Development of Pd-Catalyzed Alkyne Dimerization and Enyne Benzannulation Methodologies

BY

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THESIS

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I would also like to thank all current and former members of Gevorgyan group for creating friendly stimulating environment. It was pleasant and fruitful experience to work with these talented people. I also would like to acknowledge our collaborators in Professor Ananikov group for their help in theoretical studies.

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LIST OF ABBREVIATIONS

Å	Angstrom
Ac	Acetyl
AdBrettPhos	2-(Di-1-adamantylphosphino)-3,6-dimethoxy-2',4',6'-tri-*iso*-propyl-1,1'-biphenyl
All	Allyl
Ar	Aryl
atm	Atmosphere
B	Base
BHT	2,6-Bis(1,1-dimethylethyl)-4-methylphenol
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Boc	*t*-Butyloxycarbonyl
bp	Boiling point
BrettPhos	2-(Dicyclohexylphosphino)-3,6-dimethoxy-2',4',6'-tri-i*so*-propyl-1,1'-biphenyl
n-Bu	Butyl (normal)
s-Bu	*sec*-Butyl
t-Bu	*tert*-Butyl
tBuBrettPhos	2-(Di-*tert*-butylphosphino)-2',4',6'- tri-*iso*-propyl-3,6-dimethoxy-1,1'-biphenyl
C	Concentration
ca.	approximately
calcd.	Calculated
cat.	Catalyst
cinn	Cinnamyl
COD	Cyclooctadiene
Cp	Cyclopentadienyl
Cp*	Pentamethylcyclopentadienyl

LIST OF ABBREVIATIONS (continued)

Cy	Cyclohexyl
d	Dublet
δ	Chemical shift in parts per million downfield from tetramethylsilane
DA	Diels-Alder reaction
DABCO	1,4-Diazabicyclo[2.2.2]octane
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	Dichloroethane
DCM	Dichloromethane
dd	Dublet of dublets
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
Deoxo-Fluor	Bis(2-methoxyethyl)aminosulfur trifluoride
DFT	Density functional theory
DIBAL	Diisobutylaluminum hydride
DMA	Dimethylacetamide
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DOM	Directed *ortho*-metallation
dppe	1,2-Bis(diphenylphosphino)ethane
dppp	1,2-Bis(diphenylphosphino)propane
DPPF	1,1'-Bis(diphenylphosphino)ferrocene
dt	Dublet of triplets
E	Entgegen (opposite, trans)
ΔE	Potential energy

LIST OF ABBREVIATIONS (continued)

EDG	Electron-donating group
EI	Electron impact
ESI	Electrospray ionization
ESI-MS	Electrospray ionization - mass spectrometry
Et	Ethyl
EWG	Electron-withdrawing goriup
FDOPA	2-Fluoro-5-hydroxy-L-tyrosine
F-TEDA	*N*-Chloromethyl-*N*-fluorotriethylenediammonium
F-TMP	*N*-Fluoro-2,4,6-trimethylpyridinium
ΔG	Gibbs free energy
GC/MS	Gas chromatography/mass spectrometry
gem-	Geminal
h	Hour(s)
ΔH	Enthalpy
Hal	Halogen
HDDA	Hexadehydro-Diels-Alder Reaction
hh	Head-to-head
ht	Head-to-tail
HRMS	High resolution mass spectra
Hz	Hertz
IMes	1,3-Bis(2,4,6-trimethylphenyl)imidazol-2-ylidene
IPr	1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene
J	Coupling constant
kcal/mol	Kilocalories per mole

L	Ligand
LA	Lewis acid
LDA	Lithium diisopropylamide
LRMS	Low resolution mass spectra
LUMO	Lowest unoccupied molecular orbital
m	Multiplet
M	Mole per liter
[M]	Metal
$[M]^+$	Molecular ion
MAO	Methylaluminoxane
Me	Methyl
Mes	Mesityl
mg	Milligram(s)
MHz	Megahertz
mL	Milliliter(s)
mol	Mole
MOM	Methoxymethyl
Ms	Methanesulfonyl
MS	Mass spectrometry
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
Nf	Nonafluorobutanesulfonate
NFSI	*N*-Fluorobenzenesulfonimide
NHC	*N*-Heterocyclic carbene

LIST OF ABBREVIATIONS (continued)

NIS	*N*-Iodosuccinimide
NMO	*N*-Methylmorpholine-*N*-oxide
NMP	*N*-Methyl-2-pyrrolidinone
NMR	Nuclear magnetic resonance
PET	Positron emission tomography
Ph	Phenyl
PhDavePhos	2-Diphenylphosphino-2'-(*N*,*N*-dimethylamino)biphenyl
PhenoFluor	1,3-Bis(2,6-diisopropylphenyl)-2,2-difluoro-2,3-dihydro-1*H*-imidazole
Phth	Phthaloyl
Piv	Pivaloyl
Pivalate	2,2-Dimethylpropanoate
ppm	Parts per million
i-Pr	*iso*-Propyl
q	Quadruplet
Ref.	Reference
rt	Room temperature
RuPhos	2-Dicyclohexylphosphino-2',6'-diisopropoxybiphenyl
s	Singlet
SIPr	1,3-Bis(2,6-di-*i*-propylphenyl)imidazolidin-2-ylidene
S_EAr	Electrophilic aromatic substitution
SET	Single electron transfer
sept	Septet
t	Time
t	Triplet

LIST OF ABBREVIATIONS (continued)

T	Temperature
TBAF	Tetra-*n*-butylammonium fluoride
TBS	*tert*-Butyldimethylsilyl
TDMPP	Tris(2,6-dimethoxyphenly)phosphine
TES	Triethylsilyl
terpy	2,6-Bis(2-pyridyl)pyridine
Tf	Trifluoromethanesulfonate
TFA	Trifluoroacetate
TFP	Tri(2-furyl)phosphine
THF	Tetrahydrofuran
TIPS	Tri-*iso*-propylsilyl
TMS	Trimethylsilyl
TON	Turnover number
TOF	Turnover frequency
o-Tol	*ortho*-Tolyl
Triflate	Trifluoromethylsulfonate
Ts	*para*-Toluenesulfonyl
TS	Transition state
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
Z	Zusammen (together, *cis*)

SUMMARY

This thesis describes the development of palladium-catalyzed regiodivergent dimerization reaction of terminal alkynes and highly efficient [4+2] benzannulation reaction of enynes with diynes, as well as application of the latter for the synthesis of fluorine-containing aromatic compounds.

In the first part of the thesis, experimental and theoretical investigation of the palladium-catalyzed dimerization of terminal alkynes is presented. Chapter 1.1 summarizes advances in transition metal-catalyzed approaches toward hydroalkynylation reaction providing an overview of the existing strategies for regio- and stereoselectivity control of this process. Specific attention is given to palladium-catalyzed methodologies, including discussion of various catalytic systems, their scope and limitations, reaction mechanisms, as well as synthetic applications. Chapter 1.2 describes the development of regiodivergent dimerization of alkynes. It is shown that employment of *N*-heterocyclic carbene-based palladium catalyst in the presence of phosphine ligand allows for highly regio- and stereoselective *head-to-head* dimerization reaction. Alternatively, an addition of carboxylate anion to the reaction mixture triggers a *selective head-to-tail* coupling. The origins of this regioselectivity switch, which were revealed by the computational studies, are also discussed. The experimental details for the Pd-catalyzed dimerization reaction, described in Chapter 1.2, are presented in Chapter 1.3.

The second part of the thesis is devoted to the development of highly efficient catalytic system for the palladium-catalyzed [4+2] benzannulation of enynes with diynes. Accordingly, thermal and transition metal-catalyzed strategies for [4+2] benzannulation of enynes with various enynophiles are summarized in Chapter 2.1. It includes detailed discussion of palladium-catalyzed benzannulation reaction, which is the most explored transformation of this type. The development of a highly efficient catalytic system for this process is presented in Chapter 2.2. It is shown that employment of *N*-heterocyclic carbene-based palladium precatalyst allowed to achieve turnover numbers of the catalyst up to 1800. The presented method is proved to be general across a wide range of enynes and diynes. Additionally, developed catalytic system also expanded the scope of the [4+2] homo-benzannulation reaction. The experimental

details for the Pd-catalyzed benzannulation reaction, described in Chapter 2.2, are presented in Chapter 2.3.

Part three of the thesis describes the development of an efficient method toward fluorinated and perfluoroalkylated densely substituted benzene derivatives. In Chapter 3.1 modern methods for the synthesis of aryl fluorides via electrophilic and nucleophilic fluorination of functionalized arenes are summarized. Additionally, existing annulative approaches for the synthesis of these valuable molecules from fluoro-containing precursors are highlighted. Chapter 3.2 discribes the synthesis of fluorinated benzenes from easily available acyclic precursors via the chemo- and regioselective Pd-catalyzed [4+2] cross-benzannulation reaction. The described method also provides an efficient access for perfluoroalkylated analogs. The synthetic utility of the obtained products has been also demonstrated by efficient synthesis of various aromatic and heteroaromatic compounds. Chapter 3.3 provides experimental details for the synthesis of fluorine-containing arenes via benzannulation reaction, as well as their further transformations.

CONTRIBUTION OF AUTHORS

Several parts of this thesis are reproduced from previously published research articles co-authored with collaborators, who contributed significantly to the presented work.

The first part of the thesis is the result of fruitful collaboration between prof. Gevorgyan and prof. Ananikov research groups. Chapter 1.1. is a literature overview of the area of alkynes dimerization, which was written by me. Chapters 1.2 and 1.3 are reproduced from the published article (Zatolochnaya, O. V.; Gordeev, E. G.; Jahier, C.; Ananikov, V. P.; Gevorgyan, V. "Carboxylate Switch between Hydro- and Carbopalladation Pathways in Regiodivergent Dimerization of Alkynes" *Chem.–Eur. J.* **2014**, 20, 9578-9588), which in turn represents a full account of the original communication published earlier (Jahier, C.; Zatolochnaya, O. V.; Zvyagintsev, N. V.; Ananikov, V. P.; Gevorgyan, V. "General and Selective Head-to-Head Dimerization of Terminal Alkynes Proceeding via Hydropalladation Pathway" *Org. Lett.* **2012**, *14*, 2846-2849). Accordingly, Dr. Claire Jahier and myself have contributed equally to the synthetic part of this work (Chapters 1.2.1, 1.2.3, 1.3.1–1.3.3), which included design and execution of the experiments. The theoretical studies for these manuscripts (Chapters 1.2.3, 1.3.4) were performed by Drs. Nickolay V. Zvyagintsev and Evgeniy G. Gordeev under supervision of Prof. Valentine P. Ananikov. All authors participated in the discussion of experimental and theoretical results. I was one of the major contributors to writing both manuscripts. I wrote and revised a draft of synthetic part and provided assistance with writing the theoretical parts. My advisor, Prof. Vladimir Gevorgyan, conceived the project, established collaboration with Prof. Ananikov group, and guided the research.

The second part of the thesis includes material from two previously published articles. Several subchapters of Chapter 2.1 (Chapters 2.1.2–2.1.4) reproduced from previously published book chapter (Zatolochnaya, O. V.; Gevorgyan, V. "[4+2] Benzannulation of Enynes and Alkynes" In *Transition-Metal-Mediated Aromatic Ring Construction*; Tanaka, K., Ed.; Wiley-VCH: Weinheim, **2013**, 355-376), which I wrote along with my advisor, Prof. Vladimir Gevorgyan. Chapters 2.2 and 2.3 describe results of published work (Zatolochnaya, O. V.; Galenko, A. V.; Gevorgyan, V. "Beyond the Limits: Palladium-*N*-

Heterocyclic Carbene-Based Catalytic System Enables Highly Efficient [4+2] Benzannulation Reactions" *Adv. Synth. Catal.* **2012**, *354*, 1149-1155.). I was the primary author of this paper and the major contributor to the conducted research and to the writing the manuscript. Dr. Alexey V. Galenko performed the experiments at an early stage of the project, which included optimization of the initial reaction conditions (Chapter 2.2.1) and the discovery of the process described in Chapter 2.2.3. All authors participated in the discussion of the results. My advisor, Prof. Vladimir Gevorgyan, conceived and guided the research project.

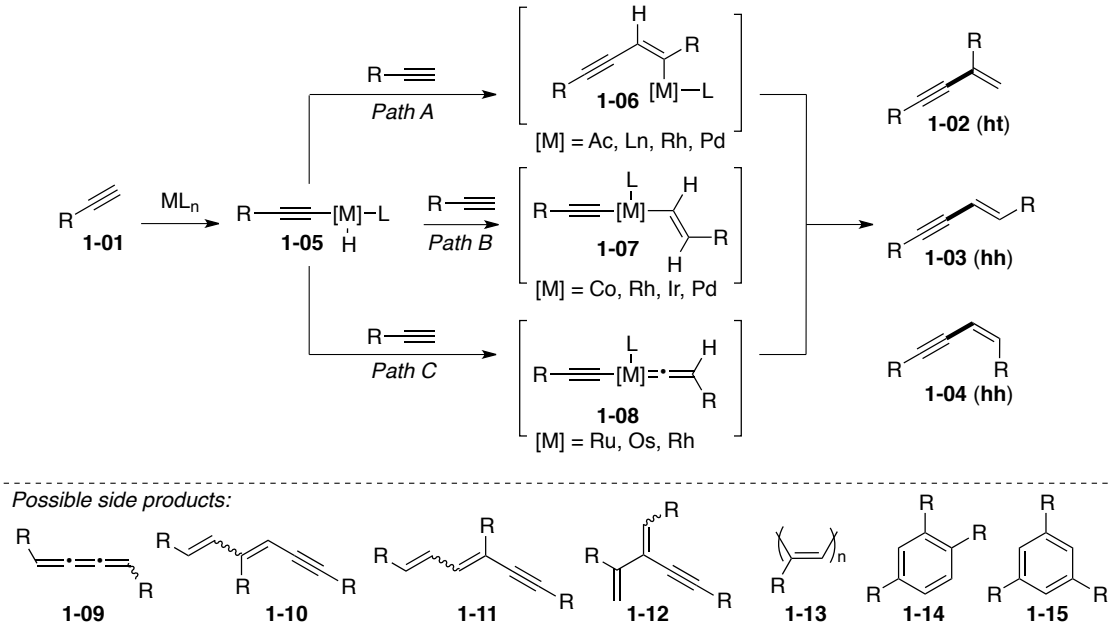
Part three of the thesis is also written based on the previously published article. Chapter 1.3. is a literature review, in which I described recent advances in the research area of synthesis of fluoroaromatic compounds. Chapters 3.2 and 3.3 are reproduced from the published article (Zatolochnaya, O. V.; Gevorgyan, V. "Synthesis of Fluoro- and Perfluoroalkyl Arenes via Palladium-Catalyzed [4+2] Benzannulation Reaction" *Org. Lett.* **2013**, *15*, 2562-2565) in which I was the only author besides my research advisor, Prof. Vladimir Gevorgyan. Accordingly, I conceived the project, designed and performed experiments, and wrote the manuscript. Prof. Vladimir Gevorgyan guided the research and contributed to the discussion of the results and manuscript writing.

PART ONE

DEVELOPMENT OF REGIODIVERGENT PALLADIUM-CATALYZED DIMERIZATION OF TERMINAL ALKYNES

1.1. INTRODUCTION

Dimerization of alkynes is one of the most straightforward and atom-economical methods for synthesis of conjugated enynes, important synthetic intermediates[1] and key structural units found in a variety of bioactive molecules,[2] as well as polymeric and optical materials.[3] A number of transition metals and main group elements have shown catalytic activity in this transformation.[4] The main challenge of alkyne dimerization is the control of regio- and sometimes stereoselectivity due to the competing *head-to-tail* (**ht**) and *head-to-head* (**hh**) reaction modes leading to the formation of *gem*-1,3-disubstituted (**1-02**), 1,4-disubsituted (*E*)-(**1-03**) or (*Z*)-(**1-04**) enynes (Scheme 1.1). Moreover, formation of side products, such as cumulenes **1-09**, linear and branched trimers **1-10** – **1-12**, higher oligomers and polymers **1-13**, as well as aromatized trimers **1-14** and **1-15**, also compromise selectivity of the dimerization reaction.

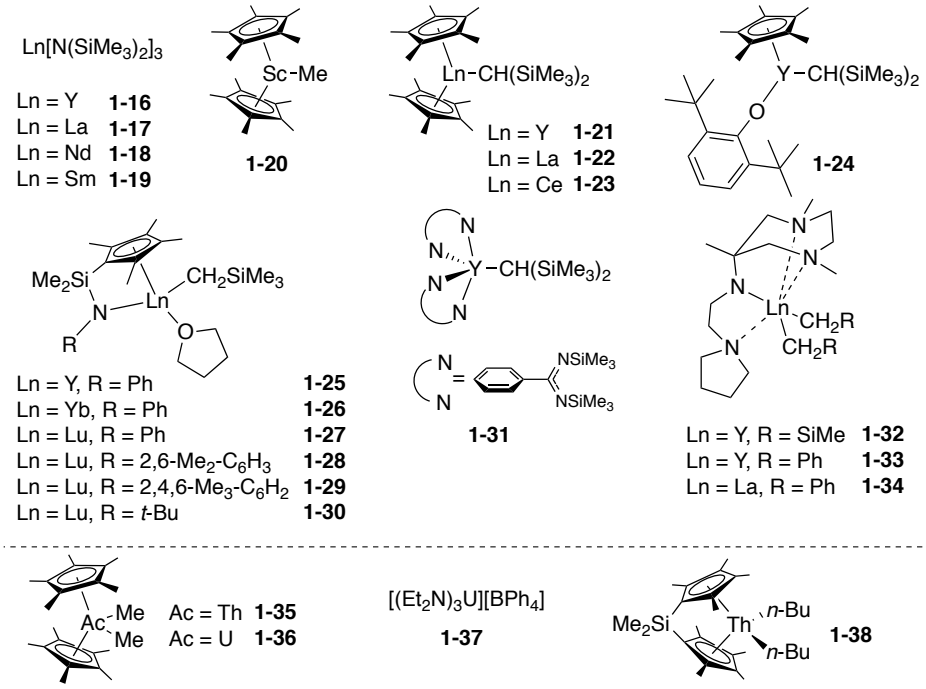


Scheme 1.1. Dimerization of Terminal Alkynes for the Synthesis of 1,3-Enynes.

Nevertheless, highly efficient and general methods for dimerization of alkynes to form single enyne products were developed by using appropriate metals and by careful tuning of the ligands at the metal center.[4] Commonly accepted reaction pathways start with the formation of metal acetylide **1-05** followed by the migratory insertion of the second alkyne molecule to form the dimeric product. Both *carbometallation*, alkyne insertion into metal–carbon bond (path A), and *hydrometallation*, alkyne insertion into metal–hydrogen bond (path B), are equally plausible for the *head-to-head* or the *head-to-tail* dimerization reactions. Alternatively, dimerization can proceed via formation of metal vinylidene intermediate **1-08** followed by insertion of the alkynyl moiety (path C). In the following section advances toward selective transition metal-catalyzed dimerization of alkynes are summarized with the emphases placed on mechanistic proposals and their investigations. Additionally, palladium-catalyzed homo- and cross-dimerization reactions are discussed in greater details, including the scope, mechanistic rationales and synthetic applications.

1.1.1. Dimerization of Alkynes Catalyzed by Early Transition Metals

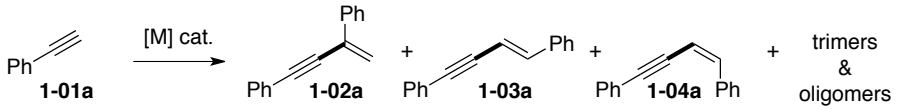
A variety of rare-earth metals complexes, of scandium,[5] yttrium,[6,7,8,9,10,11,12] lanthanum,[6b,7,12b] cerium,[6b] neodymium,[7] samarium,[7] lutetium,[11] thorium,[13,14] and uranium[13,15] catalysts, were studied in dimerization and oligomerization reactions of terminal alkynes (Scheme 1.2). Overall, most of them efficiently catalyze dimerization of alkynes with different degrees of selectivity, which strongly depend on the nature of catalyst and/or alkyne. To exemplify this dependence, comparison of selectivities in dimerization of phenylacetylene (**1-01a**) in the presence of various lanthanide and actinide complexes is given in Table 1.1. Thus, treatment of phenylacetylene with silylamides of Y, La, Nd, or Sm led to the full conversion of the substrate, yet the formation of only small amounts of enyne products **1-02a**, **1-03a**, and **1-04a** was observed (entries 1-4).[7] However, in the presence of anilines, for instance, *para*-chloroaniline, selectivity of the dimerization reaction catalyzed by yttrium silylamide **1-16** is dramatically improved as (*Z*)-1,4-diphenylenyne was formed as a sole product in 90% yield (entry 5).[8]



Scheme 1.2. Complexes of Scandium, Yttrium, Lanthanides and Actinides Used in Dimerization of Terminal Alkynes.

Reactivity of lanthanide sandwich- (**1-21** – **1-23**) or half-sandwich (**1-24** – **1-30**) complexes toward reaction with terminal alkynes was intensively investigated. It was shown, that employment of yttrium metallocene **1-21** favored *head-to-tail* coupling, whereas analogous derivatives of lanthanum **1-22** and cerium **1-23** delivered *head-to-head* (*E*)-enyne **1-03a** as a major product (entries 6-8).[6] Alternatively, formation of (*Z*)-enyne **1-04a** became predominant when half-sandwich anilido complexes **1-25** – **1-30** were used to catalyze this transformation (entries 9-11).[11] Importantly, lutetium analog **1-29** demonstrated exceptional efficiency and selectivity in dimerization of phenylacetylene, as well as other alkynes, even after being recycled for several times (entry 11). Interestingly, among other tested complexes, bis(benzoimidato)yttrium complex **1-31** demonstrated the best selectivity for the *head-to-tail* dimerization reaction (entry 12).[10] Additionally, complementary lanthanide **1-32** – **1-34** catalysts bearing *N*-based tridentetate ligand were developed for selective synthesis of (*Z*)-**1-04** (entries 13-15).[12]

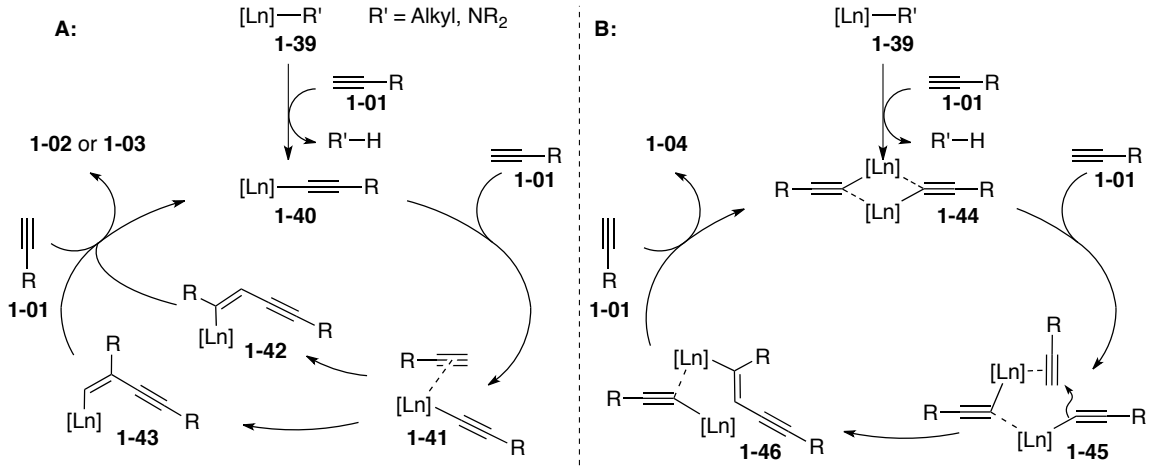
Table 1.1. Dimerization of Phenylacetylene Catalyzed by Lanthanide and Actinide Complexes.



Entry	Catalyst	Distribution of products				Yield, %	Ref.
		1-02a	**1-03a**	**1-04a**	other products		
1	**1-16**	23	0.5	0.5	76	–	7
2	**1-17**	7	4	8	81	–	7
3	**1-18**	14	2	2	82	–	7
4	**1-19**	17	13	3	67	–	7
5	**1-16**/4-Cl-$C_6H_4NH_2$	0	0	100	0	90	8a
6	**1-21**	89	11	0	0	–	6b
7	**1-22**	0	86	0	14	–	6b
8	**1-23**	0	82	0	18	–	6b
9	**1-25**	6	0	89	5	–	11
10	**1-26**	0	0	92	8	–	11
11	**1-29**	0	0	100	0	99	11
12	**1-31**	100	0	0	0	–	10
13	**1-32**/[$PhNHMe_2$][$B(C_6F_5)_4$]	0	0	100	0		12
14	**1-33**	0	0	100	0		12b
15	**1-34**	0	0	100	0		12b
16	**1-35**	28	0	0	72	–	13a
17	**1-36**	30	0	0	70	–	13a
18	**1-35**/*t*-$BuNH_2$	0	100	0	0	–	13d
19	**1-37**	32	0	0	68	–	15

Due to their high activity, the regioselectivity of the dimerization reaction catalyzed by actinide complexes **1-35** – **1-38** is often compromised by a facile formation of trimers, tetramers and other oligomeric by-products (entries 16-19).[13,14] Nevertheless, a selective *head-to-head* dimerization reaction to afford single (*E*)-enyne **1-03** was achieved in the presence of thorium matallocene **1-35** and *tert*-butylamine (entry 18).[13d] However, high selectivity in *head-to-head* reaction is specific for phenylacetylene, as predominant *head-to-tail* reaction mode was observed for aliphatic substrates.[13d]

The mechanism of dimerization and oligomerization of terminal alkynes by lanthanide[5-12] and actinide[13-15] complexes was studied in detail, and various catalytically relevant intermediates were isolated and characterized. The generally accepted mechanistic rationale for dimerization reaction with lanthanide-based catalysts is outlined in Scheme 1.3A.

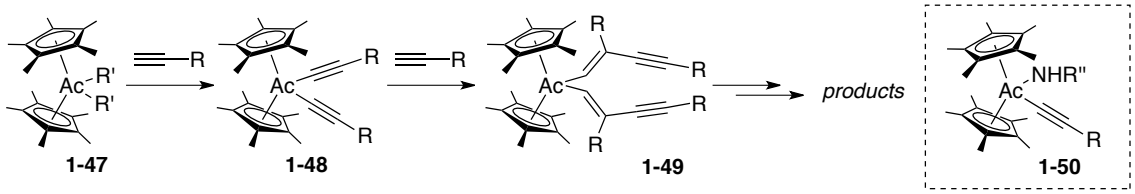


Scheme 1.3. Proposed Mechanism for the Dimerization of Terminal Alkynes Catalyzed by Lanthanides.

The reaction is initiated by σ-bond metathesis between alkyl precatalyst **1-39** and alkyne **1-01** to form the alkynyl lanthanide species **1-40**. Coordination of the second alkyne moiety followed by the migratory insertion in the *head-to-head* (**1-41** → **1-42**) or the *head-to-tail* (**1-41** → **1-43**) manner provides corresponding vinyl metal intermediates. Regio- and stereoselectivity of this step highly depends on the metal, ligands, and alkyne structure. A subsequent σ-bond metathesis with starting alkyne releases the product and returns an active lanthanide acetylide **1-40** to the catalytic cycle. On the other hand,

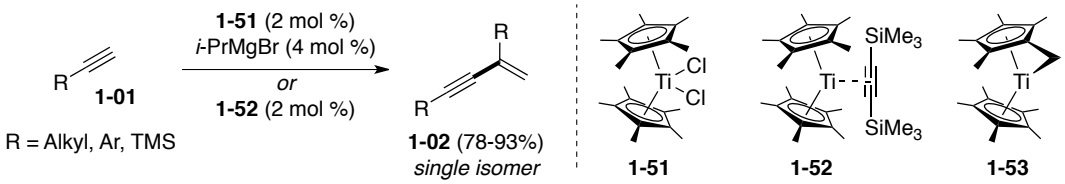
bimetallic catalytic intermediates were proposed for the *Z*-selective *head-to-head* dimerization, catalyzed by lutetium complexes (Scheme 1.3B).[11b] Accordingly, rapid formation of alkynylide-bridged dimeric intermediate **1-44** occurs upon initial σ-bond metathesis. Coordination of the second alkyne moiety to the metal center leads to the cleavage of one of the acetylide bridges. As opposed to a monometallic pathway, the C–C bond formation occurs between alkynyl units bonded to different metal centers via a nucleophilic attack of acetylide on the coordinated alkyne in intermediate **1-45**. Presumably, this step is responsible for the high regio- and stereoselectivity of the process. The catalytic cycle is then completed by the σ-bond metathesis with starting alkyne. Notably, isolated compound **1-44** (Ln = Lu) demonstrated similar catalytic activity in dimerization reaction, which supports bimetallic nature of the reactive intermediates.

Dimerization of alkynes catalyzed by actinides follows mechanistic pathway similar to that of lanthanides (see Scheme 1.3A). However, in this case, two coordination sites of the metal center allow binding of two alkyne molecules with the formation of intermediate **1-48** (Scheme 1.4). Therefore, undesired reductive eliminations from **1-48** or **1-49** might lead to the formation of oligomeric side products, which account for low selectivity of this transformation. Improved selectivity in the presence on amine additives can be explained by the formation of monoalkynyl amido intermediate **1-50**.



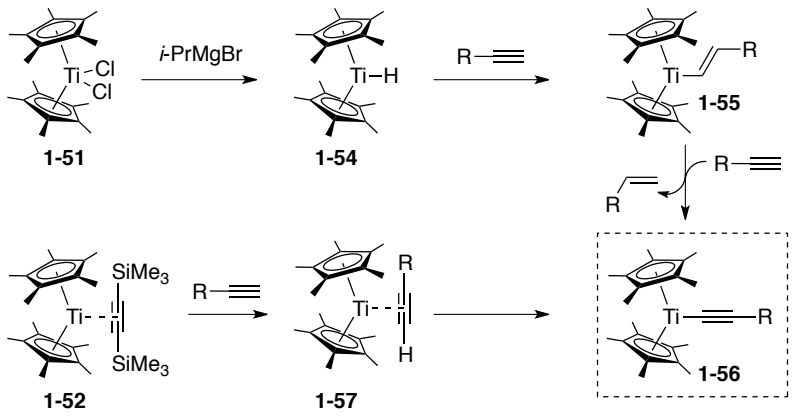
Scheme 1.4. Proposed Mechanism for the Dimerization and Oligomerization of Terminal Alkynes Catalyzed by Actinides.

Metallocenes of titanium,[16,17] zirconium,[18] and hafnium[19] exhibit strong preference for *head-to-head* dimerization reaction. It was first demonstrated by highly selective alkyne dimerization reaction catalyzed by $Cp^*_2TiCl_2$ (**1-51**)/*i*-PrMgBr system.[16] Later, similar results were achieved employing titanocene **1-52**, which did not require an additional reductant (Scheme 1.5).[17a]



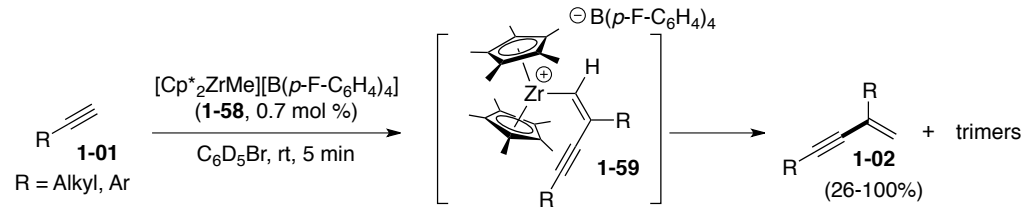
Scheme 1.5. *Head-to-tail* Dimerization of Terminal Alkynes Catalyzed by Titanocenes.

Mechanistically, this transformation is analogous to the previously described lanthanide-catalyzed reactions (see Scheme 1.3A). Catalytically relevant intermediate **1-56** is formed from titanocene dichloride **1-51** via sequence of reduction, hydrotitanation of an alkyne molecule, and σ-bond metathesis (Scheme 1.6).[16] In case of employment of **1-52** as a catalyst, the reaction is initiated by ligand exchange with terminal alkyne, followed by the formation of acetylenide **1-56**.[17a]



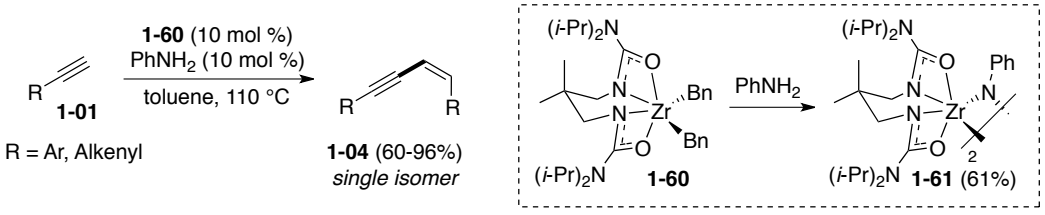
Scheme 1.6. Reaction Initiation in Dimerization of Terminal Alkynes Catalyzed by Titanocenes.

Cationic zirconocenes are also highly active catalysts for the dimerization of terminal alkynes (Scheme 1.7).[18] However, selectivity of this transformation varies depending on starting alkyne. Thus, sterically hindered substrates provide *head-to-tail* dimers with high selectivity whereas more reactive substrates tend to undergo further trimerization. Notably, cationic vinyl zirconocene species **1-59**, which were successfully isolated in stoichiometric reaction of **1-58** with alkynes **1-01**, demonstrated similar catalytic activity to that of precatalyst **1-58**.



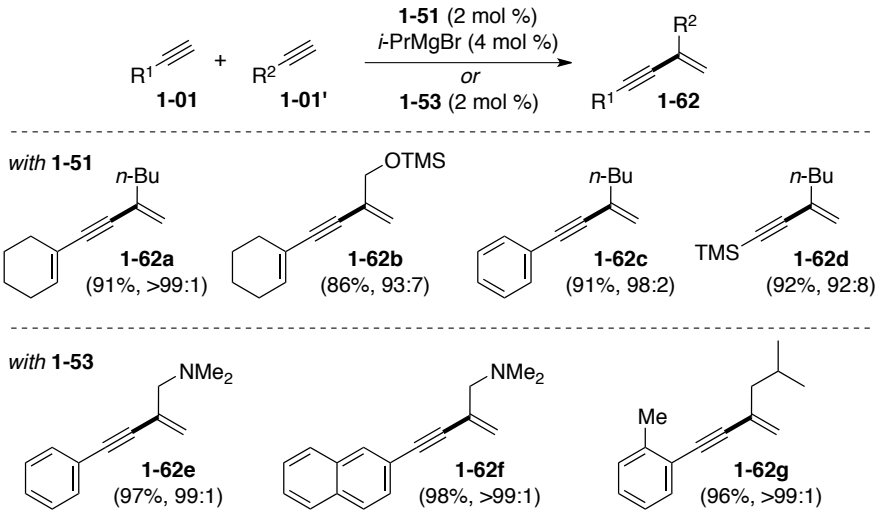
Scheme 1.7. Dimerization of Terminal Alkynes Catalyzed by Cationic Zirconocenes.

Unlike other zirconium catalysts, cationic bis(ureate)dibenzyl zirconium complex **1-60** in the presence of aniline co-catalyst promotes selective *head-to-head* dimerization with the exclusive formation of (*Z*)-enyne **1-04** (Scheme 1.8).[20] The reaction is efficient for a variety of aryl and alkenyl acetylenes. Similarly to the lanthanide-catalyzed *Z*-selective *head-to-head* dimerization reaction (see Scheme 1.3B), this transformation is believed to involve bimetallic intermediates. Accordingly, the reaction of precatalyst **1-60** with aniline gave dimeric bridged imido species **1-61**, which was shown to catalyze rapid and selective dimerization of phenylacetylene.



Scheme 1.8. *Z*-Selective *Head-to-head* Dimerization of Terminal Alkynes Catalyzed by Cationic Zirconium Complexes.

Notably, titanocene-based catalysts are able to differentiate terminal alkynes by their electronic and steric properties, thus, allowing selective cross-dimerization between two different terminal alkynes.[16,21] Thus, high chemo- and regioselectivity was achieved in cross-coupling of alkenyl and arylalkynes with various aliphatic acetylenes (Scheme 1.9). Recent study[21] revealed that dimethylpropargylamine (**1-01'**, $R^2 = CH_2NMe_2$) is especially selective coupling partner in reaction with arylalkynes catalyzed by titonocene **1-53**. Likewise, *ortho*-substituted arylacetylenes demonstrated high chemoselectivity in cross-dimerization reaction.

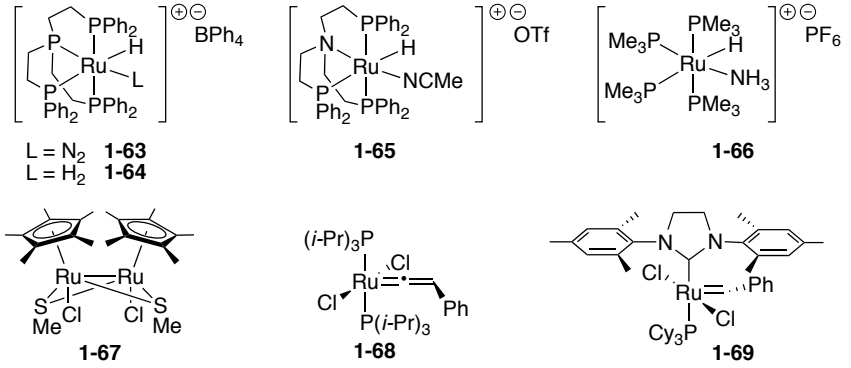


Scheme 1.9. Regioselective cross-Dimerization of Terminal Alkynes Catalyzed by Titanocenes (ratio of **1-62** to other enyne products is shown in parentheses).

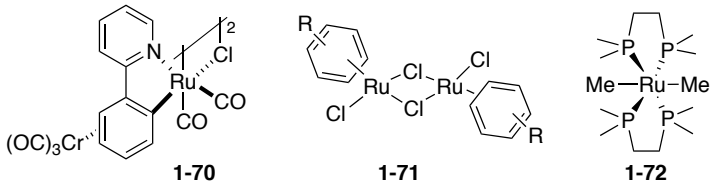
1.1.2. Dimerization of Alkynes Catalyzed by Late Transition Metals

A majority of late transition metals displayed catalytic activity in dimerization reaction of alkynes. Among them, reactions of Ru, Os, Rh, and Ir, were investigated the most. Thus, representative examples of selective dimerization reactions will be discussed below.

A vast number of ruthenium complexes was tested in stoichiometric[22] or catalytic[23] reactions with terminal alkynes. Consequently, several efficient and selective catalysts for the *head-to-head* dimerization leading to (*Z*)-[24,25,26] or (*E*)-[27,28,29]1,4-disubstituted enynes were developed (Schemes 1.10, 1.11).

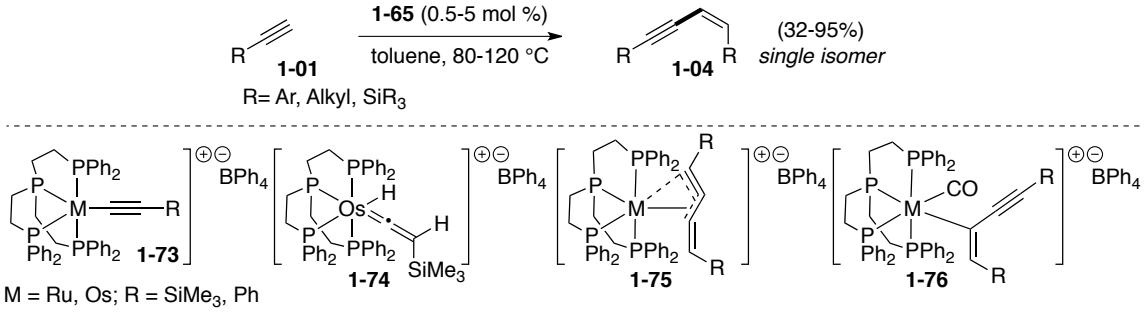


Scheme 1.10. Ruthenium Catalysts for *Z*-selective *Head-to-head* Dimerization of Terminal Alkynes.



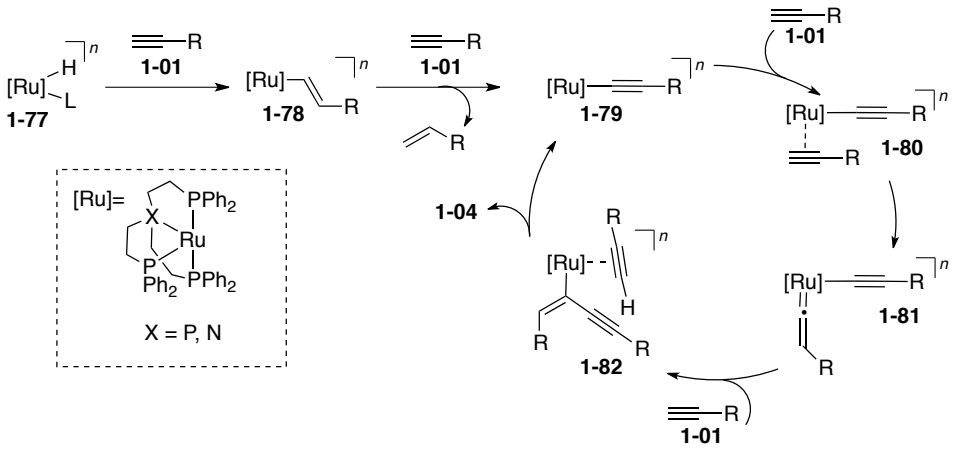
Scheme 1.11. Ruthenium Catalysts for *E*-selective *Head-to-head* Dimerization of Terminal Alkynes.

Tripodal phosphine ruthenium complexes **1-63** – **1-65** were shown to be excellent precatalysts for the *head-to-head* dimerization of acetylenes giving (*Z*)-enynes **1-04** selectively (Scheme 1.12).[24]



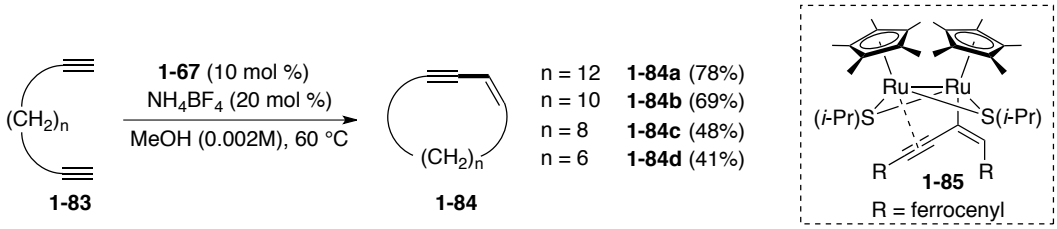
Scheme 1.12. *Z*-selective Ruthenium-catalyzed *Head-to-head* Dimerization of Terminal Alkynes.

Thorough investigation of reactivity of these Ru complexes,[24a] as well as their Os analogs,[30] in stoichiometric reactions with terminal alkynes resulted in isolation of several complexes, such as **1-73**, **1-75**, and **1-76**, which are relevant to the catalytic cycle. Based on that, the following mechanism of dimerization was suggested (Scheme 1.13). Thus, the reaction is initiated by hydroruthenation of alkyne molecule to form vinyl ruthenium species **1-78**, which upon formal σ-bond metathesis produces key ruthenium acetylide **1-79**. Next, the second alkyne moiety coordinates to the metal center to give intermediate **1-80**, which is subsequently converted to the ruthenium vinylidene **1-81**. The geometry of vinylidene, and, therefore, stereochemistry of the product, is controlled by steric interactions or alkyne substituents with the ligands at the metal center. Subsequent migration of alkynyl moiety to the vinylidene α-carbon atom results in the formation of enyne ruthenium species **1-82**, which undergoes another formal σ-bond metathesis with terminal alkyne to complete the catalytic cycle and deliver the product **1-04**.



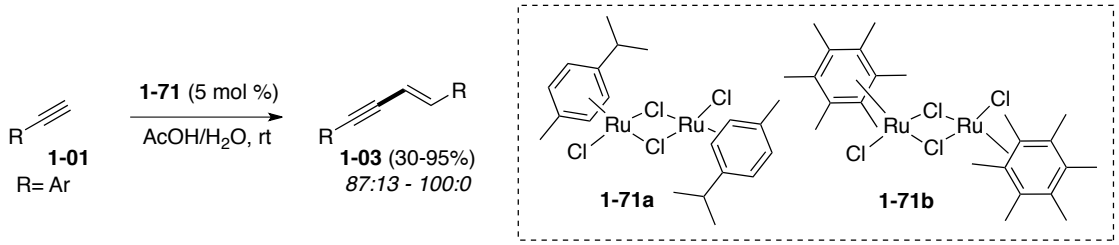
Scheme 1.13. Proposed Mechanism for *Z*-selective Ruthenium-catalyzed *Head-to-head* Dimerization of Terminal Alkynes.

Other powerful ruthenium-based catalysts for the *Z*-selective *head-to-head* dimerization are thiolate-bridged diruthenium complexes, such as **1-67**.[25] Interestingly, this catalyst also promotes intramolecular cyclization of diynes to give *endo*-macrocyclic (*Z*)-enynes **1-84** with good efficiency (Scheme 1.14).[25b] From the mechanistic standpoint, dimerization reaction in the presence of **1-67** follows the same catalytic cycle as the dimerization catalyzed by monometallic ruthenium catalysts, which was supported by isolation of intermediate **1-85**.



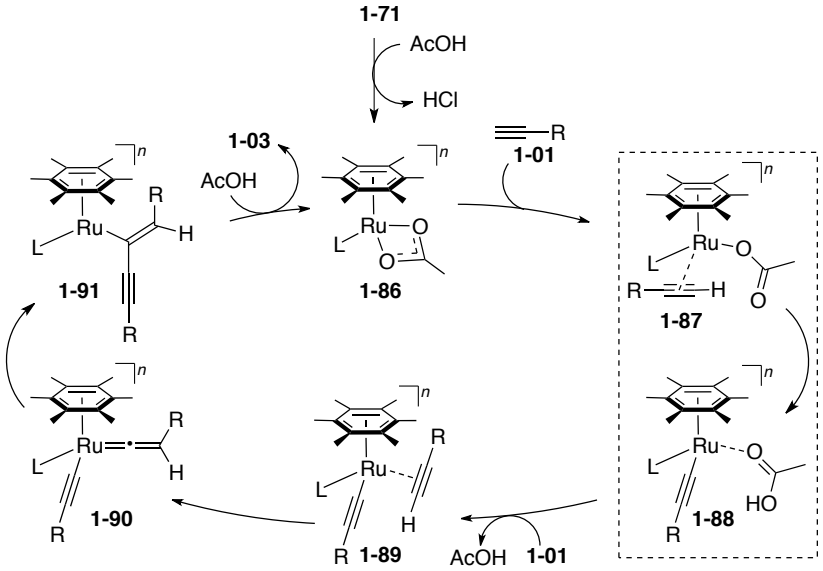
Scheme 1.14. Macrocyclization of Aliphatic Diynes through Ruthenium-catalyzed *Head-to-head* Dimerization of Terminal Alkynes.

With regards to the synthesis of (*E*)-1,4-disubstituted enynes **1-03**, an efficient *head-to-head* dimerization of arylacetylenes was developed employing dimeric ruthenium complexes **1-71a**, **1-71b** (Schemes 1.11, 1.15). Importantly, addition of acetic acid is essential for high selectivity of the reaction and the efficiency was further enhanced in the presence of NaOAc.[28d]



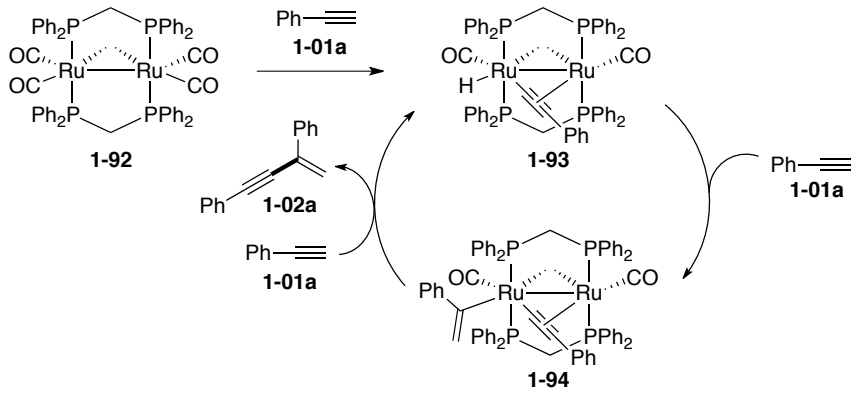
Scheme 1.15. *E*-Selective Ruthenium-catalyzed *Head-to-head* Dimerization of Terminal Alkynes.

Based on this profound effect of acetate anion, an unusual mechanistic pathway was suggested (Scheme 1.16). First, in the presence of acetic acid dimeric ruthenium tetrachloride complex **1-71b** (or **1-71a**) can be converted to the mononuclear species **1-86**, which enters the catalytic cycle. Intramolecular proton transfer from alkyne to the acetate ligand substantially facilitates the formation of necessary ruthenium acetylide **1-88** from intermediate **1-87**. Next, after coordination of second alkyne moiety, intermediate **1-89** tautomerizes into ruthenium vinylidene **1-90**. Selectivity of this stereo-determining step is dictated by steric interactions of alkyne substituents with the π-ligand. Formed upon alkynyl-vinylidene coupling, enyne-containing ruthenium complex **1-91** liberates the product **1-03** by protonation with acetic acid in inter- or intramolecular manner.



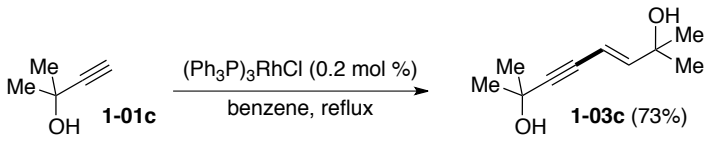
Scheme 1.16. Proposed Mechanism for *E*-selective Ruthenium-catalyzed *Head-to-head* Dimerization of Terminal Alkynes.

As opposed to the Ru-catalyzed *head-to-head* dimerization processes, which involve vinylidene intermediates **1-81** or **1-90**, alternative *head-to-tail* reaction requires formation of vinyl-alkynyl ruthenium species and a subsequent reductive elimination. *Head-to-tail* dimerization was only observed for diruthenium μ-methylene complex **1-92** in the reaction with excess of phenylacetylene (Scheme 1.17).[31]



Scheme 1.17. Ruthenium-catalyzed *Head-to-tail* Dimerization of Phenylacetylene.

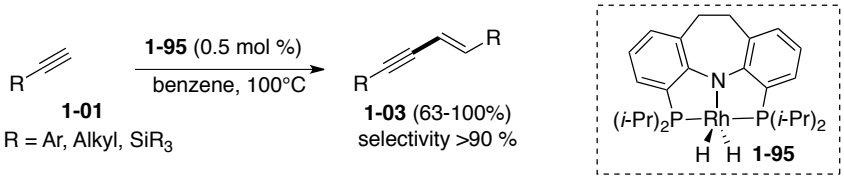
The first example of Rh-catalyzed dimerization of terminal alkynes was demonstrated by Wilkinson group in 1968.[32] They found that tris(triphenylphosphine)rhodium chloride promotes homo-coupling of substituted propargyl alcohols to form (*E*)-1,4-disubstituted enyne **1-03** (Scheme 1.18). Later reports further confirm high preference of Wilkinson's catalyst toward *E*-selective *head-to-head* dimerization reaction mode.[33]



Scheme 1.18. *Head-to-head* Dimerization of 2-Methylbut-3-yn-2-ol Promoted by Wilkinson's Catalyst.

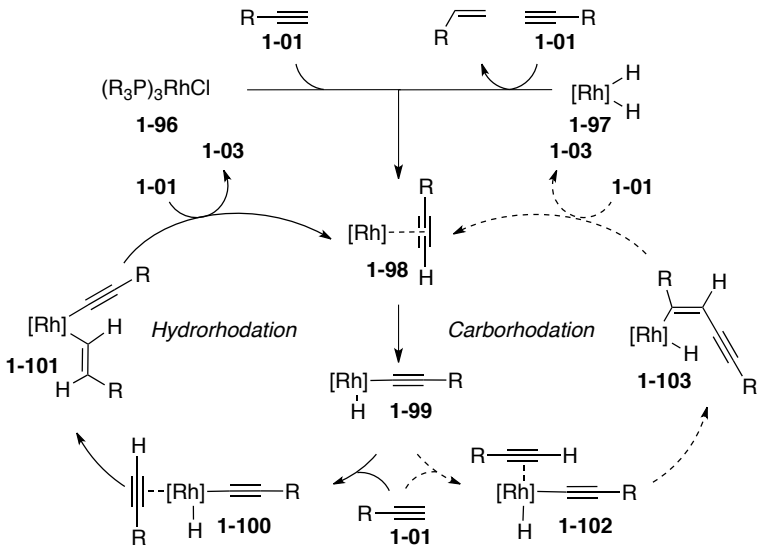
Highly regio- and stereoselective *head-to-head* dimerization was developed employing Pincer-based rhodium catalyst **1-95** (Scheme 1.19).[34] This method is general for a wide range of aryl- and alkylacetylenes, excluding only sterically demanding aliphatic substrates (e.g. *tert*-butylacetylene). Notably, bridged PNP-pincer ligand is crucial for high activity and selectivity of the reaction, as

dimerization of alkynes catalyzed by Rh-complexes, possessing non-bridged PNP[34a] or various OCO[34b] pincer ligands, required longer reaction times and provided mixtures of products.



Scheme 1.19. *Head-to-head* Dimerization of Terminal Alkynes Catalyzed by Pincer Rhodium Catalyst.

It is generally accepted that Rh-catalyzed dimerization proceeds via oxidative addition of Rh to the C–H bond of terminal alkyne to form intermediate **1-99** (Scheme 1.20).

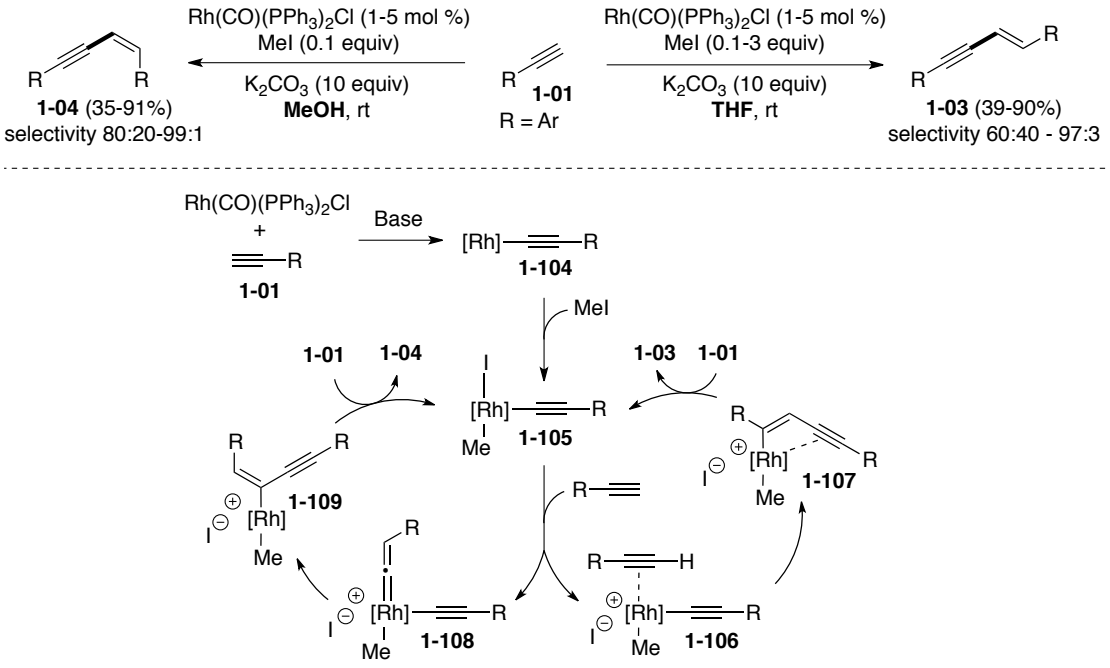


Scheme 1.20. Proposed Mechanism for Rhodium-catalyzed *Head-to-head* Dimerization of Terminal Alkynes.

Although both hydrorhodation and carborhodation were proposed for the subsequent mechanistic event, the former is normally considered the preferred route.[35] Thus, coordination of a second alkyne molecule leads to the intermediate **1-100**, which upon migratory insertion of alkyne across the Rh–H bond, is converted to vinyl-alkynyl rhodium species **1-101**. A complex of this type was isolated in the reaction of 1-pentyne with $(Me_3P)_3RhCl$, and it was shown to undergo reductive elimination to form

enyne product upon heating.[35] Therefore, reductive elimination from intermediate **1-101** completes the catalytic cycle of Rh-catalyzed *head-to-head* dimerization of alkynes.

An interesting stereoselectivity switch was observed in case of the Rh-catalyzed *head-to-head* dimerization in the presence of MeI under basic conditions.[36] It was found that depending on the reaction media, the formation of either (*E*)-(**1-03**) or (*Z*)-1,4-enynes (**1-04**) can be achieved with good to high selectivity (Scheme 1.21). Thus, in aprotic solvent, such as THF, *E*-selective dimerization is predominant whereas MeOH facilitates *Z*-selective reaction. Based on the observed change of selectivity, two distinct mechanistic routes were proposed.

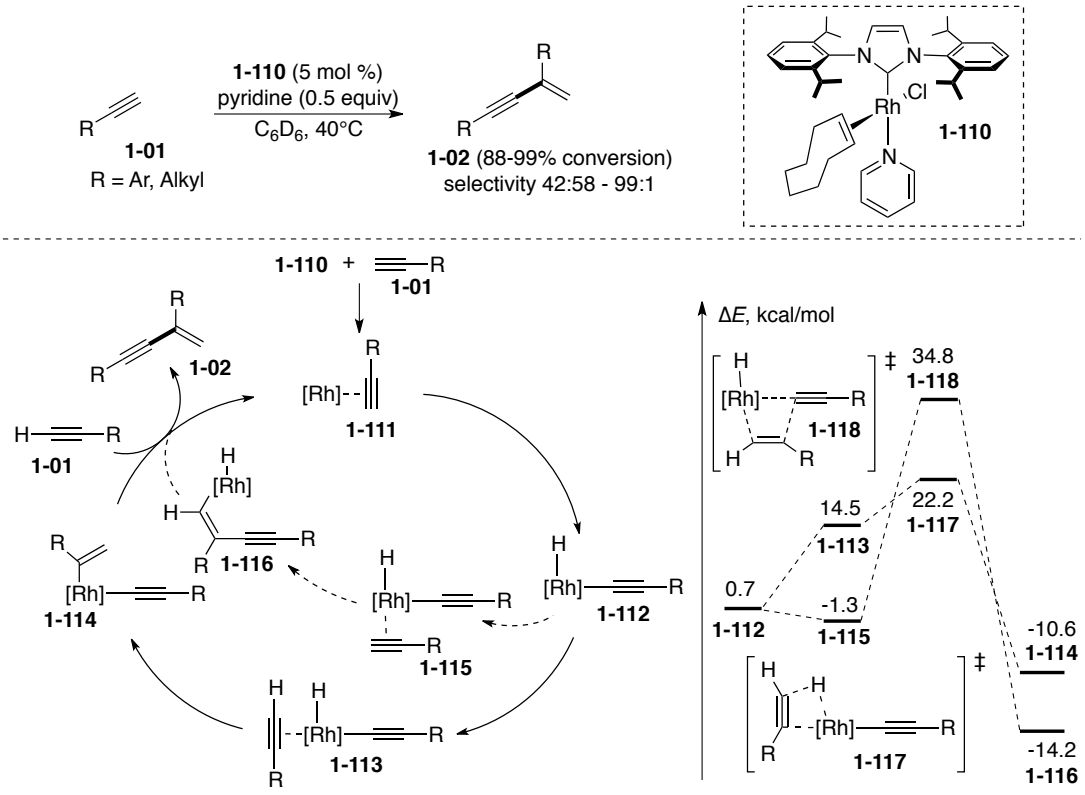


Scheme 1.21. Stereodivergent Rhodium-catalyzed *Head-to-head* Dimerization of Terminal Alkynes.

First, in the presence of base, reaction between Rh-catalyst and alkyne affords rhodium acetylide **1-104**, which undergoes oxidative addition with MeI to form key catalytic intermediate **1-105**. In fact, the formation of a small amount of cross-coupling product between alkyne in methyl iodide was observed in both reactions. Next, reaction proceeds via a carborhodation in aprotic solvent (**1-06→1-107**) or through the formation of rhodium vinylidene **1-108** in protic media. Finally, protiodemetallation or formal σ-bond

metathesis with alkyne molecule and **1-107** or **1-109** furnishes (*E*)-enyne **1-03** or (*Z*)-isomer **1-04**, respectively.

Although formation of 1,3-disubstituted enyne **1-02** via Rh-catalyzed dimerization reaction was observed in several cases,[33,35] a general and selective method for the *head-to-tail* reaction was developed only recently.[37] Particularly, employment of NHC-based Rh-catalyst **1-110** in the presence of pyridine enabled high conversion of various aryl- or alkylalkynes into *gem*-enynes **1-02**. Notably, addition of pyridine completely suppressed the [2+2+2] cycloaddition, which otherwise is a predominant reaction pathway (Scheme 1.22).

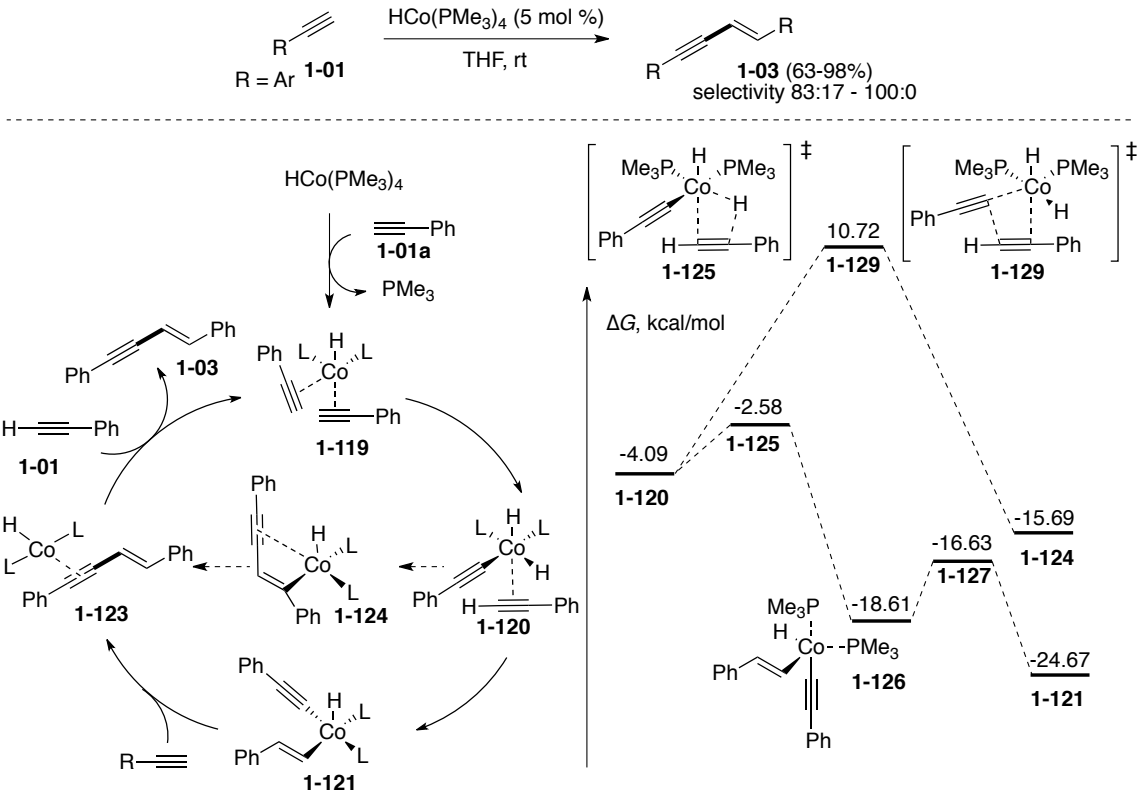


Scheme 1.22. Rhodium-catalyzed *Head-to-tail* Dimerization of Terminal Alkynes (DFT calculations are performed at B3LYP/6-31G(d,p) level).

Mechanism of this transformation was studied in detail by experimental and computational methods. In general, reaction follows oxidative addition/migratory insertion/reductive elimination manifold. Analogously to the *head-to-head* reaction, both hydro- and carborhodation should be

considered in this case. DFT calculations revealed that the former route is significantly favorable (12.6 kcal/mol) over the latter path. Particularly, addition of alkyne into Rh–H bond requires 7.7 kcal/mol (**1-113→1-114** via transition state **1-117**), whereas energy barrier for analogous insertion into Rh–C is 36.1 kcal/mol (**1-115→1-116** via transition state **1-118**). Noteworthy, in this particular system, energy gain of hydrorhodation in the *head-to-tail* over the *head-to-head* manner is about 2 kcal/mol (not shown).[37a]

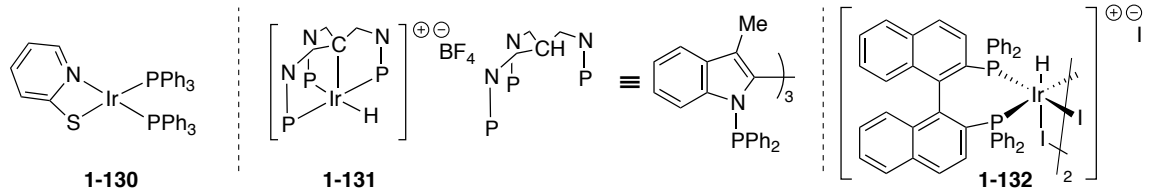
Similar preference of hydrometallation over carbometallation event was also found in Co-catalyzed *head-to-head* dimerization.[38, 39] Thus, hydride cobalt complex $HCo(PMe_3)_4$ was found to be suitable catalyst for dimerization of aryl- and heteroarylalkynes (Scheme 1.23).



Scheme 1.23. Cobalt-catalyzed *Head-to-head* Dimerization of Terminal Alkynes (DFT calculations are performed at B3LYP/SVP level).

DFT calculations indicated that reaction route, which involves insertion of alkyne moiety into Co–H bond, is energetically favorable compared to the corresponding Co–C insertion, even though the former path requires additional isomerization of formed vinylalkynyl intermediate **1-126** to **1-121**, necessary for a subsequent reductive elimination.

Several examples of Ir-catalyzed dimerization reactions were reported.[40] Among them, high selectivity toward the formation of (*E*)-1,4-disubstituted enynes **1-03** was achieved by employing structurally different catalysts, such as **1-130**,[40d] **1-131**,[40e] or **1-132**,[40f] (Scheme 1.24). From mechanistic standpoint, in all cases oxidative addition/migratory insertion/reductive elimination sequence, analogous to that of Rh- and Co-catalyzed transformations, was proposed.

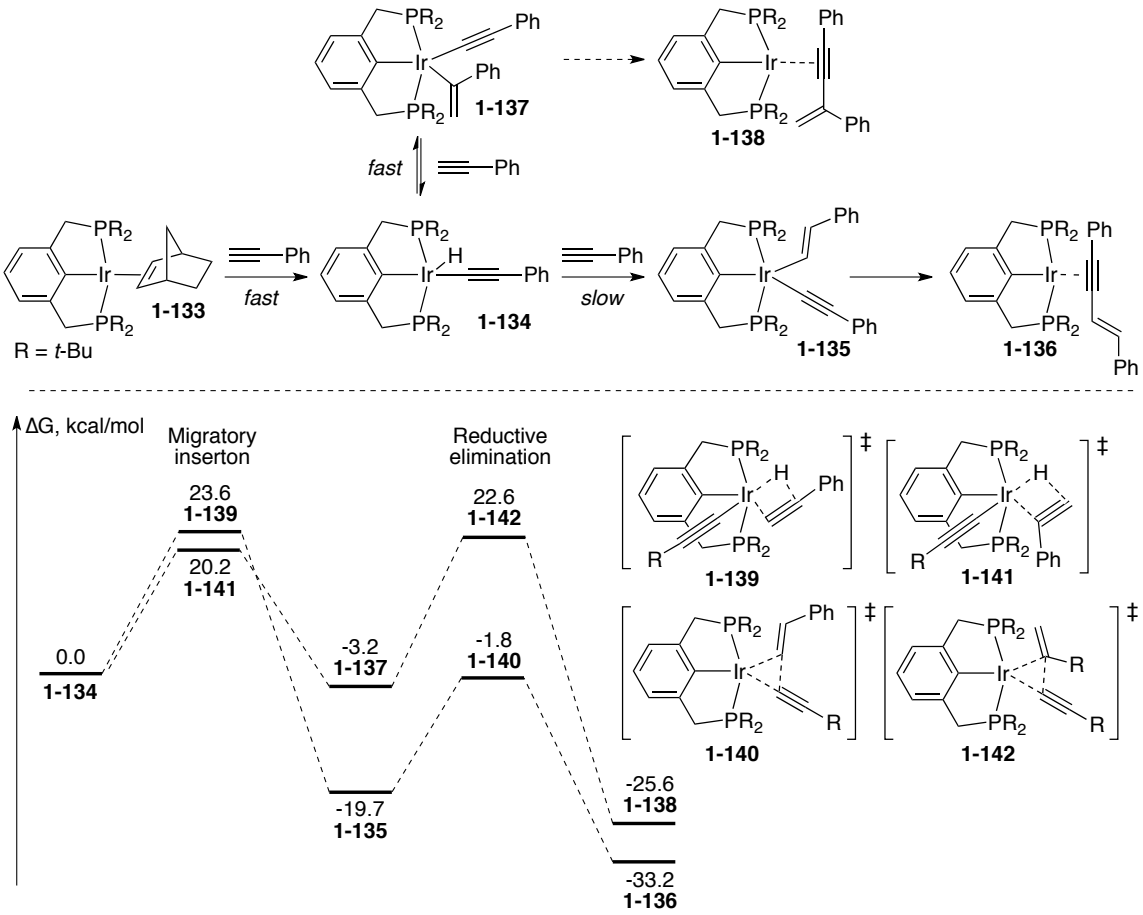


1-130 **1-131** **1-132**

Scheme 1.24. Efficient Iridium Catalysts for *Head-to-head* Dimerization of Terminal Alkynes.

An interesting mechanistic finding arose from stoichiometric reactions of the pincer-type Ir complex **1-133** with phenylacetylene.[41] Accordingly, complex **1-133** promotes dimerization of phenylacetylene to form (*E*)-1,4-enyne **1-03a** (Scheme 1.25). Even though the reaction proceeds through same sequence of steps, it was revealed that migratory insertion of the second alkyne moiety to the alkynyl iridium intermediate **1-134** was not a regioselectivity-determining step. In fact, migratory insertion with the formation of α-vinyl iridium species **1-137** is kinetically preferred over the formation of alternative β-vinyl intermediate **1-135**. Moreover, a former migratory insertion was shown to be reversible. On the other hand, reductive elimination from vinyl-alkynyl intermediate **1-137** was not observed, whereas analogous intermediate **1-135** was smoothly converted to the Ir-complex **1-136**, possessing π-coordinated (*E*)-enyne product **1-03a**. This experimental finding was further confirmed by computational studies, suggesting higher energy barrier (25.8 kcal/mol) for reductive elimination from

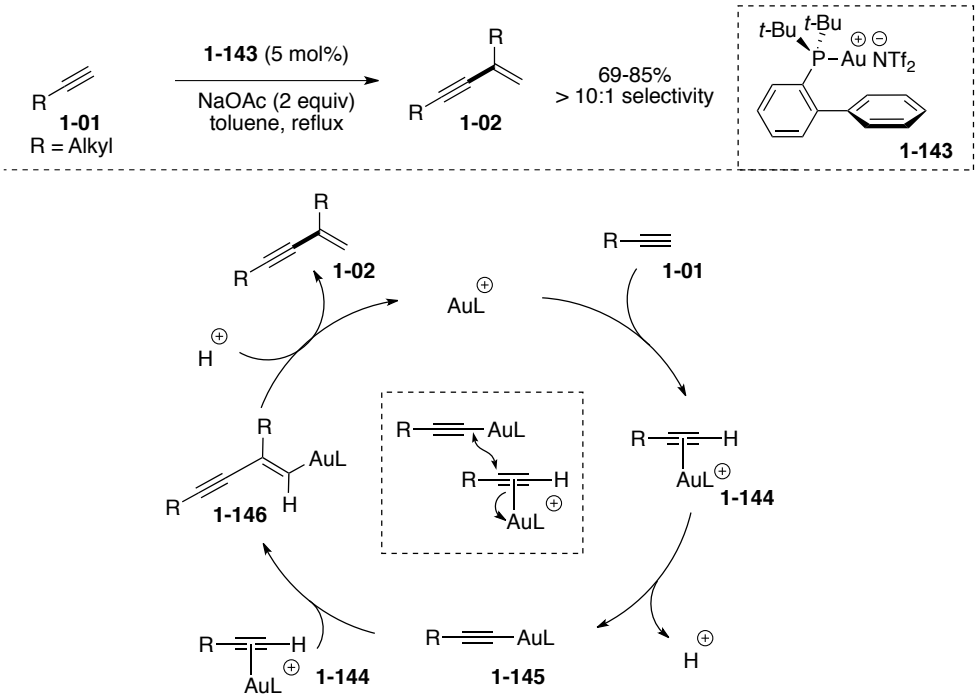
intermediate **1-137** to form **1-138** via transition state **1-142** compared to that of transformation from **1-135** to **1-136** via transition state **1-140** (17.9 kcal/mol). Notably energy difference for the corresponding migratory insertion event is much smaller (3.4 kcal/mol) favoring formation of **1-137** over **1-135**. Overall, reductive elimination step serves as a thermodynamic sink, controlling regioselectivity of this transformation.



Scheme 1.25. Regioselectivity-determining Reductive Elimination Proposed for Iridium *Head-to-head* Dimerization of Terminal Alkynes (DFT calculations are performed at PBE/STO-3G&311G(p)&SDD level).

Cationic gold complex **1-143** was also shown to be an efficient catalyst for the *head-to-tail* dimerization reaction of alkyl-substituted acetylenes (Scheme 1.26).[42] Mechanistic proposal of this transformation is quite distinct from that of other late transition metals, as it involves interaction of two alkyne-containing gold species in the C–C bond forming step. First, gold catalyst coordinates an alkyne to

form intermediate **1-144**, which is then converted to gold acetylenide **1-145** with the assistance of base. Subsequent nucleophilic addition of acetylenide **1-145** to **1-144** leads to the formation of enynyl gold intermediate **1-146**, which upon protiodeauration delivers the final product.

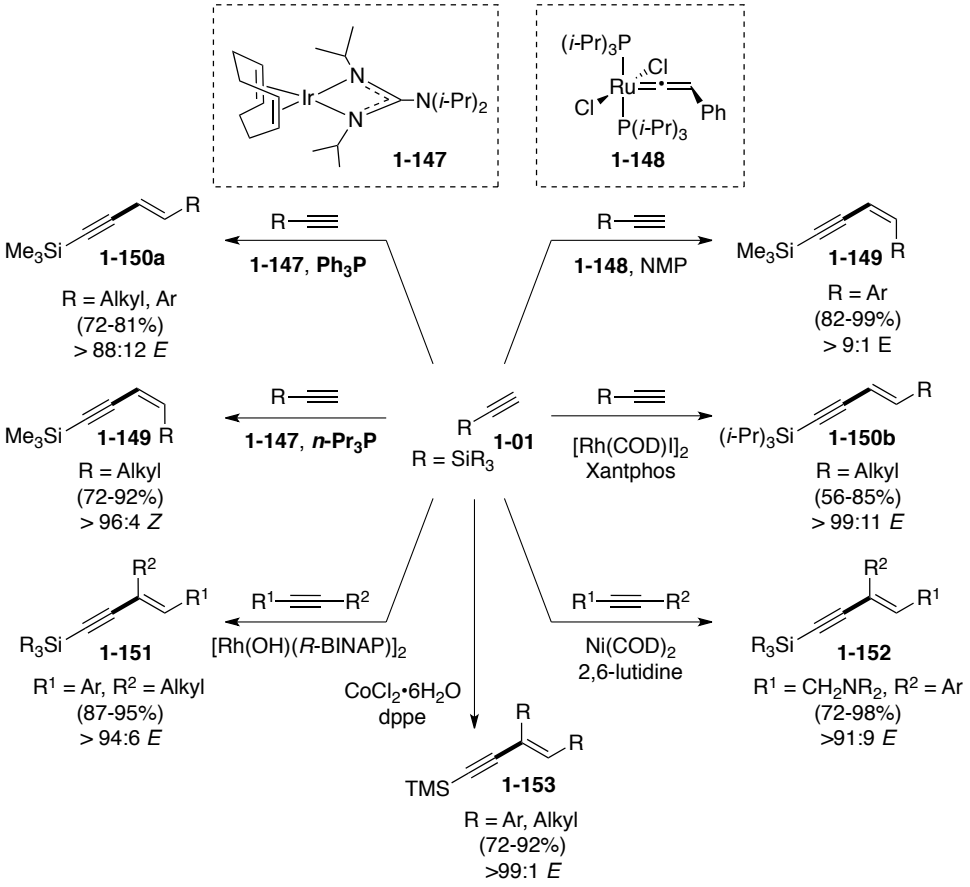


Scheme 1.26. Gold-catalyzed *Head-to-tail* Dimerization of Terminal Alkynes.

Other transition metals, such as Cr,[43] Re,[44] Fe,[45] Os,[46] Ni,[47] and Cu,[48] as well as main group metals Al,[49] Ga,[50] and In[51] displayed catalytic activity in the dimerization reaction of terminal alkynes with different degrees of efficiency and selectivity. However, these transformations were studied less extensively compared to those discussed above.

Several methods for cross-dimerization of two terminal alkynes and hydroalkynylation of internal alkynes catalyzed by late transition metals have been developed. High selectivity in these transformations was achieved by suppressing competing homo-dimerization of the terminal alkyne over the cross-coupling process. Preference for the cross-coupling event is usually controlled by tuning the reactivity of donor and acceptor alkynes using steric and electronic factors. Thus, low reactivity of silylacetylenes toward homo-dimerization reaction enables high selectivity in cross-dimerization reactions with terminal

and internal alkynes catalyzed by several transition metal complexes (Scheme 1.27). For example, stereodivergent dimerization catalyzed by iridium catalyst **1-147** afforded both stereoisomers of 1-trimethylsilyl-4-alkylenynes, (*Z*)- (**1-149**) or (*E*)-**1-150a**, depending on the choice of a phosphine ligand.[52]

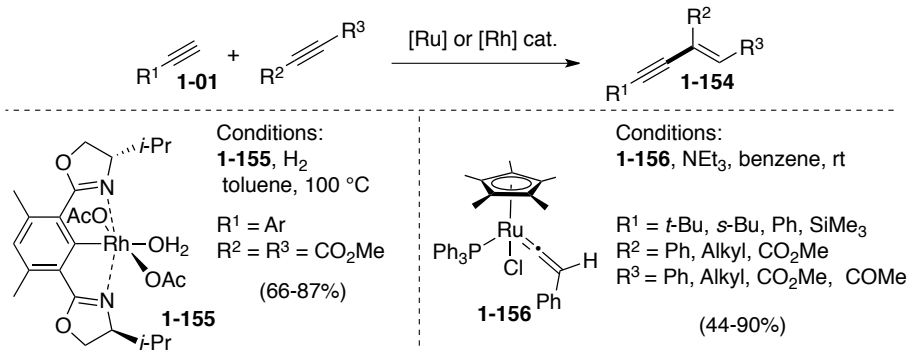


Scheme 1.27. Hydroalkynylation of Alkynes with Silyl Alkynes Catalyzed by Late Transition Metals.

Analogous reaction between TMS-acetylene and arylalkynes toward (*Z*)-enynes (**1-149**, R = Ar) can be achieved under ruthenium catalysis.[53] Additionally, $[Rh(COD)I]_2$ also promotes cross-dimerization of this type to form **1-150** although TIPS-acetylene is required to ensure high selectivity.[54] Furthermore, several methods were developed for selective hydroalkynylation of internal alkynes with silylacetylenes. Thus, complementary regioselectivity of alkyne addition to the arylalkylalkynes was achieved by Rh and Ni catalysts.[55] Under the Rh catalysis, β-styrene derivatives **1-151** can be synthesized with high regio-

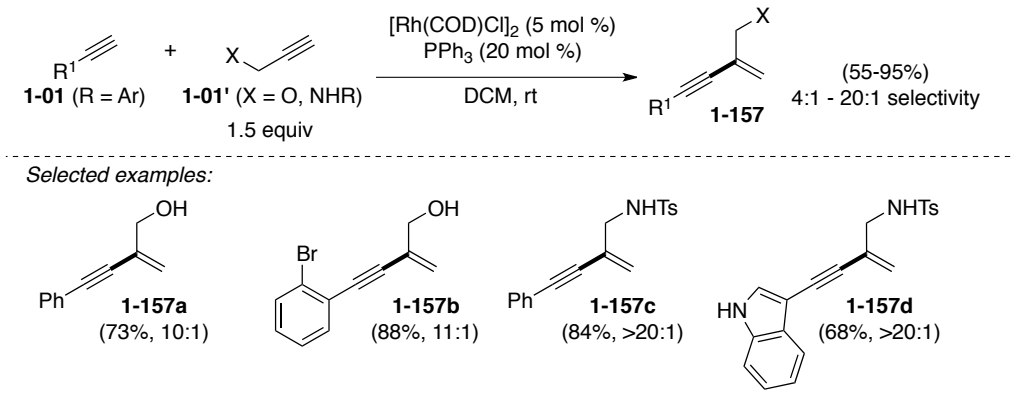
and stereoselectivity. Regioselectivity of the Ni-catalyzed transformation depends on alkyl substituent of the acceptor alkyne with the preference for the formation of α-styrenes **1-152** in cases of propargyl amine derivatives. Lastly, cobalt catalyst enables highly chemo- and stereoselective hydroalkynylation reaction to form **1-153**.[56] However, regioselectivity of this process strongly depends on substitution of the acceptor alkyne.

Hydroalkynylation of internal alkynes with terminal alkynes other than silylacetylenes is rare (Scheme 1.28). Thus, selective cross-addition of arylalkynes with highly activated symmetrical ynedioates was achieved in the presence of Rh catalyst **1-155**.[57] For the Ru-catalysis, selective hydroalkynylation was achieved only using sterically demanding donor alkynes **1-01**.[58] Notably, highly regioselective addition to unsymmetrically substituted alkynes can be achieved in case of substrates bearing an electron-withdrawing substituent.



Scheme 1.28. Hydroalkynylation of Internal Alkynes Catalyzed by Late Transition Metals.

Finally, highly chemo- and regioselective cross-dimerization of two terminal alkynes in the presence of rhodium catalyst was recently demonstrated.[59] It was shown that propargyl alcohols or amines **1-01'** can be efficiently hydroalkynylated with arylacetylenes **1-01** to form 1,3-disubstituted enynes **1-157** in good yields with excellent selectivities (Scheme 1.29).

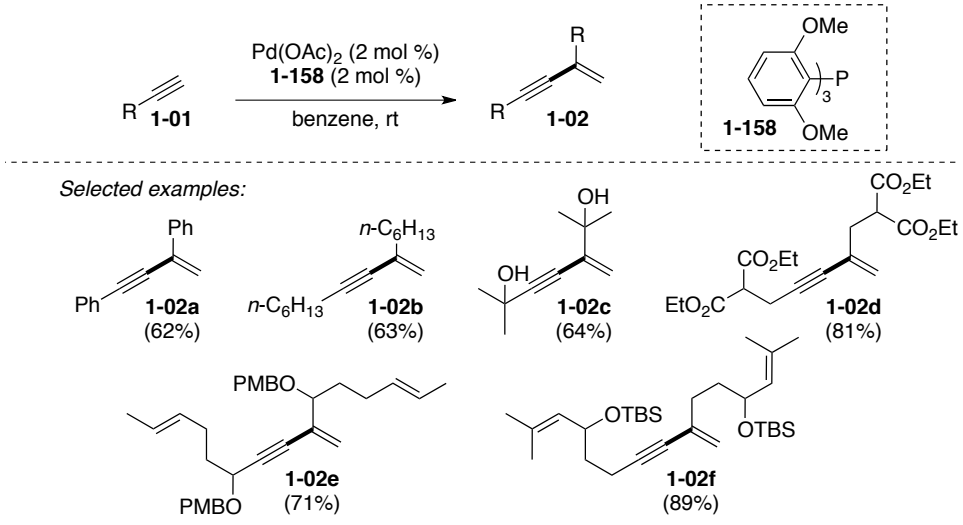


Scheme 1.29. Rhodium-catalyzed cross-Dimerization of Two Terminal Alkynes.

1.1.3. Palladium-catalyzed Dimerization of Alkynes

1.1.3.1. Palladium-catalyzed Head-to-tail Dimerization of Terminal Alkynes

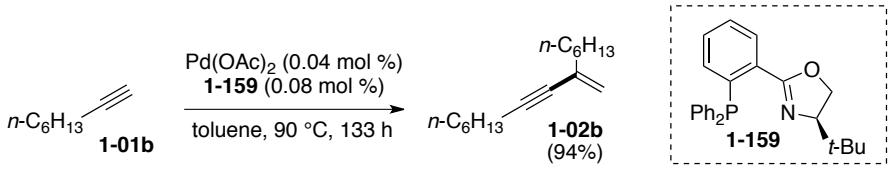
Arguably, the Pd-catalyzed dimerization reaction of alkynes is the most studied. Highly regioselective *head-to-tail* dimerization reaction of terminal alkynes was developed by Trost group in 1987.[60] Thus, in the presence of catalytic amounts of $Pd(OAc)_2$ and electron-rich sterically hindered phosphine ligand TDMPP, terminal alkynes **1-01** dimerize to form 1,3-disubstituted enynes **1-02** (Scheme 1.30).



Scheme 1.30. Palladium-catalyzed *Head-to-tail* Dimerization of Terminal Alkynes.

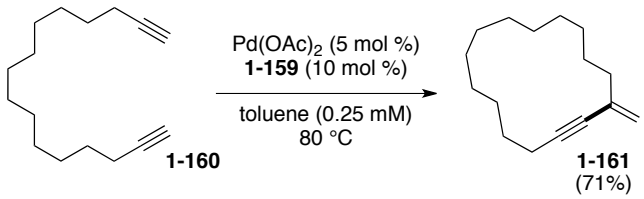
Employment of both $Pd(OAc)_2$ and TDMPP ligand **1-158** is crucial for high selectivity and efficiency of this transformation. This methodology proved to be general for a variety of aryl- (e.g. **1-01a**) or alkylalkynes (**1-01b**), including sterically demanded alkynes (**1-01c**, **1-01d**) and structurally complex substrates **1-01e** or **1-01f**.

Subsequently, Pfaltz's group demonstrated that employment of phosphinooxazoline-based ligand **1-159** allows dimerization of alkynes with catalyst loading as low as 0.04 mol % with no loss of efficiency or selectivity of the process (Scheme 1.31).[61]



Scheme 1.31. Employment of Phosphinooxazoline-based Ligand **1-159** in the Palladium-catalyzed *Head-to-tail* Dimerization of Terminal Alkynes.

