

**New Chemistry of Multiynes:
Development of Novel Aryne-Based Transformations and Click Reactions**

BY

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THESIS

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This thesis is dedicated to my beloved parents and wife

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LIST OF ABBREVIATIONS

Ac	Acetyl
Ad	Adamantyl
Ar	Aryl
Boc	<i>t</i> -Butyloxycarbonyl
Bn	Benzyl
Bu (also <i>n</i> -Bu)	<i>n</i> -Butyl
<i>t</i> -Bu (also <i>t</i> -Bu)	<i>tert</i> -Butyl
<i>c</i> -Hex	Cyclohexyl
Cat.	Catalyst
Cp	Cyclopentadienyl
dppf	1,1'-Ferrocenediyl-bis(diphenylphosphine)
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	<i>N,N'</i> -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 (base catalyst)
DME	Dimethoxyethane
DMF	Dimethylformamide (solvent)
DMSO	Dimethyl sulfoxide (solvent)

LIST OF ABBREVIATIONS (continued)

dr	Diastereomeric ratio
equiv	equivalent
E	Electrophile
EI	Electron impact
ESI	Electrospray ionization
Et ₂ O	Diethyl ether (solvent)
EtOAc	Ethyl acetate (solvent)
FG	Functional group
HHDA	Hexadehydro Diels-Alder
Hex (also <i>n</i> -Hex)	<i>n</i> -Hexyl
HRMS	High resolution mass spectrometry
Hz	Hertz
<i>i</i> -Pr	Isopropyl
IN	Intermediate
IR	Infra-red
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	<i>N</i> -Bromosuccinimide
NCS	<i>N</i> -Chlorosuccinimide
NIS	<i>N</i> -Iodosuccinimide
Nm	Nanometer
NMR	Nuclear magnetic resonance
nOe	Nuclear Overhauser effect
<i>o</i> -DCB	<i>ortho</i> -Dichlorobenzene
Ph	Phenyl
Ph(4-Cl)	4-Chlorophenyl
PhH	Benzene
PhMe	Toluene
Ph(4-OMe)	4-Methoxyphenyl
ppm	Parts per million
PMB	<i>p</i> -Methoxybenzyl
Pr also (<i>n</i> -Pr)	<i>n</i> -Propyl
rt	Room temperature
sol	solvent
TBAF	Tetra- <i>n</i> -butylammonium fluoride
TBAT	Tetrabutylammonium difluorotriphenylsilicate
TBS	<i>t</i> -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	<i>p</i> -Toluenesulfonyl
TS	Transition State
<i>t</i> -Oc	1,1,3,3-Tetramethylbutyl

SUMMARY

This thesis consists of two main parts, Part I and Part II. The six chapters in Part I cover various multicomponent coupling reactions of arynes generated *via* the hexadehydro Diels-Alder (HDDA) reactions of multiynes, whereas Part II is devoted to describe an unprecedented click reaction of terminal 1,3-diynes. Below is the brief outline of each chapter.

Chapter 1 provides a brief overview of the origins, developments and synthetic applications of HDDA reactions. Aryne-based transformations developed under thermal and metal-catalyzed conditions to generate highly functionalized aromatic systems constitute the major portion of this chapter. In addition, herein are summarized recently developed multicomponent reactions of arynes derived from multiynes.

In Chapter 2, Ritter-type transformations of arynes with nitriles are discussed. Nitriles, usually unreactive towards aryne, could be used as nucleophilic component upon activating arynes with a silver catalyst. Trapping of the initially formed aryne-nitrile adduct, a nitrilium species, with water contained in wet solvent provided amides. When nitrilium intermediate was trapped by carboxylic acid, arylimide was generated.

In Chapter 3, an unprecedented [2+2+2] annulation reaction of arynes with nitriles has been highlighted. It was found that, in the absence of water or carboxylic acid, the nitrilium species generated from an aryne and a nitrile molecule could react further with another nitrile molecule to generate quinazoline derivatives. The generality of this transformation has been studied with a broad array of multiyne systems and with different sets of aliphatic and aromatic nitriles.

Chapter 4 describes a novel and efficient [2+1+1] annulation reaction of arynes with isonitriles. In the presence of silver catalyst, arynes react with two molecules of isonitrile to generate benzocyclobutene-1,2-diimines. However, this reaction is limited to aromatic isonitriles. The mechanisms of these annulation reactions are investigated by DFT calculations. Synthetic utilities of benzocyclobutene-1,2-diimines are demonstrated in the latter part.

Continued with silver catalyzed transformations of arynes with nitriles or isonitriles, a cross condensation involving arynes, nitriles, and isonitriles has been presented in Chapter 5. Initial screenings showed the impact of the stoichiometry of nitrile and isonitrile on the formation of aryne-nitrile-isonitrile adduct. A sequential addition of nitrile and isonitrile to aryne was observed to deliver 3-iminoindolin-2-ol and 3*H*-indol-3-imine. Because of the higher reactivity of isonitrile as a nucleophile, the incorporation of less reactive nitrile was feasible only with its significantly higher concentration compared to that of isonitrile and activated aryne with a silver catalyst.

In Chapter 6, a variety of aryne-based multicomponent coupling reactions for the formation of functionalized aromatic compounds are presented. Arynes readily reacted with isonitriles to generate a nitrilium intermediate, which was intercepted with various weak nucleophiles including carboxylic acids, alcohols, sulfonamides, and water to generate the corresponding imides, imidates, amidines, and amides.

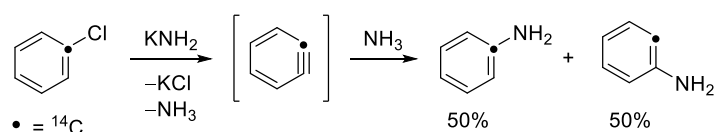
An unprecedented click reaction of terminal 1,3-diynes is presented in Chapter 7. Cu(I)-catalyzed [3+2] cycloaddition between terminal alkynes and tosyl azide generated *N*-sulfonyl triazolyl copper species, which subsequently released N₂ to generate ketenimide intermediates, which could be trapped with amines or alcohols to generate 3-alkynyl or allenyl imidamides and imidates. The selectivity for the formation of these products critically depended on the substituents of the diynes and the nucleophiles that reacted with the ketenimide intermediate. Depending on the type of nucleophiles, base additives, and the substituents patterns of the 1,3-diynes, this click reaction could promote the formation of alternative products such as heterocycles, [3]cumulenes and triple bond migrated products.

CHAPTER 1

Arynes and Multicomponent Reactions

1.1. Arynes*

Aryne, a highly electrophilic transient intermediate, has been widely used in the synthesis of functionalized aromatic compounds through the formation of carbon–carbon and carbon–heteroatom bonds.^{1–4} In 1902, Stoemer and Kahlert first postulated the existence of an aryne species (known as 2,3-didehydrobenzofuran) to justify the formation of 2-ethoxybenzofuran from 3-bromobenzofuran under basic conditions in ethanol solvent.⁵ Several decades later, Robert,⁶ Husigen,⁷ and Wittig⁸ independently investigated the aryne reactivity and its existence. The existence of aryne intermediate was first confirmed by Roberts *et al.* in 1953 through an experiment with ¹⁴C-labelled chlorobenzene and potassium amide, which generated two isomeric aniline derivatives (**Scheme 1.1**).



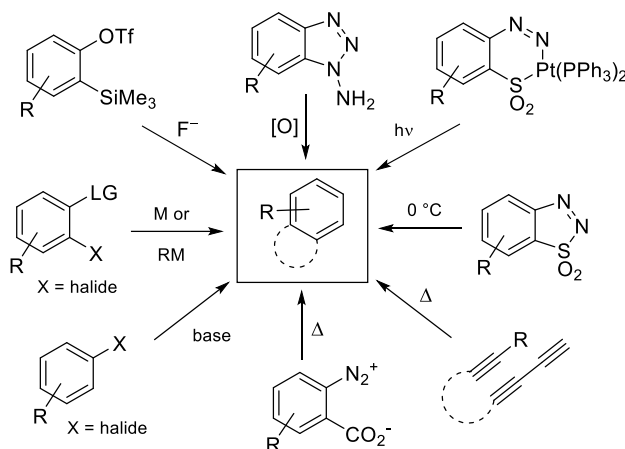
Scheme 1.1. Evidence of Aryne Intermediate with ¹⁴C-Label

1.2. Generation of Arynes

Due to high reactivity, arynes are generated in situ from suitable aromatic or non-aromatic precursors. Since the discovery of arynes, several methods have been developed for the generation of arynes. Typical methods to generate arynes include fluoride-promoted 1,2-elimination of aryl silyl triflates,⁹ metalation or base-mediated 1,2-elimination of aryl halides,¹⁰ thermal decomposition of arenediazonium-2-carboxylate,¹¹ and thermal,¹² photochemical¹³ and oxidative¹⁴ elimination of nitrogen from various precursors (**Scheme 1.2**). However, most of these traditional methods require external reagents and generate by-products, which coexist with putative aryne intermediate. These by-products significantly impact on the

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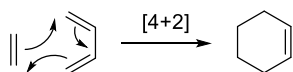
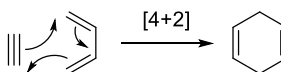
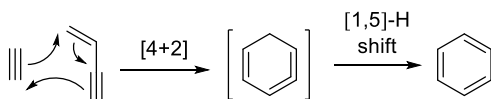
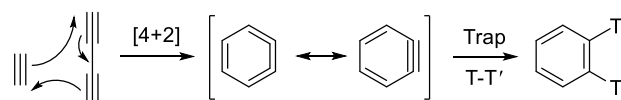
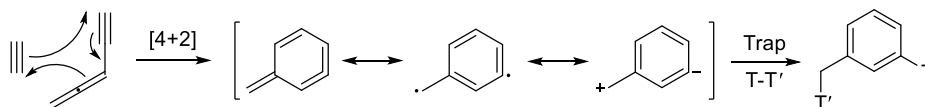
subsequent transformations of arynes by obscuring its intrinsic properties, which may cause inconsistency in interpreting arynes reactivity. This discrepancy can be clarified by the thermal conversion of acyclic multiynes to arynes intermediates, however, the generally required high temperature may introduce another layer of complication.



Scheme 1.2. Generation of Arynes in Various Conditions

1.3. Hexadehydro Diels-Alder Reactions

Cycloisomerization of 1,3-diynes and diynophiles, so called hexadehydro Diels-Alder (HDDA) reaction, is a versatile source of arynes (**Scheme 1.3**). Appropriately tethered triynes and tetraynes can undergo HDDA reaction at temperature ranging from 28 °C to as high as 580 °C depending on the structure of the multiynes. This reaction was independently reported by Ueda^{15–17} and Johnson^{18–20} in 1997, which has been subsequently explored by the groups of Hoya,^{21–27} Lee^{28–37} and Hu.^{38–40} Recently, arynes generated from HDDA have been extensively exploited in the synthesis of functionalized aromatic systems.⁴¹ As, HDDA-derived arynes are produced without forming by-products and external reagents, the intrinsic reactivity of arynes can be fully studied and explored.

Diels-Alder Reaction**Didehydro Diels-Alder Reaction****Tetradehydro Diels-Alder Reaction****Hexadehydro Diels-Alder Reaction****Pentadehydro Diels-Alder Reaction****Scheme 1.3. Types of Diels-Alder Reactions****1.3.1. Ueda's Approach with Tetraynes**

In 1997, Ueda and coworkers reported a tandem cyclization of a non-conjugated polyenyne system to generate diverse benzenoid products (**Scheme 1.4**).¹⁵ As a mechanism for this transformation, a stepwise radical reaction pathway was proposed, where the initially formed outer-ring diradical **1-1** transforms into a 1,2-didehydrobenzene diradical **1-2**. Subsequent intramolecular (**1-3**, **1-4**) or intermolecular (**1-5**, **1-6**) trapping generates functionalized aromatic compounds.

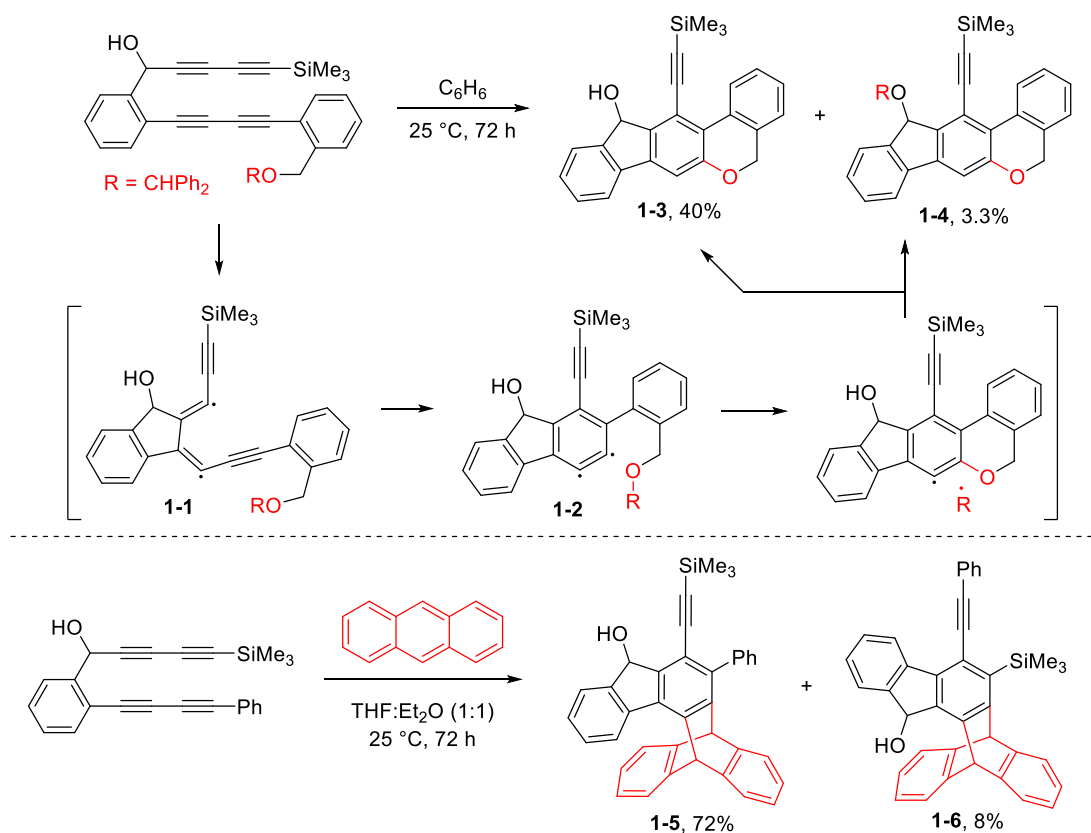
1.3.2. Johnson's Approach with Triynes

At the same time, Johnson reported the cycloaromatization of 1,3,8-nonatriyne under flash vacuum thermolysis condition to generate a mixture of indane **1-7** and indene **1-8** compounds (**Scheme 1.5A**).¹⁸ Deuterium labelling study suggests that cycloaromatization proceeds through a classical [4+2] cycloaddition *via* an aryne intermediate, which undergoes transfer hydrogenation under the conditions (**Scheme 1.5B**). Ab initio calculations were also performed to estimate the geometric and energetic feasibility of 1,3-diyne and alkyne cycloaddition, which shows that, cycloaddition between 1,3-butadiyne and ethyne is associated with high activation energy and large exothermicity (**Scheme 1.5C**). High

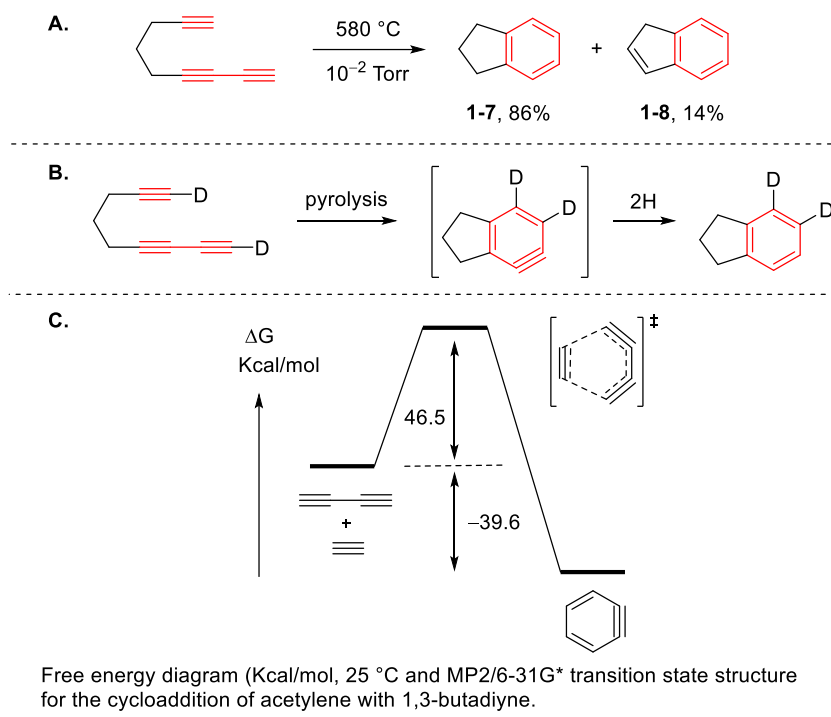
activation energy is due to the dramatic molecular distortion required to reach the transition state while the large exothermicity is consistent with the formation of a new aromatic ring.

1.3.3. Hoyer's Approach with Electronic Tuning

In 2012, the Hoyer group coined the term hexadehydro Diels-Alder reaction, and explored the general reactivity of the aryne intermediate.²¹ In this report, a wide variety of intermolecular and intramolecular nucleophilic trapping reactions with oxygen-, nitrogen-, and carbon-based nucleophiles were explored (**Scheme 1.6**). Arynes, generated from ketotriynes, are readily trapped by nucleophiles to generate the corresponding products **1-9** and **1-10** in good to excellent yields with high regioselectivity. Their results demonstrated a general scope of the HDDA reaction to synthesize structurally complexed benzenoid products.

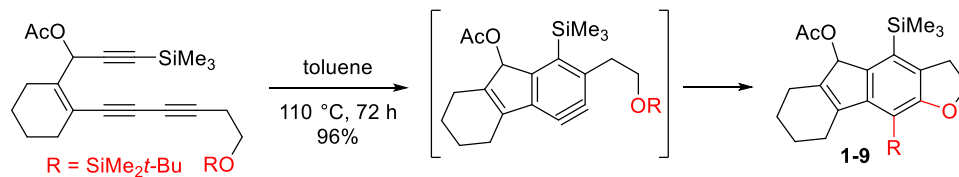


Scheme 1.4. Cycloaromatization of Tetraynes and Subsequent Trapping

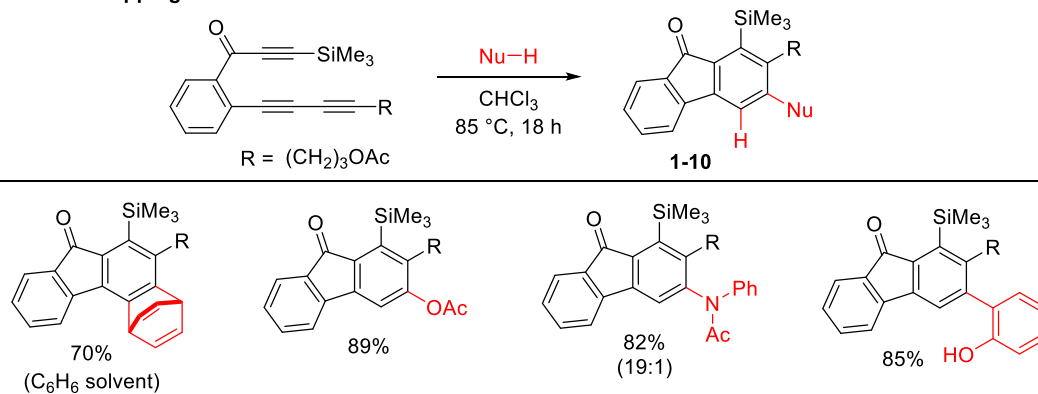


Scheme 1.5. Flash Vacuum Pyrolysis of a Triyne and the Calculated Energy Profile

Intramolecular Trapping

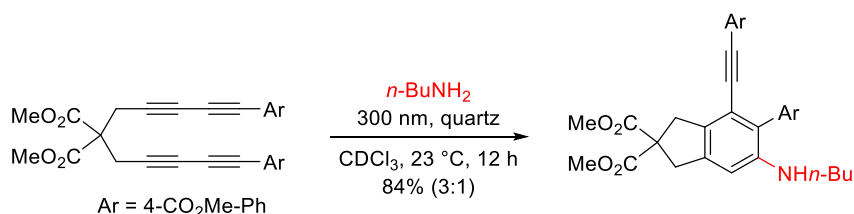


Intermolecular Trapping



Scheme 1.6. Intramolecular and Intermolecular Trapping of HDDA Arynes

In 2017, Hoye and coworkers showed that HDDA reaction could be achieved under photochemical condition (**Scheme 1.7**).⁴² One of the most notable features of this photoinduced HDDA reaction is the lower temperature (even at $-70\text{ }^{\circ}\text{C}$) compared to the thermal HDDA reactions while the arynes showed similar reactivity profile to arynes generated under thermal condition.

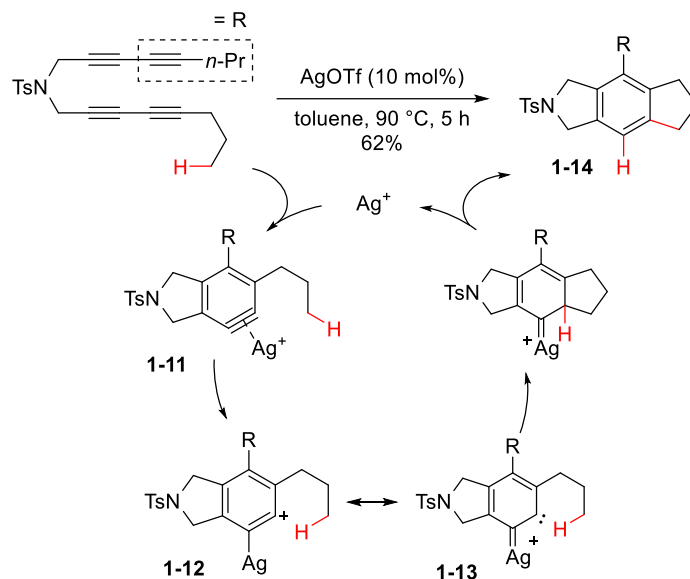


Scheme 1.7. Photochemical HDDA Reaction

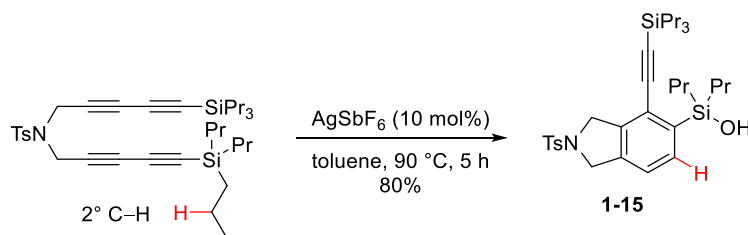
1.3.4. Lee's Approach with Silver Catalyst

It is well known that certain metal complexes can interact with aryne intermediates to convey unusual reactivity. Lee and coworkers discovered various HDDA-aryne-based transformations in the presence of silver catalyst. It was found that putative Ag^+ -complexed aryne intermediate **1-11** could be effectively inserted into 1° , 2° , and 3° alkane C–H bonds to afford product **1-14** (**Scheme 1.8**).⁴³ Although, AgOTf was used as the catalyst for the C–H insertion, other π -philic metal catalysts such as AgSbF_6 , AgNO_3 , AgOAc , AgO , $\text{Cu}(\text{OTf})_2$, $\text{Zn}(\text{OTf})_2$, $\text{Sm}(\text{OTf})_3$, $\text{In}(\text{OTf})_3$, $\text{Sc}(\text{OTf})_3$, and $\text{Ru}_3(\text{CO})_{12}$ also could promote the reaction. In terms of the reaction mechanism, either stepwise bond forming events or concerted cycloaromatization are feasible to generate silver-chelated aryne intermediate **1-12** or its resonance form **1-13**, which through subsequent hydride transfer or C–H insertion generates final product **1-14**.

In a continued study of Ag^+ -aryne-based activation of C–H bond, the Lee group found that if C–H activation involves a 2° and 3° β -carbon of a silyl group substituents, a 1,5-hydride transfer from β -carbon of a silyl group to aryne could be realized to deliver a formal hydrogenation product **1-15** (**Scheme 1.9**).⁴⁴ However, the corresponding 1° C–H bond exclusively participate in a direct C–H insertion reaction. In the



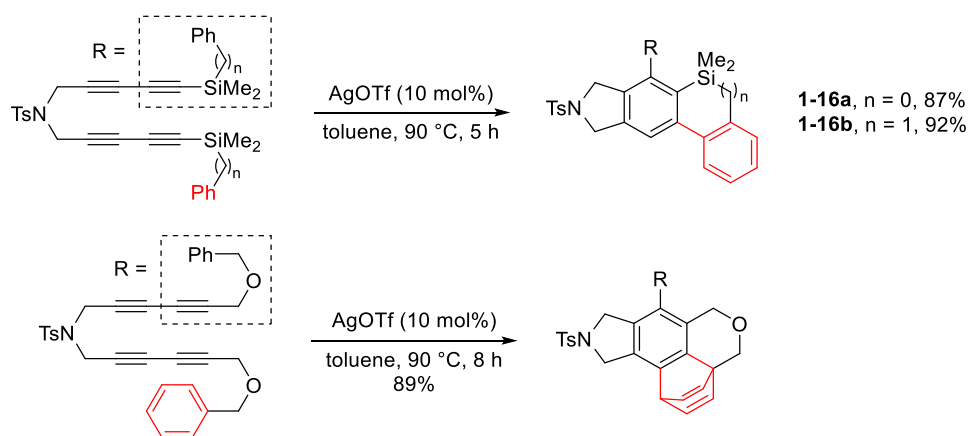
Scheme 1.8. Ag-Catalyzed C–H Insertion of Arynes



Scheme 1.9. Ag-Catalyzed Hydrogenation of Arynes

process, a hydride transfers from the β -carbon of a silyl group, while the other hydrogen atom is incorporated as a proton from adventitious water in the solvent.

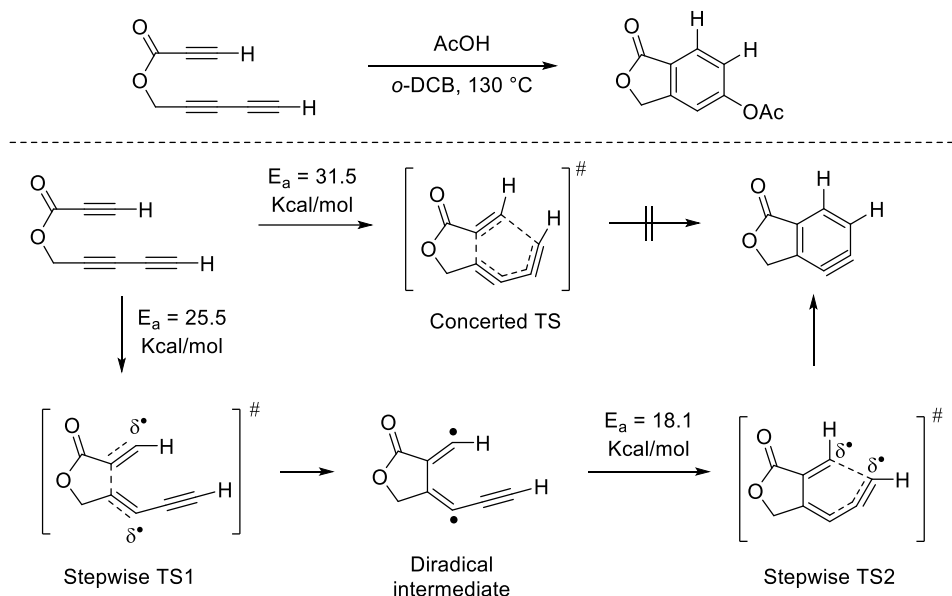
Exploiting the unique reactivity of silver-complexed arynes, Lee and coworkers developed an efficient intra- and intermolecular hydroarylation reactions of arynes (**Scheme 1.10**).⁴⁵ This formal C(sp²)–H insertion process was found to be dependent on the tether length between arynes and arene moieties. While a one- or two-atom tethered substrate afforded hydroarylated product **1-16**, a three-atom linker containing system provided only Diels-Alder product under identical reaction condition.



Scheme 1.10. Ag-Catalyzed Hydroarylation of Arynes

1.4. Mechanism of the Hexadehydro Diels-Alder Reactions

A stepwise reaction mechanism has been proposed for the intramolecular HDDA reaction to form an aryne intermediate (**Scheme 1.11**).⁴⁶ Hoyer and coworkers extensively studied an aryne-based trapping reaction using both experimental and computational methods. From the results of kinetic and DFT studies,

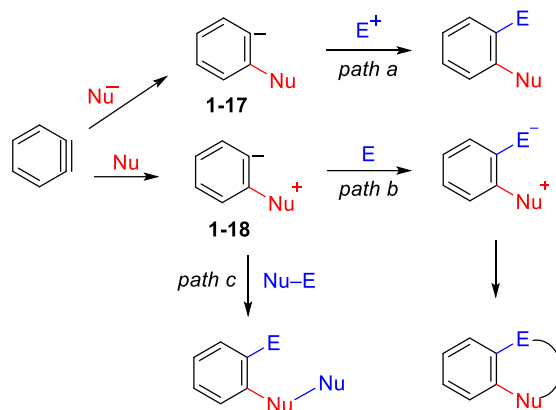


Scheme 1.11. Stepwise Mechanism of HDDA Reactions

they concluded that a stepwise mechanism *via* a diradical intermediate is an energetically favorable pathway compared to a concerted [4+2] process. Houk and coworkers also investigated the HDDA reaction by theoretical calculations and distortion/interaction analysis, which states that a stepwise diradical mechanism, is favorable for the HDDA reactions and an extra alkynyl substituent accelerate the HDDA reaction by ~5 order of magnitude by minimizing the distortion energy to achieve the diradical transition state.^{47,48}

1.5. Aryne-Based Multicomponent Reactions

Multicomponent coupling reaction (MCR) is a powerful synthetic tool to merge three or more organic compounds in a single-step operation to generate relatively complex molecular structures with high atom-economy.^{49–52} This strategy has become increasingly popular in the synthesis of a large number of small molecules. Aryne-based MCRs have been developed to generate diverse aromatic compounds.^{53,54} Due to their salient electrophilicity, arynes readily react with anionic or neutral nucleophiles to generate aryl anions **1-17** or zwitterions **1-18** (Scheme 1.12). In turn, depending on the electronic and structural features of the reaction components, these intermediates could participate in different modes of subsequent transformations. For example, once generated, aryl anion **1-17** could be trapped by a cationic electrophile to generate 1,2-disubstituted arenes (path a). On the other hand, trapping of zwitterion **1-18** with a neutral electrophile leads to benzo-annulated cyclic compounds (path b), or nucleophile-electrophile (Nu-E) insertion products (path c). Aryne-based MCRs are exploited to increase the molecular diversity and complexity on aromatic systems. Different MCR strategies have been developed, among which ‘single reactant strategy (SRR)’, ‘modular reaction sequences (MRS)’, and ‘conditions-based divergence (CBD)’ are most effective.⁵¹



Scheme 1.12. Different Modes of Coupling Reactions with Arynes

1.6. Multicomponent Reactions with HDDA-Derived Arynes

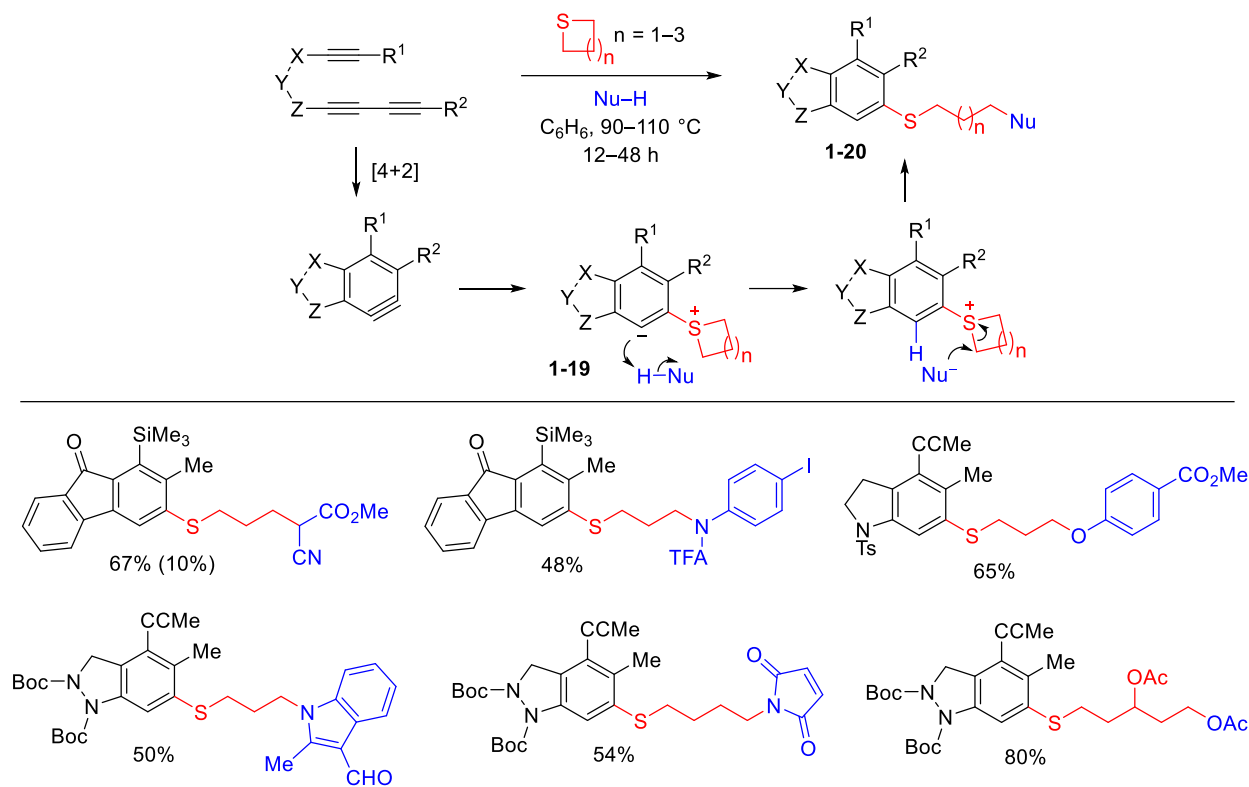
Aryne-based MCRs are versatile to construct functionalized arenes and benzo-fused heterocycles, due to the electrophilic nature of arynes it could couple with a broad range of nucleophiles. Thus, a variety of aryne-based MCRs have been developed over the last 20 years mainly with arynes generated from the fluoride-promoted 1,2-elimination of aryl silyl triflates. Compared to that, multicomponent reactions with HDDA-derived aryne have been little explored. Recently, the group of Hoye, Hu, and Lee independently developed several multicomponent reactions with arynes generated from HDDA reaction, in pursuit to explore new reactivity of HDDA-derived arynes.

1.6.1. Thermal Condition

1.6.1.1. Reaction of Arynes with Cyclic Thioethers

In 2016, Hoye reported the MCR of cyclic thioethers, thermally generated arynes, and protic nucleophiles (**Scheme 1.13**).⁵⁵ The initially formed 1,3-zwitterions **1-19** from aryne and 4–6 membered cyclic thioethers was effectively intercepted by protic nucleophiles (H–Nu) to generate a ring-opened product **1-20**. Carbon-, nitrogen-, and oxygen-centered nucleophiles, including heterocycles were explored in this reaction. Sterically hindered or relatively weakly acidic protic nucleophiles were also functional.

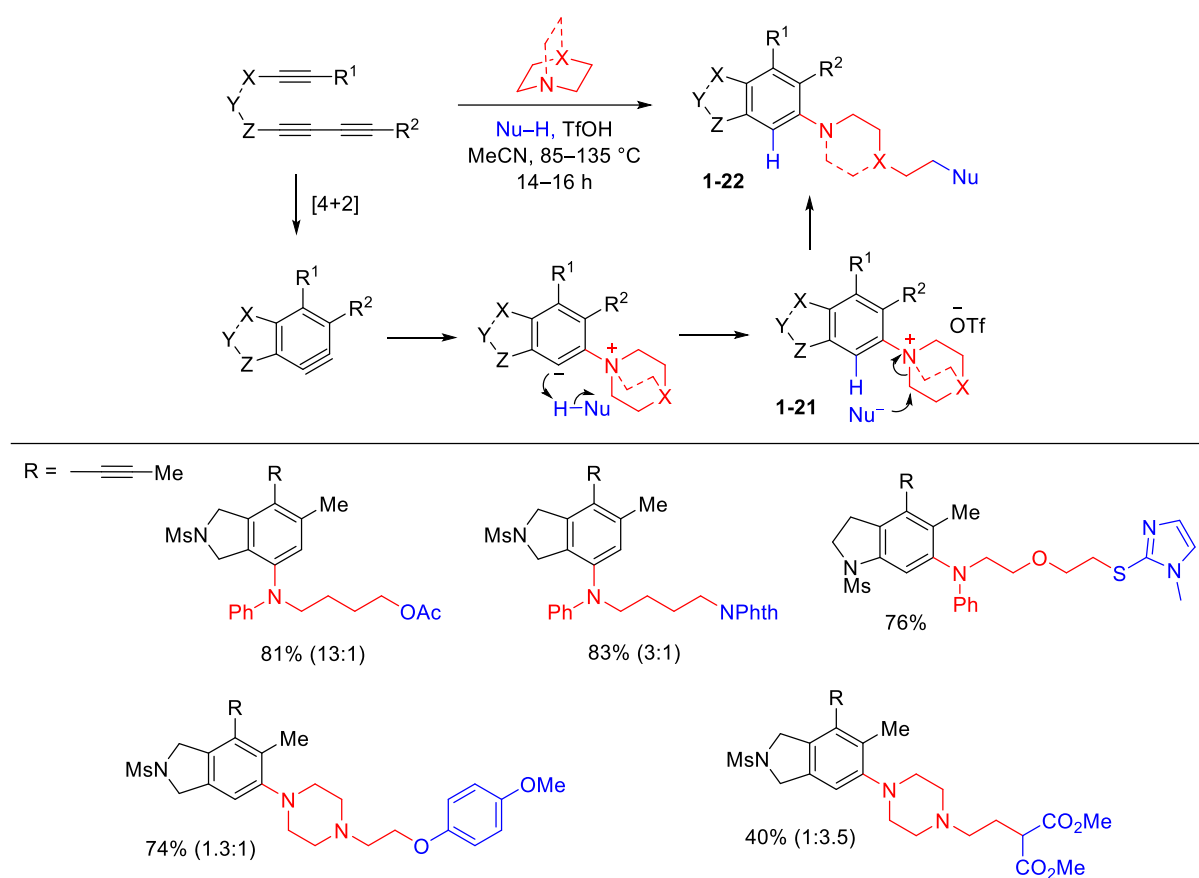
However, one limitation of this transformation is that thiirane (3-membered cyclic thioether) is not effective for this three-component coupling reactions.



Scheme 1.13. MCR of HDDA Derived Arynes with Cyclic Thioethers

1.6.1.2. Reaction of Arynes with Cyclic Amines

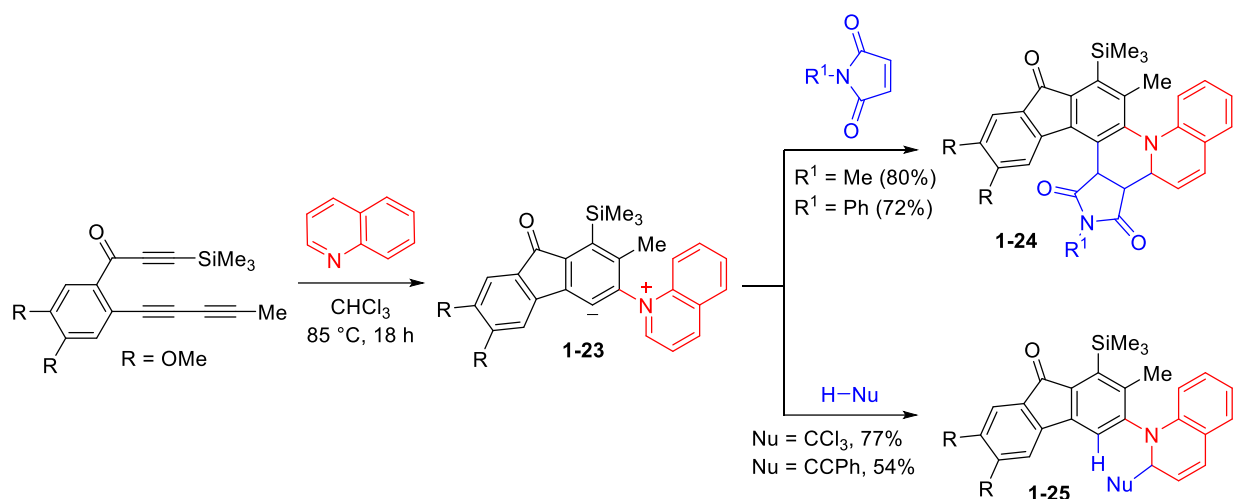
When bridged bicyclic tertiary amines were employed instead of cyclic thioether, three-component adducts **1-22** was isolated (**Scheme 1.14**).⁵⁶ A broad spectrum of amines including *N*-substituted 3–6 membered cyclic amines, bicyclic amines containing a bridgehead nitrogen atom were explored along with diverse *O*- and *N*-based nucleophiles. Use of 1.1–2.0 equiv triflic acid substantially increased the nucleophile compatibility of this transformation through the formation of ammonium triflate intermediate **1-21** and subsequent nucleophilic ring-opening process. This novel MCR strategy is quite general and have shown considerable potential for the rapid construction of structurally complex heterocyclic compounds.



Scheme 1.14. MCR of HDDA Derived Arynes with Cyclic Amines

1.6.1.3. Reaction of Arynes with Azarenes

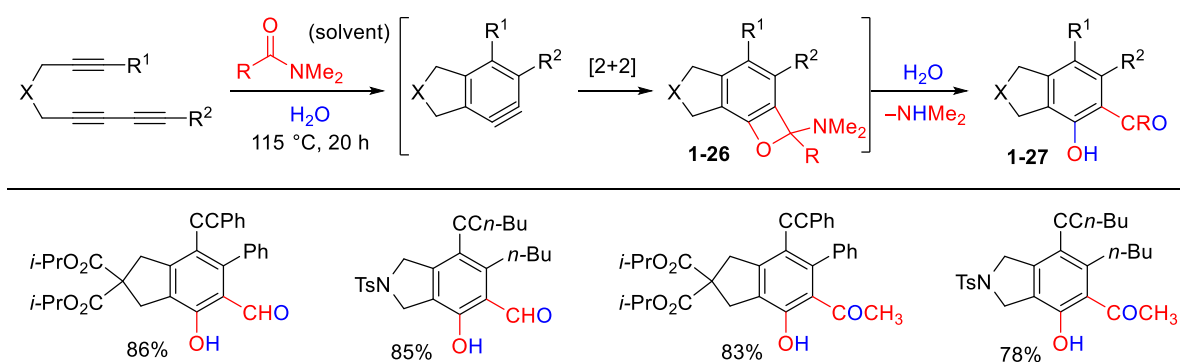
In a similar approach, Hoye and coworkers developed MCRs of arynes with azaarenes, which led to the formation of structurally diverse polyaromatic molecular frameworks **1-24** and **1-25** (Scheme 1.15).⁵⁷ Six-membered azarenes readily react with arynes to generate 1,3-zwitterionic species **1-23**, then depending on electronic nature of trapping agent, zwitterion **1-23** can produce a new 6-membered ring in product **1-24** or generate **1-25** through reacting with pronucleophiles. A diverse set of X=Y type electrophiles (C=O , C=N , C=C) and protic nucleophiles (H-Nu) were explored in this assembly process.



Scheme 1.15. MCRs of HDDA Derived Arynes and Azaarenes

1.6.1.4. Reaction of Arynes with Amides

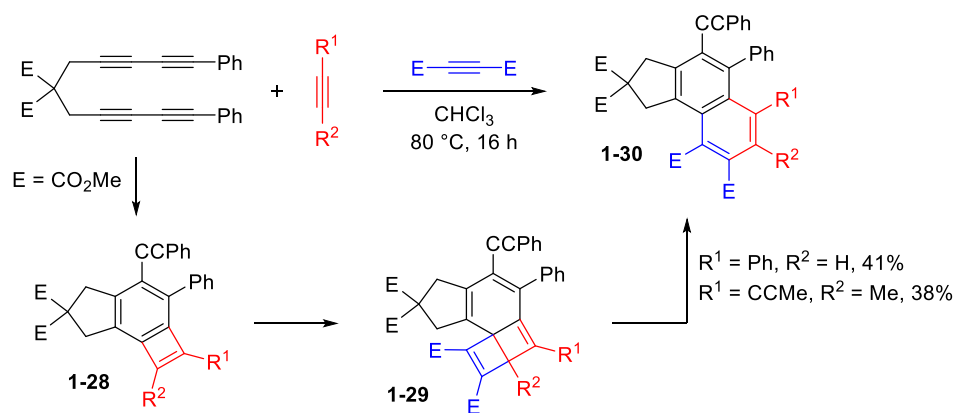
Hu reported the synthesis of fused multifunctionalized salicylaldehydes and salicylketones from tetraynes and *N,N*-dimethylformamide (DMF) or *N,N*-dimethylacetamide (DMA) as a source of a formyl group (Scheme 1.16).³⁸ The reaction proceeds via a formal [2+2] cycloaddition between arynes and amides, followed by hydrolysis generates the phenol derivatives 1-27. The reaction mechanism was justified by isotope labeling experiments.



Scheme 1.16. Synthesis of Salicylaldehydes and Salicylketones

1.6.1.5. Reaction of Arynes with Alkynes

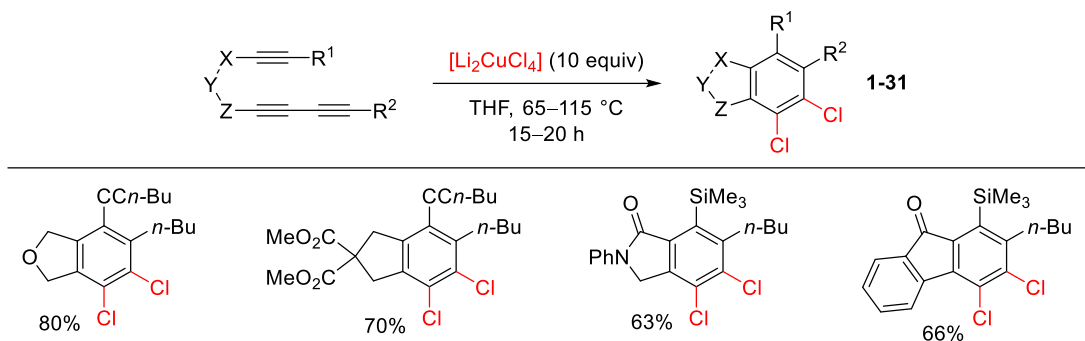
Hoye also developed a novel cascade process to build naphthalene framework by trapping benzocyclobutadiene intermediate **1-28** with an alkyne (**Scheme 1.17**).⁵⁸ Thermally generated arynes readily underwent [2+2] cycloaddition with an electron-rich alkyne to generate benzocyclobutadiene intermediate **1-28**, which subsequently reacts with an electron-deficient alkyne to generate alkynyl naphthalene derivatives **1-30**. The reaction is believed to proceed via the formation of a hemi-Dewar benzene moiety in intermediate **1-29**. This reaction shows excellent regioselectivity and delivered **1-30** preferentially over other possible constitutional isomers.



Scheme 1.17. Naphthalenes Derivatives via Benzocyclobutadiene Intermediate

1.6.1.6. Reaction of Arynes with Dilithium Tetrachlorocuprate

Hoye and coworkers developed a novel and efficient aryne dichlorination strategy using a mild chlorinating agent (**Scheme 1.18**).⁵⁹ Due to the inherent reactivity of Cl_2 with alkynes, Cl_2 is not a suitable halogenating agent in HDDA-mediated aryne chemistry. Li_2CuCl_4 (in situ generated from CuCl_2 and LiCl) in acetonitrile solvent was found to be an effective chlorinating agent for HDDA-arynes and delivered 1,2-dichlorinated arenes **1-31** in moderate to excellent yield. The rate of this trapping reaction showed first-order dependence on the concentration of Li_2CuCl_4 .

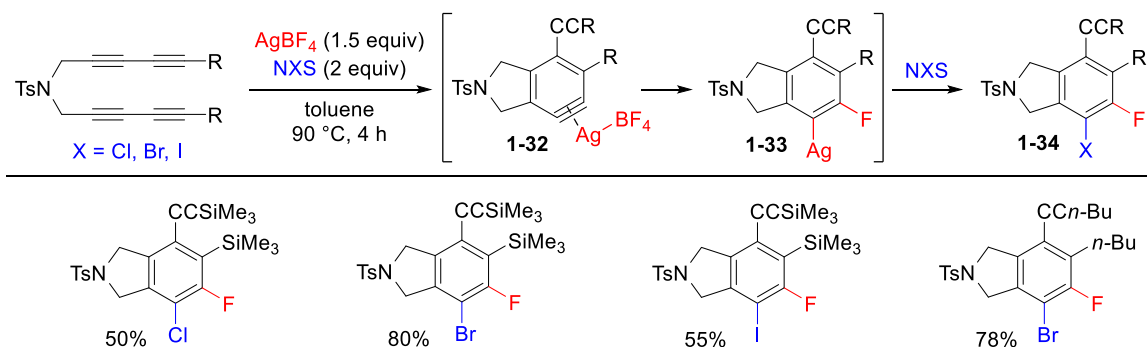


Scheme 1.18. Synthesis of bis-Halogenated Arenes

1.6.2. Metal-Catalyzed Conditions

1.6.2.1. Reaction of Arynes with Silver Tetrafluoroborate

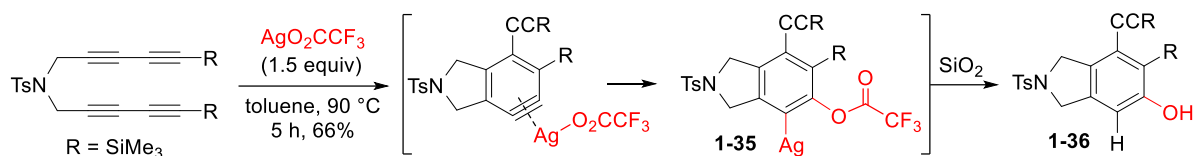
Based on the unique reactivity arynes in the presence of a silver catalyst,^{60,61} the Lee group developed a non-traditional approach for the synthesis of fluorinated arenes under conditions milder than Balz-Schumann reaction⁶² and the Halex process⁶³ (**Scheme 1.19**). With reacting silver tetrafluoroborate, *N*Ts-tethered tetrayne generate, silver-complexed aryne species **1-32** can be trapped with fluoride to provide an adduct **1-33**.⁶⁴ It was found that the organosilver species **1-33** could be trapped with other electrophiles. Thus, by employing a catalytic amount of silver catalyst in the presence of NXS, 1,2-fluorohalogenated products **1-34** were generated efficiently.



Scheme 1.19. Dihalogenation of Arynes

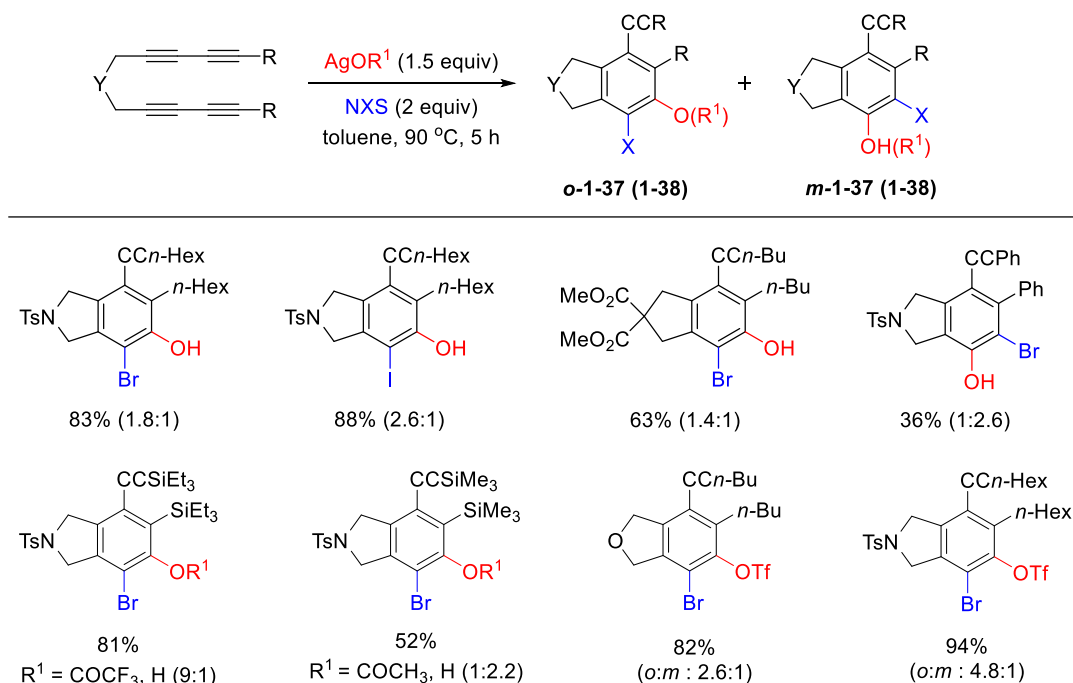
1.6.2.2. Reaction of Arynes with Silver Trifluoroacetate

Although arynes can interact with a broad spectrum of nucleophiles direct hydration of arynes to generate phenol derivatives is difficult due to immiscibility of water with organic solvent. This problem was resolved by employing silver trifluoroacetate (AgO_2CCF_3) to generate organosilver adduct **1-35**, which was readily deacylated during purification on silica gel, providing the corresponding phenol derivative **1-36** (Scheme 1.20).⁶⁵ The regioselectivity of trifluoroacetate addition into arynes was tailored by the substituents present in the tetraynes such as a trimethyl silyl group whereby the ortho-isomer was formed preferentially.



Scheme 1.20. Synthesis of Phenols via Aryne Intermediate

This aryne hydration method was further extended to the synthesis of α -halophenol derivatives by intercepting organosilver intermediate **107** with a suitable electrophilic halogen source (Scheme 1.21). Thus, with 1.5 equiv AgO_2CCF_3 , and 2 equiv NXS, the corresponding α -bromo- and α -iodophenol derivative **1-37** were generated. The ratios of ortho- and meta-isomers depend both on the substituent and halogen source. It was found that the presence of a silyl group and a halogen substituent both ortho to trifluoroacetate significantly slow down the deacylation, thus haloacylated products **1-38** were obtained as a mixture of isomers. Other silveracylates can provide the corresponding haloacylated products except for the reaction with silver benzoate and *N*-chlorosuccinimide (NCS), which provided only aryl benzoate without chloride incorporation.



Scheme 1.21. Synthesis of Halophenol Derivatives via Aryne Intermediate

1.7. Summary

Herein, the recent developments of hexadehydro Diels-Alder reaction are summarized. The formation of arynes without external reagents and by-products under relatively mild and neutral conditions makes this approach highly beneficial to investigate intrinsic reactivity of aryne species. Under thermal condition, arynes can generously participate in variety of intramolecular and intermolecular nucleophile trapping, hydrogenation, C–H insertion, Alder-ene reaction and so forth. In addition, the reactivity of aryne species can be tuned by employing appropriate transition metal catalysts. These HDDA-derived arynes were also exploited in developing novel MCRs, which are versatile tools for the synthesis of functionalized arenes and benzo-fused heterocycles and carbocycles. We envision that by using suitable trapping agents of thermodynamic and kinetic parameters, more unprecedented reactivity of arynes will emerge, which will further broaden the scope of aryne chemistry.

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CHAPTER 2

Silver-Catalyzed Reaction of Arynes with Nitriles

2.1. Introduction*

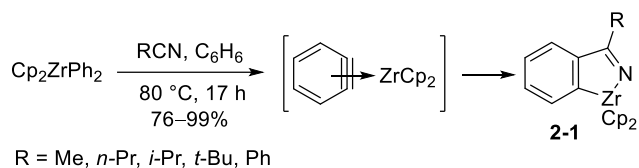
Arynes, as a form of transient electrophilic intermediate, have been employed in a large number of natural product syntheses and the development of various synthetic methodologies.¹⁻⁷ Despite the versatility, the effective formation of arynes still renders a significant challenge and barrier for further expansion of their utility in synthetic organic chemistry. Traditionally, the 1,2-elimination of suitably functionalized aromatic precursors has been employed for the formation of arynes, many of which are pericyclic reactions in nature. Among these pericyclic processes, only one protocol involves the de novo construction of the aromatic framework of arynes starting from non-aromatic precursors. Although, this particular form of pericyclic reaction was discovered more than a century ago, the reactions of the corresponding intramolecular variants pioneered by Johnson⁸ and Ueda⁹ were reported in 1997. Recently, the formation of arynes by this pericyclic reaction has been rejuvenated, and Hoye introduced a term hexadehydro Diels-Alder reaction (HDDA) reaction for the process.¹⁰

Despite the synthetic versatility of HDDA reaction and its uniqueness of forming aryne frameworks from non-aromatic precursors,¹¹ the development of this protocol still is in its infancy compared to the silyl triflate-based protocol developed by Kobayashi.¹² Compared to the rapid development of new aryne chemistry based on silyltriflates and related aryne precursors, the corresponding HDDA-based approaches starting from non-aromatic precursors are significantly underdeveloped. Thus, it is necessary to garner information about the general reactivity of the aryne species generated via HDDA reaction and expand the reaction scope.

In our recent study on silver-catalyzed transformation of arynes,¹³⁻¹⁷ we designed several aryne trapping reactions with non-conventional weak nucleophiles. We envisioned that in the presence of silver catalyst, arynes could react with weak nucleophiles such as nitriles to form a reactive adduct, which can be

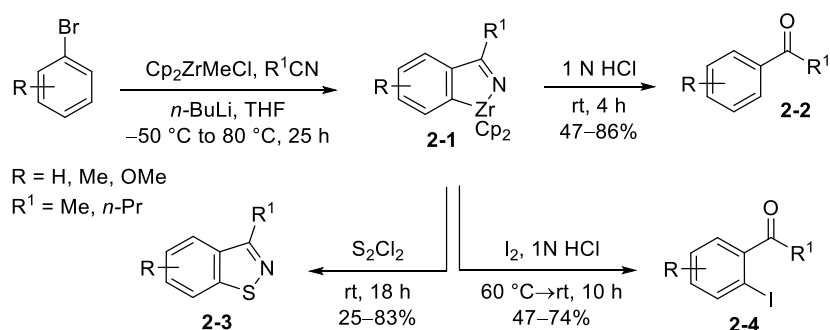
* Some parts of this chapter have been reproduced (adapted) partially from Ghorai, S.; Lee, D. "Aryne formation via the hexadehydro Diels-Alder reaction and their Ritter-type transformations catalyzed by a cationic silver complex" *Tetrahedron*. **2017**, 73, 4062; with permission of ELSEVIER.

further transformed to different final products. In 1987, Buchwald reported a zirconocene-induced coupling of arynes and nitriles under thermal condition.¹⁸ At 80 °C, diphenylzirconocene readily generates zirconocene-aryne complex which in presence of nitriles transformed into novel azametallacyclopentanes **2-1** (Scheme 2.1). These metalacyclic compounds have been shown to be synthetically useful.



Scheme 2.1. Synthesis of Azametallacyclopentenes from Arynes and Nitriles

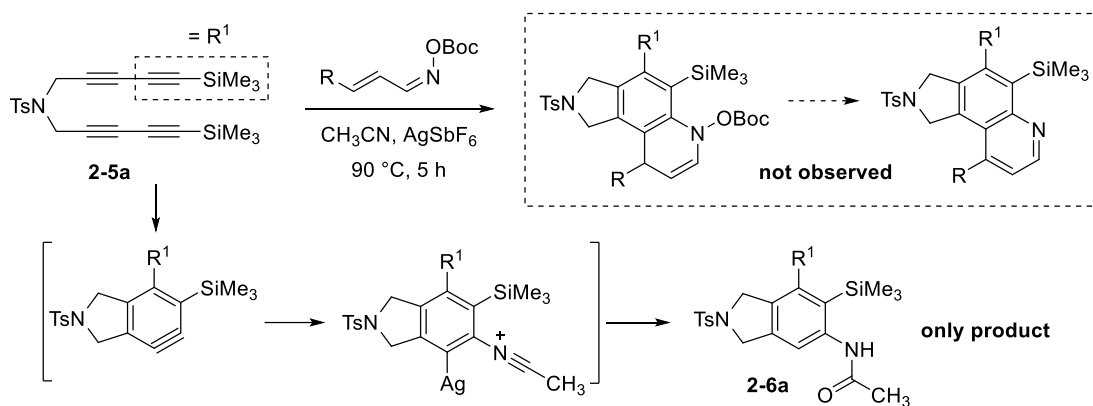
Later, using aryl bromide as aryne precursor, Buchwald and coworkers developed another efficient protocol to synthesize azametallacyclopentanes (**2-1**) (Scheme 2.2).¹⁹ It was found that these nascent metallacycles can be easily converted into functionalized aromatic compounds by using simple procedures. Acidic hydrolysis of **2-1** led to the formation of aryl ketones **2-2**. Trapping with molecular iodine followed by acidic hydrolysis generated α -iodoketones **2-2**. Isothiazoles **2-4** was isolated from metallacycles upon reacting with S_2Cl_2 in THF. Apart from these reports, examples of direct interaction between arynes and nitriles are rare.



Scheme 2.2. Transformations of Azametallacyclopentenes

2.2. Initial Observation

In light of developing a *de novo* synthesis of structurally complex pyridine derivatives, we explored the [4+2] cycloaddition reaction of arynes generated from tetrayne **2-5a** with oxime derivatives generated from acrolein and other enals (**Scheme 2.3**). When these reactions were carried out in acetonitrile solvent, we did not observe the expected cycloadduct but only derivatives of acetonitrile adduct in marginal yield. We inferred that the formation of the Ritter-type^{20–29} product **2-6a** is the consequence of the initial addition of solvent nitrile with the aryne intermediate formed from HDDA reaction followed by trapping of the nitrilium ion by adventitious water in wet solvent.



Scheme 2.3. Diels-Alder Reaction vs. Solvent Addition

2.3. Results and Discussion

Having recognized the dearth of reports on the addition of nitriles through their nitrogen atom with arynes or benzyne,³⁰ we further explored the reaction systematically and developed aryne-based new three-component coupling reactions to form arylamides and imides. This study demonstrated the importance of silver species in aryne-based transformation, the exact role of which is yet to be defined.

2.3.1. Synthesis of Amides

Our investigation commenced with optimizing reaction conditions with symmetrical tetrayne **2-5** to form amide adducts **2-6** (Table 2.1). In the presence of silver hexafluoroantimonate as a catalyst (10 mol %), the reaction of tetrayne **2-5a** in different nitrile solvent ran at 90 °C for 5 h led to complete consumption of **2-5a**, providing the corresponding amides **2-6a** – **2-6e**. Although these products could be obtained without the silver catalyst,³¹ lower yields with significantly increased amount of unknown byproducts were resulted. First, with acetonitrile, amide **2-6a** was obtained in 72% yield (entry 1). With propionitrile, **2-6b** was obtained in 75% yield (entry 2), whereas only with 24% yield of **2-6b** was observed without the catalyst. With acrylonitrile solvent, the reaction of **2-5a** provided acrylamide derivative **2-6c** in somewhat lower 56% yield (entry 3). Although addition of extra water was not necessary to form **2-6a–c**, the reaction with isobutyronitrile required addition of external water. Thus, under the same conditions with 10 equivalents of added water, amide **2-6d** was generated in 47% yield (entry 4). Aromatic nitrile behaves similarly but provided some desilylated products. Thus, after complete removal of the silyl groups with TBAF, arylbenzamide **2-6e** was obtained in 69% yield (entry 5). The formation of single regioisomer is most likely the consequence of the strong electronic directing effect of the silyl substituent.^{32–35} The structural identity of these single regioisomeric products was confirmed by nOe experiments.

Having demonstrated the successful reaction of NTs-tethered symmetrical tetrayne **2-5a** to generate different amide derivatives, we next explored the reaction of other substrates containing differently tethered tetraynes and triynes (Table 2.2).³⁶ In general, because of the structural variation with steric and electronic differences, all-carbon tethered substrate **2-5c** containing a *gem*-dicarboxylate and ester-tethered triyne **2-5e** required higher reaction temperature and extended reaction time. For most of the reactions, addition of water (10 equiv) significantly improved yields of the desired product.

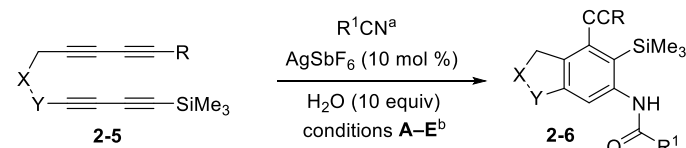
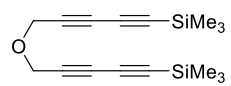
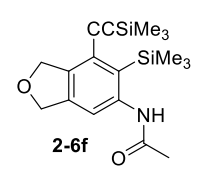
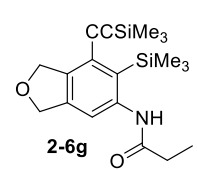
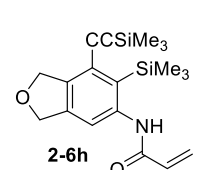
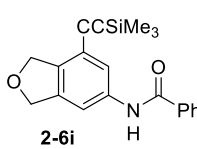
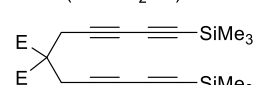
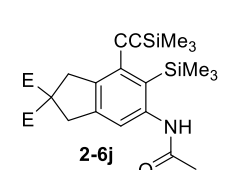
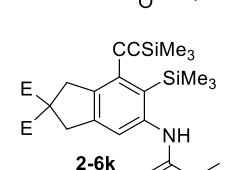
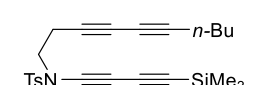
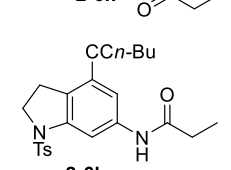
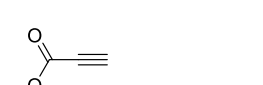
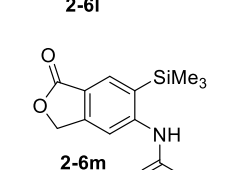
First, the reaction of an oxygen-tethered symmetrical tetrayne **2-5b** was carried out by heating at 90 °C for 5 h, which cleanly afforded acetamide **2-6f** in 78% yield (entry 1). Similar result was obtained when acetonitrile was replaced with propionitrile and acrylonitrile, where propionamide **2-6g** and

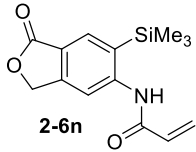
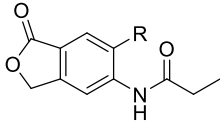
acrylamide **2-6h** were obtained in 80% and 75% yield, respectively (entries 2 and 3). In benzonitrile medium, arylbenzamide was generated with partial removal of a silyl group. After complete desilylation, amide **2-6i** was obtained in 20% overall yield (entry 4). All-carbon tethered substrate **2-5c** containing a *gem*-dicarboxylate is unreactive at 90 °C, but at 150 °C it readily participated in the reaction with acetonitrile and propionitrile to yield the corresponding amides **2-6j** and **2-6k** in 59% and 30% yield

entry	RCN	product	yield (%) ^b
1	CH ₃ CN		72
2			75
3			56
4			47 ^c
5			69 ^d

^a Non-distilled, used as the solvent. ^b Isolated yield. ^c Yield from the reaction with extra water (10 equiv). ^d Overall yield after desilylation with TBAF.

Table 2.1. Optimization for Different Amide Formation

					
entry	substrate	R ¹ CN	conditions	product	yield (%) ^c
1	 2-5b	CH ₃ CN	A	 2-6f	78
2		 CN	A	 2-6g	80
3		 CN	A	 2-6h	75
4		PhCN	A	 2-6i	20 ^d
5	(E = CO₂Me)  2-5c	CH ₃ CN	B	 2-6j	59
6		 CN	B	 2-6k	30
7	 2-5d	 CN	A	 2-6l	49
8	 2-5e	CH ₃ CN	C	 2-6m	79

9		D	 2-6n	46
10		E	 2-6o , R = SiMe ₃ 2-6o' , R = H (2.7:1)	60

^a Non-distilled, used as the solvent. ^b Conditions: **A.** 90 °C, 5 h; **B.** 150 °C, 1.5 h; **C.** 150 °C, 30 h; **D.** 150 °C, 9 h; **E.** 150 °C, 18 h; ^c Isolated Yield; ^d Overall yield after desilylation with TBAF

Table 2.2. Aryne-Based Three-Component Coupling for the Formation of Arylamides

(entries 5 and 6). However, with acrylonitrile, no expected amide product was observed, probably because of the instability of acrylonitrile at this high temperature. It is interesting to notice the difference between the reactions with acetonitrile and propionitrile, where addition of 10 equivalents of water significantly improved the yield of **2-6j** whereas the yield of **2-6k** was not improved by water additive. An ynamide-tethered non-symmetrical tetrayne **2-5d** afforded propionamide-substituted indoline **2-6l** in 49% from the reaction with propionitrile at 90 °C (entry 7). An ester-tethered triyne **2-5e** derived from propiolic acid turned out to be less reactive than tetraynes, thus the reaction was carried out at 150 °C. With acetonitrile, the reaction of **2-5e** provided **2-6m** in 79% yield at 150 °C for 30 h (entry 8). With acrylonitrile, acrylamide derivative **2-5n** was obtained in 46% yield after 9 h, and extended reaction time did not improve the yield (entry 9). With propionitrile, a mixture of amides products **2-6o** and **2-6o'** (2.6:1) was obtained after heating at 150 °C for 18 h (entry 10).

2.3.2. Synthesis of Imides

With these results in hand, we envisioned that if the putative nitrilium ion could be captured by other nucleophile rather than water, different end products would be generated. One such nucleophile is carboxylic acid.³⁷ Although carboxylic acid may complicate the reaction because they themselves are

excellent reacting counterparts with arynes, we tried to carry out the first reaction in the presence of acetic acid.

To our gratitude, the reaction of **2-5a** in acetonitrile and excess acetic acid provided the corresponding imide **2-7a** along with amide **2-6a** (Table 2.3). At this point, we assumed that by removing any adventitious water would reduce or eliminate the formation of **2-6**. Indeed, addition of 4 Å molecular sieves to the reaction improved the yield of **2-7**. Optimizing the stoichiometry of acetic acid revealed that addition of 3 equivalents provided the highest yield of the desired product. Thus, under the optimized conditions (10 mol % silver catalyst, 90 °C, 3 equivalents of AcOH, 10 wt% 4 Å molecular sieves) the reaction of NTs-tethered symmetrical tetrayne **2-5a** provided arylimide **2-7a** in 89% overall yield as a mixture with the corresponding desilylated product **2-7a'** in a 10:1 ratio (entry 1). The reaction in propionitrile afforded imide **2-7b** and desilylated product **2-7b'** in 75% yield in a 5.2:1 ratio (entry 2). The same product **2-7b** and **2-7b'** were obtained from the reaction with the combination of acetonitrile and propionic acid, but with much lower yield (54%) accompanied by increased desilylation (entry 3). The reaction of with acrylonitrile and AcOH yielded **2-7c** and **2-7c'** in 87% yield (entry 4). Replacing acetonitrile with more sterically demanding isobutyronitrile slightly lower the yield (76%, 1.7:1) and increased the extent of desilylation (entry 5). With acetonitrile and butyric acid, **2-7e** and the corresponding desilylated product **2-7e'** were obtained in 45% yield with more pronounced desilylation (entry 6). Similar to the amide forming reaction in Table 2, the reaction of all-carbon tethered substrate **2-5c**, although required higher reaction temperature (150 °C), full conversion was achieved in less than 2 h. Thus, the reaction of **2-5c** with a combination of acetonitrile and AcOH afforded **2-7f** in 55% yield with no desilylation (entry 7). From the reaction with propionitrile under otherwise identical conditions, **2-7g** was obtained in 79% yield (entry 8), and the same product was obtained in slightly lower 68% yield by employing acetonitrile and propionic acid (entry 9). With acrylonitrile and AcOH, acrylimide **2-7h** was obtained as a single product in 78% yield (entry 10), and with the combination of acetonitrile and propionic acid afforded **2-7i** in 67% yield (entry 11). Finally, an unsymmetrical ynamide-tethered substrate **2-5d**

$\begin{array}{c} \text{R}^1\text{CN}^a \\ \text{AgSbF}_6 \text{ (10 mol\%)} \\ \text{R}^2\text{CO}_2\text{H (3 equiv)} \\ \hline \text{4 \AA MS (10 wt\%)} \\ \text{conditions A or B}^b \end{array}$						
entry	substrate	R ¹ CN	R ² CO ₂ H	conditions	products	yield (%) ^c
	2-5				2-7	
1	2-5a	CH ₃ CN	CH ₃ CO ₂ H	A	2-7a	89 10:1 ^d
2			CH ₃ CO ₂ H	A	2-7b	75 5.2:1 ^d
3		CH ₃ CN		A	2-7c	54 0.91:1 ^d
4			CH ₃ CO ₂ H	A	2-7d	87 2.6:1 ^d
5			CH ₃ CO ₂ H	A	2-7e	76 1.7:1 ^d
6		CH ₃ CN		A	2-7f	45 0.27:1 ^d
7	(E = CO₂Me) 2-5c	CH ₃ CN	CH ₃ CO ₂ H	B	2-7g	55
8			CH ₃ CO ₂ H	B	2-7h	79
9		CH ₃ CN		B	2-7i	68
10			CH ₃ CO ₂ H	B	2-7j	78

11		CH ₃ CN		B		67
12		CH ₃ CN	CH ₃ CO ₂ H	A		71

^a Non-distilled, used as the solvent. ^b Conditions: **A**. 90 °C, 5 h; **B**. 150 °C, 2 h. ^c Isolated yield.

^d Ratios between intact and desilylated products in R

Table 2.3. Aryne-based Three-Component Coupling for the Formation of Arylimides

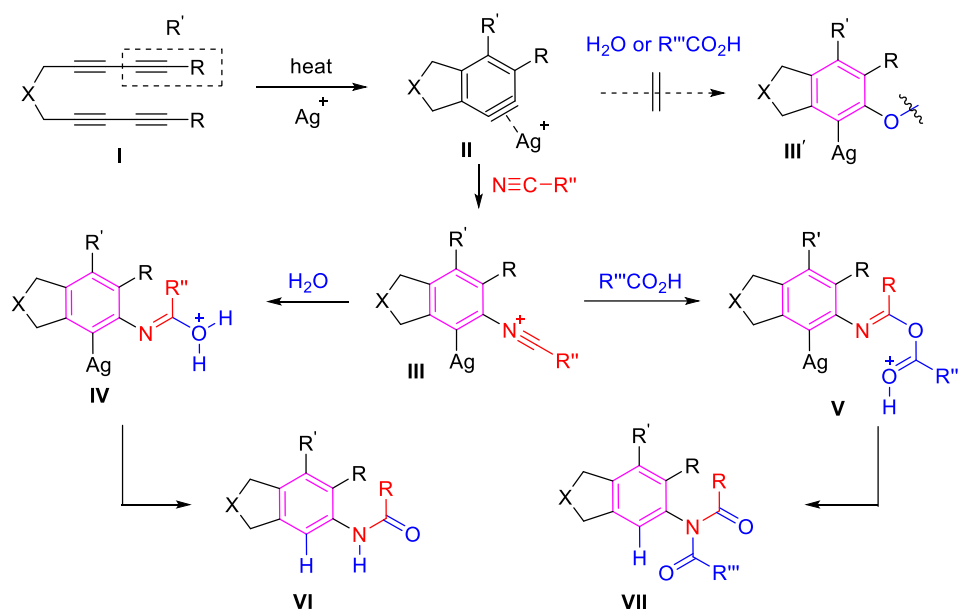
provided the corresponding indolyl imide **2-7j** in 71% when the reaction was carried out at 90 °C for 5 h (entry 12).

From these reactions, a general trend was noted that the reaction with sterically more hindered carboxylic acid provided a product in lower yield. For example, when AcOH was replaced with propionic acid (entry 3) and butyric acid (entry 6), significantly lower yields resulted in with more pronounced desilylation. Another interesting observation was the formation of products devoid of desilylation from the reaction of all-carbon tethered substrate **2-5c** even the reaction was carried out at 150 °C compared to 90 °C for other substrates.

2.3.3. Reaction Mechanism

On the basis of these results, we propose a mechanism for the formation of amides and imides (**Scheme 2.4**). Upon heating, a tetrayene or triyne substrate **I** undergoes HDDA reaction to form an aryne species, which then forms silver-aryne complex **II**. Formally, HDDA reaction is considered to be a pericyclic reaction, but recent theoretical studies suggest that the reaction should proceed in a stepwise manner via diradical intermediates.^{36,38,39} Once formed, silver-aryne complex **II**, although water or carboxylic acid can be trapped to form **III'**, under the given reaction conditions, nitrile reacts favorably to form nitrilium species **III**. Trapping of **III** by water or carboxylic acid would form penultimate intermediate

IV or **V**, respectively. Protonation of the C–Ag bond and proton or acyl shift on **IV** or **V** will generate the observed amide **VI** or imide **VII**. It was proved that under the current reaction conditions, neither nitrile converted to the corresponding amide, nor the preformed amide reacted with the aryne species, which supports the proposed reaction mechanism. Although carboxylic acid is known to be a good reacting counterpart with arynes the unique combination of their reactivity and concentration of nitrile and carboxylic acid ultimately provides the observed amide products.



Scheme 2.4. Mechanism for the Formation of Amides and Imides.

2.4. Conclusion

In conclusion, we developed aryne-based three-component coupling reactions by forming structurally diverse arynes via HDDA reaction of tetraynes and triynes. The facile trapping of arynes with nitriles to induce the Ritter-type reaction is a unique aspect of these coupling reactions. Although nitriles are not strong enough nucleophiles to react with arynes under typical conditions we found that a cationic silver catalyst can effectively promote the reaction between arynes and nitriles. Presumably, under these silver-catalyzed conditions, transiently formed aryne-silver complexes initially react with nitriles to form

nitrilium ion intermediates, which then subsequently react with either water or carboxylic acid to yield the observed arylamides or arylimides.

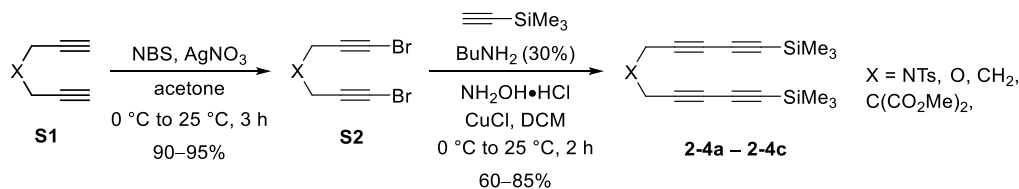
2.5. Experimental Details

2.5.1. General Information

All reactions were carried out in oven or flame-dried glassware unless otherwise noted. Reagents which were commercially available, were purchased from Sigma - Aldrich, Alfa Aesar, Acros, and Oakwood Products unless otherwise noted. Known compounds were prepared according to literature procedure. Anhydrous acetonitrile from Sigma-Aldrich was distilled over calcium hydride (CaH_2) under nitrogen atmosphere. Acetic acid was purchased from Fischer Scientific. 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). Yield was calculated on basis of chromatographically and spectroscopically pure isolated compound. FTIR spectra of pure compounds were recorded on Nicolet iS5 machine and the data were expressed in cm^{-1} . ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AV-500 spectrometer. ^1H NMR chemical shifts (δ) were reported in parts per million (ppm) downfield of TMS and were referenced relative to the residual proteated solvent peak (CDCl_3 (7.26 ppm)). ^{13}C chemical shifts (δ) were reported in parts per million downfield of TMS and are referenced to the carbon resonance of the solvent (CDCl_3 , δ 77.2 ppm). Multiplicities in ^1H NMR were abbreviated by s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sext (sextet), sept (septet) 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 (Waters Corporation, Milford, MA, USA) at 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 (Waters Corporation, Milford, MA, USA) at the University of Illinois at Urbana-Champaign.

2.5.2. General Procedures

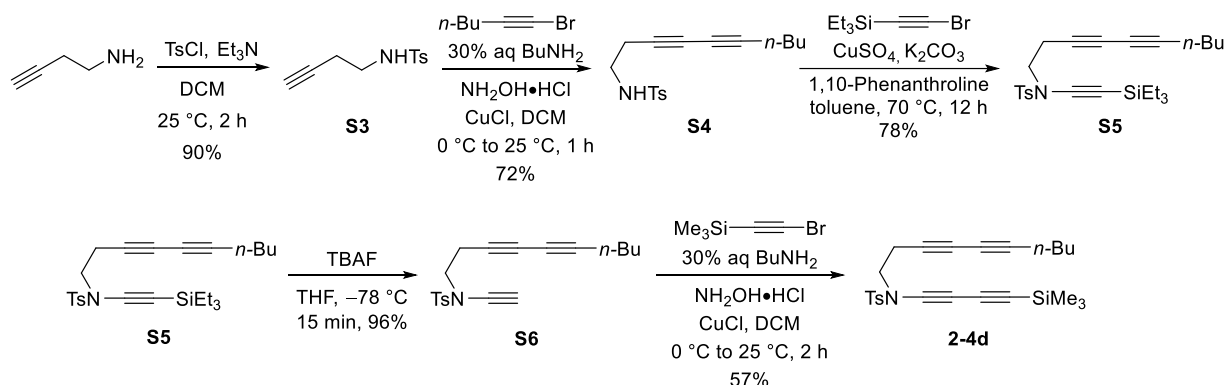
Synthesis of Symmetrical *bis*-1,3-Diynes (**2-4a – 2-4c**)



To a stirred solution of diyne **S1** (10.0 mmol) in acetone at 0 °C, *N*-bromosuccinimide (25.0 mmol) and AgNO₃ (1.0 mmol) were added sequentially under N₂ atmosphere in the dark. After addition, the ice bath was removed and stirring was continued for additional 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, EtOAc–hexane, 1:5 to 1:3) provided dibromide (**S2**) in excellent yield.

In a two-necked round-bottom flask, a solution of terminal alkyne (5.0 mmol) in CH₂Cl₂ was added slowly at 0 °C under N₂ atmosphere. Then **S2** (2.0 mmol) diluted in CH₂Cl₂ was added dropwise into the reaction mixture over 45 min. After 5 min, the ice bath was removed and stirring was continued for additional 1–2 h at room temperature (TLC monitoring). A pinch of NH₂OH·HCl was added several times into the reaction mixture when the solution becomes blue. The reaction was quenched by a sat. solution of NH₄Cl and extracted with CH₂Cl₂. The combined organic extracts were washed with water and brine sequentially and dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO, EtOAc–hexane, 1:20 to 1:10) to isolate pure symmetrical *bis*-1,3-diyne in moderate to good yield.

Synthesis of Unsymmetrical *bis*-1,3-Diyne (2-4d)



To a stirred solution of 3-butynylamine (1.5 g, 21.7 mmol) in CH_2Cl_2 at 25°C , Et_3N (4.4 g, 43.4 mmol) and 4-toluenesulfonyl chloride (4.1 g, 21.7 mmol) were added sequentially under N_2 . After 2 h, the reaction mixture was quenched with sat. NaHCO_3 and extracted with CH_2Cl_2 (X2). The combined organic extracts were washed with water and brine and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Crude **S3** (4.3 g, 90%) was subjected to the next reaction without further purification.

To a mixture of 30% aq. $n\text{-BuNH}_2$ (9 mL) and CuCl (133 mg, 1.3 mmol) in a two-necked round-bottom flask, a solution of **S3** (1.0 g, 4.5 mmol) in CH_2Cl_2 was added slowly at 0°C under N_2 atmosphere. Then 1-bromohex-1-yne, (598 mg, 3.7 mmol) diluted in CH_2Cl_2 was added dropwise into the reaction mixture over 30 min. After 5 min, the ice bath was removed, and stirring was continued for additional 1 h at room temperature. A pinch of $\text{NH}_2\text{OH}\cdot\text{HCl}$ was added several times into reaction mixture when the solution becomes blue. The reaction was quenched by a sat. solution of NH_4Cl and extracted with CH_2Cl_2 . The combined organic extracts were washed with water and brine sequentially and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO_2 , EtOAc –hexanes, 1:10) to isolate pure diyne tosylamide **S4** (980 mg, 72%).

To a stirred solution of **S4** (500 mg, 1.6 mmol) in PhCH_3 , CuSO_4 (62 mg, 0.2 mmol), 1,10-phenanthroline (88 mg, 0.5 mmol), and K_2CO_3 (458 mg, 3.3 mmol) were sequentially added under N_2

atmosphere at room temperature. After dropwise addition of (Bromoethynyl)triethylsilane (440 mg, 2.5 mmol) in PhCH₃, the reaction mixture was warmed up to 70 °C. After 12 h, the reaction mixture was filtered through silica and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO, EtOAc–hexanes, 1:10) to isolate pure triyne **S5** (513 mg, 78%).

To a stirred solution of **S5** (513 mg, 1.3 mmol) in dry THF was added TBAF (1.4 mL, 1 M solution in THF, 1.4 mmol) slowly at –78 °C under N₂ atmosphere. After 15 min, the reaction mixture was quenched with sat. NH₄Cl and extracted with EtOAc (X2). The combined organic extracts were washed with water and brine sequentially and dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. Crude **S6** (400 mg, 96%) was subjected to the next reaction without further purification.

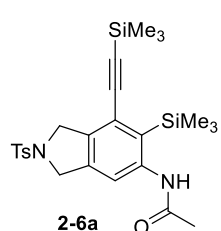
To a mixture of 30% aq. *n*-BuNH₂ (2.5 mL) and CuCl (36 mg, 0.4 mmol) in a two-necked round-bottom flask, a solution of **S6** (400 mg, 1.2 mmol) in CH₂Cl₂ was added slowly at 0 °C under N₂ atmosphere. Then (bromoethynyl)trimethylsilane, (324 mg, 1.8 mmol) diluted in CH₂Cl₂ was added dropwise into the reaction mixture over 30 min. After 5 min, the ice bath was removed and stirring was continued for additional 1 h at room temperature. A pinch of NH₂OH·HCl was added several times into reaction mixture when the solution becomes blue. The reaction was quenched by a sat. solution of NH₄Cl and extracted with CH₂Cl₂. The combined organic extracts were washed with water and brine sequentially and dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO, EtOAc–hexane, 1:15) to isolate pure tetrayne **2-4d** (294 mg, 72%).

General Procedure for HDDA Reaction

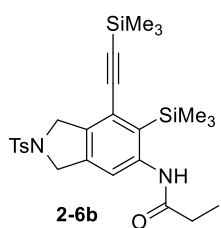
General procedure for preparation of arylamides (Procedure A): Multiyne substrate (0.1 mmol) and AgSbF₆ (0.01 mmol) in nitrile (3 mL) in a Schlenk tube was flushed with nitrogen. The mixture was stirred for 5 h at 90 °C unless otherwise noted. Water (10 equiv) was used as additive in some cases. The reaction mixture was concentrated, and then directly subjected to column chromatography for purification to afford the amide product.

General procedure for preparation of arylimides (Procedure B): Multiyne substrate (0.1 mmol), AgSbF₆ (0.01 mmol), AcOH (0.3 mmol), 4 Å MS (10 wt %) in nitrile (3 mL) in a Schlenk tube was flushed with nitrogen. The mixture was stirred for 5 h at 90 °C, unless otherwise noted. The reaction mixture was concentrated, and then purified by flash chromatography to afford the imide product.

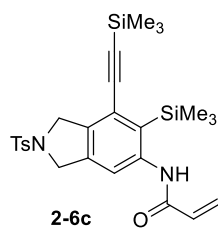
2.5.3. Characterization Data



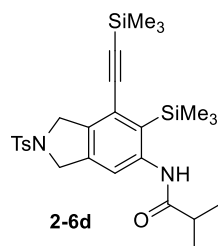
2-6a: This compound was obtained (Procedure A) in 72% yield. IR (neat): 3265, 2956, 2924, 2853, 2149, 1663, 1598, 1568, 1514 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 7.79–7.73 (m, 3H), 7.54 (s, 1H), 7.36–7.29 (m, 3H), 4.59 (s, 4H), 2.41 (s, 3H), 2.12 (s, 3H), 0.46 (s, 9H), 0.25 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz): δ 168.4, 143.8, 141.8, 137.8, 137.7, 133.7, 132.6, 129.9, 127.6, 124.4, 118.9, 104.9, 102.7, 54.4, 54.1, 24.4, 21.5, 1.7, –0.4; **HRMS** (ESI) calcd for C₂₅H₃₅N₂O₃SSi₂ [M+H]⁺ 499.1909, found 499.1928.



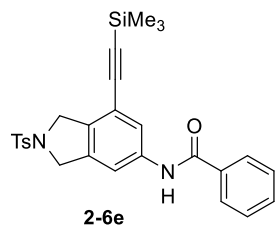
2-6b: This compound was obtained (Procedure A) in 75% yield. IR (neat): 3269, 2956, 2899, 2854, 2149, 1657, 1597, 1570, 1510 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 7.78–7.73 (m, 2H), 7.58 (s, 1H), 7.38–7.29 (m, 3H), 4.58 (s, 4H), 2.41 (s, 3H), 2.32 (q, 2H, *J* = 7.2 Hz), 1.22 (t, 3H, *J* = 7.4 Hz), 0.45 (s, 9H), 0.25 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz): δ 172.1, 143.8, 142.0, 137.7, 137.4, 133.6, 132.3, 129.9, 127.6, 124.4, 118.7, 104.8, 102.7, 54.4, 54.1, 30.6, 21.5, 9.5, 1.8, –0.4; **HRMS** (ESI) calcd for C₂₆H₃₇N₂O₃SSi₂ [M+H]⁺ 513.2063, found 513.2068.



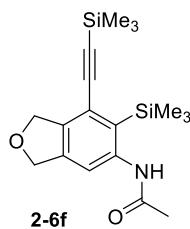
2-6c: This compound was obtained (Procedure A) in 56% yield. IR (neat): 3246, 2956, 2924, 2853, 2148, 1661, 1625, 1597, 1571, 1514 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 7.79–7.74 (m, 2H), 7.68 (s, 1H), 7.50 (s, 1H), 7.35–7.30 (m, 2H), 6.41 (d, 1H, J = 17.0 Hz), 6.15 (dd, 1H, J = 16.5 Hz, J = 10.2 Hz), 5.77 (d, 1H, J = 10.2 Hz), 4.60 (s, 4H), 2.41 (s, 3H), 0.46 (s, 9H), 0.26 (s, 9H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 163.6, 143.8, 141.7, 137.8, 137.7, 133.7, 132.4, 130.8, 129.9, 128.4, 127.6, 124.5, 118.6, 105.0, 102.6, 54.4, 54.1, 21.5, 1.8, -0.4 ; **HRMS** (ESI) calcd for $\text{C}_{26}\text{H}_{35}\text{N}_2\text{O}_3\text{SSi}_2$ $[\text{M}+\text{H}]^+$ 511.1907, found 511.1924.



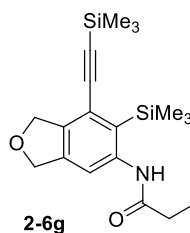
2-6d: This compound was obtained (Procedure A with 10 equiv water additive) in 47% yield. IR (neat): 3270, 2962, 2929, 2900, 2148, 1662, 1597, 1569, 1506 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 7.78–7.72 (m, 2H), 7.64 (s, 1H), 7.37 (s, 1H), 7.34–7.29 (m, 2H), 4.59 (s, 4H), 2.41 (s, 3H), 2.40 (sept, 1H, J = 6.8 Hz), 1.22 (d, 6H, J = 6.8 Hz), 0.46 (s, H), 0.25 (s, 9H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 175.4, 143.7, 142.2, 137.7, 137.3, 133.7, 131.9, 129.9, 127.5, 124.3, 118.5, 104.8, 102.8, 54.4, 54.1, 36.8, 21.5, 19.5, 1.9, -0.4 ; **HRMS** (ESI) calcd for $\text{C}_{27}\text{H}_{39}\text{N}_2\text{O}_3\text{SSi}_2$ $[\text{M}+\text{H}]^+$ 527.2220, found 527.2222.



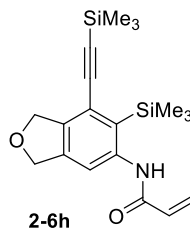
2-6e: This compound was obtained (Procedure A followed by TBAF-mediated deprotection) in 69% yield. IR (neat): 3266, 2922, 2853, 2360, 1677, 1605, 1539, 1492 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 7.96 (s, 1H), 7.86–7.81 (m, 2H), 7.79–7.75 (m, 2H), 7.69 (s, 1H), 7.57–7.51 (m, 1H), 7.50–7.42 (m, 3H), 7.35–7.30 (m, 2H), 4.62 (s, 4H), 3.25 (s, 1H), 2.41 (s, 3H); ^{13}C NMR (CDCl_3 , 125 MHz): 165.8, 143.9, 137.9, 137.4, 135.2, 134.3, 133.6, 132.2, 129.9, 128.9, 127.6, 127.0, 122.9, 117.6, 115.4, 82.0, 79.8, 54.2, 53.5, 21.5; **HRMS** (ESI) calcd for $\text{C}_{24}\text{H}_{19}\text{N}_2\text{O}_3\text{S}$ $[\text{M}-\text{H}]^-$ 415.1116, found 415.1113.



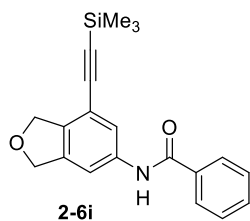
2-6f: This compound was obtained (Procedure A) in 78% yield. IR (neat): 3226, 2956, 2899, 2855, 2148, 1643, 1574, 1533 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3 , 500 MHz): δ 7.60 (s, 1H), 7.39 (s, 1H), 5.15–5.07 (m, 4H), 2.15 (s, 3H), 0.49 (s, 9H), 0.23 (s, 9H); $^{13}\text{C NMR}$ (CDCl_3 , 125 MHz): δ 168.5, 141.5, 141.1, 141.0, 131.9, 122.8, 117.7, 103.8, 103.2, 74.3, 24.4, 1.8, -0.4 ; **HRMS** (ESI) calcd for $\text{C}_{18}\text{H}_{28}\text{NO}_2\text{Si}_2$ $[\text{M}+\text{H}]^+$ 346.1659, found 346.1670.



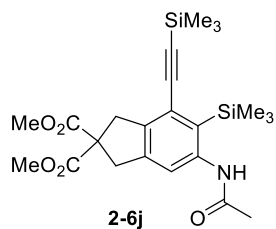
2-6g: This compound was obtained (Procedure A) in 80% yield. IR (neat): 3227, 2958, 2897, 2149, 1645, 1604, 1570, 1529 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3 , 500 MHz): δ 7.67 (s, 1H), 7.36 (s, 1H), 5.13–5.07 (m, 4H), 2.36 (q, 2H, $J = 7.6$ Hz), 1.25 (t, 3H, $J = 7.6$ Hz), 0.49 (s, 9H), 0.23 (s, 9H); $^{13}\text{C NMR}$ (CDCl_3 , 125 MHz): δ 172.0, 141.7, 141.0, 140.8, 131.4, 122.7, 117.4, 103.7, 103.3, 74.3, 74.1, 30.7, 9.6, 1.9, -0.4 ; **HRMS** (ESI) calcd for $\text{C}_{19}\text{H}_{30}\text{NO}_2\text{Si}_2$ $[\text{M}+\text{H}]^+$ 360.1815, found 360.1808.



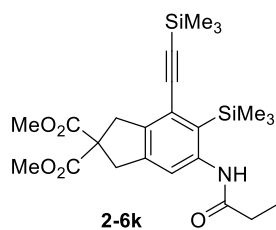
2-6h: This compound was prepared (Procedure A) in 75% yield. IR (neat): 3222, 2957, 2898, 2149, 1667, 1650, 1605, 1574, 1535 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3 , 500 MHz): δ 7.74 (s, 1H), 7.44 (s, 1H), 6.43 (d, 1H, $J = 16.8$ Hz), 6.25–6.12 (m, 1H), 5.78 (d, 1H, $J = 10.1$ Hz), 5.20–5.06 (m, 4H), 0.49 (s, 9H), 0.23 (s, 9H); $^{13}\text{C NMR}$ (CDCl_3 , 125 MHz): δ 163.7, 141.4, 141.1, 131.7, 131.0, 128.1, 122.8, 117.3, 103.8, 103.2, 74.3, 74.1, 1.8, -0.4 ; **HRMS** (ESI) calcd for $\text{C}_{19}\text{H}_{28}\text{NO}_2\text{Si}_2$ $[\text{M}+\text{H}]^+$ 358.1659, found 358.1665.



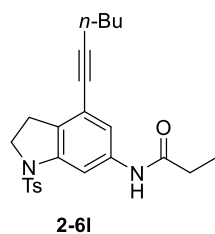
2-6i: This compound was obtained (Procedure A followed by TBAF-mediated deprotection) in 20% yield. IR (neat): 3290, 3060, 2923, 2853, 2360, 2341, 1652, 1604, 1579, 1537 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3 , 500 MHz): 7.88–7.84 (m, 3H), 7.75 (s, 1H), 7.59–7.54 (m, 1H), 7.53–7.46 (m, 3H), 5.18–5.12 (m, 4H), 3.23 (s, 1H); $^{13}\text{C NMR}$ (CDCl_3 , 125 MHz): 165.8, 140.6, 138.4, 137.6, 134.6, 132.1, 128.9, 127.0, 122.5, 116.1, 113.9, 81.1, 80.3, 74.1, 73.4; **HRMS** (ESI) calcd for $\text{C}_{17}\text{H}_{14}\text{NO}_2$ $[\text{M}+\text{H}]^+$ 264.1025, found 264.1021.



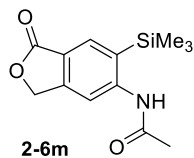
2-6j: This compound was prepared (Procedure A, but at 150 °C for 1.5 h with 10 equiv of water additive) in 59% yield. IR (neat): 3259, 2955, 2926, 2889, 2147, 1737, 1657, 1563, 1521 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 7.56 (s, 1H), 3.76 (s, 6H), 3.62 (s, 2H), 3.61 (s, 2H), 2.13 (s, 3H), 0.47 (s, 9H), 0.24 (s, 9H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 172.0, 168.4, 141.7, 141.1, 131.6, 125.5, 125.0, 120.9, 104.0, 103.7, 59.3, 53.1, 41.1, 40.8, 24.4. 1.9, -0.3; HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{34}\text{NO}_5\text{Si}_2$ $[\text{M}+\text{H}]^+$ 460.1976, found 460.1975.



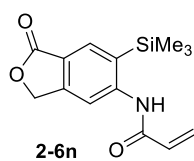
2-6k: This compound was prepared in 30% yield by using Procedure A but at 150 °C for 1.5 h. IR (neat): 3260, 2954, 2926, 2854, 2147, 1737, 1652, 1590, 1564, 1514 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 7.62 (s, 1H), 7.26 (s, 1H), 3.76 (s, 6H), 3.62 (s, 2H), 3.60 (s, 2H), 2.33 (q, 2H, $J = 7.4$ Hz), 1.24 (t, 3H, $J = 7.4$ Hz), 0.47 (s, 9H), 0.25 (s, 9H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 172.0, 141.6, 141.4, 141.3, 131.2, 125.4, 120.7, 104.1, 103.6, 59.3, 53.1, 41.1, 40.8, 30.7, 9.6, 2.0, -0.3; HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{36}\text{NO}_5\text{Si}_2$ $[\text{M}+\text{H}]^+$ 474.2132, found 474.2139.



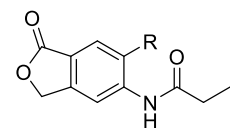
2-6l: This compound was obtained (Procedure A) in 49% yield. IR (neat): 3295, 2955, 2929, 2871, 1666, 1609, 1593, 1544 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 7.72–7.68 (m, 2H), 7.49 (s, 1H), 7.26–7.23 (m, 2H), 7.10 (s, 1H), 3.89 (t, 2H, $J = 8.4$ Hz), 2.90 (t, 2H, $J = 8.4$ Hz), 2.40 (q, 2H, $J = 7.8$ Hz), 2.38 (s, 3H), 2.36 (t, 2H, $J = 7.01$ Hz), 1.54–1.48 (m, 2H), 1.46–1.38 (m, 2H), 1.26 (t, 3H, $J = 7.6$ Hz), 0.91 (t, 2H, $J = 7.2$ Hz); ^{13}C NMR (CDCl_3 , 125 MHz): δ 171.8, 144.3, 142.3, 137.6, 133.7, 129.8, 129.6, 127.4, 121.5, 118.1, 106.0, 94.8, 77.7, 50.0, 30.8, 30.7, 27.3, 21.9, 21.6, 19.1, 13.6, 9.6; HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{29}\text{N}_2\text{O}_3\text{S}$ $[\text{M}+\text{H}]^+$ 425.1899, found 425.1913.



2-6m: This compound was prepared in 79% yield by using Procedure A but at 150 °C for 30 h with 10 equiv water additive. IR (neat): 3458, 2968, 2870, 1763, 1693, 1618, 1516, 1456 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3 , 500 MHz): δ 8.27 (s, 1H), 7.97 (s, 1H), 7.50 (s, 1H), 5.28 (s, 2H), 2.23 (s, 3H), 0.42 (s, 9H); $^{13}\text{C NMR}$ (CDCl_3 , 125 MHz): δ 170.8, 168.2, 149.4, 147.2, 132.5, 131.1, 121.2, 114.6, 69.4, 28.8, -0.4 ; **HRMS** (ESI) calcd for $\text{C}_{13}\text{H}_{18}\text{NO}_3\text{Si}$ $[\text{M}+\text{H}]^+$ 264.1056, found 264.1045.

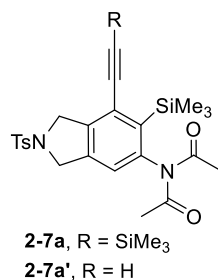


2-6n: This compound was prepared in 46% yield by using Procedure A but at 150 °C for 9 h with 10 equiv water additive. IR (neat): 3212, 3016, 2954, 1756, 1674, 1651, 1622, 1578, 1525 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3 , 500 MHz): δ 8.38 (s, 1H), 7.99 (s, 1H), 7.61 (s, 1H), 6.47 (d, 1H, $J = 17.0$ Hz), 6.23 (dd, 1H, $J = 16.9$ Hz, $J = 10.3$ Hz), 5.88 (d, 1H, $J = 10.4$ Hz), 5.29 (s, 2H), 0.44 (s, 9H); $^{13}\text{C NMR}$ (CDCl_3 , 125 MHz): δ 170.8, 163.5, 149.5, 147.2, 132.5, 130.7, 129.1, 121.3, 114.7, 69.5, -0.4 ; **HRMS** (ESI) calcd for $\text{C}_{14}\text{H}_{18}\text{NO}_3\text{Si}$ $[\text{M}+\text{H}]^+$ 276.1056 found 276.1057.

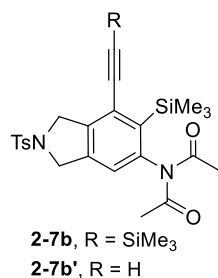


2-6o: This compound was prepared in 44% yield by using Procedure A but 150 °C for 18 h with 10 equiv water additive. IR (neat): 3301, 2923, 2853, 1741, 1699, 1682, 1604, 1547 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3 , 500 MHz): δ 8.33 (s, 1H), 7.97 (s, 1H), 7.49 (s, 1H), 5.27 (s, 2H), 2.44 (q, 3H, $J = 7.5$ Hz), 1.28 (t, 3H, $J = 7.6$ Hz), 0.42 (s, 9H); ^{13}C

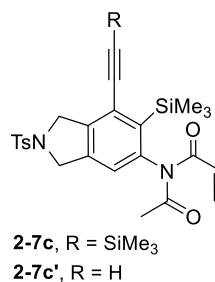
NMR (CDCl_3 , 125 MHz): δ 172.0, 170.8, 149.5, 147.4, 132.4, 130.9, 121.0, 114.4, 69.4, 31.1, 9.5, -0.4 ; **HRMS** (ESI) calcd for $\text{C}_{14}\text{H}_{20}\text{NO}_3\text{Si}$ $[\text{M}+\text{H}]^+$ 278.1212, found 278.1222. **2-6o'** (16%): IR (neat): 3301, 2923, 2853, 1741, 1699, 1682, 1604, 1547 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3 , 500 MHz): δ 8.15 (s, 1H), 7.84 (d, 1H, $J = 8.2$ Hz), 7.37 (s, 1H), 7.27 (d, 1H), 5.20 (s, 2H), 2.46 (q, 2H, $J = 7.6$ Hz), 1.28 (t, 3H, $J = 7.6$ Hz); ^{13}C **NMR** (CDCl_3 , 125 MHz): δ 172.5, 170.7, 148.7, 143.4, 126.5, 120.8, 119.9, 112.2, 69.5, 30.9, 9.4; **HRMS** (ESI) calcd for $\text{C}_{11}\text{H}_{12}\text{NO}_3$ $[\text{M}+\text{H}]^+$ 206.0817, found 206.0813.



2-7a: This compound was obtained (Procedure B) in 80% yield. IR (neat): 2956, 2899, 2852, 2150, 1708, 1597, 1567 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 7.79–7.75 (m, 2H), 7.36–7.32 (m, 2H), 6.77 (s, 1H), 4.67–4.60 (m, 4H), 2.43 (s, 3H), 2.22 (s, 3H), 0.33 (s, 9H), 0.26 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz): δ 173.0, 144.3, 144.0, 141.2, 141.0, 138.6, 133.5, 130.0, 127.6, 125.8, 123.5, 106.3, 102.1, 54.1, 27.5, 21.5, 0.5, –0.4; **HRMS** (ESI) calcd for C₂₇H₃₇N₂O₄Si₂S [M+H]⁺ 541.2013, found 541.2012. **2-7a'** (9%, obtained as an inseparable mixture with **2-7a** in a 1:1 ratio): ¹H NMR (CDCl₃, 500 MHz): δ 7.80–7.75 (m, 2H), 7.37–7.31 (m, 2H), 6.81 (s, 1H), 4.70–4.60 (m, 4H), 3.60 (s, 1H), 2.42 (s, 3H), 2.23 (s, 6H), 0.33 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz): δ (all peaks) 173.0, 144.3, 144.0, 141.9, 141.5, 141.2, 141.0, 138.7, 138.6, 133.5, 133.4, 131.3, 130.0, 127.6, 125.8, 124.7, 124.0, 123.5, 123.1, 106.3, 102.1, 88.2, 81.1, 78.8, 54.2, 54.0, 53.9, 27.5, 26.9, 21.5, 0.6, 0.5, –0.4; **HRMS** (ESI) calcd for C₂₄H₂₉N₂O₄SiS [M+H]⁺ 469.1617, found 469.1620.

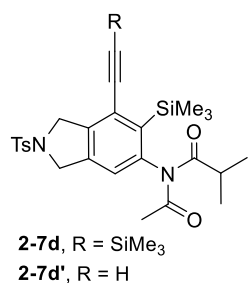


2-7b: This compound was obtained (Procedure B) in 63% yield. IR (neat): 2956, 2924, 2852, 2149, 1712, 1597, 1567, 1513, 1494 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 7.79–7.75 (m, 2H), 7.36–7.32 (m, 2H), 6.75 (s, 1H), 4.70–4.56 (m, 4H), 2.43 (s, 3H), 2.39–2.33 (m, 2H), 2.32 (s, 3H), 1.06 (t, 3H, *J* = 7.3 Hz), 0.31 (s, 9H), 0.26 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz): δ 176.3, 173.2, 144.0, 141.2, 141.1, 138.5, 133.5, 130.0, 127.6, 125.8, 123.6, 106.2, 102.2, 54.1, 32.4, 27.8, 21.5, 8.6, 0.5, –0.4; **HRMS** (ESI) calcd for C₂₈H₃₉N₂O₄SSi₂ [M+H]⁺ 555.2169, found 555.2151. **2-7b'** (12%): IR (neat): 3256, 3065, 2954, 2824, 2853, 1712, 1598, 1569, 1493 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 7.79–7.76 (m, 2H), 7.36–7.32 (m, 2H), 6.79 (s, 1H), 4.74–4.57 (m, 4H), 3.60 (s, 1H), 2.43 (s, 3H), 2.39–2.34 (m, 2H), 2.33 (s, 3H), 1.06 (t, 3H, *J* = 7.2 Hz), 0.31 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz): δ 176.3, 173.2, 150.2, 144.0, 141.8, 141.6, 138.6, 133.4, 130.0, 127.6, 124.6, 124.1, 88.2, 81.1, 54.2, 54.0, 32.5, 27.8, 21.5, 8.6, 0.6; **HRMS** (ESI) calcd for C₂₅H₃₁N₂O₄SiS [M+H]⁺ 483.1774, found 483.1775.



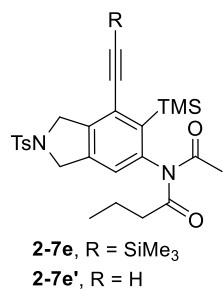
2-7c and **2-7c'** (inseparable mixture): A mixture of these compounds was obtained (Procedure B) in 87% yield with a 2.6:1 ratio. IR (neat): 3254, 2956, 2924, 2900, 2854, 2150, 1703, 1615, 1597, 1567, 1493, 1467; (major isomer) **¹H NMR** (500 MHz, CDCl₃): δ 7.80–7.75 (m, 2H), 7.37–7.33 (m, 2H), 6.76 (s, 1H), 6.46–6.41 (m, 1H), 6.20–6.11 (m, 1H), 5.69–5.64 (m, 1H), 4.76–4.52 (m, 4H), 2.47 (s, 3H), 2.43 (s, 3H),

0.30 (s, 9H), 0.26 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ (all peaks) 173.9, 167.2, 144.0, 143.3, 141.9, 141.5, 141.2, 138.7, 138.6, 133.6, 131.3, 131.2, 130.0, 129.8, 127.5, 125.8, 124.7, 124.3, 123.8, 109.8, 106.3, 102.2, 88.3, 81.1, 54.1, 54.0, 27.7, 21.5, 0.6, 0.5, –0.4; **HRMS** (ESI) calcd for C₂₈H₃₇N₂O₄Si₂S [M+H]⁺ 553.2013, found 553.2018.

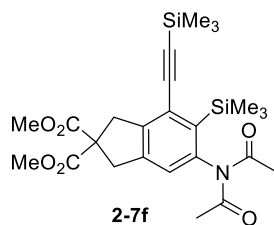


2-7d: This compound was obtained (Procedure B) in 48% yield. IR (neat): 2959, 2933, 2900, 2873, 2151, 1707, 1597, 1567 cm⁻¹; **¹H NMR** (CDCl₃, 500 MHz): δ 7.78–7.76 (m, 2H), 7.36–7.33 (m, 2H), 6.75 (s, 1H), 4.71–4.55 (m, 4H), 2.43 (s, 3H), 2.32 (s, 3H), 2.87–2.79 (m, 1H), 2.43 (s, 3H), 2.32 (s, 3H), 1.10 (d, 3H, *J* = 6.7 Hz), 1.04 (d, 3H, *J* = 6.6 Hz), 0.32 (s, 9H), 0.26 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ

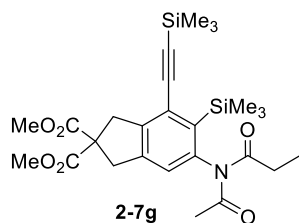
180.2, 173.5, 144.1, 144.0, 141.5, 141.1, 138.3, 133.6, 130.0, 127.6, 125.7, 123.5, 106.2, 102.2, 54.1, 54.0, 35.0, 27.8, 21.5, 19.5, 19.4, 0.6, –0.4; **HRMS** (ESI) calcd for C₂₉H₄₁N₂O₄Si₂S [M+H]⁺ 569.2326, found 569.2300. **2-7d'** (28%): IR (neat): 3255, 2956, 2920, 2850, 1708, 1597 cm⁻¹; **¹H NMR** (CDCl₃, 500 MHz): δ 7.79–7.76 (m, 2H), 7.36–7.33 (m, 2H), 6.79 (s, 1H), 4.74–4.56 (m, 4H), 3.60 (s, 1H), 2.87–2.80 (m, 1H), 2.43 (s, 3H), 2.32 (s, 3H), 1.11 (d, 2H, *J* = 6.7 Hz), 1.05 (d, 2H, *J* = 6.8 Hz), 0.32 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 180.2, 173.5, 144.1, 144.0, 142.0, 141.7, 138.4, 130.0, 127.6, 124.6, 124.0, 88.2, 81.2, 54.2, 54.0, 35.0, 27.8, 21.5, 19.5, 19.4, 0.6; **HRMS** (ESI) calcd for C₂₆H₃₃N₂O₄SiS [M+H]⁺ 497.1930, found 497.1916.



2-7e: This compound was obtained (Procedure B) in 10% (in the table it is 45% as a total yield of the mixture) yield. IR (neat): 2958, 2927, 2901, 2872, 2850, 2152, 1713, 1597 cm⁻¹; **¹H NMR** (CDCl₃, 500 MHz): δ 7.80–7.76 (m, 2H), 7.36–7.32 (m, 2H), 6.74 (s, 1H), 4.72–4.54 (m, 4H), 2.43 (s, 3H), 2.34–2.28 (m, 5H), 1.64–1.54 (m, 2H), 0.88 (t, 3H, *J* = 7.4 Hz), 0.32 (s, 9H), 0.26 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 175.4, 173.3, 144.0, 141.2, 141.1, 138.5, 133.6, 130.0, 127.6, 125.7, 123.6, 106.2, 102.2, 54.1, 40.8, 27.8, 21.5, 17.7, 13.6, 0.5, –0.4; **HRMS** (ESI) calcd for C₂₉H₄₁N₂O₄Si₂S [M+H]⁺ 569.2326, found 569.2310. **2-7e'** (35%) IR (neat): 3261, 2958, 2929, 2873, 2853, 1712, 1597, 1493 cm⁻¹; **¹H NMR** (CDCl₃, 500 MHz): δ 7.80–7.76 (m, 2H), 7.36–7.32 (m, 2H), 6.78 (s, 1H), 4.74–4.54 (m, 4H), 3.60 (s, 1H), 2.43 (s, 3H), 2.35–2.29 (m, 5H), 1.63–1.57 (m, 2H), 0.89 (t, 3H, *J* = 7.0 Hz), 0.32 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 175.4, 173.3, 144.0, 141.8, 141.7, 138.6, 133.4, 130.0, 127.6, 124.6, 124.1, 88.2, 81.1, 54.2, 54.0, 40.8, 27.8, 21.5, 17.7, 13.6, 0.6; **HRMS** (ESI) calcd for C₂₆H₃₃N₂O₄SiS [M+H]⁺ 497.1930, found 497.1946.

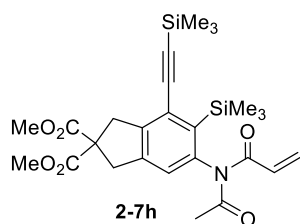


2-7f: This compound was obtained (Procedure B, but at 150 °C for 2 h) in 55% yield. IR (neat): 2955, 2900, 2148, 1736, 1708, 1590, 1562, 1432 cm⁻¹; **¹H NMR** (CDCl₃, 500 MHz): δ 6.79 (s, 1H), 3.78 (s, 6H), 3.71 (s, 2H), 3.64 (s, 2H), 2.24 (s, 3H), 0.35 (s, 9H), 0.25 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 173.2, 171.8, 144.9, 143.6, 142.5, 139.6, 104.9, 103.5, 59.1, 53.2, 40.9, 40.8, 27.5, 0.6, –0.4; **HRMS** (ESI) calcd for C₂₅H₃₆NO₆Si₂ [M+H]⁺ 502.2081, found 502.2068.



2-7g: This compound was obtained (Procedure B, but at 150 °C for 2 h) in 79% yield. IR (neat): 2955, 2901, 2149, 1736, 1708, 1589, 1561 cm⁻¹; **¹H NMR** (CDCl₃, 500 MHz): δ 6.76 (s, 1H), 3.78 (s, 6H), 3.71 (s, 2H), 3.63 (s, 2H), 2.41–2.35 (m, 2H), 2.34 (s, 3H), 1.06 (t, 3H, *J* = 7.3 Hz), 0.33 (s, 9H), 0.25 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 176.6, 173.4, 171.9, 171.8, 144.8, 143.3, 142.4, 139.7, 104.8, 103.6, 59.1,

53.2, 40.9, 40.8, 32.4, 27.8, 8.6, 0.6, -0.4; **HRMS** (ESI) calcd for $C_{26}H_{38}NO_6Si_2$ $[M+H]^+$ 516.2238, found 516.2247.

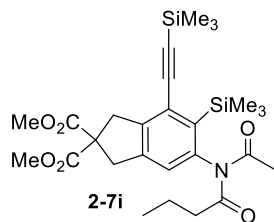


2-7h

2-7h: This compound was obtained (Procedure B, but at 150 °C for 2 h) in 78% yield. IR (neat): 2955, 2900, 2149, 1737, 1703, 1615, 1590, 1562 cm^{-1} ; **1H NMR** ($CDCl_3$, 500 MHz): δ 6.79 (s, 1H), 6.43 (dd, 1H, J = 1.6 Hz, J = 16.7 Hz),

6.19 (dd, 1H, J = 10.2 Hz, J = 16.6 Hz), 5.65 (dd, 1H, J = 1.6 Hz, J = 10.3 Hz),

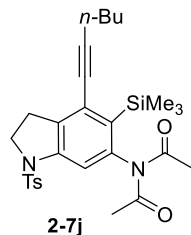
3.78 (s, 6H), 3.72 (s, 2H), 3.64 (s, 2H), 2.48 (s, 3H), 0.32 (s, 9H), 0.25 (s, 9H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 174.0, 172.0, 171.8, 167.5, 145.0, 142.6, 142.4, 140.1, 130.8, 130.3, 126.8, 125.5, 105.0, 103.5, 59.1, 53.2, 41.0, 40.8, 27.8, 0.6, -0.4; **HRMS** (ESI) calcd for $C_{26}H_{36}NO_6Si_2$ $[M+H]^+$ 514.2081, found 514.2068.



2-7i

2-7i: This compound was obtained (Procedure B) in 67% yield. In this reaction, butanoic acid was used instead of acetic acid and the reaction mix was stirred at 150 °C for 2 h. IR (neat): 2957, 2901, 2875, 2854, 2149, 1737, 1710, 1589, 1562 cm^{-1} ; **1H NMR** ($CDCl_3$, 500 MHz): δ 6.77 (s, 1H), 3.78 (s, 6H), 3.72 (s, 2H), 3.64

(s, 2H), 2.35 (t, 2H, J = 7.2 Hz), 2.33 (s, 3H), 1.66–1.57 (m, 2H), 0.90 (t, 3H, J = 7.4 Hz), 0.34 (s, 9H), 0.26 (s, 9H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 175.7, 173.4, 171.9, 171.8, 144.8, 143.3, 142.4, 139.8, 126.7, 125.4, 104.8, 103.6, 59.1, 53.2, 41.0, 40.8, 40.7, 27.8, 17.8, 13.7, 0.7, -0.4; **HRMS** (ESI) calcd for $C_{27}H_{40}NO_6Si_2$ $[M+H]^+$ 530.2394, found 530.2377.



2-7j

2-7j: This compound was obtained (Procedure B) in 71% yield. IR (neat): 2956, 2929, 2872, 2224, 1711, 1580, 1493 cm^{-1} ; **1H NMR** ($CDCl_3$, 500 MHz): δ 7.69–7.65 (m, 2H), 7.29–7.25 (m, 2H), 7.21 (s, 1H), 3.91 (t, 2H, J = 8.7 Hz), 3.02 (t, 2H, J = 8.6 Hz), 2.41 (t, 2H, J = 7.0 Hz), 2.39 (s, 3H), 2.28 (s, 6H), 1.59–1.51 (m, 2H), 1.48–1.39 (m, 2H),

1.48–1.39 (m, 2H), 0.91 (m, 3H, J = 7.4 Hz), 0.29 (s, 9H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 173.0, 144.6,

144.5, 143.6, 135.6, 134.4, 133.4, 129.9, 128.1, 127.4, 114.6, 100.8, 79.1, 49.6, 30.4, 28.1, 27.4, 22.1, 21.6, 19.3, 13.5, 0.7; **HRMS** (ESI) calcd for C₂₈H₃₇N₂O₄SSi [M+H]⁺ 525.2243, found 525.2253.

2.6. References

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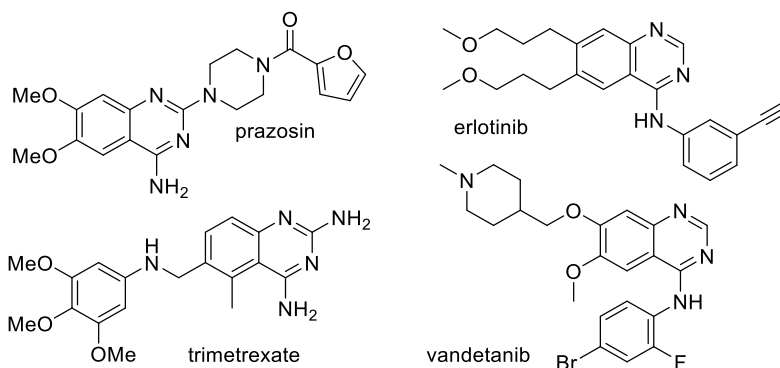
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CHAPTER 3

Silver-Catalyzed Annulation of Arynes with Nitriles: Synthesis of Quinazolines

3.1. Introduction*

Heterocyclic compounds draw significant attention of synthetic chemists because of their immense importance in human life.¹ Quinazoline, a family of nitrogen-based bicyclic aromatic compounds, constitutes the core of numerous biologically active molecules that show anticancer,^{2a} antibacterial,^{2b} antifungal,^{2c} antiviral,^{2d} antitubercular,^{2e} anti-inflammatory,^{2f} antimutagenic,^{2g} anticoccidial,^{2h} antimalarial,²ⁱ antileishmanial,^{2j} antioxidants,^{2k} neuroprotective,^{2l} antiobesity,^{2m} and antihypertensive²ⁿ activities. Prazosin,^{3a} erlotinib,^{3b} trimetrexate,^{3c} vandetanib^{3d} are representatives of marketed drugs (Scheme 3.1).^{3e-f} Also, the unique photochromic behavior of quinazoline molecules⁴ were exploited to elucidate cellular signaling processes of epidermal growth factor receptor (EGFR)^{4c-d} and α_1 -adrenergic receptors.^{4e-f} Recently, quinazolines are recognized as light-emitting materials for electronic devices.⁵

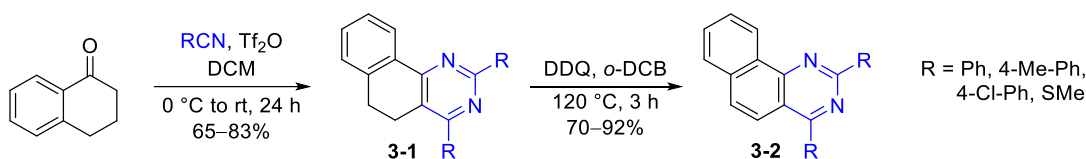


Scheme 3.1. Representative Drug a Containing Quinazoline Core

Many protocols for quinazoline synthesis via a nitrilium intermediate are reported in the literature,^{6a-g} however, the generality of these methods is often limited by the requirement of pre-functionalized arene moieties. In theory, quinazolines can be generated via a formal [2+2+2] cycloaddition between alkyne or its functional equivalent and two molecules of nitrile^{6a-c,6h-m} under thermal or acid-catalyzed conditions. In 2006, Martínez-Alvarez reported a one-pot synthesis of quinazolines from

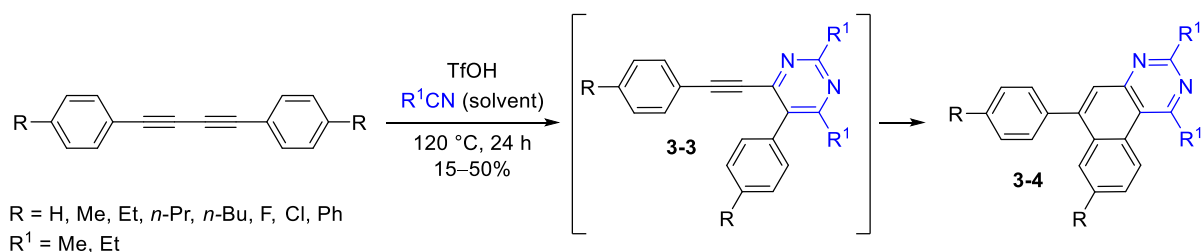
* Some parts of this chapter have been reproduced (adapted) partially from Ghorai, S.; Lin, Y.; Xia, Y.; Wink, D. J.; Lee, D. "Silver-catalyzed Annulation of Arynes with Nitriles for Efficient Synthesis of Structurally Diverse Quinazolines" *Org. Lett.* **2020**, 22, 626. Copyright 2020, American Chemical Society.

tetralones and nitriles using triflic anhydride and DDQ (**Scheme 3.2**).^{6a} Reaction of 1-tetralone with nitriles in the presence of triflic anhydride afforded 2,4-disubstituted 5,6-dihydrobenzo[*h*]quinazolines **3-1**, which oxidation with DDQ led to the corresponding benzo[*h*]quinazolines **3-2**. Similarly, reaction of 2-tetralone and nitriles generated 1,3-disubstituted benzoquinazolines.



Scheme 3.2. Synthesis of Quinazolines from Tetralones and Nitriles

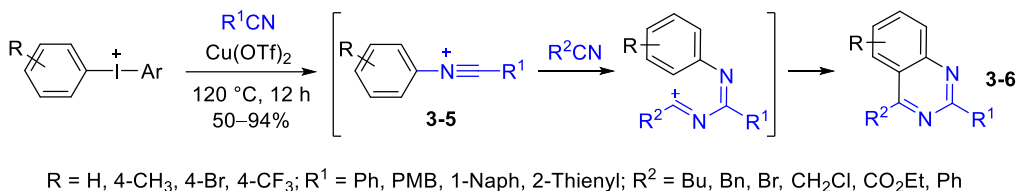
In 2013, Hua realized a TfOH-catalyzed [2+2+2] cycloaddition reaction of 1,4-diaryl-1,3-butadiyne with nitriles to synthesize quinazolines (**Scheme 3.3**).^{6b} Cycloaddition of aryl substituted 1,3-butadiynes with acetonitrile or propionitrile generated pyrimidine derivative **3-3**, followed by an intramolecular hydroarylation of the other C–C triple bond led to quinazolines **3-4**. Other Lewis acids such as CuCl₂, Cu(OTf)₂, AuCl₃, and protonic acids such as AcOH, TFA, and MeSO₃H, H₂SO₄ failed to catalyze this reaction. Although this process has notable advantages of high atom and step economy, and easy availability of starting materials, it has the limited scope for substrates and reagents.



Scheme 3.3. Synthesis of Quinazolines from 1,3-Butadiynes and Nitriles

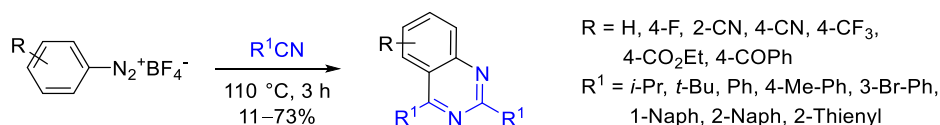
Chen developed an efficient [2+2+2] cascade annulation strategy for the synthesis of quinazolines from diaryliodoniums salts and nitriles (**Scheme 3.4**).^{6c} Reaction of diaryliodonium salt with nitrile in the presence of Cu(OTf)₂ generates reactive *N*-phenylnitrilium species **3-5**, which subsequently reacts with

another molecule of nitrile followed by an electrophilic substitution to deliver desired product **3-6**. Insertion of two different nitriles in two consecutive steps provides a high flexibility of this electrophilic annulation reaction.



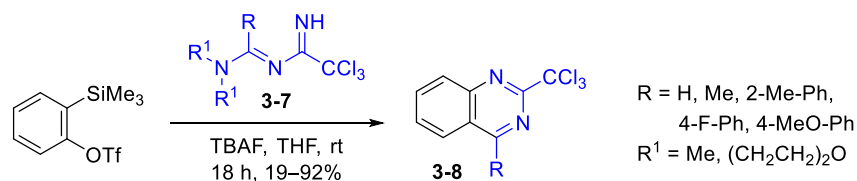
Scheme 3.4. Synthesis of Quinazolines from Diaryliodonium Salts and Nitriles

Liu and coworker developed another [2+2+2] annulation strategy for 2,4-disubstituted quinazoline synthesis by employing aryldiazonium salts with two equivalents of nitriles under thermal condition (**Scheme 3.5**).^{6c} Transition metal-free reaction conditions, readily available substrates, short reaction time, broad substrate scope, gram-scale synthesis are the advantages of this protocol.



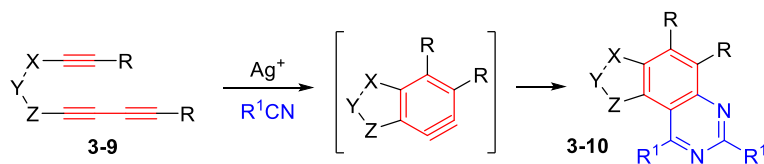
Scheme 3.5. Synthesis of Quinazolines from Aryldiazonium Salts and Nitriles

Romero-Ortega employed a [4+2] cycloaddition of aryne with 2-(trichloromethyl)-1,3-diazabutadiene **3-7** to generate 4-susbstituted 2-(trichloromethyl)quinazolines **3-8** (**Scheme 3.6**).⁷ With this methodology, a broad array of 2-trichloromethyl substituted quinazolines were synthesized in moderate to excellent yield under mild reaction conditions.



Scheme 3.6. Synthesis of Quinazolines via an Aryne Intermediate

Considering the utility of arynes, tandem processes to form arynes from non-aromatic precursors followed by trapping with nitriles would constitute an attractive strategy to synthesize quinazolines. In this regard, we envisaged that tri- and tetrayne **3-9** can be annulated to generate quinazolines **3-10** via in situ formation of an aryne followed by addition of two nitrile molecules catalyzed by silver ion (**Scheme 3.7**). If this strategy is successfully implemented, it would be a new aryne-based [A+2B] type double annulation to provide structurally diverse quinazoline derivatives. A caveat of this approach is that the 1,3-diyne moiety in **3-9** should preferentially participate in hexadehydro Diels-Alder reaction⁸ to generate an aryne intermediate before its engagement in other process.



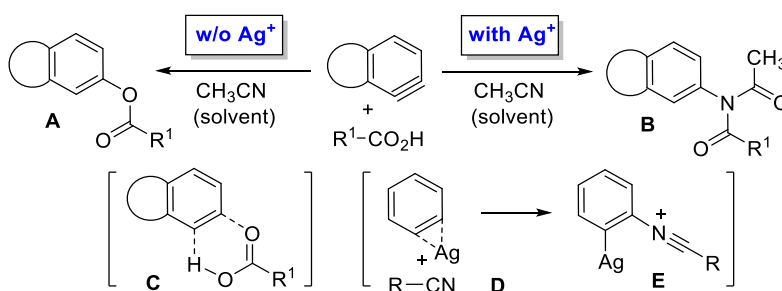
Scheme 3.7. Synthesis of Quinazolines from Multiynes via Aryne Intermediate

3.2. Results and Discussion

Silver catalysts are known to confer a profound impact on the reactivity of arynes.⁹ By employing certain silver complexes as a catalyst, we have developed many aryne-based transformations including C–H insertion,¹⁰ nucleophilic trapping,¹¹ hydroarylation,¹² hydrofluorination,¹³ hydride transfer reaction,¹⁴ and so forth.¹⁵ It was shown that the reactivity of arynes toward different nucleophiles could be switched in the absence or presence of a silver catalyst. For example, the reaction of an aryne to generate aryl ester **A** from

carboxylic acid in acetonitrile¹⁶ could be completely redirected to provide *N*-arylimide **B** in the presence of a silver complex (Scheme 3.8).^{11b} We surmised **A** is derived from a direct interaction of a more nucleophilic carboxylic acid with the aryne via **C**, whereas imide **B** results from the initial interaction of a silver-complexed aryne species with nitriles to form **D** followed by formation of a nitrilium intermediate **E**,¹⁷ which is then trapped by carboxylic acid.

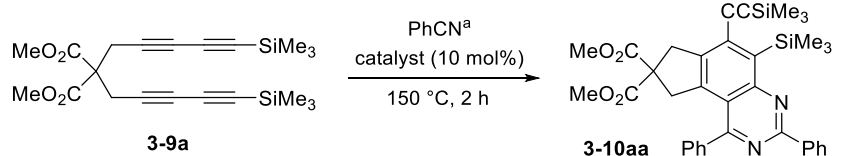
Based on these observations, we hypothesized that without carboxylic acid, the putative intermediate **E** would be trapped with another molecule of nitrile, which will set for a favorable 6-*endo-dig* cyclization¹⁸ of an organosilver moiety with the resulting nitrilium species to form a quinazoline skeleton.



Scheme 3.8. Differential Reactivity of Arynes in the Absence and Presence of Silver Catalyst

3.2.1. Optimization of Reaction Conditions

With this hypothesis in mind, we commenced our exploration with symmetric tetrayne **3-9a** and benzonitrile, and optimized the reaction conditions in terms of catalyst and temperature (Table 3.1). Among silver salts, AgSbF₆ was found to be the most effective catalyst, while other metal triflates such as Zn(OTf)₃, Mg(OTf)₂, and Sm(OTf)₃ were also effective. With AgSbF₆ (10 mol %, 150 °C, 2 h) in benzonitrile as solvent, quinazoline **3-10aa** was obtained in 97% yield (entry 4). When the reaction was carried out in toluene with 5 equivalents of benzonitrile slightly lower yield (92%) was observed. It is noteworthy that a single isomer of **3-10aa** was generated from the reaction, which was unambiguously assigned by nOe experiments.



entry	catalyst	yield (%) ^b	entry	catalyst	yield (%) ^b
1	AgOAc	5	7	Mg(OTf) ₂	91
2	Ag ₂ CO ₃	38	8	In(OTf) ₃	2
3	AgOTf	47	9	Sm(OTf) ₃	74
4	AgSbF ₆	97 ^c	10	AuCl	23
5	AgSbF ₆	92 ^d	11	Cu(OTf) ₂ ·C ₆ H ₆	34
6	Zn(OTf) ₂	93	12	none	26

^a Used as solvent. ^b NMR yields using an internal standard (1,5-difluoro-2,4-dinitrobenzene).

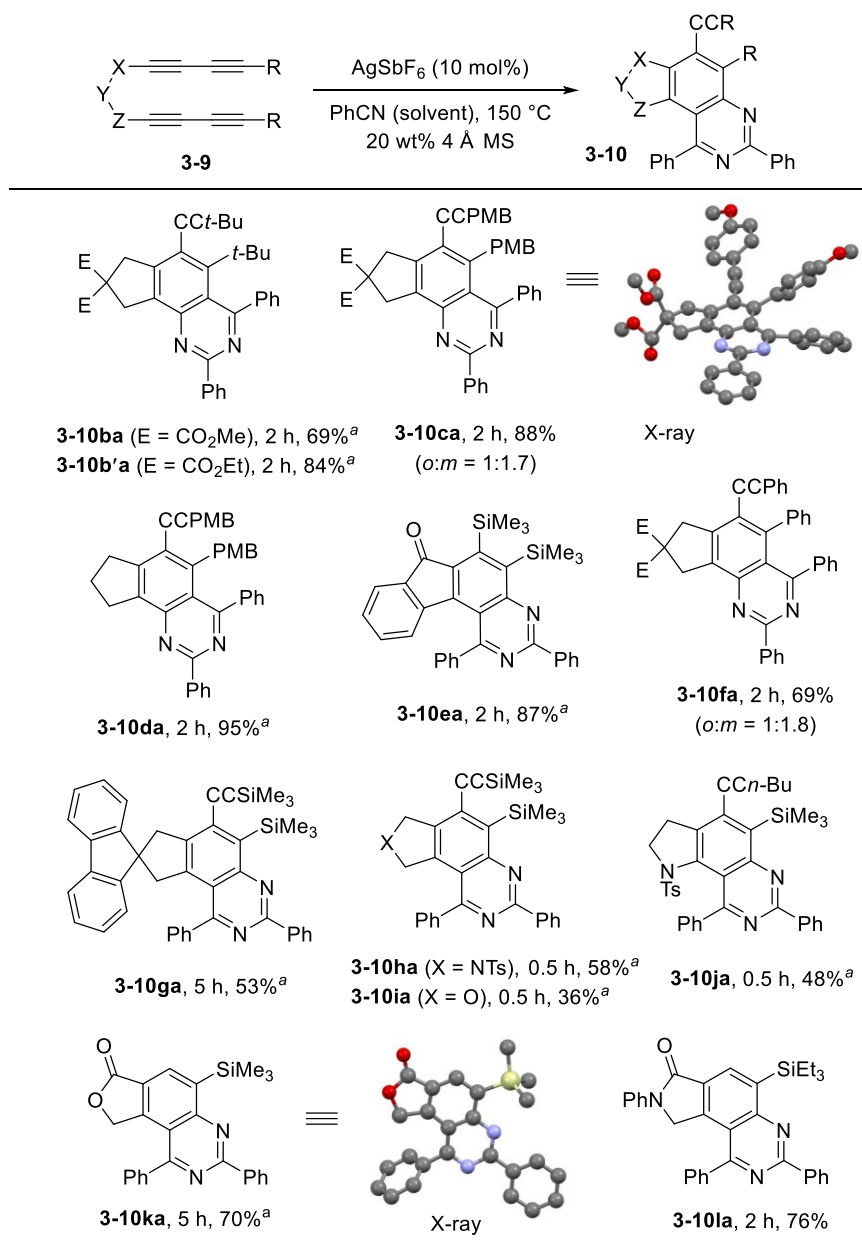
^c 92% yield at 120 °C after 12 h. ^d With 5 equiv PhCN.

Table 3.1. Optimization of Reaction Conditions

3.2.2. Scope of the Reaction

With the optimized conditions in hand, we next explored quinazoline formation from the aryne species derived from structurally different tetraynes (**3-9b** – **3-9d** and **3-9f** – **3-9j**)¹⁹ and triynes (**3-9e**, **3-9k**, **3-9l**) (Scheme 3.9). While all carbon-tethered tetraynes are generally more suitable to generate quinazolines in high yield, nitrogen- and oxygen-tethered tetraynes afford somewhat low yield of the quinazolines.²⁰ There seems to be an inverse correlation between the rate of aryne formation and the yield of quinazoline. The tetrayne precursors forming arynes slowly (2 h) result in high yield of **3-10ba–fa** in the range of 69–95%, except for **3-10ga** (5 h, 53%). On the other hand, the nitrogen- and oxygen-tethered tetraynes consumed quickly (0.5 h) tend to decompose to a larger extent, resulting in relatively lower yield of quinazolines **3-10ha** – **3-10ja** (36–58%). An ester-tethered triyne provided quinazoline **3-10ka** in 70% yield (5 h) while the corresponding amide-tethered triyne afforded **3-10la** in 76% yield (5 h). Substituents on aryne intermediates played a pivotal role for the regioselectivity of the first nitrile addition. Thus, *tert*-butyl group dictates the initial nitrile addition at the meta position from it (**3-10ba** & **3-10b'a**),²¹ whereas with the trimethylsilyl (SiMe₃) substituent,²² nitrile addition selectively occurred at the ortho position (**3-10ea**).

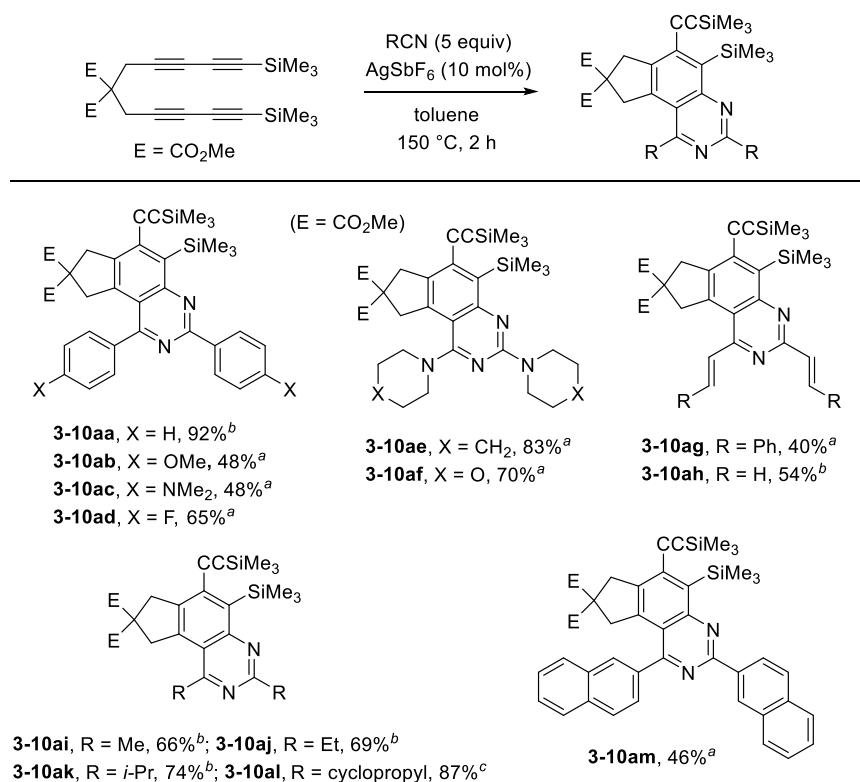
In case of aryl substituents, formation of a mixture of two isomers was observed with slight meta preference (**3-10ca** and **3-10fa**).²³ The identity of these isomers was unambiguously confirmed by X-ray diffraction analysis of **3-10ca** and **3-10ka**.²⁴



^a 20 wt% 4 Å MS was added into reaction mixture.

Scheme 3.9. Quinazoline Formation from Arynes Derived from Structurally Different Tetraynes and Triynes

Next, we examined annulation reactions of tetrayne **3-9a** with different nitriles (**Scheme 3.10**). In these reactions, the fluctuating yields with different substrates, most likely caused by adventitious water, became more consistent and improved by adding molecular sieve (4 Å, 20 wt %)²⁵ to the reaction medium. While the reaction with benzonitrile provided **3-10aa** in excellent yield (92%), with more electron-rich benzonitriles containing 4-OMe and 4-NMe₂ substituent, **3-10ab** and **3-10ac** were obtained in significantly lower yield (48%) and with 4-fluoro benzonitrile **3-10ad** was obtained in 68% yield. On the other hand, reactions with electron-rich aminonitriles such as piperidinecarbonitrile and 4-morpholinecarbonitrile afforded 2,4-diamino quinazolines²⁶ **3-10ae** and **3-10af** in 83 and 70% yield, respectively. Reactions of cinnamyl and vinyl substituted quinazolines cinnamylcarbonitrile and acrylonitrile (used as solvent) provided **3-10ag** and **3-10ah** in 40 and 54% yield. Aliphatic nitriles such as acetonitrile, propionitrile, isobutyronitrile, cyclopropane-carbonitrile provided quinazolines **3-10ai** – **3-10al** in good yield (66–87%)

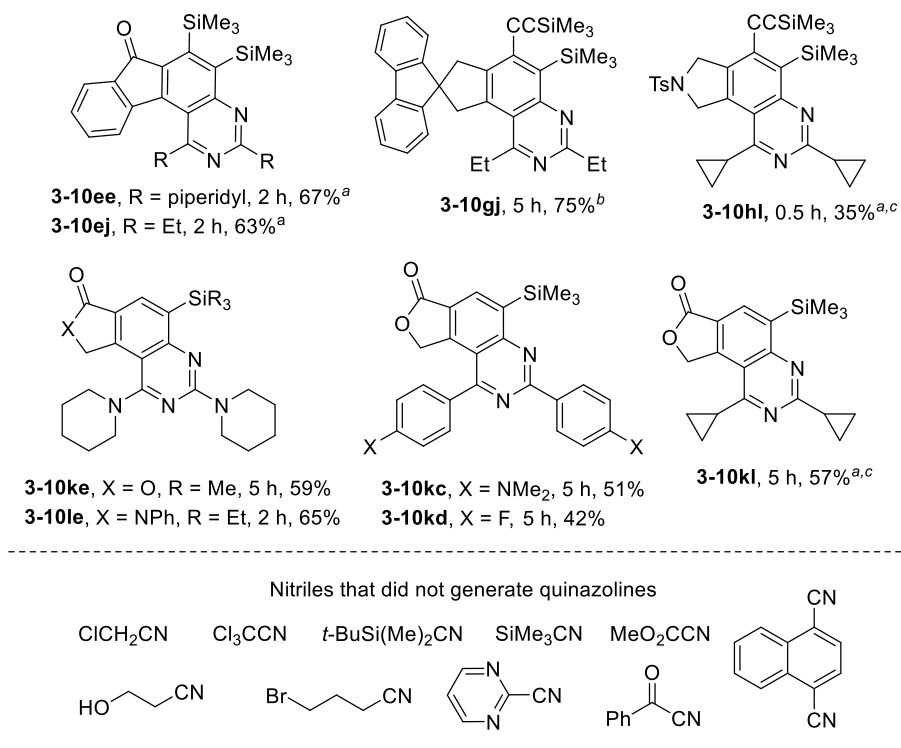


^a With 5 equiv of nitrile. ^b Nitriles used as solvent. ^c 10 Equiv nitrile was used.

Scheme 3.10. Efficiency of Quinazoline Formation with Tetrayne 3-9a and Different Nitriles

when employed as a solvent. Sterically more hindered naphthalene-2-carbonitrile (5 equiv) also provided quinazoline **3-10am** in moderate yield (46%).

Subsequently, different combinations of aryne precursors and nitriles were employed to broaden the structural space of the quinazolines (**Scheme 3.11**). The reaction of ketoarene-tethered triyne generated **3-10ee** and **3-10ej** in 67 and 63% yield within 2 h while a fluorene-tethered tetrayne generated **3-10gj** in 75% yield after 5 h. A fluorene-tethered tetrayne generated **3-10gj** in 75% yield after 5 h. A heteroatom-tethered tetrayne provided **3-10hl** within 0.5 h in marginal yield (35%) regardless of the molecular sieve additive or an increased amount of nitrile. On the other hand, an ester- or an amide-tethered triynes provided 2,4-diamino-substituted quinazolines **3-10ke** (5 h, 59%) and **3-10le** (2 h, 65%). Also, quinazolines **3-10kc** (5 h, 51%), **3-10kd** (5 h, 42%), and **3-10kl** (5 h, 57%) were generated in slightly lower yields. In general, electro-neutral or electron-rich aliphatic and aromatic nitriles can



Conditions: AgSbF₆ (10 mol%), RCN (5 equiv), toluene, 150 °C.

^a With 20 wt% 4 Å MS. ^b Nitrile as a solvent instead. ^c With 10 equiv of nitrile.

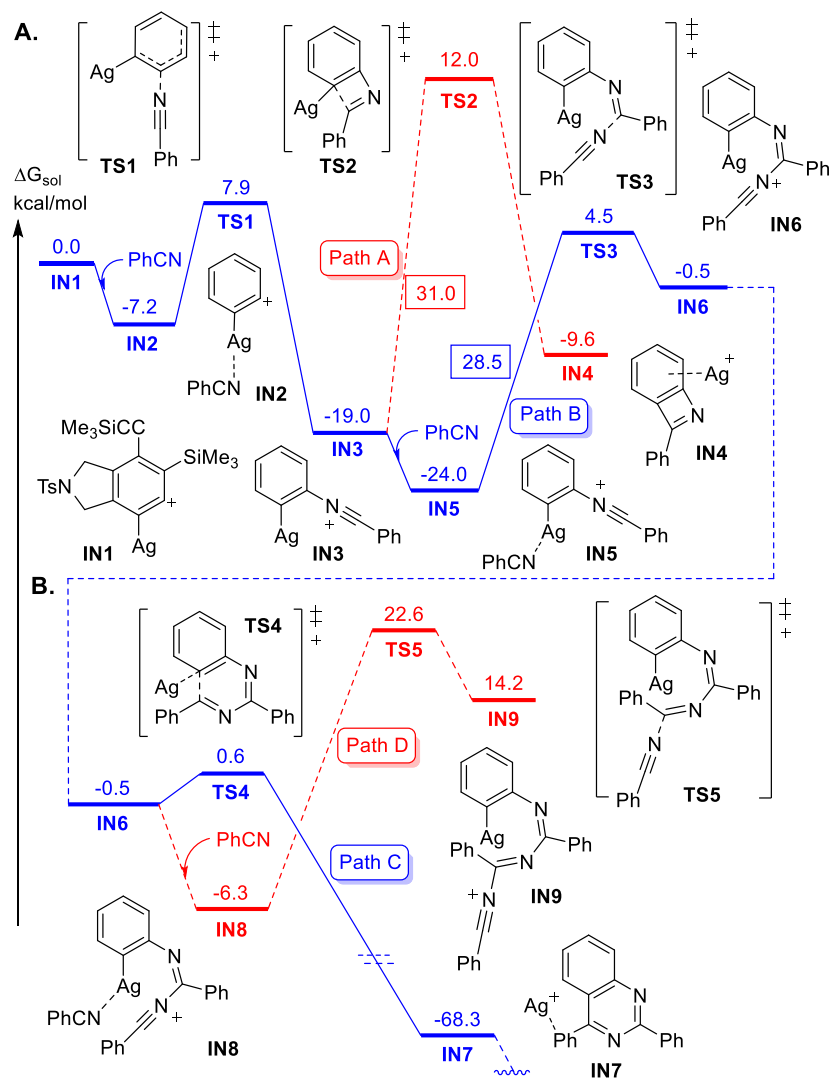
Scheme 3.11. Quinazoline Formation with Structurally Differentiated Triynes and Tetraynes with Various Nitriles

participate in the reaction with arynes to furnish 2,4-disubstituted quinazoline derivatives in moderate to high yield. On the other hand, the reaction with electron-deficient nitriles or nitriles containing a sensitive functional group (see in the legend of **Scheme 3-11**) provided no or low yield of quinazoline products.

3.2.3. DFT Studies

To gain further insight into the reaction mechanism and regioselectivity, we carried out DFT calculations²⁷ (SMD/M06/6-311++G(d,p)/SDD//B3LYP/631G*/Lanl2dz level of theory)²⁸ (**Scheme 3.12A**). Calculations employed an *N*Ts-tethered tetrayne (**3-9h**) that leads to product **3-10ha**). These calculated reaction profiles²⁷ indicate that silver-complexed aryne (**IN1**) interacts with benzonitrile forms a more stable complex **IN2**, from which nitrilium species **IN3** could be formed via **TS1**. In the next step, intermediate **IN3** could undergo ring closure to generate azabicyclo **IN4**²⁹ in Path A but it requires high barrier (31 kcal/mol). On the other hand, **IN3** interacts with another benzonitrile to generate **IN5** exergonically in Path B. Due to a highly stabilized nature of an ionic complex **IN5**, its conversion to bis-nitrile adduct **IN6** via **TS3** requires an activation barrier of 28.5 kcal/mol, being 2.5 kcal/mol lower than the highest barrier in Path A.

Once intermediate **IN6** is generated in Path B, it can take two different reaction paths leading to ring closure or triple nitrile adduct formation (**Scheme 3.12B**). The barrier for ring closure of **IN6** via **TS4** is only 1.1 kcal/mol (Path C), affording silver-complexed quinazoline **IN7**. On the other hand, the stabilized nitrile complex **IN8** formed from **IN6** in Path D should overcome a much higher barrier of 28.9 kcal/mol to proceed to the next intermediate **IN9**. Thus, the thermodynamically and kinetically favorable formation of **IN7** in Path C provides the observed quinazoline product **3-10ha**.



Scheme 3.12. A. DFT-Calculated Reaction Profiles for Selective Formation of Intermediate IN6 over IN4 (IN1 is the Actual Structure and the Rest Structures are Abbreviated). B. Reaction Profiles Leading to Quinazoline over Triple Nitrile Adduct.

3.4. Conclusion

In summary, we have developed an efficient [A+2B] annulation of aryne with nitriles to form quinazolines under silver-catalyzed conditions. Structurally diverse and noble polysubstituted quinazolines could be synthesized by tuning the aryne precursors, structure and stoichiometry of nitriles, catalyst, temperature, and reaction time. Both tetraynes and electronically activated triynes readily undergo hexadehydro Diels-Alder reaction before other undesired reactions of the diyne moiety, thus serve as an

effective platform for quinazoline formation. This double annulation process shows excellent regioselectivity, where a silyl group on the aryne intermediate plays a pivotal role to steer the initial addition of nitrile at its ortho position. DFT calculations provided important insight into the mechanism and selectivity for the formation of the observed quinazoline product from this silver catalyzed [A+2B] annulation reaction of arynes.

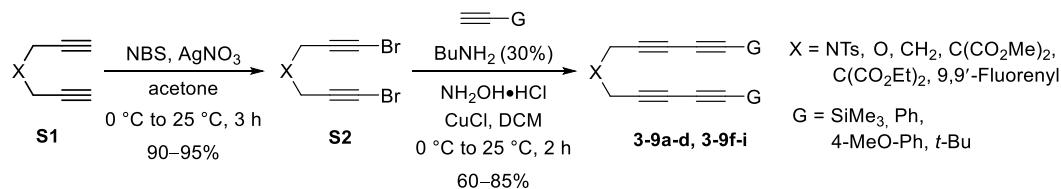
3.5. Experimental Details

3.5.1. General Information

All reactions were carried out in oven or flame-dried glassware unless otherwise noted. Reagents which were commercially available, were purchased from Sigma - Aldrich, Alfa Aesar, Acros, and Oakwood Products unless otherwise noted. Known compounds were prepared according to literature procedure. Anhydrous acetonitrile from Sigma-Aldrich was distilled over calcium hydride (CaH_2) 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). Yield was calculated on basis of chromatographically and spectroscopically pure isolated compound. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AV-500 spectrometer. ^1H NMR chemical shifts (δ) were reported in parts per million (ppm) downfield of TMS and were referenced relative to the residual proteated solvent peak (CDCl_3 (7.26 ppm)). ^{13}C chemical shifts (δ) were reported in parts per million downfield of TMS and are referenced to the carbon resonance of the solvent (CDCl_3 , δ 77.2 ppm). Multiplicities in ^1H NMR were abbreviated by s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sext (sextet), sept (septet) 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 centre 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 (Waters Corporation, Milford, MA, USA) at the University of Illinois at Urbana-Champaign. Electron impact (EI) mass spectra was obtained using a Micromass 70-VSE (Waters Corporation, Milford, MA, USA) at the University of Illinois at Urbana-Champaign.

3.5.2. Experimental Procedures

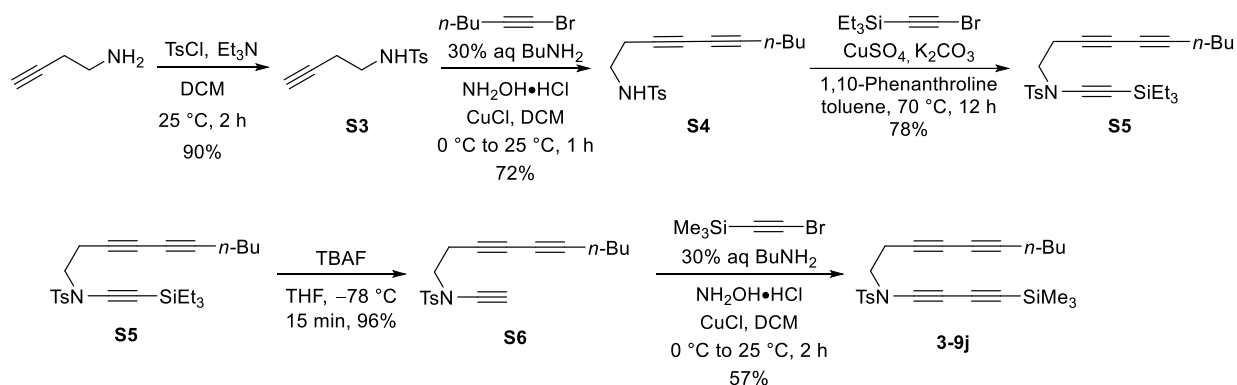
Synthesis of Symmetrical *bis*-1,3-Diyne (3-9a-d, 3-9f-i)



To a stirred solution of diyne (10.0 mmol) in acetone at 0 °C, *N*-bromosuccinimide (25.0 mmol) and AgNO₃ (1.0 mmol) were added sequentially under N₂ atmosphere in the dark. After addition, the ice bath was removed and stirring was continued for additional 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, EtOAc–hexane, 1:5 to 1:3) provided dibromide (**S2**) in excellent yield.

To a mixture of 30% aq. *n*-BuNH₂ (10 mL, 2 mL per 1 mmol of terminal alkyne) and CuCl (1.5 mmol) in a two-necked round-bottom flask, a solution of terminal alkyne (5.0 mmol) in CH₂Cl₂ was added slowly at 0 °C under N₂ atmosphere. Then **S2** (2.0 mmol) diluted in CH₂Cl₂ was added dropwise into the reaction mixture over 45 min. After 5 min, the ice bath was removed and stirring was continued for additional 1–2 h at room temperature (TLC monitoring). A pinch of NH₂OH·HCl was added several times into the reaction mixture when the solution becomes blue. The reaction was quenched by a sat. solution of NH₄Cl and extracted with CH₂Cl₂. The combined organic extracts were washed with water and brine sequentially and dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO, EtOAc–hexane, 1:20 to 1:10) to isolate pure symmetrical *bis*-1,3-diyne in moderate to good yield.

Synthesis of Unsymmetrical *bis*-1,3-Diyne (3-9j)



To a stirred solution of 3-butyne-1-amine (1.5 g, 21.7 mmol) in CH₂Cl₂ at 25 °C, Et₃N (4.4 g, 43.4 mmol) and 4-toluenesulfonyl chloride (4.1 g, 21.7 mmol) were added sequentially under N₂. After 2 h, the reaction mixture was quenched with sat. NaHCO₃ and extracted with CH₂Cl₂ (X2). The combined organic extracts were washed with water and brine and dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. Crude **S3** (4.3 g, 90%) was subjected to the next reaction without further purification.

To a mixture of 30% aq. *n*-BuNH₂ (9 mL) and CuCl (133 mg, 1.3 mmol) in a two-necked round-bottom flask, a solution of **S3** (1.0 g, 4.5 mmol) in CH₂Cl₂ was added slowly at 0 °C under N₂ atmosphere.³ Then 1-bromohex-1-yne, (598 mg, 3.7 mmol) diluted in CH₂Cl₂ was added dropwise into the reaction mixture over 30 min. After 5 min, the ice bath was removed and stirring was continued for additional 1 h at room temperature. A pinch of NH₂OH·HCl was added several times into reaction mixture when the solution becomes blue. The reaction was quenched by a sat. solution of NH₄Cl and extracted with CH₂Cl₂. The combined organic extracts were washed with water and brine sequentially and dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO, EtOAc–hexane, 1:10) to isolate pure diyne tosylamide **S4** (980 mg, 72%).

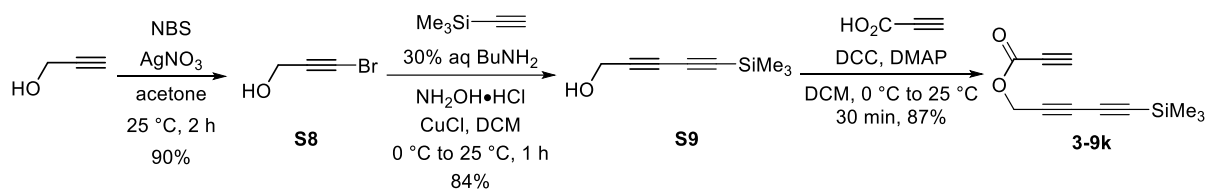
To a stirred solution of **S4** (500 mg, 1.6 mmol) in PhCH₃, CuSO₄ (62 mg, 0.2 mmol), 1,10-phenanthroline (88 mg, 0.5 mmol), and K₂CO₃ (458 mg, 3.3 mmol) were sequentially added under N₂ atmosphere at room temperature. After dropwise addition of (bromoethynyl)triethylsilane (440 mg, 2.5

mmol) in PhCH₃, the reaction mixture was warmed up to 70 °C. After 12 h, the reaction mixture was filtered through silica and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO, EtOAc–hexane, 1:10) to isolate pure triyne **S5** (513 mg, 78%).

To a stirred solution of **S5** (513 mg, 1.3 mmol) in dry THF was added TBAF (1.4 mL, 1 M solution in THF, 1.4 mmol) slowly at –78 °C under N₂ atmosphere. After 15 min, the reaction mixture was quenched with sat. NH₄Cl and extracted with EtOAc (X2). The combined organic extracts were washed with water and brine sequentially and dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. Crude **S6** (400 mg, 96%) was subjected to the next reaction without further purification.

To a mixture of 30% aq. *n*-BuNH₂ (2.5 mL) and CuCl (36 mg, 0.4 mmol) in a two-necked round-bottom flask, a solution of **S6** (400 mg, 1.2 mmol) in CH₂Cl₂ was added slowly at 0 °C under N₂ atmosphere. Then (bromoethynyl)trimethylsilane, (324 mg, 1.8 mmol) diluted in CH₂Cl₂ was added dropwise into the reaction mixture over 30 min. After 5 min, the ice bath was removed and stirring was continued for additional 1 h at room temperature. A pinch of NH₂OH·HCl was added several times into reaction mixture when the solution becomes blue. The reaction was quenched by a sat. solution of NH₄Cl and extracted with CH₂Cl₂. The combined organic extracts were washed with water and brine sequentially and dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO, EtOAc–hexane, 1:15) to isolate pure tetrayne **3-9j** (294 mg, 72%).

Procedure for Synthesis of a Triyne with an Ester Linker (3-9k)



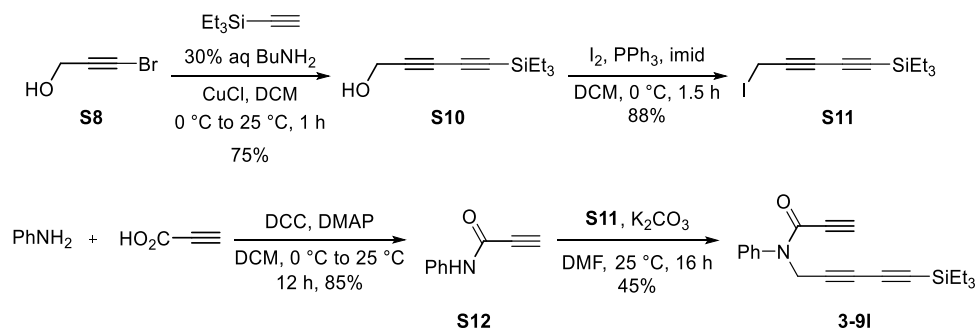
To a stirred solution of 2-propyn-1-ol (5.0 g, 89.1 mmol) in acetone at 0 °C, *N*-bromosuccinimide (19.8 g, 111.5 mmol) and AgNO₃ (1.5 g, 8.9 mmol) were added sequentially under N₂ atmosphere in the dark. After addition, the ice bath was removed and stirring was continued for additional 2 h at room

temperature. Upon complete consumption of alkyne, the reaction mixture was concentrated under reduced pressure and filtered through silica gel. Purification by flash column chromatography (SiO, EtOAc–hexane, 1:5) provided pure bromide **S8** in excellent yield (7.9 g, 90%).

To a mixture of 30% aq. *n*-BuNH₂ (22 mL) and CuCl (329 mg, 3.3 mmol) in a two-necked round-bottom flask, a solution of ethynyltrimethylsilane (1.1 g, 11.1 mmol) in CH₂Cl₂ was added slowly at 0 °C under N₂ atmosphere. Then bromide **S8** (1.0 g, 7.4 mmol) diluted in CH₂Cl₂ was added dropwise over 30 min. After 5 min, the ice bath was removed and stirring was continued for additional 1 h. A pinch of NH₂OH·HCl was added several times into the reaction mixture when the solution becomes blue. The reaction was quenched by a sat. solution NH₄Cl and extracted with CH₂Cl₂. The combined organic extracts were washed with water and brine sequentially and dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO, EtOAc–hexane, 1:10) to isolate pure 2,4-diyne-1ol **S9** in excellent yield (1.0 g, 84%).

To a solution of **S9** (500 mg, 3.3 mmol) and propiolic acid (276 mg, 4.0 mmol) in CH₂Cl₂ at 0 °C, DCC (814 mg, 4.0 mmol) and DMAP (40 mg, 0.3 mmol) were added sequentially under N₂ atmosphere. After addition, the ice bath was removed and stirring was continued at room temperature for additional 30 min. Then, the reaction mixture was concentrated under vacuum and the crude material was purified by flash column chromatography (SiO, EtOAc–hexane, 1:15) to isolate pure triyne **3-9k** (584 mg, 87%).

Procedure for Synthesis of a Triyne with a Phenylamide Linker (3-9l)



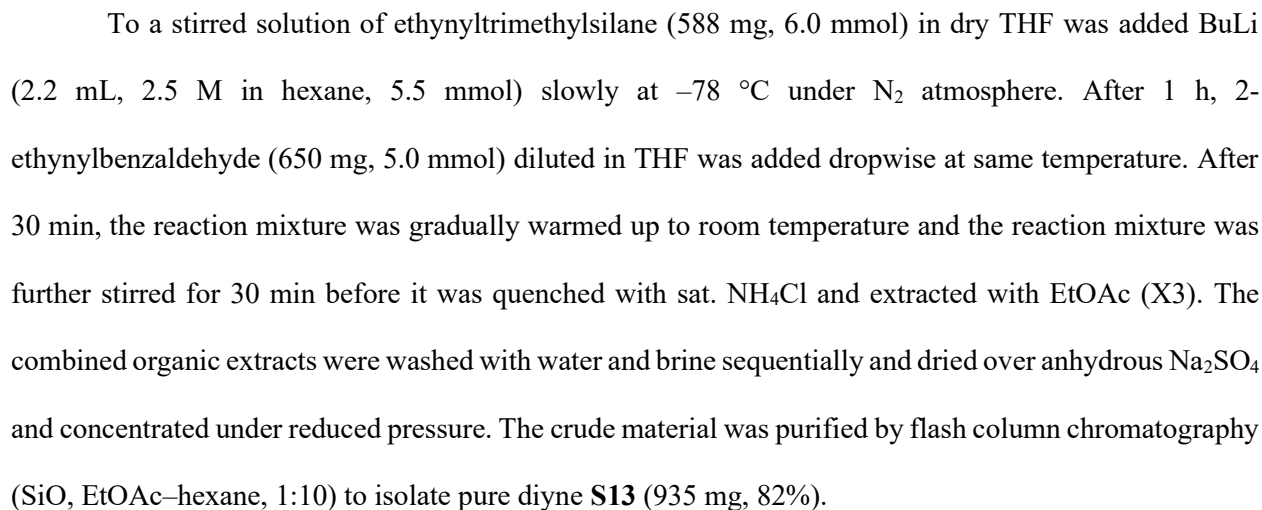
To a mixture of 30% aq. *n*-BuNH₂ (22.2 mL) and CuCl (331 mg, 3.4 mmol) in a two-necked round-bottom flask, a solution of triethyl(ethynyl)silane (1.6 g, 11.2 mmol) in CH₂Cl₂ was added slowly at 0 °C under N₂ atmosphere. Then **S8** (1.0 g, 7.4 mmol) diluted in CH₂Cl₂ was added dropwise into the reaction mixture over 30 min. After 5 min, the ice bath was removed and stirring was continued for additional 1 h. A pinch of NH₂OH·HCl was added several times into the reaction mixture when the solution becomes blue. The reaction was quenched by a sat. solution NH₄Cl and extracted with CH₂Cl₂. The combined organic extracts were washed with water and brine sequentially and dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO, EtOAc–hexane, 1:10) to isolate pure 2,4-diyne-1ol **S10** (1.1 g, 75%).

To a stirred solution of 2,4-diyne-1ol **S10** (0.8 g, 4.1 mmol) in CH₂Cl₂ at 0 °C, PPh₃ (1.2 g, 4.5 mmol), I₂ (1.2 g, 4.5 mmol), and imidazole (308 mg, 4.5 mmol) were added sequentially under N₂ atmosphere and continued stirring at same temperature. After 1.5 h, the reaction mixture was quenched by a sat. solution of Na₂S₂O₃ and extracted with CH₂Cl₂. The combined organic extracts were washed with water and brine sequentially and dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO, EtOAc–hexane, 1:20) to isolate pure propargyl iodide **S11** (1.1 g, 88%).

To a stirred solution of aniline (1.0 g, 10.8 mmol) and propiolic acid (0.8 g, 11.8 mmol) in Et₂O at 0 °C, DCC (2.7 g, 12.9 mmol) and DMAP (131 mg, 1.1 mmol) were added sequentially under N₂ atmosphere. After addition, the ice bath was removed and stirring was continued for 12 h at 25 °C. Upon complete consumption of aniline, the reaction mixture was concentrated under reduced pressure and purified by flash column chromatography (SiO, EtOAc–hexane, 1:3) to isolate pure phenylamide **S12** (1.3 g, 85%).

To stirred solution of phenylamide **S12** (286 mg, 2.0 mmol), and propargyl iodide **S11** (500 mg, 1.6 mmol) in DMF at 25 °C, K₂CO₃ (452 mg, 3.3 mmol) was added under N₂ atmosphere. After 16 h, the reaction mixture was diluted by water and extracted with EtOAc (X3). The combined organic extracts were

Procedure for Synthesis of a Triyne with a Benzoyl Linker (3-9e)

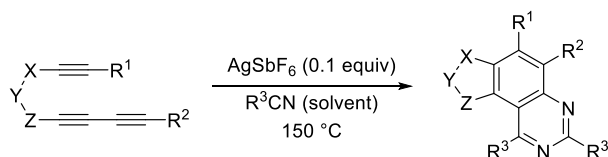


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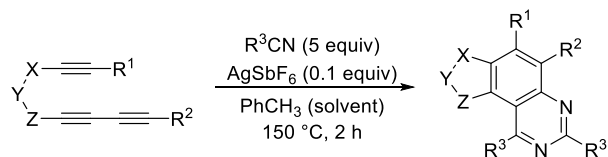
and dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO, EtOAc–hexane, 1:15) to isolate pure triyne **S14** (480 mg, 65%).

To a stirred solution of **S14** (480 mg, 1.5 mmol) in CH₂Cl₂, MnO₂ (645 mg, 7.4 mmol) was added in one portion under N₂ atmosphere at room temperature. After 2 h, the reaction mixture was filtered through celite and concentrated under reduced pressure. Crude **3-9e** (453 mg, 95%) was subjected to the next reaction without further purification.

General Procedure for Generation of Quinazoline



Procedure A: A multiyne substrate (0.1 mmol) and AgSbF₆ (0.01 mmol) in nitrile (3 mL) in a Schlenk tube was flushed with nitrogen. The mixture was stirred for 0.5 to 5 h at 150 °C unless otherwise noted. The reaction mixture was concentrated, and then directly subjected to flash column chromatography (SiO, EtOAc–hexane, 1:10 to 1:3) to isolate pure quinazoline product.

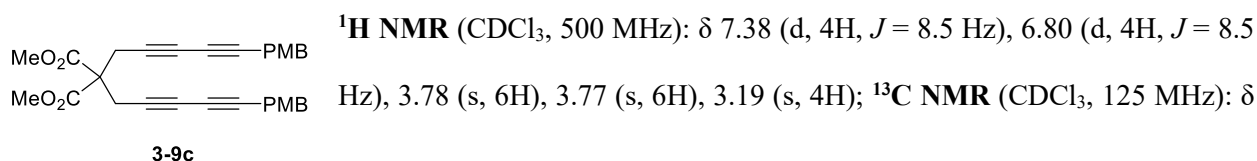
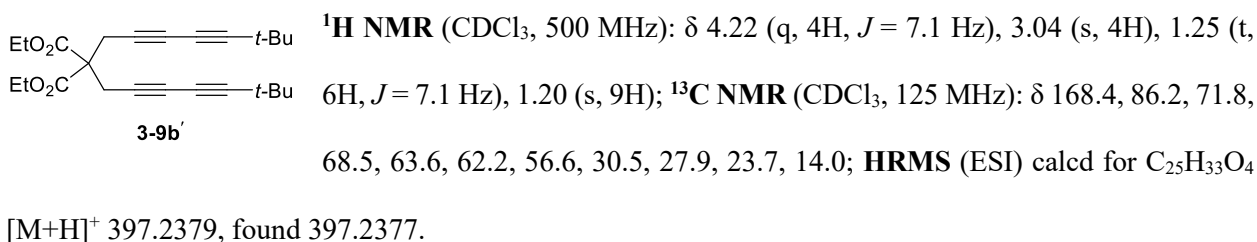
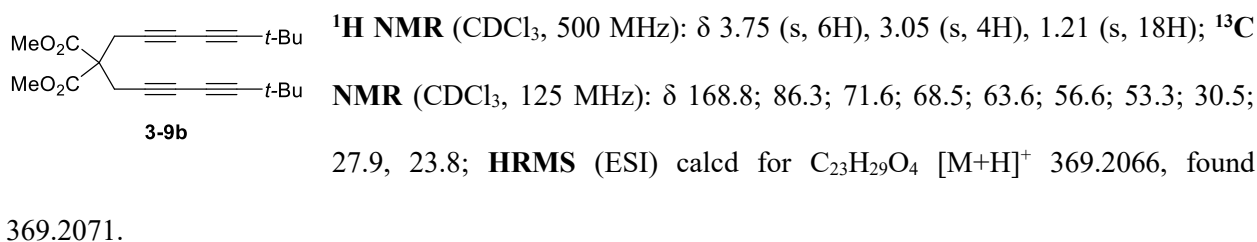
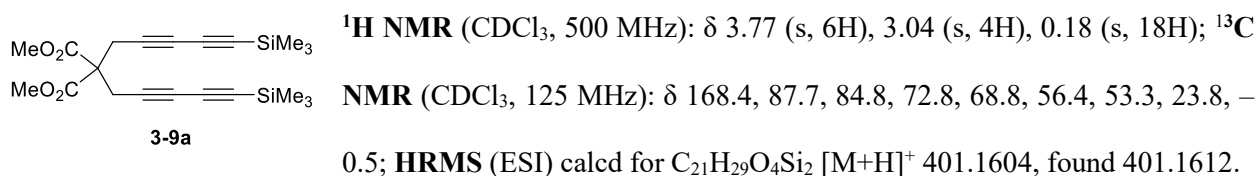


Procedure B: A multiyne substrate (0.1 mmol), nitrile (0.5 mmol) and AgSbF₆ (0.01 mmol) in dry PhCH₃ (3 mL) in a Schlenk tube was flushed with nitrogen. The mixture was stirred for 0.5 to 5 h at 150 °C unless otherwise noted. The reaction mixture was concentrated, and then directly subjected to flash column chromatography (SiO, EtOAc–hexane, 1:10 to 1:3) to isolate pure quinazoline product.

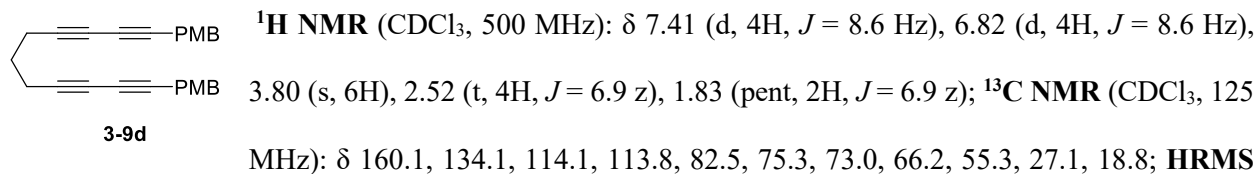
Preparation of Quinazoline 3-10aa in 1.0 mmol Scale

Multiyne substrate 1a (400 mg, 1.0 mmol) and AgSbF₆ (34.4 mg, 0.1 mmol) in benzonitrile (10 mL) in a Schlenk tube was flushed with nitrogen. The mixture was stirred for 2h at 150 °C. The reaction mixture was concentrated, and then directly subjected to flash column chromatography (SiO, EtOAc–hexane, 1:10 to 1:3) to isolate pure quinazoline **3-10aa** (533 mg, 88% yield).

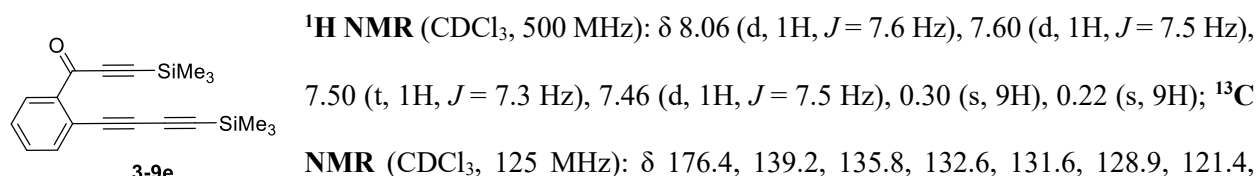
3.5.3. Characterization Data



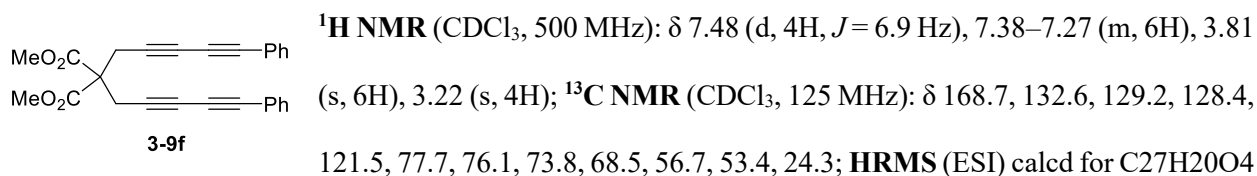
168.7, 160.3, 134.2, 114.1, 113.4, 77.0, 76.2, 72.6, 68.7, 56.7, 55.3, 53.4, 24.2; **HRMS** (ESI) calcd for $C_{29}H_{25}O_6$ $[M+H]^+$ 469.1651, found 469.1666.



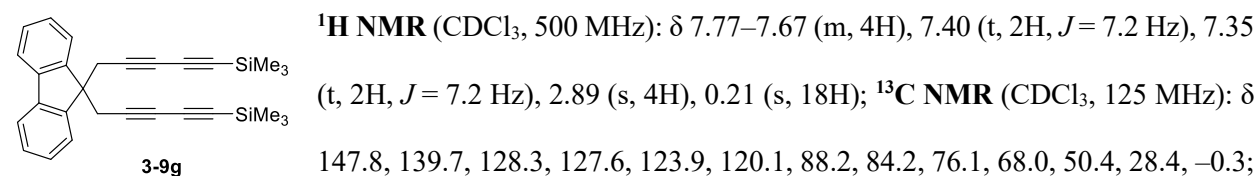
(ESI) calcd for $C_{25}H_{21}O_2$ $[M+H]^+$ 353.1542, found 353.1556.



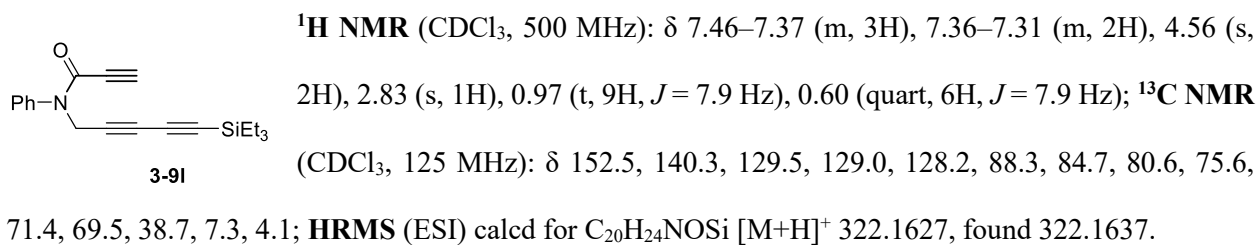
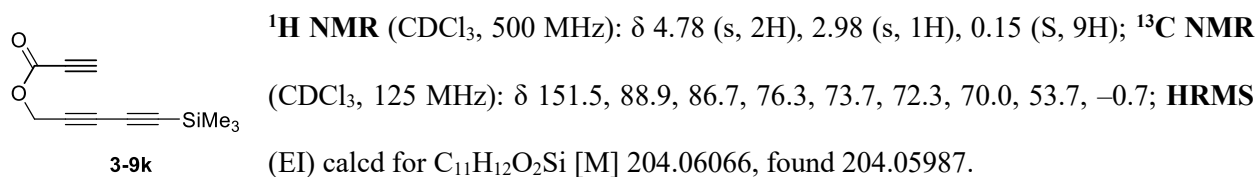
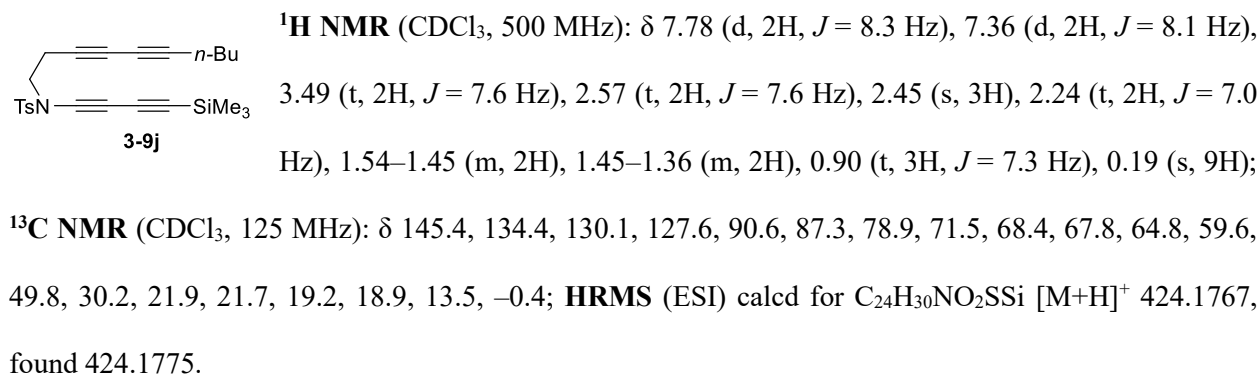
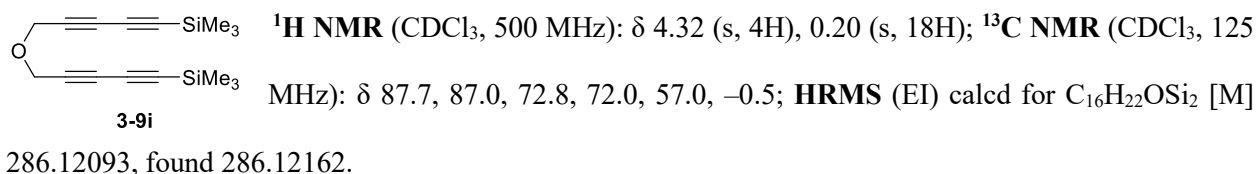
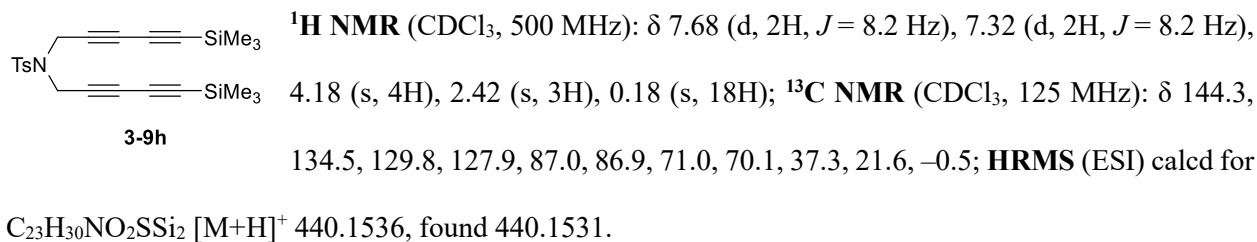
101.8, 101.4, 93.0, 88.1, 80.3, 74.5, -0.4, -0.7; **HRMS** (ESI) calcd for $C_{19}H_{23}OSi_2$ $[M+H]^+$ 323.1287, found 323.1288.

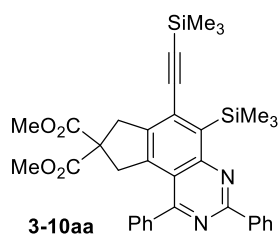


$[M+H]^+$ 409.1440, found 409.1455.

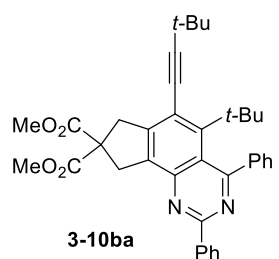


HRMS (EI) calcd for $C_{29}H_{30}Si_2$ $[M]$ 434.18861, found 434.18865.

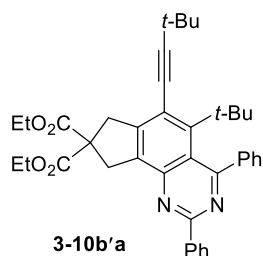




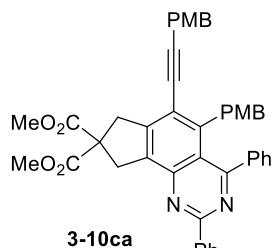
3-10aa: This product was synthesized using procedure **A** and isolated in 92% yield after stirring the reaction mixture for 2 h. **¹H NMR** (CDCl₃, 500 MHz): δ 8.64–8.60 (m, 2H), 7.60–7.44 (m, 8H), 3.73 (s, 2H), 3.69 (s, 6H), 3.14 (s, 2H), 0.64 (s, 9H), 0.31 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 171.8, 167.9, 157.3, 156.8, 142.3, 140.5, 138.1, 136.4, 131.5, 130.3, 129.5, 129.0, 128.7, 128.5, 128.3, 118.8, 105.9, 103.8, 59.1, 53.0, 43.0, 41.4, 2.9, –0.3; **HRMS** (ESI) calcd for C₃₅H₃₉N₂O₄Si₂ [M+H]⁺ 607.2448, found 607.2450.



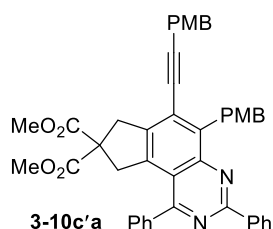
3-10ba: This product was synthesized using procedure **A** (20 wt% 4 Å MS was added into reaction mixture) and isolated in 69% yield after stirring the reaction mixture for 2 h. **¹H NMR** (CDCl₃, 500 MHz): 8.65 (d, 2H, *J* = 7.0 Hz), 8.48 (br, 1H), 7.76–7.26 (m, 6H), 7.07 (br, 1H), 4.16 (s, 2H), 3.97–3.69 (m, 8H), 1.41 (s, 9H), 1.31 (s, 9H); **¹³C NMR** (CDCl₃, 125MHz): δ 172.4, 165.6, 156.5, 151.9, 148.5, 147.3, 144.5, 137.1, 133.6, 131.0 (br), 130.5, 130.3, 128.6 (br), 128.5, 120.9, 119.7, 111.1, 78.7, 58.6, 53.1, 42.8, 39.6, 39.5, 31.4, 30.7; **HRMS** (ESI) calcd for C₃₇H₃₉N₂O₄ [M+H]⁺ 575.2910, found 575.2919.



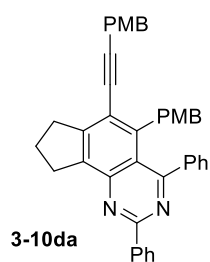
3-10b'a: This product was synthesized using procedure **A** (20 wt% 4 Å MS was used as additive) and isolated in 84% yield after stirring the reaction mixture for 2 h. **¹H NMR** (CDCl₃, 500 MHz): δ 8.65 (d, 2H, *J* = 7.8 Hz), 8.48 (br, 1H), 7.69–7.40 (m, 6H), 7.11 (br, 1H), 4.40–4.04 (m, 6H), 3.87 (d, 2H, *J* = 8.1 Hz), 1.41 (s, 9H), 1.37–1.22 (m, 6H), 1.31 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 171.9, 165.6, 156.4, 151.7, 148.5, 147.5, 144.5, 137.1, 133.7, 130.4, 130.2, 129.1, 128.5, 128.4, 120.9, 119.7, 111.0, 78.7, 61.8, 58.7, 42.7, 39.5, 31.4, 30.6, 29.7, 28.8, 14.1; **HRMS** (ESI) calcd for C₃₉H₄₃N₂O₄ [M+H]⁺ 603.3223, found 603.3207.



3-10ca: This product was synthesized using procedure **A** and isolated in 66% yield after stirring the reaction mixture for 2 h. **¹H NMR** (CDCl₃, 500 MHz): δ 8.71 (d, 2H, *J* = 7.8 Hz), 7.56–7.46 (m, 3H), 7.30–7.20 (m, 4H), 7.14–7.02 (m, 5H), 6.81 (d, 2H, *J* = 8.7 Hz), 6.56 (d, 2H, *J* = 8.5 Hz), 4.34 (s, 2H), 4.06 (s, 2H), 3.86 (s, 6H), 3.80 (s, 3H), 3.72 (s, 3H); **¹³C NMR** (CDCl₃, 125 MHz): δ 172.3, 159.9, 158.6, 149.1, 146.4, 141.7, 140.5, 137.7, 136.3, 133.0, 132.8, 131.5, 130.6, 130.0, 128.7, 128.5, 128.1, 127.3, 121.0, 120.1, 115.2, 114.0, 112.7, 97.9, 86.3, 59.0, 55.3, 53.2, 42.7, 39.9; **HRMS** (ESI) calcd for C₂₆H₃₇N₂O₃SSi₂ [M+H]⁺ 513.2063, found 513.2068.

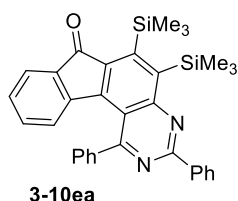


3-10c'a: This product was synthesized using procedure **A** and isolated as inseparable mix with 2ca in 88% overall yield after stirring the reaction mixture for 2 h. **¹H NMR** (CDCl₃, 500 MHz): 8.51–8.43 (m, 2H), 7.74 (d, 2H, *J* = 8.6 Hz), 7.63–7.55 (m, 5H), 7.45–7.39 (m, 3H), 7.33 (d, 2H, *J* = 8.7 Hz), 7.12 (d, 2H, *J* = 8.6 Hz), 6.86 (d, 2H, *J* = 8.7 Hz), 3.97 (s, 3H), 3.90 (s, 2H), 3.83 (s, 3H), 3.72 (s, 6H), 3.20 (s, 2H); **¹³C NMR** (CDCl₃, 125 MHz) : δ (all discernible signals for both isomers) 172.3, 171.8, 168.7, 167.7, 160.2, 159.9, 159.1, 158.6, 158.4, 150.5, 149.1, 146.4, 141.7, 141.4, 140.8, 140.5, 138.1, 137.7, 136.3, 134.2, 133.3, 133.3, 133.0, 132.8, 131.5, 130.7, 130.3, 130.0, 129.5, 129.3, 129.1, 128.7, 128.5, 128.4, 128.3, 128.1, 127.3, 124.8, 121.0, 120.1, 119.3, 115.2, 114.9, 114.1, 114.0, 112.7, 112.6, 99.6, 97.9, 86.3, 59.3, 59.0, 55.4, 55.3, 53.2, 53.1, 42.9, 42.7, 41.3, 40.0, 29.7.

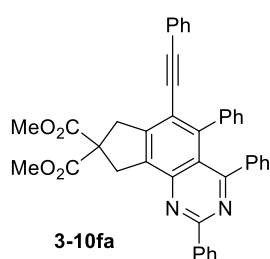


3-10da: This product was synthesized using procedure **A** (20 wt% 4 Å MS was used as additive) and isolated in 95% yield after stirring the reaction mixture for 2 h. **¹H NMR** (CDCl₃, 500 MHz): δ 8.73–8.69 (m, 2H), 7.58–7.45 (m, 3H), 7.31–7.27 (m, 2H), 7.22 (d, 2H, *J* = 8.8 Hz), 7.13–7.02 (m, 5H), 6.80 (d, 2H, *J* = 8.8 Hz), 6.56 (d, 2H, *J* = 8.6 Hz), 3.80 (s, 3H), 3.72 (s, 3H), 3.65 (t, 2H, *J* = 7.5 Hz), 3.39 (t, 2H, *J* = 7.6 Hz), 2.38 (pent, 2H, *J* = 7.5 Hz); **¹³C NMR** (CDCl₃, 125 MHz): δ 168.5, 159.7, 158.5, 158.4, 150.9, 149.6, 140.8,

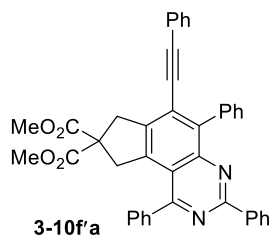
140.6, 140.4, 138.0, 132.9, 131.9, 130.4, 130.0, 128.6, 128.4, 128.0, 127.3, 120.7, 120.6, 115.5, 114.0, 112.7, 97.2, 87.0, 55.3, 35.1, 31.6, 24.0; **HRMS** (ESI) calcd for $C_{39}H_{31}N_2O_2$ $[M+H]^+$ 559.2386, found 559.2369.



3-10ea: This product was synthesized using procedure **A** (20 wt% 4 Å MS was used as additive) and isolated in 87% yield after stirring the reaction mixture for 2 h. **¹H NMR** ($CDCl_3$, 500 MHz): δ 8.75 (d, 2H, $J = 7.7$ Hz), 7.91 (d, 2H, $J = 7.5$ Hz), 7.61–7.52 (m, 5H), 7.51–7.46 (m, 2H), 7.09 (t, 1H, $J = 7.4$ Hz), 6.88 (t, 1H, $J = 7.6$ Hz), 5.98 (d, 1H, $J = 7.7$ Hz), 0.61 (s, 9H), 0.54 (s, 9H); **¹³C NMR** ($CDCl_3$, 125 MHz): δ 195.1, 167.0, 159.0, 157.0, 155.5, 143.5, 143.1, 140.4, 137.6, 133.3, 133.0, 130.9, 130.6, 128.9, 128.8, 128.7, 128.6, 126.2, 123.1, 115.3, 3.8, 2.8; **HRMS** (ESI) calcd for $C_{33}H_{33}N_2OSi_2$ $[M+H]^+$ 529.2131, found 529.2148.

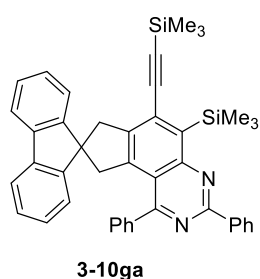


3-10fa: This product was synthesized using procedure **A** and isolated in 44% yield after stirring the reaction mixture for 2 h. **¹H NMR** ($CDCl_3$, 500 MHz): δ 8.74–8.69 (m, 2H), 7.56–7.48 (m, 3H), 7.31–7.22 (m, 7H), 7.19–7.14 (m, 2H), 7.11–7.00 (m, 6H), 4.36 (s, 2H), 4.08 (s, 2H), 3.86 (s, 6H); **¹³C NMR** ($CDCl_3$, 125 MHz): δ 172.2, 168.8, 158.9, 149.3, 146.4, 142.6, 140.4, 138.8, 137.6, 136.7, 131.9, 131.5, 130.7, 130.4, 130.0, 128.8, 128.7, 128.5, 128.4, 128.3, 127.3, 127.2, 127.1, 123.0, 120.7, 120.0, 97.8, 87.2, 59.0, 53.3, 42.7, 40.0; **HRMS** (ESI) calcd for $C_{41}H_{31}N_2O_4$ $[M+H]^+$ 615.2284, found 615.2299.



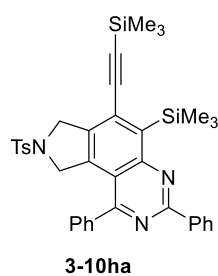
3-10fa: This product was synthesized using procedure **A** and isolated as inseparable mix with 2fa in 69% overall yield after stirring the reaction mixture for 2 h. **¹H NMR** ($CDCl_3$, 500 MHz): 8.49–8.40 (m, 2H), 7.80–7.72 (m, 2H), 7.66–7.56 (m, 7H), 7.56–7.21 (m, 9H), 3.92 (s, 2H), 3.72 (s, 6H), 3.23 (s, 2H); **¹³C NMR** ($CDCl_3$, 125 MHz): δ (all discernible signals for both isomers) 172.2, 171.8, 168.8, 167.8, 158.9, 158.5,

150.4, 149.3, 146.5, 142.6, 142.5, 140.8, 140.5, 140.4, 138.8, 137.9, 137.6, 137.0, 136.7, 134.8, 131.9, 131.8, 131.5, 130.8, 130.4, 130.0, 129.6, 129.1, 128.9, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 127.6, 127.3, 127.2, 127.1, 124.6, 123.0, 122.7, 120.7, 120.0, 119.5, 99.4, 97.8, 87.2, 87.1, 59.4, 59.0, 53.3, 53.1, 42.9, 42.7, 41.2, 40.0; **HRMS** (ESI) calcd for $C_{41}H_{31}N_2O_4$ $[M+H]^+$ 615.2284, found 615.2269.



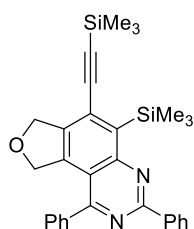
3-10ga: This product was synthesized using procedure **A** (20 wt% 4 Å MS was used as additive) and isolated in 53% yield after stirring the reaction mixture for 5 h. **¹H NMR** ($CDCl_3$, 500 MHz): δ 8.68 (d, 2H, $J = 7.0$ Hz), 7.68 (d, 2H, $J = 7.6$ Hz), 7.57–7.45 (m, 5H), 7.36–7.29 (m, 5H), 7.20 (t, 2H, $J = 7.4$ Hz), 7.17–7.13 (m, 2H), 3.60 (s, 2H), 3.03 (s, 2H), 0.72 (s, 9H), 0.20 (s, 9H); **¹³C NMR** ($CDCl_3$, 125

MHz): δ 168.2, 157.2, 156.9, 152.2, 145.2, 142.1, 140.6, 139.5, 139.2, 138.2, 132.0, 130.3, 129.4, 129.1, 128.7, 128.5, 128.1, 127.7, 127.4, 122.3, 119.8, 119.3, 105.6, 104.0, 48.1, 46.2, 3.1, –0.3; **HRMS** (ESI) calcd for $C_{43}H_{41}N_2Si_2$ $[M+H]^+$ 641.2808, found 641.2799.



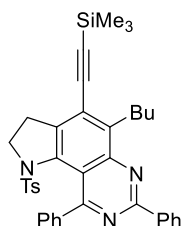
3-10ha: This product was synthesized using procedure **A** (20 wt% 4 Å MS was used as additive) and isolated in 58% yield after stirring the reaction mixture for 30 min. **¹H NMR** ($CDCl_3$, 500 MHz): δ 8.63–8.53 (m, 2H), 7.65 (t, 1H, $J = 7.5$ Hz), 7.61–7.53 (m, 4H), 7.53–7.43 (m, 3H), 7.41 (d, 2H, $J = 7.2$ Hz), 7.29 (d, 2H, $J = 8.1$ Hz), 4.69 (s, 2H), 4.05 (s, 2H), 2.39 (s, 3H), 0.61 (s, 9H), 0.31 (s, 9H); **¹³C NMR** ($CDCl_3$, 125 MHz):

δ 167.7, 158.0, 156.7, 143.8, 143.5, 139.5, 138.8, 137.7, 133.3, 132.9, 130.7, 130.0, 129.8, 128.8, 128.6, 128.4, 127.6, 117.2, 106.9, 102.6, 55.7, 54.7, 29.7, 21.5, 2.7, –0.3; **HRMS** (ESI) calcd for $C_{37}H_{40}N_3O_2SSi_2$ $[M+H]^+$ 646.2380, found 646.2390.



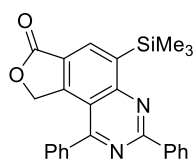
3-10ia

3-10ia: This product was synthesized using procedure A (20 wt% 4 Å MS was used as additive) and isolated in 36% yield after stirring the reaction mixture for 30 min. **¹H NMR** (CDCl₃, 500 MHz): δ 8.67–8.60 (m, 2H), 7.60–7.42 (m, 8H), 5.22–5.12 (m, 2H), 4.61–4.53 (m, 2H), 0.66 (s, 9H), 0.29 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 172.2, 168.8, 158.9, 149.3, 146.4, 142.6, 140.4, 138.8, 137.6, 136.7, 131.9, 131.5, 130.7, 130.4, 130.0, 128.8, 128.7, 128.5, 128.4, 128.3, 127.3, 127.2, 127.1, 123.0, 120.7, 120.0, 97.8, 87.2, 59.0, 53.3, 42.7, 40.0; **HRMS** (ESI) calcd for C₃₀H₃₃N₂OSi₂ [M+H]⁺ 493.2131, found 493.2130.



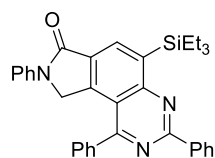
3-10ja

3-10ja: This product was synthesized using procedure A (20 wt% 4 Å MS was used as additive) and isolated in 48% yield after stirring the reaction mixture for 30 min. **¹H NMR** (CDCl₃, 500 MHz): δ 8.71 (d, 2H, *J* = 8.0 Hz), 7.87 (d, 2H, *J* = 7.0 Hz), 7.58–7.47 (m, 6H), 7.07 (d, 2H, *J* = 8.1 Hz), 6.89 (d, 2H, *J* = 8.0 Hz), 3.96–3.78 (m, 2H), 2.78–2.68 (m, 1H), 2.45 (t, 2H, *J* = 7.1 Hz), 2.37 (s, 3H), 2.36–2.28 (m, 1H), 1.62–1.54 (m, 2H), 1.49–1.40 (m, 2H), 0.94 (t, 3H), 0.65 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 144.2, 141.1, 140.2, 139.0, 138.1, 138.0, 133.8, 131.7, 130.7, 130.4, 129.5, 129.4, 128.8, 128.5, 127.8, 127.4, 114.6, 101.1, 79.8, 51.1, 30.4, 30.1, 22.1, 21.5, 19.5, 13.6, 2.8; **HRMS** (ESI) calcd for C₃₈H₄₀N₃O₂SSi [M+H]⁺ 630.2611, found 630.2615.



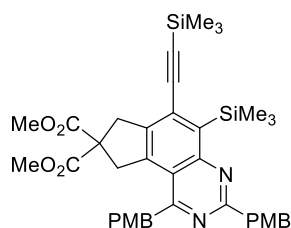
3-10ka

3-10ka: This product was synthesized using procedure A (20 wt% 4 Å MS was used as additive) and isolated in 70% yield after stirring the reaction mixture for 5 h. **¹H NMR** (CDCl₃, 500 MHz): δ 8.73–8.68 (m, 2H), 8.41 (s, 1H), 7.70–7.59 (m, 3H), 7.59–7.51 (m, 5H), 4.75 (s, 2H), 0.58 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 170.5, 168.9, 160.9, 159.1, 147.9, 145.0, 139.0, 137.4, 135.1, 131.4, 130.4, 129.1, 129.0, 128.8, 128.1, 124.2, 117.1, 69.9, –0.2; **HRMS** (ESI) calcd for C₂₅H₂₃N₂O₂Si [M+H]⁺ 411.1529, found 411.1519.



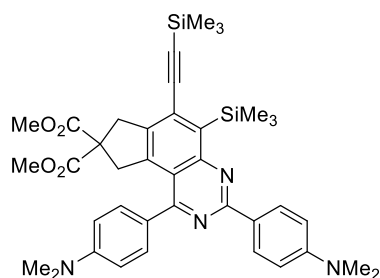
3-10la

3-10la: This product was synthesized using procedure **A** and isolated in 76% yield after stirring the reaction mixture for 2 h. **¹H NMR** (CDCl₃, 500 MHz): 8.73–8.66 (m, 2H), 8.47 (s, 1H), 7.74–7.59 (m, 5H), 7.59–7.50 (m, 5H), 7.36 (t, 2H, *J* = 7.9 Hz), 7.36 (t, 1H, *J* = 7.9 Hz), 4.30 (s, 2H), 1.20 (q, 6H, *J* = 7.8 Hz), 1.00 (t, 9H, *J* = 7.8 Hz); **¹³C NMR** (CDCl₃, 125 MHz): δ 168.6, 166.6, 159.9, 158.6, 141.2, 140.1, 139.8, 139.1, 137.8, 136.0, 131.8, 131.0, 130.0, 129.2, 129.0, 128.7, 128.2, 124.5, 118.9, 117.4, 51.4, 7.7, 4.0; **HRMS** (ESI) calcd for C₃₄H₃₄N₃OSi [M+H]⁺ 528.2471, found 528.2460.



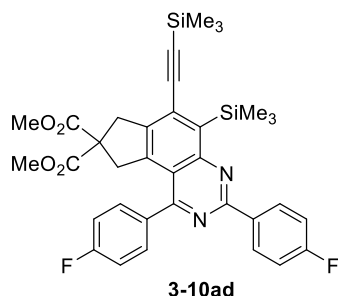
3-10ab

3-10ab: This product was synthesized using procedure **B** and isolated in 48% yield after stirring the reaction mixture for 2 h. **¹H NMR** (CDCl₃, 500 MHz): δ 8.56 (d, 2H, *J* = 8.8 Hz), 7.50 (d, 2H, *J* = 8.6 Hz), 7.06 (d, 2H, *J* = 8.5 Hz), 7.01 (d, 2H, *J* = 8.1 Hz), 3.92 (s, 3H), 3.88 (s, 3H), 3.73 (s, 2H), 3.70 (s, 6H), 3.25 (s, 2H), 0.62 (s, 9H), 0.31 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 171.9, 167.3, 161.5, 160.8, 157.1, 157.0, 141.9, 141.7, 136.4, 133.1, 131.2, 130.9, 130.8, 130.2, 118.5, 113.8, 113.7, 105.5, 103.9, 59.2, 55.4, 53.0, 43.3, 41.4, 3.0, −0.2; **HRMS** (ESI) calcd for C₃₇H₄₃N₂O₆Si₂ [M+H]⁺ 667.2660, found 667.2664.

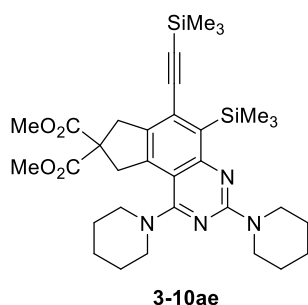


3-10ac

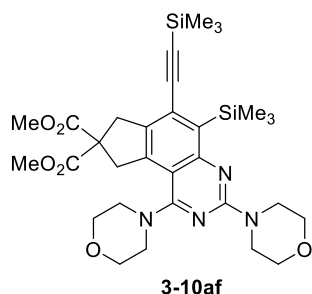
3-10ac: This product was synthesized using procedure **B** and isolated in 48% yield after stirring the reaction mixture for 2 h. **¹H NMR** (CDCl₃, 500 MHz): δ 8.51 (d, 2H, *J* = 8.9 Hz), 7.47 (d, 2H, *J* = 8.7 Hz), 6.82 (d, 2H, *J* = 8.8 Hz), 6.79 (d, 2H, *J* = 9.0 Hz), 3.72 (s, 2H), 3.70 (s, 6H), 3.37 (s, 2H), 3.07 (s, 6H), 3.05 (s, 6H), 0.61 (s, 9H), 0.30 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 172.1, 167.4, 157.5, 157.4, 151.8, 151.4, 141.4, 140.6, 136.6, 130.8, 130.6, 130.0, 128.5, 126.4, 118.3, 111.7, 111.6, 104.6, 104.2, 59.3, 52.9, 43.5, 41.4, 40.4, 40.3, 3.0; **HRMS** (ESI) calcd for C₃₉H₄₉N₄O₄Si₂ [M+H]⁺ 693.3292, found 693.3278.



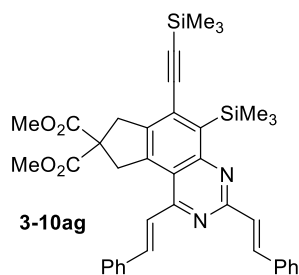
3-10ad: This product was synthesized using procedure **B** and isolated in 65% yield after stirring the reaction mixture for 2 h. ^1H NMR (CDCl_3 , 500 MHz): δ 8.60 (dd, 2H, $J = 8.9$ Hz, $J = 5.6$ Hz), 7.54 (dd, 2H, $J = 8.5$ Hz, $J = 5.4$ Hz), 7.24 (t, 2H, $J = 8.5$ Hz), 7.18 (t, 2H, $J = 8.7$ Hz), 3.74 (s, 2H), 3.71 (s, 6H), 3.17 (s, 2H), 0.62 (s, 9H), 0.31 (s, 9H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 171.8, 166.9, 164.5 (d, $J = 250.7$ Hz), 163.7 (d, $J = 249.4$ Hz), 156.9, 156.4, 142.5, 142.3, 136.6 (d, $J = 2.8$ Hz), 136.1, 134.1 (d, $J = 2.3$ Hz), 131.8, 131.1 (d, $J = 8.3$ Hz), 130.6 (d, $J = 8.5$ Hz), 118.6, 115.5 (d, $J = 21.8$ Hz), 106.3, 103.7, 59.2, 53.1, 43.2, 41.4, 2.9, -0.3 ; ^{19}F NMR (375 MHz, CDCl_3): δ -111.2 , -111.7 ; **HRMS** (ESI) calcd for $\text{C}_{35}\text{H}_{37}\text{F}_2\text{N}_2\text{O}_4\text{Si}_2$ $[\text{M}+\text{H}]^+$ 643.2260, found 643.2231.



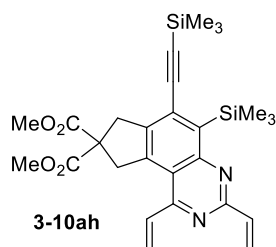
3-10ae: This product was synthesized using procedure **B** and isolated in 83% yield after stirring the reaction mixture for 2 h. ^1H NMR (CDCl_3 , 500 MHz): δ 3.95 (s, 2H), 3.87–3.80 (m, 4H), 3.76 (s, 6H), 3.64 (s, 2H), 3.57–3.39 (br, 2H), 3.01–2.85 (br, 2H), 1.89–1.37 (m, 12H), 0.46 (s, 9H), 0.26 (s, 9H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 172.4, 167.9, 159.8, 156.1, 136.8, 135.9, 135.4, 129.1, 109.6, 104.8, 103.0, 59.3, 53.0, 52.2, 45.1, 42.5, 40.8, 26.0, 25.6, 25.2, 24.6, 2.4, -0.2 ; **HRMS** (ESI) calcd for $\text{C}_{33}\text{H}_{49}\text{N}_4\text{O}_4\text{Si}_2$ $[\text{M}+\text{H}]^+$ 621.3292, found 621.3275.



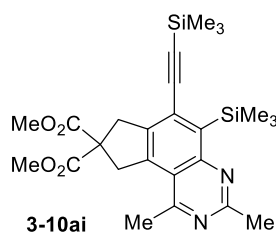
3-10af: This product was synthesized using procedure **B** and isolated in 70% yield after stirring the reaction mixture for 2 h. ^1H NMR (CDCl_3 , 500 MHz): δ 4.00–3.70 (m, 20H), 3.66 (s, 2H), 3.56–3.06 (br, 4H), 0.46 (s, 9H), 0.27 (s, 9H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 172.2, 167.4, 159.6, 156.0, 137.5, 136.6, 135.4, 130.0, 109.6, 104.3, 104.0, 67.0, 66.5, 59.3, 53.1, 51.5, 44.7, 42.6, 40.8, 2.4, -0.2 ; **HRMS** (ESI) calcd for $\text{C}_{31}\text{H}_{45}\text{N}_4\text{O}_6\text{Si}_2$ $[\text{M}+\text{H}]^+$ 625.2878, found 625.2860.



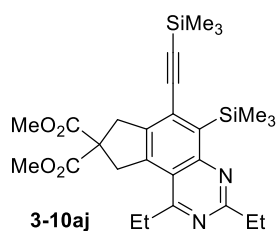
3-10ag: This product was synthesized using procedure **B** and isolated in 40% yield after stirring the reaction mixture for 2 h. **¹H NMR** (CDCl₃, 500 MHz): δ 8.14 (d, 1H, *J* = 7.7 Hz), 8.11 (d, 1H, *J* = 7.1 Hz), 7.83 (d, 1H, *J* = 15.4 Hz), 7.73–7.66 (m, 4H), 7.50–7.32 (m, 7H), 4.26 (s, 2H), 3.82 (s, 2H), 3.80 (s, 6H), 0.58 (s, 9H), 0.31 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 171.9, 162.1, 158.1, 157.3, 142.6, 141.9, 138.7, 137.4, 136.6, 136.3, 135.1, 131.2, 129.3, 129.0, 128.8, 128.5, 128.0, 127.6, 125.3, 118.9, 105.7, 103.8, 59.3, 53.3, 44.5, 41.3, 2.9, –0.3; **HRMS** (ESI) calcd for C₃₉H₄₃N₂O₄Si₂ [M+H]⁺ 659.2761, found 659.2780.



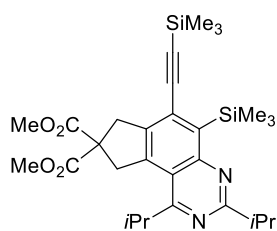
3-10ah: This product was synthesized using procedure **A** and isolated in 54% yield after stirring the reaction mixture for 2 h. **¹H NMR** (CDCl₃, 500 MHz): δ 7.51 (dd, 1H, *J* = 16.6 Hz, *J* = 10.6 Hz), 6.98 (dd, 1H, *J* = 17.2 Hz, *J* = 10.4 Hz), 6.70 (dd, 1H, *J* = 17.2 Hz, *J* = 1.6 Hz), 6.60 (dd, 1H, *J* = 16.6 Hz, *J* = 1.5 Hz), 5.77 (dd, 1H, *J* = 10.8 Hz, *J* = 1.4 Hz), 5.73 (dd, 1H, *J* = 10.6 Hz, *J* = 1.4 Hz), 4.14 (s, 2H), 3.80 (s, 6H), 3.79 (s, 2H), 0.51 (s, 9H), 0.30 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 171.9, 162.4, 157.7, 157.0, 142.7, 142.1, 137.2, 135.1, 134.8, 131.2, 124.6, 123.0, 118.6, 105.8, 103.7, 59.1, 53.2, 44.5, 41.2, 2.8, –0.3; **HRMS** (ESI) calcd for C₂₇H₃₅N₂O₄Si₂ [M+H]⁺ 507.2135, found 507.2129.



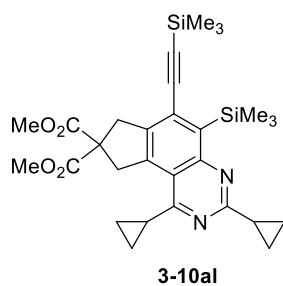
3-10ai: This product was synthesized using procedure **A** and isolated in 66% yield after stirring the reaction mixture for 2 h. **¹H NMR** (CDCl₃, 500 MHz): δ 4.16 (s, 2H), 3.80 (s, 6H), 3.78 (s, 2H), 2.96 (s, 3H), 2.73 (s, 3H), 0.49 (s, 9H), 0.29 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 172.0, 166.6, 160.8, 155.9, 142.3, 141.1, 135.7, 130.8, 119.4, 105.5, 103.8, 59.0, 53.2, 44.3, 41.1, 26.6, 25.7, 2.7, –0.3; **HRMS** (ESI) calcd for C₂₅H₃₅N₂O₄Si₂ [M+H]⁺ 483.2135, found 483.2146.



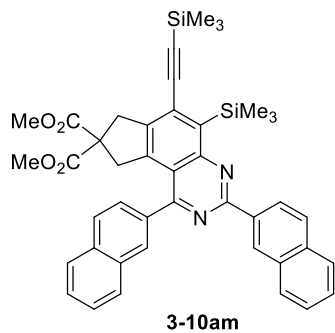
3-10aj: This product was synthesized using procedure A and isolated in 69% yield after stirring the reaction mixture for 2 h. **¹H NMR** (CDCl₃, 500 MHz): δ 4.15 (s, 2H), 3.83–3.77 (m, 8H), 3.26 (q, 2H, *J* = 7.4 Hz), 3.05 (q, 2H, *J* = 7.5 Hz), 1.41 (t, 3H, *J* = 7.6 Hz), 1.40 (t, 3H, *J* = 7.6 Hz), 0.51 (s, 9H), 0.29 (s, 2H); **¹³C NMR** (CDCl₃, 125 MHz): δ 172.0, 171.0, 164.9, 156.3, 142.4, 141.2, 135.1, 130.6, 118.8, 105.2, 103.9, 59.1, 53.2, 44.0, 41.1, 32.6, 31.3, 13.7, 12.5, 2.8; **HRMS** (ESI) calcd for C₂₇H₃₉N₂O₄Si₂ [M+H]⁺ 511.2448, found 511.2453.



3-10ak: This product was synthesized using procedure A and isolated in 74% yield after stirring the reaction mixture for 2 h. **¹H NMR** (CDCl₃, 500 MHz): δ 4.16 (s, 2H), 3.84–3.74 (m, 9H), 3.28 (sept, 1H, *J* = 6.9 Hz), 1.39 (d, 6H, *J* = 6.78 Hz), 1.38 (d, 6H, *J* = 6.4 Hz), 0.51 (s, 9H), 0.29 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 174.4, 172.0, 168.0, 156.5, 142.6, 141.2, 134.6, 130.2, 118.5, 104.9, 104.0, 59.2, 53.2, 44.2, 41.0, 37.6, 33.4, 22.4, 21.7, 2.9, −0.2; **HRMS** (ESI) calcd for C₂₉H₄₃N₂O₄Si₂ [M+H]⁺ 539.2761, found 539.2748.

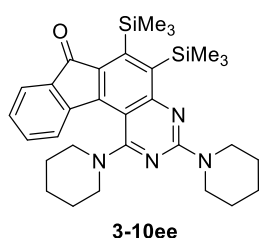


3-10al: This product was synthesized using procedure B (10 equiv cyclopropanecarbonitrile was used) and isolated in 87% yield after stirring the reaction mixture for 2 h. **¹H NMR** (CDCl₃, 500 MHz): δ 4.27 (s, 2H), 3.79 (s, 6H), 3.77 (s, 2H), 2.64–2.56 (m, 1H), 2.25–2.18 (m, 1H), 1.38–1.34 (m, 2H), 1.18–1.09 (m, 4H), 1.01–0.95 (m, 2H), 0.48 (s, 9H), 0.29 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 172.1, 169.9, 164.8, 155.9, 141.6, 140.5, 135.5, 130.4, 119.8, 105.0, 104.1, 59.2, 53.2, 44.4, 41.0, 18.2, 16.8, 11.2, 9.7, 2.8, −0.3; **HRMS** (ESI) calcd for C₂₉H₃₉N₂O₄Si₂ [M+H]⁺ 535.2448, found 535.2433.



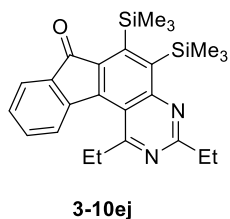
3-10am: This product was synthesized using procedure **B** and isolated in 46% yield after stirring the reaction mixture for 2 h. ¹H NMR (CDCl₃, 500 MHz): δ 9.18 (s, 1H), 8.74 (dd, 1 H, *J* = 8.7 Hz, *J* = 1.2 Hz), 8.02–7.95 (m, 4H), 7.90–7.86 (m, 1H), 7.75 (dd, 1 H, *J* = 8.4 Hz, *J* = 1.2 Hz), 7.64–7.57 (m, 2H), 7.55–7.47 (m, 2H), 3.76 (s, 2H), 3.70–3.56 (br, 6H), 3.22 (s, 2H), 0.70 (s, 9H), 0.32 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz): δ 157.1, 142.5,

142.4, 138.0, 136.4, 135.5, 134.6, 133.8, 133.4, 132.9, 131.7, 129.3, 129.1, 128.6, 128.2, 128.1, 128.0, 127.7, 127.0, 126.7, 126.1, 125.6, 118.9, 106.0, 103.8, 59.1, 53.0, 43.3, 41.5, 3.0, –0.2; HRMS (ESI) calcd for C₄₃H₄₃N₂O₄Si₂ [M+H]⁺ 707.2761, found 707.2772.



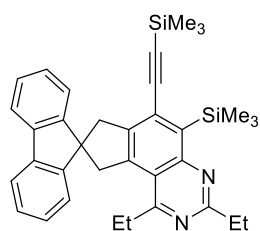
3-10ee: This product was synthesized using procedure **B** (20 wt% 4 Å MS was used as additive) and isolated in 67% yield after stirring the reaction mixture for 2 h. ¹H NMR (CDCl₃, 500 MHz): δ 7.86 (d, 2H, *J* = 7.5 Hz), 7.52 (d, 2H, *J* = 7.1 Hz), 7.38 (d, 2H, *J* = 7.4 Hz), 7.23 (d, 2H, *J* = 7.3 Hz), 4.00–3.86 (m, 4H), 3.83–

3.71 (m, 2H), 3.44–3.33 (m, 2H), 1.80–1.49 (m, 12H), 0.43 (s, 18H); ¹³C NMR (CDCl₃, 125 MHz): δ 194.0, 164.7, 162.7, 157.4, 156.2, 148.5, 143.9, 143.5, 134.4, 133.6, 132.6, 129.0, 124.8, 122.7, 104.9, 50.8, 45.3, 26.1, 25.3, 25.1, 24.7, 3.3, 2.8; HRMS (ESI) calcd for C₃₁H₄₃N₄O₄Si₂ [M+H]⁺ 543.2975, found 543.2991.



3-10ej: This product was synthesized using procedure **A** (20 wt% 4 Å MS was used as additive) and isolated in 63% yield after stirring the reaction mixture for 2 h. ¹H NMR (CDCl₃, 500 MHz): δ 7.64–7.60 (m, 1H), 7.55–7.52 (m, 1H), 7.49–7.43 (m, 1H), 7.33–7.27 (m, 1H), 3.33 (q, 2H, *J* = 7.4 Hz), 3.12 (q, 2H, *J* = 7.6 Hz), 1.49 (t,

3H, *J* = 7.6 Hz), 1.36 (t, 3H, *J* = 7.4 Hz), 0.49 (s, 9H), 0.44 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz): δ 195.0, 171.6, 166.9, 157.9, 155.9, 155.1, 144.0, 143.1, 137.3, 134.0, 133.3, 129.4, 124.9, 123.9, 115.9, 32.6, 31.5, 13.8, 12.2, 3.6, 2.6; HRMS (ESI) calcd for C₂₅H₃₃N₂O₄Si₂ [M+H]⁺ 433.2131, found 433.2133.

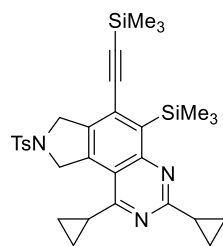


3-10gj

3-10gj: This product was synthesized using procedure **A** and isolated in 75% yield

after stirring the reaction mixture for 5 h. **¹H NMR** (CDCl₃, 500 MHz): δ 7.78 (d, 1H, *J* = 7.6 Hz), 7.52 (td, 1H, *J* = 7.4 Hz, *J* = 1.1 Hz), 7.32–7.23 (m, 2H), 4.00 (s, 2H), 3.67 (s, 2H), 3.12 (q, 2H, *J* = 7.5 Hz), 3.09 (q, 2H, *J* = 7.6 Hz), 1.46 (q, 3H, *J* = 7.6 Hz), 1.23 (q, 1H, *J* = 7.5 Hz), 0.58 (s, 9H), 0.18 (s, 9H); **¹³C NMR** (CDCl₃,

125 MHz): 171.4, 164.8, 156.3, 152.7, 144.2, 142.1, 139.6, 137.9, 131.1, 127.9, 127.6, 122.4, 119.9, 119.4, 105.0, 104.2, 55.9, 49.8, 45.7, 32.6, 31.2, 13.9, 12.5, 3.0, –0.3; **HRMS** (ESI) calcd for C₃₅H₄₁N₂Si₂ [M+H]⁺ 545.2808, found 545.2785.



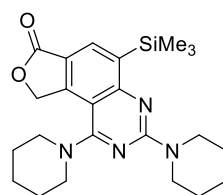
3-10hl

3-10hl: This product was synthesized using procedure **B** (10 equiv

cyclopropanecarbonitrile was added, 20 wt% 4 Å MS was used as additive) and

isolated in 35% yield after stirring the reaction mixture for 30 min. **¹H NMR** (CDCl₃, 500 MHz): δ 7.79 (d, 2H, *J* = 8.2 Hz), 7.32 (d, 2H, *J* = 8.1 Hz), 5.31–5.26 (m, 2H), 4.75–4.70 (m, 2H), 2.40 (s, 3H), 2.29–2.18 (m, 2H), 1.36–1.30 (m, 2H), 1.19–1.09

(m, 4H), 1.04–0.96 (m, 2H), 0.46 (s, 9H), 0.29 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 169.6, 165.7, 156.1, 143.9, 142.9, 136.9, 133.9, 131.8, 130.0, 128.7, 127.5, 118.2, 106.0, 102.8, 57.2, 54.4, 21.5, 18.3, 16.1, 11.3, 10.0, 2.6, –0.3; **HRMS** (ESI) calcd for C₃₁H₄₀N₃O₂SSi₂ [M+H]⁺ 574.2380, found 574.2380.

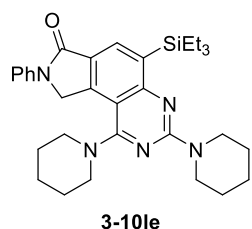


3-10ke

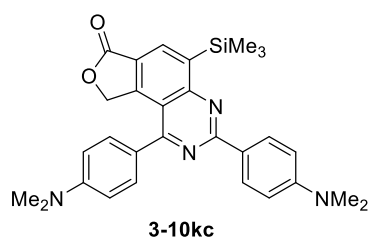
3-10ke: This product was synthesized using procedure **B** and isolated in 59% yield

after stirring the reaction mixture for 5 h. **¹H NMR** (CDCl₃, 500 MHz): δ 8.04 (s, 1H), 5.51 (s, 2H), 4.00–3.85 (m, 4H), 3.33–3.10 (br, 4H), 1.85–1.55 (m, 12 H), 0.38 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 171.6, 169.1, 163.4, 158.3, 147.6, 139.2, 134.2,

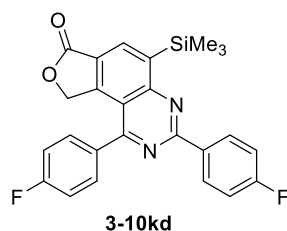
117.5, 107.5, 70.6, 52.5, 45.2, 26.0, 25.7, 25.0, 24.4, –0.8; **HRMS** (ESI) calcd for C₂₃H₃₃N₄O₂Si [M+H]⁺ 425.2373, found 425.2379.



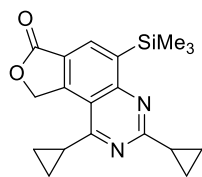
3-10le: This product was synthesized using procedure **B** and isolated in 65% yield after stirring the reaction mixture for 2 h. **¹H NMR** (CDCl₃, 500 MHz): δ 8.10 (s, 1H), 7.91 (d, 2H, *J* = 8.1 Hz), 7.48–7.42 (m, 2H), 7.19 (t, 1H, *J* = 7.4 Hz), 5.12 (s, 2H), 3.96–3.89 (m, 4H), 3.74–2.75 (br, 4H), 1.92–1.58 (m, 12H), 1.04–0.90 (m, 15H); **¹³C NMR** (CDCl₃, 125 MHz): δ 169.1, 167.7, 162.9, 157.8, 140.0, 139.9, 135.4, 134.8, 129.2, 125.7, 123.8, 118.9, 108.0, 52.6, 52.0, 45.2, 26.1, 25.9, 25.1, 24.5, 7.8, 3.5; **HRMS** (ESI) calcd for C₃₂H₄₄N₅OSi [M+H]⁺ 542.3315, found 542.3295.



3-10kc: This product was synthesized using procedure **B** and isolated in 51% yield after stirring the reaction mixture for 5 h. **¹H NMR** (CDCl₃, 500 MHz): δ 8.59 (d, 2H, *J* = 9.0 Hz), 8.30 (s, 1H), 7.45 (d, 1H, *J* = 8.6 Hz), 6.85 (d, 1H, *J* = 8.7 Hz), 6.81 (d, 1H, *J* = 9.0 Hz), 4.94 (s, 1H), 3.10 (s, 3H), 3.09 (s, 3H), 0.55 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 168.7, 161.2, 159.9, 152.5, 151.7, 148.5, 143.7, 134.4, 130.6, 129.8, 126.4, 125.3, 122.5, 116.5, 111.8, 111.6, 111.1, 70.6, 40.3, 40.2, 29.7, -0.2; **HRMS** (ESI) calcd for C₂₉H₃₃N₄O₂Si [M+H]⁺ 497.2373, found 497.2383.



3-10kd: This product was synthesized using procedure **B** and isolated in 42% yield after stirring the reaction mixture for 5 h. **¹H NMR** (CDCl₃, 500 MHz): δ 8.72–8.65 (m, 2H), 8.42 (s, 1H), 7.60–7.53 (m, 2H), 7.33 (t, 2H, *J* = 8.0 Hz), 7.23 (t, 2H, *J* = 8.7 Hz), 4.80 (s, 2H), 0.57 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 170.3, 168.0, 165.2 (d, *J* = 252.3 Hz), 164.0 (d, *J* = 251.8 Hz), 160.0, 159.2, 147.5, 145.0, 135.4, 135.0 (d, *J* = 2.7 Hz), 133.5 (d, *J* = 2.0 Hz), 131.2 (d, *J* = 8.7 Hz), 130.3 (d, *J* = 8.3 Hz), 124.3, 117.0, 116.3 (d, *J* = 21.6 Hz), 115.9 (d, *J* = 22.0 Hz), 69.9, 29.7, -0.2; **¹⁹F NMR** (375 MHz, CDCl₃): δ -109.1, -109.7; **HRMS** (ESI) calcd for C₂₅H₂₁F₂N₂O₂Si [M+H]⁺ 447.1340, found 447.1351.



3-10kl

3-10kl: This product was synthesized using procedure **B** (10 equiv cyclopropanecarbonitrile was added and 20 wt% 4 Å MS was used as additive) and isolated in 57% yield after stirring the reaction mixture for 5 h. **¹H NMR** (CDCl₃, 500 MHz): δ 8.28 (s, 1H), 5.80 (s, 2H), 2.38–2.30 (m, 1H). 2.19–2.10 (m, 1H), 1.50–1.43 (m, 2H), 1.32–1.18 (m, 4H), 1.15–1.07 (m, 2H), 0.42 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 171.1, 170.8, 169.4, 158.6, 147.4, 144.0, 134.3, 122.5, 117.6, 70.8, 18.8, 16.4, 11.4, 11.2, –0.4; **HRMS** (ESI) calcd for C₁₉H₂₃N₂O₂Si [M+H]⁺ 339.1529, found 339.1532.

3.5. Note

Computational study was conducted by Yongjia Lin and Prof. Yuanzhi Xia at Wenzhou University, China.

3.6. References

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CHAPTER 4

Silver-Catalyzed Annulation of Arynes with Isonitriles

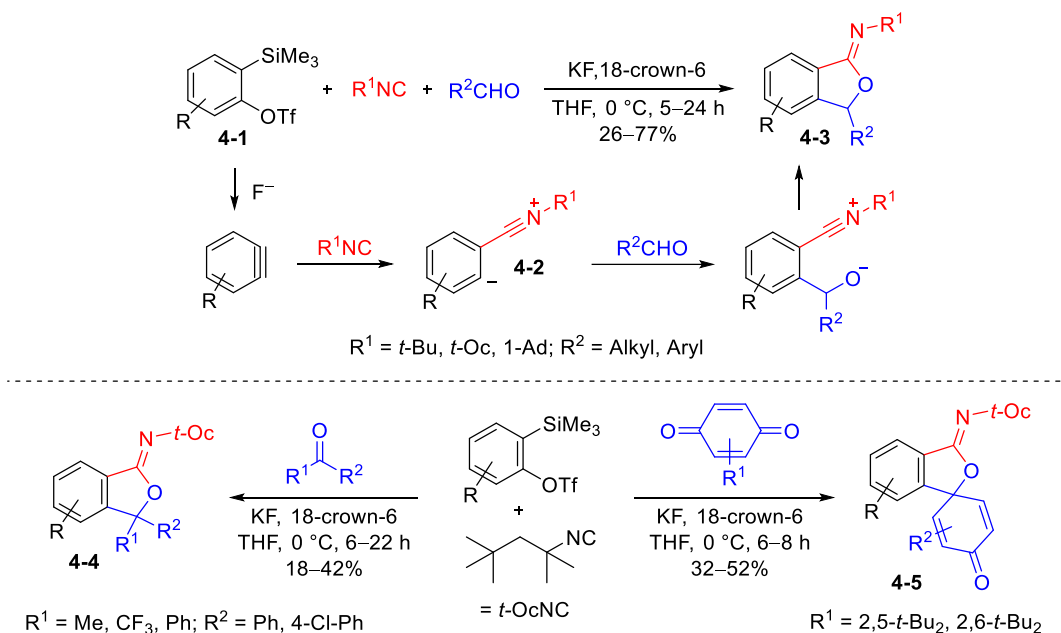
4.1. Introduction*

Aryne is a versatile reactive intermediate whereby numerous transformations have been developed to generate functionalized aromatic compounds.¹ Base-mediated 1,2-elimination of aryl halide,^{2a} fluoride-promoted 1,2-elimination of aryl silyl triflate,^{2b} or thermal decomposition of arenediazonium-2-carboxylate^{2c} are common methods to generate aryne species among many others. These 1,2-elimination protocols, albeit a powerful synthetic tool in their own right, require the preparation of prefunctionalized aromatic precursors, which often limits the structural and functional diversity of the products. On the other hand, direct cycloaromatization of tri- and tetraynes to form arynes, named as hexadehydro Diels-Alder (HDDA) reaction,³ allows for the construction of structurally more complex and diverse arene products. The temperature range for the aromatization subtly depends on the structure of the linker and the nature of the substituents.⁴ The HDDA reaction of tri- and tetraynes pioneered by Johnson and Ueda,⁵ subsequently rediscovered by Hoye, Lee and others has resulted in a significant expansion of the scope of aryne chemistry.⁶ Being formed under neutral conditions at varying range of temperature, the HDDA-derived arynes have displayed reactivity profiles different from those generated via base- or fluoride-mediated 1,2-elimination protocols.

Multicomponent coupling reaction (MCR) is a powerful synthetic tool to merge three or more reactants in a single-step operation to generate relatively complex molecular structures with high atom-economy.⁷ Aryne-based MCRs involving isonitrile⁸ have been explored over the last two decades mainly with simple arynes generated from the fluoride-promoted 1,2-elimination of aryl silyl triflate. MCRs of arynes with isonitriles have been employed for the synthesis of functionalized benzo-fused heterocycles. In 2004, Yoshida and coworkers reported that arynes derived from 2-(trimethylsilyl)phenyl triflates **4-1** in the presence of KF and 18-crown-6, readily react with isonitriles and aldehydes to generate iminodihydroisobenzofurans **4-3** in moderate to good yield (**Scheme 4.1**).^{8a} This reaction is believed to

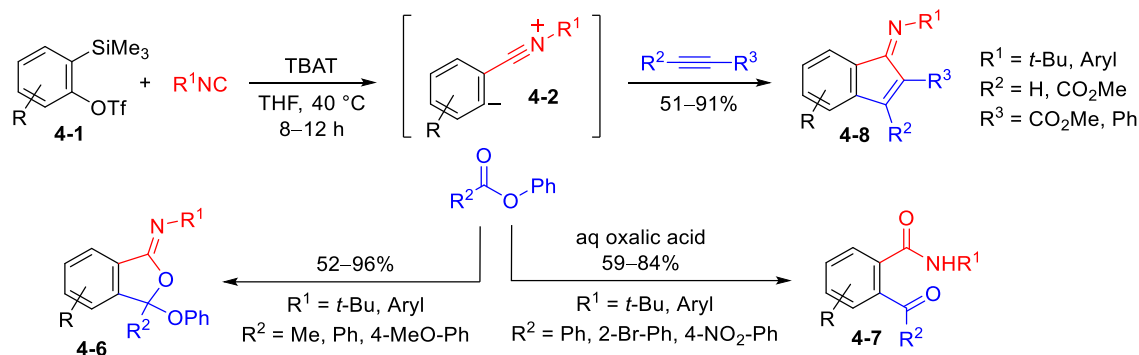
* Some parts of this chapter have been reproduced (adapted) partially with permission from Ghorai, S.; Lin, Y.; Xia, Y.; Wink, D. J.; Lee, D. "Silver-Catalyzed Selective Multicomponent Coupling Reactions of Arynes with Nitriles and Isonitriles" *Org. Lett.* **2020**, 22, 642. Copyright 2020, American Chemical Society.

involve an initial addition of isocyanide to the aryne intermediate and trapping of an aldehyde by the aryl anion **4-2**, followed by an intramolecular cyclization, leading to the observed product **4-3**. Subsequently, they found that ketones and benzoquinones also could be employed to generate iminodihydroisobenzofuran derivatives **4-4** and **4-5**.^{8b}



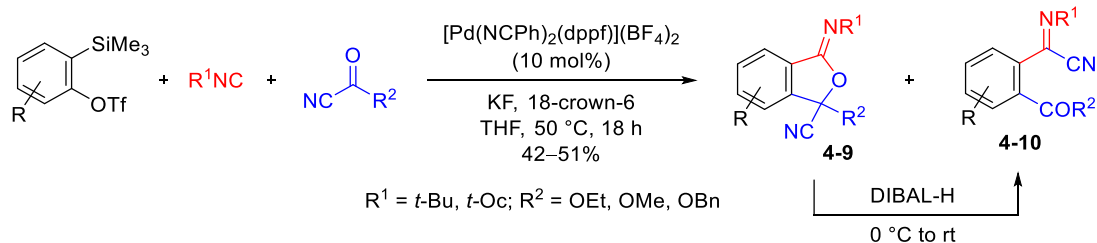
Scheme 4.1. Three-Component Coupling Reaction of Arynes, Isonitriles, and Carbonyls

These isocyanide-based MCRs were further expanded by Stoltz and coworkers via trapping intermediate **4-2** with other carbonyl compounds such as esters and electron-deficient alkynes (**Scheme 4.2**).^{8c} In situ generated zwitterionic aryne-isonitrile adduct **4-2** could be effectively trapped by phenyl esters to generate phenoxy iminoisobenzofurans **4-6**, which could be hydrolyzed in situ by aqueous oxalic acid to generate *o*-ketobenzamides **4-7**. When aryne-isonitrile adduct **4-2** was intercepted by electron-deficient alkynes such as methyl propiolate, dimethyl acetylenedicarboxylate, iminoindenones **4-8** were isolated. All three MCRs were found to be tolerant of considerable substitution on each of the three reaction components, providing a wide array of heterocycles and *o*-ketobenzamides.



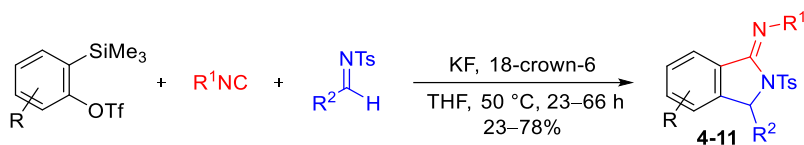
Scheme 4.2. Three-Component Coupling Reaction of Arynes, Isonitriles, and Esters/Alkynes

Nishihara employed cyanoformate as the third component in this reaction, which was activated by cationic palladium complex $[\text{Pd}(\text{PhCN})_2(\text{dppf})(\text{BF}_4)]$ (10 mol %) to afford cyano-substituted iminoisobenzofurans **4-9** along with α -iminonitriles **4-10** as the minor product (**Scheme 4.3**).^{8d} Later, it was found that isomerization of iminoisobenzofurans into α -iminonitriles could be effectively triggered by aluminum-based Lewis acids (DIBAL-H and AlMe_3).^{8e}



Scheme 4.3. Pd-Catalyzed Three-Component Coupling of Arynes, Isonitriles, and Cyanoformates

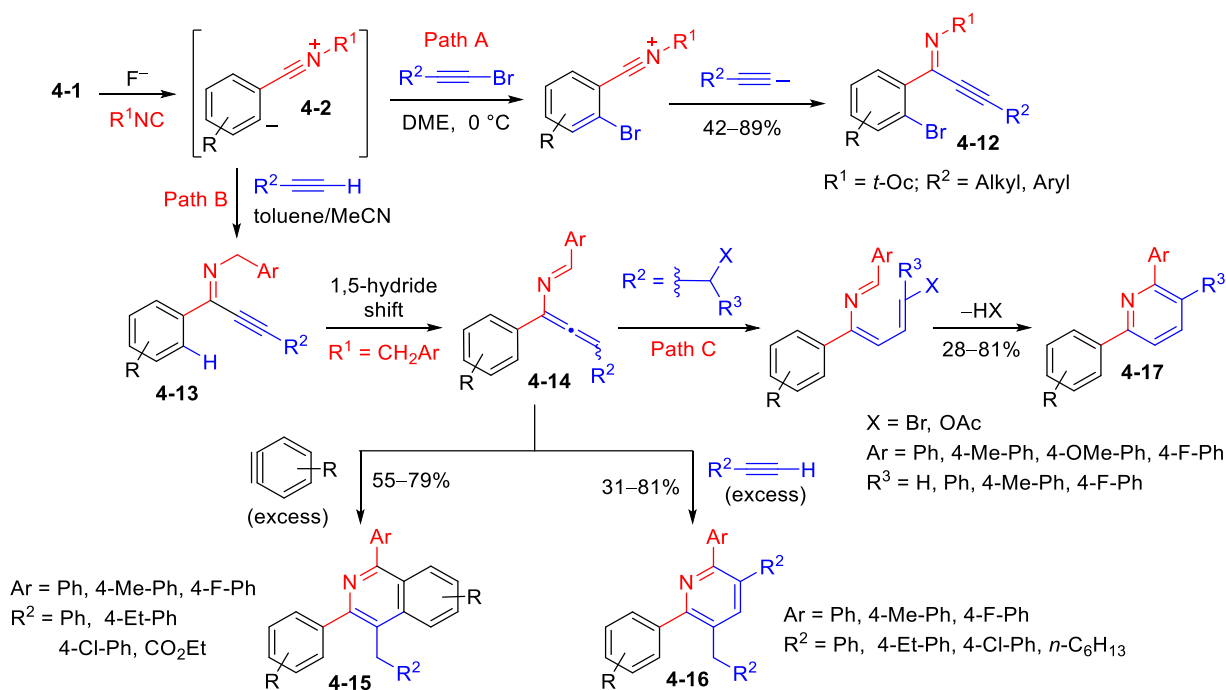
By replacing cyanoformate with imine, Yoshida and coworkers developed another MCR to form iminoisoindolines **4-11** (**Scheme 4.4**).^{8b} Reactions of arynes, isonitriles, and *N*-tosylaldimines delivered 2-isoindolinone derivatives **4-11**. Reaction with unsymmetrical arynes were also employed to study the regioselectivity of isonitrile addition to arynes, which concluded that initial addition of isonitrile is controlled by the electronic and/or steric effects of the substituents on the aryne.



$R^1 = t\text{-Bu}, 1\text{-Ad}, t\text{-Oc}; R^2 = \text{Ph}, 4\text{-OMe-Ph}, 1\text{-Naph}, 2\text{-Thienyl}$

Scheme 4.4. Three-Component Coupling Reaction of Arynes, Isonitriles, and *N*-tosylaldimines

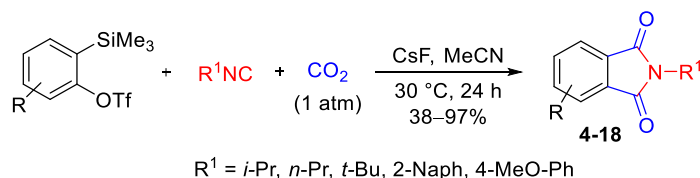
Depending on the structure of alkynes and reaction conditions, arynes react with isonitriles and alkynes to take different manifolds of reactions (**Scheme 4.5**). In 2011, Yoshida reported the synthesis of alkynyliminoaryl bromides from arynes, isonitriles, and alkynyl bromides (**Scheme 4.5**, Path A).^{8f} It was postulated the initially formed zwitterionic aryne-isonitrile adduct **4-2** reacts with alkynyl bromide to form an arene-Br bond and the corresponding acetylide, which then reacts with the nitrilium moiety to afford the final product **4-12**. Similarly, pyrimidines and isoquinolines could be generated from arynes, benzyl isonitriles, and terminal alkynes (Path B).^{8g,8h} In this reaction, the aryne-isonitrile adduct **4-2** reacts with an alkyne to form imine **4-13**, which undergoes a 1,5-hydride shift to generate imino allene **4-14**. Subsequent



Scheme 4.5. Three-Component Coupling Reaction of Arynes, Isonitriles, and Alkynes

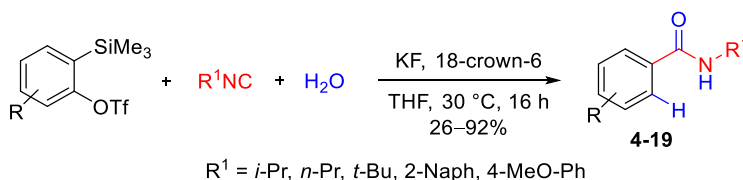
[4+2] cycloaddition of **4-14** with another aryne species or terminal alkyne provides isoquinoline derivatives **4-15** or pyrimidines **4-16**, respectively. On the other hand, *N*-allenyl imine intermediate **4-14** derived from 3-bromopropyne did not participate in the cycloaddition but engaged in a 1,3-hydride shift (Path C) to generate azatriene,⁸ⁱ which ultimately delivered disubstituted pyrimidines **4-17** via electrocyclization followed by extrusion of HBr. By employing alkynes containing a propargyl acetoxy substituent, trisubstituted pyrimidines were obtained.

Biju reported an efficient multicomponent reaction involving arynes, isonitriles and CO₂ to generate *N*-substituted phthalimides **4-18** (Scheme 4.6).^{8j} A variety of aliphatic and aryl isonitriles smoothly react with arynes followed by incorporation of CO₂, leading to desired product. Later, Wang and Ji further explored this reaction and synthesized structurally more complex phthalimides using this method.^{8m}



Scheme 4.6. Three-Component Coupling Reaction of Arynes, Isonitriles, and CO₂

Incorporation of water as the third component resulted in the formation of benzamide derivatives **4-19** (Scheme 4.7).^{8j-1} A wide variety of alkyl and aryl isonitriles were well tolerated leading to *N*-alkyl and *N*-aryl benzamides in moderate to excellent yield with high regioselectivity.



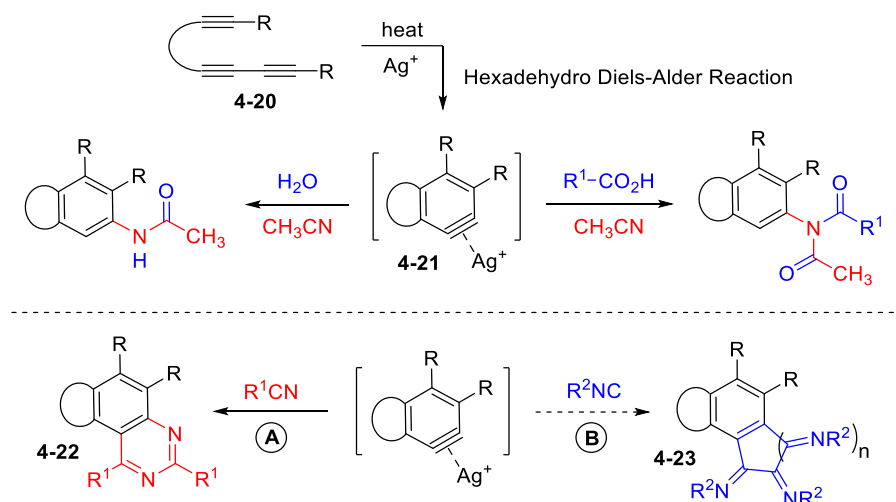
Scheme 4.7. Three-Component Coupling Reaction of Arynes, Isonitriles, and H₂O

These MCRs of arynes, isonitriles, and electrophiles constitute novel methods to generate diverse benzo-fused heterocyclic compounds or functionalized benzenoid products. In all these methods, 2-

(trimethylsilyl)phenyl triflate was efficiently used as aryne precursor. However, HDDA reaction-derived arynes from multiynes were never explored in these types of isonitrile-based MCRs. So, development of new MCRs with HDDA-derived arynes is highly desirable to investigate the intrinsic reactivity between isonitriles and thermally generated arynes. In this regard, we reported that HDDA reactions of multiynes were a versatile platform that can broaden the scope of aryne-based MCRs, which can be further expanded by employing transition metal complexes that can modulate the reactivity of arynes.⁹

4.2. Results and Discussion

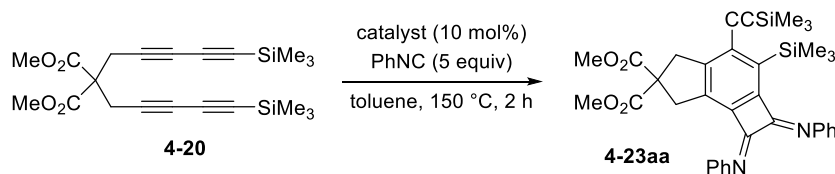
Exploitation of the prowess of silver-catalyzed MCR has shown that the reaction of putative silver-complexed aryne **4-21** with nitriles provided amides or imides in the presence of water or carboxylic acid,¹⁰ whereas in the absence of these extra nucleophiles, quinazolines **4-22** was generated through Path A (Scheme 4.8).¹¹ Based on this result, we envision a new MCR of **4-21** with isonitriles, which is expected to generate **4-23** ($n = 0$ or 1) via Path B.¹²



Scheme 4.8. Silver-Catalyzed MCRs of Arynes with Nitriles and Isonitriles

4.2.1. Optimization of Reaction Conditions

Our investigation commenced with screening of various metal catalysts for maximum yield of [A+2B] or [A+3B] type MCR products. Several catalysts displaying a good catalytic activity have been identified among which AgSbF₆ provided the highest yield of benzocyclobutene-1,2-diimine **4-23aa** (Table 4.1). The three isonitriles-incorporated product **4-23** (n = 1) was not observed. AgOTf also displayed a good catalytic activity in promoting this transformation (entry 2), however, AgOAc and AgCO₃ were almost inactive (entries 3–5), indicating an important counterion effect. Other catalysts such as Sm(OTf)₃, (CuOTf)₂·C₆H₆ were also generated product **4-23aa** (55 and 59%, entries 5–6). However, Sc(OTf)₃, Mg(OTf)₂, Zn(OTf)₂, AuCl, and InCl₃ were less effective (entries 7–11). In the absence of a catalyst under otherwise identical conditions, product **4-23aa** was not observed (entry 12).



entry	catalyst	yield (%) ^a	entry	catalyst	yield (%) ^a
1	AgSbF ₆	62	7	Sc(OTf) ₃	13
2	AgOTf	61	8	Mg(OTf) ₂	32
3	AgOAc	5	9	Zn(OTf) ₂	15
4	Ag ₂ CO ₃	7	10	AuCl	10
5	Sm(OTf) ₃	55	11	InCl ₃	trace
6	(CuOTf) ₂ · C ₆ H ₆	59	12	none	trace

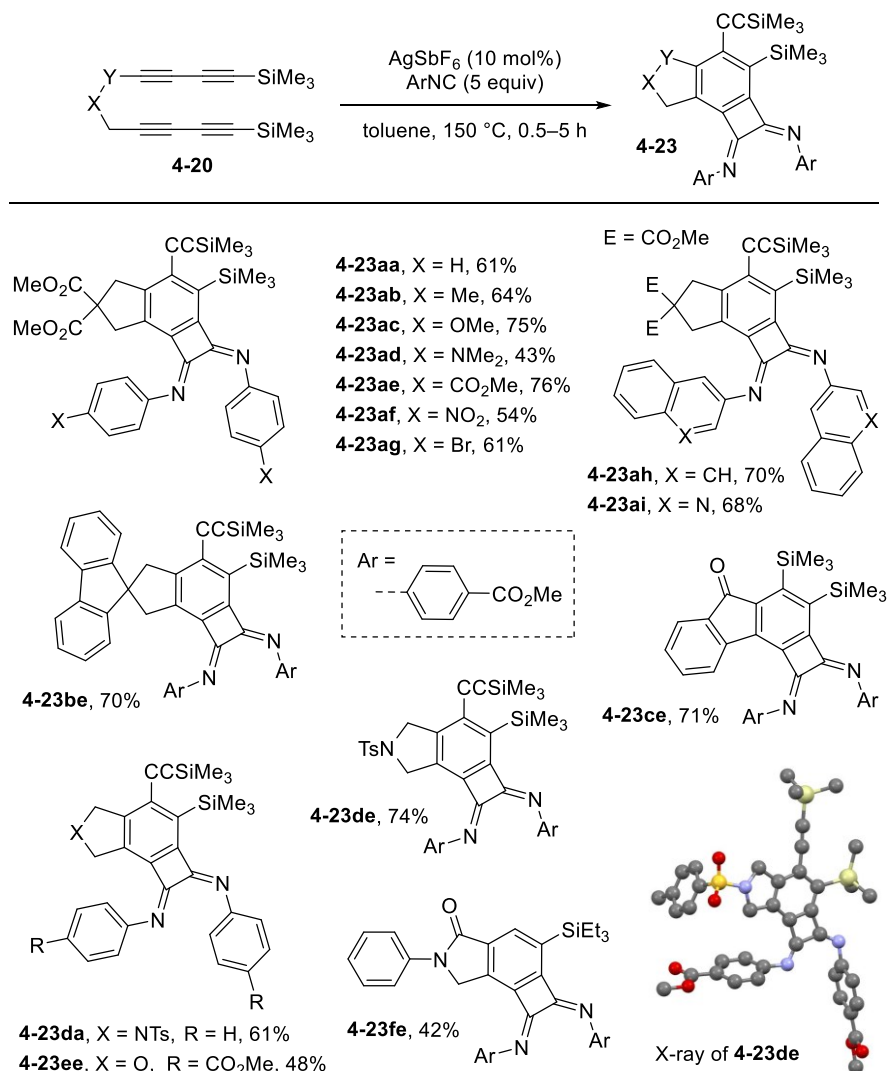
^a Measured by NMR with an internal standard (CH₂Br₂).

Table 4.1. Optimization of Metal Catalyst

4.2.2. Reaction Scope

Employing the optimized conditions, we next explored the generality of [A+2B] type MCR with isonitriles and tetraynes¹³ **4-20a** – **4-20f** (Scheme 4.9). Aromatic isonitriles containing either an electron-donating methyl (**4-23ab**), methoxy (**4-23ac**), or *para*-*N,N*-dimethyl (**4-23ad**) or an electron-withdrawing

carbomethoxy (**4-23ae**), nitro (**4-23af**) or bromo (**4-23ag**) substituent participated in the reaction, delivering desired benzocyclobutene-1,2-diimines in moderate to good (43–76%) yield. Bulkier isocyanides such as 2-isocyanonaphthalene and 3-isocyanquinoline provided products **4-23ah** (70%) and **4-23ai** (68%) in increased yield. Compared to the broad scope of aromatic isocyanides, aliphatic isocyanides¹⁴ did not afford benzocyclobutene-1,2-diimine products. The MCR reactions of different aryne precursors were also examined. The reaction of tetrayne tethered with a fluorenyl moiety afforded product **4-23be** in 70% yield while that with ketoarene-tethered triyne provided **4-23ce** in 71% yield. Tetraynes with an *N*-Ts and an ether linker participated in the reaction smoothly to generate **4-23da** and **4-23ee** in 61 and 48% yield.

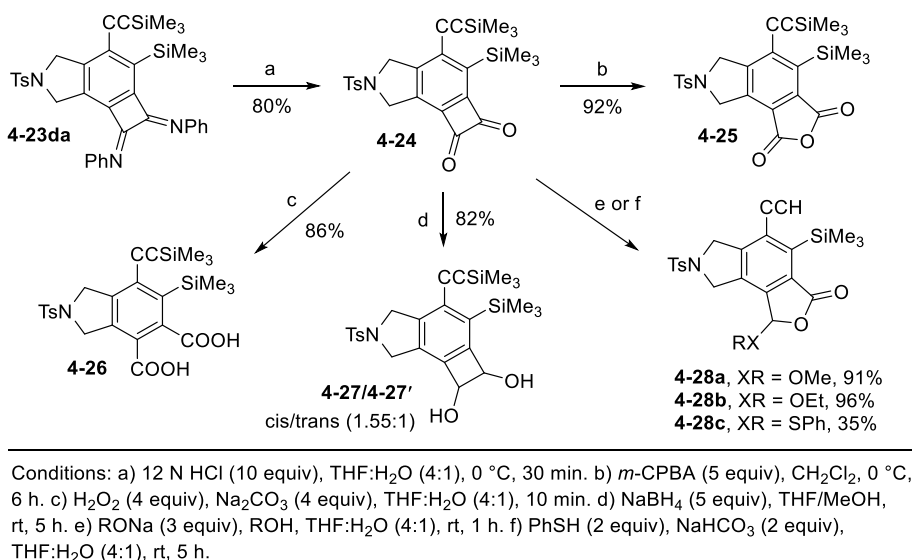


Scheme 4.9. [A+2B] MCR Reaction for Benzocyclobutene-1,2-diimines

An *N*-Ts-tethered tetrayne provided product **4-23de**, the X-ray diffraction analysis of which provided additional confirmation for these benzocyclobutene-1,2-diimine structures.¹⁵ Also, an amide-tethered triyne afforded product **4-23fe** in slightly lower yield (42%).

4.2.3. Transformation of Benzocyclobutene-1,2-diimines

Next, we explored conversion of benzocyclobutene-1,2-diimine to other functional groups (Scheme 4.10). Under acidic condition, 1,2-diimine moiety in **4-23da** was readily hydrolyzed to generate 1,2-diketone **4-24**.¹⁶ Treating **4-24** with *m*-CPBA induced Baeyer-Villiger oxidation to generate phthalic anhydride **4-25** in excellent yield,¹⁷ whereas with H₂O₂ in a basic medium formed phthalic acid **4-26**.¹⁸ Reaction with NaBH₄ afforded a mixture of *cis*/*trans*-diols **4-27/4-27'** in 82% yield.¹⁹ Interestingly, treating 1,2-diketone **4-24** with sodium alkoxide in alcoholic solvent provided 3-alkoxyphthalides **4-28a** and **4-28b**²⁰ in excellent yield, whereas sodium thiolate afforded **4-28c** in low yield.²¹

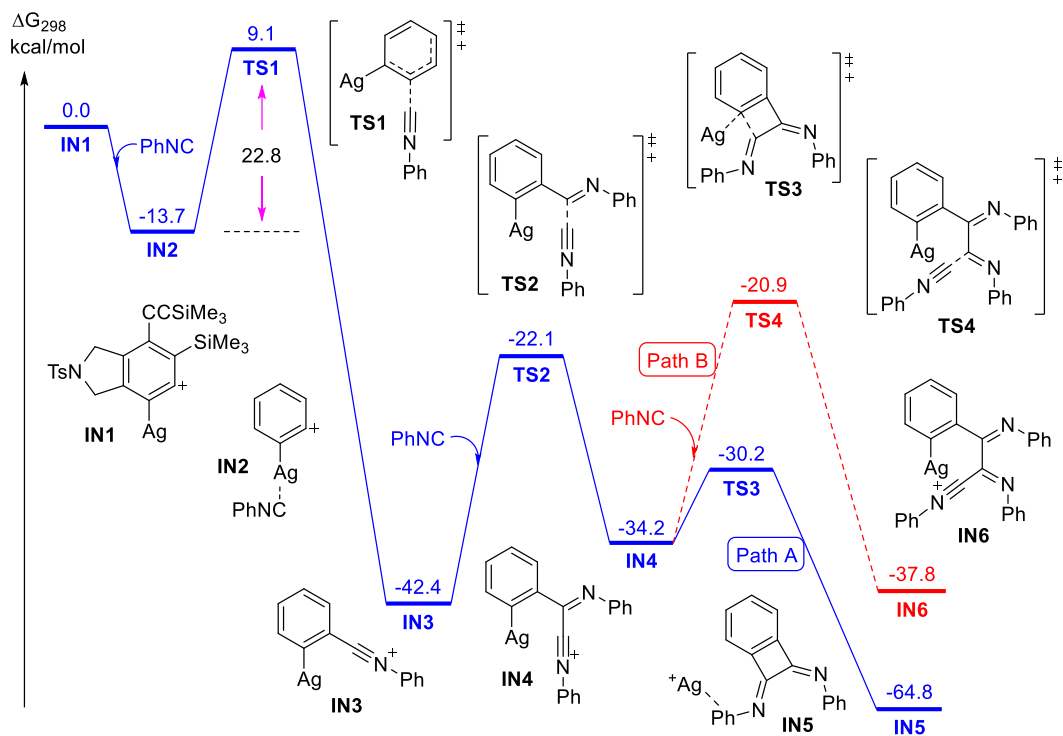


Scheme 4.10. Transformations of Benzocyclobutene-1,2-diimine

4.2.4. DFT Studies

To gain further insight into the reaction mechanism and regioselectivity, we carried out DFT calculations (SMD/M06/6-311++G(d,p)/SDD//B3LYP/631G*/Lanl2dz level of theory)²² (Scheme 4.11).

Calculations employed an *NTs*-tethered tetrayne (**4-20d**) that leads to product **4-23da**. These calculated reaction profiles indicate that silver-complexed aryne (**IN1**) interacts with benzonitrile to form more stable complex **IN2**, from which nitrilium species **IN3** could be formed via **TS1**. In the next step, intermediate **IN3** interacts with another benzonitrile to generate **IN4**. Due to a highly stabilized nature of an ionic complex **IN3**, its conversion to bis-isonitrile adduct **IN4** via **TS2** requires an activation barrier of 20.3 kcal/mol. Once intermediate **IN4** is generated, it can take two different reaction paths leading to ring closure or triple isonitrile adduct formation. The barrier for ring closure of **IN4** via **TS3** is only 4.0 kcal/mol (Path A), affording silver-complexed benzocyclobutene-1,2-diimine **IN5**. On the other hand, isonitrile complex **IN4** in Path B should overcome a much higher barrier of 13.3 kcal/mol to proceed to the next intermediate **IN6**. Thus, the thermodynamically and kinetically favorable formation of **IN5** in Path A provides the observed benzocyclobutene-1,2 diimine **4-23da**.



Scheme 4.11. DFT-Calculated Reaction Profiles for Selective Formation of Benzocyclobutene-1,2 Diimine over Triple Isonitrile Adduct (IN1 is the Actual Structure and the Rest Structures are Abbreviated)

4.3. Conclusion

In conclusion, we developed an unprecedented three-component coupling between arynes and aromatic isonitriles to synthesize poly-substituted *N*-aryl aromatic motifs. In the presence of a silver catalyst, a silver-complexed aryne intermediate form, which undergoes double addition with isonitriles to provide benzocyclobutene-1,2-diimines as the sole product. Starting with easily synthesizable alkyne building blocks, this highly atom economical protocol was developed at elevated temperature. DFT calculations revealed that the intramolecular ring closure of the bis-isonitrile adduct (**IN4**) to form benzocyclobutene-1,2-diimines is the consequence of both kinetic and thermodynamic preference over triple isonitrile adduct formation. Imine moieties of benzocyclobutene-1,2-diimines were found easily functionalizable and a series of transformations have been developed with it to generate diverse aromatic compounds. Use of no oxidant, benign reaction condition, easy operational procedure, one-pot operation, and broad substrate scope make this methodology highly valuable synthetic tool for the preparation of functionalized aromatic systems.²³

4.4. Experimental Details

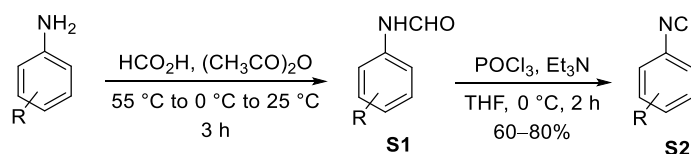
4.4.1. General Information

All reactions were carried out in oven or flame-dried glassware unless otherwise noted. Reagents which were commercially available, were purchased from Sigma-Aldrich, Alfa Aesar, Acros, and Oakwood Products unless otherwise noted. Known compounds were prepared according to literature procedure. Anhydrous acetonitrile from Sigma-Aldrich was distilled over calcium hydride (CaH_2) 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). Yield was calculated on basis of chromatographically and spectroscopically pure isolated compound. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AV-500 spectrometer. ^1H NMR chemical shifts (δ) were reported in parts per million (ppm) downfield of TMS and were referenced relative to the residual proteated solvent peak (CDCl_3 (7.26 ppm)). ^{13}C chemical shifts (δ) were reported in parts per million downfield of TMS and are referenced to the carbon resonance of the solvent (CDCl_3 , δ 77.2 ppm). Multiplicities in ^1H NMR were abbreviated by s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sext (sextet), sept (septet) 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 centre 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 (Waters Corporation, Milford, MA, USA) at the University of Illinois at Urbana-Champaign. Electron impact (EI) mass spectra was obtained using a Micromass 70-VSE (Waters Corporation, Milford, MA, USA) at the University of Illinois at Urbana-Champaign.

4.4.2. Experimental Procedures

Synthesis of Substrate: Substrate bis-1,3-diynes were prepared following the procedures mentioned in the experimental procedure section of Chapter 3.

General Procedures for Synthesis of Aromatic Isonitriles²⁴



A mixture of HCO₂H (4.0 mmol) and (CH₃CO)₂O (4.0 mmol) were stirred for 2 h at 55 °C. After cooling down the reaction mixture at 0 °C, aniline (2.0 mmol) was added slowly and continued stirring for additional 2 h at room temperature. After complete consumption of aniline, all the volatiles were removed from the reaction mixture under reduced pressure and the crude formamide **S1** was subjected to the next reaction without further purification.

To a stirred solution of formamide in dry THF at 0 °C were added Et₃N (10.0 mmol) and POCl₃ (2.4 mmol) dropwise sequentially. After additional stirring for 2 h at 0 °C, the reaction was quenched with water and extracted with EtOAc (X2). The combined organic layers were washed with water and brine sequentially and dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO, EtOAc–Hexane, 1:20 to 1:10) to isolate pure isonitriles **S2**.

Procedure A: Preparation of Benzocyclobutene-1,2-diimines (4-23)

Multiyne substrate **4-20** (0.1 mmol), isonitrile (0.5 mmol) and AgSbF₆ (0.01 mmol) were taken in dry PhCH₃ (3 mL) in a thick-walled Schlenk tube (10 mL). After flushing several times with nitrogen, the Schlenk tube was placed in a heated oil bath (150 °C) for 0.5–5 h. Upon completion, the reaction mixture was concentrated under reduced pressure and the crude material was purified by flash column chromatography (SiO, EtOAc–Hexane, 1:10 to 1:5) to isolate pure benzocyclobutene-1,2-diimine product.

