9, 19.3, 13.6. HRMS (ESI) calcd for $C_{24}H_{28}NO_4S$ $[M+H]^+$ 426.1739, found 426.1736.



3-18c **3-19c**

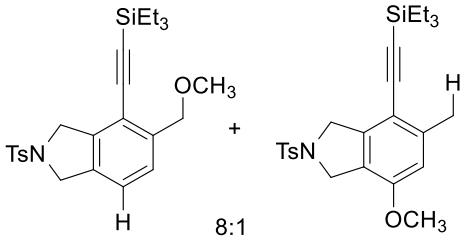
3-18c/**3-19c**: Products **3-18c** and **3-19c** are obtained as an inseparable mixture in 5:1 ratio; yellow solid; 66% total yield; 30 mg (using GPA). Major Product: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 7.9 Hz, 2H), 7.25 (d, *J* = 7.8 Hz, 1H), 7.10 (d, *J* = 7.9 Hz, 1H), 5.19 (s, 2H), 4.69 – 4.64 (m, 2H), 4.62 (s, 2H), 2.41 (s, 3H), 2.08 (s, 3H), 0.26 (s, 9H); Minor Product: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 7.9 Hz, 2H), 6.78 (s, 1H), 5.19 (s, 2H), 4.62 (s, 2H), 4.58 (s, 2H), 2.41 (s, 3H), 2.29 (s, 3H), 2.19 (s, 3H), 0.26 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) all

discernable signals for both isomers δ 170.64, 143.81, 139.54, 137.38, 136.13, 133.73, 129.91, 128.20, 127.57, 122.43, 117.94, 116.52, 104.96, 98.48, 64.27, 54.09, 53.84, 21.52, 20.82, -0.11; HRMS (ESI) calcd for $C_{23}H_{28}NO_4SiS$ $[M+H]^+$ 442.1508, found 442.1506.



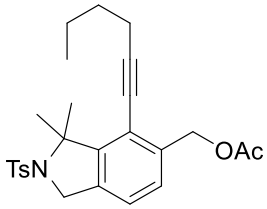
3-18d

3-18d: Products **2d** and **3d** are obtained as an inseparable mixture in 10:1 ratio; yellow liquid; 79% total yield; 34 mg (using GPA). Major Product: ^{1}H NMR ($CDCl_3$, 500 MHz): δ, 7.78–7.76 (m, 2H), 7.31–7.25 (m, 3H), 7.05 (d, 1H, *J* = 7.6 Hz), 4.64 (s, 2H), 4.62 (s, 2H), 4.52 (s, 2H), 3.39 (s, 3H), 2.47 (t, 3H, *J* =6.7 Hz), 2.40 (s, 3H), 1.59–1.56 (m, 2H), 1.51–1.47 (m, 2H), 0.97 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 143.7, 139.2, 138.9, 135.0, 133.8, 118.0, 100.0, 75.1, 72.3, 58.5, 54.2, 54.0, 30.8, 22.0, 21.5, 19.3, 13.6. HRMS (ESI) calcd for $C_{23}H_{28}NO_3S$ $[M+H]^+$ 398.1790, found 398.1786.



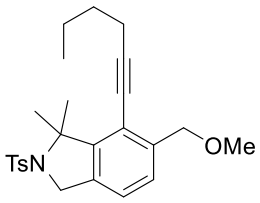
3-18e **3-19e**

3-18e/**3-19e**: Products **3-18e** and **3-19e** are obtained as an inseparable mixture in 10:1 ratio; yellow solid; 79% total yield; 32 mg obtained (using GPA). Major isomer (**2d**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.0 Hz, 2H), 7.35 – 7.28 (m, 3H), 7.10 (d, *J* = 7.9 Hz, 1H), 4.67 – 4.61 (m, 4H), 4.56 (s, 2H), 3.40 (s, 3H), 2.40 (s, 3H), 1.13 – 1.00 (m, 9H), 0.69 (q, *J* = 7.9 Hz, 6H); Minor isomer (**3d**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.0 Hz, 2H), 7.35 – 7.28 (m, 3H), 6.58 (s, 1H), 4.62 – 4.58 (m, 4H), 4.56 (s, 2H), 3.76 (s, 3H), 2.27 (s, 3H), 2.40 (s, 3H), 0.92 – 0.81 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) all discernable signals for both isomers δ 143.73, 139.79, 139.34, 135.20, 133.75, 129.86, 129.82, 127.56, 127.28, 122.38, 117.23, 104.50, 101.81, 100.16, 72.24, 58.57, 54.20, 53.95, 21.51, 7.55, 4.40.



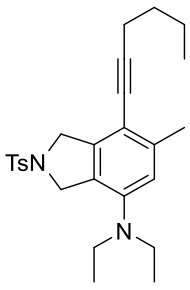
3-18f

3-18f: yellow liquid; 52% yield; 32 mg (using GPA). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.81–7.79 (m, 2H), 7.28–7.26 (m, 3H), 7.06 (d, 1H, *J* = 8.2 Hz), 5.23 (s, 2H), 4.54 (s, 2H), 2.49 (t, 2H, *J* = 7.0 Hz), 2.40 (s, 3H), 2.10 (s, 3H), 1.95 (s, 6H), 1.62–1.85 (m, 2H), 1.50–1.45 (m, 2H), 0.95 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.8, 146.6, 143.0, 138.2, 138.1, 134.1, 129.4, 127.7, 127.4, 121.5, 117.7, 102.9, 74.5, 72.5, 64.6, 52.2, 30.5, 26.7, 22.1, 21.5, 20.9, 19.4, 13.6; HRMS (ESI) calcd for $C_{26}H_{32}NO_4S$ $[M+H]^+$ 454.2052, found 454.2050.



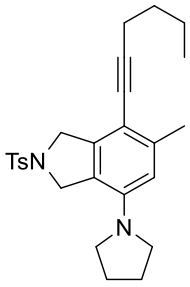
3-18g

3-18g: yellow liquid; 65% yield; 38 mg (using GPA). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.81–7.80 (m, 2H), 7.32 (d, 1H, J = 7.8 Hz), 7.28–7.26 (m, 2H), 7.06 (d, 1H, *J* = 7.8 Hz), 4.58 (s, 2H), 4.53 (s, 2H), 3.43 (s, 3H), 2.50 (t, 2H, *J* = 7.0 Hz), 2.40 (s, 3H), 1.95 (s, 6H), 1.64–1.60 (m, 2H), 1.52–1.47 (m, 2H), 0.96 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 146.2, 143.0, 140.7, 138.1, 133.1, 129.4, 126.8, 121.5, 116.7, 102.2, 74.8, 72.6, 72.5, 58.6, 52.3, 30.6, 26.7, 22.5, 21.5, 19.4, 13.6; HRMS (ESI) calcd for $C_{25}H_{32}NO_3S$ $[M+H]^+$ 426.2103, found 426.2097.



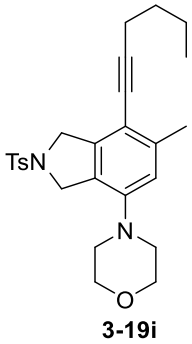
3-19g

3-19g: yellow liquid; 62% yield; 23 mg (using GPA). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.78–7.76 (m, 2H), 7.31–7.29 (m, 2H), 6.56 (s, 1H), 4.59 (s, 2H), 4.55 (s, 2H), 3.06 (q, 4H, J = 7 Hz), 2.44 (t, 2H, J = 6.8 Hz)), 2.40 (s, 3H), 2.31 (s, 3H), 1.59–1.55 (m, 2H), 1.51–1.46 (m, 2H), 1.01–0.95 (m, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 144.9, 143.5, 140.3, 134.0, 129.8, 127.6, 125.0, 118.9, 110.7, 97.1, 76.8, 54.3, 54.2, 45.8, 31.1, 22.0, 21.5, 20.5, 19.3, 13.6, 12.7. HRMS (ESI) calcd for $C_{26}H_{35}N_2O_2S$ $[M+H]^+$ 439.2419, found 439.2416.



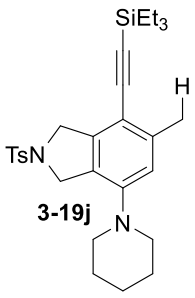
3-19h

3-19h: yellow liquid; 55% yield; 21 mg (using GPA). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.77–7.76 (m, 2H), 7.31–7.29 (m, 2H), 6.23 (s, 1H), 4.81 (s, 2H), 4.56 (s, 2H), 3.31 (t, 3H, J = 2.3 Hz), 2.42 (t, 2H, J = 6.7 Hz) 2.40 (s, 3H), 2.29 (s, 3H), 1.93 (t, 3H, J = 2.3 Hz), 1.59–1.56 (m, 2H), 1.51–1.48 (m, 2H), 0.96, (t, 3H, J = 7.0 Hz) ; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 143.51, 143.49, 140.7, 140.6, 133.9, 129.8, 127.6, 117.3, 113.1, 106.8, 96.1, 54.9, 54.0, 49.2, 31.2, 25.4, 22.0, 21.5, 20.4, 19.4, 13.7. HRMS (ESI) calcd for $C_{26}H_{33}N_2O_2S$ $[M+H]^+$ 437.2263, found 437.2264.



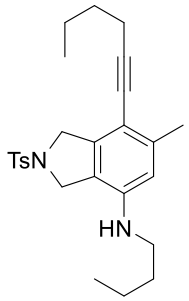
3-19i

3-19i: yellow liquid; 55% yield; 26 mg (using GPA). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.79–7.77 (m, 2H), 7.33–7.31 (m, 2H), 6.61 (s, 1H), 4.58 (s, 2H), 4.55 (s, 2H), 3.80 (t, 4H, *J* = 2.1 Hz), 2.90 (t, 4H, *J* = 2.1 Hz), , 2.44 (t, 2H, *J* = 6.3 Hz), 2.40 (s, 3H), 2.33 (s, 3H), 1.61–1.57 (m, 2H), 1.50–1.46 (m, 2H), 0.96 (t, 3H, *J* = 6.2 Hz; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 146.5, 143.6, 141.1, 140.3, 133.9, 129.8, 127.6, 125.6, 117.6, 112.6, 97.9, 76.2, 67.1, 54.2, 53.5, 50.9, 33.7, 31.0, 22.0, 21.5, 19.3, 13.6; HRMS (ESI) calcd for $C_{26}H_{33}N_2O_3S$ $[M+H]^+$ 453.2213, found 453.2214.



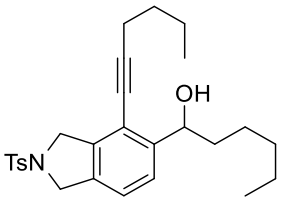
3-19j

3j: white solid; 32% yield; 18 mg (using GPA). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.7 Hz, 2H), 7.31 (d, *J* = 7.0 Hz, 2H), 6.59 (s, 1H), 4.65 – 4.47 (m, 4H), 3.01 – 2.78 (m, 4H), 2.40 (s, 3H), 2.35 (s, 3H), 1.65 (d, *J* = 7.7 Hz, 4H), 1.58–1.56 (m, 2H), 1.09 – 1.01 (m, 9H), 0.66 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.57, 141.54, 140.64, 133.82, 129.81, 127.60, 125.51, 117.68, 113.50, 102.19, 98.68, 54.17, 53.68, 51.83, 26.24, 24.19, 21.52, 20.48, 7.59, 4.56; HRMS (ESI) calcd for $C_{29}H_{41}N_2O_2SiS$ $[M+H]^+$ 509.2654, found 509.2658.



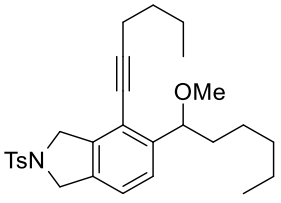
3-19f

3-19f: yellow liquid; 45% yield; 16 mg (using GPA). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.78–7.76 (m, 2H), 7.32–7.30 (m, 2H), 6.28 (s, 1H), 4.61–4.57 (m, 3H), 4.42 (s, 1H), 4.17 (brs, 1H), 3.09 (t, 2H, *J* = 7.0 Hz), 2.43–2.40 (m, 5H, mix peak), 2.31 (s, 3H), 1.59–1.54 (m, 4H), 1.50–1.46 (m, 2H), 1.42–1.38 (m, 2H), 0.97–0.93 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 143.6, 142.1, 141.5, 139.4, 133.9, 129.8, 127.5, 121.1, 117.4, 110.0, 102.6, 76.7, 54.8, 52.4, 43.3, 31.5, 31.2, 22.0, 21.5, 20.6, 20.2, 19.3, 13.9, 13.6; HRMS (ESI) calcd for $C_{26}H_{35}N_2O_2S$ $[M+H]^+$ 439.2419, found 439.2416.



3-20a

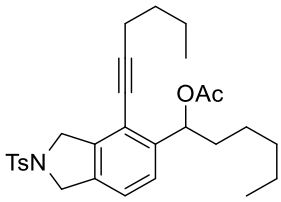
3-20a: yellow solid; 48% yield; 28 mg (using GPB). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.78–7.77 (m, 2H), 7.34–7.31 (m, 3H, mixed peak), 7.06 (d, 1H, *J* = 7.7), 5.03 (t, 1H, *J* = 4.3 Hz), 4.63 (s, 2H), 4.61 (s, 2H), 2.47 (t, 3H, *J* = 6.8 Hz), 2.40 (s, 3H) , 1.71–1.68 (m, 2H), 1.61–1.57 (m, 4H, mixed peak), 1.52–1.45 (m, 4H, mixed peak), 1.29–1.25 (m, 2H, mixed peak), 0.97 (t, 3H, *J* = 5.5 Hz), 0.87 (t, 3H, *J* = 3.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 146.1, 143.7, 139.0, 134.6, 133.9, 129.8, 127.6, 125.1, 121.7, 116.6, 100.5, 75.2, 72.2, 54.1, 54.1, 38.2, 31.7, 30.8, 25.6, 22.6, 22.1, 21.5, 19.3, 14.0, 13.6. HRMS (ESI) calcd for $C_{27}H_{36}NO_3S$ $[M+H]^+$ 454.2416, found 454.2407.



3-20b

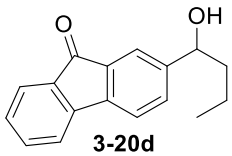
3-20b: yellow liquid; 50% yield; 22 mg (using GPA). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.79–7.77 (m, 2H), 7.33–7.31 (m, 2H), 7.27 (d, 1H, *J* = 7.8 Hz), 7.07 (d, 1H, *J* = 7.8 Hz), 4.64 (s, 2H), 4.61 (s, 2H), 4.57 (t, 1H, *J* = 4.5 Hz), 3.17 (s, 3H), 2.47 (t, 3H, *J* = 6.8 Hz), 2.40 (s, 3H), 1.62–1.59 (m, 2H), 1.62–1.59 (m, 4H, mixed peak), 1.51–1.47 (m, 2H, mixed peak), 1.34–1.26 (m, 6H, mixed peak), 0.97 (t, 3H, *J* = 5.5 Hz), 0.84 (t, 3H, *J* = 3.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 144.0, 143.6, 138.7, 134.5, 133.9, 129.8, 129.7, 127.6, 125.0,

121.7, 118.0, 100.2, 80.9, 75.2, 56.9, 54.2, 54.1, 37.6, 31.7, 30.8, 25.5, 22.6, 22.0, 21.5, 19.3, 14.1, 13.6; HRMS (ESI) calcd for $C_{28}H_{38}NO_3S$ $[M+H]^+$ 468.2572, found 468.2557.



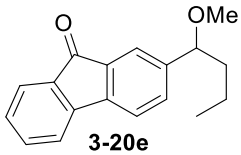
3-20c

3-20c: yellow liquid; 45% yield; 25 mg (using GPA). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.77–7.76 (m, 2H), 7.32–7.31 (m, 2H), 7.19 (d, 1H, *J* = 7.8 Hz), 7.03 (d, 1H, *J* = 7.8 Hz), 6.05 (t, 1H, *J* = 4.3 Hz), 4.67–4.54 (m, 4H), 2.47 (t, 3H, *J* = 6.8 Hz), 2.40 (s, 3H), 2.05 (s, 3H), 1.77–1.75 (m, 2H), 1.62–1.59 (m, 2H, mixed peak), 1.51–1.47 (m, 2H, mixed peak), 1.35–1.26 (m, 6H, mixed peak), 0.97 (t, 3H, *J* = 5.5 Hz), 0.86 (t, 3H, *J* = 3.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.1, 143.7, 142.5, 139.0, 134.9, 133.7, 129.9, 127.6, 124.8, 121.5, 117.3, 100.7, 74.9, 74.0, 54.2, 54.1, 35.8, 31.5, 30.7, 25.2, 22.5, 22.0, 21.5, 21.1, 19.4, 14.0, 13.6. HRMS (ESI) calcd for $C_{29}H_{38}NO_4S$ $[M+H]^+$ 496.2522, found 495.2521.



3-20d

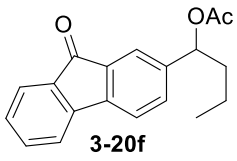
3-20d: yellow solid; 61% yield; 27 mg (using GPB). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.65–7.63 (m, 2H, mixed peak), 7.49–7.45 (m, 4H, mixed peak), 7.28 (m, 1H), 4.71 (t, 1H, *J* = 6.7 Hz), 1.98 (brs, 1H), 1.83–1.76 (m, 1H), 1.73–1.66 (m, 1H), 1.48–1.39 (m, 1H), 1.37–1.29 (m, 1H), 0.94 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 193.9, 146.5, 144.3, 143.7, 134.7, 134.44, 134.41, 132.3, 129.0, 124.4, 122.0, 120.3, 120.2, 73.9, 41.2, 18.9, 13.9; HRMS (ESI) calcd for $C_{17}H_{17}O_2$ $[M+H]^+$ 253.1230, found 253.1226.



3-20e

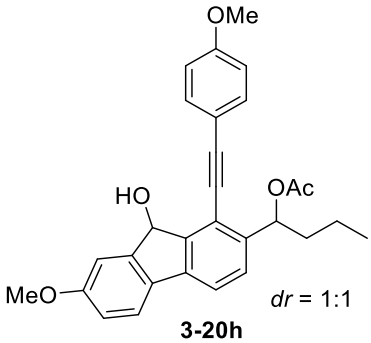
3-20e: yellow liquid; 62% yield; 22 mg (using GPA). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.66–7.64 (m, 2H), 7.58 (s, 1H), 7.51–7.46 (m, 3H, mixed peak), 7.42 (d, 1H, *J* = 7.8 Hz), 7.27 (m, 1H), 4.12 (t, 1H, J = 6.6 Hz), 3.23 (s, 3H), 1.83–1.76 (m, 1H), 1.61–1.57 (m, 1H), 1.43–1.36 (m, 1H), 1.32–1.26 (m, 1H), 0.90 (t, 3H, *J* = 7.3); ^{13}C NMR ($CDCl_3$, 125

MHz): δ 194.0, 144.4, 144.3, 143.8, 134.7, 134.5, 134.4, 132.9, 129.0, 124.4, 122.9, 120.3, 120.2, 8..4, 56.8, 40.0, 18.8, 13.9; HRMS (ESI) calcd for $C_{18}H_{19}O_2$ $[M+H]^+$ 267.1385, found 267.1382.



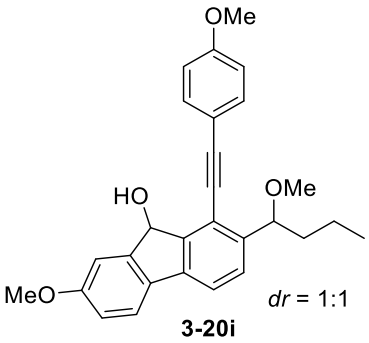
3-20f

3-20f: yellow liquid; 66% yield; 32 mg (using GPA). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.66–7.64 (m, 2H), 7.53–7.47 (m, 3H, mixed peak), 7.44–7.42 (m, 1H), 7.30–7.27 (m, 1H), 5.72 (t, 1H, J = 7.0 Hz), 2.08 (s, 3H), 1.94–1.87 (m, 1H, mixed peak), 1.78–1.71 (m, 1H, mixed peak), 1.38–1.25 (m, 2H, mixed peak), 0.93 (t, 3H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 193.7, 170.4, 144.2, 144.0, 142.4, 134.8, 134.6, 134.4, 133.2, 129.1, 124.4, 122.3, 120.4, 120.2, 75.4, 38.2, 21.2, 18.7, 13.8; HRMS (ESI) calcd for $C_{19}H_{19}O_3$ $[M+H]^+$ 295.1335, found 295.1331.



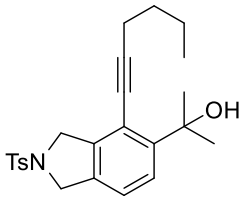
3-20h

3-20h: dark brown solid; 58% yield; 43 mg (using GPA). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.57–7.55 (m, 2H, mixed peak for both diastereomers), 7.46–7.44 (m, 2H, mixed peak for both diastereomers), 7.41–7.39 (m, 1H, mixed peak for both diastereomers), 7.24–7.22 (m, 1H, mixed peak for both diastereomers), 6.93–6.91 (m, 3H, mixed peak for both diastereomers) 5.80 (s, 1H), 5.81 (t, 1H, *J* = 5.5 Hz), 3.88 (s, 3H), 3.86 (s, 3H), 3.29 (m, 3H, mixed peak for both diastereomers), 1.82–1.75 (m, 2H, mixed peak), 1.53–1.42 (m, 2H, mixed peak), 0.96 (t, 3H, *J* = 5.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): All discernible peaks for both diastereomers δ 170.3, 170.2, 160.3, 160.2, 160.1, 146.8, 146.74, 146.72, 140.6, 140.5, 139.9, 139.8, 133.2, 132.02, 131.98, 126.6, 126.4, 120.9, 118.93, 118.90, 118.6, 118.5, 115.2, 114.7, 114.2, 110.8, 99.3, 82.97, 82.90, 74.7, 73.8, 73.7, 55.6, 55.4, 38.1, 38.0, 21.3, 18.9, 13.9; HRMS (ESI) calcd for $C_{29}H_{29}O_5$ $[M+H]^+$ 457.2015, found 457.2013.



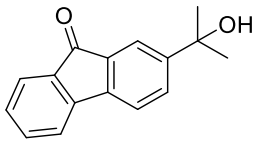
3-20i

3-20i: dark brown solid; 62% yield; 52 mg (using GPA). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.55–7.53 (m, 4H, mixed peak for both diastereomers), 7.46–7.44 (m, 1H, mixed peak for both diastereomers), 7.26–7.25 (m, 1H, mixed peak for both diastereomers), 6.94–6.93 (m, 3H, mixed peak for both diastereomers), 5.80 (s, 1H), 5.81 (t, 1H, *J* = 5.5 Hz), 3.88 (s, 3H), 3.86 (s, 3H), 3.29 (m, 3H, mixed peak for both diastereomers), 1.82–1.75 (m, 2H, mixed peak), 1.53–1.42 (m, 2H, mixed peak), 0.96 (t, 3H, *J* = 5.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): All discernible peaks for both diastereomers δ 160.2, 146.6, 142.5, 142.4, 139.4, 134.3, 133.0, 132.3, 126.5, 126.4, 120.9, 119.3, 119.0, 115.1, 114.8, 114.3, 110.8, 98.9, 83.20, 83.15, 80.8, 80.7, 74.7, 57.02, 56.97, 55.6, 55.4, 39.9, 39.8, 19.1, 14.1; HRMS (ESI) calcd for $C_{28}H_{29}O_4$ $[M+H]^+$ 429.2026, found 429.2023.



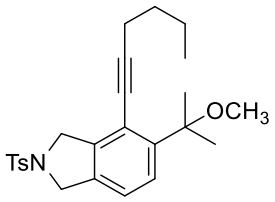
3-22a

3-22a: yellow solid; 80% yield; 31 mg (using GPB). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.78–7.76 (m, 2H), 7.38 (d, 1H, *J* = 8.0 Hz), 7.32–7.30 (m, 2H), 7.02 (d, 1H, *J* = 8.0 Hz) , 4.64 (s, 2H), 4.62 (s, 2H), 3.32 (brs, 1H), 2.50 (t, 2H, *J* = 7.0 Hz), 2.40 (s, 3H), 1.66 (s, 3H), 1.63–1.60 (m, 2H), 1.52–1.47 (m, 2H), 0.54 (s, 3H), 0.97 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 149.4, 143.7, 140.8, 134.4, 133.8, 129.8, 127.6, 124.4, 121.5, 115.4, 102.7, 77.1, 73.1, 54.4, 54.2, 30.5, 29.9, 22.1, 21.5, 19.4, 13.6; HRMS (ESI) calcd for $C_{24}H_{30}NO_3S$ $[M+H]^+$ 412.1946, found 412.1932.



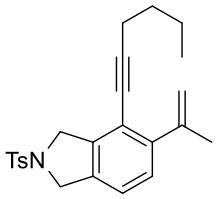
3-22b

3-22b: yellow solid; 62% yield; 24 mg (using GPB). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.75 (s, 1H), 7.69–7.67 (m, 1H), 7.65–7.63 (m, 1H), 7.51–7.46 (m, 3H), 7.29–7.27 (m, 1H), 1.60 (s, 6H), 1.25 (brs, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 194.1, 150.7, 144.3, 143.0, 134.7, 134.5, 134.3, 130.8, 128.9, 124.3, 120.8, 120.3, 120.2, 72.6, 31.7; HRMS (ESI) calcd for $C_{16}H_{15}O_2$ $[M+H]^+$ 239.1072, found 239.1071.



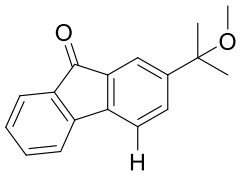
3-22c

3-22c: yellow liquid; 59% yield (along with 19% of **7c**); 28 mg (using GPA). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.79–7.77 (m, 2H), 7.35–7.31 (m, 2H), 7.01 (d, 1H, *J* = 8 Hz), 4.64 (s, 2H), 4.62 (s, 2H), 3.14 (s, 3H), 2.47 (t, 2H, *J* = 6.8 Hz), 2.40 (s, 3H), 1.62–1.59 (m, 8H), 1.53–1.48 (m, 2H), 0.97 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 146.6, 143.6, 141.1, 134.2, 133.9, 129.8, 127.6, 125.9, 121.0, 117.0, 100.9, 87.9, 77.5, 54.6, 54.3, 50.5, 30.7, 26.6, 22.1, 21.5, 19.5, 13.6; HRMS (ESI) calcd for $C_{25}H_{32}NO_3S$ $[M+H]^+$ 426.2103, found 426.2097.



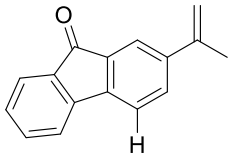
3-23c

3-23c: white solid; 75% yield; 34 mg (using GPA). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.78–7.77 (m, 2H), 7.32–7.31 (m, 2H), 7.08 (d, 1H, *J* = 7.8 Hz), 6.99 (d, 1H, *J* = 7.8 Hz), 5.17 (s, 1H), 5.06 (s,1H), 4.64 (s, 2H), 4.62 (s, 2H), 2.43 (t, 2H), 3.39–3.34 (m, 1H), 3.08 (m, 4H), 2.56 (dd, 1H, *J* = 17.0, 7.0 Hz), 2.48 (t, 2H, *J* = 6.8 Hz), 2.40 (s, 3H), 2.11 (s, 3H), 1.58–1.55 (m, 2H), 1.50–1.45 (m, 2H), 0.96 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 145.1, 144.4, 143.6, 139.4, 134.3, 133.8, 129.8, 127.6, 127.5, 121.2, 116.8, 115.8, 99.2, 76.6, 54.3, 54.3, 30.7, 23.3, 22.0, 21.5, 19.4, 13.6; HRMS (ESI) calcd for $C_{24}H_{28}NO_2S$ $[M+H]^+$ 394.1841, found 394.1832.



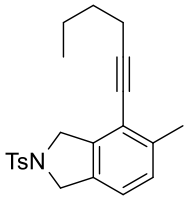
3-22d

3-22d: yellow solid; 55% yield; 33 mg; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 1.9 Hz, 1H), 7.65 (d, *J* = 7.3 Hz, 1H), 7.58 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.54 – 7.44 (m, 3H), 7.31 – 7.25 (m, 1H), 3.10 (s, 3H), 1.54 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.10, 147.91, 144.31, 143.23, 134.73, 134.50, 134.38, 132.23, 128.95, 124.35, 121.99, 120.26, 120.23, 50.71, 27.79; HRMS (ESI) calcd for $C_{17}H_{17}O_2$ $[M+H]^+$ 253.1229, found 253.1221.



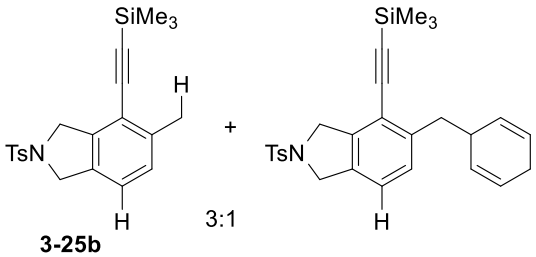
3-23d

3-23d:This product was obtained as a byproduct with **3-22d**; yellow solid; 10% yield; 6 mg; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 1.8 Hz, 1H), 7.66 (d, *J* = 7.4 Hz, 1H), 7.59 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.53 – 7.46 (m, 3H), 7.32 – 7.26 (m, 1H), 5.46 (s, 1H), 5.21 – 5.10 (m, 1H), 2.21 – 2.11 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.03, 144.36, 143.30, 142.35, 142.17, 134.77, 131.60, 128.96, 124.38, 121.47, 120.33, 120.17, 113.43, 102.65, 98.30, 21.77; HRMS (ESI) calcd for $C_{16}H_{13}O$ $[M+H]^+$ 221.0966, found 221.0960.



3-25a

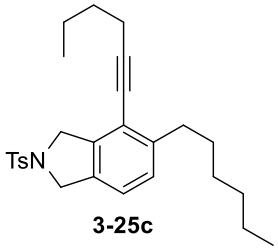
3-25a: Compound **3-25a** was isolated as a 3:1 mixture with a byproduct obtained as a result 1,4-CHD addition; colorless oil; 66% yield; 28 mg; Major Product (hydrogenation): ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.78–7.76 (m, 2H), 7.31–7.30 (m, 2H), 7.11 (d, 1H, *J* = 7.9 Hz), 7.01 (d, 1H, *J* = 7.9 Hz), 4.63 (s, 2H), 4.60 (s, 2H), 3.36 (h, 1H, *J* = 6.8 Hz), 2.47 (t, 2H, *J* = 6.9 Hz), 2.40 (s, 3H), 2.35 (s, 3H), 1.63–1.59 (m, 2H), 1.51–1.47 (m, 2H), 0.96 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 143.6, 139.3, 139.0, 138.7, 133.9, 133.0, 129.8, 128.8, 127.6, 124.2, 121.1, 99.4, 76.2, 54.21, 54.17, 30.9, 22.0, 21.5, 20.2, 19.3, 13.6; HRMS (ESI) calcd for $C_{22}H_{26}NO_2S$ $[M+H]^+$ 368.1684, found 368.1676.



3-25b

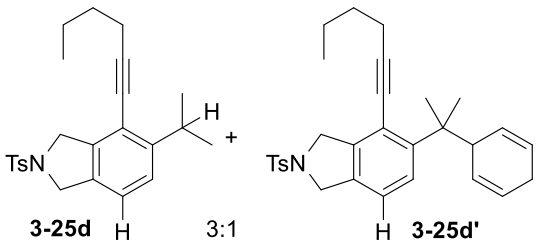
3-25b: Compound **9b** was isolated as a 3:1 mixture with a byproduct obtained as a result 1,4-CHD addition; colorless oil; 66% yield; 34 mg; Major Product (hydrogenation): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 – 7.73 (m, 2H), 7.35 – 7.30 (m, 2H), 7.06 (d, *J* = 8.0 Hz, 1H), 6.98 (d, *J* = 7.8 Hz, 1H), 4.65 (s, 2H), 4.59 (s, 2H), 2.40 (s, 3H), 2.37 (s, 3H), 0.26 (s, 9H); Minor Product (1,4-CHD adduct) : ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 – 7.73 (m, 2H), 7.35 – 7.30 (m, 2H), 7.06 (d, *J* = 8.0 Hz, 1H), 6.98 (d, *J* =

7.8 Hz, 1H), 5.89 (d, *J* = 9.1 Hz, 1H), 5.68 (dt, *J* = 20.9, 12.5 Hz, 2H), 5.54 (d, *J* = 10.0 Hz, 1H), 4.65 (s, 2H), 4.59 (s, 2H), 3.97 (s, 3H), 2.77 (dd, *J* = 13.8, 7.5 Hz, 1H), 2.62 (d, *J* = 7.8 Hz, 0H), 2.40 (s, 3H), 0.26 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) all discernable signals for both compounds δ 143.64, 142.07, 140.03, 139.24, 138.99, 133.91, 133.23, 130.48, 129.85, 129.63, 129.39, 128.90, 128.44, 127.60, 127.57, 125.42, 124.33, 124.03, 123.96, 122.10, 121.99, 121.90, 118.05, 103.45, 100.29, 54.13, 54.03, 41.77, 37.97, 36.00, 33.63, 27.95, 26.34, 21.51, 20.11, 0.05, 0.00; HRMS (ESI) calcd for $C_{21}H_{26}NO_2SiS$ $[M+H]^+$ 384.1454, found 384.1451; HRMS (ESI) calcd for $C_{21}H_{26}NO_2SiS$ $[M+H]^+$ 384.1454, found 384.1451.



3-25c

3-25c: Compound **3-25c** was isolated as a 3:1 mixture with a byproduct obtained as a result 1,4-CHD addition; colorless oil; 61% yield; 35 mg; Major Product (hydrogenation): ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.78–7.76 (m, 2H), 7.31–7.30 (m, 2H), 7.03 (d, 1H, *J* = 7.8 Hz), 6.95 (d, 1H, *J* = 7.8 Hz), 4.63 (s, 2H), 4.59 (s, 2H), 2.68 (t, 2H, *J* = 7.5 Hz), 2.46 (t, 2H, *J* = 6.8 Hz), 2.40 (s, 3H), 1.61–1.47 (m, 6H), 1.38–1.12 (m, 6H), 0.97 (t, 3H, *J* = 7.0 Hz), 0.87 (t, 3H, *J* = 4.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ144.3, 143.6, 138.9, 133.9, 133.1, 129.8, 128.2, 127.6, 121.2, 118.5, 98.8, 76.1, 54.3, 54.2, 34.2, 31.7, 30.9, 30.8, 29.2, 22.6, 22.0, 21.5, 19.3, 14.1, 13.6; HRMS (ESI) calcd for $C_{27}H_{36}NO_2S$ $[M+H]^+$ 438.2467, found 438.2463.



3-25d: Compound **3-25d** was isolated as a 3:1 mixture with a byproduct obtained as a result 1,4-CHD addition; colorless oil; 59% yield; 23 mg; Major Product (hydrogenation): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78–7.76 (m, 2H), 7.31–7.30 (m, 2H), 7.11 (d, 1H, *J* = 7.9 Hz), 7.01 (d, 1H, *J* = 7.9 Hz), 4.63 (s, 2H), 4.60 (s, 2H), 3.36 (h, 1H, *J* = 6.8 Hz), 2.47 (t, 2H, *J* = 6.9 Hz), 2.40 (s, 3H), 1.61–1.56 (m, 2H), 1.51–1.47 (m, 2H), 1.20 (d, 6H, *J* = 6.8 Hz), 0.96 (t, 3H, *J* = 7.0 Hz); Minor

Product (1,4-CHD adduct) : ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (d, 1H, *J* = 8.1 Hz), 6.97 (d, 1H, *J* = 8.1 Hz), 5.80 (dd, 1H, *J* = 13.6, 2.3 Hz), 5.75–5.72 (m, 2H, mix peak), 5.36 (d, 1H, J = 13.6 Hz), 5.40–5.30 (m, 2H), 2.60 (d, 2H, *J* = 2.3 Hz), 1.71 (d, 1H, J = 2.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) all discernable signals for both compounds δ 149.8, 143.6, 138.9, 133.9, 133.0, 129.8, 129.5, 128.3, 128.0, 127.6, 126.7, 126.6, 125.8, 124.5, 121.5, 99.3, 75.9, 54.3, 54.2, 41.6, 39.2, 37.1, 31.2, 30.8, 26.5, 24.6, 23.1, 22.1, 22.0, 21.5, 19.6, 19.3, 13.6; HRMS (ESI) calcd for $C_{24}H_{30}NO_2S$ $[M+H]^+$ 396.1997, found 396.1989.

3.6. References

(1) (a) Myers, A. G.; Proteau, P. J. *J. Am. Chem. Soc.* **1989**, *111*, 1146. (b) Myers, A. G.; Kuo, E. Y.; Finney, N. S. *J. Am. Chem. Soc.* **1989**, *111*, 8057. (c) Nagata, R.; Yamanada, H.; Okazaki, E.; Saito, I. *Tetrahedron Lett.* **1989**, *30*, 4995. (d) Myers, A. G.; Arvedson, S. P.; Lee, R. W. *J. Am. Chem. Soc*. **1996**, *118*, 4725. (e) Schreiner, P. R.; Prall, M. *J. Am. Chem. Soc.* **1999**, *121*, 8615. (f) Much, P. W.; Remenyi, C.; Helten, H.; Engels, B. *J. Am. Chem. Soc.* **2002**, *124*, 1823. (g) Feng, L.; Kumar, D.; Birney, D. M.; Kerwin, S. M. *Org. Lett.* **2004**, *6*, 2059. (h) Schmittel, M.; Mahajan, A. A.; Bucher, G. *J. Am. Chem. Soc.* **2005**, *127*, 5324. (i) Waddell, M. K.; Bekele, T.; Lipton, M. A. *J. Org. Chem*. **2006**, *71*, 8372. (j) Gaudel-Siri, A.; Campolo, D.; Mondal, S.; Nechab, M.; Siri, D.; Bertrand M. P. *J. Org. Chem.* **2014**, *79*, 9086

(2) (a) Ishida, N.; Miyazaki, K.; Kumagai, K. M.; Rikimaru, M. *J. Antibiot*. **1965**, *18*, 68. (b) Meienhofer, J.; Maeda, H.; Glaser, C. B.; Czonbos, J.; Kuromizu, K. *Science* **1972**, *178*, 875. (d) Albers-Schönberg, G.; Dewey, R. S.; Hensens, O. D.; Liesch, J. M.; Napier, M. A.; Goldberg, I. H. *Biochem. Biophys. Res. Commun.* **1980**, *95*, 135. (e) Myers, A. G.; Proteau, P. J.; Handel, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 7212. (f) Kim, K.-H.; Kwon, B.-M.; Myers, A.G.; Rees, D. C. *Science* **1993**, *262*, 1042. Monographs on enediyne antibiotics: (g) Xi, Z.; Goldberg, I. H. DNA-damaging Enediyne Compounds. In *Comprehensive Natural Products Chemistry*; Barton, S. D. Nakanishi, K.,

Meth-Cohn, O., Eds.; Pergamon: Oxford, 1999; Vol. 7, pp553–592. (h) Neocarzinostatin, The Past, Present, and Future of an Anticancer Drug, Maeda, H., Edo, K., Ishida, N., Eds.; Springer: Tokyo, 1997.

(3) Total synthesis of natural products that involve the enediyne structure to undergo Bergman cyclization, see: CalicheamicinÁ1I: (a) Nicolaou, K. C.; Hummel, C. W.; Nakada, M.; Shibayama, K.; Pitsinos, E. N.; Saimoto, H.; Mizuno, Y.; Baldenius, K.-U.; Smith, A. L. *J. Am. Chem. Soc.* **1993**, *115*, 7625. (b) Hitchcock, S. A.; Chu-Moyer, M. Y.; Boyer, S. H.; Olson, S. H.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 5750. Dynemicin A: (c) Shair, M. D.; Yoon, T.-Y.; Mosny, K. K.; Chou, T. C.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1996**, *118*, 9509. (d) Myers, A. G.; Tom, N. J.; Fraley, M. E.; Cohen, S. B.; Madar, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 6072. N1999-A: (e) Kobayashi, S.; Reddy, R. S.; Sugiura, Y.; Sasaki, D.; Miyagawa, N.; Hirama, M. *J. Am. Chem. Soc.* **2001**, *123*, 2887. (f) Kobayashi, S.; Ashizawa, S.; Takahashi, Y.; Sugiura,Y.; Nagaoka, M.; Lear, M. J.; Hirama, M. *J. Am. Chem. Soc.* **2001**, *123*, 11294. Kedarcidin chromophore aglycon: (g) Myers, A. G.; Hogan, P. C.; Hurd, A. R.; Goldberg, S. D. *Angew. Chem., Int. Ed.* **2002**, *41*, 1062.

(4) (a) Beerman, T. A.; Goldberg, I. H. *Biochem. Biophys. Res. Commun.* **1974**, *59*, 1254. (b) Beerman, T. A.; Poon, R.; Goldberg, I. H. *Biochim. Biophys. Acta* **1977**, *475*, 294. (c) Kappen, L. S.; Goldberg, I. H. *Nucleic Acids Res.* **1978**, *5*, 2959.

(5) Total and formal synthesis of neocarzinostatin chromophor: (a) Myers, A. G.; Harrington, P. M.; Kuo, E. Y. *J. Am. Chem. Soc.* **1991**, *113*, 694. (b) Myers, A. G.; Hammond, M.; Wu, Y.; Xiang, J.-N.; Harrington, P. M.; Kuo, E. Y. *J. Am. Chem. Soc.* **1996**, *118*, 10006. (c) Myers, A. G.; Liang, J.; Hammond, M.; Harrington, P. M.; Wu, Y.; Kuo, E. Y. *J. Am. Chem. Soc.* **1998**, *120*, 5319. (d) Myers, A. G.; Glatthar, R.; Hammond, M.; Harrington, P. M.; Kuo, E. Y.; Liang, J.; Schaus, S. E.; Wu, Y.; Xiang, J.-N. *J. Am. Chem. Soc.* **2002**, *124*, 5380. (e) Kobayashi, S.; Hori, M.; Wang, G. X.; Hirama, M. *J. Org. Chem.* **2006**, *71*, 636. Reviews: (f) Nicolaou, K. C.; Dai, W. M. *Angew. Chem*.,

Int. Ed. **1991**, *30*, 1387. (g) Grissom, J. W.; Gunawardena, G. U.; Klingberg, D.; Huang, D. *Tetrahedron* **1996**, *52*, 6453.

(6) (a) Jones, R. R.; Bergman, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 660. Bergman, R. G. *Acc. Chem. Res.* **1973**, *6*, 25. (b) Kim, C.-S.; Russell, K. C. *J. Org. Chem.* **1998**, *63*, 8229. (c) Alabugin, I. V.; Manoharan, M.; Kovalenko, S. V. *Org. Lett.* **2002**, *4*, 1119. (d) McMahon, R. J.; Halter, R. J.; Fimmen, R. L.; Wilson, R. J.; Peebles, S. A.; Kuczkowski, R. L.; Stanton, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 939. (e) Luxon, A. R.; Orms, N.; Kanters, R.; Krylov, A. I.; Parish, C. A. *J. Phys. Chem.* **2018**, *122*, 420. (f) Schuler, B.; Fatayer, S.; Mohn, F.; Moll, N.; Pavliček, N.; Meyer, G.; Peña, D.; Gross, Leo. *Nat. Chem.* **2016**, *8*, 220. A review: (g) Mohamed, R. K.; Peterson, P. W.; Alabugin I. V. *Chem. Rev.* **2013**, *113*, 7089.

(7) Bergman cyclization involving ionic trapping: (a) Perrin, C. L.; Rodgers, B. L.; O'Connor, J. M. *J. Am. Chem. Soc.* **2007**, *129*, 4795. (b) Das, E.; Basak, S.; Anoop, A.; Basak, A. *J. Org. Chem.* **2018**, *83*, 7730.

(8) (a) Berthlot, M. *Liebigs Ann. Chem.* **1867**, *141*, 673. (b) Wang, T.; Naredla, R. R.; Thompson, S. K.; Hoye, T. R. *Nature* **2016**, *532*, 484. A review: (c) Diamond, O. J.; Marder, T. B. *Org. Chem. Front.* **2017**, *4*, 891.

(9) Schmittel cyclization can be also considered as a pseudo-Myers-Saito cyclization. Studies on the Schmittel cyclization, see: (a) Stahl, F.; Moran, D.; Schleyer, P. R.; Prall, M.; Schreiner, P. R. *J. Org. Chem.* **2002**, *67*, 1453. (b) Schmittel, M.; Vavilala, C. *J. Org. Chem.* **2005**, *70*, 4865. (c) Schmittel, M.; Mahajan, A. A.; Bucher, G. *J. Am. Chem. Soc.* **2005**, *127*, 5324. (d) Waddell, M. K.; Bekele, T.; Lipton, M. A. *J. Org. Chem.* **2006**, *71*, 8372. (e) Schmittel, M.; Mahajan, A. A.; Bucher, G.; Bats, J. W. *J. Org. Chem.* **2007**, *72*, 2166. (f) Schmittel, M.; Steffen, J.-P.; Rodríguez, D.; Engelen, B.; Neumann, E.; Cinar, M. E. *J. Org. Chem.* **2008**, *73*, 3005. (g) Samanta, D.; Cinar, M. E.; Das, K.; Schmittel, M. *J. Org. Chem.* **2013**, *78*, 1451.

(10) (a) Bradley, A. Z.; Johnson, R. P. *J. Am. Chem. Soc.* **1997**, *119*, 9917. (b) Miyawaki, K.; Suzuki, R.; Kawano, T.; Ueda, I. *Tetrahedron Lett.* **1997**, *38*, 3943. (c) Miyawaki, K.; Kawano, T.; Ueda, I. *Tetrahedron Lett.* **1998**, *39*, 6923. (d) Kociolek, M. G. Johnson, R. P. *Tetrahedron Lett.* **1999**, *40*, 4141. (e) Ueda, I.; Sakurai, Y.; Kawano, T.; Wada, Y.; Futai, M. *Tetrahedron Lett.* **1999**, *40*, 319. (f) Miyawaki, K.; Ueno, F.; Ueda, I. *Heterocycles* **2000**, *54*, 887. (g) Hoye, T. R.; Baire, B.; Niu, D. W.; Willoughby, P. H.; Woods, B. P. *Nature* **2012**, *490*, 208. (h) Yun, S. Y.; Wang, K.; Kim, M.; Lee, D. *J. Am. Chem. Soc.* **2012**, *134*, 10783.

(11) We believe that at higher temperature, the reaction rate between nitrogen nucleophiles and the α,3-dehydrotoluene intermediate increases.

(12) (a) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc. Trans.* **1915**, *107*, 1080. (b) Boeckman, R. K., Jr.; Ko, S. S. *J. Am. Chem. Soc.* **1982**, *104*, 1033. (c) Levine M. N., Raines, R. T. *Chem. Sci.* **2012**, *3*, 2412. (d) Gupta, S., Lin, Y.; Xia, Y.; Wink, D. J.; Lee, D. *Chem. Sci.* **2019**, *10*, 2212. A general review on *gem*-dimethyl effect: (e) M. E. Jung and G. Piizzi, *Chem. Rev.* **2005**, *105*, 1735.

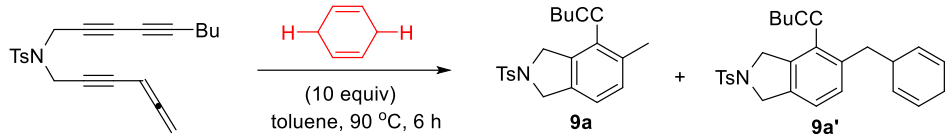
(13) In a remotely related cycloaromatization process, the reversal of the mode of addition of Nu–H has been observed caused by a relatively minor change of the substituent, see: Karmakar, R.; Yun, S. J.; Chen, J.; Xia, Y.; Lee, D. *Angew. Chem., Int. Ed.* **2015**, *54*, 6582.

(14) The exact origin of this lack of reactivity is yet to be defined but at this point we assume that the alkyl substituent(s) will destabilize the transition state of adding a nitrogen nucleophile to the endocyclic carbon of the α,3-dehydrotoluene intermediate, which ultimately develops an incipient benzylic carbon-centered anion.

(15) (a) Karmakar, R.; Yun, S. Y.; Wang, K.; Lee, D. *Org. Lett.* **2014**, *16*, 6. (b) Willoughby, P. H.; Niu, D.; Wang, T.; Haj, M. K.; Cramer, C. J.; Hoye, T. R. *J. Am. Chem. Soc.* **2014**, *136*, 13657. (c) Pogula, V. D.; Wang, T.; Hoye, T. R. *Org. Lett.* **2015**, *17*, 856. (d) Chen, J.; Palani, V.; Hoye, T. R. *J. Am. Chem. Soc.* **2016,** *138*, 4318.

(16) It was shown that the hexadehydro Diels-Alder reaction with 1,3-diyne and nitrile requires much higher activation barrier than that with alkyne and 1,3-diyne, see: Thompson, S. K.; Hoye, T. R. *J. Am. Chem. Soc.* **2019**, *141*, 19575.

(17) The isolated product also contains minor product as given below. Please see supporting information for more details.

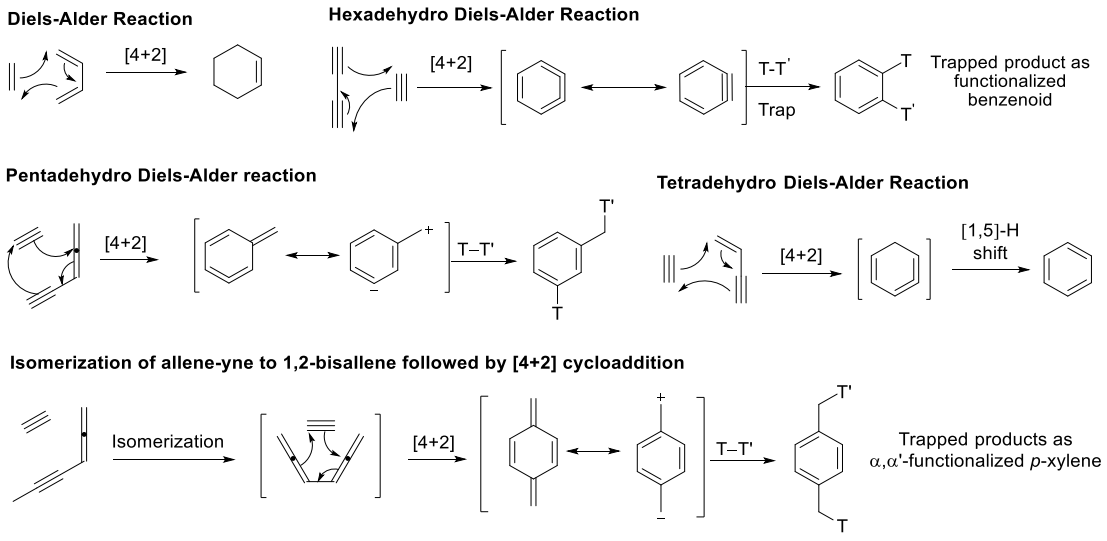


CHAPTER 4

[Allenynes + Nitrile] Cycloaddition to Form Pyridine Derivatives

4.1. Introduction

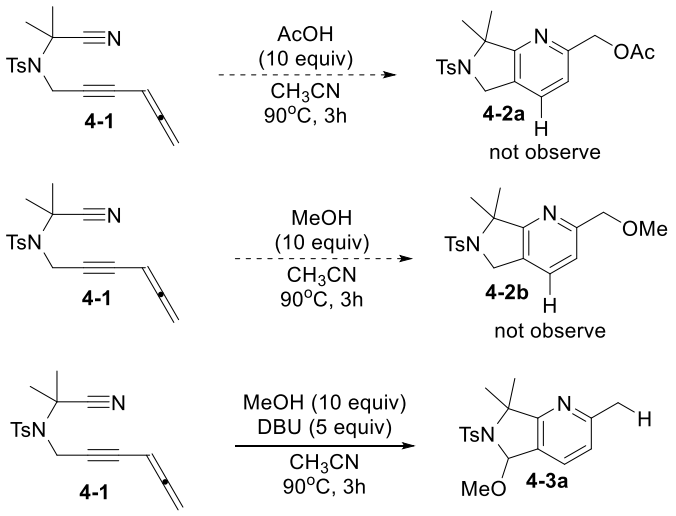
Cycloisomerization between diene and dienophile, known as Diels-Alder reaction is the most versatile method for construction of six-membered ring compounds (Scheme 4.1). Since first discovered in 1928, different modes of Diels-Alder reaction have been subsequently discovered, including tetradehydro Diels-Alder reaction,[1] pentadehydro Diels-Alder reaction (PDDAR)[2] and hexadehydro Diels-Alder reaction (HDDAR).[3] Both PDDAR and HDDAR involve components of higher degree of unsaturation, which is translated into the high strain energy of intermediates, allowing variety of chemical transformations, including hydrogenation, nucleophile trapping, Alder-ene reaction, Diels-Alder reaction, [3+2] dipolar cycloaddition and so forth. In PDDA reaction, allene–yne is employed as a "diene" component to an α,3-dehydro toluene intermediate, which ultimately leads to functionalized toluene via nucleophilic trapping. Theoretical calculations show introducing an allene instead of a diene counterpart significantly decreases the activation energy of cycloisomerization step.[1] We hypothesized that under appropriate conditions, allene–yne can undergo isomerization to the corresponding 1,2-bisallene, which is more reactive diene component for [4+2] cycloaddition with alkyne to afford *para*-quinodimethanes (*p*-xylylenes)[4] intermediate. Subsequent trapping of this intermediate under nucleophilic condition will afford α,α′-functionalized *p*-xylene.



Scheme 4.1. Types of Diels-Alder Reactions

4.2. Initial Observation

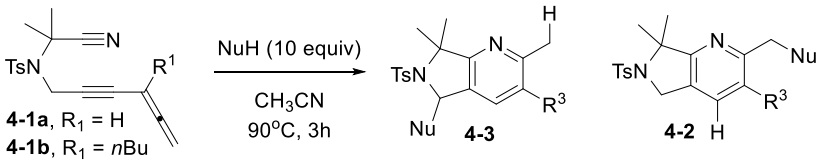
Intrigued by the possibility of an aza-PDDA reaction demonstrated by Hoye and co-workers,[2] nitrile-tethered sulfonamide-containing allene-yne **4-1** was subjected to standard thermal PDDA reaction conditions in the presence of 10 equivalents of acetic acid as a trapping reagent for the expected α,3-dehydrotoluene intermediate. Unfortunately, **4-1** remained intact after 3 h at 90 °C and even a trace of desired product **4-2a** was observed. Prolonged heating at higher temperature (150 °C) led to decomposition of the starting material after 12 h. The same behavior was observed when methanol was employed; **4-1** decomposed after 12 h at 150 °C without forming **4-2b**. Based on these results, we hypothesized that the PDDA reaction of allene-yne with nitrile requires higher activation energy compare to that with alkyne. A similar phenomenon was observed in the HDDA reaction of 1,3-diyne with nitrile, which requires higher activation energy than with alkyne.[5] Fortunately, with a non-nucleophilic base additive such as DBU, the reaction of **4-1** proceed in the presence of methanol to afford **4-3a** in 68% yield. The incorporation of nucleophile at the α-position of the aromatic ring suggests that the reaction proceeds through a 1,2-bisallene intermediate.



Scheme 4.2. Cycloaddition of Allene-yne with Nitrile

4.3. Results and Discussion

With these initial results in hand, we explored the reaction scope by employing different nucleophiles and substrates that contain different substituent patterns (**Table 4.1**). One particular structural element that was found to play a significant activating role for the cyclization of **4-1** is the Thorpe–Ingold effect induced by the *gem*-dimethylated quaternary carbon.[6] While *gem*-dimethylated substrate **4-1c** successfully delivered desired product **4-3f** in 65% yield (entry 8), under the identical condition, mono-methylated substrate **4-1d** failed in generating product **4-3g** (entry 9). Substrate **4-1d** also failed in



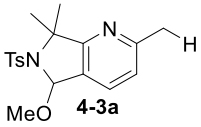
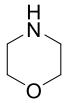
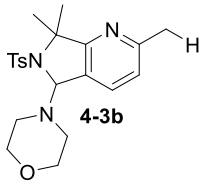
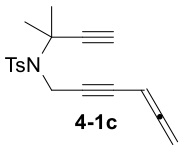
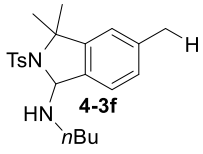
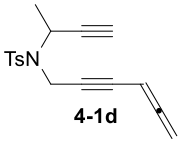
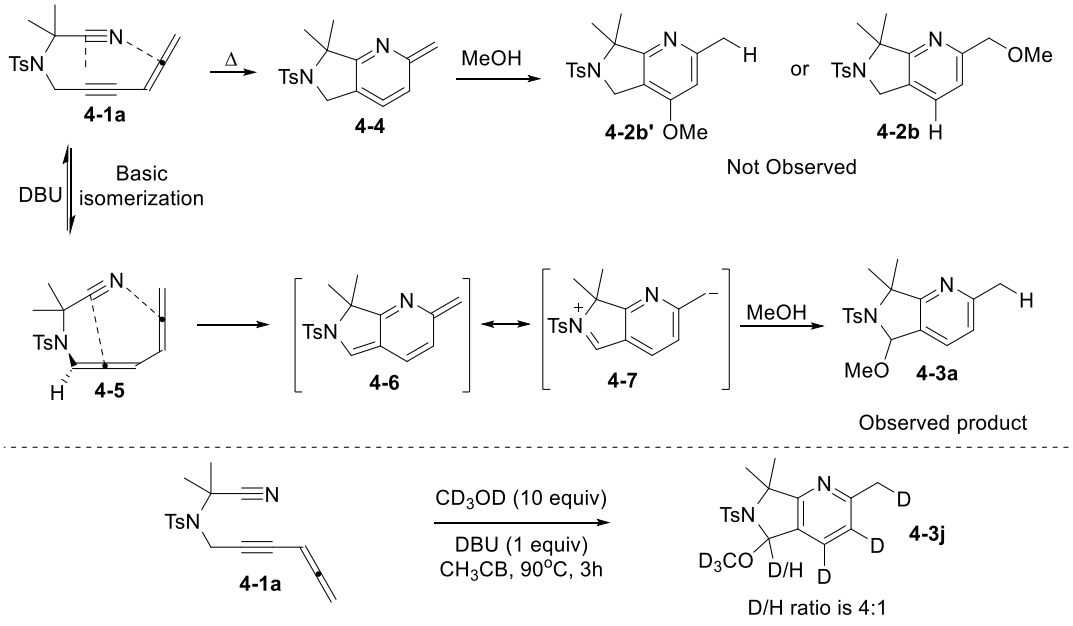
Entries	Substrate	NuH	Product	Yield (%)[a]
1	**4-1a**	AcOH	**4-2a**	0[b]
2	**4-1a**	MeOH	**4-2b**	0[b]
3	**4-1a**	MeOH[d]	 **4-3a**	68[d]
4	**4-1a**		 **4-3b**	75
5	**4-1a**	$BuNH_2$	**4-3c**	72[c]
6	**4-1a**	H_2O[d]	**4-3d**	52[d]
7	**4-1b**	$BuNH_2$	**4-3e**	65
8	 **4-1c**	$BuNH_2$	 **4-3f**	65
9	 **4-1d**	$BuNH_2$	**4-3g**	0[b]
10		MeOH[d]	**4-3h**	0[b]

Table 4.1. Reaction Profiles for Aza-PDDA Reactions Involving Nitriles

delivering product **4-3h** in the presence of DBU and methanol (entry 10). In the presence of other nucleophilic bases such as morpholine and butylamine, substrate **4-1a** afforded pyridine derivatives **4-3b** and **4-3c** in 75% and 72% yield, respectively (entries 4 and 5). Incorporation of weakly basic nucleophiles such as water was successful in the presence of 5 equivalents of DBU (entries 6), affording **4-3d** in 52% yield. Substrate **4-1b** with a butyl substituent at the proximal carbon also delivered pyridine derivative **4-3e** in the presence of butylamine (entry 7).

The formation of pyridine derivative **4-3a** can be explained on the basis of the initial isomerization of the allene–yne induced by a base additive to the corresponding 1,2-bisallene **4-5** followed by its participation in [4+2] cycloaddition with the tethered nitrile (**Scheme 4.3**). Under the conditions, the cycloadduct α-dehydropyridine intermediate **4-6** reacts with a nucleophile to form product **4-3a**. Overall, this transformation constitutes a formal PDDA reaction wherein the in situ generated 1,2-bisallene plays a temporary allene–yne surrogate under basic medium. To gain more insight into the reaction mechanism, deuterium labelling experiments were carried out with substrate **4-1a**. It was expected that by using MeOD



Scheme 4.3. Rationale for the Reaction of Allene–Yne with Nitrile in Basic Conditions

under the standard reaction conditions, reversible isomerization. Indeed, the isolated product **4-3j** from the reaction showed deuterium labeling pattern that is fully consistent with the isomerization pathway of **4-1a** to **4-5** followed by its participation in the [4+2] cycloaddition.

4.4. Conclusion

This chapter describes the development of a formal aza-PDDA reaction under basic conditions. The direct [4+2] cycloaddition of allene-yne with nitrile does not occur under thermal conditions but proceeds smoothly in the presence of a base additive. This result indicates that the initial isomerization of allene-yne to the corresponding 1,2-bisallenic followed by its participation in the [4+2] cycloaddition of with nitrile should have lower activation energy. The most notable feature of this reaction is the facile involvement of nitrile as dienophile although nitrile requires high temperature for [4+2] cycloaddition reactions. This new cycloaddition allows for synthesis of structurally novel pyridine derivatives, which is an important structural element for both natural and pharmaceutical compounds.

4.5. Experimental Details

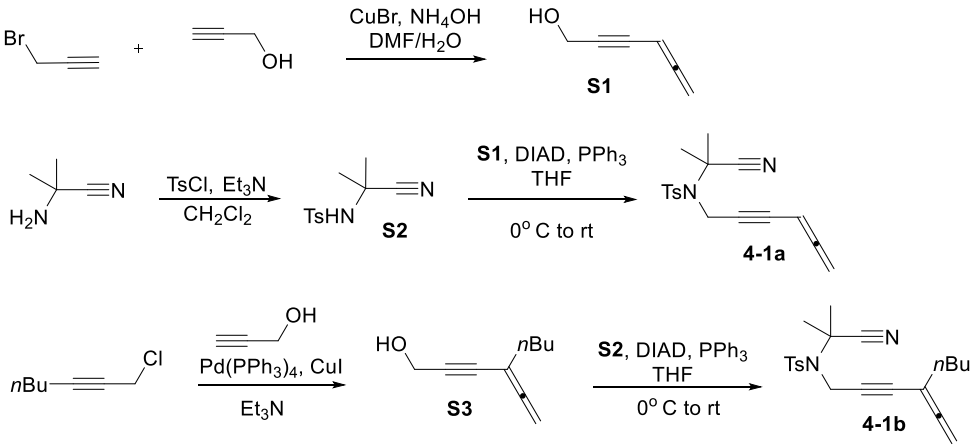
4.5.1. General Information

Reactions were carried out in oven-dried glassware unless otherwise noted. Compounds were purchased from Sigma-Aldrich or TCI America or Oakwood Chemicals unless otherwise noted. Toluene, acetonitrile, dichloromethane and triethyl amine were distilled over calcium hydride (CaH_2) under nitrogen atmosphere. THF was distilled over sodium-benzophenone ketyl under nitrogen atmosphere. Column chromatography was performed using silica gel 60 Å (32−63 mesh) purchased from Silicycle Inc. Thin layer chromatography (TLC) was performed on 0.25 mm E. Merck precoated silica gel 60 (particle size 0.040−0.063 mm). Yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AV-500 spectrometer. ^{1}H NMR chemical shifts (δ) are reported in parts per million (ppm) downfield of TMS and are referenced relative to

the residual proteated solvent peak ($CDCl_3$ (7.26 ppm)). ^{13}C chemical shifts (δ) are reported in parts per million downfield of TMS and are referenced to the carbon resonance of the solvent ($CDCl_3$ (77.2 ppm)). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sext (sextet) or m (multiplet). ^1H NMR signals that fall within a ca. 0.3 ppm range are generally reported as a multiplet, with a range of chemical shift values corresponding to the peak or center of the peak. Coupling constants, *J*, are reported in Hz (Hertz). Electrospray ionization (ESI) mass spectra were recorded on a Waters Micromass Q-Tof Ultima in the University of Illinois at Urbana-Champaign. Electron impact (EI) mass spectra and Chemical Ionization (CI) mass spectra were obtained using a Micromass 70-VSE in the University of Illinois at Urbana–Champaign.

4.5.2 Experimental Procedures

Synthesis of nitrile 4-1a and 4-1b



Propargyl alcohol (1 equiv) was added to a solution of CuBr (0.5 equiv) in NH_4OH (25% in water)/DMF (1:1). To the resulting yellow green solution was added slowly propargyl bromide (1.3 equiv, 80% in toluene) at 0 °C. The deep blue suspension was allowed to warm up slowly to room temperature over 2 h. Then water was added and filtered through a pad of Celite. The solid was washed with Et_2O and the filtrate was extracted with Et_2O. The combine organic layers were washed with water, brine and dried over Na_2SO_4. After filtration, the organic layer was concentrated, and the crude material was purified by

column chromatography using (hexanes:EtOAc, 4:1) to get pure hexa-4,5-dien-2-yn-1-ol (**S1**) as yellow liquid at 75% yield.

To a solution of 2-amino-2-methylpropanenitrile (2 mL, 31 mmol) in CH_2Cl_2 (30 mL) at 0 °C were added trimethylamine (1.5 equiv) and 4-toluenesulfonylchloride (1.1 equiv). The reaction mixture was stirred until complete consumption of starting material (monitored by TLC). After completion, the reaction mixture was transferred to a separatory funnel, diluted with Et_2O (100 mL) and washed with aqueous HCl (1 N, 200 mL), water (x2) and brine. The organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get the crude product **S2** which was used for the next reaction without further purification.

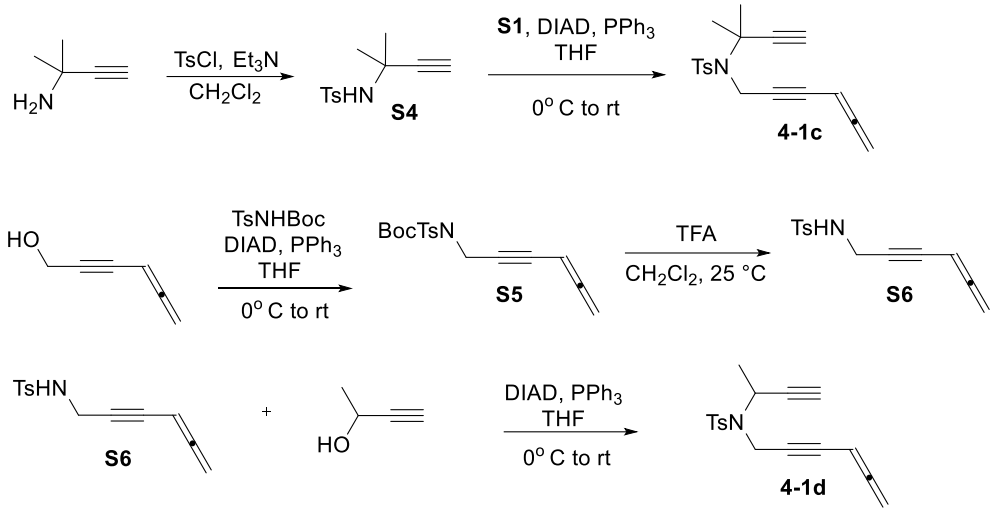
DIAD (1.2 equiv) was added dropwise to a solution of sulfonamide **S2** (1.0 equiv), PPh_3 (1.2 equiv), and alcohol **S1** (1.0 equiv) in dry THF at 0 °C under nitrogen balloon. The reaction mixture was warmed up to room temperature and further stirred overnight. After completion, the reaction mixture was concentrated and purified by silica gel column chromatography (SiO_2, hexanes:EtOAc = 10:1 to 5:1) to get pure product **4-1a** (196 mg, 62%).

To a solution of 1-chloro-2-heptyne (1 equiv) in Et_3N (20 mL) was added $(Ph_3P)_4Pd$ (0.5 mol %) and CuI (1.0 mol %) at room temperature under nitrogen. Propargyl alcohol (1.2 equiv) was added dropwise to the above solution with continuous stirring. After 15 minutes, the reaction mixture was warmed up to 40 °C and stirred until complete consumption of the alkenyl bromide (monitored by thin layer chromatography). Upon completion, the reaction mixture was filtered through Celite pad, concentrated, and directly loaded on a silica gel column and eluted (hexanes:EtOAc, 20:1 to 5:1) to obtain pure allene-yne **S3** (72%).

DIAD (1.2 equiv) was added dropwise to a solution of sulfonamide **S2** (1.0 equiv), PPh_3 (1.2 equiv), and alcohol **S3** (1.0 equiv) in dry THF at 0 °C under nitrogen balloon. The reaction mixture was warmed up to room temperature and further stirred overnight. After completion, the reaction mixture was

concentrated and purified by silica gel column chromatography (SiO_2, hexanes:EtOAc = 10:1 to 5:1) **4-1b** (218mg, 63%).

Synthesis of alkyne 4-1c and 4-1d



To a solution 2-methyl-3-butyn-2-amine (1 equiv) in CH_2Cl_2 (30 mL) at 0 °C were added trimethylamine (1.5 equiv) and 4-toluenesulfonylchloride (1.1 equiv). The reaction mixture was stirred until complete consumption of starting material (monitored by TLC). After completion, the reaction mixture was transferred to a separatory funnel, diluted with diethyl ether (100mL) and washed with aqueous HCl (1N, 200 mL), water (x2) and brine (x1). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get the crude product **S4** which was used for the next reaction without further purification.

DIAD (1.2 equiv) was added dropwise to a solution of sulfoamide **S4** (1.0 equiv), PPh_3 (1.2 equiv), and alcohol **S1** (1.0 equiv) in dry THF at 0 °C under nitrogen balloon. The reaction mixture was warmed up to room temperature and further stirred overnight. After completion, the reaction mixture was concentrated and purified by silica gel column chromatography (SiO_2, hexanes:EtOAc = 10:1 to 5:1) to get pure product **4-1c** (187 mg, 65% yield). The same procedure was repeat one more time to afford **S5** at moderate yield.

TFA (5.0 equiv) was added to a solution of Boc-protected sulfonamide (1.0 equiv) in dichloromethane at room temperature and stirred until complete consumption of starting material (monitored by TLC). After completion, the reaction mixture was transferred to a separatory funnel diluted with dichloromethane and washed with water (x2) and brine (x1). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get the crude product which was further purified by column chromatography to afford pure product **S6** (78% yield).

DIAD (1.2 equiv) was added dropwise to a solution of sulfoamide **S6** (1.0 equiv), PPh_3 (1.2 equiv), and 3-butyn-2-ol (1.0 equiv) in dry THF at 0 °C under nitrogen balloon. The reaction mixture was warmed up to room temperature and further stirred overnight. After completion, the reaction mixture was concentrated and purified by silica gel column chromatography (SiO_2, hexanes:EtOAc = 10:1 to 5:1) to afford pure product **4-1d (**214mg, 65%**)**.

General Procedure for Cyclization between Alkyne/nitrile and Allene-yne under Basic Condition

General Procedure A (GPA)

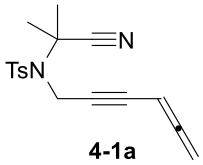
A solution of a substrate and amine (10 equiv) in toluene in a Schlenk tube was flushed with nitrogen. The mixture was stirred for 3 h at 90 °C unless otherwise noted. After completion (monitored by TLC), the reaction mixture was transferred to a round-bottom flask, concentrated, and purified by column chromatography, using ethyl acetate-hexane mixture as the eluent.

General Procedure (GPB)

A solution of a substrate, nucleophile (10 equiv) and DBU (5 equiv) in dry CH_3CN in a Schlenk tube was flushed with nitrogen. The mixture was stirred for 3 h at 90 °C unless otherwise noted. After completion, the reaction mixture was transferred to a round-bottom flask, concentrated, and subjected to column chromatography, using ethyl acetate-hexane mixture as the eluent, to get pure products.

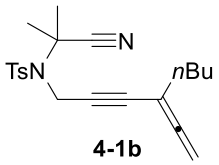
4.5.3 Characterization Data

Characterization Data of Substrates



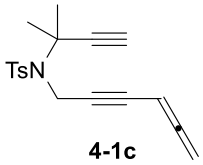
4-1a

4-1a: 196 mg, light yellow liquid, purify by flash column chromatography (SiO_2, EtOAc–Hexanes, 1:10). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.85–7.84 (m, 2H), 7.31–7.30 (m, 2H), 5.30 (m, 1H), 5.01 (d, 2H, *J* = 6.5 Hz), 4.30 (s, 2H), 2.42 (s, 3H), 1.87 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 216.8, 144.2, 137.4, 129.7, 127.8, 120.6, 85.7, 77.9, 77.4, 74.6, 54.3, 36.9, 28.7, 21.6; HRMS (ESI) calcd for $C_{17}H_{19}N_2O_2S$ $[M+H]^+$ 315.1167, found 315.1165.



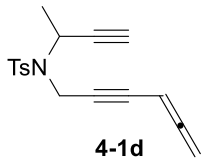
4-1b

4-1b: 218 mg, light yellow liquid, purify by flash column chromatography (SiO_2, EtOAc–Hexanes, 1:10). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.86–7.85 (m, 2H), 7.30–7.29 (m, 2H), 4.90 (s, 2H), 4.30 (s, 2H), 2.41 (s, 3H), 2.00 (t, 2H, *J* = 6.1 Hz) 1.87 (s, 6H), 1.42–1.37 (m, 2H), 1.34–1.28 (m, 2H), 0.88 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ213.7, 144.0, 137.5, 129.6, 127.8, 120.6, 88.8, 86.0, 81.0, 76.9, 60.4, 36.9, 32.5, 29.7, 28.7, 22.0, 21.9, 13.8; HRMS (ESI) calcd for $C_{21}H_{27}N_2O_2S$ $[M+H]^+$ 371.1793, found 371.1790.



4-1c

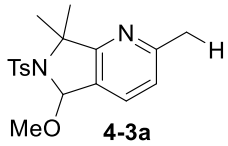
4-1c: 187 mg, light yellow liquid, purify by flash column chromatography (SiO_2, EtOAc–Hexanes, 1:10). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.79–7.78 (m, 2H), 7.24–7.23 (m, 2H), 5.33 (m, 1H), 4.97 (d, 2H, *J* = 6.5 Hz), 4.46 (s, 2H), 2.38–2.36 (m, 4H, mix peak), 1.68 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 216.7, 143.1, 139.6, 129.3, 127.4, 88.2, 85.9, 77.2, 75.0, 72.4, 56.4, 37.7, 30.2, 21.5; HRMS (ESI) calcd for $C_{18}H_{20}NO_2S$ $[M+H]^+$ 314.1215, found 314.1213.



4-1d

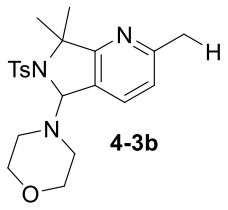
4-1d: 214 mg, light yellow liquid, purify by flash column chromatography (SiO_2, EtOAc–Hexanes, 1:10). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.70–7.68 (m, 2H), 7.23–7.21 (m, 2H), 5.22 (m, 1H), 4.91 (d, 2H, *J* = 7.8 Hz), 4.82 (m, 1H), 4.25 (d, 1H, *J* = 18.6 Hz), 4.07 (d, 1H, *J* = 18.6 Hz), 2.34 (s, 3H), 2.20 (s, 1H), 1.43 (d, 3H, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 216.6, 143.6, 136.5, 129.5, 127.6, 86.7, 80.9, 77.2, 76.4, 74.8, 73.8, 45.9, 34.3, 21.8, 21.5; HRMS (ESI) calcd for $C_{17}H_{18}NO_2S$ $[M+H]^+$ 300.1208, found 300.1206.

Characterization Data of Products



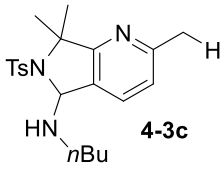
4-3a

4-3a, yellow solid, 68% yield (using GPB), 25 mg obtained. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.88–7.86 (m, 2H), 7.50 (d, 1H, *J* = 8.2 Hz), 7.27–7.25 (m, 2H), 7.08 (d, 1H, *J* = 8.2 Hz), 6.38 (s, 1H), 2.80 (s, 3H), 2.56 (s, 3H), 2.39 (s, 3H), 1.75 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 164.5, 161.0, 143.1, 139.4, 132.1, 129.2, 127.7, 123.8, 122.7, 90.7, 69.6, 50.8, 28.4, 27.5, 24.6, 21.5; HRMS (ESI) calcd for $C_{18}H_{23}N_2O_3S$ $[M+H]^+$ 347.1429, found 347.1426.



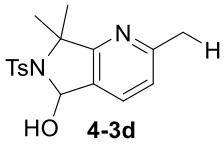
4-3b

4-3b, yellow solid, 75% yield (using GPA), 16 mg obtained. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.85–7.83 (m, 2H), 7.44 (d, 1H, *J* = 9.2 Hz), 7.27–7.26 (m, 2H), 7.02 (d, 1H, *J* = 9.2 Hz), 5.78 (s, 1H), 3.75 (m, 2H), 3.26 (m, 2H), 2.99 (m, 2H), 2.64 (s, 1H), 2.56 (s, 3H), 2.41 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ163.8, 160.1, 142.6, 140.9, 132.0, 129.0, 127.6, 124.0, 122.0, 82.1, 66.9, 66.2, 47.4, 29.6, 27.4, 25.8, 24.5, 21.5; HRMS (ESI) calcd for $C_{21}H_{28}N_3O_3S$ $[M+H]^+$ 402.1851, found 402.1849.



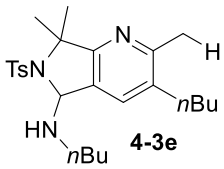
4-3c

4-3c, yellow solid, 72% yield (using GPA), 21 mg obtained. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.81–7.80 (m, 2H), 7.48 (d, 1H, *J* = 9.4 Hz), 7.27–7.25 (m, 2H), 7.04 (d, 1H, *J* = 9.4 Hz), 6.01 (s, 1H), 2.60 (m, 1H), 2.53 (s, 3H), 2.38 (s, 3H), 1.84 (m, 1H), 1.79 (s, 3H), 1.57 (s, 3H), 1.33–1.25 (m, 4H), 0.82 (t, 3H, *J* = 8.9 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ163.5, 160.2, 143.0, 139.3, 132.4, 129.5, 127.4, 125.4, 122.6, 78.0, 68.3, 40.5, 32.2, 29.0, 27.0, 24.5, 21.4, 20.4, 13.9 ; HRMS (ESI) calcd for $C_{21}H_{30}N_3O_2S$ $[M+H]^+$ 388.2059, found 388.2057.



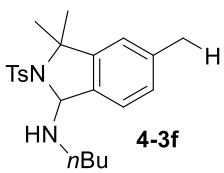
4-3d

4-3d, yellow solid, 52% yield (using GPB), 18 mg obtained. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.83–7.81 (m, 2H), 7.61 (d, 1H, *J* = 7.8 Hz), 7.27–7.25 (m, 2H), 7.07 (d, 1H, *J* = 7.8 Hz), 6.50 (s, 1H), 4.20 (brs, 1H), 2.54 (s, 3H), 2.38 (s, 3H), 1.73 (s, 3H), 1.57 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 164.2, 160.8, 143.5, 139.4, 132.3, 129.6, 127.1, 125.9, 122.6, 84.5, 69.0, 30.5, 25.8, 24.5, 21.5; HRMS (ESI) calcd for $C_{17}H_{21}N_2O_3S$ $[M+H]^+$ 333.1273, found 333.1270.



4-3e

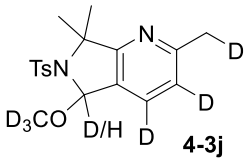
4-3e, yellow solid, 65% yield (using GPA), 22 mg obtained. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.81–7.80 (m, 2H), 7.32 (s, 1H), 7.26–7.25 (m, 2H), 6.00 (s, 1H), 2.59–2.56 (m, 3H, mix peak), 2.50 (s, 3H), 2.38 (s, 3H), 1.88–1.83 (m, 1H), 1.77 (s, 3H), 1.55–1.51 (m, 5H, mix peak), 1.39–1.26 (m, 8H, mix peak), 0.93 (t, 3H, *J* = 7.6 Hz), 0.82 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.6, 158.5, 142.9, 139.4, 135.4, 132.1, 129.5, 127.4, 125.7, 78.0, 68.2, 40.5, 32.4, 32.2, 31.9, 29.1, 27.0, 22.5, 22.3, 21.4, 20.4, 13.9; HRMS (ESI) calcd for $C_{25}H_{38}N_3O_2S$ $[M+H]^+$ 444.2685, found 444.2682.



4-3f

4-3f, yellow solid, 65% yield (using GPA), 26 mg obtained. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.80–7.79 (m, 2H), 7.26–7.24 (m, 2H), 7.18 (d, 1H, *J* = 6.5 Hz), 7.09 (d, 1H, *J* = 6.5 Hz), 6.86 (s, 1H), 6.03 (s, 1H), 2.59 (m, 1H), 2.38 (s, 3H), 2.35 (s, 3H), 1.90

(m, 1H), 1.78 (s, 3H), 1.55 (s, 3H), 1.34–1.27 (m, 4H), 0.84 (t, 3H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 146.9, 142, 9, 139.3, 139.0, 131.8, 129.4, 128.9, 127.3, 123.7, 121.4, 80.0, 68.7, 40.4, 32.3, 30.8, 28.6, 21.5, 21.4, 20.4, 14.0; HRMS (ESI) calcd for $C_{22}H_{31}N_2O_2S$ $[M+H]^+$ 387.2106, found 387.2102.



4-3j

4-3j, yellow solid, 62% yield (using GPB), 23 mg obtained. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.88–7.86 (m, 2H), 7.50 (s, 0.29H), 7.27–7.25 (m, 2H), 7.08 (s, 0.17H), 6.39 (s, 0.57H), 2.56 (s, 2H), 2.39 (s, 3H), 1.75 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 164.5, 161.0, 143.1, 139.4, 132.0, 129.2, 127.7, 123.7, 122.7, 122.6, 90.6, 69.6, 28.4, 27.5, 24.5, 21.5; HRMS (ESI) calcd for $C_{18}H_{23}N_2O_3S$ $[M+H]^+$ 347.1429, found 347.1426.

4.6. References

(1) (a) Rodriguez, D.; Navarro-Vazquez, A.; Castedo, L.; Dominguez, D.; Saa, C. *Tetrahedron Lett.* **2002**, *43*, 2717. (b) Rodriguez, D.; Navarro-Vazquez, A.; Castedo, L.; Dominguez, D. Saa, C. *J. Org. Chem.* **2003**, *68*, 1938. (c) Martinez-Esperon, M. F.; Rodriguez, D.; Castedo, L.; Saa, C. *Tetrahedron* **2008**, *64*, 3674. (d) Wessig, P.; Pick, C.; Schilde, U. *Tetrahedron Lett.* **2011**, *52*, 4221. (e) Wessig, P.; Matthes, A.; Schilde, U.; Kelling, A. *Eur. J. Org. Chem.* **2013**, 2123. For recent reviews, see: (f) Wessig, P.; Muller, G. *Chem. Rev.* **2008**, *108*, 2051. (b) Li, W.; Zhou, L.; Zhang, J. *Chem.–Eur. J.* **2016**, *22*, 1558.

(2) Wang, T.; Naredla, R. R.; Thompson, S. K.; Hoye, T. R. *Nature* **2016**, *532*, 484.

(3) (a) Bradley, A. Z.; Johnson, R. P. *J. Am. Chem. Soc.* **1997**, *119*, 9917. (b) Miyawaki, K.; Suzuki, R.; Kawano, T.; Ueda, I. *Tetrahedron Lett.* **1997**, *38*, 3943. (c) Hoye, T. R.; Baire, B.; Niu, D.; Willoughby, P. H.; Woods, B. P. *Nature* **2012**, *490*, 208.

(4) (a) For a review, see: Casado, J. *Top. Curr. Chem.* **2017**, *375*, 73. For structure and application of *para*-quinodimethanes, see: (b) Zeng, Z.; Shi, X.; Chi, C.; López Navarrete, T. J.; Casado, J.; Wu, J. *Chem. Soc. Rev.* **2015**, *44*, 6578. (c) Zeng, Z.; Wu, J. *Chem. Rec.* **2015**, *15*, 322. (d) Sun, Z.; Zeng, Z.; Wu, J. *Acc. Chem. Res.* **2014**, *47*, 2582. (e) Zeng, Z.; Ishida, M.; Zafra, J. L.; Zhu, X.; Sung, Y. M.; Bao, N.; Webster, R. D.; Lee, B. S.; Li, R.-W.; Zeng, W. Y.; Chi, C.; Lopez Navarrete, J. T.; Ding, J.; Casado, J.; Kim, D.; Wu, J. *J. Am. Chem. Soc.* **2013**, *135*, 6363.

(5) Thompson, S. K.; Hoye, T. R. *J. Am. Chem. Soc.* **2019**, *141*, 19575.

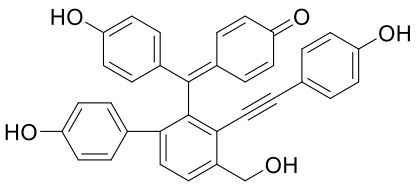
(6) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc., Trans.* **1915**, *107*, 1080.

CHAPTER 5

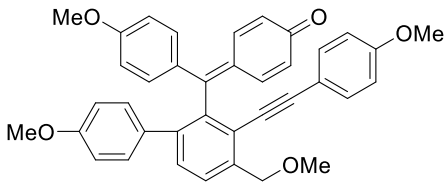
Total Synthesis of Selaginpulvilin A

5.1. Introduction

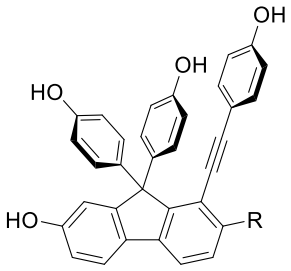
Selaginellins are a small group of pigments exclusively found in the ancient genus *Selaginella*, containing about 750 known species up to date.[1] With the estimated existence for about 400 million years, *Selaginella* species are not only evolutionarily important as the living fossils of vascular plants, but also have been widely used for the treatment of dysmenorrhea, asthma, and traumatic injury in traditional medicine in many regions.[2] The chemical investigation of genus *Selaginella* started from 1970.[3] For a long time, the biological activities of *Selaginella* were only portraited by simple alkaloids, phenylpropanoids and bioflavonoids, which abundantly exist in many other species.[4] Therefore, there are no enthusiasm conducting further investigations on extracted pigments from Selaginella until 2007, when the isolation of unusual racemic natural product selaginellin **5-1** (**Scheme 5.1**).[5] Subsequently, the synthesis of methoxy derivative **5-2** promoted a new tide of chemical and synthetic studies of this genus. The novel carbon framework, which is ultimately accountable for excellent fluorescent properties inspired the discovery of many more congeners in the following decades.[6] In 2014, selaginpulvilins A–D (**5-3**–**5-6**) were first isolated from *Selaginella pulvinate*.[7] The ethanol extracts containing selaginpulvilins A−D and other constituents display significant inhibitory activity against phosphodiesterase-4 (PDE4), an overactivation enzyme which is responsible for inflammation.[7]



selaginellin, **5-1**



5-2



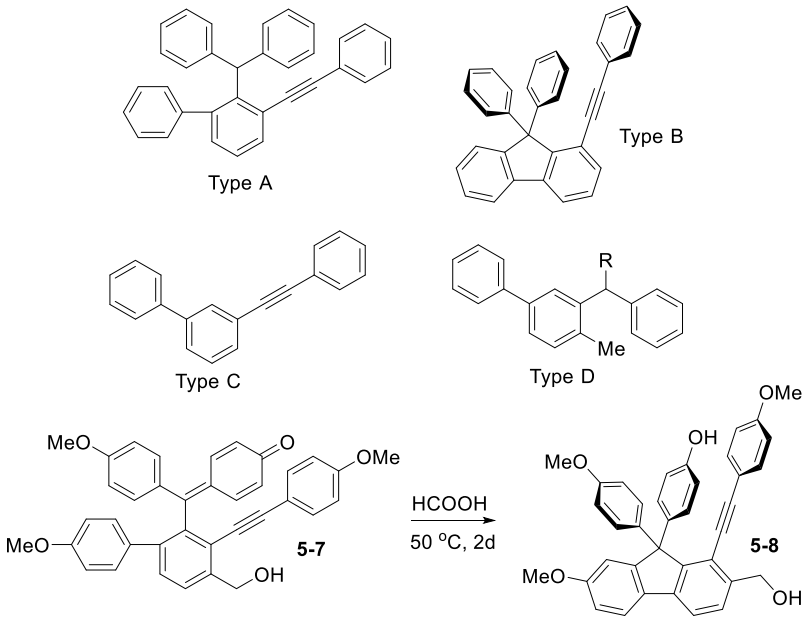
R = CH_2OH, selaginpulvilin A, **5-3**
R = CHO, selaginpulvilin B, **5-4**
R = Me, selaginpulvilin C, **5-5**
R =H, selaginpulvilin D, **5-6**

Compound	IC_{50} (μM)
5-1	0.97±0.10
5-3	0.24±0.03
5-4	0.11±0.02
5-5	0.18±0.02
5-6	0.26±0.05
rolipram	0.54±0.04

Scheme 5.1. Selaginellin and Selaginpulvilin A-D and Their Inhibitory Activity against PDE4

The novel polyphenolic structure of selaginellin family combined with their promising biological activity make them attractive targets for total synthesis, which is also provides an opportunity to develop fast and convenient access to related structures for biological activity-relationship studies. Up until now, 113 selaginellins have been documented, including 61 natural congeners and 52 synthetic analogs.[3]

Based on their skeleton of the polyphenolic compounds, they can be classified into four types. Type A contains a 2-benzhydryl-3-phenylethynyl-1,10-biphenyl skeleton, whereas type B possesses 9,9-diphenyl-1-(phenylethynyl)-9H-fluorene skeleton structure. The simpler Type C consists of 3-phenylethynyl-1,10-biphenyl skeleton, and Type D possesses 2-benzyl-1,10-biphenyl skeleton without an alkyne moiety. Yin and coworkers proposed the biogenesis pathway for selaginpulvilin A-D from a selaginellin precursor.[2] The key step for the conversion of the selaginellin skeleton to that of selaginpulvilin is a Friedel-Crafts reaction arylation between phenol ring and the C9 carbon to construct the fluorenone core. This process was later confirmed by treating trimethyl selaginellin **5-7** with formic acid at 50 °C to afford 7,14,26-trimethoxyselaginpulvilin A **5-8**. In this chapter, the prowess of a new cycloaromatization reaction of allene–yne with alkyne is demonstrated in the total synthesis of selaginpulvilins A.