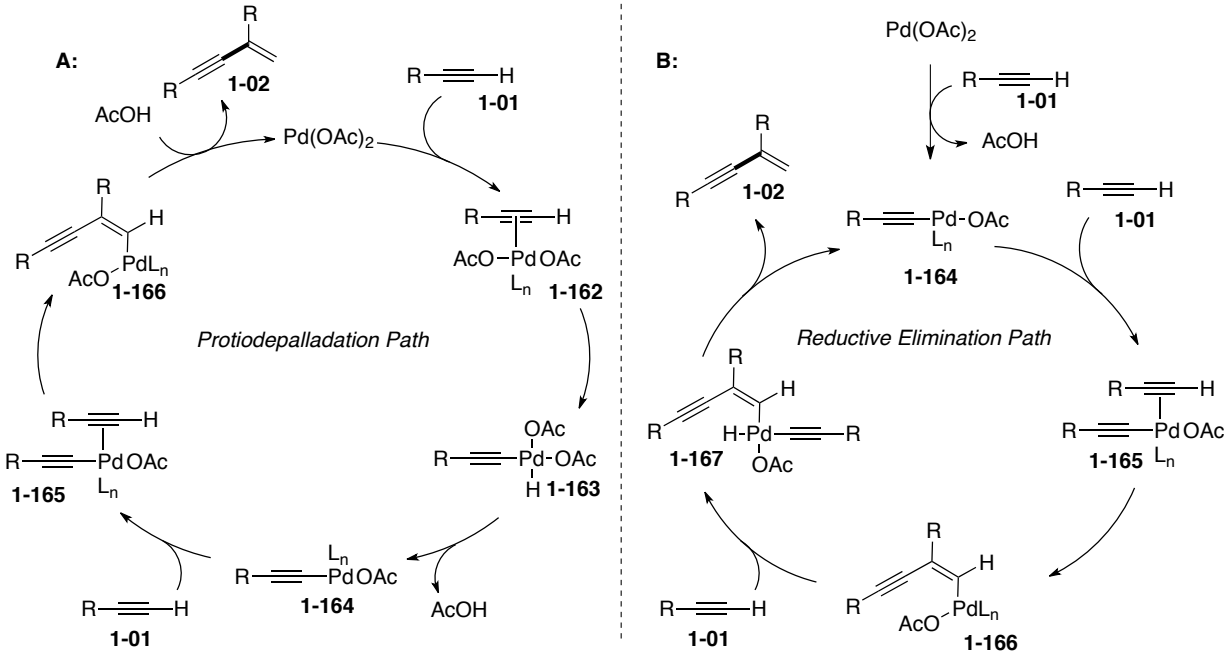
Additionally, intramolecular dimerization of alkynes was successful under these conditions[61,62] providing rapid access to macrocyclic enynes. Competing intermolecular dimerization and oligomerization processes were suppressed by slow addition of substrate **1-160** (Scheme 1.32).



Scheme 1.32. Synthesis of Macrocyclic Enynes via Palladium-catalyzed *Head-to-tail* Dimerization of Terminal Alkynes.

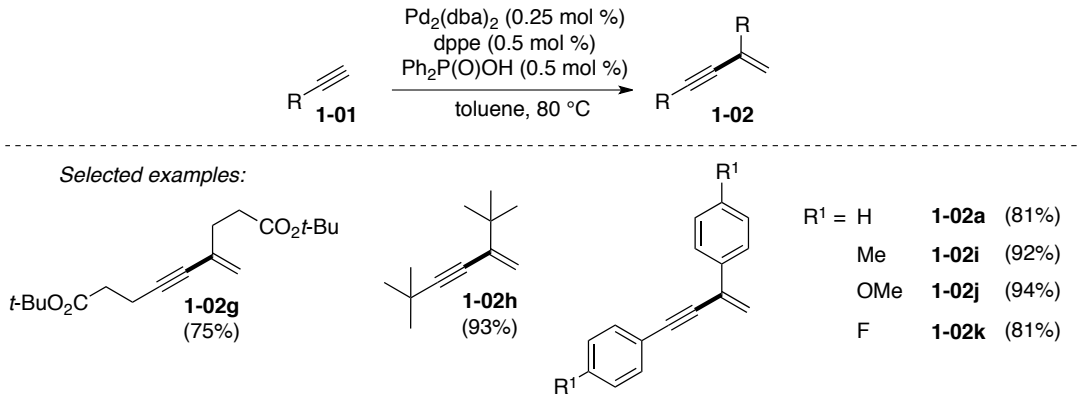
Mechanistically, the reaction starts with coordination of $Pd(OAc)_2$ to the alkyne followed by oxidative addition of palladium into the C–H bond of the alkyne with the formation alkynylpalladium species **1-163** (Scheme 1.33A). The loss of acetic acid opens coordination site on the Pd center in **1-164** allowing coordination of the second alkyne molecule to form **1-165**. Subsequent carbopalladation leads to

the formation of alkenyl palladium **1-166**, which upon protiodepalladation delivers the product **1-02** and returns $Pd(OAc)_2$ to the catalytic cycle. Alternatively, intermediate **1-164** was proposed to be an active catalytic species (Scheme 1.33B). In this case, intermediate **1-166** is converted to the final product via oxidative addition of alkyne to form alkynylpalladium species **1-167**, followed by a reductive elimination. Based on experimental observations, both of these mechanistic hypotheses are equally possible.



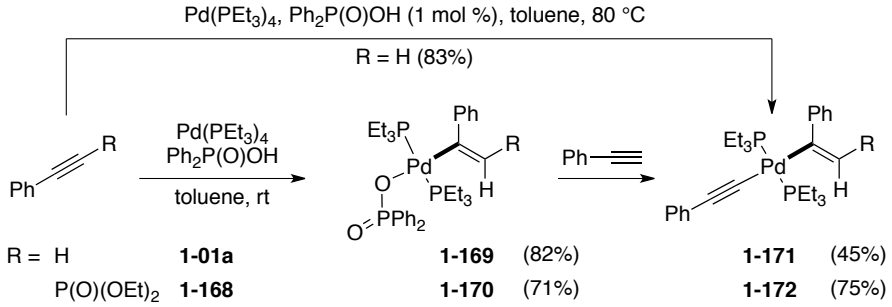
Scheme 1.33. Plausible Mechanism for the Palladium-catalyzed *Head-to-tail* Dimerization of Terminal Alkynes Involving (A) Protiodepalladaion or (B) Reductive Elimination Pathways.

Recently, a complementary approach for the *head-to-tail* dimerization of terminal alkynes was reported by Guo and Han (Scheme 1.34).[63] Thus, Pd(0) catalyst in the presence of catalytic amount of diphenylphosphinic acid triggers homo-coupling of terminal alkynes **1-01** with the exclusive formation of 1,3-enyne products **1-02**. This method is proved to be general for a variety of alkyl- and aryl-substituted alkynes regardless of steric or electronic nature of the substrate.



Scheme 1.34. *Head-to-tail* Dimerization of Terminal Alkynes Catalyzed by Palladium/Brønsted Acid System.

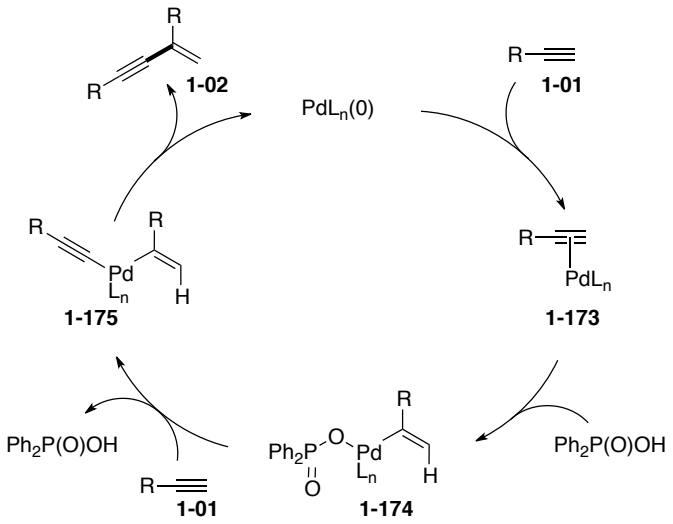
The mechanism of this transformation was investigated in a series of stoichiometric experiments (Scheme 1.35). Hence, treatment of terminal (**1-01a**) or internal (**1-168**) alkynes with $Pd(PEt_3)_4$ in the presence of diphenylphosphinic acid resulted in the formation of vinylpalladium complexes **1-169** and **1-170** with high regio- and stereoselectivity. The mechanism of this hydropalladation process is not well understood.[64] Subsequent reaction of these complexes with phenylacetylene afforded alkynylvinyl palladium species **1-171** and **1-172** presumably via a ligand exchange. Notably, alkynyl vinyl palladium complex **1-171** can be obtained directly in the reaction of phenylacetylene **1-01a** with $Pd(PEt_3)_4$ in the presence of catalytic amount of phosphinic acid.



Scheme 1.35. Brønsted Acid-catalyzed Synthesis of Alkynylvinyl Palladium Complexes.

Based on these observations, the following mechanistic rationale was proposed for the dimerization reaction catalyzed by Pd(0)/Brønsted acid system (Scheme 1.36). Accordingly, the reaction

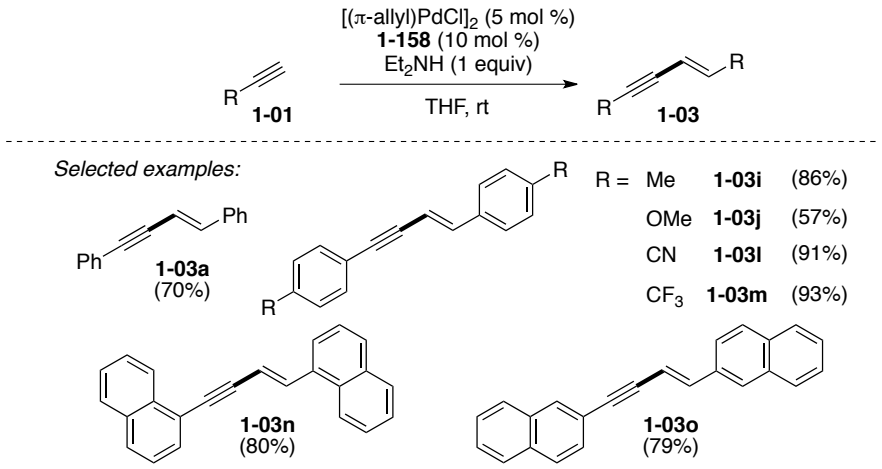
starts with the coordination of the alkyne to the metal center to afford intermediate **1-173**, which in the presence of phosphinic acid undergoes hydropalladation leading to vinyl palladium species **1-174**, which is similar to **1-169**. Subsequent ligand exchange with the second alkyne moiety delivers alkynylvinyl palladium intermediate **1-175**, which upon reductive elimination delivers 1,3-disubstituted enyne **1-02**. Initial hydropalladation (**1-173** → **1-174**) event represents regio- and stereodetermining step. Notably, this mechanistic pathway is distinct from mechanistic route, previously proposed by Trost, in which regio- and stereoselectivity is determined during the carbopalladation step (see Scheme 1.33).



Scheme 1.36. Proposed Mechanism for *Head-to-tail* Dimerization of Terminal Alkynes Catalyzed by Palladium and Brønsted Acid.

1.1.3.2. Palladium-catalyzed Head-to-head Dimerization of Terminal Alkynes

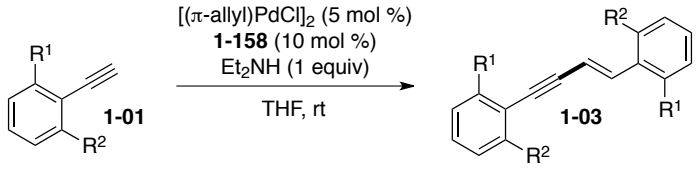
Alternative Pd-catalyzed *head-to-head* dimerization of terminal alkynes was first developed by Gevorgyan group (Scheme 1.37).[65] Thus, various arylalkynes efficiently dimerize to form 1,4-disubstituted enynes in the presence of $[(\pi\text{-allyl})PdCl]_2$, TDMPP, and Et_2NH with excellent selectivity.



Scheme 1.37. Palladium-catalyzed *Head-to-head* Dimerization of Arylalkynes.

However, unusual reactivity pattern was observed for *head-to-head* dimerization of *ortho*-substituted arylalkynes (Table 1.2). For example, *ortho*-fluorophenylacetylene (**1-01p**) smoothly underwent dimerization reaction with similar efficiency to that of phenylacetylene (entry 1).

Table 1.2. *Head-to-head* Dimerization of *ortho*-Substituted Arylalkynes.

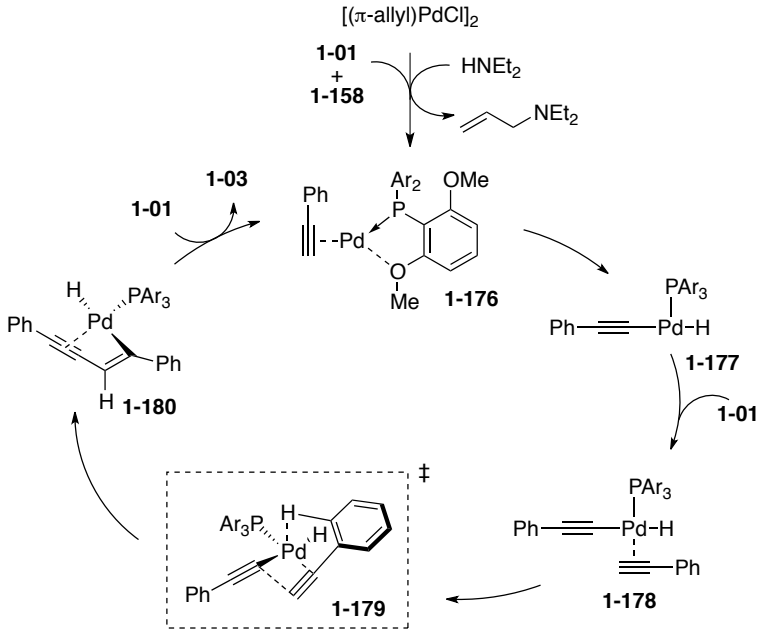


Entry	R^1	R^2		Yield of **1-03**, %
1	F	H	**1-03p**	71
2	Me	H	**1-03q**	50 + other isomers
3	Me	Me	**1-03r**	NR
4	F	F	**1-03s**	NR
5	OMe	OMe	**1-03t**	NR

On the other hand, introduction of methyl group to the *ortho*-position substantially decreased the efficacy of this transformation (entry 2). Moreover, substitution of both hydrogen atoms with groups of various

size and electronic nature completely suppressed the dimerization reaction (entries 3-5). Furthermore, subjection of alkyl-substituted substrates to the reaction conditions resulted in complete decomposition of starting materials (not shown). Therefore, it is concluded that at least one *ortho-H*-atom is required for selective *head-to-head* dimerization reaction under these reaction conditions.

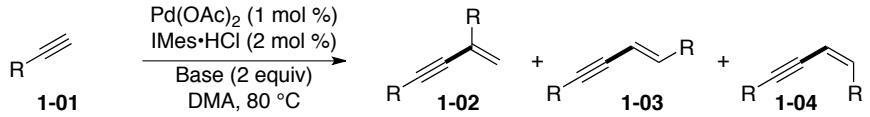
Based on the observations discussed above, the following mechanistic rationale was proposed (Scheme 1.38). Accordingly, with the aid of TDMPP and diethylamine, $[(\pi\text{-allyl})PdCl]_2$ is first converted to the active catalytic species **1-176**, which upon oxidative addition of the alkyne forms alkynyl palladium intermediate **1-177**. Next, coordination of the second alkyne molecule leads to the formation of intermediate **1-178**. The regio- and steriodetermining step involves carbopalladation of **1-178** *en route* to **1-180**, which proceeds through a key transition state **1-179**. It is believed, that agostic interactions between metal center and *ortho*-C–H bond of arylalkyne stabilize this transitions state, thus, decreasing the energy barrier of this transformation. This coordination also dictates orientation of the second alkyne moiety, providing high regio- and stereoselectivity of head-to-head dimerization.



Scheme 1.38. Proposed Mechanism for *E*-selective Palladium-catalyzed Head-to-head Dimerization of Terminal Alkynes.

Independently, Nolan group reported that an employment of *N*-heterocyclic carbene (NHC)-based palladium catalysts allows for efficient dimerization reaction favoring *head-to-head* process (Table 1.3).[66]

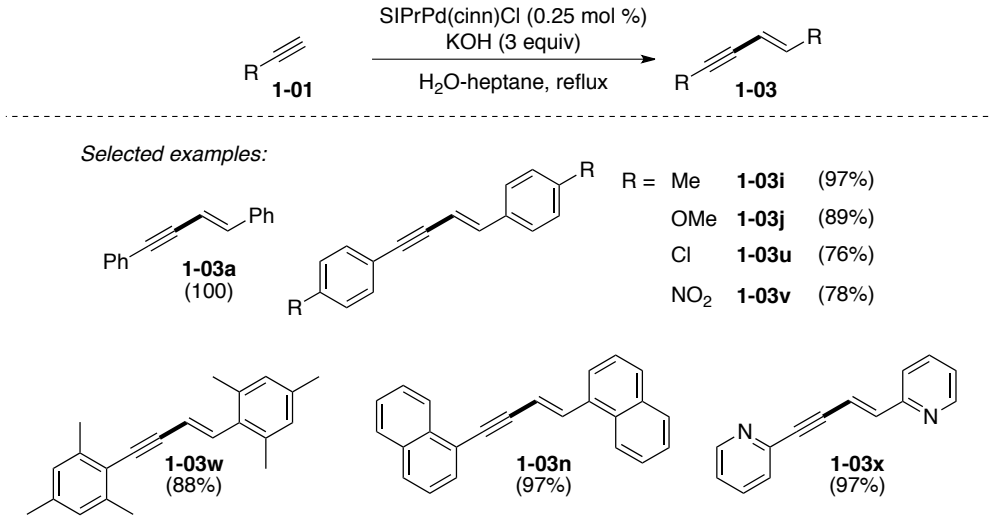
Table 1.3. Dimerization of Terminal Alkynes Catalyzed by $Pd(OAc)_2$/NHC/Base.



Entry	R	Base	**1-02** : **1-03** : **1-04**	Combined yield, %
1	Ph	Cs_2CO_3	0 : 97 : 3	98
2	Ph	K_2CO_3	26 : 69 : 5	100
3	*n*-Bu	Cs_2CO_3	6 : 91 : 3	97
4	*n*-Bu	K_2CO_3	91 : 9 : 0	89
5	*t*-Bu	Cs_2CO_3	0 : 99 : 1	90
6	*t*-Bu	K_2CO_3	52 : 44 : 4	48
7	Me_2NCH_2-	Cs_2CO_3	7 : 92 : 1	90
8	Me_2NCH_2-	K_2CO_3	76 : 24 : 0	92

Although this reaction generally gives high yields of the dimeric products, regio- and stereoselectivity of this process depends on the substrate, as well as on inorganic base used. For instance, dimerization of phenyl acetylene in the presence of Cs_2CO_3 proceeded regioselectively to afford a mixture of 1,4-enynes **1-03** and **1-04** strongly favoring (*E*)-isomer **1-03** (entry 1). However, employment of K_2CO_3 scrambles both regio- and stereoselectivity of dimerization (entry 2). Interestingly, in case of linear alkyl-substituted alkynes almost complete switch of regioselectivity was observed (entries 3, 4). Overall, despite of high selectivity achieved for particular substrates (entry 5), this method lacks generality and cannot be broadly applied for a selective *head-to-head* dimerization of alkynes. No mechanistic hypothesis was offered to explain selectivity dependence on the nature of inorganic base.

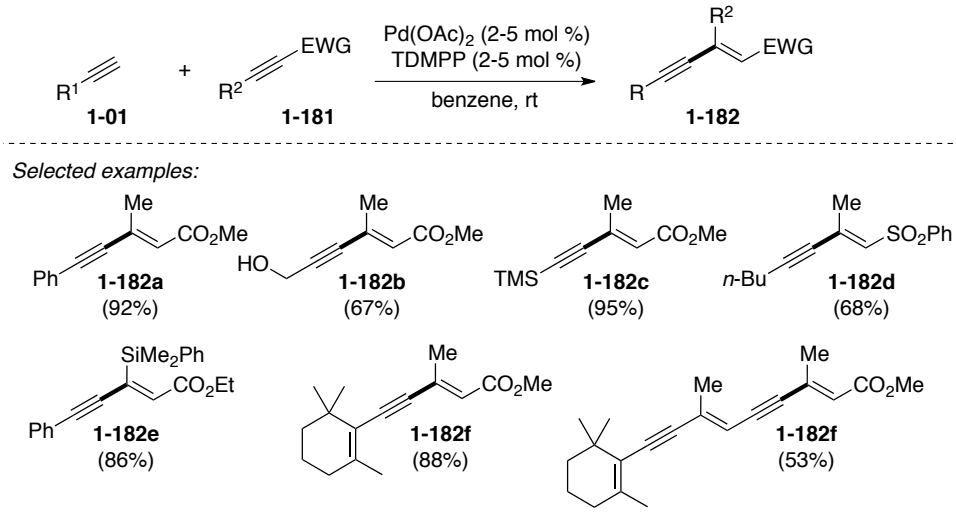
Very recently, highly efficient and selective catalytic system for the *head-to-head* dimerization of arylalkynes based on defined NHC-palladium catalyst was developed (Scheme 1.39).[67] Thus, arylalkynes were dimerized in the presence of only 0.25 mol % of SIPrPd(cinn)Cl catalyst delivering (*E*)-1,4-disubstituted enynes **1-03** in high to excellent yields. The reaction is general for arylalkynes of different electronic nature and substitution pattern, including *ortho*-substituted substrates (**1-03n**, **1-03w**), as well as heteroarenes (**1-03x**). However, this catalytic system is inefficient for dimerizing aliphatic alkynes.



Scheme 1.39. *Head-to-head* Dimerization of Arylalkynes.

1.1.3.3. Palladium-catalyzed Hydroalkynylation of Alkynes

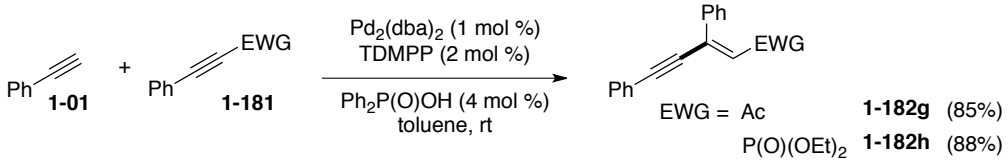
Selectivity of the Pd-catalyzed cross-dimerization can be controlled by tuning the activity of donor and acceptor alkynes. Thus, Trost's Pd-catalyzed *head-to-tail* homo-dimerization of terminal alkynes was expanded to cross-addition to activated internal alkynes **1-181** bearing an electron-withdrawing group (Scheme 1.40).[60] Importantly, homo-dimerization event was completely suppressed in the presence of acceptor alkyne securing high chemoselectivity of the process.



Scheme 1.40. Palladium-catalyzed cross-Dimerization of Alkynes.

Electron-withdrawing nature of acceptor alkyne is responsible for excellent regioselectivity of cross-addition reaction. Moreover, this reaction proceeds with high stereoselectivity leading to the formation of a sole product **1-182**. To date, this is the only hydroalkynylation methodology, which is general with respect to various donor alkynes.

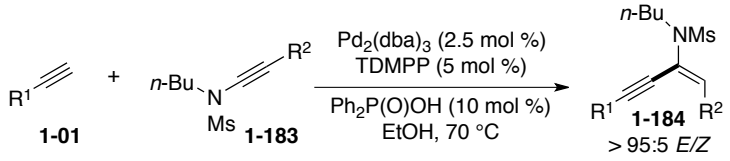
Analogously, the cross-addition of terminal alkynes to internal alkynes can be achieved using Pd(0)/Brønsted acid catalytic system (Scheme 1.41). Notably, acceptor alkynes are more reactive coupling partners in hydroalkynylation reaction compared to terminal alkynes in homo-dimerization, since cross-dimerization reaction proceeds at lower temperature with equally good efficiency.



Scheme 1.41. Cross-Dimerization of Alkynes Catalyzed by Palladium and Brønsted Acid.

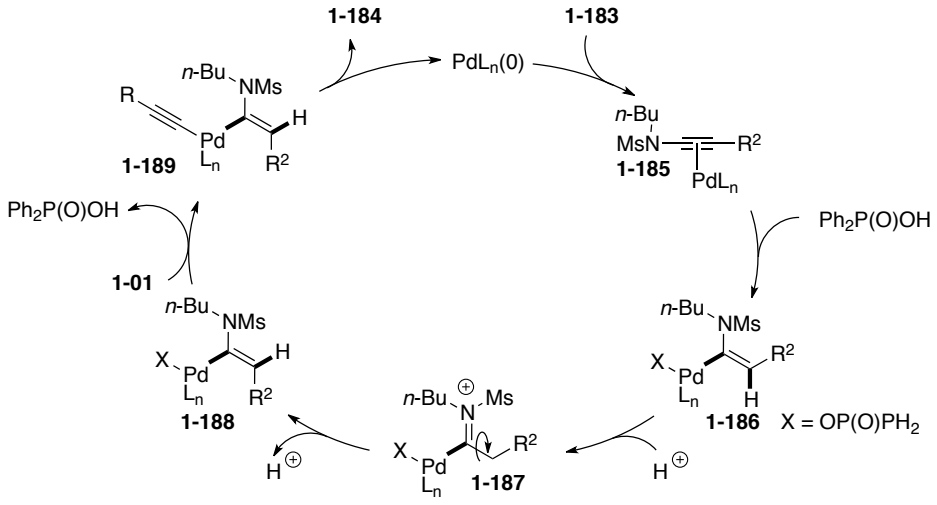
Employment of Brønsted acid co-catalyst strategy also allowed for the development of efficient hydroalkynylation reaction of ynamides (Scheme 1.42).[68] The scope of terminal alkynes was found to be quite broad as various aryl-, alkyl-, alkenyl- or silyl-substituted enynes were obtained in good yields with

high stereoselectivities. With regard to acceptor alkynes, only aryl ynamides were efficient in this transformation.



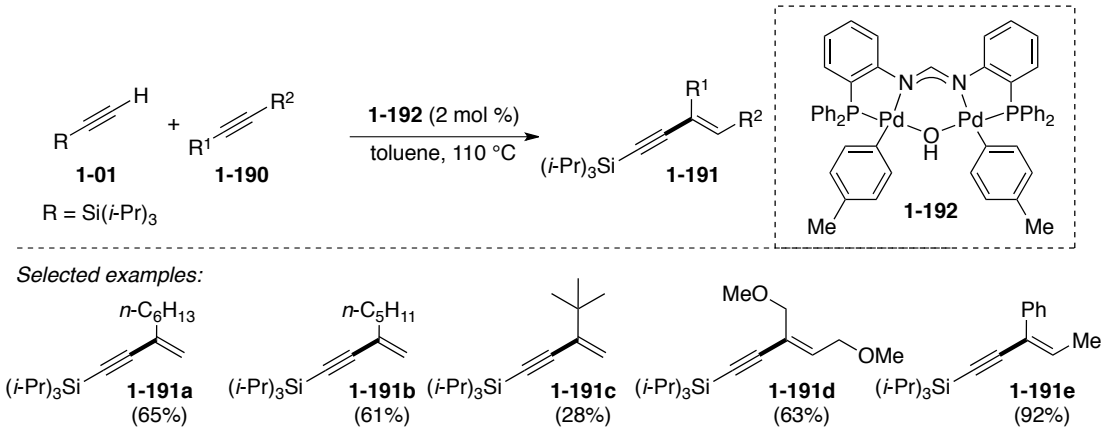
Scheme 1.42. Cross-Dimerization of Terminal Alkynes with Ynamides Promoted by Palladium/Brønsted Acid Cooperative Catalysis.

Similarly to homo-dimerization reaction, this transformation proceeds through initial hydropalladation of ynamide (**1-185 → 1-186**, Scheme 1.43). However, prior to ligand exchange (**1-188 → 1-189**) and subsequent reductive elimination (**1-189 → 1-184**), the initially formed vinyl palladium intermediate (*Z*)-**1-186** undergoes a Brønsted acid-catalyzed isomerization to form more favorable (*E*)-**1-188** through intermediacy of **1-187**. High stereoselectivity in this case is attributed to the streric interactions of alkyne substituents R^2 and NR_2 of (*Z*)-**1-186**, which are reduced in its (*E*)-analog **1-188**. Notably, this transformation represents a rare example of a formal *trans*-hydroalkynylation reaction of internal alkynes.



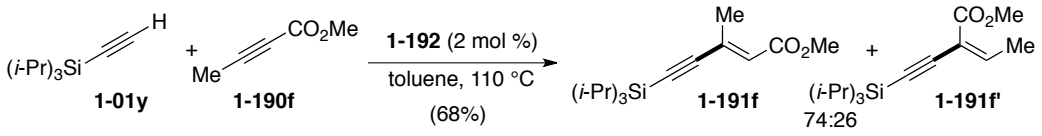
Scheme 1.43. Proposed Mechanism for cross-Dimerization of Terminal Alkynes with Ynamides Promoted by Palladium/Brønsted Acid Cooperative Catalysis.

Selective cross-addition of two unactivated alkynes was achieved by coupling of TIPS-acetylene with various terminal and internal alkynes in the presence of a binuclear palladium catalyst **1-192** (Scheme 1.44).[69] In this case, high chemoselectivity was attributed to the low reactivity of TIPS-acetylene toward homo-coupling reaction. Noteworthy, formation of TIPS-acetylene homodimers was practically suppressed (<5%) whereas no more than 20% of homodimers of the second acetylene was formed. The reaction is sensitive to sterics and is not applicable to couplings with activated terminal alkynes, such as arylacetylenes, due to their predominant dimerization.



Scheme 1.44. Selective cross-Addition of TIPS-acetylene to the Unactivated Alkynes Catalyzed by Binuclear Palladium Complex.

Interestingly, reaction of TIPS acetylene with an activated alkyne under these conditions suffers from poor regio- and stereoselectivity (Scheme 1.45), which is in sharp contrast with the selective Trost hydroalkynylation reaction. This result indicates that these two Pd-catalyzed cross-addition processes most likely proceed via different mechanistic routes.

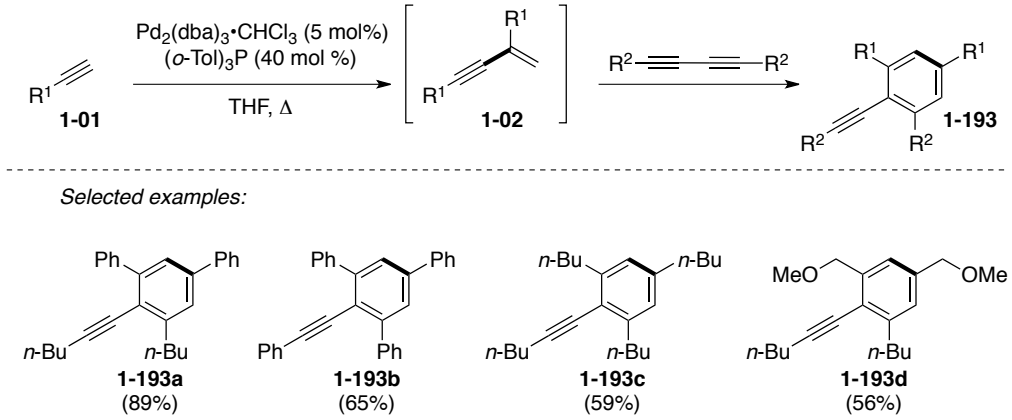


Scheme 1.45. cross-Addition of TIPS-acetylene to the Activated Alkyne Catalyzed by Binuclear Palladium Complex.

1.1.3.4. Synthetic Application of Palladium-catalyzed Dimerization Reactions of Alkynes

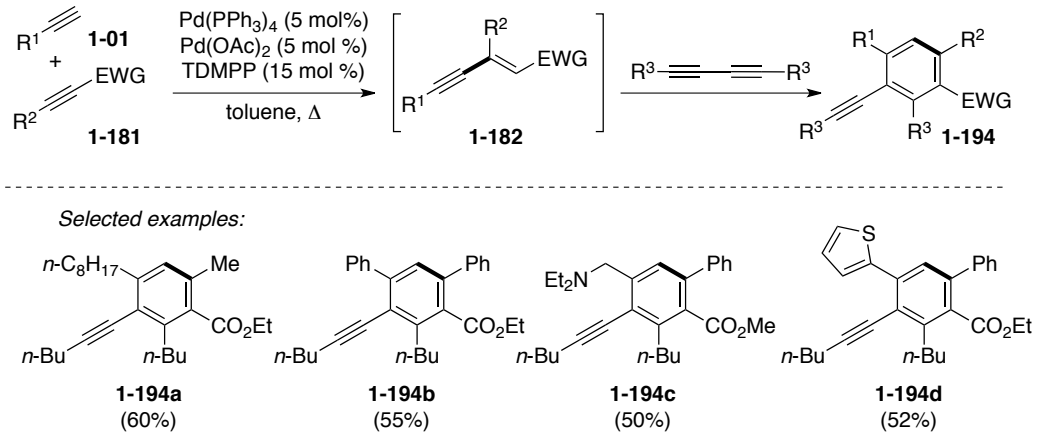
Due to high efficiency, broad functional group compatibility, and operational simplicity, both Pd-catalyzed homo- and cross-dimerization reactions found broad applications in various cascade or sequential transformations.

One-pot palladium-catalyzed dimerization/[4+2] benzannulation sequence was developed for the synthesis of polysubstituted aromatic compounds (Scheme 1.46).[70] Notably, homo-dimerization of alkynes occurred in the presence of Pd(0) catalyst as opposed to that observed in the presence of $Pd(OAc)_2/PR_3$ catalytic conditions. High regioselectivity of both processes secured the formation of a single regioisomer of the desired aromatic product **1-193** with good to high efficiency.



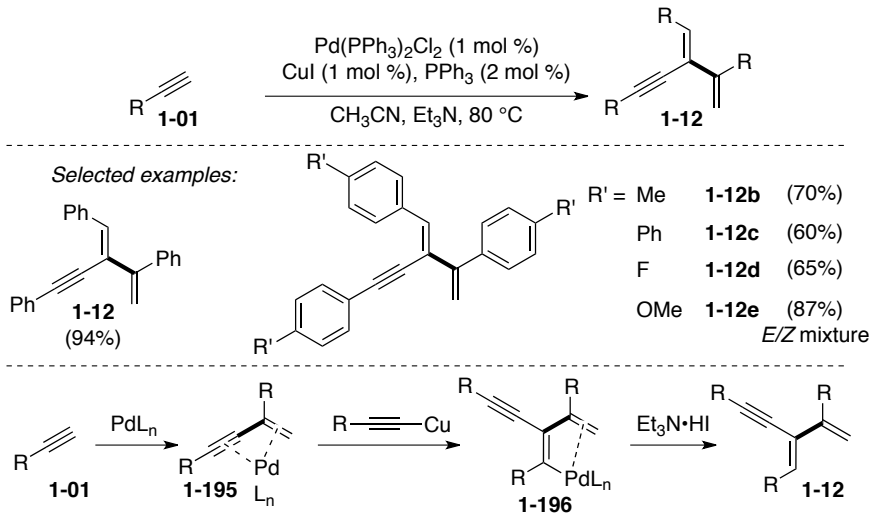
Scheme 1.46. Synthesis of Multisubstituted Benzenes via One-pot Palladium-catalyzed Dimerization/[4+2] Benzannulation Sequence.

Analogous sequence, which employs cross-dimerization of terminal alkynes with internal acceptor alkynes followed by benzannulation reaction with diyne, formally represents highly regioselective [2+2+2] cycloaddition of three different alkynes (Scheme 1.47). Thus, pentasubstituted benzenes **1-194** were obtained via a *one-pot* two steps sequence from linear starting materials in good yields.



Scheme 1.47. Synthesis of Multisubstituted Benzenes via Palladium-catalyzed cross-Dimerization/[4+2] Benzannuation Sequence.

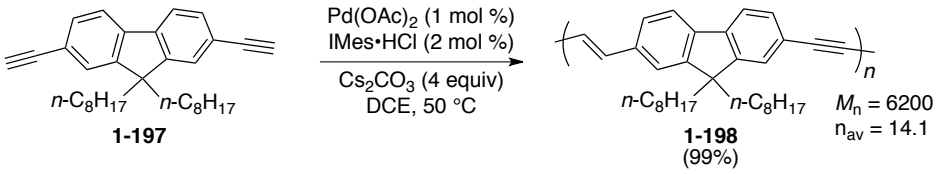
Cascade trimerization of arylalkynes to form alkynylbutadienes **1-12** was achieved in the presence of Pd and Cu catalysts (Scheme 1.48).[71] This transformation is believed to proceed through initial Pd-catalyzed dimerization to form intermediate **1-195**. Subsequent alkynylation with cooper acetylide produces butadienyl palladium species **1-196**, which upon protiodepalladation affords product **1-12**.



Scheme 1.48. Cascade Trimerization of Alkynes via Dimerization/Alkynylation Sequence.

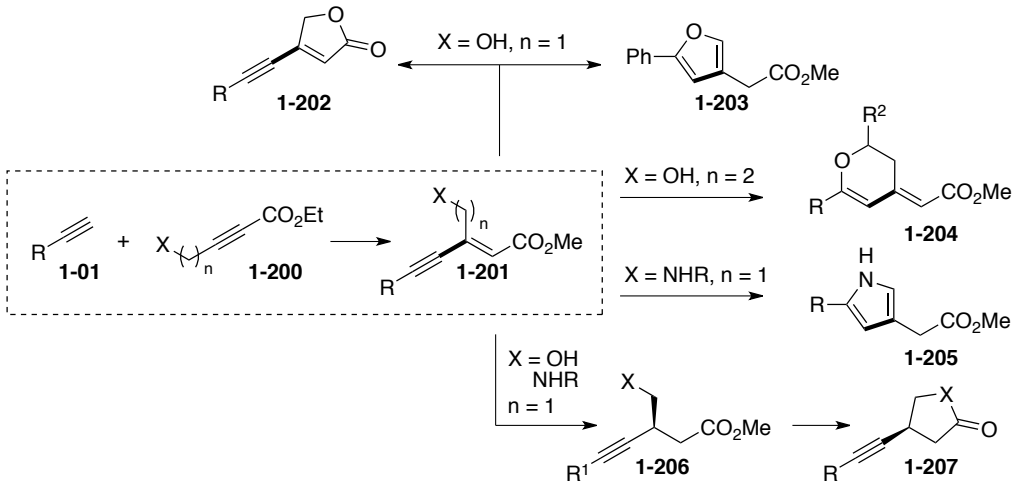
The selectivity of this transformation strongly depends on the reaction media and nature of the substrates. For instance, trimerization reaction of electron-rich methoxy-substituted arylalkyne toward **1-12e** afforded a mixture of double bond isomers with irreproducible ratio, whereas reaction of electron-deficient substrates produced single (*Z*)-isomers. Interestingly, the efficiency of cascade transformation is considerably higher compared to the analogous stepwise process presumably due to the low stability of 1,3-diarylenynes.

Head-to-head dimerization of alkynes catalyzed by NHC-based Pd catalyst was successfully applied for the synthesis of π-conjugated polymeric materials (Scheme 1.49).[72] Thus, using polyaddition strategy poly(fluoreneethynylenevinylene) **1-198** was obtained from 2,7-diethynyl-9,9-dioctylfluorene **1-197** with high efficiency. Notably, the geometry of vinylene unit of obtained polymer is translated from prototype dimerization of monoalkynyl substrate.



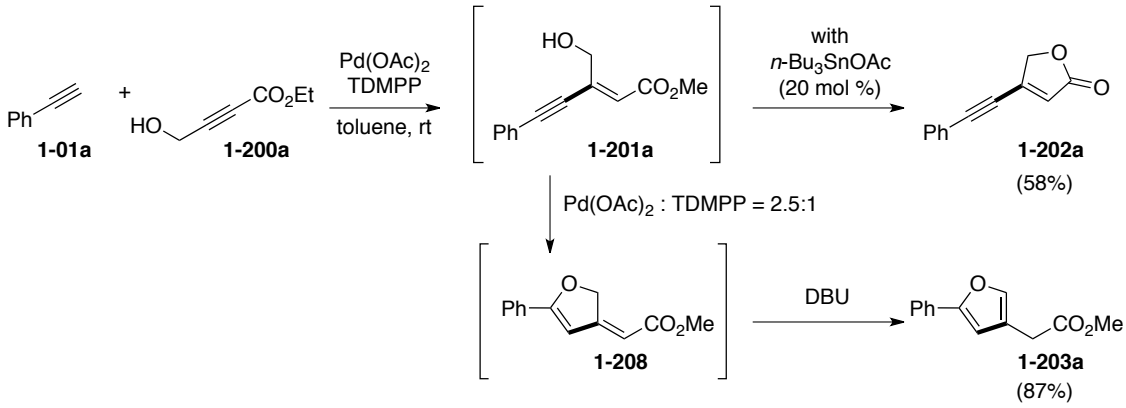
Scheme 1.49. Synthesis of Poly(fluoreneethynylenevinylene) **1-198** via Palladium-catalyzed *Head-to-head* Dimerization of Alkynes.

Trost group developed an array of methods toward heterocyclic compound via cross-dimerization/cyclization sequences (Scheme 1.50).[73] Thus, proper design of substrates for hydroalkynylation reaction allowed for the synthesis of enynes **1-201**, which posses alcohol or amine functionalities for a subsequent cyclization reaction. This strategy was applied for efficient synthesis of butenolides **1-202** or furans **1-203**,[73a] dihydropyrans **1-204**,[73b] pyroles **1-205**,[73c] dihydrofuranones and pyrrolidinones **1-207**, and other heterocycles.[73d]



Scheme 1.50. Synthesis of Various Heterocycles via Tandem Hydroalkynylation/Cyclization Reactions.

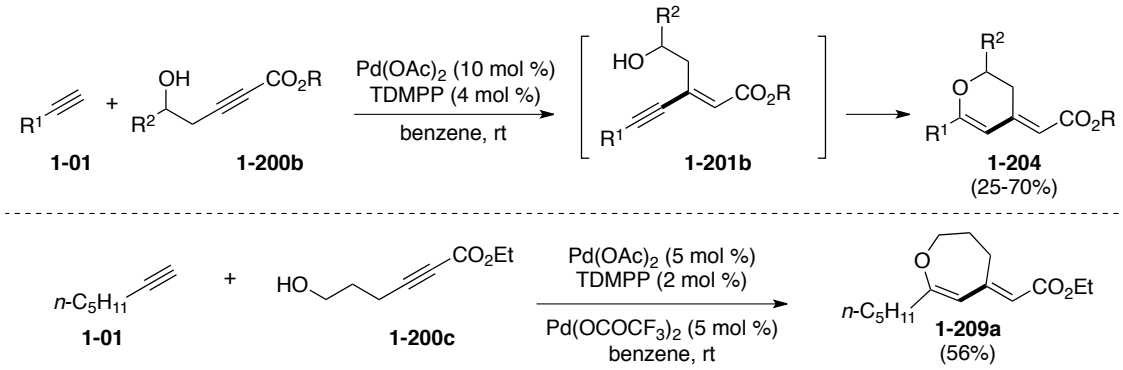
Particularly, addition of terminal alkynes to the γ-hydroxyalkynoates **1-200** led to the formation of butenolides **1-202** or furans **1-203** regioselectively depending on the reaction conditions (Scheme 1.51).[73a] Thus, employment of tributyltin acetate facilitated the lactonization reaction giving access to butenolide **1-202a**. Alternatively, selective 5-*endo*-*dig* cyclization to produce furan **1-203a** was predominant in the presence of DBU.



Scheme 1.51. Synthesis of Butenolides and Furans via Palladium-catalyzed cross-Dimerization/Cyclization Sequence.

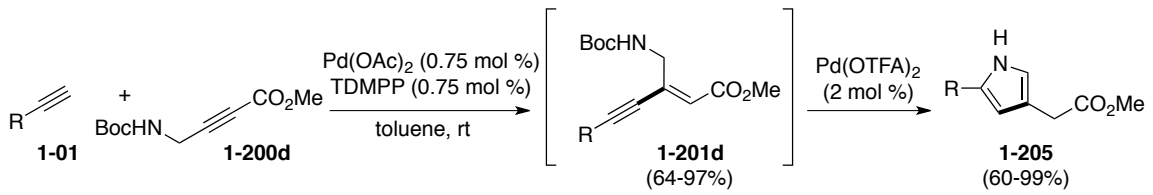
Hydroalkynylation of acceptor alkynes bearing homopropargylic alcohol moieties afforded enynes **1-201b**, which underwent *in situ* cyclization with the formation of dihydropyrans **1-204** (Scheme

1.52).[73b] Notably, in most cases the 6-*endo-dig* cyclization was predominant over the 5-*exo-dig* cyclization or lactonization processes. Interestingly, a 7-membered ring analog **1-209a** was also obtained using this strategy although addition of more electrophilic palladium trifluoroacetate was required.



Scheme 1.52. Synthesis of Oxygen Heterocycles via Palladium-catalyzed cross-Dimerization/6-*Endo-dig* Cyclization Sequence.

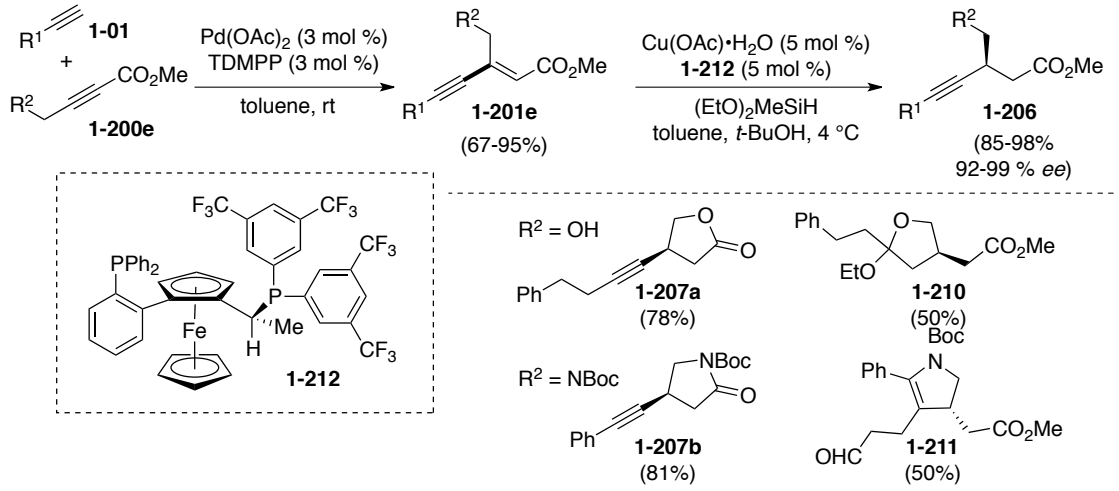
Similar approach was utilized for the synthesis of pyrroles starting from propargylic amines **1-200d** (Scheme 1.53).[73c] In this case products of the dimerization reaction, enynes **1-201d**, were isolated in good yields. Subsequent 5-*endo-dig* cyclization in the presence of catalytic amounts of $Pd(OCOCF_3)_2$ resulted in the formation of 2,4-disubstituted pyrroles **1-205**. This transformation can also be conducted in a *one-pot* manner with no loss of efficiency.



Scheme 1.53. Synthesis of Pyrroles via Palladium-catalyzed cross-Dimerization/5-*Endo-dig* Cyclization Sequence.

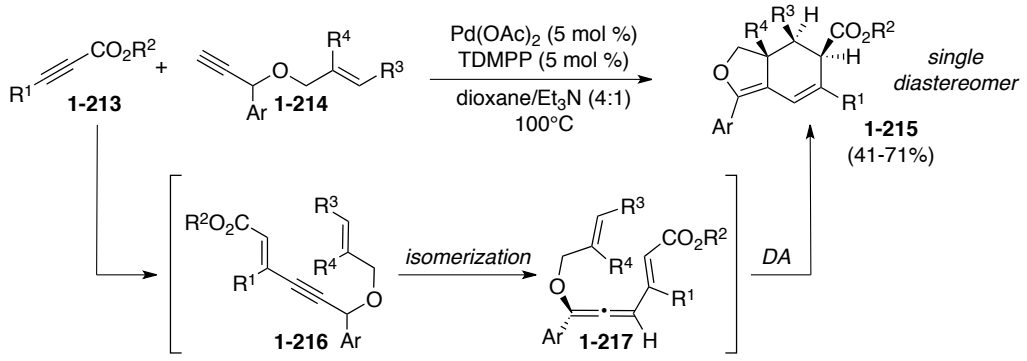
Furthermore, Trost and co-workers developed enantioselective synthesis of *β*-alkynyl esters **1-200e** (Scheme 1.54).[73d] Thus, with the aid of chiral bidentate phosphine ligand **1-212**, the Cu-catalyzed reduction of **1-201e** with diethoxymethylsilane proceeded with remarkable regio- and stereoselectivity.

Notably, careful ligand optimization was required to completely suppress a competitive 1,6-reduction of this intermediate. Additionally, high stereoselectivity of cross-dimerization reaction ensured high enantioselectivity of subsequent asymmetric reduction. Similarly to the unsaturated analogs (*vide supra*), the products of this transformation **1-206** can be converted to various heterocycles (**1-207**, **1-210**, **1-211**) via cyclization on either alkynyl or ester side.



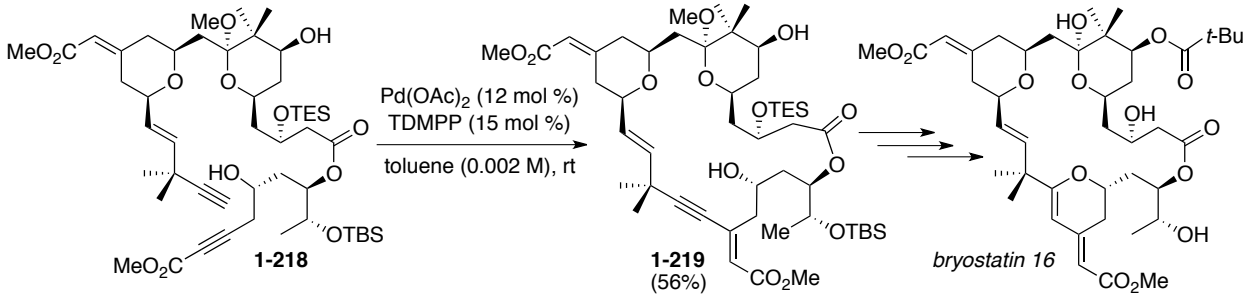
Scheme 1.54. Synthesis of *β*-Alkynyl Esters via Palladium-catalyzed cross-Dimerization/1,4-Reduction of Ynenoates.

Highly atom-economical approach toward 5,6-fused bicyclic systems **1-215** was recently developed based on hydroalkynylation reaction of ynoates (Scheme 1.55).[74] Thus, addition of allyl propargyl esters **1-214** to the acceptor alkynes **1-213** produces enynes **1-216**, which upon base-mediated isomerization form allenes **1-217**. A subsequent Diels-Alder cycloaddition delivers tetrahydrobenzofuran derivatives **1-215** as single diastereomers. This report highlights versatility of the Pd-catalyzed cross-addition reaction, as it does not interfere with other processes required for an efficient cascade of this type.



Scheme 1.55. Synthesis of Fused Bicycles via Palladium-catalyzed cross-Dimerization/Intramolecular Diels-Alder Sequence.

An exceptional functional group compatibility of this process was further exemplified in the synthesis of bryostatin 16 (Scheme 1.56).[75] Thus, advanced intermediate **1-218** was efficiently converted into macrocycle **1-219** via the intramolecular cross-addition of terminal alkyne to the tethered acceptor alkyne moiety. The macrocyclic enyne **1-219** was then elaborated into the target bryostatin 16 in just 3 steps.



Scheme 1.56. Palladium-catalyzed Hydroalkynylation Reaction Applied for a Key Macrocyclization *en route* to Bryostatin 16.

1.1.4. Summary and Outlook

Dimerization of alkynes represents a fundamental hydroalkynylation reaction for the straightforward construction of carbon–carbon bonds in highly atom-economical manner. Despite the challenges associated with selectivity of this transformation, immense progress was achieved in the development of practical methodologies with the aid of various transition metals. Particularly, the

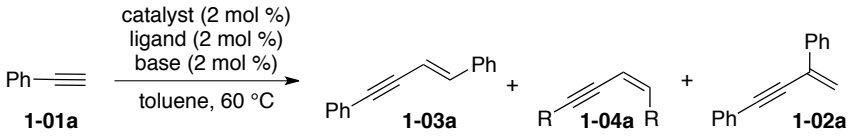
palladium-catalyzed *head-to-tail* homo- and cross-dimerization strategies became useful synthetic tool due to their high efficiency, operational simplicity, robustness and broad functional group compatibility. However, alternative *head-to-head* coupling, catalyzed by palladium complexes, received much less attention. Indeed, existing approaches for selective Pd-catalyzed *head-to-head* dimerization reaction are limited to homo-coupling of aromatic substrates or strongly depend on substitution pattern in case of aliphatic alkynes. Therefore, no clear correlation between mechanistic path and the reaction selectivity was established to date. Nonetheless, understanding the mechanistic origins of the dimerization selectivity would lay the foundation for design of novel synthetic methods based of hydroalkynylation strategy.

1.2. DEVELOPMENT OF REGIODIVERGENT PALLADIUM-CATALYZED DIMERIZATION OF TERMINAL ALKYNES

1.2.1. Development of Highly Efficient Head-to-head Dimerization of Terminal Alkynes

In continuation of our search for a highly selective Pd-catalyzed *head-to-head* dimerization reaction of terminal alkynes,[65] we turned our attention to *N*-heterocyclic carbene-based (NHC) palladium complexes as they displayed reasonable selectivity in this transformation (Table 1.4).[66]

Table 1.4. Optimization of Conditions for the Palladium-catalyzed *Head-to-head* Dimerization of Terminal Alkynes.[a]



Entry	Catalyst	Ligand	Base	Time	Conversion	**1-03a** : **1-04a** : **1-02a**[b]	Yield, %[c]
1	IPr-Pd-IPr	-	-	2 h	100%	100 : 0 : 0	67
2	IPr-Pd-IPr	PPh_3	-	24 h	78%	100 : 0 : 0	-
3	IPr-Pd-IPr	PPh_3	CsOPiv	24 h	85%	100 : 0 : 0	-
4	**IPr-Pd-IPr**	**TDMPP**	**-**	**1.5 h**	**100%**	**100 : 0 : 0**	**92**
5	IPr-Pd-IPr	TDMPP	CsOPiv	2 h	100%	98 : 2 : 0	67
6	IPr-Pd-IPr	TDMPP	K_2CO_3	1,5 h	100%	100 : 0 : 0	63
7	IPr-Pd-IPr	-	CsOPiv	24 h	73%	59 : 0 : 41	-
8	IMes-Pd-IMes	-	-	3 h	100%	100 : 0 : 0	90
9	**IMes-Pd-IMes**	**TDMPP**	**-**	**1 h**	**100%**	**100 : 0 : 0**	**94**

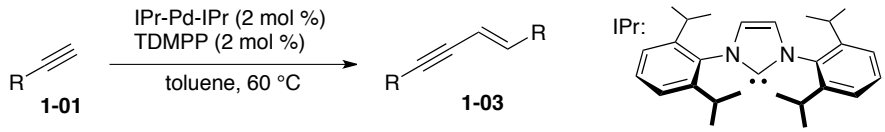
[a]Reaction conditions: catalyst (2 mol %), ligand (2 mol %), base (2 mol %), toluene (1 M), 60 °C. [b]NMR ratio. [c]Isolated yield.

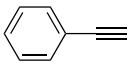
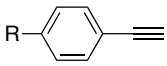
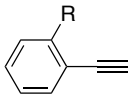
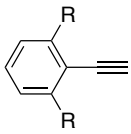
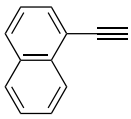
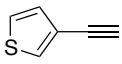
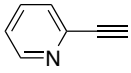
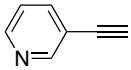
We have found that *bis*-*N*-heterocyclic carbene palladium complex (IPr-Pd-IPr) displays high selectivity toward *head-to-head* dimerization affording single isomer (*E*)-enyne **1-03** in moderate yield (entry 1). Addition of triphenylphosphine to the reaction mixture alone or in combination with inorganic

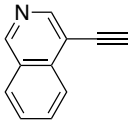
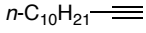
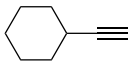
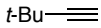
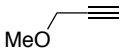
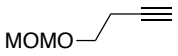
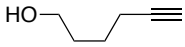
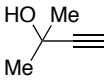
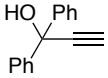
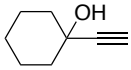
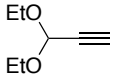
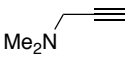
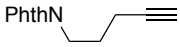
base did not improve the reaction efficacy (entries 2, 3). Nevertheless, in the presence of electron-rich and bulky phosphine ligand TDMPP (**1-158**), fast *head-to-head* dimerization of phenylacetylene **1-01a** was observed delivering (*E*)-enyne **1-03a** in 92% yield with perfect regio- and stereoselectivity (entry 4). Importantly, addition of inorganic bases to this catalytic system compromises reaction yields (entries 5, 6). On the other hand, regioselectivity of dimerization in the presence of CsOPiv additive only was low (entry 7, *vide infra*). Importantly, less sterically hindered NHC-based complex IMes-Pd-IMes was equally efficient and selective catalyst in this reaction (entries 8, 9).

Next, the generality of this transformation was examined (Table 1.5). Thus, a variety of arylalkynes, such as electron-rich alkynes **1-01j** and **1-01i** or electron-deficient alkynes **1-01l**, **1-01y**, and **1-01u** were smoothly converted to (*E*)-1,4-disubstituted enynes in good to high yields (entries 2-6). Importantly, the reaction was not sensitive to sterics as it was demonstrated by a selective dimerization reaction of *ortho*-substituted arylalkynes **1-01z** and **1-01q** (entries 7, 8). Although coupling did not proceed with 2,6-dimethylphenylacetylene (**1-01r**), it was efficient with 2,6-disubstituted alkynes **1-01s** and **1-01t**, thus eliminating involvement of agostic interactions[65] as a possible regiocontroling element of this process (entries 9-11). Additionally, an employment of 1-naphthylacetylene (**1-01n**) provided corresponding enyne in good yield (entry 12). Furthermore, alkynes bearing heteroaromatic substituents, such as 3-thiophenyl (**1-01aa**), 2- and 3-pyridyl (**1-01x**, **1-01ab**), as well as 4-isoquinolyl (**1-01ac**), underwent efficient dimerization under these reaction conditions (entries 13-16). Gratifyingly, aliphatic alkynes were also competent substrates in this dimerization reaction. Thus, dodecyne **1-01ad** was converted to (*E*)-1,4-disubstituted enyne **1-03ad** in 91% yield (entry 17). Similarly to arylalkynes, sterically hindered aliphatic acetylenes **1-01ae** and **1-01h** reacted efficiently with selective formation of enyne products (entries 18, 19). Furthermore, various functionalities, such as ethers (entries 20, 21), alcohols (entries 22-25), acetal (entry 26), amine (entry 27), and amide (entry 28), were well tolerated under the reaction conditions. Notably, the reaction was easily scalable providing comparable yield of **1-03a** even in the presence of 0.5 mol % of the catalyst (entry 1).

Table 1.5 Palladium-catalyzed Dimerization of Terminal Alkynes toward (*E*)-1,4-Disubstituted Enynes.[a]



Entry	Alkyne			Yield of **1-03**, %[b]
1			**1-01a**	92 86[c]
2		R = OMe	**1-01j**	81
3		R = Me	**1-01i**	92
4		R = CN	**1-01l**	82
5		R = COOMe	**1-01y**	67
6		R = Cl	**1-01u**	51
7		R = OMe	**1-01z**	77
8		R = Me	**1-01q**	81
9		R = Me	**1-01r**	-[d]
10		R = F	**1-01s**	88
11		R = OMe	**1-01t**	75
12			**1-01n**	66
13			**1-01aa**	65
14			**1-01x**	93
15			**1-01ab**	56

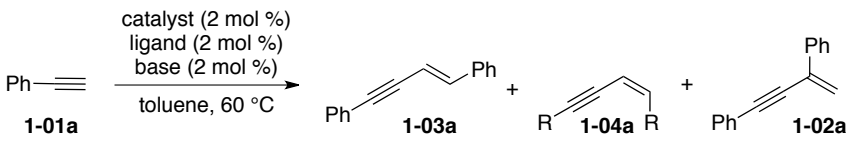
Entry	Alkyne		Yield of **1-03**, %[b]
16		**1-01ac**	78
17		**1-01ad**	91
18		**1-01ae**	91
19		**1-01h**	65
20		**1-01af**	71
21		**1-01ag**	62
22		**1-01ah**	94
23		**1-01c**	85
24		**1-01ai**	88
25		**1-01aj**	89
26		**1-01ak**	93
27		**1-01al**	81
28		**1-01am**	96

[a]Reaction conditions: **1-01** (0.5 mmol), IPr-Pd-IPr (2 mol %), TDMPP (2 mol %), toluene (0.5 mL), 60 °C. [b]Isolated yield. [c]Reaction conditions: **1-01a** (5 mmol), IPr-Pd-IPr (0.5 mol %), TDMPP (1 mol %), toluene (5.0 mL), 60 °C. [d]No reaction was observed.

1.2.2. Effect of Carboxylate Anion on Regioselectivity of Dimerization Reaction

Intrigued by Nolan's report on base-dependent reaction selectivity (Table 1.6, entries 1, 2),[66] we investigated if analogous effect could be observed in our catalytic system producing *head-to-head* dimerization products. To this end, dimerization of phenylacetylene in the presence of IPr-Pd-IPr/TDMPP catalytic system and base additives was tested. Thus, the reaction performed in the presence of K_2CO_3 under otherwise identical conditions afforded **1-03a** with similar selectivity albeit in diminished yield (entries 3, 4). Similar result was observed when less hindered IMes-based catalyst precursor was employed (entry 5). Interestingly, commercially available IPrPdAllCl complex afforded **1-03a** in good yield with slightly altered stereoselectivity of the dimerization with no effect on regioselectivity, although prolonged reaction time was required (entry 6). *Head-to-head* dimerization still remained a major pathway when reaction was run in the presence of potassium or cesium carbonates (entries 7, 8). However, when catalytic amount of cesium acetate was added, clear preference for the *head-to-tail* dimerization was observed delivering dimeric products **1-03a** and **1-02a** as a 1:4 mixture (entry 9). In the presence of potassium acetate, the ratio was further improved (entry 11). Ultimately, an employment of cesium pivalate allowed for perfect *head-to-tail* regioselectivity furnishing enyne **1-02a** (entry 10). In contrast to the inorganic bases, addition of pyridine suppressed the reaction (entry 12). Moreover, an employment of tertiary amines, such as triethylamine or DABCO, resulted in decomposition of starting phenylacetylene. These results clearly indicate that among all bases tested only carboxylate anion is capable of the selectivity switch from the *head-to-head* to the *head-to-tail* dimerization path. To further verify this observation, regioselectivity of the reaction catalyzed by define complexes $IPrPdPPh_3$[76] and $IPrPd(OPiv)_2$ [77] was compared. Thus, employment of $IPrPdPPh_3$ led to a facile formation of (*E*)-1,4-diphenylenyne **1-03a**, whereas 1,3-diphenylenyne **1-02a** formed predominately under $IPrPd(OPiv)_2$/TDMPP catalysis (entries 13, 14).

Table 1.6. Investigation of the Base Effect on the Selectivity of the Palladium-catalyzed Dimerization of Terminal Alkynes.[a]

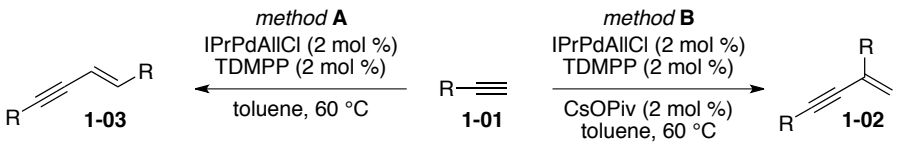


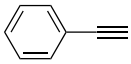
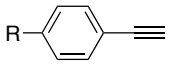
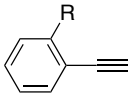
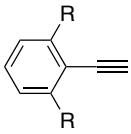
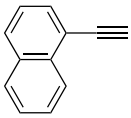
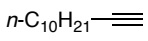
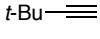
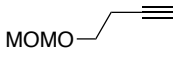
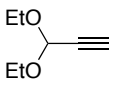
Entry	Catalyst	Ligand	Base	Time, h	**1-03a : 1-04a : 1-02a**[b]	Yield, %[c]
1[d]	$Pd(OAc)_2$	IMes·HCl	Cs_2CO_3	2	93:7:0	98
2[d]	$Pd(OAc)_2$	IMes·HCl	K_2CO_3	2	69:5:26	98
3	**IPr-Pd-IPr**	**TDMPP**	**-**	**2**	**100:0:0**	**92**
4[e]	IPr-Pd-IPr	TDMPP	K_2CO_3	2	99:1:0	63
5[e]	$Pd(IMes)_2$	TDMPP	K_2CO_3	9	99:1:0[f]	56
6	**IPrPdAllCl**	**TDMPP**	**-**	**24**	**96:4:0**[f]	**94**
7[e]	IPrPdAllCl	TDMPP	K_2CO_3	12	97:0:7	62
8[e]	IPrPdAllCl	TDMPP	Cs_2CO_3	12	100:0:0	83[g]
9	IPrPdAllCl	TDMPP	CsOAc	1	20:0:80	70[g]
10	**IPrPdAllCl**	**TDMPP**	**CsOPiv**	**1**	**0:0:100**	**62**
11	IPrPdAllCl	TDMPP	KOAc	1	10:0:90	64[g]
12	IPrPdAllCl	TDMPP	Pyridine	16	-	-[h]
13	$IPrPdPPh_3$	-	-	1	97:0:3	87[g]
14	$IPrPd(OPiv)_2$	TDMPP		1	5:0:95[f]	80[g]

[a]Reaction conditions: catalyst (2 mol %), ligand (2 mol %), base (2 mol %), toluene (1 M), 60 °C. [b]Determined by GC/MS and NMR. [c]Isolated yield. [d]Reaction conditions: catalyst (1 mol %), ligand (2 mol %), base (2 equiv), DMA (1 M), 80 °C. Reproduced from ref. 66. [e]2 equiv of base was used. [f]Formation of a small amount of diphenyldiyne was observed. [g]NMR yield of the major isomer. [h]No reaction was observed.

In order to investigate the generality of the observed carboxylate anion effect, the reactivity of several other alkynes was tested using IPrPdAllCl/TDMPP catalytic system with (method **B**) or without CsOPiv (method **A**, Table 1.7). Thus, electron-rich (**1-01j**, **1-01i**) *para*-substituted arylalkynes were converted to the corresponding enynes **1-03j**, **1-03i** or **1-02j**, **1-02i** with high efficiency and regioselectivity depending on the employed conditions (entries 2, 3). Graduate increase of steric hindrance at *ortho*-position affected *head-to-head* reaction resulting in reduced yields and selectivities in case of mono-*ortho*-substituted arylalkynes **1-01z** and **1-01q** and complete loss of reactivity in case of 2,6-disubstituted arylacetylenes **1-01r** and **1-01t**. However, the corresponding *head-to-tail* dimerization proceeded smoothly for mono-*ortho*-substituted arylalkynes **1-01z** and **1-01q**. In the case of alkyne **1-01r**, 1,3-disubstituted enyne **1-02r** was formed predominantly although efficiency and selectivity were diminished. In contrast, clean conversion of 2,6-dimethoxyphenylacetylene **1-01t** to 1,3-disubstituted enyne **1-02t** was observed (entries 4-7). 1-Naphthylacetylene (**1-01n**) underwent both reactions with formation of the corresponding enynes in good yields with perfect regio- and stereoselectivity (entry 8). Further studies indicated that combination of IPrPdAllCl and TDMPP displays poor activity in the dimerization of aliphatic alkynes. Thus, reaction of dodecyne (**1-01ad)** delivered a mixture of dimeric products favoring (*E*)-1,4-disubstituted enyne **1-03ad** in moderate yield only (entry 9). Other tested aliphatic substrates did not dimerize under these conditions. On the other hand, addition of catalytic amount of CsOPiv into the reaction mixture promoted the *head-to-tail* dimerization of alkylalkynes. Hence, linear alkynes **1-01ad** and **1-01ag** were selectively converted to the corresponding 1,3-disubstituted enynes (entries 9, 11). Similarly to the reactivity of aryl-substituted alkynes, sterically demanding aliphatic alkynes underwent the *head-to-tail* dimerization with slightly decreased selectivities (entries 10, 12).

Table 1.7. Carboxylate Effect in Palladium-catalyzed Dimerization of Terminal Alkynes.



Entry	Alkyne			Method **A**, yield of **1-03**, %[a,c]	Method **B**, yield of **1-02**, %[b,c]
1			**1a**	94 (96:4:0)	62
2		R = OMe	**1j**	77	85 (5:0:95)
3		R = Me	**1i**	88	88
4		R = OMe	**1z**	45 (83:0:17)	80
5		R = Me	**1q**	52 (70:0:30)	97
6		R = Me	**1r**	-[d]	37 (15:0:85)
7		R = OMe	**1t**	-[d]	78 (2:0:98)
8			**1n**	65	80
9			**1ad**	58 (83:7:10)	93
10			**1h**	-[d]	65 (9:0:91)[e]
11			**1ag**	-[d]	83
12			**1ak**	-[d]	81 (19:0:81)

[a]Reaction conditions for method **A**: **1-01** (0.5 mmol), IPrPdAllCl (2 mol %), TDMPP (2 mol %), toluene (0.5 mL), 60 °C. [b]Reaction conditions for method **B**: **1-01** (0.5 mmol), IPrPdAllCl (2 mol %), TDMPP (2 mol %), CsOPiv (2 mol %), toluene (0.5 mL), 60 °C. [c]Isolated yield. Ratio of **1-03** : **1-04** : **1-02** is shown in parentheses if more then one isomer was formed. [d]No reaction was observed. [e]NMR yield.

The direct comparison of these two catalytic systems clearly demonstrates a dramatic effect of carboxylate anion on the regioselectivity of Pd-catalyzed dimerization reaction. Thus, under the base-free conditions, terminal alkynes selectively undergo *head-to-head* dimerization reaction, whereas in the presence of carboxylate anion under otherwise identical conditions the *head-to-tail* dimerization becomes a predominant process.

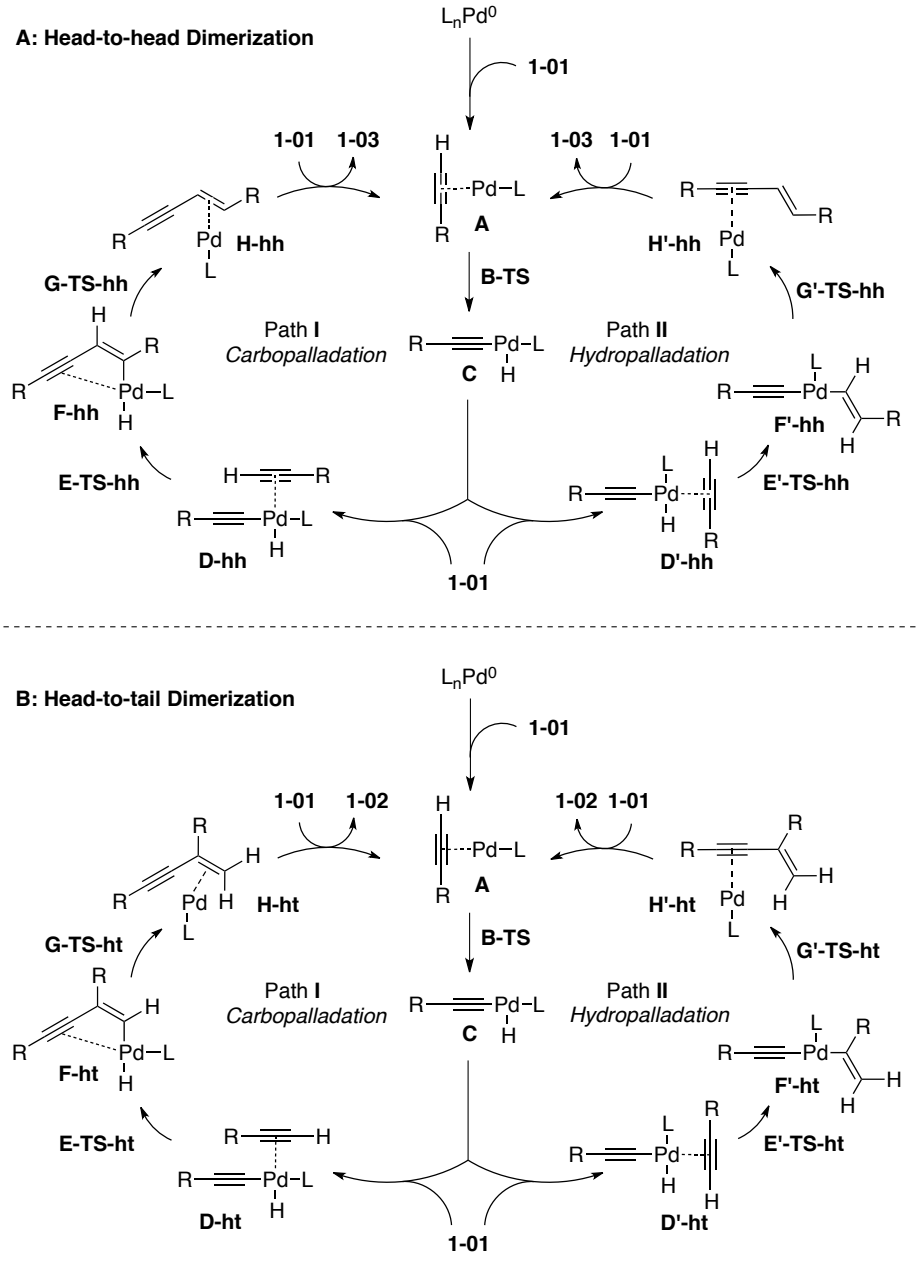
1.2.3. Investigation of the Reaction Mechanism

Having established the methods for the selective *head-to-head* and *head-to-tail* dimerization reactions of terminal alkynes, we turned our attention to the investigation of the origins of the observed regioselectivity switch. To this end, the reaction mechanism was studied computationally in the group of our collaborator, Prof. Valentine Ananikov. Theoretical calculations were carried out at B3LYP/6-311G(d)&SDD level in order to locate intermediate complexes and transition states. Free energy surfaces ΔG of the computed catalytic cycles will be discussed for detailed comparison of *head-to-head* and *head-to-tail* dimerization. For ΔE energy surface see Experimental Section.

1.2.3.1. Head-to-head Dimerization of Alkynes

As described above, it is generally considered that the Pd-catalyzed dimerization of terminal alkynes starts with the formation of the π-complex **A**, in which the first molecule of the alkyne is bound to the L–Pd(0) center (Scheme 1.57, L = NHC). The coordination of the alkyne is followed by oxidative addition of the C–H bond via the transition state **B-TS** leading to the formation of hydrido complex **C**. According to the calculated energy surface, this process was found to be endothermic with the energy change of $\Delta G_{\mathbf{A}\rightarrow\mathbf{C}}$ = 14.8 kcal/mol and activation barrier of $\Delta G^{\neq}_{\mathbf{A}\rightarrow\mathbf{B\text{-}TS}}$ = 17.6 kcal/mol (Figure 1.1). Available coordination vacancy and labile structure of complex **C** provides an access to four different reaction channels: *head-to-head* dimerization via carbopalladation or hydropalladation path (Scheme 1.57**A**), and *head-to-tail* dimerization via carbopalladation or hydropalladation path (Scheme 1.57**B**).

Accordingly, all intermediate species and transition states for complete characterization of these reaction pathways were located (Figure 1.2).



Scheme 1.57. Proposed Mechanism for the Palladium-catalyzed *Head-to-head* (**A**) and *Head-to-tail* (**B**) Dimerization of Terminal Alkynes.

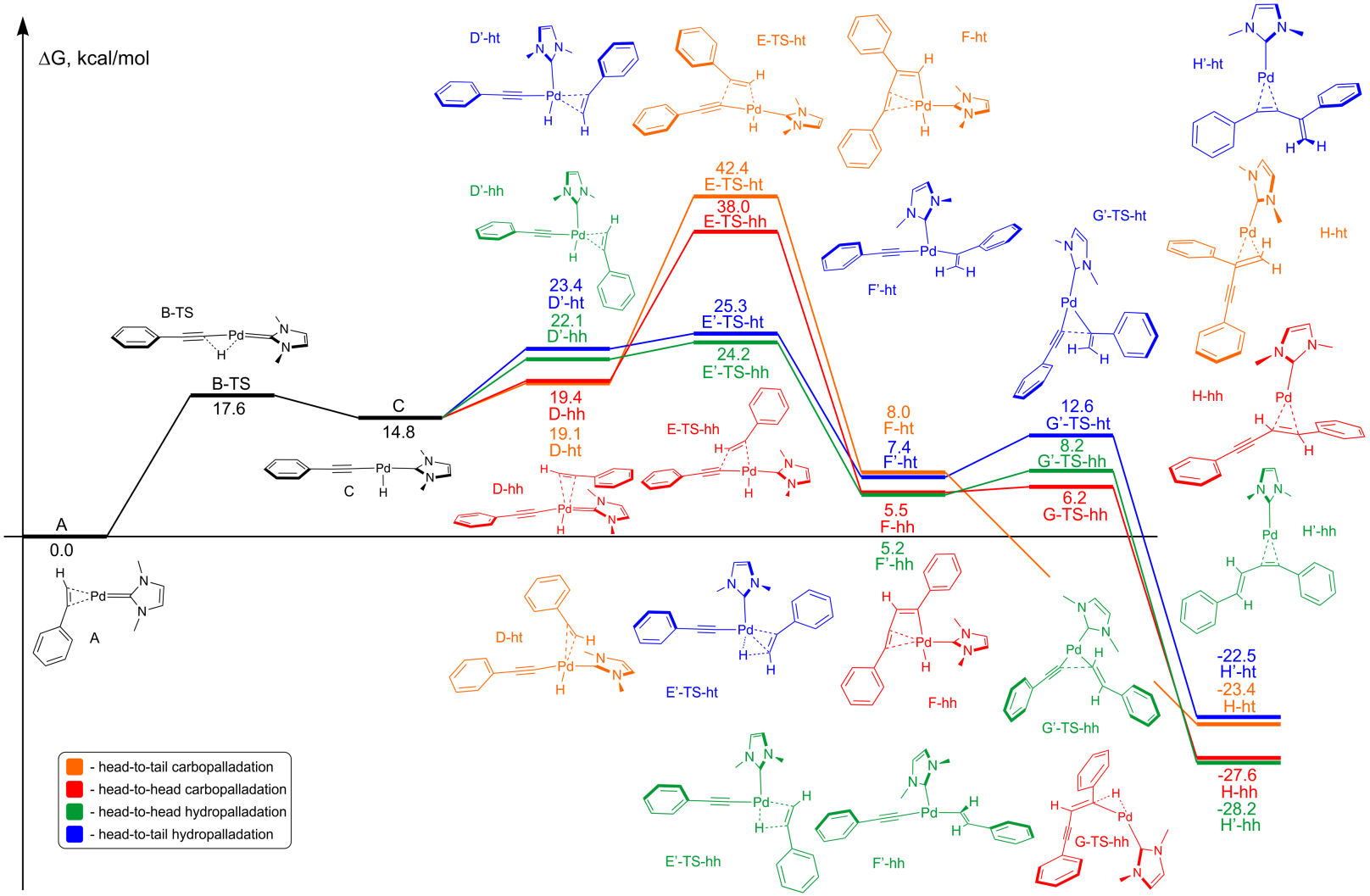


Figure 1.1. Calculated Free Energy Surface (ΔG, kcal/mol) of Palladium-catalyzed *Head-to-head* and *Head-to-tail* Dimerization of Terminal Alkynes at B3LYP/6-311G(d)&SDD Level (see Scheme 1.57 for structures and Figure 1.2 for molecular geometries).

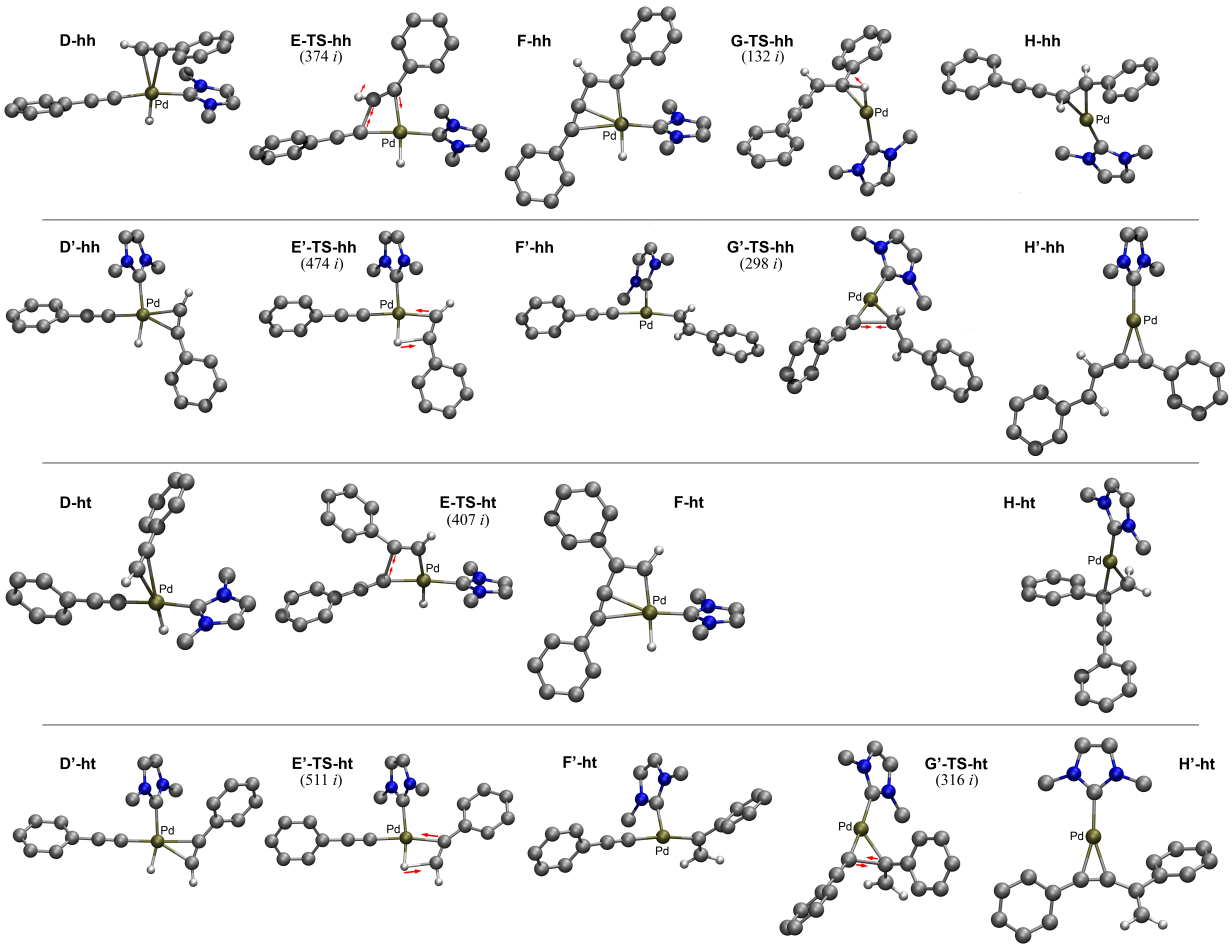


Figure 1.2. Optimized Molecular Structures of Reaction Intermediates at the B3LYP/6-311G(d)&SDD Level (normal mode corresponding to imaginary frequency in the transition state is visualized, hydrogen atoms of the complexes are omitted for clarity with the exception of reacting H atoms, see Experimental Section for geometric parameters).

Coordination of the second alkyne molecule furnishes formation of π-complexes **D-hh**, **D'-hh**, **D-ht**, **D'-ht** differentiated by orientation of alkyne molecule around Pd–C and Pd–H bonds (Figures 1.1, 1.2). Carbopalladation involves complexes **D-hh** and **D-ht**, whereas hydropalladation originated from complexes **D'-hh** and **D'-ht**. All these complexes have similar relative energies with the largest deviation of ΔG = 4.3 kcal/mol was observed between **D-ht** and **D'-ht**. Due to the small energy difference, all of the proposed pathways should be further considered. Accordingly, carbopalladation was found to be an exothermic process for both *head-to-head* ($\Delta G_{\mathbf{D\text{-}hh} \rightarrow \mathbf{F\text{-}hh}}$ = -13.9 kcal/mol) and *head-to-tail* ($\Delta G_{\mathbf{D\text{-}ht} \rightarrow \mathbf{F\text{-}ht}}$ = -11.1 kcal/mol) dimerization reactions. Alkynes insertion into the Pd–C bond requires $\Delta G^{\neq}_{\mathbf{D\text{-}hh} \rightarrow \mathbf{E\text{-}TS\text{-}hh}}$ = 18.6 kcal/mol and $\Delta G^{\neq}_{\mathbf{D\text{-}ht} \rightarrow \mathbf{E\text{-}TS\text{-}ht}}$ = 23.3 kcal/mol, respectively. Hydropalladation is also an exothermic process with a similar energy gain of $\Delta G_{\mathbf{D'\text{-}hh} \rightarrow \mathbf{F'\text{-}hh}}$ = -16.9 kcal/mol for *head-to-head* and $\Delta G_{\mathbf{D'\text{-}ht} \rightarrow \mathbf{F'\text{-}ht}}$ = -16.0 kcal/mol for *head-to-tail* dimerizations. However, the activation barriers for alkyne insertion into the Pd–H bond were dramatically lower compared to that for alkyne insertion into the Pd–C bond. Thus, it is only requires 2.1 kcal/mol and 1.9 kcal/mol of activation energy for the *head-to-head* and the *head-to-tail* dimerizations, respectively. Therefore, the activation barriers calculated for hydropalladation pathway are in order of magnitude lower than the corresponding barriers for carbopalladation path.

In all cases, the insertion of the second alkyne molecule takes place through the concerted-type transition states (Figure 1.3). For the hydropalladation pathway, lower in energy transition state **E'-TS-hh** was characterized with shorter Pd–C bond of 2.103 Å and longer C–H bond of 1.817 Å compared to the corresponding interatomic distances of **E'-TS-ht**. In case of the carbopalladation pathway, more favorable transition state **E-TS-hh** possesses longer Pd–C bond of 2.216 Å and shorter C–C bond of 1.936 Å, compared to that of **E-TS-ht**. It is interesting to note the change in the delocalization of electron density associated with the different mechanisms. Thus, an increase in the negative charge on the metal atom -0.003, -0.016, -0.026, -0.057, is accompanied with higher relative energy on the potential energy surface 24.2, 25.3, 38.0 and 42.4 kcal/mol for **E'-TS-hh**, **E'-TS-ht**, **E-TS-hh**, and **E-TS-ht**, respectively (Figures 1 and 3). The charges on the carbon atoms of the acetylenide Pd–$C_\alpha \equiv C_\beta$ group, which are equal

to *ca.* $-0.15_{\alpha}/-0.06_{\beta}$ for carbopalladation (**E-TS-hh** and **E-TS-ht**) and *ca.* $-0.16_{\alpha}/.0.19_{\beta}$ for hydropalladation (**E'-TS-hh** and **E'-TS-ht**) do not depend on the regioselectivity of the insertion of the second alkyne molecule. In contrast, significant changes in the electron density localization were observed for the carbon atoms of the alkyne molecule coordinated as π-complex. Particularly, for the highest in energy transition state **E-TS-ht**, the charges on the carbon atoms were found to be -0.353 and +0.071. Notably, it was the only case with the positive charge on the alkyne carbon atom. For the **E'-TS-hh**, **E'-TS-ht**, and **E-TS-hh** transition states, significant differences in the charge of the carbon atoms bound in π-fashion were also observed with the values in the range of -0.029 to -0.275.