Procedure B: Preparation of Benzocyclobutene-1,2-dione (4-24)

To a stirred solution of benzocyclobutene-1,2-diimine **4-23da** (210 mg, 0.32 mmol) in 4:1 THF/H₂O (4 mL) was added 12 N HCl (0.27 mL, 3.20 mmol) dropwise at 0 °C. After 30 min, the reaction mixture was diluted by water and extracted with EtOAc (X2). The combined organic extracts were washed with water and brine sequentially and dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude product of benzocyclobutene-1,2-dione **4-24** (129 mg, 80%) was subjected to the next reaction without further purification.

Procedure C: Preparation of Phthalic Anhydride (4-25)

To a stirred solution of benzocyclobutene-1,2-dione **4-24** (20 mg, 0.04 mmol) in THF at 0 °C under N₂ atmosphere was added *m*-CPBA (34.4 mg, 0.20 mmol) in one portion. After addition, the ice bath was removed and stirring was continued for 6 h at room temperature. Upon complete consumption of diketone, the reaction mixture was concentrated under reduced pressure and purified by flash column chromatography (celite, EtOAc–Hexane, 1:5) to isolate pure phthalic anhydride **4-25** (19 mg, 92%).

Procedure D: Preparation of Phthalic Acid (4-26)

To a stirred solution of benzocyclobutene-1,2-dione **4-24** (20 mg, 0.04 mmol) in 4:1 THF/H₂O (4 mL) were added H₂O₂ (0.02 mL, 30% (w/w) in H₂O, 0.16 mmol), Na₂CO₃ (17 mg, 0.16 mmol) sequentially at 0 °C. After complete addition, ice bath was removed, and the mixture was stirred for 10 min at room temperature. The reaction mixture was quenched by dropwise addition of 12 N HCl and extracted with EtOAc (x2). The combined organic extracts were washed with water and brine sequentially and dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. Pure phthalic acid **4-26** (18.2 mg, 86%) was isolated without further purification.

Procedure E: Preparation of Benzocyclobutene-1,2-diols (4-27)

To a stirred solution of benzocyclobutene-1,2-dione **4-24** (20 mg, 0.04 mmol) in THF at room temperature was added NaBH₄ (7.4 mg, 0.20 mmol) in one portion. After 5 h, the reaction mixture was

quenched with sat. NH_4Cl and extracted with EtOAc (x2). The combined organic layers were washed with water and brine sequentially and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO_2 , EtOAc–Hexane, 1:20) to isolate pure cis/trans diol compounds (16.4 mg, 82%).

Procedure F: Preparation of 3-Alkoxyphthalides (4-28a & 4-28b)

To a stirred solution of benzocyclobutene-1,2-dione **4-24** (20 mg, 0.04 mmol), R₃ONa (6.5 mg MeONa/ 8.2 mg EtONa, 0.12 mmol) was added in corresponding alcohol (MeOH/EtOH) medium at 0 °C. After addition, the ice bath was removed and the reaction mixture was stirred for 30 min at room temperature, and then the reaction was quenched with sat. NH_4Cl and extracted with EtOAc (x2). The combined organic layers were washed with water and brine sequentially and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Pure 3-alkoxyphthalides **4-28a** (16.6 mg, 91%), **4-28b** (18 mg, 96%) were isolated without further purification.

Procedure G: Preparation of 3-Thioalkoxyphthalides (4-28c)

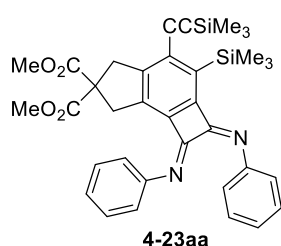
To a stirred solution of benzocyclobutene-1,2-dione **4-24** (20 mg, 0.04 mmol), in 4:1 THF/ H_2O (4 mL) were added PhSH (8.8 mg, 0.08 mmol) and NaHCO_3 (6.7 mg, 0.08 mmol) at 0 °C. After addition, the ice bath was removed, and the reaction mixture was stirred for 5 h at room temperature. The reaction was quenched with sat. NH_4Cl and extracted with EtOAc (x2). The combined organic layers were washed with water and brine sequentially and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO_2 , EtOAc–Hexane, 1:10) to isolate pure **4-28c** (8.5 mg, 35%).

Preparation of benzocyclobutene-1,2-diimine 4-23da in 1.0 mmol Scale

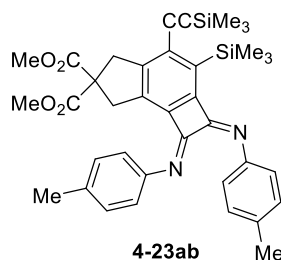
Multiyne substrate **4-20d** (440 mg, 1.0 mmol), phenyl isonitrile (515 mg, 5 mmol) and AgSbF_6 (34.4 mg, 0.1 mmol) were taken in dry PhCH_3 (10 mL) in a thick-walled Schlenk tube (25 mL). After flushing several times with nitrogen, the Schlenk tube was placed in a heated oil bath (150 °C) for 0.5 h.

Upon completion, the reaction mixture was concentrated under reduced pressure and the crude material was purified by flash column chromatography (SiO, EtOAc–Hexane, 1:10) to isolate pure benzocyclobutene-1,2-diimine **4-23da** (375 mg, 58%) product.

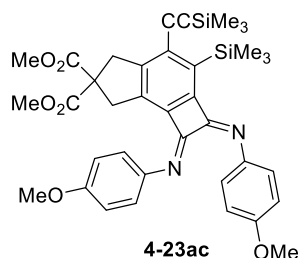
4.4.3. Characterization Data



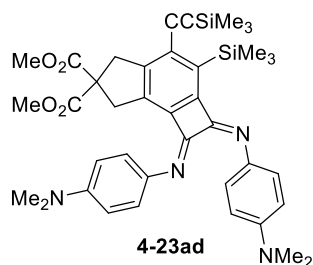
4-23aa: This product was synthesized using procedure **A** and isolated by flash column chromatography (SiO, EtOAc–Hexane, 1:10) as orange solid (61% yield, 36.4 mg) after stirring the reaction mixture for 2 h. **¹H NMR** (CDCl₃, 500 MHz): δ 7.48 (d, 2H, *J* = 7.6 Hz), 7.48 (t, 4H, *J* = 7.8 Hz), 7.2–7.12 (m, 2H), 6.90 (d, 2H, *J* = 7.4 Hz), 3.70 (s, 6H), 3.58 (s, 2H), 2.51 (s, 2H), 0.55 (s, 9H), 0.27 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 171.5, 163.6, 163.1, 163.0, 150.6, 149.6, 148.4, 146.9, 137.0, 134.4, 129.7, 128.9, 128.3, 125.5, 124.5, 123.3, 120.2, 106.1, 103.9, 58.6, 53.1, 41.7, 39.5, 0.5, –0.3; **HRMS** (ESI) calcd for C₃₅H₃₉N₂O₄Si₂ [M+H]⁺ 607.2448 found 607.2439.



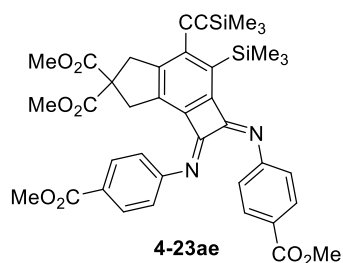
4-23ab: This product was synthesized using procedure **A** and isolated by flash column chromatography (SiO, EtOAc–Hexane, 1:10) as yellow solid (64%, 37.2 mg) yield after stirring the reaction mixture for 2 h. **¹H NMR** (CDCl₃, 500 MHz): δ 7.46 (d, 2H, *J* = 8.2 Hz), 7.16 (d, 2H, *J* = 8.0 Hz), 7.16 (d, 2H, *J* = 8.2 Hz), 6.81 (d, 2H, *J* = 8.1 Hz), 3.71 (s, 6H), 3.58 (s, 2H), 2.51 (s, 2H), 2.35 (s, 6H), 0.54 (s, 9H), 0.27 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 171.5, 163.8, 163.6, 162.3, 149.4, 148.3, 148.1, 144.3, 136.7, 135.5, 134.3, 134.0, 129.4, 129.0, 123.7, 120.3, 105.8, 104.0, 58.5, 53.3, 53.0, 41.6, 41.3, 39.4, 21.2, 20.8, 0.5, –0.3; **HRMS** (ESI) calcd for C₃₇H₄₃N₂O₄Si₂ [M+H]⁺ 635.2761 found 635.2758.



4-23ac: This product was synthesized using procedure **A** and isolated by flash column chromatography (SiO, EtOAc–Hexane, 1:10) as yellow solid (75% yield, 41.5 mg) after stirring the reaction mixture for 2 h. **¹H NMR** (CDCl₃, 500 MHz): δ 7.69 (d, 2H, *J* = 8.5 Hz), 6.96–6.87 (m, 6H), 3.82 (s, 6H), 3.71 (s, 6H), 3.59 (s, 2H), 2.65 (s, 2H), 0.54 (s, 9H), 0.27 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 171.5, 164.2, 164.0, 161.1, 158.1, 157.2, 148.9, 147.8, 144.0, 140.0, 136.3, 134.1, 129.3, 126.3, 121.6, 114.5, 113.6, 105.8, 104.1, 58.6, 55.8, 55.4, 53.0, 41.7, 39.9, 0.6, –0.3; **HRMS** (ESI) calcd for C₃₇H₄₃N₂O₆Si₂ [M+H]⁺ 667.2660 found 667.2654.

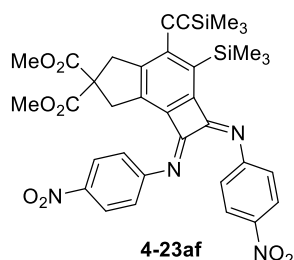


4-23ad: This product was synthesized using procedure **A** and isolated by flash column chromatography (SiO, EtOAc–Hexane, 1:10) as red solid (43% yield, 34.4 mg) after stirring the reaction mixture for 2 h. **¹H NMR** (CDCl₃, 500 MHz): δ 7.85 (d, 2H, *J* = 8.6 Hz), 6.92 (d, 2H, *J* = 8.5 Hz), 6.80 (d, 2H, *J* = 8.1 Hz), 6.73 (d, 2H, *J* = 8.5 Hz), 3.70 (s, 6H), 3.58 (s, 2H), 2.98 (s, 6H), 2.93 (s, 6H), 2.73 (s, 2H), 0.54 (s, 9H), 0.27 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 171.7, 164.8, 163.8, 158.8, 149.4, 148.8, 148.5, 147.1, 141.3, 136.5, 135.3, 133.8, 128.6, 127.3, 121.6, 113.9, 112.0, 105.0, 104.4, 58.7, 52.9, 41.6, 41.4, 40.7, 40.1, 0.7, –0.3; **HRMS** (ESI) calcd for C₃₉H₄₉N₄O₄Si₂ [M+H]⁺ 693.3292 found 693.3265.

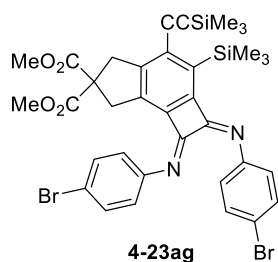


4-23ae: This product was synthesized using procedure **A** and isolated by flash column chromatography (SiO, EtOAc–Hexane, 1:10) as yellow-green solid (76% yield, 57.8 mg) after stirring the reaction mixture for 2 h. **¹H NMR** (CDCl₃, 500 MHz): δ 8.03 (d, 4H, *J* = 8.4 Hz), 7.32 (d, 2H, *J* = 8.5 Hz), 6.91 (d, 2H, *J* = 8.4 Hz), 3.92 (s, 3H), 3.89 (s, 3H), 3.69 (s, 6H), 3.60 (s, 2H), 2.50 (s, 2H), 0.53 (s, 9H), 0.28 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 171.2, 167.0, 166.7, 163.9, 163.1, 162.4, 154.3, 151.4, 149.7, 149.3, 138.0, 134.4, 130.7, 130.6, 130.1, 126.5, 126.4, 121.8, 120.2,

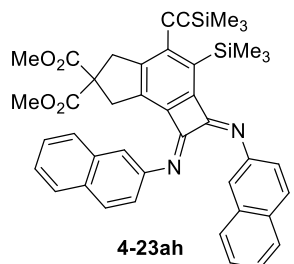
107.2, 103.5, 58.5, 53.1, 52.0, 51.9, 41.7, 39.7, 0.3, -0.4; **HRMS** (ESI) calcd for $C_{39}H_{43}N_2O_8Si_2$ $[M+H]^+$ 723.2558 found 723.2551.



4-23af: This product was synthesized using procedure **A** and isolated by flash column chromatography (SiO, EtOAc–Hexane, 1:5) as orange-yellow solid (54% yield, 38.2 mg) after stirring the reaction mixture for 2 h. **¹H NMR** ($CDCl_3$, 500 MHz): δ 9.10 (d, 2H, J = 8.3 Hz), 9.10 (d, 2H, J = 8.4 Hz), 7.31 (d, 2H, J = 8.2 Hz), 6.98 (d, 2H, J = 8.2 Hz), 3.70 (s, 6H), 3.62 (s, 2H), 2.51 (s, 2H), 0.53 (s, 9H), 0.29 (s, 9H); **¹³C NMR** ($CDCl_3$, 125 MHz): δ 171.0, 164.3, 162.8, 162.6, 155.5, 153.1, 150.2, 149.6, 144.8, 138.8, 134.3, 131.6, 125.0, 124.4, 121.9, 120.8, 108.4, 103.2, 58.4, 53.3, 41.7, 39.8, 0.2, -0.4; **HRMS** (ESI) calcd for $C_{35}H_{37}N_4O_8Si_2$ $[M+H]^+$ 697.2150 found 697.2153.

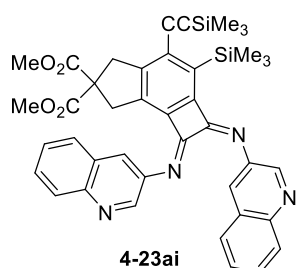


4-23ag: This product was synthesized using procedure **A** and isolated by flash column chromatography (SiO, EtOAc–Hexane, 1:10) as orange solid (61% yield, 37.6 mg) after stirring the reaction mixture for 2 h. **¹H NMR** ($CDCl_3$, 500 MHz): δ 8.48 (d, 2H, J = 8.6 Hz), 8.46 (d, 2H, J = 8.6 Hz), 7.32 (d, 2H, J = 8.6 Hz), 6.80 (d, 2H, J = 8.5 Hz), 3.74 (s, 6H), 3.60 (s, 2H), 2.54 (s, 2H), 0.52 (s, 9H), 0.27 (s, 9H); **¹³C NMR** ($CDCl_3$, 125 MHz): δ 171.3, 163.7, 163.4, 163.2, 149.4, 149.3, 148.9, 145.8, 137.5, 134.3, 132.0, 131.4, 130.3, 124.9, 122.2, 119.0, 117.7, 106.8, 103.7, 58.5, 53.2, 41.6, 39.6, 0.4, -0.4; **HRMS** (ESI) calcd for $C_{35}H_{37}N_2O_4Si_2Br_2$ $[M+H]^+$ 763.0659 found 763.0654.



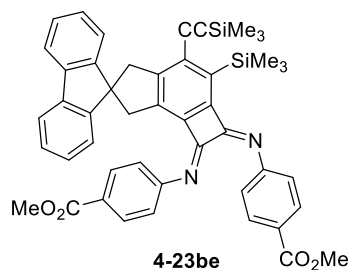
4-23ah: This product was synthesized using procedure **A** and isolated by flash column chromatography (SiO, EtOAc–Hexane, 1:10) as orange-red solid (70% yield, 53.3 mg) after stirring the reaction mixture for 2 h. **¹H NMR** ($CDCl_3$, 500 MHz): δ 8.33–8.27 (m 1H), 7.89–7.84 (m, 1H), 7.81 (d, 1H, J = 8.2 Hz), 7.68 (d, 1H, J = 8.2 Hz), 7.64 (d, 1H, J = 8.3 Hz), 7.59–7.48 (m, 5H), 7.45 (t, 1H, J = 6.6

Hz), 7.41 (t, 1H, $J = 7.8$ Hz), 7.35 (t, 1H, $J = 7.9$ Hz),), 6.84 (d, 1H, $J = 7.2$ Hz), 3.62 (s, 6H), 3.55 (s, 2H), 2.21 (s, 2H), 0.66 (s, 9H), 0.28 (s, 9H); ^{13}C NMR (CDCl₃, 125 MHz): δ 171.3, 164.6, 163.4, 162.8, 150.4, 148.8, 146.4, 144.2, 137.5, 134.2, 134.1, 133.9, 129.9, 128.4, 127.9, 127.8, 127.2, 126.2, 125.8, 125.7, 125.5, 125.4, 125.2, 124.9, 124.3, 123.9, 116.1, 114.1, 106.5, 103.8, 58.4, 53.0, 41.7, 40.1, 0.6, -0.3; HRMS (ESI) calcd for C₄₃H₄₃N₂O₄Si₂ [M+H]⁺ 707.2761 found 707.2768.



4-23ai: This product was synthesized using procedure **A** and isolated by flash column chromatography (SiO, EtOAc–Hexane, 1:5) as orange-yellow solid (68% yield, 45.1 mg) after stirring the reaction mixture for 2 h. ^1H NMR (CDCl₃, 500 MHz): δ 9.10 (d, 1H, $J = 2.4$ Hz), 8.64 (d, 1H, $J = 2.4$ Hz), 8.20 (d, 1H, $J = 2.0$ Hz), 8.10 (d, 2H, $J = 8.4$ Hz), 7.84 (d, 1H, $J = 8.0$ Hz), 7.78 (d, 1H,

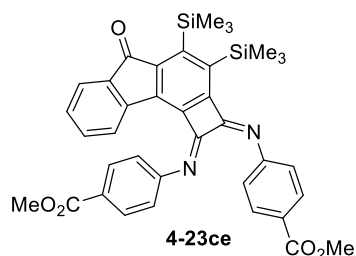
$J = 8.1$ Hz), 7.69–7.61 (m, 3H), 7.55 (td, 1H, $J = 7.6$ Hz, $J = 0.9$ Hz), 7.53 (td, 1H, $J = 7.4$ Hz, $J = 0.9$ Hz), 3.59 (s, 2H), 3.58 (s, 6H), 2.45 (s, 2H), 0.59 (s, 9H), 0.28 (s, 9H); ^{13}C NMR (CDCl₃, 125 MHz): δ 171.0, 165.0, 164.5, 163.6, 149.5, 147.5, 146.1, 145.7, 144.9, 142.9, 140.2, 138.0, 134.1, 130.9, 129.4, 129.2, 128.6, 128.4, 128.1, 128.0, 127.9, 127.4, 127.3, 127.1, 126.8, 126.6, 123.7, 123.1, 107.5, 103.5, 58.3, 53.3, 53.1, 41.7, 40.3, 0.4, -0.4; HRMS (ESI) calcd for C₄₁H₄₁N₄O₄Si₂ [M+H]⁺ 709.2666 found 709.2664.



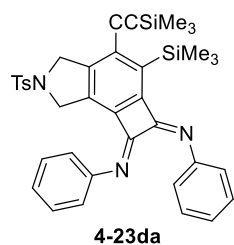
4-23be: This product was synthesized using procedure **A** and isolated by flash column chromatography (SiO, EtOAc–Hexane, 1:10) as orange-yellow solid (70% yield, 54.7 mg) after stirring the reaction mixture for 5 h. ^1H NMR (CDCl₃, 500 MHz): δ 8.04 (d, 2H, $J = 7.6$ Hz), 7.75 (d, 2H, $J = 7.4$ Hz), 7.70 (d, 2H, $J = 7.2$ Hz), 7.39–7.32 (m, 4H), 7.23 (t, 2H, $J = 6.9$

Hz), 7.12 (d, 2H, $J = 7.1$ Hz), 6.82 (d, 2H, $J = 7.5$ Hz), 3.89 (s, 3H), 3.73 (s, 3H), 3.47 (s, 2H), 2.53 (s, 2H), 0.61 (s, 9H), 0.17 (s, 9H); ^{13}C NMR (CDCl₃, 125 MHz): 167.0, 166.4, 164.4, 163.0, 161.9, 153.4, 152.5, 151.6, 151.5, 150.2, 139.5, 137.7, 137.2, 130.9, 130.6, 130.1, 127.8, 127.7, 126.4, 126.3, 122.1, 121.8,

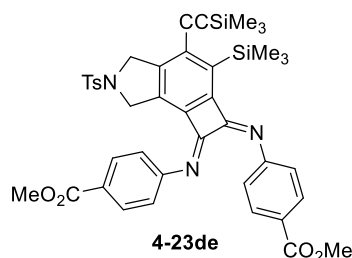
120.0, 119.9, 106.8, 103.8, 55.8, 51.9, 51.8, 46.8, 44.9, 0.5, -0.4; **HRMS** (ESI) calcd for $C_{47}H_{45}N_2O_4Si_2$ $[M+H]^+$ 757.2918 found 757.2912.



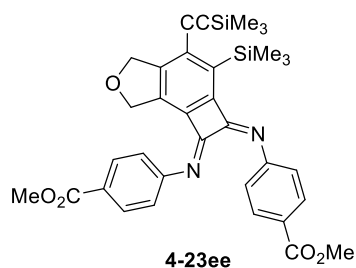
4-23ce: This product was synthesized using procedure **A** and isolated by flash column chromatography (SiO, EtOAc–Hexane, 1:10) as yellow solid (71% yield, 44.7 mg) after stirring the reaction mixture for 2 h. **¹H NMR** (CDCl₃, 500 MHz): 8.08 (d, 1H, J = 5.4 Hz), 7.69 (d, 1H, J = 6.0 Hz), 7.62–7.34 (m, 6H), 6.53 (d, 2H, J = 6.4 Hz), 6.48 (d, 2H, J = 6.6 Hz), 3.88 (s, 6H), 0.53 (s, 9H), 0.48 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 195.0, 166.6, 166.3, 163.2, 162.0, 159.1, 152.7, 152.4, 149.8, 148.4, 143.0, 141.3, 137.7, 135.4, 133.7, 130.7, 130.0, 126.5, 125.3, 124.3, 119.8, 119.4, 51.9, 2.7, 1.5; **HRMS** (ESI) calcd for $C_{37}H_{36}N_2O_5NaSi_2$ $[M+Na]^+$ 667.2060 found 667.2054.



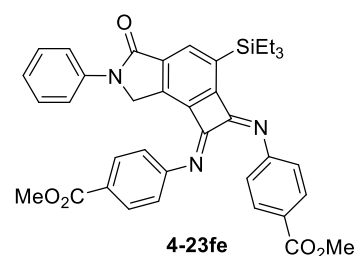
4-23da: This product was synthesized using procedure **A** and isolated by flash column chromatography (SiO, EtOAc–Hexane, 1:10) as orange-red solid (61% yield, 38.9 mg) after stirring the reaction mixture for 30 min. **¹H NMR** (CDCl₃, 500 MHz): δ 7.63 (d, 2H, J = 8.1 Hz), 7.55 (d, 2H, J = 7.8 Hz), 7.45–7.29 (m, 7H), 7.20 (t, 1H, J = 7.4 Hz), 6.87 (d, 2H, J = 7.6 Hz), 4.61 (s, 2H), 3.44 (s, 2H), 2.44 (s, 3H), 0.58 (s, 9H), 0.33 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 164.2, 162.7, 162.2, 150.4, 147.6, 146.5, 144.3, 144.0, 138.1, 133.4, 130.6, 129.8, 129.1, 128.5, 128.3, 127.6, 126.1, 125.0, 123.6, 120.0, 107.3, 102.7, 54.8, 52.5, 21.6, 0.4, -0.3; **HRMS** (ESI) calcd for $C_{37}H_{40}N_3O_2SSi_2$ $[M+H]^+$ 646.2380 found 646.2359.



4-23de: This product was synthesized using procedure **A** and isolated by flash column chromatography (SiO, EtOAc–Hexane, 1:10) as orange-yellow solid (74% yield, 54.0 mg) after stirring the reaction mixture for 30 min. **¹H NMR** (CDCl₃, 500 MHz): δ 8.08 (d, 2H, *J* = 7.9 Hz), 8.03 (d, 2H, *J* = 8.0 Hz), 7.56 (d, 2H, *J* = 7.8 Hz), 7.38 (d, 2H, *J* = 7.6 Hz), 7.33 (d, 2H, *J* = 8.1 Hz), 6.84 (d, 2H, *J* = 8.1 Hz), 4.58 (s, 2H), 4.00 (s, 3H), 3.89 (s, 3H), 3.35 (s, 2H), 2.44 (s, 3H), 0.52 (s, 9H), 0.29 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): 166.9, 166.5, 163.5, 163.2, 162.1, 154.0, 150.9, 147.8, 145.1, 144.1, 139.1, 133.1, 130.9, 130.6, 130.2, 129.9, 129.1, 127.6, 127.0, 122.0, 120.1, 108.3, 102.3, 54.7, 52.3, 52.0, 21.6, 0.2, –0.4; **HRMS** (ESI) calcd for C₄₁H₄₄N₃O₆Si₂S [M+H]⁺ 762.2489 found 762.2482.



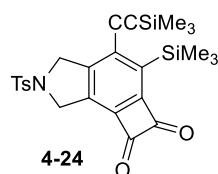
4-23ee: This product was synthesized using procedure **A** and isolated by flash column chromatography (SiO, EtOAc–Hexane, 1:10) as orange-yellow solid (48% yield, 27.2 mg) after stirring the reaction mixture for 30 min. **¹H NMR** (CDCl₃, 500 MHz): δ 8.07–8.01 (m, 4H), 7.36 (d, 2H, *J* = 7.9 Hz), 6.88 (d, 2H, *J* = 7.6 Hz), 5.05 (s, 2H), 4.07 (s, 2H), 3.92 (s, 3H), 3.89 (s, 3H), 0.56 (s, 9H), 0.26 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): 166.9, 166.5, 163.7, 163.6, 162.3, 153.8, 151.2, 148.7, 146.9, 138.3, 133.3, 130.8, 130.2, 127.8, 126.8, 126.7, 122.0, 119.9, 107.2, 102.7, 74.7, 73.0, 52.1, 52.0, 0.2, –0.5; **HRMS** (ESI) calcd for C₃₄H₃₇N₂O₅Si₂ [M+H]⁺ 609.2241 found 609.2236.



4-23fe: This product was synthesized using procedure **A** and isolated by flash column chromatography (SiO, EtOAc–Hexane, 1:5) as brown solid (42% yield, 31.5 mg) after stirring the reaction mixture for 2 h. **¹H NMR** (CDCl₃, 500 MHz): δ 8.21 (s, 1H), 8.17 (d, 2H, *J* = 7.6 Hz), 8.10 (d, 2H, *J* = 7.8 Hz), 7.56–7.48 (m, 4H), 7.34 (t, 1H, *J* = 7.5 Hz), 7.16 (t, 1H, *J* = 7.1

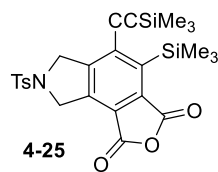
Hz), 7.08 (d, 1H, *J* = 7.5 Hz), 3.99 (s, 3H), 3.92 (s, 3H), 3.71 (s, 2H), 1.14–1.06 (m, 6H), 1.00 (t, 10H, *J* = 7.6 Hz); **¹³C NMR** (CDCl₃, 125 MHz): 167.1, 166.8, 166.4, 165.7, 163.6, 163.3, 154.9, 150.6, 149.0, 138.8,

136.3, 136.1, 136.0, 134.1, 130.8, 130.3, 129.2, 127.5, 127.1, 124.9, 122.7, 120.8, 118.7, 52.3, 52.1, 48.8, 7.4, 2.8; **HRMS** (ESI) calcd for $C_{38}H_{38}N_3O_5Si$ $[M+H]^+$ 644.2581 found 644.2584.



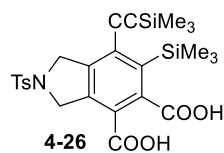
4-24: This product was synthesized using procedure **B** and isolated as orange solid (80% yield, 129 mg). **1H NMR** ($CDCl_3$, 500 MHz): δ 7.78 (d, 2H, $J = 7.9$ Hz), 7.35 (d, 2H, $J = 7.9$ Hz), 4.87 (s, 2H), 4.74 (s, 2H), 2.40 (s, 3H), 0.46 (s, 9H), 0.31 (s, 9H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 194.0, 192.8, 179.7, 165.5, 146.9, 144.3, 142.1, 133.4, 131.2, 131.0, 130.1, 127.6, 111.1, 101.5, 54.4, 53.2, 21.6, -0.5 ; **HRMS** (ESI) calcd for $C_{25}H_{30}NO_4Si_2S$ $[M+H]^+$ 496.1434 found 496.1451.



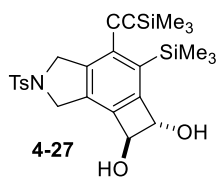
4-25: This product was synthesized using procedure **C** and isolated as orange solid (92% yield, 19 mg). **1H NMR** ($CDCl_3$, 500 MHz): δ 7.79 (d, 2H, $J = 7.2$ Hz), 7.35 (d, 2H, $J = 7.5$ Hz), 4.93 (s, 2H), 4.70 (s, 2H), 2.42 (s, 3H), 0.47 (s, 9H), 0.30 (s, 9H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 162.7, 161.9, 149.4, 144.9, 144.3, 136.4, 135.7, 133.5,

131.7, 130.1, 127.6, 124.9, 110.8, 101.5, 54.5, 53.0, 21.6, 1.0, -0.5 ; **HRMS** (ESI) calcd for $C_{25}H_{30}NO_5Si_2S$ $[M+H]^+$ 512.1383 found 512.1408.



4-26: This product was synthesized using procedure **D** and isolated as light orange solid (86% yield, 18.2 mg). **1H NMR** ($CDCl_3$, 500 MHz): δ 7.81 (d, 2H, $J = 8.2$ Hz), 7.35 (d, 2H, $J = 8.1$ Hz), 4.94 (s, 2H), 4.68 (s, 2H), 2.41 (s, 3H), 0.45 (s, 9H), 0.29 (s,

9H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 175.7, 170.5, 144.0, 142.6, 140.4, 140.2, 139.3, 133.6, 130.0, 129.2, 127.6, 121.3, 110.0, 102.0, 56.0, 54.0, 29.7, 21.5, 0.8, -0.5 ; **HRMS** (ESI) calcd for $C_{25}H_{30}NO_6Si_2S$ $[M-H]^+$ 528.1332 found 528.1328.



4-27: This product was synthesized using procedure **E** and isolated as light orange

solid (29% yield, 4.8 mg). **¹H NMR** (CDCl₃, 500 MHz): δ 7.77 (d, 2H, *J* = 8.1 Hz),

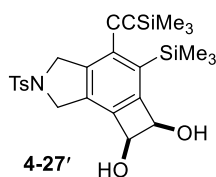
7.32 (d, 2H, *J* = 8.0 Hz), 5.32 (d, 1H, *J* = 6.8 Hz, *J* = 3.6 Hz), 5.23 (d, 1H, *J* = 6.5 Hz,

J = 3.6 Hz), 4.70–4.56 (m, 4H), 2.65 (d, 1H, *J* = 7.6 Hz), 2.56 (d, 2H, *J* = 7.1 Hz), 2.41

(s, 3H), 0.39 (s, 9H), 0.26 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 152.6, 143.8, 142.0, 140.9, 139.1, 133.7,

132.2, 129.9, 127.6, 125.3, 103.5, 102.9, 75.3, 71.8, 54.1, 52.3, 21.5, –0.3, –0.7; **HRMS** (ESI) calcd for

C₂₅H₃₄NO₄Si₂S [M+H]⁺ 500.1747 found 500.1759.



4-27': This product was synthesized using procedure **E** and isolated as light orange

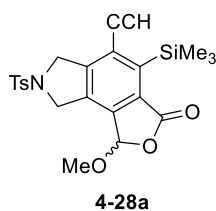
solid (53% yield, 11.6 mg). **¹H NMR** (CDCl₃, 500 MHz): δ 7.76 (d, 2H, *J* = 8.1 Hz),

7.32 (d, 2H, *J* = 8.0 Hz), 4.93 (d, 2H, *J* = 7.2 Hz), 4.92–4.88 (m, 2H), 4.66–4.55 (m,

4H), 2.41 (s, 3H), 2.39–2.34 (m, 1H), 2.30 (d, 2H, *J* = 8.0 Hz), 0.38 (s, 9H), 0.26 (s, 9H); **¹³C NMR**

(CDCl₃, 125 MHz): δ 149.3, 143.8, 142.2, 139.0, 136.8, 133.7, 132.1, 129.9, 127.6, 125.4, 103.5, 103.0,

81.1, 78.7, 54.1, 52.2, 21.5, –0.3, –0.6.



4-28a: This product was synthesized using procedure **F** and isolated in orange solid

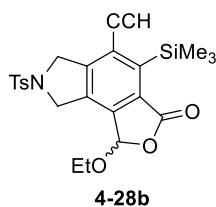
(91% yield, 16.6 mg). **¹H NMR** (CDCl₃, 500 MHz): δ 7.79 (d, 2H, *J* = 8.2 Hz), 7.34

(d, 2H, *J* = 8.1 Hz), 6.10 (s, 1H), 4.79–4.62 (m, 4H), 3.62 (s, 3H), 3.53 (s, 1H), 2.42

(s, 3H), 0.45 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 167.7, 147.4, 144.3, 144.1,

139.3, 133.6, 132.5, 132.4, 130.1, 127.5, 125.8, 100.7, 87.8, 81.1, 57.2, 54.7, 52.3, 21.6, 1.5; **HRMS** (ESI)

calcd for C₂₃H₂₆NO₅SiS [M+H]⁺ 456.1301 found 456.1311.



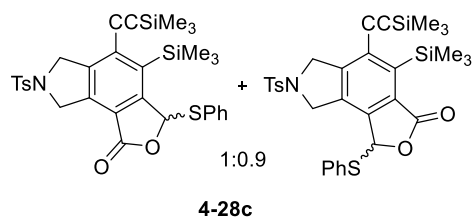
4-28b: This product was synthesized using procedure **F** and isolated as orange solid

(96% yield, 18 mg). **¹H NMR** (CDCl₃, 500 MHz): δ 7.78 (d, 2H, *J* = 8.3 Hz), 7.33 (d,

2H, *J* = 8.0 Hz), 6.17 (s, 1H), 4.80–4.62 (m, 4H), 4.02–3.93 (m, 1H), 3.87–3.80 (m,

1H), 3.53 (s, 1H), 2.41 (s, 3H), 1.31 (d, 3H, *J* = 7.1 Hz), 0.45 (s, 9H); **¹³C NMR**

(CDCl₃, 125 MHz): δ 167.9, 147.4, 144.2, 144.1, 139.6, 133.6, 132.4, 132.4, 130.0, 127.5, 125.7, 99.8, 87.7, 81.1, 66.2, 54.8, 52.3, 21.5, 15.1, 1.5; **HRMS** (ESI) calcd for C₂₄H₂₈NO₅SiS [M+H]⁺ 470.1457 found 470.1471.



4-28c: These products were isolated as orange-red solid (35% yield, 8.5 mg) as an inseparable mixture using procedure **G**. **¹H**

NMR (CDCl₃, 500 MHz): δ 7.82–7.73 (m, 4H), 7.56 (d, 2H, J = 6.6 Hz), 7.50–7.41 (m, 3H), 7.34 (d, 2H, J = 7.9 Hz), 7.29 (d,

2H, J = 8.1 Hz), 7.13–7.07 (m, 1H), 7.06–6.97 (m, 5H), 6.27 (s, 1H), 4.95–4.37 (m, 8H), 2.42 (s, 3H), 2.38 (s, 3H), 0.42 (s, 9H), 0.27 (s, 9H), 0.20 (s, 9H), –0.12 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 193.3, 180.2, 180.1, 166.1, 165.9, 149.6, 147.5, 146.4, 146.1, 144.3, 143.8, 142.5, 138.9, 138.4, 136.2, 135.3, 133.3, 132.9, 132.7, 131.1, 130.9, 130.8, 130.6, 130.1, 130.0, 129.9, 129.6, 128.7, 128.0, 127.7, 127.6, 54.2, 54.0, 53.0, 52.6, 21.5, 0.3, 0.2, –0.4, –0.7; **HRMS** (ESI) calcd for C₃₁H₃₅NO₄Si₂S₂Cl [M+Cl][–] 640.1235 found 640.1235.

4.5. Note

Computational study was conducted by Yongjia Lin and Prof. Yuanzhi Xia at Wenzhou University, China.

4.6. References

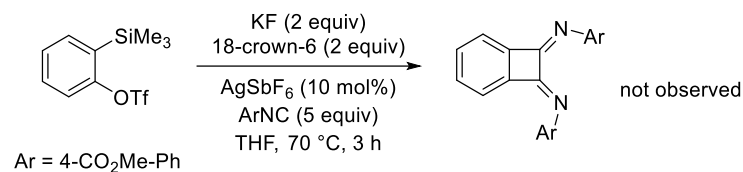
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- (21) The mechanism of these transformations is under investigations by DFT calculations.
- (22) DFT Studies were done at the SMD/M06/6-311++G(d,p)/SDD//B3LYP/6-31G*/Lanl2dz level of theory. All reported energy values are relative free energies including salvation corrections, and are relative to the energy of silver coordinated aryne complex. Computational details and full models for all transition states and intermediates are provided in supporting information.

- (23) We carried out the following experiments to compare the reaction profiles of arynes generated via a hexadehydro Diels-Alder reaction and fluoride-induced 1,2-elimination of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate.



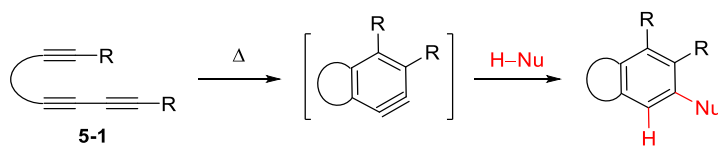
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CHAPTER 5

Silver-Catalyzed Annulation of Arynes with Nitriles and Isonitriles

5.1. Introduction*

Aryne is a versatile intermediate whereby numerous transformations have been developed to generate functionalized aromatic compounds.¹ 1,2-elimination of a prefunctionalized arene moieties is a common method to generate aryne species,² which however require prefunctionalized aromatic precursors limiting the structural and functional diversity of the products. On the other hand, direct cyclization of multiynes **5-1** to form arynes, named as hexadehydro Diels-Alder (HDDA) reaction,³ allows for the construction of structurally more complex and diverse arene products (**Scheme 5.1**). The temperature range for the aromatization subtly depends on the structure of the linker and the nature of their substituents.⁴ The HDDA reaction of tri- and tetraynes pioneered by Johnson and Ueda⁵, subsequently rediscovered by Hoyer, Lee and others has resulted in a significant expansion of the scope of aryne chemistry.⁶

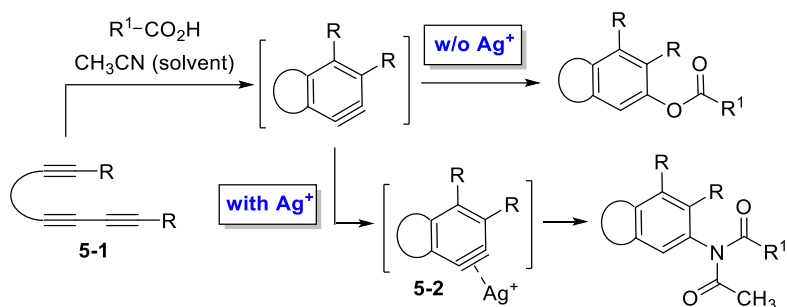


Scheme 5.1. Hexadehydro Diels-Alder Reaction

Silver catalysts are known to have a profound impact on the reactivity of arynes.⁷ By employing certain silver complexes as a catalyst, we have developed many aryne-based transformations including C–H insertion,⁸ nucleophilic trapping,⁹ hydroarylation,¹⁰ hydrofluorination,¹¹ hydride transfer reaction,¹² and so forth.¹³ It was shown that the reaction of arynes toward weak nucleophiles such as nitrile could be promoted by a silver catalyst even in the presence of nucleophiles of higher reactivity. For example, the reaction of an aryne generated from multiyne **5-1** reacts with nitrile first and subsequently with carboxylic acid to generate imide (**Scheme 5.2**).^{9b} This is surprising because, without a silver catalyst, the reaction

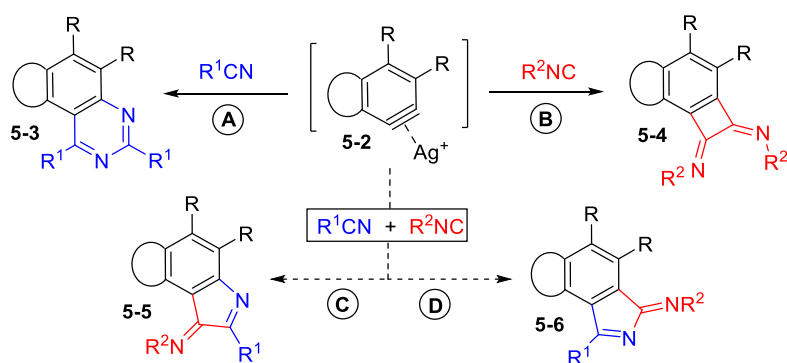
* Some parts of this chapter have been reproduced (adapted) partially with permission from Ghorai, S.; Lin, Y.; Xia, Y.; Wink, D. J.; Lee, D. “Silver-Catalyzed Selective Multicomponent Coupling Reactions of Arynes with Nitriles and Isonitriles” *Org. Lett.* **2020**, 22, 642. Copyright 2020, American Chemical Society.

between the aryne and carboxylic acid could be carried out in nitrile solvent to generate the corresponding aryl ester efficiently without participation of nitrile.¹⁴



Scheme 5.2. Different Reactivity of Aryne with and without Ag^+

Exploitation of the prowess of silver-catalyzed MCRs has shown that the reaction of the putative silver-complexed aryne **5-2** with nitriles provided quinazolines **5-3** through Path A,¹⁵ whereas in the presence of isonitriles, benzocyclobutene 1,2-diimines **5-4** was generated via Path B (Scheme 5.3).¹⁶ Having observed the reactivity of arynes toward nitriles and isonitriles under the influence of Ag^+ , we wonder about the possibility of hetero-MCR to generate products **5-5** and **5-6**. Depending on the stoichiometry and inherent reactivity of nitrile and isonitrile, aryne intermediate **5-2** might take Path C or Path D. Based on this hypothesis, we explored a new silver-catalyzed MCR of arynes with nitriles and isonitriles to generate **5-5** devoid of its constitutional isomer **5-6**.



Scheme 5.3. Silver-Catalyzed MCRs of Arynes with Nitriles and Isonitriles

5.2. Results and Discussion

Once formation of homo-coupled quinazoline **5-3** (Path A, Scheme 5.3) and benzocyclobutene-1,2-diimine **5-4** (Path B, Scheme 5.3) were realized efficiently, we pursued the possibility of generating a hetero-coupled aryne-nitrile-isonitrile adduct **5-5** (Path C in Scheme 5.3). We hypothesized that by controlling the stoichiometry of nitrile and isonitrile under the optimized conditions, appropriate kinetic and thermodynamic parameters could be found to favor the reaction Path C, leading to selective formation of adduct **5-5**. Because of the higher reactivity of isonitrile as a nucleophile,¹⁷ the incorporation of less reactive nitrile could be feasible either with its significantly higher concentration compared to that of isonitrile or activating aryne towards nitrile.

5.2.1. Optimization of Reaction Conditions

To verify these hypotheses, we first examined the impact of the stoichiometry of nitrile and isonitrile on the product distribution and yield (Table 5.1). With less than 5 equivalents of nitrile, hetero-coupled product **5-5ag** and homo-coupled product **5-4aa** were obtained in low yield and selectivity

(E = CO₂Me) **5-1a**

5-3aa **5-4aa** **5-5ag**

entry	PhCN : PhNC (equiv)	5-3aa + 5-4aa + 5-5ag (%) ^b	5-3aa : 5-4aa : 5-5ag ^b
1	1 : 1	30	0 : 0.45 : 1
2	2 : 2	43	0 : 1.2 : 1
3	2 : 1	48	0 : 0.8 : 1
4	3 : 1	52	0 : 0.7 : 1
5	5 : 5	63	0 : 10 : 1
6 ^c	300 : 3	85	0.1 : 0 : 1
7 ^c	300 : 5	83	0.1 : 0.1 : 1

^a AgSbF₆ (10 mol%), PhCN, PhNC, toluene, 150 °C, 2 h. ^b Measured by NMR with an internal standard (CH₂Br₂). ^c Toluene is replaced with PhCN.

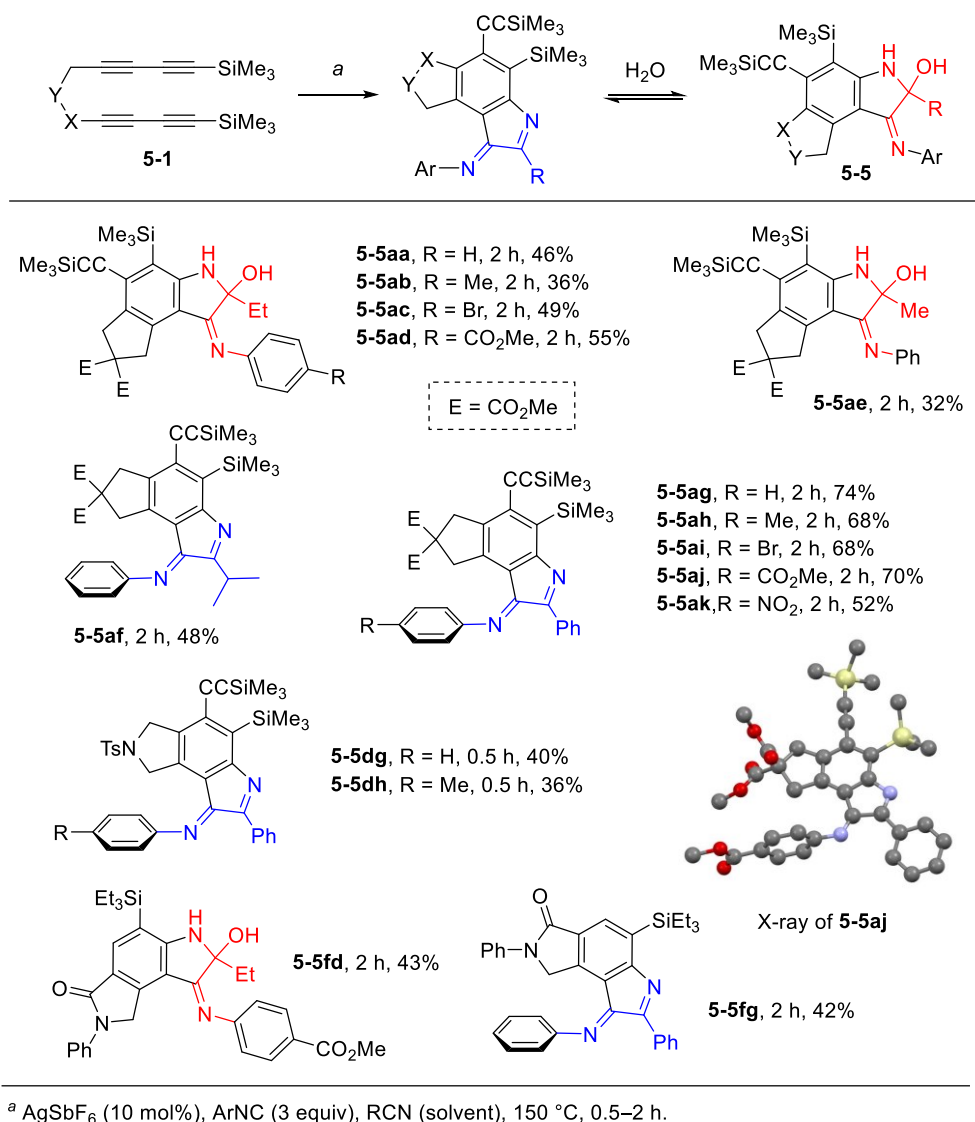
Table 5.1. Influence of Nitrile and Isonitrile Stoichiometry on the Yield and Product Distribution

(entries 1-4). When 5 equivalents of nitrile and isonitrile were employed, a good total yield of products **5-4aa** and **5-5ag** was observed with a 10:1 ratio (entry 5). Ultimately, by running the reaction in nitrile as the solvent with 3–5 equivalents of isonitrile, excellent yield and selectivity for the aryne-nitrile-isonitrile coupled product **5-5ag** was realized (entries 6 and 7). With large excess of nitrile, the small difference in isonitrile stoichiometry (3 equiv vs. 5 equiv) did not cause a significant difference for yield and selectivity. Surprisingly, even in a nitrile solvent, the formation of nitrile homo-coupled quinazolinoine **5-3aa** was observed only to a very minor extent.

5.2.2. Reaction Scope

With the optimized conditions in hand, we next explored the aryne-nitrile-isonitrile cross condensation with different combinations of substrates, nitriles and isonitriles to generate 3-iminoindolin-2-ol and 3*H*-indol-3-imine¹⁸ depending on the structure of nitrile (**Scheme 5.4**). When sterically unhindered nitriles such as acetonitrile or propionitrile were used, the expected product 3*H*-indol-3-imines were not obtained, instead 3-iminoindolin-2-ol **5-5aa** – **5-5ae** and **5-5fd** were obtained in moderate yields (36–55%). Based on extensive experimentations, we conclude that these products are derived from 3*H*-indol-3-imines via hydration by adventitious water in the reaction medium. On the contrary, sterically more hindered isobutyronitrile provided 3*H*-indol-3-imine **5-5af** (48%). This difference between methyl/ethyl versus isopropyl is due to the increased steric bulkiness of the isopropyl group, which disfavors the conversion the sp^2 -hybridized imine to the sp^3 -hybridized hemiaminal moiety. We suspect that other substituents that can electronically stabilize an imine¹⁹ should also provide 3*H*-indol-3-imine products without hydration. Indeed, the reactions with benzonitrile provided 3*H*-indol-3-imines **5-5ag** – **5-5ak** with improved yield. The reaction of *N*-Ts-tethered tetrayne with benzoisonitrile and *para*-toluene isonitrile provided 3*H*-indol-3-imines **5-5dg** and **5-5dh** in 40% and 36% yield, respectively. Triyne containing a phenyl amide tether provided 3-iminoindolin-2-ol **5-5fd** in 43% yield in propionitrile, whereas 3*H*-indol-3-imine **5-5fg** was obtained in benzonitrile in 42% yield.

The structural identity of 3*H*-indol-3-imine was ensured by X-ray crystallographic analysis of **5-5aj**²⁰ and that of iminoisoindolin-2-ol was confirmed by extensive nOe experiments. It is worth to mention that the stereochemistry of 3-imino moiety in 3*H*-indol-3-imines (**5-5ag** – **5-5ak**, **5-5fg**) is *E*-configuration, which is opposite to the *Z*-configuration of 3-iminoindolin-2-ols (**5-5aa** – **5-5ae**, **5-5fd**). Because of the *E*-configuration, the *N*-phenyl group on these 3*H*-indol-3-imines is perpendicular to the main frame of the molecule to avoid the steric clash.



Scheme 5.4. Aryne-Nitrile-Isonitrile Hetero-Coupling to Generate 3*H*-indol-3-imines and 3-Iminoindolin-2-ols

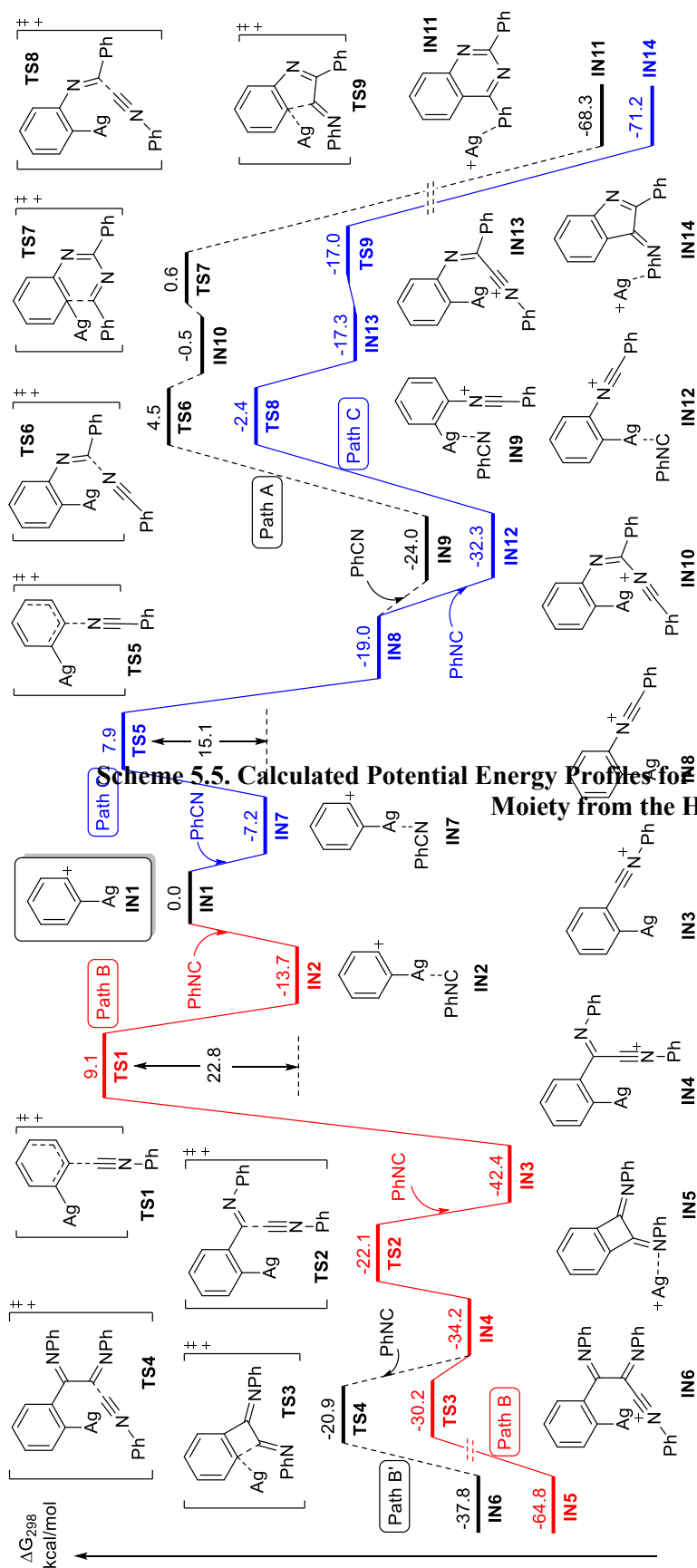
5.2.3. DFT Studies

To gain further insight into the mechanism and selectivity for the formation of 3*H*-indol-3-imines, we carried out DFT calculations (**Scheme 5.5**).²¹ The calculated reaction profiles show that the partitioning of Path B and Path C is dictated by the lower activation barrier of **IN7** to form nitrile adduct **IN8** via **TS5** (15.1 Kcal/mol) compared to that of **IN2** to form **IN3** via **TS1** (22.8 kcal/mol). Once intermediate **IN8** is generated, it reacts with isonitrile or nitrile in the subsequent step. In Path A, **IN8** reacts with nitrile to generate **IN9**, which proceeds to generate intermediate **IN10** via **TS6**, and the final ring closure of **IN10** through low barrier **TS7** yields **IN11**. On the other hand, in Path C, **IN8** forms isonitrile complex **IN12**, which leads to the next intermediate **IN13** via transition state **TS8**. Subsequently, **IN13** proceeds through a low barrier **TS9** to provide a silver complexed 3*H*-indol-3-imine **IN14**. The reaction profile in Path C, calculated to be the most favorable one, is consistent with the actual reaction occurred to generate 3*H*-indol-3-imines or 3-iminoindolin-2-ols.

5.3. Conclusion

In conclusion, we developed pathway-selective silver-catalyzed [A+B+C] and [A+B+C+D] type MCRs of arynes with isonitriles and nitriles. MCR with both nitrile and isonitrile produced 3*H*-indol-3-imines and 3-iminoindolin-2-ols via the incorporation of each molecule of nitrile and isonitrile rather than generating quinazolines via double nitrile addition or benzocyclobutene-1,2-diimines via double isonitrile addition. This intriguing pathway selectivity can be justified by DFT calculations, which show that in the first committed step the kinetically favored aryne-nitrile adduct **IN8** over aryne-isonitrile adduct **IN3**. The reversal of common reactivity trend of nitrile and isonitrile in this step is due to the presence of a silver catalyst, which forms more stable isonitrile complex **IN2** than nitrile complex **IN7**. In the second selectivity-determining step, the predominant formation of isonitrile complex **IN12** from **IN8** steers the overall reaction to proceed toward the formation of 3*H*-indol-3-imines and 3-iminoindolin-2-ols. The

different types of aryne-based MCRs render a broad substrate scope for all three components and show excellent regio- and pathway selectivity to generate novel molecular structures.²²



5.4. Experimental Details

5.4.1. General Information

All reactions were carried out in oven or flame-dried glassware unless otherwise noted. Reagents which were commercially available, were purchased from Sigma - Aldrich, Alfa Aesar, Acros, and Oakwood Products unless otherwise noted. Known compounds were prepared according to literature procedure. Anhydrous acetonitrile from Sigma-Aldrich was distilled over calcium hydride (CaH_2) 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). Yield was calculated on basis of chromatographically and spectroscopically pure isolated compound. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AV-500 spectrometer. ^1H NMR chemical shifts (δ) were reported in parts per million (ppm) downfield of TMS and were referenced relative to the residual proteated solvent peak (CDCl_3 (7.26 ppm)). ^{13}C chemical shifts (δ) were reported in parts per million downfield of TMS and are referenced to the carbon resonance of the solvent (CDCl_3 , δ 77.2 ppm). Multiplicities in ^1H NMR were abbreviated by s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sext (sextet), sept (septet) 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 centre 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 (Waters Corporation, Milford, MA, USA) at the University of Illinois at Urbana-Champaign. Electron impact (EI) mass spectra was obtained using a Micromass 70-VSE (Waters Corporation, Milford, MA, USA) at the University of Illinois at Urbana-Champaign.

5.4.2. Experimental Procedures

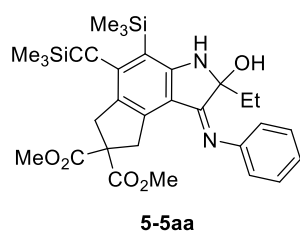
Synthesis of Substrates: The *bis*-1,3-diyne substrates were prepared following the procedures mentioned in the experimental procedure section of Chapter 3.

Synthesis of Aromatic Isonitriles: Aromatic isonitriles were prepared following the procedures mentioned in the experimental procedure section of Chapter 4.

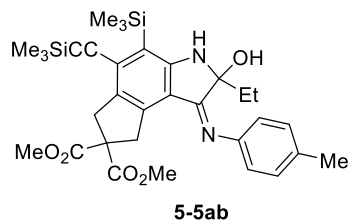
Procedure A: Preparation of 3*H*-Indol-3-imines or 3-Iminoindolin-2-ols (5-5)

Multiyne substrate **5-1** (0.1 mmol), isonitrile (0.3 mmol) and AgSbF₆ (0.01 mmol) were taken in a thick-walled Schlenk tube (10 mL) in nitrile solvent (3 mL). After flushing several times with nitrogen, the Schlenk tube was placed in a heated oil bath (150 °C) for 0.5–2 h. Upon completion, the reaction mixture was concentrated under reduced pressure, and the crude material was purified by flash column chromatography (SiO, EtOAc–Hexane, 1:10 to 1:3) to isolate pure indol-3-imine products.

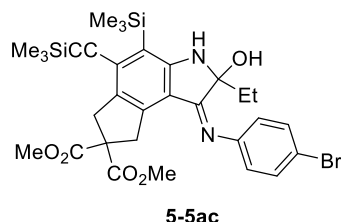
5.4.3. Characterization Data



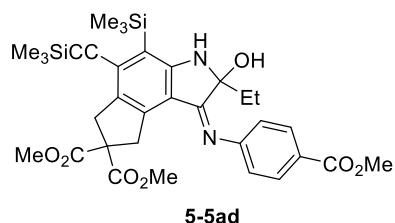
5-5aa: This product was synthesized using procedure **A** and isolated by flash column chromatography (SiO, EtOAc–Hexane, 1:5) as orange-red solid (46% yield, 26.1 mg) after stirring the reaction mixture for 2 h. **¹H NMR** (CDCl₃, 500 MHz): δ 8.16 (s, 1H), 7.11 (d, 2H, *J* = 7.8 Hz), 6.68 (t, 1H, *J* = 7.2 Hz), 6.53 (d, 2H, *J* = 7.8 Hz), 5.00 (s, 1H), 3.66 (s, 8H), 3.58 (s, 2H), 2.72 (q, 2H, *J* = 7.6 Hz), 1.24 (t, 3H, *J* = 7.7 Hz), 0.58 (s, 9H), 0.25 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 172.5, 149.1, 139.3, 138.2, 135.2, 130.4, 122.9, 121.0, 118.1, 117.5, 113.1, 112.8, 106.1, 100.4, 59.7, 52.8, 40.7, 39.8, 18.6, 13.3, 1.0, –0.1; **HRMS** (ESI) calcd for C₃₁H₃₉N₂O₅Si₂ [M-H][–] 575.2398 found 575.2390.



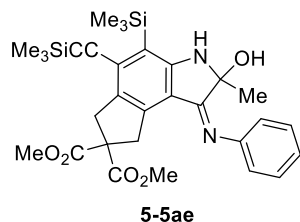
5-5ab: This product was synthesized using procedure **A** and isolated by flash column chromatography (SiO, EtOAc–Hexane, 1:5) as orange-red (36% yield, 23.8 mg) after stirring the reaction mixture for 2 h. ¹H NMR (CDCl₃, 500 MHz): δ 8.14 (s, 1H), 6.91 (d, 2H, *J* = 8.2 Hz), 6.44 (d, 2H, *J* = 8.4 Hz), 4.88 (s, 1H), 3.67 (s, 8H), 3.60 (s, 2H), 2.70 (q, 2H, *J* = 7.6 Hz), 2.22 (s, 3H), 1.23 (t, 3H, *J* = 7.6 Hz), 0.57 (s, 9H), 0.25 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz): δ 172.5, 146.8, 139.2, 138.2, 135.1, 130.5, 129.6, 126.5, 123.0, 121.0, 118.0, 113.2, 113.0, 106.1, 100.3, 59.7, 52.8, 40.7, 39.8, 20.4, 18.6, 13.3, 1.0, –0.1; **HRMS** (ESI) calcd for C₃₂H₄₃N₂O₅Si₂ [M+H]⁺ 591.2711 found 591.2688.



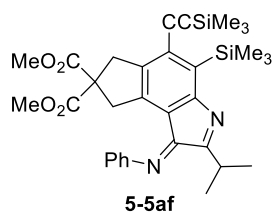
5-5ac: This product was synthesized using procedure **A** and isolated by flash column chromatography (SiO, EtOAc–Hexane, 1:5) as orange-red solid (49% yield, 32.5 mg) after stirring the reaction mixture for 2 h. ¹H NMR (CDCl₃, 500 MHz): δ 8.17 (s, 1H), 7.18 (d, 2H, *J* = 8.7 Hz), 6.40 (d, 2H, *J* = 8.8 Hz), 5.03 (s, 1H), 3.68 (s, 6H), 3.66 (s, 2H), 3.55 (s, 2H), 2.69 (q, 2H, *J* = 7.6 Hz), 1.23 (t, 3H, *J* = 7.6 Hz), 0.57 (s, 9H), 0.26 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz): δ 172.4, 148.2, 139.4, 138.2, 135.4, 131.9, 130.2, 122.6, 121.2, 118.3, 114.6, 112.2, 109.1, 105.9, 100.6, 59.7, 52.9, 40.7, 39.7, 18.6, 13.3, 1.0, –0.1; **HRMS** (ESI) calcd for C₃₁H₃₈BrN₂O₅Si₂ [M-H][–] 653.1503 found 653.1498.



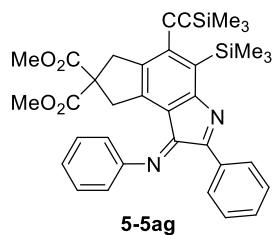
5-5ad: This product was synthesized using procedure **A** and isolated by flash column chromatography (SiO, EtOAc–Hexane, 1:5) as orange-red solid (55% yield, 31.2 mg) after stirring the reaction mixture for 2 h. ¹H NMR (CDCl₃, 500 MHz): δ 8.22 (s, 1H), 7.81 (d, 2H, *J* = 8.7 Hz), 6.52 (d, 2H, *J* = 8.4 Hz), 5.42 (s, 1H), 3.84 (s, 3H), 3.66 (s, 8H), 3.55 (s, 2H), 2.69 (q, 2H, *J* = 7.6 Hz), 1.23 (d, 3H, *J* = 7.6 Hz), 0.58 (s, 9H), 0.26 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz): δ 172.4, 167.3, 153.0, 139.3, 138.2, 135.6, 131.5, 130.2, 122.5, 121.3, 119.1, 118.5, 112.2, 111.3, 105.9, 100.7, 59.7, 52.9, 51.5, 40.7, 39.6, 18.6, 13.2, 1.0, –0.1; **HRMS** (ESI) calcd for C₃₃H₄₁N₂O₇Si₂ [M-H][–] 633.2452 found 633.2451.



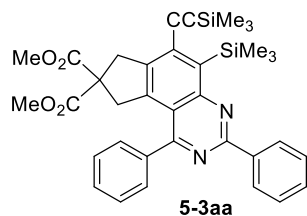
5-5ae: This product was synthesized using procedure A and isolated by flash column chromatography (SiO, EtOAc–Hexane, 1:5) as (32% yield, 27.3 mg) after stirring the reaction mixture for 2 h. **¹H NMR** (CDCl₃, 500 MHz): δ 8.09 (s, 1H), 7.11 (t, 2H, *J* = 7.3 Hz), 6.69 (t, 1H, *J* = 7.2 Hz), 6.52 (d, 2H, *J* = 7.4 Hz), 5.01 (br, 1H), 3.66 (s, 8H), 3.59 (s, 2H), 2.31 (s, 3H), 0.57 (s, 9H), 0.25 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): 172.5, 148.9, 138.3, 135.2, 133.8, 130.3, 129.2, 122.9, 121.0, 118.1, 117.6, 113.8, 113.1, 106.1, 100.5, 59.6, 52.8, 40.7, 39.7, 11.1, 1.0, –0.1; **HRMS** (ESI) calcd for C₃₀H₃₇N₂O₅Si₂ [M-H][–] 561.2241 found 561.2244.



5-5af: This product was synthesized using procedure A and isolated by flash column chromatography (SiO, EtOAc–Hexane, 1:10) as red solid (48% yield, 27.1 mg) after stirring the reaction mixture for 2 h. **¹H NMR** (CDCl₃, 500 MHz): δ 7.35 (d, 2H, *J* = 7.4 Hz), 7.15 (t, 1H, *J* = 7.5 Hz), 6.86 (d, 2H, *J* = 7.8 Hz), 3.65 (s, 6H), 3.43 (s, 2H), 3.27 (sept, 1H, *J* = 6.7 Hz), 2.20 (s, 2H), 1.33 (d, 6H, *J* = 6.6 Hz), 0.46 (s, 9H), 0.24 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 171.6, 151.4, 143.6, 138.3, 132.9, 128.7, 128.6, 124.5, 119.5, 118.2, 104.9, 104.6, 58.4, 52.8, 40.7, 40.3, 27.5, 21.0, 1.7, –0.3; **HRMS** (ESI) calcd for C₃₂H₄₁N₂O₄Si₂ [M+H]⁺ 573.2605 found 573.2602.

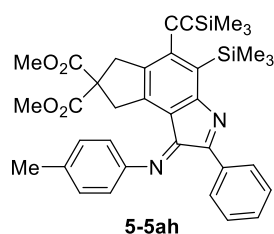


5-5ag: This product was synthesized using procedure A and isolated by flash column chromatography (SiO, EtOAc–Hexane, 1:10) as red solid (74% yield, 46.2 mg) after stirring the reaction mixture for 2 h. **¹H NMR** (CDCl₃, 500 MHz): δ 8.50–8.39 (m, 2H), 7.51–7.42 (m, 3H), 7.38 (d, 2H, *J* = 7.6 Hz), 7.17 (t, 1H, *J* = 7.4 Hz), 6.92 (d, 2H, *J* = 7.6 Hz), 3.67 (s, 6H), 3.48 (s, 2H), 2.26 (s, 2H), 0.55 (s, 9H), 0.27 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 171.6, 164.5, 164.1, 162.7, 151.2, 144.3, 138.4, 134.0, 132.6, 130.6, 130.1, 129.1, 128.7, 128.3, 124.6, 119.5, 118.0, 105.3, 104.5, 58.4, 52.9, 40.8, 40.4, 1.8, –0.3; **HRMS** (ESI) calcd for C₃₅H₃₉N₂O₄Si₂ [M+H]⁺ 607.2448 found 607.2450.



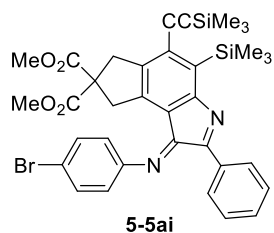
5-3aa: This product was synthesized using procedure **A** and isolated by flash column chromatography (SiO, EtOAc–Hexane, 1:10) as white solid (8% yield, 5 mg) after stirring the reaction mixture for 2 h. This is the byproduct, isolated during the optimization of reaction conditions for the formation of **5-5ag**

(**Table 5.1** in ‘Results and Discussion’ section). **¹H NMR** (CDCl₃, 500 MHz): δ 8.64–8.60 (m, 2H), 7.60–7.44 (m, 8H), 3.73 (s, 2H), 3.69 (s, 6H), 3.14 (s, 2H), 0.64 (s, 9H), 0.31 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 171.8, 167.9, 157.3, 156.8, 142.3, 140.5, 138.1, 136.4, 131.5, 130.3, 129.5, 129.0, 128.7, 128.5, 128.3, 118.8, 105.9, 103.8, 59.1, 53.0, 43.0, 41.4, 2.9, –0.3; **HRMS** (ESI) calcd for C₃₅H₃₉N₂O₄Si₂ [M+H]⁺ 607.2448, found 607.2450.



5-5ah: This product was synthesized using procedure **A** and isolated by flash column chromatography (SiO, EtOAc–Hexane, 1:10) as red solid (68% yield, 43.0 mg) after stirring the reaction mixture for 2 h. **¹H NMR** (CDCl₃, 500 MHz):

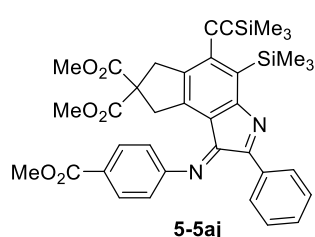
δ 8.47–8.38 (m, 2H), 7.51–7.41 (m, 3H), 7.19 (d, 2H, *J* = 7.7 Hz), 6.82 (d, 2H, *J* = 7.8 Hz), 3.67 (s, 6H), 3.49 (s, 2H), 2.37 (s, 3H), 2.30 (s, 2H), 0.54 (s, 9H), 0.26 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 171.6, 164.6, 164.0, 162.8, 148.9, 144.3, 138.3, 134.5, 133.9, 132.7, 130.5, 130.2, 129.2, 128.2, 119.7, 118.1, 105.1, 104.5, 58.4, 52.9, 40.7, 40.4, 20.9, 1.9, –0.2; **HRMS** (ESI) calcd for C₃₆H₄₁N₂O₄Si₂ [M+H]⁺ 621.2605 found 621.2603.



5-5ai: This product was synthesized using procedure **A** and isolated by flash column chromatography (SiO, EtOAc–Hexane, 1:10) as red solid (68% yield, 44.7 mg) after stirring the reaction mixture for 2 h. **¹H NMR** (CDCl₃, 500 MHz): δ 8.38

(d, 2H, *J* = 5.4 Hz), 7.50 (d, 2H, *J* = 8.3 Hz), 7.49–7.42 (m, 3H), 6.8 (d, 2H, *J* = 8.3 Hz), 3.72 (s, 6H), 3.51 (s, 2H), 2.29 (s, 2H), 0.53 (s, 9H), 0.26 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 171.5, 164.5, 164.1, 163.3, 150.2, 144.4, 138.3, 134.3, 132.4, 131.7, 130.7, 130.1, 128.3, 121.3, 117.8,

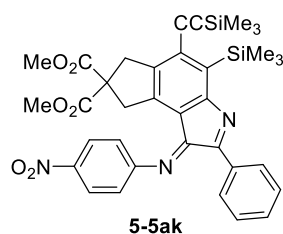
117.7, 105.7, 104.3, 58.4, 53.1, 40.9, 40.3, 1.8, -0.3; **HRMS** (ESI) calcd for $C_{35}H_{38}BrN_2O_4Si_2$ $[M+H]^+$ 685.1553 found 685.1556.



5-5aj

5-5aj: This product was synthesized using procedure **A** and isolated by flash column chromatography (SiO, EtOAc–Hexane, 1:10) as red solid (70% yield, 53.4 mg) after stirring the reaction mixture for 2 h. **¹H NMR** (CDCl₃, 500 MHz): δ 8.39 (br, 2H), 8.19–7.94 (m, 2H), 7.46 (br, 2H), 7.05–6.86 (m, 2H),

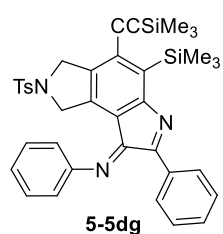
3.93 (s, 3H), 3.64 (s, 6H), 3.48 (s, 2H), 2.20 (s, 2H), 0.53 (s, 9H), 0.26 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 171.4, 166.6, 164.3, 162.7, 155.0, 144.5, 138.4, 134.5, 132.3, 130.8, 130.4, 130.0, 129.1, 128.3, 126.2, 119.2, 117.7, 105.8, 104.3, 58.3, 52.9, 52.0, 40.8, 40.3, 1.8, -0.3; **HRMS** (ESI) calcd for $C_{37}H_{41}N_2O_6Si_2$ $[M+H]^+$ 665.2503 found 665.2500.



5-5ak

5-5ak: This product was synthesized using procedure **A** and isolated by flash column chromatography (SiO, EtOAc–Hexane, 1:5) as red solid (52% yield, 31.5 mg) after stirring the reaction mixture for 2 h. **¹H NMR** (CDCl₃, 500 MHz): δ 8.48–8.12 (m, 4H), 7.50–7.31 (m, 3H), 7.12–6.94 (m, 2H), 3.65 (s, 6H), 3.49 (s,

2H), 2.22 (br, 2H), 0.53 (s, 9H), 0.26 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 171.3, 164.1, 163.1, 156.3, 144.7, 144.5, 138.4, 135.0, 132.2, 130.9, 129.8, 129.6, 128.3, 124.6, 119.7, 106.5, 104.1, 58.4, 53.1, 40.9, 40.3, 1.7, -0.3; **HRMS** (ESI) calcd for $C_{35}H_{38}N_3O_6Si_2$ $[M+H]^+$ 652.2299 found 652.2300.



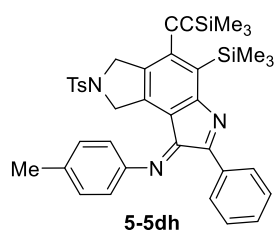
5-5dg

5-5dg: This product was synthesized using procedure **A** and isolated by flash column chromatography (SiO, EtOAc–Hexane, 1:10) as red solid (40% yield, 28.9 mg) after stirring the reaction mixture for 30 min. **¹H NMR** (CDCl₃, 500 MHz): δ 8.40 (d, 2H, $J = 6.8$ Hz), 7.54 (d, 2H, $J = 8.0$ Hz), 7.51–7.41 (m, 3H), 7.40–7.34 (m, 1H), 7.31 (d,

2H, $J = 7.9$ Hz), 6.86 (d, 2H, $J = 7.6$ Hz), 4.44 (s, 2H), 3.18 (s, 2H), 2.43 (s, 3H), 0.52 (s, 9H), 0.27 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 164.7, 164.6, 161.6, 150.4, 143.7, 140.3, 135.0, 134.3, 133.2, 132.2, 130.9,

130.2, 129.6, 128.8, 128.3, 127.8, 127.5, 125.4, 119.0, 116.0, 106.6, 103.1, 53.7, 53.5, 21.6, 1.7, -0.3;

HRMS (ESI) calcd for $C_{37}H_{40}N_3O_2SSi_2$ $[M+H]^+$ 646.2380 found 646.2388.



5-5dh: This product was synthesized using procedure **A** and isolated by flash column chromatography (SiO, EtOAc–Hexane, 1:10) as red solid (36% yield,

23.8 mg) after stirring the reaction mixture for 30 min. **1H NMR** ($CDCl_3$, 500

MHz): δ 8.39 (d, 2H, J = 6.8 Hz), 7.53 (d, 2H, J = 8.1 Hz), 7.49–7.41 (m, 3H),

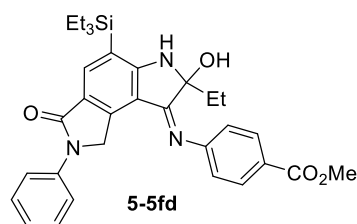
7.32 (d, 2H, J = 7.8 Hz), 7.27 (d, 2H), 6.76 (d, 2H, J = 8.0 Hz), 4.42 (s, 2H), 3.24 (s, 2H), 2.54 (s, 3H), 2.42

(s, 3H), 0.51 (s, 9H), 0.26 (s, 9H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 164.7, 164.6, 161.6, 148.2, 143.7, 140.3,

135.4, 134.9, 134.2, 133.3, 132.3, 130.9, 130.2, 129.6, 129.4, 128.3, 127.6, 127.2, 119.1, 116.1, 106.5,

103.2, 53.7, 53.6, 21.5, 21.1, 1.7, -0.3; **HRMS** (ESI) calcd for $C_{38}H_{42}N_3O_2SSi_2$ $[M+H]^+$ 660.2536 found

660.2532.



5-5fd: This product was synthesized using procedure **A** and isolated by flash column chromatography (SiO, EtOAc–Hexane, 1:3) as orange-red

solid (43% yield, 21.7 mg) after stirring the reaction mixture for 2 h. **1H**

NMR ($CDCl_3$, 500 MHz): δ 8.19 (s, 1H), 7.88 (d, 2H, J = 8.2 Hz), 7.80 (s,

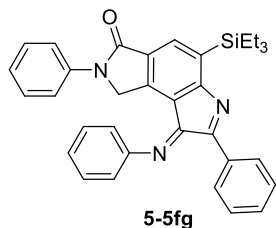
1H), 7.68 (d, 2H, J = 8.0 Hz), 7.34 (t, 2H, J = 7.5 Hz), 7.10 (t, 1H, J = 7.2 Hz), 6.65 (d, 2H, J = 7.4 Hz),

5.47 (s, 1H), 4.65 (s, 2H), 3.84 (s, 3H), 2.81 (q, 2H, J = 6.9 Hz), 1.30 (t, 2H, J = 7.4 Hz), 1.10–0.93 (m,

15H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 168.8, 167.1, 152.4, 140.8, 139.9, 139.0, 133.4, 131.8, 129.0, 125.4,

124.1, 123.8, 120.0, 119.8, 119.1, 112.3, 112.1, 51.6, 49.6, 18.7, 13.5, 7.5, 4.2; **HRMS** (ESI) calcd for

$C_{32}H_{38}N_3O_4Si$ $[M+H]^+$ 556.2632 found 556.2631.



5-5fg: This product was synthesized using procedure A and isolated by flash column chromatography (SiO, EtOAc–Hexane, 1:5) as red solid (42% yield, 33.5 mg) after stirring the reaction mixture for 2 h. **¹H NMR** (CDCl₃, 500 MHz): δ 8.50 (d, 2H, *J* = 7.6 Hz), 8.08 (s, 1H), 7.58–7.6 (m, 7H), 7.39 (d, 1H, *J* = 6.9 Hz), 7.34 (t, 2H, *J* = 7.8 Hz), 7.12 (t, 1H, *J* = 7.2 Hz), 7.04 (d, 2H, *J* = 7.6 Hz), 3.50 (s, 2H), 1.05–0.98 (m, 15H); **¹³C NMR** (CDCl₃, 125 MHz): δ 168.3, 166.3, 162.4, 151.3, 139.2, 137.7, 136.0, 132.7, 132.3, 132.2, 131.3, 130.4, 129.3, 128.9, 128.5, 125.2, 124.1, 120.7, 119.0, 118.7, 49.6, 7.6, 2.8; **HRMS** (ESI) calcd for C₃₄H₃₄N₃OSi [M+H]⁺ 528.2471 found 528.2473.

5.5. Note

Computational study was conducted by Yongjia Lin and Prof. Yuanzhi Xia at Wenzhou University, China.

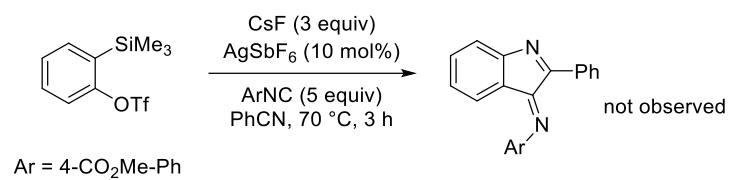
5.6. References

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- (20) The crystallographic information for **5-5aj** (CCDC 1911067) can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
- (21) DFT Studies were carried out at the SMD/M06/6-311++G(d,p)/SDD//B3LYP/6-31G*/Lanl2dz level of theory. All reported energy values are relative free energies including salvation corrections, and are relative to the energy of silver coordinated aryne complex. Computational details and full models for all transition states and intermediates are available in original publication.

- (22) We carried out the following experiments to compare the reaction profiles of arynes generated via a hexadehydro Diels-Alder reaction and fluoride-induced 1,2-elimination of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate.

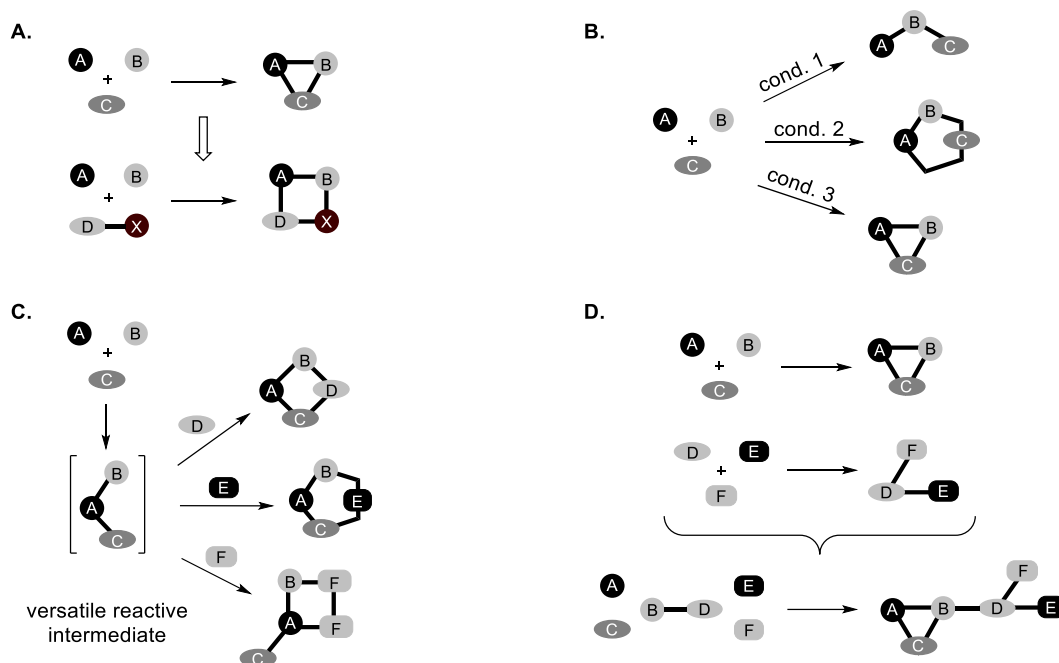


CHAPTER 6

Reaction of Arynes with Isonitriles and Weak Nucleophiles

6.1. Introduction*

Diversity-oriented synthesis (DOS) embraces various strategies¹ to effectively build complex and diverse small molecules from relatively simple and readily available starting materials. In DOS, the chemical space can be populated with functional, skeletal and stereochemical diversities. While the functional group diversity is usually achieved by employing different starting materials skeletal and stereochemical diversities are realized by changing the connectivity and topology. In general, multicomponent coupling reactions (MCRs) are considered to be one of the most effective protocols in diversity-oriented synthesis, which provides the highest degree of step and atom economy.² Different rational design strategies for MCRs have been developed to increase molecular diversity and complexity (Scheme 6.1). Among which ‘single reactant strategy (SRR)’, ‘modular reaction sequences (MRS)’,

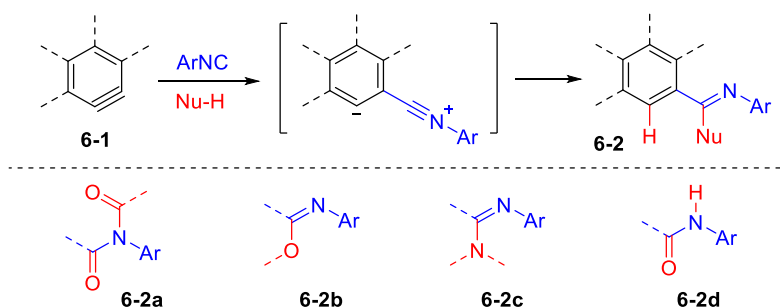


Scheme 6.1. Design Strategies for the Development of Novel Multicomponent Reactions. a) Single Reactant Replacement; b) Divergent MCRs through Changing the Conditions; c) Modular Reaction Sequences; d) Combination of MCRs

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‘condition-based divergence (CBD)’, combination of MCRs (MCR²) are mostly applied to design novel multicomponent reactions.^{2c}

In light of the utility of MCRs, we envision that the characteristic hierarchy of reactivity of arynes **6-1** toward weak nucleophiles can be exploited for MCR reactions, and we explored aryne-based DOS to generate cyclopentane-fused functionalized arenes **6-2** containing an imide, imidate, amidine or amide functionality (**Scheme 6.2**).



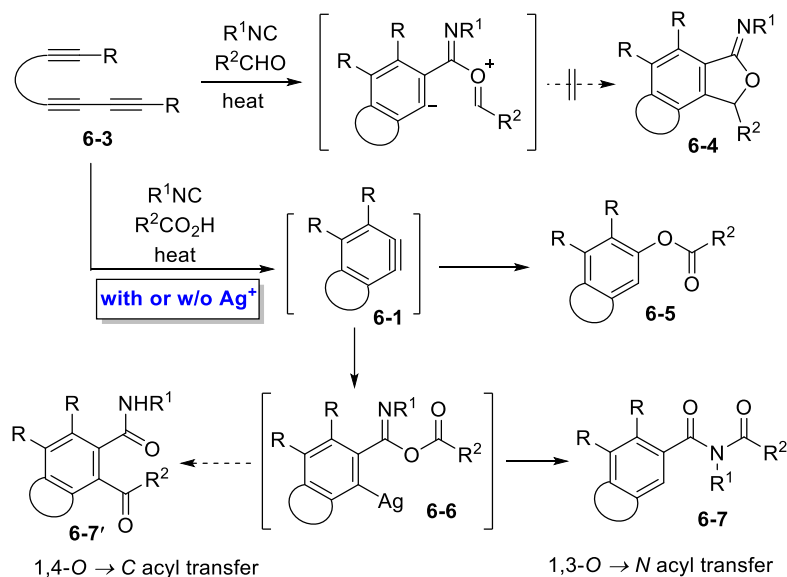
Scheme 6.2. Aromatic Functionalization through MCR

Aryne is a versatile intermediate that can be transformed into numerous functionalized aromatic compounds.³ In addition to the classical methods to generate arynes⁴, hexadehydro Diels–Alder reaction (HDDA) of multiynes⁵ allows for the formation of highly functionalized arynes through a formal intramolecular [4+2] cycloaddition. The HDDA reaction of tri- and tetraynes pioneered by Johnson and Ueda⁶ and subsequently by Hoyer, Lee and others has resulted in a significant expansion of the scope of aryne chemistry.⁷ Being formed under neutral conditions at varying range of temperature depending on the structural characteristics,⁸ the HDDA-derived arynes display reactivity profiles somewhat different from those arynes generated from base- or fluoride-mediated 1,2-elimination processes. After noticing the reactivity difference of arynes derived from different precursors, we intrigued by the possibility of modulating the reactivity of arynes toward isonitrile with transition metal catalysts. The reactions of arynes with isonitrile have been extensively exploited for heterocycle-fused arene synthesis.⁹ The groups of Yoshida,^{9a,9c} Stolz,^{9e} and Nishihara^{9g,9j} independently reported the formation of benzoannulated iminofurans

through three-component coupling of aryne, isonitrile and aldehyde/ester/cyanoformates. In 2004, Yoshida demonstrated that 2-iminoisoindoline could be prepared from aryne, isonitrile, and *N*-tosylaldimines.^{9b} Using CO₂ as a replacement for the carbonyl component in these reactions, Biju and his coworkers accomplished the synthesis of *N*-substituted phthalimide.⁹ⁱ By this protocol but replacing the carbonyl component with a terminal alkyne, Sha also demonstrated the synthesis of pyridine derivatives.^{9d,9f,9h}

6.2. Results and Discussion

After the failure of these transformations (for example, **6-3** → **6-4**) with the thermally generated arynes via HDDA, we turned our attention to promote these aryne-based reactions by using a silver catalyst (**Scheme 6.3**).¹⁰ We predicted that isonitrile and carboxylic acid could compete, thus the aryne intermediate generated from **6-3** can provide either ester **6-5** or **6-7/6-7'** depending on the potential role of a silver catalyst. If the silver catalyst can promote a preferential addition of isonitrile onto the aryne followed by carboxylic acid, a putative intermediate **6-6** would be generated. Depending on the propensity

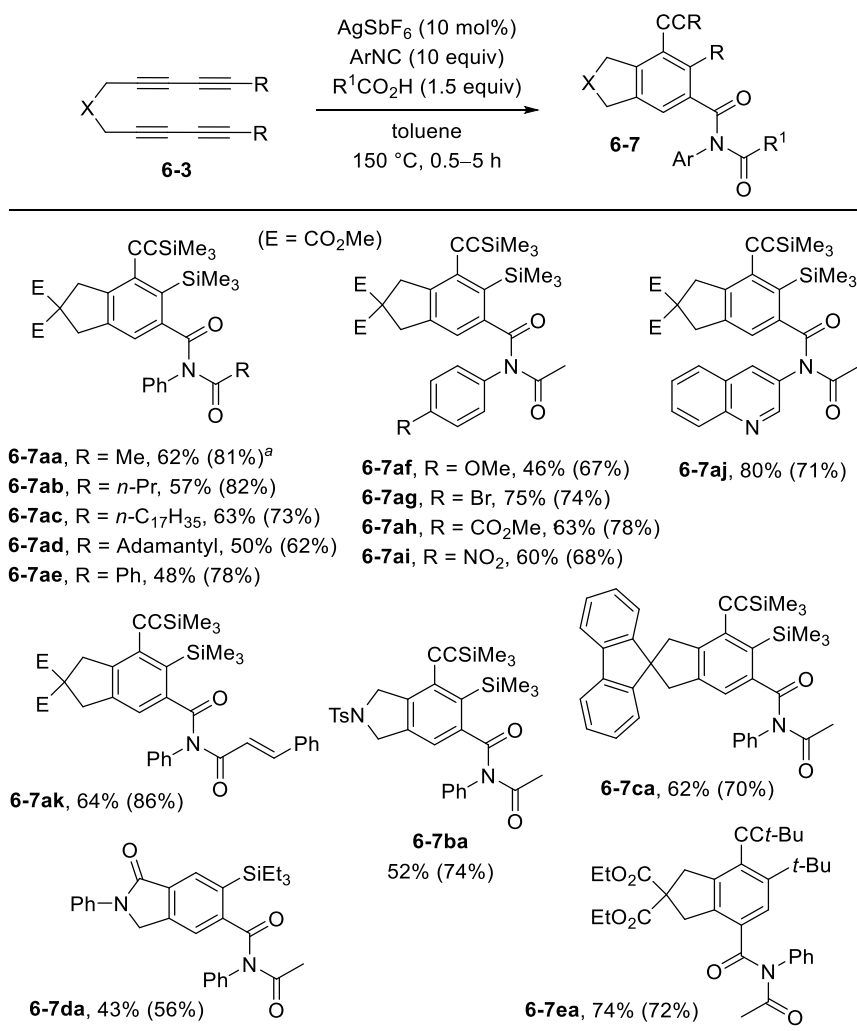


Scheme 6.3. Modulating the Reactivity of Arynes by Silver Ion to Promote Three-Component Coupling between Arynes, Isonitriles, and Carboxylic Acids

of **6-6** to undergo either a 1,4-O $\rightarrow$ C acyl migration (aryne analog of Ugi reaction¹¹) or 1,3-O $\rightarrow$ N acyl migration (Mumm rearrangement¹²), **6-7'** or **6-7** would be produced as the major product.

6.2.1. Reaction of Arynes with Isonitriles and Carboxylic Acids

Our investigation commenced with three-component coupling of an aryne, benzoisonitrile (PhNC), and acetic acid (AcOH). With malonate ester tethered tetrayne **6-3a** (X = (CO₂Me)₂C) and catalyst AgSbF₆ (10 mol%), employing AcOH (1.5 equiv) and an excess amount of PhNC (10 equiv)¹³ and at 150 °C, the corresponding imide **6-7aa** was isolated in 62% yield (**Scheme 6.4**). With the optimized condition in hand, we further investigated the generality of the reaction regarding the components of multiynes, isonitriles, and carboxylic acids. Replacing AcOH with butanoic acid provided the corresponding imide **6-7ab** in 57% yield. Long-chain fatty acid such as stearic acid and sterically encumbered 1-adamantane carboxylic acid also provided imides **6-7ac** (63%) and **6-7ad** (50%), but with benzoic acid **6-7ae** was obtained in slightly lower yield (48%). Aromatic isonitrile that bears variety of functional groups served as suitable coupling partner. Thus, 4-substituted benzoisonitriles with methoxy (**6-7af**), bromo (**6-7ag**), carbomethoxy (**6-7ah**), and nitro (**6-7ai**) moieties delivered the corresponding imides in moderate to good yield (46–75%) when AcOH was employed. Bulkier isonitrile such as 3-isocyanoquinoline was also effective and afforded *N*-quinoline imide **6-7aj** in 80% yield. The reaction with cinnamic acid also delivered the expected product **6-7ak** in 64% yield. Next, we explored the reaction with different tetraynes. Under the same conditions, *N*-Ts-tethered tetrayne **6-3b** rendered imide **6-7ba** in 52% within 30 min. In contrast, tetrayne with fluorenyl tether took much longer time (5 h) to be consumed to generate imide **6-7ca** (62%). Triyne **6-3d** containing a phenyl amide tether delivered **6-7da** in slightly lower yield (43%). In terms of regioselectivity of the isonitrile addition, the *t*-Bu-substituted tetrayne **6-3e** is the only aryne precursor that generated product **6-7ea** (74%) with reversed regioselectivity.¹⁴ The structural identity of these regioisomeric products was established unambiguously by nOe-based mutual correlation and the well-established direction effect of the silyl group.¹⁵



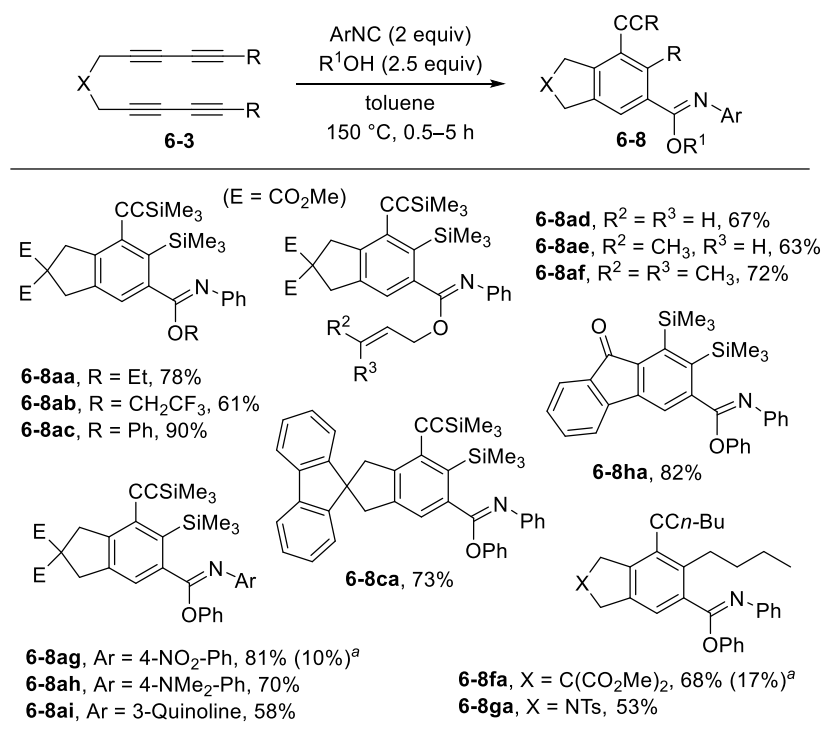
^a Yields in parentheses are for the reaction without the silver catalyst.

Scheme 6.4. Three-Component Coupling Reaction of Arynes, Isonitriles and Carboxylic Acids¹⁶

6.2.2. Reaction of Arynes with Isonitriles and Alcohols

Next, we explored the trapping of the putative aryne-isonitrile adduct with alcohols to generate the corresponding imidates.¹⁷ Although arynes can directly react with alcohols,¹⁸ we expected that the higher nucleophilicity of isonitrile should outcompete alcohols such that the right sequence of events to form imidates will be accomplished with thermally generated arynes especially in the presence of silver ions (Scheme 6.5). Through several control experiments, it was found that the reactions without silver catalyst provided even higher yields. Thus, under standard conditions employing 2 equivalents of PhNC and 2.5

equivalents of EtOH, tetrayne **6-3a** afforded *N*-phenyl-imidate **6-8aa** in 78% yield. With CF₃CH₂OH, imidate **6-8ab** was isolated in slightly lower yield (61%). Although PhOH was shown to be an efficient ene-reaction counterpart with arynes,^{17b} under the current reaction conditions, only imidate **6-8ac** was obtained in 90% yield. Allylic alcohols including allyl, crotyl, and prenyl alcohol provided the corresponding three-component coupled imidates **6-8ad**, **6-8ae**, and **6-8af** in good yields. An electron-donating or an electron-withdrawing group on ArNC did not have an impact on the reactivity, rendering imidates **6-8ag** (81%) and **6-8ah** (70%) respectively. However, when 3-isocyanoquinoline was employed the corresponding imidate **6-8ai** was obtained in a slightly lower yield (58%). Also, multiynes with different tethers and substituents were examined. The reaction of tetrayne **6-3c** tethered with a fluorenyl moiety afforded imidate **6-8ca** in 73% yield while reaction with ketoarene-tethered triyne **6-3h** provided **6-8ha** in 82% yield. Symmetrical tetraynes **6-3f** and **6-3g** with *n*-Bu substituents but with a different tether also afforded imidates **6-8fa** (68%) and **6-8ga** (53%) respectively.

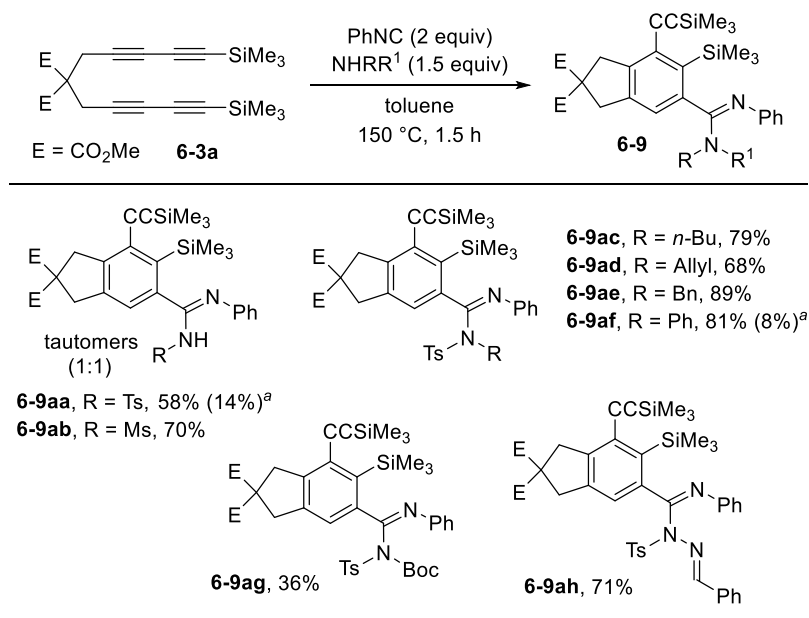


^a Yields in parentheses are for the reaction with the silver catalyst.

Scheme 6.5. Three-Component Coupling of Arynes, Isonitriles and Alcohols

6.2.3. Reaction of Arynes with Isonitriles and Sulfonamides

At this juncture, we surmised that the structural diversity of the aryne-based MCR can be further expanded by trapping of the aryne-isonitrile adduct with nitrogen-based nucleophiles. To avoid the complication of the direct addition of amines with arynes, the reactivity of the nitrogen nucleophiles should be reduced. Indeed, the reaction with alkyl and aryl amines such as *n*-BuNH₂ and PhNH₂ mainly resulted in direct amine addition products^{17a} or intractable material. On the other hand, nitrogen nucleophiles containing an electron-withdrawing group such as 4-toluenesulfonamide provided amidine¹⁹ **6-9aa** (two tautomers in a 1:1 ratio) in 58% yield upon reacting with tetrayne **6-3a** and PhNC in the absence of a silver catalyst (Scheme 6.6). With this encouraging initial result in hand, we further examined the generality of this reaction. Similar to 4-toluenesulfonamide, methanesulfonamide also provided the corresponding amidine **6-9ab** in 70% yield. Alkylated or arylated secondary sulfonamides provided amidines **6-9ac**, **6-9ad**, **6-9ae**, and **6-9af** in good yield (68–89%). Even highly deactivated amine nucleophile such as Boc-protected 4-toluenesulfonimide could participate in this reaction, affording *N*-Boc-protected amidine **6-9ag**

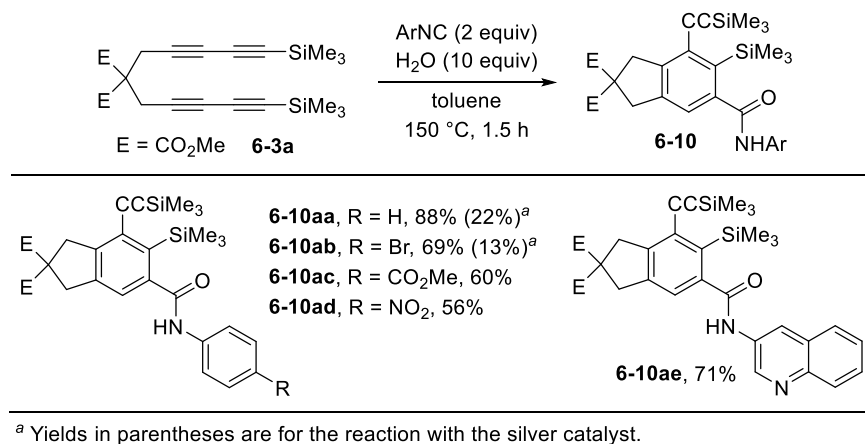


Scheme 6.6. Three-Component Coupling of Arynes, Isonitriles and Sulfonamides

but in significantly lower yield (36%). Also, (*E*)-*N*-benzylidene toluenesulfonohydrazide also efficiently participated in this reaction to provide the corresponding **6-9ah** in good yield.

6.2.4. Reaction of Arynes with Isonitriles and other Weak Nucleophiles

Although hydration of the adduct of aryne-isonitrile to generate amides has been explored,²⁰ this reaction with thermally generated arynes from multiynes has not been reported. Based on our previous study on the hydration of aryne-nitrile adduct to form amides in the presence of a silver catalyst,²¹ we expected that replacing the nitrile with isonitriles should generate amides of reversed connectivity more efficiently. Indeed, heating the mixture of tetrayne **6-3a**, benzoisonitrile, and water afforded arylamide **6-10aa** in 88% yield. (Scheme 6.7). The reaction with AgSbF₆ showed the same reaction profile but lower efficiency. Reactions with ArNC containing bromo (**6-10ab**), carbomethoxy (**6-10ac**), and nitro (**6-10ad**) group afforded the corresponding amides in slightly lower yield (56–69%). The reaction with 3-isocyanoquinoline also provided amide **6-10ae** in 71% yield.



Scheme 6.7. Three-Component Coupling of Arynes, Isonitriles and Water

6.3. Conclusion

In conclusion, we have developed new aryne-based multicomponent coupling reactions for the formation of structurally diverse aromatic compounds with functional groups including imide, amidine,

imidate, and amide. These reactions clearly demonstrate that the reactivity of arynes generated from multiynes via HDDA can be exploited in the classical isonitrile-based MCRs by careful selection of reagents and conditions. Although initially we predicted that a silver catalyst plays a key role in the activation of isonitriles, in general, the reactions with a silver catalyst resulted in more byproducts leading to lower yields of the expected products. For most transformations investigated, excellent regioselectivity was observed. The strong electronic effect of a trimethylsilyl group on arynes effectively directs the addition of isonitrile at its ortho position, which is consistent with the distortion/interaction model proposed by Houk.^{15b-c} On the other hand, the reversed directing effect of *t*-Bu substituent is due mainly to its steric effect. Relatively simple one-pot operation and broad substrate scope make these aryne-based MCRs a highly useful synthetic tool, which favorably compares with existing protocols for the preparation of aromatic functionalized aromatic compounds.

6.4. Experimental Details

6.4.1. General Information

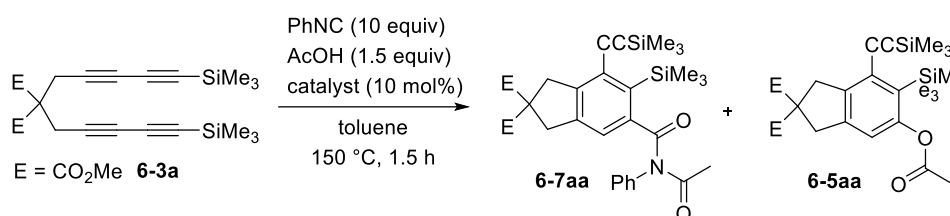
Experimental section: All reactions were carried out in oven or flame-dried glassware unless otherwise noted. Reagents which were commercially available, were purchased from Sigma - Aldrich, Alfa Aesar, Acros, and Oakwood Products unless otherwise noted. Known compounds were prepared according to literature procedure. Anhydrous acetonitrile from Sigma-Aldrich was distilled over calcium hydride (CaH_2) under nitrogen atmosphere. Acetic acid was purchased from Fischer Scientific. 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). Yield was calculated on basis of chromatographically and spectroscopically pure isolated compound. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AV-500 spectrometer at 298 K, unless otherwise stated. ^1H NMR chemical shifts (δ) were reported in parts per million (ppm) downfield of TMS and were referenced relative to the residual protiated solvent peak (CDCl_3 (7.26 ppm)). ^{13}C chemical shifts (δ) were reported in parts per million downfield of TMS and are referenced to the carbon resonance of the solvent (CDCl_3 , δ 77.2 ppm). Multiplicities in ^1H NMR were abbreviated by s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sext (sextet), sept (septet) 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 (Waters Corporation, Milford, MA, USA) at 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 (Waters Corporation, Milford, MA, USA) at the University of Illinois at Urbana-Champaign.

6.4.2. Experimental Procedures

Synthesis of Substrates: The *bis*-1,3-diyne substrates were prepared following the procedures mentioned in the experimental procedure section of Chapter 3.

Synthesis of Aromatic Isonitriles: Aromatic isonitriles were prepared following the procedures mentioned in the experimental procedure section of Chapter 4.

Stoichiometry Screening for Three-component Coupling of Aryne, Isonitrile, and Carboxylic Acid



entry	PhNC	AcOH	catalyst	6-7aa : 6-5aa	6-7aa (%) ^a
1	1.5 equiv	1.5 equiv	AgSbF ₆	0.3 : 1.0	10%
2	5 equiv	1.5 equiv	AgSbF ₆	1.5 : 1.0	38%
3	10 equiv	1.5 equiv	AgSbF ₆	5.9 : 1.0	68%
4	10 equiv	1.1 equiv	AgSbF ₆	6.7 : 1.0	49%
5	10 equiv	1.5 equiv	—	26.2 : 1.0	84%
6	5 equiv	1.5 equiv	—	10.4 : 1.0	72%
7	1.5 equiv	1.5 equiv	—	3.0 : 1.0	57%

^a NMR yield using dibromomethane as internal standard.

To maximize arylimide products from three-component coupling between aryne, isonitrile, and carboxylic acid, reactions with various stoichiometry of isonitrile and carboxylic acid were screened. In a typical procedure, malonate ester-tethered tetrayne **6-3a** (0.1 mmol), benzoisonitrile, and acetic acid were taken in a thick-walled Schlenk tube (25 mL) in dry toluene (3 mL). After flushing with nitrogen several times, the Schlenk tube was placed in a heated oil bath (150 °C) for 1.5 h. Upon completion, the reaction mixture was concentrated under reduced pressure, and NMR yield was calculated using dibromomethane as an internal standard. These results indicate that an excess amount of PhNC (10 equiv) is necessary for

improving the selectivity between imide **6-7aa** (three-component coupling product) and ester (**6-5aa**) (aryne-carboxylic acid adduct).

Procedure A: Preparation of *N*-Aryl Imides

Multiyne substrate **6-3** (0.1 mmol), isonitrile (1.0 mmol), carboxylic acid (0.15 mmol), and AgSbF₆ (0.01 mmol) were taken in a thick-walled Schlenk tube (25 mL) in dry toluene (3 mL). After flushing several times with nitrogen, the Schlenk tube was placed in a heated oil bath (150 °C) for 1.5 h. Upon completion, the reaction mixture was concentrated under reduced pressure, and the crude material was purified by flash column chromatography (SiO, EtOAc–hexane, 1:10 to 1:3) to isolate pure *N*-aryl imide product.

Procedure B: Preparation of *N*-Aryl Imidates

Multiyne substrate **6-3** (0.1 mmol), isonitrile (0.2 mmol), and alcohol (0.25 mmol) were taken in a thick-walled Schlenk tube (25 mL) in dry toluene (3 mL). After flushing several times with nitrogen, the Schlenk tube was placed in a heated oil bath (150 °C) for 1.5 h. Upon completion, the reaction mixture was concentrated under reduced pressure, and the crude material was purified by flash column chromatography (SiO, EtOAc–hexane, 1:10 to 1:3) to isolate pure *N*-aryl imidate product.

Procedure C: Preparation of *N*-Aryl Amidines

Multiyne substrate **6-3** (0.1 mmol), isonitrile (0.2 mmol), and sulfonamide (0.15 mmol) were taken in a thick-walled Schlenk tube (25 mL) in dry toluene (3 mL). After flushing several times with nitrogen, the Schlenk tube was placed in a heated oil bath (150 °C) for 1.5 h. Upon completion, the reaction mixture was concentrated under reduced pressure, and the crude material was purified by flash column chromatography (SiO, EtOAc–hexane, 1:10 to 1:3) to isolate pure *N*-aryl amidine product.

Procedure D: Preparation of *N*-Aryl Amides

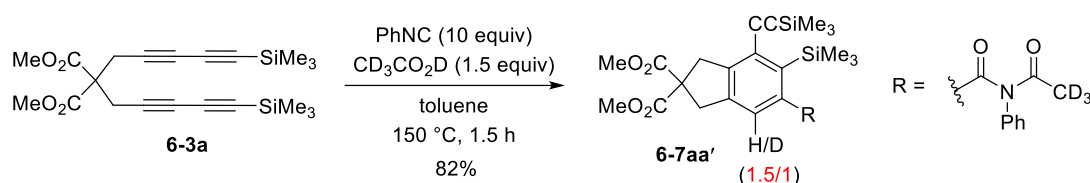
Multiyne substrate **6-3** (0.1 mmol), isonitrile (0.2 mmol), and H₂O (1.0 mmol) were taken in a thick-walled 25 mL Schlenk tube in 3 mL dry toluene. After flushing several times with nitrogen, the Schlenk tube was placed in a heated oil bath (150 °C) for 1.5 h. Upon completion, the reaction mixture was

concentrated under reduced pressure, and the crude material was purified by flash column chromatography (SiO, EtOAc–hexane, 1:10 to 1:3) to isolate pure *N*-aryl amide product.

Procedure E: Preparation of *N*-Aryl Imidate (6-8ac) at 1.0 mmol Scale

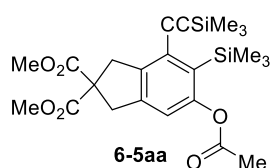
Multiyne **6-3a** (400 mg, 1.0 mmol), benzoisonitrile (206 mg, 2.0 mmol), and phenol (235 mg, 2.5 mmol) were taken in a thick-walled Schlenk tube (25 mL) in dry toluene (3 mL). After flushing with nitrogen several times, the Schlenk tube was placed in a heated oil bath (150 °C) for 1.5 h. Upon completion, the reaction mixture was concentrated under reduced pressure, and the crude material was purified by flash column chromatography (SiO, EtOAc–hexane, 1:10 to 1:3) to isolate pure *N*-aryl imidate **6-8ac** (519 mg, 87% yield).

Procedure F: Reaction with Deuterated Pro-nucleophile (AcOH-*d*₄)

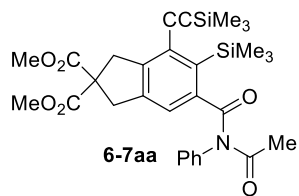


Multiyne **6-3a** (0.1 mmol), benzoisonitrile (1.0 mmol), and acetic acid-*d*₄ (0.15 mmol) were taken in a thick-walled Schlenk tube (25 mL) in dry toluene (3 mL). After flushing with nitrogen several times, the Schlenk tube was placed in a heated oil bath (150 °C) for 1.5 h. Upon completion, the reaction mixture was concentrated under reduced pressure, and the crude material was purified by flash column chromatography (SiO, EtOAc–hexane, 1:10 to 1:3) to isolate pure deuterated *N*-aryl imide **6-7aa'** (23.6 mg, 82% yield). This unexpectedly low deuterium incorporation (40%) might be the consequence of H–D exchange with adventitious H₂O in the reaction medium. Using freshly distilled solvent did not change the ratio significantly. Adding 4 Å molecular sieve (powder) to the reaction mixture further increased proton incorporation over deuterium, providing only 20% deuterium-incorporated product.

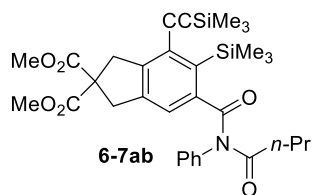
6.4.3. Characterization Data



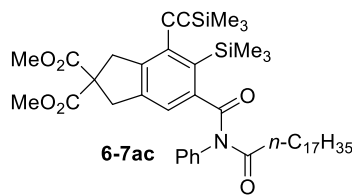
6-5aa: This product was isolated from stoichiometry screening of PhNC and AcOH and isolated in 18% yield (12 mg, entry 7) as colorless oil after stirring the reaction mixture for 1.5 h. $^1\text{H NMR}$ (CDCl_3 , 500 MHz): δ 6.79 (s, 1H), 3.76 (s, 6H), 3.64 (s, 2H), 3.61 (s, 2H), 2.26 (s, 3 H), 0.38 (s, 9H), 0.24 (s, 9H); $^{13}\text{C NMR}$ (CDCl_3 , 125 MHz): δ 171.9, 170.0, 154.6, 142.0, 141.9, 131.3, 125.7, 118.7, 103.7, 103.3, 59.4, 53.1, 40.9, 40.6, 21.6, 1.0, -0.3; **HRMS** (ESI) calcd for $\text{C}_{23}\text{H}_{33}\text{O}_6\text{Si}_2$ $[\text{M}+\text{H}]^+$ 461.1816 found 461.1810.



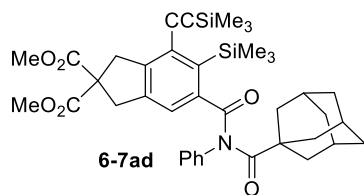
6-7aa: This product was synthesized using procedure A and isolated in (62% yield, 35.4 mg) as orange-yellow oil after stirring the reaction mixture for 1.5 h. $^1\text{H NMR}$ (CDCl_3 , 500 MHz): δ 7.45 (t, 2H, $J = 7.8$ Hz), 7.39 (t, 1H, $J = 7.2$ Hz), 7.22 (d, 2H, $J = 7.3$ Hz), 6.99 (s, 1H), 3.76 (s, 6H), 3.67 (s, 2H), 3.59 (s, 2H), 2.15 (s, 3H), 0.42 (s, 9H), 0.25 (s, 9H); $^{13}\text{C NMR}$ (CDCl_3 , 125 MHz): δ 173.2, 172.4, 171.9, 144.6, 143.6, 139.6, 139.4, 138.8, 129.8, 128.9, 128.8, 126.4, 120.4, 104.0, 103.9, 59.2, 53.1, 41.0, 41.0, 26.2, 0.9, -0.3; **HRMS** (ESI) calcd for $\text{C}_{30}\text{H}_{38}\text{NO}_6\text{Si}_2$ $[\text{M}+\text{H}]^+$ 564.2238 found 564.2239.



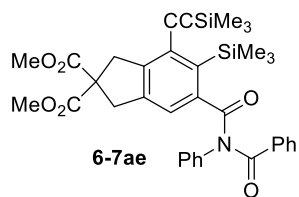
6-7ab: This product was synthesized using procedure A and isolated in (57% yield, 29.7 mg) as orange-yellow oil after stirring the reaction mixture for 1.5 h. $^1\text{H NMR}$ (CDCl_3 , 500 MHz): δ 7.48 (t, 2H, $J = 7.8$ Hz), 7.40 (t, 1H, $J = 7.3$ Hz), 7.23 (d, 2H, $J = 7.3$ Hz), 6.98 (s, 1H), 3.76 (s, 6H), 3.68 (s, 2H), 3.59 (s, 2H), 2.29 (t, 2H, $J = 7.2$ Hz), 1.60–1.52 (m, 2H), 0.83 (t, 3H, $J = 7.4$ Hz), 0.42 (s, 9H), 0.25 (s, 9H); $^{13}\text{C NMR}$ (CDCl_3 , 125 MHz): δ 175.2, 173.4, 171.9, 144.5, 143.9, 139.7, 139.4, 138.5, 129.8, 129.0, 128.9, 128.8, 126.4, 120.1, 104.0, 103.8, 59.3, 53.1, 41.0, 39.5, 18.0, 13.5, 0.9, -0.3; **HRMS** (ESI) calcd for $\text{C}_{32}\text{H}_{42}\text{NO}_6\text{Si}_2$ $[\text{M}+\text{H}]^+$ 592.2551 found 592.2554.



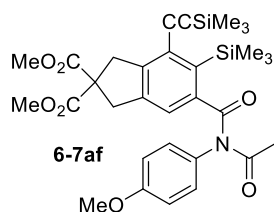
6-7ac: This product was synthesized using procedure **A** and isolated in (63% yield, 37.3 mg) as orange-red solid after stirring the reaction mixture for 1.5 h. **¹H NMR** (CDCl₃, 500 MHz): δ 7.47 (t, 2H, *J* = 7.8 Hz), 7.40 (t, 1H, *J* = 7.4 Hz), 7.23 (d, 2H, *J* = 7.2 Hz), 6.97 (s, 1H), 3.76 (s, 6H), 3.68 (s, 2H), 3.59 (s, 2H), 2.30 (t, 2H, *J* = 7.4 Hz), 1.38–1.14 (m, 30H), 0.87 (t, 3H, *J* = 6.9 Hz), 0.42 (s, 9H), 0.25 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 175.4, 173.4, 171.9, 144.5, 143.9, 139.6, 139.5, 138.5, 129.8, 128.8, 126.4, 120.1, 104.0, 103.8, 59.2, 53.1, 41.0, 41.0, 37.6, 31.9, 29.6, 29.4, 29.3, 29.0, 24.6, 22.7, 14.1, 0.9, –0.3; **HRMS** (ESI) calcd for C₄₆H₇₀NO₆Si₂ [M+H]⁺ 788.4742 found 788.4731.



6-7ad: This product was synthesized using procedure **A** and isolated in (50% yield, 32.4 mg) as orange-yellow oil after stirring the reaction mixture for 1.5 h. **¹H NMR** (CDCl₃, 500 MHz): δ 7.42 (t, 2H, *J* = 7.8 Hz), 7.36 (t, 1H, *J* = 7.3 Hz), 7.18 (d, 2H, *J* = 7.4 Hz), 6.97 (s, 1H), 3.76 (s, 6H), 3.67 (s, 2H), 3.58 (s, 2H), 2.06–1.48 (m, 15H), 0.40 (s, 9H), 0.25 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 184.1, 173.5, 171.9, 144.6, 143.0, 141.0, 139.4, 137.6, 129.3, 128.3, 126.5, 120.6, 104.1, 103.8, 59.3, 53.1, 45.9, 41.0, 40.1, 36.2, 28.0, 1.0, –0.3; **HRMS** (ESI) calcd for C₃₉H₅₀NO₆Si₂ [M+H]⁺ 684.3177 found 684.3174.



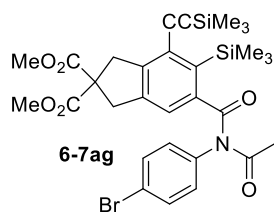
6-7ae: This product was synthesized using procedure **A** and isolated in (48% yield, 26.5 mg) as white solid after stirring the reaction mixture for 1.5 h. **¹H NMR** (CDCl₃, 500 MHz): δ 7.65 (d, 2H, *J* = 8.0 Hz), 7.38 (t, 1H, *J* = 6.9 Hz), 7.34 (t, 2H, *J* = 7.8 Hz), 7.28 (d, 2H, *J* = 7.5 Hz), 7.24 (t, 1H, *J* = 7.1 Hz), 7.20 (s, 1H), 7.18 (d, 2H, *J* = 8.2 Hz), 3.75 (s, 6H), 3.67 (s, 2H), 3.55 (s, 2H), 0.45 (s, 9H), 0.26 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 173.8, 172.0, 171.9, 145.1, 143.4, 141.4, 139.8, 139.2, 133.7, 132.5, 130.0, 129.5, 128.4, 127.9, 127.8, 126.8, 120.1, 104.0, 103.9, 59.2, 53.1, 41.0, 1.1, –0.3; **HRMS** (ESI) calcd for C₃₅H₄₀NO₆Si₂ [M+H]⁺ 626.2394 found 626.2399.



6-7af: This product was synthesized using procedure **A** and isolated in (46% yield, 22.8 mg) as orange-yellow oil after stirring the reaction mixture for 1.5 h.

¹H NMR (CDCl₃, 500 MHz): δ 7.12 (d, 2H, *J* = 8.9 Hz), 6.96 (s, 1H), 6.94 (d, 2H, *J* = 8.9 Hz), 3.82 (s, 3H), 3.76 (s, 6H), 3.66 (s, 2H), 3.58 (s, 2H), 2.17 (s, 3H),

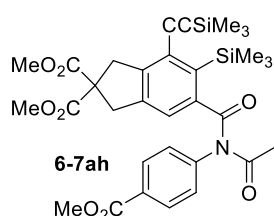
0.42 (s, 9H), 0.25 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 173.4, 172.8, 171.9, 159.6, 144.5, 143.6, 139.6, 139.3, 131.3, 129.7, 126.3, 120.4, 115.0, 104.0, 103.8, 59.2, 55.5, 53.1, 41.0, 26.2, 0.9, -0.3; **HRMS** (ESI) calcd for C₃₁H₄₀NO₇Si₂ [M+H]⁺ 594.2343 found 594.2353.



6-7ag: This product was synthesized using procedure **A** and isolated in (75% yield, 38.0 mg) as light brown solid after stirring the reaction mixture for 1.5 h.

¹H NMR (CDCl₃, 500 MHz): δ 8.56 (d, 2H, *J* = 8.6 Hz), 7.08 (d, 2H, *J* = 8.6 Hz), 6.95 (s, 1H), 3.76 (s, 6H), 3.66 (s, 2H), 3.58 (s, 2H), 2.20 (s, 3H), 0.41 (s, 9H),

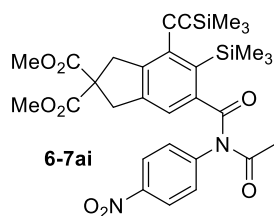
0.25 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 172.9, 172.1, 171.8, 144.9, 143.0, 139.8, 139.4, 137.8, 133.0, 130.5, 126.5, 122.9, 120.5, 104.2, 103.8, 59.2, 53.2, 41.0, 40.9, 26.3, 0.9, -0.3; **HRMS** (ESI) calcd for C₃₀H₃₇NO₆Si₂Br [M+H]⁺ 642.1343 found 642.1342.



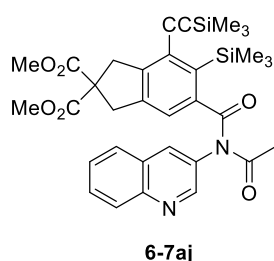
6-7ah: This product was synthesized using procedure **A** and isolated in (63% yield, 27.0 mg) as white solid after stirring the reaction mixture for 1.5 h. **¹H NMR**

(CDCl₃, 500 MHz): δ 8.10 (d, 2H, *J* = 8.4 Hz), 7.28 (d, 2H, *J* = 8.4 Hz), 6.96 (s, 1H), 3.93 (s, 3H), 3.76 (s, 6H), 3.65 (s, 2H), 3.56 (s, 2H), 2.23 (s, 3H), 0.43 (s,

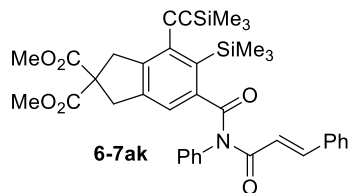
9H), 0.25 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 172.8, 172.1, 171.8, 166.0, 145.0, 142.8, 139.8, 139.5, 131.0, 130.5, 129.0, 126.5, 120.7, 104.3, 103.8, 59.2, 53.1, 52.4, 41.0, 40.9, 26.4, 1.0, -0.3; **HRMS** (ESI) calcd for C₃₂H₄₀NO₈Si₂ [M+H]⁺ 622.2292 found 622.2294.



6-7ai: This product was synthesized using procedure **A** and isolated in (60% yield, 28.3 mg) as orange-yellow solid after stirring the reaction mixture for 1.5 h. **¹H NMR** (CDCl_3 , 500 MHz): δ 8.27 (d, 2H, J = 8.8 Hz), 7.36 (d, 2H, J = 8.8 Hz), 6.94 (s, 1H), 3.76 (s, 6H), 3.64 (s, 2H), 3.54 (s, 2H), 2.32 (s, 3H), 0.44 (s, 9H), 0.26 (s, 9H); **¹³C NMR** (CDCl_3 , 125 MHz): δ 172.4, 171.9, 171.7, 147.5, 145.5, 144.6, 142.1, 140.1, 139.5, 130.1, 126.8, 124.8, 121.0, 104.8, 103.5, 59.1, 53.2, 41.0, 40.8, 26.7, 1.0, -0.3; **HRMS** (ESI) calcd for $\text{C}_{30}\text{H}_{37}\text{N}_2\text{O}_8\text{Si}_2$ $[\text{M}+\text{H}]^+$ 609.2088 found 609.2081.

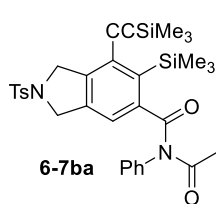


6-7aj: This product was synthesized using procedure **A** and isolated in (80% yield, 39.4 mg) as orange solid after stirring the reaction mixture for 1.5 h. **¹H NMR** (CDCl_3 , 500 MHz): δ 8.74 (d, 1H, J = 2.4 Hz), 8.13 (d, 1H, J = 8.4 Hz), 7.97 (d, 1H, J = 2.2 Hz), 7.80 (d, 1H, J = 8.3 Hz), 7.77 (td, 2H, J = 7.7 Hz, J = 1.2 Hz), 7.61 (t, 1H, J = 7.8 Hz), 7.04 (s, 1H), 3.73 (s, 6H), 3.62 (s, 2H), 3.56 (s, 2H), 2.34 (s, 3H), 0.47 (s, 9H), 0.24 (s, 9H); **¹³C NMR** (CDCl_3 , 125 MHz): δ 173.0, 172.4, 171.7, 150.3, 147.3, 145.3, 142.5, 140.0, 139.5, 135.3, 132.3, 130.6, 129.5, 127.9, 127.7, 127.6, 126.7, 120.8, 104.5, 103.6, 59.1, 53.1, 41.0, 40.9, 26.7, 1.0, -0.3; **HRMS** (ESI) calcd for $\text{C}_{33}\text{H}_{39}\text{N}_2\text{O}_6\text{Si}_2$ $[\text{M}+\text{H}]^+$ 615.2347 found 615.2352.



6-7ak: This product was synthesized using procedure **A** and isolated in (64% yield, 31.8 mg) as yellow-green solid after stirring the reaction mixture for 1.5 h. **¹H NMR** (CDCl_3 , 500 MHz): δ 7.70 (d, 1H, J = 15.5 Hz), 7.52 (t, 2H, J = 7.8 Hz), 7.49–7.43 (m, 1H), 7.38–7.27 (m, 7H), 7.09 (s, 1H), 6.37 (d, 1H, J = 15.5 Hz), 3.75 (s, 6H), 3.70 (s, 2H), 3.61 (s, 2H), 0.45 (s, 9H), 0.27 (s, 9H); **¹³C NMR** (CDCl_3 , 125 MHz): δ 173.7, 171.9, 167.6, 146.0, 144.7, 143.9, 140.1, 139.8, 138.0, 134.2, 130.7, 129.9,

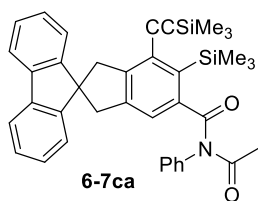
128.9, 128.7, 128.4, 126.5, 120.1, 119.1, 104.1, 103.7, 59.2, 53.1, 41.1, 41.0, 0.9, -0.3; **HRMS** (ESI) calcd for $C_{37}H_{42}NO_6Si_2$ $[M+H]^+$ 652.2551 found 652.2554.



6-7ba: This product was synthesized using procedure **A** and isolated in (52% yield, 18.0 mg) as orange-yellow solid after stirring the reaction mixture for 30 min. **¹H**

NMR ($CDCl_3$, 500 MHz): δ 7.76 (d, 2H, J = 8.1 Hz), 7.48 (t, 2H, J = 7.6 Hz), 7.42 (t, 1H, J = 7.3 Hz), 7.33 (d, 2H, J = 8.0 Hz), 7.22 (d, 2H, J = 7.8 Hz), 6.94 (s, 1H), 4.63

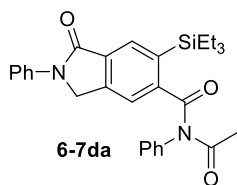
(s, 2H), 4.61 (s, 2H), 2.42 (s, 3H), 2.06 (s, 3H), 0.40 (s, 9H), 0.26 (s, 9H); **¹³C NMR** ($CDCl_3$, 125 MHz): δ 172.7, 172.3, 144.6, 143.9, 140.7, 140.4, 138.5, 135.9, 133.6, 130.0, 129.2, 128.6, 127.5, 125.2, 118.1, 105.1, 102.7, 54.3, 54.2, 25.9, 21.5, 0.7, -0.4; **HRMS** (ESI) calcd for $C_{32}H_{39}N_2O_4Si_2S$ $[M+H]^+$ 603.2169 found 603.2174.



6-7ca: This product was synthesized using procedure **A** and isolated in (62% yield, 28.4 mg) yellow-green solid after stirring the reaction mixture for 5 h. **¹H NMR**

($CDCl_3$, 500 MHz): δ 7.74 (d, 2H, J = 7.6 Hz), 7.48–7.40 (m, 3H), 7.37 (t, 2H, J = 7.5 Hz), 7.29–7.21 (m, 4H), 7.21–7.10 (m, 2H), 7.07 (s, 1H), 3.47 (s, 2H), 3.37 (s,

2H), 2.30 (s, 3H), 0.50 (s, 9H), 0.15 (s, 9H); **¹³C NMR** ($CDCl_3$, 125 MHz): δ 173.5, 172.7, 152.2, 147.6, 143.1, 142.5, 139.5, 139.0, 138.8, 129.7, 129.0, 128.7, 127.7, 127.5, 126.6, 122.5, 121.2, 119.8, 104.2, 103.6, 56.3, 45.8, 45.5, 26.6, 1.1, -0.4; **HRMS** (ESI) calcd for $C_{38}H_{40}NO_2Si_2$ $[M+H]^+$ 598.2598 found 598.2600.

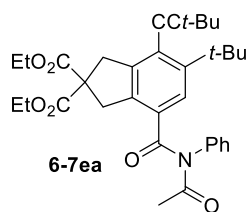


6-7da: This product was synthesized using procedure **A** and isolated in (43% yield, 17.8 mg) as orange-yellow oil after stirring the reaction mixture for 2 h. **¹H NMR**

($CDCl_3$, 500 MHz): δ 8.16 (s, 1H), 7.83 (d, 2H, J = 8.1 Hz), 7.54–7.47 (m, 3H), 7.44 (t, 3H, J = 7.6 Hz), 7.28 (d, 2H, J = 7.8 Hz), 7.20 (t, 1H, J = 7.4 Hz), 4.84 (s, 2H),

2.15 (s, 3H), 1.00–0.88 (m, 15H); **¹³C NMR** ($CDCl_3$, 125 MHz): δ 173.3, 172.4, 166.9, 146.6, 139.8, 139.4,

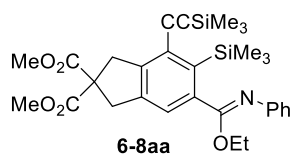
138.8, 138.0, 133.3, 132.0, 130.0, 129.2, 129.1, 128.7, 124.7, 120.2, 119.7, 50.6, 26.0, 7.5, 3.9; **HRMS** (ESI) calcd for $C_{29}H_{33}N_2O_3Si$ $[M+H]^+$ 485.2260 found 485.2259.



6-7ea: This product was synthesized using procedure **A** and isolated in (74% yield, 26.7 mg) as orange-red oil after stirring the reaction mixture for 2 h. **¹H NMR**

(CDCl₃, 500 MHz): δ 7.55–7.39 (m, 3H), 7.25 (d, 1H, J = 7.7 Hz), 6.79 (s, 1H), 4.22 (q, 2H, J = 7.1 Hz), 4.22 (q, 2H, J = 7.0 Hz), 3.64 (s, 2H), 3.59 (s, 2H), 2.02 (br,

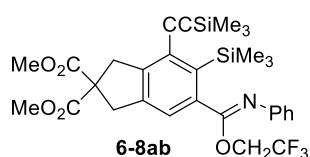
3H), 1.61 (s, 9H), 1.34 (s, 9H), 1.26 (t, 6H, J = 7.1 Hz); **¹³C NMR** (CDCl₃, 125 MHz): δ 173.8, 171.6, 145.8, 145.6, 138.9, 136.2, 129.8, 129.0, 128.7, 128.5, 121.0, 119.8, 109.9, 78.9, 61.8, 59.4, 41.7, 40.7, 30.7, 30.6, 14.0; **HRMS** (ESI) calcd for $C_{34}H_{42}NO_6$ $[M+H]^+$ 560.3012 found 560.3020.



6-8aa: This product was synthesized using procedure **B** and isolated in (78% yield, 30.6 mg) as yellow oil after stirring the reaction mixture for 1.5 h. **¹H NMR**

(CDCl₃, 500 MHz): δ 7.10 (t, 2H, J = 7.5 Hz), 6.88 (t, 1H, J = 7.2 Hz),

6.79 (s, 1H), 6.69 (d, 2H, J = 7.6 Hz), 4.32 (br, 2H), 3.73 (s, 6H), 3.61 (s, 2H), 3.48 (s, 2H), 1.38 (t, 2H, J = 7.0 Hz), 0.40 (s, 9H), 0.24 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 171.9, 162.2, 147.5, 144.4, 140.0, 139.3, 138.4, 128.6, 125.8, 124.7, 122.8, 122.4, 104.1, 104.0, 62.3, 59.0, 53.1, 41.0, 40.9, 14.1, 0.5, -0.3; **HRMS** (ESI) calcd for $C_{30}H_{40}NO_5Si_2$ $[M+H]^+$ 550.2445 found 550.2441.

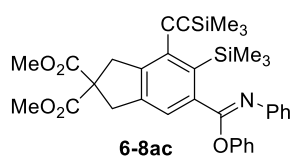


6-8ab: This product was synthesized using procedure **B** and isolated in (61% yield, 26.1 mg) as light yellow solid after stirring the reaction mixture for 1.5

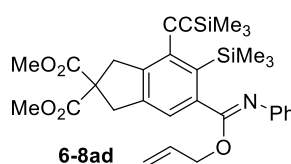
h. **¹H NMR** (CDCl₃, 500 MHz): δ 7.13 (t, 2H, J = 7.6 Hz), 6.95 (t, 1H, J = 7.0

Hz), 6.82 (s, 1H), 6.69 (d, 2H, J = 7.6 Hz), 4.83 (br, 1H), 4.50 (br, 1H), 3.75 (s, 6H), 3.64 (s, 2H), 3.51 (s, 2H), 0.36 (s, 9H), 0.24 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 171.9, 160.1, 145.7, 145.1, 140.3, 139.5, 136.4, 128.8, 126.1, 124.7, 123.8, 123.6 (q, J = 277.1 Hz), 122.3, 104.4, 103.8, 62.8 (q, J = 35.7 Hz), 58.9,

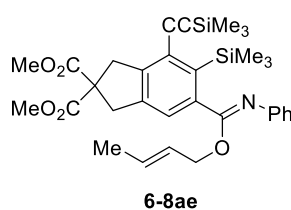
53.1, 41.0, 40.9, −0.3; **¹⁹F NMR** (375 MHz, CDCl₃): δ −73.3 Hz (t, *J* = 8.1 Hz); **HRMS** (ESI) calcd for C₃₀H₃₇NO₅F₃Si₂ [M+H]⁺ 604.2162 found 604.2166.



6-8ac: This product was synthesized using procedure **B** and isolated in (90% yield, 39.4 mg) as yellow solid after stirring the reaction mixture for 1.5 h. **¹H NMR** (CDCl₃, 500 MHz): δ 7.48–7.34 (m, 4H), 7.20 (br, 1H), 7.13–6.99 (m, 4H), 6.94–6.84 (m, 1H), 6.66 (d, 2H, *J* = 6.6 Hz), 3.76 (s, 6H), 3.67 (s, 2H), 3.58 (s, 2H), 0.44 (s, 9H), 0.25 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 171.9, 160.9, 153.0, 146.2, 144.8, 140.3, 139.2, 137.7, 129.2, 128.5, 126.0, 124.9, 123.4, 122.3, 122.0, 104.2, 104.0, 59.1, 53.1, 41.1, 40.9, 0.7, −0.3; **HRMS** (ESI) calcd for C₃₄H₄₀NO₅Si₂ [M+H]⁺ 598.2445 found 598.2466.

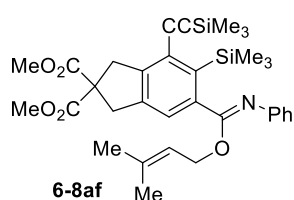


6-8ad: This product was synthesized using procedure **B** and isolated in (67% yield, 29.2 mg) as light yellow oil after stirring the reaction mixture for 1.5 h. **¹H NMR** (CDCl₃, 500 MHz): δ 7.10 (t, 2H, *J* = 7.3 Hz), 6.89 (t, 1H, *J* = 7.0 Hz), 6.79 (s, 1H), 6.69 (d, 2H, *J* = 7.4 Hz), 6.14–6.01 (m, 1H), 5.40 (d, 1H, *J* = 17.1 Hz), 5.26 (d, 1H, *J* = 10.4 Hz), 4.80 (br, 2H), 3.73 (s, 6H), 3.62 (s, 2H), 3.48 (s, 2H), 0.39 (s, 9H), 0.24 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 171.9, 161.7, 147.2, 144.5, 140.0, 139.4, 138.0, 132.7, 128.6, 125.9, 124.7, 123.0, 122.4, 118.1, 104.1, 104.0, 67.3, 59.0, 53.1, 41.0, 40.9, 0.5, −0.3; **HRMS** (ESI) calcd for C₃₁H₄₀NO₅Si₂ [M+H]⁺ 562.2445 found 562.2468.

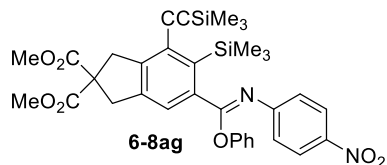


6-8ae: This product was synthesized using procedure **B** and isolated in (63% yield, 25.5 mg) as orange-yellow oil after stirring the reaction mixture for 1.5 h. **¹H NMR** (CDCl₃, 500 MHz): δ 7.15–7.05 (m, 2H), 6.92–6.85 (m, 1H), 6.80 (s, 1H), 6.69 (d, 2H, *J* = 7.2 Hz), 5.92–5.80 (m, 1H), 5.79–5.67 (m, 1H), 4.72 (br, 2H), 3.73 (s, 6H), 3.61 (s, 2H), 3.48 (s, 2H), 0.39 (s, 9H), 0.24 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 171.9, 161.8, 147.3, 144.5, 140.0, 139.3, 138.2, 131.1, 128.6, 125.8, 125.6, 124.7, 122.9, 122.4, 104.1,

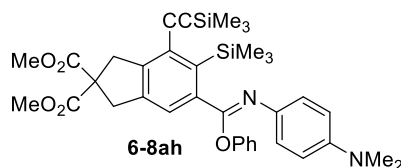
103.9, 67.4, 59.0, 53.1, 41.0, 40.9, 17.9, 0.5, -0.3; **HRMS** (ESI) calcd for $C_{32}H_{42}NO_5Si_2$ $[M+H]^+$ 576.2602 found 576.2585.



6-8af: This product was synthesized using procedure **B** with some modification and isolated in (72% yield, 35.4 mg) as orange yellow oil after stirring the reaction mixture for 1.5 h. PhNC (0.4 mmol) and alcohol (0.2 mmol) were used here to avoid possible ene-reaction between aryne and prenyl alcohol. The purification was performed using neutral alumina column chromatography. **¹H NMR** ($CDCl_3$, 500 MHz): δ 7.09 (t, 2H, $J = 7.4$ Hz), 6.89 (t, 1H, $J = 7.0$ Hz), 6.81 (s, 1H), 6.70 (d, 2H, $J = 7.5$ Hz), 5.53–5.43 (m, 1H), 4.80 (br, 2H), 3.73 (s, 6H), 3.60 (s, 2H), 3.48 (s, 2H), 1.78 (s, 3H), 1.76 (s, 3H), 0.38 (s, 9H), 0.23 (s, 9H); **¹³C NMR** ($CDCl_3$, 125 MHz): δ 171.9, 162.1, 147.3, 144.4, 139.9, 139.3, 138.3, 128.6, 125.8, 124.8, 122.9, 122.4, 119.1, 104.1, 103.9, 63.6, 59.1, 53.1, 41.0, 40.9, 25.9, 18.2, 0.5, -0.3; **HRMS** (ESI) calcd for $C_{33}H_{43}NO_5NaSi_2$ $[M+Na]^+$ 612.2578 found 612.2557.

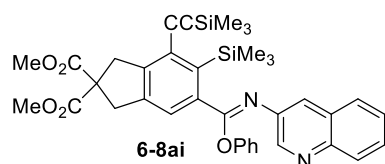


6-8ag: This product was synthesized using procedure **B** and isolated in (81% yield, 44.2 mg) as orange yellow solid after stirring the reaction mixture for 1.5 h. **¹H NMR** ($CDCl_3$, 500 MHz): δ 8.00 (d, 2H, $J = 7.9$ Hz), 7.49–7.30 (m, 4H), 7.26–7.20 (m, 1H), 7.05 (s, 1H), 6.83–6.69 (m, 2H), 3.77 (s, 6H), 3.67 (s, 2H), 3.59 (s, 2H), 0.46 (s, 9H), 0.25 (s, 9H); **¹³C NMR** ($CDCl_3$, 125 MHz): δ 171.8, 152.9, 152.7, 145.6, 143.6, 140.6, 139.1, 136.6, 129.4, 126.5, 125.6, 124.6, 122.4, 121.7, 105.0, 103.5, 59.0, 53.2, 41.0, 40.9, 0.9, -0.4; **HRMS** (ESI) calcd for $C_{34}H_{39}N_2O_7Si_2$ $[M+H]^+$ 643.2296 found 643.2307.

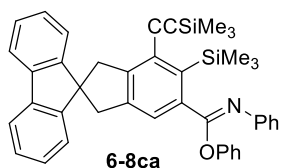


6-8ah: This product was synthesized using procedure **B** and isolated in (70% yield, 36.6 mg) as orange yellow solid after stirring the reaction mixture for 1.5 h. **¹H NMR** ($CDCl_3$, 500 MHz): δ 7.46–7.33 (m, 4H),

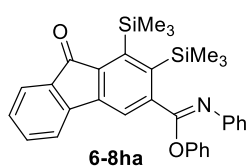
7.17 (br, 1H), 7.05 (s, 1H), 6.57 (d, 2H, $J = 7.9$ Hz), 6.50 (d, 2H, $J = 8.0$ Hz), 3.77 (s, 6H), 3.70 (s, 2H), 3.60 (s, 2H), 2.83 (s, 6H), 0.42 (s, 9H), 0.26 (s, 9H); ^{13}C NMR (CDCl_3 , 125 MHz): 172.0, 159.2, 153.2, 147.4, 144.6, 140.5, 139.3, 138.7, 135.6, 129.0, 126.0, 124.8, 124.6, 123.8, 122.0, 113.1, 104.2, 104.0, 59.0, 53.1, 41.1, 41.0, 0.6, -0.3 ; **HRMS** (ESI) calcd for $\text{C}_{36}\text{H}_{45}\text{N}_2\text{O}_5\text{Si}_2$ $[\text{M}+\text{H}]^+$ 641.2867 found 641.2869.



6-8ai: This product was synthesized using procedure **B** and isolated in (58% yield, 22.7 mg) as white solid after stirring the reaction mixture for 1.5 h. ^1H NMR (CDCl_3 , 500 MHz): δ 8.38 (s, 1H), 7.99–7.88 (m, 1H), 7.63–7.51 (m, 2H), 7.50–7.38 (m, 6H), 7.34 (s, 1H), 7.07 (s, 1H), 3.73 (s, 6H), 3.64 (s, 2H), 3.55 (s, 2H), 0.48 (s, 9H), 0.23 (s, 9H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 171.8, 163.4, 152.8, 147.2, 145.4, 144.9, 140.8, 139.8, 139.2, 137.0, 129.4, 129.0, 128.2, 127.9, 127.3, 126.7, 126.5, 125.8, 125.4, 124.6, 121.9, 104.7, 103.7, 59.1, 53.1, 41.0, 40.9, 0.8, -0.4 ; **HRMS** (ESI) calcd for $\text{C}_{37}\text{H}_{41}\text{N}_2\text{O}_5\text{Si}_2$ $[\text{M}+\text{H}]^+$ 649.2554 found 649.2586.

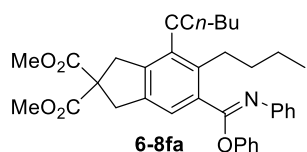


6-8ca: This product was synthesized using procedure **B** and isolated in (73% yield, 34.6 mg) as yellow solid after stirring the reaction mixture for 5 h. ^1H NMR (CDCl_3 , 500 MHz): δ 7.75 (d, 2H, $J = 7.4$ Hz), 7.52–7.42 (m, 3H), 7.39 (d, 3H, $J = 8.6$ Hz), 7.29–7.20 (m, 5H), 7.19–7.10 (m, 3H), 7.01–7.93 (m, 1H), 6.74 (d, 2H, $J = 7.2$ Hz), 3.49 (s, 2H), 3.40 (s, 2H), 0.52 (s, 9H), 0.15 (s, 9H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 161.6, 153.1, 152.0, 147.8, 146.6, 143.2, 139.6, 138.7, 137.3, 129.3, 128.4, 127.7, 127.5, 126.2, 125.4, 125.1, 123.3, 122.5, 122.4, 122.0, 119.9, 104.3, 103.8, 56.5, 45.7, 45.4, 0.9, -0.4 ; **HRMS** (ESI) calcd for $\text{C}_{42}\text{H}_{42}\text{NOSi}_2$ $[\text{M}+\text{H}]^+$ 632.2805 found 632.2789.

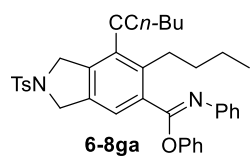


6-8ha: This product was synthesized using procedure **B** and isolated in (82% yield, 29.4 mg) as yellow solid after stirring the reaction mixture for 2 h. NMR at higher temperature (333K); ^1H NMR (CDCl_3 , 500 MHz): δ 7.60 (d, 2H, $J = 6.4$ Hz), 7.42

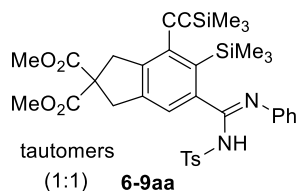
(t, 1H, $J = 7.2$ Hz), 7.39–7.24 (m, 4H), 7.22–7.01 (m, 9H), 6.96 (t, 1H, $J = 7.0$ Hz), 6.90 (br, 2H), 0.47 (s, 9H), 0.42 (s, 9H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 195.5, 154.6, 153.8 (br), 145.9 (br), 143.3, 143.2, 141.0, 134.5, 134.0, 129.3, 129.2, 128.5, 124.0, 122.5, 121.3, 120.1, 4.1, 3.0; HRMS (ESI) calcd for $\text{C}_{32}\text{H}_{34}\text{NO}_2\text{Si}_2$ $[\text{M}+\text{H}]^+$ 520.2128 found 520.2136.



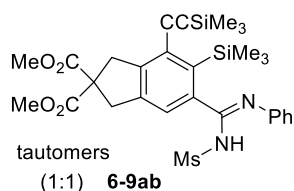
6-8fa: This product was synthesized using procedure **B** and isolated in (68% yield, 35.7 mg) as yellow solid after stirring the reaction mixture for 2 h. ^1H NMR (CDCl_3 , 500 MHz): δ 7.51–7.36 (m, 2H), 7.35–7.26 (m, 2H), 7.24–7.17 (m, 1H), 7.13–6.99 (m, 2H), 6.93 (s, 1H), 6.90–6.80 (m, 1H), 6.70–6.57 (m, 2H), 3.74 (s, 6H), 3.62 (s, 2H), 3.50 (s, 2H), 2.83 (br, 2H), 2.47 (t, 2H, $J = 6.4$ Hz), 1.76–1.40 (m, 8H), 0.96 (t, 6H, $J = 7.0$ Hz); ^{13}C NMR (CDCl_3 , 125 MHz): δ 171.9, 160.8, 153.0, 146.7, 144.4, 141.4, 136.8, 130.8, 129.4, 128.5, 125.1, 123.6, 123.2, 122.0, 121.7, 120.9, 98.7, 59.6, 53.0, 41.0, 40.6, 32.6, 32.4, 30.9, 23.5, 22.0, 19.4, 14.0, 13.6; HRMS (ESI) calcd for $\text{C}_{36}\text{H}_{40}\text{NO}_5$ $[\text{M}+\text{H}]^+$ 566.2906 found 566.2926.



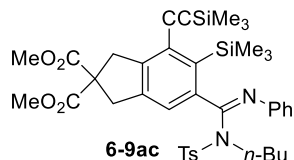
6-8ga: This product was synthesized using procedure **B** and isolated in (53% yield, 24.2 mg) as orange solid after stirring the reaction mixture for 30 min. ^1H NMR (CDCl_3 , 500 MHz): δ 7.75 (d, 2H, $J = 7.2$ Hz), 7.50–7.35 (m, 2H), 7.31 (d, 2H, $J = 7.6$ Hz), 7.29–7.16 (m, 3H), 7.13–6.97 (m, 2H), 6.96–6.78 (m, 2H), 6.68–6.51 (m, 2H), 4.58 (s, 2H), 4.51 (s, 2H), 2.91–2.75 (m, 2H), 2.46 (d, 2H, $J = 6.8$ Hz), 2.41 (s, 3H), 1.75–1.34 (m, 8H), 0.97 (t, 3H, $J = 7.3$ Hz), 0.95 (t, 3H, $J = 7.4$ Hz); ^{13}C NMR (CDCl_3 , 125 MHz): δ 160.0, 152.8, 146.5, 143.7, 142.3, 140.6, 133.8, 133.2, 131.7, 129.9, 129.4, 128.6, 127.5, 125.3, 123.3, 121.9, 121.5, 119.9, 99.9, 75.8, 54.2, 54.0, 32.5, 32.3, 30.7, 23.4, 22.0, 21.5, 19.3, 13.9, 13.6; HRMS (ESI) calcd for $\text{C}_{38}\text{H}_{41}\text{N}_2\text{O}_3\text{S}$ $[\text{M}+\text{H}]^+$ 605.2838 found 605.2823.



6-9aa: This product was synthesized using procedure **C** and isolated in (58% yield, 29.4 mg) as red yellow solid in an inseparable mixture of two tautomers (1:1) after stirring the reaction mixture for 1.5 h. **¹H NMR** (CDCl₃, 500 MHz): δ 10.26 (br, 1H), 7.88 (d, 2H, *J* = 7.0 Hz), 7.67 (d, 2H, *J* = 6.8 Hz), 7.56 (d, 2H, *J* = 7.8 Hz), 7.33 (t, 2H, *J* = 7.0 Hz), 7.29 (d, 2H, *J* = 7.3 Hz), 7.23 (t, 2H, *J* = 7.4 Hz), 7.20–7.11 (m, 3H), 7.07 (t, 1H, *J* = 6.6 Hz), 7.01 (s, 1H), 6.93 (s, 1H), 6.80 (s, 1H), 6.66 (d, 2H, *J* = 7.7 Hz), 3.83 (s, 3H), 3.79–3.61 (m, 13H), 3.58 (s, 2H), 3.52 (s, 2H), 2.41 (s, 6H), 0.42 (s, 9H), 0.27 (s, 9H), 0.26 (s, 9H), 0.22 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 172.4, 171.9, 171.5, 163.8, 145.7, 145.6, 143.3, 142.4, 140.6, 140.2, 140.1, 139.6, 139.2, 138.8, 137.3, 136.8, 129.4, 129.2, 129.1, 126.9, 126.3, 126.2, 125.9, 125.5, 124.1, 123.8, 122.8, 120.8, 104.8, 104.5, 103.7, 103.6, 59.1, 59.0, 53.1, 41.1, 41.0, 40.9, 0.6, 0.5, –0.3, –0.4; **HRMS** (ESI) calcd for C₃₅H₄₃N₂O₆Si₂S [M+H]⁺ 675.2380 found 675.2360.

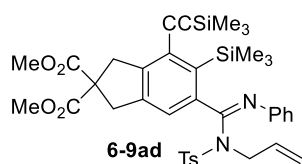


6-9ab: This product was synthesized using procedure **C** and isolated in (70% yield, 26.7 mg) as light yellow solid as an inseparable mixture of two tautomers (1:1) after stirring the reaction mixture for 1.5 h. **¹H NMR** (CDCl₃, 500 MHz): δ 9.92 (br, 1H), 7.59 (d, 2H, *J* = 7.6 Hz), 7.38 (t, 2H, *J* = 7.3 Hz), 7.29 (s, 1H), 7.21 (d, 1H, *J* = 7.2 Hz), 7.15 (d, 2H, *J* = 7.3 Hz), 7.07 (d, 1H, *J* = 7.2 Hz), 7.03 (s, 1H), 6.80 (s, 1H), 6.67 (d, 2H, *J* = 7.8 Hz), 3.85–3.59 (m, 18H), 3.58 (s, 2H), 3.11 (s, 3H), 3.04 (s, 3H), 0.42 (s, 9H), 0.36 (s, 9H), 0.26 (s, 9H), 0.23 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 172.5, 171.9, 171.7, 171.4, 164.5, 164.0, 145.9, 145.7, 140.8, 140.3, 139.7, 139.2, 138.8, 138.3, 137.4, 136.7, 129.2, 126.5, 126.3, 125.9, 125.6, 124.1, 122.8, 120.9, 104.8, 104.7, 103.7, 103.5, 59.0, 53.2, 43.4, 42.9, 41.1, 40.9, 0.7, 0.5, –0.3, –0.4; **HRMS** (ESI) calcd for C₂₉H₃₉N₂O₆Si₂S [M+H]⁺ 599.2067 found 599.2076.



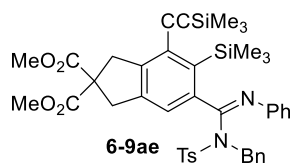
6-9ac: This product was synthesized using procedure **C** and isolated in (79% yield, 35.5 mg) as light yellow oil after stirring the reaction mixture for 1.5 h.

NMR at higher temperature (333K); ^1H NMR (CDCl_3 , 500 MHz): δ 7.55 (br, 2H), 7.24 (d, 2H, $J = 7.8$ Hz), 6.98 (t, 2H, $J = 7.2$ Hz), 6.80 (t, 1H, $J = 6.8$ Hz), 6.49 (br, 1H), 6.39 (d, 2H, $J = 6.7$ Hz), 3.99 (br, 1H), 3.88–3.67 (m, 7H), 3.63 (s, 2H), 3.50–3.29 (m, 2H), 2.44 (s, 3H), 1.91 (br, 1H), 1.72 (br, 1H), 1.40–1.18 (br, 2H), 0.92–0.81 (br, 3H), 0.27 (s, 9H), 0.22 (s, 9H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 171.8, 171.7, 155.2, 147.0, 144.4, 143.5, 140.9 (br), 138.8, 138.5, 136.9, 128.9, 128.3, 128.1, 125.7, 125.2, 122.8, 122.0, 104.3, 104.2, 59.1, 52.8, 48.4, 41.1, 41.0, 31.8, 29.6, 21.4, 20.1, 13.4, 0.5, –0.5; **HRMS** (ESI) calcd for $\text{C}_{39}\text{H}_{51}\text{N}_2\text{O}_6\text{Si}_2\text{S}$ $[\text{M}+\text{H}]^+$ 731.3006 found 731.3016.



6-9ad: This product was synthesized using procedure **C** and isolated in (68% yield, 29.3 mg) as orange oil after stirring the reaction mixture for 1.5 h. NMR

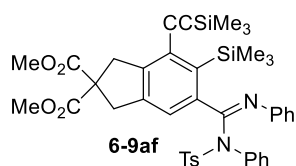
at higher temperature (333K); ^1H NMR (CDCl_3 , 500 MHz): δ 7.56 (br, 2H), 7.23 (d, 2H, $J = 7.6$ Hz), 6.98 (t, 1H, $J = 6.9$ Hz), 6.80 (t, 1H, $J = 6.7$ Hz), 6.48 (br, 1H), 6.39 (d, 2H, $J = 6.7$ Hz), 6.10–5.95 (m, 1H), 5.24–5.04 (m, 2H), 4.73 (br, 1H), 4.46 (br, 1H), 3.80 (s, 3H), 3.75 (s, 3H), 3.63 (s, 2H), 3.47–3.28 (m, 2H), 2.44 (s, 3H), 0.27 (s, 9H), 0.23 (s, 9H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 171.8, 171.7, 155.0, 146.9, 144.5, 143.6, 140.9, 138.9, 138.3, 136.6, 134.0, 128.9, 128.5, 128.1, 125.7, 125.4, 123.0, 118.4, 104.4, 104.1, 59.0, 52.8, 50.2, 41.1, 40.9, 21.4, 0.5, –0.5; **HRMS** (ESI) calcd for $\text{C}_{38}\text{H}_{47}\text{N}_2\text{O}_6\text{Si}_2\text{S}$ $[\text{M}+\text{H}]^+$ 715.2693 found 715.2724.



6-9ae: This product was synthesized using procedure **C** and isolated in (89% yield, 42.1 mg) as yellow solid after stirring the reaction mixture for 1.5 h. NMR

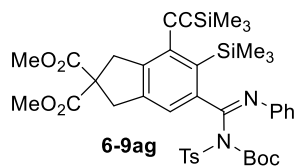
at higher temperature (333K); ^1H NMR (CDCl_3 , 500 MHz): δ 7.5–7.19 (br, 7H), 7.16 (d, 2H, $J = 6.9$ Hz), 6.97 (t, 2H, $J = 7.0$ Hz), 6.80 (t, 1H, $J = 7.5$ Hz), 6.37 (d, 2H, $J = 7.0$ Hz), 5.64 (br, 1H), 4.85 (br, 1H), 3.81 (s, 3H), 3.73 (s, 3H), 3.59 (d, 2H, $J = 10.9$ Hz), 3.34 (d, 1H, $J = 17.5$ Hz), 3.11 (d, 1H, $J = 17.4$ Hz), 2.42 (s, 3H), 0.25 (s, 9H), 0.23 (s, 9H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 171.8, 171.7,

155.2, 146.7, 144.4, 143.6, 138.6, 138.2, 137.8, 136.4, 128.9, 128.8, 128.6, 128.1, 127.2, 125.6, 125.5, 123.0, 121.9, 104.3, 104.2, 77.7, 77.1, 76.9, 76.6, 58.8, 52.8, 50.7, 41.1, 40.8, 29.6, 21.3, 0.5, -0.5; **HRMS** (ESI) calcd for C₄₂H₄₉N₂O₆Si₂S [M+H]⁺ 765.2850 found 765.2872.



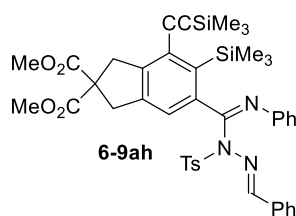
6-9af: This product was synthesized using procedure **C** and isolated in (81% yield, 44.7 mg) as light yellow solid after stirring the reaction mixture for 1.5 h.

¹H NMR (CDCl₃, 500 MHz): δ 7.71 (d, 2H, *J* = 7.6 Hz), 7.31 (d, 2H, *J* = 8.0 Hz), 7.30–7.20 (m, 5H), 6.99 (t, 2H, *J* = 7.6 Hz), 6.82 (t, 1H, *J* = 7.3 Hz), 6.78 (s, 1H), 6.41 (d, 2H, *J* = 7.8 Hz), 3.77 (s, 3H), 3.75 (s, 3H), 3.61–3.48 (m, 2H), 3.49 (s, 2H), 2.48 (s, 3H), 0.20 (s, 9H), 0.18 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 171.8, 155.3, 146.5, 144.4, 144.0, 140.1, 139.2, 137.7, 137.3, 136.6, 131.5, 129.6, 128.8, 128.7, 128.6, 128.2, 125.7, 125.6, 123.2, 122.4, 104.4, 104.0, 59.0, 53.1, 41.0, 40.8, 21.7, 0.6, -0.4; **HRMS** (ESI) calcd for C₄₁H₄₇N₂O₆Si₂S [M+H]⁺ 751.2693 found 751.2707.



6-9ag: This product was synthesized using procedure **C** and isolated in (36% yield, 19.2 mg) as orange yellow solid after stirring the reaction mixture for 1.5 h.

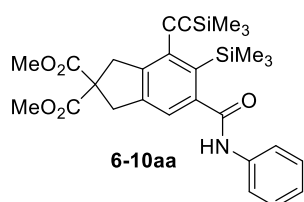
¹H NMR (CDCl₃, 500 MHz): δ 7.40 (t, 2H, *J* = 7.5 Hz), 7.35 (t, 1H, *J* = 7.1 Hz), 7.24–7.15 (m, 4H), 7.04 (d, 2H, *J* = 7.7 Hz), 6.79 (s, 1H), 3.81–3.71 (m, 8H), 3.59 (s, 2H), 2.33 (s, 3H), 1.14 (s, 9H), 0.52 (s, 9H), 0.27 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 168.4, 151.3, 144.7, 142.3, 140.7, 139.6, 139.4, 138.5, 129.1, 128.8, 128.0, 127.8, 126.4, 125.5, 121.2, 104.1, 84.7, 59.2, 53.1, 41.1, 41.0, 27.4, 21.4, 0.9, -0.3; **HRMS** (ESI) calcd for C₄₀H₅₁N₂O₈Si₂S [M+H]⁺ 775.2905 found 775.2914.



6-9ah: This product was synthesized using procedure **C** and isolated in (71% yield, 32.6 mg) as yellow solid after stirring the reaction mixture for 1.5 h.

¹H NMR (CDCl₃, 500 MHz): δ 8.24 (s, 1H), 7.55 (d, 2H, *J* = 7.8 Hz), 7.43 (d, 2H, *J* = 7.4 Hz), 7.38–7.22 (m, 10H), 6.65 (s, 1H), 3.81 (s, 3H), 3.76 (s, 3H), 3.69–3.54 (m, 2H), 3.46 (s, 2H), 2.46 (s, 3H), 0.27 (s, 9H), 0.25 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 172.1,

172.0, 162.3, 159.5, 144.1, 142.2, 139.0, 137.9, 137.3, 137.2, 134.3, 131.3, 130.5, 129.0, 128.8, 128.4, 124.9, 123.7, 104.5, 103.9, 58.8, 53.1, 41.2, 41.0, 21.6, 0.7, -0.3; **HRMS** (ESI) calcd for $C_{42}H_{48}N_3O_6Si_2S$ $[M+H]^+$ 778.2802 found 778.2809.

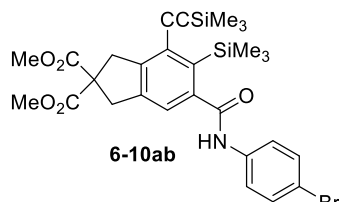


6-10aa

6-10aa: This product was synthesized using procedure **D** and isolated in (88% yield, 37.8 mg) as light yellow solid after stirring the reaction mixture for 1.5

h. **¹H NMR** ($CDCl_3$, 500 MHz): δ 7.58 (d, 2H, $J = 7.6$ Hz), 7.41–7.32 (m, 3H), 7.23 (s, 1H), 7.14 (t, 1H, $J = 7.2$ Hz), 3.78 (s, 6H), 3.69 (s, 2H), 3.61 (s, 2H),

0.40 (s, 9H), 0.27 (s, 9H); **¹³C NMR** ($CDCl_3$, 125 MHz): δ 171.9, 169.4, 145.2, 143.7, 140.6, 138.6, 138.0, 129.2, 126.4, 124.5, 122.3, 119.5, 104.3, 103.8, 59.2, 53.2, 41.0, 40.9, 0.8, -0.3; **HRMS** (ESI) calcd for $C_{28}H_{36}NO_5Si_2$ $[M+H]^+$ 522.2132 found 522.2129.

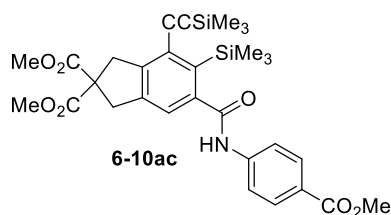


6-10ab

6-10ab: This product was synthesized using procedure **D** and isolated in (69% yield, 23.6 mg) as white solid after stirring the reaction mixture for 1.5

h. **¹H NMR** ($CDCl_3$, 500 MHz): δ 7.52–7.44 (m, 4H), 7.37 (s, 1H), 7.21 (s, 1H), 3.78 (s, 6H), 3.69 (s, 2H), 3.61 (s, 2H), 0.38 (s, 9H), 0.27 (s, 9H); **¹³C**

NMR ($CDCl_3$, 125 MHz): δ 171.8, 169.3, 145.4, 143.3, 140.7, 138.6, 137.0, 132.2, 126.5, 122.2, 121.0, 117.1, 104.5, 103.7, 59.2, 53.2, 41.0, 40.9, 0.7, -0.3; **HRMS** (ESI) calcd for $C_{28}H_{35}NO_5Si_2Br$ $[M+H]^+$ 600.1237 found 600.1230.



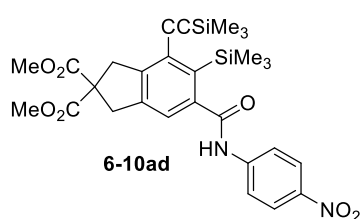
6-10ac

6-10ac: This product was synthesized using procedure **D** and isolated in (60% yield, 20.4 mg) as yellow solid after stirring the reaction

mixture for 1.5 h. **¹H NMR** ($CDCl_3$, 500 MHz): δ 8.04 (d, 2H, $J = 8.4$ Hz), 7.67 (d, 2H, $J = 8.6$ Hz), 7.52 (s, 1H), 7.24 (s, 1H), 3.91 (s, 3H),

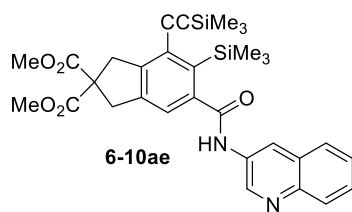
3.78 (s, 6H), 3.70 (s, 2H), 3.62 (s, 2H), 0.39 (s, 9H), 0.27 (s, 9H); **¹³C NMR** ($CDCl_3$, 125 MHz): δ 171.8,

169.5, 166.5, 145.5, 143.2, 142.0, 140.7, 138.7, 131.1, 126.6, 126.0, 122.2, 118.6, 104.6, 103.7, 59.2, 53.2, 52.1, 41.0, 40.9, 0.7, -0.3; **HRMS** (ESI) calcd for C₃₀H₃₈NO₇Si₂ [M+H]⁺ 580.2187 found 580.2168.



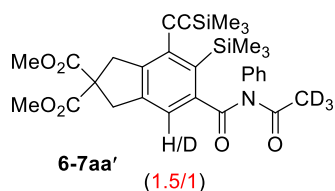
6-10ad: This product was synthesized using procedure **D** and isolated in (56% yield, 21.6 mg) as orange yellow solid after stirring the reaction mixture for 1.5 h. **¹H NMR** (CDCl₃, 500 MHz): δ 8.24 (d, 2H, *J* = 8.5 Hz),

7.76 (d, 2H, *J* = 8.5 Hz), 7.74 (s, 1H), 7.22 (s, 1H), 3.78 (s, 6H), 3.70 (s, 2H), 3.61 (s, 2H), 0.39 (s, 9H), 0.27 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 171.8, 169.6, 145.8, 143.8, 143.5, 142.7, 140.8, 138.8, 126.8, 125.3, 122.0, 118.9, 104.9, 103.5, 59.1, 53.2, 41.0, 40.9, 0.7, -0.3; **HRMS** (ESI) calcd for C₂₈H₃₅N₂O₇Si₂ [M+H]⁺ 567.1983 found 567.1973.



6-10ae: This product was synthesized using procedure **D** and isolated in (71% yield, 28.5 mg) as red yellow solid after stirring the reaction mixture for 1.5 h. **¹H NMR** (CDCl₃, 500 MHz): δ 8.94 (s, 1H), 8.71 (s, 1H), 8.03 (d, 1H, *J* = 8.4 Hz), 7.96 (s, 1H), 7.84 (d, 1H, *J* = 8.2 Hz), 7.64 (t, 1H, *J* =

7.6 Hz), 7.55 (d, 1H, *J* = 7.6 Hz), 3.77 (s, 6H), 3.70 (s, 2H), 3.62 (s, 2H), 0.40 (s, 9H), 0.27 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 171.8, 170.0, 145.5, 145.4, 143.5, 143.0, 140.7, 138.8, 131.6, 129.0, 128.5, 128.3, 128.0, 127.4, 126.6, 123.7, 122.2, 104.6, 103.7, 59.2, 53.2, 41.0, 40.9, 0.8, -0.3; **HRMS** (ESI) calcd for C₃₁H₃₇N₂O₅Si₂ [M+H]⁺ 573.2241 found 573.2222.



6-7aa': These products were isolated as an inseparable mixture using procedure **F** and isolated in 82% yield (23.6 mg) as light yellow oil after stirring the reaction mixture for 1.5 h. **¹H NMR** (CDCl₃, 500 MHz): δ 7.45 (t, 2H, *J* = 7.8 Hz), 7.38 (t, 1H, *J* = 7.2 Hz), 7.22 (d, 2H, *J* = 7.3 Hz), 6.99 (s,

1H), 3.76 (s, 6H), 3.67 (s, 2H), 3.59 (s, 2H), 2.15 (s, 3H), 0.42 (s, 9H), 0.25 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 173.2, 172.5, 171.9, 144.6, 143.5, 139.7, 139.6, 139.4, 138.8, 129.8, 128.9, 128.8, 126.4, 120.4,

104.0, 103.9, 59.2, 53.1, 41.0, 40.9, 25.7, 25.5, 25.4, 25.2, 0.9, -0.3 **HRMS** (ESI) calcd for $C_{30}H_{35}D_3NO_6Si_2$ $[M+H]^+$ (**6-7aa'-H**) 567.2426 found 567.2426, and $C_{30}H_{34}D_4NO_6Si_2$ $[M+H]^+$ (**6-7aa'-D**) 568.2489 found 568.2482.

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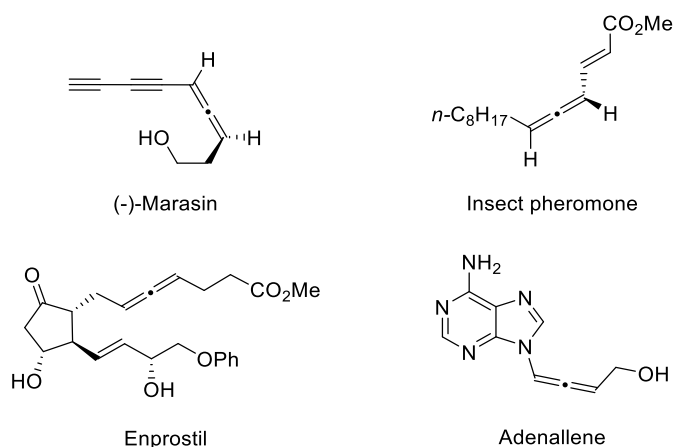
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CHAPTER 7

Copper-Catalyzed Reactions of Terminal 1,3-Diynes with Azides and Nucleophiles

7.1. Introduction

Allenes constitute a distinct class of organic compounds with two orthogonal π -bonds. There are numerous natural products and bioactive molecules that contain allene substructures (**Scheme 7.1**).^{1–3} It has been demonstrated that allene substituted bioactive compounds, like steroids,^{4,5} prostaglandins,^{6,7} carbacyclins,⁷ nucleosides,⁸ and unnatural amino acids⁹ display higher potency, increased metabolic stability, and bioavailability. Because of the strained nature of the cumulene structure, allenes has been engaged in numerous synthetic transformations as a versatile building block to form a variety of carbo- and heterocyclic frameworks.^{10–19} Axial-to-central chirality transfer is an efficient method to generate chiral compounds containing one or more stereogenic centers from chiral allenes.^{19–22}



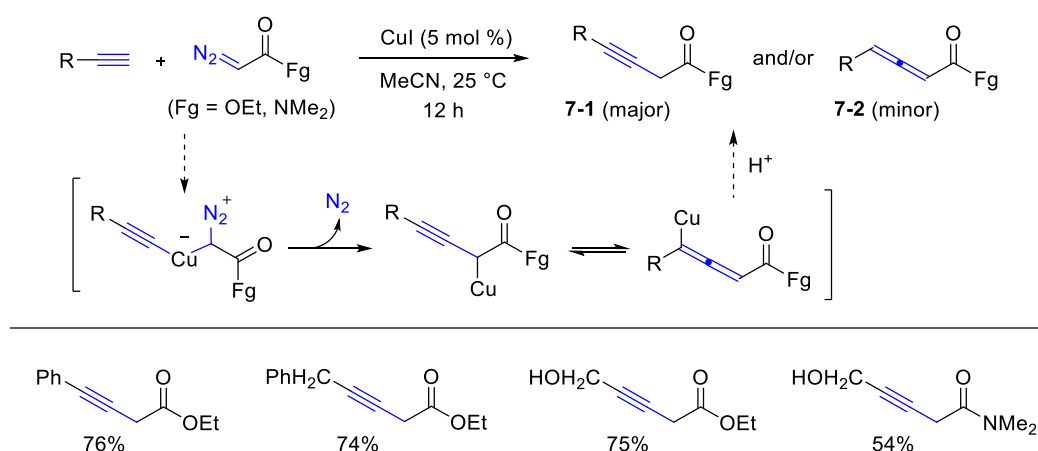
Scheme 7.1. Allene-Based Bioactive Molecules

Due to the important utility of allenes, it is highly desirable to develop new synthetic methods to generate functionalized allenes from readily available starting materials.^{23–28} One of the traditional approaches to synthesis of allenes involves 1,2-elimination of vinyl derivatives under strong basic or metal catalyzed conditions.²⁹ $\text{S}_{\text{N}}2'$ -type reactions with propargylic alcohol derivatives ($\text{FG-CH}_2\text{-C}\equiv\text{C}$)^{30–33} or isomerization of enyne³⁴ moieties also constitutes an efficient method to generate allenes. Transition metal-catalyzed coupling between terminal alkynes and carbonyl moieties in the presence of a secondary amine

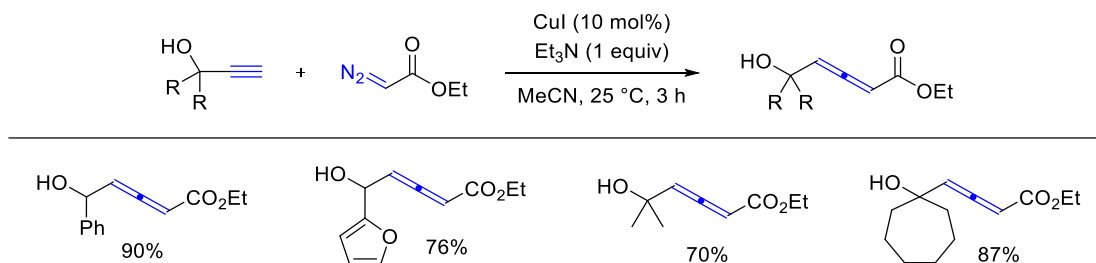
is also a well-established method,³⁵ and a Cu(I)-catalyzed cross-coupling of terminal alkynes with diazo compounds is another efficient protocol to generate allenes.³⁶

In 2004, Fu reported a Cu(I)-catalyzed coupling of alkynes and diazoacetate under mild conditions to generate 3-alkynyl carboxylate **7-1** and only small amounts of the corresponding allenoates **7-2** were observed (**Scheme 7.2**).³⁷ Although the exact mechanisms of these reactions are not well understood, on the basis of other related reactions, we propose a copper acetylide-mediated mechanism for the formation of the 3-alkynoate and allenoate.

On the other hand, Lee and coworkers found that the alkynes containing a heteroatom substituent at the propargylic carbon center preferentially generate the allenoate, and especially in the presence of base such as triethyl amine, allenoate became the exclusive product (**Scheme 7.3**).³⁸ However, under similar



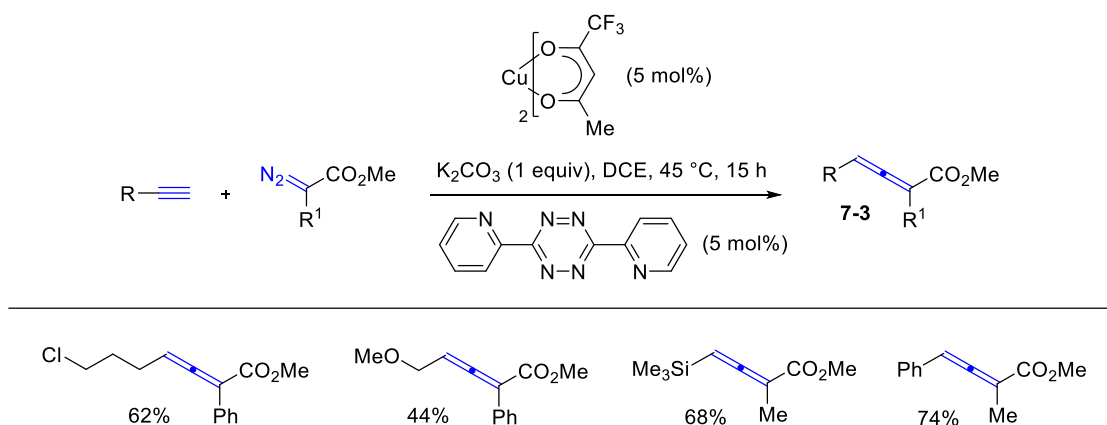
Scheme 7.2. Cu-Catalyzed Coupling Reaction of Diazo Esters and Terminal Alkynes



Scheme 7.3. Synthesis of Allenoates from Terminal Propargylic Alcohols and Ethyl Diazoacetate

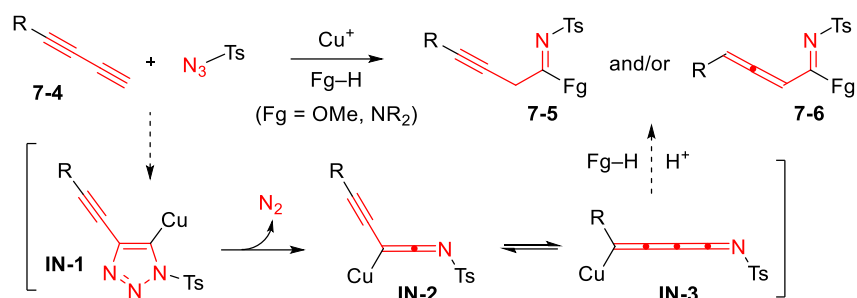
reaction conditions, alkynes without hydroxyl group provided a mixture of 3-alkynoate and allenolate derivatives.

Fox and coworkers reported a similar reaction that selectively generate allenolate as the product (**Scheme 7.4**).³⁹ In the presence of Cu(II)(trifluoroacetylacetonate)₂ catalyst and tetrazine based ligand, reaction of α -substituted- α -diazoesters and terminal alkynes delivered trisubstituted allenolates **7-3** in moderate to good yield. It is notable that equimolar amounts of base (K₂CO₃) is required for this transformation to isomerize the initially formed 3-alkynoate to the corresponding allenolate derivatives.



Scheme 7.4. Cu-Catalyzed Synthesis of 2,4-Disubstituted Allenolates from α -Diazoesters

Relying on this copper acetylide-mediated mechanism, we envision that the copper-catalyzed coupling of terminal 1,3-diyne **7-4** and azide would present a closely related selectivity issue for the formation 3-alkynyl and allenyl imidamide/imidate **7-5/7-6** (**Scheme 7.5**). We surmise that the terminal 1,3-diyne would readily form the corresponding copper acetylide, which will participate in a click reaction⁴⁰ with tosyl azide to form triazole **IN-1**. Subsequent loss of molecular nitrogen will lead to two potentially equilibrating organocopper aza-cumulenes **IN-2** and **IN-3**,⁴¹ which then react with a nucleophile such as an amine or alcohol to generate imidamide⁴² or imidate⁴³ containing either an alkyne (**7-5**) or an allene moiety (**7-6**). A unique feature of this transformation is that the selective oxidation of the terminal alkyne moiety for de novo construction of imidamide and imidate functionality. Starting from different set of starting



Scheme 7.5. Cu-Catalyzed Coupling of Terminal 1,3-Diyne and Azide

materials (terminal 1,3-diynes instead of terminal alkynes), this transformation provides an easy access to closely related products **7-5/7-6**. With these hypotheses in mind, we explored copper-catalyzed reactions of terminal 1,3-diyne **7-4** with tosylazide, which generated functionalized 1,3-disubstituted 2,3-dienyl imidamides and imidates **7-6** with good selectivity over the corresponding alkynyl derivative **7-5**. Also, it was found that the type of nucleophiles, base additives, and the substituent patterns of the 1,3-diynes not only affect the ratio of **7-5** and **7-6** but also promote formation of alternative products such as [3]cumulenes and triple bond migrated products.

7.2. Results and Discussion

7.2.1. Optimization of Reaction Conditions

Our exploration commenced with assessment of the efficiency and selectivity for the formation 3-alkynyl and allenyl imidamide **7-5** and **7-6** (**Table 7.1**). Under the conditions employing copper catalyst (CuI, 10 mol%), azide (1.2 equiv), and amine (1.2 equiv), 1,3-diynes containing different substituent were examined. A hexyl-substituted terminal 1,3-diyne **7-4a** and TsN₃ provided a mixture of alkynyl and allenyl imidamides **7-5aa** and **7-6aa** in 75% yield with a 2:1 ratio (entry 1). Reactions of **7-4a** with other azides such as diphenyl phosphoryl azide⁴⁴ and mesyl azide are also efficient affording alkynyl imidamide **7-5ab** and **7-5ac** as the major product (entries 2 and 3). On the other hand, employing piperidine as a nucleophile under otherwise identical conditions, **7-4a** provided **7-5ad** exclusively (entry 4). 1,3-Diynes with a

secondary (**7-4b**) or a tertiary alkyl group (**7-4c**) provided good yields of **7-5/7-6ba** and **7-5/7-6ca** but low selectivity with a slight preference for alkynyl product **7-5ba** and **7-5ca** (entries 5 and 6). With 1-cyclohexenyl substituted 1,3-diyne provided **7-5/7-6da** in 48% with a preference of 2,3-dienyl compound **7-6da**. 1,3-Diyne **7-4e** containing a propargylic hydroxyl group afforded allene derivative **7-6ea** predominantly (entry 8), whereas 1,3-diyne **7-4f** containing a trimethylsilyl group provided alkynyl derivative **7-5fa** selectively but in marginal yield (entry 9).

Entry	R	Nu-H	Azide	Yield % (alkyne:allene) ^a
1	a , <i>n</i> -Hex	<i>i</i> -Pr ₂ NH	TsN ₃	7-5/7-6aa , 75% (2:1)
2	a , <i>n</i> -Hex	<i>i</i> -Pr ₂ NH	(PhO) ₂ PON ₃	7-5/7-6ab , 66% (5:1)
3	a , <i>n</i> -Hex	<i>i</i> -Pr ₂ NH	MsN ₃	7-5/7-6ac , 54% (2:1)
4	a , <i>n</i> -Hex	piperidine	TsN ₃	7-5ad , 56% (1:0) ^b
5	b , <i>c</i> -Hex	<i>i</i> -Pr ₂ NH	TsN ₃	7-5/7-6ba , 79% (2.3:1)
6	c , <i>t</i> -Bu	<i>i</i> -Pr ₂ NH	TsN ₃	7-5/7-6ca , 71% (1.3:1)
7	d , 1-Cyclohex	<i>i</i> -Pr ₂ NH	TsN ₃	7-5/7-6da , 48% (1:2.5)
8	e , CH ₂ OH	<i>i</i> -Pr ₂ NH	TsN ₃	7-5/7-6ea , 73% (1:15)
9	f , SiMe ₃	<i>i</i> -Pr ₂ NH	TsN ₃	7-5fa , 45% (1:0)

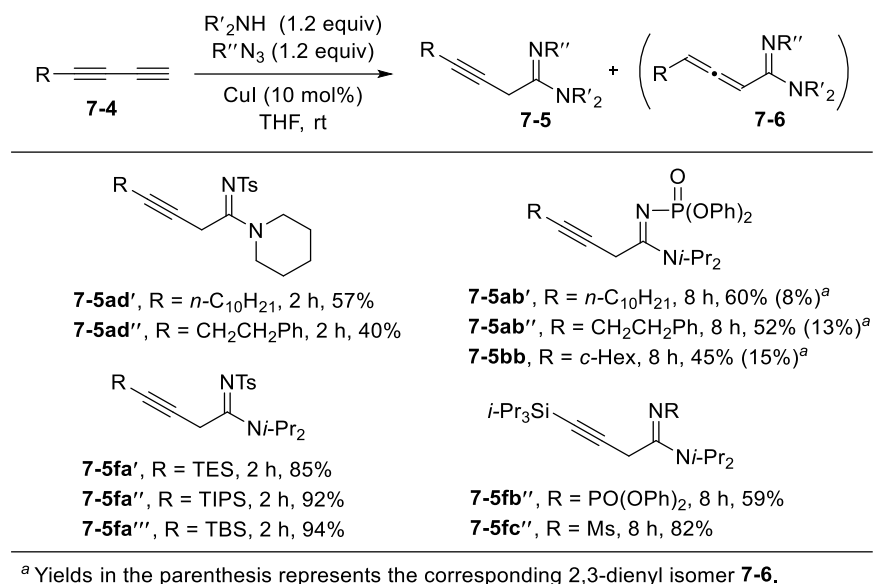
^a Isolated yield. ^b H₂O (1 equiv) and NH₂OH·HCl (1–2 mol%) were used as additives.

Table 7.1. Efficiency and Product Distribution with Assorted Nucleophiles, Azides and 1,3-Diynes of Different Substituents

7.2.2. Synthesis of 3-Alkynyl Imidamides

Once a general trend for the efficiency and selectivity between **7-5** and **7-6** has been revealed from the entries in Table 7.1, we next explored the selective formation of 3-alkynyl imidamide **7-5** (Scheme 7.6). As piperidine exclusively generated 3-alkynyl imidamide, reactions of *n*-decyl and homo-benzyl substituted 1,3-diynes with piperidine were performed, resulting corresponding 3-alkynyl imidamides **7-5ac'** and **7-5ac''** in 57% and 40% yield. Reaction with phosphoryl azide and alkyl substituted diynes predominantly generated 3-alkynyl imidamides (**7-5ab'**, **7-5ab''**, **7-5bb**) in moderate 45–60% yield. Electron-rich 1,3-

diynes with silyl substituents selectively delivered 3-alkynyl imidamides. TBS-, TIPS- and TES-substituted 1,3-diynes provided the corresponding alkynyl derivatives **7-5fa'** – **7-5fa'''** in 85–94% yield. Reactions of TIPS-substituted 1,3-diyne with phosphoryl and mesyl azide also generated 3-alkynyl imides **7-5fb''** and **7-5fc''** exclusively in 59% and 82% yield. It is evident from Scheme 7.6 that reactions with cyclic amine, phosphoryl azide and electron-rich silyl-substituted 1,3-diynes tend to generate 3-alkynyl imidamides predominantly or exclusively.

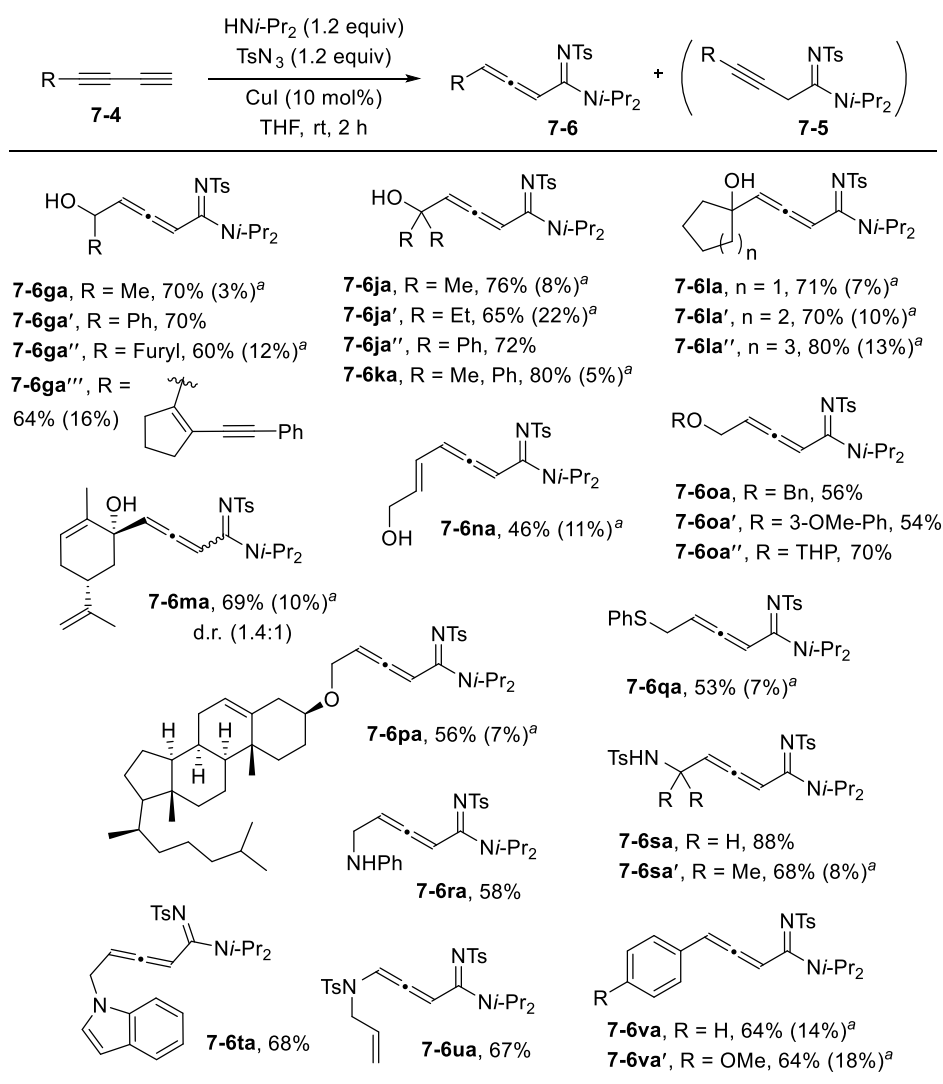


Scheme 7.6. Selective Formation of 3-Alkynyl Imidamides with Assorted Nucleophiles, Azides and 1,3-Diynes

7.2.3. Synthesis of 2,3-Dienyl Imidamides

Next, we examined reactions of different 1,3-diynes to selectively form 2,3-dienyl imidamides **7-6** (Scheme 7.7). Based on the initial observation with propargylic alcohol-containing diyne **7-4e** that selectively generated 2,3-dienyl imidamide, we further tested the reactivity of structurally diversified propargyl alcohols, thioethers, amines and amides. 1,3-Diynes containing secondary or tertiary alcohols afforded 2,3-dienyl imidamides (**7-6ga**, **7-6ga'**, **7-6ga''**, **7-6ga'''**, **7-6ja**, **7-6ja'**, **7-6ja''**, **7-6ka**) as a predominant or exclusive product in 65–76% yield. The selectivity between allenyl and alkynyl isomer depends on the substituent but no clear trend has been found. 1,3-Diynes with a tertiary alcohol and a

cycloalkyl substituent delivered 2,3-dienyl imidamides (**7-6la**, **7-6la'**, **7-6la''**) in 70–80% yield with roughly a 10:1 selectivity. Carvone-containing 1,3-diyne afforded allene **7-6ma** (allene:alkyne = 7:1) in 69% yield with a 1.4:1 diastereomeric ratio. While a vinyl conjugated 1,3-diyne containing a free hydroxyl group provided allene **7-6na** in 46% yield with a low selectivity (4:1), 1,3-diynes with benzyl-, 3-MeO-Ph-, Boc-protected primary alcohols exclusively generated allene derivative (**7-6oa**, **7-6oa'**, **7-6oa''**) in 54–70% yield. Similarly, a cholesteryl ether substituted 1,3-diyne generated allene **7-6pa** in 56% yield with a 8:1 ratio of allene:alkyne. On the other hand, the corresponding thioether afforded **7-6qa** contaminated with the alkyne



^a Yields in the parenthesis represents the corresponding 3-alkynyl compound **7-5**.

Scheme 7.7. Formation of 2,3-Dienyl Imidamides from Diverse Terminal 1,3-Diynes

isomer (allene:alkyne = 7.5:1). 1,3-Diynes containing an aniline and tosylamide substituent at the propargylic position selectively generated allenes **7-6ra** and **7-6sa** in 58% and 88% yield. A *gem*-dimethyl, however, lower the yield and selectivity for **7-6sa'** (68%, 8.5:1). An indole substituted 1,3-diyne provided only allene **7-6ta** in 68% yield and *N*-allyl tosyl-substituted 1,3-diyne provided single isomer **7-6ua** in 67% yield. On the contrary, phenyl and 4-MeO-phenyl substituted 1,3-diynes provided moderate yield and selectivity providing allenes **7-6va** (64%, 4.6:1) and **7-6va'** (64%, 3.6:1).

7.2.4. Synthesis of 2,3-Dienyl Imidates

Although the selectivity of forming allenyl imidamides is good, the formation of alkyne isomer could not be suppressed in many cases. At this juncture, we surmised that trapping the ketenimine intermediate with alcohols may have different product distribution.^{45,46} Indeed, under identical conditions except for replacing *i*-Pr₂NH (1.2 equiv) with MeOH (10 equiv) and Et₃N (2 equiv), the reaction of 1,3-diynes selectively provided 2,3-dienyl imidates without a vestige of alkyne isomer (**Table 7.2**). Lower stoichiometry of methanol led to lower efficiency of the reaction. Alkyl and alkenyl diynes, which provided

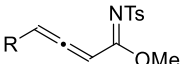
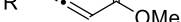
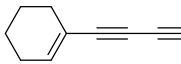
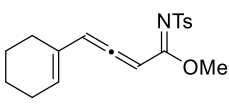
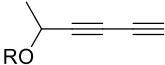
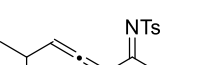
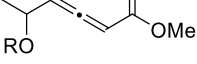
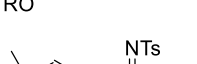
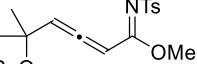
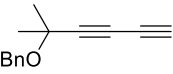
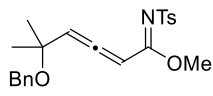
$\text{R}-\text{C}\equiv\text{C}-\text{C}\equiv\text{C} \xrightarrow[\text{Et}_3\text{N (2 equiv), THF, rt, 4 h}]{\text{TsN}_3 \text{ (1.2 equiv), MeOH (10 equiv), Cul (10 mol\%)}} \text{R}-\text{C}=\text{C}=\text{C}=\text{C}-\text{N}(\text{Ts})\text{OMe}$ 7-4 7-6				
Entry	1,3-Diyne 7-4	Allenyl imidate 7-6		Yield (%)
1			7-6ae	40
2			7-6ce	52
3	 7-4d		7-6de	64
4			7-6ge	0
5			7-6he	61
6			7-6he'	46
7			7-6he''	48
8	 7-4i		3ie	72

Table 7.2. Synthesis of 2,3-Dienyl Imidates by Trapping with Methanol

a mixture of allenyl and alkynyl imidamides previously, selectively generated allenyl imidates (**7-6ae**, **7-6ce**, **7-6de**) in moderate to good yield (entries 1–3). Even though 1,3-diyne **7-4g** containing free 2° alcohol led to decomposition (entry 4) the corresponding acyl-, benzyl-, and TBS-protected 1,3-diynes provided 2,3-dienyl imidates (**7-6he**, **7-6he'**, **7-6he''**) in good yield (entries 5–7).

7.2.5. Synthesis of [3]Cumulenes

Subsequently, we observed that under standard conditions, 1,3-diynes **7-7** containing an acetoxy or benzoyloxy substituent at the propargylic position provided mono-, di-, and trisubstituted [3]cumulenes (**Table 7.3**).^{47–51} For example, 1,3-diynes **7-7a** – **7-7c** afforded trisubstituted cumulenes **7-8a** – **7-8c** in 76–80% yield (entries 1–3). 1,3-Diynes substituted with a cycloalkyl moiety afforded the corresponding cumulenes **7-8d** – **7-8f** in good yield (entries 4–6). Unexpectedly, while the acetate derivative of tertiary alcohol afforded, the corresponding primary and secondary acetate provide a mixture of the expected [3]cumulenes and the corresponding acetoxy allene derivatives. However, upon replacing the acetate with

Entry	1,3-Diyne 7-7	[3]Cumulene 7-8	Yield (%)
1	7-7a , R = Me	7-8a	76
2	7-7b , R = Et	7-8b	79
3	7-7c	7-8c	80
4	7-7d , n = 1	7-8d	56
5	7-7e , n = 2	7-8e	82
6	7-7f , n = 3	7-8f	76
7	7-7g , R = H	7-8g	68
8	7-7h , R = Me	7-8h	74
9	7-7i , R = Ph	7-8i	77

Table 7.3. Synthesis of [3]Cumulenyl Imidamides via Eliminating Acetoxy or Benzoyloxy Group of Putative Allene Intermediate

para-nitrobenzoate (**7-7g** – **7-7i**), only cumulenes **7-8g** – **7-8i** were obtained (entries 7–9). We believe this is the consequence of a better leaving group capacity of a benzoate compared to an acetate. [3]Cumulenes is a special class of polyene organic compounds whose synthetic utilities are little explored.^{52–55} Thus, the current mild protocol to allow the preparation of [3]cumulenes containing various substituent patterns from readily available building blocks is of high synthetic utility.

7.2.6. Synthesis of Heterocycles

We envision that with a suitably tethered nucleophile, the conversion of 1,3-diynes to the corresponding conjugated allenyl imidamides and imidates would promote an intramolecular Michael-type addition (**Table 7.4**).^{12,56–60} Under standard conditions, homo-propargyl alcohol-containing 1,3-diynes **7-9a** and **7-9b** were smoothly converted to tetrahydrofuranylidene imidates **7-10a** and **7-10b** in 48% and 87% yield, respectively (entries 1 and 2). The corresponding homopropargyl sulfonamide **7-9c** led to 1-tosylpyrrolidinylidene imidamide **7-10c** in 72% yield (entry 3), however, forming 6-membered ring **7-10d** from **7-9d** failed (entry 4). 1,3-Diynes **7-9e** and **7-9f** substituted with a phenyl group containing an *ortho*-

Condition **A** or **B**
THF, rt
X = O, NH, NTs

Entry	1,3-Diyne 7-9	Conditions	Heterocycle 7-10	Yield (%)
1		7-9a , R = H A ^a		7-10a 48
2		7-9b , R = Me A		7-10b 87
3		7-9c , n = 1 A		7-10c 72
4		7-9d , n = 2 A		7-10d 0
5		7-9e , X = O B ^b		7-10e 70
6		7-9f , X = NH B		7-10f 64

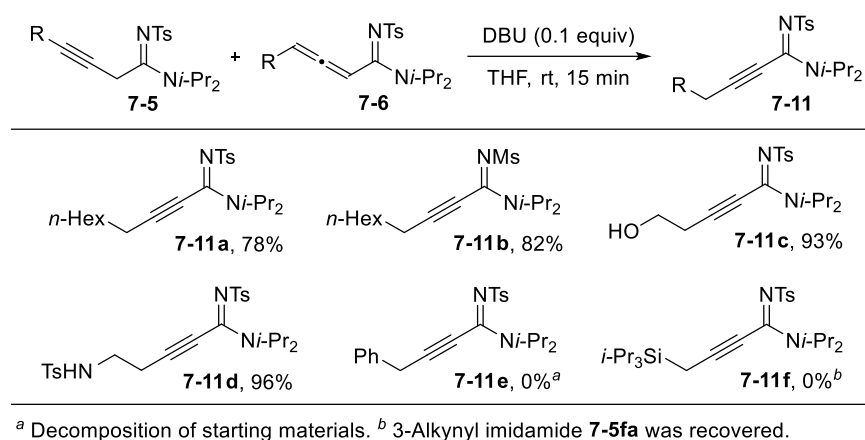
^a Condition **A**: TsN₃ (1.2 equiv), Et₃N (2 equiv), MeOH (10 equiv), CuI (10 mol%), 12 h.
^b Condition **B**: TsN₃ (1.2 equiv), *i*-Pr₂NH (1.2 equiv), CuI (10 mol%), 4 h.

Table 7.4. Synthesis of Heterocycles via Intramolecular Trapping of the Putative Allene Intermediate

OH or NH₂ participated in the cascade reaction to generate benzofuranyl imidamide **7-10e** in 70% and indolyl imidamide **7-10f** in 64% yield, respectively (entries 5 and 6).

7.2.7. Base-Induced Isomerizations

Although expected, migration of the triple bond from 3-alkynyl or 2,3-dienyl isomers to the corresponding 2-alkynyl isomer **7-11** was not observed under the conditions regardless of the reaction time. However, because of the thermodynamic preference for 2-alkynyl isomers, we surmised that the isomerization of **7-5** or **7-6** to **7-11** would happen if a stronger base than secondary amines is used (Scheme 7.8).⁶¹ Indeed, treating a mixture of **7-5** and **7-6** with DBU (0.1 equiv) rapidly induced isomerization to provide 2-alkynyl imidamides **7-11a** – **7-11d**. On the other hand, phenyl- and silyl-substituted 3-alkynyl imidamides **7-5** and **7-6** did not isomerize to the corresponding 2-alkynyl isomers **7-11e** and **7-11f**.



Scheme 7.8. Isomerization of 3-Alkynyl and 2,3-Dienyl Imidamides to the Corresponding 2-Alkynyl Isomers

7.3. Conclusion

In conclusion, we have developed efficient protocols to generate discreet isomers of 2-alkynyl, 3-alkynyl, 2,3-dienyl, and 2,3,4-trienyl imidamides and imidates from copper-catalyzed reactions of 1,3-diynes and tosylazide. The selectivity between 3-alkynyl and 2,3-dienyl imidamides could be controlled by a heteroatom substituent at the propargylic position of the 1,3-diynes and employing different trapping

reagent such as amines and alcohols. [3]Cumulene derivatives were also generated by employing 1,3-diynes that contain acetoxy or bezoyloxy substituent at the propargylic position. While trapping of the putative azacumulene intermediates with amines provided either 3-alkynyl or 2,3-dienyl imidamides depending on the structure of the trapping amines, trapping with methanol selectively generated 2,3-dienyl imidates. It was found that both 3-alkynyl and 2,3-dienyl imidamides could be isomerized to selectively generate the corresponding 2-alkynyl isomers under equilibrating conditions with stronger base such as DBU. Intramolecular trapping of the putative azacumulene intermediates provided 5-membered heterocyclic products if 1,3-diyne substrates contain a homopropargylic hydroxy or amino substituent. A unique feature of this unprecedented click chemistry is that under mild reaction conditions, terminal 1,3-diynes could be selectively converted to different compounds of unsaturated carboxylic acid derivatives with good selectivity.⁶²

7.4. Experimental Details

7.4.1. General Information

Experimental section: All reactions were carried out in oven or flame-dried glassware unless otherwise noted. Reagents which were commercially available, were purchased from Sigma - Aldrich, Alfa Aesar, Acros, and Oakwood Products unless otherwise noted. Known compounds were prepared according to literature procedure. Anhydrous acetonitrile from Sigma-Aldrich was distilled over calcium hydride (CaH_2) under nitrogen atmosphere. Acetic acid was purchased from Fischer Scientific. 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). Yield was calculated on basis of chromatographically and spectroscopically pure isolated compound. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AV-500 spectrometer at 298 K, unless otherwise stated. ^1H NMR chemical shifts (δ) were reported in parts per million (ppm) downfield of TMS and were referenced relative to the residual proteated solvent peak (CDCl_3 (7.26 ppm)). ^{13}C chemical shifts (δ) were reported in parts per million downfield of TMS and are referenced to the carbon resonance of the solvent (CDCl_3 , δ 77.2 ppm). Multiplicities in ^1H NMR were abbreviated by s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sext (sextet), sept (septet) 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 (Waters Corporation, Milford, MA, USA) at 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 (Waters Corporation, Milford, MA, USA) at the University of Illinois at Urbana-Champaign.

Synthesis of Terminal 1,3-Diynes: Diynes **7-4a–b**, **7-4d–e**, **7-4g**, **7-4j**, **7-4l'**, **7-4o**, **7-4s–s'**, **7-4h'–h''**, **7-9a** were prepared according to literature procedure starting from corresponding mono alkynes. Rest of the substrates were prepared according to the following procedures.

$$\begin{array}{c}
 \text{R}-\text{C}\equiv\text{C} \xrightarrow[\text{acetone}]{\text{NBS, AgNO}_3} \text{R}-\text{C}\equiv\text{C}-\text{Br} \xrightarrow[\text{NH}_2\text{OH}\cdot\text{HCl}]{\begin{array}{c} \text{BuNH}_2 \text{ (30\% aq)} \\ \text{CuCl, CH}_2\text{Cl}_2 \end{array}} \text{R}-\text{C}\equiv\text{C}-\text{C}\equiv\text{C}-\text{SiMe}_3 \\
 \begin{array}{c} 0^\circ\text{C} \rightarrow \text{rt, 2 h} \\ 90-95\% \end{array} \quad \text{S1} \quad \begin{array}{c} 0^\circ\text{C} \rightarrow \text{rt, 2 h} \\ 60-85\% \end{array} \quad \text{S2}
 \end{array}$$

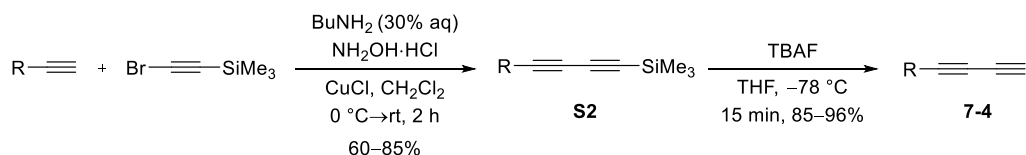
$$\begin{array}{c}
 \text{R}-\text{C}\equiv\text{C}-\text{C}\equiv\text{C}-\text{SiMe}_3 \xrightarrow[\text{THF, } -78^\circ\text{C}]{\text{TBAF}} \text{R}-\text{C}\equiv\text{C}-\text{C}\equiv\text{C} \\
 \text{S2} \quad \quad \quad 15 \text{ min, 85-96\%} \quad \quad \quad \text{7-4}
 \end{array}$$

To a mixture of 30% aqueous *n*-BuNH₂ (10.0 mL, 2 mL per 1.0 mmol of terminal alkyne) and CuCl (1.5 mmol) in a two-necked round-bottom flask, a solution of trimethylsilylacetylene (5.0 mmol) in CH₂Cl₂ was added slowly at 0 °C under N₂ atmosphere. Then **S1** (6.0 mmol) diluted in CH₂Cl₂ was added dropwise into the reaction mixture over 30–45 min. After 5 min, the ice bath was removed, and stirring was continued for additional 1–2 h at room temperature (TLC monitoring). A pinch of NH₂OH·HCl was added several times into the reaction mixture when the solution becomes blue. The reaction was quenched by a sat. solution of NH₄Cl and extracted with CH₂Cl₂. The combined organic extracts were washed with water and brine sequentially and dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude

material was purified by flash column chromatography (SiO, EtOAc–hexane, 1:20 to 1:10) to isolate pure silyl-substituted diynes **S2** in moderate to good yield.

To a stirred solution of **S2** (5 mmol) in dry THF was added TBAF (5.5 mL, 1 M solution in THF, 5.5 mmol) slowly at $-78\text{ }^{\circ}\text{C}$ under N_2 atmosphere. After 15 min, the reaction mixture was quenched with sat. NH_4Cl and extracted with EtOAc (X2). The combined organic extracts were washed with water and brine sequentially and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. 1,3-Diynes **7-4** was subjected to the click reaction without further purification.

Procedure B: Synthesis of 1,3-diynes (7-4d, 7-4g'', 7-4m–n, 7-4o', 7-4p–r, 7-4i, 7-4t–u, 7-9e)

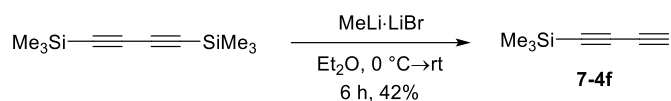


To a mixture of 30% aqueous *n*- BuNH_2 (10.0 mL, 2 mL per 1.0 mmol of terminal alkyne) and CuCl (1.5 mmol) in a two-necked round-bottom flask, a solution of terminal alkyne (5 mmol) in CH_2Cl_2 was added slowly at $0\text{ }^{\circ}\text{C}$ under N_2 atmosphere. Then trimethylsilyl alkynyl bromide (6.0 mmol) diluted in CH_2Cl_2 was added dropwise into the reaction mixture over 30–45 min. After 5 min, the ice bath was removed and stirring was continued for additional 1–2 h at room temperature (TLC monitoring). A pinch of $\text{NH}_2\text{OH}\cdot\text{HCl}$ was added several times into the reaction mixture when the solution becomes blue. The reaction was quenched by a sat. solution of NH_4Cl and extracted with CH_2Cl_2 . The combined organic extracts were washed with water and brine sequentially and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO, EtOAc–hexane, 1:20 to 1:10) to isolate silyl-substituted 1,3-diyne **S2** in moderate to good yield.

To a stirred solution of **S2** (5.0 mmol) in dry THF was added TBAF (5.5 mL, 1 M solution in THF, 5.5 mmol) slowly at $-78\text{ }^{\circ}\text{C}$ under N_2 atmosphere. After 15 min, the reaction mixture was quenched with sat. NH_4Cl and extracted with EtOAc (X2). The combined organic extracts were washed with water and

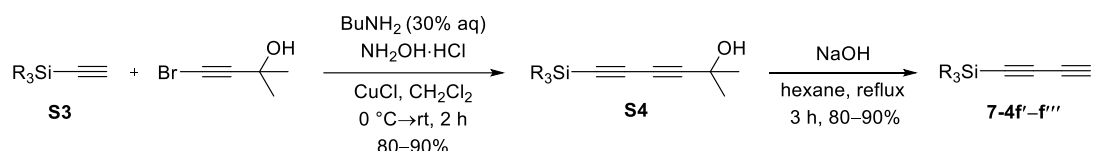
brine sequentially and dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. 1,3-Diynes **7-4** was subjected to the click reaction without further purification.

Procedure C: Synthesis of Trimethylsilylbuta-1,3-diyne (**7-4f**)



To a stirred solution of bis(trimethylsilyl)diacetylene **S** (1.2 g, 6.2 mmol) at 0 °C in Et₂O, MeLi·LiBr (6.2 mL, 2.2 M in Et₂O, 9.3 mmol) was added dropwise under N₂ atmosphere. After complete addition, the ice bath was removed, and stirring was continued for additional 6 h. The reaction was quenched by water and extracted by hexane. The crude was purified by flash column chromatography (SiO₂, pentane) to isolate pure terminal 1,3 diyne **7-4f** (318 mg, 42%).

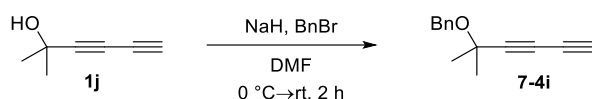
Procedure D: Synthesis of Silyl Substituted Terminal 1,3-diynes (**7-4f'** – **7-4f'''**)



To a mixture of 30% aqueous *n*-BuNH₂ (12.0 mL, 2 mL per 1.0 mmol of terminal alkyne) and CuCl (0.36 mmol) in a two-necked round-bottom flask, a solution of terminal alkyne (**S3**, 6.0 mmol) in CH₂Cl₂ was added slowly at 0 °C under N₂ atmosphere. Then 4-Bromo-2-methyl-3-butyne-2-ol (5.0 mmol) diluted in CH₂Cl₂ was added dropwise into the reaction mixture over 30–45 min. After 5 min, the ice bath was removed and stirring was continued for additional 2 h at room temperature. A pinch of NH₂OH·HCl was added several times into the reaction mixture when the solution becomes blue. The reaction was quenched by a sat. solution of NH₄Cl and extracted with CH₂Cl₂. The combined organic extracts were washed with water and brine sequentially and dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO₂, EtOAc–hexane, 1:20 to 1:10) to isolate pure silyl-substituted 1,3-diyne (**S4**) in excellent yield.

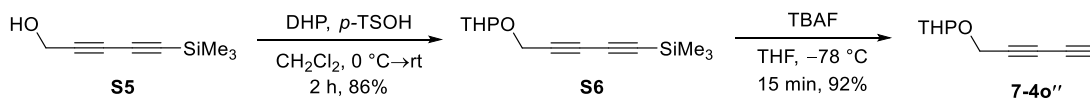
To a stirred solution of diyne (**S4**, 4.0 mmol) in hexane, sodium hydroxide (4.8 mmol) was added at room temperature. Then, the reaction mixture was stirred under reflux for 3 h. Upon complete consumption of diynes, the reaction was quenched by water and extracted by hexane. The crude was purified by flash column chromatography (SiO, hexane) to isolate pure silyl substituted terminal 1,3 diynes **7-4f'–f'''**.

Procedure E: Synthesis of 1,3-Diynes with Benzyl-Protected Alcohol (**7-4i**)



To a stirred solution of alcohol (300 mg, 2.8 mmol) and benzyl bromide (513 mg, 3.0 mmol) in dry DMF at 0 °C, NaH (120 mg, 3.0 mmol, 60 % dispersion in mineral oil) was added in one portion under argon atmosphere. After 30 min, the ice bath was removed, and stirring was continued for additional 2 h. The reaction was quenched by H₂O and extracted with Et₂O (x2). The crude material was purified by flash column chromatography (SiO, EtOAc–hexane, 1:20) to isolate pure benzyl ether **7-4i** (476 mg, 86% yield).

Procedure F: Synthesis of 1,3-Diynes with THP-Protected Alcohol (**7-4o''**)

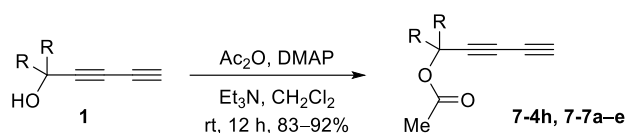


To a stirred solution of alcohol (415 mg, 2.7 mmol) and *p*-TsOH (26 mg, 0.14 mmol) in CH₂Cl₂ at 0 °C, DHP (252 mg, 3.0 mmol) was added dropwise, and stirred for 5 min. Then ice bath was removed and stirring was continued for additional 1 h. Then reaction mixture was washed by sat. NaHCO₃ (aq) and extracted with CH₂Cl₂. The crude material was purified by flash column chromatography (SiO, EtOAc–hexane, 1:10) to isolate pure **S7** (532 mg, 82%).

To a stirred solution of **S7** (532 mg, 2.5 mmol) in dry THF was added TBAF (2.8 mL, 1 M solution in THF, 2.8 mmol) slowly at –78 °C under N₂ atmosphere. After 15 min, the reaction mixture was quenched

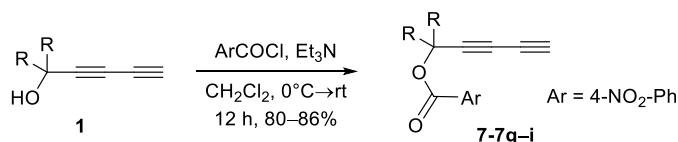
with sat. NH_4Cl and extracted with EtOAc (X2). The combined organic extracts were washed with water and brine sequentially and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Diyne **7-40''** (400 mg, 96%) was subjected to the next reaction without further purification.

Procedure G: Synthesis of Acetoxy Substituted 1,3-Diynes (7-4h, 7-7a – 7-7e)



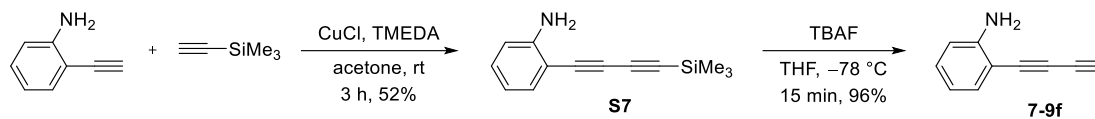
To a stirred solution of alcohol **7-4** (1.0 mmol) in dry CH_2Cl_2 (5 ml) at rt, Ac_2O (10.0 mmol), DMAP (0.2 mmol) and Et_3N (3.0 mmol) were sequentially added under N_2 atmosphere. After addition, stirring was continued for additional 12 h at the same temperature. Upon complete consumption of 1,3-diynes, the reaction mixture was concentrated under reduced pressure and purified by flash column chromatography (SiO, EtOAc–hexane, 1:20) to isolate pure acetoxy substituted terminal 1, 3 diynes.

Procedure H: Synthesis of Benzoyloxy Substituted 1,3-Diynes (7-7g – 7-7i)



To a stirred solution of alcohol **7-4** (1.0 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C, 4-nitrobenzoyl chloride (1.1 mmol) and Et_3N (1.1 mmol) were added sequentially under N_2 atmosphere. After addition, stirring was continued for additional 2 h at the same temperature. Then the ice bath was removed and stirred for additional 1 h. Upon complete consumption of 1,3-diynes, the reaction mixture was quenched by H_2O and extrated with dichloromethane (x2). The crude metarial was concentrated under reduced pressure and purified by flash column chromatography (SiO, EtOAc–hexane, 1:20) to isolate pure benzoyloxy substituted terminal 1,3-diynes **7-7g – 7-7i**.

Procedure I: Synthesis of Aniline Substituted 1,3-Diyne (7-9f)



To a stirred solution of tetramethylethylenediamine (TMEDA) (1.6 g, 13.5 mmol) in acetone at room temperature, CuCl (2.2 g, 22.6 mmol) was added and stirred for 1 h. The reaction mixture was filtered through silica gel multiple times until no precipitate was formed in the filtrate. The solid residue was further washed with acetone (x2). To a mixture of 2-aminophenylacetylene (530 mg, 4.5 mmol) and triethylsilylacetylene (1.8 g, 18.0 mmol) in acetone, the dark green solution was added dropwise for 15 min with constant bubbling of oxygen. Acetone (10 mL) was further added to reaction mixture to avoid the thickening during the oxygen bubbling. Stirring was continued for additional 2 h at the same temperature. Upon complete consumption of aniline, the reaction mixture was filtered through celite and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO, EtOAc–hexane, 1:10) to isolate pure diyne **S7** (540 mg, 56%).

To a stirred solution of **S7** (540 mg, 2.5 mmol) in dry THF was added TBAF (2.8 mL, 1 M solution in THF, 2.8 mmol) slowly at -78 °C under N₂ atmosphere. After 15 min, the reaction mixture was quenched with sat. NH₄Cl and extracted with EtOAc (x2). The combined organic extracts were washed with water and brine sequentially and dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. Terminal 1,3-diyne **7-9f** (400 mg, 96%) was subjected to the next reaction without further purification.

Procedures for Click Reactions

Procedure J: Synthesis of 3-Alkynyl Imidamides (7-5) and Allenyl Imidamides (7-6)

To a stirred solution of 1,3-diyne **7-4** (0.2 mmol) in dry THF (2 mL) were added azide (0.24 mmol), amine (0.24 mmol), and CuI (0.02 mmol) sequentially under N₂ atmosphere at room temperature (25 °C).

After addition, stirring was continued for additional 2 h (unless otherwise noted). Upon complete consumption of 1,3-diyne, the reaction mixture was concentrated under reduced pressure and purified by flash column chromatography (SiO, EtOAc–hexane, 1:5 to 1:1) to isolate pure 3-alkynyl iminamide and allenyl imidamide.

Procedure K: Synthesis of Allenyl Imidates (7-6)

To a stirred solution of 1,3-diyne **7-4** (0.2 mmol) in dry THF (2 mL) were added TsN₃ (0.24 mmol), Et₃N (0.4 mmol), MeOH (2 mmol), and CuI (0.02 mmol) sequentially under N₂ atmosphere at room temperature (25 °C). After 4 h, the reaction mixture was concentrated under reduced pressure and purified by flash column chromatography (SiO, EtOAc–hexane, 1:5 to 1:2) to isolate pure allenyl imidate.

Procedure L: Synthesis of [3]Cumulenyl Imidamides (7-8)

To a stirred solution of 1,3-diyne **7-7** (0.2 mmol) in dry THF (2 mL) were added TsN₃ (0.24 mmol), *i*-Pr₂NH (0.24 mmol), and CuI (0.02 mmol) sequentially under N₂ atmosphere at room temperature (25 °C). After 5 h, the reaction mixture was concentrated under reduced pressure and purified by flash column chromatography (SiO, EtOAc–hexane, 1:4 to 1:1) to isolate pure [3]cumulenyl imidamide.

Procedure M: Synthesis of Conjugated Imidates (7-10a – 7-10d)

To a stirred solution of 1,3-diynes **7-9a – 7-9d** (0.2 mmol) in dry THF (2 mL) were added TsN₃ (0.24 mmol), Et₃N (0.4 mmol), MeOH (2 mmol) and CuI (0.02 mmol) sequentially under N₂ atmosphere at room temperature (25 °C). After 12 h, the reaction mixture was concentrated under reduced pressure and purified by flash column chromatography (SiO, EtOAc–hexane, 1:4 to 1:1) to isolate pure imidate.

Procedure N: Synthesis of Heterocycles (7-10e, 7-10f)

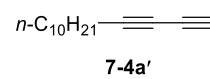
To a stirred solution of 1,3-diynes **7-9e** and **7-9f** (0.2 mmol) in dry THF (2 mL) were added TsN₃ (0.24 mmol), *i*-Pr₂NH (0.24 mmol), and CuI (0.02 mmol) sequentially under N₂ atmosphere at room

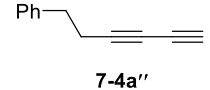
temperature (25 °C). After 4 h, the reaction mixture was concentrated under reduced pressure and purified by flash column chromatography (SiO, EtOAc–hexane, 1:4 to 1:1) to isolate pure heterocycle.

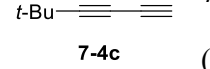
Procedure O: Synthesis of Conjugated Alkynyl Imidamides (7-11a – 7-11d)

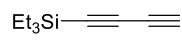
To a stirred solution of 3-alkynyl imidamides (**7-5**) and allenyl imidamides (**7-6**) (0.1 mmol) in dry THF (2 mL) was added DBU (0.01 mmol) under N₂ atmosphere at room temperature (25 °C). After 15 min, the reaction mixture was concentrated under reduced pressure and purified by flash column chromatography (SiO, EtOAc–hexane, 1:4 to 1:1) to isolate pure alkynyl imidamide.

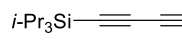
7.4.3. Characterization Data

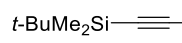
 **7-4a'**: 252 mg, colorless oil, prepared by procedure A. ¹H NMR (CDCl₃, 500 MHz): δ 2.23 (t, 2H, *J* = 7.0 Hz), 1.93 (s, 1H), 1.57–1.47 (m, 2H), 1.43–1.33 (m, 2H), 1.33–1.19 (m, 12H), 0.87 (t, 3H, *J* = 6.8 Hz); ¹³C NMR (CDCl₃, 125 MHz): δ 78.4, 68.5, 64.7, 64.4, 31.9, 29.6, 29.5, 29.3, 29.1, 28.8, 28.0, 22.7, 19.0, 14.1.

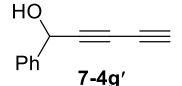
 **7-4a''**: 280 mg, light-yellow oil, prepared by procedure A. ¹H NMR (CDCl₃, 500 MHz): δ 7.39 (t, 2H, *J* = 7.2 Hz), 7.38–7.25 (m, 3H), 2.92 (t, 2H, *J* = 7.5 Hz), 2.62 (t, 2H, *J* = 7.5 Hz), 2.03 (s, 1H); ¹³C NMR (CDCl₃, 125 MHz): δ 140.0, 128.6, 128.5, 126.7, 77.6, 69.1, 68.5, 66.4, 65.6, 65.1, 34.4, 21.3.

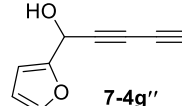
 **7-4c**: 256 mg, colorless oil, prepared by procedure A. ¹H NMR (CDCl₃, 500 MHz): δ 2.02 (s, 1H), 1.24 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz): δ 85.8, 68.3, 65.9, 65.7, 63.3, 30.3.

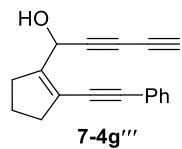

7-4f': 338 mg, colorless oil, prepared by procedure **D**. **¹H NMR** (CDCl₃, 500 MHz): δ 2.07 (s, 1H), 1.00 (t, 9H, *J* = 7.9 Hz), 0.63 (q, 6H, *J* = 7.9 Hz); **¹³C NMR** (CDCl₃, 125 MHz): δ 88.4, 82.7, 68.5, 65.9, 7.3, 4.1.

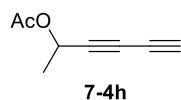

7-4f'': 355 mg, colorless oil, prepared by procedure **D**. **¹H NMR** (CDCl₃, 500 MHz): δ 2.07 (s, 1H), 1.09 (s, 21H); **¹³C NMR** (CDCl₃, 125 MHz): δ 89.1, 82.0, 68.6, 65.5, 18.5, 11.2.


7-4f''': 320 mg, colorless oil, prepared by procedure **D**. **¹H NMR** (CDCl₃, 500 MHz): δ 2.09 (s, 1H), 0.95 (s, 9H), 0.14 (s, 6H); **¹³C NMR** (CDCl₃, 125 MHz): δ 88.0, 83.4, 68.4, 66.2, 26.0, 16.7, -5.0.

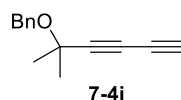

7-4g': 356 mg, colorless oil, prepared by procedure **A**. **¹H NMR** (CDCl₃, 500 MHz): δ 7.50 (d, 2H, *J* = 7.2 Hz), 7.43–7.33 (m, 3H), 5.45 (s, 1H), 3.00 (s, 1H), 2.28 (s, 1H); **¹³C NMR** (CDCl₃, 125 MHz): δ 139.3, 128.8, 126.8, 75.7, 70.8, 69.4, 67.5, 64.7.


7-4g'': 210 mg, orange oil, prepared by procedure **B**. **¹H NMR** (CDCl₃, 500 MHz): δ 7.41 (s, 1H), 6.44 (d, 1H, *J* = 3.2 Hz), 6.35 (dd, 1H, *J* = 3.0 Hz, *J* = 1.8 Hz), 5.48 (s, 1H), 3.07 (br, 1H), 2.26 (s, 1H); **¹³C NMR** (CDCl₃, 125 MHz): δ 151.5, 143.4, 110.6, 108.4, 73.2, 69.9, 69.4, 67.3, 58.2.

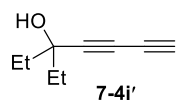

7-4g''': 386 mg, orange solid, prepared by procedure **B**. **¹H NMR** (CDCl₃, 500 MHz): δ 7.50–7.42 (m, 2H), 7.37–7.28 (m, 3H), 5.56 (s, 1H), 2.72–2.55 (m, 5H), 2.23 (s, 1H), 2.04–1.88 (m, 2H); **¹³C NMR** (CDCl₃, 125 MHz): δ 146.7, 131.6, 128.5, 128.4, 122.9, 122.6, 95.9, 84.1, 74.8, 69.6, 69.0, 67.6, 60.3, 37.1, 31.4, 22.3.



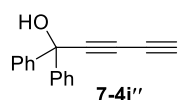
7-4h: 130 mg, colorless oil, prepared by procedure **G**. ^1H NMR (CDCl_3 , 500 MHz): δ 5.39 (q, 1H, $J = 6.7$ Hz), 2.19 (s, 1H), 2.03 (s, 3H), 1.46 (d, 3H, $J = 6.7$ Hz); ^{13}C NMR (CDCl_3 , 125 MHz): δ 169.6, 74.3, 68.9, 67.1, 60.1, 20.8.



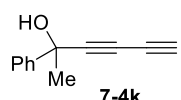
7-4i: 476 mg, colorless oil, prepared by procedure **E**. ^1H NMR (CDCl_3 , 500 MHz): δ 7.42–7.28 (m, 5H), 4.66 (s, 2H), 2.24 (s, 1H), 1.60 (s, 6H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 138.5, 128.4, 127.8, 127.6, 78.8, 71.0, 68.5, 67.6, 67.0, 28.6.



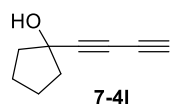
7-4j': 438 mg, colorless oil, prepared by procedure **A**. ^1H NMR (CDCl_3 , 500 MHz): δ 2.17 (s, 2H), 1.76–1.61 (m, 4H), 1.02 (t, 6H, $J = 7.4$ Hz); ^{13}C NMR (CDCl_3 , 125 MHz): δ 79.1, 72.6, 68.5, 68.0, 67.5, 34.2, 8.4.



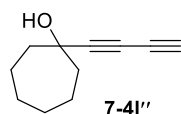
7-4j'': 359 mg, colorless oil, prepared by procedure **A**. ^1H NMR (CDCl_3 , 500 MHz): δ 7.62 (d, 4H, $J = 7.5$ Hz), 7.40 (t, 4H, $J = 7.6$ Hz), 7.35 (t, 2H, $J = 7.1$ Hz), 3.17 (s, 1H), 2.35 (s, 1H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 143.9, 128.5, 128.2, 126.2, 78.3, 74.9, 71.5, 70.3, 67.6.



7-4k: 315 mg, colorless oil, prepared by procedure **A**. ^1H NMR (CDCl_3 , 500 MHz): δ 7.62 (d, 2H, $J = 7.8$ Hz), 7.39 (t, 2H, $J = 7.5$ Hz), 7.35–7.28 (m, 1H), 2.96 (s, 1H), 2.29 (s, 1H), 1.79 (s, 3H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 144.3, 128.5, 128.1, 124.9, 79.2, 70.3, 69.4, 69.2, 67.5, 32.8.

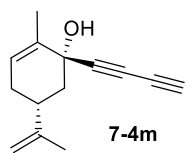


7-4l: 295 mg, colorless oil, prepared by procedure **A**. ^1H NMR (CDCl_3 , 500 MHz): δ 2.21 (s, 1H), 2.04–1.88 (m, 4H), 1.88–1.69 (m, 4H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 79.8, 74.6, 68.7, 67.6, 67.5, 42.3, 23.5.



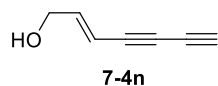
7-4l'': 320 mg, colorless oil, prepared by procedure **A**. ^1H NMR (CDCl_3 , 500 MHz): δ 2.20 (s, 1H), 2.09–1.99 (m, 2H), 1.97 (s, 1H), 1.91–1.79 (m, 2H), 1.73–1.48 (m, 8H); ^{13}C

NMR (CDCl₃, 125 MHz): δ 81.0, 72.1, 68.4, 67.7, 67.6, 42.7, 28.0, 22.0; **HRMS** (CI) calcd for C₁₁H₁₅O [M+H]⁺ 163.11230, found 163.11163.



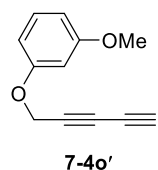
7-4m

7-4m: 267 mg, colorless oil, prepared by procedure **B**. **¹H NMR** (CDCl₃, 500 MHz): δ 5.55–5.49 (m, 1H), 4.74 (d, 2H, J = 9.8 Hz), 2.59 (br, 1H), 2.53–2.42 (m, 1H), 2.29–2.21 (m, 2H), 2.19–2.10 (m, 1H), 1.97–1.87 (m, 1H), 1.82 (s, 3H), 1.79–1.71 (m, 1H), 1.73 (s, 3H); **¹³C NMR** (CDCl₃, 125 MHz): δ 148.0, 134.7, 125.6, 109.5, 78.8, 70.2, 69.0, 68.4, 67.6, 43.0, 39.4, 30.9, 20.7, 17.2.



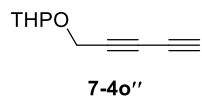
7-4n

7-4n: 240 mg, light yellow oil, prepared by procedure **B**. **¹H NMR** (CDCl₃, 500 MHz): δ 6.40 (dt, 1H, J = 4.7 Hz, J = 15.7 Hz), 5.72 (d, 1H, J = 15.9 Hz), 4.16 (d, 2H, J = 2.7 Hz), 3.04 (br, 1H), 2.43 (s, 1H); **¹³C NMR** (CDCl₃, 125 MHz): δ 146.8, 108.0, 74.1, 73.7, 71.3, 68.1, 62.4.



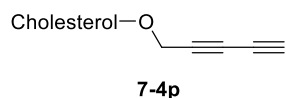
7-4o'

7-4o': 256 mg, colorless oil, prepared by procedure **B**. **¹H NMR** (CDCl₃, 500 MHz): δ 7.22 (t, 1H, J = 8.2 Hz), 6.57 (dd, 2H, J = 8.6 Hz, J = 2.0 Hz), 6.55–6.52 (m, 1H), 4.72 (s, 2H), 3.80 (s, 3H), 2.22 (s, 1H); **¹³C NMR** (CDCl₃, 125 MHz): δ 160.9, 158.7, 130.1, 107.5, 106.8, 101.5, 71.4, 71.3, 68.9, 67.3, 56.1, 55.3.



7-4o''

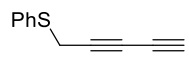
7-4o'': 532 mg, colorless oil, prepared by procedure **F**. **¹H NMR** (CDCl₃, 500 MHz): δ 4.77–4.71 (m, 1H), 4.25 (s, 2H), 3.81–3.71 (m, 1H), 3.53–3.44 (m, 1H), 2.15 (s, 1H), 1.83–1.62 (m, 2H), 1.62–1.42 (m, 4H); **¹³C NMR** (CDCl₃, 125 MHz): δ 96.9, 72.8, 69.9, 67.9, 67.5, 61.9, 54.2, 30.1, 25.3, 18.9.

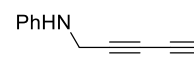


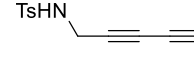
7-4p

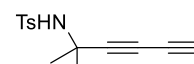
7-4p: 245 mg, colorless oil, prepared by procedure **B**. **¹H NMR** (CDCl₃, 500 MHz): δ 5.39–5.33 (m, 1H), 4.24 (s, 2H), 3.42–3.31 (m, 1H), 2.41–2.31 (m, 1H), 2.26–2.16 (m, 1H), 2.15 (s, 1H), 2.05–1.75 (m, 5H), 1.63–0.94 (m, 20H), 1.00 (s, 3H), 0.96–0.89 (m, 4H),

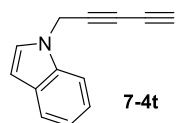
0.92–0.83 (m, 6H), 0.68 (s, 3H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 140.4, 122.1, 78.5, 73.5, 69.8, 67.8, 67.5, 56.8, 56.2, 55.6, 55.4, 50.2, 42.3, 39.8, 39.5, 38.7, 37.1, 36.8, 36.2, 35.8, 32.0, 31.9, 28.3, 28.1, 28.0, 24.3, 23.8, 22.8, 22.6, 21.1, 19.3, 18.7, 11.9.


7-4q: 275 mg, light yellow oil, prepared by procedure **B**. ^1H NMR (CDCl_3 , 500 MHz): δ 7.47 (d, 2H, $J = 7.9$ Hz), 5.72 (t, 2H, $J = 7.6$ Hz), 5.72 (t, 1H, $J = 6.6$ Hz), 3.65 (s, 2H), 2.10 (s, 1H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 134.4, 130.7, 129.2, 127.5, 73.0, 67.9, 67.7, 67.2, 23.6.

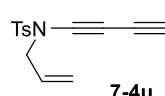

7-4r: 785 mg, orange oil, prepared by procedure **B**. ^1H NMR (CDCl_3 , 500 MHz): δ 7.26 (t, 2H, $J = 7.8$ Hz), 6.85 (t, 1H, $J = 7.3$ Hz), 6.70 (d, 2H, $J = 7.7$ Hz), 4.01 (s, 2H), 3.89 (br, 1H), 2.09 (s, 1H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 146.5, 129.4, 118.9, 113.6, 74.4, 67.8, 67.4, 67.0, 34.1.

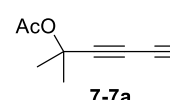

7-4s: 215 mg, light yellow solid, prepared by procedure **A**. ^1H NMR (CDCl_3 , 500 MHz): δ 7.76 (d, 2H, $J = 7.5$ Hz), 7.30 (d, 2H, $J = 7.2$ Hz), 5.26–5.15 (m, 1H), 3.88 (d, 2H, $J = 5.2$ Hz), 2.41 (s, 3H), 2.06 (s, 1H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 144.1, 136.3, 129.8, 127.4, 70.8, 68.8, 67.8, 67.1, 33.3, 21.6.

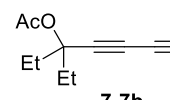

7-4s'': 278 mg, light yellow solid, prepared by procedure **A**. ^1H NMR (CDCl_3 , 500 MHz): δ 7.80 (d, 2H, $J = 6.8$ Hz), 7.29 (d, 2H, $J = 6.7$ Hz), 5.55 (br, 1H), 2.40 (s, 3H), 2.09 (s, 1H), 1.53 (s, 6H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 143.5, 137.9, 129.5, 127.7, 77.2, 68.4, 67.6, 67.3, 50.0, 30.4, 21.6.

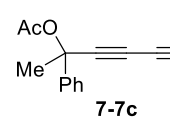

7-4t: 196 mg, orange oil, prepared by procedure **B**. ^1H NMR (CDCl_3 , 500 MHz): δ 7.70 (d, 1H, $J = 7.9$ Hz), 7.41 (d, 1H, $J = 8.2$ Hz), 7.32 (t, 1H, $J = 7.6$ Hz), 7.21 (t, 1H, $J = 7.4$ Hz).

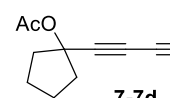
Hz), 7.18 (d, 1H, $J = 3.1$ Hz), 6.60 (d, 1H, $J = 2.8$ Hz), 4.93 (s, 2H), 2.17 (s, 1H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 135.8, 128.9, 127.3, 122.2, 121.3, 120.1, 109.3, 102.6, 70.6, 69.4, 68.3, 67.4, 36.2.

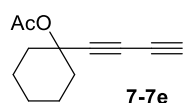
 **7-4u**: 259 mg, light orange solid, prepared by procedure **B**. ^1H NMR (CDCl_3 , 500 MHz): δ 7.76 (d, 2H, $J = 8.2$ Hz), 7.35 (d, 2H, $J = 8.0$ Hz), 5.73–5.61 (m, 1H), 5.27–5.17 (m, 2H), 3.95 (d, 2H, $J = 6.3$ Hz), 2.44 (s, 3H), 2.41 (s, 1H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 145.4, 134.4, 130.1, 127.7, 120.8, 71.4, 67.9, 67.7, 58.4, 54.1, 21.7.

 **7-7a**: 178 mg, colorless oil, prepared by procedure **G**. ^1H NMR (CDCl_3 , 500 MHz): δ 2.20 (s, 1H), 1.97 (s, 3H), 1.61 (s, 6H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 169.0, 76.5, 71.4, 69.2, 68.5, 67.4, 28.5, 21.6.

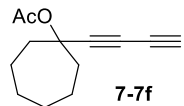
 **7-7b**: 210 mg, colorless oil, prepared by procedure **G**. ^1H NMR (CDCl_3 , 500 MHz): δ 2.19 (s, 1H), 2.04–1.85 (m, 4H), 2.00 (s, 3H), 0.95 (t, 6H, $J = 7.4$ Hz); ^{13}C NMR (CDCl_3 , 125 MHz): δ 169.1, 79.2, 75.4, 70.2, 68.7, 67.5, 30.6, 21.6, 8.2.

 **7-7c**: 160 mg, colorless oil, prepared by procedure **G**. ^1H NMR (CDCl_3 , 500 MHz): δ 7.54 (d, 2H, $J = 7.6$ Hz), 7.38 (t, 2H, $J = 7.6$ Hz), 7.32 (t, 1H, $J = 7.4$ Hz), 2.31 (s, 1H), 2.08 (s, 3H), 1.91 (s, 3H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 168.5, 141.7, 128.5, 128.2, 124.8, 75.4, 75.0, 71.6, 69.9, 67.4, 31.6, 21.6.

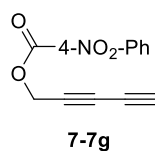
 **7-7d**: 215 mg, colorless oil, prepared by procedure **G**. ^1H NMR (CDCl_3 , 500 MHz): δ 2.21 (s, 1H), 2.18–2.07 (m, 4H), 1.98 (s, 3H), 1.75–1.65 (m, 4H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 169.3, 80.0, 76.2, 69.3, 69.0, 67.5, 40.3, 23.4, 21.4.



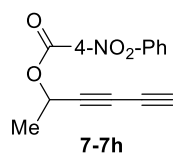
7-7e: 172 mg, colorless oil, prepared by procedure **G**. $^1\text{H NMR}$ (CDCl_3 , 500 MHz): δ 2.21 (s, 1H), 2.15–2.06 (m, 2H), 2.02 (s, 3H), 1.86–1.77 (m, 2H), 1.66–1.46 (m, 5H), 1.36–1.26 (m, 1H); $^{13}\text{C NMR}$ (CDCl_3 , 125 MHz): δ 169.0, 75.8, 75.0, 70.5, 69.0, 67.6, 36.7, 25.0, 22.4, 21.7.



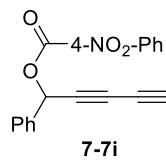
7-7f: 186 mg, colorless oil, prepared by procedure **G**. $^1\text{H NMR}$ (CDCl_3 , 500 MHz): δ 2.24–2.16 (m, 3H), 2.08–2.00 (m, 2H), 1.99 (s, 3H) 1.63–1.49 (m, 8H); $^{13}\text{C NMR}$ (CDCl_3 , 125 MHz): δ 169.0, 78.2, 76.9, 69.6, 69.1, 67.6, 39.9, 28.3, 22.1, 21.7.



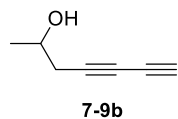
7-7g: 146 mg, orange solid, prepared by procedure **H**. $^1\text{H NMR}$ (CDCl_3 , 500 MHz): δ 8.30 (d, 2H, $J = 8.0$ Hz), 8.23 (d, 2H, $J = 8.4$ Hz), 5.02 (s, 2H), 2.24 (s, 1H); $^{13}\text{C NMR}$ (CDCl_3 , 125 MHz): δ 163.8, 150.8, 134.5, 131.0, 123.7, 71.5, 69.4, 69.3, 67.0, 53.5.



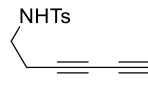
7-7h: 225 mg, orange solid, prepared by procedure **H**. $^1\text{H NMR}$ (CDCl_3 , 500 MHz): δ 8.27 (d, 2H, $J = 8.8$ Hz), 8.20 (d, 2H, $J = 8.8$ Hz), 5.70 (q, 1H, $J = 6.7$ Hz), 2.25 (s, 1H), 1.66 (d, 3H, $J = 6.7$ Hz); $^{13}\text{C NMR}$ (CDCl_3 , 125 MHz): δ 163.4, 150.7, 134.9, 131.0, 123.6, 73.5, 69.7, 69.4, 67.0, 61.9, 20.9.

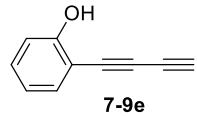


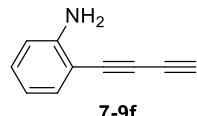
7-7i: 180 mg, orange solid, prepared by procedure **H**. $^1\text{H NMR}$ (CDCl_3 , 500 MHz): δ 8.27 (d, 2H, $J = 8.8$ Hz), 8.23 (d, 2H, $J = 8.9$ Hz), 7.65–7.56 (m, 2H), 7.49–7.40 (m, 3H), 6.73 (s, 1H), 2.31 (s, 1H); $^{13}\text{C NMR}$ (CDCl_3 , 125 MHz): δ 163.4, 150.8, 135.3, 134.7, 131.1, 129.7, 129.0, 127.9, 123.6, 72.1, 71.7, 70.2, 67.2, 67.1.

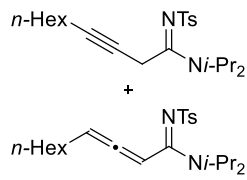


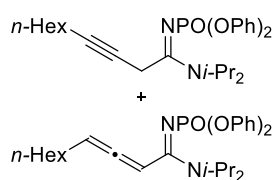
7-9b: 378 mg, colorless oil, prepared by procedure **A**. $^1\text{H NMR}$ (CDCl_3 , 500 MHz): δ 3.94 (q, 1H, $J = 6.0$ Hz), 2.81 (br, 1H), 2.39 (d, 2H, $J = 5.8$ Hz), 2.00 (s, 1H), 1.22 (d, 3H, $J = 6.2$ Hz); $^{13}\text{C NMR}$ (CDCl_3 , 125 MHz): δ 74.9, 68.2, 66.7, 66.1, 65.4, 29.4, 22.4.

 **7-9c**: 258 mg, colorless oil, prepared by procedure **B**. $^1\text{H NMR}$ (CDCl_3 , 500 MHz): δ 7.74 (d, 2H, $J = 8.1$ Hz), 7.30 (d, 2H, $J = 8.0$ Hz), 5.25 (br, 1H), 3.13–3.04 (m, 2H), 2.42 (t, 2H, $J = 7.0$ Hz), 2.41 (s, 3H), 2.00 (s, 1H); $^{13}\text{C NMR}$ (CDCl_3 , 125 MHz): δ 143.7, 136.8, 129.9, 127.1, 74.2, 67.9, 66.7, 65.7, 21.6, 20.6.

 **7-9e**: 346 mg, colorless oil, prepared by procedure **B**. $^1\text{H NMR}$ (CDCl_3 , 500 MHz): δ 7.40 (d, 1H, $J = 7.6$ Hz), 7.30 (t, 1H, $J = 7.9$ Hz), 6.94 (d, 1H, $J = 8.2$ Hz), 6.88 (t, 1H, $J = 7.5$ Hz), 5.67 (s, 1H), 2.62 (s, 1H); $^{13}\text{C NMR}$ (CDCl_3 , 125 MHz): δ 158.6, 133.1, 131.7, 120.7, 115.3, 107.5, 80.1, 73.3, 69.9, 67.5.

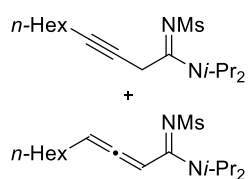
 **7-9f**: 400 mg, orange oil, prepared by procedure **I**. $^1\text{H NMR}$ (CDCl_3 , 500 MHz): δ 7.35 (d, 1H, $J = 7.6$ Hz), 7.18 (t, 1H, $J = 7.7$ Hz), 6.72–6.64 (m, 2H), 4.31 (br, 2H), 2.63 (s, 1H); $^{13}\text{C NMR}$ (CDCl_3 , 125 MHz): δ 150.1, 133.4, 131.1, 118.0, 114.6, 105.1, 78.7, 72.8, 68.3.

 **7-5/7-6aa**: These two products were synthesized using procedure **J** and isolated by flash column chromatography (SiO_2 , EtOAc-Hexane , 1:3) as light-yellow oil (75% yield, 68.7 mg) in an inseparable mixture with a 2:1 ratio. $^1\text{H NMR}$ (CDCl_3 , 500 MHz) **7-5aa**: δ 7.78 (d, 2H, $J = 8.0$ Hz), 7.19 (d, 2H, $J = 8.0$ Hz), 4.39–4.26 (m, 1H), 3.83 (s, 2H), 3.55–3.42 (m, 1H), 2.34 (s, 3H), 2.08–2.01 (m, 2H), 1.42–1.08 (m, 8H), 1.32 (d, 6H, $J = 6.7$ Hz), 1.19 (d, 6H, $J = 6.5$ Hz), 0.84 (t, 3H, $J = 6.8$ Hz); **7-6aa**: δ 7.74 (d, 2H, $J = 8.0$ Hz), 7.19 (d, 2H, $J = 8.0$ Hz), 6.26–6.20 (m, 1H), 5.25 (q, 1H, $J = 7.0$ Hz), 4.50 (br, 1H), 3.83 (s, 2H), 3.55 (br, 1H), 2.34 (s, 3H), 1.98–1.90 (m, 2H), 1.42–1.08 (m, 20H), 0.84 (t, 3H, $J = 6.8$ Hz); $^{13}\text{C NMR}$ (CDCl_3 , 125 MHz): δ (all discernible signals for both isomers) 204.5, 160.2, 159.3, 141.5, 141.3, 129.0, 128.9, 126.3, 126.2, 94.5, 86.5, 83.7, 71.6, 51.9, 50.6, 48.3, 31.5, 31.3, 29.1, 28.7, 28.6, 27.7, 22.7, 22.5, 21.4, 20.1, 19.8, 18.7, 14.0.



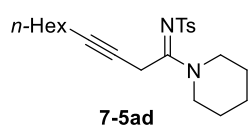
7-5ab:7-6ab = 5:1

7-5/7-6ab: These two products were synthesized using procedure **J** and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:2) as light-yellow oil (66% yield, 46.8 mg) in an inseparable mixture with a 5:1 ratio. **¹H NMR** (CDCl₃, 500 MHz) **7-5ab**: δ 7.33–7.21 (m, 8H), 7.13–7.03 (m, 2H), 4.39–4.24 (m, 1H), 3.76 (s, 2H), 3.49–3.29 (m, 1H), 2.13 (t, 2H, *J* = 6.9 Hz), 1.50–1.13 (m, 8H), 1.19 (d, 6H, *J* = 6.5 Hz), 1.12 (d, 6H, *J* = 6.8 Hz), 0.87 (t, 3H, *J* = 6.9 Hz); **7-6ab**: δ 7.33–7.21 (m, 8H), 7.13–7.03 (m, 2H), 6.22–6.15 (m, 1H), 5.43–5.35 (m, 1H), 4.58–4.40 (m, 1H), 3.61–3.44 (m, 1H), 2.08–1.98 (m, 2H), 1.50–1.05 (m, 20H), 0.94–0.79 (m, 3H); **¹³C NMR** (CDCl₃, 125 MHz): δ (all discernible signals for both isomers) 204.5, 162.7, 162.6, 161.2, 161.1, 152.1, 151.9, 129.3, 124.0, 123.9, 120.7, 94.8, 88.8, 83.9, 72.5, 51.7, 50.8, 47.9, 31.6, 31.4, 29.1, 28.7, 28.6, 28.0, 26.2, 26.1, 22.6, 20.6, 20.2, 19.7, 19.4, 18.8, 14.1.



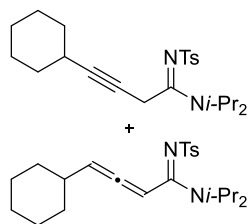
7-5ac:7-6ac = 3:1

7-5/7-6ac: These two products were synthesized using procedure **J** and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:3) as light-yellow oil (66% yield, 41.0 mg) in an inseparable mixture with a 3:1 ratio. **¹H NMR** (CDCl₃, 500 MHz) **7-5ac**: δ 4.42–4.28 (m, 1H), 3.79 (s, 2H), 3.64–3.48 (m, 1H), 2.99 (s, 3H), 2.19–2.07 (m, 2H), 1.49–1.17 (m, 8H), 1.44 (d, 6H, *J* = 6.7 Hz), 1.24 (d, 6H, *J* = 6.4 Hz), 0.91–0.80 (m, 3H); **7-6ac**: δ 6.24–6.16 (m, 1H), 5.46 (q, 1H, *J* = 6.9 Hz), 4.62–4.42 (br, 1H), 3.70–3.52 (br, 1H), 2.96 (s, 3H), 2.19–2.07 (m, 2H), 1.49–1.17 (m, 20H), 0.91–0.80 (m, 3H); **¹³C NMR** (CDCl₃, 125 MHz): δ (all discernible signals for both isomers) 204.8, 160.4, 159.0, 94.9, 86.5, 84.0, 71.7, 50.5, 48.2, 43.3, 31.6, 31.3, 29.1, 28.7, 28.6, 27.8, 23.4, 22.5, 20.2, 19.9, 18.8, 14.0.



7-5ad: This product was synthesized using procedure **J** and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:2) as light-orange oil (56% yield, 42.2 mg). **¹H NMR** (CDCl₃, 500 MHz): δ 7.82 (d, 2H, *J* = 7.8 Hz), 7.23 (d, 2H, *J* = 7.8 Hz), 3.88 (s, 2H), 3.74–3.66 (m, 2H), 3.62–3.52 (m, 2H), 2.39 (s, 3H), 2.10–2.02 (m, 2H), 1.72–1.51 (m,

6H), 1.45–1.18 (m, 8H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 161.2, 141.7, 141.2, 129.1, 126.5, 83.9, 71.2, 48.1, 46.2, 31.3, 28.6, 28.6, 26.3, 25.3, 24.1, 22.6, 21.5, 21.2, 18.7, 14.1.

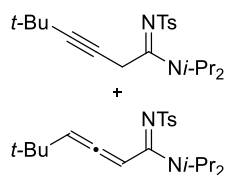


7-5ba:7-6ba = 2.3:1

7-5/7-6ba: These two products were synthesized using procedure **J** and isolated by flash column chromatography (SiO , EtOAc -Hexane, 1:3) as light-yellow oil (79% yield, 68.6 mg) in an inseparable mixture with a 2.3:1 ratio. ^1H NMR (CDCl_3 , 500

MHz) **7-5ba**: δ 7.80 (d, 2H, J = 8.2 Hz), 7.22 (d, 2H, J = 8.0 Hz), 4.42–4.30 (m, 1H), 3.87 (s, 2H), 3.57–3.46 (m, 1H), 2.38 (s, 3H), 2.29–2.17 (m, 1H), 1.74–1.57

(m, 4H), 1.46–0.97 (m, 6H), 1.36 (d, 6H, J = 6.8 Hz), 1.22 (d, 6H, J = 6.6 Hz); **7-6ba** : δ 7.78 (d, 2H, J = 8.2 Hz), 7.22 (d, 2H, J = 8.0 Hz), 6.38–6.32 (m, 1H), 5.27 (t, 1H, J = 6.7 Hz), 4.56 (br, 1H), 3.56 (br, 1H), 2.38 (s, 3H), 2.04–1.93 (m, 2H), 1.55–0.98 (m, 22H); ^{13}C NMR (CDCl_3 , 125 MHz): δ (all discernible signals for both isomers) 203.9, 160.3, 159.2, 141.6, 141.5, 141.4, 141.3, 129.0, 128.9, 126.4, 126.3, 100.2, 87.7, 87.3, 71.6, 50.5, 48.3, 37.0, 32.9, 32.6, 29.1, 25.9, 25.8, 24.9, 22.5, 21.4, 20.2, 19.9.



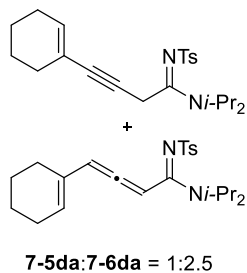
7-5ca:7-6ca = 1.3:1

7-5/7-6ca: These two products were synthesized using procedure **J** and isolated by flash column chromatography (SiO , EtOAc -Hexane, 1:3) as light-yellow oil (71% yield, 48.8 mg) in an inseparable mixture with a 1.3:1 ratio. ^1H NMR (CDCl_3 , 500

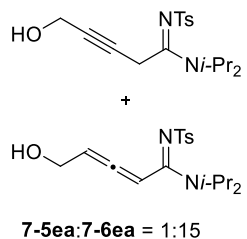
MHz) **7-5ca**: δ 7.79 (d, 2H, J = 8.9 Hz), 7.21 (d, 2H, J = 7.4 Hz), 4.40–4.27 (m, 1H),

3.85 (s, 2H), 3.56–3.40 (m, 1H), 2.36 (s, 3H), 1.36 (d, 6H, J = 6.7 Hz), 1.21 (d, 6H, J = 6.5 Hz), 1.09 (s, 9H); **7-6ca**: δ 7.77 (d, 2H, J = 8.9 Hz), 7.21 (d, 2H, J = 7.4 Hz), 6.41 (d, 1H, J = 6.5 Hz), 5.34 (d, 1H, J = 6.5 Hz), 4.59 (br, 1H), 3.56 (br, 1H), 2.36 (s, 3H), 1.45–1.11 (m, 12H), 1.02 (s, 9H); ^{13}C NMR (CDCl_3 , 125 MHz): δ (all discernible signals for both isomers) 202.9, 160.4, 158.8, 141.7, 141.5, 141.4, 129.1, 129.0, 126.2, 106.2, 91.7, 88.5, 70.4, 51.6, 50.5, 48.3, 32.7, 30.8, 30.0, 29.6, 27.3, 22.1, 21.4, 20.2, 19.9;

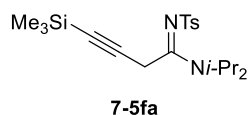
HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{33}\text{N}_2\text{O}_2\text{S}$ $[\text{M}+\text{H}]^+$ 377.2263, found 377.2254.



7-5/7-6da: These two products were synthesized using procedure **J** and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:3) as light-yellow oil (48% yield, 50.8 mg) in an inseparable mixture with a 1:2.5 ratio. **¹H NMR** (CDCl₃, 500 MHz) **7-5da:** δ 7.81 (d, 2H, *J* = 8.3 Hz), 7.23 (d, 2H, *J* = 7.5 Hz), 5.98–5.93 (m, 1H), 4.41–4.31 (m, 1H), 4.01 (s, 2H), 3.67–3.46 (m, 1H), 2.38 (s, 3H), 2.14–1.81 (m, 4H), 1.68–1.49 (m, 4H), 1.49–1.08 (m, 14H); **7-6da:** δ 7.79 (d, 2H, *J* = 8.3 Hz), 7.23 (d, 2H, *J* = 7.5 Hz), 6.56 (d, 1H, *J* = 5.3 Hz), 6.00 (d, 1H, *J* = 6.5 Hz), 5.74–5.69 (m, 1H), 4.60 (br, 1H), 3.69–3.44 (m, 1H), 2.39 (s, 3H), 2.14–1.81 (m, 4H), 1.68–1.49 (m, 4H), 1.49–1.08 (m, 14H); **¹³C NMR** (CDCl₃, 125 MHz): δ (all discernible signals for both isomers) 205.9, 159.8, 158.5, 141.5, 141.4, 141.3, 136.7, 134.9, 130.3, 130.2, 129.1, 129.0, 127.6, 126.7, 126.3, 101.1, 99.5, 89.8, 85.1, 78.4, 51.9, 50.7, 48.4, 48.0, 29.1, 26.1, 25.9, 25.6, 23.1, 22.4, 22.2, 22.1, 21.5, 20.6, 20.2; **HRMS** (ESI) calcd for C₂₃H₃₃N₂O₂S [M+H]⁺ 401.2263, found 401.2255.

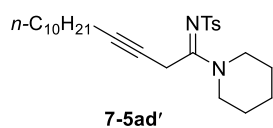


7-5/7-6ea: These two products were synthesized using procedure **J** and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:1) as white solid (73% yield, 74.1 mg) in an inseparable mixture with a 1:15 ratio. **¹H NMR** (CDCl₃, 500 MHz) **7-5ea:** δ 7.77 (d, 2H, *J* = 8.1 Hz), 7.22 (d, 2H, *J* = 8.0 Hz), 6.22–6.13 (m, 1H), 5.75–5.64 (m, 1H), 4.41 (br, 1H), 4.25 (s, 2H), 3.86–3.73 (m, 2H), 3.61 (br, 1H), 2.37 (s, 3H), 1.42–1.11 (m, 12H); **7-6ea:** δ 7.77 (d, 2H, *J* = 8.1 Hz), 7.22 (d, 2H, *J* = 8.0 Hz), 4.33–4.20 (m, 1H), 4.17 (s, 2H), 3.93 (s, 2H), 3.90–3.85 (br, 1H), 3.57–3.46 (br, 1H), 2.37 (s, 3H), 1.42–1.11 (m, 12H); **¹³C NMR** (CDCl₃, 125 MHz): δ (all discernible signals for both isomers) 205.3, 159.2, 158.1, 142.0, 141.8, 141.7, 141.2, 129.1, 126.2, 126.1, 97.0, 89.9, 81.9, 77.6, 60.0, 58.7, 51.9, 50.9, 50.8, 48.5, 48.2, 47.9, 24.7, 23.0, 21.4, 20.4, 20.3, 20.2, 20.0, 19.8, 19.7, 19.5; **HRMS** (ESI) calcd for C₁₈H₂₇N₂O₃S [M+H]⁺ 351.1742, found 351.1743



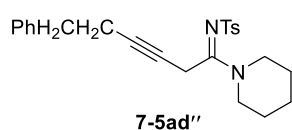
7-5fa: This product was synthesized using procedure **J** and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:5) as colorless oil (45% yield, 34.1 mg).

¹H NMR (CDCl₃, 500 MHz): δ 7.80 (d, 2H, *J* = 8.2 Hz), 7.22 (d, 2H, *J* = 8.0 Hz), 4.42–4.31 (m, 1H), 3.98 (s, 2H), 3.59–3.44 (m, 1H), 2.38 (s, 3H), 1.36 (d, 6H, *J* = 6.8 Hz), 1.22 (d, 6H, *J* = 6.5 Hz), 0.09 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 159.1, 141.7, 141.2, 129.1, 126.2, 97.6, 88.2, 50.7, 48.5, 23.4, 21.5, 20.1, 19.9, –0.2; **HRMS** (ESI) calcd for C₂₀H₃₃N₂O₂SSi [M+H]⁺ 393.2032, found 393.2030.



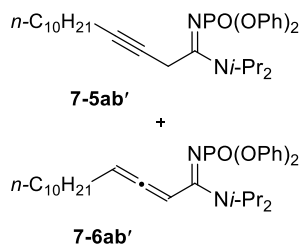
7-5ad': This product was synthesized using procedure **J** (1 equiv. of H₂O and pinch of NH₂OH·HCl were used as additive) and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:3) as light orange solid (57% yield, 36.5

mg). **¹H NMR** (CDCl₃, 500 MHz): δ 7.82 (d, 2H, *J* = 8.1 Hz), 7.23 (d, 2H, *J* = 7.9 Hz), 3.88 (s, 2H), 3.74–3.66 (m, 2H), 3.61–3.53 (m, 2H), 2.39 (s, 3H), 2.09–2.01 (m, 2H), 1.70–1.18 (m, 22H), 0.88 (t, 3H, *J* = 6.8 Hz); **¹³C NMR** (CDCl₃, 125 MHz): δ 161.2, 141.7, 129.1, 126.5, 83.9, 71.2, 48.1, 46.2, 31.9, 29.6, 29.3, 29.2, 28.9, 28.6, 26.3, 25.3, 24.1, 22.7, 21.5, 21.2, 18.7, 14.1.



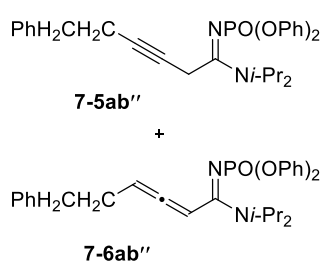
7-5ad'': This product was synthesized using procedure **J** (1 equiv. of H₂O and pinch of NH₂OH·HCl were used as additive) and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:2) as light orange solid (40% yield,

33.7 mg). **¹H NMR** (CDCl₃, 500 MHz): δ 7.77 (d, 2H, *J* = 7.9 Hz), 7.33–7.27 (m, 2H), 7.23–7.16 (m, 4H), 3.91 (s, 2H), 3.73–3.66 (m, 2H), 3.37–3.29 (m, 2H), 2.67 (t, 2H, *J* = 7.6 Hz), 2.46–2.37 (m, 2H), 2.36 (s, 3H), 1.91–1.81 (m, 2H), 1.68–1.50 (m, 4H); **¹³C NMR** (CDCl₃, 125 MHz): δ 161.4, 156.0, 141.7, 141.3, 129.7, 129.0, 128.5, 128.4, 126.5, 126.3, 125.9, 91.4, 88.2, 47.9, 46.0, 35.9, 35.5, 27.8, 27.1, 26.3, 25.2, 24.0, 21.4.



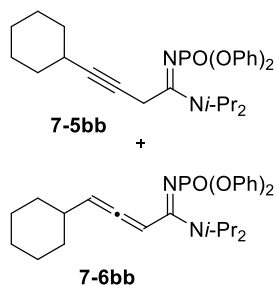
7-5/7-6ab': These two products were synthesized using procedure **J** and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:3) as white solid (**7-5ab'**: 60% yield, 46.7 mg; **7-6ab'**: 8% yield, 6.2 mg) after stirring the reaction mixture for 8 h. $^1\text{H NMR}$ (CDCl_3 , 500 MHz) **7-5ab'**: δ 7.35–7.22 (m, 8H), 7.14–7.03 (m, 2H), 4.39–4.24 (m, 1H), 3.77 (s, 2H), 3.47–3.30 (br, 1H),

2.18–2.09 (m, 2H), 1.48–1.08 (m, 16H), 1.19 (d, 6H, $J = 6.6$ Hz), 1.12 (d, 6H, $J = 6.8$ Hz), 0.88 (t, 3H, $J = 6.9$ Hz); **7-6ab'**: δ 7.35–7.22 (m, 8H), 7.14–7.03 (m, 2H), 6.23–6.16 (m, 1H), 5.43–5.35 (m, 1H), 4.56–4.41 (br, 1H), 3.60–3.44 (m, 1H), 2.08–1.98 (m, 2H), 1.48–1.06 (m, 28H), 0.88 (t, 3H, $J = 6.9$ Hz); $^{13}\text{C NMR}$ (CDCl_3 , 125 MHz): δ (all discernible signals for both isomers) 204.5, 162.7, 162.6, 161.2, 161.1, 152.1, 152.0, 151.9, 129.3, 124.0, 123.9, 120.7, 94.8, 88.8, 83.9, 72.5, 51.7, 50.8, 47.9, 31.9, 29.6, 29.4, 29.3, 29.2, 29.1, 29.0, 28.7, 28.0, 26.2, 26.1, 22.7, 20.2, 19.4, 18.8, 14.1.