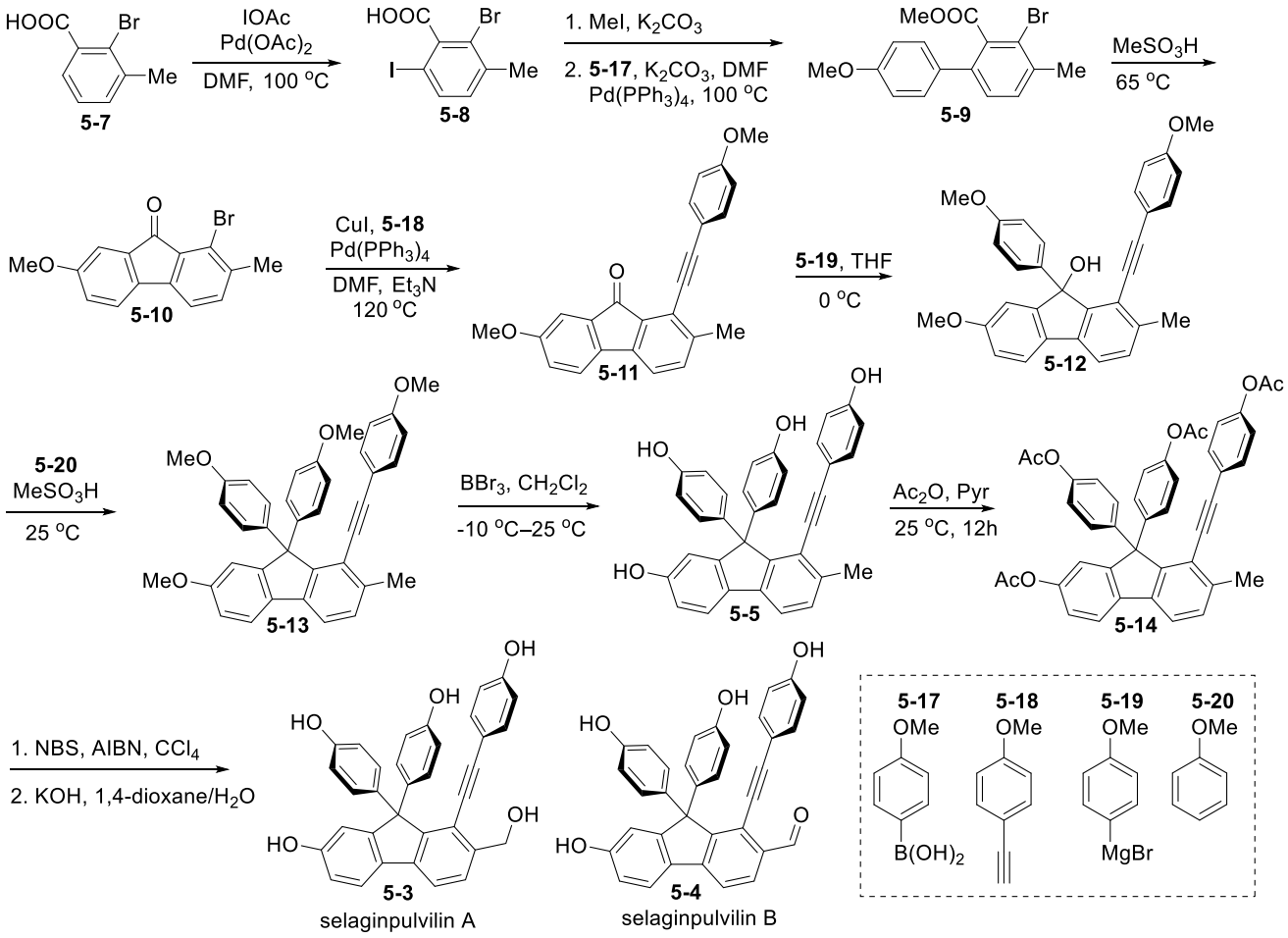


Scheme 5.2 Types of Selaginellins and Synthesis of Trimethoxyselaginpulvilin A from Selaginellin

5.2. Previous Total Synthesis of Selaginpulvilin

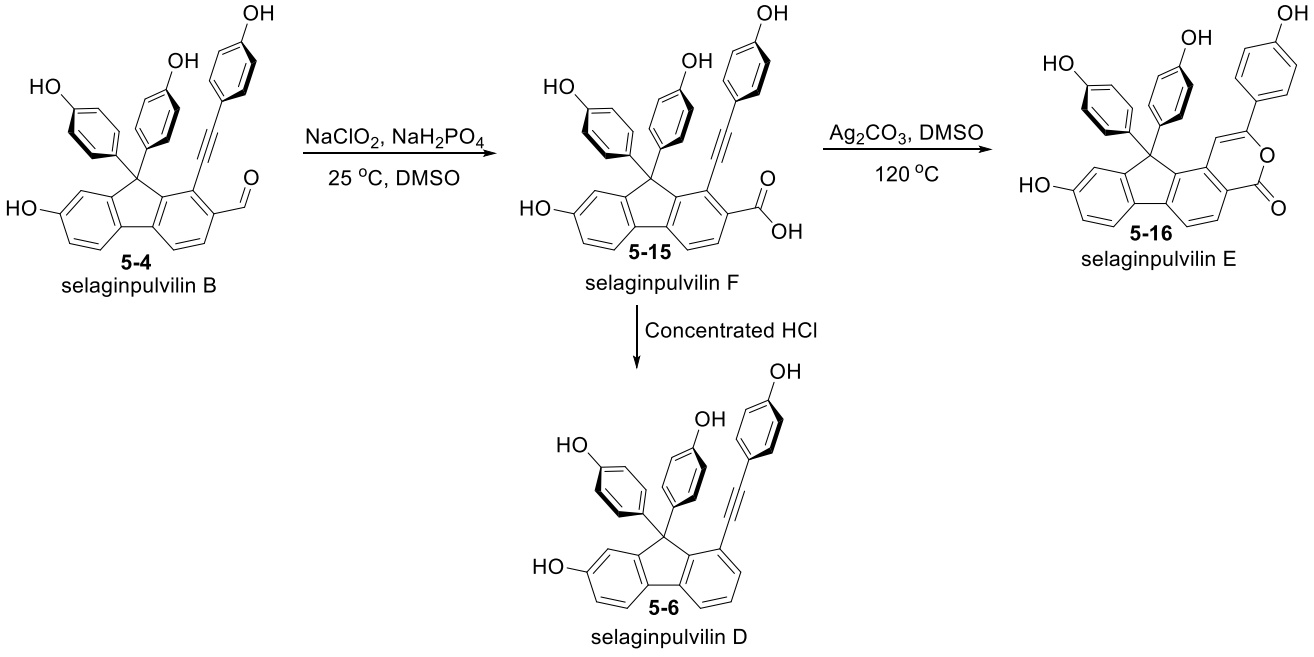
5.2.1. Yin's Friedel-Crafts Approach

The discovery of selginpulvilin A–D by the Yin group in 2014[7] promoted further investigations toward synthesis of new triaryl fluorene structures. The same group reported the total synthesis of selaginpulvilin A–F in 7 to 11 steps employing intramolecular a Friedel-Crafts reaction of biphenyl-2-methyl carboxylate to afford a fluorenone core (**Scheme 5.3**).[8] The total synthesis commenced from commercially available 2-bromo-3-methyl benzoic acid, Pd(II)-mediated *ortho*-C–H iodination employing IOAc afforded aryl iodide **5-8**. Methylation of the carboxylic acid follow by Suzuki coupling with 4-methoxyphenyl boronic acid afforded biphenyl **5-9**. An intramolecular Friedel-Crafts reaction of **5-9** in the



Scheme 5.3. Total Synthesis of Selaginpulvilin A–C Employing Friedel-Crafts Reactions

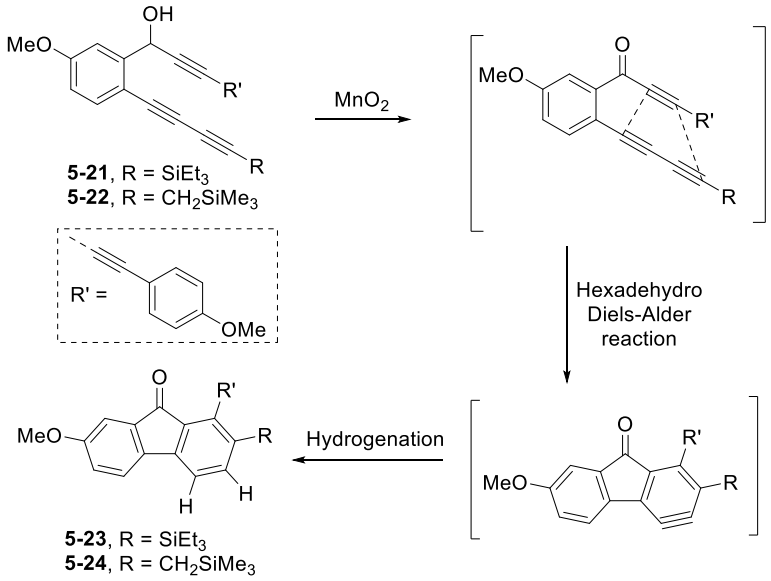
presence of methanesulfonic acid afforded 1-bromo-2-methyl-7-methoxy-9-fluorenone **5-10**, which was subjected to Sonogashira coupling conditions with 4-ethynyl anisole **5-18** to produce 1-phenylethynyl-2-methyl-7-methoxy-9-fluorenone **5-11**. Fluorenone **5-11** was then treated with Grignard reagent **5-19** followed by a Friedel-Crafts reaction with anisole to produce tetramethyl selaginpulvilin C **5-13**. Demethylation of **5-13** with BBr_3 furnished selaginpulvilin C. Selaginpulvilin A and B could be synthesized from Selaginpulvilin C via a three-step sequence. Acetylation of **5-5** with Ac_2O generated peracetylated product **5-14**, which was treated with NBS for benzylic bromination. The bromide was treated with and KOH to replace the bromide with hydroxide and concomitant removal of acetates, which afforded both selaginpulvilin A (**5-3**, 55% yield) and selaginpulvilin B (**5-4**, 30% yield). In turn, selginpulvilin B (**5-4)** was used as a precursor to synthesize selaginpulvin D–F. Pinnick oxidation of **5-4** afforded selaginpulvilin F (**5-15**), which underwent decarboxylation when treated with concentrated hydrochloric acid to produce selaginpulvilin D (**5-6**). Finally, lactonization of **5-15** catalyzed by Ag(I) furnished selaginpulvilin E (**5-16**).



Scheme 5.4. Synthesis of Selaginpulvilin D–F from Selaginpulvilin B

5.2.2. Lee's HDDA Approach

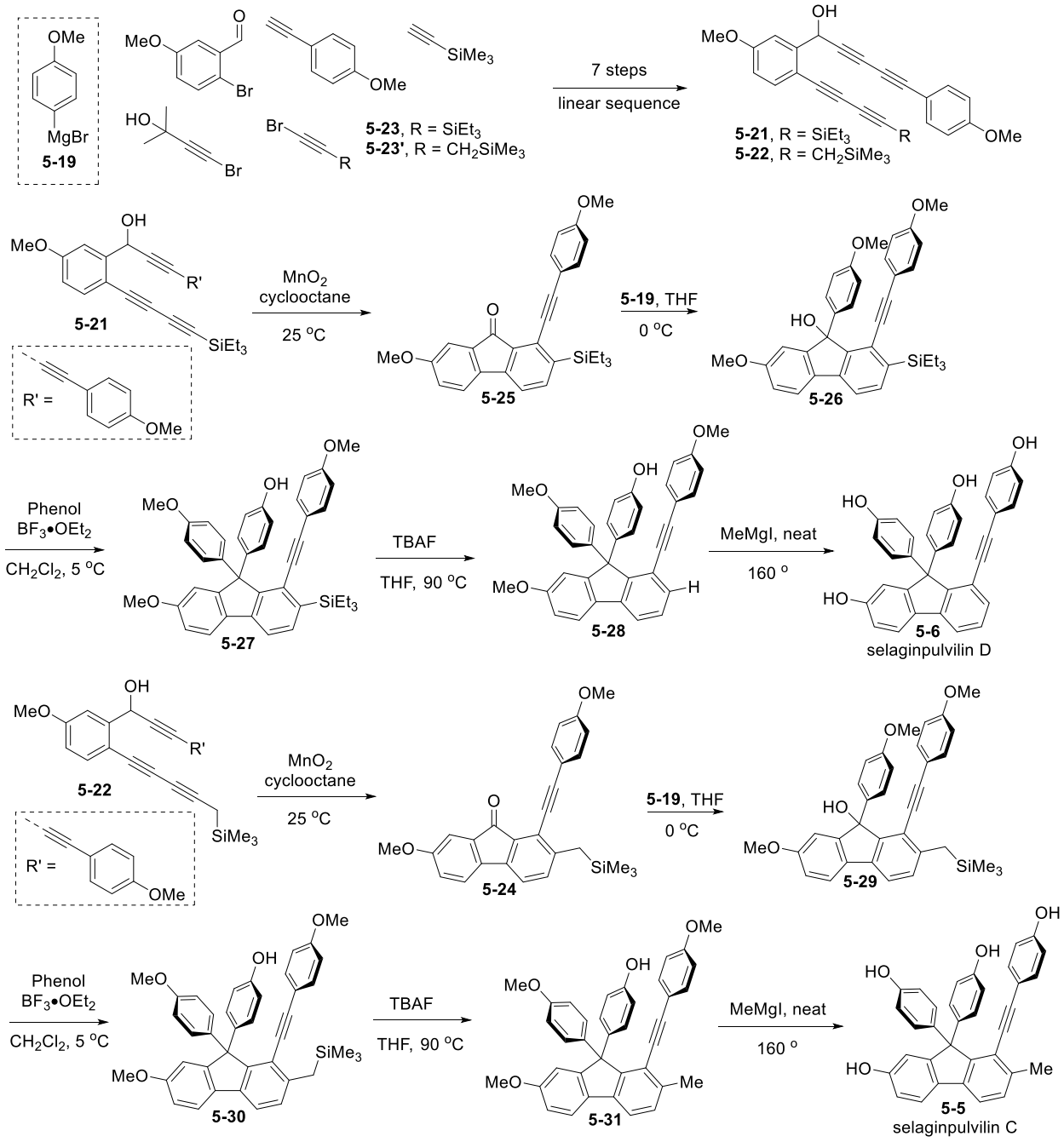
In 2016, Lee and coworker developed a novel approach to a total synthesis of selaginpulvilin C and D relying on a strategy that allows for de novo construction of the fluorenone core. This approach employed *in situ* generation of aryne intermediate *via* hexadehydro Diels-Alder reaction (HDDAR) followed by formal hydrogenation of the aryne moiety (**Scheme 5.5**).[9]



Scheme 5.5. Construction of Fluorenone Core via a HDDA Reaction

Key tetrayne intermediate **5-21** and **5-22** can be synthesized from commercially available arene and alkyne building blocks by series of conventional transformations including Sonogashira coupling, Cadiot-Chodkiewicz coupling and alkynide addition.[5] Next, the intramolecular HDDA reaction of **5-21** and **5-22** under oxidation conditions generated aryne intermediates, which underwent hydrogenation in the presence of cyclooctane as a hydrogen donor to afford 1-phenylethynyl-7-methoxy-9- fluorenone **5-23** and **5-24**. Installation of the two aryl groups at the fluorenyl ketone moiety by double Friedel-Crafts arylation could not be achieved, thus fluorenones **5-25** and **5-24** were treated with Grignard reagent **5-19** and the resulting tertiary alcohol was subjected to Friedel-Crafts arylation with phenol to afford **5-27** and **5-30**, respectively. The intermediates **5-27** and **5-30** containing 9,9-diphenyl-1-(phenylethynyl)-9H-fluorene

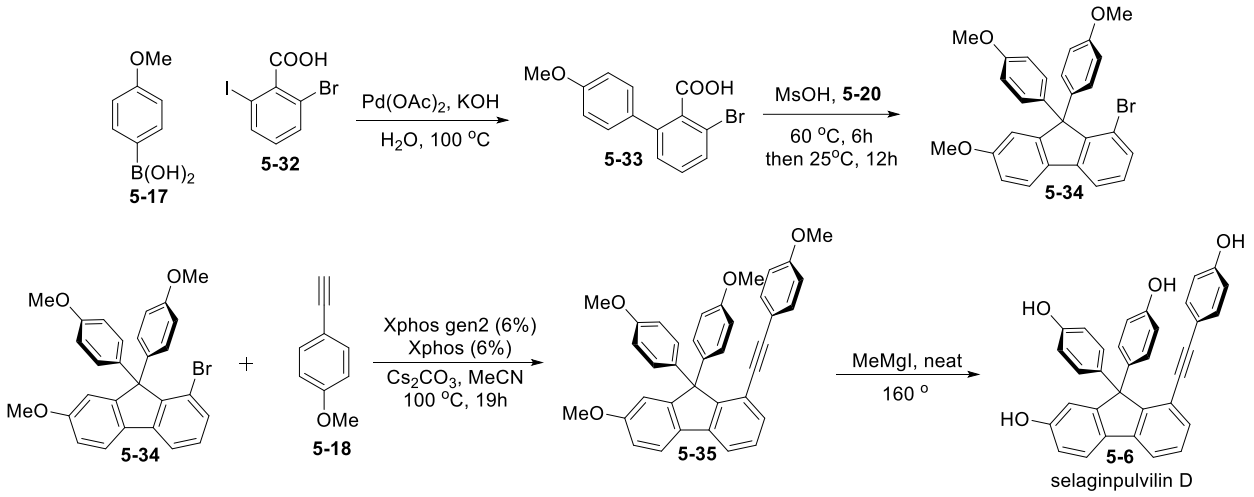
skeleton were subjected to desilylation conditions with TBAF to afford trimethoxy derivatives of selaginpulvilin D (**5-28**) and selaginpulvilin C (**5-31**). Finally, demethylation of **5-28** and **5-31** in neat MeMgI at 160 °C produced selaginpulvilin D and C, respectively (**Scheme 5.6**).



Scheme 5.6. Synthesis of Selaginpulvilin C and D by the Lee Group

5.2.3. Sherburn's S_EAr Approach

In 2017, Sherburn's group reported an extremely concise total synthesis of selaginpulvilin D in four steps, involving a one-pot, 3-fold aromatic substitution sequence to assemble a 9,9-diarylfuorene core (**Scheme 5.7**).[10] Sherburn's synthesis was initiated by a Suzuki−Miyaura coupling of 4-methoxyphenyl boronic acid with 2-bromo-6-iodobenzoic acid in an aqueous medium to generate 2-bromo-5-(4-methoxyphenyl) benzoic acid **5-33**. On heating in methane sulfonic acid, an intramolecular S_EAr reaction gave the 2-bromo-7-methoxy-9-fluorenone intermediate, which was converted *in situ* to the 1- bromo-9,9-diarylfluorene core **5-34** upon addition of anisole. Subsequent Sonogashira coupling between bromo arene and 4-ethynyl anisole **5-18** turned out to be recalcitrant. Only Buchwald's second-generation XPhos ligand was fruitful to deliver Sonogashira coupling product **5-35**, which was subjected to precedented demethylation conditions[9] to furnish selaginpulvilin D.

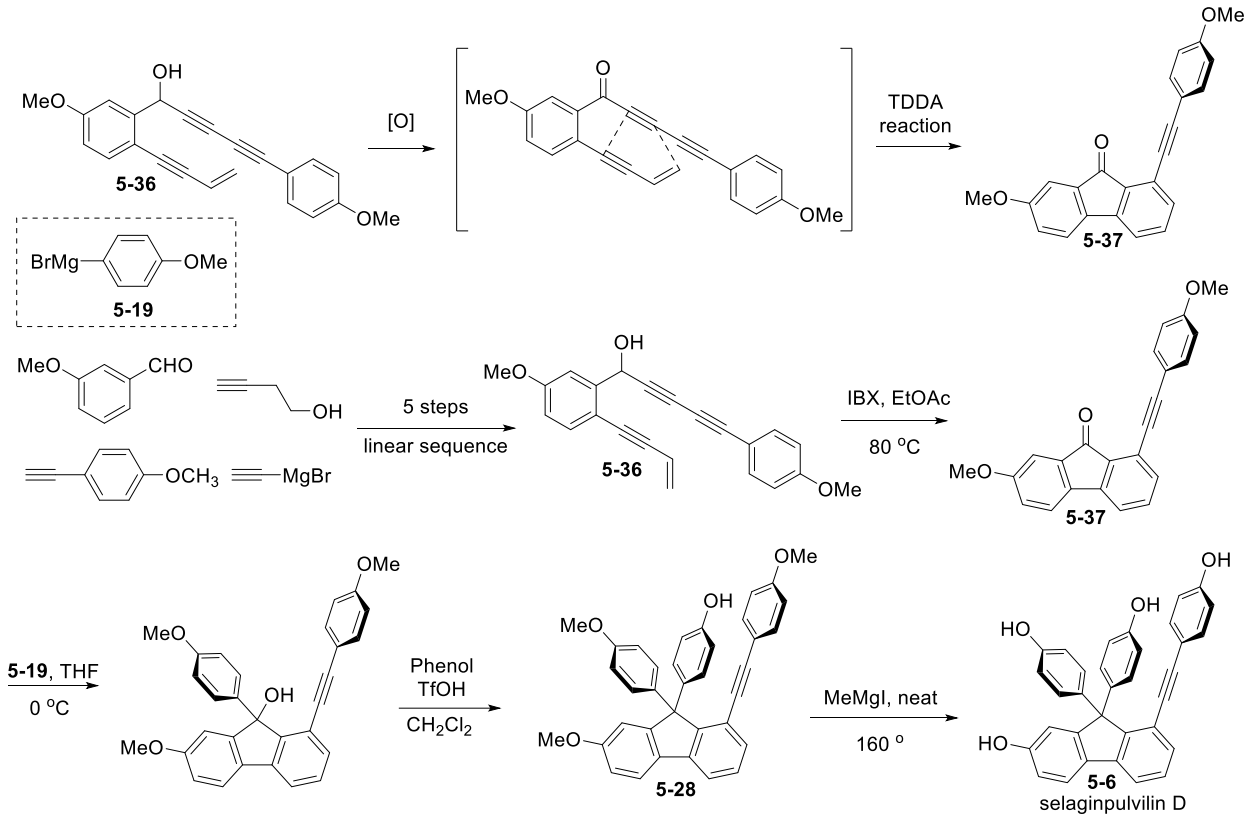


Scheme 5.7. Four-steps Total Synthesis of Selaginpulvilin D by the Sherburn Group

5.2.4. Baire's Tetradehydro Diels-Alder (TDDA) Approach

Shortly after the reports of Lee, Yin and Sherburn, Baire published an efficient and mild synthetic strategy for the total synthesis of selaginpulvilin D, involving highly chemoselective enyne–alkyne tetradehydro Diels–Alder (TDDA) reaction to construct the fluorene core (**Scheme 5.8**).[11] The synthesis

was commenced by the construction of eneyne-diyne intermediate **5-36** from commercially available arene and alkyne building blocks employing series of conventional reactions, including Sonogashira and Cadiot–Chodkiewicz coupling reactions. Tetradehyro Diels-Alder reaction of **5-36** under IBX oxidation at 80 °C afforded fluorenone **5-37**. Double arylation was archived by treating **5-37** with Grignard reagent **5-19** follow by Friedel-Crafts arylation with phenol afford **5-28**. Removal of the three methyl groups from **5-28** was realized by treating with MeMgI in neat conditions at 160 °C to deliver selaginpulvillin D.

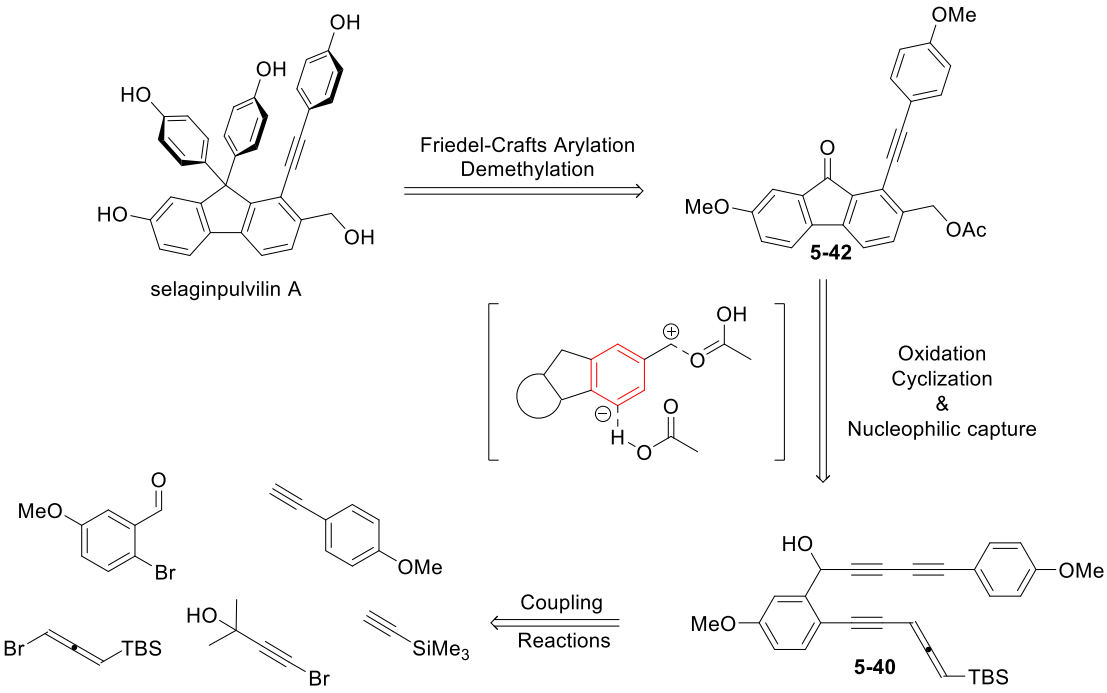


Scheme 5.8. Total Synthesis of Selaginpulvin D by the Baire Group

5.3. Total synthesis of Selaginpulvilin A

The construction of fluorenone core is the key step in all reported synthetic strategies for successful total synthesis of selaginpulvilins. To achieve this goal, four different routes have been developed, including Friedel-Crafts reaction, S_EAr reaction, HDDA and TDDA reactions. With the knowledge of pentadehydro

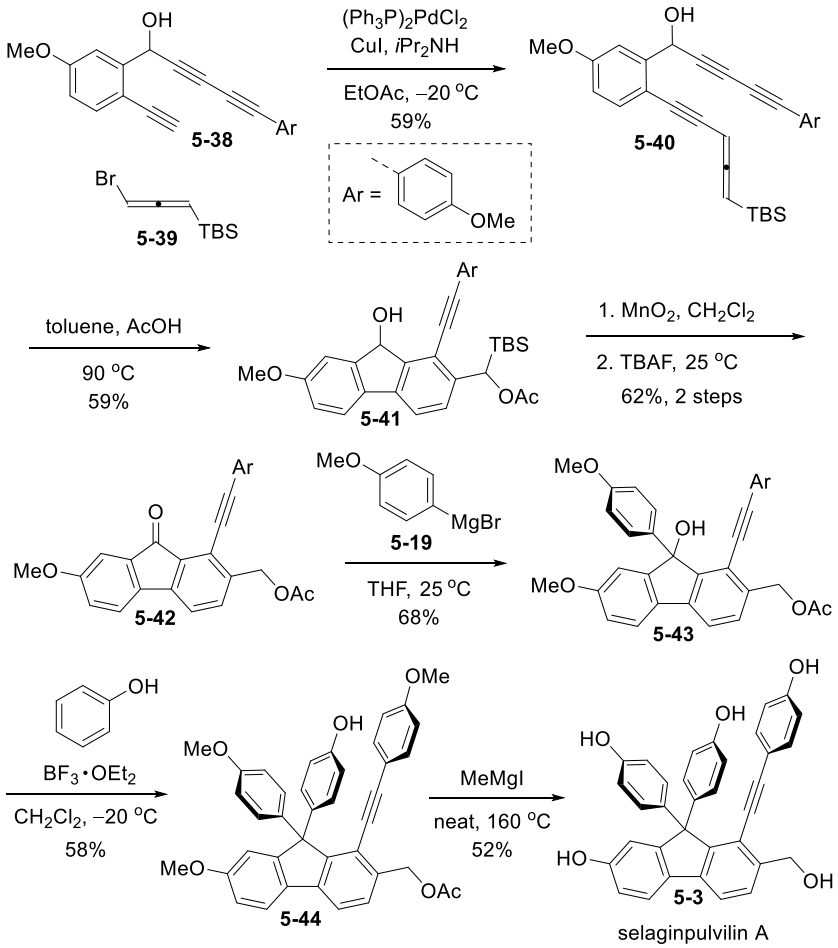
Diels−Alder reaction in hand, we demonstrated the prowess of this new cycloaromatization reaction for a synthesis of selaginpulvilins A, an alkynyl polyphenol natural product of selaginella family. We envision that the core fluorenone skeleton **5-42** of selaginpulvillin A can be constructed via cycloaromatization of key intermediate **5-40** upon oxidation followed by nucleophilic trapping of the α,3-dehydrotoluene intermediate (**scheme 5.9**). Once obtained, fluorenone **5-42** can be converted to 9,9-diphenyl-1-(phenylethynyl)-9H-fluorene skeleton by established protocol in literature.[9] In turn, **5-40** can be quickly assembled from readily available alkyne and arene building blocks.



Scheme 5.9. Retrosynthesis of Selaginpulvilin A

Our approach to total synthesis of selaginpulvilin A was initiated by a Sonogashira coupling of allenyl bromide **5-39**[12] with known terminal alkyne **5-38**[5] to provide **5-40** (59%), which was subjected to the established protocol (AcOH, toluene, 90 °C) to generate fluorenol **5-41** (59%). Oxidation of **5-41** followed by removal of the *tert*-butyldimethylsilyl group afforded phenylethylnyl-9H-fluorenone **5-42** (62%, 2 steps), which was treated with **5-19** to generate tertiary alcohol **5-43** (68%). Friedel-Crafts arylation of **5-43** to form **5-44** was interfered with double arylation but it was found that careful control of the reaction

temperature at –20 °C suppressed the arylation of the benzylic acetoxy group, generating **5-44** in 58% yield. Global removal of the three methoxy and acetoxy groups from **5-44** was realized by treating with MeMgI in neat conditions at 160 °C to deliver selaginpulvillin A (52%) (**scheme 5.10**).



Scheme 5.10. Total Synthesis of Selaginpulvilin A

5.4. Conclusion

In this chapter, an efficient total synthesis of selaginpuvilin A is achieved (6 steps, 11% total yield) relying on the newly developed pentadehydro Diels-Alder reaction (PDDAR) as a key strategy. Compared to the hexadehydro Diels-Alder approach to the synthesis of Selaginpulvilins,[5] this approach is more effective because it can avoid the relatively inefficient hydrogenation step of an aryne intermediate. This

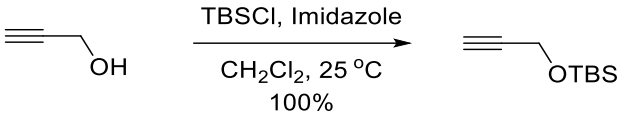
approach to a successful total synthesis of selaginpulvilin A proved that PDDAR is an efficient transformation to synthesize other related structures.

3.5. Experimental Details

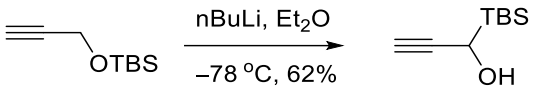
3.5.1. General Information

Reactions were carried out in oven-dried glassware unless otherwise noted. Compounds were purchased from Sigma-Aldrich or TCI America or Oakwood Chemicals unless otherwise noted. Toluene, acetonitrile, dichloromethane and triethyl amine were distilled over calcium hydride (CaH_2) under nitrogen atmosphere. THF was distilled over sodium-benzophenone ketyl under nitrogen atmosphere. Column chromatography was performed using silica gel 60 Å (32−63 mesh) purchased from Silicycle Inc. Thin layer chromatography (TLC) was performed on 0.25 mm E. Merck precoated silica gel 60 (particle size 0.040−0.063 mm). Yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AV-500 spectrometer. ^{1}H NMR chemical shifts (δ) are reported in parts per million (ppm) downfield of TMS and are referenced relative to the residual proteated solvent peak ($CDCl_3$ (7.26 ppm)). ^{13}C chemical shifts (δ) are reported in parts per million downfield of TMS and are referenced to the carbon resonance of the solvent ($CDCl_3$ (77.2 ppm)). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sext (sextet) or m (multiplet). ^{1}H NMR signals that fall within a ca. 0.3 ppm range are generally reported as a multiplet, with a range of chemical shift values corresponding to the peak or center of the peak. Coupling constants, *J*, are reported in Hz (Hertz). Electrospray ionization (ESI) mass spectra were recorded on a Waters Micromass Q-Tof Ultima in the University of Illinois at Urbana-Champaign. Electron impact (EI) mass spectra and Chemical Ionization (CI) mass spectra were obtained using a Micromass 70-VSE in the University of Illinois at Urbana–Champaign.

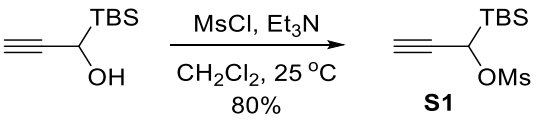
3.5.2. Experimental Procedures



To a solution of propargyl alcohol (1.0 equiv) in methylene chloride was added TBSCl (1.5 equiv) follow by imidazole (1.5 equiv) at room temperature. The reaction mixture was stirred under nitrogen atmosphere until completion (monitor by TLC). The resulting mixture was concentrated under reduced pressure and the crude was purified by a silica gel column chromatography using hexane as eluent. Yield: 100%. Characterization data match the known compound in literature.[13]

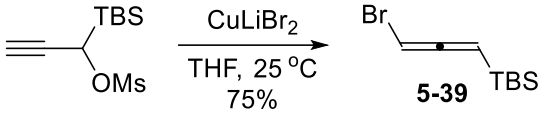


A solution of *tert*-butyldimethyl (prop-2-yn-1-yloxy) silane (1.0 equiv) in dry Et_2O was added *n*-BuLi dropwise (2.5 equiv) over 30 mins. The resulting mixture was stirred at –78 °C for another 30 mins and then slowly warmed to rt and stirred for addition 4 h. Once completed, the reaction mixture was cooled back to –78 °C, and saturated NH_4Cl was added. The reaction was allowed to warm up to room temperature and extracted with ether (3 x 50 mL). The combined organic layer was dried over $MgSO_4$, concentrated and purified by column chromatography (hexanes:EtOAc, 5:1), which yielded 1-(*tert*-butyldimethylsilyl) prop-2-yn-1-ol (62% yield). Characterization data match the known compound in literature.[13]



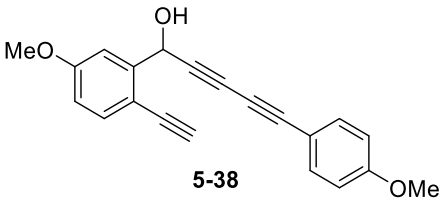
To a solution of 1-(*tert*-butyldimethylsilyl) prop-2-yn-1-ol (1.0 equiv) in dry CH_2Cl_2 was added MsCl (1.5 equiv) followed by Et_3N (1.5 equiv) and the mixture was stirred at 25 °C. After complete consumption of the starting material (monitored by TLC), water was added to the reaction mixture and the two layers were separated. The resulting mixture was extracted with CH_2Cl_2 (2 x 10 mL). The combine

organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by column chromatography (hexanes:EtOAc, 10:1), which delivered product **S1** (80% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.04 (d, 1H, *J* = 1.8 Hz), 3.11 (s, 3H), 2.87 (d, 1H, *J* = 1.8 Hz), 0.97 (s, 9H), 0.16 (s, 3H), 0.13 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 80.1, 79.5, 64.8, 39.5, 26.6, 17.1, -7.8, -8.5; HRMS (ESI) calcd for $C_{10}H_{20}O_3SSi$ $[M+H]^+$ 249.0980, found 249.0976.



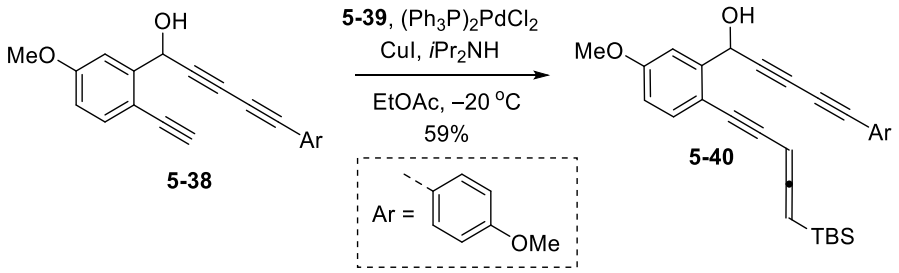
5-39

To a solution of CuBr (1.5 equiv) in dry THF was added LiBr (1.5 equiv) at 25 °C and the mixture was stirred at the same temperature for 30 mins. The mixture turned light green. Then solution of 1-(*tert*-butyldimethylsilyl) prop-2-yn-1-yl methanesulfonate (1 equiv) in THF was added to the mixture. The reaction was allowed to stir at room temperature until complete consumption of the starting material. Upon completion, the reaction mixture was filter to a short path of silica gel, concentrated under reduced pressure and the crude was purified by column chromatography (hexanes:EtOAc, 20:1), which yielded allenyl bromide **5-39** (75% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.70 (d, 1H, *J* = 6.4 Hz), 5.24 (d, 1H, *J* = 6.4 Hz), 0.92 (s, 9H), 0.11 (s, 6H)); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 207.4, 90.8, 68.1, 26.1, 17.1, -5.9, -6.0; HRMS (ESI) calcd for $C_9H_{17}BrSi$ $[M+H]^+$ 233.2161, found 233.2158.

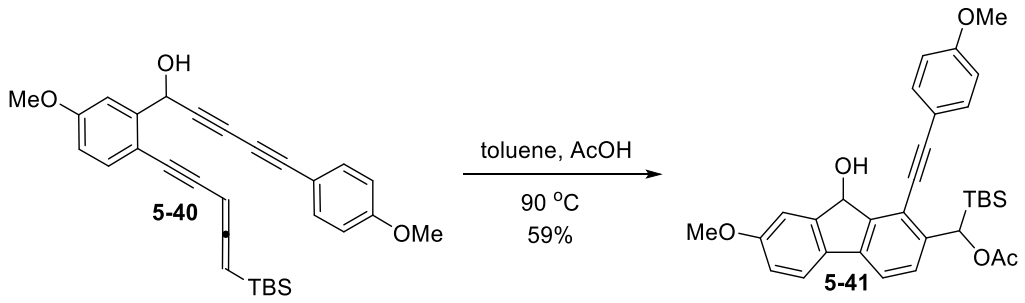


5-38

Triyne **5-38** was prepare according to well established protocol in literature.[5] See the references for more information. The characterization data in an agreement with the known value in the literature.

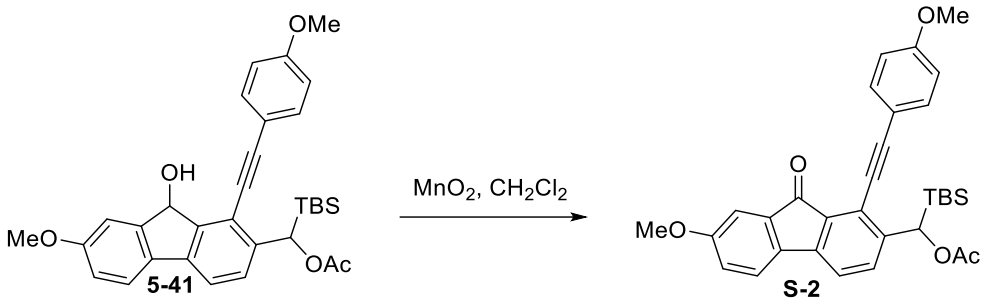


To a solution of **5-38** (1.0 equiv) in EtOAc was added $(Ph_3P)_2PdCl_2$ (2 mol%), CuI (8 mol%), allenyl bromide **5-39** (1.05 equiv) and *i*Pr_2NH (3 equiv) at –20 °C and the reaction mixture was stirred at the same temperature until complete consumption of the starting material. Upon completion, the reaction mixture was filter to a short path of celite, concentrated under reduced pressure and the crude was purified by column chromatography (hexanes:EtOAc, 10:1 to 5:1), which delivered **5-40** (59% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.42–7.40 (m, 2H), 7.35 (d, 1H, *J* = 8.5 Hz), 7.20 (s, 1H,), 6.84–6.80 (m, 3H), 5.90 (s, 1H), 5.32–5.30 (m, 2H), 3.83 (s, 3H), 3.80 (s, 3H), 0.95 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 215.9, 160.4, 159.7, 142.74, 142.71, 134.2, 133.6, 114.3, 114.1, 112.1, 87.3, 87.0, 82.6, 80.7, 79.4, 72.4, 71.2, 68.7, 63.7, 55.5, 55.3, 26.2, 17.2, -5.70, -5.73; HRMS (ESI) calcd for $C_{30}H_{32}O_3Si$ $[M+H]^+$ 469.2199, found 469.2187.

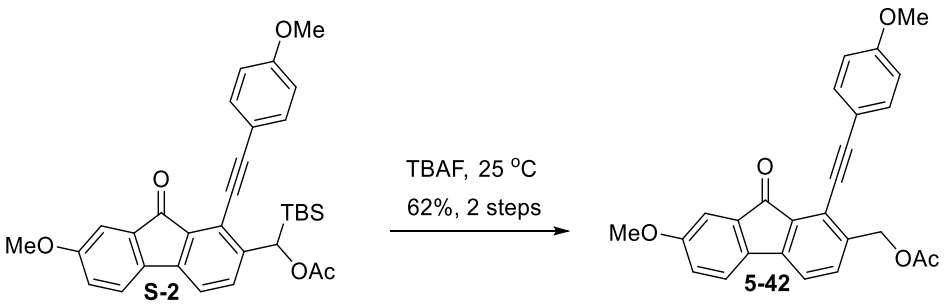


In a sealed Schlenk tube, a solution of **5-40** (325 mg, 0.69 mmol) in dry $PhCH_3$ was added acetic acid (8.1 mmol). The reaction mixture was heated at 90 °C for 6 h. After completion, the reaction mixture was transferred to a round-bottom flask, concentrated, and subjected to column chromatography (hexanes:EtOAc, 5:1), which delivered cyclization product **5-41** (215 mg, 59% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.54 (d, 2H, *J* = 8.7 Hz), 7.50 (d, 1H, *J* = 8.3 Hz), 7.46 (d, 1H, *J* = 8.0 Hz), 7.26–7.23 (m,

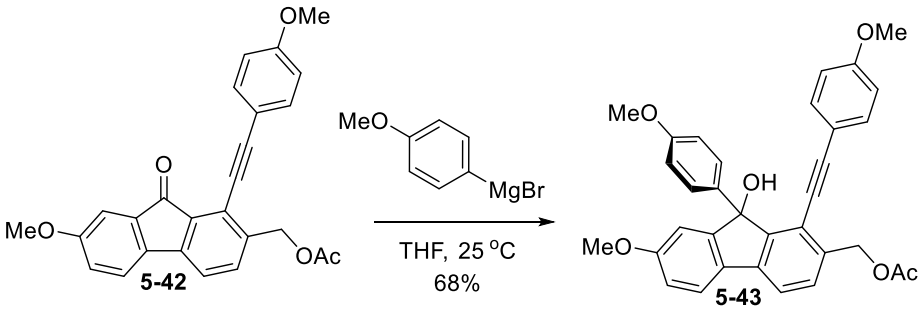
3H), 6.93–6.90 (m, 3H), 6.47 (s, 1H), 5.77 (s, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 2.95 (brs, 1H), 2.11 (s, 3H), 0.98 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ170.4, 160.1, 146.3, 140.8, 138.5, 133.1, 132.3. 126.5, 126.3, 120.7, 118.9, 117.5, 115.2, 114.9, 114.2, 110.8, 99.5, 83.7, 74.8, 67.3, 55.6, 55.4, 26.8, 21.3, 17.2, -7.0, -8.9; HRMS (ESI) calcd for $C_{32}H_{36}O_5Si$ $[M+H]^+$ 529.2410, found 529.2406.



To a solution of **5-41** (215 mg, 1.0 equiv) in dry CH_2Cl_2 was added MnO_2 (354 mg, 10 equiv) at 25 °C and the reaction mixture was stirred at the same temperature until complete consumption of the starting material (monitor by TLC). Upon completion, the reaction mixture was filtered through silica gel pad and concentrated under reduced pressure to afford of the fluorenone product. The crude product was used for the next step without any further purification. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.66 (m, 2H), 7.35 (d, 1H, *J* = 8.1 Hz), 7.30 (s, 2H), 7.20, (d, 1H, *J* = 1.9 Hz), 6.95 (dd, 1H, J = 8.1, 2.1 Hz), 6.90, (m, 2H), 6.49 (s, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 2.11 (s, 3H), 1.00 (s, 9H), 0.11 (s, 3H) 0.09 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 192.0, 170.3, 160.9, 160.1, 143.3, 142.9. 136.1, 135.5, 133.7, 133.5, 131.0, 120.9, 120.0, 118.7, 118.6, 115.4, 114.1, 109.1, 101.6, 83.7, 77.3, 77.0, 76.8, 66.7, 55.7, 55.3, 29.7, 26.9, 21.2, 17.3, -7.0, -8.9; HRMS (ESI) calcd for $C_{32}H_{34}O_5Si$ $[M+H]^+$ 527.2254, found 527.2253.

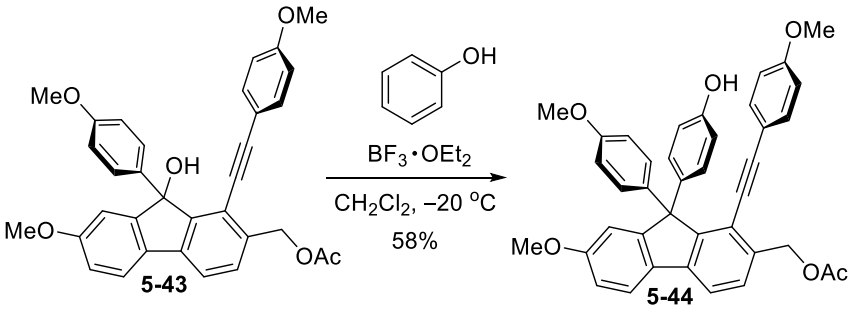


To a solution of fluorenone **S-2** (214 mg, 1.0 equiv) in dry THF was added TBAF (0.32 mL, 1M solution in THF, 1.5 equiv) at -78 °C and the reaction mixture was allowed to warm up to room temperature. The reaction mixture was stirred at the room temperature until complete consumption of the starting material (monitor by TLC). Upon completion, saturated NH_4Cl was added and the mixture was extracted by EtOAc (3 x 10 mL). The combine organic layer was dry over $MgSO_4$, concentrated under reduced pressure and the crude was purified by column chromatography (hexanes:EtOAc, 10:1), which delivered fluorenone **5-42** (132 mg, 62% yield, 2 steps) . ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.65 (m, 2H), 7.46 (d, 1H *J* = 7.5 Hz), 7.39 (d, 1H, *J* = 8.1 Hz), 7.31 (d, 1H, *J* = 7.5 Hz), 7.21 (d, 1H, *J* = 2.4 Hz), 6.98 (dd, 1H, *J* = 8.1, 2.4 Hz), 6.91 (m, 2H), 5.32 (s, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 2.12 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 191.6, 170.8, 161.2, 160.4, 145.2, 137.0, 136.3, 135.2, 134.5, 133.9, 133.7, 121.4, 121.1, 120.2, 118.3, 114.9, 114.1, 109.1, 101.2, 82.7, 64.2, 55.7, 55.3 21.0; HRMS (ESI), calcd for $C_{26}H_{20}O_5$ $[M+H]^+$ 413.1389, found 413.1382.

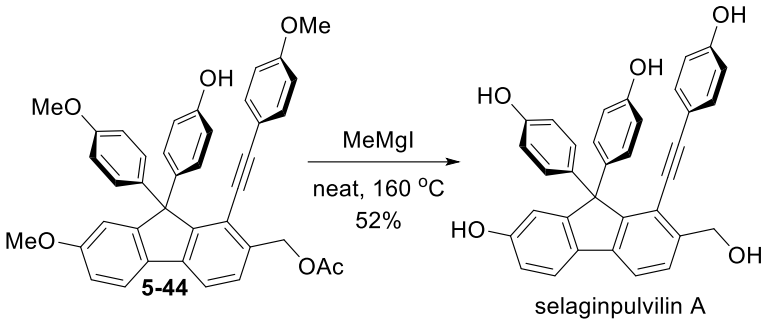


To a solution of **5-42** (131 mg, 1.0 equiv) in dry THF was added 4-Methoxyphenylmagnesium bromide (0.36 mL, 1M solution in THF, 1.5 equiv) at 0 °C and the reaction mixture was allowed to warm up to room temperature. The reaction mixture was stirred at the room temperature until complete consumption of the starting material (monitor by TLC). Upon completion, water was added slowly, and the mixture was extracted by EtOAc (3×5 mL). The combine organic layer was dry over $MgSO_4$, concentrated under reduced pressure and the crude was purified by column chromatography (hexanes:EtOAc, 10:1), which delivered tertiary alcohol **5-43** (68% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.54 (d, 1H, *J* = 2.4 Hz), 7.53 (s, 1H), 7.43 (d, 1H, *J* = 7.8 Hz), 7.35 (m, 2H), 7.16 (m, 2H), 6.87–6.85 (m, 2H), 6.83–6.80 (m, 4H),

5.34 (d, 1H, *J* =12.6), 5.27 (d, 1H, *J* = 12.6 Hz), 3.82 (s, 3H), 3.77 (s, 3H), 3.75 (s, 3H), 3.35 (brs, 1H), 2.11 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.9, 160.7, 160.0, 158.8, 152.4, 150.8, 141.0, 135.6, 135.0, 133.0, 130.5, 129.8, 126.5, 121.2, 119.4, 118.6, 115.0, 114.5, 114.0, 113.6, 110.0, 100.3, 83.8, 82.3, 64.6, 55.5, 55.3, 55.2, 21.0; HRMS (ESI) calcd for $C_{33}H_{28}O_6$ $[M+H]^+$ 520.1886, found 520.1885.



To a solution of **5-43** (18.1 mg, 0.035 mmol 1.0 equiv) in dry methylene chloride was added phenol (6.2 mg, 0.07 mmol, 2 equiv) followed by 8.6 µL $BF_3.Et_2O$ (2 equiv) at -20 °C. The reaction mixture was stirred at the same temperature until complete consumption of the starting material (monitor by TLC). Upon completion, ice water and CH_2Cl_2 was added slowly and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2×5 mL). The combine organic layer was dry over $MgSO_4$, concentrated under reduced pressure and the crude was purified by column chromatography (hexanes:EtOAc, 10:1), which delivered **5-44** (12 mg, 58%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.64 (d, 2H, *J* = 8.0 Hz), 7.41 (d, 1H, *J* = 7.8 Hz), 7.23 (d, 2H, *J* = 6.3 Hz), 7.18 (d, 2H, *J* = 8.7 Hz), 6.97 (d, 2H, *J* = 8.8 Hz), 6.88 (dd, 1H, *J* = 6.0 Hz, 2.3 Hz), 6.82 (d, 1H, *J* = 2.3), 6.79 (d, 2H, *J* = 7.9 Hz), 6.72 (d, 2H, *J* = 8.0 Hz), 6.64 (d, 2H, *J* = 7.8 Hz), 5.32 (s, 2H), 4.67 (brs, 1H), 3.80 (s, 3H), 3.75 (s, 3H), 3.73 (s, 3H), 2.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 171.1, 160.4, 159.7, 158.2, 154.3, 152.2, 140.8, 135.7, 134.8, 134.6, 132.7, 131.6, 130.4, 130.2, 128.0, 120.7, 118.8, 115.3, 114.5, 114.0, 113.5, 113.1, 111.1, 101.3, 84.5, 65.1, 60.4, 55.5, 55.3, 55.2, 21.1; HRMS (ESI) calcd for $C_{39}H_{32}O_6$ $[M+H]^+$ 596.2199, found 596.2197.



A solution of MeMgI in ether (3.0 M, 1.0 mL) was added to solution of **5-44** in diethyl ether (12 mg, 0.02 mmol) at 0 °C. After 5 min, the ice water bath was removed, and the reaction mixture was dried slowly using nitrogen flow created by nitrogen balloon at one end and low pressure (using water aspirator) at another end. After the reaction mixture dried out to leave only white sticky liquid residue, the nitrogen balloon was removed, and the residue was heated at 160 °C under reduced pressure. After 1 h, the reaction was cooled down to room temperature and ether (5 mL) was added, and the excess Grignard reagent was carefully quenched with water. To the biphasic mixture, 1 N HCl was added until the water layer becomes pH 3–4, and ethyl acetate was added (5 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (X2). The combined organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by column chromatography (hexanes:EtOAc, 10:1), which provided selaginpulvilin A (5.8 mg, 52% yield).[2] ^{1}H NMR (CD_3OD, 500 MHz): δ 7.68 (d, 1H, *J* = 7.8), 7.60 (d, 1H, *J* = 8.2), 7.49 (d, 1H, *J* = 7.8), 7.10–7.08 (m, 4H), 6.87 (m, 2H), 6.77 (d, 1H, *J* = 8.2), 6.70–6.68 (m, 3H), 6.58–6.56 (m, 4H), 4.79 (s, 2H), 1.91 (brs, 1H); ^{13}C NMR (CD_3OD, 125 MHz): δ 157.7, 157.6, 155.5, 140.4, 140.2, 133.8, 132.3, 130.7, 130.0, 126.2, 120.2, 119.3, 118.1, 120.2, 119.3, 118.1, 115.0, 114.3, 114.1, 113.7, 112.0, 101.0, 84.0, 64.8, 62.3; HRMS (ESI) calcd for $C_{34}H_{23}O_5$ $[M\text{-}H]^+$ 511.1545, found 511.1542.

5.6. References

(1) Weststrand, S.; Korall, P. *Am. J. Bot.* **2016**, *103*, 2160.

(2) (a) Banks, J. A. *Annu. Rev. Plant Biol.* **2009**, *60*, 223. (b) Li, X.; Cao, J.; Miao. X. Pu. *LiShiZhen Med. Mat. Med. Res.* **1991**, *2*, 59. (c) Ma, S. C.; Du, J.; Paul, P. H. B.; Deng, X. L.; Zhang, Y. W.; Vincent, E. C. O.; Xu, H. X.; Spencer, H. S. L. *J. Ethnopharmacol.* **2002**, *79*, 205. (d) Darias, V.; Bravo, L.; Rabanal, R.; Sanchez Mateo, C.; Gonzalez-Luis, R. M.; Hernandez-Perez, A. M. *J. Ethnopharmacol.* **1989**, *25*, 77. (e) MacFoy, C. A.; Sama, A. M. *J. Ethnopharmacol.* **1983**, *8*, 215. (f) Winkelman, M. *J. Ethnopharmacol.* **1986**, *18*, 109.

(3) Li, W.; Tang, G.-H.; Yin, S. *Nat. Prod. Rep.* **2021**. DOI: 10.1039/d0np00065e.

(4) (a) Yu, J. D.; Hu, J. Y.; Cheng, X. L.; Ma. S. C. *Chin. Pharm. Aff.* **2007**, *21*, 763. (b) Ma, S. C.; Paul, P. H. B.; Vincent, E. C. O.; He, Y. H.; Spencer, H. S. L.; Lee, S. F.; Lin, R. C. *Biol. Pharm. Bull.* **2001**, *24*, 311. (c) Dai, Z.; Ma, S. C.; Wang, G. L.; Wang, F.; Lin, R. C. *J. Asian Nat. Prod. Res.* **2006**, *8*, 529.

(5) Zhang, L. P.; Liang, Y. M.; Wei, X. C.; Cheng, D. L. *J. Org. Chem.* **2007**, *72*, 3921.

(6) (a) Cao, Y.; Yao, Y.; Huang, X. J.; Oberer, L.; Wagner, T.; Guo, J. M.; Gu, W.; Liu, W. D.; Lv, G. X.; Shen, Y. N.; Duan, J. A. *Tetrahedron* **2015**, *71*, 1581. (b) Nguyen, P. H.; Zhao, B. T.; Ali, M. Y.; Choi, J. S.; Rhyu, D. Y.; Min, B. S.; Woo, M. H. *J. Nat. Prod.* **2015**, *78*, 34. (c) Tan, G. S.; Xu, K. P.; Li, F. S.; Wang, C. J.; Li, T. Y.; Hu, C. P.; Shen, J.; Zhou, Y. J.; Li, Y. J. *J. Asian Nat. Prod. Res.* **2009**, *11*, 1001. (d) Cao, Y.; Chen, J. J.; Tan, N. H.; Oberer, L.; Wagner, T.; Wu, Y. P.; Zeng, G. Z.; Yan, H.; Wang, Q. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2456. (e) Cao, Y.; Chen, J. J.; Tan, N. H.; Wu, Y. P.; Yang, J.; Q. Wang, Q. *Magn. Reson. Chem.* **2010**, *48*, 656.

(7) Liu, X.; Luo, H. B.; Huang, Y. Y.; Bao, J.-M.; Tang, G.-H.; Chen, Y. Y.; Wang, J.; Yin, S. *Org. Lett.* **2014**, *16*, 282.

(8) Zhang, J.-S.; Liu, X.; Weng, J.; Guo, Y.-Q.; Li, Y.-Q.; Ahmed, A.; Tang, G.-H.; Yin, S. *Org. Chem. Front*. **2017**, *4*, 170.

(9) Karmakar, R.; Lee, D. *Org. Lett.* **2016**, *18*, 6105.

(10) Sowden, M. J.; Sherburn, M. S. *Org. Lett*. **2017**, *19*, 636.

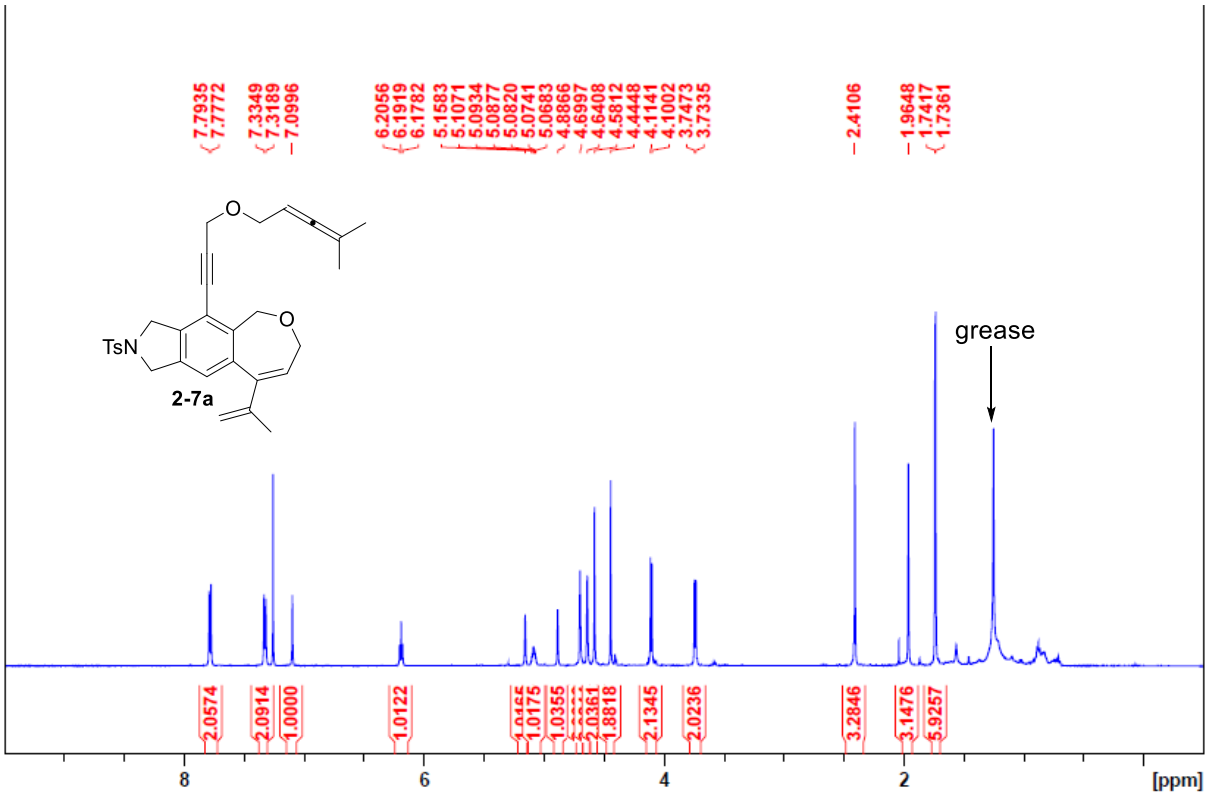
(11) Chinta, B. S.; Baire, B. *Org. Biomol. Chem.* **2017**, *15*, 5908.

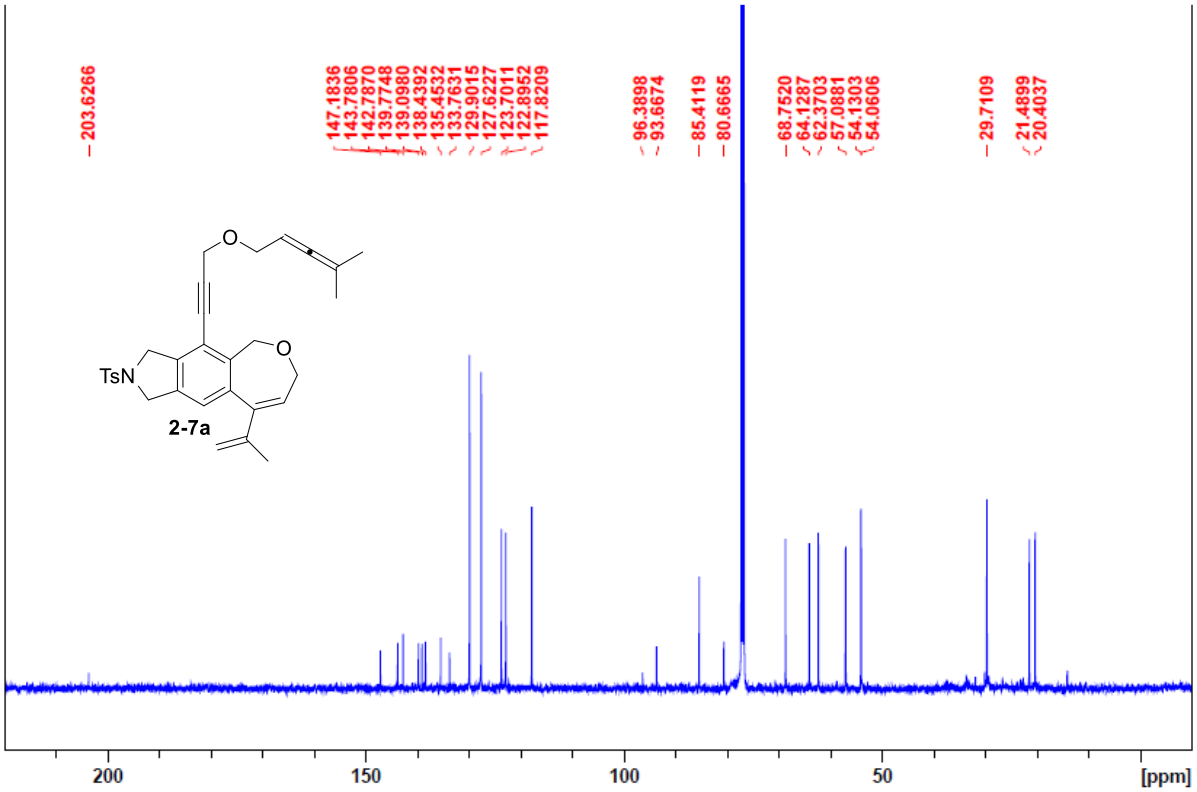
(12) The TBS group is not needed but it facilitates the preparation and coupling of the three carbon-allene unit. The preparation of allenyl bromide **5-39** is described in the Experimental section.

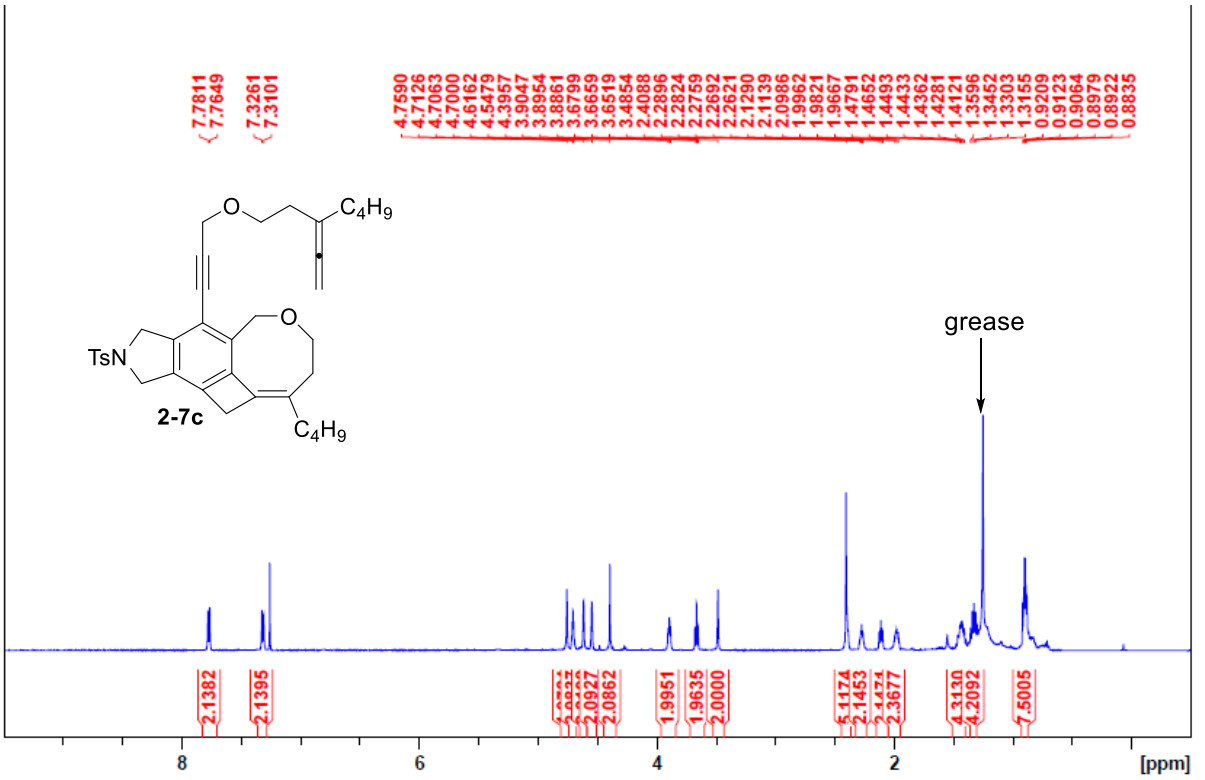
(13) Wang, X.; Gao, X.; Buevich, A.X.; Yasuda, N.; Zhang, Y.; Yang, R.; Zhang, L.; Martin, G.E.; Williamson, T. *J. Org. Chem.* **2019**, *84*, 10024.

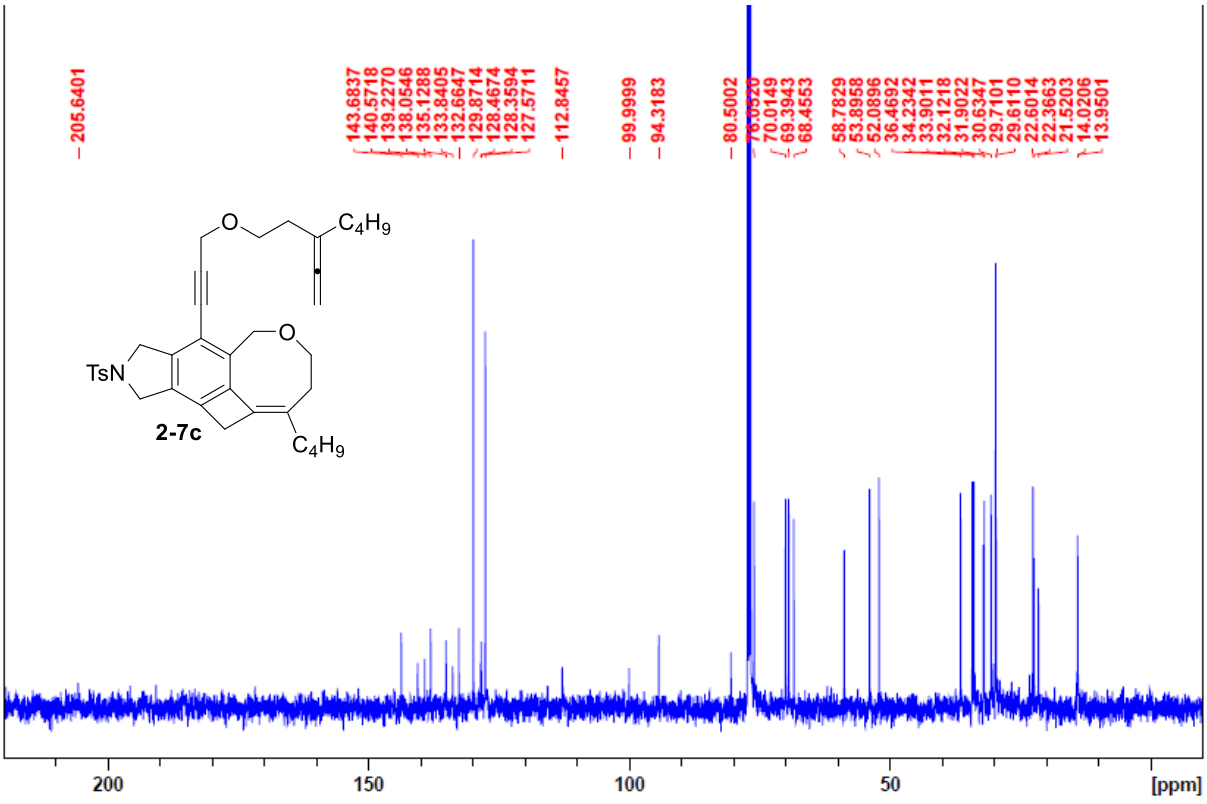
Appendix I

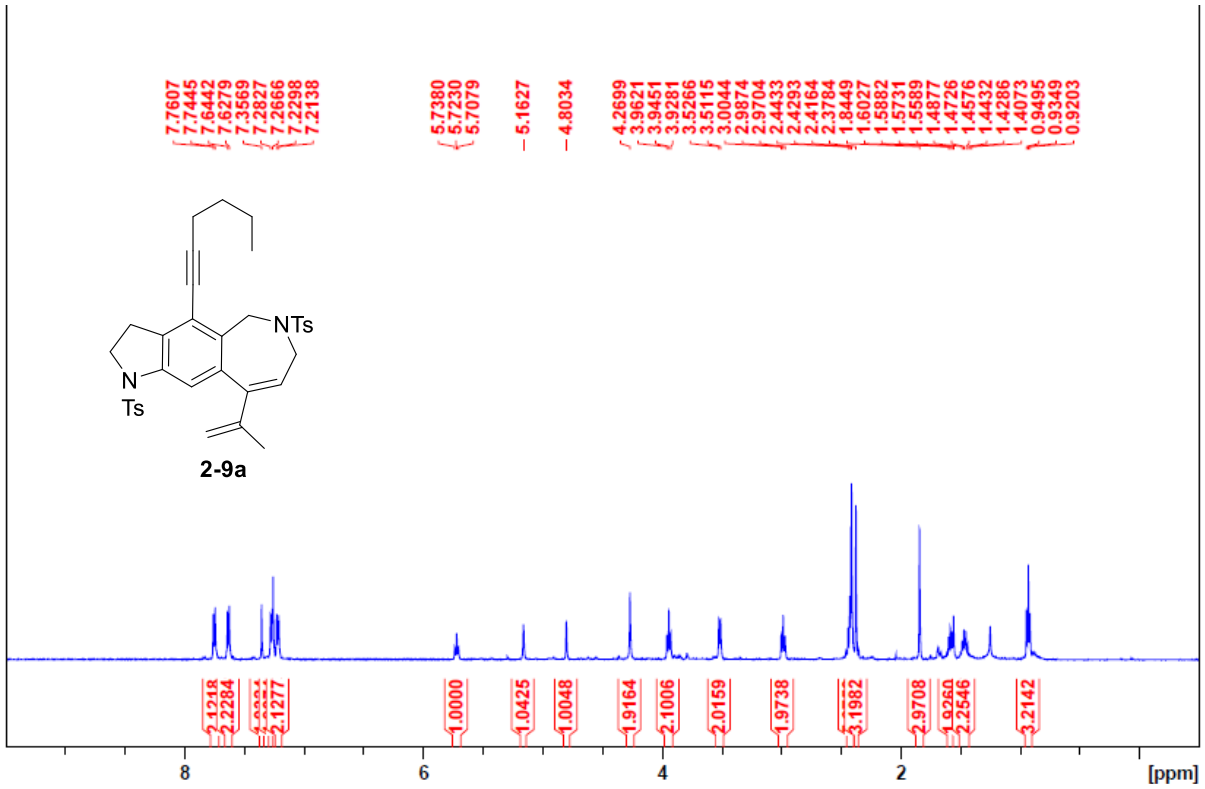
Selected NMR Spectra for Chapter 2

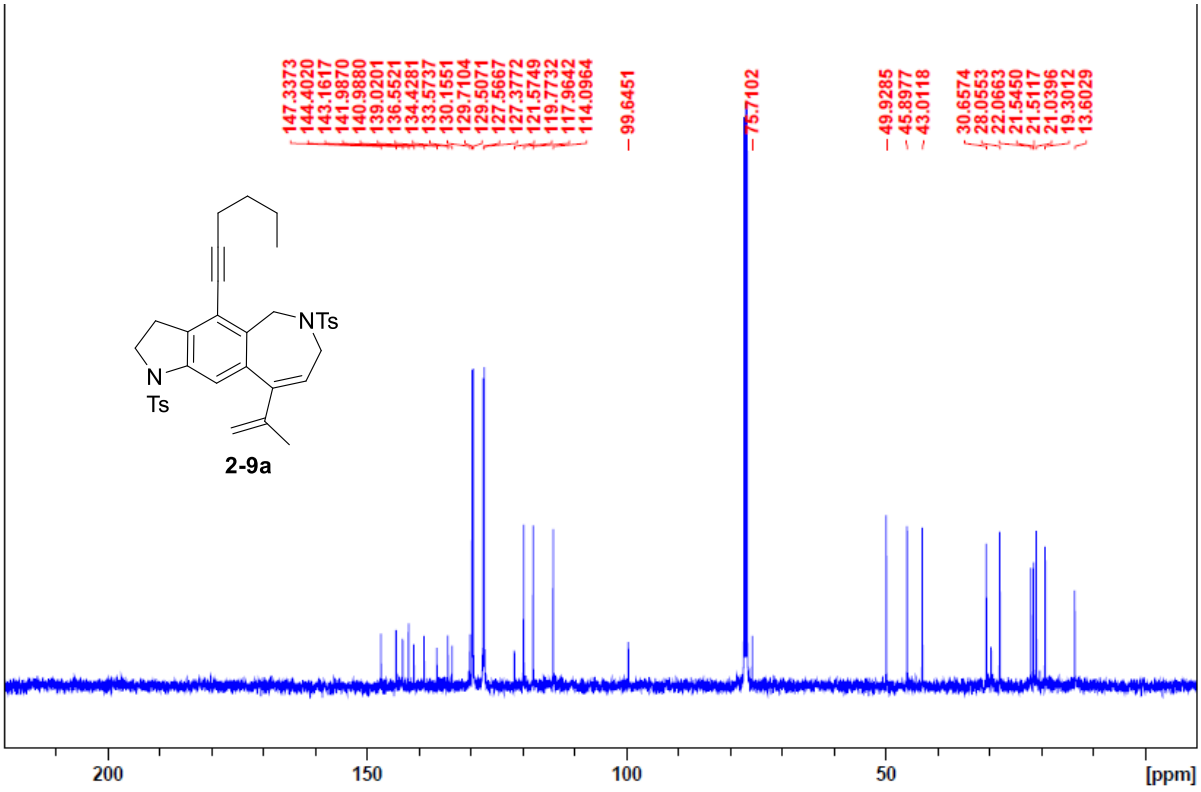

7.7935
7.7772
7.3349
7.3189
7.0996
6.2056
6.1919
6.1782
5.1583
5.1071
5.0934
5.0877
5.0820
5.0741
5.0683
4.8866
4.6997
4.6408
4.5812
4.4448
4.1141
4.1002
3.7473
3.7335
2.4106
1.9648
1.7417
1.7361
TsN
O
O
2-7a
grease
2.0574
2.0914
1.0000
1.0122
1.0175
1.0355
1.8818
2.1345
2.0236
3.2846
3.1476
5.9257
8
6
4
2
[ppm]

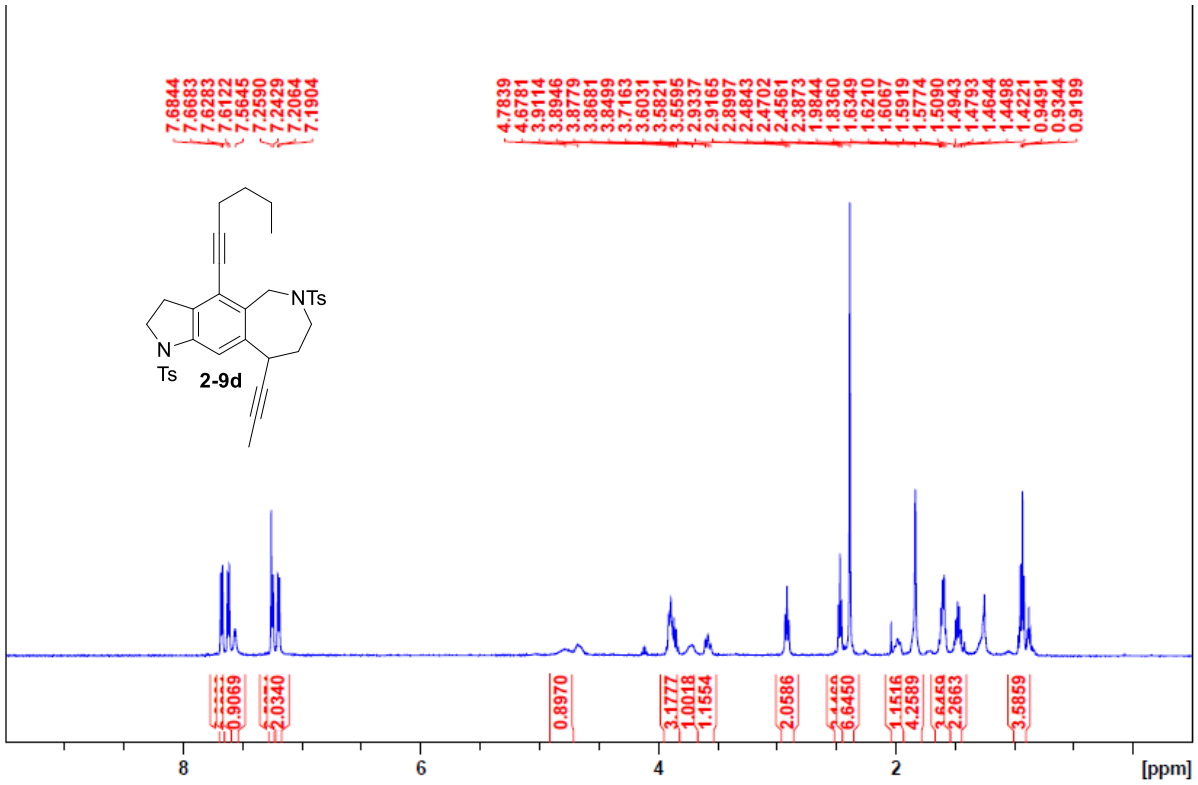

203.6266
147.1836
143.7806
142.7870
139.7748
139.0980
138.4392
135.4532
133.7631
129.9015
127.6227
123.7011
122.8952
117.8209
96.3898
93.6674
85.4119
80.6665
68.7520
64.1287
62.3703
57.0881
54.1303
54.0606
29.7109
21.4899
20.4037
TsN
O
O
2-7a
200
150
100
50
[ppm]

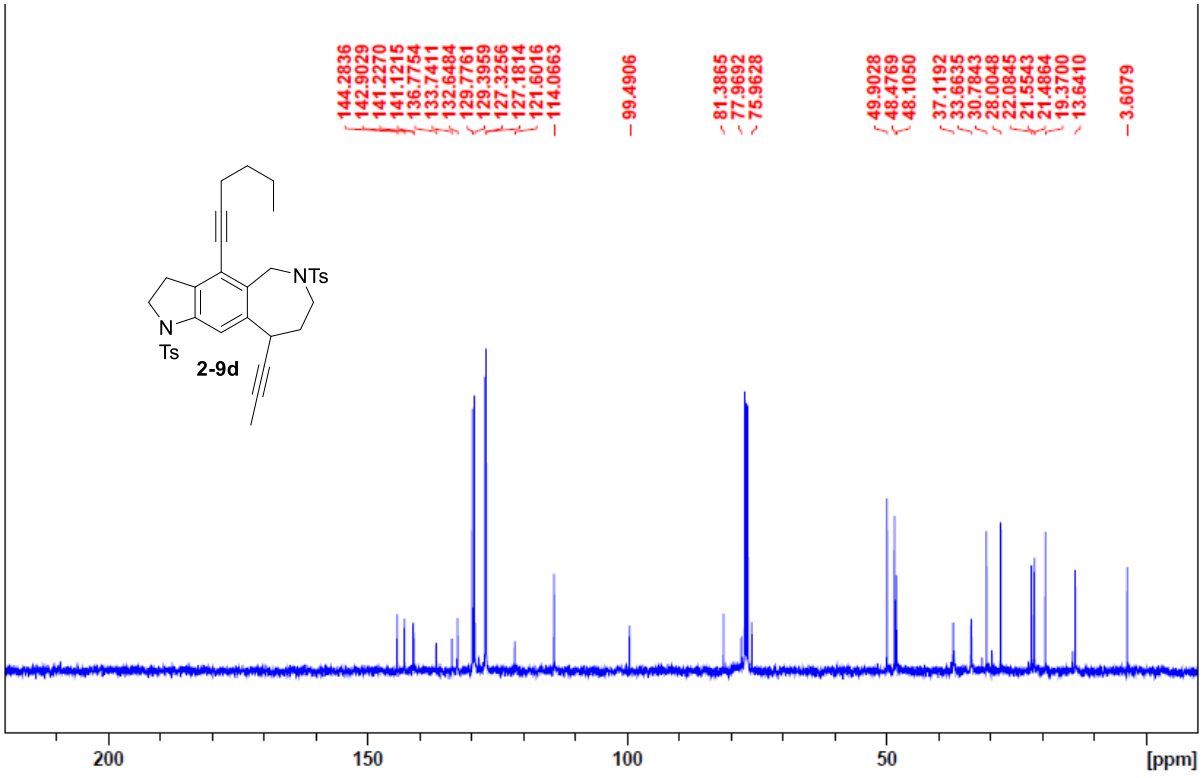

7.7811
7.7649
7.3261
7.3101
4.7590
4.7126
4.7063
4.7000
4.6162
4.5479
4.3957
3.9047
3.8954
3.8861
3.6799
3.6659
3.6519
3.4854
2.4088
2.2896
2.2824
2.2759
2.2692
2.2621
2.1290
2.1139
2.0986
1.9962
1.9821
1.9667
1.4791
1.4652
1.4493
1.4433
1.4362
1.4281
1.4121
1.3596
1.3452
1.3303
1.3155
0.9209
0.9123
0.9064
0.8979
0.8922
0.8835
O
C4H9
TsN
O
2-7c
C4H9
grease
2.1382
2.1395
1.9951
1.9635
2.0000
5.1174
2.1453
2.3677
4.3130
4.2092
7.5005
8
6
4
2
[ppm]

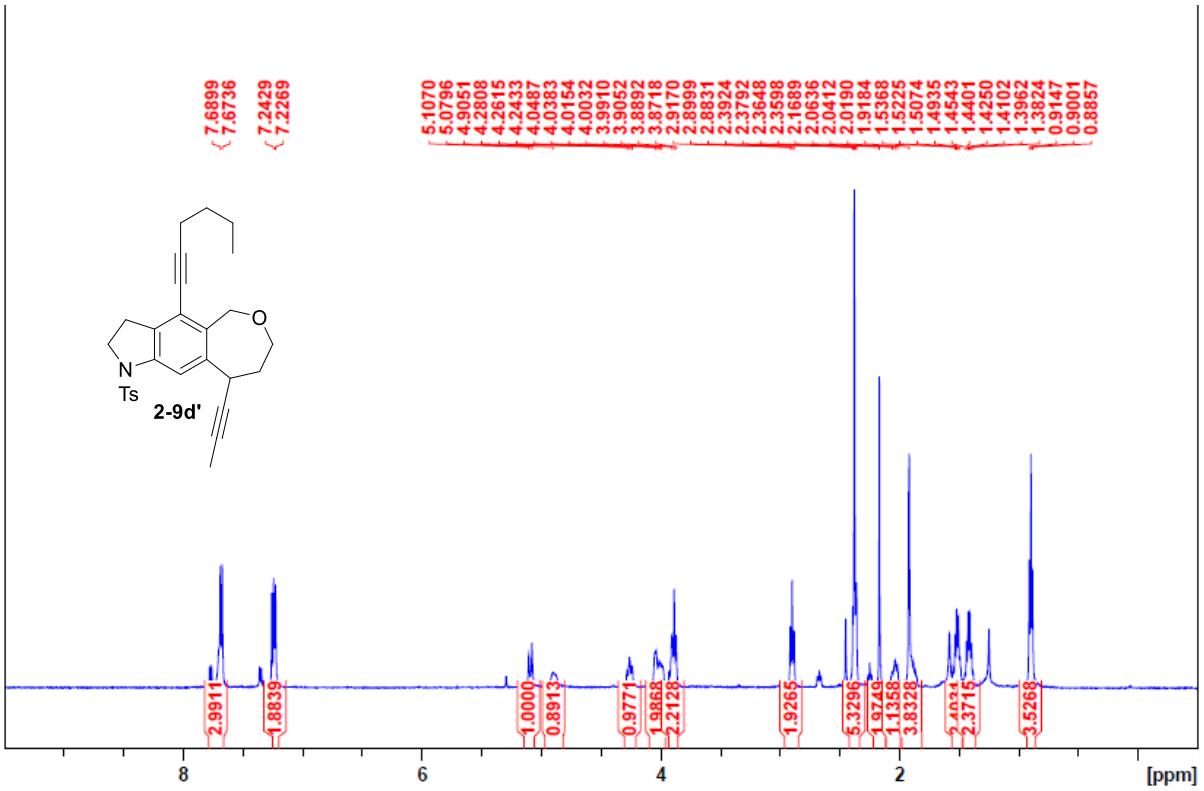

205.6401
143.6837
140.5718
139.2270
138.0546
135.1288
133.8405
132.6647
129.8714
128.4674
128.3594
127.5711
112.8457
99.9999
94.3183
80.5002
70.0149
69.3943
68.4553
58.7829
53.8958
52.0896
36.4692
34.2342
33.9011
32.1218
31.9022
30.6347
29.7101
29.6110
22.6014
22.3663
21.5203
14.0206
13.9501
O
C4H9
TsN
O
2-7c
C4H9
200
150
100
50
[ppm]

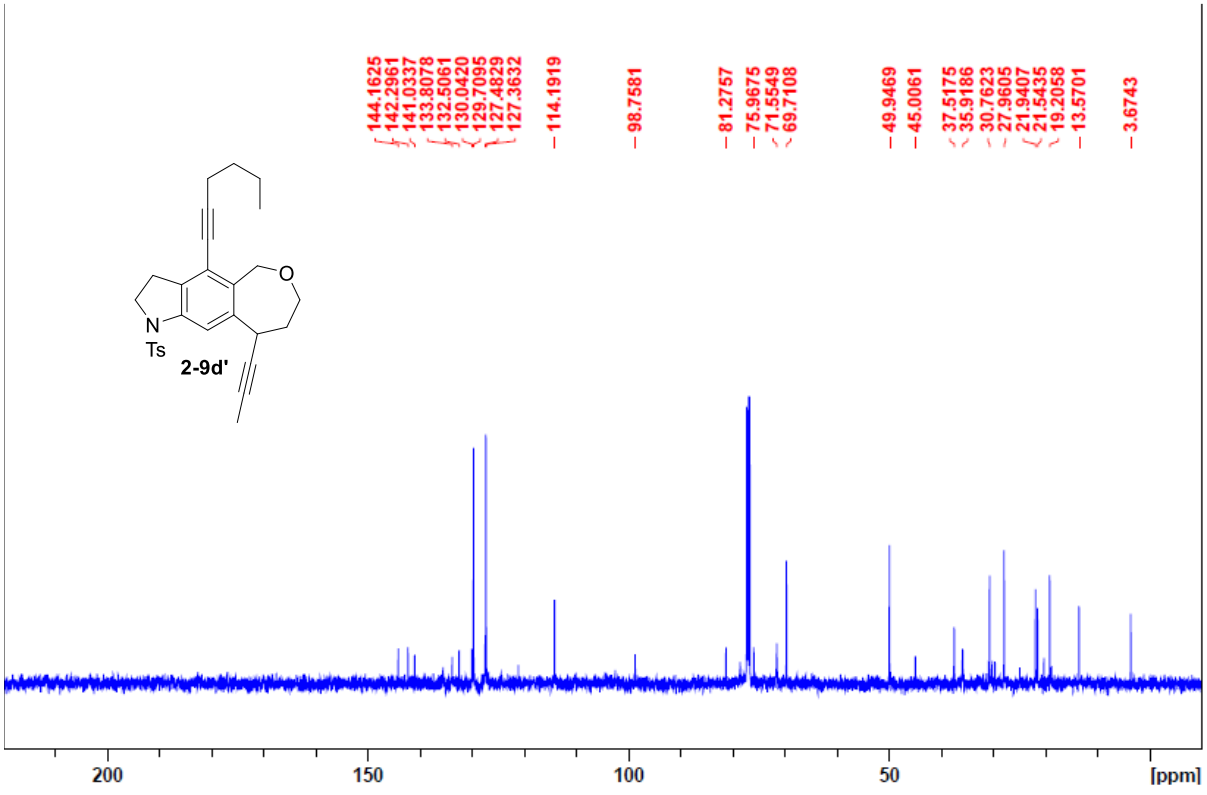

7.7607
7.7445
7.6442
7.6279
7.3569
7.2827
7.2666
7.2298
7.2138
5.7380
5.7230
5.7079
5.1627
4.8034
4.2699
3.9621
3.9451
3.9281
3.5266
3.5115
3.0044
2.9874
2.9704
2.4433
2.4293
2.4164
2.3784
1.8449
1.6027
1.5882
1.5731
1.5589
1.4877
1.4726
1.4576
1.4432
1.4286
1.4073
0.9495
0.9349
0.9203
NTs
N
Ts
2-9a
2.1218
2.2284
2.1277
1.0000
1.0425
1.0048
1.9164
2.1006
2.0159
1.9738
3.1982
2.9708
1.9260
2.2546
3.2142
8
6
4
2
[ppm]

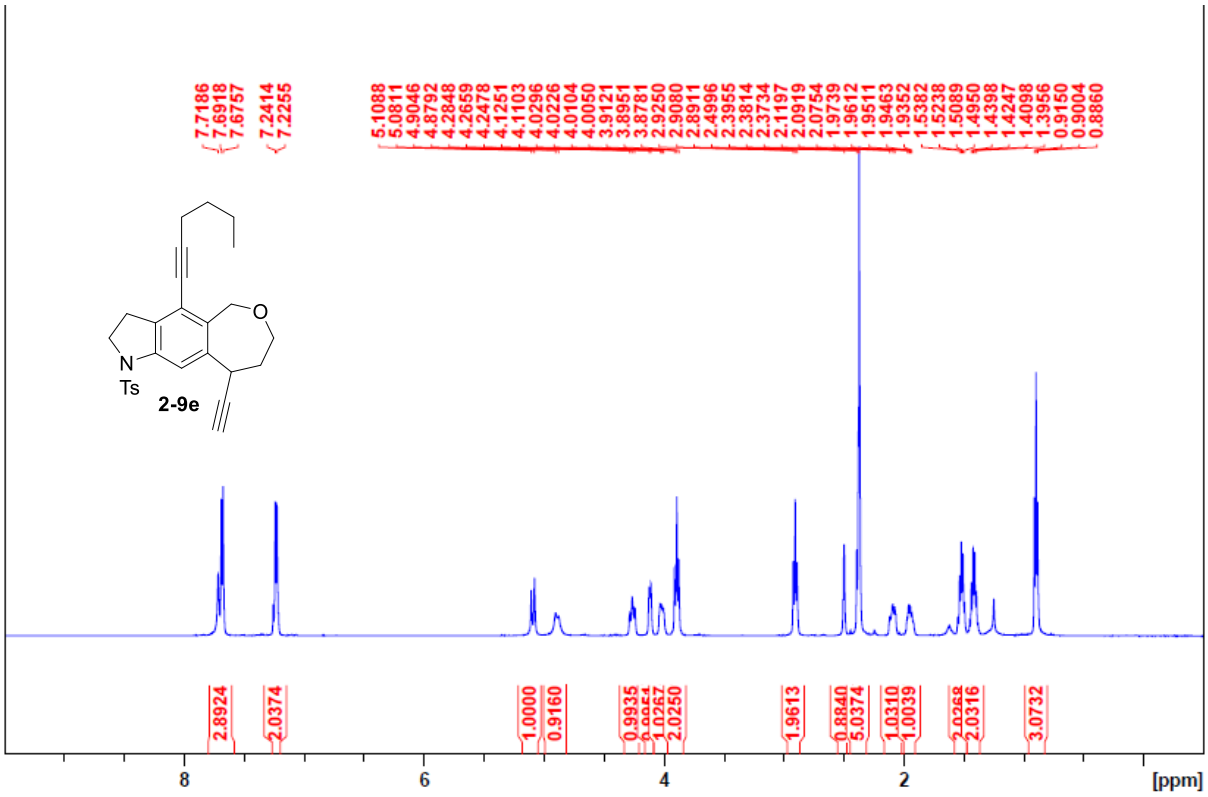

147.3373
144.4020
143.1617
141.9870
140.9880
139.0201
136.5521
134.4281
133.5737
130.1551
129.7104
129.5071
127.5667
127.3772
121.5749
119.7732
117.9642
114.0964
99.6451
75.7102
49.9285
45.8977
43.0118
30.6574
28.0553
22.0663
21.5450
21.5117
21.0396
19.3012
13.6029
NTs
N
Ts
2-9a
200
150
100
50
[ppm]

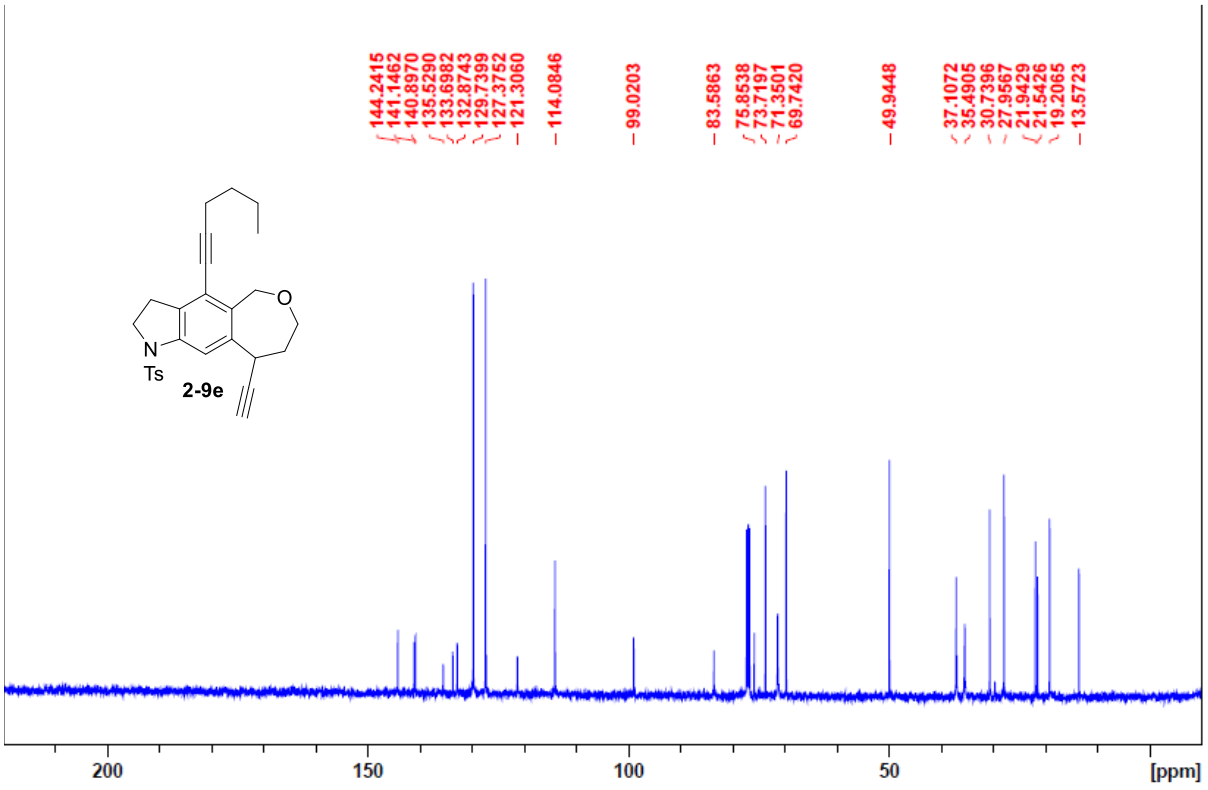

7.6844
7.6683
7.6283
7.6122
7.5645
7.2590
7.2429
7.2064
7.1904
4.7839
4.6781
3.9114
3.8946
3.8779
3.8681
3.8499
3.7163
3.6031
3.5821
3.5595
2.9337
2.9165
2.8997
2.4843
2.4702
2.4561
2.3873
1.9844
1.8360
1.6349
1.6210
1.6067
1.5919
1.5774
1.5090
1.4943
1.4793
1.4644
1.4498
1.4221
0.9491
0.9344
0.9199
NTs
N
Ts
2-9d
0.9069
2.0340
0.8970
3.1777
1.0018
1.1554
2.0586
6.6450
1.1516
4.2589
2.2663
3.5859
8
6
4
2
[ppm]