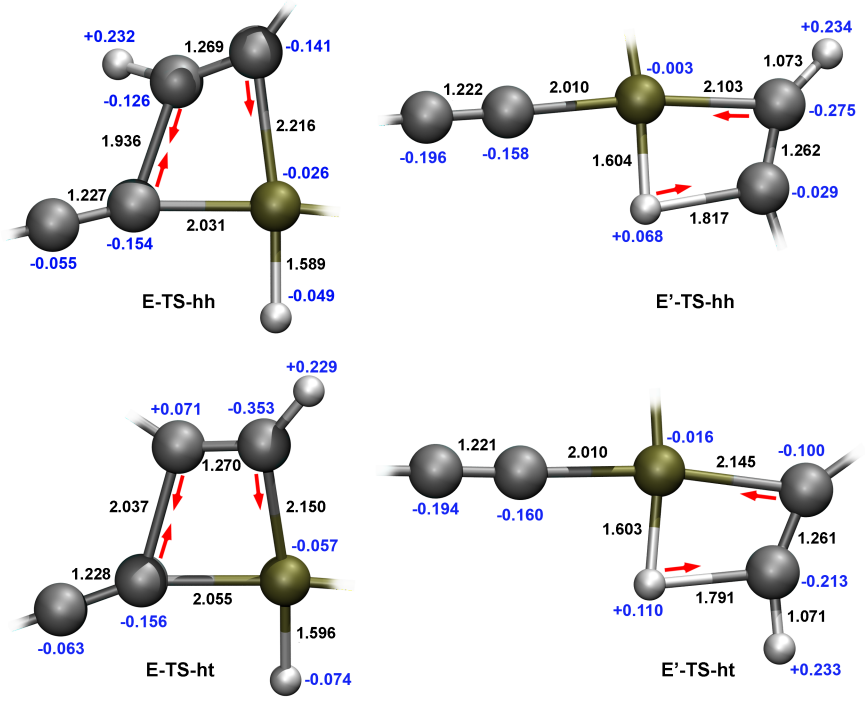


Figure 1.3. Interatomic Distances and Atomic NBO Charges (in parenthesis) for Optimized Molecular Structures of **E-TS-hh**, **E'-TS-hh**, **E-TS-ht** and **E'-TS-ht** Calculated at the B3LYP/6-311G(d)&SDD Level (other atoms are omitted for clarity; normal mode corresponding to imaginary frequency in the transition state is visualized by arrows).

The last step of the catalytic cycle involves the reductive elimination with the formation of product **1-03** for the *head-to-head* dimerization and product **1-02** for the *head-to-tail* dimerization. This step proceeds easily by overcoming corresponding activation barriers in the range of $\Delta G^{\neq}_{\mathbf{F} \rightarrow \mathbf{G\text{-}TS}} = 0.7 –$

5.2 kcal/mol (Figure 1). For the **F-ht → H-ht** reaction the barrier of <1 kcal/mol was estimated, as the direct transformation towards the product was observed. Transition state **G-TS-ht** was not localized due to a very shallow energy surface.

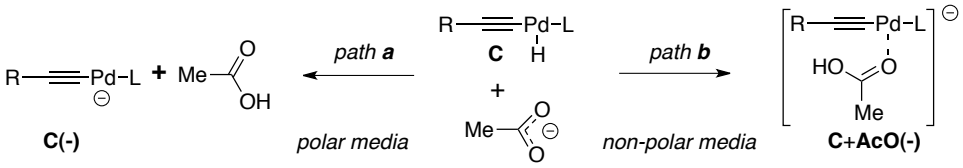
In all cases, formation of complexes **H-hh**, **H-ht**, **H'-hh** and **H'-ht** is a highly exothermic process with the energy gain of >30 kcal/mol relative to that of complexes **F-hh**, **F-ht**, **F'-hh** and **F'-ht**, and with energy gain of >22 kcal/mol relative to initial point of the catalytic cycle **A**. The change in the free energy between points **A** and **H** ensures the overall driving force of the dimerization reaction. Additionally, comparison of relative energy of complexes **H-hh**, **H'-hh** with **H-ht**, **H'-ht** indicated that the products of the *head-to-head* dimerization are more stable by ~5 kcal/mol. Dissociation of the product and coordination of new molecule of alkyne **1-01** completes turnover of the catalytic cycle (Scheme 1.57).

Analysis of the calculated energy surface clearly indicated that hydropalladation is the kinetically preferred reaction pathway for both *head-to-head* and *head-to-tail* dimerizations. Substantial energy difference in the calculated activation barriers indicates that alkyne insertion into the Pd–H bond will occur wherever possible. Alkyne insertion into the Pd–C bond may only take place if Pd–H would be unavailable for the insertion. Among the studied reactions pathways, the *head-to-head* alkyne dimerization through *hydropalladation* mechanism represents the most favorable transformation on the overall energy surface. This result is in agreement with the experimental findings.

1.2.3.2. Hydro-/Carbopalladation Mechanism Switch

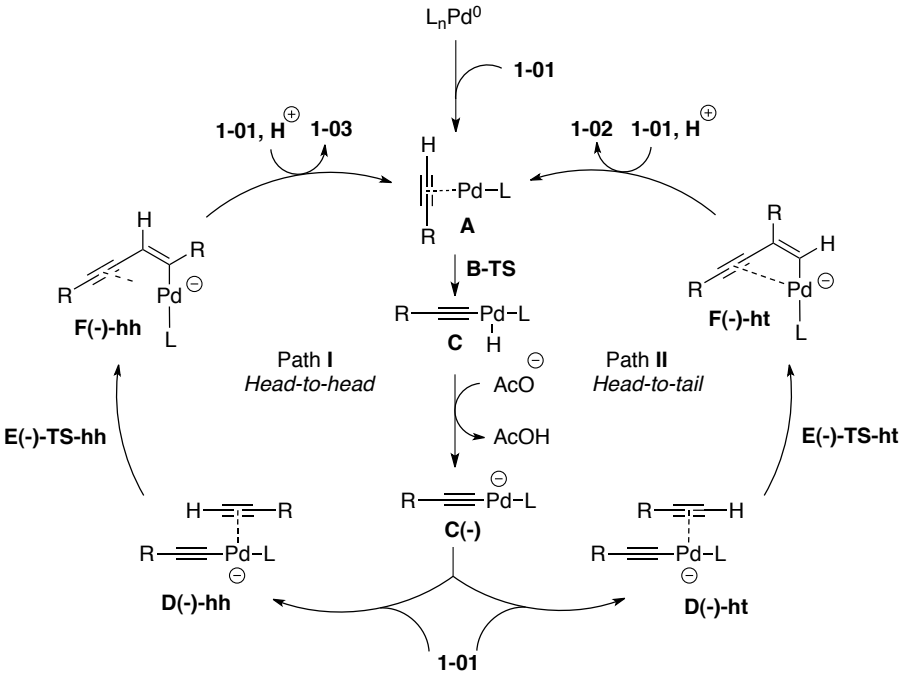
A facile reaction is an important advantage of hydropalladation pathway governed by small activation barriers. However, since the activation barriers are low, the difference in the activation energies between the *head-to-head* and the *head-to-tail* dimerizations is also negligible. In practice, this suggests that the regioselectivity of the reaction proceeding through the hydropalladation mechanism would be difficult to control. Therefore, the outcome of the reaction would depend on several factors, such as reaction conditions, nature of substituents in the reagents, ligands, etc. In contrast, the carbopalladation mechanism was characterized with high activation barriers, which resulted in larger difference between

energies of the transition states corresponding to the *head-to-head* and the *head-to-tail* dimerizations. Particularly, the difference between the **E'-TS-hh** and **E'-TS-ht** was of only 1.1 kcal/mol for hydropalladation path, while the difference between the **E-TS-hh** and **E-TS-ht** was 4.4 kcal/mol for carbopalladation pathway (Figure 1.1). As evident from the calculations, in order to direct alkyne insertion into the Pd–C bond, the hydropalladation path should be deactivated. Potentially, addition of a suitable base that will interact with hydrogen ligand would deactivate Pd–H bond. In order to test this hypothesis, acetate anion was employed to simulate the interaction of palladium acetylenide **C** with mild carboxylate base. For mimicking reaction in polar media, a complete dissociation of ions was considered (Scheme 1.58, path **a**). Additionally, a model for reaction in regular organic solvents with low or medium polarity, which most likely would involve ion pairs, was also studied (Scheme 1.58, path **b**). Full size IPr-NHC ligand was involved in the calculations.



Scheme 1.58. Interaction of Complex **C** with Acetate Anion.

The process involving complete dissociation of ions was considered first (Scheme 1.58, path **a**). The calculations revealed that proton removal from complex **C** leading to the formation of acetic acid and anionic complex **C(-)** is energetically favorable process with $\Delta G_{C \rightarrow C(-)}$ = -19.8 kcal/mol (Scheme 1.59, Figure 1.4). Coordination of the second alkyne molecule to **C(-)** gave π-complexes **D(-)-hh** and **D(-)-ht** depending on the orientation of the second alkyne molecule. Notably, **D(-)-ht** was found to be considerably more stable than **D(-)-hh** by the value of 5.5 kcal/mol on the calculated energy surface.



Scheme 1.59. Proposed Mechanism for the Anionic Pd-catalyzed *Head-to-head* and *Head-to-tail* Dimerization of Terminal Alkynes.

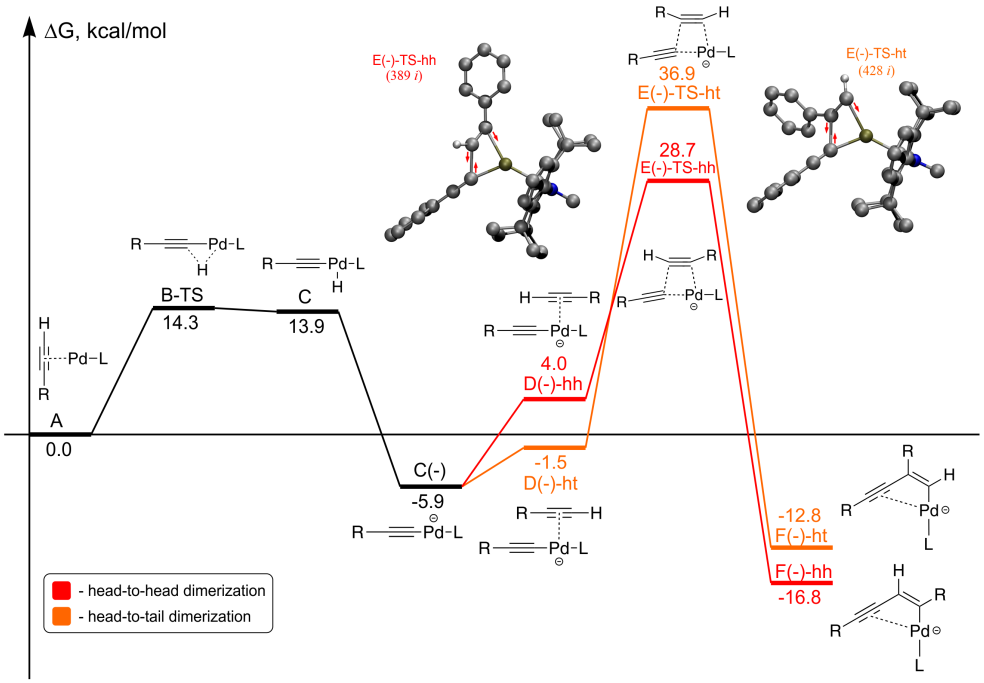


Figure 1.4. Calculated Energy Surface (ΔG, kcal/mol) of Anionic Palladium-catalyzed *Head-to-head* and *Head-to-tail* Dimerization of Terminal Alkynes (different reactions paths are denoted by different colors; see Experimental Section for optimized structures; B3LYP/6-311G(d)&SDD).

Due to the absence of Pd–H bonds, only carbopalladation pathway was possible for the located π-complexes. Thus, formation of palladium complexes **F(-)-hh** and **F(-)-ht** via the transition states **E(-)-TS-hh** and **E(-)-TS-ht** were found to be an exothermic process ($\Delta G_{\textbf{D-hh} \rightarrow \textbf{F-hh}}$ = -20.8 kcal/mol, $\Delta G_{\textbf{D-ht} \rightarrow \textbf{F-ht}}$ = -11.3 kcal/mol) requiring 24.7 kcal/mol and 38.4 kcal/mol of activation energy, respectively. Therefore, under anionic manifold, the dimerization proceeds via the carbopalladation route, whereas a competitive hydropalladation path is eliminated. The overall energy surface indicates that the *head-to-head* dimerization remains more favorable compared to the *head-to-tail* dimerization in this case.

Another possible interaction of complex **C** with acetate ion involves formation of the ion-pair complex (Scheme 1.58, path **b**). The calculations carried out with the Pd–O distance of 2.20 Å indicated that formation of ion-pair complex is possible since computed difference in free energies for this event is small (ΔG = +0.7 kcal/mol). Furthermore, geometry optimization for coordination of the second alkyne molecule and formation of complex **D-ht** with bound acetate ligand (**D-ht+AcO(-)**) have revealed a plausible structure with the hydrogen atom migrated from Pd to the oxygen atom of the carboxylate group (Figure 1.5). Within this complex, both alkyne units remained bound to the metal rendering the possibility for the *head-to-tail* dimerization. In contrast, during the geometry optimization of the analogous complex corresponding to the *head-to-head* dimerization mechanism, a dissociation of one of the alkyne molecules was observed (Figure 1.5). This process involved movement of the hydrogen atom from the carboxylate group to the neighboring acetylenide residue.

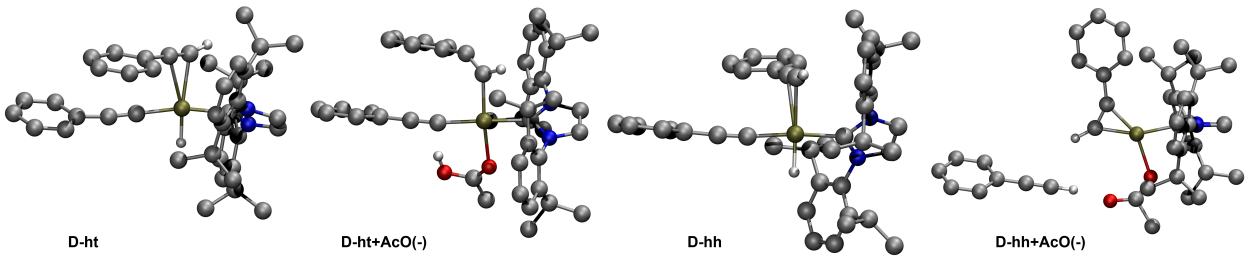
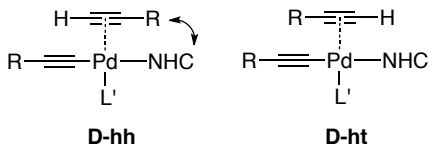


Figure 1.5. Comparison of Initial and Optimized Molecular Structures of **D-ht**, **D-ht+AcO(-)** and **D-hh** and **D-hh+AcO(-)**.

These results suggest that in case of ion-pair structures, the *head-to-head* dimerization may be disfavored due to instability of the intermediate complex. Observed elimination of one of the alkyne molecules from the coordination sphere of palladium might be attributed to the induced steric strain after the coordination of acetate anion to the palladium complex. Complex **D-hh** should be more sensitive to the steric effects due to the existing interactions of alkyne substituent R with the NHC ligand (Scheme 1.60). In analogous complex **D-ht** the steric strain is relived due to opposite alignments of the R substituent. Similar effect was observed in the calculated pathway for anionic complex. Thus, **D(-)-hh** was found higher in energy by ΔG = +5.5 kcal/mol compared to **D(-)-ht** (Figure 1.5). Notably, calculated energy difference for the complexes **D-hh**/**D-ht** and **D'-hh**/**D'-ht** was much smaller in the reaction without acetate ion additive (Figure 1.1).



Scheme 1.60. Steric Strain in the Complexes **D-hh** and **D-ht**.

Thus, addition of the acetate ion played a dual role in the studied system: i) removal of hydrogen atom from palladium thus deactivating favorable hydropalladation pathway; and ii) imposing larger difference in the stability of palladium complexes involved in the *head-to-tail* and the *head-to-head* dimerizations. Therefore, the calculations strongly suggested that the *head-to-tail* dimerization is a more favorable process in the case of ion-pair intermediates.

1.2.4. Summary

A highly regio- and stereoselective method for the palladium-catalyzed *head-to-head* dimerization reaction of terminal alkynes toward 1,4-disubstituted enynes based on IPrPdIPr/TDMPP catalytic system has been developed. This methodology is general for a variety of terminal alkynes possessing various functional groups such as aryl, heteroaryl, alkyl, hydroxyl, ether, acetal, amino, and

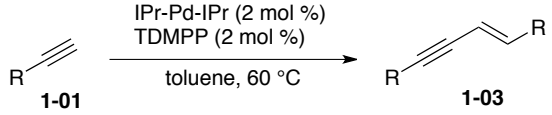
amido groups. Another feature of this method is its insensitivity to sterics, as bulky aryl or aliphatic substrates can be efficiently converted to the corresponding enynes. The reaction is also easily scalable and operates under mild conditions. It was also found that combination of several NHC-based palladium precursors with phosphine additives selectively promotes the *head-to-head* dimerization of terminal alkynes. However, an addition of carboxylate anion to the catalytic system dramatically affects the selectivity favoring the *head-to-tail* dimerization reaction. The effect of carboxylate was found to be general for a wide range of terminal alkynes, including sterically demanding aromatic or aliphatic substrates. The DFT calculations revealed that under neutral reaction conditions, the hydropalladation pathway is kinetically preferred over the carbopalladation path for both *head-to-head* and *head-to-tail* dimerizations. Analysis of the calculated energy surfaces indicated that the *head-to-head* alkyne dimerization is the most favorable among the routes studied. However, it has been found that the formation of anionic Pd-complexes or ion-pairs in the presence of carboxylate anion deactivates the hydropalladation pathway. Furthermore, only intermediates leading to the *head-to-tail* dimerization were located upon optimization of ion-paired structures. Coordination of second alkyne molecule in *head-to-head* fashion was restricted by a steric demand of the corresponding intermediates. Therefore, based on computational studies, the *head-to-tail* dimerization via the carbopalladation pathway was found preferential for the carboxylate-assisted reaction. We believe that this observation might have an impact beyond dimerization of acetylenes. Particularly, it would provide a basis for the development of selective processes in which hydro- and carbometallation are competing reaction pathways.

1.3. EXPERIMENTAL SECTION

1.3.1. General Information

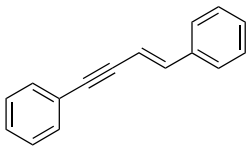
NMR spectra were recorded on a Bruker Avance DRX-500 (500 MHz) and Bruker Avance DRX-400 (400 MHz) spectrometers. LRMS and HRMS analysis was performed on Micromass 70 VSE high-resolution mass spectrometer or Micromass LCT spectrometer equipped with a time-of-flight analyzer. GC/MS analysis was performed on a Hewlett Packard Model 6890 GC interfaced to a Hewlett Packard Model 5973 mass selective detector (15 m x 0.25 mm capillary column, HP-5MS). Column chromatography was carried out employing Silicycle Silica-P Flash silica gel (40-63 μm). Precoated silica gel plates Merck 60 F-254 were used for thin-layer analytical chromatography. All manipulations with transition metal catalysts were conducted in oven-dried glassware under inert atmosphere using a combination of glovebox and standard Schlenk techniques. Small-scale reactions were carried in Wheaton V-vials equipped with Mininert Syringe valve and stirring bar. Anhydrous solvents purchased from Aldrich were additionally purified on PureSolv PS-400-4 by Innovative Technology, Inc. purification system and/or stored over calcium hydride; toluene was additionally redistilled over calcium hydride, degased and kept in the glovebox. All other starting materials were purchased from Alfa Aesar, Oakwood Products, Sigma Aldrich, Strem Chemicals, and SynQuest Laboratories. Catalysts IPr-Pd-IPr,[76] $IPrPdPPh_3$[76] and $IPrPd(OPiv)_2$[77] were prepared using known procedures. The spectral data for new compounds are provided below.

1.3.2. Synthesis of 1,4-Disubstituted (*E*)-Enynes

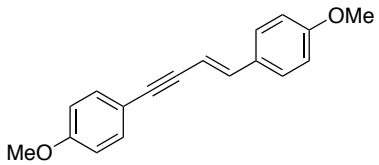


General procedure: An oven-dried 1 mL Wheaton microreactor was loaded with IPr-Pd-IPr (8.9 mg, 2 mol %) and tris(2,6-dimethoxyphenyl)phosphine (4.4 mg, 2 mol %). Anhydrous toluene (0.5 mL) was added followed by alkyne **1-01** (0.5 mmol). The reaction mixture was stirred at 60 °C until the

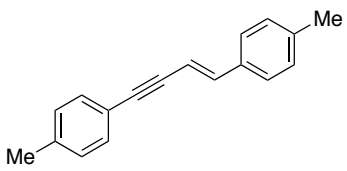
completion. The reaction course was monitored by GC/MS analysis. After the reaction completion, the reaction mixture was filtered through a short celite plug and concentrated. The product was purified by column chromatography.



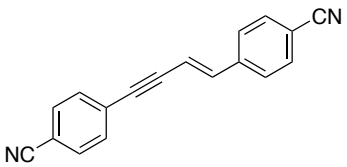
1-03a:[78] 0.5 mmol scale, 1.5 h, 60 °C; eluent: 100% hexanes; obtained: 47 mg (**92%**), white solid; 5 mmol scale, 0.5 mol % of IPr-Pd-IPr; 2h, 60 °C; eluent: 100% hexanes; obtained: 440 mg (**86%**), white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.53–7.49 (m, 2H), 7.47–7.43 (m, 2H), 7.39–7.29 (m, 6H), 7.07 (d, *J* = 16.3 Hz, 1H), 6.42 (d, *J* = 16.2 Hz, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 141.3, 136.4, 131.5, 128.8, 128.6, 128.4, 128.2, 126.3, 123.4, 108.2, 91.8, 88.9. **HRMS** (ESI) calcd. for $C_{16}H_{12}$ $[M]^+$: 204.0939; found: 204.0945.



1-03j:[33d] 0.5 mmol scale, 5 h, 60 °C; eluent: 100% hexanes; obtained: 53 mg (**81%**), white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.41 (d, *J* = 8.8 Hz, 2H), 7.36 (d, *J* = 8.8 Hz, 2H), 6.96 (d, *J* =16.2 Hz, 1H), 6.89–6.85 (m, 4H), 6.24 (d, *J* = 16.2 Hz, 1H), 3.82 (s, 6H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 160.0, 159.5, 140.0, 132.9, 129.4, 127.6, 115.8, 114.2, 114.0, 106.0, 91.0, 88.0, 55.33, 55.30. **HRMS** (EI) calcd. for $C_{18}H_{17}O_2$ $[M+H]^+$: 265.1229; found: 265.1229.

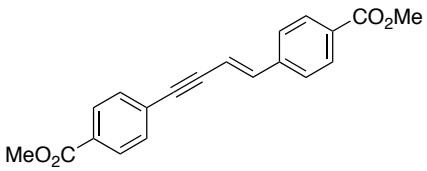


1-03i:[33d] 0.5 mmol scale, 1.5 h, 60 °C; eluent 100% hexanes; obtained: 53 mg (**92%**), white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.39–7.36 (m, 2H), 7.34–7.31 (m, 2H), 7.18–7.12 (m, 4H), 7.01 (d, *J*=16.2 Hz, 1H), 6.34 (d, *J*=16.2 Hz, 1H), 2.36 (s, 6H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 140.9, 138.6, 138.2, 133.7, 131.4, 129.4, 129.1, 126.2, 120.4, 107.2, 91.6, 88.5, 21.5, 21.3. **HRMS** (ESI) calcd. for $C_{18}H_{16}$ $[M]^+$: 232.1252; found: 232.1253.

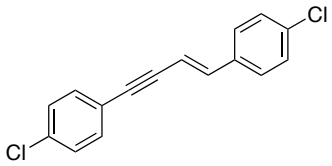


1-03l:[65] 0.5 mmol scale, 3 h, 60 °C. eluent 30% EtOAc in hexanes; obtained: 52 mg (**82%**), yellow solid; **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.67–7.62 (m, 4H), 7.57–7.50 (m, 4H), 7.08 (d, *J* = 16.3 Hz, 1H), 6.49 (d,

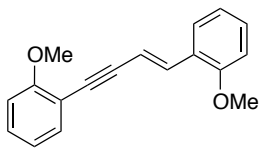
J = 16.2 Hz, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 140.7, 140.1, 132.6, 132.09, 132.07, 127.7 126.8, 118.6, 118.4, 112.2, 111.9, 111.2, 92.2, 92.0. **HRMS** (EI) calcd. for $C_{18}H_{11}N_2$ $[M+H]^+$: 255.0922; found: 255.0925.



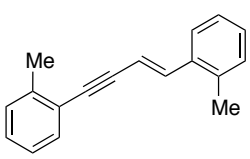
1-03y: 0.5 mmol scale, 2 h, 60 °C; eluent 10% EtOAc in hexanes; obtained: 54 mg (**67%**), yellow solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 8.03–7.99 (m, 4H), 7.53 (d, J = 8.4 Hz, 2H), 7.49 (d, J = 8.3 Hz, 2H), 7.09 (d, J = 16.2 Hz, 1H), 6.49 (d, J = 16.2 Hz, 1H), 3.93 (s, 6H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 166.6, 166.5, 141.0, 140.3, 131.5, 130.1, 129.6, 129.5, 127.8, 126.2, 110.3, 92.3, 91.4, 52.2, 52.1. **HRMS** (ESI) calcd. for $C_{20}H_{16}O_4$ $[M]^+$: 320.1049; found: 320.1040.



1-03u:[28a] 0.5 mmol scale, 3 h, 60 °C; eluent 100% hexanes; obtained: 35 mg (**51%**), white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.41–7.30 (m, 8H), 6.99 (d, J = 16.2 Hz, 1H), 6.34 (d, J = 16.2 Hz, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 140.2, 134.7, 134.5, 134.3, 132.7, 129.0, 128.7, 127.5, 121.8, 108.5, 91.1, 89.5. **HRMS** (ESI) calcd. for $C_{16}H_{10}Cl_2$ $[M]^+$: 272.0160; found: 272.0168.

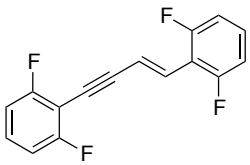


1-03z:[79] 0.5 mmol scale, 2 h, 60 °C; eluent 100% hexanes; obtained: 51 mg (**77%**), light yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.48–7.44 (m, 2H), 7.38 (d, J = 16.4 Hz, 1H), 7.31–7.24 (m, 2H), 6.97–6.87 (m, 4H), 6.55 (d, J = 16.4 Hz, 1H), 3.92 (s, 3H), 3.88 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 159.8, 157.0 136.4, 133.5, 129.5, 126.9, 125.5, 120.7, 120.5, 112.9, 111.0, 110.6, 109.1, 93.8, 87.6, 55.8, 55.5. **HRMS** (EI) calcd. for $C_{18}H_{17}O_2$ $[M+H]^+$: 265.1229; found: 265.1225.

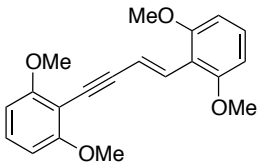


1-03q:[12a] 0.5 mmol scale, 1.5 h, 60 °C; eluent 100% hexanes; obtained: 47 mg (**81%**), light yellow solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.54–7.52 (m, 1H), 7.48 (d, J = 7.6 Hz, 1H), 7.30 (d, J = 16.1 Hz, 1H), 7.25–7.15 (m, 6H), 6.37 (d, J = 16.1 Hz, 1H), 2.51 (s, 3H), 2.42 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 140.1, 138.7, 135.8, 135.4,

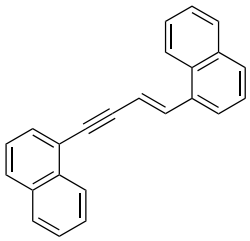
131.9, 130.6, 129.5, 128.5, 128.2, 126.3, 125.6, 125.0, 123.2, 109.4, 93.1, 90.4, 20.7, 19.8. **HRMS** (ESI) calcd. for $C_{18}H_{16}$ $[M]^+$: 232.1252; found: 232.1251.



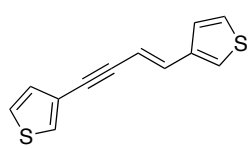
1-03s: 0.5 mmol scale, 2 h, 60 °C; eluent 100% hexanes. obtained: 61 mg (**88%**), white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.31–7.19 (m, 2H), 7.17 (d, *J* = 16.8 Hz, 1H), 6.96–6.88 (m, 4H), 6.78 (d, *J* = 16.7 Hz, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 163.0 (dd, *J* = 6.2 Hz, *J* = 238.4 Hz), 160.9 (dd, *J* = 6.1 Hz, *J* = 238.2 Hz), 129.8 (t, *J* = 9.9 Hz), 129.4 (t, *J* = 10.9 Hz), 129.1, 114.1 (t, *J* = 9.9 Hz), 113.7 (t, *J* = 15.5 Hz), 111.7 (dd, *J* = 4.8 Hz, *J* = 21.1 Hz), 111.2 (dd, *J* = 4.6 Hz, *J* = 19.8 Hz), 102.4 (t, *J* = 19.5 Hz), 98.7, 79.7. **HRMS** (ESI) calcd. for $C_{16}H_8F_4$ $[M]^+$: 276.05621; found: 276.05616.



1-03t: 0.5 mmol scale, 22 h, 100 °C; eluent 25% EtOAc in hexanes; obtained: 61 mg (**75%** yield), yellow solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.45 (d, *J* = 16.6 Hz, 1H), 7.20 (t, *J* = 8.4 Hz, 1H), 7.15 (d, *J* = 8.3 Hz, 1H), 7.06 (d, *J* = 16.6 Hz, 1H), 6.56–6.53 (m, 4H), 3.91 (s, 6H), 3.85 (s, 6H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 161.1, 158.9, 132.0, 129.2, 128.7, 114.4, 112.3, 102.3, 100.9, 103.5, 99.6, 83.3, 56.1, 55.7. **HRMS** (EI) calcd. for $C_{20}H_{21}O_4$ $[M+H]^+$: 325.1440; found: 325.1443.

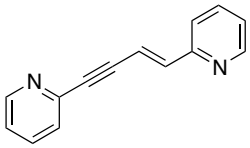


1-03n:[33d] 0.5 mmol scale, 24 h, 60 °C; eluent 100% hexanes; obtained: 50 mg (**66%**), yellow solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 8.48 (d, *J* = 8.3 Hz, 1H), 8.25 (d, *J* = 8.4 Hz, 1H), 7.98 (d, *J* = 16.0 Hz, 1H), 7.91–7.84 (m, 4H), 7.80–7.74 (m, 2H), 7.67–7.45 (m, 6H), 6.64 (d, *J* = 16.0 Hz, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 138.4, 133.8, 133.7, 133.3, 130.9, 130.5, 129.1, 128.8, 128.7, 128.4, 126.8, 126.5, 126.3, 126.1, 125.6, 125.4, 123.6, 123.5, 121.1, 110.9, 94.1, 89.8. **HRMS** (ESI) calcd. for $C_{24}H_{16}$ $[M]^+$: 304.1252; found: 304.1247.

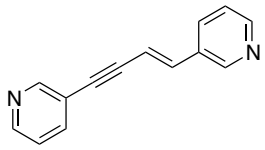


1-03aa:[12a] 0.5 mmol scale, 2 h, 60 °C; eluent 100% hexanes; obtained: 35 mg (**65%**), white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.46–7.44 (m, 1H),

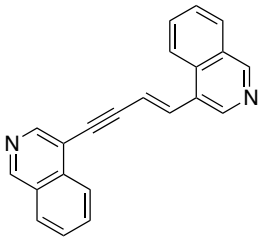
7.32–7.23 (m, 4H), 7.15–7.13 (m, 1H), 7.02 (d, *J* = 16.2 Hz, 1H), 6.19 (d, *J* = 16.1Hz, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 139.3, 135.1, 129.8, 128.3, 126.5, 125.3, 124.4, 123.6, 122.5, 107.8, 88.3, 86.7. **HRMS** (EI) calcd. for $C_{12}H_8S_2$ $[M]^+$: 216.0068; found: 216.0079.



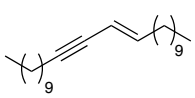
1-03x:[12a] 0.5 mmol scale, 24 h, 60 °C; eluent 50% EtOAc in hexanes; obtained: 48 mg (**93%**), yellow oil; **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 8.62–8.58 (m, 2H), 7.68–7.63 (m, 2H), 7.48 (d, *J* = 7.8 Hz 1H), 7.29–7.26 (m, 1H), 7.24–7.18 (m, 2H), 7.16 (d, *J* = 15.9 Hz, 1H), 6.98 (d, *J* = 15.9 Hz, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 153.8, 150.1, 149.9, 143.4, 141.8, 136.6, 136.1, 127.2, 123.2, 122.8, 122.7, 111.8, 92.4, 88.5. **HRMS** (EI) calcd. for $C_{14}H_{11}N_2$ $[M+H]^+$: 207.0922; found: 207.0921.



1-03ab: 0.5 mmol scale, 24 h, 60 °C; eluent 50% EtOAc in hexanes; obtained: 29 mg (**56%**), white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 8.72 (s, 1H), 8.66 (s, 1H), 8.55–8.52 (m, 2H), 7.77–7.74 (m, 2H), 7.31–7.275 (m, 2H), 7.06 (d, *J* = 16.3 Hz, 1H), 6.45 (d, *J* = 16.3 Hz, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 152.2, 149.8, 148.7, 148.4, 138.5, 138.3, 132.5, 131.7, 123.6, 123.1, 120.3, 109.8, 91.4, 89.2. **HRMS** (EI) calcd. for $C_{14}H_{11}N_2$ $[M+H]^+$: 207.0922; found: 207.0919.

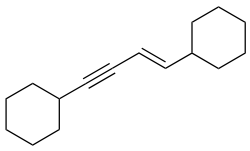


1-03ac: 0.5 mmol scale, 24 h, 60 °C; eluent 100% EtOAc; obtained: 60 mg (**78%**), yellow solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 9.24– 9.21 (m, 2H), 8.78–8.76 (m, 2H), 8.35–8.32 (m, 1H), 8.20–8.17 (m, 1H), 8.05–8.01 (m, 2H), 7.86–7.79 (m, 3H), 7.71–7.67 (m, 2H), 6.69 (d, *J* = 16.1 Hz, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 152.8, 152.1, 146.6, 140.1, 136.0, 135.5, 133.2, 131.2, 131.1 128.3, 128.2, 128.0, 127.8, 127.6, 127.5, 125.1, 122.7, 115.9, 112.0, 95.7, 87.4. **HRMS** (EI) calcd. for $C_{22}H_{15}N_2$ $[M+H]^+$: 307.1235; found: 307.1235.

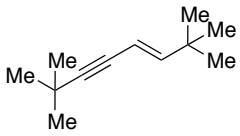


1-03ad:[66] 0.5 mmol scale, 20 h, 60 °C; eluent 100% hexanes; obtained: 75 mg (**91%**), colourless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 6.04 (dt, *J* = 7.1 Hz, 15.6 Hz, 1H),

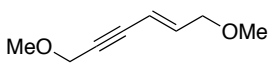
5.48–5.42 (m, 1H), 2.32–2.22 (m, 2H), 2.13–2.03 (m, 2H), 1.55–1.48 (m, 2H), 1.41–1.21 (m, 30H), 0.91–0.86 (m, 6H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 143.4, 110.7, 89.7, 79.2, 33.0, 31.9, 30.0, 29.6, 29.54, 29.47, 29.3, 29.2, 29.1, 28.94, 28.9, 22.7, 19.4, 14.1. **HRMS** (ESI) calcd. for $C_{24}H_{44}$ $[M]^+$: 332.3443; found: 332.3437.



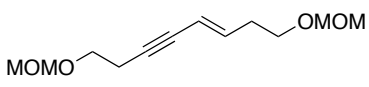
1-03ae:[80] 0.5 mmol scale, 16 h, 60 °C; eluent 100% hexanes; obtained: 49 mg (**91%**), colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 6.00 (dd, *J* = 16.1 Hz, *J* = 7.1 Hz, 1H), 5.43 (dt, *J* = 1.6 Hz, 16.0 Hz, 1H), 2.49–2.40 (m, 1H), 2.04–1.95 (m, 1H), 1.84–1.05 (m, 20H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 148.6, 107.5, 93.0, 79.1, 41.1, 32.8, 32.4, 29.7, 26.0, 25.89, 25.85, 25.0. **HRMS** (EI) calcd. for $C_{16}H_{24}$ $[M]^+$: 216.1878; found: 216.1874.



1-03h:[66] 0.5 mmol scale, 24 h, 60 °C; eluent 100% hexanes; obtained: 27 mg (**65%**), colourless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 6.08 (d, *J* = 16.2 Hz, 1H), 5.41 (d, *J* = 16.2 Hz, 1H), 1.24 (s, 9H), 1.01 (s, 9H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 153.3, 105.3, 97.3, 77.7, 33.7, 31.1, 29.1, 27.9. **HRMS** (ESI) calcd. For $C_{12}H_{20}$ $[M]^+$: 164.1565; found: 164.1556.

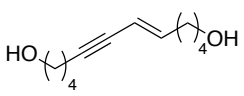


1-03af: 0.5 mmol scale, 13 h, 60 °C; eluent 10% EtOAc in hexanes; obtained: 25 mg (**71%**), colourless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 6.19 (dt, *J* = 5.5 Hz, 16.0 Hz, 1H), 5.76 (dqn, *J* = 1.8 Hz, 16.0 Hz, 1H), 4.21 (d, *J* = 1.9 Hz, 2H), 3.97 (dd, *J* = 1.7 Hz, 5.5 Hz, 2H), 3.39 (s, 3H), 3.34 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 139.9, 111.0, 85.5, 84.3, 72.1, 60.3, 58.2, 57.6. **HRMS** (EI) calcd. For $C_8H_{12}O_2Na$ $[M]^+$: 163.0735; found: 163.0738.

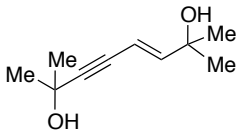


1-03ag: 0.5 mmol scale, 16 h, 60 °C; eluent 10% EtOAc in hexanes; obtained: 35 mg (**61%**), colourless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 6.07 (dt, *J* = 7.1 Hz, *J* = 15.8 Hz, 1H), 5.56–5.51 (m, 1H), 4.65 (s, 2H), 4.60 (s, 2H), 3.64 (t, *J* = 6.8 Hz, 2H), 3.55 (t, *J* = 6.6 Hz, 2H), 3.37 (s, 3H), 3.35 (s, 3H), 2.61–2.56 (m, 2H), 2.40–2.34 (m, 2H). **^{13}C**

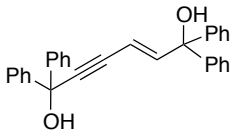
NMR (125 MHz, $CDCl_3$) δ ppm 139.8, 111.7, 96.4, 85.7, 79.9, 66.7, 66.0, 55.2, 33.4, 20.9. **HRMS** (EI) calcd. for $C_{12}H_{20}O_4Na$ $[M+Na]^+$: 251.1259; found: 251.1260.



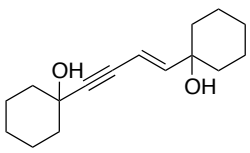
1-03ah: 0.5 mmol scale, 16 h, 60 °C; eluent 50% EtOAc in hexanes; obtained: 46 mg (**94%**), colourless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 6.01 (dt, *J* = 7.0 Hz, 15.5 Hz, 1H), 5.50–5.43 (m, 1H), 3.68 (t, *J* = 6.3 Hz, 2H), 3.66 (t, *J* = 6.5 Hz, 2H), 2.36–2.31 (m, 2H), 2.12 (q, *J* = 7.2 Hz, 2H), 1.72–1.66 (m, 2H), 1.64–1.54 (m, 4H), 1.50 – 1.43 (m, 2H), 1.40 (s, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 142.9, 110.2, 88.4, 79.5, 62.7, 62.5, 32.6, 32.1, 31.9, 25.0, 24.9, 19.1. **HRMS** (EI) calcd. for $C_{12}H_{21}O_2$ $[M+H]^+$: 197.1542. Found: 197.1545.



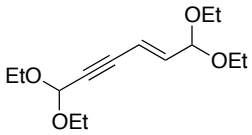
1-03c:[32] 1 mmol scale, 16 h, 60 °C; eluent 20% EtOAc in hexanes; obtained: 71 mg (**85%**), white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 6.23 (d, *J* = 16.1 Hz, 1H), 5.72 (d, *J* = 16.0 Hz, 1H), 2.22 (s, 1H), 1.67 (s, 1H), 1.52 (s, 6H), 1.31 (s, 6H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 150.5, 106.3, 94.4, 80.2, 71.0, 65.5, 31.4, 29.4. **HRMS** (EI) calcd. for $C_{10}H_{16}O_2Na$ $[M+Na]^+$: 191.1048; found: 191.1050.



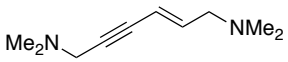
1-03ai:[81] 0.5 mmol scale, 16 h, 60 °C; eluent 20% EtOAc in hexanes; obtained: 91 mg (**88%**), white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.60 (d, *J* = 7.6 Hz, 4H), 7.39–7.25 (m, 16H), 6.82 (d, *J* = 16.0 Hz, 1H), 5.99 (d, *J* = 15.8 Hz, 1H), 2.82 (s, 1H), 2.32 (s, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 148.4, 145.0, 144.9, 128.4, 128.3, 127.71, 127.65, 126.9, 126.1, 108.9, 93.2, 85.2, 79.3, 74.8. **HRMS** (EI) calcd. for $C_{30}H_{24}O_2Na$ $[M+Na]^+$: 439.1674; found: 439.1678.



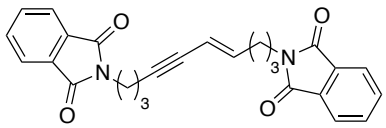
1-03aj:[32] 0.5 mmol scale, 16 h, 60 °C; eluent 20% EtOAc in hexanes; obtained: 55 mg (**89%**), white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 6.24 (d, *J* = 16.0 Hz, 1H), 5.79 (d, *J* = 16.0 Hz, 1H), 1.93–1.87 (m, 2H), 1.71–1.45 (m, 20H), 1.32–1.20 (m, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 150.4, 107.0, 93.5, 72.5, 71.9, 69.0, 40.0, 37.5, 25.3, 25.2, 23.3, 21.8. **HRMS** (EI) calcd. for $C_{16}H_{24}O_2Na$ $[M+Na]^+$: 271.1674; found: 271.1682.



1-03ak: 0.5 mmol scale, 3 h, 60 °C; eluent 10% EtOAc in hexanes, obtained: 59 mg (**93%**), colourless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 6.14 (dd, *J* = 4.4 Hz, 16.1 Hz, 1H), 5.87 (dt, *J* = 1.3 Hz, 16.1 Hz, 1H), 5.37 (d, *J* = 1.2 Hz, 1H), 4.93 (dd, *J* = 1.1 Hz, 4.3 Hz, 1H), 3.79–3.70 (m, 2H), 3.65–3.55 (m, 4H), 3.52–3.44 (m, 2H), 1.26-1.17 (m, 12H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 141.3, 112.0, 99.8, 91.7, 86.2, 82.7, 61.1, 60.9, 15.2, 15.1. **HRMS** (EI) calcd. For $C_{14}H_{24}O_4Na$ $[M+Na]^+$: 279.1572; found: 279.1579.

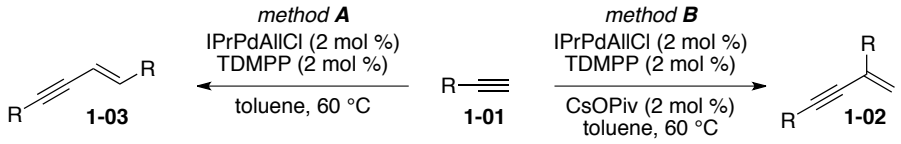


1-03al:[66] 0.5 mmol scale, 16 h, 60 °C; eluent 60% EtOAc in hexanes; obtained: 34 mg (**81%**), yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 6.14–6.04 (m, 1H), 5.61 (d, *J* = 15.8 Hz, 1H), 3.31 (s, 2H), 2.92 (d, *J* = 7.0 Hz, 2H), 2.26 (s, 6H), 2.18 (s, 6H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 140.6, 112.0, 84.5, 83.2, 61.6, 48.6, 45.6, 44.2. **HRMS** (EI) calcd. for $C_{10}H_{19}N_2$ $[M+H]^+$: 167.1548; found: 167.1548.



1-03am: 0.5 mmol scale, 16 h, 60 °C; eluent 20% EtOAc in hexanes; obtained: 102 mg (**96%**), white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.86–7.81 (m, 4H), 7.73–7.68 (m, 4H), 5.88 (dt, *J* = 7.0 Hz, 15.7 Hz, 1H), 5.31 (dt, *J* = 1.7 Hz, 15.8 Hz, 1H), 3.78 (t, *J* = 7.0 Hz, 2H), 3.66 (t, *J* = 7.2 Hz, 2H), 2.35 (dt, *J* = 1.8 Hz, 2H), 2.10–2.04 (m, 2H), 1.91 (q, *J* = 7.0 Hz, 2H), 1.72 (q, *J* = 7.4 Hz, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 168.3, 141.4, 133.9, 133.8, 132.2, 132.1, 123.2, 110.5, 87.6, 79.5, 37.44, 37.36, 30.18, 27.5, 27.3, 17.2. **HRMS** (EI) calcd. for $C_{10}H_{19}N_2$ $[M+H]^+$: 427.1658. Found: 427.1658.

1.3.3. Comparison of Carboxylate-free and Carboxylate-assisted Palladium-catalyzed Dimerization of Terminal Alkynes



General procedure for method A: An oven-dried 1 mL Wheaton microreactor was loaded with IPrPdAllCl (5.7 mg, 2 mol %) and tris(2,6-dimethoxyphenyl)phosphine (4.4 mg, 2 mol %). Anhydrous toluene (0.5 mL) was added followed by alkyne **1-01** (0.5 mmol). The reaction mixture was stirred at 60 °C until the completion. The reaction course was monitored by GC/MS analysis. After the reaction completion, the reaction mixture was concentrated and filtered through a short silica gel plug. The product was purified by column chromatography. Spectral data for compounds **1-03** obtained by this method are identical to those described above.

1-03a: 0.5 mmol scale, 24 h, 60 °C; obtained: 48 mg (**94%**, **2**:**3**:**4** = 96:4:0).

1-03j: 0.5 mmol scale, 30 h, 60 °C; obtained: 51 mg (**88%**).

1-03i: 0.5 mmol scale, 48 h, 60 °C; obtained: 51 mg (**77%**).

1-03z: 0.5 mmol scale, 22 h, 60 °C; obtained: 30 mg (**42%**, **2**:**3**:**4** = 83:0:17).

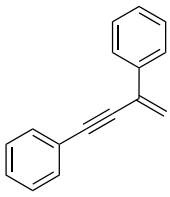
1-03q: 0.5 mmol scale, 24 h, 60 °C; obtained: 30 mg (**52%**, **2**:**3**:**4** = 70:0:30).

1-03n: 0.5 mmol scale, 30 h, 60 °C; obtained: 40 mg (**65%**).

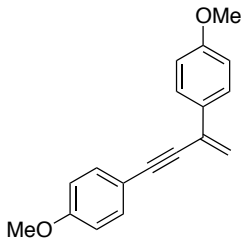
1-03ad: 0.5 mmol scale, 48 h, 60 °C; obtained: 48 mg (**58%**, **2**:**3**:**4** = 83:7:10).

General procedure for method B: An oven-dried 1 mL Wheaton microreactor was loaded with IPrPdAllCl (5.7 mg, 2 mol %), tris(2,6-dimethoxyphenyl)phosphine (4.4 mg, 2 mol %), and cesium pivalate (2.3 mg, 2 mol %). Anhydrous toluene (0.5 mL) was added followed by alkyne **1-01** (0.5 mmol). The reaction mixture was stirred at 60 °C until the completion. The reaction course was monitored by

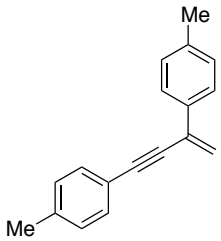
GC/MS analysis. After the reaction completion, the reaction mixture was concentrated and filtered through a short silica gel plug. The product was purified by column chromatography.



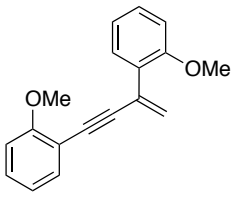
1-02a:[60] 0.5 mmol scale, 3 h, 60 °C; eluent 100% hexanes; obtained: 32 mg (**62%**), colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.75–7.70 (m, 2H), 7.56–7.53 (m, 2H), 7.42–7.32 (m, 6H), 6.01 (d, *J* = 1.0 Hz, 1H), 5.79 (d, *J* = 1.0 Hz, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 137.3, 131.7, 130.6, 128.4, 128.3, 126.1, 123.1, 120.6, 90.8, 88.6. **HRMS** (ESI) calcd. for $C_{16}H_{12}$ $[M]^+$: 204.09390 found: 204.0941.



1-02j:[63a] 0.5 mmol scale, 5 h, 60 °C; eluent 5% EtOAc in hexanes; obtained: 56 mg (**85%**, **2**:**3**:**4** = 5:0:95), yellow solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.69–7.65 (m, 2H), 7.49–7.45 (m, 2H), 6.93–6.85 (m, 4H), 5.85 (d, *J* = 0.7 Hz, 1H), 5.63 (d, *J* = 0.7 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 159.7, 159.6, 133.1, 130.1, 127.6, 127.3, 118.1, 115.3, 114.0, 113.7, 90.6, 87.5, 55.35, 55.32. **HRMS** (ESI) calcd. for $C_{18}H_{17}O_2$ $[M+H]^+$: 265.1229; found: 265.1222.

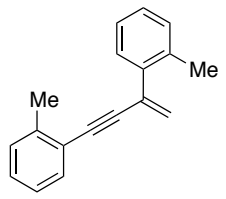


1-02i:[63a] 0.5 mmol scale, 2 h, 60 °C; eluent 100% hexanes; obtained: 51 mg (**88%**), white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.65–7.61 (m, 2H), 7.45–7.42 (m, 2H), 7.21–7.14 (m, 4H), 5.93 (d, *J* = 1.0 Hz, 1H), 5.70 (d, *J* = 0.9 Hz, 1H), 2.38 (s, 6H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 138.5, 138.2, 134.6, 131.6, 130.6, 129.10, 129.07, 126.0, 120.1, 119.4, 90.8, 88.1, 21.5, 21.2. **HRMS** (ESI) calcd. for $C_{18}H_{16}$ $[M]^+$: 232.1252; found: 232.1252.

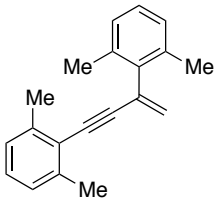


1-02z:[12a] 0.5 mmol scale, 2 h, 60 °C; eluent 5% EtOAc in hexanes; obtained: 53 mg (**80%**), light yellow solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.75–7.70 (m, 1H), 7.47–7.43 (m, 1H), 7.31–7.25 (m, 2H), 7.02–6.97 (m, 1H), 6.97–6.86 (m, 3H), 6.11 (dd, *J* = 0.97 Hz, 1.9 Hz, 1H), 5.97 (dd, *J* = 1.0, 1.9 Hz, 1H), 3.89 (s, 6H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 160.1, 157.3, 133.5, 130.6, 129.6, 129.1, 128.0, 127.2, 125.4, 120.5,

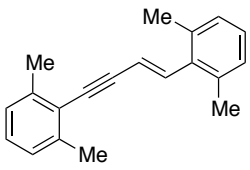
120.4, 112.8, 111.5, 110.7, 94.1, 85.3, 55.8, 55.6. **HRMS** (ESI) calcd. for $C_{18}H_{16}O_2$ $[M]^+$: 264.1150: found: 264.1159.



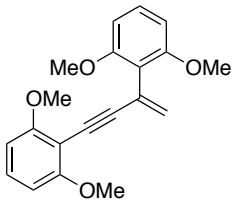
1-02q:[12a] 0.5 mmol scale, 2 h, 60 °C; eluent 100% hexanes; obtained: 56 mg (**97%**), colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.44–7.40 (m, 1H), 7.37–7.33 (m, 1H), 7.28–7.18 (m, 5H), 7.16–7 .10 (m, 1H), 5.89 (d, *J* = 1.8 Hz, 1H), 5.55 (d, *J* = 1.7 Hz, 1H), 2.52 (s, 3H), 2.44 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 140.2, 139.4, 135.5, 132.0, 131.9, 130.4, 129.4, 128.8, 128.3, 127.9, 125.9, 125.5, 124.9, 123.0, 93.3, 89.6, 20.7, 20.3. **HRMS** (ESI) calcd. for $C_{18}H_{16}$ $[M]^+$: 232.1252. Found: 232.1257.



1-02r: 0.5 mmol scale, 24 h, 80 °C; eluent 100% hexanes; obtained: 24 mg (**37%**, **2**:**3**:**4** = 15:0:85), colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm . 7.14–7. 10 (m, 1H), 7.09 – 7.05 (m, 3H), 7.03 – 7.00 (m, 2H), 5.93 (d, *J* = 2.0 Hz, 1H), 5.36 (d, *J* = 2.0 Hz, 1H), 2.40 (s, 6H), 2.38 (s, 6H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 140.3, 139.4, 135.5, 130.2, 127.7, 127.4, 127.2, 126.6, 129.6, 124.6, 122.9, 97.5, 87.0, 21.0, 20.2. **HRMS** (ESI) calcd. for $C_{20}H_{20}$ $[M]^+$: 260.1565; found: 260.1573.

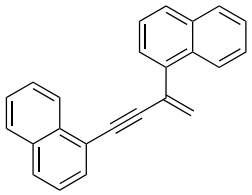


1-03r (minor isomer): **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.15–7.05 (m, 7H), 6.06 (d, *J* = 16.7 Hz, 1H), 2.51 (s, 6H), 2.40 (s, 6H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 140.2, 139.1, 136.2, 135.6, 128.1, 127.7, 127.3, 126.7, 123.1, 114.2, 96.9, 88.6, 21.1. **HRMS** (EI) calcd. for $C_{20}H_{20}$ $[M]^+$: 260.1565; found: 260.1585.

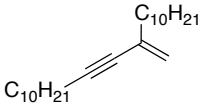


1-02t: 0.5 mmol scale, 24 h, 80 °C; eluent 25% EtOAc in hexanes; obtained: 63 mg (**78%**, **2**:**3**:**4** = 2:0:98), yellow solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.21 (t, *J* = 8.3 Hz, 1H), 7.16 (t, *J* = 8.4 Hz, 1H), 6.60 (d, *J* = 8.4 Hz, 2H), 6.48 (d, *J* = 8.4 Hz, 2H), 6.04 (d, *J* = 2.1 Hz, 1H), 5.55 (d, *J* = 2.1 Hz, 1H), 3.85 (s, 6H), 3.81

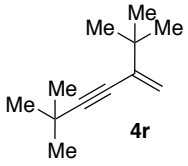
(s, 6H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 161.5, 157.8, 129.2, 128.7, 126.9, 123.6, 118.0, 104.5, 103.8, 103.6, 98.7, 79.5, 56.2, 56.0. **HRMS** (ESI) calcd. for $C_{20}H_{21}O_4$ $[M+H]^+$: 325.1440; found: 325.1440.



1-02n: 0.5 mmol scale, 2 h, 60 °C; eluent 100% hexanes; obtained: 61 mg (**80%**), colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 8.54–8.49 (m, 1H), 8.25–8.21 (m, 1H), 7.94–7.86 (m, 2H), 7.95–7.79 (m, 2H), 7.67–7.60 (m, 2H), 7.58–7.44 (m, 5H), 7.43–7.38 (m, 1H), 6.17 (d, *J* = 1.8 Hz, 1H), 5.85 (d, *J* = 1.8 Hz, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 137.7, 133.8, 133.2, 133.1, 130.9, 130.8, 130.5, 128.8, 128.6, 128.3, 128.2, 126.7, 126.4, 126.3, 126.1, 126.0, 125.8, 125.4, 125.2, 120.8, 94.9, 89.2. **HRMS** (ESI) calcd. for $C_{24}H_{16}$ $[M]^+$: 304.1252. Found: 304.1239.

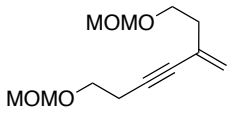


1-02ad:[66] 0.5 mmol scale, 7 h, 60 °C; eluent 100% hexanes; obtained: 77 mg (**93%**), colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 5.20 (d, *J* = 2.1 Hz, 1H), 5.12 (s, 1H), 2.30 (t, *J* = 7.1 Hz, 2H), 2.11 (t, *J* = 7.6 Hz, 2H), 1.57–1.47 (m, 4H), 1.43–1.36 (m, 2H), 1.32–1.21 (m, 26H), 0.91–0.86 (m, 6H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 132.5, 119.2, 90.1, 81.1, 37.6, 31.9, 29.63, 29.60, 29.57, 29.5, 29.36, 29.35, 29.2, 29.0, 28.9, 28.8, 28.1, 22.7, 19.3, 14.1. **HRMS** (ESI) calcd. for $C_{24}H_{44}$ $[M]^+$: 332.3443. Found: 332.3447.



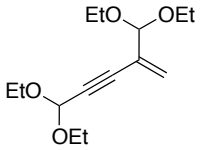
4r

1-02h:[63a] 0.5 mmol scale, 7 h, 60 °C; due to high volatility product was not isolated in pure form, **65% NMR** yield (**2**:**3**:**4** = 9:0:91). **^{1}H NMR** (500 MHz, C_6D_6) δ ppm 5.41 (d, *J* = 1.5 Hz, 1H), 5.20 (d, *J* = 1.4 Hz, 1H), 1.28 (s, 9H), 1.25 (s, 9H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 142.4, 115.8, 98.9, 79.3, 35.9, 31.9, 30.9, 28.9, 18.8.



1-02ag: 6 mmol scale, 12 h, 60 °C; eluent 20% EtOAc in hexanes; obtained: 567 mg (**83%**), colorless liquid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 5.31 (m, 1 H), 5.23 (m, 1 H), 4.63 (s, 2 H), 4.61 (s, 2 H), 3.68 (t, *J* = 6.7 Hz, 2 H), 3.64 (t, *J* = 6.9 Hz, 2 H), 3.35 (s, 3 H), 3.34 (s, 3 H), 2.59 (t, *J* = 6.9 Hz, 2 H), 2.39 (t, *J* = 6.6 Hz, 2 H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 128.4,

122.0, 96.4, 87.0, 81.2, 66.0, 65.7, 55.2, 55.1, 37.7, 20.8 **HRMS** (ESI) calcd. for $C_{12}H_{20}O_4Na$ $[M+Na]^+$: 251.1259; found: 251.1258.



1-02ak: 0.5 mmol scale, 6 h, 60 °C; eluent 10% EtOAc in hexanes; obtained: 52 mg (**81%, 2**:**3**:**4** = 19:0:81), yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 5.78 (t, *J* = 1.5 Hz, 1H), 5.69–5.67 (m, 1H), 5.38 (s, 1H), 4.90–4.89 (m, 1H), 3.79–3.72 (m, 2H), 3.67–3.56 (m, 4H), 3.54–3.46 (m, 2H), 1.25–1.18 (m, 12H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 128.7, 125.0, 100.2, 91.7, 85.5, 83.0, 61.4, 60.9, 15.2, 15.1. calcd. for $C_{14}H_{24}O_4Na$ $[M+Na]^+$: 279.1572; found: 279.1569.

1.3.4. Theoretical Study

The standard 6-311G(d) basis set[82] for H, C, N, O and the triple-z basis set with the Stuttgart/Dresden effective core potentials[83] (SDD) for Pd were used for all calculations with the some exceptions (this basis sets combination is denoted as 6-311G(d)&SDD). The B3LYP hybrid density functional[84] was applied for geometry optimization and thermochemical calculations of initial complexes, transition states, intermediate complexes and products. B3LYP/6-311G(d)&SDD level of theory adequately describes the energy and geometry parameters of the palladium complexes as was shown in previous studies.[85] The normal coordinate analysis was performed to characterize the nature of the stationary points for all optimized structures. Thermodynamic properties of all studies structures were calculated for 298.15 K and 1 atm. Correctness of the obtained transition states was proved by IRC (Intrinsic Reaction Coordinate) calculations.[86] All calculations were carried out using the Gaussian 09 program.[87]

Investigation of the reactions with neutral palladium complexes (Scheme 1.57) were performed for model complexes. The model complexes contain simplified ligand, which has methyl groups on the nitrogen atoms. Such model systems adequately represent of relative energy surfaces of metal-mediated dimerization of alkynes.[88]

Calculated free energy surface of Pd-catalyzed *head-to-head* and *head-to-tail* dimerization of phenylacetylene is shown on Figure 1.1. Calculated ΔE, ΔH and ΔG energy data is given in Table 1.8 and ΔE energy surface is shown on Figure 1.6.

Anionic palladium complexes (Scheme 1.58, 1.59, Figure 1.4), generated as a result of interaction with acetate anion, contain real-size NHC ligand for reproducing of the steric effects in catalytic cycle. Calculated ΔE, ΔH and ΔG energy data is given in Table 1.9, and ΔE energy surface is shown on Figure 1.7.

The calculations of the interaction with base (acetate ion) and formation of the ion pairs in different cases of the substrate molecules orientation (Figure 1.5) were carried out with the standard DGDZVP[89] basis set for H, C, N, O (+SDD basis for Pd) and the M06L[90] density functional method. The AcO(-) anion is coordinated with Pd atom by fixation of the Pd-O distance at 2.2 angstroms (ModReduntant option of the Gaussian program package).

Table 1.8. Calculated ΔE, ΔH and ΔG (in kcal/mol) Energy Data for the Studied Catalytic Reaction with Phenylacetylene at B3LYP/SDD&6-311G(d) Level (Scheme 1.57, Figure 1.1).

Point	ΔE	ΔH	ΔG	Point	ΔE	ΔH	ΔG
Head-to-head carbopalladation				*Head-to-head* hydropalladation			
A	0.0	0.0	0.0	**A**	0.0	0.0	0.0
B-TS	20.4	17.6	17.6	**B-TS**	20.4	17.6	17.6
C	16.8	15.2	14.8	**C**	16.8	15.2	14.8
D-hh	9.0	9.0	19.4	**D'-hh**	11.2	11.2	22.1
E-TS-hh	26.3	25.4	38.0	**E'-TS-hh**	13.3	12.2	24.2
F-hh	-8.8	-8.0	5.5	**F'-hh**	-7.9	-5.1	5.2
G-TS-hh	-7.2	-7.2	6.2	**G'-TS-hh**	-5.6	-3.7	8.2
H-hh	-42.5	-39.0	-27.6	**H'-hh**	-42.8	-39.4	-28.2
Head-to-tail carbopalladation				*Head-to-tail* hydropalladation			
A	0.0	0.0	0.0	**A**	0.0	0.0	0.0
B-TS	20.4	17.6	17.6	**B-TS**	20.4	17.6	17.6
C	16.8	15.2	14.8	**C**	16.8	15.2	14.8
D-ht	8.8	8.8	19.1	**D'-ht**	11.7	11.8	23.4
E-TS-ht	30.9	29.6	42.4	**E'-TS-ht**	13.3	12.5	25.3
F-ht	-6.2	-5.6	8.0	**F'-ht**	-7.1	-4.5	7.4
G-TS-ht	-	-	-	**G'-TS-ht**	-1.5	0.0	12.6
H-ht	-39.2	-35.9	-23.4	**H'-ht**	-37.9	-34.7	-22.5

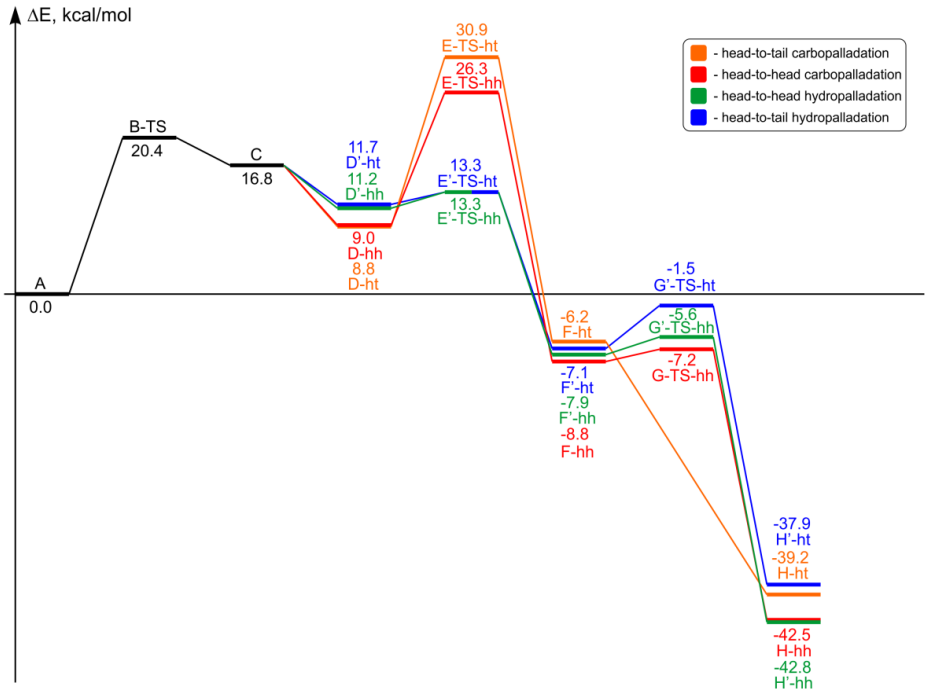


Figure 1.6. Calculated Energy Surface (ΔE, kcal/mol) of Palladium-catalyzed *Head-to-head* and *Head-to-tail* Dimerization of Terminal Alkynes (see Scheme 1.57; different reactions paths are denoted by different colors; B3LYP/6-311G(d)&SDD).

Complete Dissociation Involving Anionic Pd Species in the Catalytic Cycle

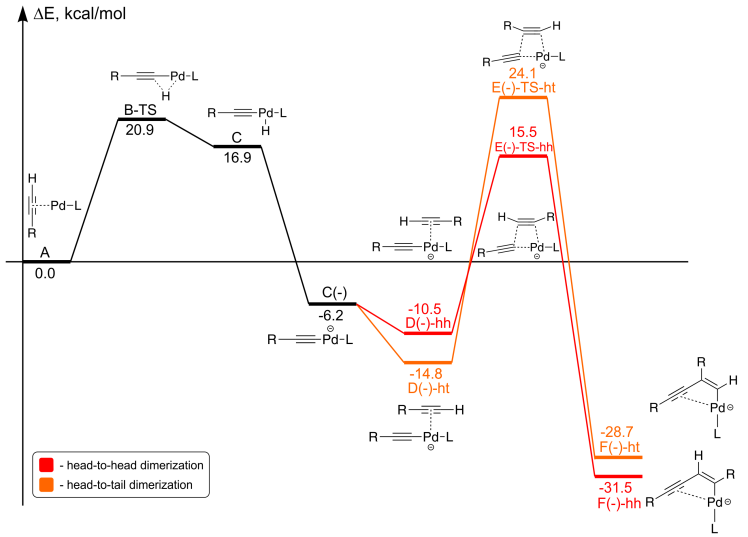


Figure 1.7. Calculated Energy Surface (ΔE, kcal/mol) of Pd(-)-catalyzed *Head-to-head* and *Head-to-tail* Dimerization of Terminal Alkynes (see Scheme 1.59; different reactions paths are denoted by different colors; B3LYP/6-311G(d)&SDD).

Table 1.9. Calculated ΔE, ΔH and ΔG (in kcal/mol) Energy Data of Pd(-)-Catalyzed *Head-to-head* and *Head-to-tail* Dimerization of Phenylacetylene (see Scheme 1.59) at B3LYP/SDD&6-311G(d) Level.

Point	ΔE	ΔH	ΔG	Point	ΔE	ΔH	ΔG
Head-to-head carbopalladation				*Head-to-tail* hydropalladation			
A	0.0	0.0	0.0	**A**	0.0	0.0	0.0
B-TS	20.9	18.0	14.3	**B-TS**	20.9	18.0	14.3
C	16.9	15.5	13.9	**C**	16.9	15.5	13.9
C(-)	-6.2	-5.6	-5.9	**C(-)**	-6.2	-5.6	-5.9
D(-)-hh	-10.5	-8.5	4.0	**D(-)-ht**	-14.8	-12.9	-1.5
E(-)-TS-hh	15.5	16.1	28.7	**E(-)-TS-ht**	24.1	24.3	36.9
F(-)-hh	-31.5	-28.8	-16.8	**F(-)-ht**	-28.7	-25.8	-12.8

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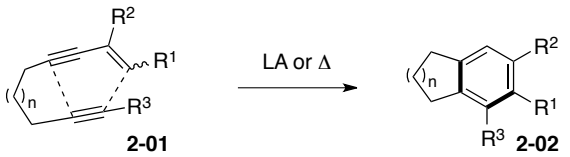
PART TWO

DEVELOPMENT OF HIGHLY EFFICIENT CATALYTIC SYSTEM FOR THE PALLADIUM-CATALYZED [4+2] BENZANNULATION REACTION OF ENYNES

2.1. INTRODUCTION

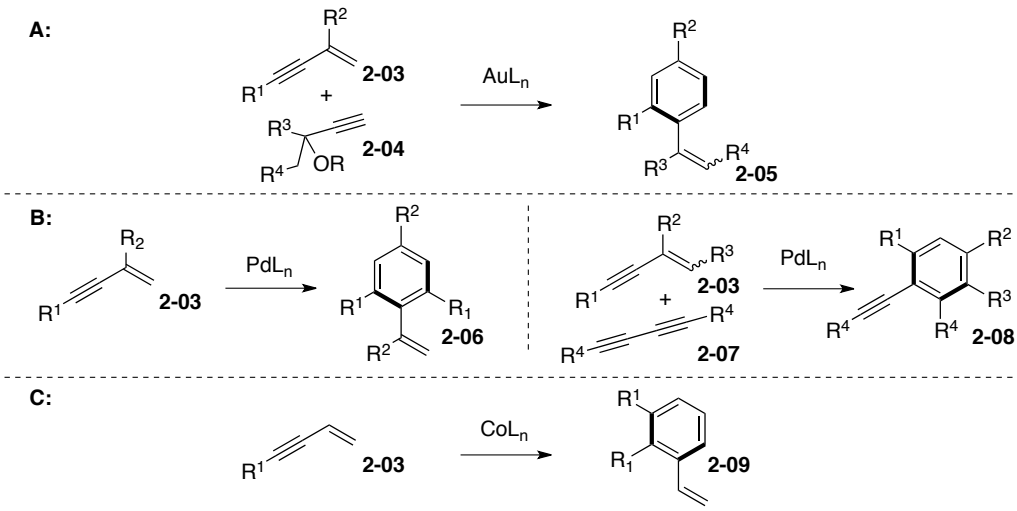
The ability of conjugated enynes to serve as a four-carbon unit in thermal or Lewis-acid mediated cycloaddition reaction with alkynes to form aromatic products was first recognized by Danheiser[1] (Scheme 2.1). Although this enyne-yne cycloaddition reaction represents powerful method for the synthesis of bicyclic aromatic compounds, it is limited to intramolecular processes.



Scheme 2.1. Danheiser [4+2] Benzannulation Reaction of Conjugated Enyne with Alkyne.

With the aid of transition metals, intermolecular catalytic analogs for this transformation became available, opening an easy access to densely substituted aromatic products from acyclic starting materials via a formal [4+2] cycloaddition of enyne with enynophile (Scheme 2.2). The first example of the [4+2] benzannulation reaction between two molecules of conjugated enynes **2-03** under palladium catalysis was reported in 1996 by Yamamoto group[2] (Scheme 2.2B). Since then, the palladium-catalyzed formal cycloaddition of this type has been intensively investigated and became a useful synthetic tool for construction of polysubstituted benzenes.[3] Besides that, synthetic potential of enynes was realized in benzannulation reaction, catalyzed by gold (Scheme 2.2A) or cobalt (Scheme 2.2C) complexes. Three types of enynophiles, such as simple alkynes **2-04** (Scheme 2.2A), alkynes conjugated with double **2-03** (Scheme 2.2B, C) or triple bonds **2-07** (Scheme 2.2B), were shown to participate in these formal [4+2] cycloaddition reactions, leading to the formation of diversely substituted styrenes **2-05**, **2-06**, and **2-09**, as well as aryl acetylenes **2-08**. Therefore, besides the construction of aromatic ring, useful functionalities,

such as double or triple bond, are introduced to the product via a single operation through the [4+2] benzannulation of enynes with alkenyl- or alkynyl-containing enynophiles. Accordingly, advances in thermal and transition-metal catalyzed [4+2] benzannulation reactions are summarized in the following section.

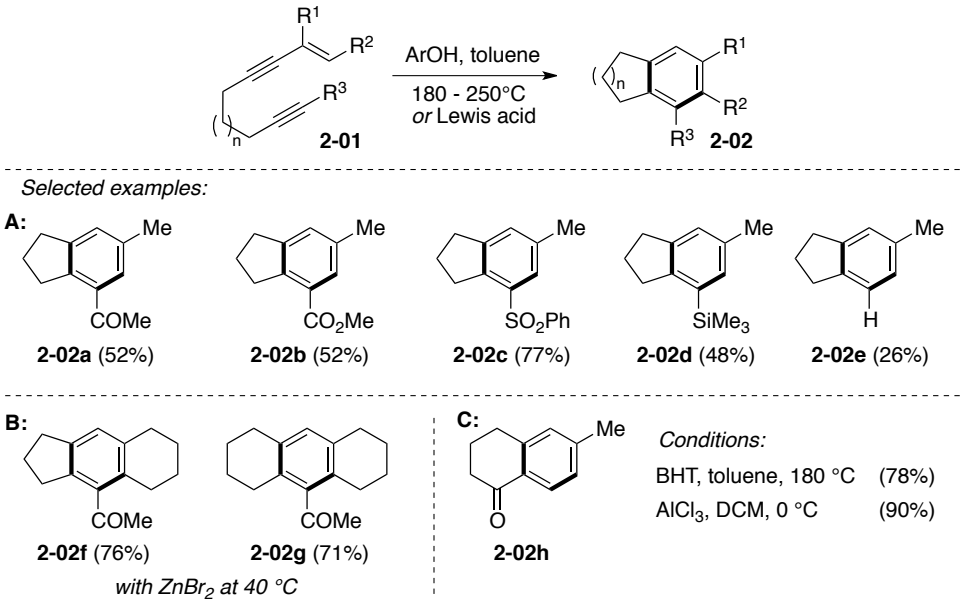


Scheme 2.2. Transition Metal-catalyzed Intermolecular Benzannulation Reactions of Conjugated Enynes with Enynophiles: (A) Gold-catalyzed [4+2] Benzannulation of Enynes with Alkynes; (B) Palladium-catalyzed [4+2] Benzannulation of Enynes with Enynes or Diynes; (C) Cobalt-catalyzed [4+2] homo-Benzannulation of Enynes.

2.1.1. Danheiser Intramolecular [4+2] Benzannulation Reaction of Enynes with Alkynes

In 1994, Danheiser group reported the first example of intramolecular cycloaromatization (benzannulation) reaction between conjugated enyne and alkyne.[1] It was found that thermolysis of yne-enynes **2-01** in the presence of phenol additives leads to the formation of aromatized products **2-02** with good yields (Scheme 2.3A). Substrates possessing electron-deficient alkynes (**2-01a**–**2-01c**) demonstrated higher reactivity toward cycloaddition reaction compared to their electron neutral analogs (**2-01d**, **2-01e**) presumably due to the lower LUMO energies of enynophile. Notably, various Lewis acids additives greatly facilitate the reaction. For example, addition of stoichiometric amount of $ZnBr_2$ allowed for smooth conversion of disubstituted enynes to the desired aromatic compounds **2-02f**, **2-02g** at 40 °C (Scheme 2.3B). Additionally, a direct comparison of thermal and Lewis acid mediated conditions

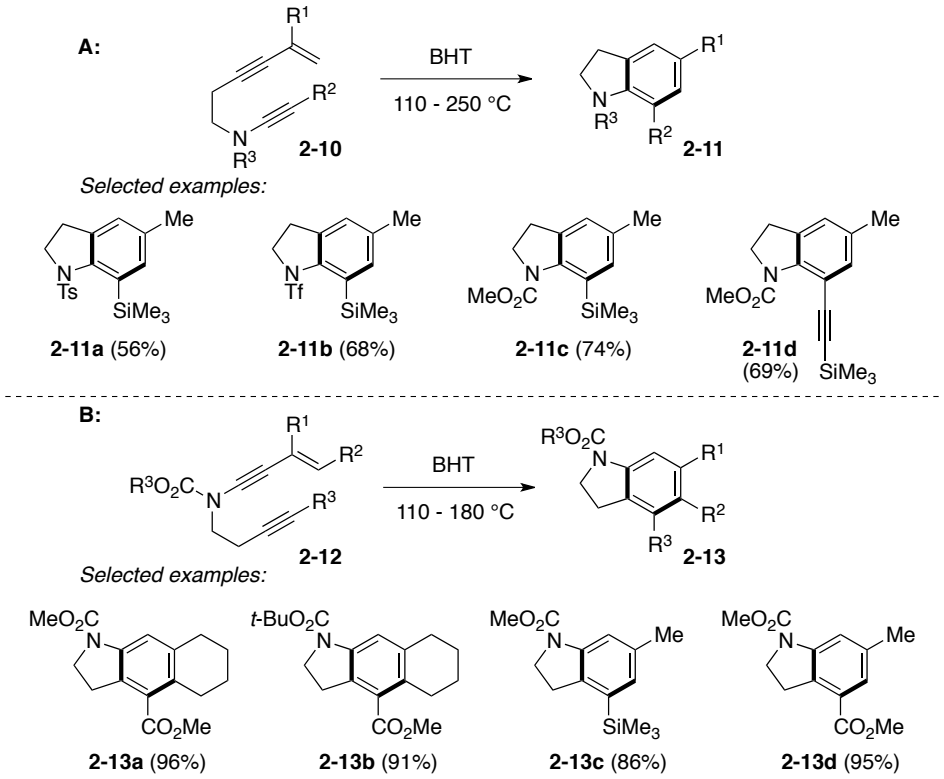
revealed that employment of $AlCl_3$ provided desired product **2-02h** with higher efficiency under considerably milder reaction conditions (Scheme 2.3C).



Scheme 2.3. Danheiser Intramoleculat [4+2] Benzannulation Reaction of Enynes with Alkynes: (A) Selected Examples of Thermal [4+2] Benzannulation Reaction; (B) Selected Examples of Lewis Acid-mediated [4+2] Benzannulation Reaction; (C) Comparison of Thermal and Lewis Acid-mediated [4+2] Benzannulation Reaction.

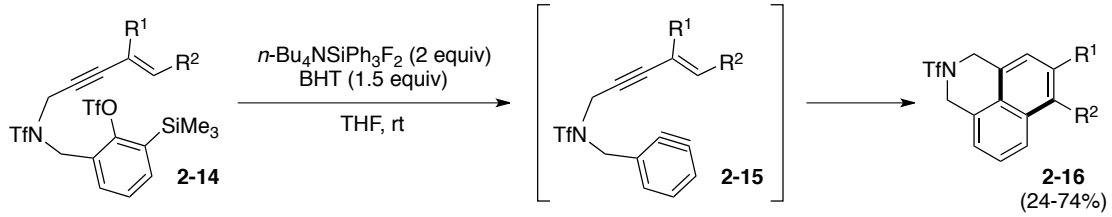
The developed method was applied for synthesis of various indolines (Scheme 2.4A).[4] The distinct feature of this approach is the construction of aromatic ring of indoline core from linear precursors as opposed to widely used strategy of heterocycle installation onto the existent aromatic core. Subsequently, this method allows decorating aromatic ring of indolines with various substituents. Thus, easily available ynamides **2-10** underwent efficient [4+2] benzannulation reaction to form the corresponding indolines **2-11**. Interestingly, diyneamide was also compatible substrate for this transformation providing easy entry to the corresponding alkynyl indoline **2-11d**. Additionally, employment of enyneamides allows for synthesis of indolines with alternative substitution pattern (Scheme 2.4B). Particularly, it allows introducing substituent at C-4 position, which is not accessible via cycloaddition of enynes with yneamides. The reaction proceeds smoothly for a variety of enyneamides

2-12 with the formation of cyclized product **2-13** in high yields. Overall, this thermal intramolecular cycloaddition methodology provides two complementary routes toward indoline derivatives.



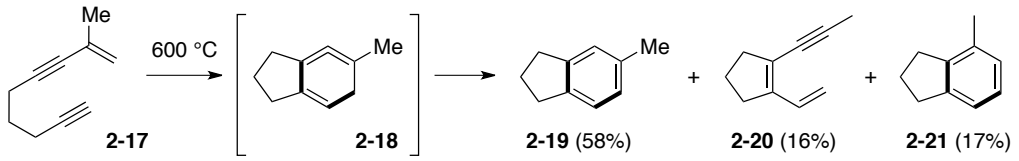
Scheme 2.4. Synthesis of Indolines via Danheiser [4+2] Benzannulation Reaction of (A) Enynes with Ynamides and (B) Enyne Amides with Alkynes.

Later, this methodology was further expanded to the reaction of enynes with benzynes (Scheme 2.5).[5] Employment of a nitrogen-containing tether allows for a rapid synthesis of the corresponding dihydrobenzoisoquinoline derivatives **2-16**. Notably, this benzannulation reaction smoothly proceeds at ambient temperatures presumably due to the high reactivity of benzyne intermediate **2-15** toward the cycloaddition reaction.



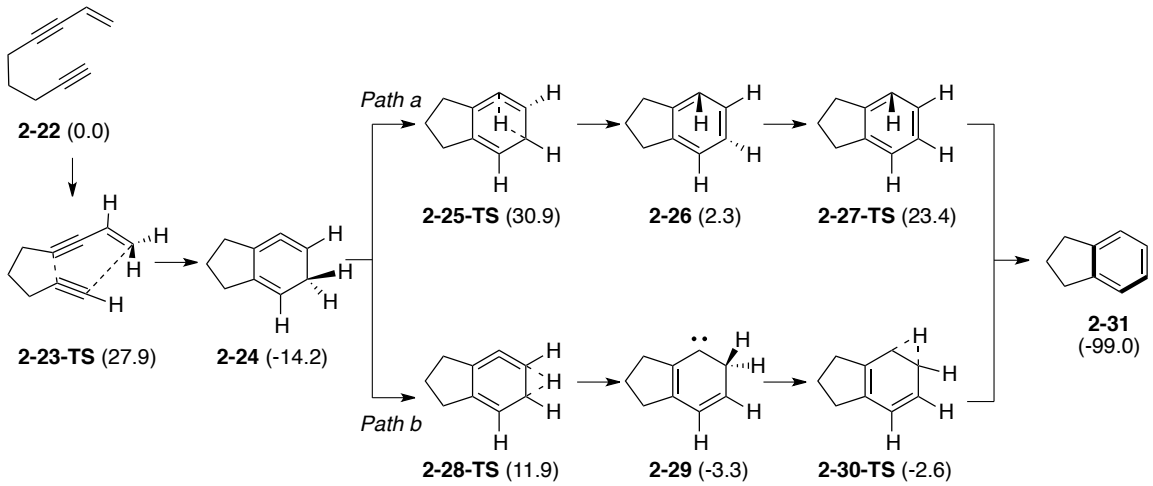
Scheme 2.5. Danheiser Intramolecular [4+2] Benzannulation Reaction of Enynes with Benzynes.

Besides being useful synthetic tool for the synthesis of bicyclic and polycyclic scaffolds, this transformation is also intriguing form mechanistic standpoint. Extensive experimental and theoretical mechanistic studies suggest intermediacy of strained cyclic allene in this transformation.[6] Thus, a flash vacuum thermolysis of compound **2-17** led to the formation of three products, which presumably derived from cumulene intermediate **2-18**. (Scheme 2.6).



Scheme 2.6. Gas-Phase Thermal Intramolecular [4+2] Benzannulation Reaction.

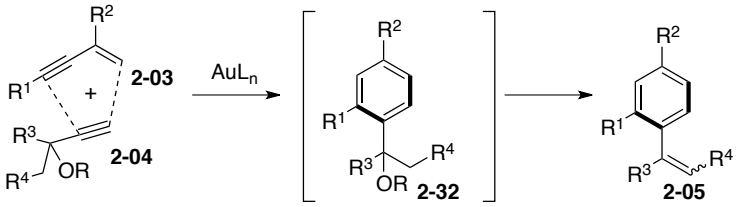
The formation of analogous cumulene intermediate **2-24** via a cycloaddition of **2-22** was also confirmed by computational methods.[6b,c] The rearrangement of this intermediate into the final product **2-31** was proposed to proceed through two possible pathways: via 1,3-*H*-migration followed by isomerization of the double bond (Scheme 2.7, path a), or via two consecutive 1,2-*H*-migrations though a carbene intermediate **2-29** (Scheme 2.7, path b). DFT calculations suggested preference of the second reaction route as energy barrier for transformation of intermediate **2-24** into intermediate **2-26** via transition state **2-25-TS** was found considerably higher compared to that of formation **2-29** from **2-24** via **2-28-TS**. Additionally, subsequent hydrogen migration in carbene intermediate **2-29** to form product **2-31** is energetically more favorable than double bond isomerization of **2-26** via **2-27-TS**. This route also explains the experimentally observed formation of isomeric products **2-19** and **2-21** via competitive H or Me migrations (Scheme 2.6). The formation of product **2-20** can be explained by the six-π-electron electrocyclic ring opening of intermediate **2-18**. The influence of the reaction media into the reaction mechanism was also studied theoretically, but no strong dependence was revealed. Therefore, it is assumed that the thermal [4+2] cycloaddition in solution proceeds via similar mechanistic path.



Scheme 2.7. Mechanistic Rationale for Intramolecular [4+2] Benzannulation Reaction Studied by Computational Methods (Gibbs free energy ΔG, kcal/mol, is given in parentheses, level of theory MP2/6–31G*).

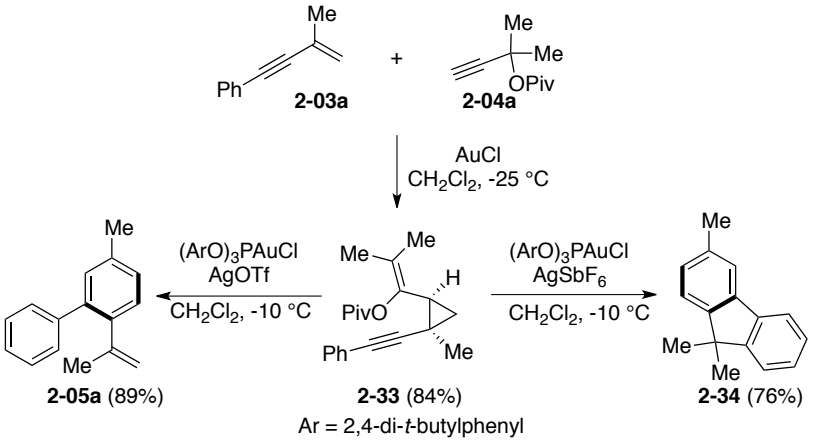
2.1.2. Gold-catalyzed Formal [4+2] Benzannulation Reaction of Enyne with Alkyne

Transition metal-catalyzed [4+2] benzannulation reaction of enyne with alkyne enynophile was reported by Toste group.[7] The reaction between enynes **2-03** and propargyl ethers **2-04** in the presence of gold catalyst led to the formation of multisubstituted arenes **2-05** via a formal [4+2] cross-benzannulation reaction (Scheme 2.8).