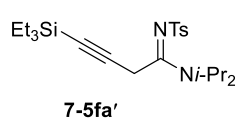
7-5/7-6ab'': These two products were synthesized using procedure **J** and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:3) as light yellow solid (**7-5ab''**: 52% yield, 37.2 mg; **7-6ab''**: 13% yield, 9.3 mg) after stirring the reaction mixture for 8 h. $^1\text{H NMR}$ (CDCl_3 , 500 MHz): δ (**7-5ab''**) 7.36–7.03 (m, 15H), 4.28–4.15 (m, 1H), 3.77 (s, 2H), 3.38 (br, 1H), 2.76 (t,

2H, $J = 7.5$ Hz), 2.43 (t, 2H, $J = 7.4$ Hz), 1.24–1.04 (m, 12H); δ (**7-6ab''**) 7.36–7.03 (m, 15H), 6.21–6.14 (m, 1H), 6.17 (t, 1H, $J = 2.9$ Hz), 4.42 (br, 1H), 3.42 (br, 1H), 2.73–2.66 (m, 2H), 2.40–2.34 (m, 2H), 1.24–1.04 (m, 12H); $^{13}\text{C NMR}$ (CDCl_3 , 125 MHz): δ (all discernible signals for both isomers) 204.5, 162.5, 162.4, 160.9, 160.8, 152.1, 152.0, 151.9, 141.3, 141.0, 140.6, 129.3, 128.5, 128.4, 126.3, 126.1, 124.1, 123.9, 120.7, 120.7, 120.6, 94.0, 89.2, 89.1, 82.9, 73.4, 51.7, 50.8, 47.9, 47.6, 35.3, 35.0, 29.6, 26.1, 20.9, 20.6, 20.1, 19.7, 19.4.



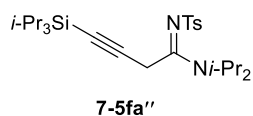
7-5/7-6bb: These two products were synthesized using procedure **J** and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:3) as light yellow solid (**7-5bb**: 45% yield, 41.6 mg; **7-6bb**: 15% yield, 13.8 mg) after stirring the reaction mixture for 8 h. **¹H NMR** (CDCl₃, 500 MHz) **7-5bb**: δ 7.32–7.22 (m, 8H), 7.12–7.03 (m, 2H), 4.38–4.26 (m, 1H), 3.79 (s, 2H), 3.39 (br, 1H), 2.36–2.26 (m, 1H),

1.79–1.04 (m, 10H), 1.19 (d, 6H, *J* = 6.6 Hz), 1.10 (d, 6H, *J* = 6.8 Hz); **7-6bb**: δ 7.32–7.22 (m, 8H), 7.12–7.03 (m, 2H), 6.30–6.23 (m, 1H), 5.36 (t, 1H, *J* = 6.6 Hz), 4.53 (br, 1H), 3.49 (br, 1H), 2.12–2.00 (m, 1H), 1.79–0.99 (m, 22H); **¹³C NMR** (CDCl₃, 125 MHz): δ (all discernible signals for both isomers) 203.6, 162.8, 162.7, 161.1, 161.0, 152.2, 152.1, 152.0, 151.9, 129.3, 124.0, 123.9, 120.8, 120.7, 120.6, 100.4, 89.7, 89.6, 87.9, 72.5, 51.7, 50.8, 47.8, 37.1, 32.9, 32.7, 29.2, 26.2, 26.1, 25.9, 25.8, 24.9, 20.3, 19.4.



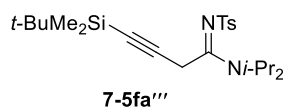
7-5fa': This product was synthesized using procedure **J** and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:5) as colorless oil (85% yield, 74.8 mg). **¹H NMR** (CDCl₃, 500 MHz): δ 7.80 (d, 2H, *J* = 8.1 Hz), 7.21 (d, 2H, *J* = 8.0 Hz), 4.44–

4.32 (m, 1H), 4.00 (s, 2H), 3.61–3.48 (m, 1H), 2.38 (s, 3H), 1.37 (d, 6H, *J* = 6.8 Hz), 1.23 (d, 6H, *J* = 6.5 Hz), 0.91 (t, 9H, *J* = 7.9 Hz), 0.52 (q, 6H, *J* = 7.9 Hz); **¹³C NMR** (CDCl₃, 125 MHz): δ 159.2, 141.6, 141.2, 129.1, 126.2, 98.7, 85.6, 50.6, 48.5, 23.1, 21.5, 20.1, 19.9, 7.4, 4.2.

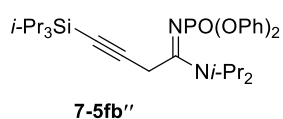


7-5fa'': This product was synthesized using procedure **J** and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:5) as colorless oil (92% yield, 86.7 mg). **¹H NMR** (CDCl₃, 500 MHz): δ 7.80 (d, 2H, *J* = 8.1 Hz), 7.21 (d, 2H, *J* = 7.9

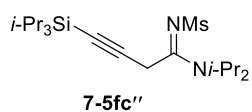
Hz), 4.44–4.34 (m, 1H), 4.03 (s, 2H), 3.60–3.48 (m, 1H), 2.37 (s, 3H), 1.36 (d, 6H, *J* = 6.8 Hz), 1.24 (d, 6H, *J* = 6.6 Hz), 1.06–0.95 (m, 21H); **¹³C NMR** (CDCl₃, 125 MHz): δ 159.1, 141.6, 141.3, 129.1, 126.2, 99.3, 84.4, 50.6, 48.4, 23.1, 21.4, 20.3, 19.9, 18.5, 11.2.



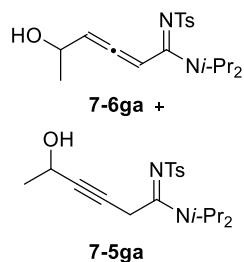
7-5fa''': This product was synthesized using procedure **J** and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:5) as colorless oil (94% yield, 75.8 mg). ¹H NMR (CDCl₃, 500 MHz): δ 7.81 (d, 2H, *J* = 8.0 Hz), 7.23 (d, 2H, *J* = 7.9 Hz), 4.44–4.32 (m, 1H), 4.01 (s, 2H), 3.60–3.47 (m, 1H), 2.38 (s, 3H), 1.36 (d, 6H, *J* = 6.7 Hz), 1.24 (d, 6H, *J* = 6.6 Hz), 0.88 (s, 9H), 0.04 (s, 6H); ¹³C NMR (CDCl₃, 125 MHz): δ 159.1, 141.6, 141.2, 129.1, 126.2, 98.3, 86.5, 50.6, 48.4, 26.0, 23.3, 21.5, 20.2, 19.9, –4.7.



7-5fb'': This product was synthesized using procedure **J** and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:5) as colorless oil (59% yield, 41.5 mg). ¹H NMR (CDCl₃, 500 MHz): δ 7.36–7.22 (m, 8H), 1.33–7.04 (m, 2H), 4.44–4.30 (m, 1H), 3.96 (s, 2H), 3.42 (br, 1H), 1.22 (d, 6H, *J* = 6.5 Hz), 1.12 (d, 6H, *J* = 6.8 Hz), 1.09–0.97 (m, 21H); ¹³C NMR (CDCl₃, 125 MHz): δ 161.7, 161.6, 151.9, 129.3, 124.0, 120.7, 100.1, 84.5, 50.9, 47.9, 27.2, 20.4, 19.4, 18.6, 11.2.

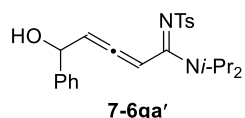


7-5fc'': This product was synthesized using procedure **J** and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:5) as colorless oil (82% yield, 55.0 mg). ¹H NMR (CDCl₃, 500 MHz): δ 4.44–4.31 (m, 1H), 3.96 (s, 2H), 3.60 (br, 1H), 3.01 (s, 3H), 1.45 (d, 6H, *J* = 6.7 Hz), 1.27 (d, 6H, *J* = 6.5 Hz), 1.08–0.97 (m, 21H); ¹³C NMR (CDCl₃, 125 MHz): δ 159.6, 99.4, 84.9, 50.5, 48.3, 43.2, 23.6, 20.4, 19.9, 18.5, 11.2.

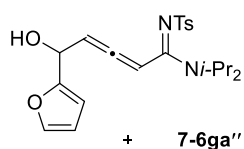


7-6/7-5ga: These two products were synthesized using procedure **J** and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:1) as white solid (**7-6ga**: 70% yield, 78.7 mg; **7-5ga**: 3% yield, 3.4 mg). ¹H NMR (CDCl₃, 500 MHz): δ (**7-6ga**) 7.77 (d, 2H, *J* = 8.0 Hz), 7.22 (d, 2H, *J* = 7.9 Hz), 6.26–6.07 (m, 1H), 5.62–5.53 (m, 1H), 4.74–4.32 (m, 2H), 3.98–3.83 (m, 1H), 3.71–3.45 (m, 1H), 2.37 (s, 3H), 1.33 (d, 6H, *J* = 6.5 Hz), 1.30 (d, 6H, *J* = 6.5 Hz), 1.17 (d, 3H, *J* = 6.6 Hz); δ (**7-5ga**) 7.77 (d, 2H, *J* = 8.0 Hz), 7.22 (d, 2H, *J* = 7.9 Hz),

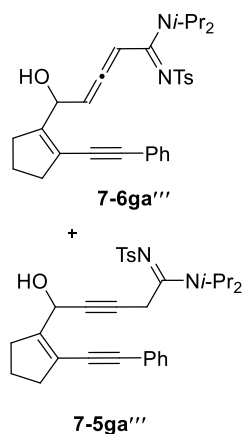
4.75–3.75 (m, 5H), 2.37 (s, 3H), 1.38–1.12 (m, 15H); ^{13}C NMR (CDCl_3 , 125 MHz): δ (all discernible signals for both isomers) 205.1, 203.4, 158.1, 158.0, 146.4, 141.9, 141.7, 141.7, 141.3, 141.2, 140.8, 129.0, 126.2, 126.1, 126.0, 104.2, 101.9, 101.2, 90.3, 89.1, 73.0, 65.8, 64.9, 64.6, 51.8, 48.2, 47.8, 30.6, 23.1, 22.4, 21.4, 20.6, 20.4, 20.0, 19.7, 19.5; **HRMS** (ESI) calcd for $\text{C}_{19}\text{H}_{29}\text{N}_2\text{O}_3\text{S}$ $[\text{M}+\text{H}]^+$ 365.1899, found 365.1895.



7-6ga': This product was synthesized using procedure **J** and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:1) as white solid (70% yield, 64.7 mg). ^1H NMR (CDCl_3 , 500 MHz): δ 7.82 (d, 2H, J = 8.1 Hz), 7.49–7.39 (m, 2H), 7.35 (t, 2H, J = 7.4 Hz), 7.31–7.22 (m, 3H), 6.43–6.16 (m, 1H), 5.85–5.71 (m, 1H), 5.64–5.42 (m, 1H), 4.54–4.12 (m, 2H), 3.64 (br, 1H), 2.44–2.37 (m, 3H), 1.45–1.08 (m, 12H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 205.5, 203.3, 157.9, 157.8, 142.4, 142.3, 142.0, 141.8, 141.8, 141.3, 141.1, 129.1, 128.5, 128.4, 127.8, 127.6, 126.3, 126.2, 126.1, 101.5, 100.4, 90.9, 89.6, 70.7, 51.9, 48.5, 48.3, 21.5, 20.4, 20.2, 19.9, 19.8; **HRMS** (ESI) calcd for $\text{C}_{24}\text{H}_{31}\text{N}_2\text{O}_3\text{S}$ $[\text{M}+\text{H}]^+$ 427.2055, found 427.2052.



7-6/7-5ga'': These two products were synthesized using procedure **J** and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:1) as orange solid (**7-6ja''**: 60% yield, 53.3 mg; **7-5ga''**: 12% yield, 10.7 mg). ^1H NMR (CDCl_3 , 500 MHz) **7-6ga''**: δ 7.79 (d, 2H, J = 7.9 Hz), 7.40–7.33 (m, 1H), 7.24 (d, 2H, J = 7.9 Hz), 6.42–6.19 (m, 3H), 5.96–5.80 (m, 1H), 5.60–5.43 (m, 1H), 4.82–4.20 (m, 1H), 3.63 (m, 1H), 2.96 (d, 2H, J = 5.8 Hz), 2.38 (s, 3H), 1.49–1.03 (m, 12H); **7-5ga''**: δ 7.79 (d, 2H, J = 7.9 Hz), 7.40–7.33 (m, 1H), 7.24 (d, 2H, J = 7.9 Hz), 6.41–6.28 (m, 2H), 5.19–5.10 (m, 1H), 4.83–4.20 (m, 3H), 3.78 (br, 1H), 2.38 (s, 3H), 1.49–1.03 (m, 12H); ^{13}C NMR (CDCl_3 , 125 MHz): δ (all discernible signals for both isomers) 205.7, 203.9, 157.7, 157.6, 154.8, 154.5, 154.4, 146.3, 142.3, 142.0, 141.9, 141.8, 141.1, 129.1, 126.2, 126.1, 110.3, 106.9, 106.8, 106.4, 103.2, 98.3, 97.3, 91.2, 90.0, 73.3, 65.9, 64.7, 64.6, 51.9, 48.3, 48.2, 47.9, 28.3, 21.5, 20.6, 20.4, 19.9, 19.7, 19.5; **HRMS** (ESI) calcd for $\text{C}_{22}\text{H}_{29}\text{N}_2\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$ 417.1848, found 417.1845.



7-6/7-5ga''': These two products were synthesized using procedure **J** and isolated

by flash column chromatography (SiO, EtOAc-Hexane, 1:1) as orange solid (**7-**

6ga''': 65% yield, 88.0 mg; **7-5ga'''**: 17% yield, 22.0 mg). **¹H NMR** (CDCl₃, 500

MHz) **7-6ga'''**: δ 7.80 (d, 2H, *J* = 7.6 Hz), 7.48–7.39 (m, 2H), 7.34–7.19 (m, 5H),

6.39–6.22 (m, 1H), 5.71–5.62 (m, 1H), 5.56–5.46 (m, 1H), 4.58–4.39 (m, 1H), 4.16–

4.02 (m, 1H), 3.63 (br, 1H), 2.89–2.42 (m, 4H), 2.01–1.84 (m, 2H), 1.45–1.08 (m,

12H); **7-5ga'''**: δ 7.80 (d, 2H, *J* = 7.6 Hz), 7.48–7.39 (m, 2H), 7.34–7.19 (m, 5H),

5.20–5.12 (m, 1H), 4.76–4.58 (m, 1H), 4.39–4.33 (m, 1H), 4.06 (s, 2H), 3.86–3.67 (m, 2H), 2.88–2.42 (m,

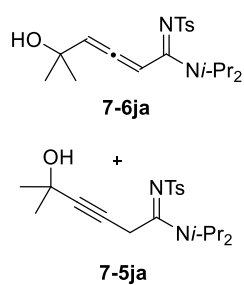
4H), 2.36 (s, 3H), 2.01–1.84 (m, 2H), 1.45–1.08 (m, 12H); **¹³C NMR** (CDCl₃, 125 MHz): δ (all discernible

signals for both isomers) 203.9, 203.3, 158.1, 157.9, 151.3, 151.0, 150.9, 143.3, 141.9, 141.8, 141.2, 141.1,

131.5, 129.6, 129.1, 128.3, 128.1, 126.4, 126.3, 126.2, 123.5, 123.4, 119.8, 119.7, 119.5, 99.2, 98.1, 95.2,

95.1, 91.1, 90.4, 85.1, 68.0, 67.1, 66.7, 52.0, 48.3, 47.9, 37.1, 37.0, 31.7, 31.3, 31.1, 28.0, 22.4, 22.3, 21.5,

20.6, 20.4, 19.9, 19.8, 19.5.



7-6/7-5ja: These two products were synthesized using procedure **J** and isolated by

flash column chromatography (SiO, EtOAc-Hexane, 1:1) as orange solid (**7-6ja**:

76% yield, 61.5 mg; **7-5ja**: 8% yield, 6.5 mg). **¹H NMR** (CDCl₃, 500 MHz) **7-6ja**:

δ 7.76 (d, 2H, *J* = 8.1 Hz), 7.20 (d, 2H, *J* = 7.9 Hz), 6.24 (d, 2H, *J* = 6.5 Hz), 5.63

(d, 2H, *J* = 6.5 Hz), 4.46 (br, 1H), 3.79 (s, 1H), 3.59 (br, 1H), 2.35 (s, 3H), 1.38 (s,

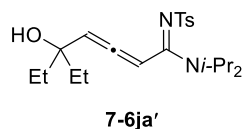
3H), 1.37 (s, 3H), 1.35–1.09 (m, 12 H); **7-5ja**: δ 7.76 (d, 2H, *J* = 8.1 Hz), 7.20 (d, 2H, *J* = 7.9 Hz), 4.31–

4.22 (m, 1H), 3.88 (s, 2H), 3.66–3.45 (br, 1H), 2.35 (s, 3H), 1.43–1.07 (m, 18H); **¹³C NMR** (CDCl₃, 125

MHz): δ (all discernible signals for both isomers) 202.4, 159.5, 158.1, 141.8, 141.6, 141.3, 129.1, 129.0,

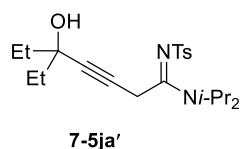
126.2, 126.1, 105.6, 90.3, 88.1, 74.1, 69.8, 64.8, 51.8, 50.7, 48.4, 48.2, 31.3, 30.6, 30.0, 22.3, 21.4, 20.5,

20.4, 20.2, 19.8; **HRMS** (ESI) calcd for C₂₀H₃₁N₂O₃S [M+H]⁺ 379.2055, found 379.2047.



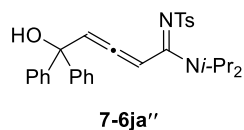
7-6ja': This product was synthesized using procedure **J** and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:1) as white solid (65% yield, 49.7 mg). ¹H

NMR (CDCl₃, 500 MHz): δ 7.80 (d, 2H, *J* = 8.1 Hz), 7.23 (d, 2H, *J* = 7.9 Hz), 6.28 (d, 1H, *J* = 6.5 Hz), 5.46 (d, 2H, *J* = 6.6 Hz), 4.55 (br, 1H), 3.60 (br, 2H), 3.29 (s, 3H), 1.71–1.52 (m, 4H), 1.40–1.14 (m, 12H), 0.98–0.86 (m, 6H); ¹³C **NMR** (CDCl₃, 125 MHz): δ 202.3, 158.4, 141.7, 141.2, 129.0, 126.2, 102.9, 90.3, 75.1, 52.1, 48.2, 33.7, 33.3, 21.5, 20.6, 20.3, 19.9, 19.7, 8.1.



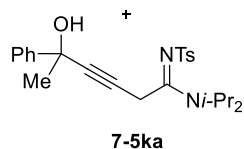
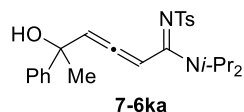
7-5ja': This product was synthesized using procedure **J** and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:1) as white solid (22% yield, 16.8 mg). ¹H

NMR (CDCl₃, 500 MHz): δ 7.81 (d, 2H, *J* = 7.8 Hz), 7.24 (d, 2H, *J* = 7.9 Hz), 4.35–4.24 (m, 1H), 3.95 (s, 3H), 3.61–3.49 (m, 1H), 2.39 (s, 3H), 1.62–1.53 (m, 4H), 1.37 (d, 6H, *J* = 6.6 Hz), 1.24 (d, 6H, *J* = 6.3 Hz), 0.94 (t, 6H, *J* = 7.3 Hz); ¹³C **NMR** (CDCl₃, 125 MHz): δ 159.5, 141.8, 141.3, 129.1, 126.3, 85.9, 76.5, 72.0, 50.6, 48.5, 34.2, 22.2, 21.4, 20.3, 19.9, 8.5.

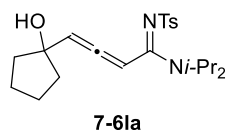


7-6ja'': This product was synthesized using procedure **J** and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:1) as white solid (72% yield, 69.8 mg). ¹H

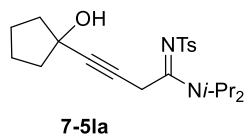
NMR (CDCl₃, 500 MHz): δ 7.77 (d, 2H, *J* = 8.2 Hz), 7.47 (d, 2H, *J* = 7.3 Hz), 7.42 (d, 2H, *J* = 7.3 Hz), 7.35–7.28 (m, 4H), 7.26–7.22 (m, 2H), 7.21 (d, 2H, *J* = 8.1 Hz), 6.42 (d, 1H, *J* = 6.5 Hz), 6.26 (d, 1H, *J* = 6.5 Hz), 4.50 (s, 1H), 4.38 (br, 1H), 3.60 (br, 1H), 2.38 (s, 3H), 1.39–1.23 (m, 6H), 1.16–1.04 (m, 6H); ¹³C **NMR** (CDCl₃, 125 MHz): δ 202.0, 157.6, 146.4, 145.7, 141.7, 141.1, 129.0, 128.2, 127.3, 126.6, 126.0, 104.8, 91.5, 77.6, 52.0, 48.3, 21.5, 20.6, 20.3, 19.8; **HRMS** (ESI) calcd for C₃₀H₃₅N₂O₃S [M+H]⁺ 503.2368, found 503.2370.



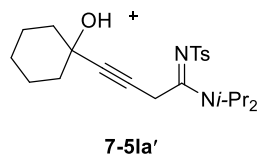
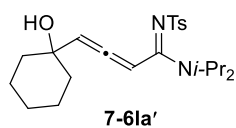
7-6/7-5ka: These two products were synthesized using procedure **J** and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:1) as white solid (**7-6ka**: 80% yield, 56.5 mg; **7-5ka**: 5% yield, 3.5 mg). ^1H NMR (CDCl_3 , 500 MHz): δ (**7-6ka**) 7.84–7.73 (m, 2H), 7.58–7.45 (m, 2H), 7.38–7.18 (m, 5H), 6.42–6.28 (m, 1H), 5.97–5.85 (m, 1H), 4.51–4.31 (m, 1H), 4.31–4.12 (m, 1H), 3.59 (br, 1H), 2.38 (s, 3H), 1.79–1.69 (m, 3H), 1.45–1.04 (m, 12H); δ (**7-5ka**) 7.84–7.73 (m, 2H), 7.58–7.45 (m, 2H), 7.38–7.18 (m, 5H), 4.56–3.98 (m, 4H), 3.77–3.70 (m, 1H), 2.38 (s, 3H), 1.75–1.65 (m, 3H), 1.45–1.04 (m, 12H); ^{13}C NMR (CDCl_3 , 125 MHz): δ (all discernible signals for both isomers) 202.2, 202.1, 157.9, 157.8, 147.2, 146.4, 143.2, 141.7, 141.2, 141.1, 139.5, 129.6, 129.1, 128.2, 127.7, 127.0, 126.9, 126.4, 126.3, 126.2, 125.0, 124.9, 105.8, 105.4, 91.0, 90.9, 87.0, 73.3, 69.7, 52.0, 48.5, 48.3, 31.1, 30.6, 21.5, 20.5, 20.3, 19.9.



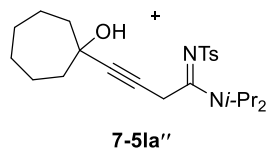
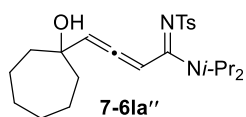
7-6la: This product was synthesized using procedure **J** and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:1) as white solid (71% yield, 60.8 mg). ^1H NMR (CDCl_3 , 500 MHz): δ 7.80 (d, 2H, $J = 8.1$ Hz), 7.23 (d, 2H, $J = 8.0$ Hz), 6.26 (d, 1H, $J = 6.5$ Hz), 5.69 (d, 1H, $J = 6.4$ Hz), 4.48 (br, 1H), 3.79–3.44 (m, 2H), 2.39 (s, 3H), 1.97–1.83 (m, 4H), 1.76–1.60 (m, 4H), 1.43–1.11 (m, 12 H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 203.3, 158.2, 141.6, 141.3, 129.0, 126.2, 104.5, 90.4, 79.7, 51.7, 48.2, 41.3, 40.6, 23.9, 23.6, 21.5, 20.5, 19.9, 19.8; HRMS (ESI) calcd for $\text{C}_{22}\text{H}_{33}\text{N}_2\text{O}_3\text{S}$ $[\text{M}+\text{H}]^+$ 405.2212, found 405.2208.



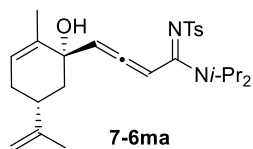
7-5la: This product was synthesized using procedure **J** and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:1) as white solid (7% yield, 6.0 mg). ^1H NMR (CDCl_3 , 500 MHz): δ 7.80 (d, 2H, $J = 8.1$ Hz), 7.23 (d, 2H, $J = 8.0$ Hz), 4.35–4.27 (m, 1H), 3.95 (s, 2H), 3.81–3.48 (m, 2H), 2.39 (s, 3H), 1.97–1.60 (m, 8 H), 1.43–1.11 (m, 12H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 203.3, 159.5, 158.2, 141.8, 141.6, 141.3, 129.1, 129.0, 126.3, 126.1, 104.5, 90.4, 87.1, 79.7, 75.2, 74.3, 51.7, 50.7, 48.5, 48.2, 42.3, 41.3, 40.6, 23.8, 23.6, 23.4, 22.5, 21.5, 20.5, 20.2, 19.9, 19.9.



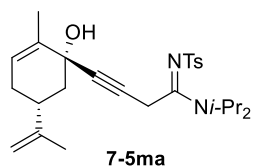
7-6/7-5la': These two products were synthesized using procedure **J** and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:1) as orange solid (**7-6la'**: 70% yield, 57.2 mg; **7-5la'**: 10% yield, 8.2 mg). ¹H NMR (CDCl₃, 500 MHz) **7-6la'**: δ 7.79 (d, 2H, *J* = 8.0 Hz), 7.23 (d, 2H, *J* = 7.9 Hz), 6.27 (d, 2H, *J* = 6.5 Hz), 5.65 (d, 2H, *J* = 6.5 Hz), 4.49 (br, 1H), 3.71–3.39 (m, 2H), 2.38 (s, 3H), 1.83–1.09 (m, 22H); **7-5la'**: 7.79 (d, 2H, *J* = 8.0 Hz), 7.23 (d, 2H, *J* = 7.9 Hz), 4.36–4.25 (m, 1H), 3.71–3.39 (m, 2H), 2.38 (s, 3H), 1.83–1.09 (m, 22H); ¹³C NMR (CDCl₃, 125 MHz): δ (all discernible signals for both isomers) 203.0, 159.5, 158.2, 143.3, 141.8, 141.6, 141.3, 129.6, 129.1, 129.0, 126.5, 126.2, 104.9, 90.2, 87.1, 76.1, 71.2, 68.4, 53.5, 51.8, 51.5, 50.6, 48.4, 48.2, 39.8, 38.8, 38.3, 25.5, 25.1, 23.1, 22.4, 22.3, 21.5, 20.6, 20.4, 20.3, 19.9; HRMS (ESI) calcd for C₂₃H₃₅N₂O₃S [M+H]⁺ 419.2368, found 419.2366.



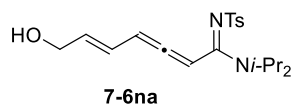
7-6/7-5la'': These two products were synthesized using procedure **J** and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:1) as orange solid (**7-6la''**: 80% yield, 69.0 mg; **7-5la''**: 13% yield, 11.2 mg). ¹H NMR (CDCl₃, 500 MHz) **7-6la''**: δ 7.80 (d, 2H, *J* = 8.0 Hz), 7.23 (d, 2H, *J* = 7.9 Hz), 6.28 (d, 2H, *J* = 6.5 Hz), 5.70 (d, 2H, *J* = 6.5 Hz), 4.50 (br, 1H), 3.62 (br, 1H), 3.42 (s, 1H), 2.38 (s, 3H); 1.97–1.07 (m, 24H); **7-6la''**: δ 7.80 (d, 2H, *J* = 8.0 Hz), 7.23 (d, 2H, *J* = 7.9 Hz), 4.37–4.24 (m, 1H), 3.95 (s, 2H), 3.70–3.49 (m, 1H), 2.38 (s, 3H), 1.97–1.07 (m, 24H); ¹³C NMR (CDCl₃, 125 MHz): δ (all discernible signals for both isomers) 202.2, 159.5, 158.3, 141.7, 141.6, 141.3, 129.1, 129.0, 126.3, 126.2, 105.9, 90.4, 88.2, 75.3, 74.8, 71.6, 51.8, 50.6, 48.4, 48.2, 43.0, 42.4, 41.7, 29.4, 29.3, 28.1, 22.4, 22.2, 22.0, 21.5, 20.6, 20.4, 20.3, 19.9; HRMS (ESI) calcd for C₂₄H₃₇N₂O₃S [M+H]⁺ 433.2525, found 433.2521.



7-6ma: This product was synthesized using procedure **J** and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:1) as white solid (69% yield, 55.8 mg). ¹H NMR (CDCl₃, 500 MHz) one diastereomer: δ 7.80 (d, 2H, *J* = 8.2 Hz), 7.24 (d, 2H, *J* = 8.0 Hz), 6.34 (d, 1H, *J* = 6.5 Hz), 5.72 (d, 1H, *J* = 6.5 Hz), 5.51–5.44 (m, 1H), 4.73 (d, 2H, *J* = 7.7 Hz), 4.61–4.46 (m, 1H), 3.95 (s, 1H), 3.62 (br, 1H), 2.39 (s, 3H), 2.35–1.79 (m, 5H), 1.74 (s, 3H), 1.72 (s, 3H), 1.42–1.11 (m, 12H); other diastereomer: δ 7.80 (d, 2H, *J* = 8.2 Hz), 7.24 (d, 2H, *J* = 8.0 Hz), 6.30 (d, 1H, *J* = 6.5 Hz), 5.68 (d, 1H, *J* = 6.6 Hz), 5.51–5.44 (m, 1H), 4.73 (d, 2H, *J* = 7.7 Hz), 4.61–4.46 (m, 1H), 4.10 (s, 1H), 3.62 (br, 1H), 2.39 (s, 3H), 2.35–1.79 (m, 5H), 1.75 (s, 3H), 1.70 (s, 3H), 1.42–1.11 (m, 12H); ¹³C NMR (CDCl₃, 125 MHz): δ (all discernible signals for both isomers) 202.7, 201.4, 158.2, 157.9, 148.6, 148.5, 141.7, 141.3, 141.2, 137.0, 136.9, 129.1, 129.0, 126.2, 124.2, 124.1, 109.3, 103.1, 102.4, 90.9, 90.5, 73.6, 73.5, 52.2, 51.8, 48.3, 43.1, 42.2, 39.6, 31.0, 21.5, 20.6, 20.5, 20.3, 19.9, 19.7, 16.9, 16.7; **HRMS** (ESI) calcd for C₂₇H₃₉N₂O₃S [M+H]⁺ 471.2681, found 471.2675.

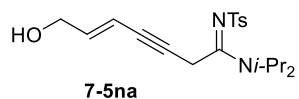


7-5ma: This product was synthesized using procedure **J** and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:1) as white solid (10% yield, 8.0 mg). ¹H NMR (CDCl₃, 500 MHz): δ 7.80 (d, 2H, *J* = 8.2 Hz), 7.24 (d, 2H, *J* = 8.0 Hz), 5.45–5.40 (m, 1H), 4.78–4.65 (m, 2H), 4.31–4.20 (m, 1H), 4.03–3.88 (m, 2H), 3.55 (br, 1H), 2.38 (s, 1H), 2.35–1.79 (m, 5H), 1.76–1.66 (m, 6H), 1.42–1.11 (m, 12H); ¹³C NMR (CDCl₃, 125 MHz): δ (all discernible signals for both isomers) 202.7, 201.4, 159.3, 158.2, 157.9, 148.6, 148.5, 148.2, 141.8, 141.7, 141.2, 141.2, 136.9, 136.8, 135.8, 129.6, 129.1, 129.0, 126.5, 126.2, 124.3, 124.2, 124.1, 109.3, 103.1, 102.4, 90.9, 90.5, 86.3, 76.4, 73.6, 73.5, 69.6, 52.2, 51.9, 50.7, 48.5, 48.3, 43.1, 42.2, 39.7, 39.6, 31.0, 22.3, 21.5, 20.6, 20.5, 20.3, 19.9, 19.7, 17.1, 16.9, 16.7.

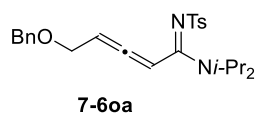


7-6na: This product was synthesized using procedure **J** and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:1) as white solid (46% yield, 30.8 mg). ¹H NMR (CDCl₃, 500 MHz): δ 7.78 (d, 2H, *J* = 8.2 Hz), 7.24 (d, 2H,

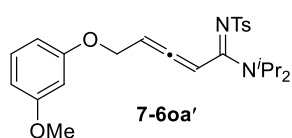
$J = 8.1$ Hz), 6.46 (d, 1H, $J = 5.2$ Hz), 6.08–5.95 (m, 2H), 5.89–5.81 (m, 1H), 4.49 (br, 1H), 4.17 (d, 2H, $J = 5.5$ Hz), 3.61 (br, 1H), 2.40 (s, 3H), 1.53–1.02 (m, 12H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 207.5, 158.0, 141.6, 141.3, 133.7, 129.0, 126.3, 123.5, 96.4, 88.4, 63.0, 52.1, 48.4, 21.5, 20.5, 19.9; HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{29}\text{N}_2\text{O}_3\text{S}$ $[\text{M}+\text{H}]^+$ 377.1899, found 377.1889.



7-5na: This product was synthesized using procedure **J** and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:1) as white solid (11% yield, 7.4 mg). ^1H NMR (CDCl_3 , 500 MHz): δ 7.81 (d, 2H, $J = 8.2$ Hz), 7.24 (d, 2H, $J = 8.0$ Hz), 6.15 (dt, 1H, $J = 5.1$ Hz, $J = 15.9$ Hz), 5.67 (d, 1H, $J = 16.0$ Hz), 4.40–4.26 (m, 2H), 4.19 (s, 2H), 4.05 (s, 2H), 3.62–3.47 (m, 1H), 2.39 (s, 1H), 1.36 (d, 6H, $J = 6.8$ Hz), 1.24 (d, 6H, $J = 6.6$ Hz); ^{13}C NMR (CDCl_3 , 125 MHz): δ 159.2, 142.0, 141.7, 141.2, 129.1, 126.3, 109.9, 82.1, 81.3, 62.8, 50.8, 48.5, 23.4, 21.5, 20.2, 19.8.

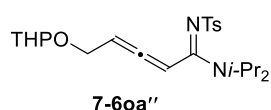


7-6oa: This product was synthesized using procedure **J** and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:2) as white solid (56% yield, 40.6 mg). ^1H NMR (CDCl_3 , 500 MHz): δ 7.78 (d, 2H, $J = 8.1$ Hz), 7.39–7.26 (m, 5H), 7.22 (d, 2H, $J = 8.0$ Hz), 6.43–6.36 (m, 1H), 5.49–5.42 (m, 1H), 4.58–4.44 (m, 1H), 4.50 (s, 2H), 4.15–4.03 (m, 2H), 3.57 (br, 1H), 2.38 (s, 3H), 1.49–0.98 (m, 12H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 204.2, 158.2, 141.5, 141.4, 137.8, 129.0, 128.4, 127.8, 126.4, 92.3, 88.1, 72.4, 66.3, 52.1, 48.5, 21.5, 20.4, 20.0; HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{33}\text{N}_2\text{O}_3\text{S}$ $[\text{M}+\text{H}]^+$ 441.2212, found 441.2210.

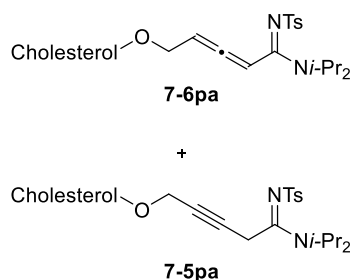


7-6oa': This product was synthesized using procedure **J** and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:2) as white solid (54% yield, 43.5 mg). ^1H NMR (CDCl_3 , 500 MHz): δ 7.79 (d, 2H, $J = 8.1$ Hz), 7.23 (d, 2H, $J = 8.0$ Hz), 7.16 (t, 1H, $J = 8.2$ Hz), 6.54–6.38 (m, 4H), 5.57 (q, 1H, $J = 6.1$ Hz), 4.67–4.47 (m, 3H), 3.78 (s, 3H), 3.60 (br, 1H), 2.37 (s, 3H), 1.46–1.08 (m, 12H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 204.2, 160.9,

159.2, 157.8, 141.6, 141.4, 130.0, 129.0, 126.3, 106.9, 106.8, 101.3, 91.6, 88.8, 64.0, 55.3, 52.1, 48.4, 21.4, 20.4, 19.9; **HRMS** (ESI) calcd for C₂₅H₃₃N₂O₄S [M+H]⁺ 457.2161, found 457.2160

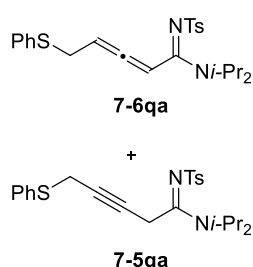


7-6oa'': This product was synthesized using procedure **J** and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:1) as white solid (70% yield, 58.0 mg). **¹H NMR** (CDCl₃, 500 MHz): δ 7.78 (d, 2H, *J* = 8.2 Hz), 7.23 (d, 2H, *J* = 8.1 Hz), 6.45–6.39 (m, 1H), 5.50–5.42 (m, 1H), 4.69–4.49 (m, 2H), 4.28–4.19 (m, 1H), 4.08–3.99 (m, 1H), 3.88–3.78 (m, 1H), 3.60 (br, 1H), 3.54–3.45 (m, 1H), 2.39 (s, 3H), 1.87–1.65 (m, 2H), 1.64–1.02 (m, 16 H); **¹³C NMR** (CDCl₃, 125 MHz): δ 204.2, 204.1, 158.3, 141.5, 141.4, 129.0, 126.4, 98.5, 98.1, 92.6, 92.4, 88.2, 88.0, 63.3, 63.2, 62.6, 62.3, 51.9, 48.5, 30.6, 30.5, 25.4, 21.5, 20.4, 20.1, 19.6, 19.4; **HRMS** (ESI) calcd for C₂₃H₃₅N₂O₄S [M+H]⁺ 435.2318, found 435.2314.

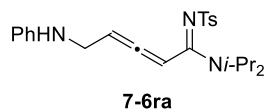


7-6/7-5pa: These two products were synthesized using procedure **J** and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:2) as white solid (**7-6pa**: 56% yield, 41.6 mg; **7-5pa**: 7% yield, 13.8 mg). **¹H NMR** (CDCl₃, 500 MHz) **7-6pa**: δ 7.78 (d, 2H, *J* = 8.2 Hz), 7.73 (d, 2H, *J* = 8.0 Hz), 6.43–6.34 (m, 1H), 5.42 (q, 1H, *J* = 6.2 Hz), 5.37–5.29 (m, 1H), 4.59 (br, 1H), 4.15–3.98 (m, 2H), 3.60 (br, 1H), 3.25–3.13 (m, 1H), 2.39 (s, 3H), 2.36–2.26 (m, 1H), 2.22–2.12 (m, 1H), 2.06–1.91 (m, 2H), 1.91–1.77 (m, 3H); 1.66–0.81 (m, 45H), 0.67 (s, 3H); **7-5pa**: δ 7.78 (d, 2H, *J* = 8.2 Hz), 7.73 (d, 2H, *J* = 8.0 Hz), 5.37–5.29 (m, 1H), 4.37–4.27 (m, 1H), 4.18–3.90 (m, 5H), 3.70–3.47 (m, 1H), 3.35–3.26 (m, 1H), 2.39 (s, 3H), 2.36–2.26 (m, 1H), 2.22–2.12 (m, 1H), 2.06–1.91 (m, 2H), 1.91–1.77 (m, 3H); 1.66–0.81 (m, 45H), 0.67 (s, 3H); **¹³C NMR** (CDCl₃, 125 MHz): δ (all discernible signals for both isomers) 204.1, 204.0, 159.1, 158.4, 141.7, 141.5, 141.4, 140.6, 140.5, 129.1, 129.0, 126.4, 126.3, 121.9, 93.0, 92.9, 88.0, 87.9, 80.0, 78.7, 78.6, 77.9, 77.7, 64.0, 56.8, 56.2, 55.4, 52.0, 51.8, 50.7, 50.2, 48.4, 42.3, 39.8, 39.5, 39.1, 39.0, 38.8, 37.2, 36.8, 36.2, 35.8, 31.9, 29.7, 28.4, 28.2, 28.0, 24.3, 23.8,

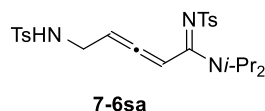
22.9, 22.8, 22.6, 21.5, 21.1, 20.5, 20.2, 20.1, 19.8, 19.4, 18.7, 11.9; **HRMS** (ESI) calcd for C₄₅H₇₁N₂O₃S [M+H]⁺ 719.5185, found 719.5182.



7-6/7-5qa: These two products were synthesized using procedure **J** and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:2) as yellow solid (**7-6qa**: 53% yield, 44.0 mg; **7-5qa**: 13% yield, 10.8 mg). **¹H NMR** (CDCl₃, 500 MHz) **7-6qa**: δ 7.79 (d, 2H, *J* = 8.2 Hz), 7.39–7.14 (m, 7H), 6.22–6.16 (m, 1H), 5.43 (q, 1H, *J* = 7.2 Hz), 4.39 (br, 1H), 3.66–3.42 (m, 3H), 2.38 (s, 2H), 1.42–0.99 (m, 12H); **7-5qa**: δ 7.81 (d, 2H, *J* = 8.3 Hz), 7.39–7.14 (m, 7H), 4.24–4.15 (m, 1H), 3.91 (s, 2H), 3.66–3.42 (m, 3H), 2.38 (s, 3H), 1.42–0.99 (m, 12H); **¹³C NMR** (CDCl₃, 125 MHz): δ (all discernible signals for both isomers) 205.1, 159.0, 158.0, 141.7, 141.6, 141.4, 141.2, 135.4, 134.9, 129.9, 129.4, 129.1, 129.0, 126.6, 126.5, 126.3, 92.0, 88.1, 79.1, 75.4, 51.9, 50.7, 48.4, 31.5, 22.8, 22.7, 21.4, 20.5, 20.3, 20.1, 19.9, 19.8; **HRMS** (ESI) calcd for C₂₄H₃₁N₂O₂S₂ [M+H]⁺ 443.1827, found 443.1821.

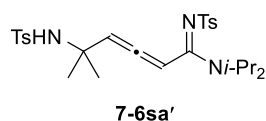


7-6ra: These two products were synthesized using procedure **J** and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:3) as white solid (58% yield, 46.1 mg). **¹H NMR** (CDCl₃, 500 MHz): δ 7.82 (d, 2H, *J* = 8.2 Hz), 7.24 (d, 2H, *J* = 8.0 Hz), 7.14 (d, 2H, *J* = 7.9 Hz), 6.71–6.46 (m, 3H), 6.28–6.22 (m, 1H), 5.64–5.60 (m, 1H), 4.74–4.31 (m, 2H), 3.92–3.83 (m, 2H), 3.57 (br, 1H), 2.38 (s, 3H), 1.37–1.26 (m, 6H), 1.19–1.04 (m, 6H); **¹³C NMR** (CDCl₃, 125 MHz): δ 204.5, 158.0, 147.6, 141.7, 141.5, 129.1, 126.2, 117.5, 113.3, 93.6, 89.4, 51.9, 48.3, 41.2, 21.5, 20.5, 20.3, 19.9.

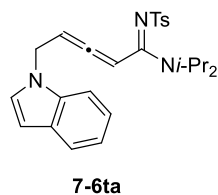


7-6sa: These two products were synthesized using procedure **J** and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:2) as white solid (88% yield, 68.9 mg). **¹H NMR** (CDCl₃, 500 MHz): δ 7.83–7.76 (m, 4H), 7.30–7.20 (m, 4H), 6.35–6.26 (m, 1H), 6.04–5.96 (m, 1H), 5.59–5.51 (m, 1H), 4.38–4.24 (m, 1H), 3.80–3.68 (m, 2H),

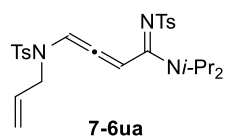
3.60 (br, 1H), 2.40 (s, 3H), 2.38 (s, 3H), 1.39–1.10 (m, 12 H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 205.7, 157.2, 142.9, 141.8, 141.1, 137.6, 129.5, 129.1, 127.4, 126.1, 93.0, 90.2, 51.8, 48.2, 40.5, 21.5, 20.4, 20.3, 19.9, 19.6, 19.4; HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{34}\text{N}_3\text{O}_4\text{S}_2$ $[\text{M}+\text{H}]^+$ 504.1991, found 504.1993.



7-6sa': These two products were synthesized using procedure **J** and isolated by flash column chromatography (SiO , EtOAc-Hexane, 1:2) as white solid (68% yield, 45.8 mg). ^1H NMR (CDCl_3 , 500 MHz): δ 7.82 (d, 2H, $J = 7.6$ Hz), 7.81 (d, 2H, $J = 6.8$ Hz), 7.29–7.21 (m, 4H), 6.31 (d, 1H, $J = 6.6$ Hz), 5.69 (br, 1H), 6.31 (d, 1H, $J = 6.6$ Hz), 4.40 (br, 1H), 3.69–3.51 (m, 1H), 2.40 (s, 3H), 2.39 (s, 3H), 1.40 (s, 3H), 1.37 (s, 3H), 1.34–1.11 (m, 12H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 202.6, 157.3, 142.8, 141.6, 141.3, 140.3, 129.4, 129.0, 127.3, 126.2, 104.0, 90.7, 55.7, 52.0, 48.3, 28.9, 28.8, 21.5, 20.7, 20.4, 20.0, 19.8; HRMS (ESI) calcd for $\text{C}_{27}\text{H}_{38}\text{N}_3\text{O}_4\text{S}_2$ $[\text{M}+\text{H}]^+$ 532.2304, found 532.2307.

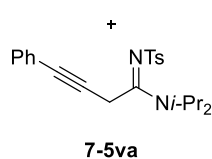
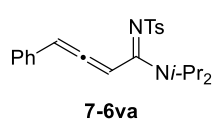


7-6ta: This product was synthesized using procedure **J** and isolated by flash column chromatography (SiO , EtOAc-Hexane, 1:3) as light-yellow solid (68% yield, 53.8 mg). ^1H NMR (CDCl_3 , 500 MHz): δ 7.83 (d, 2H, $J = 7.8$ Hz), 7.60 (d, 1H, $J = 7.8$ Hz), 7.35 (d, 1H, $J = 8.2$ Hz), 7.25 (d, 2H, $J = 7.9$ Hz), 7.18 (t, 1H, $J = 7.5$ Hz), 7.14–7.06 (m, 2H), 6.48 (d, 1H, $J = 2.4$ Hz), 6.34–6.26 (m, 1H), 5.60 (q, 1H, $J = 6.4$ Hz), 4.87–4.80 (m, 2H), 4.10 (br, 1H), 3.55 (br, 1H), 2.36 (s, 3H), 1.42–0.90 (m, 12H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 204.6, 157.5, 141.7, 141.5, 135.9, 129.1, 128.8, 127.7, 126.3, 121.7, 120.9, 119.6, 109.7, 101.8, 92.2, 89.1, 51.9, 48.3, 43.9, 21.4, 20.4, 20.1, 19.9, 19.7; HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{32}\text{N}_3\text{O}_2\text{S}$ $[\text{M}+\text{H}]^+$ 450.2215, found 450.2213.

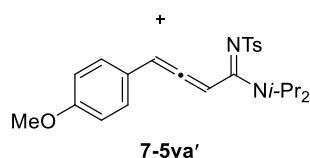
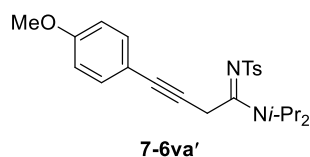


7-6ua: This product was synthesized using procedure **J** and isolated by flash column chromatography (SiO , EtOAc-Hexane, 1:1) as orange solid (67% yield, 48.8 mg). ^1H NMR (CDCl_3 , 500 MHz): δ 7.75 (d, 2H, $J = 8.1$ Hz), 7.67 (d, 2H, $J = 8.1$ Hz), 7.32 (d, 2H, $J = 8.0$ Hz), 7.23 (d, 2H, $J = 8.0$ Hz), 7.02 (d, 1H, $J = 6.0$ Hz), 6.82 (d, 1H, $J = 6.1$ Hz), 5.76–5.65

(m, 1H), 5.34 (d, 1H, $J = 17.1$ Hz), 5.11 (d, 1H, $J = 10.3$ Hz), 4.50–4.37 (m, 1H), 3.98–3.90 (m, 1H), 3.85–3.76 (m, 1H), 3.61–3.44 (m, 1H), 2.44 (s, 3H), 2.39 (s, 3H), 1.38–1.27 (m, 6H), 1.20–1.07 (m, 6H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 198.2, 157.0, 144.2, 141.8, 141.3, 135.4, 131.8, 129.9, 129.1, 127.1, 126.1, 118.5, 102.9, 98.0, 51.9, 49.1, 48.5, 21.6, 21.5, 20.7, 20.3, 20.0, 19.6; HRMS (ESI) calcd for $\text{C}_{27}\text{H}_{36}\text{N}_3\text{O}_4\text{S}_2$ $[\text{M}+\text{H}]^+$ 530.2147, found 530.2150.

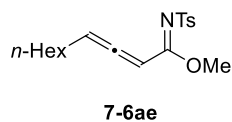


7-6/7-5va: These two products were synthesized using procedure **J** and isolated by flash column chromatography (SiO_2 , EtOAc-Hexane, 1:2) as orange solid (**7-6va**: 64% yield, 50.6 mg; **7-5va**: 14% yield, 11.0 mg). ^1H NMR (CDCl_3 , 500 MHz) **7-6va**: δ 7.83 (d, 2H, $J = 7.9$ Hz), 7.35–7.19 (m, 7H), 6.80 (d, 1H, $J = 6.6$ Hz), 6.35 (d, 1H, $J = 6.6$ Hz), 4.58 (br, 1H), 3.57 (br, 2H), 2.41 (s, 3H), 1.47–0.96 (m, 12H); **7-5va**: δ 7.83 (d, 2H, $J = 7.9$ Hz), 7.35–7.19 (m, 7H), 4.48–4.37 (m, 1H), 4.15 (s, 2H), 3.57 (s, 1H), 2.33 (s, 3H), 1.47–0.96 (m, 12H); ^{13}C NMR (CDCl_3 , 125 MHz): δ (all discernible signals for both isomers) 206.2, 159.4, 157.7, 141.8, 141.6, 141.4, 141.2, 131.8, 131.6, 129.1, 128.9, 128.8, 128.3, 128.2, 128.1, 128.0, 127.6, 126.6, 126.4, 126.3, 126.2, 97.8, 90.3, 83.3, 81.4, 52.2, 50.9, 48.5, 48.1, 23.1, 21.5, 20.4, 20.3, 20.0, 19.9; HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{29}\text{N}_2\text{O}_2\text{S}$ $[\text{M}+\text{H}]^+$ 397.1950, found 397.1945.



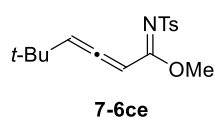
7-6/7-5va': These two products were synthesized using procedure **J** and isolated by flash column chromatography (SiO_2 , EtOAc-Hexane, 1:1) as orange solid (**7-6va'**: 64% yield, 48.7 mg; **7-5va'**: 18% yield, 13.7 mg). ^1H NMR (CDCl_3 , 500 MHz) **7-6va'**: δ 7.83 (d, 2H, $J = 7.1$ Hz), 7.25 (d, 2H, $J = 7.1$ Hz), 7.19 (d, 2H, $J = 8.5$ Hz), 6.85 (d, 2H, $J = 8.4$ Hz), 6.76 (d, 1H, $J = 6.6$ Hz), 6.31 (d, 1H, $J = 6.6$ Hz), 4.58 (br, 1H), 3.79 (s, 3H), 3.57 (br, 1H), 2.41 (s, 3H), 1.48–0.93 (m, 12H); **7-5va'**: δ 7.83 (d, 2H, $J = 7.1$ Hz), 7.25 (d, 2H, $J = 7.1$ Hz), 7.23–7.20 (m, 2H), 6.80 (d, 2H, $J = 8.7$ Hz), 4.49–4.38 (m, 1H), 4.12 (s, 2H), 3.79 (s, 3H), 3.57 (br, 1H), 2.34 (s, 3H), 1.48–0.93 (m, 12H); ^{13}C NMR (CDCl_3 , 125 MHz): δ (all discernible signals for both isomers) 206.1, 159.6, 159.5,

158.1, 141.7, 141.5, 141.3, 133.5, 133.0, 130.4, 129.2, 129.1, 128.8, 126.6, 126.5, 126.4, 124.0, 114.4, 114.3, 113.9, 97.3, 90.4, 83.2, 79.9, 55.3, 52.2, 50.8, 48.5, 23.2, 21.5, 21.4, 20.5, 20.3, 20.0, 19.9, 19.8.



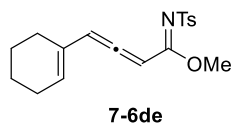
7-6ae: This product was synthesized using procedure **K** and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:5) as colorless oil (40% yield, 27.4 mg). **¹H**

NMR (CDCl₃, 500 MHz): δ 7.84 (d, 2H, *J* = 8.0 Hz), 7.29 (d, 2H, *J* = 7.9 Hz), 6.77–6.71 (m, 1H), 5.68–5.60 (m, 1H), 3.76 (s, 3H), 2.42 (s, 3H), 2.18–2.08 (m, 2H), 1.51–1.39 (m, 2H), 1.38–1.20 (m, 6H), 0.88 (t, 3H, *J* = 6.7 Hz); **¹³C NMR** (CDCl₃, 125 MHz): δ 212.8, 167.3, 143.2, 139.2, 129.4, 126.8, 126.7, 95.6, 86.1, 55.4, 31.5, 28.7, 28.6, 27.4, 22.6, 21.6, 14.1; **HRMS** (ESI) calcd for C₁₈H₂₆NO₃S [M+H]⁺ 336.1633, found 336.1626.



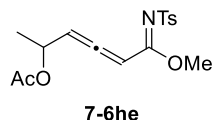
7-6ce: This product was synthesized using procedure **K** and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:5) as colorless oil (52% yield, 34.3 mg). **¹H**

NMR (CDCl₃, 500 MHz): δ 7.84 (d, 2H, *J* = 8.1 Hz), 7.29 (d, 2H, *J* = 7.9 Hz), 6.79 (d, 1H, *J* = 6.0 Hz), 5.64 (d, 1H, *J* = 6.0 Hz), 3.76 (s, 3H), 2.42 (s, 3H), 1.10 (s, 9H); **¹³C NMR** (CDCl₃, 125 MHz): δ 211.0, 167.3, 143.2, 139.2, 129.4, 126.7, 106.9, 87.6, 55.5, 30.0, 21.5; **HRMS** (ESI) calcd for C₁₆H₂₂NO₃S [M+H]⁺ 308.1320, found 308.1320.



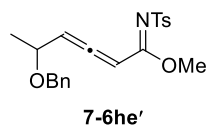
7-6de: This product was synthesized using procedure **K** and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:5) as colorless oil (64% yield, 41.5 mg). **¹H**

NMR (CDCl₃, 500 MHz): δ 7.85 (d, 2H, *J* = 8.2 Hz), 7.30 (d, 2H, *J* = 7.9 Hz), 7.00 (d, 1H, *J* = 5.0 Hz), 6.31 (d, 1H, *J* = 6.0 Hz), 5.83–5.79 (m, 1H), 3.77 (s, 3H), 2.43 (s, 3H), 2.18–2.10 (m, 2H), 2.03–1.98 (m, 2H), 1.71–1.53 (m, 4H); **¹³C NMR** (CDCl₃, 125 MHz): δ 215.2, 166.5, 143.2, 139.1, 129.9, 129.4, 129.0, 126.8, 102.0, 89.1, 55.6, 26.0, 22.2, 22.0, 21.6; **HRMS** (ESI) calcd for C₁₈H₂₂NO₃S [M+H]⁺ 332.1320, found 332.1317.



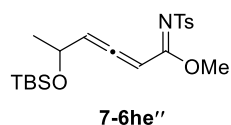
7-6he: This product was synthesized using procedure **K** and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:5) as colorless oil (61% yield, 44.9 mg). **¹H**

NMR (CDCl₃, 500 MHz) one diastereomer: δ 7.84 (d, 2H, J = 8.2 Hz), 7.30 (d, 2H, J = 8.0 Hz), 7.00–6.94 (m, 1H), 5.85 (t, 1H, J = 5.8 Hz), 5.51–5.41 (m, 1H), 3.76 (s, 3H), 2.43 (s, 3H); 2.06 (s, 3H), 1.37 (d, 1H, J = 4.1 Hz); other diastereomer: δ 7.84 (d, 2H, J = 8.2 Hz), 7.30 (d, 2H, J = 8.0 Hz), 7.00–6.94 (m, 1H), 5.82 (t, 1H, J = 6.0 Hz), 5.51–5.41 (m, 1H), 3.76 (s, 3H), 2.43 (s, 3H); 2.05 (s, 3H), 1.39 (d, 3H, J = 4.1 Hz); **¹³C NMR** CDCl₃, 125 MHz): δ (all discernable peaks for both diastereomers) 212.1, 211.8, 170.2, 170.1, 166.0, 165.9, 143.4, 138.9, 129.4, 126.8, 97.7, 97.5, 88.8, 88.7, 66.7, 66.6, 55.7, 21.6, 21.1, 19.9, 19.6; **HRMS** (ESI) calcd for C₁₆H₂₀NO₅S [M+H]⁺ 338.1062, found 338.1061.



7-6he': This product was synthesized using procedure **K** and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:5) as colorless oil (46% yield, 27.6 mg). **¹H**

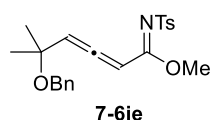
NMR (CDCl₃, 500 MHz): δ (one diastereomer) 7.85 (d, 2H, J = 9.6 Hz), 7.39–7.25 (m, 7H), 6.90 (d, 1H, J = 5.9 Hz), 5.64 (t, 1H, J = 7.0 Hz), 4.67 (d, 1H, J = 11.7 Hz), 4.44 (d, 1H, J = 11.7 Hz), 4.23–4.12 (m, 1H), 3.79 (s, 3H), 2.43 (s, 3H), 1.39 (d, 3H, J = 5.4 Hz); δ (other diastereomer) 7.85 (d, 2H, J = 9.6 Hz), 7.39–7.25 (m, 7H), 6.93 (d, 1H, J = 6.0 Hz), 5.68 (t, 1H, J = 7.0 Hz), 4.63 (d, 1H, J = 11.8 Hz), 4.45 (d, 1H, J = 11.5 Hz), 4.23–4.12 (m, 1H), 3.76 (s, 3H), 2.43 (s, 3H), 1.39 (d, 3H, J = 5.4 Hz); **¹³C NMR** (CDCl₃, 125 MHz): δ (all discernable signals for both diastereomers) 212.0, 211.6, 166.3, 146.8, 143.4, 138.9, 138.1, 137.9, 129.4, 128.5, 127.8, 127.7, 126.8, 98.3, 97.9, 87.2, 86.8, 72.7, 72.4, 70.6, 70.4, 55.6, 21.9, 21.6; **HRMS** (ESI) calcd for C₂₁H₂₄NO₄S [M+H]⁺ 386.1426, found 386.1419.



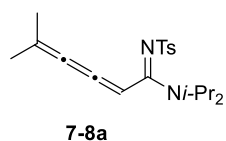
7-6he'': This product was synthesized using procedure **K** and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:5) as colorless oil (48% yield, 38.4 mg). **¹H**

NMR (CDCl₃, 500 MHz): δ 7.84 (d, 2H, J = 8.0 Hz), 7.30 (d, 2H, J = 7.8 Hz), 6.89–6.81 (m, 1H), 5.73–5.65 (m, 1H), 4.54–4.44 (m, 1H), 3.76 (s, 3H), 2.42 (s, 3H), 1.34–1.28 (m, 3H), 0.91–0.84 (m 9H), 0.09–0.03 (m, 6H); **¹³C NMR** (CDCl₃, 125 MHz): δ 211.0, 166.6, 166.5, 143.3, 139.1, 129.4,

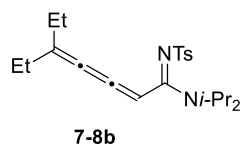
126.8, 101.6, 101.2, 87.6, 87.3, 66.6, 66.4, 55.4, 25.7, 24.8, 21.6, 18.2, -4.8, -5.0, -5.1; **HRMS** (ESI) calcd for $C_{20}H_{32}NO_4SSi$ $[M+H]^+$ 410.1821, found 410.1829.



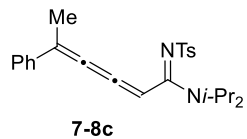
7-6ie: This product was synthesized using procedure **K** and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:5) as colorless oil (72% yield, 52.5 mg). **¹H NMR** ($CDCl_3$, 500 MHz): δ 7.86 (d, 2H, J = 8.2 Hz), 7.38–7.23 (m, 7H), 6.96 (d, 1H, J = 6.0 Hz), 5.76 (d, 2H, J = 6.0 Hz), 4.52 (d, 1H, J = 11.4 Hz), 4.46 (d, 1H, J = 11.4 Hz), 3.76 (s, 3H), 2.43 (s, 3H), 1.44 (s, 3H), 1.44 (s, 3H); **¹³C NMR** ($CDCl_3$, 125 MHz): δ 211.5, 166.4, 143.4, 139.0, 129.5, 128.4, 127.5, 126.8, 102.2, 87.9, 75.4, 65.6, 55.6, 27.6, 26.6, 21.6; **HRMS** (ESI) calcd for $C_{22}H_{26}NO_4S$ $[M+H]^+$ 400.1583, found 400.1572.



7-8a: This product was synthesized using procedure **L** and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:5) as white solid (76% yield, 46.4 mg). **¹H NMR** ($CDCl_3$, 500 MHz): δ 7.79 (d, 2H, J = 8.0 Hz), 7.21 (d, 2H, J = 7.9 Hz), 5.46 (s, 1H), 4.64 (br, 1H), 3.83 (br, 1H), 2.38 (s, 3H), 2.03 (s, 3H), 1.89 (s, 3H), 1.37 (d, 6H, J = 6.1 Hz), 1.25 (d, 6H, J = 5.8 Hz); **¹³C NMR** ($CDCl_3$, 125 MHz): δ 157.1, 147.3, 141.4, 141.1, 128.9, 126.6, 103.7, 101.4, 80.9, 47.9, 25.5, 22.0, 21.5, 20.6, 19.7; **HRMS** (ESI) calcd for $C_{20}H_{29}N_2O_2S$ $[M+H]^+$ 361.1950, found 361.1951.

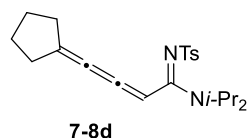


7-8b: This product was synthesized using procedure **L** and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:5) as white solid (79% yield, 53.7 mg). **¹H NMR** ($CDCl_3$, 500 MHz): δ 7.79 (d, 2H, J = 8.1 Hz), 7.21 (d, 2H, J = 8.0 Hz), 5.44 (s, 1H), 4.65 (br, 1H), 3.80 (br, 1H), 2.42 (q, 2H, J = 7.6 Hz), 2.38 (s, 3H), 2.20 (q, 2H, J = 7.3 Hz), 1.38 (d, 6H, J = 6.2 Hz), 1.25 (d, 6H, J = 6.0 Hz), 1.08–1.02 (m, 6H); **¹³C NMR** ($CDCl_3$, 125 MHz): δ 167.7, 147.4, 141.4, 141.1, 128.9, 126.6, 101.3, 93.4, 81.4, 52.1, 47.9, 28.9, 27.5, 21.5, 20.6, 19.7, 13.0, 11.9; **HRMS** (ESI) calcd for $C_{22}H_{33}N_2O_2S$ $[M+H]^+$ 389.2263, found 389.2254.



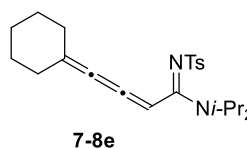
7-8c: This product was synthesized using procedure **L** and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:5) as white solid (80% yield, 61.9 mg). **¹H**

NMR (CDCl₃, 500 MHz): δ 7.82 (d, 2H, *J* = 8.1 Hz), 7.52–7.44 (m, 2H), 7.41–7.32 (m, 3H), 7.23 (d, 2H, *J* = 8.0 Hz), 6.06 (s, 1H), 4.70 (br, 1H), 3.86 (br, 1H), 2.46 (s, 3H), 2.39 (s, 3H), 1.40 (d, 6H, *J* = 6.2 Hz), 1.29 (d, 6H, *J* = 6.0 Hz); **¹³C NMR** (CDCl₃, 125 MHz): δ 155.4, 147.0, 141.6, 141.1, 140.0, 129.2, 128.9, 128.6, 126.6, 125.7, 104.2, 101.3, 83.8, 52.2, 48.0, 21.5, 20.7, 19.7, 19.4.



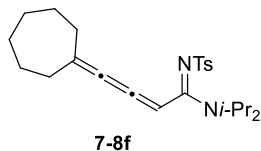
7-8d: This product was synthesized using procedure **L** and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:5) as white solid (56% yield, 49.0 mg). **¹H**

NMR (CDCl₃, 500 MHz): δ 7.79 (d, 2H, *J* = 8.1 Hz), 7.21 (d, 2H, *J* = 8.0 Hz), 5.58 (s, 1H), 4.64 (br, 1H), 3.84 (br, 1H), 2.59–2.52 (m, 2H), 2.45–2.40 (m, 2H), 2.38 (s, 3H), 1.77–1.65 (m, 4H), 1.37 (d, 6H, *J* = 6.4 Hz), 1.25 (d, 6H, *J* = 6.2 Hz); **¹³C NMR** (CDCl₃, 125 MHz): δ 169.6, 147.4, 141.4, 141.2, 128.8, 126.6, 101.8, 98.5, 81.3, 52.1, 47.9, 34.7, 32.9, 26.4, 26.2, 21.5, 20.6, 19.7; **HRMS** (ESI) calcd for C₂₂H₃₁N₂O₂S [M+H]⁺ 387.2106, found 387.2101.



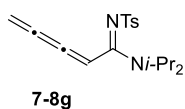
7-8e: This product was synthesized using procedure **L** and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:5) as white solid (82% yield, 57.8 mg). **¹H**

NMR (CDCl₃, 500 MHz): δ 7.78 (d, 2H, *J* = 8.1 Hz), 7.21 (d, 2H, *J* = 7.9 Hz), 5.39 (s, 1H), 4.62 (br, 1H), 3.83 (br, 1H), 2.51 (t, 2H, *J* = 5.6 Hz), 2.38 (s, 3H), 2.22 (t, 2H, *J* = 5.6 Hz), 1.70–1.53 (m, 6H), 1.37 (d, 6H, *J* = 6.4 Hz), 1.24 (d, 6H, *J* = 6.3 Hz); **¹³C NMR** (CDCl₃, 125 MHz): δ 164.5, 147.5, 141.4, 141.1, 128.8, 126.6, 101.4, 100.0, 80.8, 52.3, 51.8, 47.9, 36.4, 32.5, 28.3, 27.8, 26.0, 21.5, 20.6, 19.7; **HRMS** (ESI) calcd for C₂₃H₃₃N₂O₂S [M+H]⁺ 401.2263, found 401.2257.



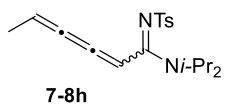
7-8f: This product was synthesized using procedure **L** and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:5) as white solid (76% yield, 52.2 mg).

¹H NMR (CDCl₃, 500 MHz): δ 7.78 (d, 2H, *J* = 8.1 Hz), 7.21 (d, 2H, *J* = 8.1 Hz), 5.47 (s, 1H), 4.65 (br, 1H), 3.83 (br, 1H), 2.63–2.57 (m, 2H), 2.42–2.34 (m, 5H), 1.67–1.47 (m, 8H), 1.37 (d, 6H, *J* = 6.6 Hz), 1.24 (d, 6H, *J* = 6.4 Hz); **¹³C NMR** (CDCl₃, 125 MHz): δ 167.1, 147.5, 141.4, 141.1, 128.8, 126.6, 103.2, 101.5, 81.9, 52.0, 47.9, 37.6, 33.8, 29.9, 29.1, 27.8, 27.2, 21.5, 20.6, 19.7; **HRMS** (ESI) calcd for C₂₄H₃₅N₂O₂S [M+H]⁺ 415.2419, found 415.2411.



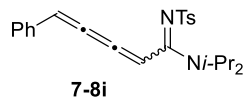
7-8g: This product was synthesized using procedure **L** and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:5) as white solid (68% yield, 41.7 mg).

¹H NMR (CDCl₃, 500 MHz): δ 7.79 (d, 2H, *J* = 8.0 Hz), 7.22 (d, 2H, *J* = 7.9 Hz), 5.96 (d, 2H, *J* = 6.5 Hz), 5.80 (t, 1H, *J* = 6.5 Hz), 4.54 (br, 1H), 3.89 (br, 1H), 2.39 (s, 3H), 1.38 (d, 6H, *J* = 6.1 Hz), 1.26 (d, 6H, *J* = 6.3 Hz); **¹³C NMR** (CDCl₃, 125 MHz): δ 146.9, 141.7, 140.8, 132.6, 128.9, 126.7, 115.2, 100.9, 78.9, 52.1, 48.1, 21.5, 20.7, 19.6; **HRMS** (ESI) calcd for C₁₈H₂₅N₂O₂S [M+H]⁺ 333.1637, found 333.1631.



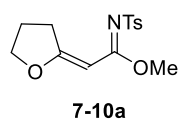
7-8h: This product was synthesized using procedure **L** and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:5) as colorless oil (74% yield, 45.8 mg).

¹H NMR (CDCl₃, 500 MHz): δ (One diastereomer) 7.78 (d, 2H, *J* = 7.9 Hz), 7.21 (d, 2H, *J* = 7.2 Hz), 6.35–6.24 (m, 1H), 5.65–5.61 (m, 1H), 4.63 (br, 1H), 3.85 (br, 1H), 2.38 (s, 3H), 1.88 (d, 3H, *J* = 6.7 Hz), 1.42–1.32 (m, 6H), 1.30–1.20 (m, 6H); δ (other diastereomer) 7.78 (d, 2H, *J* = 7.9 Hz), 7.21 (d, 2H, *J* = 7.2 Hz), 6.58–6.43 (m, 1H), 5.69–5.65 (m, 1H), 4.54 (br, 1H), 3.85 (br, 1H), 2.38 (s, 3H), 1.99 (d, 3H, *J* = 6.9 Hz), 1.42–1.32 (m, 6H), 1.30–1.20 (m, 6H); **¹³C NMR** (CDCl₃, 125 MHz): δ (all discernible signals for both isomers) 147.4, 147.0, 145.5, 141.5, 141.0, 140.9, 128.9, 126.6, 108.9, 108.2, 102.1, 99.6, 82.7, 52.1, 48.0, 21.5, 20.7, 20.6, 19.6, 19.3, 16.9; **HRMS** (ESI) calcd for C₁₉H₂₇N₂O₂S [M+H]⁺ 347.1793, found 347.1793.



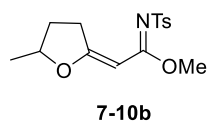
7-8i: This product was synthesized using procedure **L** and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:5) as orange solid (77%, 42.5 mg). **¹H**

NMR (CDCl₃, 500 MHz): δ 7.87–7.80 (m, 2H), 7.50–7.41 (m, 2H), 7.51–7.29 (m, 3H), 7.27–7.16 (m, 3H), 6.30 (d, 1H, *J* = 16.2 Hz), 4.61 (br, 1H), 3.93 (br, 1H), 2.39 (s, 3H), 1.40 (d, 6H, *J* = 6.0 Hz), 1.29 (d, 6H, *J* = 5.8 Hz); **¹³C NMR** (CDCl₃, 125 MHz): δ 146.9, 143.4, 141.6, 141.0, 135.3, 129.9, 129.0, 128.9, 128.9, 127.0, 126.7, 105.3, 80.5, 52.3, 48.1, 21.5, 20.7, 19.6.



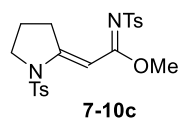
7-10a: This product was synthesized using procedure **M** and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:2) as colorless oil (48% yield, 34.5 mg). **¹H**

NMR (CDCl₃, 500 MHz): δ 7.84 (d, 2H, *J* = 8.0 Hz), 7.26 (d, 2H, *J* = 6.5 Hz), 6.31 (s, 1H), 4.28 (t, 2H, *J* = 7.1 Hz), 3.78 (s, 3H), 3.00 (t, 2H, *J* = 7.4 Hz), 2.40 (s, 3H), 2.14–2.05 (m, 2H); **¹³C NMR** (CDCl₃, 125 MHz): δ 178.2, 169.2, 142.5, 139.9, 129.2, 126.6, 89.5, 72.5, 54.6, 32.1, 23.7, 21.5; **HRMS** (ESI) calcd for C₁₄H₁₈NO₄S [M+H]⁺ 296.0957, found 296.0962.



7-10b: This product was synthesized using procedure **M** and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:2) as colorless oil (87% yield, 57.9 mg). **¹H**

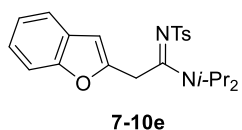
NMR (CDCl₃, 500 MHz): δ 7.84 (d, 2H, *J* = 8.0 Hz), 7.26 (d, 2H, *J* = 7.8 Hz), 6.25 (s, 1H), 4.61–4.53 (m, 1H), 3.77 (s, 3H), 3.22–3.10 (m, 1H), 2.97–2.85 (m, 1H), 2.40 (s, 3H), 2.27–2.17 (m, 1H), 1.71–1.56 (m, 1H), 1.35 (d, 3H, *J* = 6.2 Hz); **¹³C NMR** (CDCl₃, 125 MHz): δ 178.1, 169.4, 142.5, 140.0, 129.2, 126.6, 89.2, 81.3, 54.5, 32.6, 30.9, 21.5, 20.4; **HRMS** (ESI) calcd for C₁₅H₂₀NO₄S [M+H]⁺ 310.1113, found 310.1114.



7-10c: This product was synthesized using procedure **M** and isolated by flash column chromatography (SiO, EtOAc-Hexane, 1:2) as white solid (72% yield, 40.6 mg). **¹H NMR**

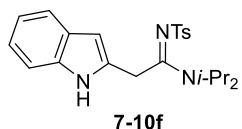
(CDCl₃, 500 MHz): δ 7.95 (d, 2H, *J* = 8.2 Hz), 7.92 (d, 2H, *J* = 8.2 Hz), 7.37 (d, 2H, *J* = 8.0 Hz), 7.29 (d, 2H, *J* = 8.0 Hz), 7.01 (s, 1H), 3.85 (t, 2H, *J* = 7.0 Hz), 3.74 (s, 3H), 2.91 (t, 2H, *J* = 7.6 Hz), 2.43 (s, 3H),

2.41 (s, 3H), 1.92–1.82 (m, 2H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 168.4, 157.3, 145.2, 142.7, 139.5, 133.7, 130.1, 129.3, 128.0, 126.9, 92.7, 54.7, 51.8, 34.0, 21.7, 21.6, 20.9; **HRMS** (ESI) calcd for $\text{C}_{21}\text{H}_{25}\text{N}_2\text{O}_5\text{S}_2$ $[\text{M}+\text{H}]^+$ 449.1205, found 449.1202.



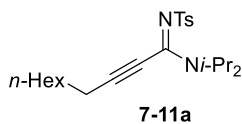
7-10e: This product was synthesized using procedure **N** and isolated by flash column chromatography (SiO_2 , EtOAc-Hexane, 1:1) as white solid (70% yield, 58.7 mg). ^1H

NMR (CDCl_3 , 500 MHz): δ 7.78 (d, 2H, $J = 8.1$ Hz), 7.46 (d, 1H, $J = 7.5$ Hz), 7.38 (d, 1H, $J = 8.0$ Hz), 7.23 (t, 1H, $J = 7.2$ Hz), 7.19 (t, 1H, $J = 7.8$ Hz), 7.16 (d, 2H, $J = 8.0$ Hz), 6.57 (s, 1H), 4.57 (s, 2H), 4.37–4.24 (m, 1H), 3.57 (br, 1H), 3.13 (s, 3H), 1.40 (d, 6H, $J = 6.8$ Hz), 1.12 (d, 6H, $J = 6.4$ Hz); ^{13}C NMR (CDCl_3 , 125 MHz): δ 160.1, 154.5, 151.0, 141.7, 141.2, 129.0, 128.5, 126.2, 123.9, 122.8, 120.9, 110.8, 104.9, 50.8, 48.4, 31.5, 21.4, 20.3, 19.9; **HRMS** (ESI) calcd for $\text{C}_{23}\text{H}_{29}\text{N}_2\text{O}_3\text{S}$ $[\text{M}+\text{H}]^+$ 413.1899, found 413.1894.



7-10f: This product was synthesized using procedure **M** and isolated by flash column chromatography (SiO_2 , EtOAc-Hexane, 1:2) as light-yellow solid (64% yield, 57.8

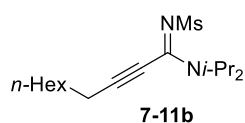
mg). ^1H NMR (CDCl_3 , 500 MHz): δ 10.04 (br, 1H), 7.90 (d, 2H, $J = 8.1$ Hz), 7.54 (d, 1H, $J = 7.8$ Hz), 7.41 (d, 1H, $J = 8.1$ Hz), 7.31 (d, 2H, $J = 8.0$ Hz), 7.16 (t, 1H, $J = 7.2$ Hz), 7.09 (t, 1H, $J = 7.6$ Hz), 6.31 (s, 1H), 4.68–4.54 (m, 1H), 4.48 (s, 2H), 3.51–3.38 (m, 1H), 2.43 (s, 3H), 1.28 (d, 6H, $J = 6.7$ Hz), 1.04 (d, 6H, $J = 6.5$ Hz); ^{13}C NMR (CDCl_3 , 125 MHz): δ 161.5, 142.2, 141.0, 136.6, 131.2, 129.3, 128.1, 126.1, 121.8, 120.0, 119.5, 111.4, 101.8, 50.5, 48.6, 32.8, 21.5, 20.1, 19.7; **HRMS** (ESI) calcd for $\text{C}_{23}\text{H}_{30}\text{N}_3\text{O}_2\text{S}$ $[\text{M}+\text{H}]^+$ 412.2059, found 412.2049.



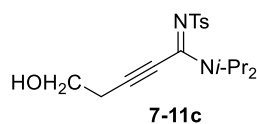
7-11a: This product was synthesized using procedure **O** and isolated by flash column chromatography (SiO_2 , EtOAc-Hexane, 1:2) as white solid (78% yield, 13.6 mg). ^1H

NMR (CDCl_3 , 500 MHz): δ 7.78 (d, 2H, $J = 8.0$ Hz), 7.23 (d, 2H, $J = 7.9$ Hz), 4.61 (br, 1H), 3.87 (br, 1H), 2.46–2.36 (m, 2H), 2.39 (s, 3H), 1.63–1.52 (m, 2H), 1.45–1.16 (m, 20 H), 0.88 (t,

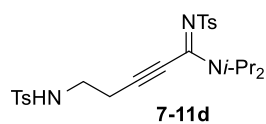
3H, $J = 6.4$ Hz); ^{13}C NMR (CDCl_3 , 125 MHz): δ 147.4, 141.5, 141.1, 128.9, 126.6, 106.2, 71.1, 52.4, 52.0, 47.9, 31.7, 29.0, 28.7, 27.3, 22.6, 21.5, 20.6, 19.7, 19.6, 14.1.



7-11b: This product was synthesized using procedure **O** and isolated by flash column chromatography (SiO , EtOAc-Hexane, 1:2) as white solid (82%, 11.5 mg). ^1H NMR (CDCl_3 , 500 MHz): δ 4.63 (br, 1H), 3.80 (br, 1H), 2.98 (s, 3H), 2.48 (t, 2H, $J = 7.2$ Hz), 1.71–1.56 (m, 2H), 1.50–1.17 (m, 20H), 0.92–0.82 (m, 3H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 146.8, 106.0, 70.9, 51.9, 47.7, 42.4, 31.7, 29.0, 28.7, 27.3, 22.6, 20.6, 19.6, 14.1.



7-11c: This product was synthesized using procedure **O** and isolated by flash column chromatography (SiO , EtOAc-Hexane, 1:1) as white solid (93% yield, 14.1 mg). ^1H NMR (CDCl_3 , 500 MHz): δ 7.81 (d, 2H, $J = 8.0$ Hz), 7.25 (d, 2H, $J = 7.9$ Hz), 4.68 (br, 1H), 3.92 (t, 1H, $J = 6.6$ Hz), 4.01–3.88 (m, 2H), 3.78 (br, 1H), 2.66 (t, 2H, $J = 5.6$ Hz), 2.40 (s, 3H), 1.33 (d, 6H, $J = 6.6$ Hz), 1.27 (d, 6H, $J = 6.3$ Hz); ^{13}C NMR (CDCl_3 , 125 MHz): δ 146.5, 141.9, 140.8, 129.1, 126.2, 105.2, 72.9, 60.0, 52.6, 47.8, 24.8, 21.5, 20.6, 19.5.



7-11d: This product was synthesized using procedure **O** and isolated by flash column chromatography (SiO , EtOAc-Hexane, 1:1) as white solid (93% yield, 12.0 mg). ^1H NMR (CDCl_3 , 500 MHz): δ 7.83 (d, 2H, $J = 7.7$ Hz), 7.80 (d, 2H, $J = 7.7$ Hz), 7.32–7.19 (m, 4H), 6.89–6.79 (m, 1H), 4.62 (br, 1H), 3.75 (br, 1H), 3.37–3.22 (m, 2H), 2.67–2.58 (m, 2H), 2.41 (s, 3H), 2.38 (s, 3H), 1.32 (d, 6H, $J = 6.4$ Hz), 1.29–1.21 (m, 6H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 146.0, 142.8, 142.0, 140.7, 137.9, 129.5, 129.1, 127.2, 126.2, 103.1, 73.0, 52.6, 47.9, 41.0, 29.7, 21.9, 21.5, 20.6, 19.4.

7.5. References

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- (62) A manuscript describing all click reactions has been prepared and will be submitted to “*Angew. Chem. Int. Ed.*”. A draft of the manuscript has been attached with this chapter.

The Selectivity for Alkynyl- or Allenyl Imidamides and Imidates in Copper-Catalyzed Reactions of Terminal 1,3-Diynes and Azides

Sourav Ghorai and Daesung Lee*

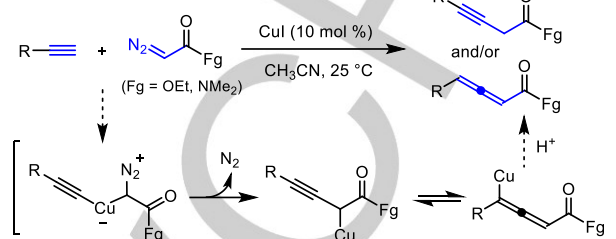
Abstract: Copper-catalyzed reactions of terminal 1,3-diynes with electron-deficient azide to generate either 3-alkynyl or 2,3-dienyl imidamides and imidates are described. The selectivity for the formation of these products critically depends not only on the substituent of the diyne but also on the nucleophile that reacts with the ketenimide intermediate generated from the corresponding triazole precursor. In general, reactions of 1,3-diynes containing a hydrocarbon substituent generates a mixture of alkynyl and allenyl imidamides but a heteroatom substituent at the propargylic position of the 1,3-diyne significantly improves the selectivity for 2,3-dienyl imidamides. Under otherwise same conditions, only 3-alkynyl imidamides are generated with piperidine as the trapping agent. Reactions of 1,3-diynes containing a propargylic acetate afford [3]cumulenyl imidamides while the reactions using methanol as trapping agent selectively generate 2,3-dienyl imidates. Also, 5-membered heterocyclic products can be generated from 1,3-diynes containing a homopropargylic alcohol or amine substituent.

Allenes constitute a distinct class of organic compounds with two orthogonal π -bonds. There are numerous natural products and bioactive molecules that contain allene substructures.^{1–3} It has been demonstrated that allene substituted bioactive compounds, like steroids,^{4,5} prostaglandins,^{6,7} carbacyclins,⁷ nucleosides,⁸ and unnatural amino acids⁹ display higher potency, increased metabolic stability, and bioavailability. Because of the strained nature of the cumulene structure, allenes has been engaged in numerous synthetic transformations as a versatile building block to form a variety of carbo- and heterocyclic frameworks.^{10–19} Axial-to-central chirality transfer is an efficient method to generate chiral compounds containing one or more stereogenic centers from chiral allenes.^{19–22}

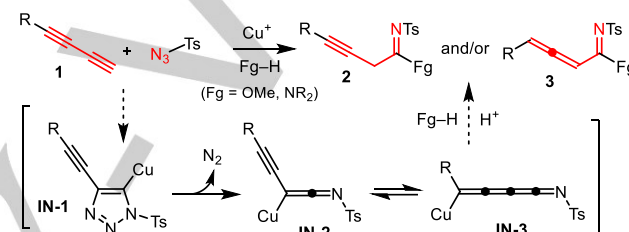
Due to the important utility of allenes, it is highly desirable to develop new synthetic methods to generate functionalized allenes from readily available starting materials.^{23–28} One of the traditional approaches to synthesis of allenes involves 1,2-elimination of vinyl derivatives under strong basic or metal catalyzed conditions.²⁹ S_N2' -type reactions with propargylic alcohol derivatives ($FG-CH_2-C\equiv C$)^{30–33} or isomerization of enyne moieties³⁴ also constitutes an efficient method to generate allenes. Transition metal-catalyzed coupling between terminal alkyne and carbonyl moieties in the presence of a secondary amine is also a well-established method³⁵ and a Cu(I)-catalyzed cross-coupling of terminal alkynes with diazo compounds is another efficient protocol to generate allenes.³⁶

In 2004, Fu reported a Cu(I)-catalyzed coupling of alkynes and diazoacetate under mild conditions to generate 3-alkynyl carboxylate and only small amounts of the corresponding allenates were observed (Scheme 1A).³⁷ On the other hand,

A) Fu's Cu-catalyzed coupling of terminal alkyne and diazo compound



B) This work: Cu-catalyzed coupling of diyne and azide



Scheme 1. Two different click approaches for the formation of closely related functional groups.

Lee and others found that the alkynes containing a heteroatom substituent at the propargylic or homopropargylic carbon center preferentially generate the allenate and especially in the presence of base such as triethyl amine, allenate became the exclusive product.³⁸ Fox also reported a similar reaction that selectively generate allenate as the product.³⁹ Although the exact mechanisms of these reactions are not well understood, on the basis of other related reaction, we propose a copper acetylide-mediated mechanism for the formation of the 3-alkynoate and allenate. Relying on this copper acetylide-mediated mechanism, we envision that the copper-catalyzed coupling of terminal 1,3-diyne **1** and azide would generate 3-alkynyl and allenyl imidamide/imidate **2/3** (Scheme 1B). We surmise that the terminal 1,3-diyne would form the corresponding copper acetylide, which will participate in a click reaction⁴⁰ with tosylazide to form triazole **IN-1**. Subsequent loss of molecular nitrogen will lead to two equilibrating organocopper aza-cummulenes **IN-2** and **IN-3**,⁴¹ which then react with a nucleophile such as an amine or alcohol to generate imidamide⁴² or imidate⁴³ containing either an alkyne (**2**) or an allene moiety (**3**). A unique feature of this transformation is that the selective transformation of the terminal alkyne moiety for the construction of imidamide and imidate functionality. Although starting from different set of starting materials, formation of closely related products from transformations in A and B is noteworthy. Herein describe our exploration of copper-catalyzed reactions of terminal 1,3-diyne **1** with tosylazide, which generated functionalized 1,3-di-substituted 2,3-dienyl imidamides and imidates **3** with good selectivity over the corresponding alkyne derivative **2**. Also, it was found that the type of nucleophiles, base additives, and the substituent

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patterns of the 1,3-diynes not only affect the ratio of **2** and **3** but also promote formation of alternative products such as [3]cumulenes and triple bond migrated products.

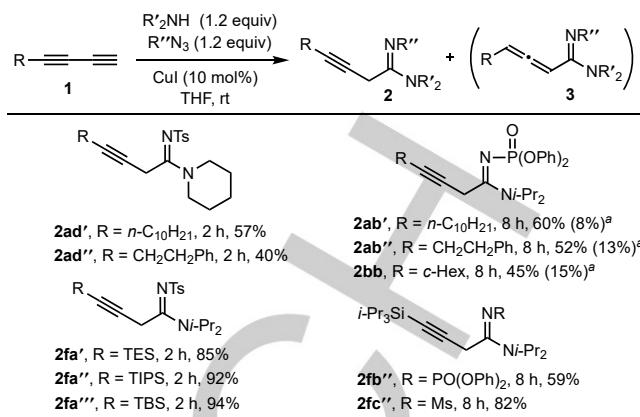
Our exploration commenced with assessment of the efficiency and selectivity for the formation 3-alkynyl and allenyl imidamide **2** and **3** (Table 1). Under the conditions employing copper catalyst (CuI, 10 mol%), azide (1.2 equiv), and amine (1.2 equiv), 1,3-diynes containing different substituent were examined. A hexyl-substituted terminal 1,3-diyne **1a** and TsN₃ provided a mixture of alkynyl and allenyl imidamides **2aa** and **3aa** in 75% yield with a 2:1 ratio (entry 1). Reactions of **1a** with other azides such as diphenyl phosphoryl azide⁴⁴ and mesyl azide are also efficient affording alkynyl imidamide **2ab** and **2ac** as the major product (entries 2 and 3). On the other hand, employing piperidine as a nucleophile under otherwise identical conditions, **1a** provided **2ad** exclusively (entry 4). 1,3-Diynes with a secondary (**1b**) or a tertiary alkyl group (**1c**) provided good yields of **2/3ba** and **2/3ca** but low selectivity with a slight preference for alkynyl product **2ba** and **2ca** (entries 5 and 6). With 1-cyclohexenyl substituted 1,3-diyne provided **2/3da** in 48% with a preference of 2,3-dienyl compound **3da**. 1,3-diyne **1e** containing a propargylic hydroxyl group afforded allene derivative **3ea** predominantly (entry 8), whereas 1,3-diyne **1f** containing a trimethylsilyl group provided alkyne derivative **2fa** selectively but in marginal yield (entry 9).

Table 1. Efficiency and product distribution with assorted nucleophiles, azides and 1,3-diynes of different substituent.

$\text{R}-\text{C}\equiv\text{C}-\text{C}\equiv\text{C}-\text{R}' \xrightarrow[\text{THF, rt, 2-8 h}]{\text{N}_3-\text{R}' (1.2 \text{ equiv}), \text{Nu-H} (1.2 \text{ equiv}), \text{CuI} (0.1 \text{ equiv})} \text{R}-\text{C}\equiv\text{C}-\text{C}(\text{NR}')=\text{C}(\text{Nu})-\text{R}' + \text{R}-\text{C}(\text{NR}')=\text{C}(\text{Nu})-\text{C}(\text{R}')=\text{C}=\text{C}-\text{R}'$				
Entry	R	Nu-H	Azide	Yield % (alkyne:allene) ^a
1	a, <i>n</i> -Hex	<i>i</i> -Pr ₂ NH	TsN ₃	2/3aa , 75% (2:1)
2	a, <i>n</i> -Hex	<i>i</i> -Pr ₂ NH	(PhO) ₂ PON ₃	2/3ab , 66% (5:1)
3	a, <i>n</i> -Hex	<i>i</i> -Pr ₂ NH	MsN ₃	2/3ac , 54% (2:1)
4	a, <i>n</i> -Hex	piperidine	TsN ₃	2ad , 56% (1:0) ^b
5	b, <i>c</i> -Hex	<i>i</i> -Pr ₂ NH	TsN ₃	2/3ba , 79% (2.3:1)
6	c, <i>t</i> -Bu	<i>i</i> -Pr ₂ NH	TsN ₃	2/3ca , 71% (1.3:1)
7	d, 1-Cyclohex	<i>i</i> -Pr ₂ NH	TsN ₃	2/3da , 48% (1:2.5)
8	e, CH ₂ OH	<i>i</i> -Pr ₂ NH	TsN ₃	2/3ea , 73% (1:15)
9	f, SiMe ₃	<i>i</i> -Pr ₂ NH	TsN ₃	2fa , 45% (1:0)

^a Isolated yield. ^b H₂O (1 equiv) and NH₂OH·HCl (1–2 mol%) were used as additives.

Once a general trend for the efficiency and selectivity between **2** and **3** has been revealed from the entries in Table 1, we next explored the selective formation of 3-alkynyl imidamide **2** (Scheme 2). As piperidine exclusively generated 3-alkynyl imidamide, reactions of *n*-decyl and homo-benzyl substituted 1,3-diynes with piperidine were performed, resulting corresponding 3-alkynyl imidamides **2ac'** and **2ac''** in 57% and 40% yield. Reaction with phosphoryl azide and alkyl substituted diynes predominantly generated 3-alkynyl imidamides (**2ab'**, **2ab''**, **2bb**) in moderate 45–60% yield. Electron-rich 1,3-diynes with silyl substituents selectively delivered 3-alkynyl imidamides. TBS-, TIPS- and TES-substituted 1,3-diynes provided the corresponding alkynyl derivatives **2fa'–2fa'''** in 85–94% yield. Reactions of TIPS-substituted 1,3-diyne with phosphoryl and mesyl azide also generated 3-alkynyl imides **2fb''** and **2fc''**



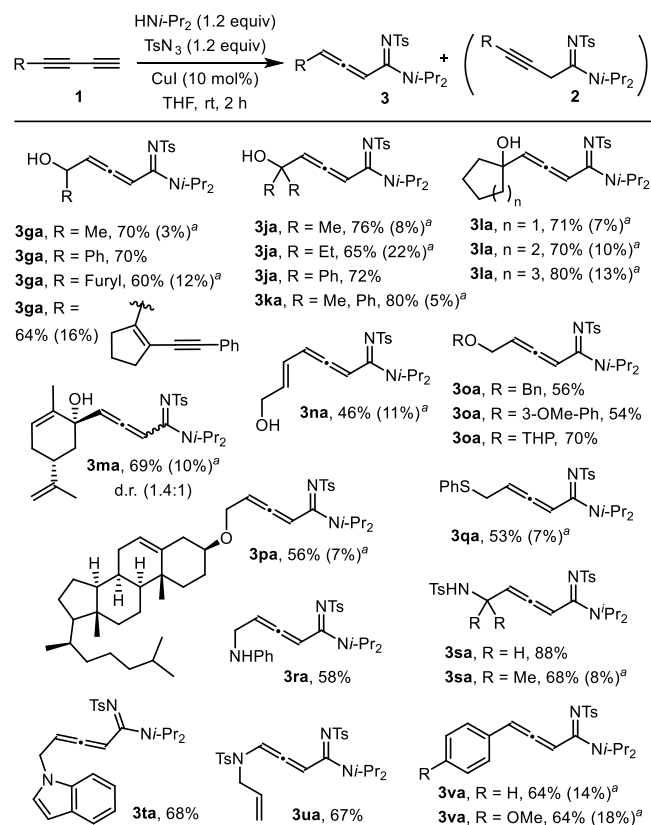
^a Yields in the parenthesis represents the corresponding 2,3-dienyl isomer **3**.

Scheme 2. Selective formation of 3-alkynyl imidamides with assorted nucleophiles, azides and 1,3-diynes

exclusively in 59% and 82% yield. It is evident from Scheme 2 that reactions with cyclic amine, phosphoryl azide and electron-rich silyl-substituted 1,3-diynes tend to generate 3-alkynyl imidamide predominantly or exclusively.

Next, we examined reactions of different 1,3-diynes to selectively form 2,3-dienyl imidamide **3** (Scheme 3). Based on the initial observation with propargylic alcohol-containing diyne **1e** that selectively generated 2,3-dienyl imidamide, we further tested the reactivity of structurally diversified propargyl alcohols, (thio)ethers, amines and amides. 1,3-Diynes containing secondary or tertiary alcohols afforded 2,3-dienyl imidamides (**3ga**, **3ga'**, **3ga''**, **3ga'''**, **3ja**, **3ja'**, **3ja''**, **3ka**) as a predominant or exclusive product in 65–76% yield. The selectivity between allenyl and alkynyl isomer depends on the substituent but no clear trend has been found. 1,3-Diynes with a tertiary alcohol and a cycloalkyl substituent delivered 2,3-dienyl imidamides (**3la**, **3la'**, **3la''**) in 70–80% yield with roughly a 10:1 selectivity. Carvone-containing 1,3-diyne afforded allene **3ma** (allene:alkyne = 7:1) in 69% yield with a 1.4:1 diastereomeric ratio. While a vinyl conjugated 1,3-diyne containing a free hydroxyl group provided allene **3na** in 46% yield with a low selectivity (4:1), 1,3-diynes with benzyl-, 3-MeO-Ph-, Boc-protected primary alcohols exclusively generated allene derivative (**3oa**, **3oa'**, **3oa''**) in 54–70% yield. Similarly, a cholesteryl ether substituted 1,3-diyne generated allene **3pa** in 56% yield with a 8:1 ratio of allene:alkyne. On the other hand, the corresponding thioether afforded **3qa** contaminated with the alkyne isomer (allene:alkyne = 7.5:1). 1,3-Diynes containing an aniline and tosylamido substituent at the propargylic position selectively generated allenes **3ra** and **3sa** in 58% and 88% yield. A *gem*-dimethyl, however, lower the yield and selectivity for **3sa'** (68%, 8:5:1). An indole substituted 1,3-diyne provided only allene **3ta** in 68% yield and *N*-allyl tosyl-substituted 1,3-diyne provided single isomer **3ua** in 67% yield. On the contrary, Phenyl and 4-MeO-phenyl substituted 1,3-diynes provided moderate yield and selectivity providing allenes **3va** (64%, 4.6:1) and **3va'** (64%, 3.6:1).

Although the selectivity of forming allenyl imidamides is good, the formation of alkyne isomer could not be suppressed in many cases. At this juncture, we surmised that trapping the ketenimine intermediate with alcohols may have different product distribution.^{45,46} Indeed, under identical conditions



Scheme 3. Formation of allenyl imidates from diverse 1,3-terminal diynes

except for replacing $i\text{-Pr}_2\text{NH}$ (1.2 equiv) with MeOH (10 equiv) and Et_3N (2 equiv), the reaction of 1,3-diyne selectively provided 2,3-dienyl imidates without a vestige of alkyne isomer (Table 2). Lower stoichiometry of methanol led to lower efficiency of the reaction. Alkyl and alkenyl diynes, which provided a mixture of allenyl and alkynyl imidamides previously, selectively generated allenyl imidates (**3ae**, **3ce**, **3de**) in moderate to good yield (entries 1–3). Even though 1,3-diyne **1g** containing free 2° alcohol led to decomposition (entry 4) the corresponding acyl-, benzyl-, and tert-butyldimethylsilyl-protected 1,3-diyne provided 2,3-dienyl imidates (**3he**, **3he'**, **3he''**) in good yield (entries 5–7).

Subsequently, we observed that under standard conditions, 1,3-diyne **4** containing an acetoxy or benzyloxy substituent at the propargylic position provided mono-, di-, and trisubstituted [3]cumulenes (Table 3).^{47–51} For example, 1,3-diyne **4a–c** afforded trisubstituted cumulene **5a–c** in 76–80% yield (entries 1–3). 1,3-Diyne substituted with a cycloalkyl moiety afforded the corresponding cumulenes **5d–f** in good yield (entries 4–6). Unexpectedly, while the acetate derivative of tertiary alcohol afforded, the corresponding primary and secondary acetate provide a mixture of the expected [3]cumulenes and the corresponding acetoxy allene derivatives. However, upon replacing the acetate with para-nitrobenzoate (**4g–i**), only cumulenes **5g–i** were obtained (entries 7–9). We believe this is the consequence of a better leaving group capacity of a benzoate compared to an acetate. [3]Cumulene is a special class of polyene organic compounds whose synthetic utilities are

Table 2. Synthesis of allenyl imidates by trapping with methanol.

Reaction scheme: $\text{R}-\text{C}\equiv\text{C}-\text{C}\equiv\text{C}-\text{R}' \xrightarrow[\text{Et}_3\text{N (2 equiv), THF, rt, 4 h}]{\text{CuI (10 mol\%), TsN}_3 \text{ (1.2 equiv), MeOH (10 equiv)}} \text{R}-\text{C}=\text{C}=\text{C}(\text{OMe})-\text{NTs}$				
Entry	1,3-Diyne 1	Allenyl imidate 3		Yield (%) ^a
1			3ae	40
2			3ce	52
3			3de	64
4			3ge	0
5			3he	61
6			3he'	46
7			3he''	48
8			3ie	72

Table 3. Synthesis of [3]cumulenyl imidamides via eliminating acetoxy or benzyloxy group of putative allene intermediate.

Reaction scheme: $\text{R}-\text{C}(\text{OR}^1)(\text{OR}^2)-\text{C}\equiv\text{C}-\text{R}' \xrightarrow[\text{CuI (0.1 equiv), THF, rt, 5 h}]{i\text{-Pr}_2\text{NH (1.2 equiv), TsN}_3 \text{ (1.2 equiv)}} \text{R}-\text{C}=\text{C}=\text{C}(\text{NTs})-\text{R}'$				
Entry	1,3-Diyne 4	[3]Cumulene 5		Yield (%)
1			5a	76
2			5b	79
3			5c	80
4			5d	56
5			5e	82
6			5f	76
7			5g	68
8			5h	74
9			5i	77

little explored.^{52–55} Thus, the current mild protocol to allow the preparation of [3]cumulenes containing various substituent patterns from readily available building blocks is of high synthetic utility.

We envision that with a suitably tethered nucleophile, the conversion of 1,3-diyne to the corresponding conjugated allenyl imidamide and imidates would promote an intramolecular Michael-type addition (Table 4).^{56–60} Under standard conditions, homo-propargyl alcohol-containing 1,3-diyne **6a** and **6b** were smoothly converted to tetrahydrofuran-ylidene imidates **7a** and **7b** in 48% and 87% yield, respectively (entries 1 and 2). The corresponding homopropargyl sulfonamide **6c** led to 1-tosylpyrrolidinylidene imidamide **7c** in 72% yield (entry 3), however, forming 6-membered ring **7d** from **6d** failed (entry 4). 1,3-Diyne **6e** and **6f** substituted with a phenyl group containing an *ortho*-OH or NH_2 participated in the cascade reaction to generate benzofuran-ylidene imidamide **7e** in 70% and indolyl imidamide **7f** in 64% yield, respectively (entries 5 and 6).

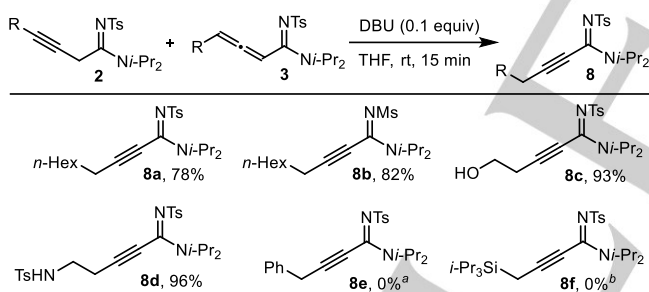
Table 4. Synthesis of heterocycles via intramolecular trapping of the putative allene intermediate.

Entry		1,3-Diyne 6	Conditions	Heterocycle 7	Yield (%)
1		6a , R = H	A	7a	48
2		6b , R = Me	A	7b	87
3		6c , n = 1	A	7c	72
4		6d , n = 2	A	7d	0
5		6e , X = O	B	7e	70
6		6f , X = NH	B	7f	64

^a Condition **A**: TsN₃ (1.2 equiv), Et₃N (2 equiv), MeOH (10 equiv), 12 h.

^b Condition **B**: TsN₃ (1.2 equiv), *i*-Pr₂NH (1.2 equiv), 4 h.

Although expected, migration of the triple bond from 3-alkynyl or 2,3-dienyl isomers to the corresponding 2-alkynyl isomer **8** was not observed under the conditions regardless of the reaction time. However, because of the thermodynamic preference for 2-alkynyl isomers, we surmised that the isomerization of **2** or **3** to **8** would happen if a stronger base than secondary amines is used (Scheme 4).⁶¹ Indeed, treating a mixture of **2** and **3** with DBU (0.1 equiv) rapidly induced isomerization to provide 2-alkynyl imidamides **8a–d**. On the other hand, phenyl- and silyl-substituted 3-alkynyl imidamides **2** and **3** did not isomerize to the corresponding 2-alkynyl isomers **8e** and **8f**.



^a Decomposition of starting materials. ^b 3-Alkynyl imidamide **2** was recovered.

Scheme 4. Isomerization of 3-alkynyl and 2,3-dienyl imidamides to the corresponding 2-alkynyl isomers.

In conclusion, we have developed efficient protocols to generate discreet isomers of 2-alkynyl, 3-alkynyl, 2,3-dienyl, and 2,3,4-trienyl imidamides and imidates from copper-catalyzed reactions of 1,3-diynes and tosylazide. The selectivity between 3-alkynyl and 2,3-dienyl imidamides could be controlled by a heteroatom substituent at the propargylic position of the 1,3-diynes and employing different trapping reagent such as amines and alcohols. [3]Cumulene derivatives were also generated by employing 1,3-diynes that contain acetoxy or bezoyloxy substituent at the propargylic position. While trapping of the putative azacumulene intermediates with amines provided either 3-alkynyl or 2,3-dienyl imidamides depending on the structure of the trapping amines, trapping with methanol selectively generated 2,3-dienyl imidates. It was found that both 3-alkynyl

and 2,3-dienyl imidamides could be isomerized to selectively generate the corresponding 2-alkynyl isomers under equilibrating conditions with stronger base such as DBU. Intramolecular trapping of the putative azacumulene intermediates provided 5-membered heterocyclic products if 1,3-diyne substrates contain a homopropargylic hydroxy or amino substituent. A unique feature of this unprecedented click chemistry is that under mild reaction conditions, terminal 1,3-diynes could be selectively converted to different compounds of unsaturated carboxylic acid derivatives with good selectivity.

Acknowledgements

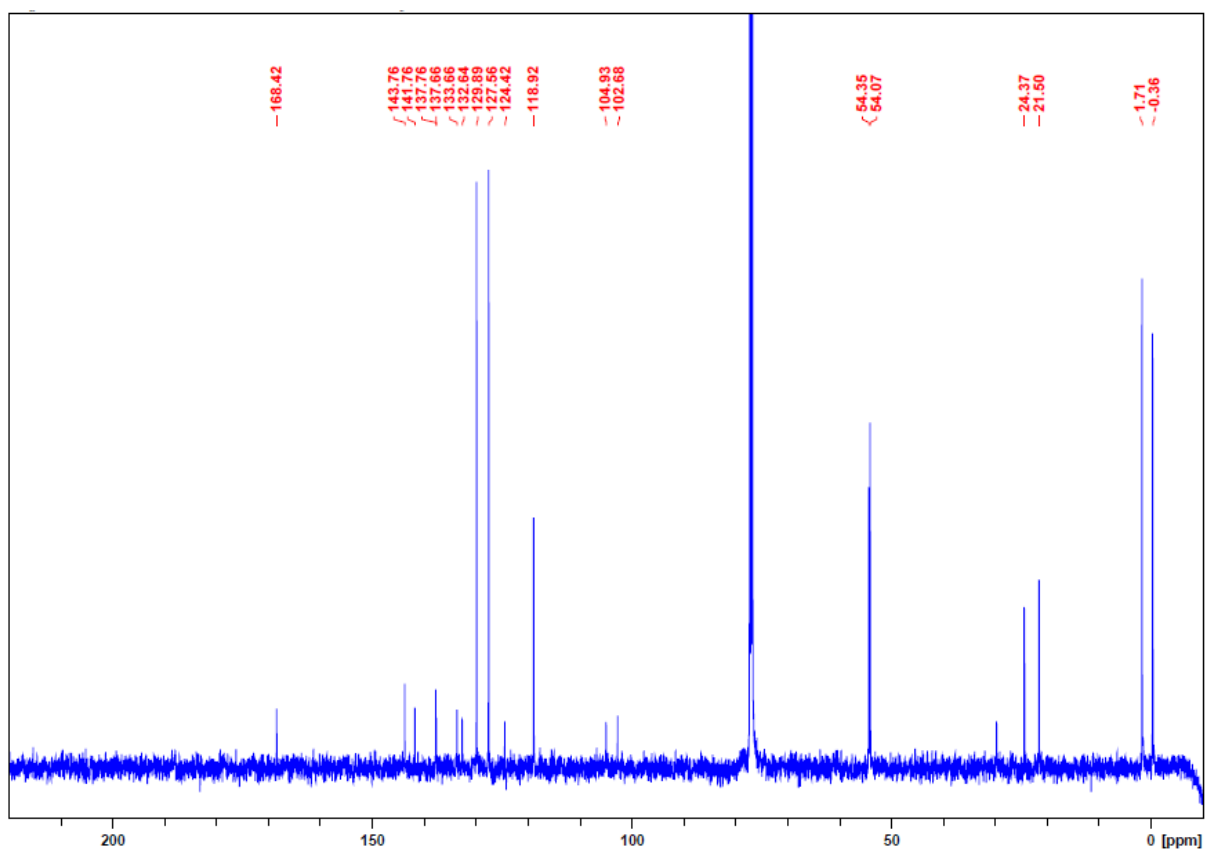
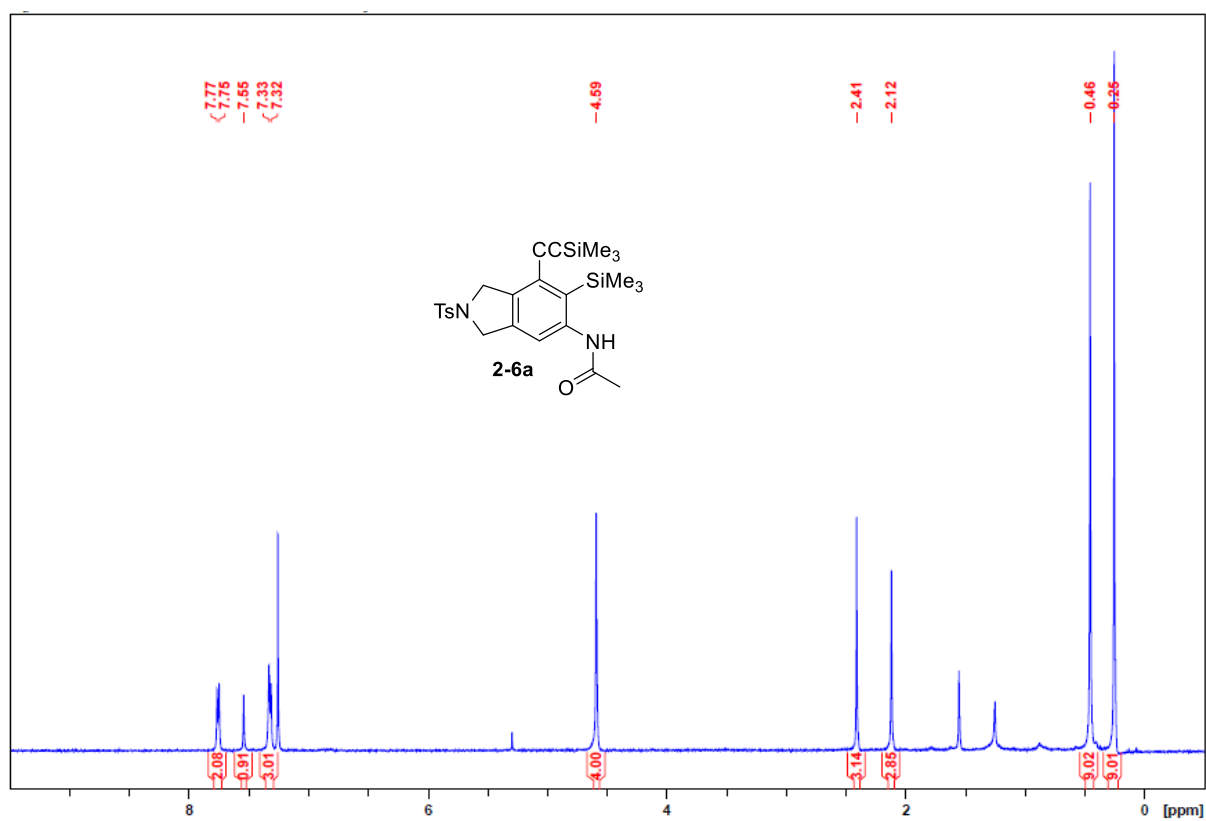
Authors thank NSF (CHE-1764141) for financial supports. The Mass Spectrometry Laboratory at UIUC is acknowledged.

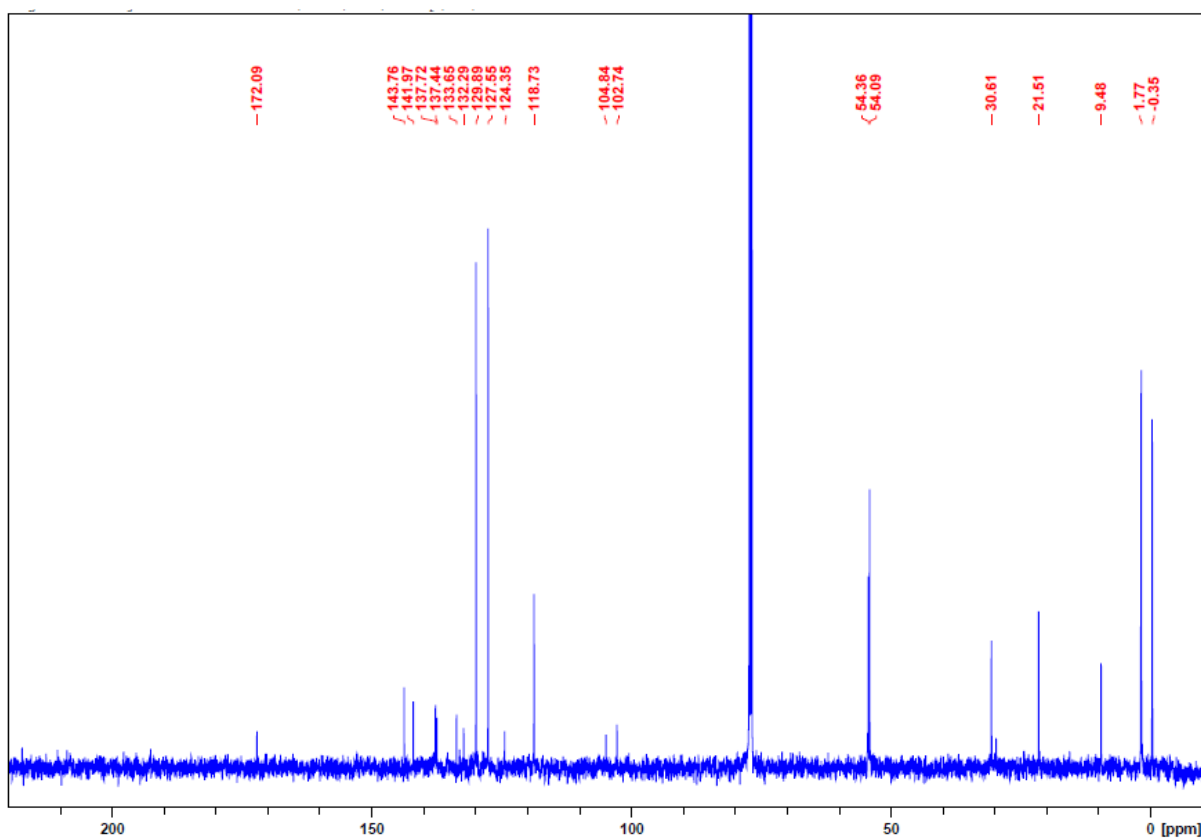
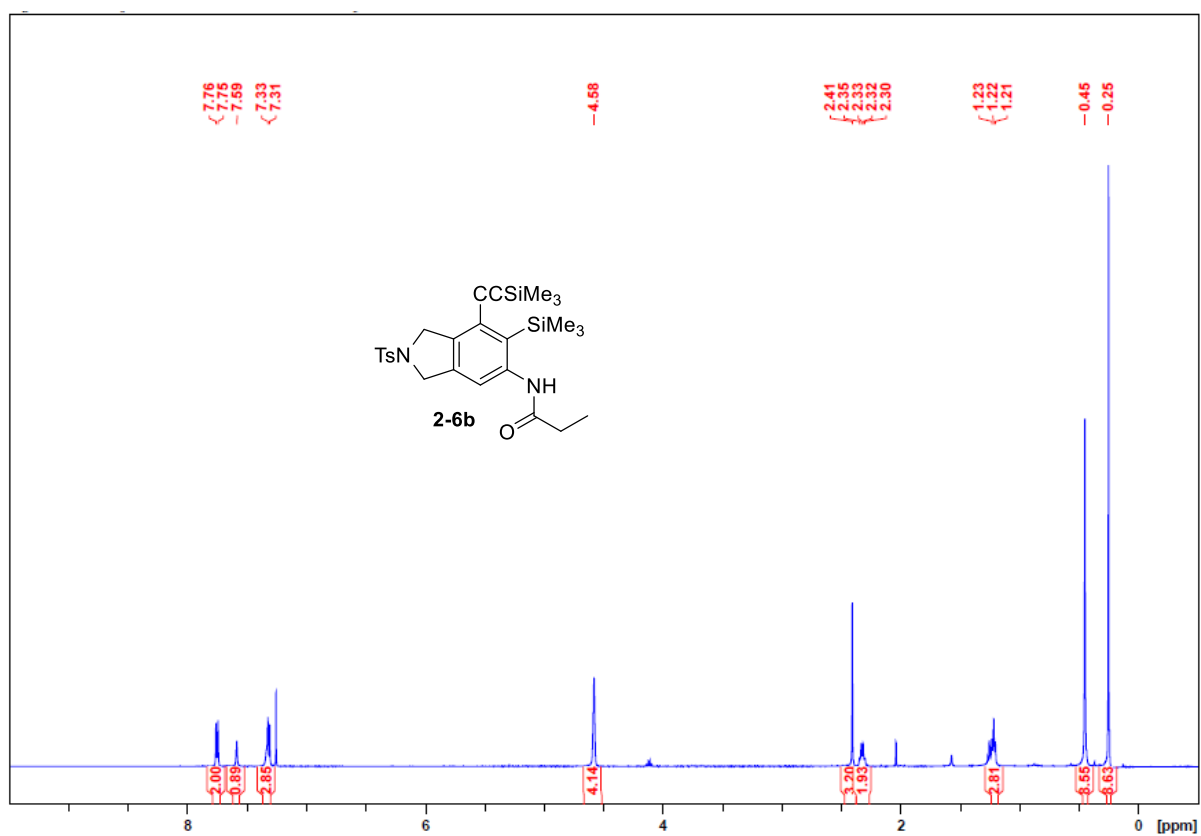
Keywords: allenes • copper • azides • [3]cumulenes • click chemistry

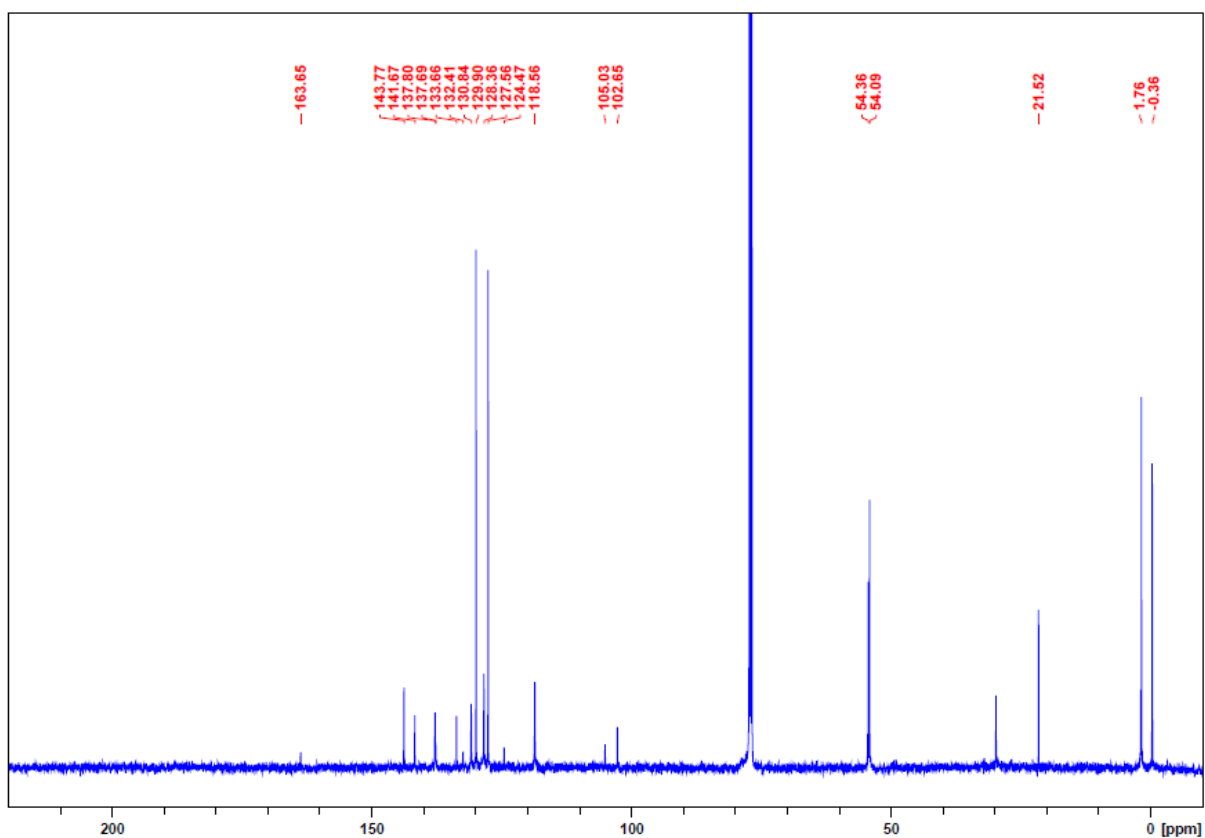
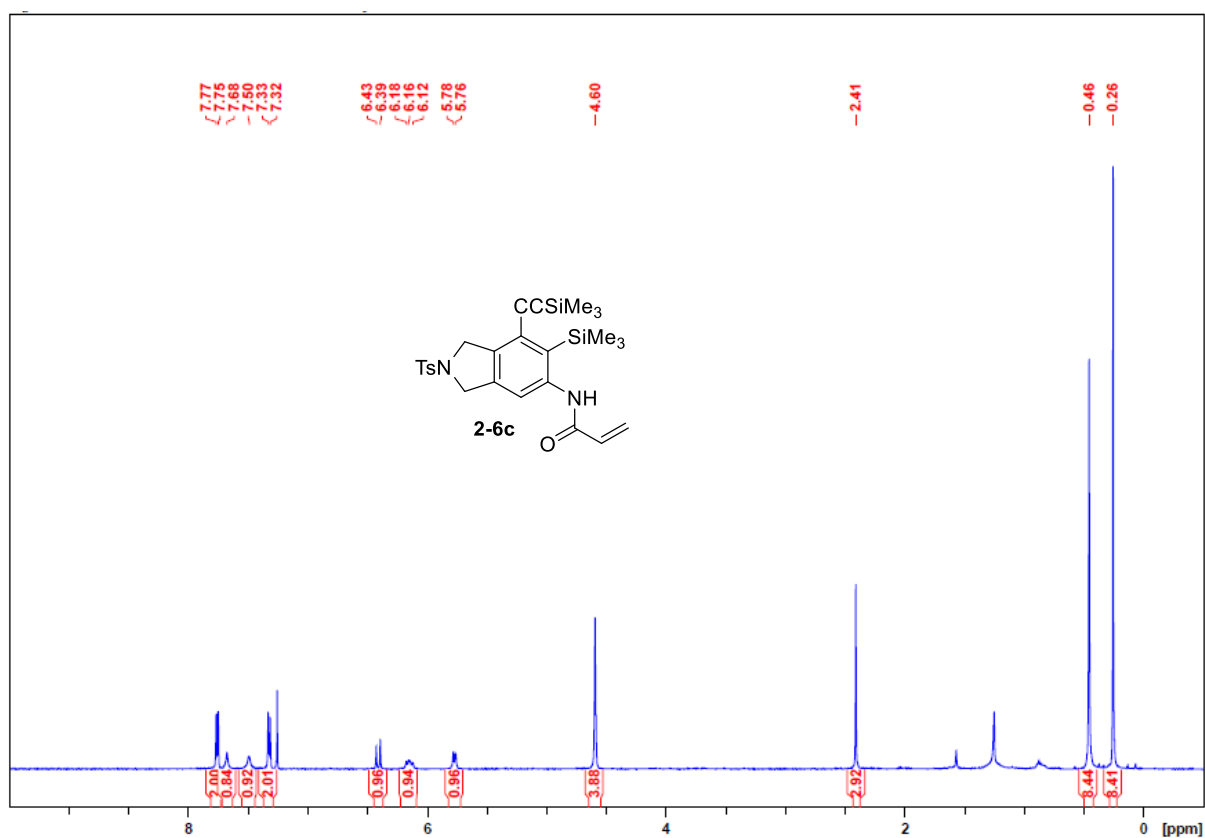
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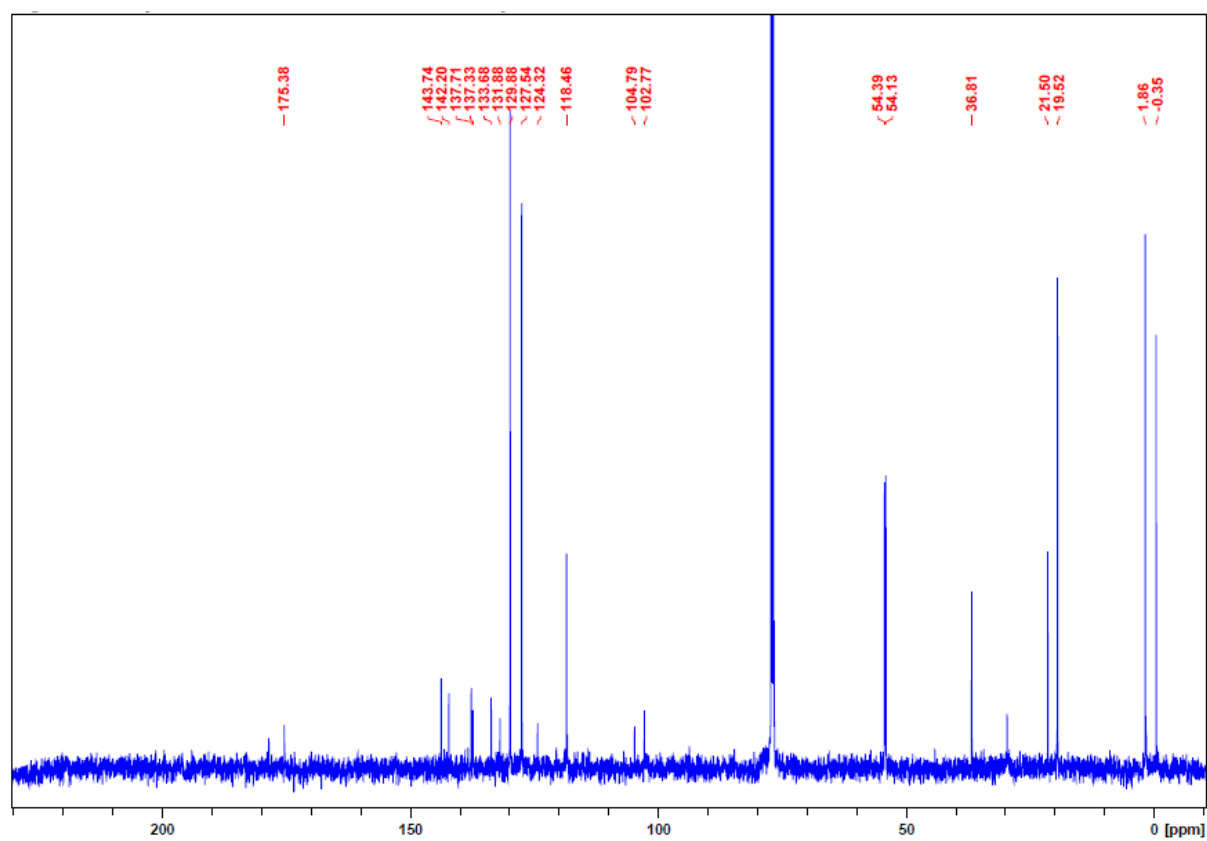
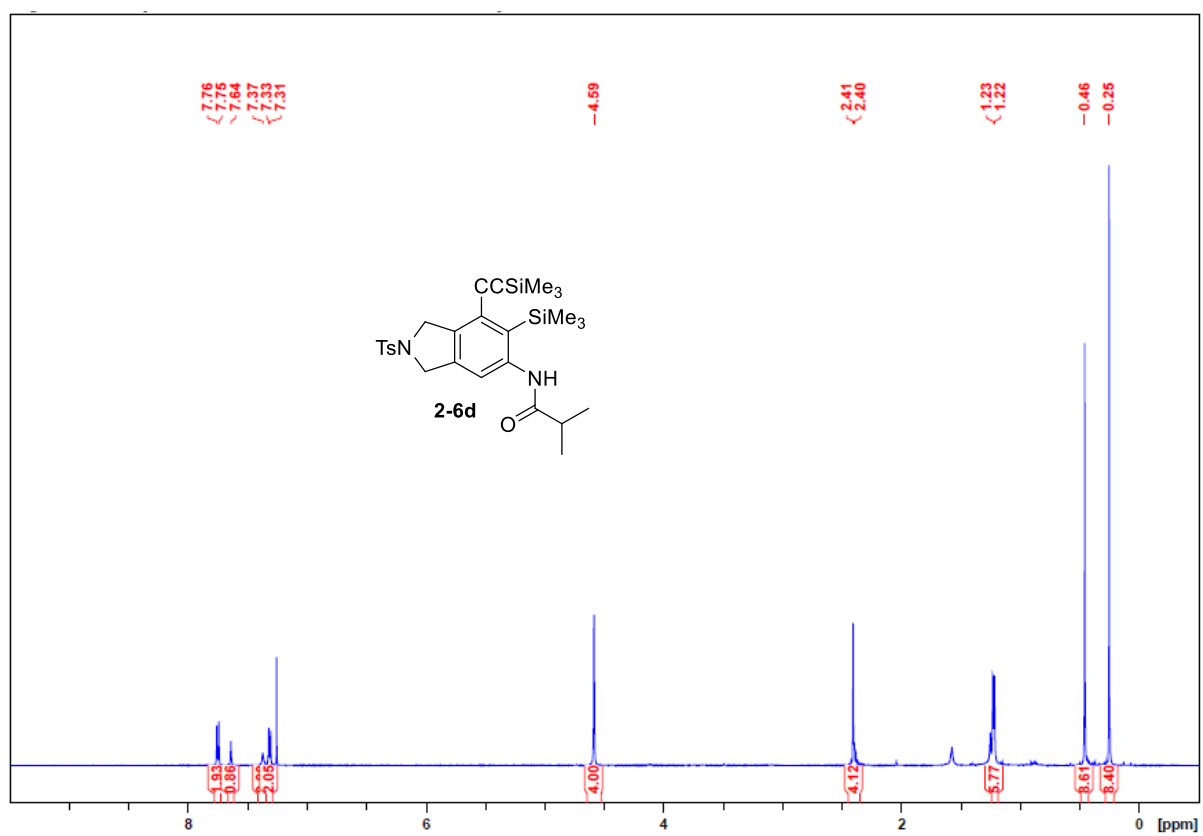
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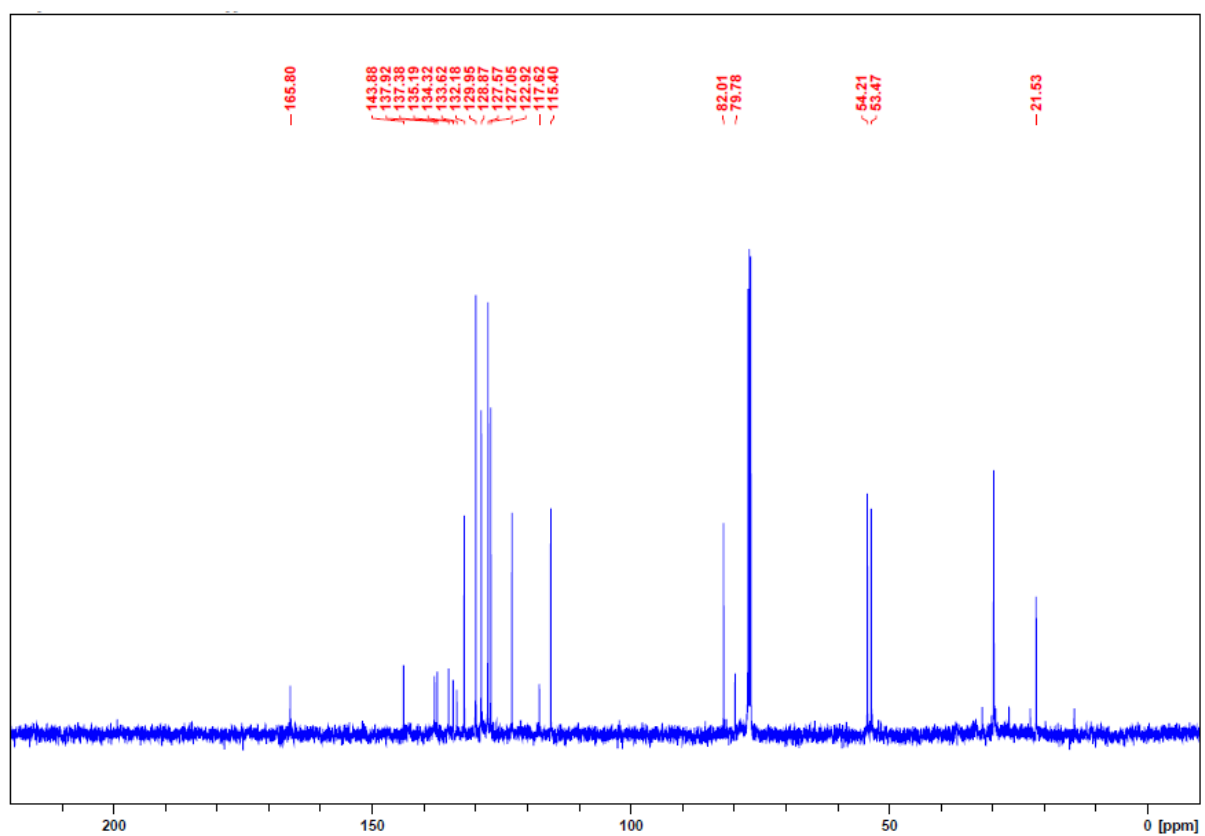
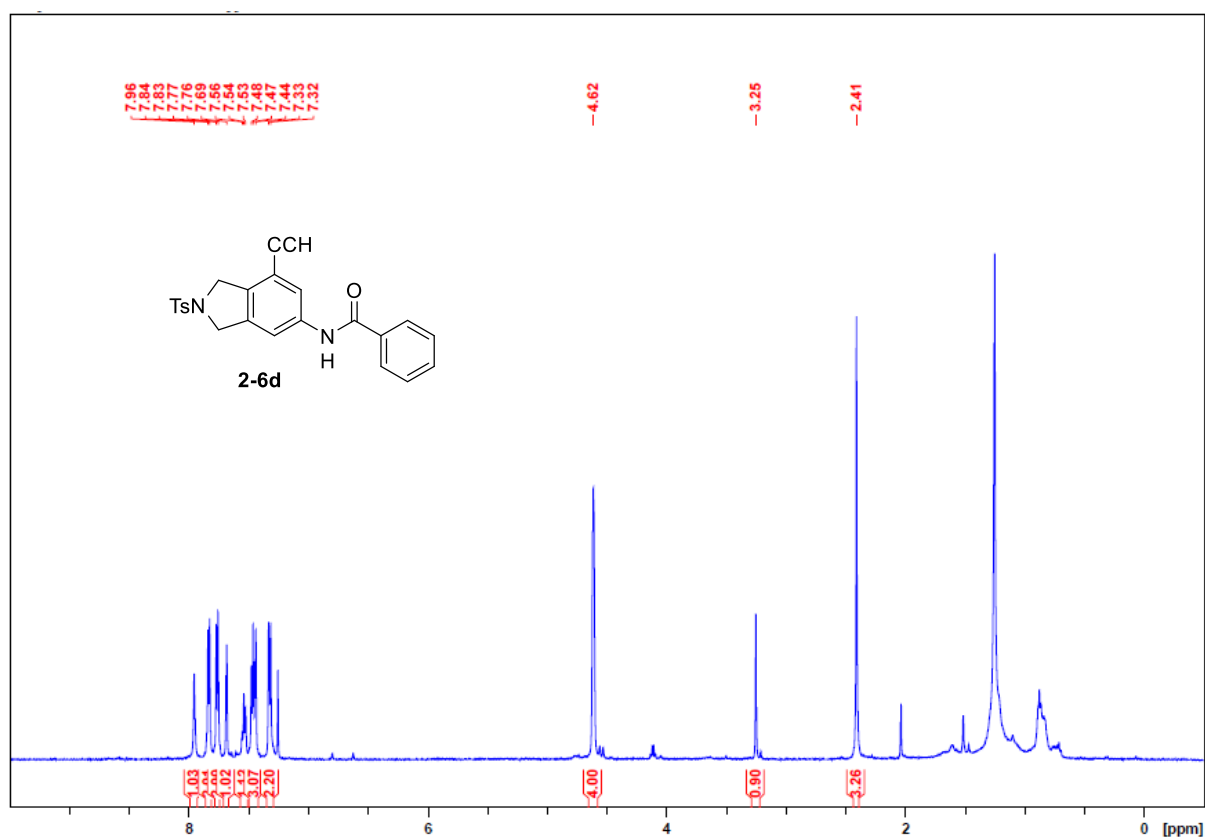
Appendix I
Selected NMR Spectra for Chapter 2

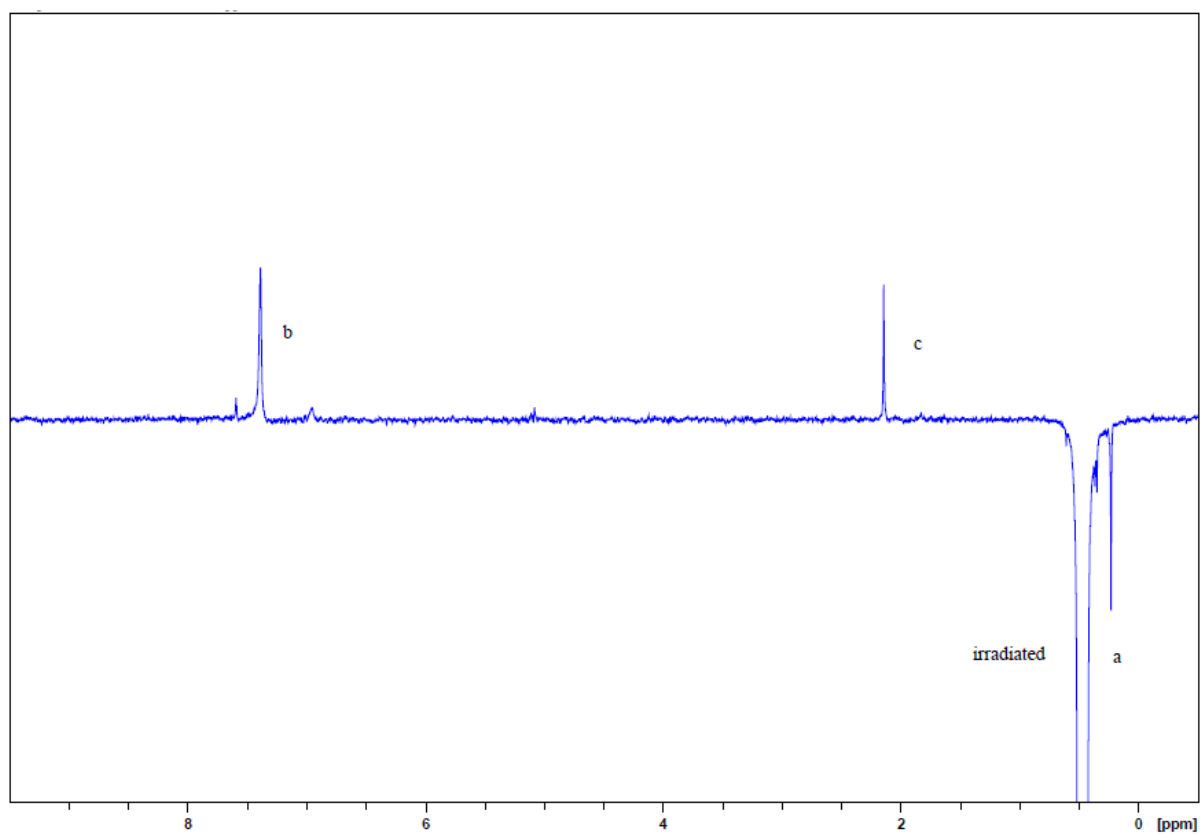
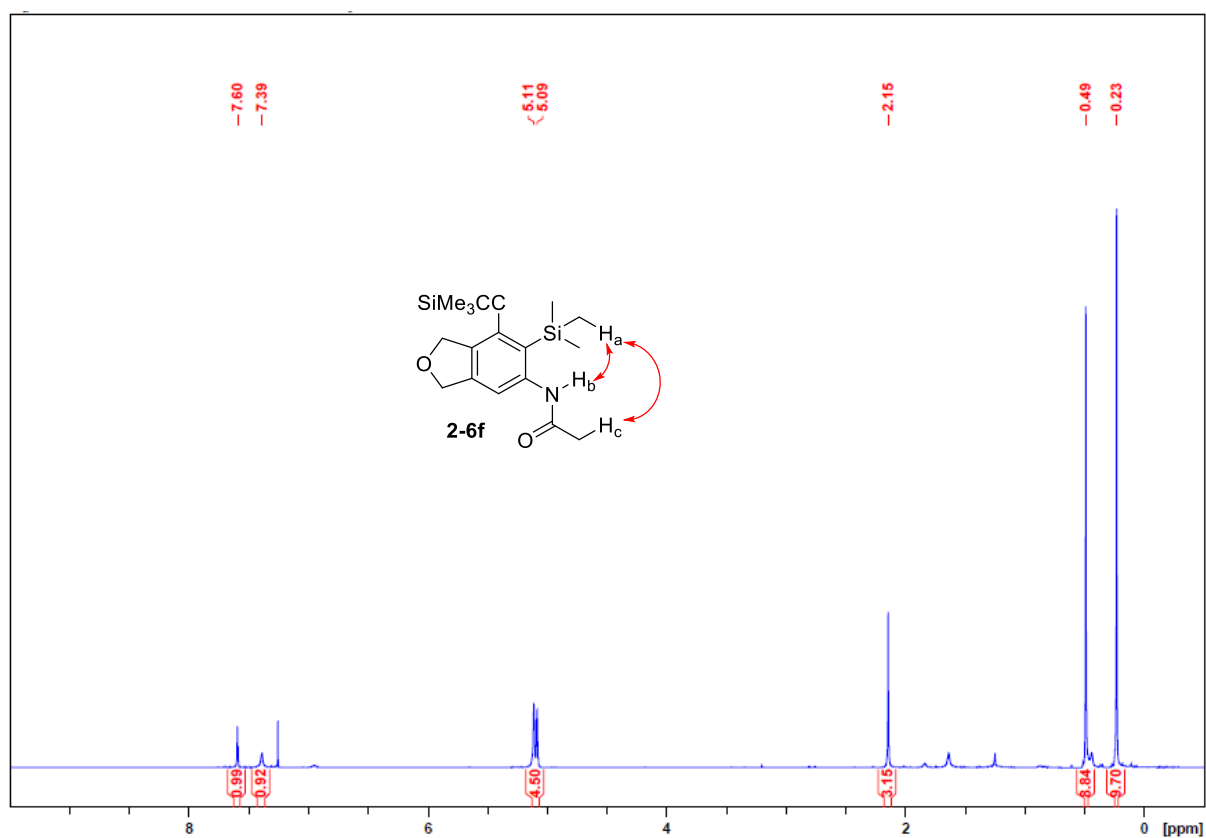


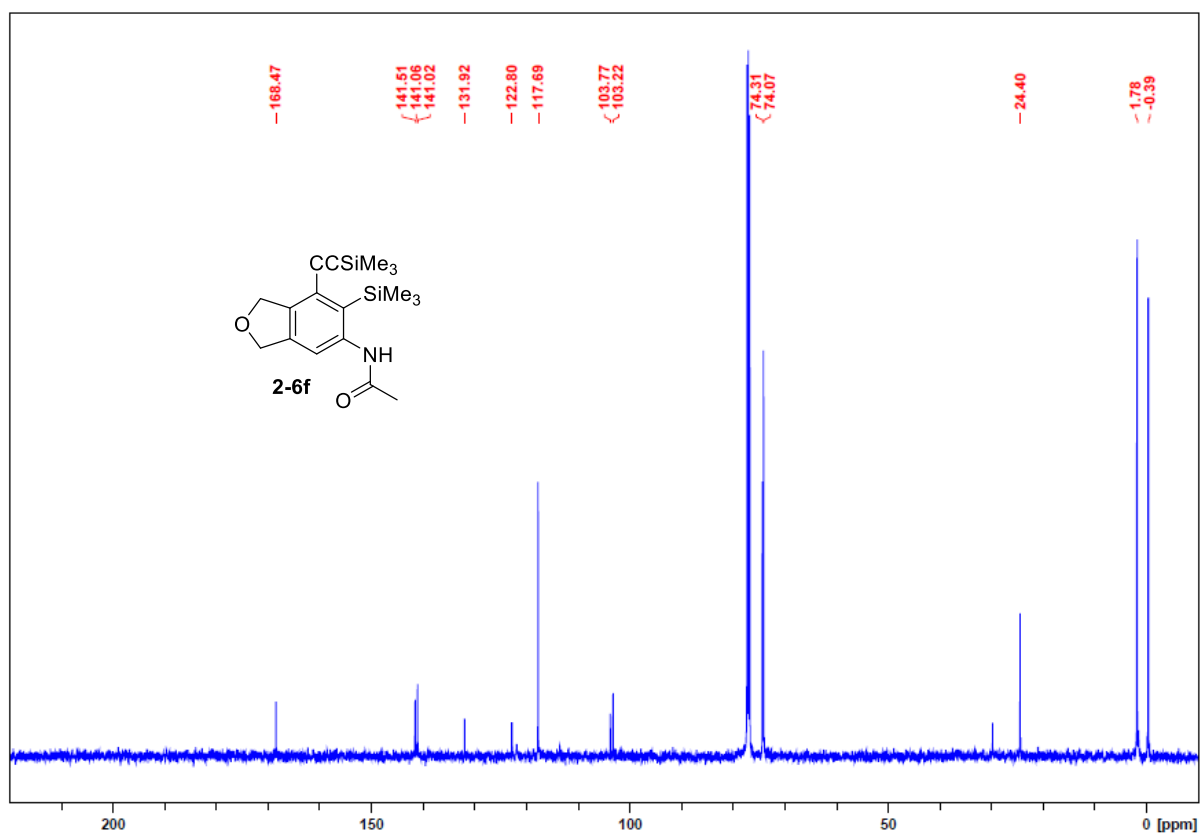


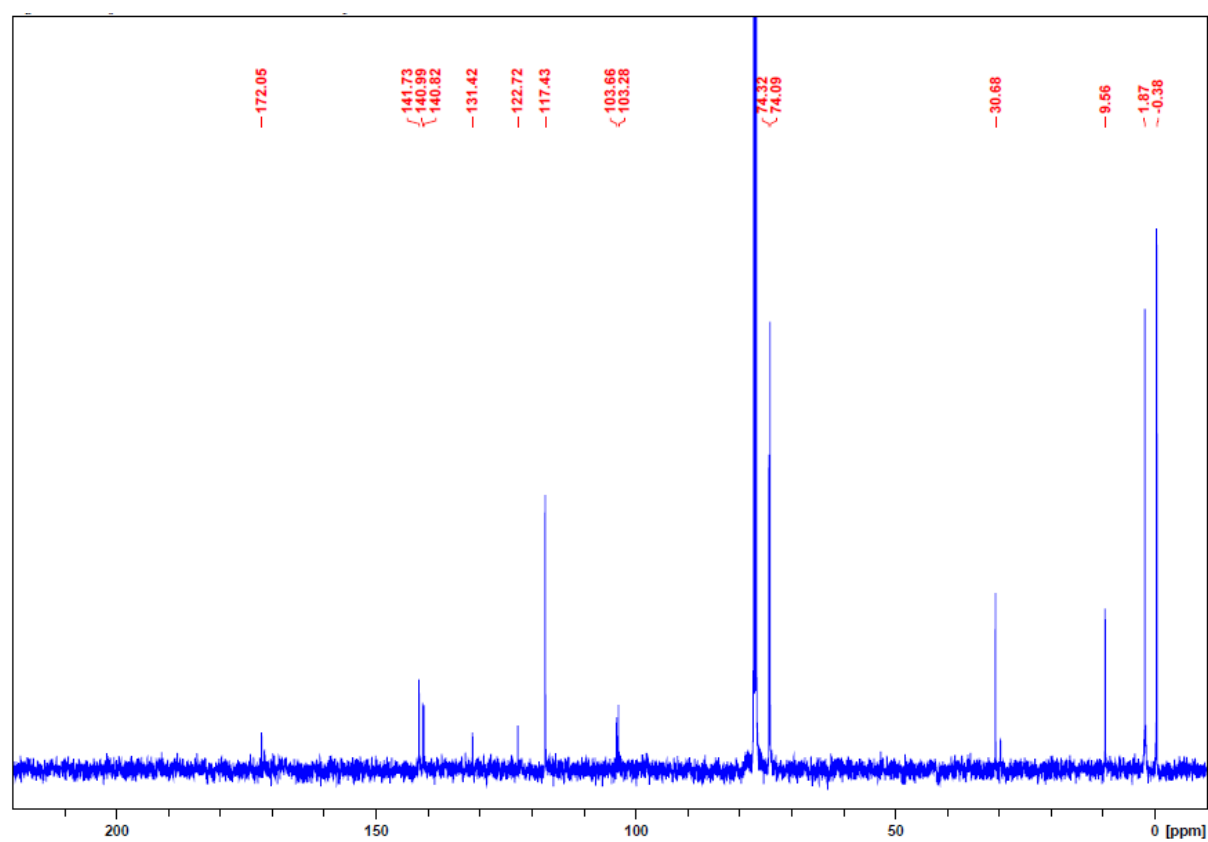
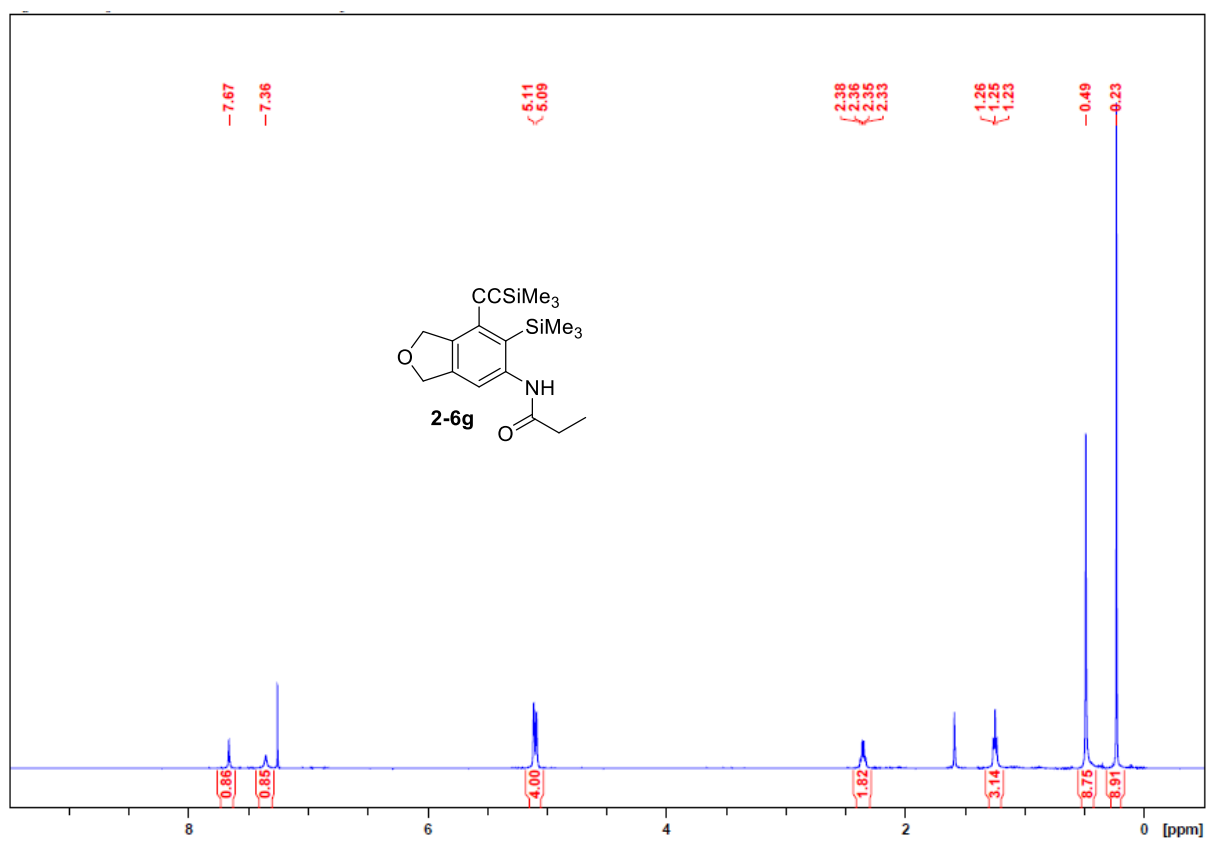


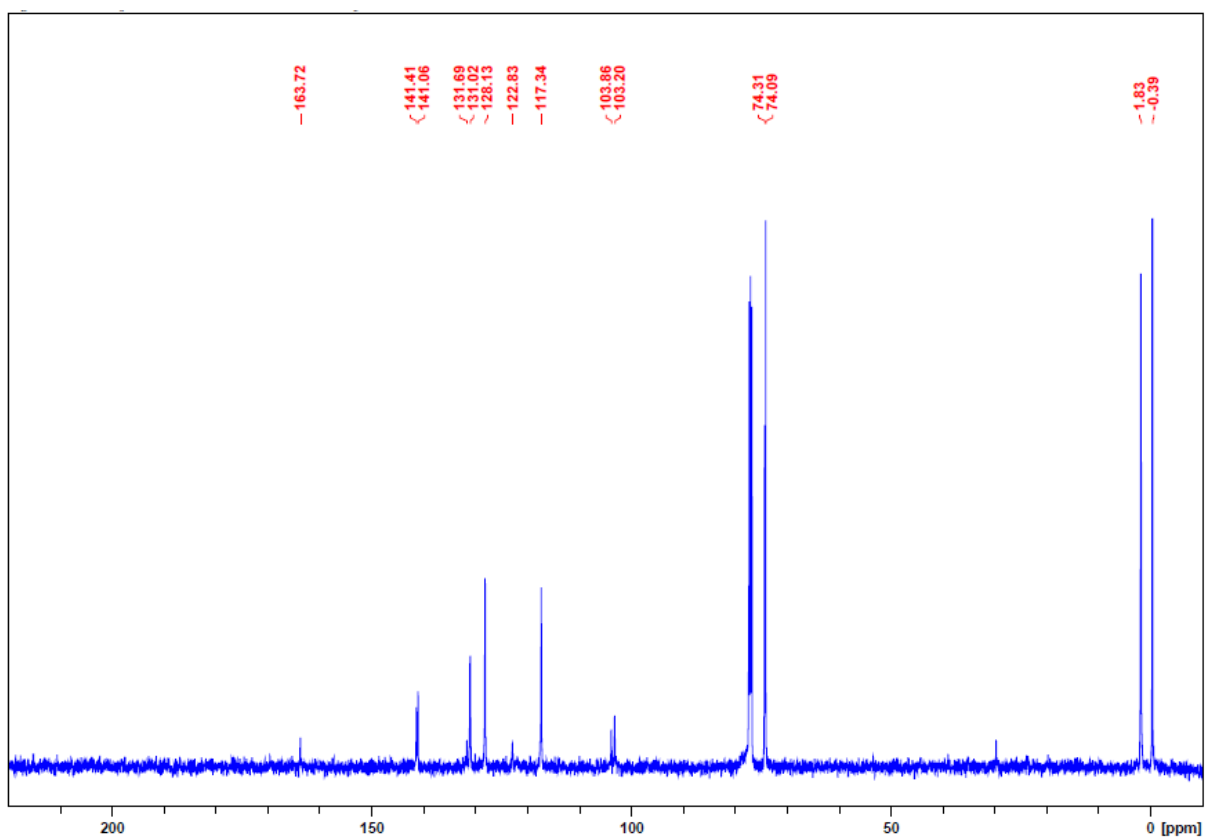
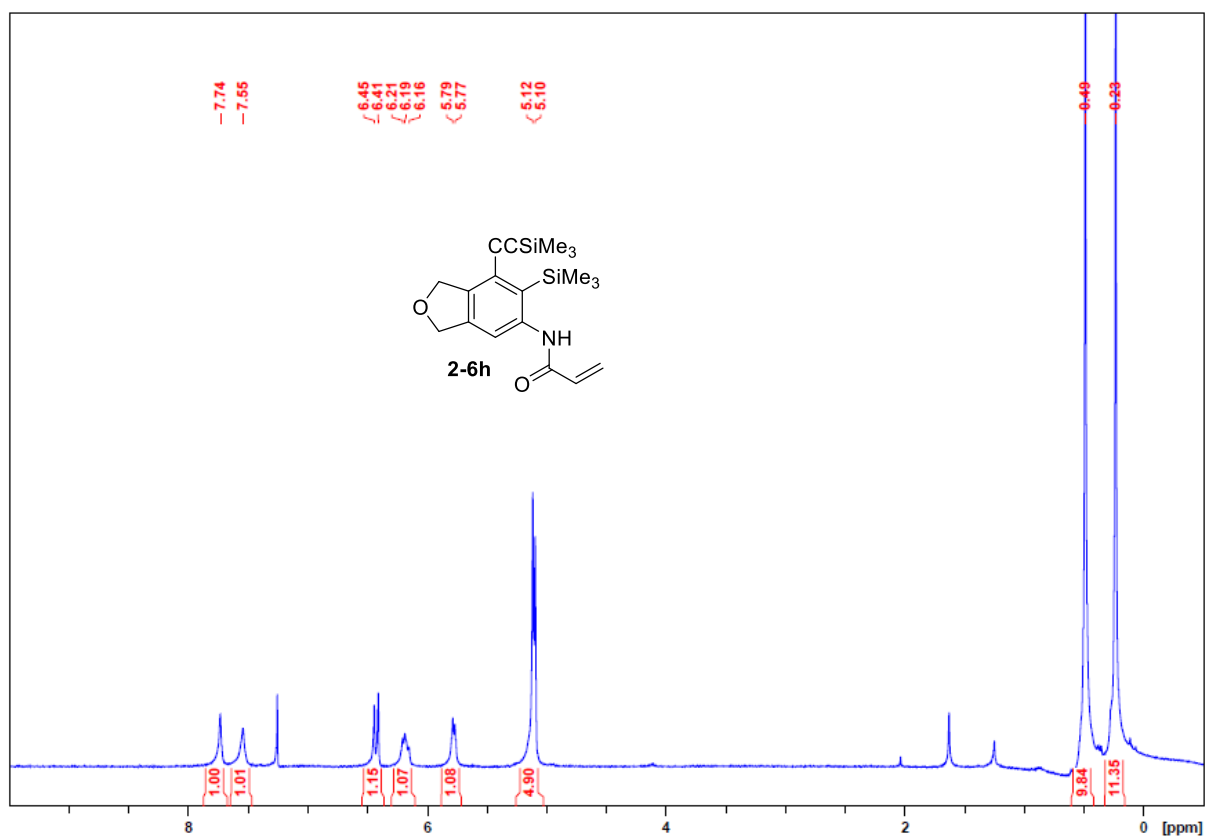


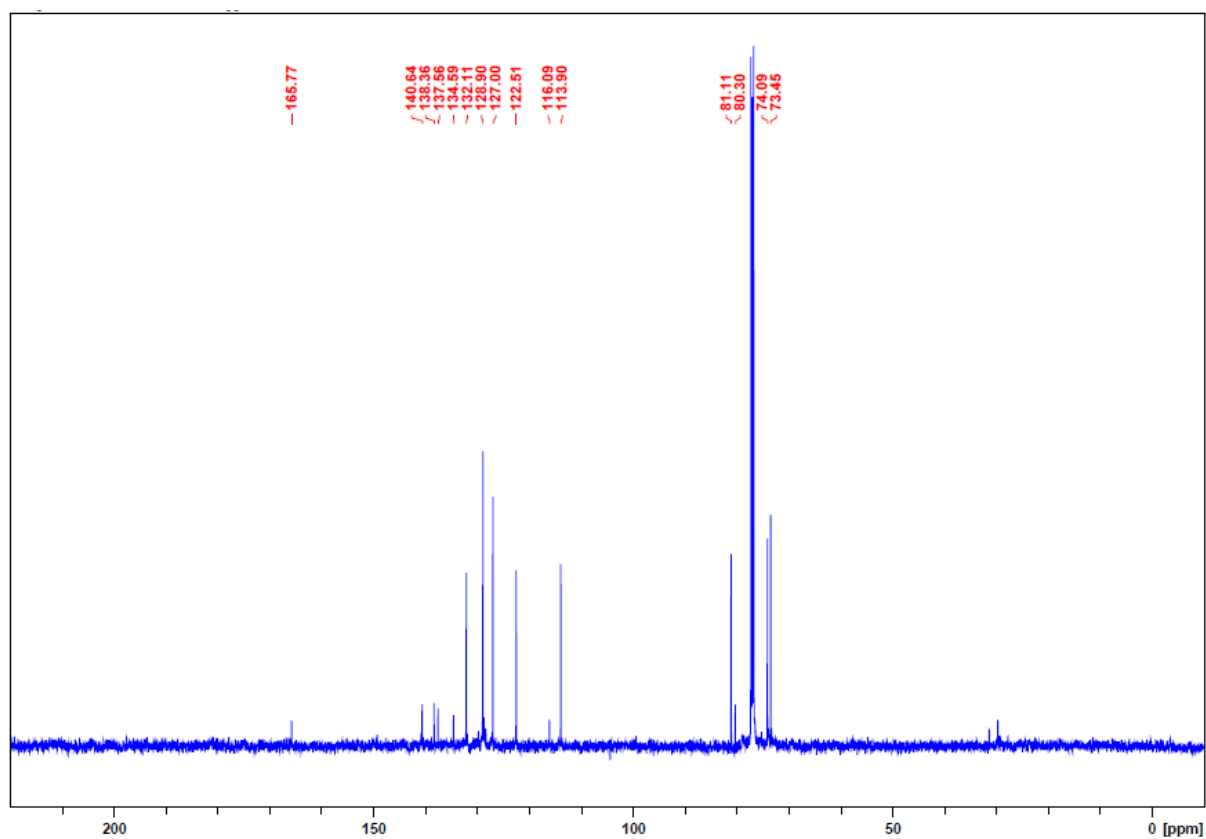
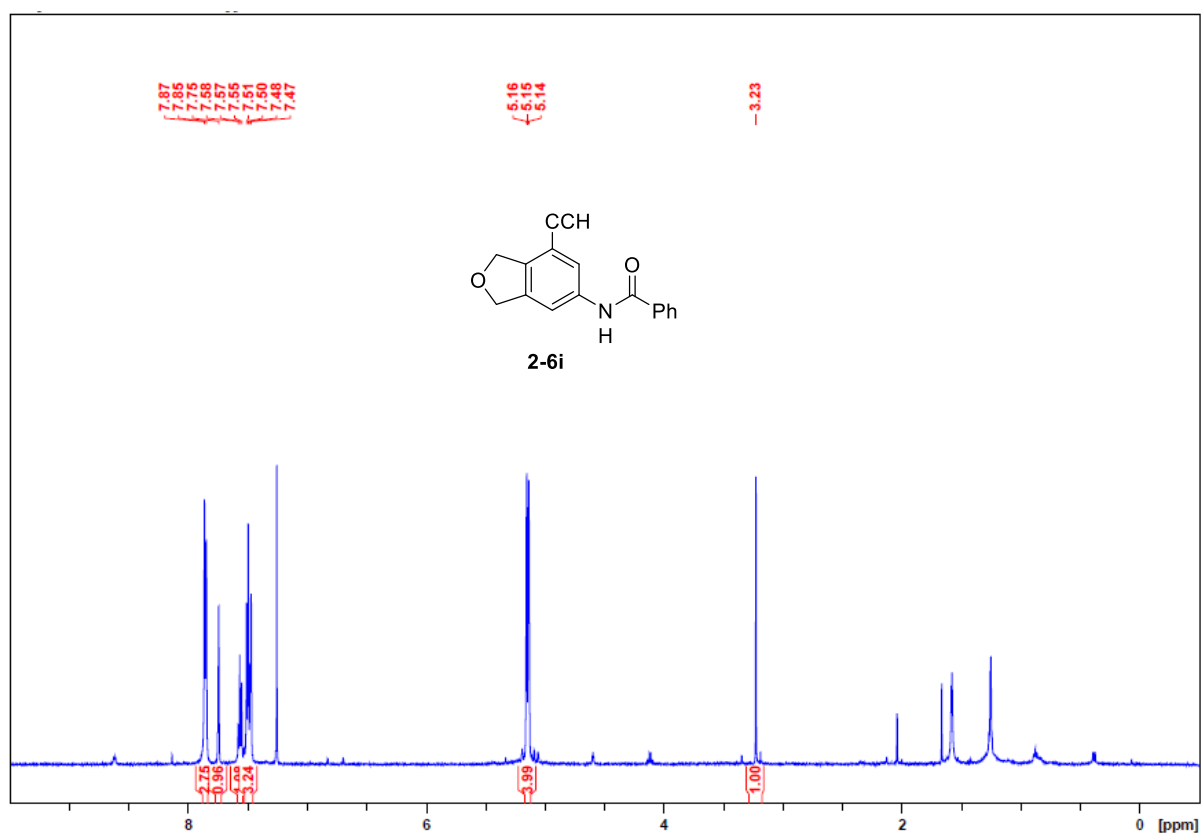


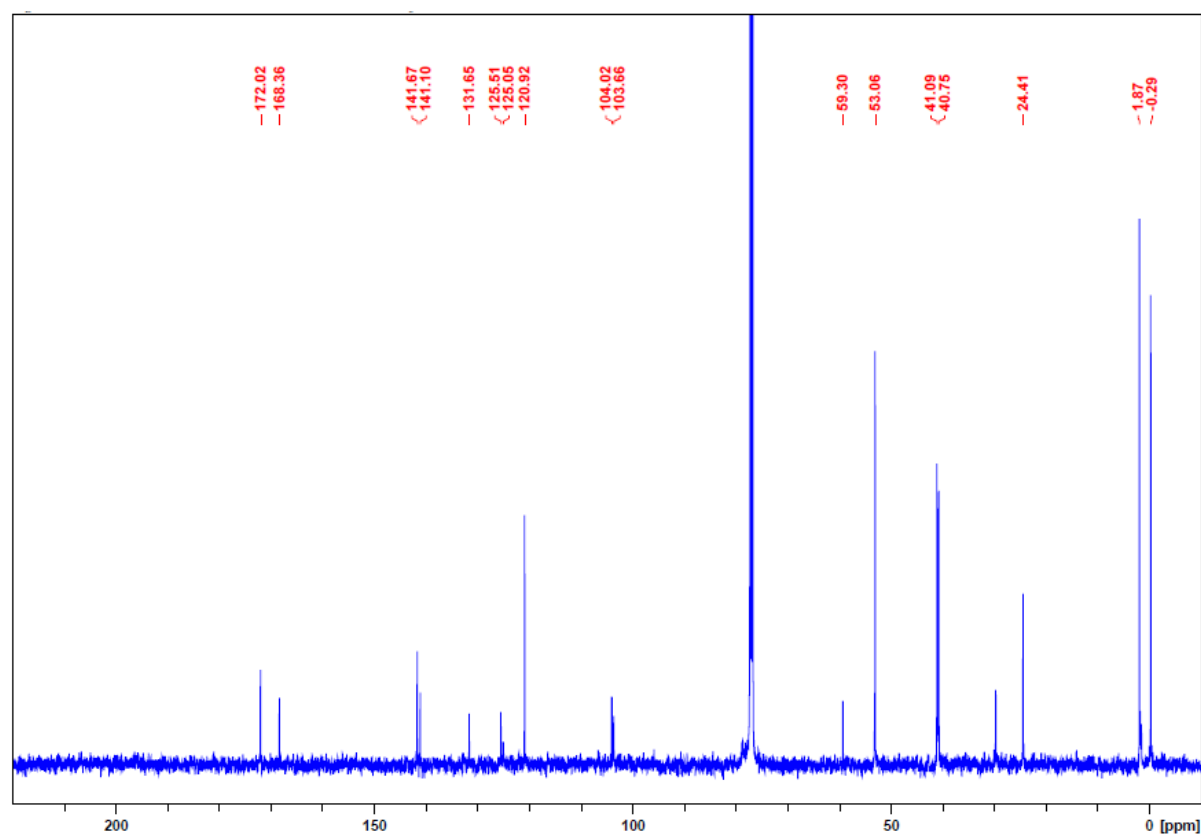
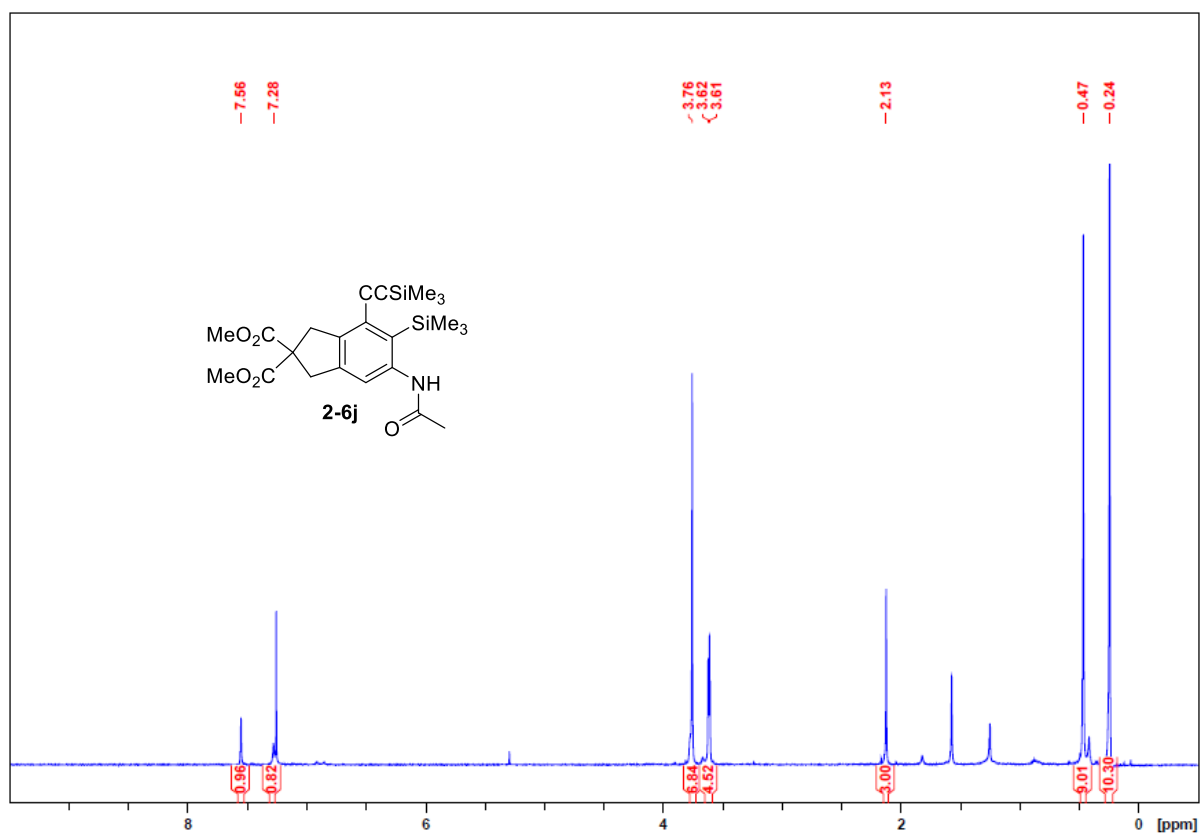


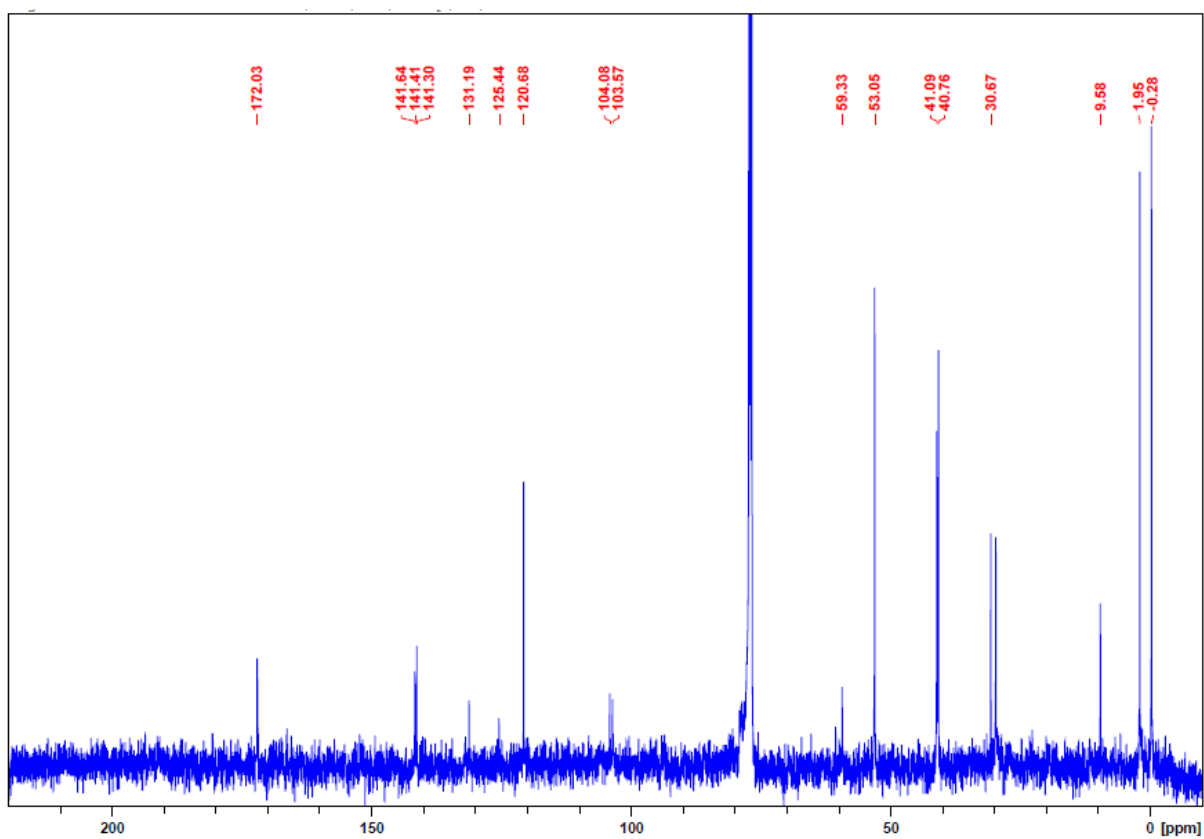
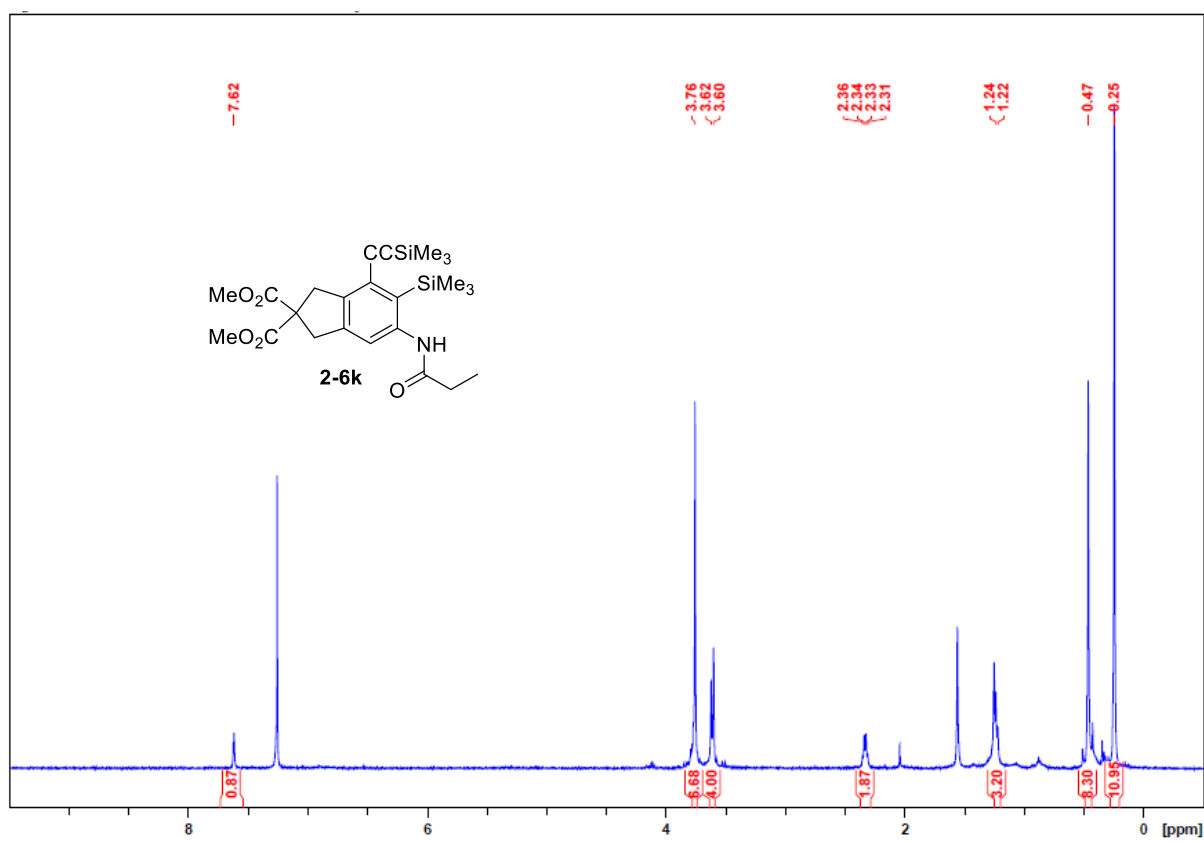


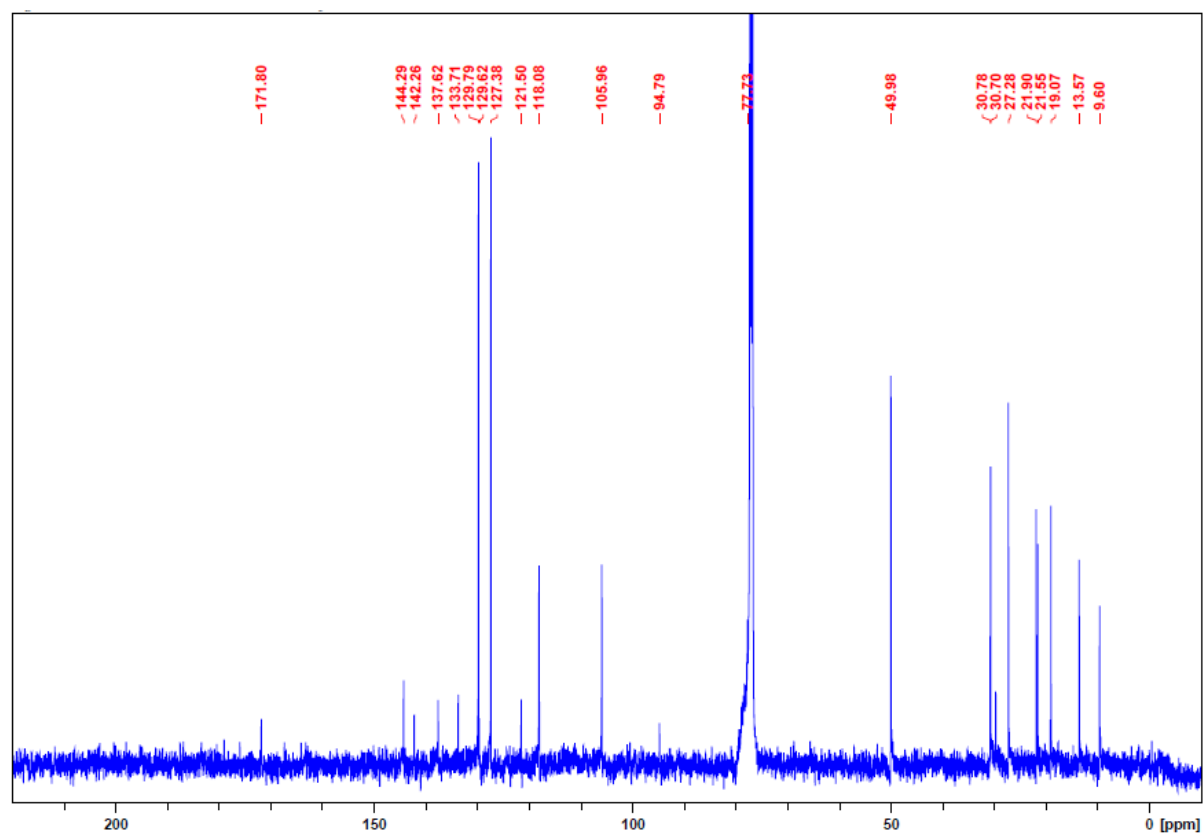
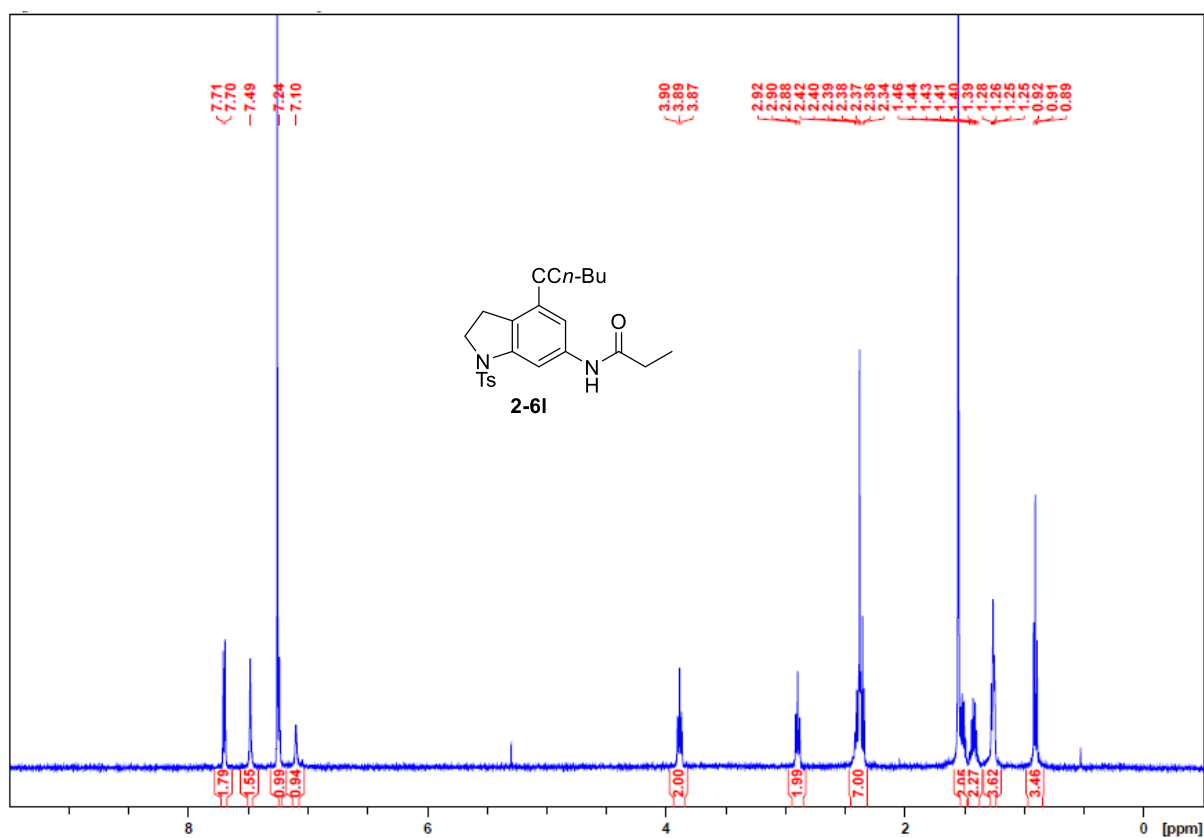


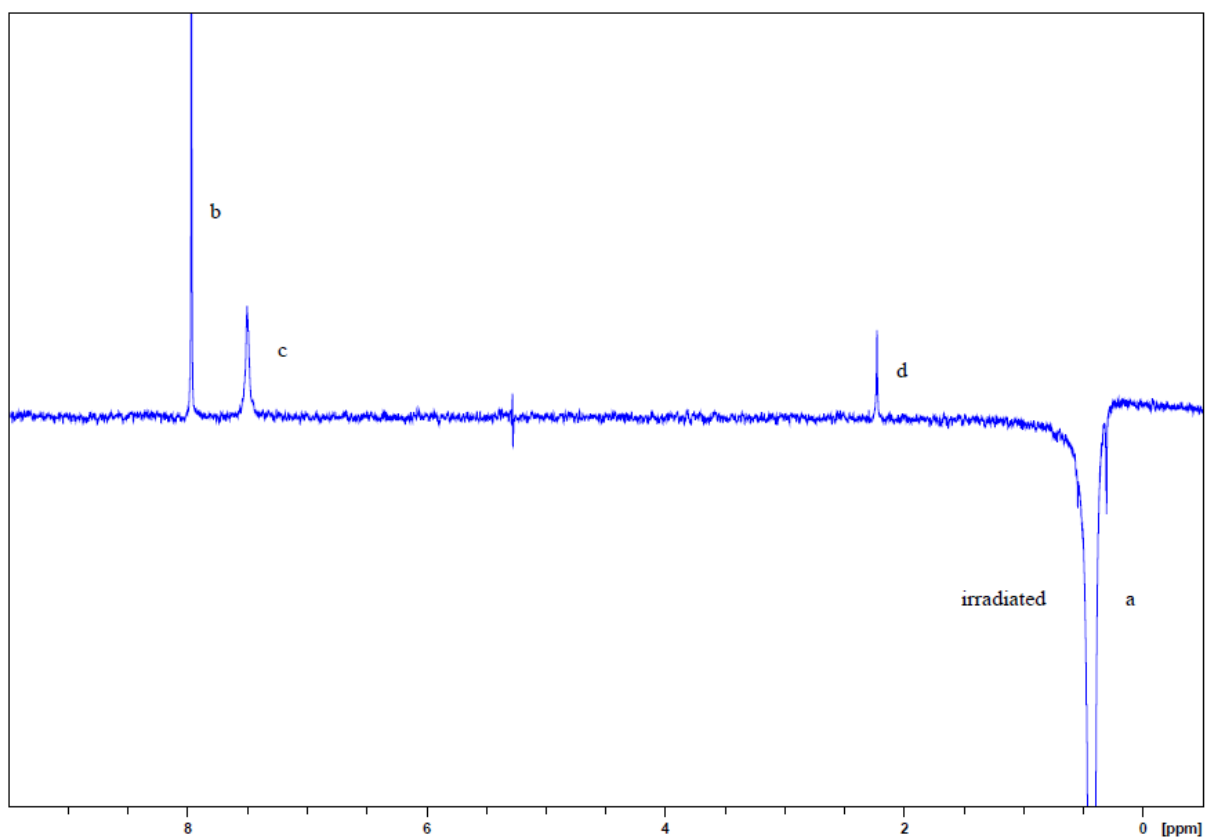
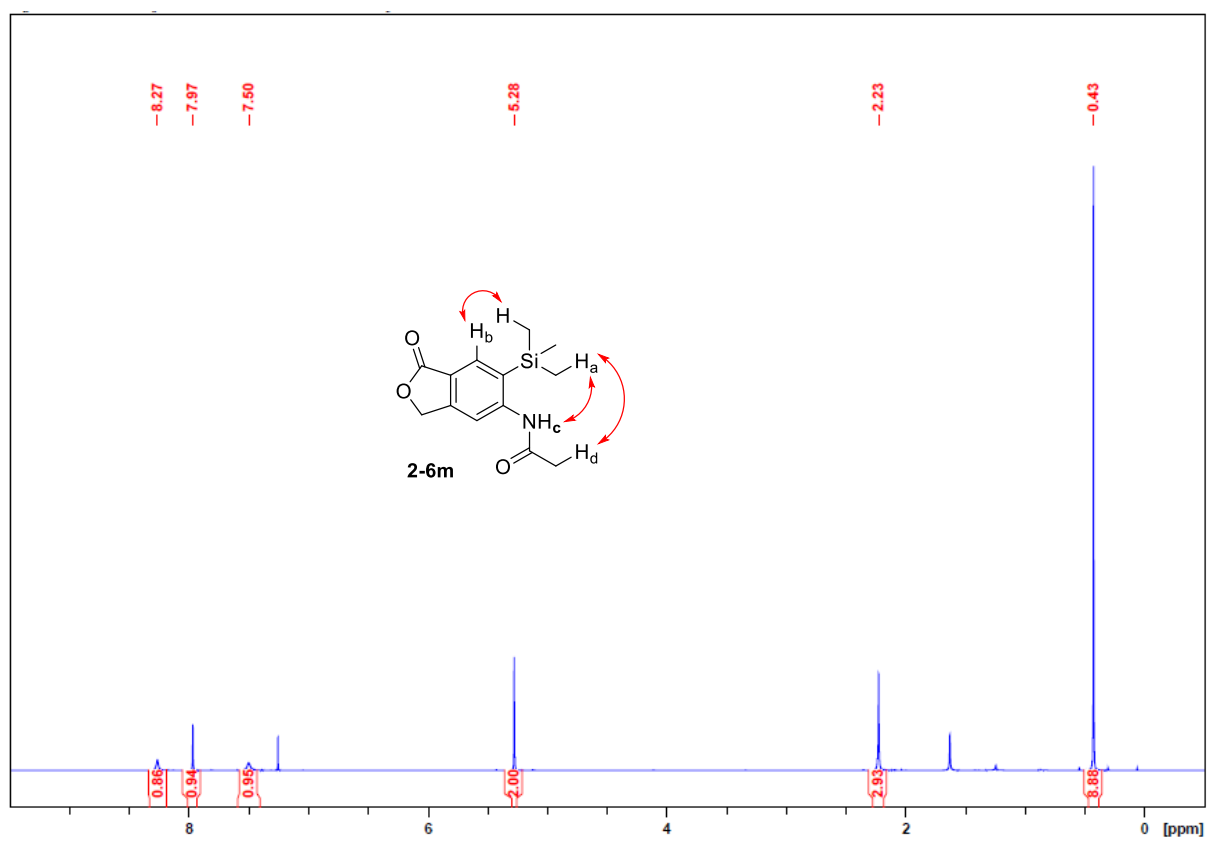


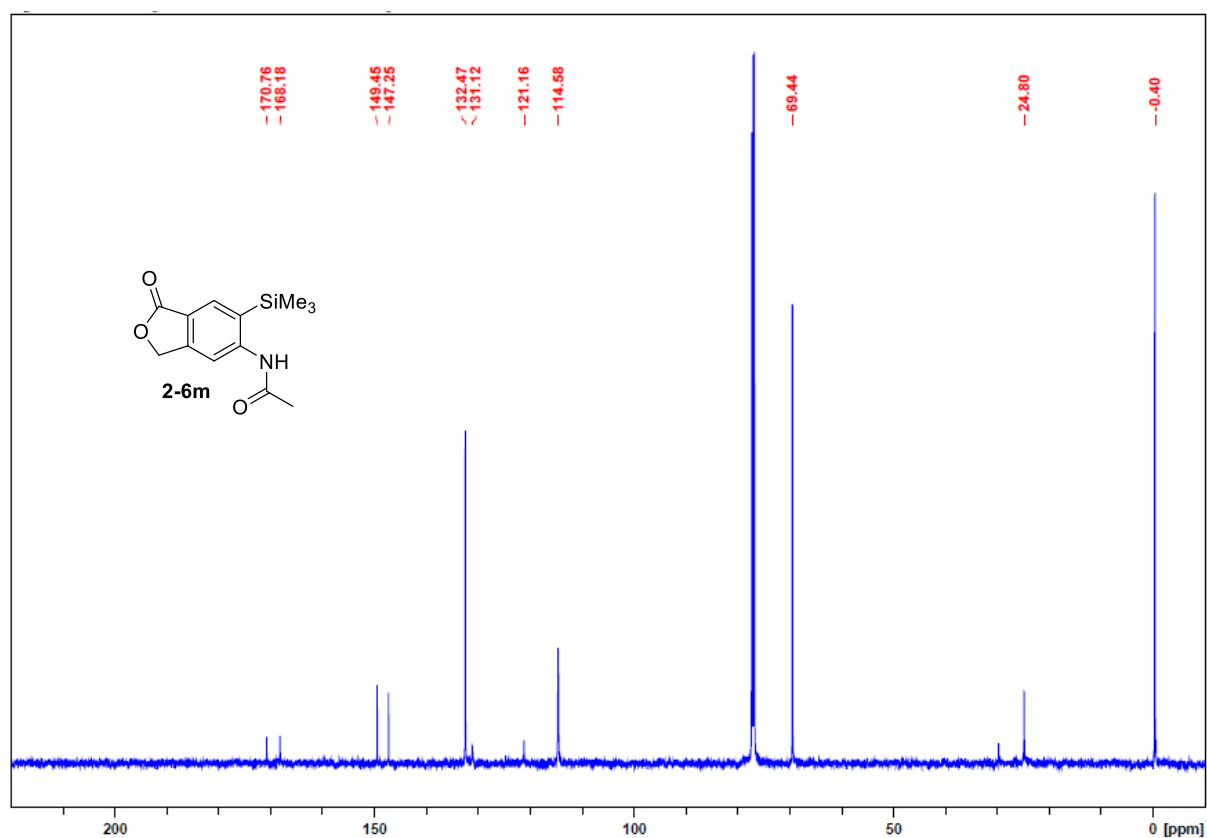


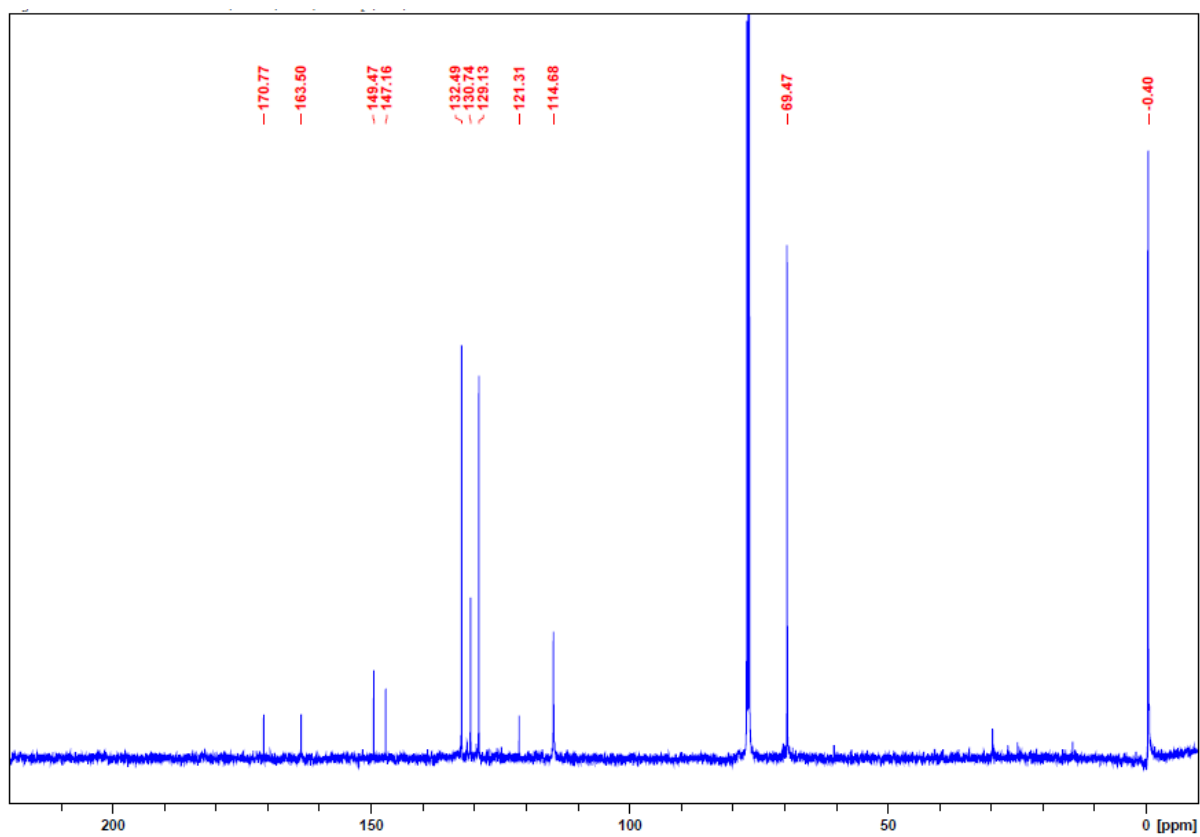
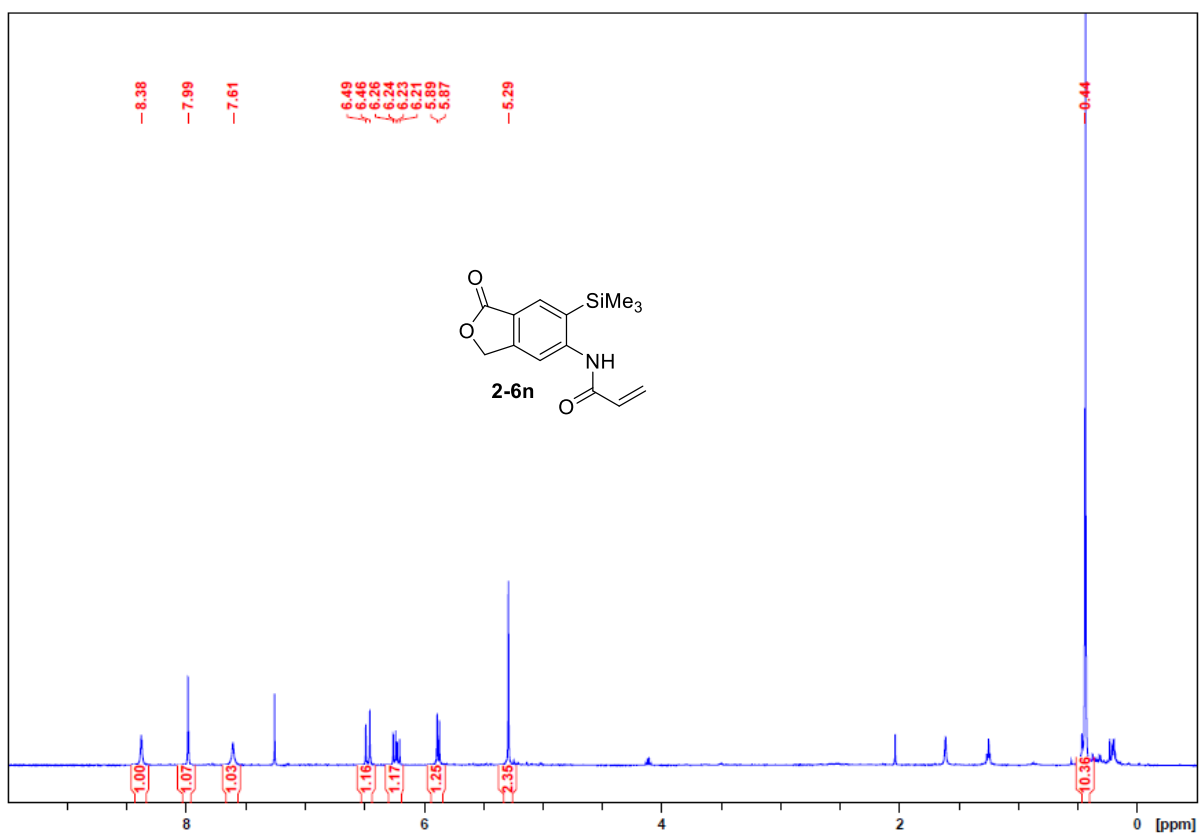


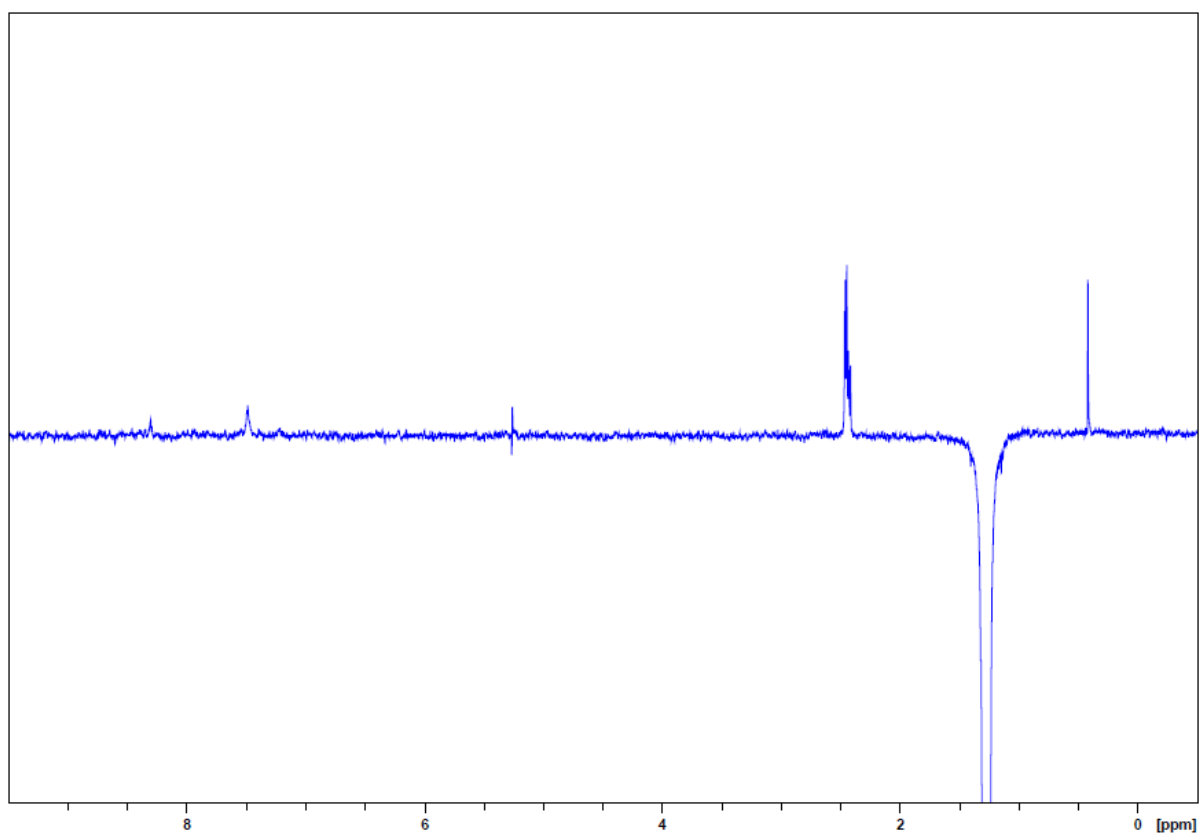
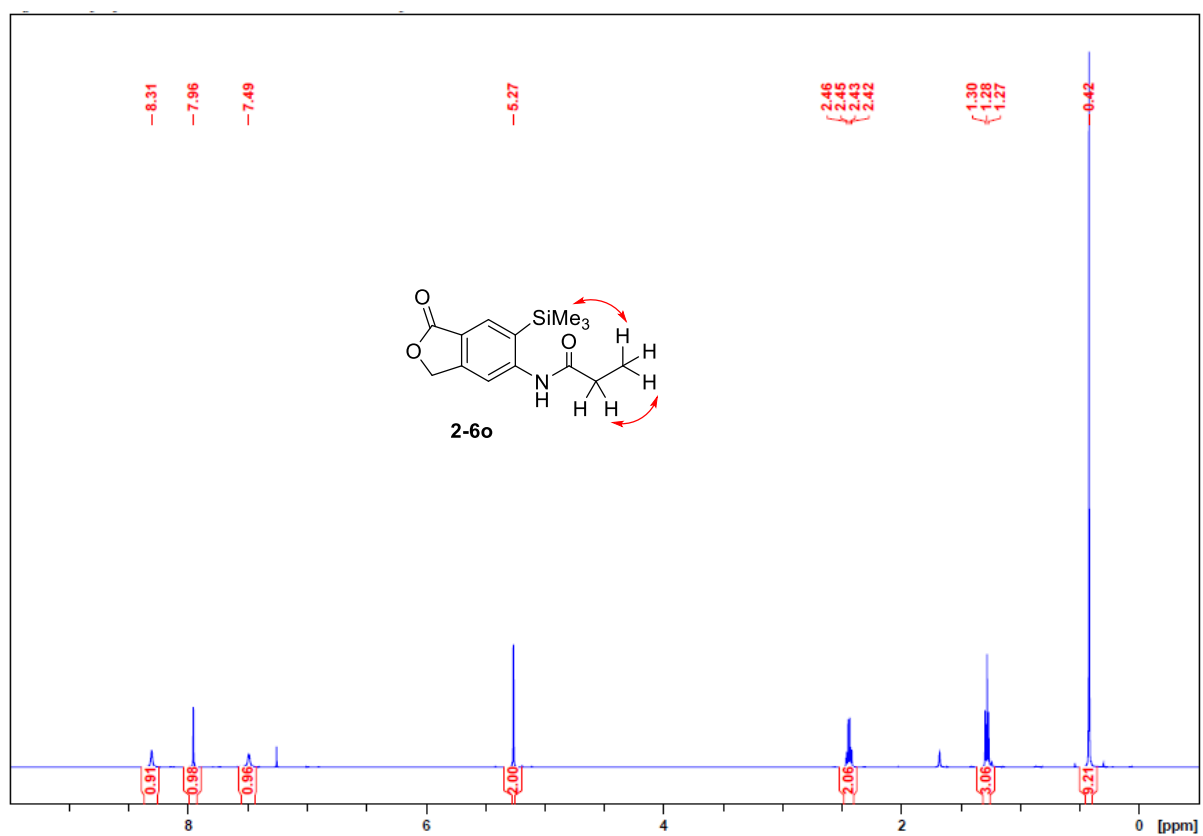


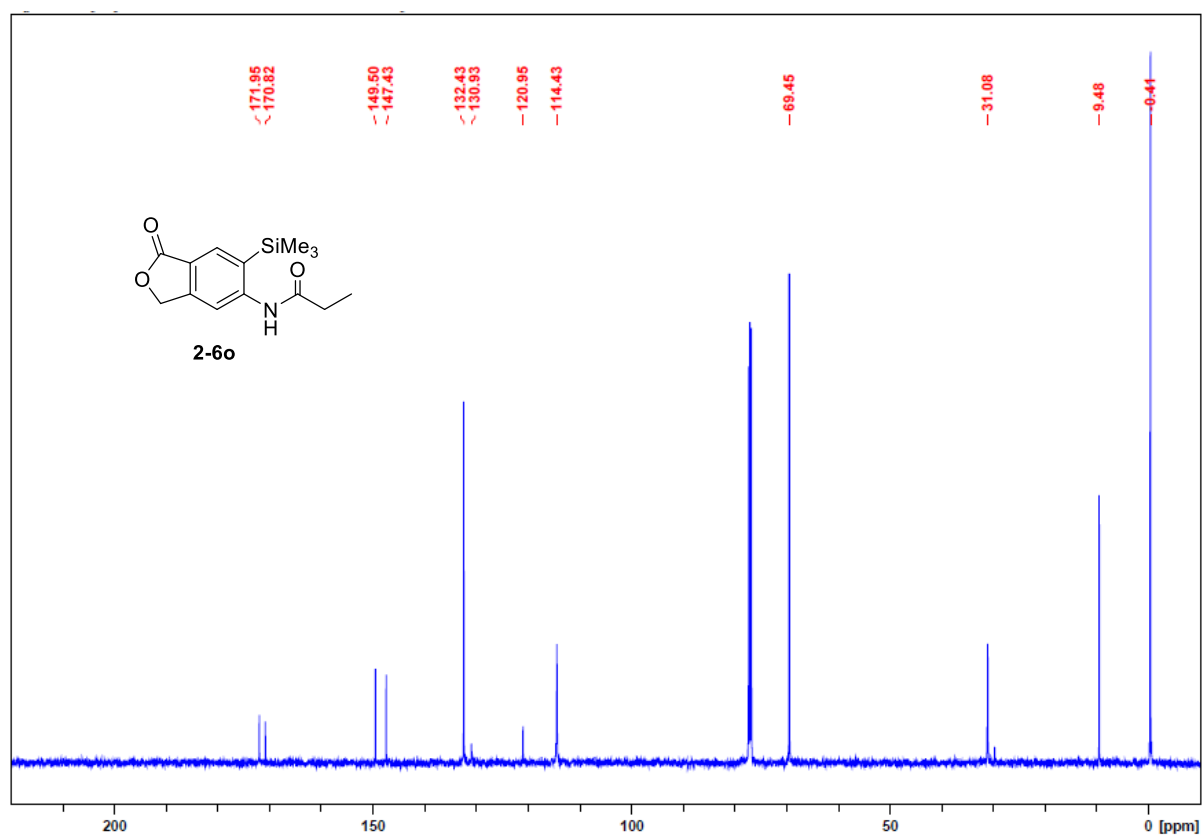


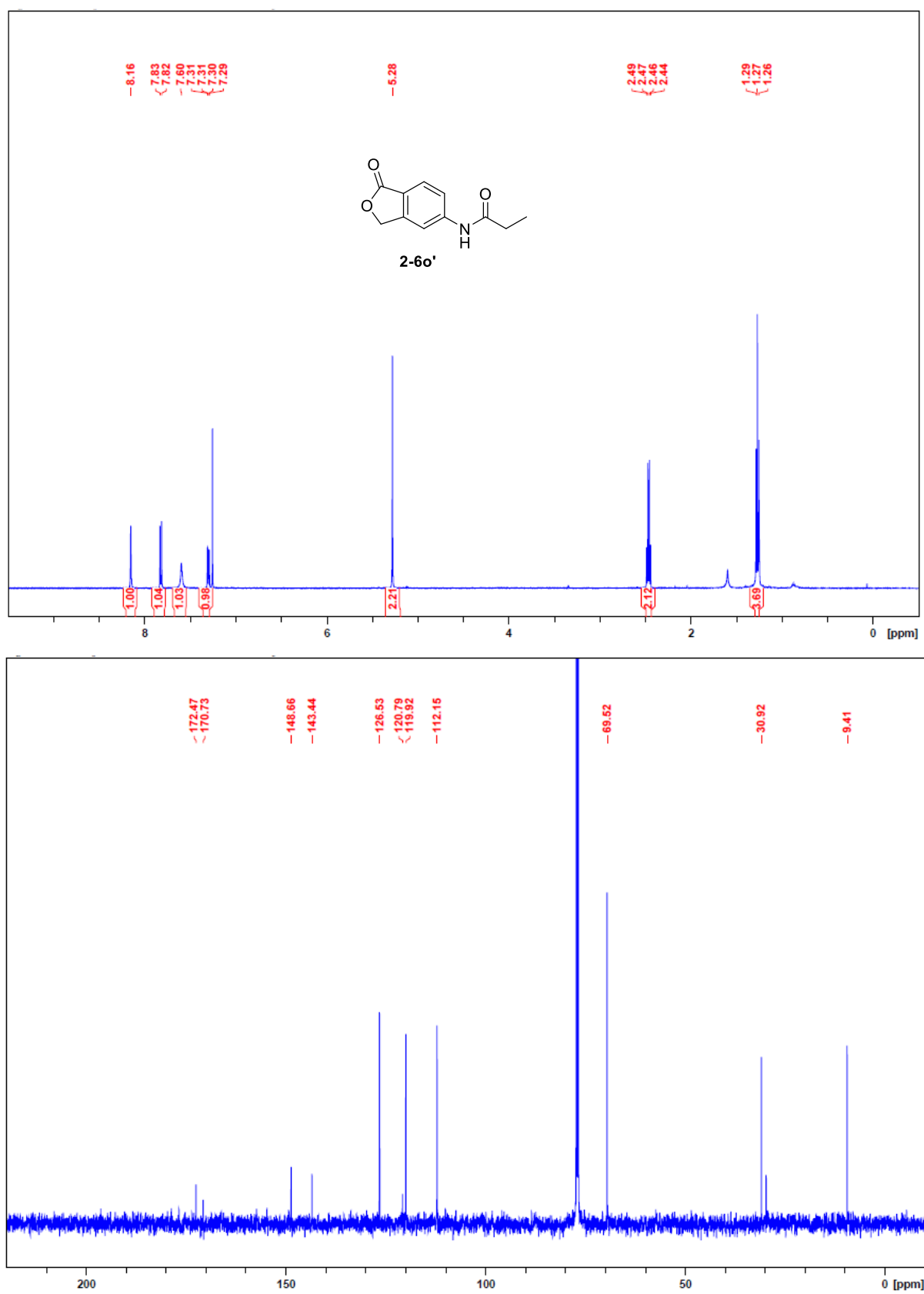


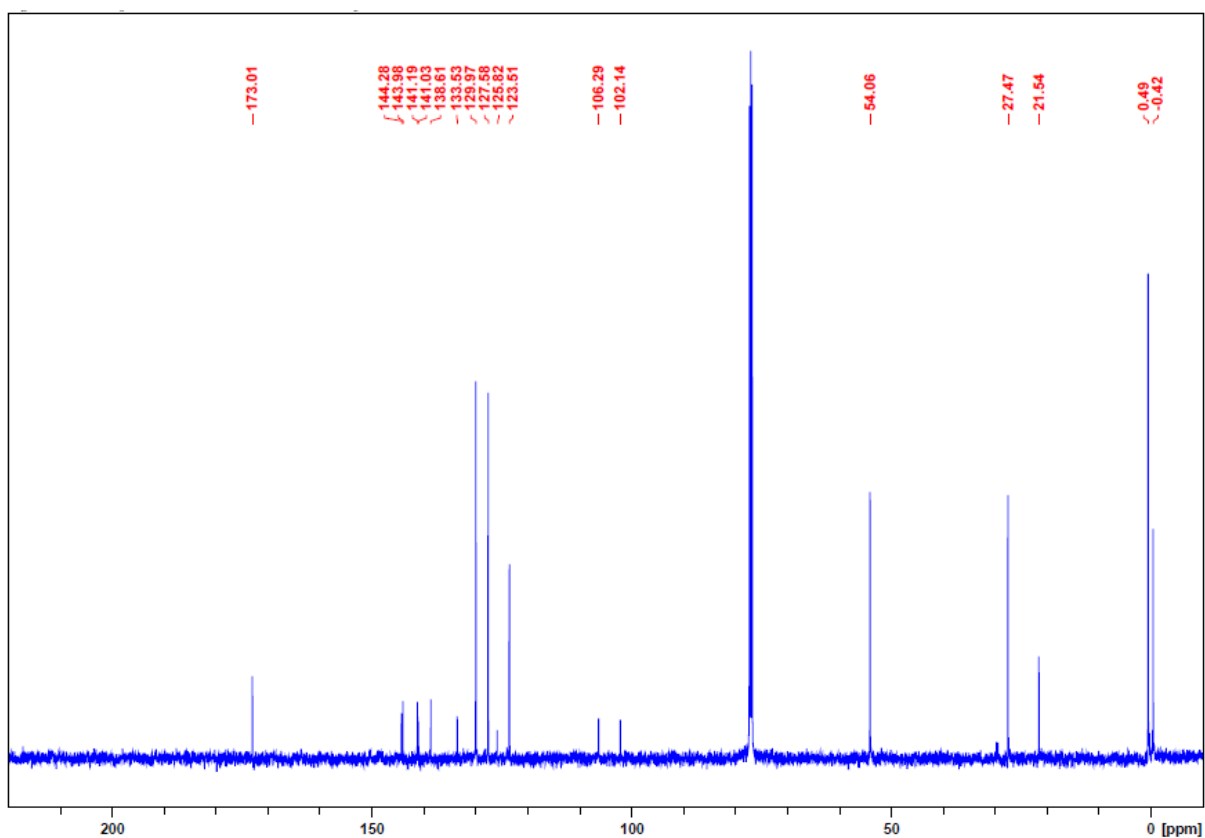
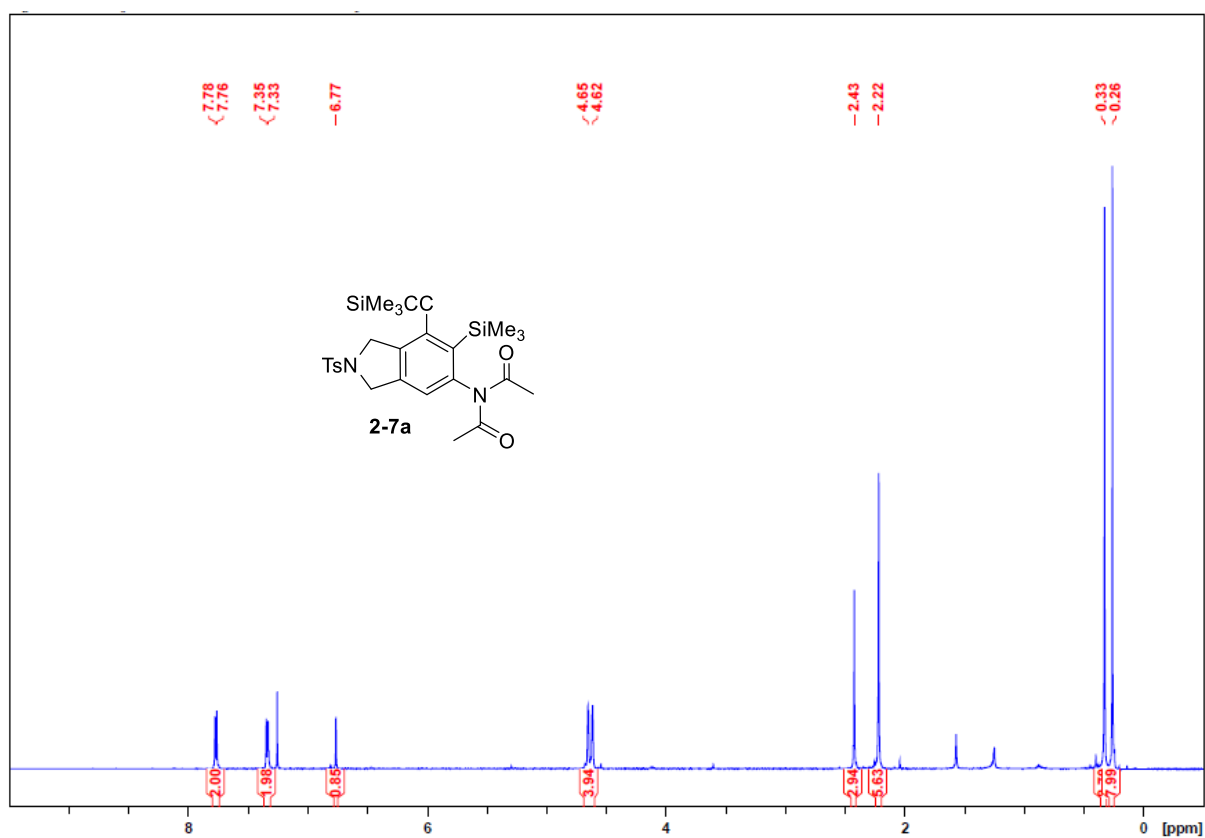


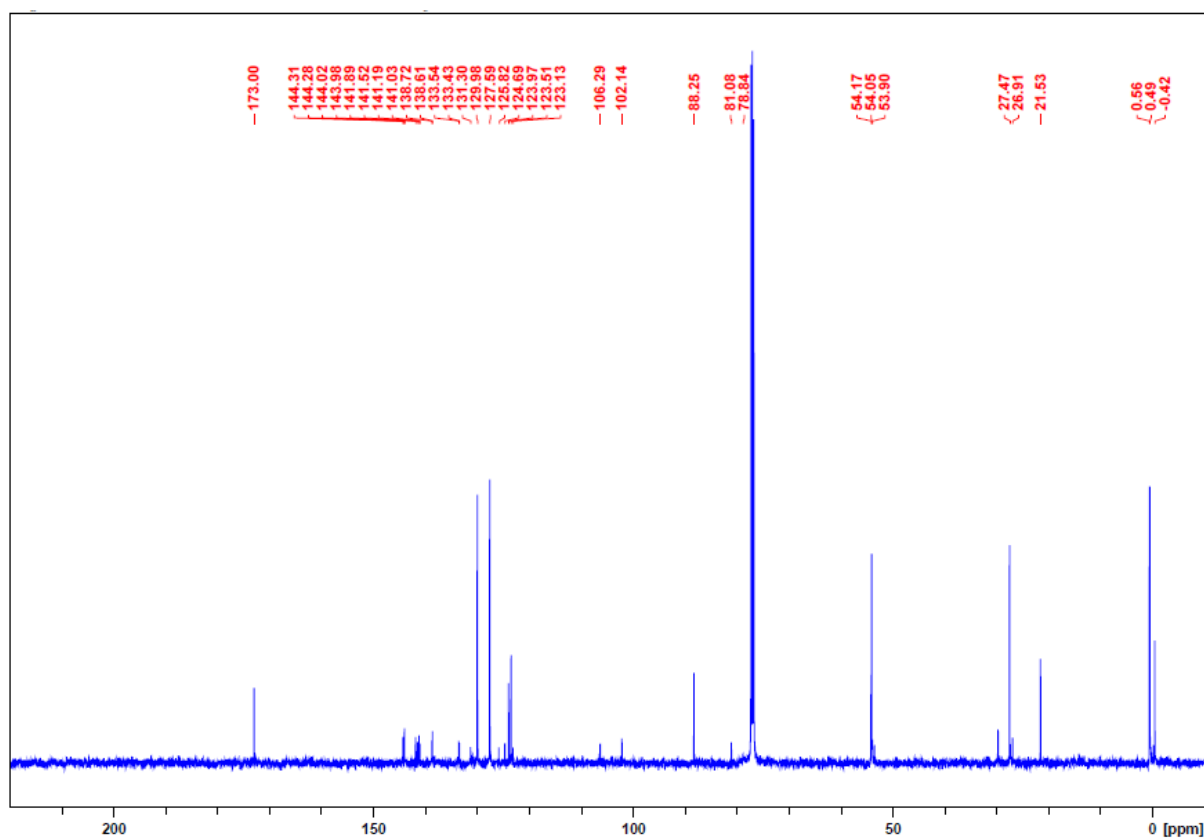
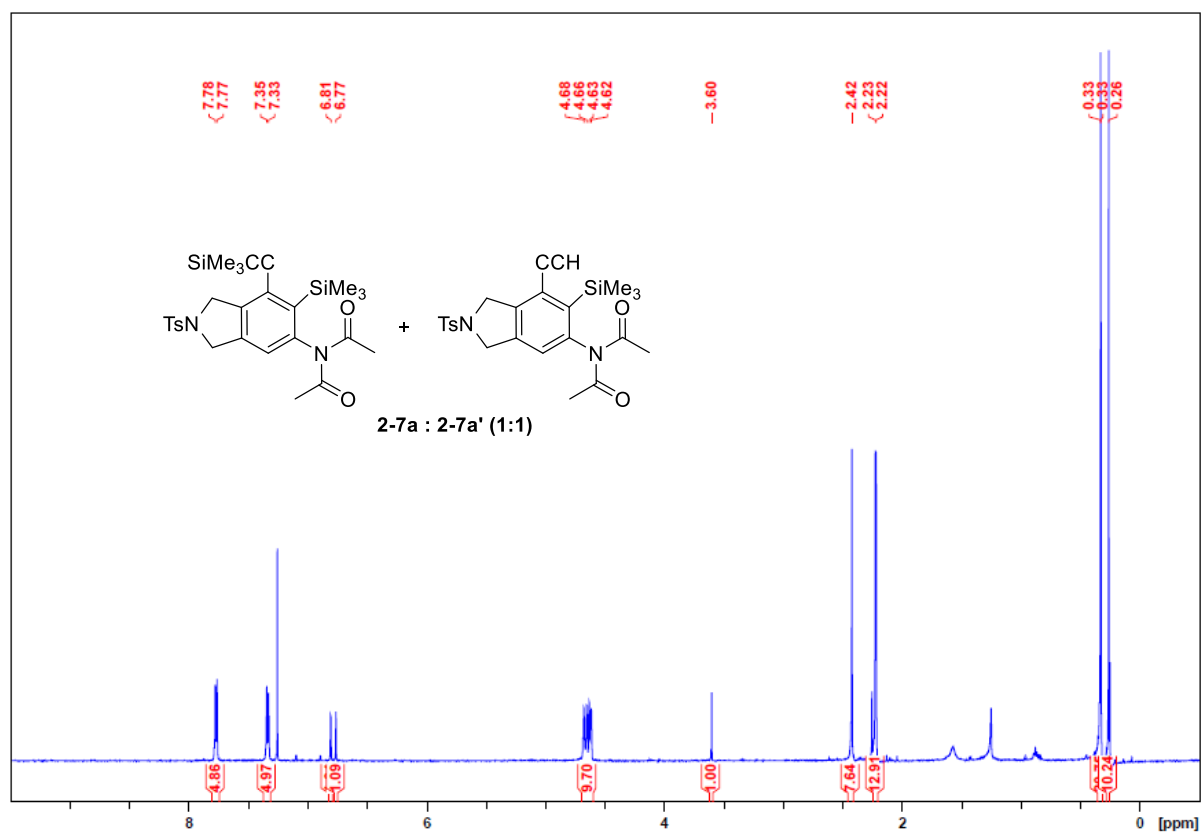


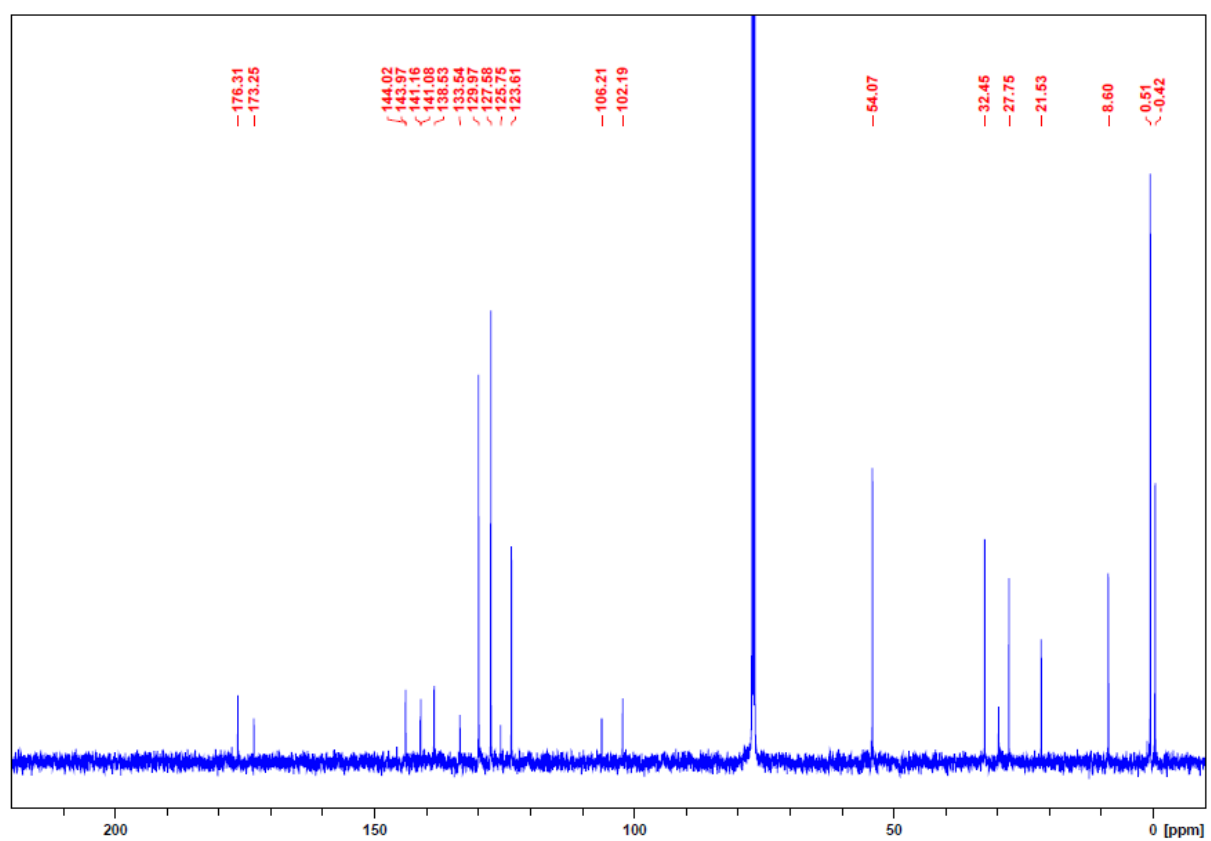
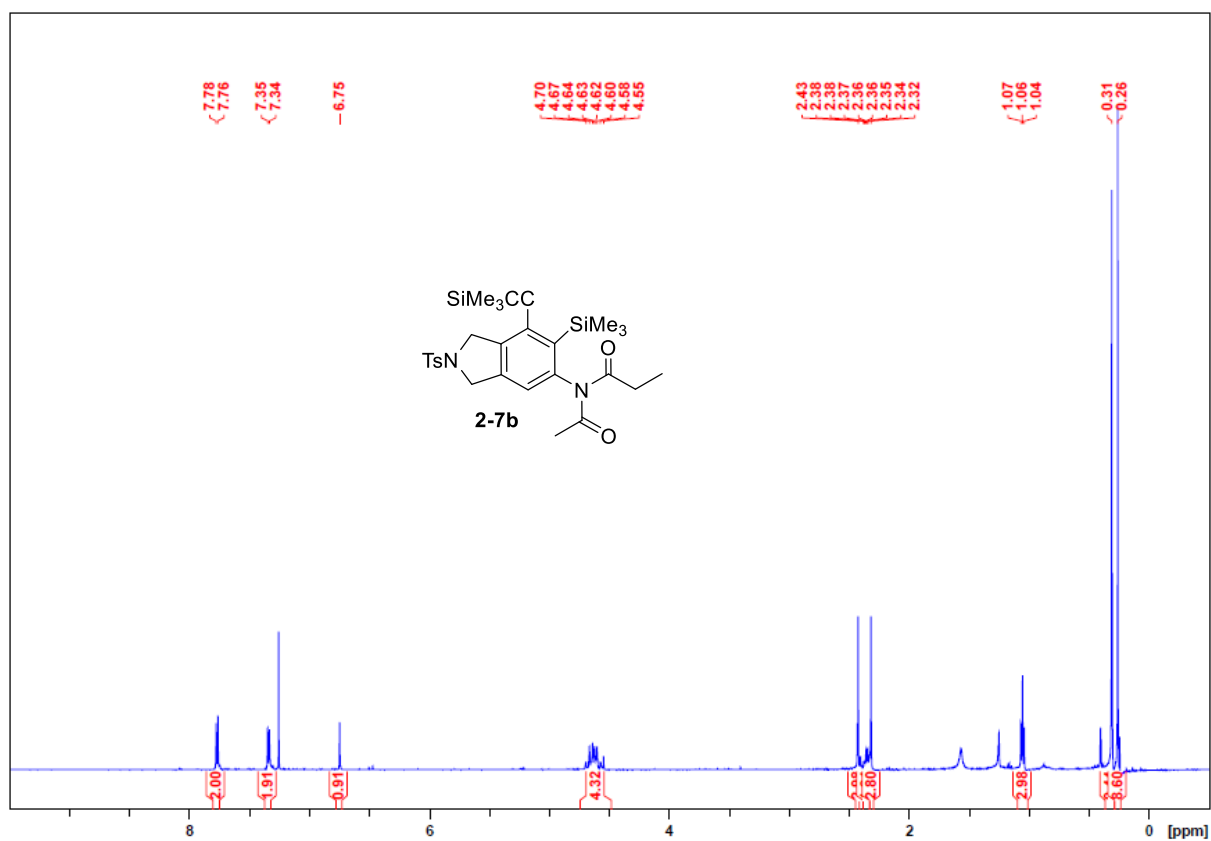


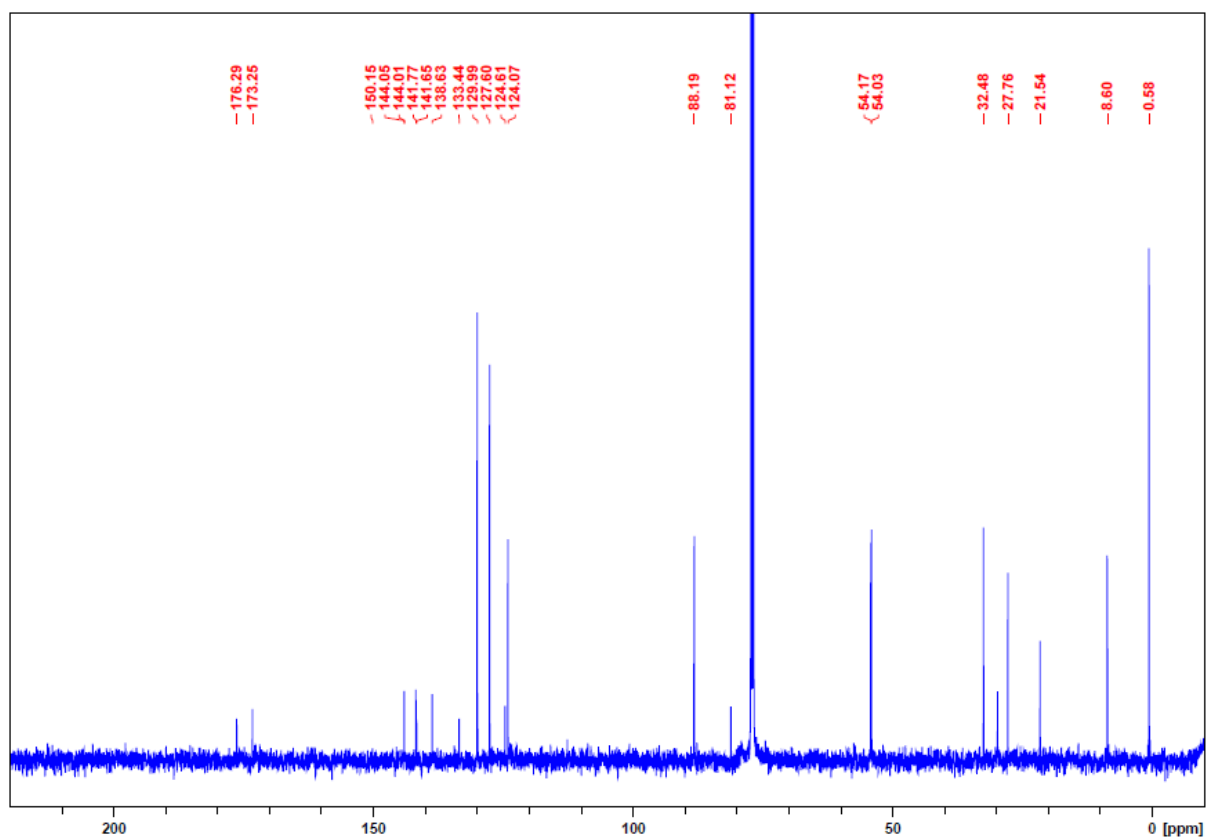
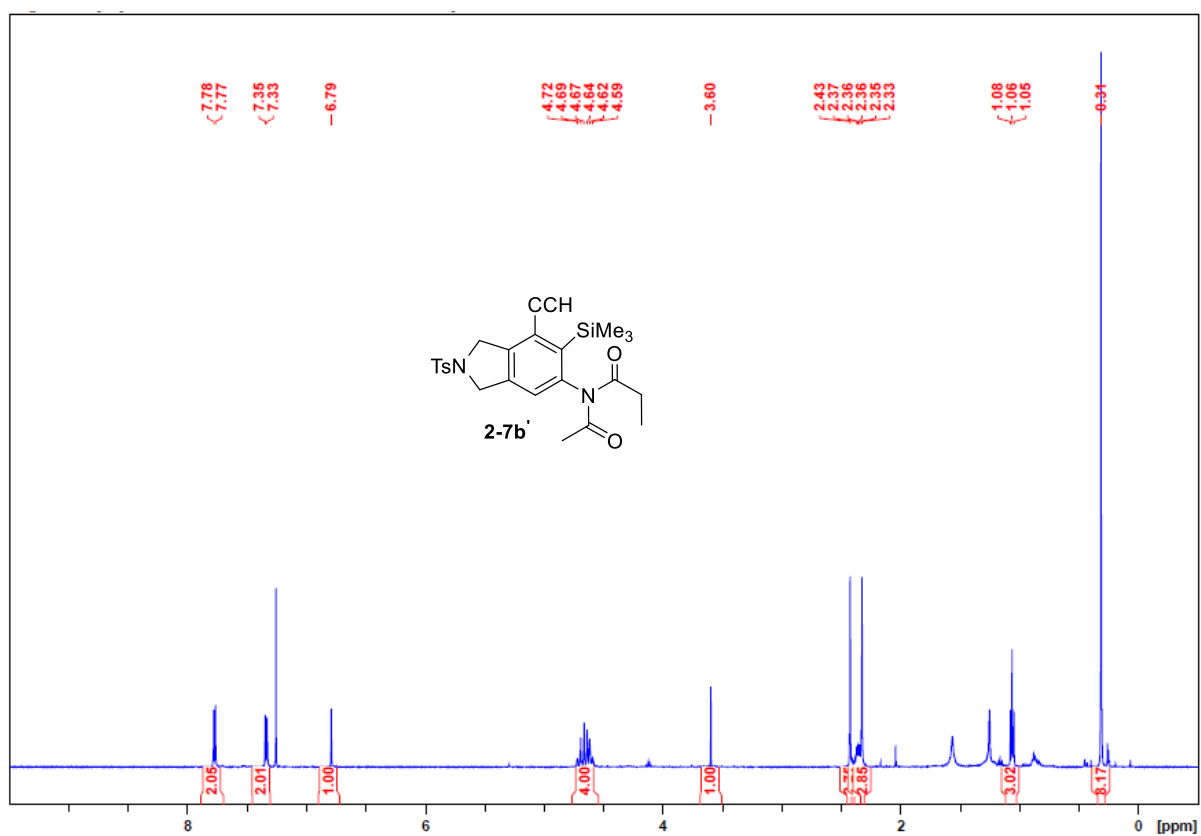


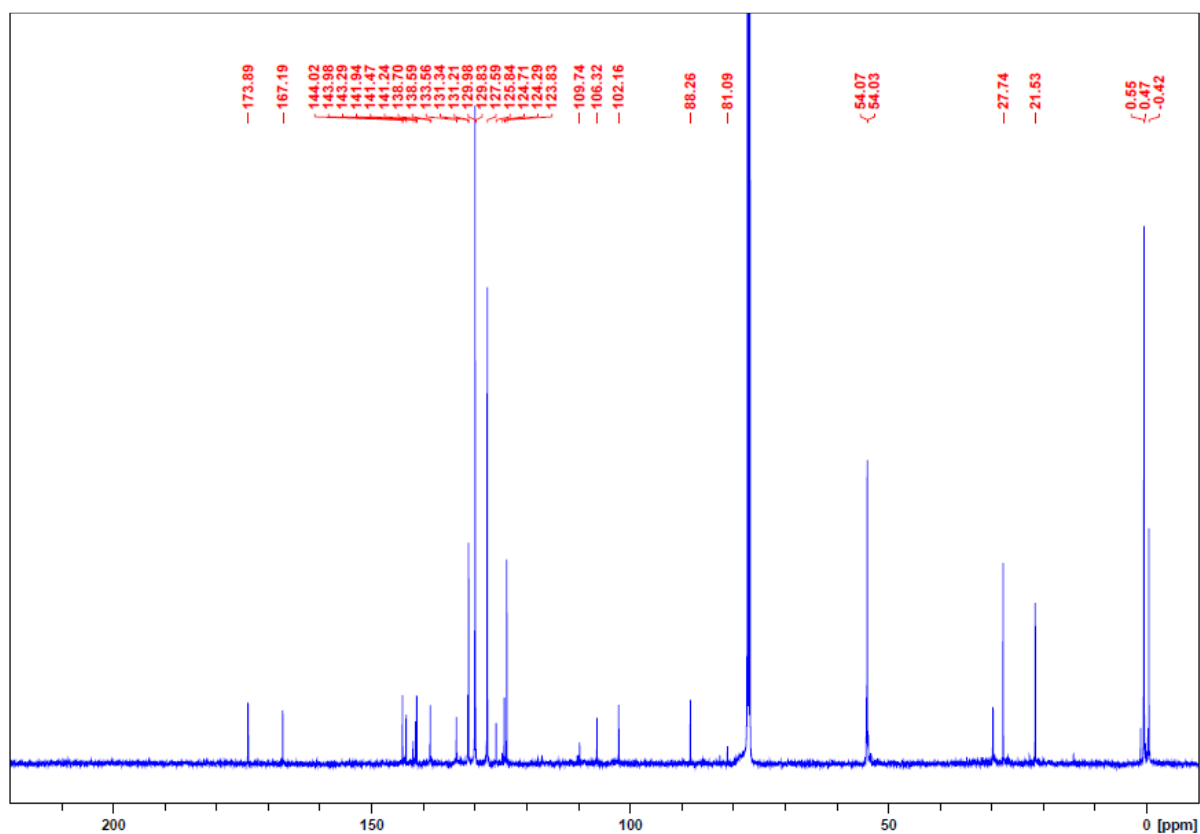
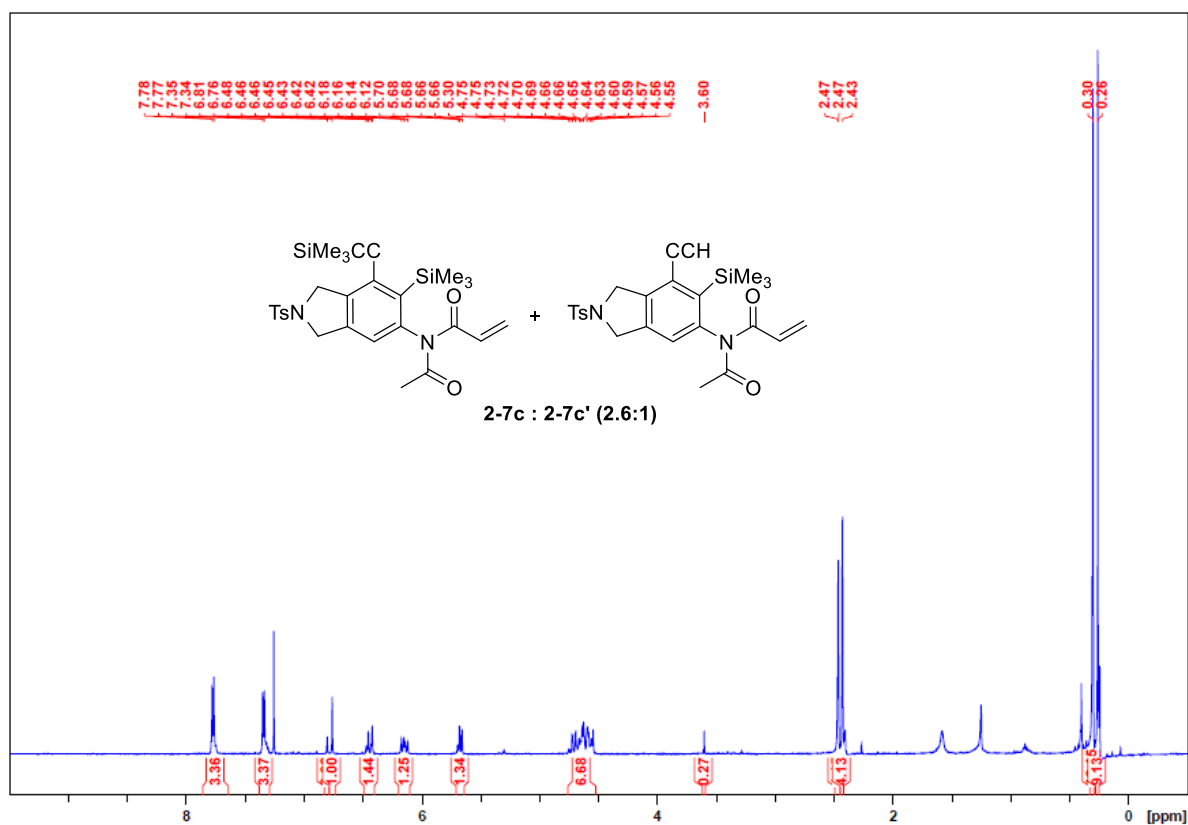


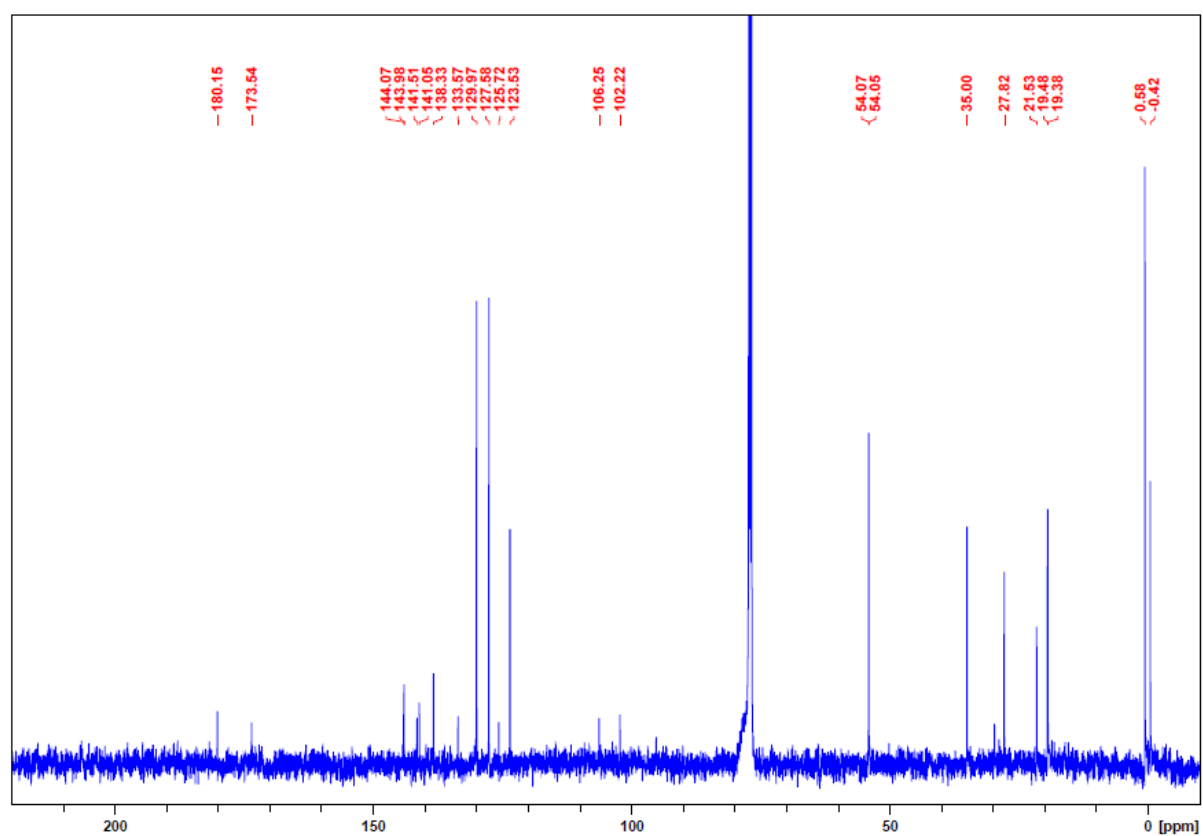
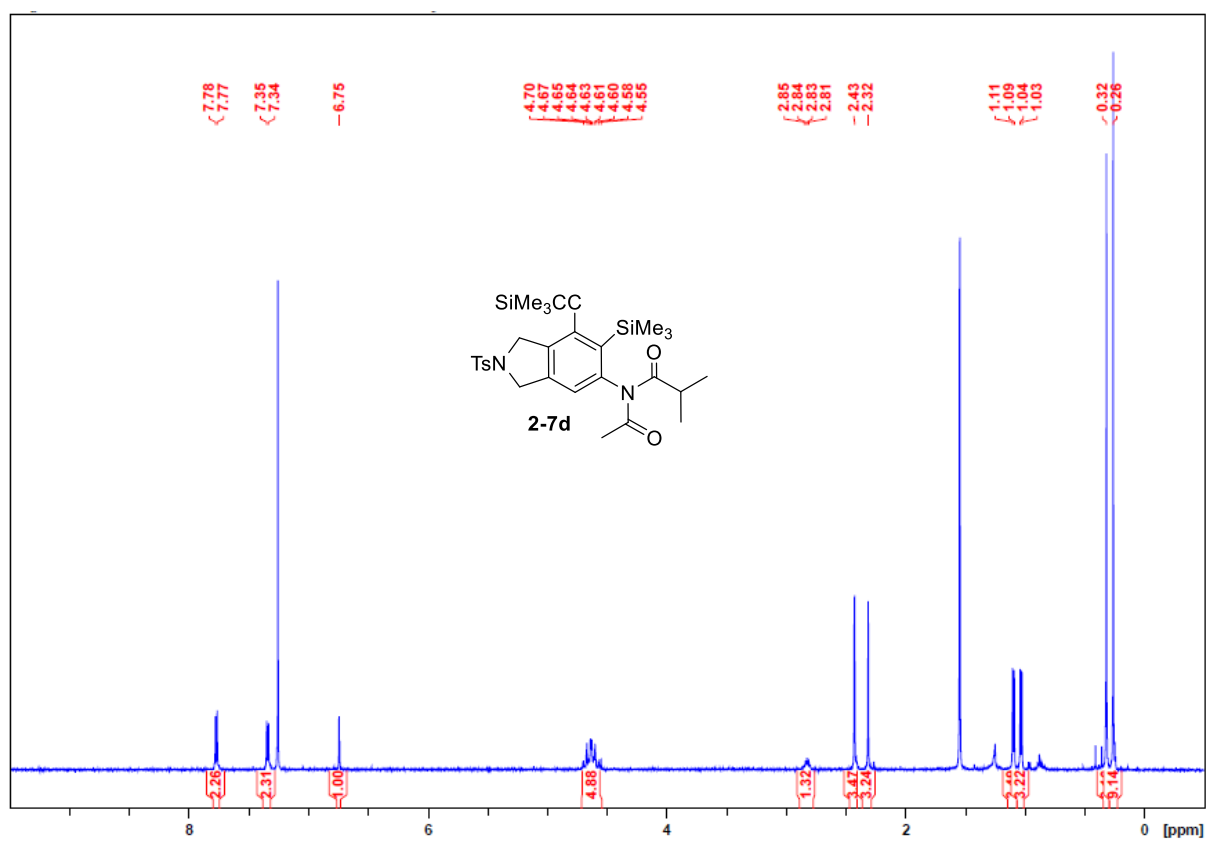


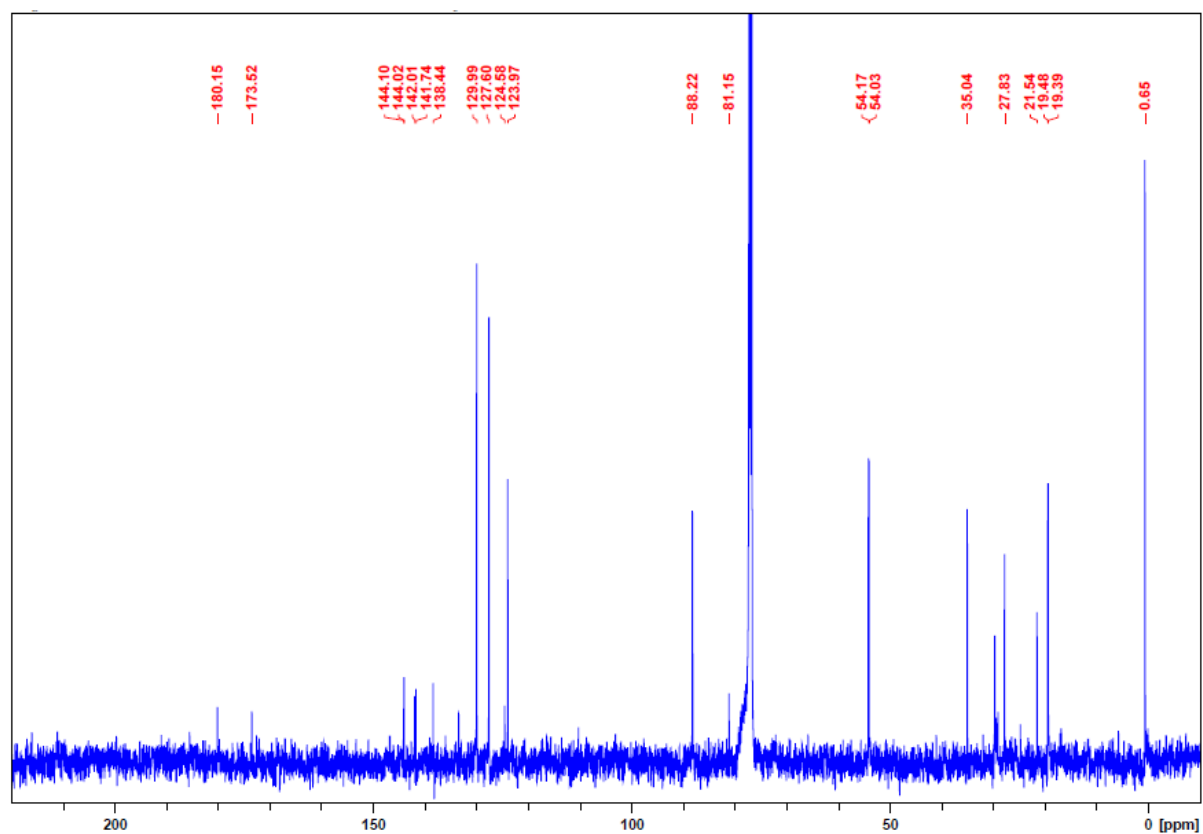
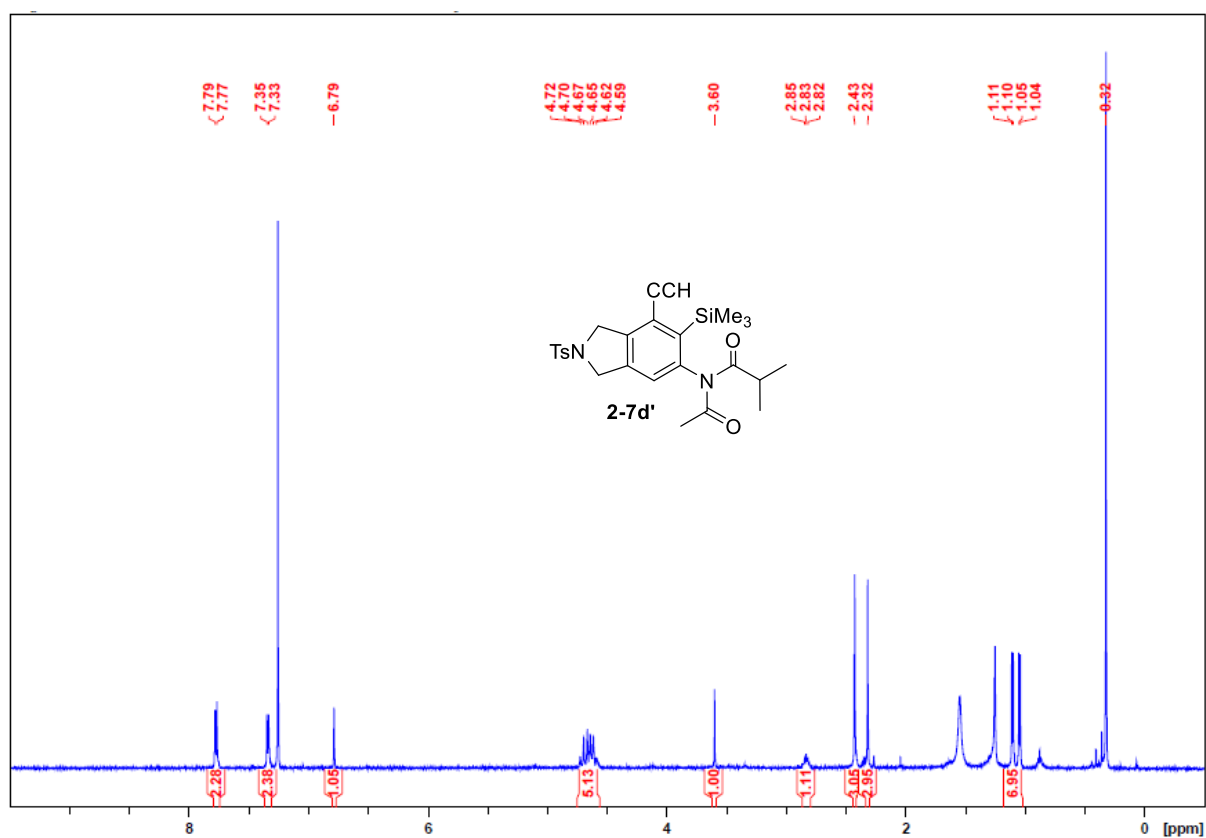


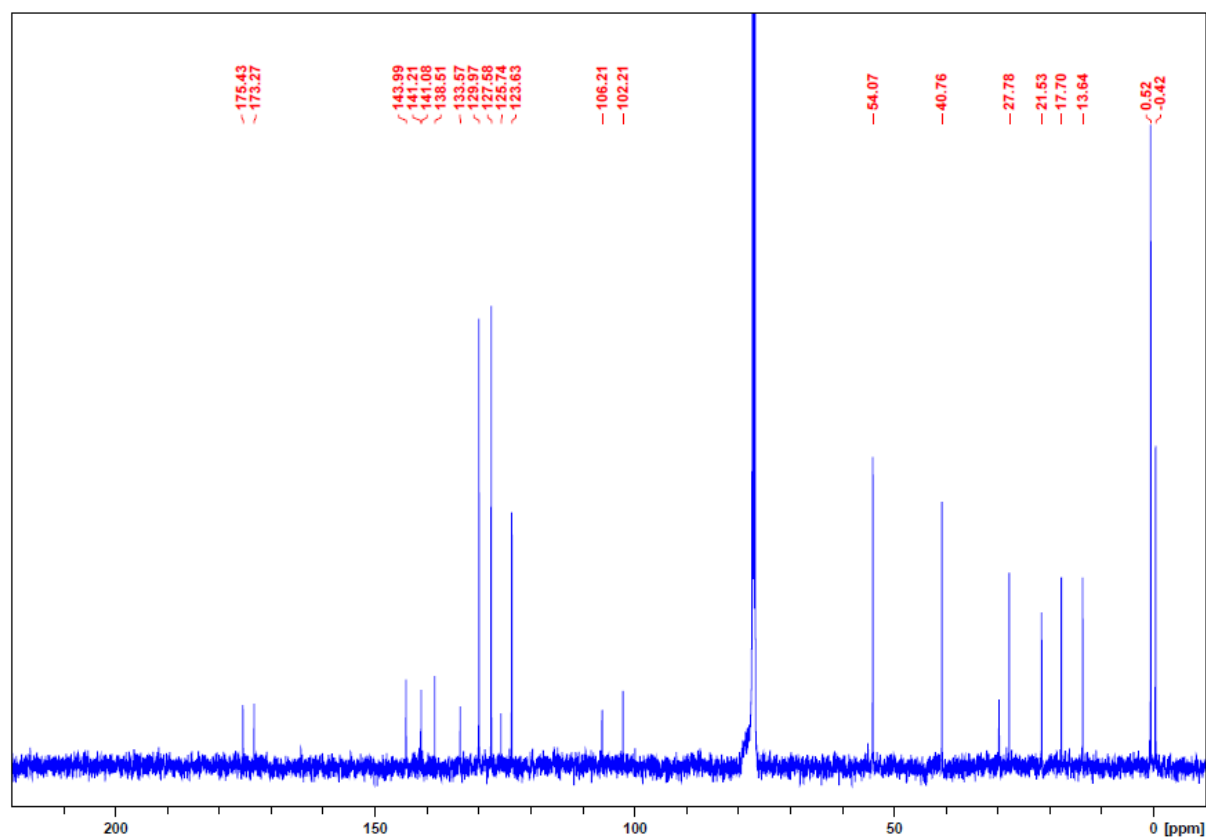
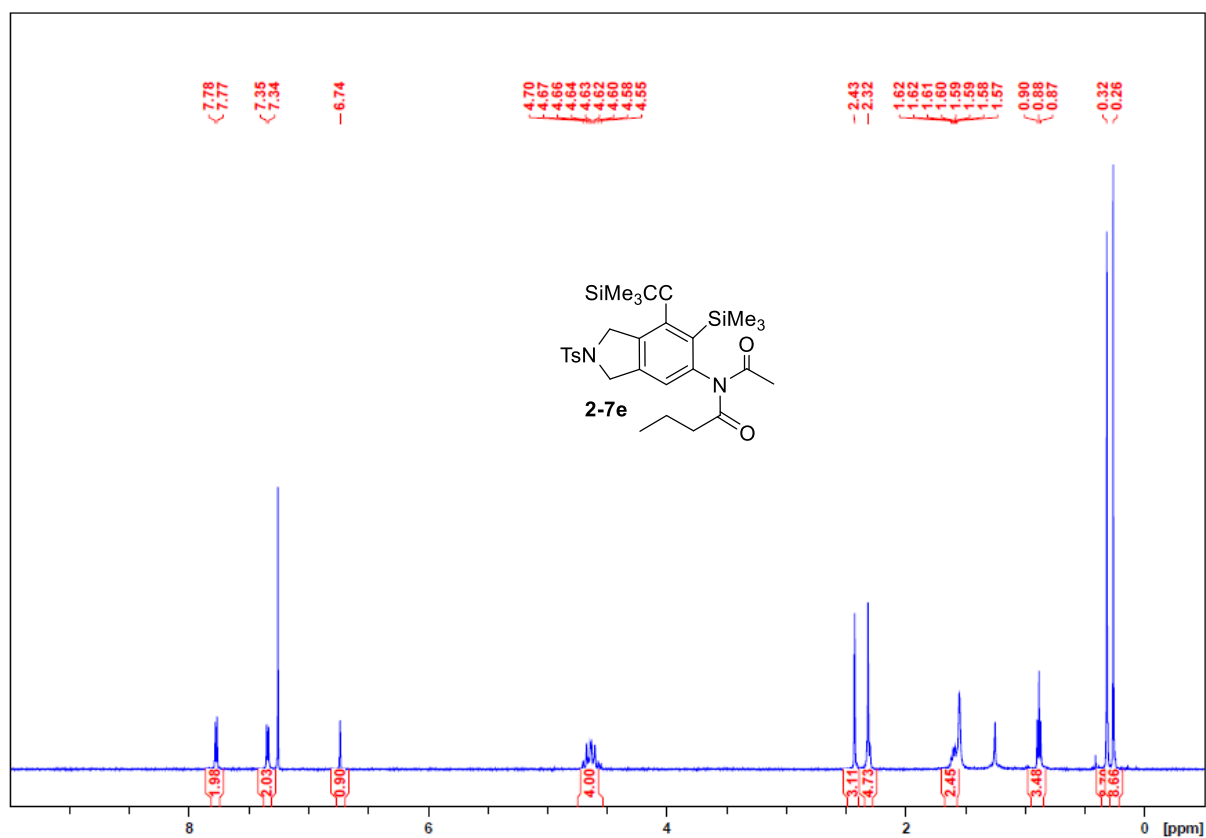