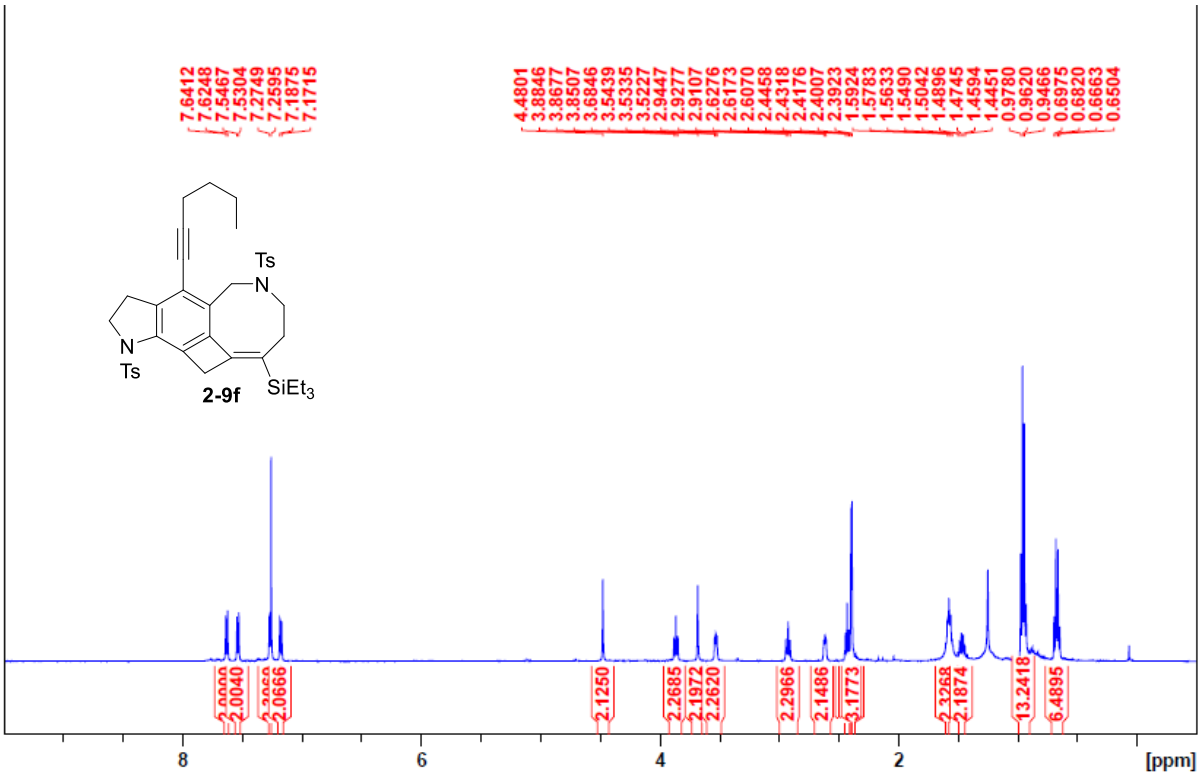

144.2836
142.9029
141.2270
141.1215
136.7754
133.7411
132.6484
129.7761
129.3959
127.3256
127.1814
121.6016
114.0663
99.4906
81.3865
77.9692
75.9628
49.9028
48.4769
48.1050
37.1192
33.6635
30.7843
28.0048
22.0845
21.5543
21.4864
19.3700
13.6410
3.6079
NTs
N
Ts
2-9d
200
150
100
50
[ppm]

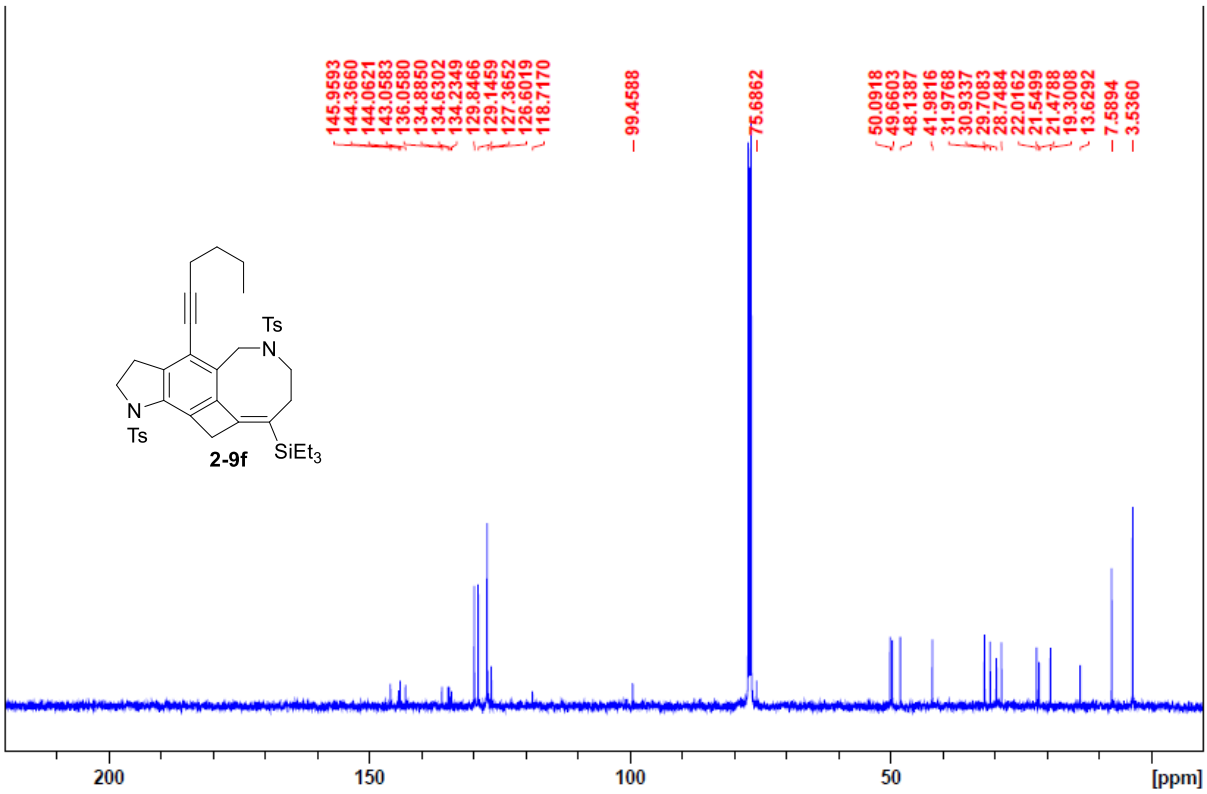

7.6899
7.6736
7.2429
7.2269
5.1070
5.0796
4.9051
4.2808
4.2615
4.2433
4.0487
4.0383
4.0154
4.0032
3.9910
3.9052
3.8892
3.8718
2.9170
2.8999
2.8831
2.3924
2.3792
2.3648
2.3598
2.1689
2.0636
2.0412
2.0190
1.9184
1.5368
1.5225
1.5074
1.4935
1.4543
1.4401
1.4250
1.4102
1.3962
1.3824
0.9147
0.9001
0.8857
O
N
Ts
2-9d'
2.9911
1.8839
1.0000
0.8913
0.9771
1.9868
2.2128
1.9265
5.3296
1.9749
1.1358
3.8328
3.5268
8
6
4
2
[ppm]

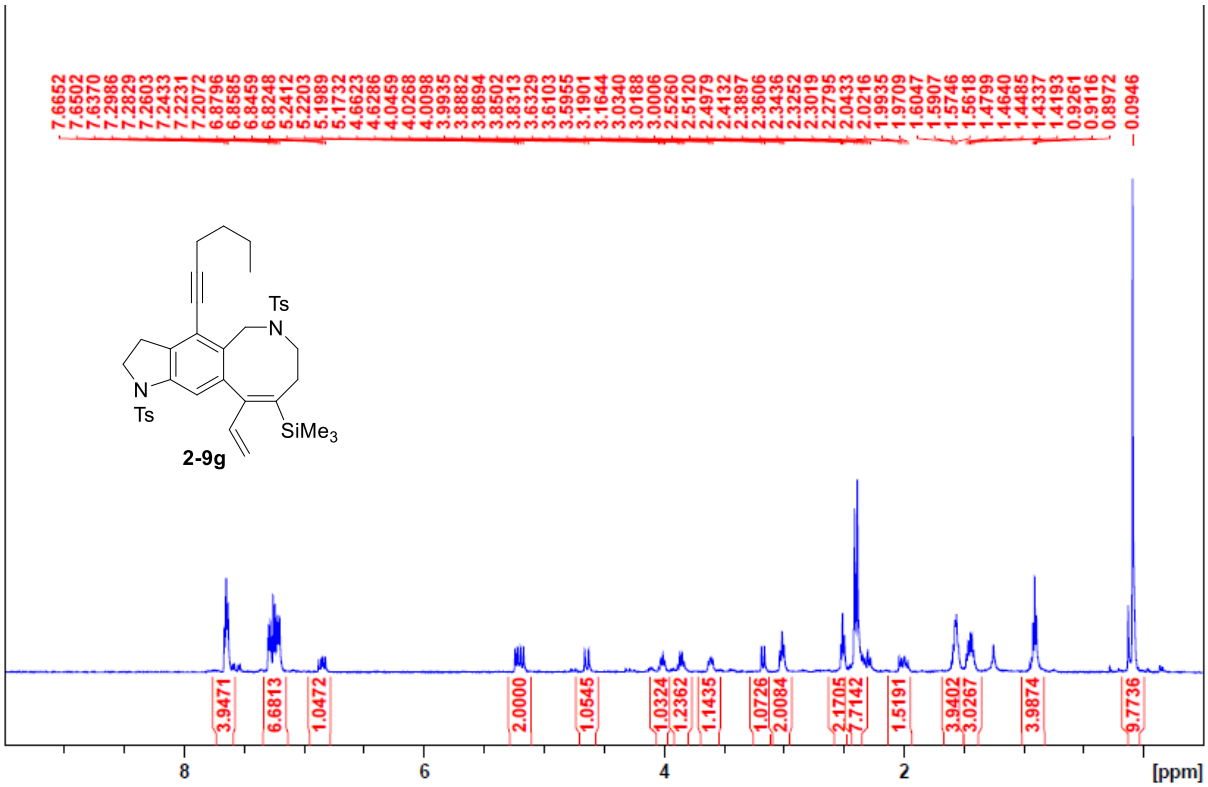

144.1625
142.2961
141.0337
133.8078
132.5061
130.0420
129.7095
127.4829
127.3632
114.1919
98.7581
81.2757
75.9675
71.5549
69.7108
49.9469
45.0061
37.5175
35.9186
30.7623
27.9605
21.9407
21.5435
19.2058
13.5701
3.6743
O
N
Ts
2-9d'
200
150
100
50
[ppm]

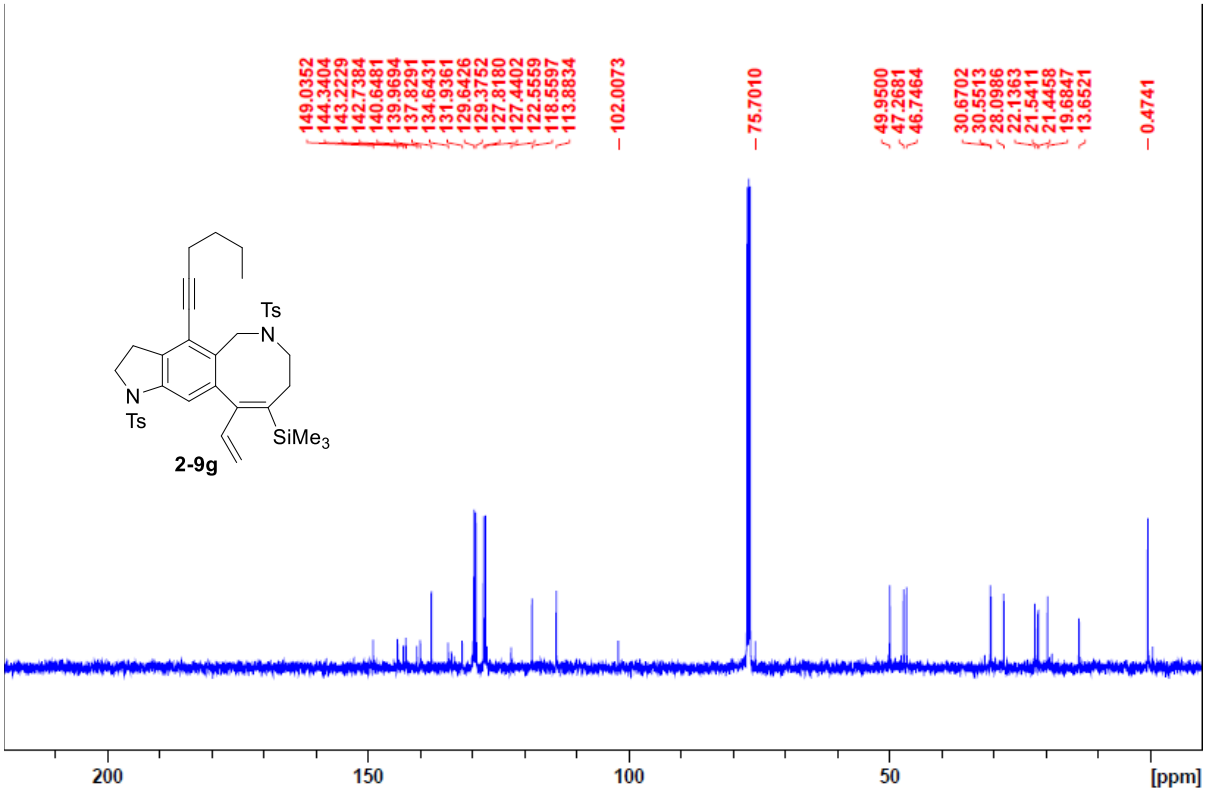

7.7186
7.6918
7.6757
7.2414
7.2255
5.1088
5.0811
4.9046
4.8792
4.2848
4.2659
4.2478
4.1251
4.1103
4.0296
4.0226
4.0104
4.0050
3.9121
3.8951
3.8781
3.9250
2.9080
2.8911
2.4996
2.3955
2.3814
2.3734
2.1197
2.0919
2.0754
1.9739
1.9612
1.9511
1.9463
1.9352
1.5382
1.5238
1.5089
1.4950
1.4398
1.4247
1.4098
1.3956
0.9150
0.9004
0.8860
N
Ts
O
2-9e
2.8924
2.0374
1.0000
0.9160
0.9935
1.0267
2.0250
1.9613
0.8840
5.0374
1.0310
1.0039
2.0316
3.0732
8
6
4
2
[ppm]

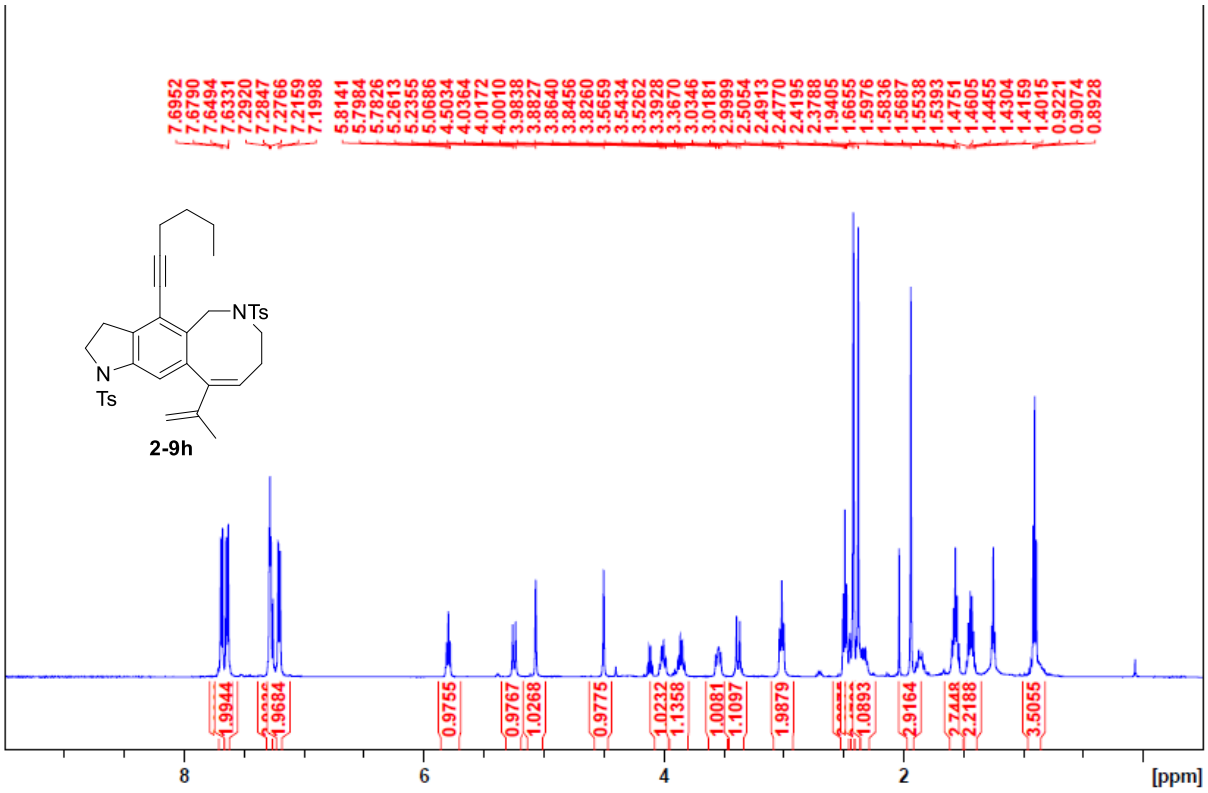

144.2415
141.1462
140.8970
135.5290
133.6982
132.8743
129.7399
127.3752
121.3060
114.0846
99.0203
83.5863
75.8538
73.7197
71.3501
69.7420
49.9448
37.1072
35.4905
30.7396
27.9567
21.9429
21.5426
19.2065
13.5723
N
Ts
O
2-9e
200
150
100
50
[ppm]

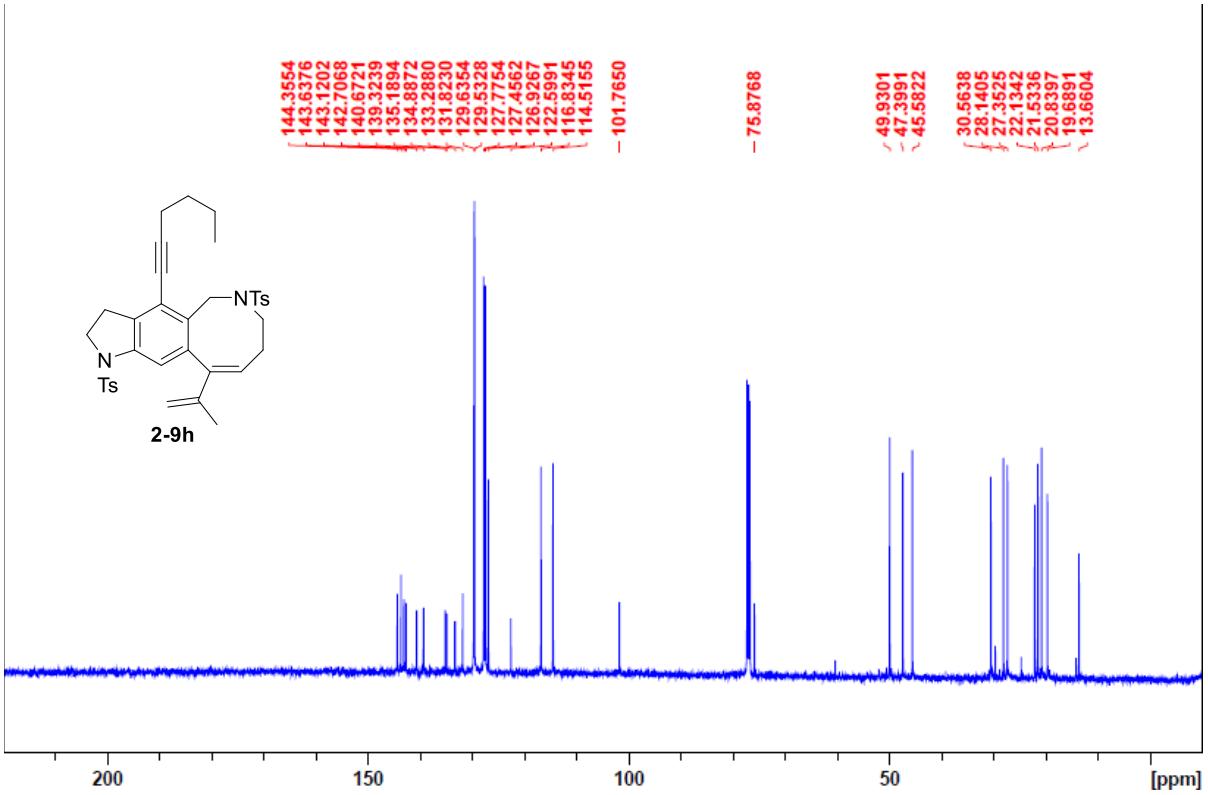

7.6412
7.6248
7.5467
7.5304
7.2749
7.2595
7.1875
7.1715
4.4801
3.8846
3.8677
3.8507
3.6846
3.5439
3.5335
3.5227
2.9447
2.9277
2.9107
2.6276
2.6173
2.6070
2.4458
2.4318
2.4176
2.4007
2.3923
1.5924
1.5783
1.5633
1.5490
1.5042
1.4896
1.4745
1.4594
1.4451
0.9780
0.9620
0.9466
0.6975
0.6820
0.6663
0.6504
Ts
N
N
Ts
SiEt3
2-9f
2.0000
2.0040
2.0666
2.1250
2.2685
2.1972
2.2620
2.2966
2.1486
3.1773
2.3268
2.1874
13.2418
6.4895
8
6
4
2
[ppm]

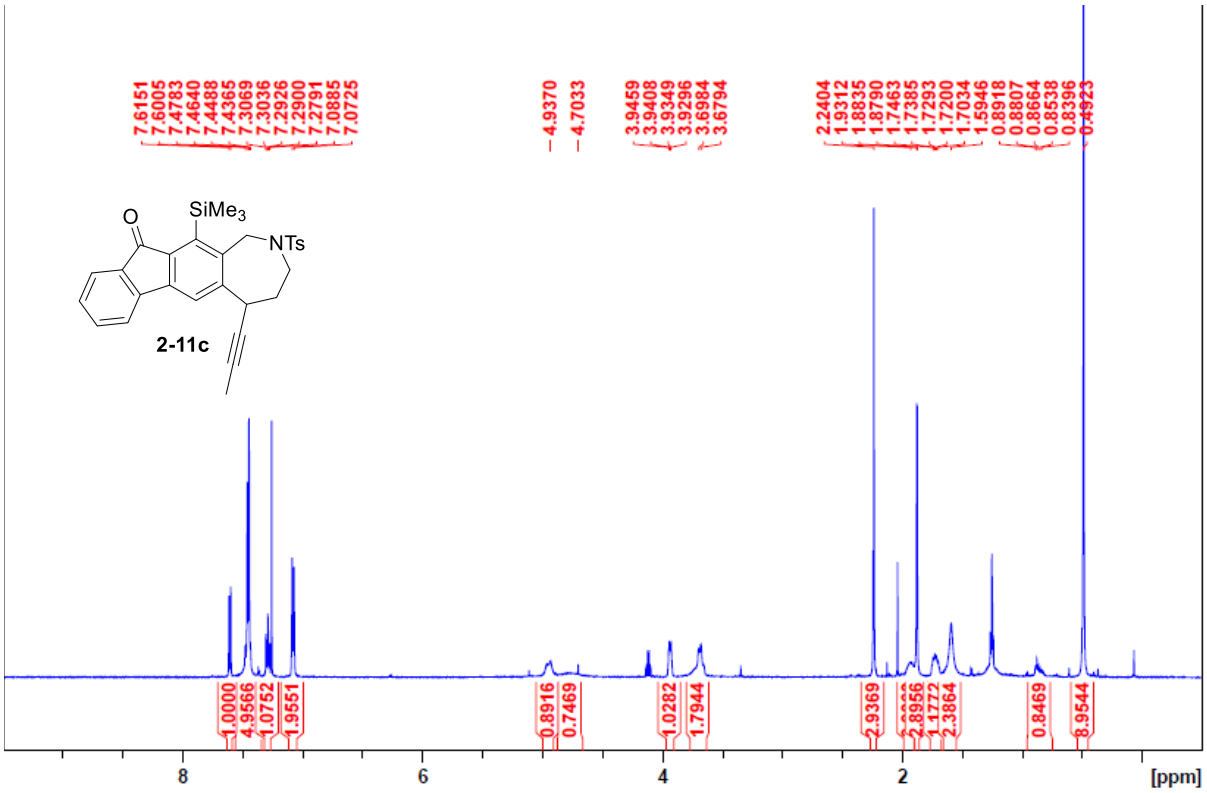

145.9593
144.3660
144.0621
143.0583
136.0580
134.8850
134.6302
134.2349
129.8466
129.1459
127.3652
126.6019
118.7170
99.4588
75.6862
50.0918
49.6603
48.1387
41.9816
31.9768
30.9337
29.7083
28.7484
22.0162
21.5499
21.4788
19.3008
13.6292
7.5894
3.5360
Ts
N
N
Ts
SiEt3
2-9f
200
150
100
50
[ppm]

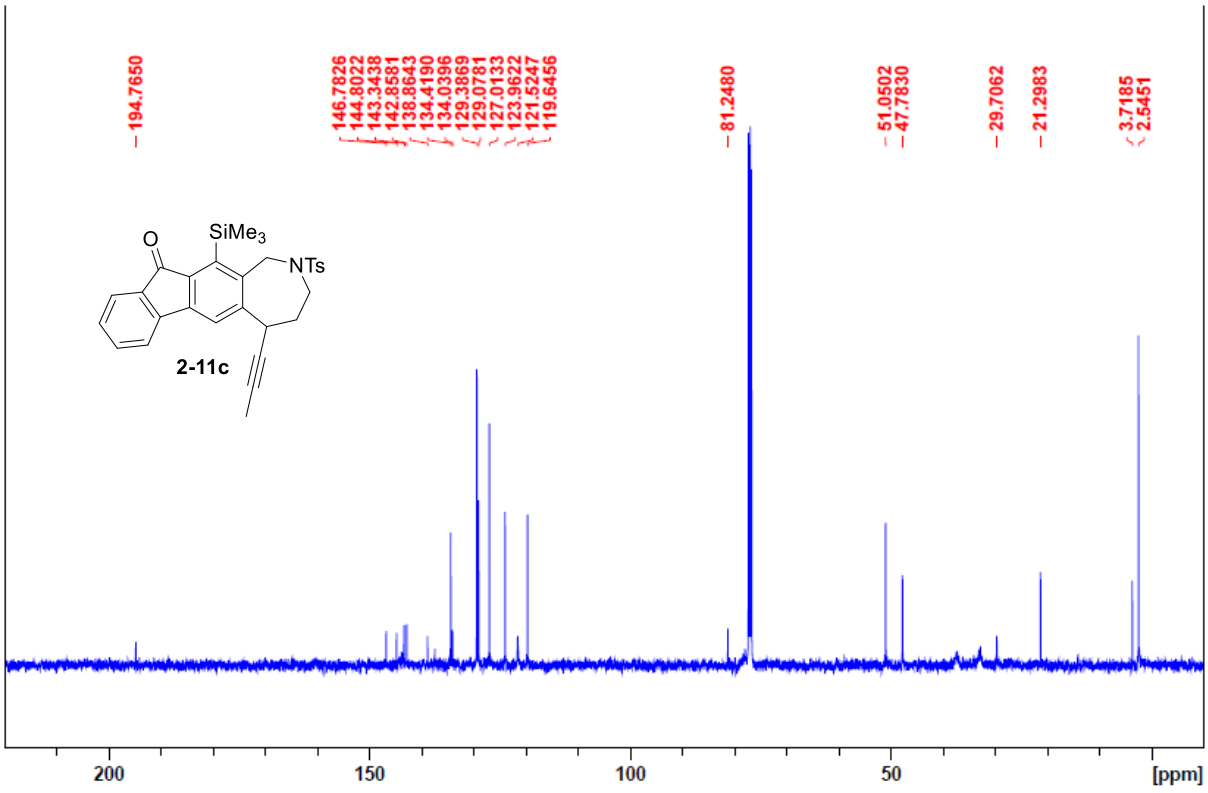

7.6652
7.6502
7.6370
7.2986
7.2829
7.2603
7.2433
7.2231
7.2072
6.8796
6.8585
6.8459
6.8248
5.2412
5.2203
5.1989
5.1732
4.6623
4.6286
4.0459
4.0268
4.0098
3.9935
3.8882
3.8694
3.8502
3.8313
3.6329
3.6103
3.5955
3.1901
3.1644
3.0340
3.0188
3.0006
2.5260
2.5120
2.4979
2.4132
2.3897
2.3606
2.3436
2.3252
2.3019
2.2795
2.0433
2.0216
1.9935
1.9709
1.6047
1.5907
1.5746
1.5618
1.4799
1.4640
1.4485
1.4337
1.4193
0.9261
0.9116
0.8972
0.0946
Ts
N
N
Ts
SiMe3
2-9g
3.9471
6.6813
1.0472
2.0000
1.0545
1.0324
1.2362
1.1435
1.0726
2.0084
2.1705
7.7142
1.5191
3.9402
3.0267
3.9874
6.7736
8
6
4
2
[ppm]

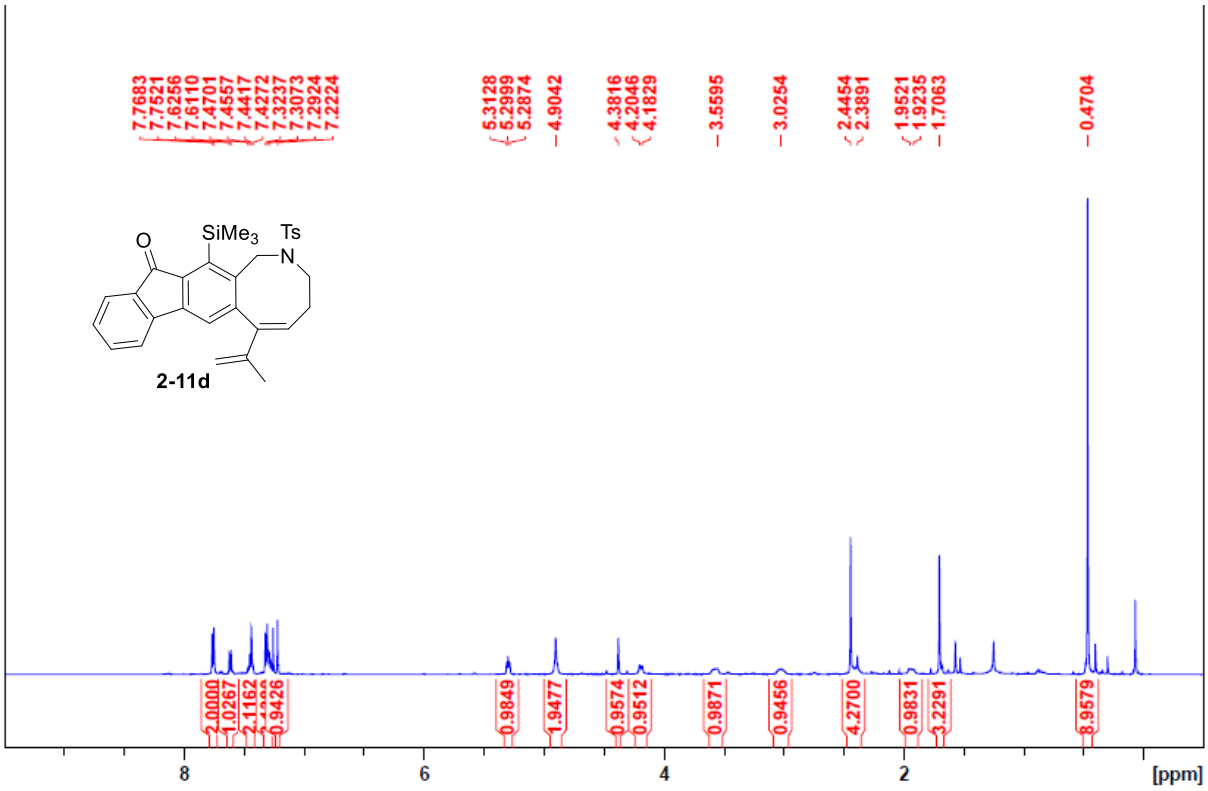

149.0352
144.3404
143.2229
142.7384
140.6481
139.9694
137.8291
134.6431
131.9361
129.6426
129.3752
127.8180
127.4402
122.5559
118.5597
113.8834
102.0073
75.7010
49.9500
47.2681
46.7464
30.6702
30.5513
28.0986
22.1363
21.5411
21.4458
19.6847
13.6521
0.4741
Ts
N
N
Ts
SiMe3
2-9g
200
150
100
50
[ppm]

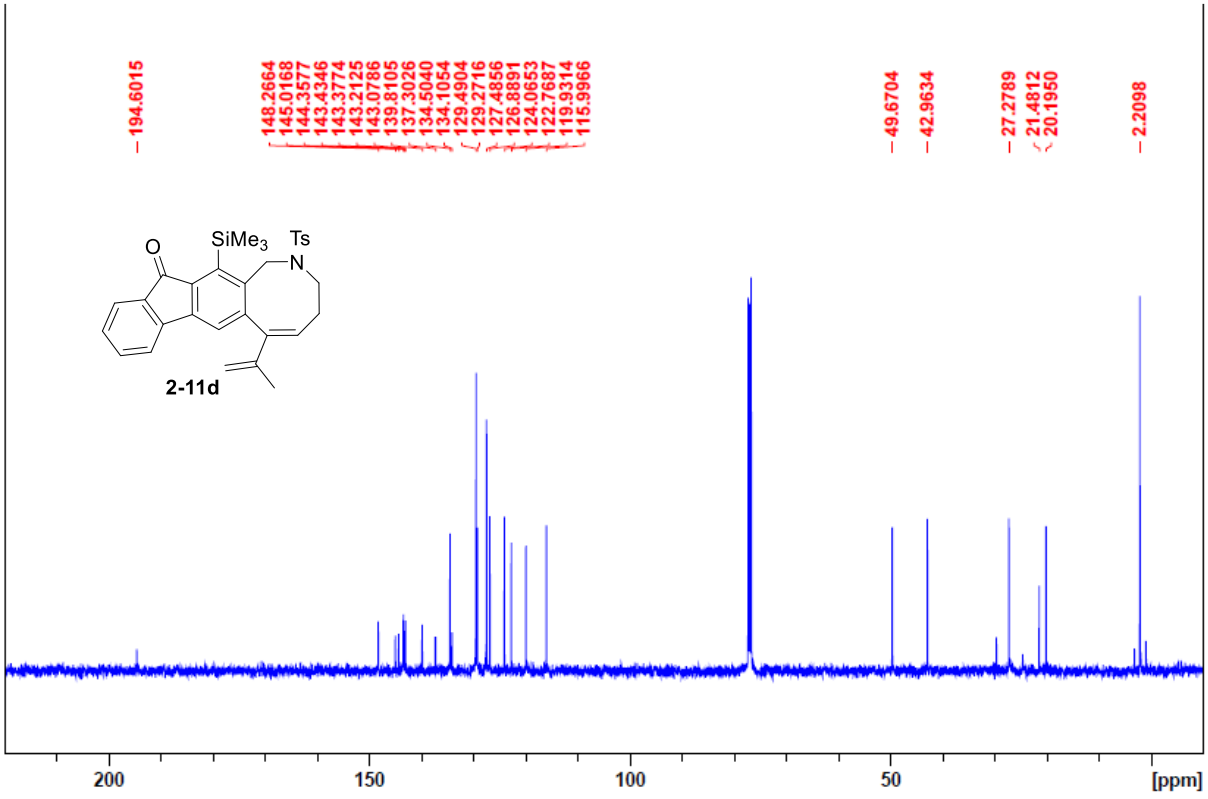

NTs
N
Ts
2-9h
[ppm]

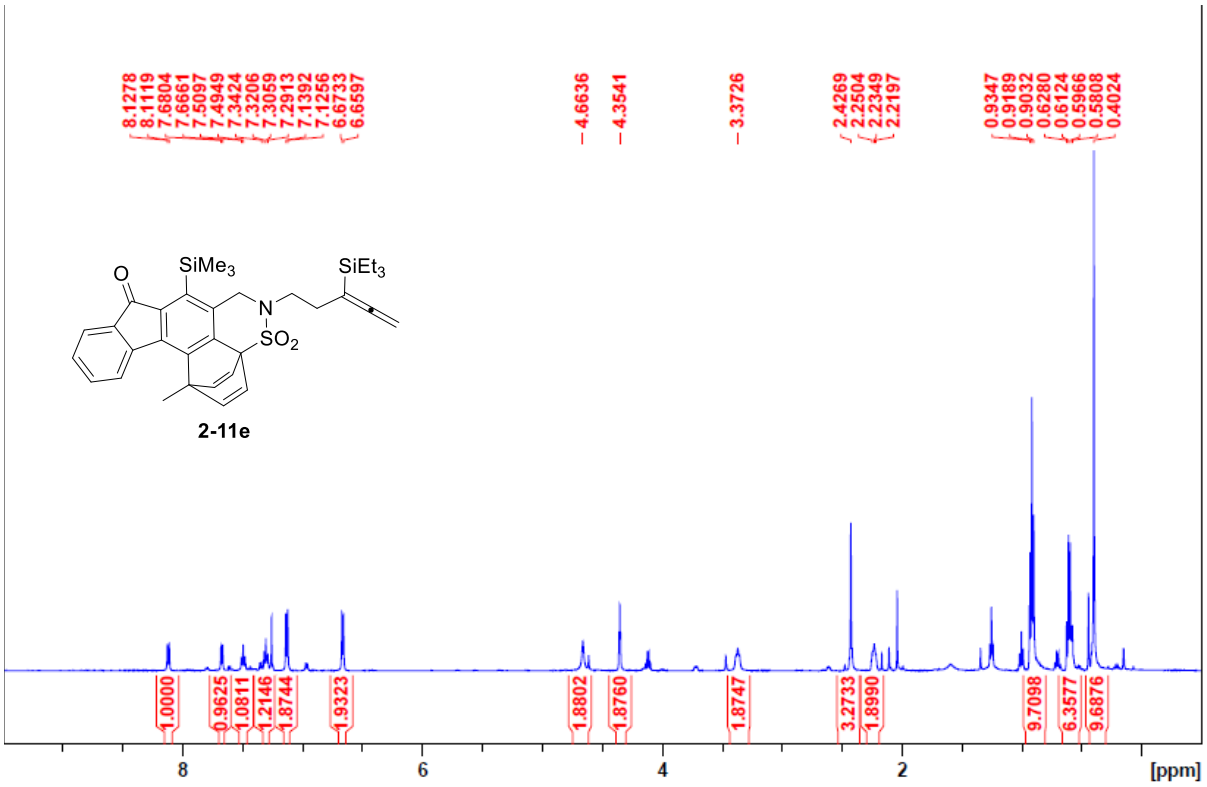

NTs
N
Ts
2-9h
[ppm]

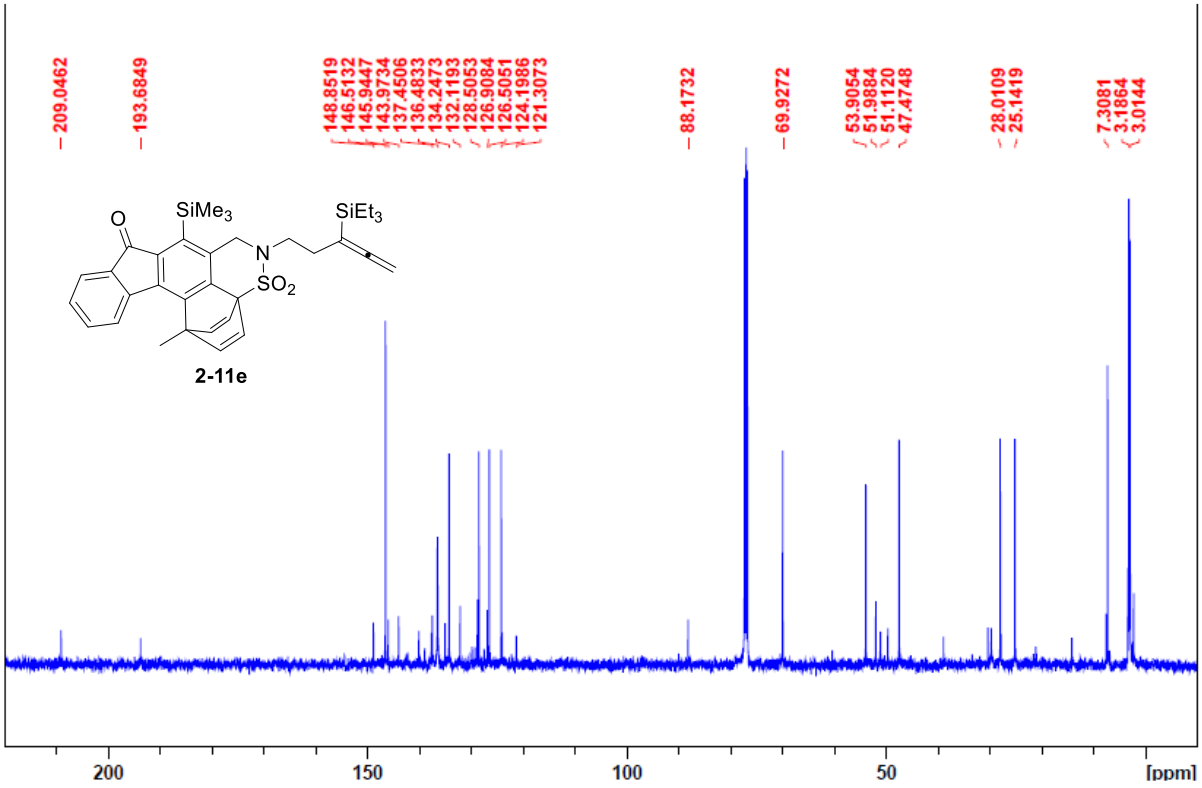

7.6151
7.6005
7.4783
7.4640
7.4488
7.4365
7.3069
7.3036
7.2926
7.2900
7.2791
7.0885
7.0725
4.9370
4.7033
3.9459
3.9408
3.9349
3.9296
3.6984
3.6794
2.2404
1.9312
1.8835
1.8790
1.7463
1.7385
1.7293
1.7200
1.7034
1.5946
0.8918
0.8807
0.8664
0.8538
0.8396
0.4923
SiMe3
O
NTs
2-11c
1.0000
4.9566
1.0752
1.9551
0.8916
0.7469
1.0282
1.7944
2.9369
2.8956
1.1772
2.3864
0.8469
8.9544
8
6
4
2
[ppm]

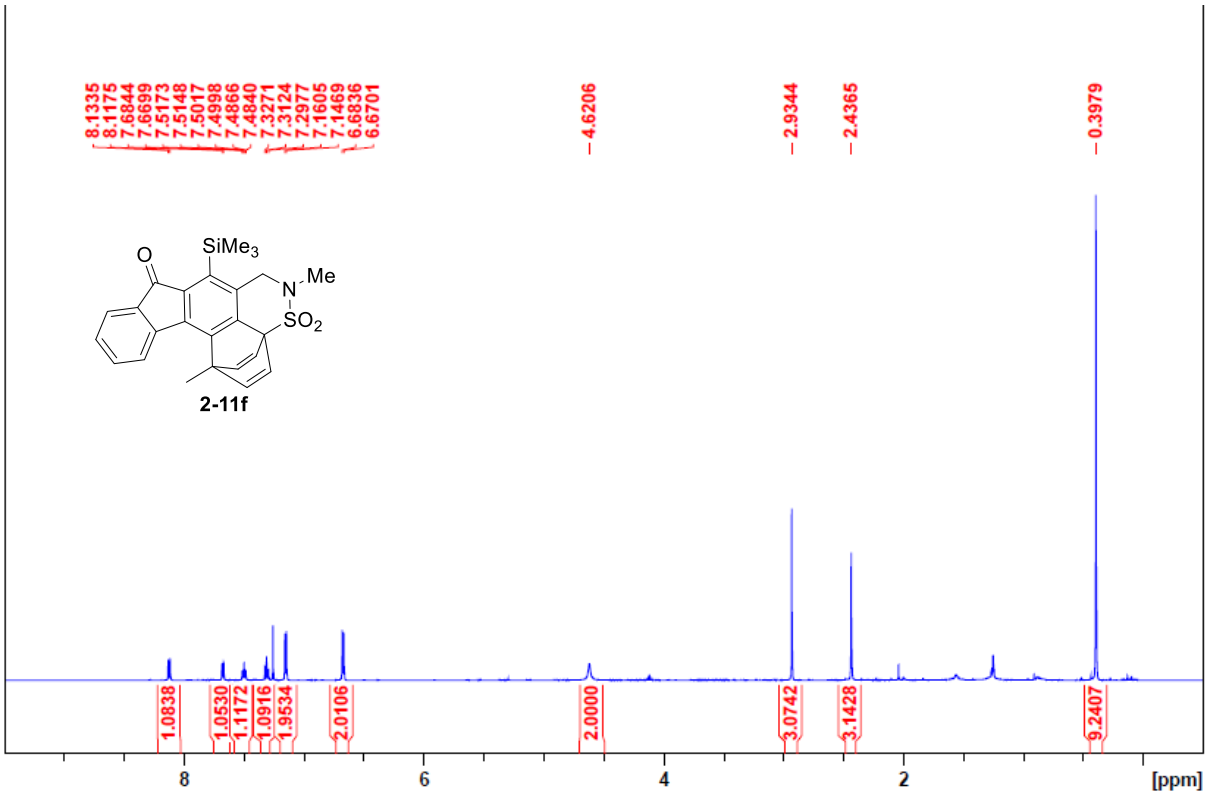

194.7650
146.7826
144.8022
143.3438
142.8581
138.8643
134.4190
134.0396
129.3869
129.0781
127.0133
123.9622
121.5247
119.6456
81.2480
51.0502
47.7830
29.7062
21.2983
3.7185
2.5451
SiMe3
O
NTs
2-11c
200
150
100
50
[ppm]

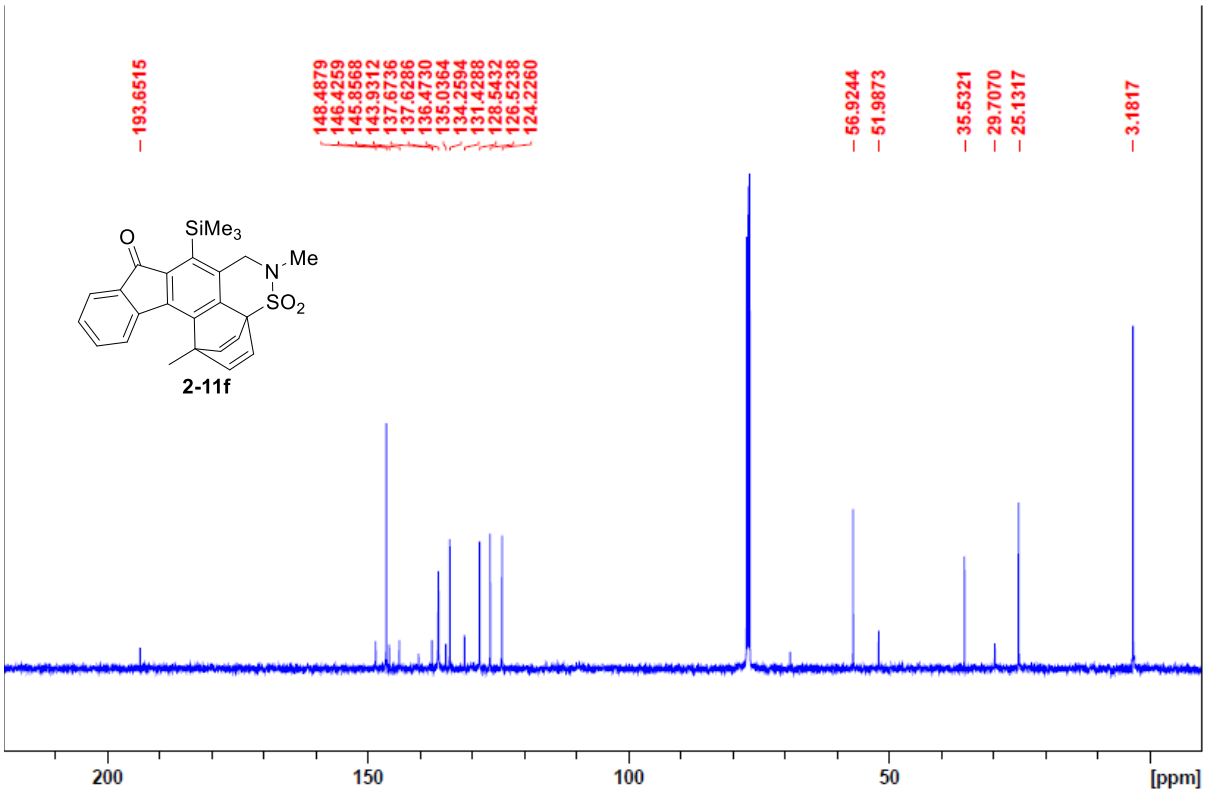

7.7683
7.7521
7.6256
7.6110
7.4701
7.4557
7.4417
7.4272
7.3237
7.3073
7.2924
7.2224
5.3128
5.2999
5.2874
4.9042
4.3816
4.2046
4.1829
3.5595
3.0254
2.4454
2.3891
1.9521
1.9235
1.7063
0.4704
O
SiMe3
Ts
N
2-11d
2.0000
1.0267
2.1162
0.9426
0.9849
1.9477
0.9574
0.9512
0.9871
0.9456
4.2700
0.9831
3.2291
8.9579
8
6
4
2
[ppm]

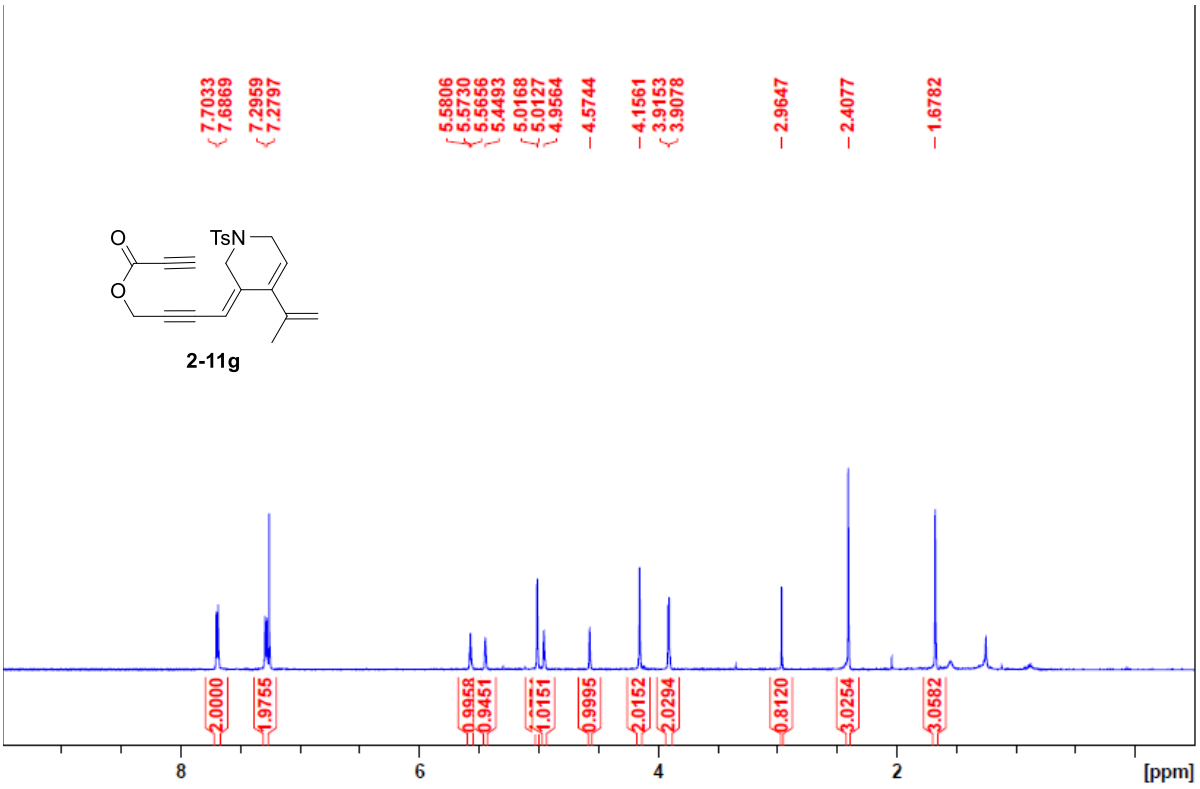

194.6015
148.2664
145.0168
144.3577
143.4346
143.3774
143.2125
143.0786
139.8105
137.3026
134.5040
134.1054
129.4904
129.2716
127.4856
126.8891
124.0653
122.7687
119.9314
115.9966
49.6704
42.9634
27.2789
21.4812
20.1950
2.2098
O
SiMe3
Ts
N
2-11d
200
150
100
50
[ppm]

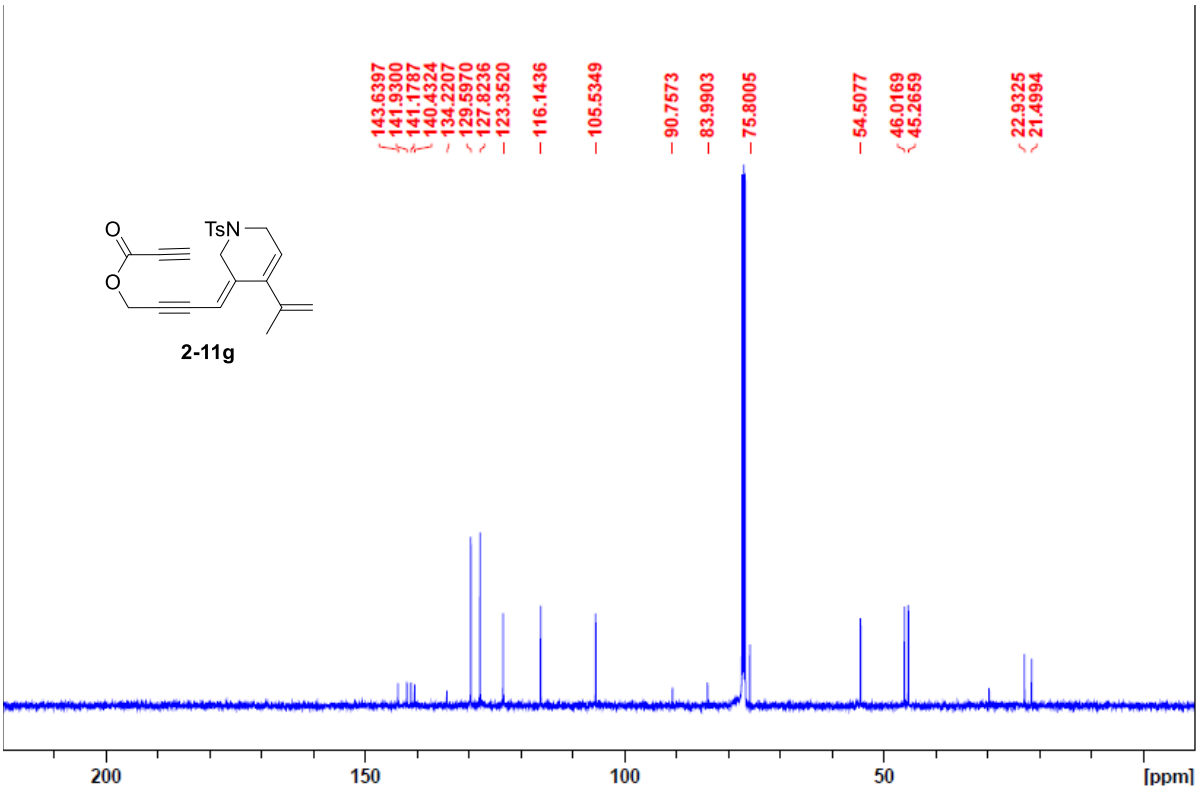

8.1278
8.1119
7.6804
7.6661
7.5097
7.4949
7.3424
7.3206
7.3059
7.2913
7.1392
7.1256
6.6733
6.6597
4.6636
4.3541
3.3726
2.4269
2.2504
2.2349
2.2197
0.9347
0.9189
0.9032
0.6280
0.6124
0.5966
0.5808
0.4024
SiMe3
SiEt3
O
N
SO2
2-11e
1.0000
0.9625
1.0811
1.2146
1.8744
1.9323
1.8802
1.8760
1.8747
3.2733
1.8990
9.7098
6.3577
9.6876
8
6
4
2
[ppm]

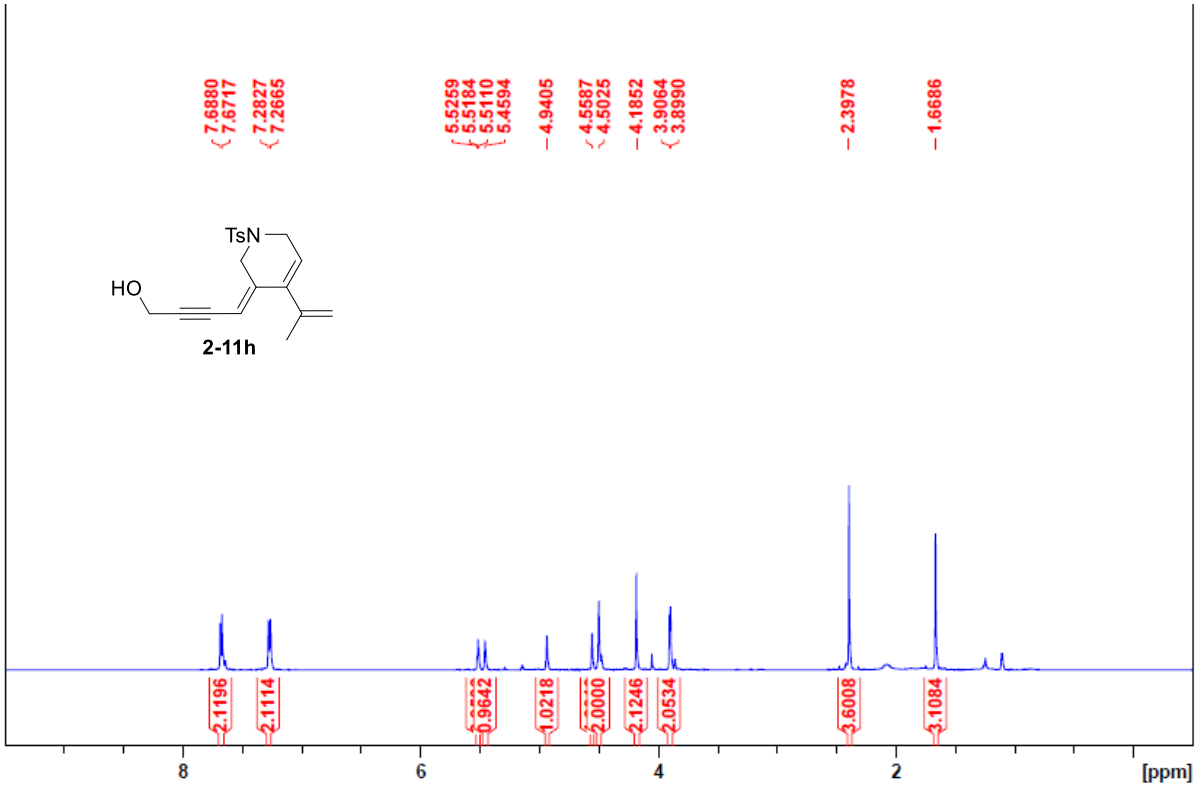

209.0462
193.6849
148.8519
146.5132
145.9447
143.9734
137.4506
136.4833
134.2473
132.1193
128.5053
126.9084
126.5051
124.1986
121.3073
88.1732
69.9272
53.9054
51.9884
51.1120
47.4748
28.0109
25.1419
7.3081
3.1864
3.0144
SiMe3
SiEt3
O
N
SO2
2-11e
200
150
100
50
[ppm]

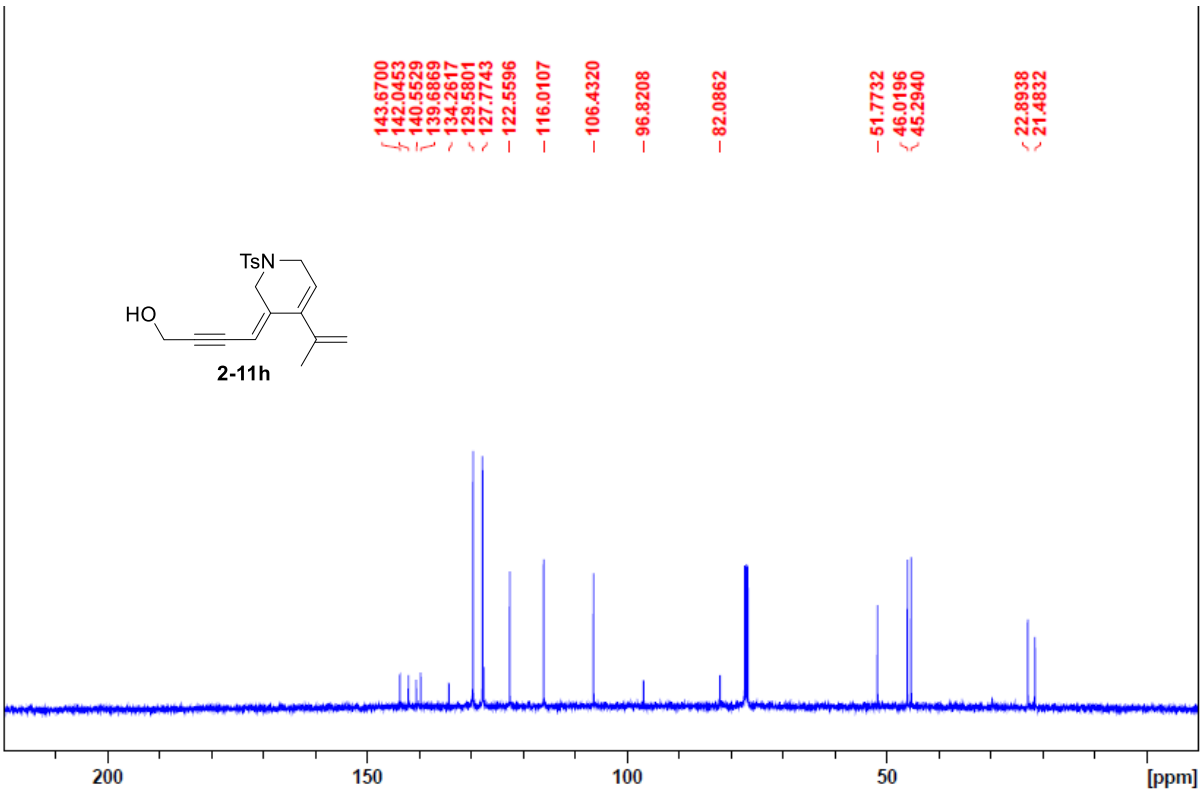

8.1335
8.1175
7.6844
7.6699
7.5173
7.5148
7.5017
7.4998
7.4866
7.4840
7.3271
7.3124
7.2977
7.1605
7.1469
6.6836
6.6701
4.6206
2.9344
2.4365
0.3979
SiMe3
O
N
Me
SO2
2-11f
1.0838
1.0530
1.1172
1.0916
1.9534
2.0106
2.0000
3.0742
3.1428
9.2407
8
6
4
2
[ppm]

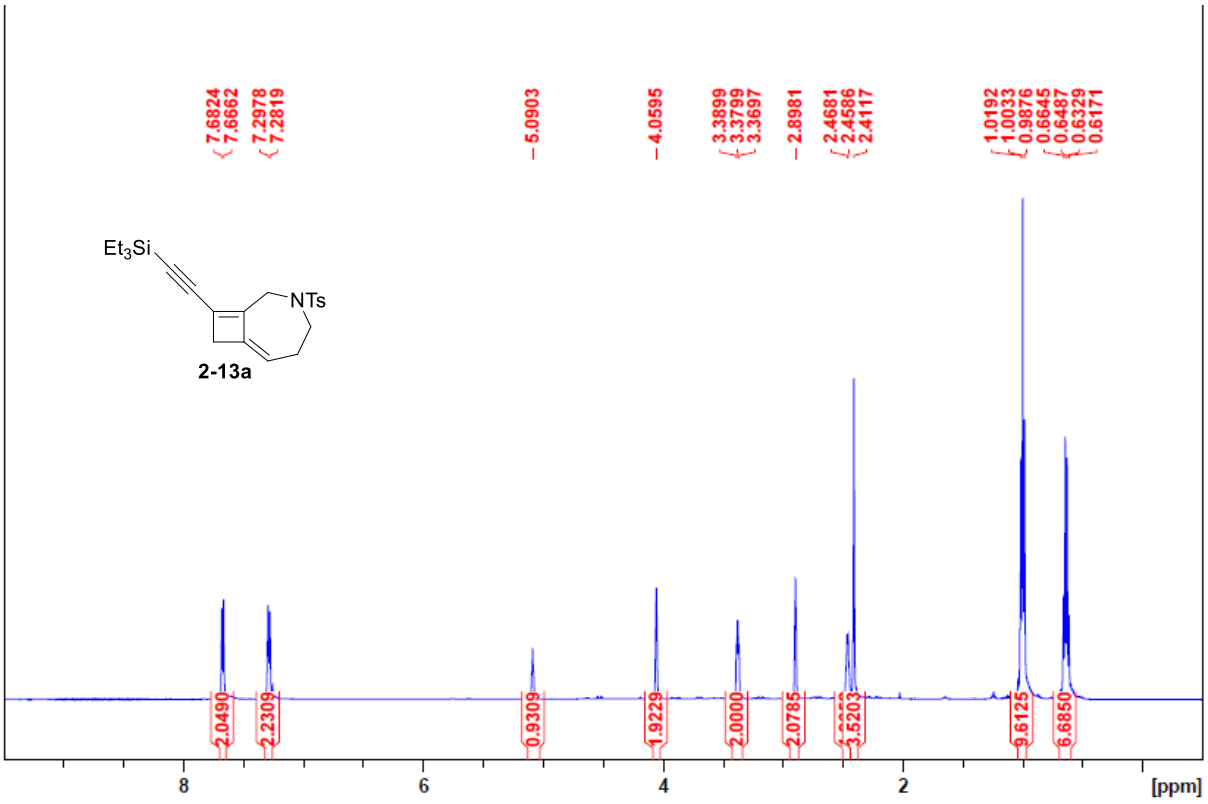

193.6515
148.4879
146.4259
145.8568
143.9312
137.6736
137.6286
136.4730
135.0364
134.2594
131.4288
128.5432
126.5238
124.2260
56.9244
51.9873
35.5321
29.7070
25.1317
3.1817
SiMe3
O
N
Me
SO2
2-11f
200
150
100
50
[ppm]

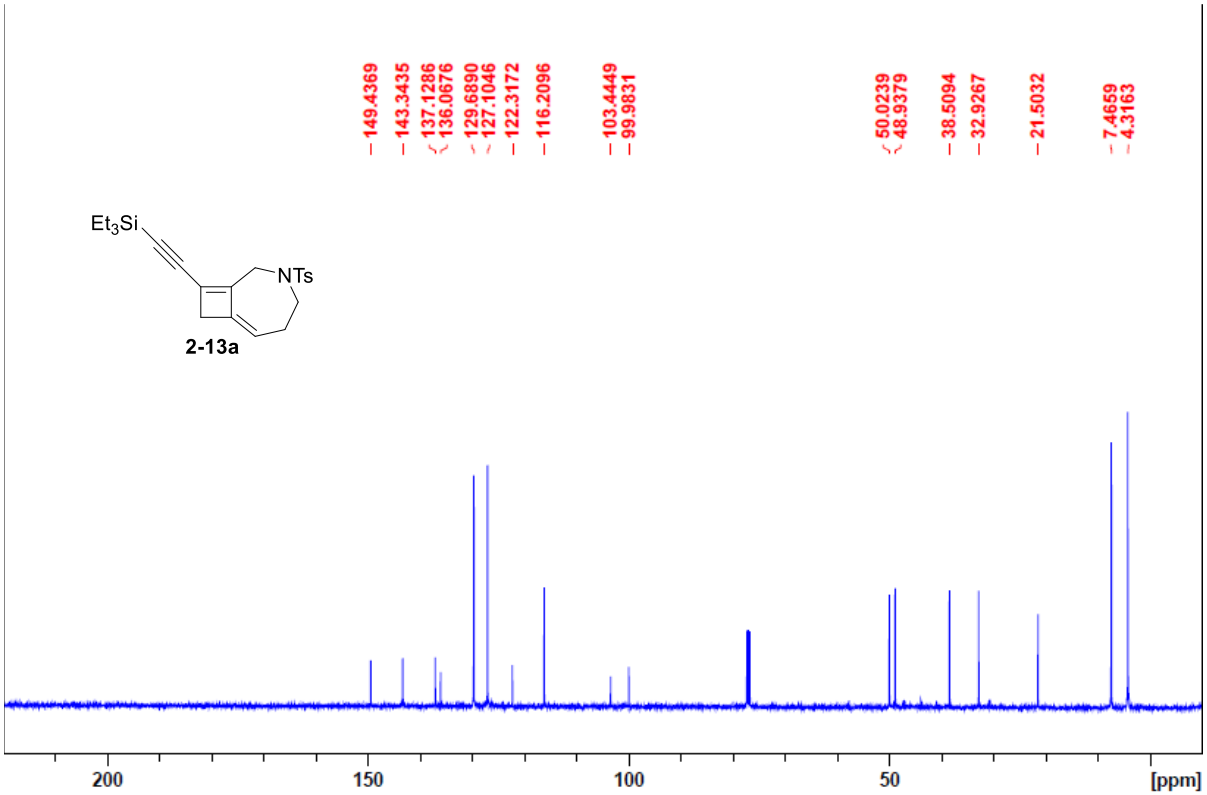

7.7033
7.6869
7.2959
7.2797
5.5806
5.5730
5.5656
5.4493
5.0168
5.0127
4.9564
4.5744
4.1561
3.9153
3.9078
2.9647
2.4077
1.6782
TsN
O
O
2-11g
2.0000
1.9755
0.9958
0.9451
1.0151
0.9995
2.0152
2.0294
0.8120
3.0254
3.0582
8
6
4
2
[ppm]

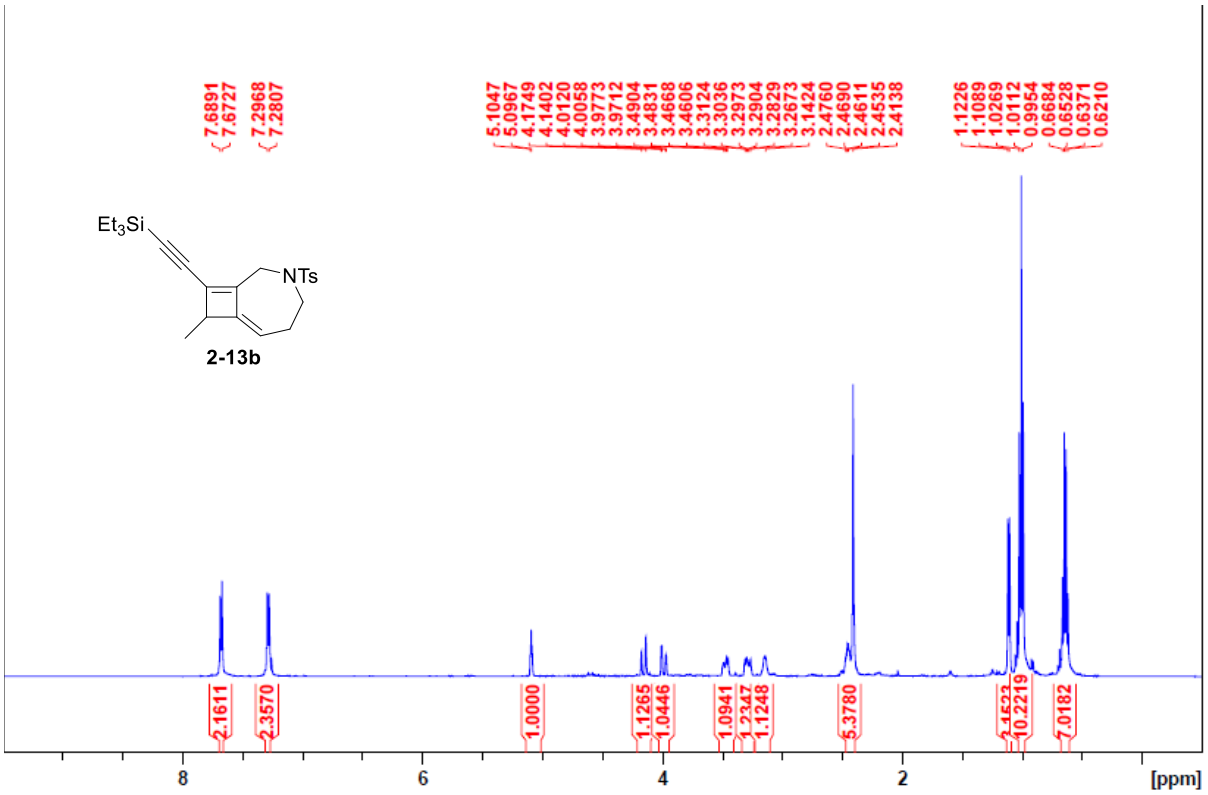

143.6397
141.9300
141.1787
140.4324
134.2207
129.5970
127.8236
123.3520
116.1436
105.5349
90.7573
83.9903
75.8005
54.5077
46.0169
45.2659
22.9325
21.4994
TsN
O
O
2-11g
200
150
100
50
[ppm]

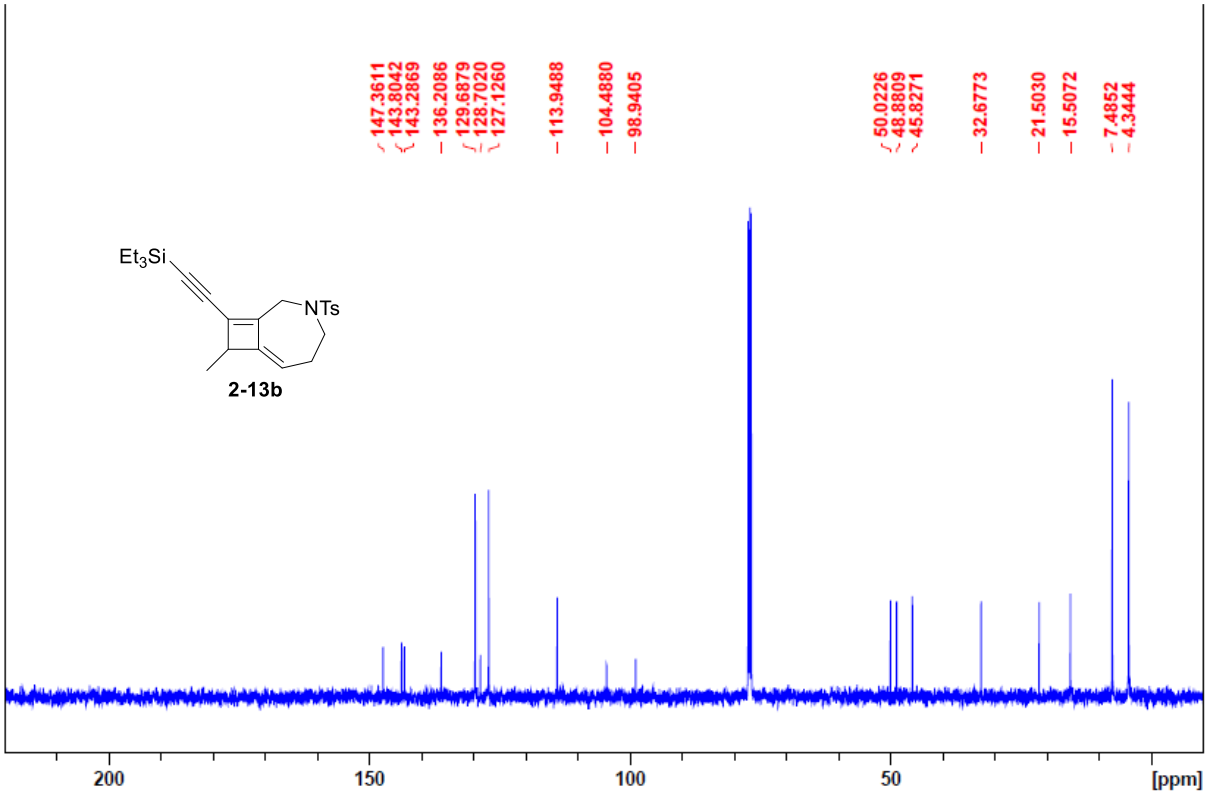

7.6880
7.6717
7.2827
7.2665
5.5259
5.5184
5.5110
5.4594
4.9405
4.5587
4.5025
4.1852
3.9064
3.8990
2.3978
1.6686
TsN
HO
2-11h
2.1196
2.1114
0.9642
1.0218
2.0000
2.1246
2.0534
3.6008
3.1084
8
6
4
2
[ppm]

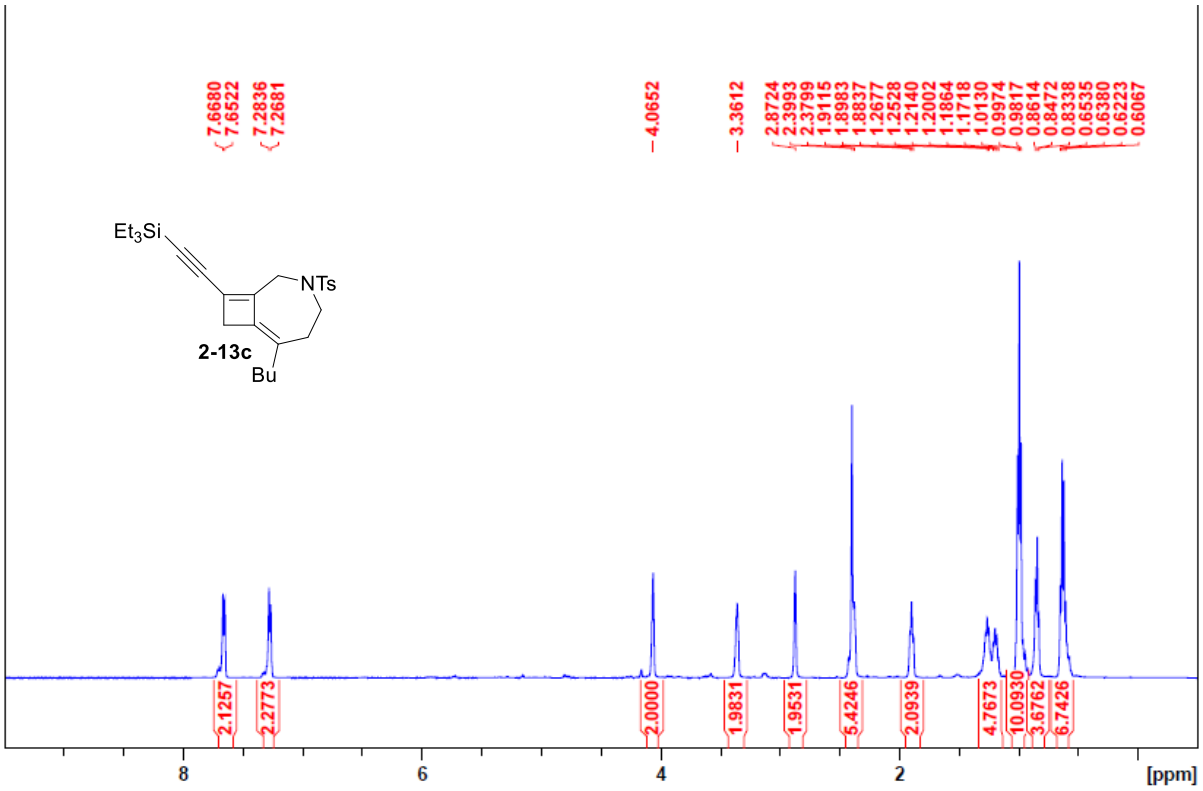

143.6700
142.0453
140.5529
139.6869
134.2617
129.5801
127.7743
122.5596
116.0107
106.4320
96.8208
82.0862
51.7732
46.0196
45.2940
22.8938
21.4832
TsN
HO
2-11h
200
150
100
50
[ppm]

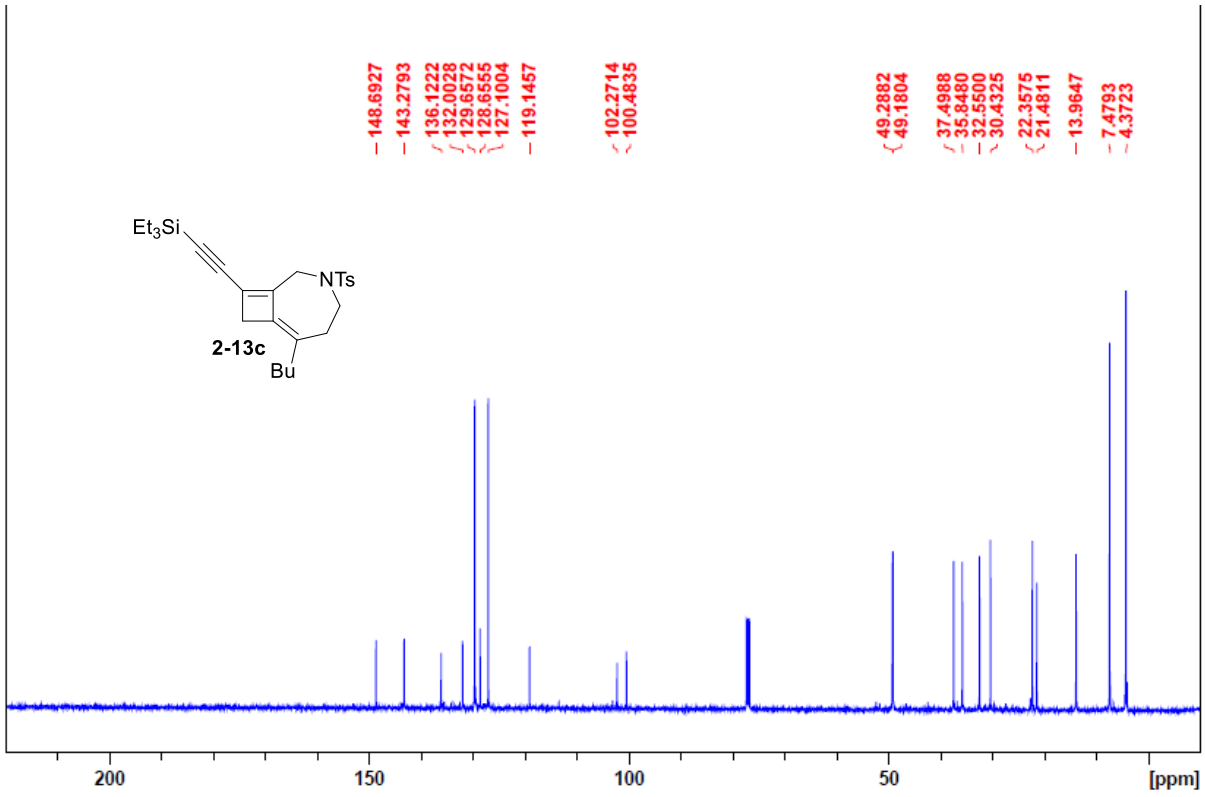

7.6824
7.6662
7.2978
7.2819
5.0903
4.0595
3.3899
3.3799
3.3697
2.8981
2.4681
2.4586
2.4117
1.0192
1.0033
0.9876
0.6645
0.6487
0.6329
0.6171
Et3Si
NTs
2-13a
2.0490
2.2309
0.9309
1.9229
2.0000
2.0785
4.5203
9.6125
6.6850
8
6
4
2
[ppm]

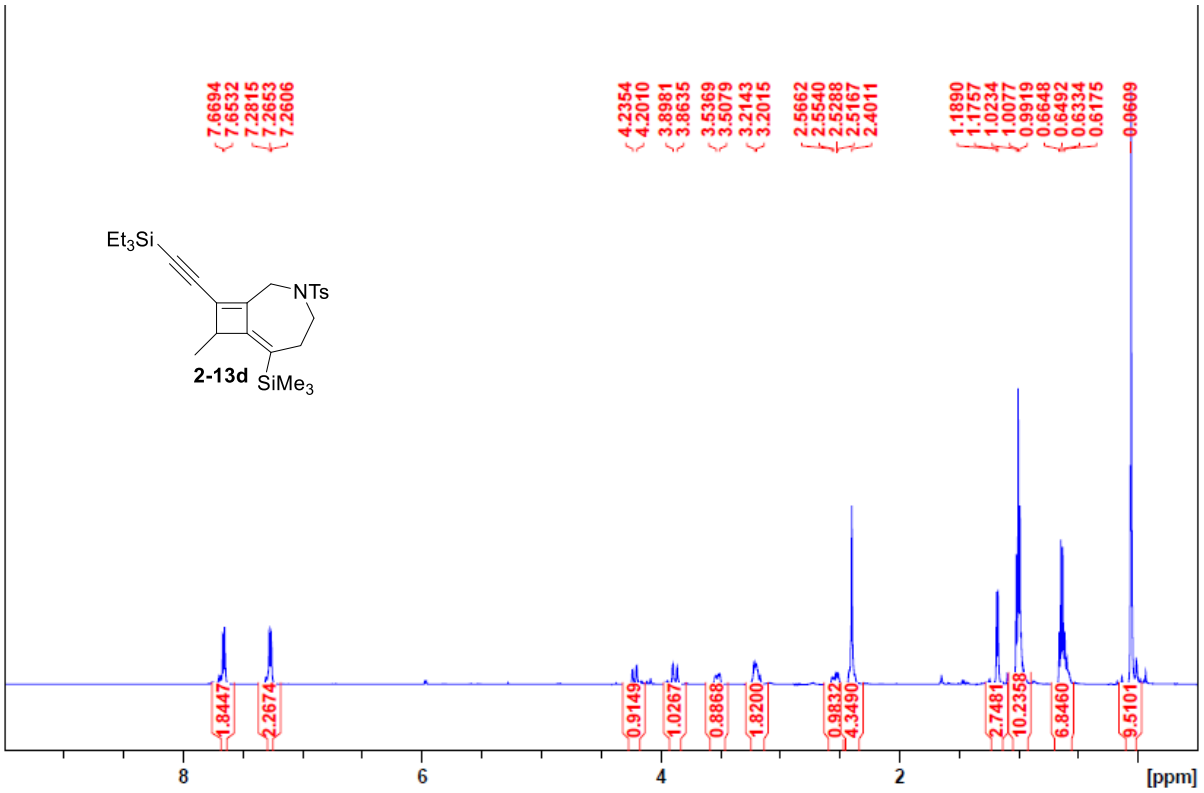

149.4369
143.3435
137.1286
136.0676
129.6890
127.1046
122.3172
116.2096
103.4449
99.9831
50.0239
48.9379
38.5094
32.9267
21.5032
7.4659
4.3163
Et3Si
NTs
2-13a
200
150
100
50
[ppm]

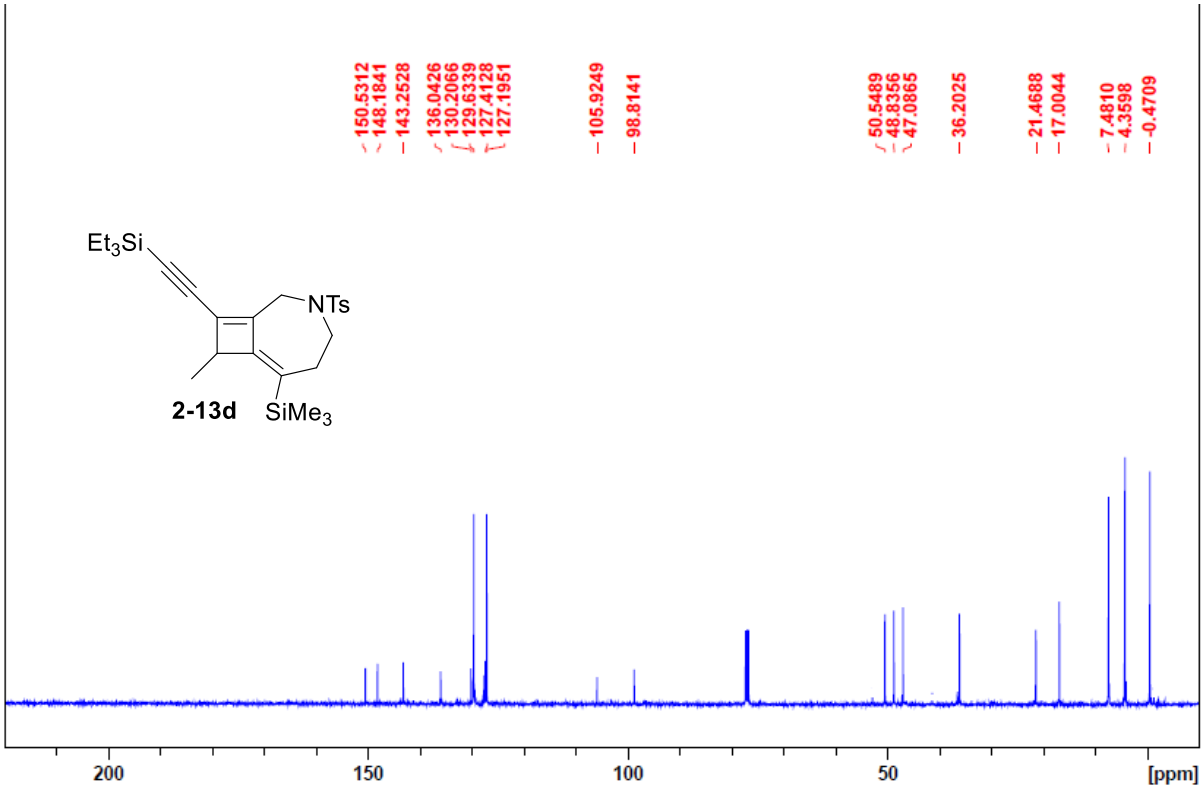

7.6891
7.6727
7.2968
7.2807
5.1047
5.0967
4.1749
4.1402
4.0120
4.0058
3.9773
3.9712
3.4904
3.4831
3.4668
3.4606
3.3124
3.3036
3.2973
3.2904
3.2829
3.2673
3.1424
2.4760
2.4690
2.4611
2.4535
2.4138
1.1226
1.1089
1.0269
1.0112
0.9954
0.6684
0.6528
0.6371
0.6210
Et3Si
NTs
2-13b
2.1611
2.3570
1.0000
1.1265
1.0446
1.0941
1.2347
1.1248
5.3780
2.1622
10.2219
7.0182
8
6
4
2
[ppm]

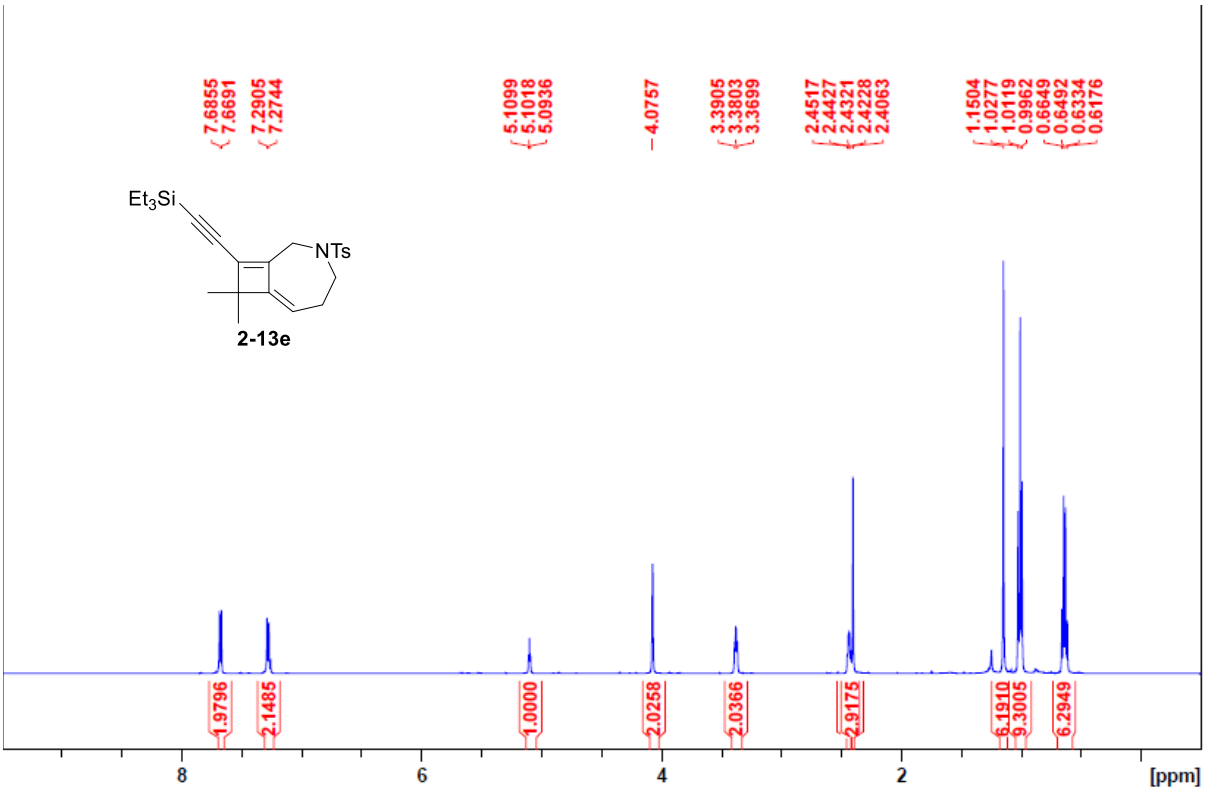

147.3611
143.8042
143.2869
136.2086
129.6879
128.7020
127.1260
113.9488
104.4880
98.9405
50.0226
48.8809
45.8271
32.6773
21.5030
15.5072
7.4852
4.3444
Et3Si
NTs
2-13b
200
150
100
50
[ppm]

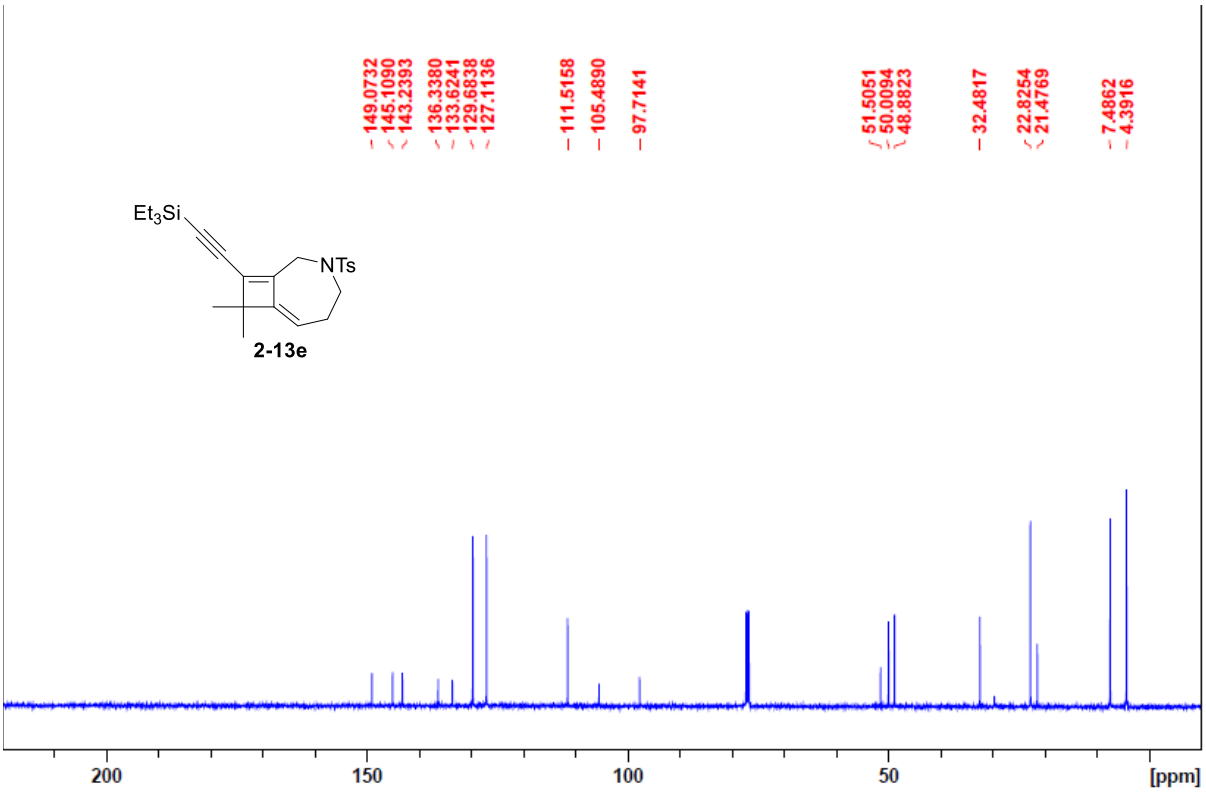

7.6680
7.6522
7.2836
7.2681
4.0652
3.3612
2.8724
2.3993
2.3799
1.9115
1.8983
1.8837
1.2677
1.2528
1.2140
1.2002
1.1864
1.1718
1.0130
0.9974
0.9817
0.8614
0.8472
0.8338
0.6535
0.6380
0.6223
0.6067
Et3Si
NTs
2-13c
Bu
2.1257
2.2773
2.0000
1.9831
1.9531
5.4246
2.0939
4.7673
10.0930
3.6762
6.7426
8
6
4
2
[ppm]