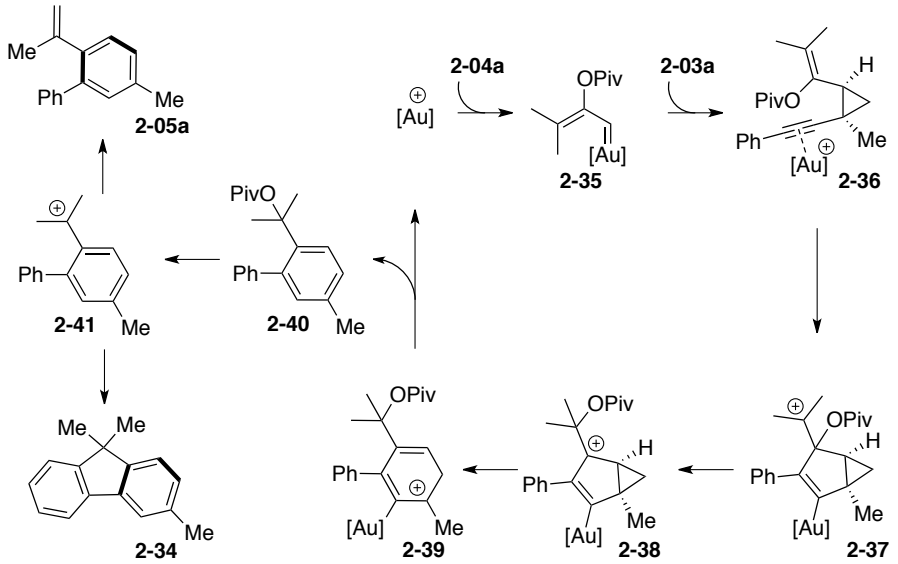
Scheme 2.8. Gold-catalyzed Formal [4+2] Benzannulation Reaction of Enynes and Alkynes.

Synthesis of aromatic products was achieved in a stepwise fashion. For example, reaction between conjugated enyne **2-03a** and propargyl ether **2-04a** in the presence of catalytic amounts of AuCl afforded cyclopropane **2-33** as a single regioisomer with high *cis*-diastereoselectivity, which in the presence of triarylphosphitegold(I) chloride was selectively converted to the styrene **2-05a** or fluorene **2-34**, depending on a silver co-catalyst used (Scheme 2.9).



Scheme 2.9. Synthesis of Styrenes and Fluorenes via Gold-catalyzed Formal [4+2] Benzannulation Reaction of Enyne and Alkyne.

Mechanistically, this reaction involves intermolecular cyclopropanation of enyne **2-03a** via the gold carbenoid **2-35**, formed from rearrangement of propargyl ether **2-04a**, followed by the 5-*endo-dig* cyclization induced by a cationic gold catalyst with the formation of bycyclic intermediate **2-37** (Scheme 2.10). Pivaloyloxy group migration (**2-37** → **2-38**) and a subsequent cycloisomerization through pentadientyl cation **2-39** lead to the aromatic product **2-40**, which under electrophilic conditions undergoes E1 elimination or Friedel-Crafts alkylation to furnish **2-05a** or **2-34**, respectively.

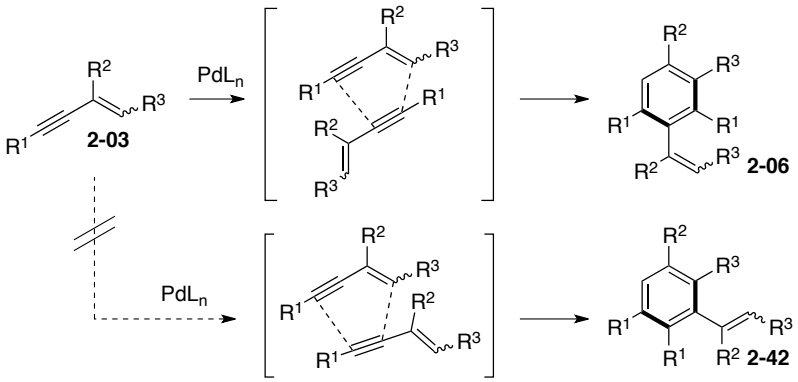


Scheme 2.10. Proposed Mechanism for Gold-catalyzed Formal [4+2] Benzannulation Reaction of Enyne and Alkyne.

2.1.3. Palladium-catalyzed [4+2] Benzannulation Reaction

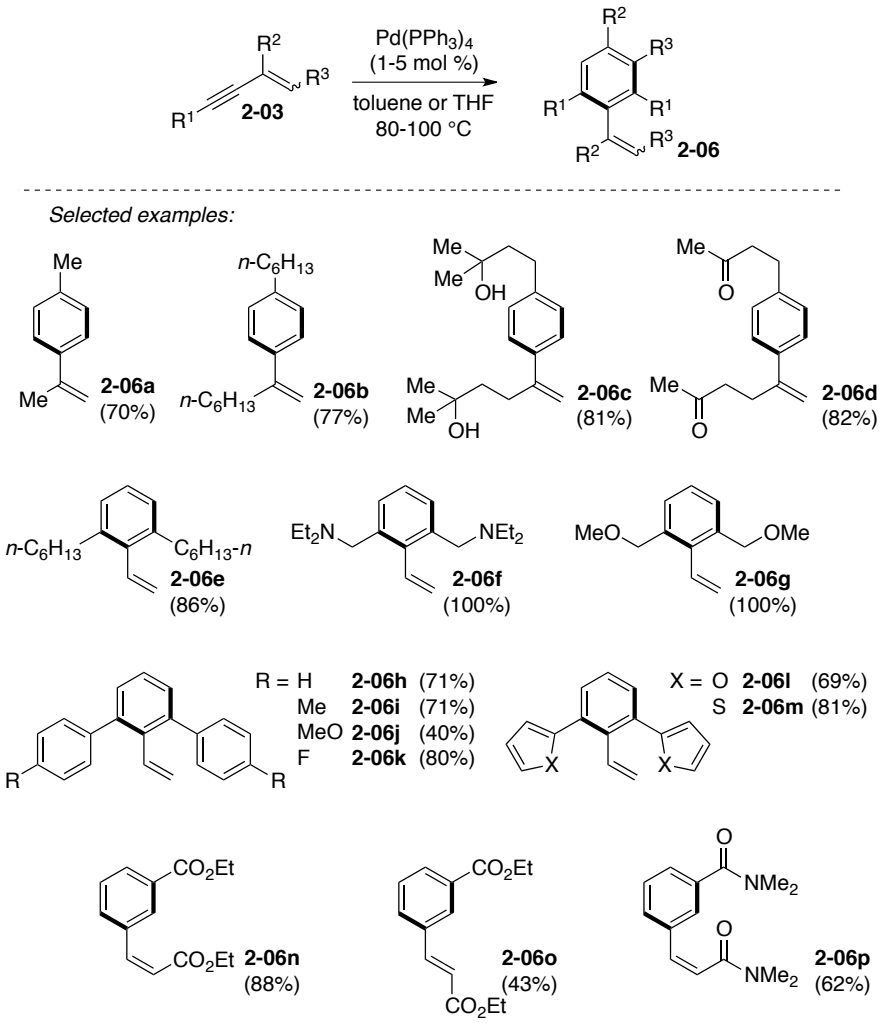
2.1.3.1. Palladium-catalyzed [4+2] Benzannulation Reaction of Enynes

Yamamoto group demonstrated that conjugated enynes **2-03** cyclodimerize in the presence of Pd(0) catalyst to form styrene derivatives **2-06** (Scheme 2.11).[2] The main feature of this reaction is its exclusive regiospecificity. Thus, selective formation of a single isomer **2-06** occurred upon reaction, whereas isomeric products **2-42**, as well as possible products of alkyne trimerization, were never detected.



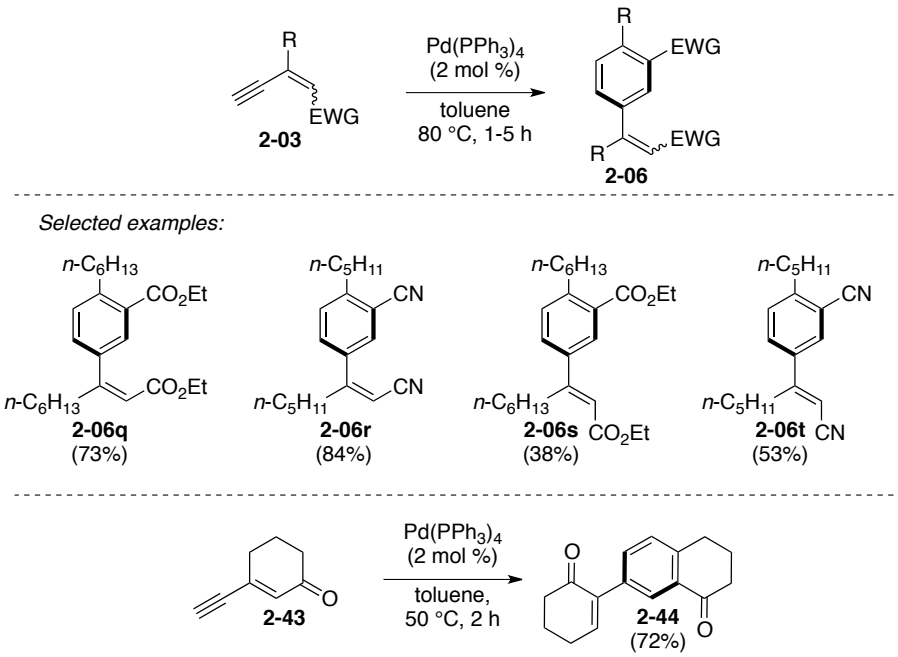
Scheme 2.11. Palladium-catalyzed [4+2] homo-Benzannulation Reaction.

The generality of this transformation was intensively studied.[2,8] The scope of monosubstituted enynes is summarized in Scheme 2.12. Thus, 3-substituted enynes underwent benzannulation to form 1,4-disubsituted benzenes **2-06a-d**. Likewise, enynes bearing 1-alkyl, 1-aryl, or 1-heretoaryl substitution reacted with the formation of 2,6-disubstituted styrenes **2-06e-m** in good to high yields. As shown, various functional groups, such as hydroxyl, carbonyl and amino groups, were well tolerated in this reaction. Among 4-substituted enynes, only ones possessing electron-withdrawing groups were reactive toward cyclodimerization. Notably, (*Z*)-substituted enyne gave desired product **2-06n** in higher yield compared to its (*E*)-analog **2-06o**.



Scheme 2.12. Palladium-catalyzed [4+2] homo-Benzannulation Reaction of Monosubstituted Enynes.

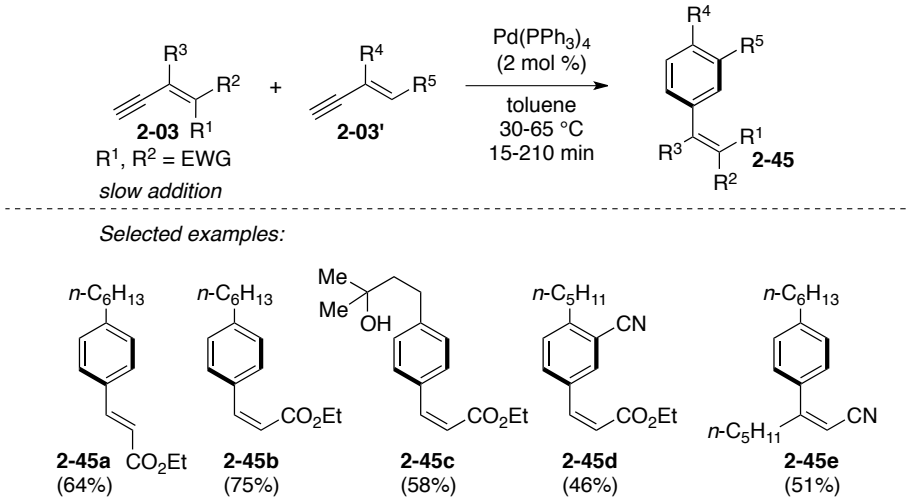
Homo-benzannulation reaction of di- or trisubstituted enynes is a less facile process.[8b,c] Thus, neither 3,4- nor 1,3-dialkyl enynes underwent homo-benzannulation in the presence of $Pd(PPh_3)_4$. However, introduction of electron-withdrawing substituent led to a dramatic enhancement of their reactivity, providing styrene derivatives with moderate to good yields starting from 3,4-disubstituted enynes (Scheme 2.13). Analogously to monosubstituted substrates, disubstituted (*Z*)-enynes **2-06q** and **2-06r** afforded the corresponding products with higher efficiency. Using this dimerization approach, naphthalenone derivative **2-44** can be obtained via the single operation starting from cyclic enyne **2-43**.



Scheme 2.13. Palladium-catalyzed [4+2] homo-Benzannulation Reaction of 3,4-Disubstituted Enynes.

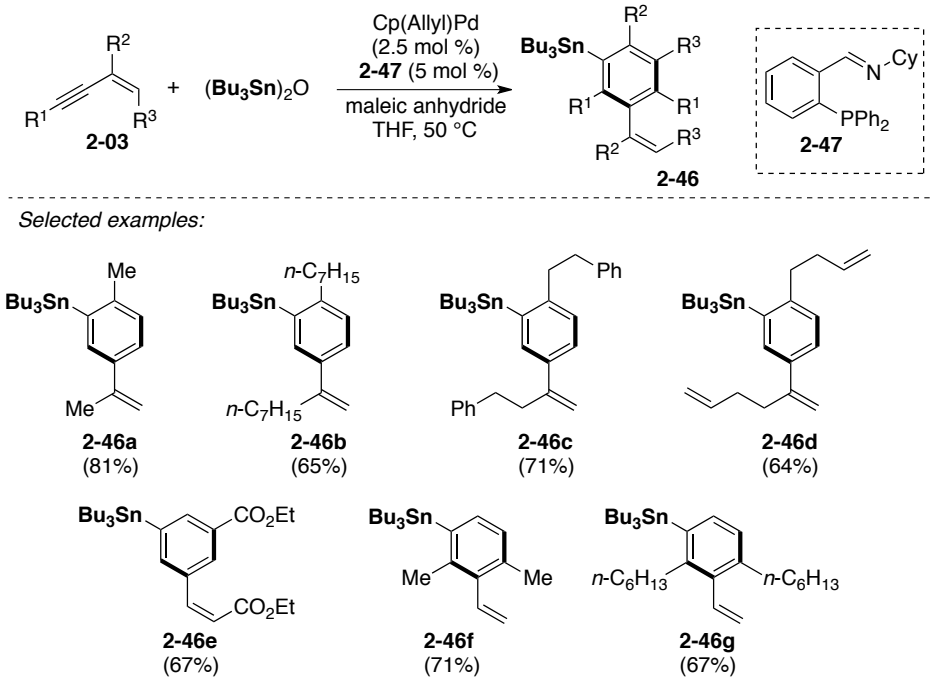
Overall, the reactivity of enynes toward the Pd-catalyzed [4+2] homo-benzannulation reaction depends on both electronic and steric properties of the substrate. The reaction is more facile with electron-deficient substrates. Substitution at the third position of enyne generally promotes benzannulation reaction, whereas 4-substituted substrates are the least reactive. Reactivity also becomes lower as number of substituents increases.

Differences in enynes reactivity allowed for control of selective cross-benzannulation reaction between two enynes[9] (Scheme 2.14). Thus, reaction between highly active electron-deficient enynes **2-03** and less reactive enynes **2-03'** occurred in a regio- and chemoselective manner, which was achieved via a slow addition of more reactive enyne. Notably, only one isomer of two potential cross-benzannulation products was generally obtained.



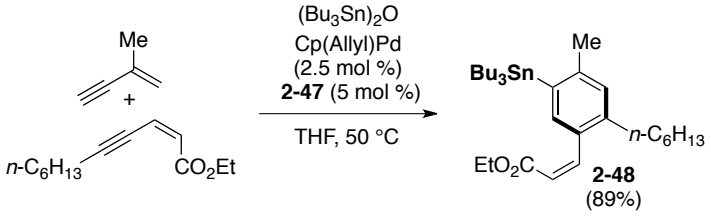
Scheme 2.14. Palladium-catalyzed [4+2] cross-Benzannulation Reaction of Two Enynes.

Nakao, Shirakawa, Hiyama, and co-workers developed metallative version of the Pd-catalyzed [4+2] benzannulation reaction.[10] They have demonstrated that benzannulation reaction of enynes **2-03** in the presence of bis(tributyl)tin oxide offers easy access to the 3-alkenylarylstannanes **2-46** (Scheme 2.15). Reaction was shown to proceed with good yields for a variety of monosubstituted enynes, whereas amount of non-stannylated byproduct varied from 4 to 30%.



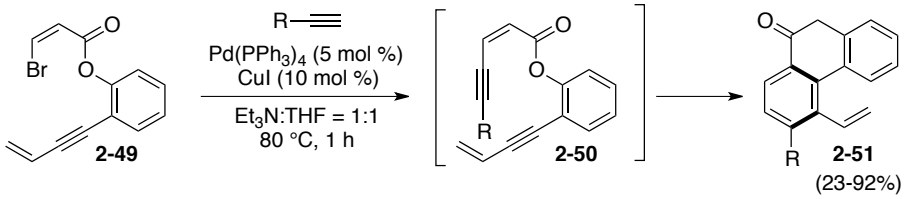
Scheme 2.15. Stannylative Palladium-catalyzed [4+2] homo-Benzannulation Reaction.

Additionally, the metallative version was also applicable to cross-benzannulation reaction between two different enynes (Scheme 2.16).



Scheme 2.16. Stannylative Palladium-catalyzed [4+2] cross-Benzannulation Reaction of Two Enynes.

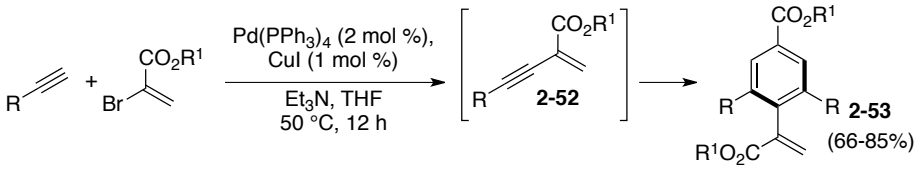
One of the widely used methods for the synthesis of enynes is the Sonogashira cross-coupling reaction between vinyl bromides and terminal alkynes. Base on that, a cascade transformation for the Pd-catalyzed [4+2] benzannulation reaction between two enynes has been developed.[11] Thus, enyne formed via the Sonogashira cross-coupling protocol reacted with another enyne moiety to form the corresponding aromatic product. In intramolecular version of the cascade sequence, the substrate **2-49** with aryl ester tether between vinylbromide and enyne moieties underwent the *in situ* benzannulation after the Sonogashira cross-coupling reaction with the formation of phenanthren-9(10*H*)-ones **2-51** (Scheme 2.17).[11a] The use of nonflexible aryl tether was essential for the *one-pot* transformation, as the authors have shown that reaction stops at the formation of the corresponding bis-enyne intermediate, similar to **2-50**, if flexible alkyl linkage was employed. Presumably, rigid tether brings alkyne unit closer to an enyne moiety thus promoting the benzannulation step.



Scheme 2.17. Sonogashira cross-Coupling /Intramolecular cross-Benzannulation Sequence.

Analogous intermolecular *one-pot* cascade transformation has been developed by Xi *et al.*[11b] Consequently, α-bromoacrylates reacted with terminal alkynes with the formation of densely substituted

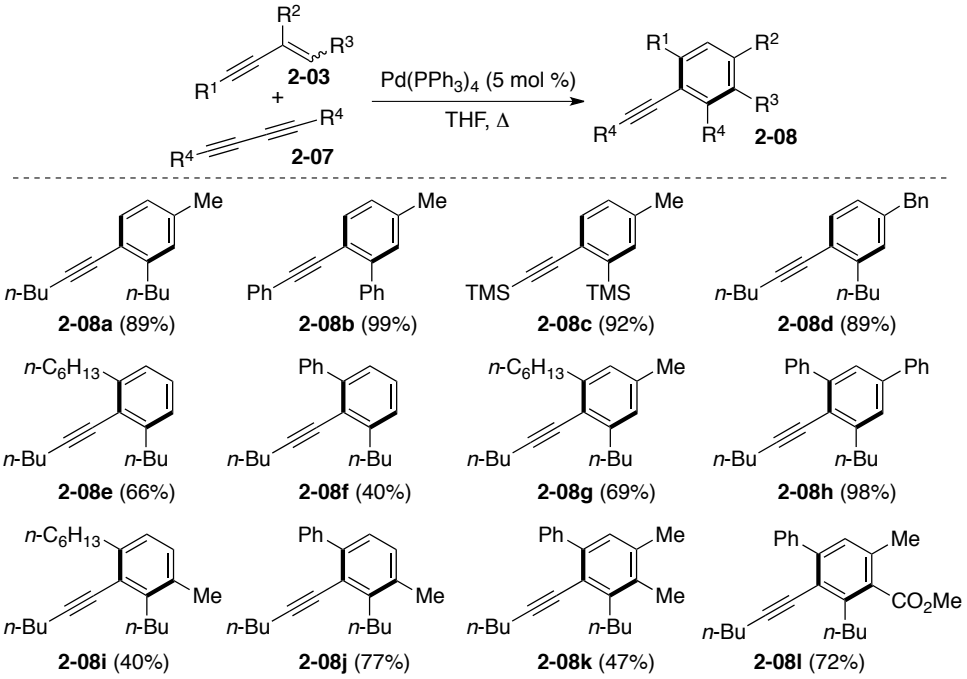
styrenes in a single transformation under the Sonogashira cross-coupling reaction conditions (Scheme 2.18). This method was efficient for both aryl and alkyl acetylenes. Among vinyl bromides, only acrylate derivatives were shown to produce styrene derivatives in good yields.



Scheme 2.18. Sonogashira cross-Coupling /Intermolecular homo-Benzannulation Sequence.

2.1.3.2. Palladium-catalyzed [4+2] cross-Benzannulation Reaction of Enynes with Diynes

Shortly after palladium-catalyzed [4+2] homo-benzannulation reaction of two enynes was discovered,[2] a cross-benzannulation of enynes with diyne enynophiles was developed,[12] thus substantially expanding the scope of this transformation. Similarly to homo-, the cross-benzannulation reaction occurs in high regioselective manner offering an easy access to densely substituted aryl acetylenes **2-08** as sole regioisomers (Scheme 2.19).[12,13]

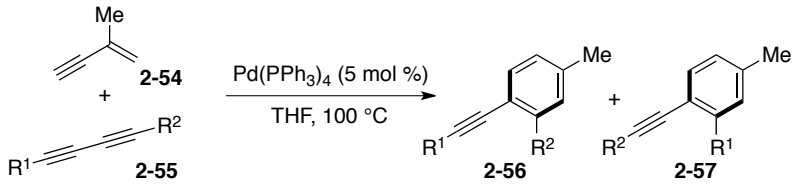


Scheme 2.19. Scope of the Palladium-catalyzed [4+2] cross-Benzannulation Reaction of Enynes with Diynes.

In most cases, the reaction is chemoselective, providing product of the cross-benzannulation reaction only. The reactivity trend of enynes in the cross-benzanulation reaction remains consistent to that of the palladium-catalyzed homo-benzannulation of two enynes. However, in this case, the scope was expanded to 1,4-disubstituted and 1,3,4-trisubstituted substrates providing access toward aromatic products **2-08i-l**.

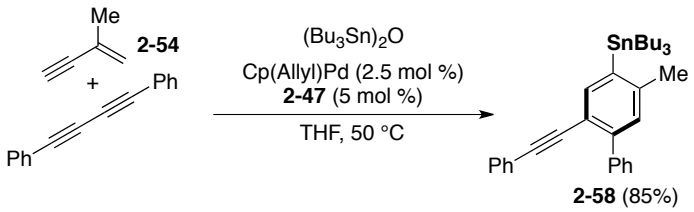
Being perfectly regiospecific with regard to the orientation of enynes, the reaction is less selective with respect to the regioselectivity with unsymmetrically-substituted diyne enynophiles. Expectedly, single products are formed in the reaction with symmetrically substituted diynes (Scheme 2.19). However, if unsymmetrical diynes are employed, both triple bonds are capable to undergo benzannulation reaction with the formation of two regioisomers **2-56** and **2-57** (Table 2.1). The regioselectivity pattern of unsymmetrically-substituted substrates is not well understood. Experiment showed that in some cases only one triple bond of unsymmetrical diyne was reactive toward the benzannulation reaction. Thus, terminal diynes, possessing tertiary substituents at the second alkyne moiety, reacted with 3-methylenyne **2-54** selectively to produce single products (entries 2, 3). In both arylacetylene products the bulky groups were attached to the aromatic ring. Similar result was obtained for the disubstituted diyne (entry 6). Interestingly, silylsubstituted diyne reacted selectively at silylalkyne unit to form *o*-alkynylarylsilane (entry 7), which was not the case for terminal alkyne (entry 4), thus indicating that steric demand is not the only factor affecting the reaction regioselectivity. Nonetheless, for the majority of the substrates, both triple bonds of the diyne participated in the benzannulation reaction to afford mixtures of two regioisomers with moderate to good selectivity (entries 1, 4, 5).

Table 2.1. Palladium-catalyzed [4+2] cross-Benzannulation Reaction of 3-Methylenyne **2-54** with Unsymmetrically Substituted Diynes.



Entry	R^1	R^2	Yield of **2-56**, %		Yield of **2-57**, %	
1	H	*n*-C_6H_{13}-	**2-56a**	50	**2-57a**	28
2	H	*t*-Bu-	**2-56b**	52	**2-57b**	traces
3	H	MOMOC$(Me)_2$-	**2-56c**	80	**2-57c**	none
4	H	TMS	**2-56d**	23	**2-57d**	18
5	*n*-Bu	Ph	**2-56e**	46	**2-57e**	54
6	*n*-Bu	MOMOC$(Me)_2$-	**2-56f**	54	**2-57f**	traces
7	Ph	TMS	**2-56g**	78	**2-57g**	none

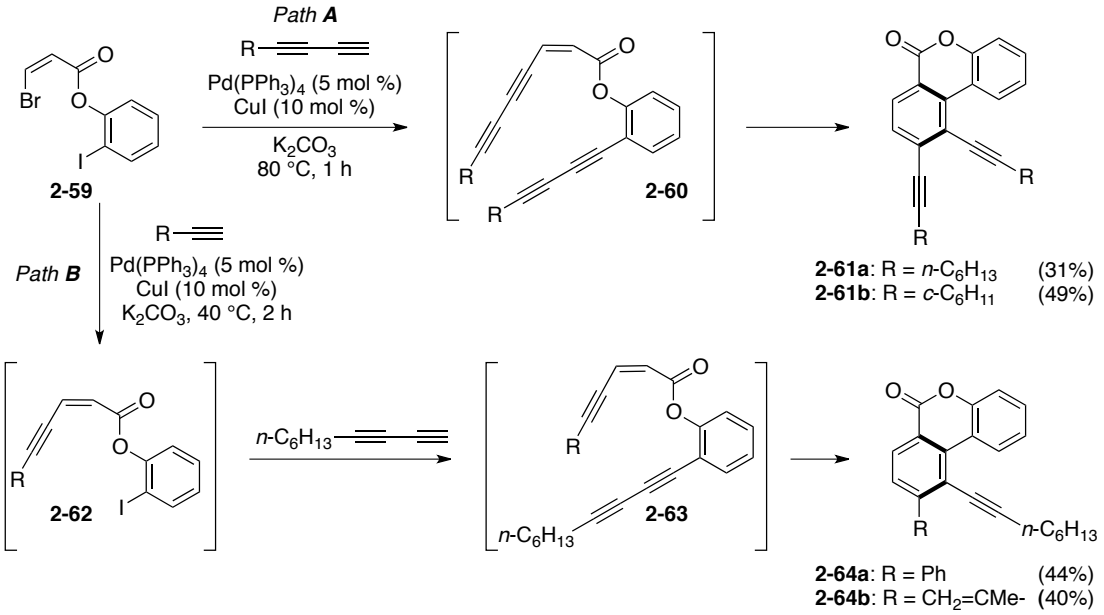
Analogously to the palladium-catalyzed [4+2] benzannulation reaction of two enynes, the stannylative version of benzannulation reaction of enyne **2-54** with diphenylbutadiyne was also successful providing 3-alkynylarylstannane **2-58** in 85% yield[10] (Scheme 2.20). Notably, the metallative version of this reaction allowed introducing substitution at the *meta*- position to the alkynyl moiety, which is the only nonfunctionalizable position via the non-metallative method.



Scheme 2.20. Stannylative Palladium-catalyzed [4+2] cross-Benzannulation Reaction of Enyne with Dyine.

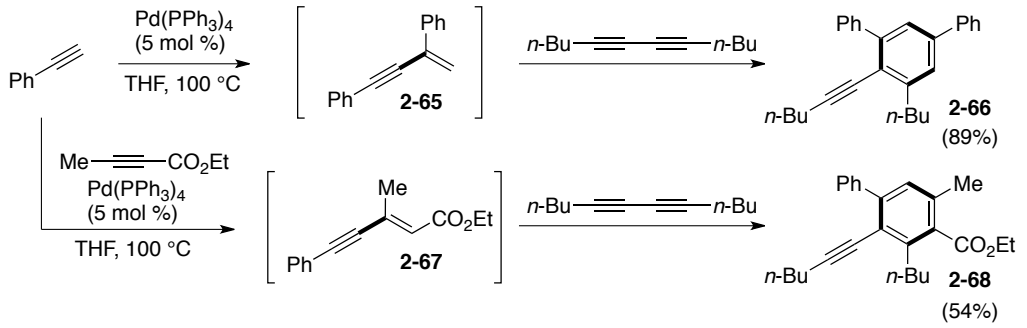
Two possible approaches were shown for the Sonogashira cross-coupling/benzannulation cascade transformation of enyne with diyne (Scheme 2.21).[11a] Accordingly, three component coupling between

dihalide **2-59** and two molecules of terminal diyne produced phenanthren-9(10*H*)-one derivatives **2-61** with modest yields under the Sonogashira cross-coupling conditions (Path **A**). Alternatively, incorporation of two different substituents to the final product **2-64** was achieved via a stepwise addition of terminal alkyne and dyine moieties (Path **B**).



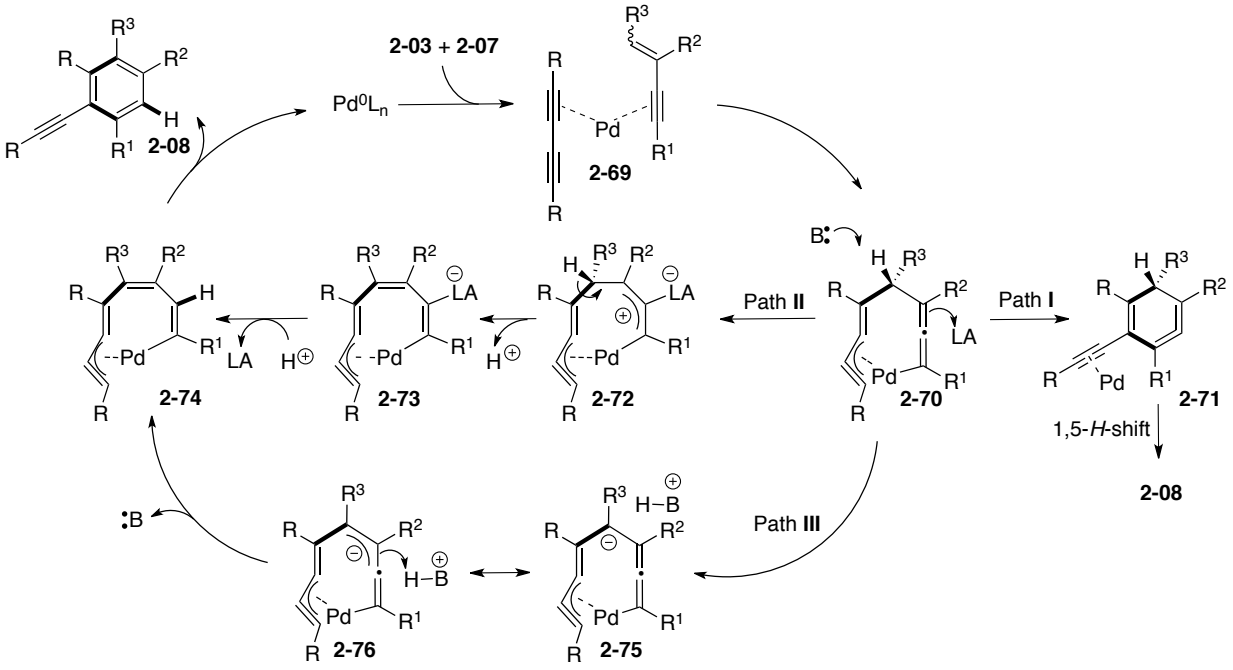
Scheme 2.21. Sonogashira cross-Coupling /Intramolecular cross-Benzannulation Sequence.

Cascade transformation that employs Pd-catalyzed Trost's dimerization of alkynes [14] and subsequent benzannulation reaction allowed for a highly atom-economical synthesis of multisubstituted benzenes[15] (Scheme 2.22). Formal [2+2+2] cycloaddition reaction proceeded through the formation of 2,4-enyne followed by the [4+2] benzannulation reaction with diyne, representing a highly chemo- and regioselective trimerization reaction of alkynes. For example, homo-dimerization of terminal alkynes followed by a benzannulation reaction led to the 1,2,4,6-tertasubstituted benzenes **2-66** through the intermediacy of enyne **2-65**. Additionally, the cross-dimerization reaction between two different acetylenic units afforded trisubstituted enyne **2-67**, which, upon sequential benzannulation reaction, furnished multisubstituted aromatic compound **2-68**. It is worth mentioning that low reactivity of di- and trisubstituted enynes toward homo-benzannulation reaction accounts for the observed high chemoselectivity of this process.



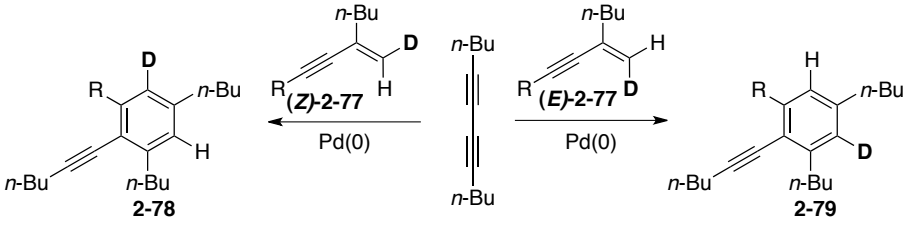
Scheme 2.22. Palladium-catalyzed Dimerization of Acetylenes followed by Intramolecular [4+2] cross-Benzannulation Reaction.

As discussed above, the Pd-catalyzed benzannulation reaction requires an activating group (alkenyl or alkynyl) in the molecule of enynophile, as no benzannulation was observed with alkynes lacking adjacent multiple bond functionality. Activating group also serves as a directing group providing perfect regioselectivity with respect to enyne leading to the formation of a single regioisomer in both homo- and cross-benzannulation reactions. These unique features of the process cannot be explained by mechanistic rationale available for the intramolecular Danheiser reaction.[6] To expose these issues, alternative pathway for the palladium catalyzed benzannulation was proposed (Scheme 2.23).



Scheme 2.23. Proposed Mechanism for Palladium-catalyzed [4+2] Benzannulation Reaction.

Thus, coordination of palladium catalyst to triple bonds of substrates followed by metallacycloaddition leads to the formation of the key intermediate **2-70**, which gained additional stabilization by bounding with an activating alkenyl or alkynyl group. These species can undergo reductive elimination to form strained cyclic allene **2-71** similar to the intermediate **2-18** (Scheme 2.6) involved in the Danheiser cycloaddition reaction (Scheme 2.23, path I). However, this route does not explain stereoselectivity of hydrogen migration observed in the benzannulation of monodeuterated (*E*)-**2-77** and (*Z*)-**2-77** enynes (Scheme 2.24),[13b] since 1,5-hydride shift should not exhibit stereochemical preference in planar cyclic cumulene **2-71**.



Scheme 2.24. Deuterium Labeling Studies on Stereoselectivity of Hydrogen Migration.

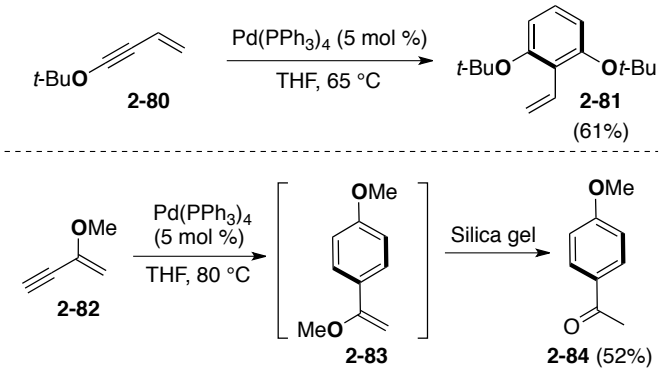
Therefore, alternative pathways involving a formal 1,3-hydrogen shift were considered: electrophilic pathway (path II) and deprotonation/protonation sequence (path III) (Scheme 2.23).[16] Prototropic rearrangement (path II) is consistent with the positive effect of Lewis acidic additives. Moreover, substitution at 1st and 3rd position of enyne (R^1, $R^2 \neq H$) would provide necessary cation stabilization, which is in agreement with the reactivity trend of enyne. On the other hand, the anionic pathway (path III) is strongly supported by the acceleration of the reaction in the presence of Brønsted bases. Additionally, enynes, possessing geminal electron-withdrawing group (R^3), are generally more reactive compared to the substrates with electron-neutral substituents, presumably due to possibility of a more facile deprotonation. Besides that, if reaction performed in the presence of Et_3N/D_2O mixture, 55% of deuterium incorporation was observed. Apparently, in the absence of additives under neutral reaction conditions either of the pathways can be operative, as phosphine ligand can serve as basic component and eventual proton source always exists in the reaction mixture. Moreover, theoretical calculations revealed

more favorable migration of the (*E*)-hydrogen atom compared to that of (*Z*)-hydrogen, regardless of the pathway, as latter atom is significantly more hindered by the vicinal substituents and by ligands at palladium atom.

2.1.3.3. Synthetic Applications of Palladium-catalyzed [4+2] Benzannulation Reaction

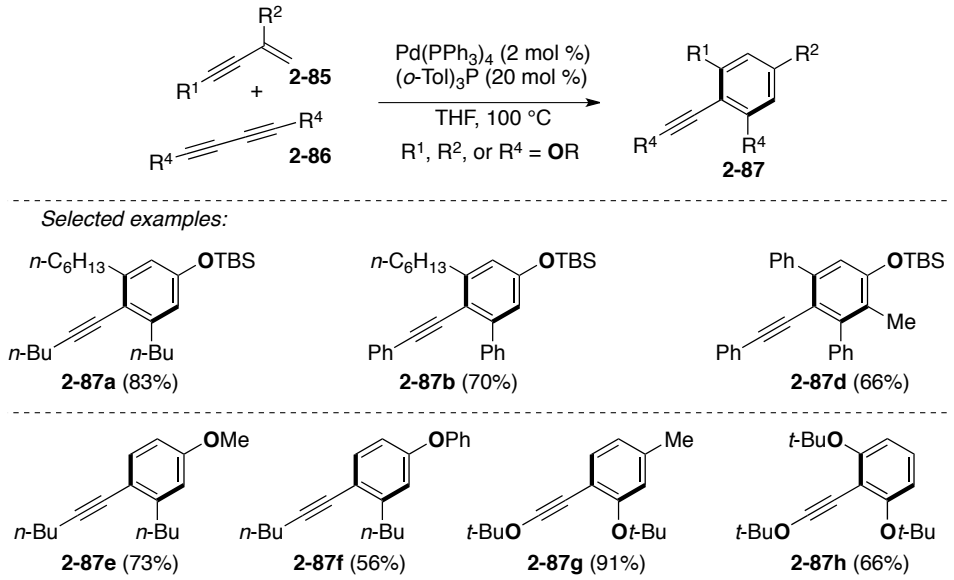
Excellent functional group compatibility is another important feature of the palladium-catalyzed [4+2] benzannulation reaction, therefore, its synthetic potential was systematically investigated. As a result, a variety of methods for the synthesis of diversely substituted aromatic compounds were developed. Selected examples are discussed bellow.

Often introduction of a heteroatom-based functionality to the aromatic ring through the Pd-catalyzed benzannulation strategy is complicated by lack of stability and availability of the corresponding starting materials. Nevertheless, proper design of substrates allowed for the synthesis of both oxygen and nitrogen containing arenes (Schemes 2.25-2.29).[17,18] For example, 1-(**2-80**) and 3-alkoxysubstituted enynes (**2-82**) under homo-benzannulation reaction conditions were transformed into the corresponding resorcinol derivative **2-81**[17b] and *p*-methoxyacetophenone **2-84**[17a] (Scheme 2.25). In the former case, *tert*-butyl ether group assured necessary stability of the starting enyne. 3-Alkoxyenynes are generally more stable, however, *α*-methoxystyrene **2-83**, formed upon benzannulation, hydrolyzed rapidly on the silica gel affording the acetophenone derivative **2-84**.



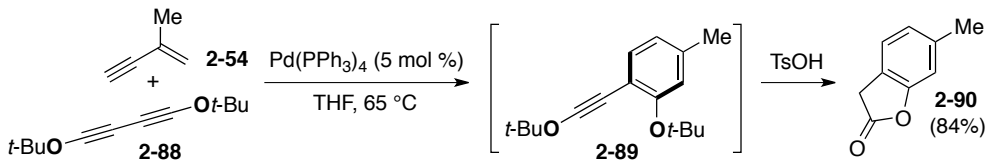
Scheme 2.25. Synthesis of Aryl Ethers via Palladium-catalyzed [4+2] homo-Benzannulation of Enynes.

Similarly, a variety of arylethers can be obtained via the [4+2] cross-benzannulation reaction of enynes with diynes (Scheme 2.26).[17] Notably, using this strategy, alkoxy substituent can be introduced at the positions 2, 4, and 6 of arylacethylene product **2-87** with the use of appropriate coupling partners. Moreover, starting from silylethers, the corresponding *p*-alkynylphenols can be synthesized upon silyl group removal.[17b]



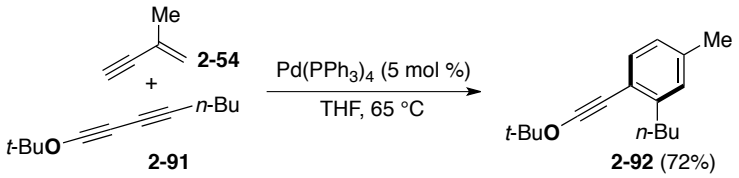
Scheme 2.26. Synthesis of Aryl Ethers via Palladium-catalyzed cross-Benzannulation of Enynes with Dyines.

Methodology for synthesis of *β*-alkoxy alkynyl ethers was further elaborated into the *one-pot* procedure for the synthesis of coumaranones (Scheme 2.27). Thus, TsOH was directly added to the reaction mixture upon completion of the benzannulation step, which resulted in the hydrolysis of the *tert*-butyl ether and a subsequent cyclization producing coumaranone **2-90** in high yield starting from linear precursors.[17a]



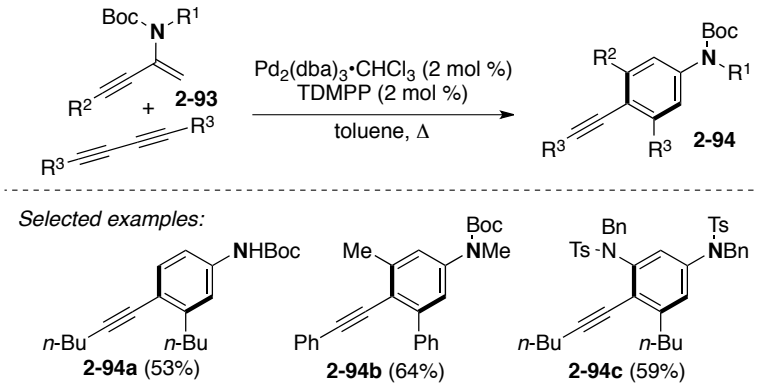
Scheme 2.27. One-pot Synthesis of Coumaranone **2-90** via Palladium-catalyzed [4+2] Benzannulation/Acid-mediated Cyclization.

Importantly, unsymmetrically substituted diyne **2-91** underwent a cross-benzannylation reaction with 3-methylenyne **2-54** in highly regioselective manner with the formation of alkoxysubstituted arylalkyne **2-92** as a single reaction product (Scheme 2.28). Similar preference was observed for differently substituted enynes, although up to 20% of another regioisomer was formed in some cases.[17b]



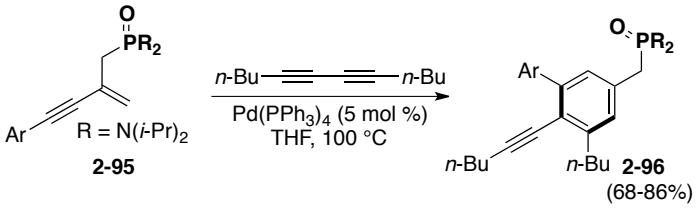
Scheme 2.28. Regioselective Palladium-catalyzed [4+2] cross-Benzannulation Reaction of Alkoxysubstituted Diyne.

Reactivity of nitrogen-containing enynes is lower compared to that of oxygen-based analogs. Thus, 3-aminosubstituted enynes **2-93** are inert toward homo-dimerization reaction in the presence of palladium catalyst. However, reaction between aminoenynes **2-93** with diynes proceeded smoothly with the formation of aniline derivatives **2-94** in acceptable yields (Scheme 2.29).[18]



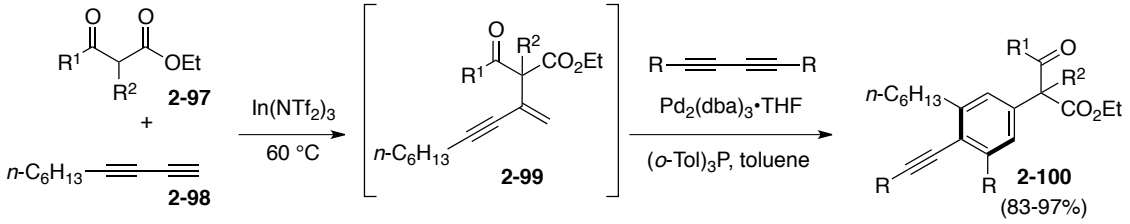
Scheme 2.29. Synthesis of Protected Anilines via Palladium-catalyzed [4+2] cross-Benzannulation Reaction of Aminoenynes with Diynes.

Phosphine oxides are among various functionalities that can be introduced into the aromatic alkynes via the Pd-catalyzed benzannulation reaction. Thus, the reaction between readily available enynes **2-95** with 5,7-dodecadiyne resulted in the formation of corresponding benzylphosphine oxides **2-96** in good yields (Scheme 2.30). [19]



Scheme 2.30. Synthesis of Arylphosphine Oxides Palladium-catalyzed [4+2] cross-Benzannulation Reaction.

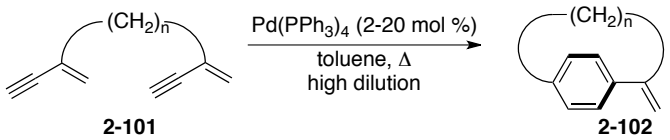
An efficient strategy toward α-aryl carbonyl compounds has been developed based on combination of an In-catalyzed Conia-ene reaction and the Pd-catalyzed cross-benzannulation reaction (Scheme 2.31).[20] Thus, regioselective In-catalyzed addition of ketoesters to terminal diynes allowed for efficient synthesis of enynes **2-99**, which subsequently underwent smooth benzannulation reaction to form densely substituted α-aryl ketones **2-100** in high to excellent yields.



Scheme 2.31. Synthesis of α-Arylated Carbonyl Compounds via Sequential Indium-catalyzed Conia-ene and Palladium-catalyzed [4+2] cross-Benzannulation Reactions.

Both intramolecular homo-benzannulation of enynes and intermolecular cross-benzannulation of enynes with diynes were applied for the synthesis of cyclophane-type compounds.[2,21] As shown in Table 2.2, bisenynes **2-101** in the presence of palladium catalyst under high dilution underwent [4+2] benzannulation producing exomethylene paracyclophanes **2-102**.[21a] The efficiency of this transformation varied significantly depending on the length of the carbon chain in the starting bisenyne **2-101**. Thus, cyclophanes **2-102e**–**f**, bearing a relatively longer tether, were synthesized in good yields (entries 5-10), whereas highly strained cyclophanes **2-102a** and **2-102b** were formed in 2 and 18% yields, respectively (entries 1,2).

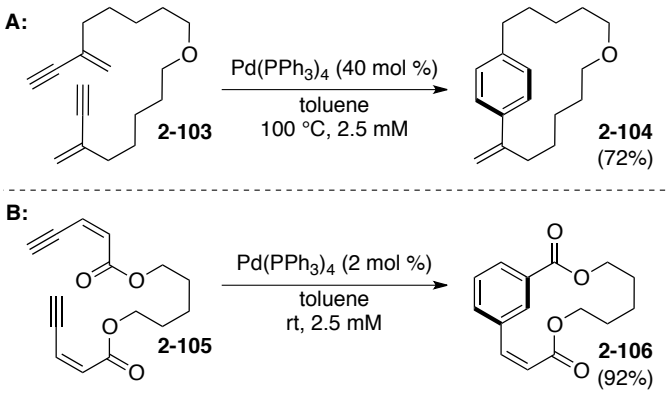
Table 2.2. Synthesis of Exomethylene Paracyclophanes via Intramolecular Palladium-catalyzed [4+2] homo-Benzannulation of Enynes.



2-101 **2-102**

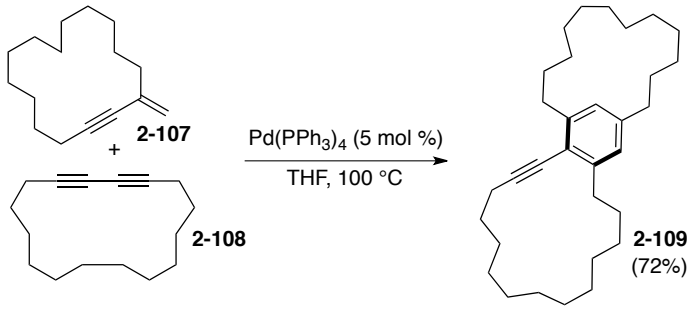
Entry	N	$Pd(PPh_3)_4$, mol %	C, M		Yield, %
1	7	40	0.001	**2-102a**	1.7
2	8	40	0.001	**2-102b**	18
3	9	40	0.001	**2-102c**	36
4	10	40	0.001	**2-102d**	47
5	11	40	0.001	**2-102e**	61
6		10	0.001		51
7	12	40	0.005	**2-102f**	71
8		10	0.005		59
9	14	40	0.005	**2-102g**	71
10		10	0.005		67

Analogously to the all carbon cyclophanes, ether-containing exomethylene paracyclophanes can be easily prepared via the Pd-catalyzed benzannulation of bisenynes **2-103** (Scheme 2.32A).[21b] Additionally, introduction of ester tether at C-4 position of tethered enynes allowed for the smooth synthesis of methacyclophanes, containing endocyclic double bond (Scheme 2.31B).[21b] In agreement with general reactivity profile of enynes toward the Pd-catalyzed homo-benzannulation, the ester-containing substrates **2-105** provided better yields of desired cyclophanes under milder reaction conditions compared to that of alkyl substituted bisenynes **2-101** or **2-103**.



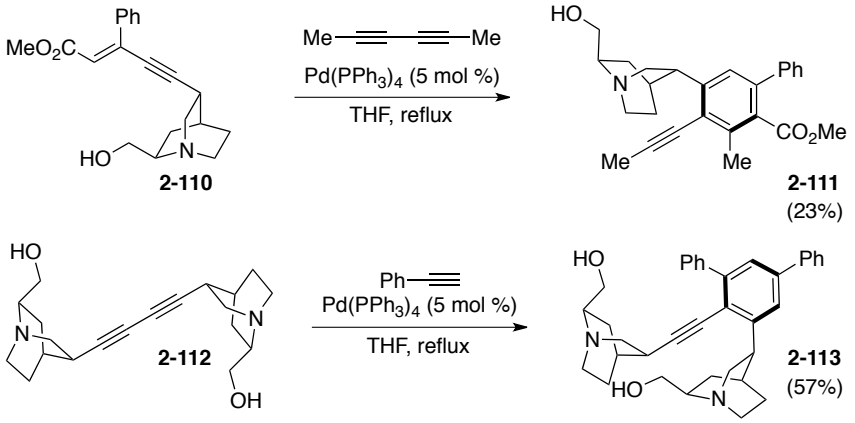
Scheme 2.32. Synthesis of Para- (A) and Metacyclophanes (B) via Intramolecular Palladium-catalyzed [4+2] homo-Benzannulation of Enynes.

Different types of cyclophanes, such as ortho-, meta-, or paracyclophanes, were obtained via the intermolecular Pd-catalyzed [4+2] cross-benzannulation of cyclic enynes with diynes.[21d] For example, compound **2-109**, containing both meta- and orthocyclophane motifs, was synthesized upon reaction of enyne **2-107** and diyne **2-108** in 72% yield (Scheme 2.33).



Scheme 2.33. Synthesis of Cyclophane **2-109** via Palladium-catalyzed [4+2] cross-Benzannulation of Enyne with Diyne.

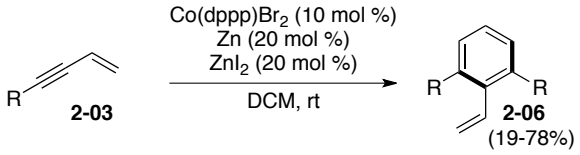
Besides a wide use of the Pd-catalyzed [4+2] benzannulation reaction to the direct synthesis of adducts with desired functionalities, it was also employed for a late stage derivatization of molecules of interest. For instance, novel quinuclidine derivatives were prepared via this methodology (Scheme 2.34).[22] Thus, enyne-containing quinuclidine derivative **2-110** underwent benzannulation reaction to form pentasubstituted benzene **2-111** in a fair yield. On the other hand, a formal [2+2+2] benzannulation of phenylacethylene with diyne **2-112**, possessing quinuclidine moieties, furnished aromatized product **2-113** with good efficiency.



Scheme 2.34. Modification of Quinuclidine Derivatives via Palladium-catalyzed [4+2] cross-Benzannulation Reaction.

2.1.4. Cobalt-catalyzed [4+2] homo-Benzannulation Reaction

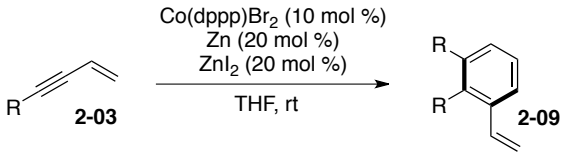
Complementary to the palladium-catalyzed version, the [4+2] homo-benzannulation of enynes under a cobalt-catalysis was reported by Hilt group.[23] It was found that 1-substituted enynes formed the corresponding 2,6-disubstituted styrenes **2-06** in moderate to good yields in the presence catalytic amounts of $Co(dppp)Br_2$, zinc powder, and zinc iodide under mild reaction conditions (Scheme 2.35).

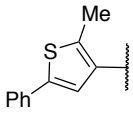
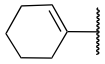


Scheme 2.35. Cobalt-catalyzed [4+2] Homo-Benzannulation Reaction toward 2,6-Substituted Styrenes.

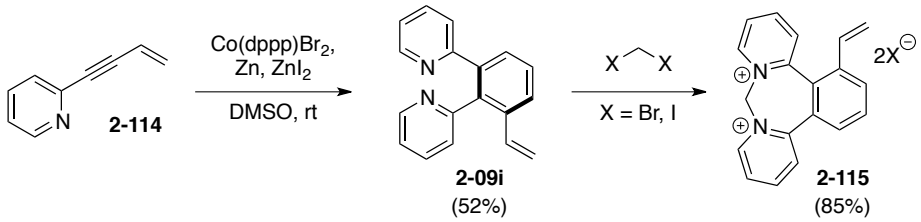
Remarkably, a change of solvent from DCM to THF resulted in an unprecedented switch of reaction regioselectivity leading to the formation of 2,3-substituted styrenes **2-09**. A variety of 1-aryl- or heteroarylsubstituted enynes **2-03** were shown to react with good efficiency (Table 2.3). Notably, in the case of bromo-substituted enyne, a clean reaction without protodebromination or formation of cross-coupling products occurred (entry 4). For a dienyne substrate, having both terminal and endocyclic double bonds, the former double bond reacted regioselectively, while the double bond of the cyclohexene subunit remained untouched (entry 8).

Table 2.3. Cobalt-catalyzed [4+2] homo-Benzannulation Reaction Toward 2,3-Substituted Styrenes.



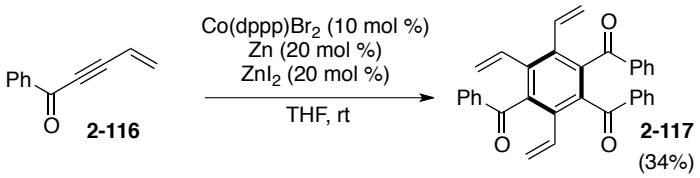
Entry	R		Yield, %	Entry	R		Yield, %
1	Ph	**2-09a**	60	5	(3,5-*t*-Bu)$_2$-C$_6$H$_3$-	**2-09e**	86
2	*p*-MeO-C$_6$H$_4$-	**2-09b**	39	6	2-naphthyl-	**2-09f**	76
3	*p*-Cl-C$_6$H$_4$-	**2-09c**	66	7		**2-09g**	55
4	*m*-Br-C$_6$H$_4$-	**2-09d**	65	8		**2-09h**	39

Enyne **2-114**, possessing 2-pyridyl substituent, afforded bispyridyl derivatieves **2-09i**, which reacted efficiently with dihalomethane to form planar chiral bispyridinium salts **2-115** (Scheme 2.36).[24]



Scheme 2.36. Cobalt-catalyzed Dimerization of Pyridylenyne.

Interestingly, under the same reaction conditions the benzannulation reaction did not take place when electron deficient enynes, such as **2-116**, were used as substrates. Instead, the corresponding alkyne trimerization product **2-117** was formed (Scheme 2.37). These results highlight significant difference between the cobalt- and the palladium-catalyzed benzannulation reactions, as electron poor enynes were the most reactive substrates for the latter [4+2] benzannulation reaction.



Scheme 2.37. Cobalt-catalyzed Cyclotrimerization of Electron-Deficient Conjugated Enyne.

Solvent coordinating ability was proposed to be a major factor for selectivity control in the cobalt-catalyzed transformation. Presumably, a more coordinating solvent, such as THF, can serve as additional ligand, therefore establishing an alternative arrangement of the bidentate phosphine ligand (dppp) and the coordinated starting material at the metal center. However, no experimental evidences were obtained to support this hypothesis so far.

2.1.5. Summary and Outlook

The thermal, Lewis acid-mediated, and transition metal-catalyzed [4+2] benzannulation reactions of enynes with various alkyne-containing enynophiles are powerful atom-economical methods for the aromatic ring construction from easily accessible starting materials. The proper choice of the coupling partners allows for the synthesis of densely substituted benzenes with high chemo- and regioselectivity. Despite of significant progress achieved during the past years expanding the utility of benzannulation reaction, several challenges remain unsolved, such as necessity for the activating group at enynophile or regioselectivity control in case of the reaction with unsymmetricaly substituted diynes. Additionally, further development of general approaches for the synthesis of aromatic compounds possessing valuable functionalities is highly desirable.

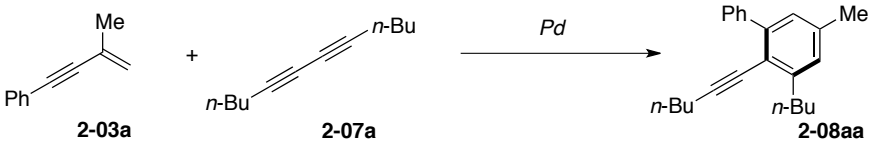
2.2. DEVELOPMENT OF HIGHLY EFFICIENT CATALYTIC SYSTEM FOR THE PALLADIUM-CATALYZED [4+2] BENZANNULATION REACTION

2.2.1. Optimization of the Reaction Conditions toward High TON Benzannulation Reaction

In the era of sustainable chemistry, development of highly active catalytic systems for atom and step economical processes is on high demand.[25] One of the ways to improve activity of the catalytic system in transition-metal catalysis is the stabilization of the reactive metal complex, which allows for high turnover numbers (TONs) of the catalyst. Although the immense progress has been achieved in the development of high TON Pd-catalyzed cross-coupling reactions,[26] cycloaddition reactions catalyzed by palladium complexes with high TONs are rare.[27]

Despite remarkable selectivity and broad scope, the palladium-catalyzed [4+2] benzannulation reaction employing di- and trisubstituted enynes usually required prolonged heating (up to 14 days) and high catalyst loading (5 mol % of $Pd(PPh_3)_4$ to ensure complete conversion of starting materials. In order to improve catalytic activity, systematic studies of additives and ligands effects on the benzannulation reaction were performed (Table 2.4).[16] First, a dramatic acceleration was observed in a presence of Lewis acids, in particularly, methylaluminoxane (MAO) in combination with electron-rich bulky tris(2,6-dimethoxyphenyl)phosphine (TDMPP) ligand. The use of these reaction conditions resulted in shorter reaction times at lower temperatures (entries 1,2). Furthermore, investigation of a base effect on the benzannulation reaction revealed that additions of tertiary amine to the reaction media enabled full conversion within 6 hours giving quantitative NMR yields (entry 3). However, it was shown that amine caused substantial decomposition of enyne in several cases. Although introduction of stoichiometric additives significantly improved the catalytic system, catalyst loading remained relatively high with its turnover number limited to 20. Therefore, we were interested in improving efficacy of the palladium-catalyzed [4+2] benzannulation reaction.

Table 2.4. Comparison of Different Catalytic Systems for Palladium-catalyzed cross-Benzannulation Reaction.[a]



Entry	*Pd* (mol %)	Conditions	Time, h	Yield, %	TON	TOF	Ref.
1	$Pd(PPh_3)_4$ (5.0)	**A**	96	90	18.0	10^{-4}	13b
2	$Pd(OAc)_2$ (5.0)	**B**	17	72	14.4	10^{-3}	16
3	$Pd(PPh_3)_4$ (5.0)	**C**	6	100	20	10^{-2}	16

[a]Conditions: **A**: $Pd(PPh_3)_4$ (5 mol %), toluene, 100 °C; **B**: $Pd(OAc)_2$ (5 mol %), TDMPP (0.5 equiv), *tert*-butylacetylene (20 mol %), MAO (0.2 equiv), toluene, 80 °C; **C:** $Pd(PPh_3)_4$ (5 mol %), Et_3N (2 equiv), toluene, 100 °C.

To this end, the cross-benzannulation reaction of enyne **2-03a** and diyne **2-04a** toward arylalkyne **2-08aa** was tested. We turned our attention to the ligands, which show superior performance in high TON Pd-catalyzed cross-coupling reactions and related processes. Thus, biphenyl phosphine ligands **A**,[28] multidentate ferrocene-based ligands **B**,[29] and *N*-heterocyclic carbene (NHC) ligands **C**[30] were examined (Figure 1).

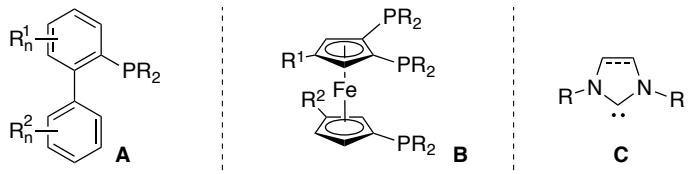


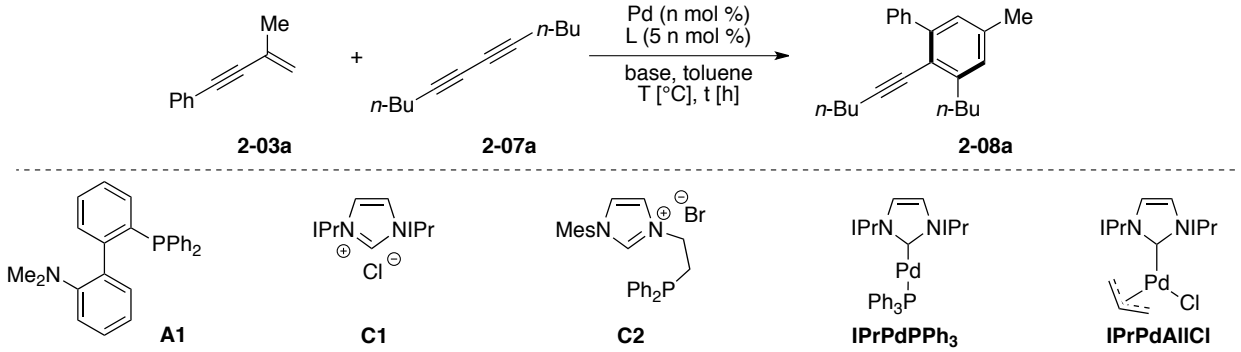
Figure 2.1. Typical Ligands for High TON Catalytic Systems in the Palladium-catalyzed Transformations.

It was found that the employment of 2-diphenylphosphino-2′-(*N*,*N*-dimethylamino)-biphenyl (PhDavePhos, **A1**) did not provide any improvement compared to the standard reaction conditions (Table 2.5, entries 1, 2). Disappointedly, no reaction was observed in the presence of 1,1'-bis(diphenylphosphino)ferrocene (DPPF) (entry 3). Several commercially available bidentate ligands were also tested to mimic the highly active multidentate analogs **B**. However, ferrocene-based

phosphines, as well as other bidentate ligands, were ineffective in this reaction. Likewise, employment of 1,3-bis(2,6-di-*i*-propylphenyl)imidazolium chloride (IPr•HCl, **C1**) as an NHC-ligand precursor did not promote the reaction (entry 4). On the other hand, combination of NHC and phosphine ligands resulted in improvement of the reaction yield (entry 5).[31] Utilization of the mixed ligand **C2**[32] or defined $IPrPdPPh_3$ catalyst[33] was not beneficial (entries 6, 7). Gratifyingly, employment of Pd NHC-based pre-catalyst IPrPdAllCl resulted in shortened reaction time (entry 8). It also allowed reducing the amount of catalyst to 0.5 mol % (entry 9). Further decreasing the catalyst loading led to the termination of the reaction at about 20% conversion (entry 10). Among phosphine co-ligands, electron-rich phosphines were the most efficient (entries 11, 12). Cesium carboxylates were found to be superior compared to other inorganic bases tested. Thus, reaction was completed within 8 hours in 85% yield in the presence of CsOPiv (entry 13), although high TON were still illusionary (entry 14). Expectedly, increase of concentration gave reasonable improvement of the reaction yield (entry 15). Finally, in the presence of tri(2-furyl)phosphine (TFP) ligand under nearly neat conditions, a *TON higher than 1700* has been achieved (Table 1, entry 17)![*]

[*] See experimental section **2.3.4.** for detailed optimization of the reaction conditions.

Table 2.5. Conditions Optimization for the Palladium-catalyzed [4+2] Benzannulation Reaction.[a]



Entry	[Pd] cat., n mol %	Ligand	Base	T, °C; t, h	C, M	Yield, %[b]
1	Pd_2dba_3, 1.5	PPh_3	-	80, 80	1.0	74
2	Pd_2dba_3, 1.5	**A1**	-	80, 80	1.0	69
3	Pd_2dba_3, 1.5	DPPF	-	80, 80	1.0	0[c]
4	Pd_2dba_3, 1.5	**C1**	Cs_2CO_3	80 120	1.0	0[c]
5	Pd_2dba_3, 1.5	**C1**, PPh_3	Cs_2CO_3	80, 66	1.0	82
6	Pd_2dba_3, 1.5	**C2**	Cs_2CO_3	120, 20	1.0	58
7	$IPrPdPPh_3$, 1.5	-	-	80, 40	1.0	67
8	IPrPdAllCl, 1.5	PPh_3	Cs_2CO_3	80, 40	1.0	77
9	IPrPdAllCl, 0.5	PPh_3	Cs_2CO_3	80, 100	1.0	75
10	IPrPdAllCl, 0.1	PPh_3	Cs_2CO_3	80, 100	1.0	21[d]
11	IPrPdAllCl, 1.0	TFP	Cs_2CO_3	100, 25	1.0	80
12	IPrPdAllCl, 1.0	**A1**	Cs_2CO_3	100, 25	1.0	83
13	IPrPdAllCl, 1.0	**A1**	CsOPiv	100, 8	1.0	85
14	IPrPdAllCl, 0.1	**A1**	CsOPiv	120, 15	1.0	39[d]
15	IPrPdAllCl, 0.1	**A1**	CsOPiv	120, 15	2.5	74
16	**IPrPdAllCl, 0.1**	**TFP**	**CsOPiv**	**120, 15**	**10**	**86**
17	**IPrPdAllCl, 0.05**	**TFP**	**CsOPiv**	**120, 40**	**20**	**85**

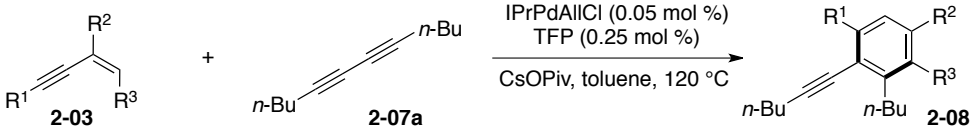
[a]Reaction conditions: **2-03a** (0.1 mmol), **2-07a** (0.11 mmol), *Pd* (n mol %), ligand (5n mol %), base (10n mol %) in dry toluene. [b]GC/MS yield at 100% conversion of enyne. [c]No reaction was observed. [d]Conversion was not complete.

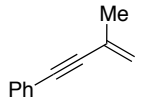
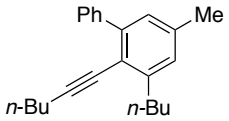
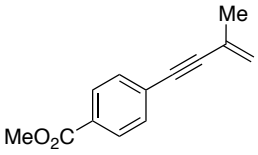
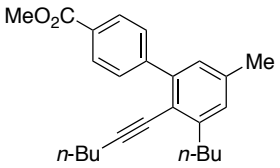
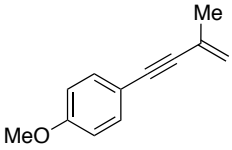
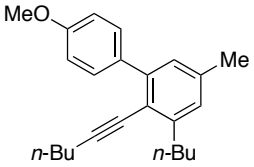
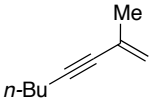
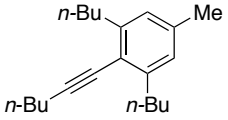
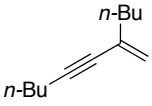
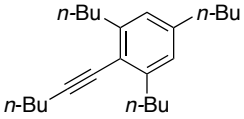
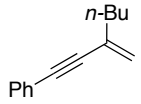
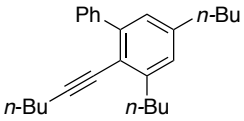
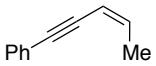
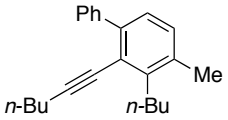
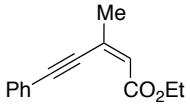
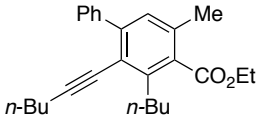
2.2.2. Scope of Enynes and Diynes

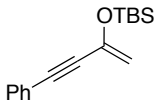
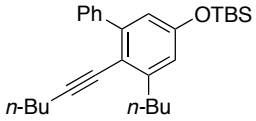
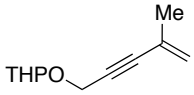
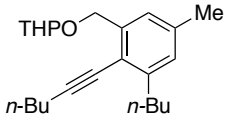
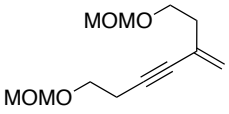
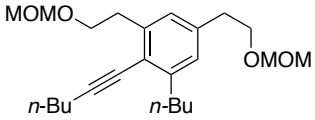
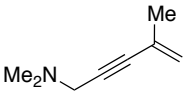
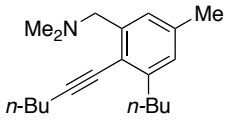
Next, the scope of enynes in the [4+2] cross-benzannulation reaction, catalyzed by IPrPdAllCl/TFP/CsOPiv system, was investigated (Table 2.6). It was found that arylenynes possessing electron-poor aromatic substituents were slightly more efficient compared to their electron-rich counterparts (entries 1 – 3). Enynes bearing 1,3-dialkyl substitution smoothly underwent benzannulation reaction regardless of the substituent size at the C-3 position (entries 4, 5). The least reactive 1,4-disubstituted substrate **2-03g** gave the product in diminished yield (entry 7), however 1,3,4-trisubstituted enyne **2-03h** reacted well (entry 8). Enynes bearing masked hydroxyl group provided access to phenol **2-08ia**, benzyl- **2-08ja**, and homobenzyl alcohol **2-08ka** derivatives (entries 9 – 11). Substrate **2-03l** possessing tertiary amine group reacted smoothly to give the corresponding *ortho*-alkynyl benzylamine **2-08la** (entry 12).

The scope of diynes is presented in Table 2.7. Due to low solubility of 1,4-diphenylbutadiyne under the reaction conditions, the benzannulation proceeded to about 50% conversion, thus providing poor yield of the product (entry 1). However, decreasing the concentration allowed to obtain the corresponding biarylalkyne **2-08db** in 84% yield, although higher catalyst loading was required under more dilute conditions (entries 2, 3). Analogous to the reactivity trend observed for enynes, electron-deficient diaryldiyne **2-07d** gave better yield of the corresponding product compared to that for electron-rich compound **2-07c** (entries 4, 5). Diyne possessing protected alcohol moiety underwent benzannulation in slightly diminished yield (entry 6). Unlike the corresponding enyne **2-03l**, diyne **2-07f** bearing amine functionality gave unsatisfactory yield due to its decomposition (entry 7).

Table 2.6. The Scope of Enynes in the Palladium-catalyzed [4+2] Benzannulation Reaction.[a]

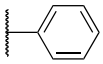
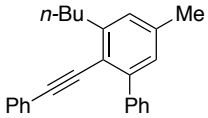
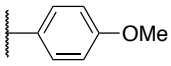
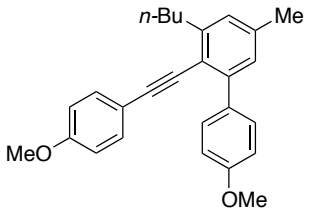
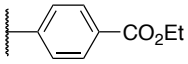
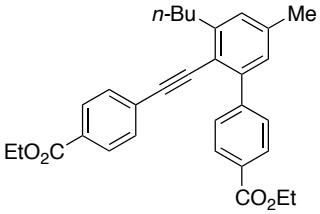
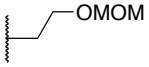
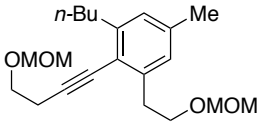
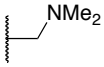
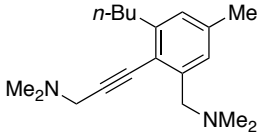
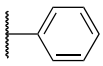
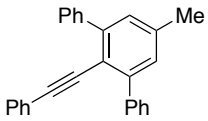


Entry	Enyne		Product		Yield, %[b]	TON[c]
1		**2-03a**		**2-08aa**	83	1660 (20)[16]
2		**2-03b**		**2-08ba**	86	1720
3		**2-03c**		**2-08ca**	71	1420
4		**2-03d**		**2-08da**	85	1700
5		**2-03e**		**2-08ea**	87	1740 (17)[15]
6		**2-03f**		**2-08fa**	84	1680
7		**2-03g**		**2-08ga**	53	1060
8		**2-03h**		**2-08ha**	75	1480 (15)[16]

Entry	Enyne		Product		Yield, %[b]	TON[c]
9		**2-03i**		**2-08ia**	41	820 (15)[16]
10		**2-03j**		**2-08ja**	77	1540
11		**2-03k**		**2-08ka**	69	1380 (11)[15]
12		**2-03l**		**2-08la**	90	1800

[a]Reaction conditions: **2-03** (1 equiv), **2-07a** (1.1 equiv), IPrPdAllCl (0.05 mol %), TFP (0.25 mol %), CsOPiv (0.5 mol %) in dry toluene (20 M). [b]Isolated yield, %. [c]TON is equal to [(product mol)×(catalyst mol)$^{-1}$], previously reported TONs are in parentheses.

Table 2.7. The Scope of Diynes in the Palladium-catalyzed [4+2] Benzannulation Reaction.[a]

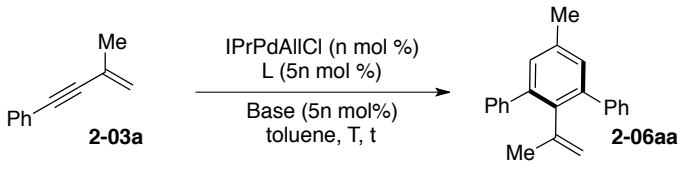
Entry	R		Product		Yield, %[b]	TON[c]
1					41	820
2		**2-07b**		**2-08db**	62[d]	620
3					84[e]	168
4		**2-07c**		**2-08dc**	77[e]	154
5		**2-07d**		**2-08dd**	88[e]	196
6		**2-07e**		**2-08de**	59	1180
7		**2-07f**		**2-08df**	32	620
8		**2-07b**		**2-08ab**	55[d,f]	550 (17)[13b]

[a]Reaction conditions: **2-03d** (1 equiv), **2-07** (1.1 equiv), IPrPdAllCl (0.05 mol %), TFP (0.25 mol %), CsOPiv (0.5 mol %) in dry toluene (20 M). [b]Isolated yield, %. [c]TON is equal to [(product mol)×(catalyst mol)$^{-1}$], previously reported TON is in parentheses. [d]IPrPdAllCl (0.1 mol %), TFP (0.5 mol %), CsOPiv (1.0 mol %) in dry toluene (10 M). [e]IPrPdAllCl (0.5 mol %), TFP (2.5 mol %), CsOPiv (2.5 mol %) in dry toluene (2 M). [f](3-methylbut-3-en-1-ynyl)benzene **2-03a** was used.

2.2.3. Optimization of Reaction Conditions and Scope of the Palladium-catalyzed [4+2] homo-Benzannulation Reaction

Next, we turned our attention to the Pd-catalyzed [4+2] homo-benzannulation reaction. Although the [4+2] homo-benzannulation of 1- or 3-monosubstituted enynes is well elaborated, homo-benzannulation of disubstituted enynes was limited to electron deficient substrates. Notably, during the initial optimization of the cross-benzannulation reaction, formation of trace amount of enyne dimer was observed. We found this result quite surprising, as 1,3-disubstituted electron-neutral enynes did not undergo homo-dimerization reaction before.[2,8] We decided to investigate the potential homo-benzannulation reaction of disubstituted enyne **2-03a** in the absence of diyne coupling partner (Table 2.8). Thus, it was found that in the presence of 1.5 mol % of IPrPdAllCl, 3 mol % of tris(*p*-methoxyphenyl)phosphine and 3 mol % of Cs_2CO_3 in toluene (1 M) enyne **2-03a** underwent homo-benzannulation providing the corresponding styrene derivative **2-06aa** in 65% unoptimized yield (entry 1). Employment of catalytic conditions effective for cross-benzannulation reaction did not improve reaction efficiency (entry 2). Further optimization of ligand revealed than biarylphosphines, such as RuPhos and PhDavePhos, were the most effective (entries 3-6). Ultimately, it was found that the catalyst loading could be reduced to 0.5 mol % with enhanced yield upon prolonged heating (entries 7, 8). Further decreasing of catalyst amount gave unsatisfactory results (entries 9, 10).

Table 2.8. Optimization of Conditions for Palladium-catalyzed [4+2] homo-Benzannulation Reaction of Disubstituted Enynes.[a]

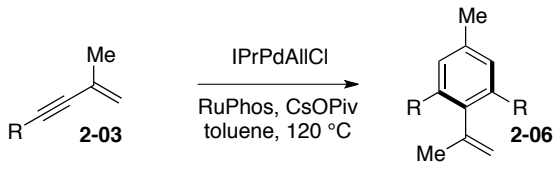


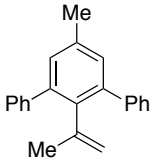
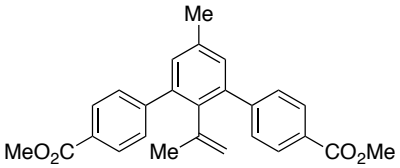
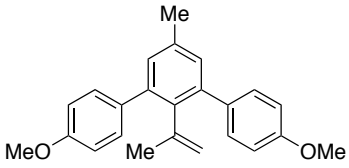
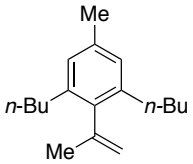
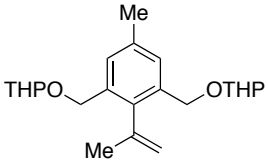
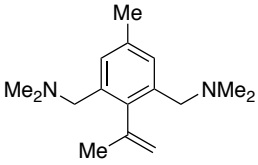
Entry	n of Pd, mol %	Ligand	Base	C, M	T, °C	t, h	Yield, %[b]
1	1.5	(p-$MeOC_6H_4)_3P$	Cs_2CO_3	1.0	80	80	65
2	1.5	TFP	CsOPiv	1.0	120	48	50
3	1.5	RuPhos	CsOPiv	1.0	120	20	80
4	1.0	PPh_3	CsOPiv	1.0	120	15	0[c]
5	1.0	TTMPP	CsOPiv	1.0	120	15	55
6	1.0	PhDavePhos	CsOPiv	1.0	120	20	74
7	0.5	PhDavePhos	CsOPiv	1.0	120	48	78
8	**0.5**	**RuPhos**	**CsOPiv**	**1.0**	**120**	**48**	**80**
9	0.25	PhDavePhos	CsOPiv	1.0	120	120	32[d]
10	0.25	RuPhos	CsOPiv	1.0	120	120	37[d]

[a]Reaction conditions: **2-03a** (0.1 mmol), IPrPdAllCl (n mol %), ligand (5n mol %), base (2n mol %) in dry toluene. [b]GC/MS yield at 100% conversion of enyne. [c]No reaction was observed. [d]Conversion was not complete.

The scope of this transformation was also examined (Table 2.9). Expectedly, electron-deficient substrate **2-03b** provided desired product in higher yield (entry 2), whereas reactivity of electron-rich enyne **2-03c** was lower (entry 3). Bis-1,3-dialkyl substituted enyne **2-03d** reacted efficiently to afford styrene **2-06dd** (entry 4). Likewise, styrenes **2-06jj** and **2-06ll** with alkoxy- and alkylamine moieties were effectively synthesized in good yields from the corresponding alkoxymethyl- and aminomethylenynes (entries 5, 6). Unfortunately, trisubstituted enynes did not undergo homo-benzannulation reaction even under these highly efficient conditions.

Table 2.9. The Scope of the Palladium-catalyzed [4+2] homo-Benzannulation of 1,3-Disubstituted Enynes.[a]



Entry	Enyne	Product		Yield, %[b]
1	**2-03a**		**2-06aa**	80
2	**2-03b**		**2-06bb**	89
3	**2-03c**		**2-06cc**	47
4	**2-03d**		**2-06dd**	77
5	**2-03j**		**2-06jj**	73
6	**2-03l**		**2-06ll**	76

[a]Reaction conditions: **2-03** (1 equiv), IPrPdAllCl (0.5 mol %), RuPhos (2.5 mol %), CsOPiv (2.5 mol %) in dry toluene (5 M). [b]Isolated yield, %.

2.2.3. Summary

In summary, a highly efficient catalytic system for [4+2] benzannulation of enynes with enynophiles has been developed. Newly found conditions enabled synthesis of variety of densely substituted arylacetylenes with high turnover number of the palladium catalyst. Moreover, the new catalytic system allowed to expand the scope of this transformation, as previously unreactive 1,3-disubstituted enynes underwent efficient homo-benzannulation to afford multisubstituted styrenes.

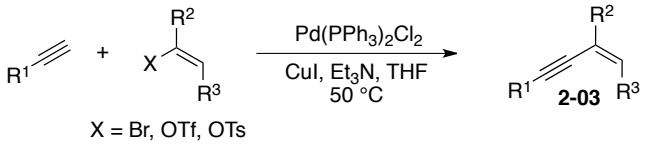
2.3. EXPERIMENTAL SECTION

2.3.1. General Information

NMR spectra were recorded on a Bruker Avance DRX-500 (500 MHz) and Bruker Avance DRX-400 (400 MHz) spectrometers. LRMS and HRMS analysis was performed on Micromass 70 VSE high-resolution mass spectrometer or Micromass LCT spectrometer equipped with a time-of-flight analyzer. GC/MS analysis was performed on a Hewlett Packard Model 6890 GC interfaced to a Hewlett Packard Model 5973 mass selective detector (15 m x 0.25 mm capillary column, HP-5MS). Column chromatography was carried out employing Silicycle Silica-P Flash silica gel (40-63 μm). Precoated silica gel plates F-254 were used for thin-layer analytical chromatography. All manipulations with transition metal catalysts were conducted in oven-dried glassware under inert atmosphere using a combination of glovebox and standard Schlenk techniques. Small-scale reactions were carried in Wheaton V-vials equipped with Mininert Syringe valve and stirring bar. Anhydrous solvents purchased from Aldrich were additionally purified on PureSolv PS-400-4 purification system by Innovative Technology, Inc. and/or stored over calcium hydride; toluene was additionally redistilled over calcium hydride, degased and kept in the glovebox. All other starting materials were purchased from Strem Chemicals, Sigma Aldrich, or Alfa Aesar.

2.3.2. Preparation of Enynes

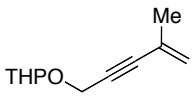
Enynes **2-03a-d**, **2-03f-h**, **2-03j**, **2-03l** were obtained via Sonogashira cross-coupling reaction:



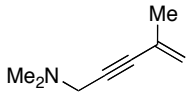
General procedure: A Schlenk flask was charged with $Pd(PPh_3)_2Cl_2$ (2 mol %) and CuI (5 mol %) under N_2 atmosphere. THF and Et_3N were added subsequently in 1:1 ratio (1M). Vinyl bromide (in case of **2-03a–d**, **2-03g**), trifluoromethylsulfonate (**2-03f**), or tosylate (**2-03h**) (1 equiv) was added to the reaction mixture, followed by dropwise addition of corresponding alkyne (1.1 equiv). The reaction

mixture was heated to 50 °C and stirred until completion. The reaction was then quenched with saturated NH_4Cl solution and extracted with EtOAc (3 × 5 mL). Combined extracts were dried over Na_2SO_4 and solvent was removed under vacuum. The residue was purified by flash column chromatography (**2-03b–d**, **2-03f**, **2-03g**, **2-03h, 2-03j**) or by Kugelrohr distillation under reduced pressure (**2-03a**, **2-03d**, **2-03l**) to afford corresponding enyne **2-03**.

Compounds **2-03a**,[34] **2-03b**,[35] **2-03c**,[36] **2-03f**,[37] **2-03g**,[38] **2-03h**[15] are known and their analytical data are in agreement with literature data.

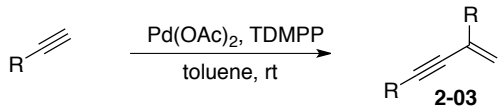


2-03j: 60% yield, colorless liquid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 5.30 (m, 1 H), 5.23 (m, 1 H), 4.82 (t, *J* = 3.4 Hz, 1 H), 4.29 – 4.41 (m, 2 H), 3.88 – 3.82 (m, 1 H), 3.56 – 3.51 (m, 1 H), 1.89 (s, 3 H), 1.88 – 1.79 (m, 1 H), 1.78 – 1.70 (m, 1 H), 1.67 – 1.50 (m, 4 H) **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 126.4, 122.2, 96.8, 87.0, 84.1, 62.0, 54.7, 30.3, 25.4, 23.4, 19.0 **HRMS** (ESI) calculated for $C_{11}H_{16}O_2Na$ [M+Na]: 203.1048, found: 203.1049.