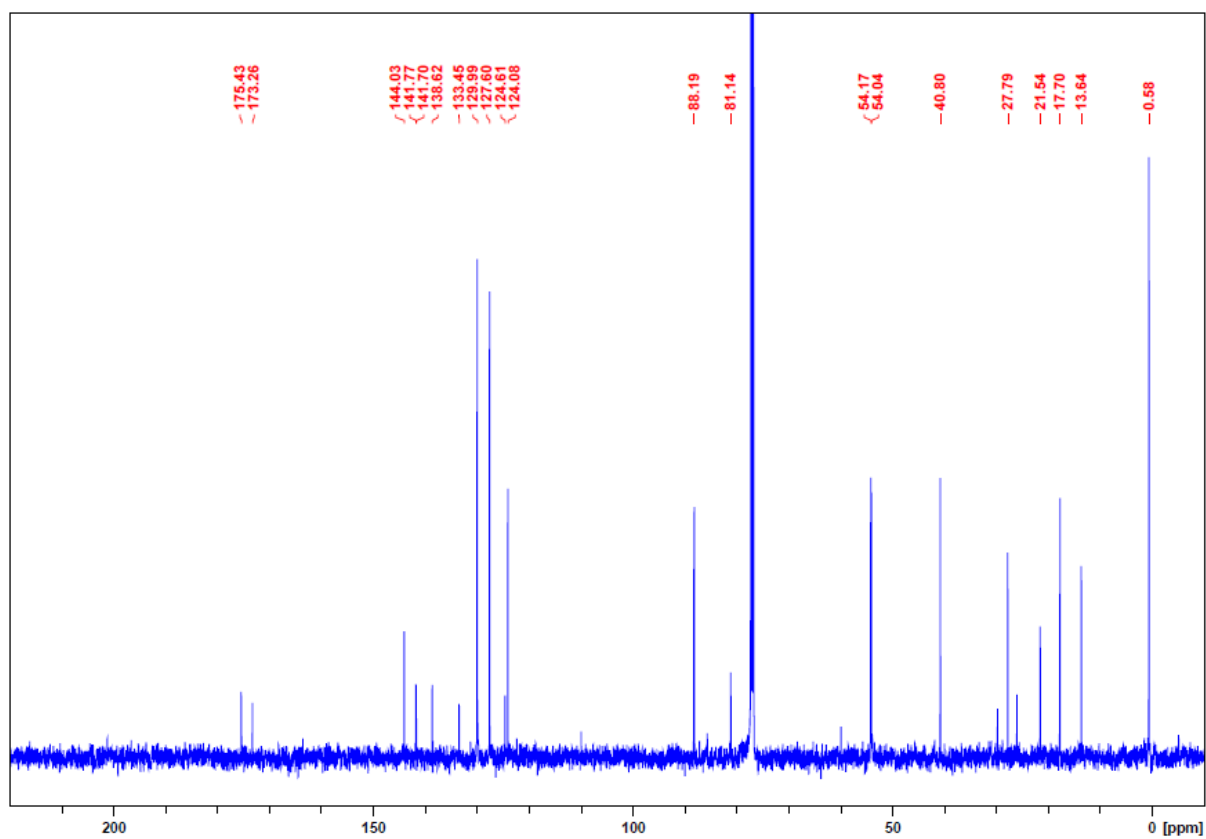
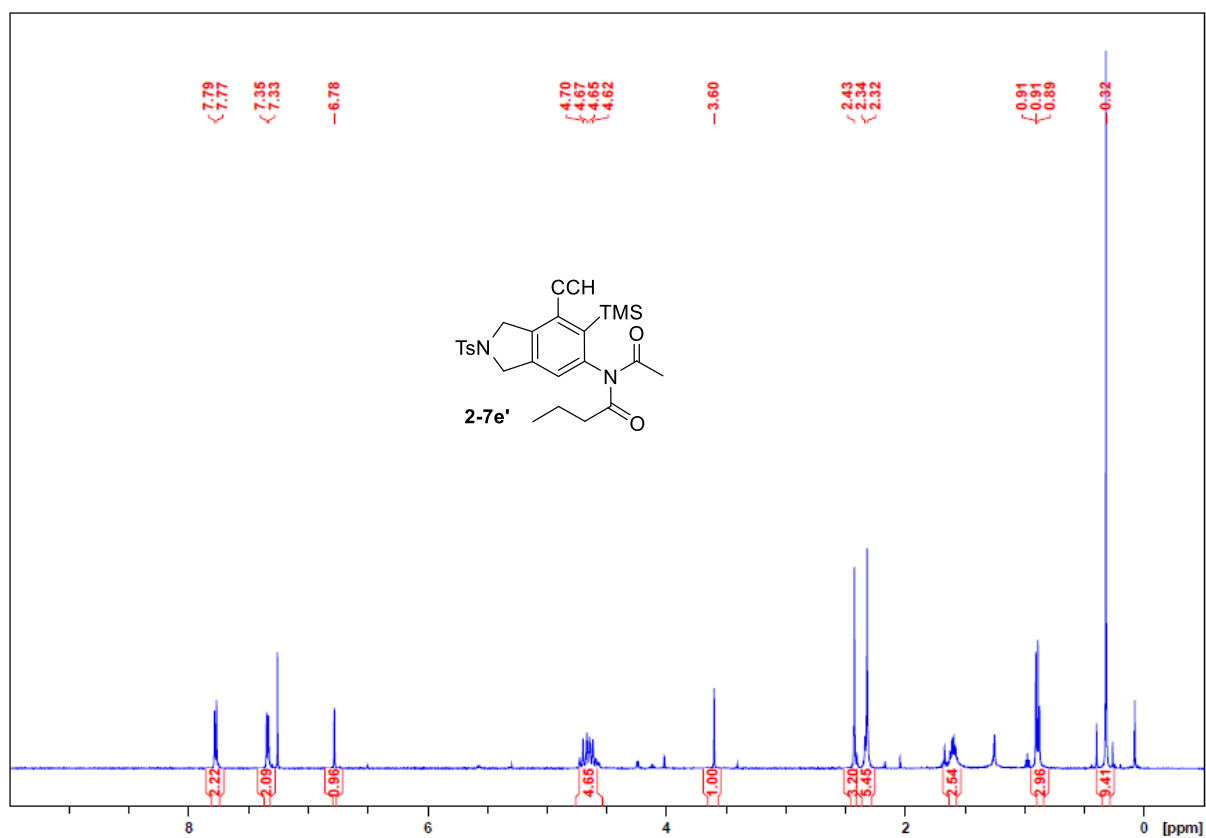


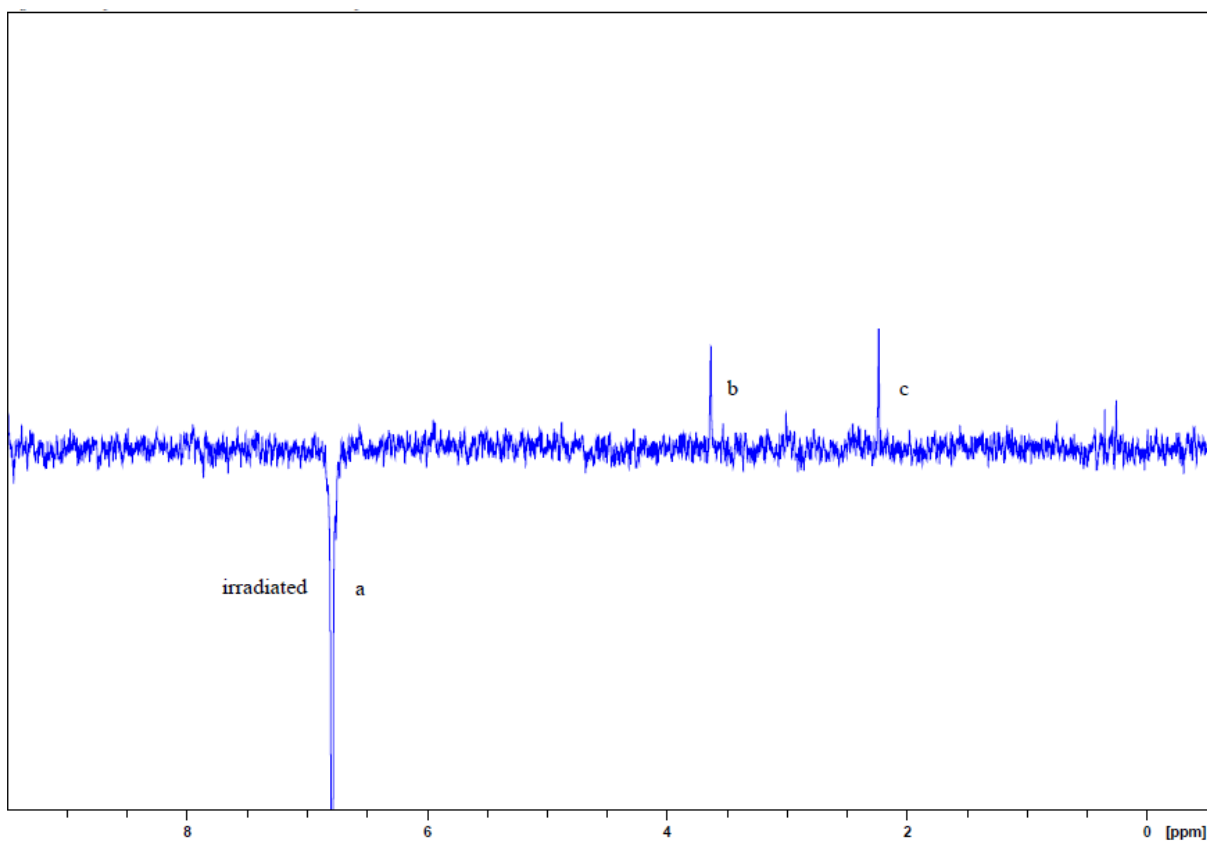
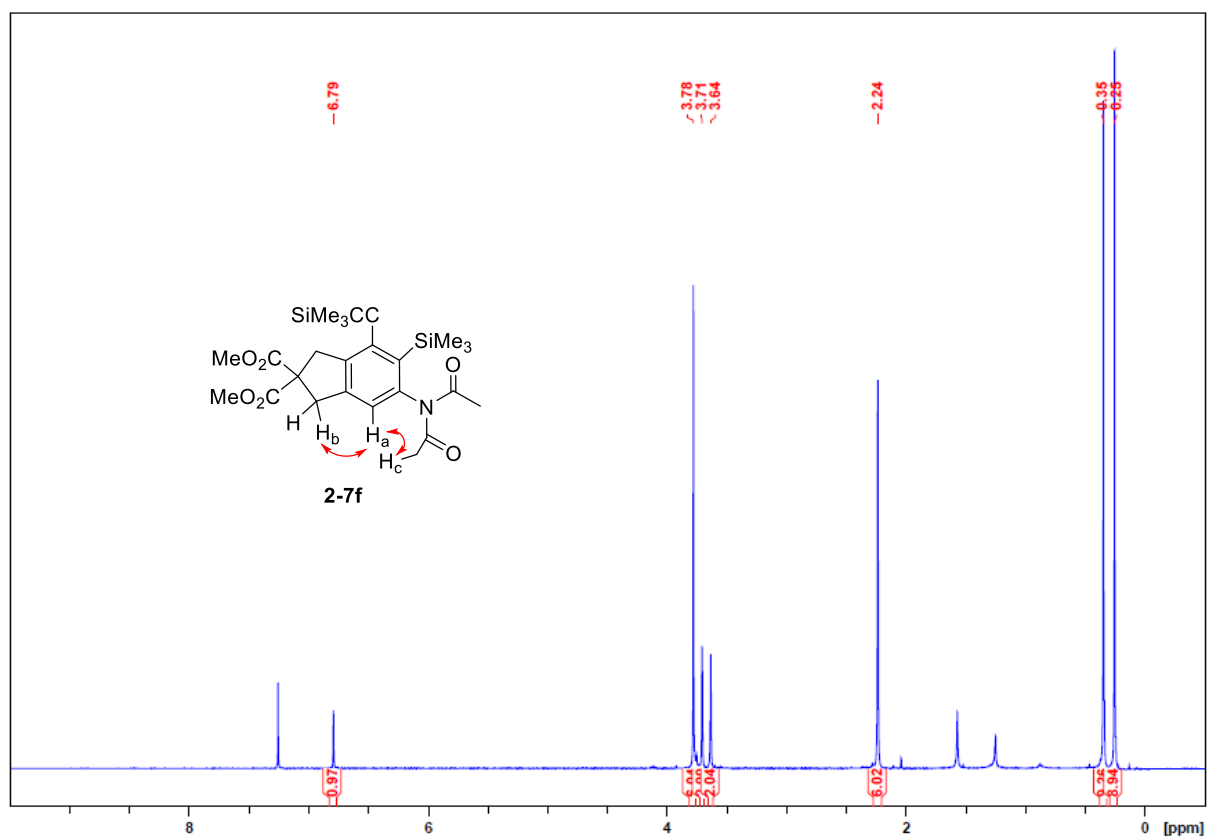


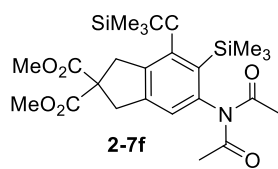


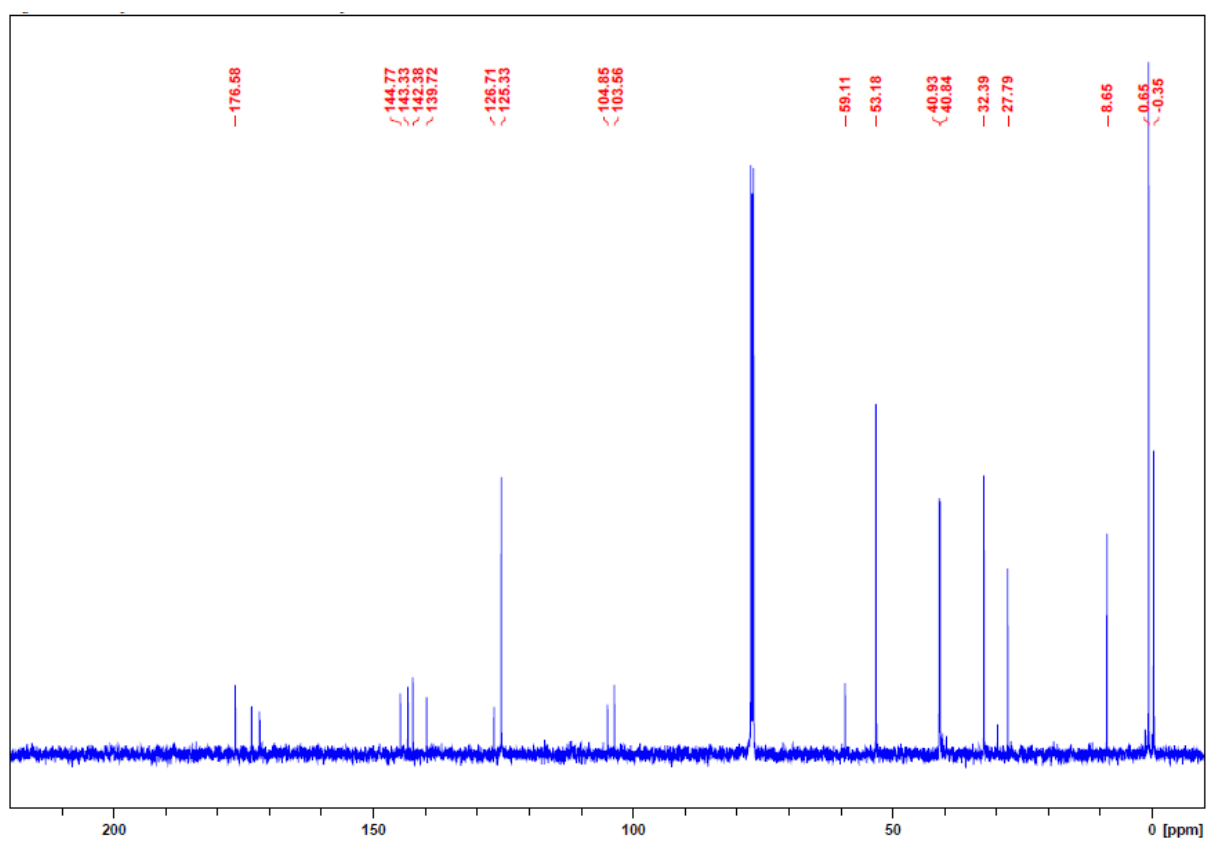
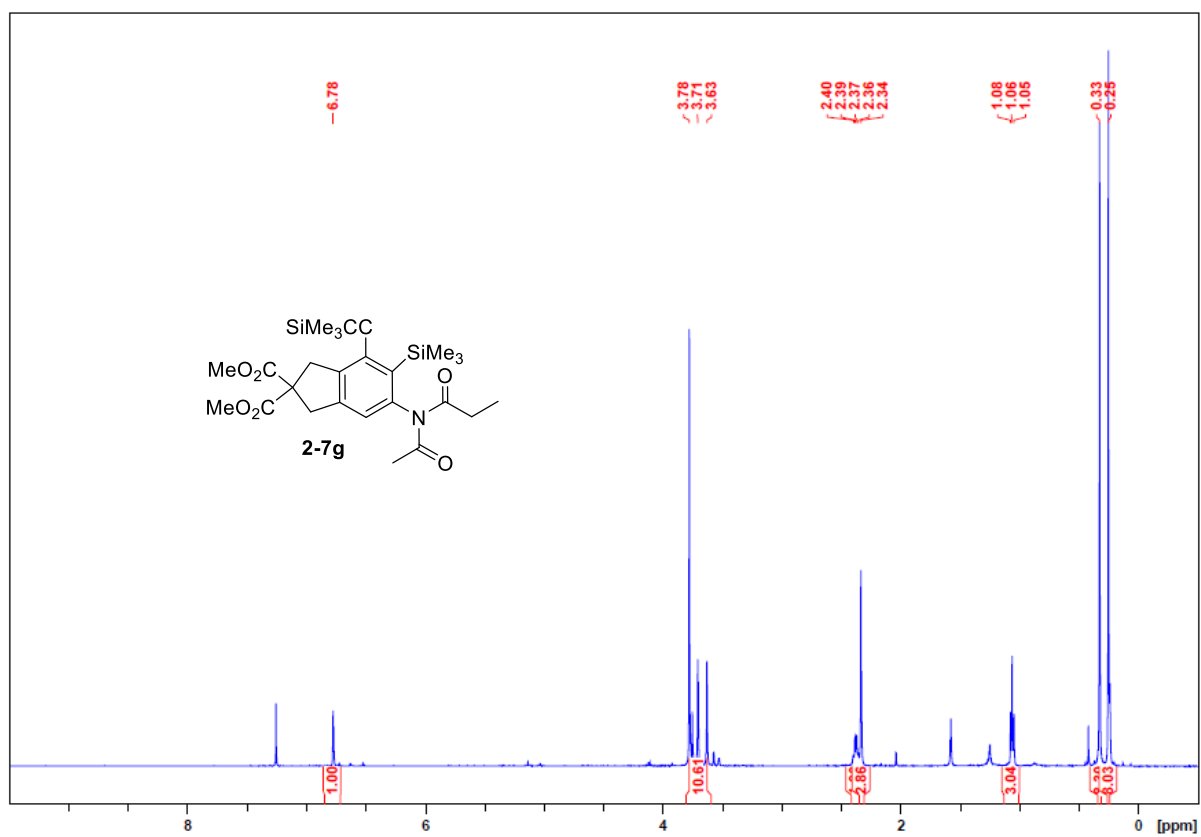


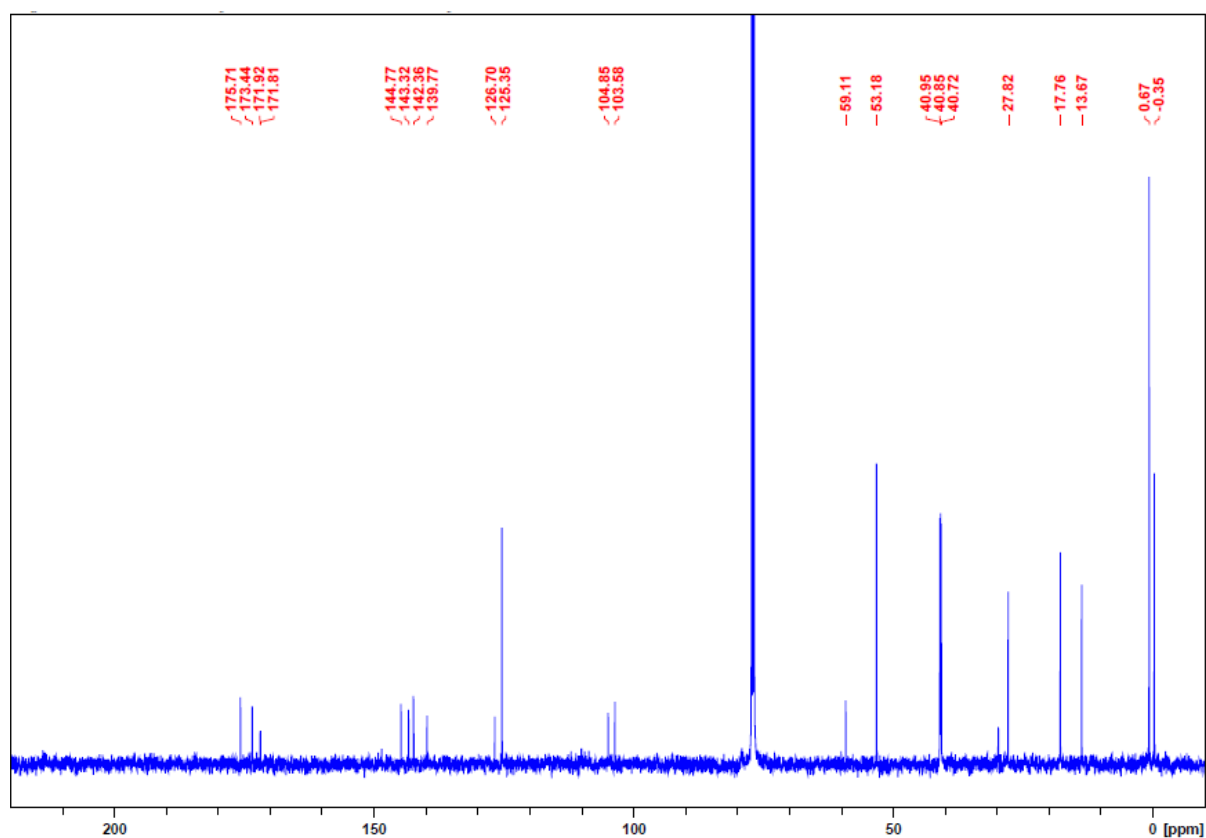
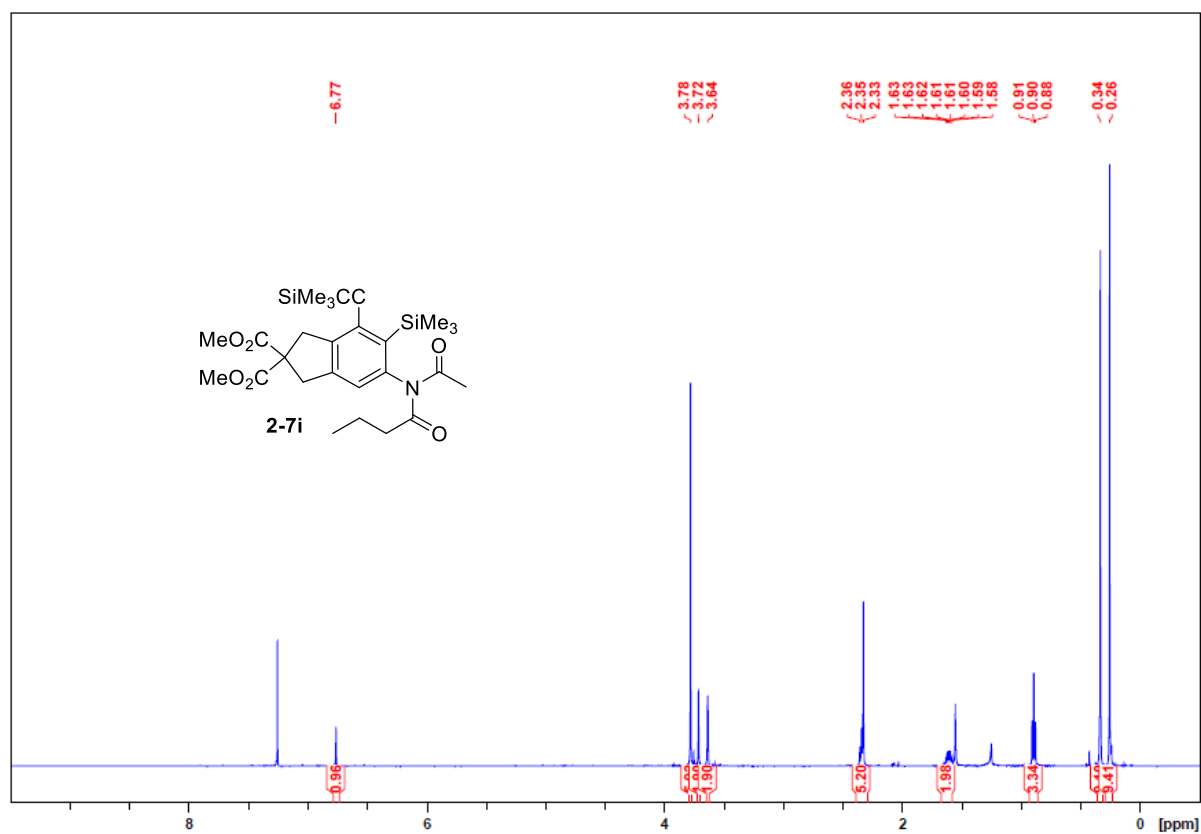


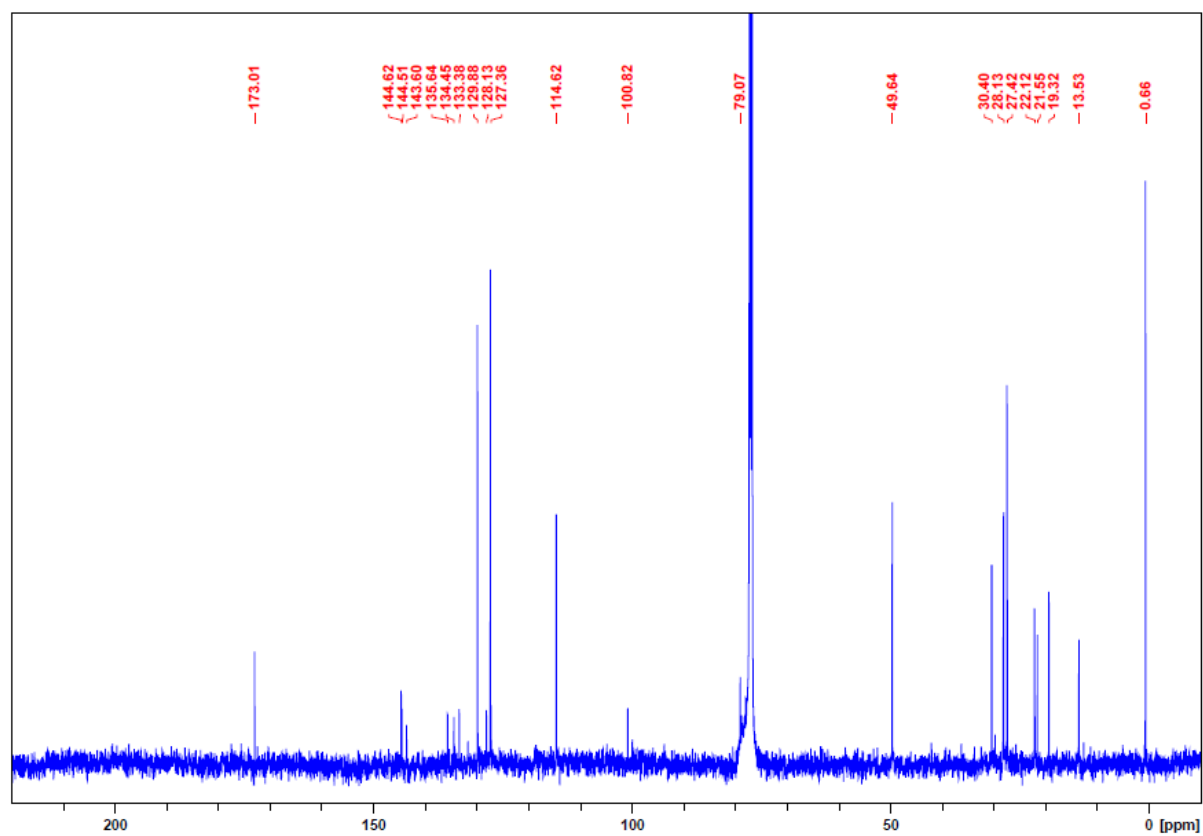
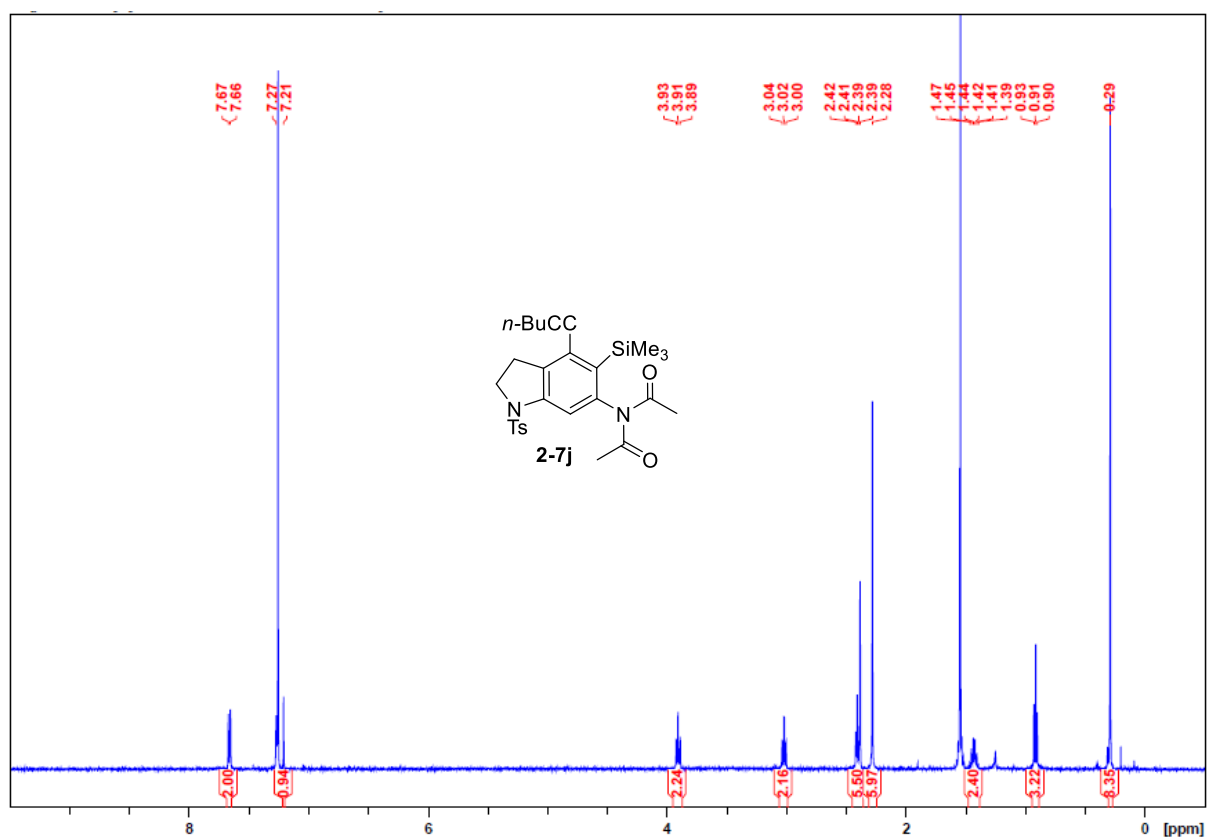






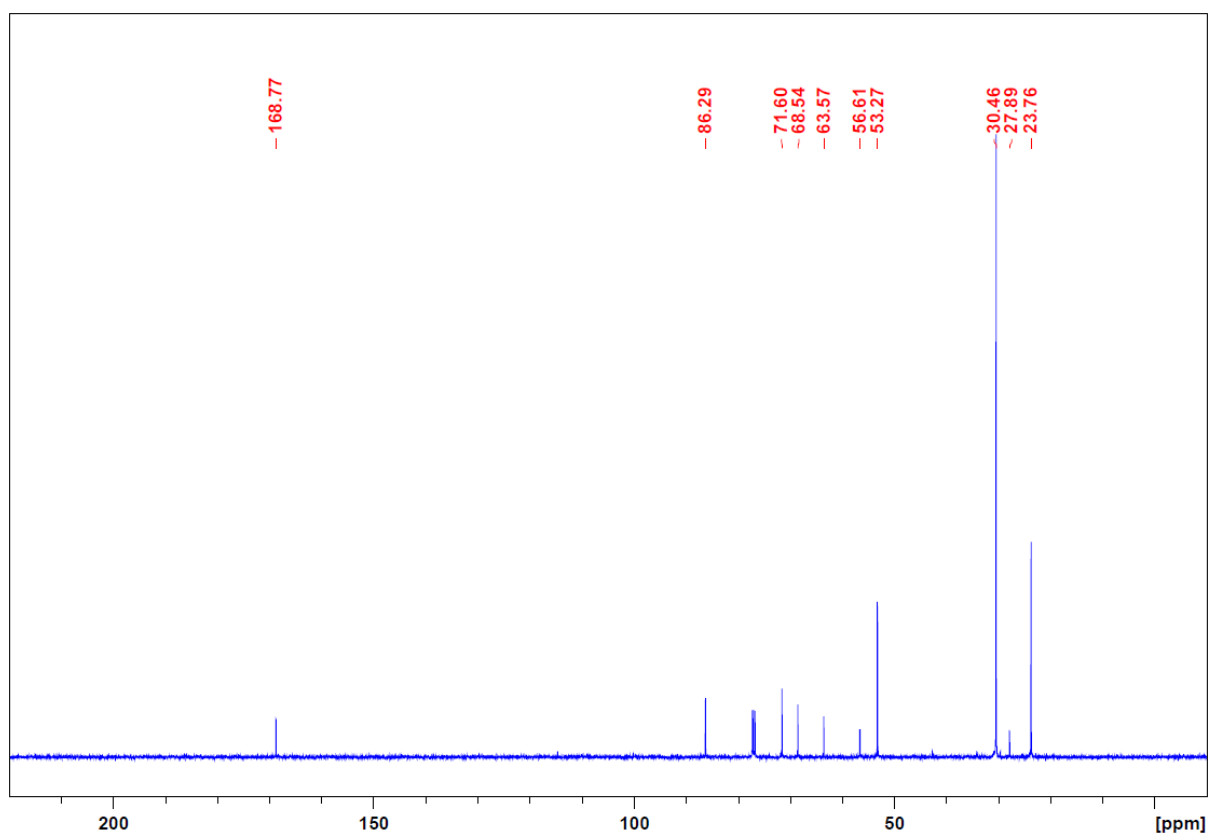
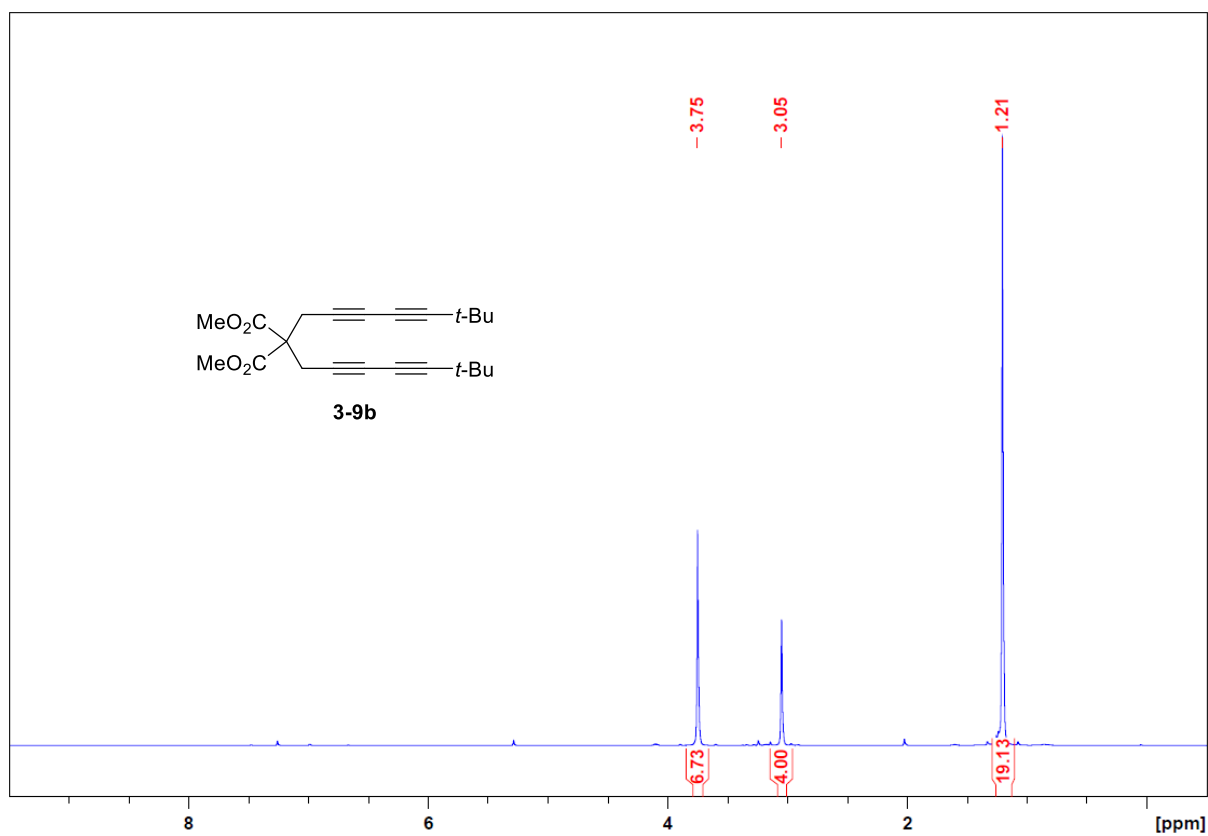


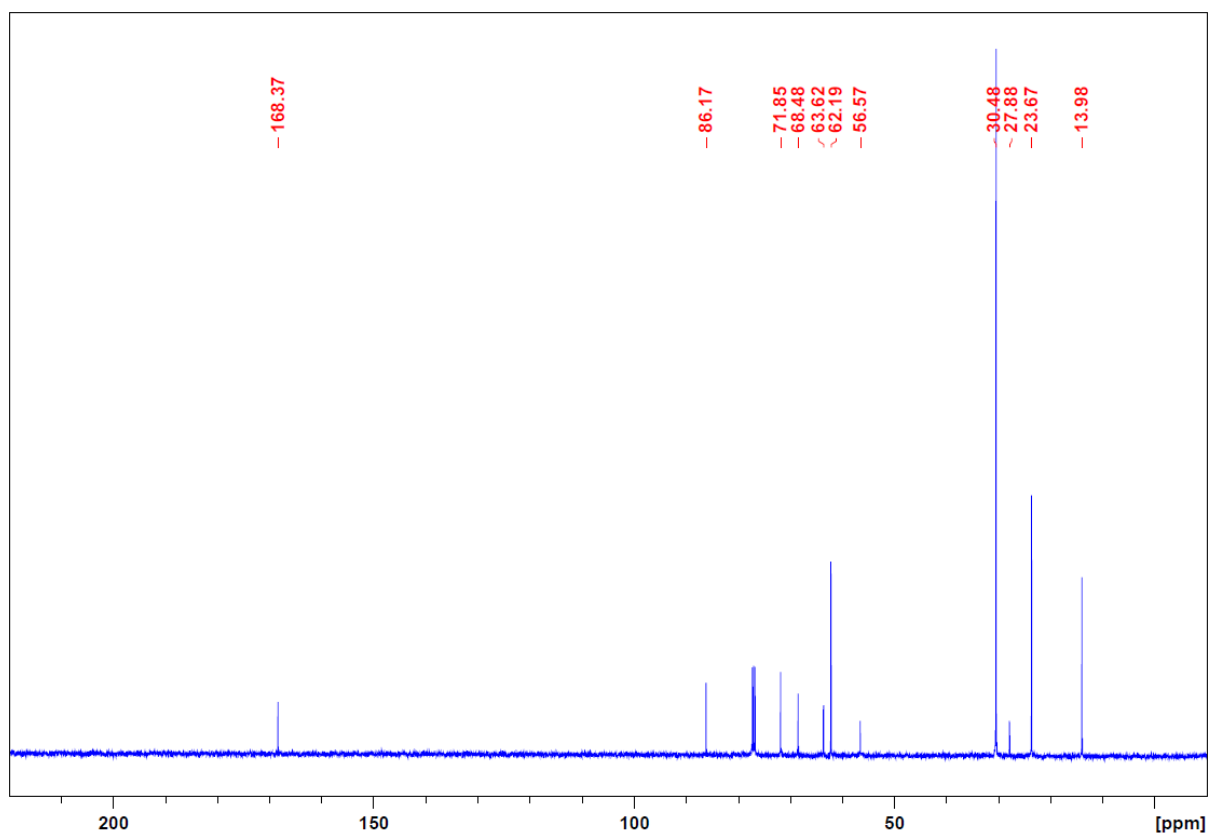
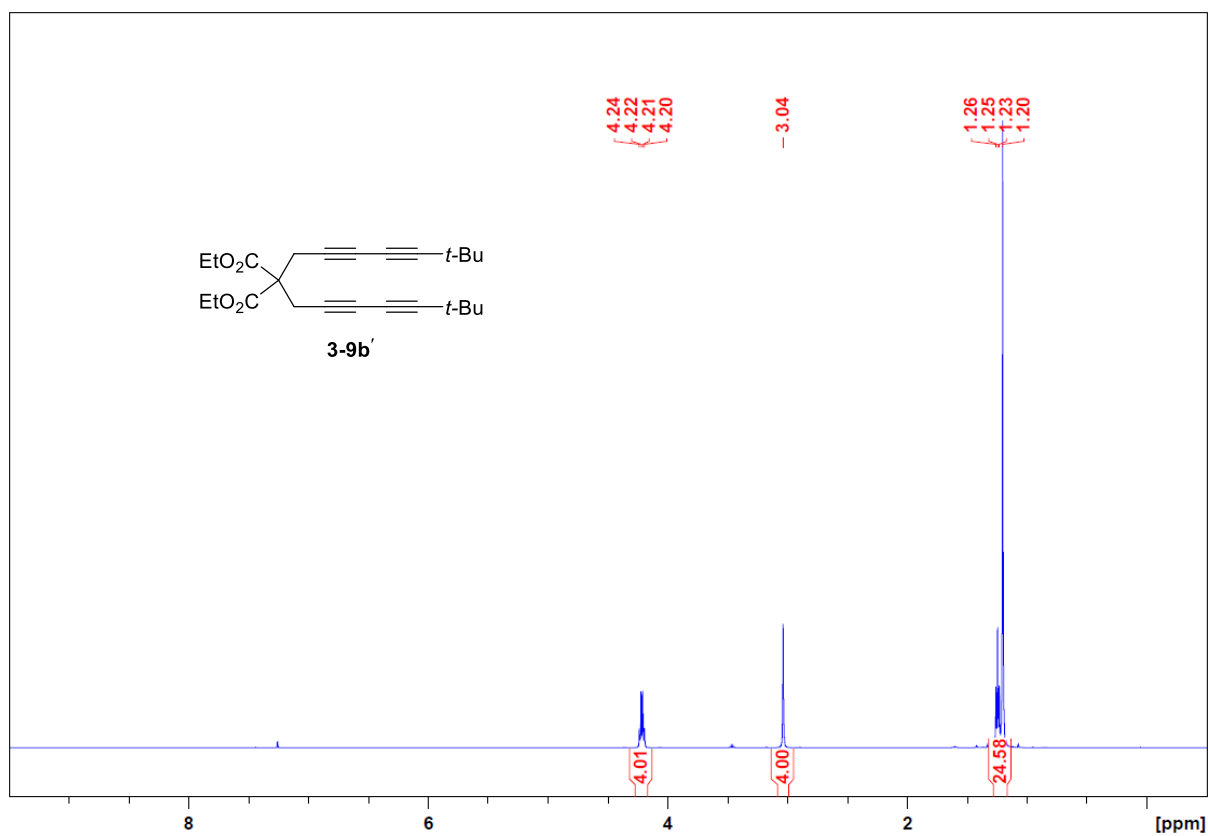


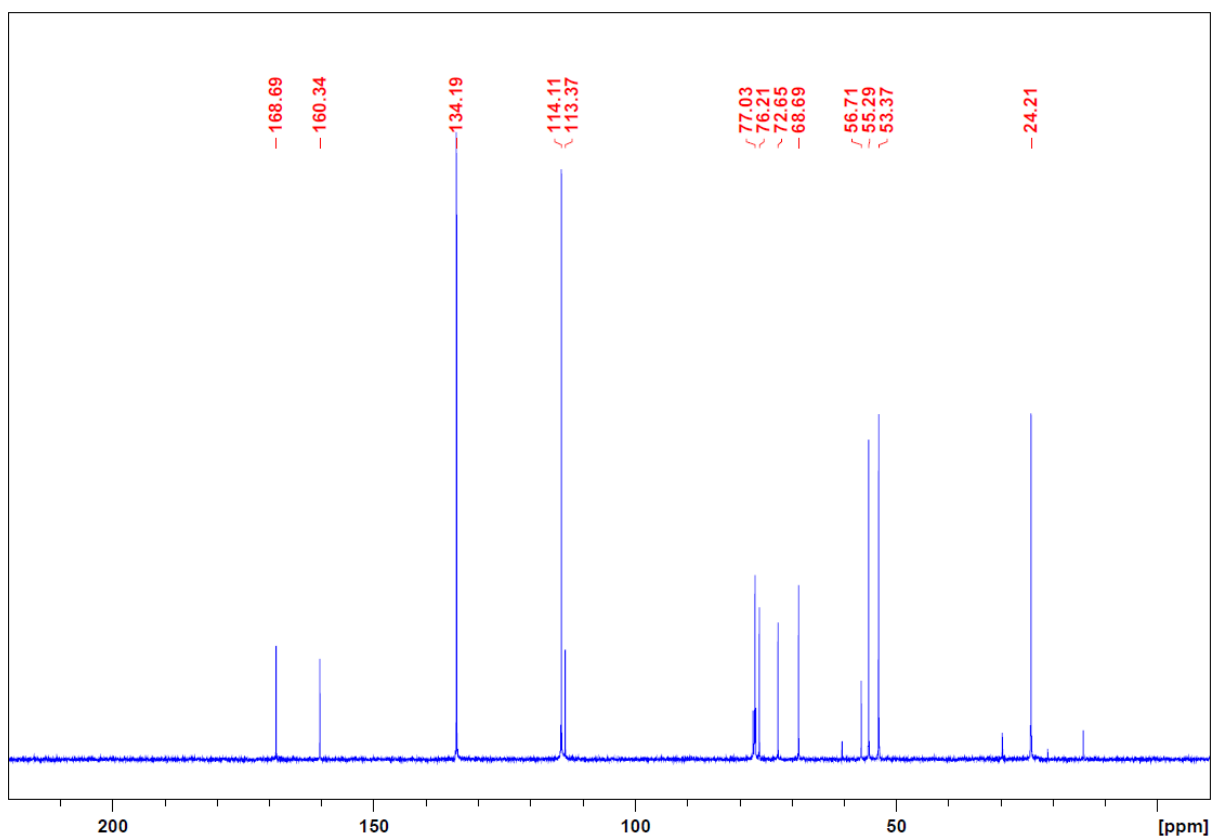
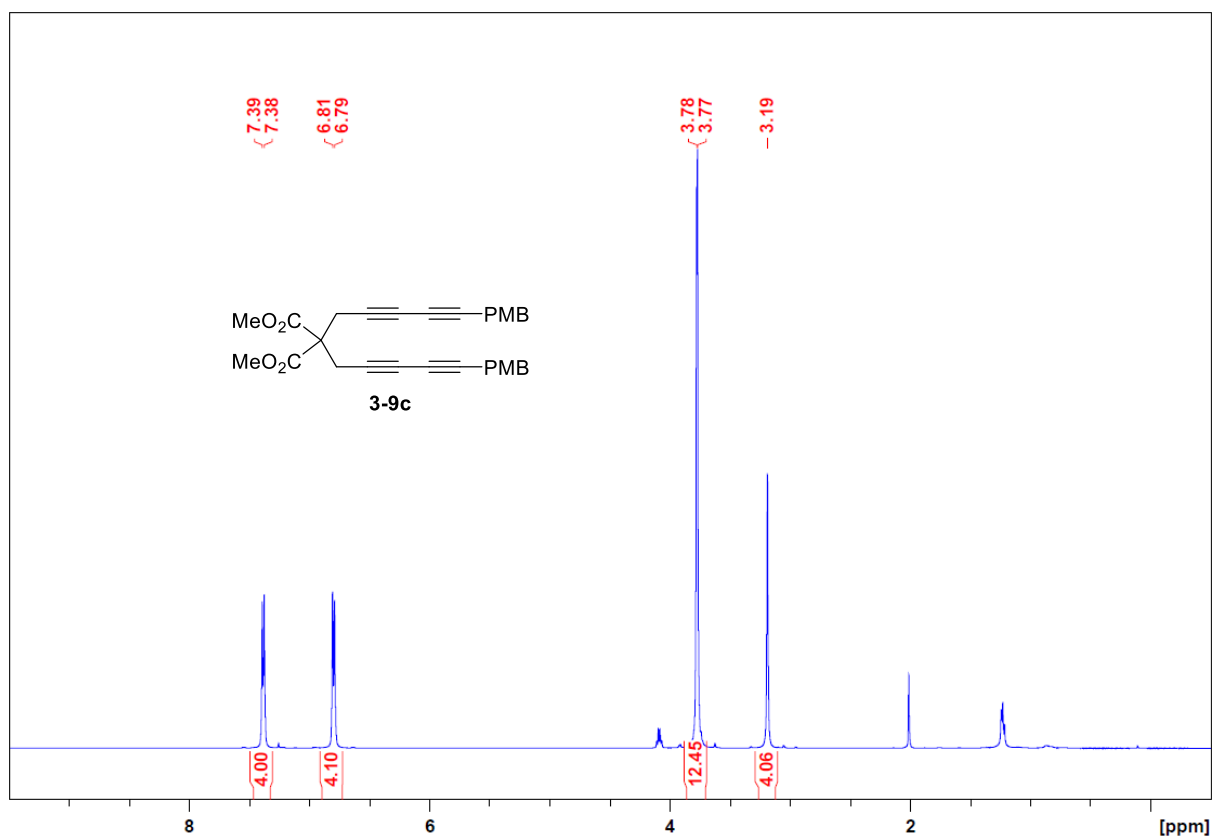


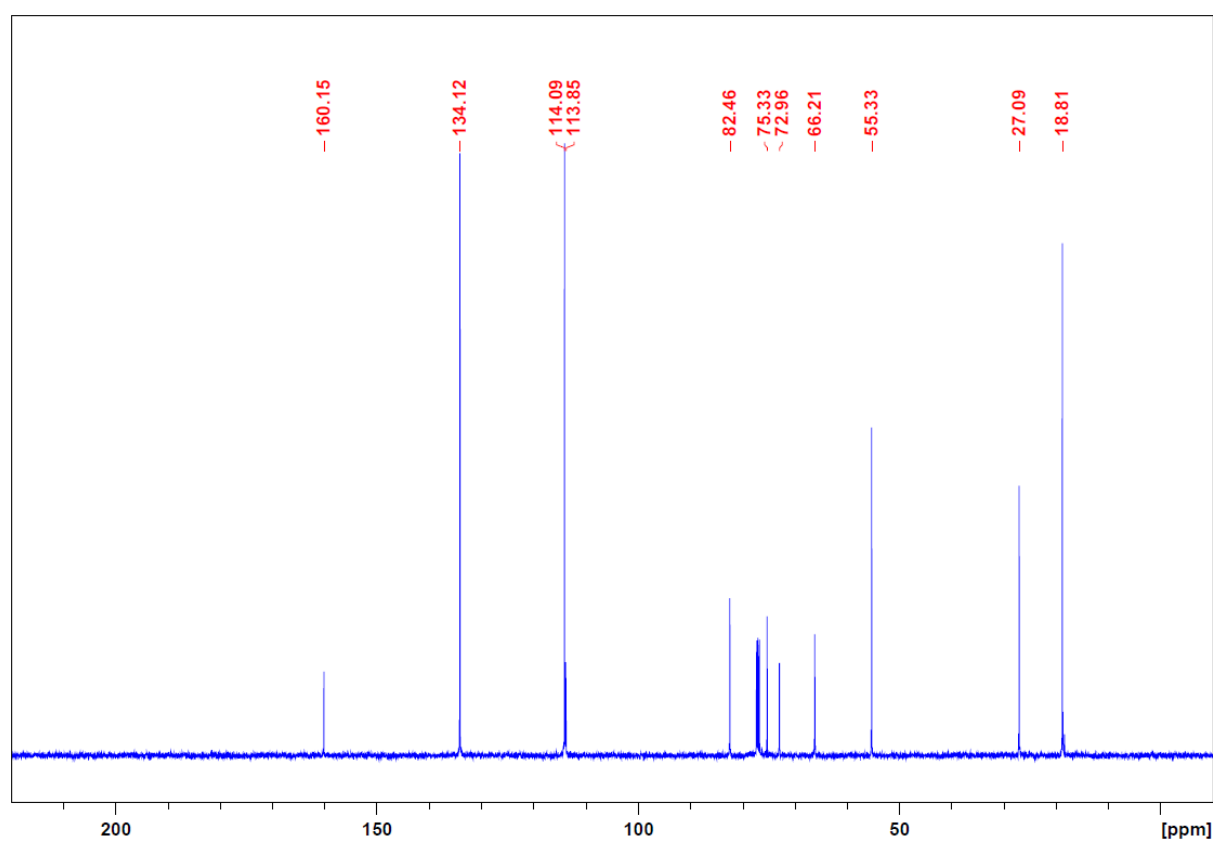
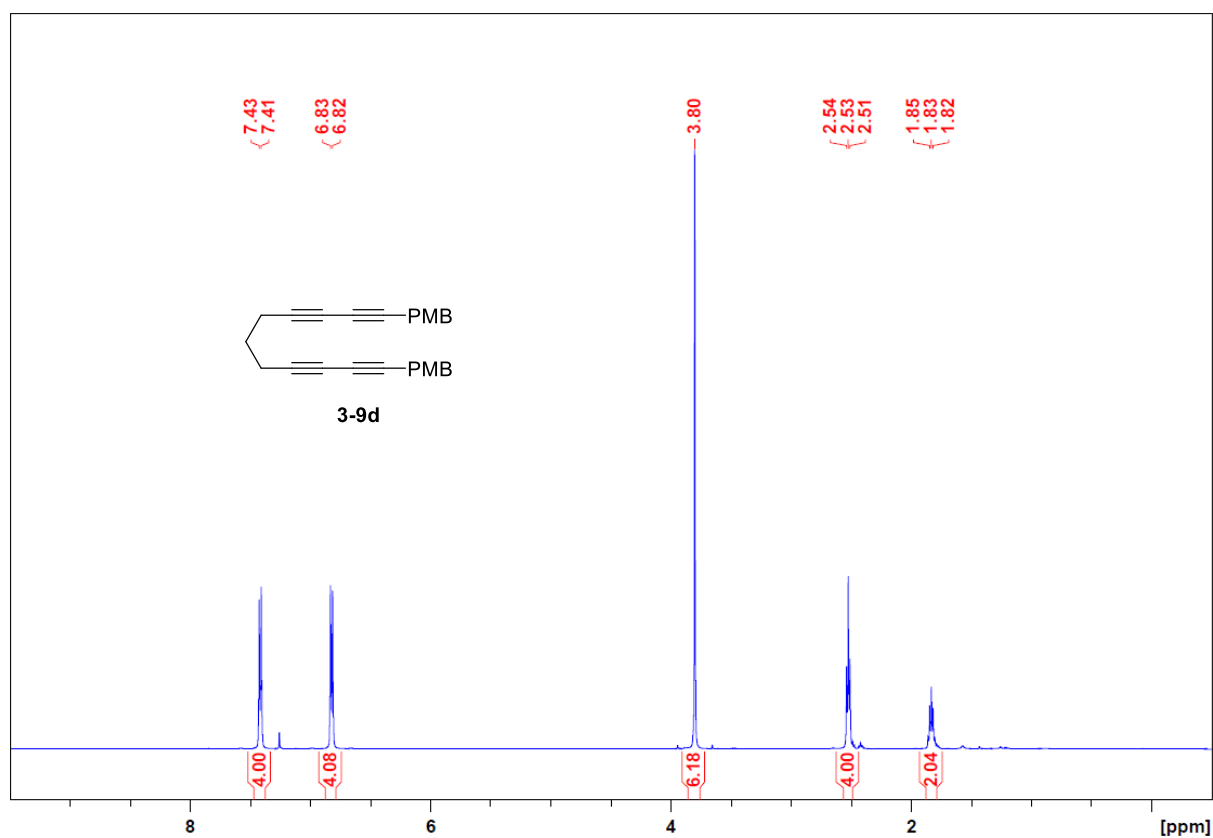
Appendix II
Selected NMR Spectra for Chapter 3

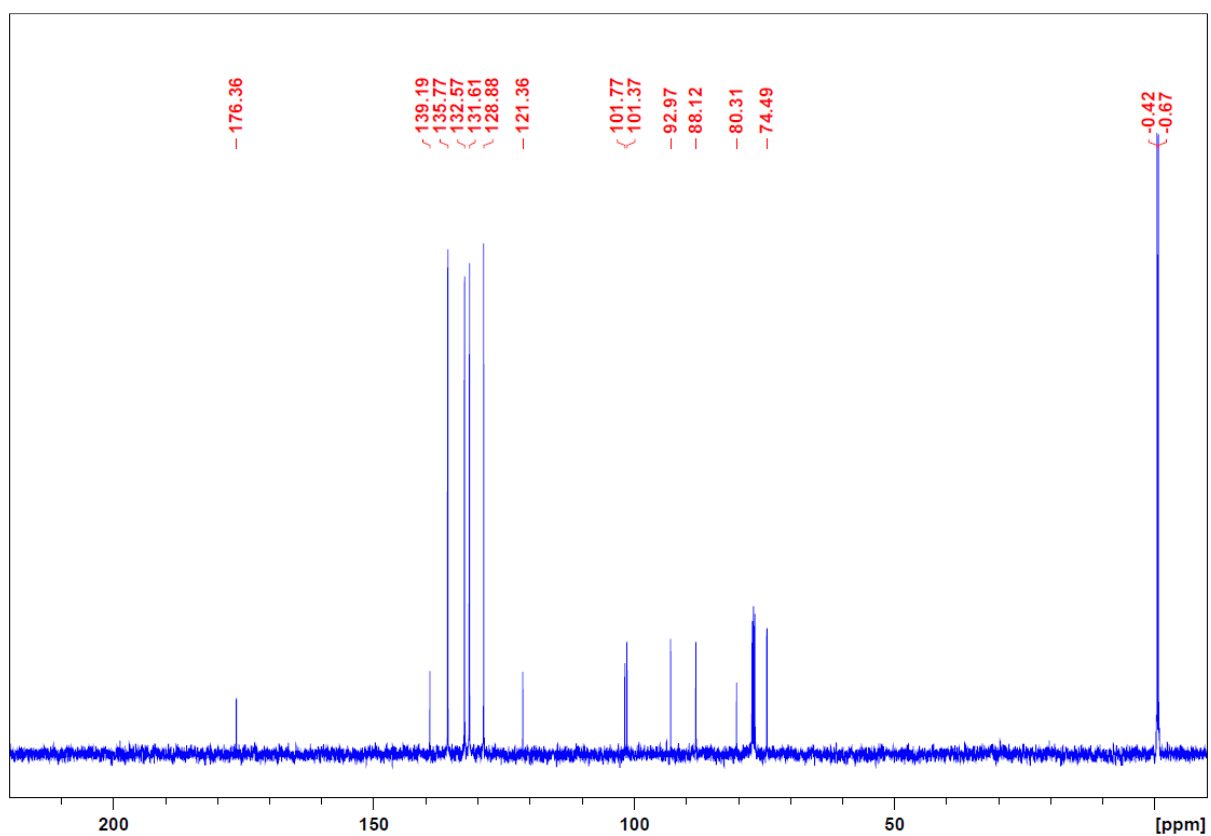
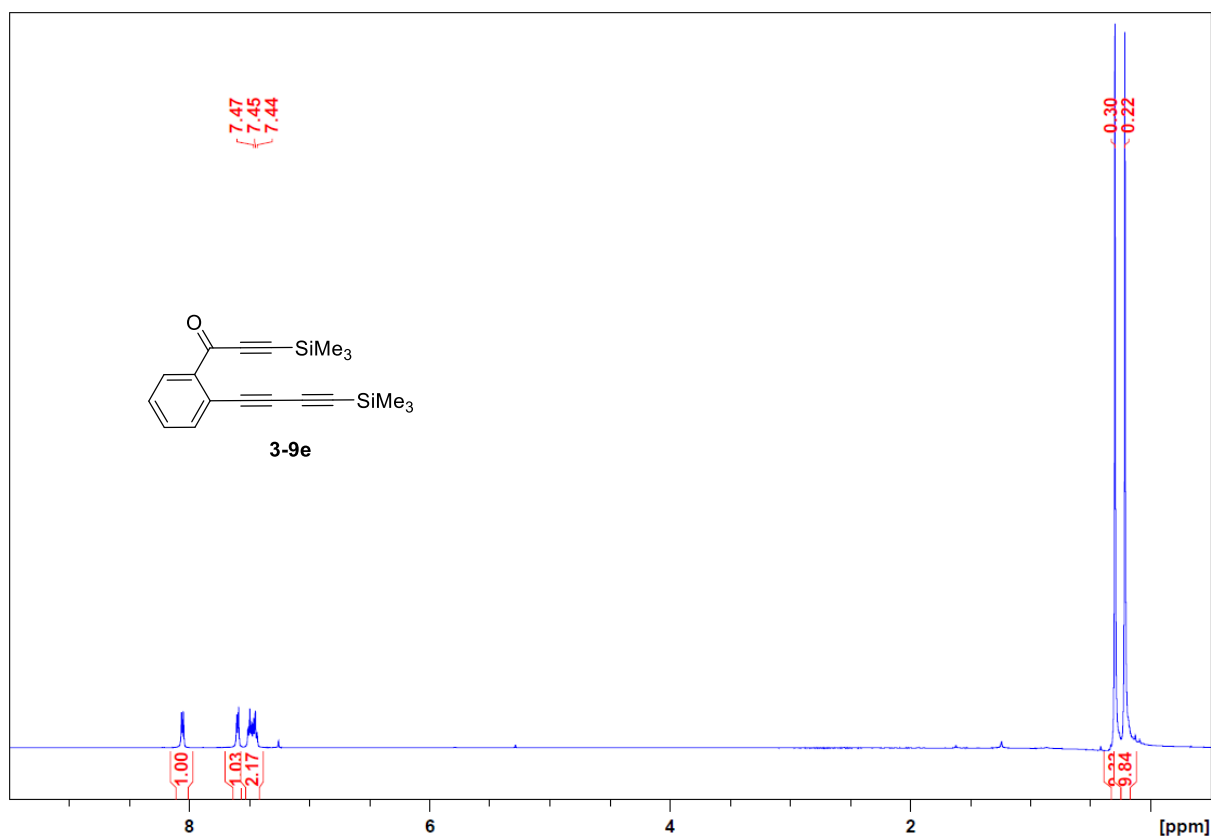
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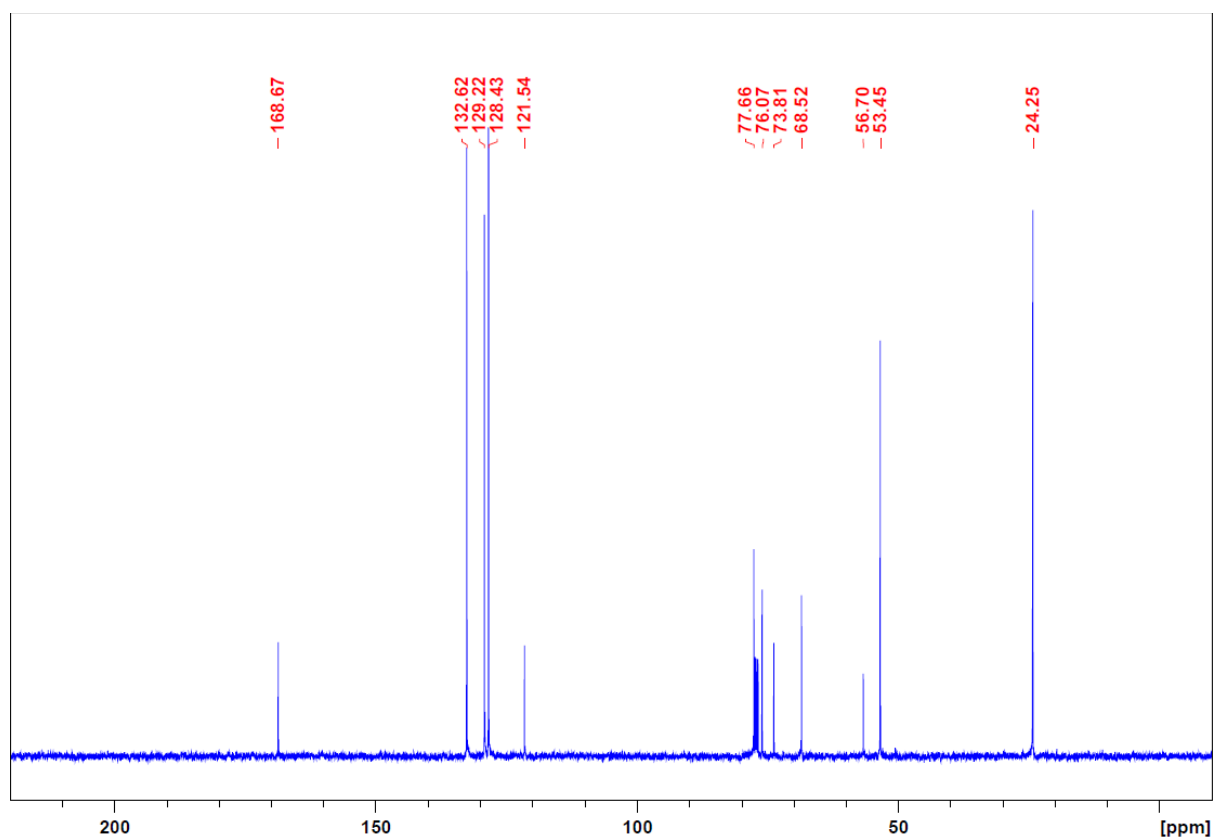
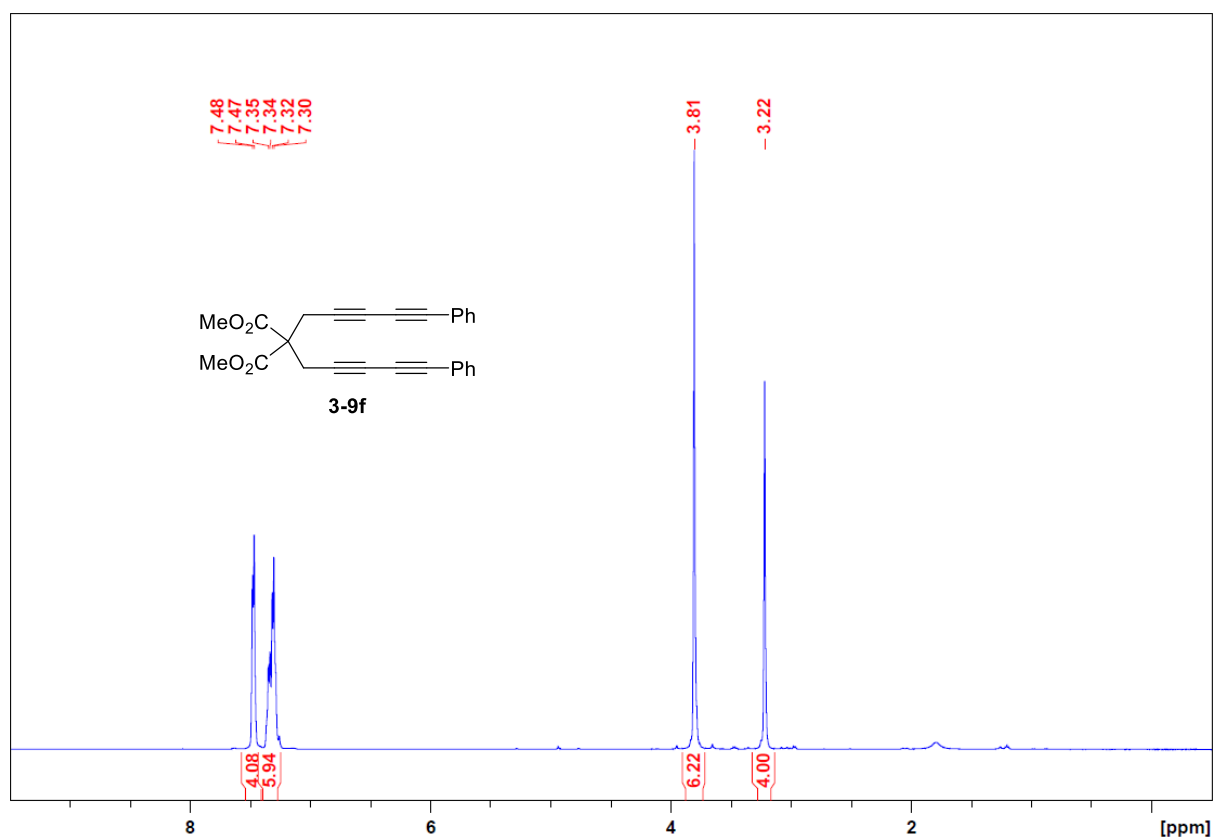


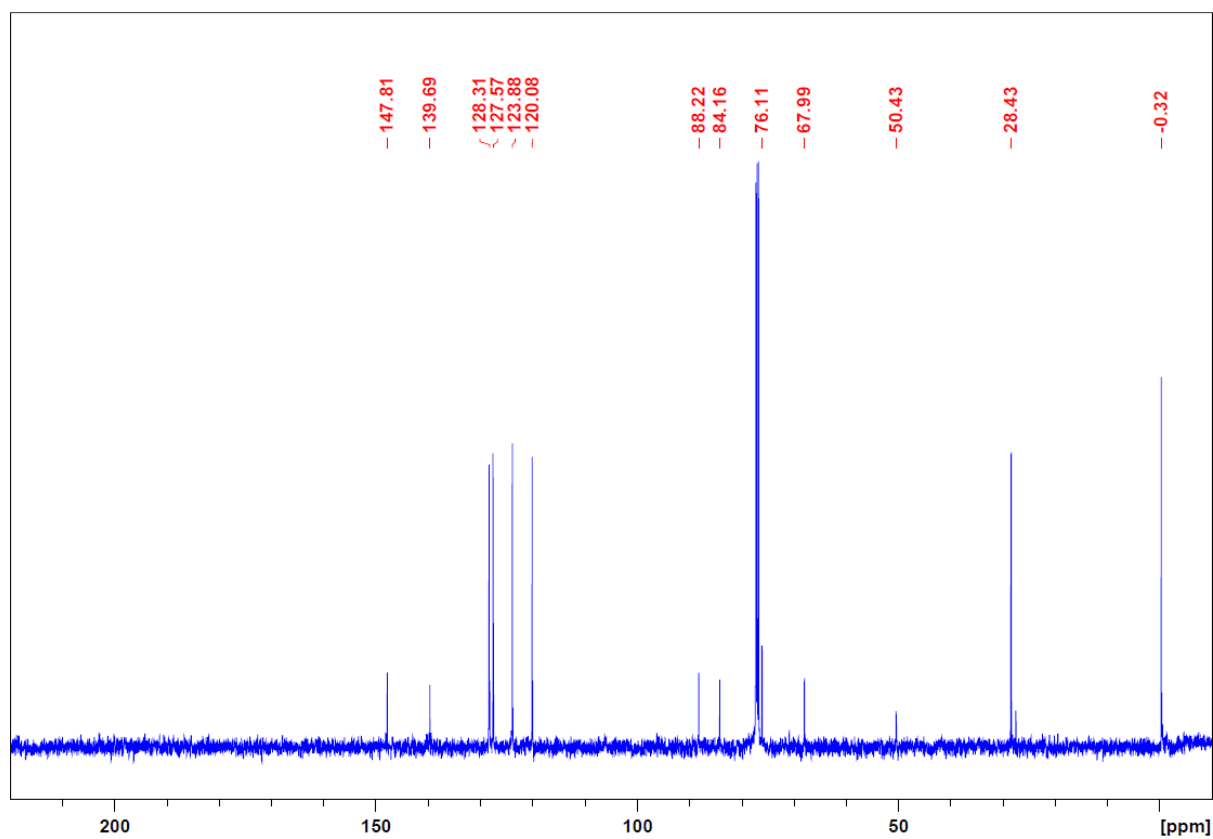
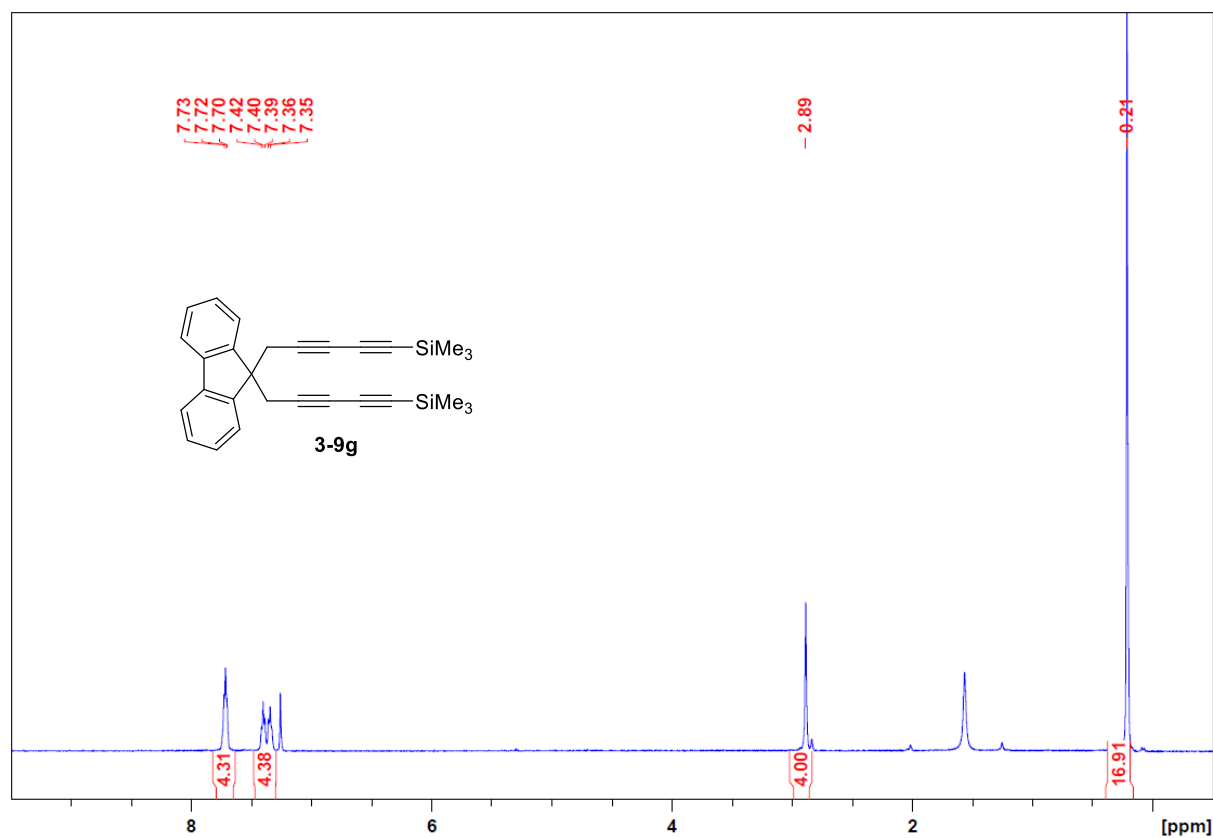


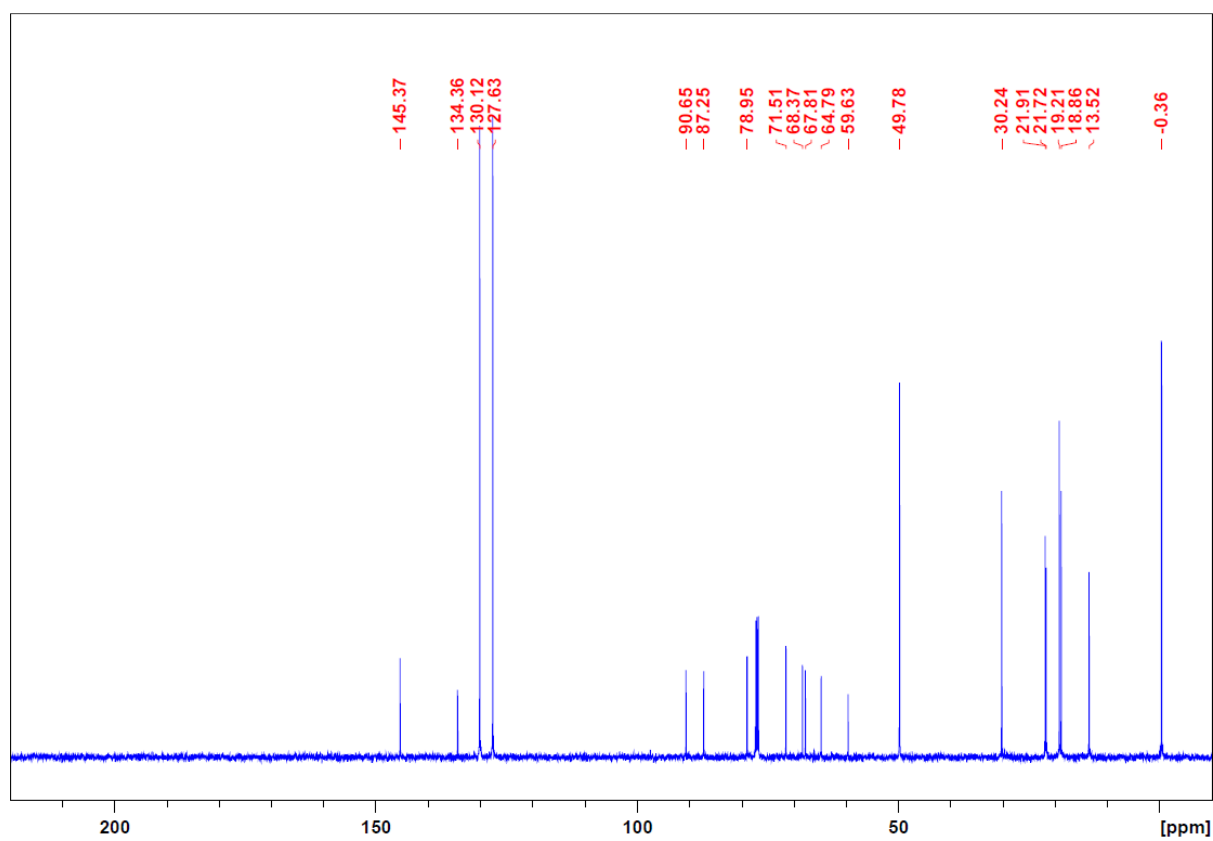
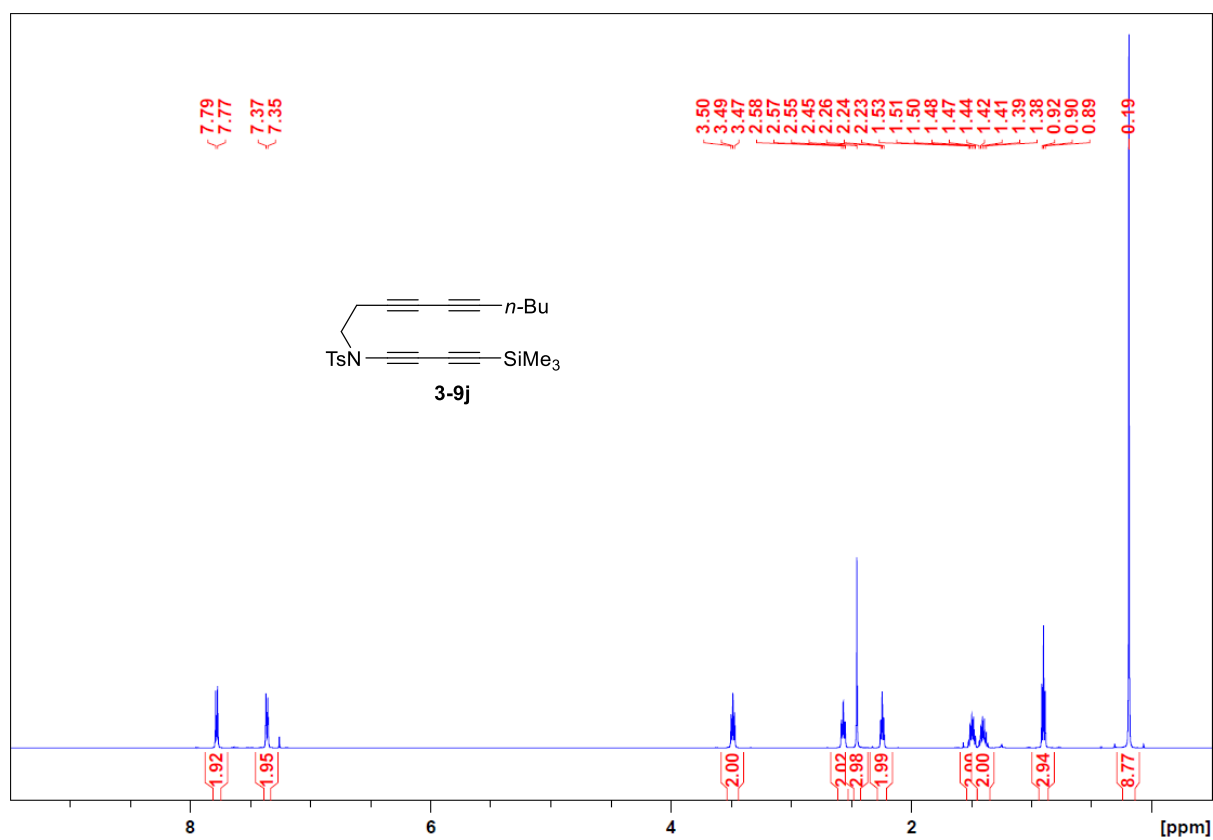


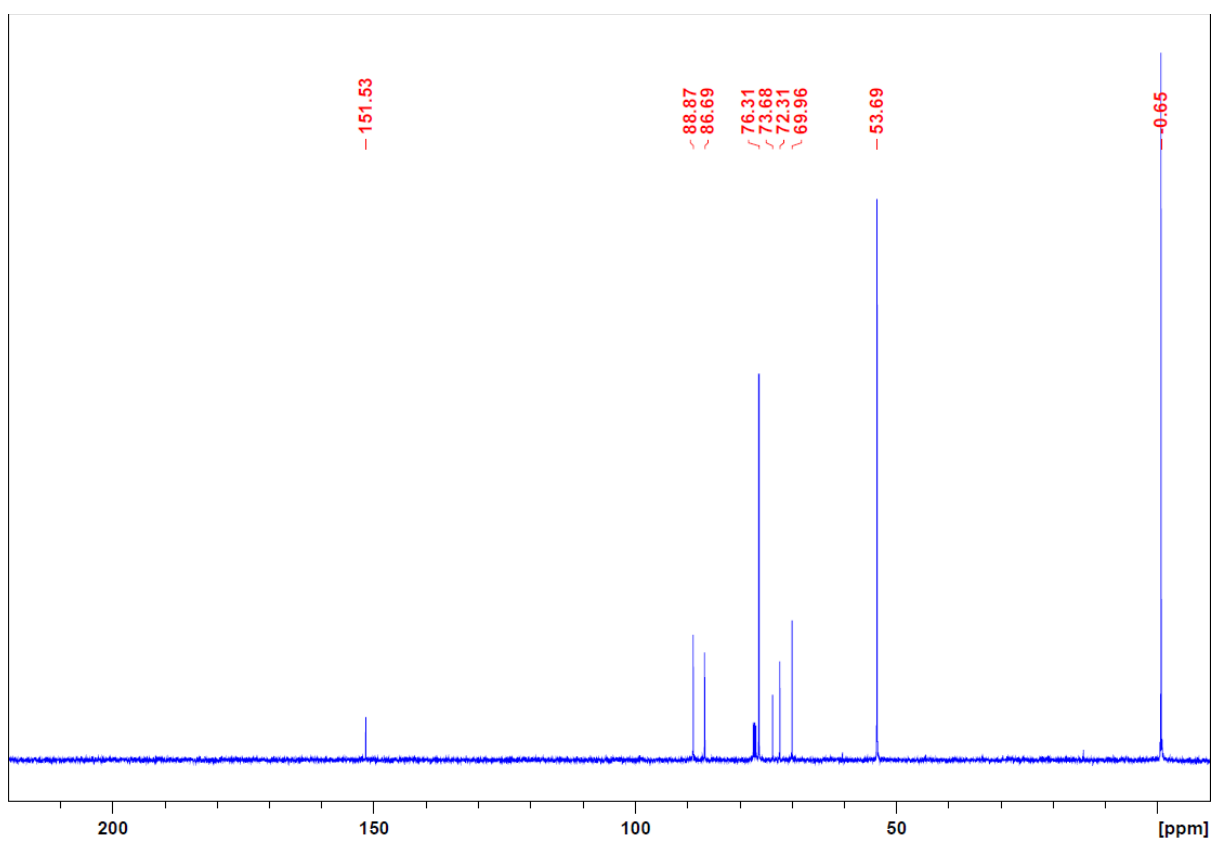
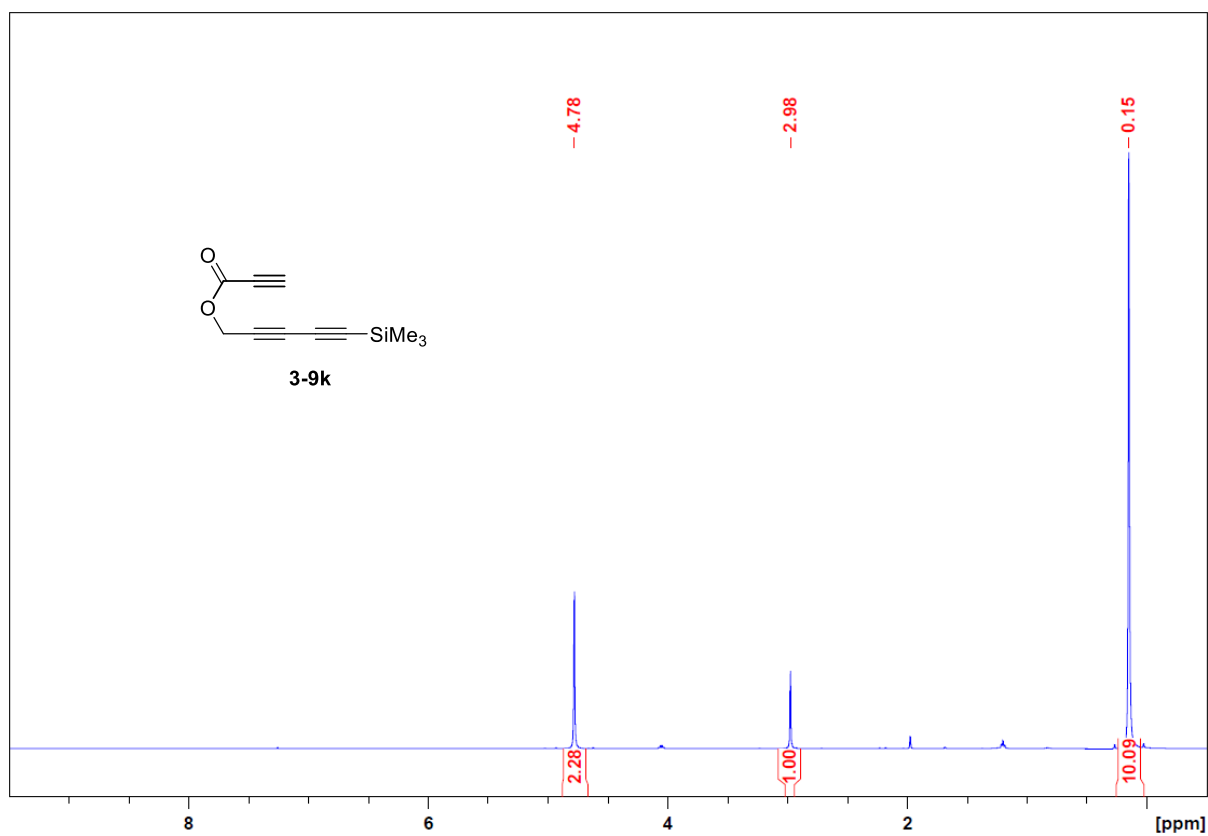


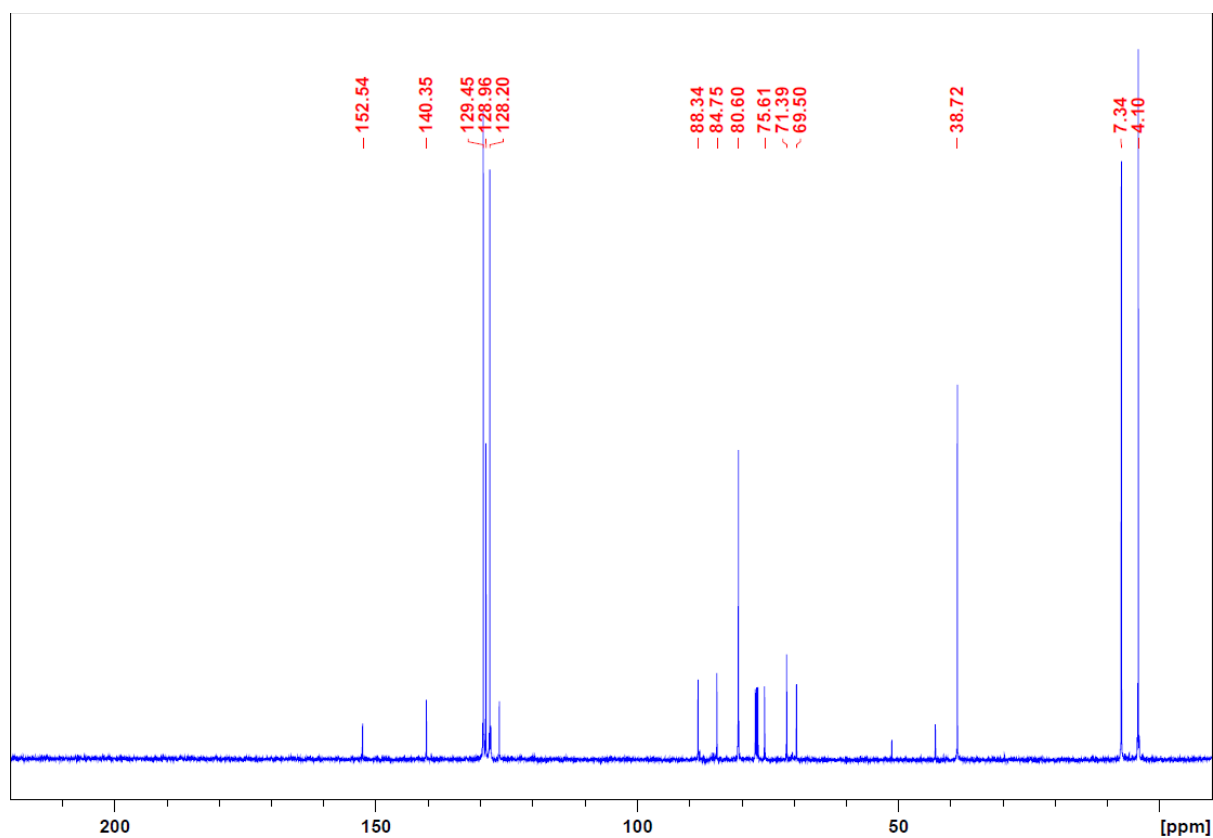
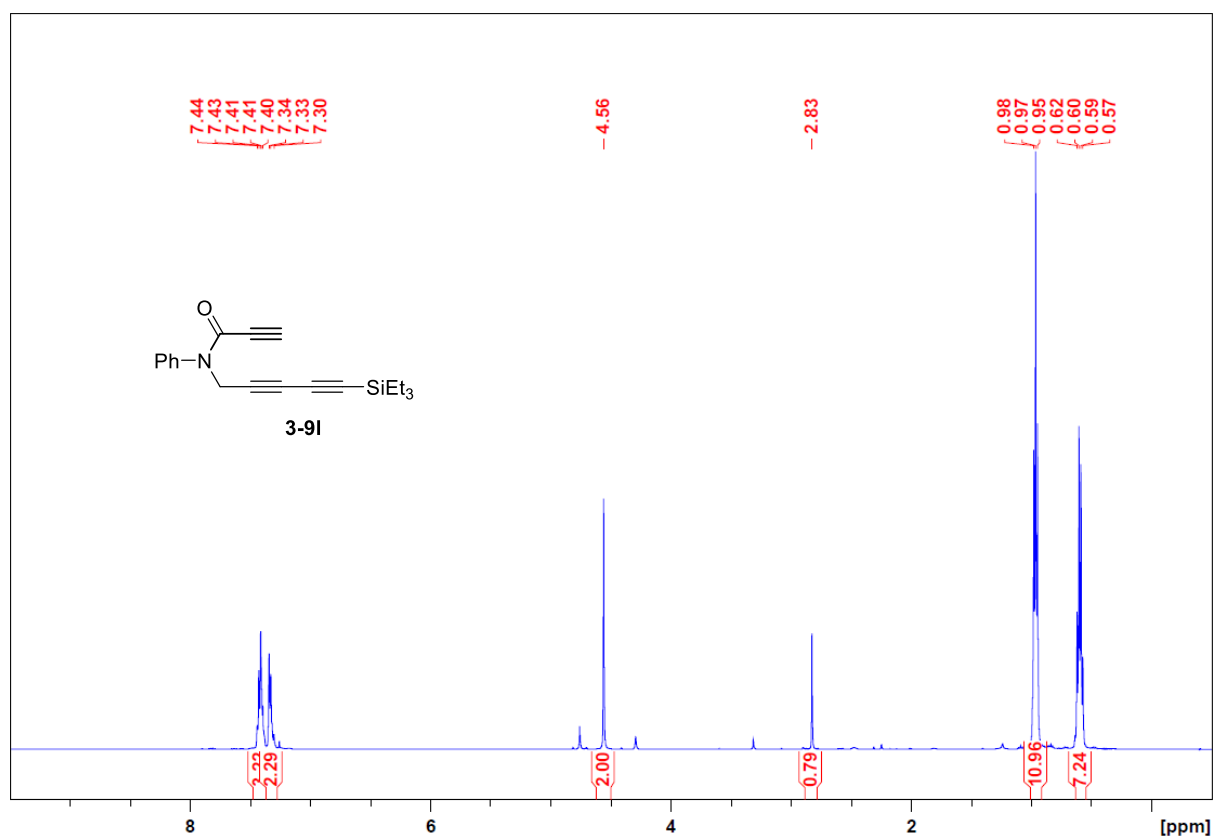






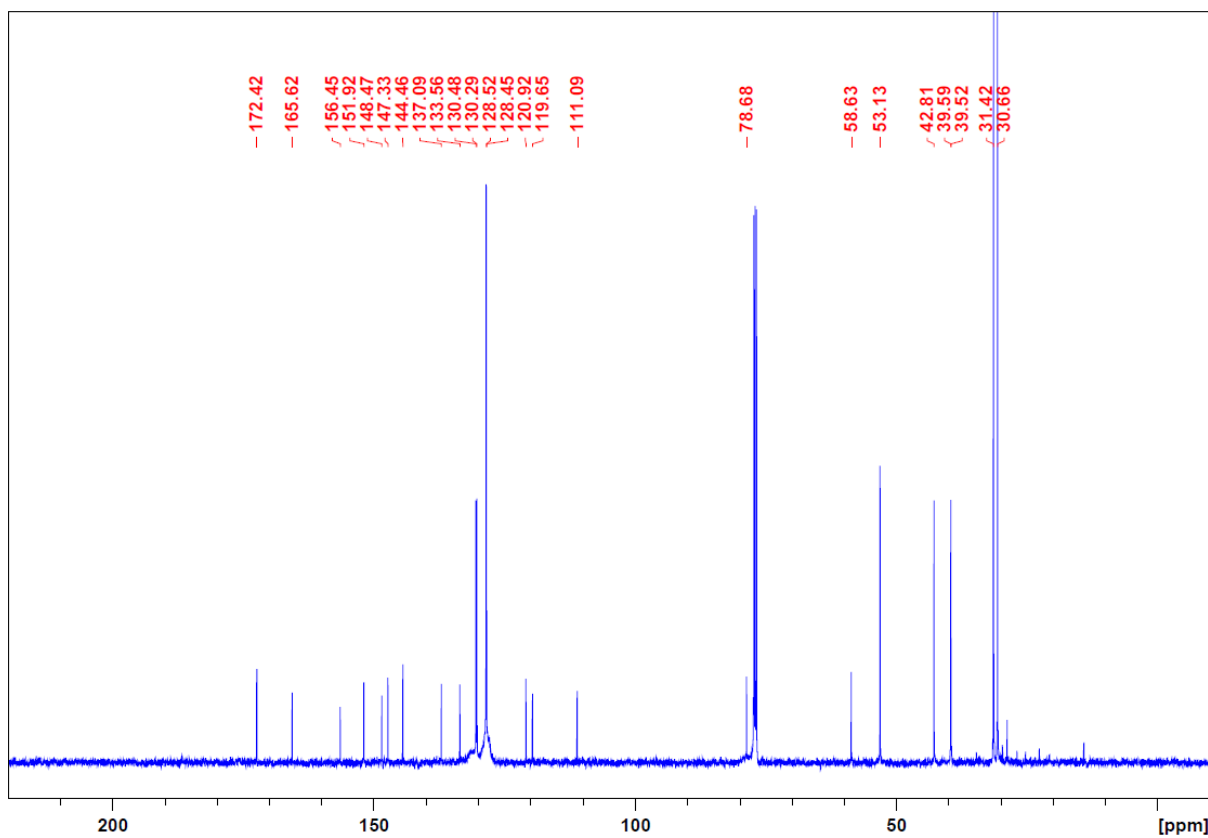
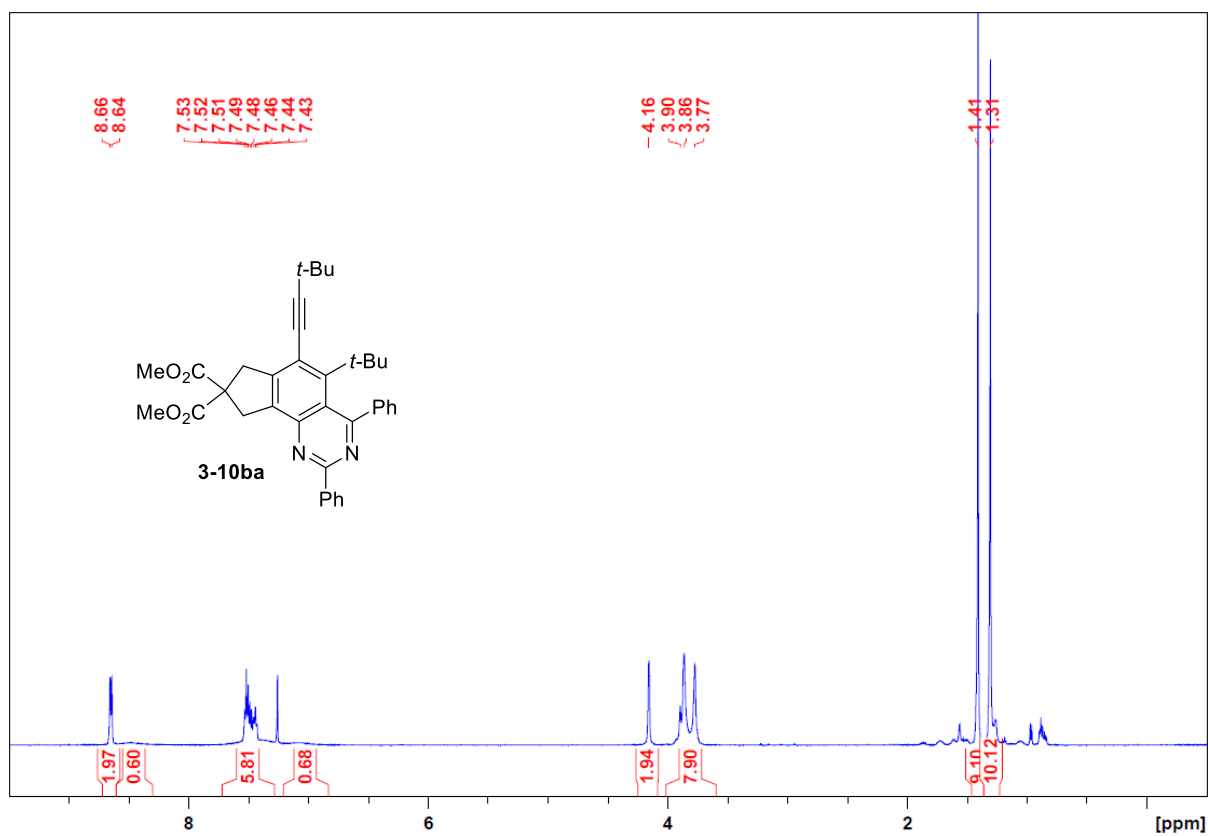


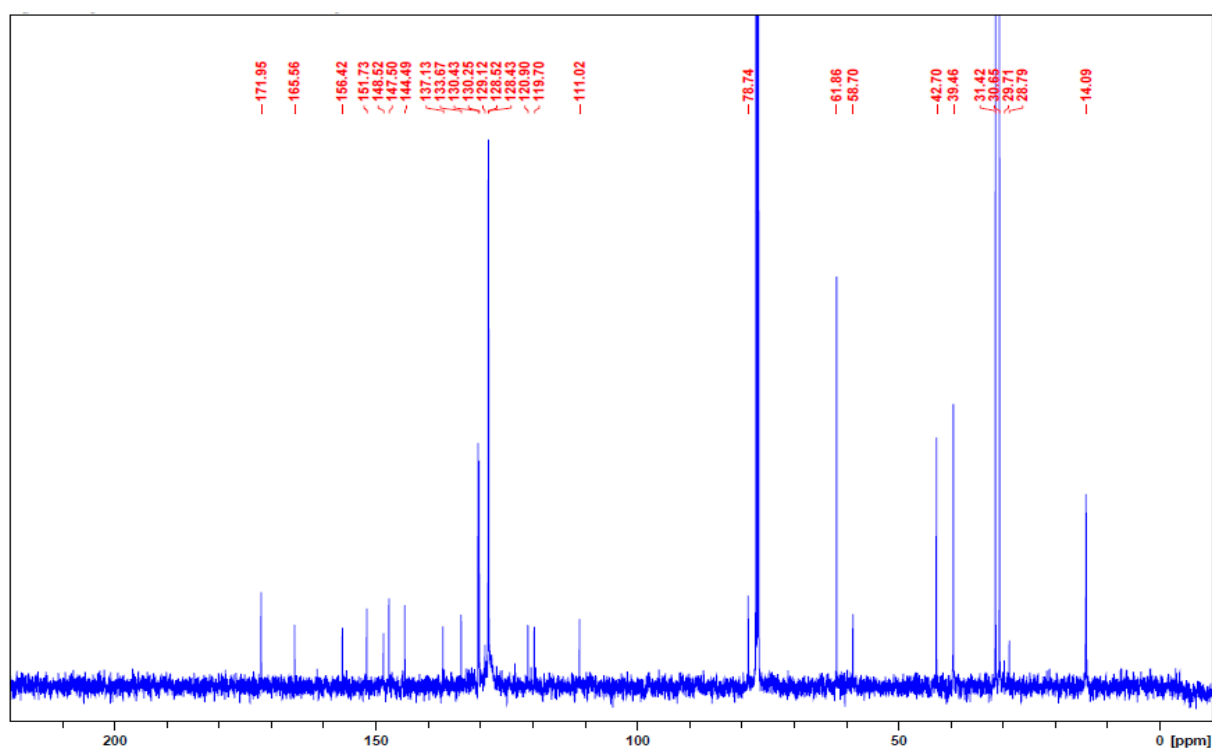
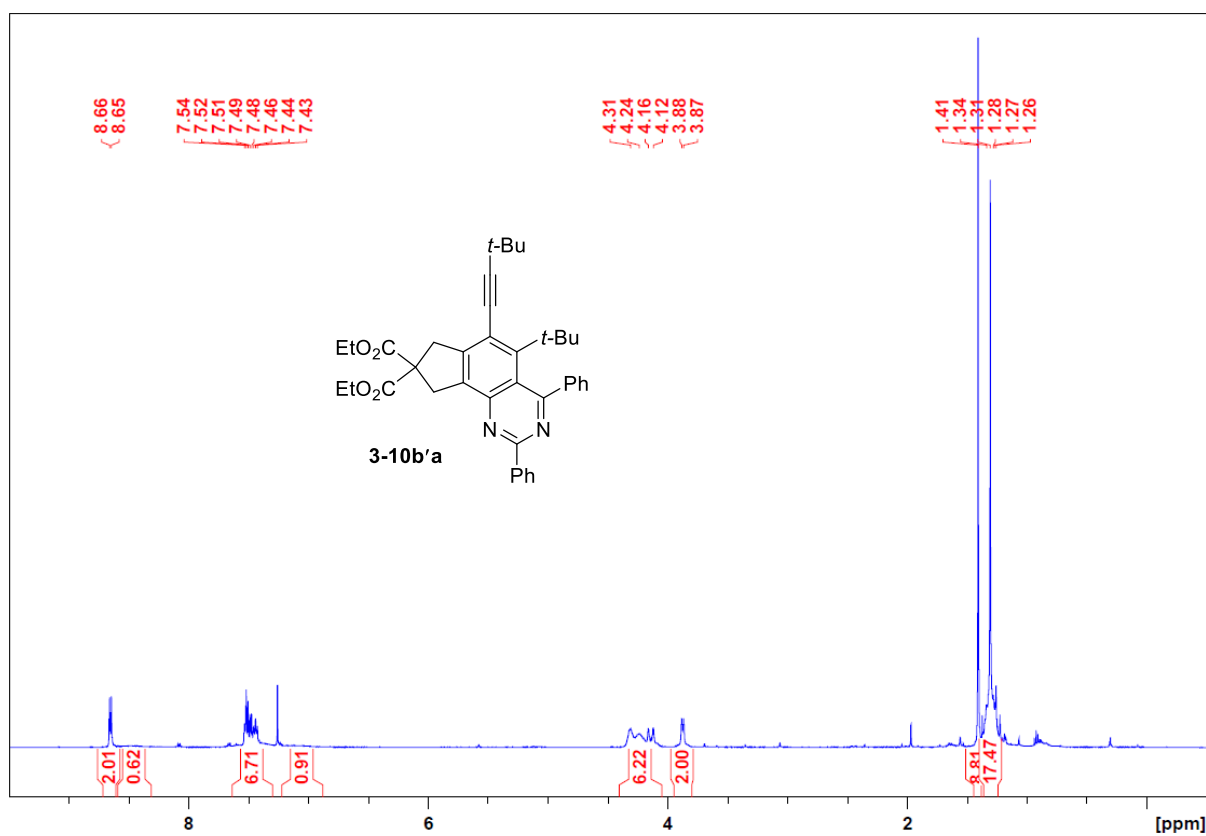


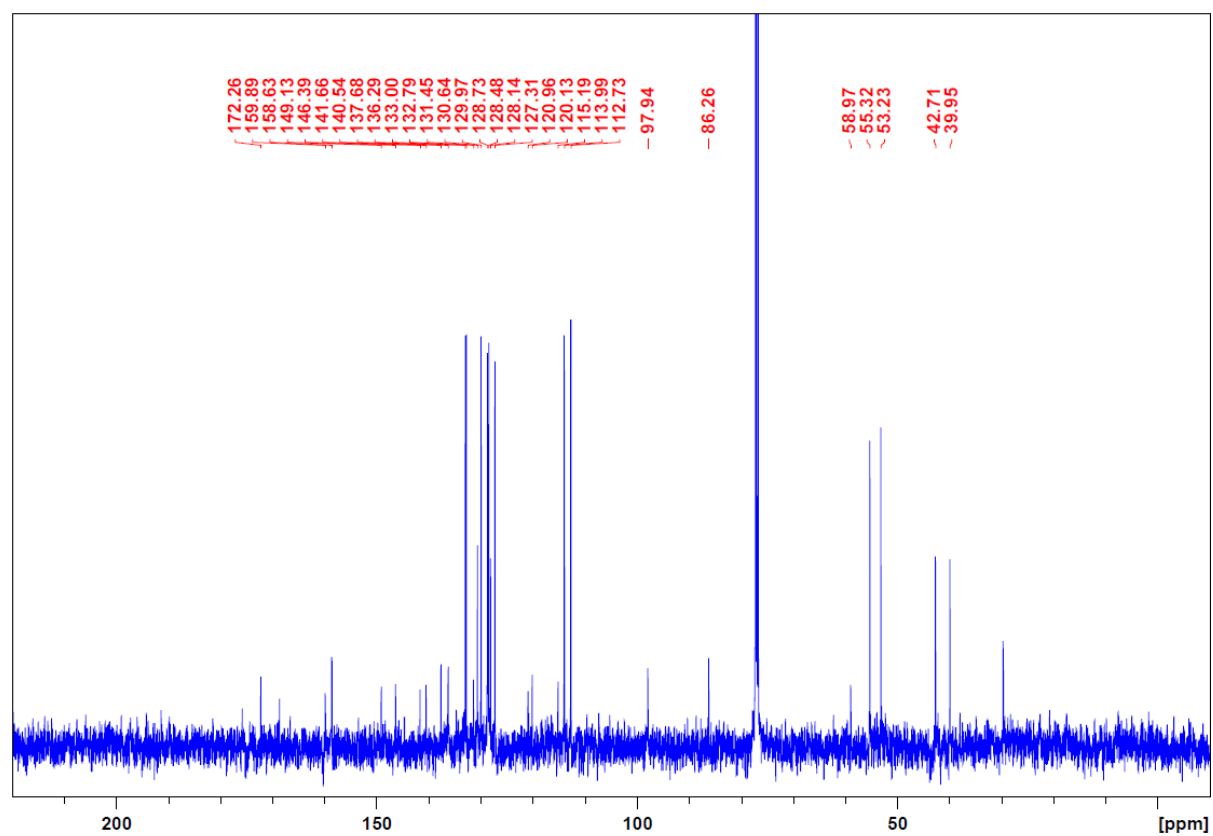
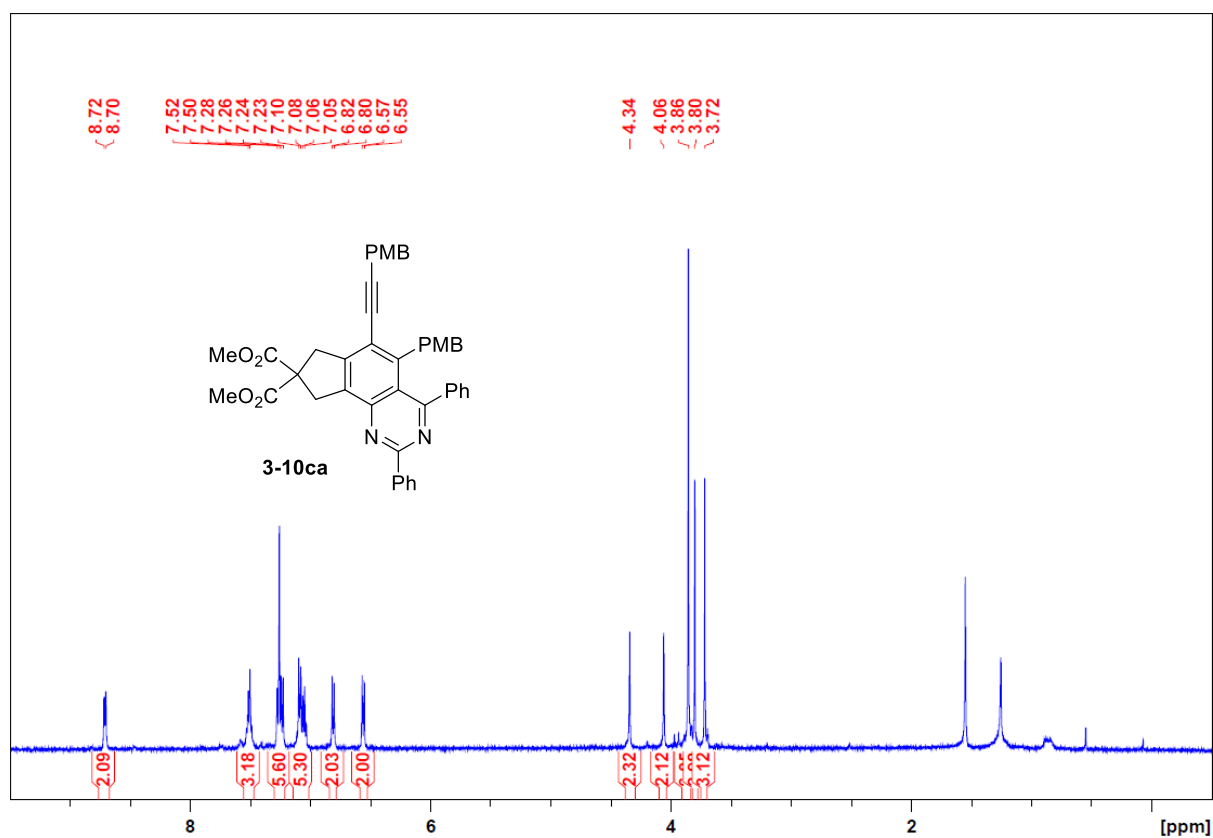


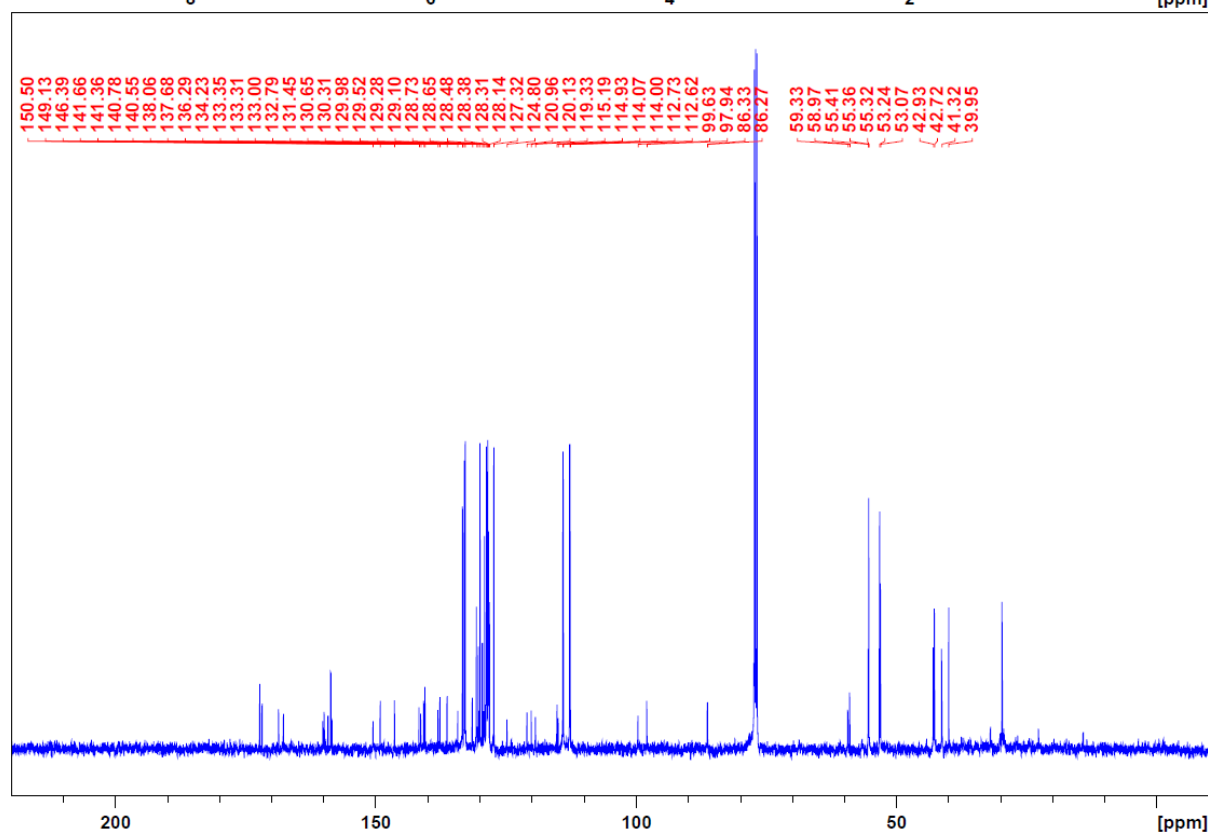
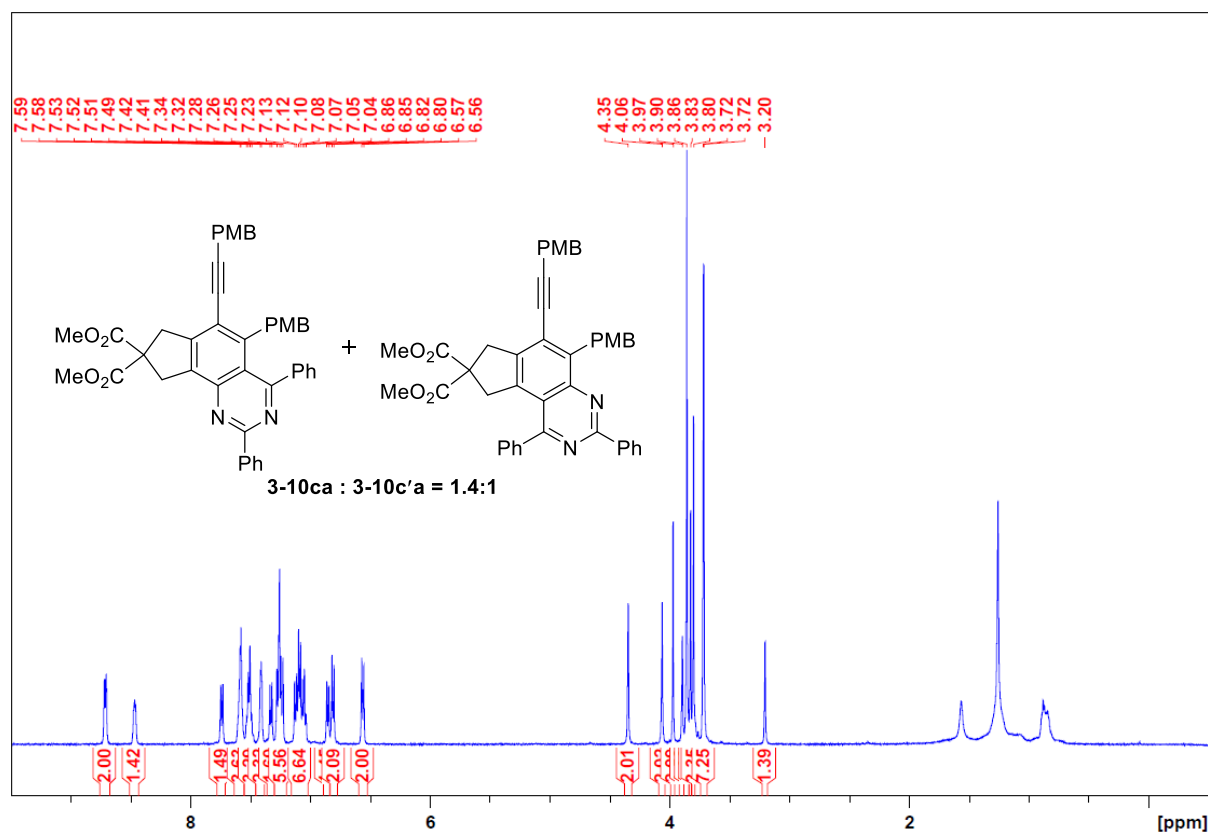
NMR Spectra of Quinazoline Products

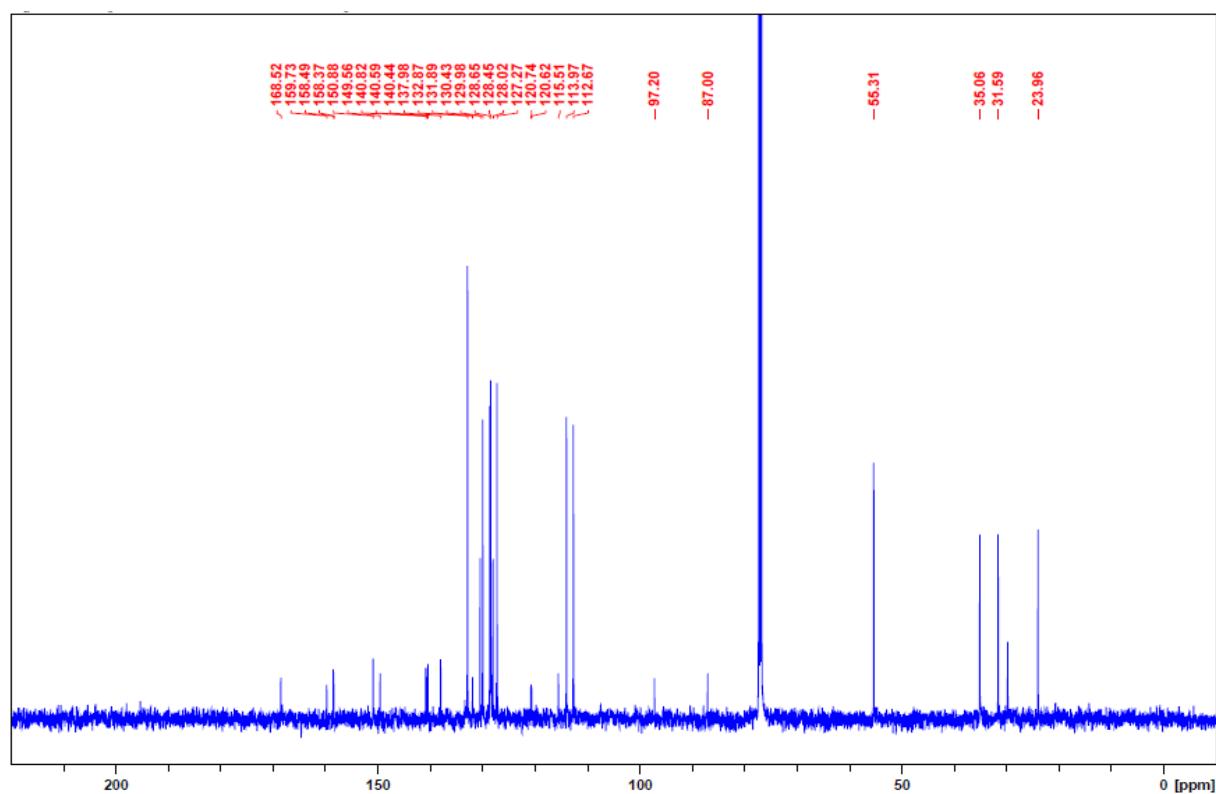
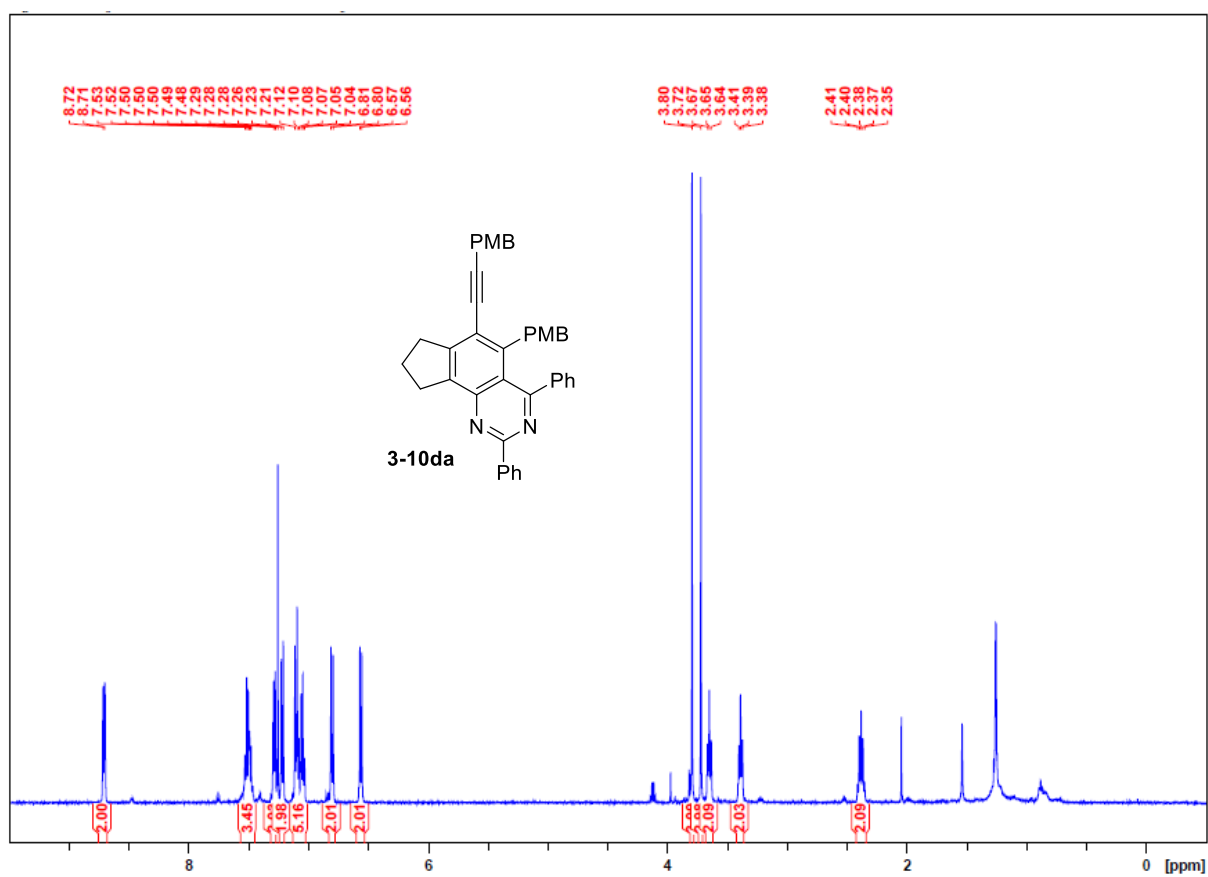


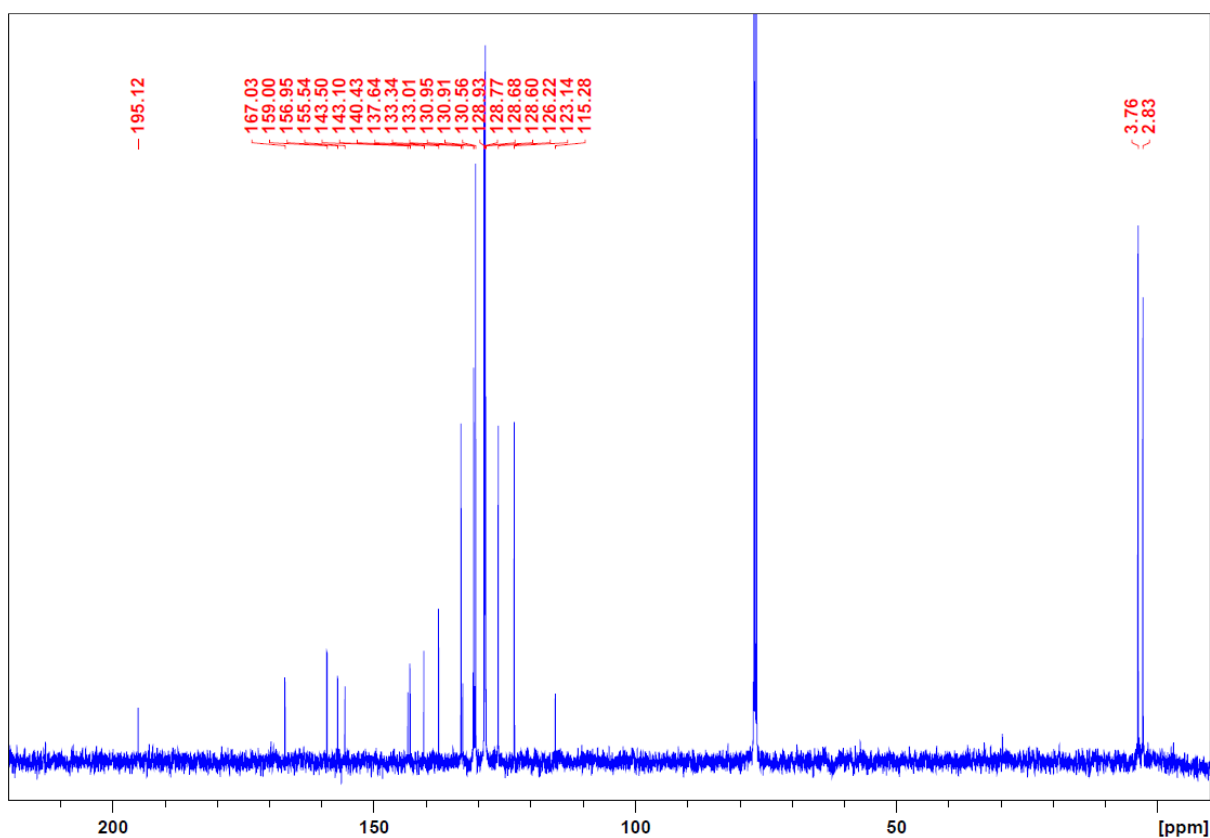
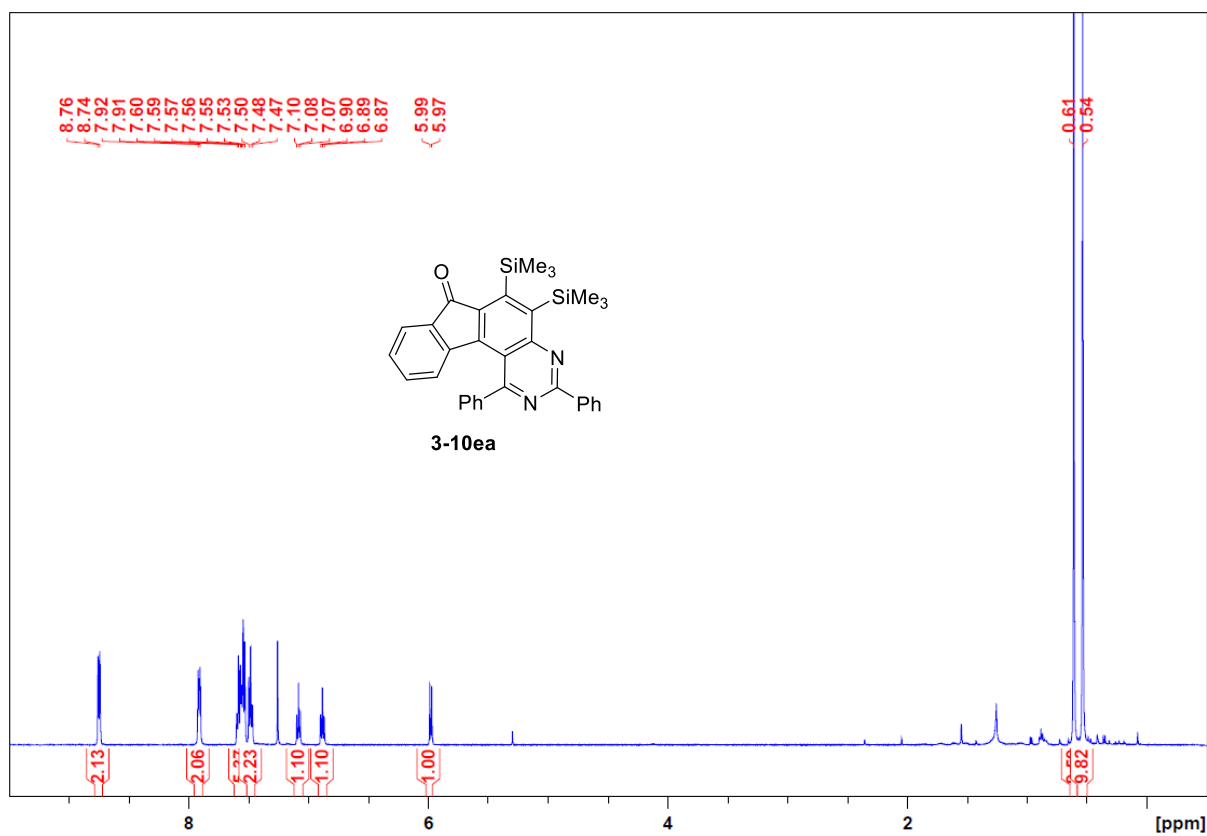


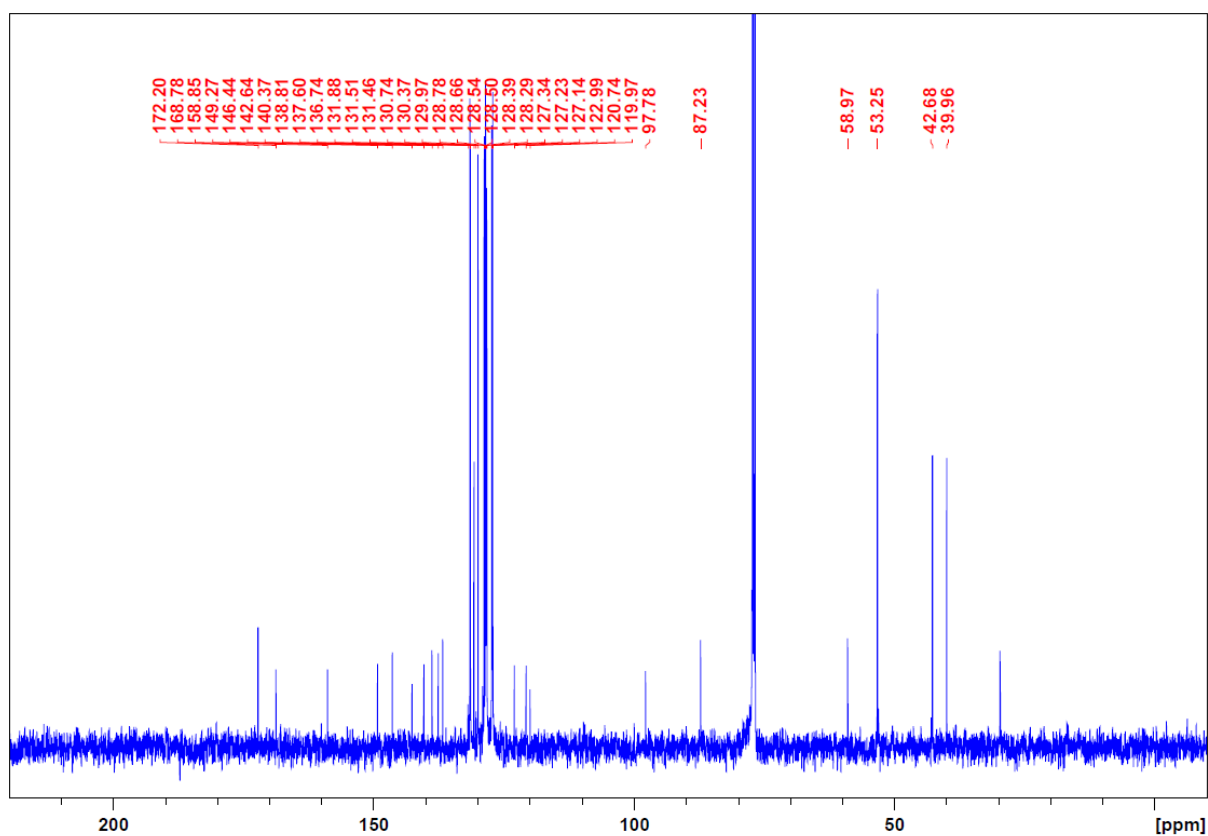
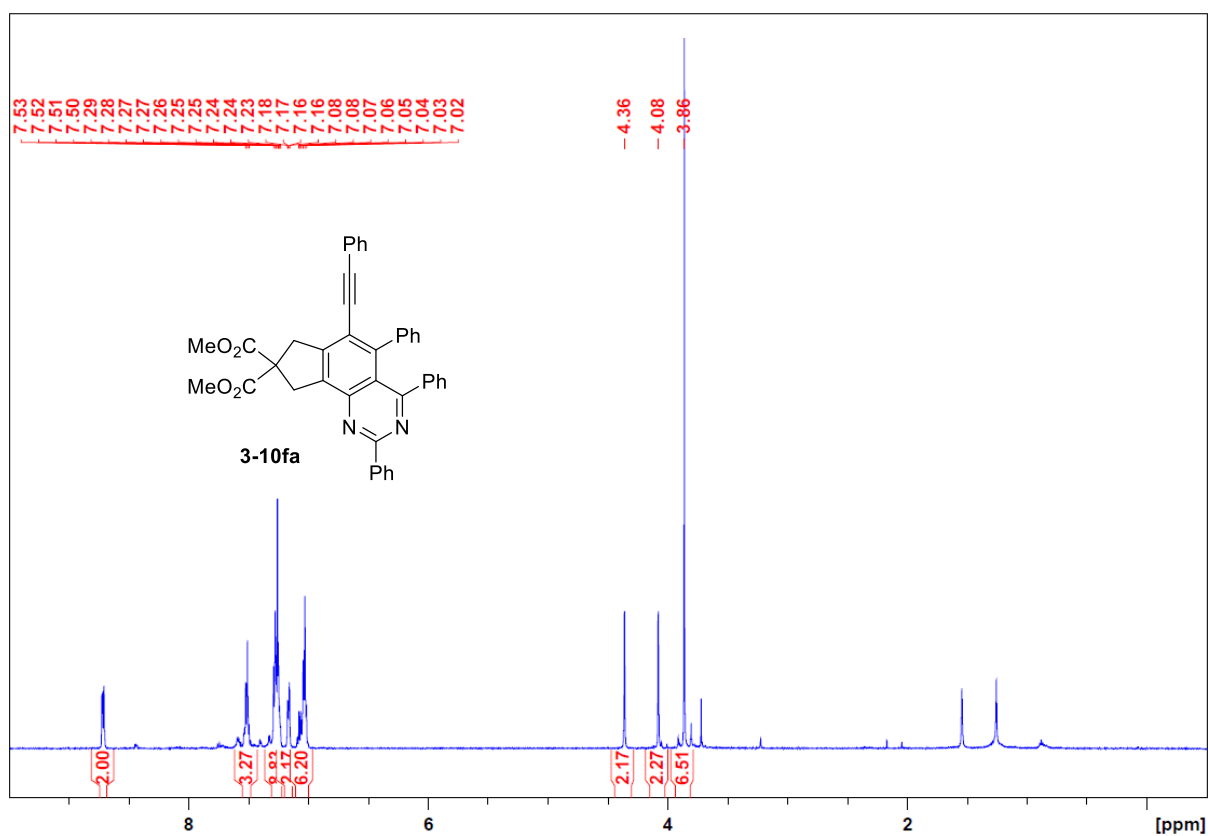


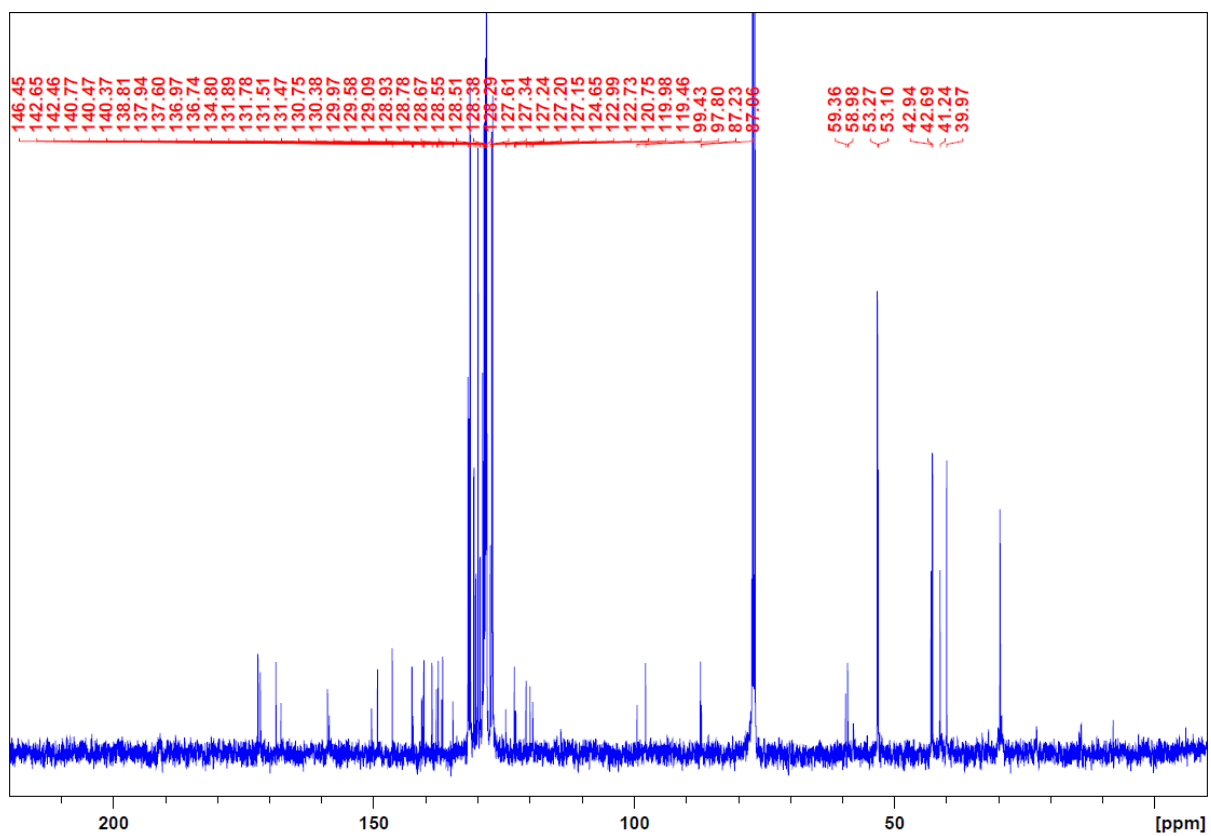
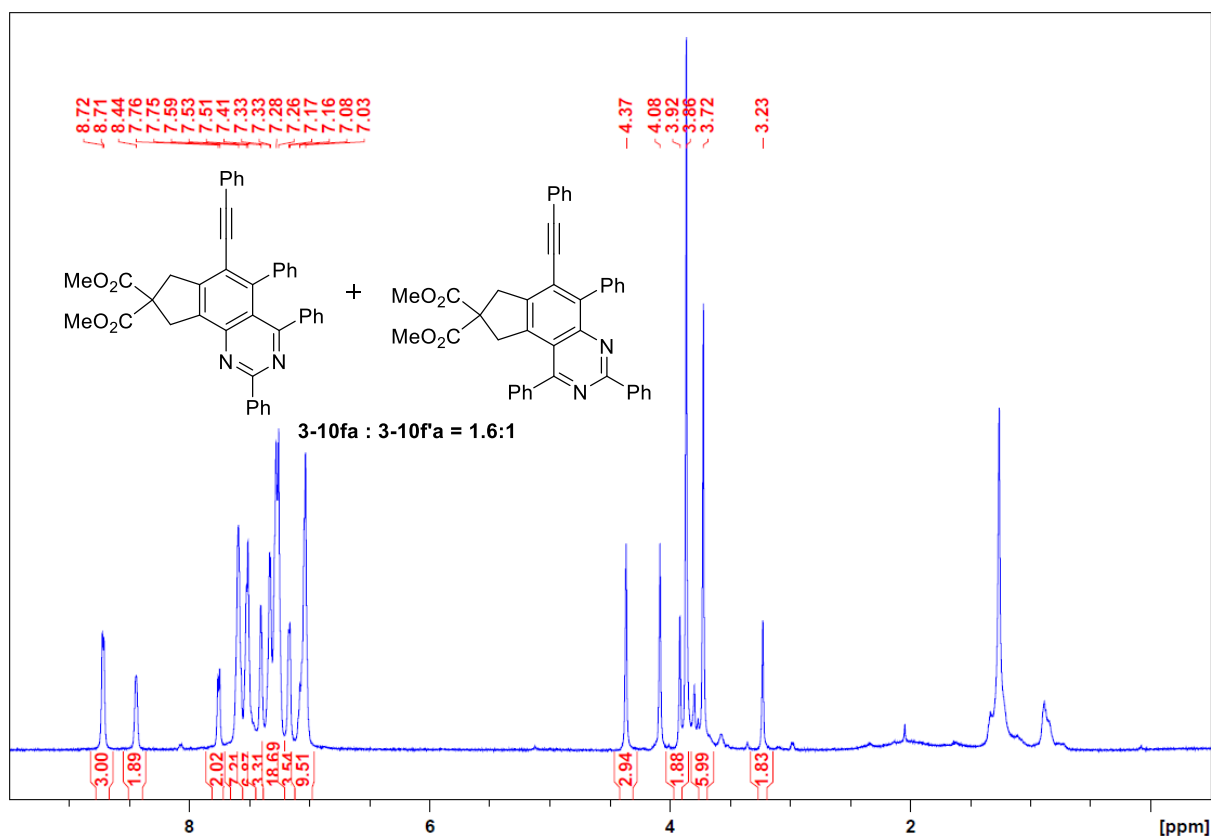


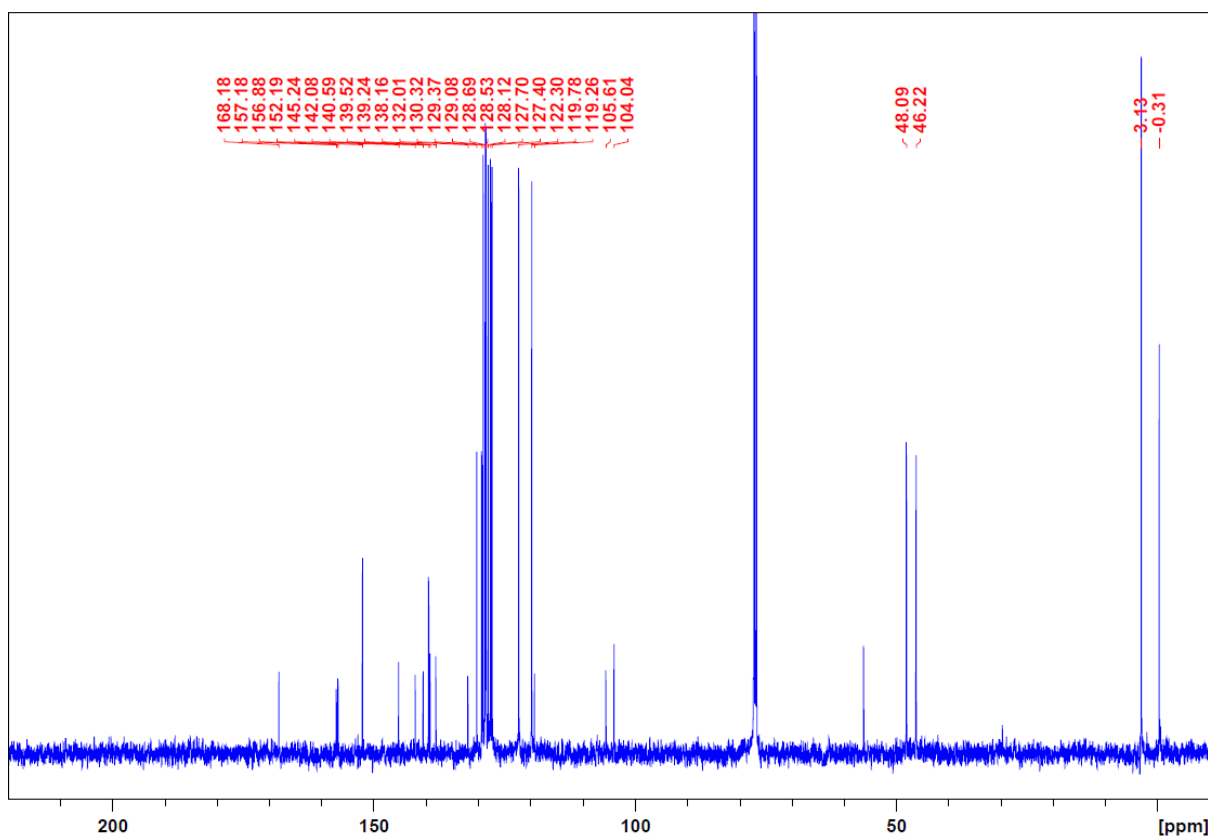
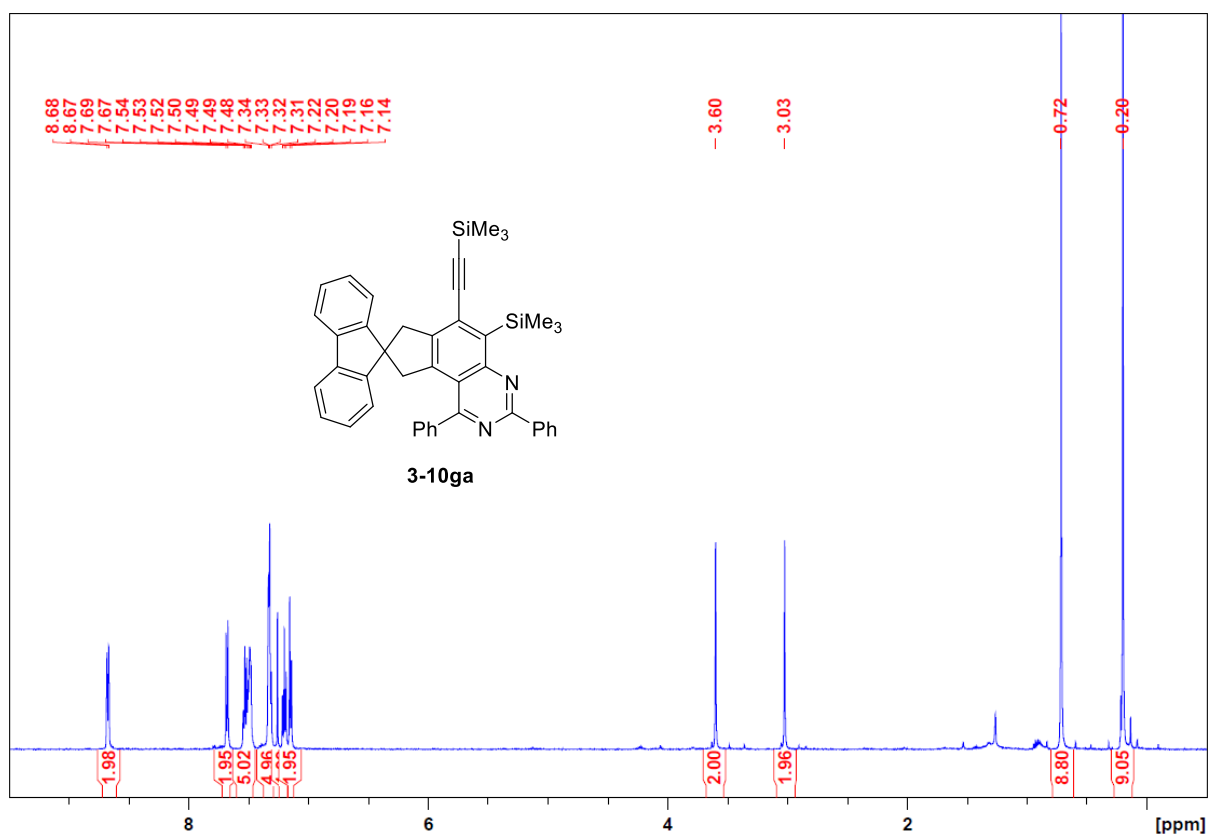


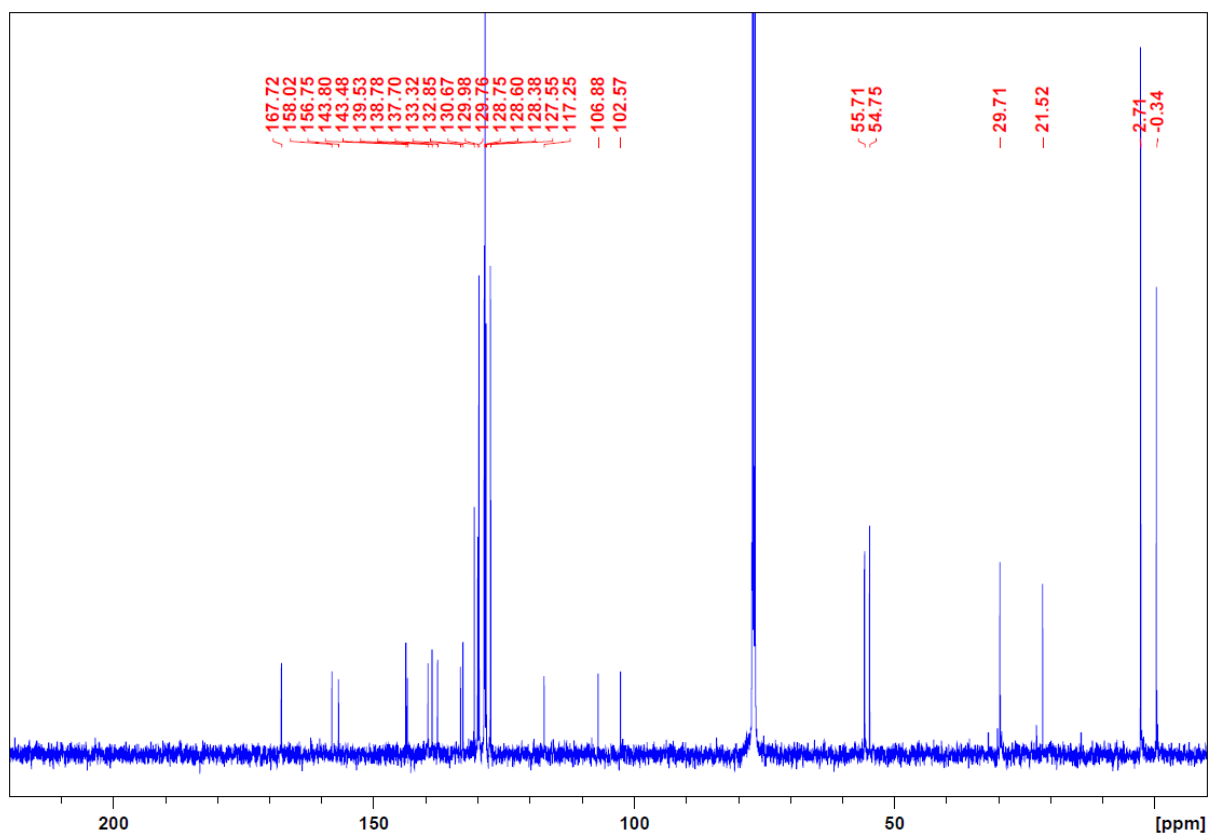
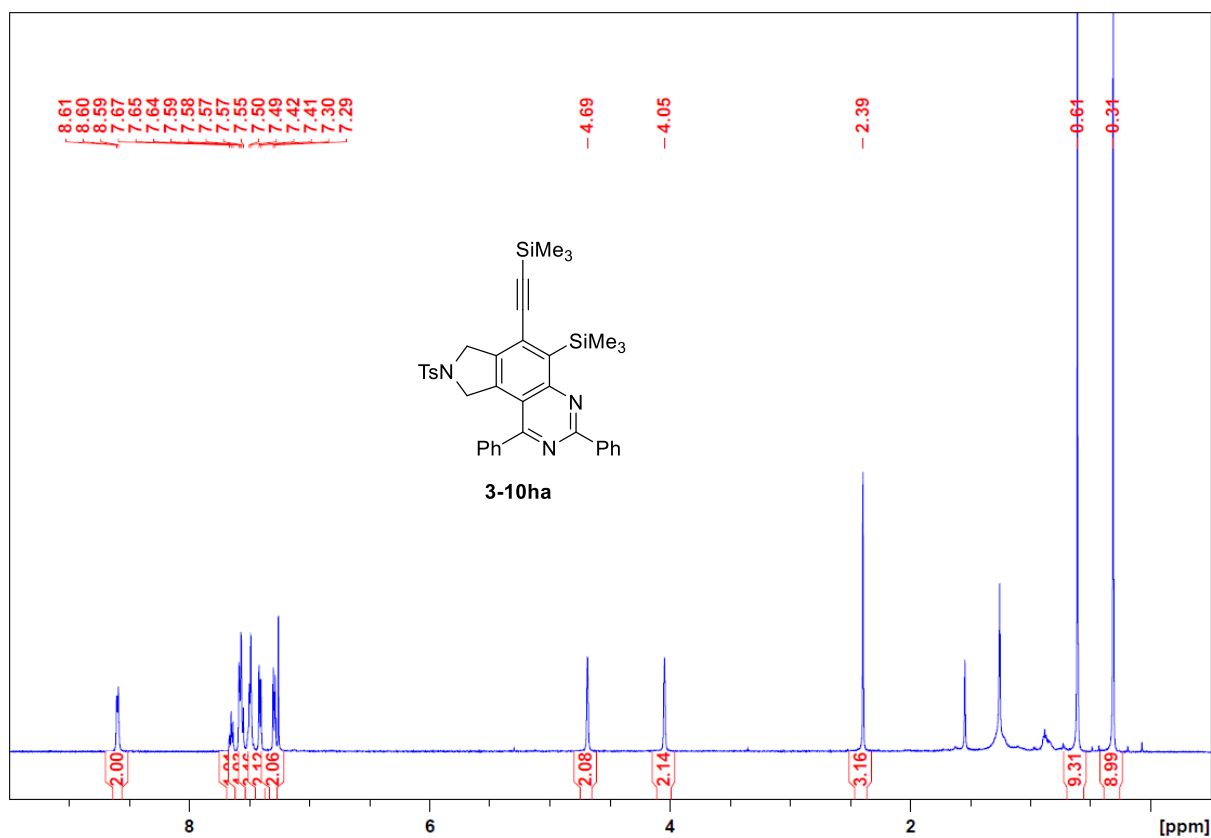


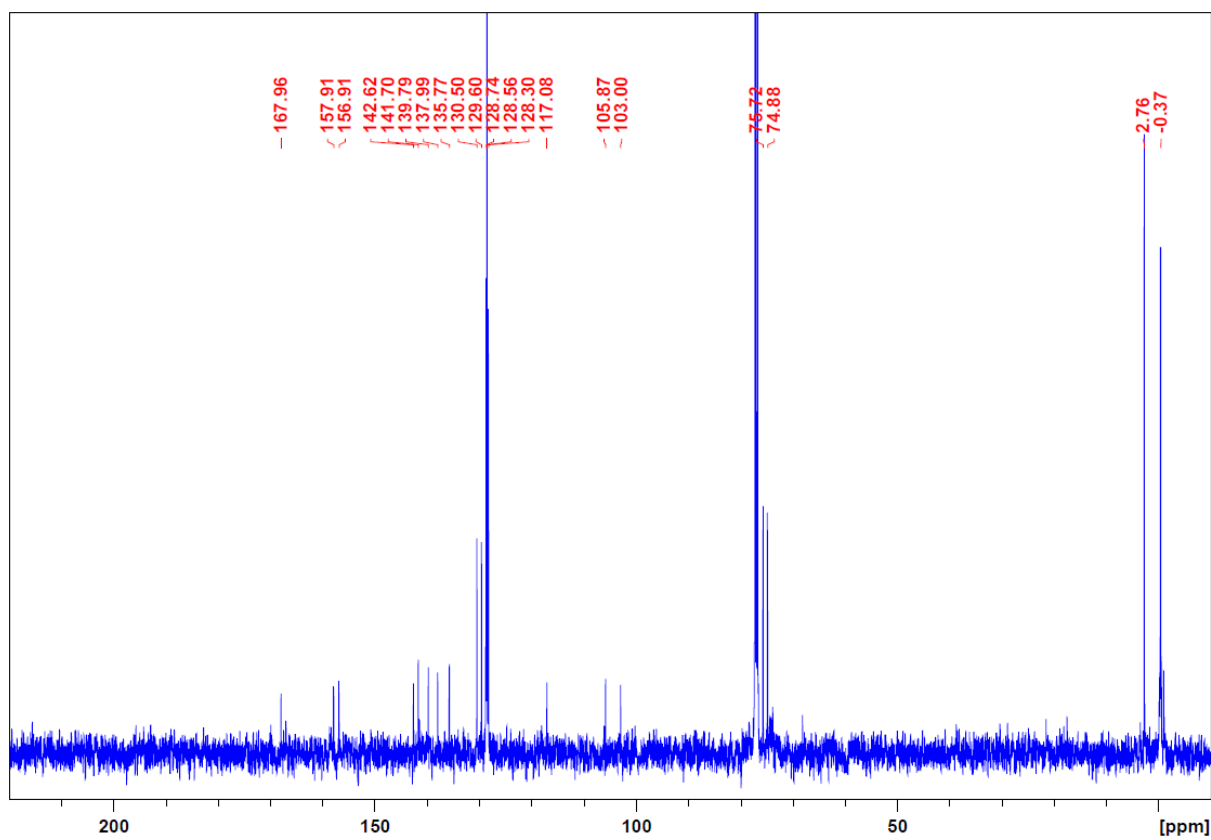
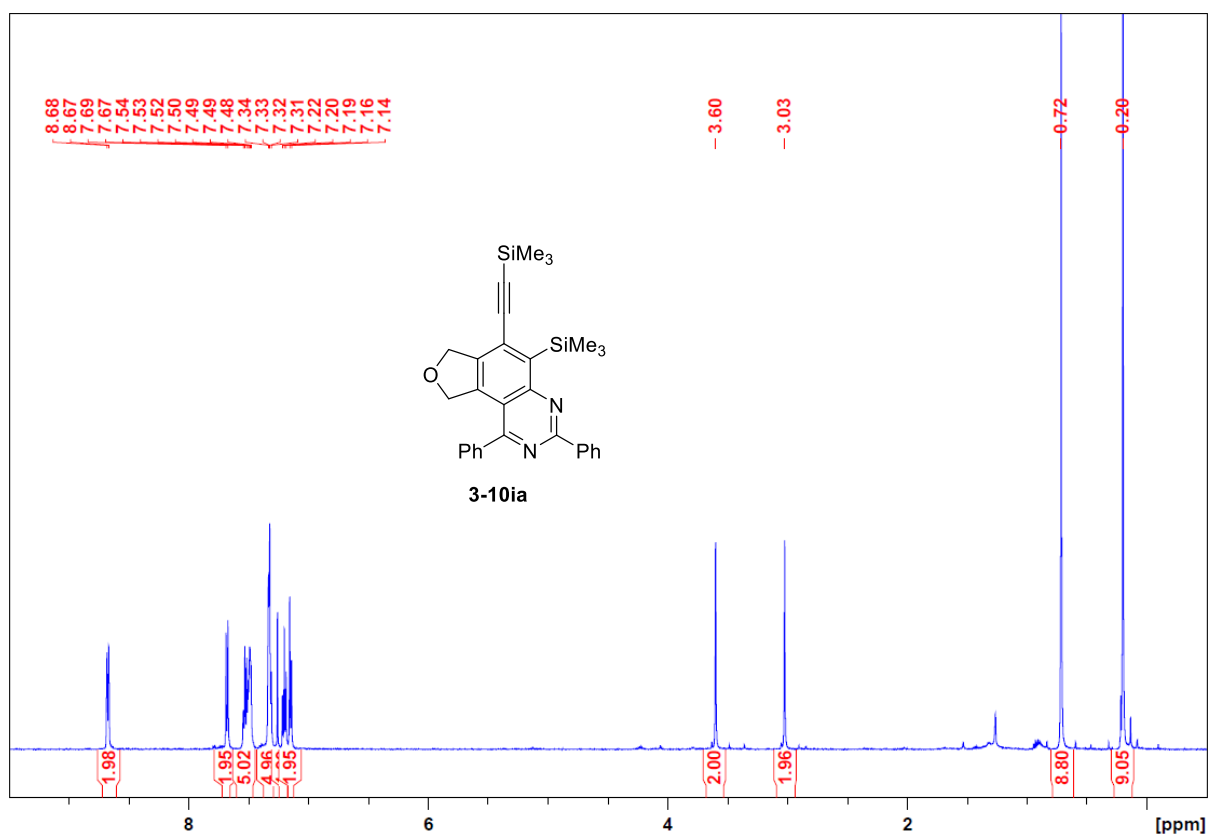


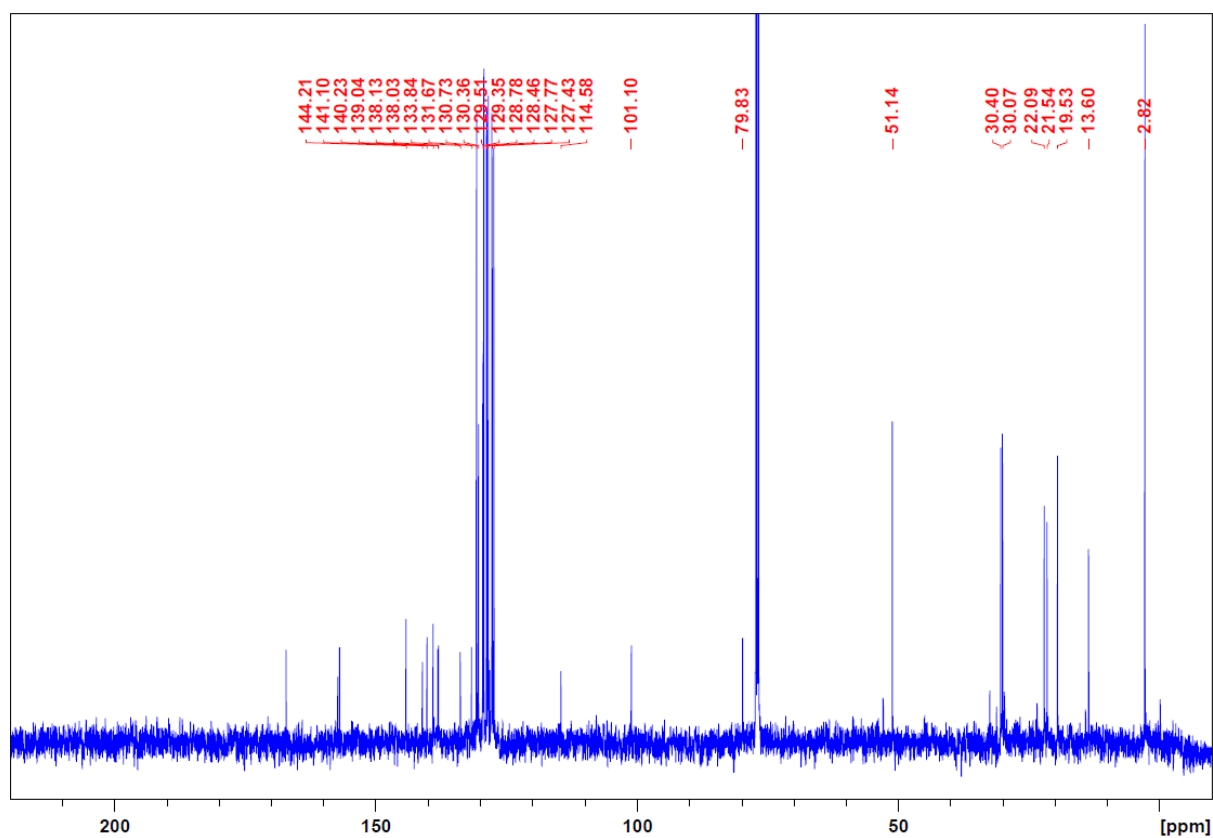
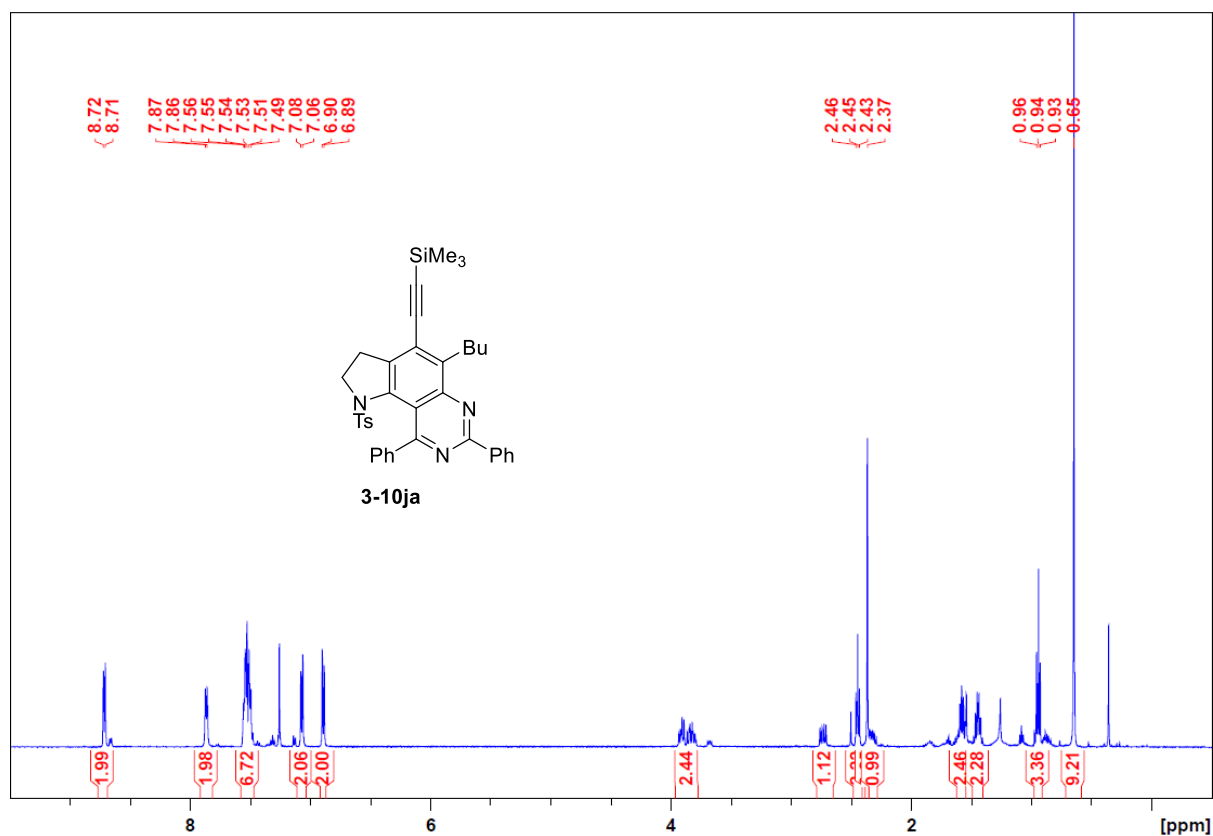


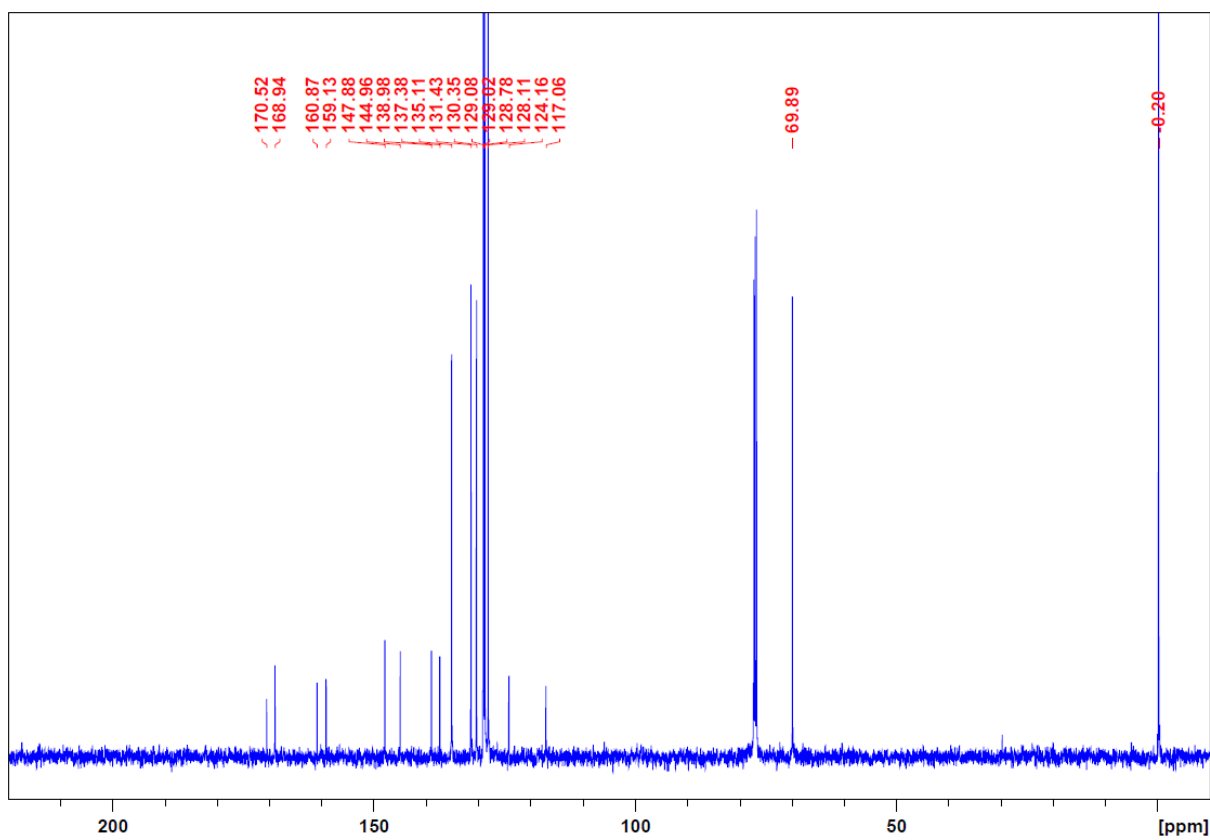
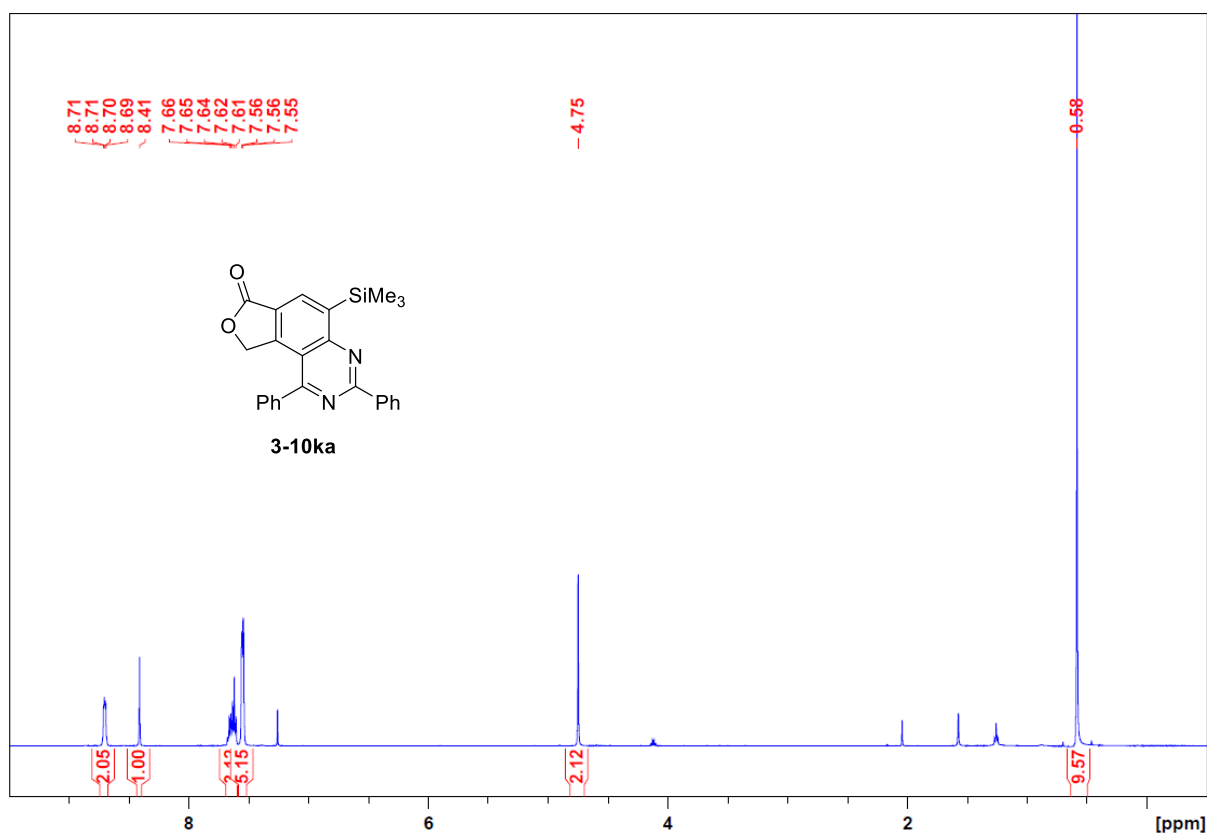


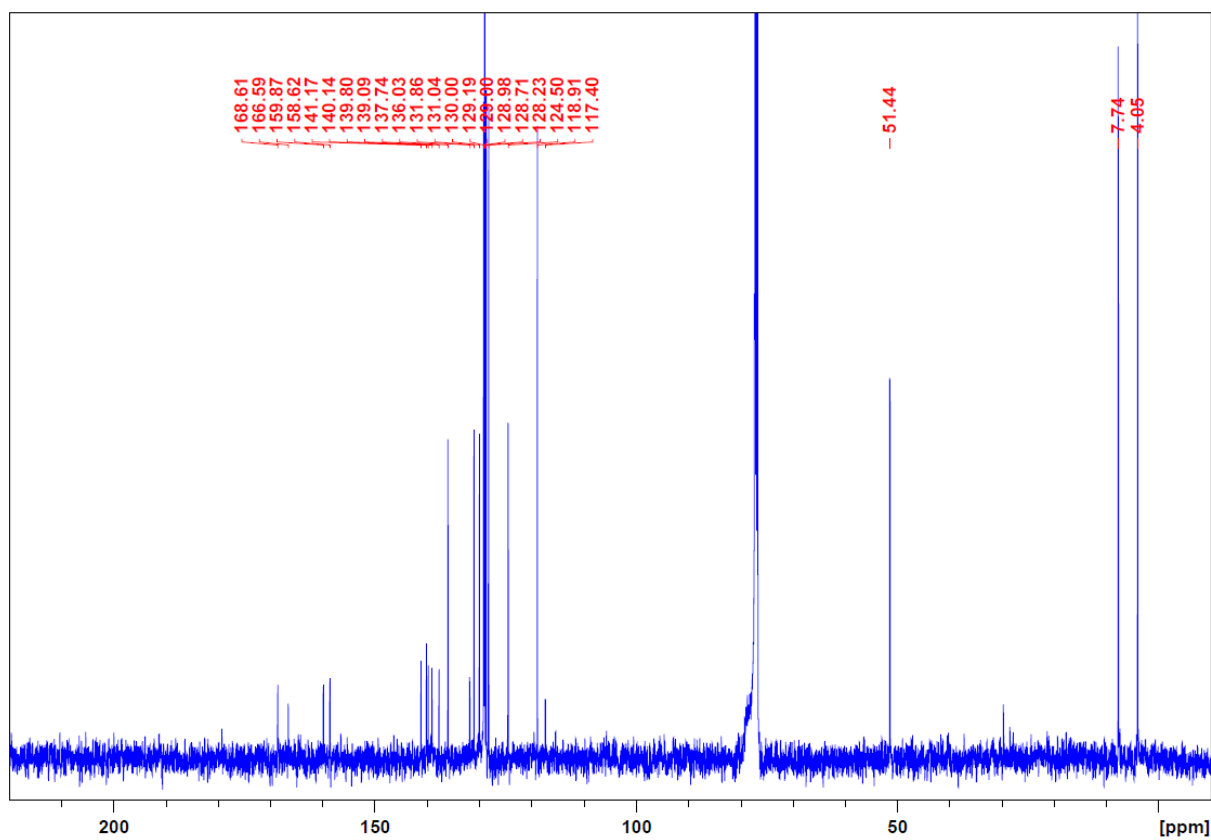
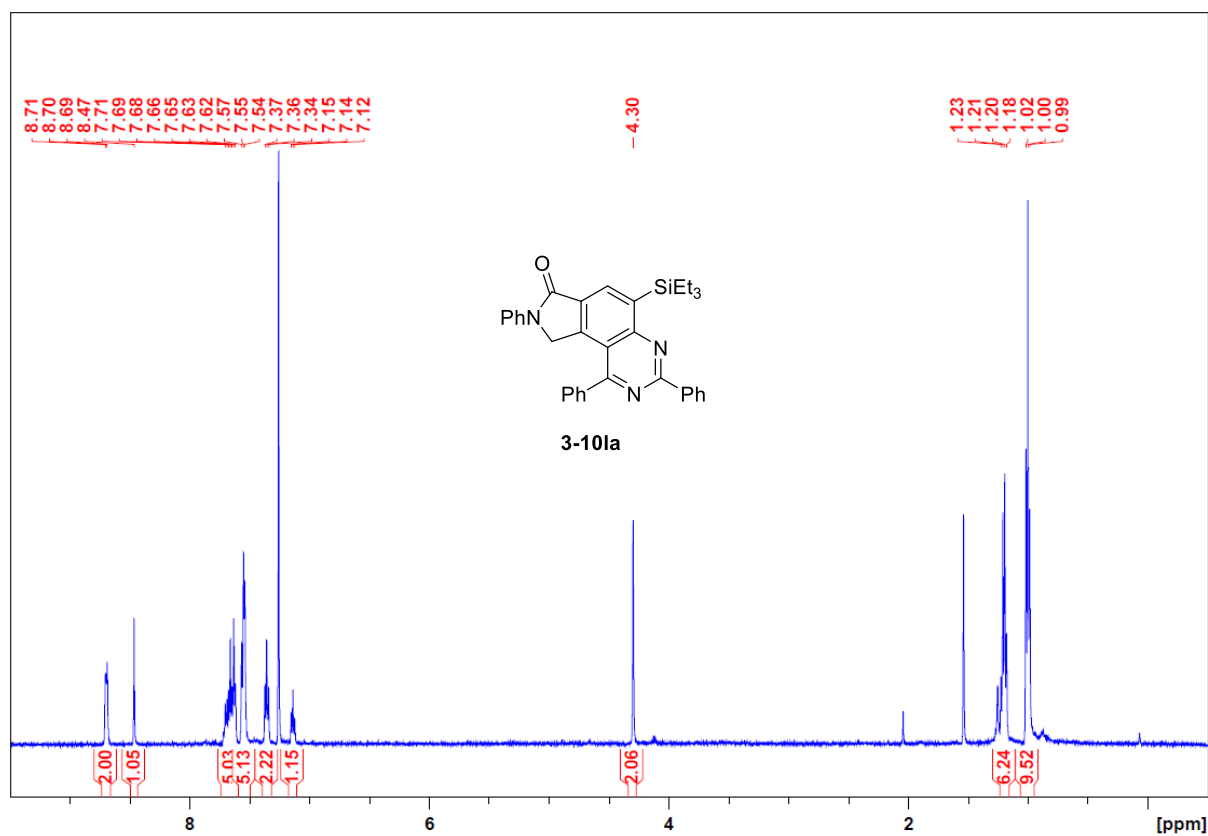


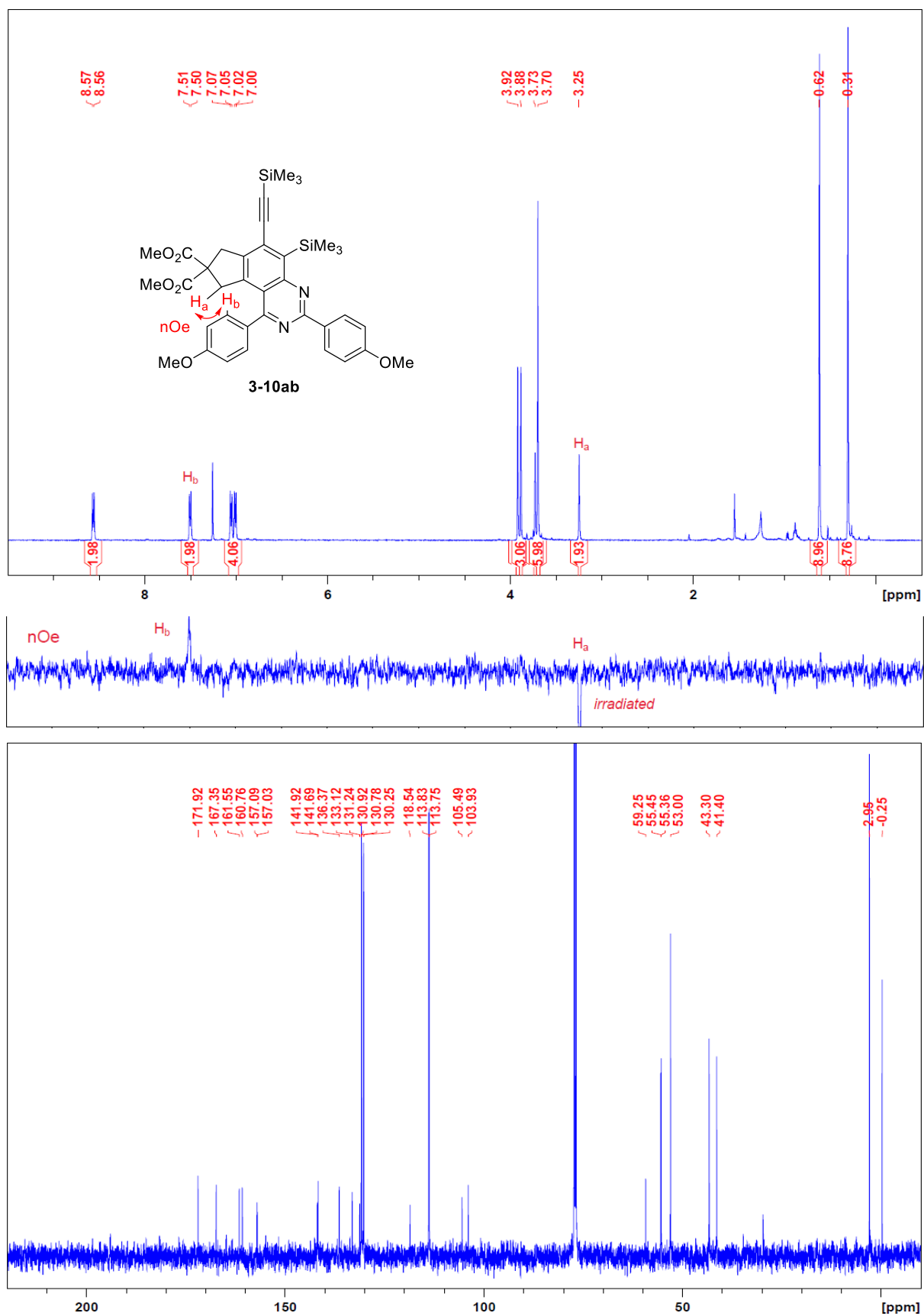


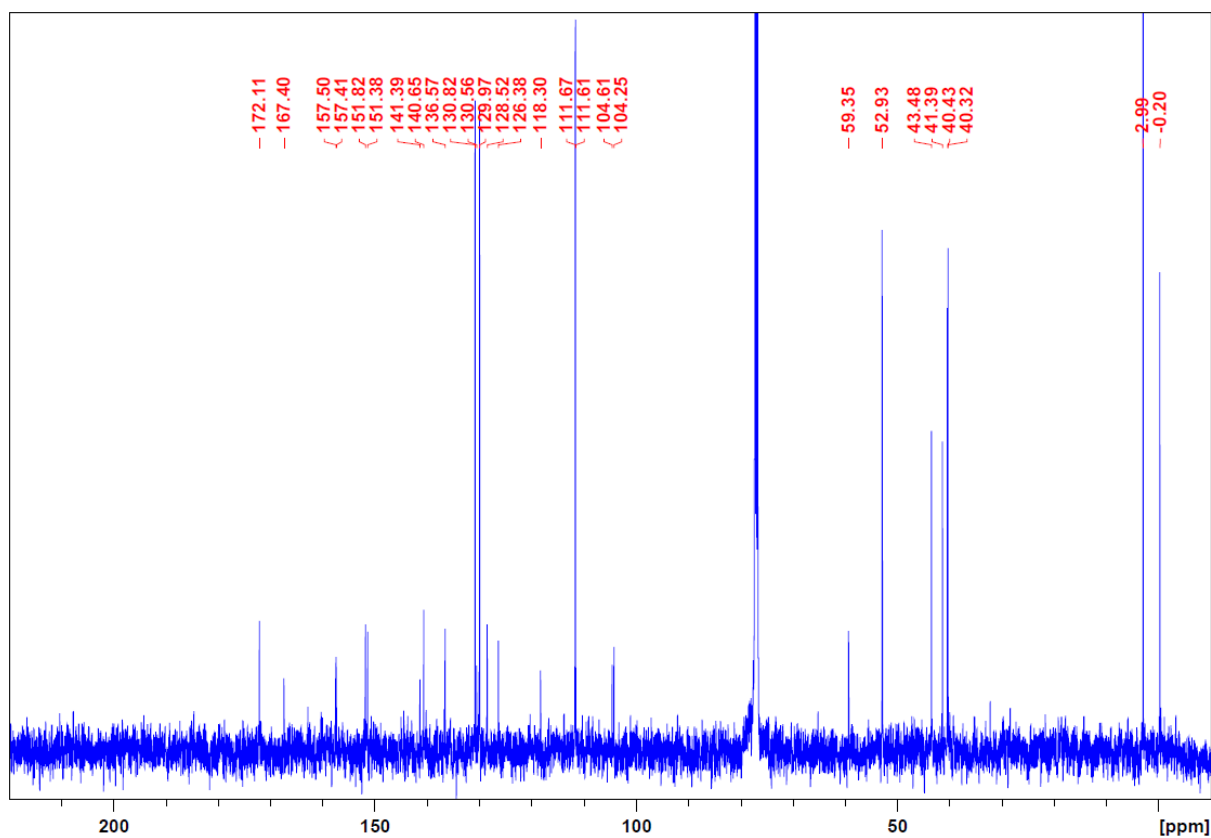
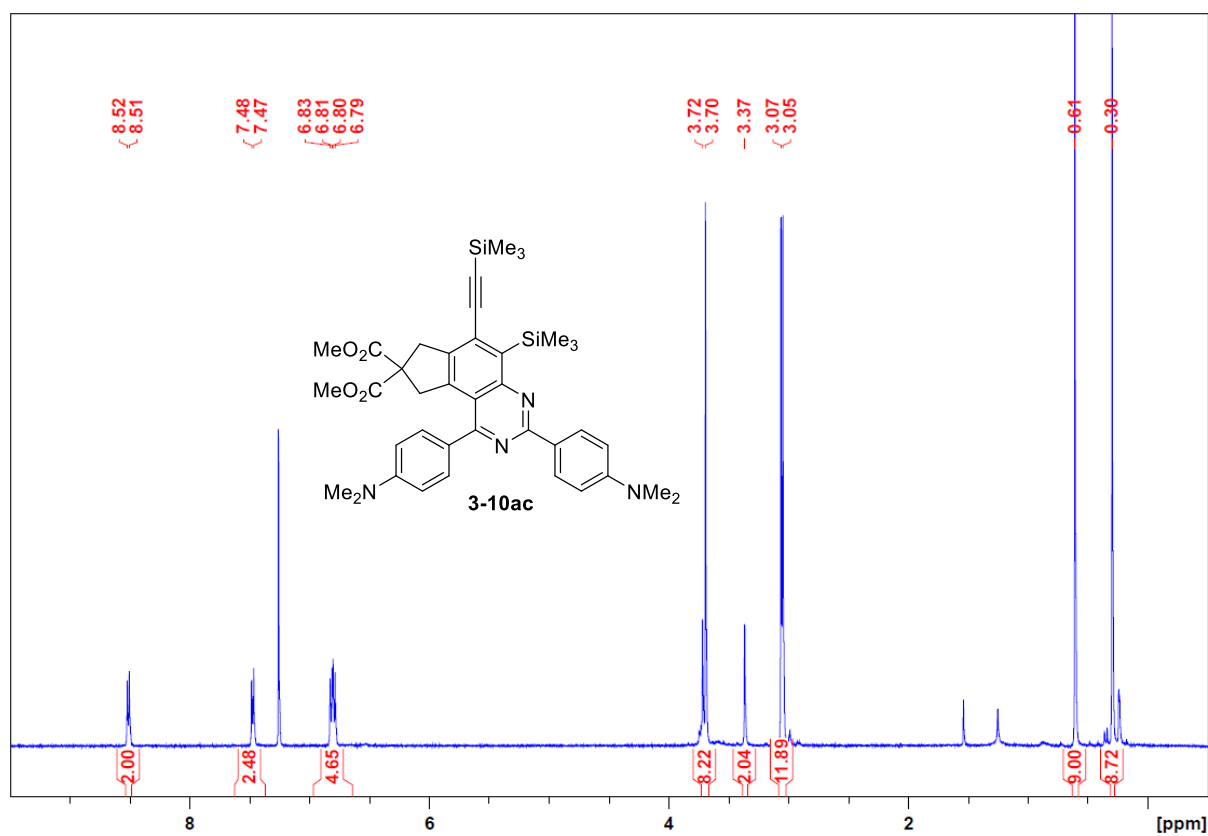


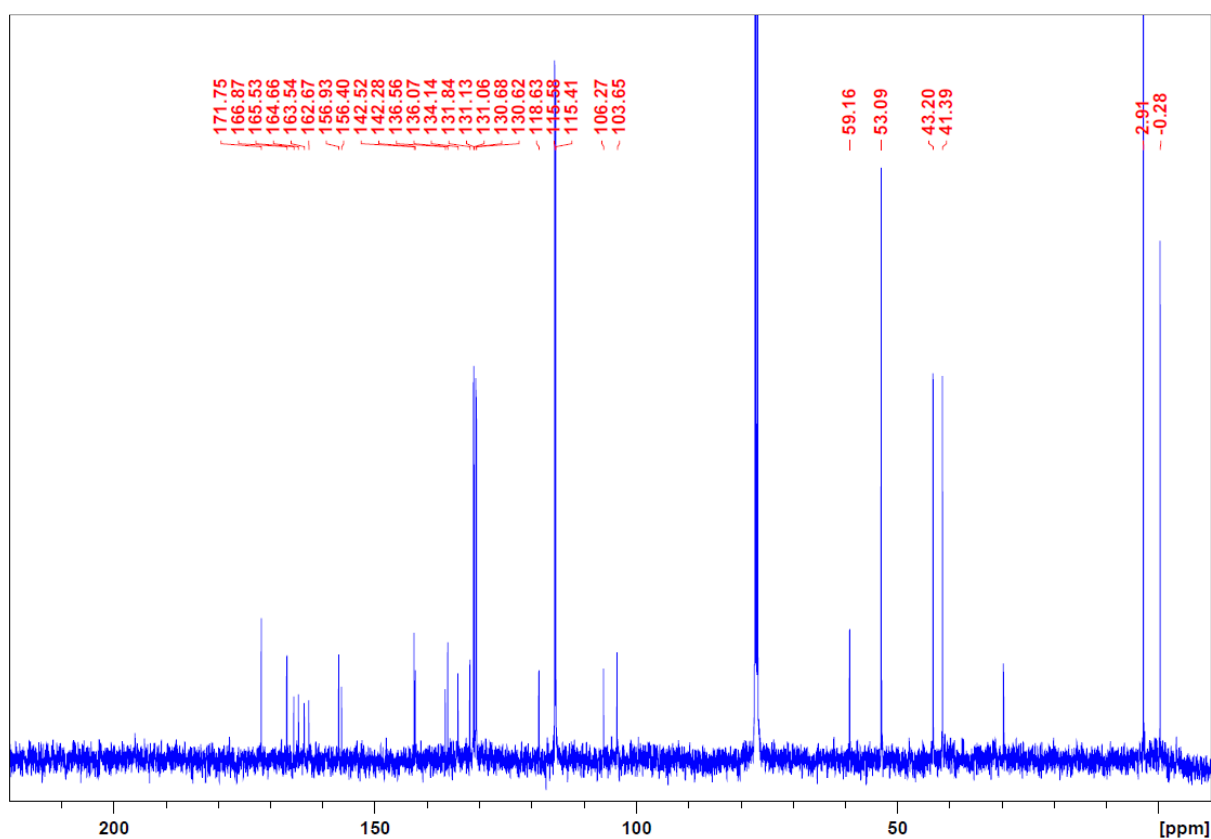
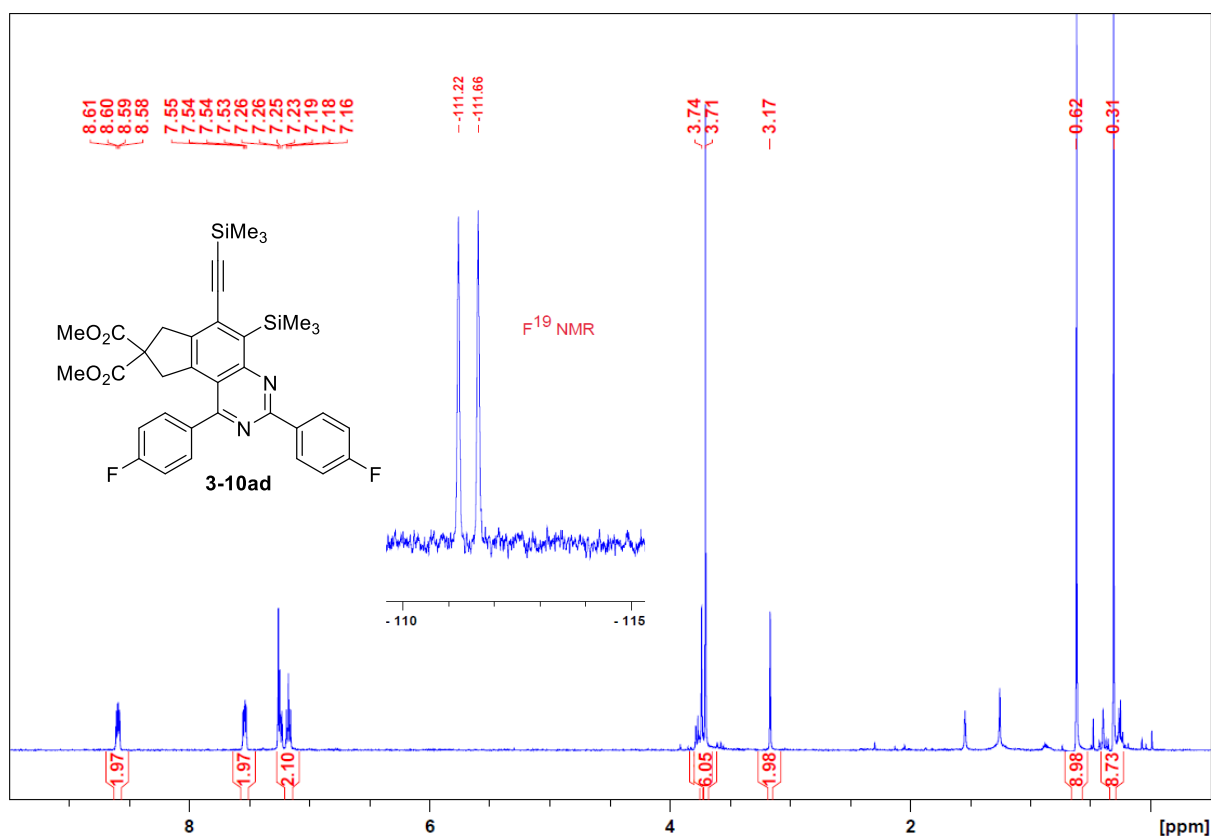


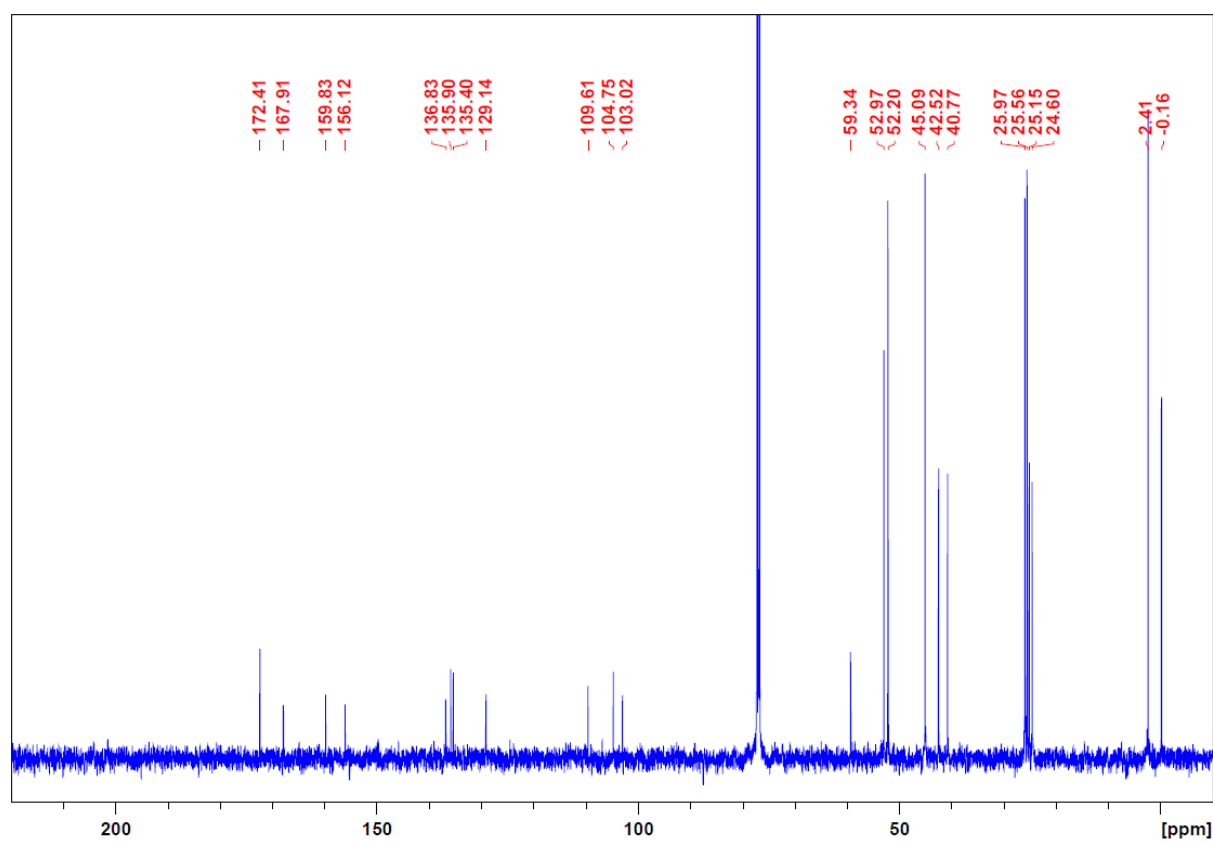
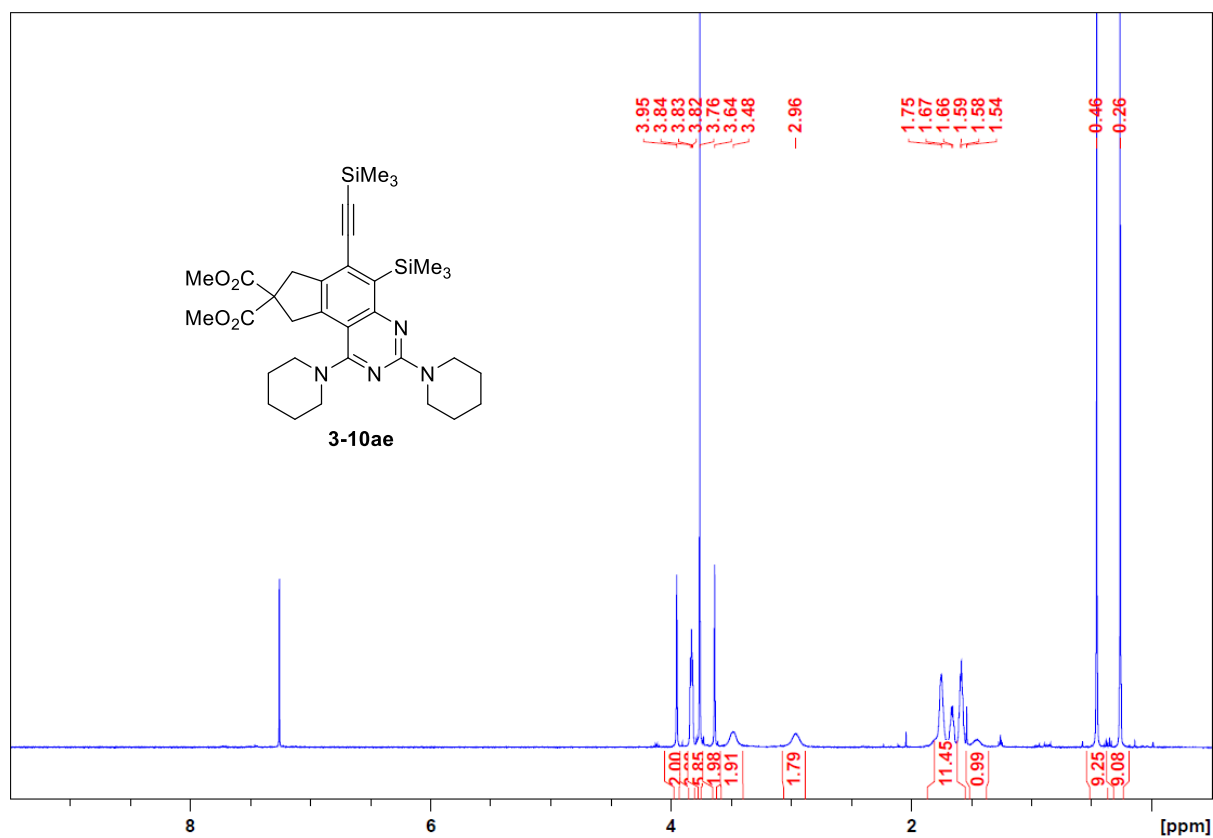


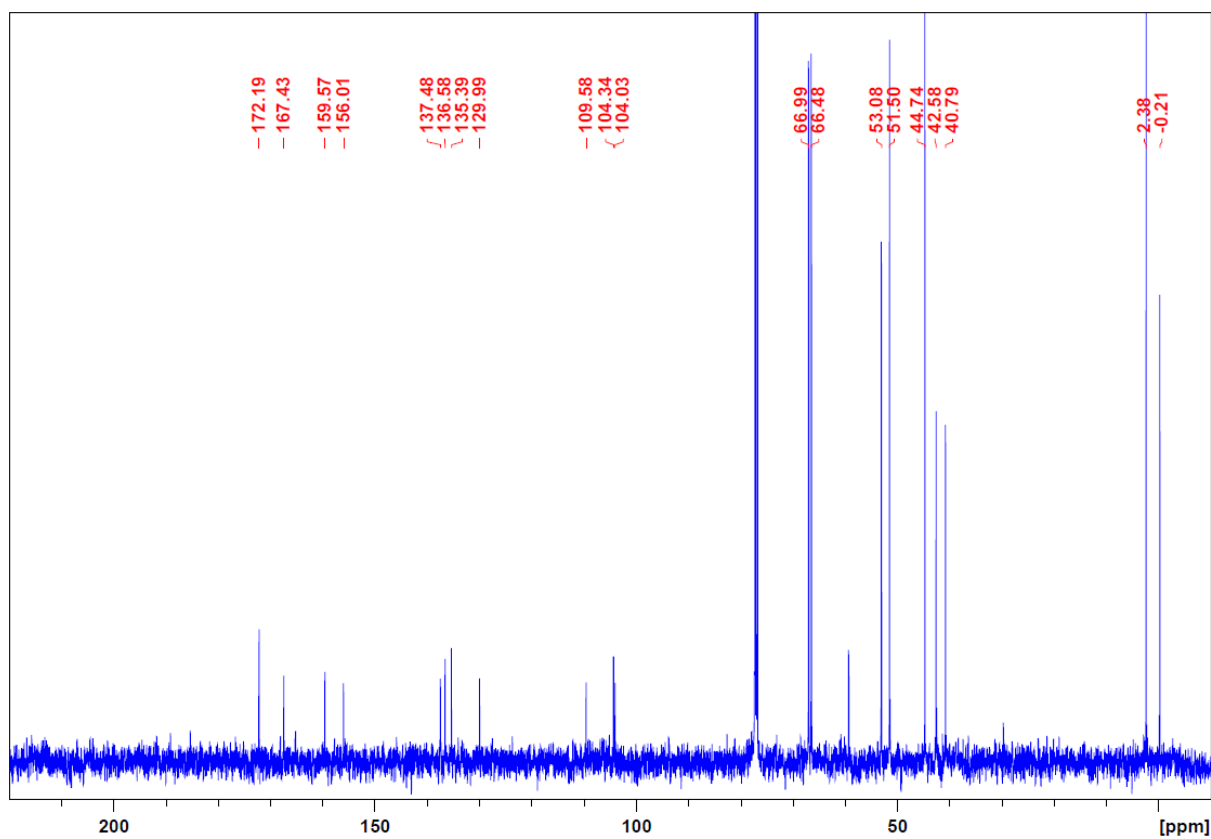
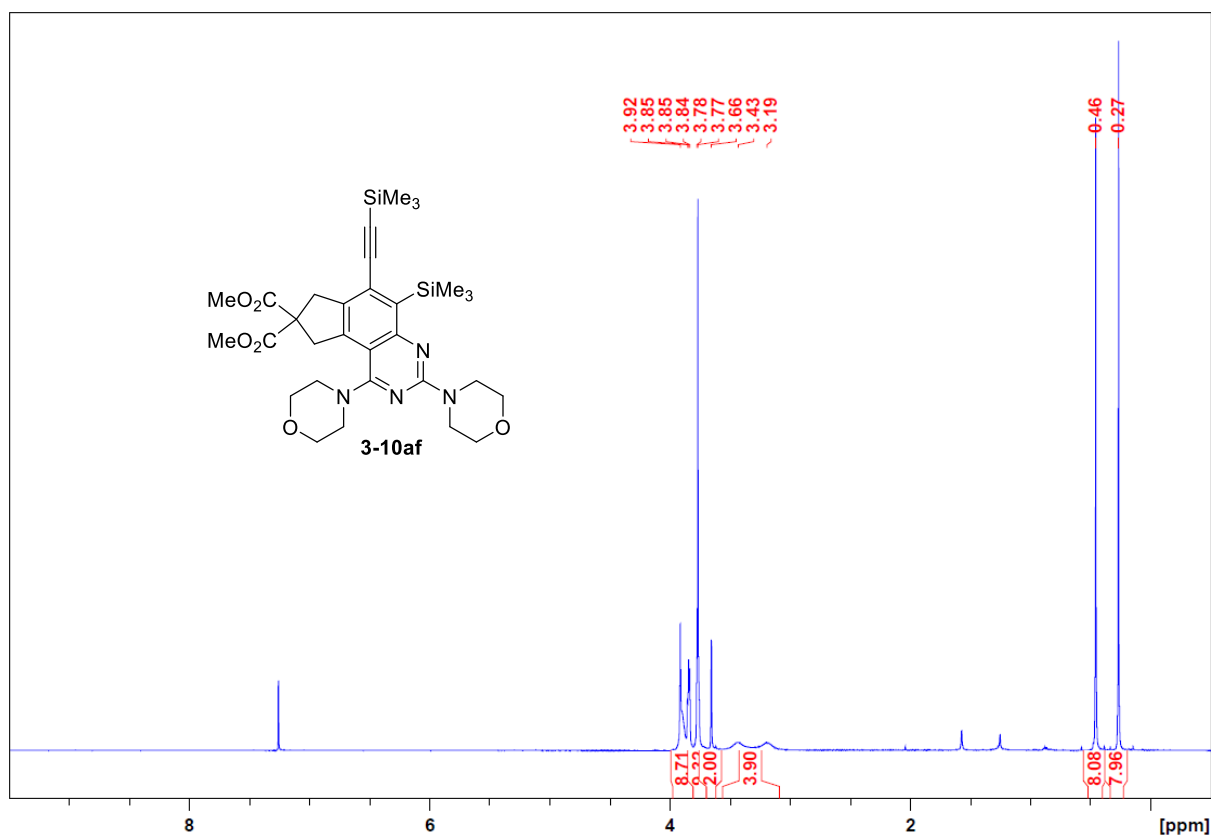


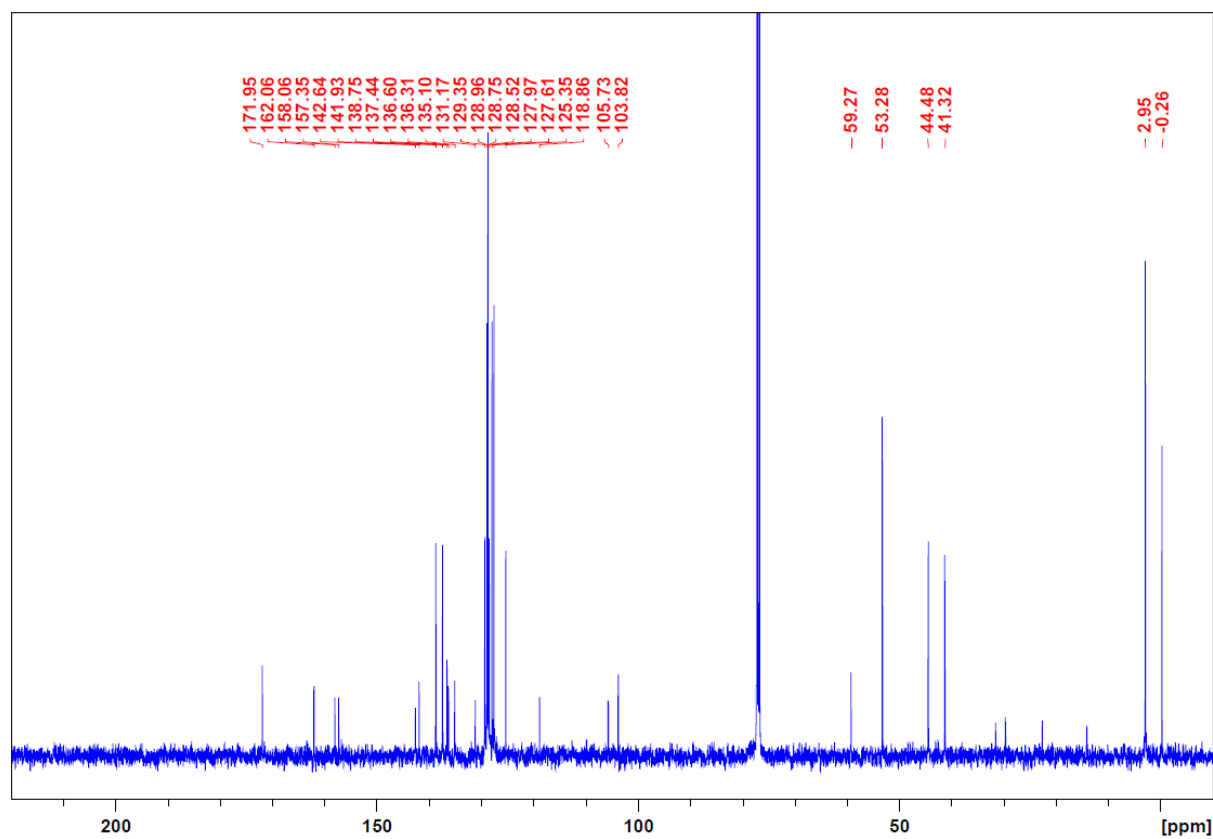
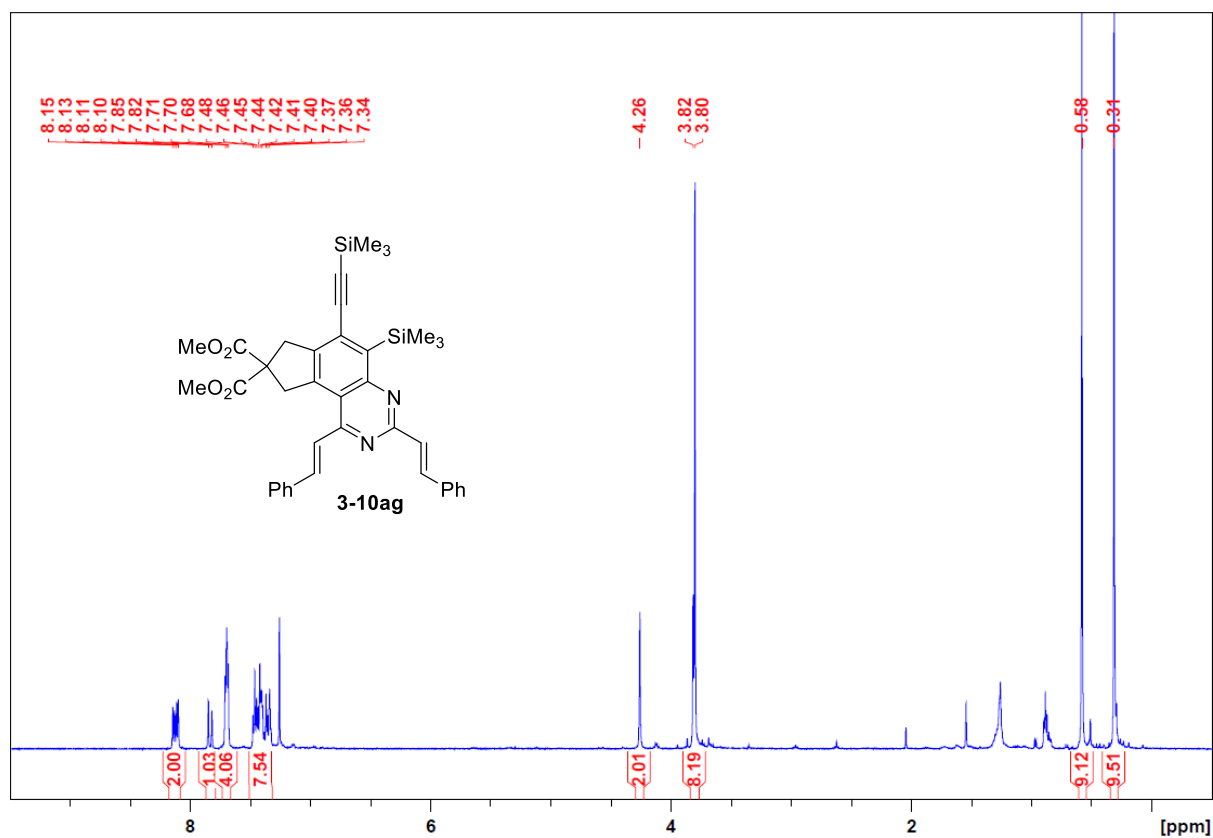


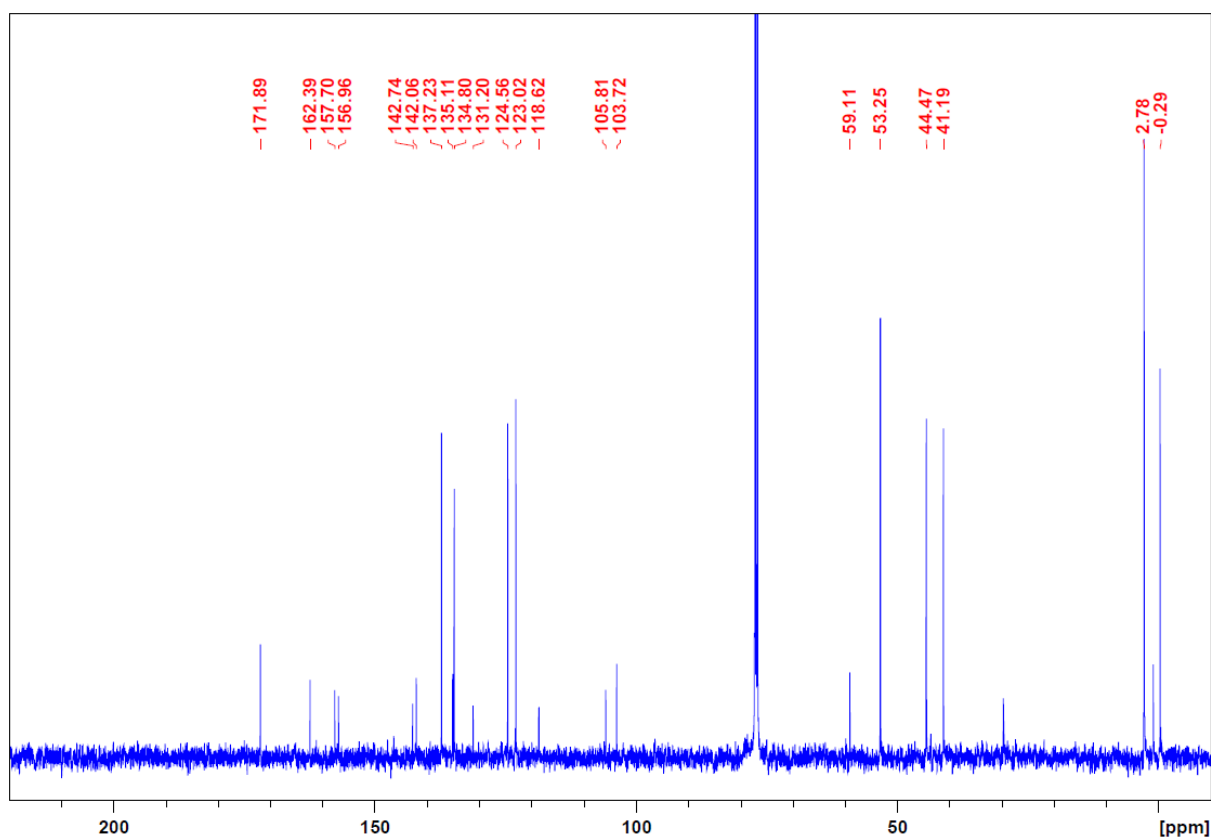
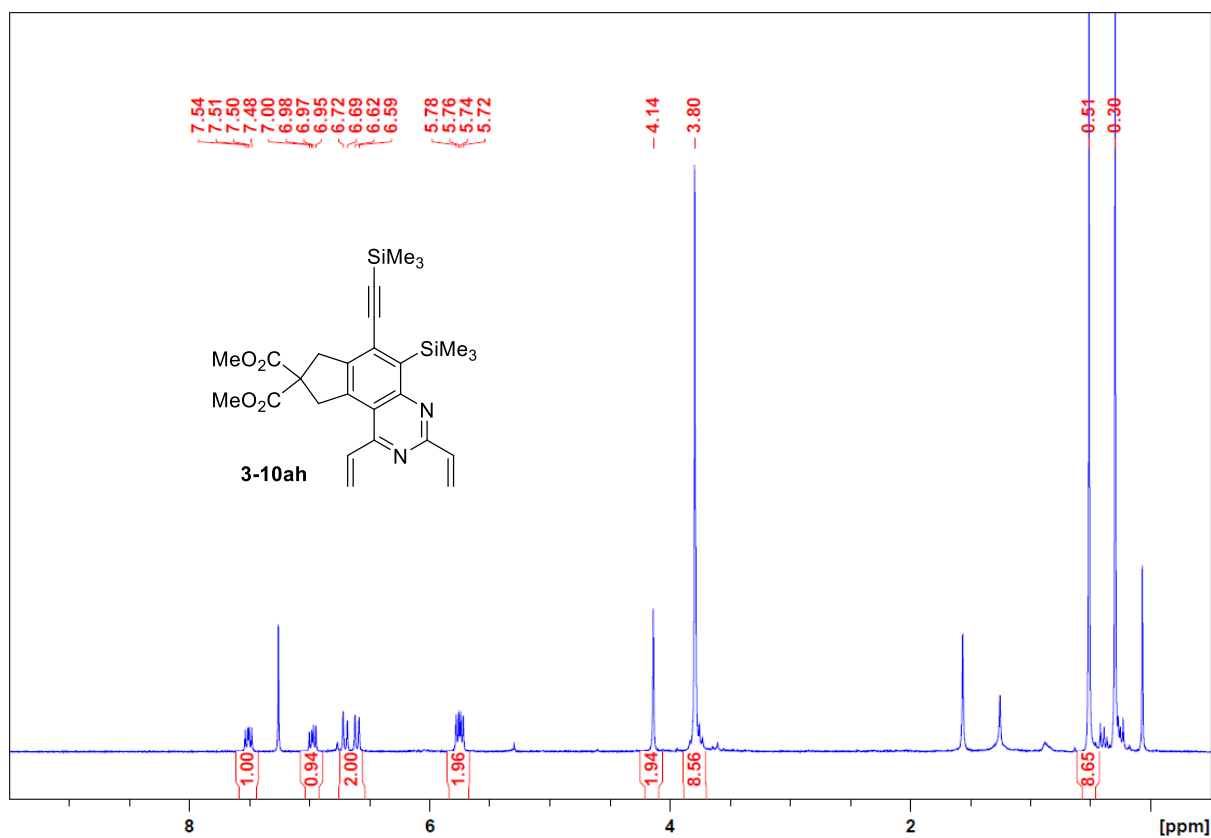


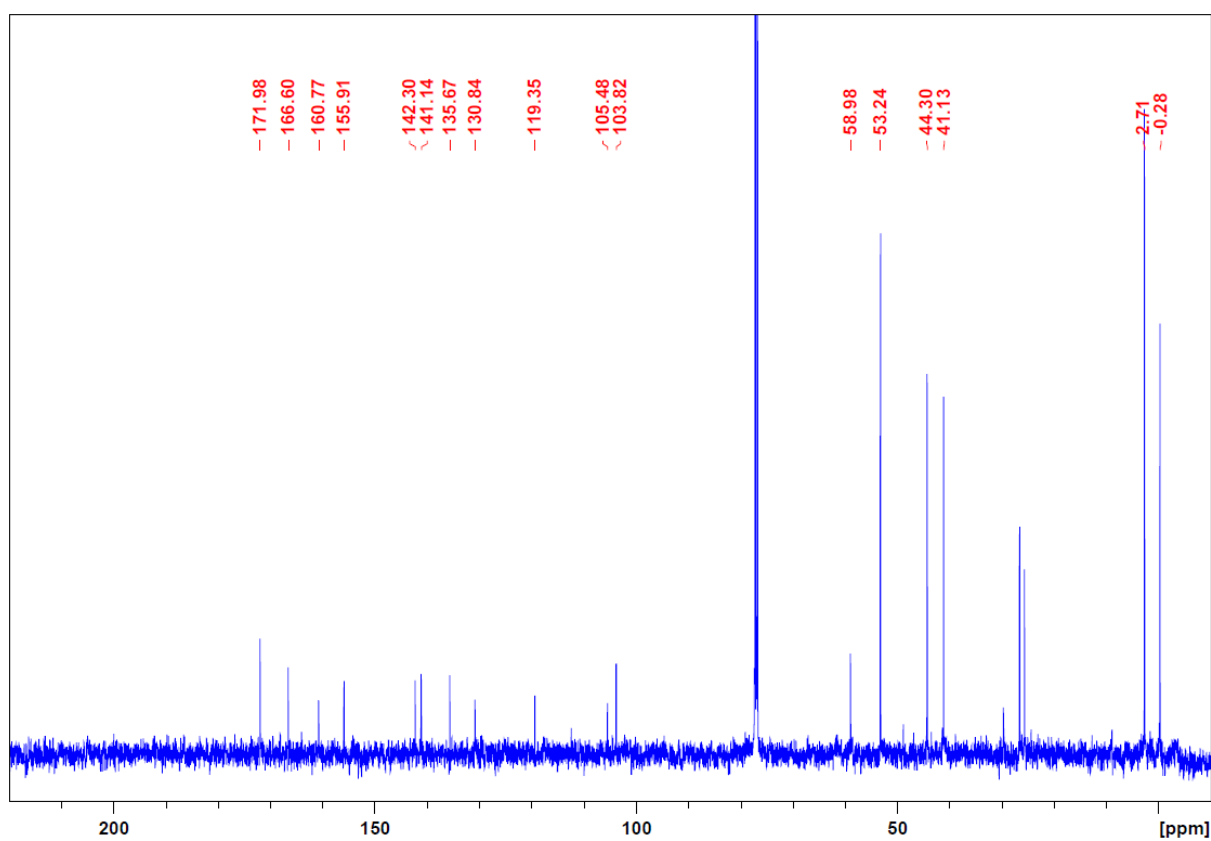
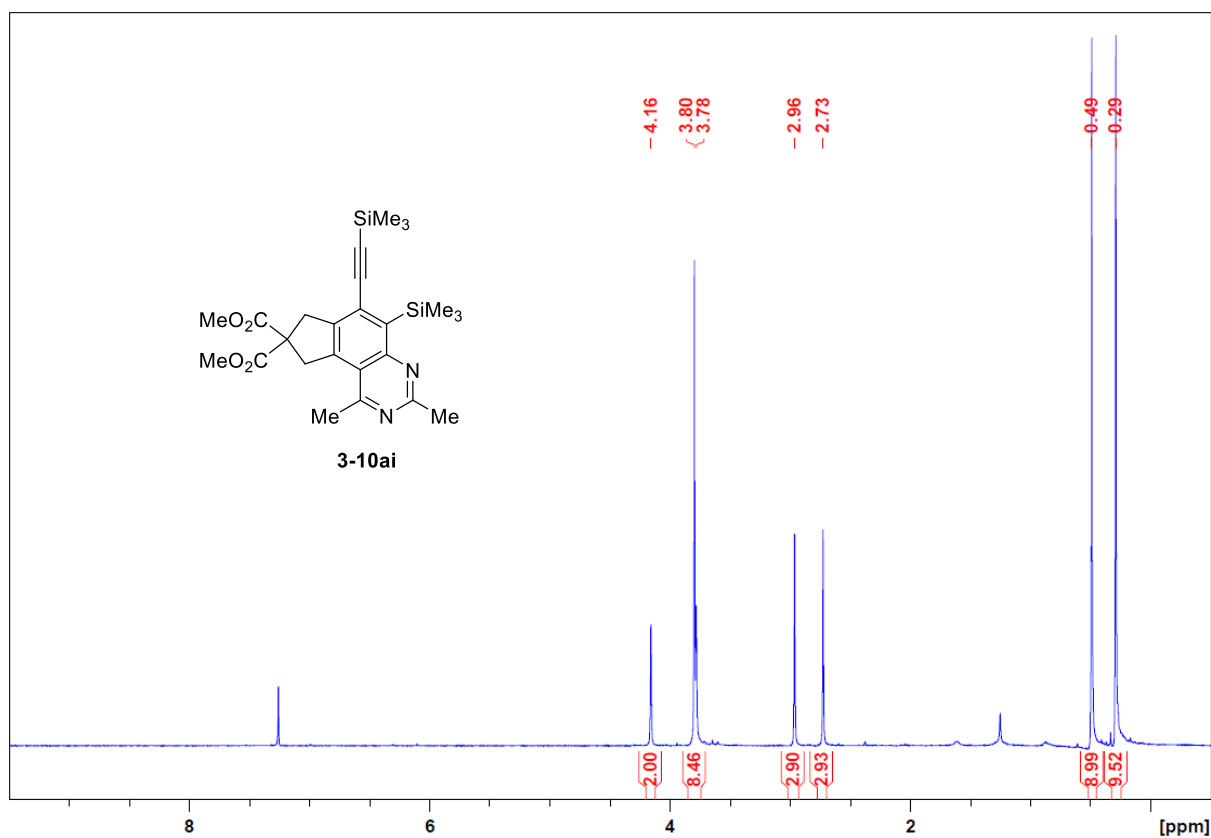


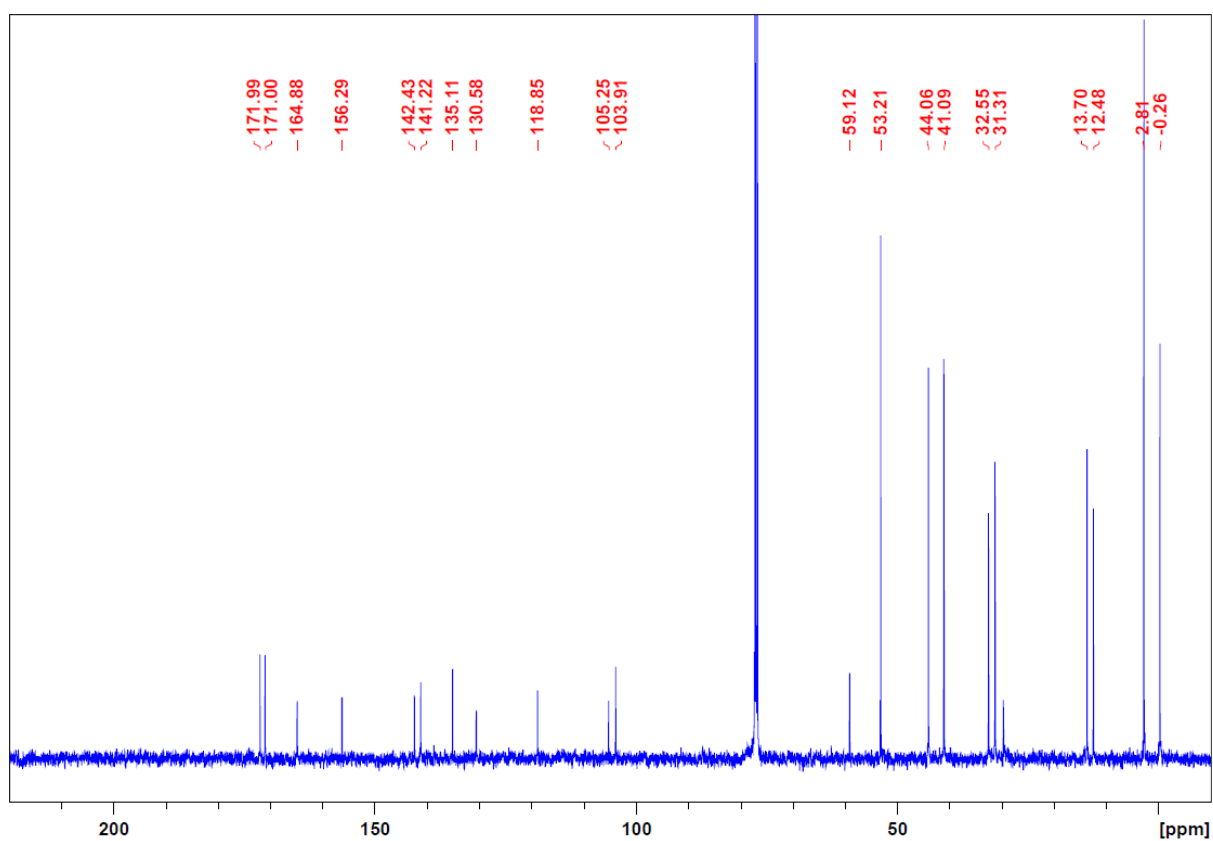
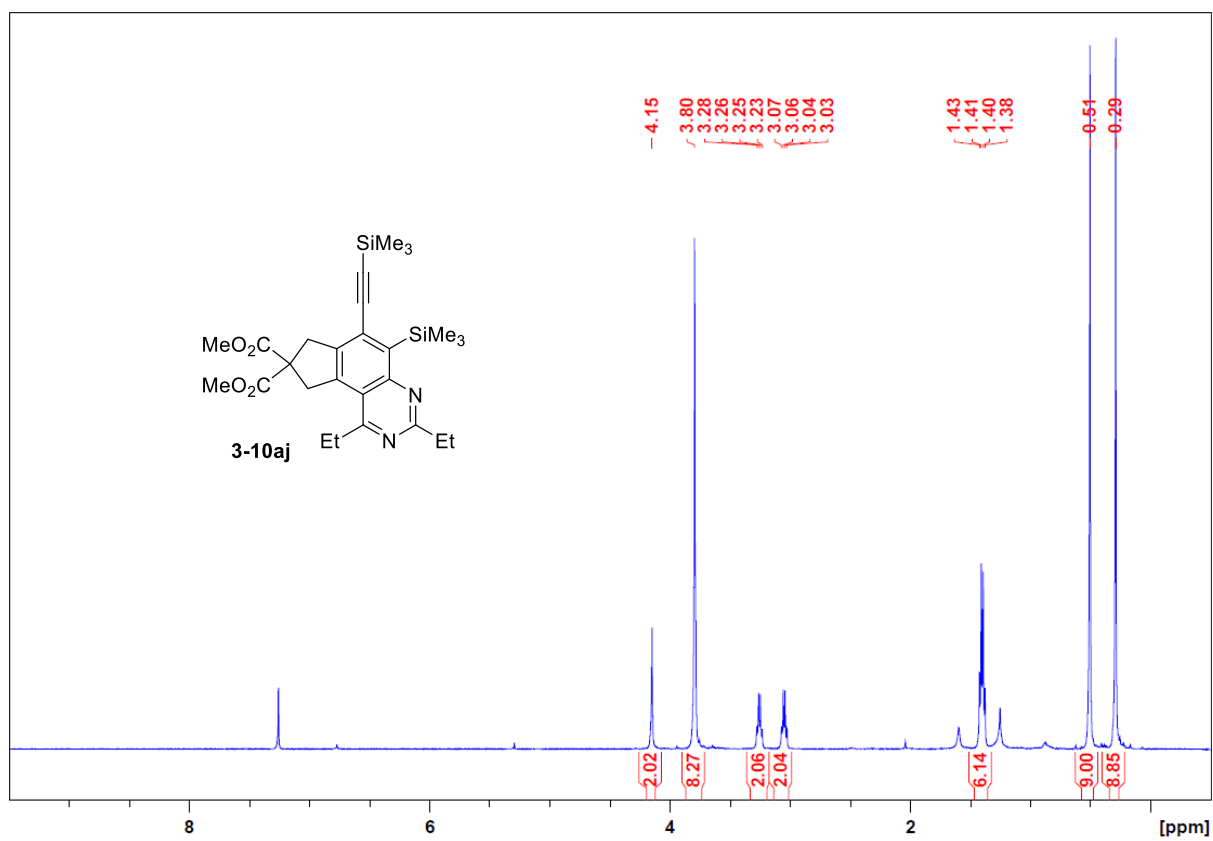


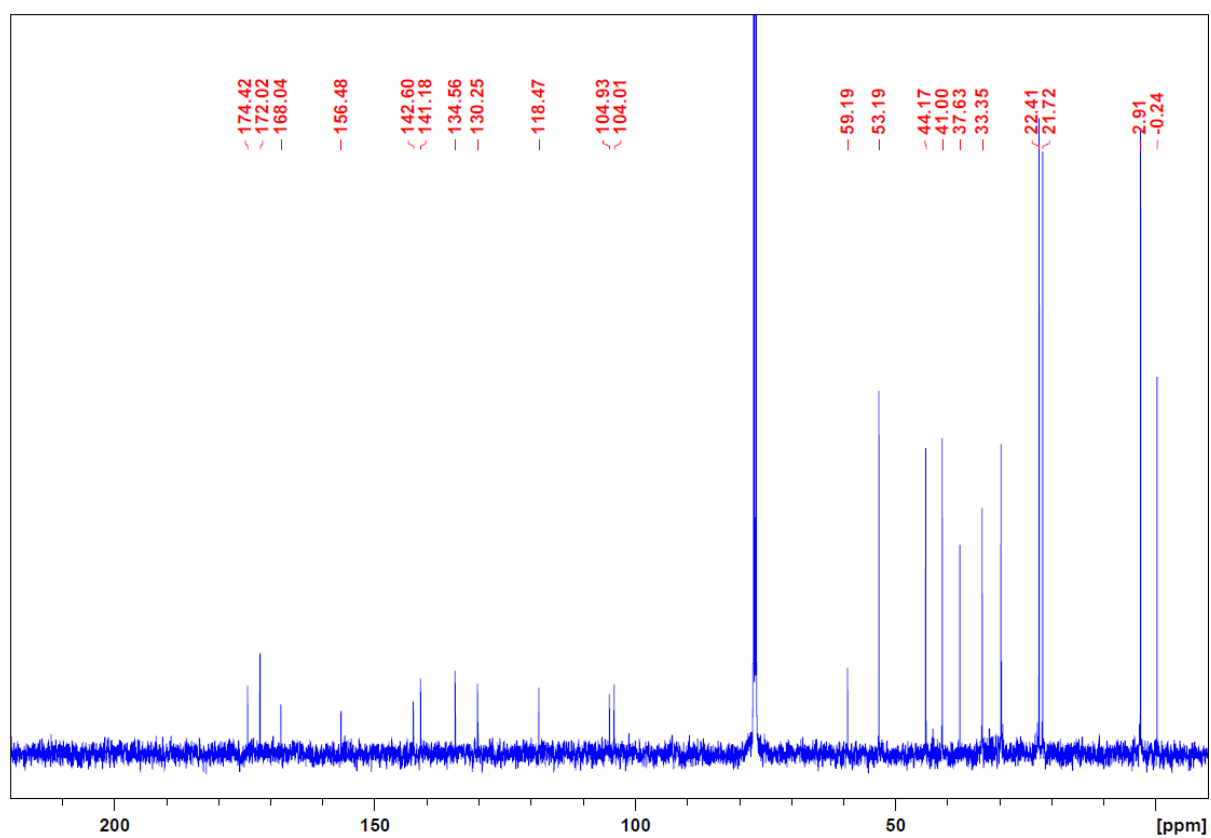
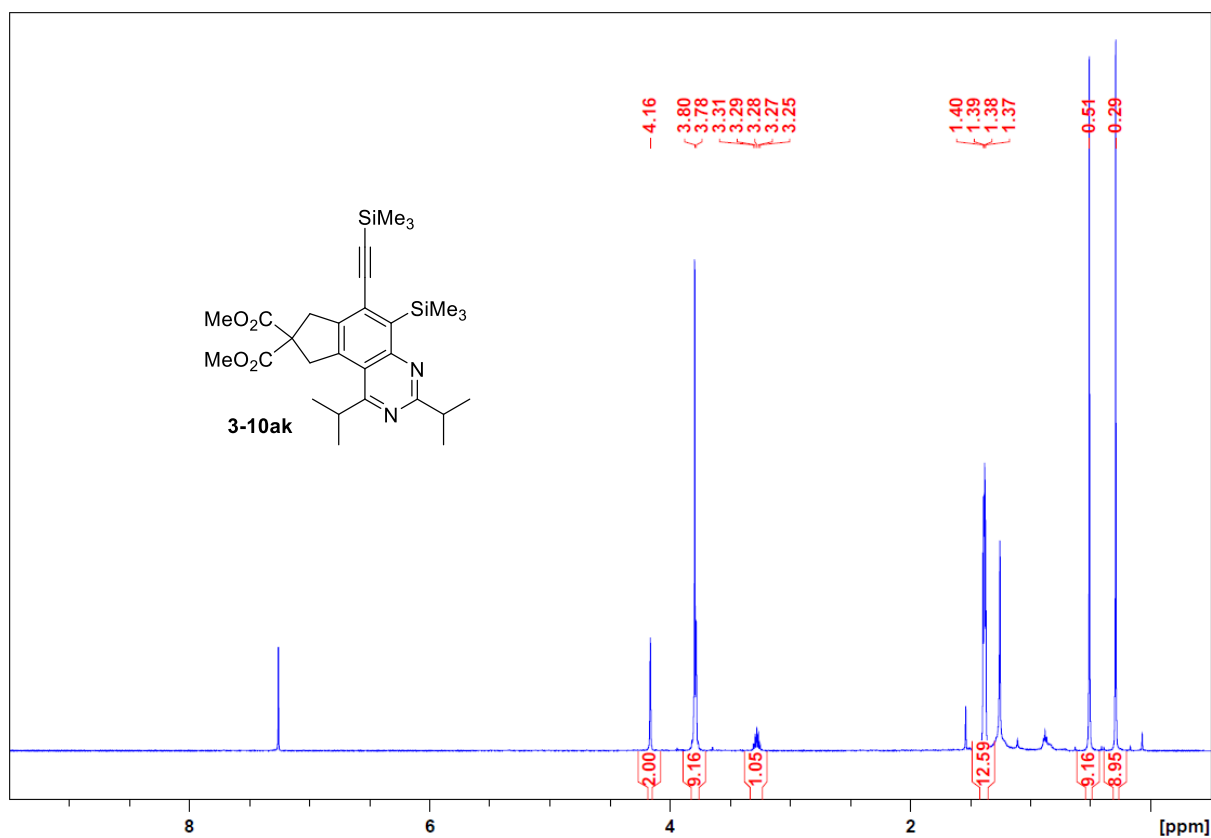


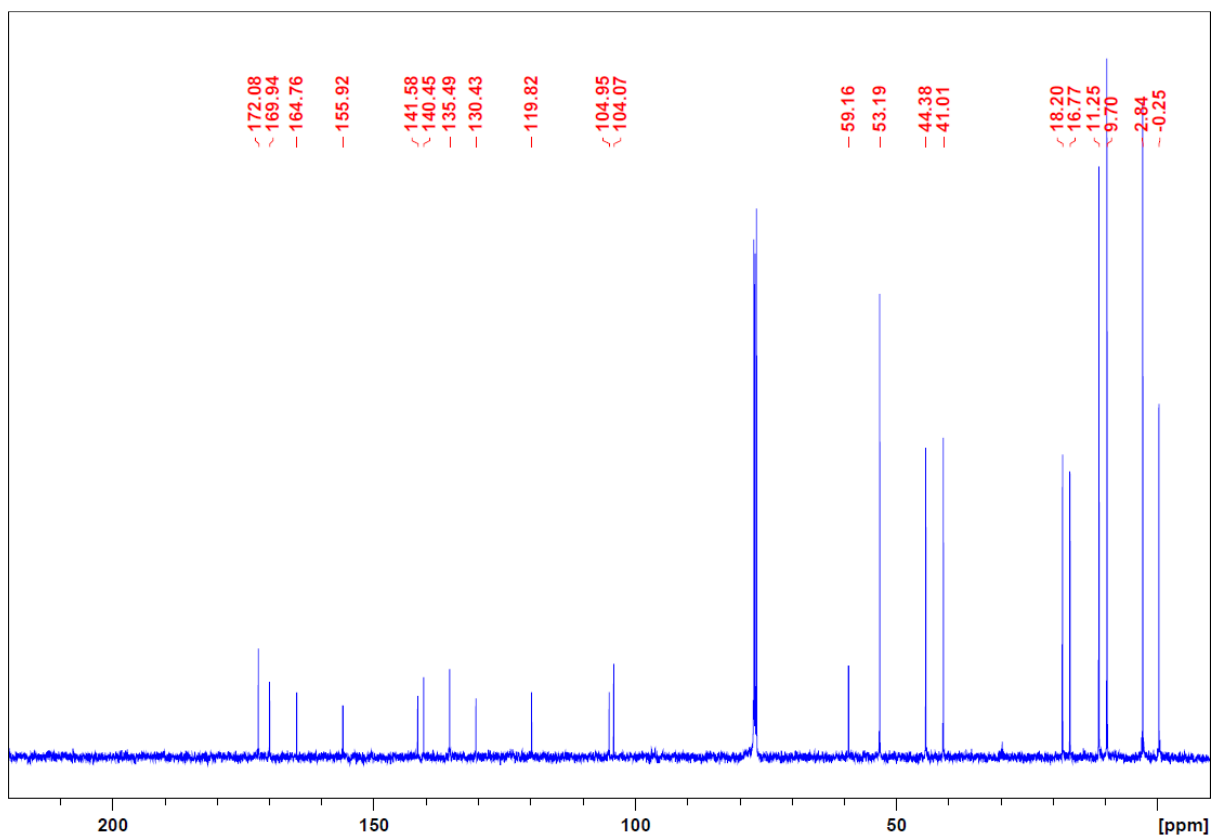
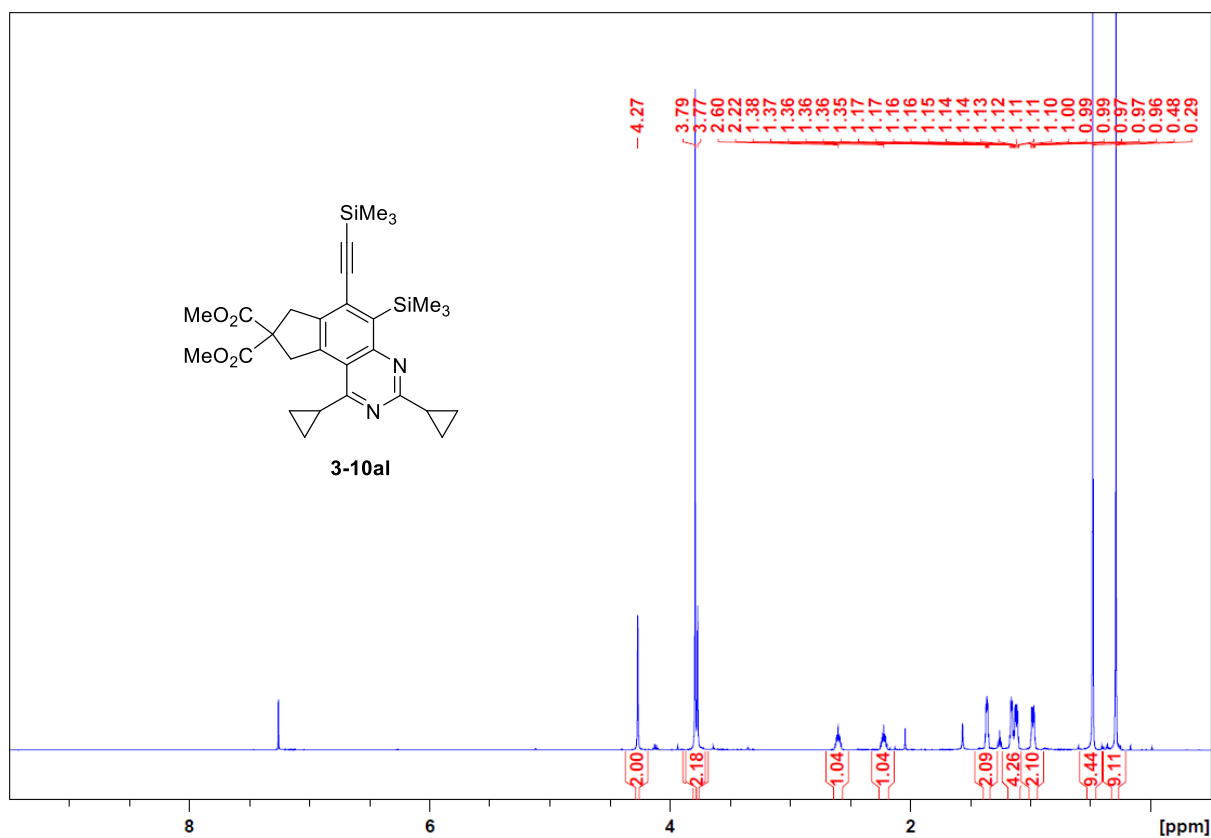


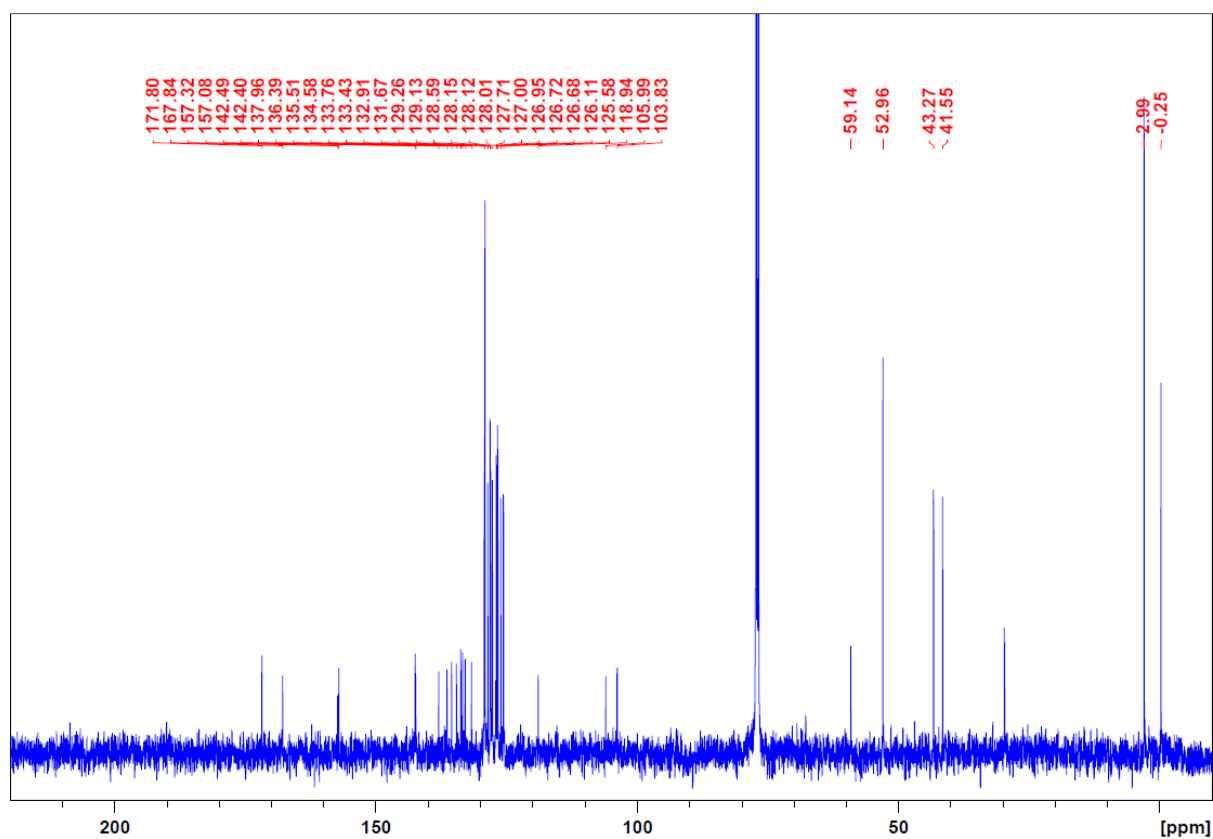
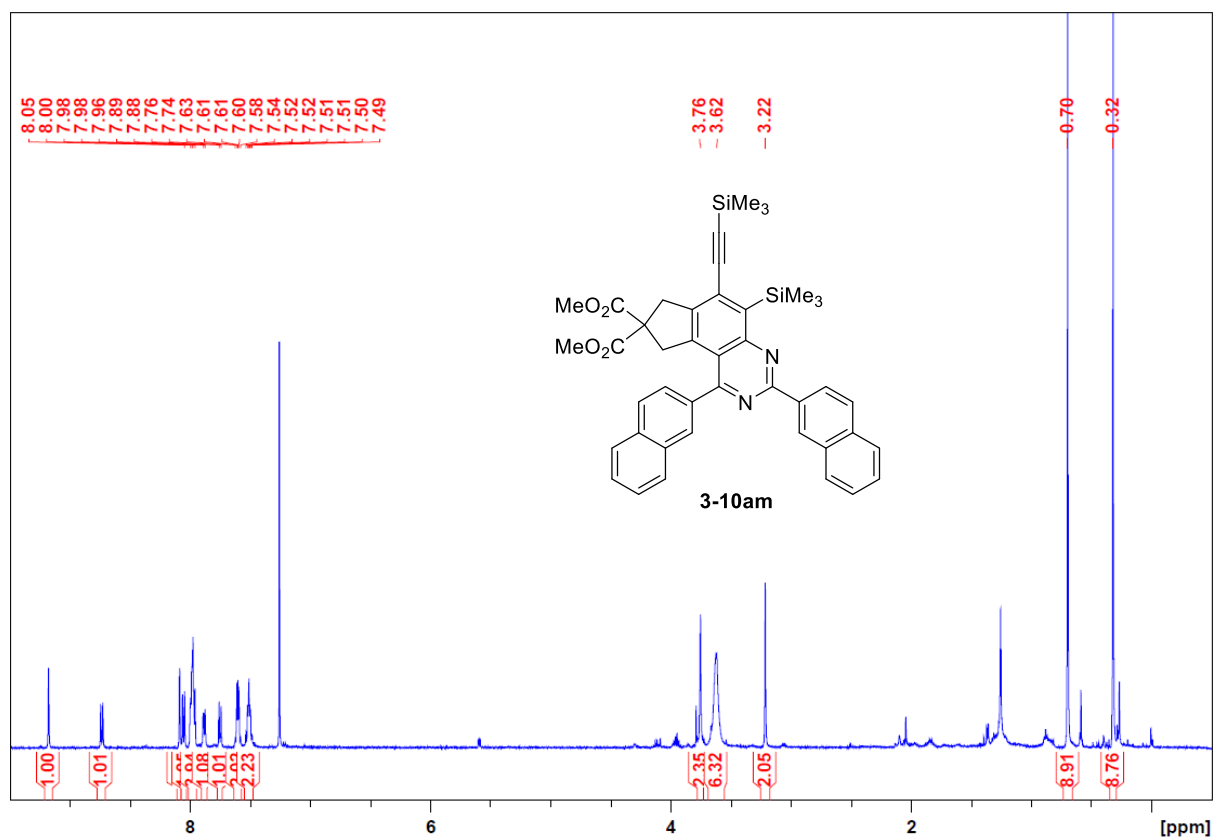


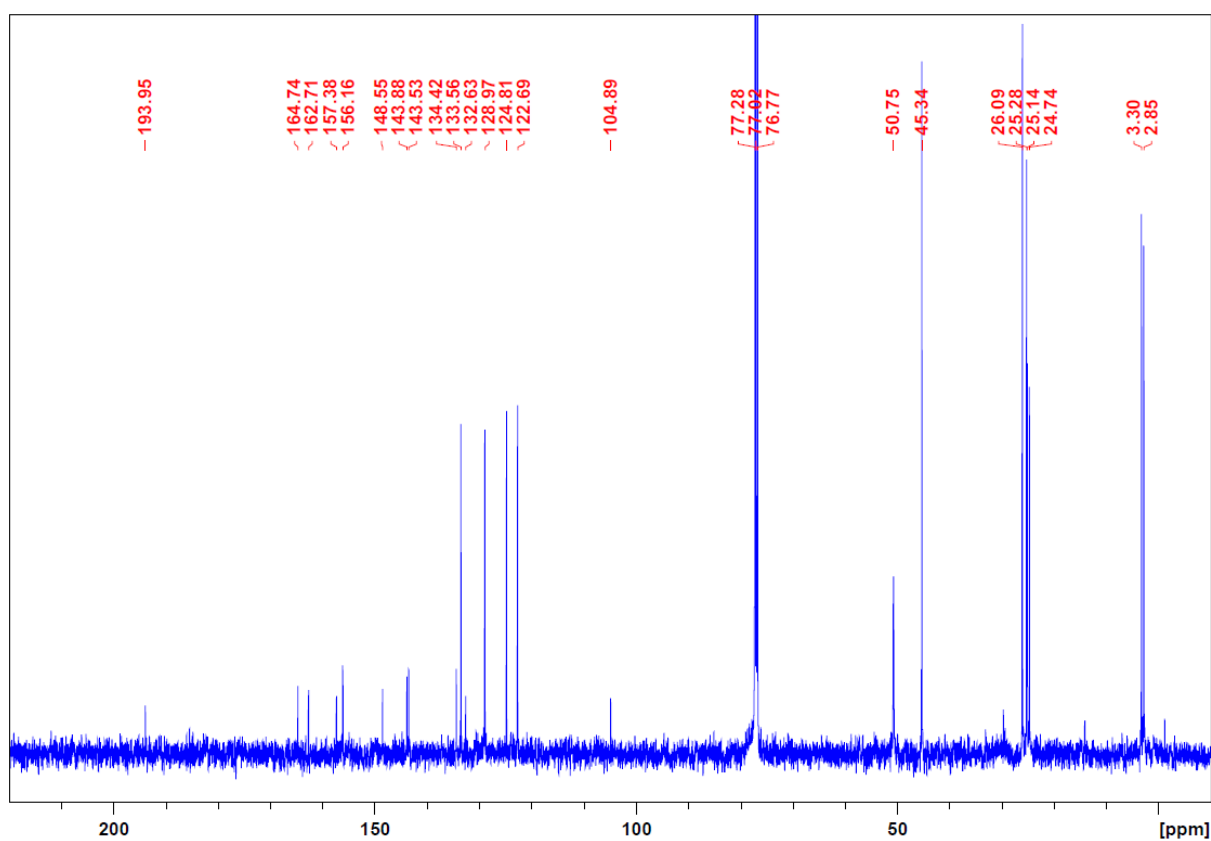
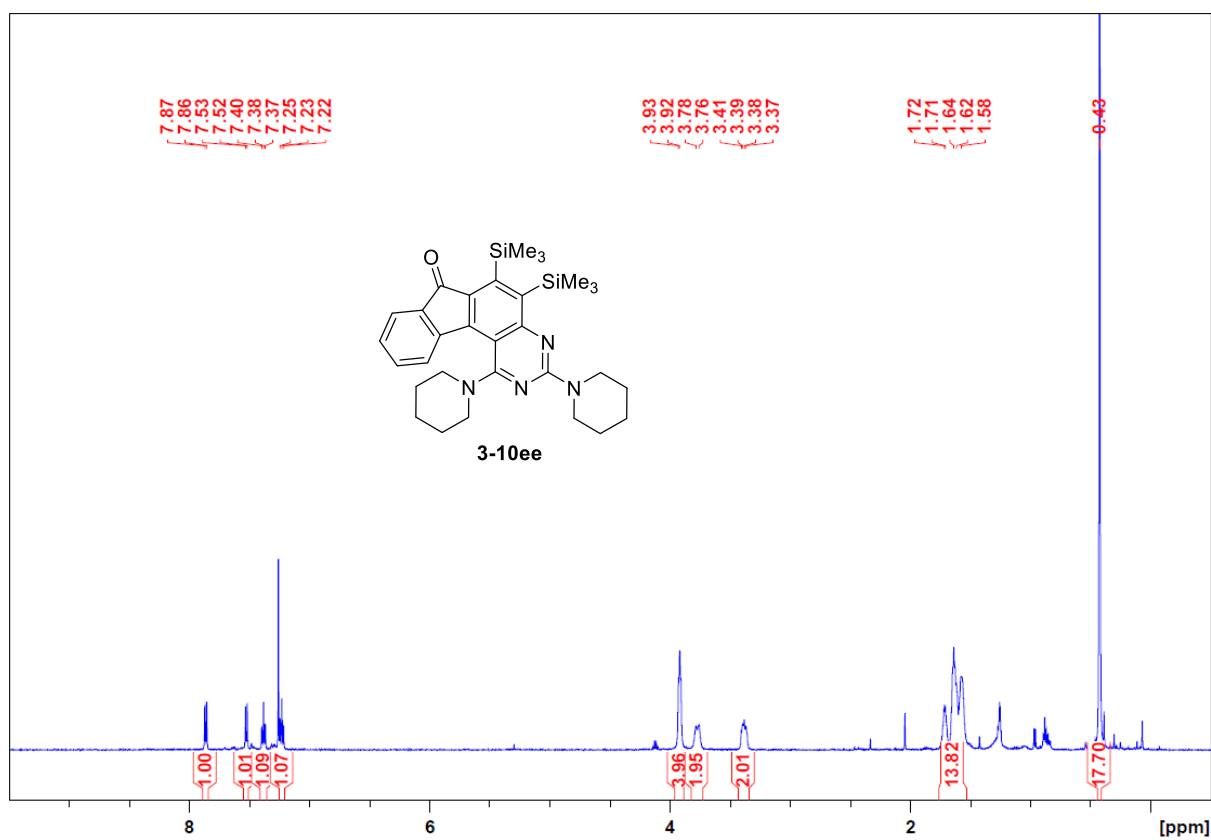


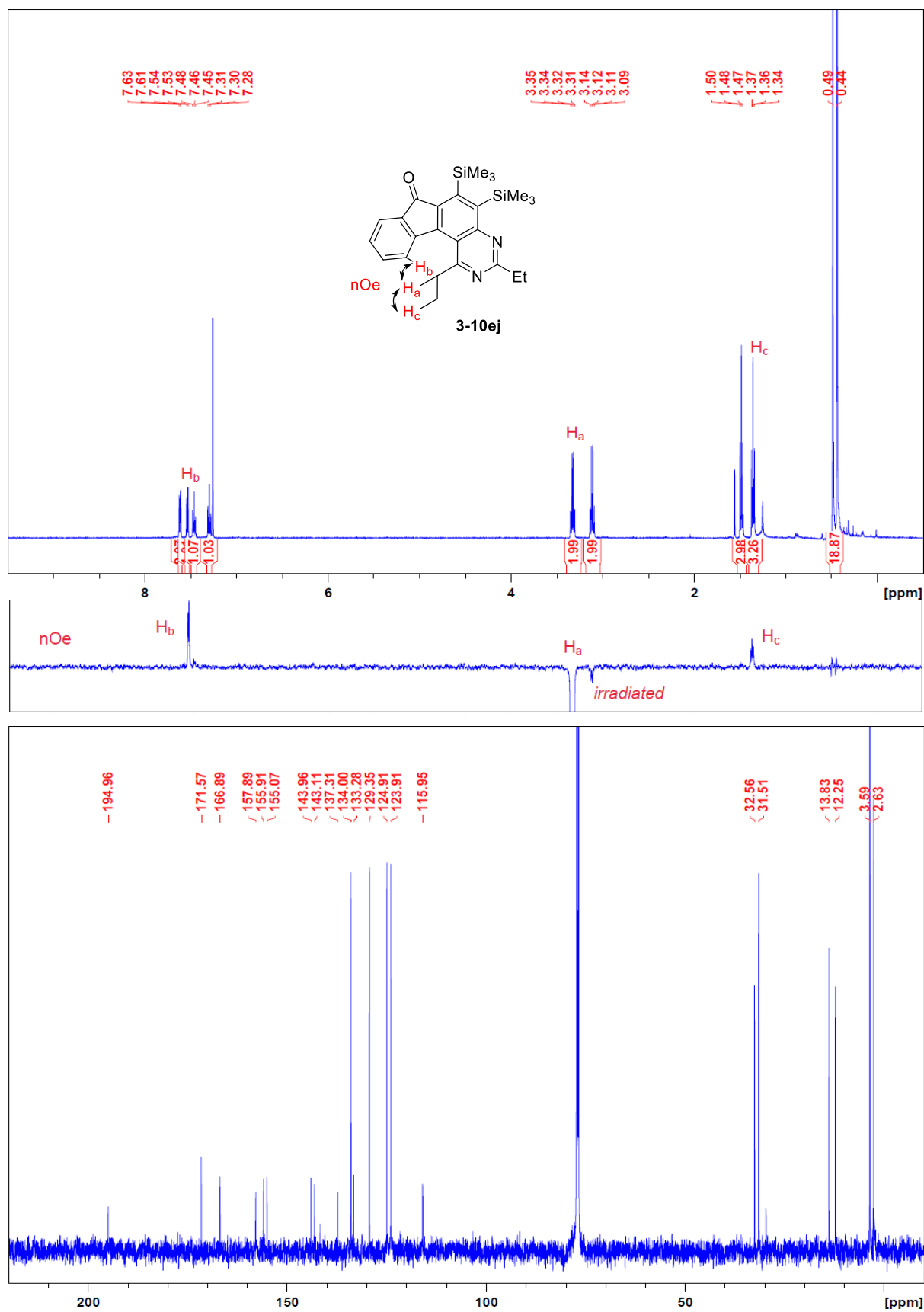


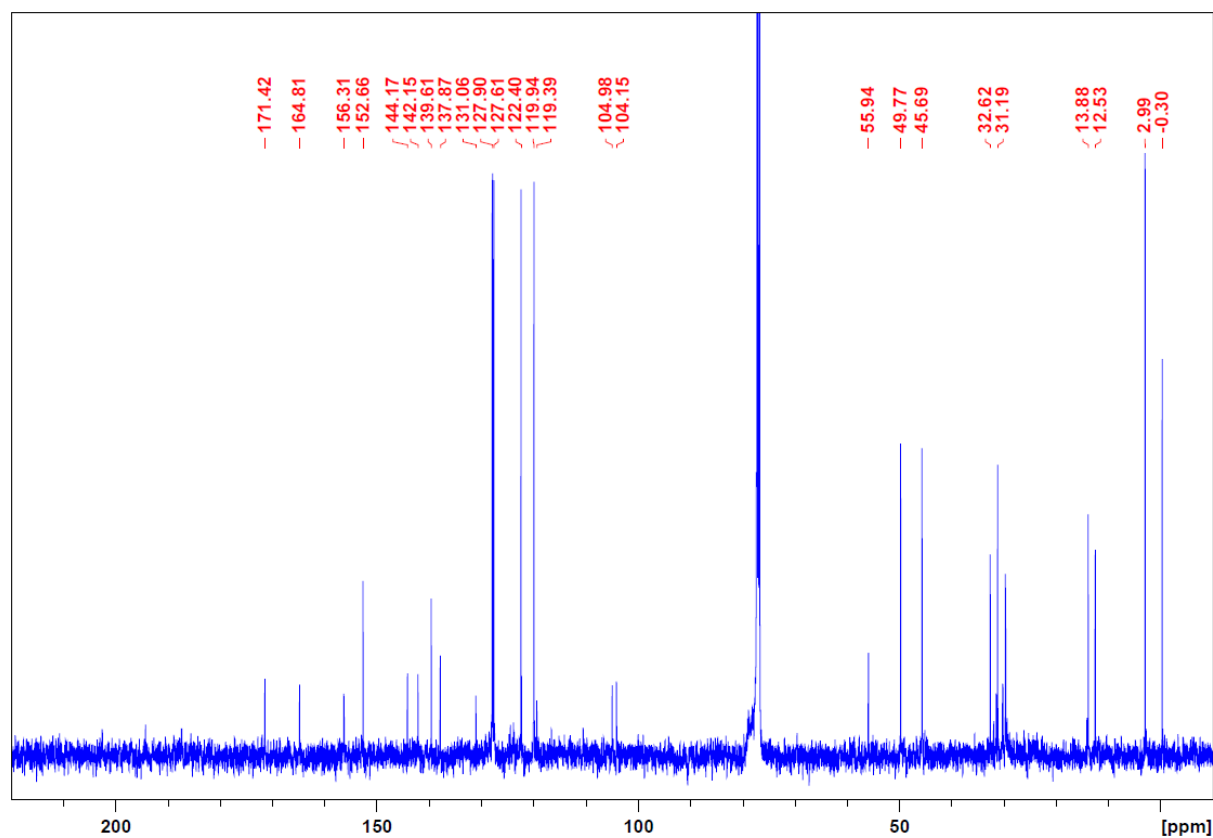
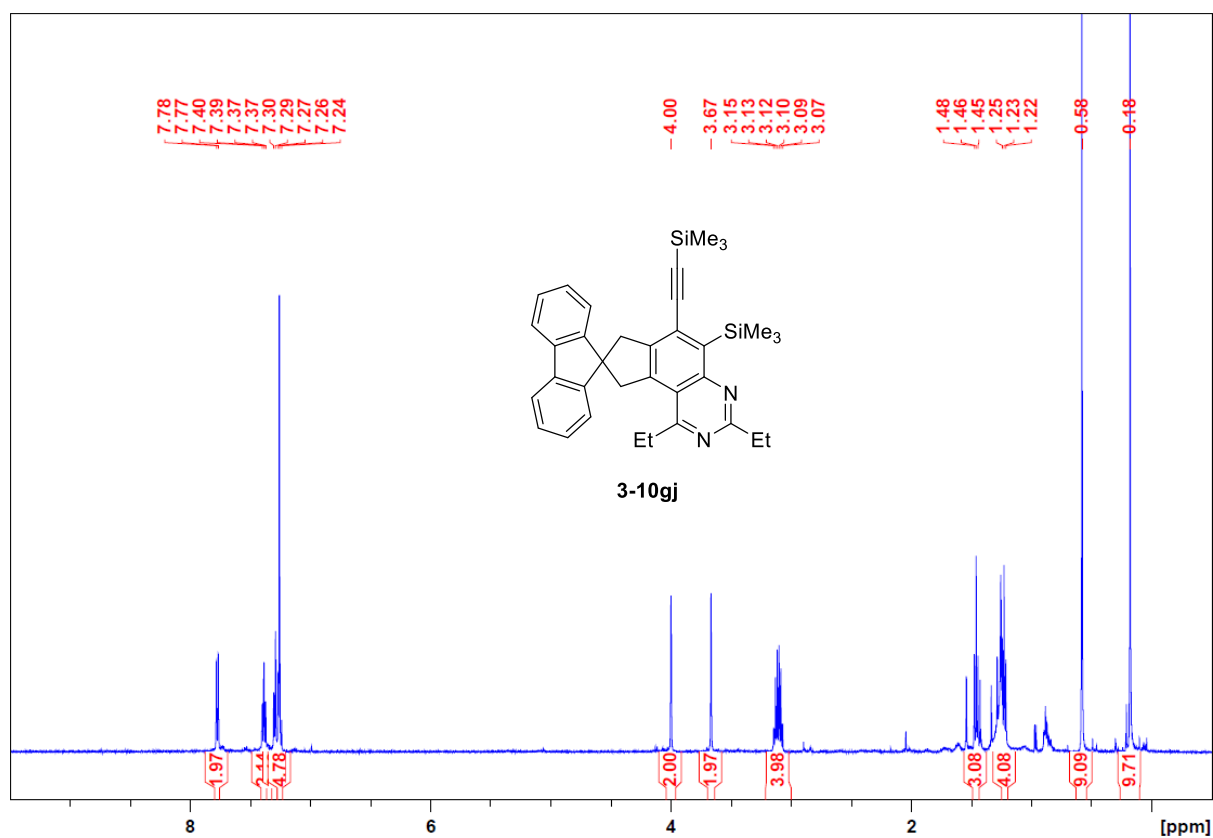