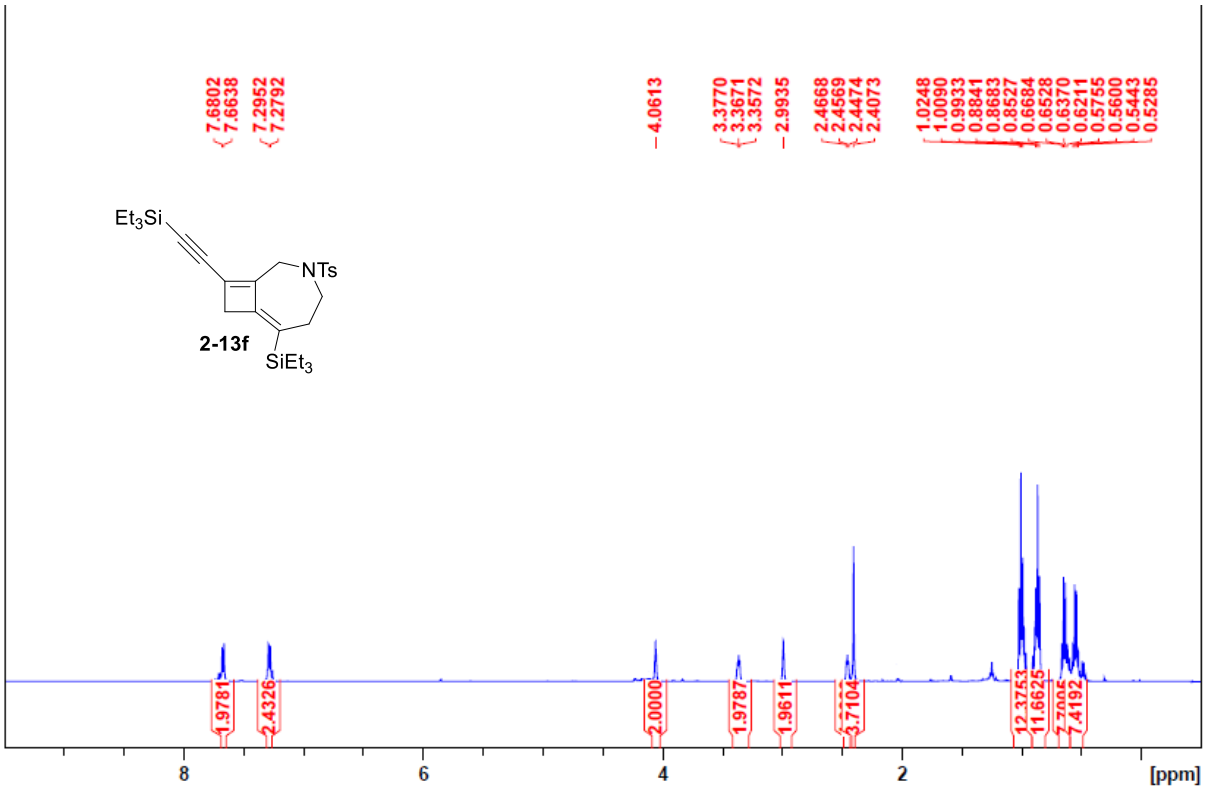

148.6927
143.2793
136.1222
132.0028
129.6572
128.6555
127.1004
119.1457
102.2714
100.4835
49.2882
49.1804
37.4988
35.8480
32.5500
30.4325
22.3575
21.4811
13.9647
7.4793
4.3723
Et3Si
NTs
2-13c
Bu
200
150
100
50
[ppm]

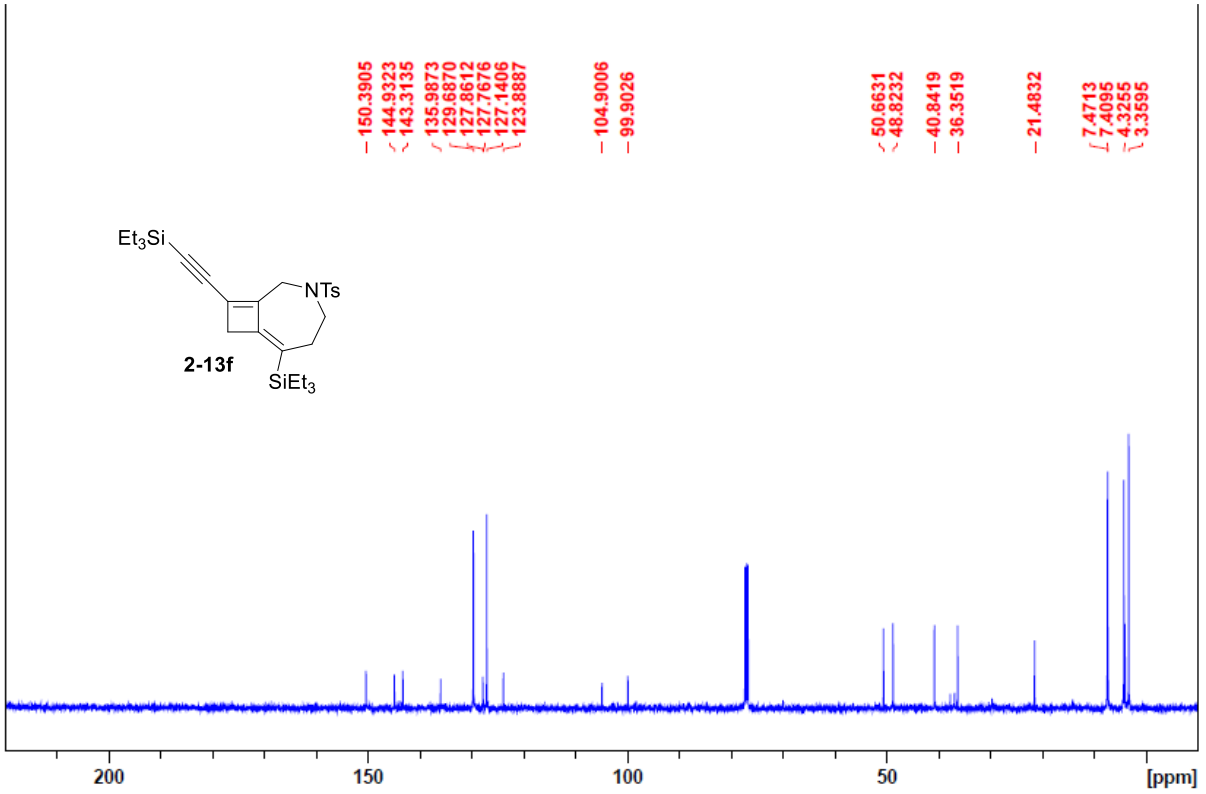

7.6694
7.6532
7.2815
7.2653
7.2606
4.2354
4.2010
3.8981
3.8635
3.5369
3.5079
3.2143
3.2015
2.5662
2.5540
2.5288
2.5167
2.4011
1.1890
1.1757
1.0234
1.0077
0.9919
0.6648
0.6492
0.6334
0.6175
0.0609
Et3Si
NTs
2-13d
SiMe3
1.8447
2.2674
0.9149
1.0267
0.8868
1.8200
0.9832
4.3490
2.7481
10.2358
6.8460
9.5101
8
6
4
2
[ppm]


150.5312
148.1841
143.2528
136.0426
130.2066
129.6339
127.4128
127.1951
105.9249
98.8141
50.5489
48.8356
47.0865
36.2025
21.4688
17.0044
7.4810
4.3598
-0.4709
Et3Si
NTs
2-13d
SiMe3
200
150
100
50
[ppm]


7.6855
7.6691
7.2905
7.2744
5.1099
5.1018
5.0936
4.0757
3.3905
3.3803
3.3699
2.4517
2.4427
2.4321
2.4228
2.4063
1.1504
1.0277
1.0119
0.9962
0.6649
0.6492
0.6334
0.6176
Et3Si
NTs
2-13e
1.9796
2.1485
1.0000
2.0258
2.0366
2.9175
6.1910
9.3005
6.2949
8
6
4
2
[ppm]

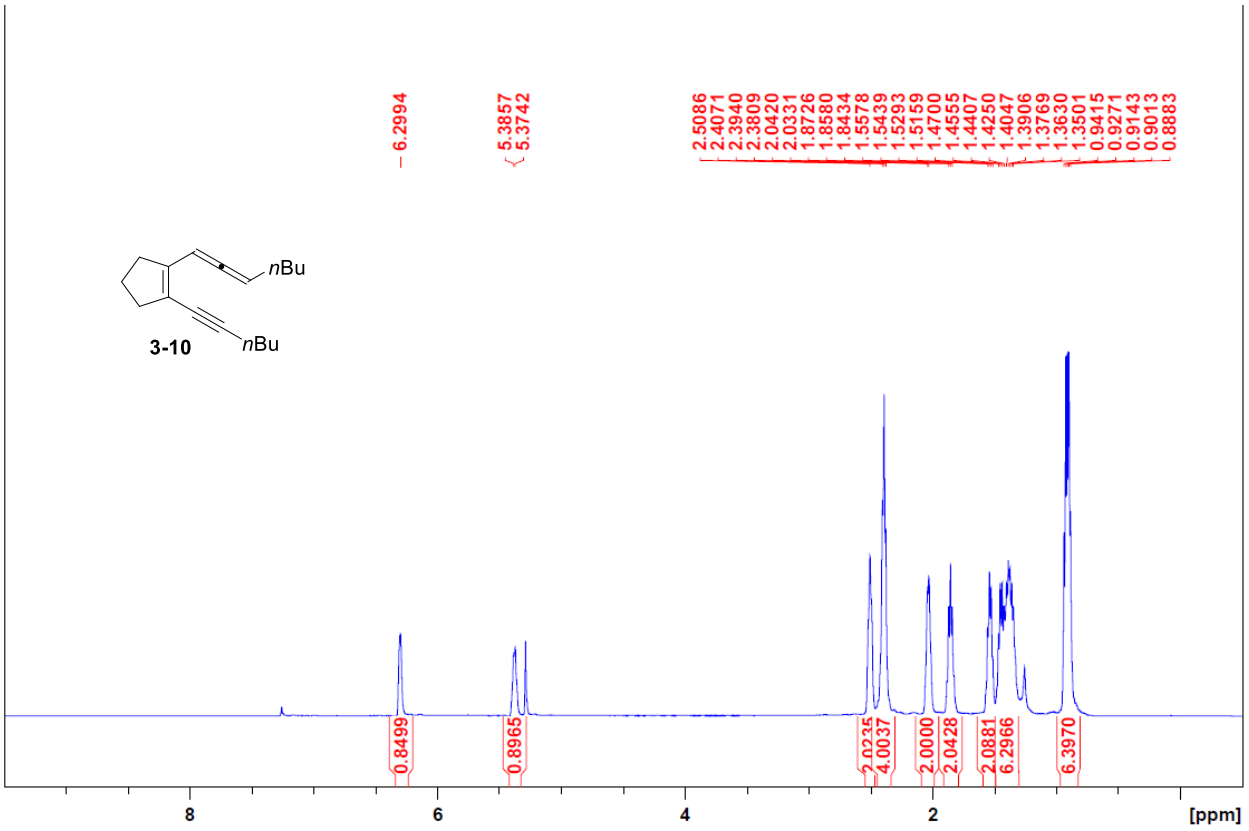

149.0732
145.1090
143.2393
136.3380
133.6241
129.6838
127.1136
111.5158
105.4890
97.7141
51.5051
50.0094
48.8823
32.4817
22.8254
21.4769
7.4862
4.3916
Et3Si
NTs
2-13e
200
150
100
50
[ppm]

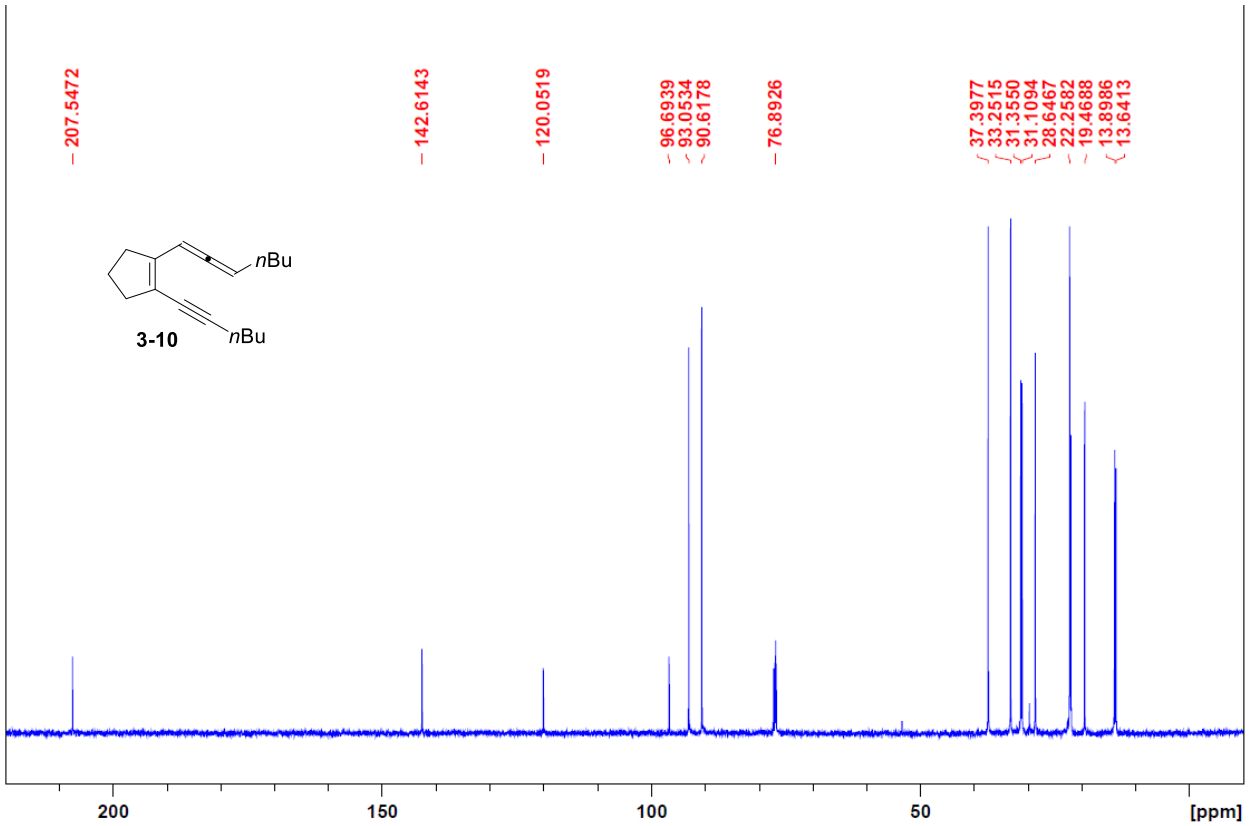

7.6802
7.6638
7.2952
7.2792
4.0613
3.3770
3.3671
3.3572
2.9935
2.4668
2.4569
2.4474
2.4073
1.0248
1.0090
0.9933
0.8841
0.8683
0.8527
0.6684
0.6528
0.6370
0.6211
0.5755
0.5600
0.5443
0.5285
Et3Si
NTs
2-13f
SiEt3
1.9781
2.4326
2.0000
1.9787
1.9611
3.7104
12.3753
11.6625
7.4192
8
6
4
2
[ppm]

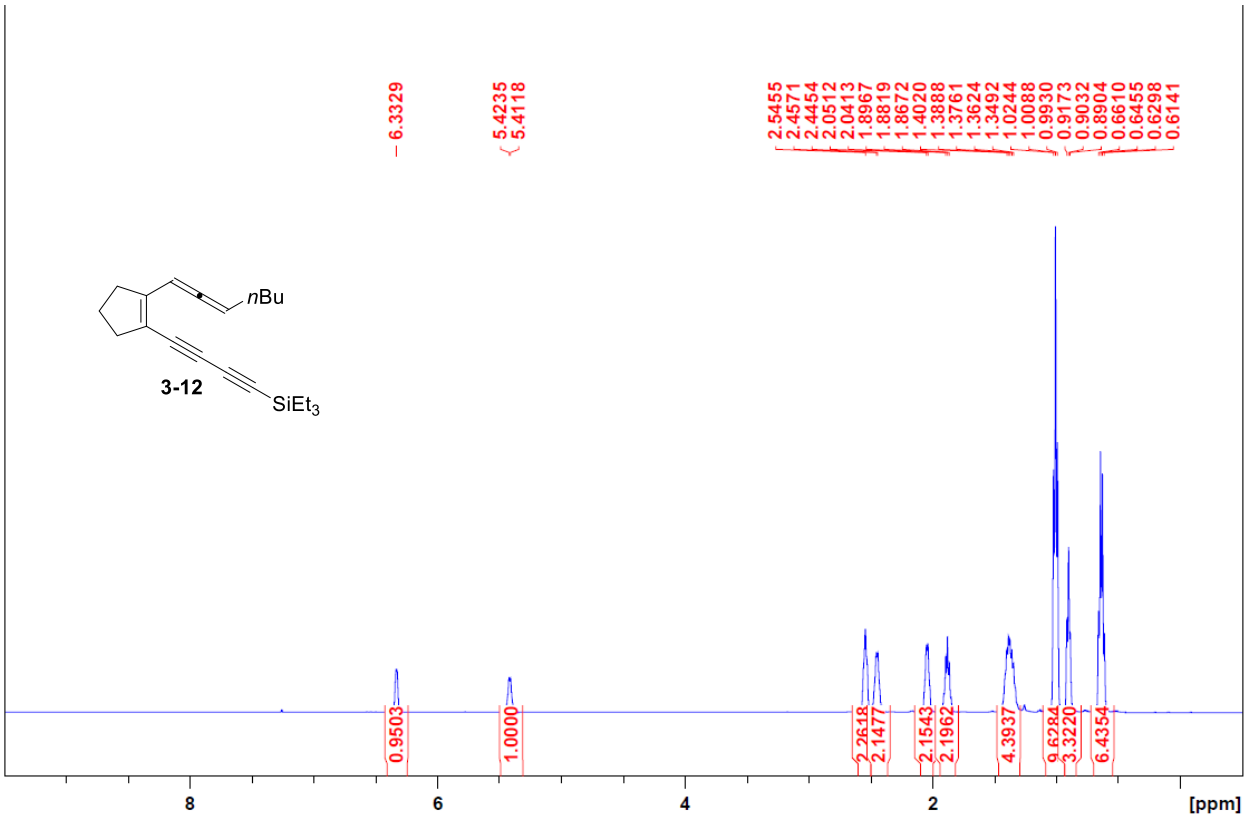

150.3905
144.9323
143.3135
135.9873
129.6870
127.8612
127.7676
127.1406
123.8887
104.9006
99.9026
50.6631
48.8232
40.8419
36.3519
21.4832
7.4713
7.4095
4.3255
3.3595
Et3Si
NTs
2-13f
SiEt3
200
150
100
50
[ppm]

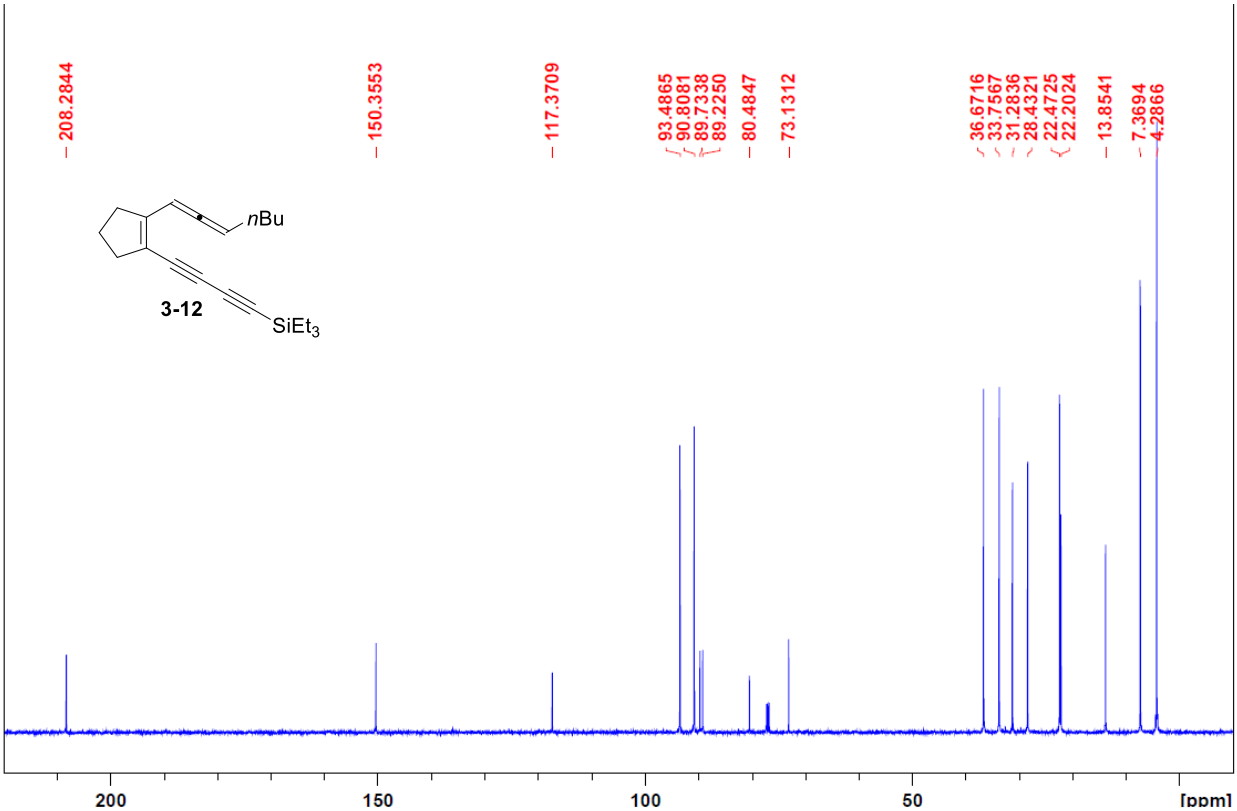
Appendix II

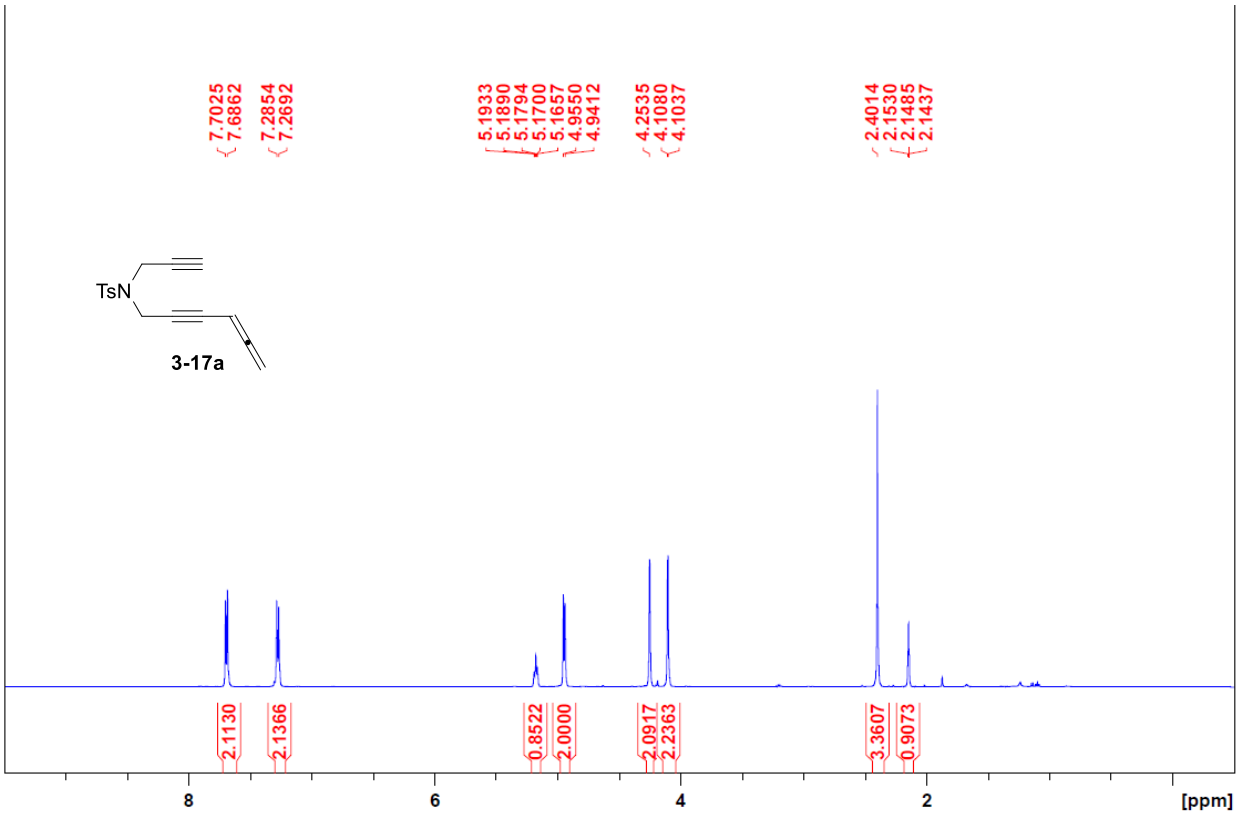
Selected NMR Spectra for Chapter 3

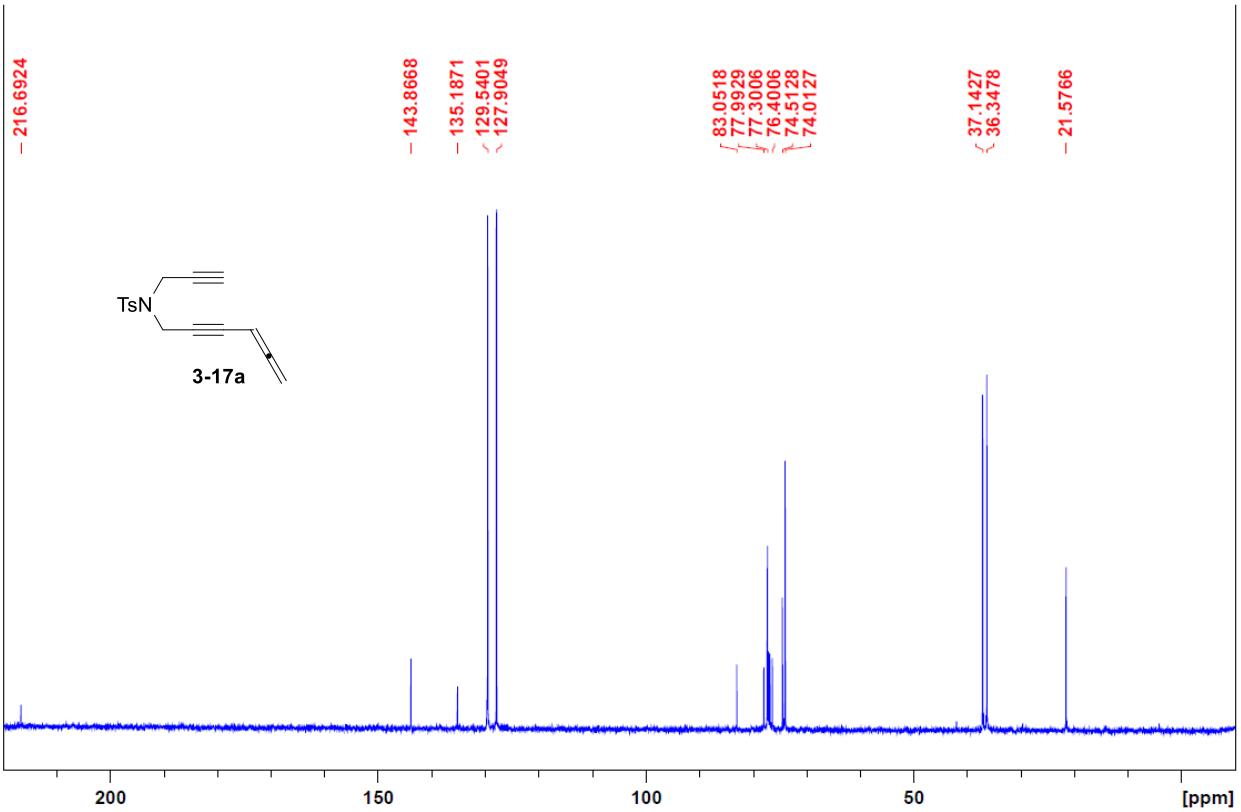

6.2994
5.3857
5.3742
2.5086
2.4071
2.3940
2.3809
2.0420
2.0331
1.8726
1.8580
1.8434
1.5578
1.5439
1.5293
1.5159
1.4700
1.4555
1.4407
1.4250
1.4047
1.3906
1.3769
1.3630
1.3501
0.9415
0.9271
0.9143
0.9013
0.8883
nBu
nBu
3-10
0.8499
0.8965
2.0235
4.0037
2.0000
2.0428
2.0881
6.2966
6.3970
8
6
4
2
[ppm]

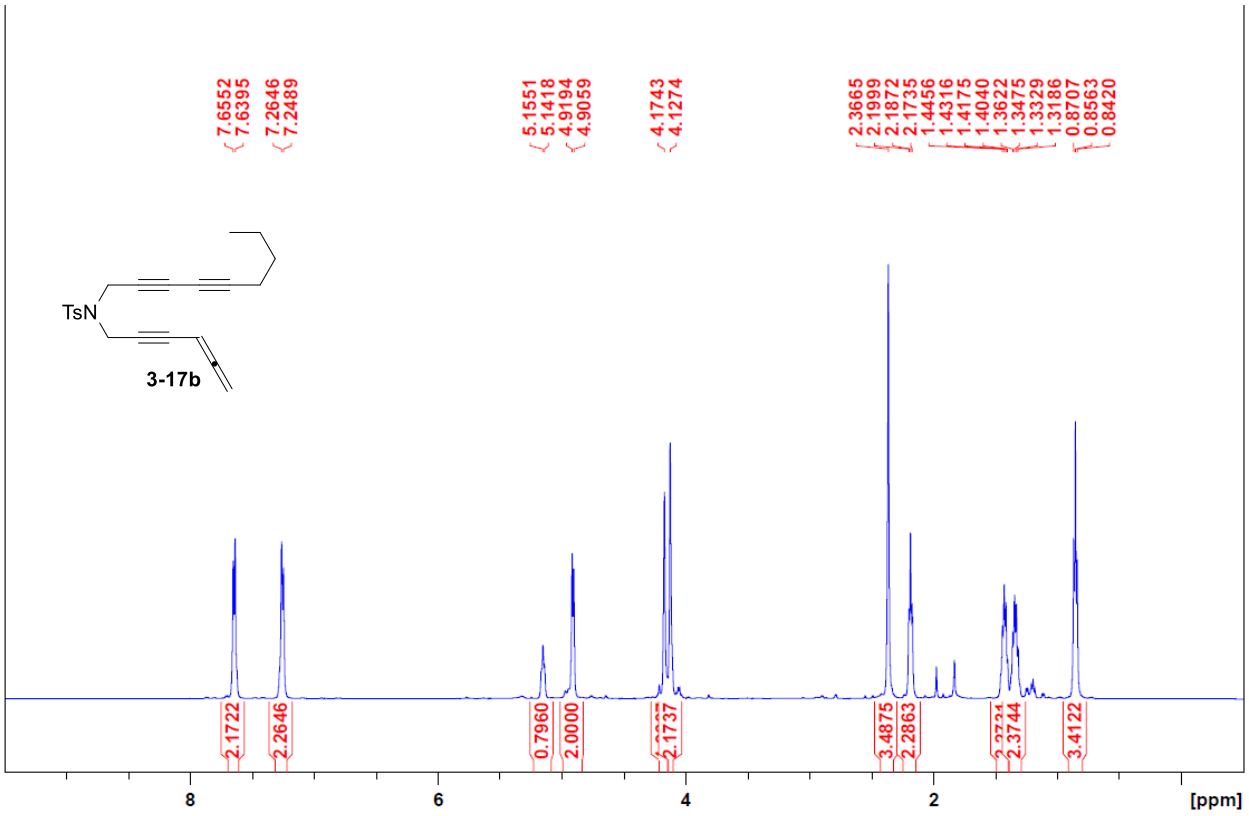

207.5472
142.6143
120.0519
96.6939
93.0534
90.6178
76.8926
37.3977
33.2515
31.3550
31.1094
28.6467
22.2582
19.4688
13.8986
13.6413
nBu
nBu
3-10
200
150
100
50
[ppm]

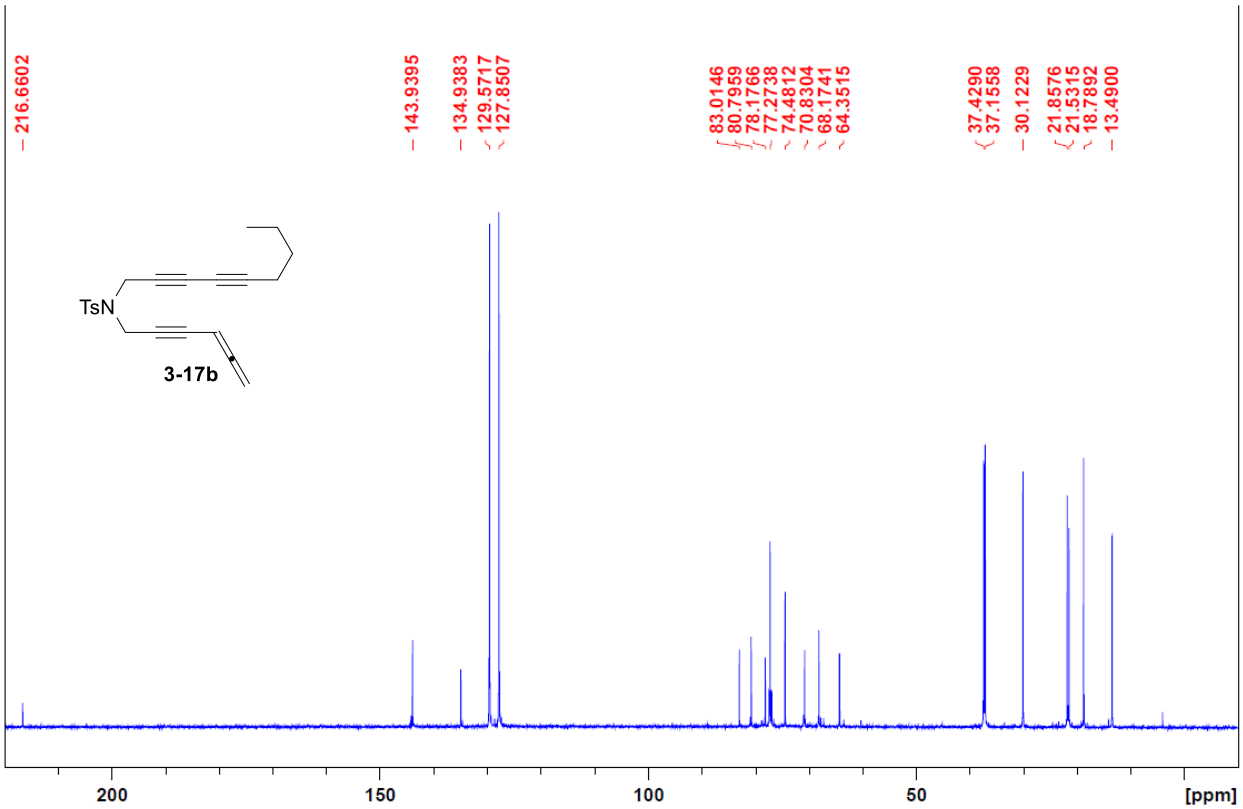

6.3329
5.4235
5.4118
2.5455
2.4571
2.4454
2.0512
2.0413
1.8967
1.8819
1.8672
1.4020
1.3888
1.3761
1.3624
1.3492
1.0244
1.0088
0.9930
0.9173
0.9032
0.8904
0.6610
0.6455
0.6298
0.6141
nBu
3-12
SiEt3
0.9503
1.0000
2.2618
2.1477
2.1543
2.1962
4.3937
9.6284
3.3220
6.4354
8
6
4
2
[ppm]

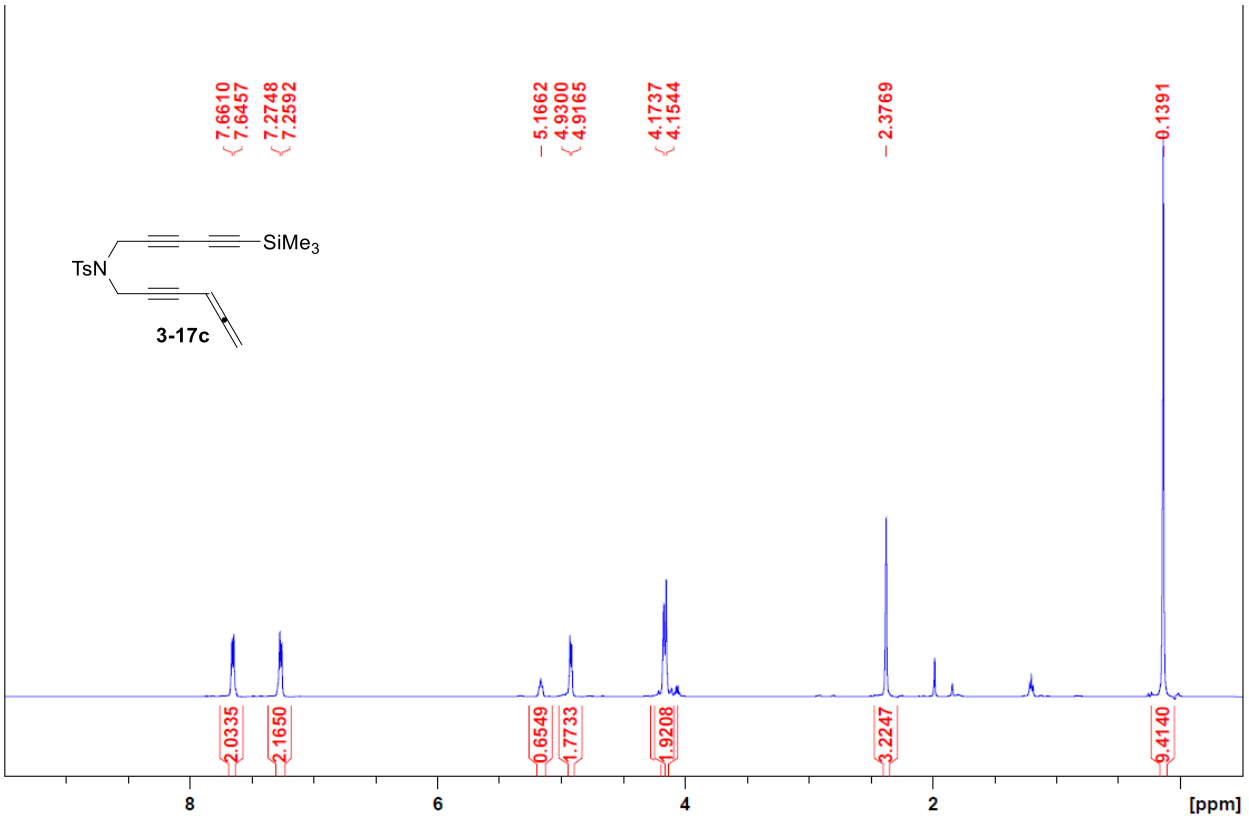

208.2844
150.3553
117.3709
93.4865
90.8081
89.7338
89.2250
80.4847
73.1312
36.6716
33.7567
31.2836
28.4321
22.4725
22.2024
13.8541
7.3694
4.2866
nBu
3-12
SiEt3
200
150
100
50
[ppm]

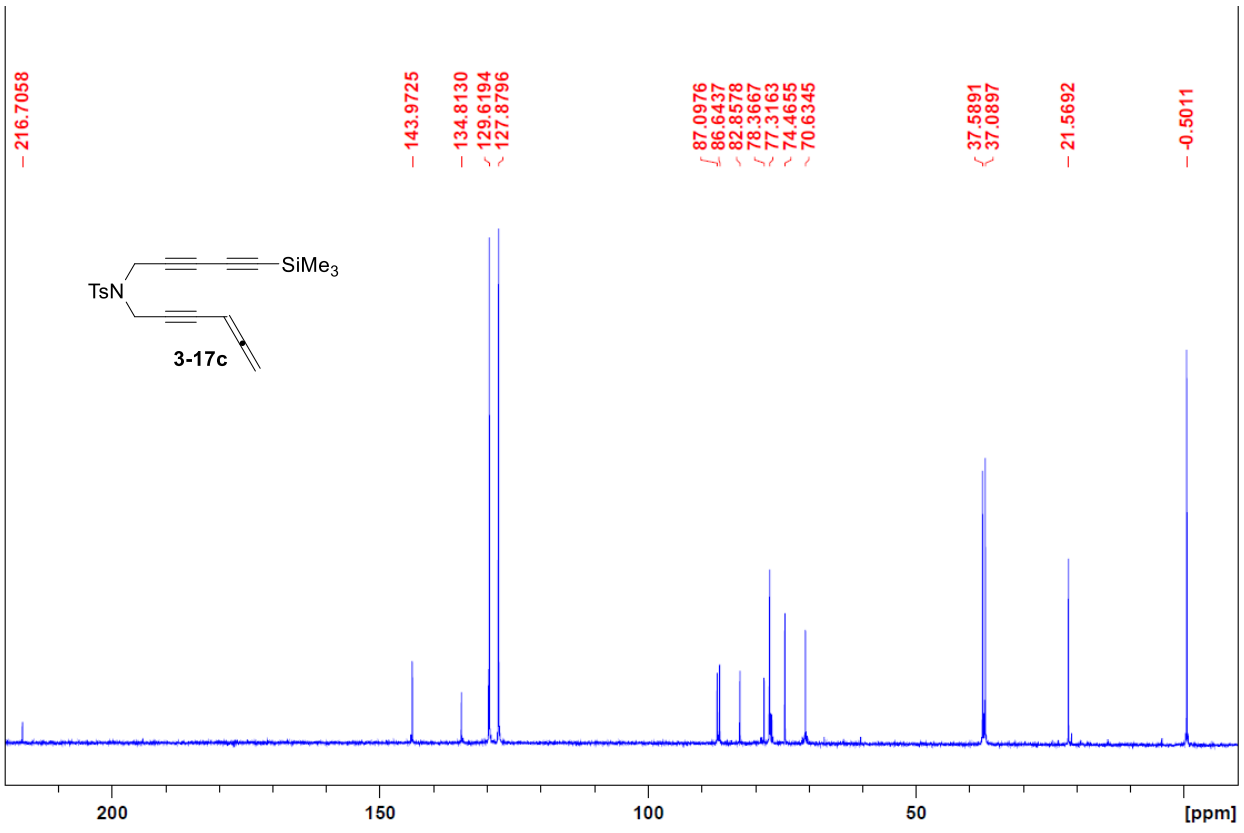

7.7025
7.6862
7.2854
7.2692
5.1933
5.1890
5.1794
5.1700
5.1657
4.9550
4.9412
4.2535
4.1080
4.1037
2.4014
2.1530
2.1485
2.1437
TsN
3-17a
2.1130
2.1366
0.8522
2.0000
2.0917
2.2363
3.3607
0.9073
8
6
4
2
[ppm]

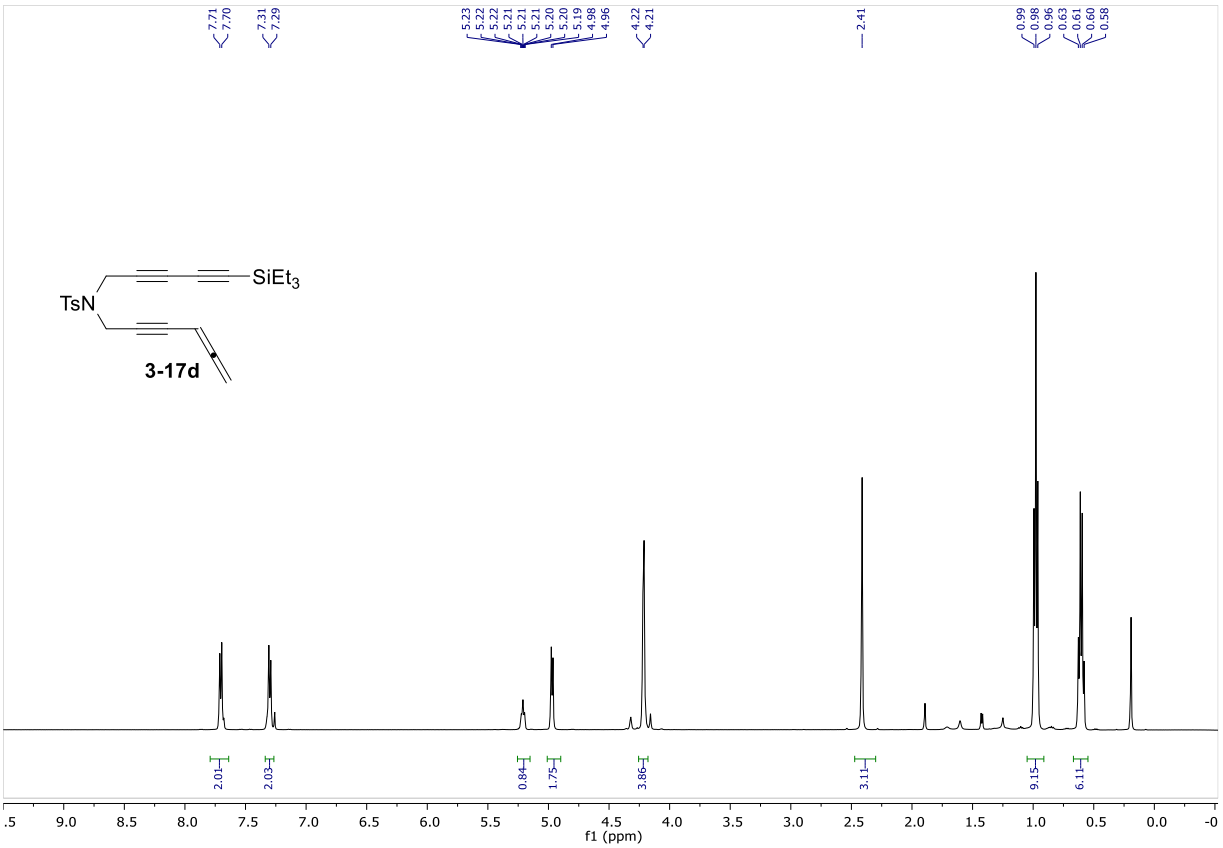

216.6924
143.8668
135.1871
129.5401
127.9049
83.0518
77.9929
77.3006
76.4006
74.5128
74.0127
37.1427
36.3478
21.5766
TsN
3-17a
200
150
100
50
[ppm]

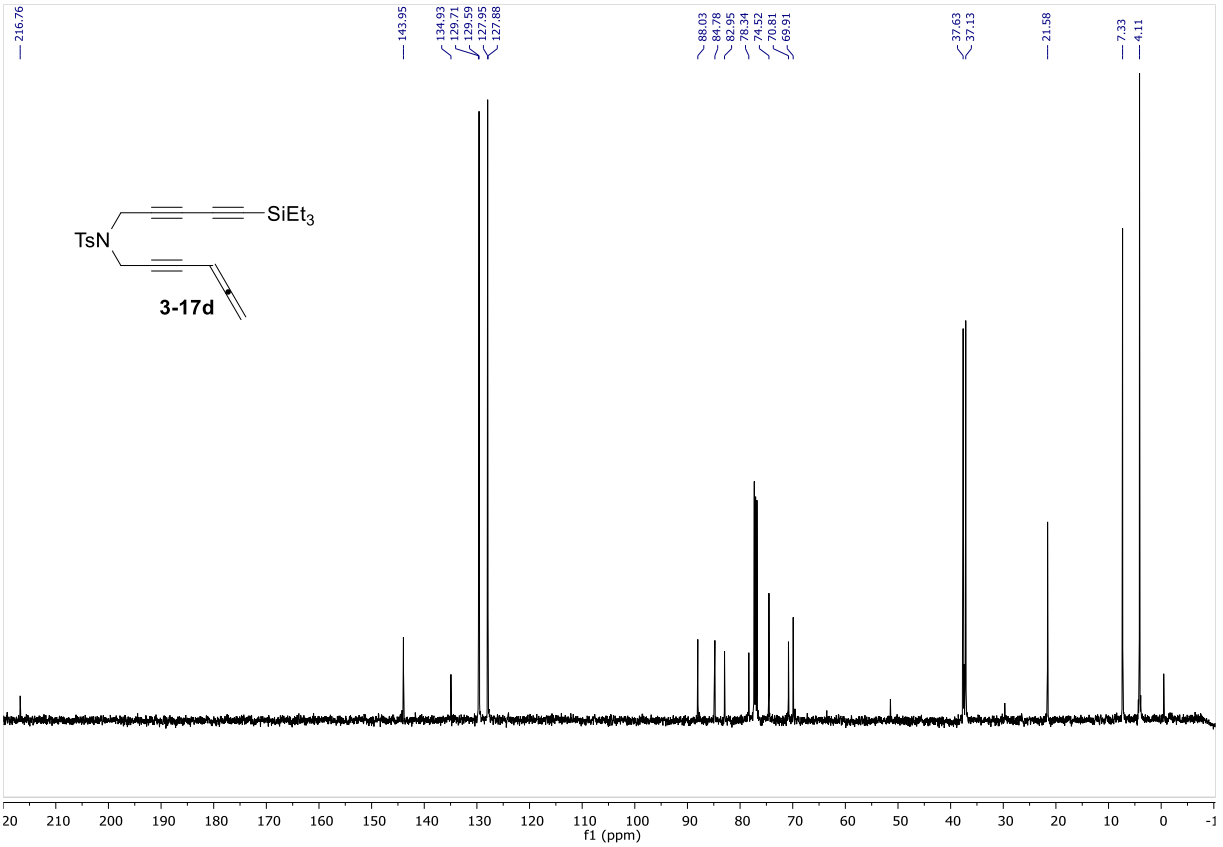

7.6552
7.6395
7.2646
7.2489
5.1551
5.1418
4.9194
4.9059
4.1743
4.1274
2.3665
2.1999
2.1872
2.1735
1.4456
1.4316
1.4175
1.4040
1.3622
1.3475
1.3329
1.3186
0.8707
0.8563
0.8420
TsN
3-17b
2.1722
2.2646
0.7960
2.0000
2.1737
3.4875
2.2863
3.4122
8
6
4
2
[ppm]

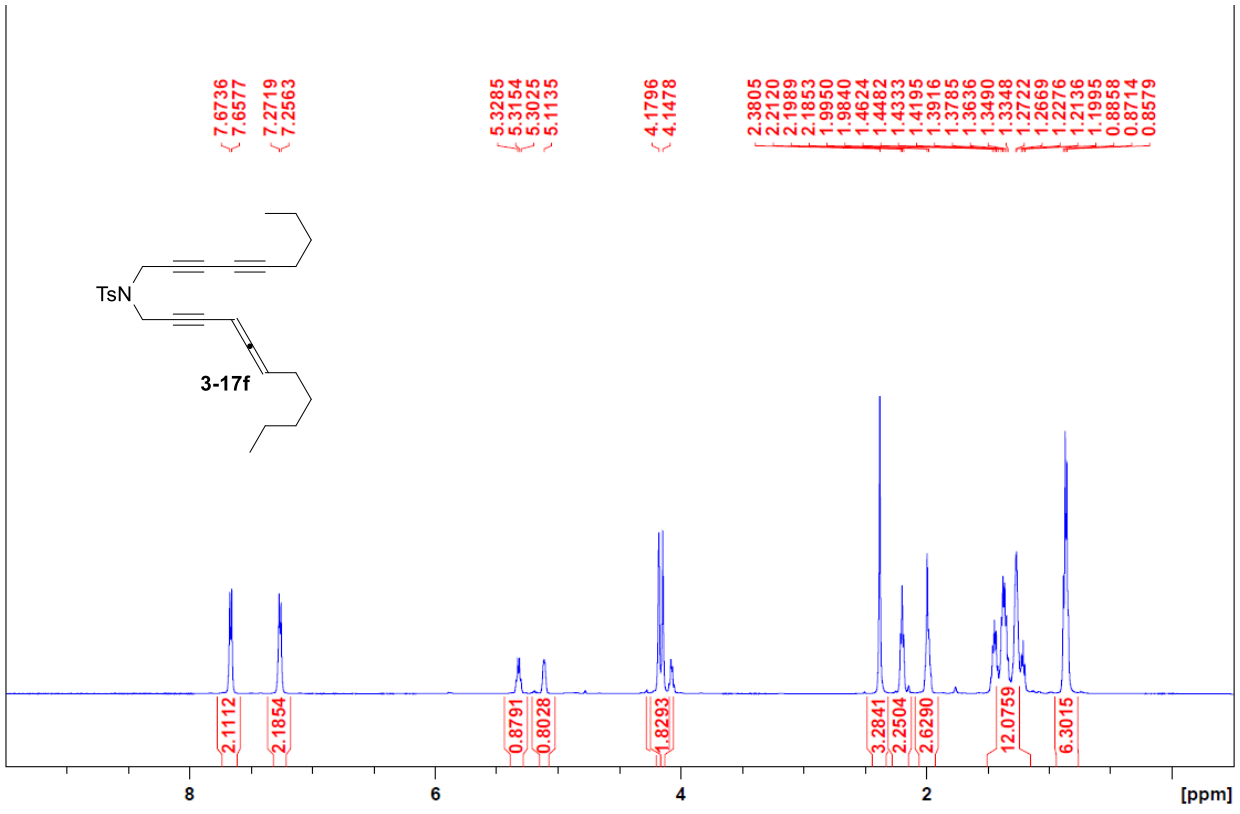

216.6602
143.9395
134.9383
129.5717
127.8507
83.0146
80.7959
78.1766
77.2738
74.4812
70.8304
68.1741
64.3515
37.4290
37.1558
30.1229
21.8576
21.5315
18.7892
13.4900
TsN
3-17b
200
150
100
50
[ppm]

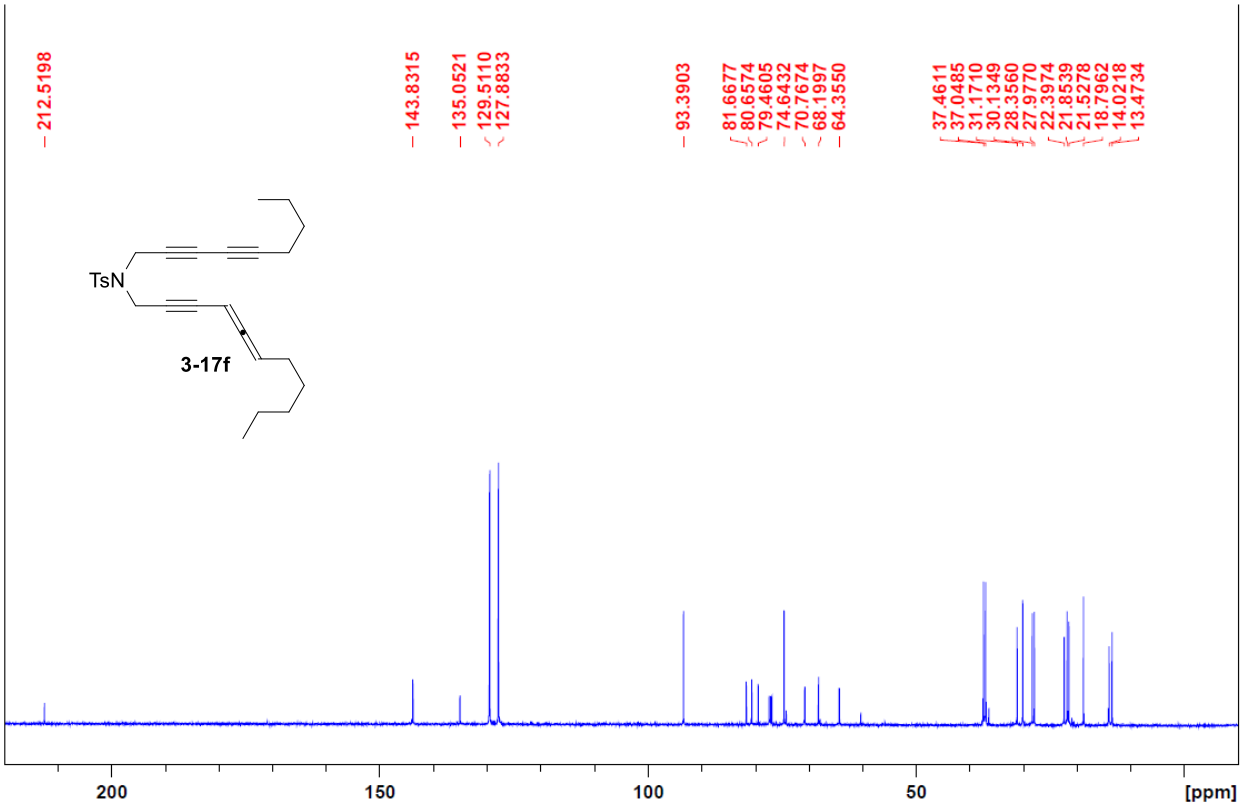

7.6610
7.6457
7.2748
7.2592
5.1662
4.9300
4.9165
4.1737
4.1544
2.3769
0.1391
SiMe3
TsN
3-17c
2.0335
2.1650
0.6549
1.7733
1.9208
3.2247
9.4140
8
6
4
2
[ppm]

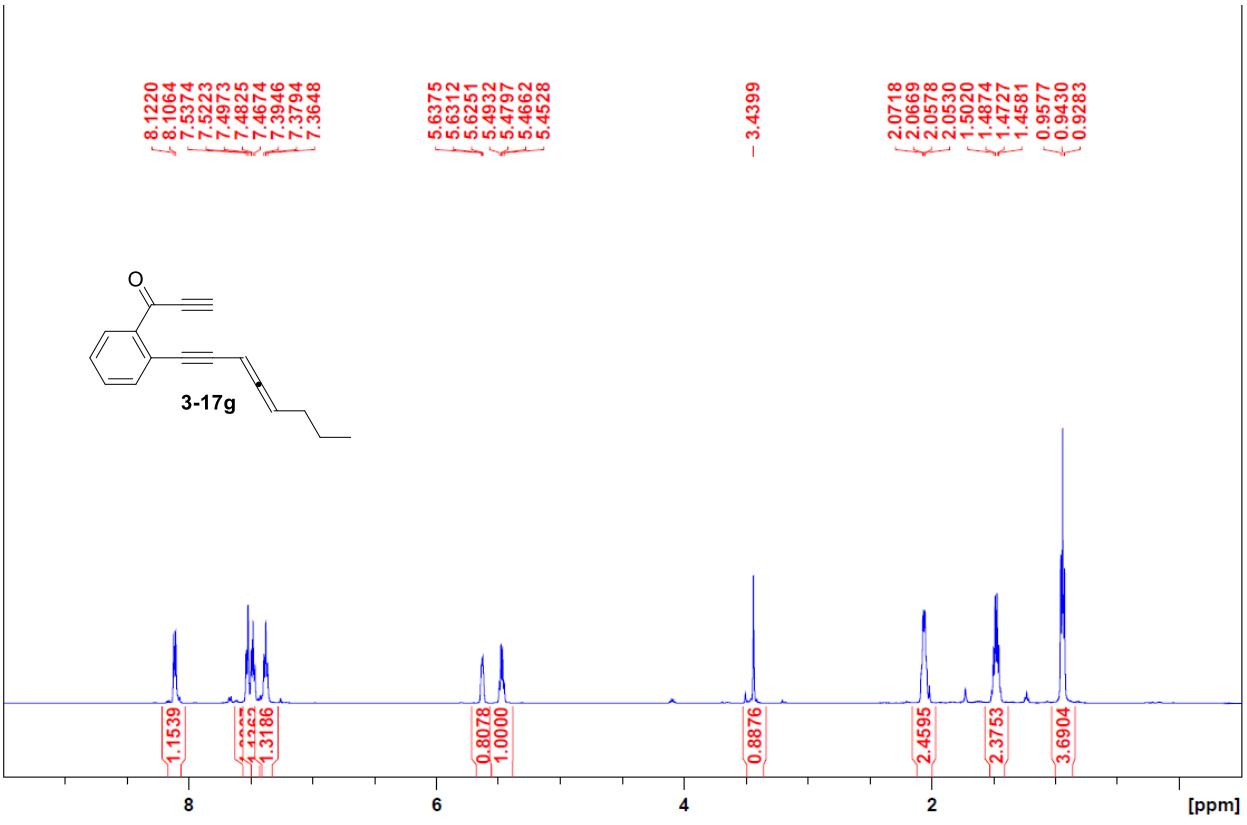

216.7058
143.9725
134.8130
129.6194
127.8796
87.0976
86.6437
82.8578
78.3667
77.3163
74.4655
70.6345
37.5891
37.0897
21.5692
-0.5011
SiMe3
TsN
3-17c
200
150
100
50
[ppm]

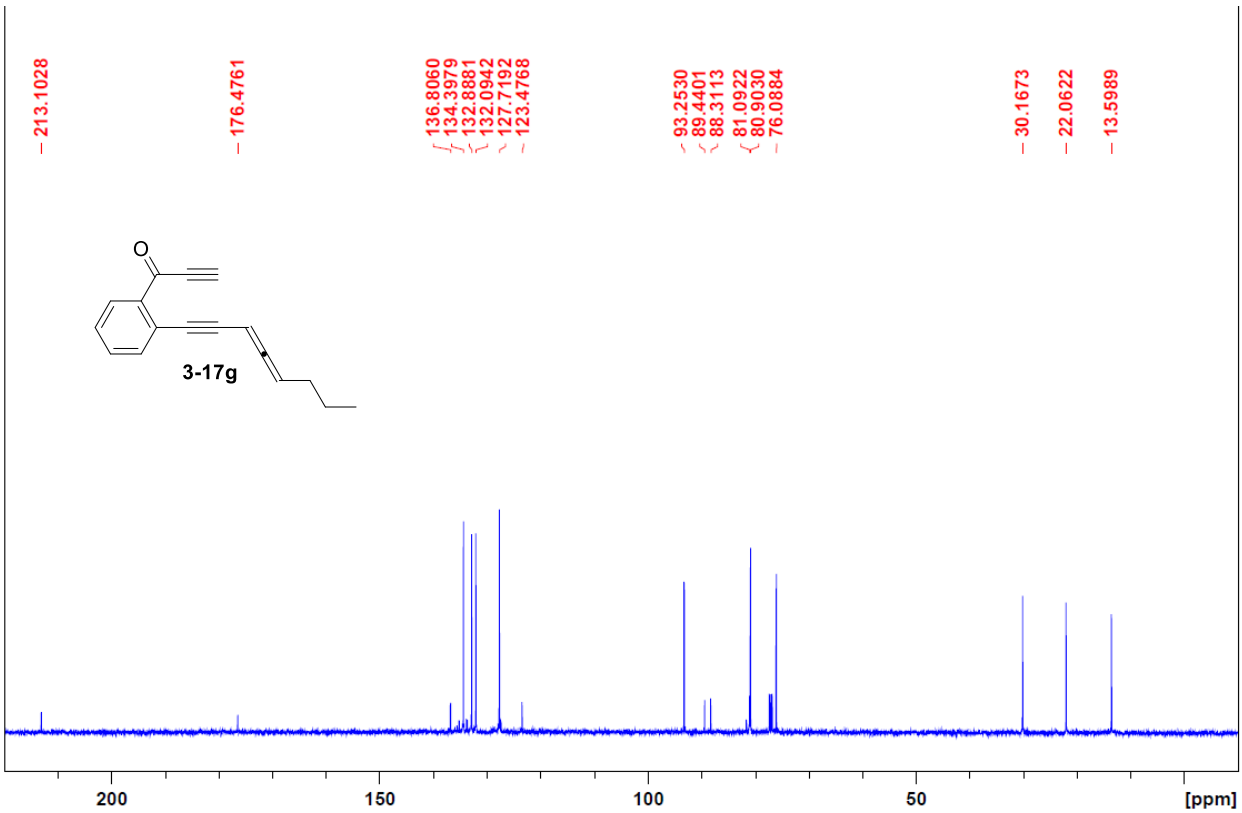

7.71
7.70
7.31
7.29
5.23
5.22
5.22
5.21
5.21
5.21
5.20
5.20
5.19
4.98
4.96
4.22
4.21
2.41
0.99
0.98
0.96
0.63
0.61
0.60
0.58
SiEt3
TsN
3-17d
2.01
2.03
0.84
1.75
3.86
3.11
9.15
6.11
f1 (ppm)

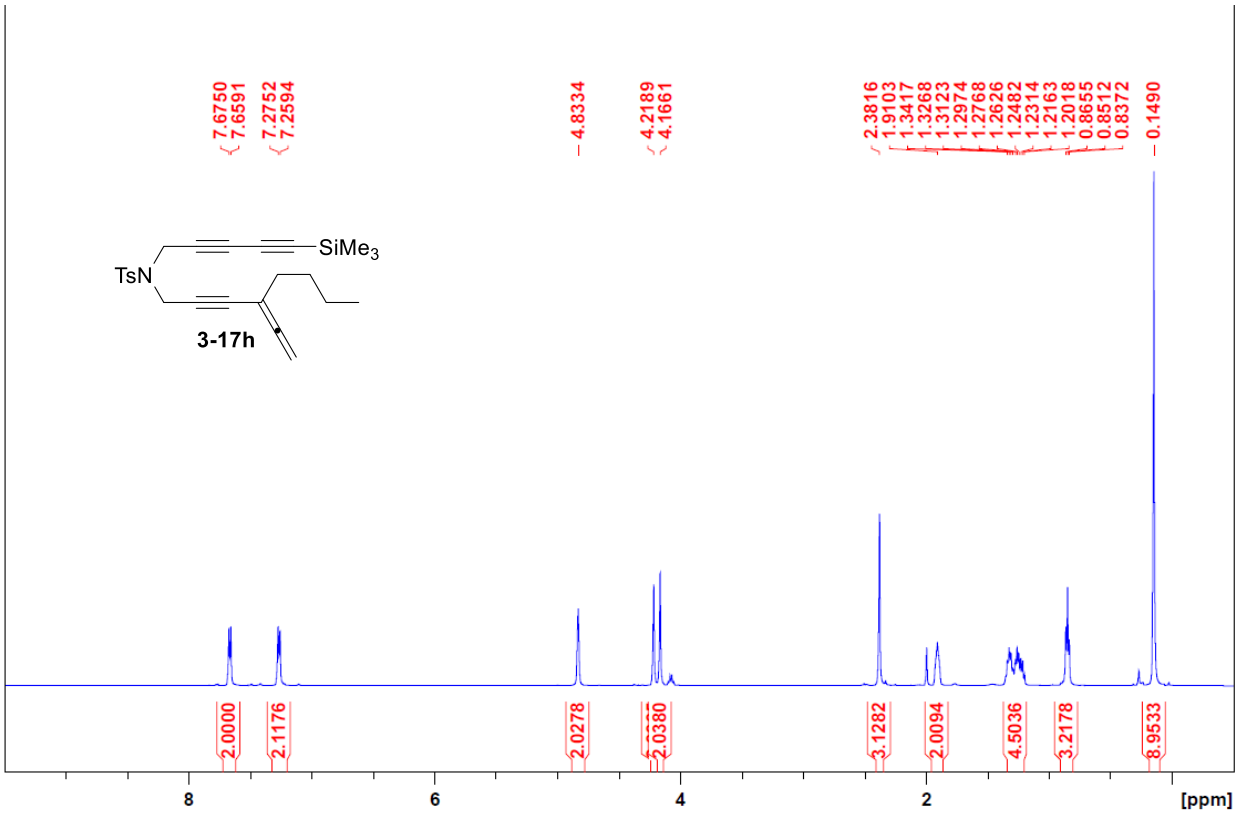

216.76
143.95
134.93
129.71
129.59
127.95
127.88
88.03
84.78
82.95
78.34
74.52
70.81
69.91
37.63
37.13
21.58
7.33
4.11
SiEt3
TsN
3-17d
f1 (ppm)

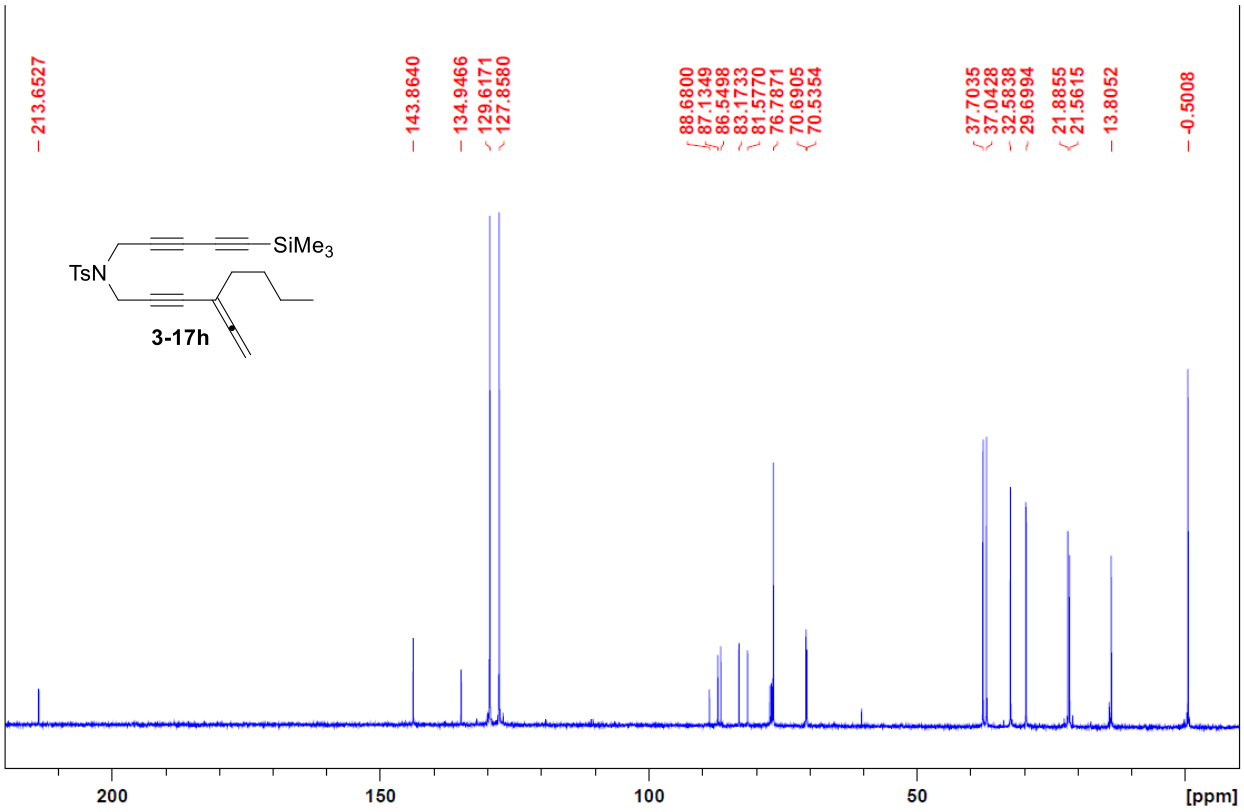

7.6736
7.6577
7.2719
7.2563
5.3285
5.3154
5.3025
5.1135
4.1796
4.1478
2.3805
2.2120
2.1989
2.1853
1.9950
1.9840
1.4624
1.4482
1.4333
1.4195
1.3916
1.3785
1.3636
1.3490
1.3348
1.2722
1.2669
1.2276
1.2136
1.1995
0.8858
0.8714
0.8579
TsN
3-17f
2.1112
2.1854
0.8791
0.8028
1.8293
3.2841
2.2504
2.6290
12.0759
6.3015
8
6
4
2
[ppm]

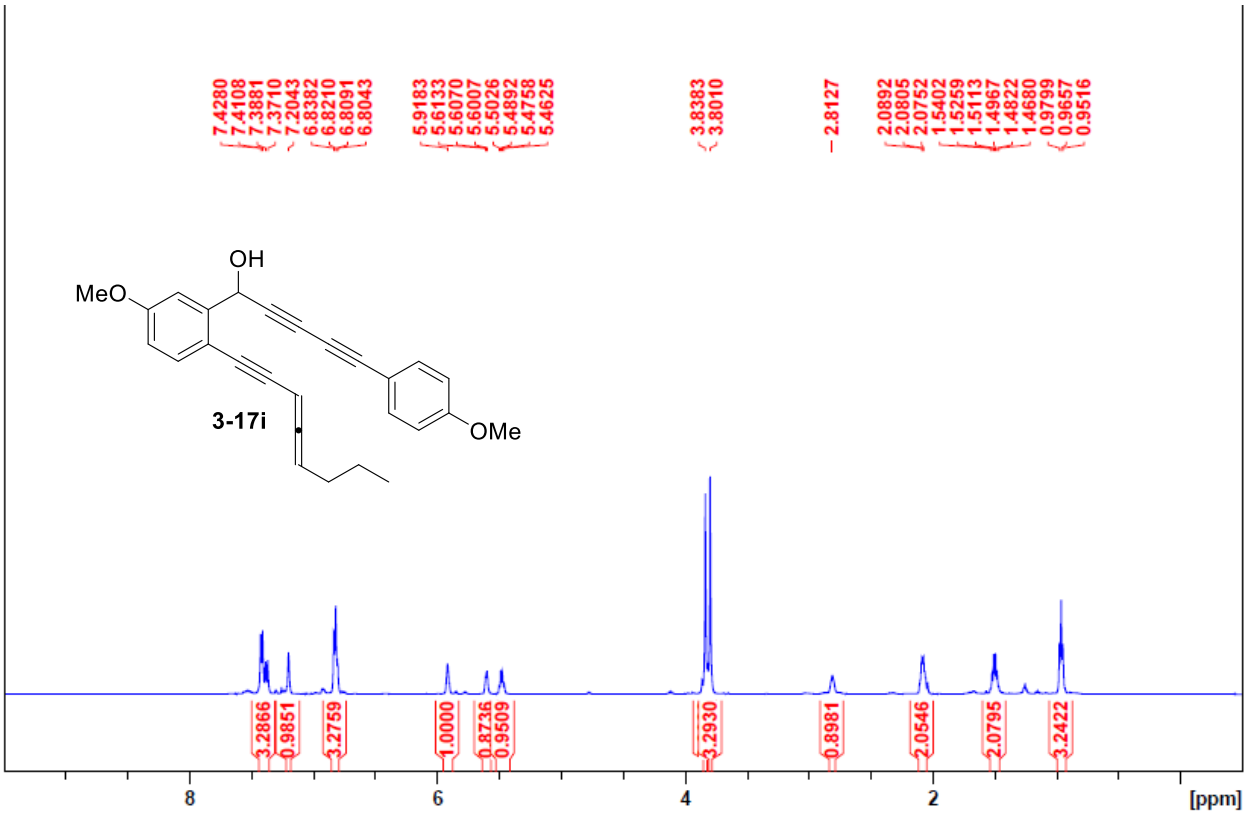

212.5198
143.8315
135.0521
129.5110
127.8833
93.3903
81.6677
80.6574
79.4605
74.6432
70.7674
68.1997
64.3550
37.4611
37.0485
31.1710
30.1349
28.3560
27.9770
22.3974
21.8539
21.5278
18.7962
14.0218
13.4734
TsN
3-17f
200
150
100
50
[ppm]

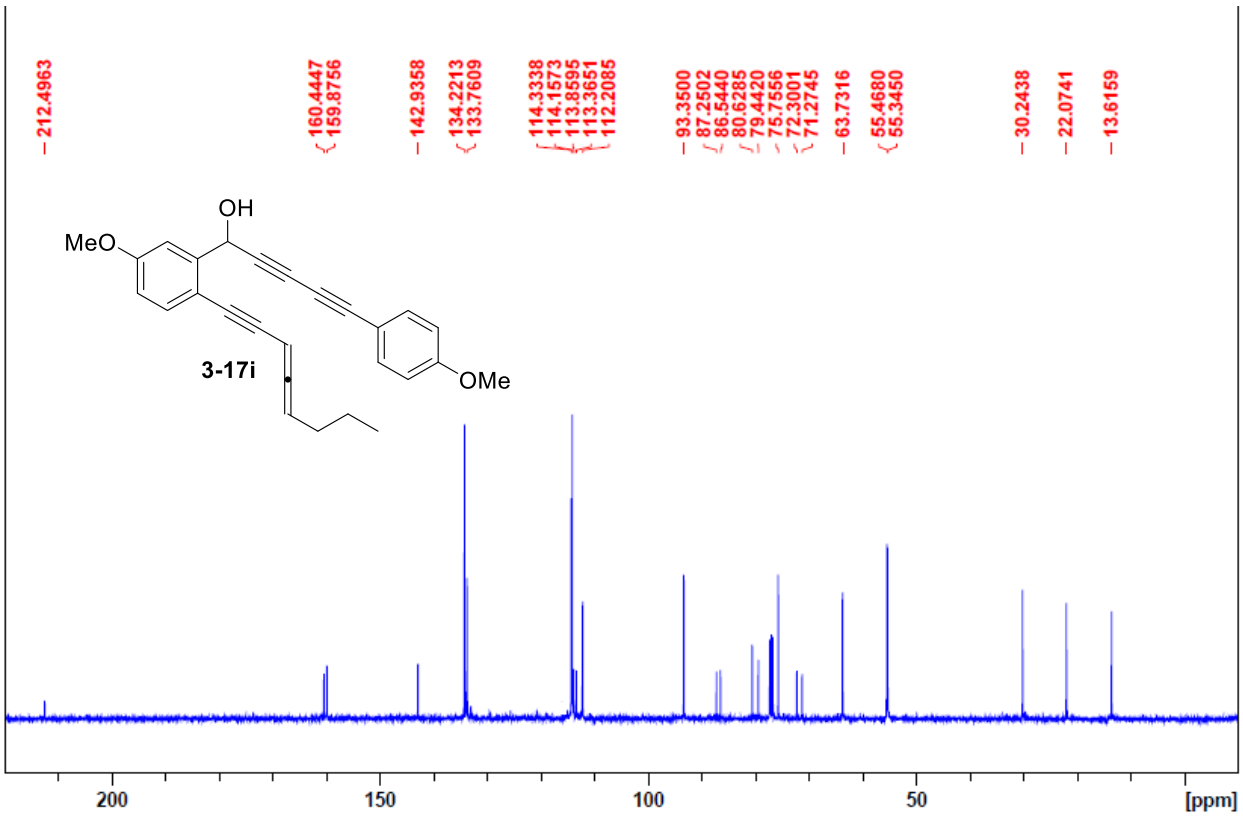

8.1220
8.1064
7.5374
7.5223
7.4973
7.4825
7.4674
7.3946
7.3794
7.3648
5.6375
5.6312
5.6251
5.4932
5.4797
5.4662
5.4528
3.4399
2.0718
2.0669
2.0578
2.0530
1.5020
1.4874
1.4727
1.4581
0.9577
0.9430
0.9283
O
3-17g
1.1539
1.3186
0.8078
1.0000
0.8876
2.4595
2.3753
3.6904
8
6
4
2
[ppm]

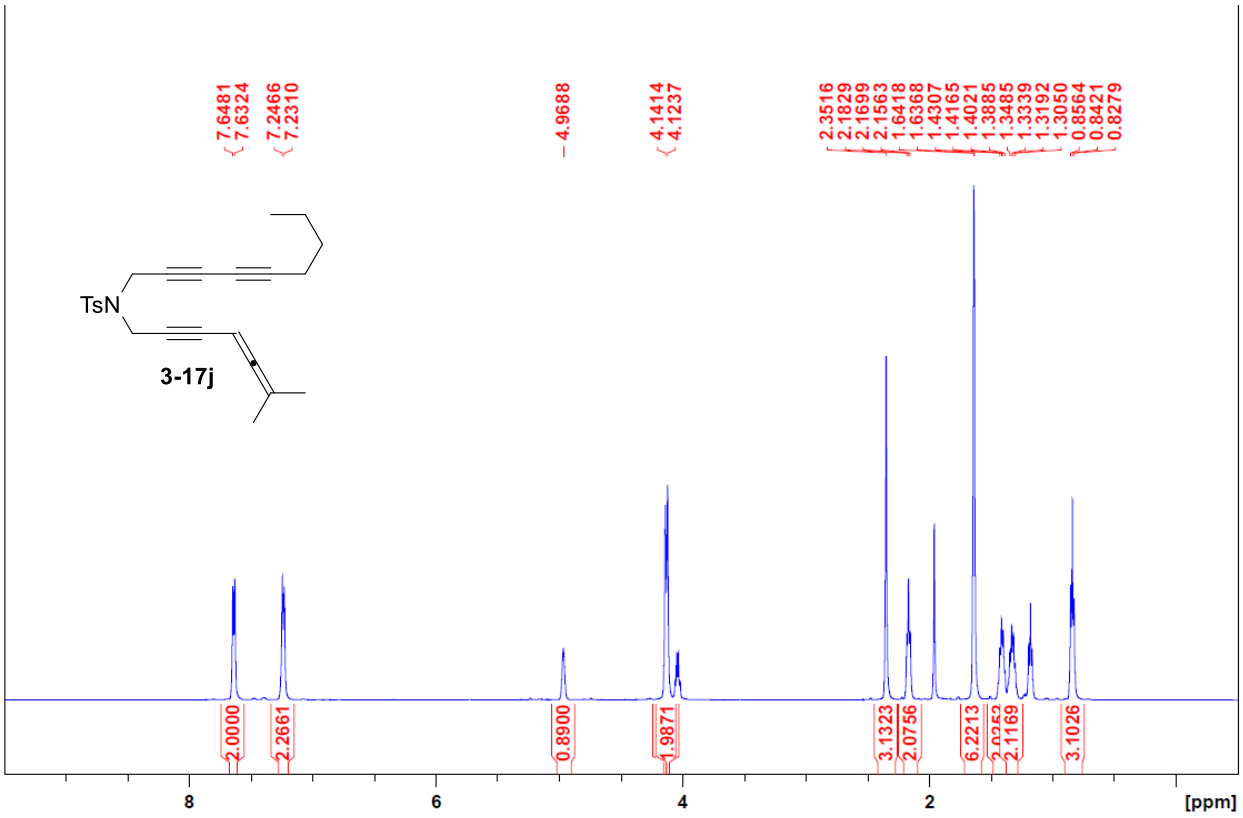

213.1028
176.4761
136.8060
134.3979
132.8881
132.0942
127.7192
123.4768
93.2530
89.4401
88.3113
81.0922
80.9030
76.0884
30.1673
22.0622
13.5989
O
3-17g
200
150
100
50
[ppm]

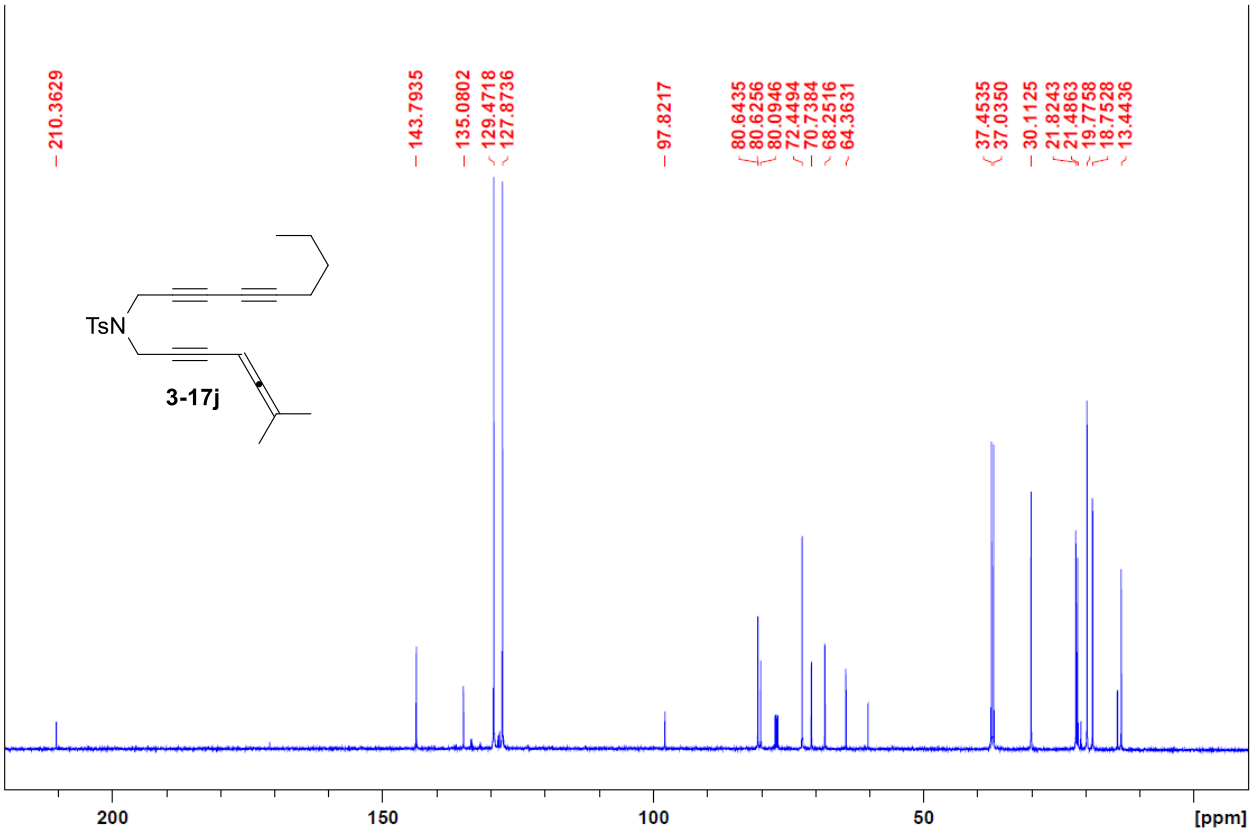

7.6750
7.6591
7.2752
7.2594
4.8334
4.2189
4.1661
2.3816
1.9103
1.3417
1.3268
1.3123
1.2974
1.2768
1.2626
1.2482
1.2314
1.2163
1.2018
0.8655
0.8512
0.8372
0.1490
SiMe3
TsN
3-17h
2.0000
2.1176
2.0278
2.0380
3.1282
2.0094
4.5036
3.2178
8.9533
8
6
4
2
[ppm]

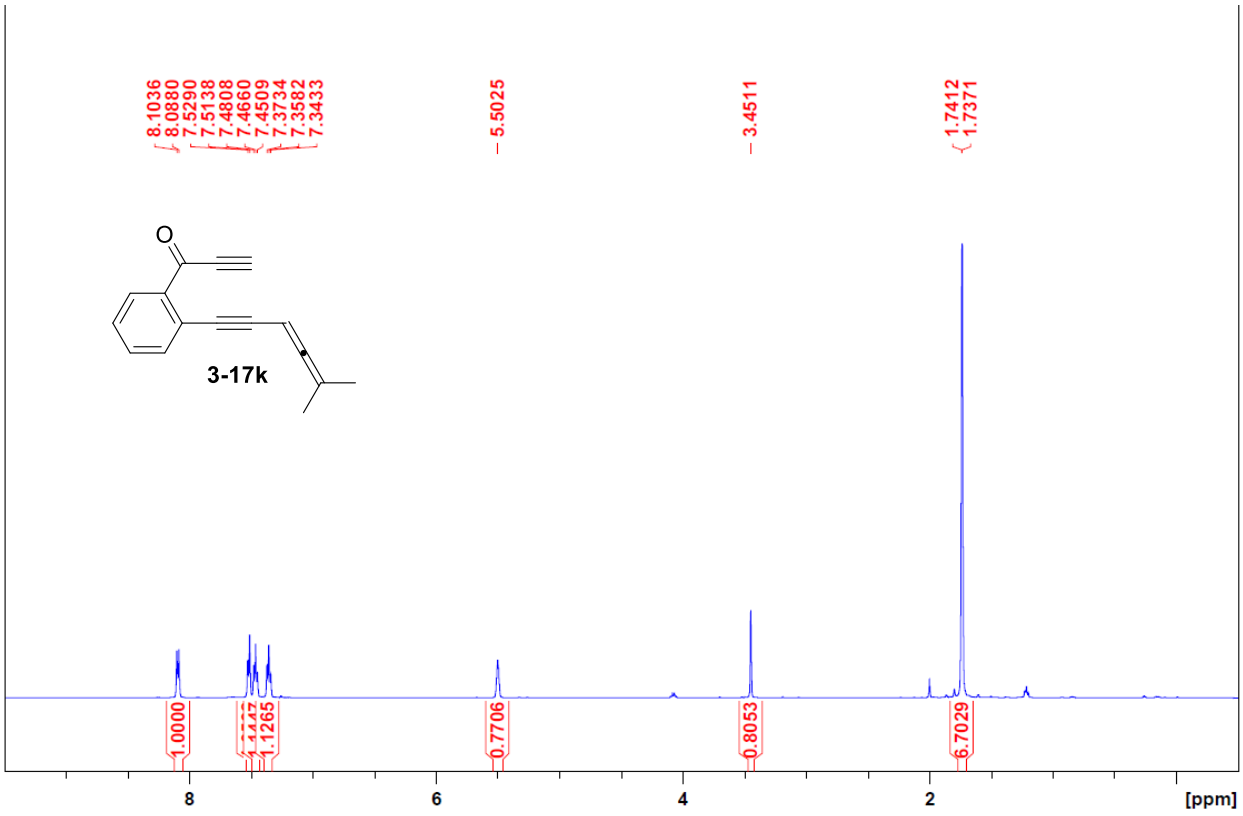

213.6527
143.8640
134.9466
129.6171
127.8580
88.6800
87.1349
86.5498
83.1733
81.5770
76.7871
70.6905
70.5354
37.7035
37.0428
32.5838
29.6994
21.8855
21.5615
13.8052
0.5008
SiMe3
TsN
3-17h
200
150
100
50
[ppm]

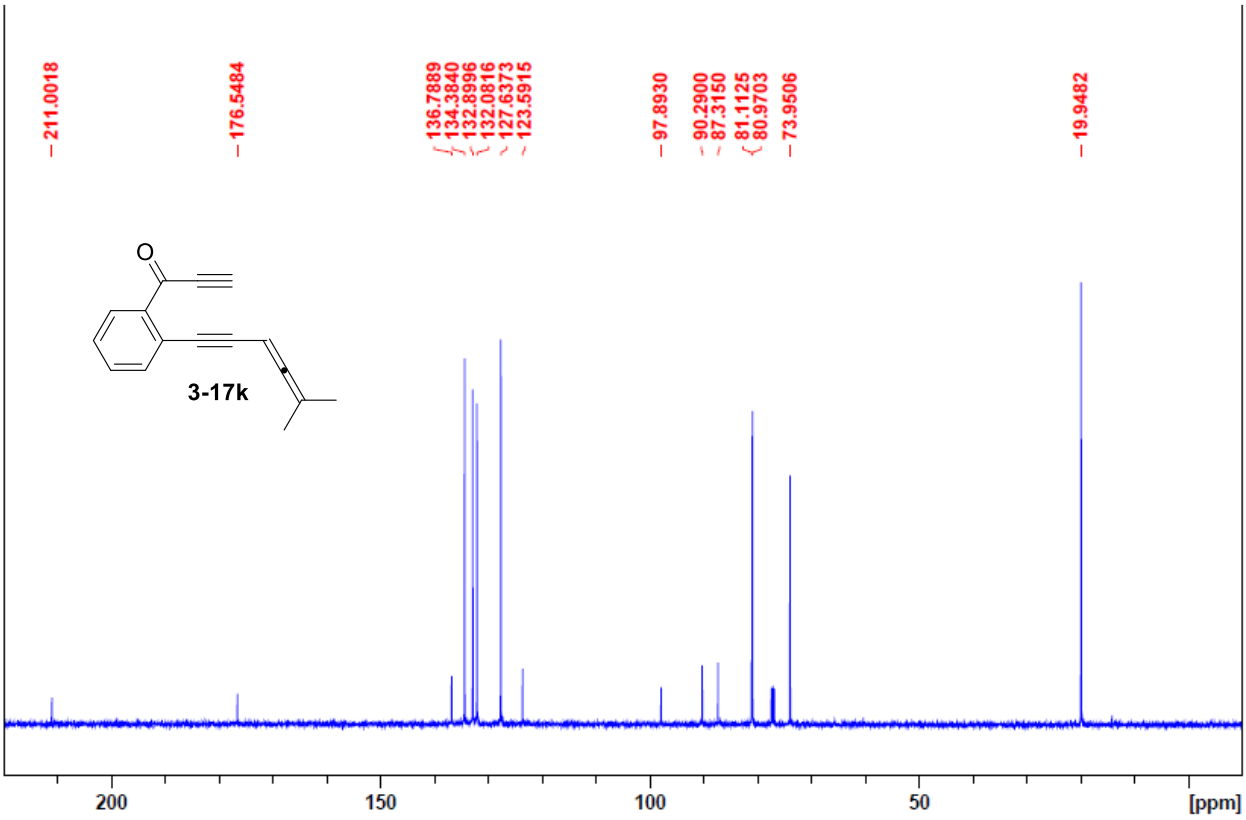

7.4280
7.4108
7.3881
7.3710
7.2043
6.8382
6.8210
6.8091
6.8043
5.9183
5.6133
5.6070
5.6007
5.5026
5.4892
5.4758
5.4625
3.8383
3.8010
2.8127
2.0892
2.0805
2.0752
1.5402
1.5259
1.5113
1.4967
1.4822
1.4680
0.9799
0.9657
0.9516
OH
MeO
OMe
3-17i
3.2866
0.9851
3.2759
1.0000
0.8736
0.9509
3.2930
0.8981
2.0546
2.0795
3.2422
8
6
4
2
[ppm]