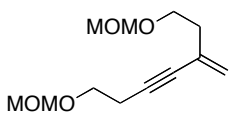


2-03l: 30% yield, colorless liquid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 5.26 (m, 1 H), 5.19 (m, 1 H), 3.34 (s, 2 H), 2.29 (s, 6 H), 1.89 (m, 3 H) **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 126.7, 121.3, 88.5, 83.7, 48.4, 44.2, 23.7 **HRMS** (EI+) calculated for $C_8H_{12}N^{0-1}$ [M–1]: 122.09697, found: 122.09636.

Enynes **2-03e, 2-03k** were obtained via dimerization of terminal alkynes according to literature procedure:[14]



Compounds **2-03e**[39] is known and its analytical data is in agreement with literature data.



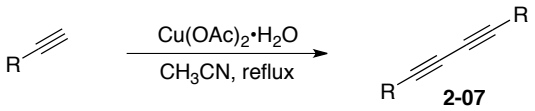
2-03k: 83% yield, colorless liquid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 5.31 (m, 1 H), 5.23 (m, 1 H), 4.63 (s, 2 H), 4.61 (s, 2 H), 3.68 (t, *J* = 6.7 Hz, 2 H), 3.64 (t, *J* = 6.9 Hz, 2 H), 3.35 (s, 3 H), 3.34 (s, 3 H), 2.59 (t, *J* = 6.9 Hz, 2 H), 2.39 (t, *J* = 6.6 Hz, 2 H) **^{13}C NMR** (125

MHz, $CDCl_3$) δ ppm 128.4, 122.0, 96.4, 87.0, 81.2, 66.0, 65.7, 55.2, 55.1, 37.7, 20.8 **HRMS** (ESI) calculated for $C_{12}H_{20}O_4Na$ $[M+Na]^+$: 251.1259, found: 251.1258.

Enyne **2-03i** was obtained via known procedure and its analytical data is in agreement with literature data.[17b]

2.3.3. Preparation of Diynes

Diynes **2-07a, 2-07c–f** were prepared via Cu-mediated Glaser coupling of alkynes according to literature procedure:[40]



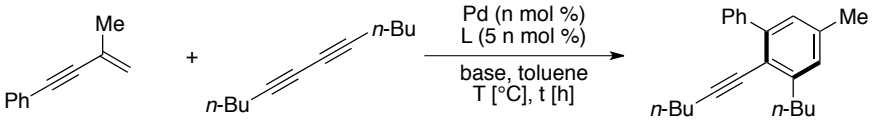
Compounds **2-07a**,[40] **2-07c–d**,[41] **2-07f**,[42] are known and their analytical data are in agreement with literature data.

2-07e: 99% yield, colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 4.62 (m, 4 H), 3.62 (dt, *J* = 6.7 Hz, *J* = 1.1 Hz, 4 H), 3.35 (s, 6 H), 2.53 (dt, *J* = 6.8 Hz, *J* = 1.1 Hz, 4 H) **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 96.4, 74.4, 66.1, 65.5, 55.3, 20.8 **HRMS** (ESI) calculated for $C_{12}H_{18}O_4Na$ $[M+Na]^+$: 249.1103, found: 249.1104.

2.3.4. Palladium-catalyzed [4+2] cross-Benzannulation of Enynes with Diynes

Optimization of conditions for palladium-catalyzed [4+2] cross-benzannulation, general procedure: A mixture of (3-methylbut-3-en-1-ynyl)benzene **2-03a** (0.1 mmol, 1 equiv) and dodeca-5,7-diyne **2-07a** (1.1 mmol, 1.1 equiv) was placed to an oven-dried 0.5 mL V-vial, equipped with a stirring bar. Base (2n mol %) and phosphine ligand (2n mol %) was added under N_2 atmosphere. Solution of IPrPdAllCl (n mol %) in toluene was added via microsyringe under N_2 atmosphere and the reaction vessel was capped with syringe valve. The reaction mixture was stirred at elevated temperature upon completion, which was monitored by GC/MS (Table 2.10).

Table 2.10. Optimization of Conditions for Palladium-catalyzed [4+2] cross–Benzannulation Reaction.

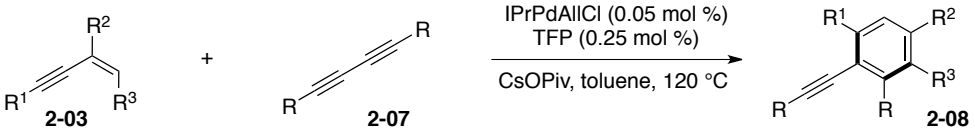


2-03a **2-07a** **2-08a**

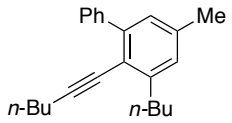
Entry	Pd source	n, mol %	Ligand	Base	C, M	T, °C	t, h	Yield, %
Optimization of palladium sourse								
1	Pd_2dba_3	1.5	PPh_3	-	1.0	80	80	74
2	Pd_2dba_3	1.5	**C1**	Cs_2CO_3	1.0	120	120	0
3	**Pd_2dba_3**	**1.5**	**C1, PPh_3**	**Cs_2CO_3**	**1.0**	**80**	**66**	**82**
4	Pd_2dba_3	1.5	**C2**	Cs_2CO_3	1.0	120	20	58
5	Pd_2dba_3	1.5	PhDavePhos	-	1.0	80	72	69
6	Pd_2dba_3	1.5	dppf	-	1.0	120	120	0
7	$IPrPdPPh_3$	1.5	-	-	1.0	80	40	67
8	**IPrPdAllCl**	**1.5**	**PPh_3**	**Cs_2CO_3**	**1.0**	**80**	**40**	**78**
9	IMesPdAllCl	1.0	PPh_3	Cs_2CO_3	1.0	80	100	79
10	IMesPdAllCl	0.5	PPh_3	Cs_2CO_3	1.0	80	100	41
11	IPrPdAllCl	1.0	PPh_3	Cs_2CO_3	1.0	80	40	79
12	**IPrPdAllCl**	**0.5**	**PPh_3**	**Cs_2CO_3**	**1.0**	**80**	**100**	**75**
13	IPrPdAllCl	0.1	PPh_3	Cs_2CO_3	1.0	80	100	21
14	SIPrPdAllCl	1.0	PPh_3	Cs_2CO_3	1.0	80	100	79
15	SIPrPdAllCl	0.5	PPh_3	Cs_2CO_3	1.0	80	100	75
16	SIPrPdAllCl	0.1	PPh_3	Cs_2CO_3	1.0	80	100	0

Entry	Pd source	n, mol %	Ligand	Base	C, M	T, °C	t, h	Yield, %
Optimization of phosphine ligand								
1	IPrPdAllCl	1.0	PPh_3	Cs_2CO_3	1.0	100	40	79
2	IPrPdAllCl	1.0	$(p\text{-}MeC_6H_4)_3P$	Cs_2CO_3	1.0	100	40	85
3	IPrPdAllCl	1.0	$(p\text{-}MeOC_6H_4)_3P$	Cs_2CO_3	1.0	100	40	84
4	IPrPdAllCl	1.0	TDMPP	Cs_2CO_3	1.0	100	40	53
5	**IPrPdAllCl**	**1.0**	**TFP**	**Cs_2CO_3**	**1.0**	**100**	**25**	**80**
6	IPrPdAllCl	1.0	$(p\text{-}F_3CC_6H_4)_3P$	Cs_2CO_3	1.0	100	40	80
7	IPrPdAllCl	1.0	$(F_5C_6)_3P$	Cs_2CO_3	1.0	100	40	0
8	IPrPdAllCl	1.0	RuPhos	Cs_2CO_3	1.0	100	40	74
9	**IPrPdAllCl**	**1.0**	**PhDavePhos**	**Cs_2CO_3**	**1.0**	**100**	**25**	**83**
10	IPrPdAllCl	1.0	dppf	Cs_2CO_3	1.0	100	40	0
11	IPrPdAllCl	1.0	Cy_3P	Cs_2CO_3	1.0	100	40	17
12	IPrPdAllCl	1.0	$Ph_3P(CH_2)_2PPh_3$	Cs_2CO_3	1.0	100	40	0
Optimization of inorganic base								
1	**IPrPdAllCl**	**1.0**	**PhDavePhos**	**CsOAc**	**1.0**	**100**	**8**	**83**
2	**IPrPdAllCl**	**1.0**	**PhDavePhos**	**CsOPiv**	**1.0**	**100**	**8**	**85**
3	IPrPdAllCl	1.0	PhDavePhos	K_2CO_3	1.0	100	25	83
4	IPrPdAllCl	1.0	PhDavePhos	KOAc	1.0	100	25	63
5	IPrPdAllCl	1.0	PhDavePhos	Na_2CO_3	1.0	100	25	31
6	IPrPdAllCl	1.0	PhDavePhos	NaOAc	1.0	100	25	48

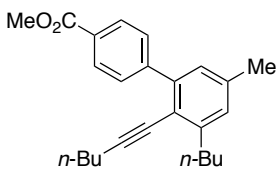
Entry	Pd source	n, mol %	Ligand	Base	C, M	T, °C	t, h	Yield, %
Optimization of catalyst loading and concentration								
1	IPrPdAllCl	0.5	PhDavePhos	CsOPiv	1.0	120	8	86
2	IPrPdAllCl	0.25	PhDavePhos	CsOPiv	1.0	120	20	85
3	IPrPdAllCl	0.1	PhDavePhos	CsOPiv	1.0	120	20	39
4	IPrPdAllCl	0.1	PhDavePhos	CsOPiv	0.5	120	15	43
5	IPrPdAllCl	0.1	PhDavePhos	CsOPiv	2.5	120	15	74
6	IPrPdAllCl	0.1	PhDavePhos	CsOPiv	5.0	120	15	67
7	IPrPdAllCl	0.1	TFP	CsOPiv	2.5	120	15	77
8	IPrPdAllCl	0.1	TFP	CsOPiv	5.0	120	15	80
9	**IPrPdAllCl**	**0.1**	**TFP**	**CsOPiv**	**10**	**120**	**15**	**86**
10	**IPrPdAllCl**	**0.05**	**TFP**	**CsOPiv**	**10**	**120**	**15**	**84**
11	**IPrPdAllCl**	**0.05**	**TFP**	**CsOPiv**	**20**	**120**	**15**	**85**
12	IPrPdAllCl	0.01	TFP	CsOPiv	neat	120	15	0



General procedure for palladium-catalyzed [4+2] cross-benzannulation: A mixture of enyne **2-03** (1.0 mmol, 1 equiv) and diyne **2-07** (1.1 mmol, 1.1 equiv) was placed to an oven-dried 0.5 mL V-vial, equipped with a stirring bar. CsOPiv (1.2 mg, 0.005 mmol, 0.5 mol %) was added under N_2 atmosphere. 50 ml of stock solution of IPrPdAllCl (0.0005 mmol, 0.05 mol %) and $(2\text{-furyl})_3P$ (0.0025 mmol, 0.25 mol %) in toluene [prepared by dissolving IPrPdAllCl (5.7 mg, 0.01 mmol) and $(2\text{-furyl})_3P$ (11.6 mg, 0.05 mmol) in 1 mL of toluene] was added via microsyringe under N_2 atmosphere and the reaction vessel was capped with syringe valve. The reaction mixture was stirred at 120 °C for 40-120 h. Resulting mixture was cooled down to room temperature, diluted with DCM, and filtered through a celite plug. The filtrate was concentrated under a reduced pressure, and the crude product was purified by column chromatography on silica gel to afford **2-08**.

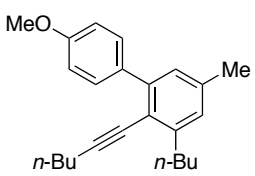


2-08aa:[13b] 253.8 mg (1 mmol scale), 83% yield, colorless oil (eluent: hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.60 – 7.56 (m, 2 H), 7.42 – 7.37 (m, 2 H), 7.35 – 7.31 (m, 1 H), 7.02 (s, 2 H), 2.83 (m, 2 H), 2.37 (s, 3 H), 2.34 – 2.29 (m, 2 H), 1.72 – 1.64 (m, 2 H), 1.50 – 1.40 (m, 4 H), 1.39 – 1.28 (m, 2 H), 0.99 (dt, *J* = 7.3 Hz, *J* = 1.6 Hz, 3 H), 0.89 (dt, *J* = 7.3 Hz, *J* = 1.6 Hz, 3 H) **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 145.5, 144.2, 141.7, 136.9, 129.5, 128.4, 127.8, 127.6, 126.8, 119.0, 96.6, 78.5, 35.0, 33.0, 30.7, 22.9, 21.9, 21.4, 19.3, 14.1, 13.7 **HRMS** (ESI) calculated for $C_{23}H_{29}$ $[M+H]^+$: 305.2269, found: 305.2271.

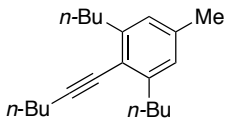


2-08ba: 156.1 mg (0.5 mmol scale), 86% yield, pale yellow oil (hexanes : EtOAc = 10:1). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 8.08 – 8.04 (m, 2 H), 7.65 – 7.61 (m, 2 H), 7.03 (d, *J* = 1.0 Hz, 1 H), 6.99 (d, *J* = 1.0 Hz, 1 H), 3.94 (s, 3 H), 2.81 (m, 2 H), 2.35 (s, 3 H), 2.29 (t, *J* = 6.9 Hz, 2 H), 1.69 – 1.59 (m, 2 H), 1.47 – 1.38 (m, 4 H), 1.34 – 1.28 (m, 2 H), 0.97 (t, *J* = 7.4 Hz, 3 H), 0.86 (t, *J* = 7.3 Hz, 3 H) **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 167.2, 146.5, 145.7, 143.0, 137.0, 129.5, 129.0, 128.9, 128.5, 127.5, 118.9, 97.1, 78.1, 52.0, 34.9, 32.9,

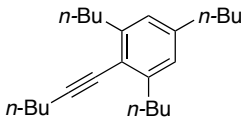
30.6, 22.8, 21.9, 21.4, 19.3, 14.0, 13.6 **HRMS** (ESI) calculated for $C_{25}H_{31}O_2$ $[M+H]^+$: 363.2324, found: 363.2323.



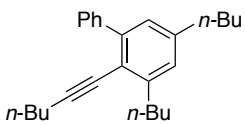
2-08ca: 118.5 mg (0.5 mmol scale), 71% yield, colorless oil (hexanes : EtOAc = 20:1). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.53 (d, J = 8.7 Hz, 2 H), 6.99 (s, 2 H), 6.94 (d, J = 8.7 Hz, 2 H), 3.87 (s, 3 H), 2.82 (m, 2H), 2.37 – 2.32 (m, 5 H), 1.71 – 1.63 (m, 2 H), 1.53 – 1.33 (m, 6 H), 0.98 (t, J = 7.4 Hz, 3 H), 0.90 (t, J = 7.3 Hz, 3 H) **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 158.7, 145.6, 143.7, 136.8, 134.2, 130.5, 128.0, 127.7, 118.9, 113.0, 96.4, 78.6, 55.3, 35.0, 33.0, 30.8, 22.9, 21.9, 21.4, 19.4, 14.1, 13.7 **HRMS** (ESI) calculated for $C_{24}H_{31}O$ $[M+H]^+$: 335.2375, found: 335.2378.



2-08da: 242.0 mg, 85% yield, colorless oil (hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 6.83 (s, 2 H), 2.75 – 2.70 (m, 4 H), 2.49 (t, J = 6.9 Hz, 2 H), 2.29 (s, 3 H), 1.65 – 1.48 (m, 8 H), 1.44 – 1.35 (m, 4 H), 0.98 – 0.93 (m, 9 H) **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 144.9, 136.6, 126.8, 119.8, 96.6, 77.8, 34.8, 33.0, 31.1, 22.8, 22.0, 21.4, 19.4, 14.0, 13.6 **HRMS** (ESI) calculated for $C_{21}H_{33}$ $[M+H]^+$: 285.2582, found: 285.2578.

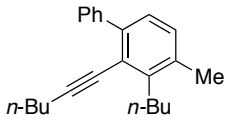


2-08ea:[15] 285.1 mg (1 mmol scale), 87% yield, colorless oil (hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 6.84 (s, 2 H), 2.76 – 2.72 (m, 4 H), 2.57 – 2.47 (m, 4 H), 1.67 – 1.49 (m, 10 H), 1.45 – 1.31 (m, 6 H), 1.00 – 0.91 (m, 12 H) **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 144.8, 141.7, 126.1, 120.0, 96.6, 77.9, 35.6, 34.8, 33.6, 33.0, 31.2, 22.8, 22.4, 22.5, 19.4, 14.03, 13.97, 13.6 **HRMS** (ESI) calculated for $C_{24}H_{39}$ $[M+H]^+$: 327.3052, found: 327.3057.

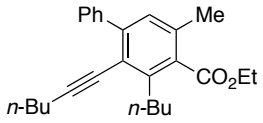


2-08fa: 144.7 mg (0.5 mmol scale), 84% yield, colorless oil (hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.61 – 7.58 (m, 2 H), 7.43 – 7.39 (m, 2 H), 7.36 – 7.32 (m, 1 H), 7.03 (s, 2 H), 2.86 – 2.82 (m, 2 H), 2.65 – 2.60 (m, 2 H), 2.33 (t, J = 6.9 Hz, 2 H), 1.73 – 1.60 (m, 4 H), 1.50 – 1.31 (m, 8 H), 0.99 (t, J = 7.4 Hz, 3 H), 0.95 (t, J = 7.3 Hz, 3 H), 0.89 (t, J = 7.3 Hz, 3 H) **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 145.5, 144.1, 142.0, 141.8, 129.5, 127.8,

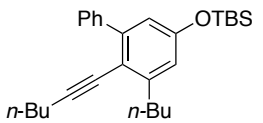
127.6, 127.1, 126.9, 119.1, 96.5, 78.5, 35.6, 35.0, 33.6, 33.0, 30.7, 22.9, 22.5, 21.9, 19.3, 14.1, 14.0, 13.7 **HRMS** (ESI) calculated for $C_{26}H_{35}$ $[M+H]^+$: 347.2739, found: 347.2737.



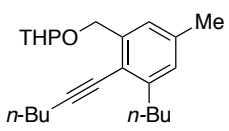
2-08ga:[13b] 161.7 mg (1 mmol scale), 53% yield, colorless oil (hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.58 – 7.56 (m, 2 H), 7.41 – 7.38 (m, 2 H), 7.35 – 7.31 (m, 1 H), 7.14 – 7.08 (m, 2 H), 2.92 – 2.88 (m, 2 H), 2.38 (s, 3 H), 2.32 (t, *J* = 6.9 Hz, 2 H), 1.64 – 1.57 (m, 2 H), 1.54 – 1.43 (m, 4 H), 1.39 – 1.31 (m, 2 H), 1.00 (t, *J* = 7.4 Hz, 3 H), 0.89 (t, *J* = 7.3 Hz, 3 H) **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 143.9, 142.2, 141.8, 134.7, 129.5, 129.3, 127.6, 126.7, 126.6, 122.1, 96.8, 78.9, 31.8, 31.7, 30.6, 23.3, 21.9, 19.7, 19.3, 14.0, 13.6 **HRMS** (ESI) calculated for $C_{23}H_{29}$ $[M+H]^+$: 305.2269, found: 305.2271.



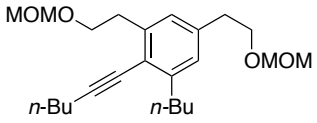
2-08ha:[15] 281.7 mg, 75% yield, colorless oil (hexanes : EtOAc = 20:1). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.54 – 7.51 (m, 2 H), 7.41 – 7.37 (m, 2 H), 7.36 – 7.32 (m, 1 H), 7.04 (s, 1 H), 4.43 (q, *J* = 7.2 Hz, 2 H), 2.83 – 2.77 (m, 2 H), 2.33 (s, 3 H), 2.29 (t, *J* = 6.9 Hz, 2 H), 1.70 – 1.62 (m, 2 H), 1.47 – 1.38 (m, 7 H), 1.36 – 1.27 (m, 2 H), 0.96 (t, *J* = 7.4 Hz, 3 H), 0.87 (t, *J* = 7.3 Hz, 3 H) **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 169.8, 145.1, 142.2, 141.0, 133.4, 133.3, 129.3, 128.8, 127.7, 127.2, 120.2, 97.3, 77.9, 61.1, 33.0, 32.8, 30.5, 23.3, 21.9, 19.6, 19.3, 14.3, 13.9, 13.6 **HRMS** (ESI) calculated for $C_{26}H_{33}O_2$ $[M+H]^+$: 377.2481, found: 377.2480.



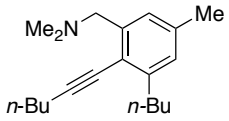
2-08ia:[16] 85.4 mg (0.5 mmol scale), 41% yield, colorless oil (hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.59 – 7.55 (m, 2 H), 7.42 – 7.37 (m, 2 H), 7.36 – 7.31 (m, 1 H), 6.69 (s, 2 H), 2.82 – 2.77 (m, 2 H), 2.30 (t, *J* = 6.89 Hz, 2 H), 1.70 – 1.62 (m, 2 H), 1.48 – 1.36 (m, 4 H), 1.37 – 1.29 (m, 2 H), 1.02 – 0.95 (m, 12 H), 0.88 (t, *J* = 7.3 Hz, 3 H), 0.23 (s, 6 H) **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 154.5, 147.2, 145.6, 141.4, 129.3, 127.6, 127.0, 119.3, 118.7, 115.0, 95.7, 78.3, 35.0, 32.7, 30.7, 25.7, 22.7, 21.9, 19.3, 18.3, 14.0, 13.6, –4.3 **HRMS** (ESI) calculated for $C_{28}H_{41}OSi$ $[M+H]^+$: 421.2927, found: 421.2927.



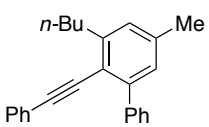
2-08ja: 132.5 mg (0.5 mmol scale), 77% yield, colorless oil (hexanes : EtOAc = 10:1). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.12 (s, 1 H), 6.92 (s, 1 H), 4.87 (d, *J* = 12.8 Hz, 1 H), 4.78 (t, *J* = 3.5 Hz, 1 H), 4.66 (d, *J* = 12.8 Hz, 1 H), 4.00 – 3.95 (m, 1 H), 3.60 – 3.54 (m, 1 H), 2.76 – 2.72 (m, 2 H), 2.48 (t, *J* = 6.9 Hz, 2 H), 2.32 (s, 3 H), 1.96 – 1.87 (m, 1 H), 1.81 – 1.69 (m, 2 H), 1.67 – 1.47 (m, 9 H), 1.43 – 1.33 (m, 2 H), 0.98 – 0.92 (m, 6 H) **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 144.9, 140.0, 137.0, 128.3, 125.4, 118.9, 98.5, 97.9, 76.8, 67.9, 62.0, 34.5, 32.9, 31.0, 30.6, 25.6, 22.7, 22.0, 21.5, 19.5, 19.4, 14.0, 13.6 **HRMS** (ESI) calculated for $C_{23}H_{35}O_2$ $[M+H]^+$: 343.2637, found: 343.2634.



2-08ka:[15] 133.9 mg (0.5 mmol scale), 69% yield, pale yellow oil (hexanes : EtOAc = 10:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 6.93 (s, 1 H), 6.92 (s, 1 H), 4.63 (s, 2 H), 4.61 (s, 2 H), 3.77 (t, *J* = 7.4 Hz, 2 H), 3.73 (t, *J* = 7.1 Hz, 2 H), 3.33 (s, 3 H), 3.30 (s, 3 H), 3.06 (t, *J* = 7.4 Hz, 2 H), 2.83 (t, *J* = 7.1 Hz, 2 H), 2.73 (m, 2 H), 2.47 (t, *J* = 6.9 Hz, 2 H), 1.64 – 1.55 (m, 4 H), 1.54 – 1.46 (m, 2 H), 1.42 – 1.33 (m, 2 H), 0.97 – 0.91 (m, 6 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 145.2, 140.3, 137.7, 127.3, 121.2, 97.5, 96.4, 96.3, 77.3, 68.3, 67.6, 55.14, 55.06, 36.2, 35.4, 34.8, 32.9, 31.1, 22.7, 22.0, 19.4, 14.0, 13.6 HRMS (ESI) calculated for $C_{24}H_{39}O_4$ $[M+H]^+$: 391.2848, found: 391.2851.

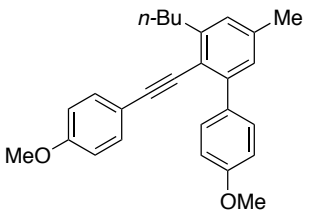


2-08la: 129.1 mg (0.5 mmol scale), 90% yield, pale yellow oil (EtOAc : MeOH = 10:1). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.04 (s, 1 H), 6.89 (s, 1 H), 3.57 (s, 2 H), 2.76 – 2.71 (m, 2 H), 2.50 (t, *J* = 6.9 Hz, 2 H), 2.32 – 2.27 (m, 9 H), 1.66 – 1.49 (m, 6 H), 1.44 – 1.34 (m, 2 H), 0.99 – 0.92 (m, 6 H) **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 144.9, 140.4, 136.7, 128.0, 127.3, 120.5, 97.6, 77.5, 62.2, 45.7, 34.7, 33.0, 31.1, 22.8, 22.1, 21.4, 19.4, 14.0, 13.6 **HRMS** (ESI) calculated for $C_{20}H_{32}N$ $[M+H]^+$: 286.2535, found: 286.2531

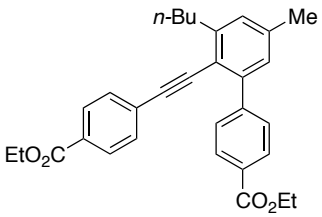


2-08db: 121.6 mg (1 mmol scale, 0.05 mol % IPrPdAllCl, 41% yield); 200.6 mg (1 mmol scale, 0.1 mol % IPrPdAllCl, 62% yield); 271.6 mg (1 mmol scale, 0.5 mol %

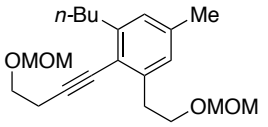
IPrPdAllCl, 84% yield), colorless oil (hexanes : EtOAc = 20:1). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.75 – 7.72 (m, 2 H), 7.53 – 7.51 (m, 2 H), 7.50 – 7.47 (m, 1 H), 7.36 – 7.32 (m, 5 H), 7.16 (s, 1 H), 7.14 (s, 1 H), 3.01 (m, 2 H), 2.46 (s, 3 H), 1.86 – 1.79 (m, 2 H), 1.60 – 1.54 (m, 2 H), 1.08 (t, *J* = 7.3 Hz, 3 H) **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 145.7, 144.5, 141.3, 138.1, 131.1, 129.6, 128.7, 128.3, 127.9, 127.83, 127.76, 127.3, 124.1, 118.2, 96.6, 88.3, 35.1, 33.2, 23.0, 21.6, 14.2 **HRMS** (ESI) calculated for $C_{25}H_{25}$ $[M+H]^+$: 325.1956, found: 325.1956.



2-08dc: 148.2 mg (0.5 mmol scale, 0.5 mol % IPrPdAllCl), 77% yield, colorless oil (hexanes : EtOAc = 20:1). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.61 (d, *J* = 8.7 Hz, 2 H), 7.27 (d, *J* = 8.8 Hz, 2 H), 7.06 (s, 1 H), 7.03 (s, 1 H), 6.99 (d, *J* = 8.8 Hz, 2 H), 6.84 (d, *J* = 8.8 Hz, 2 H), 3.89 (s, 3 H), 3.81 (s, 3 H), 2.92 (m, 2 H), 2.39 (s, 3 H), 1.79 – 1.71 (m, 2 H), 1.54 – 1.45 (m, 2 H), 1.00 (t, *J* = 7.4 Hz, 3 H) **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 159.3, 158.9, 145.4, 143.7, 137.6, 134.0, 132.5, 130.7, 128.2, 127.7, 118.4, 116.3, 114.0, 113.1, 95.4, 87.0, 55.33, 55.28, 35.1, 33.0, 22.9, 21.5, 14.1 **HRMS** (ESI) calculated for $C_{27}H_{29}O_2$ $[M+H]^+$: 385.2168, found: 385.2171.

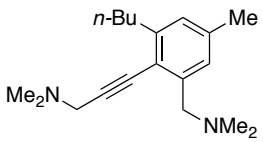


2-08dd: 205.8 mg (0.5 mmol scale, 0.5 mol % IPrPdAllCl), 88% yield, colorless oil (hexanes : EtOAc = 4:1). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 8.13 (d, *J* = 8.1 Hz, 2 H), 7.97 (d, *J* = 8.1 Hz, 2 H), 7.67 (d, *J* = 8.1 Hz, 2 H), 7.31 (d, *J* = 8.1 Hz, 2 H), 7.10 (s, 1 H), 7.08 (s, 1 H), 4.43 (q, *J* = 7.05 Hz, 2 H), 4.36 (q, *J* = 7.05 Hz, 2 H), 2.91 (m, 2 H), 2.40 (s, 3 H), 1.74 – 1.68 (m, 2 H), 1.53 – 1.33 (m, 8 H), 0.99 (t, *J* = 7.3 Hz, 3 H) **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 166.6, 166.0, 146.2, 145.7, 143.6, 138.8, 130.9, 129.52, 129.46, 129.3, 129.0, 128.3, 127.8, 117.5, 95.2, 90.8, 61.1, 61.0, 35.0, 33.1, 22.8, 21.5, 14.4, 14.3, 14.1 **HRMS** (ESI) calculated for $C_{31}H_{33}O_4$ $[M+H]^+$: 469.2379, found: 469.2380.

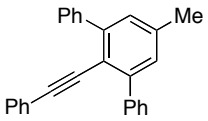


2-08de: 102.2 mg (0.5 mmol scale), 59% yield, colorless oil (hexanes : EtOAc = 4:1). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 6.88 (s, 1 H), 6.86 (s, 1 H), 4.68 (s, 2 H), 4.64 (s, 2 H), 3.80 – 3.73 (m, 4 H), 3.39 (s, 3 H), 3.33 (s, 3 H), 3.05 (t, *J* = 7.4 Hz, 2 H), 2.78 (t, *J* =

7.0 Hz, 2 H), 2.72 (m, 2 H), 2.28 (s, 3 H), 1.63 – 1.55 (m, 2 H), 1.42 – 1.33 (m, 2 H), 0.94 (t, *J* = 7.4 Hz, 3 H) **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 145.2, 140.4, 137.1, 127.5, 119.8, 96.5, 96.2, 93.3, 78.5, 67.6, 66.5, 55.3, 55.1, 35.3, 34.6, 32.9, 22.7, 21.4, 21.3, 14.0 **HRMS** (ESI) calculated for $C_{21}H_{32}O_4Na$ $[M+Na]^+$: 371.2198, found: 371.2202.

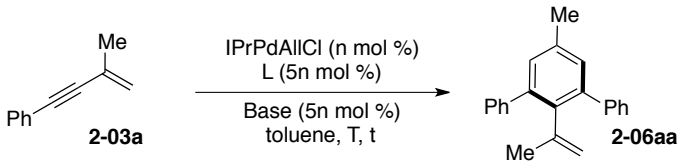


2-08df: 45.8 mg (0.5 mmol scale), 32% yield, yellow oil (EtOAc : MeOH = 10:1). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.07 (s, 1 H), 6.91 (s, 1 H), 3.58 (s, 4 H), 2.76 (m, 2 H), 2.39 (s, 6 H), 2.31 (s, 3 H), 2.28 (s, 6 H), 1.65 – 1.56 (m, 2 H), 1.42 – 1.33 (m, 2 H), 0.93 (t, *J* = 7.3 Hz, 3 H) **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 145.1, 140.8, 137.5, 128.1, 127.3, 119.6, 91.8, 82.4, 62.2, 48.9, 45.7, 44.2, 34.7, 33.0, 22.8, 21.4, 14.0 **HRMS** (ESI) calculated for $C_{19}H_{31}N_2$ $[M+H]^+$: 287.2487, found: 287.2489.



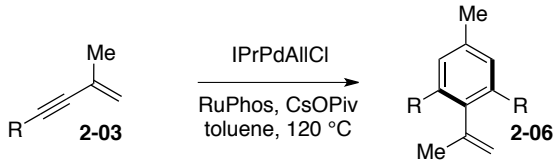
2-08ab:[13b] 190.0 mg (1 mmol scale), 55% yield, white solid (hexanes : EtOAc = 20:1). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.71 – 7.68 (m, 4 H), 7.50 – 7.47 (m, 4 H), 7.44 – 7.40 (m, 2 H), 7.25 (s, 2 H), 7.21 – 7.17 (m, 3 H), 7.03 – 6.99 (m, 2 H), 2.47 (s, 3 H) **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 144.9, 141.2, 138.2, 131.0, 129.7, 129.3, 128.1, 127.7, 127.4, 123.8, 117.4, 95.1, 89.1, 21.5 **HRMS** (ESI) calculated for $C_{27}H_{21}$ $[M+H]^+$: 345.1643, found: 345.1652.

2.3.5. Palladium-catalyzed [4+2] homo-Benzannulation of Enynes

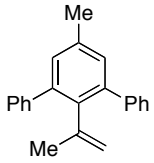


Optimization of conditions for palladium-catalyzed [4+2] homo-benzannulation, general procedure: (3-methylbut-3-en-1-ynyl)benzene **2-03a** (0.1 mmol, 1 equiv) was placed to an oven-dried 0.5 mL V-vial, equipped with a stirring bar. Base (5n mol %) and phosphine ligand (5n mol %) were added under N_2 atmosphere. Solution of IPrPdAllCl (n mol %) in toluene was added via microsyringe

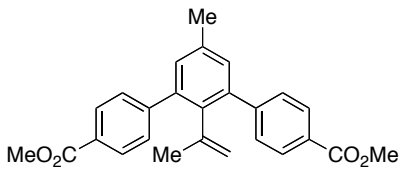
under N_2 atmosphere and the reaction vessel was capped with syringe valve. The reaction mixture was stirred at elevated temperature upon completion, which was monitored by GC/MS (Table 2.8).



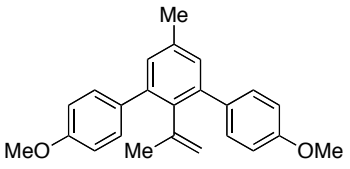
General procedure for palladium-catalyzed [4+2] homo-benzannulation of enynes: Enyne **2-03** (0.5 mmol, 1 equiv) was placed to an oven-dried 0.5 mL V-vial, equipped with a stirring bar. IPrPdAllCl (1.4 mg, 0.0025 mmol, 0.5 mol %), RuPhos (5.8 mg, 0.0125 mmol, 2.5 mol %), CsOPiv (1.2 mg, 0.005 mmol, 1 mol %). 100 ml of toluene were added under N_2 atmosphere and the reaction vessel was capped with syringe valve. The reaction mixture was stirred at 120 °C for 15-48 h. Resulting mixture was cooled down to room temperature, diluted with DCM and filtered through a celite plug. The filtrate was concentrated under reduced pressure and the crude product was purified by column chromatography on silica gel to afford styrene **2-06.**



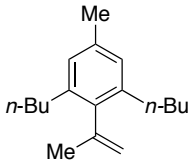
2-06aa: 114.0 mg (1 mmol scale), 80% yield, colorless liquid (hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.43 – 7.28 (m, 10 H), 7.17 (s, 2 H), 5.00 (m, 1 H), 4.68 (m, 1 H), 2.44 (s, 3 H), 1.53 (m, 3 H) **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 143.0, 142.6, 140.8, 138.3, 136.0, 130.2, 129.2, 127.7, 126.6, 119.7, 24.9, 21.1 **HRMS** (ESI) calculated for $C_{22}H_{21}$ $[M+H]^+$: 285.1643, found: 285.1641.



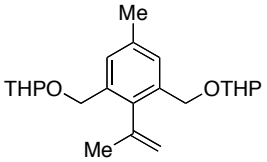
2-06bb: 107.2 mg (0.6 mmol scale), 89% yield, white solid (hexanes : EtOAc = 10:1). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 8.03 (d, J = 8.3 Hz, 4 H), 7.44 (d, J = 8.3 Hz, 4 H), 7.15 (s, 2 H), 4.95 (m, 1 H), 4.63 (m, 1 H), 3.94 (s, 6 H), 2.42 (s, 3 H), 1.47 (s, 3 H) **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 167.1, 147.2, 142.2, 139.9, 138.1, 136.5, 130.3, 129.2, 129.1, 128.5, 120.5, 52.1, 24.8, 21.0 **HRMS** (ESI) calculated for $C_{26}H_{25}O_4$ $[M+H]^+$: 401.1753, found: 401.1755.



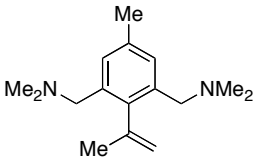
2-06cc: 48.3 mg (0.6 mmol scale), 47% yield, white solid (hexanes : EtOAc = 20:1). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.32 (d, *J* = 8.7 Hz, 4 H), 7.12 (s, 2 H), 6.91 (d, *J* = 8.7 Hz, 4 H), 5.01 (m, 1 H), 4.67 (m, 1 H), 3.86 (s, 6 H), 2.41 (s, 3 H), 1.55 (s, 3 H) **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 158.4, 143.2, 140.4, 138.4, 136.0, 135.0, 130.2, 130.0, 119.5, 113.1, 55.2, 24.9, 21.0 **HRMS** (ESI) calculated for $C_{24}H_{25}O_2$ $[M+H]^+$: 345.1855, found: 345.1858.



2-06dd: 126.5 mg (1.34 mmol scale), 77% yield, colorless oil (hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 6.91 (s, 2 H), 5.30 (m, 1 H), 4.80 (m, 1 H), 2.54 (m, 4 H), 2.33 (s, 3 H), 2.00 (m, 3 H), 1.64 – 1.49 (m, 4 H), 1.45 – 1.36 (m, 4 H), 0.96 (t, *J* = 7.3 Hz, 6 H) **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 144.1, 139.6, 139.5, 135.8, 127.0, 115.6, 34.5, 32.9, 25.5, 23.0, 21.2, 14.1 **HRMS** (ESI) calculated for $C_{18}H_{29}$ $[M+H]^+$: 245.2269, found: 245.2270.



2-06jj: 44.7 mg (0.34 mmol scale), 73% yield, colorless oil (hexanes : EtOAc = 4:1). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.24 (s, 2 H), 5.28 (m, 1 H), 4.80 (m, 1 H), 4.76 (dd, *J* = 11.7 Hz, *J* = 2.6 Hz, 1 H), 4.72 – 4.65 (m, 3 H), 4.45 (dd, *J* = 11.9 Hz, *J* = 2.0 Hz, 1 H), 4.39 (d, *J* = 11.7 Hz, 1 H), 3.95 – 3.89 (m, 2 H), 3.58 – 3.51 (m, 2 H), 2.36 (s, 3 H), 2.01 (m, 3 H), 1.91 – 1.82 (m, 2 H), 1.77 – 1.49 (m, 12 H) **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 142.7, 139.5, 136.4, 134.9, 128.7, 128.5, 116.2, 116.0, 115.9, 98.2, 98.1, 67.0, 66.9, 62.0, 30.7, 25.5, 21.2, 19.4 **HRMS** (ESI) calculated for $C_{22}H_{32}O_4Na$ $[M+Na]^+$: 383.2198, found: 383.2197.



2-06ll: 93.5 mg (1 mmol scale), 76% yield, yellow solid (EtOAc : MeOH = 10:1). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.22 (s, 2 H), 5.26 (m, 1 H), 4.70 (m, 1 H), 3.42 – 3.37 (m, 2 H), 3.33 – 3.28 (m, 2 H), 2.33 (s, 3 H), 2.24 (s, 12 H), 1.95 (m, 3 H) **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 143.7, 140.0, 136.2, 135.5, 128.0, 115.8, 60.9, 45.6, 25.6, 21.1 **HRMS** (ESI) calculated for $C_{16}H_{27}N_2$ $[M+H]^+$: 247.2174, found: 247.2176.

2.4. CITED LITERATURE

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PART THREE

DEVELOPMENT OF PALLADIUM-CATALYZED [4+2] BENZANNULATION REACTION TOWARD FLUORO- AND PERFLUOROALKYLARENES

3.1. INTRODUCTION

Due to their unique physical, chemical, and biological properties,[1] fluoro- and perfluoroalkyl-containing aromatic compounds are garnering increasing attention in various research areas, such as pharmaceutical,[2] agrochemical,[3] and material[4] sciences, as well as positron emission tomography (Figure 3.1).[5] The widespread application of fluoroarenes triggered immense progress in fluoroorganic chemistry, which resulted in the development of efficient methodologies toward synthesis of aryl fluorides.[6]

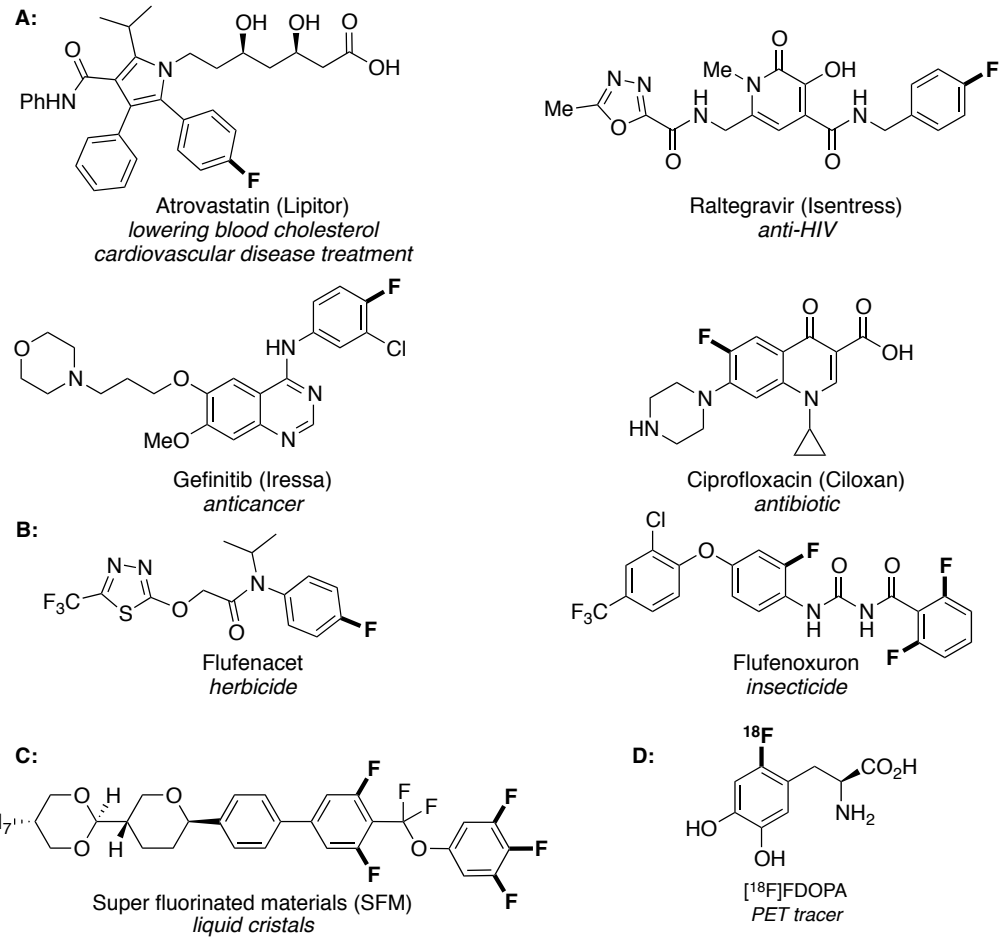
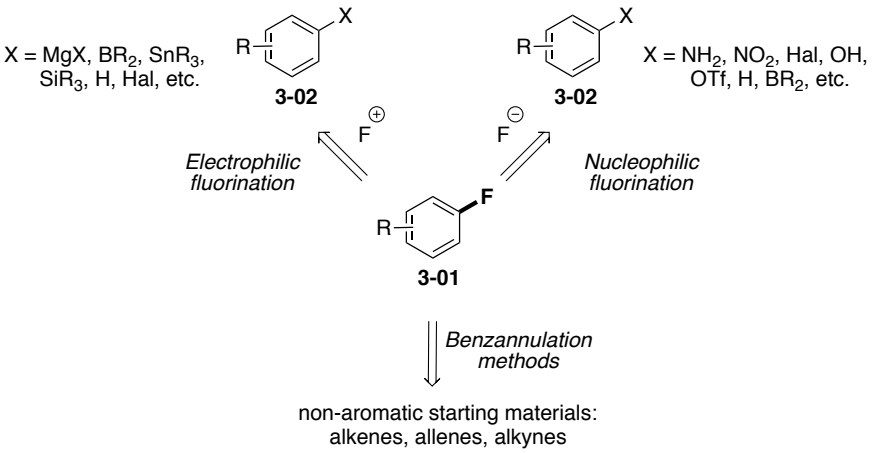


Figure 3.1. Examples of Fluorinated Arenes in Pharmaceuticals (**A**), Agrochemicals (**B**), Advanced Organic Materials (**C**), and PET tracers (**D**).

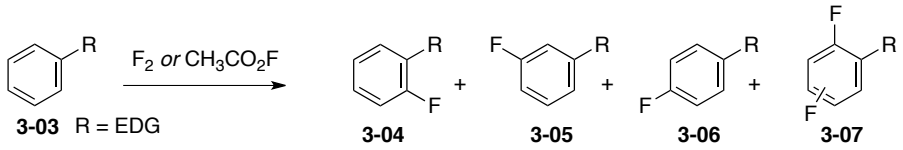
Fluoroarenes **3-01** are generally synthesized via modification of prefunctionalized aromatic compounds via electrophilic or nucleophilic fluorination (Scheme 3.1). Advances in this area associated with the introduction of novel fluorinating reagents for both electrophilic and nucleophilic processes. Moreover, transition metal-mediated or -catalyzed procedures dramatically increase efficiency, practicality and functional groups compatibility of these methods. Additionally, several approaches for synthesis of fluoroarenes from non-aromatic precursors were recently demonstrated. Accordingly, synthetic methods toward aryl fluorides via electrophilic or nucleophilic fluorination, as well as via benzannulation methods, are summarized in the following section.



Scheme 3.1. Synthetic Strategies toward Fluorinated Aromatic Ring.

3.1.1. Fluorination of Aromatic Compounds with Electrophilic Fluorinating Reagents

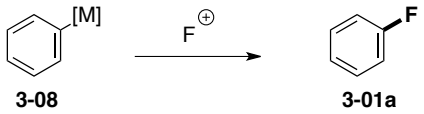
Early examples of synthesis of fluoroarenes rely on direct fluorination of aromatic compounds with molecular fluorine[7] or acetyl hypofluorite[8] via electrophilic aromatic substitution (Scheme 3.2). Expectedly, the marginal regioselectivity of these processes strongly depends on the substrate nature. In case of milder electrophilic source, such as acetyl hypofluorite, the scope of the reaction is limited to the activated electron-rich systems.



Scheme 3.2. Direct Fluorination of Aromatic Compounds via S_EAr.

To address these issues, metal-halogen exchange of organometallic compounds, such as aryl-tin,[9, 10 11] germanium,[9d] silicon,[9b,d,12,13,14] boron, [15] lead,[16] and mercury[10,17,18] derivatives, were studied. Besides fluorine[9,12] and acetyl hypofluorite,[9,12,14,18] other fluorinating reagents, such as CF_3OF,[10] $CsSO_4F$,[11,15] XeF_2,[12,17] and BF_3,[16] found applications in the synthesis of fluorinated benzenes (Table 3.1).

Table 3.1. Synthesis of Fluorobenzene via Fluorination of Organometallic Reagents.

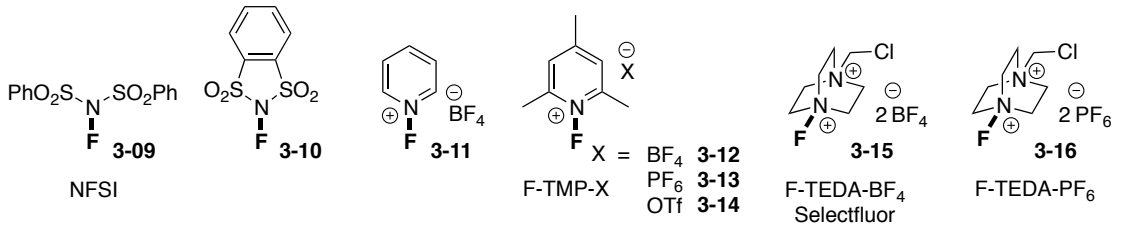


Entry	Organometallic substrate	Fluorinating reagent	Yield of **3-01a**, %	Ref.
1	$PhSn(n\text{-}Bu)_3$	F_2	70	9
2	$PhSn(n\text{-}Bu)_3$	$CH_3CO_2{}^{18}F$	72[a]	9c
3	$PhSnMe_3$	CF_3OF	50	10
4	$PhSnMe_3$	$CsSO_4F$	69	11
5	$PhSiMe_3$	F_2	23	12
6	$PhSiMe_3$	$BF_3{\cdot}OEt_2/Pb(OAc)_4$	83	16
7	$PhSiMe_3$	XeF_2	65	13
8	$K_2[PhSiF_5]$	$CH_3CO_2{}^{18}F$	20[a]	14
9	Ph_2Hg	CF_3OF	83	10
10	PhHgOAc	CH_3CO_2F	58	18
11	Ph_4Pb	F_2	48	9b
12	$PhPb(OAc)_3$	$BF_3{\cdot}OEt_2$	62	16

[a]Radiochemical yield, %.

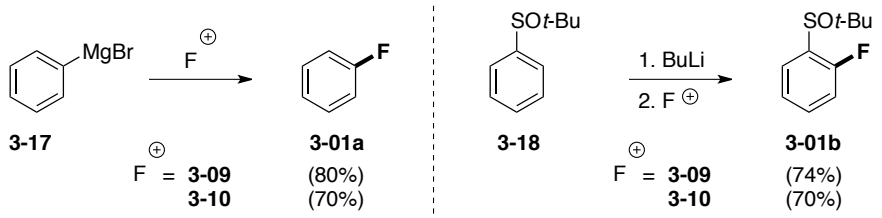
Although good yields were achieved for the synthesis of fluorobenzene using phenyltrialkylstannanes (entries 1, 2, 4), phenyltrimethylsilane (entry 6), or diphenylmercury (entry 9), these strategies often suffer from side protiodemetallation and overfluorination reactions, especially if more reactive aryl derivatives are used. Additionally, organolithium and organomagnesium reagents were tested in fluorination reactions with fluorine[19] or perchloryl fluoride ($FClO_3$)[20] providing only moderate yields of desired fluoroaromatic products. Moreover, these processes also operationally difficult, as they require handling of hazardous reagents.

The major breakthrough in electrophilic fluorination is associated with introduction of modern nitrogen-based fluorinating reagents, which are non-toxic, non-explosive, stable and easy to handle (Scheme 3.3).[21] Importantly, these mild reagents allow selective mono-fluorination and are compatible with various functional groups.



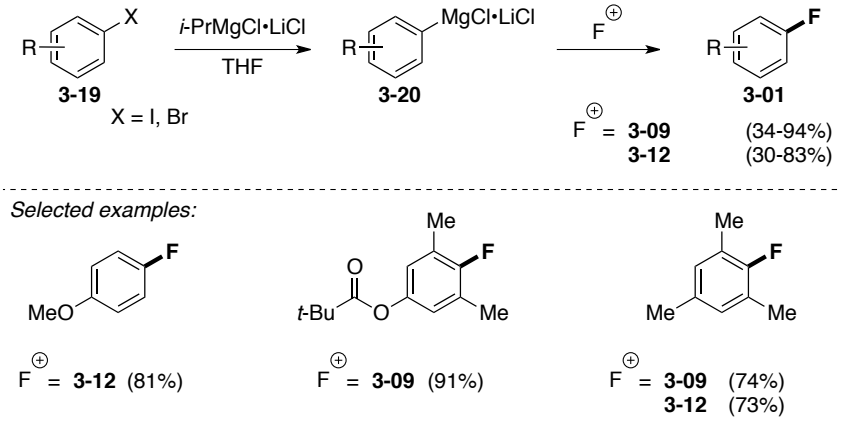
Scheme 3.3. Commonly Used Reagents for Electrophilic Fluorination.

Accordingly, the early examples employing these reagents include fluorination of aryl Grignard reagents or aryllithium derivatievs with *N*-fluorosulfonimides, such as **3-09** (NFSI) or **3-10** (Scheme 3.4).[22] Interestingly, an efficient *ortho*-fluorination can be achieved using directed *ortho*-metallation (DOM) strategy (e.g. **3-18** → **3-19**). Although clean conversions to the desired fluorinated products were often observed, the availability, stability and reactivity of metallated precursors significantly limit the scope of this methodology.



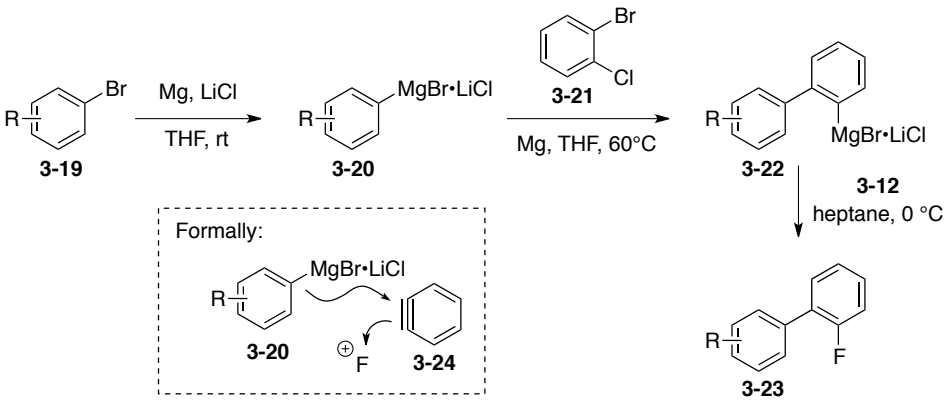
Scheme 3.4. Electrophilic Fluorination of Organomagnesium and Organolithium Compounds.

Efficient strategy for halogen-magnesium exchange of aryl halides, developed by Knochel,[23] dramatically enhanced synthetic applicability of this method.[24] It was demonstrated, that various fluoroarenes can be accessed using *N*-fluorosulfonimide (NFSI) **3-09**[24a] or *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate (F-TMP-BF_4) **3-12** (Scheme 3.5).[24b] Careful optimization of the reaction conditions, such as employed fluorinating agent and reaction solvent, resulted in minimized protonation of Grignard reagents and good yields of aryl fluorides.



Scheme 3.5. Electrophilic Fluorination of Grignard Reagents Stabilized by LiCl.

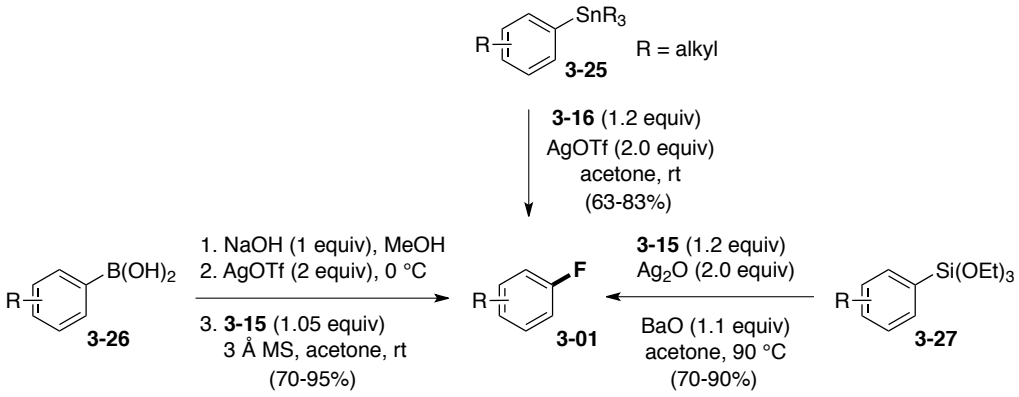
This methodology was further applied for the synthesis of *ortho*-fluorobiaryls via domino Gringard addition/fluorination reaction (Scheme 3.6).[25] Thus, coupling of Gringard reagents **3-20** with benzyne, generated form 1-bromo-2-chlorobenzene (**3-21**), afforded biaryl organomagnesium species **3-22**, which in turn underwent electrophilic fluorination with F-TMP-BF_4 (**3-12**). Overall, this transformation can be considered as arylative fluorination of benzynes.



Scheme 3.6. Synthesis of *ortho*-Fluorobiaryls via Arylative Fluorination.

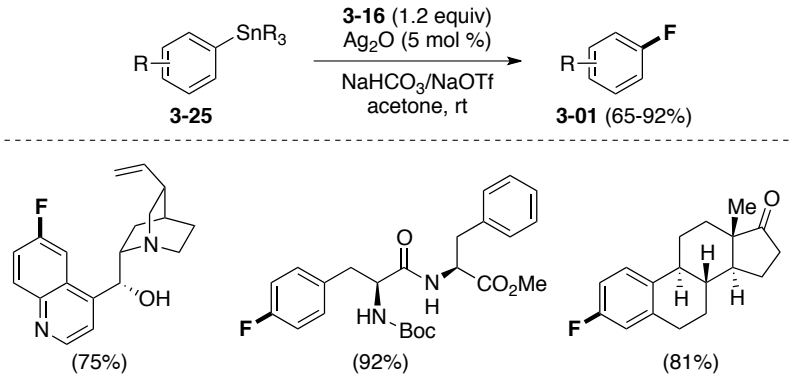
The reaction of Grignard reagents with fluorine electrophiles is efficient for a variety of haloarenes, including highly activated electron-rich or sterically hindered *ortho*-disubstituted substrates. However, these procedures are not compatible with functionalities, which are sensitive to organomagnesium reagents. In a search for a more general method, several approaches for transition metal-mediated or -catalyzed electrophilic fluorination were developed.

Accordingly, Ritter group has found that aryl stannanes **3-25** can be converted to fluoroarenes using F-TEDA-BF_4 (**3-15**) or F-TEDA-PF_6 (**3-16**) in the presence of silver triflate (Scheme 3.7).[26] Notably, this method tolerates a variety of functional groups, including cyanides, aldehydes, phenols, and aliphatic alcohols. In order to avoid employment of toxic aryl tin reagents, analogous silver-mediated fluorination of boronic acids **3-26** or silanes **3-27** was subsequently developed.



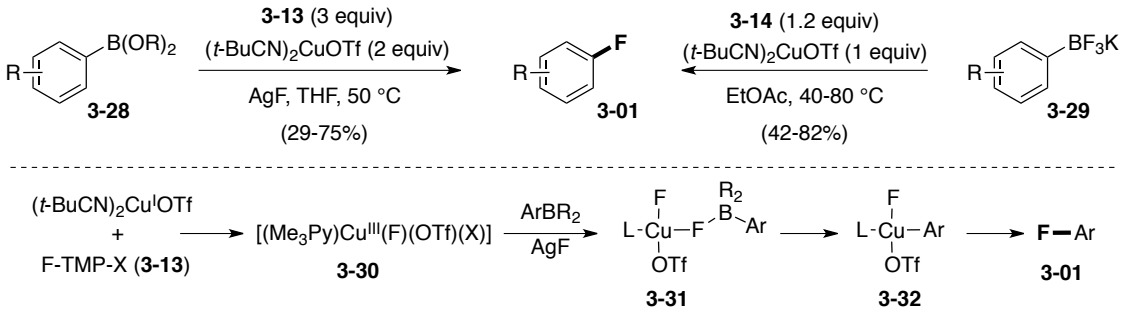
Scheme 3.7. Silver-mediated Electrophilic Fluorination of Organometallic Reagents.

Further development led to the introduction of silver-catalyzed fluorination of aryl stannanes with F-TEDA-PF_6 (**3-16**) (Scheme 3.8).[27] Thus, in the presence of silver oxide and $NaHCO_3$/NaOTf additives desired fluoroarenes were obtained in good to high yields. Importantly, addition of sodium salts suppressed protiodemetallation side reaction, which is otherwise a predominant process. Synthetic utility of this methodology was demonstrated by a late stage fluorination of various biologically relevant molecules.



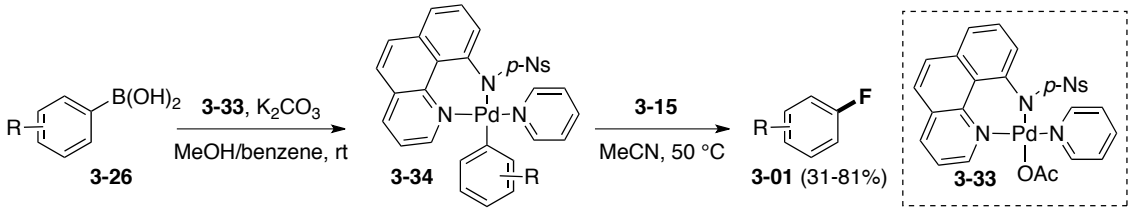
Scheme 3.8. Silver-catalyzed Electrophilic Fluorination of Organostannanes.

Alternative copper-mediated method employs F-TMP-PF_6 (**3-13**) and F-TMP-OTf (**3-14**) as fluorinating reagents. Thus, Sanford[28] and Hartwig[29] groups independently reported that aryl boronic esters or aryl trifluoroborate salts could be converted to fluoroarenes in the presence of electrophilic copper (I) triflate (Scheme 3.9). These reactions exhibit broad substrates scope and functional group tolerance, which is a significant improvement compared to the analogous copper-free fluorination reaction.[30] Similar reactivity was also observed for aryl stannanes. Copper mediated homocoupling to form biaryls, which is the major side reaction of this process, was suppressed by premixing (*t*-BuCN)$_2$CuOTf and F-TMP-X prior to addition of an organometallic substrate. In this case, reagent F-TMP-X serves not only as a source of fluorine atom, but also as an oxidant for copper. Accordingly, NMR studies indicated formation of Cu(III) intermediate in the reaction of (*t*-BuCN)$_2$CuOTf with **3-30**, which then underwent transmetallation with aryl boronic reagent presumably via intermediacy of **3-31**. Final reductive elimination delivered the desired fluorinated product **3-01**.



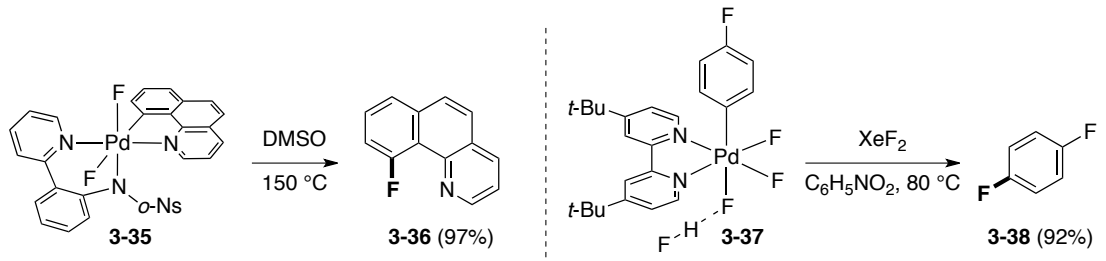
Scheme 3.9. Copper-mediated Electrophilic Fluorination of Organoboron Reagents.

Fluorination of aromatic compounds involving aryl palladium species was extensively studied by Ritter group. A step-wise procedure for palladium-mediated fluorination of boronic acids was developed first (Scheme 3.10).[31] It was shown, that transmetallation of aryl boronic acids **3-26** with palladium acetate complex **3-33** led to the formation of a stable aryl palladium complexes **3-34**. Subsequent treatment of the latter with Selectfluor (**3-15**) afforded desired fluoroarenes **3-01** in good yields. Noteworthy, mild reaction conditions and fast reaction times make this strategy applicable for the synthesis of PET tracers, as for this purpose reaction time becomes the most crucial factor.



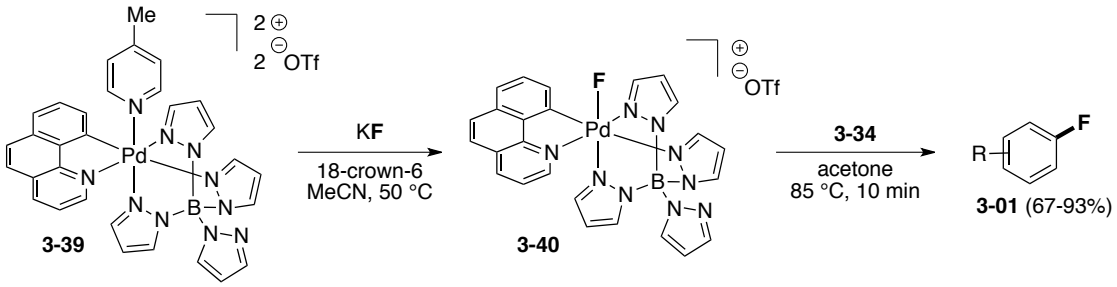
Scheme 3.10. Palladium-mediated Electrophilic Fluorination of Aryl Boronic Acids.

This process is also of a fundamental importance, hence, the reaction mechanism was investigated in detail (Scheme 3.11).[32] It was proposed, that the C–F bond forms via a key reductive elimination from Pd(IV) metal center. Indeed, related Pd(IV) complexes **3-35** and **3-37**, that possess both aryl and fluoride ligands, were successfully isolated. Under forcing conditions, these complexes released fluoroarenes **3-36** or **3-38**, thus, confirming feasibility of reductive elimination step.



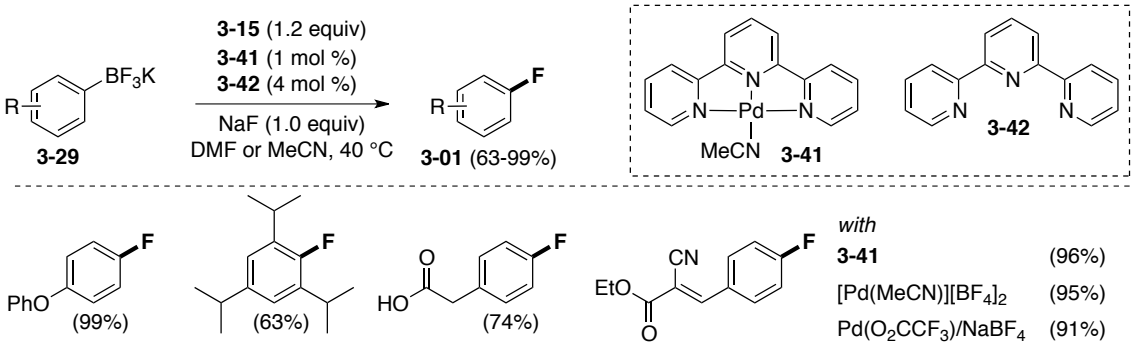
Scheme 3.11. Reductive Elimination from Palladium(IV) Center to Form C–F Bond.

Recently, Ritter group introduced a novel palladium-based electrophilic fluorinating reagent **3-40** (Scheme 3.12), which was prepared by treatment of palladium complex **3-39** with potassium fluoride.[33] Reaction of this compound with arylpalladium complex **3-34** (see Scheme 10) provides fast and efficient access to fluoroarenes. Single electron transfer (SET) mechanism was proposed for the transfer of fluoride from one palladium complex to the other.[33b]



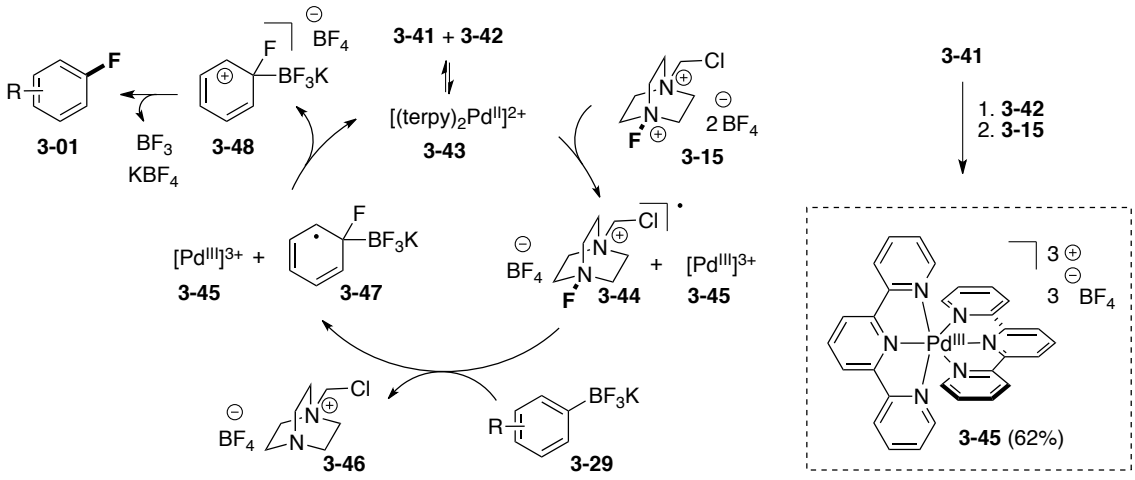
Scheme 3.12. Palladium-mediated Electrophilic Fluorination of with Pd-based Fluorinating Reagent.

The first transition metal-catalyzed fluorination of aryl trifluoroborates was also developed by Ritter and co-workers (Scheme 3.13).[34] With the aid of terpyridine palladium catalyst **3-41** and Selectfluor (**3-15**), fluoroarenes were synthesized with exceptional efficiency. Variety of substrates, including electron-rich or sterically hindered aryltrifluoroborates, reacted smoothly under these reaction conditions. In case of electron-deficient analogs, formation of small amounts of other regioisomers was observed. Notably, the reaction is equally efficient in the presence of other palladium catalysts, such as $[Pd(MeCN)][BF_4]_2$ or $Pd(O_2CCF_3)_2$.



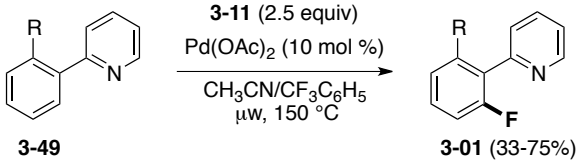
Scheme 3.13. Palladium-catalyzed Electrophilic Fluorination of Aryl Trifluoroborates.

As opposed to other transition metal-mediated or catalyzed processes (*vide supra*), SET-mechanism, which does not involve formation of aryl-palladium intermediates, was proposed for this catalytic system (Scheme 3.14). The reaction starts with the formation of bisterpyrydyl Pd-complex **3-43**, which, in the presence of Selectfluor (**3-15**), undergoes oxidation to form an unusual Pd(III) intermediate **3-45** and radical cation **3-44**. Next, fluorine radical transfer to trifluoroborate **3-29** generates radical species **3-47**, which upon subsequent oxidation with Pd(III) intermediate **3-45** delivers the corresponding cyclohexadienyl cation **3-48** and returns Pd(II) complex **3-43** to the catalytic cycle. Finally, elimination of BF_3 leads to the fluorinated product **3-01**. Indeed, a separately prepared well-defined Pd(III) complex **3-45** possesses catalytic activity in fluorination reaction of **3-29** in the presence of Selectfluor. On the other hand, further oxidation of **3-45** with Selectfluor to form Pd(IV) species was not observed.



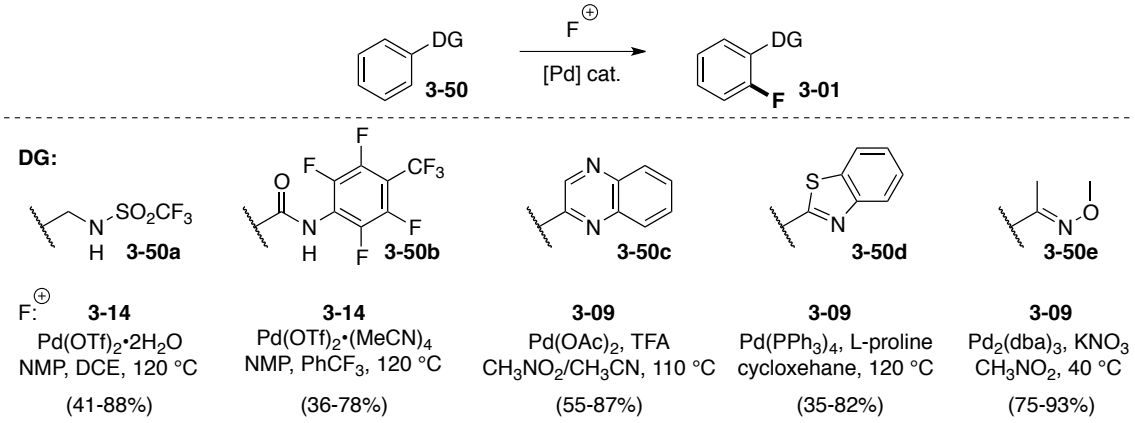
Scheme 3.14. Proposed Mechanism for Palladium-catalyzed Electrophilic Fluorination of Aryl Trifluoroborates.

Site selectivity of fluorination methods described above is controlled by the C–M bond preinstalled at the aromatic core. Another powerful strategy for selective functionalization of aromatic compounds is a directed C–H activation. The first example of directed Pd-catalyzed C–H fluorination was demonstrated by Sanford group in 2006 (Scheme 3.15).[35] They found, that employment of F-pyridine-BF_4 reagent (**3-11**) allows fluorination of 2-pyridylarenes **3-49** in good yields. Although this reaction exhibited poor selectivity for mono- versus bis-*ortho*-fluorination, it demonstrated feasibility of the Pd(II)-catalyzed electrophilic fluorination.



Scheme 3.15. Palladium-catalyzed Directed Electrophilic C–H Fluorination of 2-Pyridylarenes.

This seminal work has triggered development of several protocols for directed Pd-catalyzed *ortho*-fluorination (Scheme 3.16).[36,37]

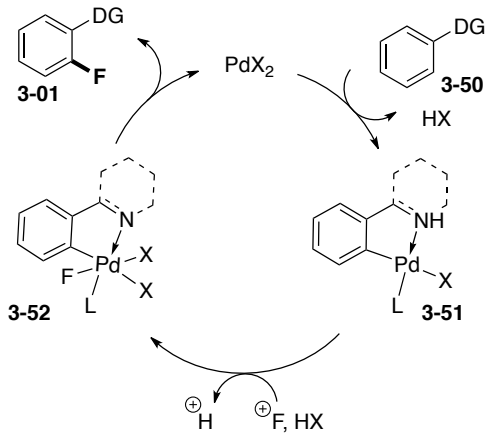


Scheme 3.16. Palladium-catalyzed Directed Electrophilic C–H Fluorination.

Accordingly, Yu group found that $Pd(OTf)_2$/NMP catalytic system is highly efficient for fluorination of benzyltriftamides **3-50a** and benzamides **3-50b** with F-TMP-BF_4 (**3-14**).[36a,b] Noteworthy, selective mono-fluorination can be achieved by employment of weakly-coordinating directing group as in **3-50b**. A number of *N*-heterocyclic directing groups, such as quinoxaline (**3-50c**) and benzothiazole

(**3-50d**), as well as pyrazole, benzoxazole, and pyrazine (not shown), were efficient in fluorination of aromatic C–H bonds using NFSI (**3-09**).[36c,d] Ultimately, a very mild procedure for Pd-catalyzed C–F bond formation directed by oxime ethers (**3-50e**) was developed.[36e]

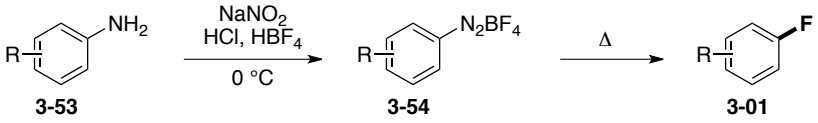
The mechanism of these transformation involves formation of aryl Pd(II) intermediate **3-51**, its oxidation with fluorinating reagent to Pd(IV) species **3-52**, and reductive elimination to form C–F bond (Scheme 3.17). Recent ESI-MS studies[36e] suggested that palladium is bound to two molecules of substrate (L = **3-50**) during the reaction.



Scheme 3.17. Proposed Mechanism for Palladium-catalyzed Directed Electrophilic C–H Fluorination.

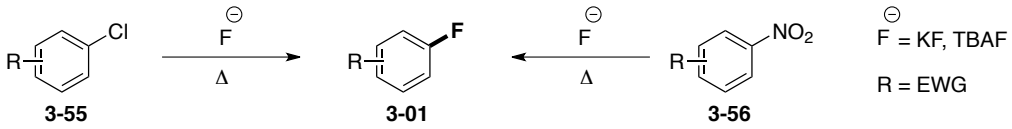
3.1.2. Fluorination of Aromatic Compounds with Nucleophilic Fluorinating Reagents

The Balz-Schiemann reaction, a thermal decomposition of aryl diazonium tetrafluoroborates **3-54**, is the classical method for synthesis of aromatic fluorides (Scheme 3.18).[38] However, several drawbacks, such as strongly acidic conditions required for the synthesis of aryl diazonium tetrafluoroborates, their limited stability, harsh conditions necessary for the decomposition step, and formation of byproducts, significantly limit applicability of this method. Nevertheless, recent development of procedures employing continuous flow systems allows highly efficient synthesis of aryl fluorides from anilines on a kilogram scale, though the scope of this transformation remains narrow.[38e,f]



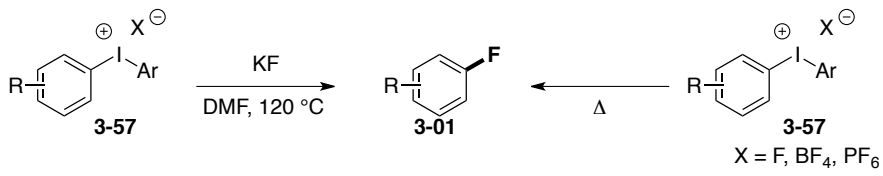
Scheme 3.18. Balz-Schiemann Fluorination.

Another traditional approach toward fluorobenzenes is nucleophilic aromatic substitution with potassium fluoride (Scheme 3.19).[39] Although used on industrial scale, displacement of both chloride (Halex process) and nitro-groups typically require harsh reaction conditions due to low solubility of potassium fluoride. Mild conditions for this transformation were developed by DiMagno group.[40] They have demonstrated that employment of anhydrous tetrabutylamonium fluoride (TBAF) in DMSO allows fluorination under ambient temperature delivering desired products in excellent yields. However, at least one electron-withdrawing substituent on the aromatic ring is required for a facile nucleophilic displacement of this type.



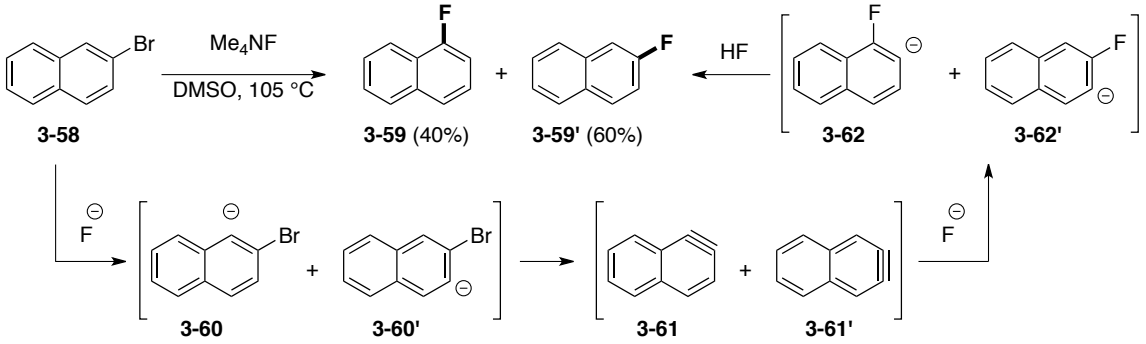
Scheme 3.19. Nucleophilic Aromatic Substitution toward Fluoroarenes.

Fluoroarenes can be also obtained by decomposition of biarylidonium salts in the presence of potassium fluoride [41] or by thermal decomposition of iodonium salts bearing fluorine-containing counterion (Scheme 3.20).[42] Fluorination of symmetrical iodonium salts provides fluorobenzenes in modest yields, whereas reactions of unsymmetricaly-substituted substrates often suffer from poor selectivity. Nonetheless, selective aryl transfer was demonstrated when iodonium reagents bearing 2-thienyl group (Ar = 2-thienyl) were employed in this transformation.[41b]



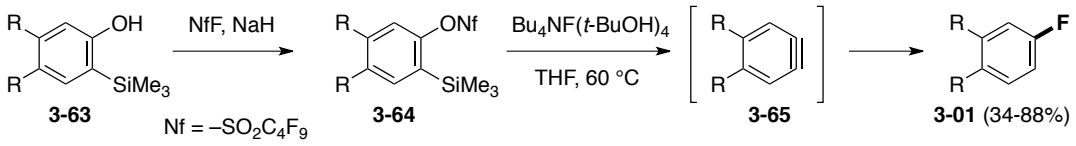
Scheme 3.20. Fluorination of Iodonium Salts.

In 2008, Grushin group reported, that treatment of aryl bromides with tetramethylammonium fluoride led to the formation of isomeric fluorinated products.[43] For instance, under these reaction conditions 2-bromonaphthalene (**3-58**) was converted to a mixture of 1-(**3-59**)- and 2-(**3-59'**)-fluoronaphthalenes in a 2:3 ratio (Scheme 3.21). It was suggested, that this reaction proceeds through the intermediacy of isomeric benzynes **3-61** and **3-61'**, which formed upon deprotonation and subsequent bromide elimination. Nucleophilic addition of fluoride followed by protonation furnished fluorinated products.



Scheme 3.21. Nucleophilic Fluorination of Aryl Bromides via Formation of Benzyne Intermediates.

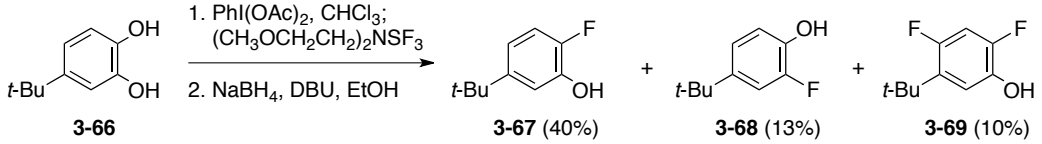
The strategy for nucleophilic fluorination of benzyne was later applied for the synthesis of various disubstituted fluoroarenes from corresponding *ortho*-silyl-arylnonaflates **3-64** (Scheme 3.22).[43b] Formation of benzyne was realized via silicon abstraction by fluoride anion and a subsequent elimination of the nonaflate leaving group. One-pot nonaflylation/fluorination procedure of *ortho*-silylphenols **3-63** was also developed.



Scheme 3.22. Nucleophilic Fluorination of *ortho*-Silylphenols.

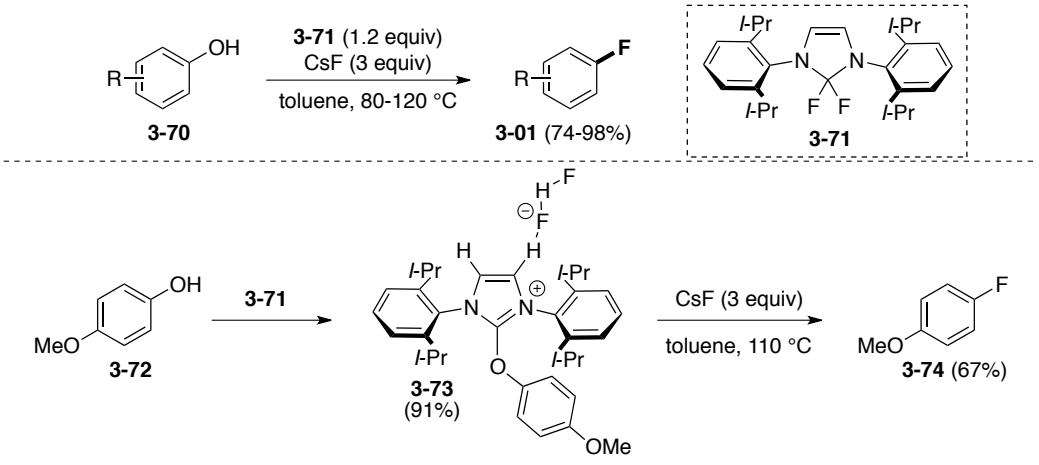
Fluorination of catechols was achieved via sequence of oxidation, deoxyfluorination with $(CH_3OCH_2CH_2)_2NSF_3$ (Deoxo-Fluor), and reduction (Scheme 3.23).[44] However, the regioselectivity of

this transformation is hard to control. For example, fluorination of 4-(*tert*-butyl)catechol (**3-66**) afforded a mixture of three products favoring fluorinated derivative **3-67**.



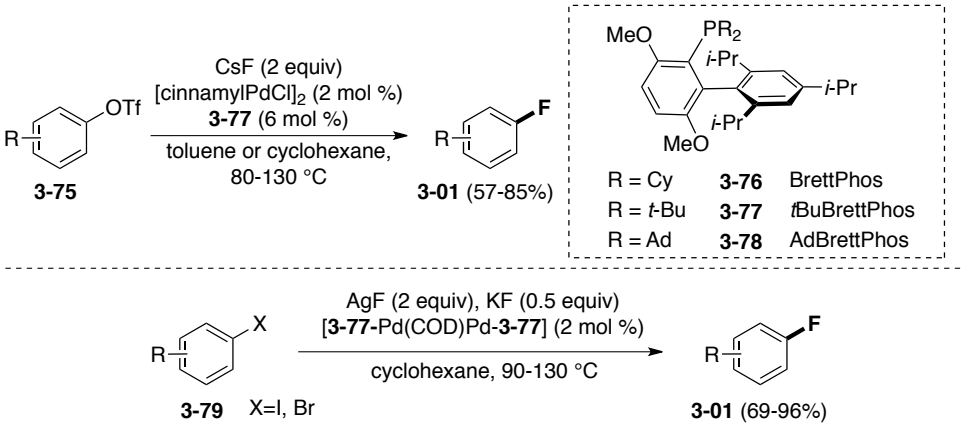
Scheme 3.23. Fluorination of Catechols with Deoxo-Fluor.

A straightforward fluorination strategy based on *ipso*-substitution of phenols was developed by Ritter group.[45] It was shown that treatment of phenols with PhenoFluor (**3-71**) and cesium fluoride afforded the corresponding aryl fluorides in high yields (Scheme 3.24). This methodology is general for a wide range of electron-rich, as well as electron-deficient substrates, and tolerates a variety of functional groups with exception to hydrogen bond donors, such as alcohols or amides. Reaction of phenol **3-72** with PhenoFluor in the absence of CsF resulted in the formation of intermediate **3-73**, in which $[HF_2]^-$ anion is coordinated to the imidazolium heterocycle through a hydrogen bonding. Subsequent reaction of **3-73** with cesium fluoride delivered the product **3-74**. Notably, hydrogen bonding between protons of imidazolium and fluoride is essential for efficient substitution, as PhenoFluor analogs, that lack the opportunity for similar hydrogen bonding, e.g. 4,5-dichloroimidazolium or saturated dihydroimidazolium congeners, were not efficient in this transformation.



Scheme 3.24. Nucleophilic Deoxyfluorination of Phenols with PhenoFluor.

Several transition metal-mediated methodologies based on palladium, nickel, and copper complexes, were recently developed. Thus, Buchwald group reported the first example of transition metal-catalyzed nucleophilic fluorination of aryl triflates (Scheme 3.25).[46] The main challenge associated with nucleophilic fluorination by Pd(0) is the reductive elimination step. As it was previously discussed, reductive elimination from ArPd(IV)F intermediates leads to the facile formation of desired C–F bond. However, analogous reductive elimination from ArPd(II)F complexes proved to be restricted due to the formation of stable fluoride-bridged dimers $[ArPd(\mu\text{-}F)]_2$ and competing formation of P–F bonds with the phosphine ligands.[47] Both of these issues were addressed by introducing extremely sterically bulky ligand BrettPhos (**3-76**). Steric bulk around the metal center, posed by this ligand, facilitates reductive elimination from ArPd(II)F as it has been demonstrated in a stoichiometric experiment.[46a]

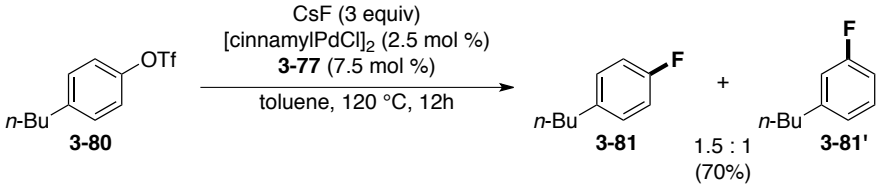


Scheme 3.25. Synthesis of Aryl Fluorides via Palladium(0)-catalyzed Nucleophilic Fluorination.