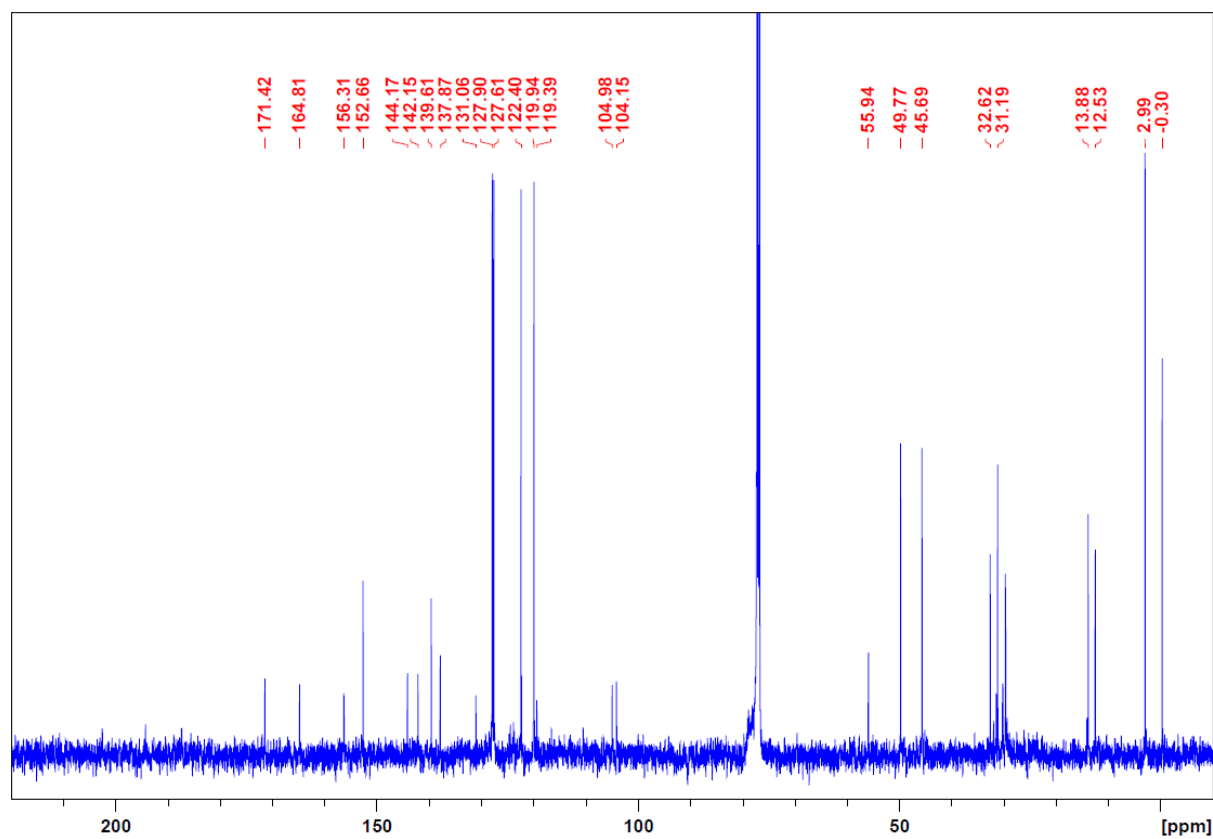
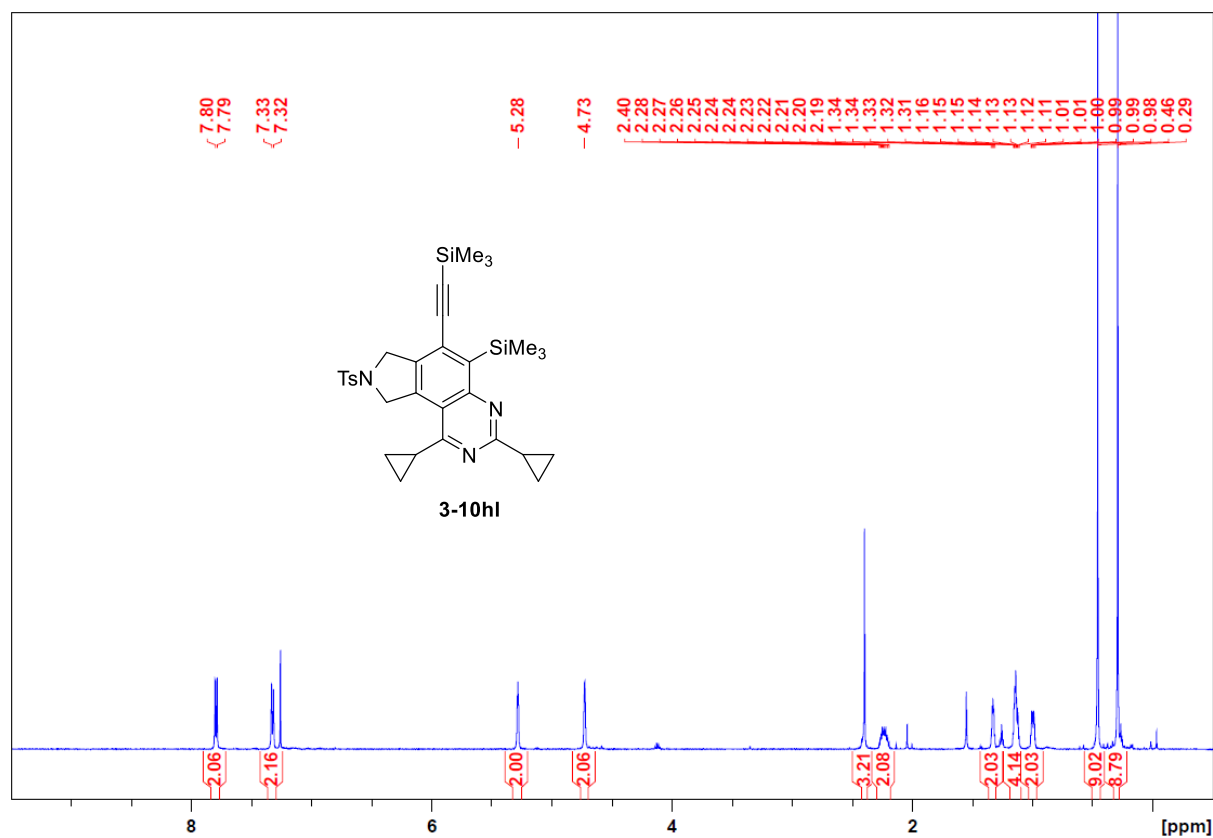


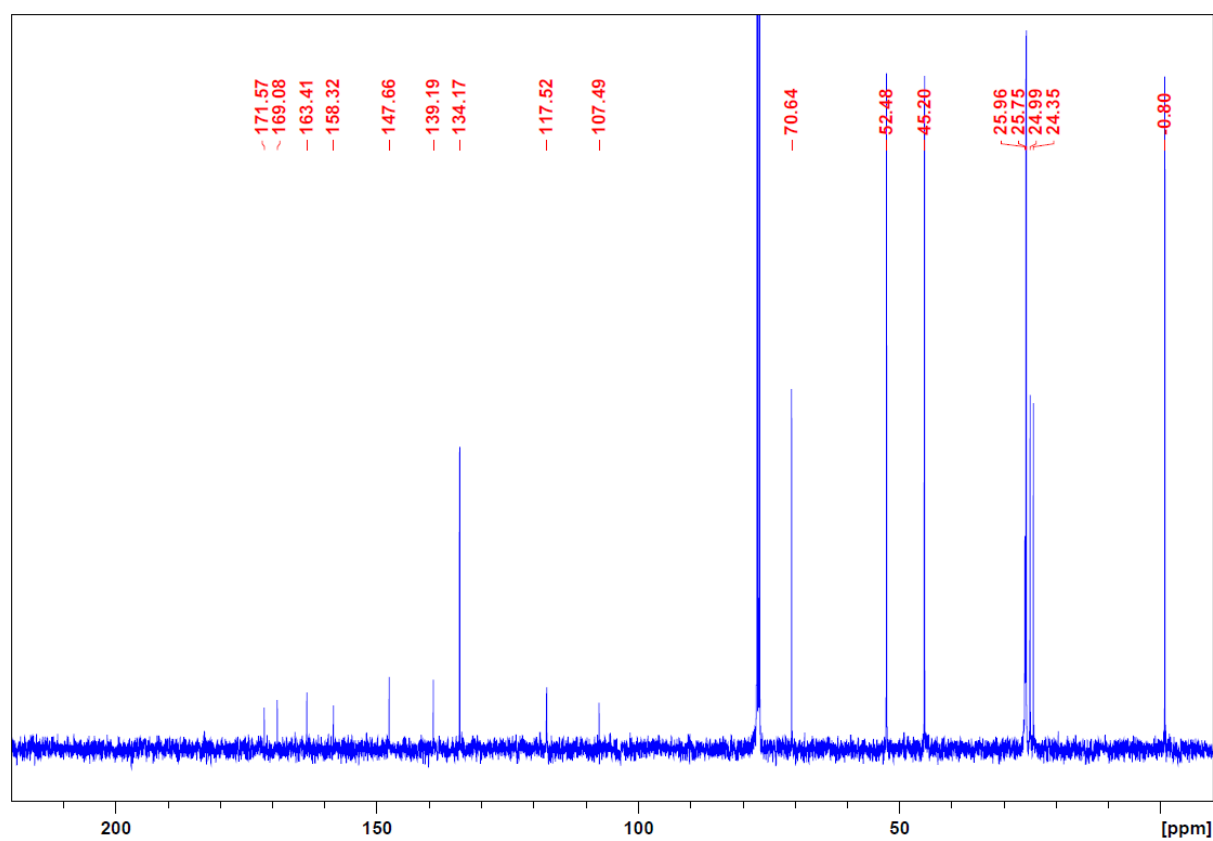
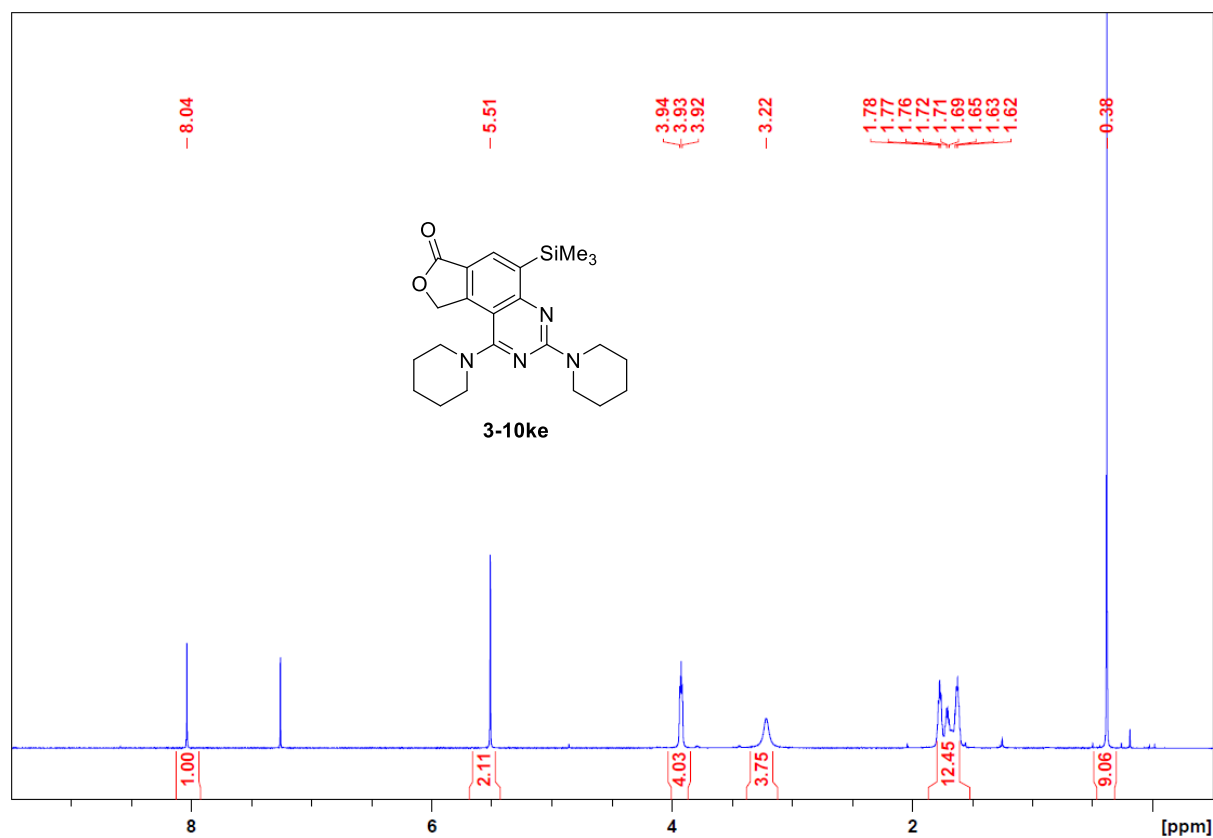


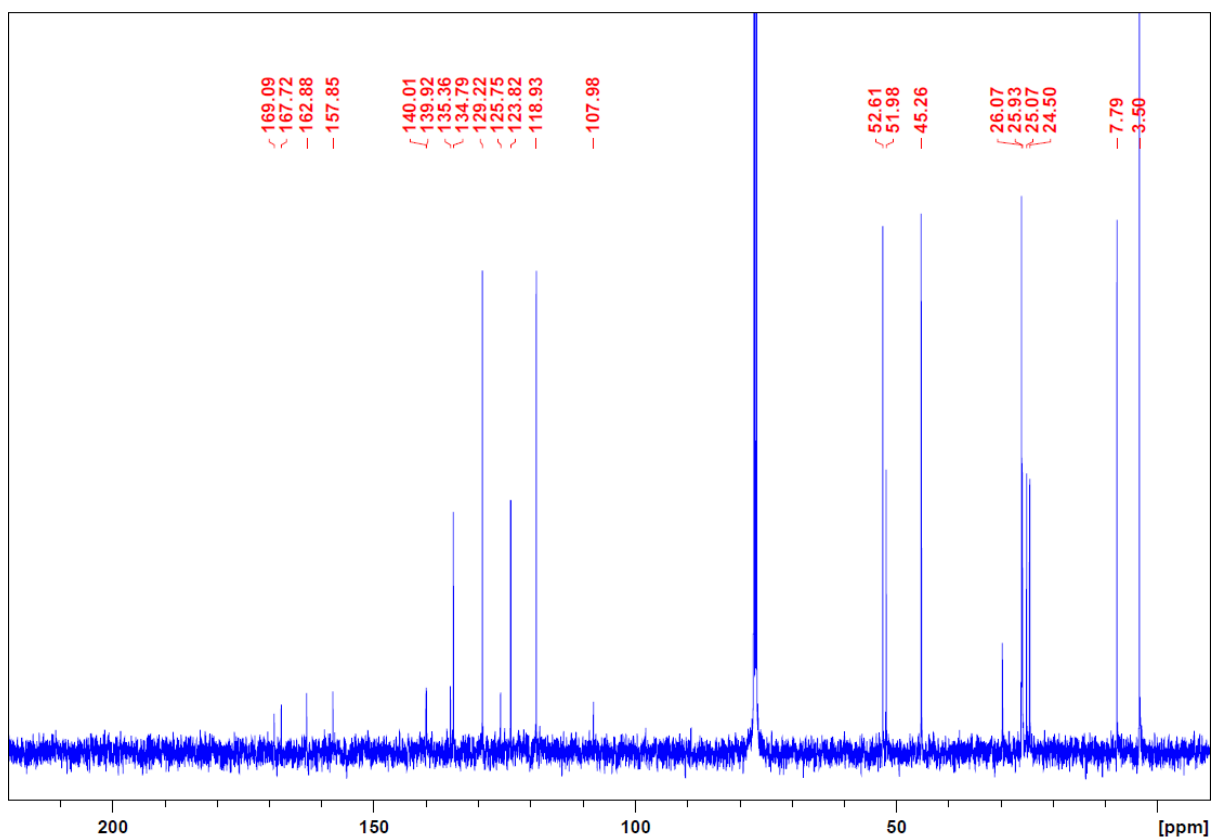
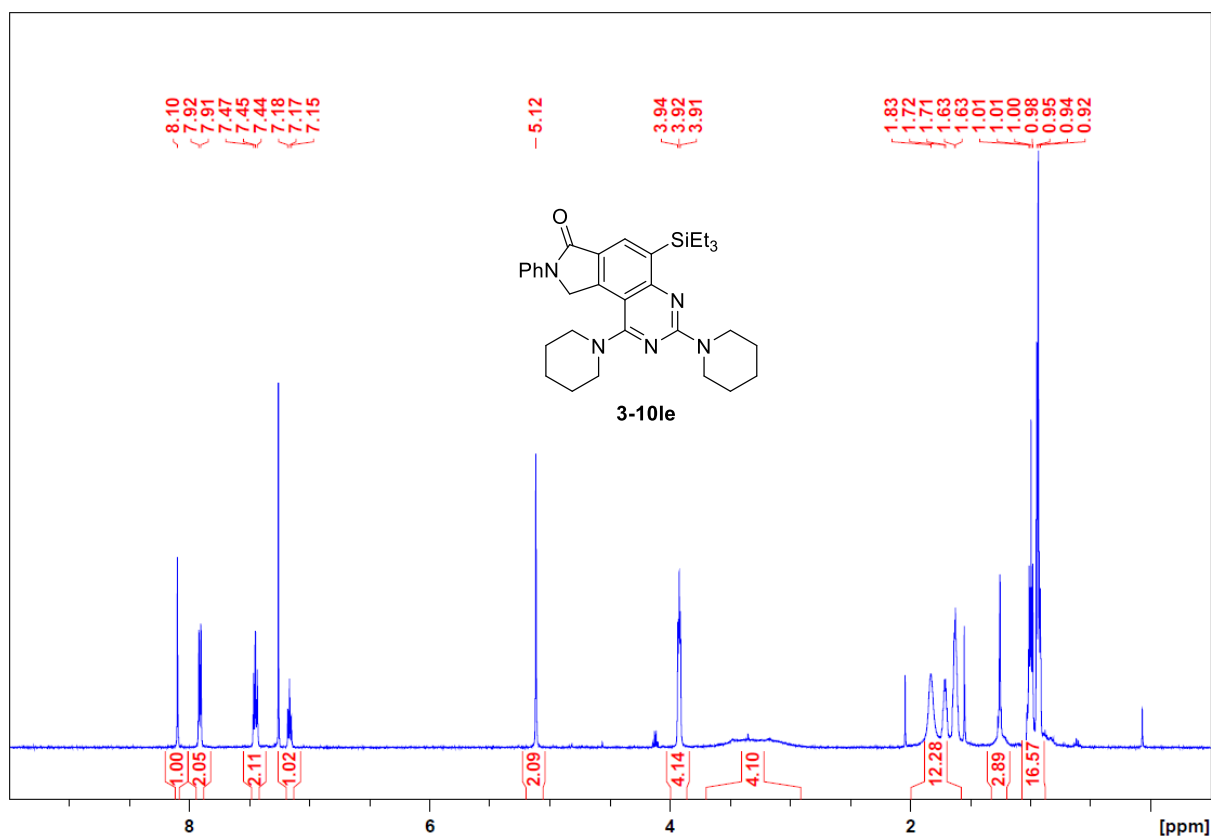


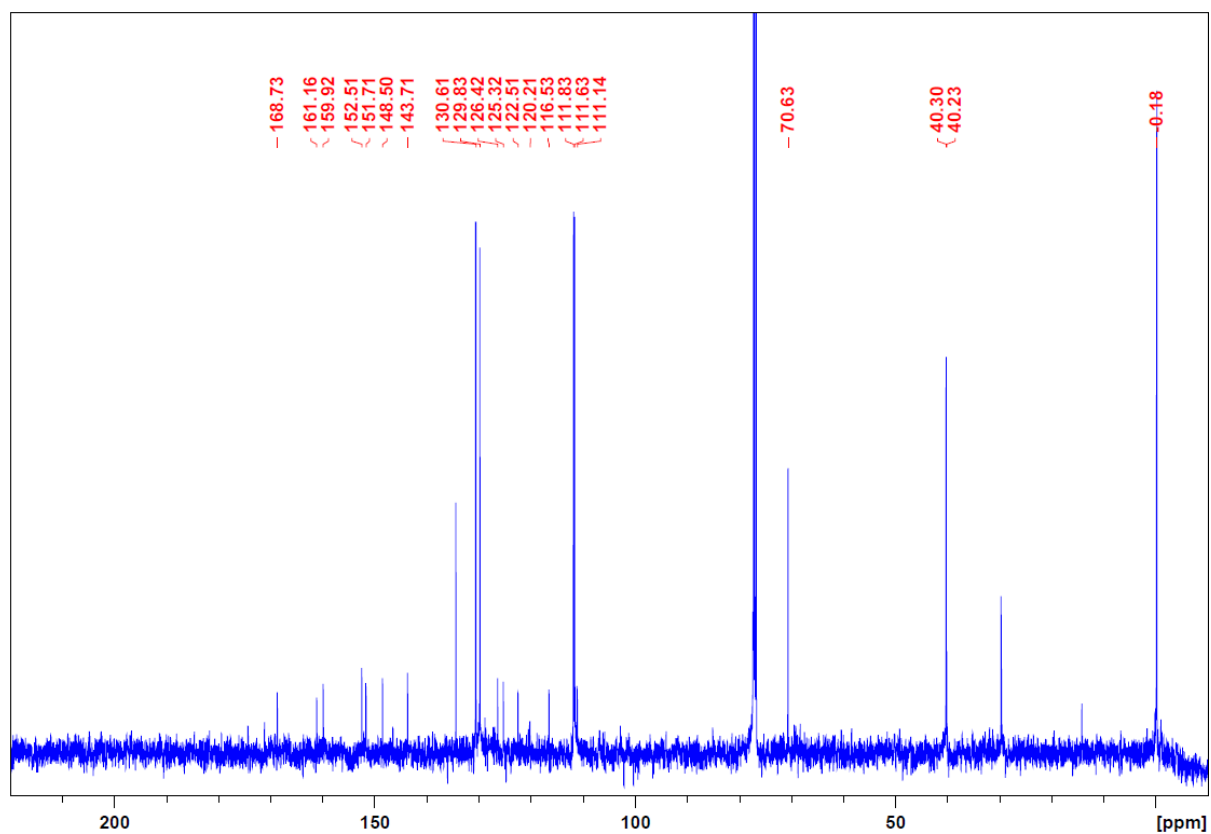
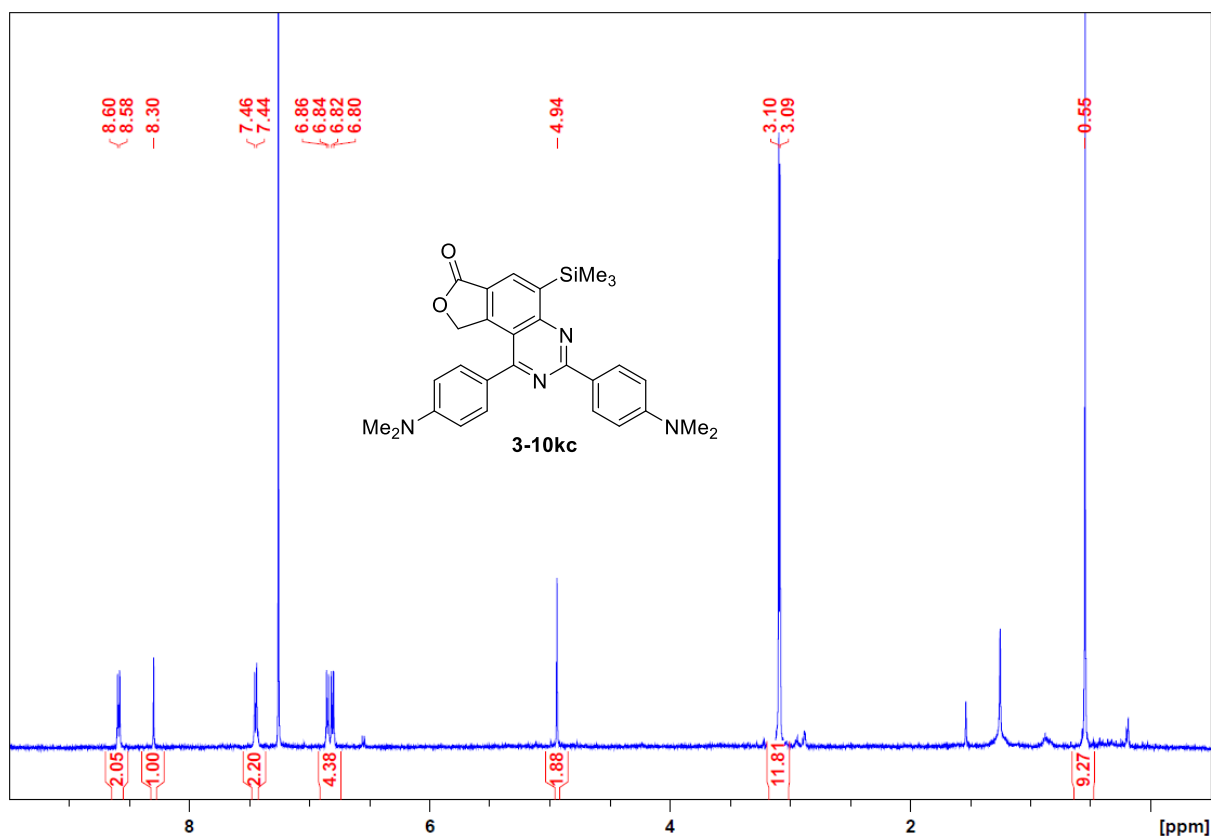


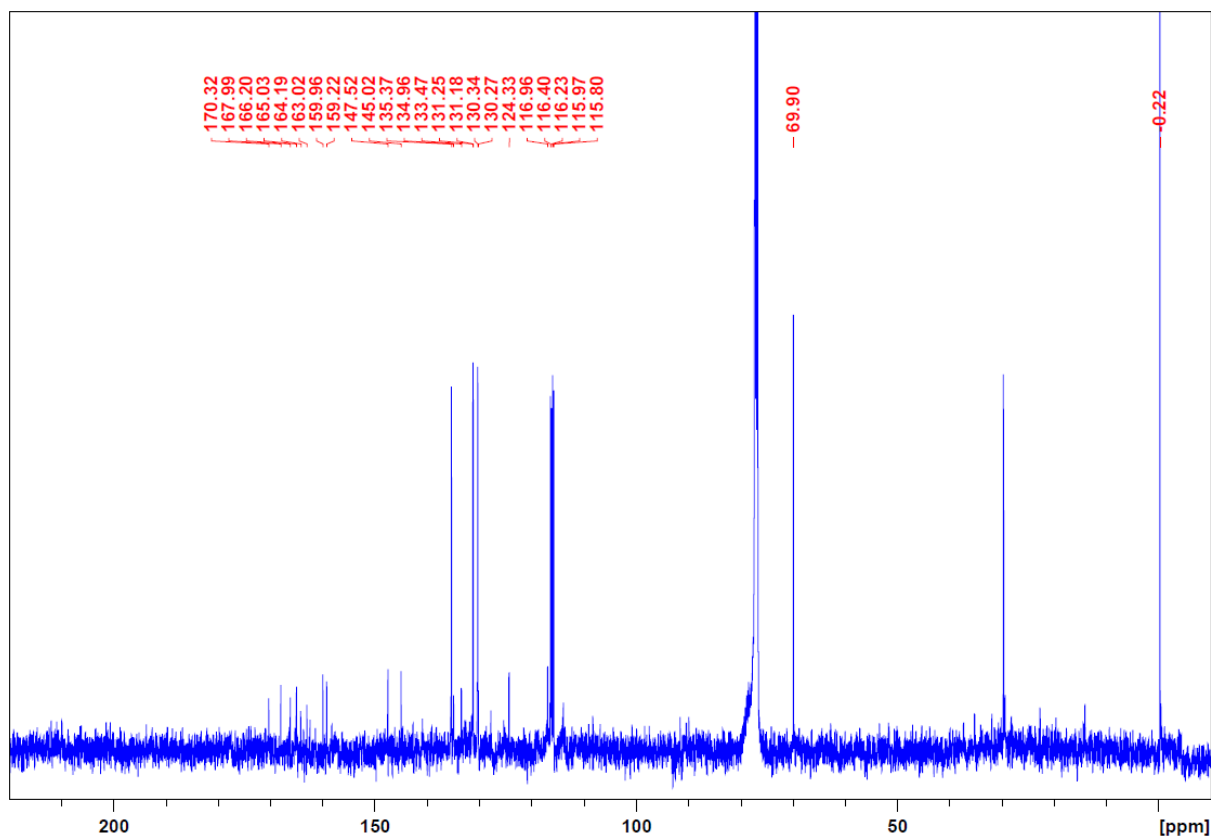
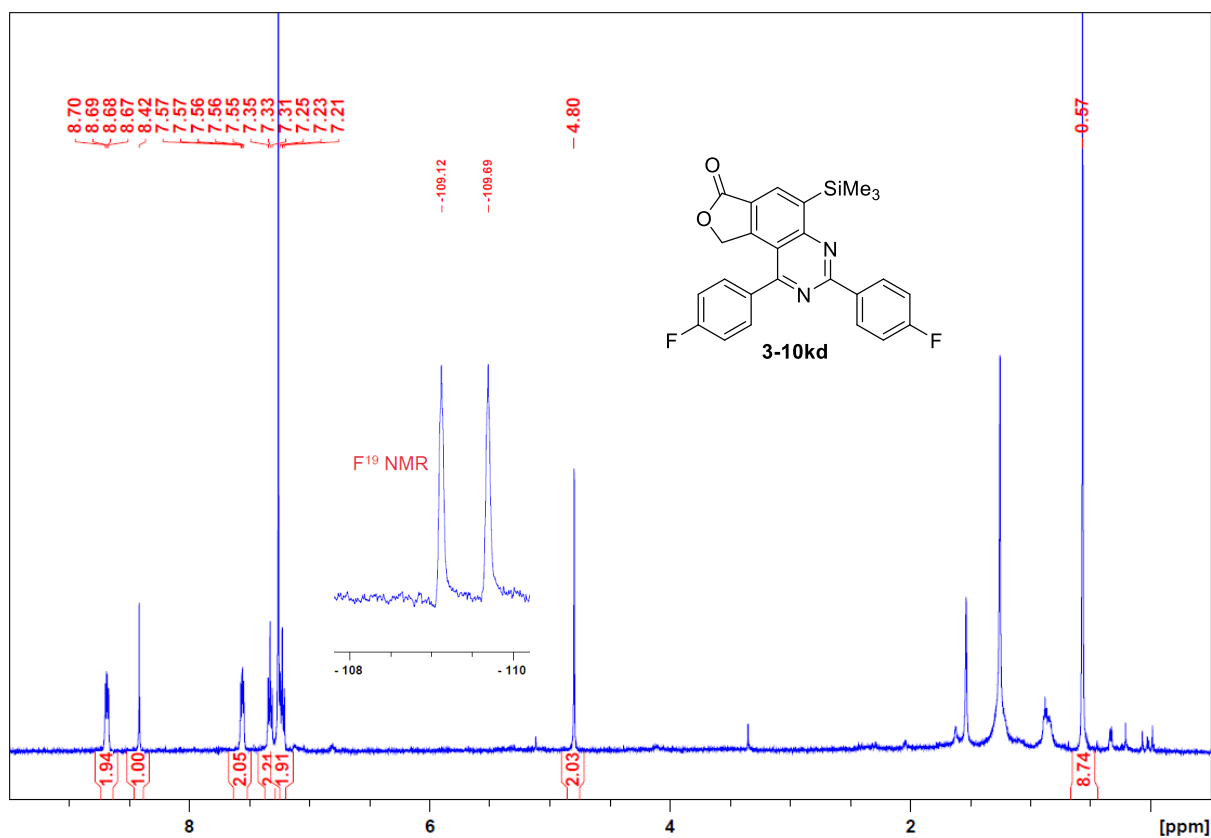


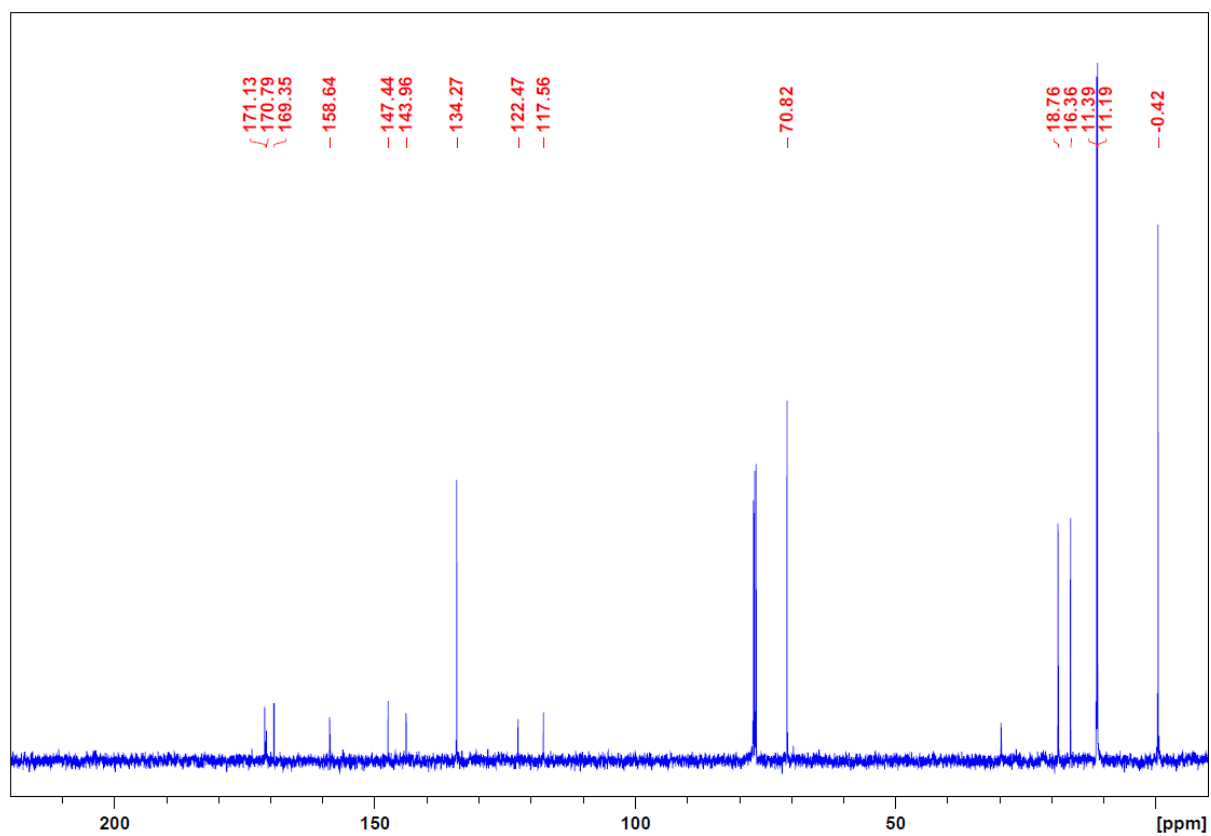
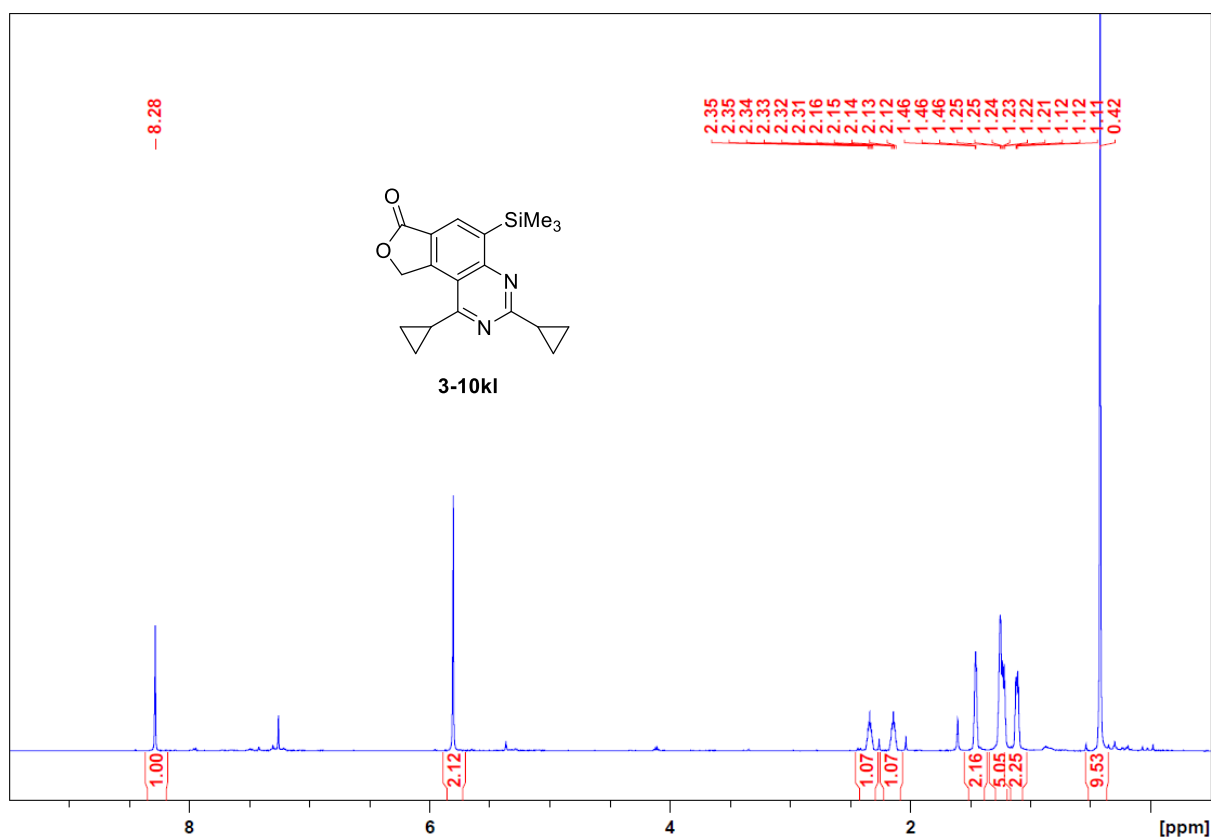






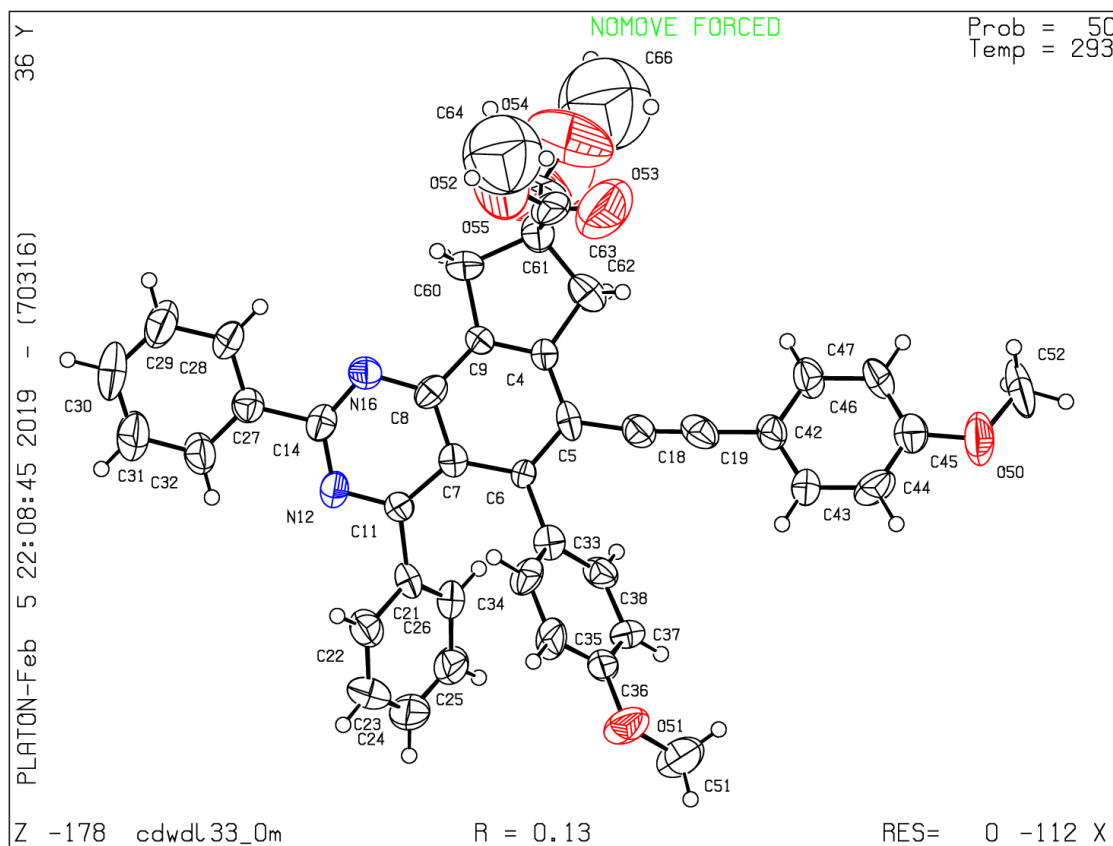
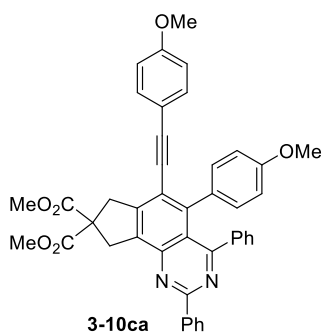






X-Ray Structures of Quinazoline 3-10ca and 3-10ka

CCDC 1903501 (**3-10ca**) and CCDC 1903113 (**3-10ka**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.





Computational Details

All calculations were carried out with the Gaussian 09 suite of computational programs.^[1] The geometry optimizations and frequency calculations for all intermediates and transition states were done at the B3LYP/6-31G(d) (Lanl2dz for Ag) level of theory.^[2] To evaluate the effects of solvent, single point calculations in PhCN solvent were done at a higher level of M06/6-311++G(d,p) (SDD for Ag) with the SMD model.^[3] Unless stated otherwise, all the energy values discussed in the main text are relative free energies in solution (ΔG_{sol} , kcal/mol). Only the intermediate or transition state that has the lowest energy value among all possible conformers is used for discussion.

[1] Gaussian 09, Revision A.01, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, Jr. J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J.; Gaussian, Inc., Wallingford CT, 2009.

[2] (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648; *J. Chem. Phys.*, **1993**, *98*, 1372. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B*, **1988**, *37*, 785.

[3] Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215; *Acc. Chem. Res.* **2008**, *41*, 157.

DFT-calculated reaction profiles of substrate 3-9h leading to product 3-10ha

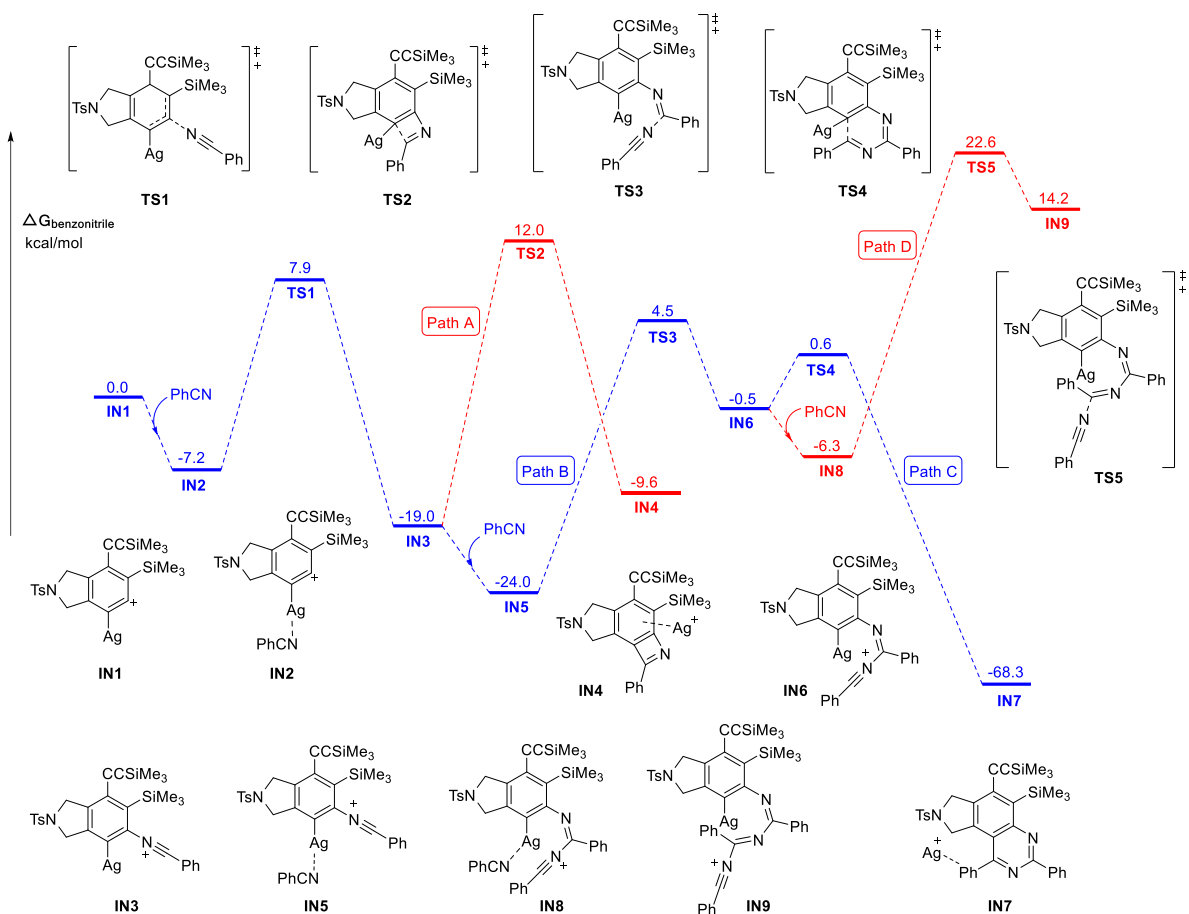
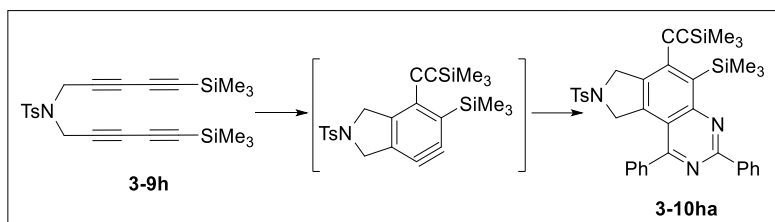


Table of Energy Values (in a.u.)

Table S1: Energies (in Hartree) calculated at SMD-M06/6-311++G(d,p)/SDD//B3LYP/6-31G(d)/LANL2DZ

Species	G ₂₉₈ ^a	E ^b	G _{Sol} ^c
IN1	-2221.303242	-2221.6892597	-2222.49967543
IN2	-2545.768723	-2546.2382366	-2546.86137157
TS1	-2545.717761	-2546.1909057	-2546.84089336
IN3	-2545.762602	-2546.2428241	-2546.89097255
TS2	-2545.714839	-2546.2000087	-2546.84644963
IN4	-2545.755738	-2546.2408277	-2546.88083133
IN5	-2870.213261	-2870.7805772	-2871.2526512
TS3	-2870.151831	-2870.7223625	-2871.21046332
IN6	-2870.162116	-2870.7362036	-2871.22194566
TS4	-2870.151587	-2870.72675	-2871.22136809
IN7	-2870.269461	-2870.8526612	-2871.33920379
IN8	-3194.606568	-3195.2686842	-3195.58607526
TS5	-3194.548634	-3195.2142097	-3195.54344772
IN9	-3194.555495	-3195.2254724	-3195.56124176

^a Sum of electronic and thermal free energies

^b Electronic energies

^c Single point energies in solution

Cartesian Coordinates

IN1

C	-3.25978100	0.67779300	-0.33584100
H	-3.82799900	1.59204000	-0.53427800
H	-3.89874800	-0.18776000	-0.58629300
C	-1.41374700	0.11066200	1.16604400
H	-0.83639700	0.67554400	1.90291500
H	-1.40232900	-0.95032600	1.46631500
C	-1.95866600	0.60628500	-1.09997600
C	-0.90127700	0.27256600	-0.24244600
C	-1.74361500	0.82446300	-2.49774100
C	0.42969000	0.12454100	-0.69116700
C	-0.45717600	0.62370500	-2.63114700
C	1.46511200	-0.21648400	0.21327700
C	0.72664500	0.33352700	-2.11240500
C	2.31577200	-0.50990600	1.04253500
Si	2.45082600	0.22331000	-2.99916200
C	3.56139300	1.51112800	-2.19957700
H	4.55885700	1.46819200	-2.65478300
H	3.17367700	2.52524700	-2.34675800
H	3.67570100	1.34072700	-1.12472500
C	2.09254000	0.62869300	-4.80514900
H	1.39840300	-0.08928700	-5.25856700
H	1.67968300	1.63757000	-4.92593700
H	3.02027400	0.59012800	-5.38848400
C	3.06545400	-1.54090900	-2.78861500
H	3.16214400	-1.81542100	-1.73368300
H	2.39627000	-2.26208300	-3.27086500
H	4.05359700	-1.64260500	-3.25457300
Si	3.57854600	-0.95116100	2.35072600
C	5.10896500	0.10389000	2.03400300
H	5.54183400	-0.09333600	1.04676700
H	4.88370700	1.17417800	2.09987600
H	5.87928200	-0.11840200	2.78254500
C	2.79895700	-0.56410100	4.02190200
H	1.88971200	-1.15174000	4.19045300
H	3.50157300	-0.80159000	4.82999100
H	2.53805100	0.49627500	4.11059500
C	3.95289400	-2.79017800	2.16337500
H	3.05359500	-3.40159900	2.29690400
H	4.37646900	-3.02050700	1.17933100
H	4.68289700	-3.10371600	2.91964800
Ag	-3.11551700	1.42200900	-4.01341400
N	-2.77591300	0.66114400	1.04851200
S	-3.86938900	0.53502500	2.32603400
O	-5.01275300	1.34600600	1.90838200
O	-3.07719600	0.80669500	3.52342100
C	-4.38991500	-1.17572200	2.37996400
C	-5.50747500	-1.58214600	1.64380100
C	-3.66652200	-2.09266000	3.14990000
C	-5.88875600	-2.92236000	1.67356000
H	-6.08709800	-0.85102200	1.09004500
C	-4.06411000	-3.42783100	3.16541100
H	-2.82964300	-1.75446200	3.75181700
C	-5.17720200	-3.86513600	2.43092200
H	-6.76379100	-3.23942800	1.11196800
H	-3.51005000	-4.14078100	3.77062100
C	-5.62297400	-5.30591800	2.49089600
H	-4.77395900	-5.98384900	2.62513100
H	-6.30379900	-5.46621600	3.33698500
H	-6.15759700	-5.60034100	1.58242400

IN2

C	-2.87417700	0.30421700	-0.30284200
H	-3.41721500	1.25398700	-0.34868500

H	-3.55038000	-0.48392200	-0.66534200
C	-0.98481400	-0.47068300	1.05131600
H	-0.38390000	0.00309700	1.83543200
H	-0.95712100	-1.55839400	1.21000400
C	-1.59900400	0.32345800	-1.10535400
C	-0.51722700	-0.11552600	-0.33462300
C	-1.44264100	0.69820800	-2.48284200
C	0.79492000	-0.21514200	-0.84938800
C	-0.16747300	0.51253600	-2.67898700
C	1.86271100	-0.66439700	-0.03004500
C	1.03760900	0.15619900	-2.24241400
C	2.74802300	-1.05646700	0.71728400
Si	2.71355200	0.12907300	-3.20492400
C	3.87825900	1.32228800	-2.33360600
H	4.85863900	1.31053100	-2.82592400
H	3.50111400	2.35045600	-2.36915000
H	4.02571300	1.04893800	-1.28410600
C	2.29533900	0.71583900	-4.94824200
H	1.57195800	0.05498200	-5.44104400
H	1.89127100	1.73540400	-4.95315200
H	3.19944000	0.72404000	-5.56876400
C	3.33176600	-1.64710000	-3.20227700
H	3.47867600	-2.02289600	-2.18507300
H	2.63366600	-2.31681900	-3.71679600
H	4.29448800	-1.70536200	-3.72533000
Si	4.07493900	-1.65639500	1.88271500
C	4.97717500	-0.13667000	2.54281700
H	5.44850200	0.43622800	1.73622200
H	4.29812200	0.53434500	3.08050700
H	5.76794500	-0.43930900	3.24019900
C	3.21892500	-2.60766200	3.26771900
H	2.66628400	-3.47122700	2.88119900
H	3.95927400	-2.98087200	3.98584800
H	2.51418800	-1.97314700	3.81680000
C	5.23673900	-2.77071000	0.89909700
H	4.70893700	-3.63469900	0.47990500
H	5.71329600	-2.23073000	0.07307200
H	6.03418800	-3.15233500	1.54836000
Ag	-2.90013700	1.33854200	-3.86984500
N	-2.37183300	0.05743700	1.07100600
S	-3.47910600	-0.72776800	2.10669400
O	-3.22847300	-2.17532300	2.09871900
O	-4.78305600	-0.18927700	1.70950100
C	-3.01084000	-0.09140200	3.70641300
C	-2.41276600	-0.94398900	4.63411700
C	-3.29011400	1.24267400	4.02289700
C	-2.07953000	-0.44414000	5.89380900
H	-2.22656000	-1.98052300	4.37457100
C	-2.94920800	1.72108100	5.28282800
H	-3.77410300	1.88681400	3.29625800
C	-2.34100700	0.88803100	6.23850400
H	-1.61647900	-1.10445600	6.62220900
H	-3.16437300	2.75613100	5.53614500
C	-2.00328500	1.41924600	7.61044100
H	-2.91327100	1.57492700	8.20374300
H	-1.36214300	0.72680100	8.16362100
H	-1.49006400	2.38556500	7.54944800
C	-6.41224400	2.09294800	-8.12388100
C	-6.32608400	2.66831700	-6.84122600
C	-7.27322300	3.61599500	-6.40695500
C	-8.30495800	3.98271600	-7.26458400
C	-8.39374600	3.41359600	-8.53905200
C	-7.45132300	2.47284800	-8.96679600
H	-5.67538200	1.36337300	-8.44355500

H	-7.19397200	4.04944700	-5.41535800	C	-4.07574800	1.31544900	-7.78808600
H	-9.04054200	4.71155500	-6.93976300	C	-3.63549900	2.29226500	-6.87490600
H	-9.20251100	3.70442100	-9.20271200	C	-3.57344300	3.64884800	-7.24734600
H	-7.52743200	2.03543100	-9.95709900	C	-3.95521000	4.01940600	-8.53321100
C	-5.26841500	2.28390600	-5.96783100	C	-4.39419800	3.05081100	-9.44118900
N	-4.40693500	1.97120500	-5.25425600	C	-4.45360400	1.70391900	-9.06966800
TS1				H	-4.11339400	0.27225300	-7.49129900
C	-3.96057900	0.56254700	0.95706800	H	-3.22670900	4.39190100	-6.53617200
H	-4.57614700	1.45684000	1.09695100	H	-3.90865400	5.06287300	-8.82819600
H	-4.63453400	-0.30564400	0.85316500	H	-4.68987900	3.34646100	-10.44333300
C	-1.66752400	-0.01597800	1.59684200	H	-4.79258000	0.95672100	-9.78026400
H	-0.88203500	0.52583000	2.13058700	C	-3.24015900	1.90271900	-5.55792300
H	-1.49189800	-1.09426100	1.74404100	N	-2.91379600	1.58647900	-4.48473800
C	-3.03666700	0.65804300	-0.23326600	IN3			
C	-1.73112200	0.32112600	0.12969300	C	-4.02860200	0.61943000	0.78945100
C	-3.36523400	1.01838600	-1.56677800	H	-4.65785100	1.50359000	0.93429700
C	-0.66271900	0.31271500	-0.79411200	H	-4.68985100	-0.26055600	0.70443200
C	-2.22851400	0.94084600	-2.23577100	C	-1.73118300	0.06828900	1.40869100
C	0.62345300	-0.05204500	-0.31422100	H	-0.93677600	0.61457400	1.92514000
C	-0.91503300	0.67611100	-2.18550800	H	-1.54446800	-1.00872100	1.55826100
C	1.66702200	-0.38255800	0.23053800	C	-3.12294200	0.72056600	-0.41598000
Si	0.37129800	0.77673700	-3.64424500	C	-1.81549600	0.39142100	-0.05799900
C	0.36492800	2.56757700	-4.23701200	C	-3.45125500	1.06823300	-1.72043700
H	1.02653800	2.67016100	-5.10635200	C	-0.75704500	0.37565700	-0.99131400
H	-0.62867800	2.92069600	-4.52424400	C	-2.37221900	1.05338500	-2.63266100
H	0.74849400	3.23190300	-3.45385700	C	0.52210000	0.00554300	-0.47548100
C	-0.19256800	-0.46880700	-4.94438700	C	-1.01720600	0.72026300	-2.34357700
H	-0.10722700	-1.49176200	-4.55959500	C	1.54077300	-0.32733700	0.11150300
H	-1.22503900	-0.31301000	-5.26746400	Si	0.32954900	0.76733600	-3.73627900
H	0.45411000	-0.39654900	-5.82787400	C	0.41362500	2.53945800	-4.40849600
C	2.11177200	0.33189600	-3.09142400	H	1.19542000	2.59597800	-5.17602900
H	2.50176000	1.00765000	-2.32578600	H	-0.51140300	2.90917400	-4.86265400
H	2.19636700	-0.69220900	-2.71892000	H	0.69260400	3.23802000	-3.61084200
H	2.75584500	0.42137200	-3.97704200	C	-0.17172800	-0.47560000	-5.07940600
Si	3.26048400	-0.87388700	1.06346400	H	-0.20473500	-1.49147400	-4.66827700
C	4.32880500	0.67433000	1.20496000	H	-1.13830500	-0.28065200	-5.55539300
H	4.56387200	1.09631600	0.22140400	H	0.58607200	-0.47237600	-5.87265500
H	3.83326200	1.45190600	1.79685800	C	2.06705800	0.30800700	-3.17911000
H	5.27860700	0.43516600	1.69888800	H	2.46242800	0.98817000	-2.42048200
C	2.81974400	-1.56235600	2.76286200	H	2.13485100	-0.71011500	-2.78782600
H	2.17662100	-2.44630700	2.68550800	H	2.71511000	0.37453000	-4.06349600
H	3.72920700	-1.86042100	3.29878700	Si	3.10543700	-0.82185700	0.98826700
H	2.30137400	-0.81883500	3.37857100	C	4.20702800	0.70582400	1.10718000
C	4.08621100	-2.18641100	-0.01203700	H	4.46817800	1.09510600	0.11660800
H	3.45499900	-3.07590200	-0.11742500	H	3.71795300	1.51021500	1.66791600
H	4.30848600	-1.80764600	-1.01604800	H	5.14269200	0.46087200	1.62471500
H	5.03408300	-2.50389800	0.43955200	C	2.62643300	-1.44983400	2.70173100
Ag	-5.23299300	1.62237200	-2.38250500	H	1.97146700	-2.32649000	2.64084000
N	-2.99944400	0.41823600	2.05793400	H	3.52126300	-1.74359600	3.26403500
S	-3.53870900	0.03495300	3.60365600	H	2.10767400	-0.67973300	3.28374300
O	-4.78546000	0.78462800	3.76024600	C	3.93114800	-2.18389100	-0.02523800
O	-2.37437200	0.21551600	4.46868300	H	3.28344700	-3.06280600	-0.11991500
C	-3.94410900	-1.70919100	3.58022700	H	4.18507600	-1.84044100	-1.03450600
C	-5.24112200	-2.11373600	3.24629700	H	4.86094300	-2.50736400	0.45854700
C	-2.95587500	-2.65173300	3.88004300	Ag	-5.45618900	1.60060400	-2.16185400
C	-5.53812900	-3.47404000	3.20228100	N	-3.05669500	0.49861200	1.88450300
H	-6.00897400	-1.36971000	3.06207600	S	-3.57295600	0.12264300	3.43797200
C	-3.27327300	-4.00824700	3.82953900	O	-4.83029500	0.85289100	3.60317800
H	-1.96647400	-2.32292800	4.18016800	O	-2.40386800	0.32888000	4.29121800
C	-4.56344000	-4.44189200	3.49144500	C	-3.94944000	-1.62860300	3.43553600
H	-6.54821600	-3.79066000	2.95427100	C	-5.24319800	-2.05858400	3.12564800
H	-2.50933600	-4.74258400	4.07162300	C	-2.93960000	-2.55185500	3.72668800
C	-4.91045700	-5.91113700	3.47886900	C	-5.51670900	-3.42520500	3.09665900
H	-5.41583500	-6.19936600	4.40974400	H	-6.02680900	-1.32979800	2.94699900
H	-5.58824400	-6.15680200	2.65431500	C	-3.23293600	-3.91334400	3.69124000
H	-4.01644100	-6.53491800	3.38480700	H	-1.95162300	-2.20300200	4.00830000

C	-4.52120900	-4.37277700	3.37706200	C	-4.35177300	-1.03011700	3.00194400
H	-6.52459300	-3.76172000	2.86701800	C	-5.69720300	-0.87561400	2.64917400
H	-2.45174900	-4.63207100	3.92581100	C	-3.63439700	-2.14852700	2.56632200
C	-4.83629400	-5.84922100	3.38413600	C	-6.31153200	-1.82996600	1.80581100
H	-5.09205800	-6.18751300	4.39670700	H	-6.27429200	-0.05738100	3.06891000
H	-5.68825600	-6.08219300	2.73774900	C	-4.24865400	-3.09494600	1.74484600
H	-3.97989800	-6.44448000	3.05077500	H	-2.60651100	-2.28620400	2.88616900
C	-3.82311200	1.10551500	-7.23319100	C	-5.59068800	-2.96290500	1.34823800
C	-3.40144100	2.09618900	-6.31874600	H	-7.38444400	-1.77162600	1.62835700
C	-3.35179000	3.45780900	-6.69192100	H	-3.68497400	-3.96742500	1.42583400
C	-3.72625000	3.81682000	-7.98104400	C	-6.26936900	-4.04313500	0.54223700
C	-4.14439700	2.83653700	-8.88849000	H	-5.61301000	-4.43395000	-0.24173800
C	-4.19284200	1.48784800	-8.51688900	H	-6.53320300	-4.88640900	1.19299700
H	-3.85253800	0.06349600	-6.93191600	H	-7.19351500	-3.68763500	0.07712700
H	-3.02250900	4.20622400	-5.97851500	C	-6.86531400	1.97967700	-2.52124800
H	-3.69120000	4.85906200	-8.28098200	C	-5.65153300	1.70418500	-3.18327000
H	-4.43403500	3.12588300	-9.89422500	C	-5.42674000	2.20039400	-4.49158000
H	-4.51704400	0.73673500	-9.22978400	C	-6.42464600	2.93000200	-5.12397400
C	-3.01611900	1.71858100	-5.01072500	C	-7.63164700	3.19000200	-4.46368700
N	-2.68626700	1.41017700	-3.94136200	C	-7.84983400	2.71909300	-3.16350200
TS2				H	-7.00917000	1.63020200	-1.50263600
C	-3.65572900	1.88939200	1.89153300	H	-4.48540100	1.99100000	-4.98839800
H	-3.50078600	2.97467300	1.82691800	H	-6.26166700	3.30435400	-6.12970500
H	-4.71553800	1.73374900	2.10230900	H	-8.40243700	3.77085300	-4.96137600
C	-1.48677500	0.99580900	2.36309500	H	-8.78320000	2.93768100	-2.65473300
H	-0.79456200	1.83391000	2.51838900	C	-4.63168900	0.91682000	-2.58576700
H	-1.04825300	0.12487600	2.85477200	N	-3.58363300	0.29022100	-2.78375800
C	-3.12130400	1.20915700	0.64650200	IN4			
C	-1.80221800	0.78958200	0.89395200	C	-4.04307300	2.01611600	1.31738700
C	-3.71602700	0.83583000	-0.54924200	H	-3.84616900	3.08325000	1.15239300
C	-0.99202200	0.19473300	-0.09012500	H	-5.12097700	1.89340200	1.44166200
C	-2.85646800	0.29832200	-1.56338800	C	-1.92736000	1.20170700	2.07836200
C	0.32023000	-0.18203400	0.32033600	H	-1.28244900	2.08492300	2.16794200
C	-1.50500600	-0.01190200	-1.41718400	H	-1.51301900	0.42424300	2.72258400
C	1.41178000	-0.46426300	0.79362300	C	-3.41421200	1.18410400	0.21572100
Si	-0.52797300	-0.63870500	-2.96448800	C	-2.12459700	0.77963300	0.63637900
C	-0.54654000	0.76248400	-4.23526400	C	-3.84339400	0.68639500	-1.02076900
H	-0.00527500	0.45415800	-5.13818600	C	-1.22809000	0.06786700	-0.18339000
H	-1.56395500	1.03446800	-4.53484800	C	-2.87507700	0.03409300	-1.85953600
H	-0.05331100	1.66192200	-3.84837400	C	0.02925500	-0.25620400	0.39298800
C	-1.43689300	-2.16460600	-3.61624400	C	-1.57730300	-0.30023800	-1.54981800
H	-1.44116900	-2.97294900	-2.87500300	C	1.07871200	-0.49820700	0.97419400
H	-2.47421400	-1.94429800	-3.88865300	Si	-0.45257700	-1.02970400	-2.93766700
H	-0.93081200	-2.54602400	-4.51167200	C	0.01446500	0.42051800	-4.05478600
C	1.26083600	-1.10596300	-2.60017000	H	0.62739700	0.07372300	-4.89582700
H	1.85013000	-0.26466800	-2.22442800	H	-0.87717100	0.90419000	-4.46923400
H	1.34574900	-1.92534500	-1.88069300	C	0.59346200	1.17899700	-3.51495300
H	1.71453800	-1.43909000	-3.54304100	H	-1.50855600	-2.28971200	-3.86671400
Si	3.09452800	-0.88812000	1.46829500	H	-1.78093300	-3.13753400	-3.22605000
C	4.35849500	0.17060700	0.55077400	H	-2.42947700	-1.83855600	-4.25002700
H	4.33846500	-0.01993700	-0.52809500	H	-0.95008000	-2.69298700	-4.72034400
H	4.17740700	1.23967600	0.70885100	C	1.09469100	-1.87838800	-2.27246900
H	5.37114200	-0.05166600	0.90905800	H	1.80535700	-1.17149300	-1.83561600
C	3.09162300	-0.49798200	3.31382000	H	0.86655700	-2.63993200	-1.51922300
H	2.33826200	-1.08374600	3.85265400	H	1.59363900	-2.38132100	-3.11090100
H	4.06904100	-0.73266500	3.75284600	Si	2.69132300	-0.90247700	1.81993800
H	2.89195300	0.56308600	3.50148200	C	4.06743600	-0.06892900	0.83494300
C	3.38883000	-2.72736900	1.16159500	H	4.10980900	-0.43925400	-0.19543400
H	2.64042800	-3.34584200	1.66980700	H	3.93655300	1.01831700	0.79871800
H	3.35881600	-2.96848700	0.09304000	H	5.03969400	-0.27130600	1.30075400
H	4.37511400	-3.02194400	1.54062600	C	2.60179900	-0.22597500	3.57851200
Ag	-5.49491800	-0.33672800	-0.00564200	H	1.77273600	-0.67002500	4.14112400
N	-2.79863900	1.34639800	2.96875100	H	3.52814200	-0.45365000	4.11993700
S	-3.54419400	0.23972200	4.01698700	H	2.47350700	0.86239900	3.58681200
O	-4.63449000	0.97363600	4.65312500	C	2.87041600	-2.78001500	1.81290100
O	-2.46393300	-0.41499900	4.74952800	H	2.06030700	-3.26425700	2.36954500

H	2.86711400	-3.17978800	0.79283800	H	4.17628700	2.30552200	3.59330500
H	3.81766700	-3.07172300	2.28274400	C	2.94059100	-0.76225600	3.14921400
Ag	-4.78063400	-1.03976500	0.37345700	H	2.83254700	-1.69790300	2.58893300
N	-3.29977300	1.58967900	2.53364400	H	3.83015900	-0.85560100	3.78422700
S	-4.10389500	0.40524800	3.47273500	H	2.07049500	-0.66120700	3.80791800
O	-3.07997900	-0.23867800	4.29115800	C	4.57307300	0.49687000	0.82119900
O	-4.96456200	-0.48285400	2.61587500	H	4.47398500	-0.41807900	0.22634900
C	-5.22805600	1.38541700	4.43892400	H	4.66699400	1.34085000	0.12833800
C	-4.72495900	2.46331400	5.17829700	H	5.50979200	0.42635000	1.38768500
C	-6.57001600	1.00793600	4.52311900	Ag	-5.07343200	-0.00472500	-2.66784600
C	-5.59370600	3.17604000	5.99607900	N	-2.61422200	-1.96090200	1.02050200
H	-3.67937300	2.74229400	5.10510900	S	-2.63140600	-3.58580200	1.51209100
C	-7.42088200	1.73776300	5.35211300	O	-1.51000800	-4.31721700	0.90450300
H	-6.93792500	0.16129900	3.95494100	O	-4.01295600	-4.02354700	1.28867200
C	-6.95176700	2.82600400	6.10056900	C	-2.31025500	-3.44358500	3.26418600
H	-5.21289700	4.01818700	6.56751500	C	-1.11040800	-3.92848000	3.78289600
H	-8.46671100	1.45192500	5.42065000	C	-3.28457000	-2.88412300	4.09791000
C	-7.87115000	3.59669900	7.01461900	C	-0.88194100	-3.83860000	5.15710200
H	-7.66921200	3.34895000	8.06444900	H	-0.37763000	-4.37527900	3.11975600
H	-7.72787000	4.67717100	6.90543200	C	-3.03767900	-2.80234600	5.46366800
H	-8.92199900	3.36811800	6.81630300	H	-4.21974700	-2.52658900	3.67979200
C	-6.59809700	2.18651100	-1.86136800	C	-1.83539000	-3.27807700	6.01595800
C	-5.76206100	1.54980000	-2.79795300	H	0.05083600	-4.21686000	5.56705600
C	-6.10811000	1.55956400	-4.16603200	H	-3.79072500	-2.36839300	6.11687900
C	-7.27373500	2.19170600	-4.57792700	C	-1.59521300	-3.20183200	7.50458700
C	-8.10206900	2.82092400	-3.63884700	H	-2.23701100	-3.91157900	8.04185400
C	-7.76476600	2.81829800	-2.28220800	H	-0.55717000	-3.43736600	7.75694200
H	-6.32596700	2.18912300	-0.80892600	H	-1.82284800	-2.20334000	7.89509500
H	-5.45349300	1.06783000	-4.87839300	C	-4.53518500	4.93703900	-4.59026300
H	-7.54239200	2.19958800	-5.62978600	C	-3.72433200	3.82963700	-4.91968000
H	-9.01096000	3.31626100	-3.96764000	C	-3.40813400	3.53547700	-6.26355400
H	-8.40834800	3.31103900	-1.55990000	C	-3.90612400	4.35573500	-7.26914100
C	-4.56005000	0.88058900	-2.37230600	C	-4.70879000	5.45497700	-6.94428200
N	-3.67208600	0.20952700	-3.07008000	C	-5.02258100	5.74416300	-5.61156700
IN5				H	-4.76818600	5.14996800	-3.55211100
C	-3.44076500	-1.65140800	-0.17336500	H	-2.78249000	2.68104000	-6.49990300
H	-4.48018600	-1.47691000	0.12199300	H	-3.66790700	4.14118600	-8.30589600
H	-3.43837300	-2.46339400	-0.91588900	H	-5.09198700	6.09192800	-7.73591100
C	-1.29223200	-1.29754100	0.92866900	H	-5.64503700	6.59982400	-5.37065600
H	-0.99246800	-0.89491500	1.90253900	C	-3.21206000	3.00611600	-3.88658000
H	-0.50159400	-1.98577900	0.59293800	N	-2.77439400	2.34208500	-3.04187300
C	-2.76546600	-0.41944200	-0.72536500	C	-9.17521700	-1.66378600	-4.34445600
C	-1.54095900	-0.22491000	-0.09440000	C	-10.39738000	-1.21290000	-3.81064500
C	-3.23101900	0.42002500	-1.74007400	C	-11.58339600	-1.79450000	-4.24706100
C	-0.67839100	0.84156000	-0.43251700	C	-11.55456000	-2.81388100	-5.20394400
C	-2.34125600	1.47903500	-2.03658000	C	-10.33883600	-3.26002700	-5.73159600
C	0.55489700	0.90256200	0.28611600	C	-9.14261500	-2.69049400	-5.30725300
C	-1.07555300	1.75582800	-1.44012600	H	-10.40640200	-0.42321600	-3.06645600
C	1.56384500	0.82212500	0.97064300	H	-12.53043900	-1.45485800	-3.83991600
Si	-0.02936300	3.27891900	-2.00618000	H	-12.48421200	-3.26435500	-5.53865500
C	-1.04929800	4.84966600	-1.69404100	H	-10.32355100	-4.05349400	-6.47196600
H	-0.45806100	5.72742000	-1.98332400	H	-8.19264500	-3.03049300	-5.70654900
H	-1.99693100	4.90433900	-2.23985300	C	-7.95283000	-1.07947400	-3.89856200
H	-1.27737700	4.95045400	-0.62626500	N	-6.95648000	-0.60460100	-3.53694500
C	0.38230600	3.06972100	-3.84737200	TS3			
H	0.97036300	2.15821000	-4.00700900	C	-4.34496200	-2.37636600	0.55031100
H	-0.48728500	3.02173400	-4.51102800	H	-5.40939200	-2.18067000	0.72773300
H	0.99745200	3.91528500	-4.17940100	H	-4.21941900	-3.45435700	0.36461900
C	1.60575800	3.50857200	-1.10034000	C	-2.23003900	-1.38381900	1.22323000
H	1.47802200	3.65156600	-0.02422400	H	-1.91492200	-0.53524400	1.83569200
H	2.29343500	2.67228500	-1.24916100	H	-1.42246400	-2.13012600	1.26231800
H	2.07784800	4.41255900	-1.50837000	C	-3.77241900	-1.56615100	-0.58933500
Si	3.10888800	0.72040400	1.99219500	C	-2.54980100	-1.01795700	-0.19969400
C	3.26931900	2.32438100	2.97653400	C	-4.28730800	-1.36358700	-1.86412400
H	3.33467400	3.19732600	2.31709800	C	-1.75790700	-0.27867700	-1.09433900
H	2.41441900	2.47145100	3.64621700	C	-3.49192300	-0.58399300	-2.74047400

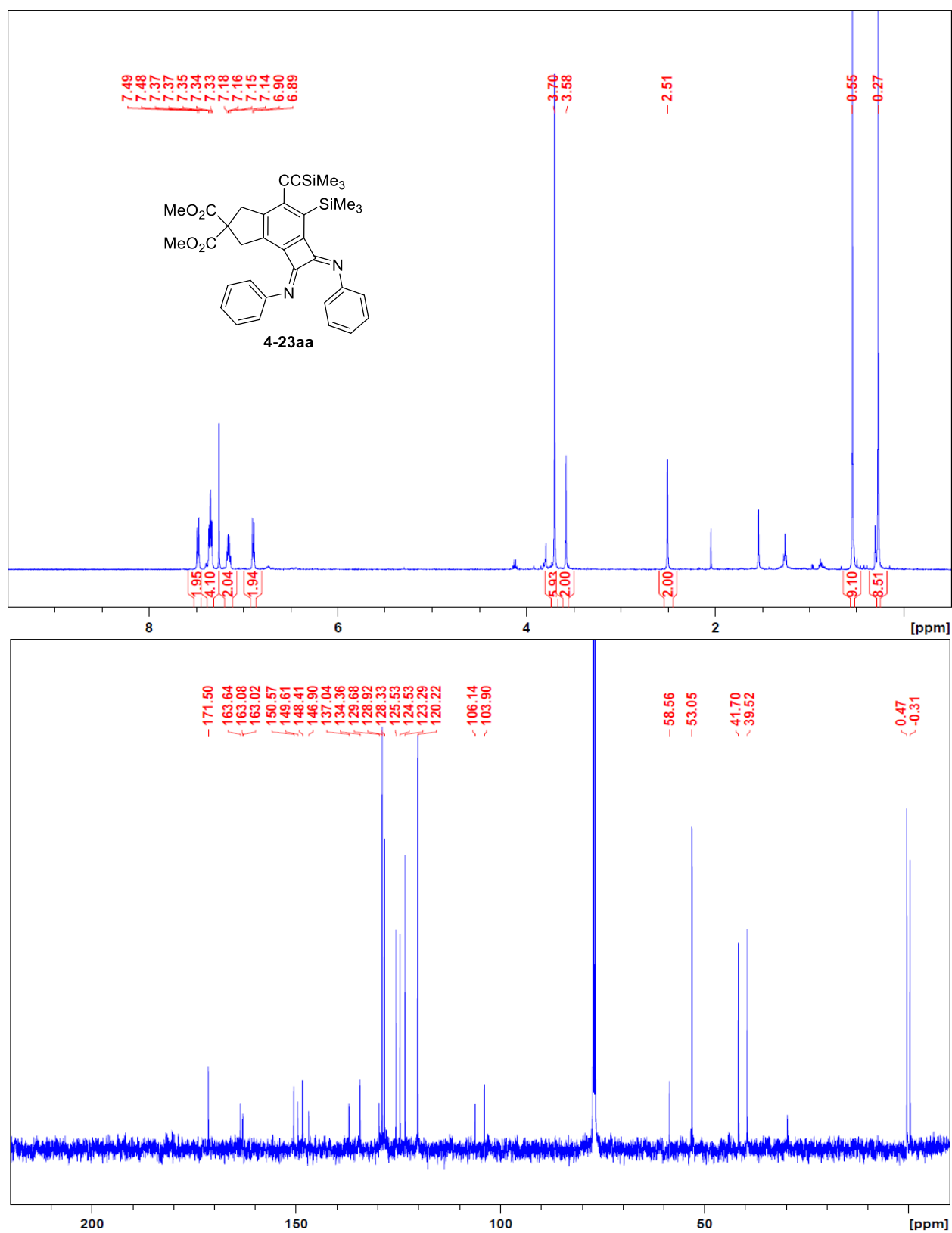
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C	0.52420500	0.57546700	-0.05596300	H	-4.86630000	4.74316800	1.97623500
Si	-1.03908400	0.86219100	-3.65849000	H	-5.45649900	5.90366400	-0.13692100
C	-0.75761800	2.62171800	-3.02268500	H	-5.76750100	4.59608500	-2.22559300
H	-0.04165400	3.14015800	-3.67262800	C	-5.53639700	1.95429100	-2.45586500
H	-1.68874600	3.20196800	-3.03497200	N	-5.77581100	1.38566700	-3.45012600
H	-0.36026400	2.63774400	-2.00445300				
C	-1.72823300	1.00882800	-5.41736100	IN6			
H	-1.97850500	0.04134400	-5.86458700	C	-3.69699300	-4.85555700	-2.22114800
H	-2.60044700	1.66549700	-5.50025700	H	-4.73221900	-4.56466500	-1.99370700
H	-0.93548300	1.45202400	-6.03427500	H	-3.73603200	-5.74345900	-2.85618100
C	0.55846500	-0.13723000	-3.79088600	C	-2.25388200	-3.92793100	-0.53482800
H	1.03275100	-0.30682500	-2.82126600	H	-2.84234900	-3.38377100	0.21525000
H	0.36769100	-1.11411300	-4.25142800	H	-1.29134900	-4.17494500	-0.08028300
H	1.27467200	0.39301500	-4.43111100	C	-2.92439500	-3.69168700	-2.80742100
Si	2.10305400	1.09977700	0.77312900	C	-2.11689000	-3.13886400	-1.81593400
C	3.24586900	-0.39995500	0.84252200	C	-2.96638000	-3.15964800	-4.09041800
H	2.79534700	-1.22089000	1.41149700	C	-1.36312600	-1.97252000	-2.04291000
H	3.48133900	-0.77453400	-0.15998800	C	-2.15870400	-2.02054300	-4.33075900
H	4.19237600	-0.13660000	1.33057900	C	-0.62134300	-1.48496400	-0.92223700
C	2.86882600	2.49258000	-0.24634200	C	-1.39054900	-1.36094800	-3.32817700
H	2.19986000	3.35814100	-0.31427600	C	-0.04487400	-1.18855600	0.11393100
H	3.80454200	2.83171700	0.21474600	Si	-0.52211600	0.30722800	-3.77362800
H	3.10143600	2.16547600	-1.26607200	C	-1.87952100	1.54943300	-4.22241600
C	1.66409300	1.69893600	2.50899900	H	-1.43318900	2.49119100	-4.56548800
H	0.97771900	2.55291200	2.47945400	H	-2.54475700	1.18032700	-5.00808800
H	1.19271300	0.90547600	3.09992200	H	-2.49359800	1.77957600	-3.34360600
H	2.56798200	2.01778100	3.04247700	C	0.69159000	0.05182300	-5.21412500
Ag	-6.08639200	-2.32711400	-2.43739600	H	1.36086700	-0.79813500	-5.02972600
N	-3.53802000	-1.91347800	1.70303700	H	0.20483200	-0.09523100	-6.18274500
S	-3.42609600	-2.97855800	3.03112200	H	1.32583000	0.94256600	-5.30313100
O	-2.37946400	-2.40292200	3.87894900	C	0.49091200	1.06369700	-2.37138200
O	-3.33768500	-4.36589700	2.55518900	H	-0.11250300	1.30386700	-1.49221600
C	-5.01767400	-2.76726600	3.81740300	H	1.31822400	0.42590500	-2.04792800
C	-5.24979100	-1.63020300	4.59742700	H	0.91749200	2.00116000	-2.75353300
C	-5.99063700	-3.75775300	3.68075500	Si	0.83746600	-0.67869500	1.66183700
C	-6.47976900	-1.48574700	5.23133900	C	0.84157600	-2.15265400	2.84423000
H	-4.46985300	-0.88540400	4.71718700	H	-0.17724100	-2.45951900	3.10723700
C	-7.21841000	-3.59411800	4.32359300	H	1.35248900	-3.01766400	2.40596600
H	-5.77747100	-4.64745300	3.09776200	H	1.36158900	-1.89626300	3.77547600
C	-7.48225200	-2.46281800	5.10720100	C	2.60205000	-0.18766600	1.20250200
H	-6.66400300	-0.60713300	5.84470700	H	2.61300900	0.64381700	0.48880100
H	-7.97787300	-4.36543300	4.22504400	H	3.15648000	0.13131700	2.09364300
C	-8.79664600	-2.30996100	5.83388500	H	3.14779500	-1.02503100	0.75289500
H	-8.69541900	-2.60347600	6.88673600	C	-0.09468100	0.77893700	2.41794400
H	-9.14441800	-1.27134400	5.82076000	H	-0.12504300	1.63519200	1.73472200
H	-9.57635100	-2.93800600	5.39241900	H	-1.12788900	0.50969300	2.66469800
C	-5.01301400	-0.50816800	-6.86790600	H	0.39423700	1.10844700	3.34303000
C	-5.52606200	0.34679700	-5.86889800	Ag	-4.40969300	-3.88775300	-5.46410900
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C	-7.10848100	1.25472400	-7.45518200	C	-2.41394300	-0.16005300	-8.21286400
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H	-7.92192100	1.93539000	-7.68549200	C	-2.52259000	0.38648800	-9.48656200
H	-7.01551600	0.43646600	-9.44642300	H	-2.72314800	0.40238500	-7.33905900
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C	-4.91775700	0.26490500	-4.55664900	H	-1.30482100	-2.21672200	-11.31648700
N	-4.02467300	-0.34820100	-4.01876700	H	-2.21088200	0.07979900	-11.59959800
C	-5.34278800	2.69753400	-1.26480300	H	-2.92118700	1.38892400	-9.60849700
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C	-5.33252100	4.82562200	-0.12510300	C	0.26771700	-5.65614500	-4.43041300
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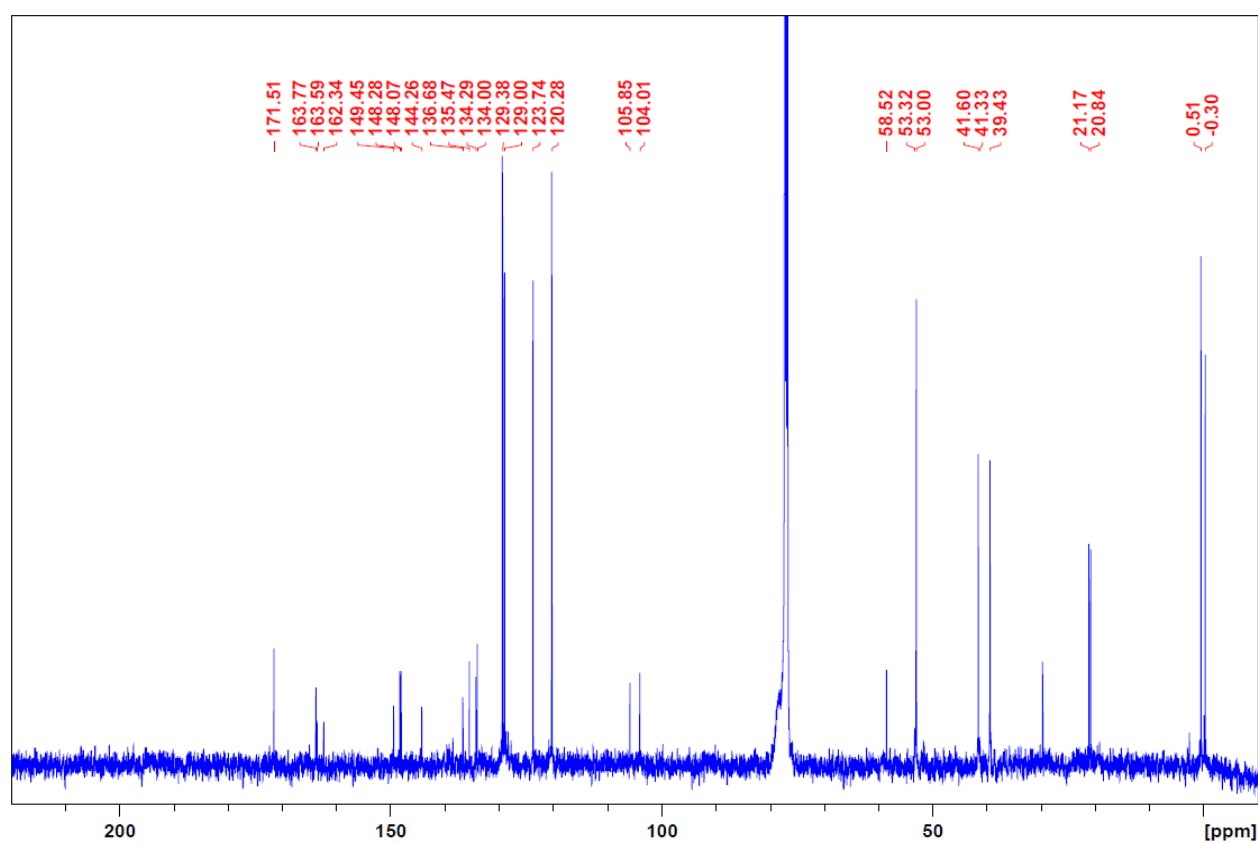
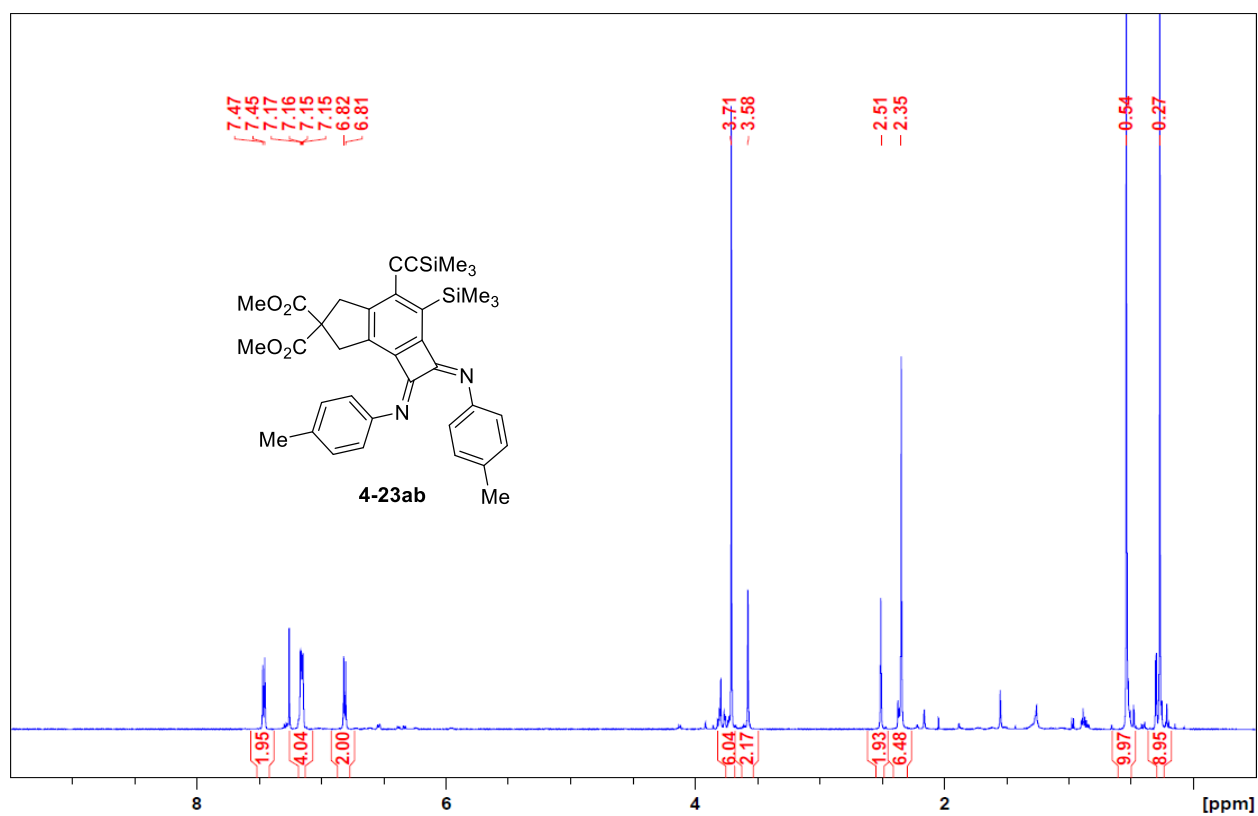
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H	-3.70694400	3.51565400	-3.31868600	C	-1.28735000	-3.95304500	-0.04904100
C	-0.91834500	1.96470900	-2.94532000	H	-2.16875300	-3.73490900	0.56799500
H	-0.77481400	3.02603500	-3.18474600	H	-0.40427100	-3.66947600	0.52929800
H	-0.06038900	1.63419100	-2.35491700	C	-1.57780900	-4.18749400	-2.40514100
H	-0.91259500	1.41461000	-3.89433800	C	-1.35313000	-3.26352100	-1.38947700
Si	1.81157500	1.38558600	1.06525900	C	-1.65053100	-3.82820900	-3.75227700
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H	3.14763500	-0.72003600	1.35157700	C	-1.50515300	-2.43543900	-3.99865500
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H	4.19909900	0.70169500	1.27510400	C	-1.37716600	-1.42732400	-2.99703100
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H	2.94632700	3.54733300	0.56855900	C	-3.11789100	0.75237200	-4.32308000
H	2.25989900	2.85736300	-0.91053400	H	-3.15447000	1.77244400	-4.72597100
C	1.44626300	1.67137100	2.89540200	H	-3.34122100	0.05459000	-5.13557900
H	0.56016800	2.30089800	3.03366800	H	-3.91653900	0.66576300	-3.57649200
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Ag	-3.76882600	-7.08732700	0.62301100	H	-0.15590100	0.39574600	-5.73169200
N	-1.31364700	-4.22657800	0.33980200	H	0.07543100	1.90255300	-4.84509100
S	-1.07321600	-5.31414500	1.59381700	C	-1.24653700	1.65960000	-2.10484000
O	-1.63326400	-6.60856100	1.05893000	H	-2.03200000	1.56045400	-1.35083300
O	-1.61629400	-4.85415600	2.87617800	H	-0.28131500	1.58567700	-1.59571300
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C	2.79276600	-5.99806000	0.66703500	H	-1.39031400	-1.27298100	3.63705100
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C	2.68711500	-5.42311200	3.01041800	H	-0.31609100	-0.13922100	4.47021900
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H	-5.71451600	1.05312700	-4.61450300	C	-1.16323600	-1.18743300	-10.36678300
H	-7.99184000	-2.54547400	-4.08748400	C	-2.10002200	-0.76112800	-9.41894700
H	-9.65669800	-1.73822200	-5.73858600	H	-2.69244200	-0.81499100	-7.34503600
H	-9.34945200	0.47291400	-6.83452900	H	0.87559500	-3.00960500	-8.35145100
H	-7.36888700	1.86723700	-6.26780900	H	0.63317800	-2.33137600	-10.70987800
C	-5.75190400	-1.29052800	-3.25188000	H	-1.26856800	-0.89061600	-11.40609100
N	-4.75660300	-0.50500800	-2.86347700	H	-2.93334500	-0.13370500	-9.72064700
C	-5.41543700	-4.42982600	-1.40771600	C	-0.77230200	-2.32078300	-6.27252900
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C	-6.20298100	-5.83324700	0.42061300	C	3.40967000	-4.77518700	-2.56510300
C	-5.92343000	-4.56842900	-0.10693500	C	4.66820200	-4.72437500	-3.17338900
H	-4.86368700	-5.46812000	-3.21579200	C	4.82330700	-4.22985500	-4.47702200
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H	-6.30452000	-7.96588500	-0.00584000	H	1.31014900	-4.35626100	-2.78484300
H	-6.64683000	-5.92600900	1.40786400	H	3.28080200	-5.15566400	-1.55820600
H	-6.10910300	-3.68284800	0.49376300	H	5.54178800	-5.06964200	-2.62804000
C	-5.08833900	-3.06307100	-1.94671700	H	5.80679800	-4.19354400	-4.93471900
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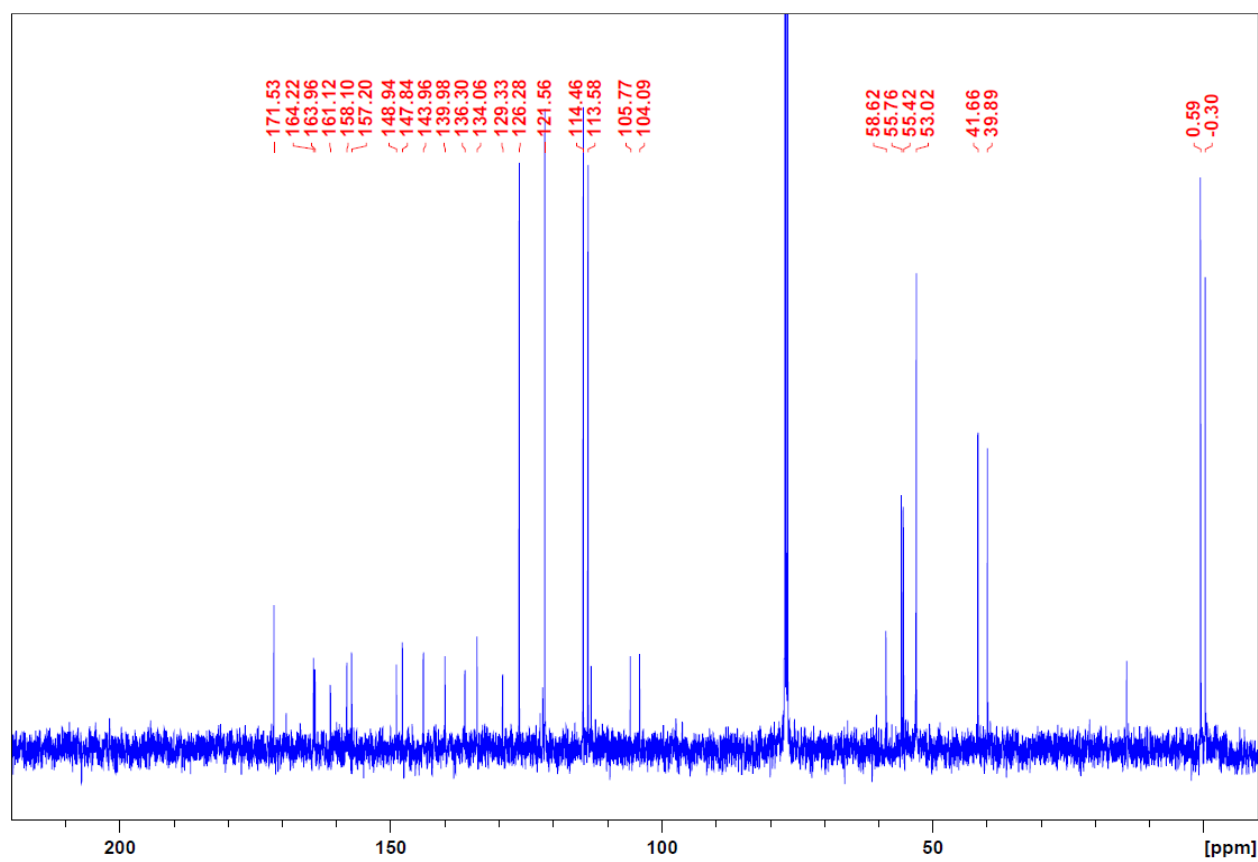
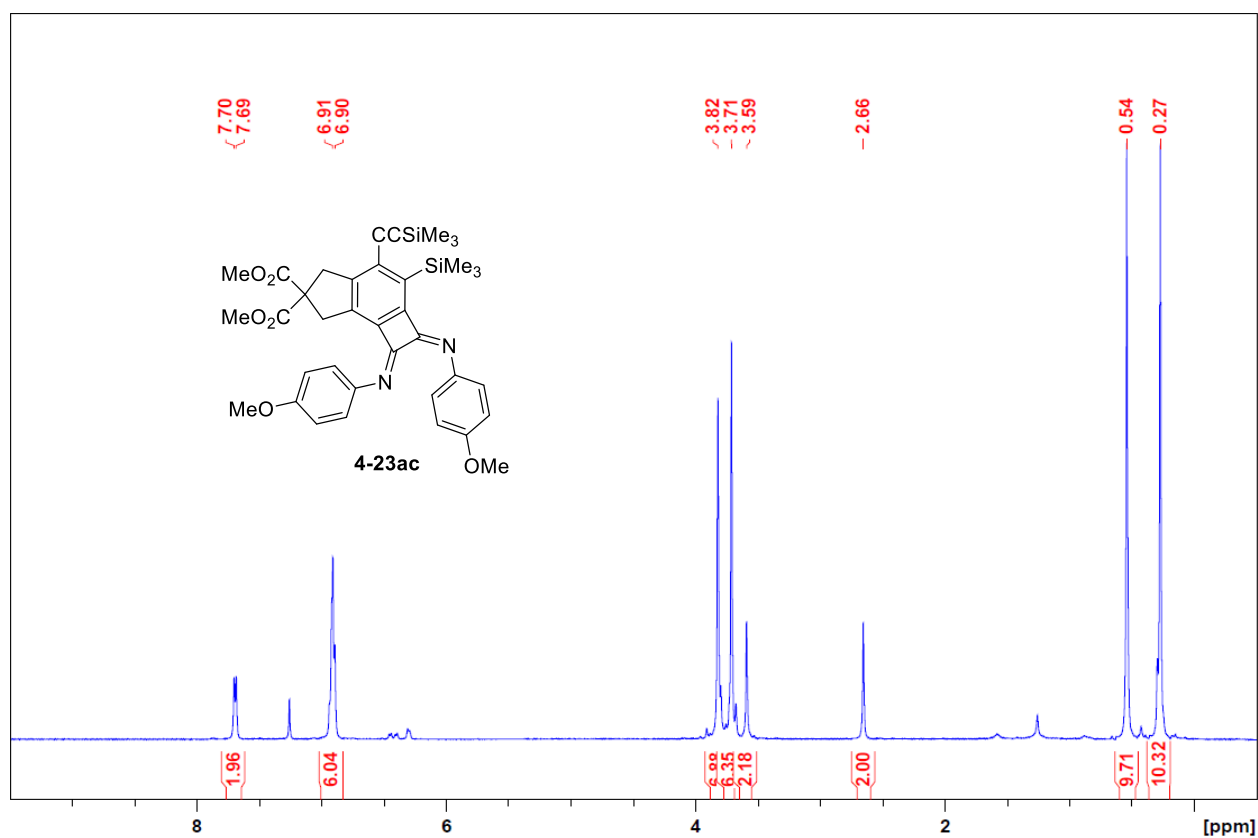
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N	0.40973200	-3.10417100	-5.95023900	H	2.66482800	0.68571200	2.27754800
S	0.17480400	-6.22649800	-0.02642300	H	2.77838500	-0.47934200	0.94874600
O	1.35452400	-5.35954800	-0.23837500	C	-0.62965200	1.06345600	2.53810100
O	0.09593600	-7.50343600	-0.74422200	H	-0.72742600	1.90231100	1.83982200
C	0.01417900	-6.48967900	1.73100800	H	-1.63828700	0.71079800	2.78153900
C	-1.04007000	-7.27556000	2.21030200	H	-0.17854600	1.44843000	3.46103500
C	0.96730700	-5.95740000	2.59606700	Ag	-4.21333800	-4.05142400	-5.47966300
C	-1.13626600	-7.51281600	3.57630600	N	-2.82971800	-5.22430600	-0.86857200
H	-1.77371300	-7.68520300	1.52380800	C	-1.95222400	-0.51458000	-8.24101700
C	0.85326300	-6.20668000	3.96479500	C	-1.36785100	-1.74147000	-7.88009100
H	1.78039700	-6.35875700	2.20196300	C	-0.69747600	-2.49930100	-8.85337500
C	-0.19203800	-6.98500500	4.47606000	C	-0.60905700	-2.03644800	-10.16551100
H	-1.95702200	-8.11651300	3.95611500	C	-1.18816600	-0.81569300	-10.51686700
H	1.59103400	-5.78960900	4.64473100	C	-1.85975500	-0.05774800	-9.55172400
C	-0.30507900	-7.27671500	5.95323400	H	-2.46986600	0.06557700	-7.48537500
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H	0.37999200	-6.65893100	6.53999500	H	-1.11830600	-0.45536400	-11.53907300
C	-3.91830800	-8.64469900	-8.04844600	H	-2.31164600	0.89167400	-9.82293800
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C	-4.18361500	-10.98967000	-8.56240800	N	-2.09212000	-1.57128100	-5.56862500
C	-5.00263700	-10.64915100	-9.64338800	C	1.27321200	-3.76594300	-4.83125200
C	-5.28110400	-9.30918600	-9.92866900	C	1.62603100	-4.48311300	-3.67518000
C	-4.74297600	-8.29963400	-9.13682800	C	2.82968900	-4.19000400	-3.04156500
H	-3.00175100	-10.24674600	-6.91424400	C	3.68475600	-3.21407200	-3.56270000
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H	-5.91739800	-9.05017000	-10.76858400	H	0.95431000	-5.22537100	-3.25705600
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C	-3.36623000	-7.61333700	-7.22889500	H	4.62898700	-3.00358400	-3.06901000
N	-2.92715600	-6.76952800	-6.56317000	H	4.00197400	-1.75416300	-5.12373300
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C	-3.58548300	-4.95996900	-2.12669400	C	0.01667200	-3.96839800	-5.51362600
H	-4.63217400	-4.76262100	-1.85653700	N	-0.81395500	-3.44473100	-6.20842300
H	-3.57214400	-5.83518000	-2.77803300	S	-1.68627000	-6.48137900	-0.99883800
C	-2.25499300	-3.91586700	-0.42683700	O	-0.37108800	-6.01419600	-1.48249800
H	-2.92894800	-3.47665100	0.31980200	O	-2.36152900	-7.54791600	-1.76203200
H	-1.28004000	-4.04740100	0.04901300	C	-1.50323600	-6.97071900	0.70623700
C	-2.92370600	-3.72727000	-2.70325900	C	-2.62946100	-7.36285400	1.43683300
C	-2.19432200	-3.09819600	-1.69648300	C	-0.22614500	-7.01612700	1.26652800
C	-2.95595000	-3.22183600	-3.99407100	C	-2.46341500	-7.79436800	2.74878800
C	-1.56579900	-1.86065200	-1.91220700	H	-3.61556100	-7.32407600	0.98660300
C	-2.21483200	-2.04432900	-4.23966500	C	-0.08200900	-7.45281000	2.58297000
C	-0.90819900	-1.28879700	-0.77831500	H	0.63333700	-6.71441400	0.67830900
C	-1.59878200	-1.27714600	-3.21273300	C	-1.19175900	-7.84486700	3.34417500
C	-0.37674000	-0.92746300	0.26149100	H	-3.33464900	-8.09906400	3.32263500
Si	-1.02230300	0.51687400	-3.62886900	H	0.91019300	-7.49046100	3.02491200
C	-2.53741400	1.43997200	-4.29446800	C	-1.02985700	-8.29371800	4.77602000
H	-2.25543500	2.45292400	-4.60815700	H	-1.17007200	-7.45287800	5.46748200
H	-2.99336400	0.93099400	-5.14815500	H	-1.76651300	-9.05909300	5.04095800
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C	0.39373600	0.53829200	-4.89275200	C	-1.47126400	-8.00640700	-5.81151600
H	1.23667600	-0.07653400	-4.55605000	C	-2.07637400	-8.73684000	-4.76859200
H	0.09254100	0.19764600	-5.88804400	C	-2.64542100	-9.97204900	-5.06657000
H	0.76273700	1.56682500	-4.99503100	C	-2.61232100	-10.47142400	-6.37191000
C	-0.40539000	1.49382800	-2.13243100	C	-2.00752400	-9.74050300	-7.40125000
H	-1.14126600	1.54349900	-1.32495000	C	-1.43218100	-8.50483600	-7.13094300
H	0.52406600	1.09703700	-1.71514000	H	-2.09288800	-8.34364500	-3.75580300
H	-0.21206900	2.51996400	-2.47373400	H	-3.11297800	-10.54686900	-4.27350800
Si	0.42866400	-0.32167500	1.81126100	H	-3.05772700	-11.43751600	-6.59057700
C	0.54310600	-1.76979900	3.02157900	H	-1.98311000	-10.13651700	-8.41146800
H	-0.44913900	-2.16264000	3.27169800	H	-0.95531200	-7.92960200	-7.91804700
H	1.13720800	-2.59328800	2.60869900	C	-0.87415500	-6.74625700	-5.53431900
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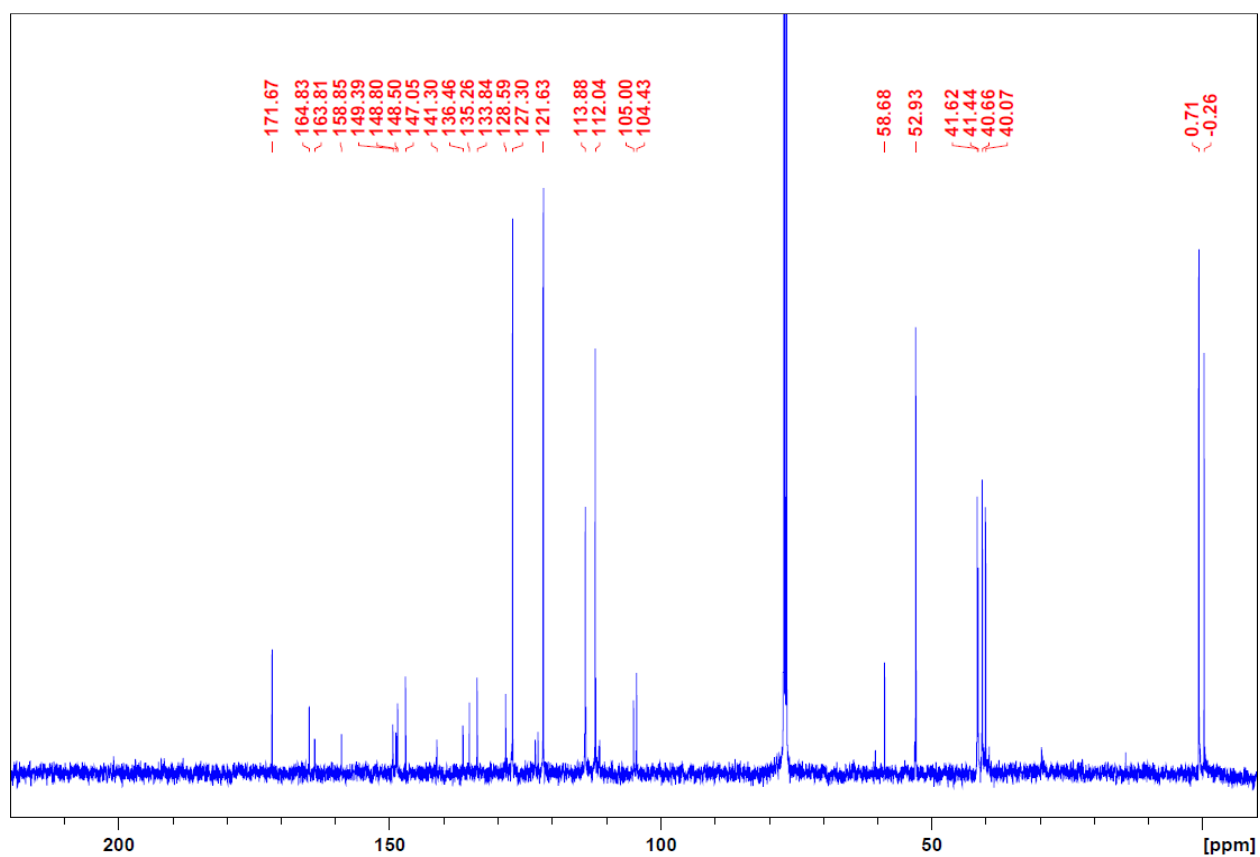
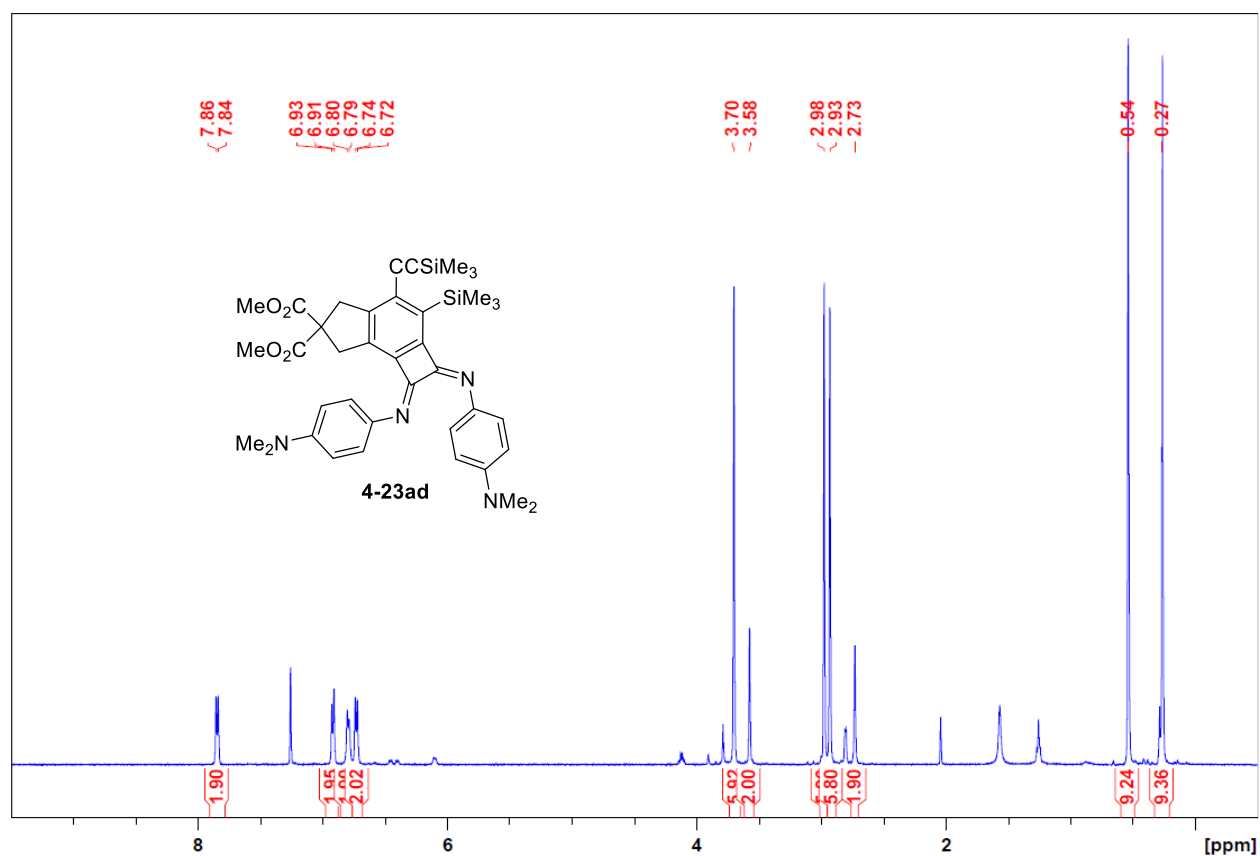
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H	-5.01332300	-4.27575600	-1.80815100	H	-0.85250000	-0.16537600	-11.42189100
H	-4.16958300	-5.45890900	-2.81248600	H	-1.50124100	1.32946000	-9.54263900
C	-2.51899000	-3.82655900	-0.44664200	C	-1.62529800	-2.17151000	-6.49599600
H	-3.12248000	-3.34112400	0.33093400	N	-2.01419100	-1.42351600	-5.53131300
H	-1.56195900	-4.09587100	0.00807200	C	0.70697900	-3.73447400	-5.13701100
C	-3.20046900	-3.47507000	-2.69971700	C	1.11765500	-4.23336700	-3.88732100
C	-2.37916100	-2.97796400	-1.68846800	C	2.33877600	-3.82418000	-3.35827700
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C	-1.60224600	-1.82555400	-1.88241300	C	2.75498600	-2.46299500	-5.32085700
C	-2.25132800	-1.89573400	-4.21995100	C	1.52612400	-2.84581600	-5.85272400
C	-0.86380300	-1.36906000	-0.74571600	H	0.47534900	-4.90172500	-3.31987100
C	-1.57184100	-1.21442900	-3.17073300	H	2.65001000	-4.18973400	-2.38462200
C	-0.27008200	-1.10272600	0.28928600	H	4.11850800	-2.64582300	-3.66250500
Si	-0.87429600	0.54714400	-3.53293600	H	3.39532000	-1.78765000	-5.87967800
C	-2.32452600	1.57141500	-4.19923100	H	1.21240100	-2.47780500	-6.82440700
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H	-2.78607200	1.11689900	-5.08010300	N	-1.48890500	-3.58983700	-6.37809400
H	-3.10027200	1.68514900	-3.43231000	S	-2.28360100	-6.39825900	-1.19518300
C	0.57599700	0.54968000	-4.75252300	O	-1.01784500	-6.08430300	-1.89637000
H	1.40925900	-0.05491900	-4.37777200	O	-3.16614400	-7.39412100	-1.83558700
H	0.30623200	0.18017700	-5.74609900	C	-1.89275700	-6.90313800	0.46834700
H	0.94234700	1.57832800	-4.86608300	C	-2.93169000	-7.24756400	1.34118400
C	-0.25864200	1.44625000	-1.98597800	C	-0.55738800	-7.00187800	0.85713300
H	-1.00660400	1.48573000	-1.18876400	C	-2.61442800	-7.68667900	2.62104200
H	0.65144700	1.00514800	-1.57059600	H	-3.96511800	-7.16651500	1.02162400
H	-0.02967800	2.47932700	-2.28095800	C	-0.26156700	-7.44572100	2.14676700
Si	0.62465100	-0.61859300	1.83133400	H	0.23012400	-6.73496100	0.16104200
C	0.64478600	-2.10844600	2.99661000	C	-1.27780800	-7.79328900	3.04570100
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H	1.14968700	-2.96842500	2.54140000	H	0.77676700	-7.52203500	2.45771800
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H	2.95105800	0.17961600	2.26446900	H	0.12007900	-8.27600500	4.62752300
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C	-0.28928300	0.82901200	2.62818000	C	-1.88797100	-8.72044900	-4.44349200
H	-0.33166300	1.69302200	1.95555500	C	-2.04263300	-10.10266700	-4.44497500
H	-1.31835600	0.55727300	2.88923200	C	-1.45016900	-10.88177800	-5.44357600
H	0.21645000	1.14641500	3.54853400	C	-0.68798400	-10.29075300	-6.46032100
Ag	-4.49176700	-3.61368500	-5.49200900	C	-0.51418000	-8.91467900	-6.48655600
N	-3.26482000	-5.03765400	-0.91815700	H	-2.33657500	-8.11430300	-3.66125600
C	-1.58096000	-0.25732100	-8.09864800	H	-2.62677300	-10.56928700	-3.65855000
C	-1.41915200	-1.63429800	-7.86276100	H	-1.57990400	-11.95997300	-5.43178800
C	-1.05725800	-2.47309900	-8.93034400	H	-0.23123800	-10.90533500	-7.22918500
C	-0.85411800	-1.94507900	-10.20525700	H	0.07305200	-8.44118100	-7.26650000
C	-1.01052000	-0.57627100	-10.42893100	C	-0.94724500	-6.73520400	-5.51527600
C	-1.37519900	0.26432000	-9.37197600	N	-0.77730700	-5.59262700	-5.61426000
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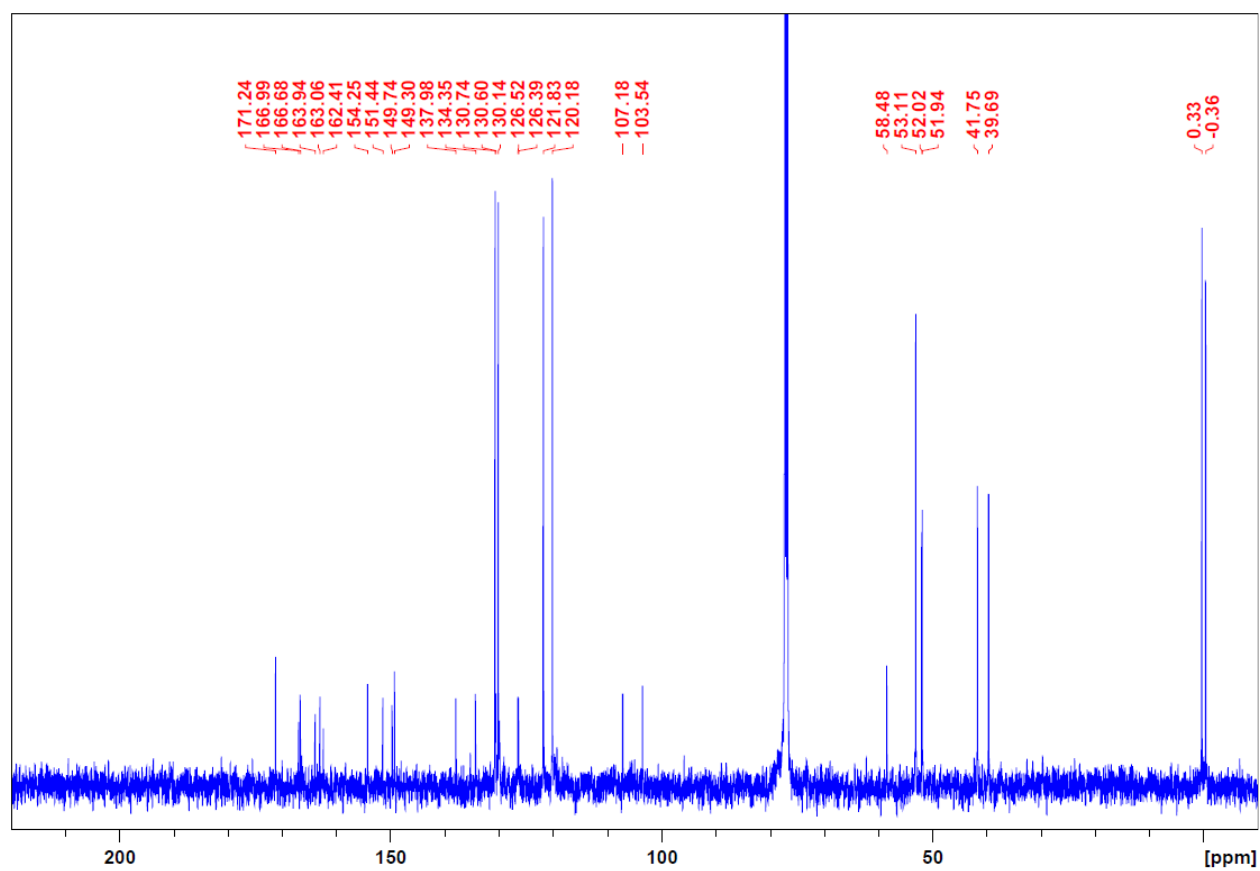
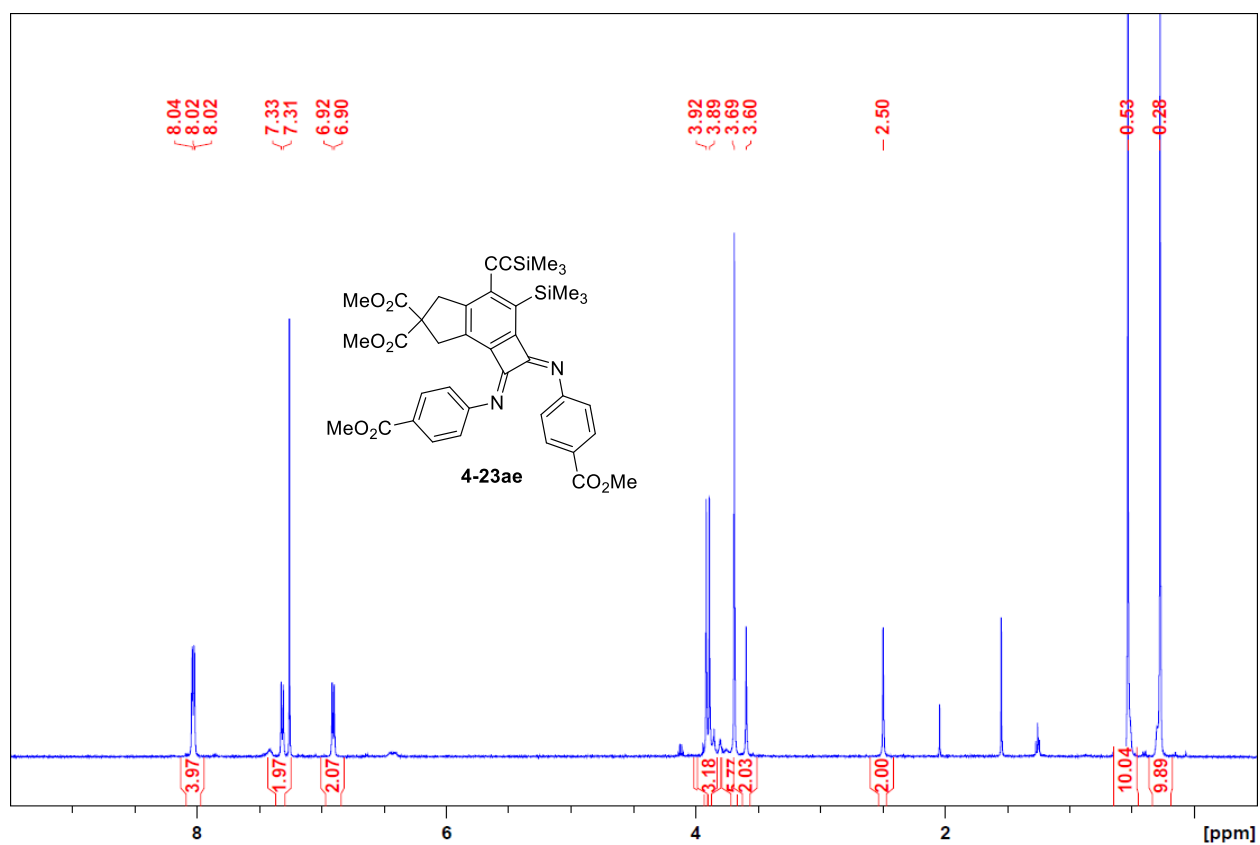
Appendix III
Selected NMR Spectra for Chapter 4

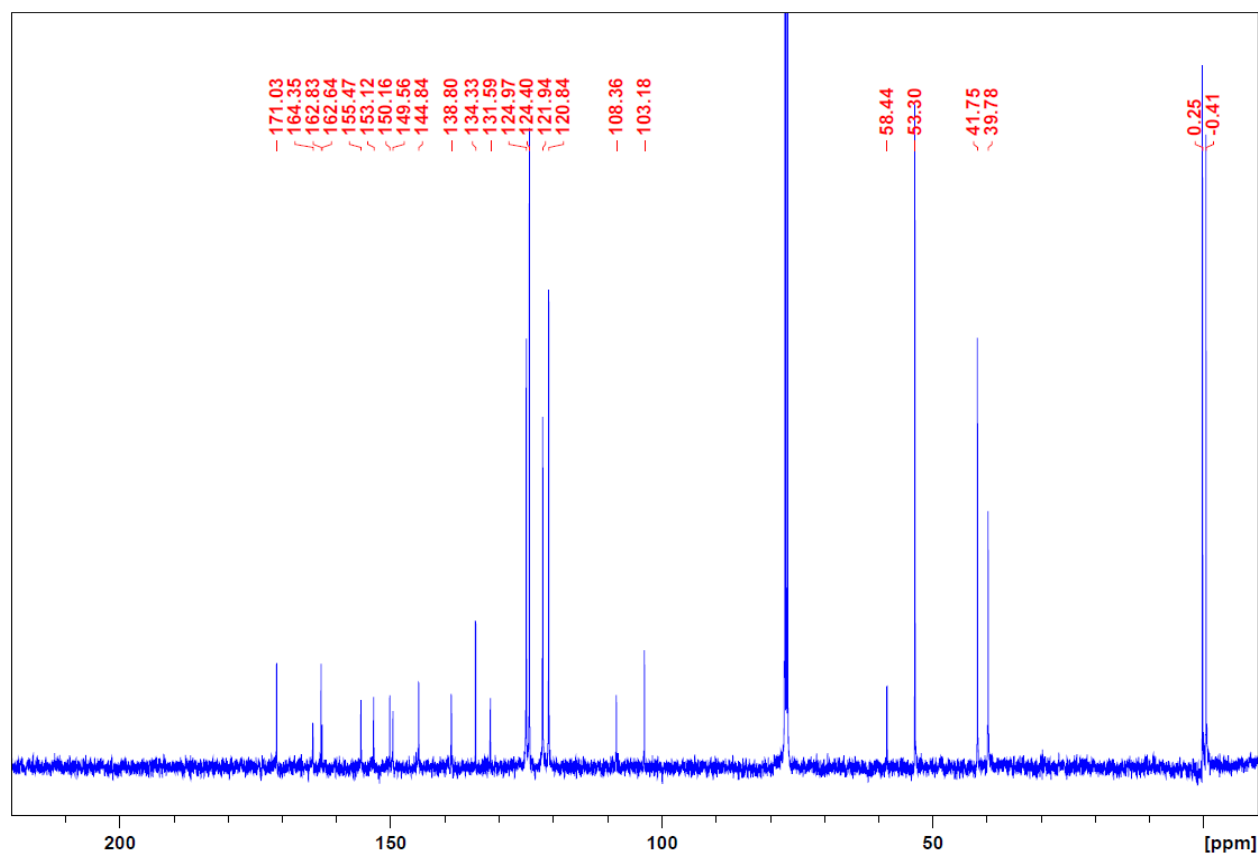
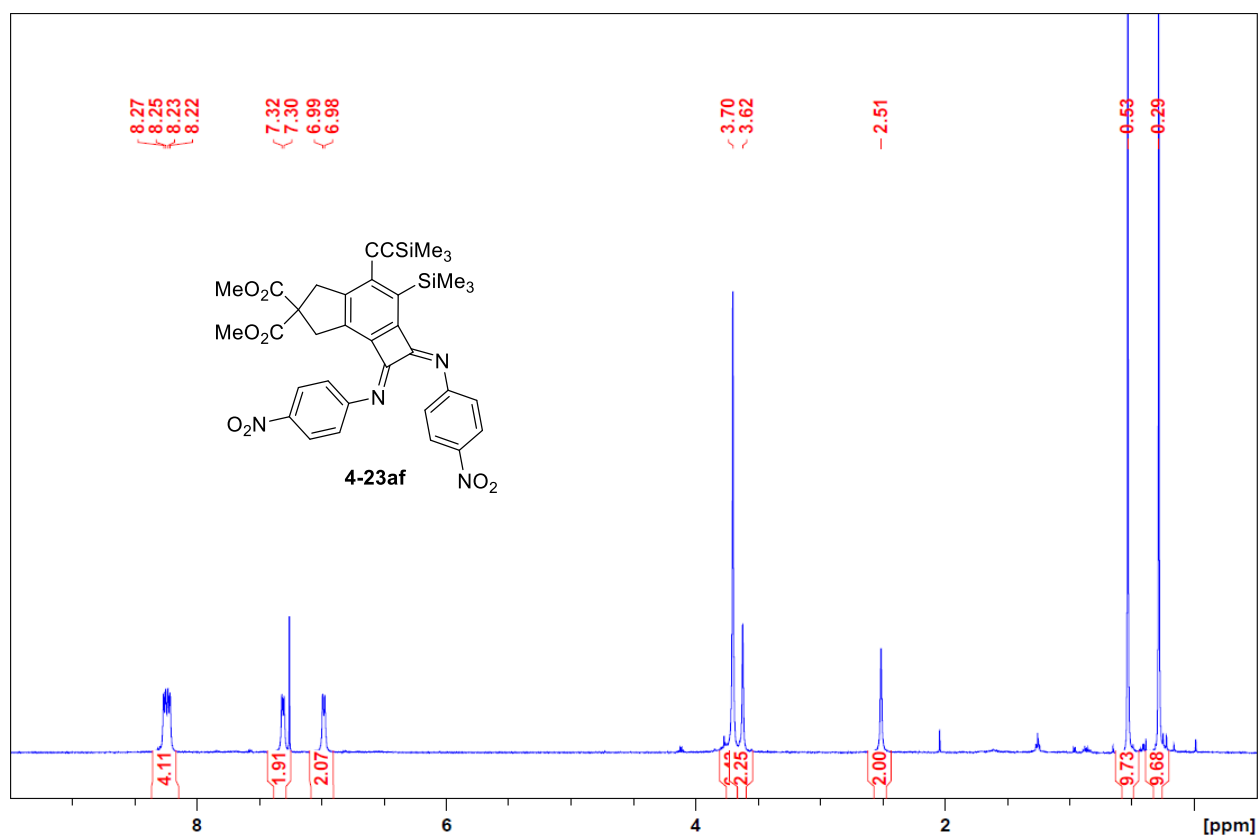


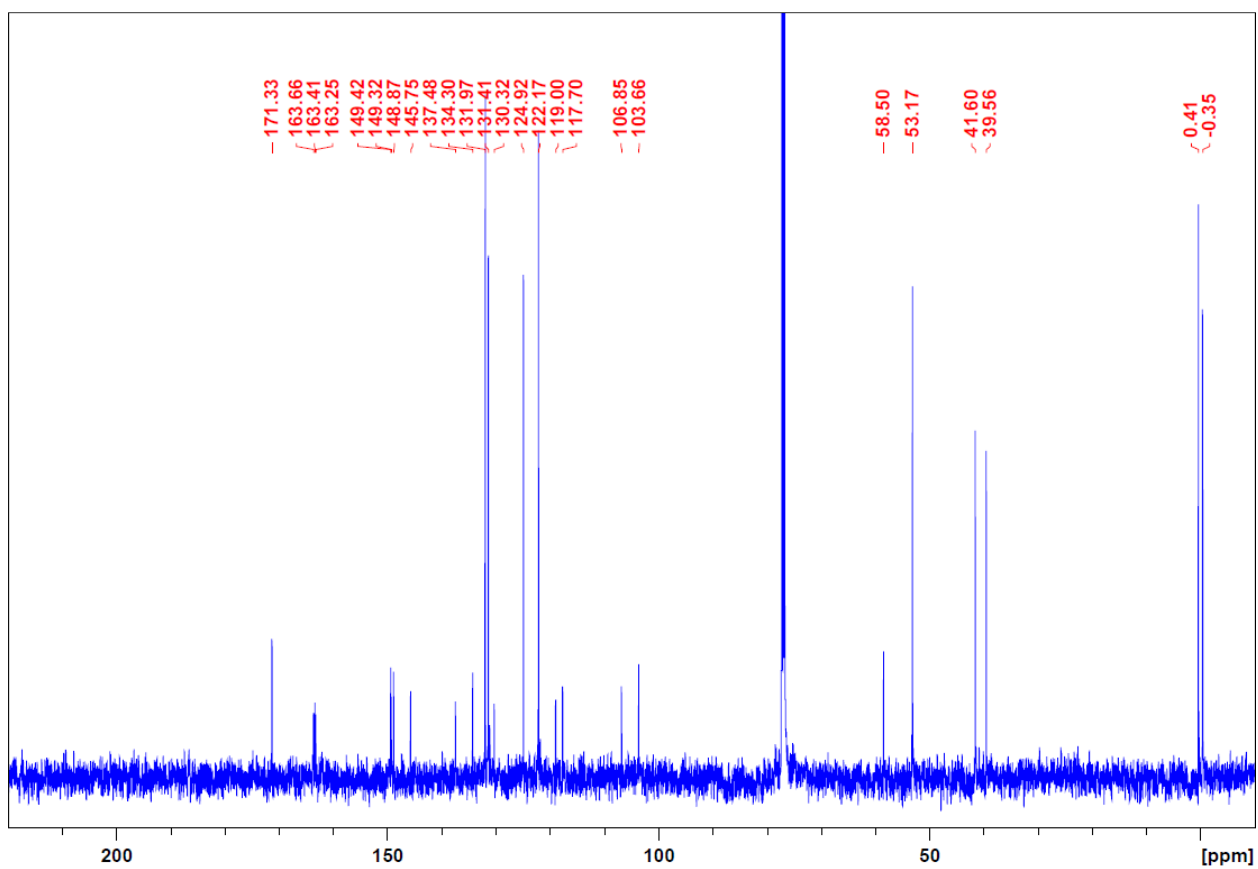
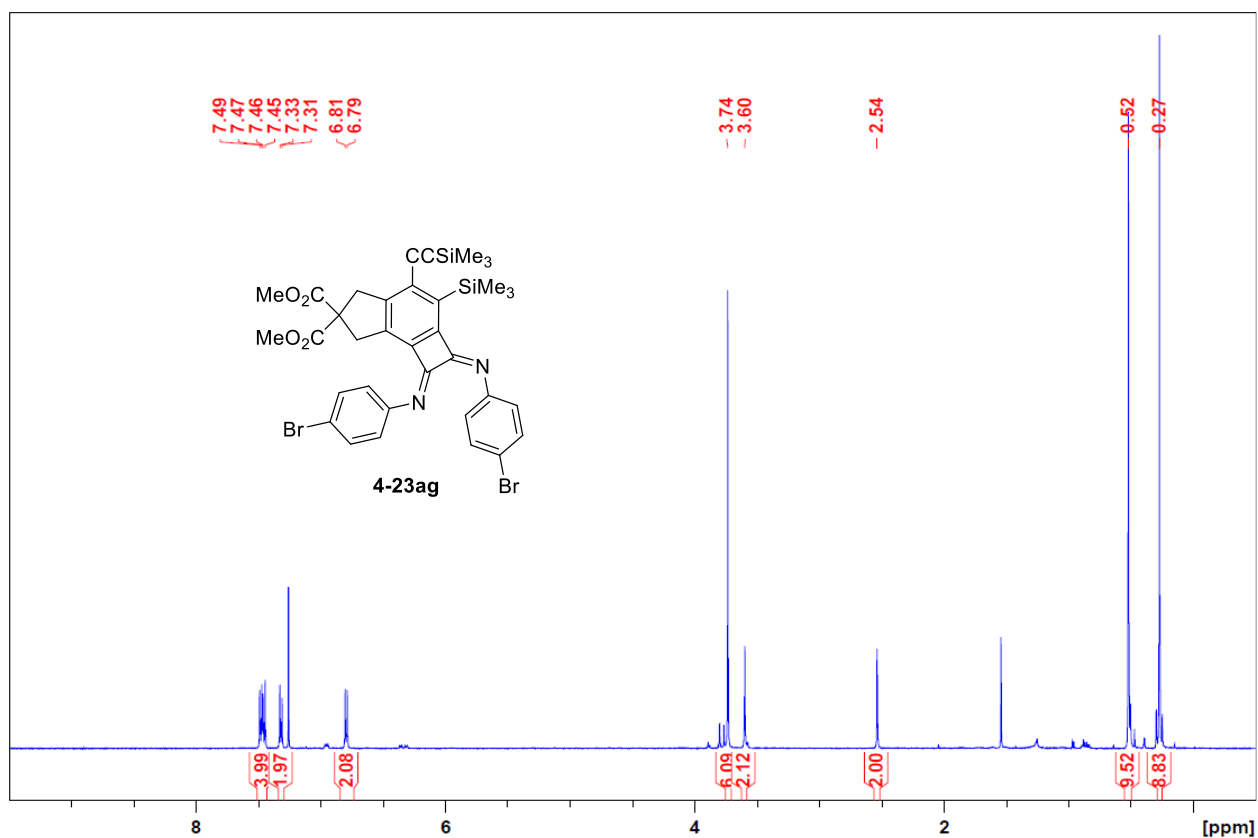


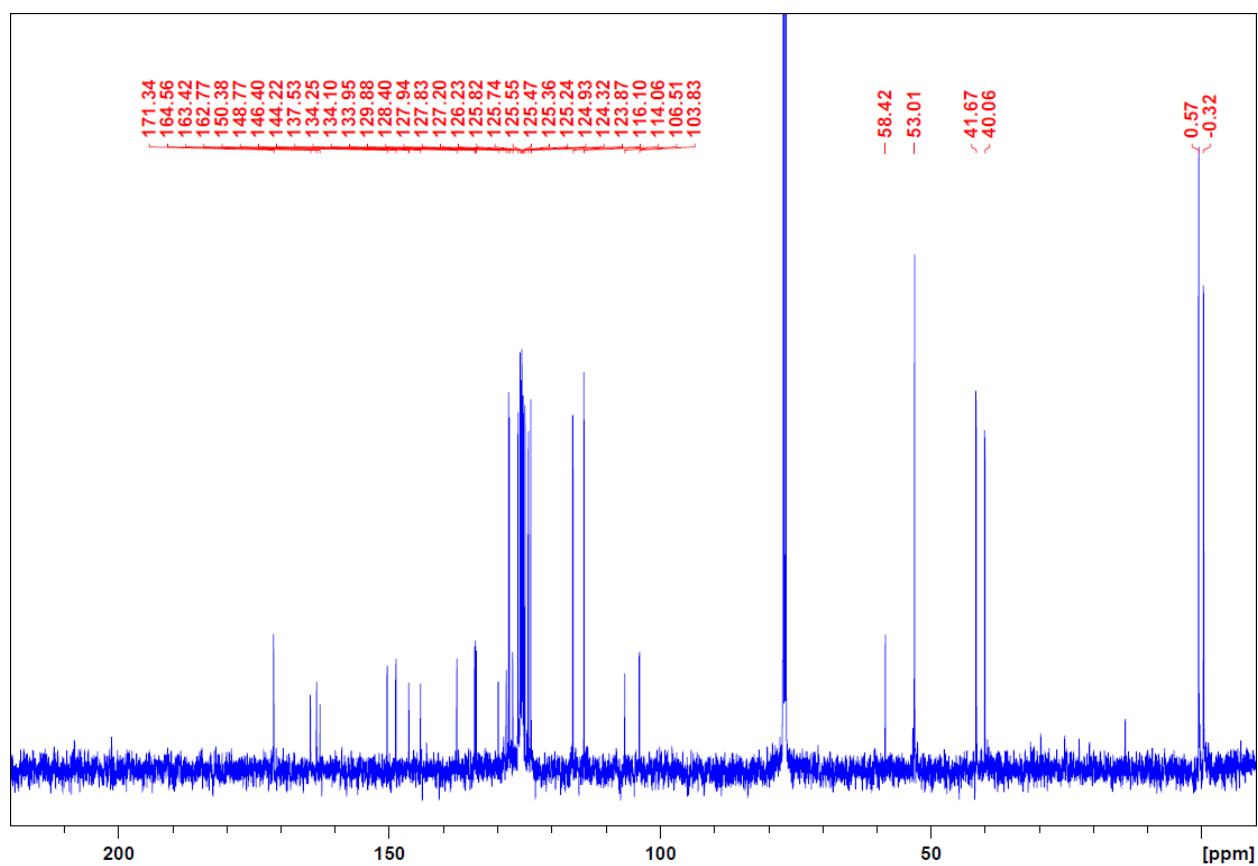
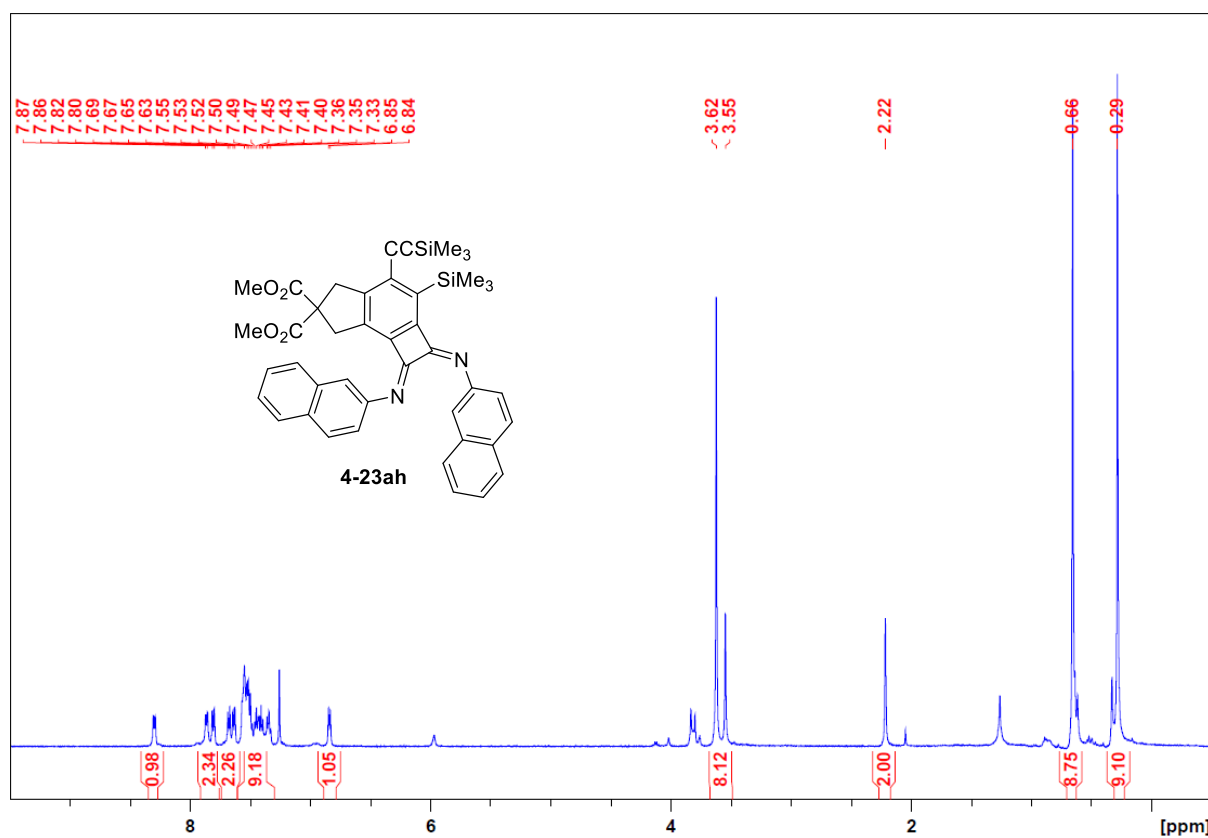


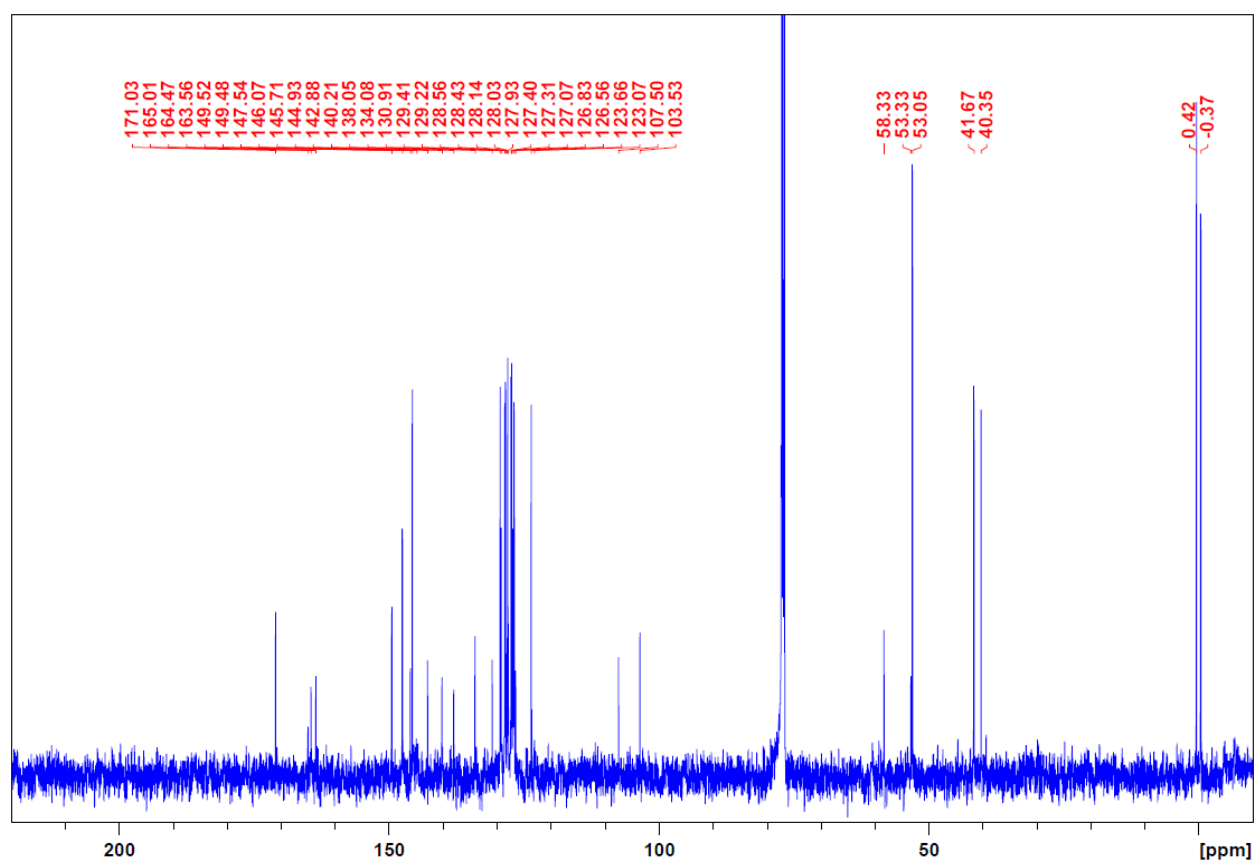
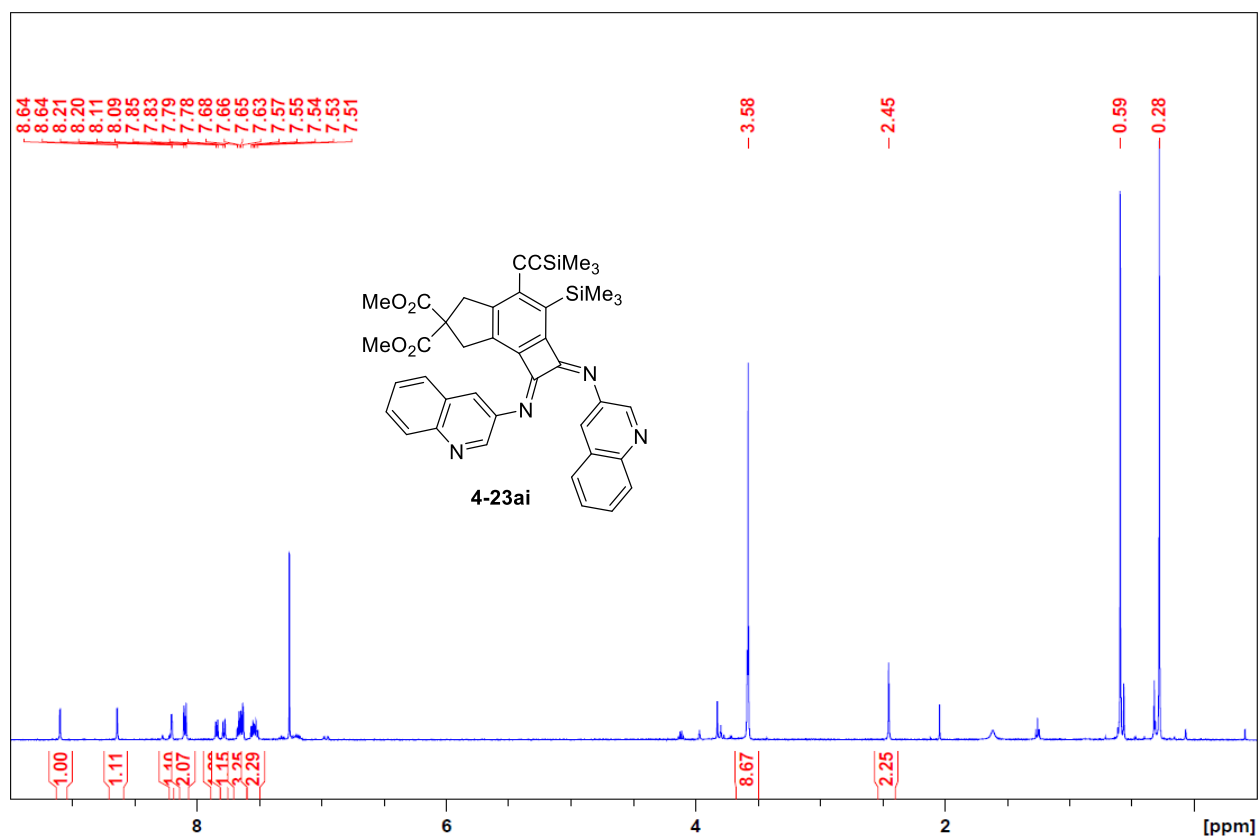


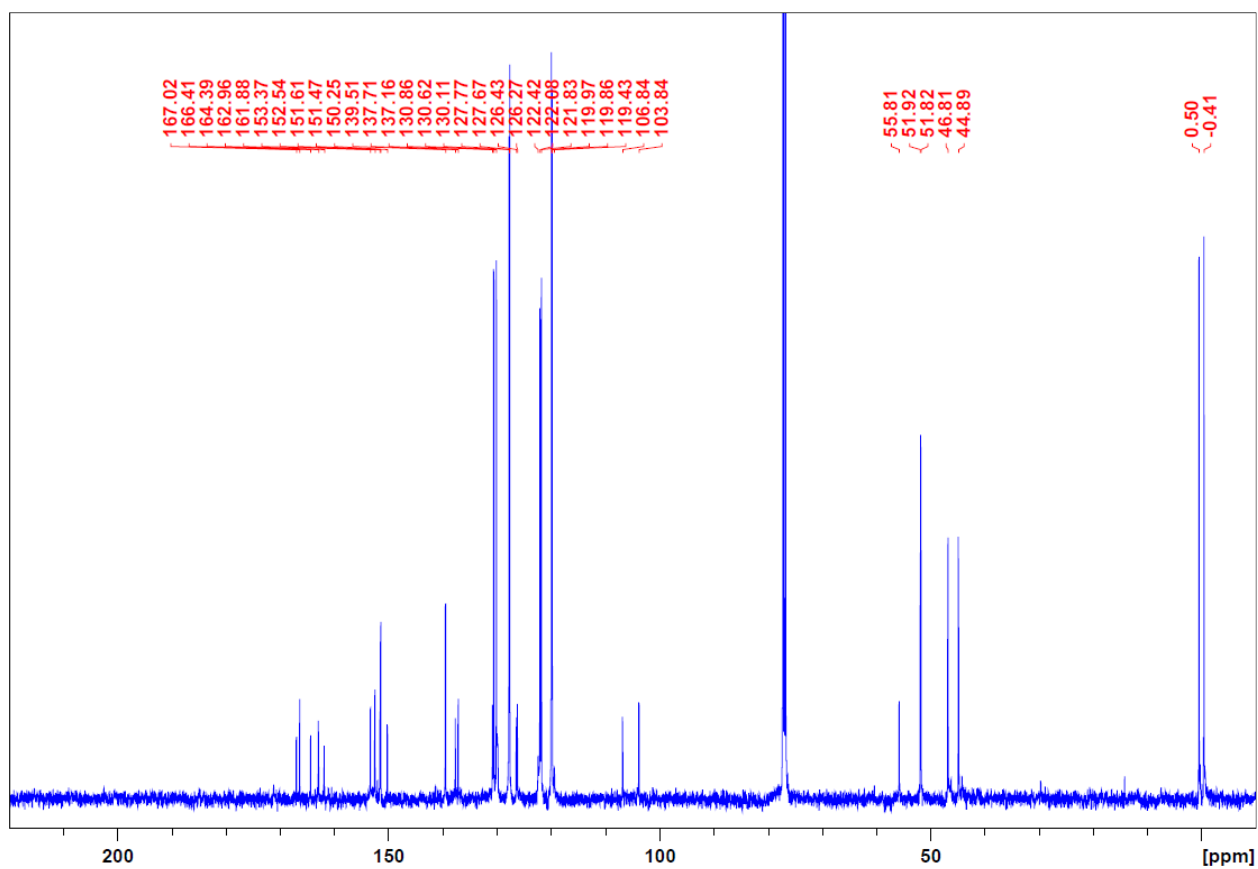
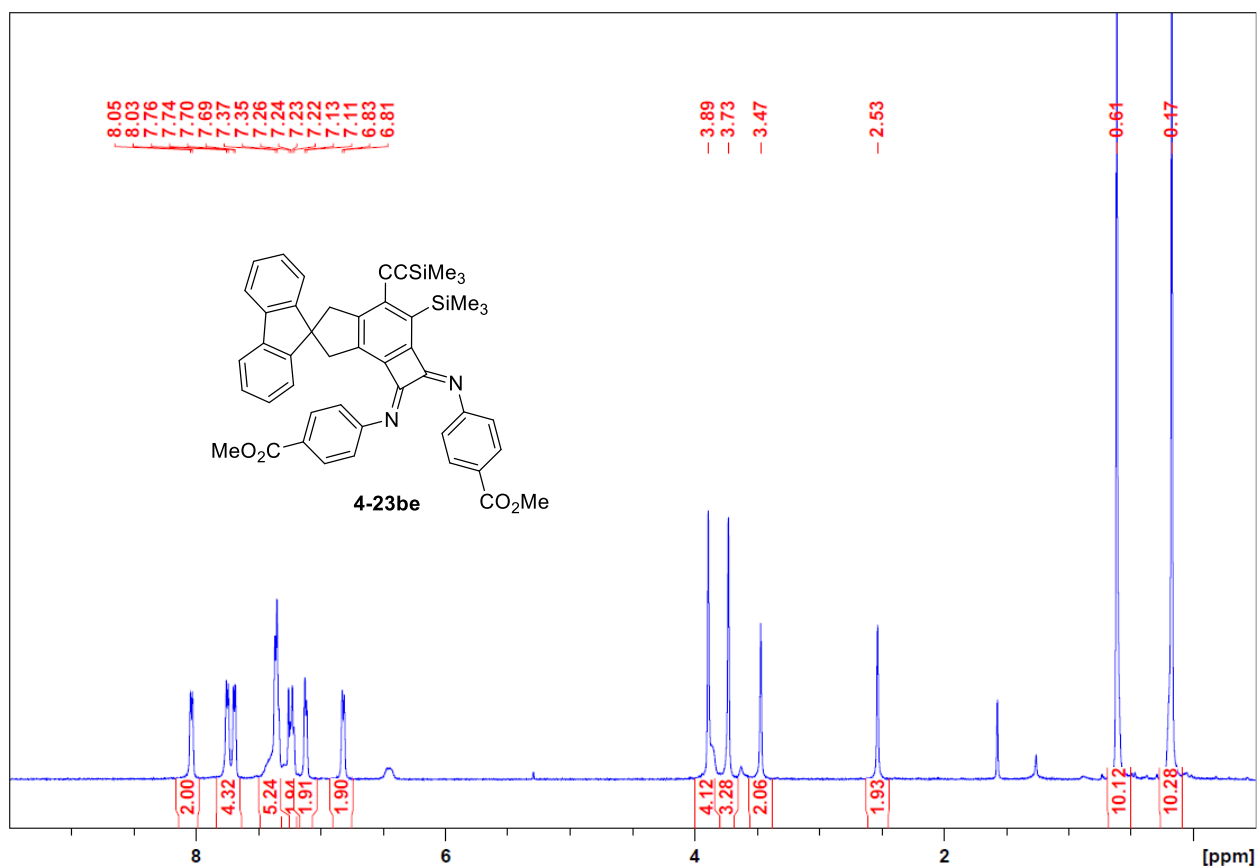


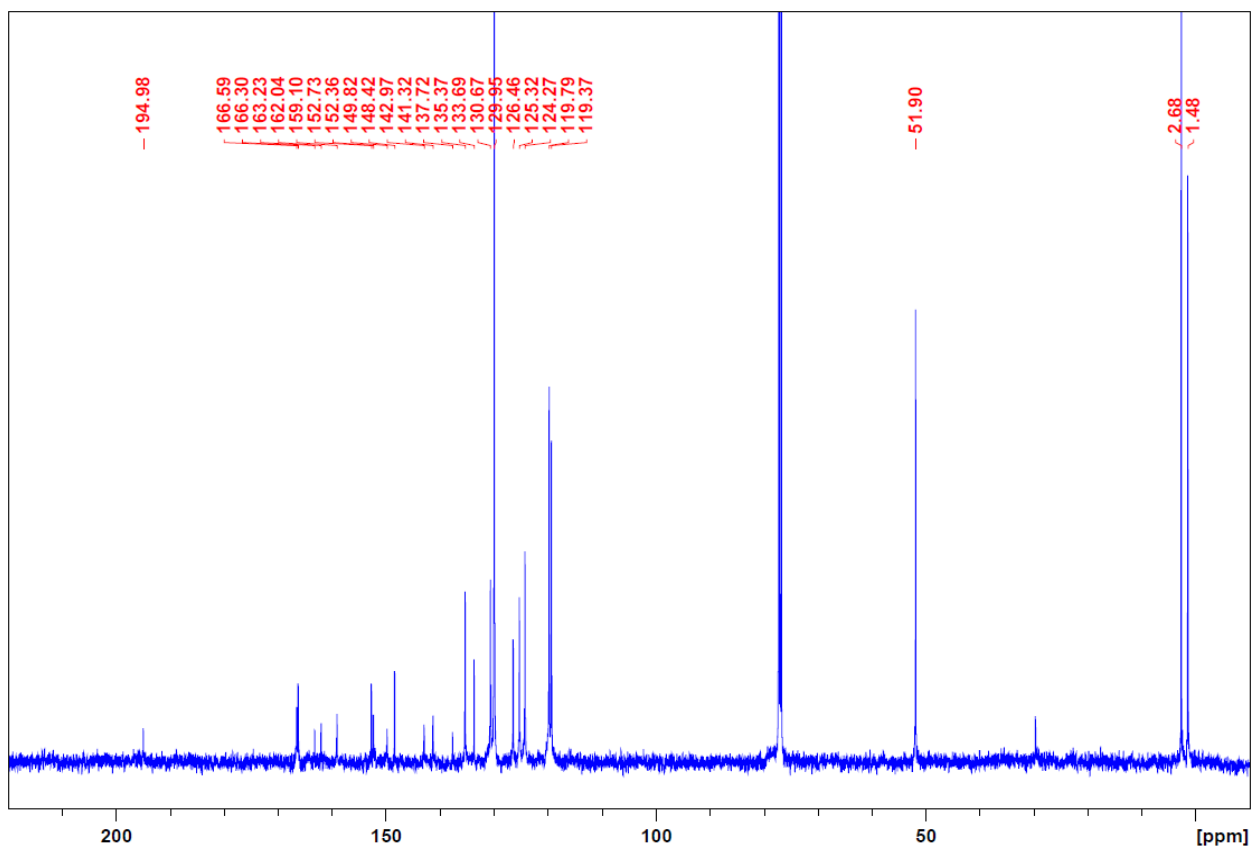
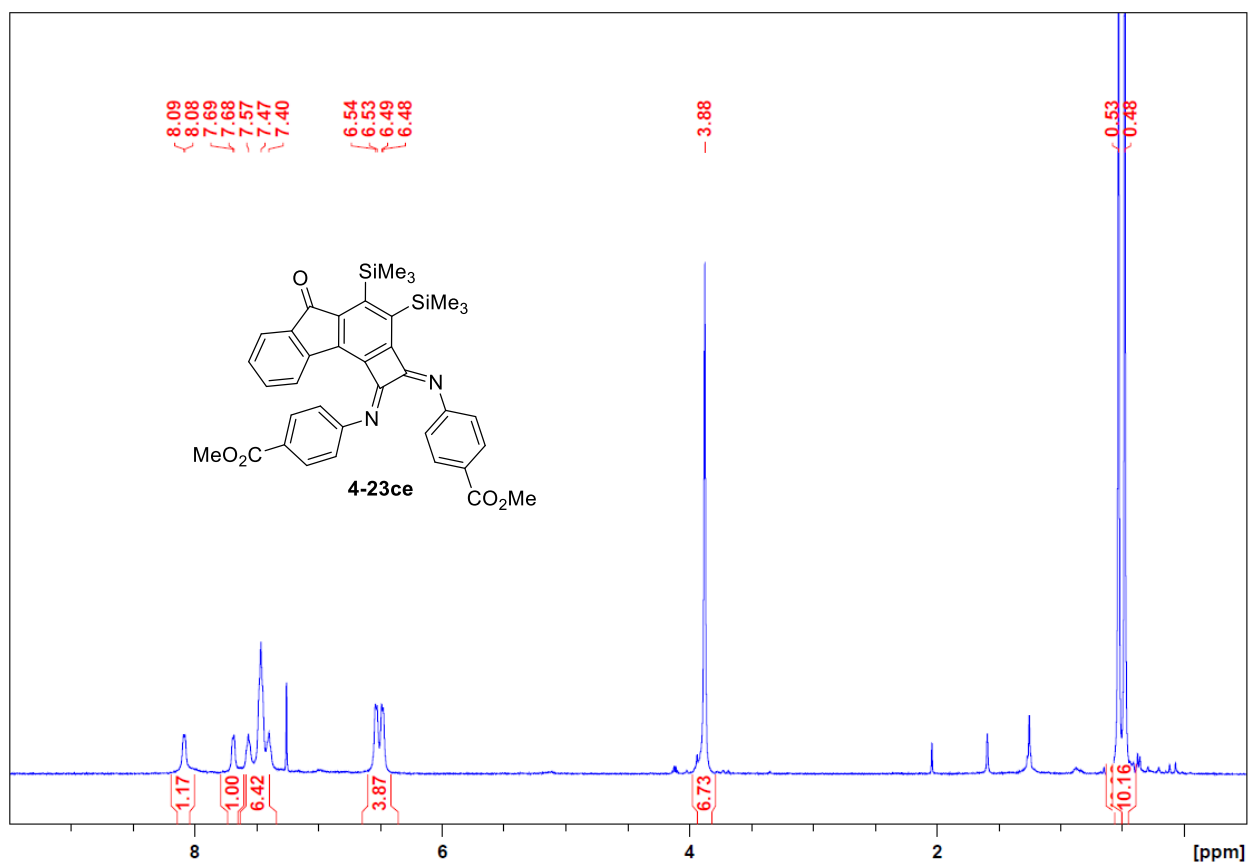


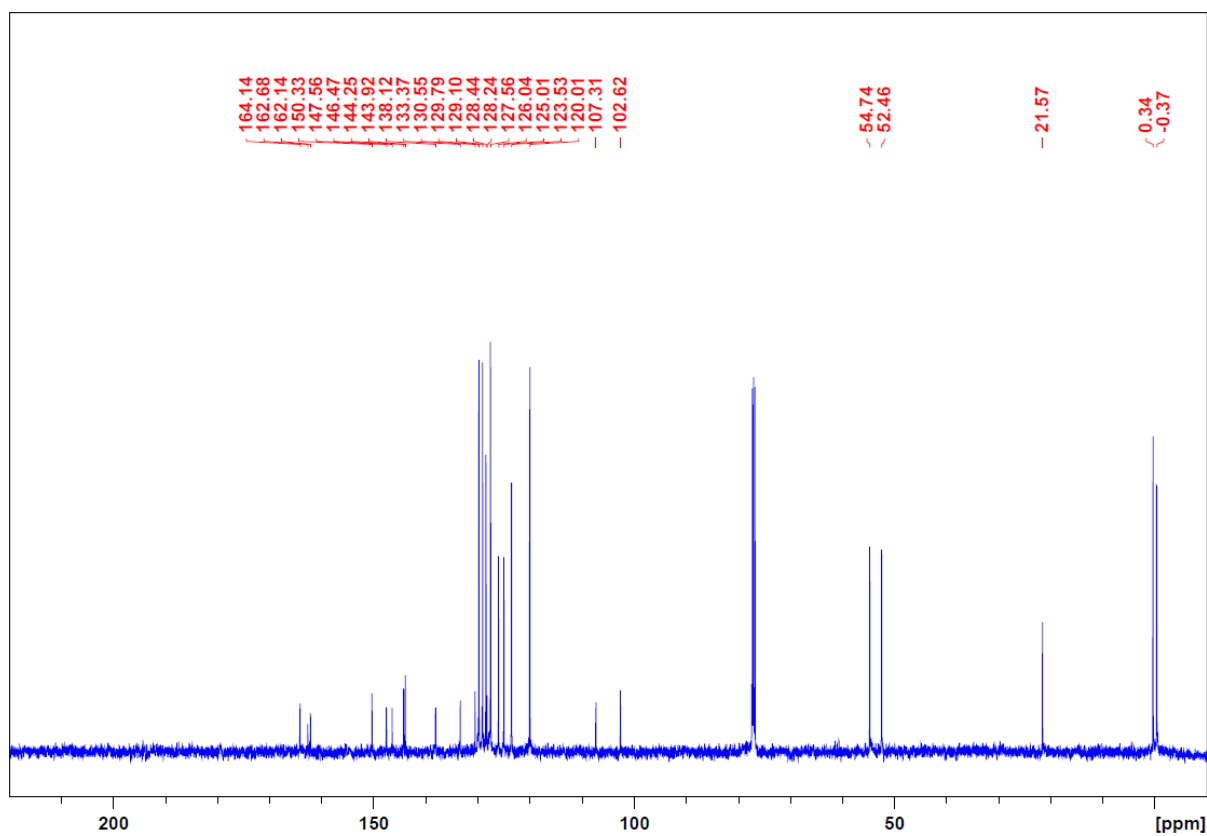
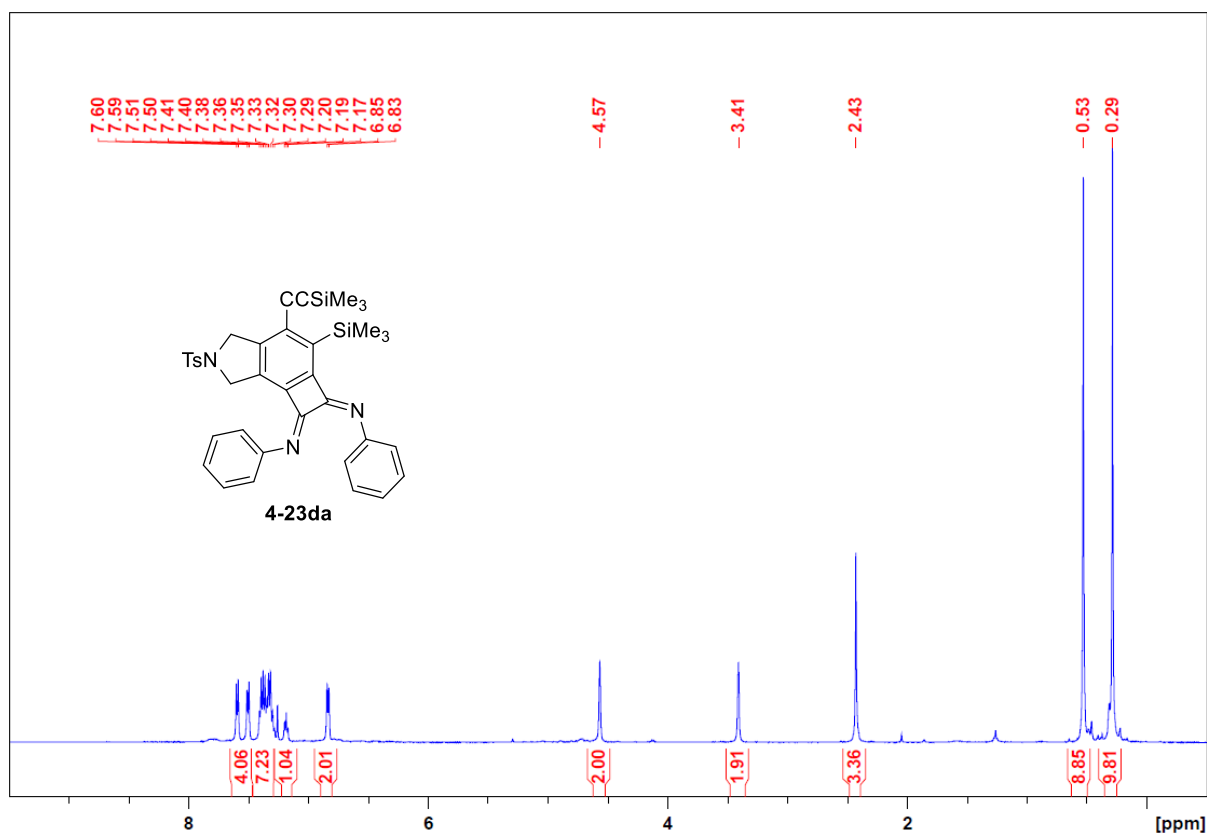


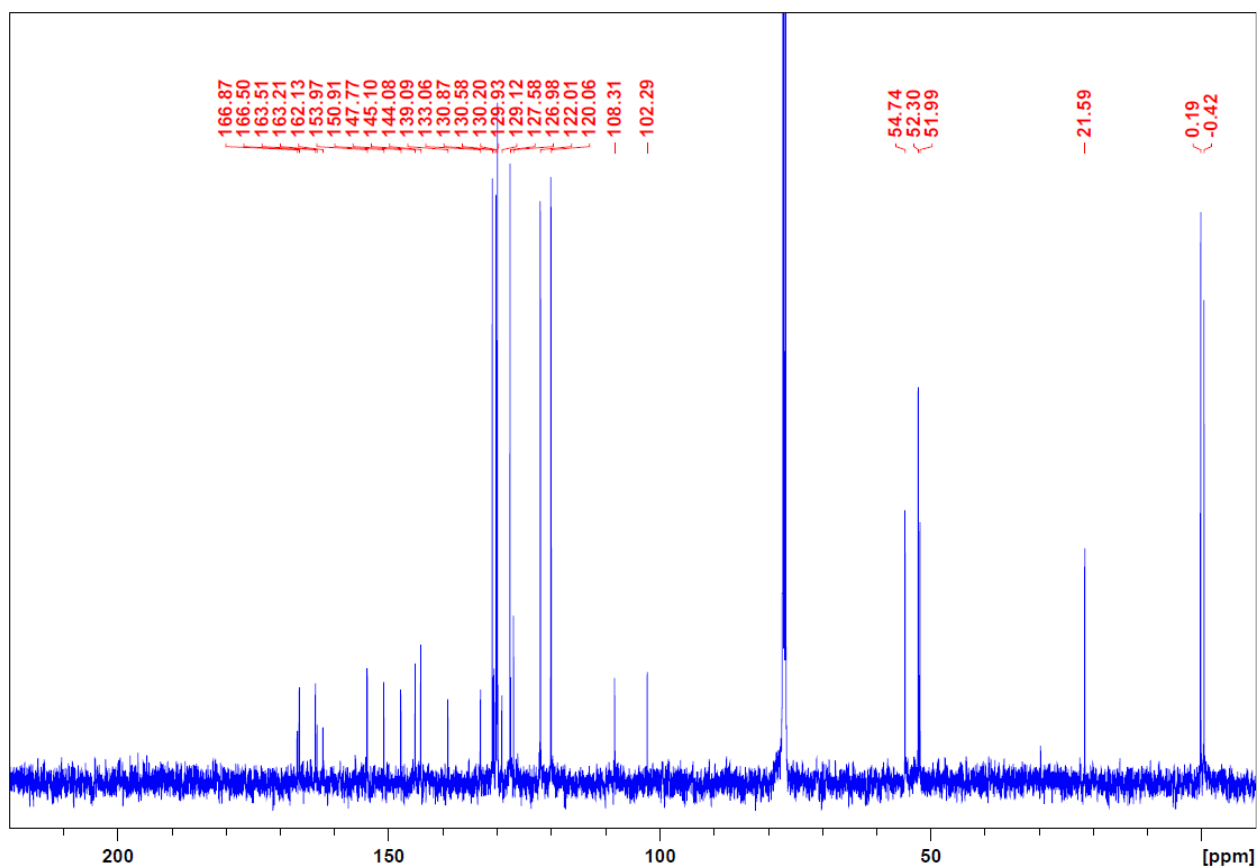
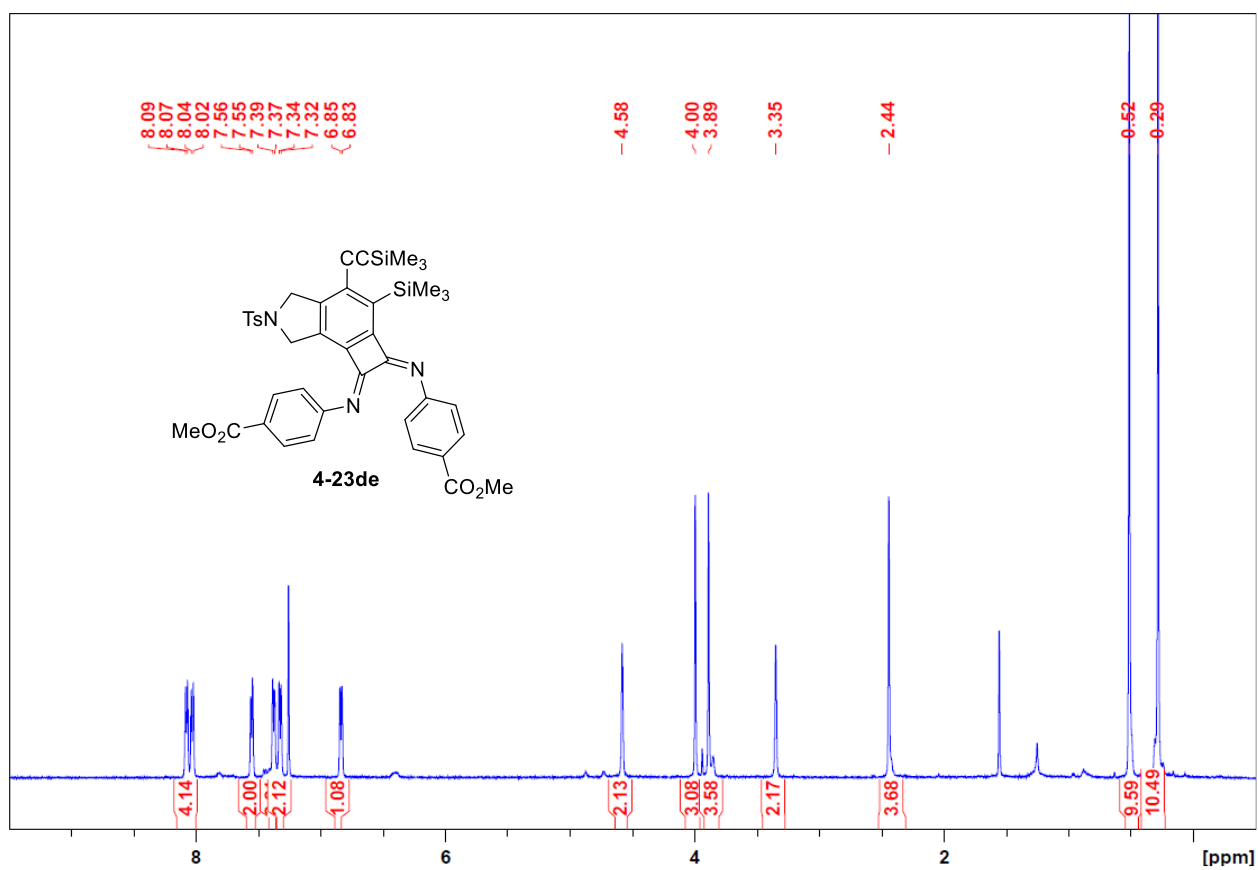


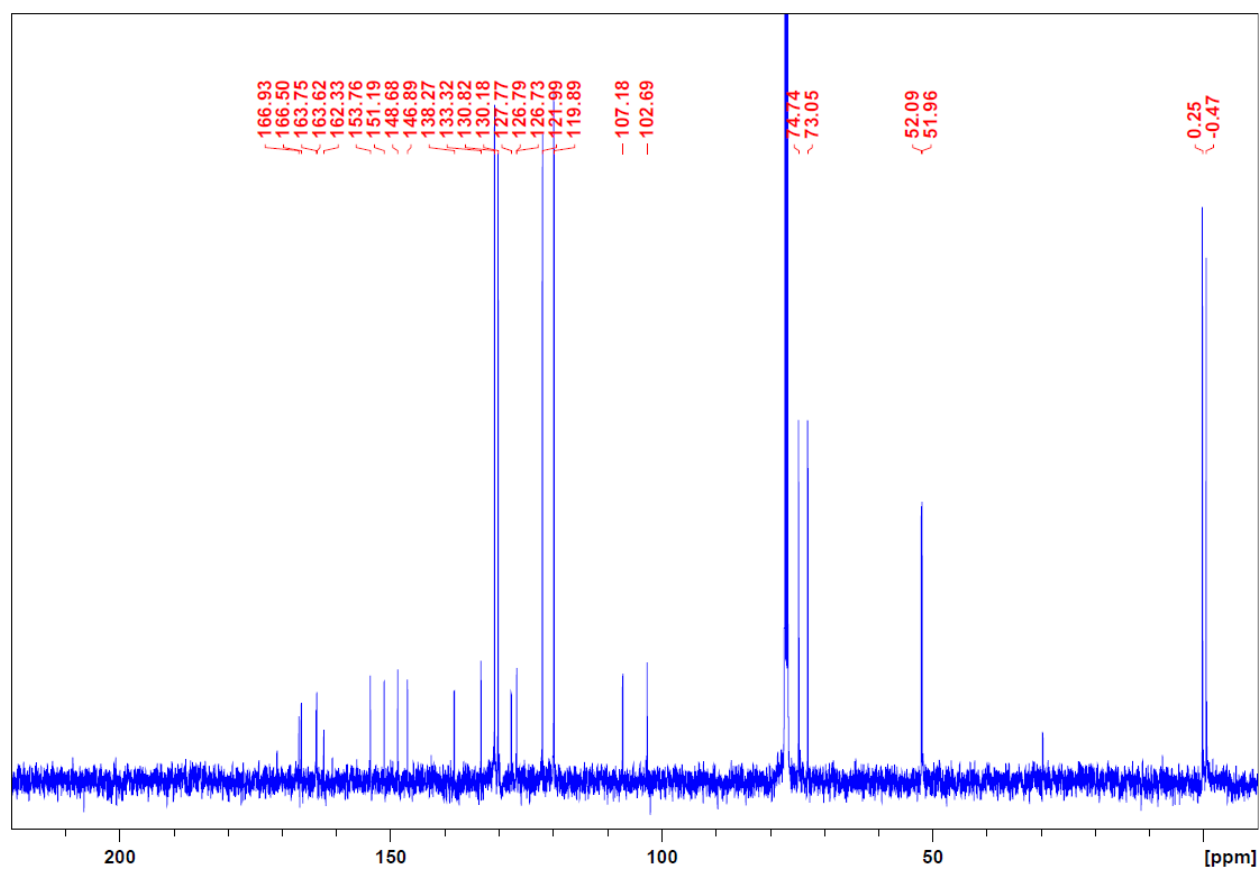
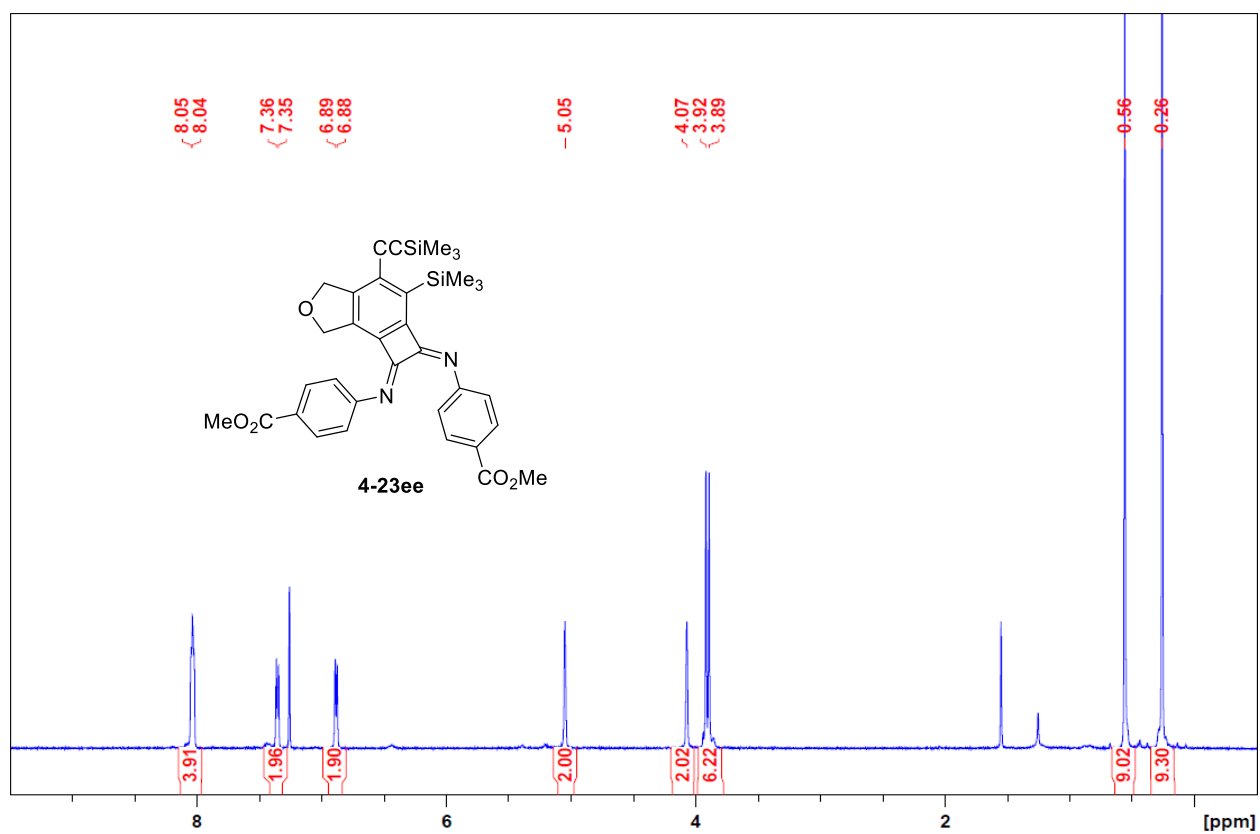


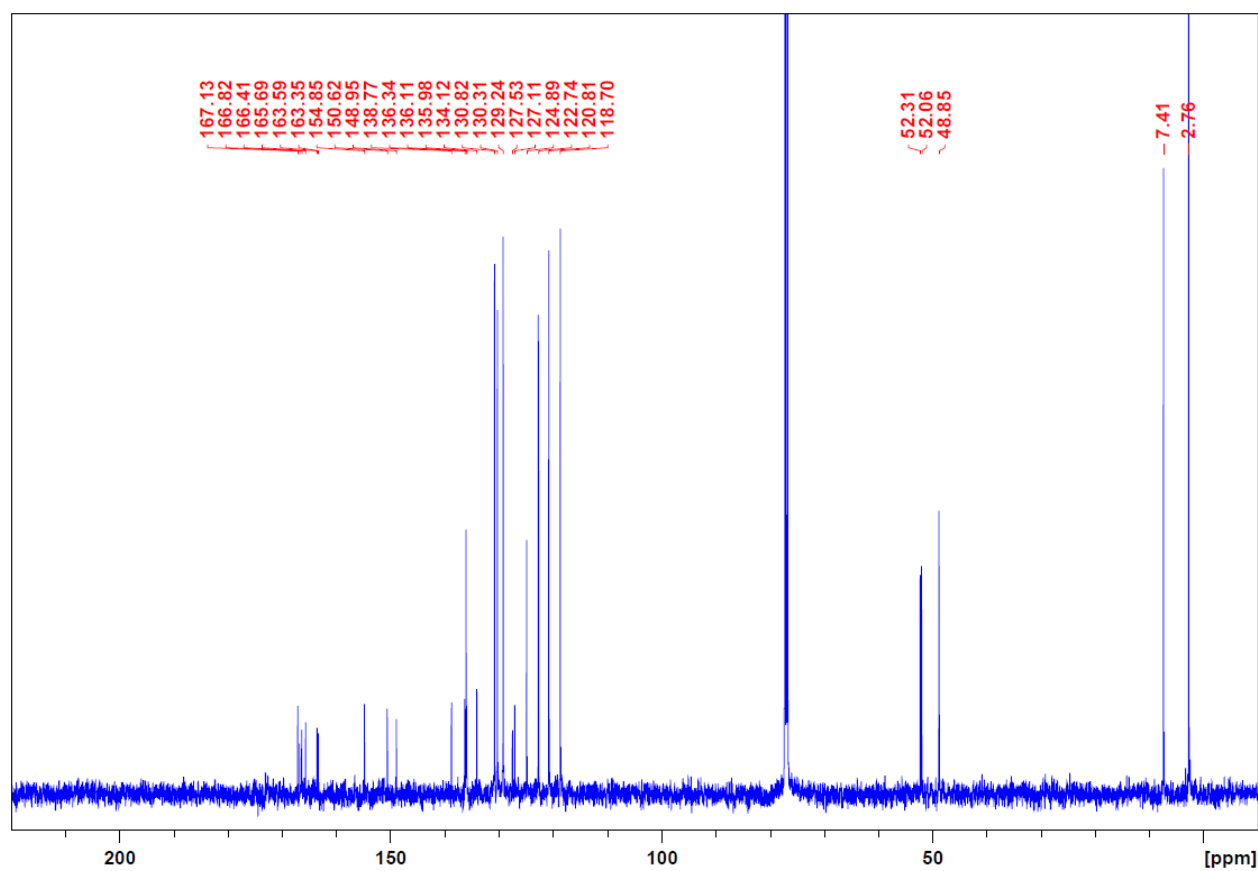
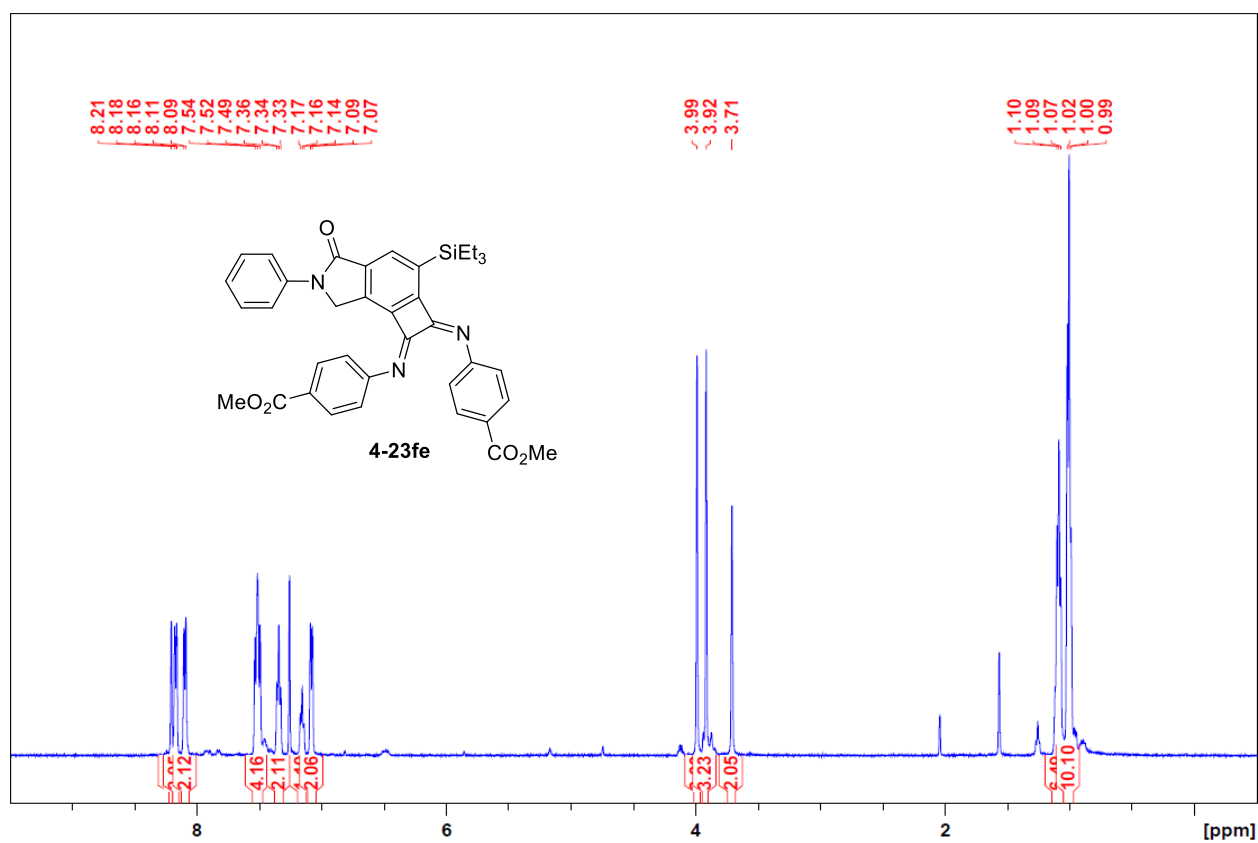


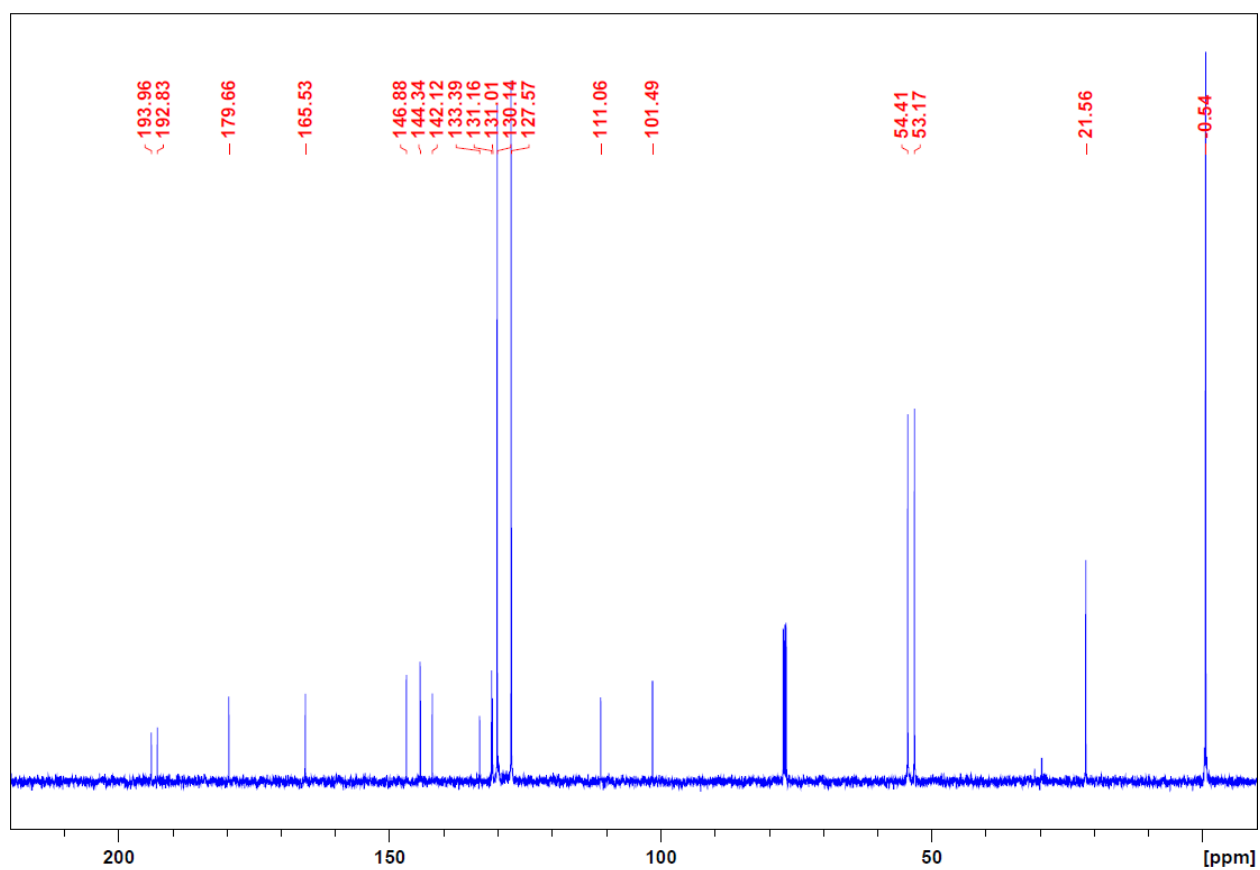
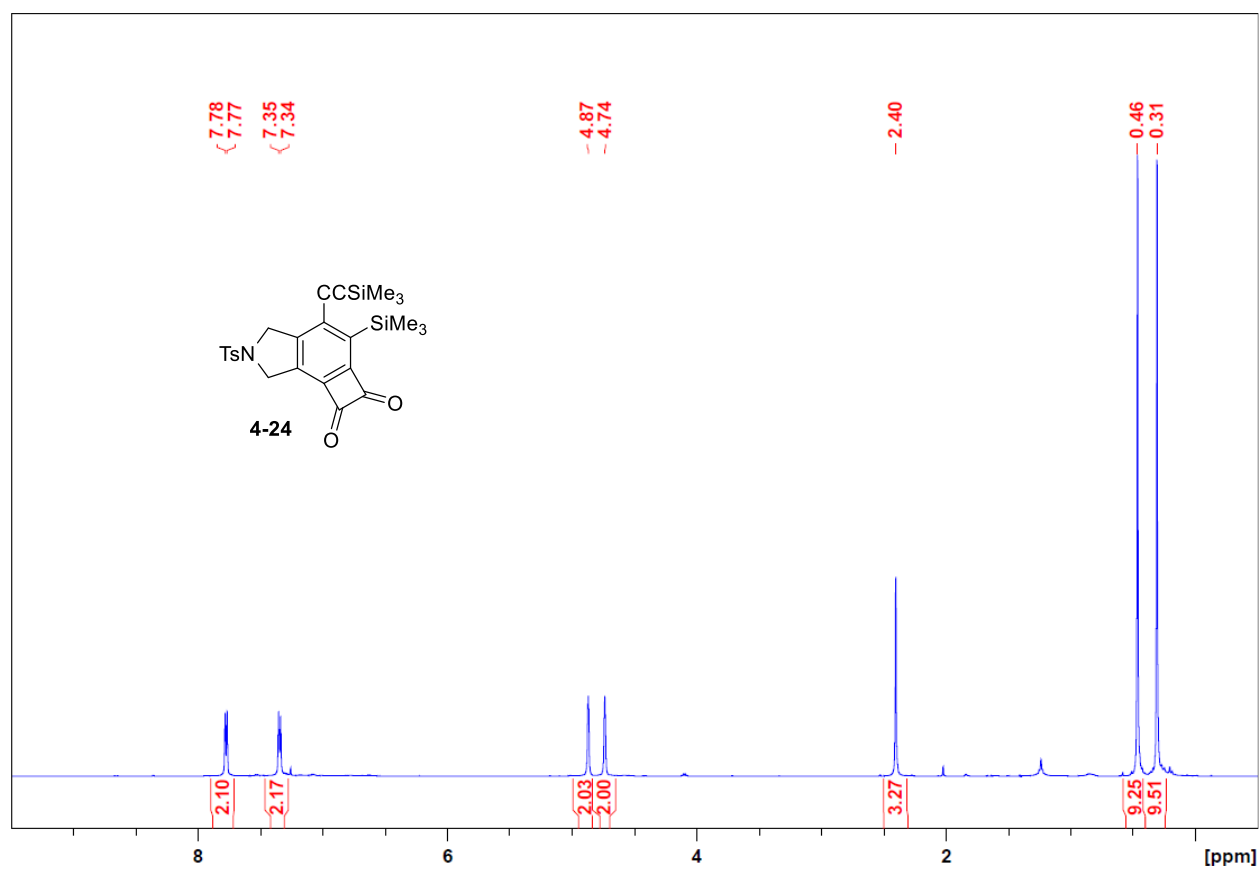


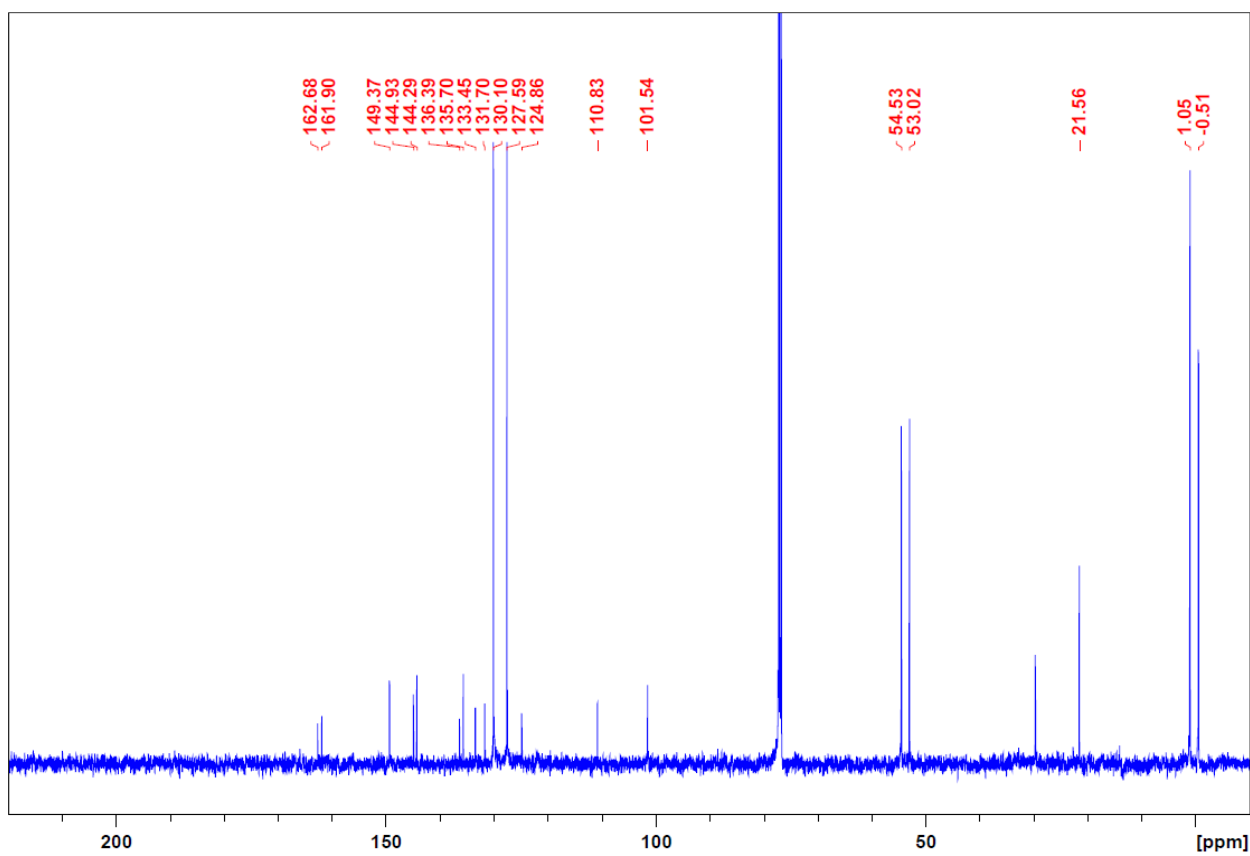
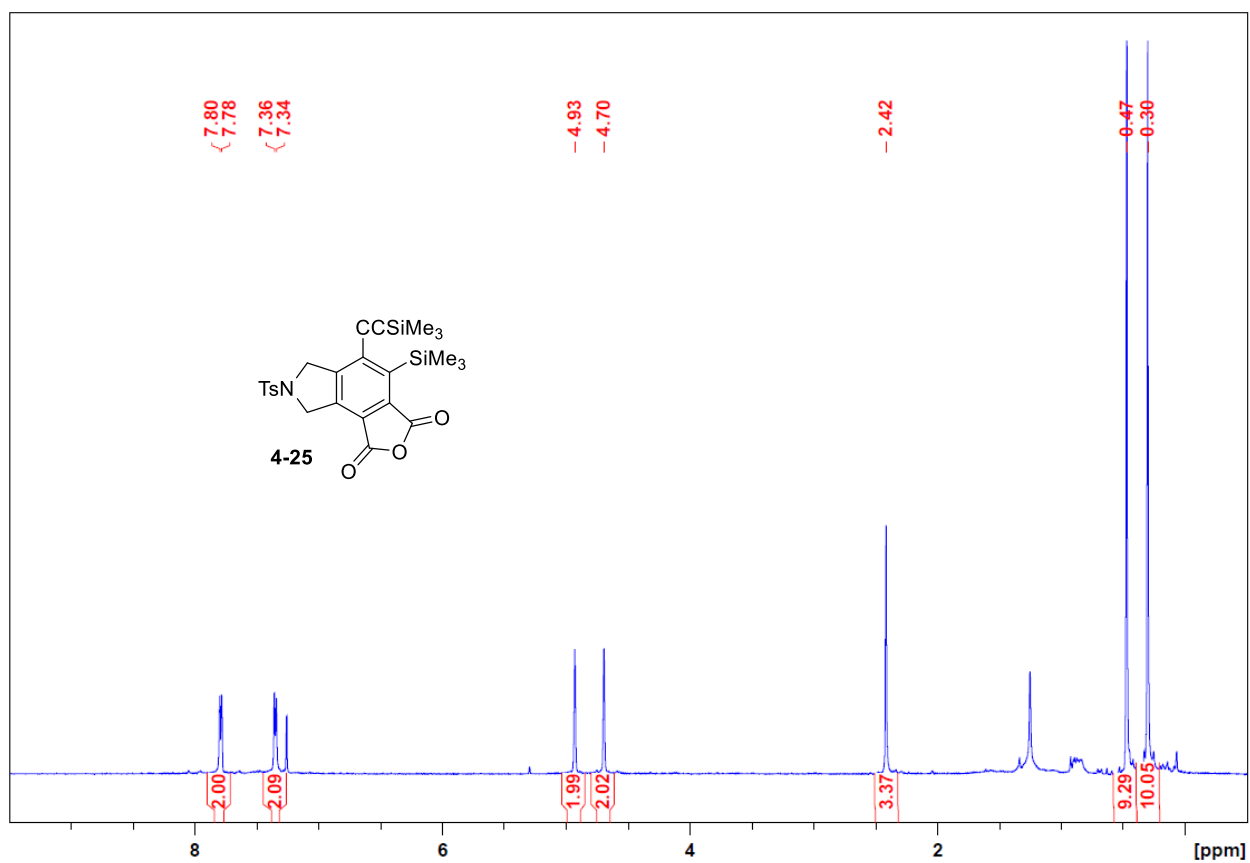


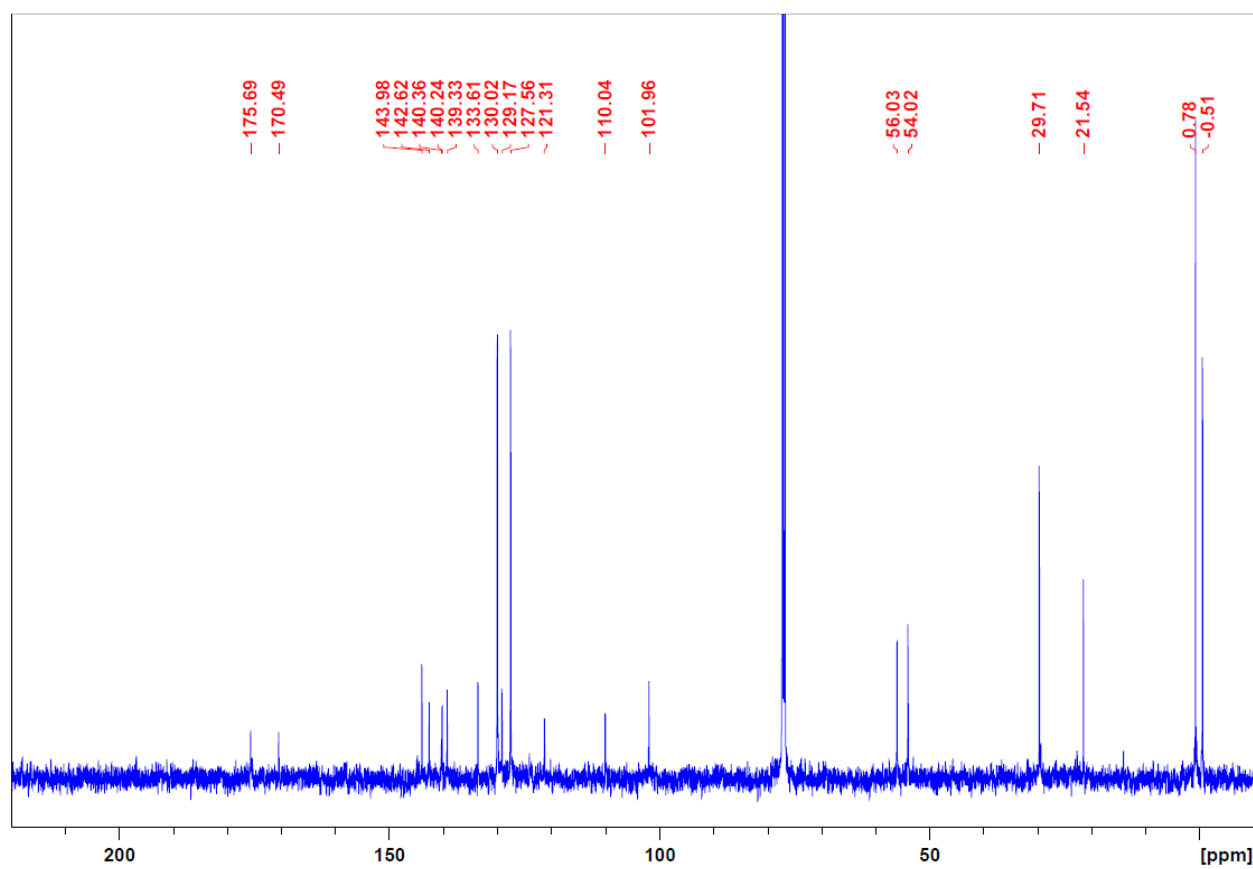
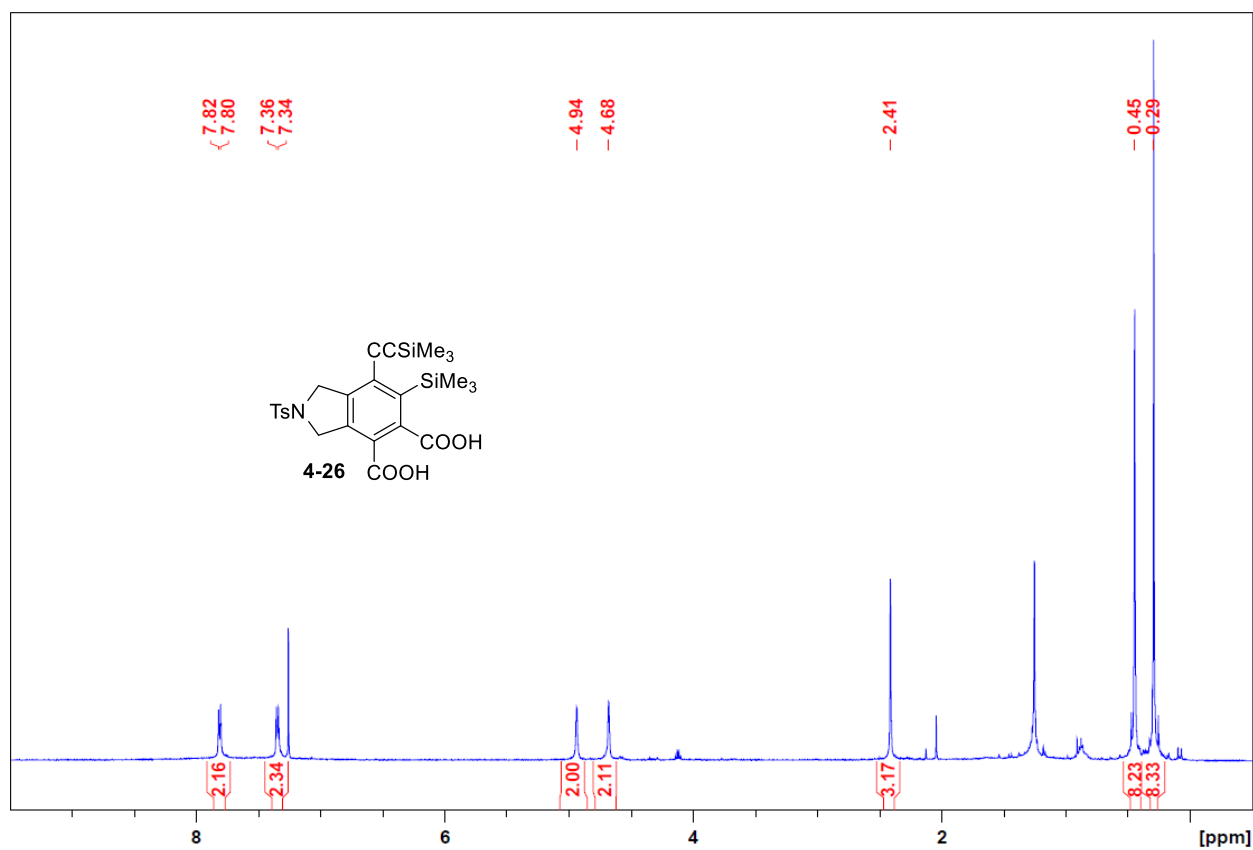


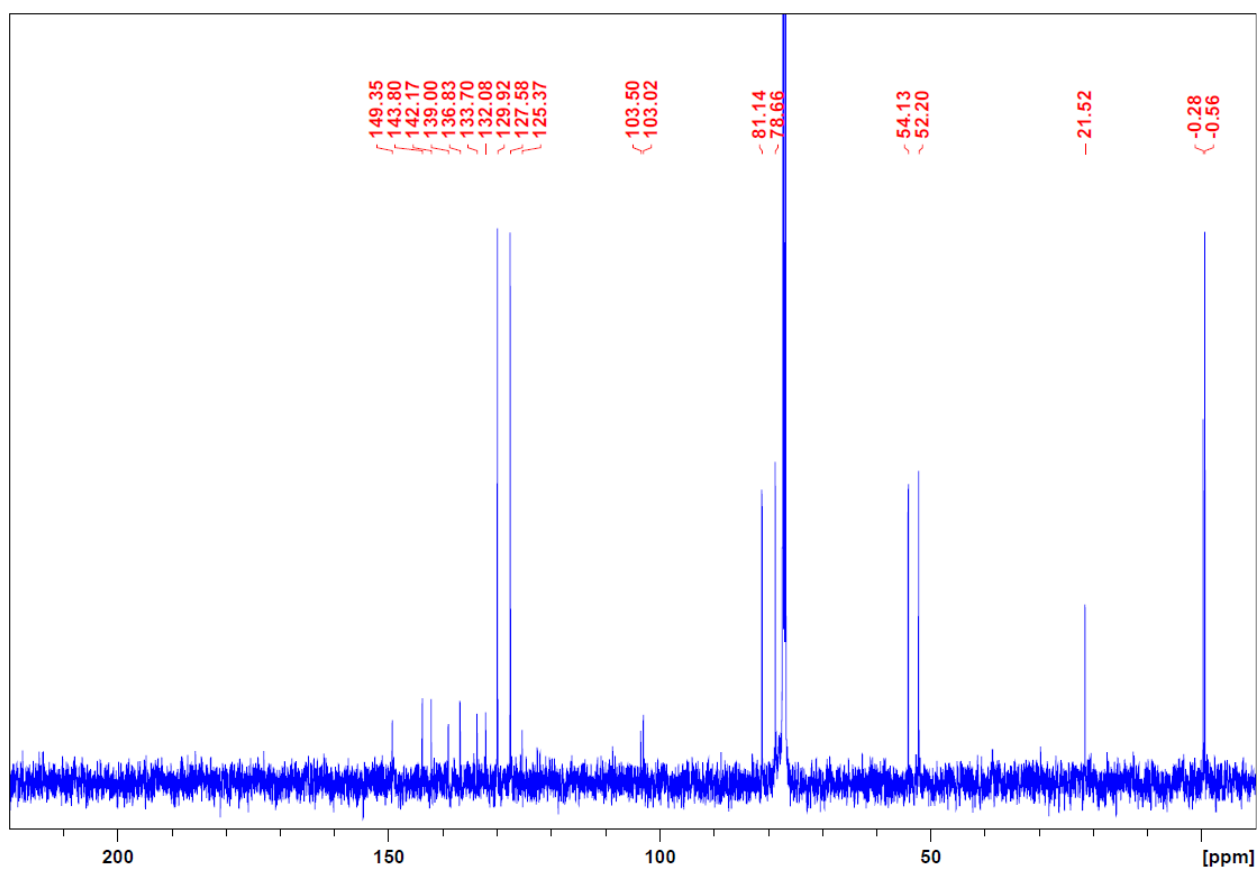
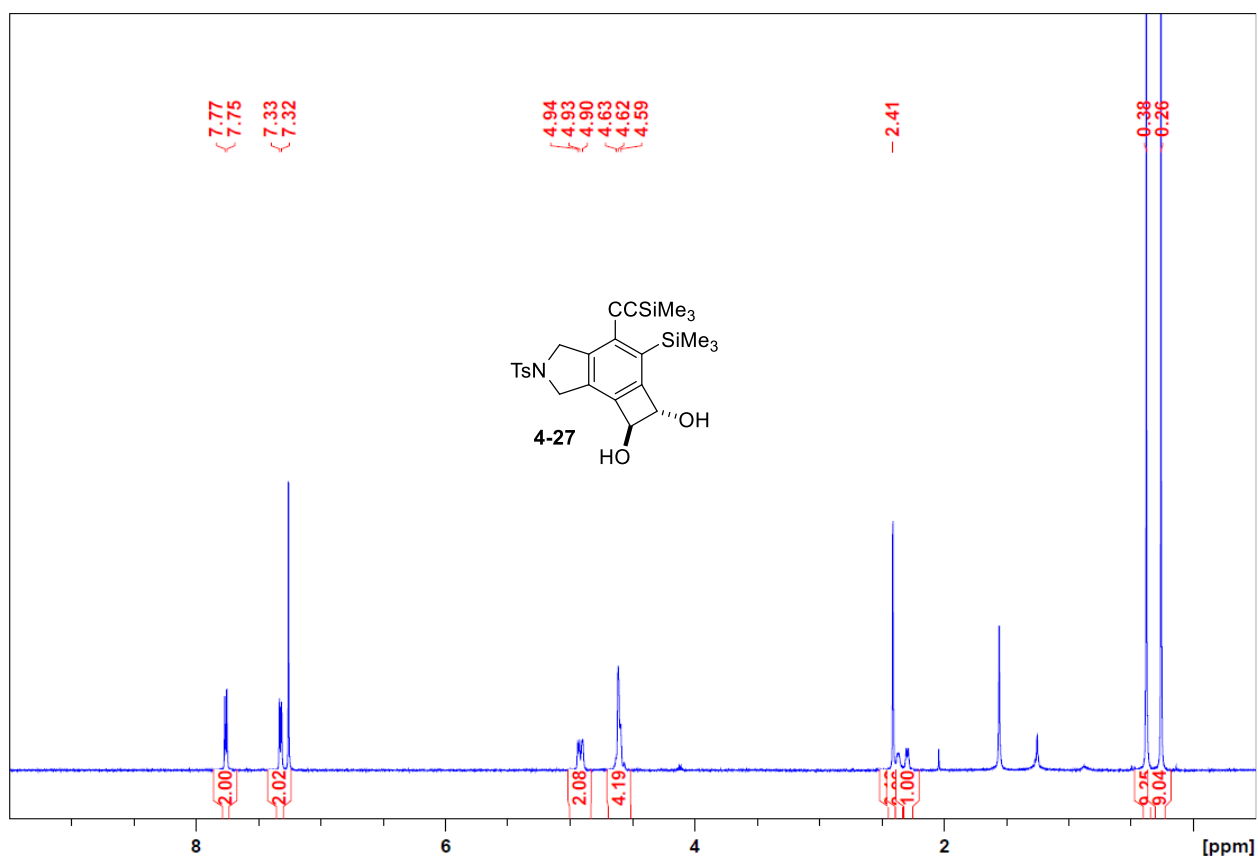


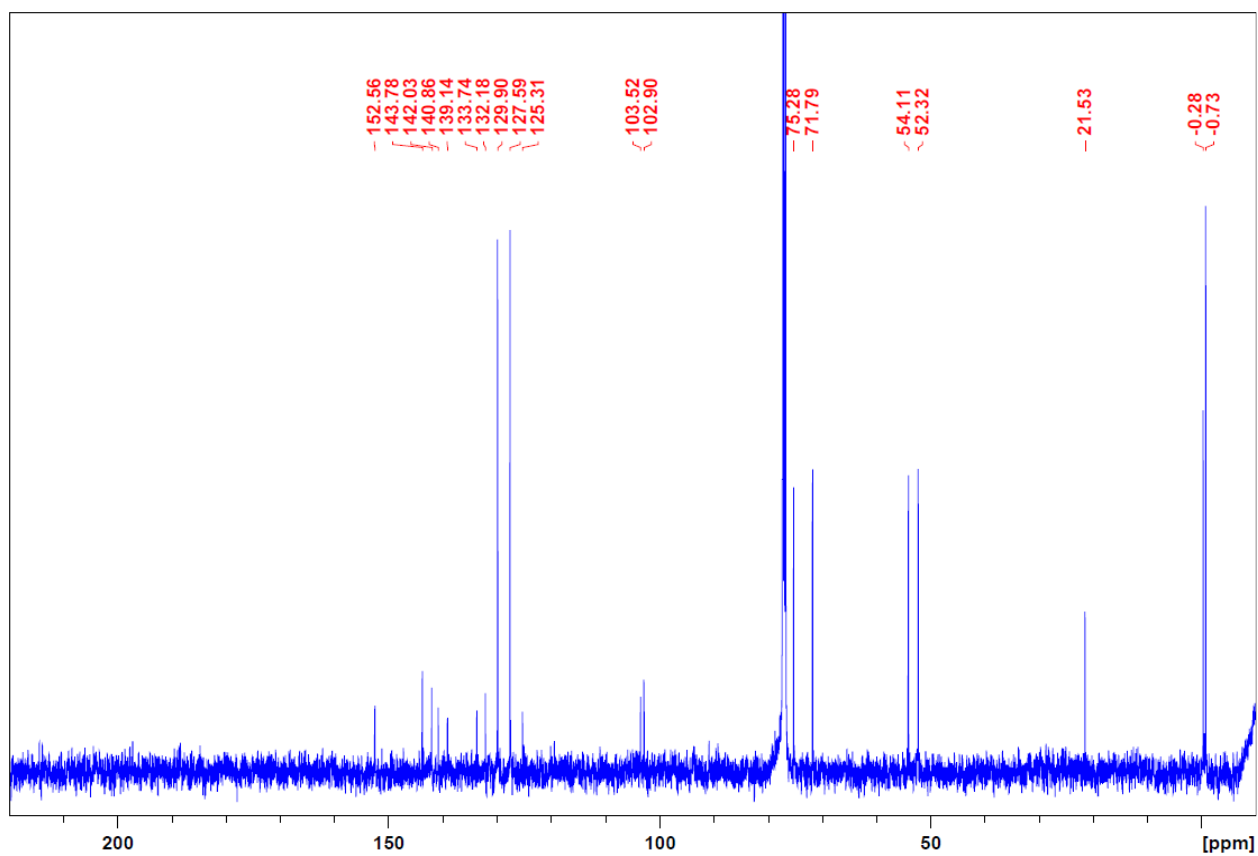
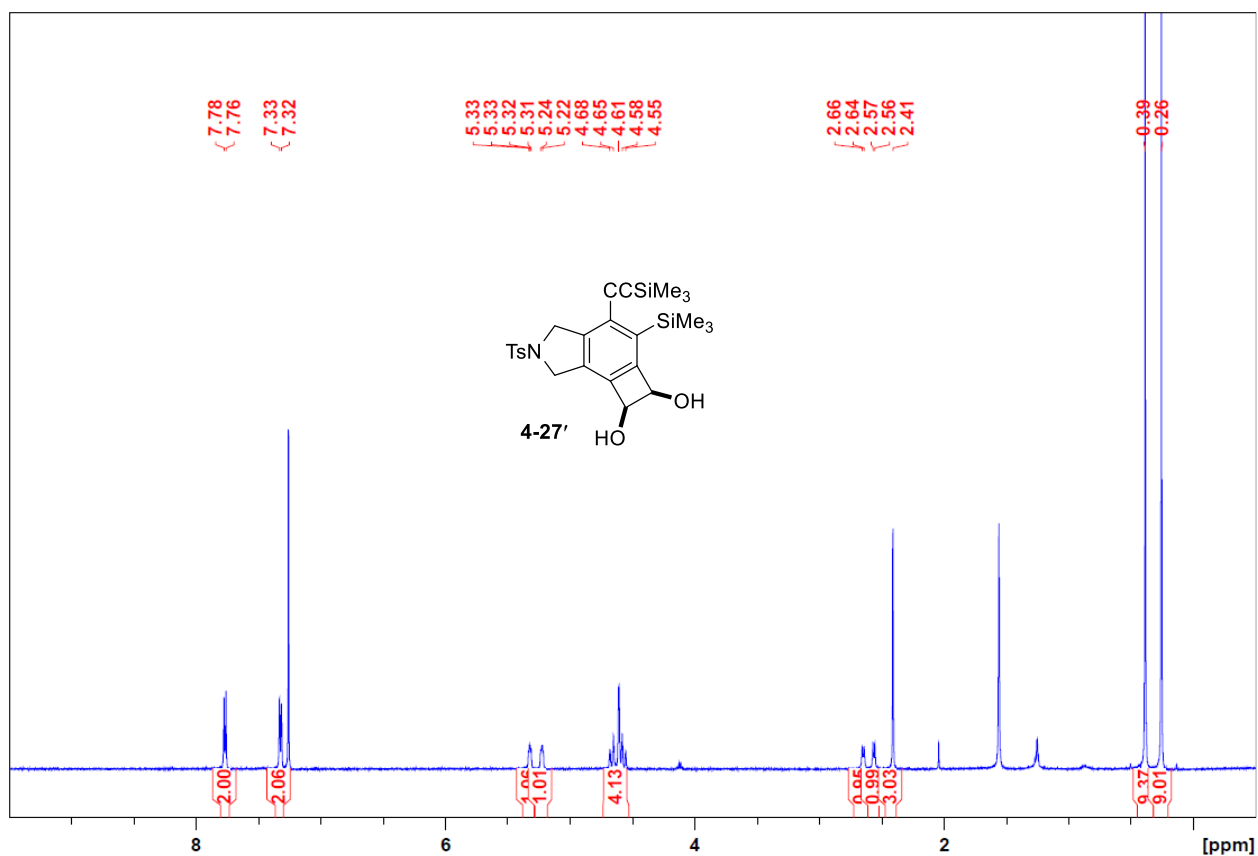


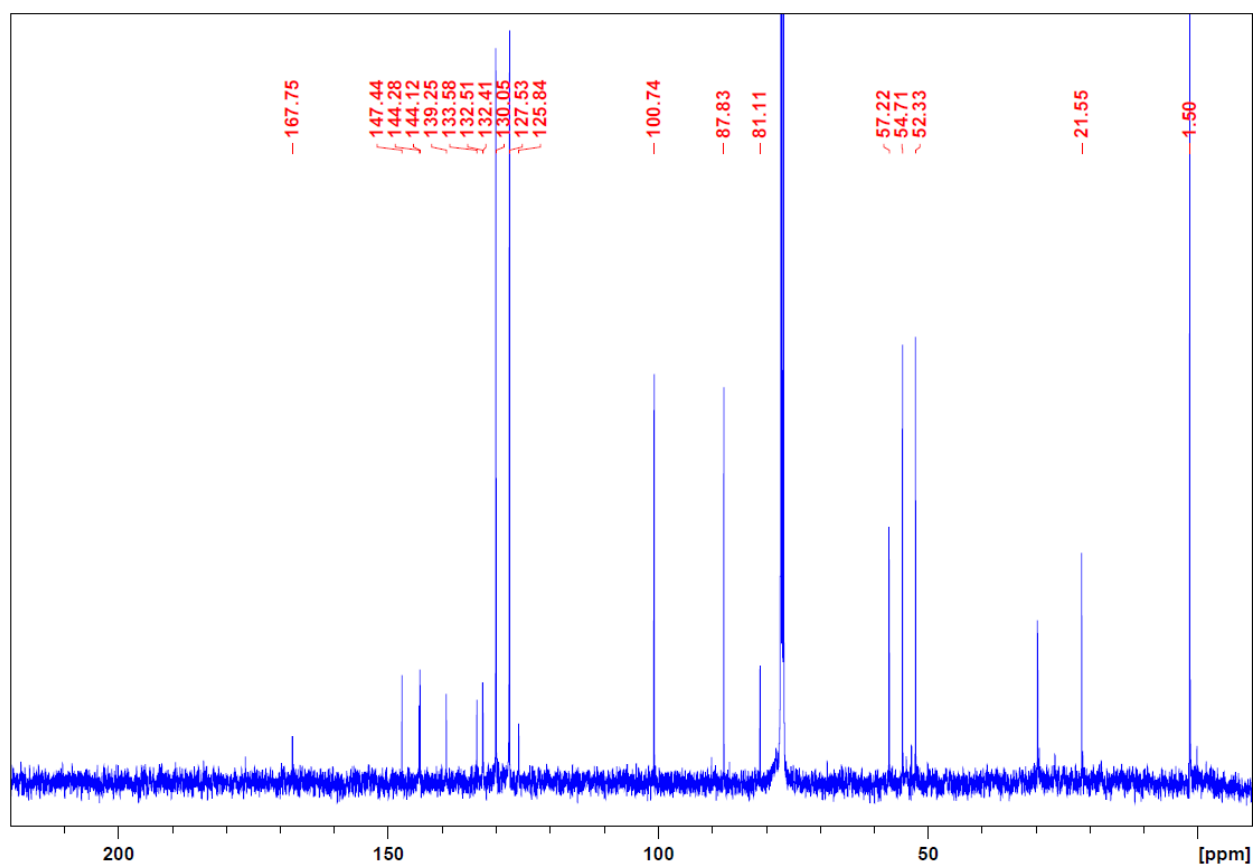
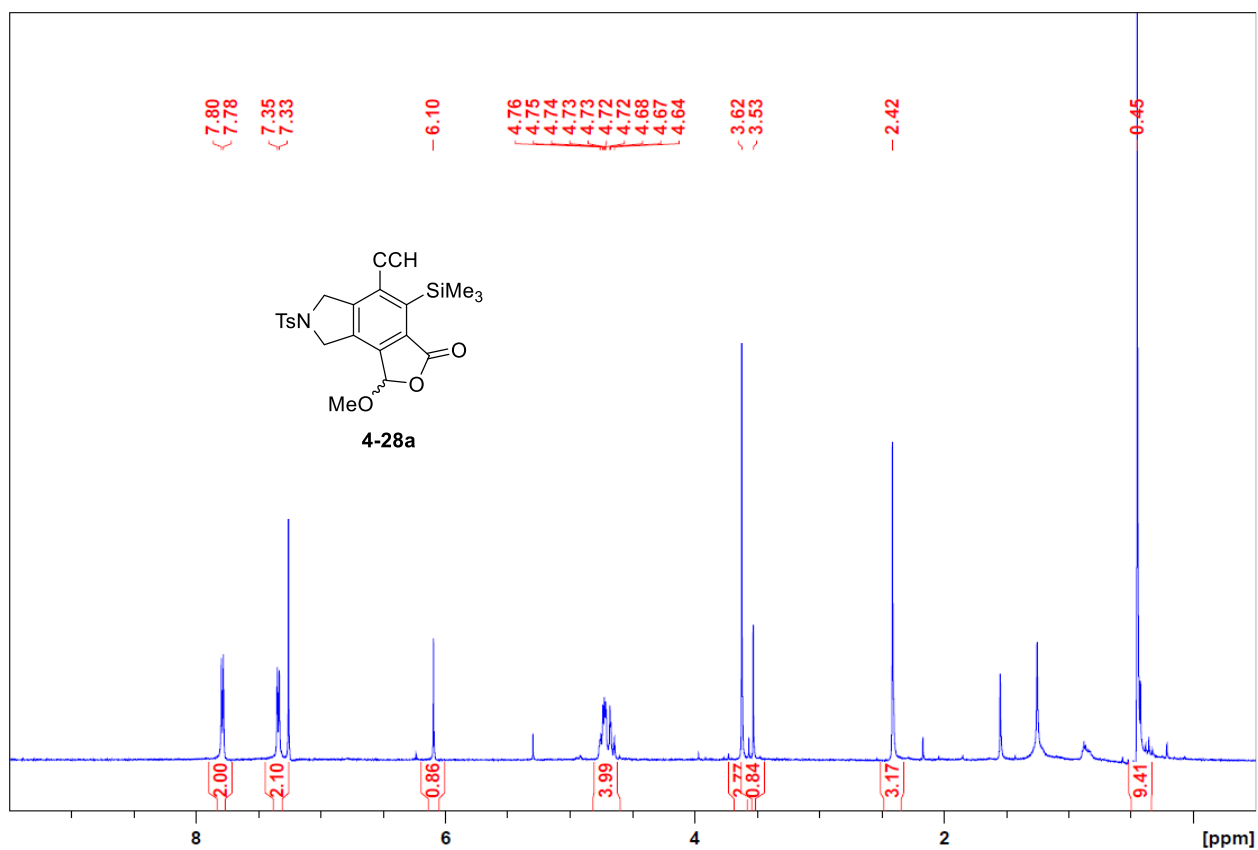


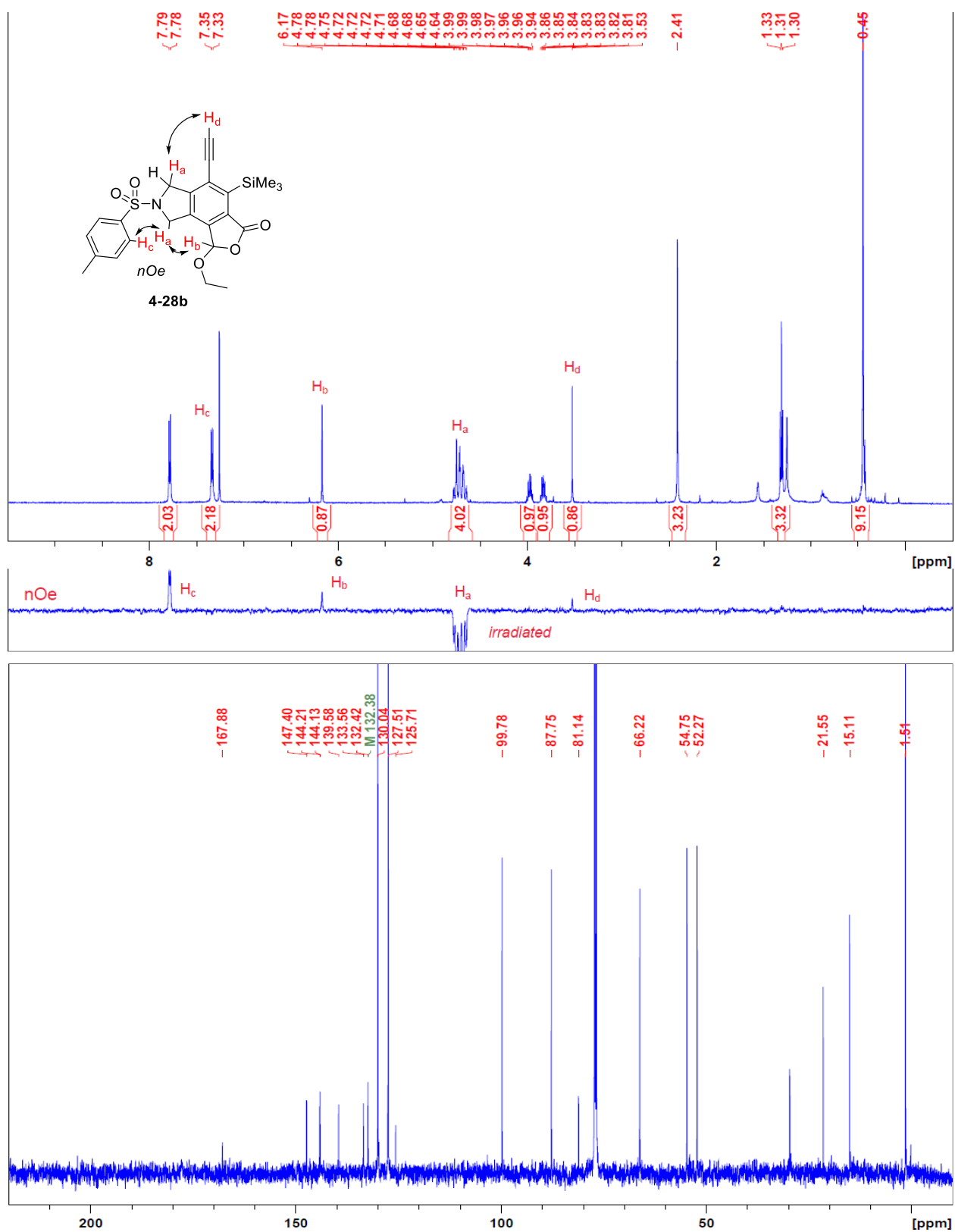


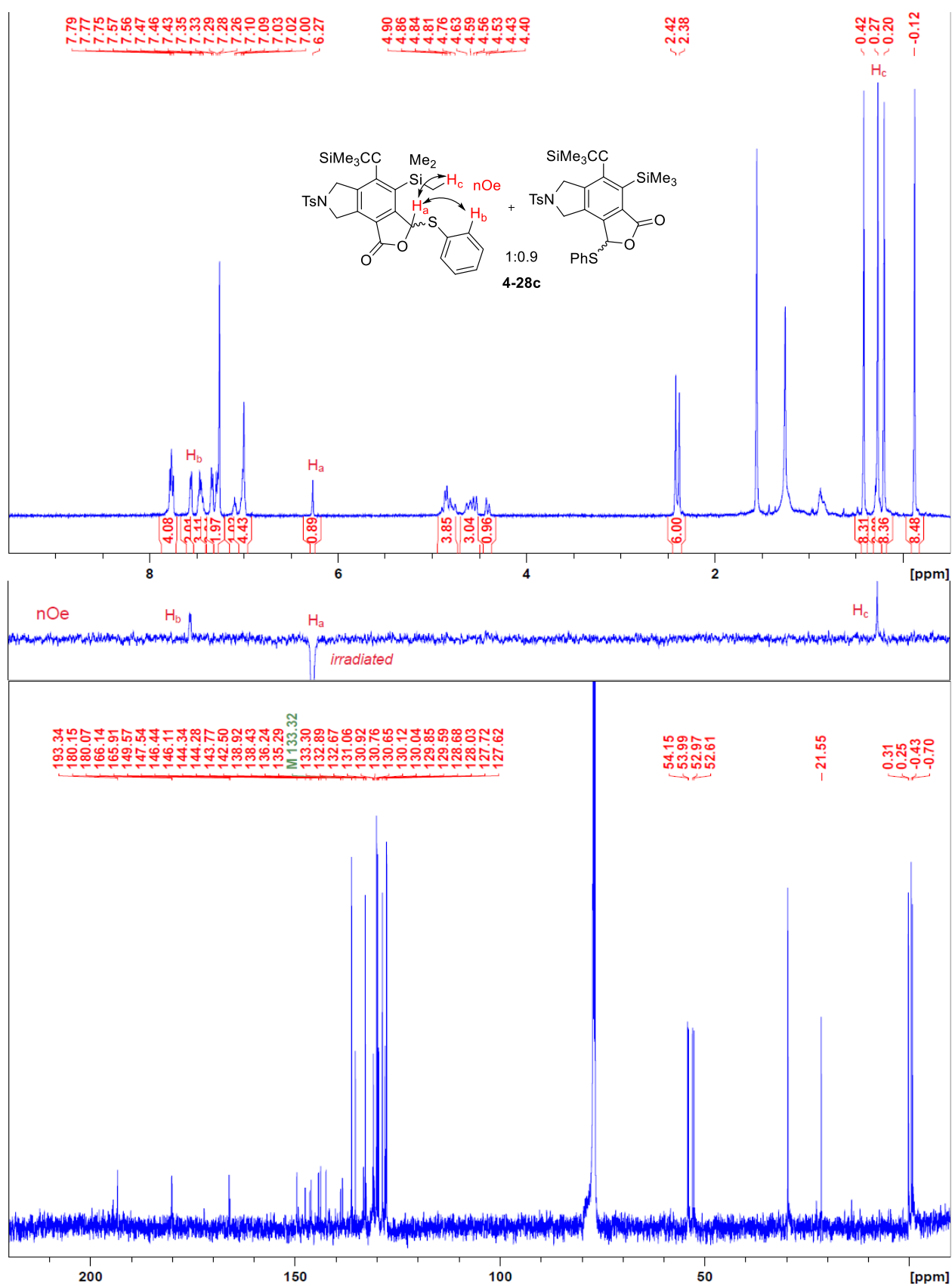






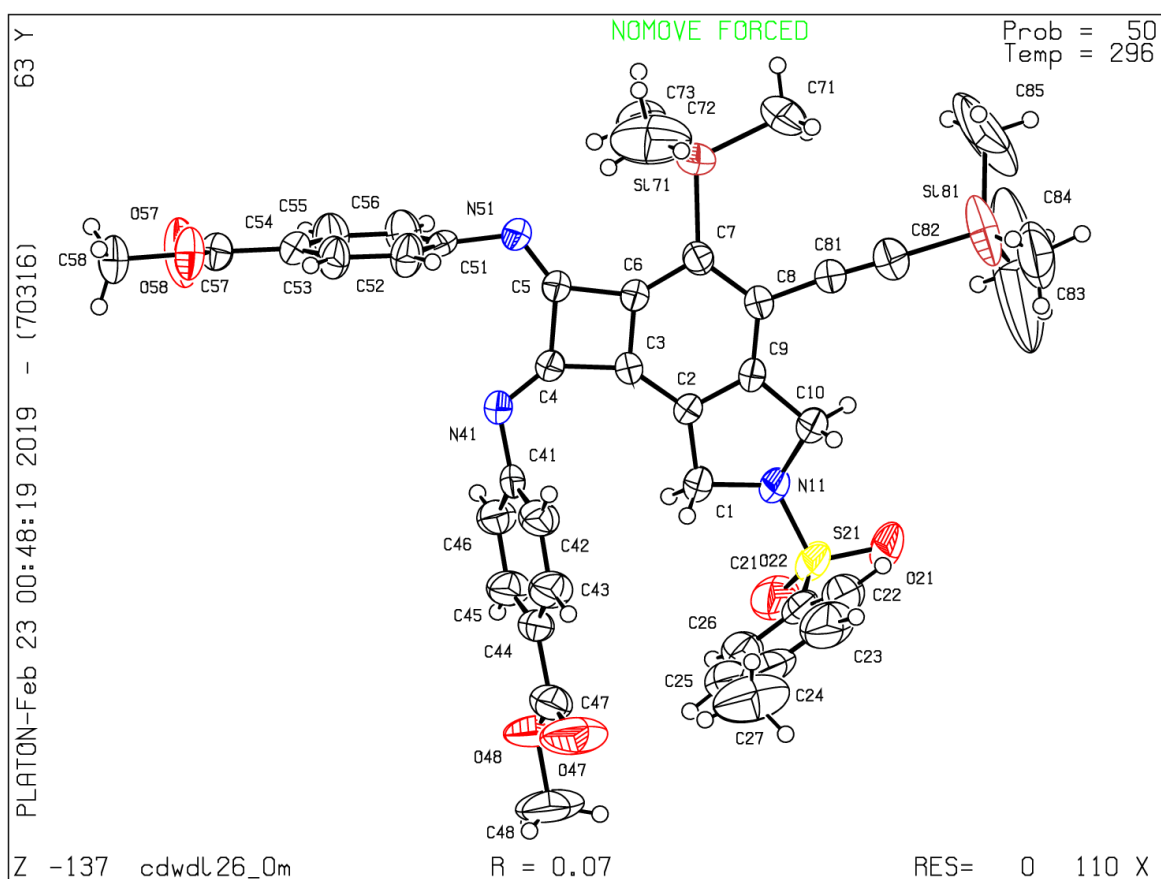
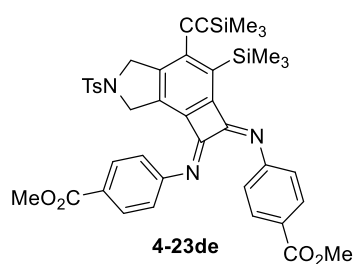




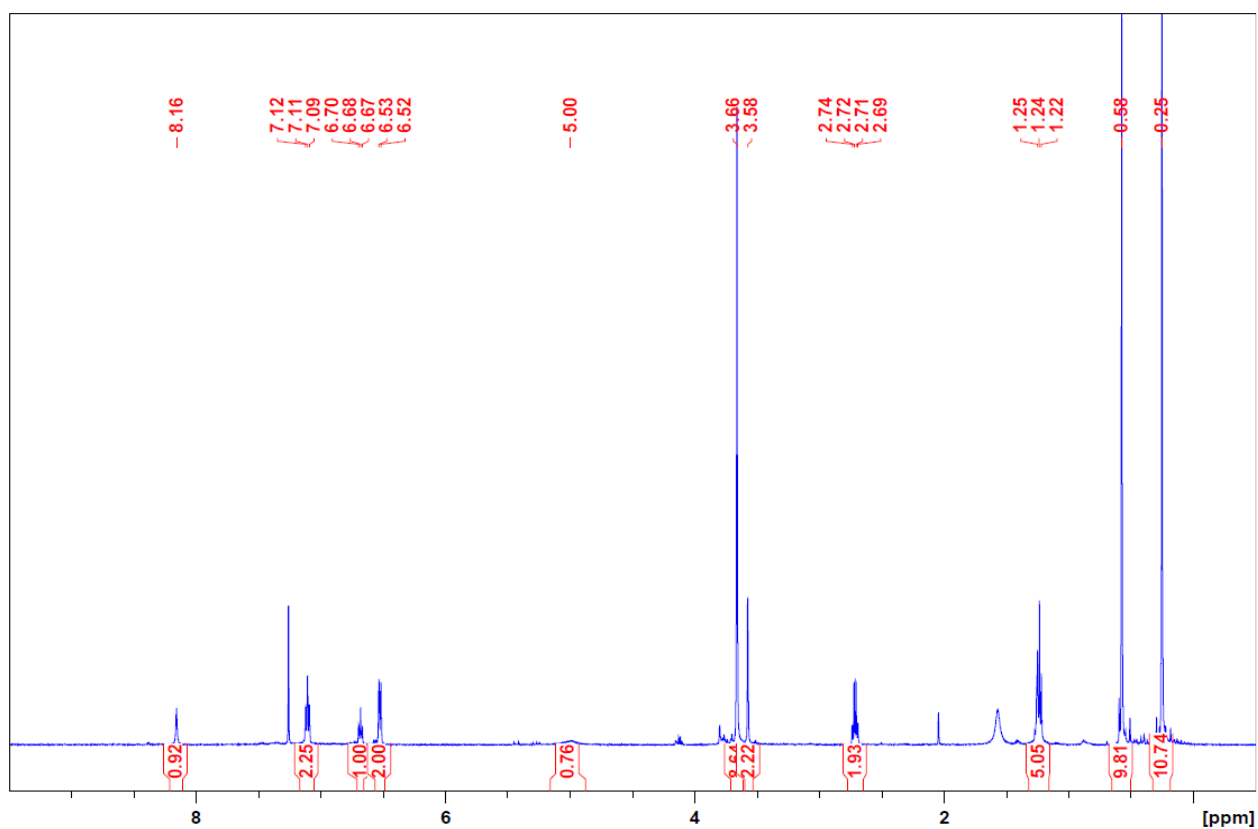
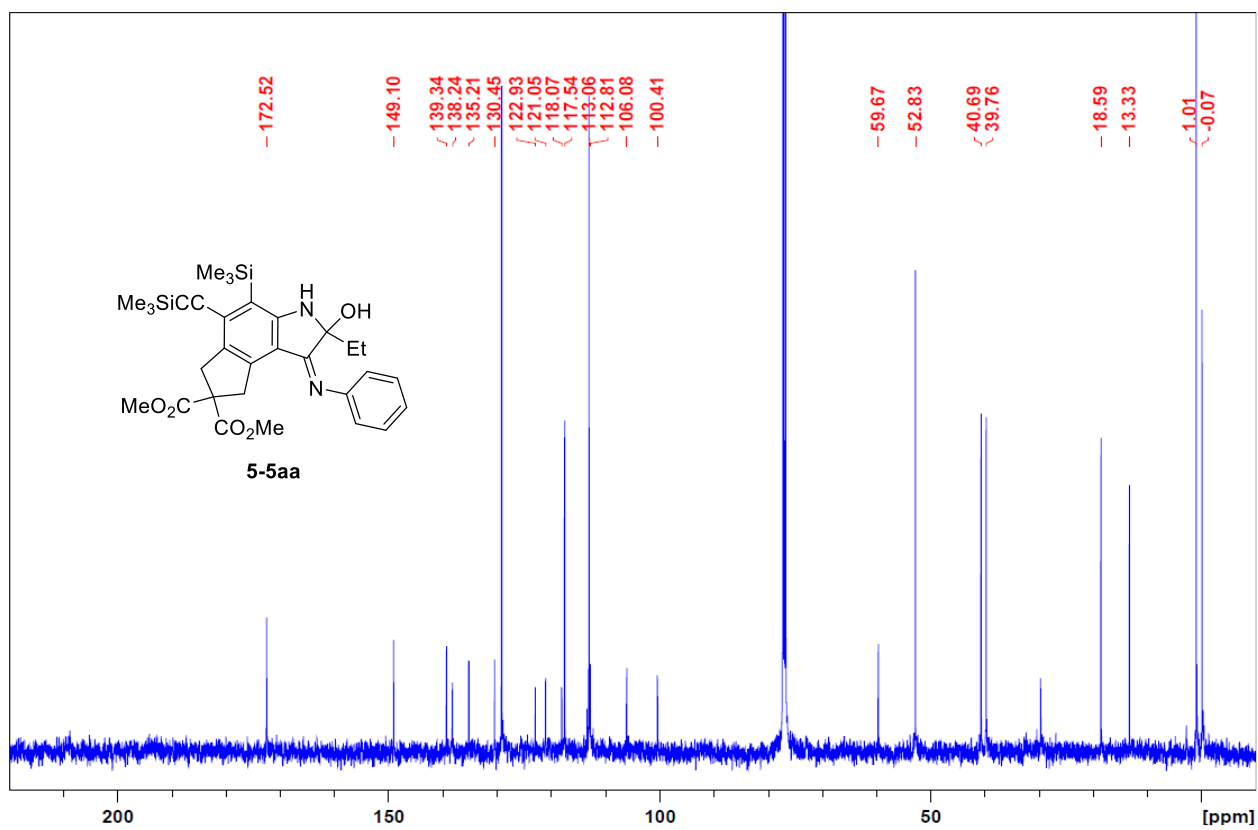


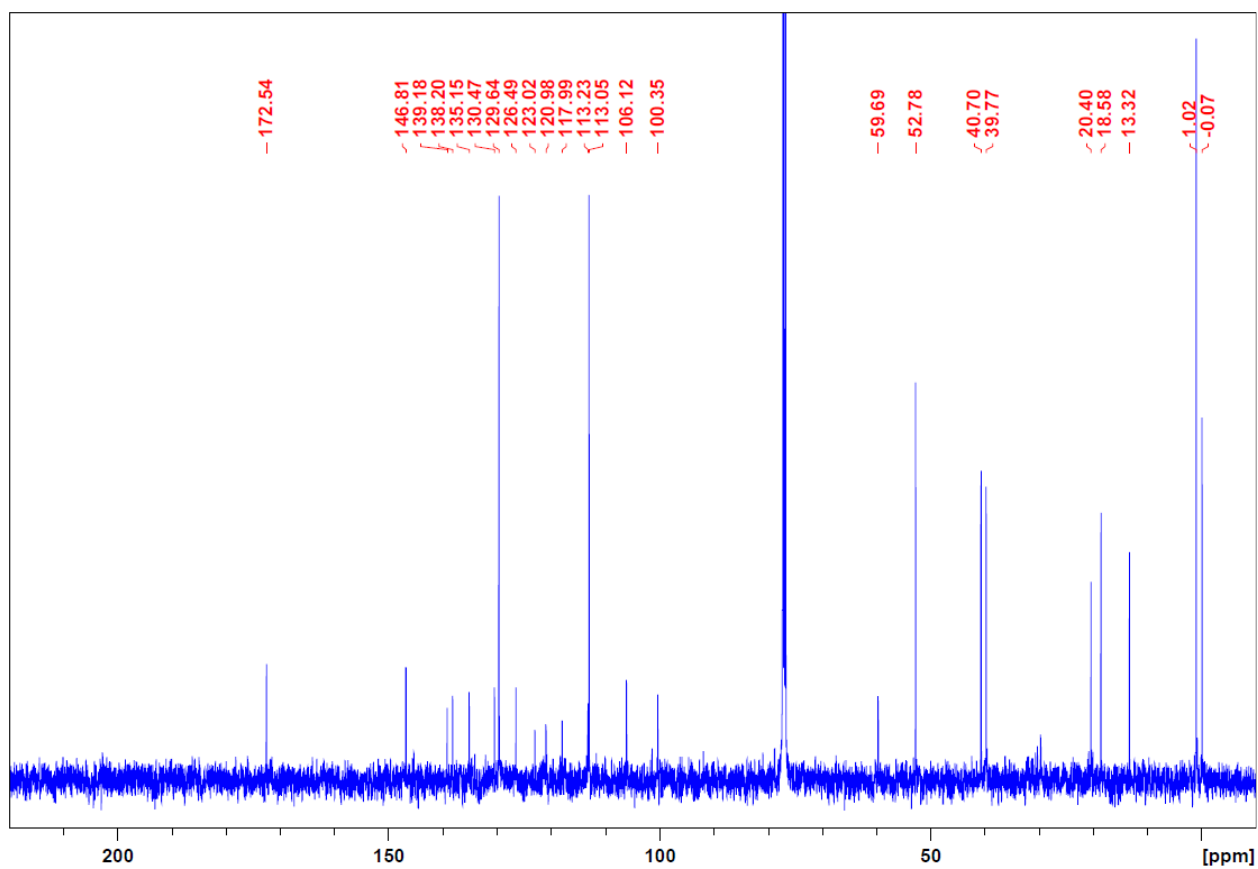
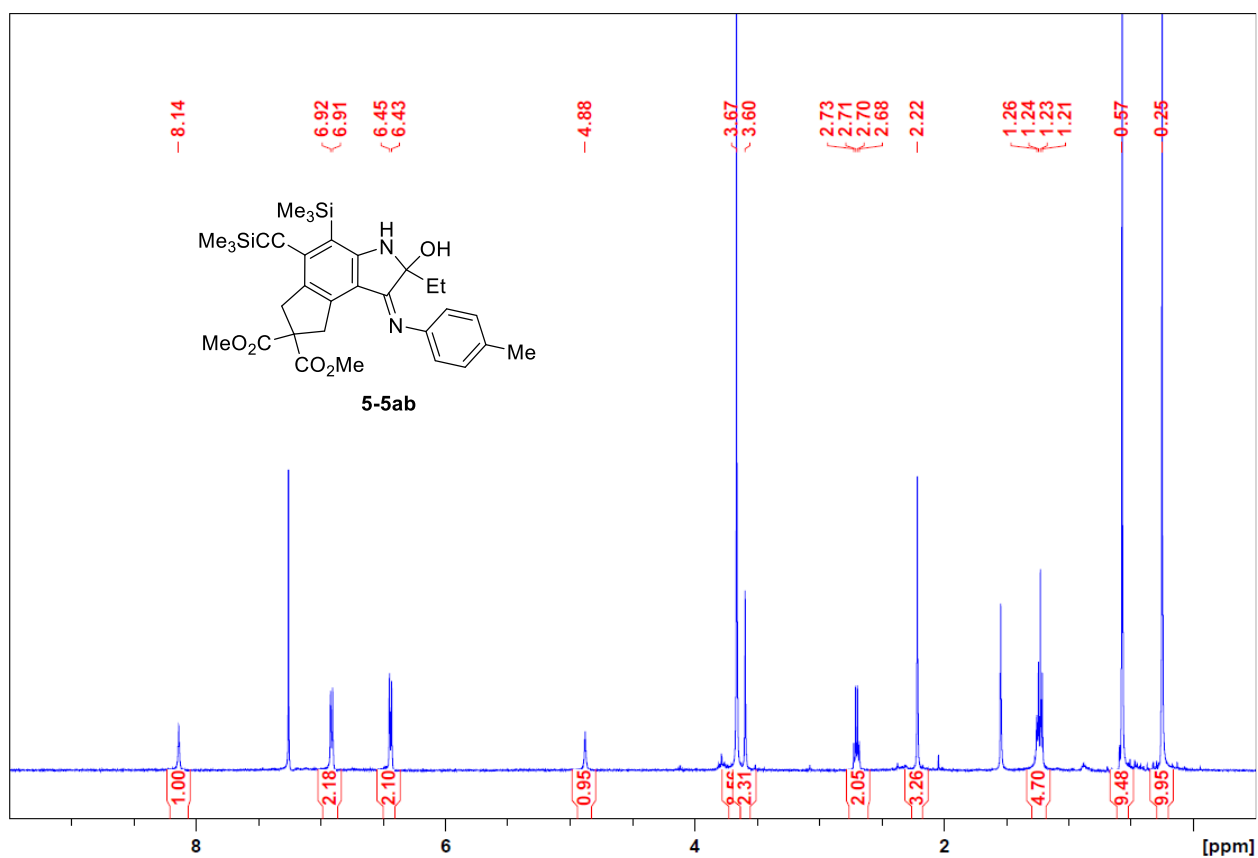
X-Ray Structures of Quinazoline 4-23de

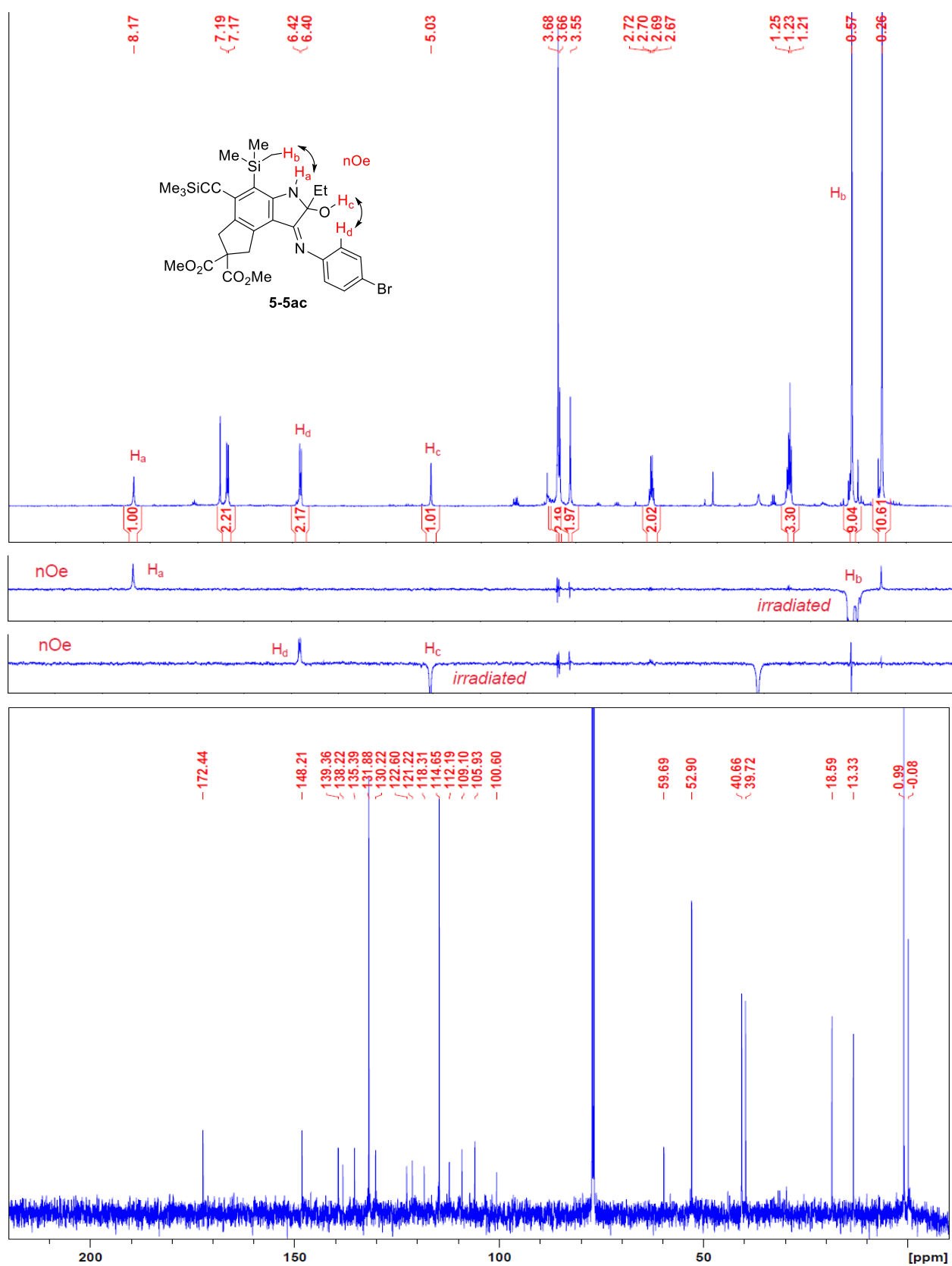
CCDC 1911066, contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

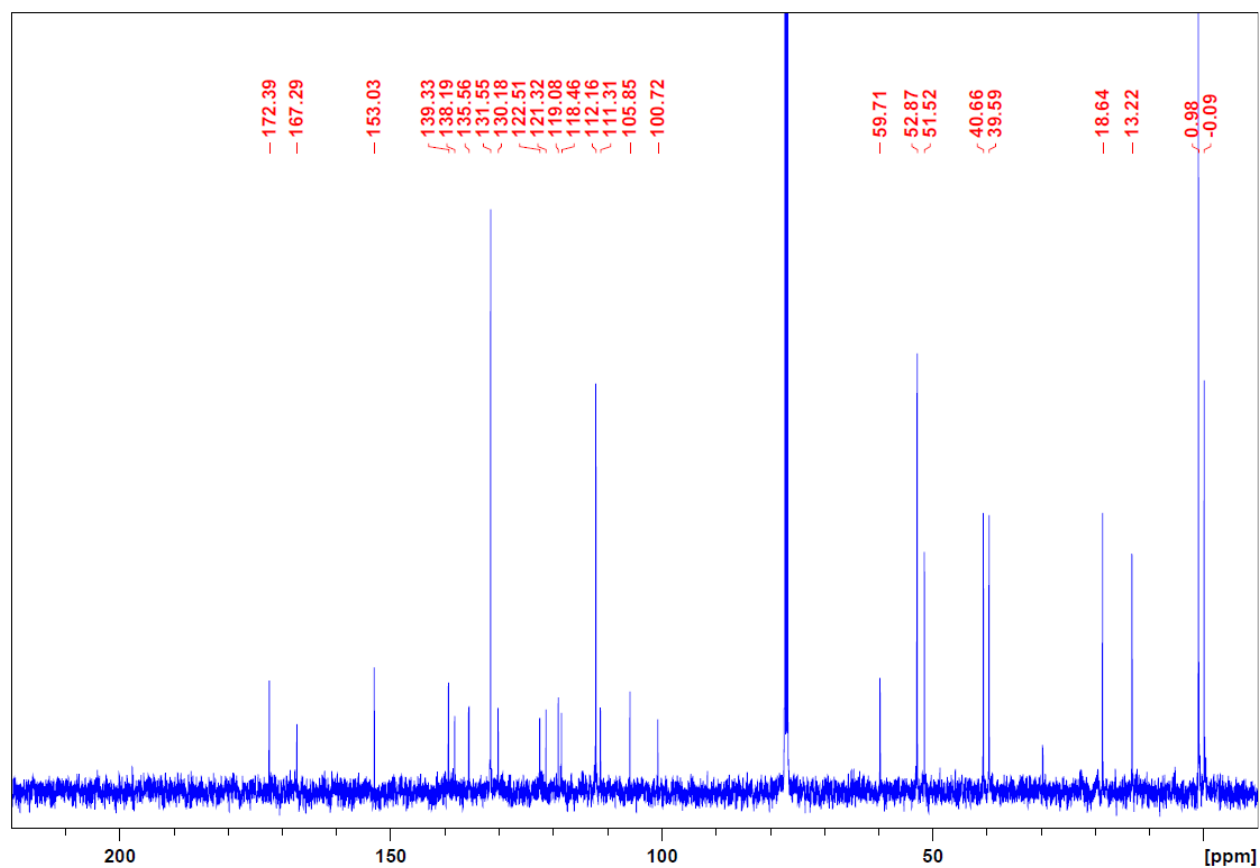
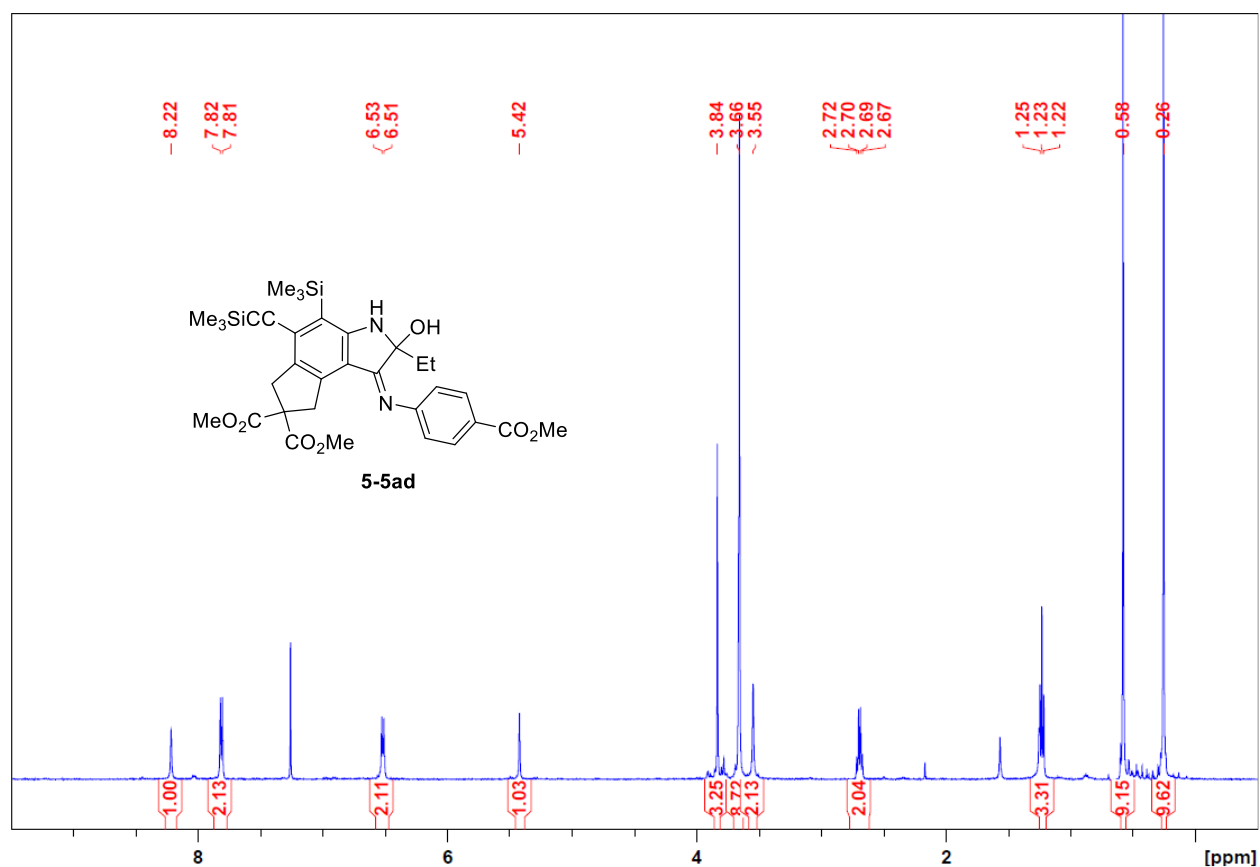