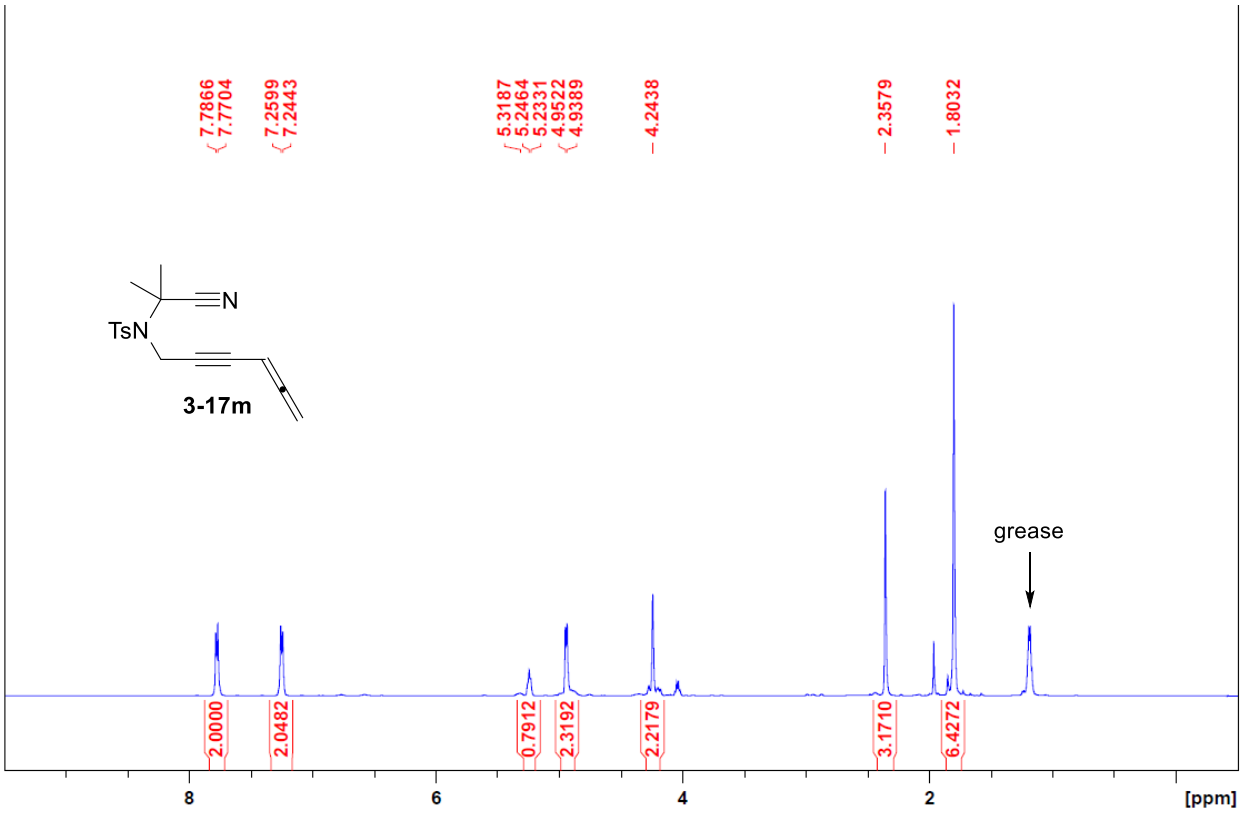

212.4963
160.4447
159.8756
142.9358
134.2213
133.7609
114.3338
114.1573
113.8595
113.3651
112.2085
93.3500
87.2502
86.5440
80.6285
79.4420
75.7556
72.3001
71.2745
63.7316
55.4680
55.3450
30.2438
22.0741
13.6159
OH
MeO
OMe
3-17i
200
150
100
50
[ppm]

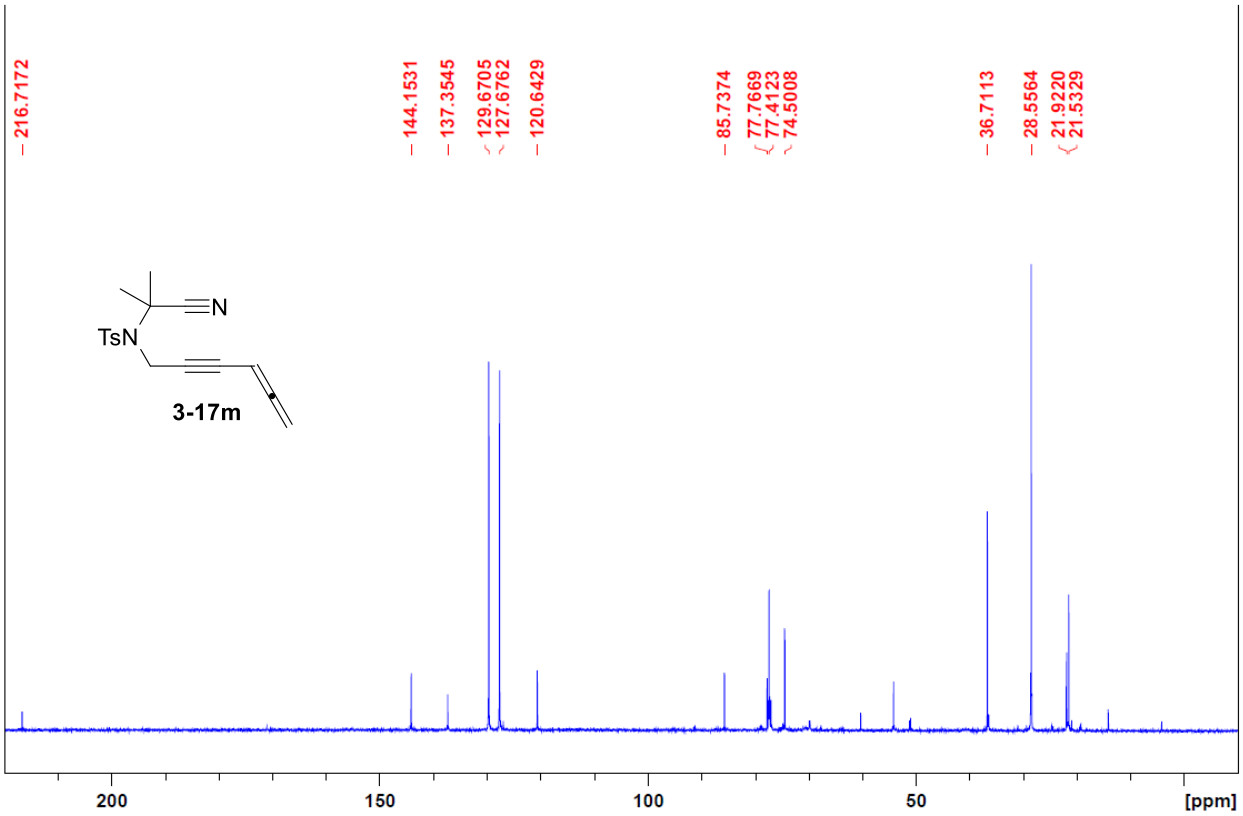

7.6481
7.6324
7.2466
7.2310
4.9688
4.1414
4.1237
2.3516
2.1829
2.1699
2.1563
1.6418
1.6368
1.4307
1.4165
1.4021
1.3885
1.3485
1.3339
1.3192
1.3050
0.8564
0.8421
0.8279
TsN
3-17j
2.0000
2.2661
0.8900
1.9871
3.1323
2.0756
6.2213
2.1169
3.1026
8
6
4
2
[ppm]

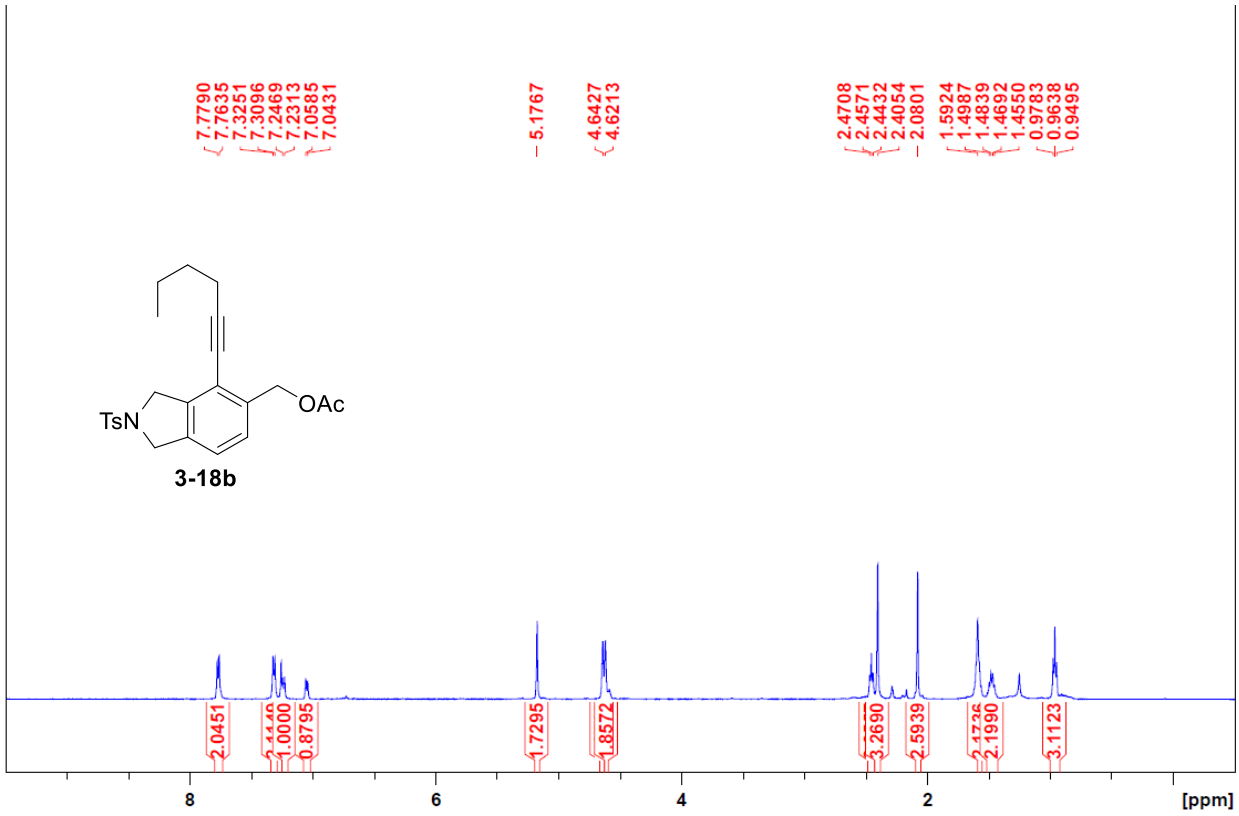

210.3629
143.7935
135.0802
129.4718
127.8736
97.8217
80.6435
80.6256
80.0946
72.4494
70.7384
68.2516
64.3631
37.4535
37.0350
30.1125
21.8243
21.4863
19.7758
18.7528
13.4436
TsN
3-17j
200
150
100
50
[ppm]

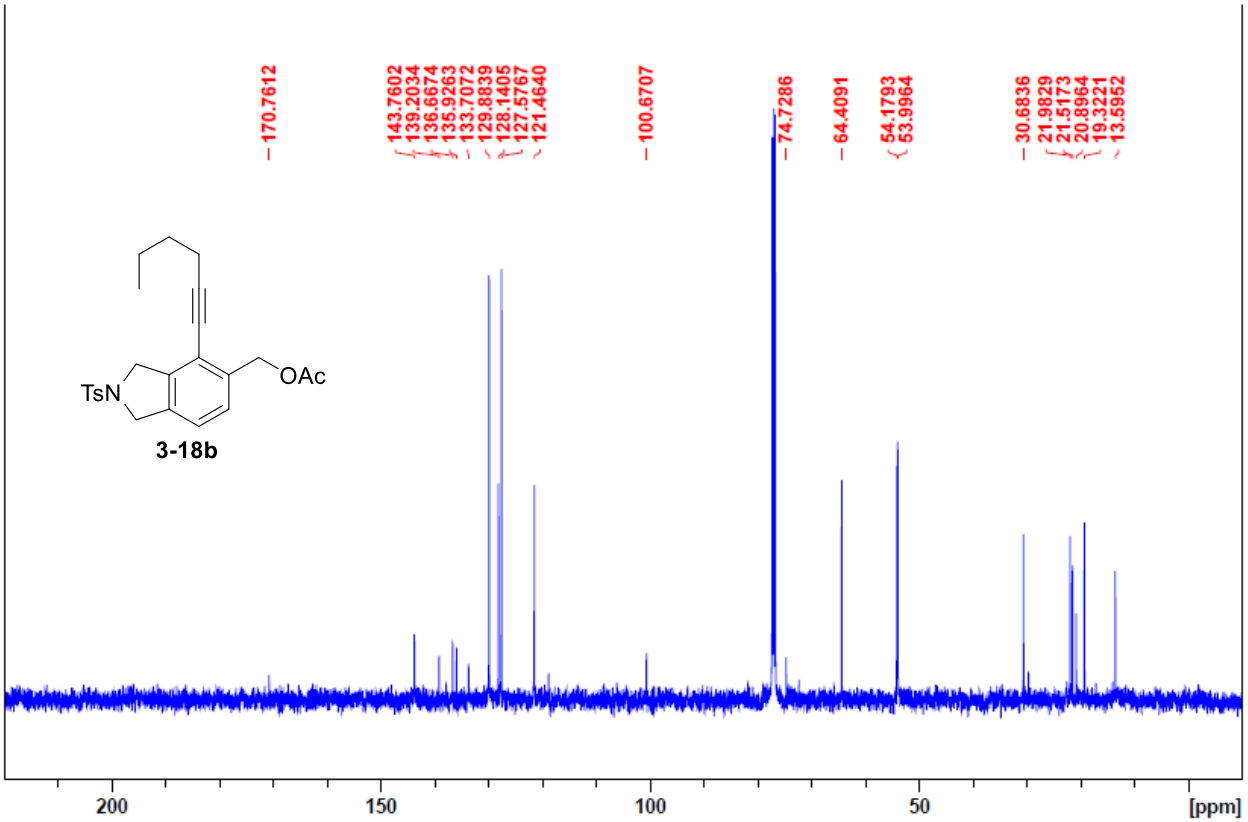

8.1036
8.0880
7.5290
7.5138
7.4808
7.4660
7.4509
7.3734
7.3582
7.3433
5.5025
3.4511
1.7412
1.7371
O
3-17k
1.0000
1.1265
0.7706
0.8053
6.7029
8
6
4
2
[ppm]

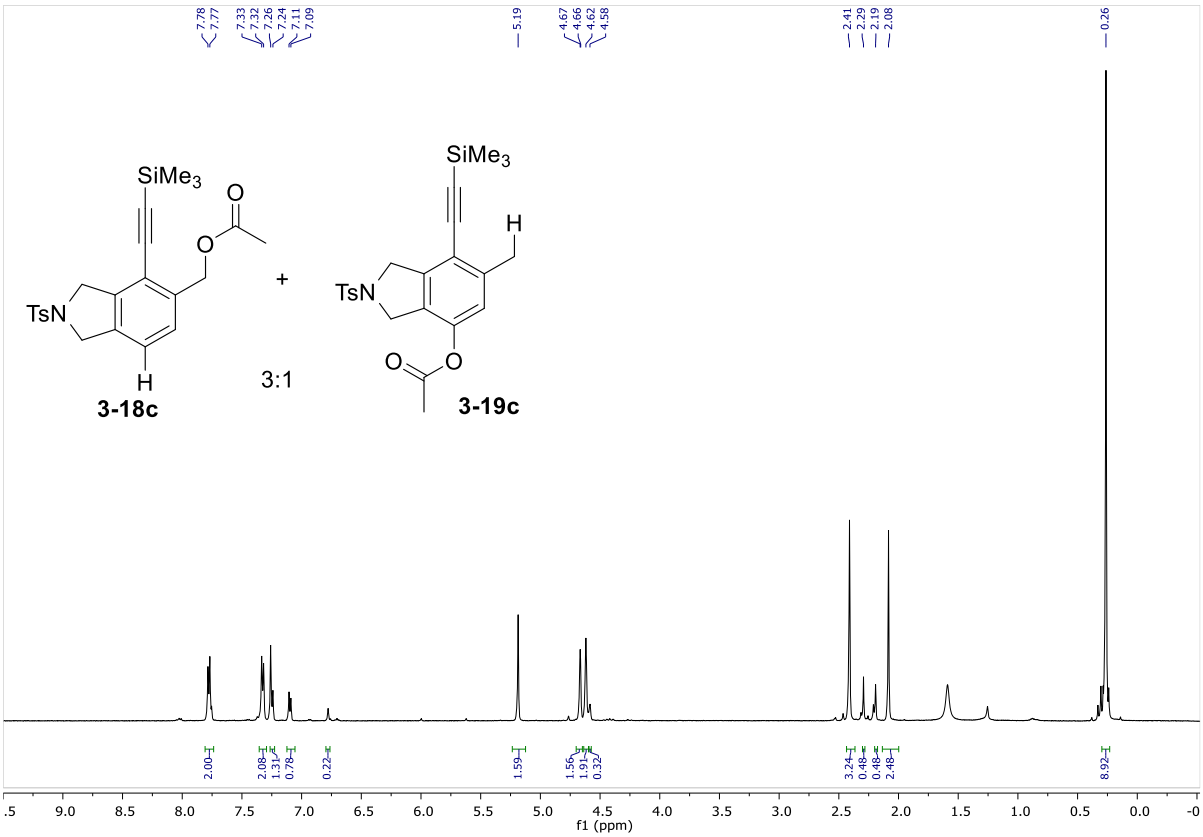

211.0018
176.5484
136.7889
134.3840
132.8996
132.0816
127.6373
123.5915
97.8930
90.2900
87.3150
81.1125
80.9703
73.9506
19.9482
O
3-17k
200
150
100
50
[ppm]

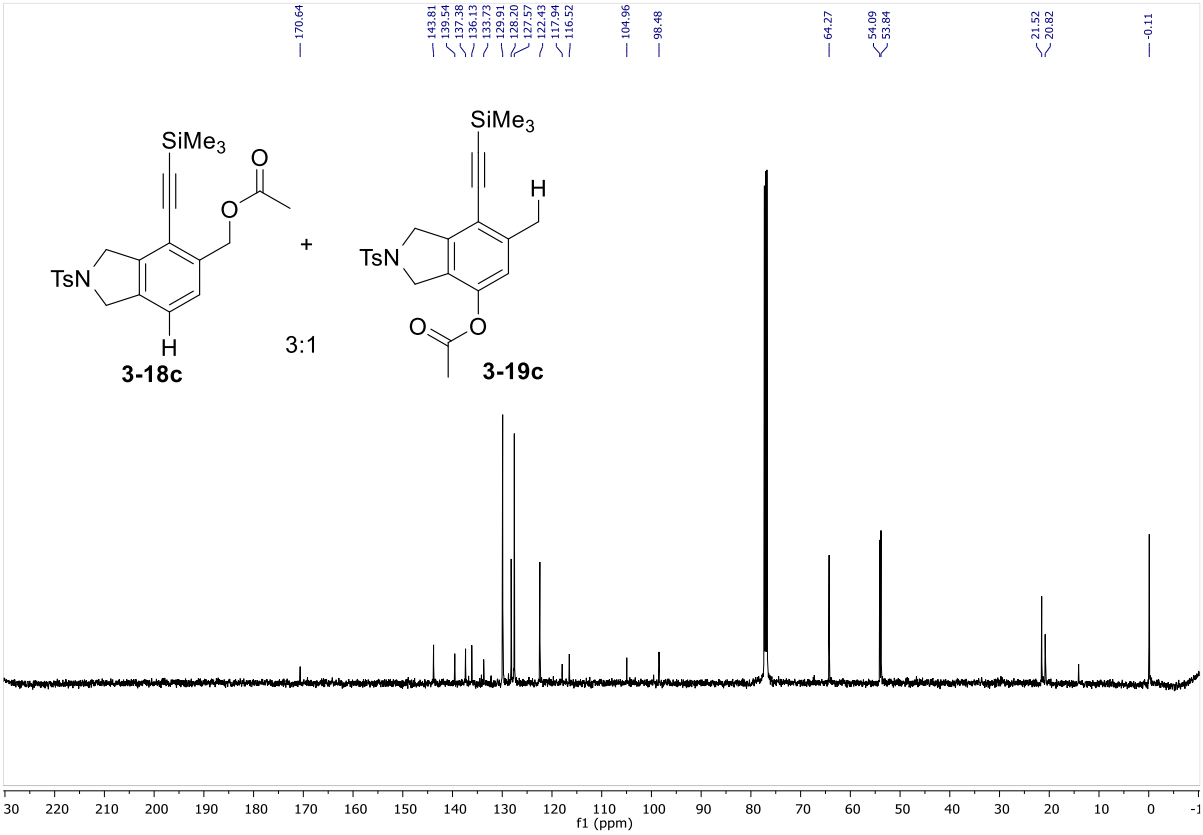

7.7866
7.7704
7.2599
7.2443
5.3187
5.2464
5.2331
4.9522
4.9389
4.2438
2.3579
1.8032
TsN
N
3-17m
grease
2.0000
2.0482
0.7912
2.3192
2.2179
3.1710
6.4272
8
6
4
2
[ppm]

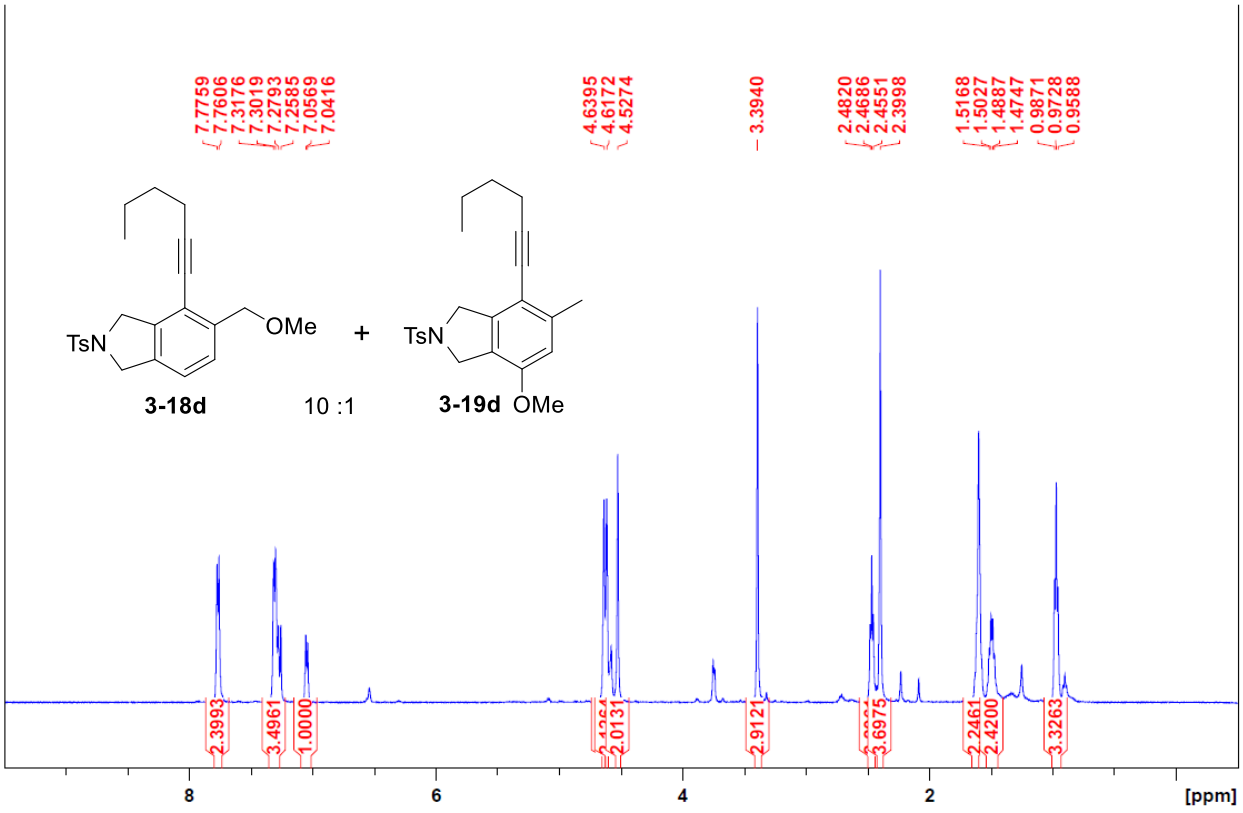

216.7172
144.1531
137.3545
129.6705
127.6762
120.6429
85.7374
77.7669
77.4123
74.5008
36.7113
28.5564
21.9220
21.5329
TsN
N
3-17m
200
150
100
50
[ppm]

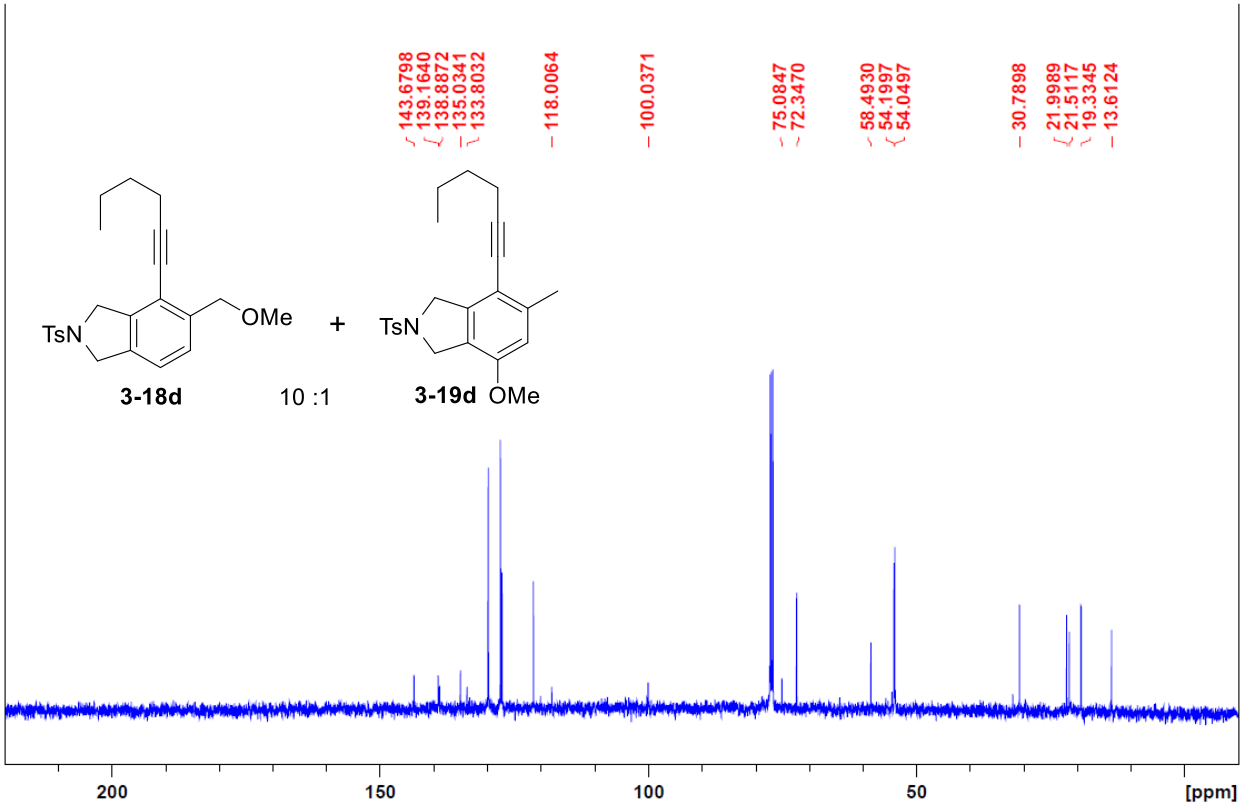

7.7790
7.7635
7.3251
7.3096
7.2469
7.2313
7.0585
7.0431
5.1767
4.6427
4.6213
2.4708
2.4571
2.4432
2.4054
2.0801
1.5924
1.4987
1.4839
1.4692
1.4550
0.9783
0.9638
0.9495
TsN
OAc
3-18b
2.0451
1.0000
0.8795
1.7295
1.8572
3.2690
2.5939
2.1990
3.1123
8
6
4
2
[ppm]

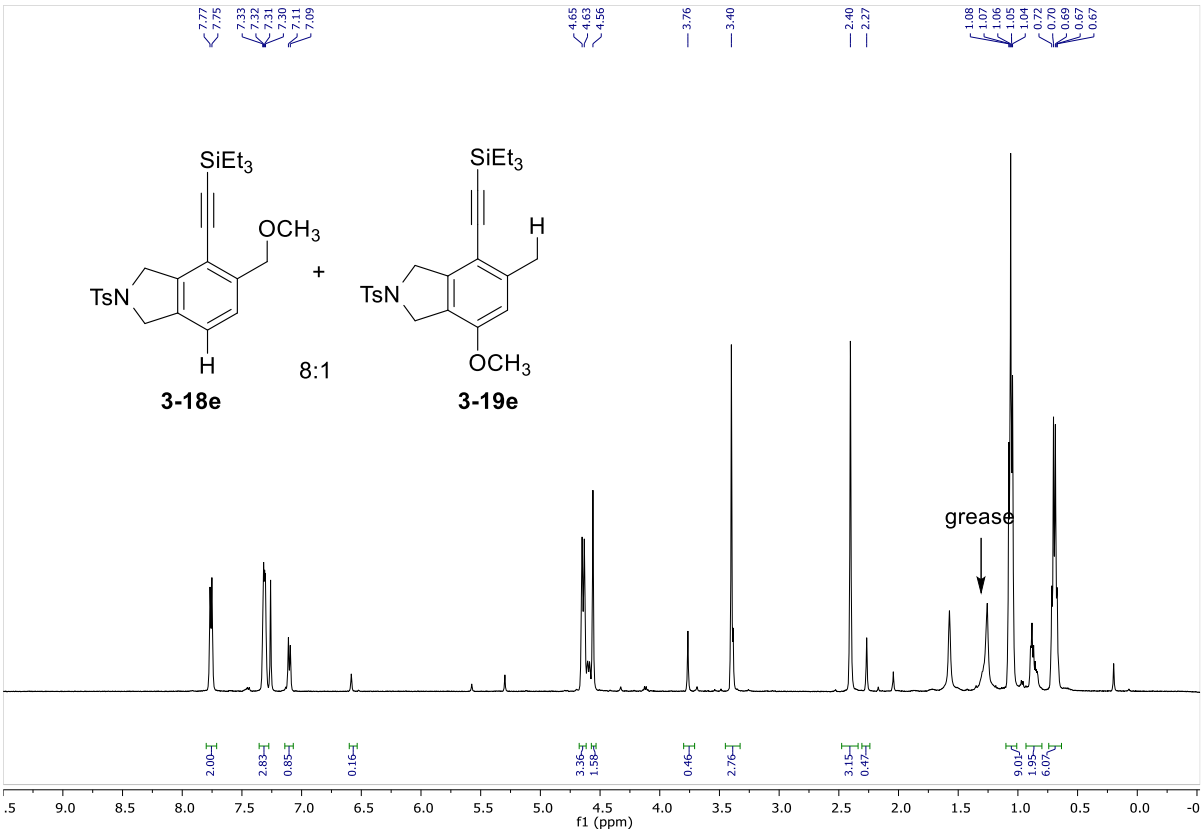

170.7612
143.7602
139.2034
136.6674
135.9263
133.7072
129.8839
128.1405
127.5767
121.4640
100.6707
74.7286
64.4091
54.1793
53.9964
30.6836
21.9829
21.5173
20.8964
19.3221
13.5952
TsN
OAc
3-18b
200
150
100
50
[ppm]


SiMe3
O
O
TsN
H
3-18c
+
3:1
SiMe3
H
TsN
O
O
3-19c
7.78
7.77
7.33
7.32
7.26
7.24
7.11
7.09
5.19
4.67
4.66
4.62
4.58
2.41
2.29
2.19
2.08
0.26
2.00
2.08
1.31
0.78
0.22
1.59
1.56
1.91
0.32
3.24
0.48
0.48
2.48
8.92
f1 (ppm)

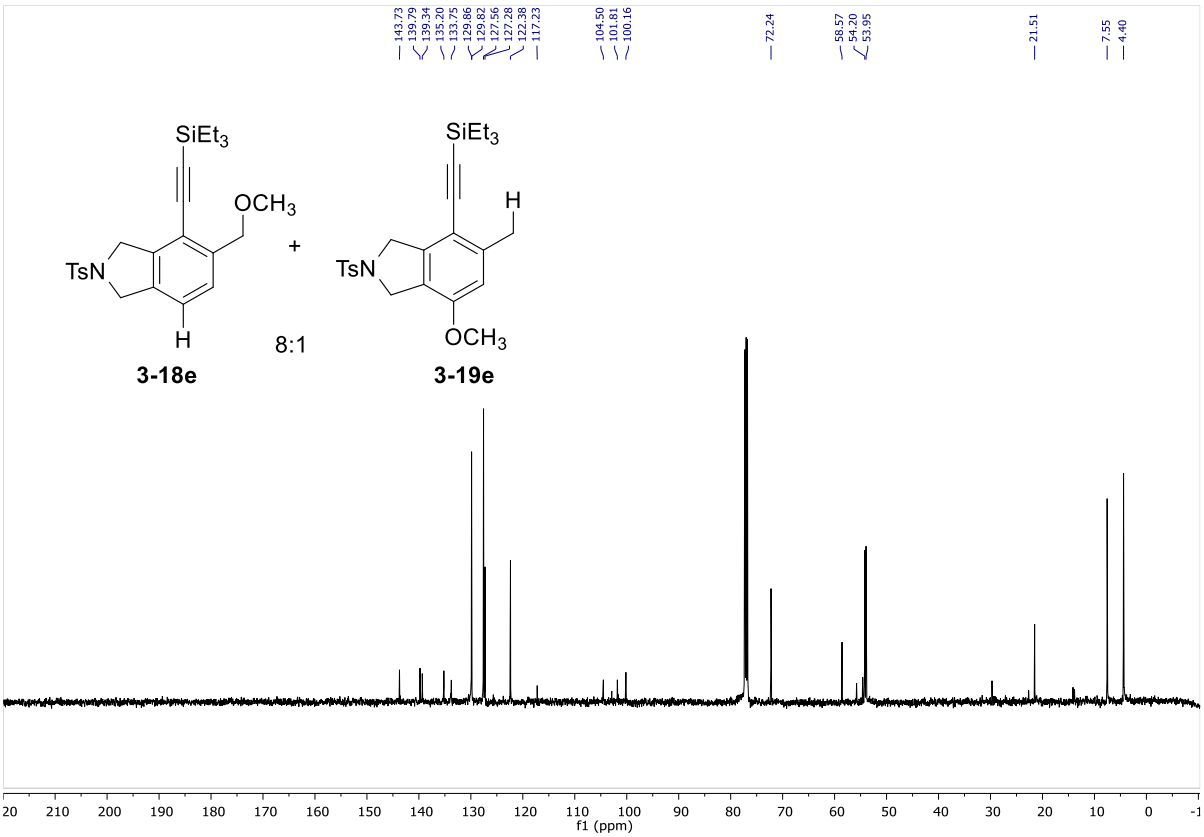

SiMe3
O
O
TsN
H
3-18c
+
3:1
SiMe3
H
TsN
O
O
3-19c
170.64
143.81
139.54
137.38
136.13
133.73
129.91
128.20
127.57
122.43
117.94
116.52
104.96
98.48
64.27
54.09
53.84
21.52
20.82
-0.11
f1 (ppm)


7.7759
7.7606
7.3176
7.3019
7.2793
7.2585
7.0569
7.0416
4.6395
4.6172
4.5274
3.3940
2.4820
2.4686
2.4551
2.3998
1.5168
1.5027
1.4887
1.4747
0.9871
0.9728
0.9588
TsN
OMe
+
TsN
3-18d
10 :1
3-19d
OMe
2.3993
3.4961
1.0000
2.0131
2.9121
3.6975
2.2461
2.4200
3.3263
8
6
4
2
[ppm]

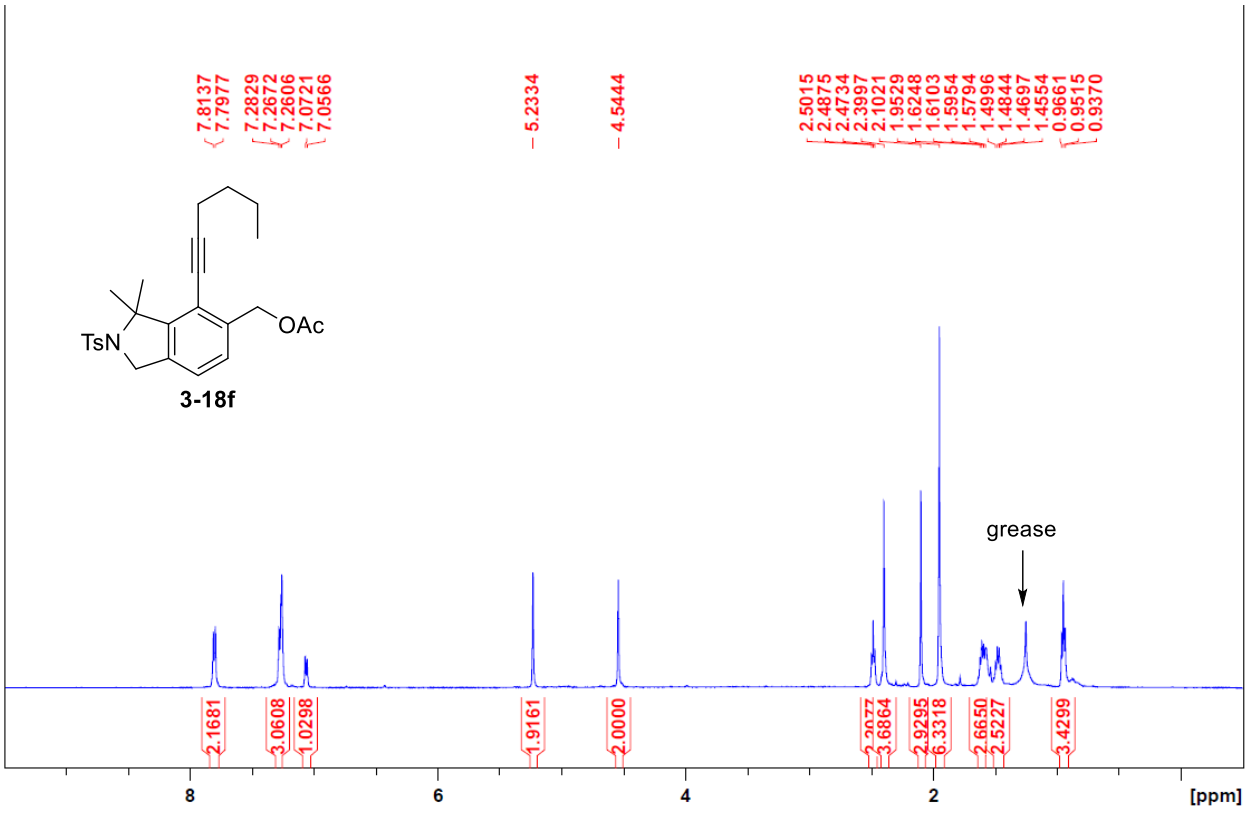

143.6798
139.1640
138.8872
135.0341
133.8032
118.0064
100.0371
75.0847
72.3470
58.4930
54.1997
54.0497
30.7898
21.9989
21.5117
19.3345
13.6124
TsN
OMe
+
TsN
3-18d
10 :1
3-19d
OMe
200
150
100
50
[ppm]

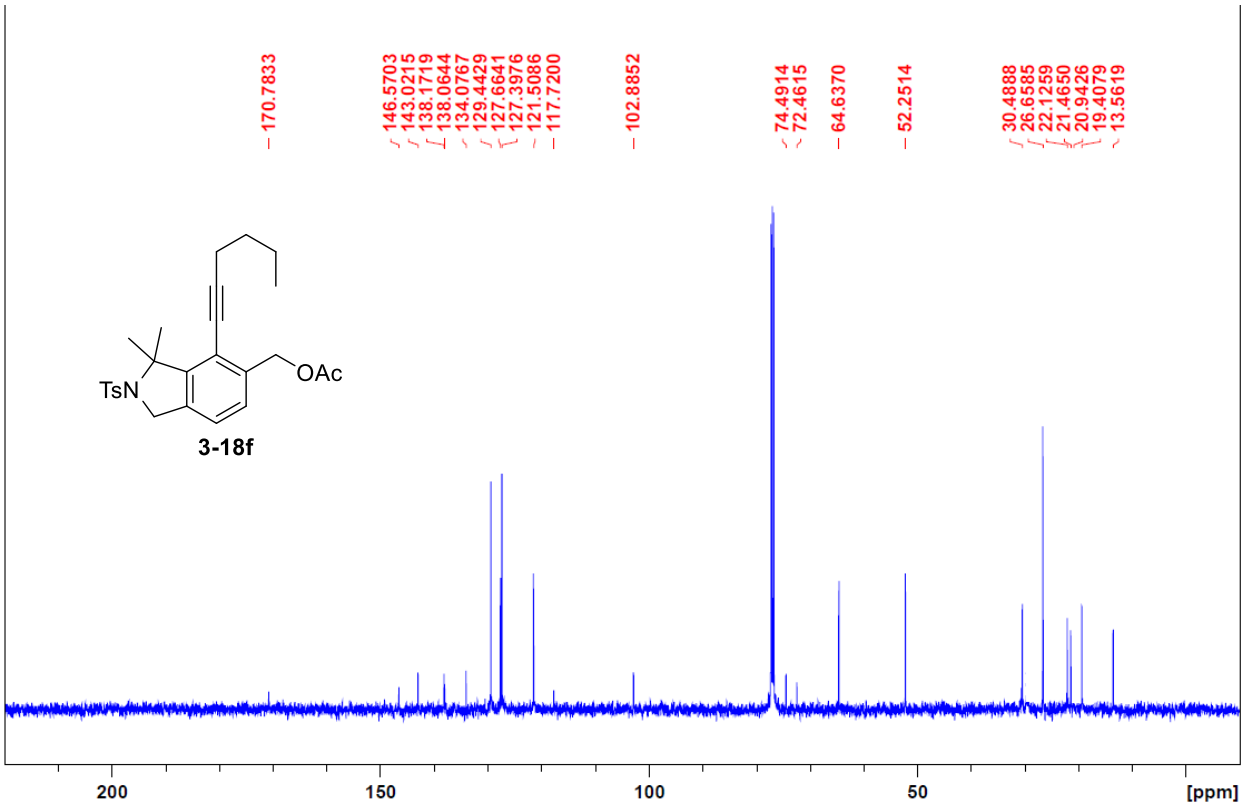


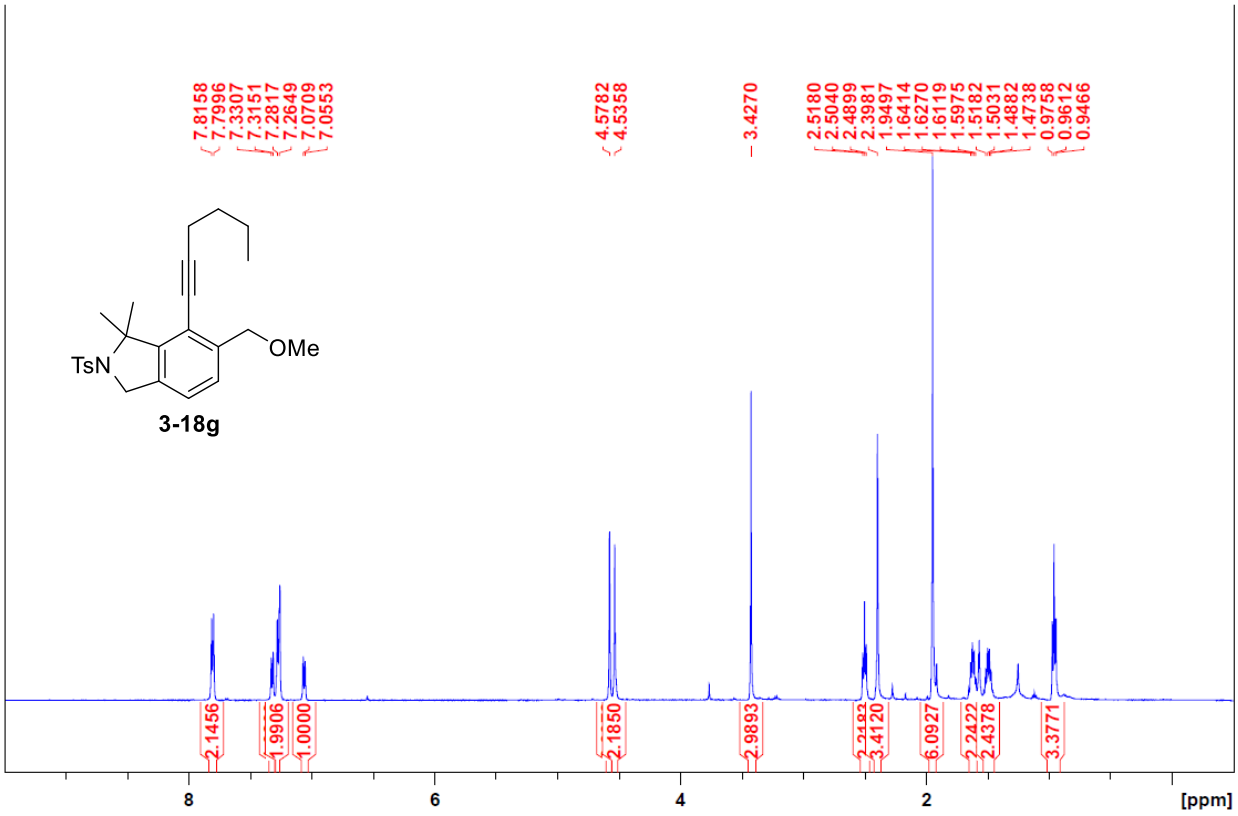
3-18e **3-19e**

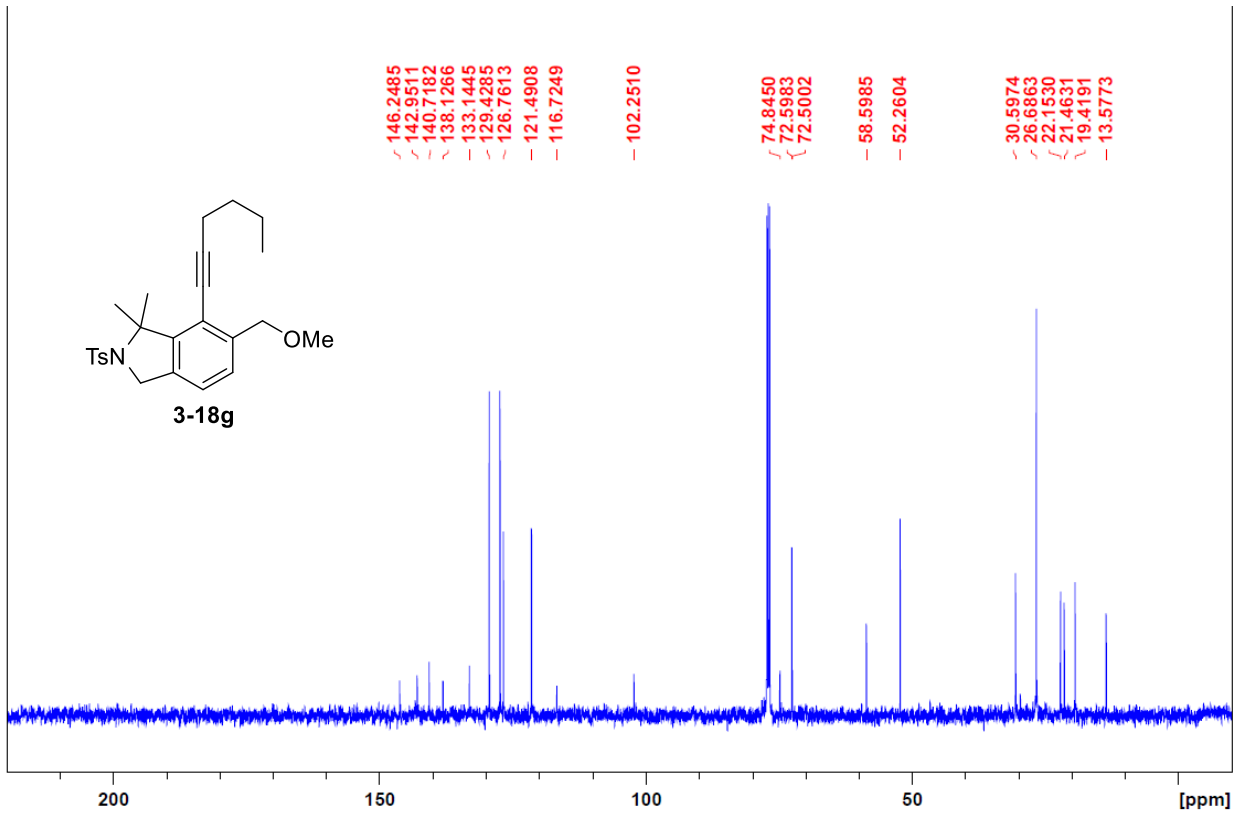


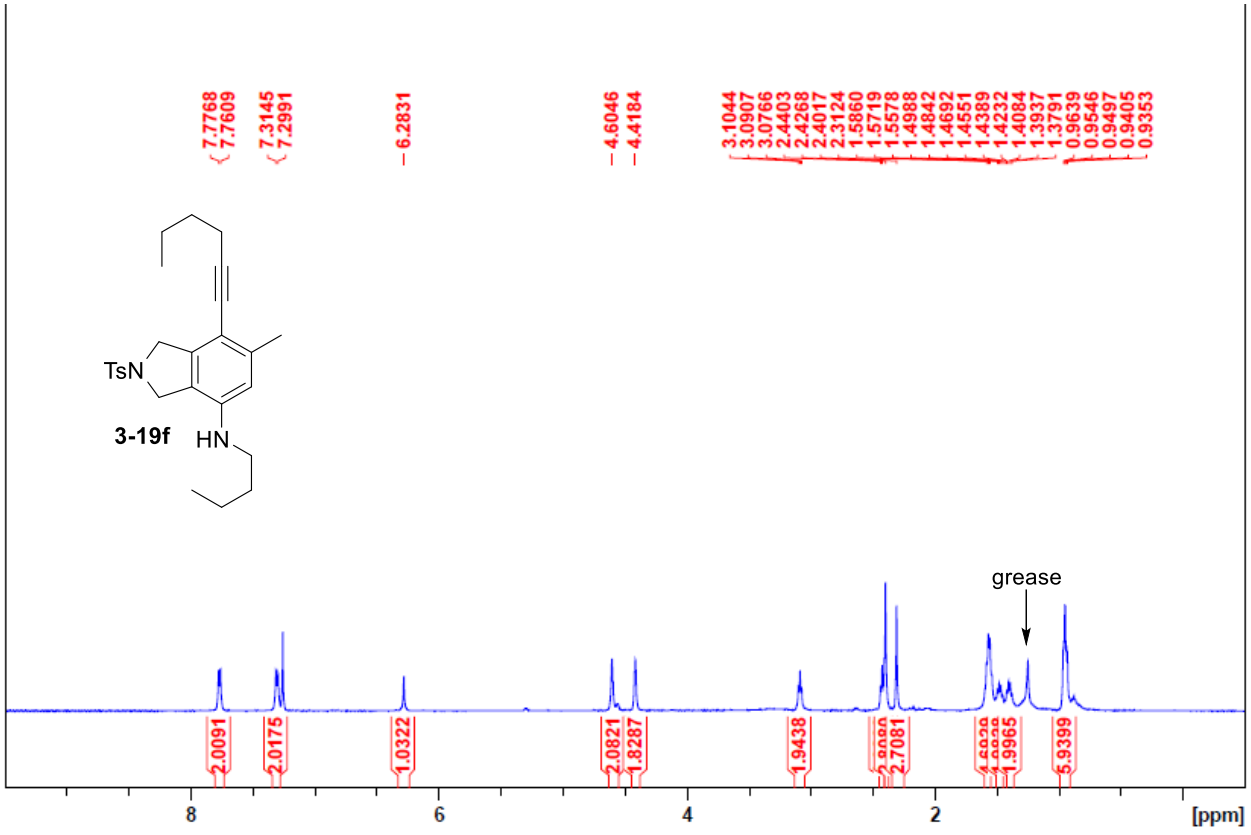
3-18e **3-19e**

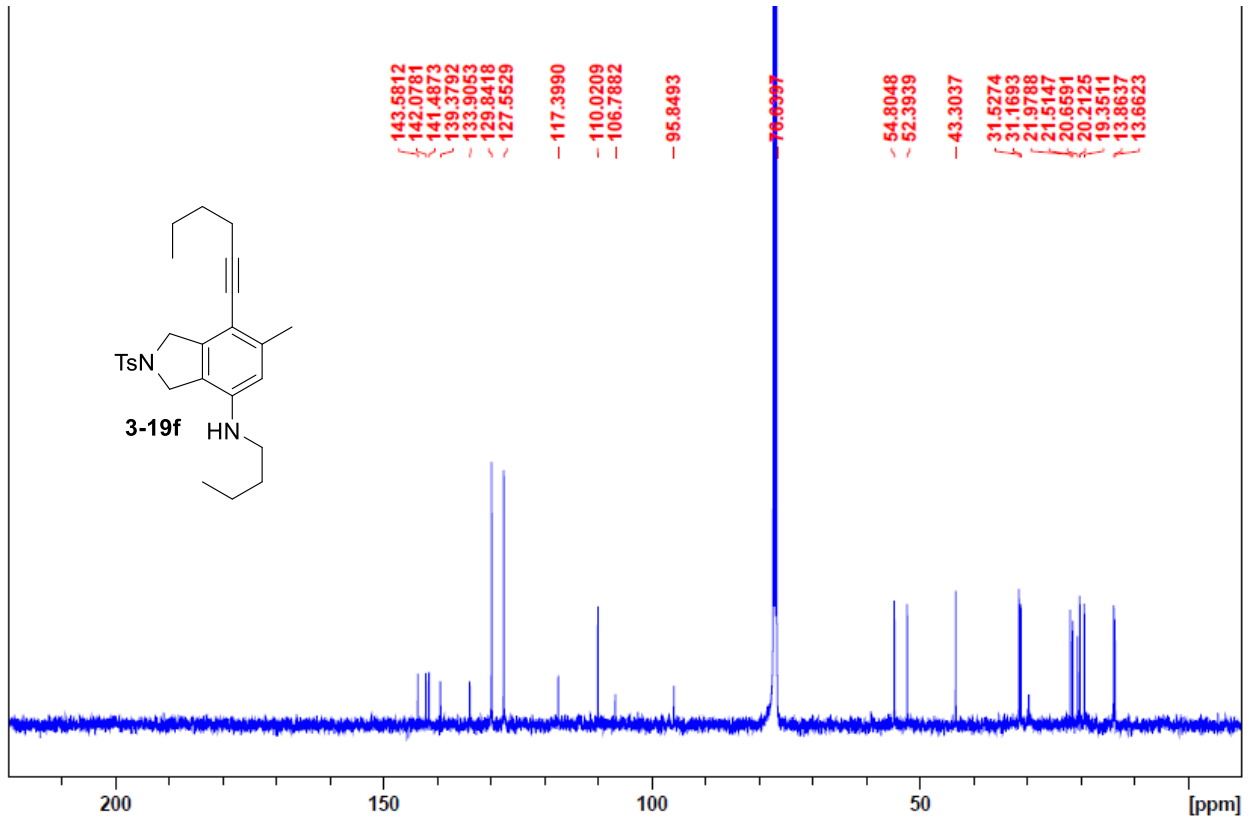

7.8137
7.7977
7.2829
7.2672
7.2606
7.0721
7.0566
5.2334
4.5444
2.5015
2.4875
2.4734
2.3997
2.1021
1.9529
1.6248
1.6103
1.5954
1.5794
1.4996
1.4844
1.4697
1.4554
0.9661
0.9515
0.9370
TsN
OAc
3-18f
grease
2.1681
3.0608
1.0298
1.9161
2.0000
2.2077
3.6864
2.9295
6.3318
2.6650
2.5227
3.4299
8
6
4
2
[ppm]

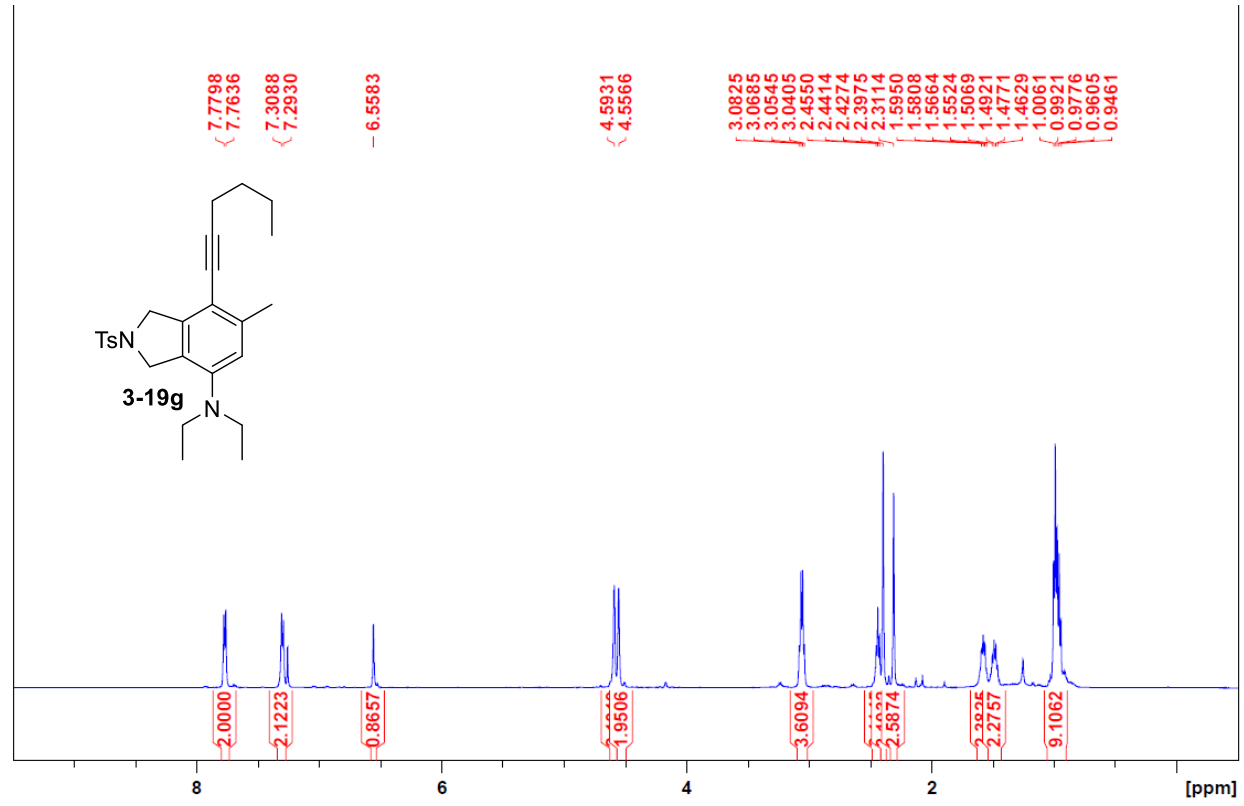

170.7833
146.5703
143.0215
138.1719
138.0644
134.0767
129.4429
127.6641
127.3976
121.5086
117.7200
102.8852
74.4914
72.4615
64.6370
52.2514
30.4888
26.6585
22.1259
21.4650
20.9426
19.4079
13.5619
TsN
OAc
3-18f
200
150
100
50
[ppm]

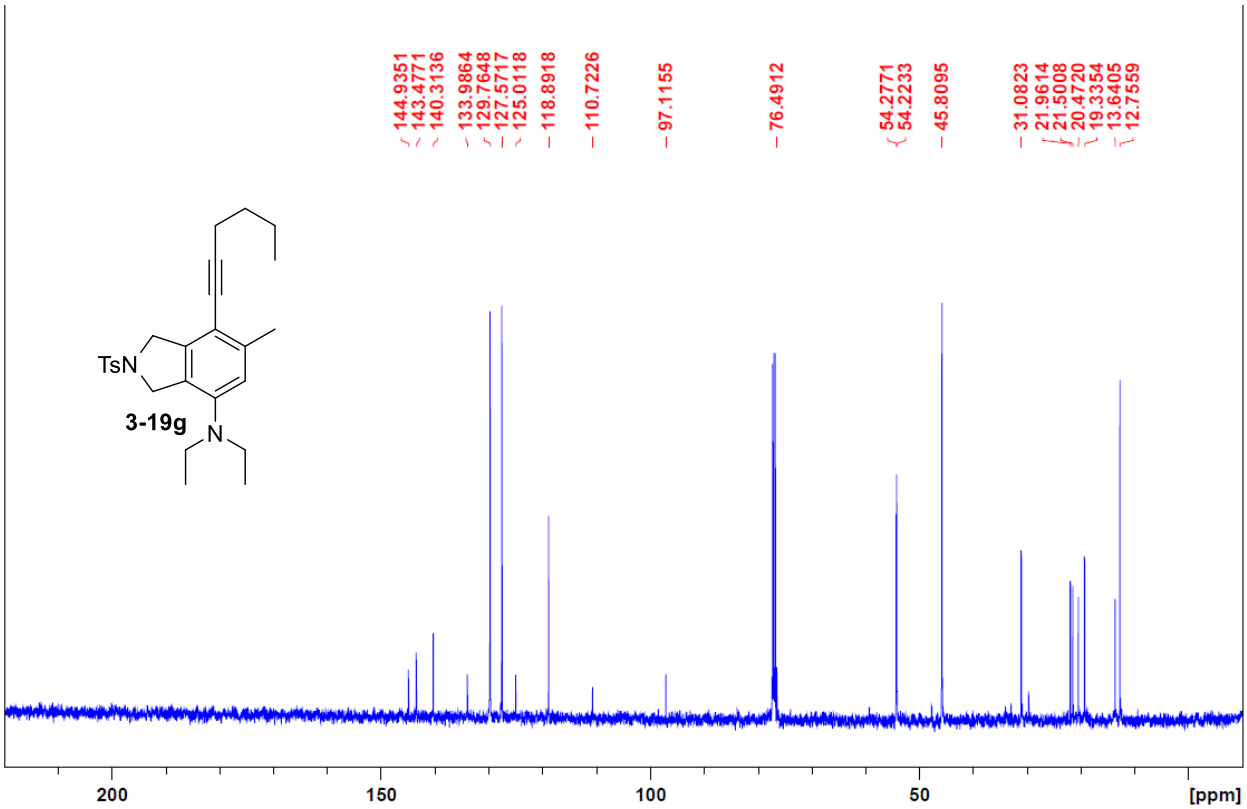

7.8158
7.7996
7.3307
7.3151
7.2817
7.2649
7.0709
7.0553
4.5782
4.5358
3.4270
2.5180
2.5040
2.4899
2.3981
1.9497
1.6414
1.6270
1.6119
1.5975
1.5182
1.5031
1.4882
1.4738
0.9758
0.9612
0.9466
TsN
OMe
3-18g
2.1456
1.9906
1.0000
2.1850
2.9893
2.2483
3.4120
6.0927
2.2422
2.4378
3.3771
8
6
4
2
[ppm]

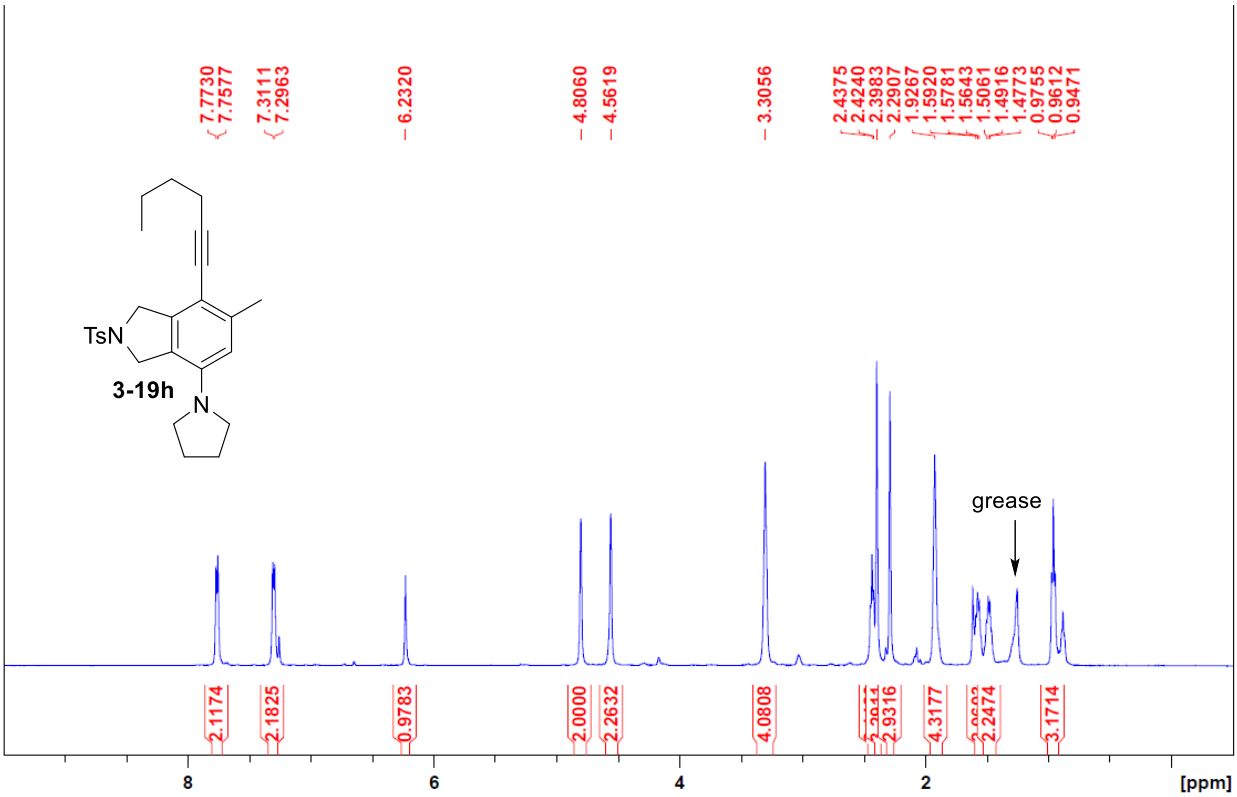

146.2485
142.9511
140.7182
138.1266
133.1445
129.4285
126.7613
121.4908
116.7249
102.2510
74.8450
72.5983
72.5002
58.5985
52.2604
30.5974
26.6863
22.1530
21.4631
19.4191
13.5773
TsN
OMe
3-18g
200
150
100
50
[ppm]

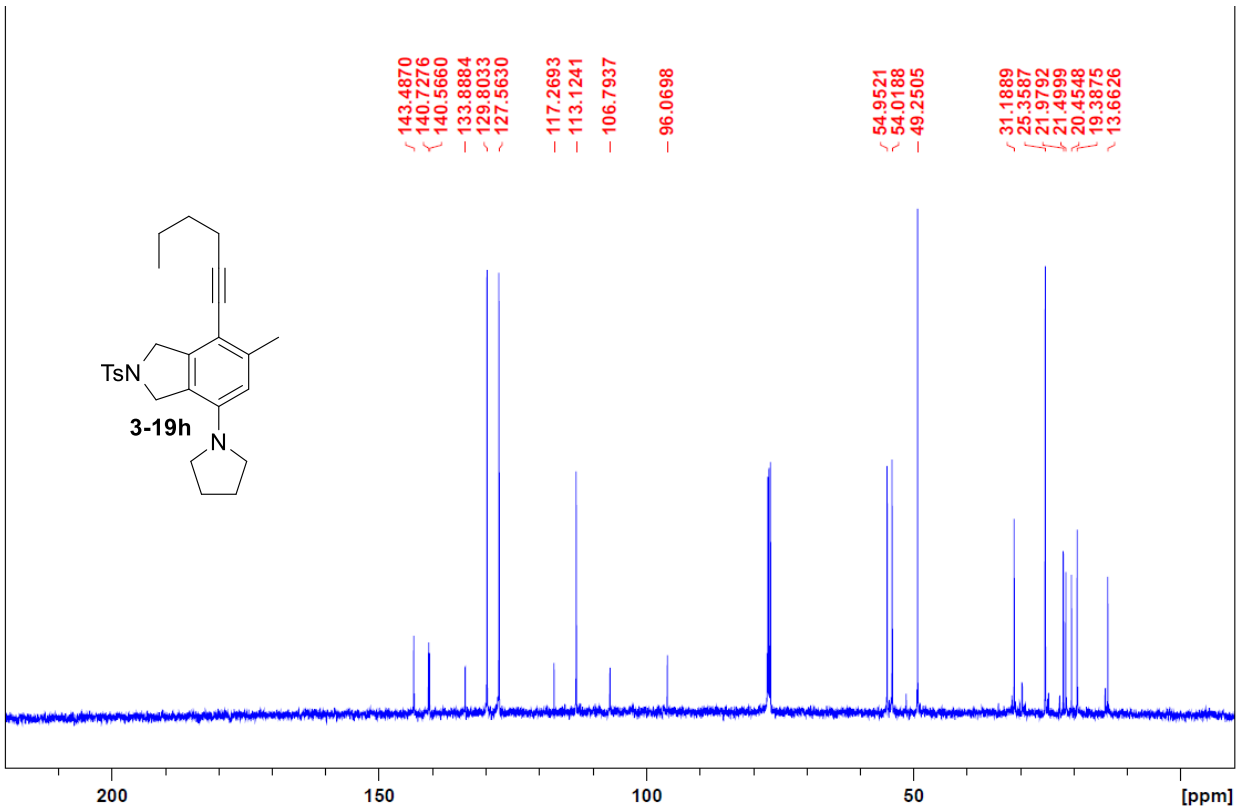

7.7768
7.7609
7.3145
7.2991
6.2831
4.6046
4.4184
3.1044
3.0907
3.0766
2.4403
2.4268
2.4017
2.3124
1.5860
1.5719
1.5578
1.4988
1.4842
1.4692
1.4551
1.4389
1.4232
1.4084
1.3937
1.3791
0.9639
0.9546
0.9497
0.9405
0.9353
TsN
3-19f
HN
grease
2.0091
2.0175
1.0322
2.0821
1.8287
1.9438
2.7081
1.9965
5.9399
8
6
4
2
[ppm]

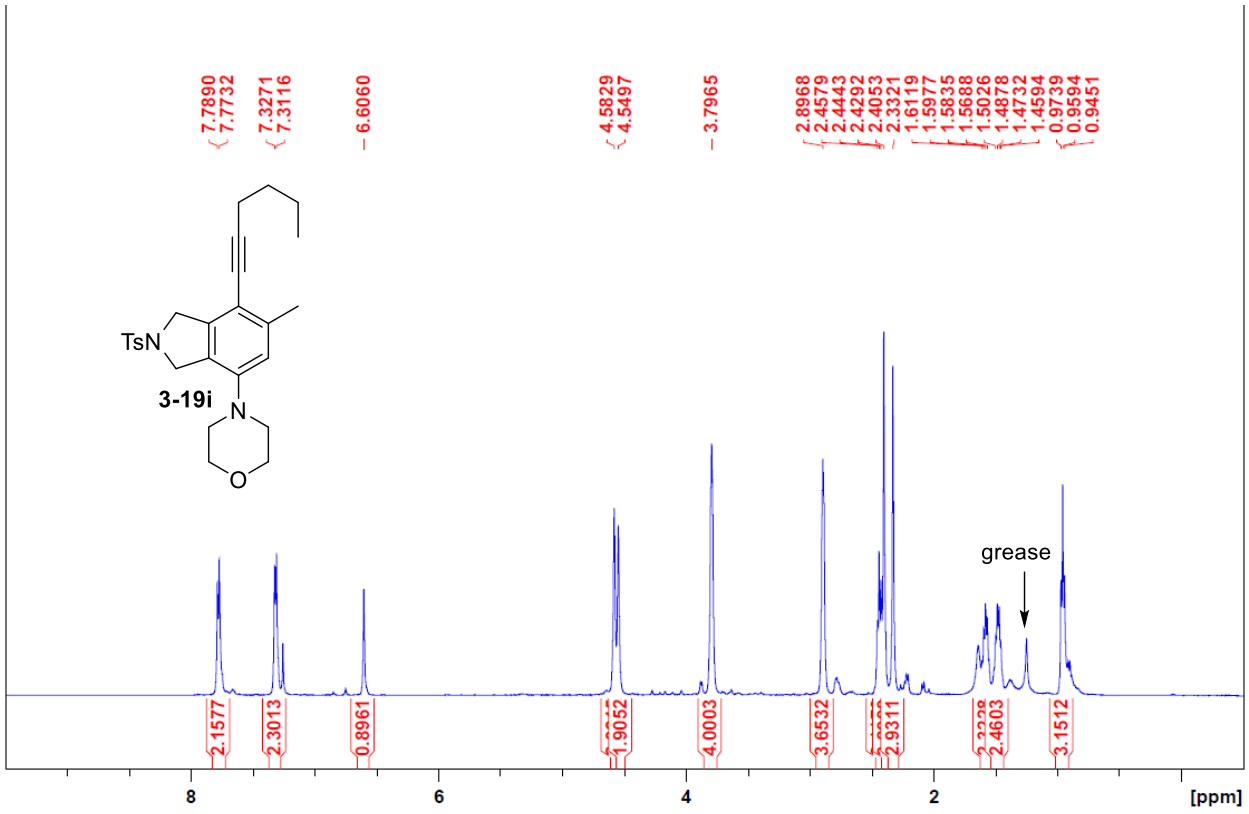

143.5812
142.0781
141.4873
139.3792
133.9053
129.8418
127.5529
117.3990
110.0209
106.7882
95.8493
54.8048
52.3939
43.3037
31.5274
31.1693
21.9788
21.5147
20.6591
20.2125
19.3511
13.8637
13.6623
TsN
3-19f
HN
200
150
100
50
[ppm]

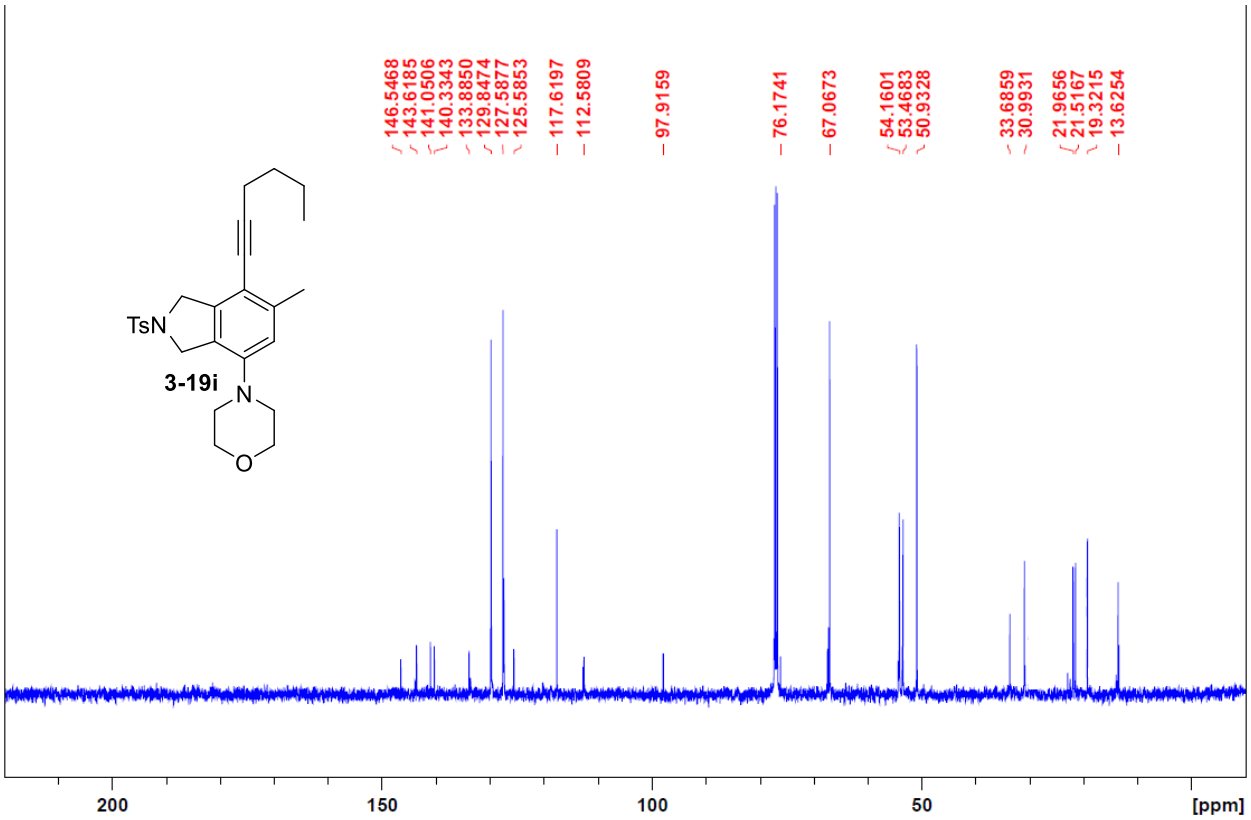

7.7798
7.7636
7.3088
7.2930
6.5583
4.5931
4.5566
3.0825
3.0685
3.0545
3.0405
2.4550
2.4414
2.4274
2.3975
2.3114
1.5950
1.5808
1.5664
1.5524
1.5069
1.4921
1.4771
1.4629
1.0061
0.9921
0.9776
0.9605
0.9461
TsN
3-19g
N
2.0000
2.1223
0.8657
1.9506
3.6094
2.5874
2.2757
9.1062
8
6
4
2
[ppm]

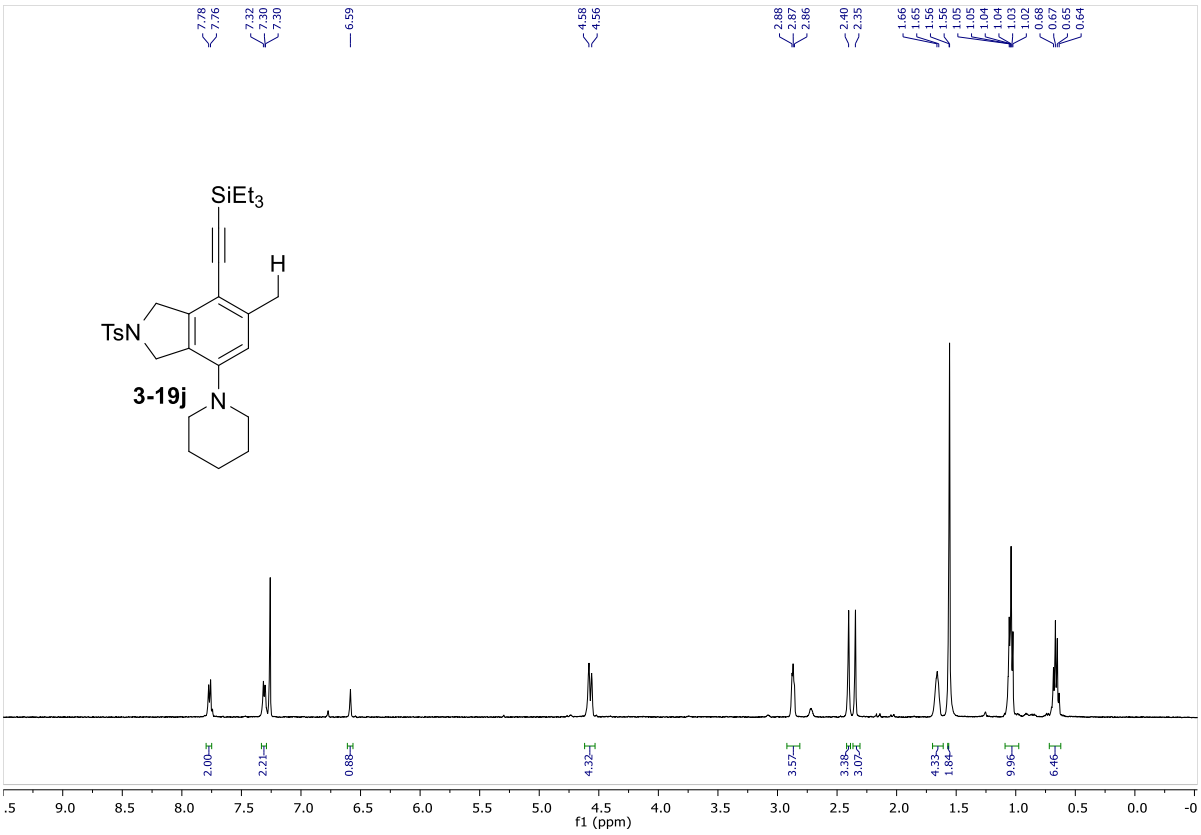

144.9351
143.4771
140.3136
133.9864
129.7648
127.5717
125.0118
118.8918
110.7226
97.1155
76.4912
54.2771
54.2233
45.8095
31.0823
21.9614
21.5008
20.4720
19.3354
13.6405
12.7559
TsN
3-19g
N
200
150
100
50
[ppm]

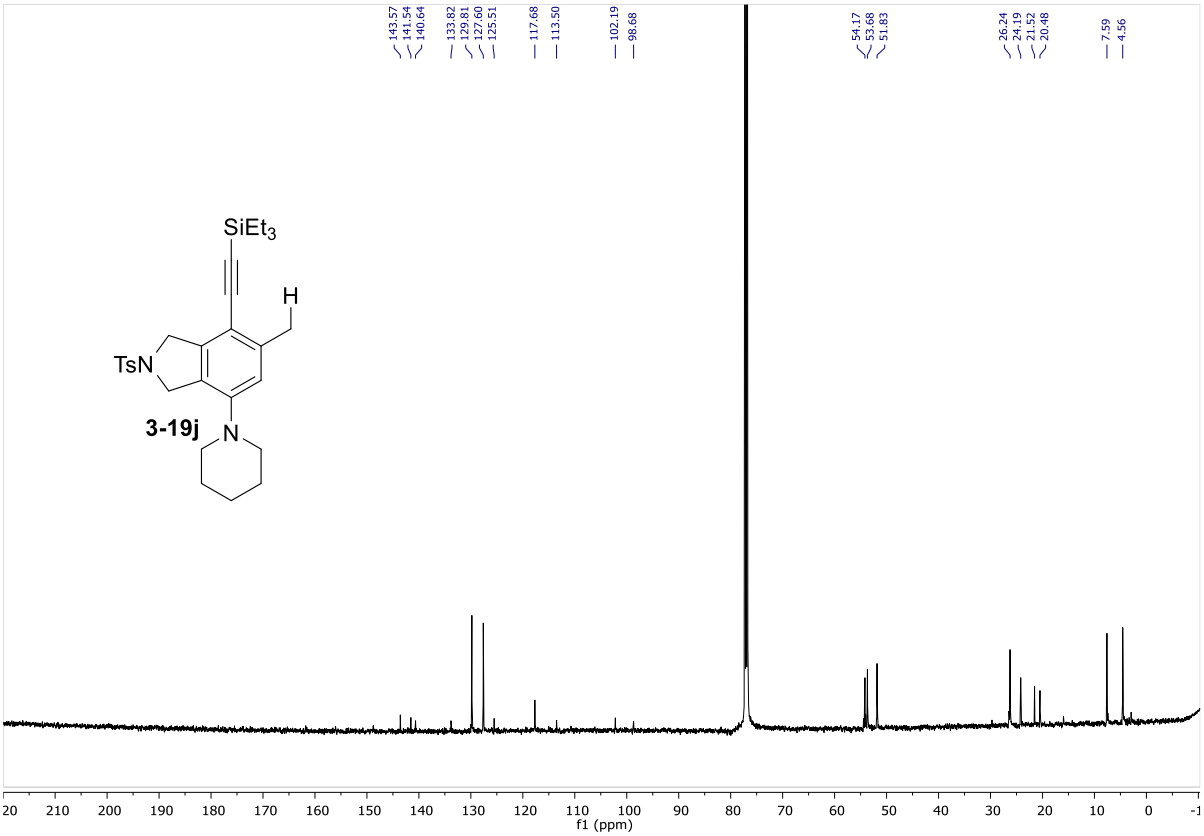

7.7730
7.7577
7.3111
7.2963
6.2320
4.8060
4.5619
3.3056
2.4375
2.4240
2.3983
2.2907
1.9267
1.5920
1.5781
1.5643
1.5061
1.4916
1.4773
0.9755
0.9612
0.9471
TsN
3-19h
N
grease
2.1174
2.1825
0.9783
2.0000
2.2632
4.0808
2.9316
4.3177
2.2474
3.1714
8
6
4
2
[ppm]

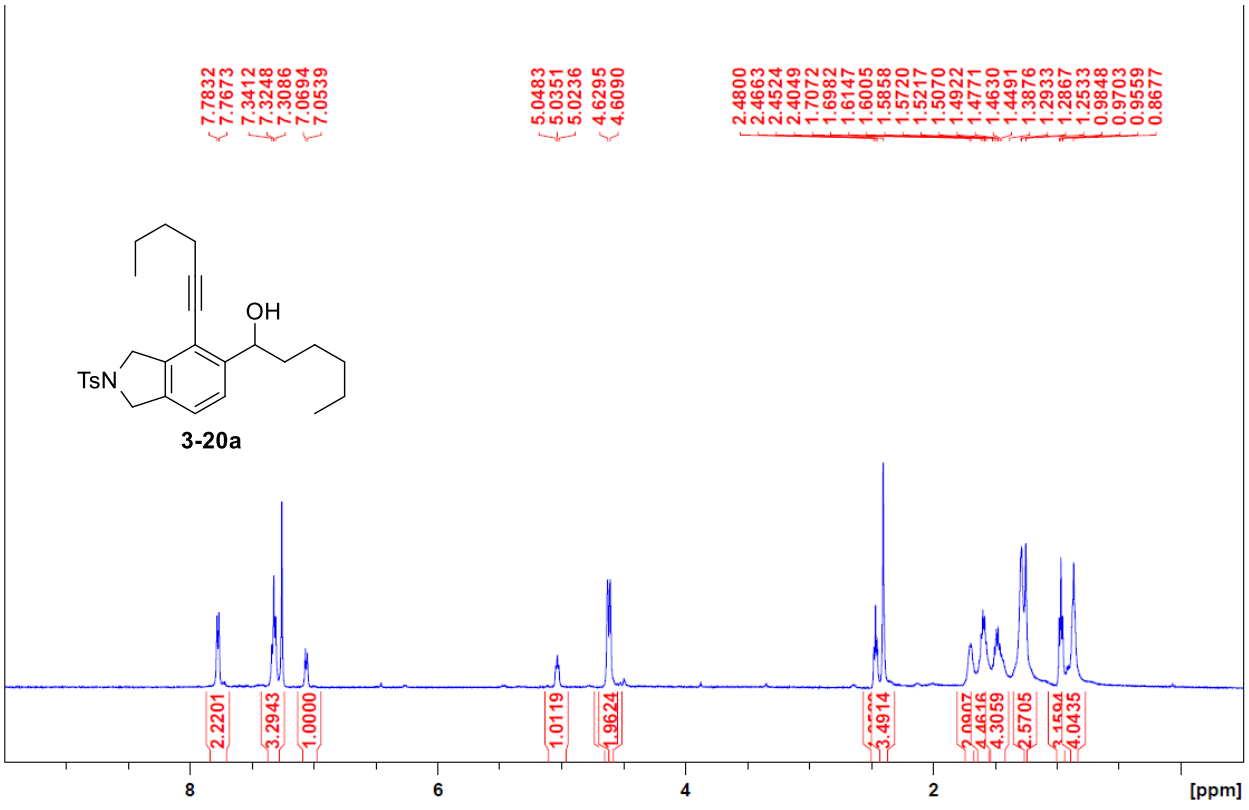

143.4870
140.7276
140.5660
133.8884
129.8033
127.5630
117.2693
113.1241
106.7937
96.0698
54.9521
54.0188
49.2505
31.1889
25.3587
21.9792
21.4999
20.4548
19.3875
13.6626
TsN
3-19h
N
200
150
100
50
[ppm]

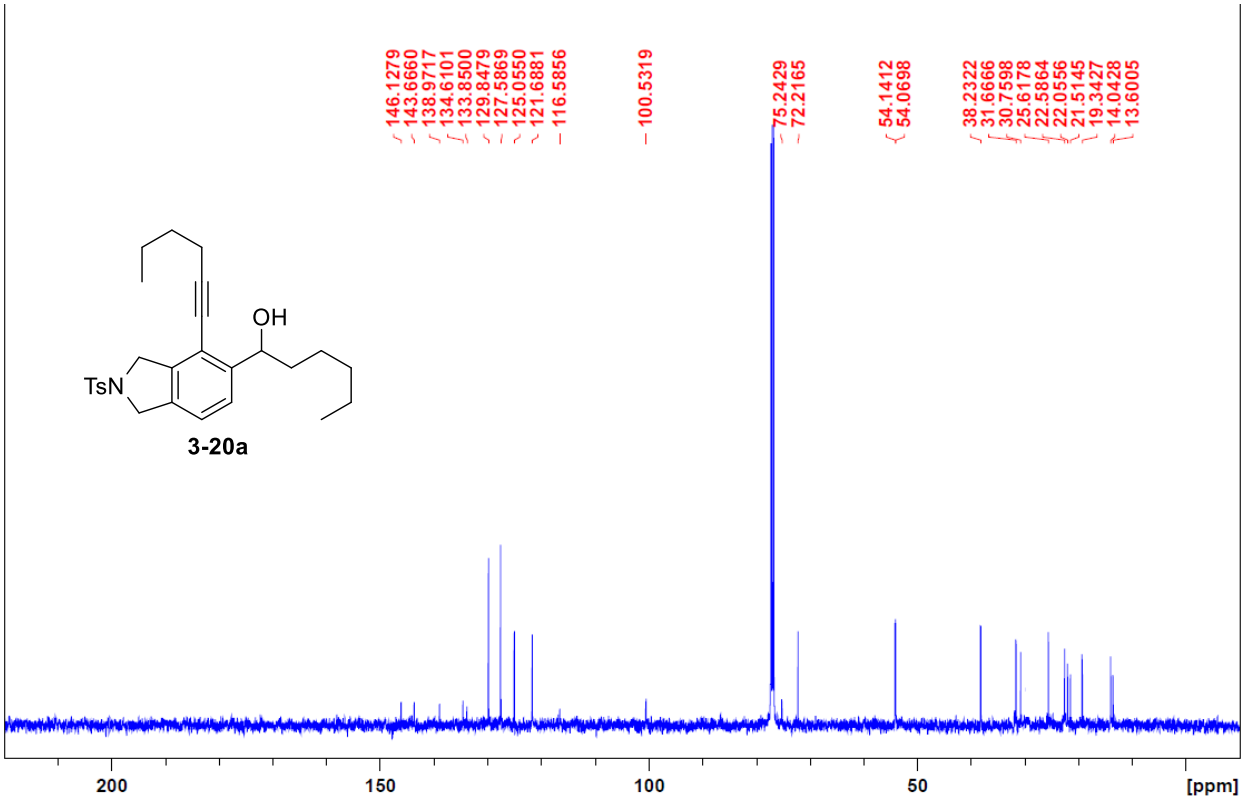

7.7890
7.7732
7.3271
7.3116
6.6060
4.5829
4.5497
3.7965
2.8968
2.4579
2.4443
2.4292
2.4053
2.3321
1.6119
1.5977
1.5835
1.5688
1.5026
1.4878
1.4732
1.4594
0.9739
0.9594
0.9451
TsN
3-19i
N
O
grease
2.1577
2.3013
0.8961
1.9052
4.0003
3.6532
2.9311
2.4603
3.1512
8
6
4
2
[ppm]

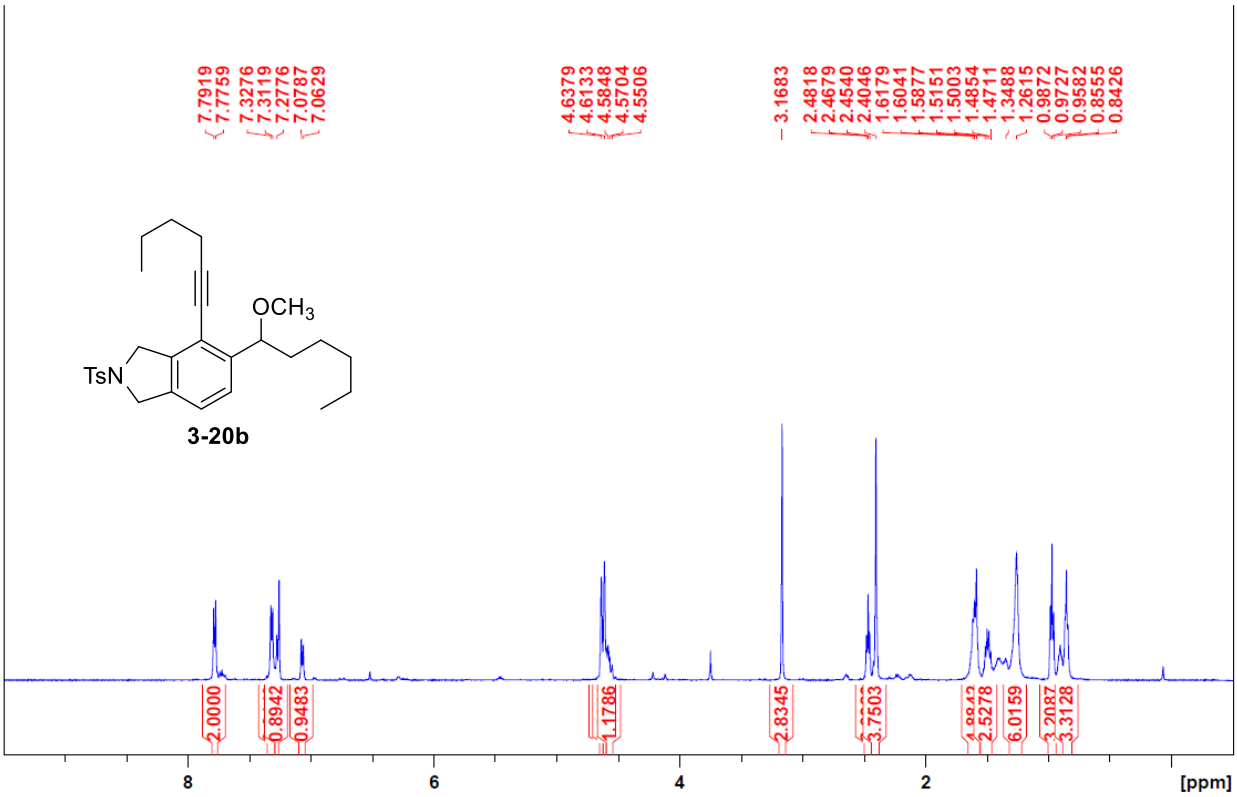

146.5468
143.6185
141.0506
140.3343
133.8850
129.8474
127.5877
125.5853
117.6197
112.5809
97.9159
76.1741
67.0673
54.1601
53.4683
50.9328
33.6859
30.9931
21.9656
21.5167
19.3215
13.6254
TsN
3-19i
N
O
200
150
100
50
[ppm]