The developed method tolerates various functional groups and is efficient for a variety of substrates, including sterically demanding *ortho*-substituted aryltriflates. In order to further improve efficiency of this methodology, CsF packed-bed flow reactor was designed. Performing this reaction in flow eliminated the difficulties related to low solubility of cesium fluoride and shortened reaction times from 12 h to 20 min.[46b] Moreover, more efficient catalytic system was developed by replacement of $[cynnamylPdCl]_2$ with well-defined $[(t\text{-BuBrettPhos-Pd})_2(COD)]$ precatalyst, which excluded the possibility of competing C–Cl bond formation observed with the former catalyst.[46c] Furthermore,

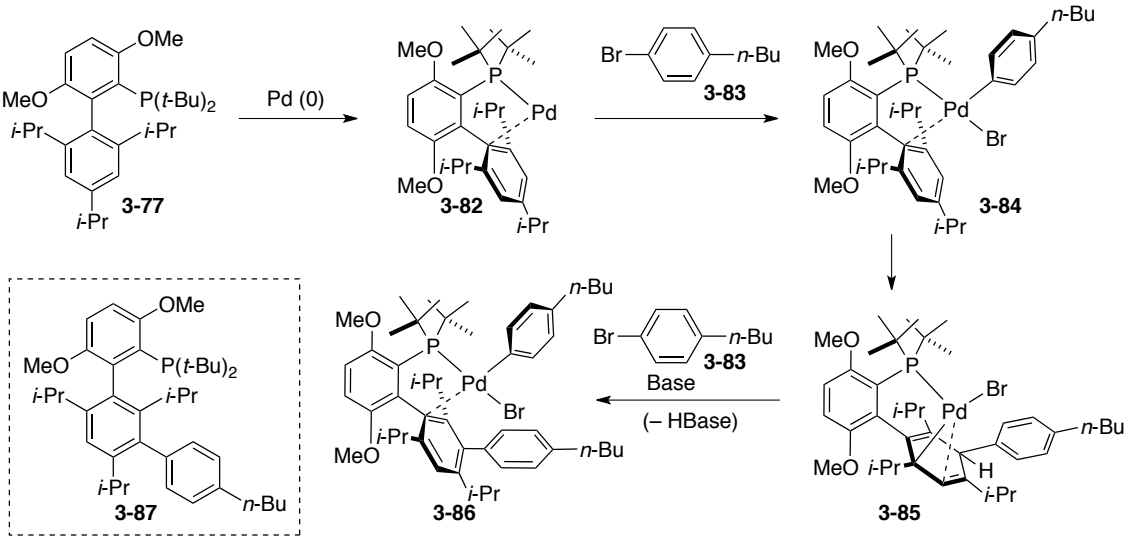
employment of this precatalyst, together with halophilic fluoride source AgF and basic promoter KF, allowed an efficient fluorination of aryl bromides and aryl iodides **3-79**.[48]

Surprisingly, fluorination of *para*-substituted electron-rich substrates often produces mixtures of *para*- and *meta*-fluoroarenes (Scheme 3.26). For example, reaction of *p*-butylphenyltriflate (**3-80**) afforded the mixture of *para*- (**3-81**) and *meta*- (**3-81'**) isomers in a 1.5:1 ratio. Diminished selectivity sometimes observed for *meta*-substituted substrates also. Notably, formation of unexpected isomer can be decreased by changing reaction solvent to cyclohexene.



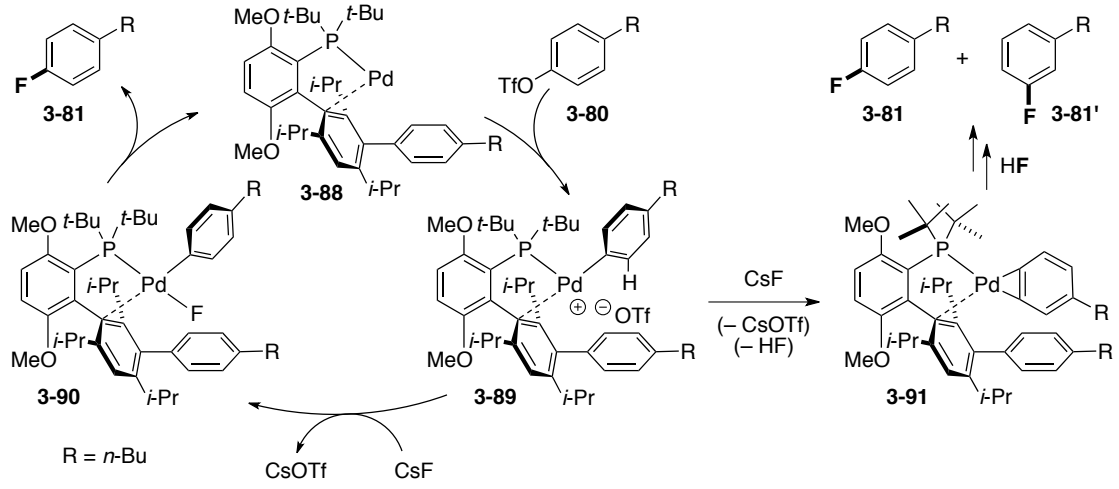
Scheme 3.26. Palladium(0)-catalyzed Nucleophilic Fluorination of *para*-Substituted Aryl Triflate.

The unusual behavior of these substrates elicited extensive mechanistic investigations, which provide more insides on this transformation.[49] It was found that ligand **3-77** was not an actual supporting ligand in a key C–F bond forming process (Scheme 3.27). Thus, the initial product of oxidative addition of Pd(0) complex **3-82** into C–Br bond of aryl bromide **3-83**, aryl Pd(II) intermediate **3-84**, isomerizes to the stable Pd(II) complex **3-85** bearing dearomatized ligand. Treatment of this complex with aryl bromide under basic conditions afforded new Pd(II) complex **3-86**, indicating that Pd(0) could be restored by rearomatization of **3-85** in the presence of a base. No further arylation of the ligand was observed. Notably, modified ligand **3-87** was isolated from the catalytic fluorination reaction. Therefore, it is concluded, that reductive elimination to form C–F bond is more facile if the metal center is supported by ligands similar to **3-87** as opposed to the original ligand **3-77**. In fact, phosphine **3-87** is the only ligand, which promotes fluorination of heteroaryl bromides.



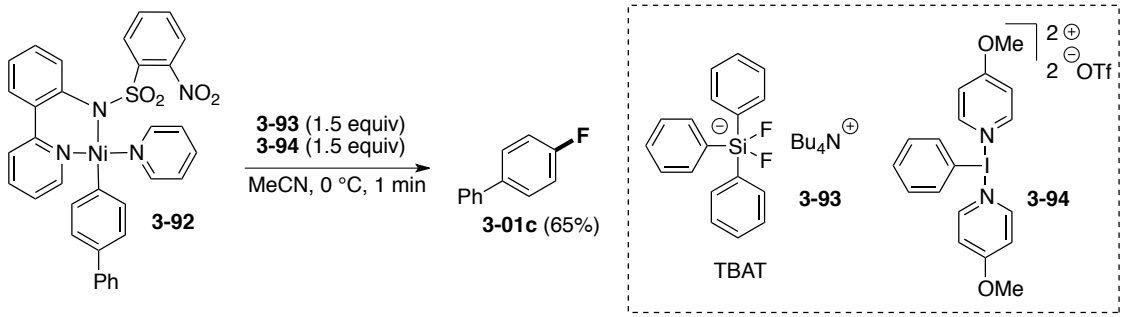
Scheme 3.27. Ligand Modification in Palladium(0)-catalyzed Nucleophilic Fluorination.

Overall, mechanistic cycle of the Pd(0)-catalyzed fluorination is initiated by the formation of Pd(0) species **3-88**, followed by oxidative addition of aryl (pseudo)halide leading to **3-89**. Subsequent transmetallation with CsF (or AgF) to form **3-90** and reductive elimination deliver final aryl fluoride and return palladium to its resting state (**3-88**). Observed formation of regioisomeric products in case of *para*-subatituted substrates is attributed to the competing *ortho*-deprotonation of **3-89** with cesium fluoride to form Pd-benzyne intermediate **3-91**.[49b] Upon reaction with HF, **3-91** forms two isomeric L·Pd(Ar)F complexes leading to regioisomeric arylfluorides **3-81** and **3-81'** after subsequent reductive elimination.



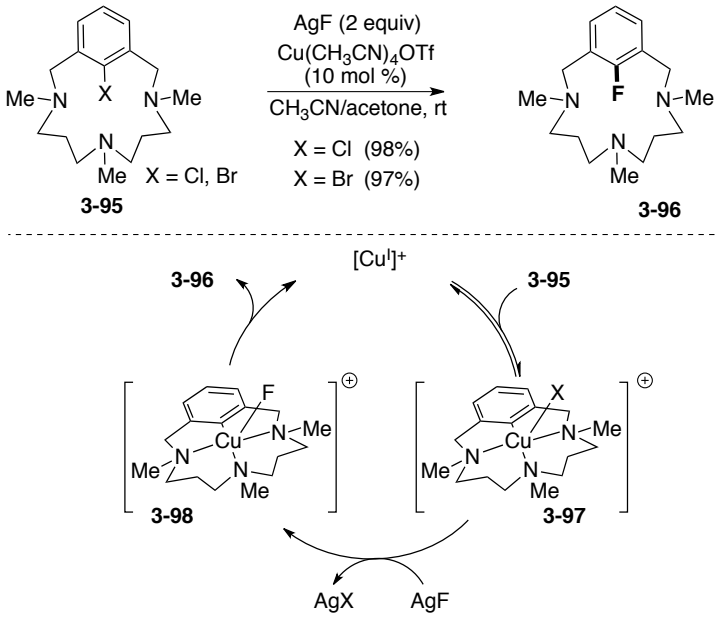
Scheme 3.28. Mechanistic Rationale for Palladium(0)-catalyzed Nucleophilic Fluorination.

A facile formation of aryl fluoride was observed upon treatment of Ni-complex **3-92** with TBAT (**3-93**) and iodonium oxidant **3-94** (Scheme 3.29).[50] Remarkably, this reaction was completed within one minute, which makes it suitable for the synthesis of PET tracers. Indeed, fluorination of various nickel-based analogs of **3-92** with [^{18}F]fluoride delivered desired ^{18}F-aryl fluorides with good radiochemical yields. The necessary nickel complexes are stable to air or moisture and can be synthesized from aryl bromides via a two-step procedure.



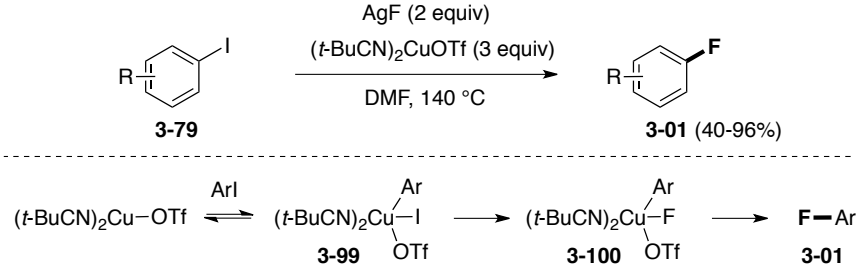
Scheme 3.29. Nickel-mediated Fluorination of Aromatic Compounds.

The feasibility of copper-mediated fluorination reaction using nucleophilic fluorine sources[51] was first observed in halogen exchange reaction of macrocyclic tris(amine) substrate **3-95** using silver fluoride (Scheme 3.30).[52] It was established, that Cu-catalyst undergoes reversible oxidative addition to the carbon-halogen bond (X = Cl, Br) of **3-95** to form Cu(III) intermediate **3-97**. Subsequent salt metathesis with AgF leads to Cu–F intermediate **3-98**, which upon reductive elimination gives the final product. Importantly, reductive elimination to form C–F bond from Cu(III) center is a facile process as intermediate **3-98** was not detected, and only formation of final product **3-96** was observed.



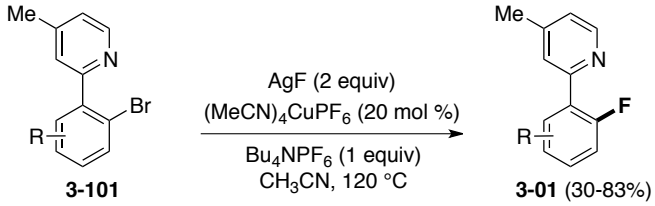
Scheme 3.30. Copper-catalyzed Fluorination of Aromatic Ring in Macrocyclic System.

Building on this strategy, Hartwig group reported copper-mediated iodine/fluorine exchange in aryl iodides with silver fluoride (Scheme 3.31).[53] They found that easily available (*t*-BuCN)$_2$CuOTf is suitable promoter for this transformation. The reaction is general for a variety of aryl iodides of different electronic nature, as well as for sterically hindered substrates. Mechanistically, this process is similar to that described above, involving oxidative addition, ligand exchange, and reductive elimination steps. Alternative pathway, in which ligand exchange occurs prior to the oxidative addition, was ruled out due to the low stability of Cu(I) fluorides.



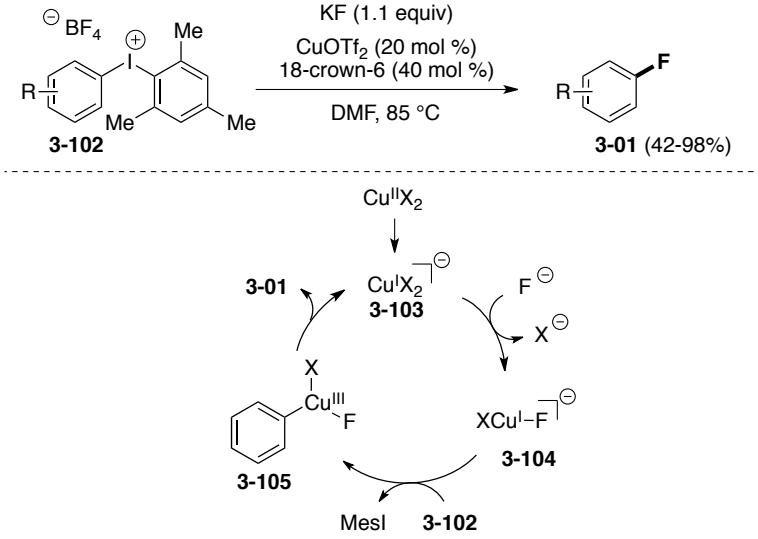
Scheme 3.31. Copper-mediated Fluorination of Aryl Iodides.

Similar catalytic reaction was developed for *ortho*-pyridyl-substituted aryl bromides **3-101** (Scheme 3.32).[54] In this case, pyridyl group facilitates oxidative addition step and provides additional stabilization of intermediates throughout the catalytic cycle.



Scheme 3.32. Copper-catalyzed Fluorination of 2-Pyrydyl-substituted Aryl Bromides.

Unsymmetrical aryl(mesityl)-iodonium salts were also shown to be suitable substrates for nucleophilic copper-catalyzed fluorination (Scheme 3.33).[55] Employment of copper catalyst was essential for high selectivity of fluoride transfer to the less hindered aryl group. Thus, in the presence of copper, formation of mesitylfluoride by-product is minimized whereas its predominant formation observed for a Cu-free fluorination. Notably, this reaction tolerates a wide range of functional groups, including halogen substituents, such as Br and Cl.

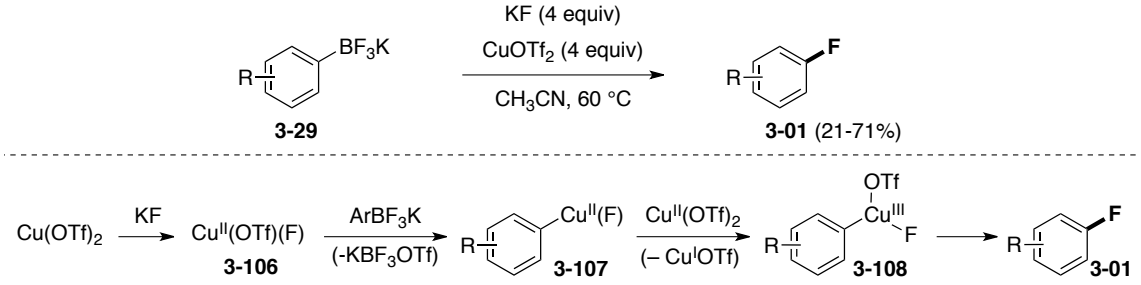


Scheme 3.33. Copper-catalyzed Fluorination of Aryl Iodonium Salts.

From the mechanistic standpoint, reaction starts with disproportionation of Cu(II) triflate to form Cu(I) species **3-103**. As suggested by computational studies, halogen exchange of this intermediate with

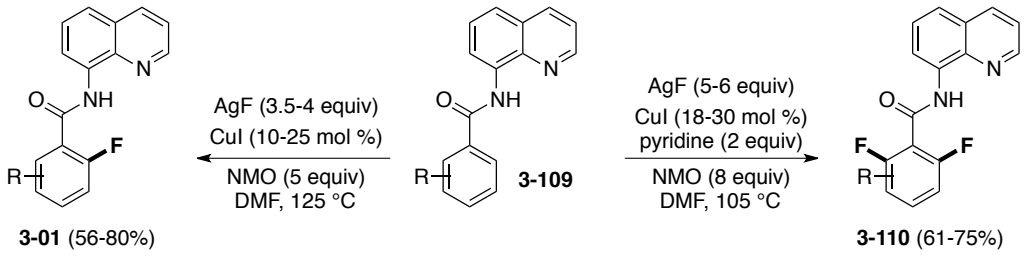
fluoride anion leads to the formation of Cu(III) intermediate **3-104** prior to the oxidative addition to the C–I bond of **3-102** to afford aryl Cu(III) fluoride **3-105**. Subsequent reductive elimination completes the catalytic cycle.

Oxidative copper-mediated fluorination of aryl trifluoroborates with potassium fluoride was established by Sanford group (Scheme 3.34).[56] The reaction is efficient for a number of electron-rich or electron-deficient substrates, only excluding halogen-containing starting materials. Interestingly, $Cu(OTf)_2$ plays a dual role in this transformation; it promotes the C–F bond formation, and oxidizes ArCu(II)F intermediate **3-107** into ArCu(III)F **3-108** species, thus facilitating reductive elimination. Notably, a ligand exchange between copper triflate and potassium fluoride prior to transmetallation with aryltrifluoroborate was proposed in this case. Recently, Gouverneur group[56] developed the copper-mediated nucleophilic ^{18}F-fluorination of aryl boronic esters using similar strategy.



Scheme 3.34. Copper-mediated Fluorination of Aryl Trifluorobrates.

Direct conversion of aryl C–H bond to C–F bond was achieved by Daugulis group via the copper-catalyzed directed fluorination reaction employing 8-aminoquinoline axillary (Scheme 3.35).[57] Thus, fluorine atom was introduced at the *ortho*-position of benzoic acid derivative using silver fluoride in the presence of Cu-catalyst and an external oxidant. Mono- or difluorination can conveniently be controlled by choosing appropriate reaction conditions. It was also shown, that the directing group can efficiently be removed upon basic hydrolysis to liberate fluorinated benzoic acids.

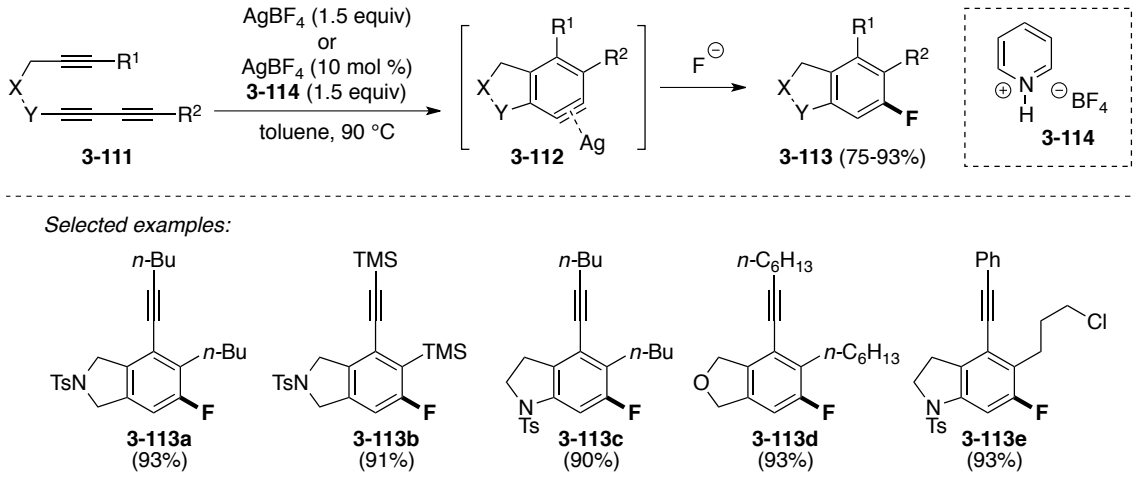


Scheme 3.35. Directed Copper-catalyzed Fluorination of Benzoic Acid Derivatives.

3.1.3. Synthesis of Fluoroarenes via Benzannulation Methods

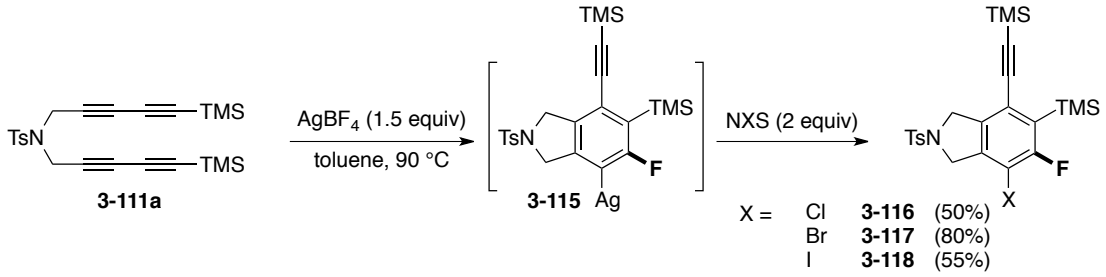
Compared to various methods for fluorination of preexisting aromatic cores emerging in recent years (*vide supra*), the synthesis of fluoroarenes starting from linear non-aromatic precursors received much less attention.

An efficient strategy for the synthesis of fluorinated aromatic compound from bis-1,3-diynes was developed by Lee group (Scheme 3.36).[58] They have demonstrated regioselective addition of fluoride anion onto aryne intermediates **3-112**, formed upon silver-mediated hexadehydro-Diels-Alder reaction of bis-1,3-diynes **3-111**.[59,60] Silver-catalyzed protocol employing pyridinium tetrafluorobarate (**3-114**) as a fluoride source was equally facile. This approach provides quick access to densely substituted fluorinated indolines, isoindolines, and dihydroisobenzofurans.



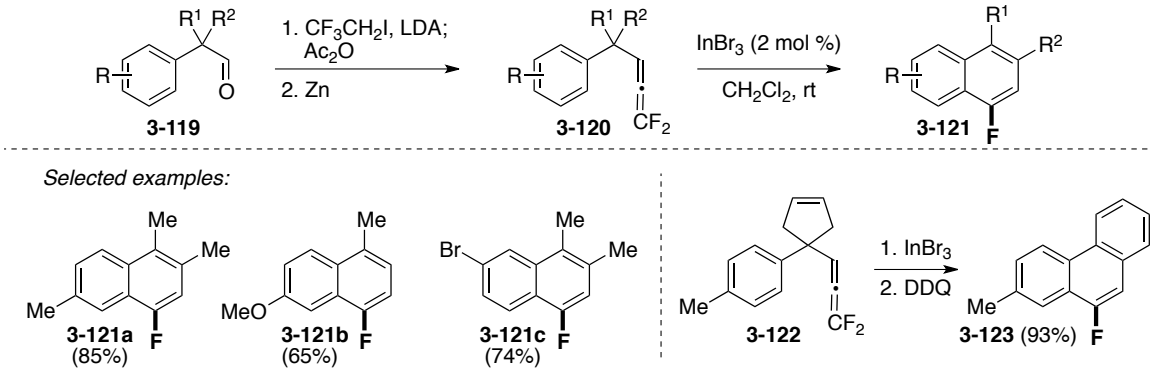
Scheme 3.36. Synthesis of Fluoroarenes via Tandem Hexadehydro-Diels-Alder Reaction/Fluorination Sequence.

Moreover, dihalogenated aromatic core can be constructed using this strategy (Scheme 3.37). Thus, aryl silver intermediate **3-115**, produced upon fluorination of aryne, in the presence of electrophilic halogenating reagents, can be converted to the corresponding *ortho*-halo-fluoroarenes **3-116** – **3-118** in good to high yields.



Scheme 3.37. Synthesis of Halofluoroarenes via HDDA/Fluorination/Halogenation Sequence.

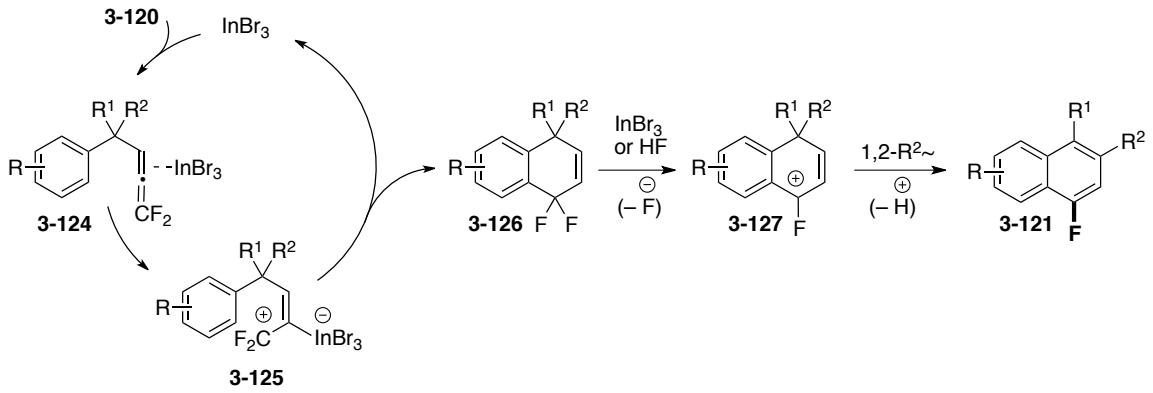
Intramolecular cyclization of fluorine-containing substrates to form fluorinated aromatic core was also demonstrated. Thus, benzylic difluoroallenes **3-120** were converted to the corresponding fluoronaphthalenes **3-121** via indium catalyzed cyclization reaction (Scheme 3.38).[61] Analogously, fluorinated phenanthrenes (e.g. **3-123**) were synthesized via sequential cyclization, ring expansion, and *in situ* oxidation of cyclopentene-containing substrates, such as **3-122**. Notably, starting 1,1-difluoroallenes **3-120** are easily available from corresponding aldehydes **3-119** and 2-iodo-1,1,1-trifluoroethane.



Scheme 3.38. Synthesis of Fluoronaphthalenes via Indium-catalyzed Intramolecular Cyclization of Difluoroallenes.

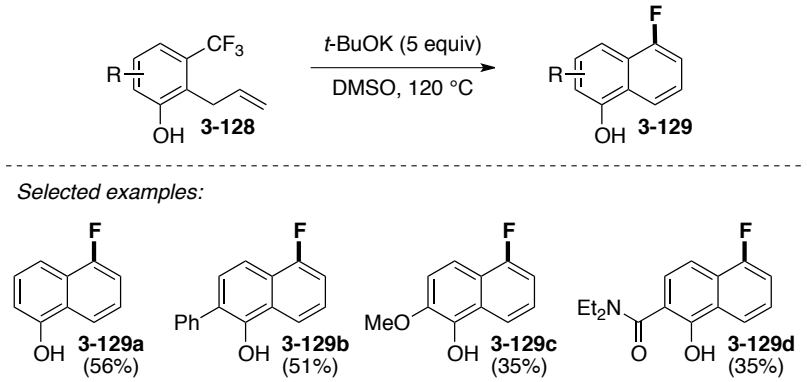
Mechanistically, this transformation involves formation of allylic difluorocarbocation **3-125**, promoted by indium catalyst upon coordination to the allenic moiety of **3-120** (Scheme 3.39). A

subsequent Fridel-Crafts-type cyclization and protonation of C–In bond affords intermediate **3-126**. Elimination of fluorine to form another cationic intermediate **3-127**, followed by an 1,2-alkyl group migration and deprotonation, delivers the final product **3-121**.



Scheme 3.39. Mechanism of Indium-catalyzed Cyclization of Difluoroallenes.

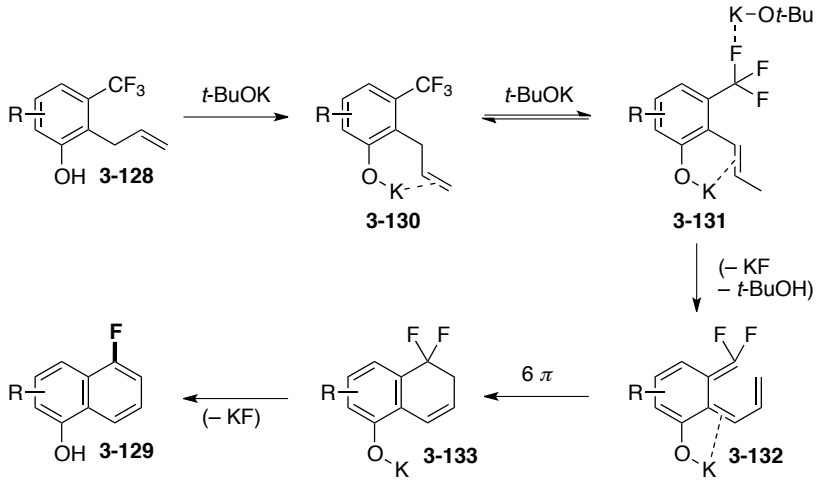
Another example of intramolecular cyclization of fluorinated precursors *en route* to fluoroarenes was recently reported by Magauer group.[62] They have developed a base mediated cyclization of 2-allyl-3-(trifluoromethyl)phenols leading to the formation of fluorinated naphthols in moderate yields (Scheme 3.40).



Scheme 3.40. Base-mediated Cyclization toward Fluorinated Naphthols.

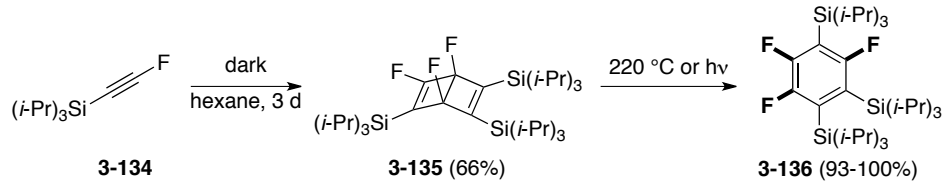
This transformation relies on sequential activation of two C–F bonds (Scheme 3.41). Accordingly, a base mediated isomerization of allyl moiety in **3-130** and an abstraction of fluorine atom from trifluoromethyl group of **3-131** results in the formation of triene intermediate **3-132**. A subsequent

6-π-electrocyclization and aromatization afford the desired fluorinated arene **3-129**. Notably, this reaction requires *ortho*-hyrdoxyl group to facilitate allylic isomerization event.



Scheme 3.41. Mechanism of Base-mediated Cyclization.

Lastly, a formal [2+2+2] cycloaddition of triisopropylsilylfluoroacetylene to form 1,2,4-trifluorobenzene was demonstrated.[63] Thus, alkyne **3-134** trimerizes to form stable Dewar benzene **3-135** under exclusion of light to prevent competing polymerization. Fluorinated Dewar benzene **3-135** can be selectively converted to fluorinated benzene **3-136** in excellent yields upon thermolysis or under UV-irradiation. However, this process is unique to the particular sterically hindered fluoroalkyne.[64]



Scheme 3.42. Synthesis of 1,2,4-Trifluorobenzene via Dewar Benzene Derived from TIPS-fluoroacetylene.

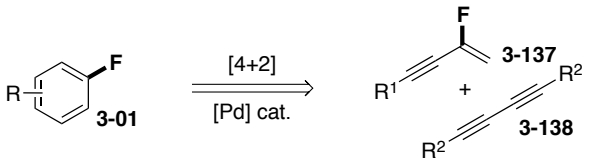
3.1.4. Summary and Outlook

In recent years, significant progress toward the synthesis of aryl fluorides has been achieved. Introduction of mild and efficient fluorinating reagents triggered the rapid growth in the area of electrophilic and nucleophilic fluorination of aromatic compounds. Additionally, merging organofluorine

chemistry with the transition metal catalysis resulted in the development of innovative strategies for the construction of carbon–fluorine bond. Consequently, various methods for installation of fluorine functionality onto broad range of aromatic substrates became available. Much less established strategy for the synthesis of aryl fluorides starting from non-aromatic precursors was proved to be efficient for several types of substrates. Therefore, the development of novel methodologies toward privileged fluoro-containing aromatic compounds from easily available acyclic precursors continues to be in high demand.

3.2. SYNTHESIS OF FLUORO- AND PERFLUOROALKYLARYL ALKYNES VIA PALLADIUM-CATALYZED [4+2] BENZANNULATION REACTION.

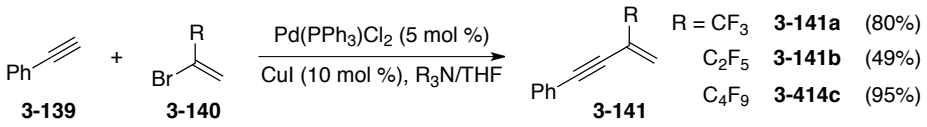
Cycloaddition methods serve as a powerful toolset for a rapid assembly of an aromatic core.[65] Although several examples are known for the introduction of perfluoroalkyl groups[66] to the benzene ring via [2+2+2] cycloaddition reaction of perfluoroalkylated alkynes,[67,68] to the best of our knowledge, a general strategy for construction of aryl fluorides via similar methods has not been previously described, presumably due to an explosive nature of required starting fluoroalkynes.[64,69] We envisioned that Pd-catalyzed [4+2] cross-benzannulation reaction between conjugated enynes and diynes (see Part II) might provide an alternative route for a facile synthesis of fluorinated benzene core (Scheme 3.43). In this case the fluorine atom could be introduced at the alkene moiety of an enyne coupling partner **3-137**, thus avoiding an employment of fluoroalkynes. Importantly, compared to the other vinyl halides, vinyl fluorides are less reactive toward the oxidative addition of low-valent transition metals,[70] which would allow the Pd(0)-catalyzed benzannulation process of fluoroenynes **3-137** to proceed without the defluorination reaction.



Scheme 3.43. Palladium-catalyzed [4+2] Benzannulation for the Synthesis of Aryl Fluorides.

3.2.1. Synthesis of Perfluoroalkyl-substituted Arylalkynes

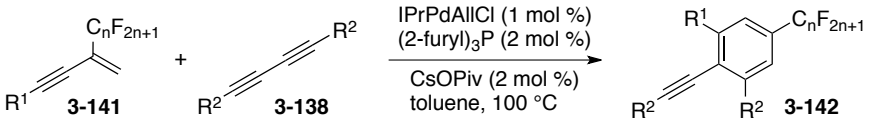
To test our benzannulation strategy toward fluoroarenes, the cycloaddition of perfluoroalkylenynes **3-141** was examined first. The required conjugated enynes **3-141** were easily prepared via the Sonogashira cross-coupling reaction of perfluoroalkyl-containing vinyl bromides **3-140** with terminal alkynes (Scheme 3.44). For example, 3-trifluoromethyl-1-phenylenyne **3-141a** was prepared from commercially available 2-bromo-3,3,3-trifluoropropene **3-140a** and phenylacetylene in 80% yield. Analogously, enynes possessing substituents with longer perfluoroalkyl chains (**4-141b**, **3-141c**) can routinely be obtained using this method.

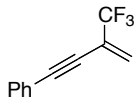
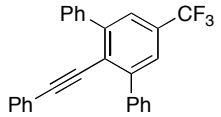
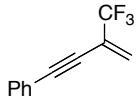
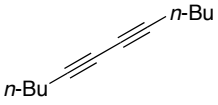
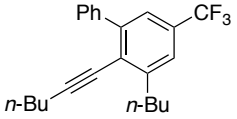
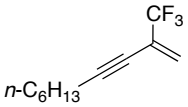
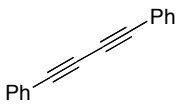
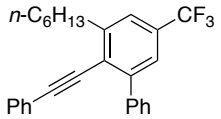
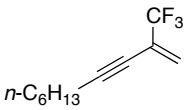
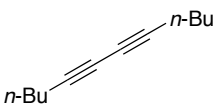
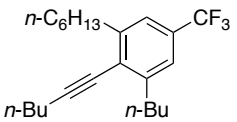
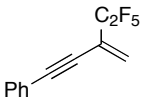
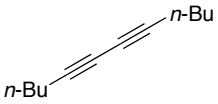
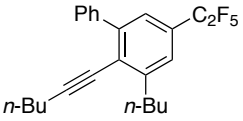
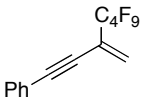
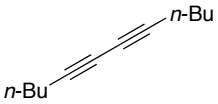
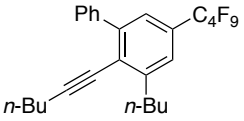


Scheme 3.44. Synthesis of 3-Perfluoroalkyl Enynes via Sonogashira cross-Coupling Reaction.

Having starting materials in hands, we first examined the reactivity of trifluoromethylenynes toward the benzannulation reaction with the aid of recently developed highly efficient catalytic system (see Part II). Gratifyingly, the cross-benzannulation reaction between enyne **3-141a** and diphenyldiyne **3-138a**, in the presence of 1 mol % of a Pd-catalyst, afforded the desired trifluoromethyl-containing arene **3-142aa** in 84% yield in a highly regio- and chemoselective manner (Table 3.2, entry 1). Analogously, reaction between enyne **3-141a** and dialkylsubstituted diyne **3-138b** proceeded with good efficiency (entry 2). Employment of alkyl substituted enyne **3-141d** afforded the corresponding trifluoromethylarene **3-142da** in high yield (entry 3). However, 3,5-dialkyl substituted trifluoromethylarene **3-142db** was obtained in 72% yield along with 15% of the homo-benzannulation product of **3-141d** (entry 4). Presumably, the high reactivity of enyne **3-141d** and the low reactivity of diyne **3-138b** both accounted for this result. Similarly to trifluoromethylarenes, arylalkynes bearing a perfluoroalkyl chain can also be obtained with high efficiency via the benzannulation reaction of enynes **3-141b** and **3-141c** (entries 5, 6).

Table 3.2. Palladium-catalyzed [4+2] Benzannulation Reaction toward Perfluoroalkylbenzenes.[a]



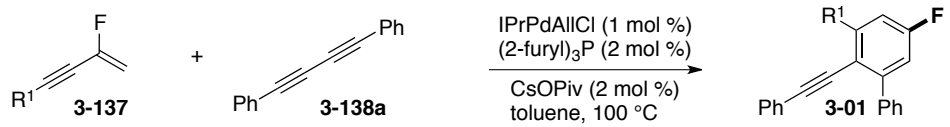
Entry	Enyne	Diyne	Product	Yield, %[b]
1	 **3-141a**	 **3-138a**	 **3-142aa**	84
2	 **3-141a**	 **3-138b**	 **3-142ab**	76
3	 **3-141d**	 **3-138a**	 **3-142da**	89
4	 **3-141d**	 **3-138b**	 **3-142db**	72
5	 **3-141b**	 **3-138b**	 **3-142bb**	77
6	 **3-141c**	 **3-138b**	 **3-142cb**	87

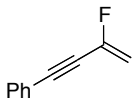
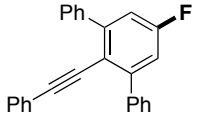
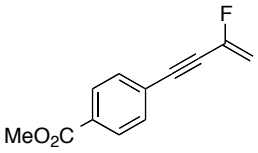
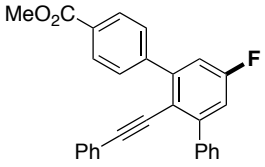
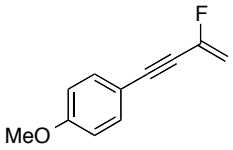
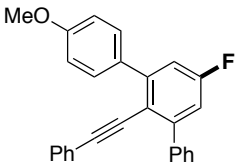
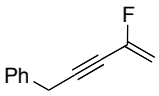
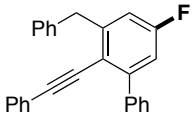
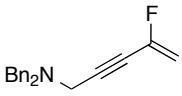
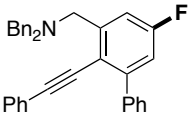
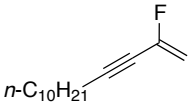
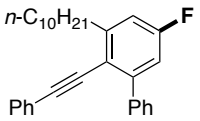
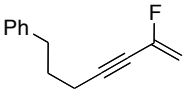
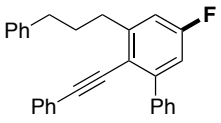
[a]Reaction conditions: **3-141** (0.6 mmol), **3-138** (0.5 mmol), IPrPdAllCl (1 mol %), (2-furyl)$_3$P (2 mol %), CsOPiv (2 mol %), toluene (1 M), 100 °C, 16–24 h. [b]Isolated yields, %.

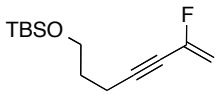
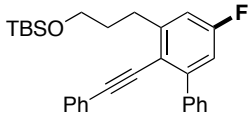
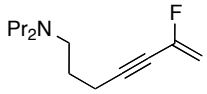
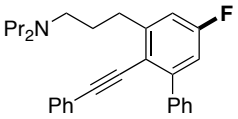
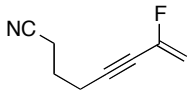
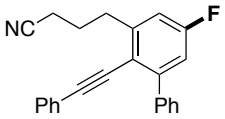
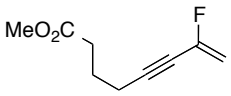
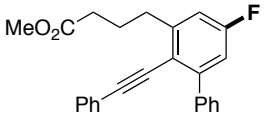
3.2.2. Synthesis of Fluoroarylalkynes

Encouraged by these results, we turned our attention to the synthesis of aryl fluorides via the benzannulation of fluoro-containing enynes **3-137**, which were prepared by Sonogashira coupling of various alkynes with 1-bromo-1-fluoroethylene. To our delight, 3-fluoro-1-phenylenyne **3-137a** underwent a facile benzannulation reaction with diphenyldiyne **3-138a**, thus giving access to *p*-alkynylaryl fluoride **3-01aa** in 85% yield (Table 2, entry 1). Likewise, fluoroenyne **3-137b** provided the cross-benzannulation product **3-01ba** in good yield (entry 2). As expected, enyne **3-137c** bearing an electron-donating group delivered the corresponding fluoroarene with moderate efficiency (entry 3). Substrates **3-137d**, **3-137e** substituted at the propargylic position were smoothly converted to the corresponding fluoroarene derivatives (entries 4, 5). Similarly, alkyl substituted fluoroenynes were competent substrates for the benzannulation reaction (entries 6, 7). Differently substituted alkyl enynes possessing valuable functionalities, such as silyloxy (entry 8), amino (entries 5, 9), cyano (entry 10), and ester (entry 11) groups, were well tolerated under these reaction conditions.

Table 3.3. Scope of Enynes in Palladium-catalyzed [4+2] Benzannulation Reaction toward *para*-Fluoroarylalkynes.[a]

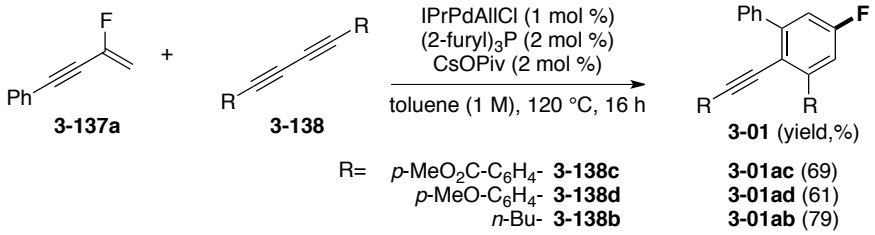


Entry	Enyne	Product	Time, h	Yield (%)[b]
1	 **3-137a**	 **3-01aa**	16	85
2	 **3-137b**	 **3-01ba**	16	78
3	 **3-137c**	 **3-01ca**	24	51
4	 **3-137d**	 **3-01da**	20	57
5	 **3-137e**	 **3-01ea**	16	84
6	 **3-137f**	 **3-01fa**	20	71
7	 **3-137g**	 **3-01ga**	20	86

Entry	Enyne	Product	Time, h	Yield (%)[b]
8	 **3-137h**	 **3-01ha**	20	83
9	 **3-137i**	 **3-01ia**	16	82
10	 **3-137j**	 **3-01ja**	24	60
11	 **3-137k**	 **3-01ka**	24	62

[a]Reaction conditions: **3-137** (0.6 mmol), **3-138a** (0.5 mmol), IPrPdAllCl (1 mol %), (2-furyl)$_3$P (2 mol %), CsOPiv (2 mol %), toluene (1 M), 120 °C, 16–24 h. [b]Isolated yields, %.

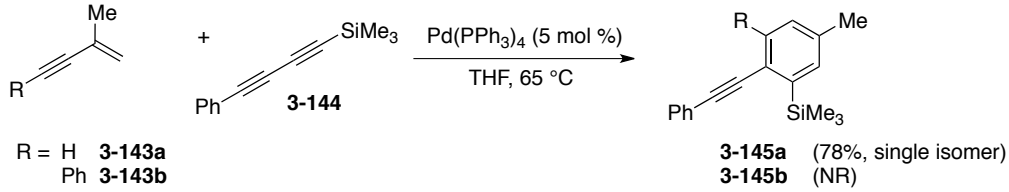
Next, the reactivity of different diynes in benzannulation with enyne **3-137a** was examined (Scheme 3.45). Thus, employment of either electron-deficient (**3-138c**) or electron-rich (**3-138d**) symmetrical diaryldiynes, led to the formation of fluorinated arenes in good yields. Likewise, dialkyl-substituted diyne (**3-138b**) smoothly underwent benzannulation reaction with enyne **3-137a**.



Scheme 3.45. Scope of Diynes in Palladium-catalyzed [4+2] Benzannulation Reaction toward *para*-Fluoroarylalkynes.

3.2.3. Development of Regioselective Palladium-catalyzed [4+2] Benzannulation Reaction

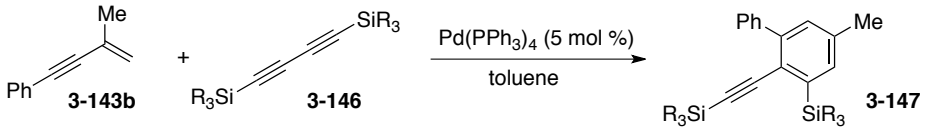
As discussed in section 2.1.3.2, palladium-catalyzed benzannulation reaction of unsymmetrically substituted substrates suffers from poor regioselectivity (see Table 2.1). Nonetheless, good regioselectivity was observed in the reaction between 3-methylenyne **3-143a** and 1-trimethylsilyl-4-phenyl-1,3-diyne (**3-144**) leading to the formation of single regioisomer **3-145a** in good yield (Scheme 3.46). Unfortunately, analogous reaction with less reactive disubstituted enyne **3-143b** did not proceed. We believe, that even though introduction of silyl group allows controlling regioselectivity of the Pd-catalyzed benzannulation reaction, it substantially decreases the reactivity of diynes toward this transformation. Additionally, benzannulation reaction of silyl-substituded compounds is restricted to the employment of neutral reaction conditions due to the low stability of starting diyne in the presence of a strong base required in more efficient catalytic conditions.



Scheme 3.46. Regioselective Palladium-catalyzed [4+2] Benzannulation of Silyldiyne.

We hypothesized that reactivity of silyldiynes might be improved by changing substitution at the silyl group. Therefore, benzannulation reaction of various symmetrical silyl-substituted diynes with enyne **3-143b** was tested (Table 3.4). Similarly to the unsymmetrical trimethylsilyldiyne **3-144**, bis(trimetylsilyl)diyne **3-146a** did not undergo benzannulation reaction (entry 1). Diynes, possessing smaller silyl groups, such as bis(dimethylsilyl)diyne (**3-146b**) or bis(dimethylfluorosilyl)diyne (**3-146c**), rapidly decomposed in the presence of palladium catalyst (entries 2, 3). Although the formation of desired product was observed employing bis(dimethylphenylsilyl)diyne (**3-146d**), this reaction was slow and did not proceed to the completion (entry 4). Gratifyingly, full conversion of starting materials was achieved in benzannulation reaction of enyne **3-143b** with bis(dimethylmethoxysilyl)diyne **3-146e** providing desired product in 67% yield (entry 5). We believe that methoxy group on silicon provides necessary balance between stability and reactivity of diyne due to favorable stereoelectronic nature of dimethylmethoxysilyl functionality.

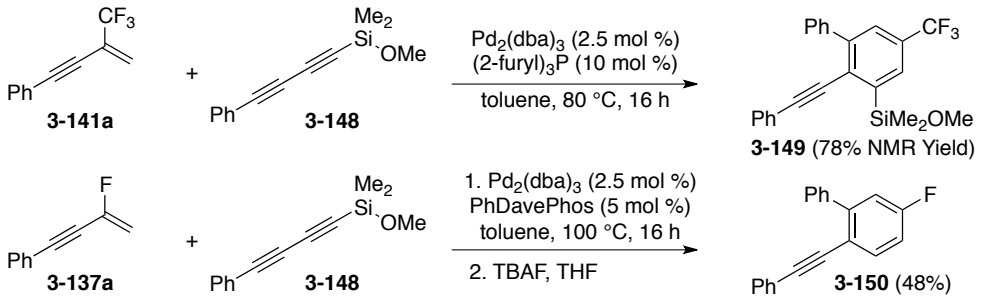
Table 3.4. Optimization of Silyl-substituted Diyne Coupling Partner in Palladium-catalyzed [4+2] Benzannulation Reaction.[a]



Entry	SiR_3		Results	Yield, %[b]
1	$SiMe_3$	**3-146a**	no reaction	–
2	$SiMe_2H$	**3-146b**	fast diyne decomposition	–
3	$SiMe_2F$	**3-146c**	fast diyne decomposition	–
4	$SiMe_2Ph$	**3-146d**	slow incomplete reaction	–
5	**$SiMe_2OMe$**	**3-146e**	**full conversion in 5 days**	**67**

[a]Reaction conditions: **3-143b** (1.2 equiv), **3-146** (1 equiv), $Pd(PPh_3)_4$ (5 mol %), toluene (1 M), 80-100 °C. [b]Isolated yield, %

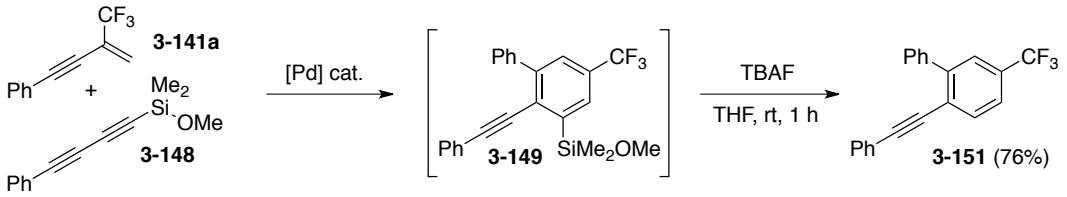
Encouraged by these results, we tested the reactivity of unsymmetrically substituted diyne **3-148**, possessing dimethylmetoxysilyl moiety. After slight optimization of the reaction conditions, we found, that silyldiyne **3-148** reacted with enyne **3-141a** to produce trifluoromethyarene **3-149** in 78% NMR yield with perfect regioselectivity (Scheme 3.47). Although hydrolytically unstable, product **5ac** possesses a valuable *ortho*-alkynyl arylsilyl ether functionality that can be further utilized in the synthesis of various aromatic scaffolds (*vide infra*). Similarly, 3-fluoroenyne **3-137a** underwent benzannulation reaction with unsymmetrically substituted silyldiyne **3-148**. In this case, the product was isolated as desilylated adduct **3-150** after treatment of the reaction mixture with TBAF in a one-pot fashion.



Scheme 3.47. Regioselective Palladium-catalyzed [4+2] Benzannulation of Trifluoromethyl- and Fluorine-containing Enynes with Unsymmetrical Diyne **3-148**.

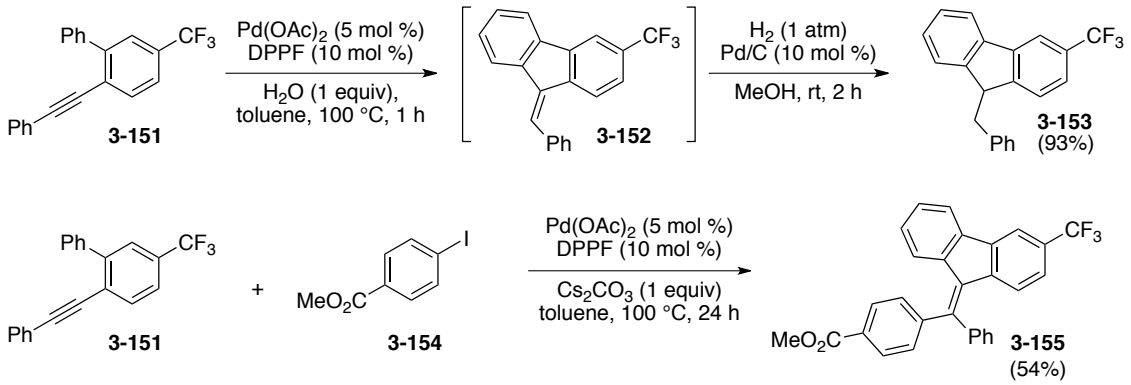
3.2.4. Synthetic Applications

Benzannulation strategy, which leads to alkynyl-containing arenes, offers a unique opportunity for accessing various aromatic and heteroaromatic scaffolds. It seems particularly attractive for the synthesis of molecules possessing a modifiable silyl group at the aromatic ring. Accordingly, we explored further transformations of trifluoromethyl-containing *o*-alkynylsilylether **3-149**. Given the hydrolytical instability of **3-149**, it was used as a crude material. *ortho*-Alkynylbiaryls are valuable substrates in the synthesis of polycyclic aromatic scaffolds. Thus, benzannulation product **3-149** was desilylated to afford the corresponding *o*-alkynylbiaryl **3-151** in 76% yield via a one-pot operation (Scheme 3.48).



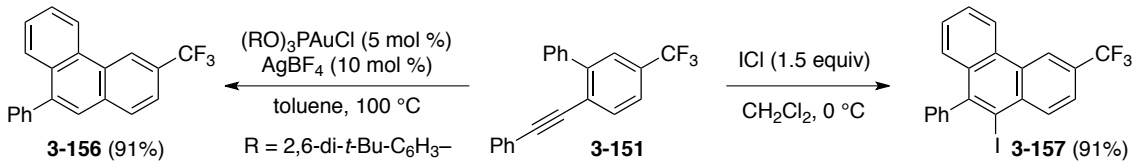
Scheme 3.48. Synthesis of *ortho*-Alkynyl Biaryl **3-151** via *One-pot* Palladium-catalyzed [4+2] Benzannulation/Desilylation Sequence.

Obtained *o*-alkynylbiaryl **3-151** underwent smooth Pd-catalyzed 5-*exo*-dig cyclization[71] followed by hydrogenation to form the corresponding trifluoromethyl-containing fluorene **3-153** (Scheme 3.49). Alternatively, arylative 5-*exo*-dig cyclization[71b] of **3-151** afforded unsymmetrically substituted fluorene **3-155** as a single stereoisomer.



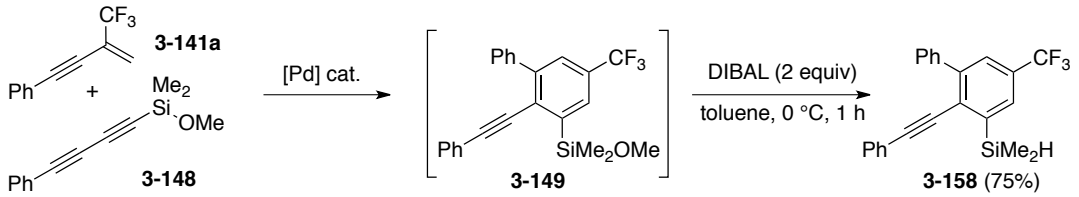
Scheme 3.49. Synthesis of Perfluoroalkyl-containing Fluorenes via Palladium-catalyzed 5-*exo-dig* Cyclization.

Furthermore, electrophilic 6-*endo*-dig cyclization[72] of *o*-alkynylbiaryl **3-151** under gold catalysis delivered the CF_3-containing phenanthrene **3-156** in excellent yield (Scheme 3.50). Iodo-containing phenanthrene **3-157** was efficiently assembled from **3-151** via an ICl-induced 6-*endo*-dig cyclization.[73]



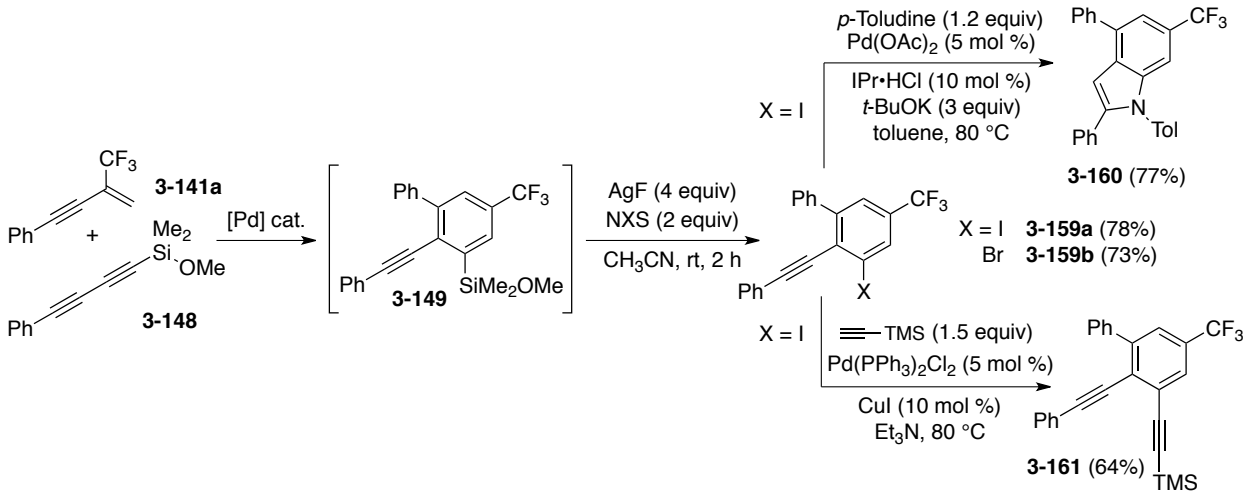
Scheme 3.50. Synthesis of Perfluoroalkyl-containing Phenanthrenes via Electrophilic 6-*endo-dig* Cyclization.

Naturally, we were interested in exploring the advantages provided by the silyl group located at the *ortho*-position to the triple bond. Thus, reduction of the silyl ether group with DIBAL provided access to hydrosilane **3-158** in 75% yield over a two-steps sequence (Scheme 3.51). This compound represents not only a hydrolytically stable analog of **3-149**, but it is also a potential substrate for the synthesis of benzosilols.[74]



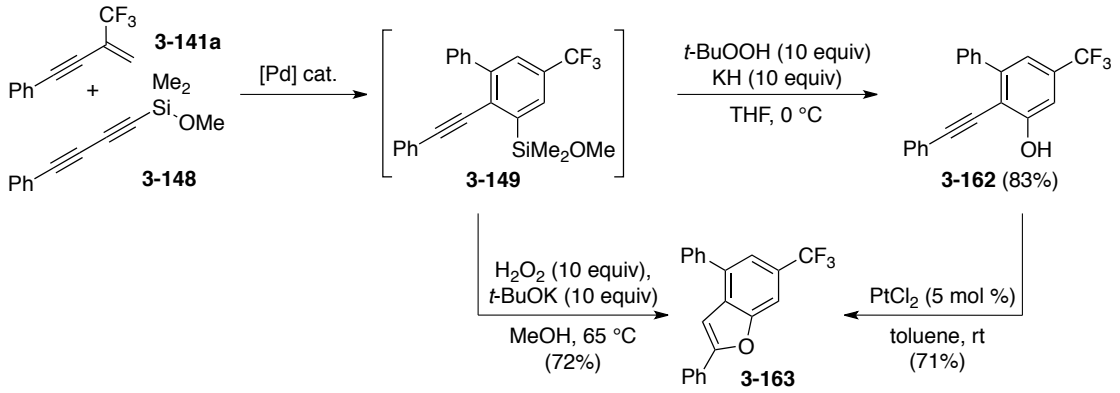
Scheme 3.51. Synthesis of *ortho*-Alkynylaryldimethylsilane via *One-pot* Palladium-catalyzed [4+2] Benzannulation/Reduction Sequence.

Alternatively, silver fluoride-mediated electrophilic halogenation of **3-149** afforded haloarenes **3-159a** and **3-159b** in good yields (Scheme 3.52). *ortho*-Alkynylaryliodide **3-159a** was then efficiently converted to a densely substituted indole **3-160** via the Pd-catalyzed amination/cyclization sequence.[75] Notably, the overall procedure allows for synthesis of 6-substituted indole in just three steps starting from acyclic precursors **3-141a** and **3-148**. Additionally, Sonogashira cross-coupling of **3-159a** with trimethylsilylacetylene afforded the Bergman cyclization precursor **3-161**.



Scheme 3.52. Synthesis of *ortho*-Alkynylhaloarenes via *One-pot* Palladium-catalyzed [4+2] Benzannulation/Electrophilic Halogenation Sequence and their Further Applications.

Finally, the Tamao oxidation of **3-149** under mildly basic conditions offered an access toward *o*-alkynylphenol **3-162**, leaving the triple bond unaffected (Scheme 3.53). Further electrophilic cyclization under Pt-catalysis[76] delivered the benzofuran **3-163**. Interestingly, under forcing oxidation conditions, an unprecedented direct transformation of *o*-alkynylsilylbenzene **3-149** into benzofuran **3-163** was observed.



Scheme 3.53. Synthesis of *ortho*-Alkynylphenol and Benzofuran via *One-pot* Palladium-catalyzed [4+2] Benzannulation/Oxidation Sequence.

3.2.5. Summary

In conclusion, an efficient and selective method for synthesis of fluoro- and perfluoroalkylaromatic compounds via the Pd-catalyzed [4+2] cross-benzannulation reaction has been developed. Cycloaddition strategy is proved to be effective for the rapid construction of aromatic fluorides from fluorine-containing easily available acyclic starting materials. The developed method allowed for synthesis of densely substituted *p*-trifluoromethyl- and *p*-perfluoroalkylarenes. Additionally, regioselective Pd-catalyzed [4+2] cross-benzannulation reaction of unsymmetrically-substituted diynes has been demonstrated. Importantly, this benzannulation reaction with fluoro-containing enynes provides an efficient route toward versatile synthons, possessing *o*-alkynylsilyl structural motif, which could be easily transformed into a variety of diverse aromatic and heteroaromatic structures, such as fluorenes, phenanthrenes, *o*-alkynylphenols, *bis*-*o*-alkynylbenzenes, benzofurans, and indoles. Accordingly, the developed strategy offers a viable and very general alternative to the existing fluorination and perfluoroalkylation methods towards these valuable molecules.

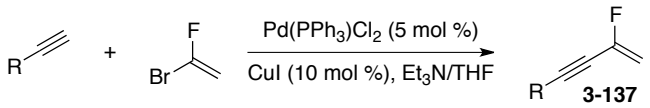
3.3. EXPERIMENTAL SECTION

3.3.1. General Information

NMR spectra were recorded on a Bruker Avance DRX-500 (500 MHz) and Bruker Avance DRX-400 (400 MHz) spectrometers. LRMS and HRMS analysis was performed on Micromass 70 VSE high-resolution mass spectrometer or Micromass LCT spectrometer equipped with a time-of-flight analyzer. GC/MS analysis was performed on a Hewlett Packard Model 6890 GC interfaced to a Hewlett Packard Model 5973 mass selective detector (15 m x 0.25 mm capillary column, HP-5MS). Column chromatography was carried out employing Silicycle Silica-P Flash silica gel (40-63 μm) or Fluka Florisil (60-100 mesh). Precoated silica gel plates Merck 60 F-254 were used for thin-layer analytical chromatography. All manipulations with transition metal catalysts were conducted in oven-dried glassware under inert atmosphere using a combination of glovebox and standard Schlenk techniques. Small-scale reactions were carried in Wheaton V-vials equipped with Mininert Syringe valve and stirring bar. Anhydrous solvents purchased from Aldrich were additionally purified on PureSolv PS-400-4 purification system by Innovative Technology, Inc. and/or stored over calcium hydride; toluene was additionally redistilled over calcium hydride, degased and kept in the glovebox. All other starting materials were purchased from Alfa Aesar, Oakwood Products, Sigma Aldrich, Strem Chemicals, and SynQuest Laboratories.

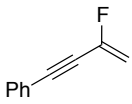
3.3.2. Starting Materials Synthesis

Enynes **3-137a–k** and **3-141a–d** were obtained via Sonogashira cross-coupling reaction.

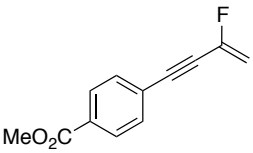


General procedure for the synthesis of enynes 3-137a-k: 1-Bromo-1-fluoroethylene (~1.2 equiv) was condensed into the cold Schlenk tube (acetone/dry ice cooling bath) followed by the addition of dry triethylamine under Ar atmosphere. $Pd(PPh_3)_2Cl_2$ (5 mol %), CuI (10 mol %) and corresponding

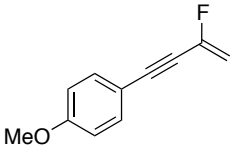
alkyne (1.0 equiv) were subsequently added to the reaction mixture. The Schlenk tube was sealed and the reaction mixture was allowed to warm to ambient temperature and stirred overnight. Upon completion the reaction mixture was quenched with saturated NH_4Cl solution and extracted with pentane (**3-137a–3-137d**, **3-137j**) or EtOAc (**3-137e–3-137i**, **3-137k**). Combined extracts were dried over Na_2SO_4 and solvent was removed under reduced pressure. The residue was purified by column chromatography to afford corresponding enyne **3-137**. Enynes **3-137** tend to decompose upon storage and therefore were used immediately. Although enynes **3-137** could be stored in a solution in freezer, repurification is recommended prior to use.



3-137a: 99% yield, colorless liquid (eluent: pentane). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.53 – 7.48 (m, 2 H), 7.40 – 7.34 (m, 3 H), 5.13 (dd, *J* = 3.0 Hz, 11.7 Hz, 1 H), 4.97 (dd, *J* = 3.0 Hz, 44.2 Hz, 1 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 146.7 (d, *J* = 240.7 Hz), 131.8, 129.4, 128.4, 121.1, 100.3 (d, *J* = 24.7 Hz), 91.0 (d, *J* = 6.3 Hz), 80.6 (d, *J* = 44.1 Hz) ^{19}F NMR (470 MHz, $CDCl_3$) δ ppm -97.2 (dd, *J* = 11.4 Hz, 44.3 Hz, 1 F) HRMS (EI+) calculated for $C_{10}H_7F$ $[M]^+$: 146.0532, found: 146.0539.

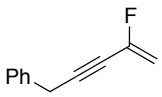


3-137b: 78% yield, colorless liquid (eluent: hexanes : EtOAc = 10 : 1). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.03 – 8.00 (m, 2 H), 7.56 – 7.53 (m, 2 H), 5.17 (dd, *J* = 3.2 Hz, 11.6 Hz, 1 H), 5.00 (dd, *J* = 3.2 Hz, 44.0 Hz, 1 H), 3.92 (s, 3 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 166.2, 146.3 (d, *J* = 241.0 Hz), 131.7, 130.6, 129.5, 125.6, 101.3 (d, *J* = 24.2 Hz), 90.0 (d, *J* = 6.4 Hz), 83.1 (d, *J* = 44.1 Hz), 52.3 ^{19}F NMR (470 MHz, $CDCl_3$) δ ppm -98.0 (dd, *J* = 11.5 Hz, 43.9 Hz, 1 F) HRMS (EI+) calculated for $C_{12}H_9FO_2$ $[M]^+$: 204.0587, found: 204.0595.

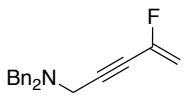


3-137c: 95% yield, colorless liquid (eluent: pentane : Et_2O = 10 : 1). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.45 – 7.43 (m, 2 H), 6.89 – 6.86 (m, 2 H), 5.08 (ddd, *J* = 1.6 Hz, 3.0 Hz, 11.6 Hz, 1 H), 4.92 (ddd, *J* = 1.7 Hz, 3.0 Hz, 44.4 Hz, 1 H), 3.83 (s, 3

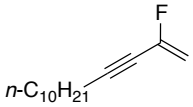
H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 160.5, 146.9 (d, *J* = 240.3 Hz), 133.4, 114.1, 113.1, 99.6 (d, *J* = 25.2 Hz), 91.2 (d, *J* = 6.3 Hz), 79.5 (d, *J* = 43.8 Hz), 55.3 ^{19}F NMR (470 MHz, $CDCl_3$) δ ppm -96.6 (dd, *J* = 10.5 Hz, 44.3 Hz, 1 F) HRMS (EI+) calculated for $C_{11}H_9FO$ $[M]^+$: 176.0638, found: 176.0630.



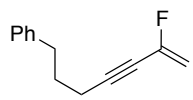
3-137d: 96% yield, colorless liquid (eluent: pentane). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.37 – 7.34 (m, 4 H), 7.31 – 7.27 (m, 1 H), 5.02 (ddd, *J* = 2.0 Hz, 2.8 Hz, 11.8 Hz, 1 H), 4.84 (ddd, *J* = 2.0 Hz, 2.7 Hz, 44.3 Hz, 1 H), 3.78 (d, *J* = 4.6 Hz, 2 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 146.6 (d, *J* = 240.4 Hz), 135.2, 128.7 128.0, 127.0, 99.4 (d, *J* = 24.8 Hz), 90.3 (d, *J* = 6.3 Hz), 74.5 (d, *J* = 44.0 Hz), 25.4 ^{19}F NMR (470 MHz, $CDCl_3$) δ ppm -96.3 (dd, *J* = 6.9 Hz, 45.0 Hz, 1 F) HRMS (EI+) calculated for $C_{11}H_8F$ $[M-H]^+$: 159.0610, found: 159.0617.



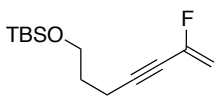
3-137e: 70% yield, pale yellow oil (eluent: hexanes : EtOAc = 10 : 1). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.60 – 7.57 (m, 4 H), 7.53 – 7.48 (m, 4 H), 7.46 – 7.41 (m, 2 H), 5.24 (ddd, *J* = 1.7 Hz, 3.0 Hz, 11.8 Hz, 1 H), 5.06 (ddd, *J* = 1.2 Hz, 3.0 Hz, 44.3 Hz, 1 H), 3.88 (s, 4H), 3.57 (d, *J* = 4.2 Hz, 2 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 146.6 (d, *J* = 240.9 Hz), 138.7, 129.2 128.6, 127.5, 99.9 (d, *J* = 24.7 Hz), 87.7 (d, *J* = 6.2 Hz), 77.9 (d, *J* = 43.9 Hz), 57.9, 41.7 ^{19}F NMR (470 MHz, $CDCl_3$) δ ppm -95.5 (dd, *J* = 10.1 Hz, 44.1 Hz, 1 F) HRMS (ESI) calculated for $C_{19}H_{19}FN$ $[M+H]^+$: 280.1502, found: 280.1504.



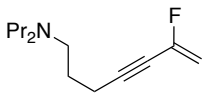
3-137f: quant yield, colorless liquid (eluent: hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 4.94 (dd, *J* = 2.9 Hz, 11.8 Hz, 1 H), 4.84 (dd, *J* = 2.9 Hz, 44.7 Hz, 1 H), 2.33 (dt, *J* = 4.8 Hz, 7.1 Hz, 2 H), 1.59 – 1.52 (m, 2 H), 1.43 – 1.35 (m, 2 H), 1.32 – 1.25 (m, 12 H), 0.89 (t, *J* = 6.9 Hz, 3 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 146.9 (d, *J* = 239.8 Hz), 98.5 (d, *J* = 25.4 Hz), 93.2 (d, *J* = 6.5 Hz), 75.6 (d, *J* = 44.0 Hz), 31.9, 29.54, 29.46, 29.3, 29.1, 28.8, 28.0, 22.7, 19.0, 14.1 ^{19}F NMR (470 MHz, $CDCl_3$) δ ppm -95.4 (ddd, *J* = 3.8 Hz, 7.1 Hz, 44.7 Hz, 1 F) HRMS (EI+) calculated $C_{14}H_{23}F$ $[M]^+$: 210.1784, found: 210.1775.



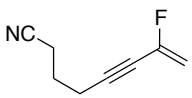
3-137g: 84% yield, colorless liquid (eluent: hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.33 – 7.29 (m, 2 H), 7.24 – 7.19 (m, 3 H), 4.98 (ddd, *J* = 2.7 Hz, 2.7 Hz, 11.8 Hz, 1 H), 4.78 (ddd, *J* = 2.7 Hz, 2.7 Hz, 44.7 Hz, 1 H), 2.75 (dt, *J* = 2.2 Hz, 7.9 Hz, 2 H), 2.39 – 2.34 (m, 2 H), 1.94 – 1.87 (m, 2 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 146.8 (d, *J* = 240.0 Hz), 141.1, 128.5, 128.4, 126.1, 98.8 (d, *J* = 25.3 Hz), 92.6 (d, *J* = 6.2 Hz), 73.1 (d, *J* = 43.8 Hz), 34.7, 29.5, 18.4 ^{19}F NMR (470 MHz, $CDCl_3$) δ ppm -95.6 (d, *J* = 44.2 Hz, 1 F) HRMS (EI+) calculated for $C_{13}H_{12}F$ $[M-H]^+$: 187.0923, found: 187.0928.



3-137h: 80% yield, colorless liquid (eluent: hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 4.94 (dd, *J* = 2.9 Hz, 11.8 Hz, 1 H), 4.74 (dd, *J* = 2.9 Hz, 44.7 Hz, 1 H), 3.70 (t, *J* = 5.9 Hz, 2 H), 2.46 – 2.41 (m, 2 H), 1.79 – 1.73 (m, 2 H), 0.90 (s, 9 H), 0.06 (s, 6 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 146.8 (d, *J* = 239.7 Hz), 98.6 (d, *J* = 25.3 Hz), 92.7 (d, *J* = 6.3 Hz), 72.7 (d, *J* = 43.8 Hz), 61.3, 30.1, 25.9, 18.3, 15.5, -5.4 ^{19}F NMR (470 MHz, $CDCl_3$) δ ppm -95.6 (ddd, *J* = 4.3 Hz, 6.5 Hz, 44.8 Hz, 1 F).

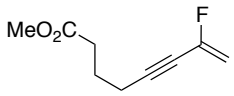


3-137i: 50% yield, pale yellow liquid (eluent: hexanes : EtOAc = 10 : 1). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 4.94 (dd, *J* = 2.9 Hz, 11.8 Hz, 1 H), 4.73 (dd, *J* = 2.9 Hz, 44.7 Hz, 1 H), 2.47 (t, *J* = 7.0 Hz, 2 H), 2.42 – 2.32 (m, 6 H), 1.70 – 1.64 (m, 2 H), 1.48 – 1.39 (m, 4 H), 0.87 (t, *J* = 7.4 Hz, 6 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 146.9 (d, *J* = 240.0 Hz), 98.5 (d, *J* = 25.6 Hz), 93.2 (d, *J* = 6.2 Hz), 72.6 (d, *J* = 43.9 Hz), 56.3, 52.8, 26.0, 20.4, 16.9, 11.9 ^{19}F NMR (470 MHz, $CDCl_3$) δ ppm -95.5 (ddd, *J* = 4.5 Hz, 6.5 Hz, 44.7 Hz, 1 F) HRMS (ESI) calculated for $C_{13}H_{23}FN$ $[M+H]^+$: 212.1815, found: 212.1812.

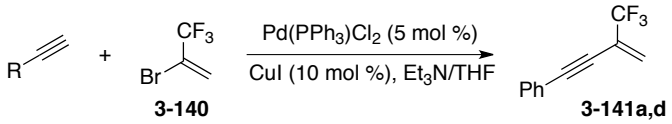


3-137j: 85% yield, colorless liquid (eluent: hexanes : EtOAc = 10 : 1). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 4.96 (dd, *J* = 2.6 Hz, 11.9 Hz, 1 H), 4.77 (dd, *J* = 2.4 Hz, 44.7 Hz, 1 H), 2.53 – 2.43 (m, 4 H), 1.92 – 1.84 (m, 2 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 146.2 (d, *J* = 240.0 Hz), 118.8, 99.6 (d, *J* = 24.6 Hz), 89.9 (d, *J* = 6.5 Hz), 74.1 (d, *J* = 44.3 Hz), 23.9, 18.1, 16.1 ^{19}F NMR

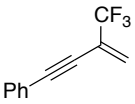
(470 MHz, $CDCl_3$) δ ppm -96.7 (dd, *J* = 11.2 Hz, 44.7 Hz, 1 F) HRMS (EI+) calculated for C_8H_8FN $[M]^+$: 137.0641, found: 137.0637.



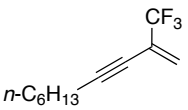
3-137k: quant yield, colorless liquid (eluent: hexanes : EtOAc = 10 : 1). ^1H NMR (500 MHz, $CDCl_3$) δ ppm 4.91 (dd, *J* = 3.0 Hz, 11.9 Hz, 1 H), 4.77 (dd, *J* = 2.9 Hz, 44.7 Hz, 1 H), 3.64 (s, 3 H), 2.42 – 2.36 (m, 4 H), 1.84 (quint, *J* = 7.2 Hz, 2 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 173.2, 146.6 (d, *J* = 240.0 Hz), 98.9 (d, *J* = 25.1 Hz), 91.6 (d, *J* = 6.5 Hz), 73.3 (d, *J* = 44.0 Hz), 51.5, 32.6, 23.1, 18.4 ^{19}F NMR (470 MHz, $CDCl_3$) δ ppm -96.0 (dd, *J* = 11.0 Hz, 44.6 Hz, 1 F) HRMS (EI+) calculated for $C_9H_{11}FO_2$ $[M]^+$: 170.0743, found: 170.0752.



General procedure for the synthesis of enynes 3-141a, d: A Schlenk flask was charged with $Pd(PPh_3)_2Cl_2$ (2 mol %) and CuI (5 mol %) under N_2 atmosphere. Dry triethyamine/THF (1:1 ratio, 1M) and 2-bromo-3,3,3-trifluoro-1-propene (**3-140**, 1.0 equiv) were added subsequently followed by dropwise addition of the corresponding alkyne (1.1 equiv). The reaction mixture was stirred at ambient temperature until completion. The reaction was then quenched with saturated NH_4Cl solution and extracted with pentane. Combined extracts were dried over Na_2SO_4 and solvent was removed under vacuum. The residue was purified by column chromatography to afford the corresponding enyne **3-141**.

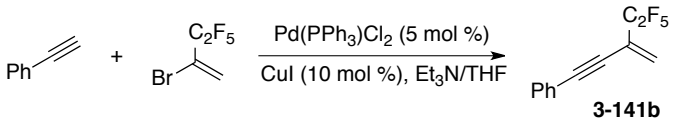


3-141a: 80% yield, colorless liquid (eluent: pentane). ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.52 – 7.49 (m, 2 H), 7.40 – 7.33 (m, 3 H), 6.12 – 6.11 (m, 1 H), 5.97 – 5.95 (m, 1 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 131.8, 129.2, 128.4, 126.7 (q, *J* = 3.8 Hz), 122.8 (q, *J* = 35.2 Hz), 121.7, 121.4 (q, *J* = 273.7 Hz), 93.2, 81.4 ^{19}F NMR (470 MHz, $CDCl_3$) δ ppm -69.5 (s, 3 F) HRMS (EI+) calculated for $C_{11}H_7F_3$ $[M]^+$: 196.0500, found: 196.0506.



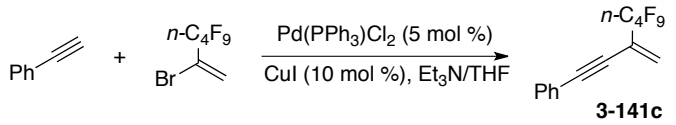
3-141d: 76% yield, colorless liquid (eluent: pentane). ^1H NMR (500 MHz, $CDCl_3$) δ ppm 5.94 – 5.96 (m, 1 H), 5.75 – 5.76 (m, 1 H), 2.34 (t, *J* = 7.1 Hz, 2 H), 1.60 – 1.52

(m, 2 H), 1.44 – 1.37 (m, 2 H), 1.36 – 1.26 (m, 4 H), 0.90 (t, J = 7.0 Hz, 3 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 125.3 (m), 122.9 (d, J = 34.9 Hz), 121.4 (d, J = 273.7 Hz), 95.2, 73.2, 31.2, 28.4, 28.1, 22.5, 19.2, 13.9 ^{19}F NMR (470 MHz, $CDCl_3$) δ ppm -70.0 (s, 3 F) HRMS (EI+) calculated for $C_{11}H_{16}F_3$ $[M+H]^+$: 205.1204, found: 205.1212.



3-141b

Synthesis of enyne 3-141b: A Schlenk flask was charged with $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol), CuI (10 mg, 0.05 mmol), and 1,4-diazabicyclo[2.2.2]octane (112 mg, 1.0 mmol) under N_2 atmosphere. Dry THF (2.0 mL) and 2-bromo-3,3,4,4,4-pentafluoro-1-butene (112 mg, 0.5 mmol) were added sequentially, followed by dropwise addition of phenylacetylene (66 mL, 0.6 mmol). The reaction mixture was stirred at ambient temperature until completion. The reaction was then quenched with saturated NH_4Cl solution and extracted with pentane. Combined extracts were dried over Na_2SO_4 and solvent was removed under vacuum. The residue was purified by column chromatography (eluent: pentane) to afford enyne **3-141b** (60.0 mg, 49%) as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.51 – 7.47 (m, 2 H), 7.39 – 7.33 (m, 3 H), 6.16 – 6.14 (m, 1 H), 6.11 – 6.10 (m, 1 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 131.8, 129.2, 128.4, 121.7, 93.8, 81.7 Carbon atoms corresponding to C_2F_5 group and double bond can not be identified due to C-F coupling. ^{19}F NMR (470 MHz, $CDCl_3$) δ ppm -85.1 (s, 3 F), -117.6 (s, 2 F) HRMS (EI+) calculated for $C_{12}H_7F_5$ $[M]^+$: 246.0468, found: 246.0473



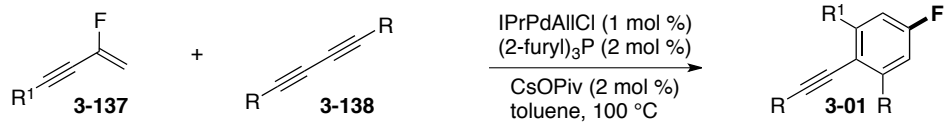
3-141c

Synthesis of enyne 3-141c: A Schlenk flask was charged with $Pd(PPh_3)_2Cl_2$ (105 mg, 0.15 mmol), CuI (60 mg, 0.3 mmol) under N_2 atmosphere. Dry THF (10 mL), dry triethylamine (835 mL, 6.0 mmol), and 2-bromo-3,3,4,4,5,5,6,6,6-nonafluoro-1-hexene (972 mg, 3.0 mmol) were added subsequently, followed by dropwise addition of phenylacetylene (395 mL, 3.6 mmol). The reaction

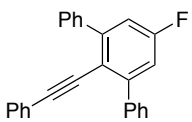
mixture was stirred at ambient temperature until completion. The reaction was then quenched with saturated NH_4Cl solution and extracted with hexane (3 × 5 mL). Combined extracts were dried over Na_2SO_4 and solvent was removed under vacuum. The residue was purified by column chromatography (eluent: hexanes) to afford the corresponding enyne **3-141c** (982 mg, 95%) as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.51 – 7.46 (m, 2 H), 7.39 – 7.33 (m, 3 H), 6.15 – 6.11 (m, 2 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 131.8, 129.6, 129.3, 128.4, 121.7, 93.7, 81.8 Carbon atoms corresponding to C_4F_9 group and double bond can not be identified due to C-F coupling. ^{19}F NMR (470 MHz, $CDCl_3$) δ ppm -82.5 (t, *J* = 8.3 Hz, 3 F), -113.7 (t, *J* = 11.7 Hz, 2 F), -124.0 (m, 2 F), -127.4 (t, *J* = 11.7 Hz, 2 F) HRMS (EI+) calculated for $C_{14}H_7F_9$ $[M]^+$: 346.0403, found: 346.0402.

Diynes **3-138b**, **3-138c**, and **3-138d** were synthesized via Glaser coupling, analytical data of obtained compounds **3-138b**[77] and **3-138c**, **3-138d**[78] are in agreement with the literature data.

3.3.3. Synthesis of *para*-Fluoroarylalkynes

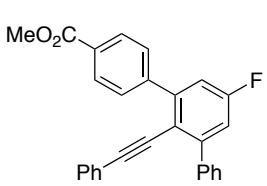


General procedure: An oven-dried 1.0 mL V-vial equipped with a stirring bar was charged with IPrPdAllCl (2.8 mg, 0.005 mmol, 1 mol %), (2-furyl)$_3$P (1.2 mg, 0.01 mmol, 2 mol %), CsOPiv (1.2 mg, 0.01 mmol, 2 mol %), and toluene (0.5 mL) under N_2 atmosphere. Enyne **3-137** (0.6 mmol, 1.2 equiv) and diyne **3-138** (0.5 mmol, 1.0 equiv) were subsequently added. The reaction vessel was caped with Mininert syringe valve and the reaction mixture was stirred at 120 °C for 16-24 h. Upon reaction completion the resultant mixture was cooled to room temperature, diluted with CH_2Cl_2, and filtered through a celite plug. The filtrate was concentrated under reduced pressure, and the crude product was purified by column chromatography to afford **3-01**.

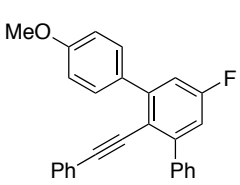


3-01aa: 147.4 mg (0.5 mmol scale), 85% yield, colorless solid (eluent: hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.71 – 7.67 (m, 4 H), 7.53 – 7.44 (m, 6 H), 7.23 – 7.19

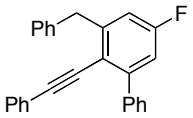
(m, 3 H), 7.16 (s, 1H), 7.14 (s, 1H), 7.03 – 6.99 (m, 2 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 161.9 (d, *J* = 250.1 Hz), 147.2 (d, *J* = 8.3 Hz), 140.1, 130.9, 129. 5, 128.1, 127.93, 127.90, 123.5, 116.6, 115.5 (d, *J* = 22.2 Hz), 95.3, 88.1 ^{19}F NMR (470 MHz, $CDCl_3$) δ ppm -113.2 (t, *J* = 8.7 Hz, 1 F) HRMS (EI+) calculated for $C_{26}H_{17}F$ $[M]^+$: 348.1314, found: 348.1316.