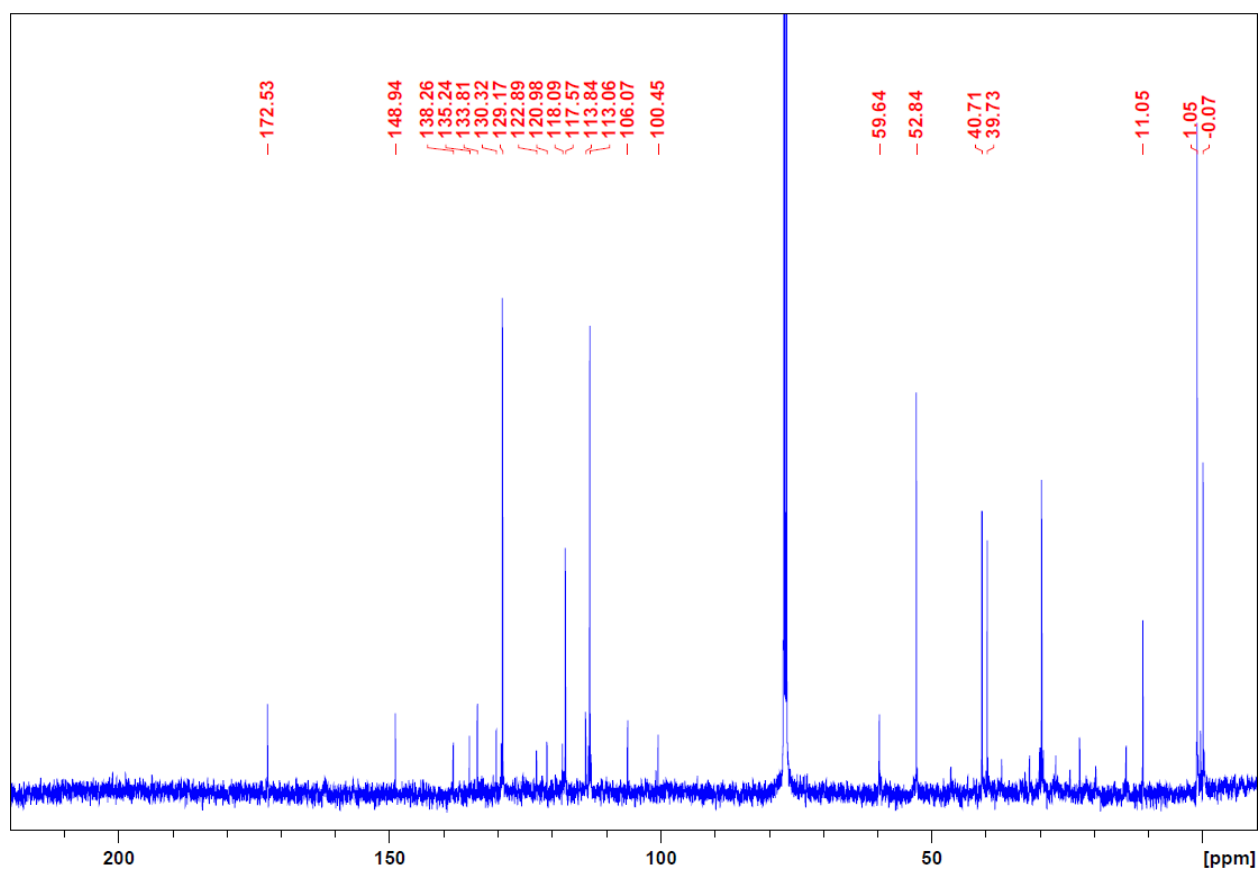
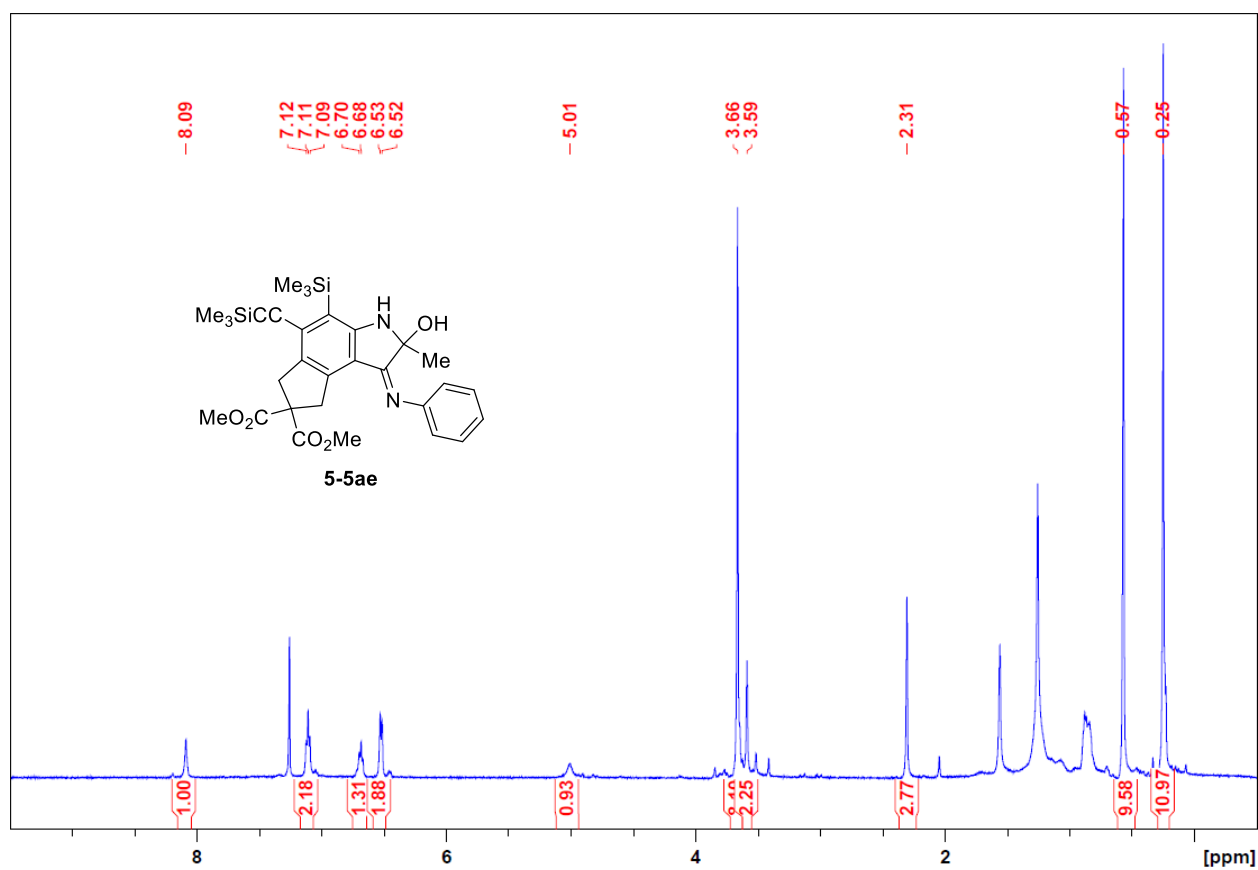
Appendix IV
Selected NMR Spectra for Chapter 5

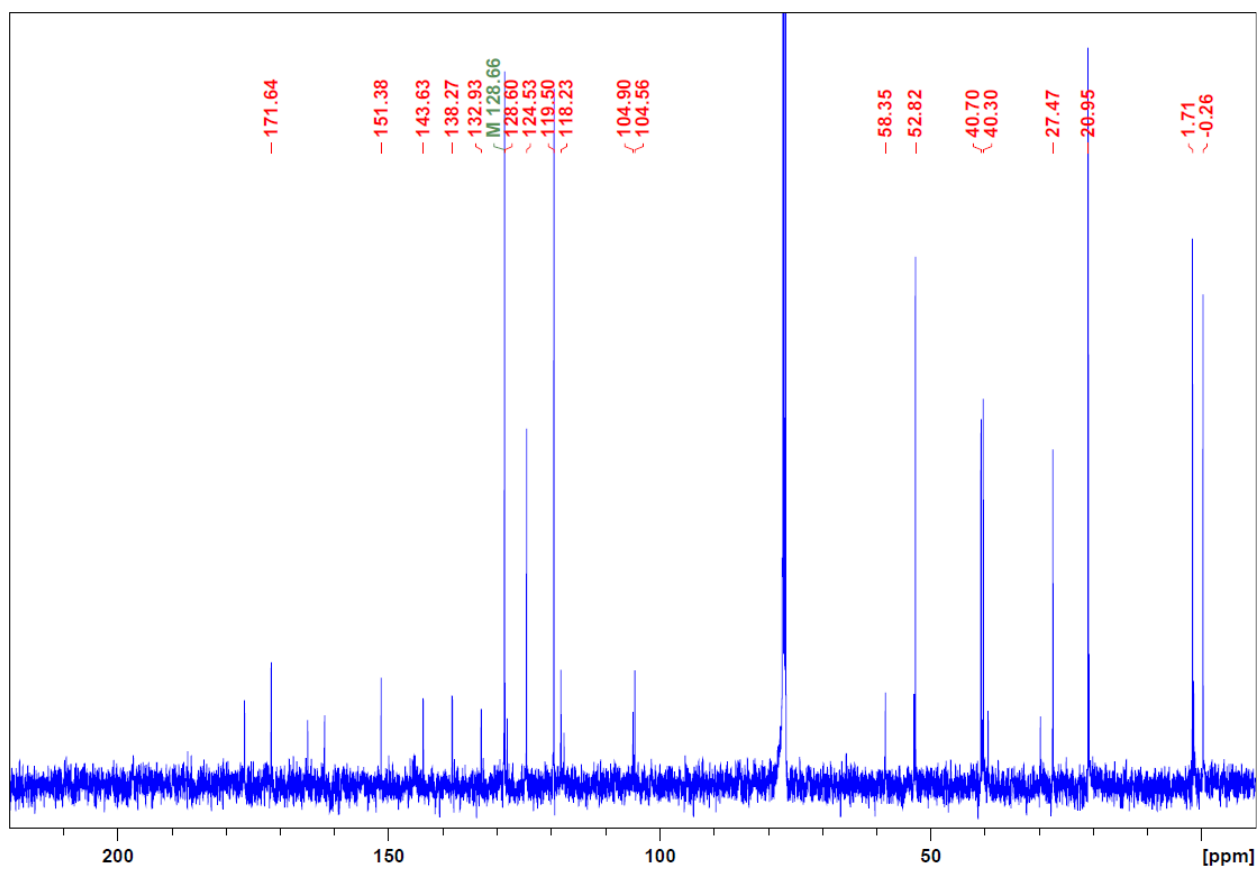
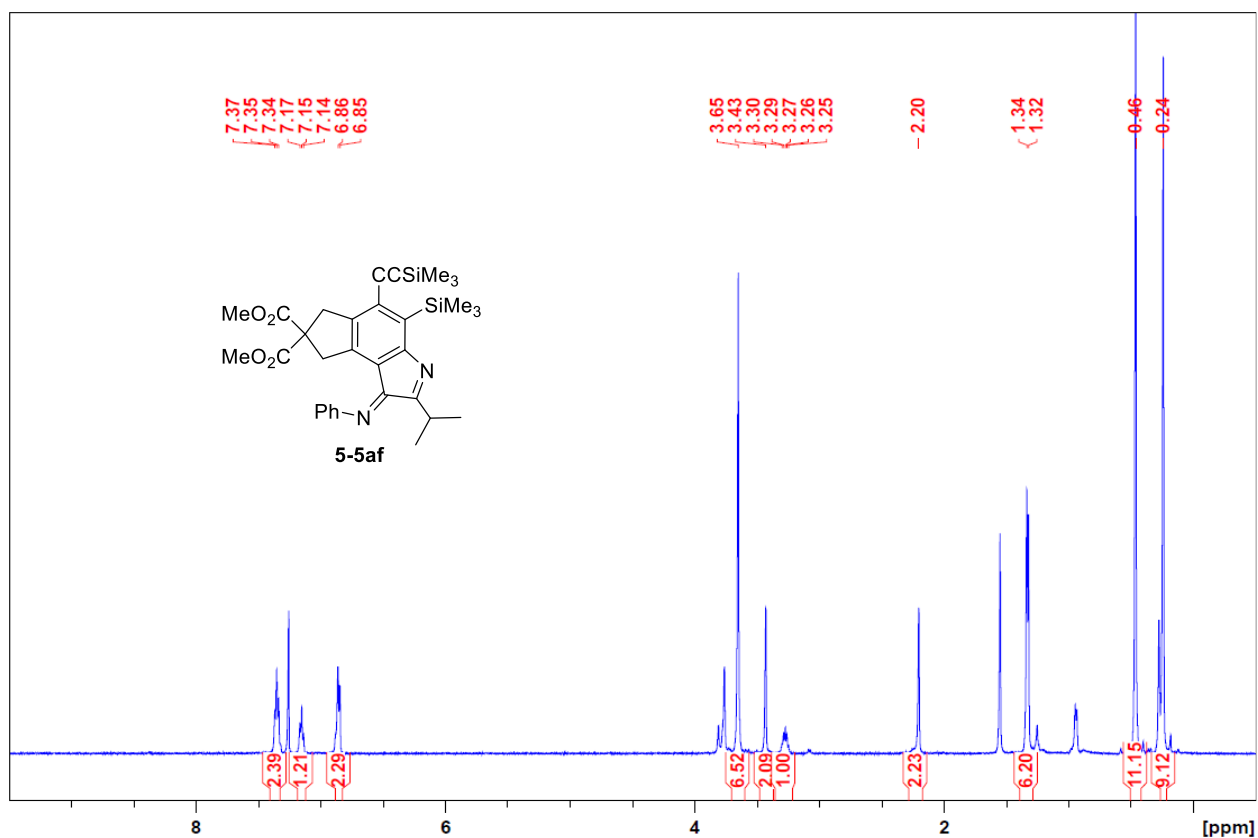


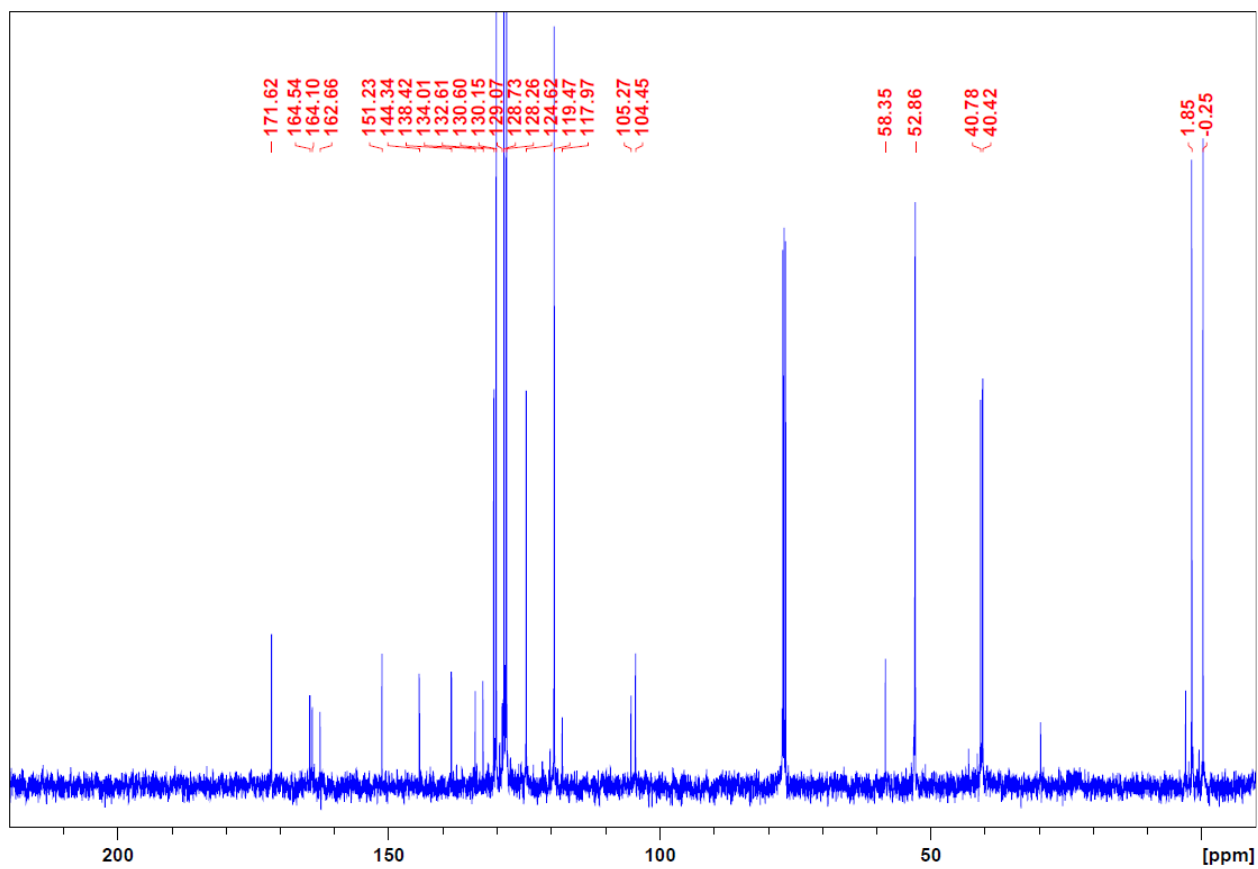
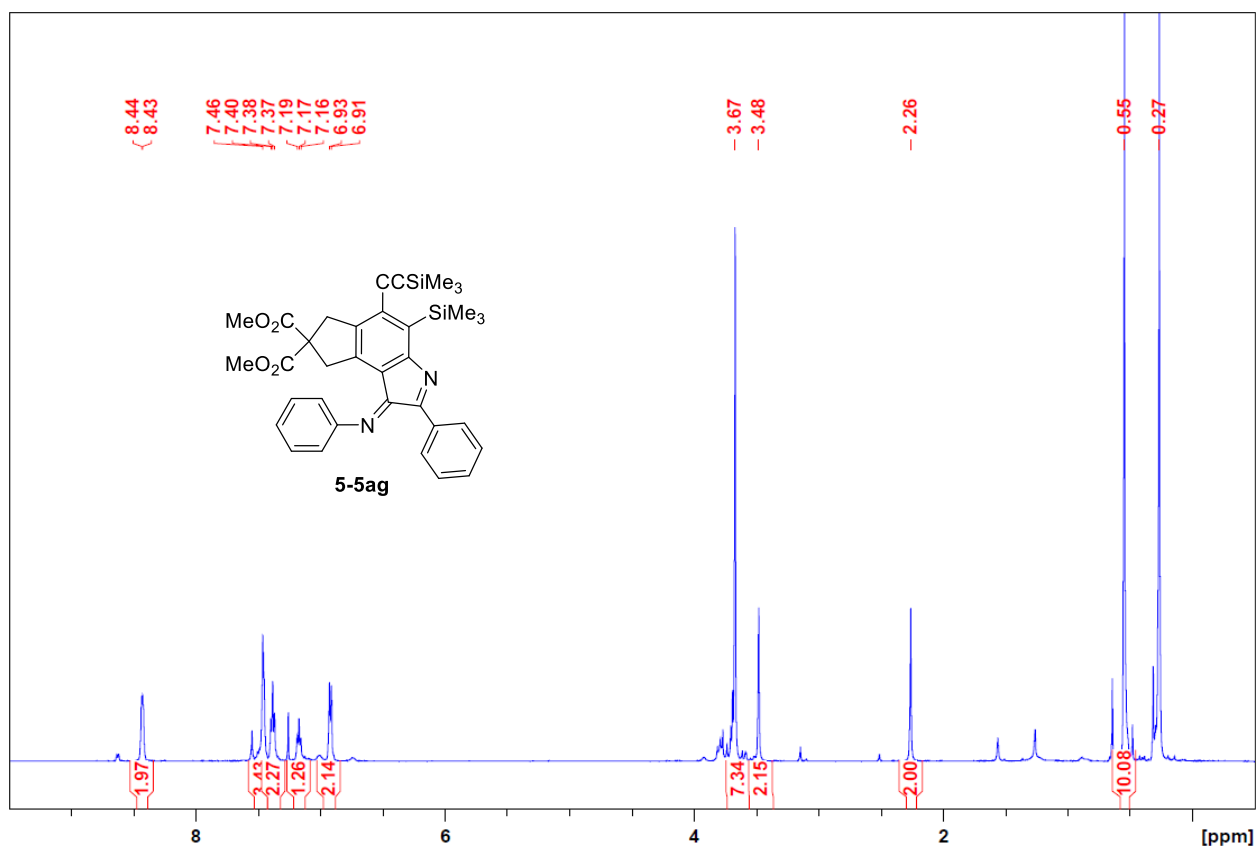


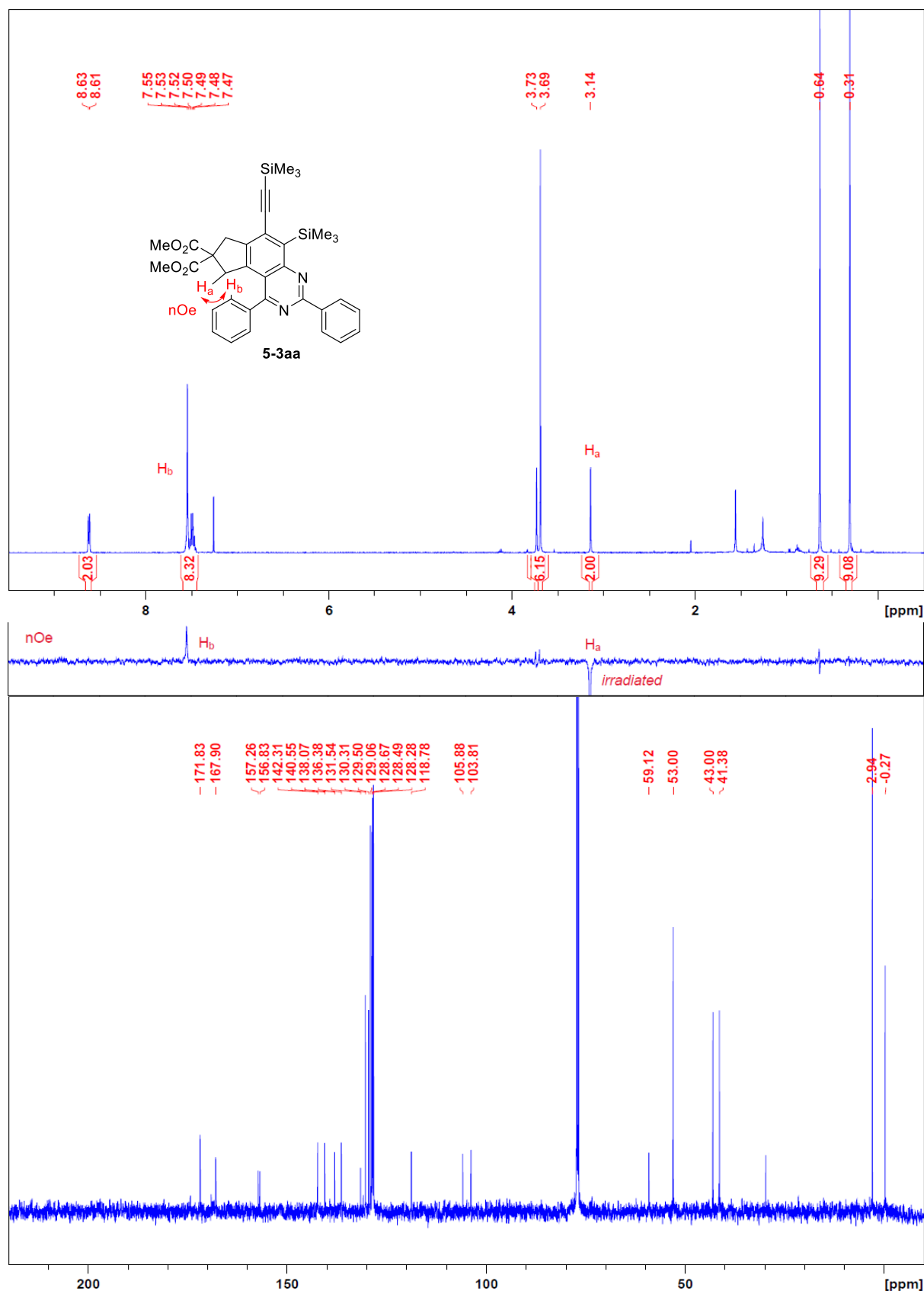


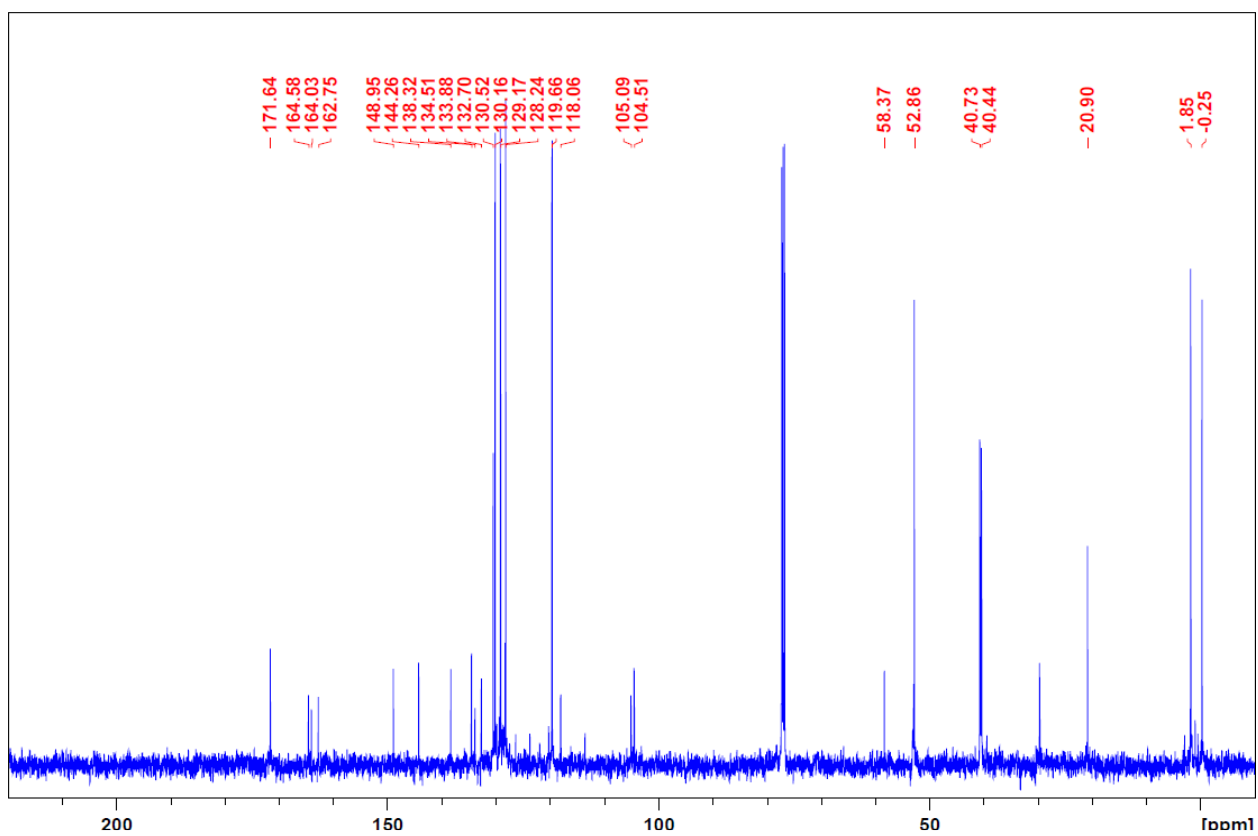
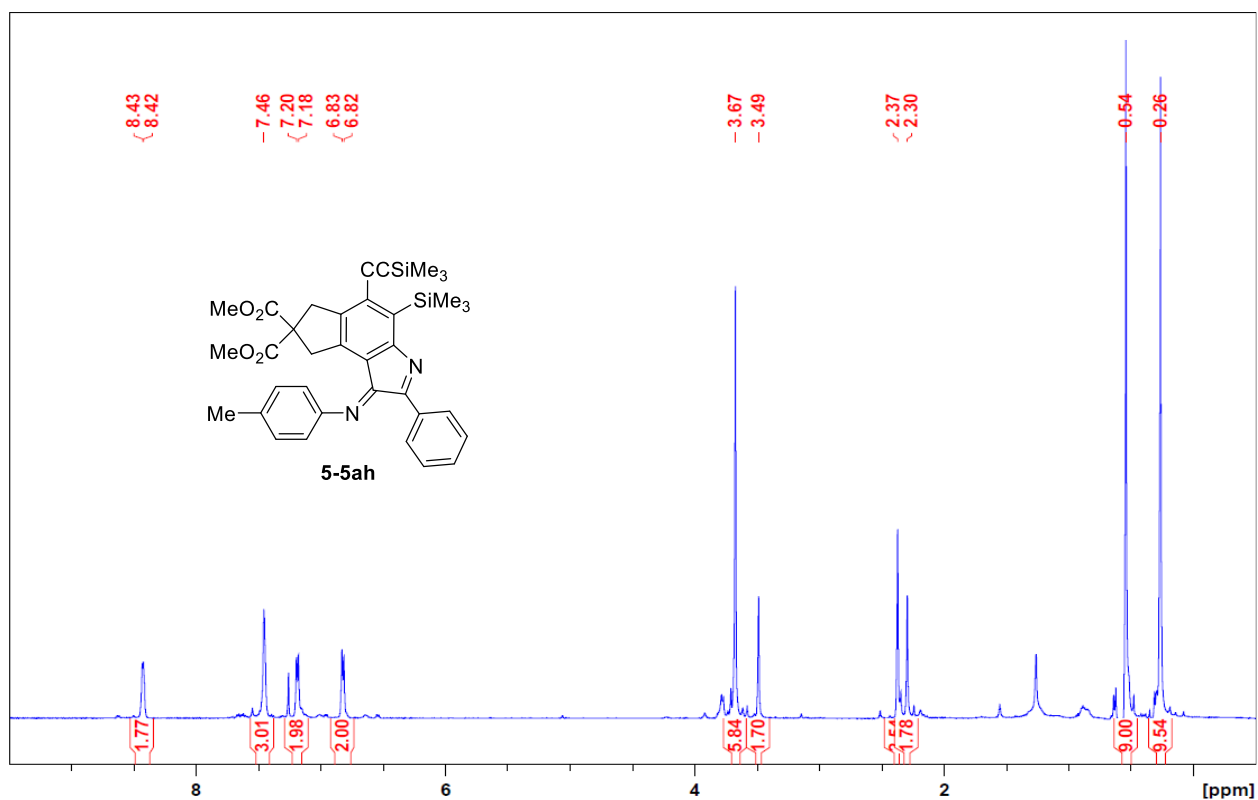


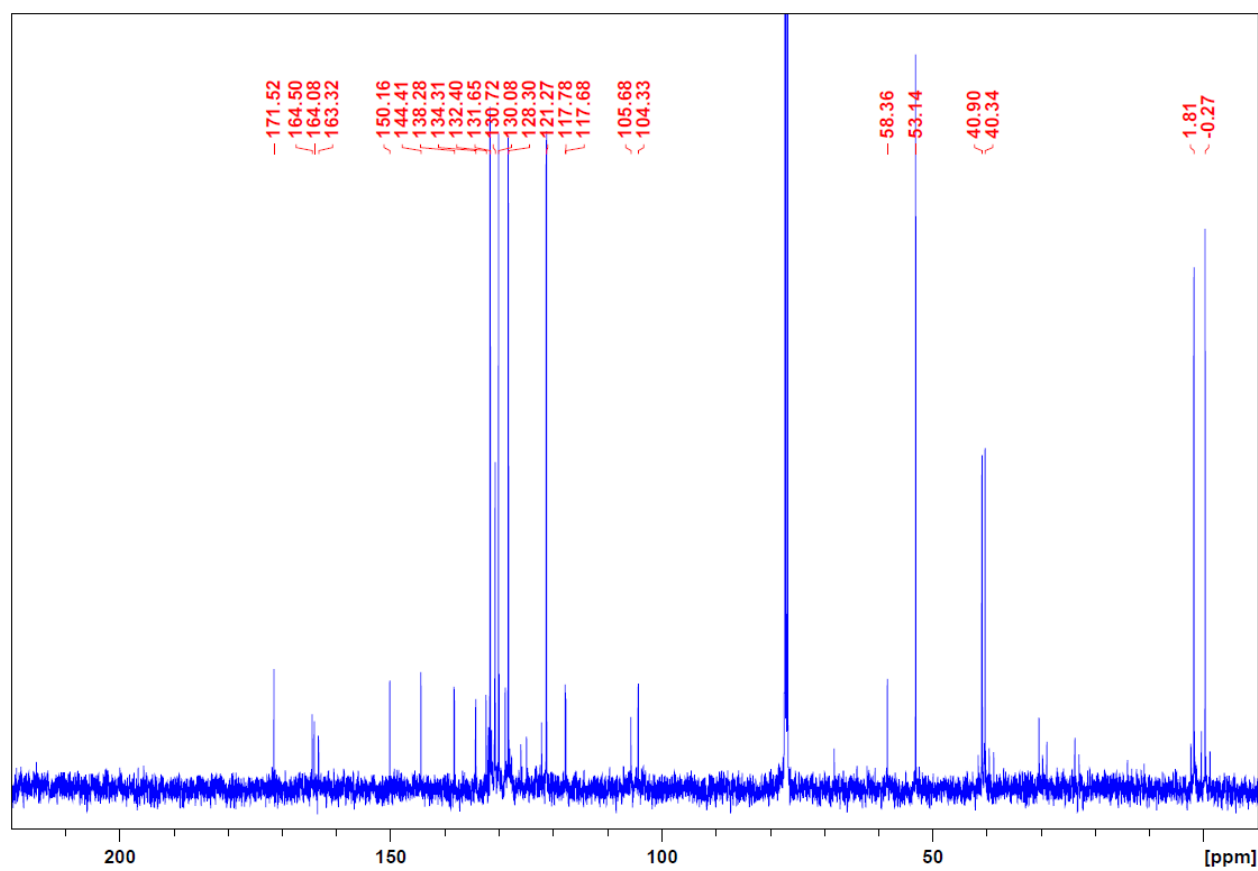
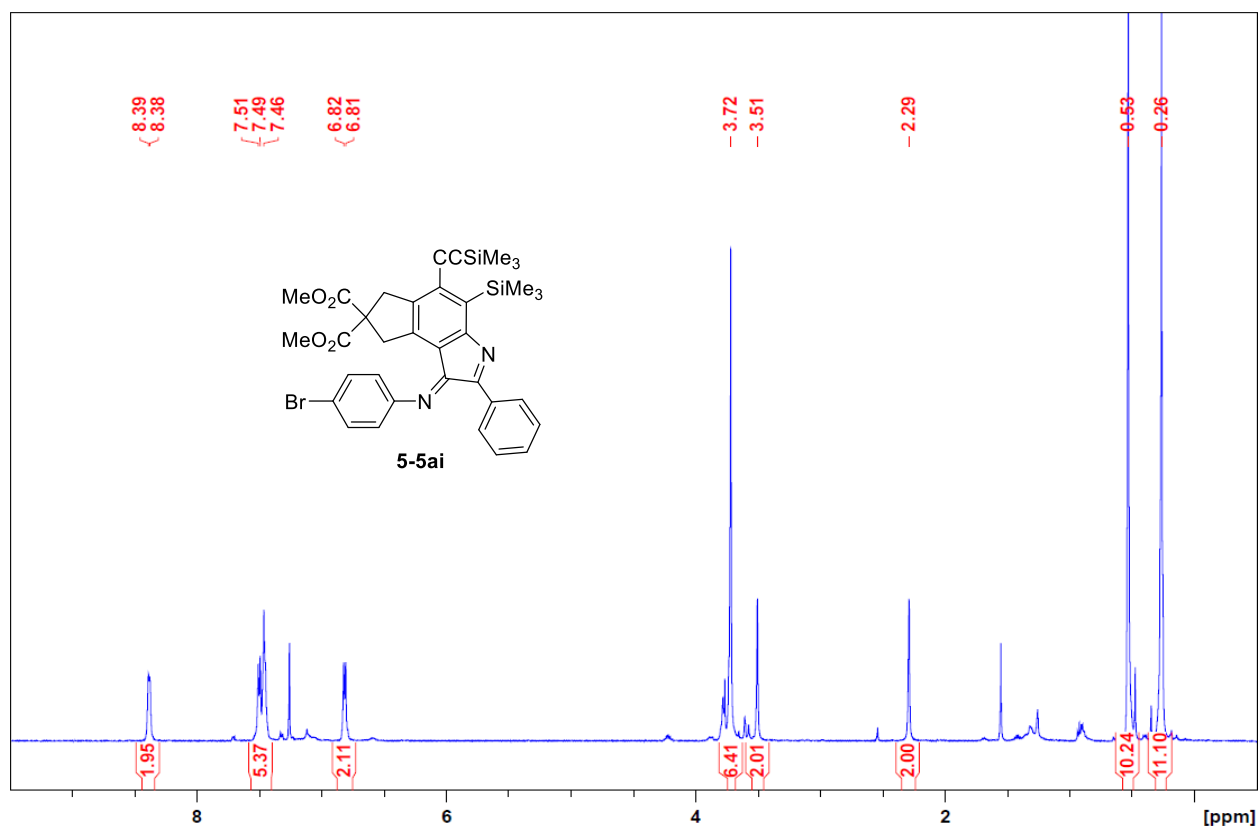


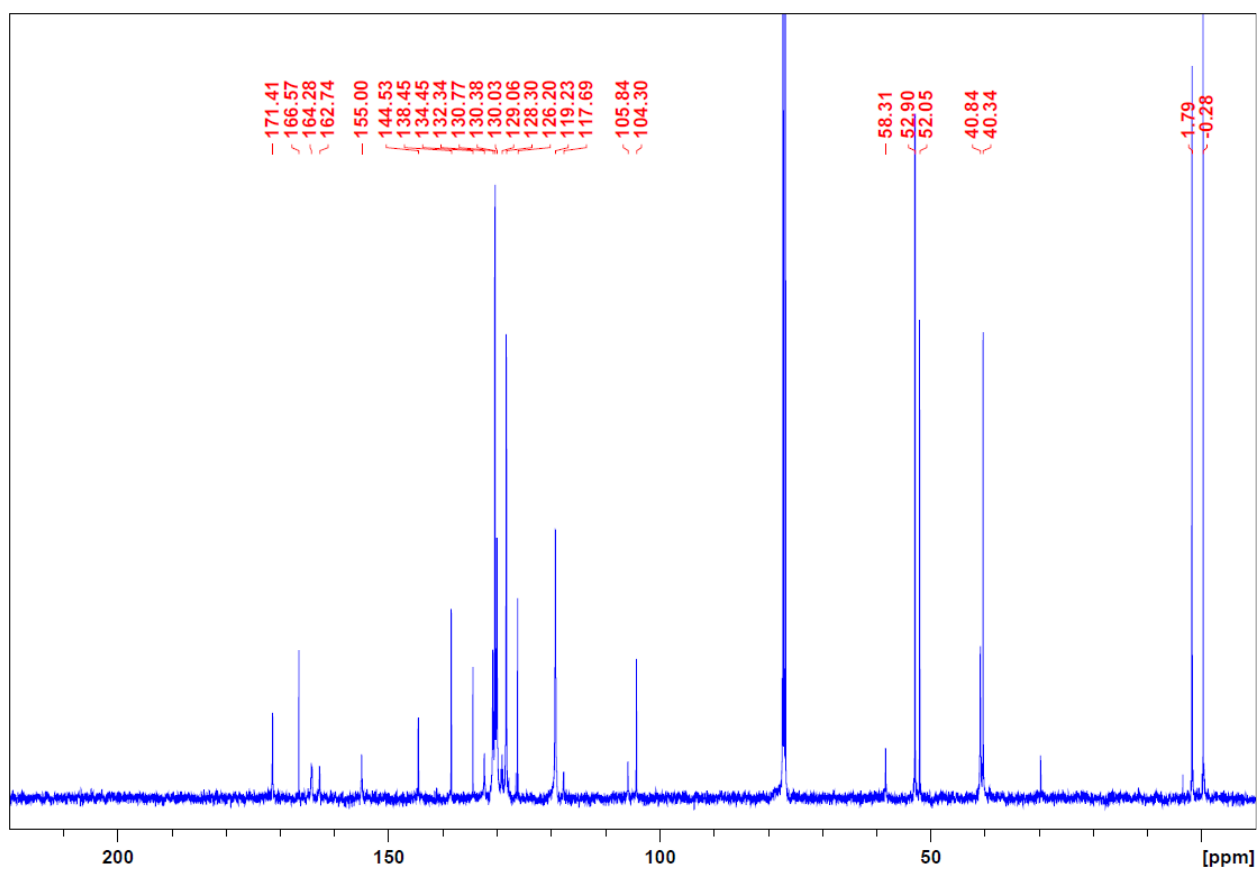
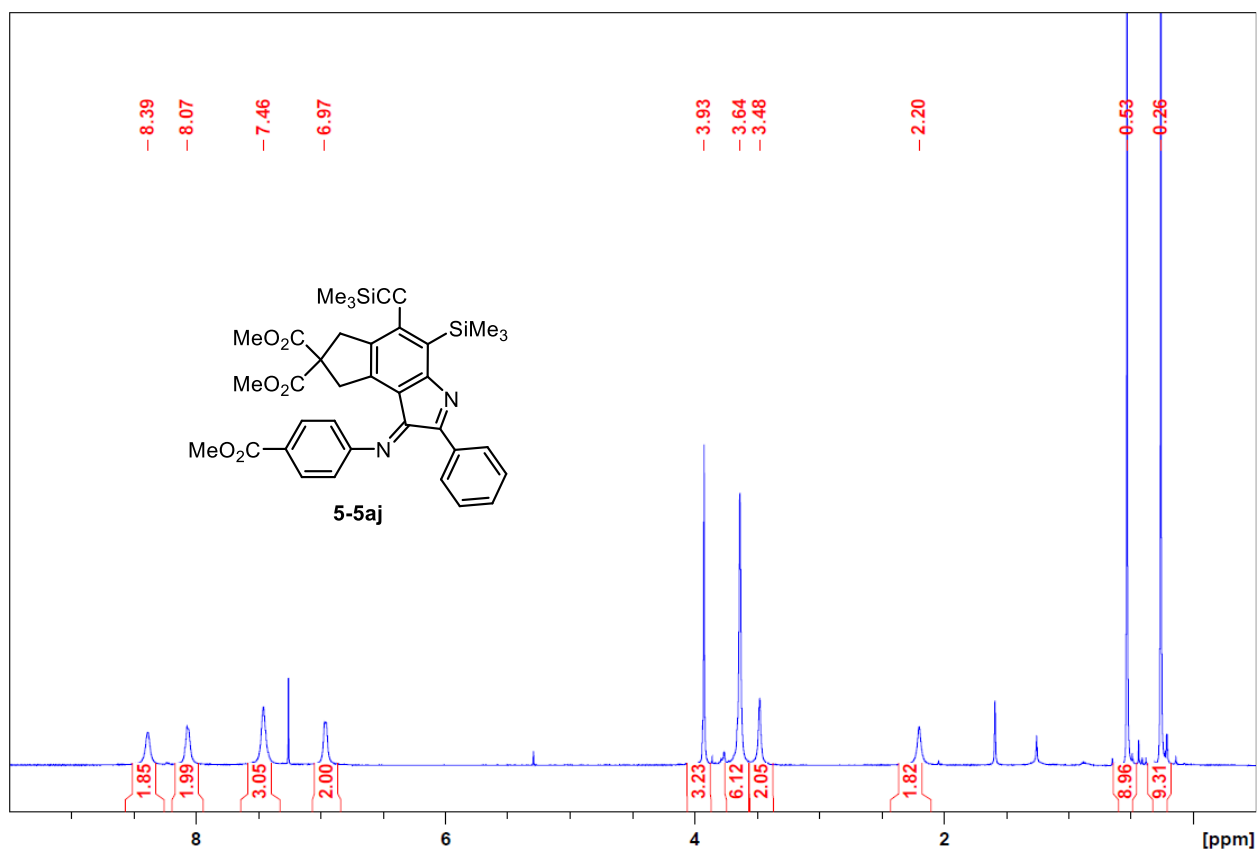


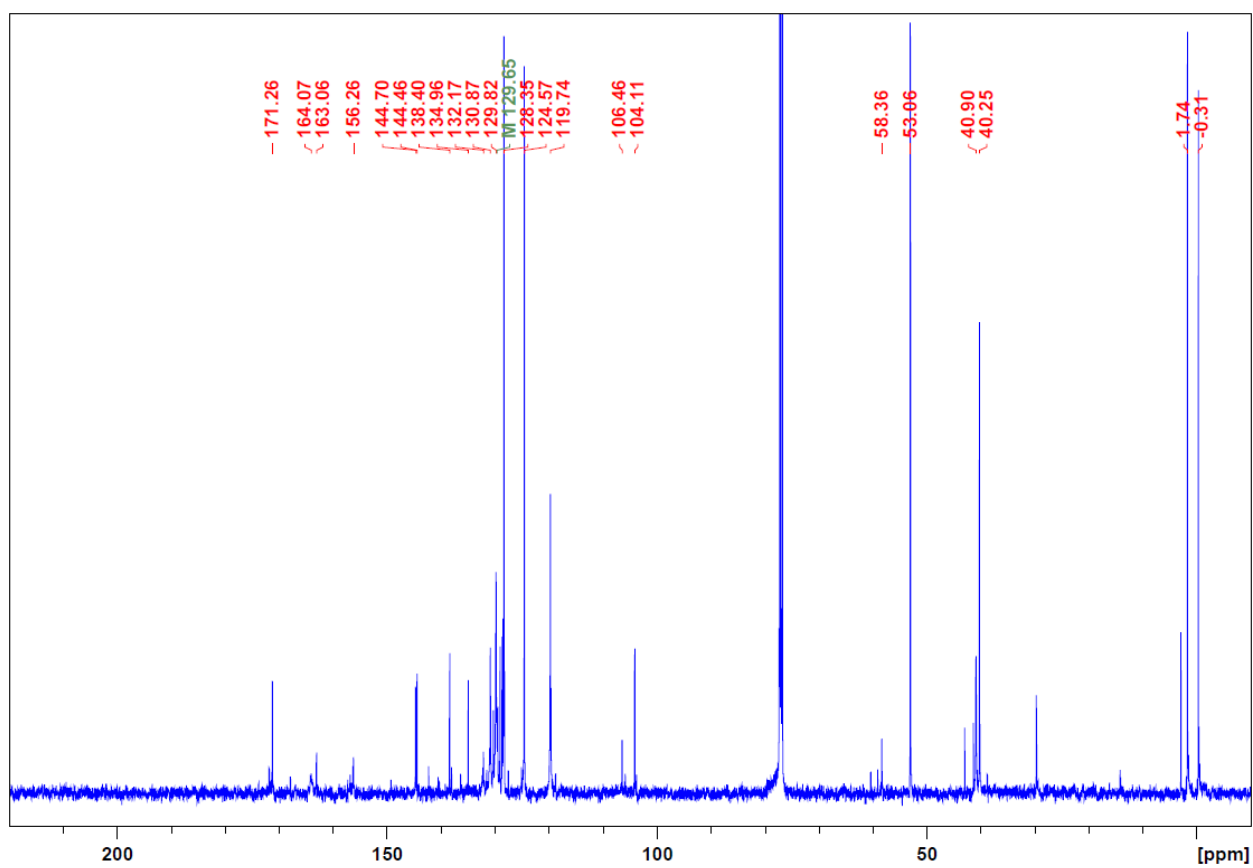
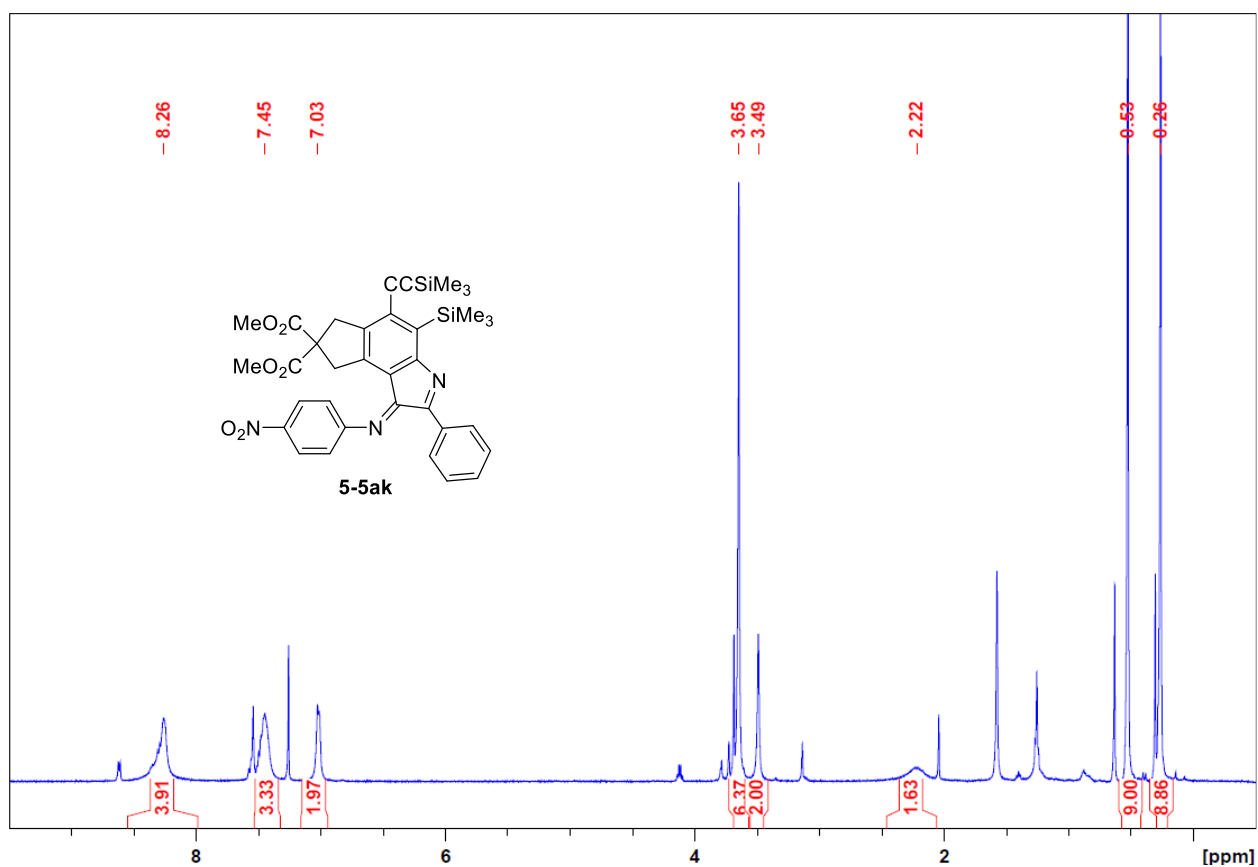


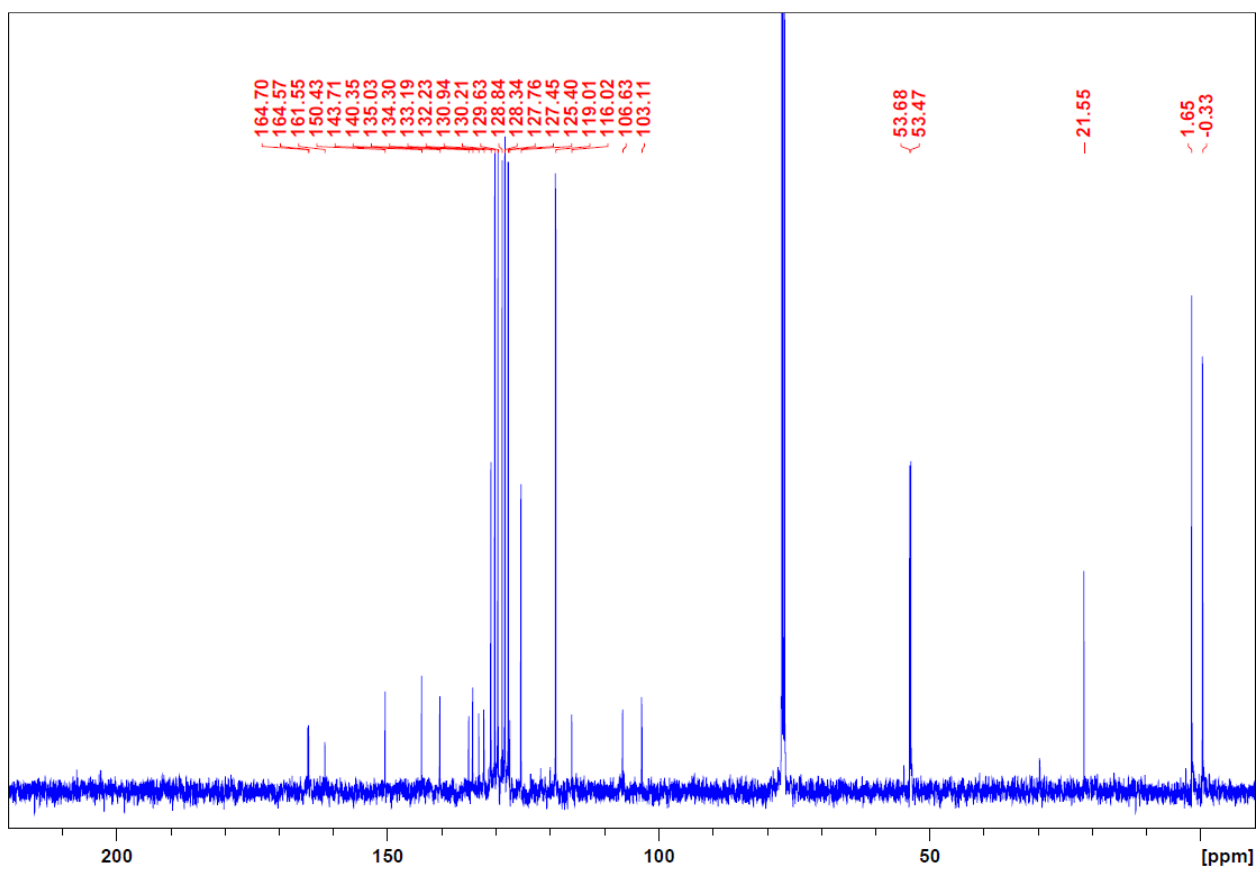
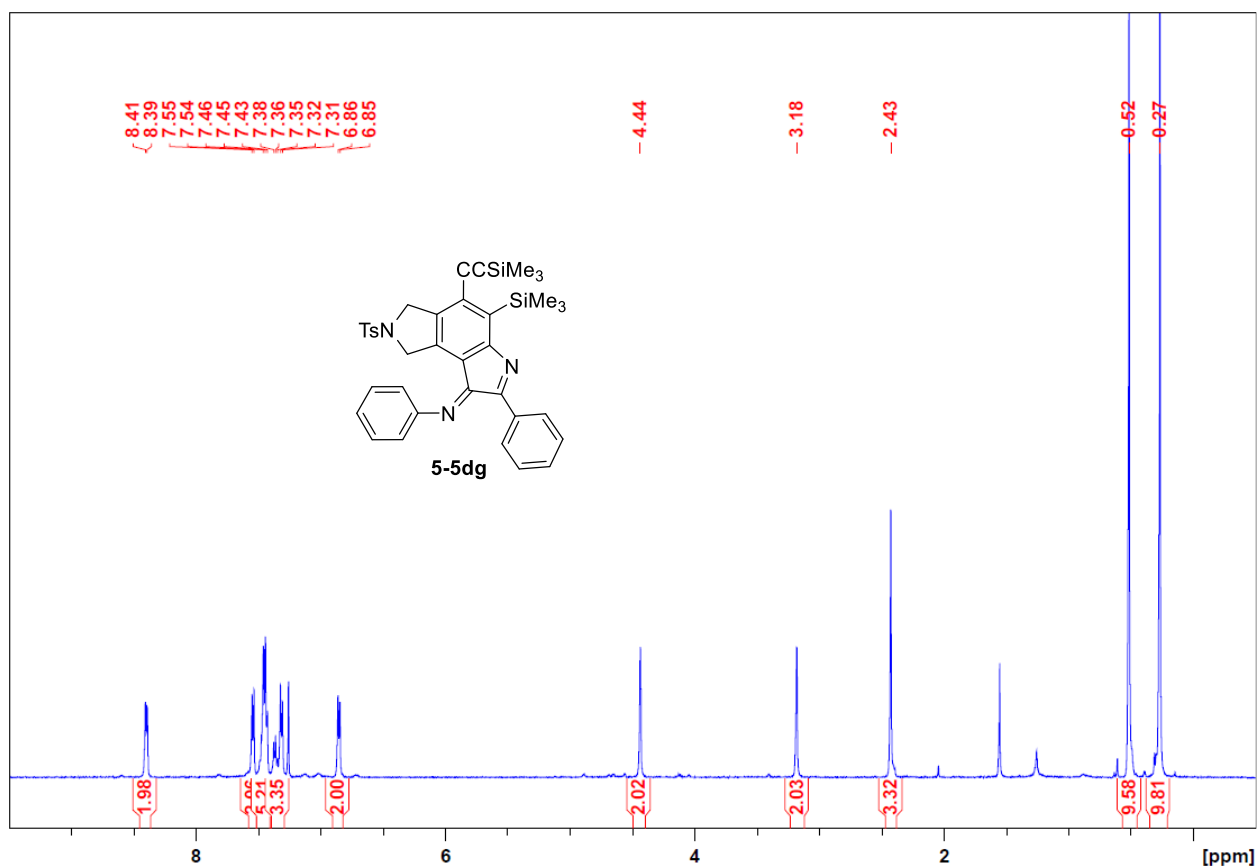


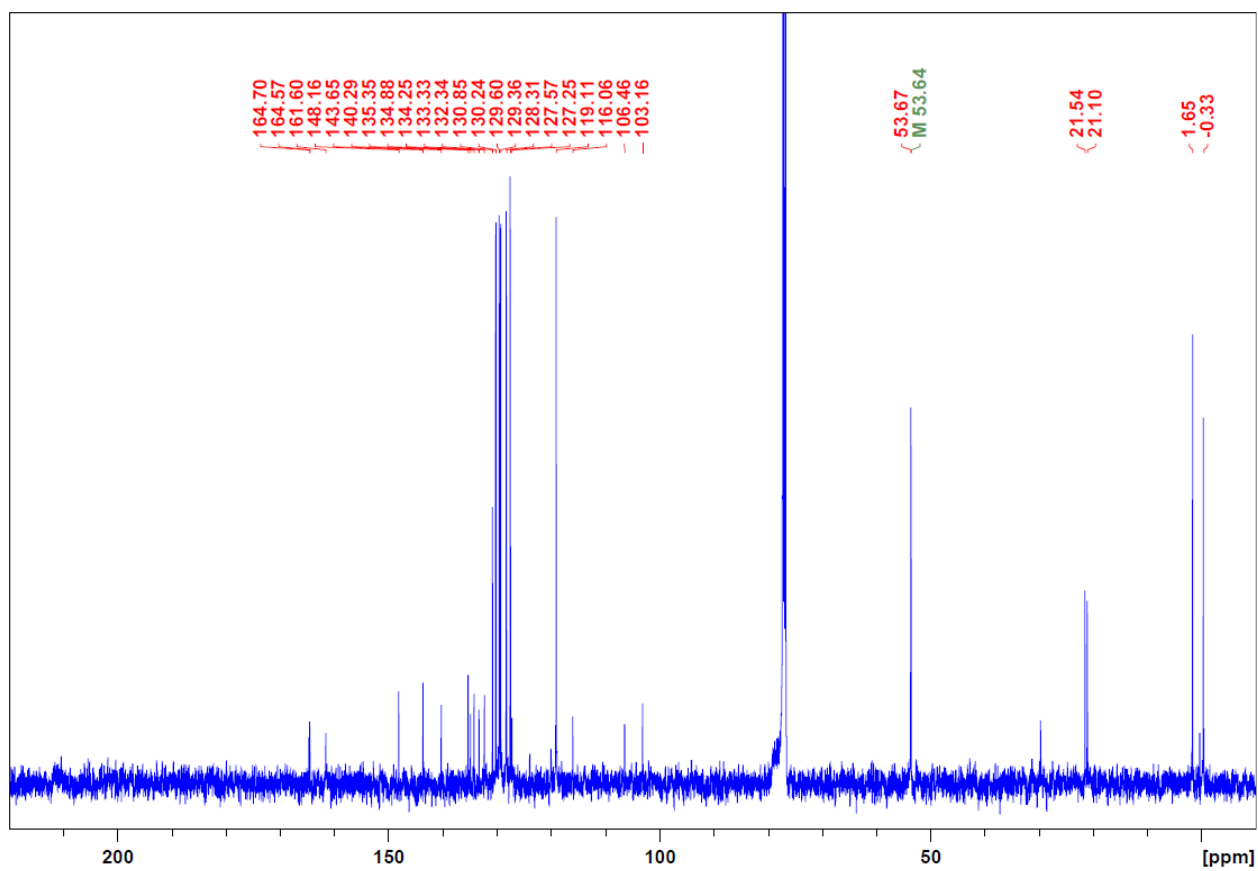
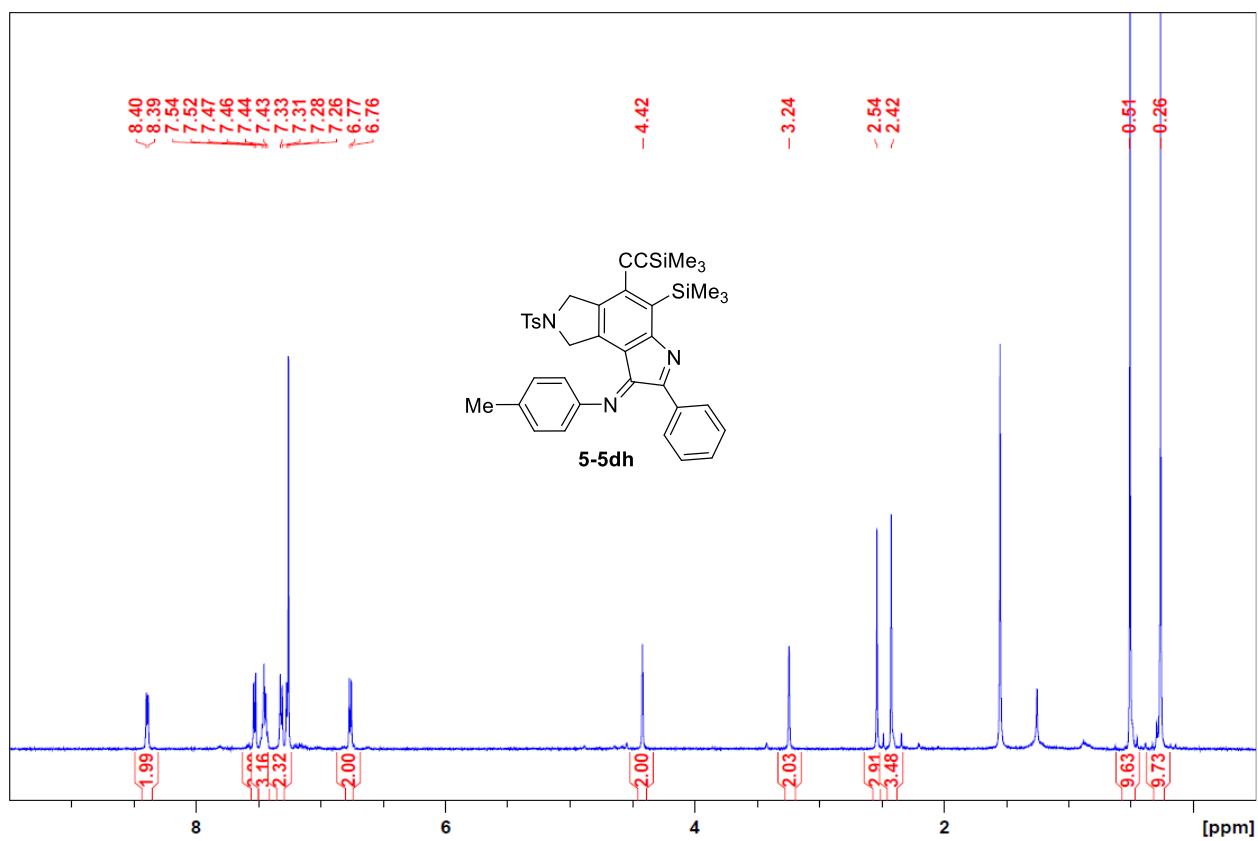


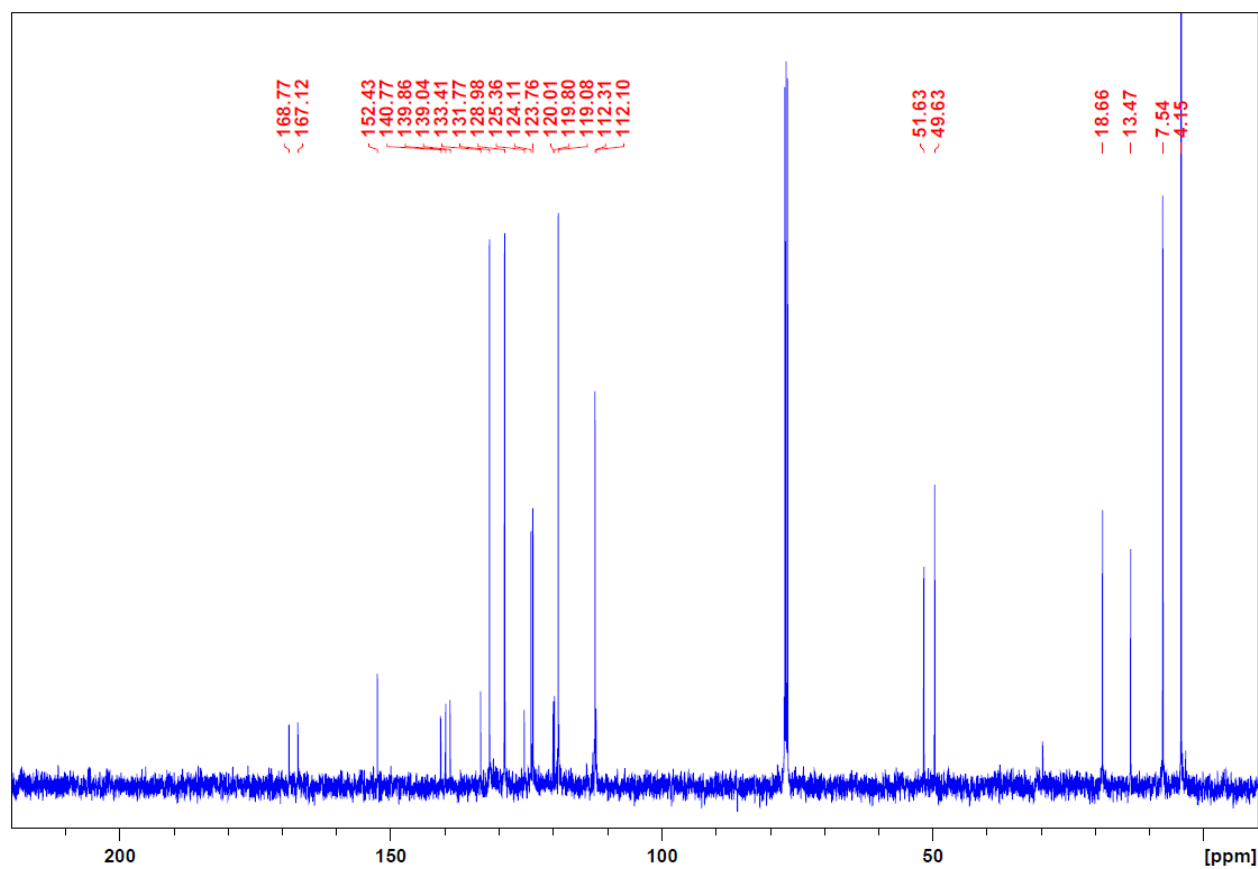
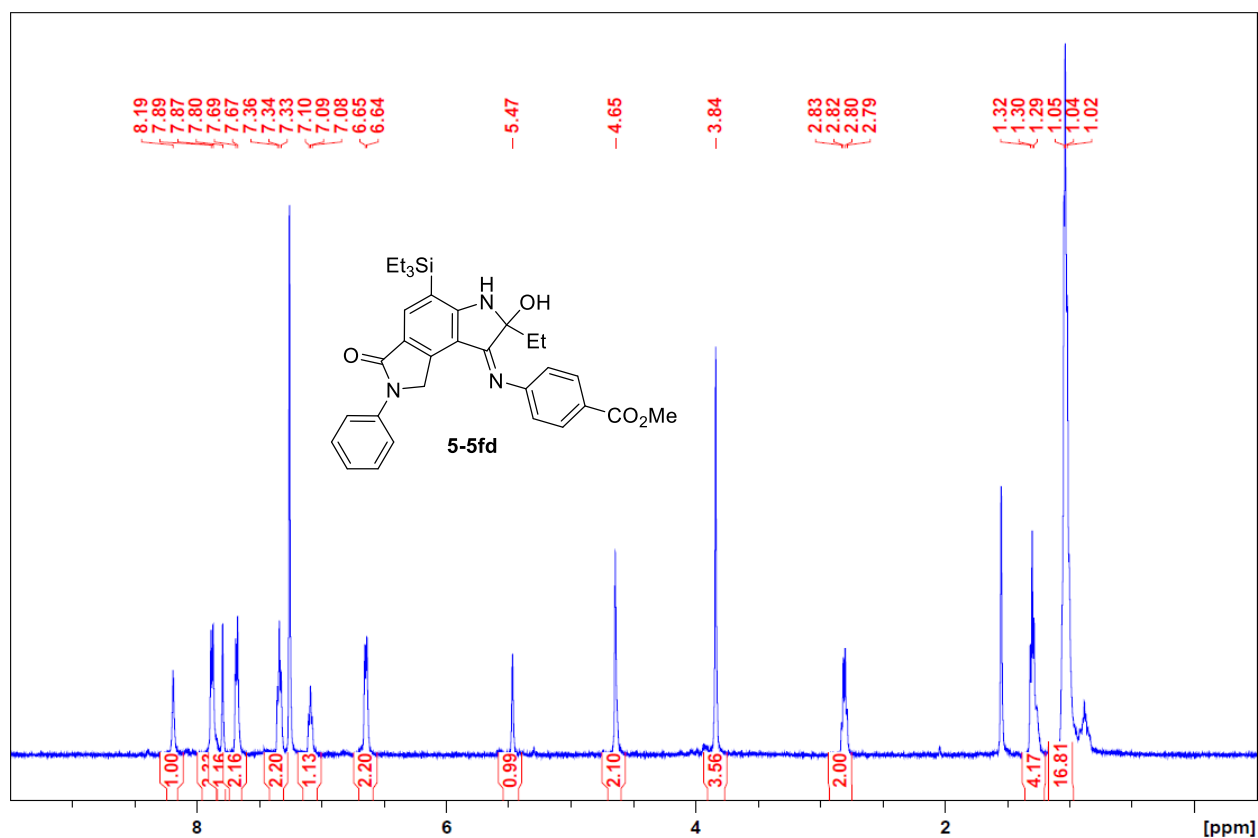


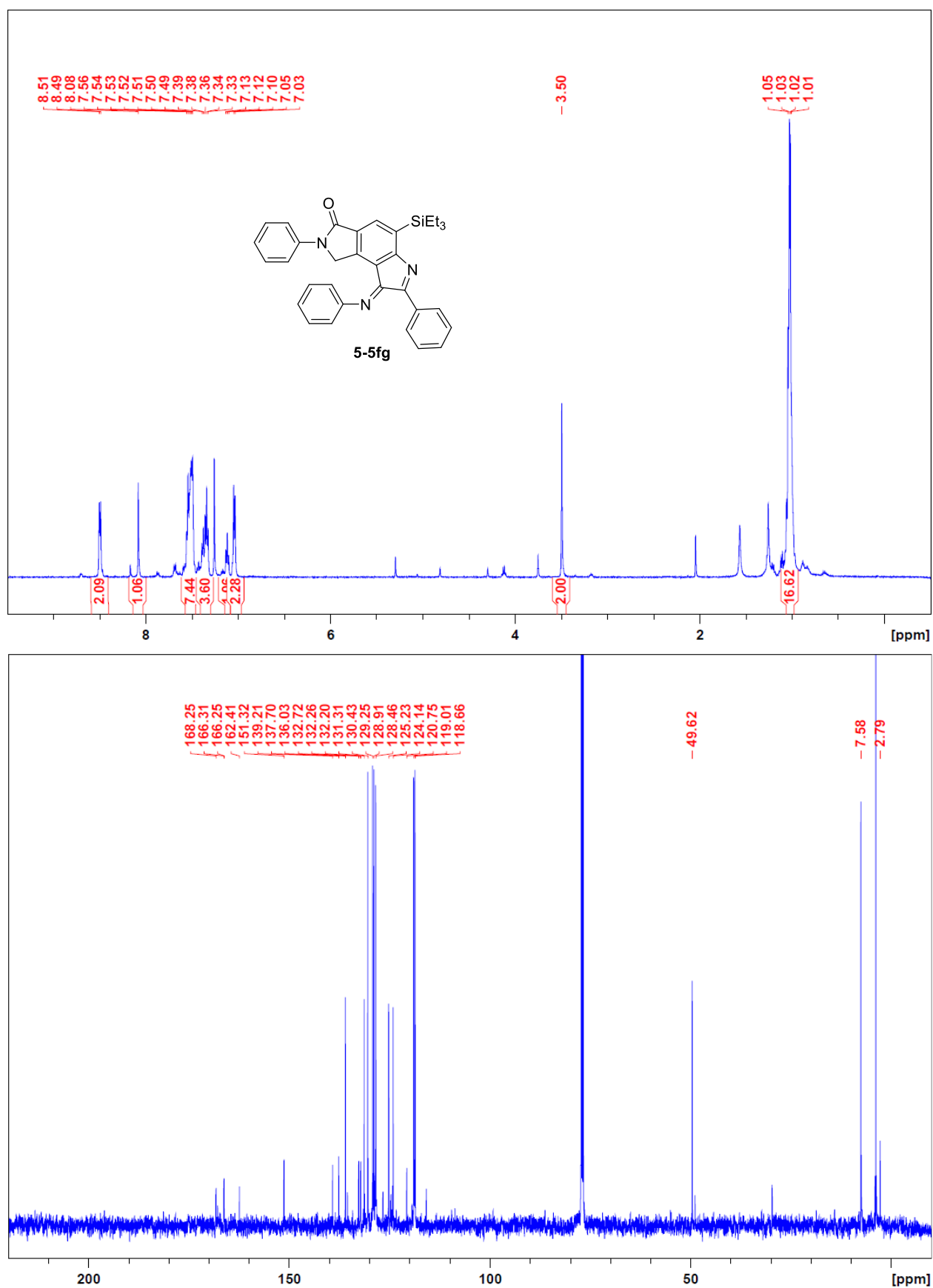






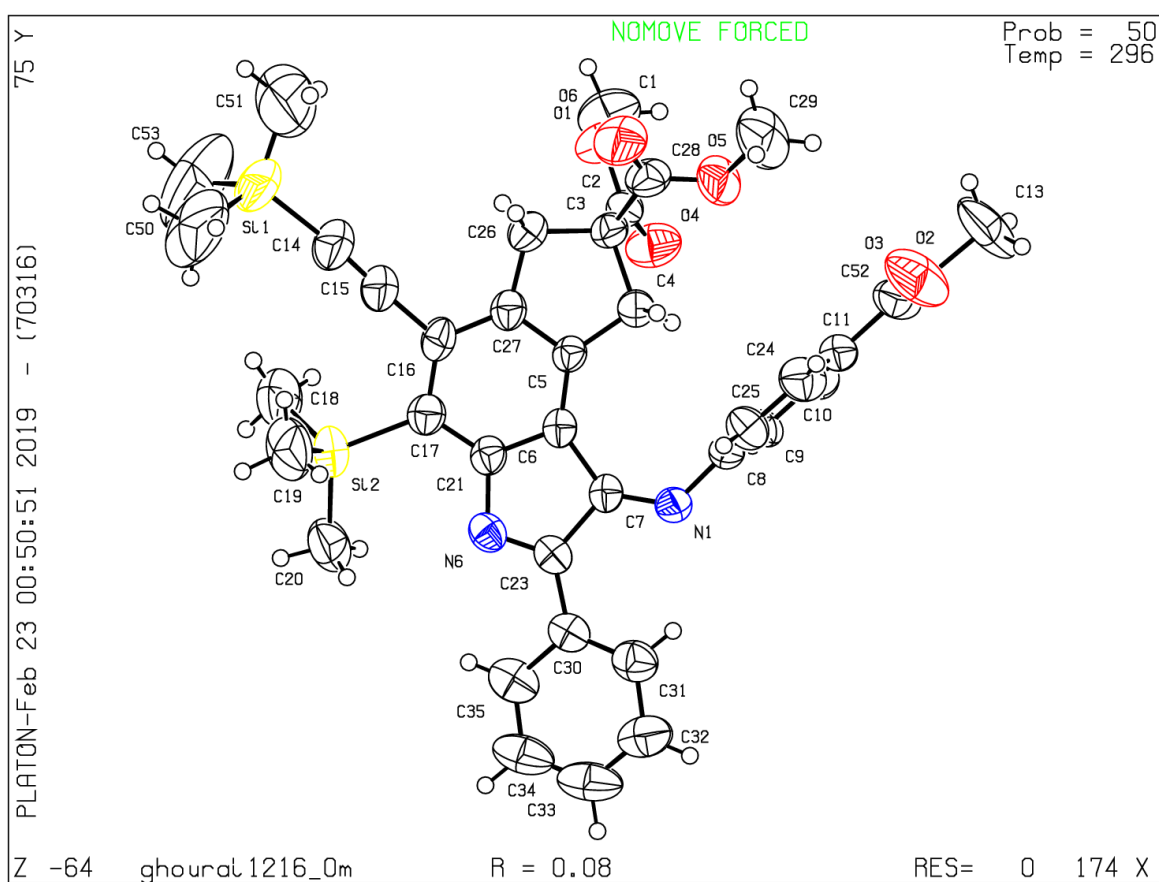
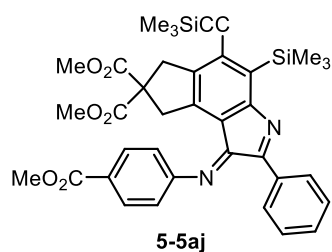






X-Ray Structures of Quinazoline 5-5aj

CCDC 1911067 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif



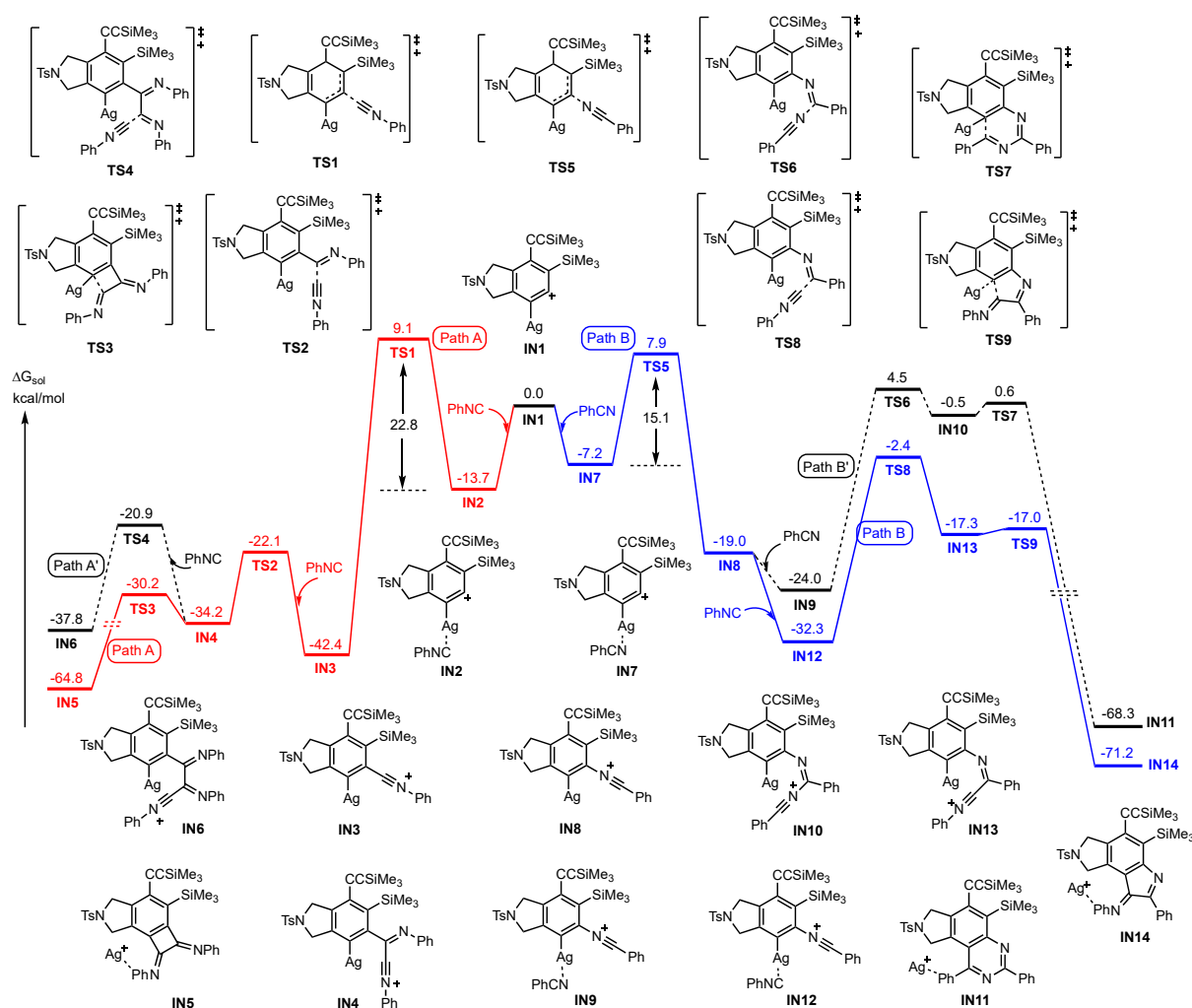
Computational Details

All DFT calculations were carried out with the Gaussian 09 suite of computational programs.^[1] The geometries of all stationary points were optimized using the B3LYP hybrid functional^[2]. The 6-31G(d) basis set was applied for all atoms except Ag, which was described by the LanL2DZ basis set and effective core potential implemented. Frequencies were analytically computed at the same level of theory to obtain the free energies and to confirm whether the structures are minima (no imaginary frequency) or TS (only one imaginary frequency). The solvation effect was examined by performing single-point self-consistent reaction field (SCRF) calculations based on the SMD solvation model for gas-phase optimized structures. PhCH₃ and PhCN were used as solvents, corresponding to the original experimental conditions. All SCRF calculations were done at the M06 level by using a larger basis set of SDD for Ag and 6-311++G(d,p) for the rest elements. All TS were confirmed to connect the proposed reactants and products by intrinsic reaction coordinate calculations. All energies are relative free energies corrected with solvation effects.

[1] Gaussian 09, Revision D.01, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, Jr. J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J.; Gaussian, Inc., Wallingford CT, 2009.

[2] Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215; *Acc. Chem. Res.* **2008**, *41*, 157.

Computational Details



Starting from the be intermediate **IN1**, the reaction with PhNC in toluene solution follows the Path D to generate **IN3** and **IN4**. The latter intermediate undergoes the intramolecular cyclization via Path B easily, while the incorporation of another PhNC via Path B' is unfavorable in both kinetic and thermodynamic aspects. When the reaction was carried out in nitrile solution containing excess PhNC, the reaction follows Path C to form **IN8**, which could be captured by another PhCN to form **IN9** and undergoes cyclization to form product complex **IN11**. However, from **IN8**, the incorporation of PhNC forms **IN12** more favorably, from which cyclization occurs via **TS8** in Path D will finally form complex **IN14**. In this case, the formation of quinazoline would be inhibited due to the higher relative free energy of **TS6** compared with **TS8**.

Calculated Energy Values (in a.u.)

Table S1. Energies (in Hartree) calculated at SMD-M06/6-311++G(d,p)/SDD//B3LYP/6-31G(d)/LANL2DZ

Species	G ₂₉₈ ^a	E ^b	G _{Sol} ^c
IN1	-2221.303242	-2221.6892597	-2222.49967543
IN2	-2545.743222	-2546.2166266	-2546.83962575
TS1	-2545.683442	-2546.1569371	-2546.80341308
IN3	-2545.767367	-2546.24777	-2546.89235245
TS2	-2870.124417	-2870.6942505	-2871.18012438
IN4	-2870.140514	-2870.7132188	-2871.20224631
TS3	-2870.127935	-2870.7001397	-2871.19537256
IN5	-2870.195431	-2870.7742634	-2871.25719761
TS4	-3194.505318	-3195.1666689	-3195.50042945
IN6	-3194.53696	-3195.2032204	-3195.53218143
IN7	-2545.768723	-2546.2382366	-2546.86137157
TS5	-2545.717761	-2546.1909057	-2546.84089336
IN8	-2545.762602	-2546.2428241	-2546.89097255
IN9	-2870.213261	-2870.7805772	-2871.2526512
TS6	-2870.151831	-2870.7223625	-2871.21046332
IN10	-2870.162116	-2870.7362036	-2871.22194566
TS7	-2870.151587	-2870.72675	-2871.22136809
IN11	-2870.269461	-2870.8526612	-2871.33920379
IN12	-2870.193653	-2870.7604644	-2871.22938983
TS8	-2870.131274	-2870.700824	-2871.18447739
IN13	-2870.157202	-2870.7315146	-2871.21296527
TS9	-2870.155025	-2870.7292171	-2871.2123423
IN14	-2870.246841	-2870.8282164	-2871.3059746
PhCN	-324.423046	-324.4922181	-324.335911402
PhNC	-324.38947	-324.4578961	-324.299123233

^a Sum of electronic and thermal free energies

^b Electronic energies

^c Single point energies in solution

Cartesian Coordinates

IN1

C	-3.25978100	0.67779300	-0.33584100
H	-3.82799900	1.59204000	-0.53427800
H	-3.89874800	-0.18776000	-0.58629300
C	-1.41374700	0.11066200	1.16604400
H	-0.83639700	0.67554400	1.90291500
H	-1.40232900	-0.95032600	1.46631500
C	-1.95866600	0.60628500	-1.09997600
C	-0.90127700	0.27256600	-0.24244600
C	-1.74361500	0.82446300	-2.49774100
C	0.42969000	0.12454100	-0.69116700
C	-0.45717600	0.62370500	-2.63114700
C	1.46511200	-0.21648400	0.21327700
C	0.72664500	0.33352700	-2.11240500
C	2.31577200	-0.50990600	1.04253500
Si	2.45082600	0.22331000	-2.99916200
C	3.56139300	1.51112800	-2.19957700
H	4.55885700	1.46819200	-2.65478300
H	3.17367700	2.52524700	-2.34675800
H	3.67570100	1.34072700	-1.12472500
C	2.09254000	0.62869300	-4.80514900
H	1.39840300	-0.08928700	-5.25856700
H	1.67968300	1.63757000	-4.92593700
H	3.02027400	0.59012800	-5.38848400
C	3.06545400	-1.54090900	-2.78861500
H	3.16214400	-1.81542100	-1.73368300
H	2.39627000	-2.26208300	-3.27086500
H	4.05359700	-1.64260500	-3.25457300
Si	3.57854600	-0.95116100	2.35072600
C	5.10896500	0.10389000	2.03400300
H	5.54183400	-0.09333600	1.04676700
H	4.88370700	1.17417800	2.09987600
H	5.87928200	-0.11840200	2.78254500
C	2.79895700	-0.56410100	4.02190200
H	1.88971200	-1.15174000	4.19045300
H	3.50157300	-0.80159000	4.82999100
H	2.53805100	0.49627500	4.11059500
C	3.95289400	-2.79017800	2.16337500
H	3.05359500	-3.40159900	2.29690400
H	4.37646900	-3.02050700	1.17933100
H	4.68289700	-3.10371600	2.91964800
Ag	-3.11551700	1.42200900	-4.01341400
N	-2.77591300	0.66114400	1.04851200
S	-3.86938900	0.53502500	2.32603400
O	-5.01275300	1.34600600	1.90838200
O	-3.07719600	0.80669500	3.52342100
C	-4.38991500	-1.17572200	2.37996400
C	-5.50747500	-1.58214600	1.64380100
C	-3.66652200	-2.09266000	3.14990000
C	-5.88875600	-2.92236000	1.67356000
H	-6.08709800	-0.85102200	1.09004500
C	-4.06411000	-3.42783100	3.16541100
H	-2.82964300	-1.75446200	3.75181700
C	-5.17720200	-3.86513600	2.43092200
H	-6.76379100	-3.23942800	1.11196800

H	-3.51005000	-4.14078100	3.77062100
C	-5.62297400	-5.30591800	2.49089600
H	-4.77395900	-5.98384900	2.62513100
H	-6.30379900	-5.46621600	3.33698500
H	-6.15759700	-5.60034100	1.58242400

IN2

C	-3.26596400	0.73069600	-0.32205900
H	-3.81985200	1.65269200	-0.52347600
H	-3.91888000	-0.12397600	-0.57089900
C	-1.42179500	0.16095800	1.18732400
H	-0.84423100	0.73589100	1.91635600
H	-1.40956400	-0.89530900	1.50305400
C	-1.96556700	0.63878000	-1.08369200
C	-0.91214800	0.30476200	-0.22345200
C	-1.75814900	0.84322300	-2.49017400
C	0.41664800	0.13861700	-0.67401100
C	-0.47846600	0.62715100	-2.61222200
C	1.45136000	-0.20571800	0.23337200
C	0.70941100	0.32915600	-2.09371900
C	2.30229200	-0.50229100	1.06047900
Si	2.41703000	0.19210700	-2.98901100
C	3.55999900	1.47011100	-2.21659600
H	4.55160900	1.40929800	-2.68221800
H	3.18477700	2.48852400	-2.36722500
H	3.68309400	1.30714500	-1.14145800
C	2.05621200	0.58528300	-4.79831000
H	1.35112600	-0.12879200	-5.24087200
H	1.65025800	1.59630500	-4.92445900
H	2.98015800	0.53315000	-5.38656900
C	3.02363600	-1.57572800	-2.77303200
H	3.12746700	-1.84184300	-1.71648300
H	2.34256800	-2.29512400	-3.24135300
H	4.00604200	-1.69093600	-3.24767400
Si	3.56675500	-0.94899300	2.35865700
C	5.09980300	0.10516100	2.04709000
H	5.52864900	-0.08537600	1.05672600
H	4.87576300	1.17527000	2.12022500
H	5.87247100	-0.12302800	2.79145000
C	2.79953100	-0.57327100	4.03894700
H	1.89058000	-1.16111600	4.20863900
H	3.50655800	-0.81614500	4.84159300
H	2.53905100	0.48656200	4.13552700
C	3.94613100	-2.78725800	2.16582300
H	3.04819100	-3.40066300	2.29984000
H	4.36567800	-3.01300900	1.17892500
H	4.67963900	-3.10270200	2.91792800
Ag	-3.12357000	1.44014800	-4.00205600
N	-2.78701100	0.70723800	1.06658700
S	-3.88156500	0.55449600	2.33492400
O	-5.03866300	1.35087300	1.92557500
O	-3.10329300	0.82351800	3.54268900
C	-4.37865800	-1.16524000	2.37222700
C	-5.47876200	-1.58458400	1.61751100
C	-3.65162500	-2.07670100	3.14488000
C	-5.83872700	-2.93097900	1.63176000
H	-6.06095200	-0.85892400	1.05931300
C	-4.02747100	-3.41838600	3.14510300

H	-2.82798400	-1.72930800	3.75961600
C	-5.12269700	-3.86793700	2.39184000
H	-6.69980400	-3.25806200	1.05441300
H	-3.46958400	-4.12703800	3.75196400
C	-5.54515300	-5.31657800	2.43387400
H	-4.68647500	-5.98143700	2.57243700
H	-6.23364700	-5.49654400	3.26981000
H	-6.06310300	-5.61176300	1.51594900
C	-6.74753900	2.94544300	-9.61320900
C	-5.85137800	2.51397700	-8.63927900
C	-6.10710900	2.84208000	-7.30109200
C	-7.23234600	3.58660200	-6.92244600
C	-8.11544500	4.00761100	-7.91291500
C	-7.87522900	3.68925000	-9.25290500
H	-6.56450000	2.70025600	-10.65446700
H	-4.97073300	1.93591200	-8.89846600
H	-7.40087500	3.82403300	-5.87741200
H	-8.99176900	4.58533800	-7.63707200
H	-8.56894000	4.02198700	-10.01879800
N	-5.21811800	2.41719700	-6.32136800
C	-4.47227100	2.06271200	-5.50028400

TS1

C	-4.03610100	0.56637400	0.85385500
H	-4.65601200	1.46240400	0.95669000
H	-4.70603400	-0.30472300	0.74896400
C	-1.76167800	0.00204100	1.57102000
H	-0.99119800	0.55499000	2.11514700
H	-1.59187400	-1.07292000	1.74646200
C	-3.07827700	0.63632600	-0.31097900
C	-1.78261900	0.30678600	0.09540900
C	-3.36393200	0.97596900	-1.66099600
C	-0.68761100	0.27520500	-0.79706800
C	-2.20598300	0.88201600	-2.28407400
C	0.58621700	-0.07555700	-0.27853900
C	-0.90041200	0.60358000	-2.20671400
C	1.62211800	-0.38419900	0.29327200
Si	0.40325300	0.61508200	-3.65335400
C	0.57093400	2.41028800	-4.20535700
H	1.28332900	2.47468000	-5.03728800
H	-0.37664100	2.84142300	-4.54121200
H	0.95841500	3.03408300	-3.39166100
C	-0.28180400	-0.52552600	-4.99080500
H	-0.34472400	-1.55778100	-4.62718100
H	-1.27455000	-0.22722600	-5.33932600
H	0.39289400	-0.52338500	-5.85599500
C	2.07612000	-0.03434000	-3.09735100
H	2.55657400	0.60845800	-2.35557800
H	2.02752600	-1.04824600	-2.69076100
H	2.71908700	-0.06084000	-3.98768900
Si	3.20221700	-0.84983900	1.16798700
C	4.31253800	0.67502100	1.18485100
H	4.56132400	1.00705900	0.17055100
H	3.83760900	1.51227300	1.70819800
H	5.25435300	0.45163500	1.70094800
C	2.73999900	-1.38528400	2.91581600
H	2.07100700	-2.25319400	2.90744300
H	3.63962900	-1.66593700	3.47702900

H	2.24314400	-0.57957800	3.46774300
C	3.99005800	-2.26606400	0.20141700
H	3.33518800	-3.14395900	0.16729100
H	4.22004200	-1.97432100	-0.82950200
H	4.93007300	-2.57133900	0.67716700
Ag	-5.14197200	1.58175600	-2.66308100
N	-3.10577100	0.44706300	1.98419200
S	-3.68855700	0.09593200	3.52250900
O	-4.93849900	0.84883700	3.62824300
O	-2.54817900	0.29494700	4.41515500
C	-4.09313300	-1.64827500	3.52425200
C	-5.37804400	-2.06052700	3.15719000
C	-3.11496700	-2.58366500	3.87695400
C	-5.67358000	-3.42228100	3.13301900
H	-6.13966500	-1.32158100	2.93133700
C	-3.43059300	-3.94052700	3.84630000
H	-2.13597500	-2.24743100	4.20188700
C	-4.70972400	-4.38257100	3.47561400
H	-6.67475500	-3.74486900	2.85846800
H	-2.67488400	-4.66891200	4.12928300
C	-5.05297400	-5.85255700	3.48837000
H	-4.17884600	-6.47177500	3.26289600
H	-5.42103500	-6.15664200	4.47691900
H	-5.83751400	-6.08904200	2.76256300
C	-4.17581400	2.59944700	-9.30985600
C	-3.85822800	2.01903200	-8.08438200
C	-3.51112200	2.85228800	-7.01229400
C	-3.47749300	4.24679700	-7.14886900
C	-3.79850800	4.80811500	-8.38237700
C	-4.14714000	3.98891500	-9.46007900
H	-4.44442300	1.96502400	-10.14861500
H	-3.87122500	0.94236200	-7.95078800
H	-3.19996400	4.86730100	-6.30307100
H	-3.77435900	5.88669900	-8.50179200
H	-4.39555700	4.43395700	-10.41862900
N	-3.18980600	2.28181000	-5.78465500
C	-2.89271600	1.79649200	-4.75700000

IN3

C	-4.00475400	0.97059300	0.63622500
H	-4.56127400	1.89981000	0.79477000
H	-4.73409000	0.15260900	0.50238300
C	-1.78722400	0.19560800	1.29768300
H	-0.96027100	0.64457000	1.85562200
H	-1.70613600	-0.89973600	1.40774100
C	-3.05743900	1.03335100	-0.54027200
C	-1.79406100	0.57539900	-0.15678200
C	-3.30838700	1.45495900	-1.83750400
C	-0.71152500	0.49441000	-1.05714800
C	-2.19985600	1.37626200	-2.73602300
C	0.52323500	-0.00187300	-0.53656600
C	-0.89023400	0.90284700	-2.40350600
C	1.52370700	-0.43507600	0.01606400
Si	0.61641100	0.77832300	-3.61777100
C	0.20202200	1.36060800	-5.37448600
H	1.12150400	1.22803700	-5.95969100
H	-0.57119100	0.76774100	-5.87490800
H	-0.06040400	2.42151800	-5.44689100

C	1.11295600	-1.03844700	-3.73975600	C	-2.17028000	0.10664900	1.35146500
H	1.34482500	-1.47279600	-2.76410800	H	-1.44791100	0.68556200	1.93353700
H	0.31711800	-1.63643200	-4.19971500	H	-1.91176500	-0.95995700	1.46615500
H	2.00371000	-1.13421600	-4.37311900	C	-3.52526300	0.70647000	-0.51929100
C	1.98890800	1.89863200	-2.96892300	C	-2.21121000	0.48925900	-0.10374200
H	1.67686700	2.94982900	-2.97185700	C	-3.81567300	1.09171400	-1.82224600
H	2.29389000	1.63732000	-1.95264800	C	-1.11981100	0.61861800	-0.98347300
H	2.86937900	1.81522900	-3.61817900	C	-2.70521100	1.24392500	-2.69321700
Si	3.04683000	-1.08274700	0.87328800	C	0.17625800	0.35020400	-0.44293400
C	3.25249600	-0.10878000	2.47505300	C	-1.34690100	1.01751100	-2.33018800
H	3.38389100	0.96155900	2.28085400	C	1.23117400	0.10398600	0.12350900
H	2.38655300	-0.22727100	3.13594500	Si	0.17965500	1.13487900	-3.51554300
H	4.13738100	-0.45860900	3.02076400	C	-0.27482900	1.57041300	-5.30554500
C	2.76961600	-2.91836300	1.21327300	H	0.66942000	1.57691400	-5.86617700
H	2.61955500	-3.48246300	0.28588500	H	-0.92016400	0.82343900	-5.77915500
H	3.64166600	-3.34447500	1.72425900	H	-0.72788000	2.55740700	-5.44414800
H	1.89635500	-3.08294800	1.85438100	C	1.00527800	-0.56227500	-3.58935300
C	4.51606900	-0.82040200	-0.28139500	H	1.32817900	-0.92047400	-2.60914600
H	4.39109600	-1.36332500	-1.22511400	H	0.32544300	-1.30821600	-4.01823600
H	4.66041100	0.24005500	-0.51729700	H	1.88774000	-0.51059900	-4.23956900
H	5.43793500	-1.18276100	0.18969800	C	1.33338200	2.48873600	-2.87421600
Ag	-5.24988000	2.17831500	-2.31059800	H	0.85436300	3.47486400	-2.90801800
N	-3.07964900	0.73242700	1.75213100	H	1.65261400	2.30262700	-1.84516300
S	-3.67081300	0.36061800	3.28155100	H	2.23133300	2.54011800	-3.50253900
O	-4.85531700	1.20462600	3.43960300	Si	2.83410200	-0.27896000	0.98558700
O	-2.50827100	0.42779600	4.16529200	C	3.78042300	1.34188800	1.19077700
C	-4.21365300	-1.34437100	3.21272900	H	3.99390300	1.80945900	0.22272300
C	-5.53248800	-1.63533800	2.85003100	H	3.21845000	2.06109000	1.79718900
C	-3.30950600	-2.37051200	3.50596100	H	4.73987600	1.16307300	1.69153800
C	-5.93718300	-2.96658000	2.76906000	C	2.41666900	-1.04135500	2.65994200
H	-6.23525400	-0.82827700	2.67154700	H	1.85109000	-1.97310300	2.54577100
C	-3.73377100	-3.69499100	3.41897400	H	3.33484700	-1.27654200	3.21203700
H	-2.30250000	-2.12929800	3.82971200	H	1.82278300	-0.35937000	2.77882700
C	-5.04913200	-4.01563800	3.05028100	C	3.79617200	-1.49455400	-0.09164000
H	-6.96483400	-3.19509400	2.49793800	H	3.24223000	-2.42899600	-0.23627500
H	-3.03570400	-4.49403300	3.65553600	H	4.01385500	-1.07523000	-1.08047900
C	-5.50854200	-5.45284200	3.00116500	H	4.75391200	-1.74588900	0.38037200
H	-5.86976100	-5.77900100	3.98520100	Ag	-5.84712500	1.34799000	-2.38354700
H	-6.33081800	-5.58846900	2.29151400	N	-3.54763300	0.41659600	1.77366600
H	-4.69366100	-6.12574300	2.71537500	S	-4.09863900	-0.04504400	3.29155600
C	-3.41316100	4.55416200	-7.85308600	O	-5.41711200	0.57716800	3.41962800
C	-3.04150800	4.08132200	-6.59778600	O	-2.98866600	0.23271500	4.20267700
C	-3.20896900	2.71663900	-6.31856700	C	-4.33054800	-1.81987500	3.23058400
C	-3.73756800	1.82581000	-7.26472700	C	-5.56896000	-2.34329100	2.84700200
C	-4.10261300	2.32075800	-8.51349500	C	-3.26310700	-2.66686800	3.54675700
C	-3.94132300	3.67859400	-8.80726500	C	-5.72796200	-3.72606900	2.76961700
H	-3.28873200	5.60655200	-8.08695700	H	-6.40018700	-1.67531500	2.64721300
H	-2.62728600	4.74387100	-5.84497700	C	-3.44195400	-4.04590300	3.46211800
H	-3.85100900	0.77515800	-7.01870700	H	-2.32100300	-2.24759200	3.88391900
H	-4.51118900	1.64548400	-9.25836500	C	-4.67225400	-4.59806800	3.07342400
H	-4.22723400	4.05574300	-9.78428500	H	-6.69275800	-4.13573900	2.48140900
N	-2.83930300	2.23467900	-5.07232000	H	-2.61620700	-4.70621500	3.71511900
C	-2.49357300	1.83298200	-4.03557800	C	-4.86419400	-6.09471600	3.02499000
				H	-5.67129300	-6.37509400	2.34104300
				H	-3.95043400	-6.60634300	2.70524200
				H	-5.12496400	-6.48603600	4.01698700
				C	-5.35372000	3.86495900	-7.18882100
				C	-4.85372100	3.24302100	-6.04472500
TS2							
C	-4.47336700	0.45942200	0.63153100				
H	-5.20852300	1.25846100	0.76787200				
H	-5.02054200	-0.48896600	0.48940600				

C	-4.08353900	2.07638400	-6.18296500
C	-3.84070400	1.51850400	-7.44622300
C	-4.33321500	2.16134800	-8.57790400
C	-5.08877500	3.33238600	-8.45216400
H	-5.95984600	4.76048100	-7.09014600
H	-5.08035900	3.63384000	-5.05825800
H	-3.26419400	0.60279100	-7.52417300
H	-4.13770600	1.74237900	-9.56004300
H	-5.48336000	3.81959500	-9.33853400
N	-3.57316600	1.42774000	-5.05654100
C	-3.04738000	1.73796600	-4.01386100
C	-1.64393100	5.78777400	-2.84064100
C	-1.39150600	6.89609500	-3.66040500
C	-0.83770700	8.03673300	-3.08569100
C	-0.54475900	8.06561100	-1.71875700
C	-0.80262300	6.95107700	-0.91490400
C	-1.35513900	5.79931000	-1.46872800
H	-1.62642900	6.85334000	-4.71860800
H	-0.63541300	8.90400600	-3.70601100
H	-0.11413400	8.95968900	-1.27855200
H	-0.57394000	6.97751000	0.14569800
H	-1.56241600	4.92370700	-0.86273900
N	-2.19828700	4.64285900	-3.40014600
C	-2.67339500	3.68287200	-3.86511300

IN4

C	-4.41283500	0.46677900	0.79906500
H	-5.20866800	1.19926700	0.96666600
H	-4.89124600	-0.49805500	0.57419200
C	-2.09726800	0.29877500	1.56291600
H	-1.46201500	0.93814800	2.18691300
H	-1.71579000	-0.73040700	1.63932100
C	-3.46647500	0.86305700	-0.30613700
C	-2.14862600	0.74579300	0.12861500
C	-3.76809400	1.30557200	-1.58905300
C	-1.06364400	0.97084900	-0.73967800
C	-2.67366500	1.58156800	-2.44558200
C	0.24592000	0.78103100	-0.19889300
C	-1.30991200	1.36640800	-2.08523300
C	1.31787500	0.61540800	0.36561100
Si	0.16249200	1.21851800	-3.33323500
C	-0.37594300	1.38356100	-5.15180400
H	0.47202900	1.03098000	-5.75339600
H	-1.22807300	0.74201700	-5.40125000
H	-0.59459500	2.39872200	-5.50034000
C	0.84427700	-0.53797400	-3.19709000
H	1.19526700	-0.78301200	-2.19238600
H	0.07920300	-1.27124000	-3.47888400
H	1.68659100	-0.65891500	-3.89001800
C	1.48572800	2.52445900	-2.97793700
H	1.12839600	3.54358200	-3.17035400
H	1.82481700	2.47419600	-1.93907700
H	2.35607100	2.35937300	-3.62513100
Si	2.93120700	0.33205700	1.23950900
C	3.80381800	1.99902900	1.41314300
H	4.01648900	2.44674300	0.43544800
H	3.19971200	2.71118200	1.98664300
H	4.76006300	1.87681600	1.93655600

C	2.54425800	-0.40690900	2.93244100
H	2.01707100	-1.36300500	2.83843300
H	3.47012300	-0.59093600	3.49106900
H	1.92046700	0.26468600	3.53322900
C	3.96171100	-0.86156100	0.20172000
H	3.45904900	-1.82824600	0.08449300
H	4.15961100	-0.46137200	-0.79912300
H	4.92993300	-1.04680600	0.68289400
Ag	-5.77674000	1.34419900	-2.28709100
N	-3.51572200	0.40175300	1.98191200
S	-4.02989200	-0.64568200	3.21951800
O	-3.40586700	-1.96641500	3.05637300
O	-5.48862400	-0.50317100	3.23926700
C	-3.32713400	0.11739100	4.67437700
C	-2.23261300	-0.47796100	5.30165700
C	-3.90870600	1.28126900	5.18639200
C	-1.70776100	0.11325000	6.45131500
H	-1.81341600	-1.39466800	4.90101200
C	-3.37154000	1.85487800	6.33427700
H	-4.77306400	1.71804100	4.69729400
C	-2.26620500	1.28188300	6.98579100
H	-0.85660500	-0.34798500	6.94558400
H	-3.82094900	2.75823500	6.73908000
C	-1.71837100	1.89576400	8.25163800
H	-1.74763100	2.98992800	8.21260500
H	-2.31133500	1.58708200	9.12243300
H	-0.68447400	1.58695000	8.43365800
C	-5.23261700	4.62595200	-6.65774300
C	-4.72541900	3.95597900	-5.54483600
C	-4.39173000	2.58887100	-5.64040100
C	-4.61777800	1.90150500	-6.84852400
C	-5.09025100	2.58937200	-7.96096300
C	-5.39893600	3.95178100	-7.87038600
H	-5.51971300	5.66992500	-6.57105300
H	-4.66683300	4.46617800	-4.58699200
H	-4.39188400	0.84107700	-6.89581700
H	-5.23777700	2.05951900	-8.89706400
H	-5.79532600	4.47747500	-8.73369800
N	-3.90853600	1.83567800	-4.56434800
C	-3.01429800	2.24605200	-3.73013700
C	-1.10301100	5.72906200	-4.10098600
C	-1.21151400	6.41721900	-5.32088400
C	-0.55369600	7.63546400	-5.45112100
C	0.19418000	8.15012800	-4.38612900
C	0.29007600	7.45043600	-3.17806500
C	-0.35860700	6.23019700	-3.02057000
H	-1.79805800	5.99693200	-6.13097800
H	-0.62274900	8.18367100	-6.38505100
H	0.70533500	9.10120400	-4.49833000
H	0.87124600	7.85653800	-2.35664200
H	-0.30044800	5.67139900	-2.09278200
N	-1.75911400	4.52245300	-3.96231200
C	-2.34191600	3.51987800	-3.88700500

TS3

C	-4.47247900	0.18958700	0.39740700
H	-5.30881100	0.89412400	0.45486000
H	-4.89832300	-0.81475200	0.23497800

C	-2.21076500	0.13546100	1.30198700	C	-3.04745900	2.87519200	-6.15443000
H	-1.61338700	0.81795000	1.91531900	C	-2.33599800	3.91048000	-6.79089200
H	-1.83681900	-0.88613500	1.46916500	C	-2.86906300	4.53814900	-7.91201700
C	-3.46844300	0.52904800	-0.67495200	C	-4.08841300	4.10970700	-8.44592300
C	-2.17726000	0.48335800	-0.16156200	H	-5.70521400	2.68998500	-8.28318500
C	-3.64363900	0.81566500	-2.02754800	H	-4.78812600	1.59067200	-6.26758700
C	-1.03155500	0.67142100	-0.97264100	H	-1.37842000	4.21571900	-6.38222800
C	-2.49939100	1.12275200	-2.81999600	H	-2.32330800	5.34969100	-8.38370400
C	0.21072900	0.54487600	-0.28509200	H	-4.48975600	4.58477600	-9.33599600
C	-1.16559100	1.00313000	-2.35626800	N	-2.44444500	2.27163300	-5.04995100
C	1.17991000	0.41690200	0.44951000	C	-3.02532600	1.81931000	-4.00971000
Si	0.35758300	1.23545900	-3.54655500	C	-6.52095800	3.34241600	-3.13246100
C	0.04590200	0.21114300	-5.10697500	C	-7.42381300	4.00876000	-3.97480200
H	0.89017300	0.34723500	-5.79476300	C	-8.64253900	4.43746900	-3.45605600
H	0.00464700	-0.85667100	-4.85824900	C	-8.94834100	4.22219100	-2.10843000
H	-0.86508000	0.48170500	-5.64294600	C	-8.03343400	3.57603500	-1.26968200
C	1.97148000	0.55164700	-2.83868600	C	-6.81430600	3.13149100	-1.77301000
H	2.38387900	1.16055600	-2.03170100	H	-7.15856900	4.17426700	-5.01381700
H	1.88267700	-0.47768600	-2.47791300	H	-9.35082600	4.94866500	-4.10036400
H	2.69578700	0.54941400	-3.66475500	H	-9.89620900	4.56790800	-1.70750300
C	0.60520900	3.08470800	-3.85620300	H	-8.26755500	3.42640200	-0.22010300
H	-0.29504500	3.57558000	-4.23357700	H	-6.08155000	2.65455400	-1.13032000
H	0.91128000	3.58950200	-2.93213400	N	-5.31845100	2.90354400	-3.66965300
H	1.40649700	3.23321200	-4.59102700	C	-4.42592000	2.10064300	-3.56681900
Si	2.67617800	0.20424500	1.53506500				
C	4.05550800	1.29747900	0.85575700				
H	4.32154900	1.02096000	-0.17063000	IN5			
H	3.76874800	2.35517900	0.85755200	C	-3.00646300	-2.85129800	-0.55522400
H	4.95814600	1.19738300	1.47095800	H	-4.04986300	-3.08386000	-0.78160700
C	2.19018800	0.73782000	3.27990800	H	-2.45879400	-3.80086600	-0.62674400
H	1.35177600	0.14690100	3.66609200	C	-1.64104700	-1.43227200	0.82699000
H	3.03467300	0.60604100	3.96746600	H	-1.77931600	-0.59164300	1.50885900
H	1.90054000	1.79439800	3.30967100	H	-0.78283100	-2.01154000	1.19029700
C	3.15792700	-1.61952200	1.48631300	C	-2.34551400	-1.79484000	-1.41734500
H	2.35051500	-2.26107400	1.85658700	C	-1.48754500	-1.03439400	-0.62216900
H	3.40497300	-1.94212100	0.46878100	C	-2.33757700	-1.50069100	-2.77499300
H	4.03951100	-1.79622800	2.11470600	C	-0.59485600	-0.05566000	-1.13462800
Ag	-5.31057300	-0.32736200	-2.86147100	C	-1.42546200	-0.54633100	-3.29536800
N	-3.65186100	0.27006700	1.62848400	C	0.20700300	0.60176500	-0.15587600
S	-4.24975400	-0.67941100	2.91500400	C	-0.52388600	0.21652100	-2.53894000
O	-3.71042500	-2.04345600	2.82427300	C	0.83198800	1.09381300	0.77273200
O	-5.69751200	-0.44955200	2.88065100	Si	0.64311600	1.48062600	-3.42279800
C	-3.52287600	0.11985300	4.33338300	C	1.71882800	0.48563600	-4.61472400
C	-2.52724200	-0.54044000	5.05427700	H	2.38264800	1.15939100	-5.17115300
C	-3.98973300	1.37831500	4.72719500	H	2.35344600	-0.23078900	-4.07952500
C	-1.98411000	0.08118400	6.17899500	H	1.11004300	-0.06197400	-5.34007200
H	-2.19782200	-1.52609400	4.74369900	C	1.76826700	2.43880800	-2.24835000
C	-3.43417500	1.98085800	5.85068000	H	1.21232800	3.04622000	-1.52829500
H	-4.77853100	1.86828400	4.16618600	H	2.45278900	1.79264300	-1.69130500
C	-2.42591900	1.34427600	6.59505600	H	2.37460100	3.11848900	-2.86190500
H	-1.21047800	-0.42874800	6.74686100	C	-0.46687900	2.71392500	-4.32626900
H	-3.79175700	2.95875700	6.16284300	H	-1.11439100	2.21643300	-5.05407200
C	-1.85653900	1.99875500	7.83024500	H	-1.09560300	3.27660300	-3.62568700
H	-1.69892000	3.07202300	7.67827700	H	0.15044800	3.44138400	-4.86824400
H	-2.54298100	1.88988300	8.67980200	Si	1.81224800	1.89312700	2.13698400
H	-0.90164900	1.54988100	8.11915200	C	3.63671400	1.52741800	1.82251500
C	-4.77673700	3.04908000	-7.84849000	H	3.83846100	0.45039800	1.82929500
C	-4.26941700	2.43824700	-6.70533300	H	3.96680400	1.92664300	0.85697700
				H	4.25615900	1.98723000	2.60234400

C	1.46237900	3.74639000	2.08230100	C	-1.90941400	0.74004400	1.66482100
H	0.39943600	3.96029200	2.24078200	H	-0.99165200	0.98586000	2.21008000
H	2.02706900	4.26448900	2.86711600	H	-2.02281200	-0.35455400	1.67314400
H	1.75470900	4.18119100	1.11995300	C	-3.13805700	1.90514700	-0.01132100
C	1.24391700	1.14268800	3.77331800	C	-1.92656600	1.27277000	0.25670300
H	0.17536600	1.31376000	3.94675400	C	-3.41115000	2.41216100	-1.27640800
H	1.42405400	0.06204300	3.80676400	C	-0.92632600	1.15870200	-0.72353900
H	1.79141200	1.59476200	4.60941000	C	-2.41013400	2.29748600	-2.26672200
Ag	-5.85129300	-1.44720800	-1.47361000	C	0.24580700	0.42828500	-0.35139700
N	-2.84469900	-2.32556800	0.82598100	C	-1.13577700	1.71992100	-2.02036800
S	-4.22556500	-1.69357400	1.56661300	C	1.17869800	-0.24511500	0.06224500
O	-5.15424300	-1.02606800	0.58128400	Si	0.36515400	1.71793600	-3.23872700
O	-3.77758200	-0.84558200	2.66527400	C	0.13754900	2.83121000	-4.75914200
C	-5.06760700	-3.15566000	2.13462900	H	1.13311200	2.99241100	-5.19211200
C	-6.46530000	-3.13552200	2.20017900	H	-0.48420800	2.38294700	-5.53734100
C	-4.33660200	-4.24128100	2.62874700	H	-0.26229000	3.82427200	-4.51649000
C	-7.13029600	-4.22985200	2.74758200	C	0.70464000	-0.04280300	-3.82675100
H	-7.02107700	-2.27645200	1.83995300	H	0.89205000	-0.72297700	-2.99050200
C	-5.02387400	-5.32561900	3.16723800	H	-0.14767000	-0.43122100	-4.39628000
H	-3.25344000	-4.23966900	2.58250200	H	1.58294700	-0.06264100	-4.48393900
C	-6.42587600	-5.33889100	3.24143100	C	1.84725200	2.48739300	-2.33934100
H	-8.21556000	-4.21854100	2.79998700	H	1.65085200	3.53896700	-2.09355000
H	-4.46021600	-6.17506900	3.54322300	H	2.11960900	1.96921900	-1.41803000
C	-7.15356500	-6.50272700	3.86649900	H	2.71796000	2.46959800	-3.00745000
H	-6.62876700	-7.44677700	3.68980600	Si	2.58706800	-1.28213600	0.67983700
H	-7.22701600	-6.36996000	4.95370300	C	4.08175000	-0.15321800	0.92929300
H	-8.17269000	-6.59630000	3.47963000	H	4.37412800	0.34061400	-0.00442700
C	-3.29142900	-1.52345200	-8.84540400	H	3.87653100	0.62543800	1.67278800
C	-2.97489700	-1.38228400	-7.49727500	H	4.94379700	-0.73216500	1.28300100
C	-1.92399600	-0.52549300	-7.10914300	C	2.05675300	-2.05933300	2.31716700
C	-1.21283000	0.17488000	-8.10329400	H	1.17346200	-2.69552200	2.19082500
C	-1.53690500	0.02837600	-9.44876100	H	2.86144200	-2.68426100	2.72360200
C	-2.57823600	-0.82321900	-9.82438500	H	1.81819000	-1.29560200	3.06632300
H	-4.10232600	-2.18526600	-9.13732700	C	2.95317300	-2.61117600	-0.60942300
H	-3.54080400	-1.92337100	-6.74839800	H	2.08581900	-3.26139800	-0.76982000
H	-0.40564100	0.82925400	-7.79033300	H	3.22781100	-2.17191700	-1.57518800
H	-0.97838700	0.57530900	-10.20268000	H	3.78764700	-3.24332100	-0.28180200
H	-2.83452700	-0.94220000	-10.87324400	Ag	-5.39605100	3.09177700	-1.60637100
N	-1.48667300	-0.28628800	-5.80094800	N	-3.07511300	1.43106000	2.26899200
C	-1.90327600	-0.76293800	-4.69925000	S	-3.79960400	0.69266700	3.61959200
C	-5.00210400	-2.88631900	-3.86101000	O	-3.82388400	-0.76656800	3.44981600
C	-6.25834700	-2.24229700	-3.62615800	O	-5.04093100	1.44513800	3.82678400
C	-7.33150600	-2.97720200	-3.05108800	C	-2.64139800	1.07535800	4.92561400
C	-7.15704000	-4.31362200	-2.68259900	C	-1.78995500	0.07926700	5.40422600
C	-5.92206500	-4.93085300	-2.91389500	C	-2.63344400	2.35956400	5.47838000
C	-4.85615600	-4.23536900	-3.48699200	C	-0.90920000	0.38344600	6.44277900
H	-6.44512000	-1.28499500	-4.10924600	H	-1.83228000	-0.91765000	4.97879100
H	-8.30580300	-2.50376700	-2.96090300	C	-1.74950600	2.64261700	6.51471300
H	-7.98218800	-4.87522100	-2.25747500	H	-3.32054100	3.11405800	5.10984200
H	-5.78959100	-5.97748100	-2.65442300	C	-0.87591100	1.66211900	7.01479400
H	-3.91854800	-4.73998700	-3.69854700	H	-0.24588000	-0.38981900	6.82162600
N	-4.03806500	-2.20363200	-4.58635700	H	-1.74230500	3.63752400	6.95315200
C	-2.96888000	-1.70340800	-4.10677700	C	0.04929100	1.97381600	8.16643100
				H	0.88868200	1.27306900	8.21001300
				H	0.45381800	2.98910300	8.09333100
				H	-0.48409000	1.90665800	9.12356700
				C	-4.60530700	1.12655800	-7.76657800
				C	-4.15996500	1.05165800	-6.45022000
TS4							
C	-4.02402600	1.85833600	1.20892900				
H	-4.46371100	2.82764900	1.46528200				
H	-4.85006900	1.14508400	1.06427300				

C	-3.33218500	2.06111400	-5.92251300	C	1.80178000	1.89436100	-3.09562700
C	-2.90087800	3.10790700	-6.76091900	H	1.75483100	2.97388700	-2.90903700
C	-3.31702600	3.14757400	-8.09083800	H	1.98204800	1.39271900	-2.14269600
C	-4.18253300	2.17165900	-8.59336400	H	2.66663200	1.71243800	-3.74628700
H	-5.26055300	0.35335400	-8.15637600	C	0.17830400	2.29750100	-5.58390000
H	-4.44618000	0.22560500	-5.80704900	H	-0.59361700	2.00518900	-6.30063300
H	-2.20560800	3.85292200	-6.39015900	H	0.07339900	3.37069700	-5.38915800
H	-2.95446700	3.93970400	-8.73999300	H	1.14798700	2.15424400	-6.07872600
H	-4.50513600	2.21185600	-9.62943200	Si	1.70313800	-1.67500500	0.31800600
N	-2.92176100	1.87979100	-4.59663800	C	3.40808800	-0.87625400	0.45569600
C	-2.82918500	2.72110000	-3.63877200	H	3.79403300	-0.58034500	-0.52637700
C	-4.62921300	6.01876400	-4.74345100	H	3.38149300	0.01756300	1.08903300
C	-5.26674000	6.16123400	-5.98624500	H	4.12635700	-1.57743400	0.89815300
C	-5.84811500	7.38364900	-6.31080200	C	1.03042700	-2.12663400	2.02433900
C	-5.81241100	8.44295100	-5.39894700	H	0.03024700	-2.56981000	1.95668800
C	-5.18877400	8.28678000	-4.15566600	H	1.68577000	-2.85734700	2.51403100
C	-4.59061500	7.07690900	-3.81810600	H	0.96751700	-1.24793300	2.67627000
H	-5.28293100	5.32267900	-6.67432400	C	1.75985000	-3.19805300	-0.79841900
H	-6.33651700	7.50825100	-7.27204800	H	0.77201400	-3.66389200	-0.89083200
H	-6.27672400	9.39085600	-5.65337600	H	2.11024700	-2.94601600	-1.80589400
H	-5.17237100	9.10972100	-3.44777500	H	2.44466300	-3.94992400	-0.38730400
H	-4.11023200	6.94115500	-2.85497100	Ag	-4.38534400	4.84596200	-2.83190000
N	-4.05266300	4.79695800	-4.44133200	N	-3.24577900	2.47710400	1.45395100
C	-3.29311500	4.12730400	-3.80731300	S	-4.52023100	1.52993200	2.07573300
C	0.99940800	7.89453000	-0.01039100	O	-4.52598000	0.18851200	1.45026700
C	0.08930100	7.40811700	-0.94515500	O	-5.72104400	2.36724600	1.99354400
C	-0.44871500	6.12878000	-0.75504600	C	-4.03956800	1.31994300	3.78123900
C	-0.09683700	5.33201400	0.34373700	C	-3.71122400	0.05107400	4.25571900
C	0.81498700	5.83874500	1.26604200	C	-4.04062300	2.43265500	4.62974600
C	1.36128800	7.11379600	1.09149400	C	-3.36901600	-0.10004800	5.60062100
H	1.42675900	8.88331600	-0.14329600	H	-3.73043400	-0.79998900	3.58408300
H	-0.20246500	7.99729900	-1.80813200	C	-3.69781700	2.26065500	5.96551200
H	-0.53186200	4.34467000	0.45797000	H	-4.30956800	3.41206500	4.24827600
H	1.09935300	5.23518600	2.12210200	C	-3.35686300	0.99445000	6.47374700
H	2.07199500	7.50012900	1.81563500	H	-3.11155700	-1.08682200	5.97604200
N	-1.35713900	5.62678100	-1.67950900	H	-3.69688600	3.12116200	6.62970100
C	-2.12251500	5.13275900	-2.41019200	C	-3.00208200	0.82760200	7.93129500
IN6				H	-2.22933300	1.54243800	8.23672000
C	-3.62276300	3.43917200	0.38035600	H	-3.87593100	1.00628000	8.57027200
H	-3.23867400	4.43455800	0.64419400	H	-2.63470100	-0.18058400	8.14340700
H	-4.70797600	3.51632100	0.29112600	C	-3.53662600	5.16344600	-8.53457900
C	-2.04293100	1.71925400	1.01163100	C	-2.90281200	4.84063700	-7.33606400
H	-1.14880400	2.13185600	1.49727400	C	-3.58837200	4.10531100	-6.35857200
H	-2.11310000	0.66435000	1.28869000	C	-4.93036300	3.74914800	-6.57241100
C	-2.93607300	2.90303400	-0.85647600	C	-5.56435900	4.10306500	-7.76342400
C	-2.00622300	1.93397900	-0.48275400	C	-4.86839700	4.79982200	-8.75433800
C	-3.13513100	3.24464700	-2.19005900	H	-2.99179400	5.71780900	-9.29342800
C	-1.14537600	1.34635200	-1.42496000	H	-1.87600200	5.13932000	-7.15000200
C	-2.32682500	2.58993500	-3.15126000	H	-5.47451100	3.21025100	-5.80032900
C	-0.20051100	0.38938800	-0.93924600	H	-6.60651600	3.83497400	-7.91482200
C	-1.26079300	1.70588800	-2.80238700	H	-5.36418400	5.07314500	-9.68089500
C	0.54661100	-0.44066100	-0.44087500	N	-2.95008300	3.86555000	-5.12208000
Si	0.23219400	1.30351200	-3.97106800	C	-2.74943800	2.72591300	-4.58035700
C	0.32289100	-0.54788000	-4.36552900	C	-3.22229500	0.01603000	-7.20058300
H	1.27334700	-0.77341500	-4.86497900	C	-3.61324900	0.19303300	-8.54551300
H	0.26939100	-1.15856700	-3.45873800	C	-3.90269300	-0.91093300	-9.33933000
H	-0.47626200	-0.86685400	-5.04567300	C	-3.75079600	-2.20233900	-8.82440600
				C	-3.30975100	-2.38840300	-7.50805700

C	-3.05383300	-1.29232100	-6.69163200	H	2.51418800	-1.97314700	3.81680000
H	-3.70536200	1.20567500	-8.92401100	C	5.23673900	-2.77071000	0.89909700
H	-4.22585600	-0.76801800	-10.36575400	H	4.70893700	-3.63469900	0.47990500
H	-3.94958500	-3.06454100	-9.45386000	H	5.71329600	-2.23073000	0.07307200
H	-3.14726000	-3.39232800	-7.12722000	H	6.03418800	-3.15233500	1.54836000
H	-2.65403000	-1.44985600	-5.69493200	Ag	-2.90013700	1.33854200	-3.86984500
N	-2.98428100	1.18602600	-6.49618400	N	-2.37183300	0.05743700	1.07100600
C	-3.08809100	1.39871600	-5.23328500	S	-3.47910600	-0.72776800	2.10669400
C	-6.51368900	-3.00526900	-2.68559500	O	-3.22847300	-2.17532300	2.09871900
C	-5.75312300	-2.15906600	-3.48265100	O	-4.78305600	-0.18927700	1.70950100
C	-5.05418400	-1.10906900	-2.85920000	C	-3.01084000	-0.09140200	3.70641300
C	-5.10202300	-0.89157400	-1.47304400	C	-2.41276600	-0.94398900	4.63411700
C	-5.87429500	-1.75190300	-0.69957600	C	-3.29011400	1.24267400	4.02289700
C	-6.57586700	-2.80194900	-1.30069900	C	-2.07953000	-0.44414000	5.89380900
H	-7.06299100	-3.82170200	-3.14337300	H	-2.22656000	-1.98052300	4.37457100
H	-5.69301300	-2.29003300	-4.55804300	C	-2.94920800	1.72108100	5.28282800
H	-4.55249600	-0.08047600	-1.00954500	H	-3.77410300	1.88681400	3.29625800
H	-5.91427500	-1.58353700	0.37078100	C	-2.34100700	0.88803100	6.23850400
H	-7.17761600	-3.46704500	-0.68870200	H	-1.61647900	-1.10445600	6.62220900
N	-4.30356100	-0.26092700	-3.64568300	H	-3.16437300	2.75613100	5.53614500
C	-3.64454500	0.43565500	-4.30408200	C	-2.00328500	1.41924600	7.61044100
IN7				H	-2.91327100	1.57492700	8.20374300
C	-2.87417700	0.30421700	-0.30284200	H	-1.36214300	0.72680100	8.16362100
H	-3.41721500	1.25398700	-0.34868500	H	-1.49006400	2.38556500	7.54944800
H	-3.55038000	-0.48392200	-0.66534200	C	-6.41224400	2.09294800	-8.12388100
C	-0.98481400	-0.47068300	1.05131600	C	-6.32608400	2.66831700	-6.84122600
H	-0.38390000	0.00309700	1.83543200	C	-7.27322300	3.61599500	-6.40695500
H	-0.95712100	-1.55839400	1.21000400	C	-8.30495800	3.98271600	-7.26458400
C	-1.59900400	0.32345800	-1.10535400	C	-8.39374600	3.41359600	-8.53905200
C	-0.51722700	-0.11552600	-0.33462300	C	-7.45132300	2.47284800	-8.96679600
C	-1.44264100	0.69820800	-2.48284200	H	-5.67538200	1.36337300	-8.44355500
C	0.79492000	-0.21514200	-0.84938800	H	-7.19397200	4.04944700	-5.41535800
C	-0.16747300	0.51253600	-2.67898700	H	-9.04054200	4.71155500	-6.93976300
C	1.86271100	-0.66439700	-0.03004500	H	-9.20251100	3.70442100	-9.20271200
C	1.03760900	0.15619900	-2.24241400	H	-7.52743200	2.03543100	-9.95709900
C	2.74802300	-1.05646700	0.71728400	C	-5.26841500	2.28390600	-5.96783100
Si	2.71355200	0.12907300	-3.20492400	N	-4.40693500	1.97120500	-5.25425600
C	3.87825900	1.32228800	-2.33360600	TS5			
H	4.85863900	1.31053100	-2.82592400	C	-3.96057900	0.56254700	0.95706800
H	3.50111400	2.35045600	-2.36915000	H	-4.57614700	1.45684000	1.09695100
H	4.02571300	1.04893800	-1.28410600	H	-4.63453400	-0.30564400	0.85316500
C	2.29533900	0.71583900	-4.94824200	C	-1.66752400	-0.01597800	1.59684200
H	1.57195800	0.05498200	-5.44104400	H	-0.88203500	0.52583000	2.13058700
H	1.89127100	1.73540400	-4.95315200	H	-1.49189800	-1.09426100	1.74404100
H	3.19944000	0.72404000	-5.56876400	C	-3.03666700	0.65804300	-0.23326600
C	3.33176600	-1.64710000	-3.20227700	C	-1.73112200	0.32112600	0.12969300
H	3.47867600	-2.02289600	-2.18507300	C	-3.36523400	1.01838600	-1.56677800
H	2.63366600	-2.31681900	-3.71679600	C	-0.66271900	0.31271500	-0.79411200
H	4.29448800	-1.70536200	-3.72533000	C	-2.22851400	0.94084600	-2.23577100
Si	4.07493900	-1.65639500	1.88271500	C	0.62345300	-0.05204500	-0.31422100
C	4.97717500	-0.13667000	2.54281700	C	-0.91503300	0.67611100	-2.18550800
H	5.44850200	0.43622800	1.73622200	C	1.66702200	-0.38255800	0.23053800
H	4.29812200	0.53434500	3.08050700	Si	0.37129800	0.77673700	-3.64424500
H	5.76794500	-0.43930900	3.24019900	C	0.36492800	2.56757700	-4.23701200
C	3.21892500	-2.60766200	3.26771900	H	1.02653800	2.67016100	-5.10635200
H	2.66628400	-3.47122700	2.88119900	H	-0.62867800	2.92069600	-4.52424400
H	3.95927400	-2.98087200	3.98584800	H	0.74849400	3.23190300	-3.45385700

C	-0.19256800	-0.46880700	-4.94438700	C	-1.73118300	0.06828900	1.40869100
H	-0.10722700	-1.49176200	-4.55959500	H	-0.93677600	0.61457400	1.92514000
H	-1.22503900	-0.31301000	-5.26746400	H	-1.54446800	-1.00872100	1.55826100
H	0.45411000	-0.39654900	-5.82787400	C	-3.12294200	0.72056600	-0.41598000
C	2.11177200	0.33189600	-3.09142400	C	-1.81549600	0.39142100	-0.05799900
H	2.50176000	1.00765000	-2.32578600	C	-3.45125500	1.06823300	-1.72043700
H	2.19636700	-0.69220900	-2.71892000	C	-0.75704500	0.37565700	-0.99131400
H	2.75584500	0.42137200	-3.97704200	C	-2.37221900	1.05338500	-2.63266100
Si	3.26048400	-0.87388700	1.06346400	C	0.52210000	0.00554300	-0.47548100
C	4.32880500	0.67433000	1.20496000	C	-1.01720600	0.72026300	-2.34357700
H	4.56387200	1.09631600	0.22140400	C	1.54077300	-0.32733700	0.11150300
H	3.83326200	1.45190600	1.79685800	Si	0.32954900	0.76733600	-3.73627900
H	5.27860700	0.43516600	1.69888800	C	0.41362500	2.53945800	-4.40849600
C	2.81974400	-1.56235600	2.76286200	H	1.19542000	2.59597800	-5.17602900
H	2.17662100	-2.44630700	2.68550800	H	-0.51140300	2.90917400	-4.86265400
H	3.72920700	-1.86042100	3.29878700	H	0.69260400	3.23802000	-3.61084200
H	2.30137400	-0.81883500	3.37857100	C	-0.17172800	-0.47560000	-5.07940600
C	4.08621100	-2.18641100	-0.01203700	H	-0.20473500	-1.49147400	-4.66827700
H	3.45499900	-3.07590200	-0.11742500	H	-1.13830500	-0.28065200	-5.55539300
H	4.30848600	-1.80764600	-1.01604800	H	0.58607200	-0.47237600	-5.87265500
H	5.03408300	-2.50389800	0.43955200	C	2.06705800	0.30800700	-3.17911000
Ag	-5.23299300	1.62237200	-2.38250500	H	2.46242800	0.98817000	-2.42048200
N	-2.99944400	0.41823600	2.05793400	H	2.13485100	-0.71011500	-2.78782600
S	-3.53870900	0.03495300	3.60365600	H	2.71511000	0.37453000	-4.06349600
O	-4.78546000	0.78462800	3.76024600	Si	3.10543700	-0.82185700	0.98826700
O	-2.37437200	0.21551600	4.46868300	C	4.20702800	0.70582400	1.10718000
C	-3.94410900	-1.70919100	3.58022700	H	4.46817800	1.09510600	0.11660800
C	-5.24112200	-2.11373600	3.24629700	H	3.71795300	1.51021500	1.66791600
C	-2.95587500	-2.65173300	3.88004300	H	5.14269200	0.46087200	1.62471500
C	-5.53812900	-3.47404000	3.20228100	C	2.62643300	-1.44983400	2.70173100
H	-6.00897400	-1.36971000	3.06207600	H	1.97146700	-2.32649000	2.64084000
C	-3.27327300	-4.00824700	3.82953900	H	3.52126300	-1.74359600	3.26403500
H	-1.96647400	-2.32292800	4.18016800	H	2.10767400	-0.67973300	3.28374300
C	-4.56344000	-4.44189200	3.49144500	C	3.93114800	-2.18389100	-0.02523800
H	-6.54821600	-3.79066000	2.95427100	H	3.28344700	-3.06280600	-0.11991500
H	-2.50933600	-4.74258400	4.07162300	H	4.18507600	-1.84044100	-1.03450600
C	-4.91045700	-5.91113700	3.47886900	H	4.86094300	-2.50736400	0.45854700
H	-5.41583500	-6.19936600	4.40974400	Ag	-5.45618900	1.60060400	-2.16185400
H	-5.58824400	-6.15680200	2.65431500	N	-3.05669500	0.49861200	1.88450300
H	-4.01644100	-6.53491800	3.38480700	S	-3.57295600	0.12264300	3.43797200
C	-4.07574800	1.31544900	-7.78808600	O	-4.83029500	0.85289100	3.60317800
C	-3.63549900	2.29226500	-6.87490600	O	-2.40386800	0.32888000	4.29121800
C	-3.57344300	3.64884800	-7.24734600	C	-3.94944000	-1.62860300	3.43553600
C	-3.95521000	4.01940600	-8.53321100	C	-5.24319800	-2.05858400	3.12564800
C	-4.39419800	3.05081100	-9.44118900	C	-2.93960000	-2.55185500	3.72668800
C	-4.45360400	1.70391900	-9.06966800	C	-5.51670900	-3.42520500	3.09665900
H	-4.11339400	0.27225300	-7.49129900	H	-6.02680900	-1.32979800	2.94699900
H	-3.22670900	4.39190100	-6.53617200	C	-3.23293600	-3.91334400	3.69124000
H	-3.90865400	5.06287300	-8.82819600	H	-1.95162300	-2.20300200	4.00830000
H	-4.68987900	3.34646100	-10.44333300	C	-4.52120900	-4.37277700	3.37706200
H	-4.79258000	0.95672100	-9.78026400	H	-6.52459300	-3.76172000	2.86701800
C	-3.24015900	1.90271900	-5.55792300	H	-2.45174900	-4.63207100	3.92581100
N	-2.91379600	1.58647900	-4.48473800	C	-4.83629400	-5.84922100	3.38413600
				H	-5.09205800	-6.18751300	4.39670700
				H	-5.68825600	-6.08219300	2.73774900
				H	-3.97989800	-6.44448000	3.05077500
				C	-3.82311200	1.10551500	-7.23319100
				C	-3.40144100	2.09618900	-6.31874600
IN8							
C	-4.02860200	0.61943000	0.78945100				
H	-4.65785100	1.50359000	0.93429700				
H	-4.68985100	-0.26055600	0.70443200				

C	-3.35179000	3.45780900	-6.69192100
C	-3.72625000	3.81682000	-7.98104400
C	-4.14439700	2.83653700	-8.88849000
C	-4.19284200	1.48784800	-8.51688900
H	-3.85253800	0.06349600	-6.93191600
H	-3.02250900	4.20622400	-5.97851500
H	-3.69120000	4.85906200	-8.28098200
H	-4.43403500	3.12588300	-9.89422500
H	-4.51704400	0.73673500	-9.22978400
C	-3.01611900	1.71858100	-5.01072500
N	-2.68626700	1.41017700	-3.94136200

IN9

C	-3.44076500	-1.65140800	-0.17336500
H	-4.48018600	-1.47691000	0.12199300
H	-3.43837300	-2.46339400	-0.91588900
C	-1.29223200	-1.29754100	0.92866900
H	-0.99246800	-0.89491500	1.90253900
H	-0.50159400	-1.98577900	0.59293800
C	-2.76546600	-0.41944200	-0.72536500
C	-1.54095900	-0.22491000	-0.09440000
C	-3.23101900	0.42002500	-1.74007400
C	-0.67839100	0.84156000	-0.43251700
C	-2.34125600	1.47903500	-2.03658000
C	0.55489700	0.90256200	0.28611600
C	-1.07555300	1.75582800	-1.44012600
C	1.56384500	0.82212500	0.97064300
Si	-0.02936300	3.27891900	-2.00618000
C	-1.04929800	4.84966600	-1.69404100
H	-0.45806100	5.72742000	-1.98332400
H	-1.99693100	4.90433900	-2.23985300
H	-1.27737700	4.95045400	-0.62626500
C	0.38230600	3.06972100	-3.84737200
H	0.97036300	2.15821000	-4.00700900
H	-0.48728500	3.02173400	-4.51102800
H	0.99745200	3.91528500	-4.17940100
C	1.60575800	3.50857200	-1.10034000
H	1.47802200	3.65156600	-0.02422400
H	2.29343500	2.67228500	-1.24916100
H	2.07784800	4.41255900	-1.50837000
Si	3.10888800	0.72040400	1.99219500
C	3.26931900	2.32438100	2.97653400
H	3.33467400	3.19732600	2.31709800
H	2.41441900	2.47145100	3.64621700
H	4.17628700	2.30552200	3.59330500
C	2.94059100	-0.76225600	3.14921400
H	2.83254700	-1.69790300	2.58893300
H	3.83015900	-0.85560100	3.78422700
H	2.07049500	-0.66120700	3.80791800
C	4.57307300	0.49687000	0.82119900
H	4.47398500	-0.41807900	0.22634900
H	4.66699400	1.34085000	0.12833800
H	5.50979200	0.42635000	1.38768500
Ag	-5.07343200	-0.00472500	-2.66784600
N	-2.61422200	-1.96090200	1.02050200
S	-2.63140600	-3.58580200	1.51209100
O	-1.51000800	-4.31721700	0.90450300
O	-4.01295600	-4.02354700	1.28867200

C	-2.31025500	-3.44358500	3.26418600
C	-1.11040800	-3.92848000	3.78289600
C	-3.28457000	-2.88412300	4.09791000
C	-0.88194100	-3.83860000	5.15710200
H	-0.37763000	-4.37527900	3.11975600
C	-3.03767900	-2.80234600	5.46366800
H	-4.21974700	-2.52658900	3.67979200
C	-1.83539000	-3.27807700	6.01595800
H	0.05083600	-4.21686000	5.56705600
H	-3.79072500	-2.36839300	6.11687900
C	-1.59521300	-3.20183200	7.50458700
H	-2.23701100	-3.91157900	8.04185400
H	-0.55717000	-3.43736600	7.75694200
H	-1.82284800	-2.20334000	7.89509500
C	-4.53518500	4.93703900	-4.59026300
C	-3.72433200	3.82963700	-4.91968000
C	-3.40813400	3.53547700	-6.26355400
C	-3.90612400	4.35573500	-7.26914100
C	-4.70879000	5.45497700	-6.94428200
C	-5.02258100	5.74416300	-5.61156700
H	-4.76818600	5.14996800	-3.55211100
H	-2.78249000	2.68104000	-6.49990300
H	-3.66790700	4.14118600	-8.30589600
H	-5.09198700	6.09192800	-7.73591100
H	-5.64503700	6.59982400	-5.37065600
C	-3.21206000	3.00611600	-3.88658000
N	-2.77439400	2.34208500	-3.04187300
C	-9.17521700	-1.66378600	-4.34445600
C	-10.39738000	-1.21290000	-3.81064500
C	-11.58339600	-1.79450000	-4.24706100
C	-11.55456000	-2.81388100	-5.20394400
C	-10.33883600	-3.26002700	-5.73159600
C	-9.14261500	-2.69049400	-5.30725300
H	-10.40640200	-0.42321600	-3.06645600
H	-12.53043900	-1.45485800	-3.83991600
H	-12.48421200	-3.26435500	-5.53865500
H	-10.32355100	-4.05349400	-6.47196600
H	-8.19264500	-3.03049300	-5.70659400
C	-7.95283000	-1.07947400	-3.89856200
N	-6.95648000	-0.60460100	-3.53694500

TS6

C	-4.34496200	-2.37636600	0.55031100
H	-5.40939200	-2.18067000	0.72773300
H	-4.21941900	-3.45435700	0.36461900
C	-2.23003900	-1.38381900	1.22323000
H	-1.91492200	-0.53524400	1.83569200
H	-1.42246400	-2.13012600	1.26231800
C	-3.77241900	-1.56615100	-0.58933500
C	-2.54980100	-1.01795700	-0.19969400
C	-4.28730800	-1.36358700	-1.86412400
C	-1.75790700	-0.27867700	-1.09433900
C	-3.49192300	-0.58399300	-2.74047400
C	-0.51177200	0.21034800	-0.59254700
C	-2.21207100	-0.06024300	-2.42848400
C	0.52420500	0.57546700	-0.05596300
Si	-1.03908400	0.86219100	-3.65849000
C	-0.75761800	2.62171800	-3.02268500

H	-0.04165400	3.14015800	-3.67262800	C	-4.83534500	2.77900400	1.09186900
H	-1.68874600	3.20196800	-3.03497200	C	-5.00007400	4.16793700	1.06494000
H	-0.36026400	2.63774400	-2.00445300	C	-5.33252100	4.82562200	-0.12510300
C	-1.72823300	1.00882800	-5.41736100	C	-5.50645400	4.09963900	-1.29679600
H	-1.97850500	0.04134400	-5.86458700	H	-4.86149800	0.95658700	-0.06637000
H	-2.60044700	1.66549700	-5.50025700	H	-4.57194200	2.27747400	2.01751700
H	-0.93548300	1.45202400	-6.03427500	H	-4.86630000	4.74316800	1.97623500
C	0.55846500	-0.13723000	-3.79088600	H	-5.45649900	5.90366400	-0.13692100
H	1.03275100	-0.30682500	-2.82126600	H	-5.76750100	4.59608500	-2.22559300
H	0.36769100	-1.11411300	-4.25142800	C	-5.53639700	1.95429100	-2.45586500
H	1.27467200	0.39301500	-4.43111100	N	-5.77581100	1.38566700	-3.45012600
Si	2.10305400	1.09977700	0.77312900				
C	3.24586900	-0.39995500	0.84252200				
H	2.79534700	-1.22089000	1.41149700	IN10			
H	3.48133900	-0.77453400	-0.15998800	C	-3.69699300	-4.85555700	-2.22114800
H	4.19237600	-0.13660000	1.33057900	H	-4.73221900	-4.56466500	-1.99370700
C	2.86882600	2.49258000	-0.24634200	H	-3.73603200	-5.74345900	-2.85618100
H	2.19986000	3.35814100	-0.31427600	C	-2.25388200	-3.92793100	-0.53482800
H	3.80454200	2.83171700	0.21474600	H	-2.84234900	-3.38377100	0.21525000
H	3.10143600	2.16547600	-1.26607200	H	-1.29134900	-4.17494500	-0.08028300
C	1.66409300	1.69893600	2.50899900	C	-2.92439500	-3.69168700	-2.80742100
H	0.97771900	2.55291200	2.47945400	C	-2.11689000	-3.13886400	-1.81593400
H	1.19271300	0.90547600	3.09992200	C	-2.96638000	-3.15964800	-4.09041800
H	2.56798200	2.01778100	3.04247700	C	-1.36312600	-1.97252000	-2.04291000
Ag	-6.08639200	-2.32711400	-2.43739600	C	-2.15870400	-2.02054300	-4.33075900
N	-3.53802000	-1.91347800	1.70303700	C	-0.62134300	-1.48496400	-0.92223700
S	-3.42609600	-2.97855800	3.03112200	C	-1.39054900	-1.36094800	-3.32817700
O	-2.37946400	-2.40292200	3.87894900	C	-0.04487400	-1.18855600	0.11393100
O	-3.33768500	-4.36589700	2.55518900	Si	-0.52211600	0.30722800	-3.77362800
C	-5.01767400	-2.76726600	3.81740300	C	-1.87952100	1.54943300	-4.22241600
C	-5.24979100	-1.63020300	4.59742700	H	-1.43318900	2.49119100	-4.56548800
C	-5.99063700	-3.75775300	3.68075500	H	-2.54475700	1.18032700	-5.00808800
C	-6.47976900	-1.48574700	5.23133900	H	-2.49359800	1.77957600	-3.34360600
H	-4.46985300	-0.88540400	4.71718700	C	0.69159000	0.05182300	-5.21412500
C	-7.21841000	-3.59411800	4.32359300	H	1.36086700	-0.79813500	-5.02972600
H	-5.77747100	-4.64745300	3.09776200	H	0.20483200	-0.09523100	-6.18274500
C	-7.48225200	-2.46281800	5.10720100	H	1.32583000	0.94256600	-5.30313100
H	-6.66400300	-0.60713300	5.84470700	C	0.49091200	1.06369700	-2.37138200
H	-7.97787300	-4.36543300	4.22504400	H	-0.11250300	1.30386700	-1.49221600
C	-8.79664600	-2.30996100	5.83388500	H	1.31822400	0.42590500	-2.04792800
H	-8.69541900	-2.60347600	6.88673600	H	0.91749200	2.00116000	-2.75353300
H	-9.14441800	-1.27134400	5.82076000	Si	0.83746600	-0.67869500	1.66183700
H	-9.57635100	-2.93800600	5.39241900	C	0.84157600	-2.15265400	2.84423000
C	-5.01301400	-0.50816800	-6.86790600	H	-0.17724100	-2.45951900	3.10723700
C	-5.52606200	0.34679700	-5.86889800	H	1.35248900	-3.01766400	2.40596600
C	-6.57831200	1.22662100	-6.16814000	H	1.36158900	-1.89626300	3.77547600
C	-7.10848100	1.25472400	-7.45518200	C	2.60205000	-0.18766600	1.20250200
C	-6.59771500	0.41070500	-8.44443700	H	2.61300900	0.64381700	0.48880100
C	-5.55136100	-0.46975500	-8.14832100	H	3.15648000	0.13131700	2.09364300
H	-4.20158800	-1.18667400	-6.62785800	H	3.14779500	-1.02503100	0.75289500
H	-6.97693800	1.87610600	-5.39808500	C	-0.09468100	0.77893700	2.41794400
H	-7.92192100	1.93539000	-7.68549200	H	-0.12504300	1.63519200	1.73472200
H	-7.01551600	0.43646600	-9.44642300	H	-1.12788900	0.50969300	2.66469800
H	-5.15594300	-1.12687500	-8.91651500	H	0.39423700	1.10844700	3.34303000
C	-4.91775700	0.26490500	-4.55664900	Ag	-4.40969300	-3.88775300	-5.46410900
N	-4.02467300	-0.34820100	-4.01876700	N	-2.99788000	-5.15424800	-0.94158000
C	-5.34278800	2.69753400	-1.26480300	C	-2.41394300	-0.16005300	-8.21286400
C	-5.00201400	2.03179400	-0.06847400	C	-1.89357300	-1.45704600	-8.04805200
				C	-1.49545500	-2.19414100	-9.17575700

C	-1.61171800	-1.64081200	-10.44892500	H	-3.29905900	2.71092000	-4.27150800
C	-2.12232900	-0.35067600	-10.60659000	H	-3.83482700	1.04034900	-4.52828000
C	-2.52259000	0.38648800	-9.48656200	H	-3.57802600	1.65040700	-2.88515500
H	-2.72314800	0.40238500	-7.33905900	C	-0.65732200	1.31717000	-5.71533800
H	-1.10326600	-3.20047000	-9.06464400	H	0.32984300	0.84467300	-5.79219200
H	-1.30482100	-2.21672200	-11.31648700	H	-1.29879900	0.90039900	-6.49721700
H	-2.21088200	0.07979900	-11.59959800	H	-0.51980900	2.38135300	-5.94379900
H	-2.92118700	1.38892400	-9.60849700	C	-0.40802900	2.35956200	-2.87864600
C	-1.78444100	-2.00685700	-6.69067600	H	-0.76913500	2.38549600	-1.84733800
N	-2.16314400	-1.44763200	-5.61936900	H	0.66493600	2.14933000	-2.85612800
C	0.43425100	-5.13739500	-5.73635300	H	-0.54497000	3.36123900	-3.30811300
C	0.26771700	-5.65614500	-4.43041300	Si	1.76521400	1.21733100	0.77962800
C	1.09727600	-6.68929800	-4.01300300	C	0.59369800	2.45891100	1.58361400
C	2.07799400	-7.19230100	-4.87459700	H	0.19613300	3.16990900	0.85069200
C	2.24532100	-6.67027300	-6.16591500	H	-0.25483300	1.95698200	2.06182600
C	1.42987400	-5.64154900	-6.61052400	H	1.11857800	3.03504300	2.35548400
H	-0.48607000	-5.25838400	-3.76079400	C	2.41524500	-0.01766500	2.05186600
H	0.96054700	-7.08721800	-3.01376500	H	3.07281600	-0.76402600	1.59155500
H	2.72231600	-7.99980500	-4.53948900	H	2.99296500	0.50176900	2.82617700
H	3.01240400	-7.06984800	-6.82125900	H	1.59583100	-0.54859000	2.54963700
H	1.54520800	-5.22660500	-7.60637100	C	3.19058800	2.09084200	-0.09841200
C	-0.40608500	-4.10665000	-6.18022100	H	3.86116500	1.37597300	-0.58866700
N	-1.13147000	-3.30278400	-6.61646400	H	2.82537800	2.78897400	-0.85996100
S	-2.06124400	-6.58367300	-0.97383500	H	3.78618300	2.66597200	0.62108900
O	-0.67340800	-6.30275800	-1.40647600	Ag	-3.57403300	-4.34032000	-4.55672200
O	-2.85418600	-7.55910900	-1.73038300	N	-0.25653500	-4.62110200	-0.96914100
C	-2.01078700	-7.02458900	0.75271600	C	-4.31712000	-0.58211000	-7.59980500
C	-3.20077800	-7.36626100	1.40558400	C	-3.12661200	-1.32767100	-7.69865900
C	-0.78362300	-7.07801000	1.41225700	C	-2.65819500	-1.72935600	-8.96155000
C	-3.14821400	-7.75321100	2.73920700	C	-3.36813200	-1.38464100	-10.10923900
H	-4.14674800	-7.32894800	0.87579600	C	-4.54806800	-0.64435900	-10.00578600
C	-0.75329800	-7.46932800	2.75177000	C	-5.02031400	-0.24446600	-8.74983600
H	0.12741100	-6.82177000	0.88289700	H	-4.67280800	-0.27562100	-6.62194400
C	-1.92696500	-7.81116900	3.43454200	H	-1.73918700	-2.30094900	-9.04304000
H	-4.06856800	-8.01957300	3.25260400	H	-3.00052200	-1.69260000	-11.08311900
H	0.20001100	-7.51237200	3.27154200	H	-5.10086600	-0.37827900	-10.90189500
C	-1.89351200	-8.23734200	4.88196200	H	-5.93703000	0.33176600	-8.67109200
H	-2.29704300	-9.24968900	5.00403500	C	-2.39411000	-1.66999000	-6.48004700
H	-0.87484200	-8.23126800	5.27995700	N	-2.65980800	-1.27622000	-5.30292800
H	-2.50344300	-7.57144100	5.50428600	C	0.45234300	-4.09232800	-5.55332300
				C	1.44364600	-3.66880500	-4.64162800
				C	2.47301200	-4.54219200	-4.31297000
				C	2.51031200	-5.82590700	-4.86862300
				C	1.51973100	-6.24823100	-5.76399000
				C	0.48547700	-5.39017900	-6.11366100
				H	1.39431600	-2.67396800	-4.21346500
				H	3.24474000	-4.22568400	-3.61906300
				H	3.31637700	-6.50330800	-4.60335000
				H	1.55929600	-7.24502100	-6.19131300
				H	-0.28354500	-5.70054000	-6.81345700
				C	-0.57483300	-3.19991900	-5.93850200
				N	-1.22537300	-2.52404000	-6.67610000
				S	-0.37351000	-5.68544500	0.35741300
				O	-0.74978100	-6.97004800	-0.24079100
				O	-1.19121800	-5.08197300	1.41813900
				C	1.31576200	-5.75932500	0.93381200
				C	1.68206300	-5.05898300	2.08348100
				C	2.23869800	-6.55508300	0.24786100
TS7							
C	-1.32746200	-4.79684100	-1.98432400				
H	-2.30010600	-5.05864100	-1.53937900				
H	-1.05805500	-5.59611900	-2.68252200				
C	-0.07723400	-3.18048000	-0.65881000				
H	-0.61579900	-2.87891600	0.25218300				
H	0.98311100	-2.94818200	-0.51223700				
C	-1.38508600	-3.43512600	-2.62802100				
C	-0.66841900	-2.51904100	-1.87479400				
C	-2.06998700	-3.04606100	-3.78272200				
C	-0.60769000	-1.14776300	-2.22732700				
C	-1.98189300	-1.67650700	-4.14577600				
C	0.13897600	-0.31676700	-1.33854600				
C	-1.28004600	-0.68761800	-3.38993000				
C	0.80091800	0.26921600	-0.49423800				
Si	-1.37744600	1.15951100	-3.96562100				
C	-3.19589500	1.67938800	-3.91247000				

C	2.99821000	-5.14685600	2.53856400
H	0.94289500	-4.47217300	2.61814700
C	3.54545100	-6.63135100	0.71879500
H	1.92663600	-7.11654200	-0.62655000
C	3.94698100	-5.93121000	1.86942900
H	3.28796300	-4.60613600	3.43563800
H	4.26647200	-7.25447900	0.19524300
C	5.35941000	-6.05369000	2.38801000
H	6.08902600	-6.05051200	1.57091500
H	5.60893300	-5.23756500	3.07258800
H	5.49247300	-6.99534500	2.93610500

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C	-2.69485600	-4.25203700	-0.20457100
H	-3.43653700	-4.46183300	0.58004100
H	-2.77074400	-5.02161500	-0.97848300
C	-0.85678600	-2.81294600	0.52130700
H	-0.91610900	-2.48991400	1.57015700
H	0.18039200	-2.71181400	0.18931000
C	-2.87626300	-2.85980100	-0.73673100
C	-1.83726700	-2.05999900	-0.34463800
C	-3.92129400	-2.34711700	-1.53923400
C	-1.76617600	-0.68717000	-0.72749200
C	-3.81985600	-0.98906900	-2.00216200
C	-0.65022700	0.03330400	-0.19907900
C	-2.74398900	-0.12779500	-1.57266300
C	0.33493100	0.54311600	0.31524700
Si	-2.57634100	1.74407700	-2.05655400
C	-2.67598400	2.73486800	-0.44424000
H	-2.48941900	3.79558800	-0.65480000
H	-3.68034200	2.66244600	-0.00924500
H	-1.95475900	2.40955000	0.31000600
C	-3.89564700	2.43924600	-3.20754800
H	-3.84413200	1.98817200	-4.20262800
H	-4.91000900	2.30912700	-2.82278500
H	-3.70694400	3.51565400	-3.31868600
C	-0.91834500	1.96470900	-2.94532000
H	-0.77481400	3.02603500	-3.18474600
H	-0.06038900	1.63419100	-2.35491700
H	-0.91259500	1.41461000	-3.89433800
Si	1.81157500	1.38558600	1.06525900
C	3.29974100	0.24150700	0.84773900
H	3.14763500	-0.72003600	1.35157700
H	3.50065800	0.04128900	-0.21081800
H	4.19909900	0.70169500	1.27510400
C	2.07807300	3.01733600	0.15815900
H	1.20849500	3.67671100	0.25558000
H	2.94632700	3.54733300	0.56855900
H	2.25989900	2.85736300	-0.91053400
C	1.44626300	1.67137100	2.89540200
H	0.56016800	2.30089800	3.03366800
H	1.27456800	0.72793900	3.42605700
H	2.29164100	2.17646800	3.37863100
Ag	-3.76882600	-7.08732700	0.62301100
N	-1.31364700	-4.22657800	0.33980200
S	-1.07321600	-5.31414500	1.59381700
O	-1.63326400	-6.60856100	1.05893000
O	-1.61629400	-4.85415600	2.87617800

C	0.68658700	-5.47432400	1.68794200
C	1.41595700	-5.84675500	0.55202100
C	1.30561800	-5.26193300	2.92182900
C	2.79276600	-5.99806000	0.66703500
H	0.91750800	-6.00653300	-0.39809100
C	2.68711500	-5.42311200	3.01041800
H	0.71667300	-4.97599200	3.78648100
C	3.45004800	-5.79434500	1.89380900
H	3.37072900	-6.28106000	-0.20846500
H	3.17934800	-5.25704700	3.96444200
C	4.94055300	-5.99473500	2.00537500
H	5.35396900	-5.46841500	2.87041400
H	5.17801800	-7.06005200	2.12282500
H	5.45996700	-5.64450200	1.10753500
C	-6.57603300	0.44839800	-4.86291700
C	-6.74054400	-0.79906000	-4.23815500
C	-7.86122100	-1.58288600	-4.56756800
C	-8.79339000	-1.12516400	-5.49559500
C	-8.62150100	0.11736600	-6.11061100
C	-7.50929100	0.90114000	-5.79137000
H	-5.71451600	1.05312700	-4.61450300
H	-7.99184000	-2.54547400	-4.08748400
H	-9.65669800	-1.73822200	-5.73858600
H	-9.34945200	0.47291400	-6.83452900
H	-7.36888700	1.86723700	-6.26780900
C	-5.75190400	-1.29052800	-3.25188000
N	-4.75660300	-0.50500800	-2.86347700
C	-5.41543700	-4.42982600	-1.40771600
C	-5.21935400	-5.57639200	-2.19569100
C	-5.47382100	-6.84749400	-1.67817500
C	-5.95597700	-6.99448400	-0.35316100
C	-6.20298100	-5.83324700	0.42061300
C	-5.92343000	-4.56842900	-0.10693500
H	-4.86368700	-5.46812000	-3.21579200
H	-5.34136200	-7.72652100	-2.30237400
H	-6.30452000	-7.96588500	-0.00584000
H	-6.64683000	-5.92600900	1.40786400
H	-6.10910300	-3.68284800	0.49376300
C	-5.08833900	-3.06307100	-1.94671700
N	-5.96403600	-2.56352600	-2.78508600

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C	-3.60287000	-1.70170500	2.06900100
H	-4.42572100	-1.16550700	2.55239000
H	-3.97499300	-2.69829500	1.78785800
C	-1.17207600	-1.55083000	2.22399800
H	-0.48145500	-0.91846800	2.79298600
H	-0.65515900	-2.49655300	2.00011600
C	-3.04681100	-0.97858700	0.86552800
C	-1.66049800	-0.89631900	0.96242100
C	-3.75981300	-0.47881700	-0.22615700
C	-0.87779900	-0.29029900	-0.03982100
C	-2.92985000	0.12429900	-1.20449000
C	0.53704100	-0.27605300	0.16333600
C	-1.51485000	0.26111600	-1.18397000
C	1.72866400	-0.32418600	0.43139100
Si	-0.40624700	1.10775200	-2.52318500
C	-1.37406600	1.83322900	-3.98731100

H	-0.63280400	2.29710700	-4.65075400	C	-10.41327100	-1.61368800	0.24362900
H	-1.90227700	1.08268200	-4.58542300	C	-11.40063200	-0.87728000	-0.42363400
H	-2.07778200	2.62336600	-3.70307200	C	-12.73736200	-1.19747300	-0.20162000
C	0.75985600	-0.19267100	-3.24214100	C	-13.07770000	-2.23461800	0.67159200
H	1.37265700	-0.67261800	-2.47515800	H	-12.34719100	-3.76424800	2.00832900
H	0.19970400	-0.97554100	-3.76781600	H	-9.94962600	-3.20689900	1.62467400
H	1.43299300	0.27529900	-3.97144100	H	-11.11663700	-0.07481900	-1.09619000
C	0.49216200	2.56033800	-1.71548100	H	-13.51388200	-0.63535000	-0.71065400
H	-0.22059900	3.32356500	-1.38006900	H	-14.12231200	-2.47780500	0.83973300
H	1.09204500	2.25660300	-0.85416400	N	-9.07546300	-1.30329600	0.03265300
H	1.16121500	3.03423400	-2.44485600	C	-7.94566500	-1.06022800	-0.12360600
Si	3.54057600	-0.40706400	0.82841700				
C	4.23355600	1.34884300	0.77301700				
H	4.10413100	1.80183300	-0.21650700				
H	3.74327300	1.99804400	1.50726700	TS8			
H	5.30721300	1.34336600	0.99782400	C	-3.04392000	1.62564600	1.49898800
C	3.71954300	-1.14892100	2.55505300	H	-3.12117700	2.52610600	2.11576600
H	3.30488100	-2.16230400	2.60039200	H	-4.04603500	1.16563300	1.43958000
H	4.77788200	-1.20937500	2.83687900	C	-1.29168500	0.01464100	0.98364800
H	3.20829600	-0.54068200	3.30982500	H	-0.24073700	-0.10954800	1.25853000
C	4.37074800	-1.50280100	-0.46564800	H	-1.69956100	-0.98630500	0.76125600
H	3.95925500	-2.51836400	-0.45424100	C	-2.49417600	1.88376200	0.11427200
H	4.24365500	-1.09950400	-1.47680400	C	-1.50073200	0.94770200	-0.17897600
H	5.44765700	-1.57724500	-0.27055700	C	-2.87759100	2.84736300	-0.80870500
Ag	-5.86289900	-0.71368200	-0.25869500	C	-0.84176500	0.92985900	-1.42263000
N	-2.43046100	-1.76271800	2.97819500	C	-2.17278800	2.83961900	-2.03907100
S	-2.45472000	-3.03514600	4.10268400	C	0.14175000	-0.08979700	-1.61429200
O	-1.73723900	-4.20233100	3.56936200	C	-1.16930800	1.90280400	-2.40692400
O	-3.86106500	-3.14513300	4.50385700	C	0.95664200	-0.99891500	-1.67365300
C	-1.48935700	-2.36438300	5.44760800	Si	-0.21370500	1.87590400	-4.08881900
C	-0.22337800	-2.88632300	5.71014500	C	-0.73147500	3.24837300	-5.28731100
C	-2.03443500	-1.35342600	6.24642900	H	-0.13363600	3.11817000	-6.19904600
C	0.50929700	-2.37701300	6.78355300	H	-1.78302400	3.19214600	-5.58571400
H	0.16985900	-3.68490100	5.09043700	H	-0.52895300	4.25776300	-4.91442300
C	-1.28880500	-0.85907000	7.31073000	C	-0.57995900	0.22982900	-4.94064700
H	-3.02873200	-0.97182500	6.03924000	H	-0.31021100	-0.63011300	-4.32236300
C	-0.00771900	-1.36203300	7.59818700	H	-1.64410200	0.14665400	-5.19279300
H	1.49545700	-2.78227500	6.99440800	H	-0.01436700	0.16369000	-5.87863200
H	-1.70740100	-0.07447100	7.93622100	C	1.62478600	2.13268400	-3.73061200
C	0.77598800	-0.82994600	8.77372700	H	1.80749500	3.12864000	-3.30881100
H	0.79429300	0.26593200	8.77852900	H	2.02569400	1.39061700	-3.03553500
H	0.32437600	-1.14834800	9.72184300	H	2.19552600	2.06471500	-4.66535100
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C	-5.12443700	1.43745700	-4.23662700	H	4.05853000	-0.93111000	-2.63674000
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C	-6.71177000	2.31901100	-6.33787100	C	1.96081600	-3.48364000	-0.26440200
C	-6.43582100	3.18107400	-5.27072400	H	0.95711300	-3.92316300	-0.24317900
H	-5.41668600	3.40868000	-3.38172400	H	2.68374800	-4.30846800	-0.27857500
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H	-6.83692000	4.18944100	-5.26591200	H	1.97587900	-2.69094500	-4.25291300
C	-4.30526300	0.98935900	-3.17016700	H	2.59565100	-4.15493900	-3.47539700
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C	-12.08058000	-2.95989800	1.33016400	N	-2.02895500	0.71530800	2.05088300
C	-10.73770300	-2.65612700	1.12211300	S	-2.26258700	-0.00985300	3.54675800
				O	-2.87302700	1.02920700	4.37813800
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C	-3.47455500	-1.30604200	3.30574500	H	-0.48729600	-0.36901900	-4.80759200
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C	-3.05204200	-2.58627100	2.93172700	H	-1.90792200	0.49089500	-4.19745200
C	-5.77041200	-2.03018900	3.25217800	C	0.54467500	-2.03192200	-2.23610900
H	-5.14234500	-0.03722400	3.80662100	H	1.05723100	-2.13195500	-1.27536400
C	-4.00450100	-3.57894100	2.71316200	H	-0.09033900	-2.91517900	-2.37708800
H	-1.99256900	-2.80387100	2.84726900	H	1.30409300	-2.04710500	-3.02801200
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H	-6.82669900	-1.81496600	3.39221800	H	0.00327600	2.01736600	-2.39177400
H	-3.67811000	-4.57657500	2.43010300	H	1.13827800	1.20686300	-1.29794900
C	-6.39364900	-4.41578900	2.66596900	H	1.35723200	1.09392200	-3.05239300
H	-6.11578800	-5.07334300	1.83541300	Si	3.16968500	-0.37003700	1.66960200
H	-6.47394400	-5.04348700	3.56296600	C	4.01905400	1.13382300	0.90849900
H	-7.38835200	-4.00781700	2.46186300	H	3.97356000	1.11092400	-0.18616500
C	-4.07933400	5.19093300	-5.22791500	H	3.55715200	2.06898200	1.24465200
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C	-4.68604500	5.95977100	-6.21420400	H	2.73394100	0.64344900	3.92052600
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H	-5.18796900	7.94953900	-6.87470900	H	5.01006400	-2.02023300	1.34830500
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C	-2.84421000	4.97500600	-3.13928300	N	-3.00419600	-0.34422200	3.72845100
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N	-1.53621300	6.37437600	-0.82231700	H	-2.15886200	0.18113300	8.82140500
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C	-4.04234100	-0.58174000	2.61269100
H	-4.50397500	0.39936500	2.79988600
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H	-0.01054300	2.25875600	-2.22380700
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C	3.23515000	-0.20065400	3.56925100
H	2.75155300	-1.09422800	3.98013200
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O	-2.34277400	-3.35878400	3.72364000
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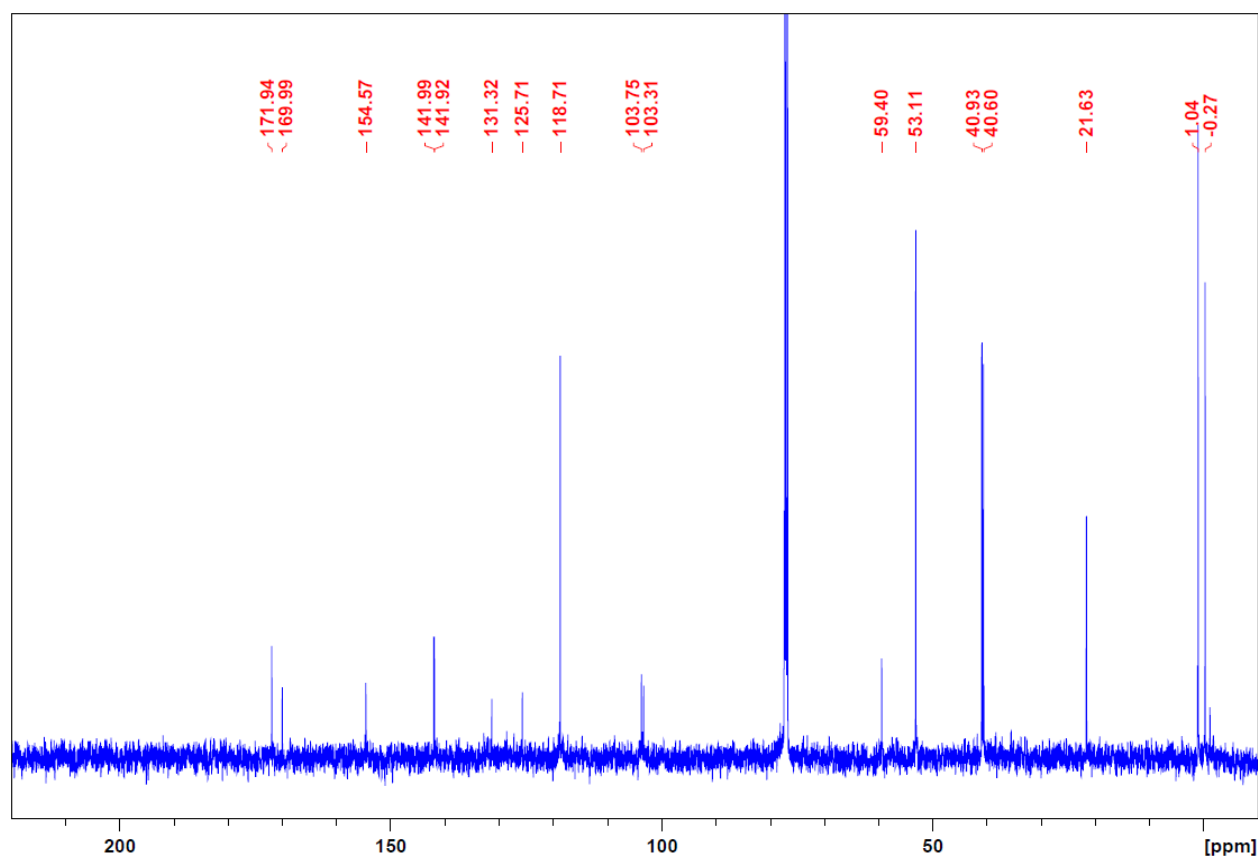
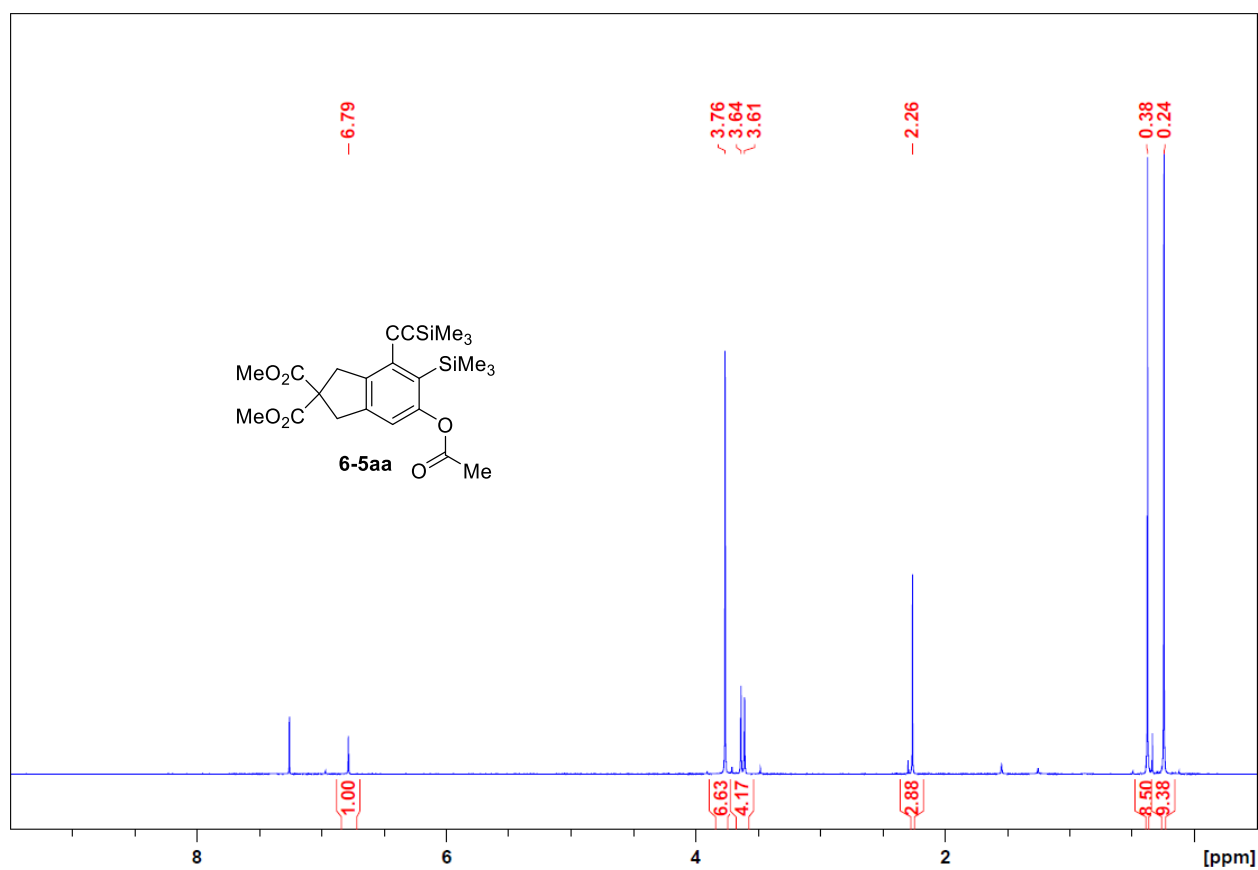
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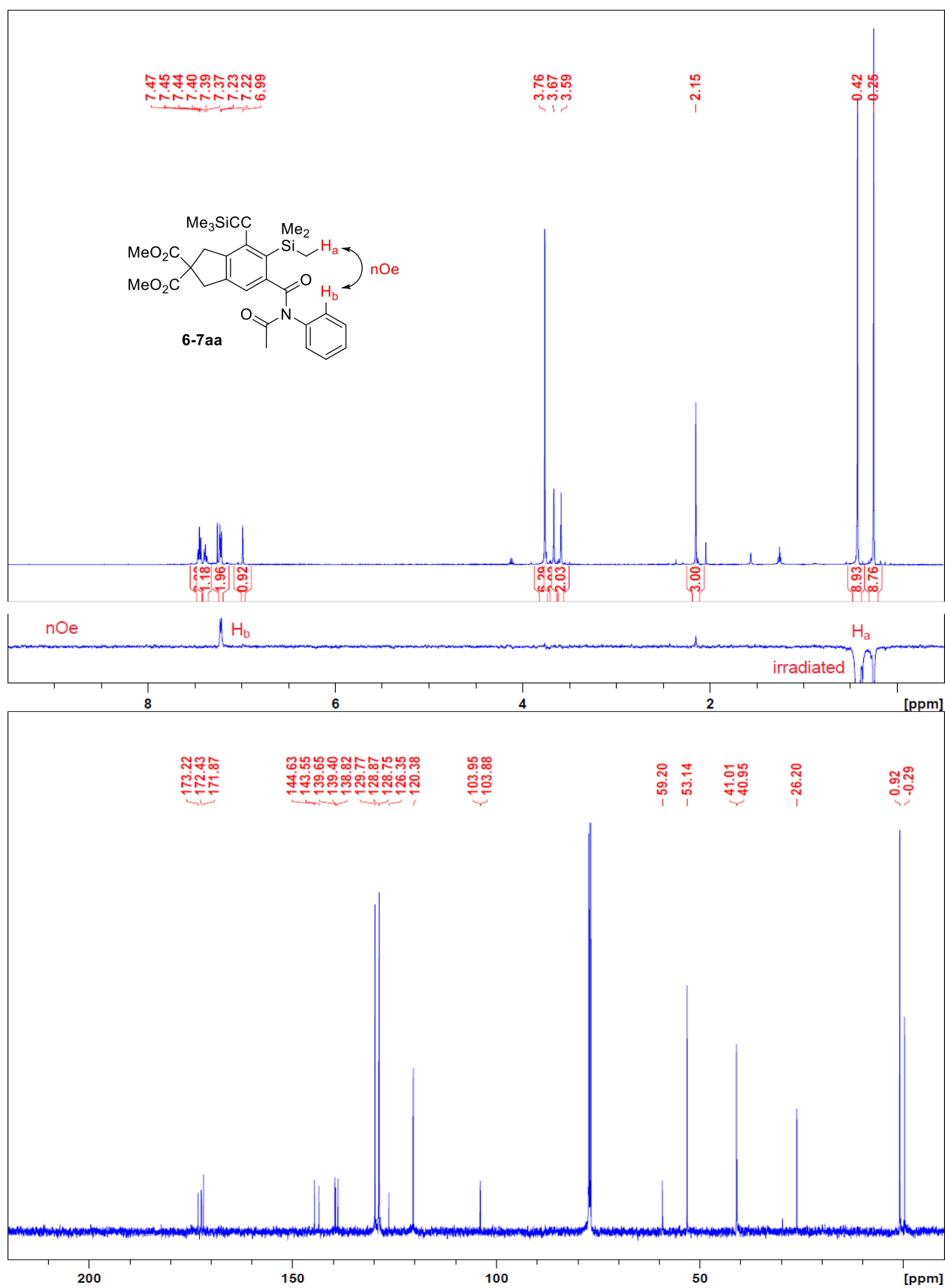
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C	-2.52603900	-1.36502900	-1.36465900
C	0.50675600	-0.68237000	0.70448400
C	-1.22335900	-0.92620000	-1.10740000
C	1.59355800	-0.38632300	1.18120700
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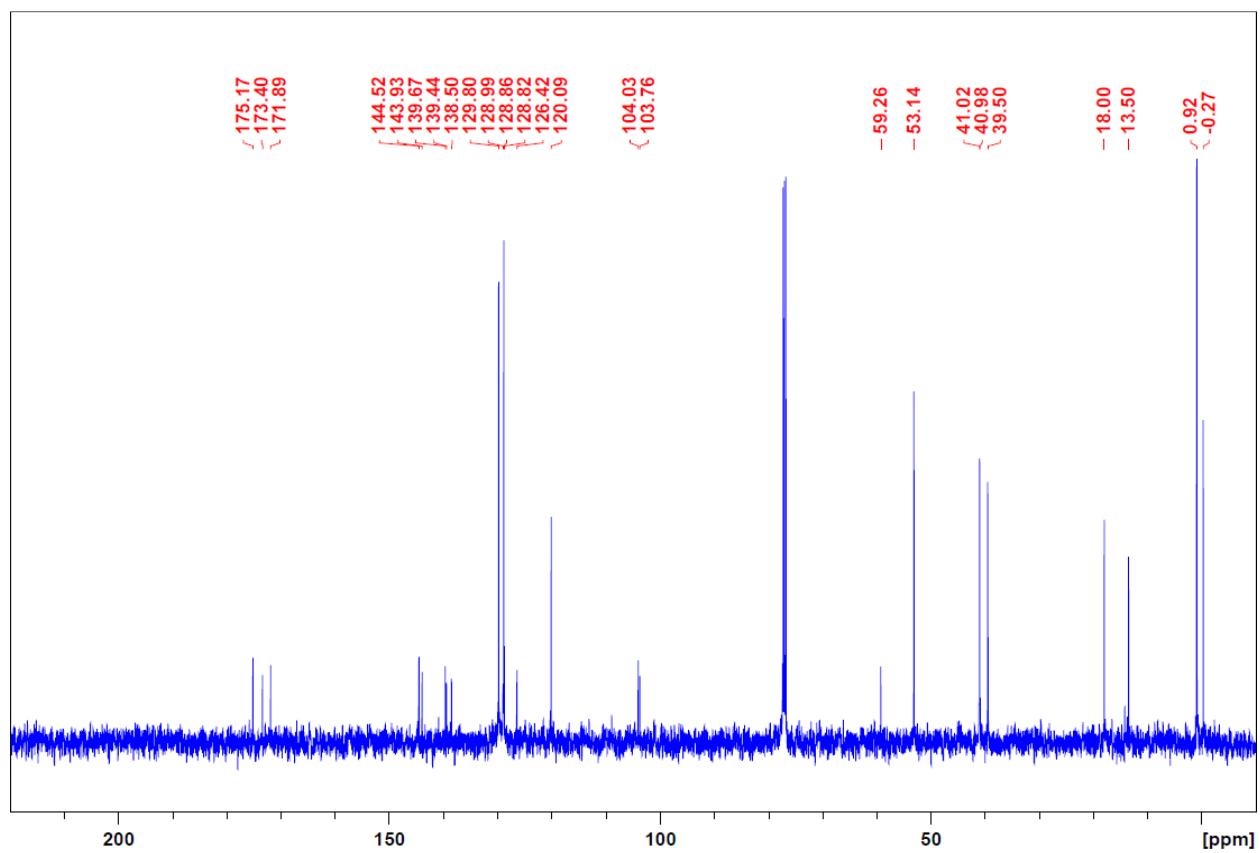
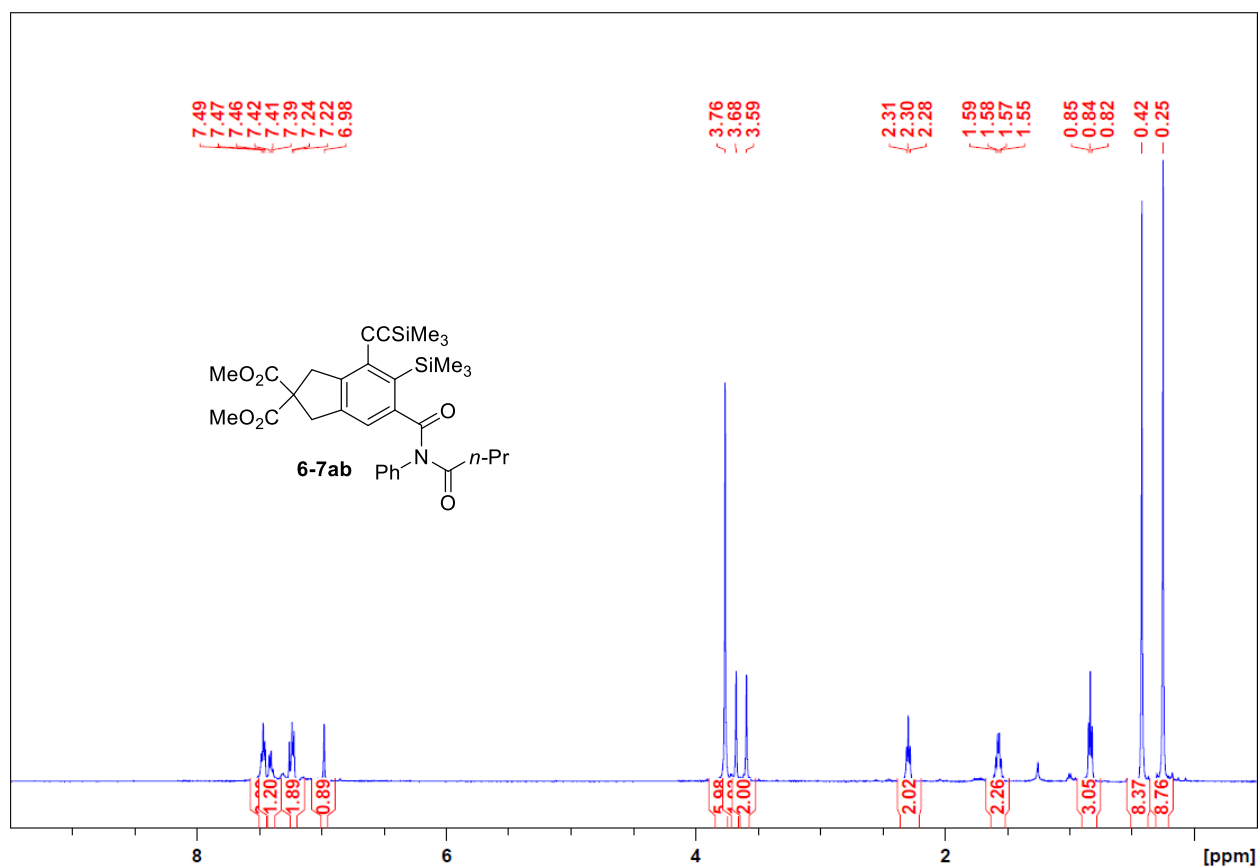
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H	1.24843200	-2.26004100	-2.90130000	H	-4.55291800	-5.25570700	-0.17748700
H	2.20586100	-0.81880300	-3.25617900	H	-7.60479000	-2.41136600	0.90116500
C	0.35417500	1.60115500	-1.91274000	H	-8.42687700	-3.94746400	2.66095300
H	-0.54688300	2.22622300	-1.92383000	H	-7.39792700	-6.22237000	2.91968800
H	0.79217100	1.65548200	-0.91179800	N	-5.68350800	-2.93586600	-0.82478400
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C	3.40805200	1.94936600	1.82748800	PhCN			
H	3.30549200	2.34565600	0.81108200	C	-2.65302000	0.80856800	-0.03457100
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S	-2.76466600	-3.05536700	4.62214200				
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C	-1.71960900	-0.09817700	7.15727500	H	-3.78580600	0.25089900	-0.12785000
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H	-8.60016400	-2.04323900	-4.48669800				
H	-7.65286400	-1.74640400	-6.76428500				
H	-5.19972500	-1.44661000	-7.05521000				
C	-4.37647600	-1.72825400	-2.52182100				
N	-3.16770200	-1.26790400	-2.62509200				
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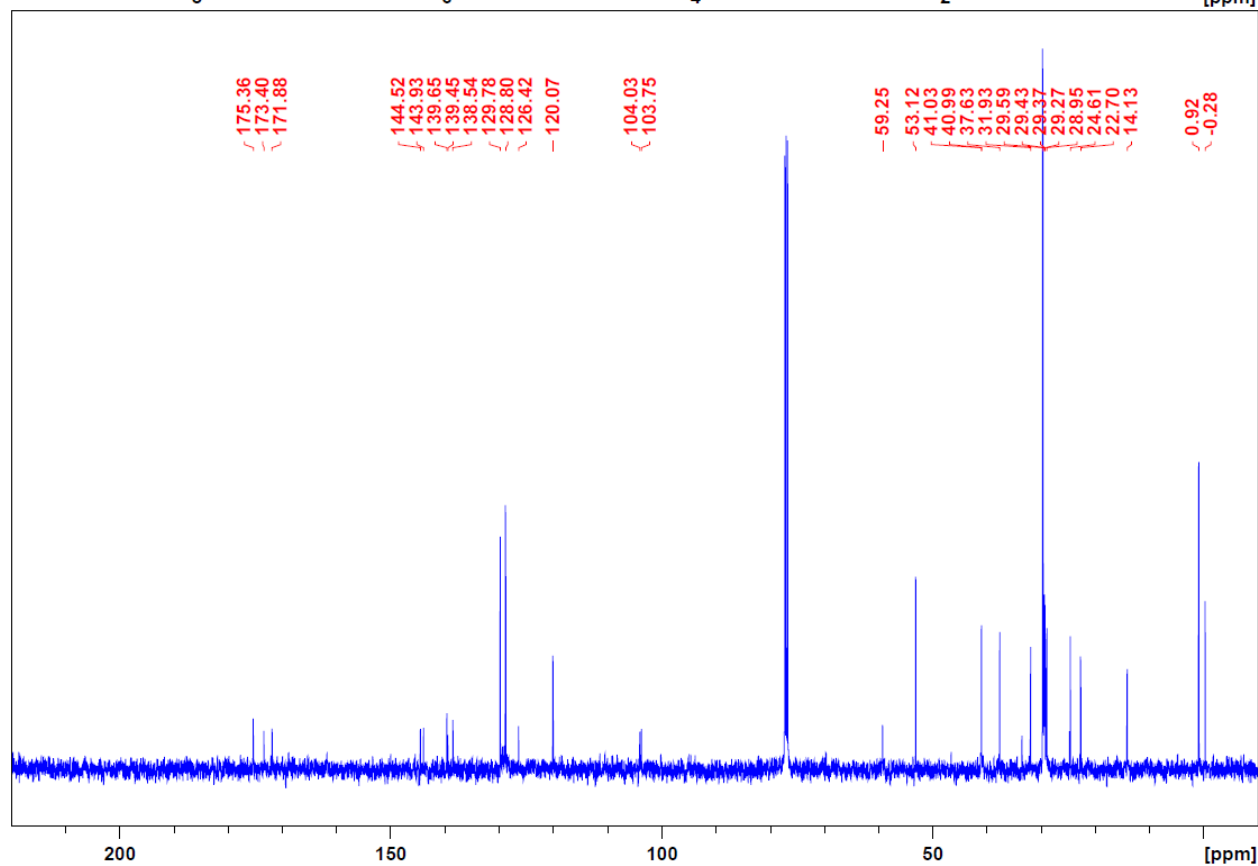
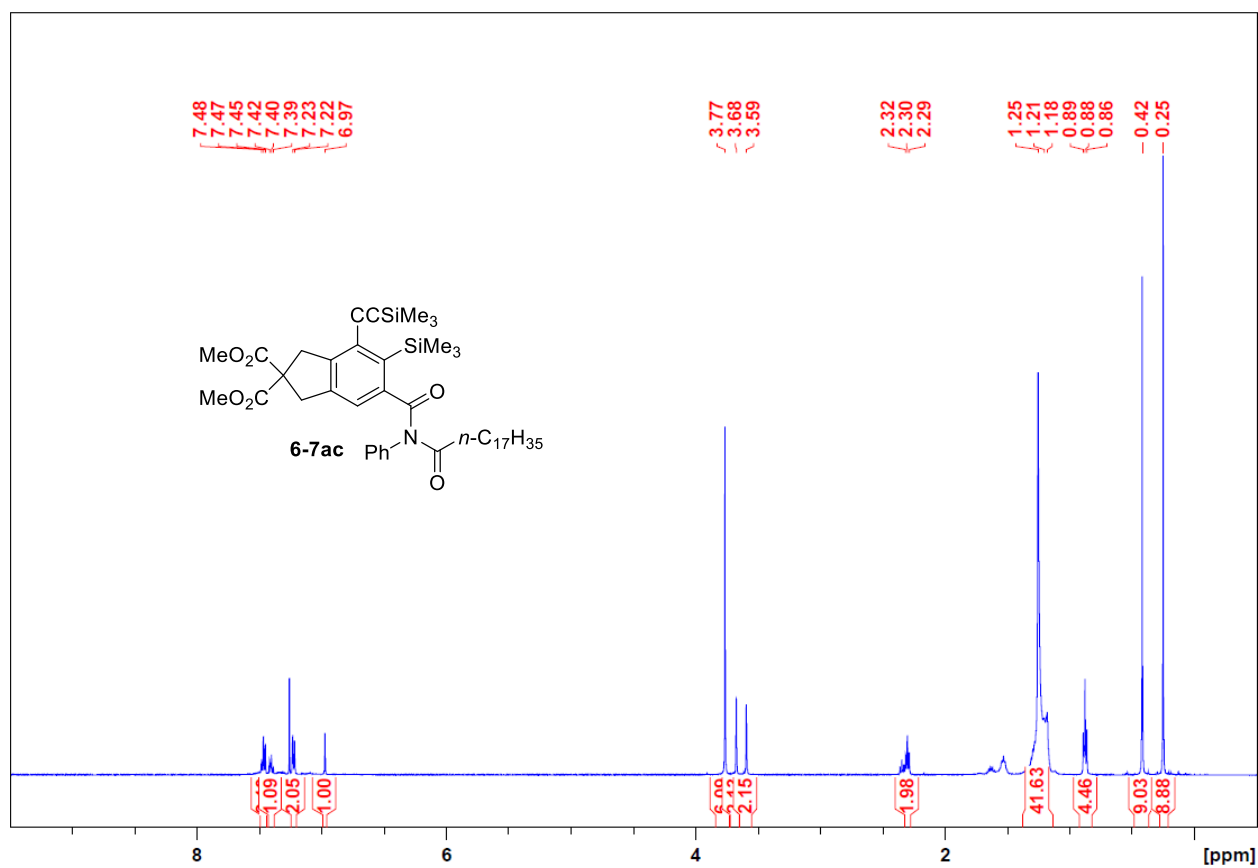
Appendix V

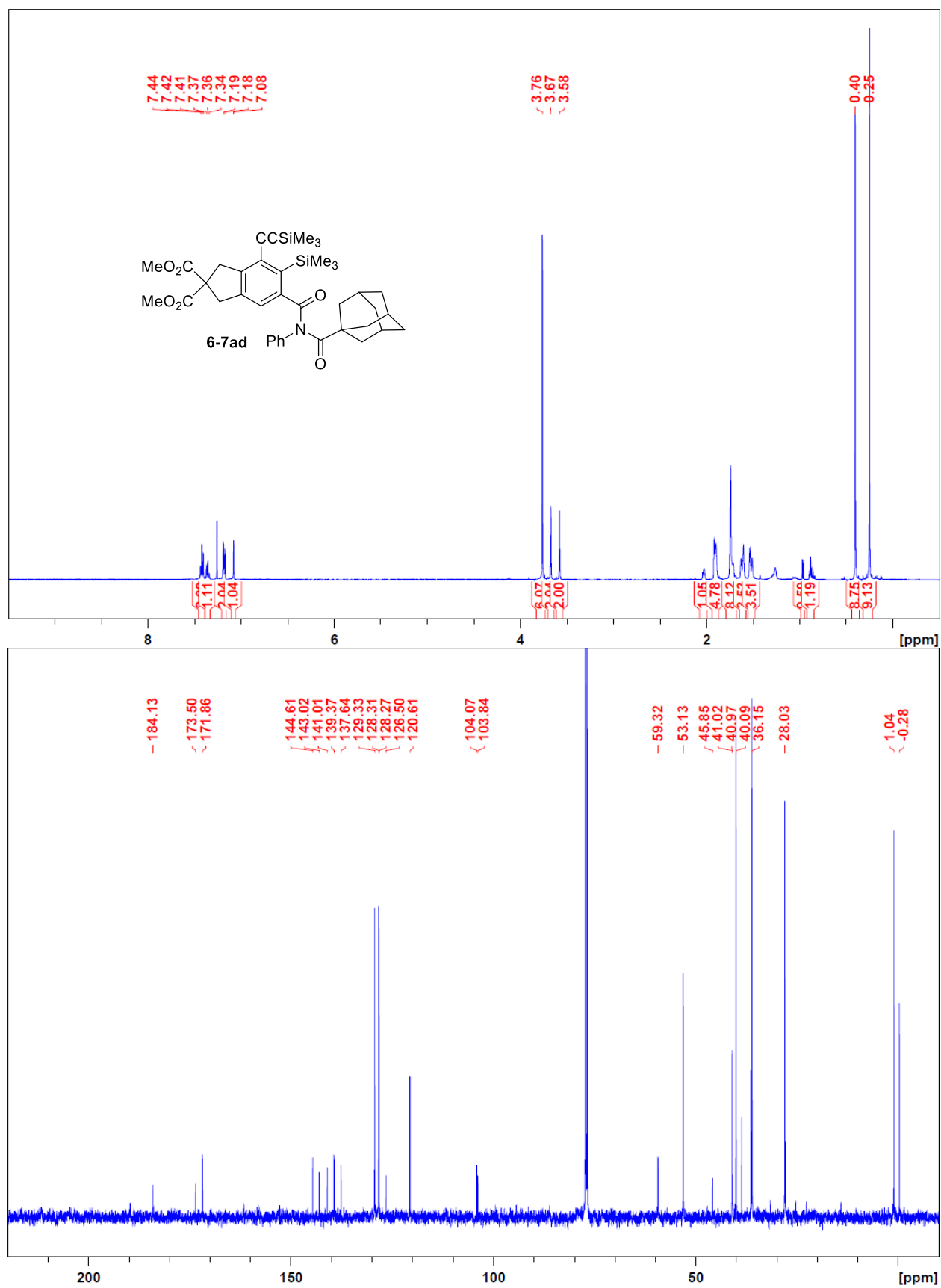
Selected NMR Spectra for Chapter 6

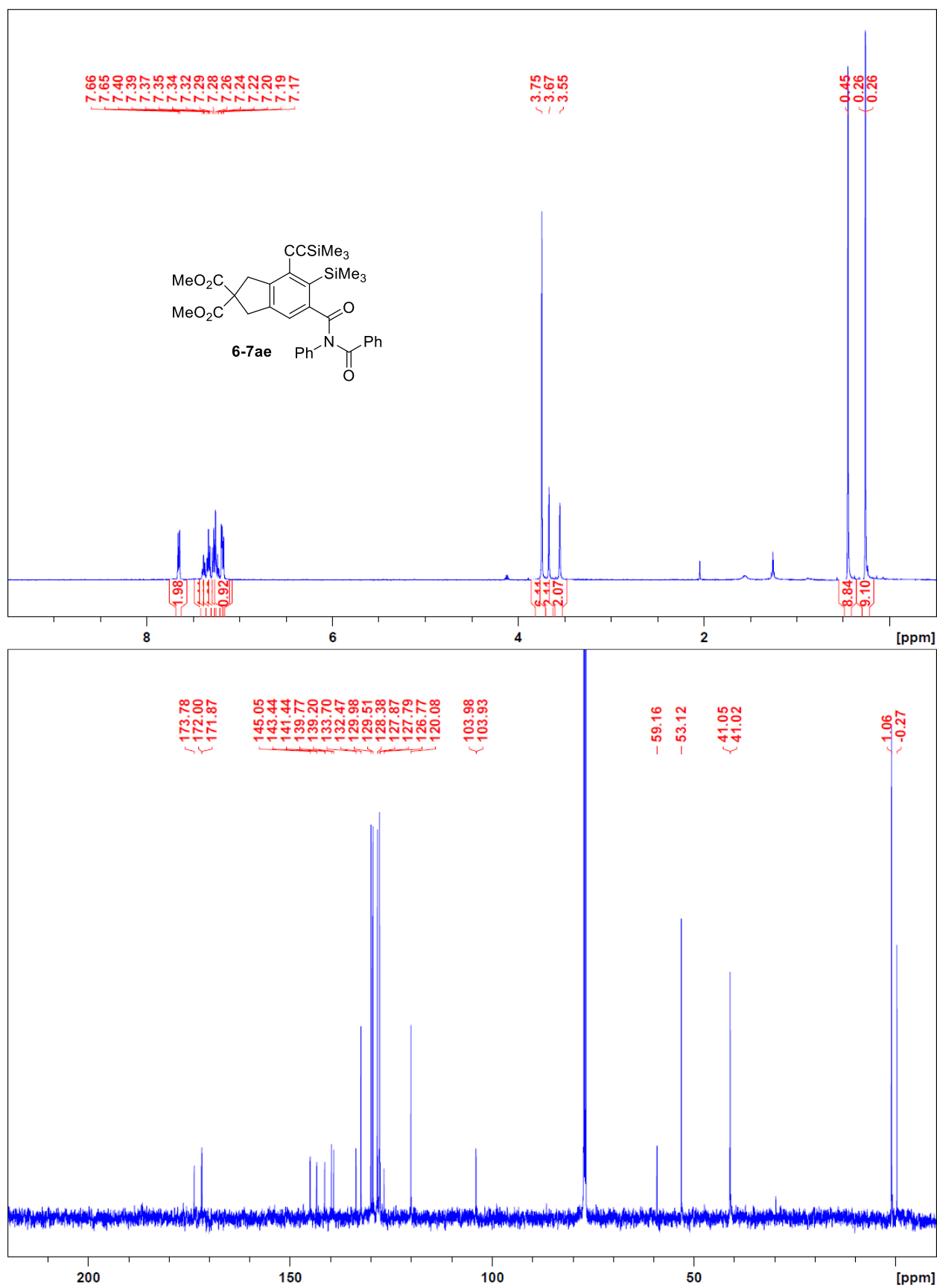


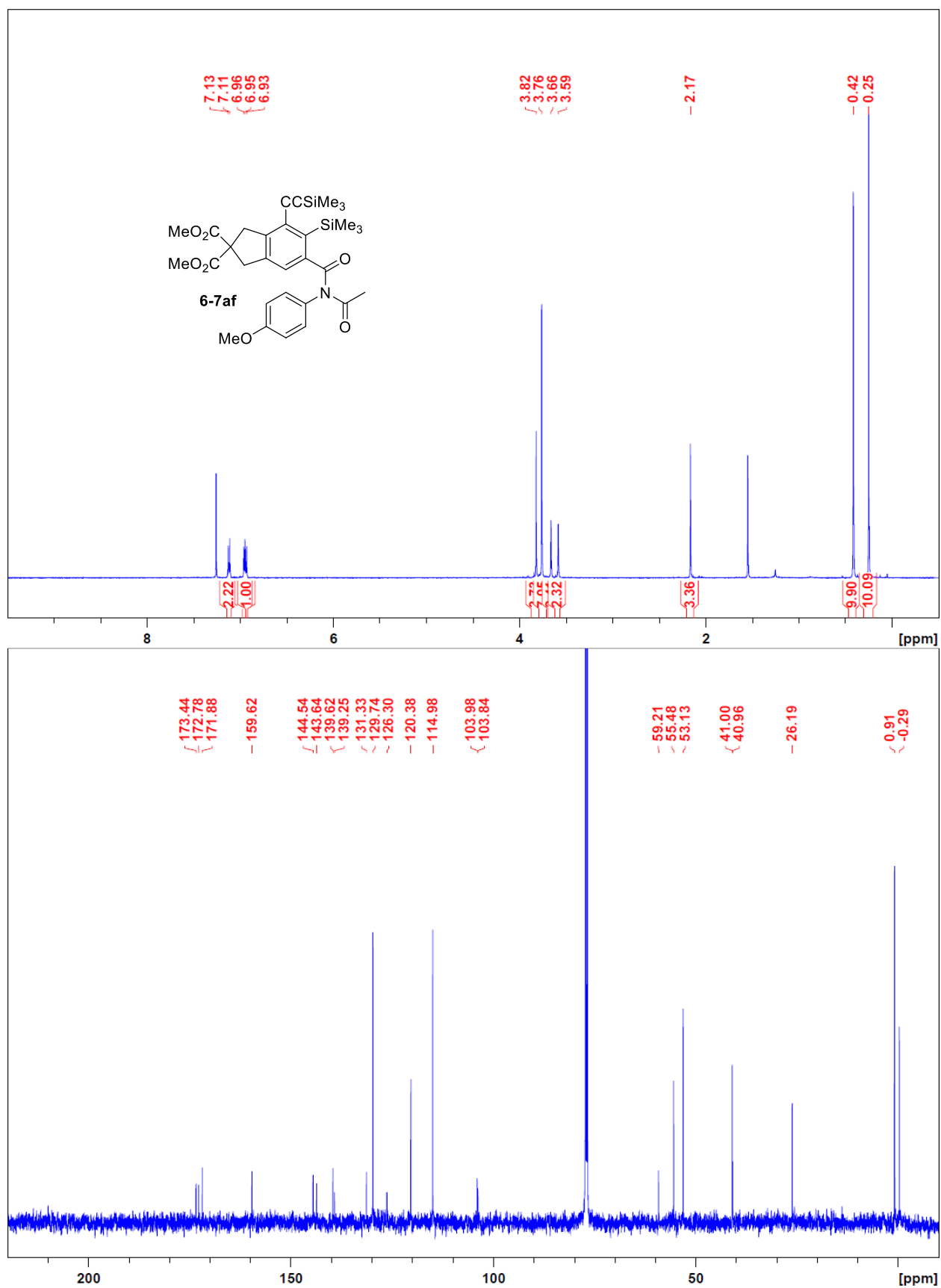


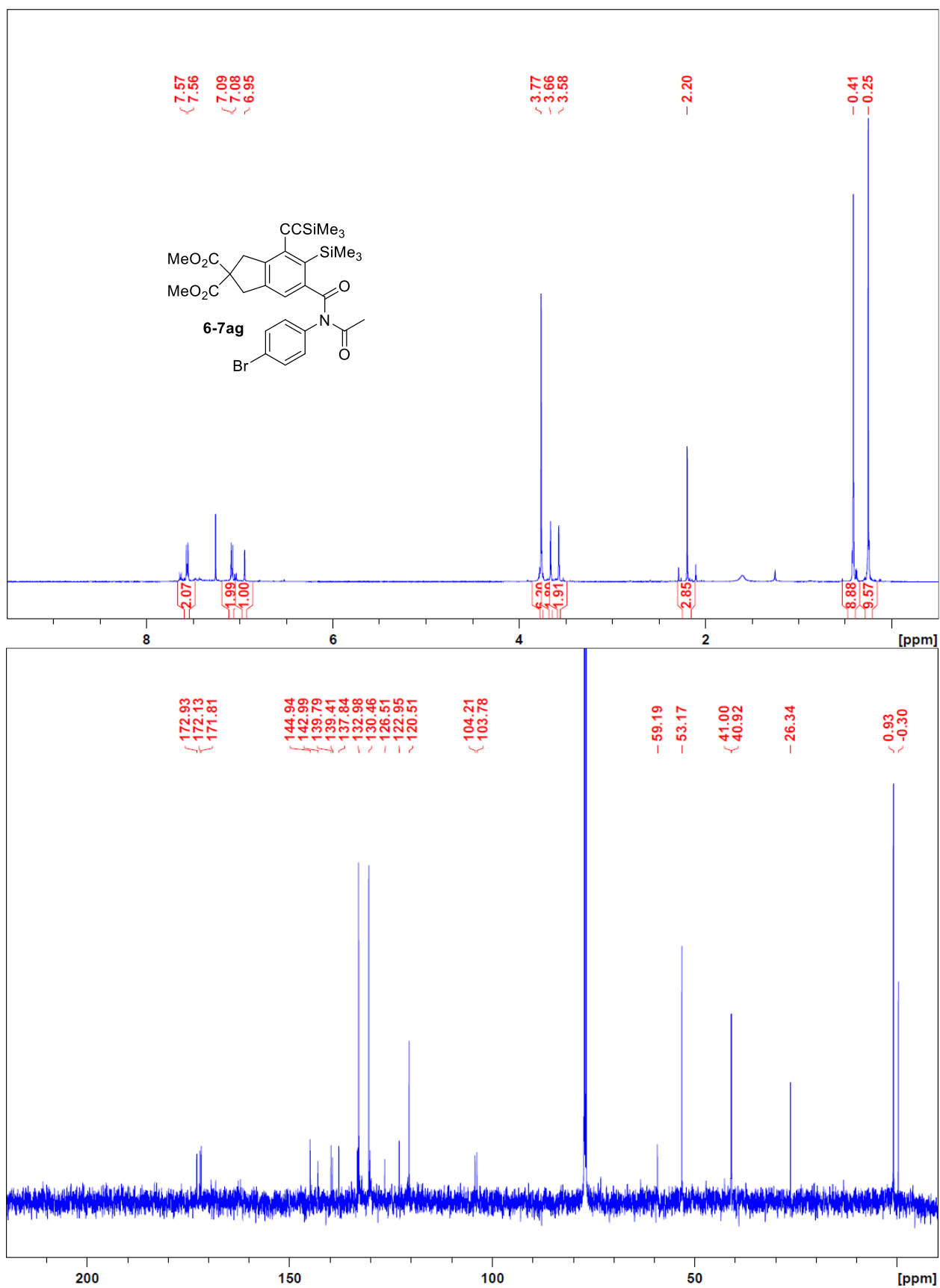


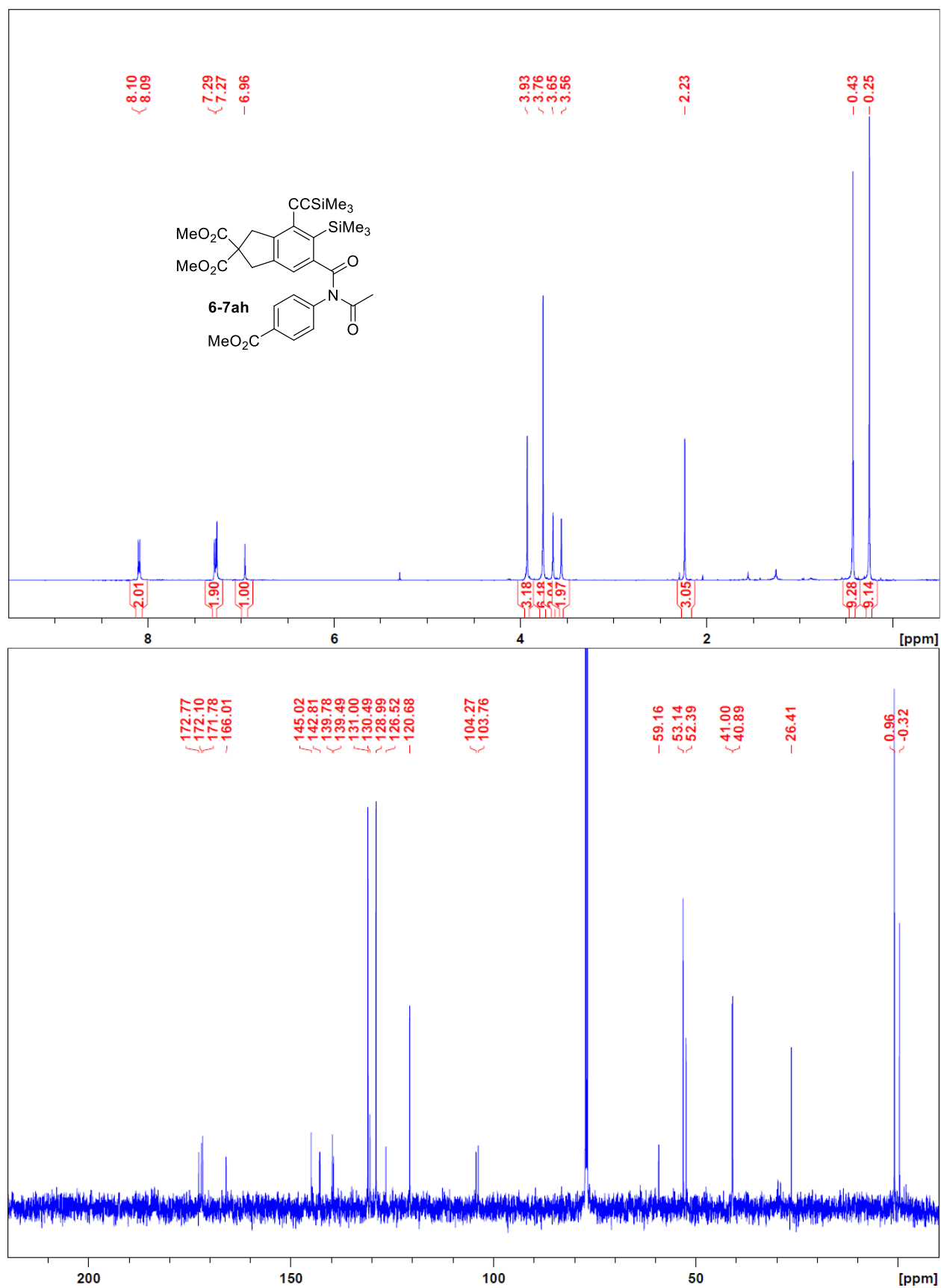


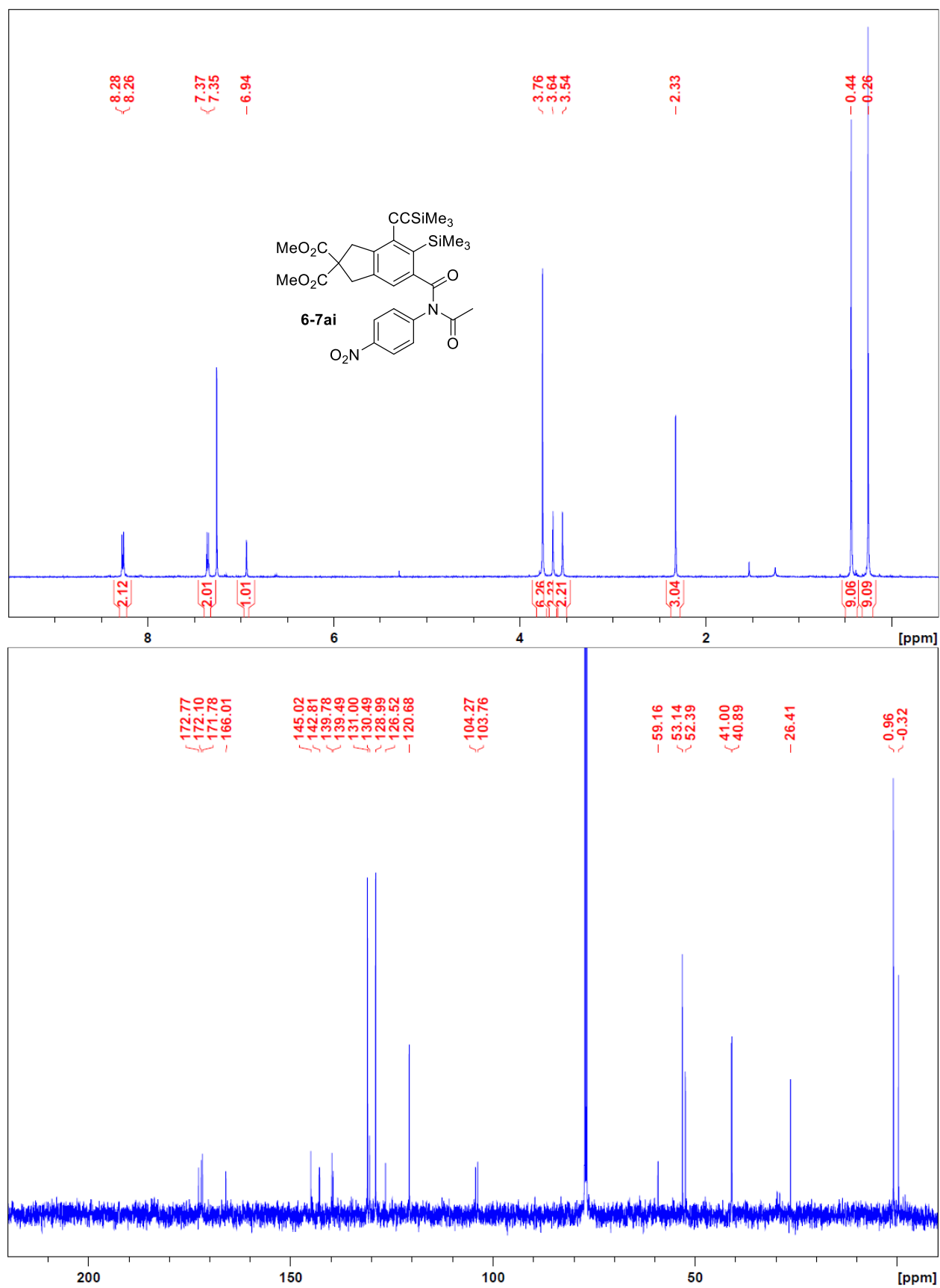


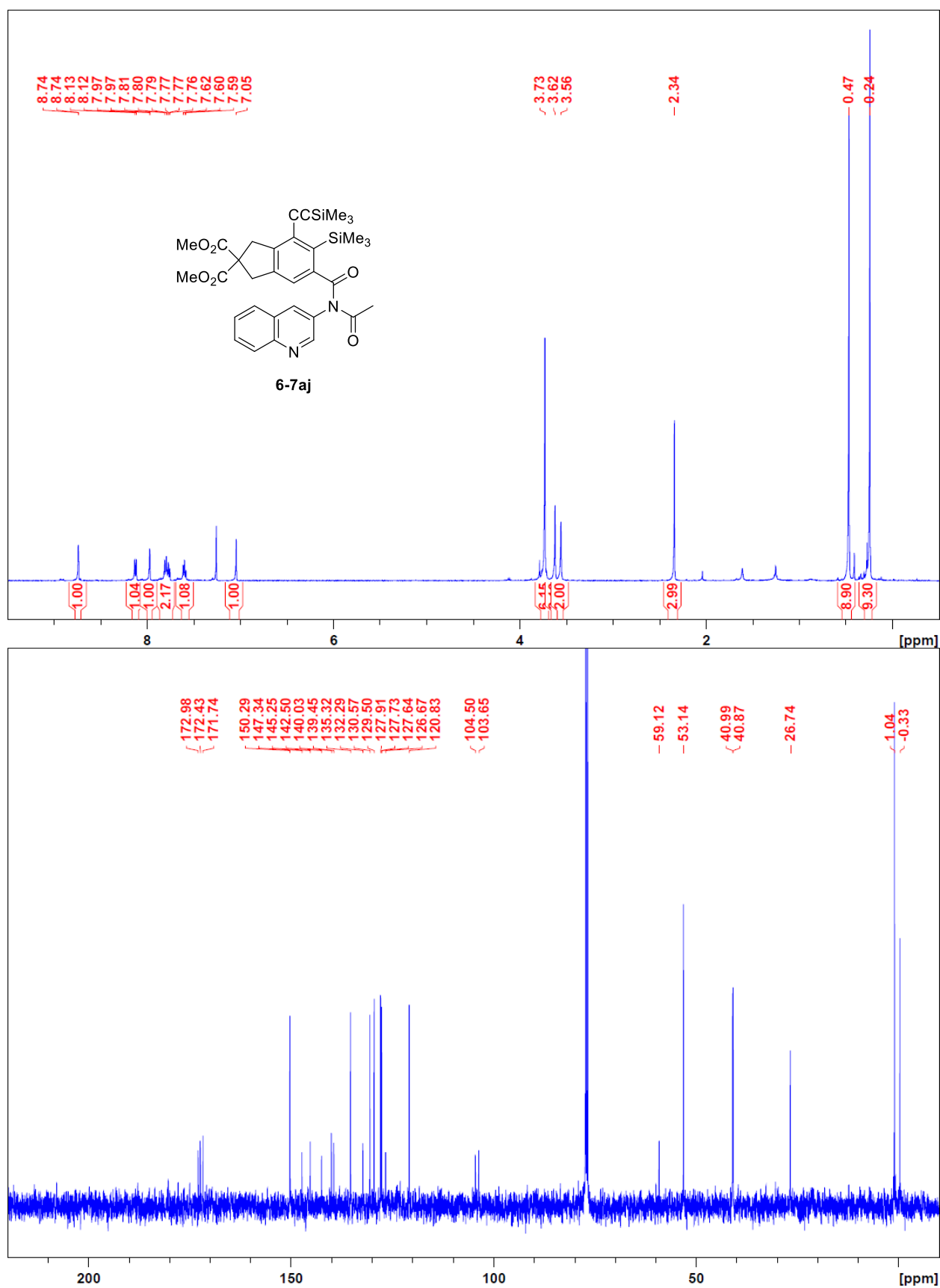


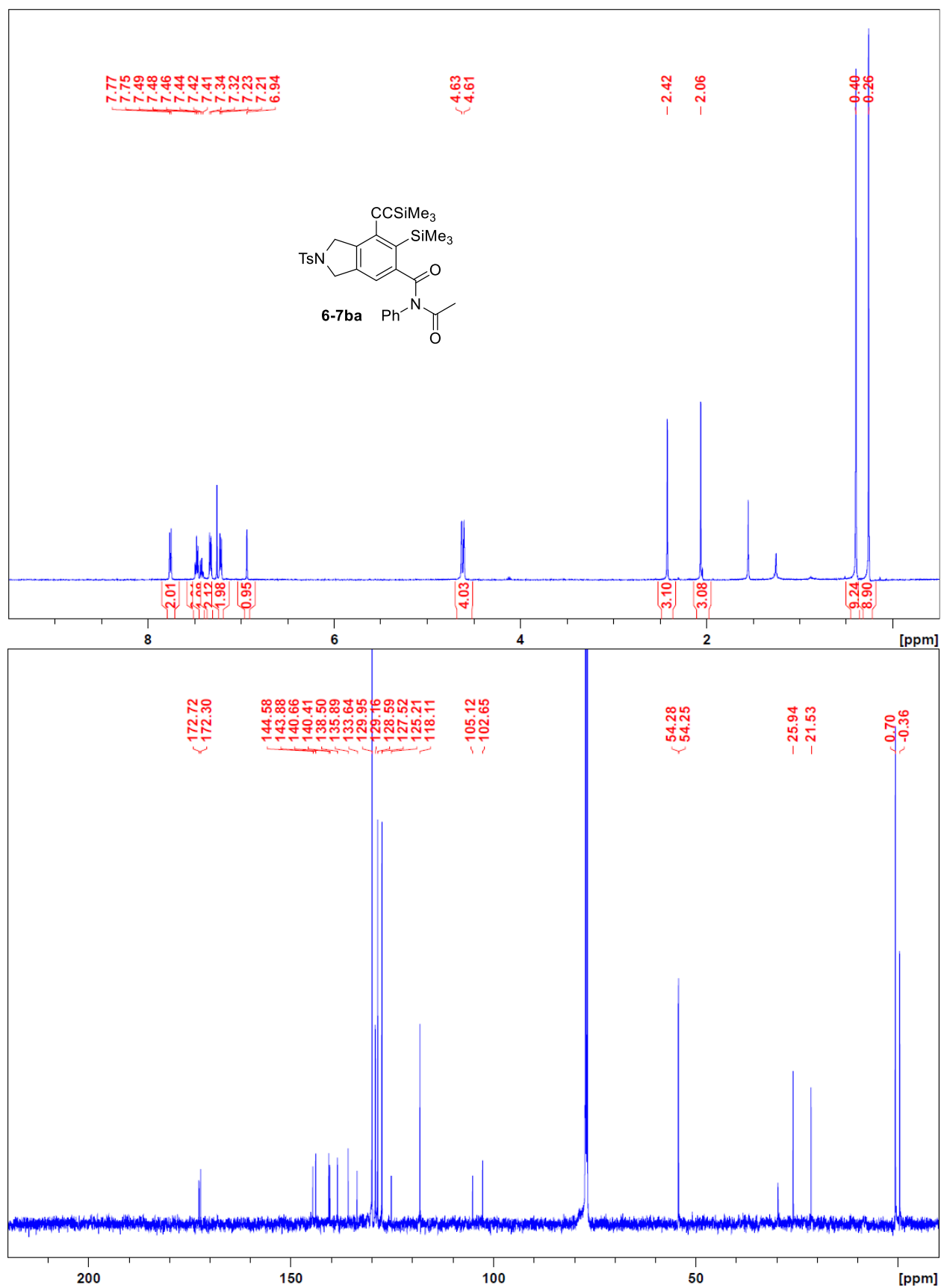


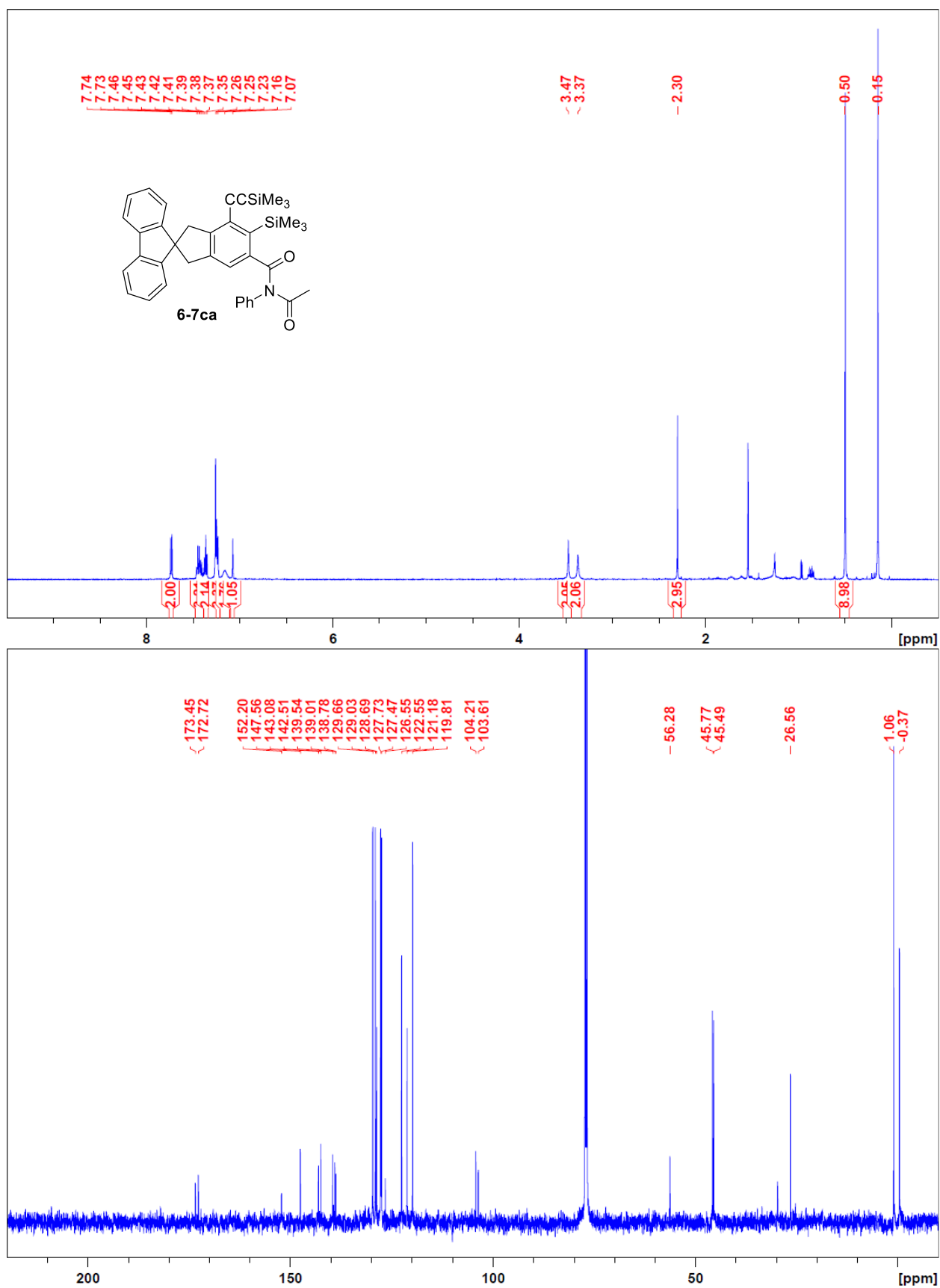


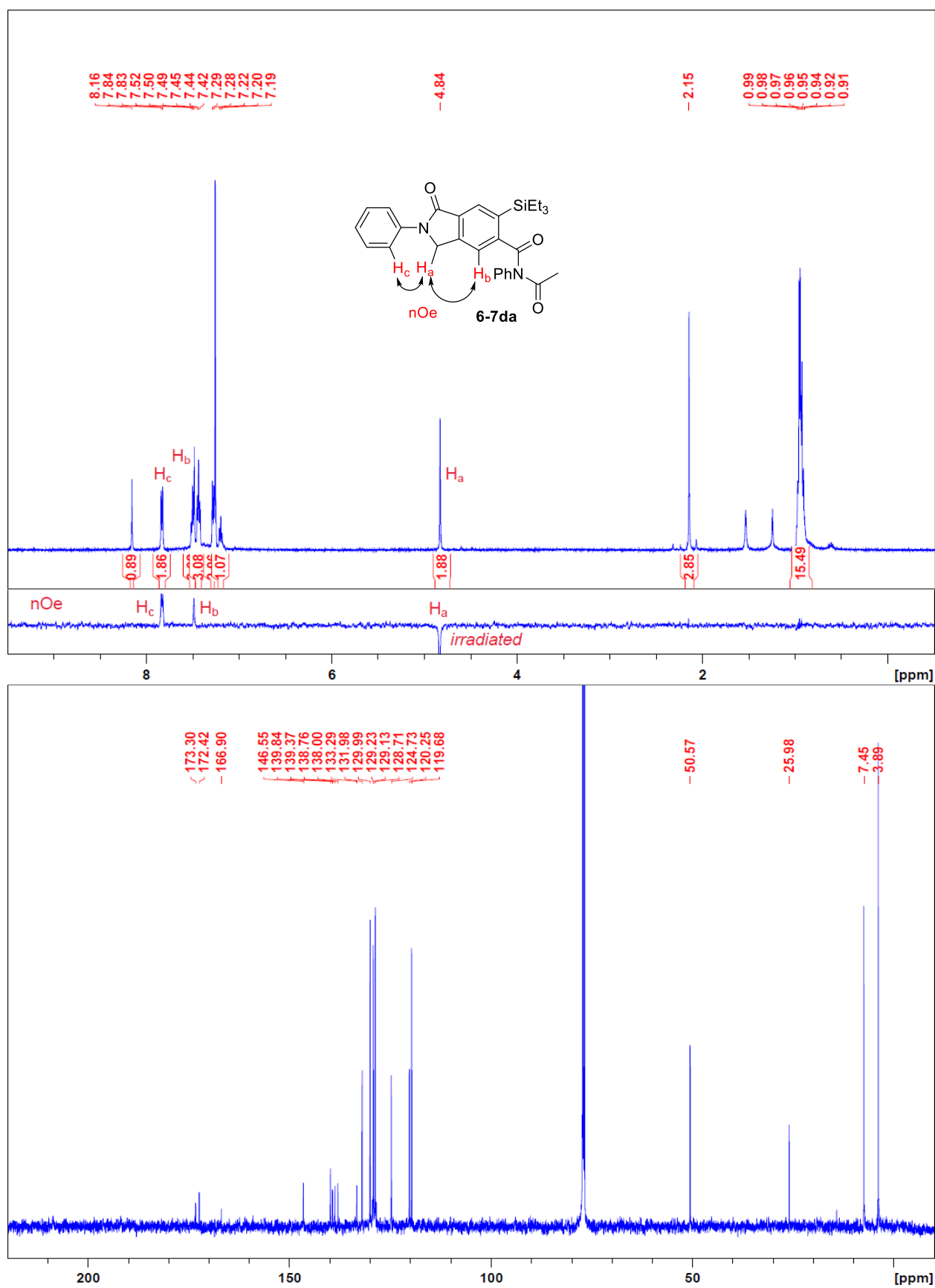


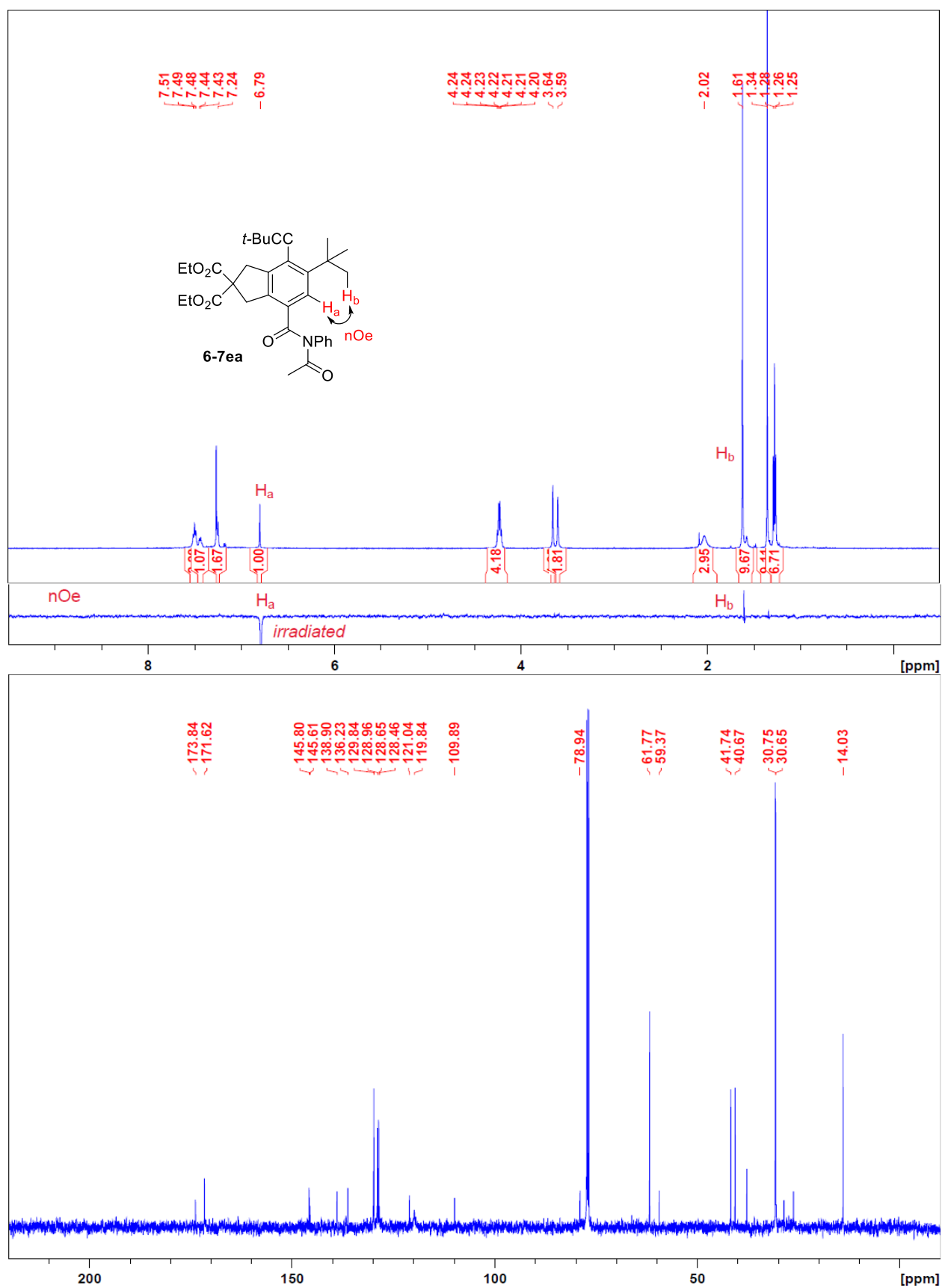


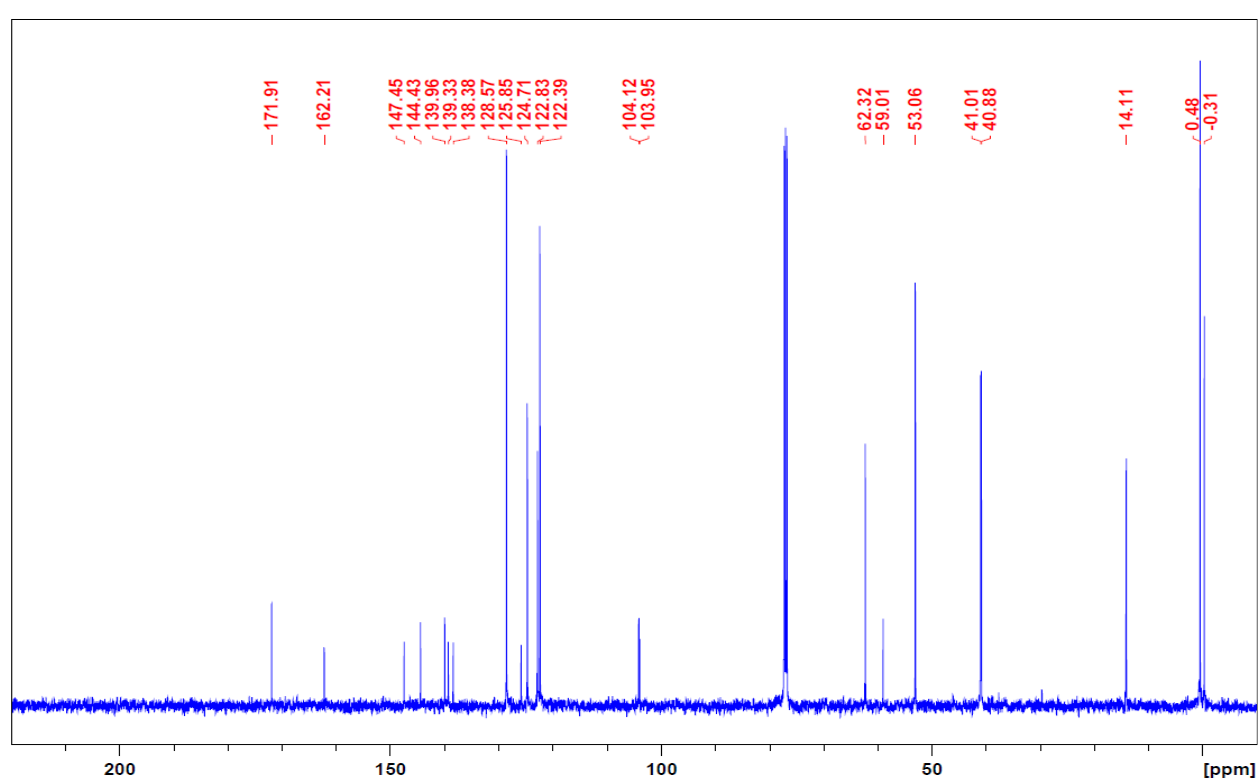


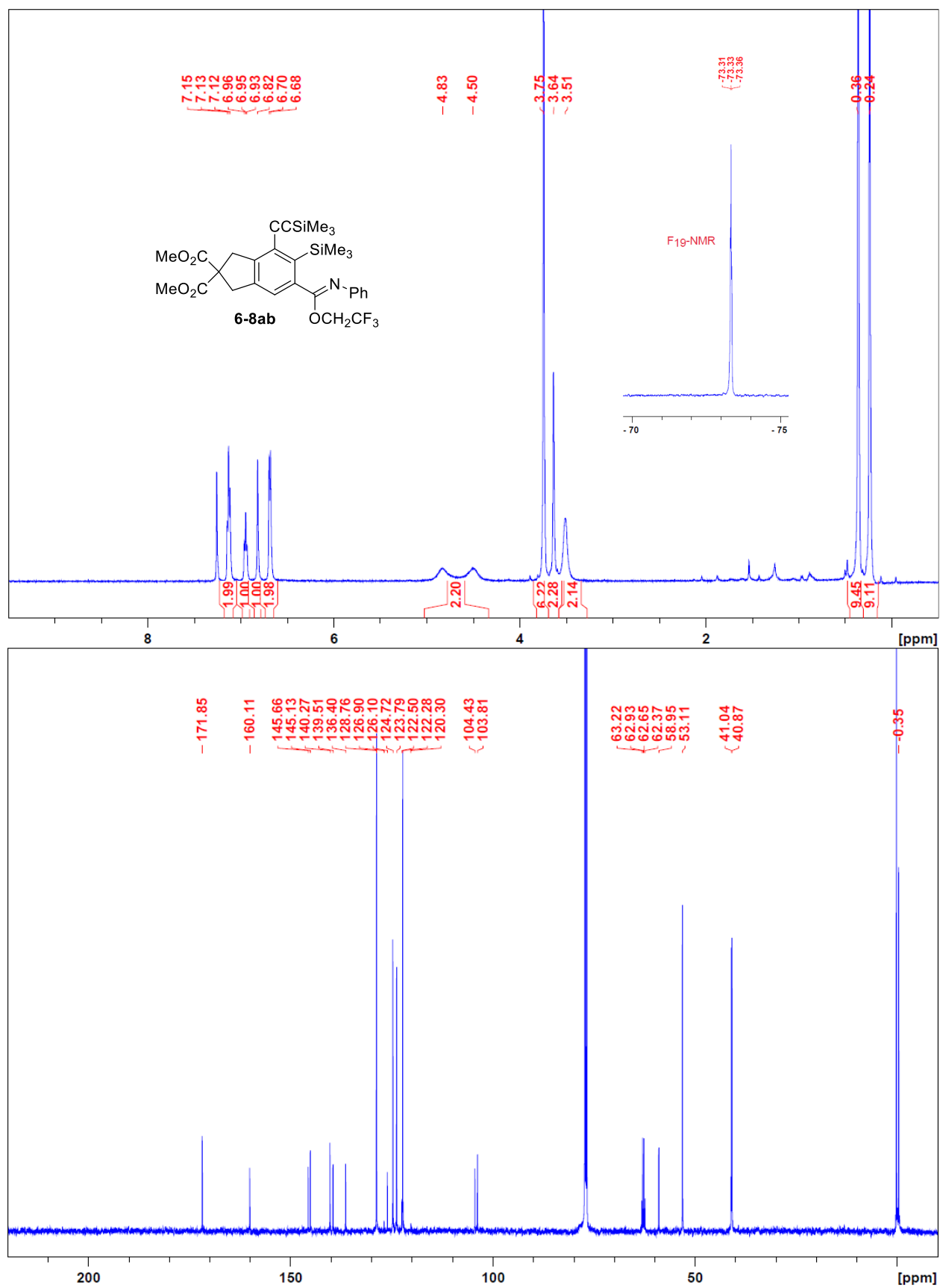


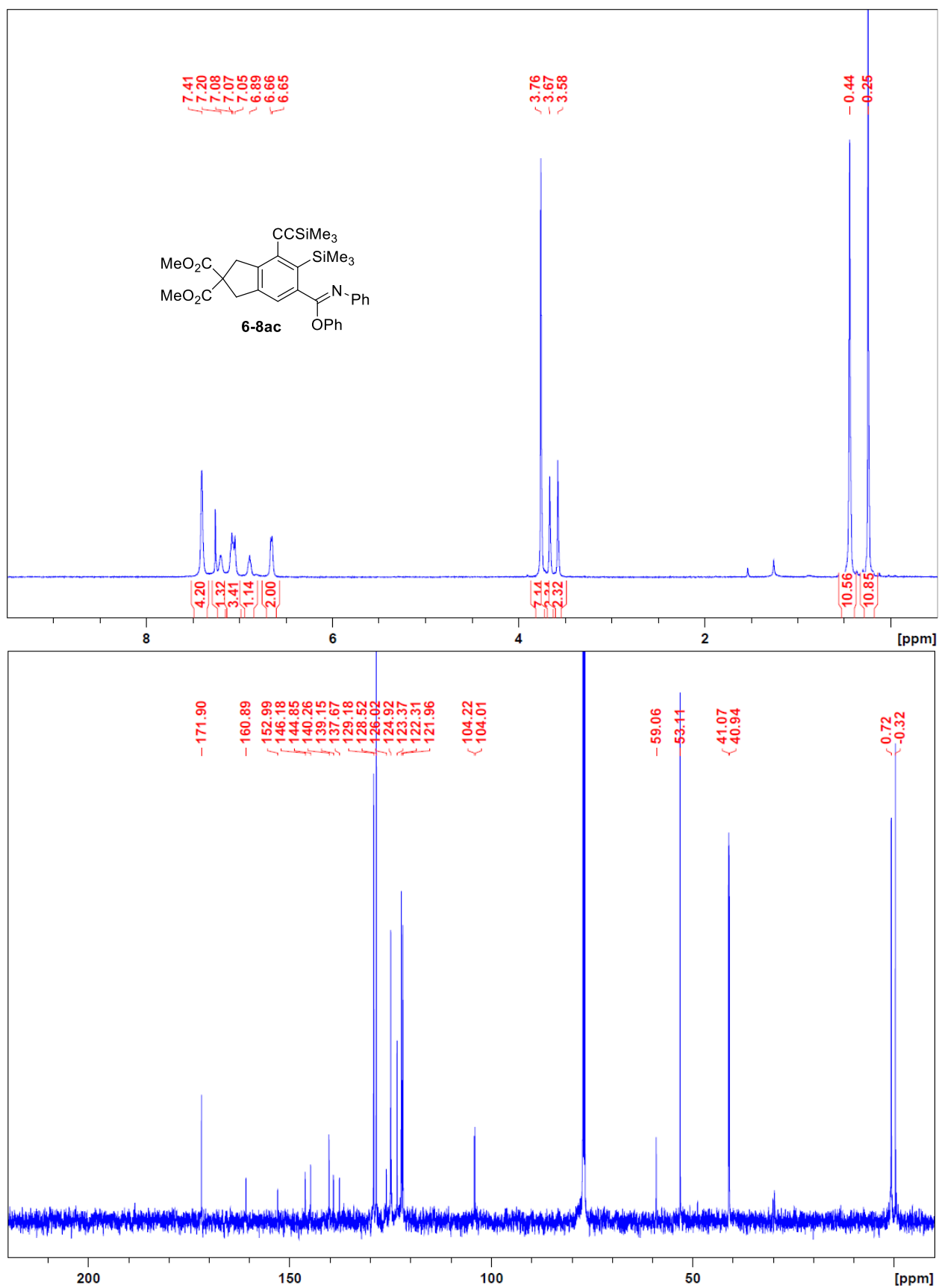


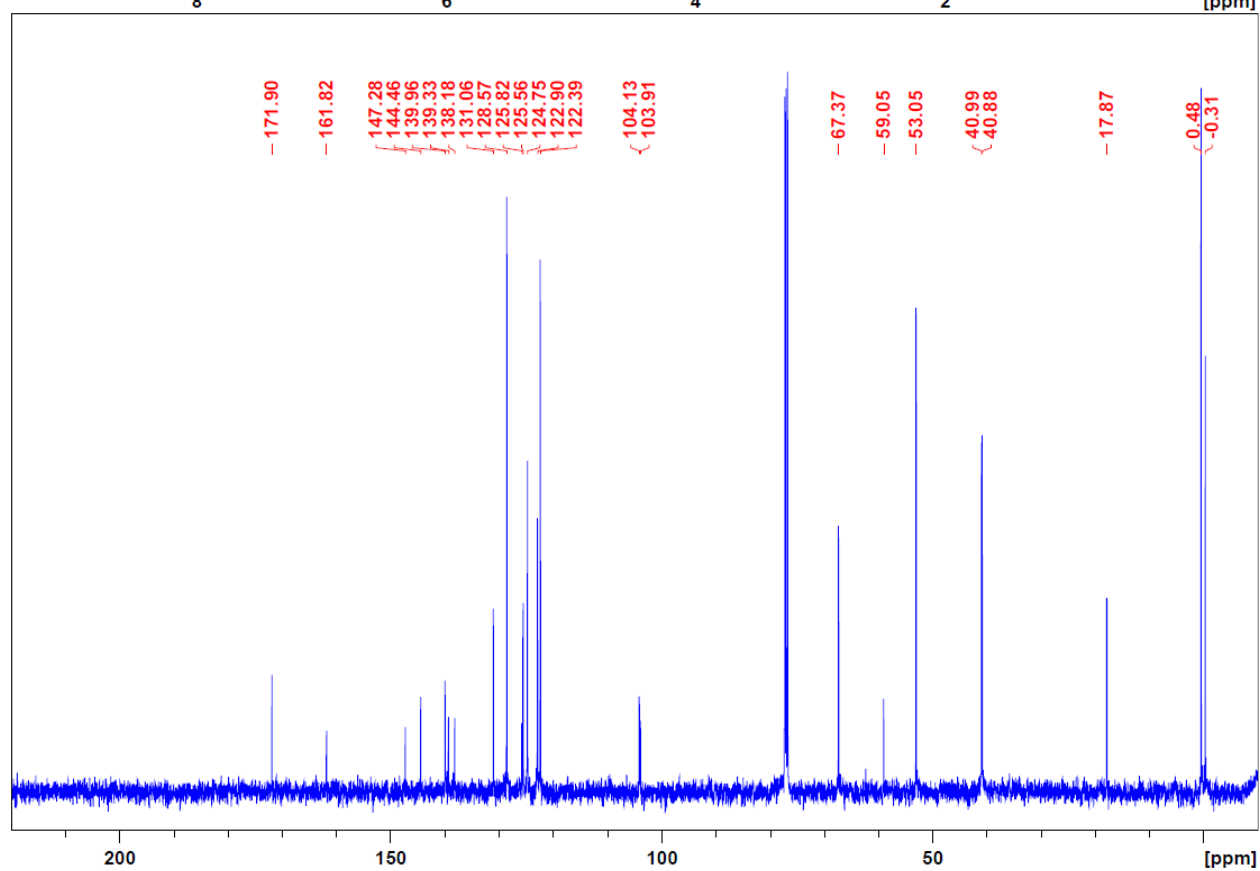


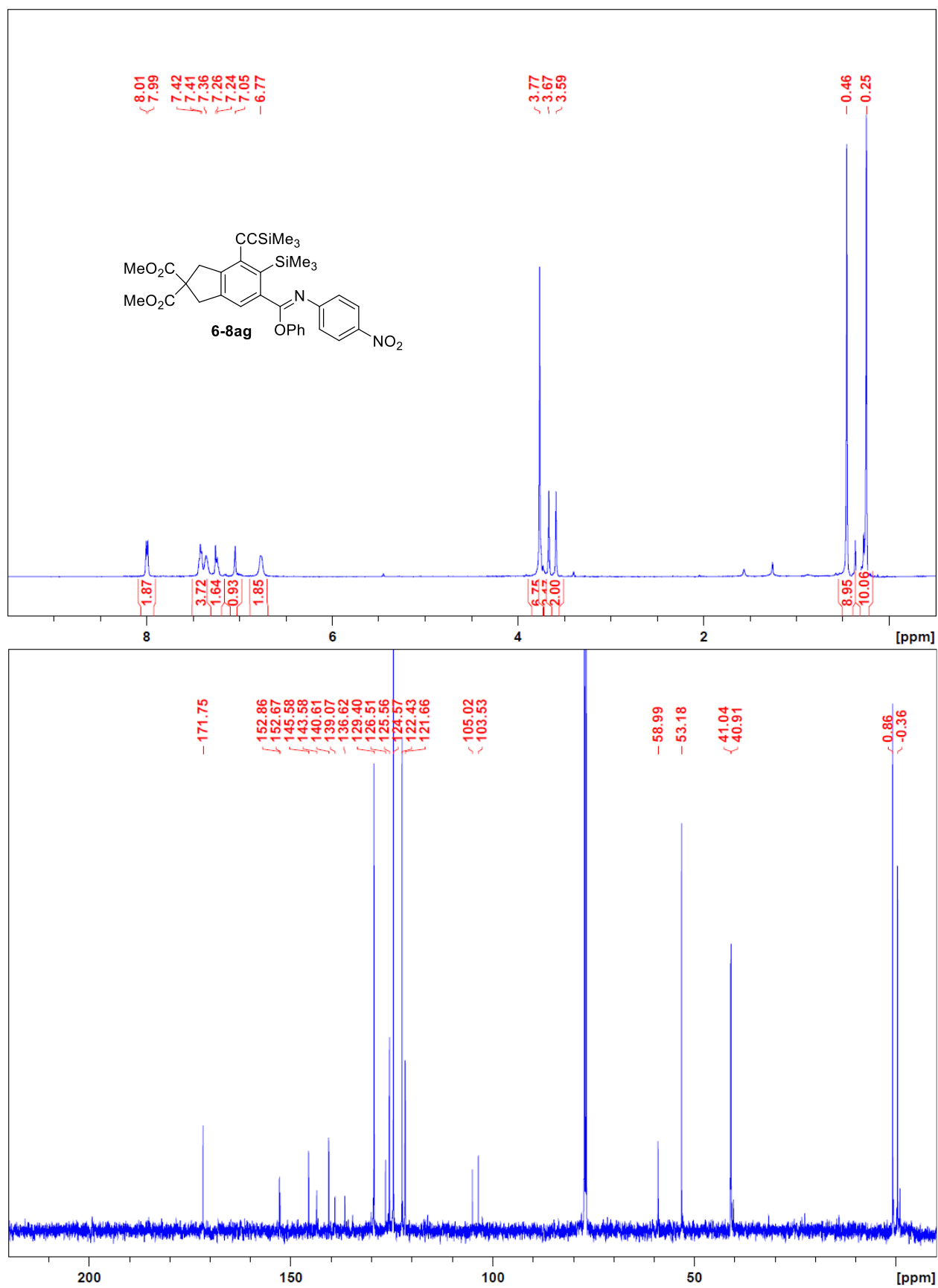


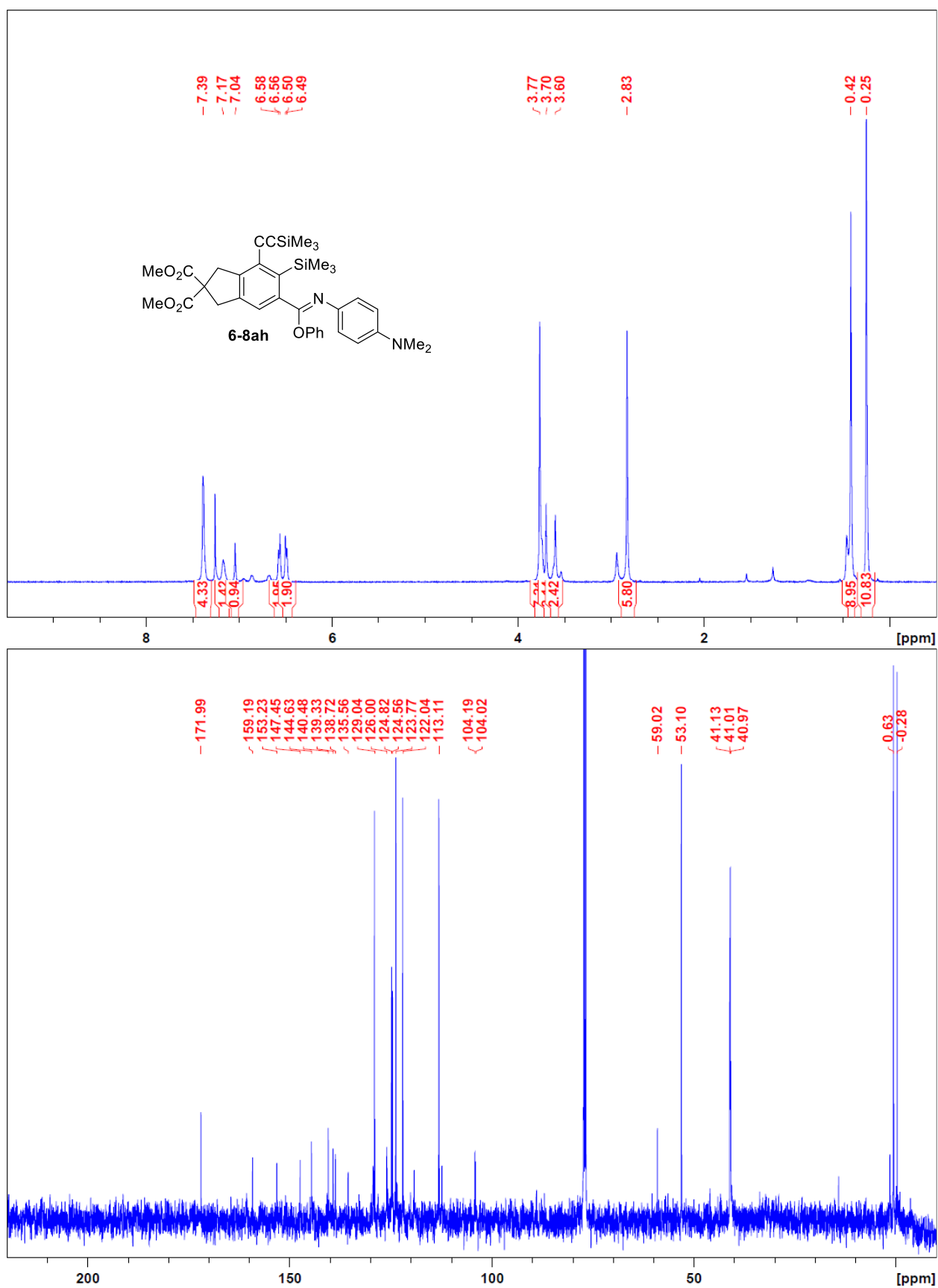


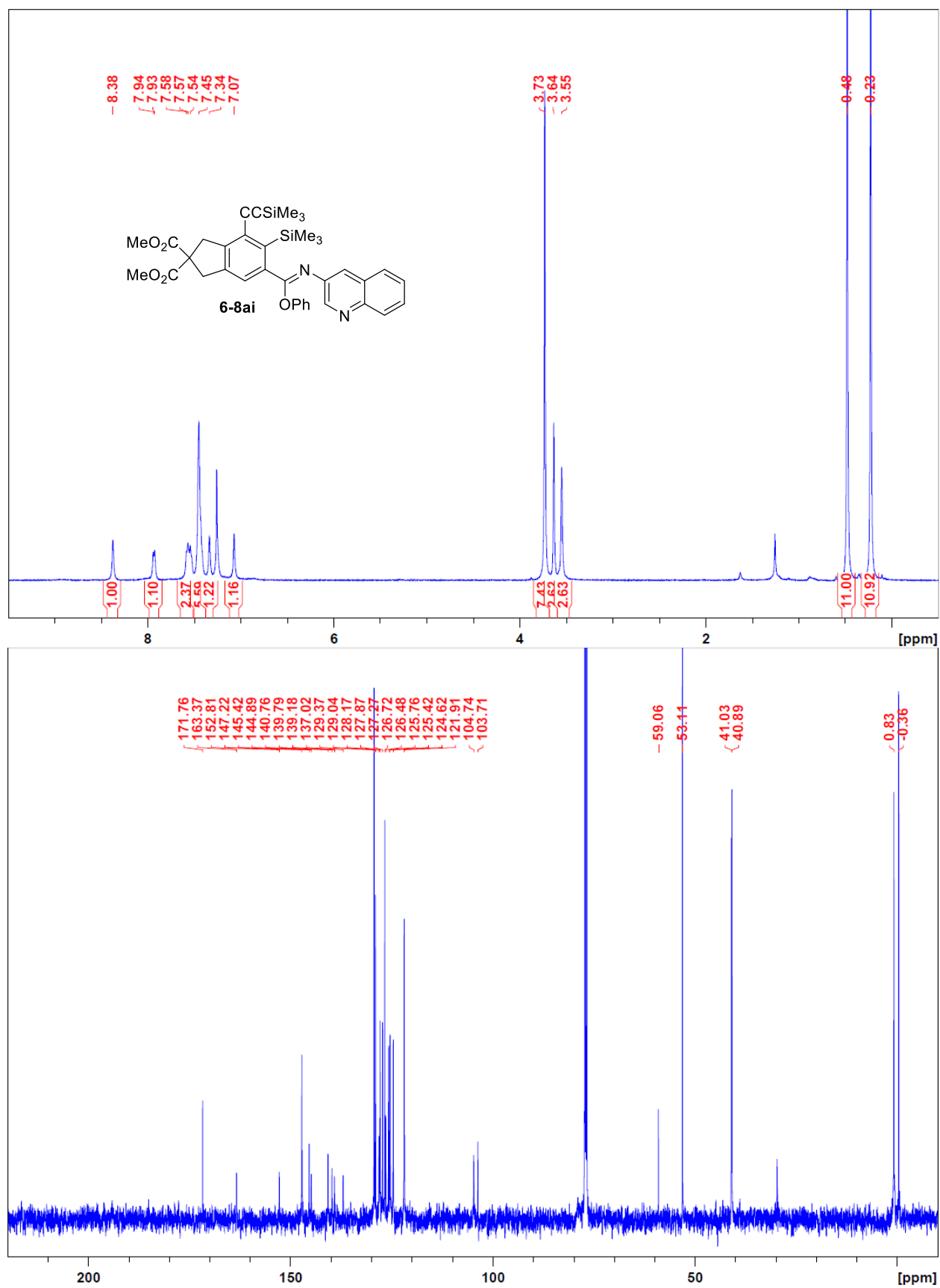


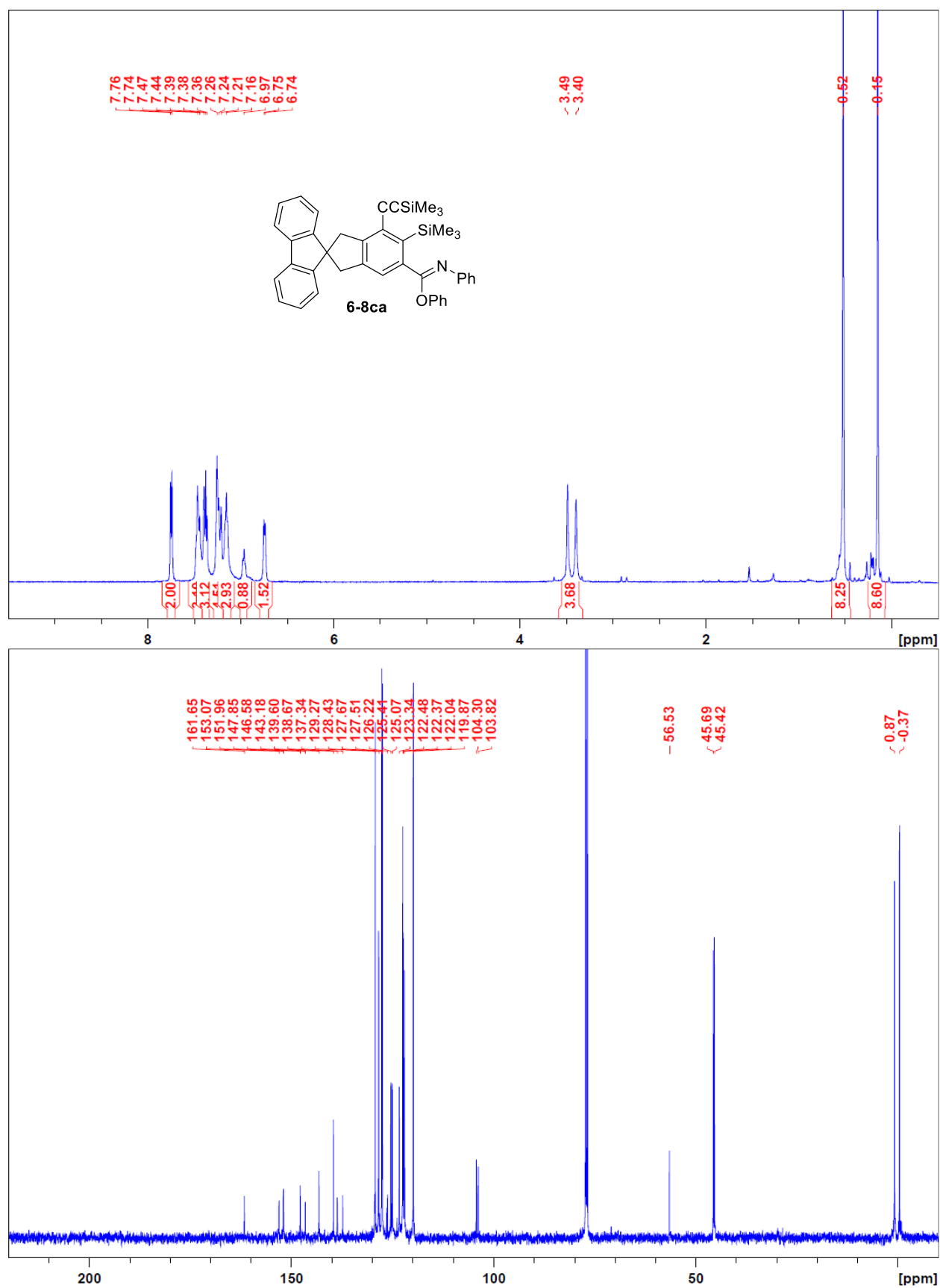


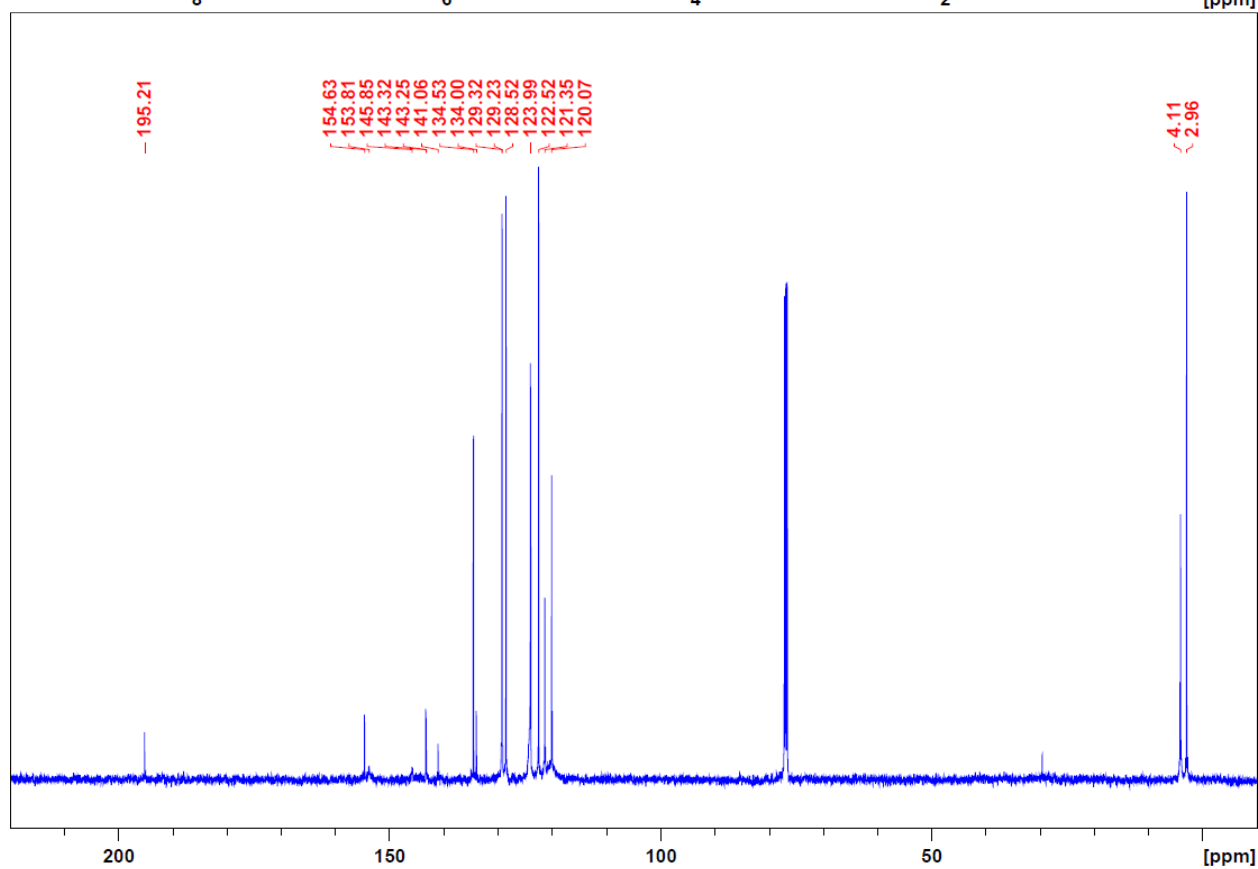
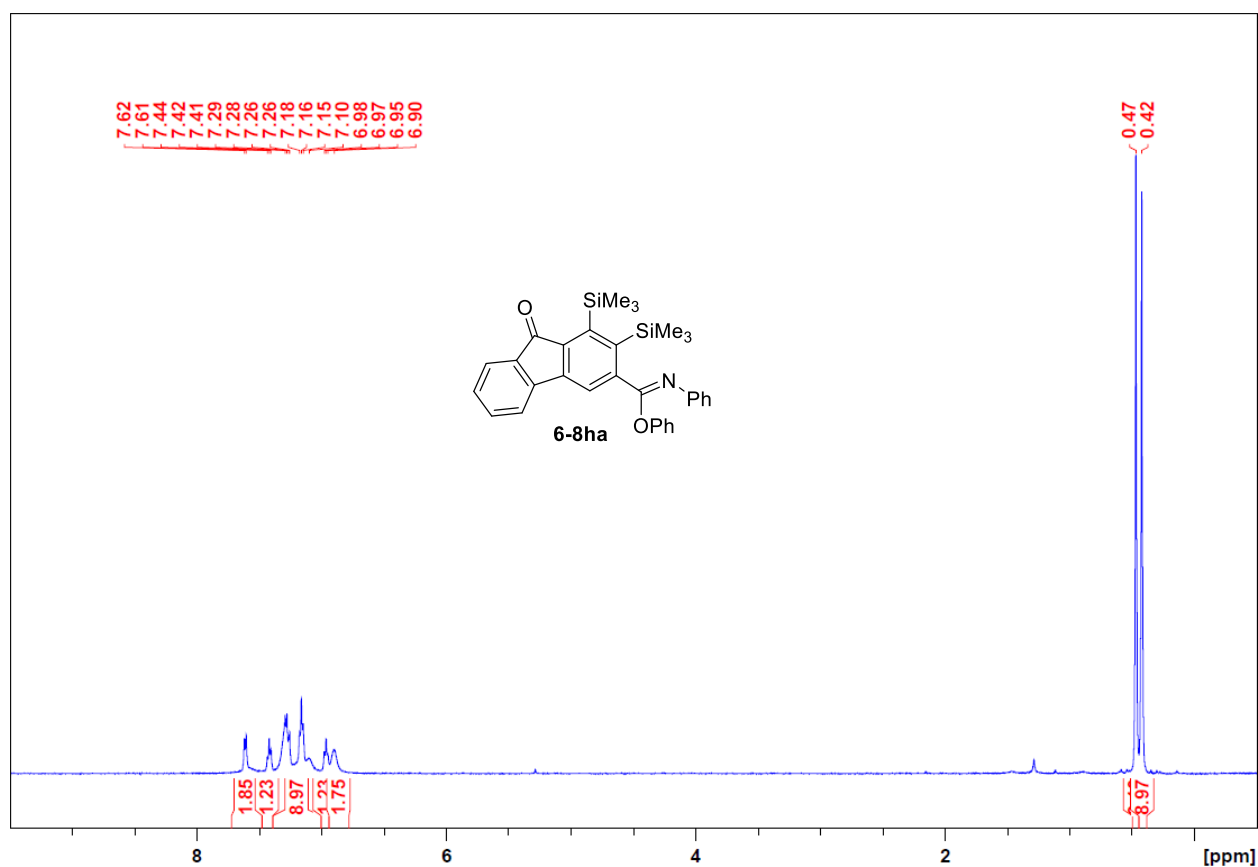