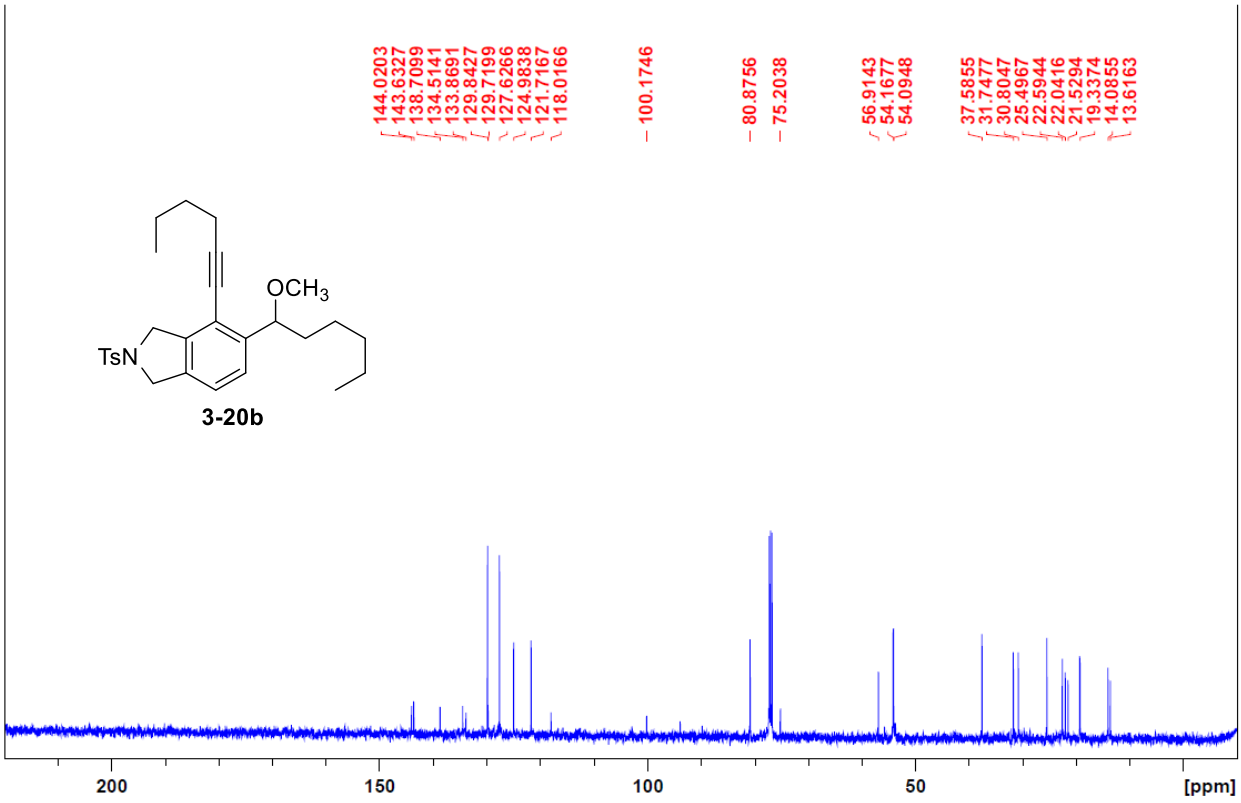

7.78
7.76
7.32
7.30
7.30
6.59
4.58
4.56
2.88
2.87
2.86
2.40
2.35
1.66
1.65
1.56
1.56
1.56
1.05
1.05
1.04
1.04
1.03
1.02
0.68
0.67
0.65
0.64
SiEt3
H
TsN
3-19j
N
2.00
2.21
0.88
4.32
3.57
3.38
3.07
4.33
1.84
9.96
6.46
f1 (ppm)

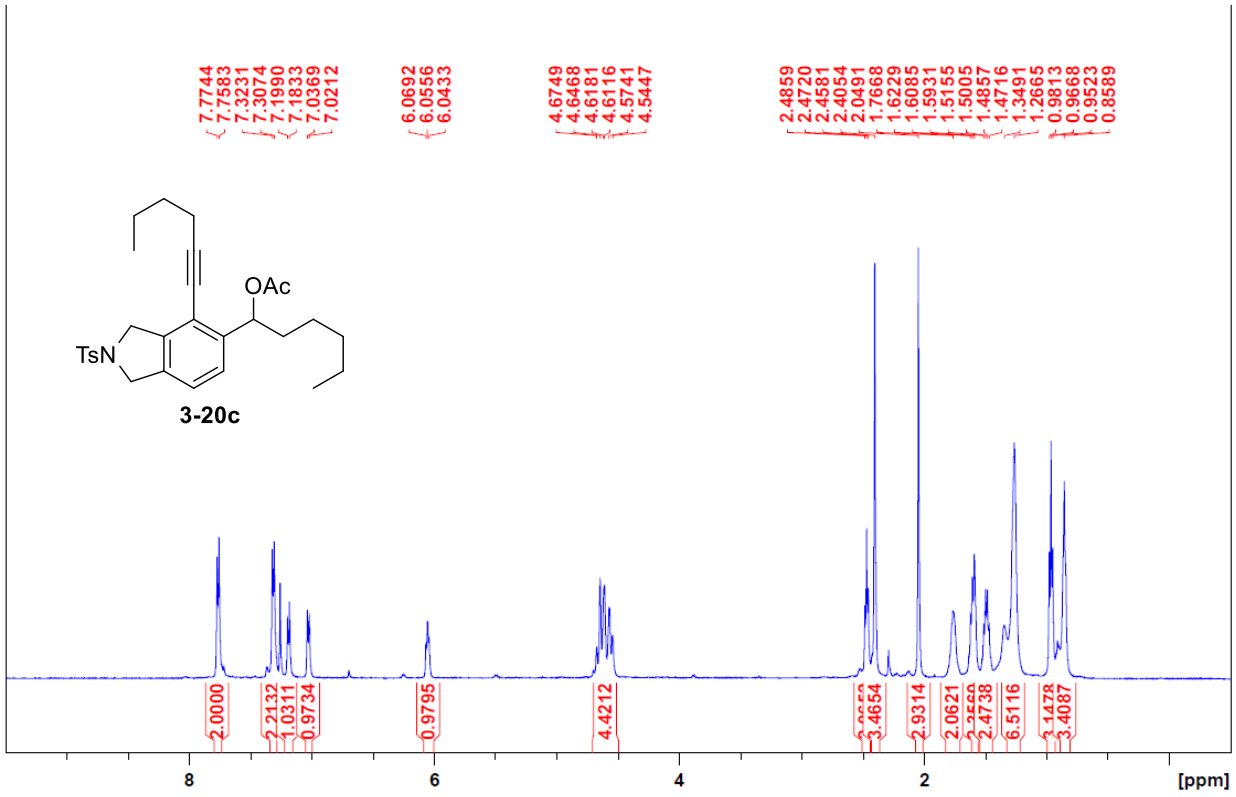

143.57
141.54
140.64
133.82
129.81
127.60
125.51
117.68
113.50
102.19
98.68
54.17
53.68
51.83
26.24
24.19
21.52
20.48
7.59
4.56
SiEt3
H
TsN
3-19j
N
f1 (ppm)

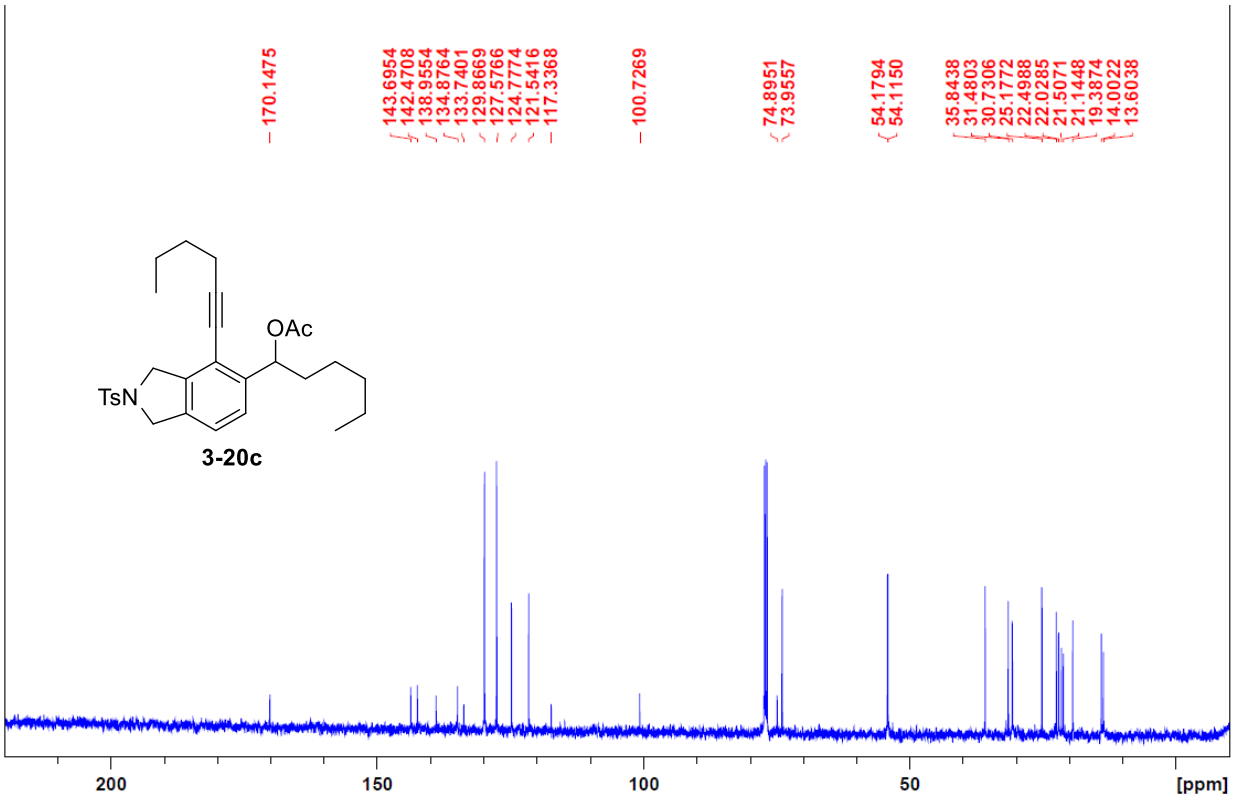

7.7832
7.7673
7.3412
7.3248
7.3086
7.0694
7.0539
5.0483
5.0351
5.0236
4.6295
4.6090
2.4800
2.4663
2.4524
2.4049
1.7072
1.6982
1.6147
1.6005
1.5858
1.5720
1.5217
1.5070
1.4922
1.4771
1.4630
1.4491
1.3876
1.2933
1.2867
1.2533
0.9848
0.9703
0.9559
0.8677
OH
TsN
3-20a
2.2201
3.2943
1.0000
1.0119
1.9624
3.4914
4.3059
2.5705
4.0435
8
6
4
2
[ppm]

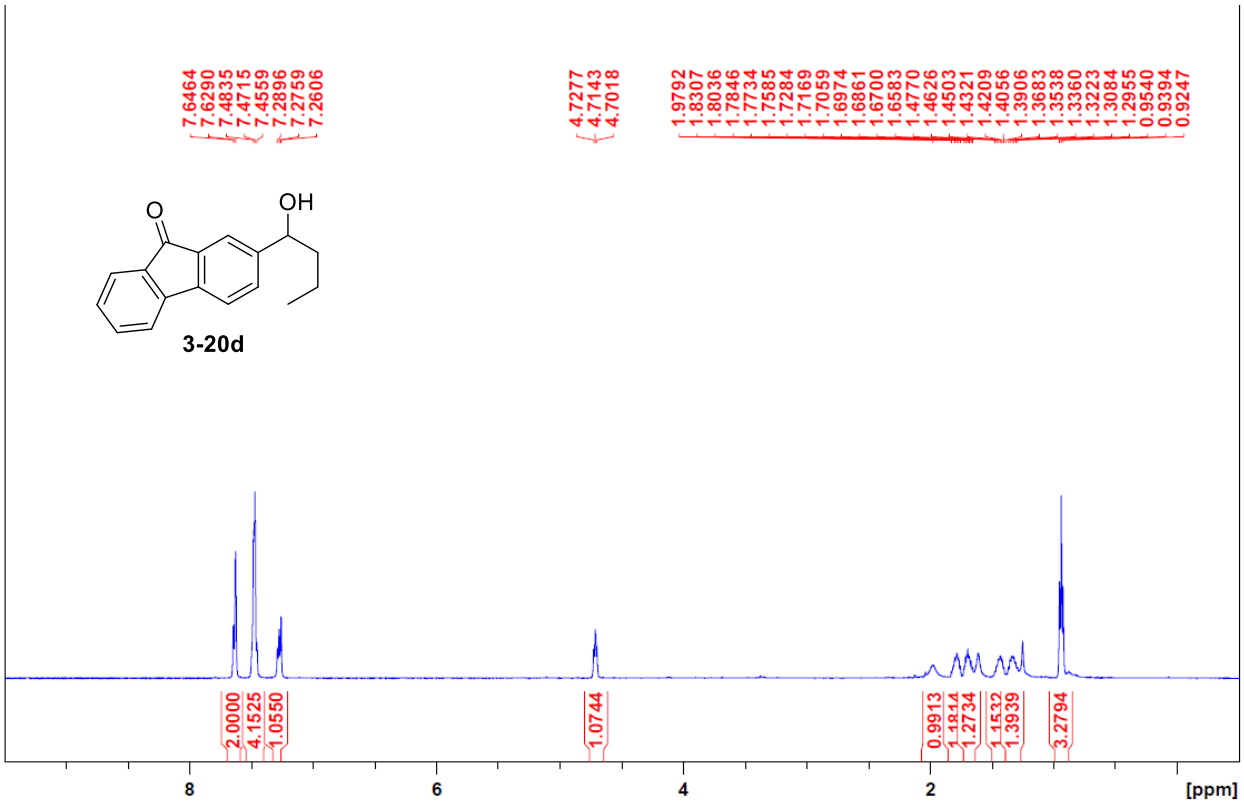

146.1279
143.6660
138.9717
134.6101
133.8500
129.8479
127.5869
125.0550
121.6881
116.5856
100.5319
75.2429
72.2165
54.1412
54.0698
38.2322
31.6666
30.7598
25.6178
22.5864
22.0556
21.5145
19.3427
14.0428
13.6005
OH
TsN
3-20a
200
150
100
50
[ppm]

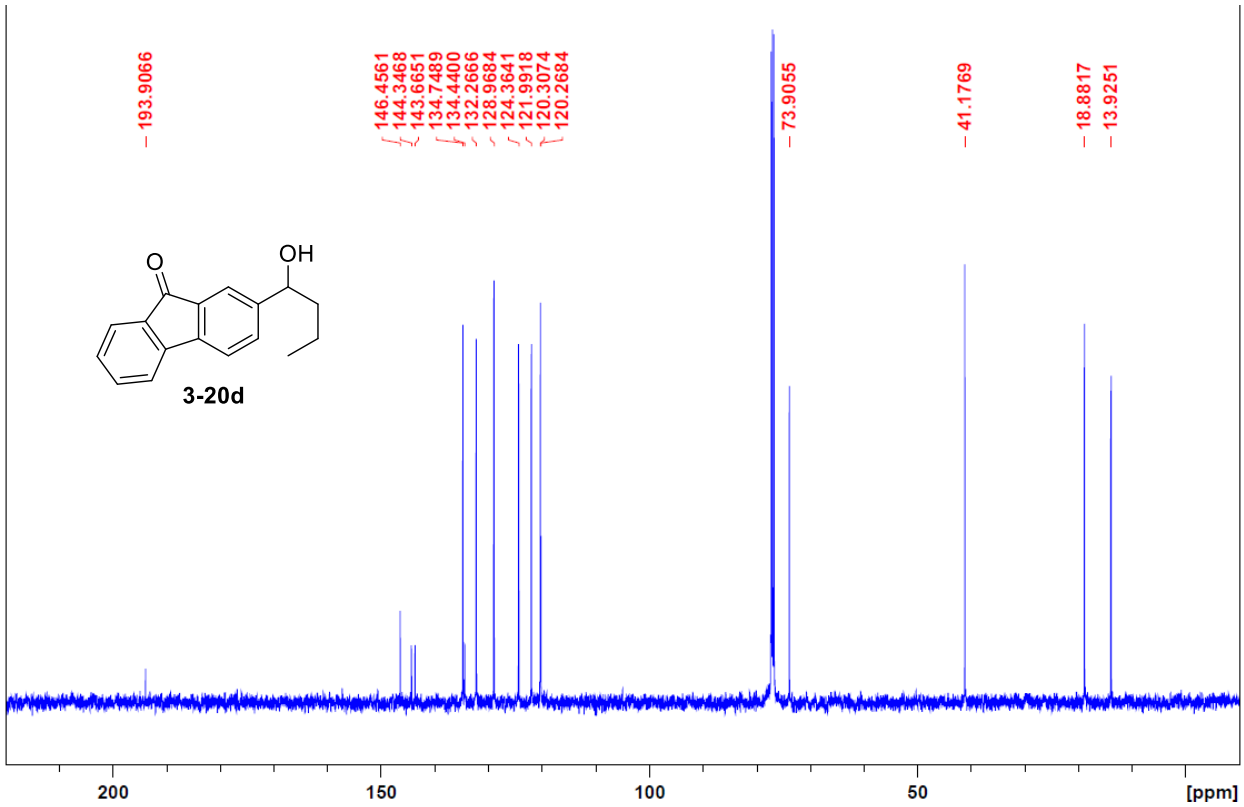

7.7919
7.7759
7.3276
7.3119
7.2776
7.0787
7.0629
4.6379
4.6133
4.5848
4.5704
4.5506
3.1683
2.4818
2.4679
2.4540
2.4046
1.6179
1.6041
1.5877
1.5151
1.5003
1.4854
1.4711
1.3488
1.2615
0.9872
0.9727
0.9582
0.8555
0.8426
OCH3
TsN
3-20b
2.0000
0.8942
0.9483
1.1786
2.8345
3.7503
2.5278
6.0159
3.2087
3.3128
8
6
4
2
[ppm]

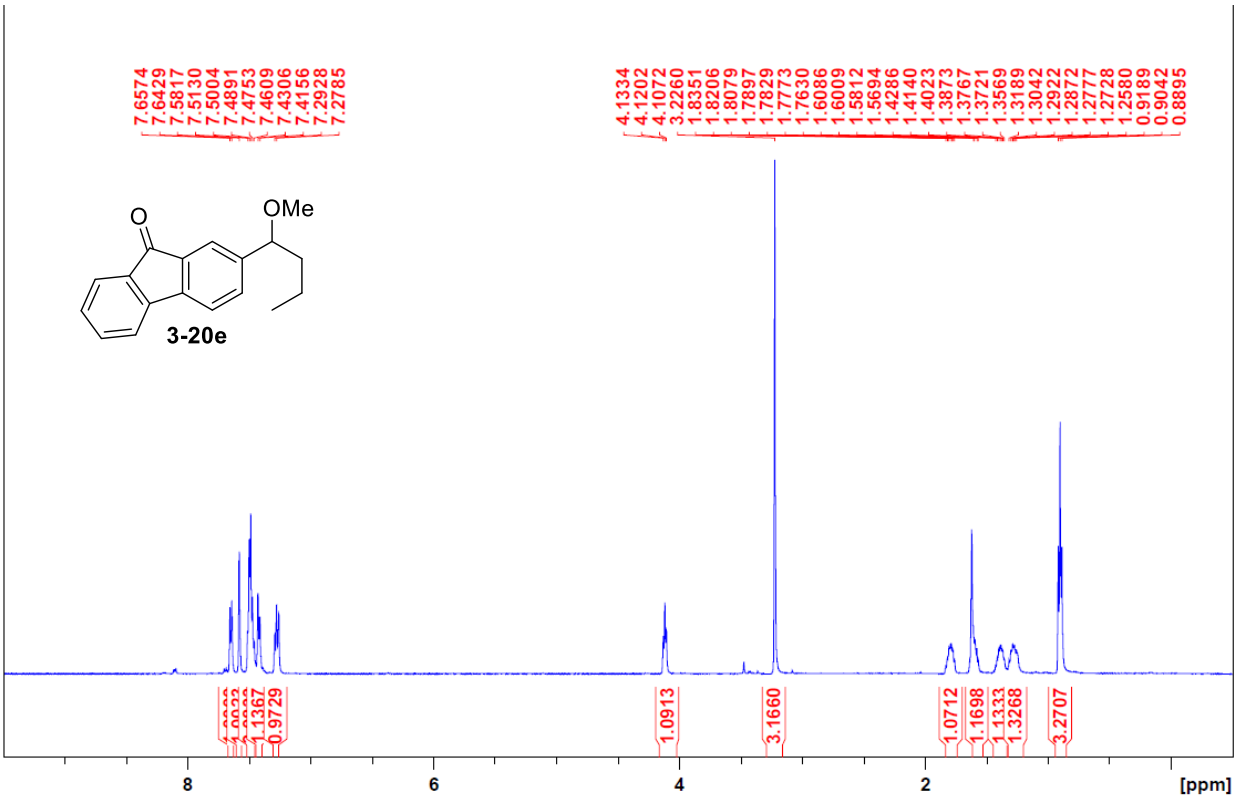

144.0203
143.6327
138.7099
134.5141
133.8691
129.8427
129.7199
127.6266
124.9838
121.7167
118.0166
100.1746
80.8756
75.2038
56.9143
54.1677
54.0948
37.5855
31.7477
30.8047
25.4967
22.5944
22.0416
21.5294
19.3374
14.0855
13.6163
OCH3
TsN
3-20b
200
150
100
50
[ppm]

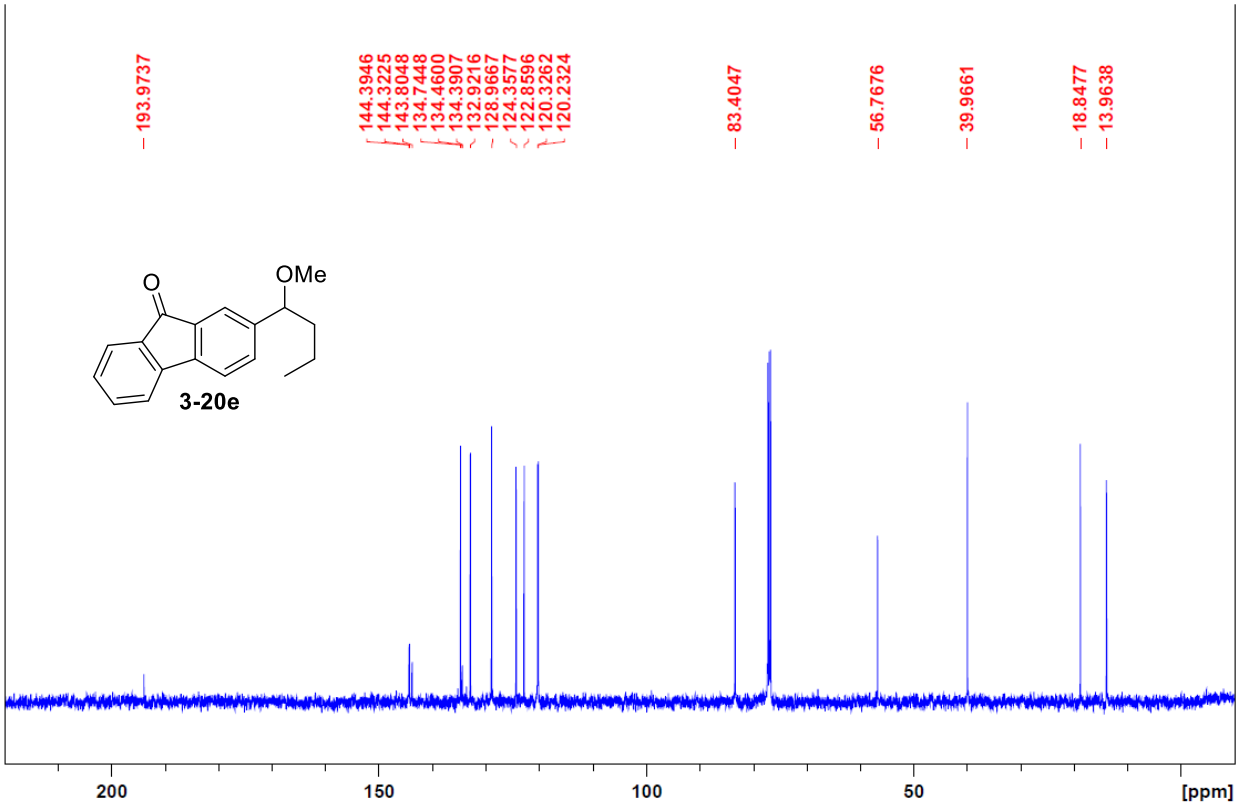

7.7744
7.7583
7.3231
7.3074
7.1990
7.1833
7.0369
7.0212
6.0692
6.0556
6.0433
4.6749
4.6468
4.6181
4.6116
4.5741
4.5447
2.4859
2.4720
2.4581
2.4054
2.0491
1.7668
1.6229
1.6085
1.5931
1.5155
1.5005
1.4857
1.4716
1.3491
1.2665
0.9813
0.9668
0.9523
0.8589
OAc
TsN
3-20c
2.0000
2.2132
1.0311
0.9734
0.9795
4.4212
3.4654
2.9314
2.0621
2.4738
6.5116
3.1478
3.4087
8
6
4
2
[ppm]

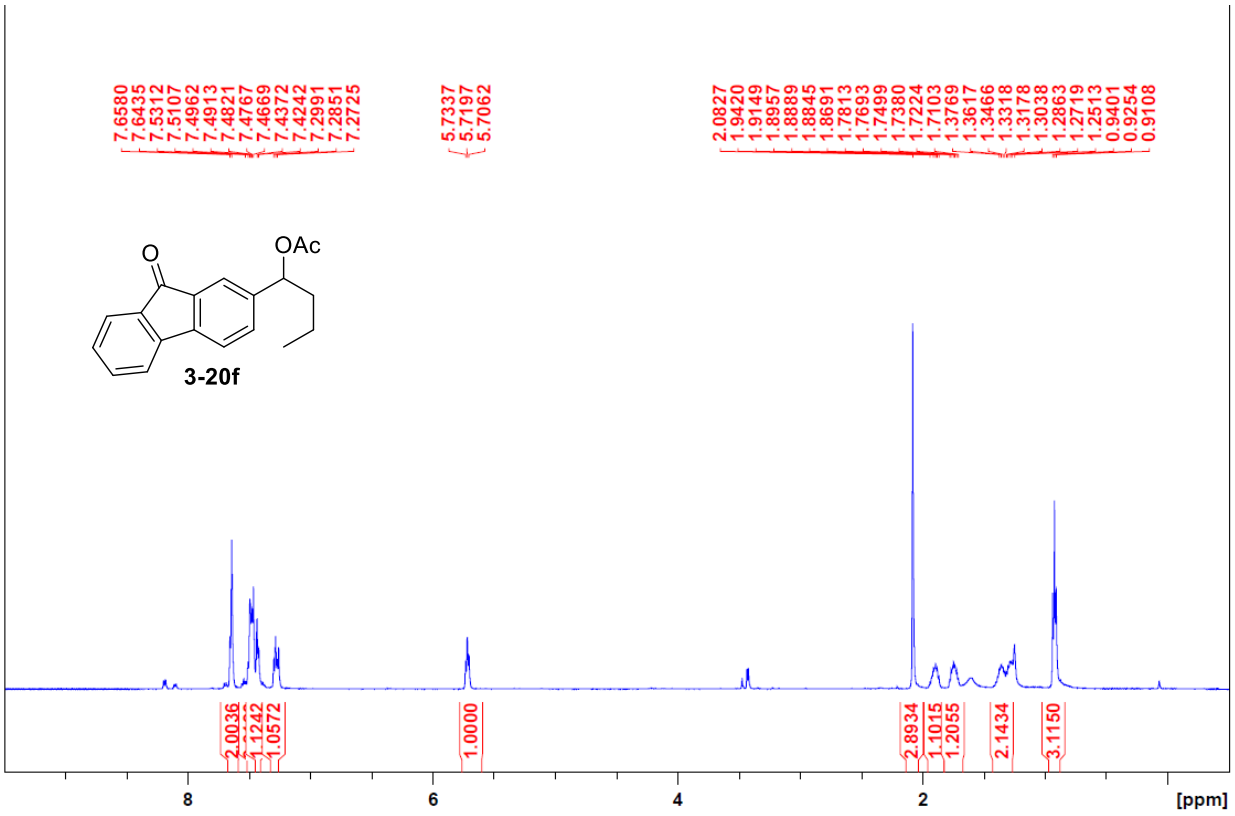

170.1475
143.6954
142.4708
138.9554
134.8764
133.7401
129.8669
127.5766
124.7774
121.5416
117.3368
100.7269
74.8951
73.9557
54.1794
54.1150
35.8438
31.4803
30.7306
25.1772
22.4988
22.0285
21.5071
21.1448
19.3874
14.0022
13.6038
OAc
TsN
3-20c
200
150
100
50
[ppm]

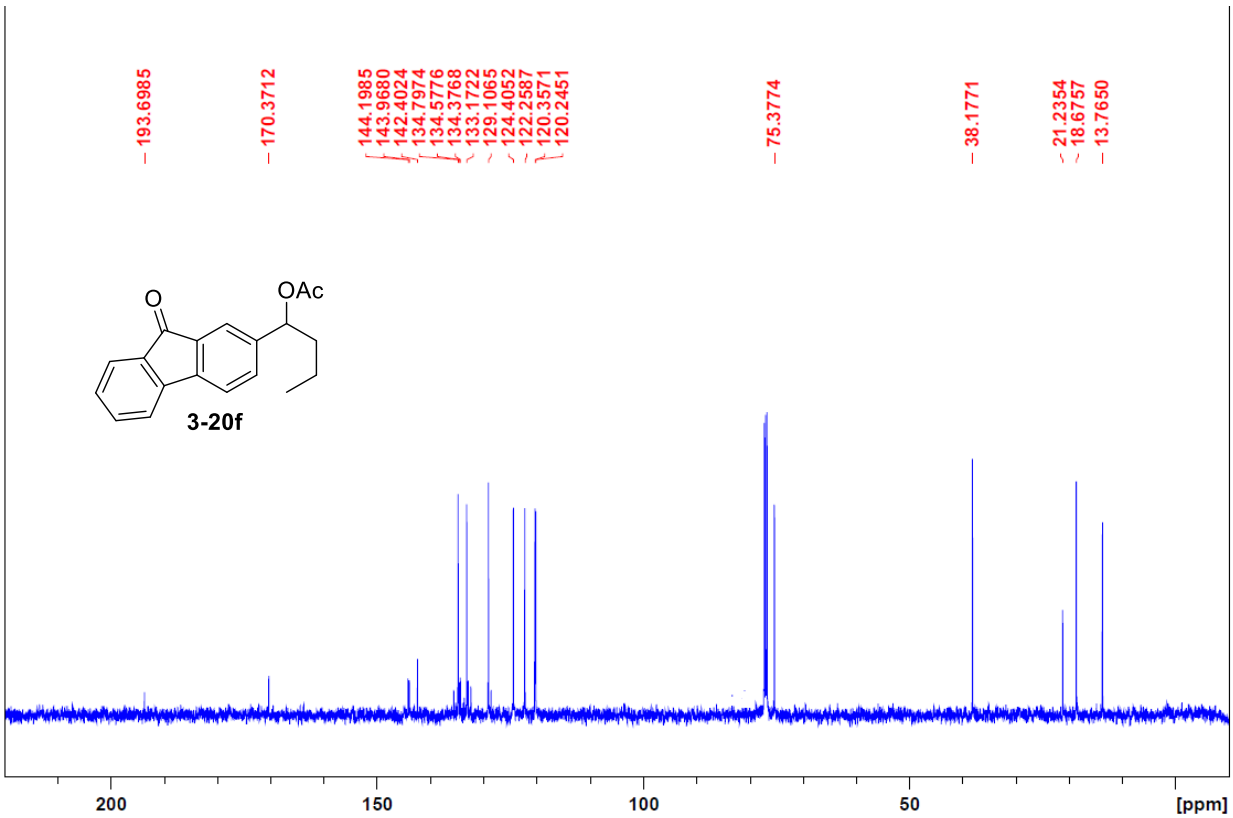

7.6464
7.6290
7.4835
7.4715
7.4559
7.2896
7.2759
7.2606
4.7277
4.7143
4.7018
1.9792
1.8307
1.8036
1.7846
1.7734
1.7585
1.7284
1.7169
1.7059
1.6974
1.6861
1.6700
1.6583
1.4770
1.4626
1.4503
1.4321
1.4209
1.4056
1.3906
1.3683
1.3538
1.3360
1.3223
1.3084
1.2955
0.9540
0.9394
0.9247
O
OH
3-20d
2.0000
4.1525
1.0550
1.0744
0.9913
1.1814
1.2734
1.1532
1.3939
3.2794
8
6
4
2
[ppm]

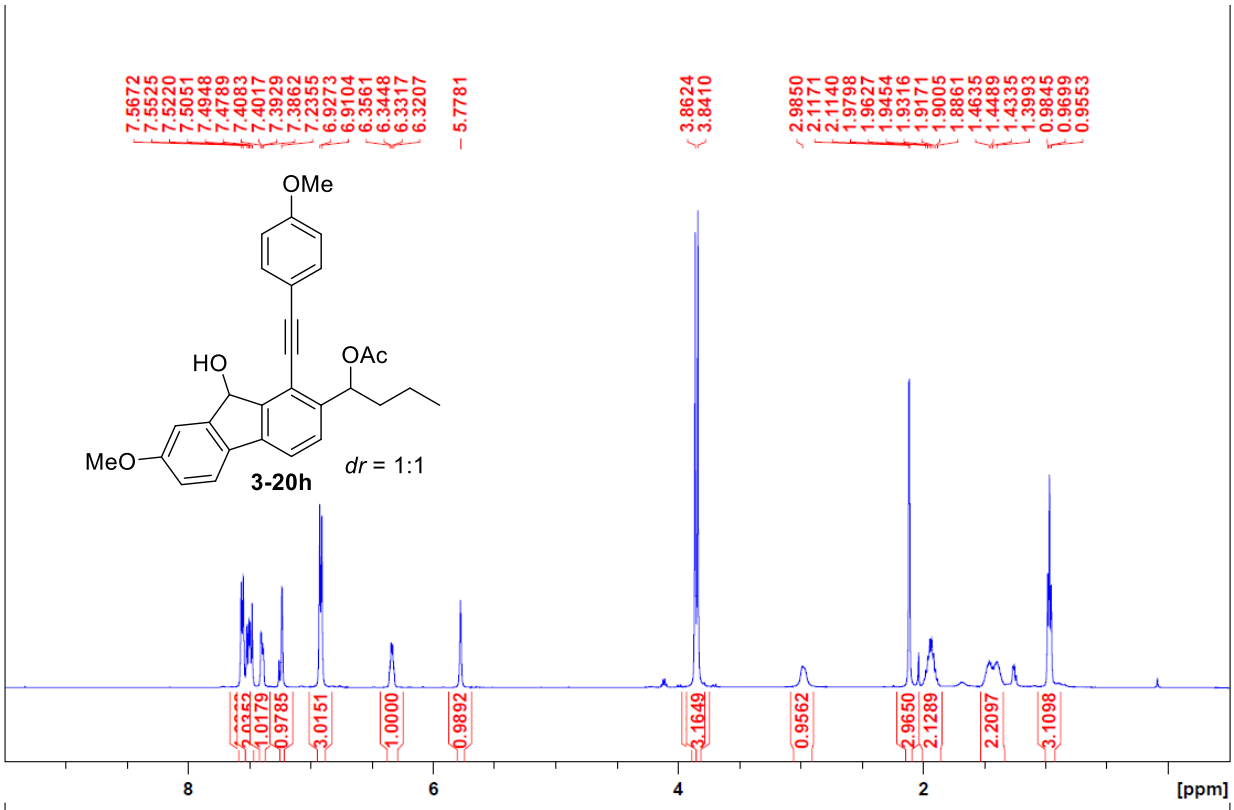

193.9066
146.4561
144.3468
143.6651
134.7489
134.4400
132.2666
128.9684
124.3641
121.9918
120.3074
120.2684
73.9055
41.1769
18.8817
13.9251
O
OH
3-20d
200
150
100
50
[ppm]

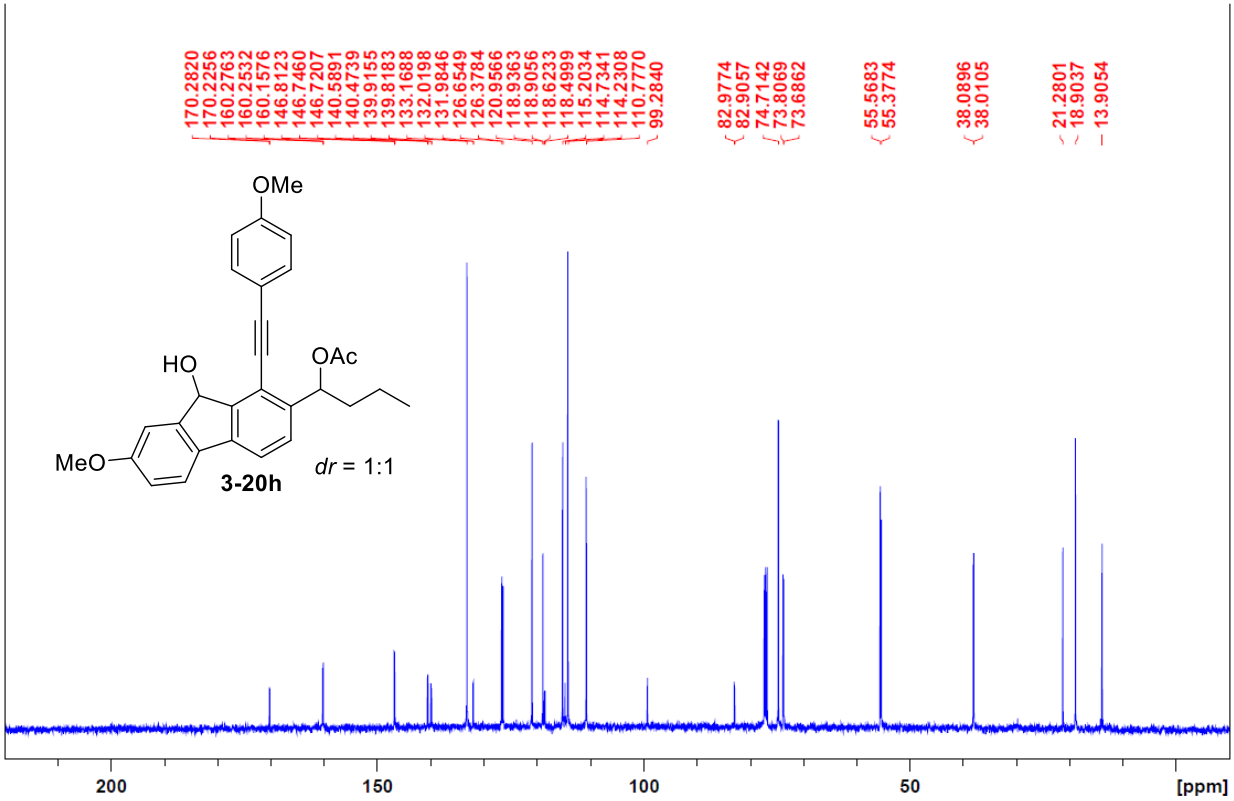

7.6574
7.6429
7.5817
7.5130
7.5004
7.4891
7.4753
7.4609
7.4306
7.4156
7.2928
7.2785
4.1334
4.1202
4.1072
3.2260
1.8351
1.8206
1.8079
1.7897
1.7829
1.7773
1.7630
1.6086
1.6009
1.5812
1.5694
1.4286
1.4140
1.4023
1.3873
1.3767
1.3721
1.3569
1.3189
1.3042
1.2922
1.2872
1.2777
1.2728
1.2580
0.9189
0.9042
0.8895
O
OMe
3-20e
1.0913
3.1660
1.0712
1.1698
1.1333
1.3268
3.2707
8
6
4
2
[ppm]

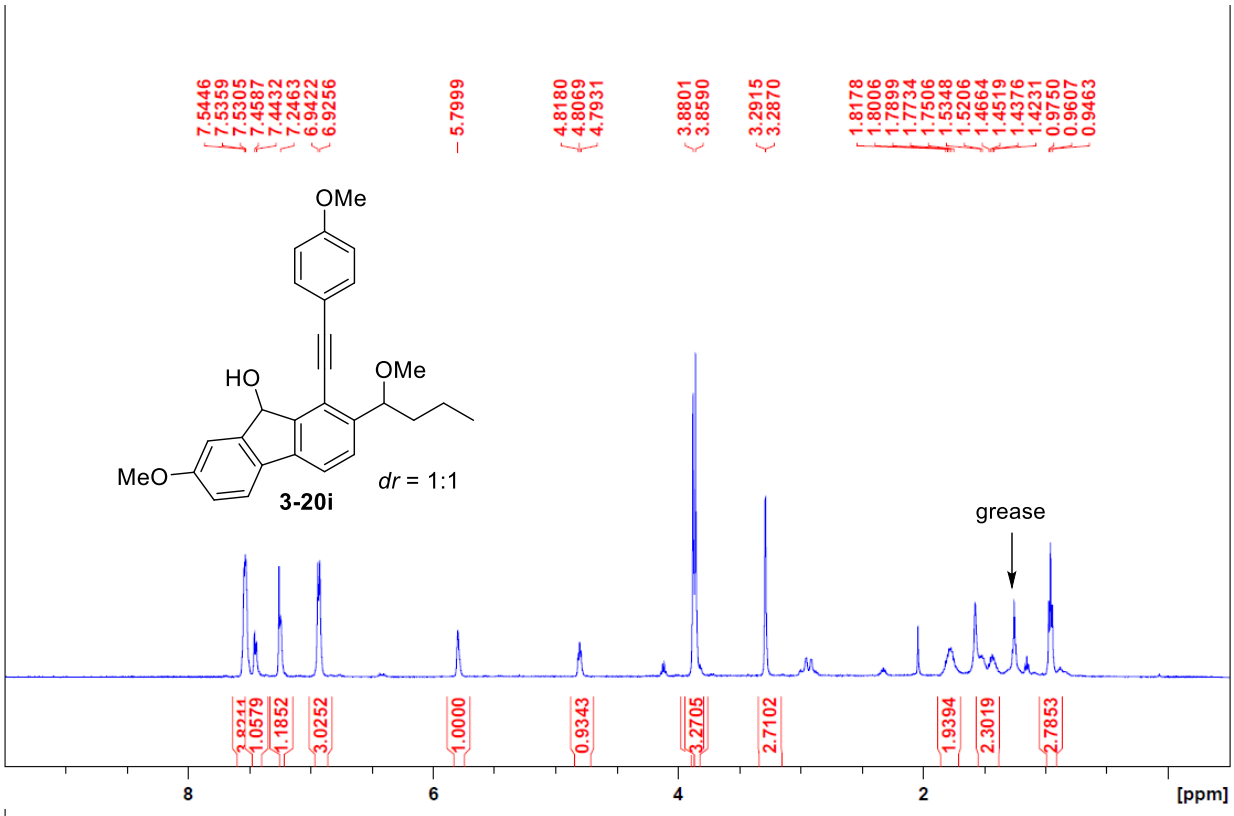

193.9737
144.3946
144.3225
143.8048
134.7448
134.4600
134.3907
132.9216
128.9667
124.3577
122.8596
120.3262
120.2324
83.4047
56.7676
39.9661
18.8477
13.9638
O
OMe
3-20e
200
150
100
50
[ppm]

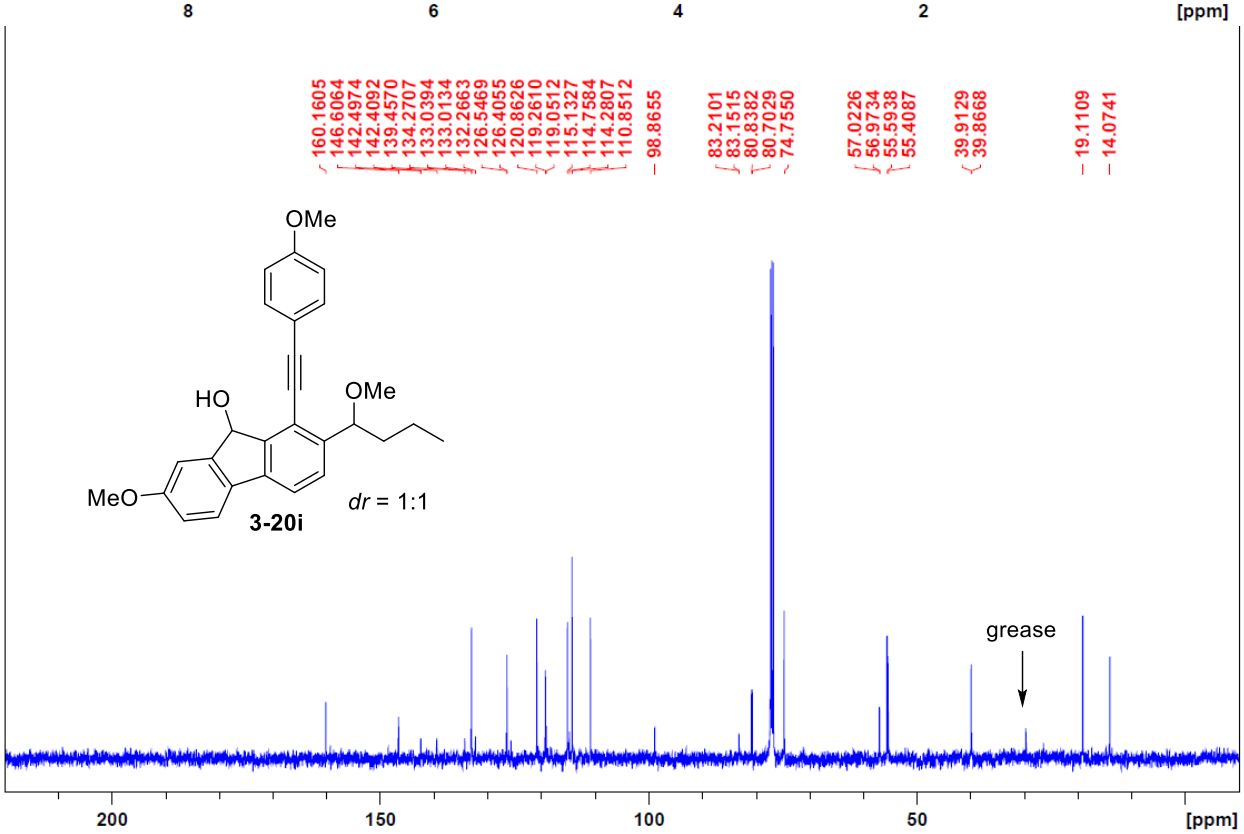

7.6580
7.6435
7.5312
7.5107
7.4962
7.4913
7.4821
7.4767
7.4669
7.4372
7.4242
7.2991
7.2851
7.2725
5.7337
5.7197
5.7062
2.0827
1.9420
1.9149
1.8957
1.8889
1.8845
1.8691
1.7813
1.7693
1.7499
1.7380
1.7224
1.7103
1.3769
1.3617
1.3466
1.3318
1.3178
1.3038
1.2863
1.2719
1.2513
0.9401
0.9254
0.9108
O
OAc
3-20f
2.0036
1.1242
1.0572
1.0000
2.8934
1.1015
1.2055
2.1434
3.1150
8
6
4
2
[ppm]

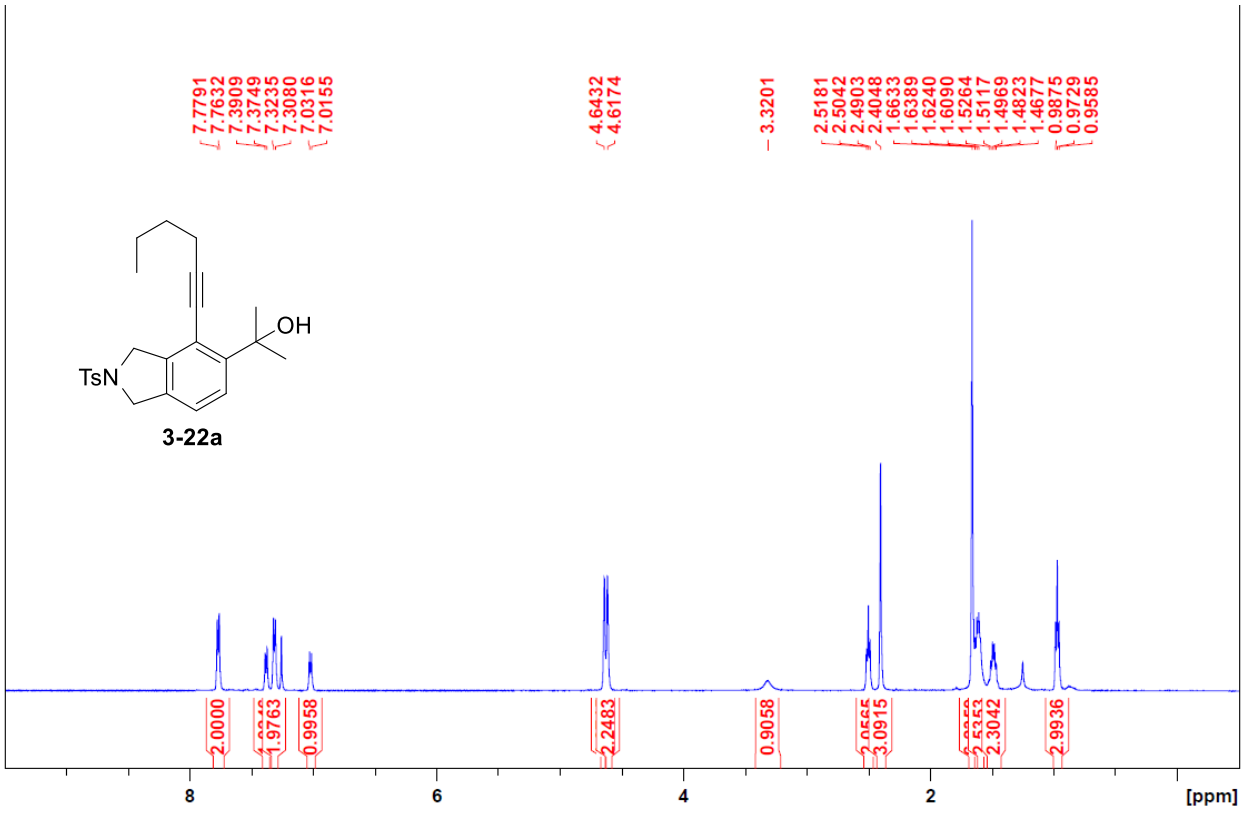

193.6985
170.3712
144.1985
143.9680
142.4024
134.7974
134.5776
134.3768
133.1722
129.1065
124.4052
122.2587
120.3571
120.2451
75.3774
38.1771
21.2354
18.6757
13.7650
O
OAc
3-20f
200
150
100
50
[ppm]

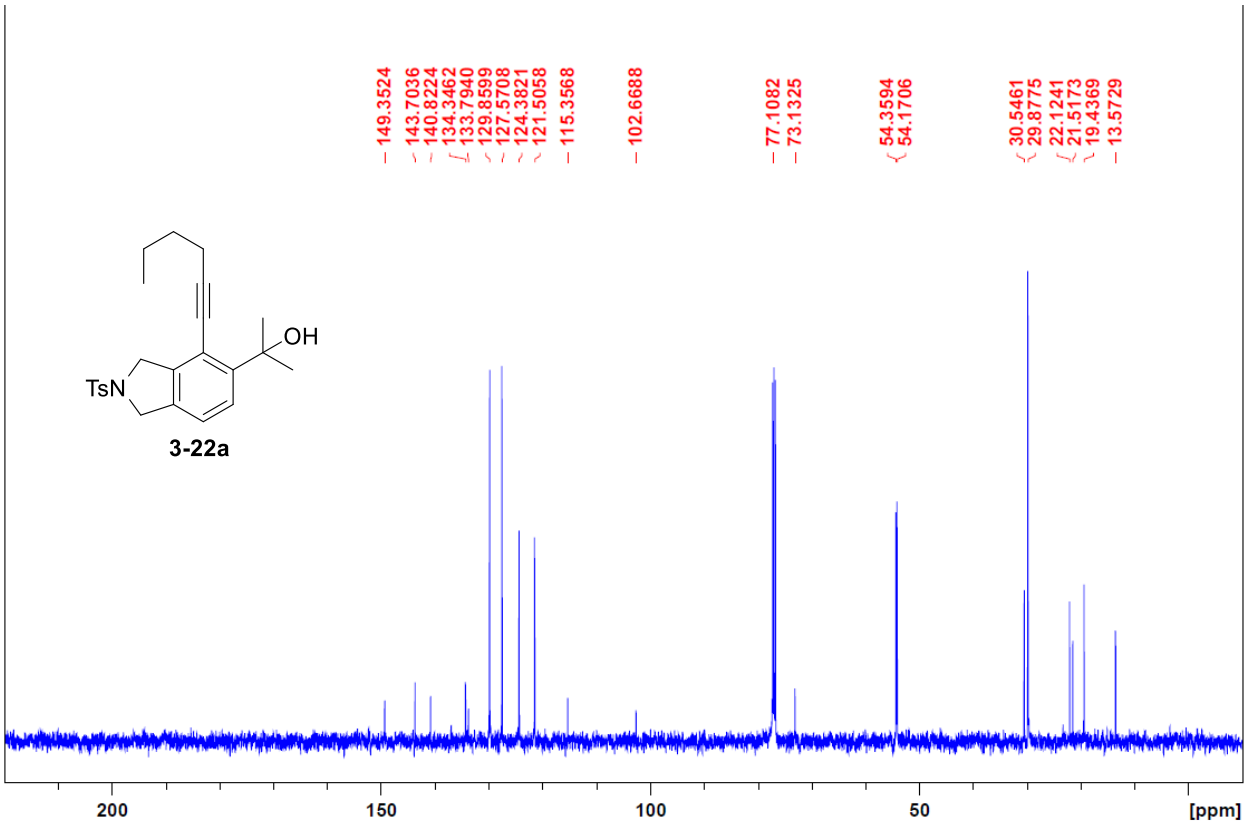

7.5672
7.5525
7.5220
7.5051
7.4948
7.4789
7.4083
7.4017
7.3929
7.3862
7.2355
6.9273
6.9104
6.3561
6.3448
6.3317
6.3207
5.7781
3.8624
3.8410
2.9850
2.1171
2.1140
1.9798
1.9627
1.9454
1.9316
1.9171
1.9005
1.8861
1.4635
1.4489
1.4335
1.3993
0.9845
0.9699
0.9553
OMe
HO
OAc
MeO
3-20h
dr = 1:1
1.0179
0.9785
3.0151
1.0000
0.9892
3.1649
0.9562
2.9650
2.1289
2.2097
3.1098
8
6
4
2
[ppm]

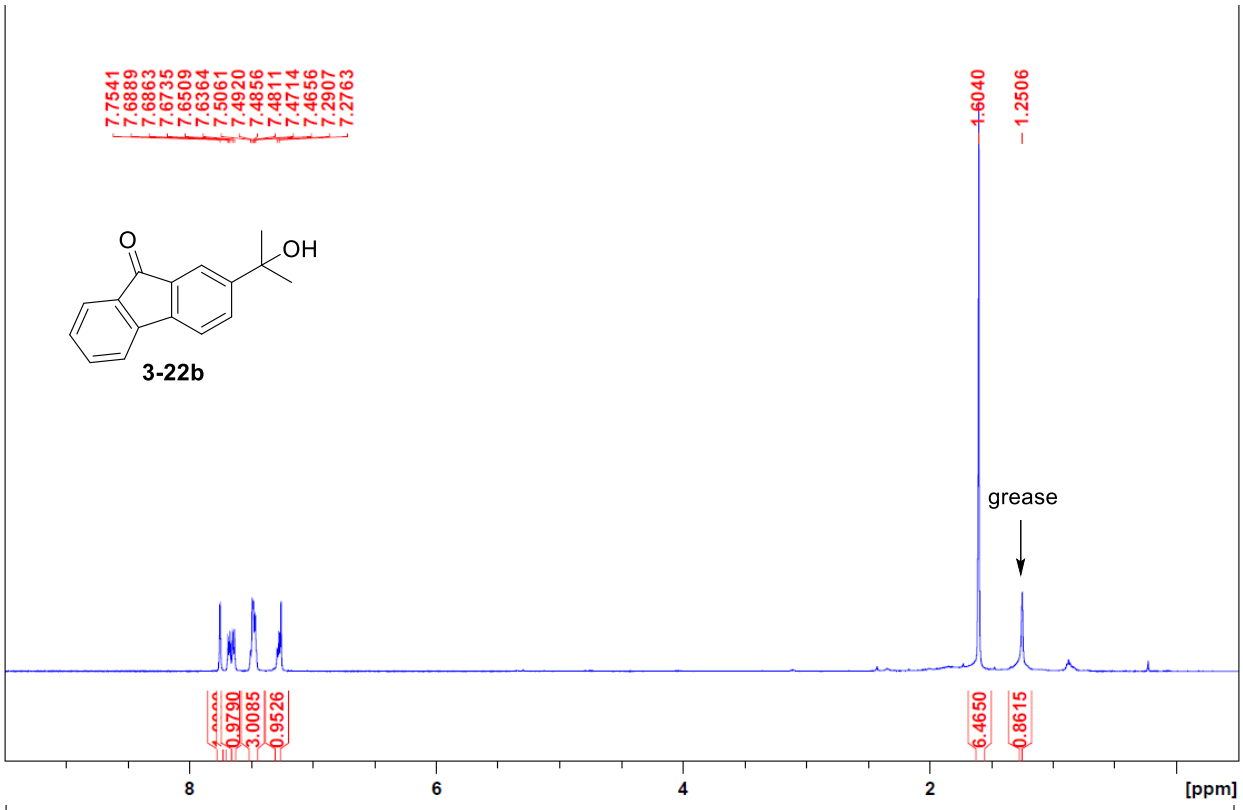

170.2820
170.2256
160.2763
160.2532
160.1576
146.8123
146.7460
146.7207
140.5891
140.4739
139.9155
139.8183
133.1688
132.0198
131.9846
126.6549
126.3784
120.9566
118.9363
118.9056
118.6233
118.4999
115.2034
114.7341
114.2308
110.7770
99.2840
82.9774
82.9057
74.7142
73.8069
73.6862
55.5683
55.3774
38.0896
38.0105
21.2801
18.9037
13.9054
OMe
HO
OAc
MeO
3-20h
dr = 1:1
200
150
100
50
[ppm]

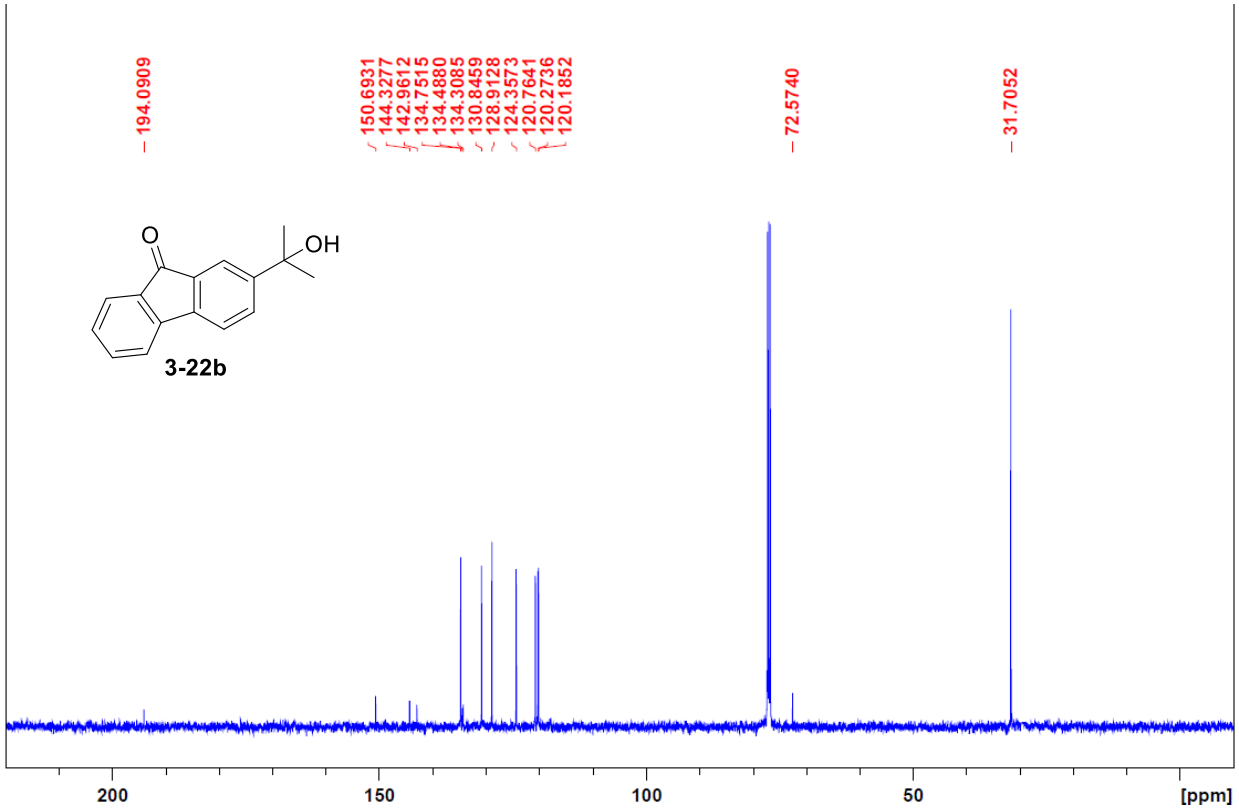

7.5446
7.5359
7.5305
7.4587
7.4432
7.2463
6.9422
6.9256
5.7999
4.8180
4.8069
4.7931
3.8801
3.8590
3.2915
3.2870
1.8178
1.8006
1.7899
1.7734
1.7506
1.5348
1.5206
1.4664
1.4519
1.4376
1.4231
0.9750
0.9607
0.9463
OMe
HO
OMe
MeO
dr = 1:1
3-20i
grease
2.9211
1.0579
1.1852
3.0252
1.0000
0.9343
3.2705
2.7102
1.9394
2.3019
2.7853
8
6
4
2
[ppm]

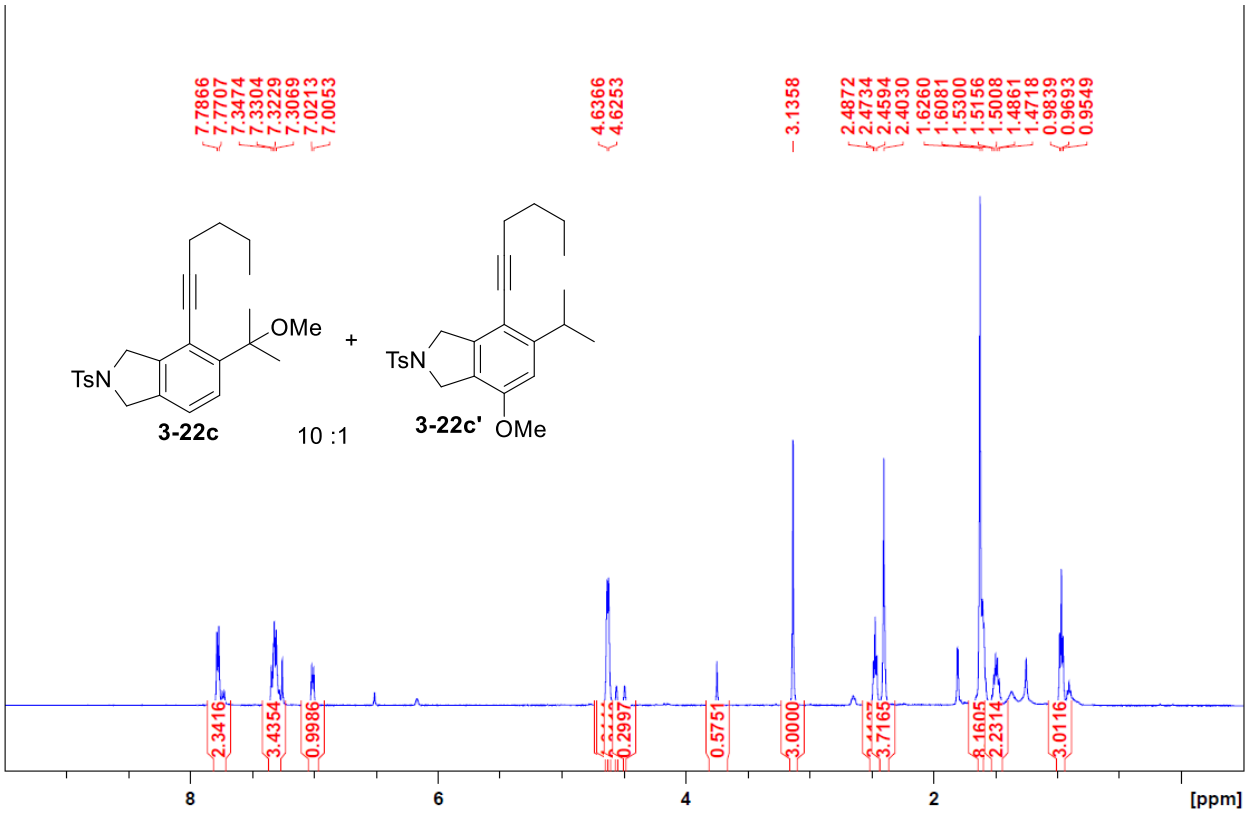

160.1605
146.6064
142.4974
142.4092
139.4570
134.2707
133.0394
133.0134
132.2663
126.5469
126.4055
120.8626
119.2610
119.0512
115.1327
114.7584
114.2807
110.8512
98.8655
83.2101
83.1515
80.8382
80.7029
74.7550
57.0226
56.9734
55.5938
55.4087
39.9129
39.8668
19.1109
14.0741
OMe
HO
OMe
MeO
dr = 1:1
3-20i
grease
200
150
100
50
[ppm]

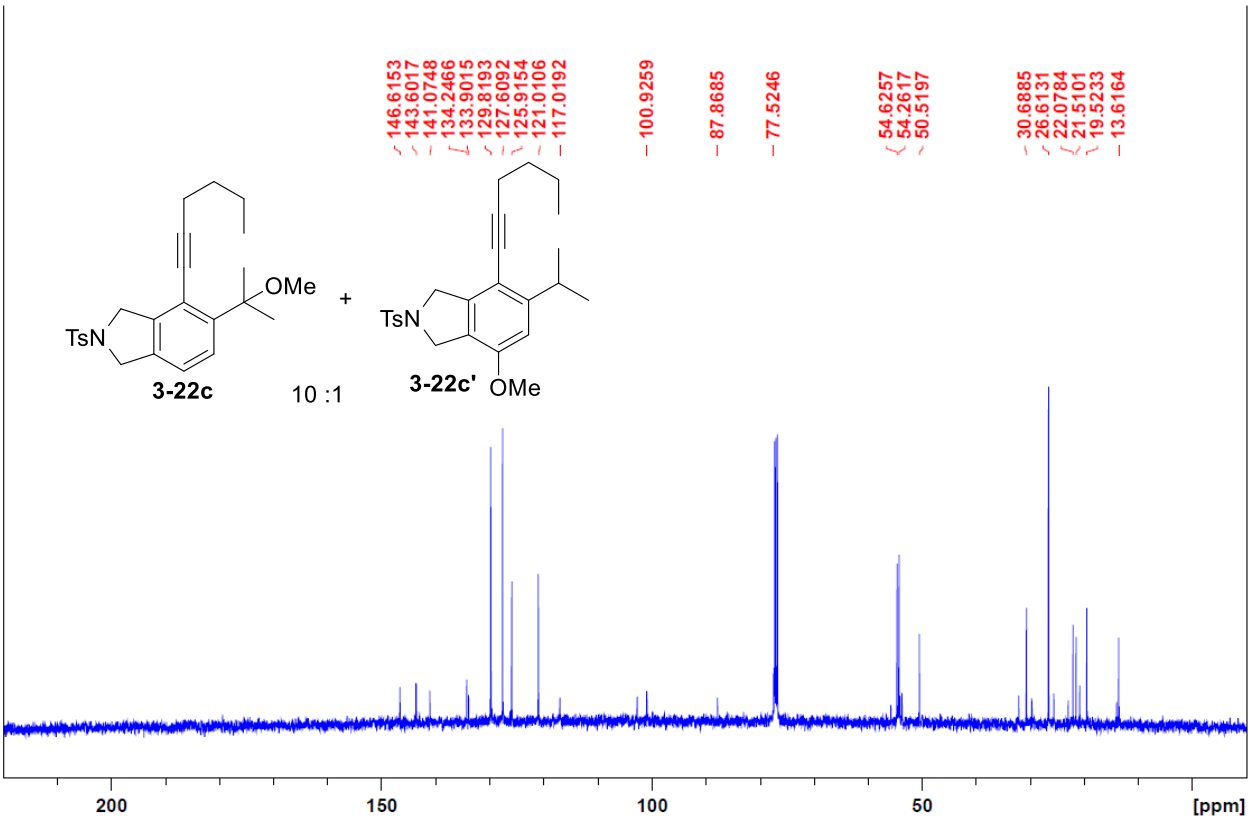

7.7791
7.7632
7.3909
7.3749
7.3235
7.3080
7.0316
7.0155
4.6432
4.6174
3.3201
2.5181
2.5042
2.4903
2.4048
1.6633
1.6389
1.6240
1.6090
1.5264
1.5117
1.4969
1.4823
1.4677
0.9875
0.9729
0.9585
OH
TsN
3-22a
2.0000
1.9763
0.9958
2.2483
0.9058
3.0915
2.3042
2.9936
8
6
4
2
[ppm]

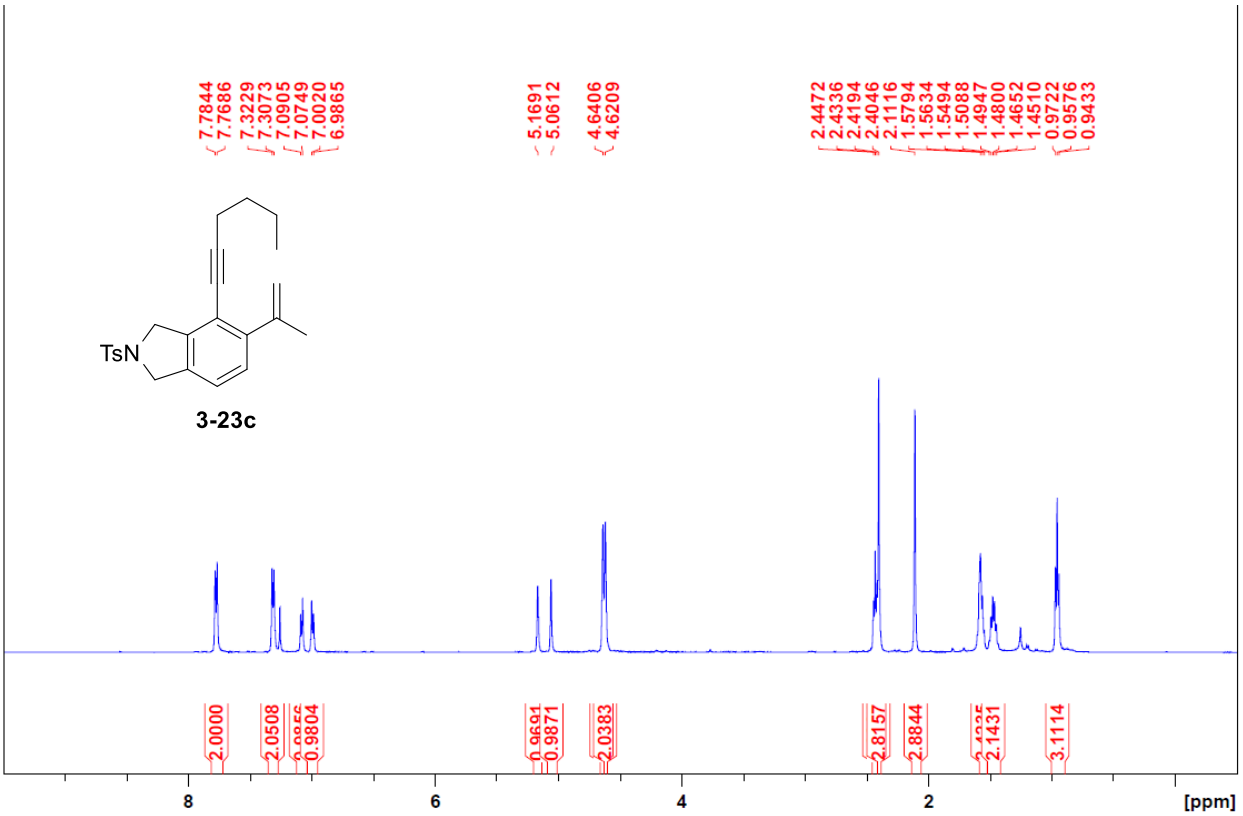

149.3524
143.7036
140.8224
134.3462
133.7940
129.8599
127.5708
124.3821
121.5058
115.3568
102.6688
77.1082
73.1325
54.3594
54.1706
30.5461
29.8775
22.1241
21.5173
19.4369
13.5729
OH
TsN
3-22a
200
150
100
50
[ppm]

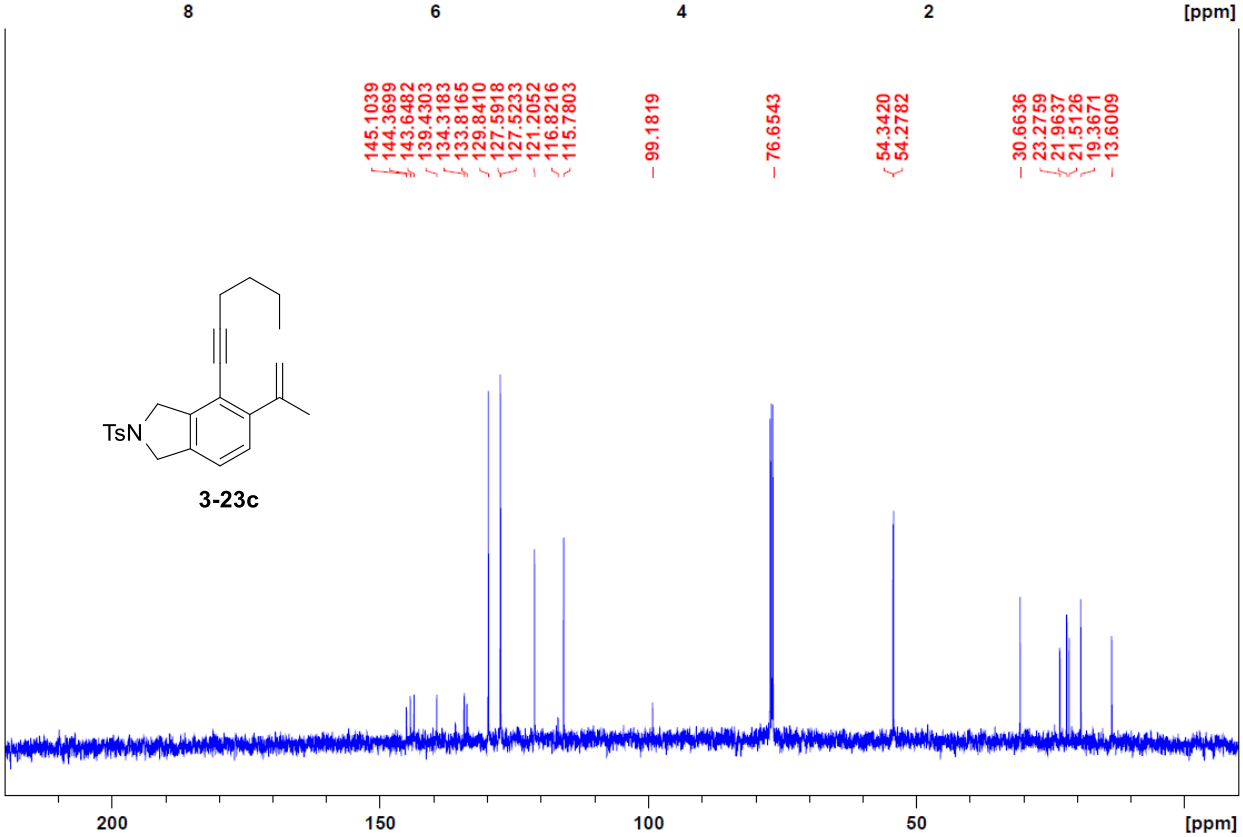

7.7541
7.6889
7.6863
7.6735
7.6509
7.6364
7.5061
7.4920
7.4856
7.4811
7.4714
7.4656
7.2907
7.2763
1.6040
1.2506
O
OH
3-22b
grease
0.9790
3.0085
0.9526
6.4650
0.8615
8
6
4
2
[ppm]

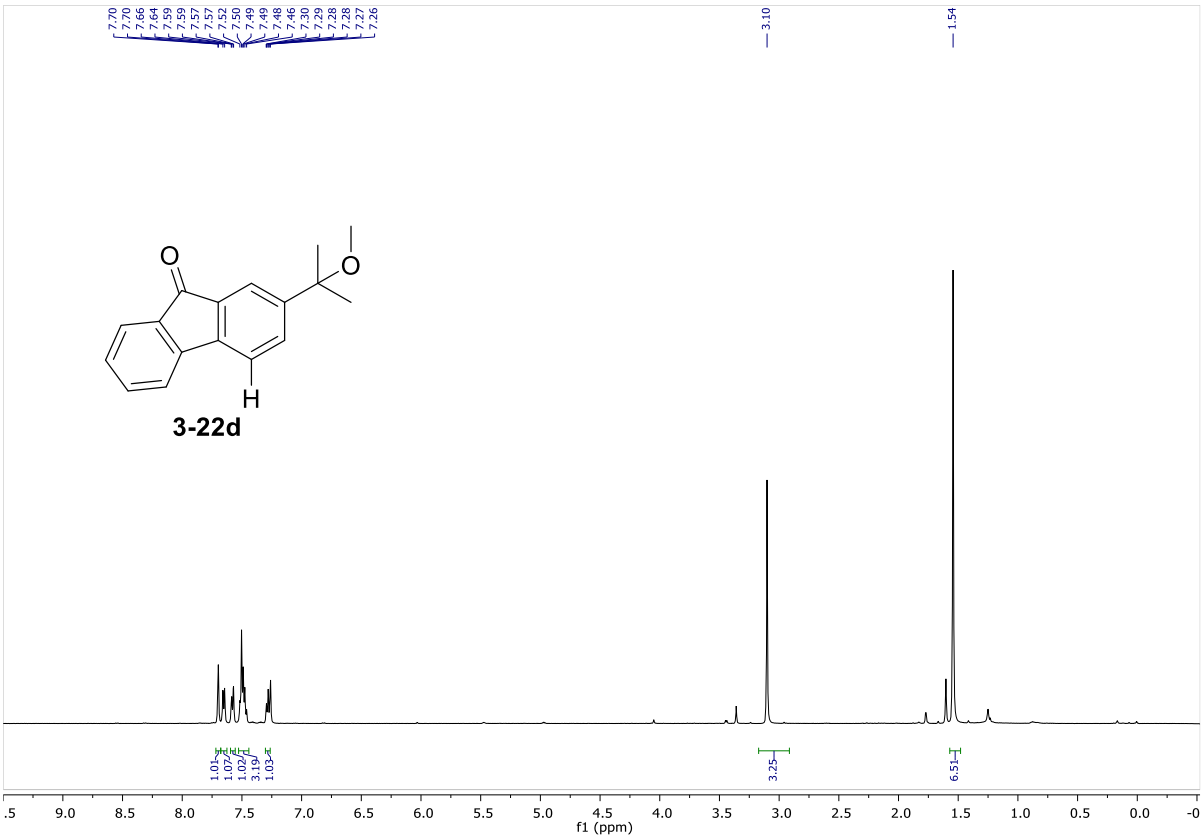

194.0909
150.6931
144.3277
142.9612
134.7515
134.4880
134.3085
130.8459
128.9128
124.3573
120.7641
120.2736
120.1852
72.5740
31.7052
O
OH
3-22b
200
150
100
50
[ppm]

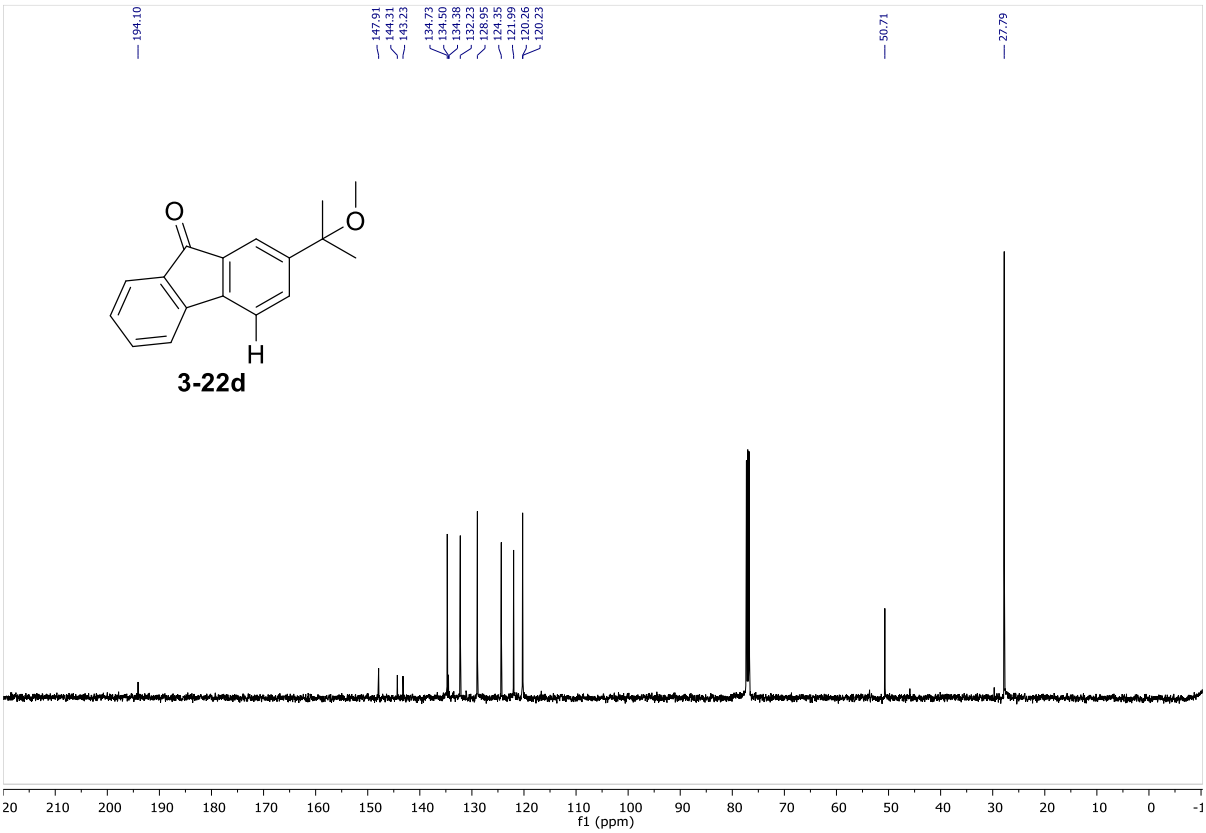

7.7866
7.7707
7.3474
7.3304
7.3229
7.3069
7.0213
7.0053
4.6366
4.6253
3.1358
2.4872
2.4734
2.4594
2.4030
1.6260
1.6081
1.5300
1.5156
1.5008
1.4861
1.4718
0.9839
0.9693
0.9549
OMe
TsN
3-22c
10 :1
+
TsN
3-22c'
OMe
2.3416
3.4354
0.9986
0.2997
0.5751
3.0000
3.7165
8.1605
2.2314
3.0116
8
6
4
2
[ppm]

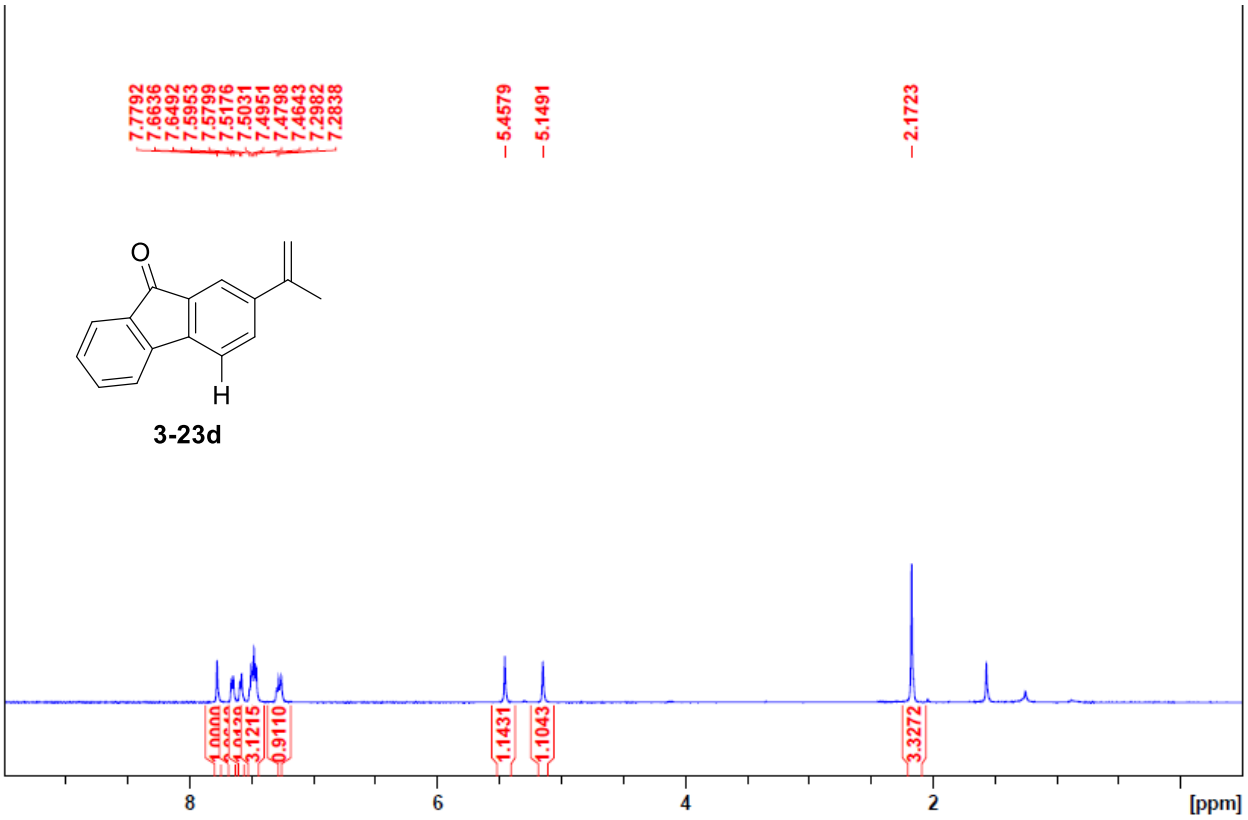

146.6153
143.6017
141.0748
134.2466
133.9015
129.8193
127.6092
125.9154
121.0106
117.0192
100.9259
87.8685
77.5246
54.6257
54.2617
50.5197
30.6885
26.6131
22.0784
21.5101
19.5233
13.6164
OMe
TsN
3-22c
10 :1
+
TsN
3-22c'
OMe
200
150
100
50
[ppm]

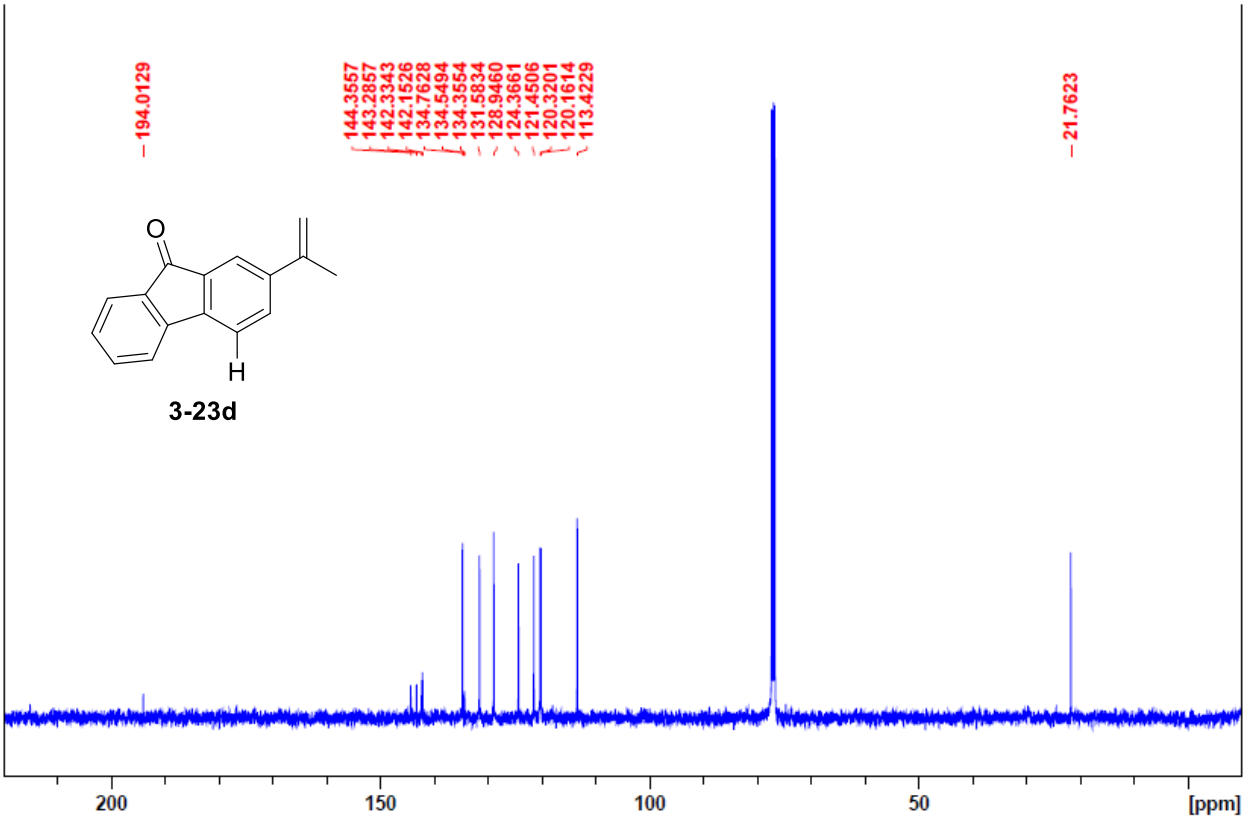

7.7844
7.7686
7.3229
7.3073
7.0905
7.0749
7.0020
6.9865
5.1691
5.0612
4.6406
4.6209
2.4472
2.4336
2.4194
2.4046
2.1116
1.5794
1.5634
1.5494
1.5088
1.4947
1.4800
1.4652
1.4510
0.9722
0.9576
0.9433
TsN
3-23c
2.0000
2.0508
0.9804
0.9871
2.0383
2.8157
2.8844
2.1431
3.1114
8
6
4
2
[ppm]

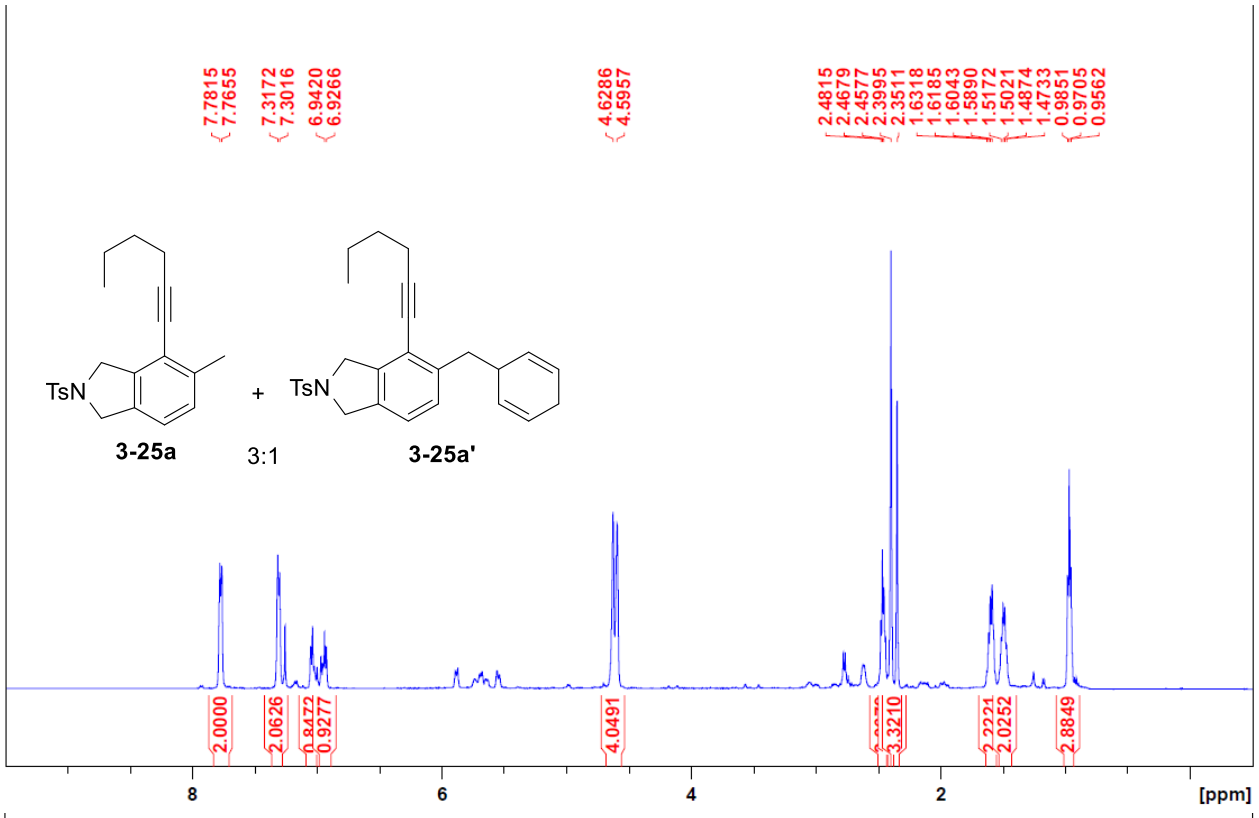

145.1039
144.3699
143.6482
139.4303
134.3183
133.8165
129.8410
127.5918
127.5233
121.2052
116.8216
115.7803
99.1819
76.6543
54.3420
54.2782
30.6636
23.2759
21.9637
21.5126
19.3671
13.6009
TsN
3-23c
200
150
100
50
[ppm]

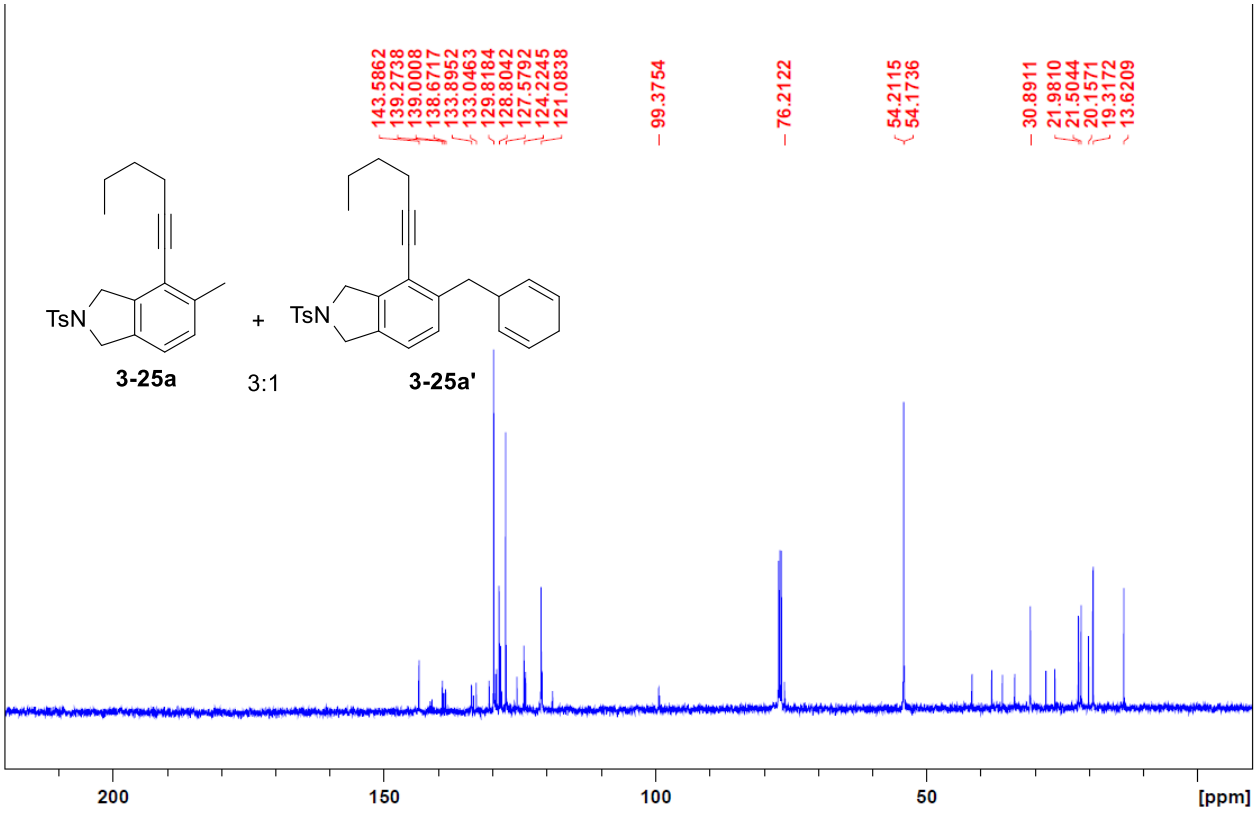

7.70
7.70
7.66
7.64
7.59
7.59
7.57
7.57
7.52
7.50
7.49
7.49
7.48
7.46
7.30
7.29
7.28
7.28
7.27
7.26
3.10
1.54
O
O
H
3-22d
1.01
1.07
1.02
3.19
1.03
3.25
6.51
f1 (ppm)

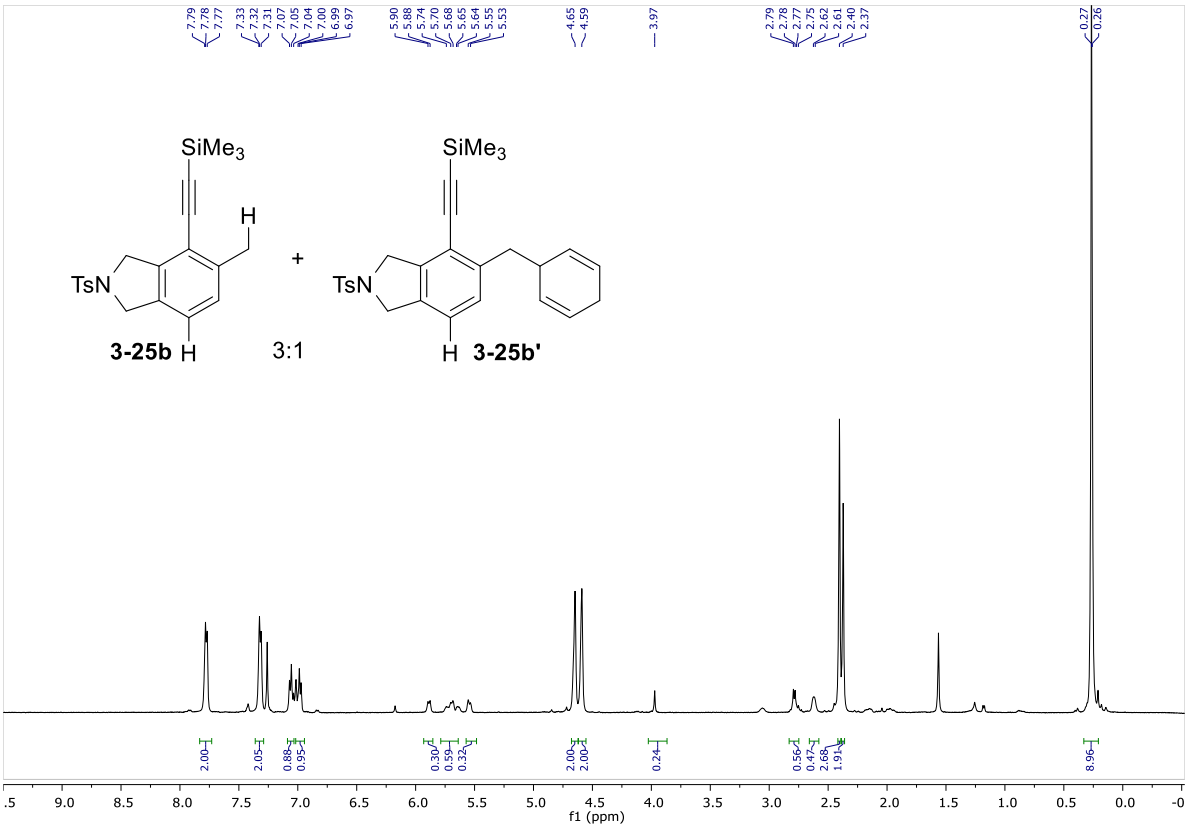

194.10
147.91
144.31
143.23
134.73
134.50
134.38
132.23
128.95
124.35
121.99
120.26
120.23
50.71
27.79
O
O
H
3-22d
f1 (ppm)

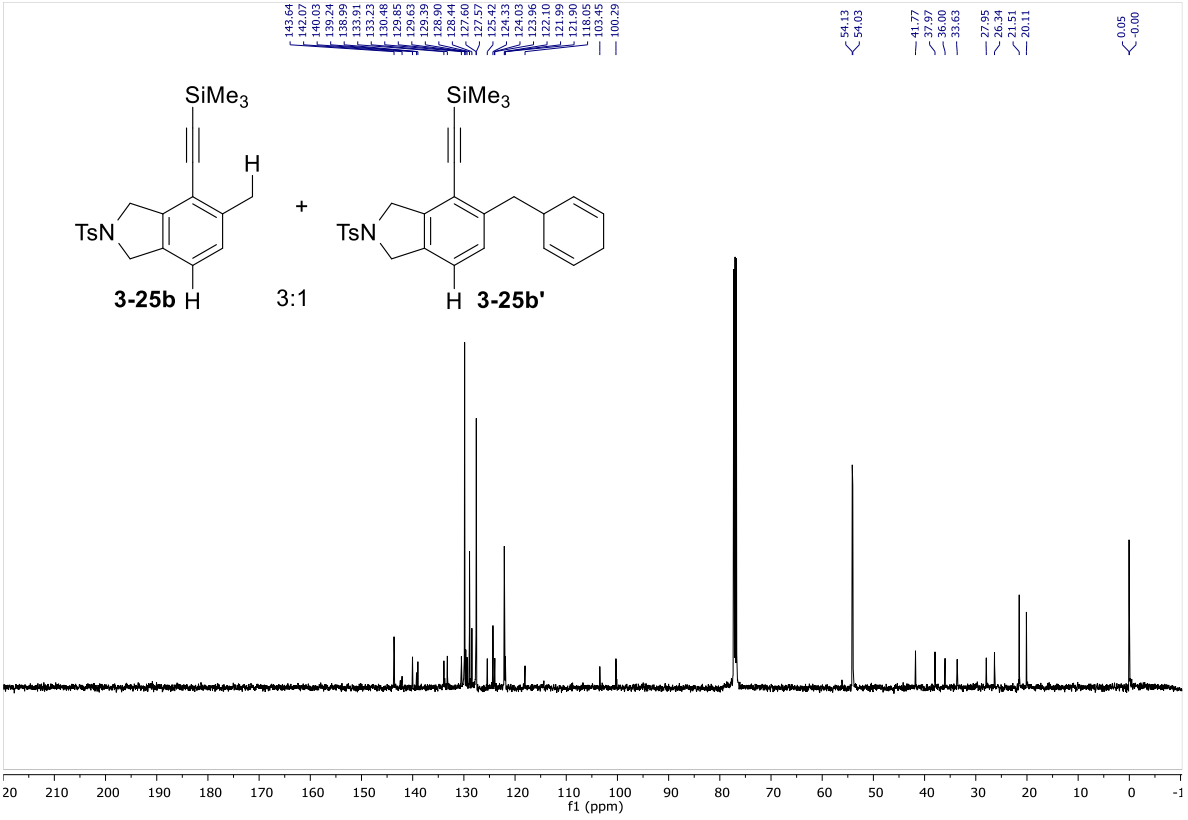

7.7792
7.6636
7.6492
7.5953
7.5799
7.5176
7.5031
7.4951
7.4798
7.4643
7.2982
7.2838
5.4579
5.1491
2.1723
O
H
3-23d
1.0000
3.1215
0.9110
1.1431
1.1043
3.3272
8
6
4
2
[ppm]

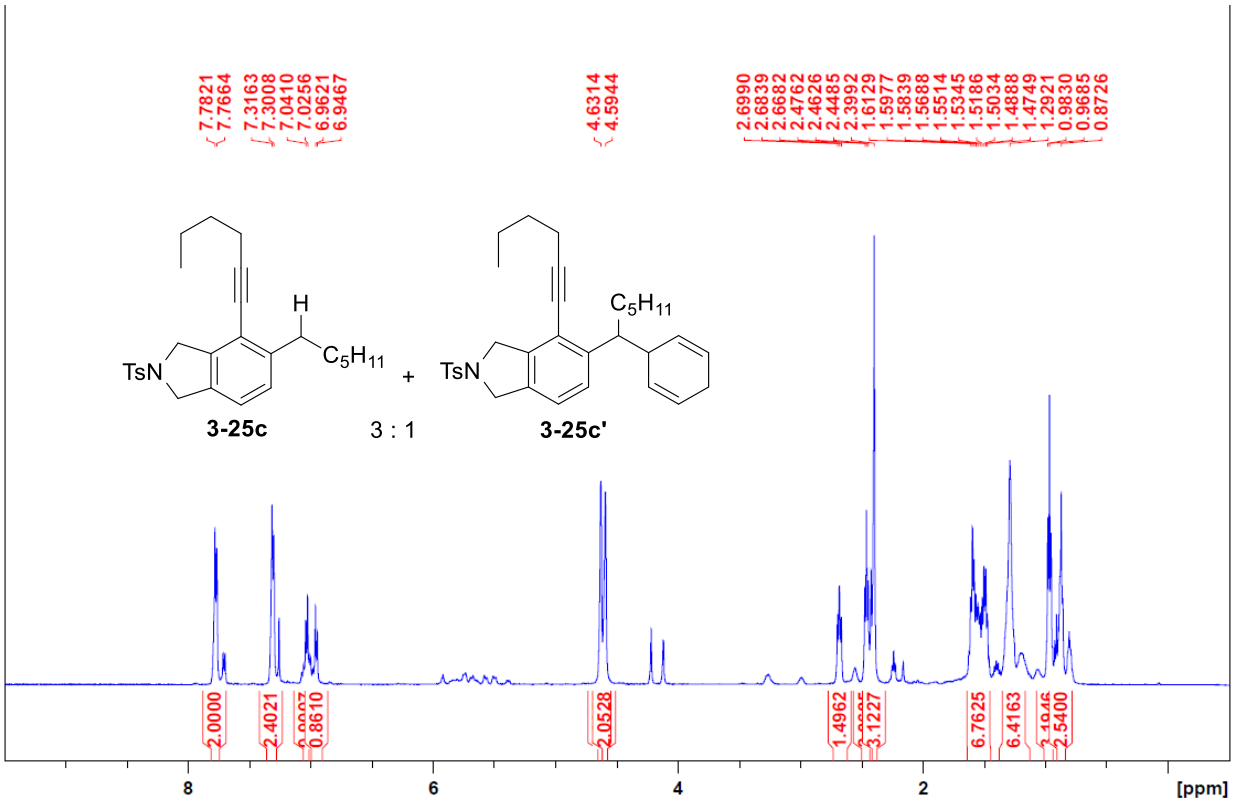

194.0129
144.3557
143.2857
142.3343
142.1526
134.7628
134.5494
134.3554
131.5834
128.9460
124.3661
121.4506
120.3201
120.1614
113.4229
21.7623
O
H
3-23d
200
150
100
50
[ppm]

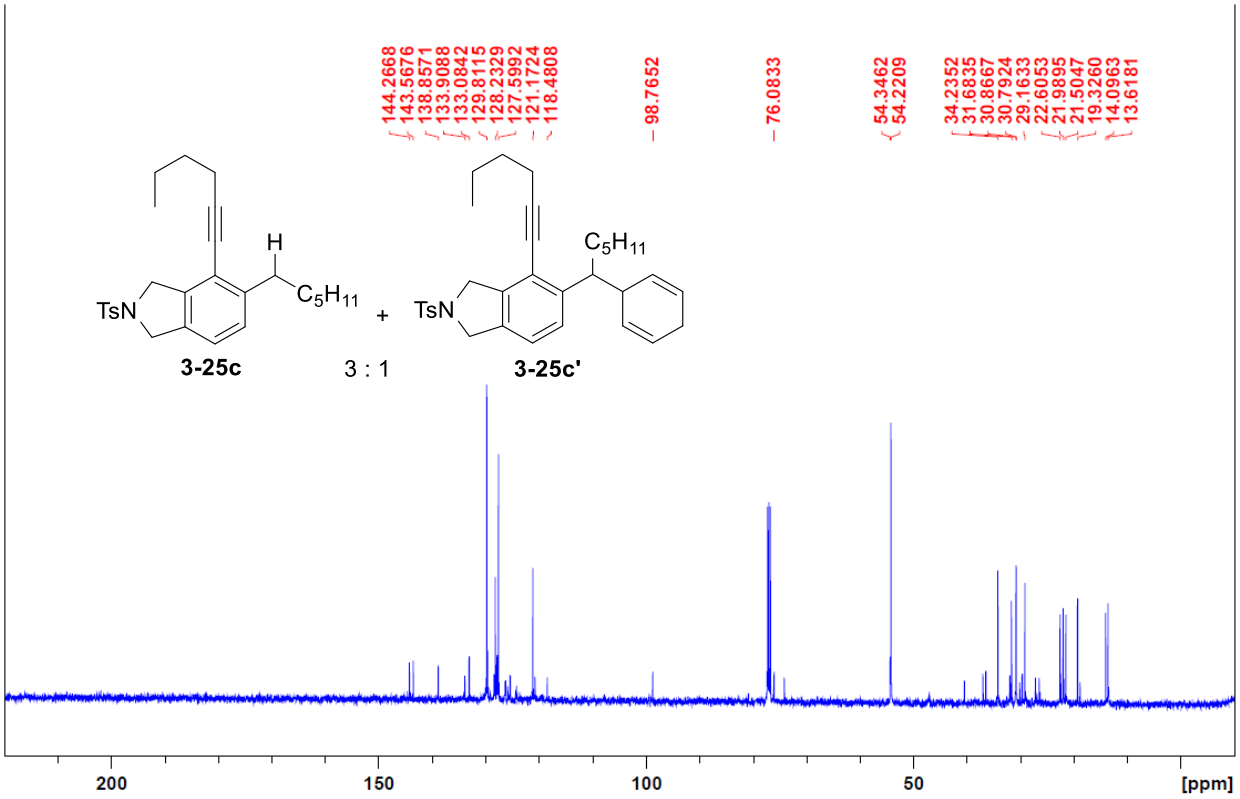

7.7815
7.7655
7.3172
7.3016
6.9420
6.9266
4.6286
4.5957
2.4815
2.4679
2.4577
2.3995
2.3511
1.6318
1.6185
1.6043
1.5890
1.5172
1.5021
1.4874
1.4733
0.9851
0.9705
0.9562
TsN
+
TsN
3-25a
3:1
3-25a'
2.0000
2.0626
0.8472
0.9277
4.0491
3.3210
2.2221
2.0252
2.8849
8
6
4
2
[ppm]

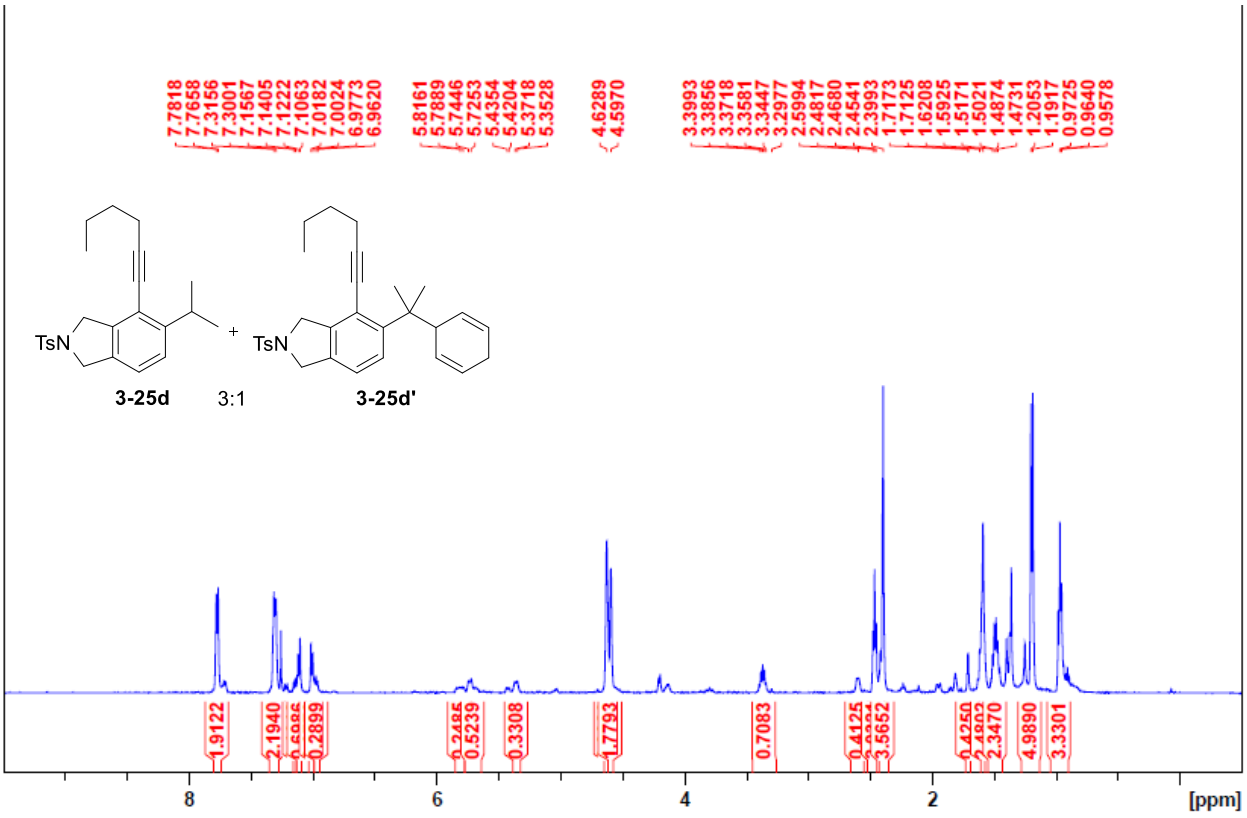

143.5862
139.2738
139.0008
138.6717
133.8952
133.0463
129.8184
128.8042
127.5792
124.2245
121.0838
99.3754
76.2122
54.2115
54.1736
30.8911
21.9810
21.5044
20.1571
19.3172
13.6209
TsN
+
TsN
3-25a
3:1
3-25a'
200
150
100
50
[ppm]

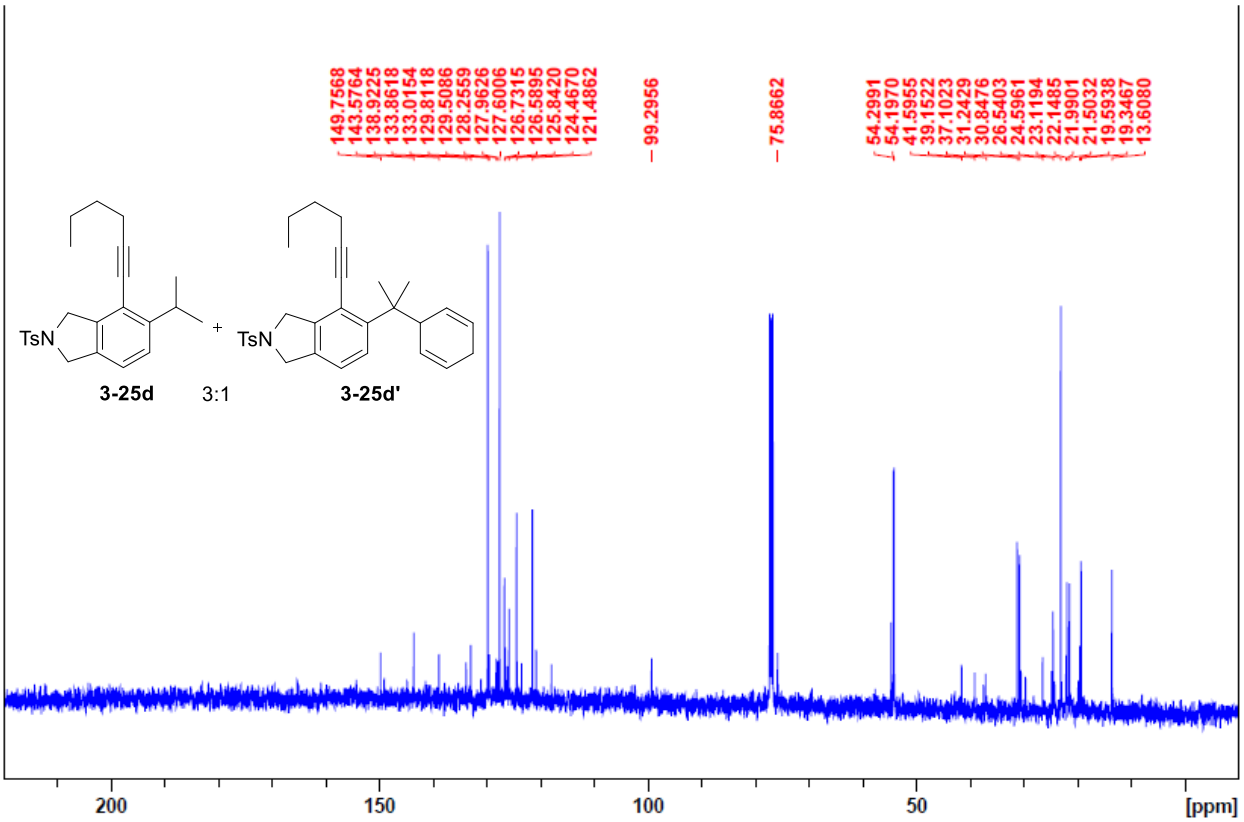

SiMe3
H
TsN
3-25b H
+
3:1
SiMe3
TsN
H 3-25b'
f1 (ppm)


SiMe3
H
TsN
3-25b H
+
3:1
SiMe3
TsN
H 3-25b'
f1 (ppm)


7.7821
7.7664
7.3163
7.3008
7.0410
7.0256
6.9621
6.9467
4.6314
4.5944
2.6990
2.6839
2.6682
2.4762
2.4626
2.4485
2.3992
1.6129
1.5977
1.5839
1.5688
1.5514
1.5345
1.5186
1.5034
1.4888
1.4749
1.2921
0.9830
0.9685
0.8726
TsN
H
C5H11
+
TsN
C5H11
3-25c
3 : 1
3-25c'
2.0000
2.4021
0.8610
2.0528
1.4962
3.1227
6.7625
6.4163
2.5400
8
6
4
2
[ppm]

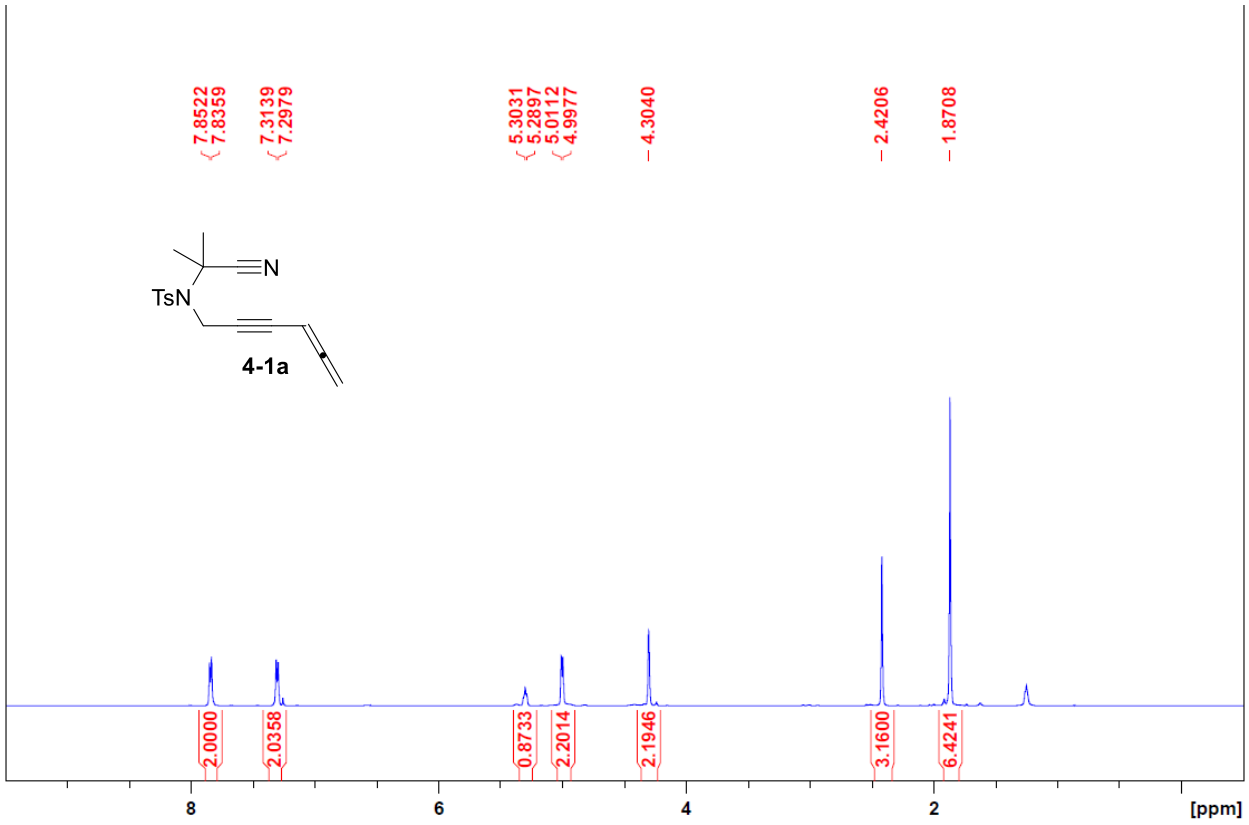

144.2668
143.5676
138.8571
133.9088
133.0842
129.8115
128.2329
127.5992
121.1724
118.4808
98.7652
76.0833
54.3462
54.2209
34.2352
31.6835
30.8667
30.7924
29.1633
22.6053
21.9895
21.5047
19.3260
14.0963
13.6181
TsN
H
C5H11
+
TsN
C5H11
3-25c
3 : 1
3-25c'
200
150
100
50
[ppm]

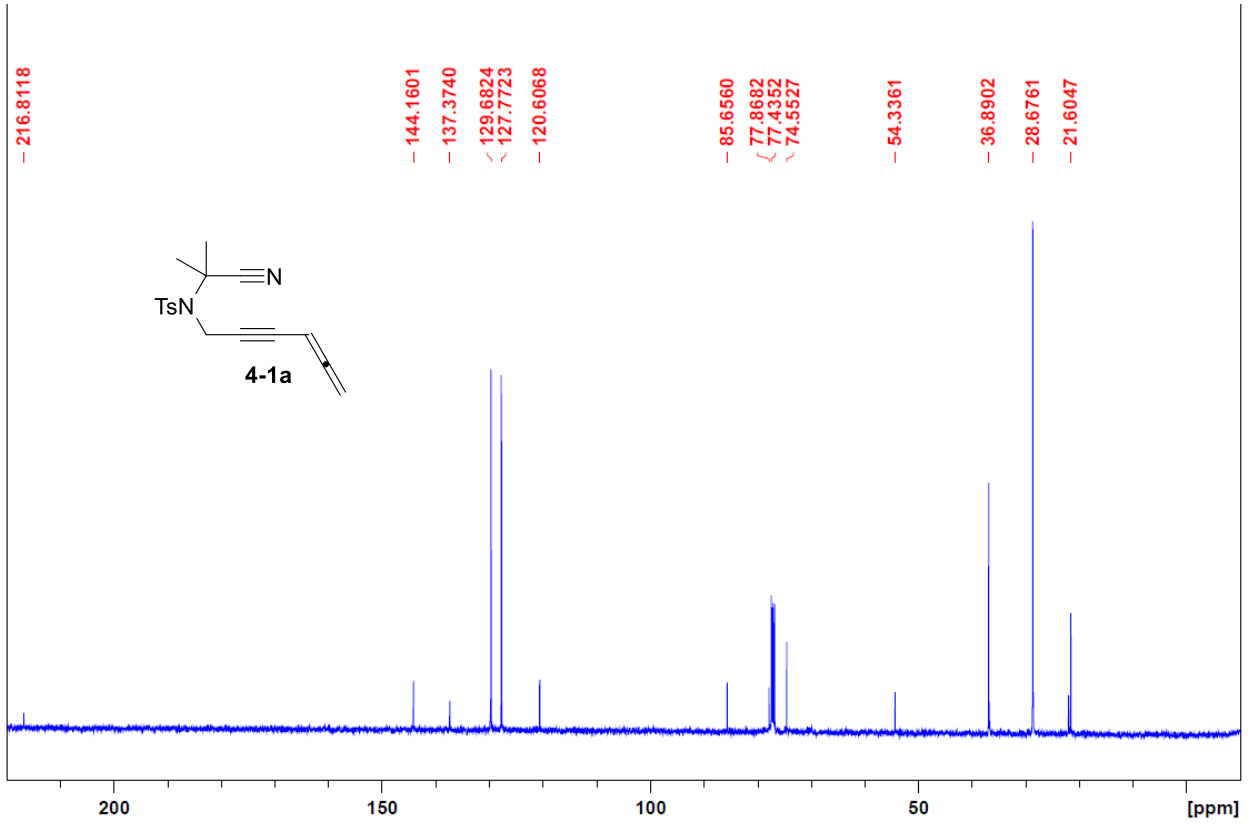

7.7818
7.7658
7.3156
7.3001
7.1567
7.1405
7.1222
7.1063
7.0182
7.0024
6.9773
6.9620
5.8161
5.7889
5.7446
5.7253
5.4354
5.4204
5.3718
5.3528
4.6289
4.5970
3.3993
3.3856
3.3718
3.3581
3.3447
3.2977
2.5994
2.4817
2.4680
2.4541
2.3993
1.7173
1.7125
1.6208
1.5925
1.5171
1.5021
1.4874
1.4731
1.2053
1.1917
0.9725
0.9640
0.9578
TsN
TsN
3-25d
3:1
3-25d'
1.9122
2.1940
0.2899
0.2485
0.5239
0.3308
1.7793
0.7083
0.4125
3.5652
0.4250
2.3470
4.9890
3.3301
8
6
4
2
[ppm]

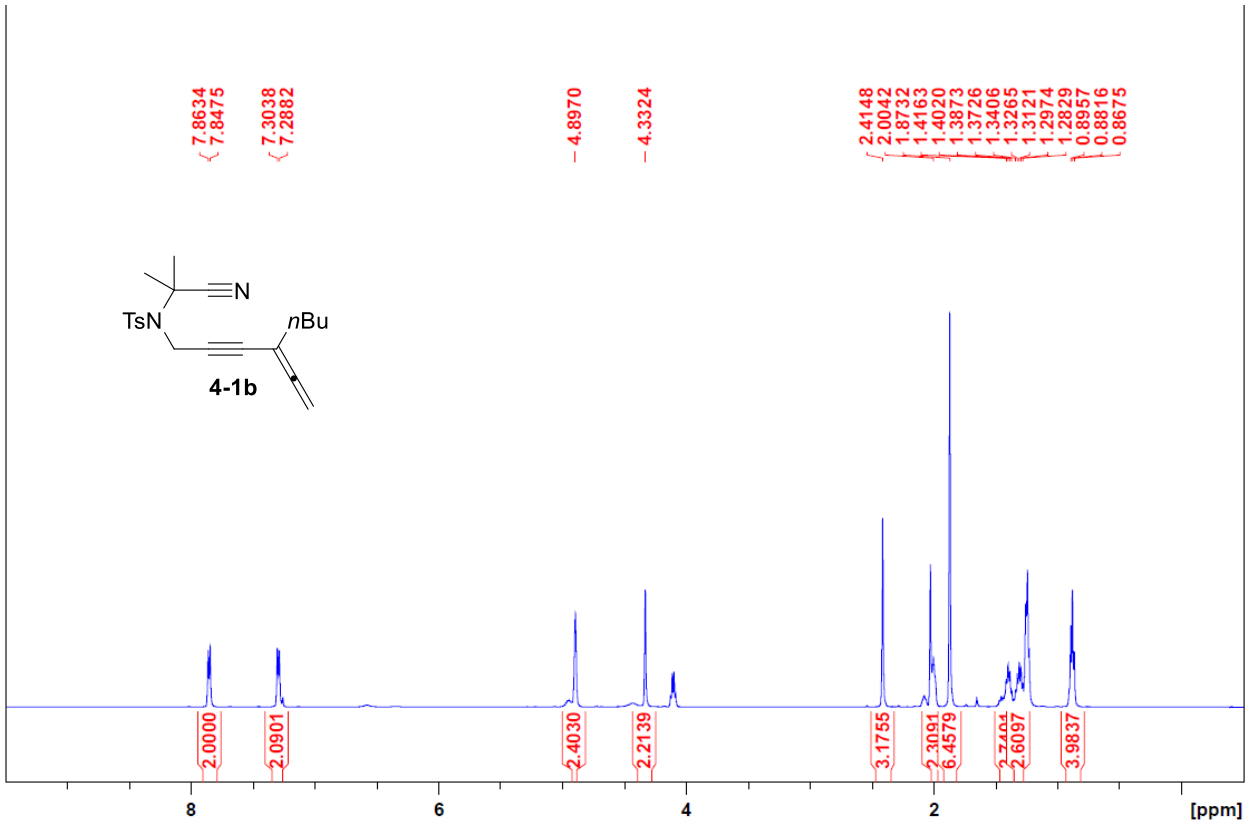

149.7568
143.5764
138.9225
133.8618
133.0154
129.8118
129.5086
128.2559
127.9626
127.6006
126.7315
126.5895
125.8420
124.4670
121.4862
99.2956
75.8662
54.2991
54.1970
41.5955
39.1522
37.1023
31.2429
30.8476
26.5403
24.5961
23.1194
22.1485
21.9901
21.5032
19.5938
19.3467
13.6080
TsN
TsN
3-25d
3:1
3-25d'
200
150
100
50
[ppm]

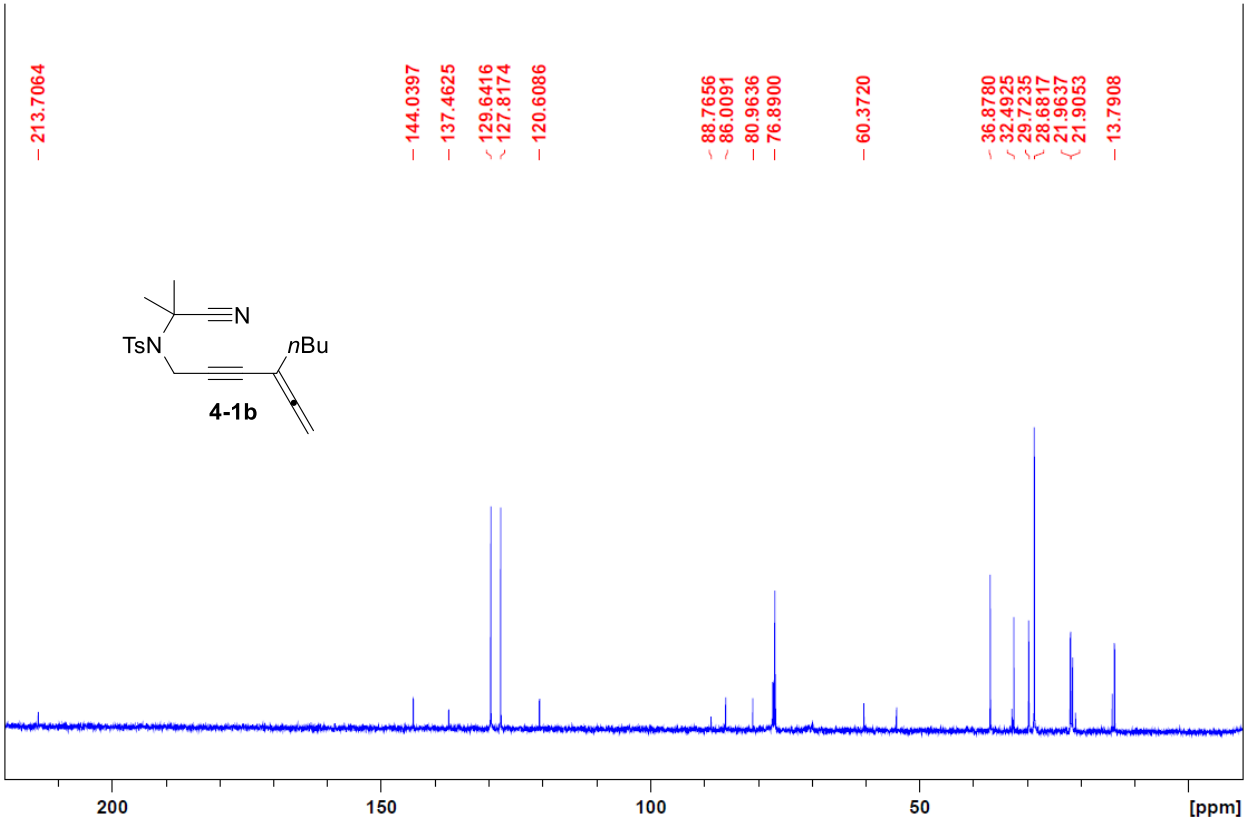
Appendix III

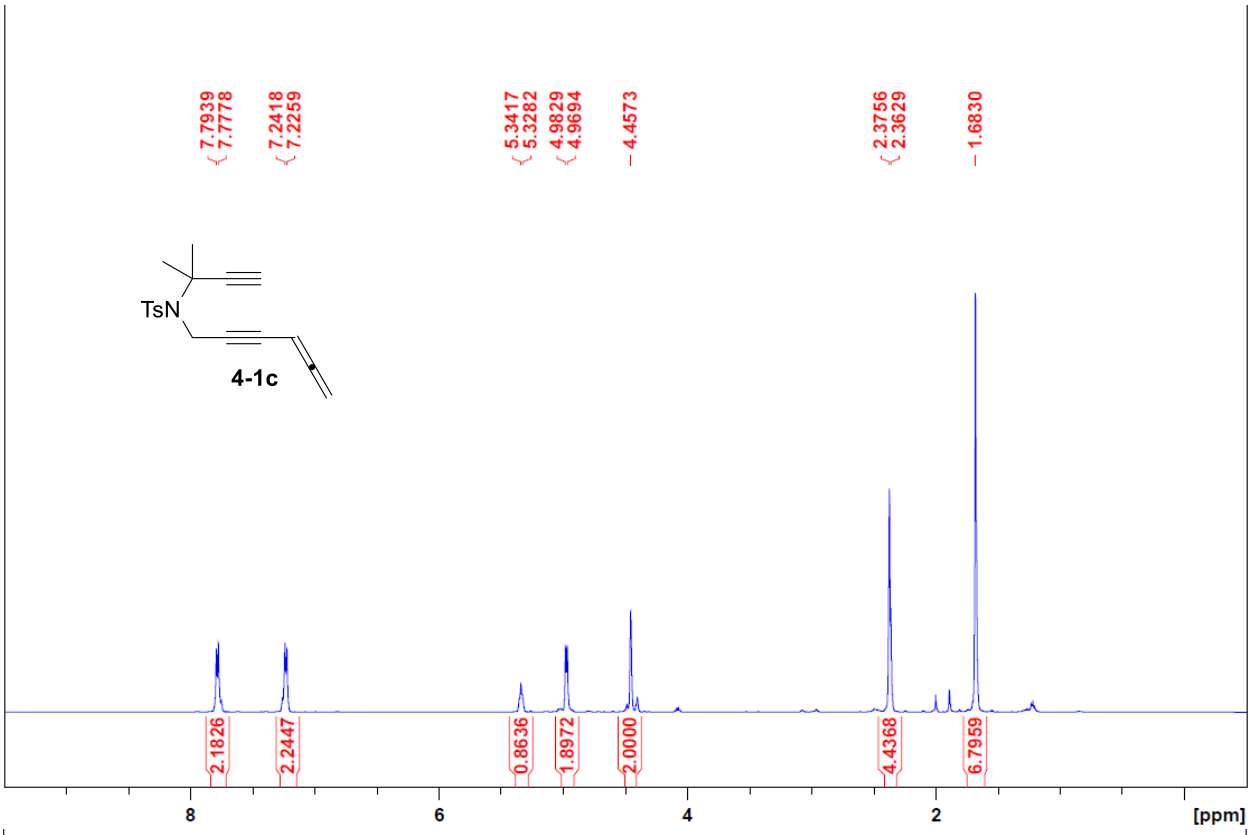
Selected NMR Spectra for Chapter 4

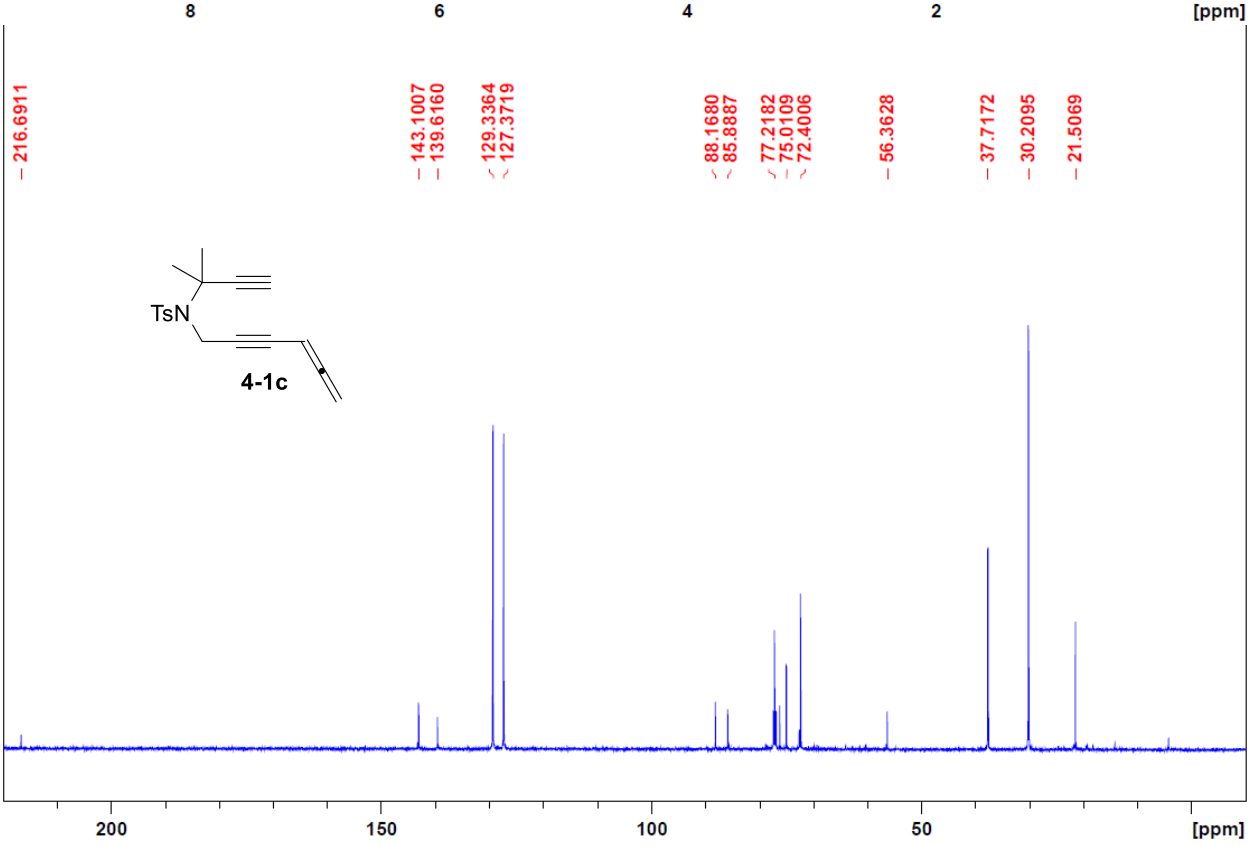

7.8522
7.8359
7.3139
7.2979
5.3031
5.2897
5.0112
4.9977
4.3040
2.4206
1.8708
TsN
N
4-1a
2.0000
2.0358
0.8733
2.2014
2.1946
3.1600
6.4241
8
6
4
2
[ppm]

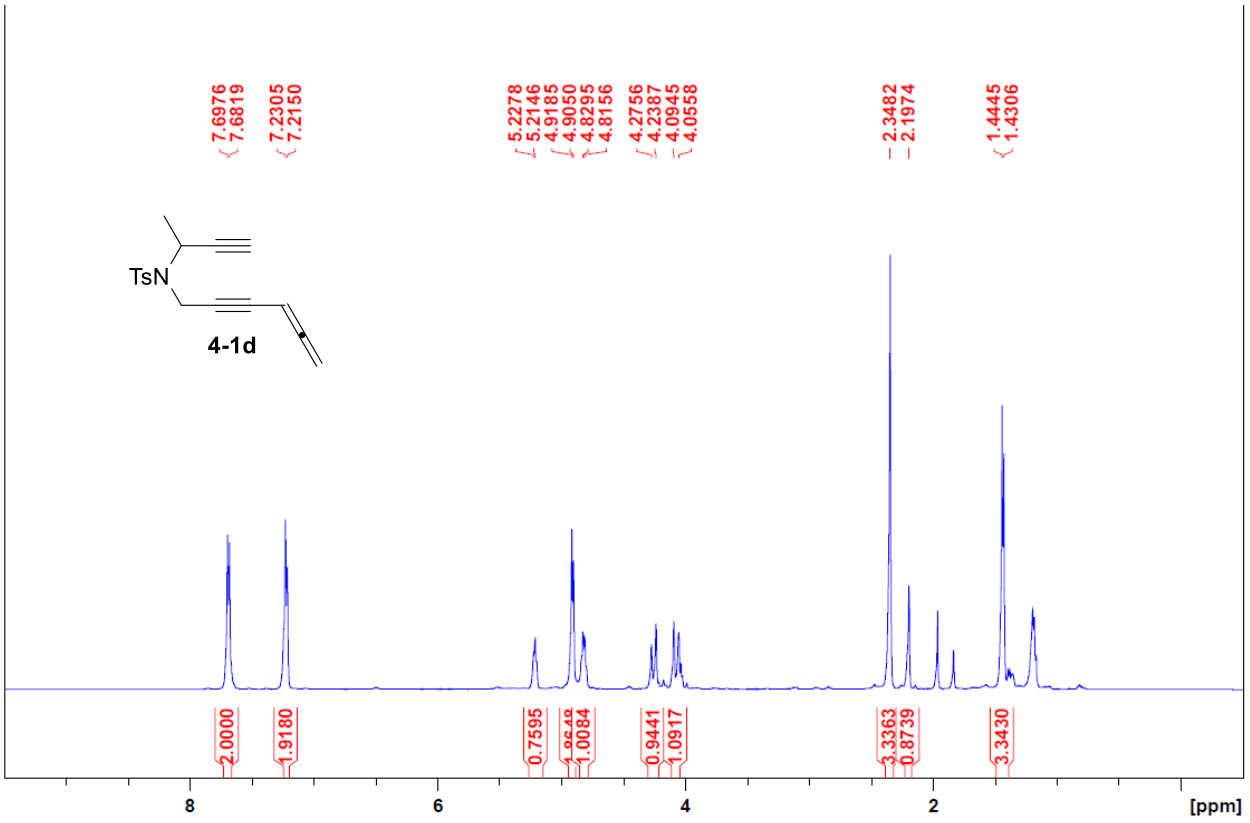

216.8118
144.1601
137.3740
129.6824
127.7723
120.6068
85.6560
77.8682
77.4352
74.5527
54.3361
36.8902
28.6761
21.6047
TsN
N
4-1a
200
150
100
50
[ppm]

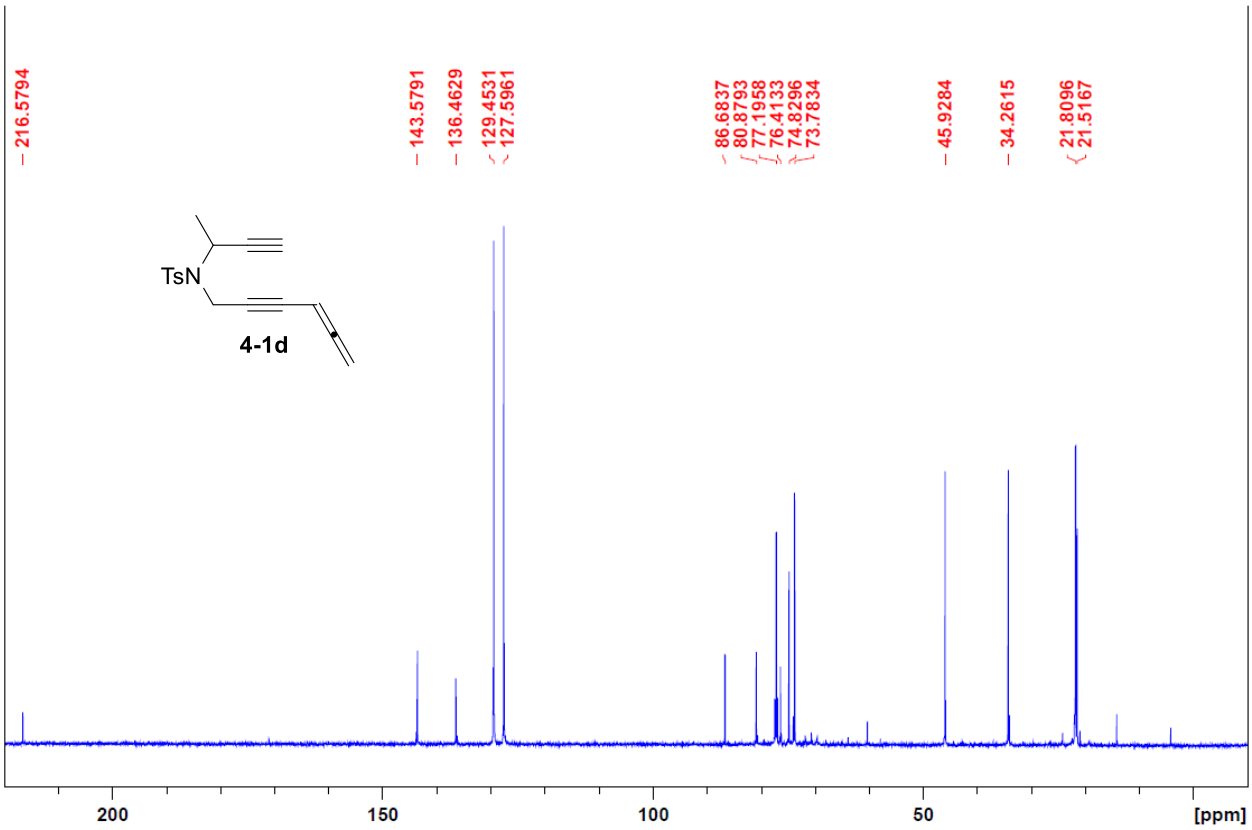

7.8634
7.8475
7.3038
7.2882
4.8970
4.3324
2.4148
2.0042
1.8732
1.4163
1.4020
1.3873
1.3726
1.3406
1.3265
1.3121
1.2974
1.2829
0.8957
0.8816
0.8675
TsN
N
nBu
4-1b
2.0000
2.0901
2.4030
2.2139
3.1755
2.3091
6.4579
2.6097
3.9837
8
6
4
2
[ppm]

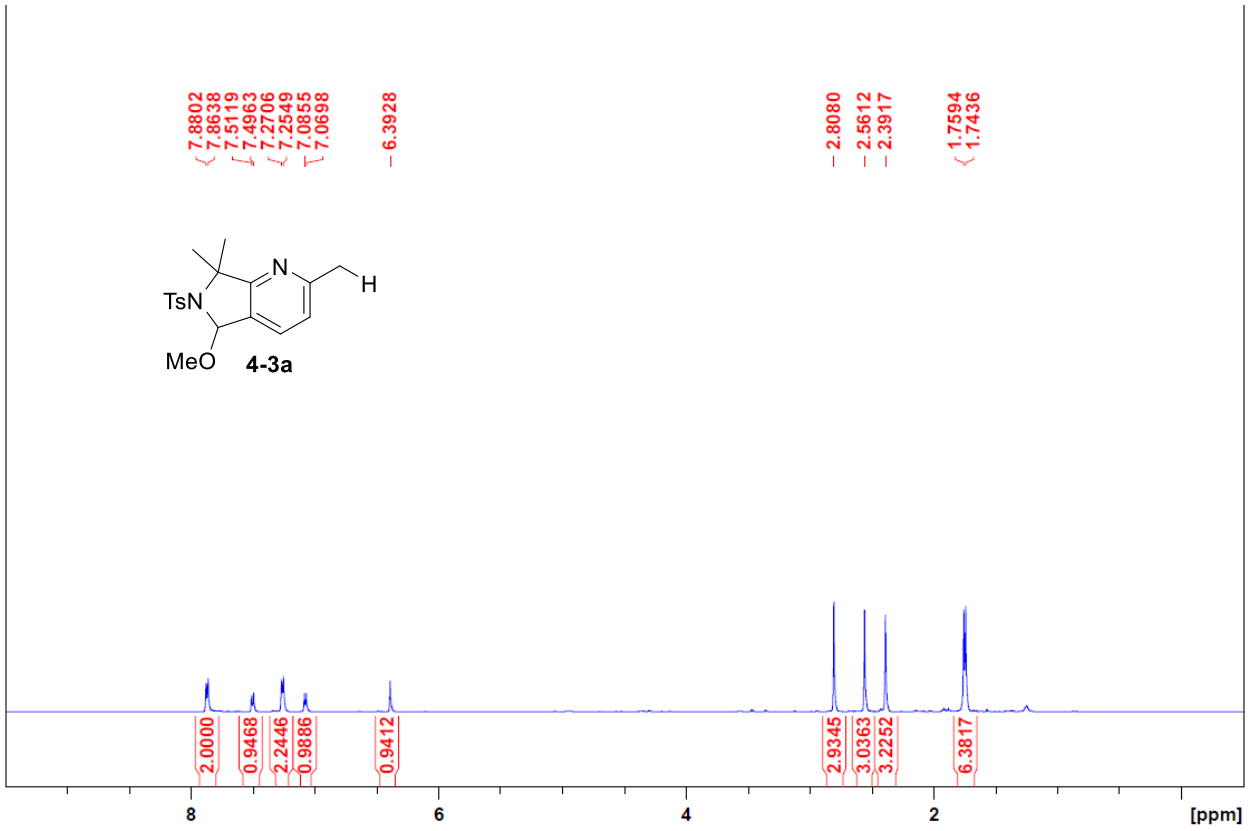

213.7064
144.0397
137.4625
129.6416
127.8174
120.6086
88.7656
86.0091
80.9636
76.8900
60.3720
36.8780
32.4925
29.7235
28.6817
21.9637
21.9053
13.7908
TsN
N
nBu
4-1b
200
150
100
50
[ppm]

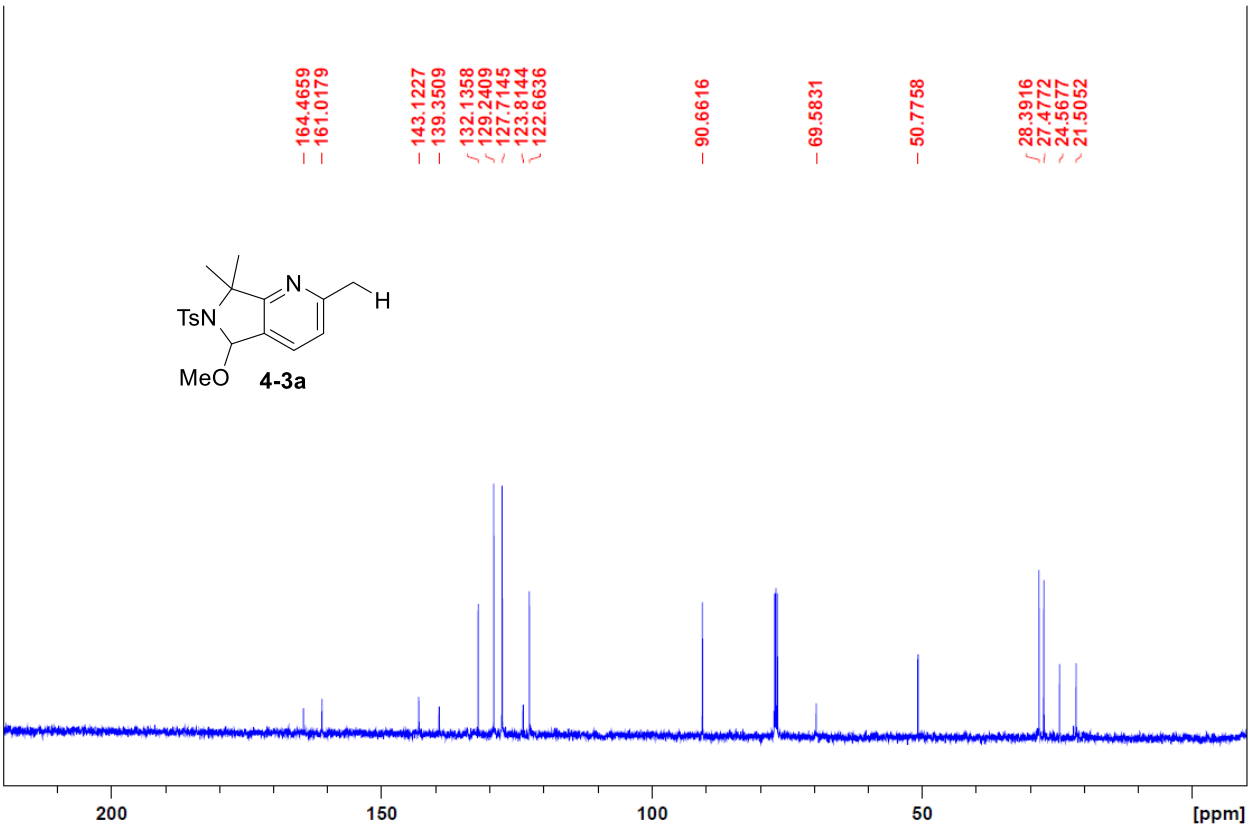

7.7939
7.7778
7.2418
7.2259
5.3417
5.3282
4.9829
4.9694
4.4573
2.3756
2.3629
1.6830
TsN
4-1c
2.1826
2.2447
0.8636
1.8972
2.0000
4.4368
6.7959
8
6
4
2
[ppm]

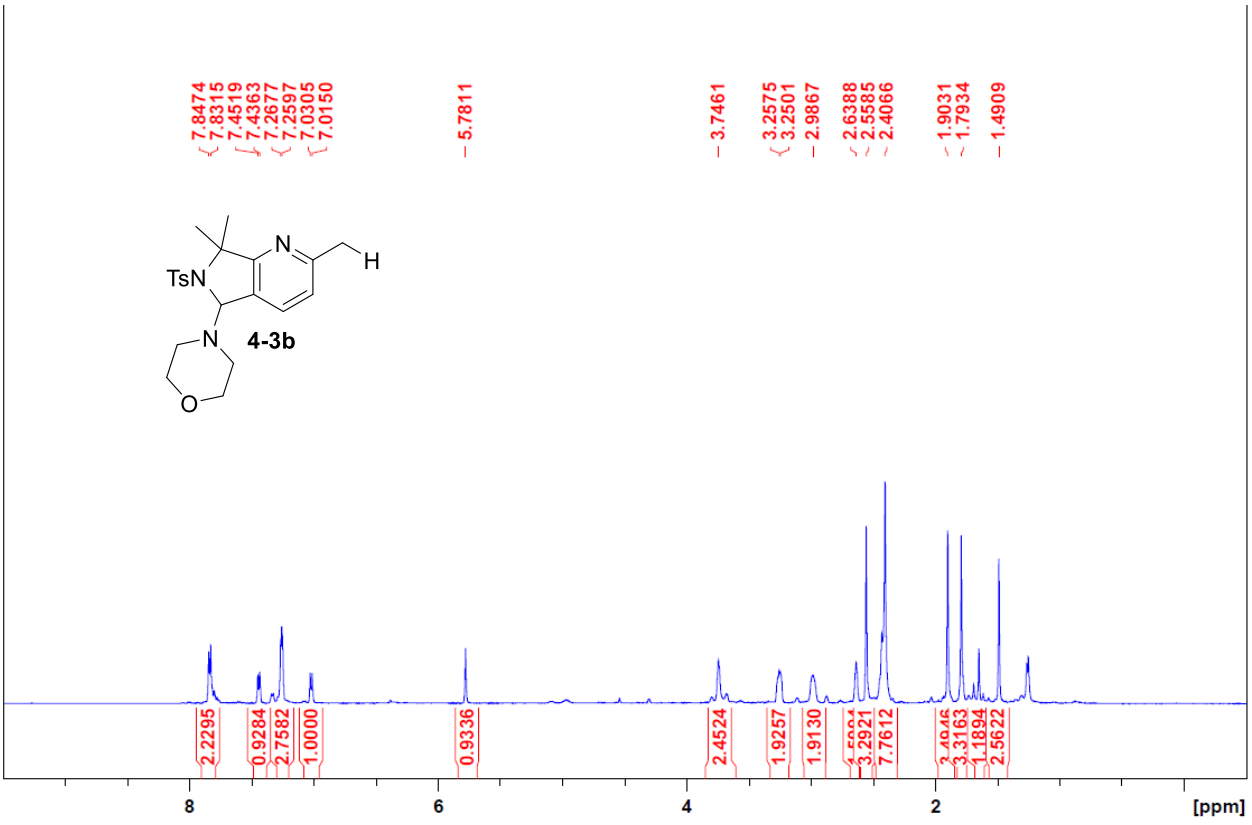

216.6911
143.1007
139.6160
129.3364
127.3719
88.1680
85.8887
77.2182
75.0109
72.4006
56.3628
37.7172
30.2095
21.5069
TsN
4-1c
200
150
100
50
[ppm]

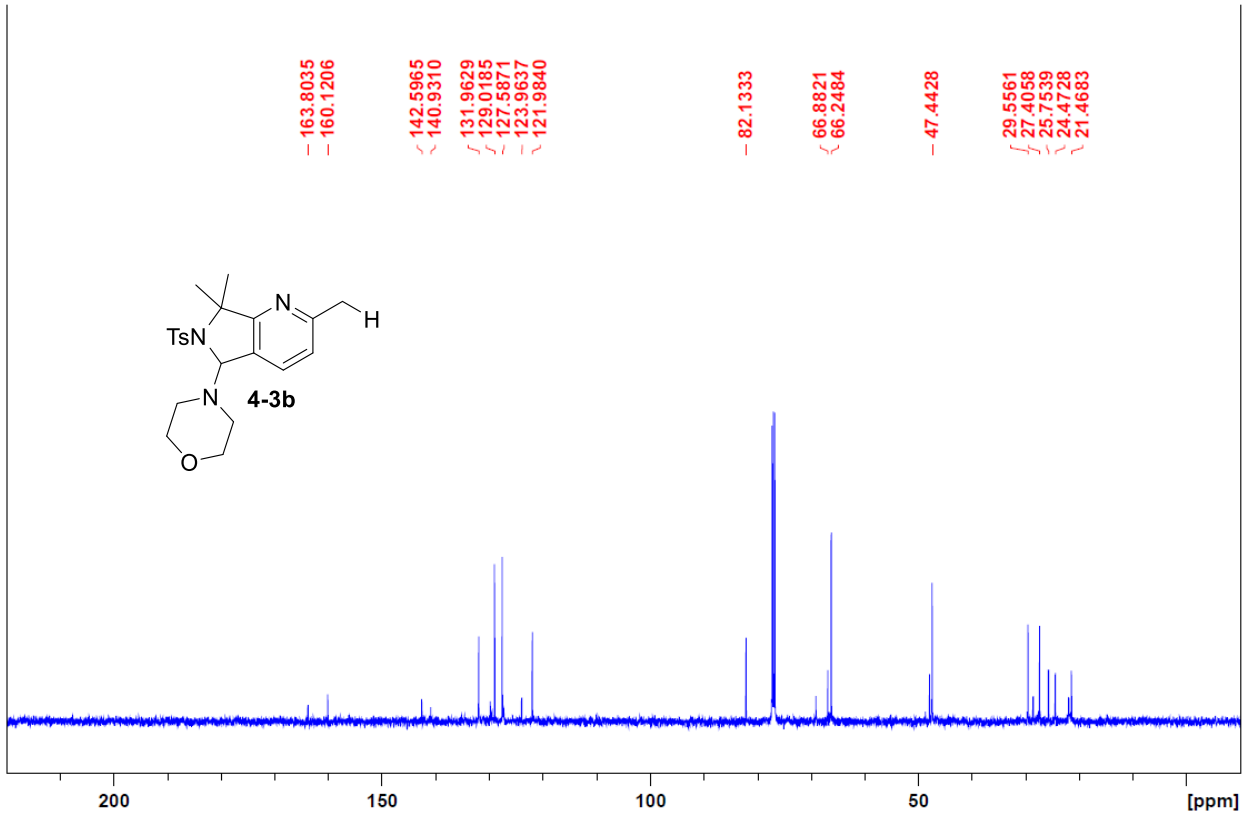

7.6976
7.6819
7.2305
7.2150
5.2278
5.2146
4.9185
4.9050
4.8295
4.8156
4.2756
4.2387
4.0945
4.0558
2.3482
2.1974
1.4445
1.4306
TsN
4-1d
2.0000
1.9180
0.7595
1.0084
0.9441
1.0917
3.3363
0.8739
3.3430
8
6
4
2
[ppm]

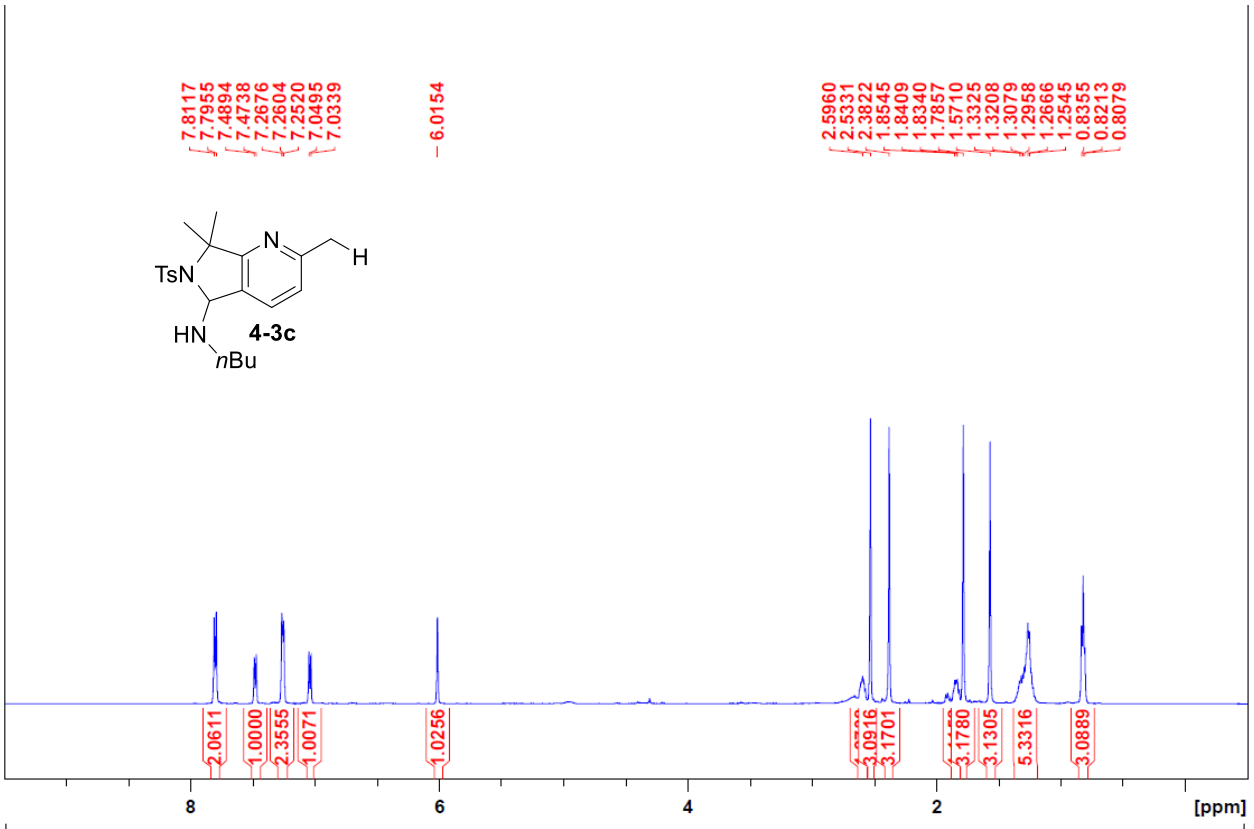

216.5794
143.5791
136.4629
129.4531
127.5961
86.6837
80.8793
77.1958
76.4133
74.8296
73.7834
45.9284
34.2615
21.8096
21.5167
TsN
4-1d
200
150
100
50
[ppm]

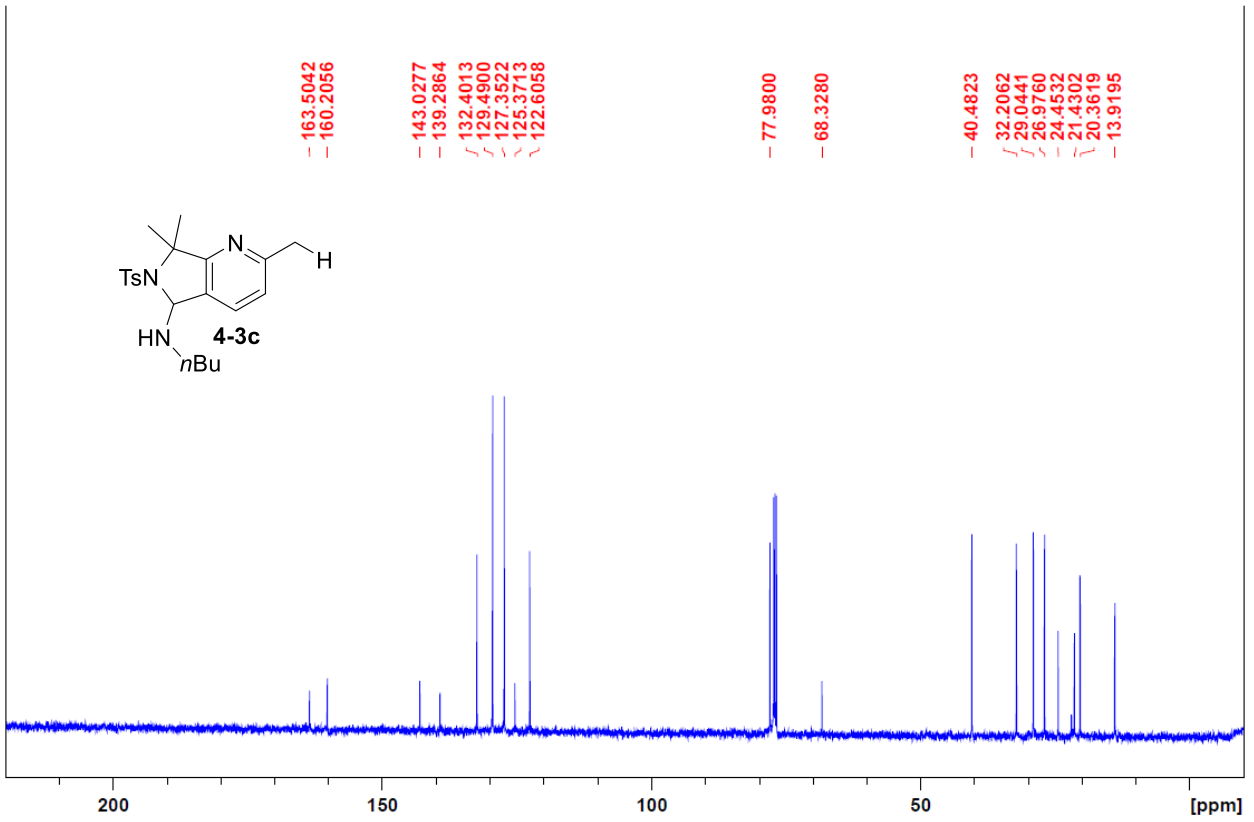

7.8802
7.8638
7.5119
7.4963
7.2706
7.2549
7.0855
7.0698
6.3928
2.8080
2.5612
2.3917
1.7594
1.7436
TsN
N
H
MeO
4-3a
2.0000
0.9468
2.2446
0.9886
0.9412
2.9345
3.0363
3.2252
6.3817
8
6
4
2
[ppm]

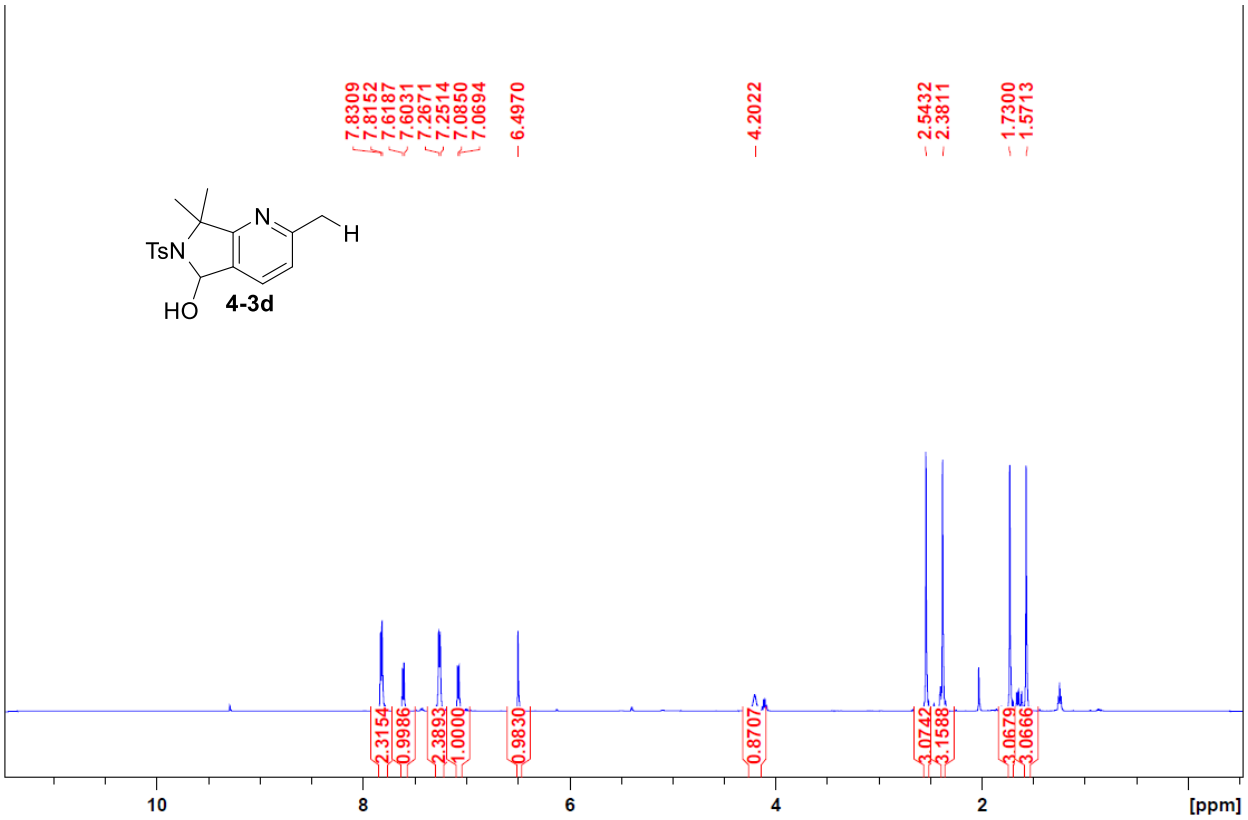

164.4659
161.0179
143.1227
139.3509
132.1358
129.2409
127.7145
123.8144
122.6636
90.6616
69.5831
50.7758
28.3916
27.4772
24.5677
21.5052
TsN
N
H
MeO
4-3a
200
150
100
50
[ppm]

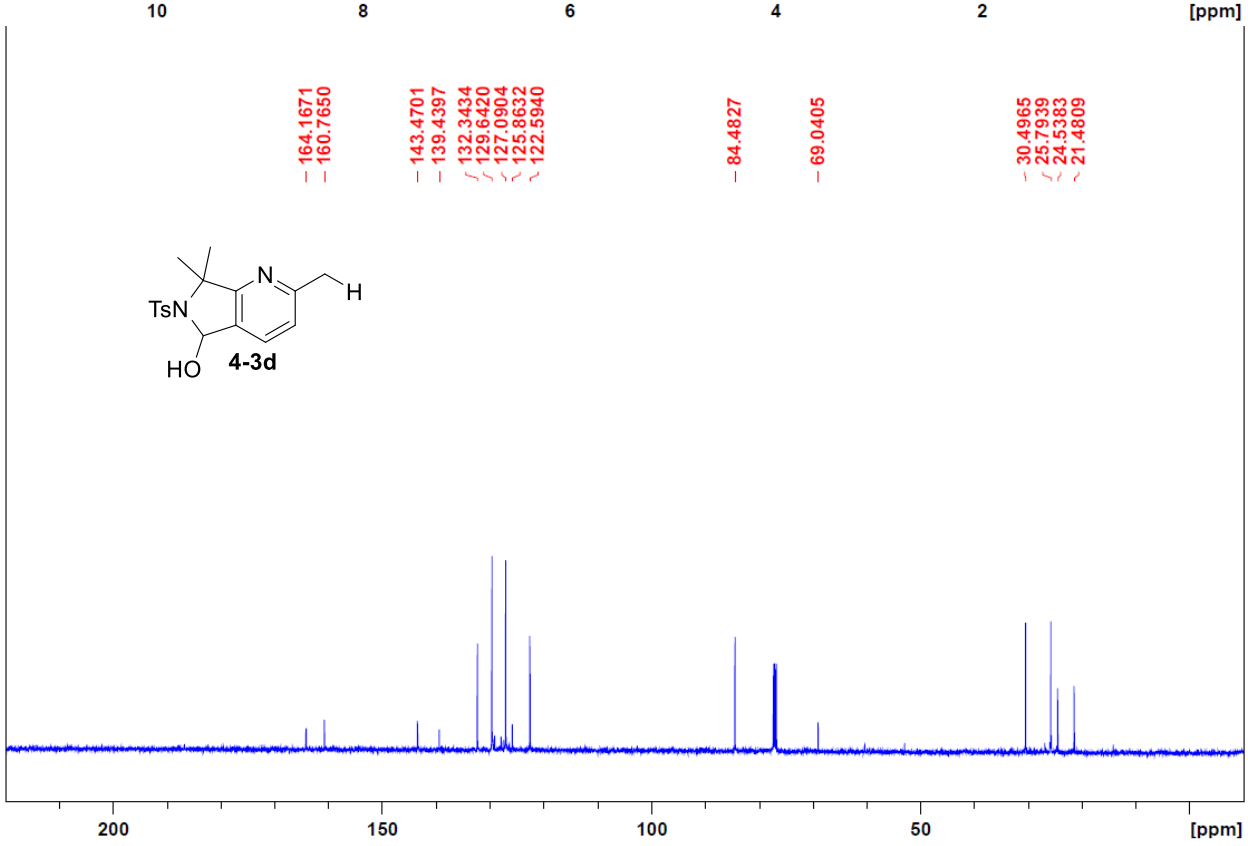

7.8474
7.8315
7.4519
7.4363
7.2677
7.2597
7.0305
7.0150
5.7811
3.7461
3.2575
3.2501
2.9867
2.6388
2.5585
2.4066
1.9031
1.7934
1.4909
TsN
N
H
N
O
4-3b
2.2295
0.9284
2.7582
1.0000
0.9336
2.4524
1.9257
1.9130
3.2921
7.7612
3.3163
1.1894
2.5622
8
6
4
2
[ppm]

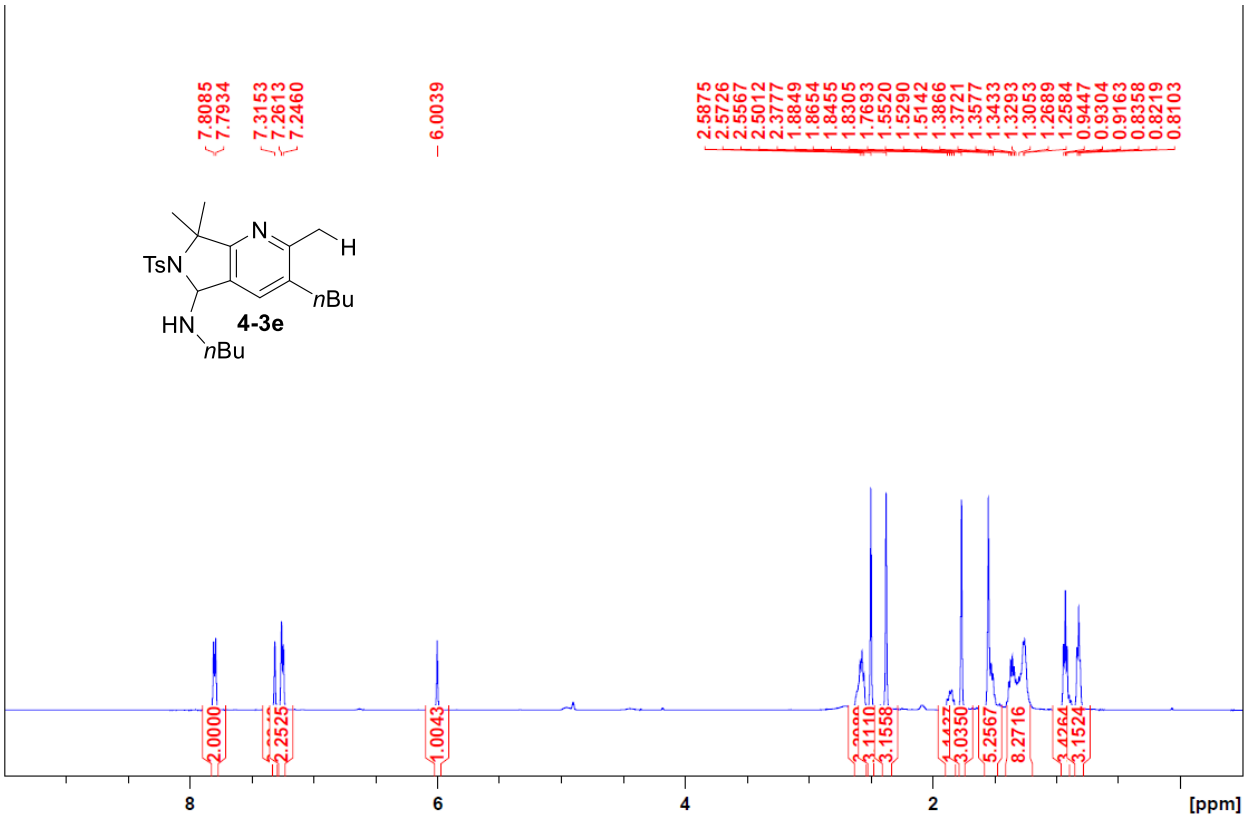

163.8035
160.1206
142.5965
140.9310
131.9629
129.0185
127.5871
123.9637
121.9840
82.1333
66.8821
66.2484
47.4428
29.5561
27.4058
25.7539
24.4728
21.4683
TsN
N
H
N
O
4-3b
200
150
100
50
[ppm]

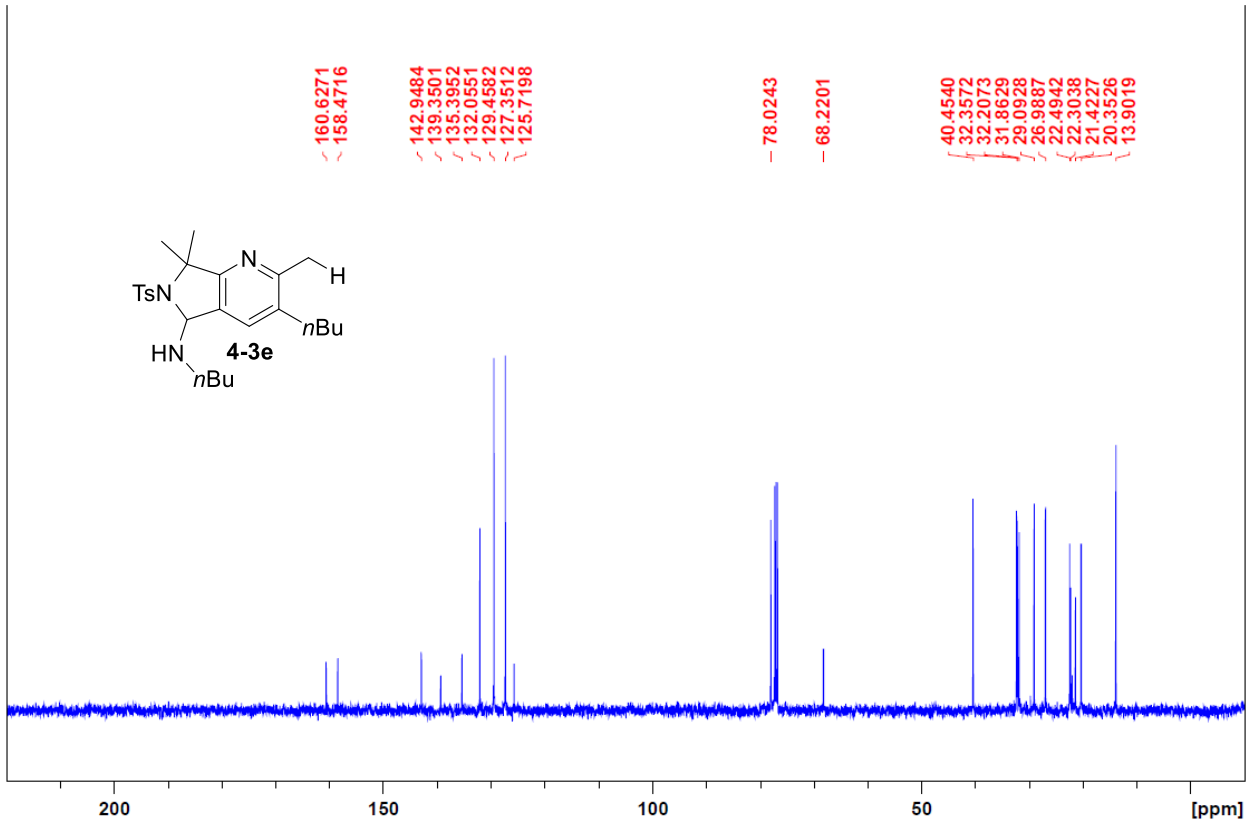

7.8117
7.7955
7.4894
7.4738
7.2676
7.2604
7.2520
7.0495
7.0339
6.0154
2.5960
2.5331
2.3822
1.8545
1.8409
1.8340
1.7857
1.5710
1.3325
1.3208
1.3079
1.2958
1.2666
1.2545
0.8355
0.8213
0.8079
TsN
N
H
HN
nBu
4-3c
2.0611
1.0000
2.3555
1.0071
1.0256
3.0916
3.1701
3.1780
3.1305
5.3316
3.0889
8
6
4
2
[ppm]

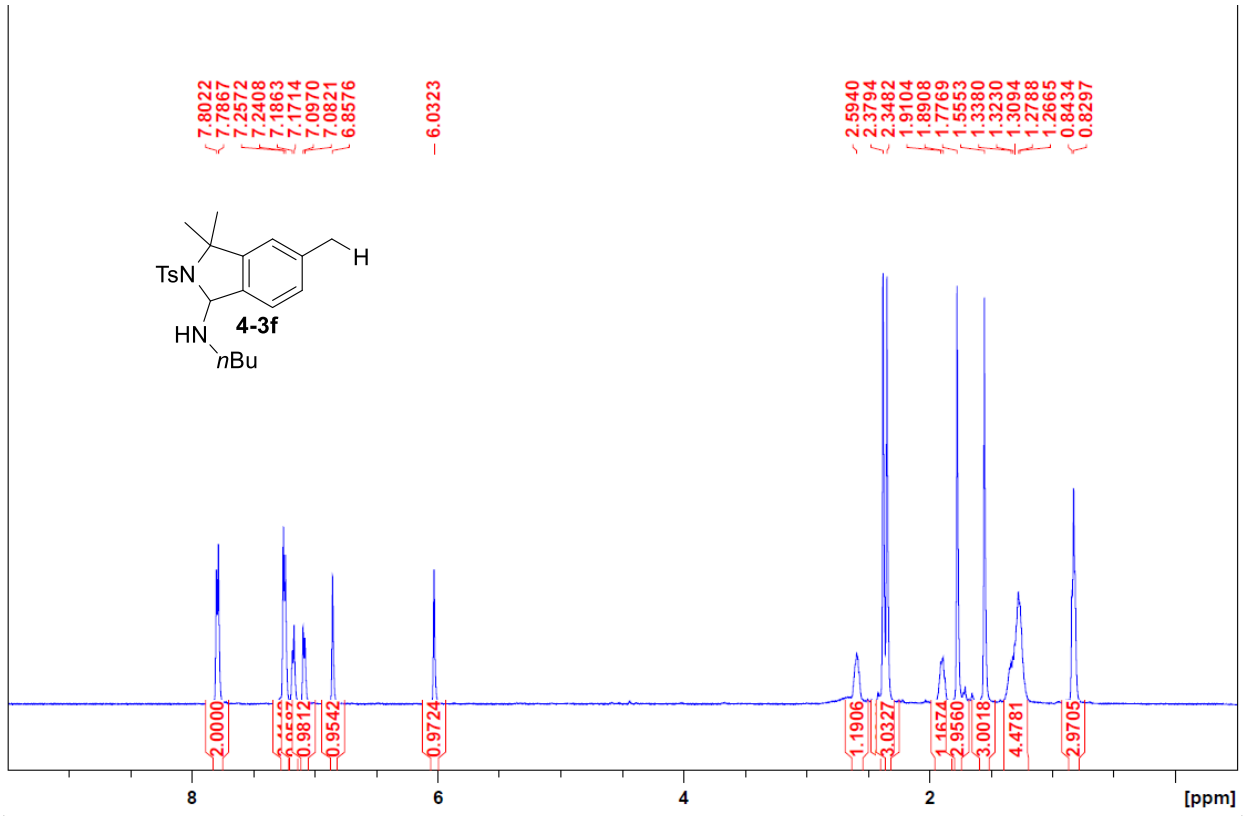

163.5042
160.2056
143.0277
139.2864
132.4013
129.4900
127.3522
125.3713
122.6058
77.9800
68.3280
40.4823
32.2062
29.0441
26.9760
24.4532
21.4302
20.3619
13.9195
TsN
N
H
HN
nBu
4-3c
200
150
100
50
[ppm]

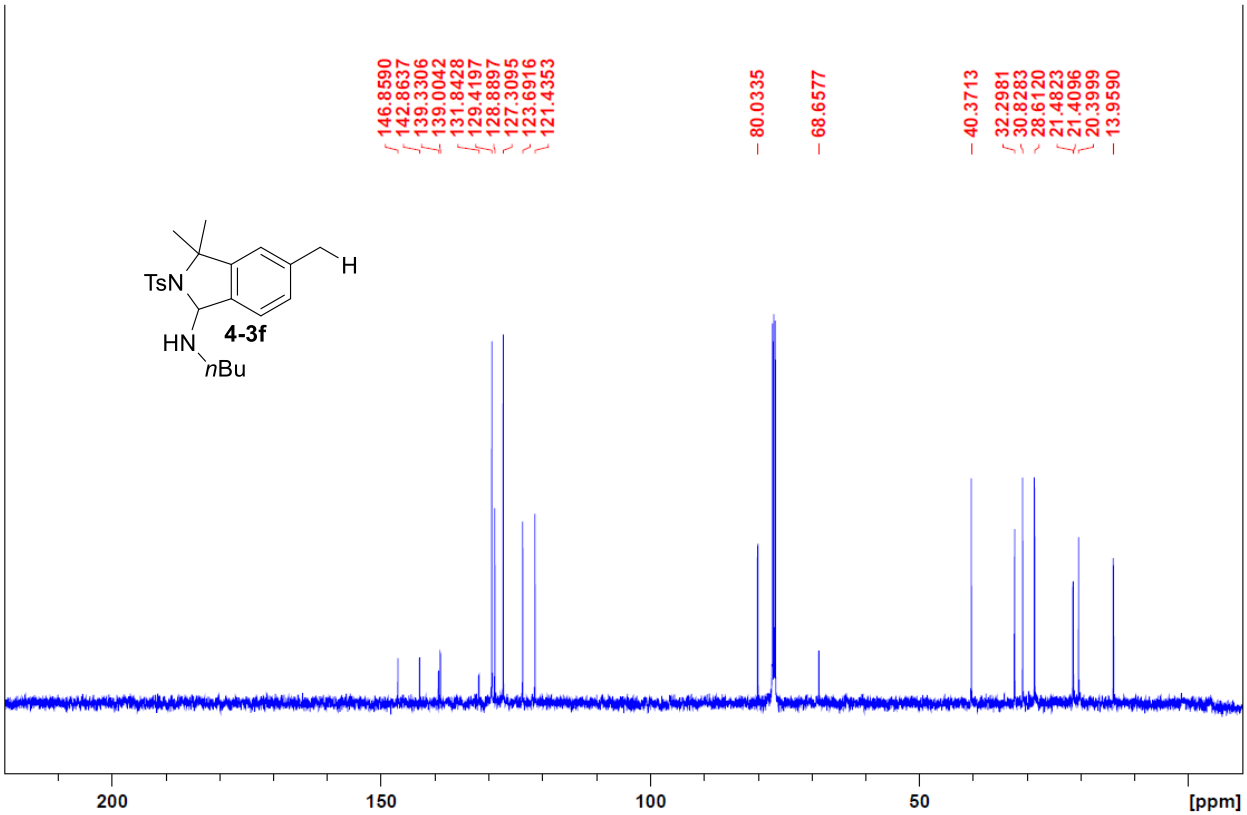

7.8309
7.8152
7.6187
7.6031
7.2671
7.2514
7.0850
7.0694
6.4970
4.2022
2.5432
2.3811
1.7300
1.5713
TsN
N
H
HO
4-3d
2.3154
0.9986
2.3893
1.0000
0.9830
0.8707
3.0742
3.1588
3.0679
3.0666
10
8
6
4
2
[ppm]