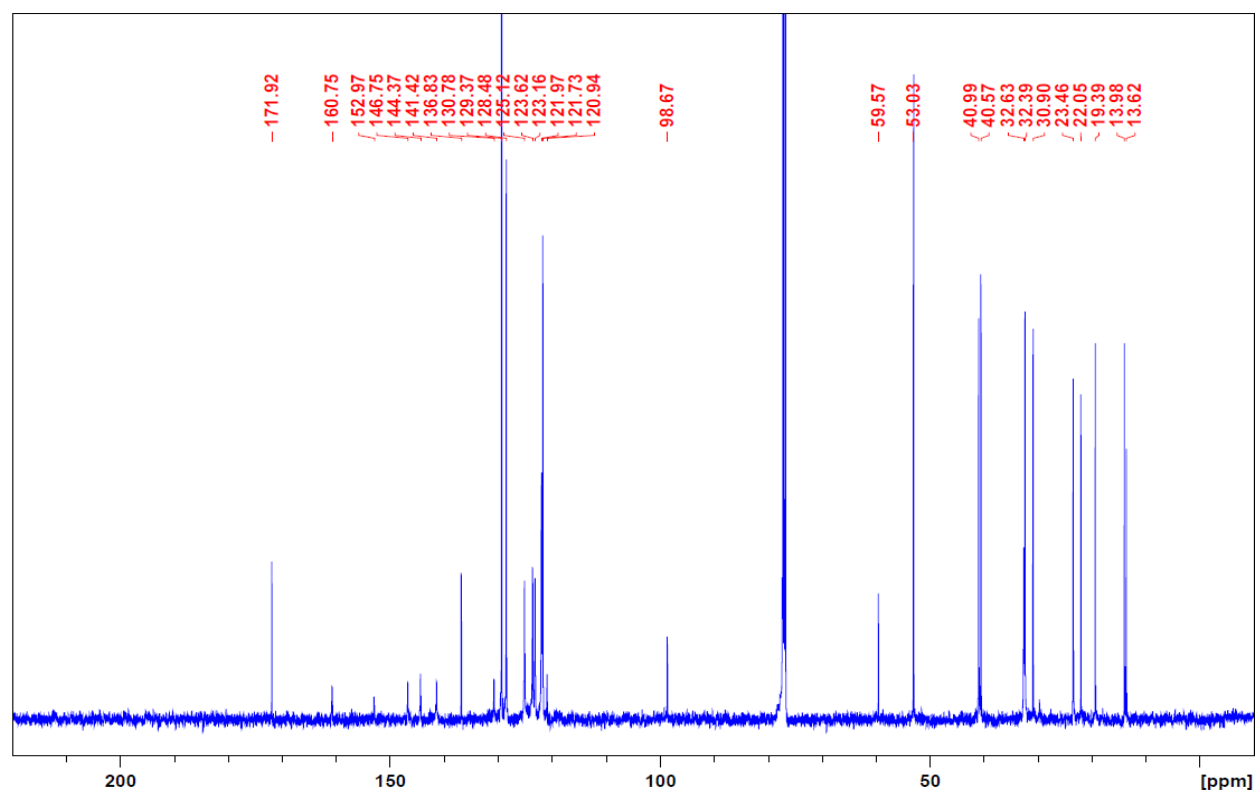
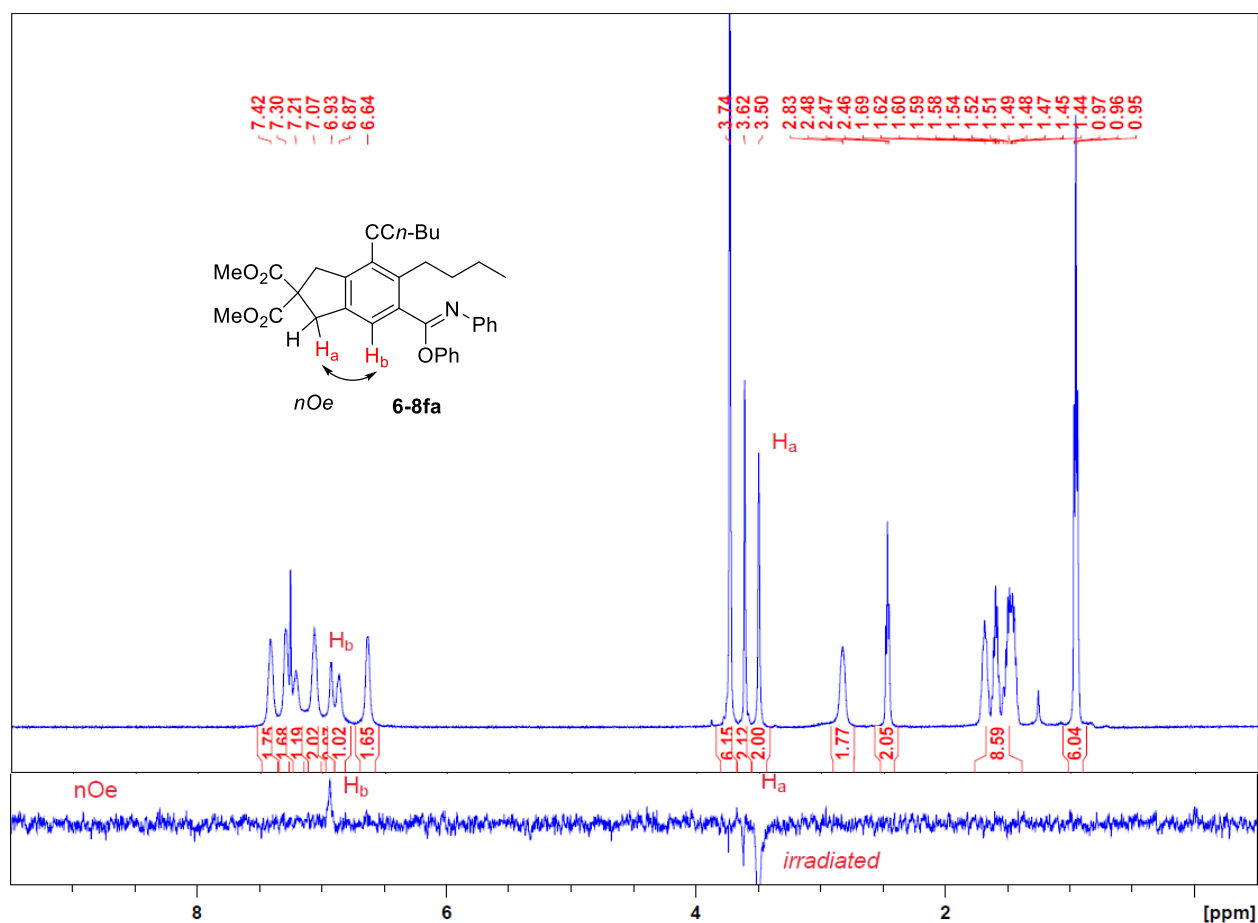


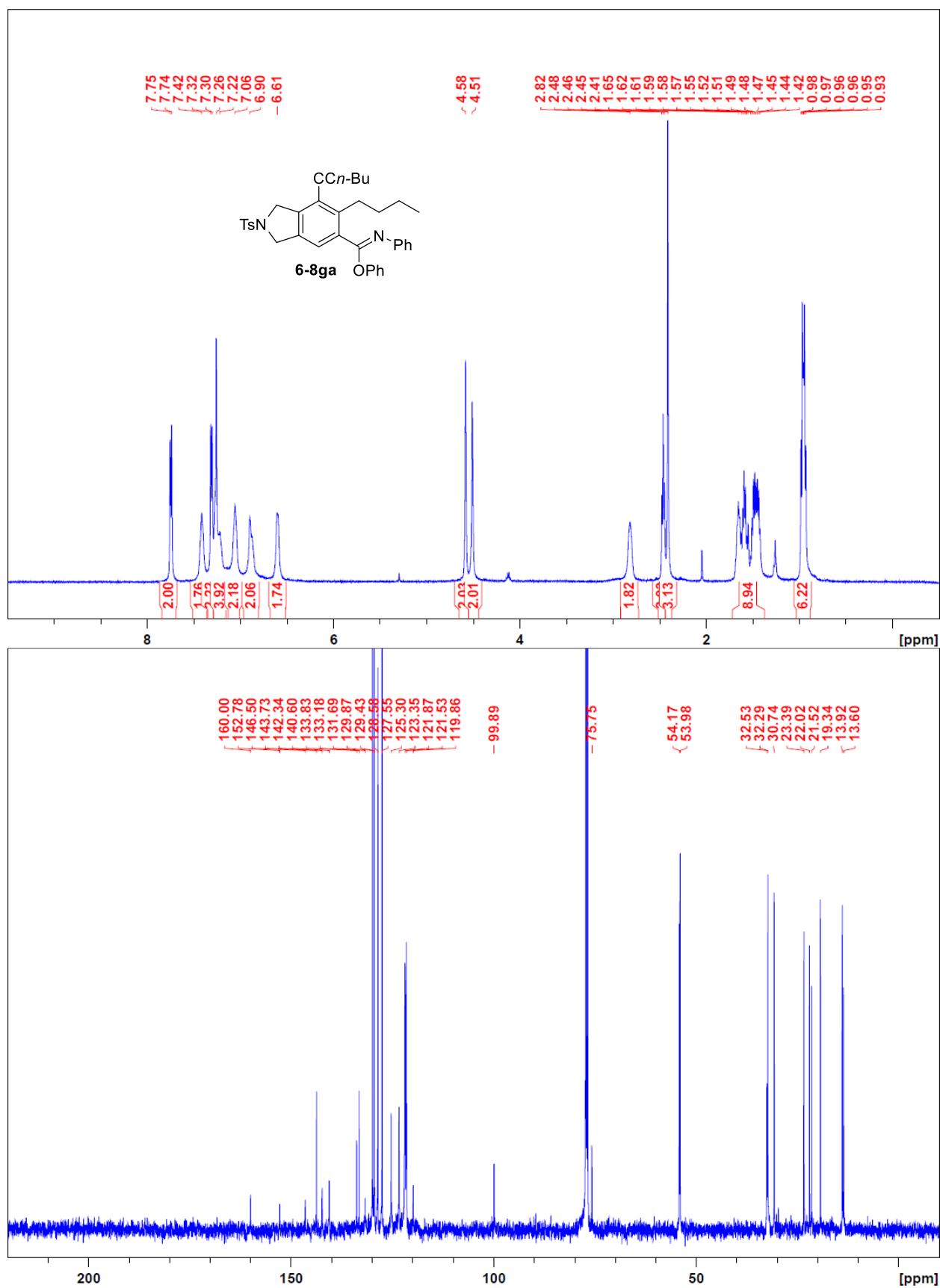


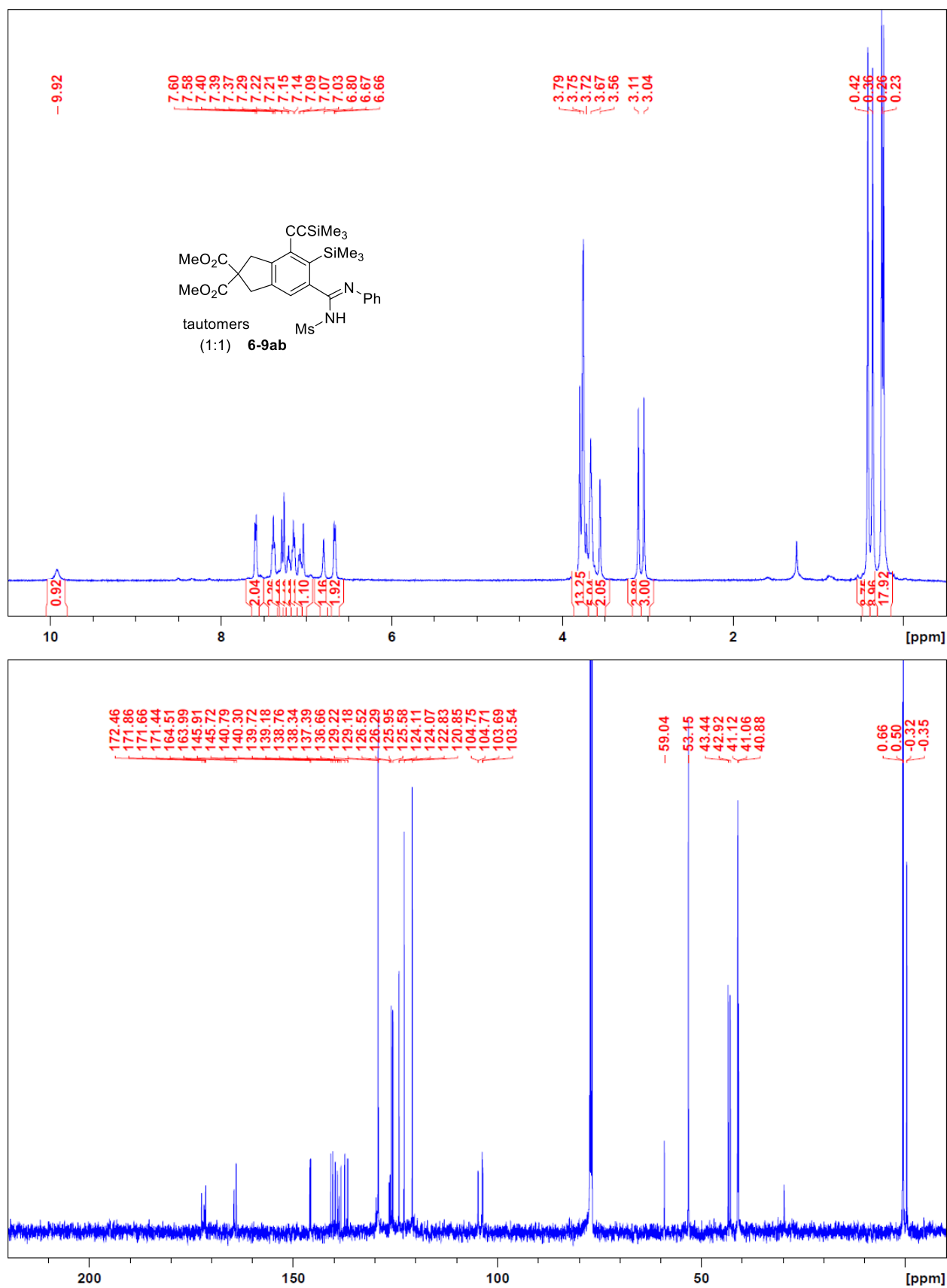


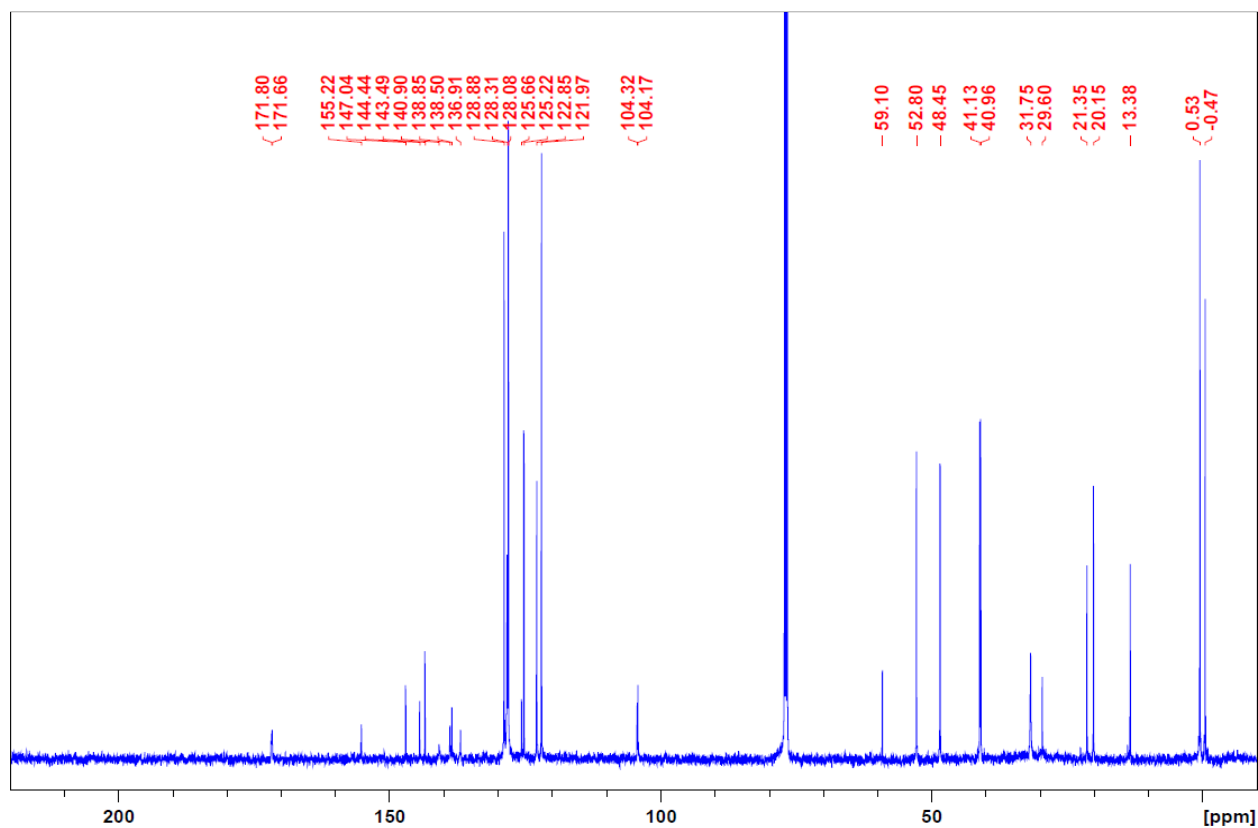
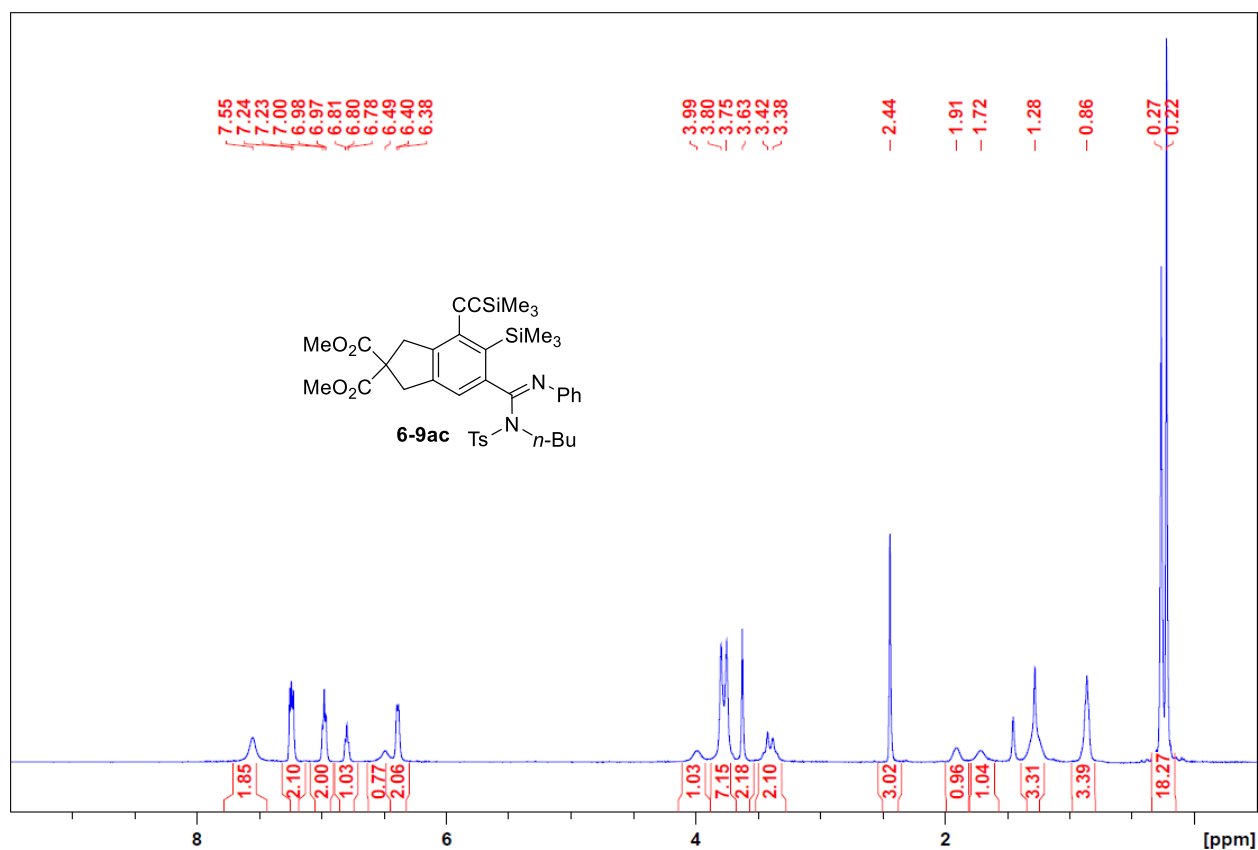


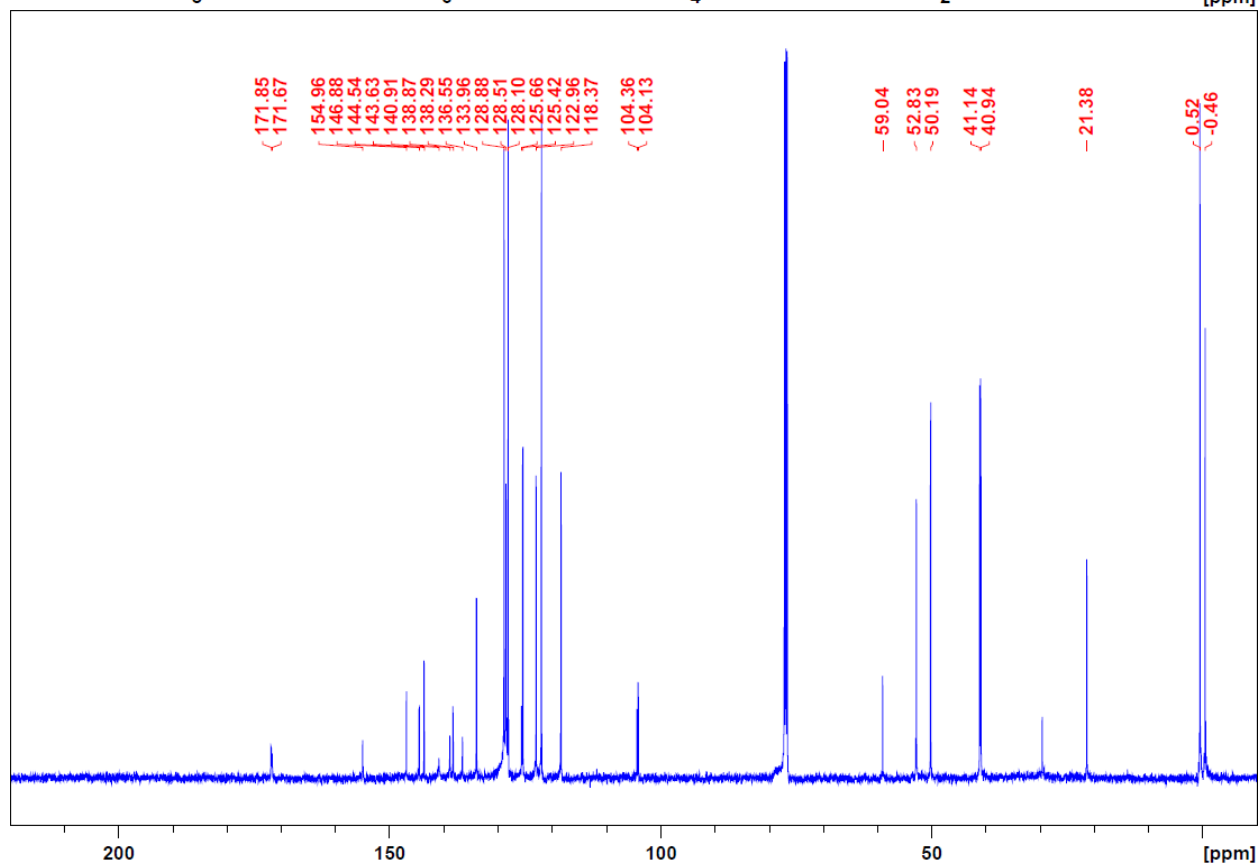
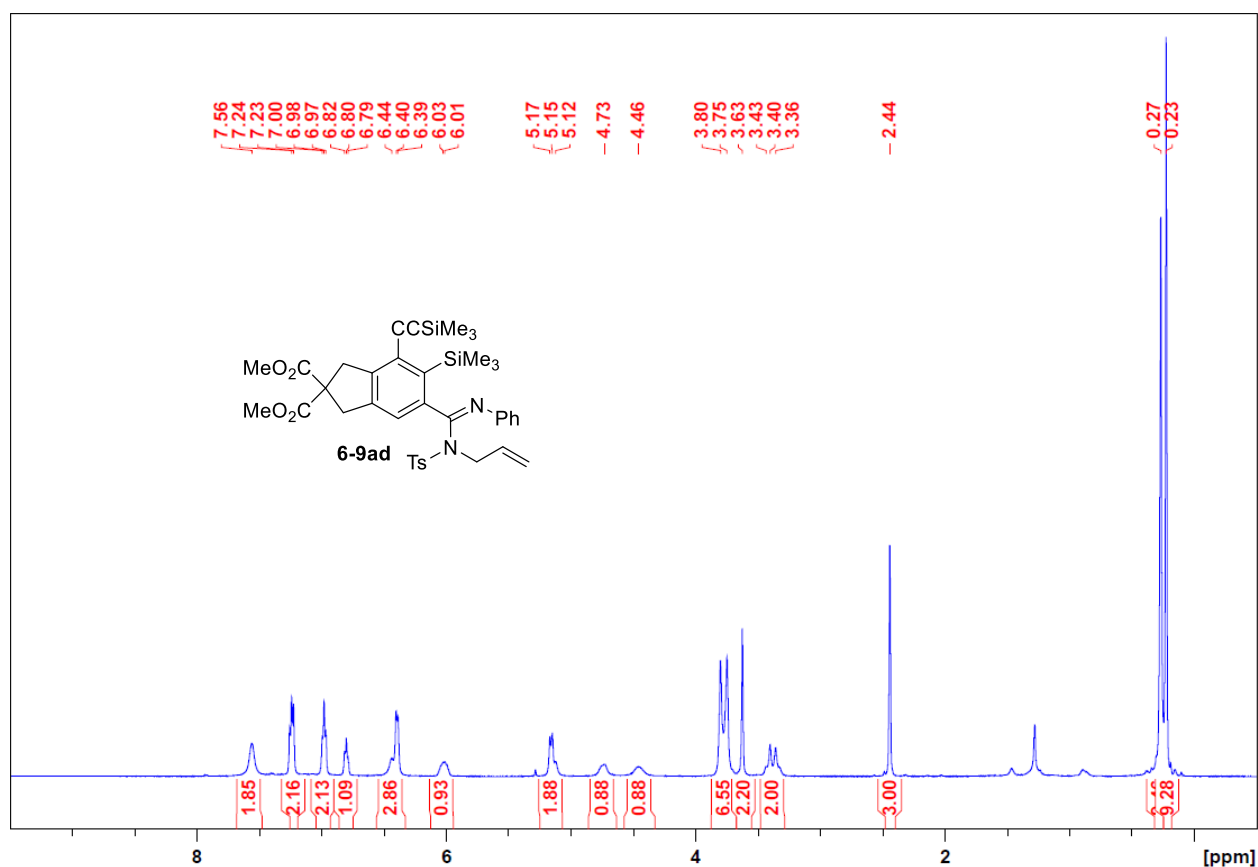


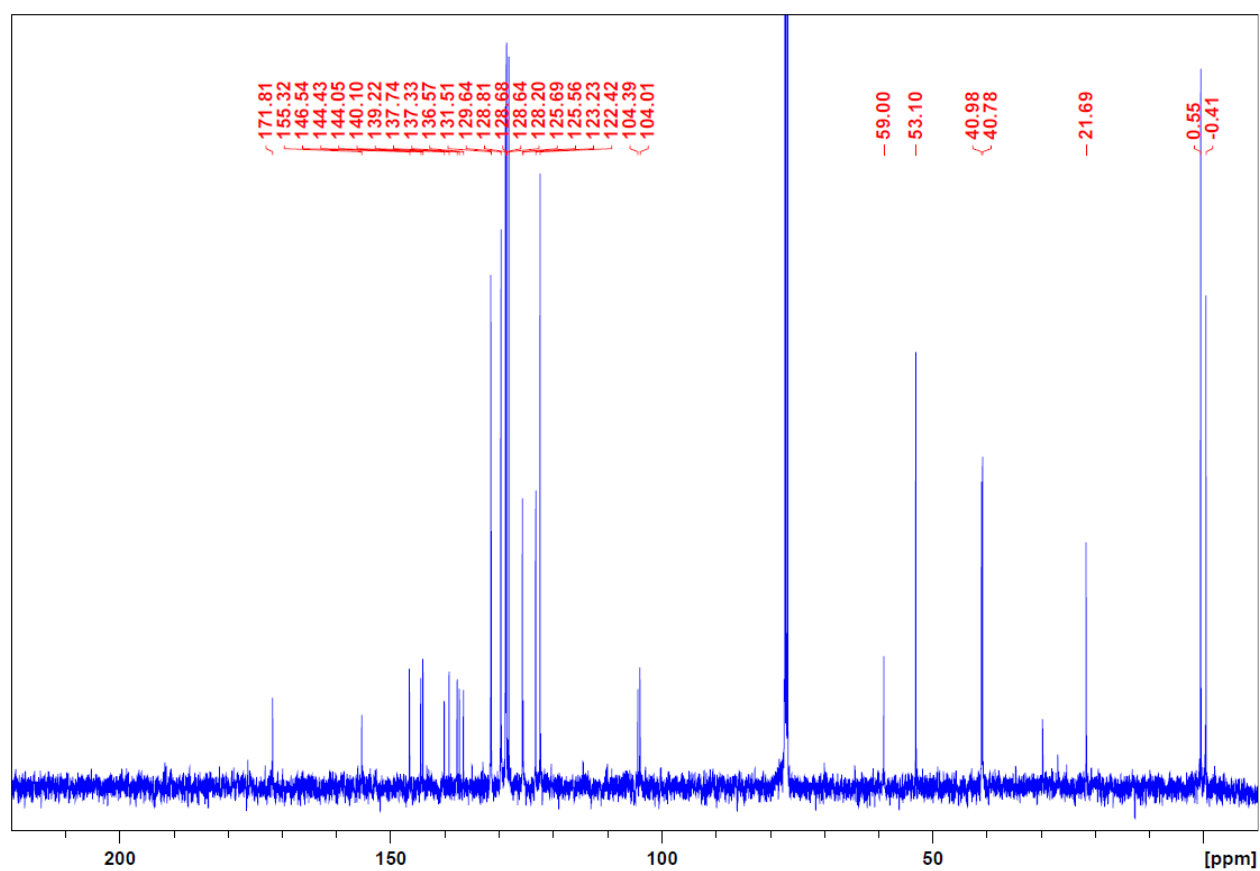
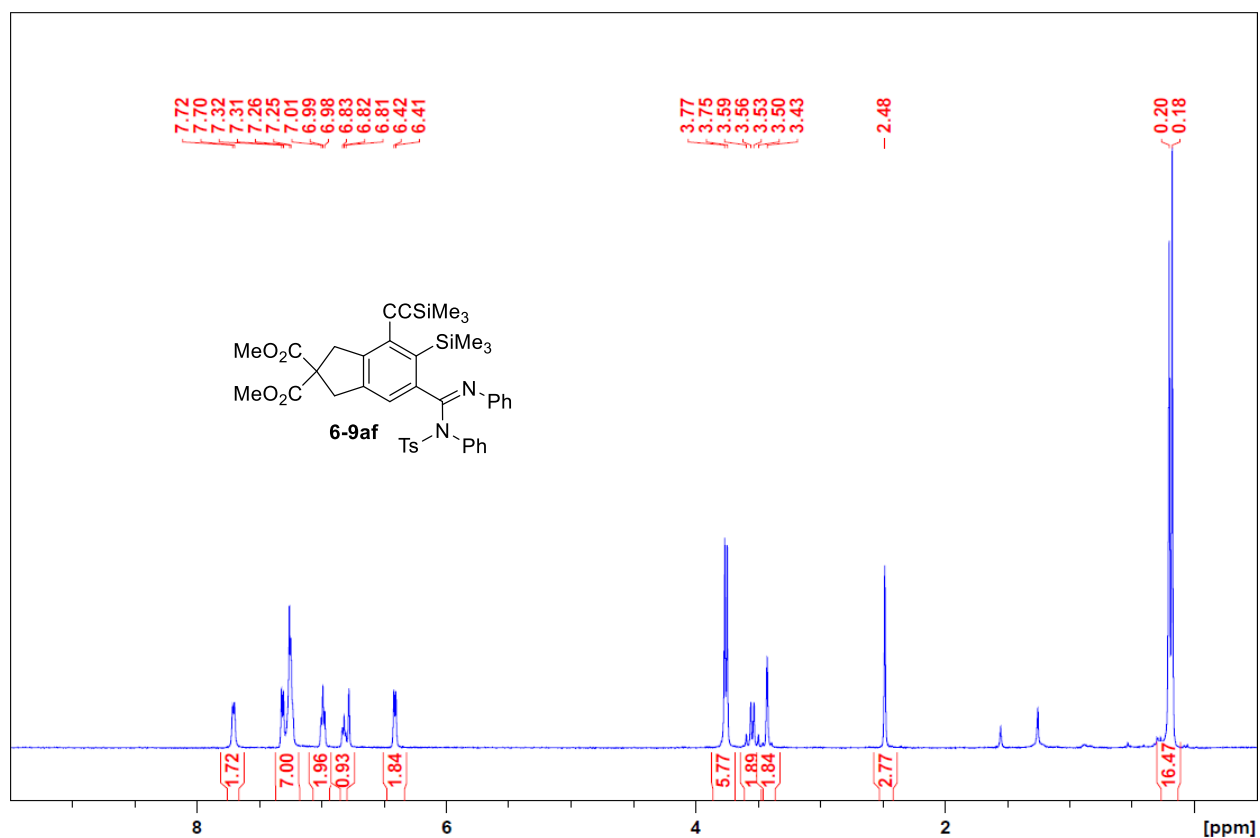


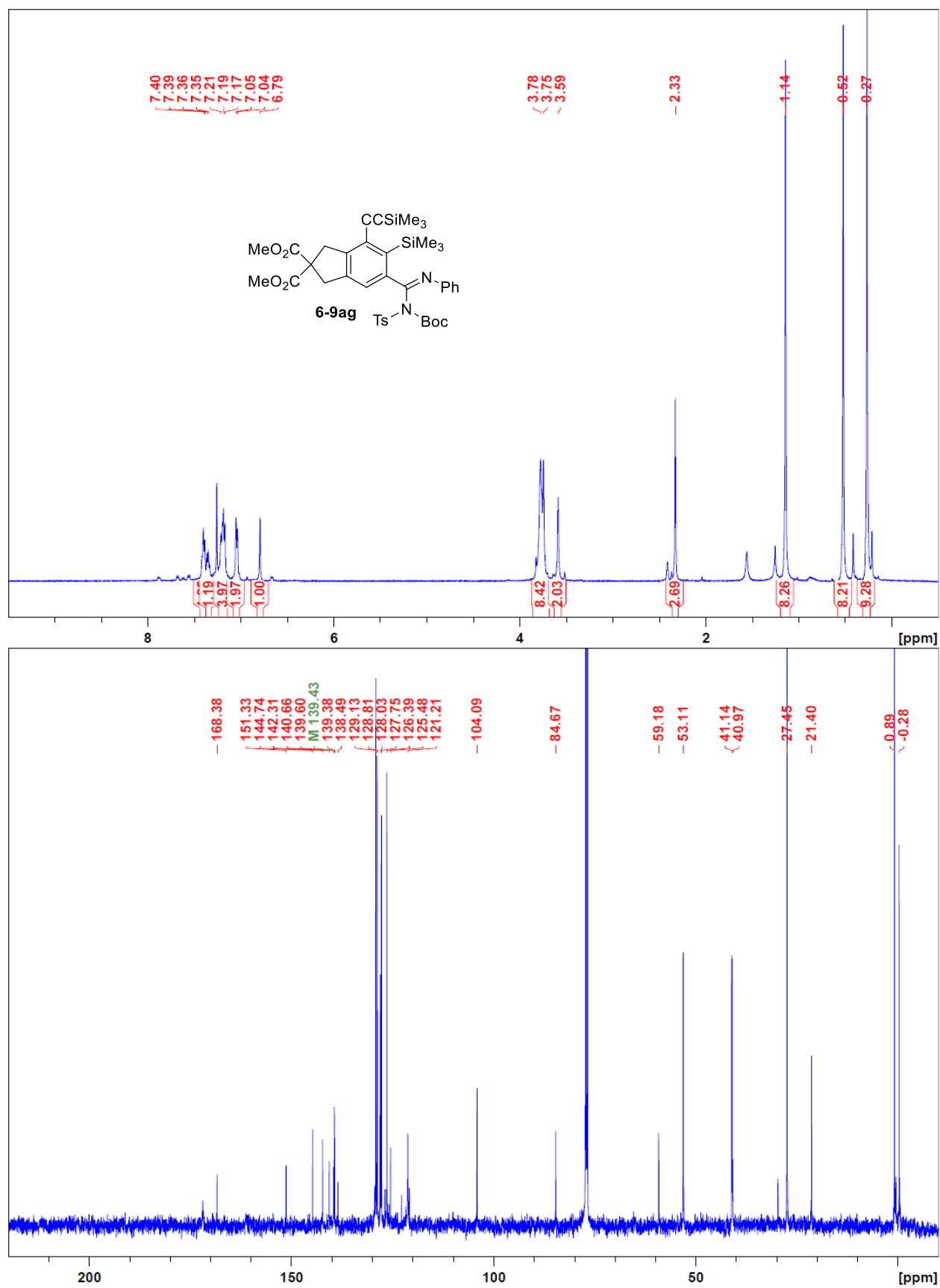




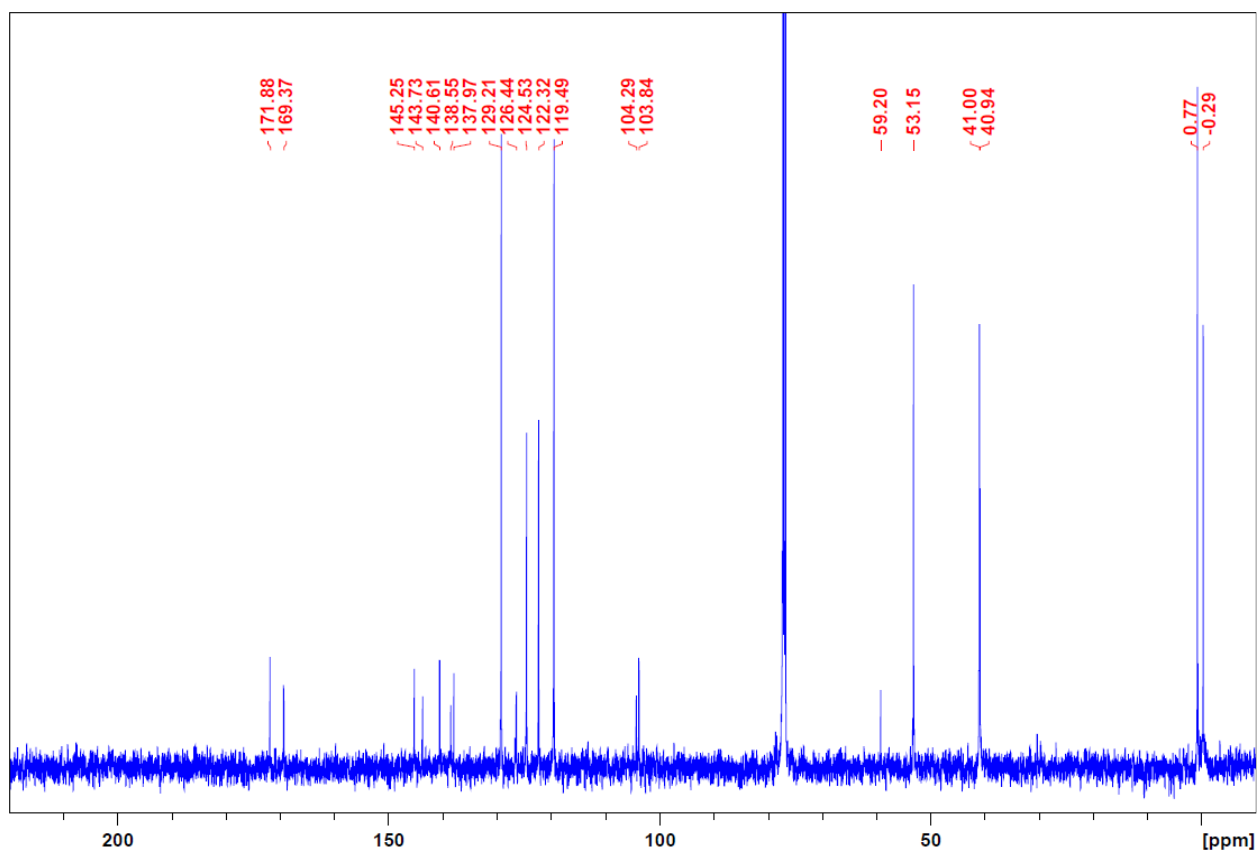
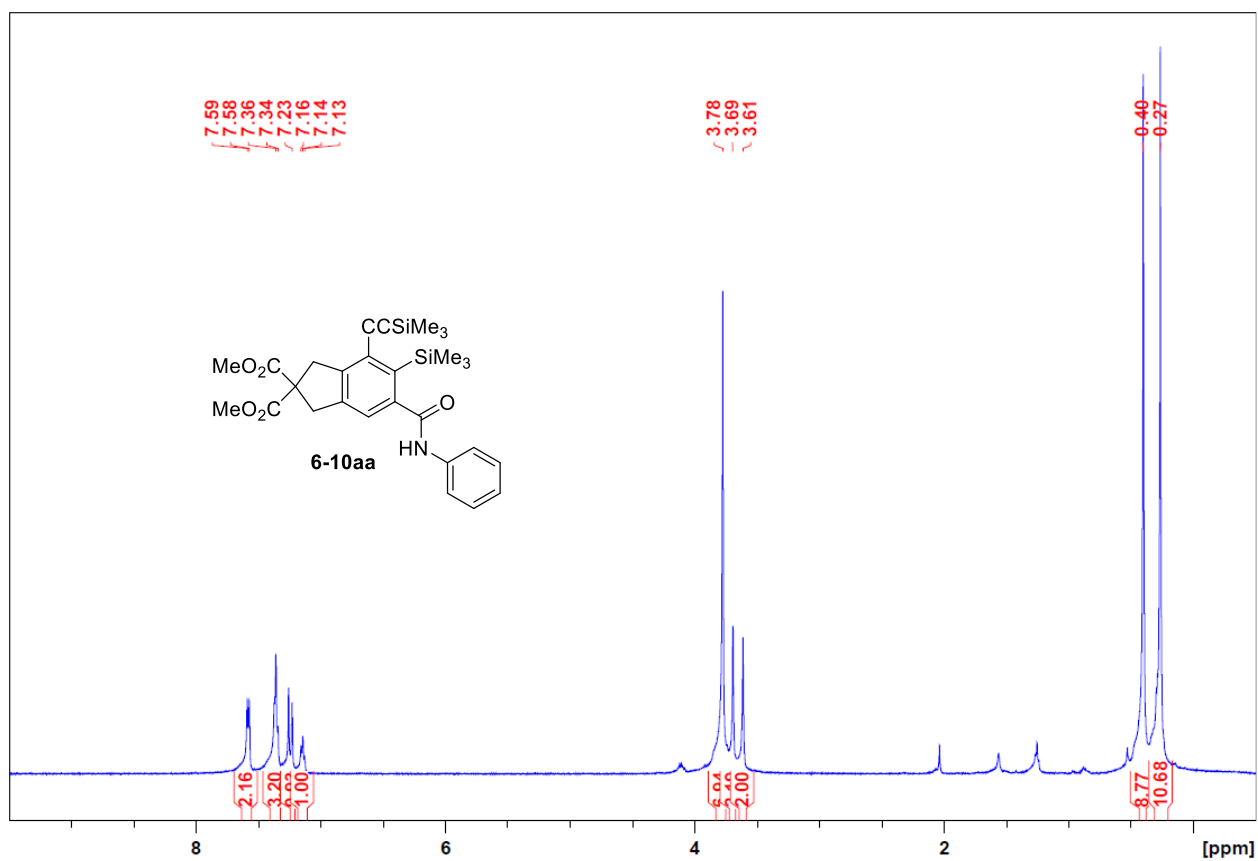


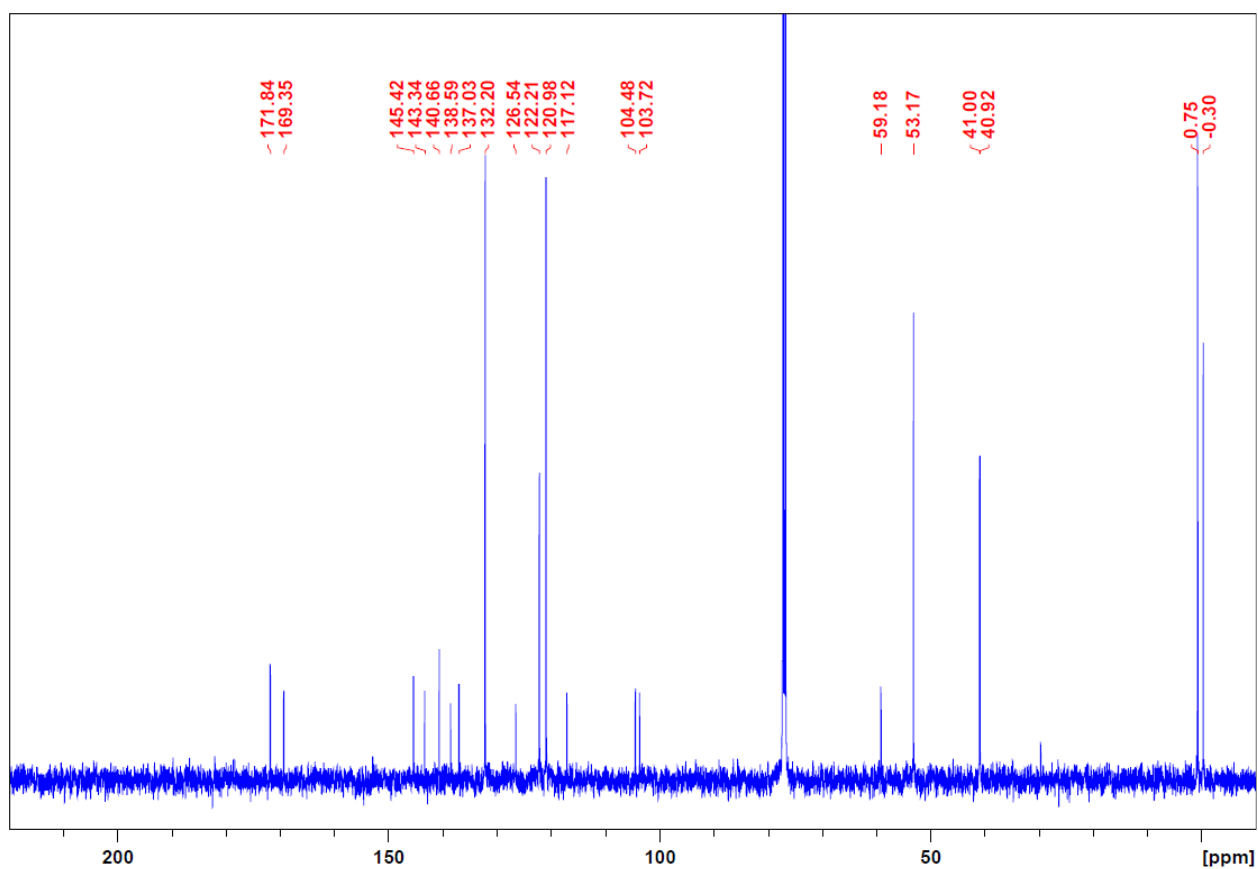
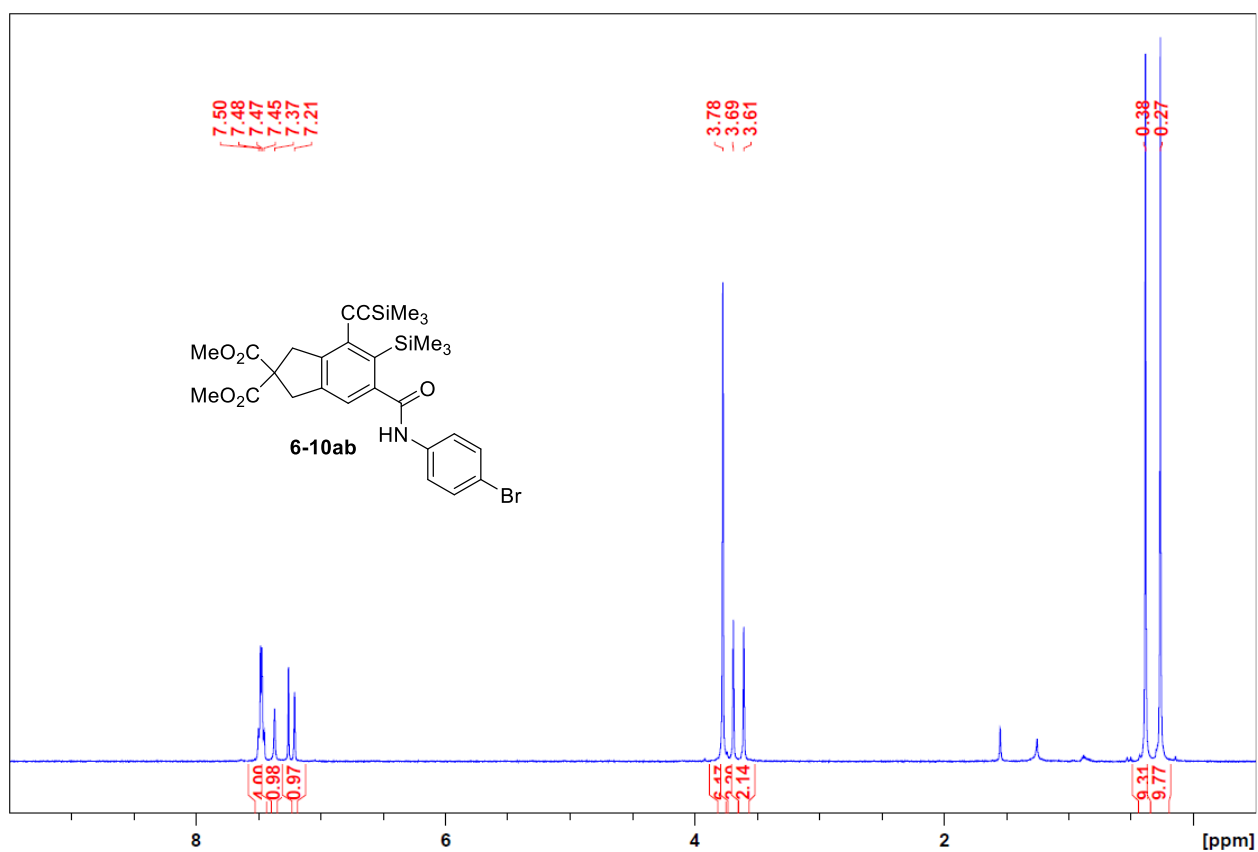


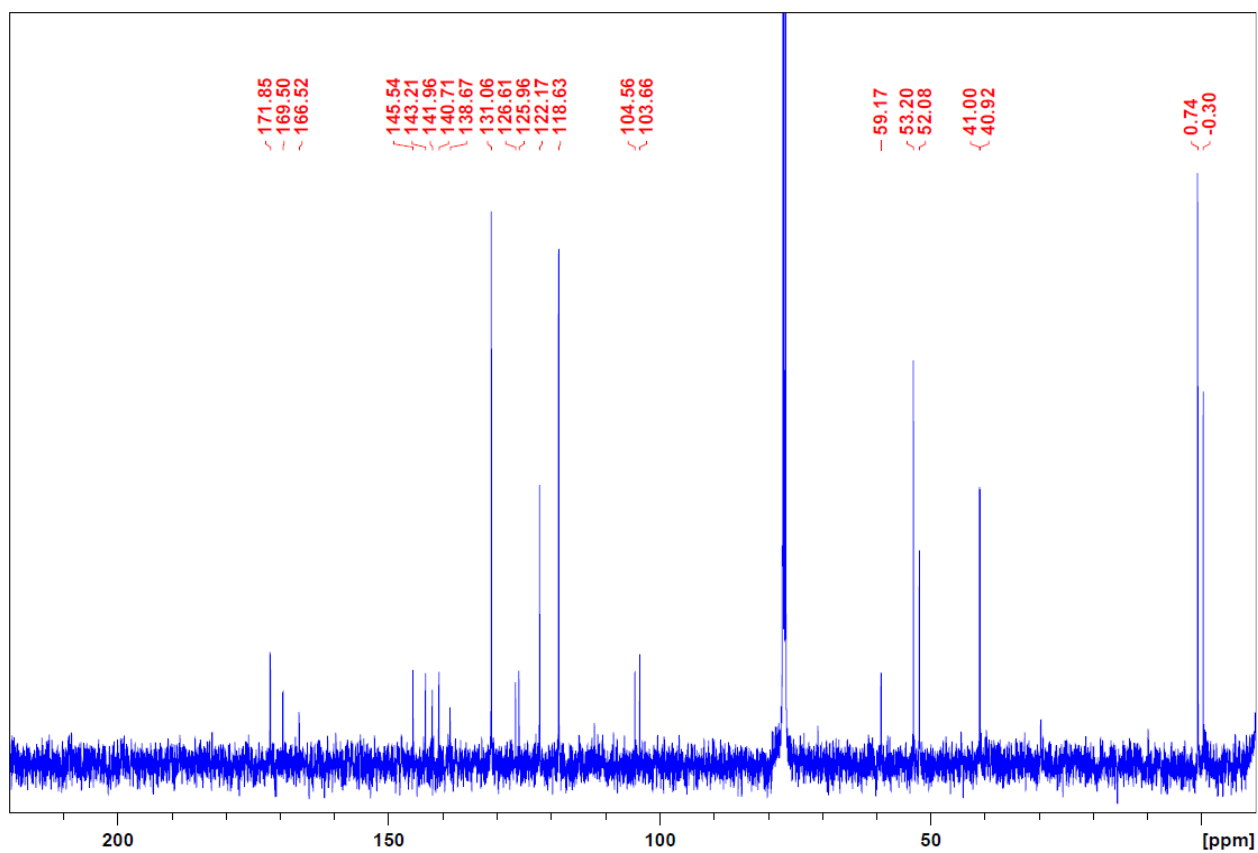
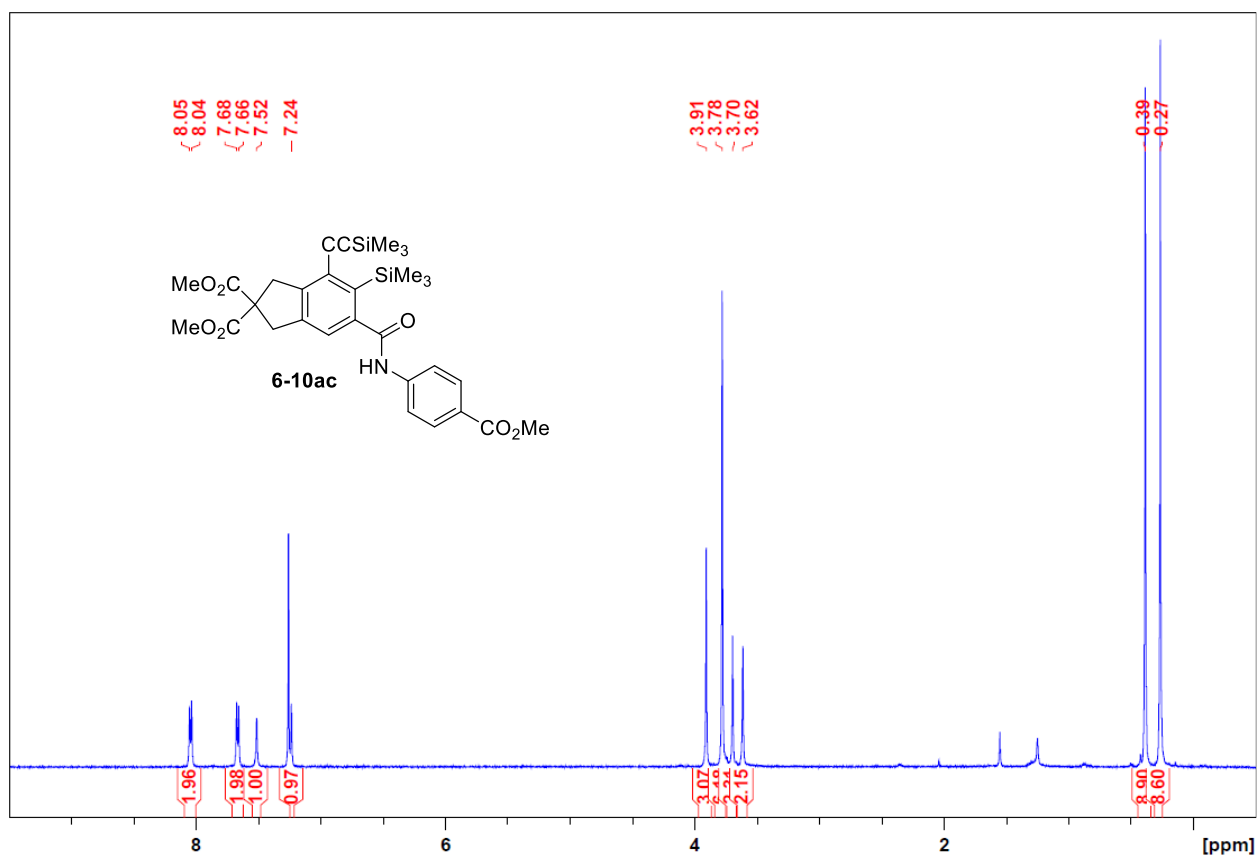


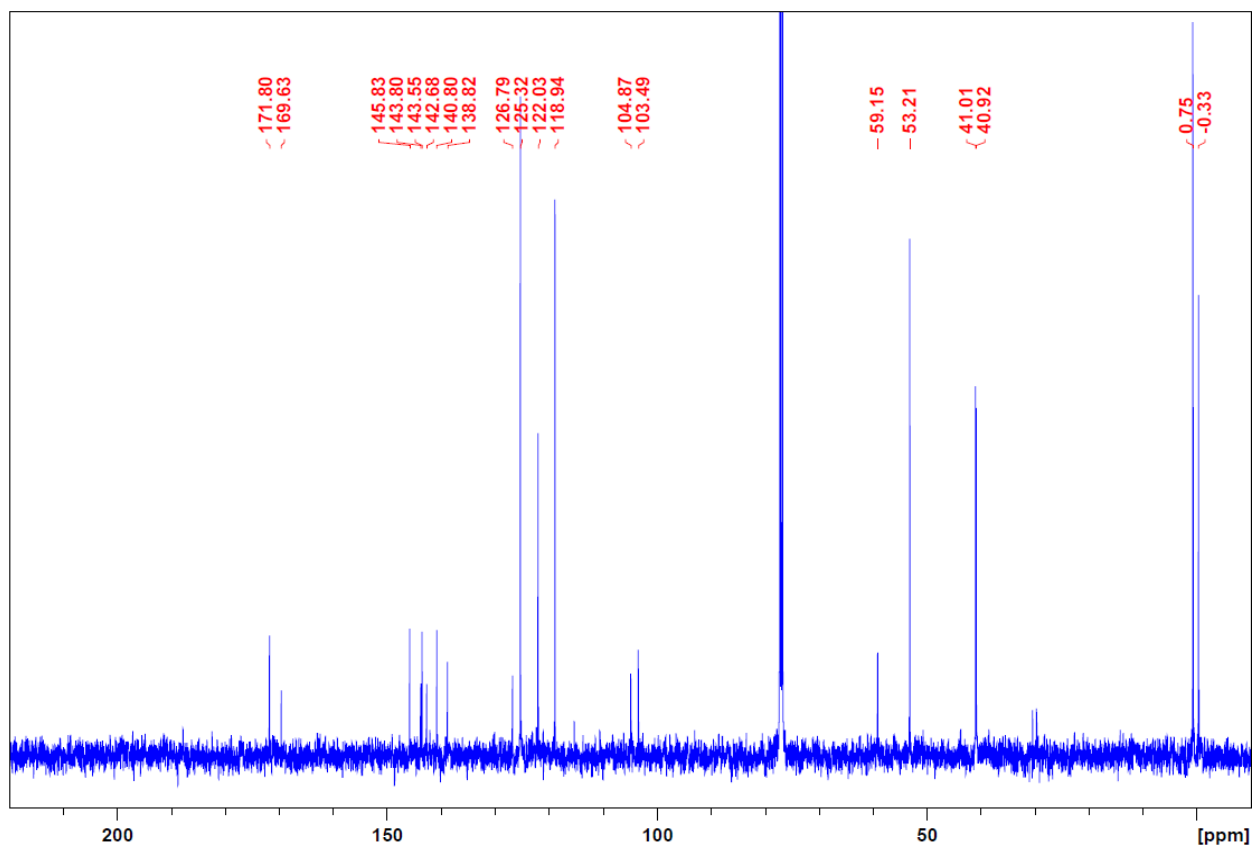
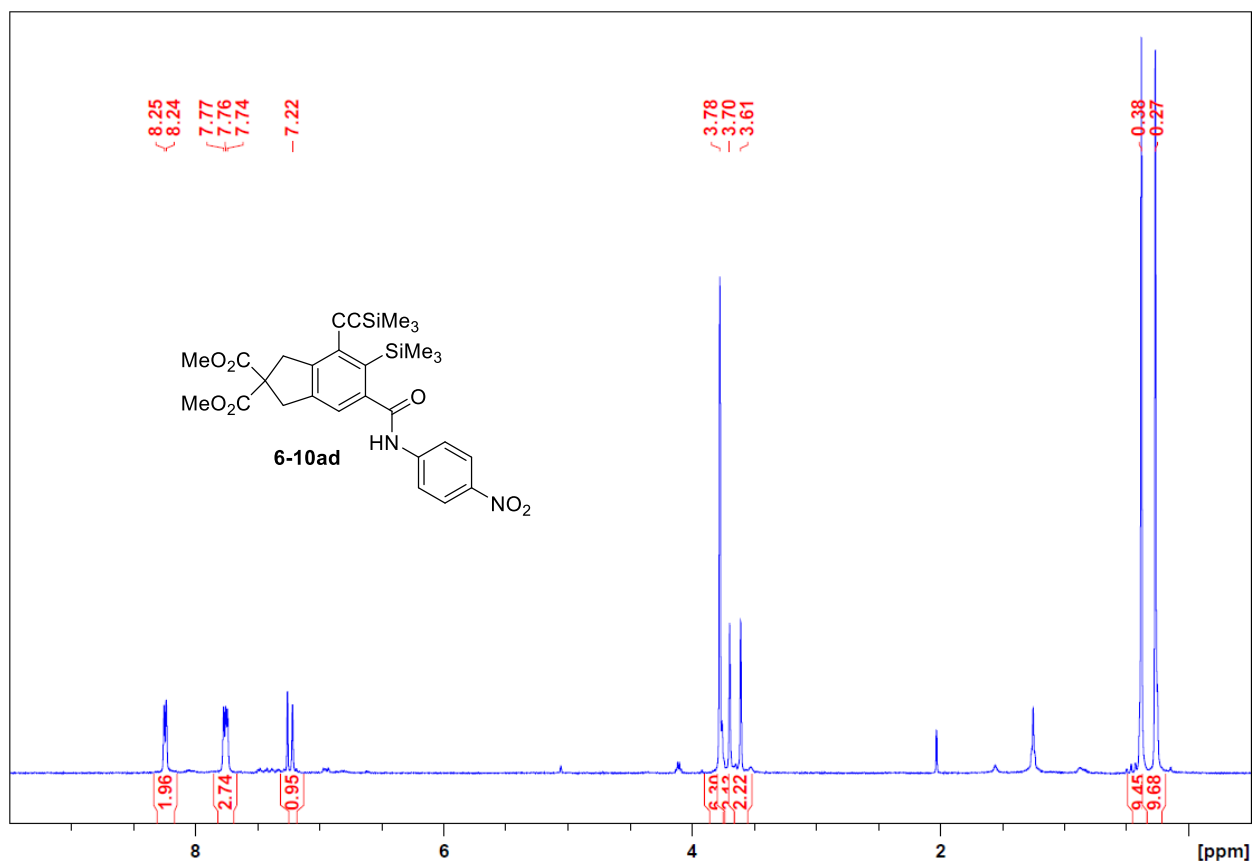


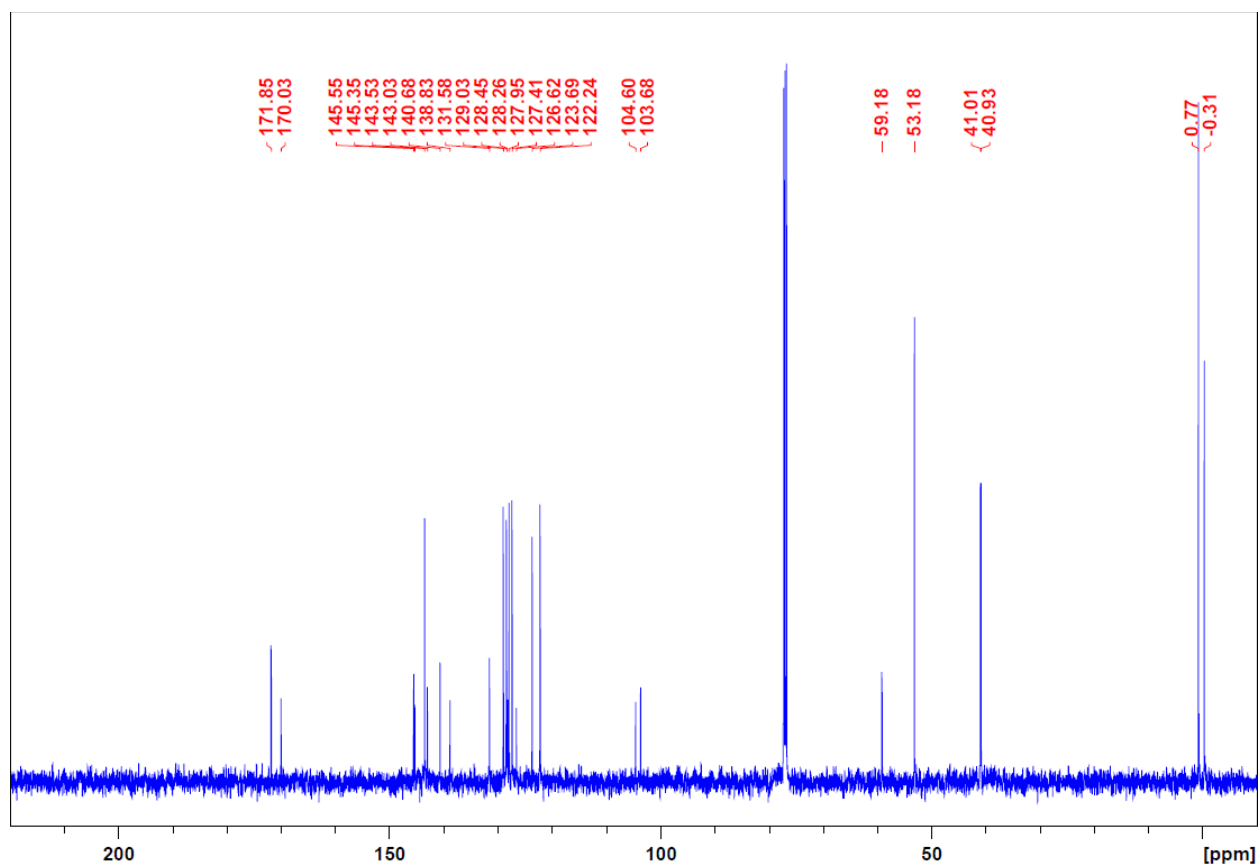
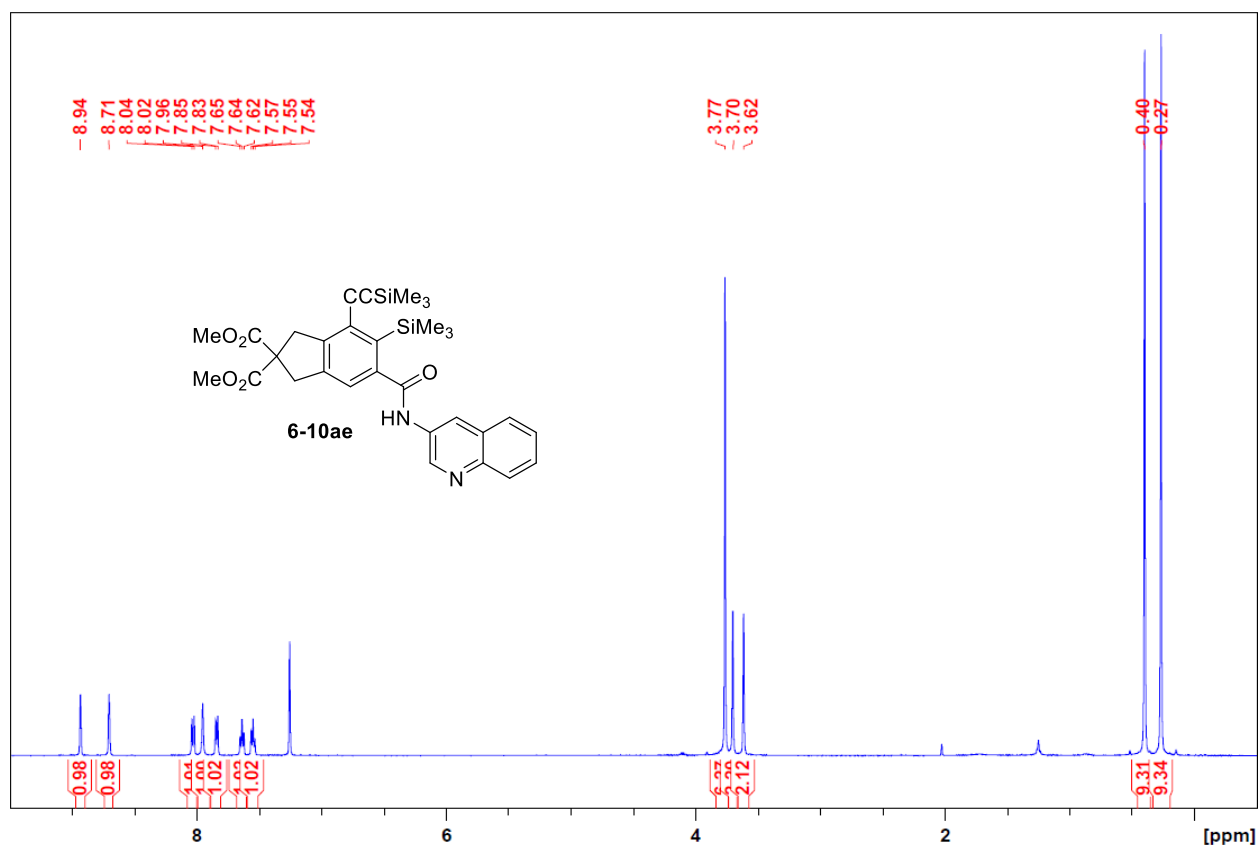






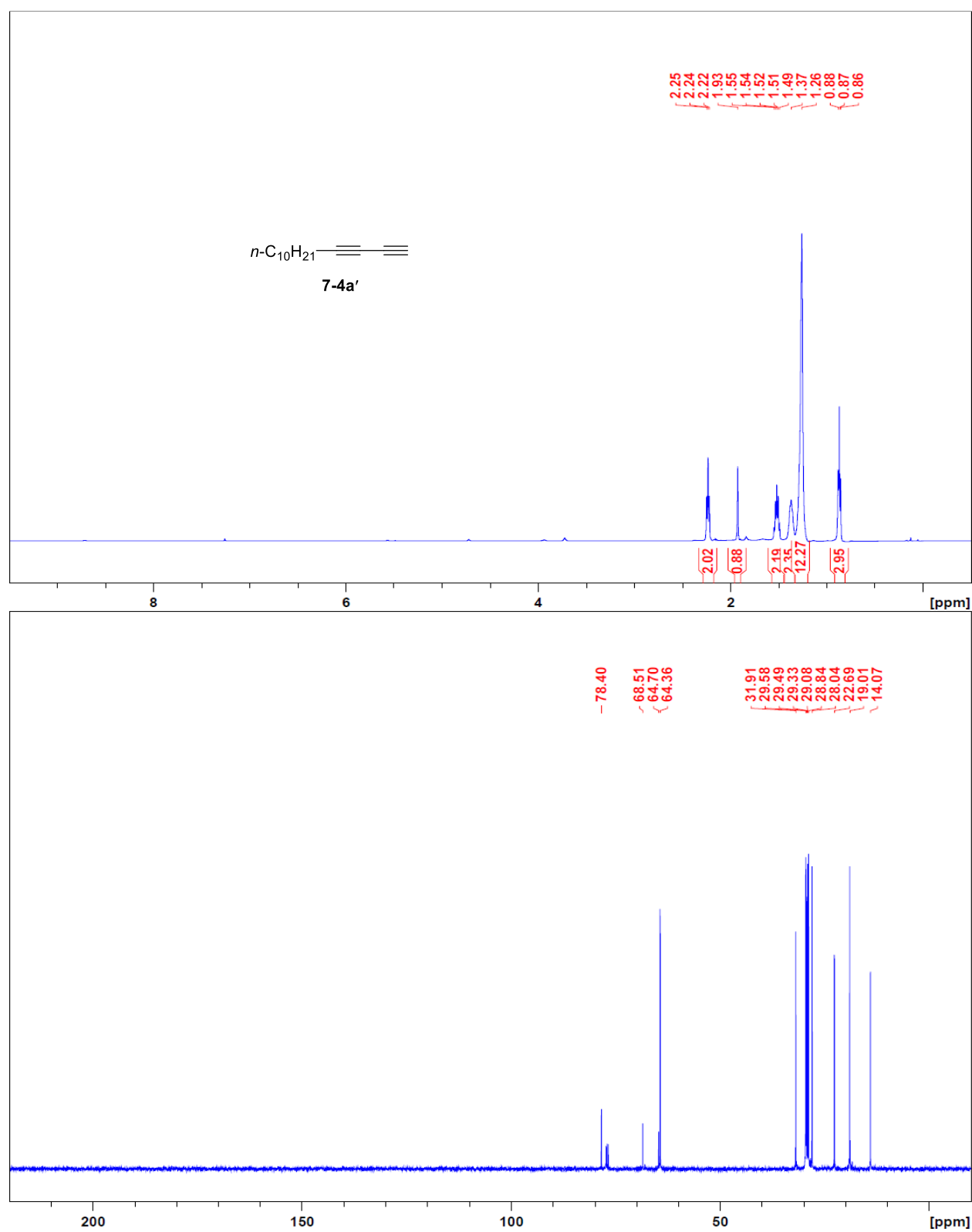


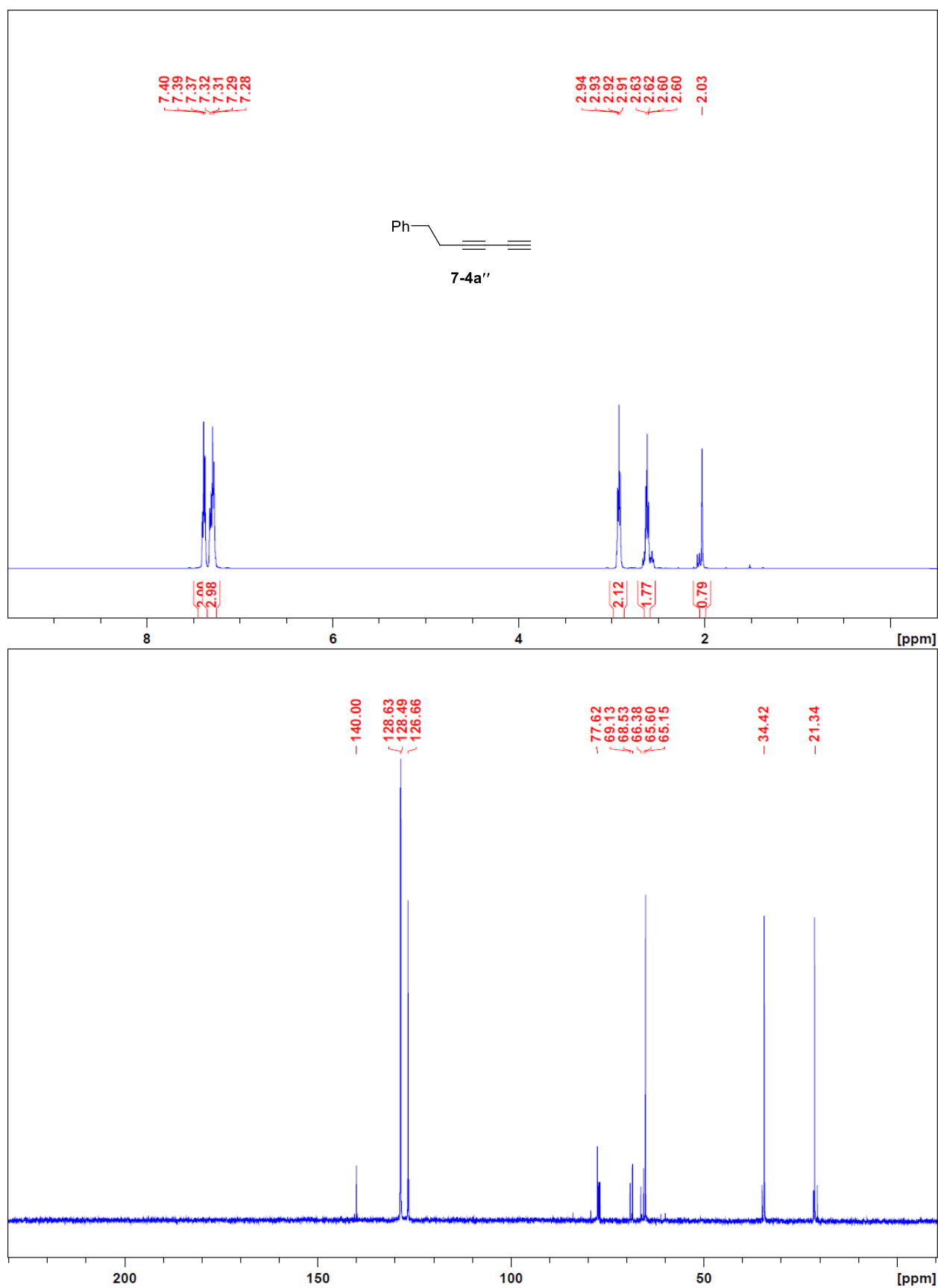


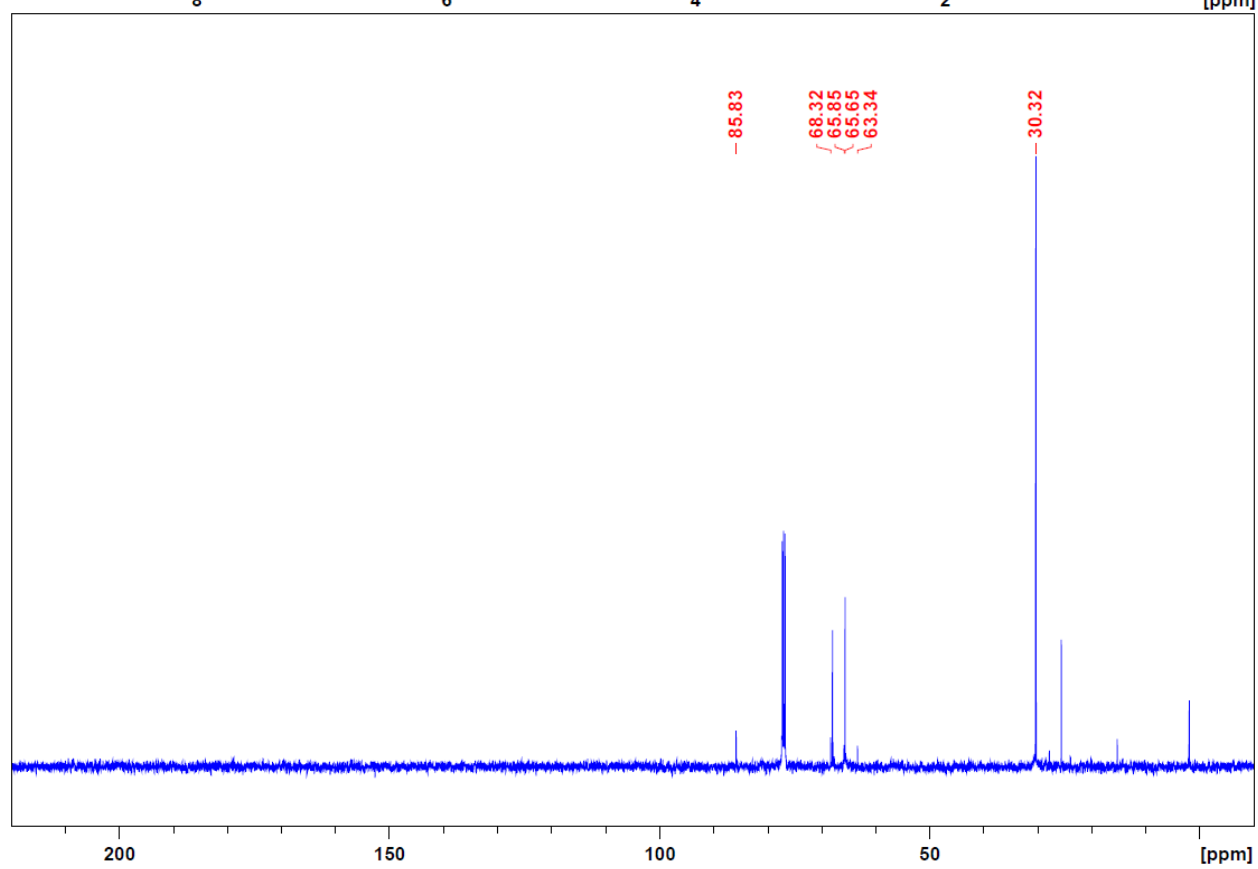
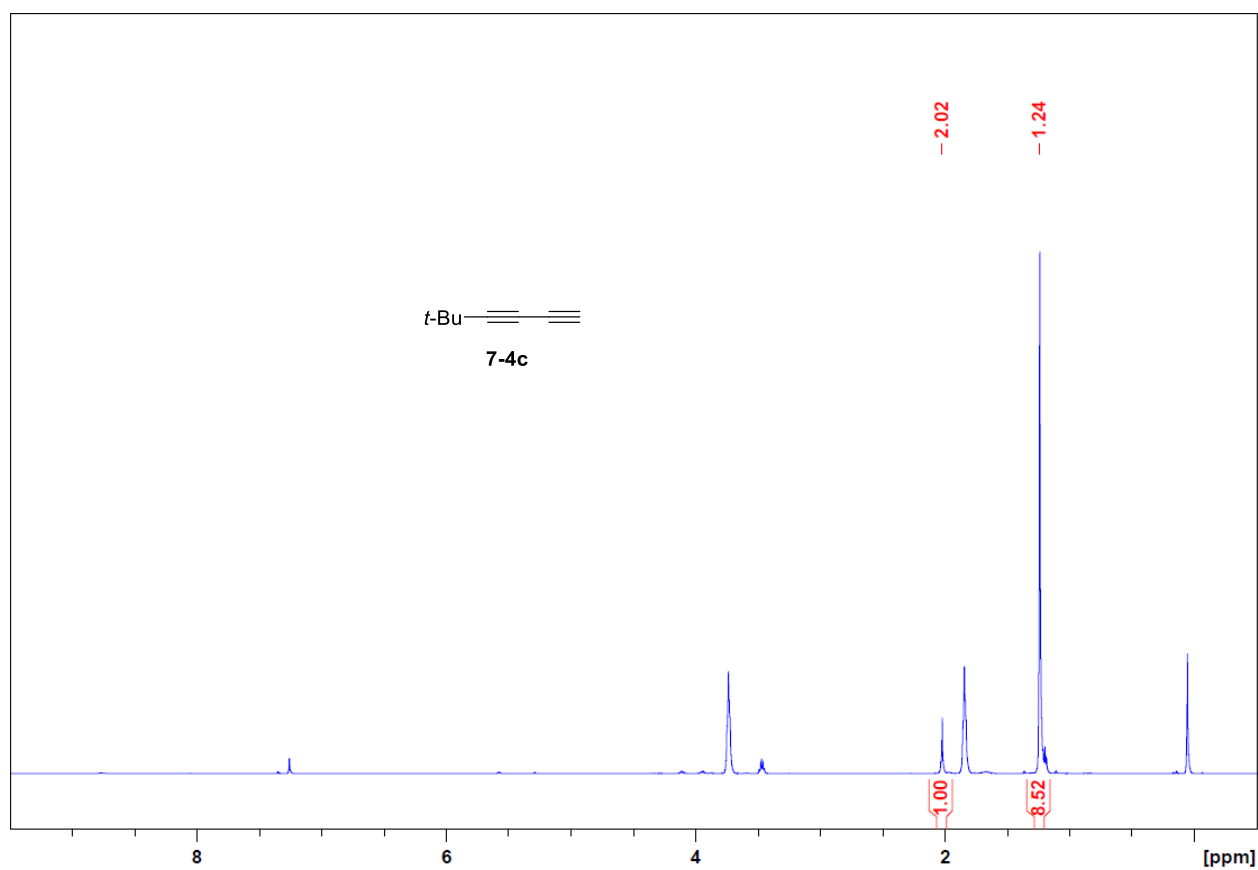


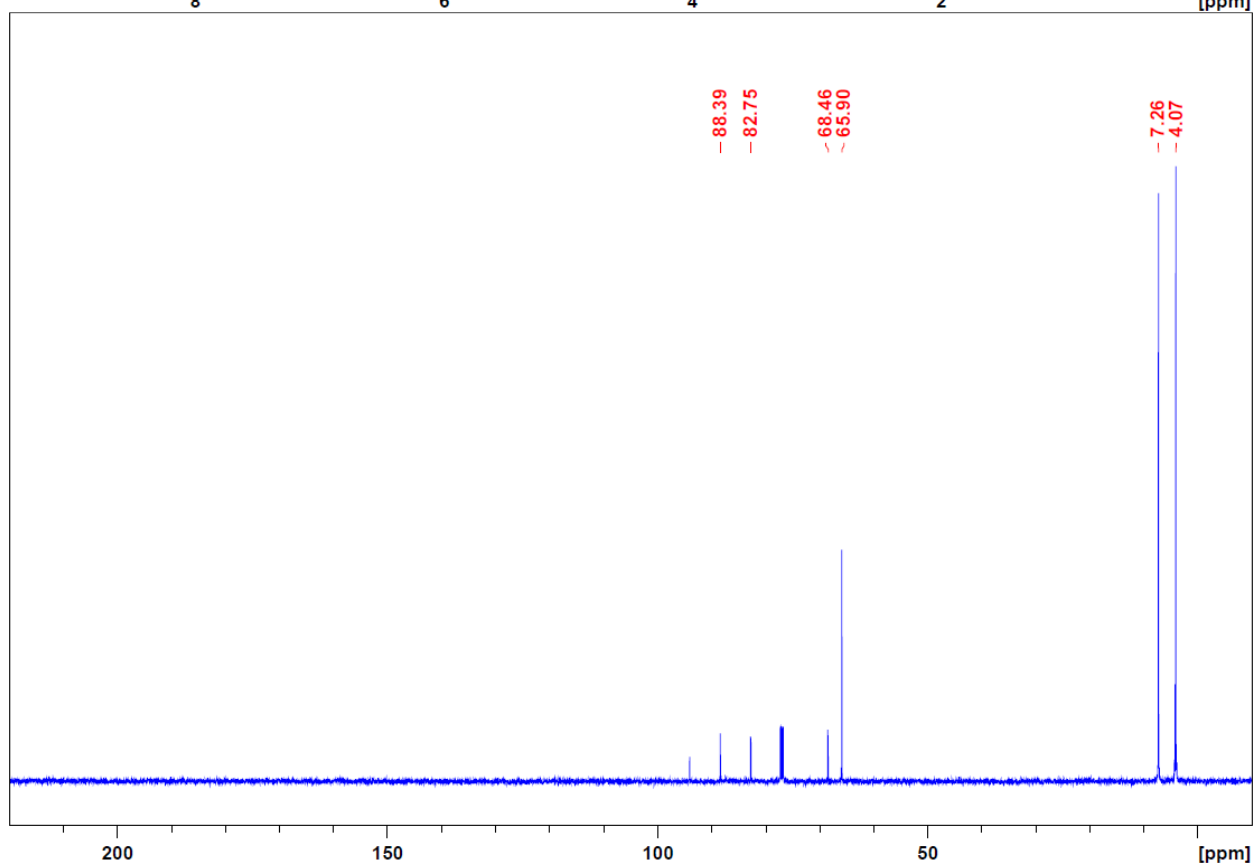
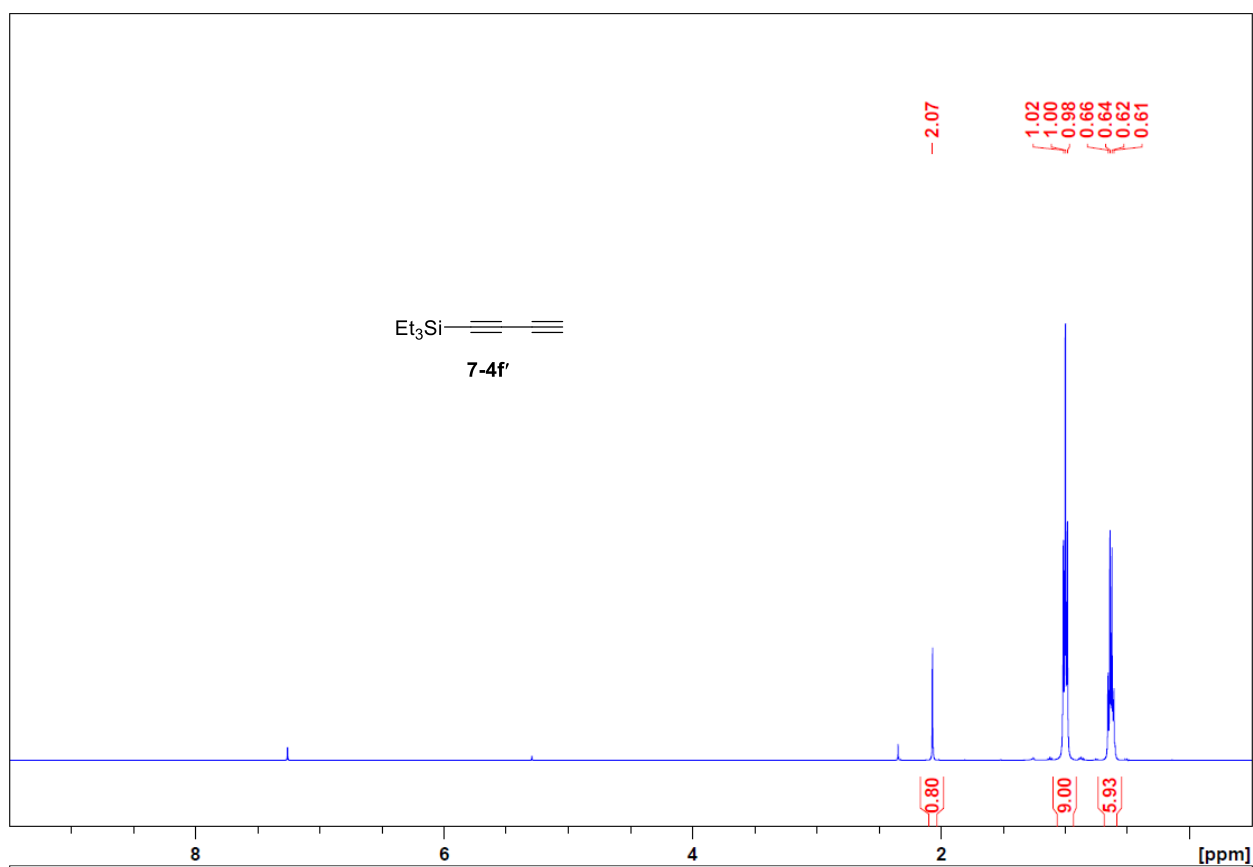
Appendix VI
Selected NMR Spectra for Chapter 7

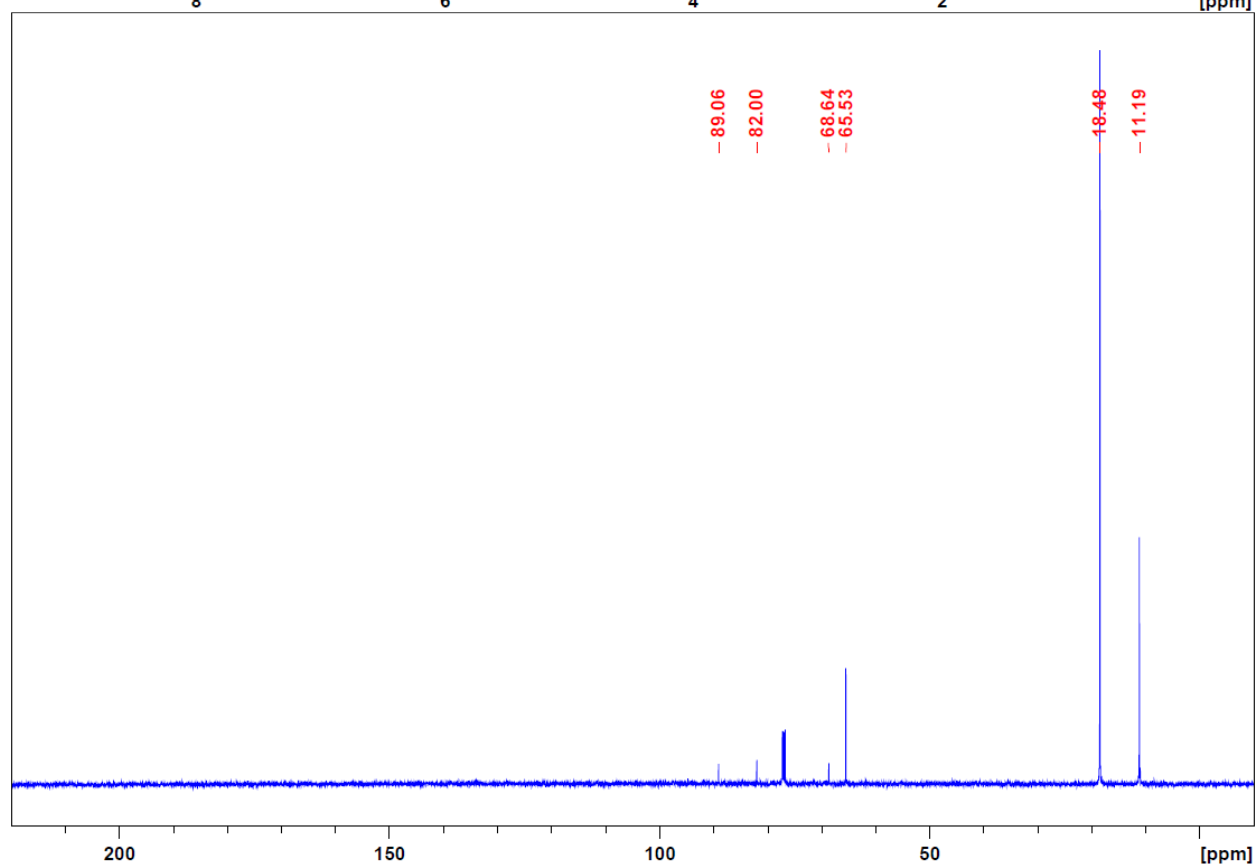
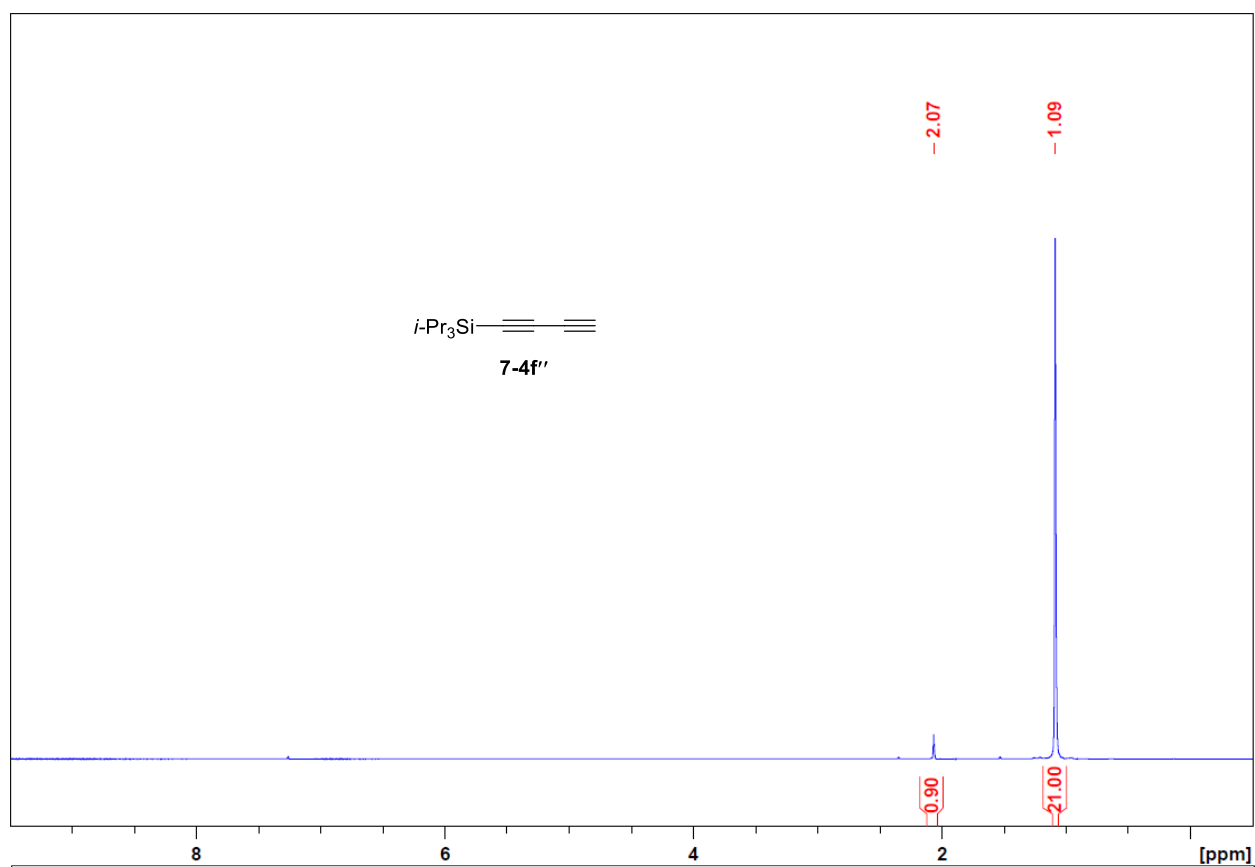
¹H and ¹³C NMR Spectra of Substrates

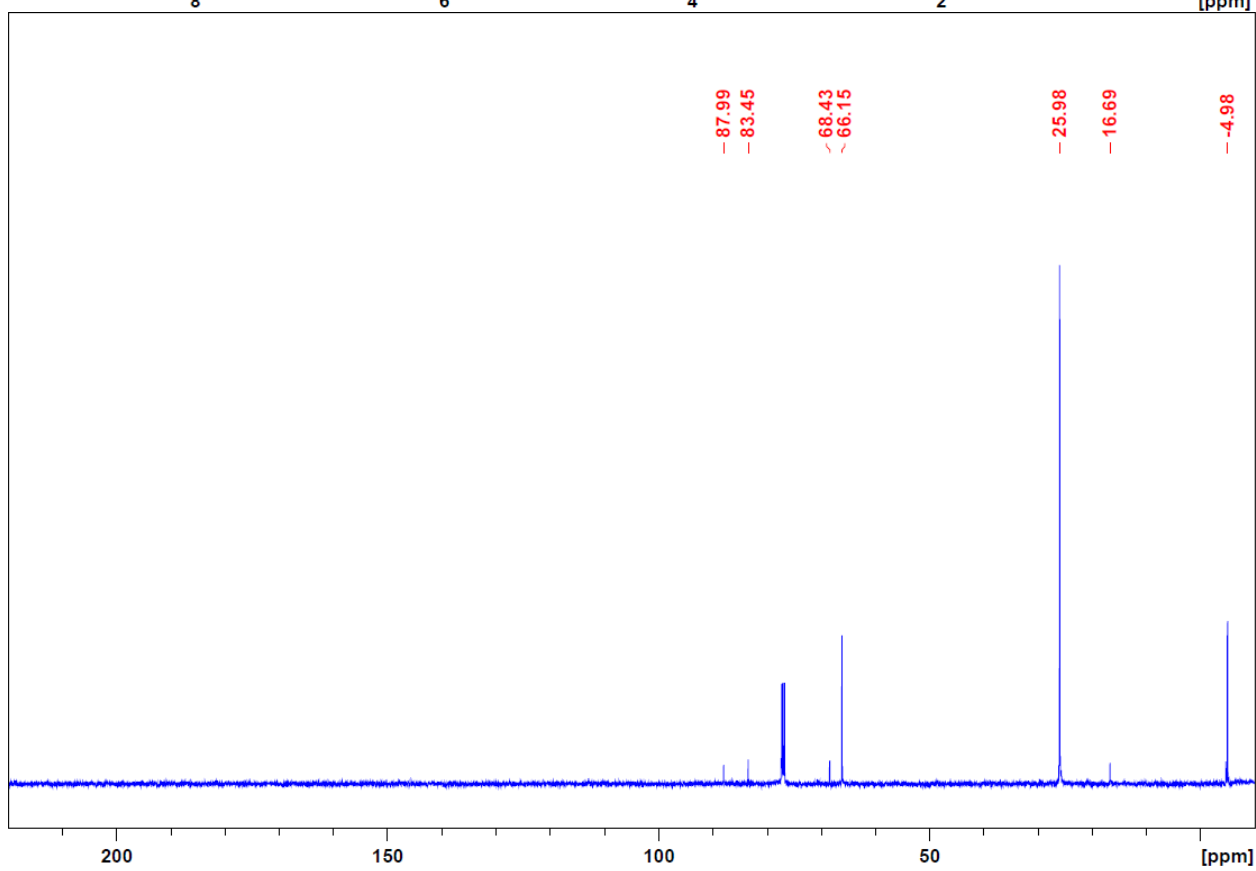
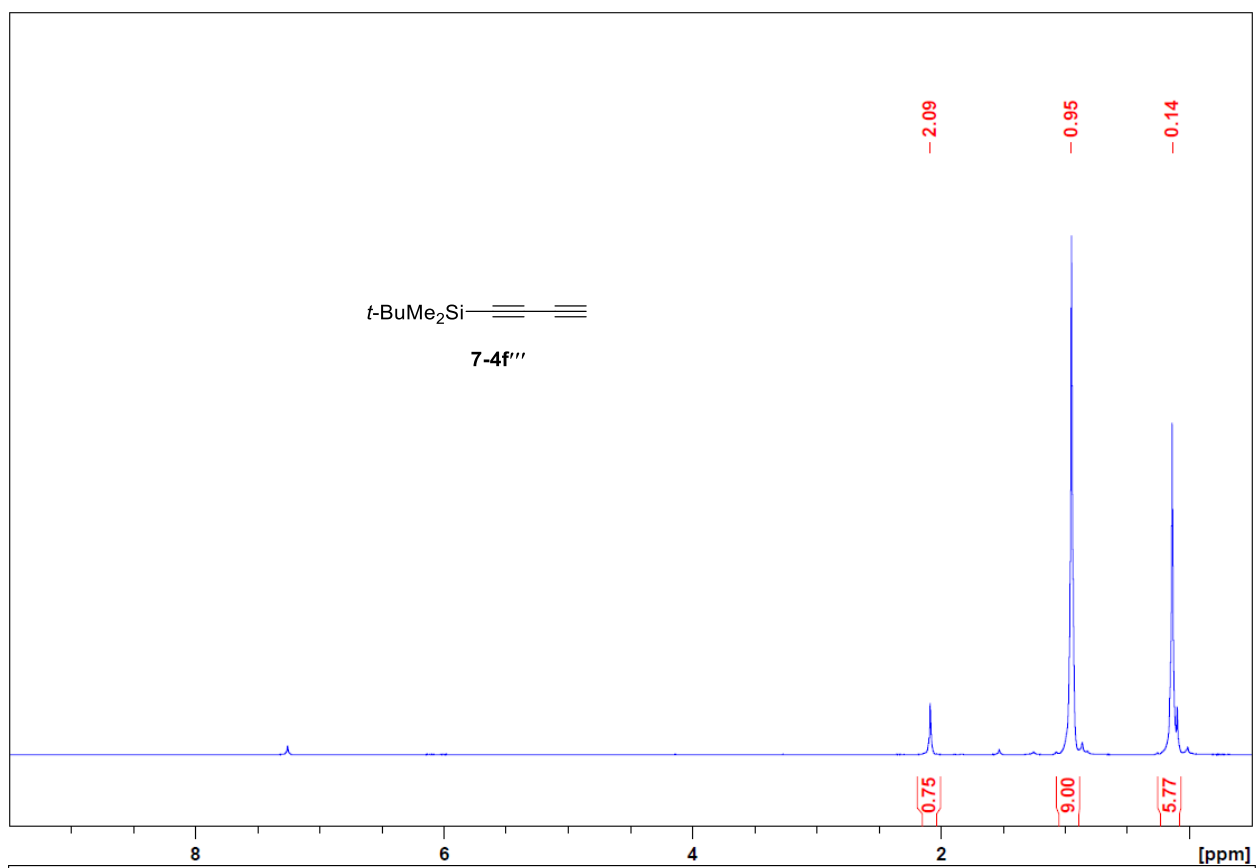


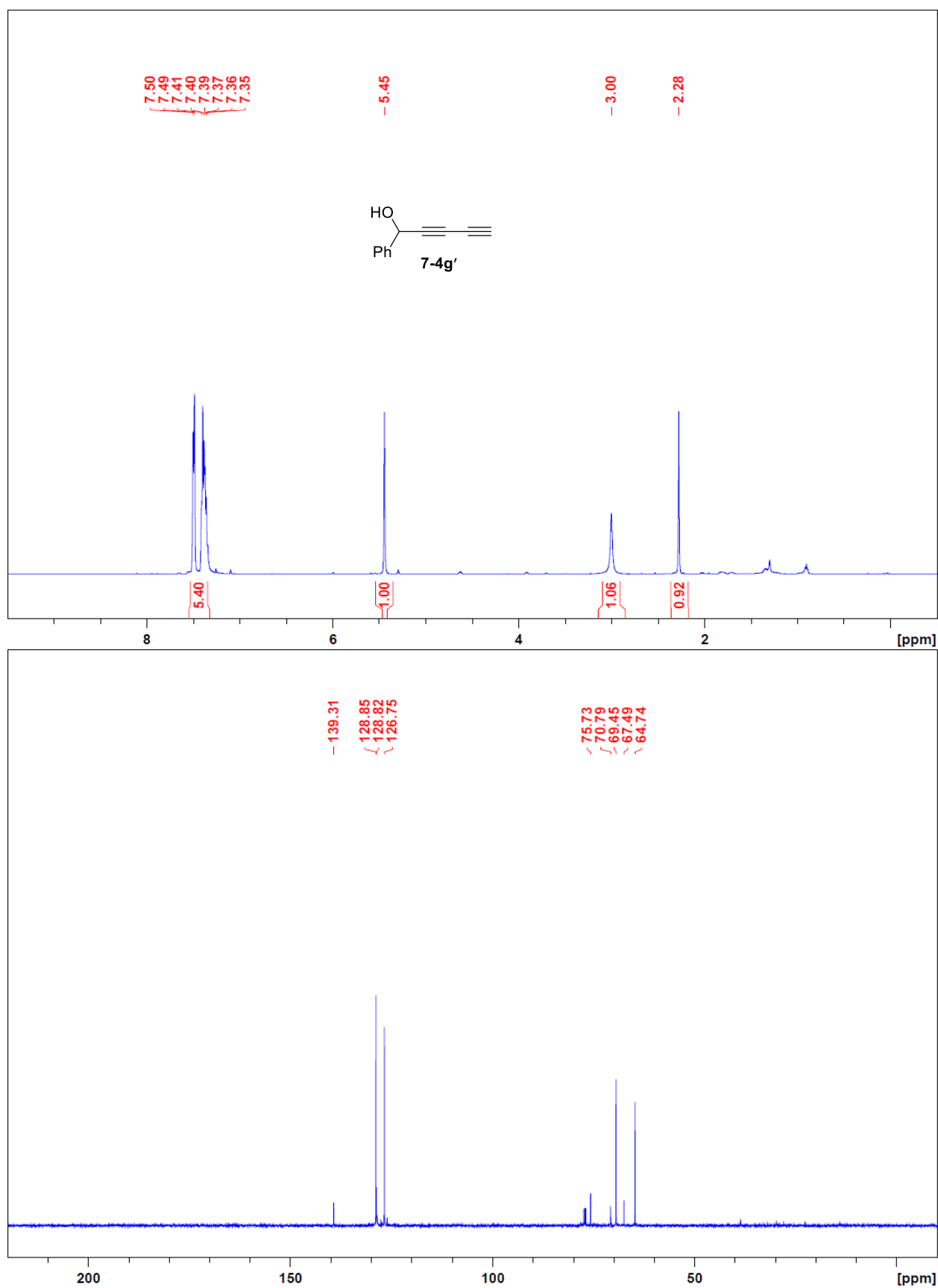


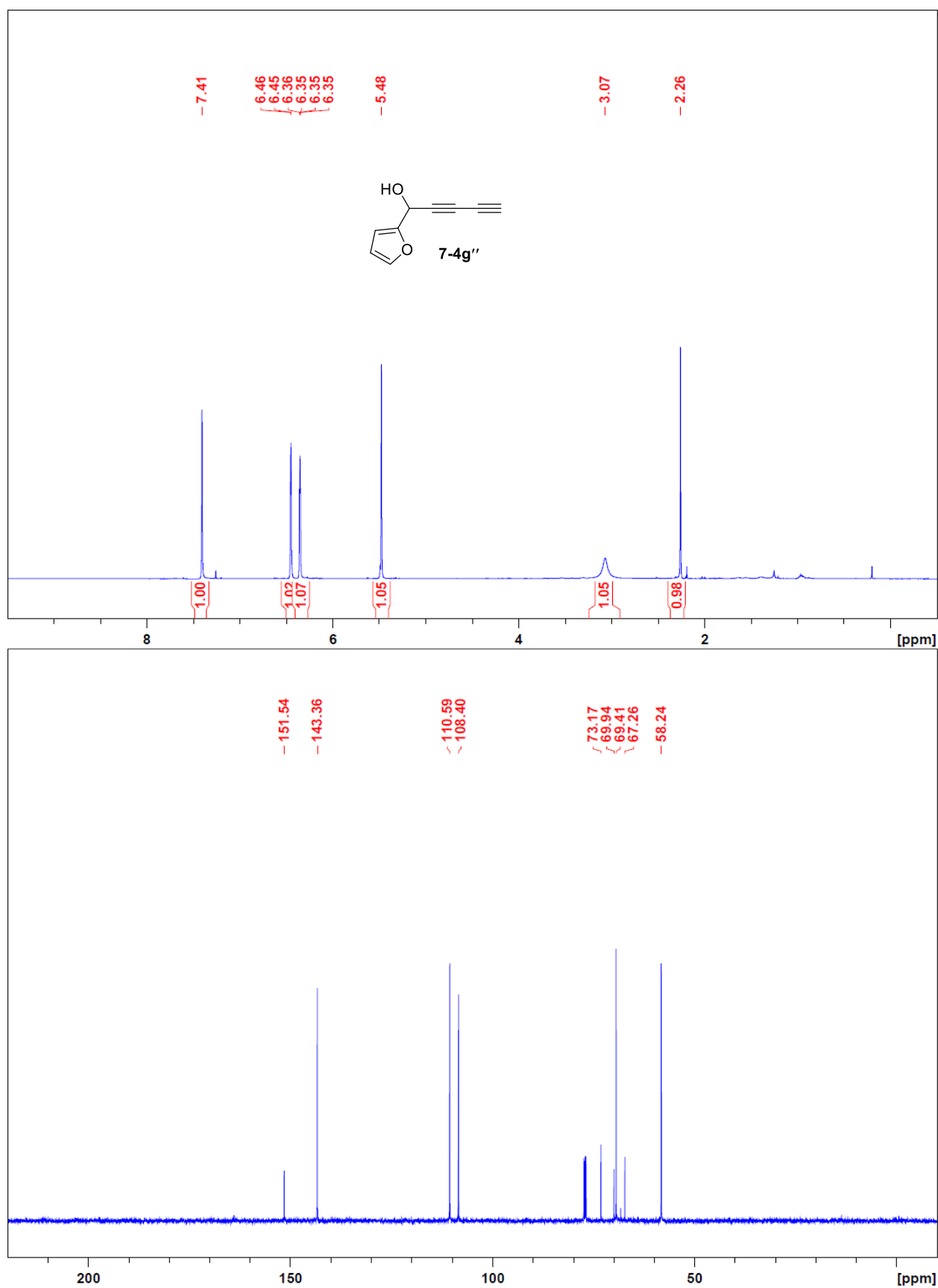


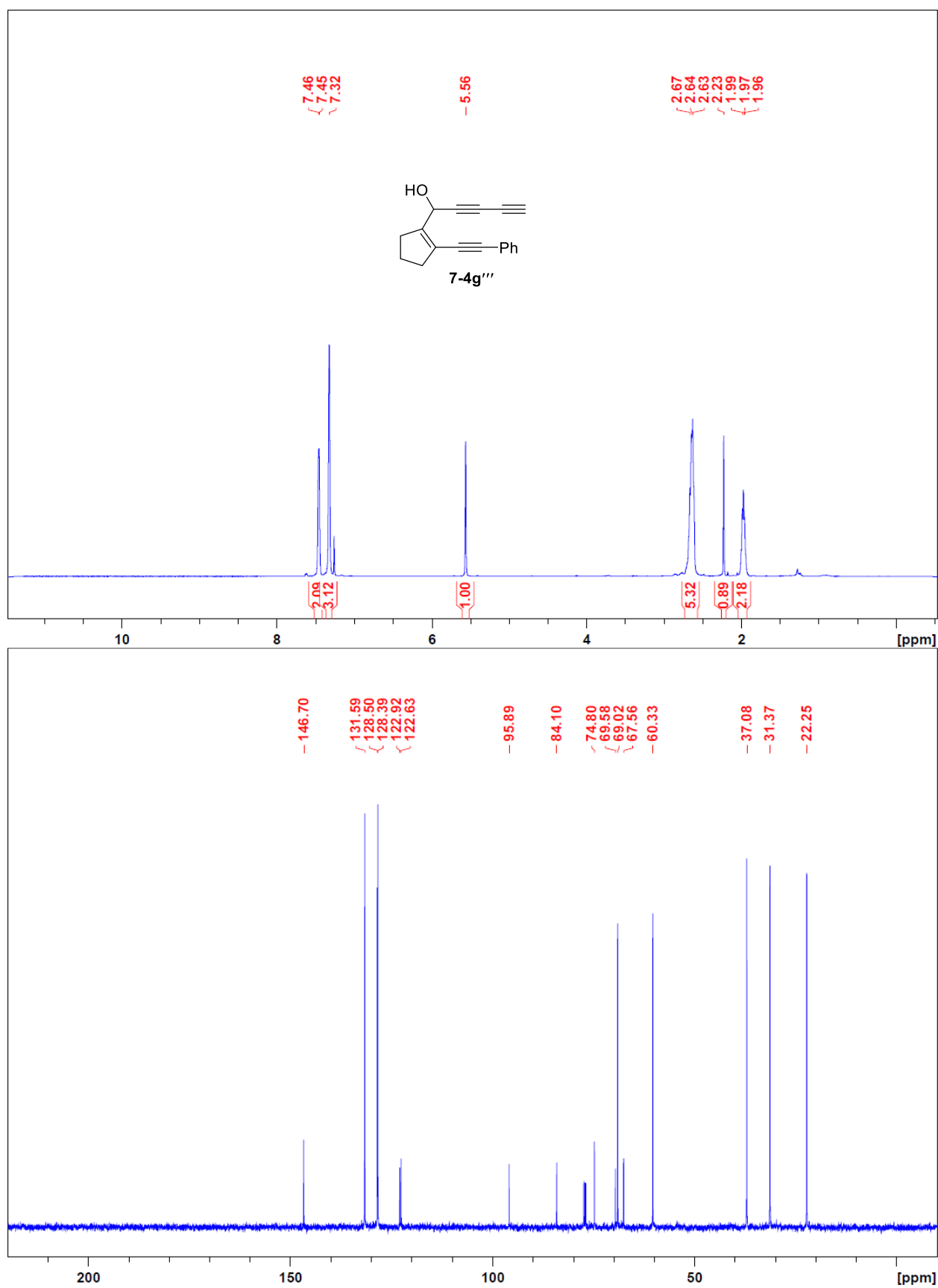


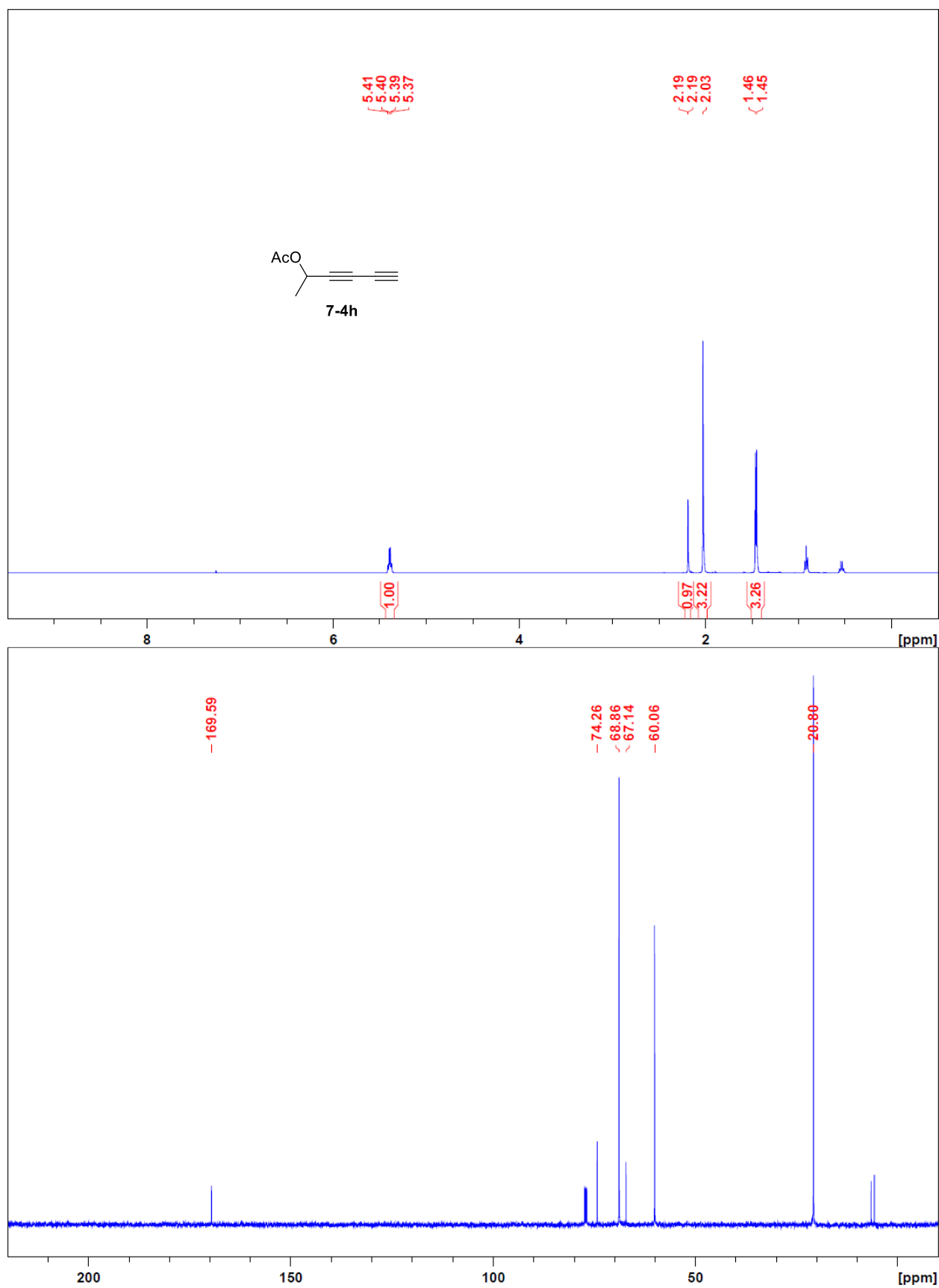


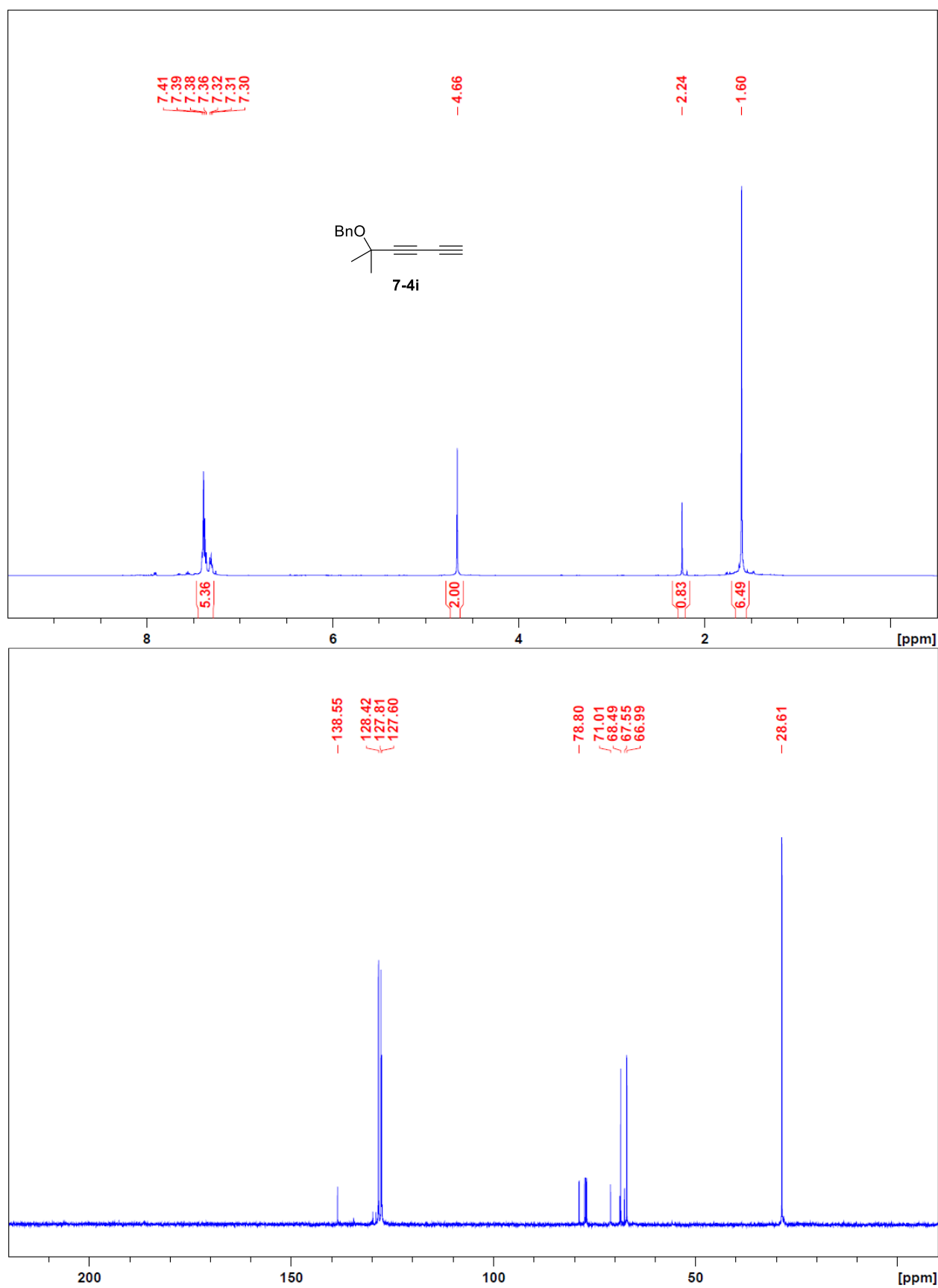


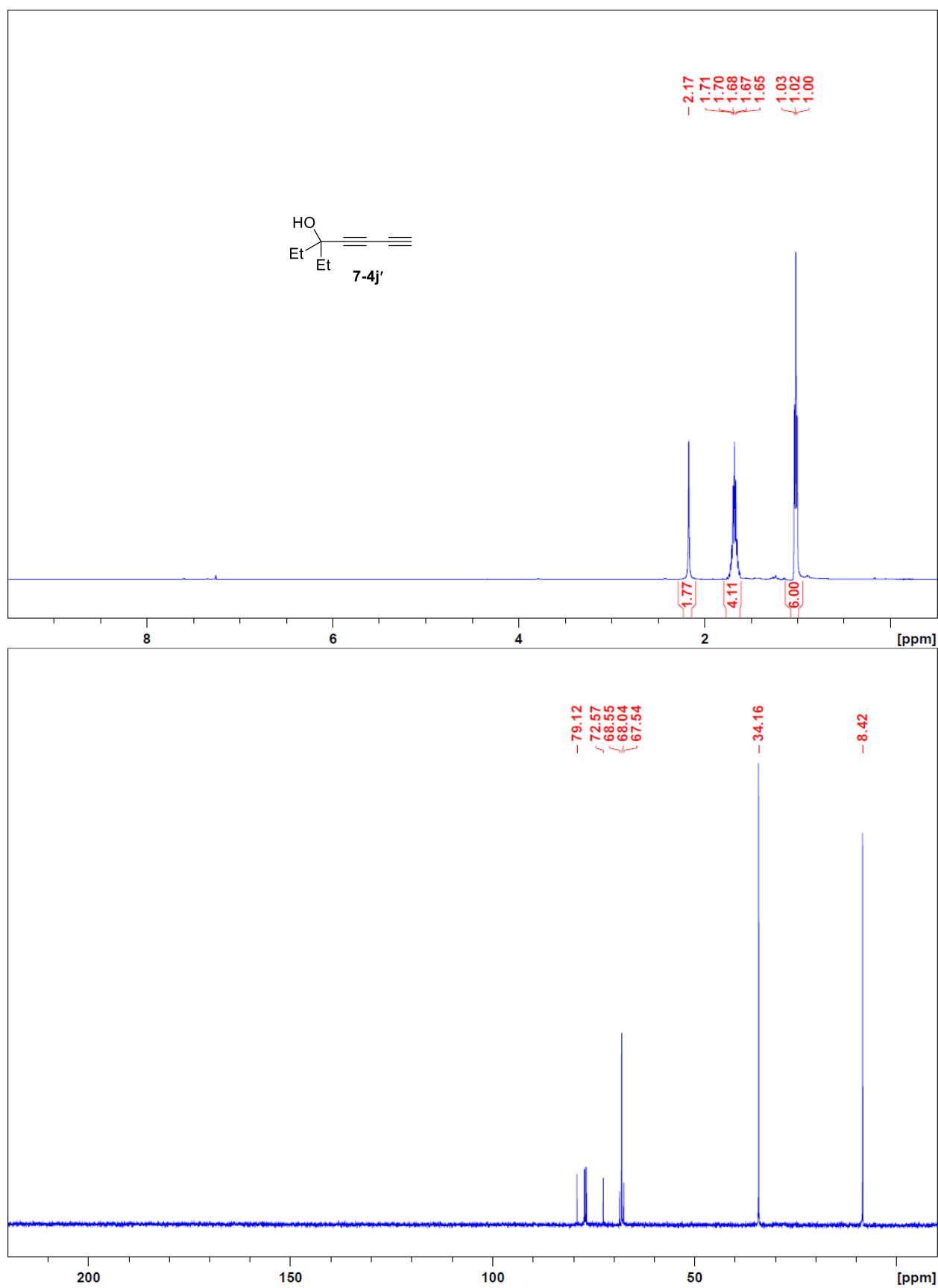


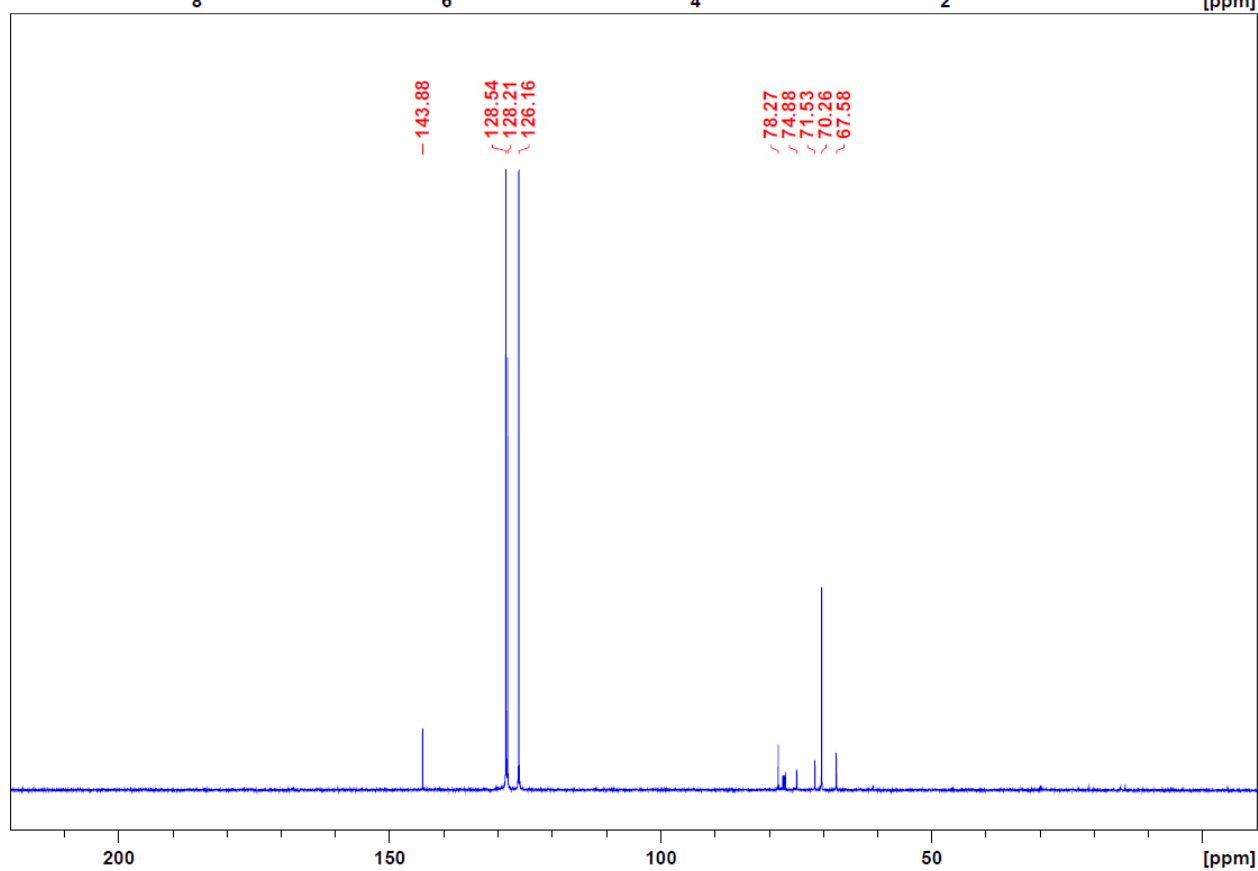
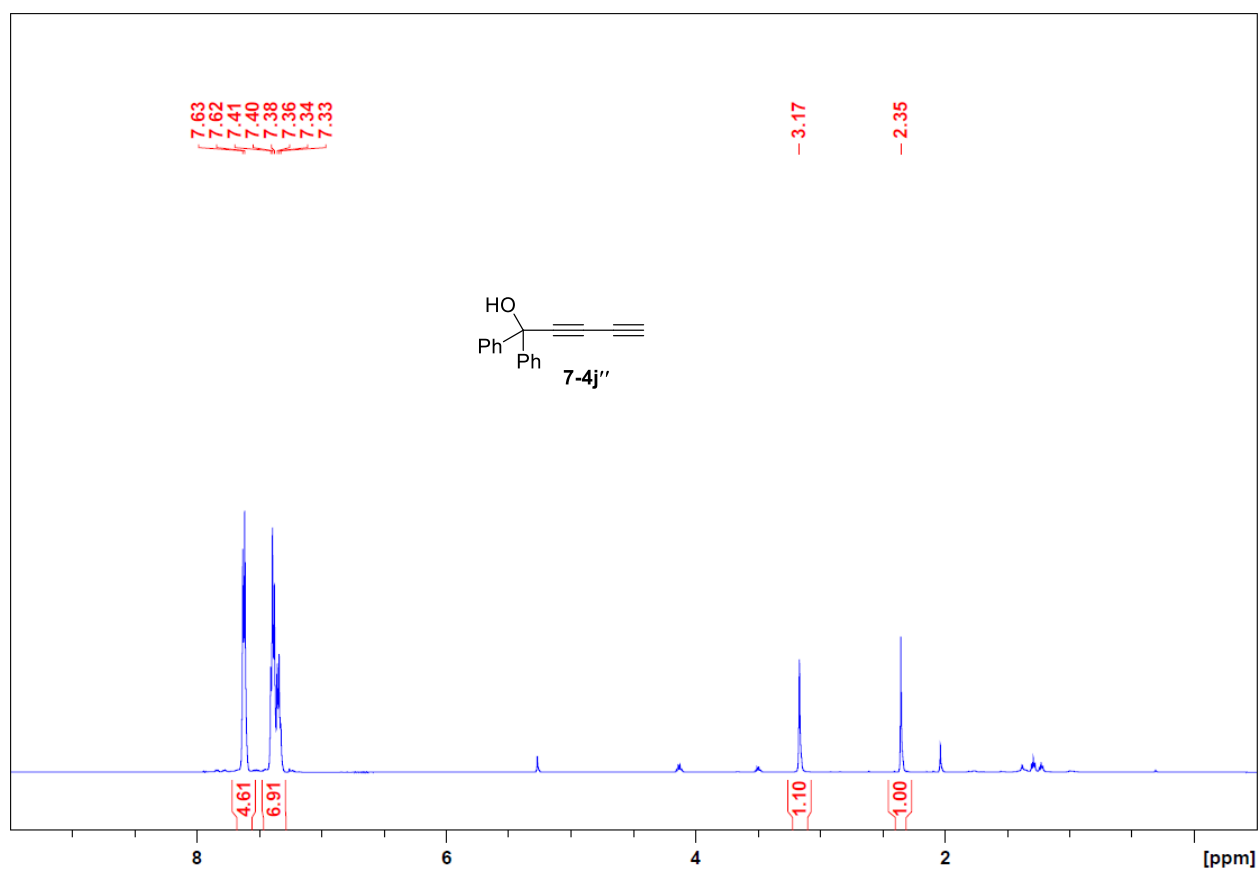


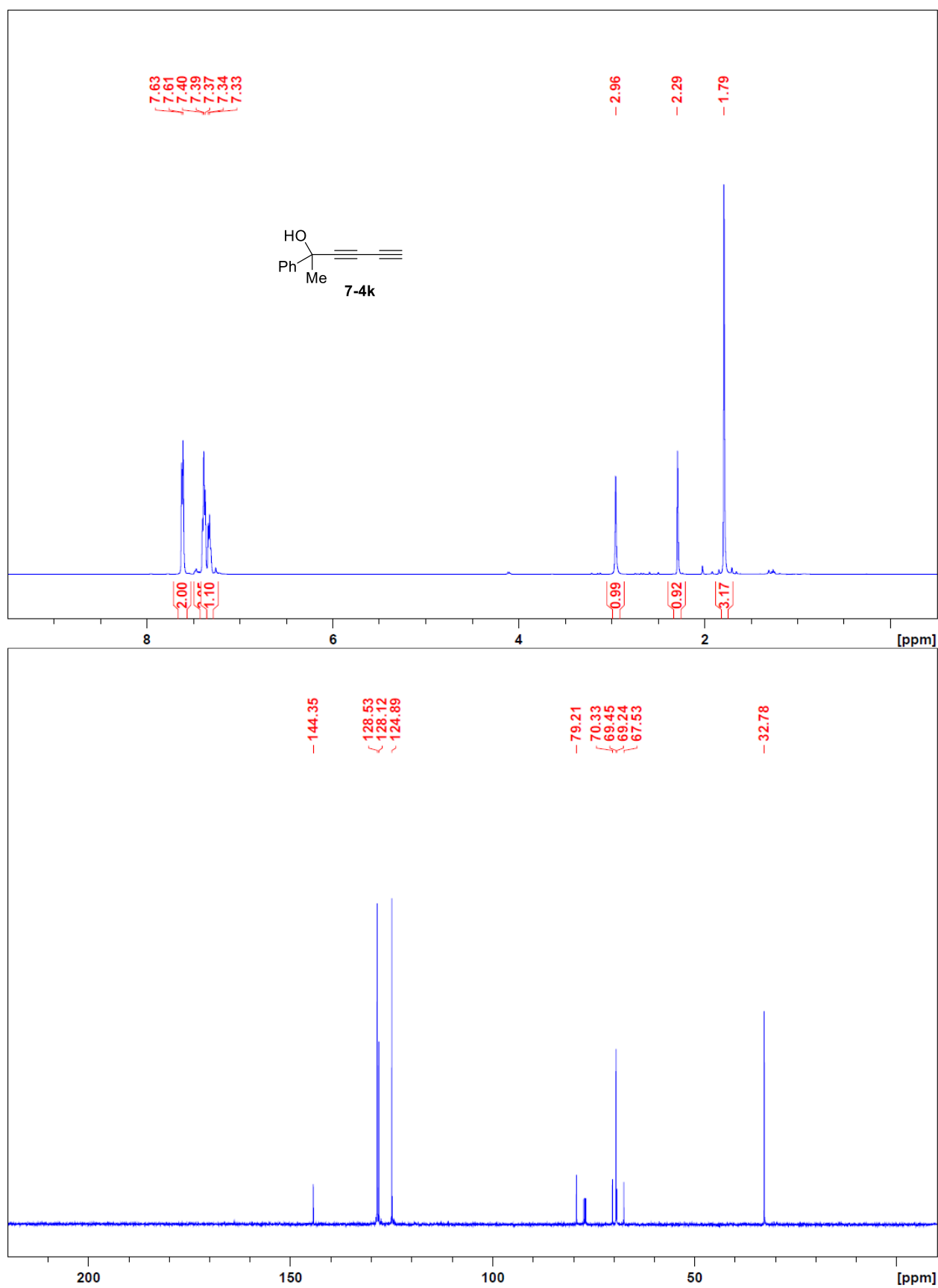


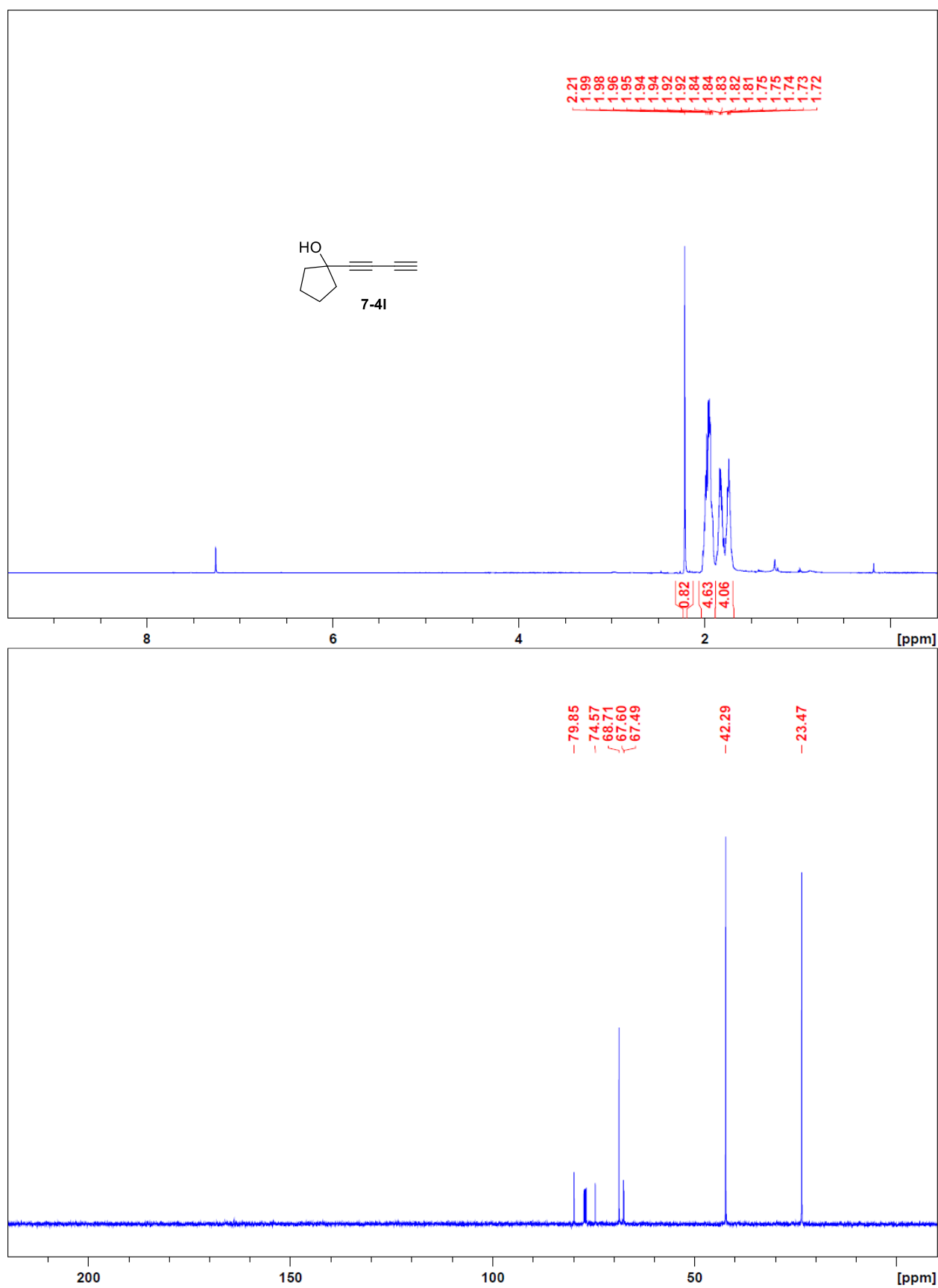


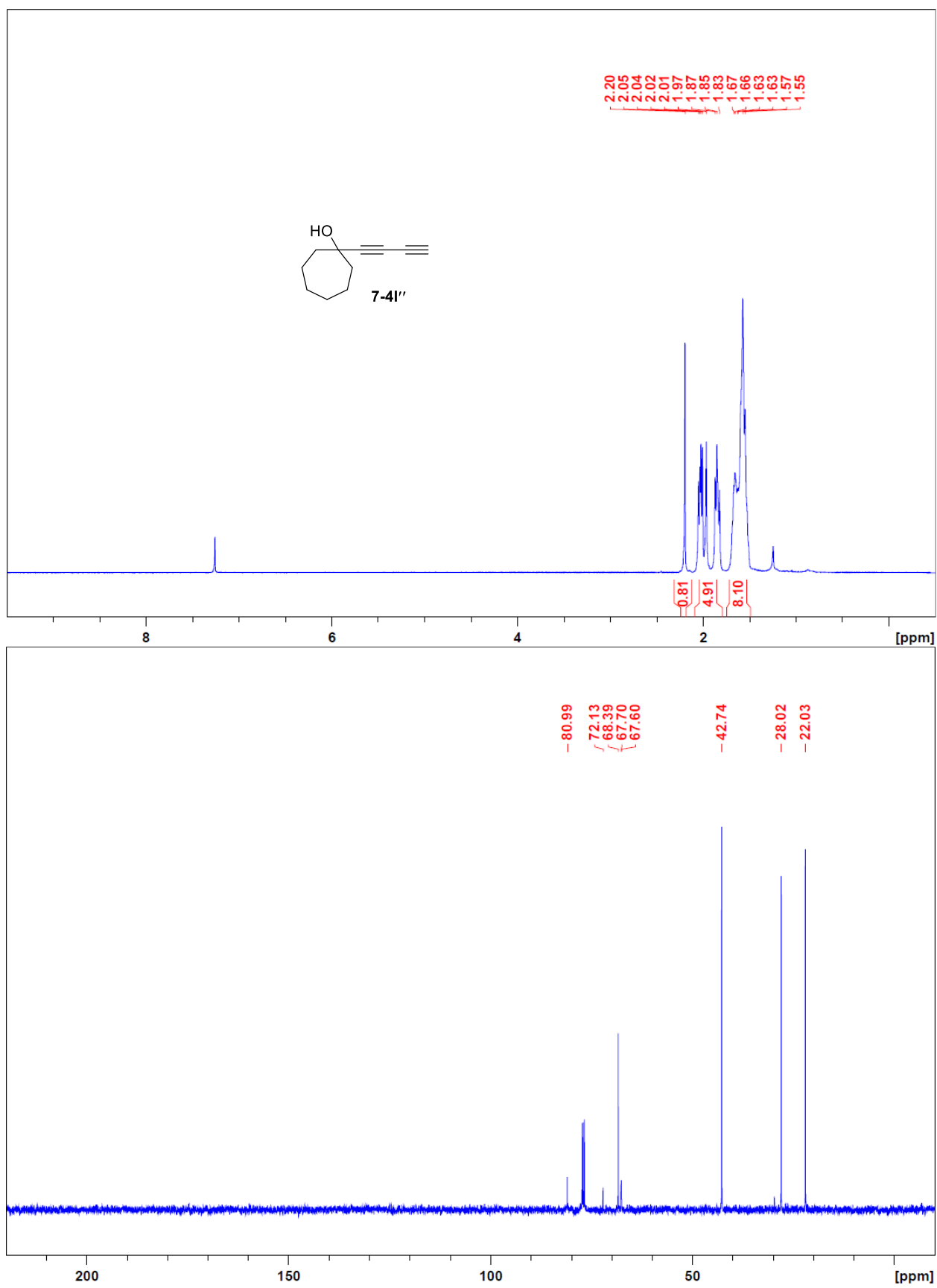


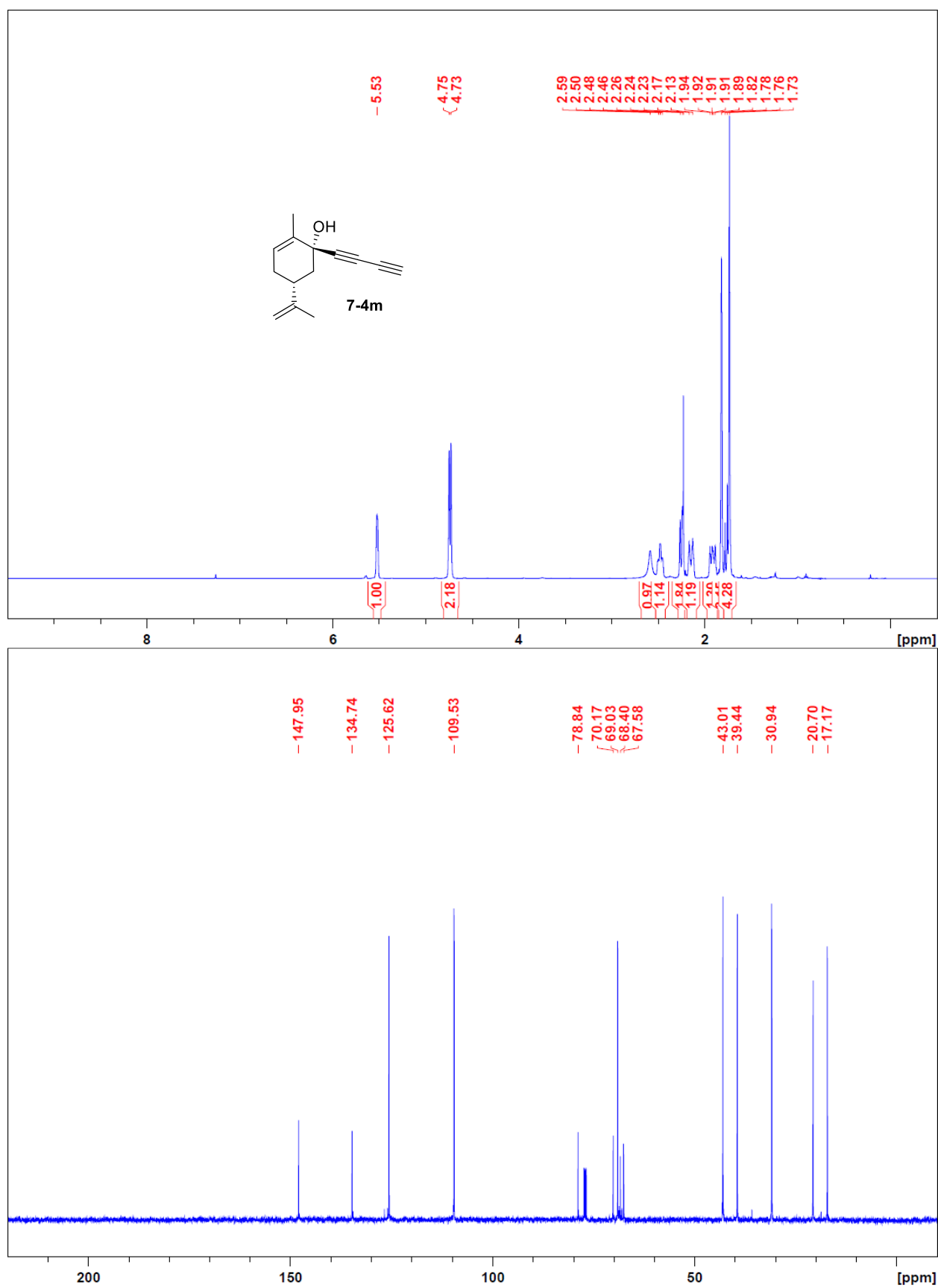


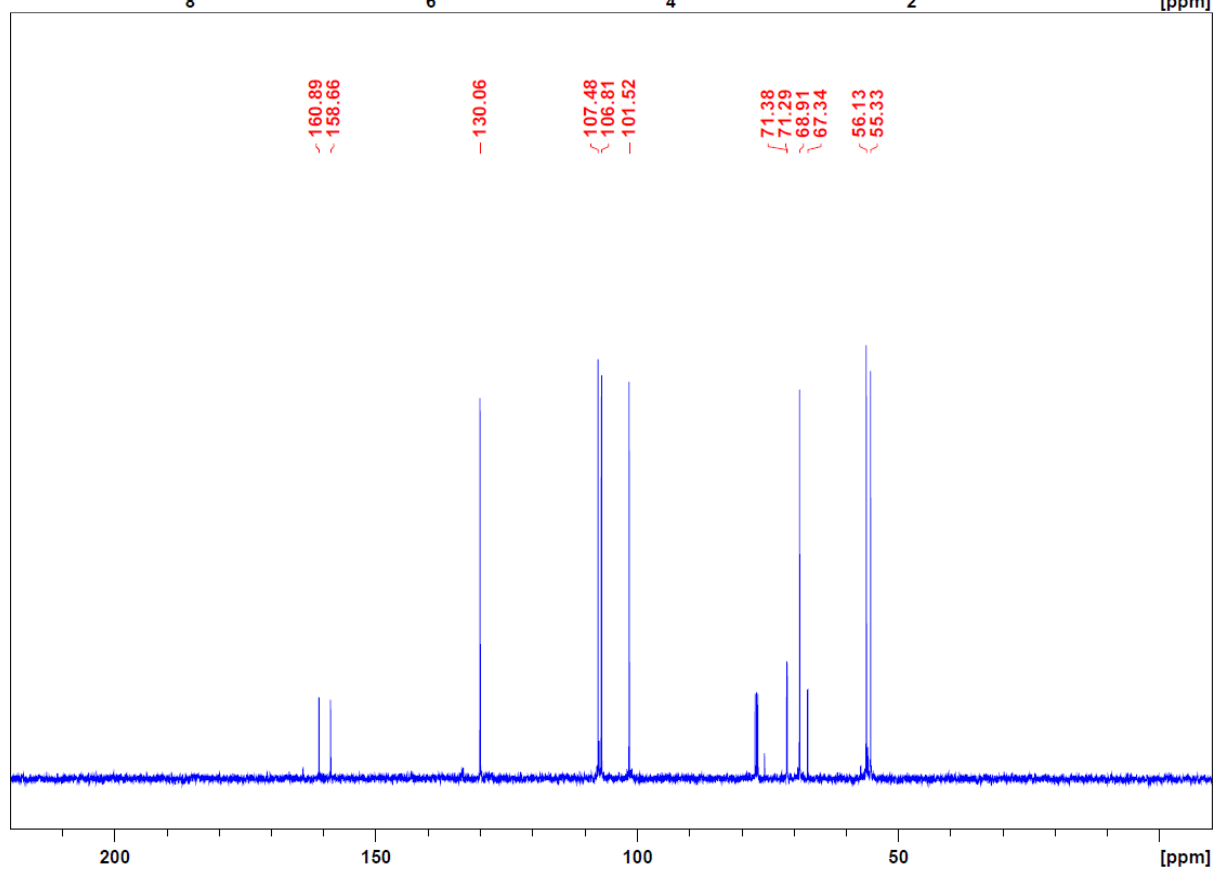
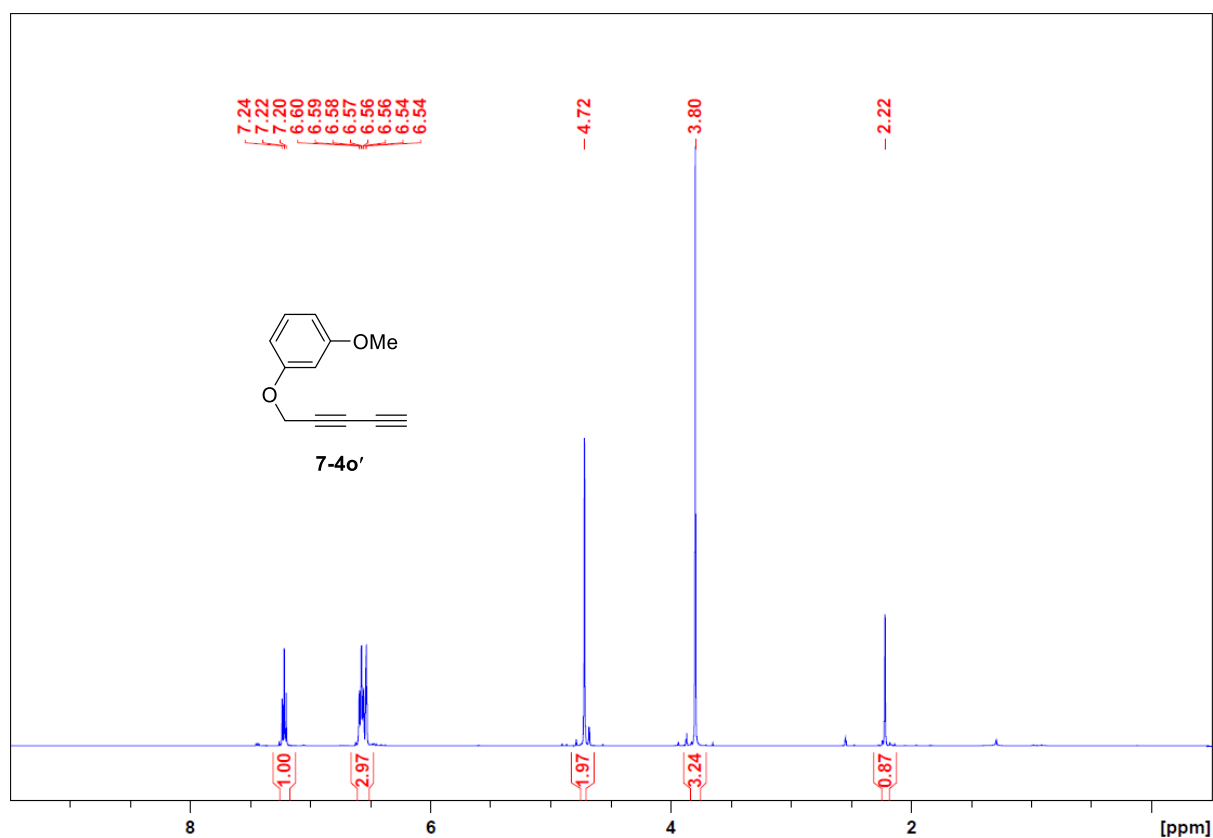


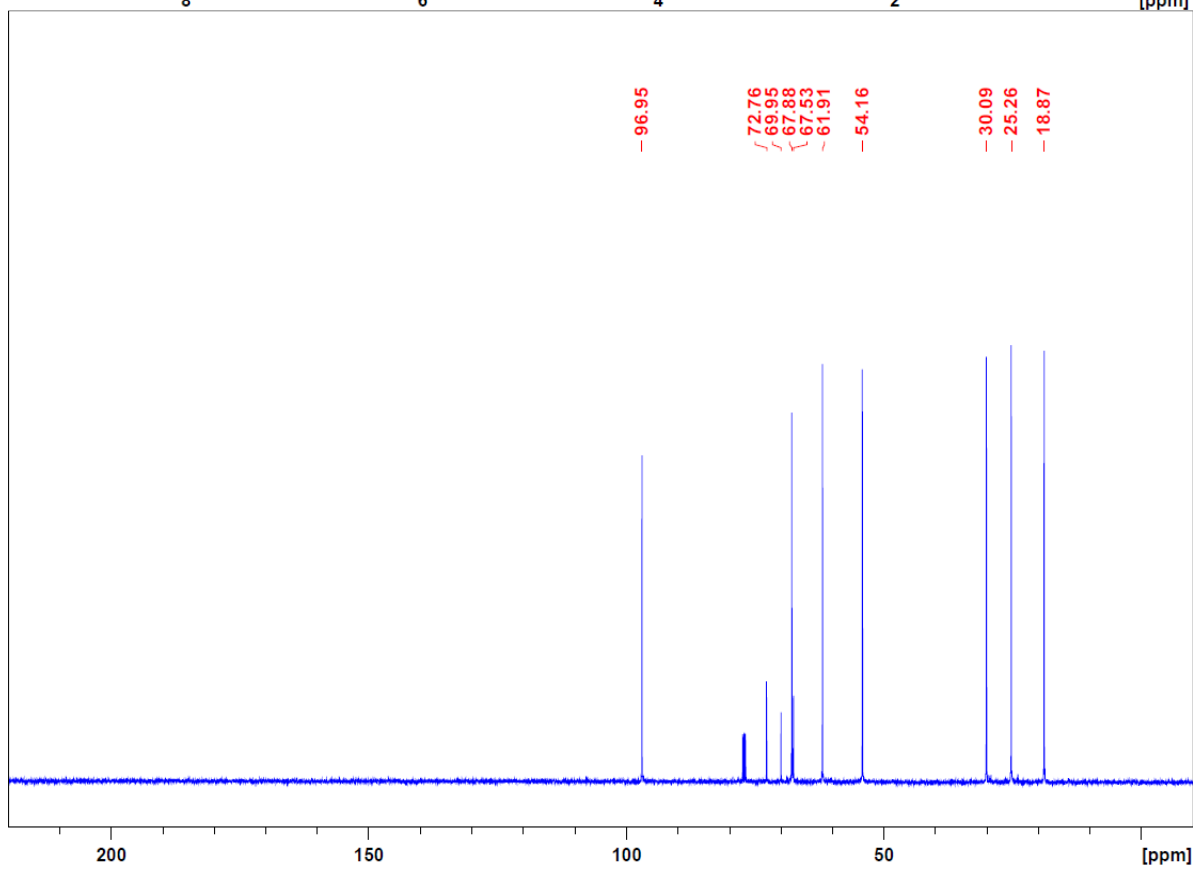
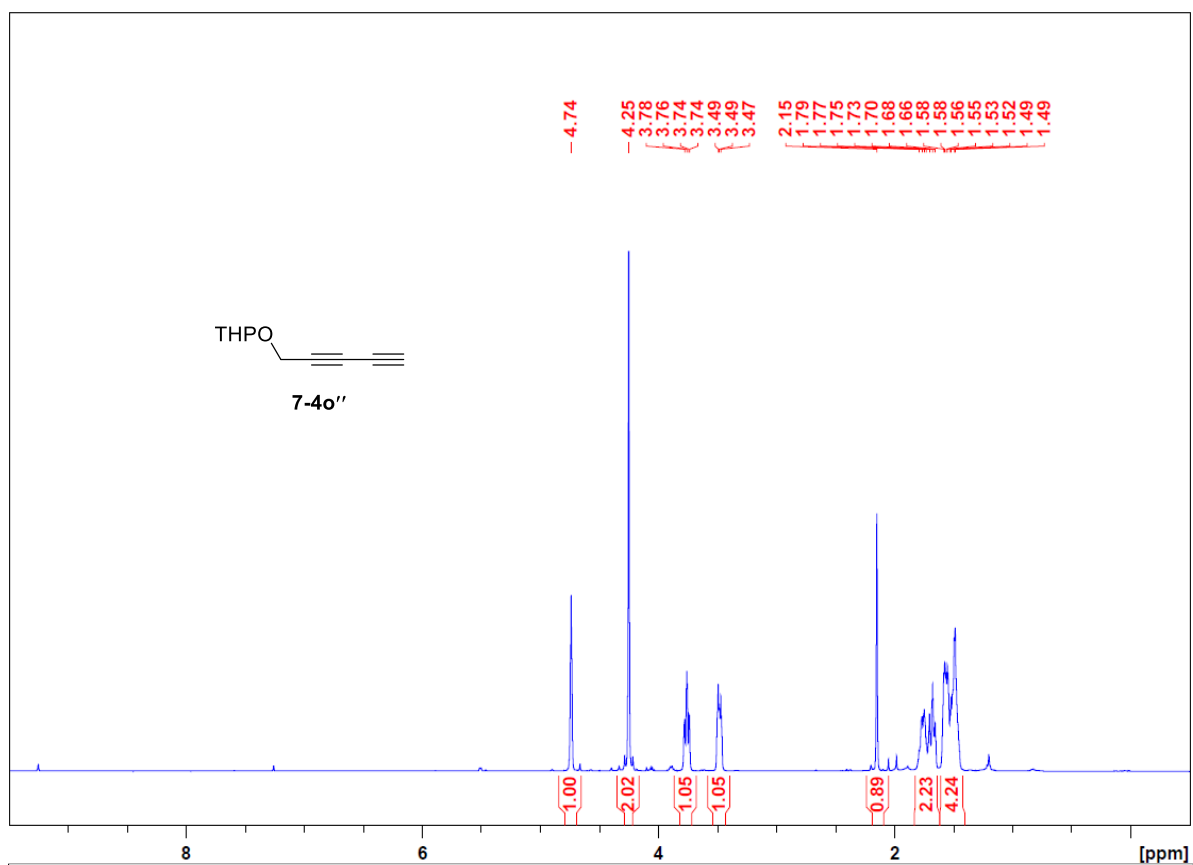


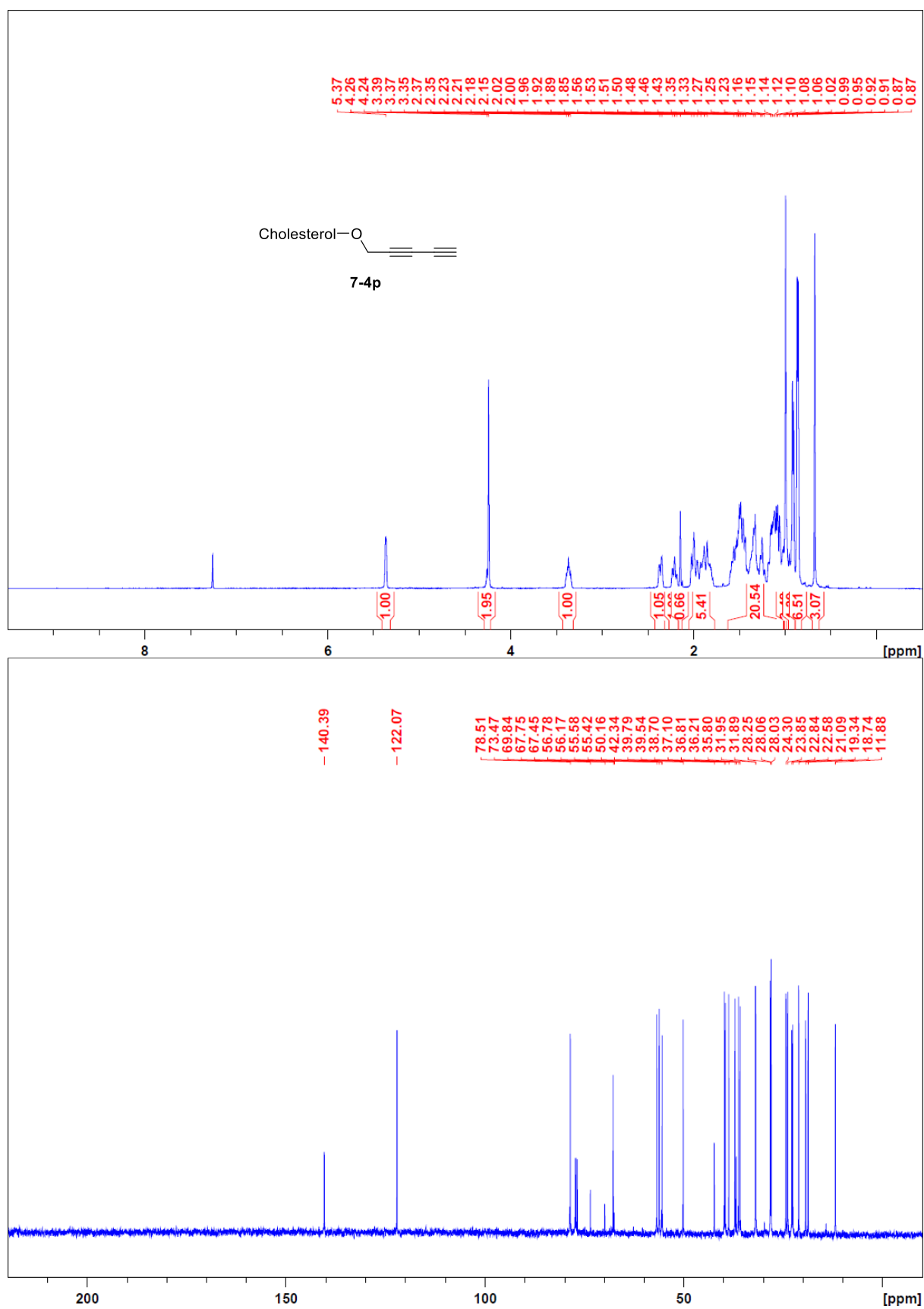


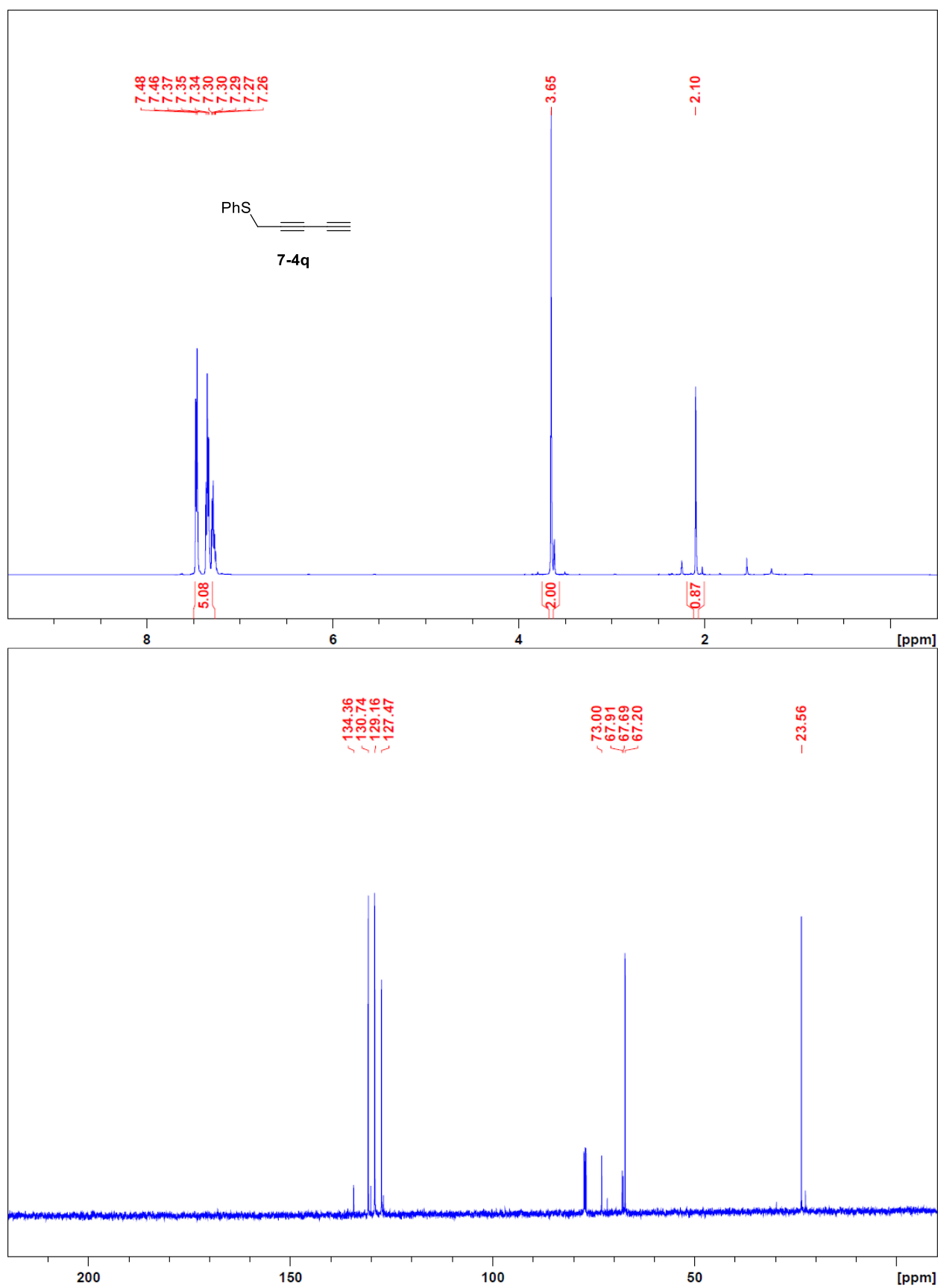


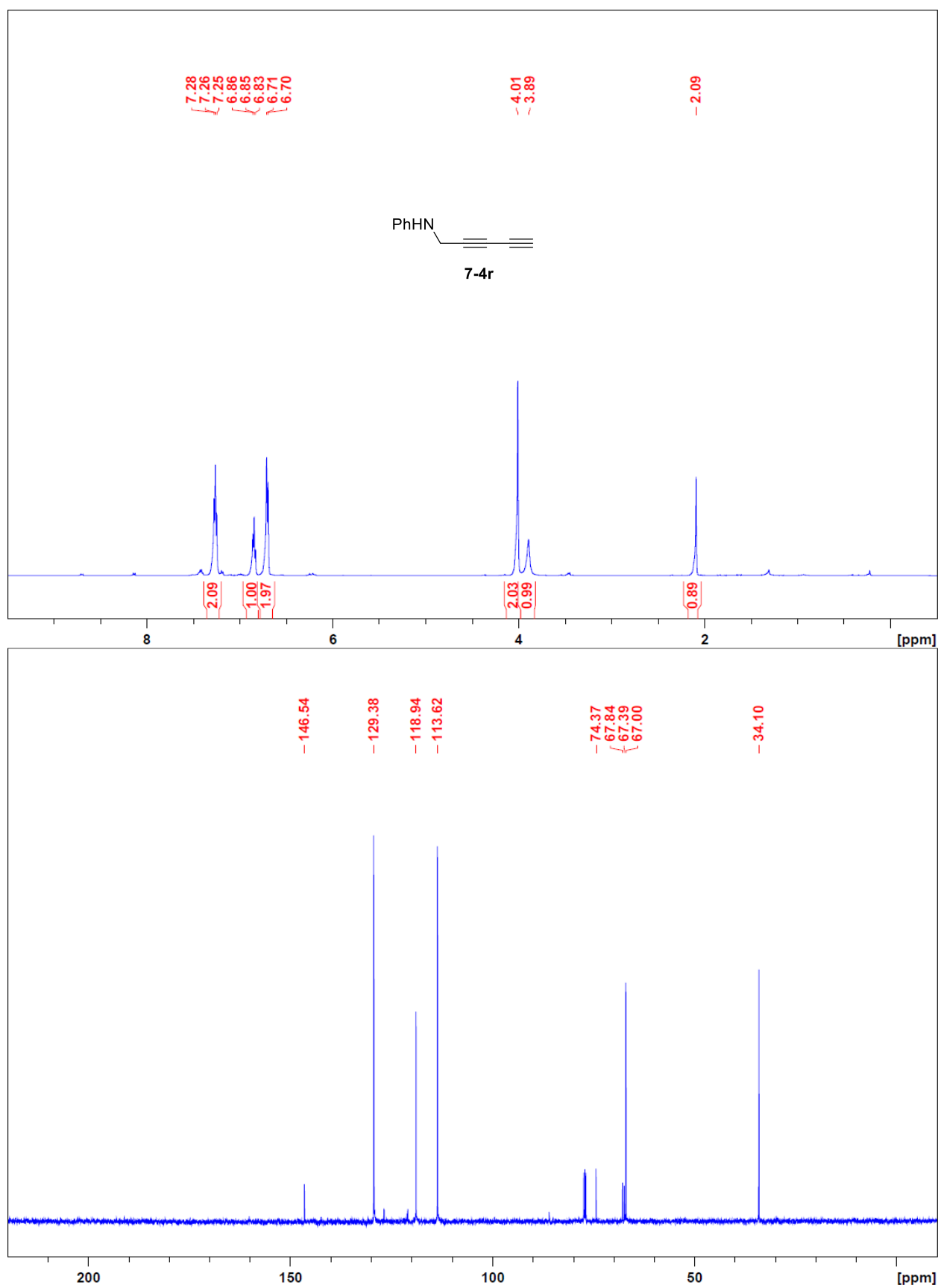


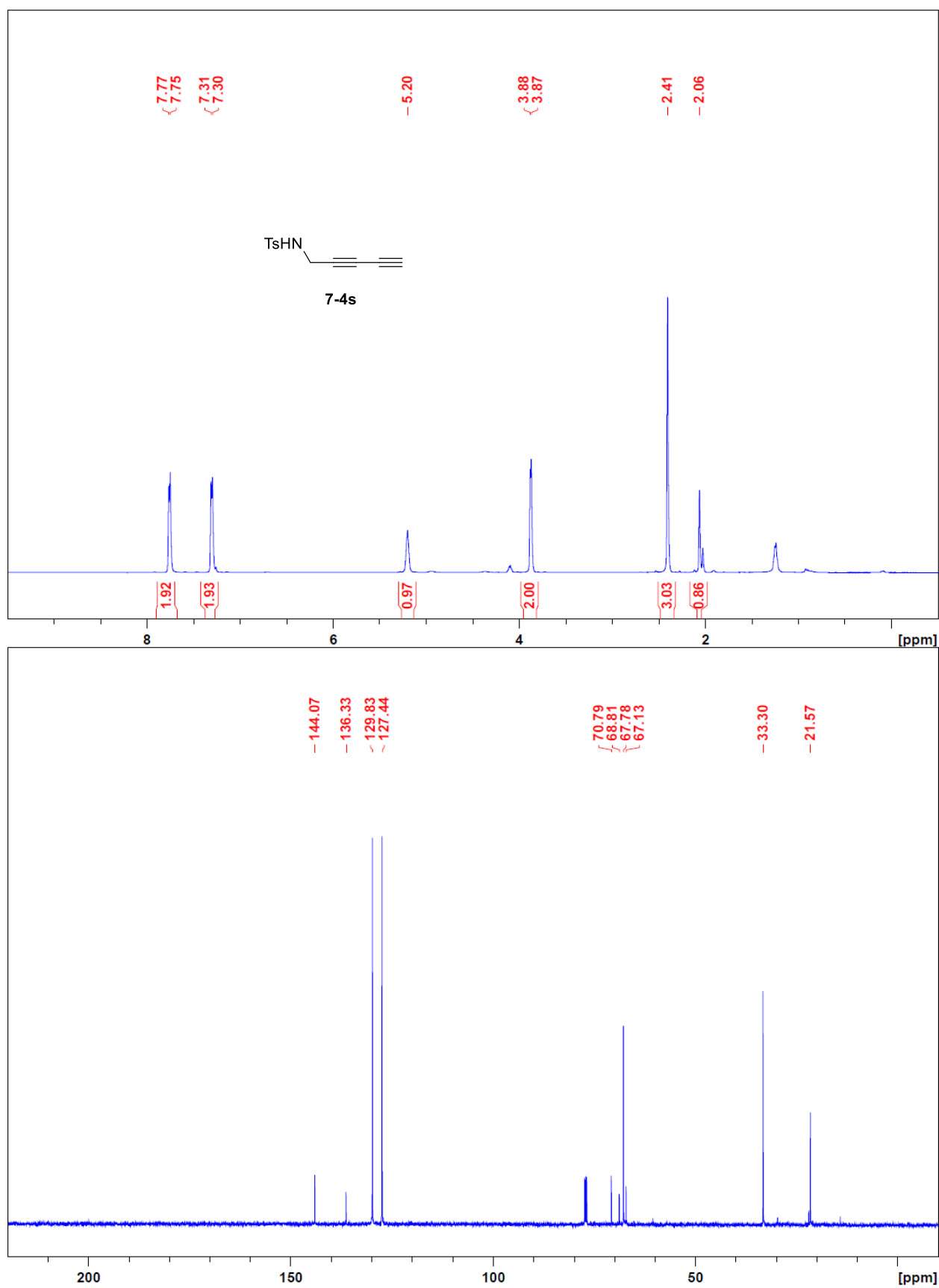


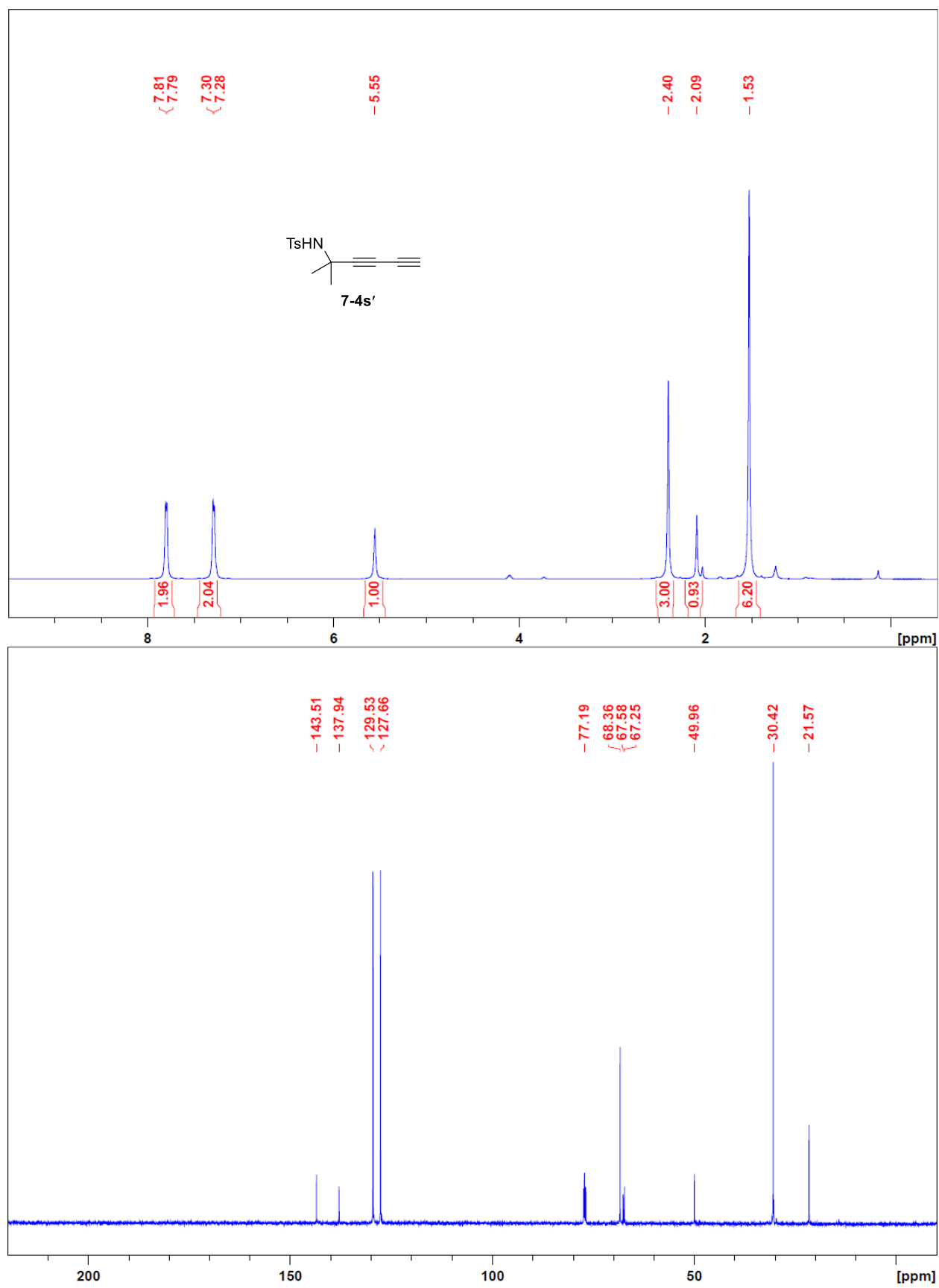


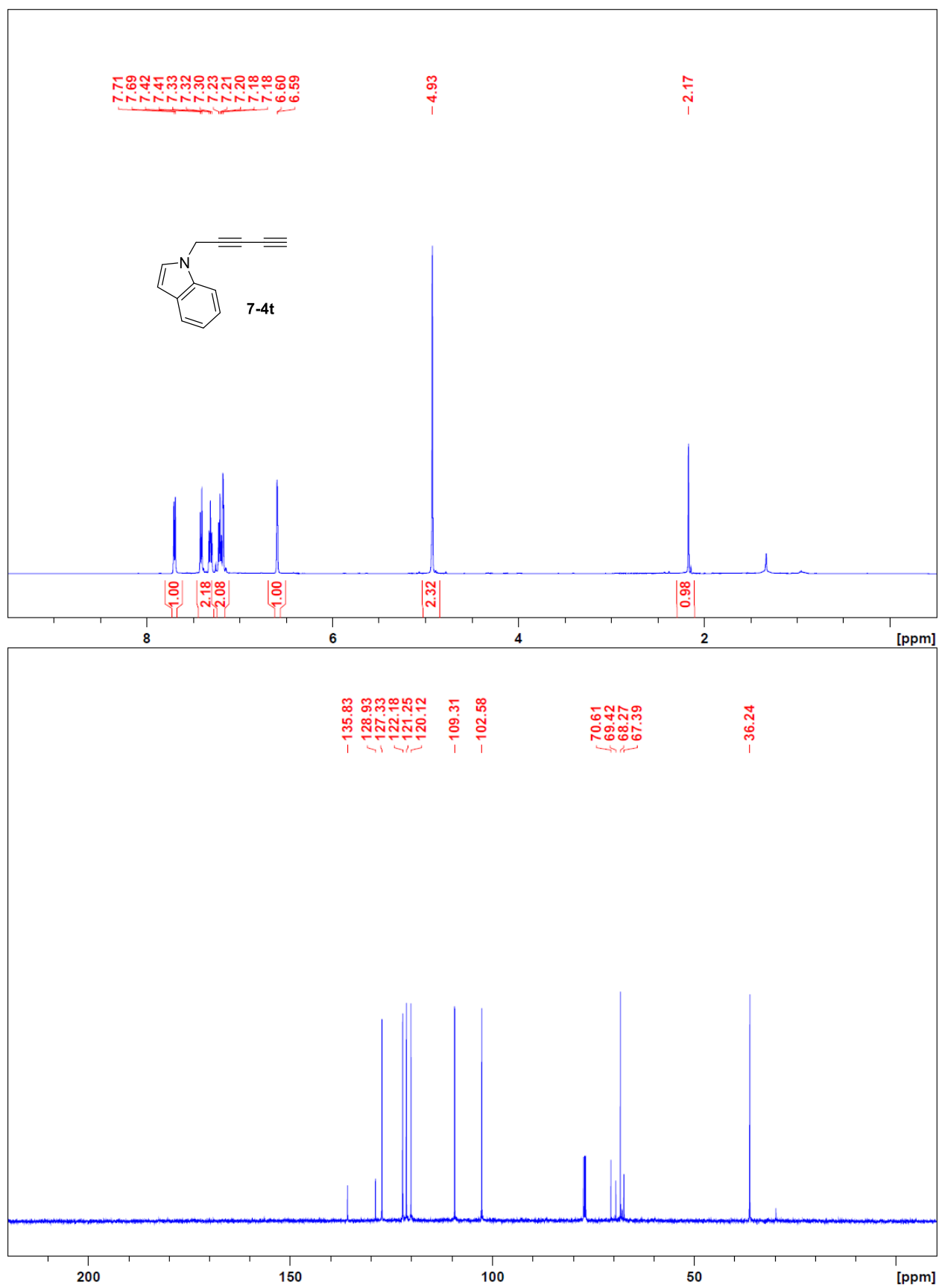


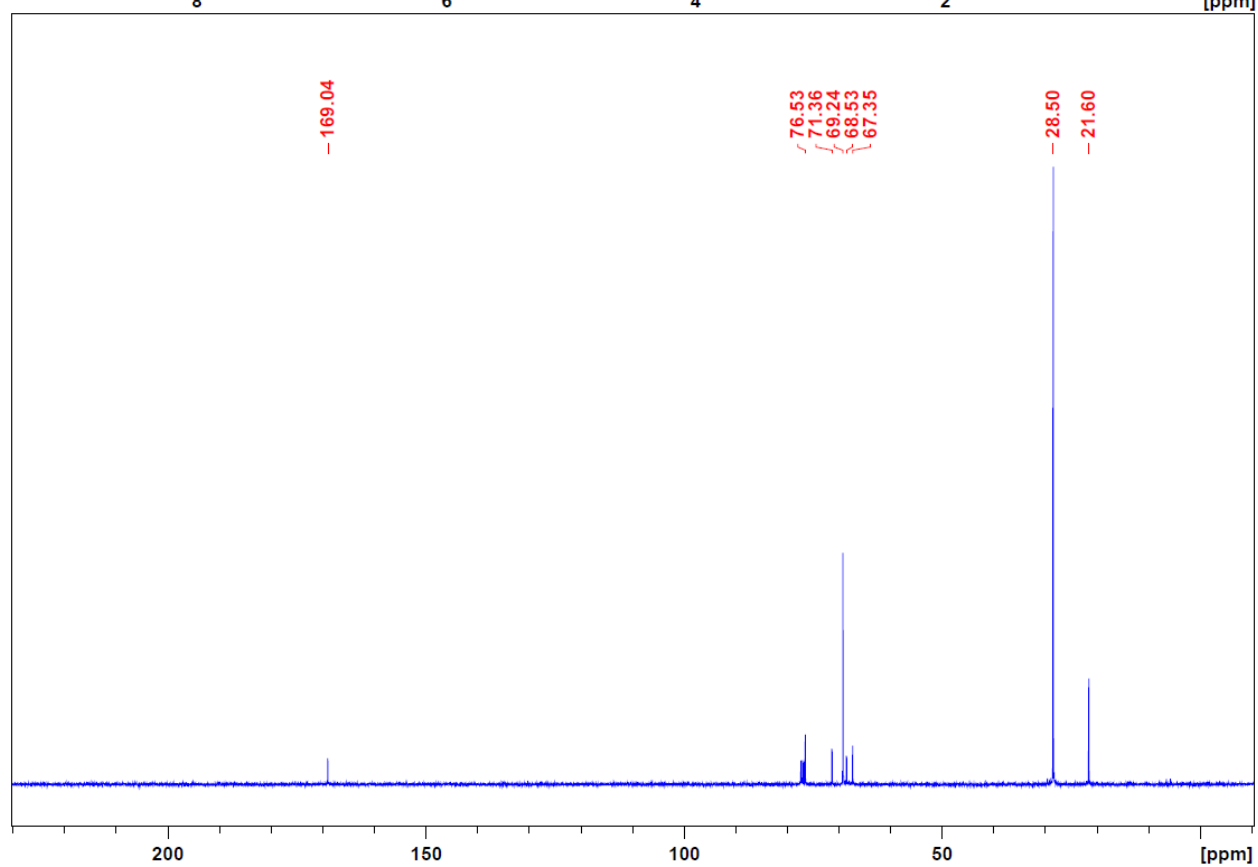
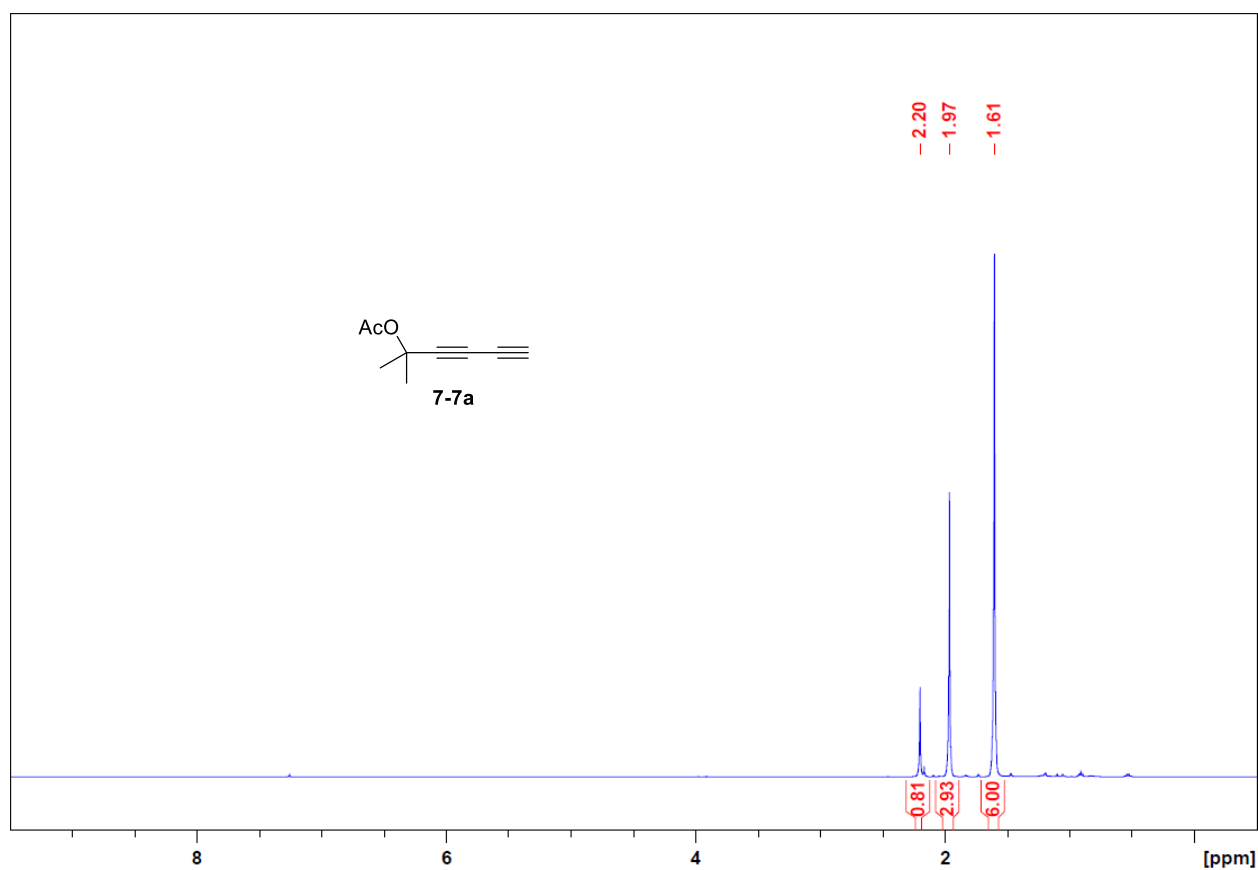


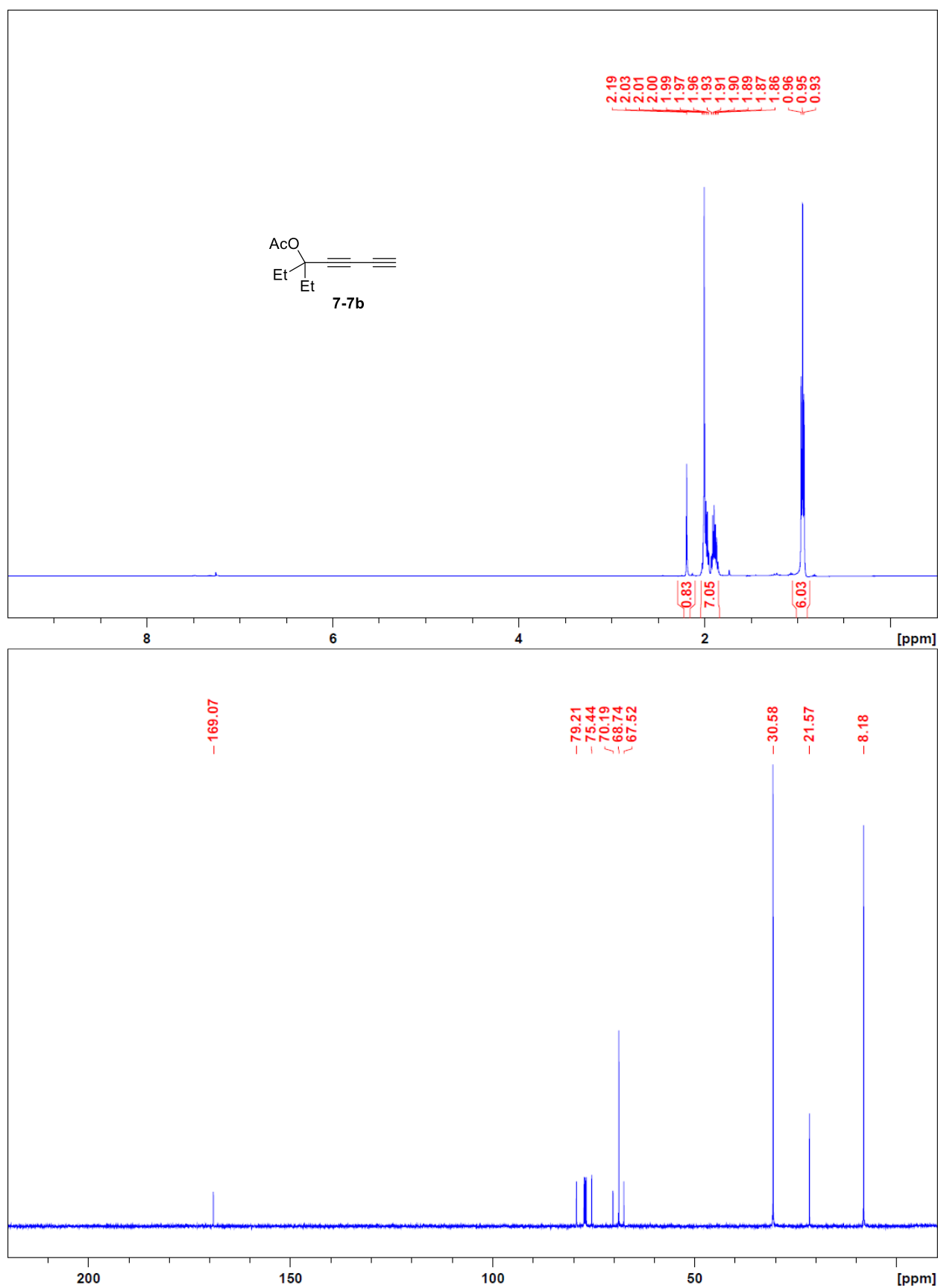


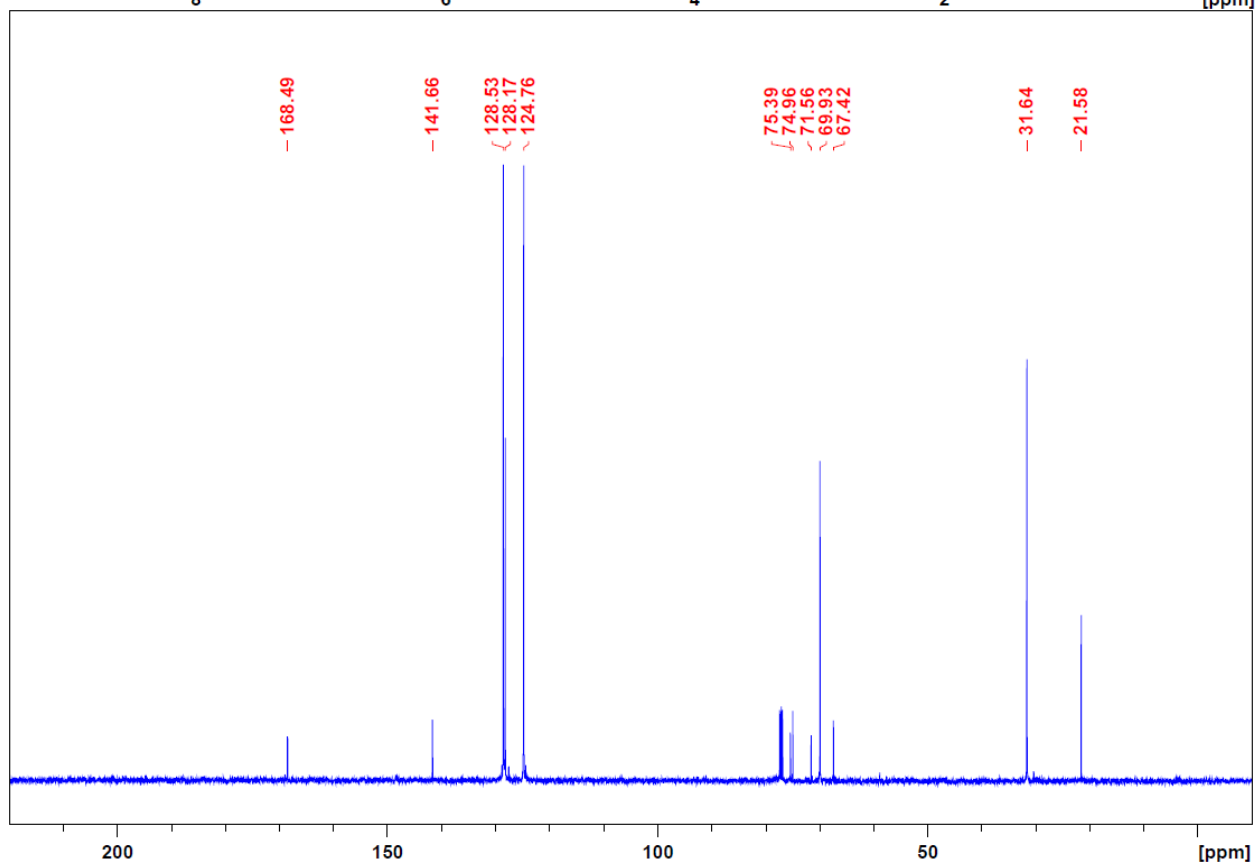
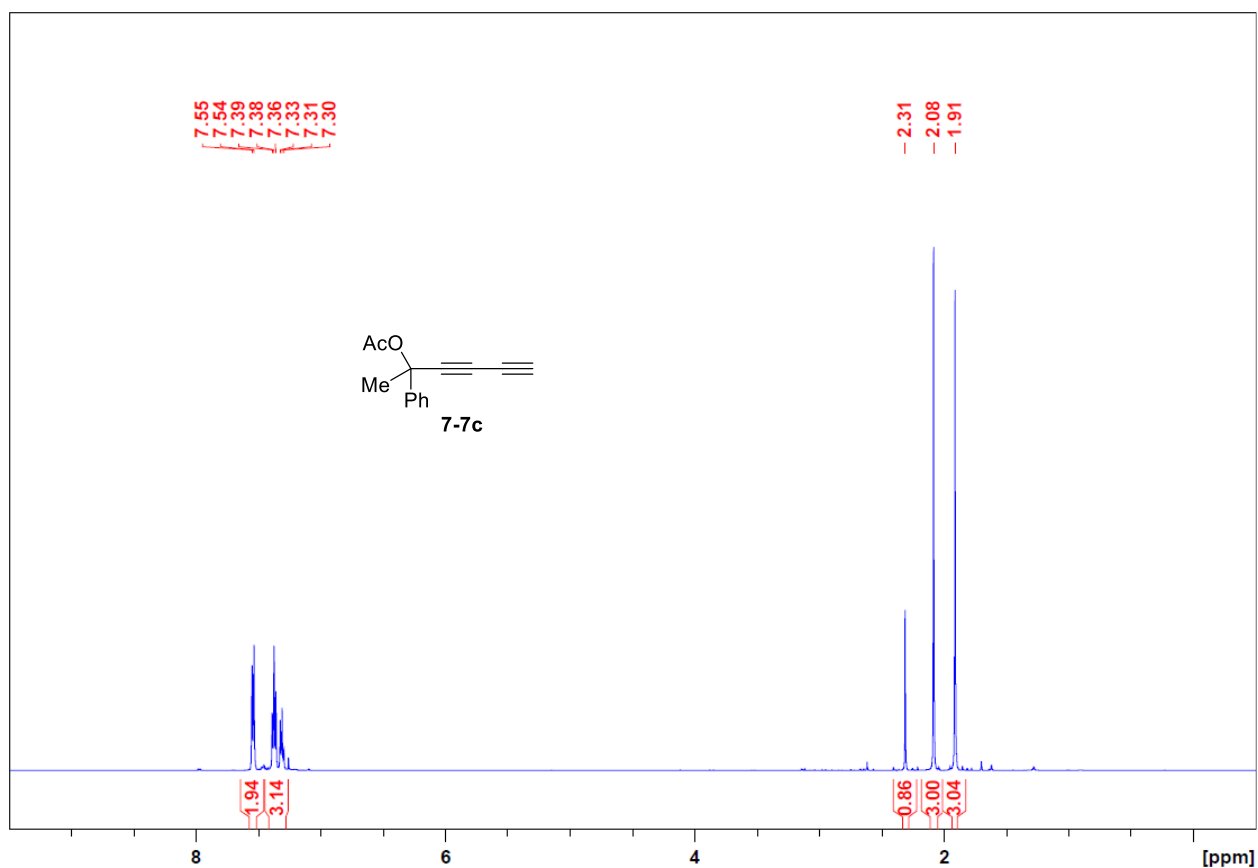


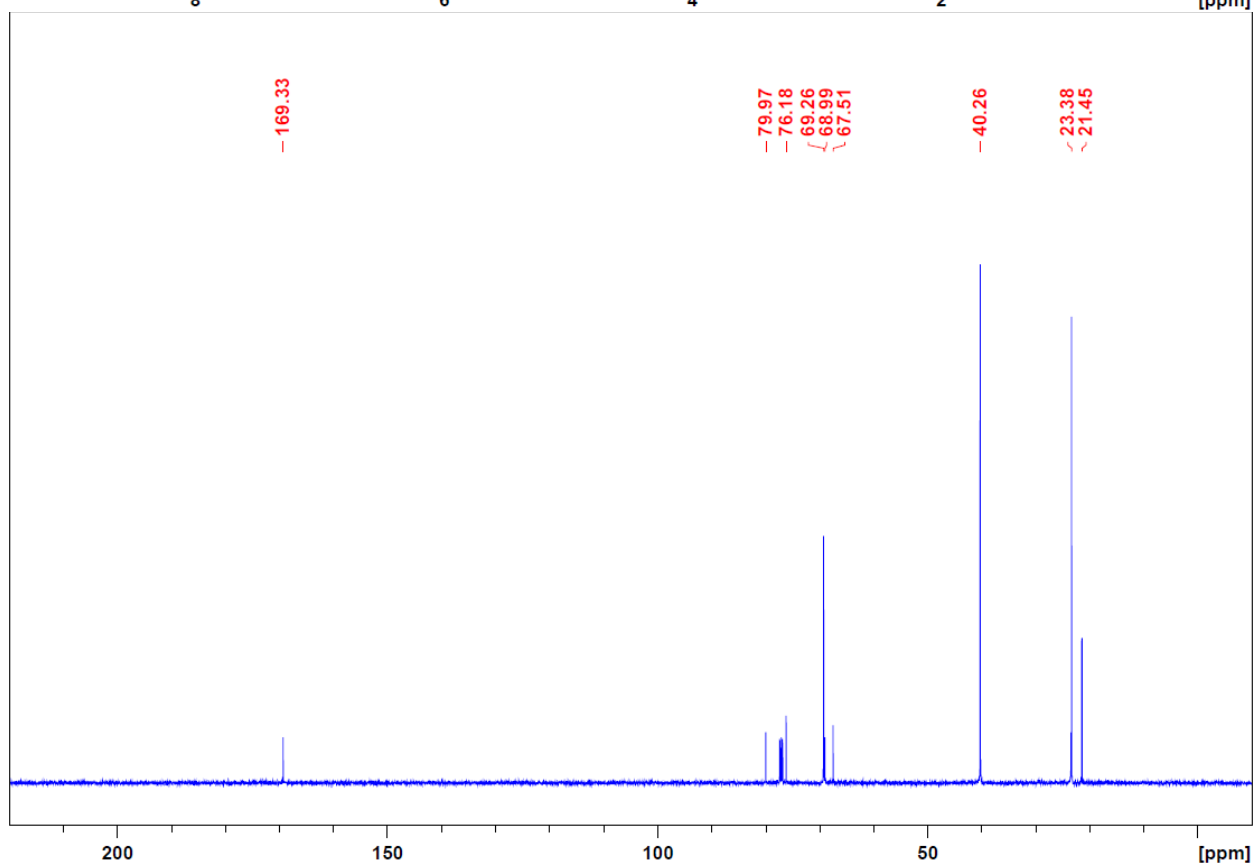
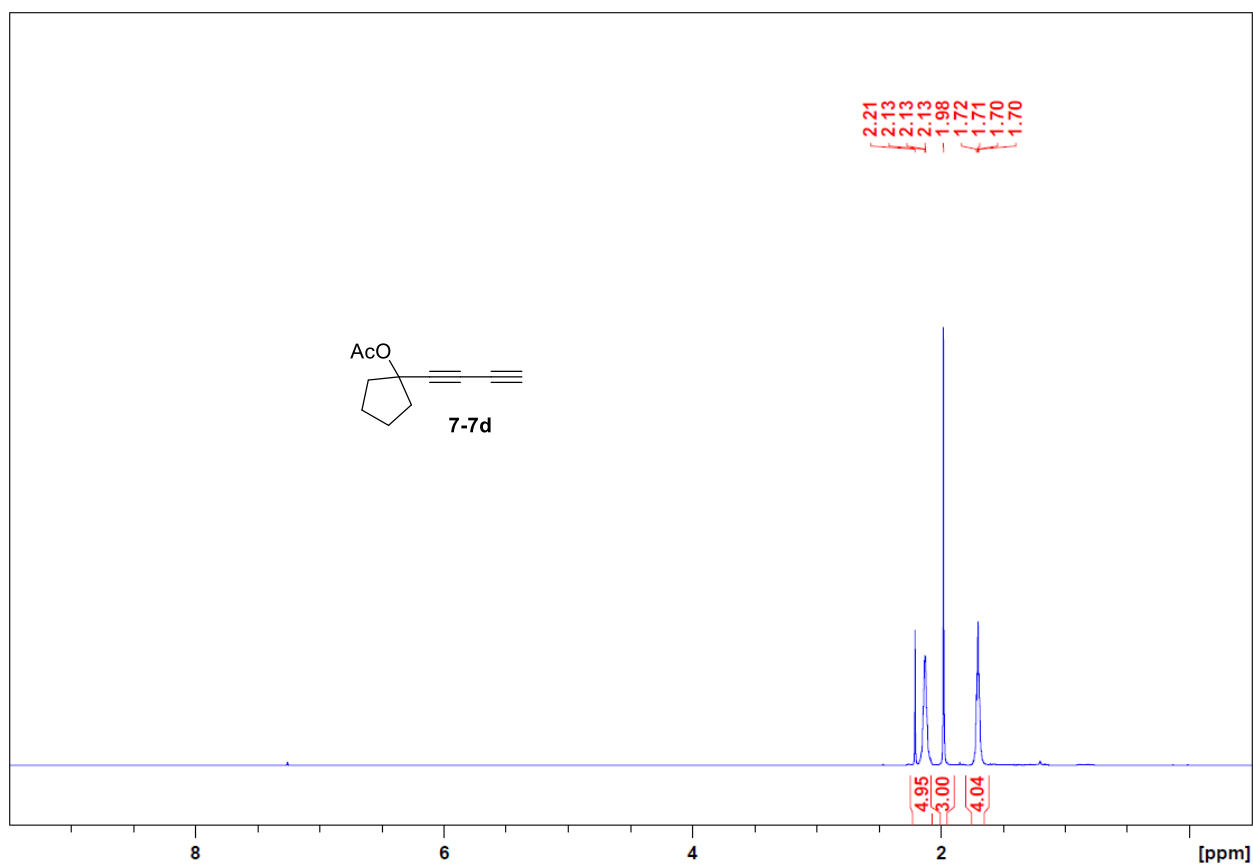


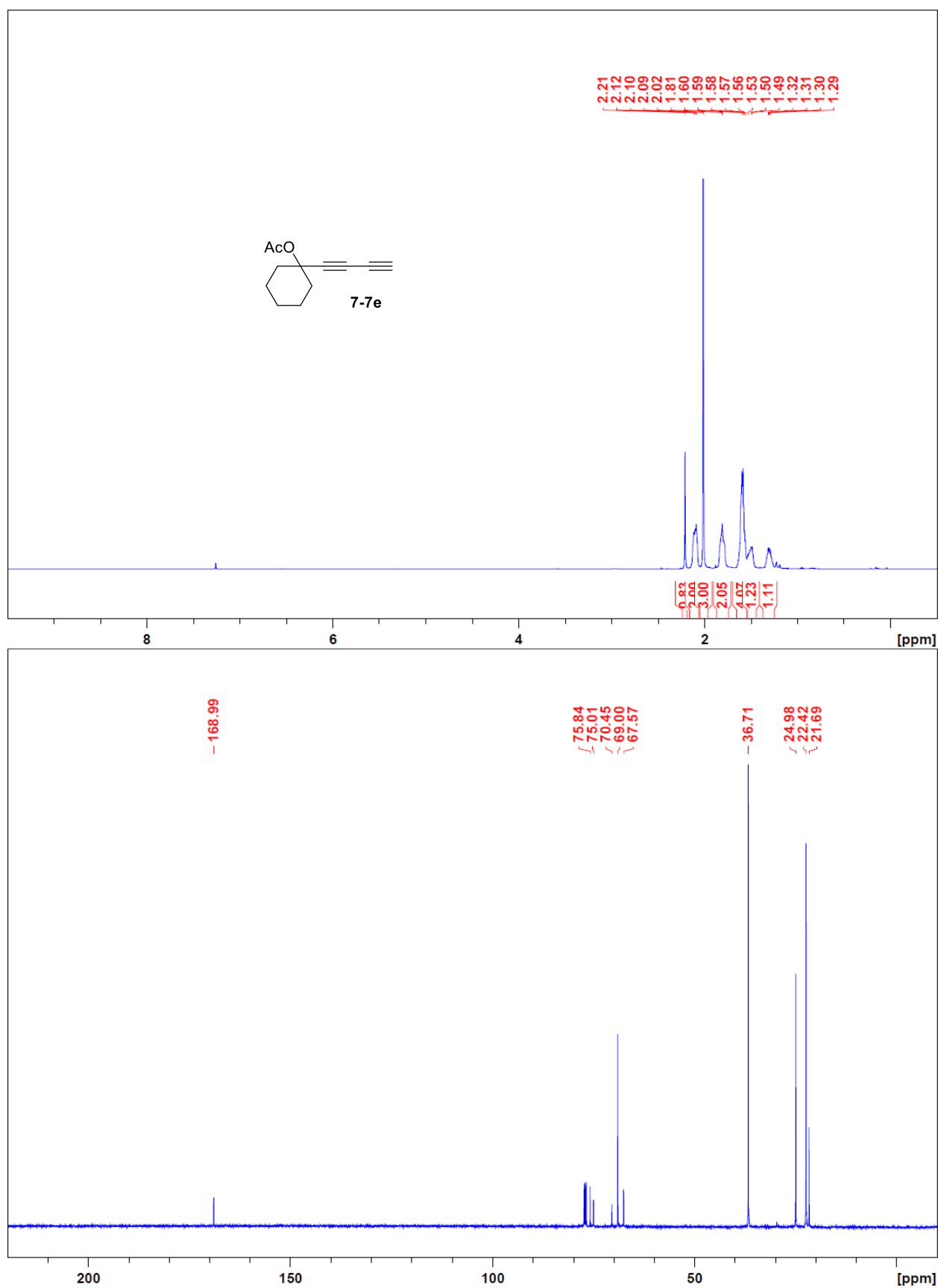


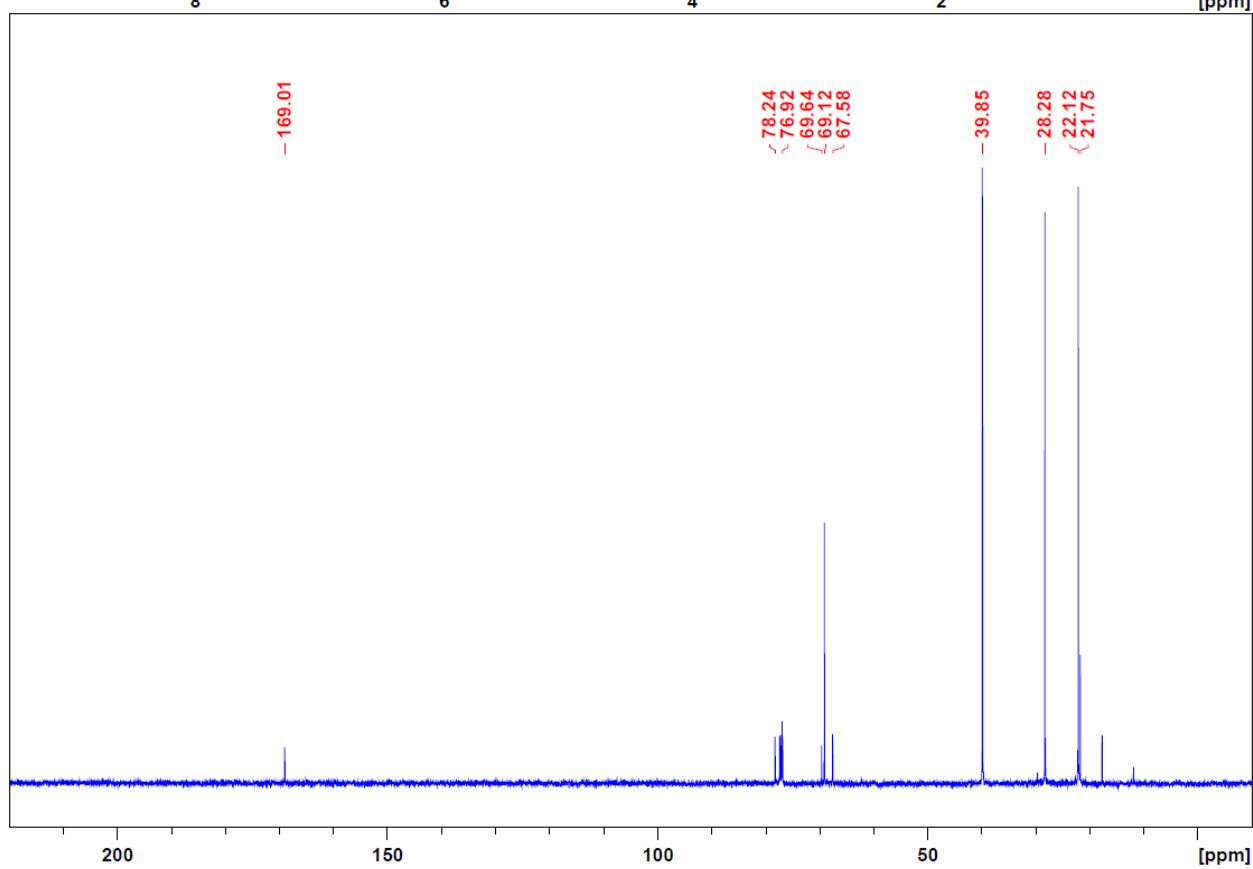
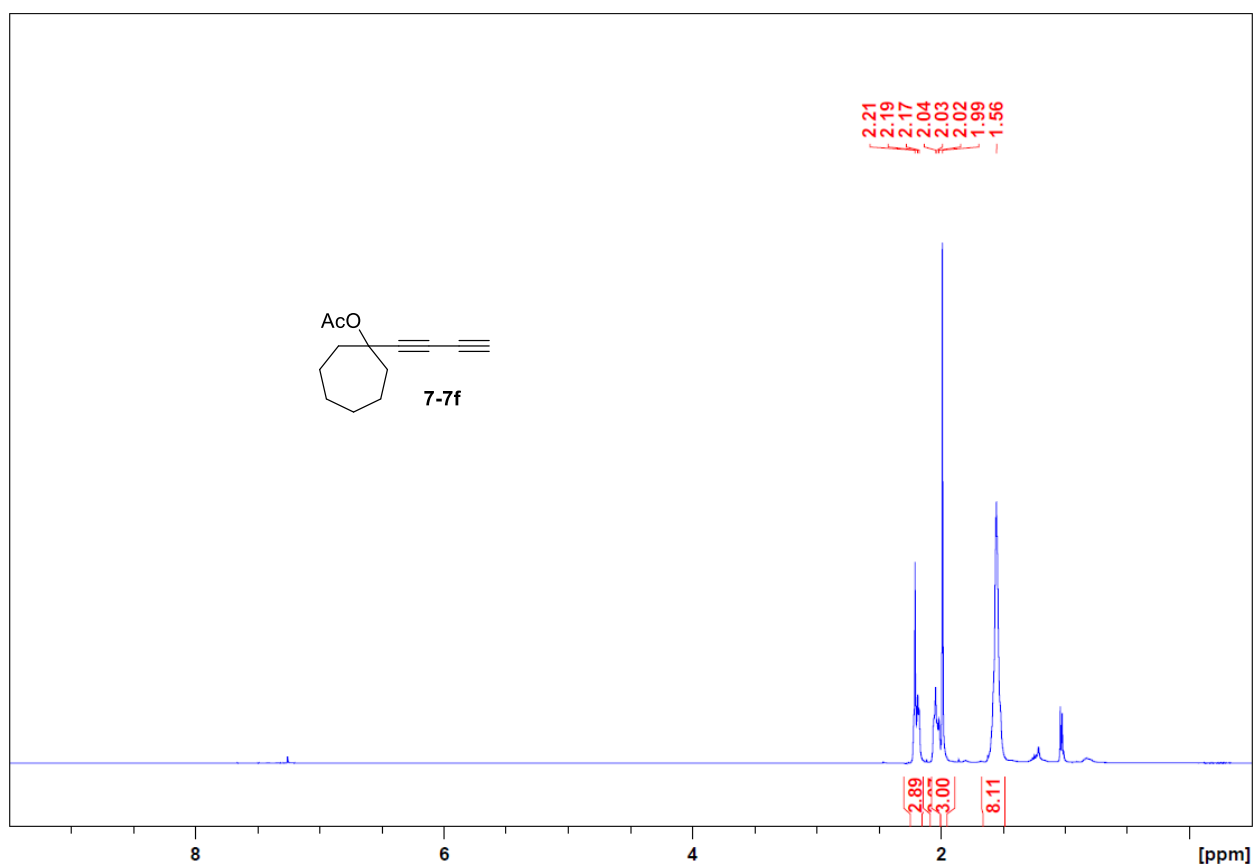


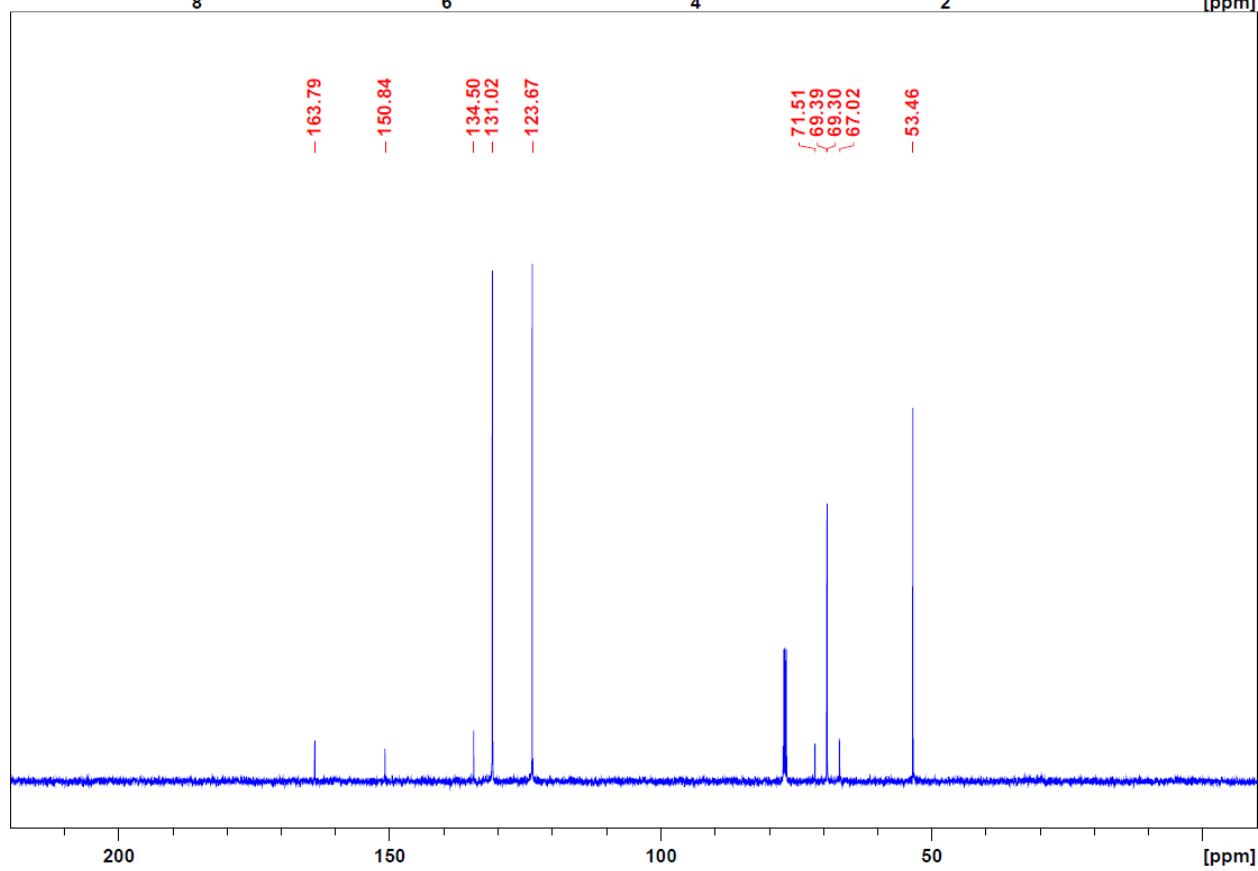
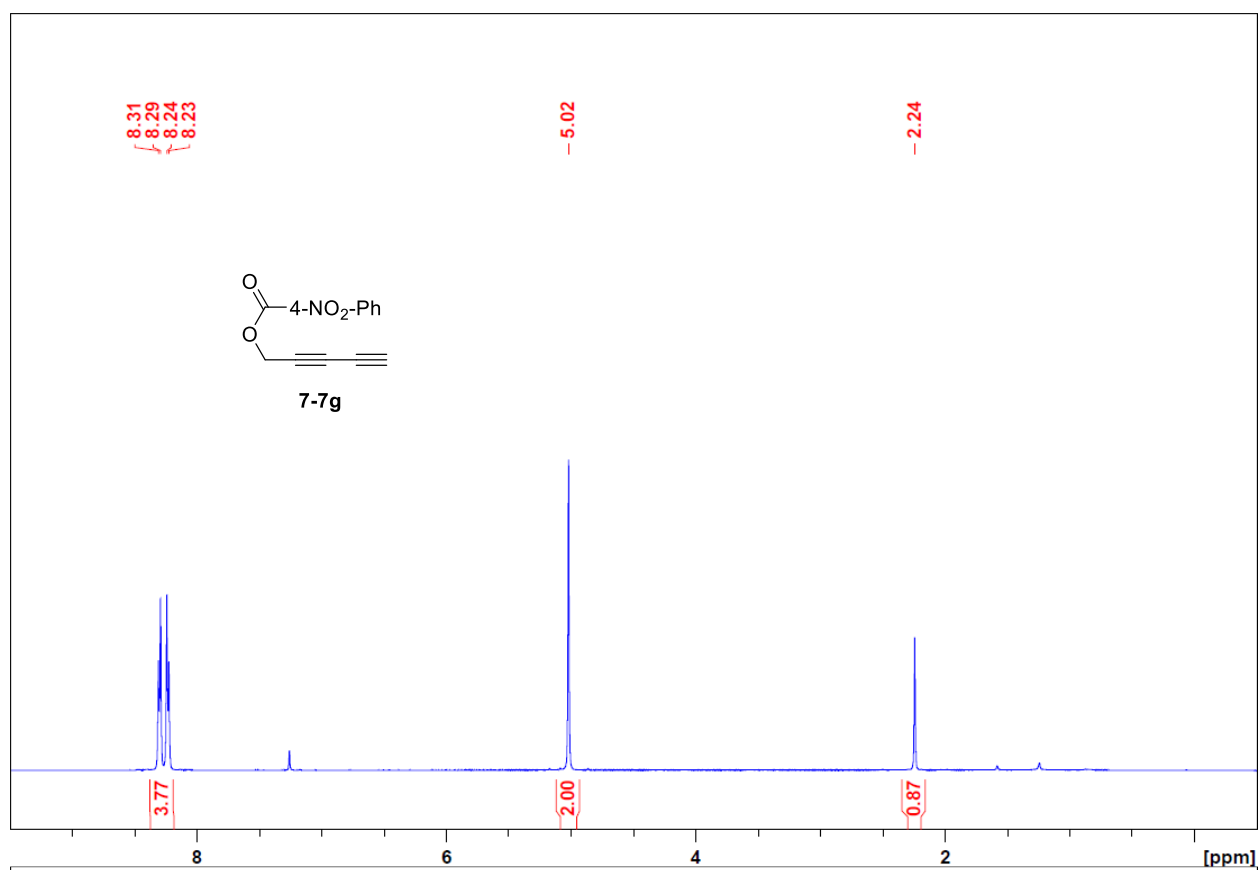


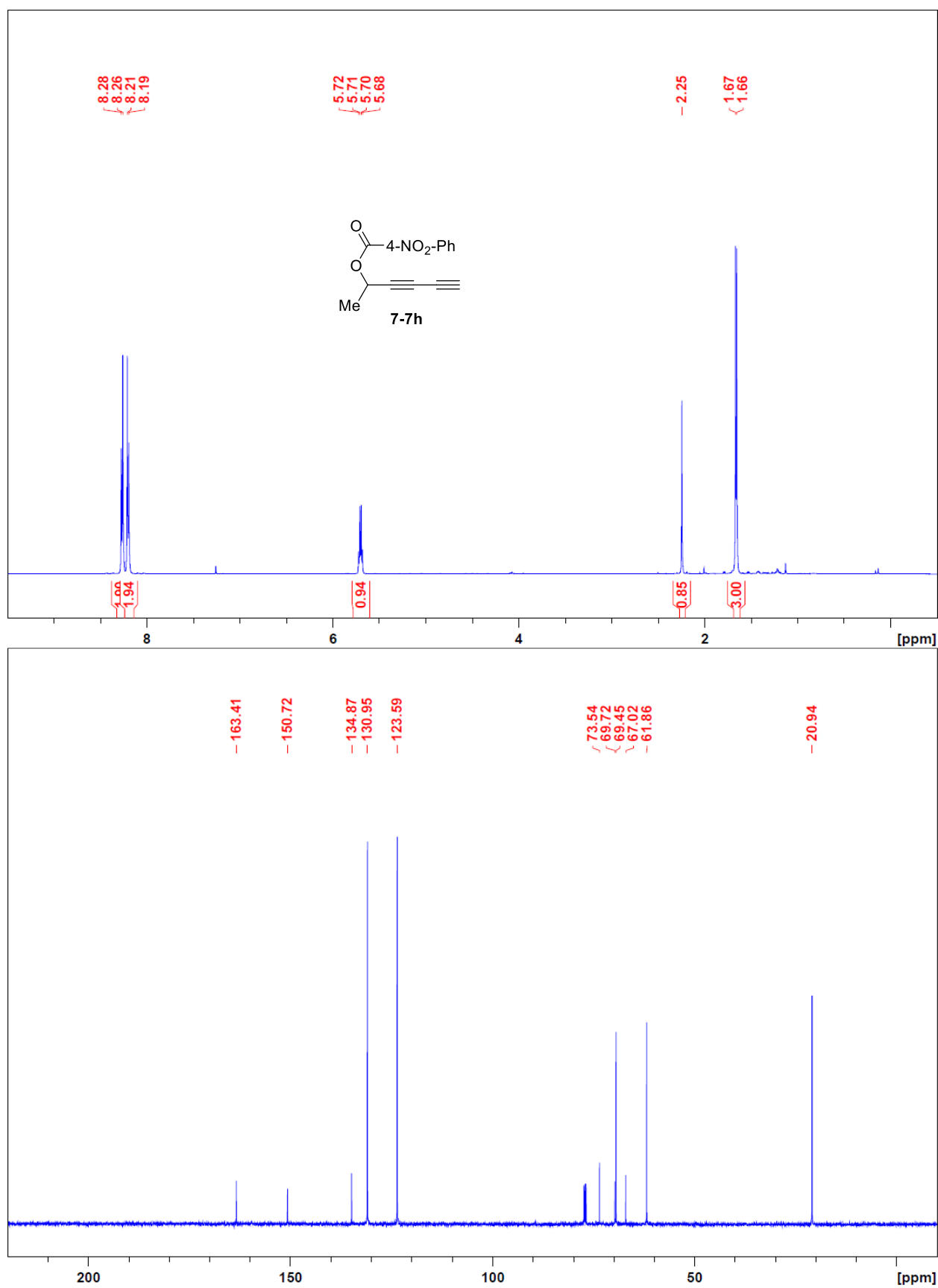


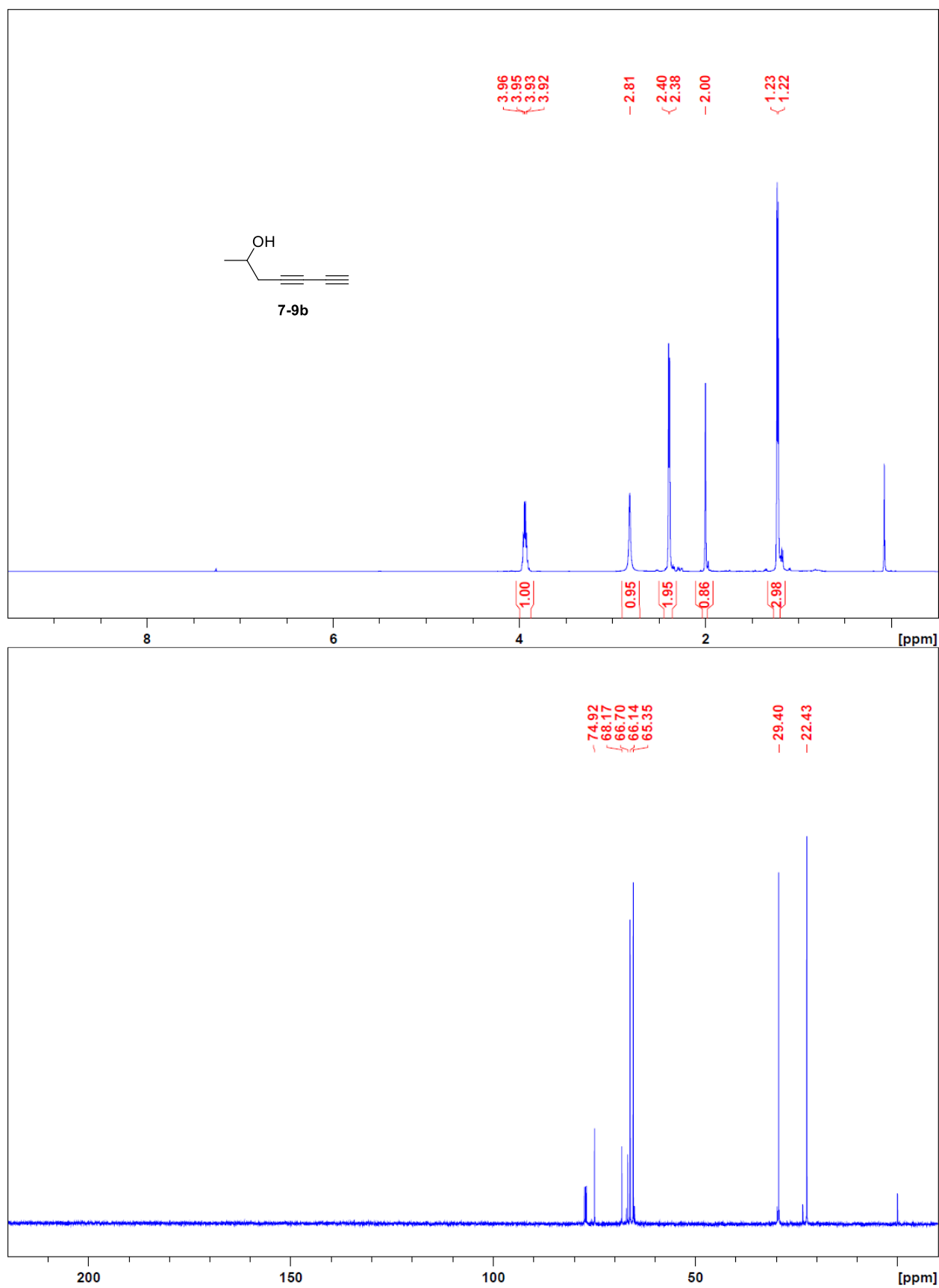


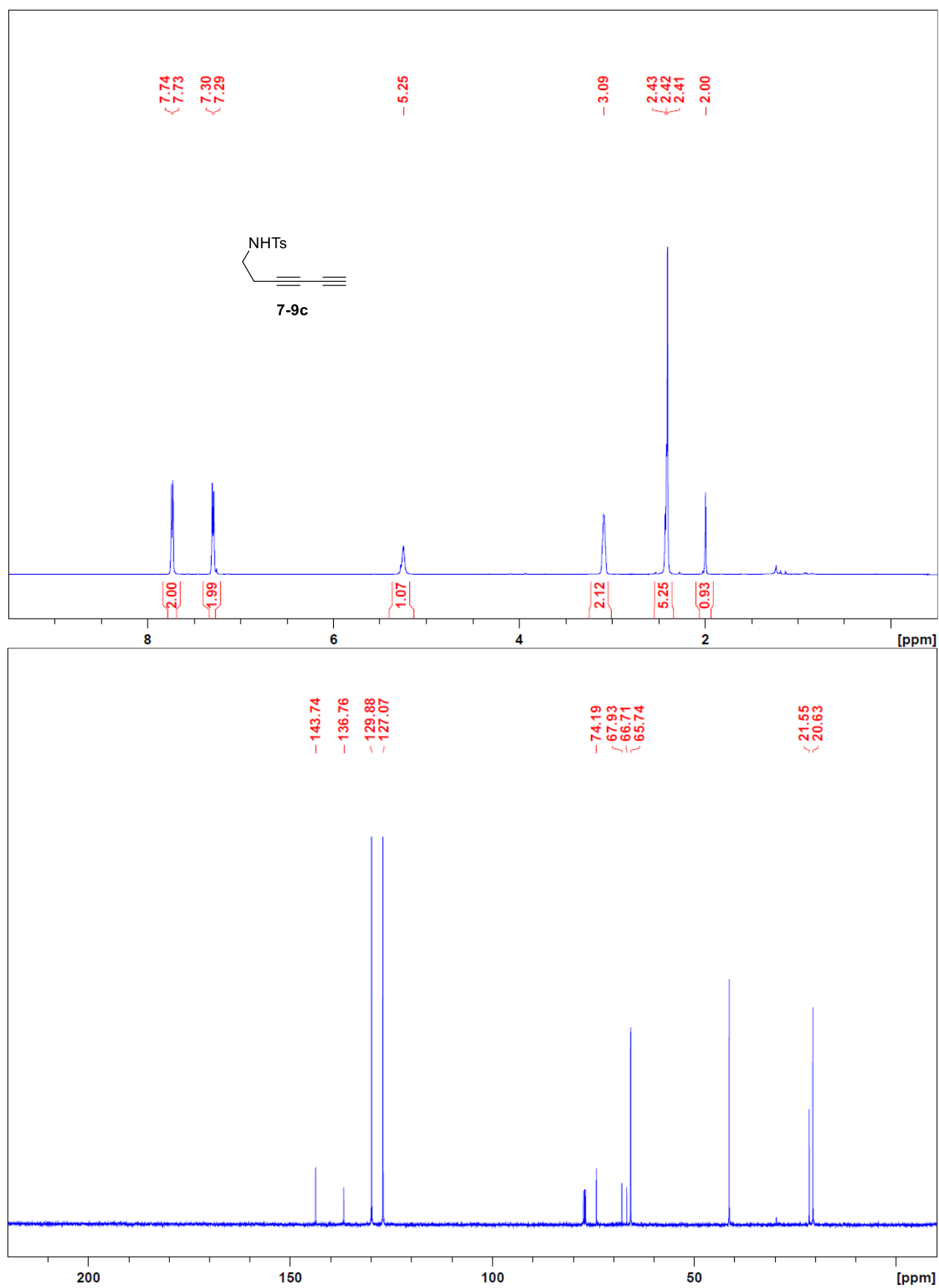


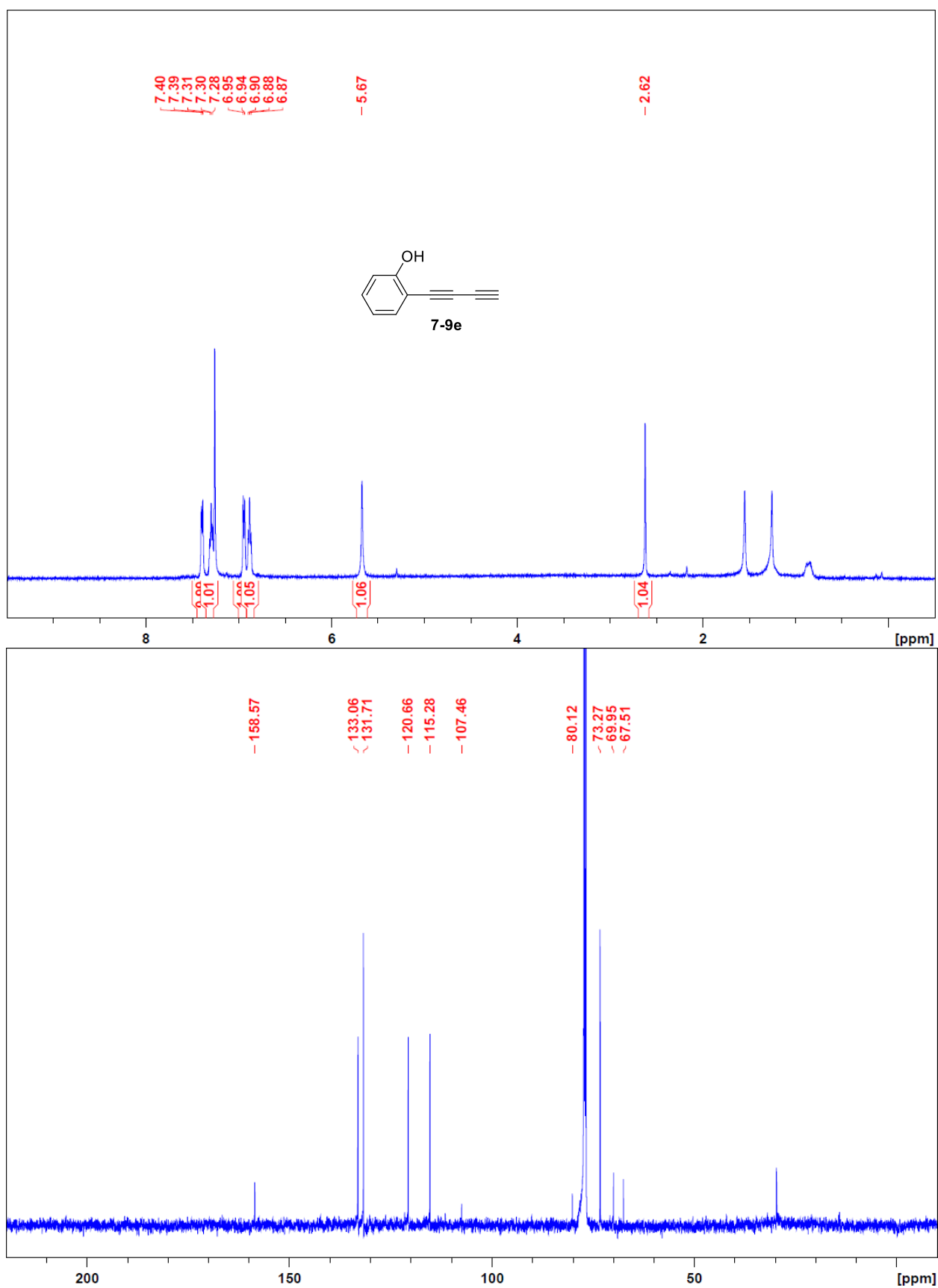


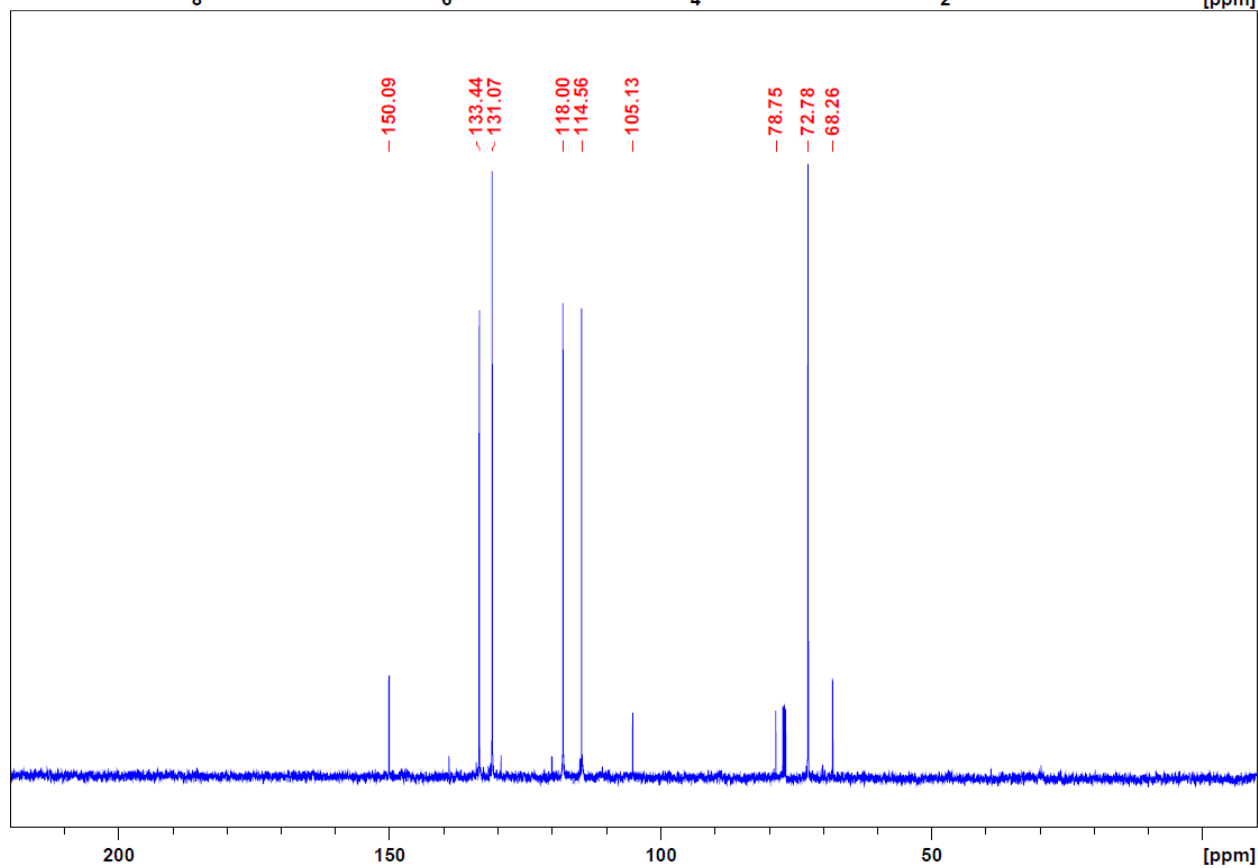
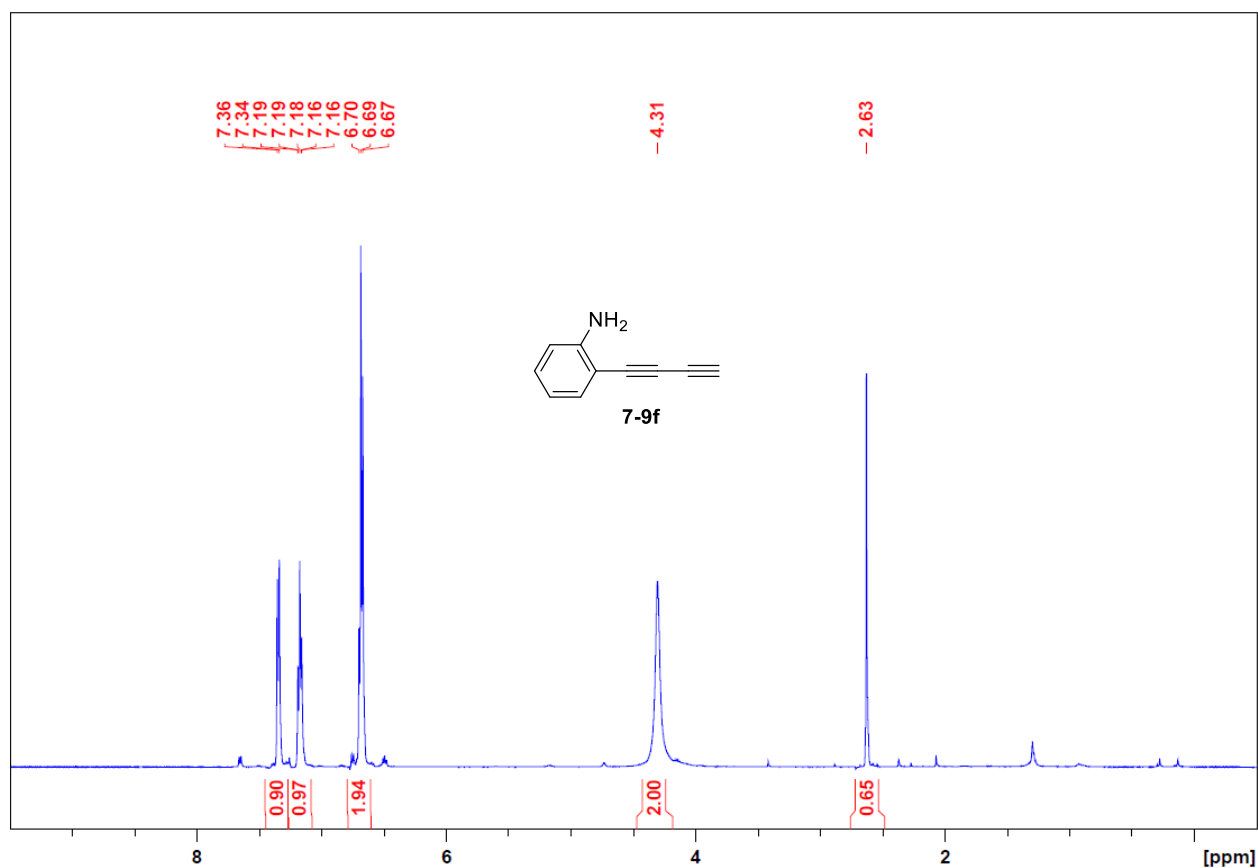