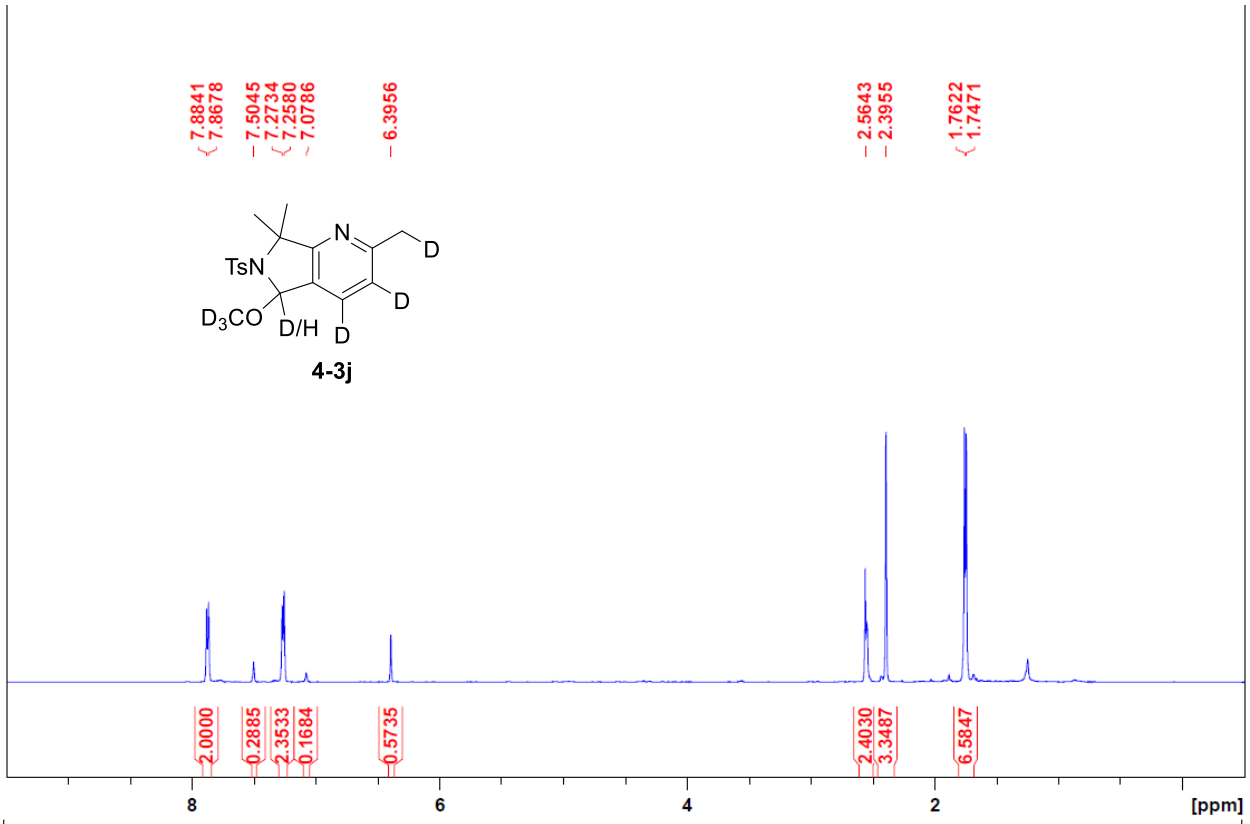

164.1671
160.7650
143.4701
139.4397
132.3434
129.6420
127.0904
125.8632
122.5940
84.4827
69.0405
30.4965
25.7939
24.5383
21.4809
TsN
N
H
HO
4-3d
200
150
100
50
[ppm]

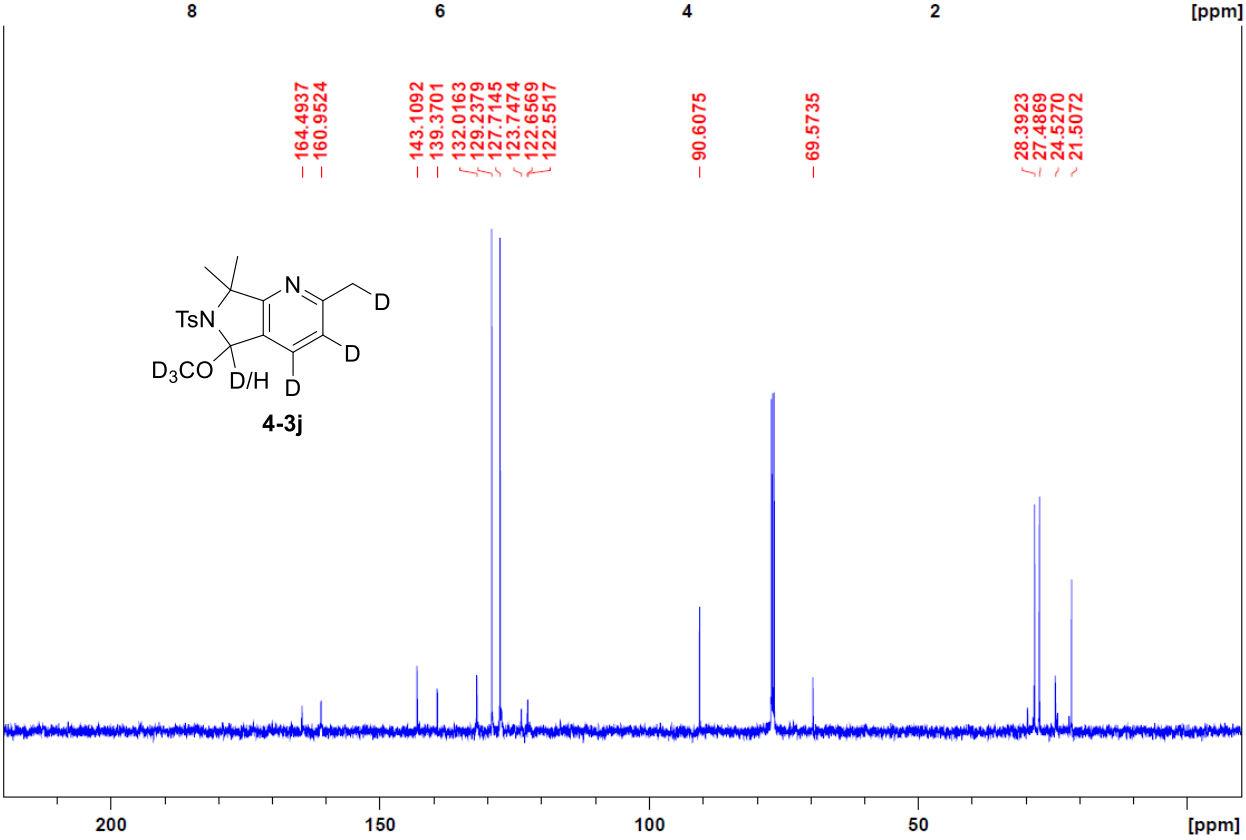

7.8085
7.7934
7.3153
7.2613
7.2460
6.0039
2.5875
2.5726
2.5567
2.5012
2.3777
1.8849
1.8654
1.8455
1.8305
1.7693
1.5520
1.5290
1.5142
1.3866
1.3721
1.3577
1.3433
1.3293
1.3053
1.2689
1.2584
0.9447
0.9304
0.9163
0.8358
0.8219
0.8103
TsN
N
H
nBu
HN
nBu
4-3e
2.0000
2.2525
1.0043
3.1110
3.1558
3.0350
5.2567
8.2716
3.4264
3.1524
8
6
4
2
[ppm]

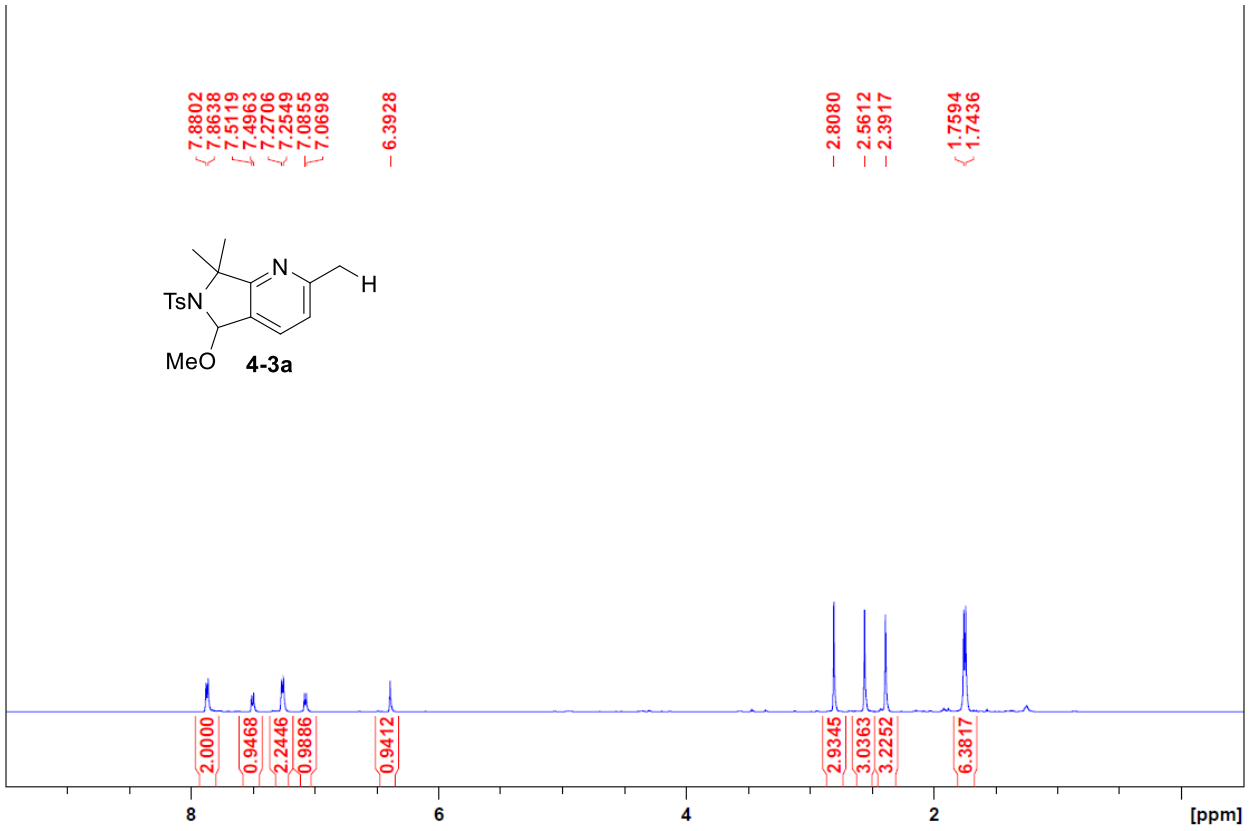

160.6271
158.4716
142.9484
139.3501
135.3952
132.0551
129.4582
127.3512
125.7198
78.0243
68.2201
40.4540
32.3572
32.2073
31.8629
29.0928
26.9887
22.4942
22.3038
21.4227
20.3526
13.9019
TsN
N
H
nBu
HN
nBu
4-3e
200
150
100
50
[ppm]

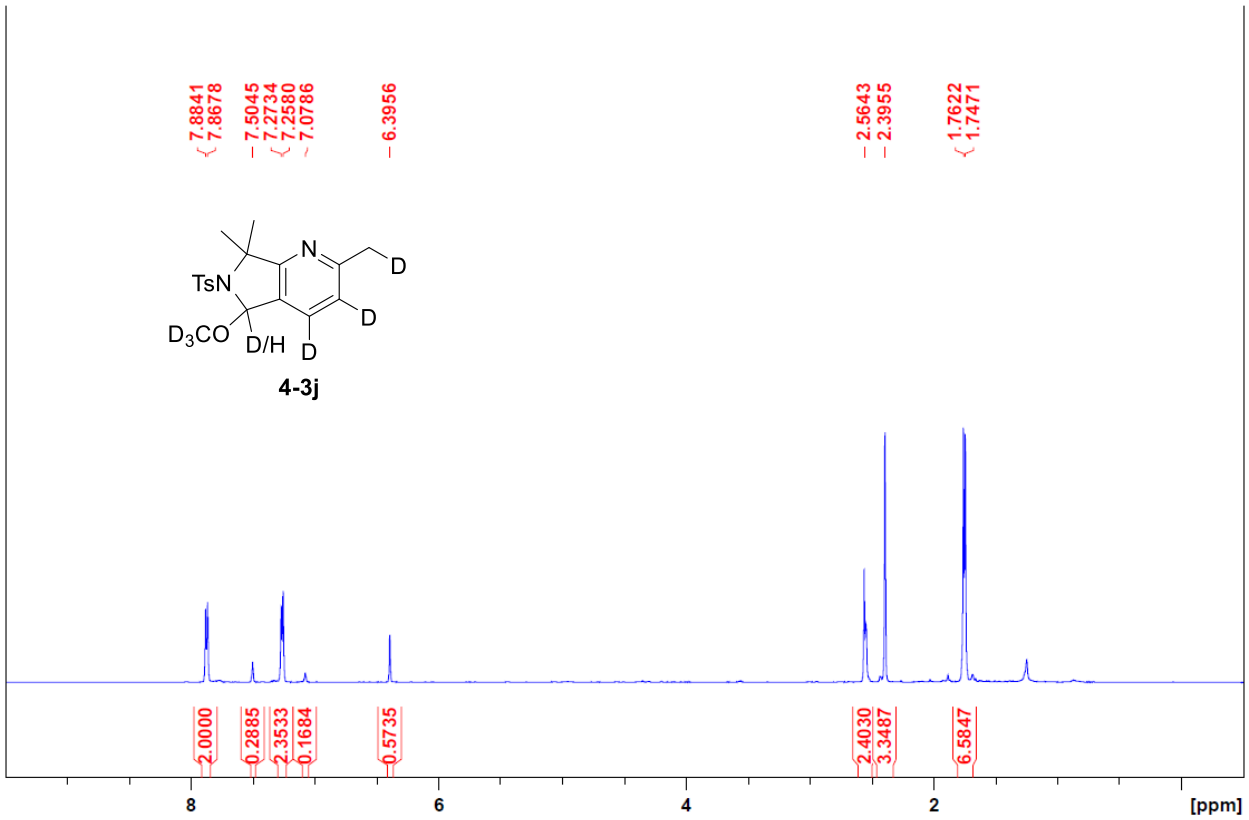

7.8022
7.7867
7.2572
7.2408
7.1863
7.1714
7.0970
7.0821
6.8576
6.0323
2.5940
2.3794
2.3482
1.9104
1.8908
1.7769
1.5553
1.3380
1.3230
1.3094
1.2788
1.2665
0.8434
0.8297
TsN
HN
nBu
H
4-3f
2.0000
0.9812
0.9542
0.9724
1.1906
3.0327
1.1674
2.9560
3.0018
4.4781
2.9705
8
6
4
2
[ppm]


146.8590
142.8637
139.3306
139.0042
131.8428
129.4197
128.8897
127.3095
123.6916
121.4353
80.0335
68.6577
40.3713
32.2981
30.8283
28.6120
21.4823
21.4096
20.3999
13.9590
TsN
HN
nBu
H
4-3f
200
150
100
50
[ppm]


7.8841
7.8678
7.5045
7.2734
7.2580
7.0786
6.3956
2.5643
2.3955
1.7622
1.7471
TsN
N
D
D
D3CO
D/H
D
4-3j
2.0000
0.2885
2.3533
0.1684
0.5735
2.4030
3.3487
6.5847
8
6
4
2
[ppm]

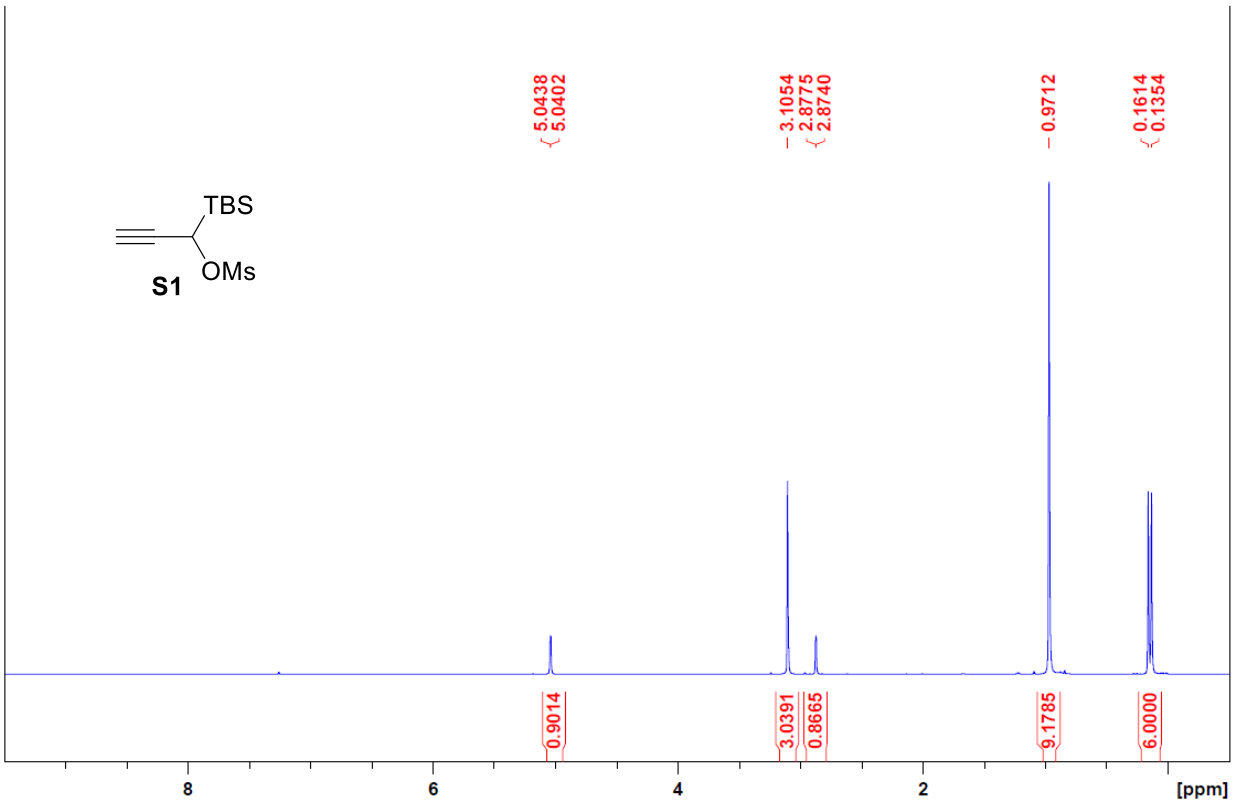

164.4937
160.9524
143.1092
139.3701
132.0163
129.2379
127.7145
123.7474
122.6569
122.5517
90.6075
69.5735
28.3923
27.4869
24.5270
21.5072
TsN
N
D
D
D3CO
D/H
D
4-3j
200
150
100
50
[ppm]

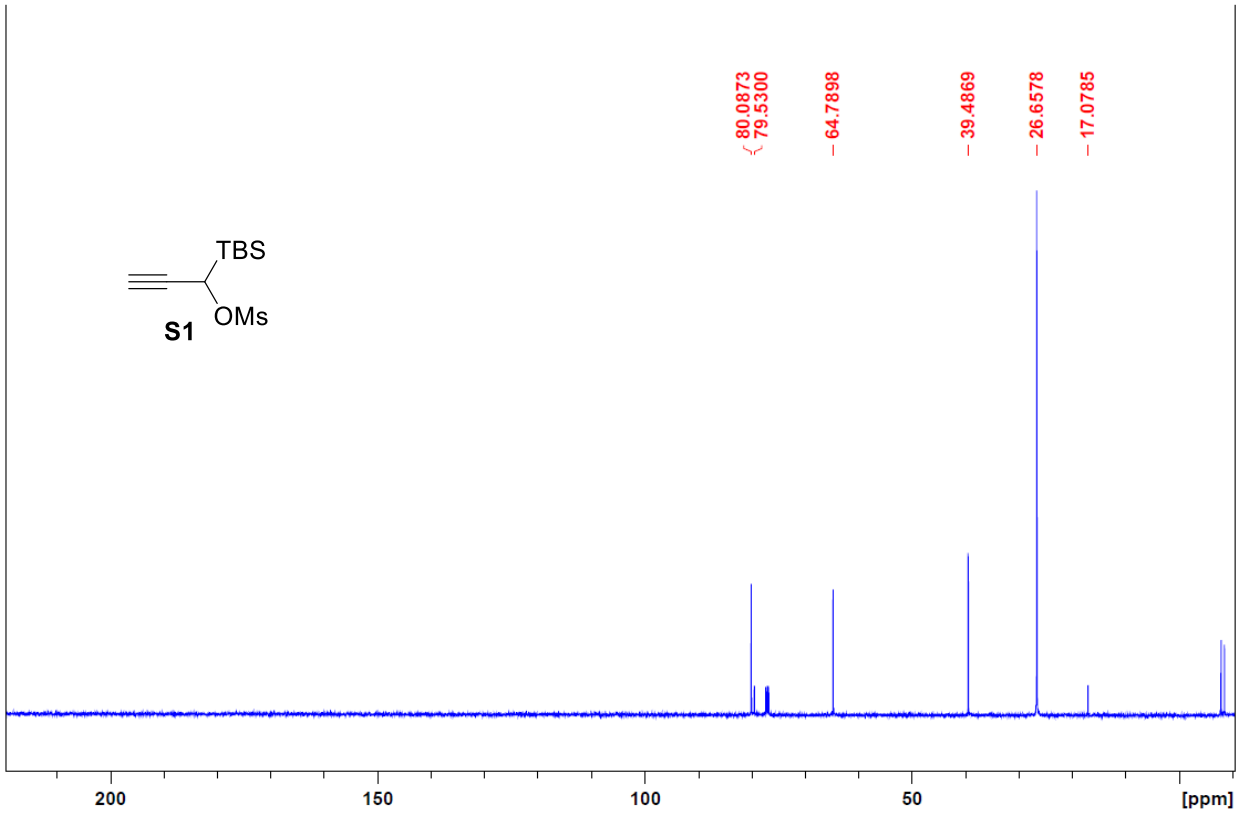

7.8802
7.8638
7.5119
7.4963
7.2706
7.2549
7.0855
7.0698
6.3928
2.8080
2.5612
2.3917
1.7594
1.7436
TsN
MeO
N
H
4-3a
2.0000
0.9468
2.2446
0.9886
0.9412
2.9345
3.0363
3.2252
6.3817
8
6
4
2
[ppm]

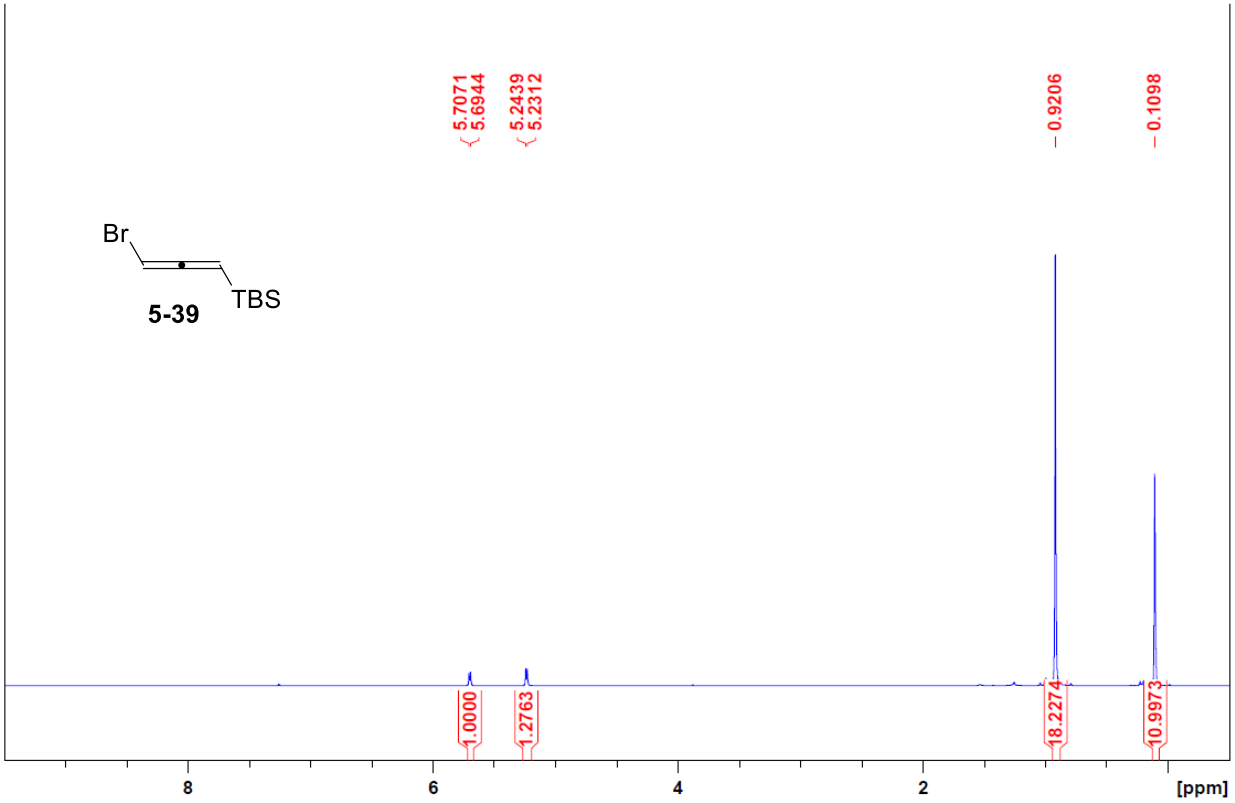

7.8841
7.8678
7.5045
7.2734
7.2580
7.0786
6.3956
2.5643
2.3955
1.7622
1.7471
TsN
D3CO
D/H
N
D
D
D
4-3j
2.0000
0.2885
2.3533
0.1684
0.5735
2.4030
3.3487
6.5847
8
6
4
2
[ppm]

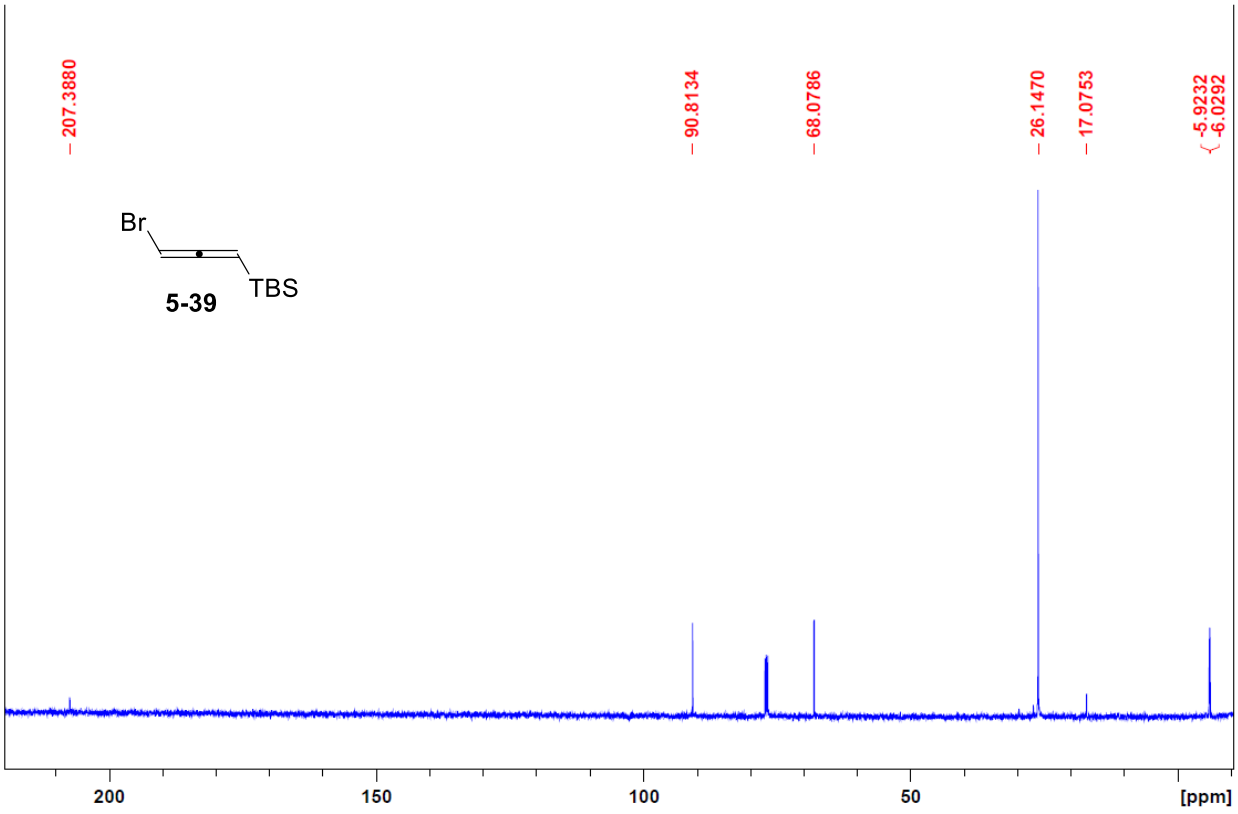
Appendix IV

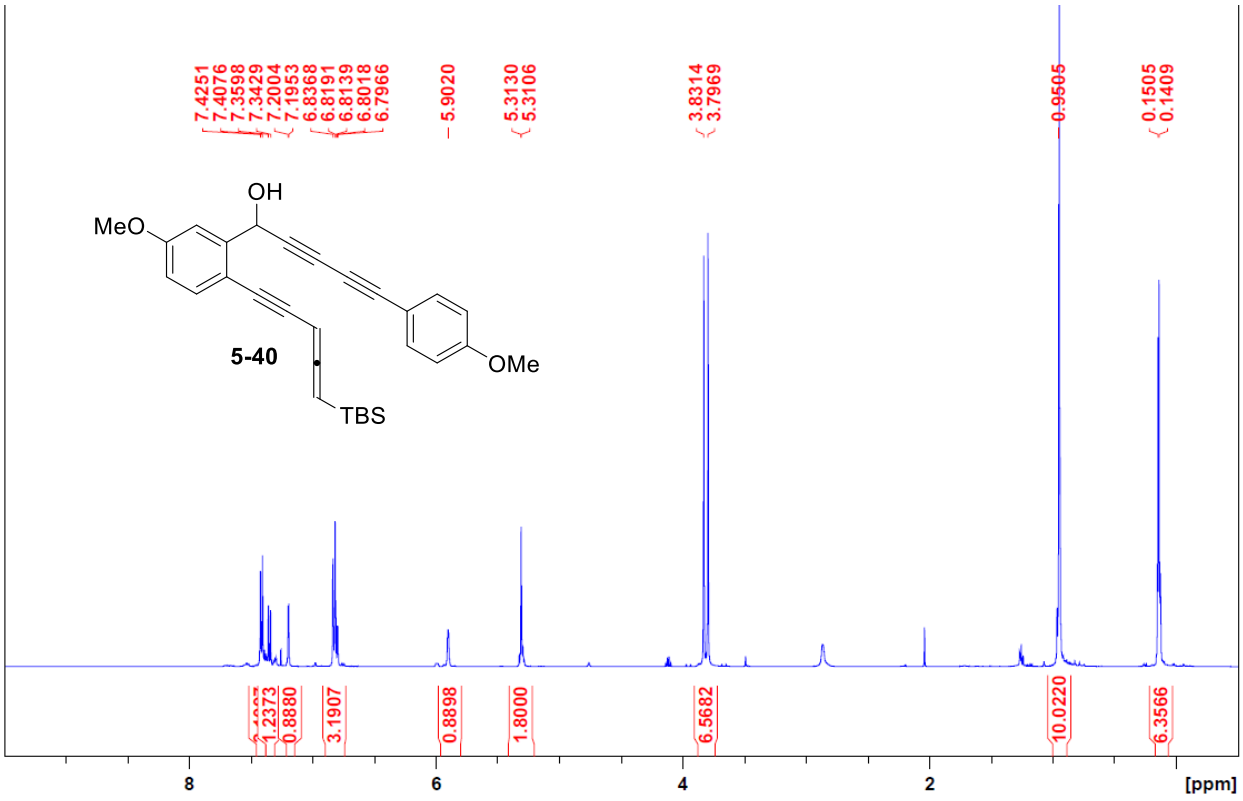
Selected NMR Spectra for Chapter 5

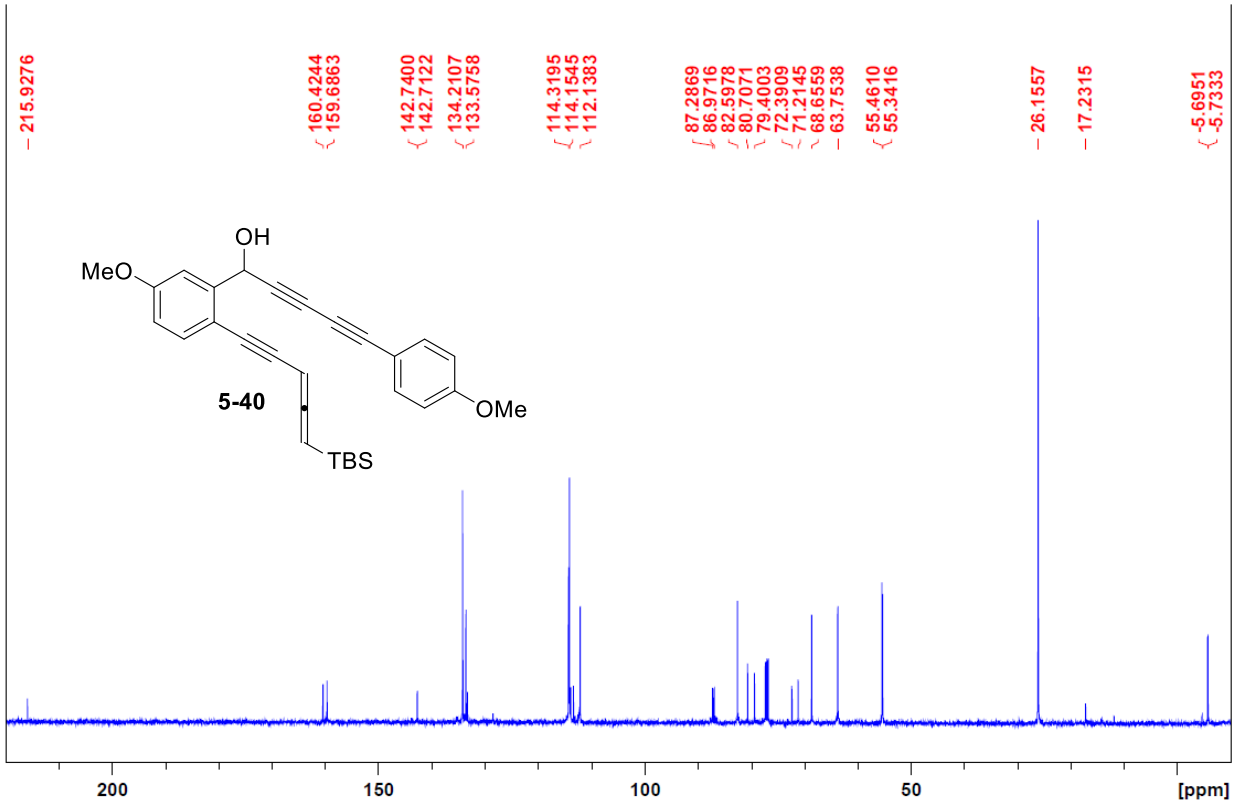

5.0438
5.0402
3.1054
2.8775
2.8740
0.9712
0.1614
0.1354
TBS
OMs
S1
0.9014
3.0391
0.8665
9.1785
6.0000
8
6
4
2
[ppm]

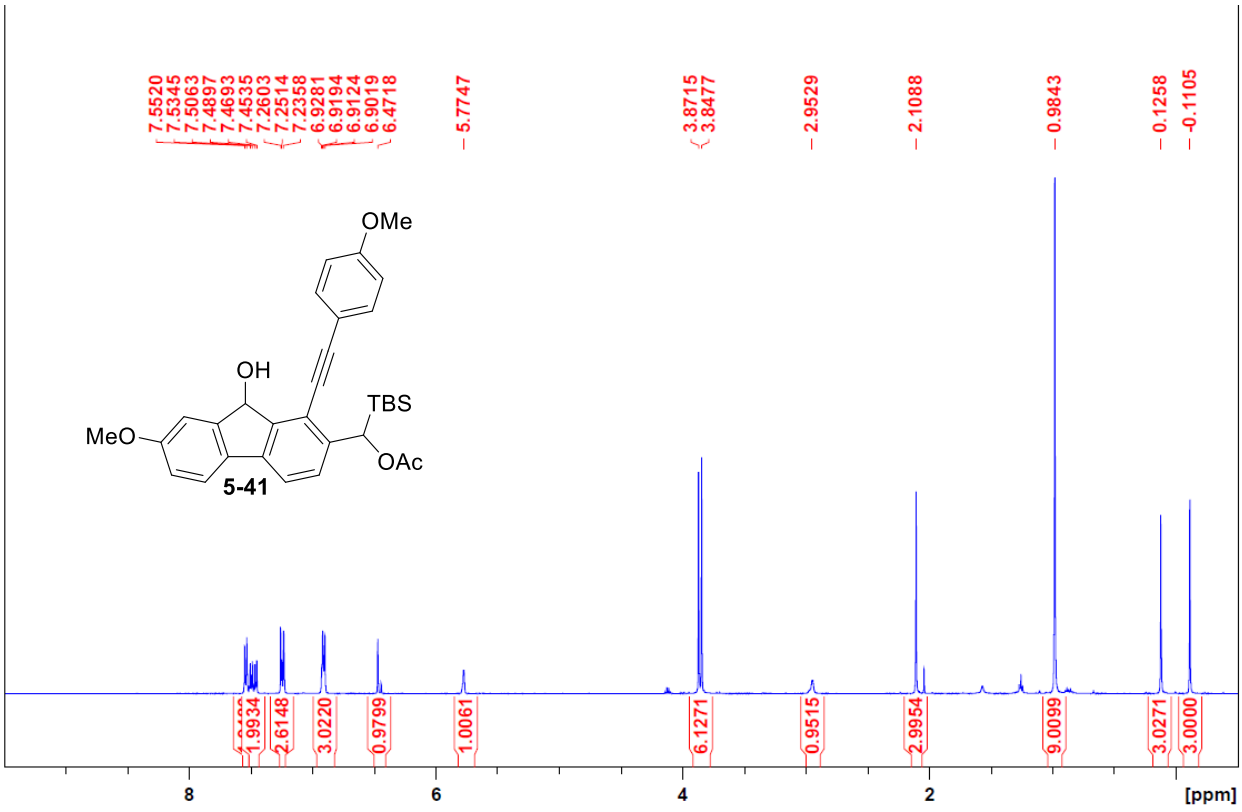

80.0873
79.5300
64.7898
39.4869
26.6578
17.0785
TBS
OMs
S1
200
150
100
50
[ppm]

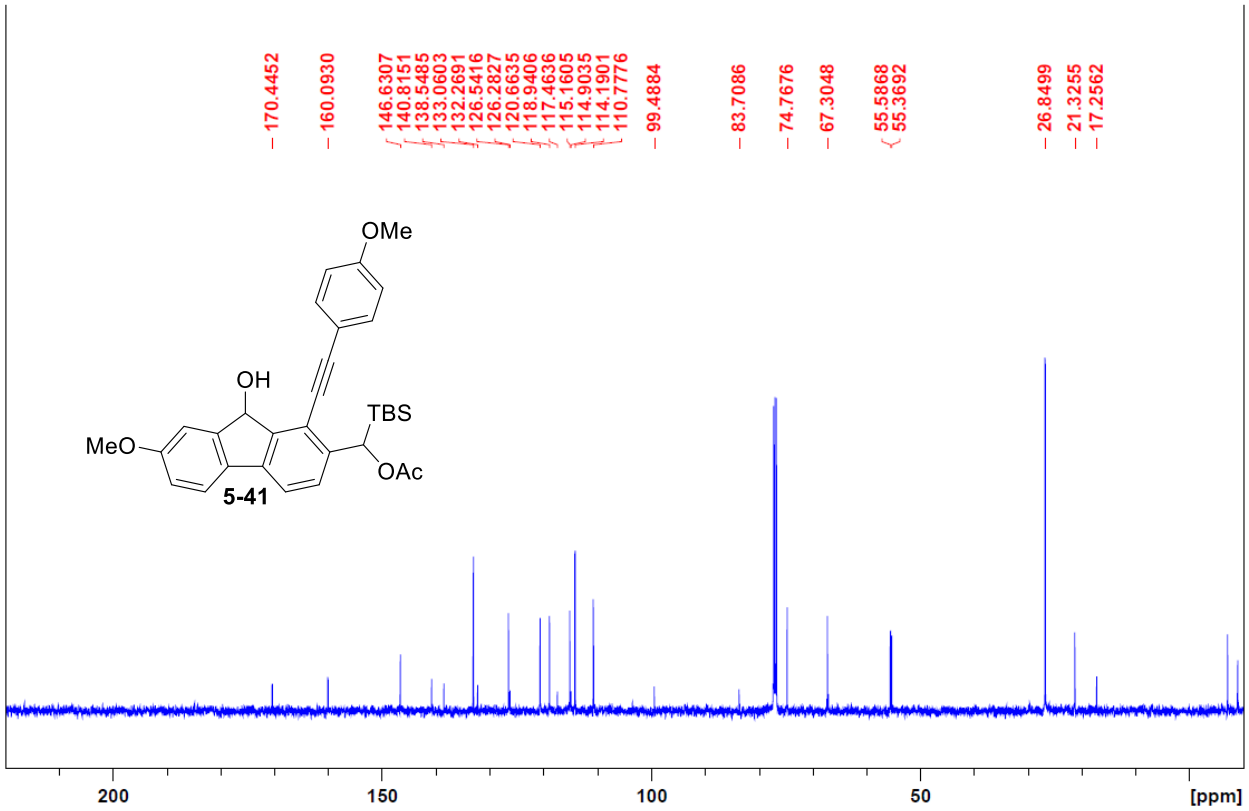

5.7071
5.6944
5.2439
5.2312
0.9206
0.1098
Br
TBS
5-39
1.0000
1.2763
18.2274
10.9973
8
6
4
2
[ppm]

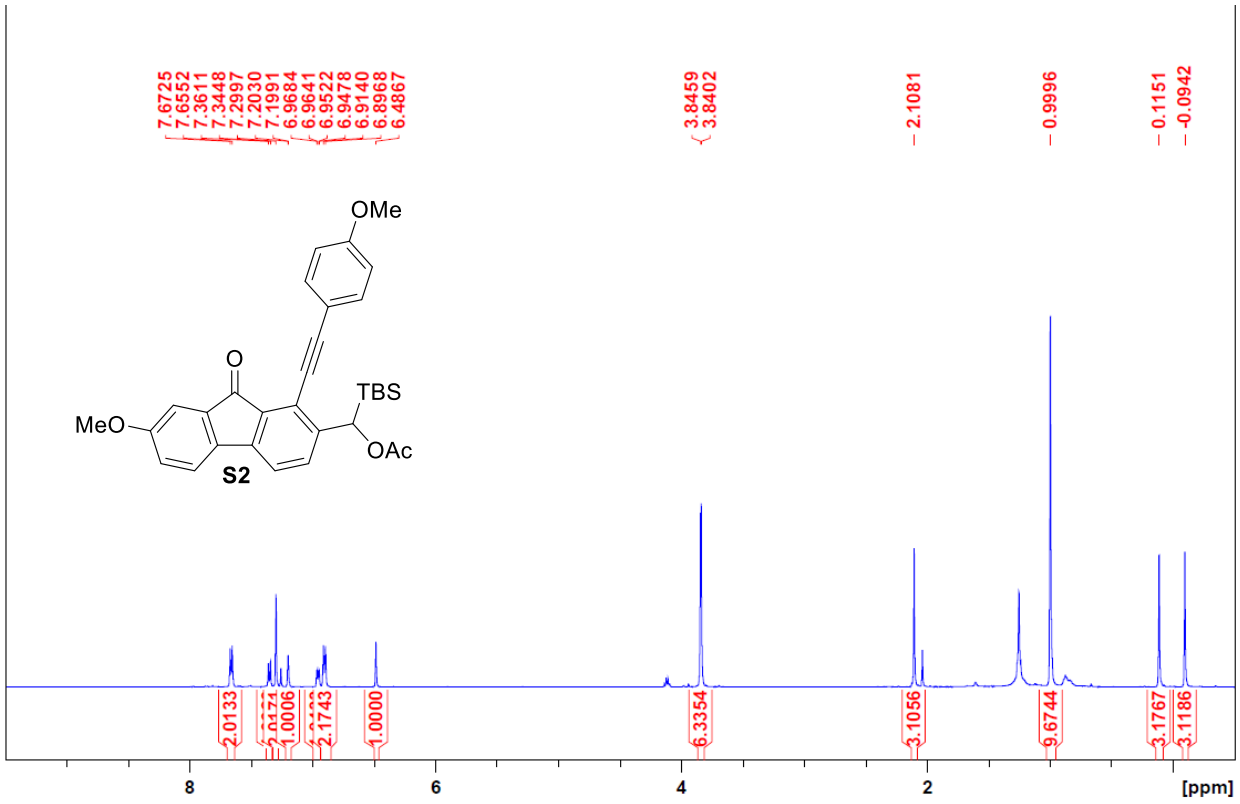

207.3880
90.8134
68.0786
26.1470
17.0753
-5.9232
-6.0292
Br
TBS
5-39
200
150
100
50
[ppm]

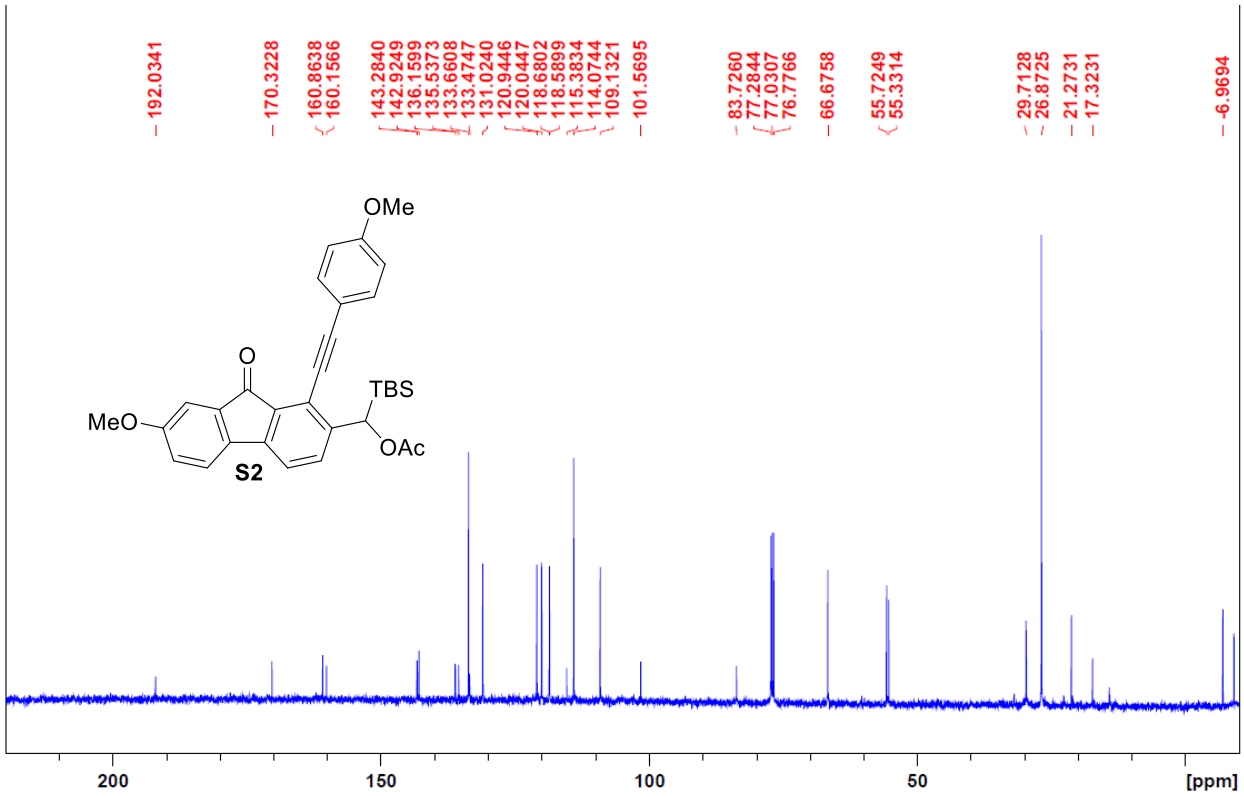

7.4251
7.4076
7.3598
7.3429
7.2004
7.1953
6.8368
6.8191
6.8139
6.8018
6.7966
5.9020
5.3130
5.3106
3.8314
3.7969
0.9505
0.1505
0.1409
OH
MeO
OMe
5-40
TBS
1.2373
0.8880
3.1907
0.8898
1.8000
6.5682
10.0220
6.3566
8
6
4
2
[ppm]

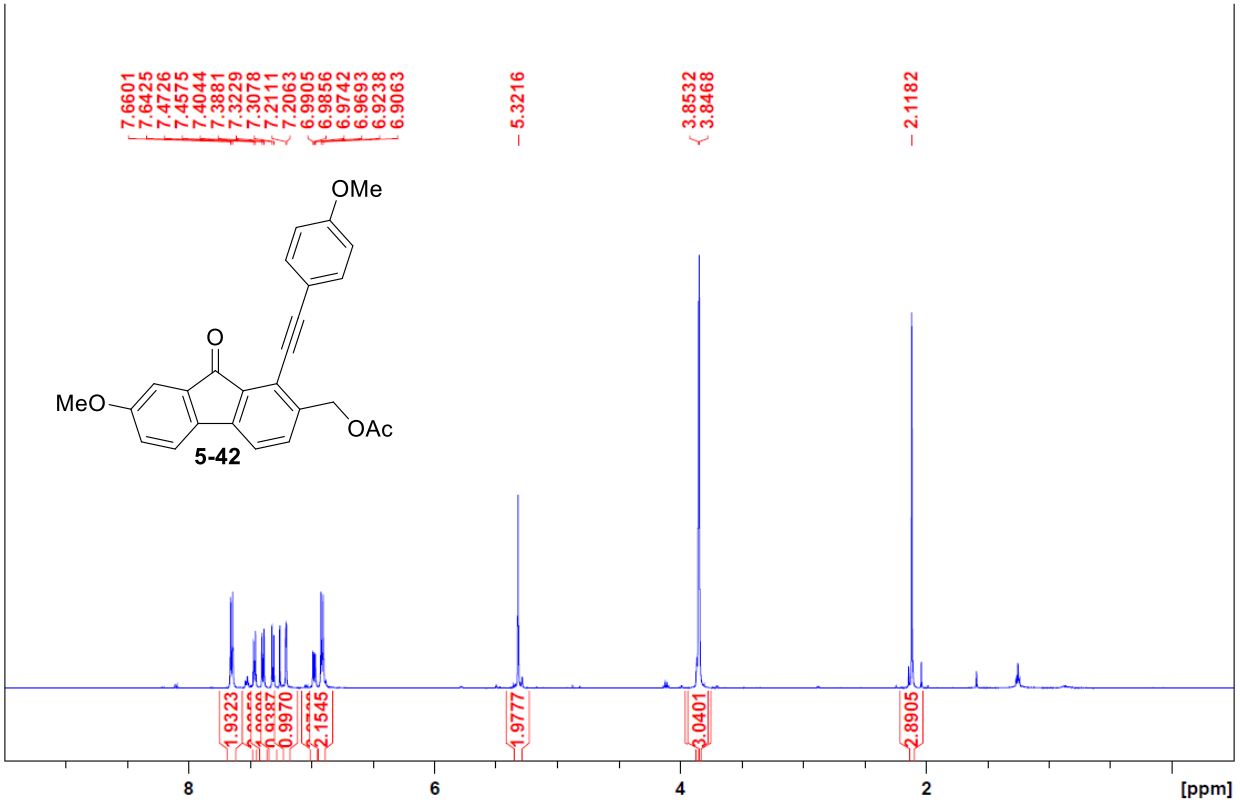

215.9276
160.4244
159.6863
142.7400
142.7122
134.2107
133.5758
114.3195
114.1545
112.1383
87.2869
86.9716
82.5978
80.7071
79.4003
72.3909
71.2145
68.6559
63.7538
55.4610
55.3416
26.1557
17.2315
-5.6951
-5.7333
OH
MeO
OMe
5-40
TBS
200
150
100
50
[ppm]

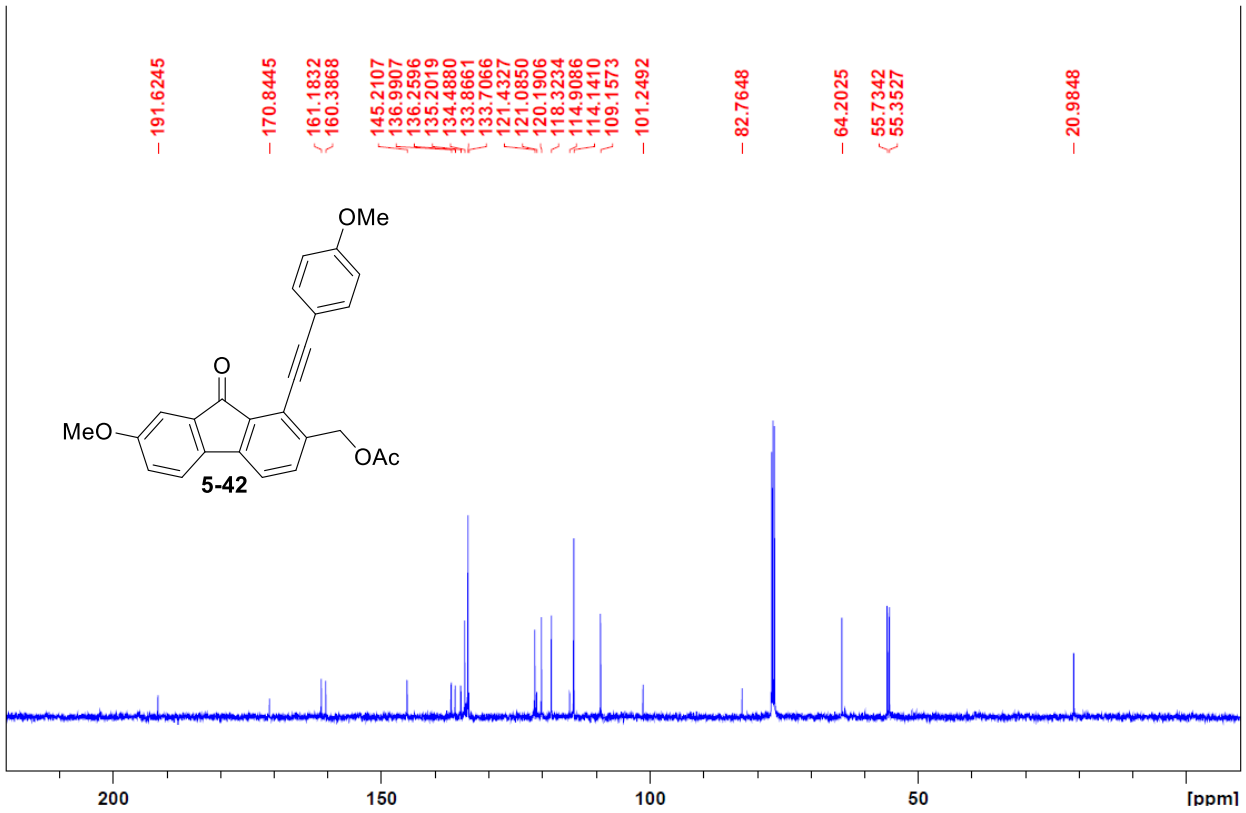

7.5520
7.5345
7.5063
7.4897
7.4693
7.4535
7.2603
7.2514
7.2358
6.9281
6.9194
6.9124
6.9019
6.4718
5.7747
3.8715
3.8477
2.9529
2.1088
0.9843
0.1258
-0.1105
OMe
OH
TBS
MeO
OAc
5-41
1.9934
2.6148
3.0220
0.9799
1.0061
6.1271
0.9515
2.9954
9.0099
3.0271
3.0000
8
6
4
2
[ppm]

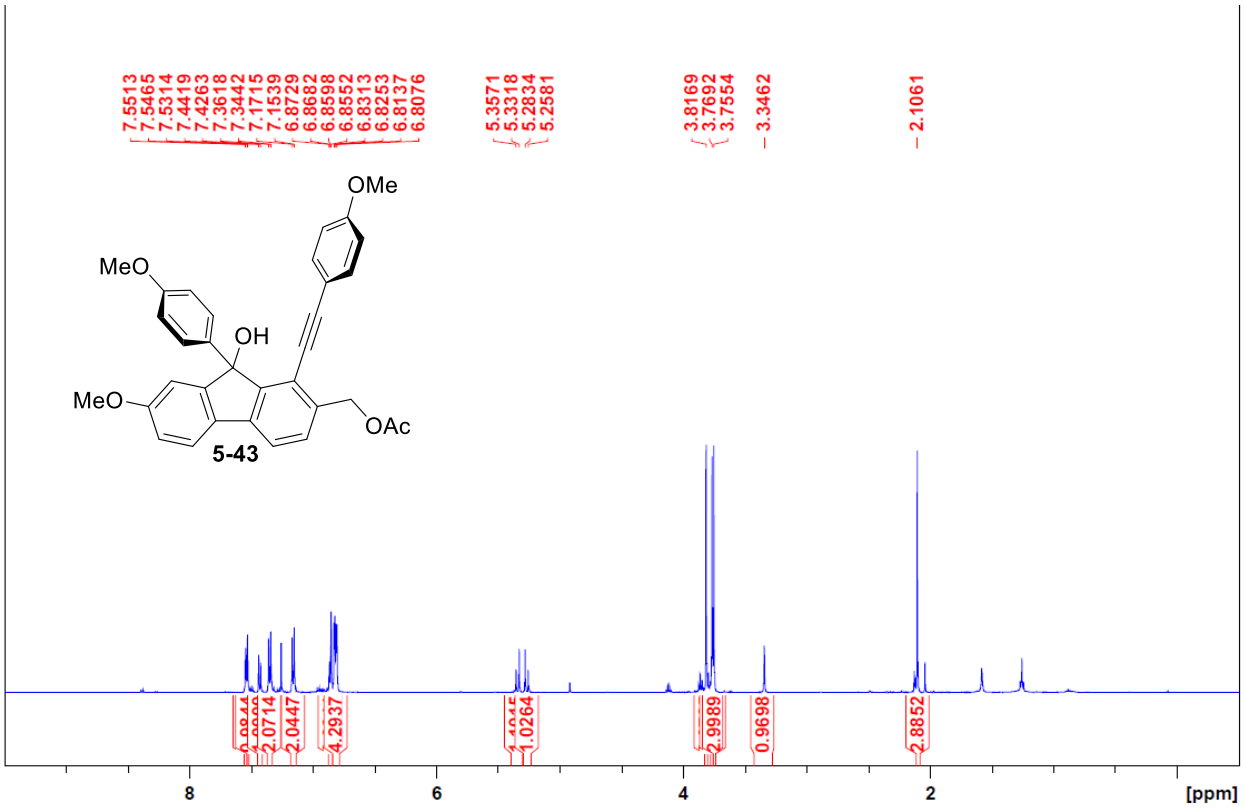

170.4452
160.0930
146.6307
140.8151
138.5485
133.0603
132.2691
126.5416
126.2827
120.6635
118.9406
117.4636
115.1605
114.9035
114.1901
110.7776
99.4884
83.7086
74.7676
67.3048
55.5868
55.3692
26.8499
21.3255
17.2562
OMe
OH
TBS
MeO
OAc
5-41
200
150
100
50
[ppm]

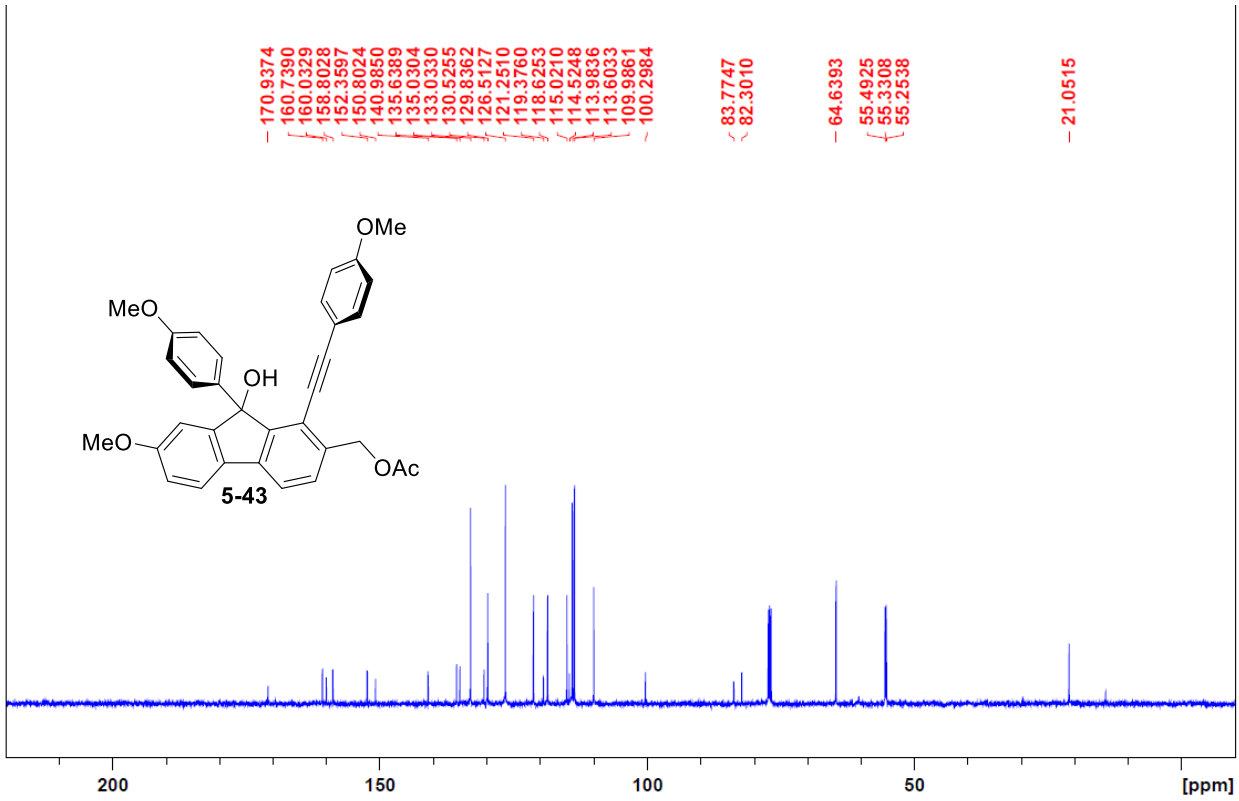

7.6725
7.6552
7.3611
7.3448
7.2997
7.2030
7.1991
6.9684
6.9641
6.9522
6.9478
6.9140
6.8968
6.4867
3.8459
3.8402
2.1081
0.9996
0.1151
-0.0942
OMe
O
TBS
MeO
OAc
S2
2.0133
1.0006
2.1743
1.0000
6.3354
3.1056
9.6744
3.1767
3.1186
8
6
4
2
[ppm]

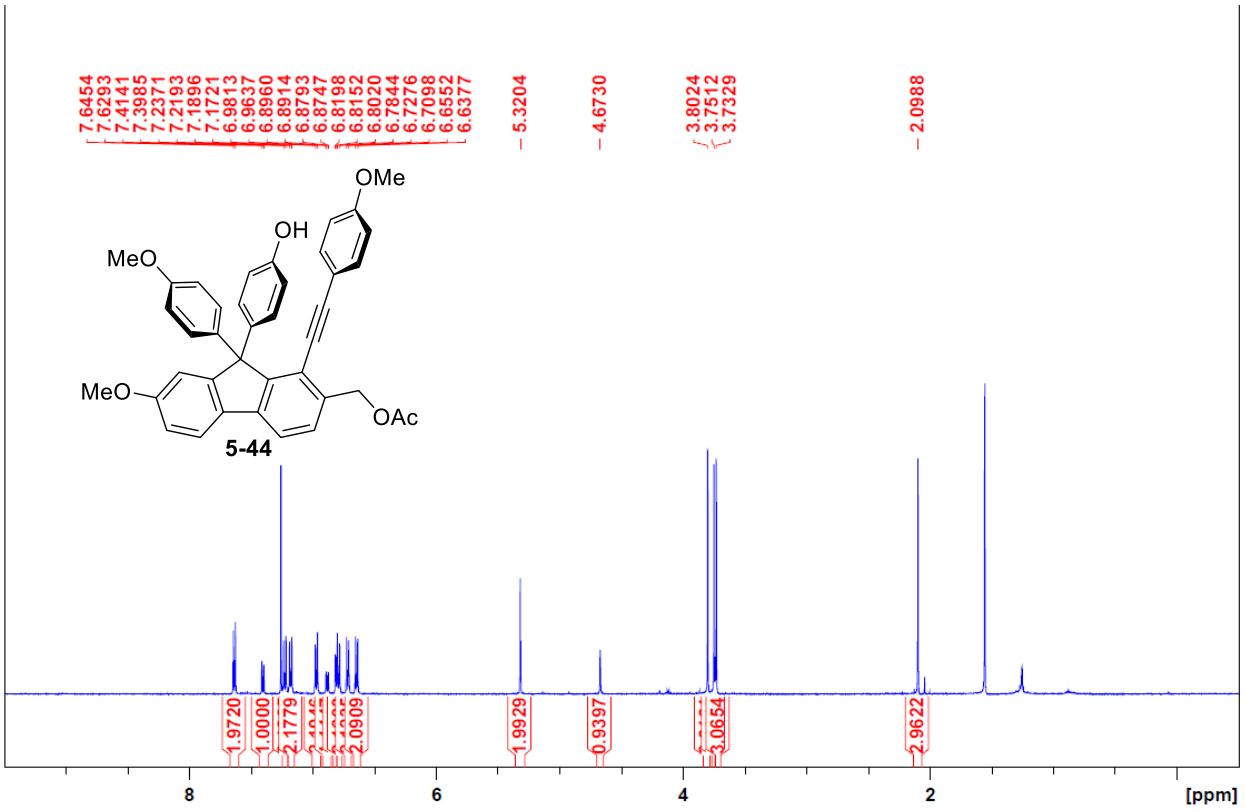

192.0341
170.3228
160.8638
160.1566
143.2840
142.9249
136.1599
135.5373
133.6608
133.4747
131.0240
120.9446
120.0447
118.6802
118.5899
115.3834
114.0744
109.1321
101.5695
83.7260
77.2844
77.0307
76.7766
66.6758
55.7249
55.3314
29.7128
26.8725
21.2731
17.3231
-6.9694
OMe
O
TBS
MeO
OAc
S2
200
150
100
50
[ppm]

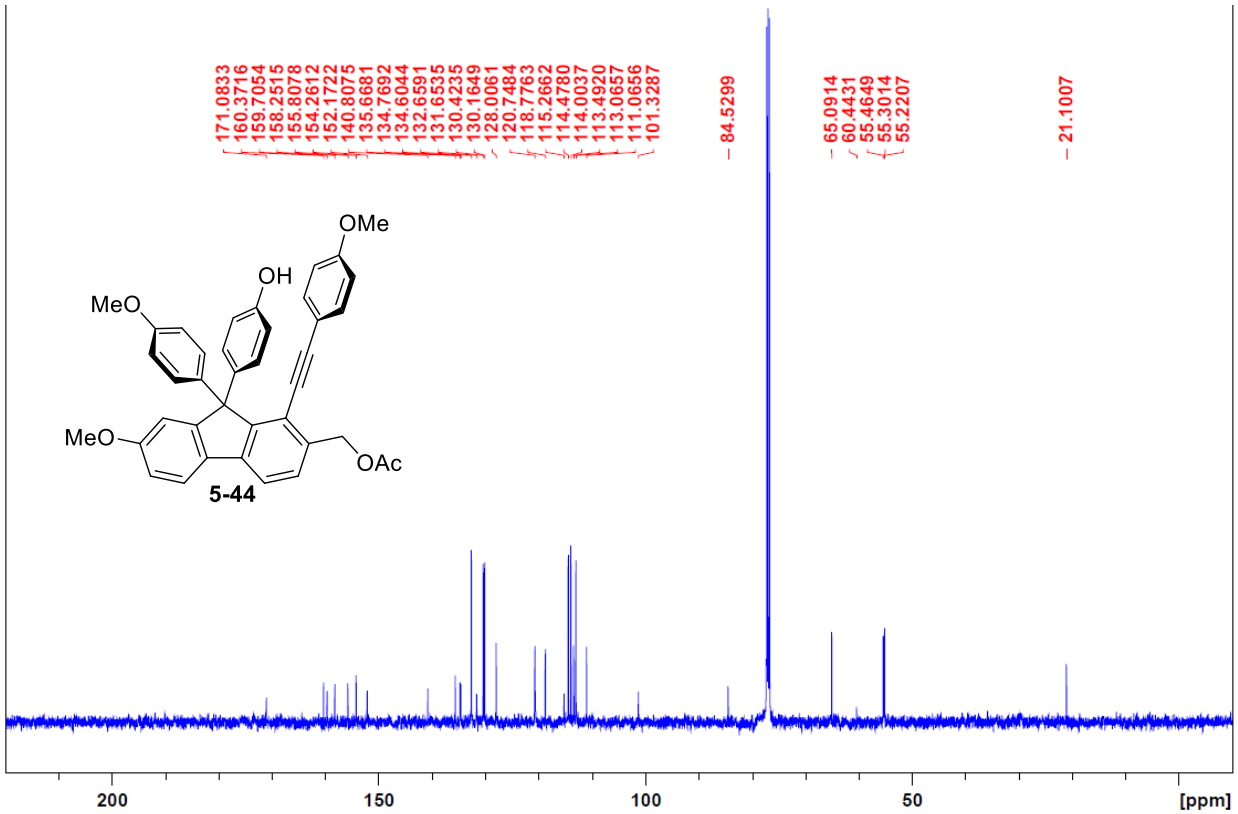

7.6601
7.6425
7.4726
7.4575
7.4044
7.3881
7.3229
7.3078
7.2111
7.2063
6.9905
6.9856
6.9742
6.9693
6.9238
6.9063
5.3216
3.8532
3.8468
2.1182
OMe
O
MeO
OAc
5-42
1.9323
0.9970
2.1545
1.9777
3.0401
2.8905
8
6
4
2
[ppm]

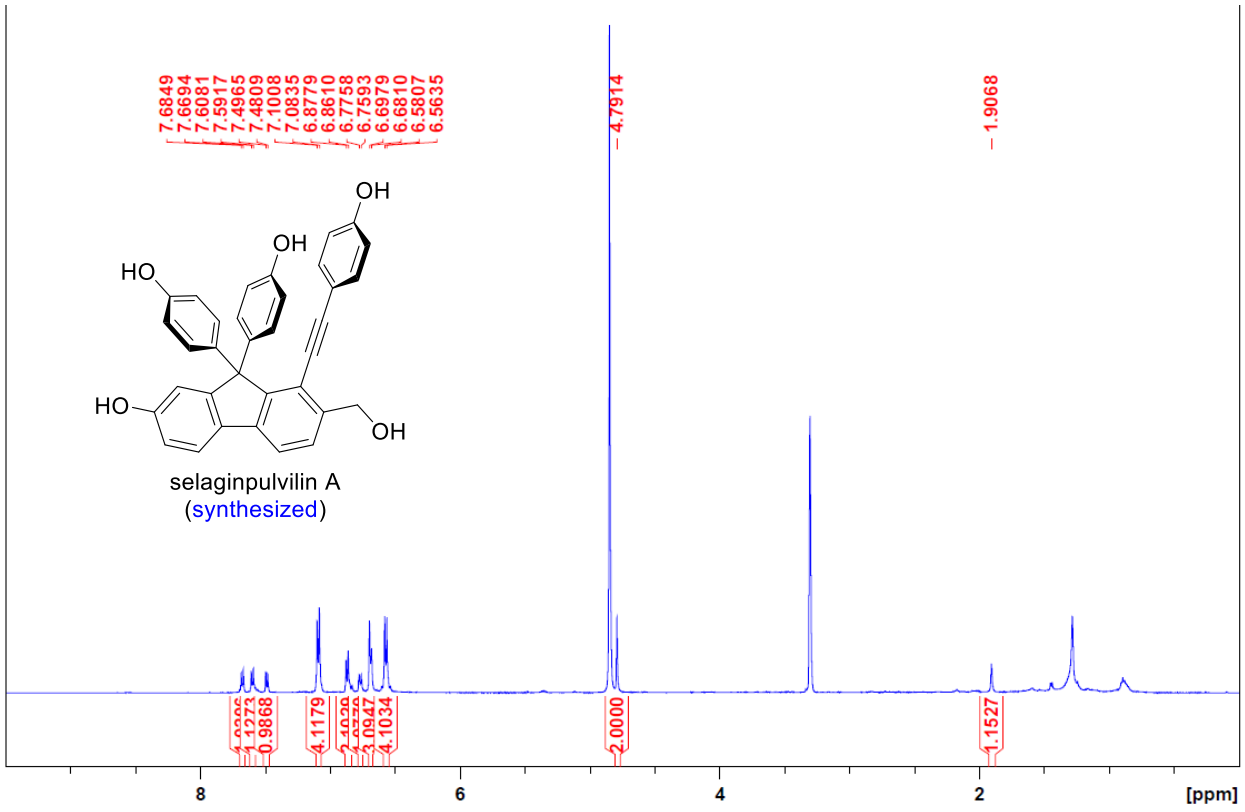

191.6245
170.8445
161.1832
160.3868
145.2107
136.9907
136.2596
135.2019
134.4880
133.8661
133.7066
121.4327
121.0850
120.1906
118.3234
114.9086
114.1410
109.1573
101.2492
82.7648
64.2025
55.7342
55.3527
20.9848
OMe
O
MeO
OAc
5-42
200
150
100
50
[ppm]

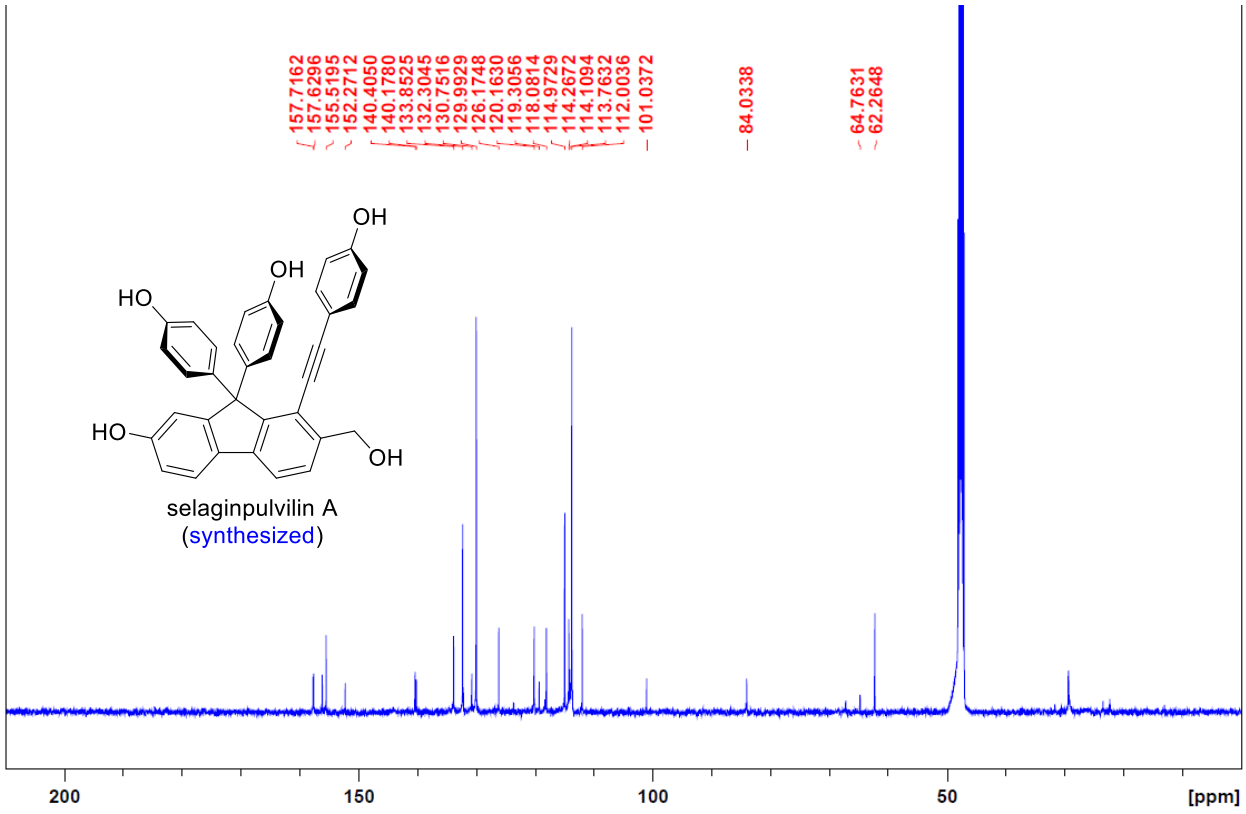

7.5513
7.5465
7.5314
7.4419
7.4263
7.3618
7.3442
7.1715
7.1539
6.8729
6.8682
6.8598
6.8552
6.8313
6.8253
6.8137
6.8076
5.3571
5.3318
5.2834
5.2581
3.8169
3.7692
3.7554
3.3462
2.1061
OMe
MeO
OH
MeO
OAc
5-43
2.0714
2.0447
4.2937
1.0264
2.9989
0.9698
2.8852
8
6
4
2
[ppm]

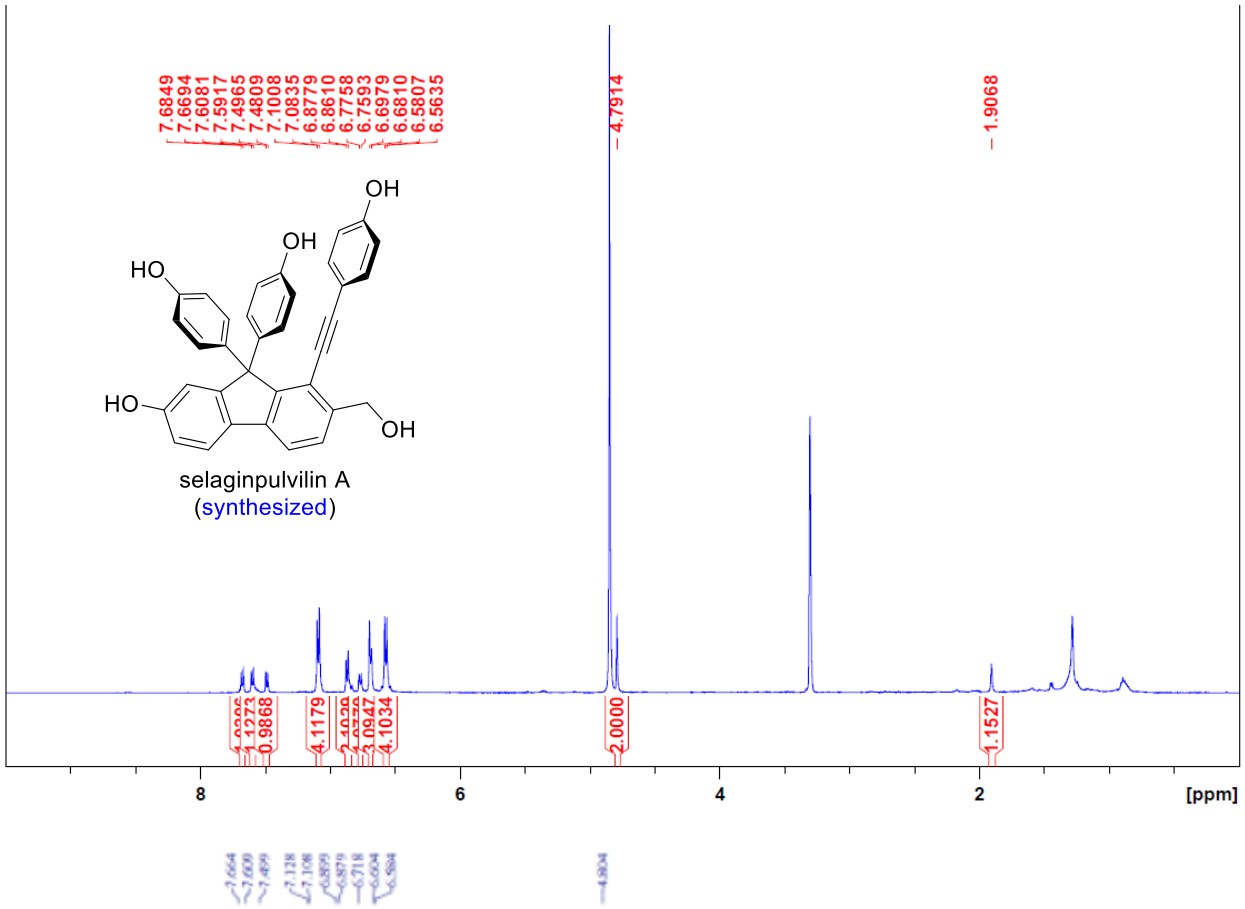

170.9374
160.7390
160.0329
158.8028
152.3597
150.8024
140.9850
135.6389
135.0304
133.0330
130.5255
129.8362
126.5127
121.2510
119.3760
118.6253
115.0210
114.5248
113.9836
113.6033
109.9861
100.2984
83.7747
82.3010
64.6393
55.4925
55.3308
55.2538
21.0515
OMe
MeO
OH
MeO
OAc
5-43
200
150
100
50
[ppm]

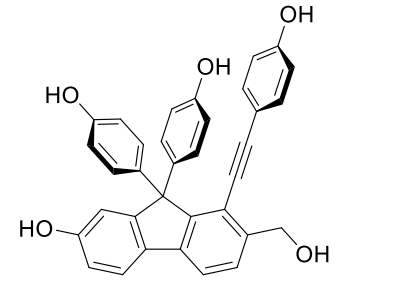

7.6454
7.6293
7.4141
7.3985
7.2371
7.2193
7.1896
7.1721
6.9813
6.9637
6.8960
6.8914
6.8793
6.8747
6.8198
6.8152
6.8020
6.7844
6.7276
6.7098
6.6552
6.6377
5.3204
4.6730
3.8024
3.7512
3.7329
2.0988
OMe
OH
MeO
MeO
OAc
5-44
1.9720
1.0000
2.1779
2.0909
1.9929
0.9397
3.0654
2.9622
8
6
4
2
[ppm]

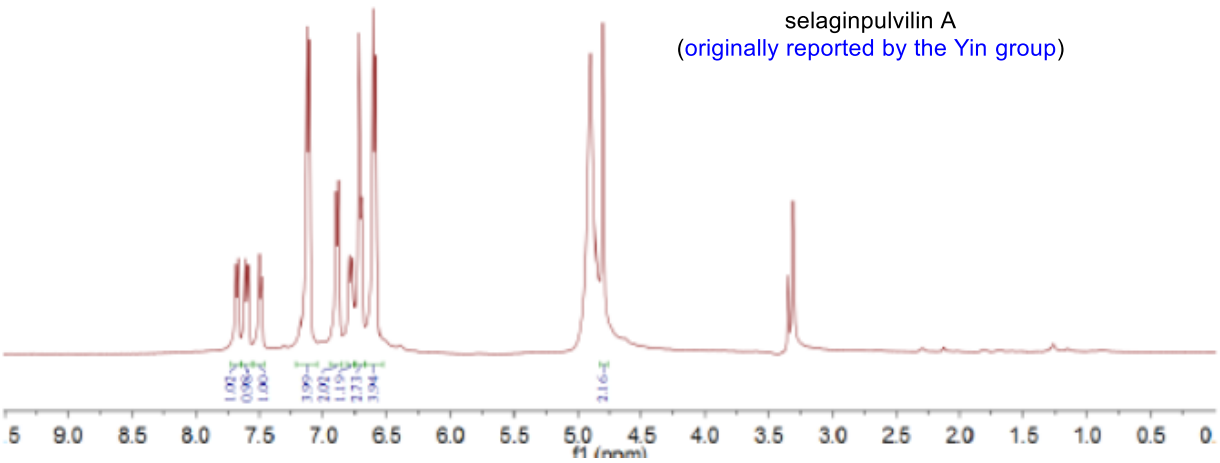

171.0833
160.3716
159.7054
158.2515
155.8078
154.2612
152.1722
140.8075
135.6681
134.7692
134.6044
132.6591
131.6535
130.4235
130.1649
128.0061
120.7484
118.7763
115.2662
114.4780
114.0037
113.4920
113.0657
111.0656
101.3287
84.5299
65.0914
60.4431
55.4649
55.3014
55.2207
21.1007
OMe
OH
MeO
MeO
OAc
5-44
200
150
100
50
[ppm]

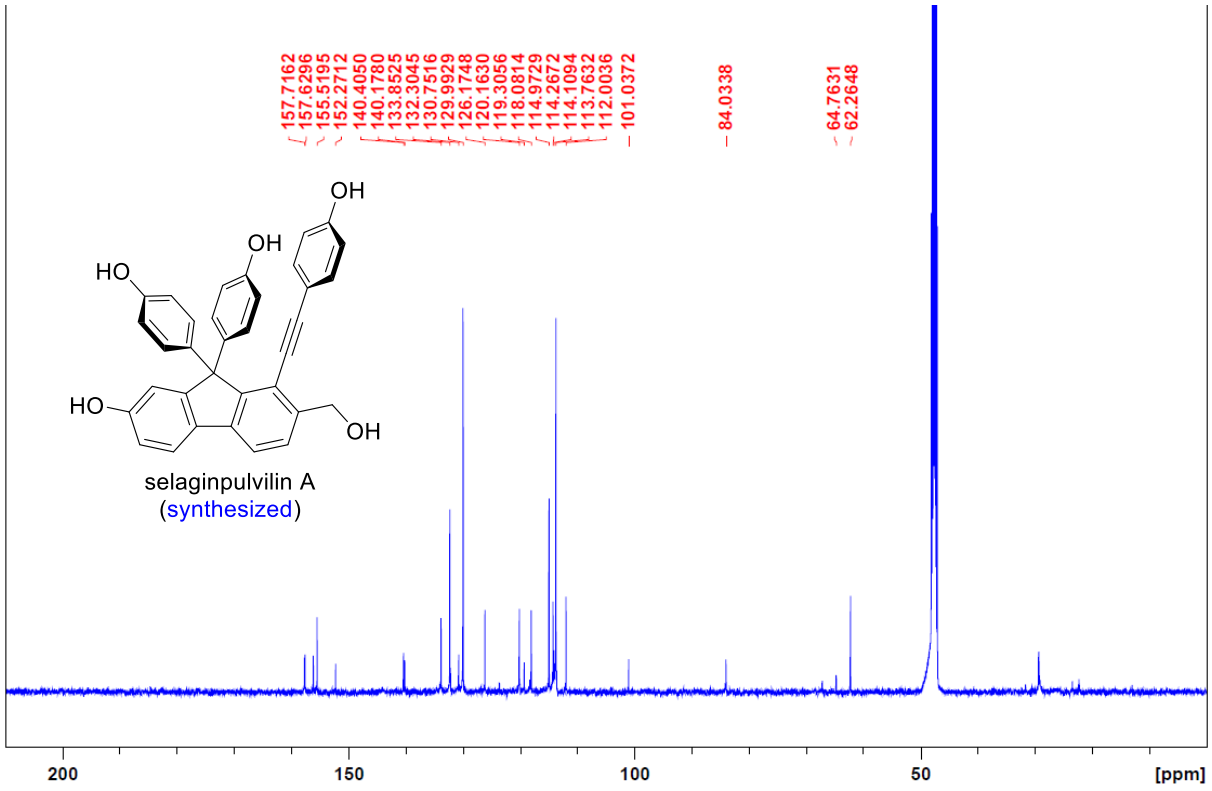

7.6849
7.6694
7.6081
7.5917
7.4965
7.4809
7.1008
7.0835
6.8779
6.8610
6.7758
6.7593
6.6979
6.6810
6.5807
6.5635
4.7914
1.9068
OH
OH
HO
HO
OH
selaginpulvilin A
(synthesized)
0.9868
4.1179
4.1034
2.0000
1.1527
8
6
4
2
[ppm]

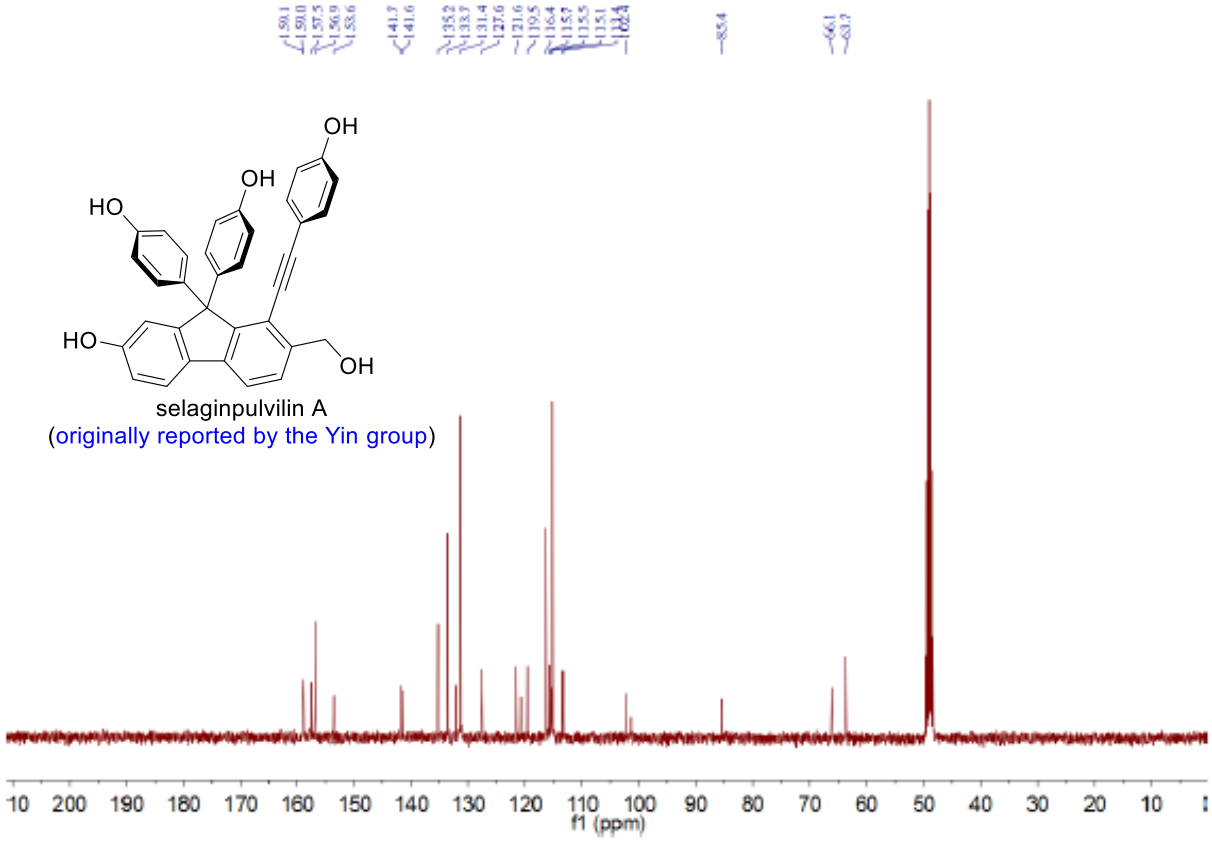

157.7162
157.6296
155.5195
152.2712
140.4050
140.1780
133.8525
132.3045
130.7516
129.9929
126.1748
120.1630
119.3056
118.0814
114.9729
114.2672
114.1094
113.7632
112.0036
101.0372
84.0338
64.7631
62.2648
OH
OH
HO
HO
OH
selaginpulvilin A
(synthesized)
200
150
100
50
[ppm]


7.6849
7.6694
7.6081
7.5917
7.4965
7.4809
7.1008
7.0835
6.8779
6.8610
6.7758
6.7593
6.6979
6.6810
6.5807
6.5635
4.7914
1.9068
OH
OH
HO
HO
OH
selaginpulvilin A
(synthesized)
0.9868
4.1179
4.1034
2.0000
1.1527
8
6
4
2
[ppm]


OH
OH
HO
HO
OH
selaginpulvilin A
(originally reported by the Yin group)


9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0


157.7162
157.6296
155.5195
152.2712
140.4050
140.1780
133.8525
132.3045
130.7516
129.9929
126.1748
120.1630
119.3056
118.0814
114.9729
114.2672
114.1094
113.7632
112.0036
101.0372
84.0338
64.7631
62.2648
OH
OH
HO
HO
OH
selaginpulvilin A
(synthesized)
200
150
100
50
[ppm]


OH
OH
HO
HO
OH
selaginpulvilin A
(originally reported by the Yin group)
f1 (ppm)

Permission Proof

Selectivity between an Alder–ene reaction and a [2 + 2] cycloaddition in the intramolecular reactions of allene-tethered arynes†

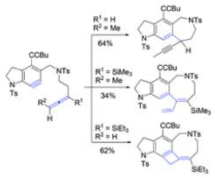
Check for updates

Anh Le [a] and Daesung Lee *[a]

Author affiliations

Abstract

Substituent-dependent reactivity and selectivity in the intramolecular reactions of arynes tethered with an allene are described. With a 1,3-disubstituted allene moiety, an Alder–ene reaction of an allenic C–H bond is preferred over a [2 + 2] cycloaddition, whereas a [2 + 2] cycloaddition of the terminal π-bond of the allene is preferred with a 1,1-disubstituted allene. With a 1,1,3-trisubstituted allene-tethered aryne, an Alder–ene reaction with an allylic C–H bond is preferred over a [2 + 2] cycloaddition.



VITA

Name: Anh Le

Education: B.S., Chemistry, University of Illinois at Chicago, Chicago, Illinois, USA, 2015

Ph.D., Organic Chemistry, University of Illinois at Chicago, Chicago, Illinois, USA, 2021

TEACHING: Department of Chemistry, University of Illinois at Chicago, Chicago, Illinois:

General Chemistry (CHEM 101), General Chemistry II (Chem 124), Organic Chemistry I (CHEM 232), Organic Chemistry Laboratory (CHEM 233).

PUBLICATIONS: **Le, A.**; Gupta, S.; Man, X.; Xia, Y.; Lee, D. "[Allenynes+Alkynes] Cycloaddition to Generate α, 3-Dehydrotoluene and Their Reactivities with Nucleophiles and Hydrogen Donors." **2021**, manuscript in preparation.

Le, A.; Lee, D. "Selectivity between an Alder-Ene Reaction and a [2+2] Cycloaddition in the Intramolecular Reactions of Allene-Tethered Arynes." **2021**, submitted.

Karmakar, R.; **Le, A.**; Xie, P.; Xia, Y.; Lee, D. "Aryne-mediated Dearomatization of Arylsulfonyl Group" *Org. Lett.* **2018**, *20*, 4168.

PRESENTATIONS: **Le, A.**; Gupta, S. "Formal [4+2] Cycloaddition between Alkynes and Allenynes to generate Functionalized Toluene." ACS National Meeting, Philadelphia, PA, USA, March 22-26, **2020**. (Oral presentation)

Le, A.; Gupta, S. "Formal [4+2] Cycloaddition between Alkynes and Allenynes to generate Functionalized Toluene." Chemistry Research Symposium, University of Illinois at Chicago, Chicago, IL, Oct 4th, **2019**. (Poster)