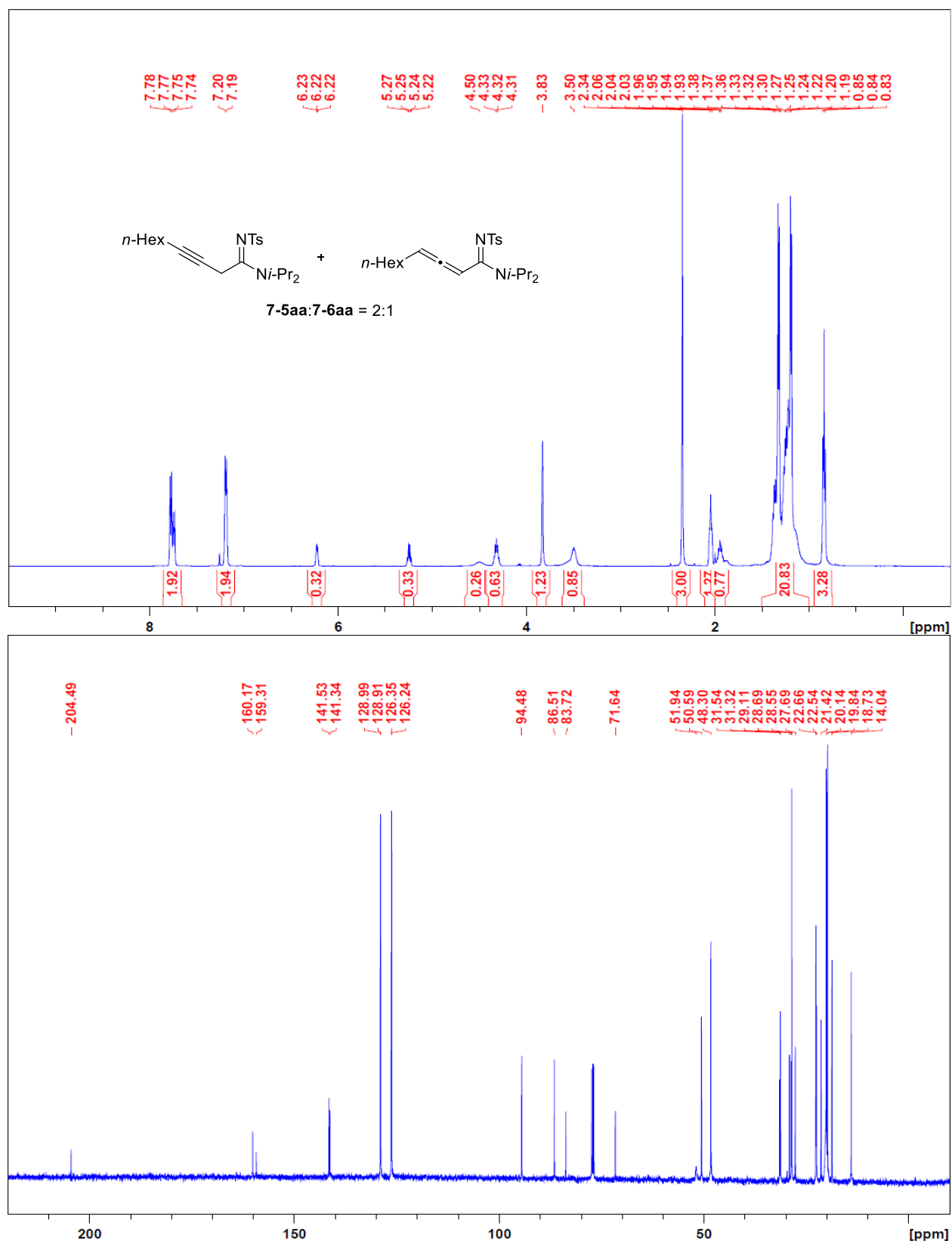


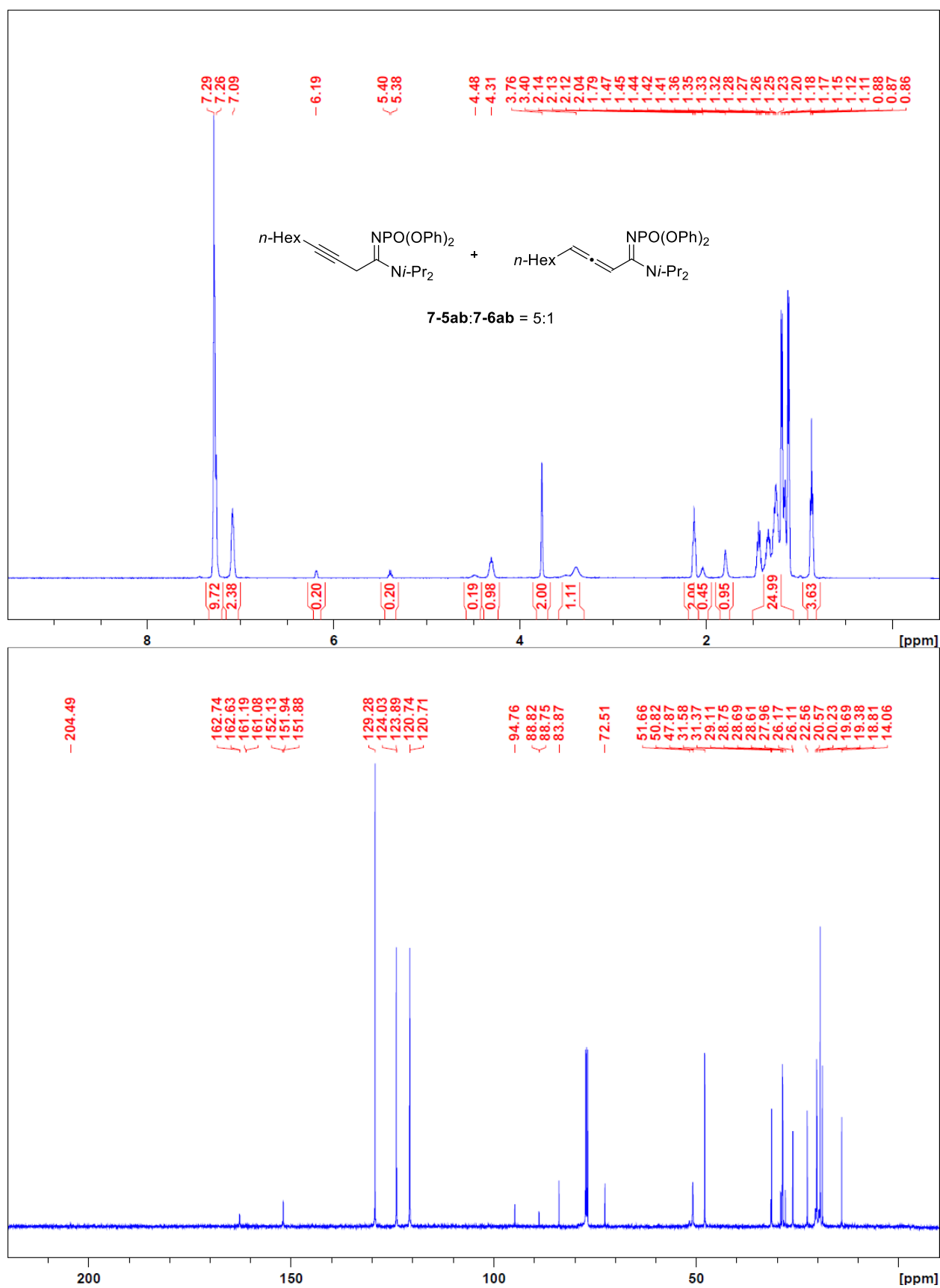


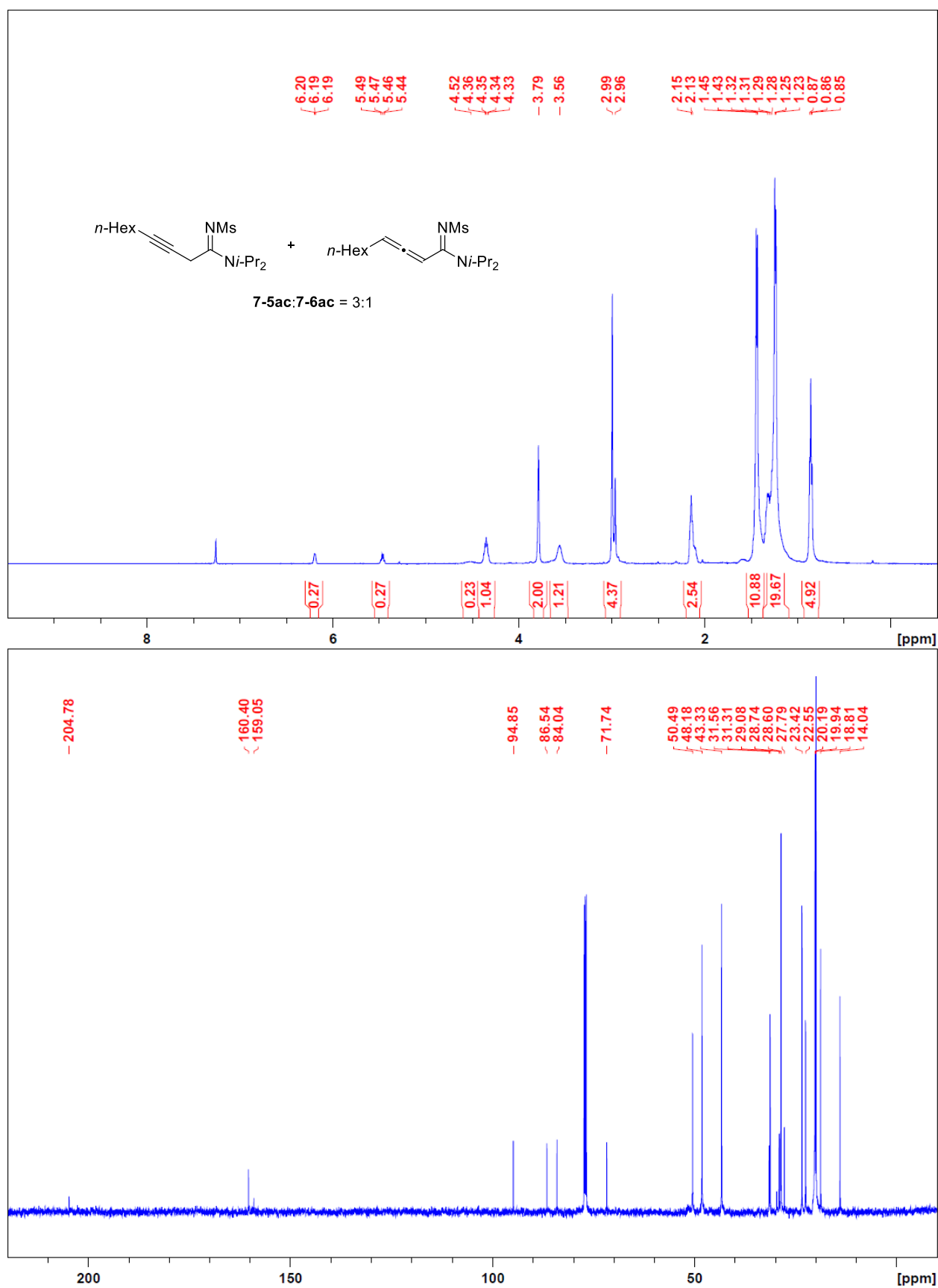


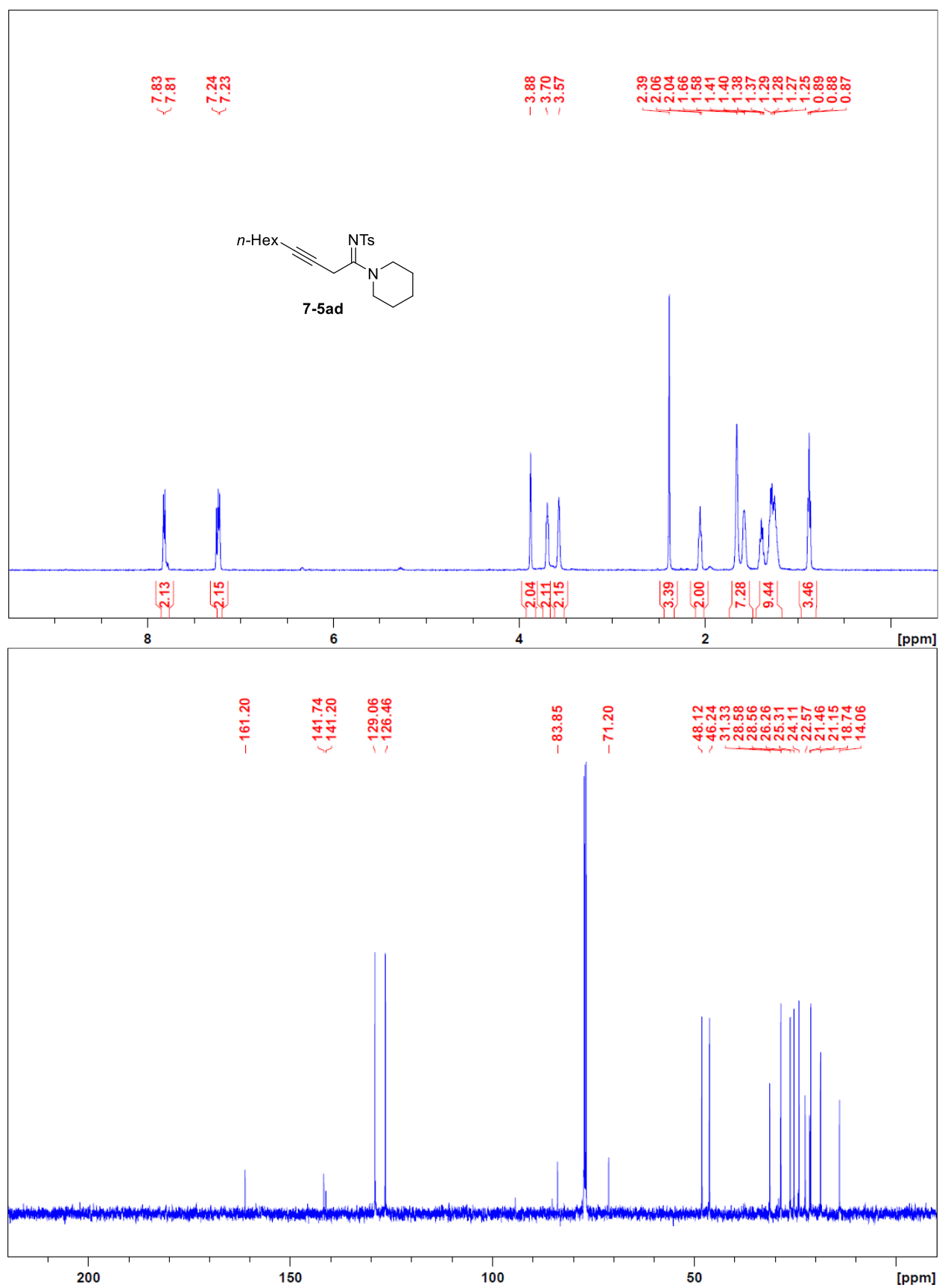


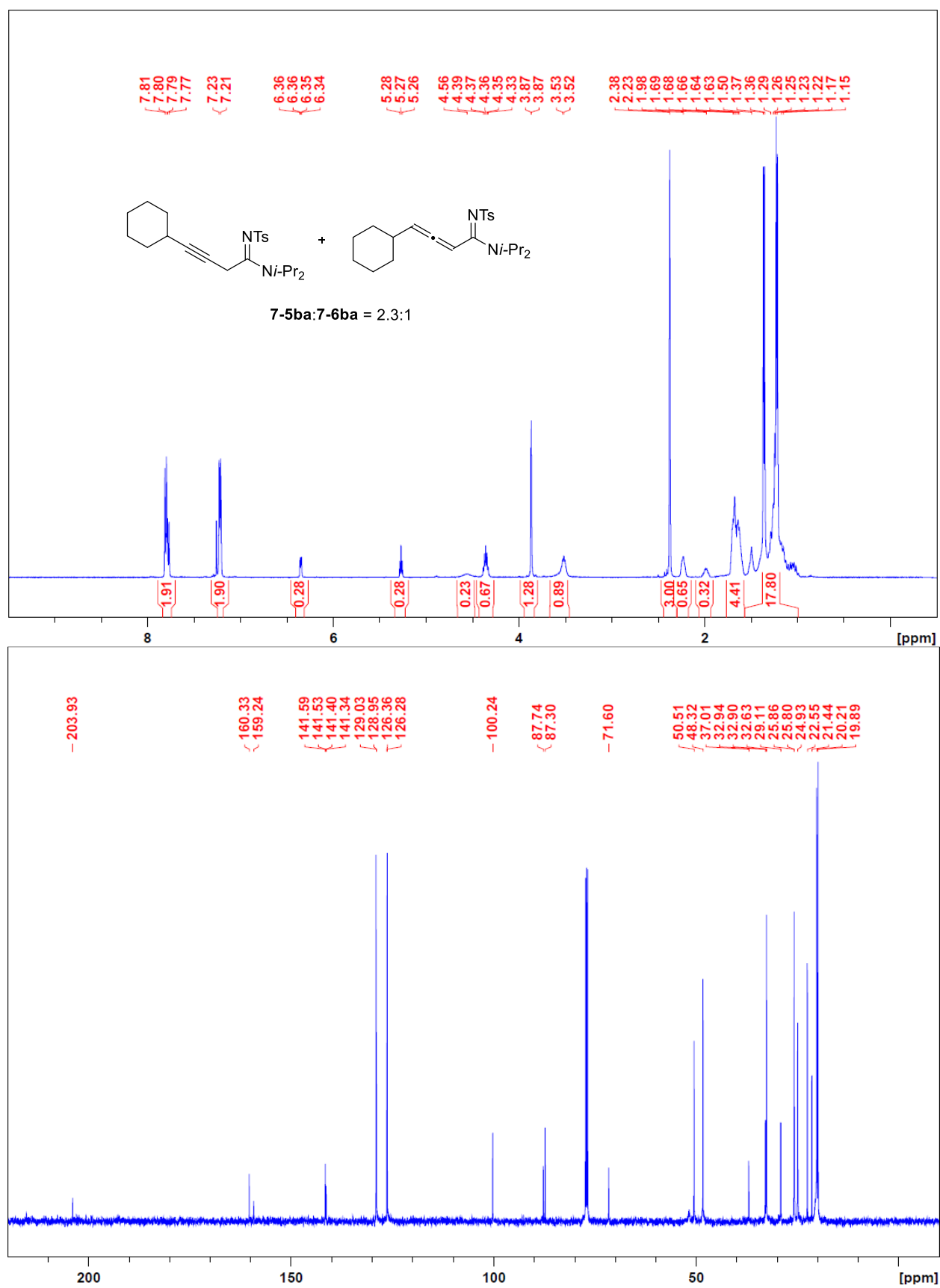
¹H and ¹³C NMR Spectra of Products

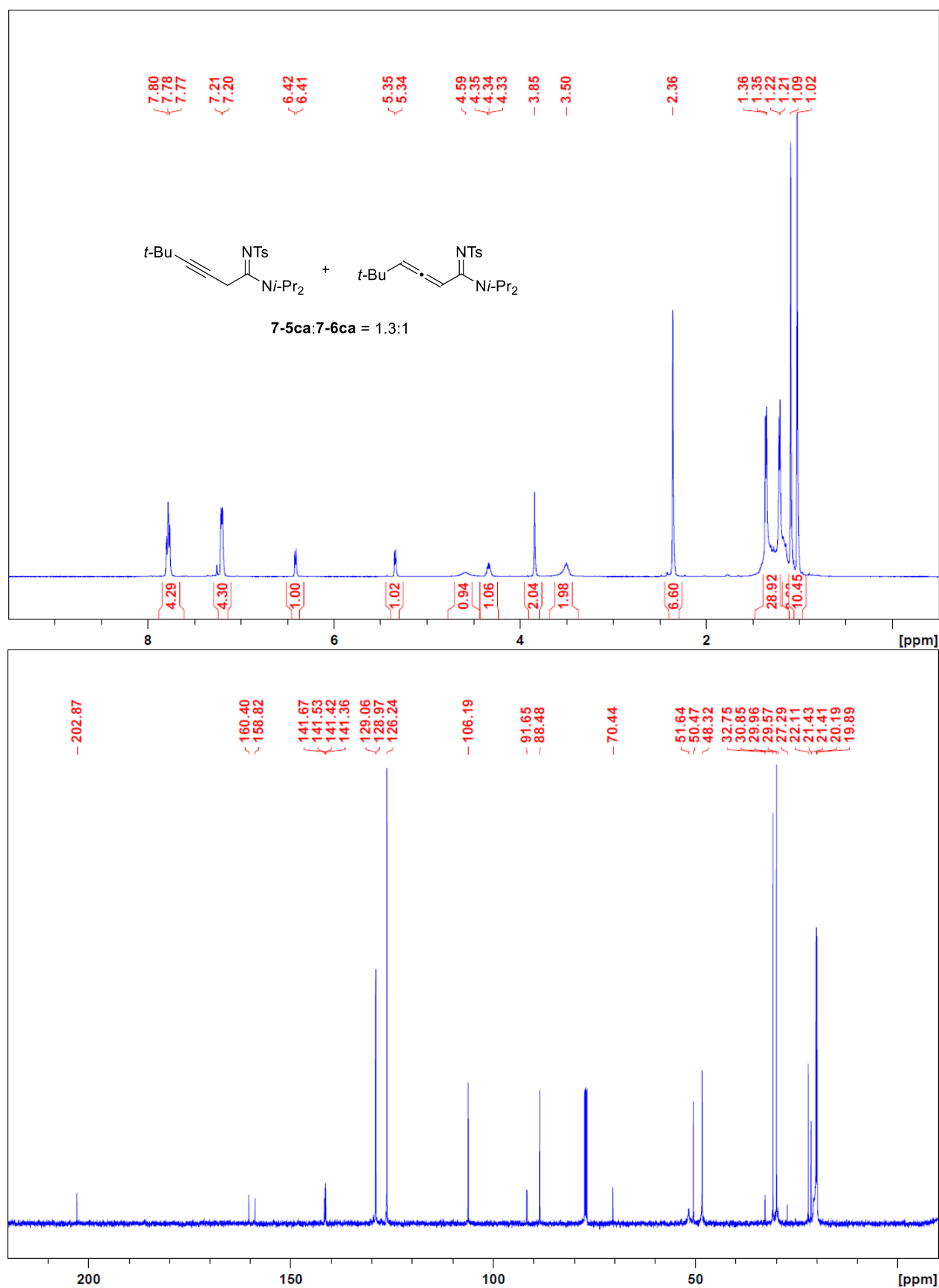


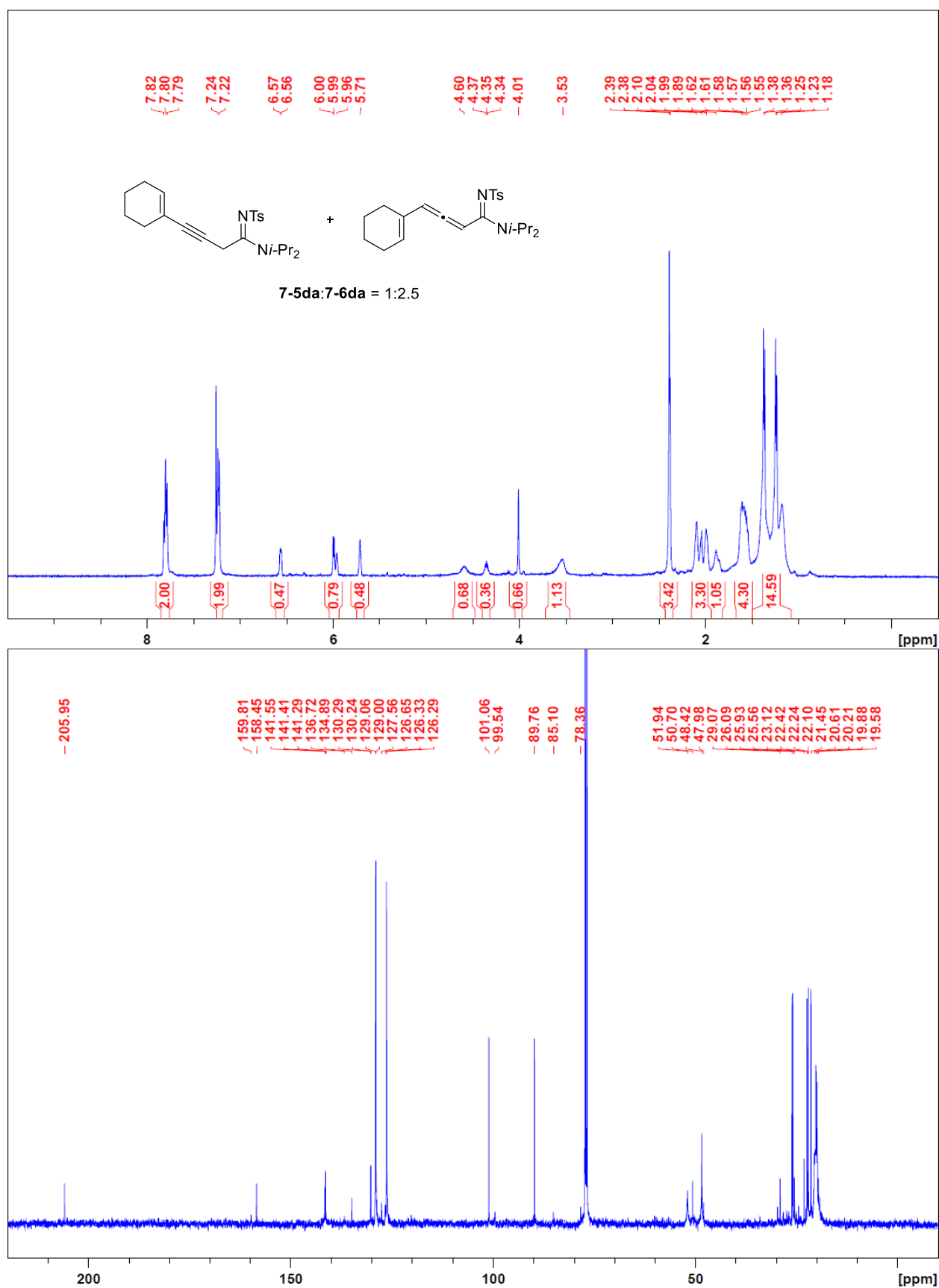


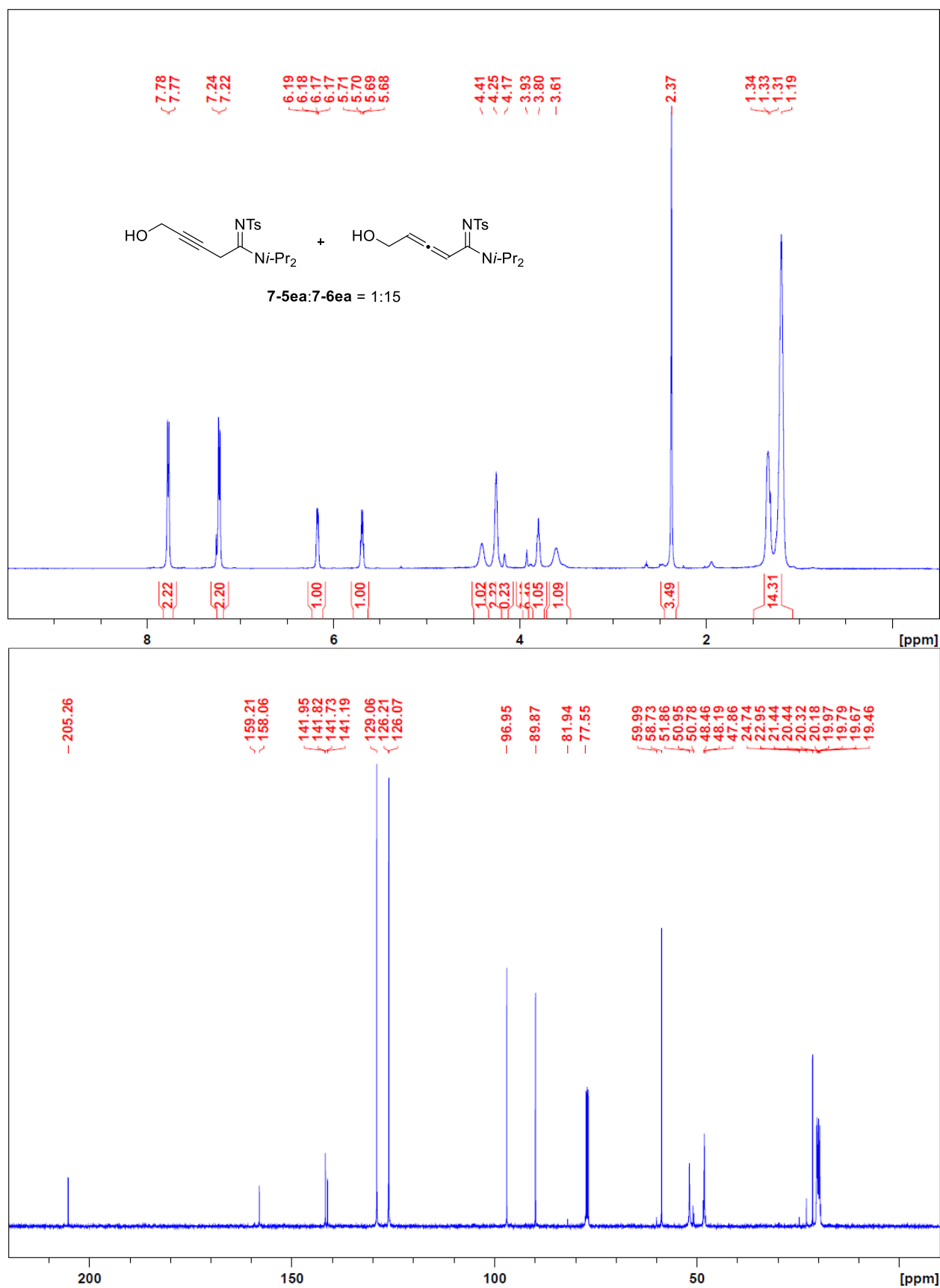


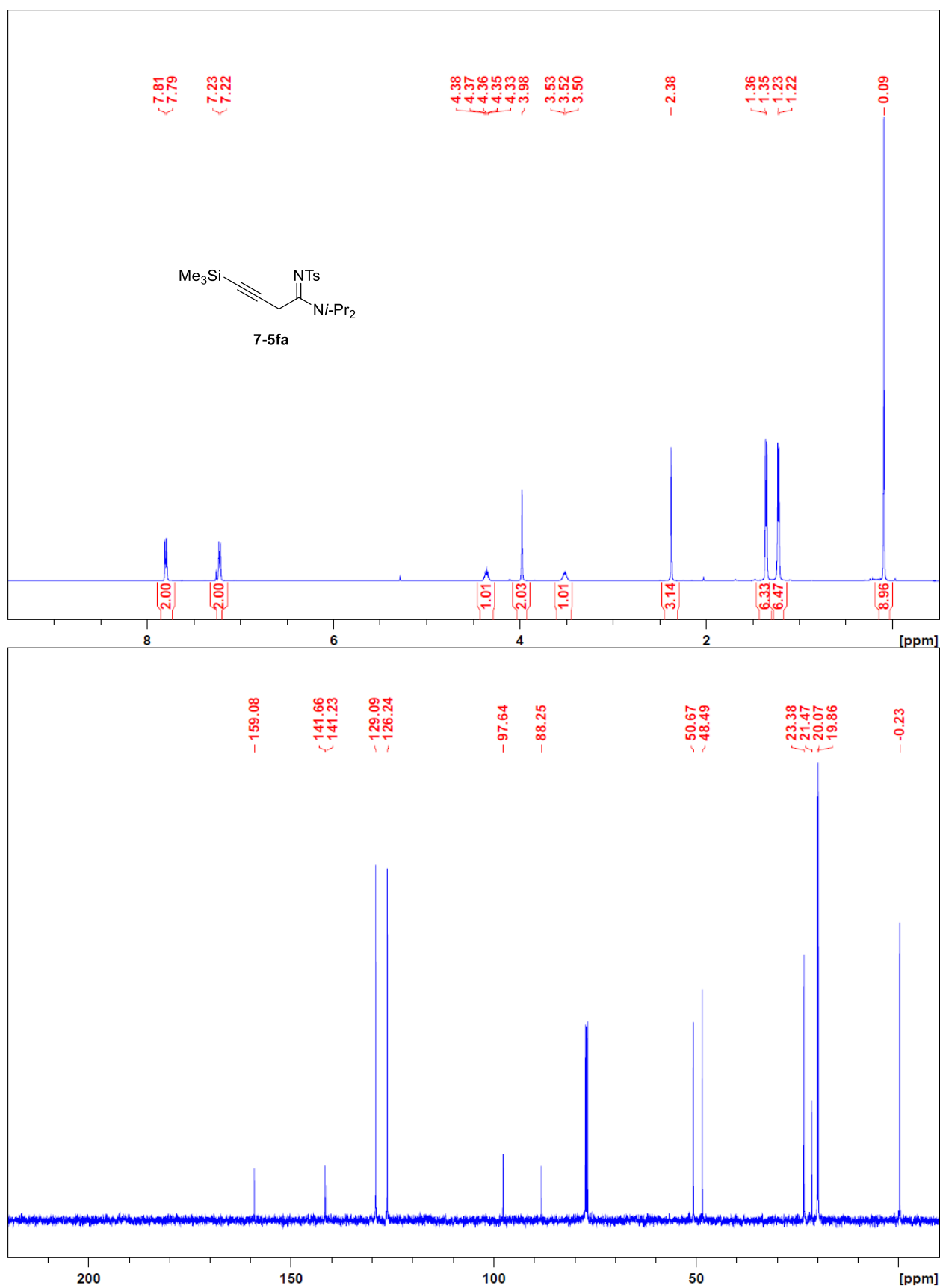


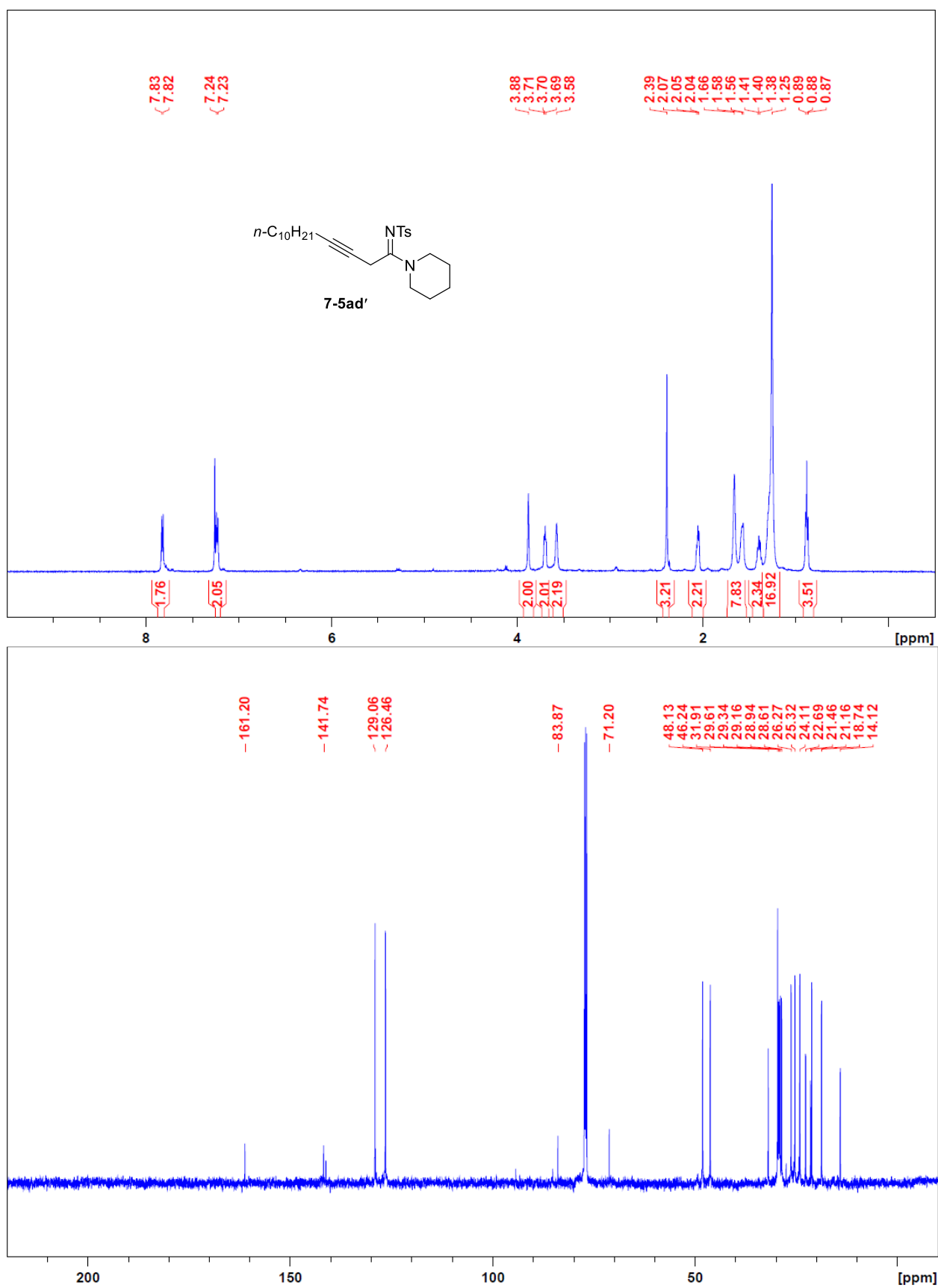


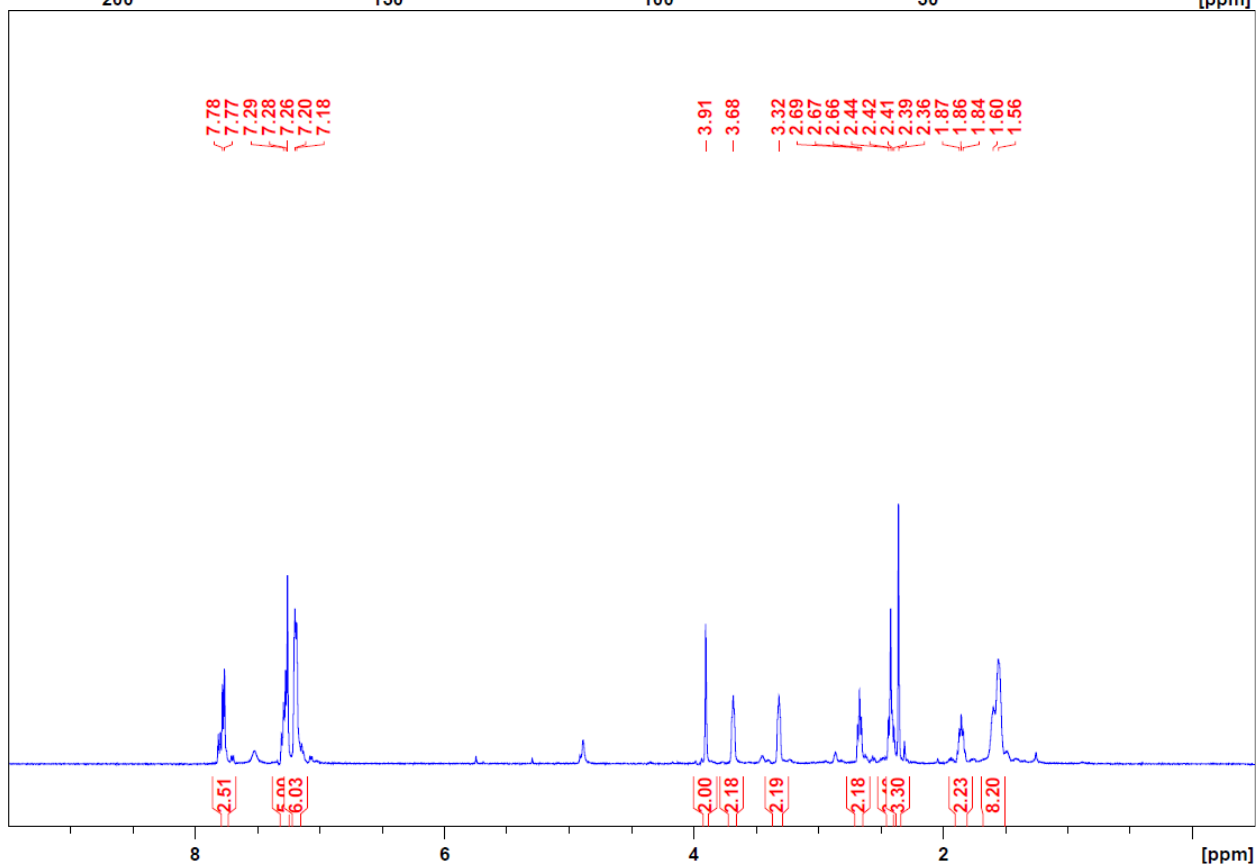
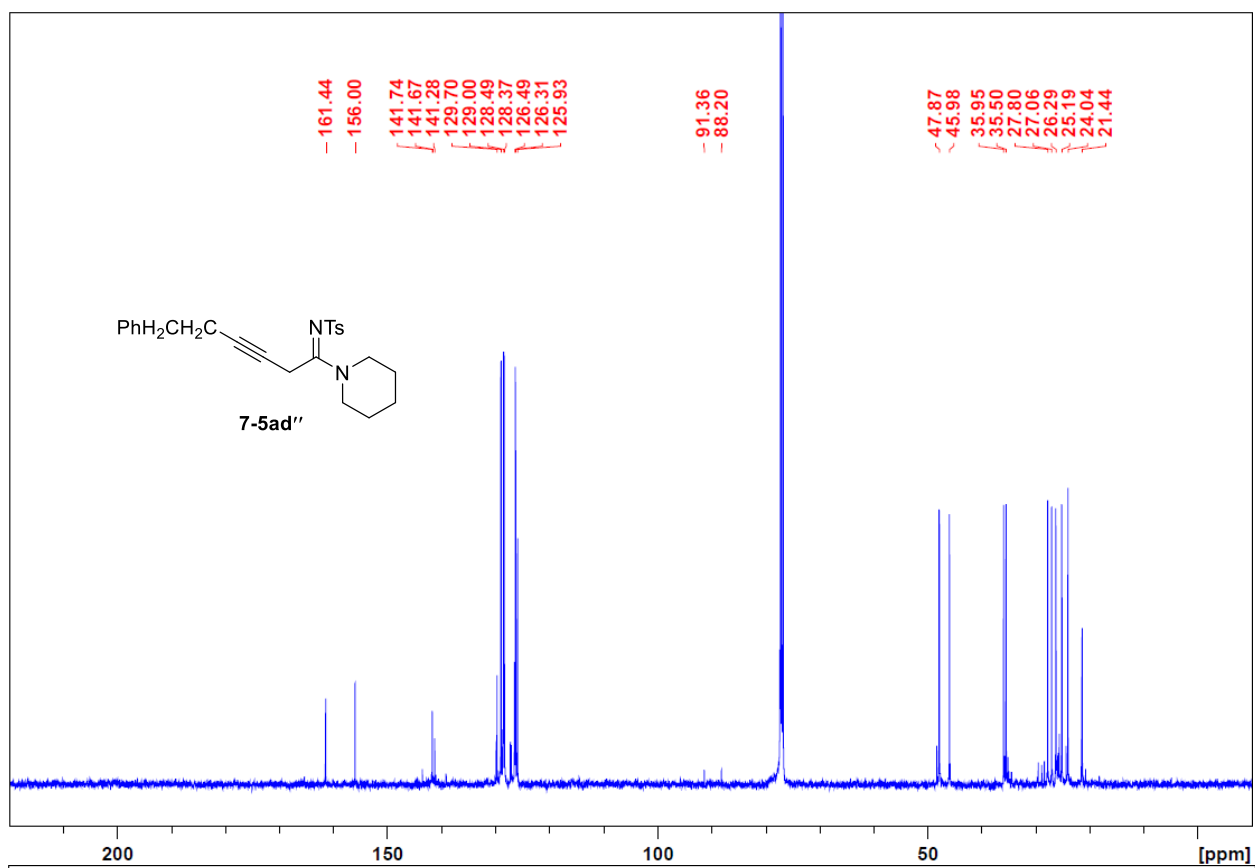


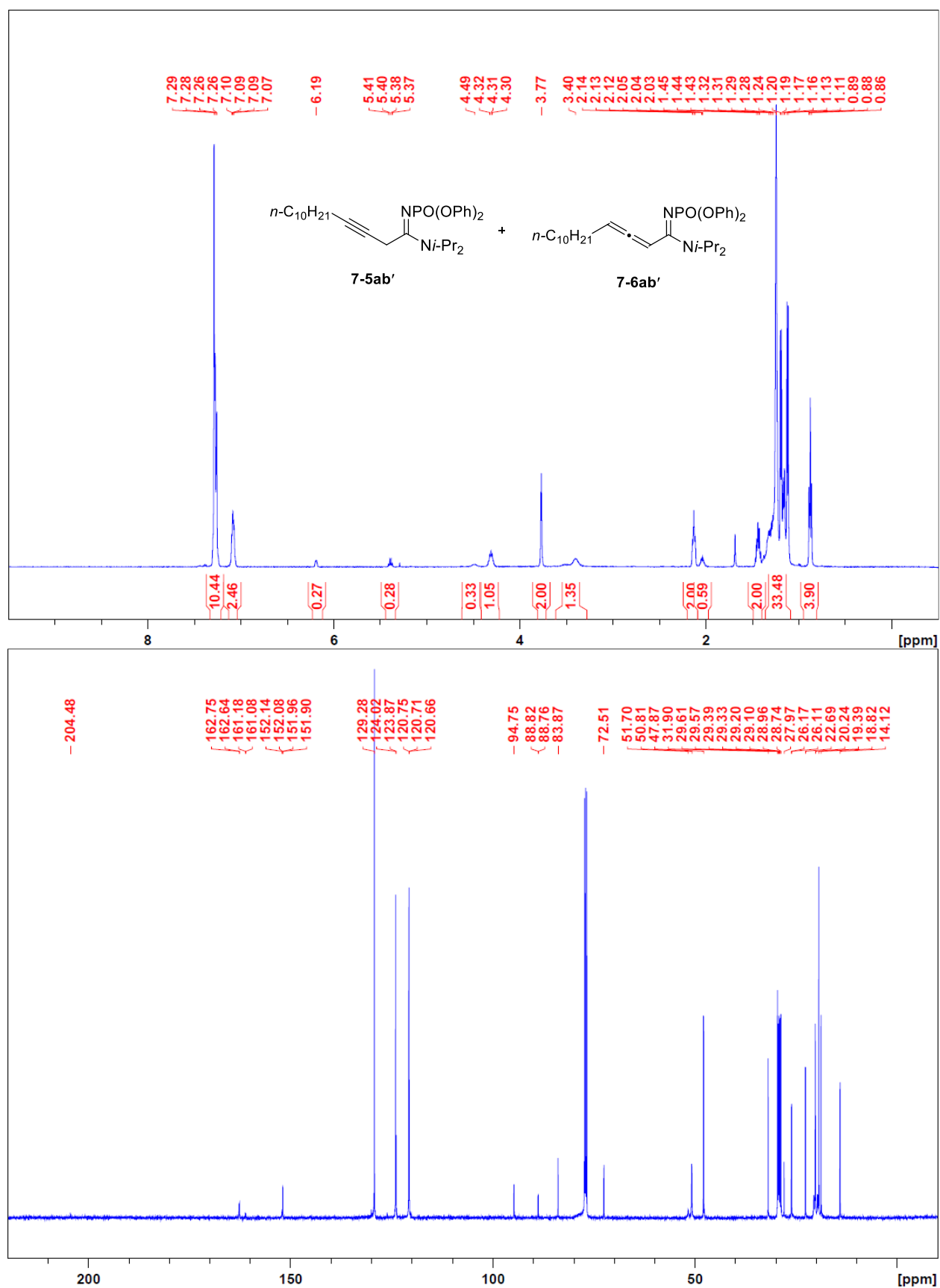


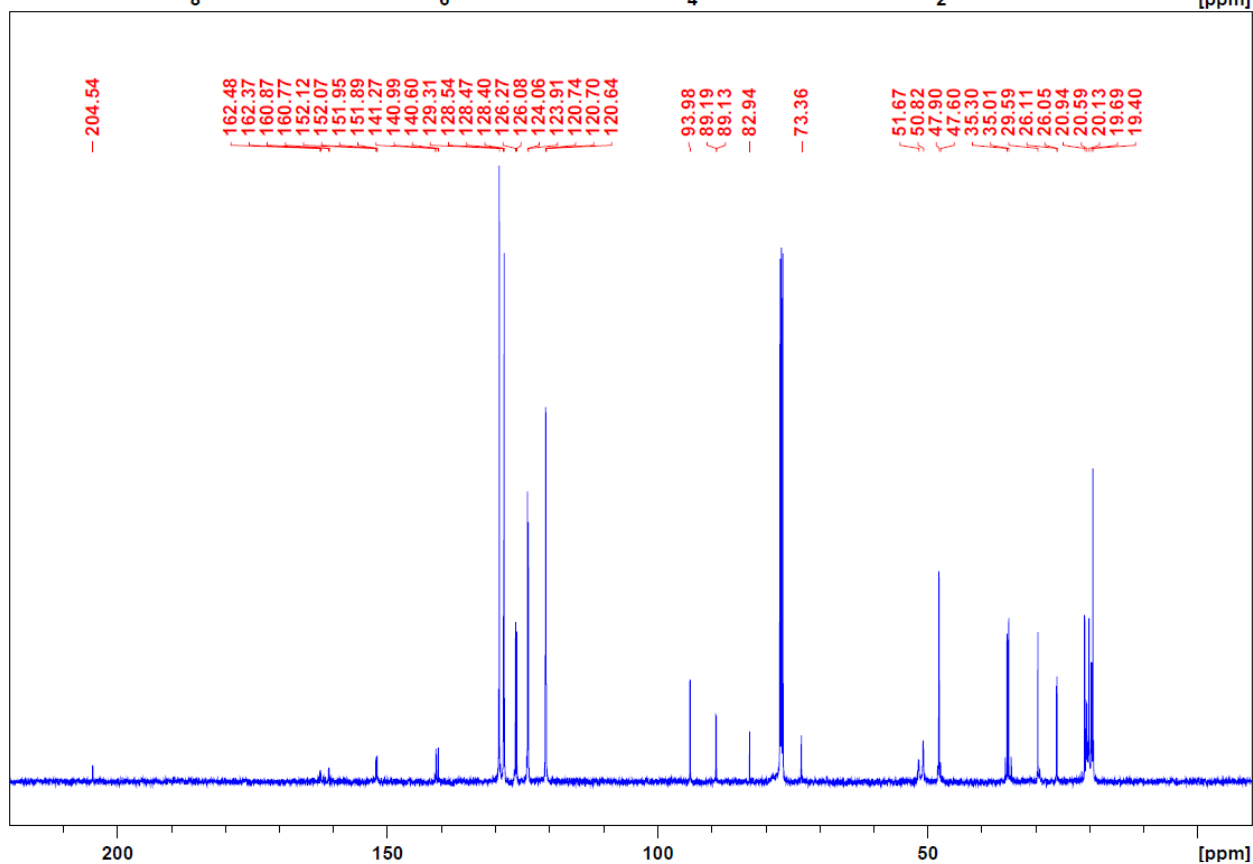
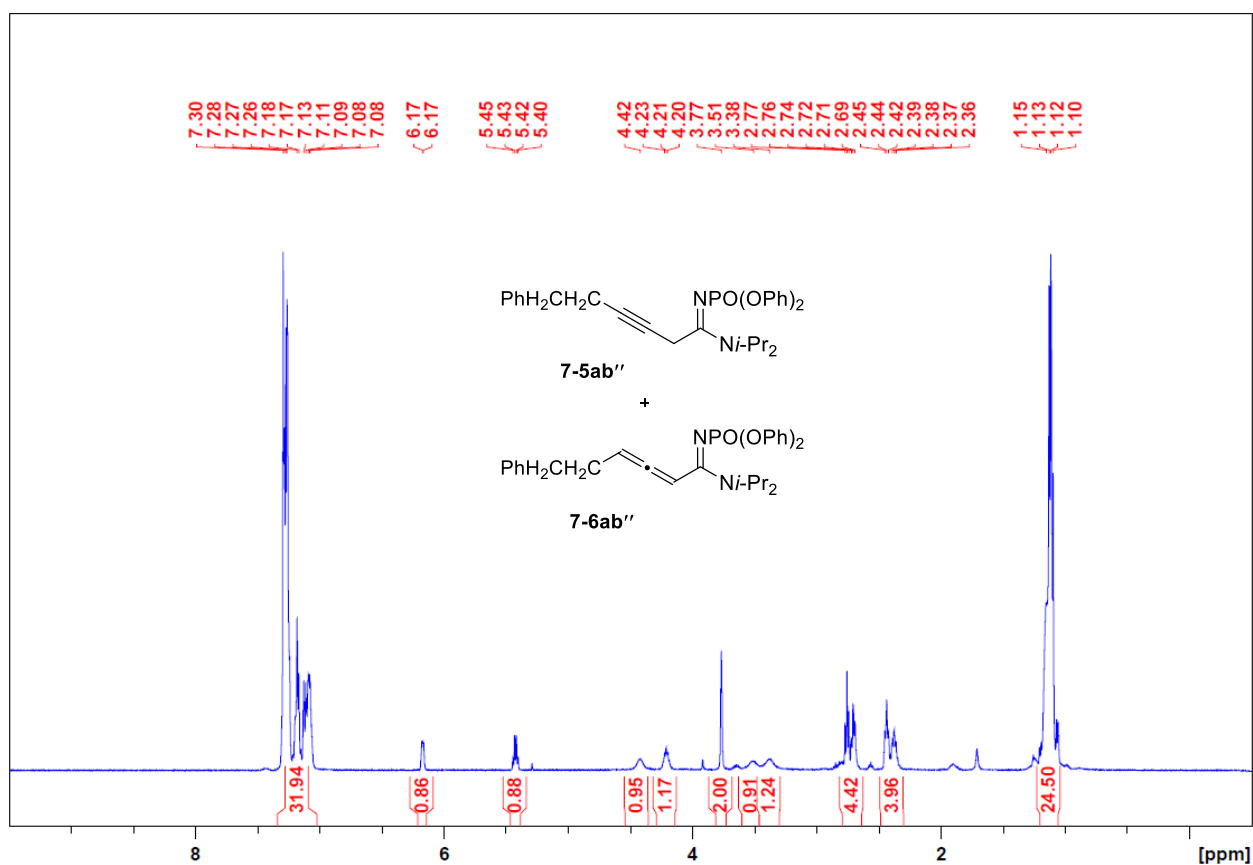


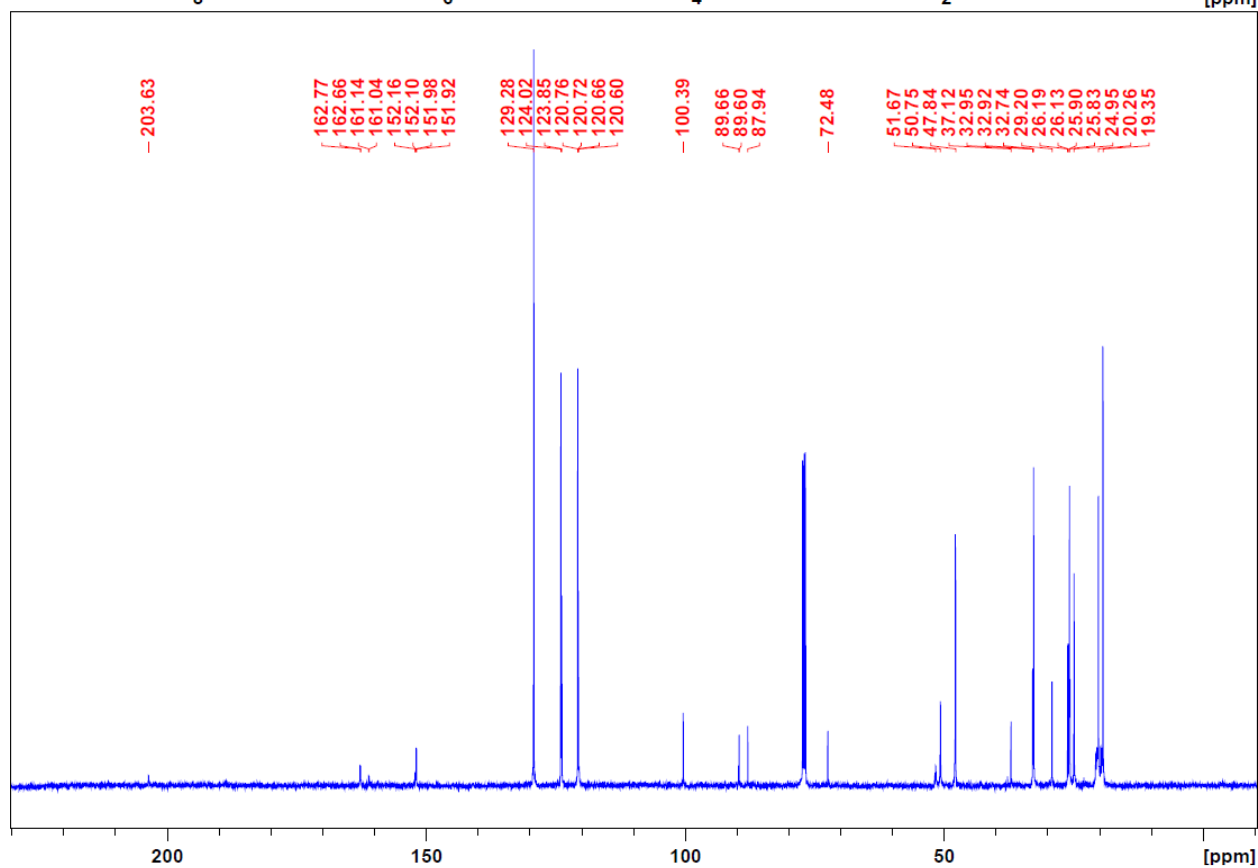
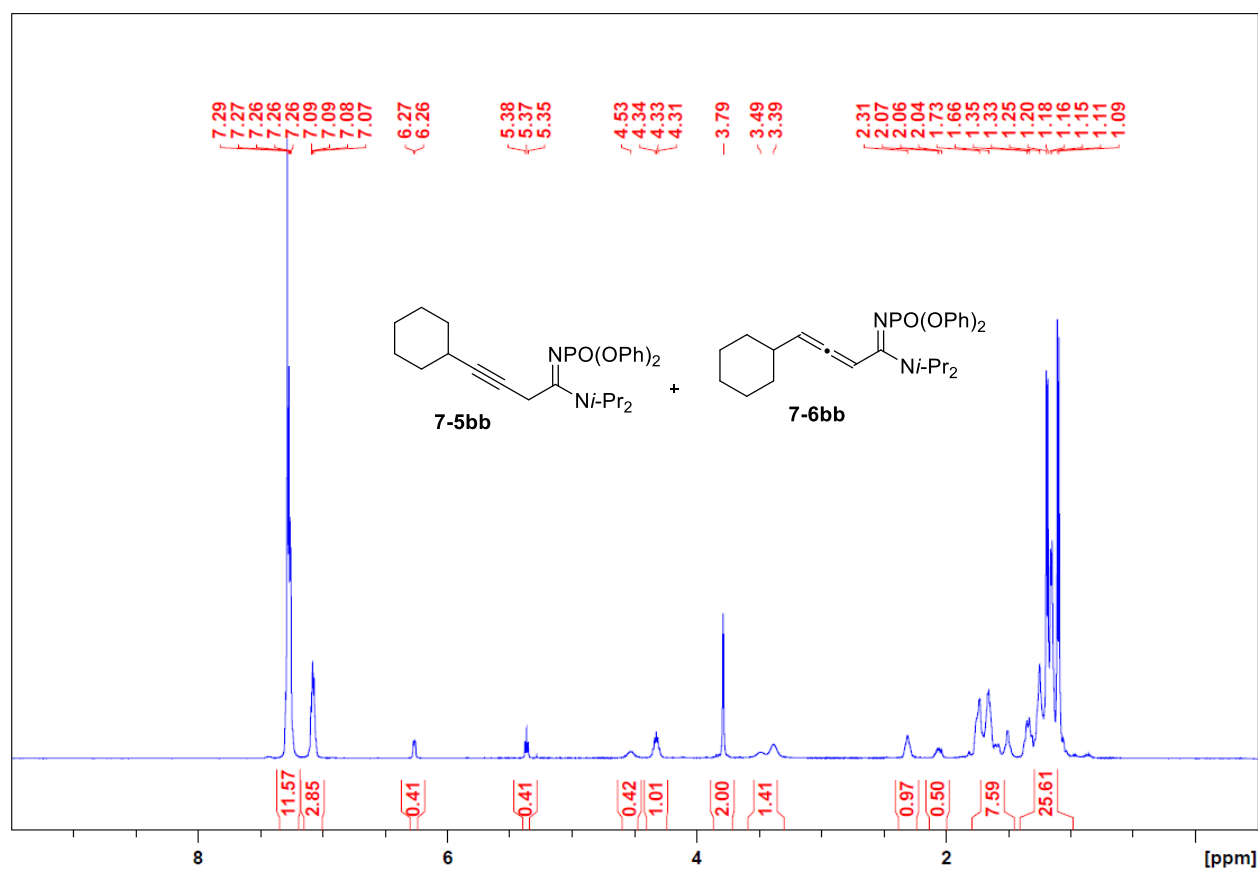


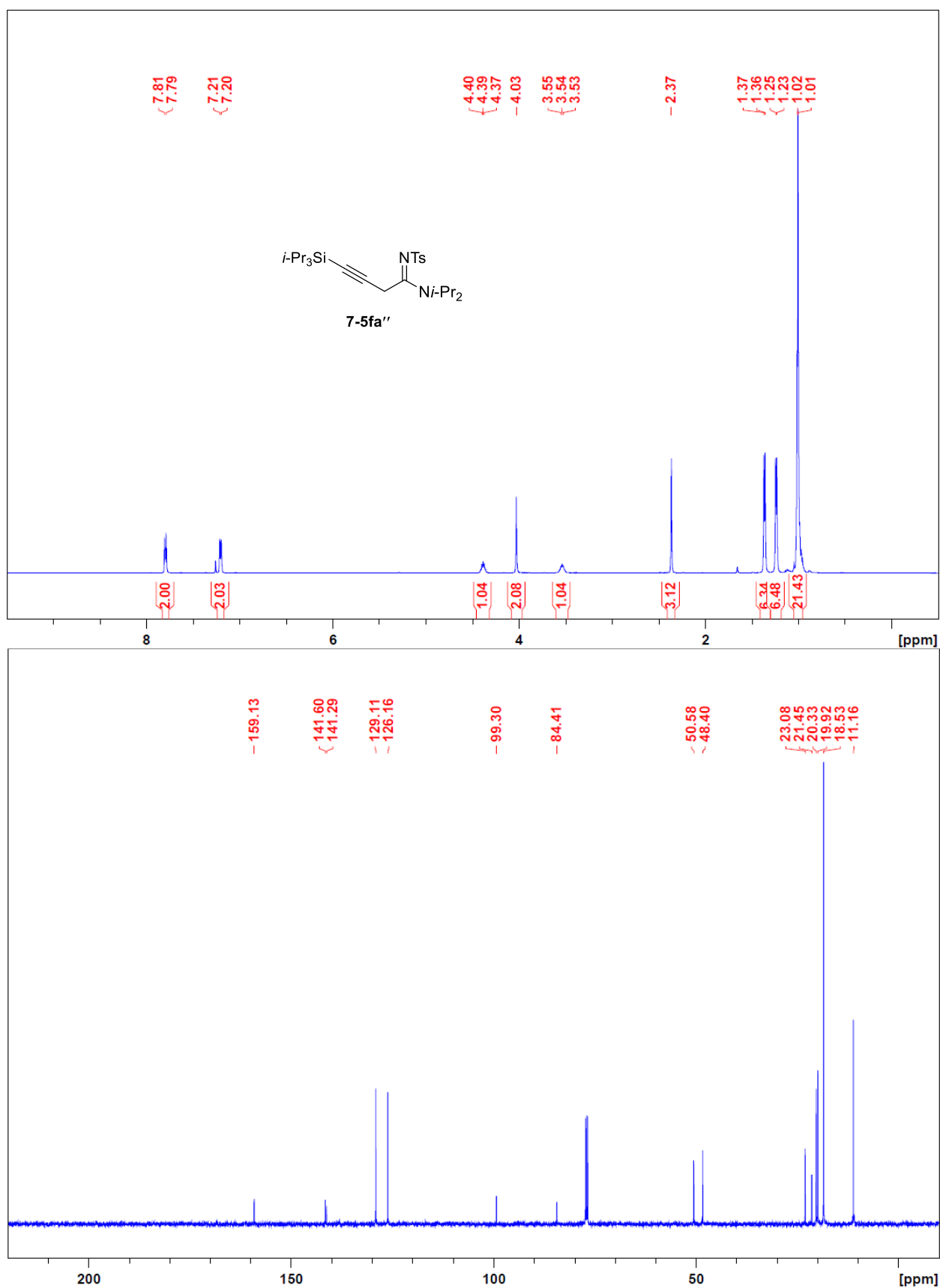


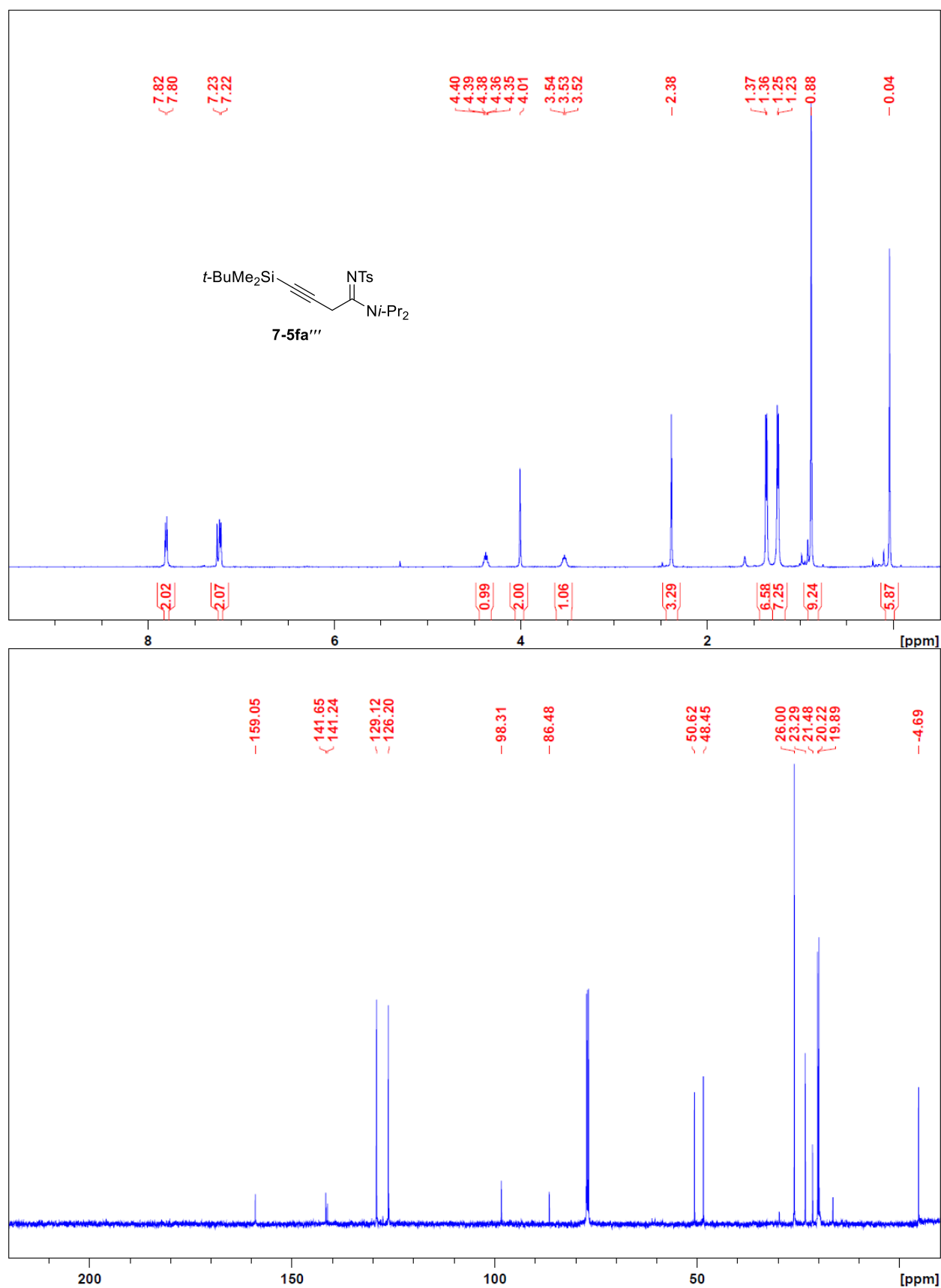


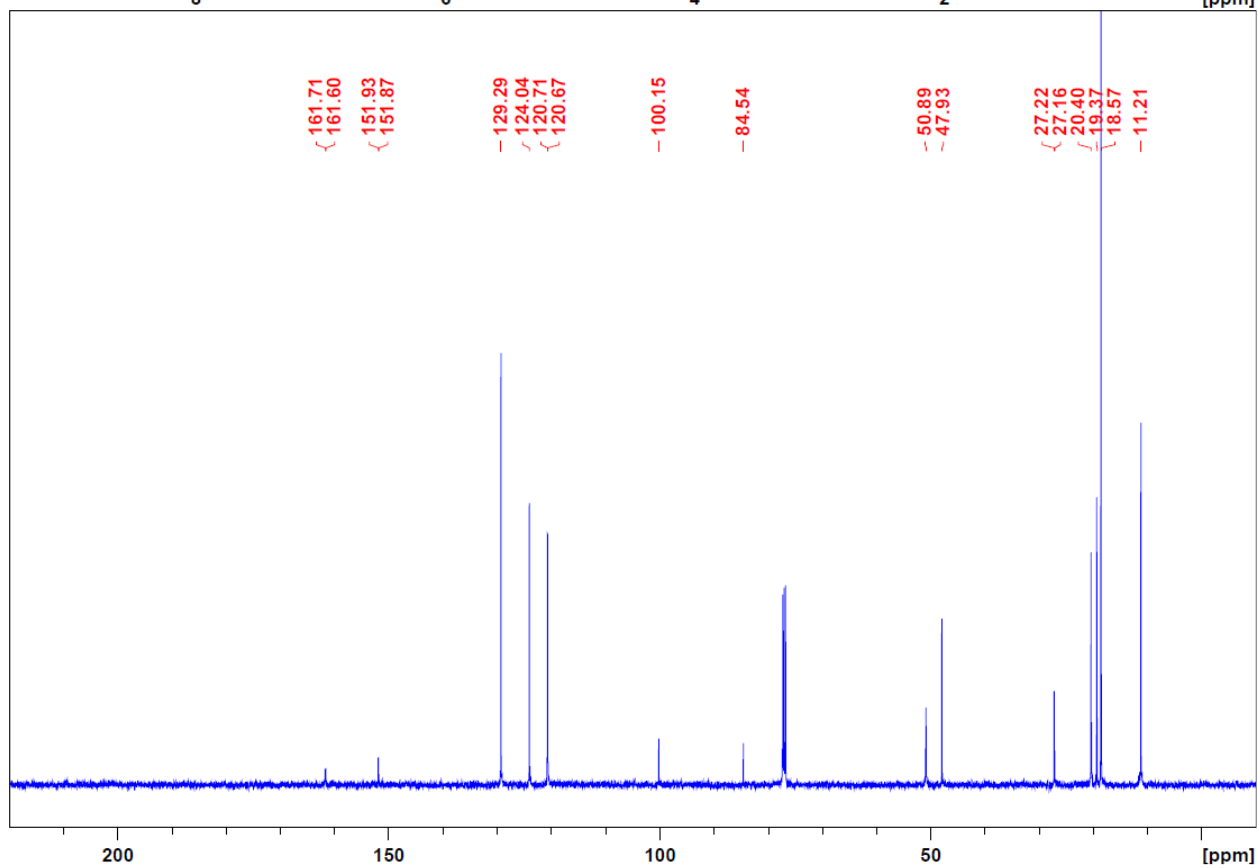
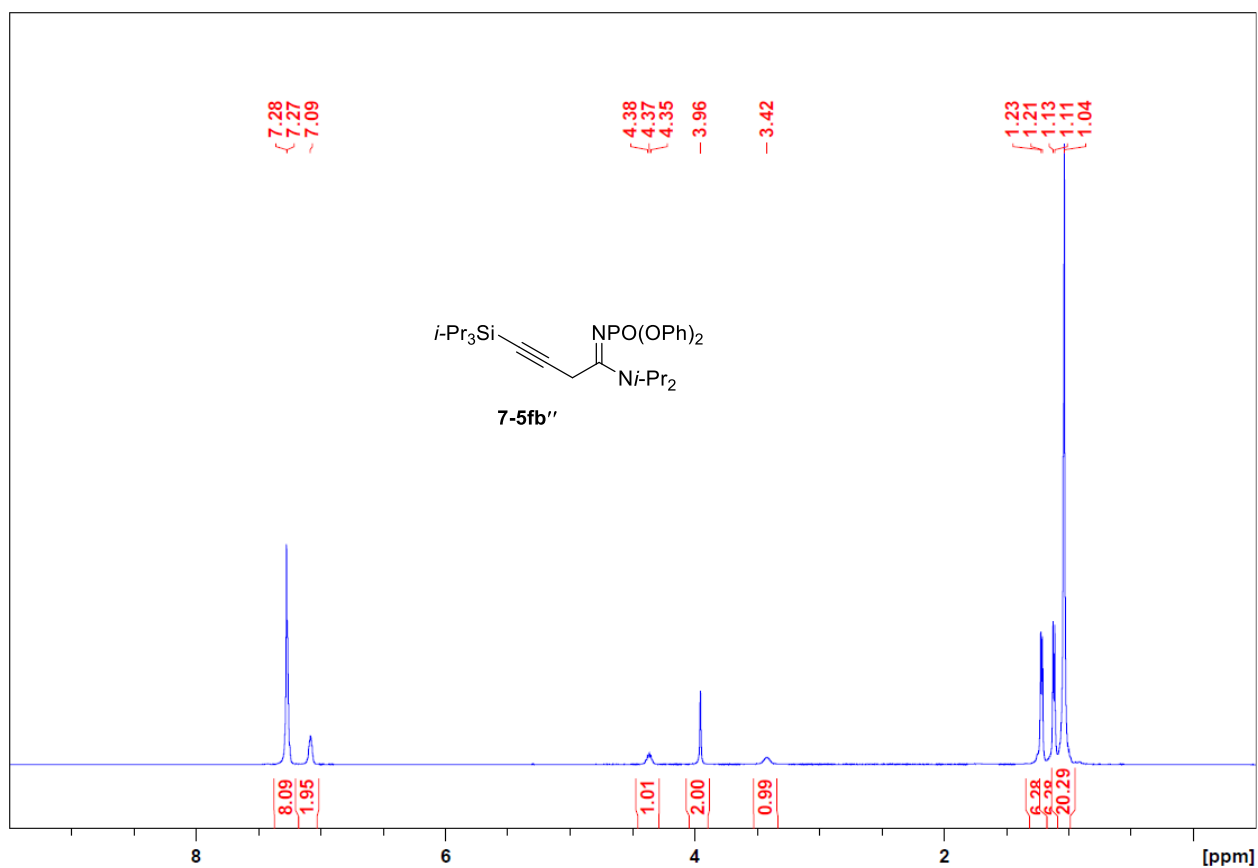


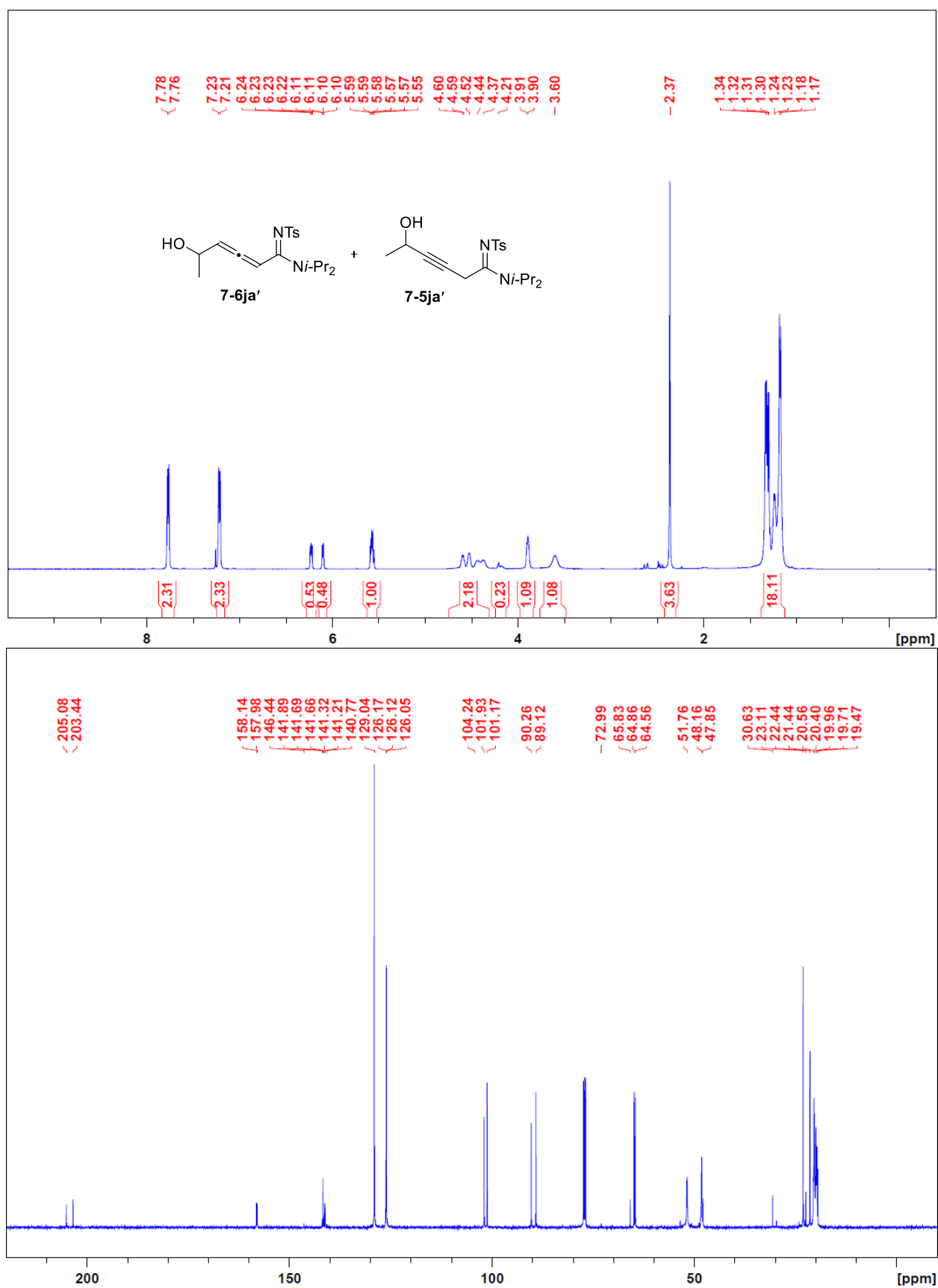


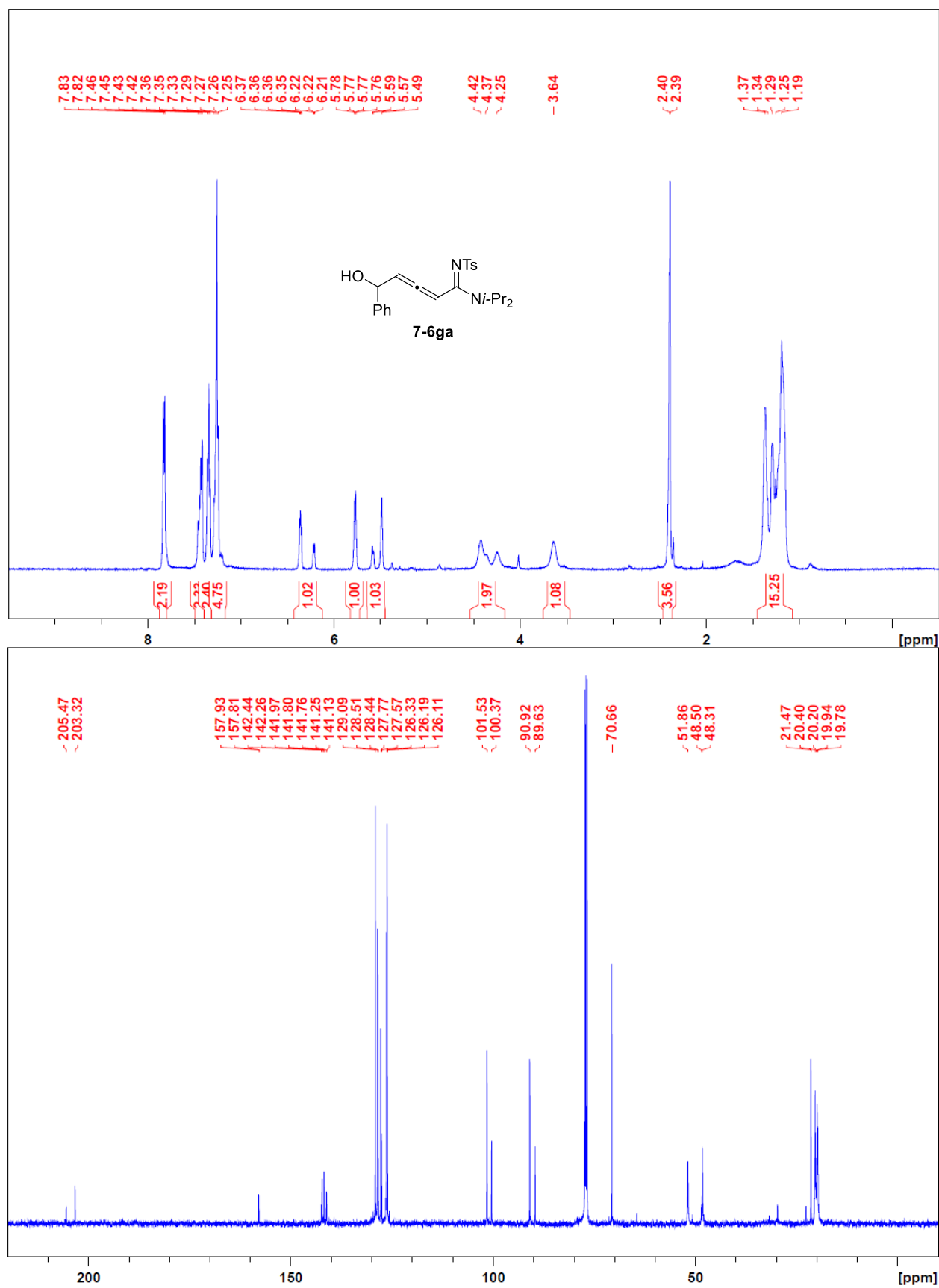


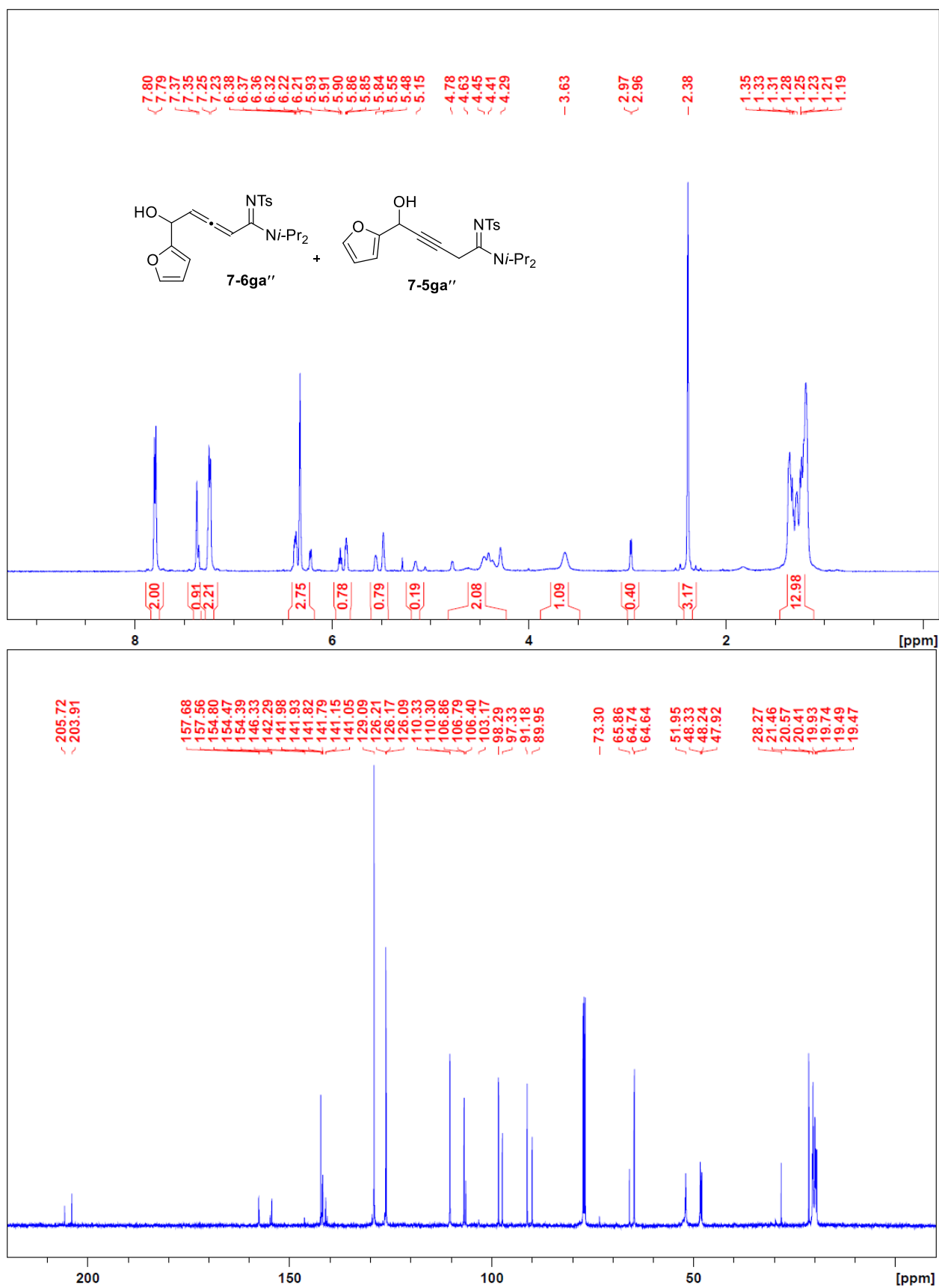


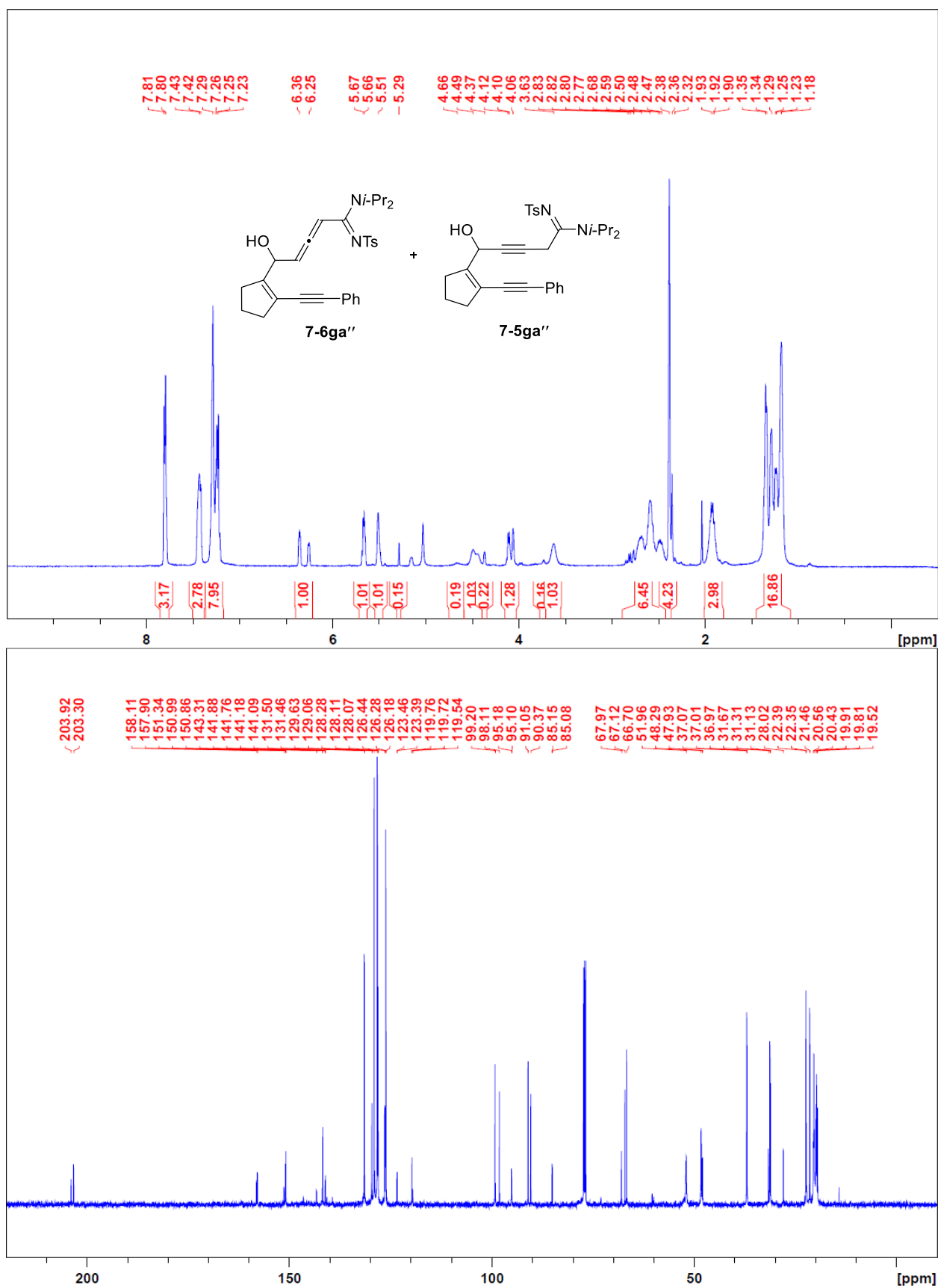


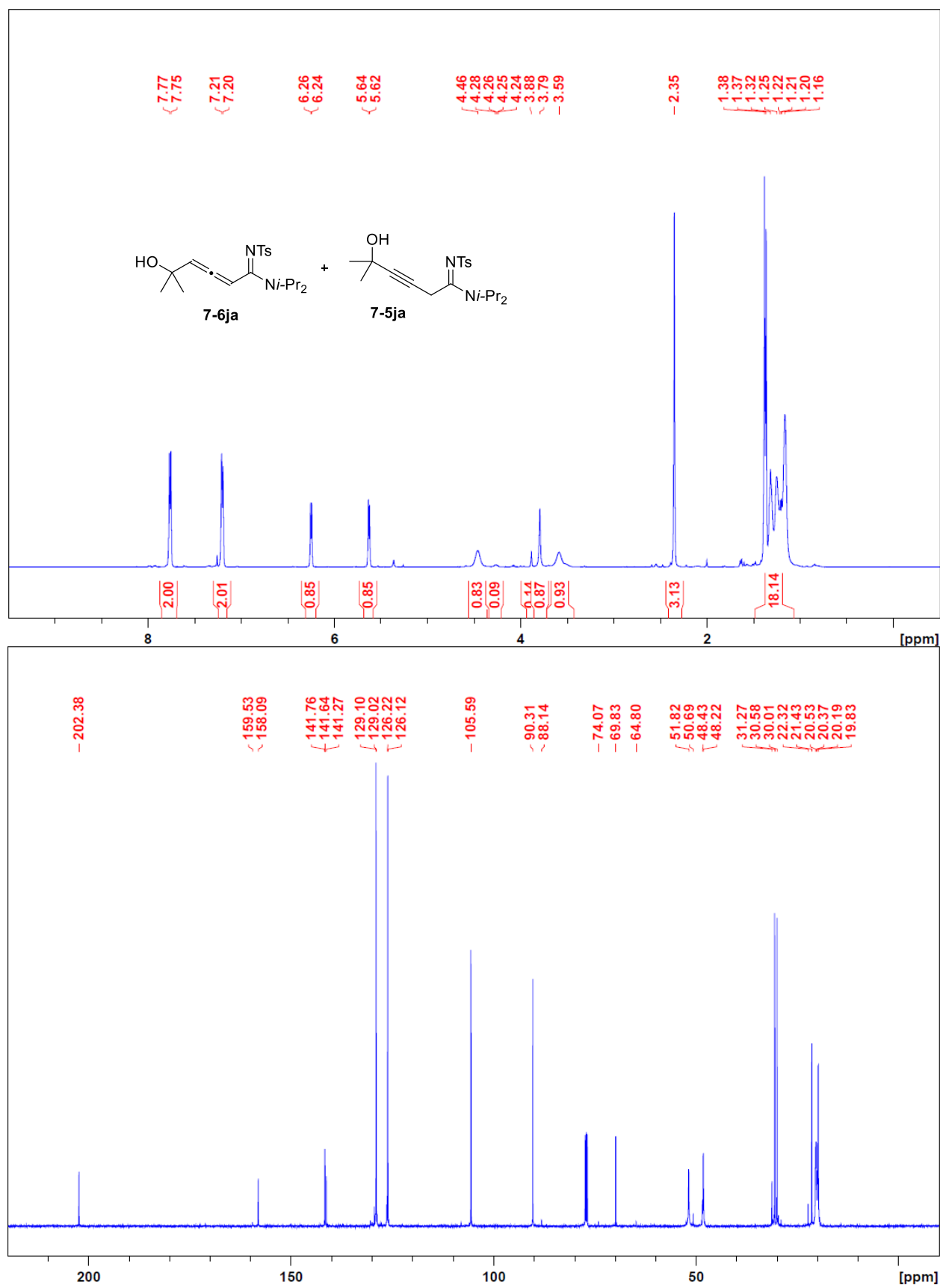


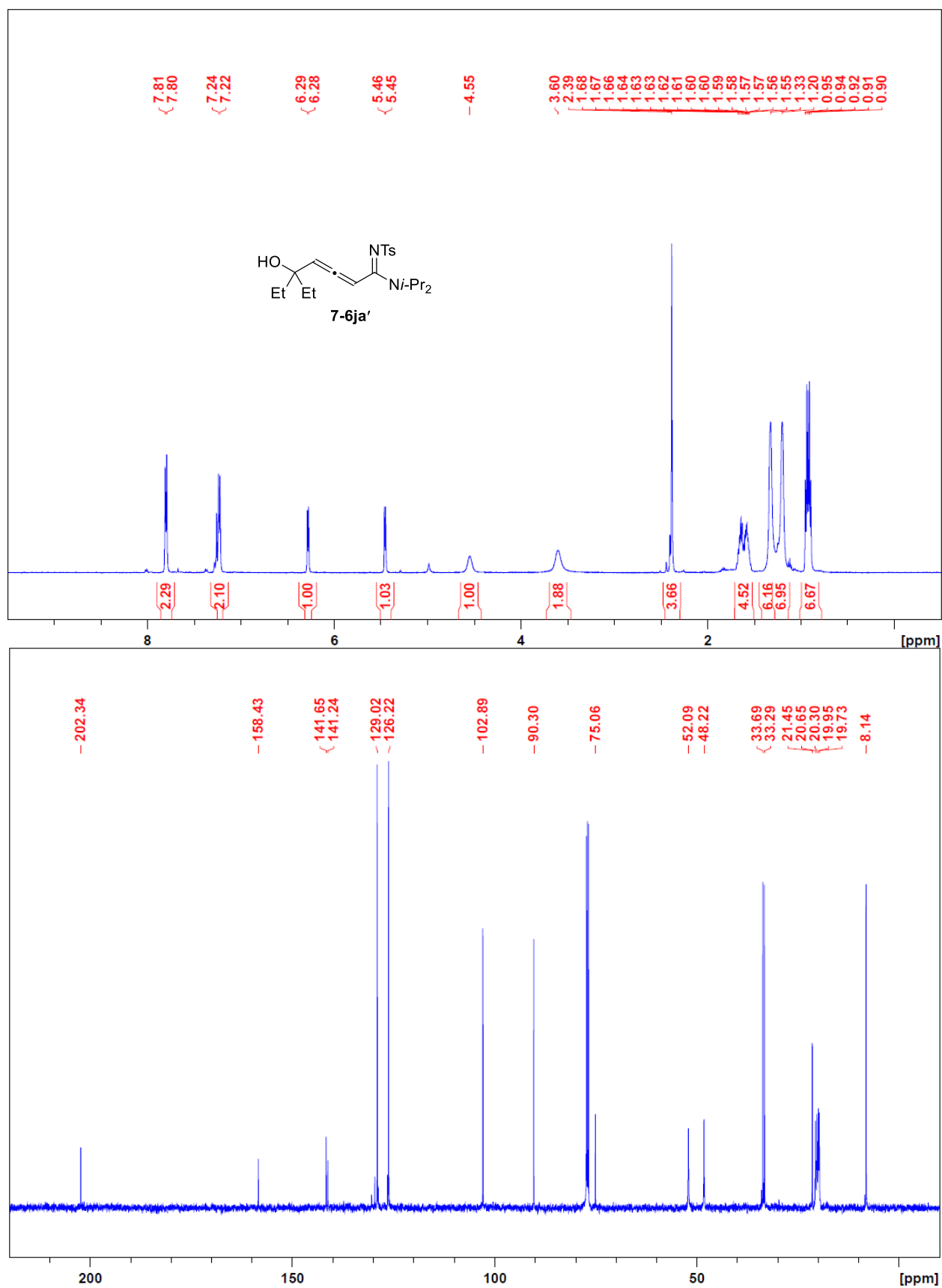


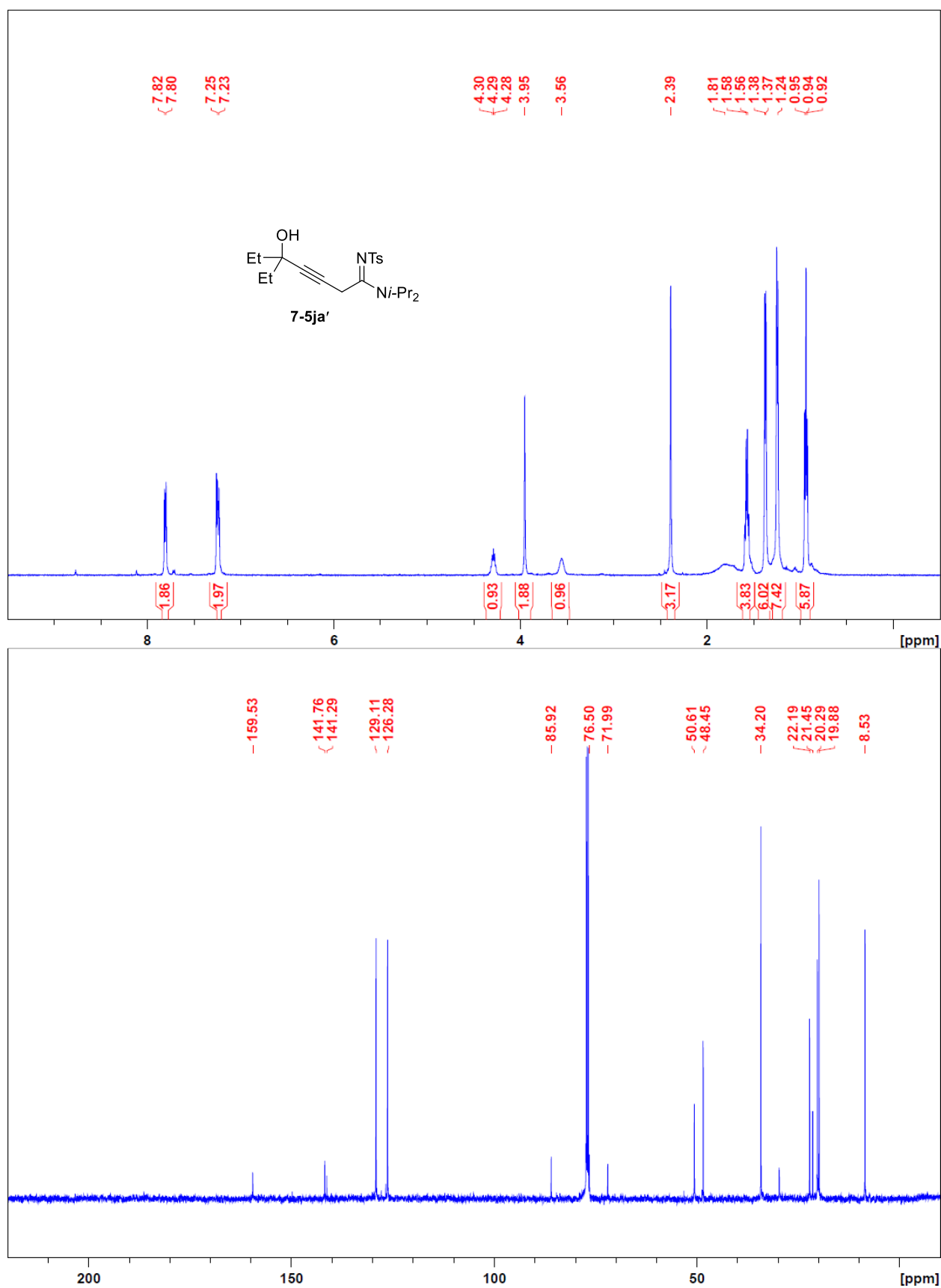


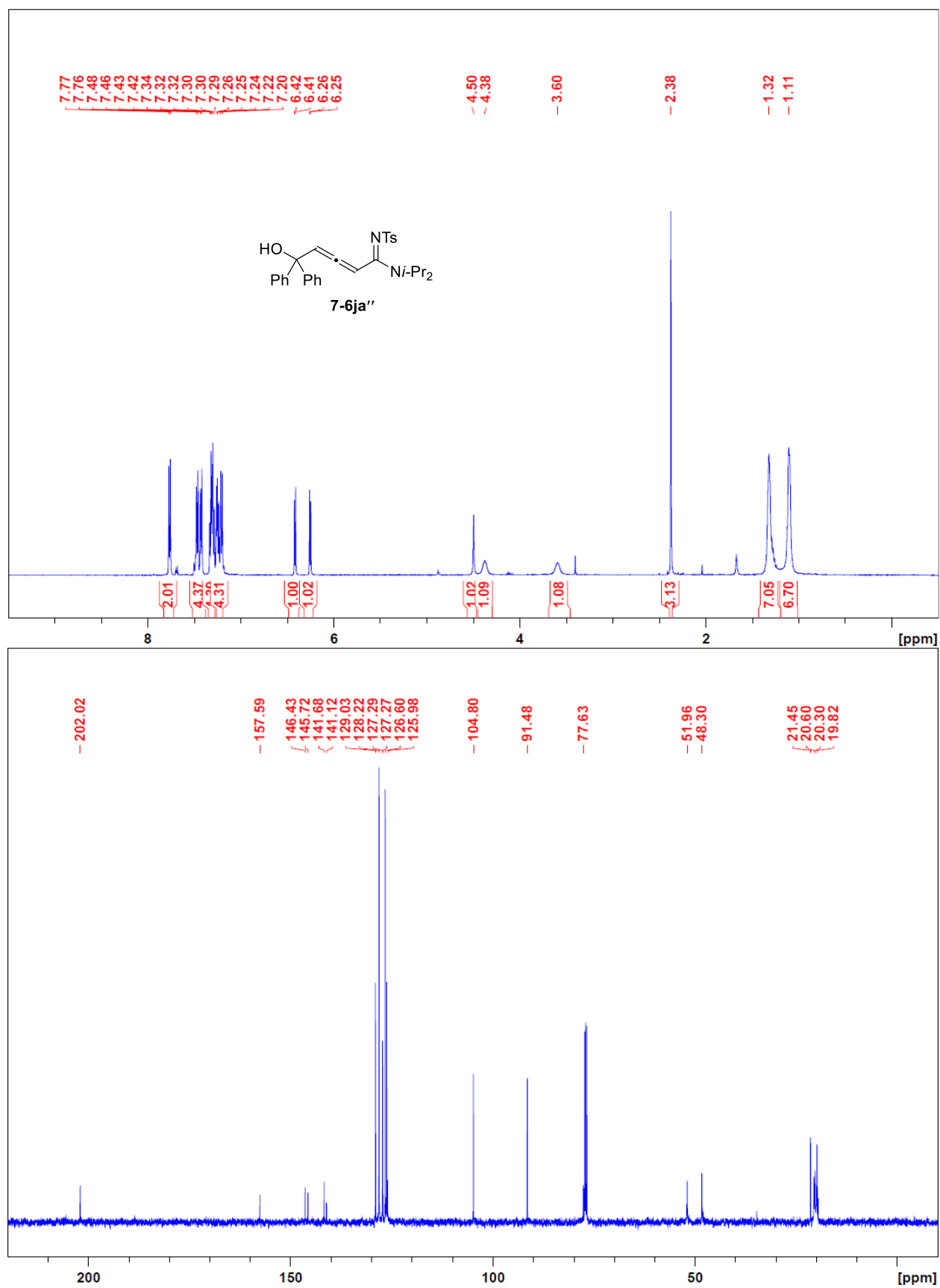


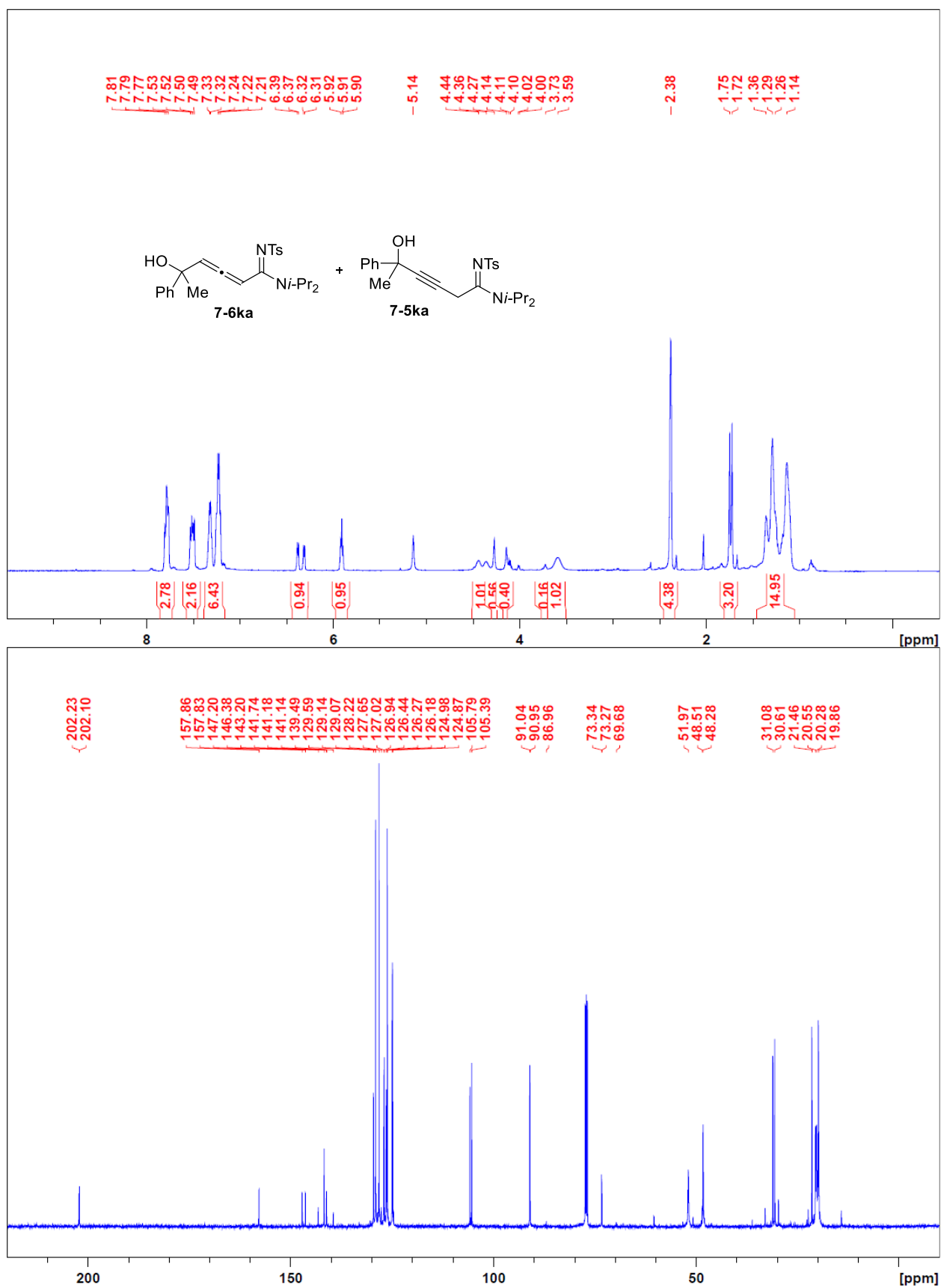


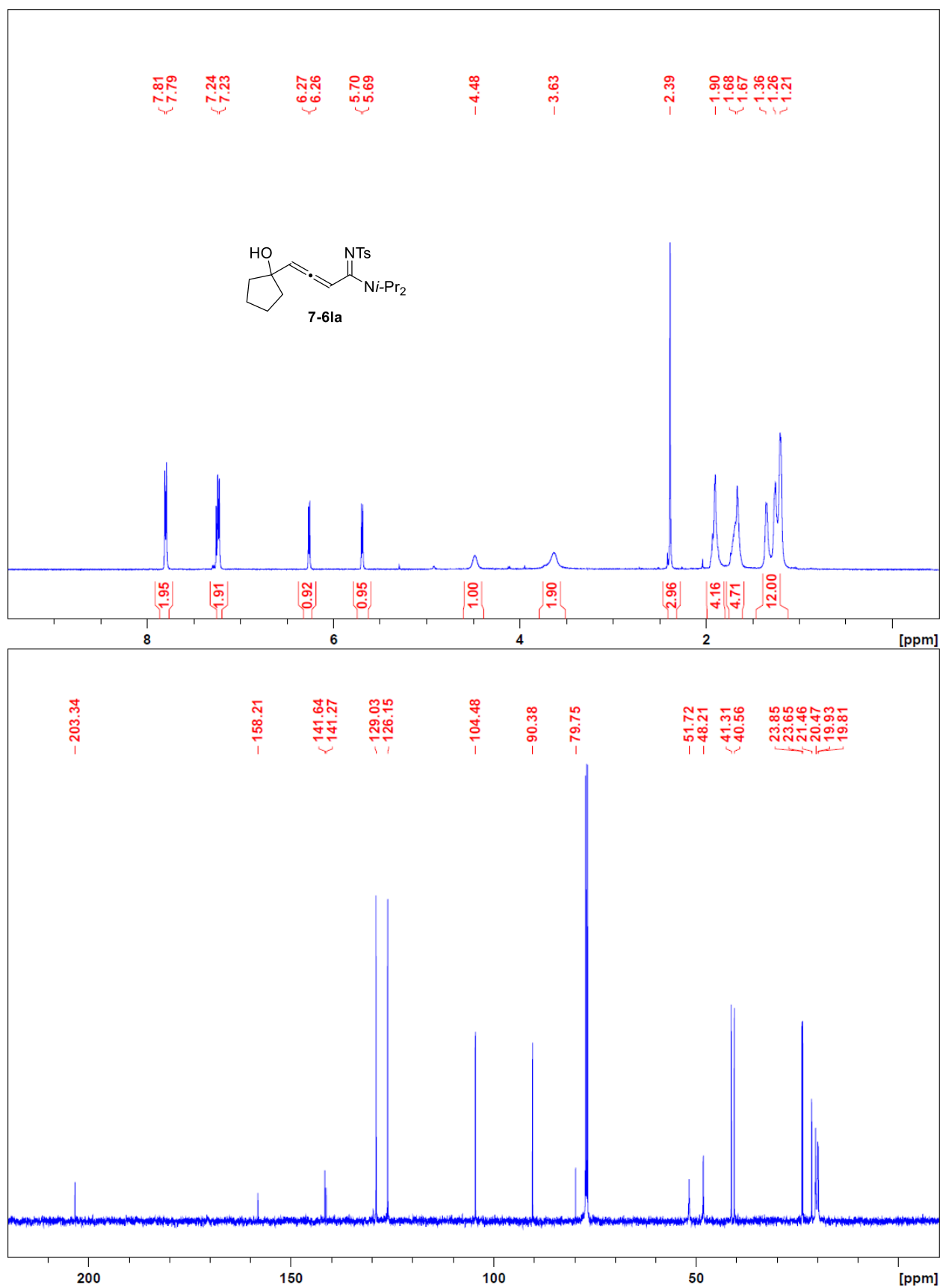


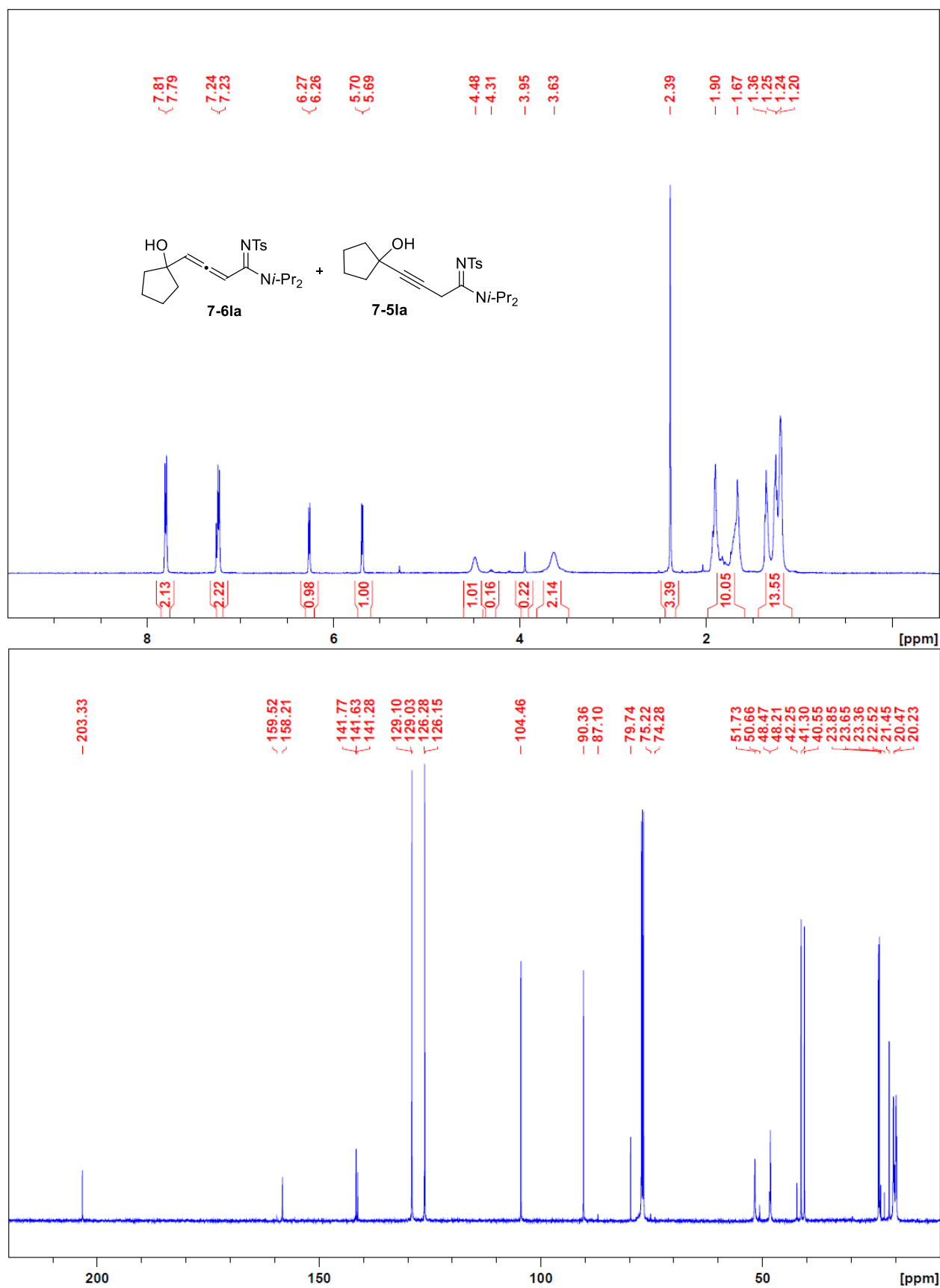


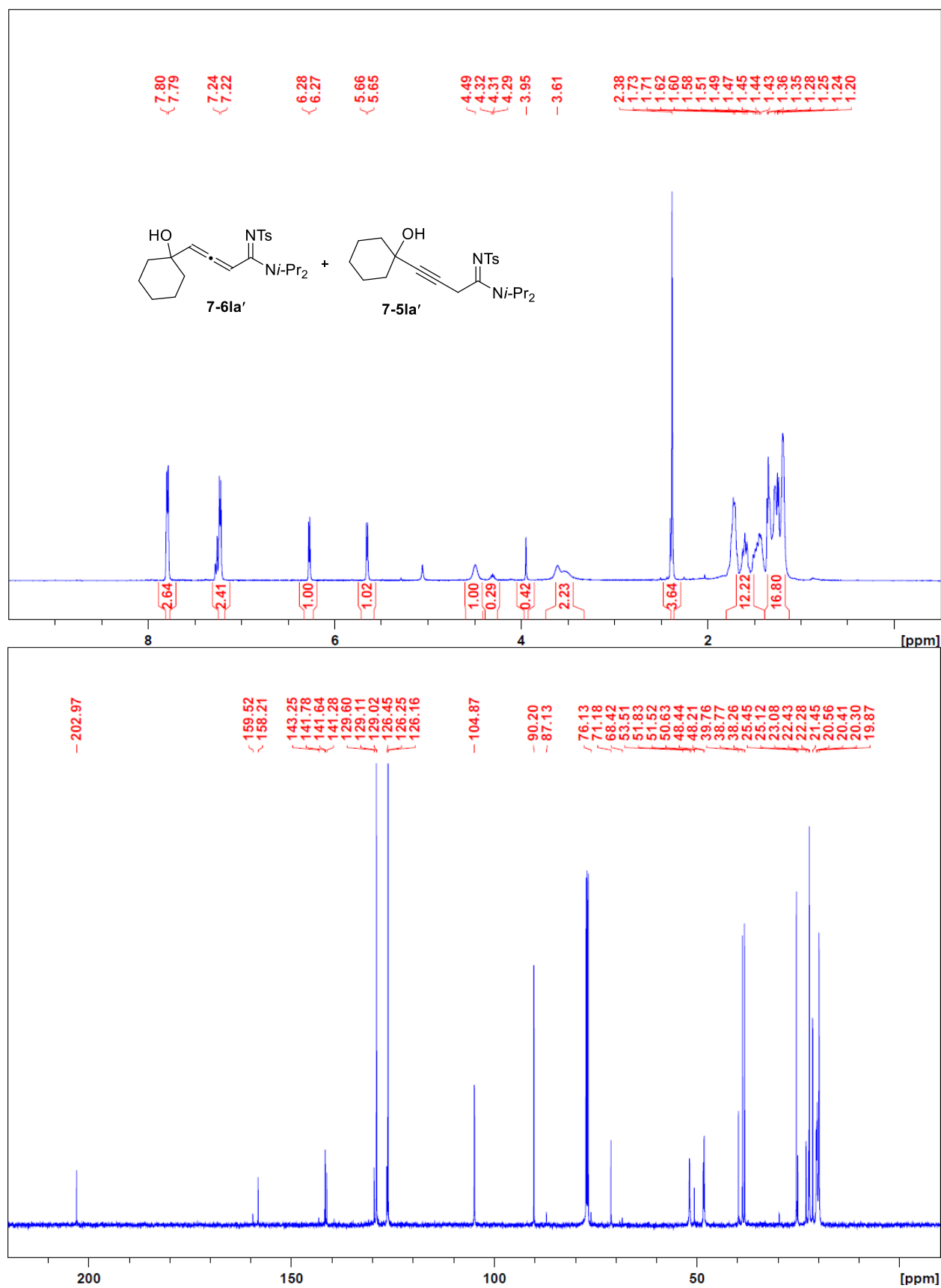


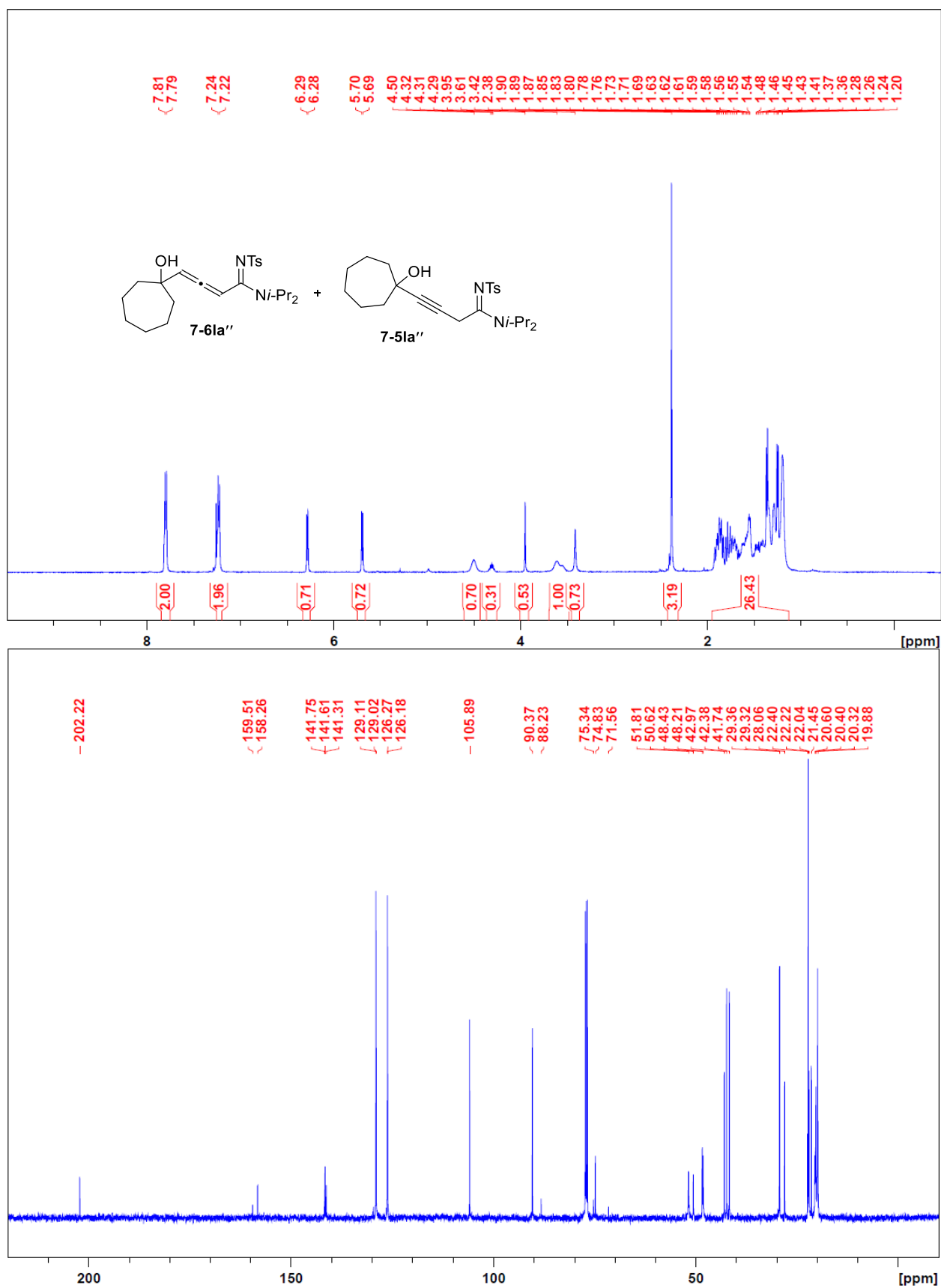


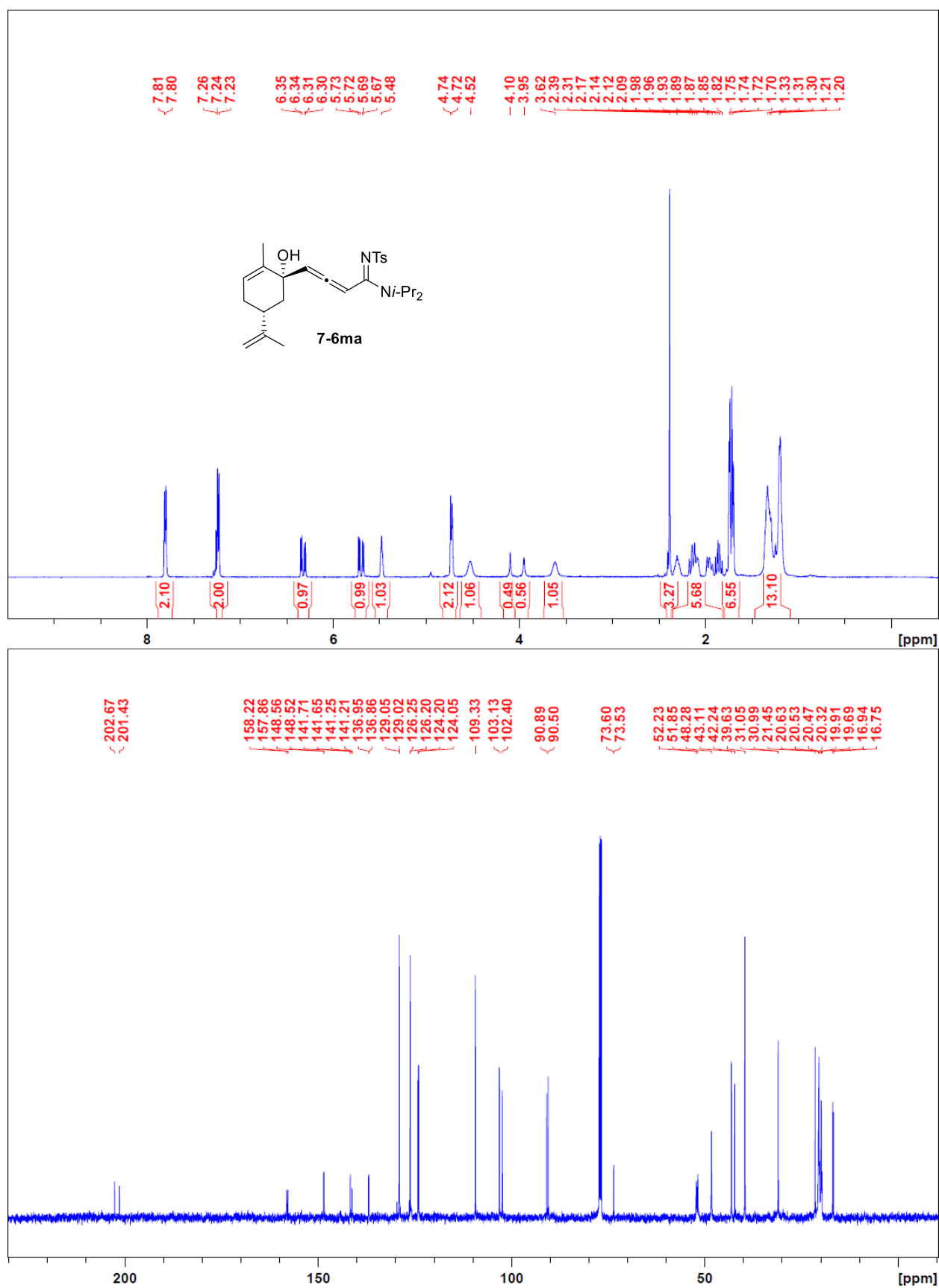


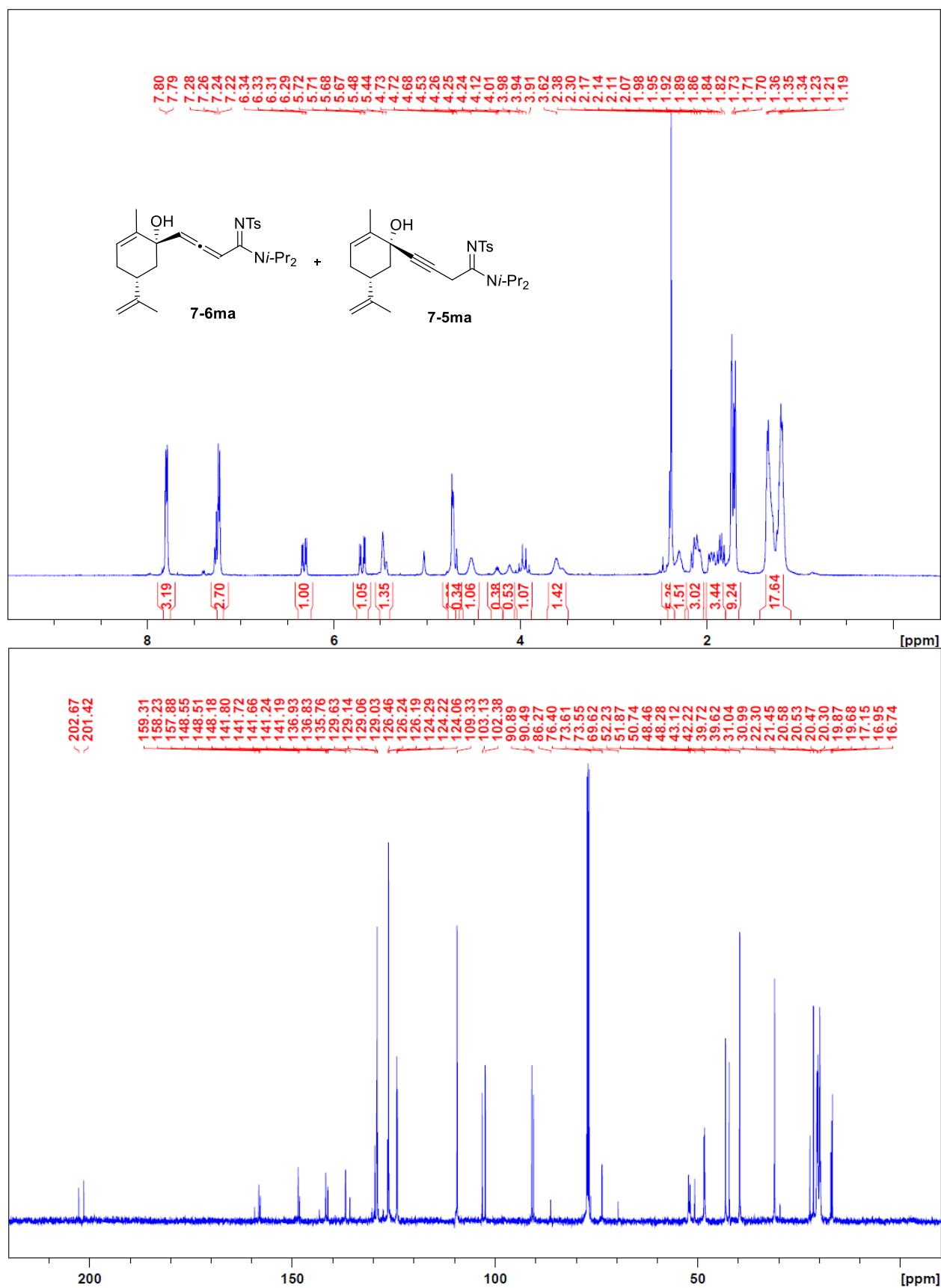


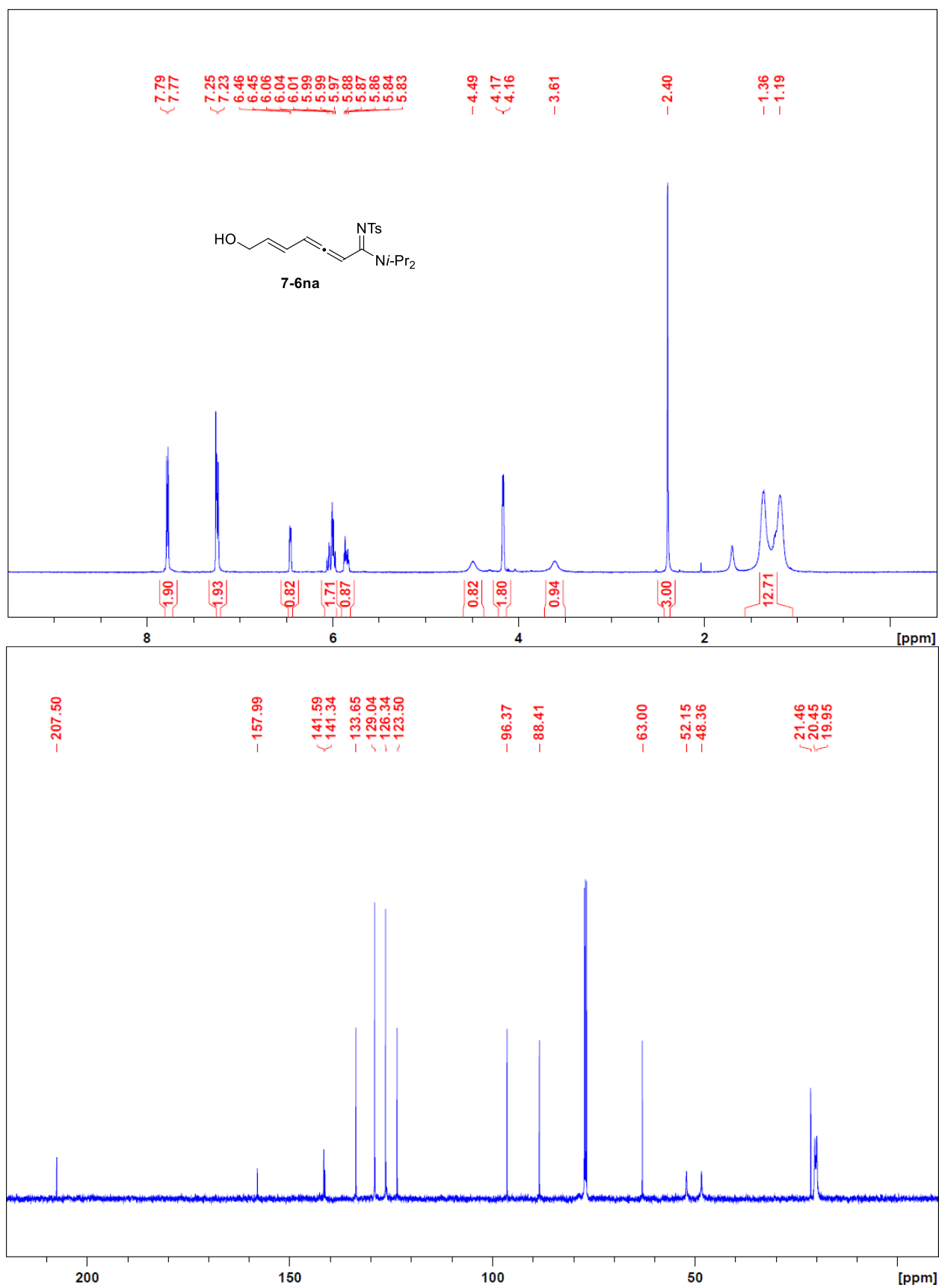


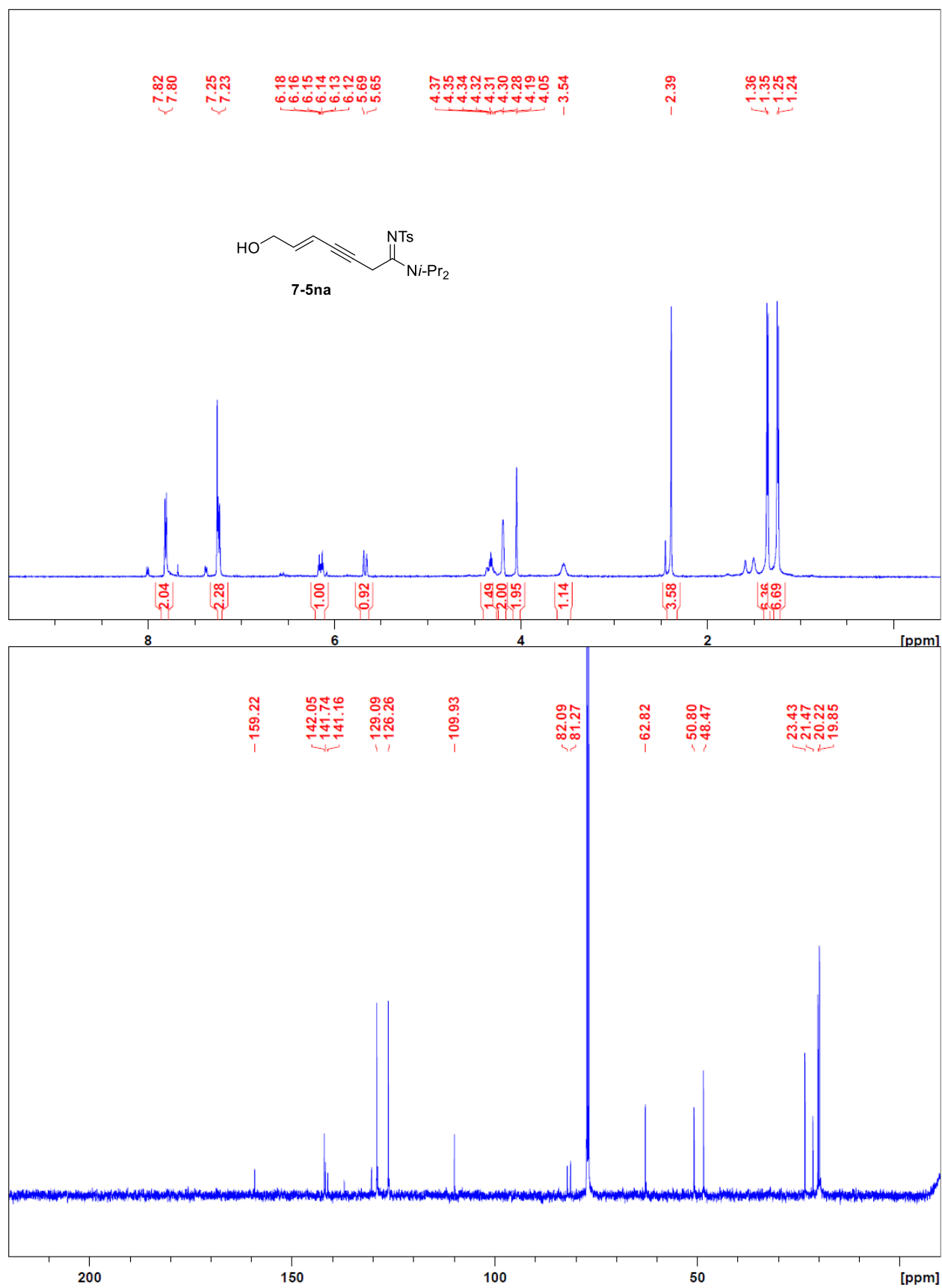


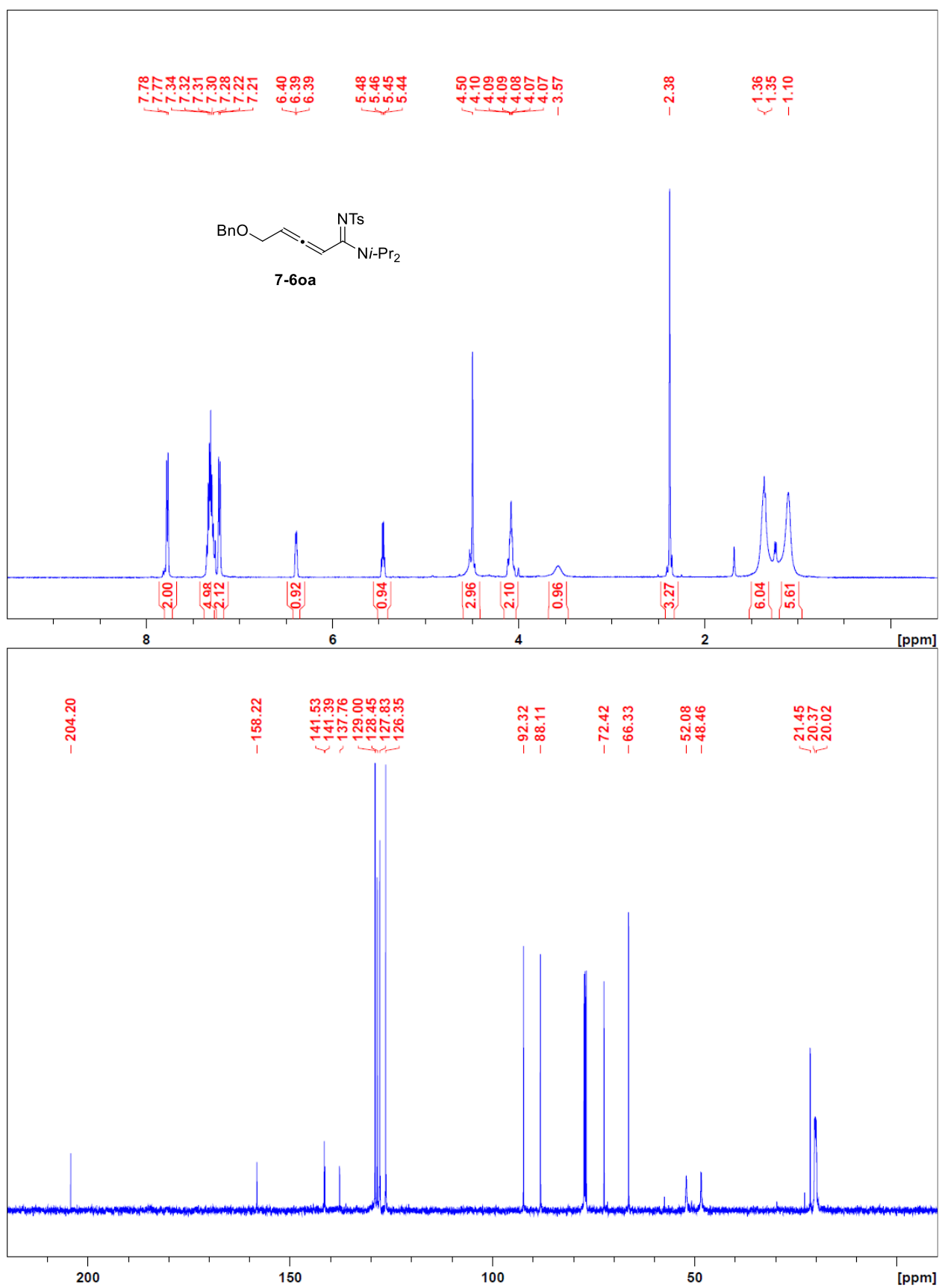


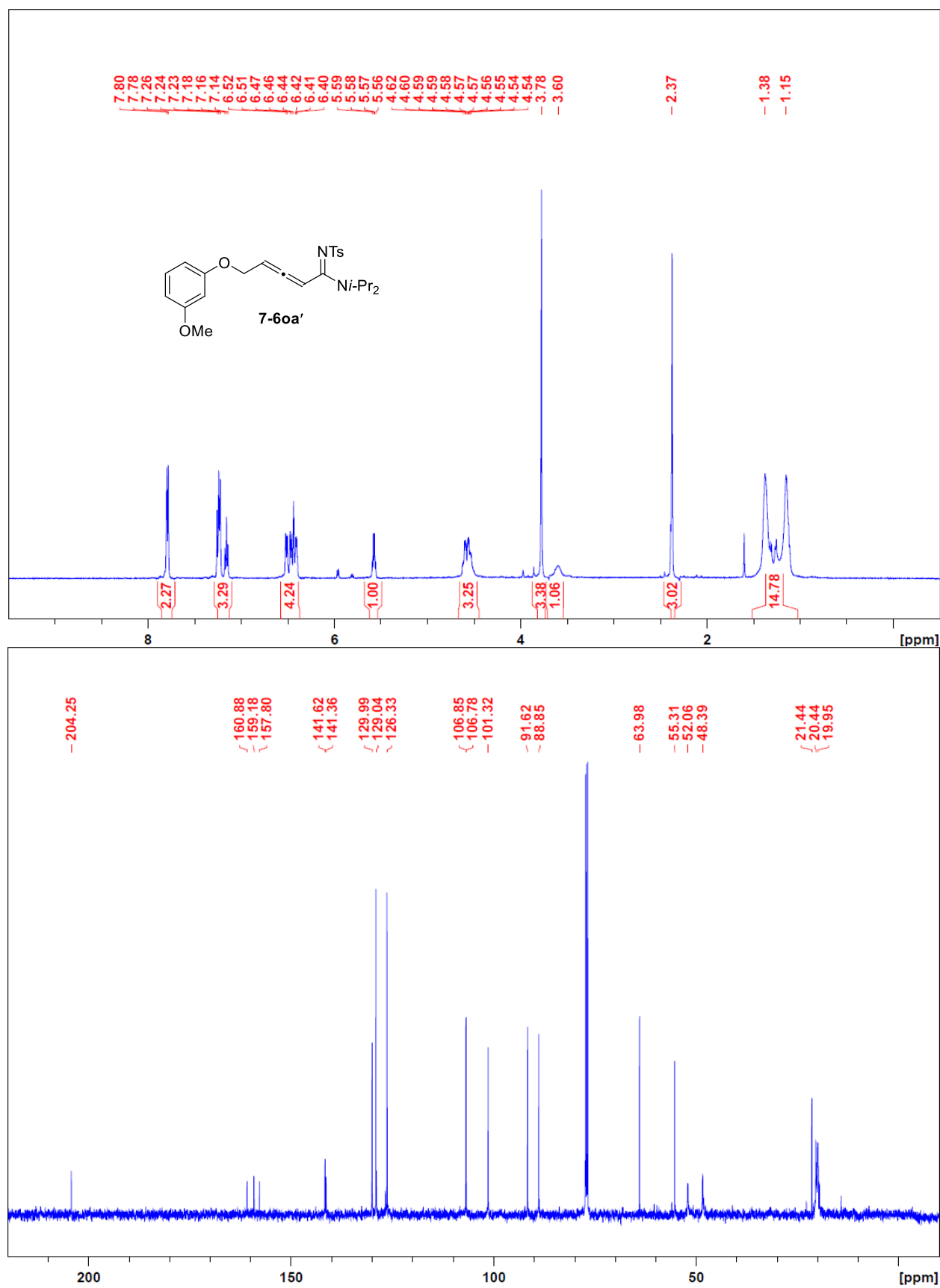


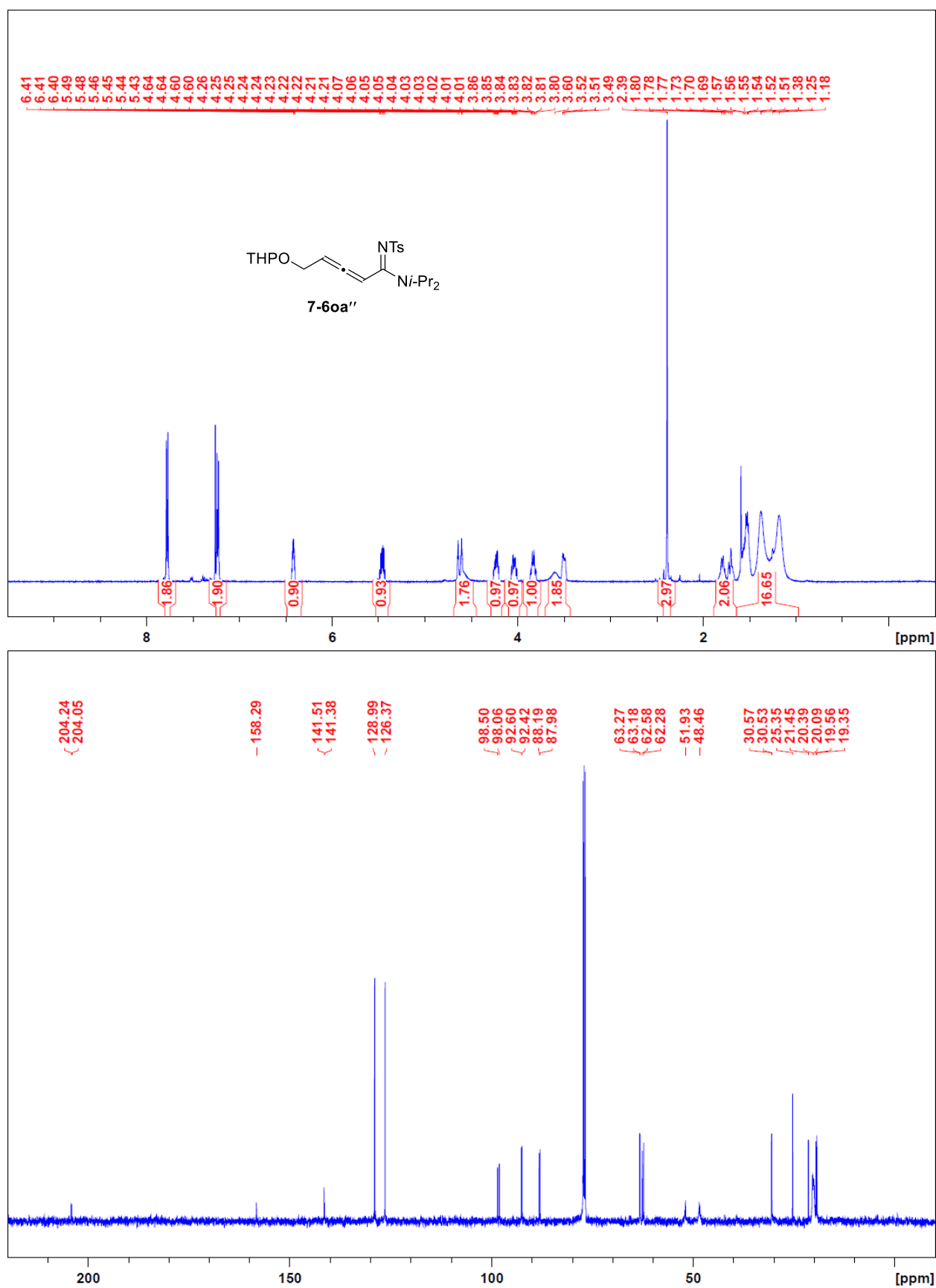


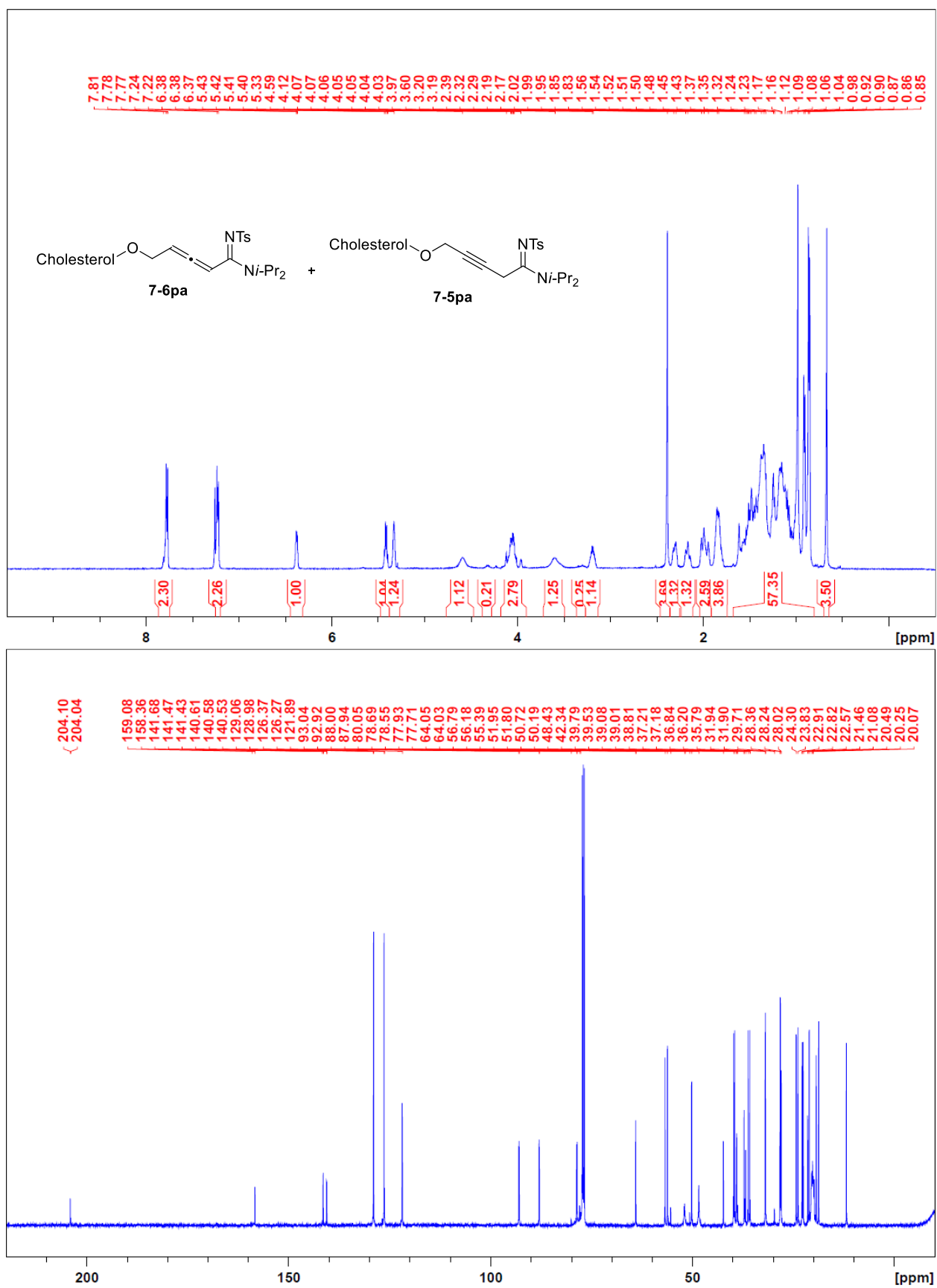


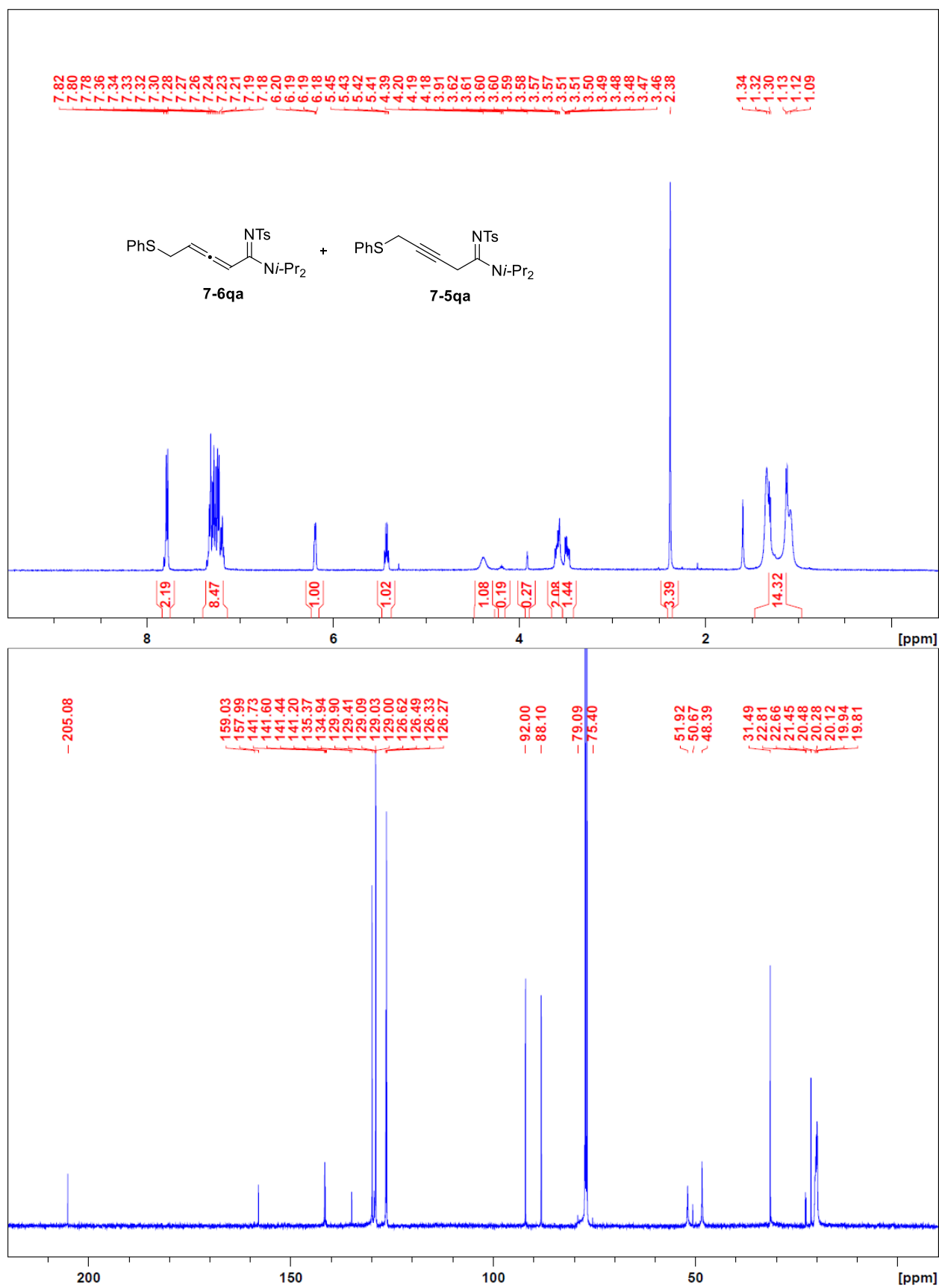


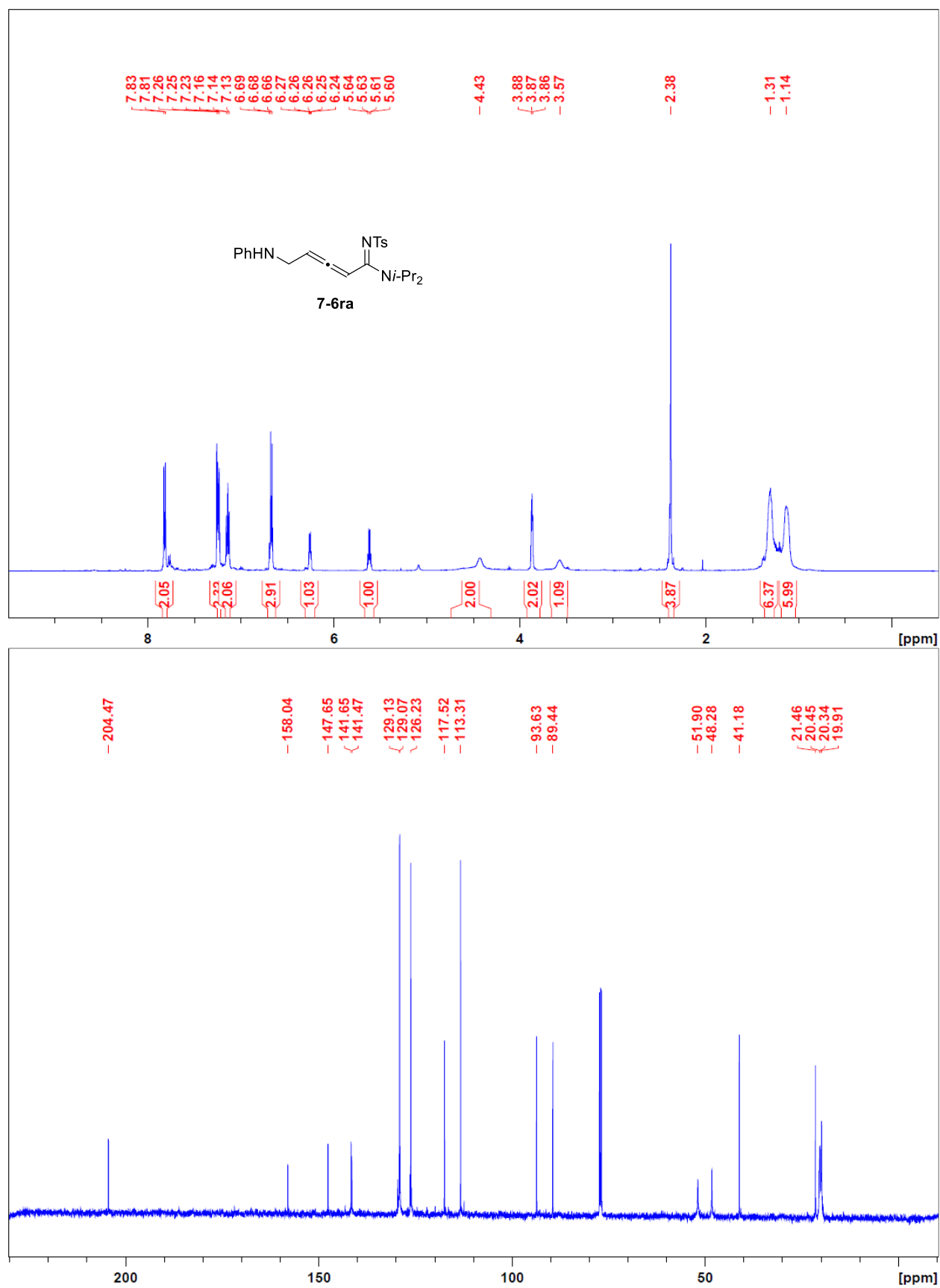


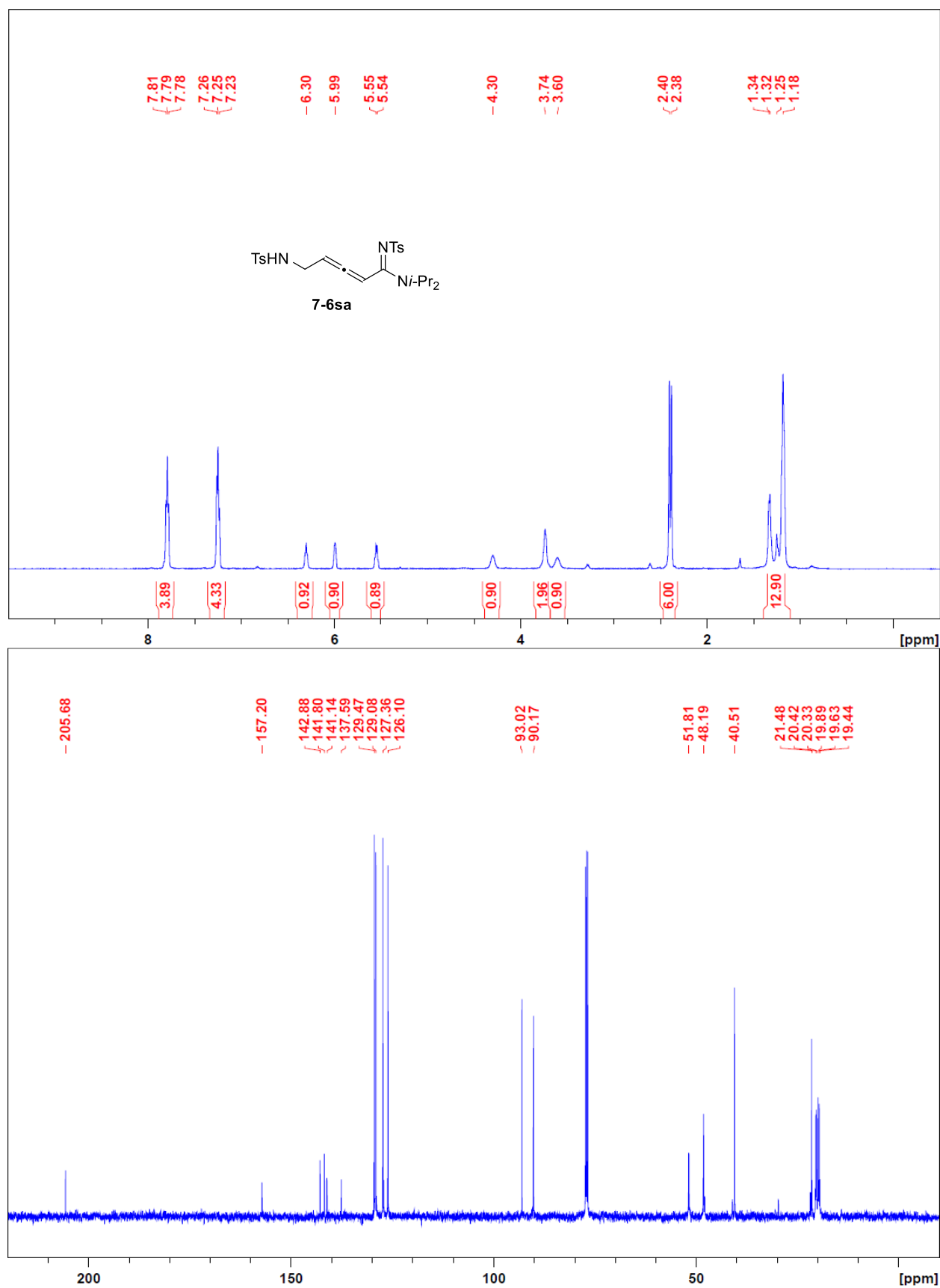


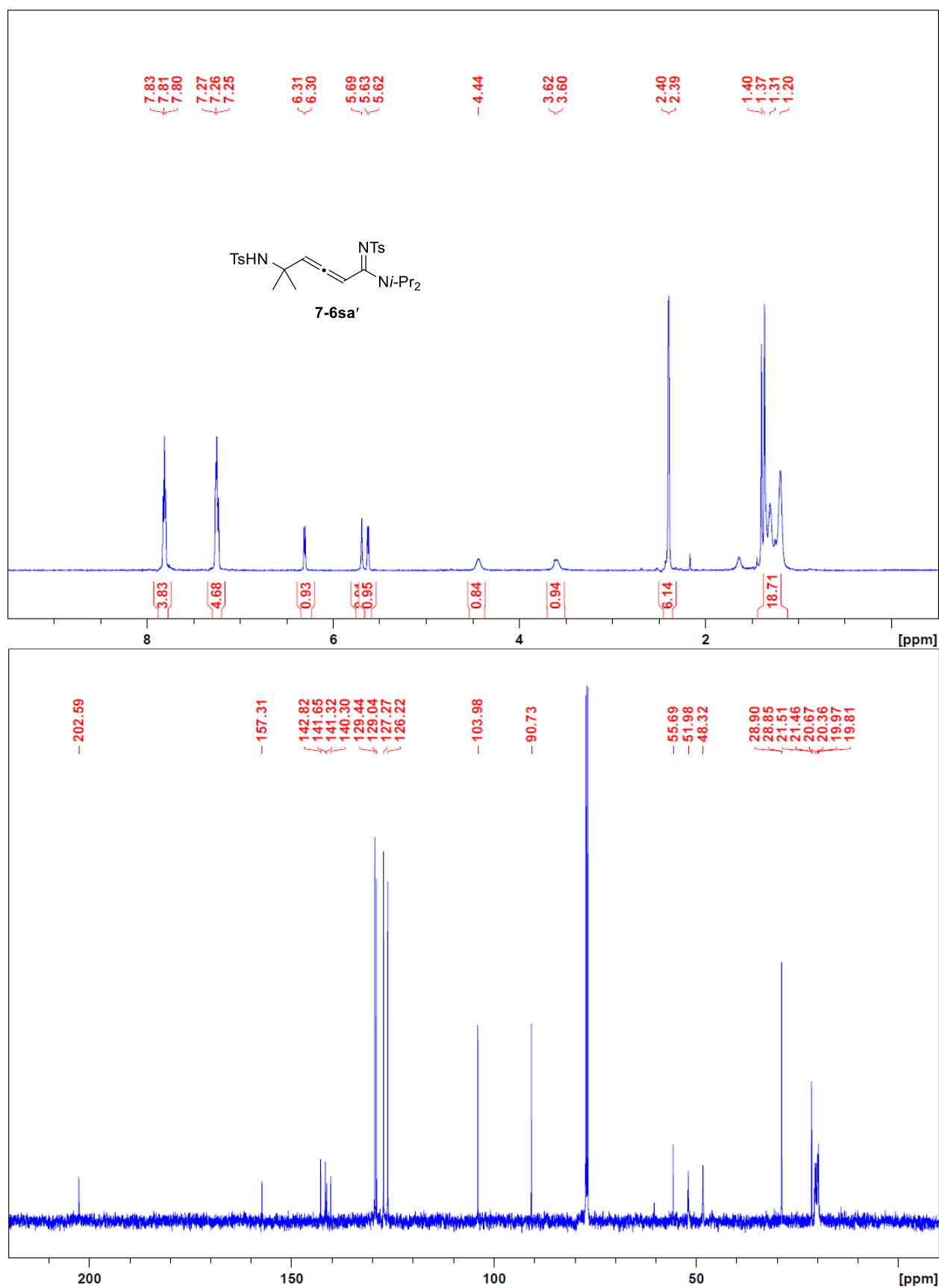


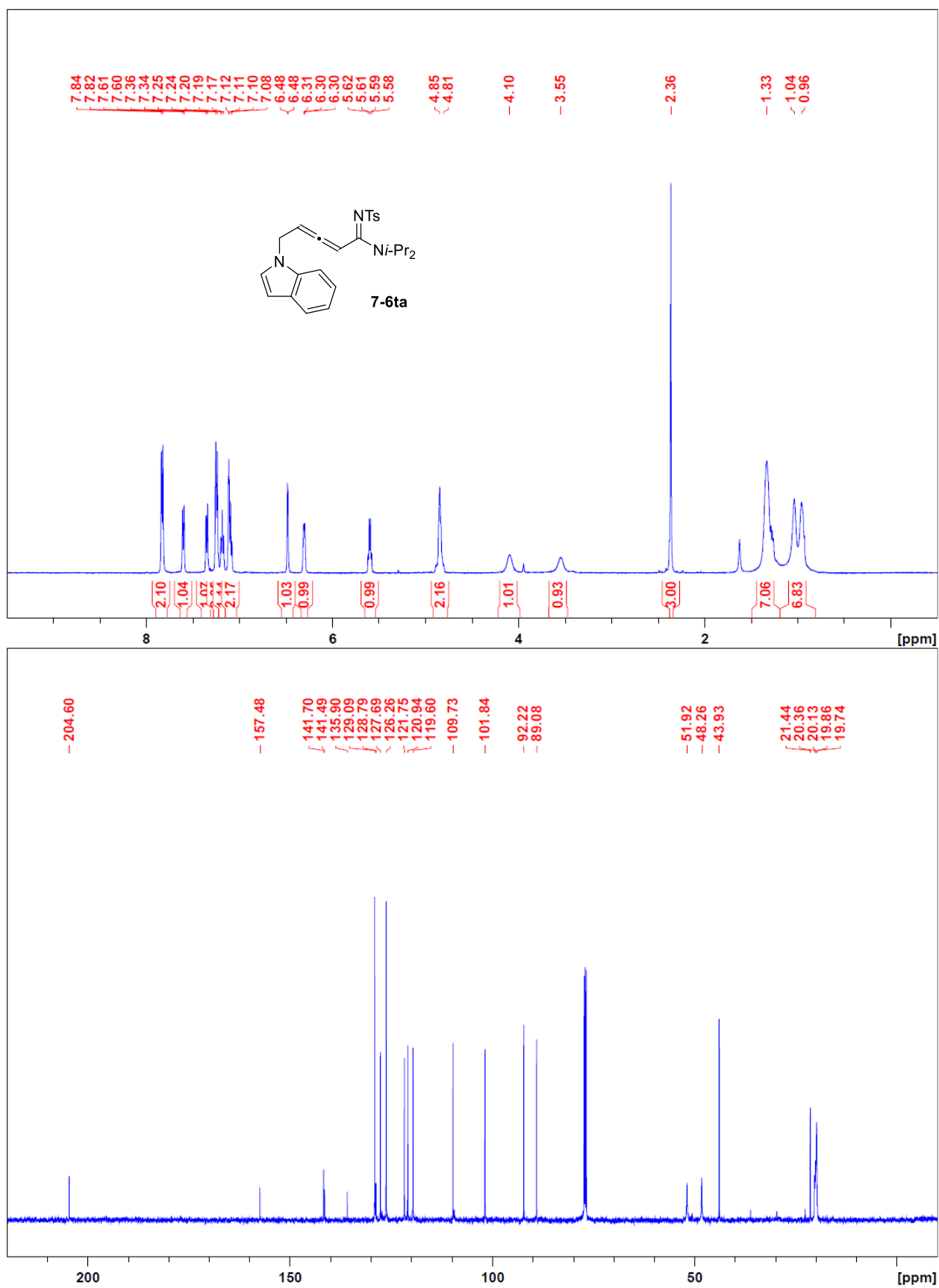


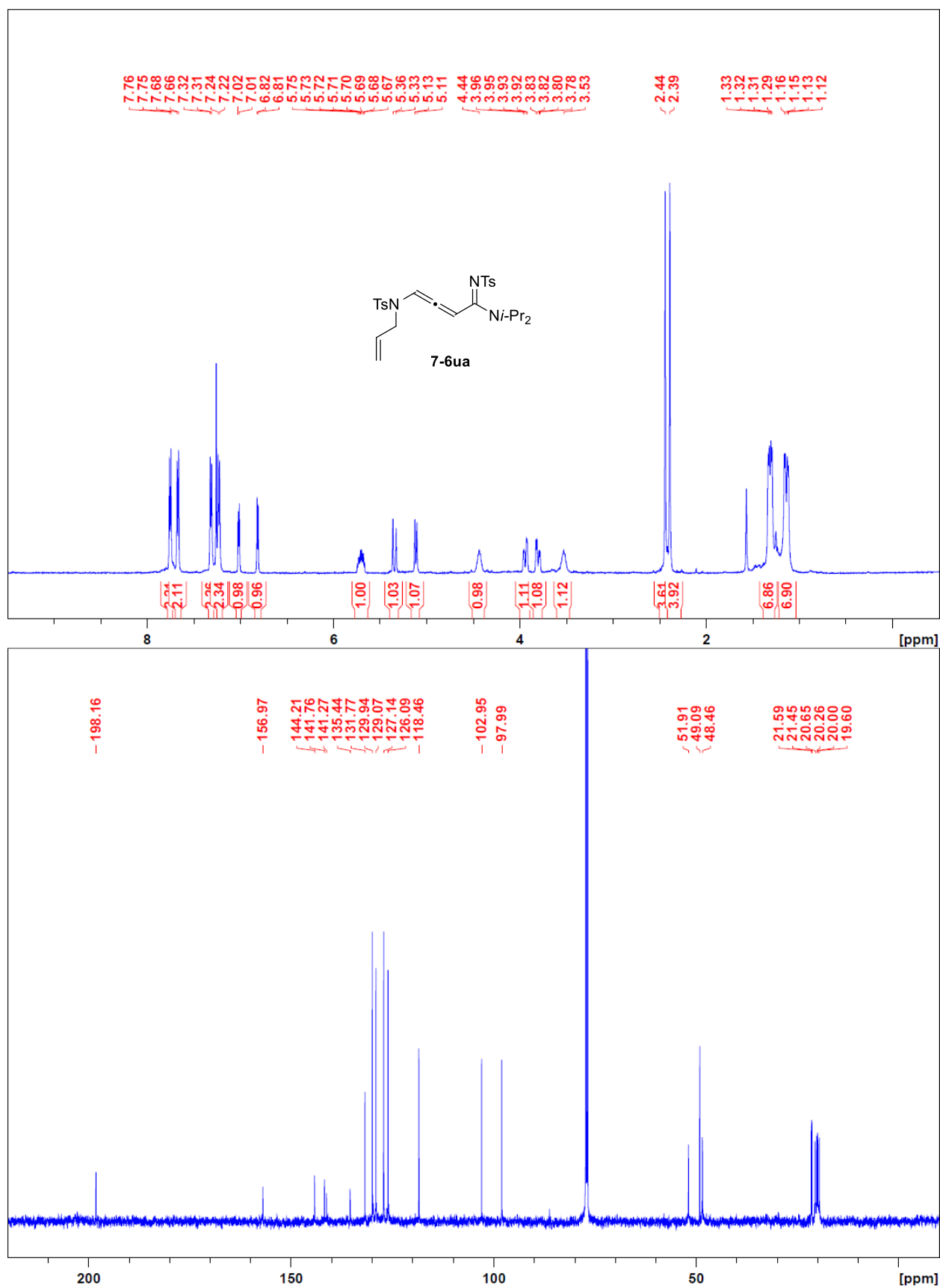


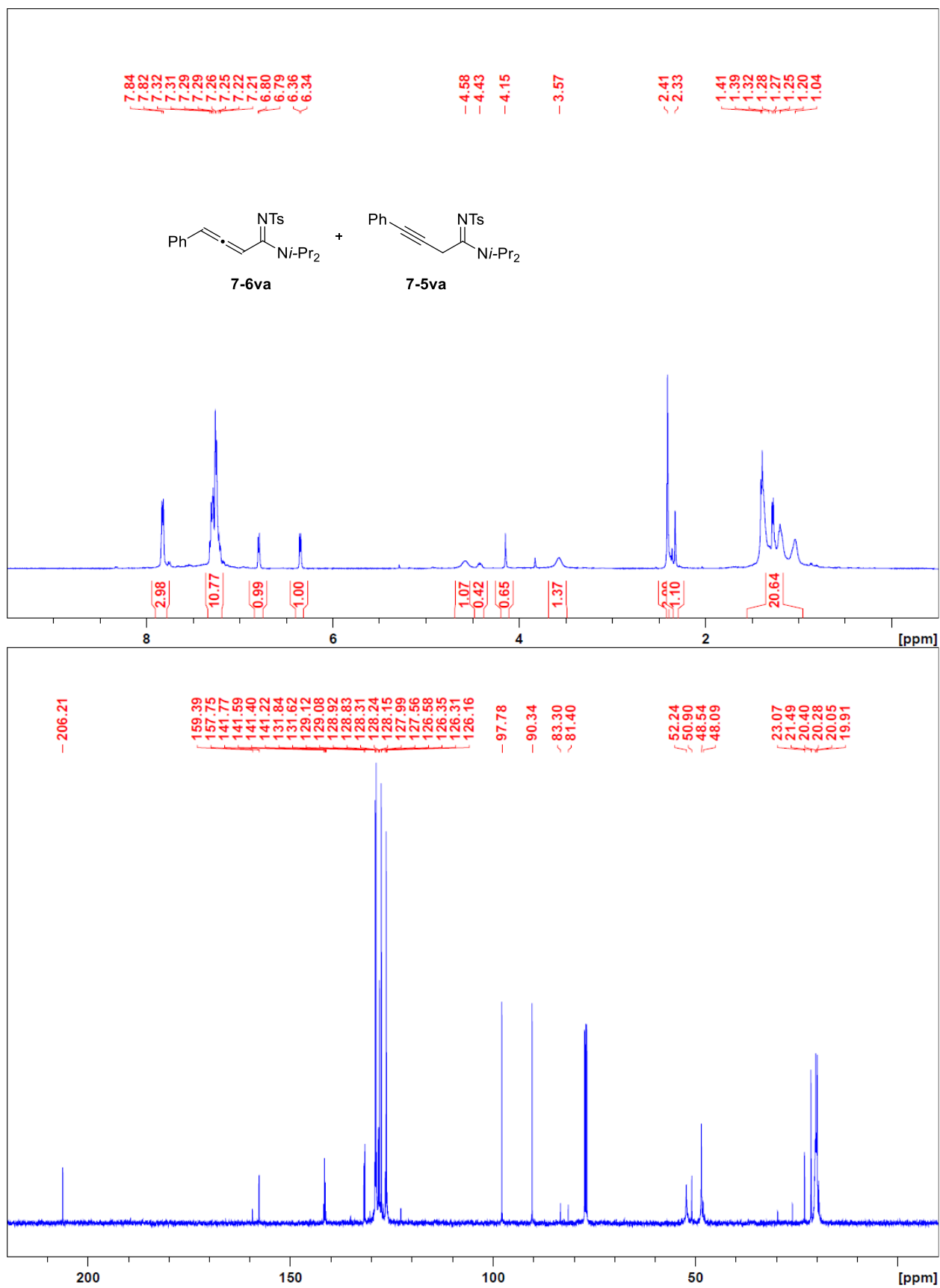


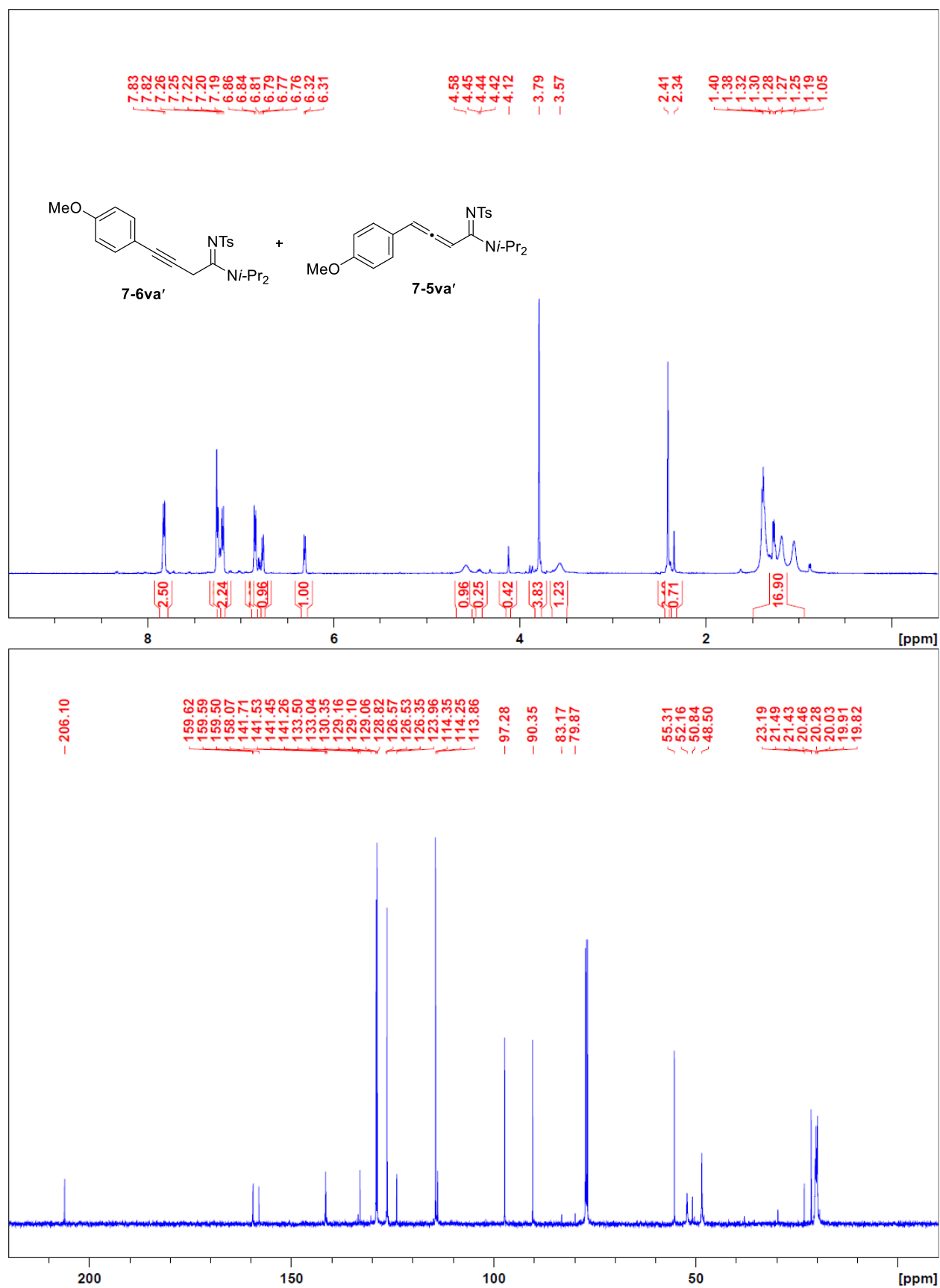


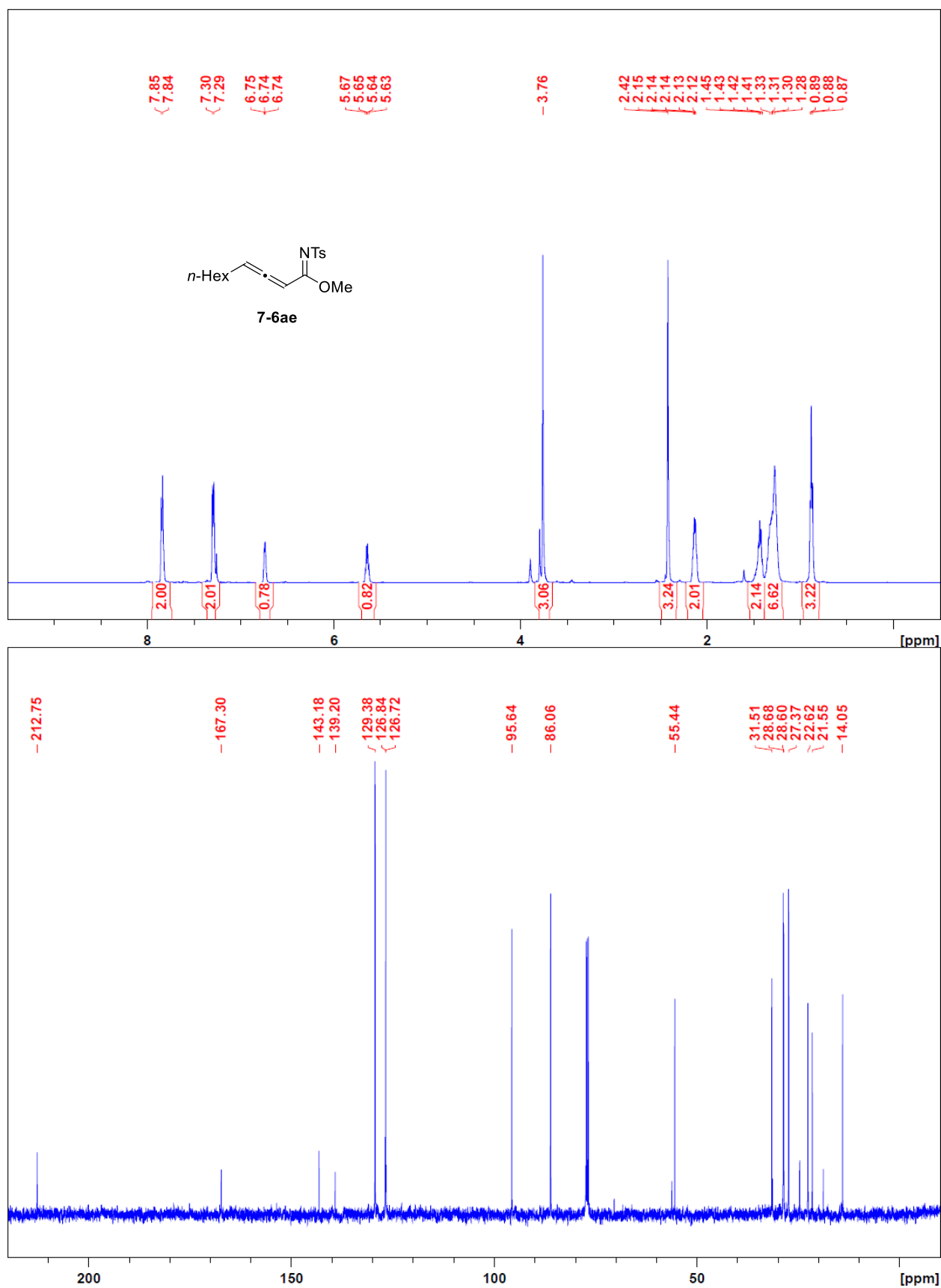


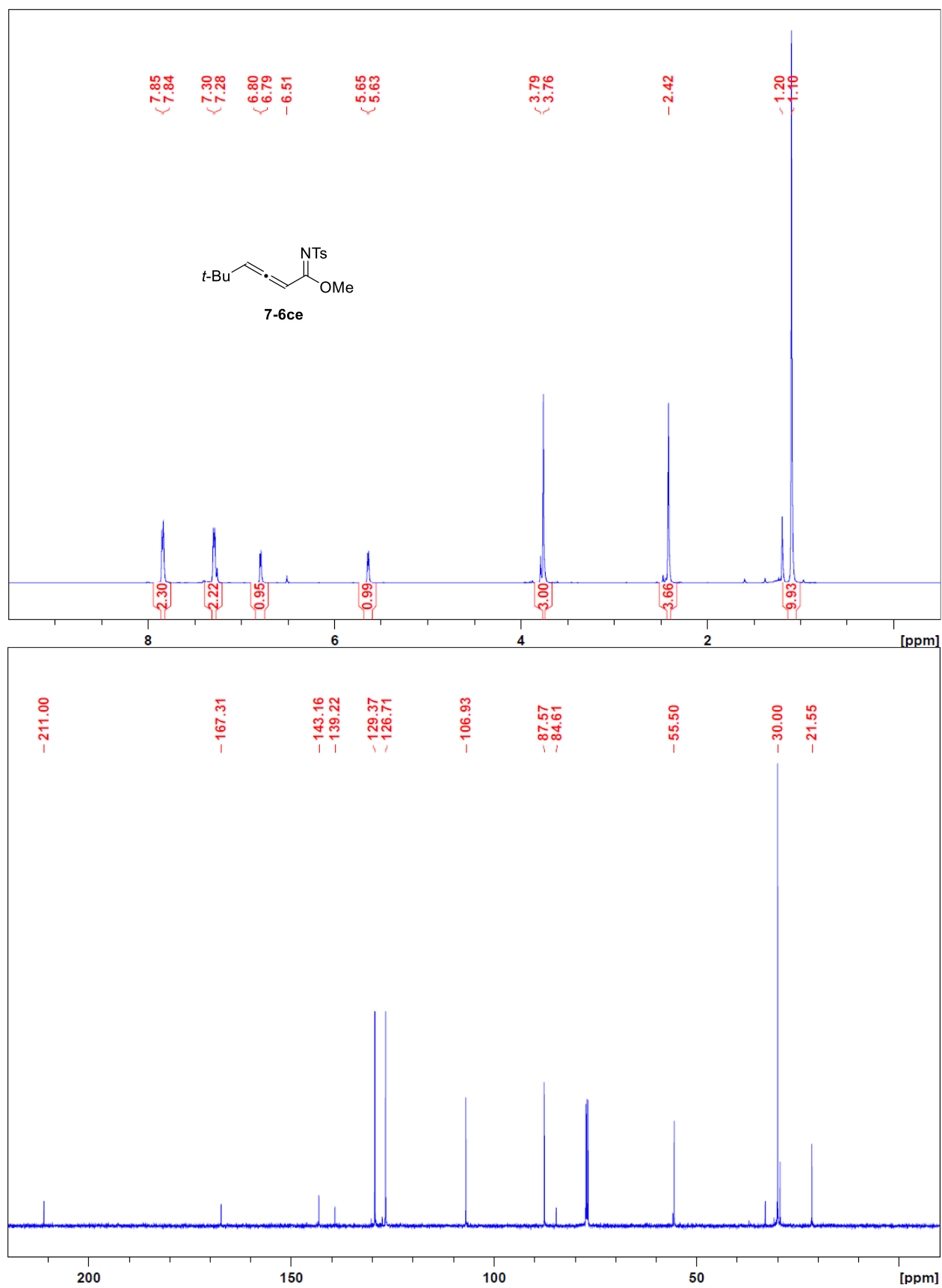


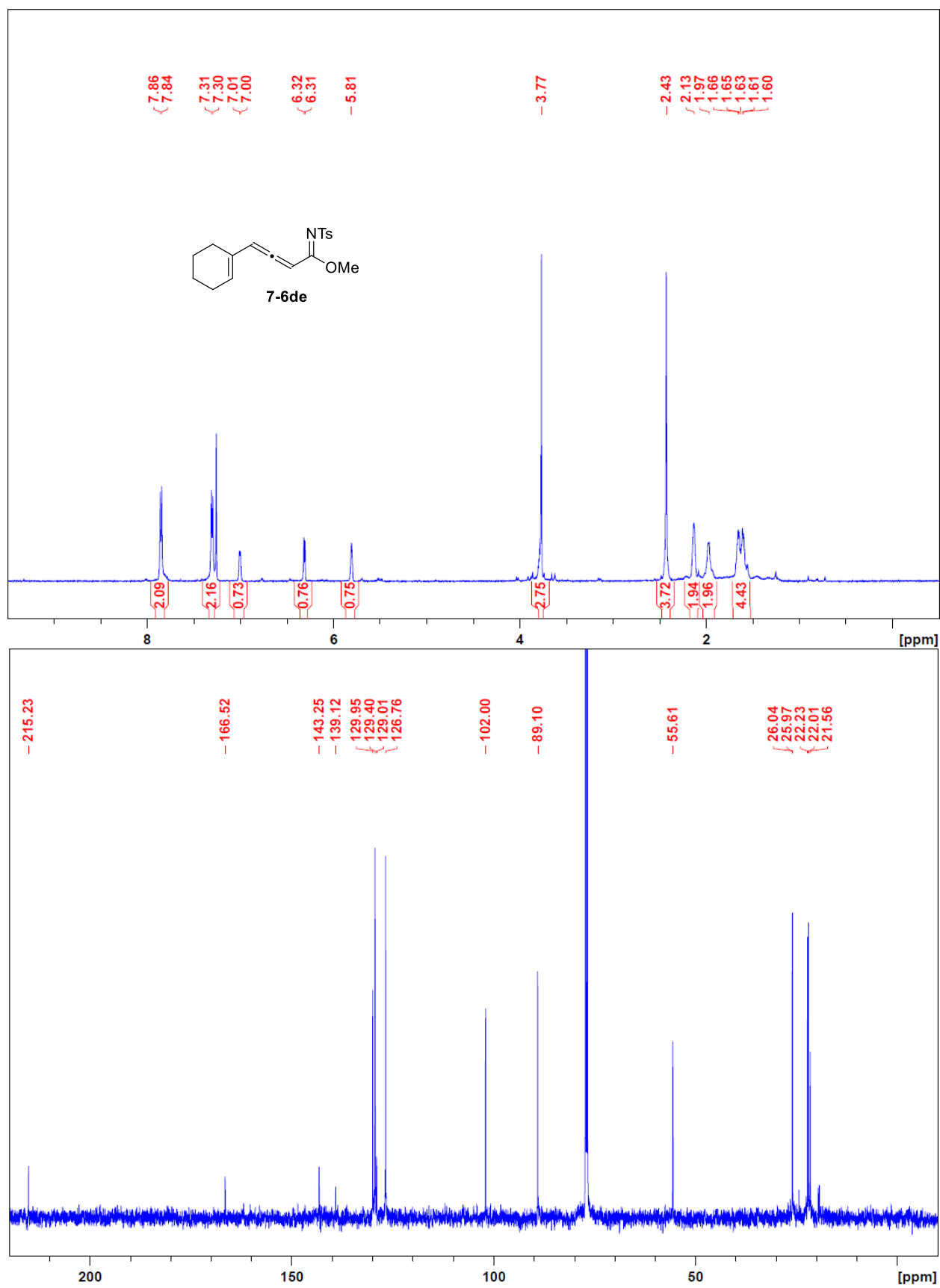


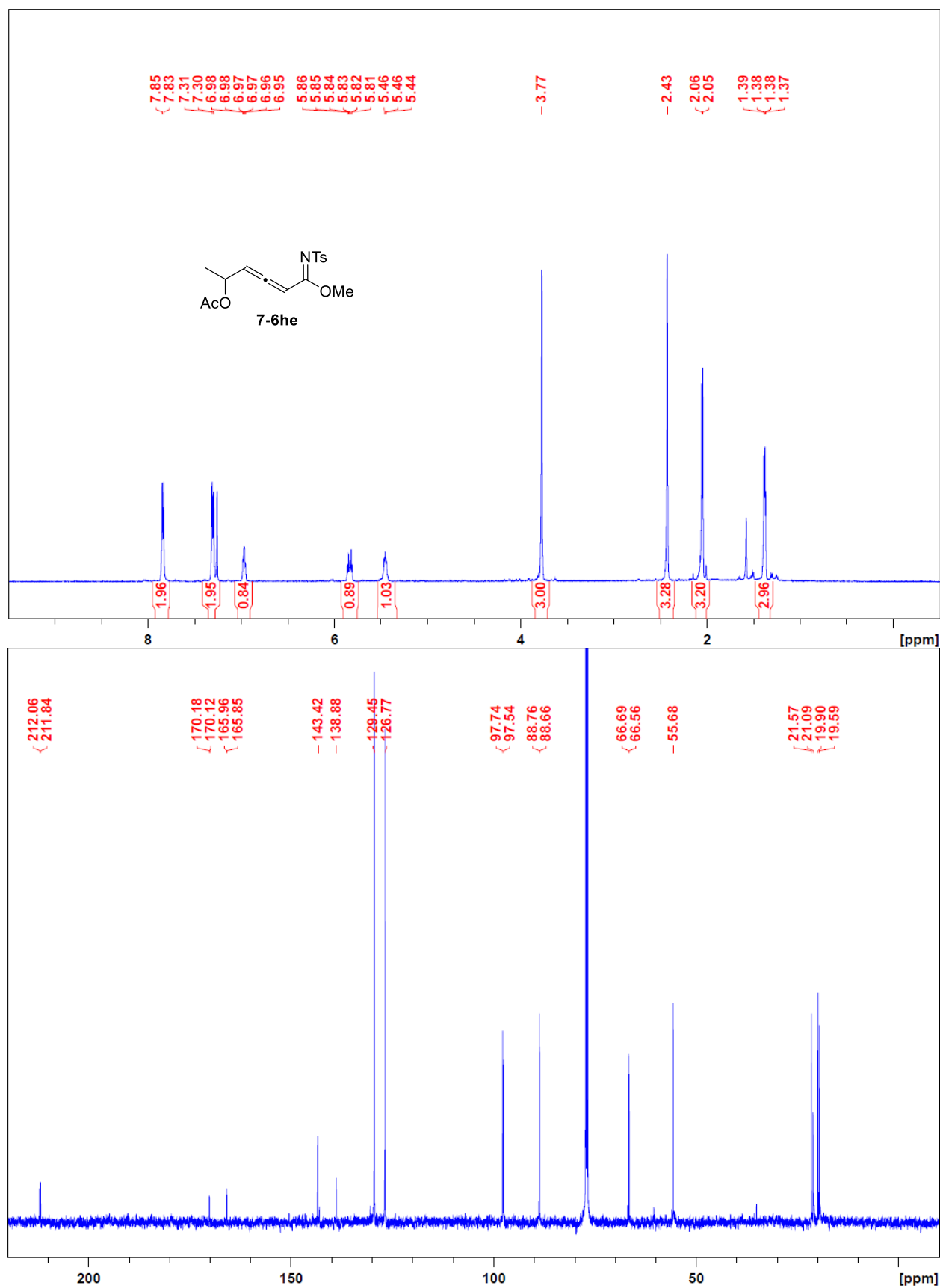


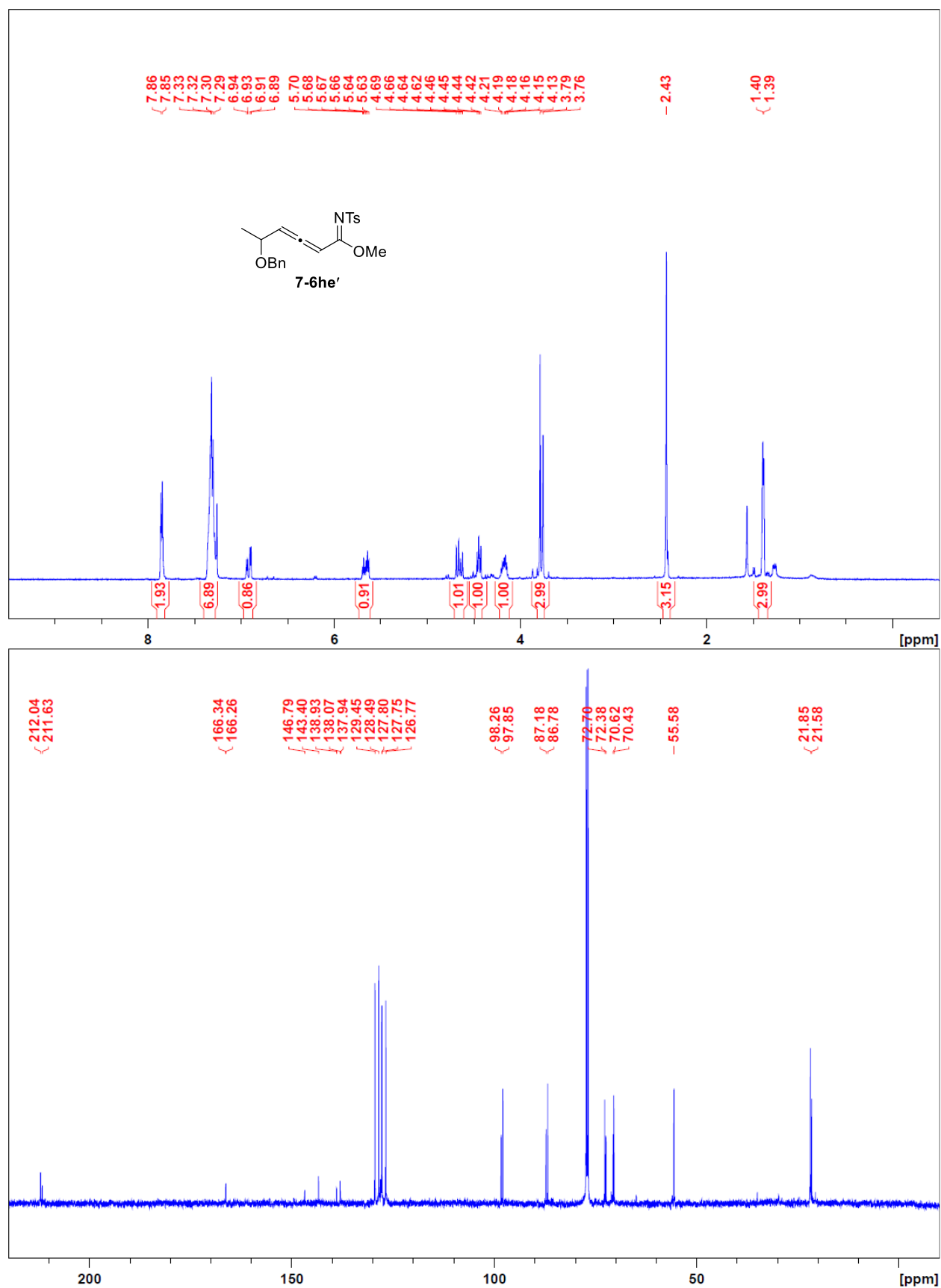


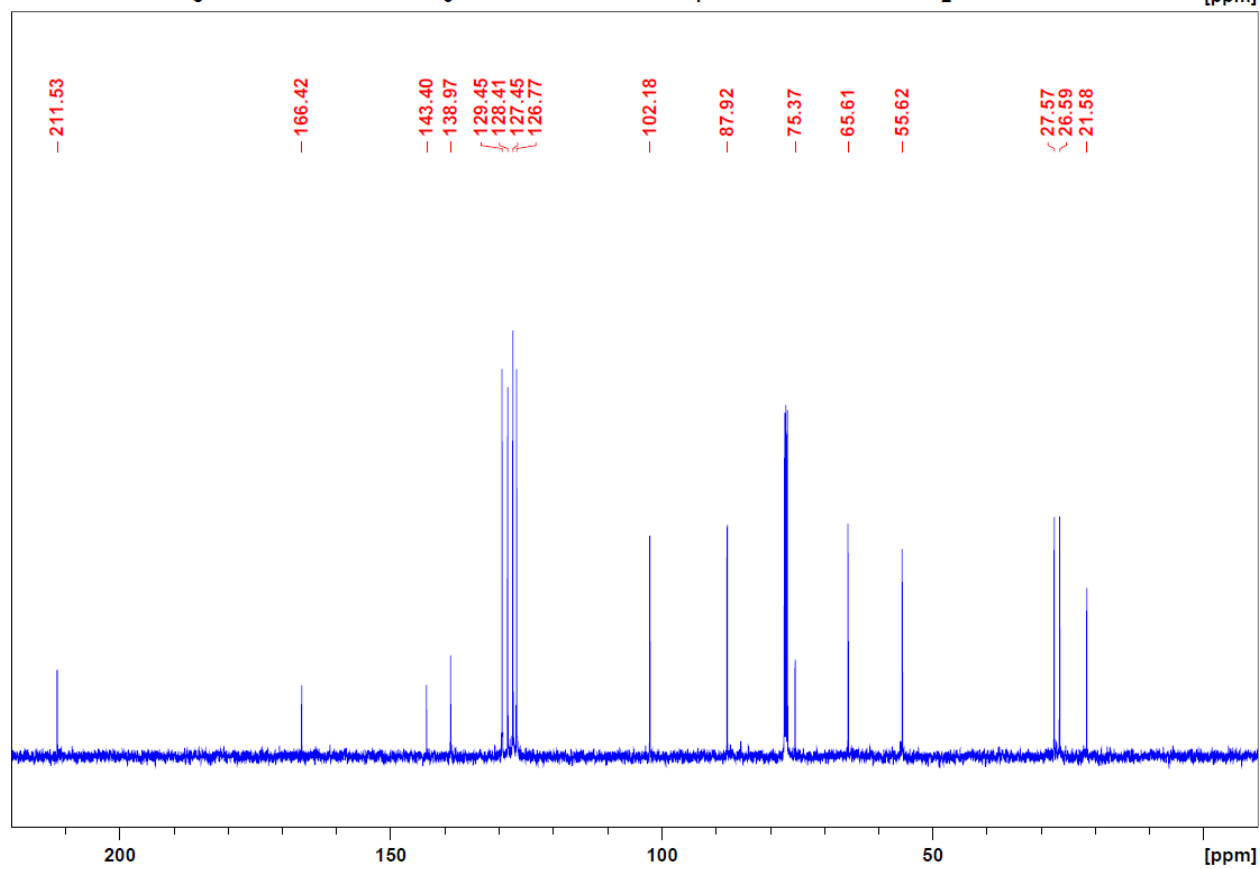
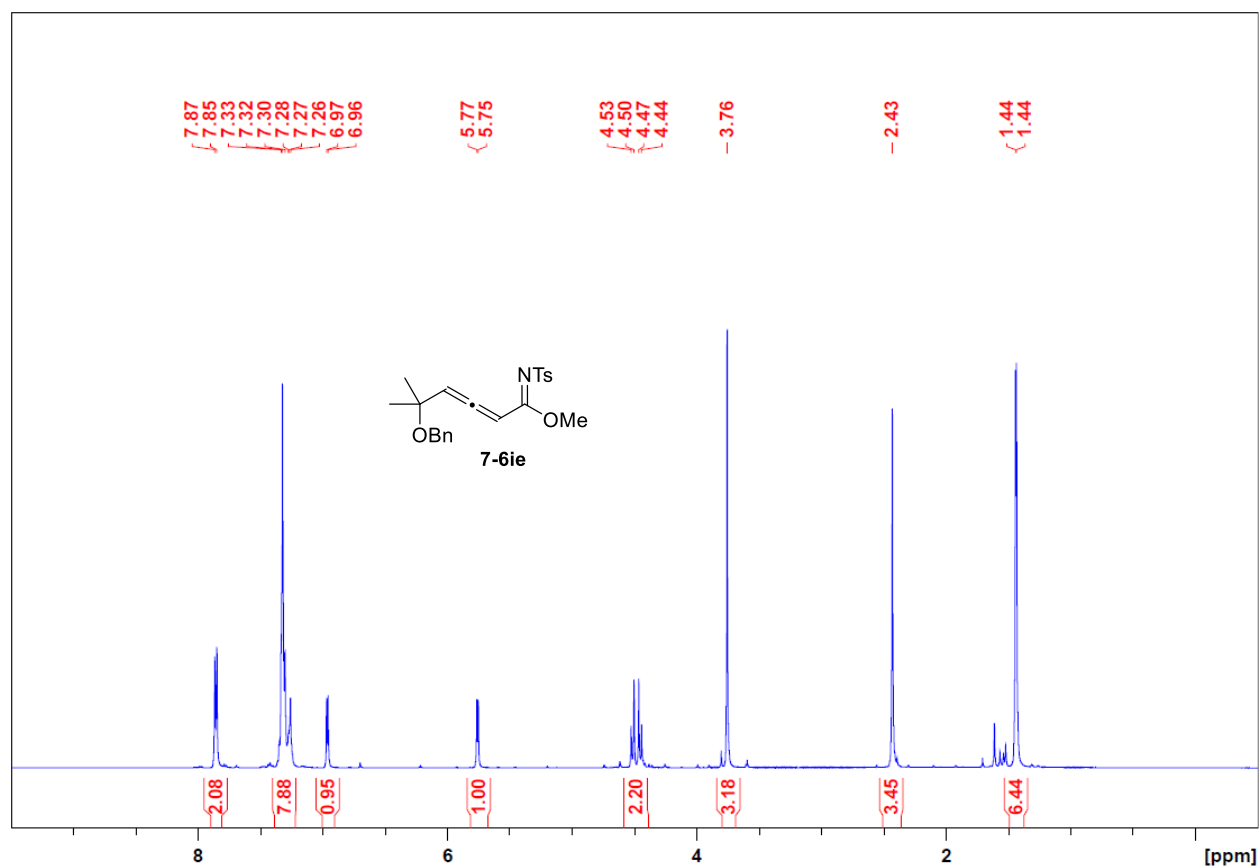


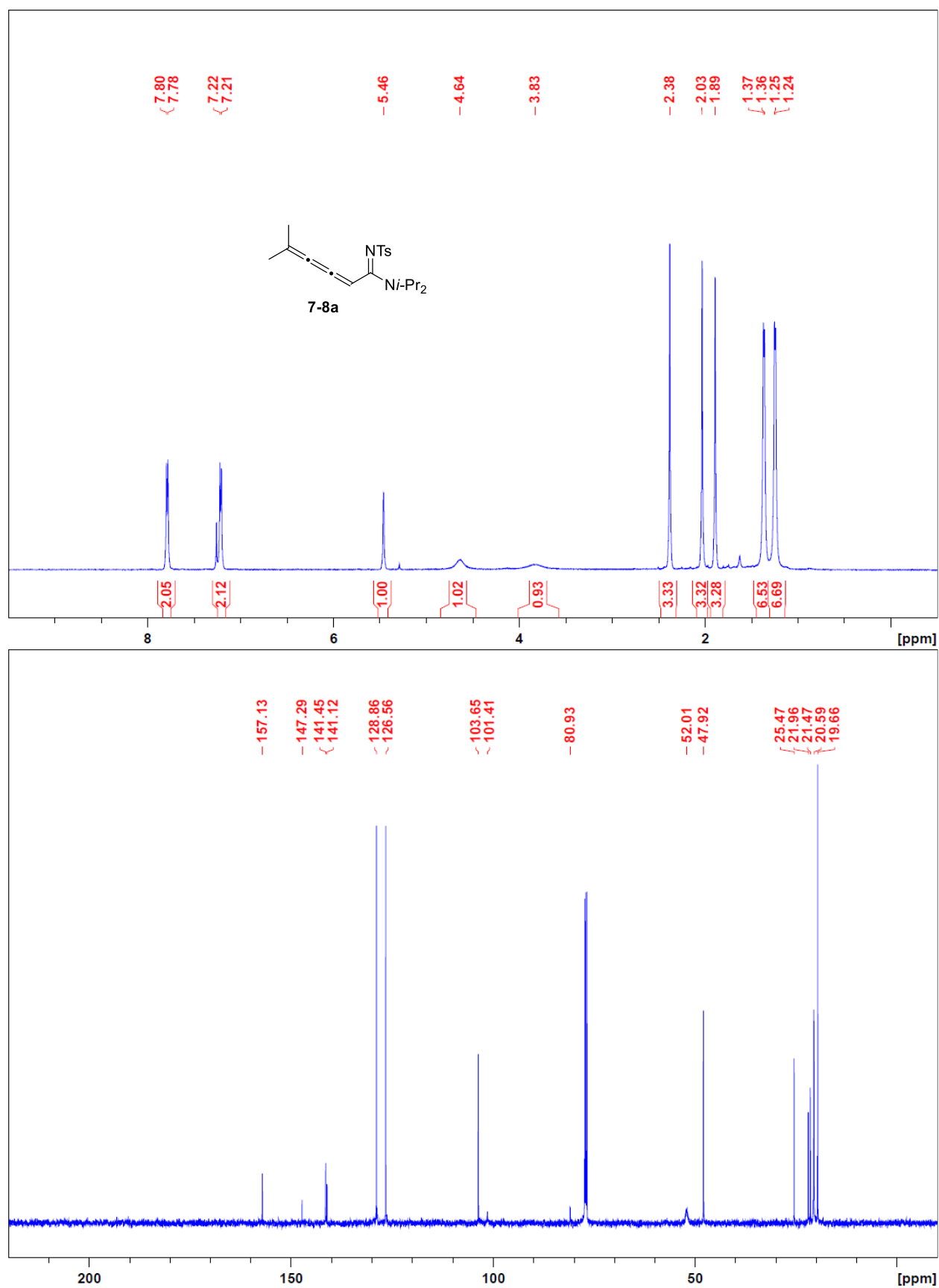


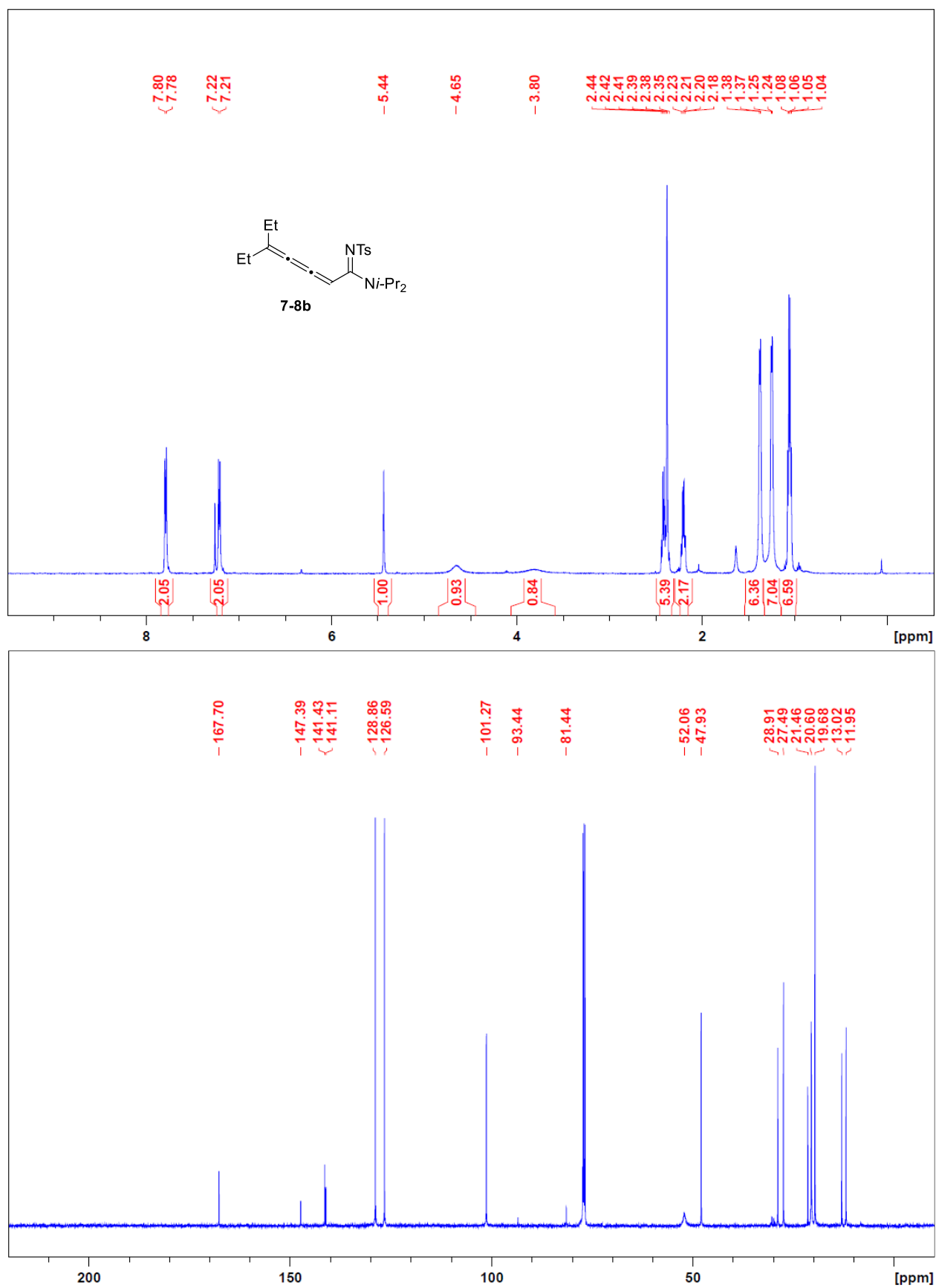


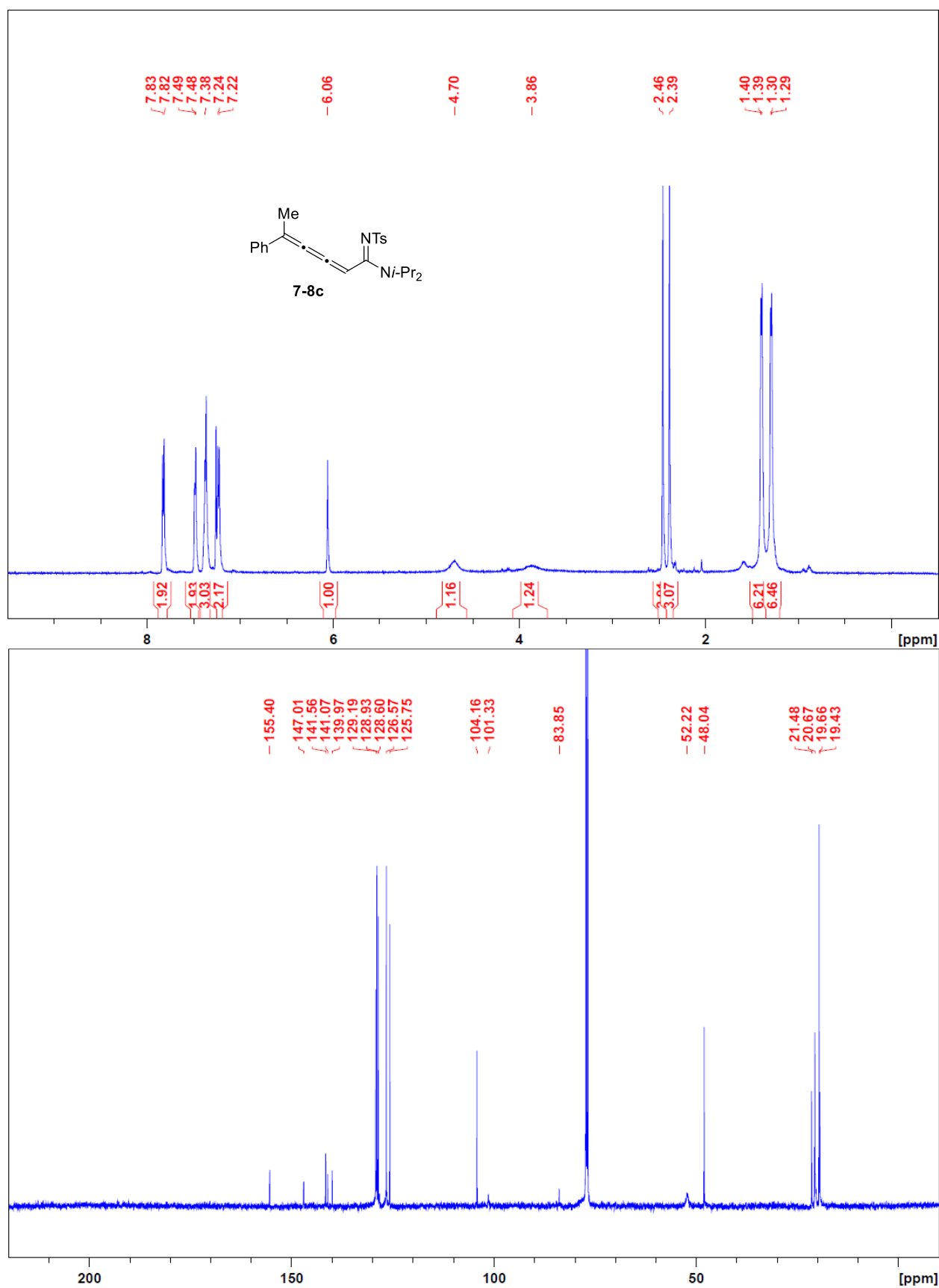


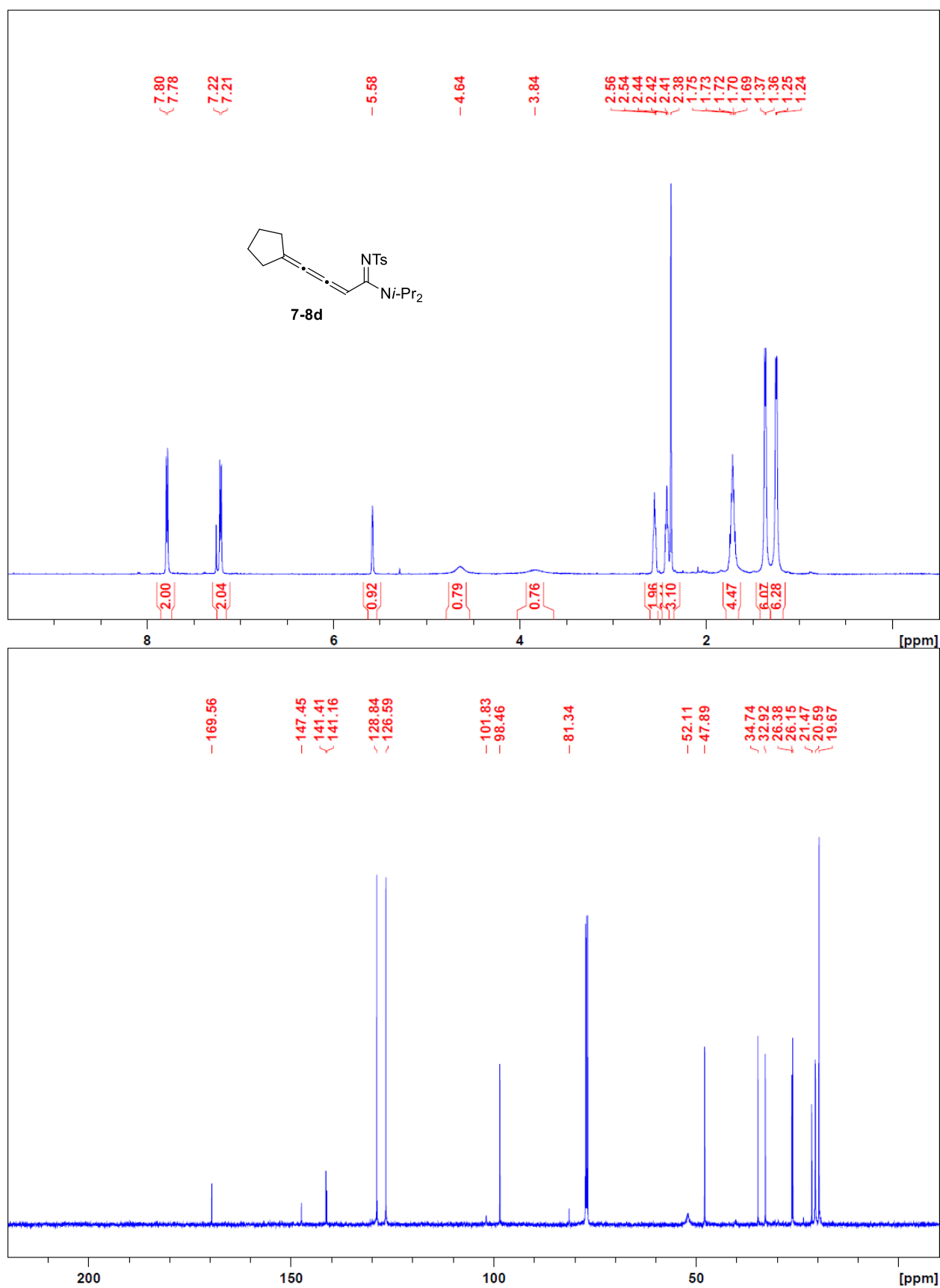


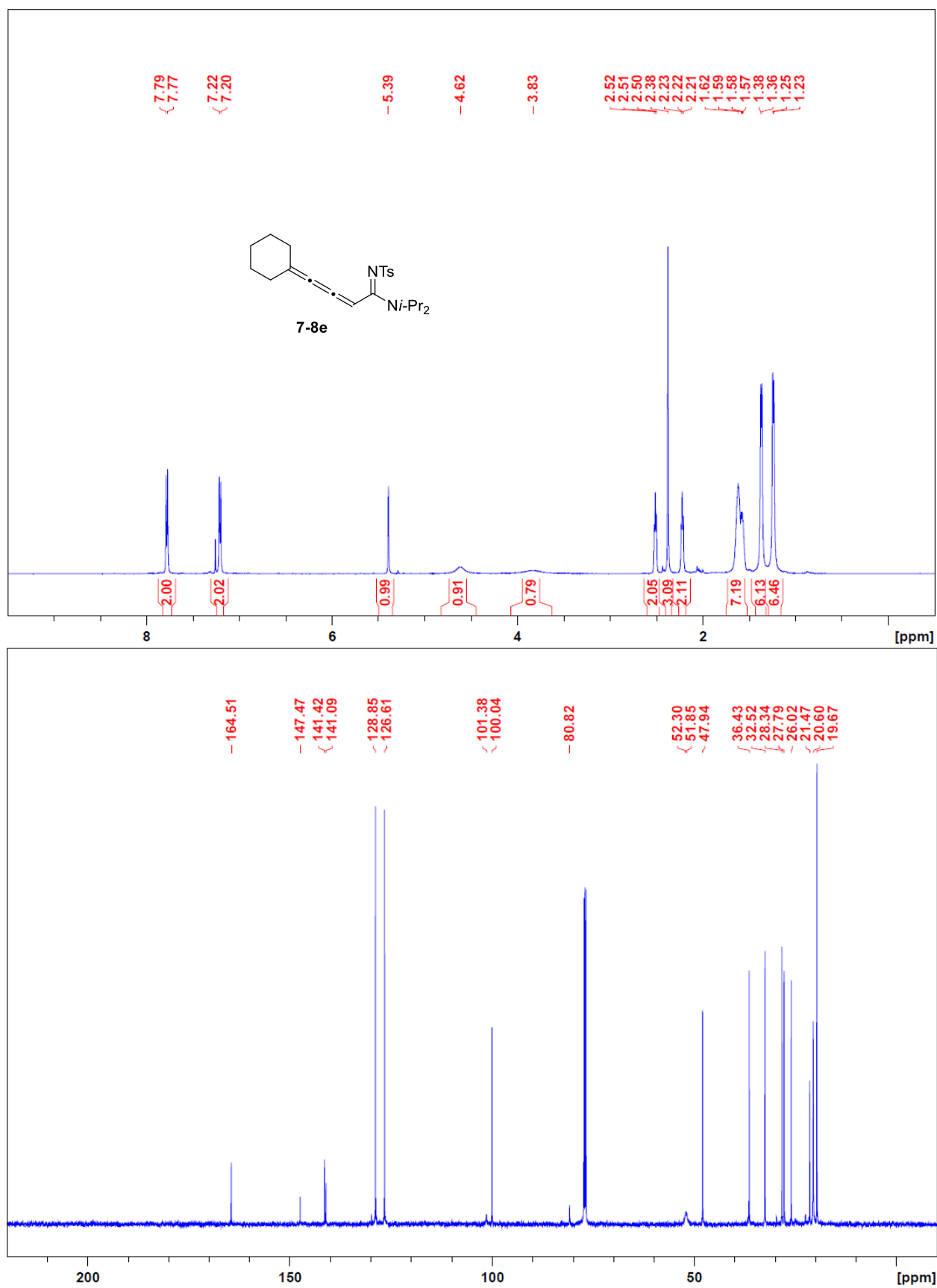


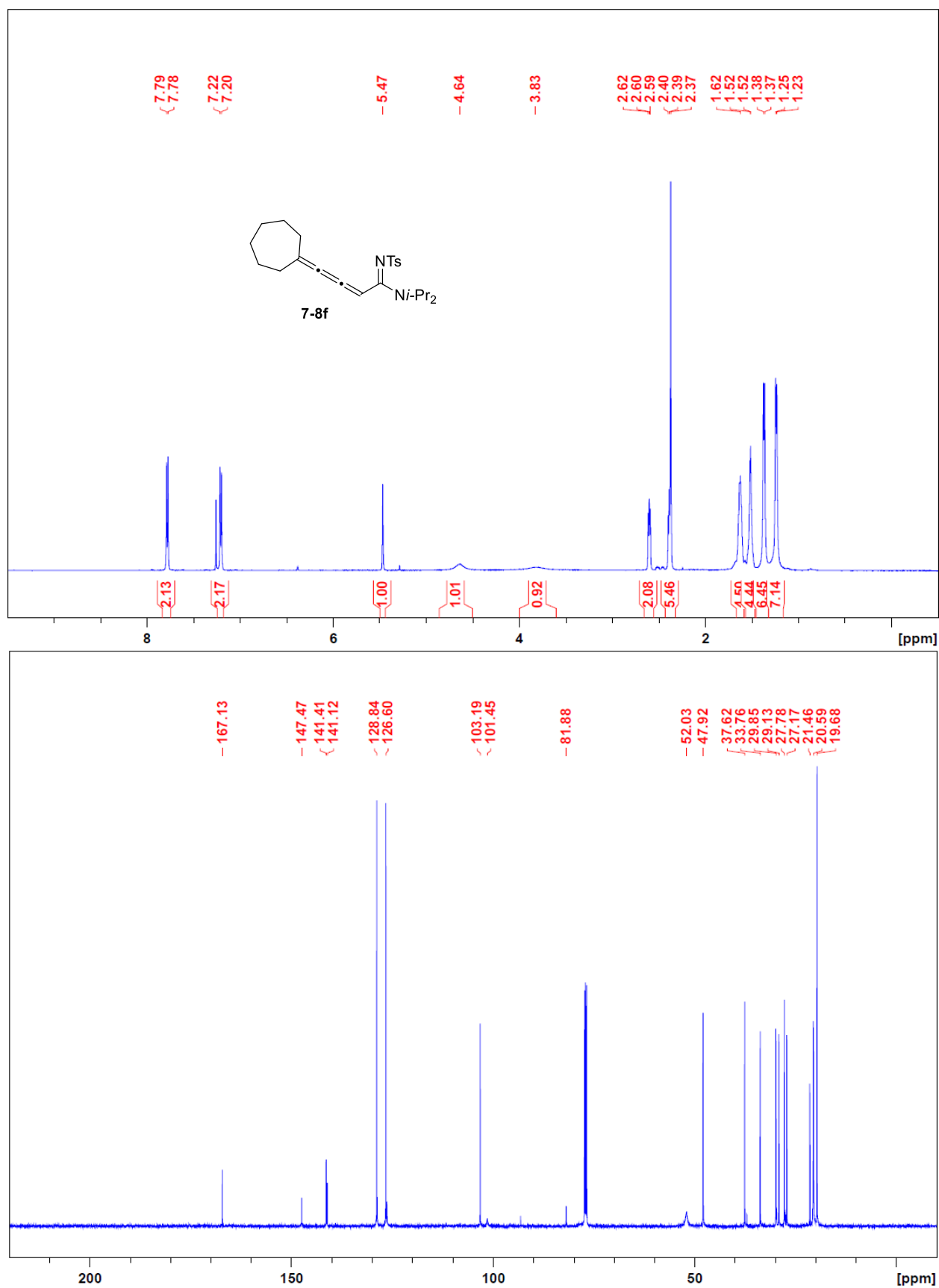


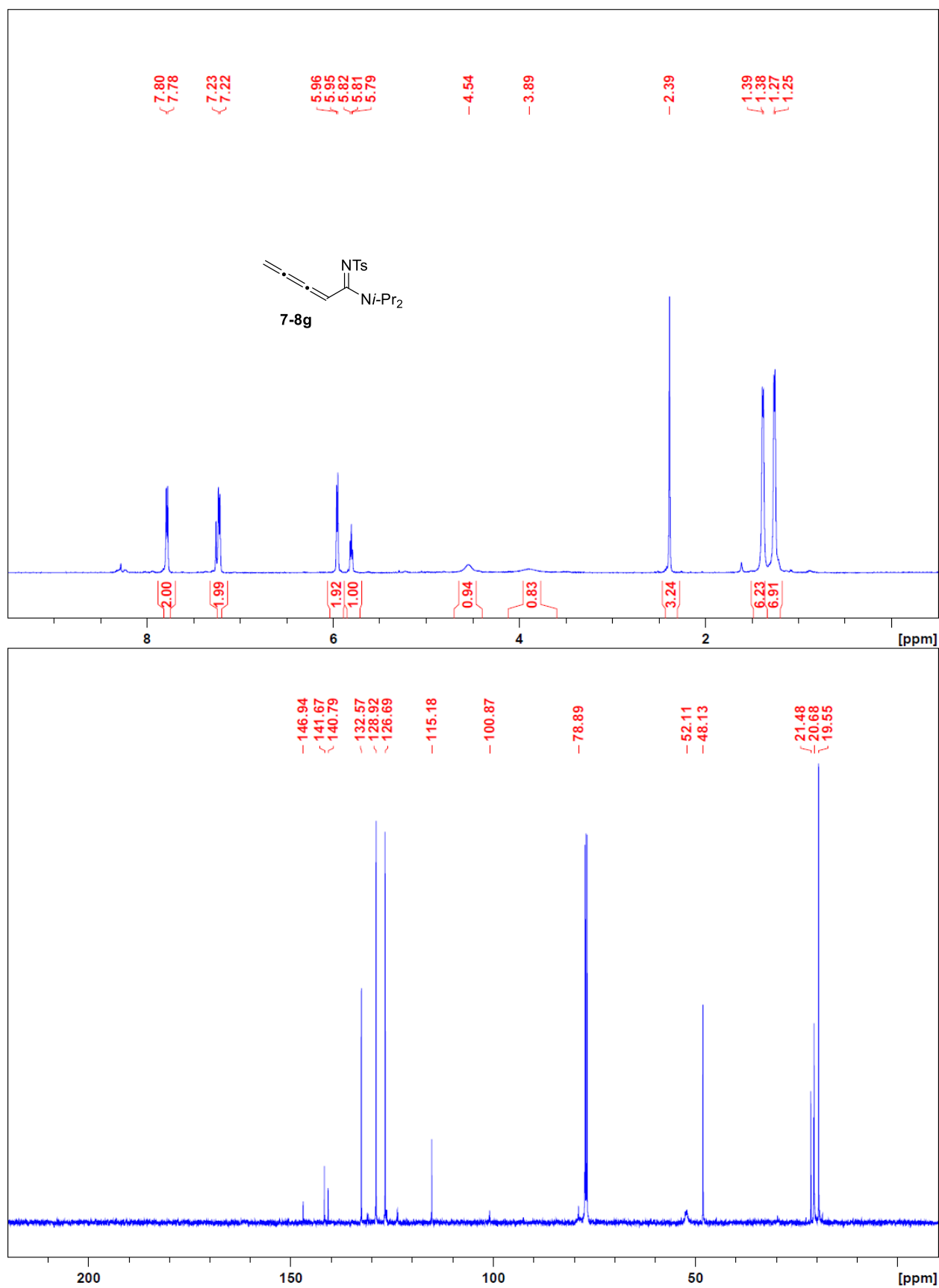


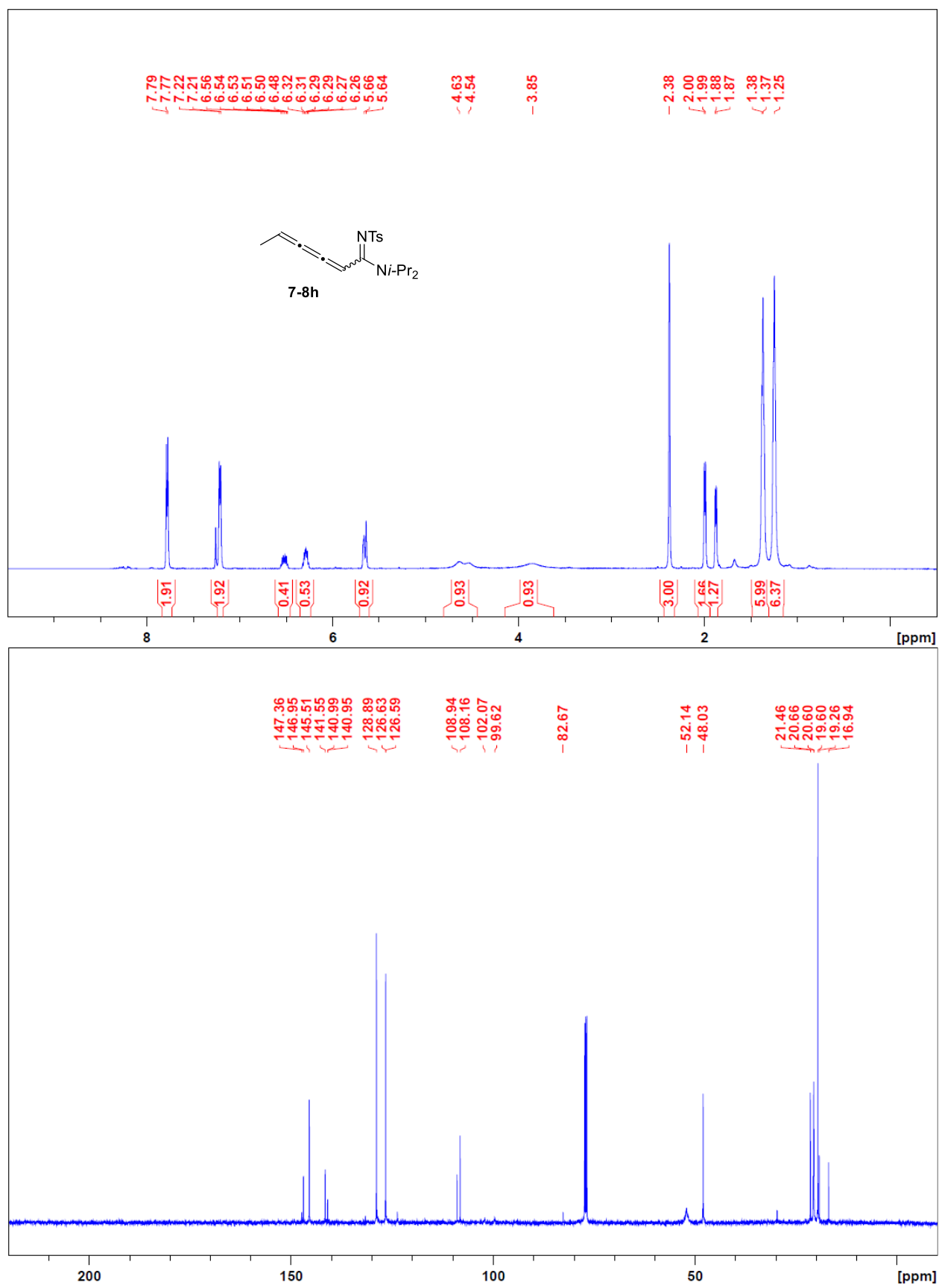


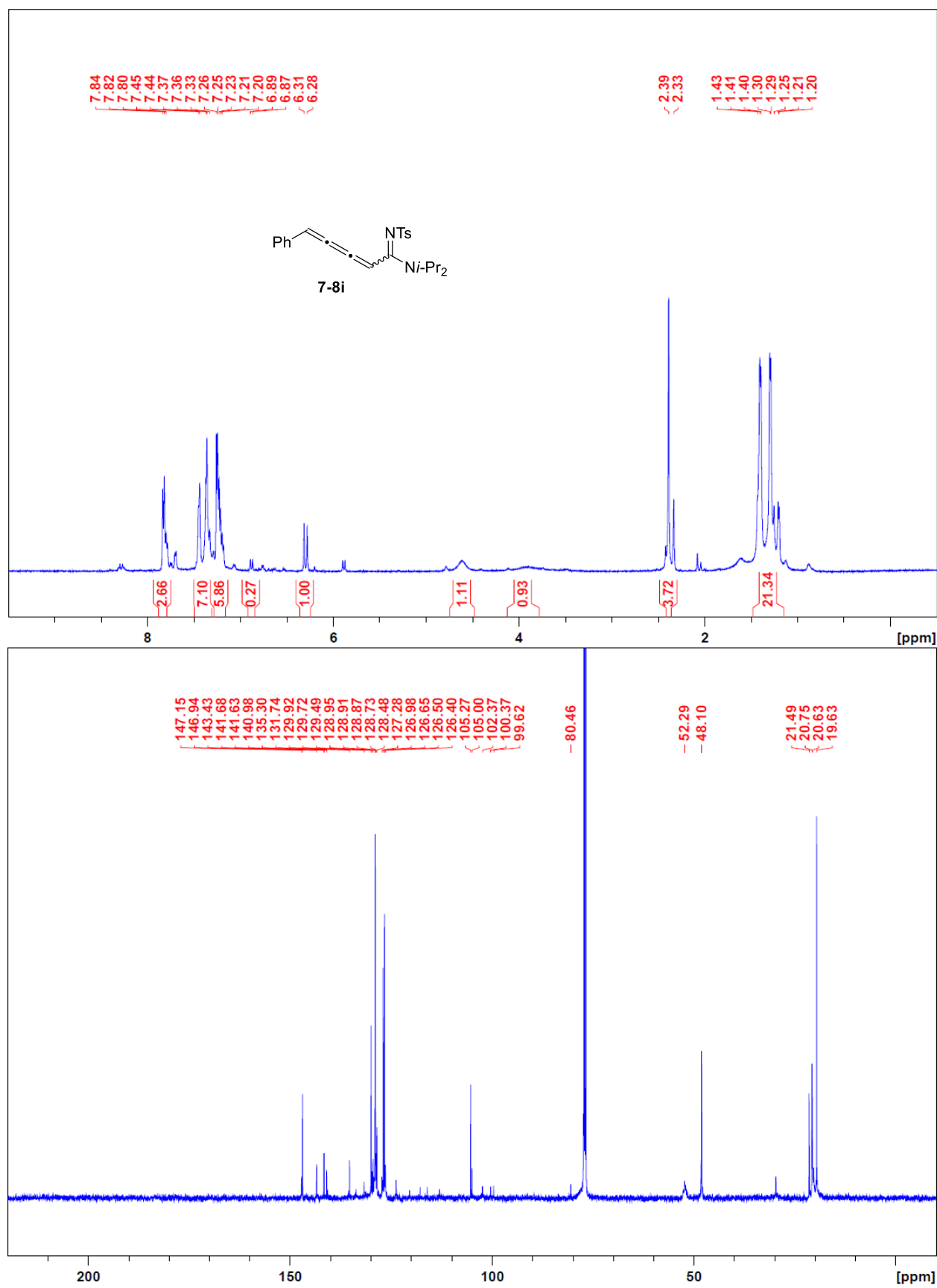


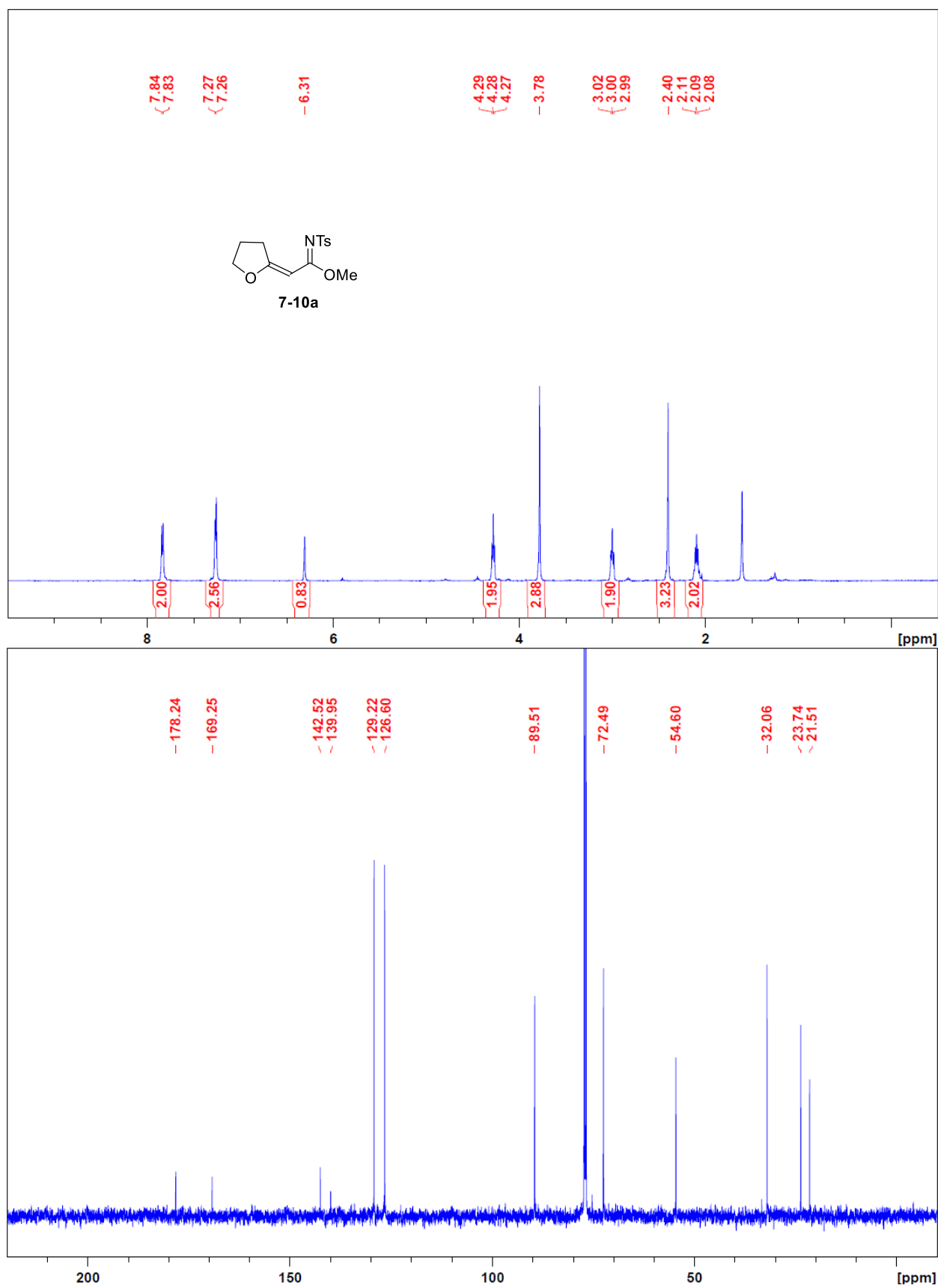


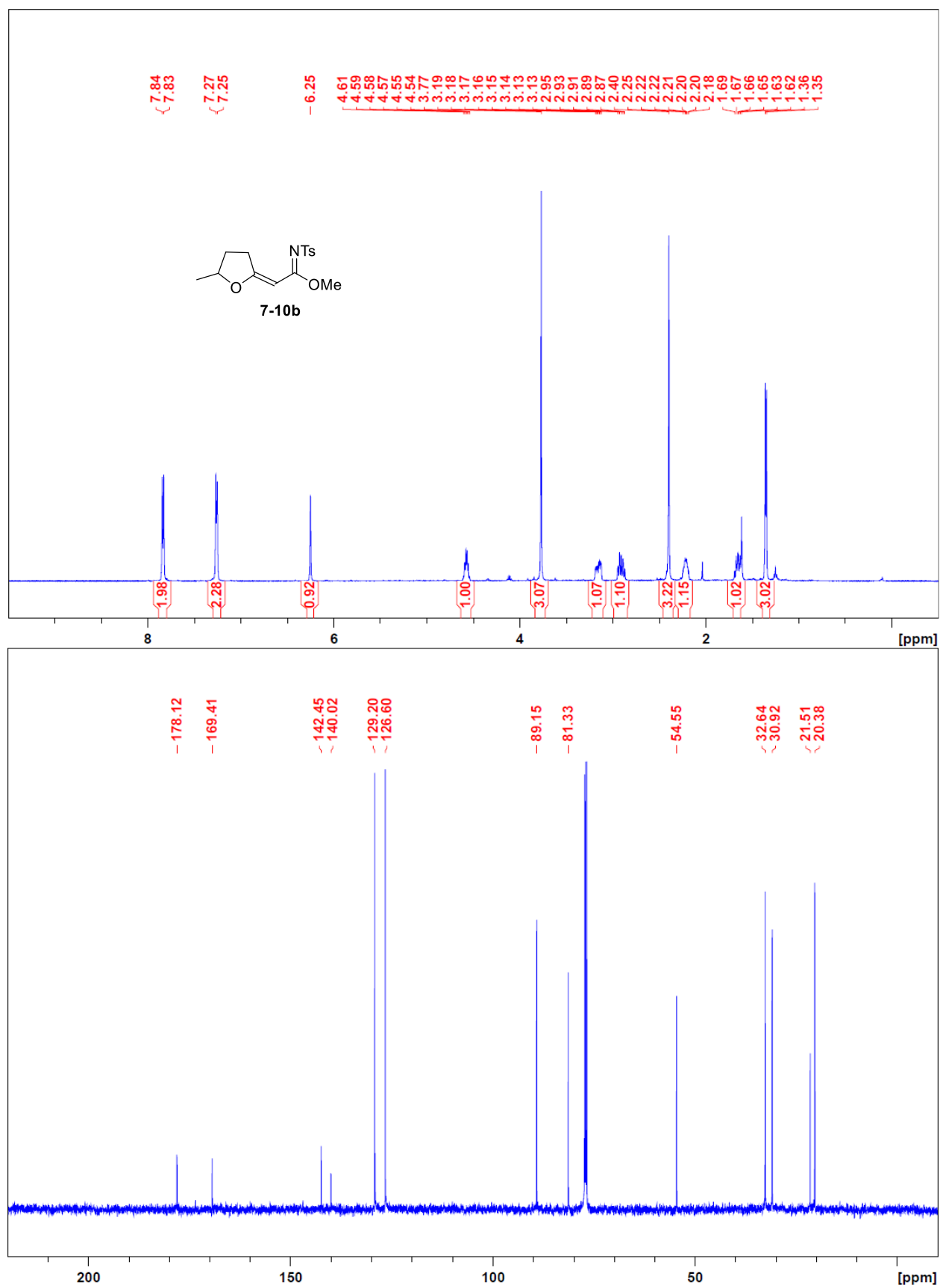


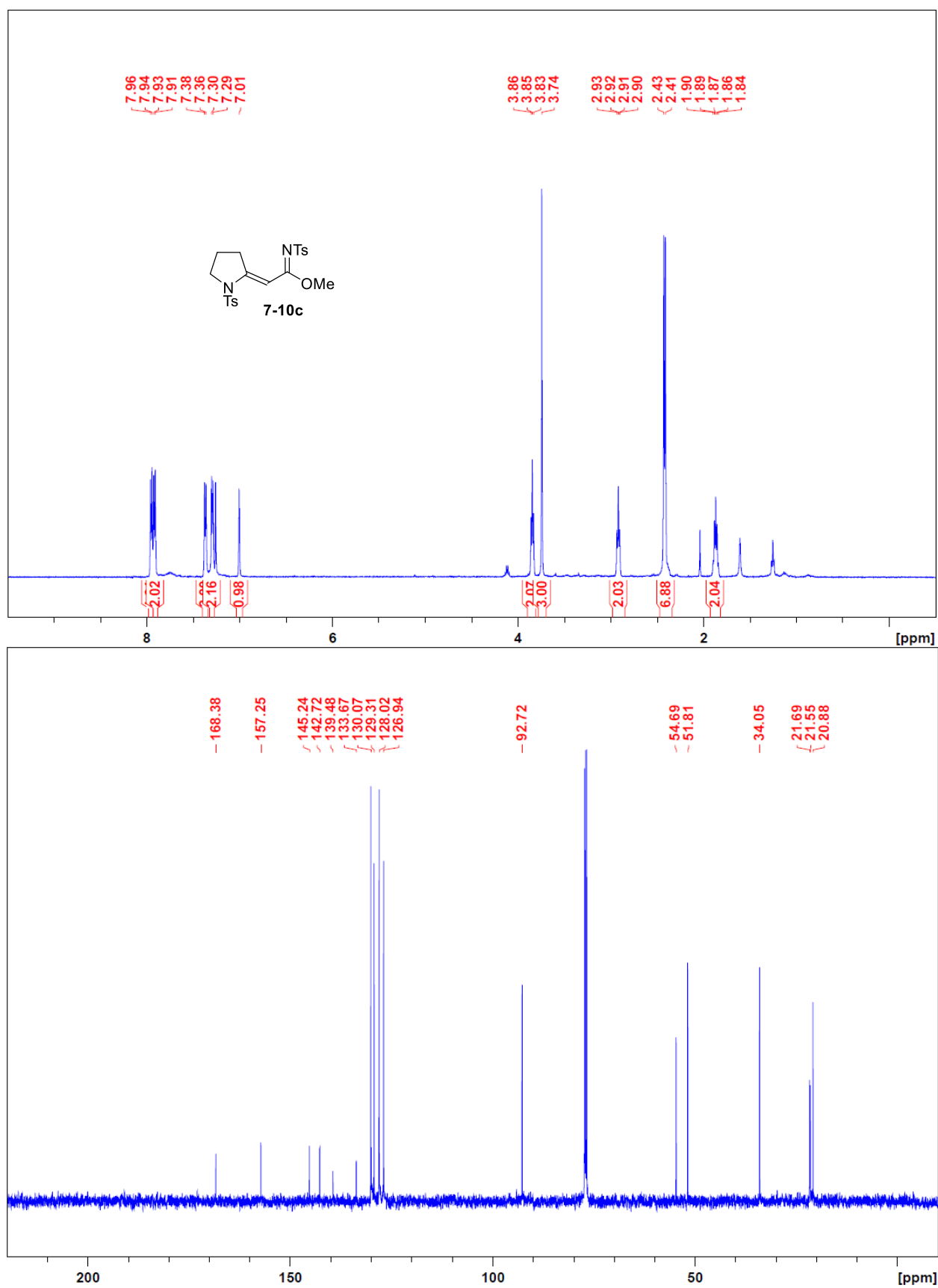


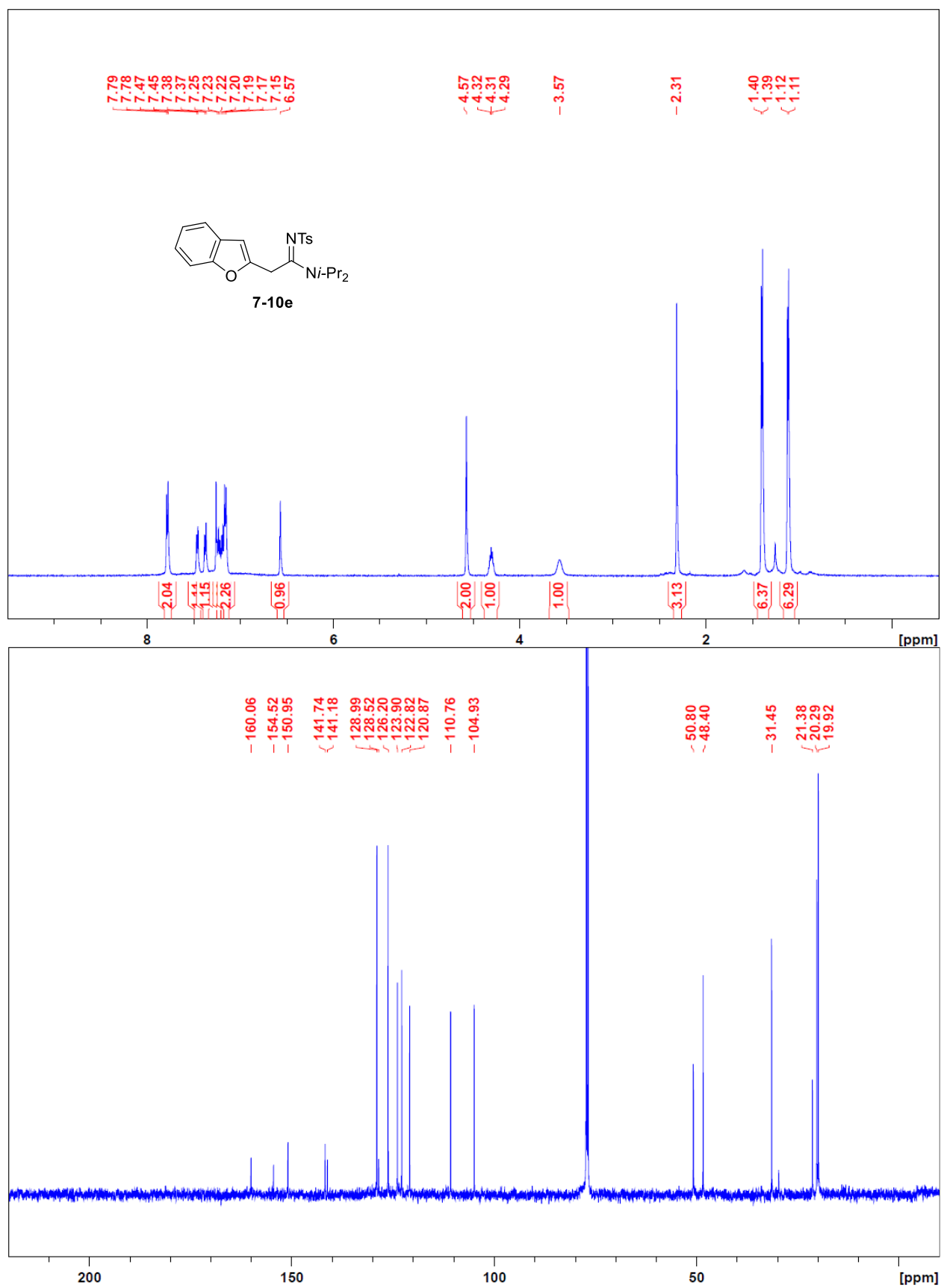


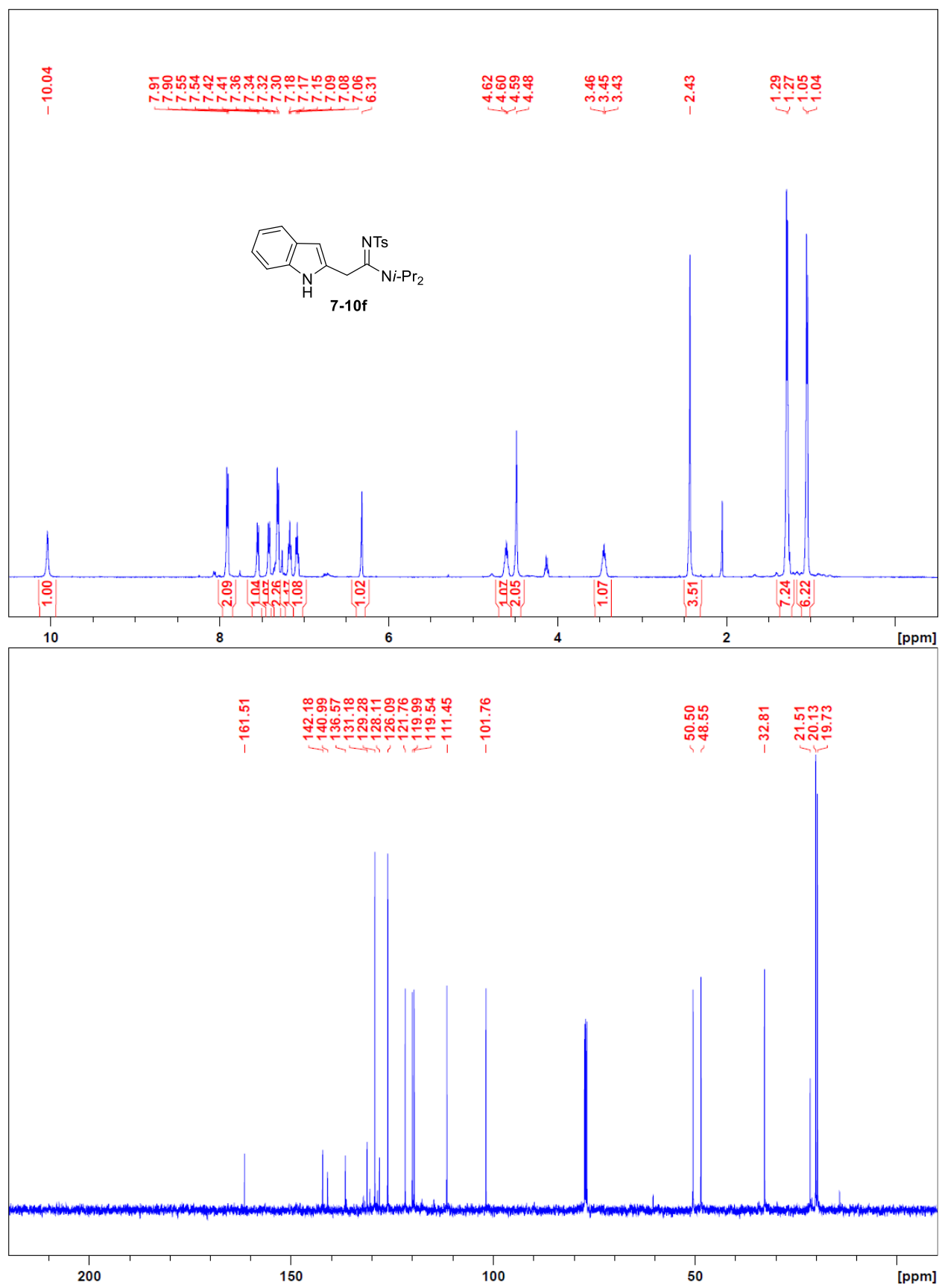


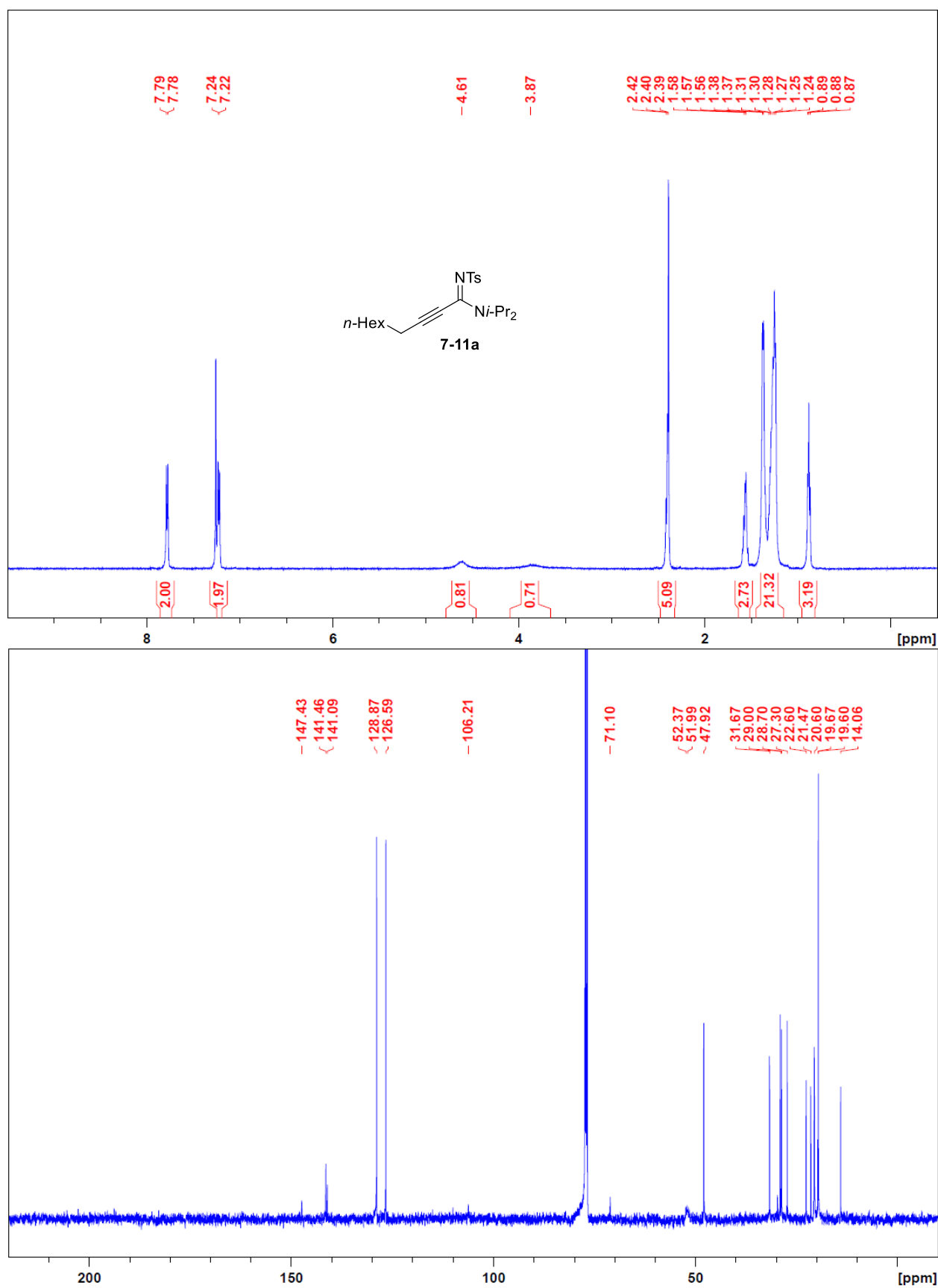


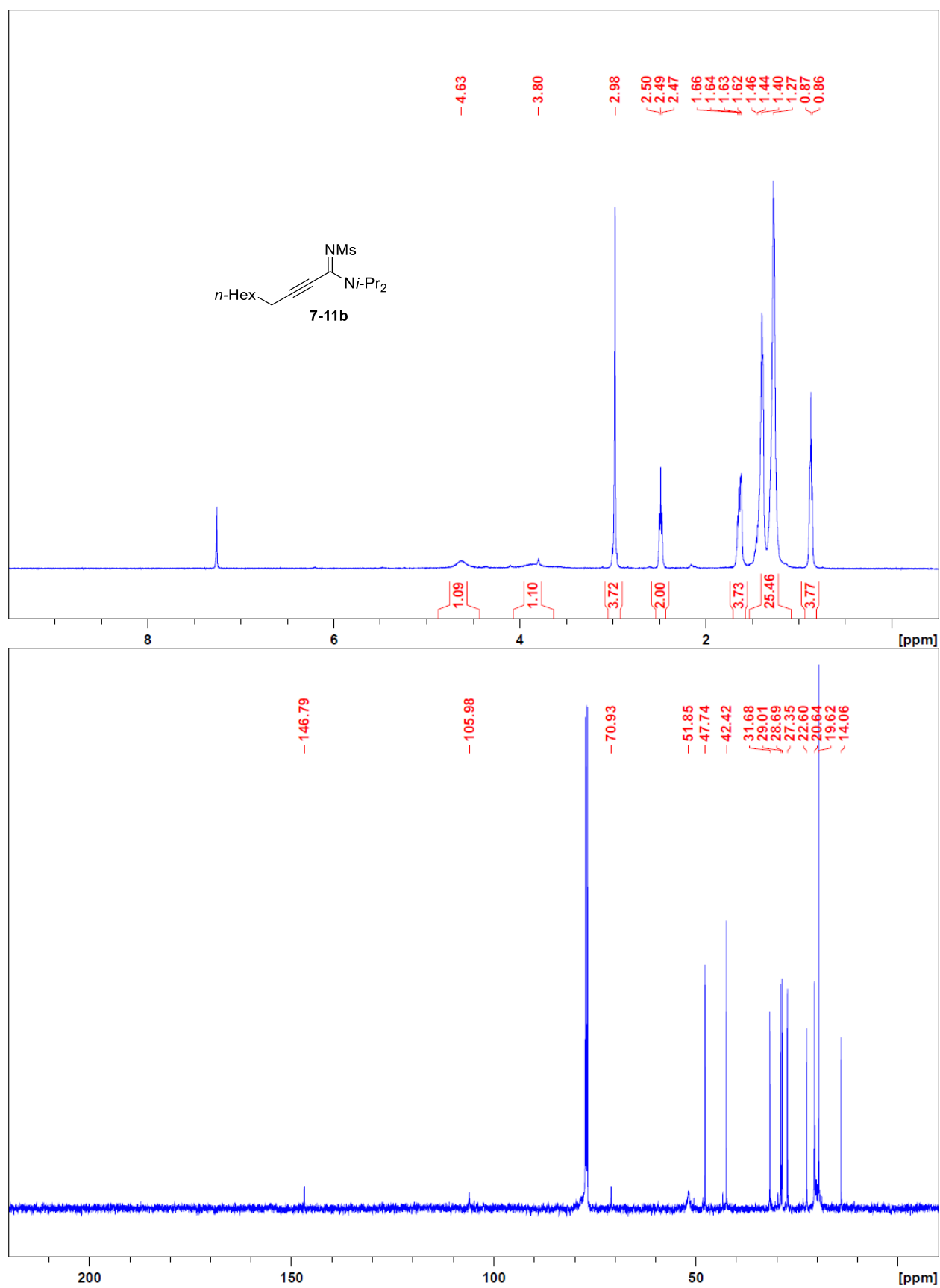


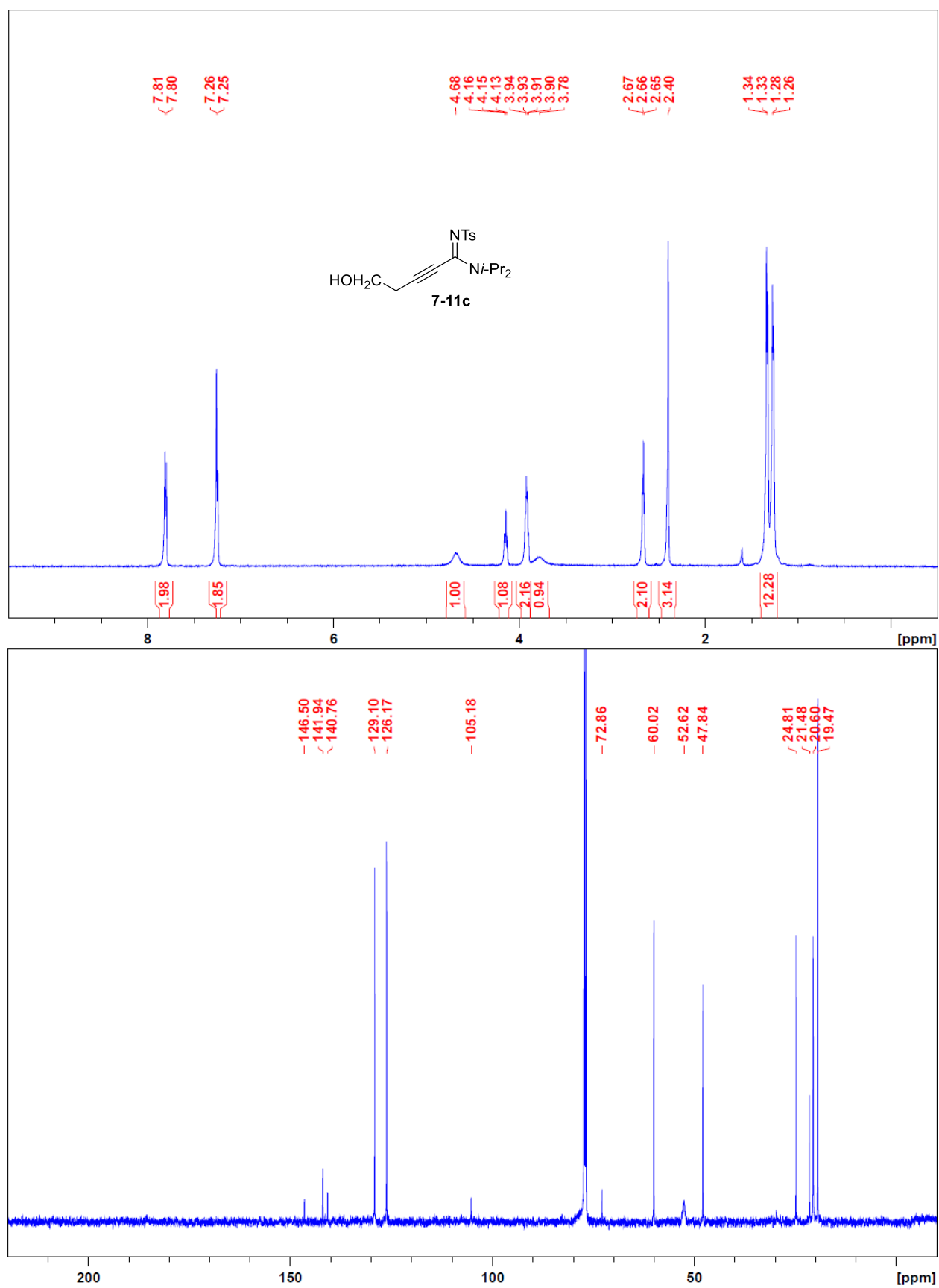


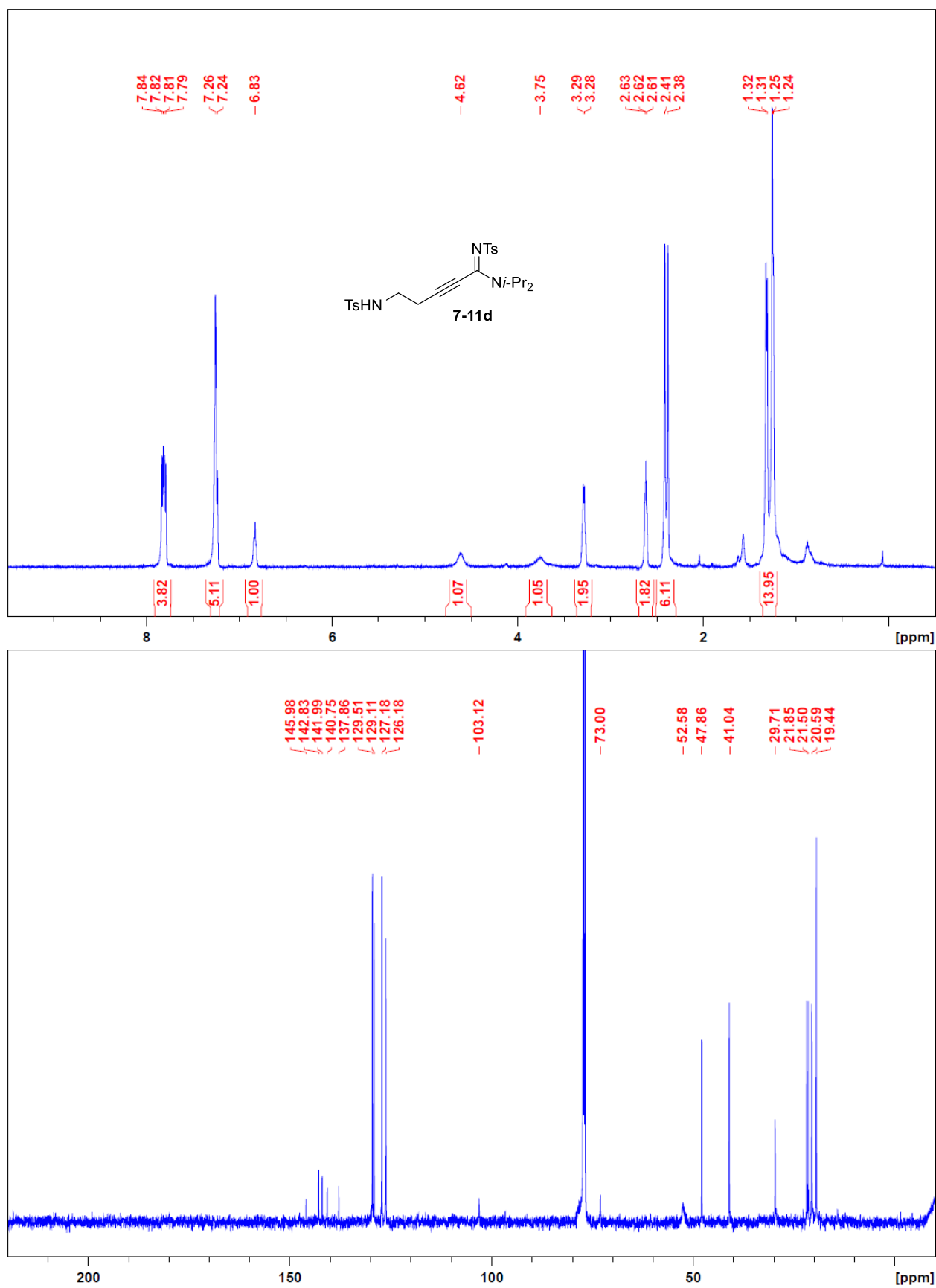












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Aryne formation via the hexadehydro Diels-Alder reaction and their Ritter-type transformations catalyzed by a cationic silver complex

Author: Sourav Ghorai, Daesung Lee

Publication: Tetrahedron

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Silver-Catalyzed Annulation of Arynes with Nitriles for Synthesis of Structurally Diverse Quinazolines

Author: Sourav Ghorai, Yongjia Lin, Yuanzhi Xia, et al

Publication: Organic Letters

Publisher: American Chemical Society

Date: Jan 1, 2020

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Author: Sourav Ghorai, Yongjia Lin, Yuanzhi Xia, et al

Publication: Organic Letters

Publisher: American Chemical Society

Date: Jan 1, 2020

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