3-01ba: 159.4 mg (0.5 mmol scale), 78% yield, white solid (eluent: hexanes : EtOAc = 4 : 1). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.18 – 8.15 (m, 2 H), 7.78– 7.76 (m, 2 H), 7.68 – 7.66 (m, 2 H), 7.52 – 7.43 (m, 3 H), 7.24 – 7.12 (m, 5 H), 7.00 – 6.97 (m, 2 H), 3.98 (s, 3 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 166.9, 161.8 (d, *J* = 250.6 Hz), 147.5 (d, *J* = 8.4 Hz), 145.8 (d, *J* = 8.3 Hz), 144.6, 139.9, 130.9, 129.6, 129.5, 129.2, 128.2, 128.1, 128.05, 127.95, 123.1, 116.5, 116.1 (d, *J* = 22.1 Hz), 115.4 (d, *J* = 22.5 Hz), 95.7, 87.6, 52.2 ^{19}F NMR (470 MHz, $CDCl_3$) δ ppm -112.6 (m, 1 F) HRMS (EI+) calculated for $C_{28}H_{19}FO_2$ $[M]^+$: 406.1369, found: 406.1373.

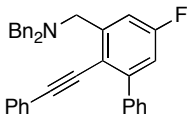


3-01ca: 95.5 mg (0.5 mmol scale), 51% yield, white solid (eluent: hexanes : EtOAc = 20 : 1). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.70 – 7.64 (m, 4 H), 7.51– 7.43 (m, 3 H), 7.25 – 7.19 (m, 3 H), 7.14 – 7.08 (m, 2 H), 7.07 – 7.01 (m, 4 H), 3.90 (s, 3 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 161.9 (d, *J* = 249.8 Hz), 159.5, 147.3 (d, *J* = 8.6 Hz), 146.7 (d, *J* = 8.5 Hz), 140.2, 132.5, 130.9, 130.7, 129.5, 128.1, 127.90, 127.87, 123.5, 116.4, 115.3 (d, *J* = 22.1 Hz), 115.1 (d, *J* = 22.4 Hz), 113.3, 95.2, 88.3, 55.4 ^{19}F NMR (470 MHz, $CDCl_3$) δ ppm -113.3 (m, 1 F) HRMS (EI+) calculated for $C_{27}H_{19}FO$ $[M]^+$: 378.1420, found: 378.1413.

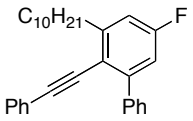


3-01da: 102.7 mg (0.5 mmol scale), 57% yield, pale yellow oil (eluent: hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.69 – 7.66 (m, 2 H), 7.51 – 7.47 (m, 2 H), 7.46 – 7.42 (m, 1 H), 7.37 – 7.34 (m, 4 H), 7.31 – 7.26 (m, 6 H), 7.03 (dd, *J* = 2.6 Hz, *J* = 9.2 Hz, 1 H), 6.89 (dd, *J* = 2.6 Hz, *J* = 9.3 Hz, 1 H), 4.36 (s, 2 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 162.1 (d, *J* = 249.7 Hz), 146.8 (d, *J* = 8.5 Hz), 146.5 (d, *J* = 7.9 Hz), 140.1, 139.8, 131.2, 129.4, 129.1, 128.6, 128.3, 128.2, 127.93, 127.90, 126.5, 123.5, 117.6, 115.3 (d, *J* = 22.2 Hz), 114.6 (d, *J* = 22.4 Hz), 96.5, 87.3, 40.8 ^{19}F NMR (470

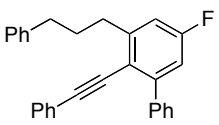
MHz, $CDCl_3$) δ ppm -112.8 (m, 1 F) HRMS (EI+) calculated for $C_{27}H_{19}F$ $[M]^+$: 362.1471, found: 362.1473.



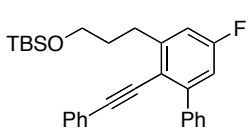
3-01ea: 219.7 mg (0.5 mmol scale), 84% yield + ~8% of enyne dimer, yellow oil (eluent: hexanes : EtOAc = 10:1). ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.65 – 7.62 (m, 2 H), 7.60 (dd, *J* = 2.6 Hz, 9.6 Hz, 1 H), 7.50 – 7.25 (m, 18 H), 7.04 (dd, *J* = 2.6 Hz, 9.1 Hz, 1 H), 3.99 (s, 2 H), 3.74 (s, 4 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 162.6 (d, *J* = 249.1 Hz), 146.7 (d, *J* = 8.2 Hz), 145.5 (d, *J* = 7.9 Hz), 140.0, 139.2, 131.1, 129.4, 128.8, 128.4, 128.3, 128.2, 127.9, 127.8, 127.1, 123.5, 117.1, 115.1 (d, *J* = 22.8 Hz), 114.2 (d, *J* = 22.8 Hz), 96.9, 86.6, 58.4, 55.9 ^{19}F NMR (470 MHz, $CDCl_3$) δ ppm -112.6 (m, 1 F) HRMS (ESI) calculated for $C_{35}H_{29}FN$ $[M+H]^+$: 482.2284, found: 482.2278.



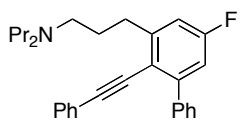
3-01fa: 145.8 mg (0.5 mmol scale), 71% yield, pale yellow oil (eluent: hexanes). ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.66 – 7.63 (m, 2 H), 7.49 – 7.40 (m, 3 H), 7.30 – 7.27 (m, 5 H), 6.97 (dt, *J* = 2.6 Hz, *J* = 9.4 Hz, 2 H), 2.97 – 2.92 (m, 2 H), 1.79 – 1.72 (m, 2 H), 1.48 – 1.22 (m, 14 H), 0.89 (t, *J* = 6.9 Hz, 3 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 162.1 (d, *J* = 249.3 Hz), 148.5 (d, *J* = 7.9 Hz), 146.7 (d, *J* = 8.4 Hz), 140.2, 131.6, 128.6, 129.4, 128.3, 128.0, 127.9, 127.8, 123.7, 117.2, 114.6 (d, *J* = 21.6 Hz), 114.0 (d, *J* = 22.3 Hz), 95.7, 87.1, 35.4, 31.9, 30.5, 29.64, 29.56, 29.3, 22.7, 14.1 ^{19}F NMR (470 MHz, $CDCl_3$) δ ppm -113.6 (m, 1 F) HRMS (EI+) calculated for $C_{30}H_{33}F$ $[M]^+$: 412.2566, found: 412.2556.



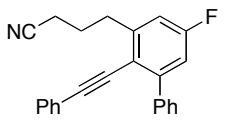
3-01ga: 167.1 mg (0.5 mmol scale), 86% yield + ~3% of enyne dimer, pale yellow oil (eluent: hexanes). ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.66 – 7.62 (m, 2 H), 7.49 – 7.40 (m, 3 H), 7.32 – 7.18 (m, 10 H), 7.01 – 6.95 (m, 2 H), 3.03 – 2.98 (m, 2 H), 2.79 (t, *J* = 7.6 Hz, 3 H), 2.15 – 2.08 (m, 2 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 162.1 (d, *J* = 249.2 Hz), 147.9 (d, *J* = 7.8 Hz), 146.8 (d, *J* = 8.5 Hz), 142.1, 140.2, 131.2, 129.5, 128.6, 128.5, 128.3, 128.1, 127.94, 127.86, 125.9, 123.6, 117.4 (d, *J* = 2.9 Hz), 114.7 (d, *J* = 21.5 Hz), 114.2 (d, *J* = 22.3 Hz), 96.0, 87.1, 36.0, 35.0, 32.0 ^{19}F NMR (470 MHz, $CDCl_3$) δ ppm -113.5 (m, 1 F) HRMS (EI+) calculated for $C_{29}H_{23}F$ $[M]^+$: 390.1783, found: 390.1780.



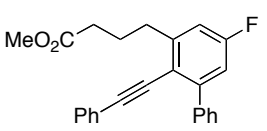
3-01ha: 184.0 mg (0.5 mmol scale), 83% yield, pale yellow oil (eluent: hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.65 – 7.62 (m, 2 H), 7.49 – 7.44 (m, 2 H), 7.43 – 7.39 (m, 1 H), 7.29 – 7.27 (m, 5 H), 6.99 (s, 1 H), 6.98 (s, 1 H), 3.74 (t, *J* = 6.2 Hz, 3 H), 3.03 – 2.99 (m, 2 H), 2.03 – 1.96 (m, 2 H), 0.92 (s, 9 H), 0.08 (s, 6 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 162.0 (d, *J* = 249.3 Hz), 147.7 (d, *J* = 7.9 Hz), 146.7 (d, *J* = 8.2 Hz), 140.1, 131.1, 129.4, 128.3, 128.0, 127.9, 127.8, 123.6, 117.3, 114.7 (d, *J* = 21.6 Hz), 114.1 (d, *J* = 22.3 Hz), 96.0, 86.9, 62.6, 33.1, 31.8, 26.0, 18.4, -5.3 ^{19}F NMR (470 MHz, $CDCl_3$) δ ppm -113.6 (m, 1 F) HRMS (EI+) calculated for $C_{29}H_{33}FOSi$ $[M]^+$: 444.2285, found: 444.2294.



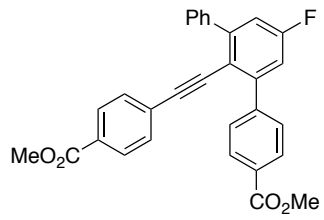
3-01ia: 168.8 mg (0.5 mmol scale), 82% yield, pale yellow oil (eluent: hexanes : EtOAc = 10 : 1). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.66 – 7.63 (m, 2 H), 7.49 – 7.45 (m, 2 H), 7.43 – 7.40 (m, 1 H), 7.30 – 7.27 (m, 5 H), 7.00 (s, 1 H), 6.98 (s, 1 H), 2.98 – 2.93 (m, 2 H), 2.61 – 2.57 (m, 2 H), 2.43– 2.39 (m, 4 H), 1.96 – 1.88 (m, 2 H), 1.51– 1.43 (m, 4 H), 0.88 (t, *J* = 7.5 Hz, 6 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 162.0 (d, *J* = 249.4 Hz), 148.1 (d, *J* = 7.9 Hz), 146.7 (d, *J* = 8.4 Hz), 140.2, 131.1, 129.4, 128.2, 128.0, 127.9, 127.8, 123.6, 117.3, 114.6 (d, *J* = 21.6 Hz), 114.0 (d, *J* = 22.3 Hz), 95.9, 87.0, 56.3, 53.9, 33.4, 27.8, 20.4, 12.0 ^{19}F NMR (470 MHz, $CDCl_3$) δ ppm -113.5 (m, 1 F) HRMS (ESI) calculated for $C_{29}H_{33}FN$ $[M+H]^+$: 414.2597, found: 414.2586.



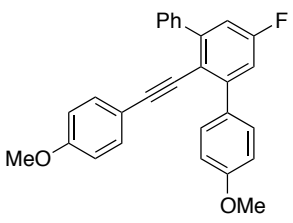
3-01ja: 102.5 mg (0.5 mmol scale), 60% yield, pale yellow oil (eluent: hexanes : EtOAc = 10:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.66 – 7.62 (m, 2 H), 7.50 – 7.46 (m, 2 H), 7.45 – 7.42 (m, 1 H), 7.31 – 7.30 (m, 5 H), 7.05 (dd, *J* = 2.6 Hz, 9.2 Hz, 1 H), 6.99 (dd, *J* = 2.6 Hz, 8.8 Hz, 1 H), 3.14 – 3.10 (m, 2 H), 2.45 (t, *J* = 7.2 Hz, 2 H), 2.19 – 2.11 (m, 2 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 162.0 (d, *J* = 250.4 Hz), 147.3 (d, *J* = 8.3 Hz), 145.0 (d, *J* = 8.0 Hz), 139.8, 131.1, 129.3, 128.39, 128.37, 128.01, 127.97, 123.1, 119.4, 117.5, 115.0 (d, *J* = 22.2 Hz), 114.9 (d, *J* = 21.8 Hz), 96.5, 86.4, 34.0, 25.9, 16.8 ^{19}F NMR (470 MHz, $CDCl_3$) δ ppm -112.6 (m, 1 F) HRMS (EI+) calculated for $C_{24}H_{18}FN$ $[M]^+$: 339.1423, found: 339.1431.



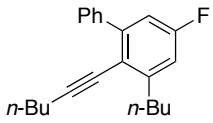
3-01ka: 115.6 mg (0.5 mmol scale), 62% yield, pale yellow oil (eluent: hexanes : EtOAc = 10:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.64 – 7.61 (m, 2 H), 7.49 – 7.44 (m, 2 H), 7.43 – 7.39 (m, 1 H), 7.31 – 7.27 (m, 5 H), 6.98 (ddd, *J* = 2.6 Hz, 9.2 Hz, 16.6 Hz, 2 H), 3.66 (s, 3 H), 3.02 – 2.98 (m, 2 H), 2.44 (t, *J* = 7.4 Hz, 2 H), 2.15 – 2.08 (m, 2 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 173.7, 162.0 (d, *J* = 249.8 Hz), 146.87 (d, *J* = 8.4 Hz), 146.75 (d, *J* = 8.1 Hz), 140.0, 131.1, 129.4, 128.3, 128.1, 127.9, 127.8, 123.4, 117.4, 114.8 (d, *J* = 21.6 Hz), 114.4 (d, *J* = 22.3 Hz), 96.0, 86.8, 51.6, 34.4, 33.5, 25.5 ^{19}F NMR (470 MHz, $CDCl_3$) δ ppm -113.2 (m, 1 F) HRMS (EI+) calculated for $C_{25}H_{21}FO_2$ $[M]^+$: 372.15256, found: 372.1517.



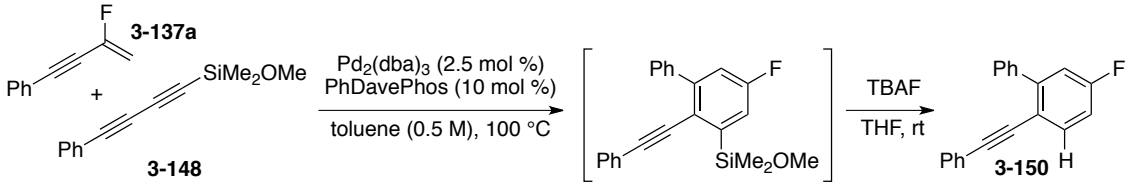
3-01ac: 159.8 mg (0.5 mmol scale), 69% yield, white solid (eluent: hexanes : EtOAc = 4 : 1). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.17 (d, *J* = 8.2 Hz, 2 H), 7.86 (d, *J* = 8.2 Hz, 2 H), 7.74 (d, *J* = 8.2 Hz, 2 H), 7.66 – 7.63 (m, 2 H), 7.52 – 7.44 (m, 3 H), 7.18 (dd, *J* = 2.4 Hz, 9.0 Hz, 1 H), 7.14 (dd, *J* = 2.4 Hz, 8.8 Hz, 1 H), 7.01 (s, 1 H), 6.99 (s, 1 H), 3.98 (s, 3 H), 3.88 (s, 3 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 166.8, 166.4, 161.1 (d, *J* = 251.8 Hz), 148.0 (d, *J* = 8.3 Hz), 146.2 (d, *J* = 8.4 Hz), 144.4, 139.8, 130.7, 129.7, 129.5, 129.41, 129.35, 129.3, 128.2, 128.0, 127.7, 116.2 (d, *J* = 22.2 Hz), 116.0, 115.5 (d, *J* = 22.7 Hz), 94.9, 90.6, 52.23, 52.15 ^{19}F NMR (470 MHz, $CDCl_3$) δ ppm -111.7 (m, 1 F) HRMS (EI+) calculated for $C_{30}H_{21}FO_4$ $[M]^+$: 464.1424, found: 464.1415.



3-01ad: 124.8 mg (0.5 mmol scale), 61% yield, white solid (eluent: hexanes : EtOAc = 4 : 1). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.69 – 7.63 (m, 4 H), 7.50 – 7.41 (m, 3 H), 7.12 – 7.08 (m, 2 H), 7.03 – 6.97 (m, 4 H), 6.76 – 6.73 (m, 2 H), 3.90 (s, 3 H), 3.77 (s, 3 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 161.7 (d, *J* = 249.8 Hz), 159.42, 159.38, 146.9 (d, *J* = 8.5 Hz), 146.3 (d, *J* = 8.4 Hz), 140.3, 132.6, 132.4, 130.7, 129.5, 127.84, 127.80, 116.8, 115.7, 115.2 (d, *J* = 22.2 Hz), 115.0 (d, *J* = 22.4 Hz), 113.8, 113.3, 95.2, 87.0, 55.4, 55.3 ^{19}F NMR (470 MHz, $CDCl_3$) δ ppm -114.0 (m, 1 F) HRMS (EI+) calculated for $C_{28}H_{21}FO_2$ $[M]^+$: 408.1526, found: 408.15160.



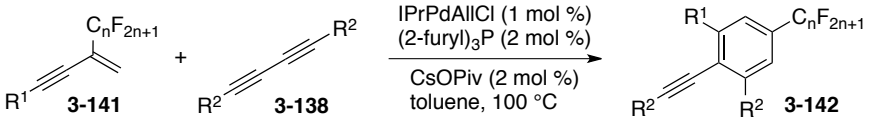
3-01ab: 121.6 mg (0.5 mmol scale), 79% yield, pale yellow oil (eluent: hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.59 – 7.56 (m, 2 H), 7.44 – 7.35 (m, 3 H), 6.92 (s, 1 H), 6.91 (s, 1 H), 2.88 – 2.83 (m, 2 H), 2.32 (t, *J* = 6.9 Hz, 2 H), 1.72 – 1.66 (m, 2 H), 1.50 – 1.42 (m, 4 H), 1.38 – 1.31 (m, 2 H), 0.99 (t, *J* = 7.4 Hz, 3 H), 0.89 (t, *J* = 7.3 Hz, 3 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 161.4 (d, *J* = 247.7 Hz), 148.2 (d, *J* = 7.7 Hz), 146.3 (d, *J* = 8.2 Hz), 140.5, 129.3, 127.7, 127.4, 118.8, 114.3 (d, *J* = 21.4 Hz), 113.8 (d, *J* = 22.2 Hz), 96.9, 77.6, 34.9, 32.5, 30.6, 22.7, 21.9, 19.2, 14.0, 13.6 ^{19}F NMR (470 MHz, $CDCl_3$) δ ppm -113.2 (m, 1 F) HRMS (EI+) calculated for $C_{22}H_{25}F$ $[M]^+$: 308.1940, found: 308.1934.



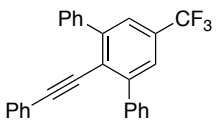
Synthesis of 3-150: An oven-dried 3 mL V-vial equipped with a stirring bar was charged with $Pd_2(dba)_3$ (11.4 mg, 0.0125 mmol, 2.5 mol %), diphenylphosphino-2'-(N,N-dimethylamino)biphenyl (PhDavePhos, 19.1 mg, 0.025 mmol, 10 mol %), and toluene (1 mL) under N_2 atmosphere. Enyne **3-137a** (73.0 mg, 0.5 mmol, 1 equiv) and diyne **3-148** (160.5 mg, 0.75 mmol, 1.5 equiv) were sequentially added. The reaction vessel was caped with Mininert syringe valve and the reaction mixture was stirred at 100 °C for 72 h. Upon reaction completion resultant mixture was cooled to room temperature and solution of TBAF (1M in THF, 1.0 mL, 1.0 mmol) was added. The reaction mixture was stirred at ambient temperature for 1 h, diluted with CH_2Cl_2, and filtered through a celite plug. The filtrate was concentrated under reduced pressure and the crude product was purified by column chromatography (eluent: hexanes) to afford **3-150** (67.3 mg, 48%) as a pale yellow oil. The product was obtained as an inseparable mixture with corresponding enyne dimer (~ 8%). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.70 – 7.67 (m, 2 H), 7.65 (dd, *J* = 5.8 Hz, 8.6 Hz, 1 H), 7.52 – 7.47 (m, 2 H), 7.46 – 7.42 (m, 1 H), 7.36 – 7.29 (m, 5 H), 7.17 (dd, *J* = 2.7 Hz, 9.6 Hz, 1 H), 7.06 (dd, *J* = 2.7 Hz, 8.3 Hz, 1 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 162.4 (d, *J* = 249.9 Hz), 146.2 (d, *J* = 8.0 Hz), 139.5, 134.7 (d, *J* = 8.5 Hz), 131.3, 129.2, 128.8, 128.3, 128.2, 128.03,

128.00, 123.3, 116.5 (d, J = 22.4 Hz), 114.3 (d, J = 21.9 Hz), 91.8, 88.4 ^{19}F NMR (470 MHz, $CDCl_3$) δ ppm -112.5 (m, 1 F) HRMS (EI+) calculated for $C_{20}H_{13}F$ $[M]^+$: 272.1001, found: 272.1001.

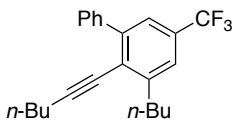
3.3.4. Synthesis of Perfluoroalkyl Arylalkynes.



General procedure: An oven-dried 1.0 mL V-vial equipped with a stirring bar was carged with IPrPdAllCl (2.8 mg, 0.005 mmol, 1 mol %), $(2\text{-furyl})_3P$ (1.2 mg, 0.01 mmol, 2 mol %), CsOPiv (1.2 mg, 0.01 mmol, 2 mol %), and toluene (0.5 mL) under N_2 atmosphere. Enyne **3-141** (0.6 mmol, 1.2 equiv) and diyne **3-138** (0.5 mmol, 1.0 equiv) were subsequently added. The reaction vessel was caped with Mininert syringe valve and the reaction mixture was stirred at 100 °C for 16-24 h. Upon reaction completion resultant mixture was cooled to room temperature, diluted with CH_2Cl_2, and filtered through a celite plug. The filtrate was concentrated under a reduced pressure, and the crude product was purified by column chromatography on silica gel to afford **3-142**.

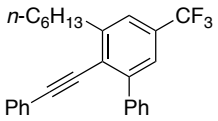


3-142aa: 167.9 mg (0.5 mmol scale), 84% yield, pale yellow oil (eluent: hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.72 – 7.68 (m, 4 H), 7.68 – 7.66 (m, 2 H), 7.54 – 7.45 (m, 6 H), 7.28 – 7.20 (m, 3 H), 7.04 – 7.00 (m, 2 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 145.6, 139.9, 131.3, 129.8 (q, J = 32.8 Hz), 129.5, 128.5, 128.2, 128.1, 128.0, 125.0 (m), 124.1, 123.9 (q, J = 270.0 Hz), 122.9, 98.1, 87.8 ^{19}F NMR (470 MHz, $CDCl_3$) δ ppm -64.2 (s, 3 F) HRMS (EI+) calculated for $C_{27}H_{17}F_3$ $[M]^+$: 398.1282, found: 398.1286.

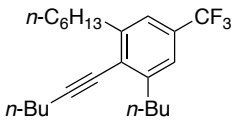


3-142ab: 136.8 mg (0.5 mmol scale), 76% yield, pale yellow oil (eluent: hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.57 – 7.54 (m, 2 H), 7.44 – 7.35 (m, 5 H), 2.91 – 2.88 (m, 2 H), 2.35 – 2.31 (m, 2 H), 1.72 – 1.64 (m, 2 H), 1.61 – 1.49 (m, 4 H), 1.36 – 1.26 (m, 2 H), 0.98 (t, J = 7.3 Hz, 3 H), 0.87 (t, J = 7.3 Hz, 3 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 146.4, 144.9, 140.3, 129.3, 128.8 (q, J = 32.4 Hz), 127.8, 127.6, 125.6, 124.2 (q, J = 271.9 Hz), 123.9 (m), 123.5 (m),

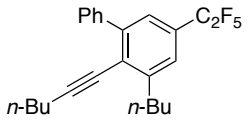
100.1, 77.6, 34.9, 32.6, 30.4, 22.7, 21.8, 19.3, 13.9, 13.5 ^{19}F NMR (470 MHz, $CDCl_3$) δ ppm -64.1 (s, 3 F) HRMS (EI+) calculated for $C_{23}H_{25}F_3$ $[M]^+$: 358.1908, found: 358.1901.



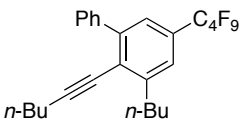
3-142da: 181.0 mg (0.5 mmol scale), 89% yield, pale yellow oil (eluent: hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.77 – 7.66 (m, 2 H), 7.58 – 7.44 (m, 5 H), 7.40 – 7.31 (m, 5 H), 3.05 – 3.01 (m, 2 H), 1.85 – 1.78 (m, 2 H), 1.55 – 1.48 (m, 2 H), 1.44 – 1.37 (m, 4 H), 0.94 (t, *J* = 7.1 Hz, 3 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 146.5, 145.1, 140.7, 132.5, 131.4, 129.7 (q, *J* = 32.4 Hz), 129.5, 128.6, 128.4, 128.0, 127.9, 124.1 (q, *J* = 272.0 Hz), 124.12 (m), 123.7 (m), 98.4, 86.8, 35.4, 31.8, 30.6, 29.4, 22.7, 14.1 ^{19}F NMR (470 MHz, $CDCl_3$) δ ppm -64.1 (s, 3 F) HRMS (EI+) calculated for $C_{27}H_{25}F_3$ $[M]^+$: 406.1908, found: 406.1911.



3-142db: 131.1 mg (0.5 mmol scale), 72% yield + 15% of enyne dimer, pale yellow oil (eluent: hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.25 (s, 2 H), 2.83 – 2.77 (m, 4 H), 2.52 (t, *J* = 6.9 Hz, 2 H), 1.67 – 1.58 (m, 6 H), 1.57 – 1.49 (m, 3 H), 1.44 – 1.28 (m, 10 H), 1.00 – 0.94 (m, 6 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 145.72, 145.65, 143.3, 128.5 (q, *J* = 31.9 Hz), 124.3 (q, *J* = 272.5 Hz), 122.5 (m, 2C), 100.1, 76.9, 35.1, 34.7, 32.6, 31.7, 30.8, 30.4, 29.3, 22.64, 22.58, 22.0, 19.4, 14.0, 13.9, 13.6 ^{19}F NMR (470 MHz, $CDCl_3$) δ ppm -64.1 (s, 3 F) HRMS (EI+) calculated for $C_{23}H_{33}F_3$ $[M]^+$: 366.2534, found: 366.2543.

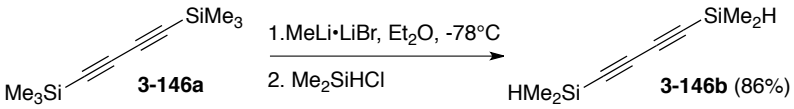


3-142bb: 89.5 mg (0.3 mmol scale), 77% yield, pale yellow oil (eluent: hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.58 – 7.55 (m, 2 H), 7.45 – 7.36 (m, 5 H), 2.92 – 2.88 (m, 2 H), 2.34 (t, *J* = 6.8 Hz, 2 H), 1.72 – 1.65 (m, 2 H), 1.49 – 1.40 (m, 4 H), 1.37 – 1.29 (m, 2 H), 0.99 (t, *J* = 7.3 Hz, 3 H), 0.88 (t, *J* = 7.3 Hz, 3 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 146.3, 144.8, 140.3, 129.3, 127.8, 127.6, 126.9 (t, *J* = 23.7 Hz), 125.8, 125.0 (t, *J* = 5.4 Hz), 124.7 (t, *J* = 5.8 Hz), 100.4, 77.6, 35.0, 32.5, 30.4, 22.7, 21.8, 19.3, 13.9, 13.5 Carbon atoms corresponding to C_2F_5 group can not be identified due to C-F coupling. ^{19}F NMR (470 MHz, $CDCl_3$) δ ppm -86.2 (s, 3F), -116.4 (s, 2F) HRMS (EI+) calculated for $C_{24}H_{25}F_5$ $[M]^+$: 408.1877, found: 408.1872.

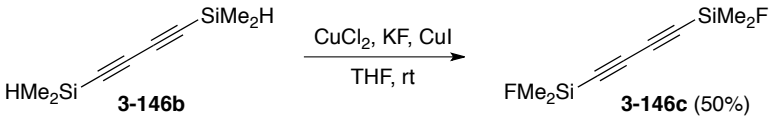


3-142cb: 178.0 mg (0.4 mmol scale), 87% yield, pale yellow oil (eluent: hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.57 – 7.54 (m, 2 H), 7.45 – 7.37 (m, 5 H), 2.92 – 2.87 (m, 2 H), 2.33 (t, *J* = 7.0 Hz, 2 H), 1.71 – 1.64 (m, 2 H), 1.49 – 1.40 (m, 4 H), 1.36 – 1.28 (m, 2 H), 0.98 (t, *J* = 7.3 Hz, 3 H), 0.87 (t, *J* = 7.3 Hz, 3 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 146.2, 144.7, 140.3, 129.3, 127.8, 127.6, 127.0 (t, *J* = 24.1 Hz), 125.9, 125.5 (t, *J* = 5.5 Hz), 125.1 (t, *J* = 5.8 Hz), 100.5, 77.6, 34.9, 32.5, 30.3, 22.6, 21.8, 19.3, 13.9, 13.5 Carbon atoms corresponding to C_4F_9 group can not be identified due to C-F coupling. ^{19}F NMR (470 MHz, $CDCl_3$) δ ppm -82.6 (m, 3 F), -112.6 (m, 2 F), -124.2 (m, 2 F), -127.1 (m, 2 F) HRMS (EI+) calculated for $C_{26}H_{25}F_9$ $[M]^+$: 508.1812, found: 508.1818.

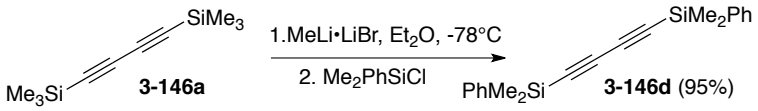
3.3.5. Synthesis of Silyl-substituted Diynes and their Application in Pd-catalyzed [4+2] Benzannulation Reaction



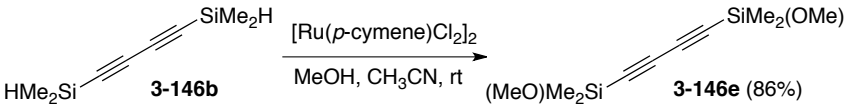
Synthesis of diyne 3-146b: Bis(trimethylsilyl)butadiyne **1-146a** (7.78 g, 40 mmol) was dissolved in dry THF (100 mL) under Ar atmosphere and the resultant solution was cooled to -78 °C. Solution of MeLi·LiBr in ether (1.5 M, 66 mL, 84 mmol) was then slowly added, and the reaction mixture was allowed to warm to room temperature and stirred for additional 1.0 h. After this time it was cooled to -78 °C and freshly redistilled dimethylchlorosilane (9.33 mL, 84 mmol) was slowly added. The reaction mixture was allowed to warm to room temperature and stirred for 15 min. Upon reaction completion solvent was evaporated under reduced pressure and residue was purified by distillation (~60 °C, 20 mm Hg) to afford diyne **1-146b** (5.72 g, 78%) as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 4.17 – 4.12 (m, 2 H), 0.26 (d, *J* = 3.8 Hz, 6 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 89.1, 83.3, -3.54.



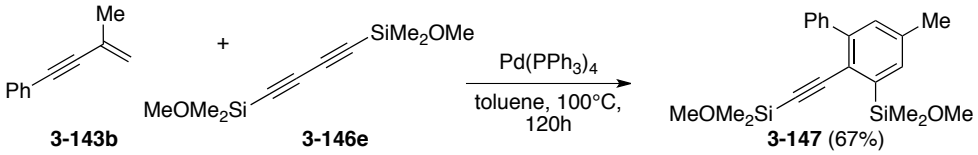
Synthesis of diyne 3-146c: Synthesis of diyne **3-146c** was achieved using modified literature method.[79] To a solution of silane **1-146b** (1.66 g, 10 mmol) in dry THF (30 mL) was added $CuCl_2$ (2.69 g, 20 mmol), CuI (190 mg, 1 mmol), and KF (640 mg, 11 mmol) under Ar atmosphere. The reaction mixture was stirred at ambient temperature for 5 h. Upon reaction completion, the reaction mixture was filtered through celite, solvent were removed under reduced pressure and residue was purified by Kugelrohr distillation (~60 °C, 20 mm Hg), which afforded diyne **1-146c** (1.01 g, 50%) as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.43 – 0.39 (m, 12 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 88.0 (d, J = 4.3 Hz), 82.8 (d, J = 25.5 Hz), 0.1 (d, J = 16.1 Hz) ^{19}F NMR (470 MHz, $CDCl_3$) δ ppm -158.1 (m, 2 F).



Synthesis of diyne 3-146d: Bis(trimethylsilyl)butadiyne **1-146a** (0.97 g, 5 mmol) was dissolved in dry THF (15 mL) under Ar atmosphere and the resultant solution was cooled to -78 °C. Solution of MeLi·LiBr in ether (1.5 M, 8 mL, 12 mmol) was then slowly added, and the reaction mixture was allowed to warm to room temperature and stirred for additional 1.0 h. After this time it was cooled to -78 °C and dimethylphenylchlorosilane (2.00 mL, 12 mmol) was slowly added. The reaction mixture was allowed to warm to room temperature and stirred for 15 min. Upon reaction completion, solvent was evaporated under reduced pressure and residue was purified by column chromatography to afford diyne **1-146d** (1.51 g, 95%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.71 – 7.66 (m, 4 H), 7.48 – 7.41 (m, 6 H), 0.55 – 0.51 (m, 12 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 135.6, 133.8, 129.8, 128.1, 89.6, 84.5, -1.3.

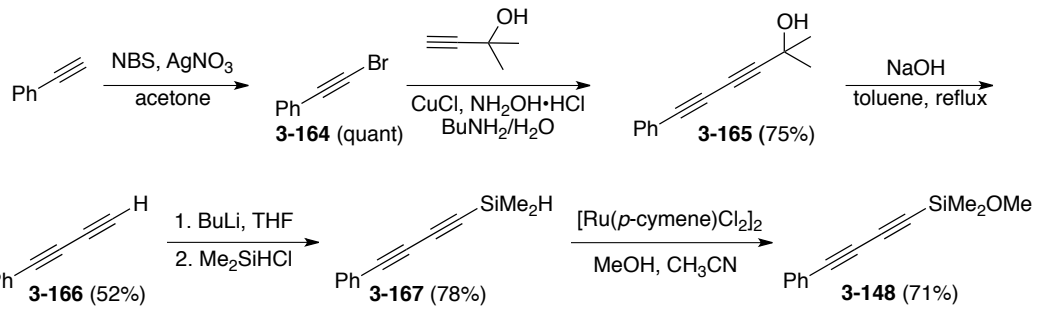


Synthesis of diyne 3-146e: Synthesis of diyne **3-146e** was achieved using modified literature method.[80] To a solution of silane **1-146b** (1.66 g, 10 mmol) in dry acetonitrile (5 mL) was added [Ru(*p*-cymene)Cl_2]$_2$ (61 mg, 0.1 mmol) and dry MeOH (3 mL) under Ar atmosphere. The reaction mixture was stirred at ambient temperature for 10 min. Upon reaction completion solvents were removed under reduced pressure and residue was purified by Kugelrohr distillation (~100 °C, 20 mm Hg) which afforded diyne **1-146e** (1.94 g, 86%) as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 3.50 (s, 6 H), 0.27 (m, 12 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 87.7, 83.6, 51.0, -0.8.



Synthesis of 3-147e: An oven-dried 3 mL V-vial equipped with a stirring bar was charged with Pd(PPh_3)$_4$ (28 mg, 0.025 mmol, 5 mol %), and toluene (0.5 mL) under N_2 atmosphere. Enyne **3-141b** (71.0 mg, 0.5 mmol, 1 equiv) and diyne **3-148** (135.6 mg, 0.6 mmol, 1.2 equiv) were subsequently added. The reaction vessel was caped with Mininert syringe valve and the reaction mixture was stirred at 100 °C for 120 h. Upon reaction completion, resultant mixture was cooled to room temperature, diluted with CH_2Cl_2, and filtered through a celite plug. The filtrate was concentrated under reduced pressure, and the crude product was purified by column chromatography on Florisil (eluent: hexanes : EtOAc = 50 : 1) to afford **3-147** (123.5 mg, 67%) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.58 – 7.53 (m, 2 H), 7.45 (s, 1 H), 7.41 – 7.37 (m, 2 H), 7.36 – 7.31 (m, 1 H), 7.22 (s, 1 H), 3.60 (s, 3 H), 3.34 (s, 3 H), 2.41 (s, 3 H), 0.52 (m, 6 H), 0.18 (s, 6 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 145.5, 141.9, 140.8, 138.1, 133.8, 131.5, 129.5, 127.6, 127.2, 122.2, 105.9, 97.5, 50.9, 50.7, 21.6, -1.0, -1.7.

Diyne **3-148** was synthesized via the following sequence:



Synthesis of diyne 3-165: To a solution of phenylacetylene (5.5 mL, 50 mmol) in acetone (50 mL) was added N-bromosuccinimide (10.6 g, 60 mmol) and $AgNO_3$ (850 mg, 5 mmol). The reaction mixture was stirred at room temperature under exclusion of light for 2 h. Upon completion the reaction mixture was concentrated under reduced pressure and filtered through a celite plug to afford crude **3-164** which was submitted to the next step without further purification.

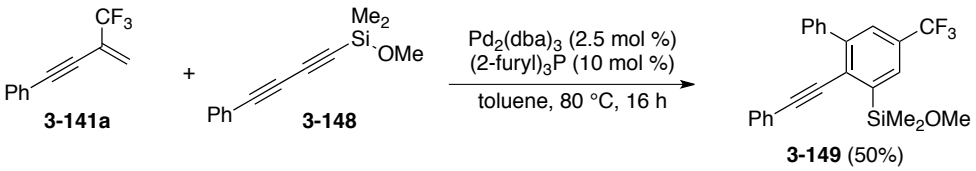
To an aqueous solution of *n*-$BuNH_2$ (30%, 20 mL) was added copper(I) chloride (990 mg, 10 mmol) at 0 ^oC which resulted in a blue solution. After stirring of the mixture for 5 min few crystals of $NH_2OH{\cdot}HCl$ were added which resulted in a colorless solution. 2-methylbut-3-yn-2-ol (5.0 mL, 50 mmol) was then added and resultant yellow solution was stirred for an additional 10 min. A solution of freshly prepared (bromoethynyl)benzene **3-164** (9.05 g, 50 mmol) in CH_2Cl_2 (20 mL) was slowly added under a flow of Ar, and the reaction mixture was allowed to warm up to room temperature and stirred for 1 h. Upon completion the reaction mixture was extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography (eluent: hexanes : EtOAc = 4 : 1) to afford diyne **3-165** (6.9 g, 75%) as a white solid. Analytical data of compound **3-165** are in agreement with the literature data

Synthesis of diyne 3-166: Diyne **3-166** was prepared according to the literature procedure.[81] Alcohol **3-165** (6.44 g, 35.0 mmol) was dissolved in dry toluene. NaOH powder (4.20 g, 105 mmol) was added and the reaction mixture was heated for 15 min at 135 °C under Ar atmosphere. Upon completion of the reaction solvent was evaporated under reduced pressure, and the residue was purified by column

chromatography (eluent: pentane) to afford **3-166** (2.3 g, 52%) as a colorless liquid. Compound **3-166** is unstable neat and was immediately submitted to the next step. Analytical data of compound **3-166** are in agreement with the literature data.

Synthesis of diyne 3-167: Phenylbutadiyne **3-166** (2.3 g, 18 mmol) was dissolved in dry THF (20 mL) under Ar atmosphere and the resultant solution was cooled to -78 °C. Solution of *n*-BuLi in hexane (2.5 M, 8 mL, 20 mmol) was then added dropwise, and the reaction mixture was allowed to warm to room temperature and stirred for additional 1.5 h. After this time it was cooled to -78 °C and freshly redistilled dimethylchlorosilane (2.22 mL, 20 mmol) was slowly added. The reaction mixture was allowed to warm to room temperature and stirred for 15 min. Upon reaction completion solvent was evaporated under reduced pressure and residue was purified by the column chromatography on Florisil (eluent: hexanes) to afford **3-167** (2.58 g, 78%) as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.52 – 7.49 (m, 2 H), 7.38 – 7.30 (m, 3 H), 4.24 – 4.19 (m, 1 H), 0.32 – 0.30 (m, 6 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 132.7, 129.4, 128.4, 121.2, 89.1, 87.5, 74.1, 71.2, -3.3.

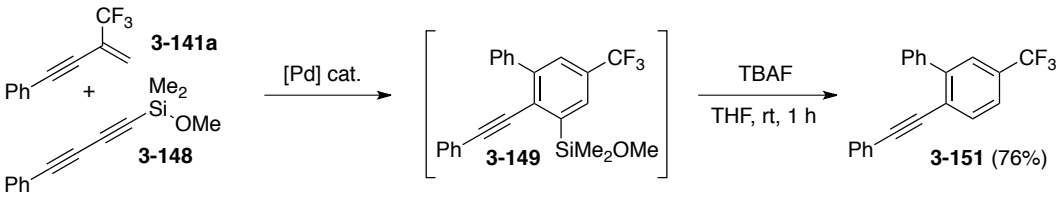
Synthesis of diyne 3-148: Synthesis of diyne **3-148** was achieved using modified literature method.[80] To a solution of silane **3-167** (2.58 g, 14 mmol) in dry acetonitrile (5 mL) was added $[Ru(p\text{-cymene})Cl_2]_2$ (42 mg, 0.07 mmol) and dry MeOH (3 mL) under Ar atmosphere. The reaction mixture was stirred at ambient temperature for 10 min. Upon reaction completion solvents were removed under reduced pressure and residue was purified by Kugelrohr distillation (~80 °C, 0.5 mm Hg) which afforded diyne **3-148** (2.1 g, 71%) as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.53 – 7.49 (m, 2 H), 7.40 – 7.37 (m, 1 H), 7.35 – 7.30 (m, 2 H), 3.54 (s, 3 H), 0.32 (s, 6 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 132.7, 129.5, 128.4, 121.1, 88.0, 87.3, 77.5, 73.9, 51.0, -0.7 HRMS (EI+) calculated for $C_{13}H_{14}OSi$ $[M]^+$: 214.0814, found: 214.0815.



Synthesis of 3-149: An oven-dried 3 mL V-vial equipped with a stirring bar was charged with $Pd_2(dba)_3$ (5.7 mg, 0.00625 mmol, 2.5 mol %), $(2\text{-furyl})_3P$ (5.8 mg, 0.0025 mmol, 10 mol %), and toluene (0.5 mL) under N_2 atmosphere. Enyne **3-141a** (49.0 mg, 0.25 mmol, 1 equiv) and diyne **3-148** (80.0 mg, 0.375 mmol, 1.5 equiv) were subsequently added. The reaction vessel was caped with Mininert syringe valve and the reaction mixture was stirred at 80 °C for 16 h. Upon reaction completion resultant mixture was cooled to room temperature, diluted with CH_2Cl_2, and filtered through a celite plug. The filtrate was concentrated under reduced pressure, and the crude product (NMR yield 78%) was purified by column chromatography on Florisil (eluent: hexanes : EtOAc = 50 : 1) to afford **3-149** (50.9 mg, 50%) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.90 – 7.89 (m, 1 H), 7.70 – 7.67 (m, 1 H), 7.65 – 7.62 (m, 2 H), 7.52 – 7.42 (m, 3 H), 7.33 – 7.26 (m, 5 H), 3.63 (s, 3 H), 0.59 (s, 6 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 144.9, 142.7, 139.8, 131.11, 131.06, 129.6 (m), 129.5, 129.2 (q, J = 31.3 Hz), 128.7, 128.4, 127.98, 127.95, 127.3 (m), 124.2 (q, J = 271.2 Hz), 122.8, 97.4, 89.3, 50.9, -1.73 ^{19}F NMR (470 MHz, $CDCl_3$) δ ppm -64.2 (s, 3 F) HRMS (EI+) calculated for $C_{24}H_{21}F_3OSi$ $[M]^+$: 410.1314, found: 410.1320.

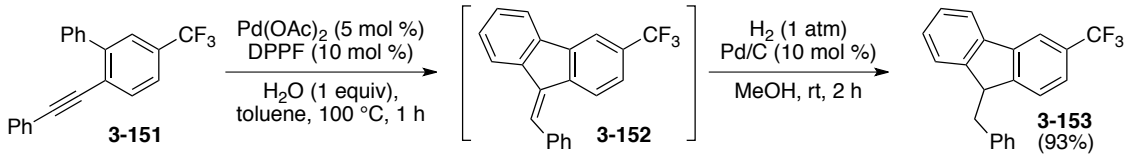
Due to its limited stability toward chromatographic agents **3-149** was used without purification in following transformations.

3.3.6. Synthetic Applications of *ortho*-Silylaryl Alkynes



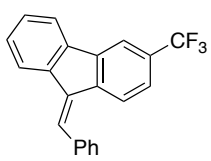
Synthesis of 3-151: An oven-dried 3 mL V-vial equipped with a stirring bar was charged with $Pd_2(dba)_3$ (22.9 mg, 0.025 mmol, 2.5 mol %), $(2\text{-furyl})_3P$ (23.2 mg, 0.1 mmol, 10 mol %), and toluene (1

mL) under N_2 atmosphere. Enyne **3-141a** (196.0 mg, 1.0 mmol, 1 equiv) and diyne **3-148** (321.0 mg, 1.5 mmol, 1.5 equiv) were subsequently added. The reaction vessel was caped with Mininert syringe valve and the reaction mixture was stirred at 80 °C for 16 h. Upon reaction completion resultant mixture was cooled to room temperature and solution of TBAF (1M in THF, 2.0 mL, 2.0 mmol) was added. The reaction mixture was stirred at room temperature for 1 h, diluted with CH_2Cl_2, and filtered through a celite plug. The filtrate was concentrated under reduced pressure and the crude product was purified by column chromatography (eluent: hexanes) to afford **3-151** (243.9 mg, 76%) as a pale yellow oil. The product was obtained as an inseparable mixture with corresponding enyne dimer (~ 5%). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.77 – 7.74 (m, 1 H), 7.70 – 7.66 (m, 3 H), 7.61 – 7.57 (m, 1 H), 7.53 – 7.43 (m, 3 H), 7.37 – 7.29 (m, 5 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 144.4, 139.3, 133.1, 131.5, 130.2 (q, J = 32.3 Hz), 129.3, 128.7, 128.3, 128.1, 126.3 (m), 125.4, 123.7 (m), 123.6 (q, J = 271.6 Hz), 122.8, 94.5, 88.1 ^{19}F NMR (470 MHz, $CDCl_3$) δ ppm -64.3 (s, 3 F) HRMS (EI+) calculated for $C_{21}H_{13}F_3$ $[M]^+$: 322.0969, found: 322.0961.

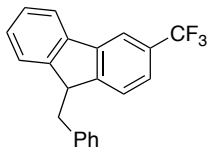


Synthesis of 3-153: Synthesis of compound **3-152** was achieved via a modified literature method.[71a] *o*-Alkynylbiaryl **3-151** (46.0 mg, 0.143 mmol) was placed to an oven-dried 1 mL V-vial equipped with a stirring bar. $Pd(OAc)_2$ (1.6 mg, 0.007 mmol), 1,1'-bis(diphenylphosphino)ferrocene (DPPF, 8.3 mg, 0.014 mmol), and toluene (0.3 mL) were added under N_2 atmosphere. The reaction vessel was caped with Mininert syringe valve and the reaction mixture was stirred at room temperature for 5 min. Water (2.5 mL, 0.14 mmol) was then added via microsyringe. The reaction mixture was heated to 100 °C and stirred at this temperature for 1 h. Upon reaction completion resultant mixture was cooled to room temperature, diluted with CH_2Cl_2, and filtered through a celite plug. The filtrate was concentrated under reduced pressure, and the crude product was submitted to hydrogenation without further purification. Intermediate **3-152** was dissolved in dry MeOH (1.0 mL) and Pd/C (10 wt.%, 7.5 mg, 0.014

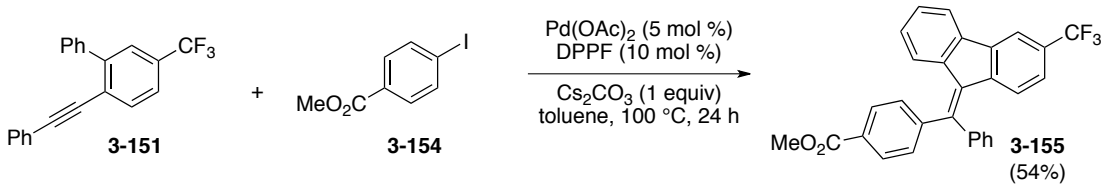
mmol) was added. Flask was flushed with Ar, then Ar balloon was replaced with H_2 balloon, and reaction mixture was stirred for 2 h at ambient temperature. Upon reaction completion the resultant mixture was diluted with CH_2Cl_2, and filtered through a celite plug. The filtrate was concentrated under reduced pressure and the crude product was purified by column chromatography (eluent: hexanes) to afford **3-153** (43.0 mg, 93%) as a pale yellow oil.



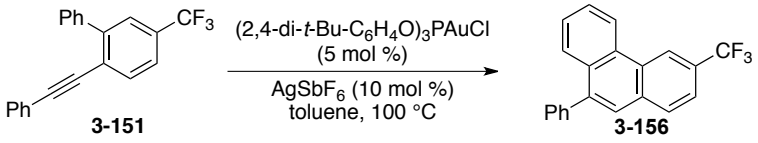
3-152: 75.7 mg (0.25 mmol scale), 94% yield, white solid (eluent: hexanes), the product was obtained as an inseparable mixture with regio- and stereoisomers (<5%). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.94 (s, 1 H), 7.84 – 7.81 (m, 2 H), 7.62 (d, *J* = 8.4 Hz, 1 H), 7.59 – 7.56 (m, 2 H), 7.51 – 7.47 (m, 2 H), 7.46 – 7.38 (m, 3 H), 7.33 – 7.30 (m, 2 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 141.6, 139.55, 139.48, 137.9, 136.3, 135.6, 130.0 (q, *J* = 31.5 Hz), 129.7, 129.2, 128.7, 128.53, 128.51, 127.8, 124.5, 124.4 (q, *J* = 272.0 Hz), 123.5 (m), 120.4, 120.0, 116.5 (m) ^{19}F NMR (470 MHz, $CDCl_3$) δ ppm -63.9 (s, 3 F) HRMS (EI+) calculated for $C_{21}H_{13}F_3$ $[M]^+$: 322.0969, found: 322.0972.



3-153: 43.0 mg (0.14 mmol scale), 93% yield, white solid (eluent: hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.97 (s, 1 H), 7.79 (d, *J* = 7.6 Hz, 1 H), 7.47 (d, *J* = 7.9 Hz, 1 H), 7.40 (t, *J* = 7.4 Hz, 1 H), 7.36 – 7.19 (m, 8 H), 4.28 (d, *J* = 7.6 Hz, 1 H), 3.19 (dd, *J* = 13.8 Hz, 7.4 Hz, 1 H), 3.06 (dd, *J* = 13.8 Hz, 8.0 Hz, 1 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 150.3, 147.0, 141.5, 139.5, 139.2, 129.5, 129.4 (q, *J* = 32.4 Hz), 128.4, 127.6, 127.5, 126.6, 125.1, 124.9, 123.4 (m), 120.2, 116.7 (m), 48.8, 39.8 ^{19}F NMR (470 MHz, $CDCl_3$) δ ppm -63.5 (s, 3 F) HRMS (EI+) calculated for $C_{21}H_{14}F_3$ $[M\text{-}H]^+$: 323.1047, found: 323.1041.

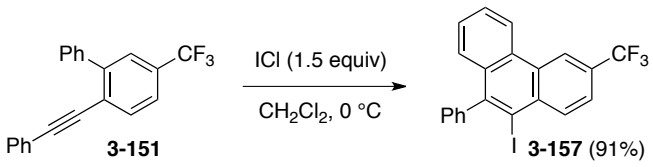


Synthesis of 3-155: Synthesis of compound **3-155** was achieved via a modified literature method.[71b] *o*-Alkynylbiaryl **3-151** (48.0 mg, 0.15 mmol) and methyl 4-iodobenzoate **3-154** (78.6 mg, 0.3 mmol) were placed to an oven-dried 1 mL V-vial equipped with a stirring bar. $Pd(OAc)_2$ (1.7 mg, 0.0075 mmol), 1,1'-bis(diphenylphosphino)ferrocene (DPPF, 8.3 mg, 0.015 mmol), Cs_2CO_3 (97.5 mg, 0.3 mmol), and toluene (0.75 mL) were added under N_2 atmosphere. The reaction vessel was caped with Mininert syringe valve and the reaction mixture was heated to 100 °C and stirred at this temperature for 24 h. Upon reaction completion the resultant mixture was cooled to room temperature, diluted with CH_2Cl_2, and filtered through a celite plug. The filtrate was concentrated under reduced pressure and the crude product was purified by column chromatography (eluent: hexanes : EtOAc = 10 : 1) to afford **3-155** (37.1 mg, 54%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.11 (d, J = 8.3 Hz, 2 H), 7.92 (s, 1 H), 7.75 (d, J = 7.6 Hz, 1 H), 7.49 (d, J = 8.3 Hz, 2 H), 7.46 – 7.44 (m, 3 H), 7.37 – 7.34 (m, 2 H), 7.31 (dt, J = 7.5 Hz, 0.9 Hz, 1 H), 7.19 (d, J = 8.2 Hz, 1 H), 6.99 (dt, J = 7.8 Hz, 1.1 Hz, 1 H), 6.68 (t, J = 8.5 Hz, 2 H), 3.97 (s, 3 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 166.7, 147.0, 146.4, 141.8, 141.4, 140.9, 139.4, 138.4, 134.1, 130.2, 130.1, 129.7, 129.6, 129.1, 128.9, 128.3, 127.4, 125.1, 124.9, 123.3 (m), 119.8, 116.1 (m), 52.3 ^{19}F NMR (470 MHz, $CDCl_3$) δ ppm -63.9 (s, 3 F) HRMS (EI+) calculated for $C_{29}H_{19}F_3O_2$ $[M]^+$: 456.1337, found: 456.1341.



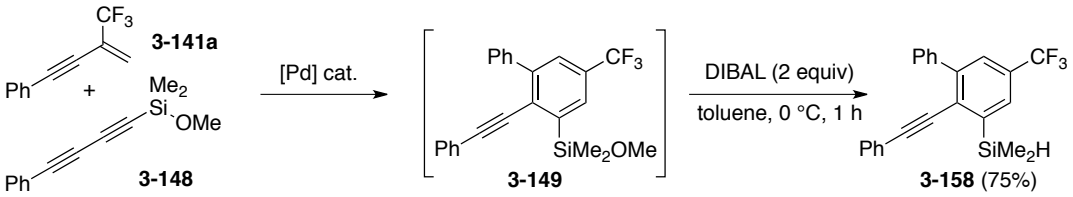
Synthesis of 3-156: Synthesis of compound **3-156** was achieved via a modified literature method.[72] *o*-Alkynylbiaryl **3-151** (80.5 mg, 0.25 mmol) was placed to an oven-dried 3 mL V-vial equipped with a stirring bar. [Tris(2,4-di-*tert*-butylphenyl)phosphite]gold chloride (11.0 mg, 0.0125

mmol), $AgSbF_6$ (8.6 mg, 0.025 mmol), and toluene (1.0 mL) were added under N_2 atmosphere. The reaction vessel was caped with Mininert syringe valve and the reaction mixture was heated to 100 °C and stirred at this temperature for 3 h. Upon reaction completion the resultant mixture was diluted with CH_2Cl_2 and filtered through a celite plug. The filtrate was concentrated under reduced pressure and the crude product was purified by column chromatography (eluent: hexanes) to afford **3-156** (72.9 mg, 91%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 9.01 (s, 1 H), 8.80 (d, *J* = 8.3 Hz, 1 H), 7.99 (d, *J* = 8.4 Hz, 1 H), 7.97 (dd, *J* = 1.0 Hz, 8.5 Hz, 1 H), 7.82 (dd, *J* = 1.3 Hz, 8.3 Hz, 1 H), 7.77 – 7.72 (m, 2 H), 7.61 (ddd, *J* = 1.1 Hz, 6.9 Hz, 8.1 Hz, 1H), 7.57 – 7.48 (m, 5 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 141.2, 140.2, 133.4, 131.4, 130.4, 129.9, 129.4, 128.4, 127.7, 127.4 (q, *J* = 32.3 Hz), 127.3, 127.2, 127.1, 126.7, 124.7 (q, *J* = 272.0 Hz), 122.9, 122.7 (m), 120.1 (m) ^{19}F NMR (470 MHz, $CDCl_3$) δ ppm -63.2 (s, 3 F) HRMS (EI+) calculated for $C_{21}H_{13}F_3$ $[M]^+$: 322.0969, found: 322.0975.

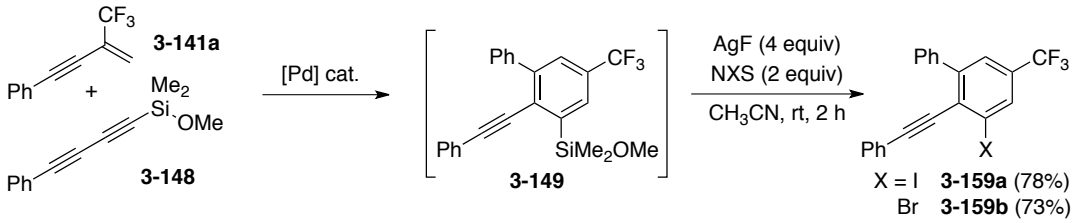


Synthesis of 3-157: Synthesis of compound **3-157** was according to the literature method.[73] To a solution of arylalkyne **3-151** (103.0 mg, 0.32 mmol) in dry CH_2Cl_2 (3.0 mL) was slowly added solution of ICl (1M in CH_2Cl_2, 0.6 mL, 0.6 mmol) at 0 °C and the reaction mixture stirred for 30 min at this temperature. Upon completion the reaction was diluted with CH_2Cl_2 (10 mL), washed with saturated aqueous $Na_2S_2O_3$, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: hexanes) to afford **3-157** (130.7 mg, 91%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.98 (s, 1 H), 8.75 (d, *J* = 8.4 Hz, 1H), 8.61 (d, *J* = 8.7 Hz, 1 H), 7.88 (dd, 1.5 Hz, *J* = 8.7 Hz, 1 H), 7.74 (ddd, *J* = 1.5 Hz, 6.8 Hz, 8.3 Hz, 1 H), 7.61 – 7.53 (m, 3 H), 7.52 – 7.44 (m, 2 H), 7.31 – 7.27 (m, 2 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 147.6, 144.9, 135.7, 134.3, 132.6, 130.08, 129.99, 129.7, 128.9, 128.6, 128.1, 127.9, 127.7, 124.4 (q, *J* = 272.6 Hz), 123.8 (m), 122.6, 120.2 (m),

105.1 ^{19}F NMR (470 MHz, $CDCl_3$) δ ppm -63.3 (s, 3 F) HRMS (EI+) calculated for $C_{21}H_{12}F_3I$ $[M]^+$: 447.9936, found: 447.9933.

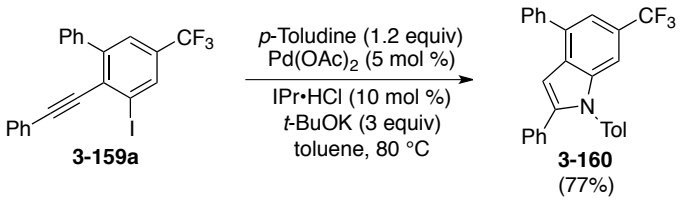


Synthesis of 3-158: An oven-dried 3 mL V-vial equipped with a stirring bar was charged with $Pd_2(dba)_3$ (5.7 mg, 0.00625 mmol, 2.5 mol %), $(2\text{-furyl})_3P$ (5.8 mg, 0.0025 mmol, 10 mol %), and toluene (0.5 mL) under N_2 atmosphere. Enyne **3-141a** (49.0 mg, 0.25 mmol, 1 equiv) and diyne **3-148** (80.0 mg, 0.375 mmol, 1.5 equiv) were subsequently added. The reaction vessel was caped with Mininert syringe valve and the reaction mixture was stirred at 80 °C for 16 h. Upon reaction completion resultant mixture was cooled to room temperature, diluted with hexanes and filtered through a short Florisil column to remove Pd residue. The filtrate was concentrated under reduced pressure, and the crude product was submitted to the next step without further purification. Intermediate **3-149** was dissolved in dry toluene (1.0 mL) and solution of diisobutylaluminium hydride (1M in toluene, 0.5 mL, 0.5 mmol) was slowly added at 0 °C. The reaction mixture was stirred at this temperature for 1 h and then $Na_2SO_4 \cdot 10H_2O$ was added. The resultant mixture was stirred for an additional 15 min, diluted with hexanes, dried over Na_2SO_4, and filtered through a celite plug. The filtrate was concentrated under reduced pressure and the crude product was purified by column chromatography (eluent: hexanes) to afford **3-158** (71.0 mg, 75% over two steps) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.81 – 7.79 (m, 1 H), 7.71 – 7.69 (m, 1 H), 7.68 – 7.65 (m, 2 H), 7.53 – 7.45 (m, 3 H), 7.34 – 7.32 (m, 5 H), 4.74 (sept, J = 3.7 Hz, 1 H), 0.56 (d, J = 3.8 Hz, 6 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 144.5, 142.3, 139.7, 131.2, 130.6, 129.2 (q, J = 32.2 Hz), 129.9 (q, J = 3.6 Hz), 129.5, 128.8, 128.4, 128.04, 128.02, 127.2 (q, J = 3.9 Hz), 124.2 (q, J = 272.8 Hz), 122.9, 97.8, 88.9, -3.91 ^{19}F NMR (470 MHz, $CDCl_3$) δ ppm -64.2 (s, 3 F) HRMS (EI+) calculated for $C_{23}H_{19}F_3Si$ $[M]^+$: 380.1208, found: 380.1215.

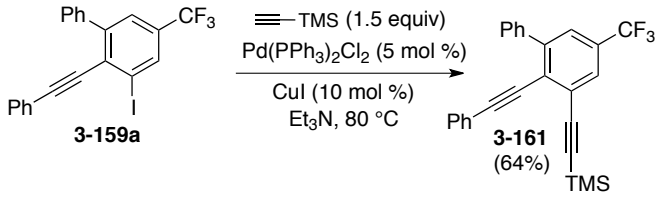


Synthesis of 3-159: An intermediate **3-149** (0.25 mmol scale) was obtained according to the procedure described for the synthesis of **3-158**. To a solution of **3-149** in dry acetonitrile (3.0 mL) were added AgF (127.0 mg, 1.0 mmol) and *N*-iodosuccinimide (112.0 mg, 0.5 mmol) under Ar atmosphere. The reaction mixture was stirred at ambient temperature for 3 h under exclusion of light. The resultant mixture was diluted with CH_2Cl_2 and filtered through a celite plug. The filtrate was concentrated under reduced pressure and the crude product was purified by column chromatography (eluent: hexanes) to afford **3-159a** (87.6 mg, 78% over two steps) as a white solid. The product was obtained as an inseparable mixture with corresponding enyne dimer (~ 6%). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.14 – 8.12 (m, 1 H), 7.64 – 7.61 (m, 3 H), 7.52 – 7.43 (m, 3 H), 7.40 – 7.29 (m, 5 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 145.7, 139.4, 134.2 (m), 131.5, 130.4 (q, J = 32.4 Hz), 129.2, 129.1, 128.5, 128.4, 128.1, 128.0, 125.9 (m), 122.8 (q, J = 271.9 Hz), 122.4, 102.4, 98.7, 91.0 ^{19}F NMR (470 MHz, $CDCl_3$) δ ppm -62.0 (s, 3 F) HRMS (EI+) calculated for $C_{21}H_{12}F_3I$ $[M]^+$: 447.9936, found: 447.9943.

Analogous procedure with the use of *N*-bromosuccinimide (75.0 mg, 0.5 mmol) afforded **3-159b** (73.5 mg, 73%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.90 – 7.88 (m, 1 H), 7.65 – 7.60 (m, 3 H), 7.52 – 7.44 (m, 3 H), 7.38 – 7.29 (m, 5 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 146.5, 139.1, 131.6, 130.4 (q, J = 32.4 Hz), 129.3, 129.1, 128.5, 128.4, 128.1, 127.9 (m), 127.6, 126.9, 125.0 (m), 123.1 (q, J = 272.0 Hz), 122.4, 99.7, 87.1 ^{19}F NMR (470 MHz, $CDCl_3$) δ ppm -64.4 (s, 3 F) HRMS (EI+) calculated for $C_{21}H_{12}BrF_3$ $[M]^+$: 400.0074, found: 400.0067.

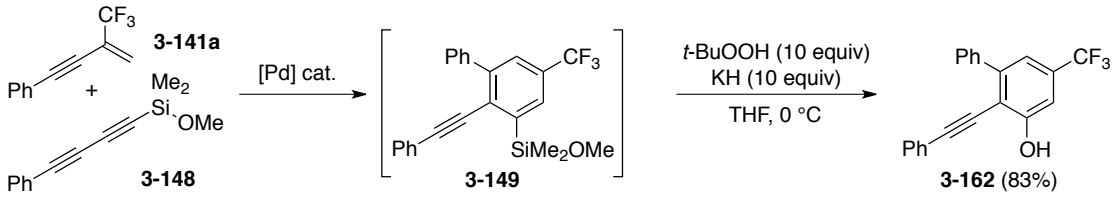


Synthesis of 3-160: Synthesis of compound **3-160** was achieved via a modified literature method.[75] *o*-Iodoarylalkyne **3-159a** (62.7 mg, 0.15 mmol) was placed to an oven-dried 3 mL V-vial equipped with a stirring bar. $Pd(OAc)_2$ (1.7 mg, 0.0075 mmol), 1,3-(2,6-diisopropylphenyl)imidazolium chloride (IPr·HCl, 6.3 mg, 0.015 mmol), *t*-BuOK (50.4 mg, 0.45 mmol), and toluene (0.1 mL) were added under N_2 atmosphere. The reaction vessel was caped with Mininert syringe valve and the reaction mixture was stirred at 80 °C for 3 h. Upon completion the reaction was diluted with CH_2Cl_2 (10 mL), filtered through a celite plug, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: hexanes) to afford **3-160** (49.5 mg, 77%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.78 – 7.75 (m, 2 H), 7.56 – 7.52 (m, 2 H), 7.50 – 7.42 (m, 3 H), 7.29 – 7.25 (m, 7 H), 7.19 – 7.16 (m, 2 H), 6.99 (d, *J* = 0.7 Hz, 1 H), 2.44 (s, 3 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 143.7, 140.0, 138.7, 137.9, 135.1, 134.8, 131.8, 130.2, 129.0, 128.8, 128.7, 128.2, 127.84, 127.79, 127.6, 124.7 (q, *J* = 32.6 Hz), 124.0 (q, *J* = 271.6 Hz), 117.0 (m), 107.3 (m), 102.9, 21.2 ^{19}F NMR (470 MHz, $CDCl_3$) δ ppm -62.0 (s, 3 F) HRMS (EI+) calculated for $C_{28}H_{20}F_3N$ $[M]^+$: 427.1548, found: 427.1538.

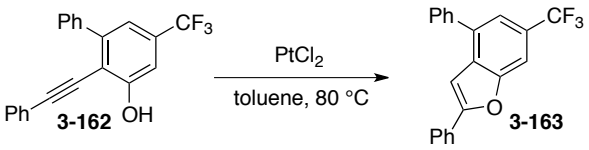


Synthesis of 3-161: Aryiodide **3-159a** (62.7 mg, 0.15 mmol) was placed to an oven-dried 3 mL V-vial equipped with a stirring bar. $Pd(PPh_3)_2Cl_2$ (5.3 mg, 0.0075 mmol), CuI (3.0 mg, 0.015 mmol) were added under N_2 atmosphere. Dry THF (0.5 mL) and dry Et_3N (0.5 mL) were subsequently added followed by addition of the trimethysilylacetylene (30 mL, 0.3 mmol). The reaction vessel was caped with Mininert syringe valve and the reaction mixture was stirred at 80 °C for 12 h. Upon completion the reaction was

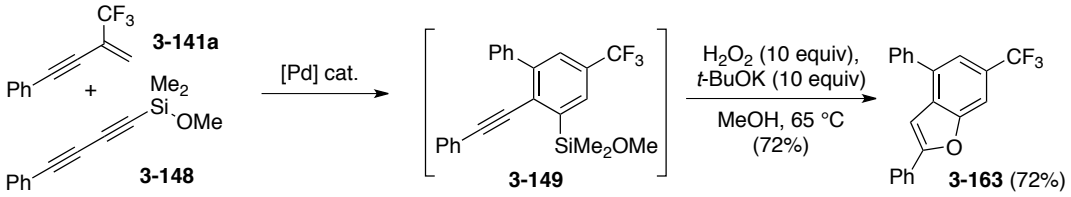
quenched with saturated NH_4Cl solution and extracted with EtOAc. Combined extracts were dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexanes) to afford **3-161** (40.2 mg, 64%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.78 – 7.76 (m, 1 H), 7.65 – 7.62 (m, 2 H), 7.60 – 7.58 (m, 1 H), 7.51 – 7.43 (m, 3 H), 7.36 – 7.28 (m, 5 H), -0.31 (s, 9 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 144.9, 139.1, 131.6, 129.7 (q, J = 32.6 Hz), 129.2, 128.8, 128.3, 128.1, 127.80 (m), 127.75, 127.1, 125.8 (m), 123.5 (q, J = 272.2 Hz), 122.8, 102.5, 100.4, 99.0, 87.0, -0.1 ^{19}F NMR (470 MHz, $CDCl_3$) δ ppm -64.5 (s, 3 F) HRMS (EI+) calculated for $C_{26}H_{21}F_3Si$ $[M]^+$: 418.1365, found: 418.1357.



Synthesis of 3-162: An intermediate **3-149** (0.25 mmol scale) was obtained according to the procedure described for the synthesis of **3-158**. To a solution of **3-158** in dry THF (5.0 mL) were added solution of *t*-BuOOH (5.5 M in decane, 450 mL, 2.5 mmol) and KH (100.0 mg, 2.5 mmol) at 0 °C. The reaction mixture was stirred for 30 min. Upon completion the reaction was quenched with saturated NH_4Cl solution and extracted with EtOAc. Combined extracts were dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexanes : EtOAc = 10 : 1) to afford **3-162** (70.5 mg, 83%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.69 – 7.66 (m, 2 H), 7.52 – 7.42 (m, 3 H), 7.41 – 7.32 (m, 5 H), 7.36 – 7.28 (m, 2 H), 6.26 (s, 1 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 157.0, 145.0, 139.0, 131.4, 131.6 (q, J = 32.4 Hz), 129.3, 129.0, 128.5, 128.3, 128.2, 121.8, 123.7 (q, J = 272.8 Hz), 118.0 (m), 111.9, 110.3 (m), 101.2, 81.7 ^{19}F NMR (470 MHz, $CDCl_3$) δ ppm -64.6 (s, 3 F) HRMS (EI+) calculated for $C_{21}H_{13}F_3O$ $[M]^+$: 338.0919, found: 338.0915.



Synthesis of 3-163: Compound **3-163** was prepared according to the literature method.[76] *o*-Alkinylphenol **3-162** (50.7 mg, 0.15 mmol) was placed to an oven-dried 3 mL V-vial equipped with a stirring bar. $PtCl_2$ (2.5 mg, 0.0075 mmol) and toluene (0.3 mL) were added under N_2 atmosphere. The reaction vessel was caped with Mininert syringe valve and the reaction mixture was stirred at 80 °C for 16 h. Upon completion the reaction was diluted with CH_2Cl_2 (10 mL), filtered through a celite plug, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: hexanes) to afford **3-163** (36.1 mg, 71%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.89 (d, J = 7.5 Hz, 2 H), 7.79 (s, 1 H), 7.69 (d, J = 7.2 Hz, 2 H), 7.59 – 7.53 (m, 3 H), 7.50 – 7.46 (m, 3 H), 7.43 – 7.39 (m, 1 H), 7.23 (s, 1 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 158.8, 154.3, 139.0, 132.5, 130.6, 129.6, 129.4, 129.0, 128.9, 128.4, 128.1, 126.7 (q, J = 32.7 Hz), 125.2, 124.6 (q, J = 271.5 Hz), 119.5 (m), 107.5 (m), 100.6 ^{19}F NMR (470 MHz, $CDCl_3$) δ ppm -62.6 (s, 3 F) HRMS (EI+) calculated for $C_{21}H_{13}F_3O$ $[M]^+$: 338.0919, found: 338.0921.



Synthesis of 3-163: An intermediate **3-149** (0.25 mmol scale) was obtained according to the procedure described for the synthesis of **3-158**. To a solution of 5ac in MeOH - THF mixture (MeOH : THF = 1:1; 10.0 mL) were added H_2O_2 solution (50 wt.% in water, 200 mL, ~2.5 mmol) and *t*-BuOK (84.0 mg, 0.75 mmol) at room temperature. The reaction mixture was stirred for 30 min at this temperature and then heated to 65 °C and stirred for 24 h. Upon completion the reaction was quenched with saturated NH_4Cl solution and extracted with EtOAc. Combined extracts were dried over Na_2SO_4,

and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexanes) to afford **3-163** (60.7 mg, 72%) as a white solid.

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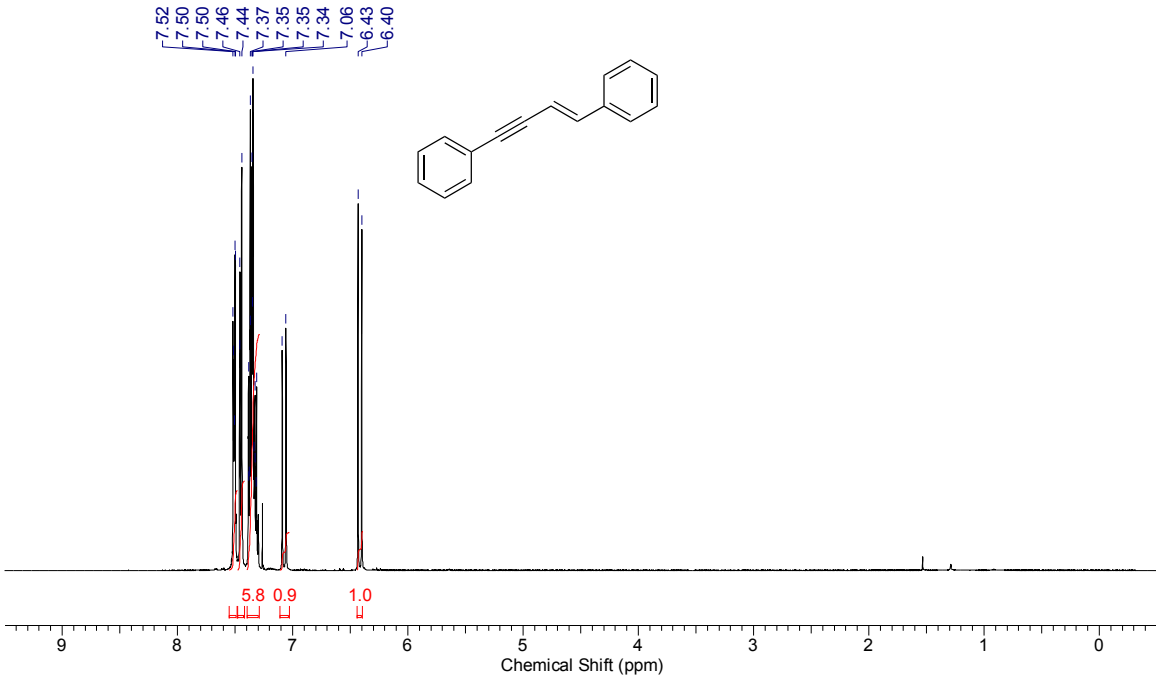
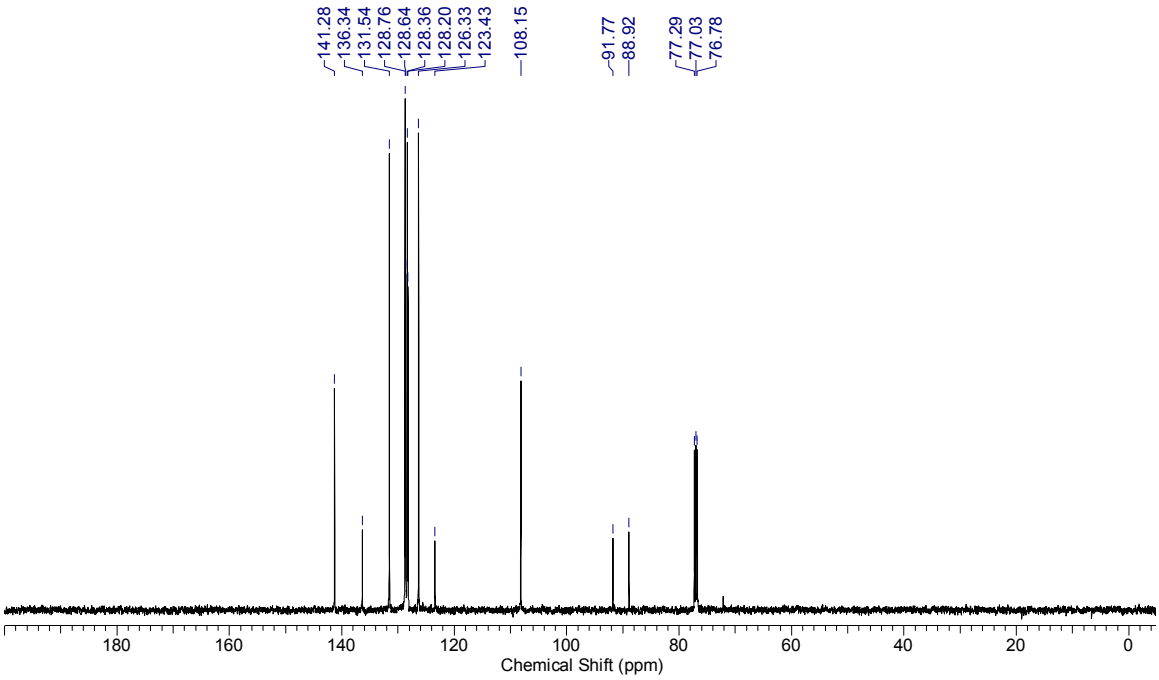
APPENDIX I

Selected NMR Spectra for Part One

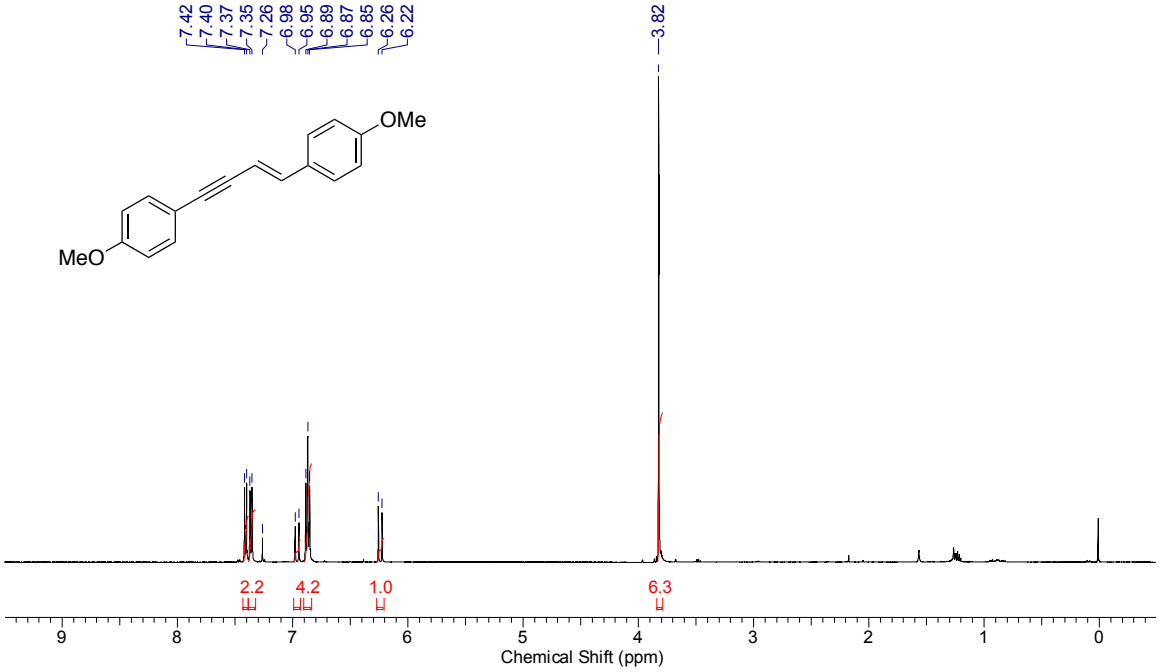
^{1}H NMR spectrum of **1-03a**:



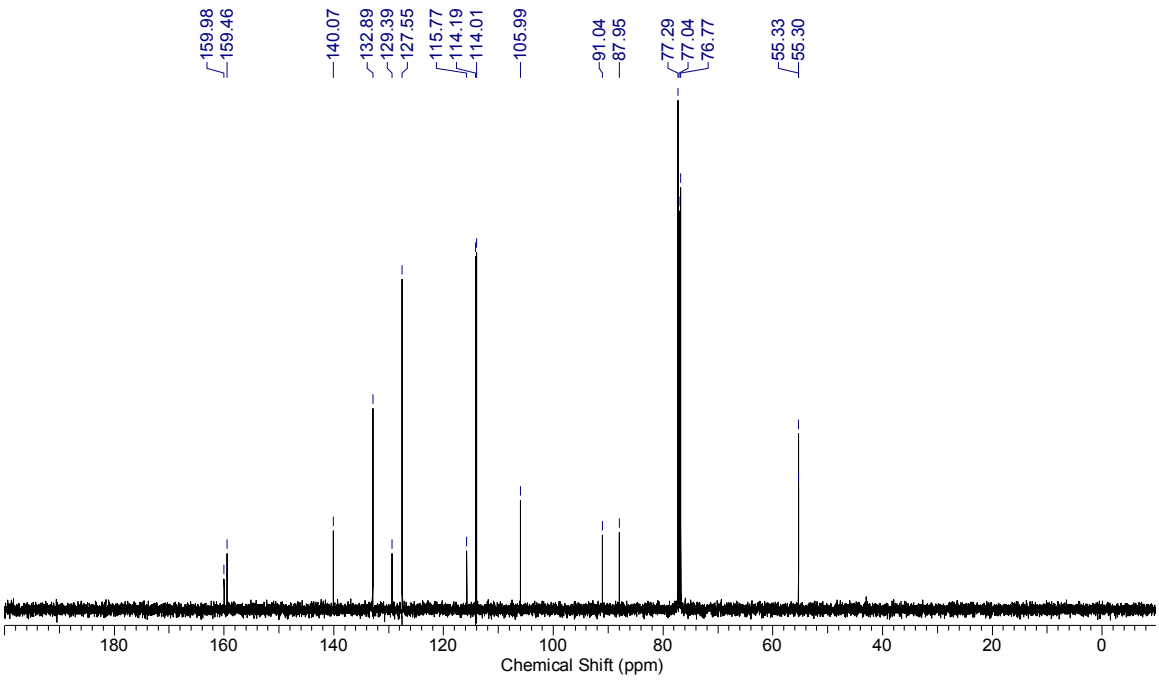
^{13}C NMR spectrum of **1-03a**:



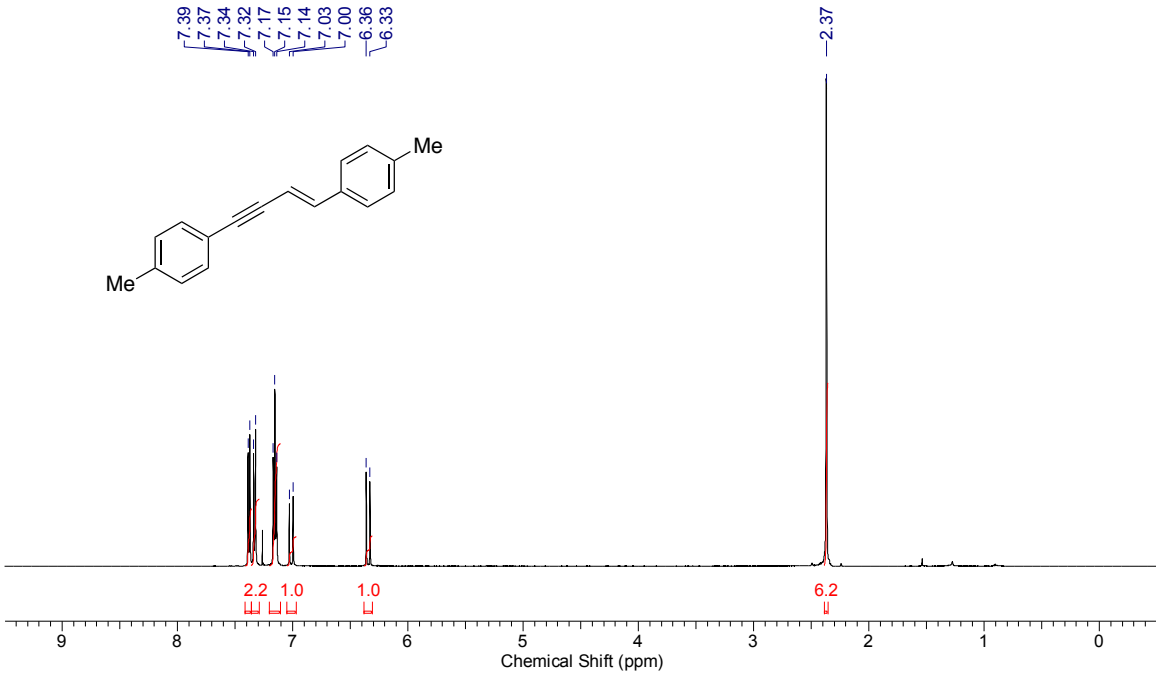
^{1}H NMR spectrum of **1-03j**:



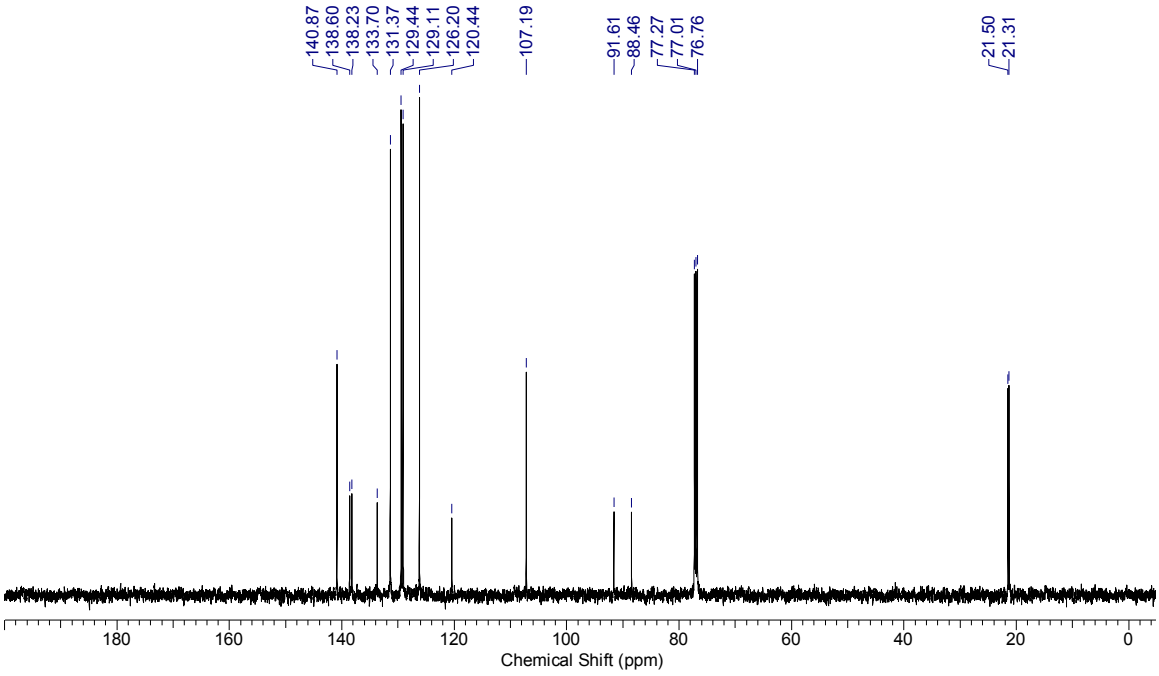
^{13}C NMR spectrum of **1-03j**:



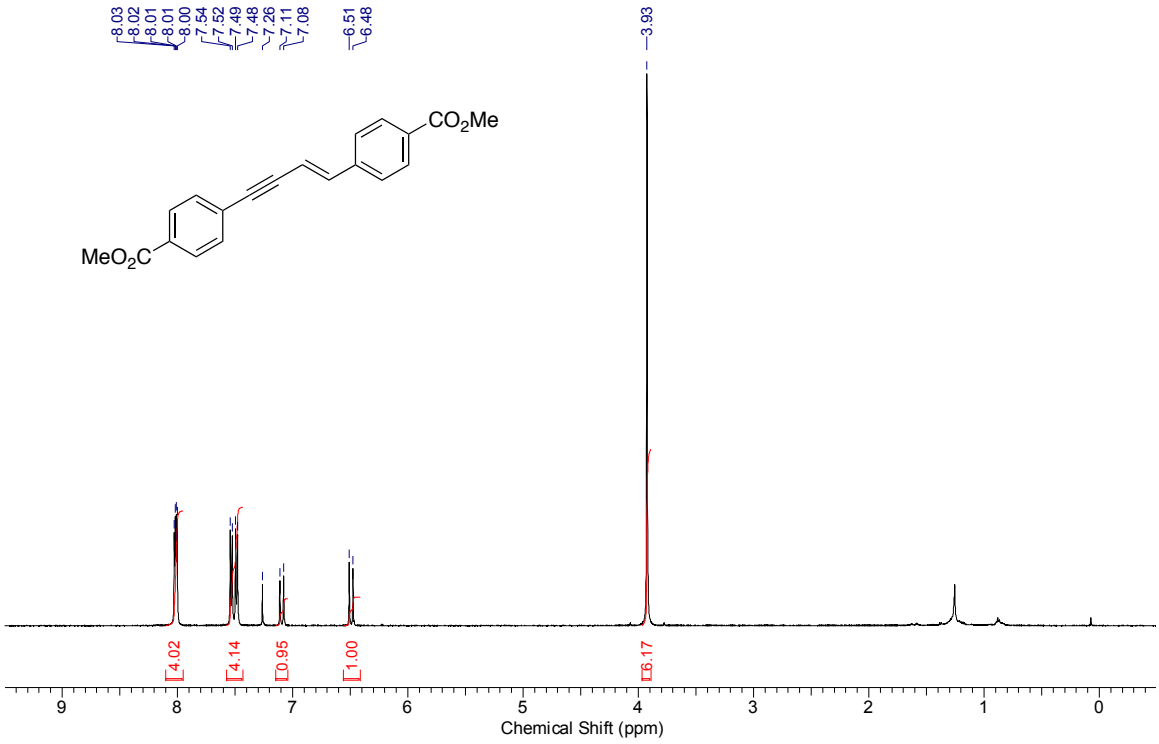
^{1}H NMR spectrum of **1-03i**:



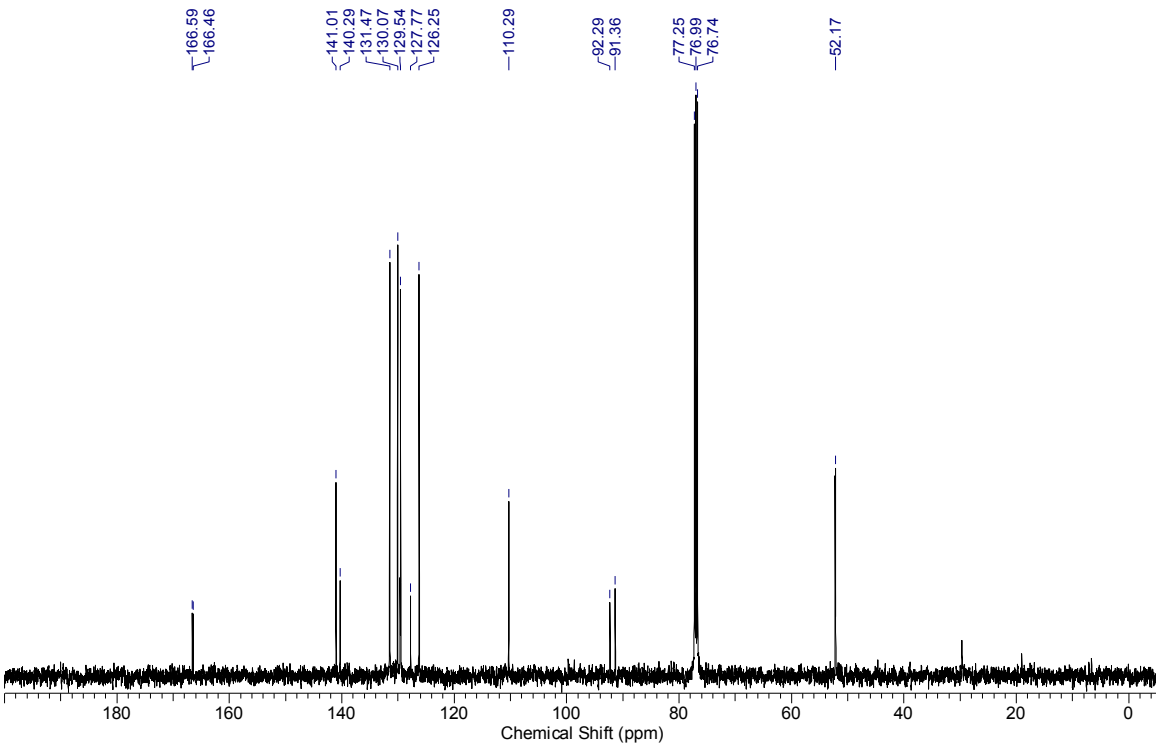
^{13}C NMR spectrum of **1-03i**:



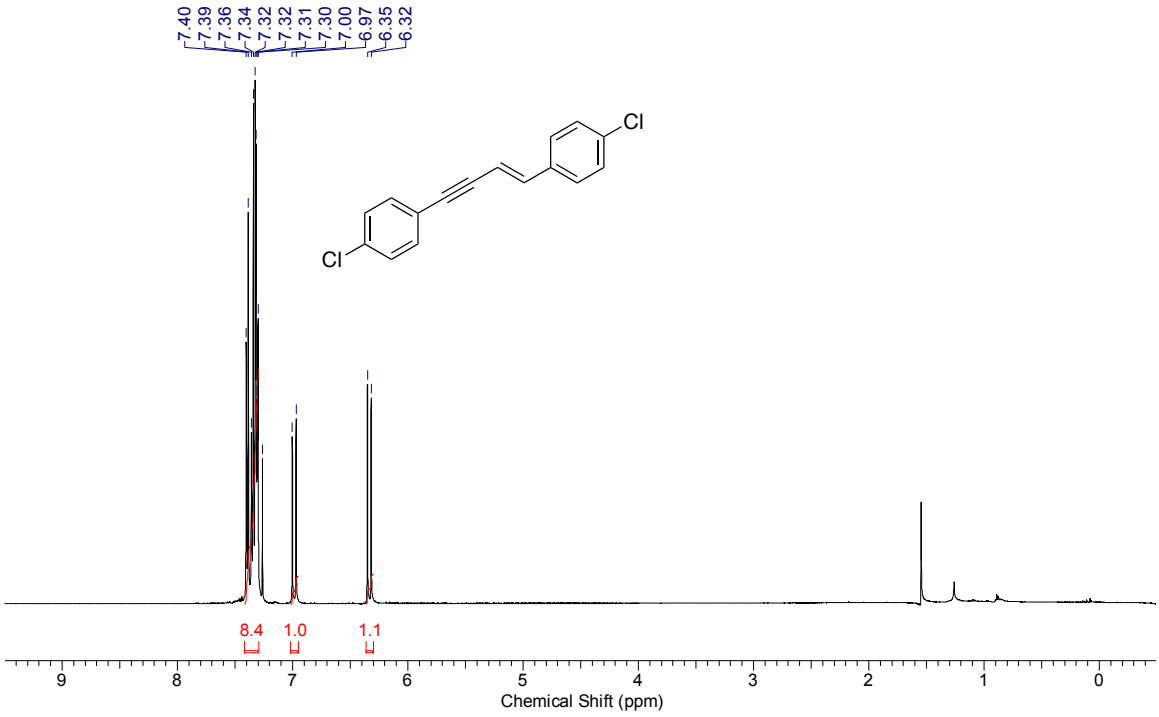
^{1}H NMR spectrum of **1-03y**:



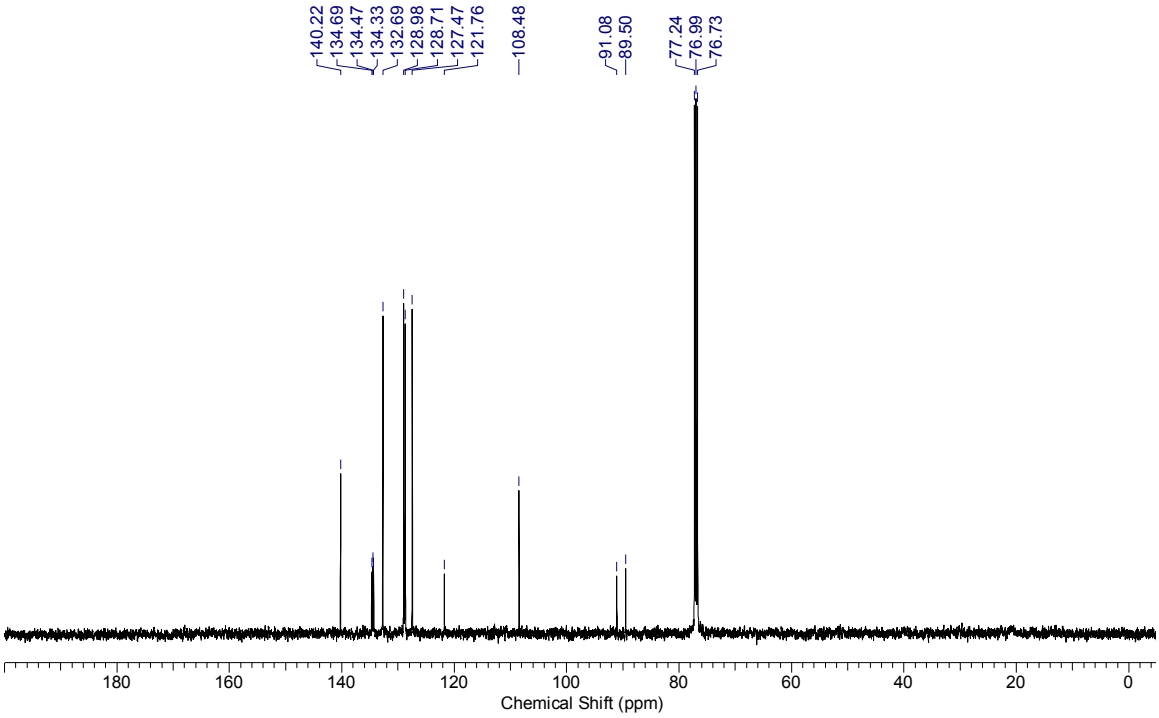
^{13}C NMR spectrum of **1-03y**:



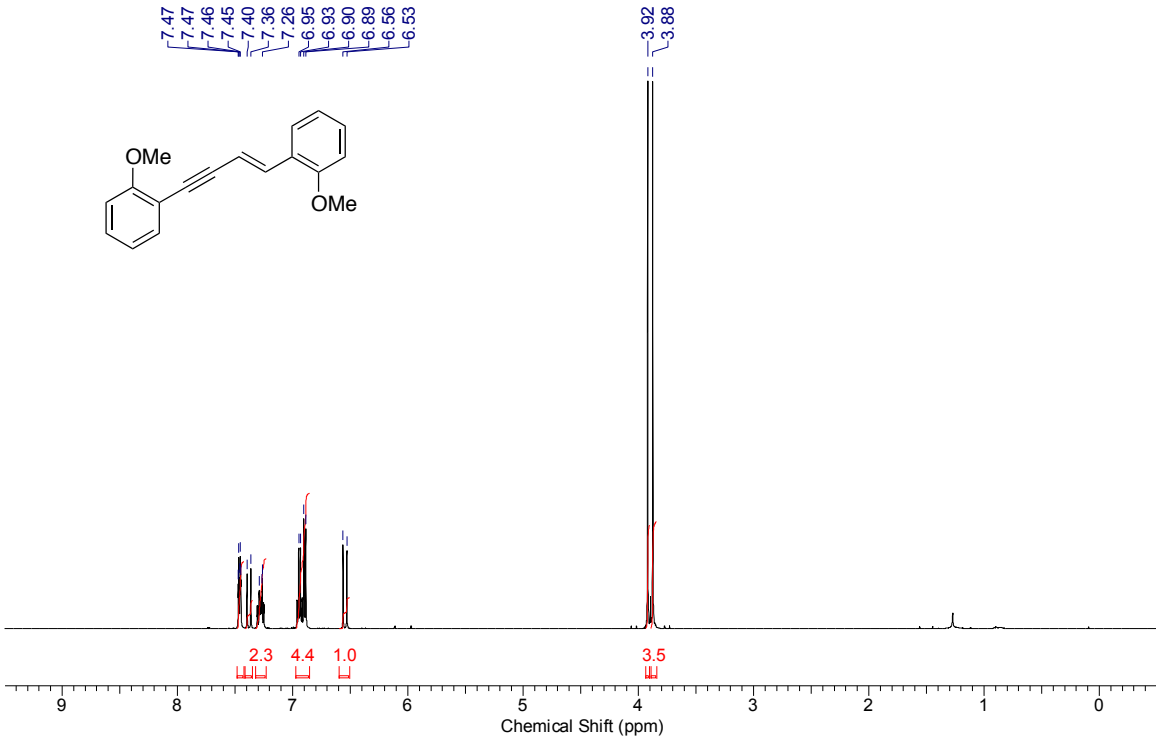
^{1}H NMR spectrum of **1-03u**:



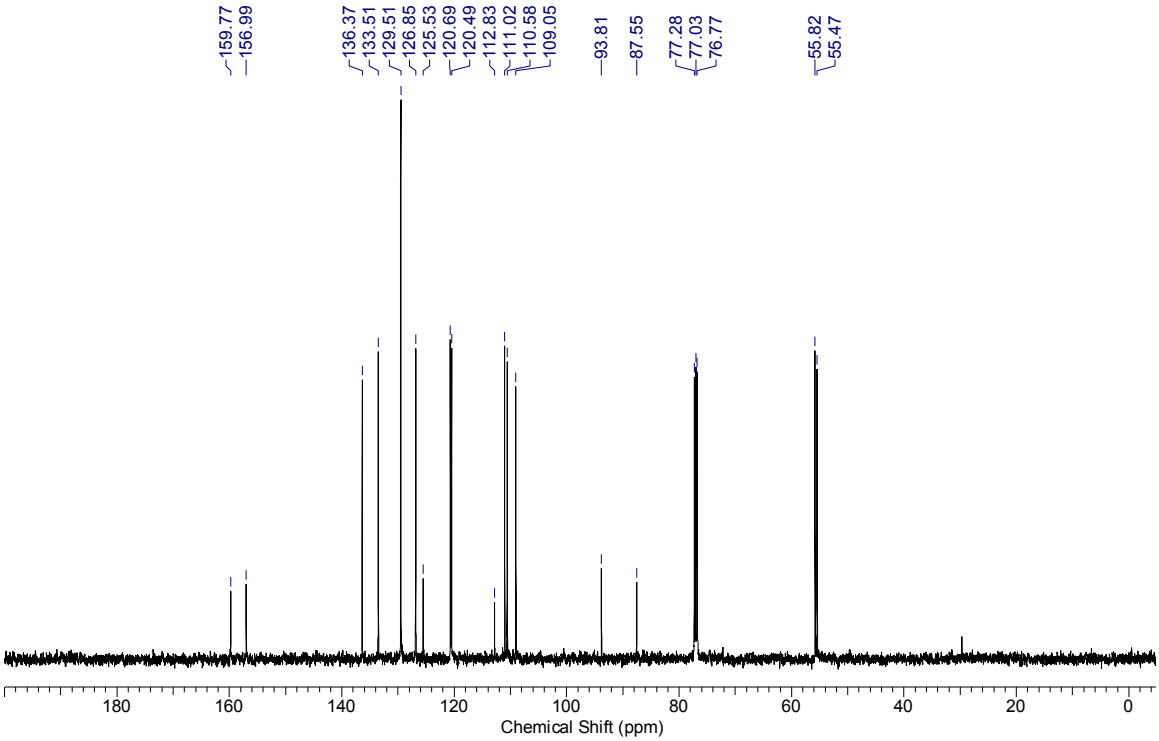
^{13}C NMR spectrum of **1-03u**:



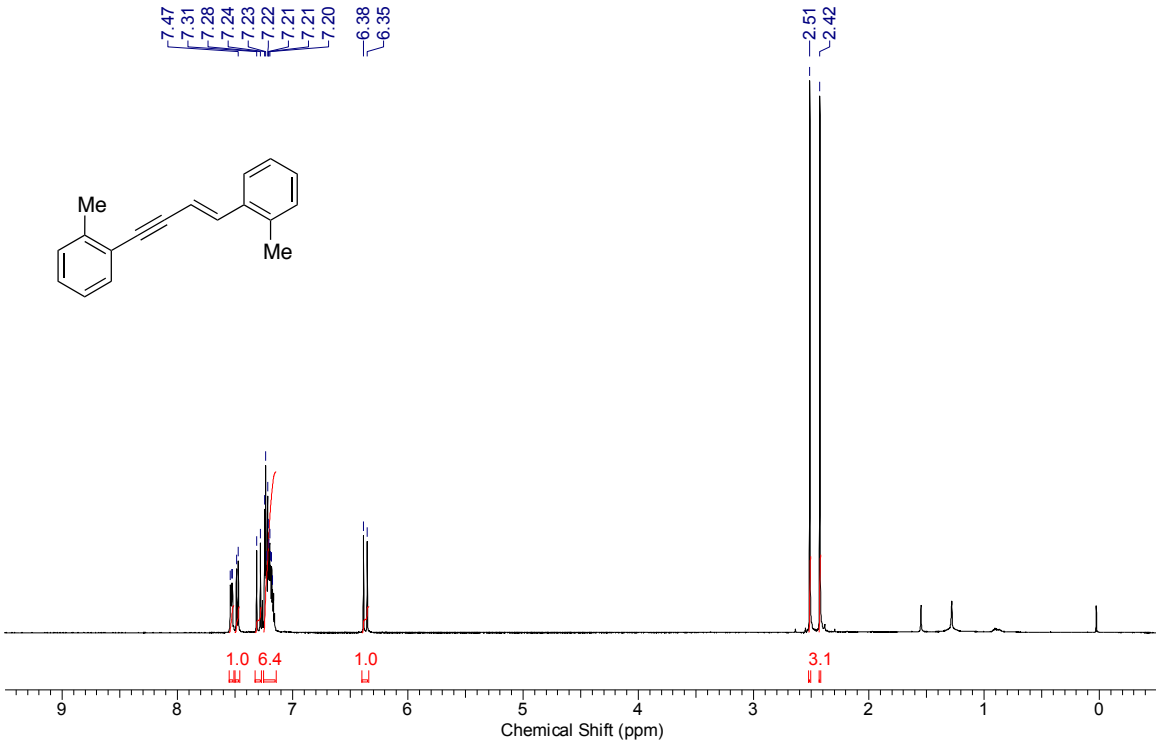
^{1}H NMR spectrum of **1-03z**:



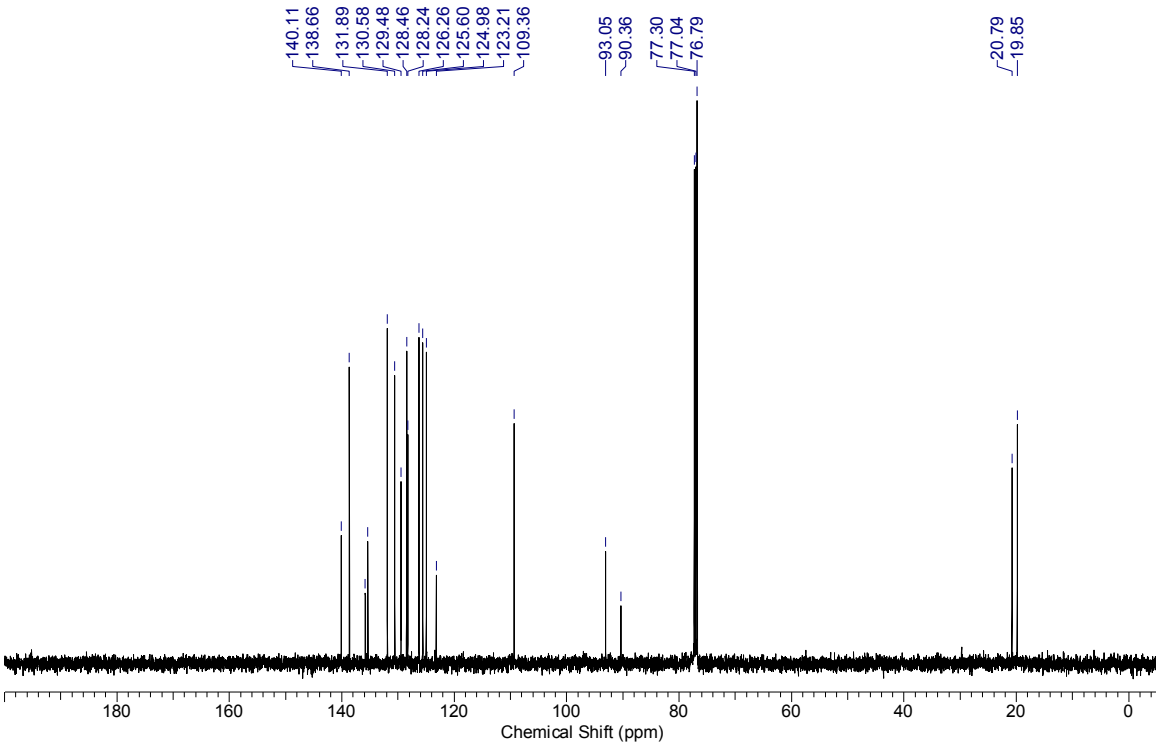
^{13}C NMR spectrum of **1-03z**:



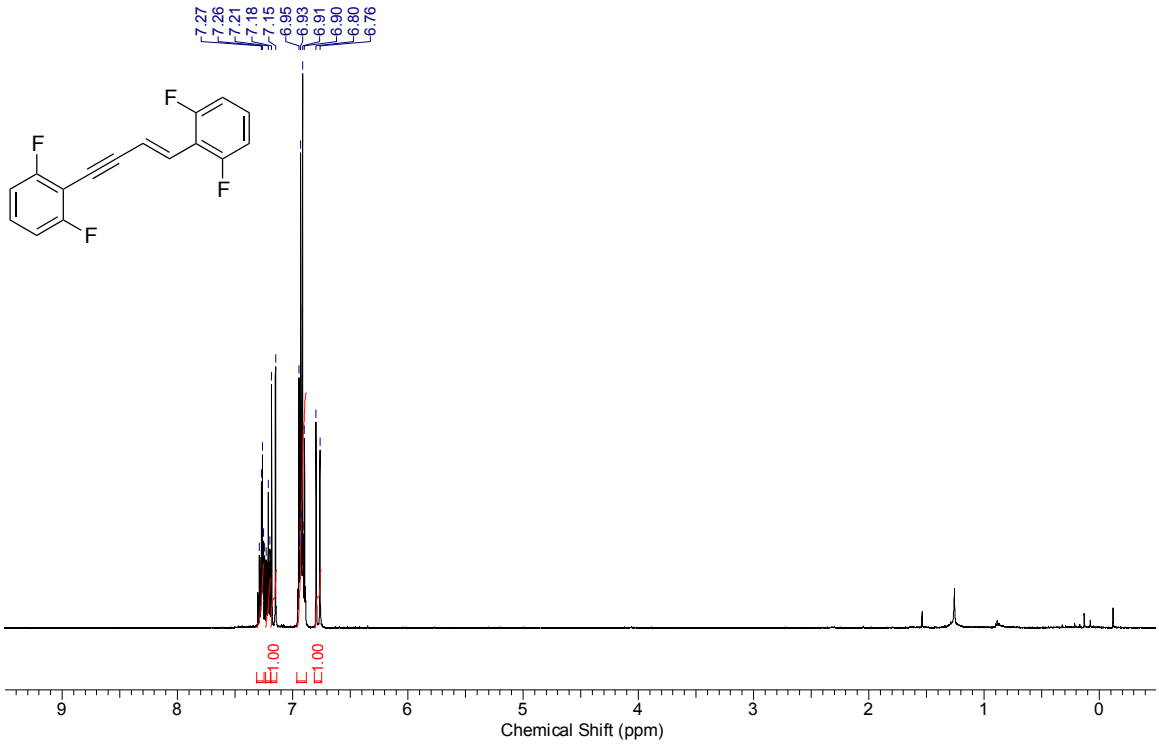
^{1}H NMR spectrum of **1-03q**:



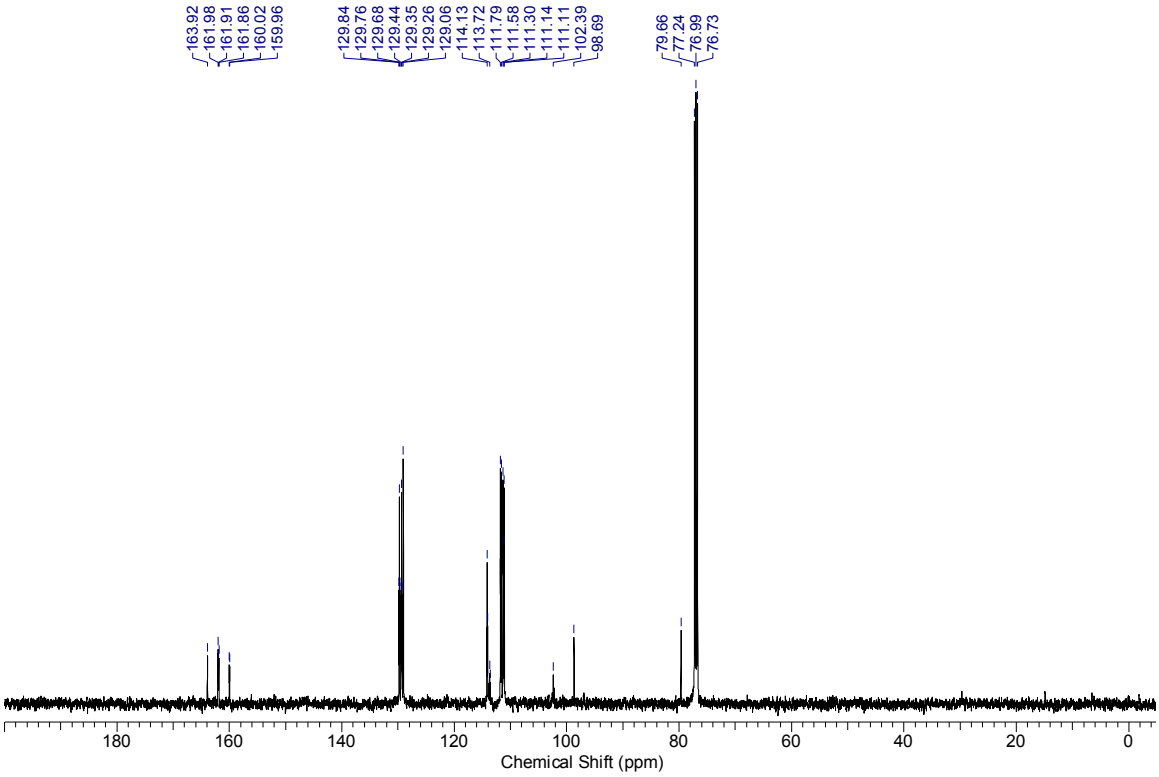
^{13}C NMR spectrum of **1-03q**:



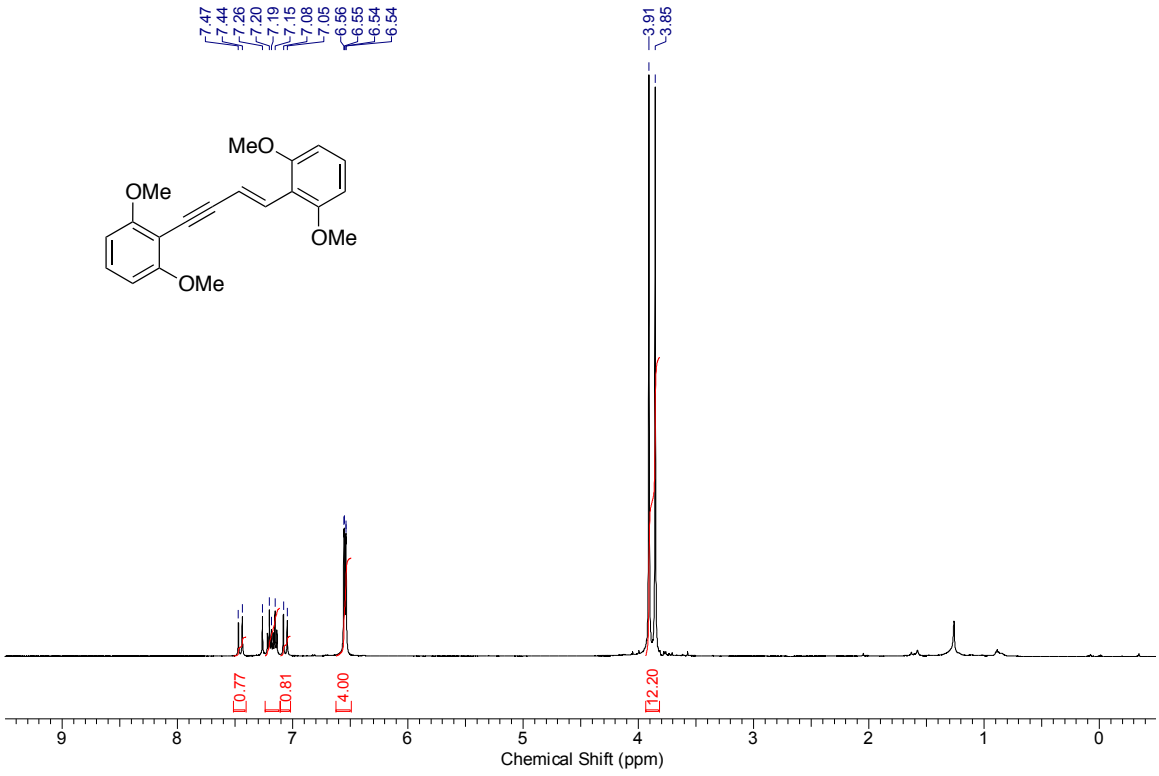
^{1}H NMR spectrum of **1-03s**:



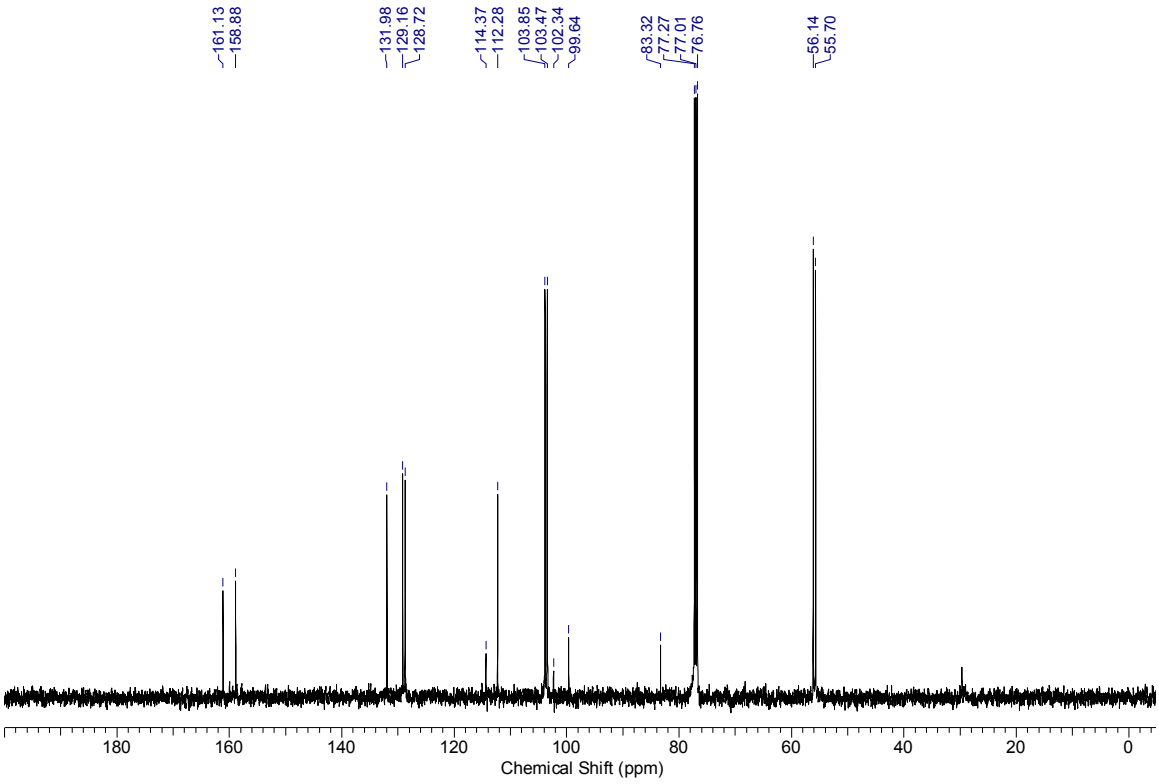
^{13}C NMR spectrum of **1-03s**:



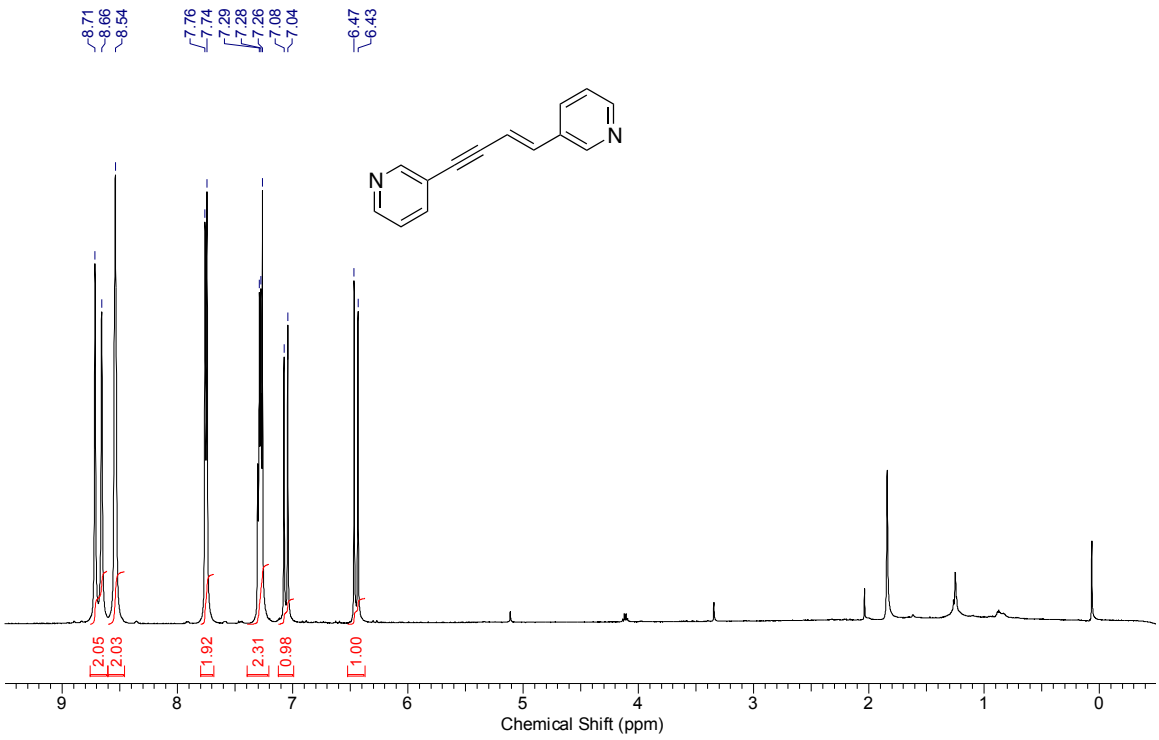
^{1}H NMR spectrum of **1-03t**:



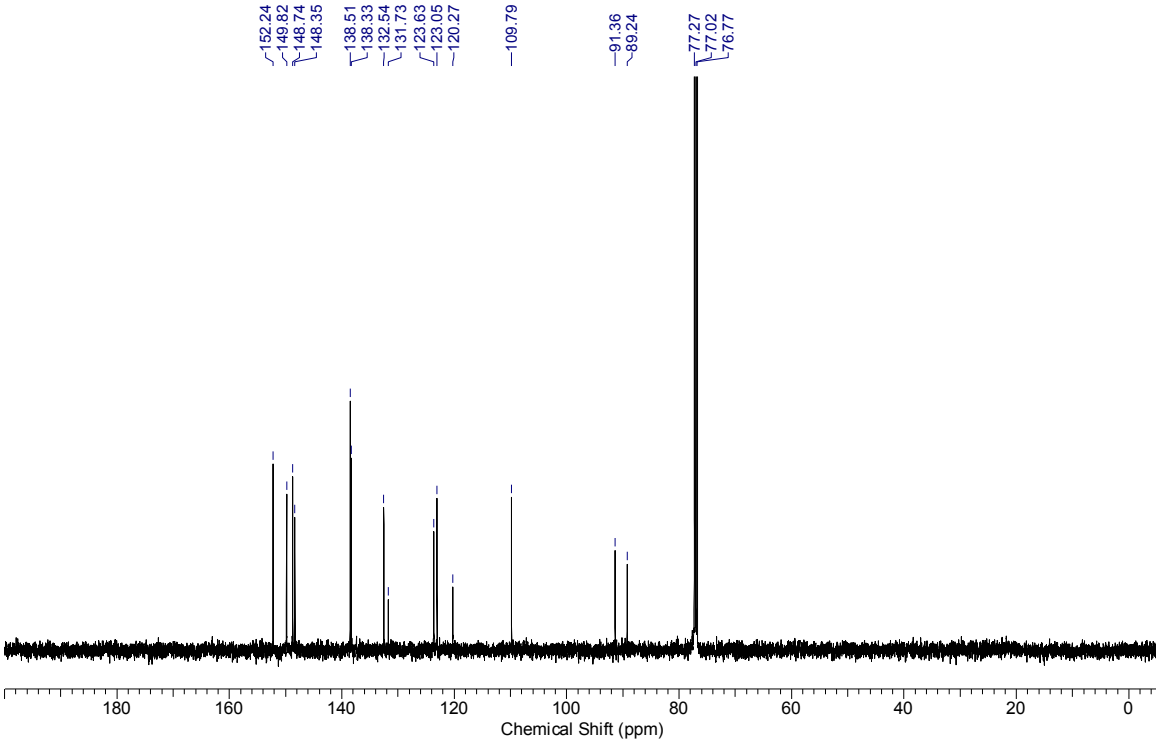
^{13}C NMR spectrum of **1-03t**:



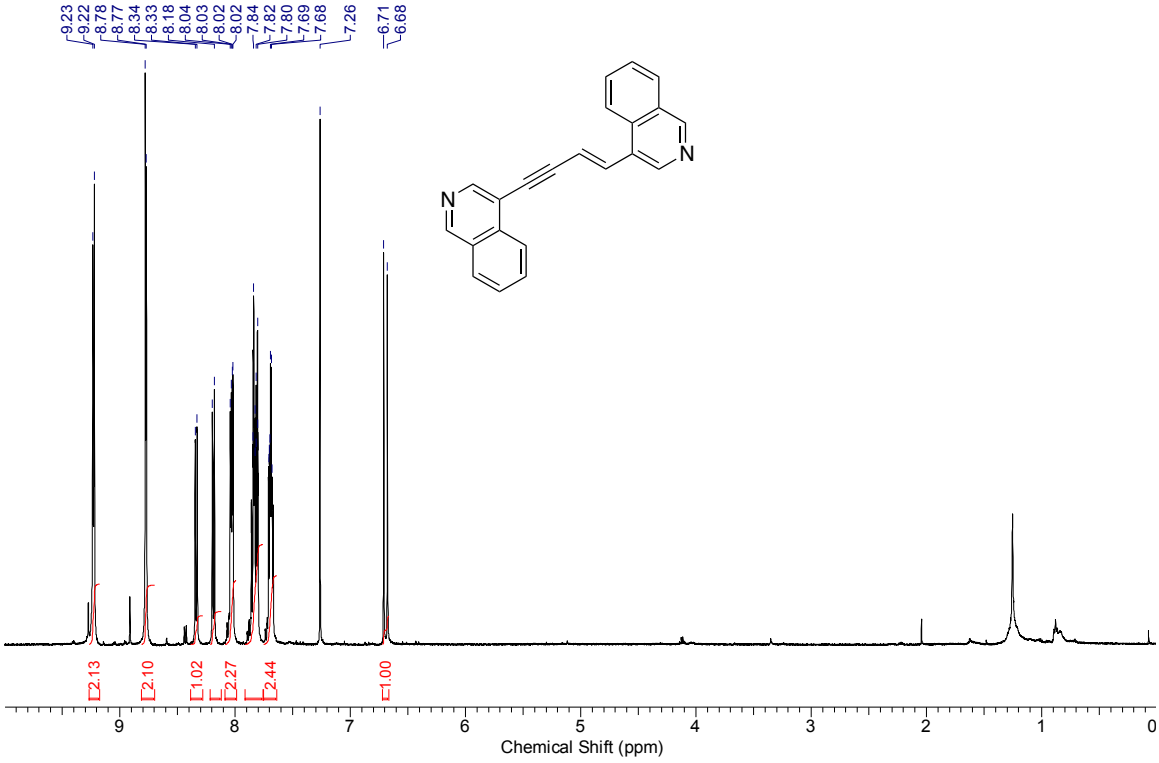
^{1}H NMR spectrum of **1-03ab**:



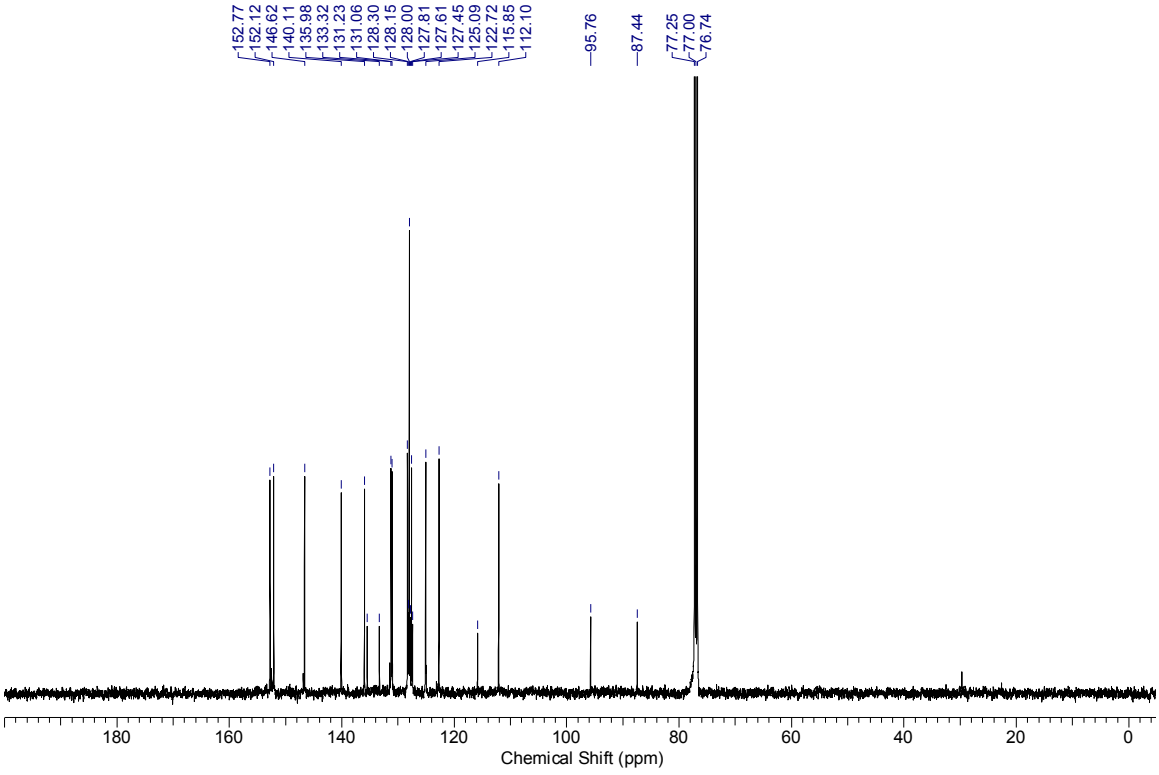
^{13}C NMR spectrum of **1-03ab**:



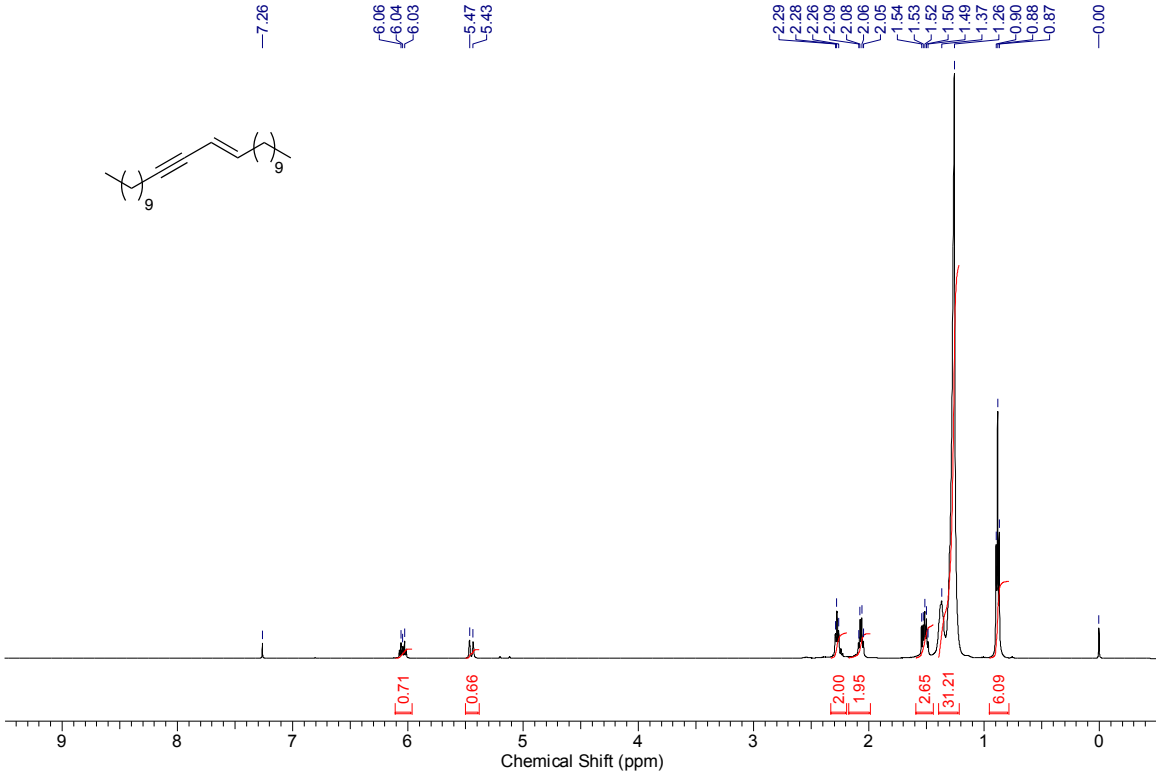
^{1}H NMR spectrum of **1-03ac**:



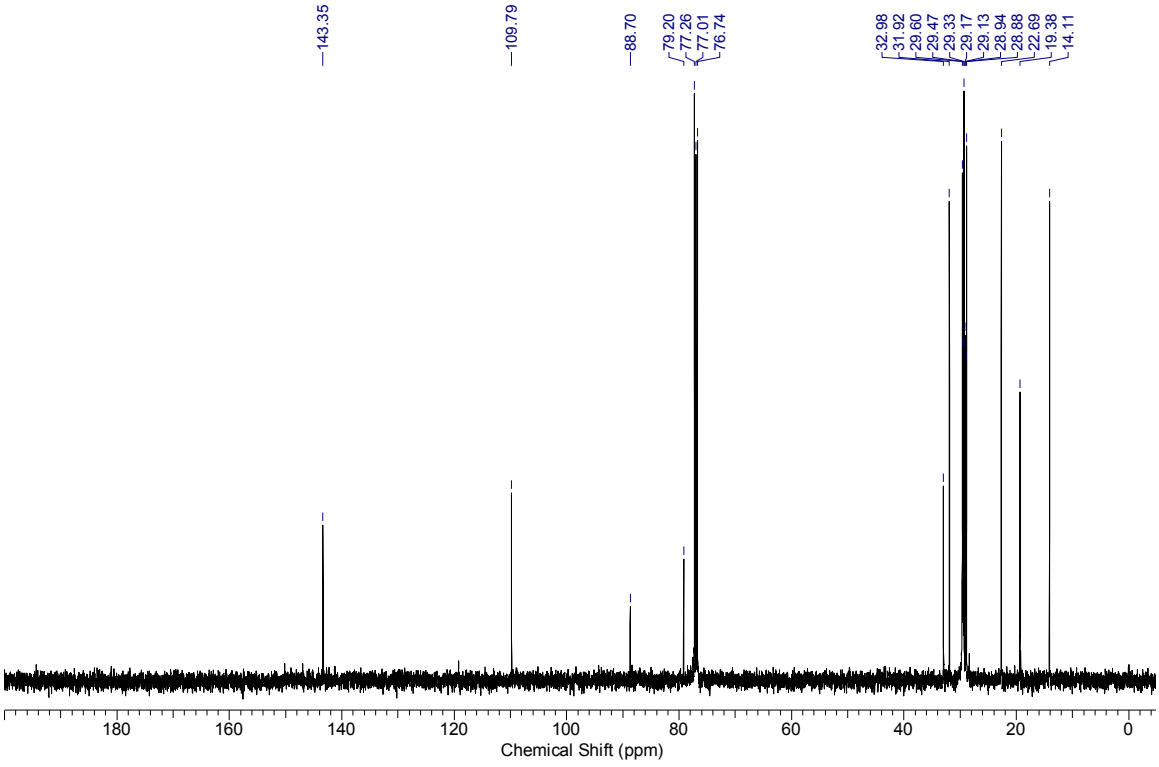
^{13}C NMR spectrum of **1-03ac**:



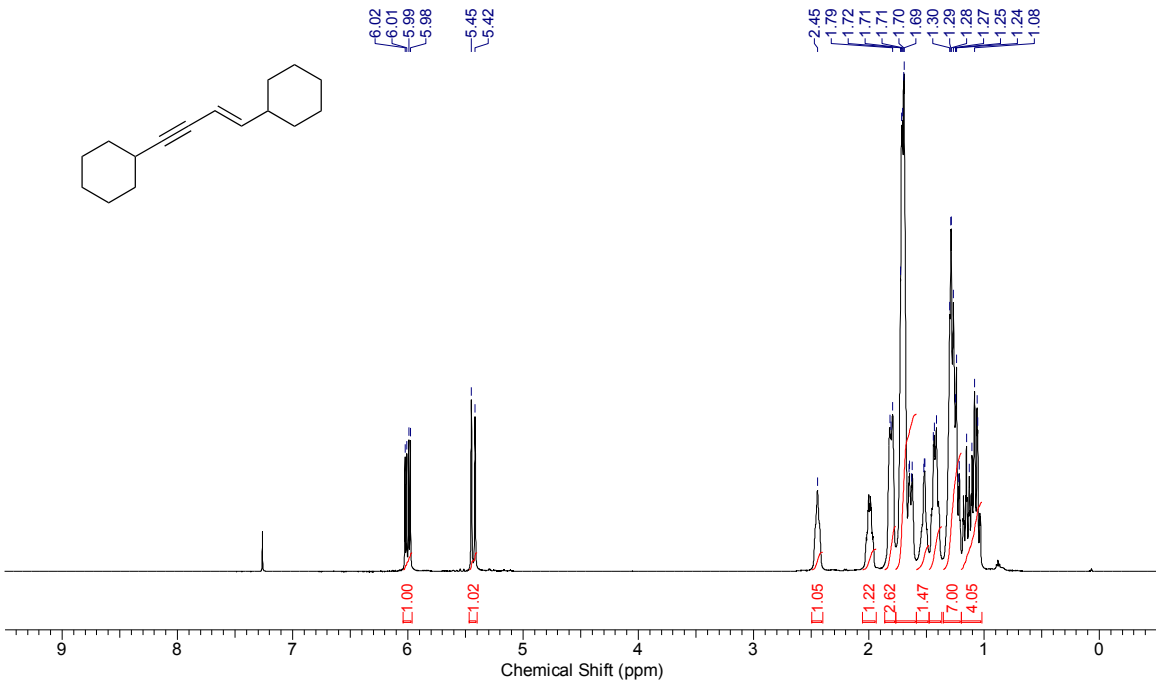
^{1}H NMR spectrum of **1-03ad**:



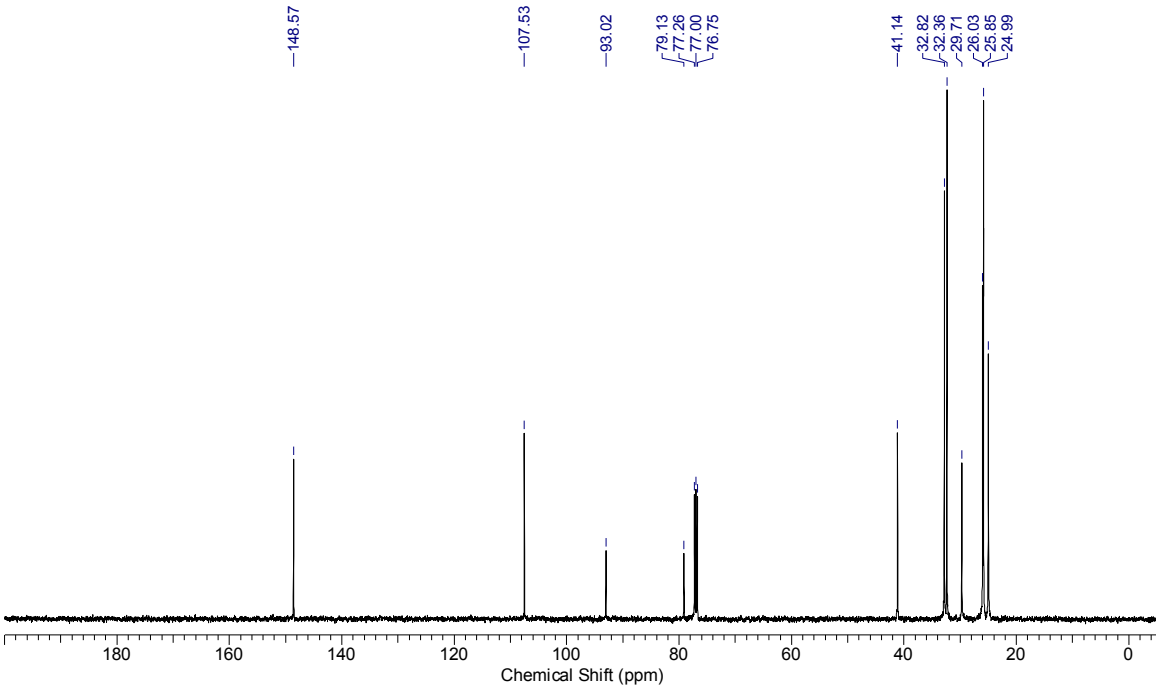
^{13}C NMR spectrum of **1-03ad**:



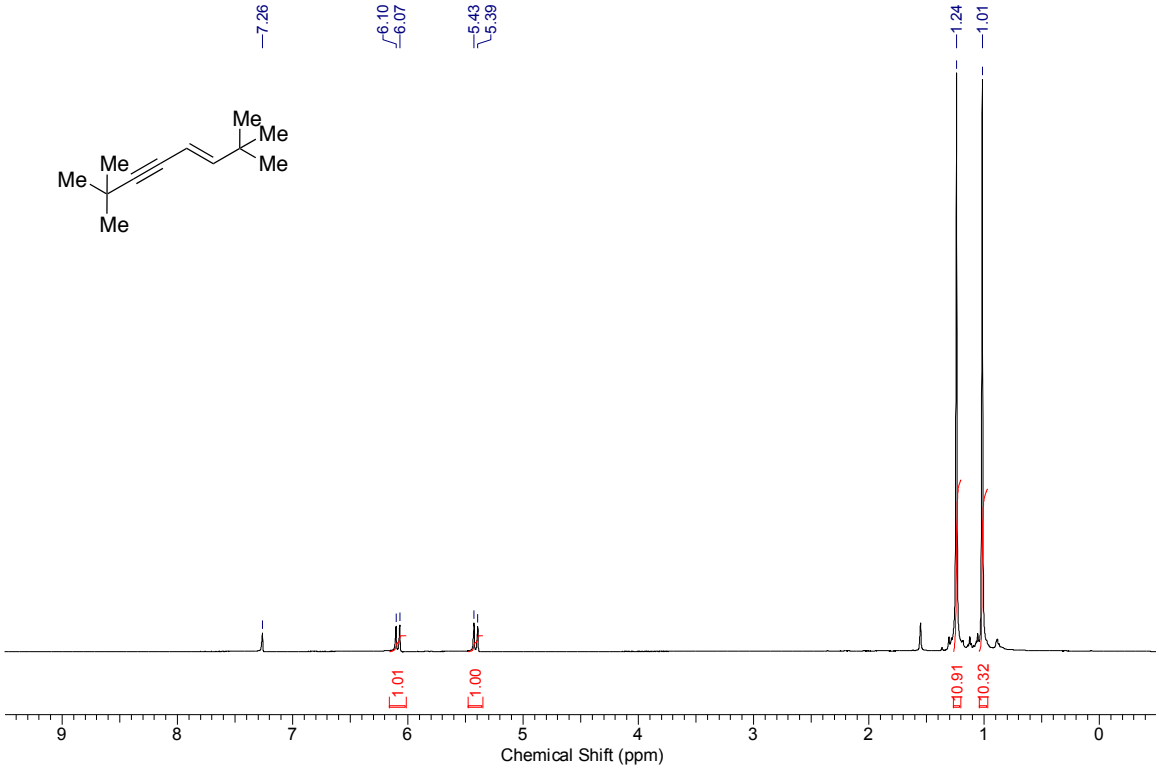
^{1}H NMR spectrum of **1-03ae**:



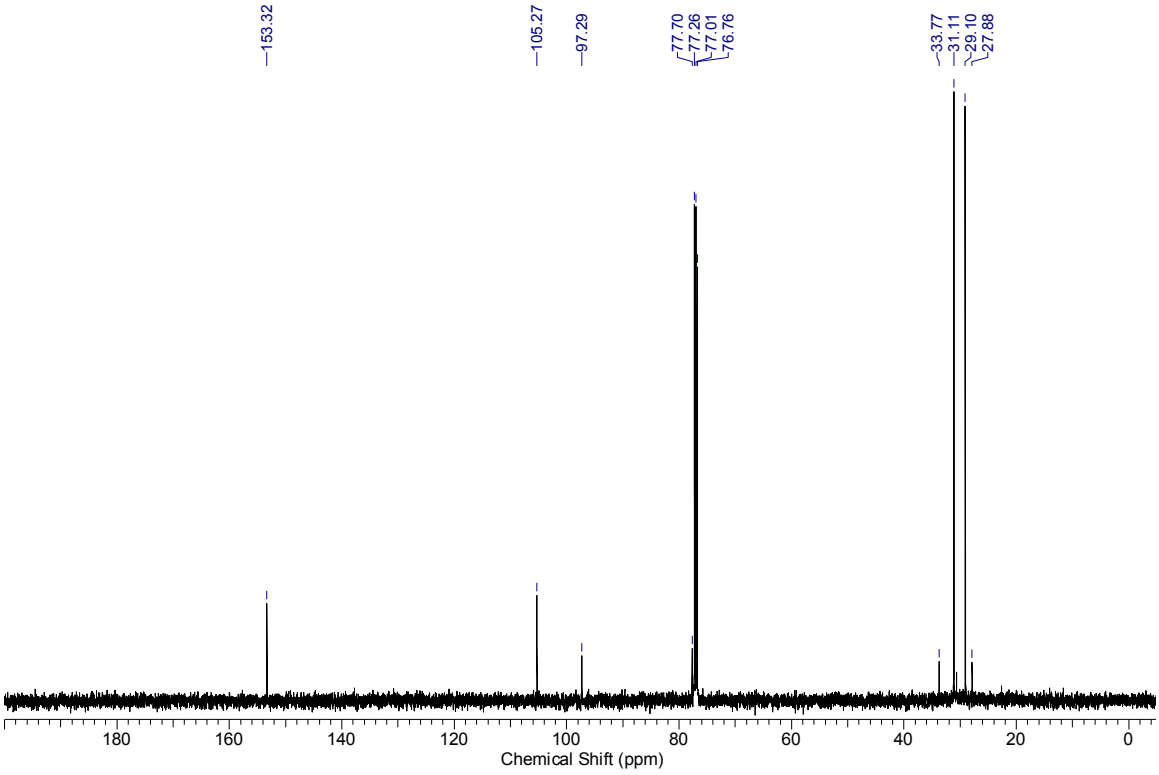
^{13}C NMR spectrum of **1-03ae**:



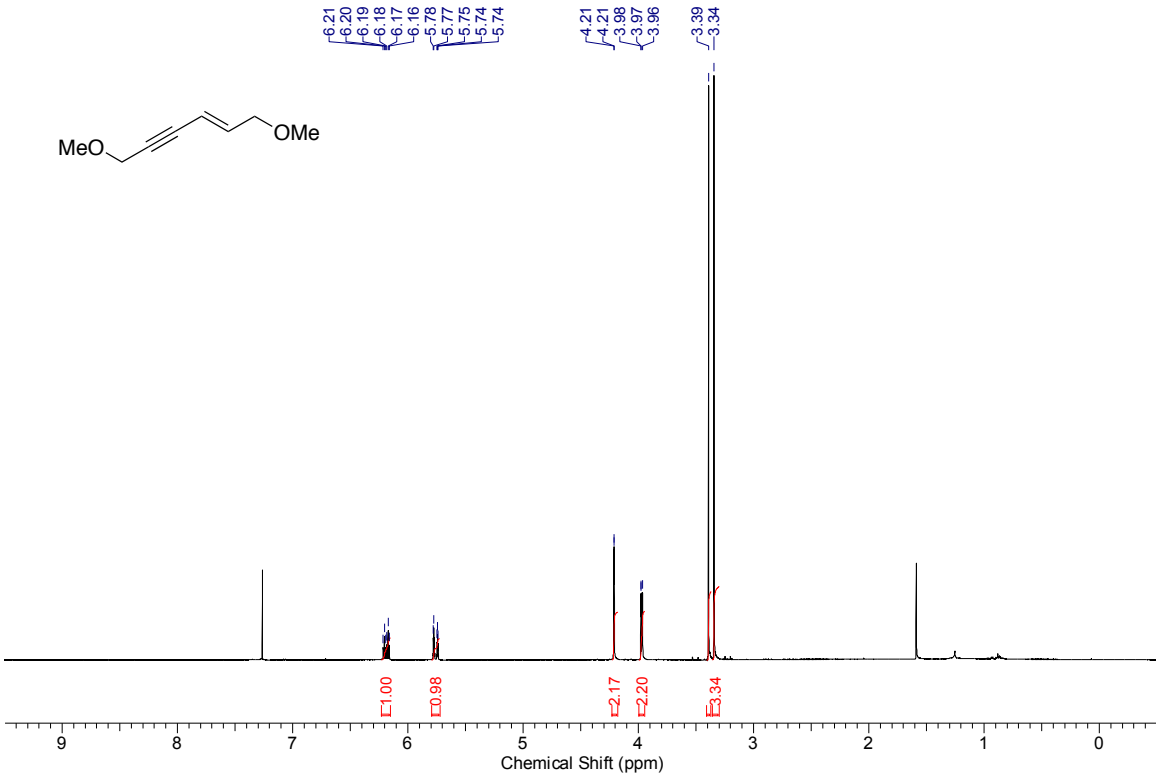
^{1}H NMR spectrum of **1-03h**:



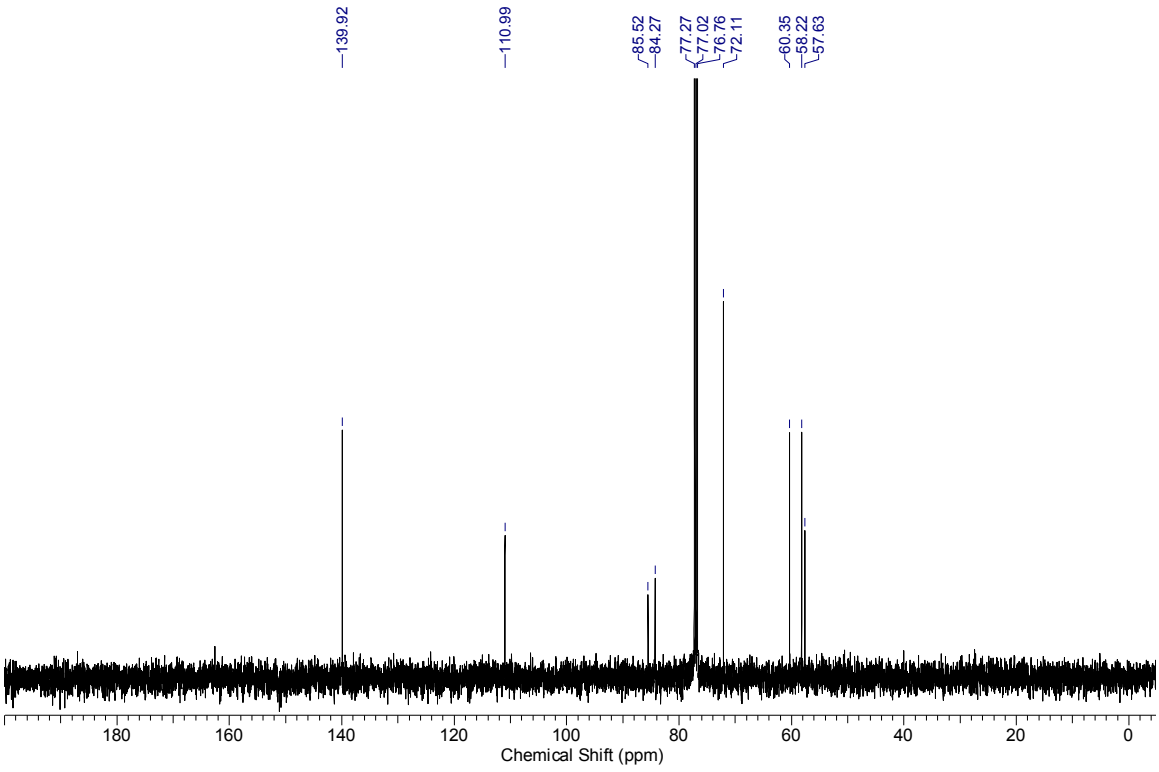
^{13}C NMR spectrum of **1-03h**:



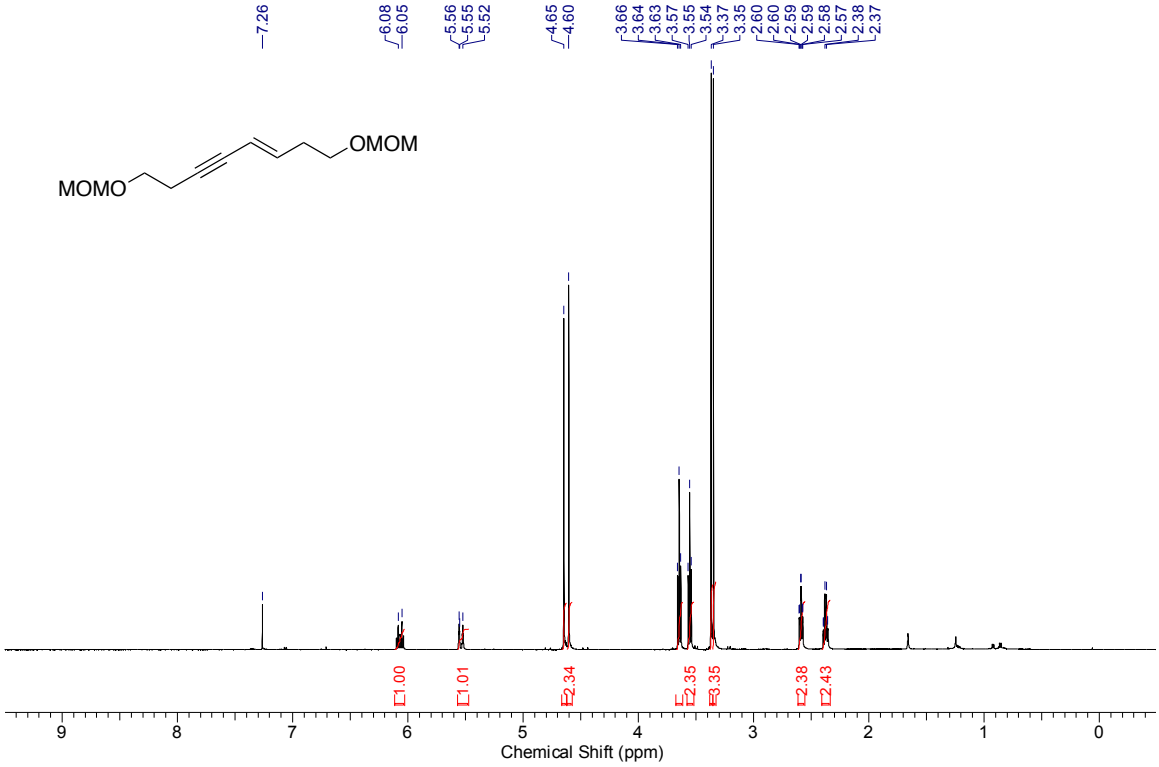
^{1}H NMR spectrum of **1-03af**:



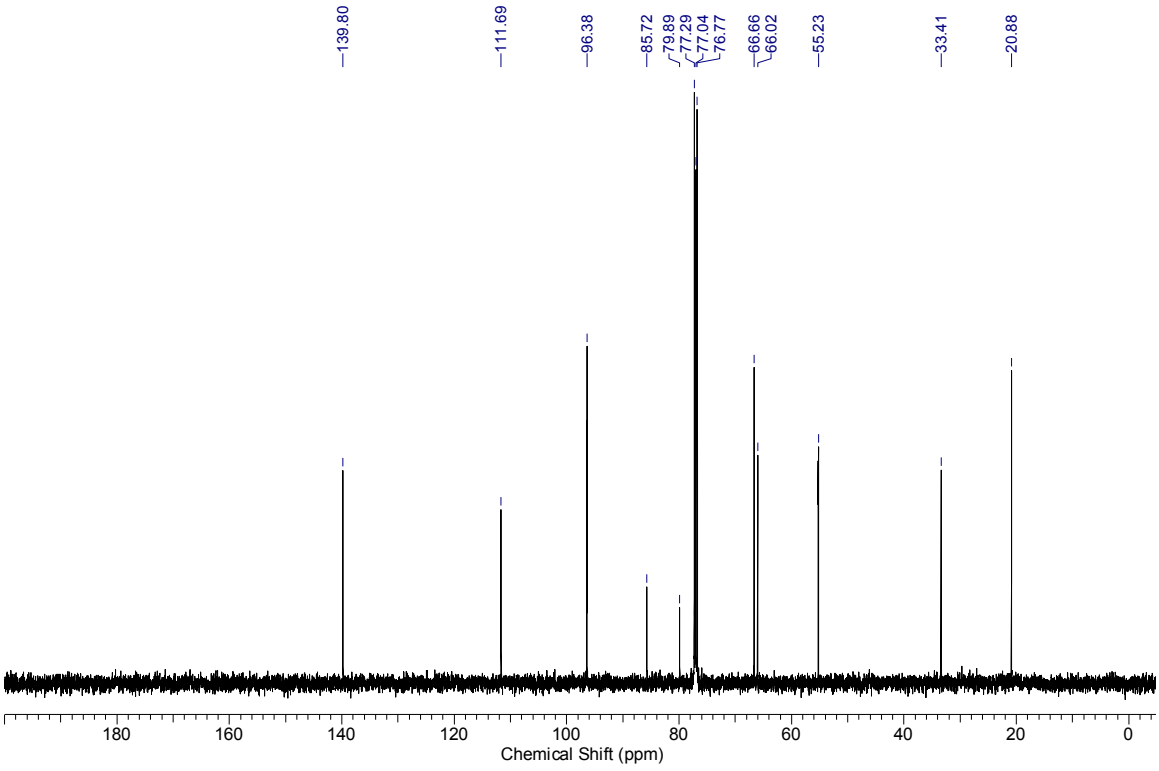
^{13}C NMR spectrum of **1-03af**:



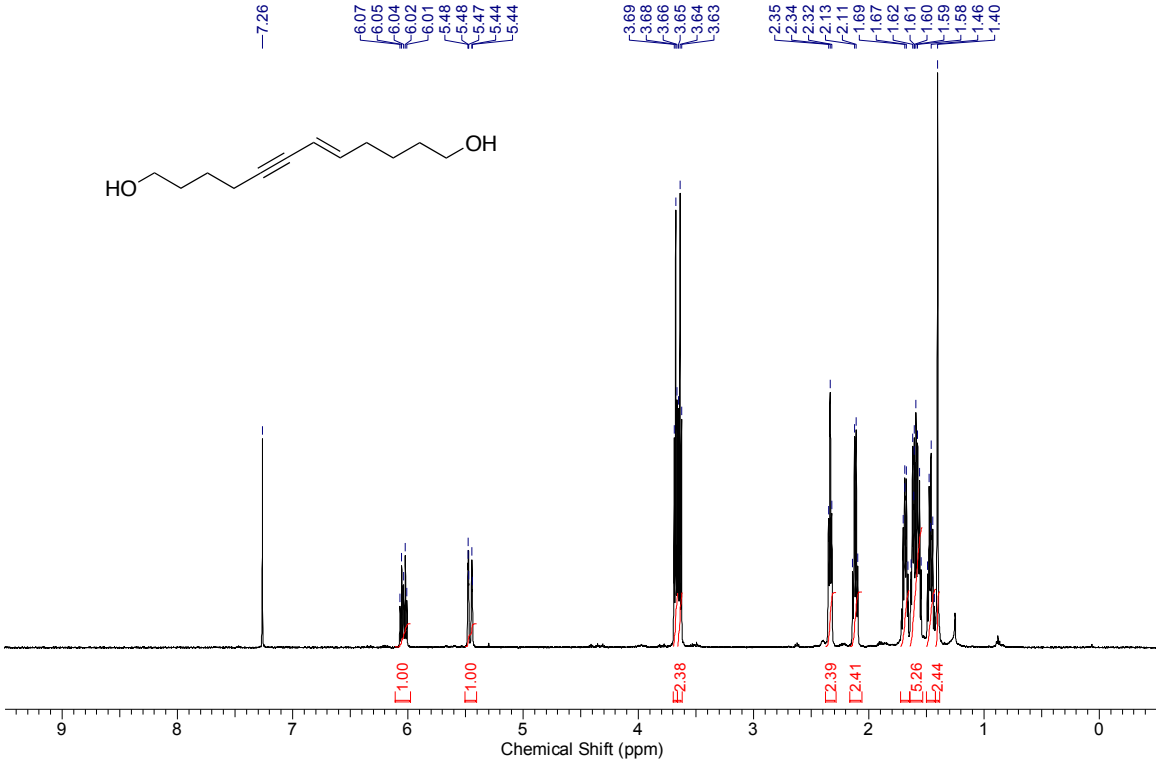
^{1}H NMR spectrum of **1-03ag**:



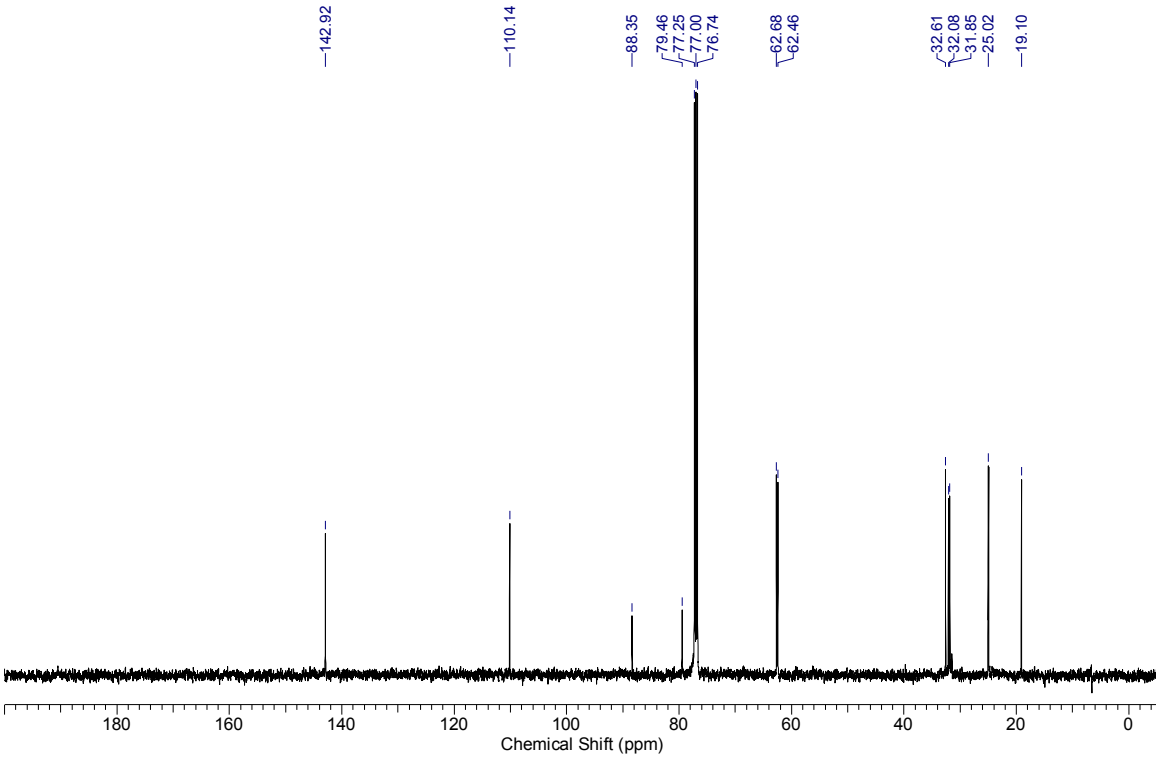
^{13}C NMR spectrum of **1-03ag**:



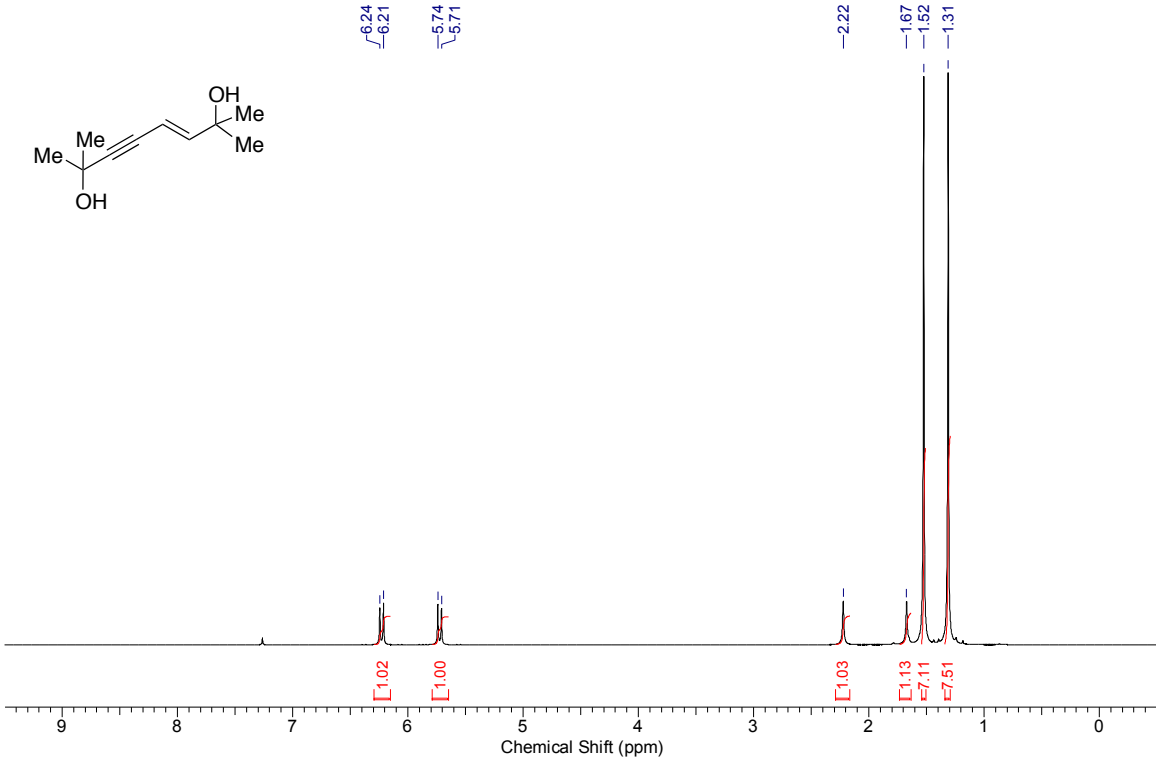
^{1}H NMR spectrum of **1-03ah**:



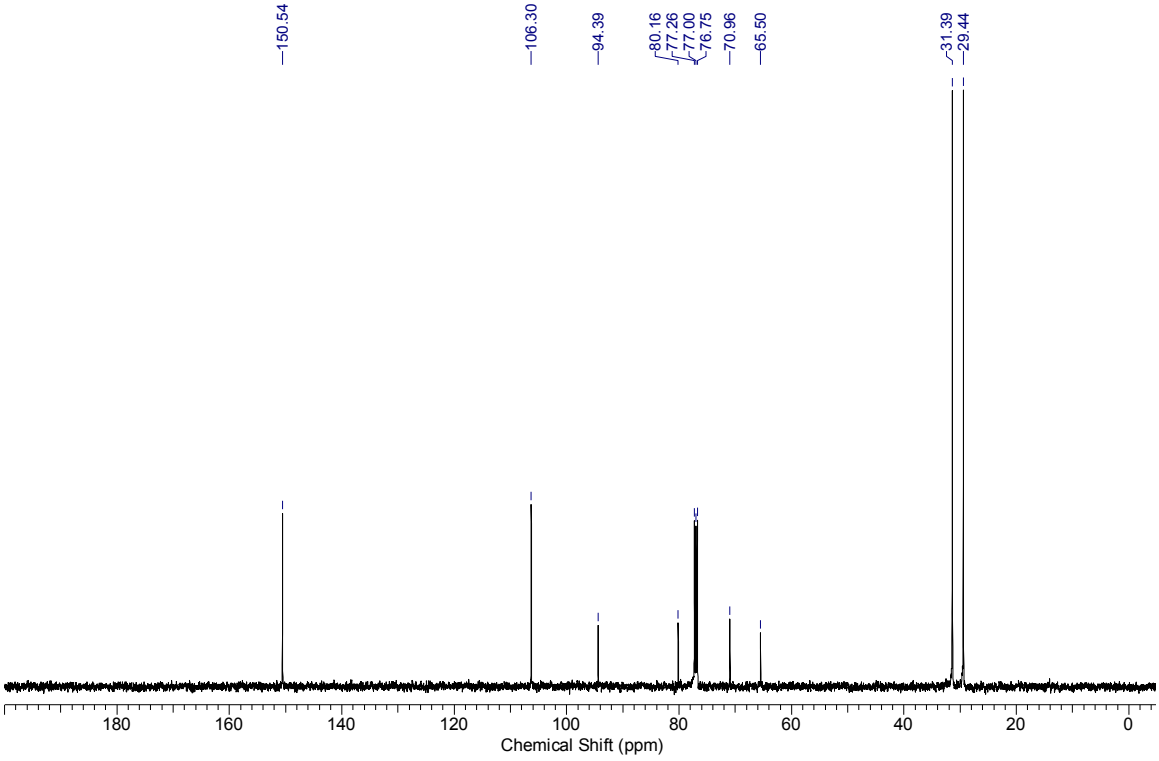
^{13}C NMR spectrum of **1-03ah**:



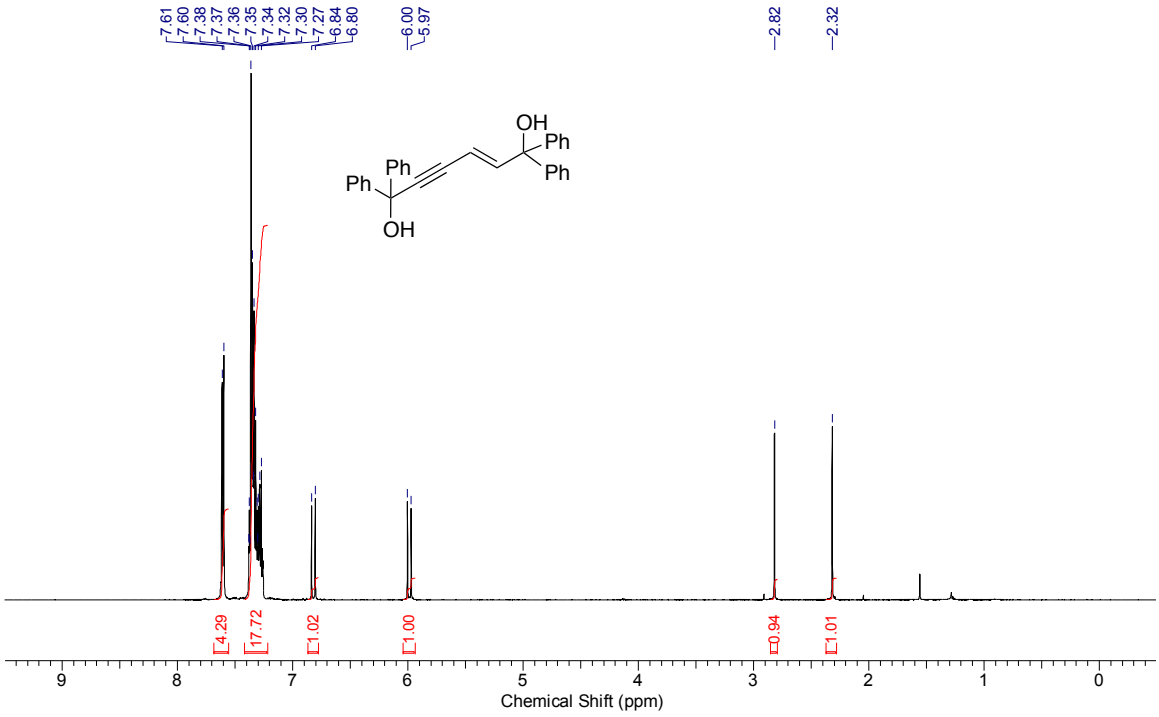
^{1}H NMR spectrum of **1-03c**:



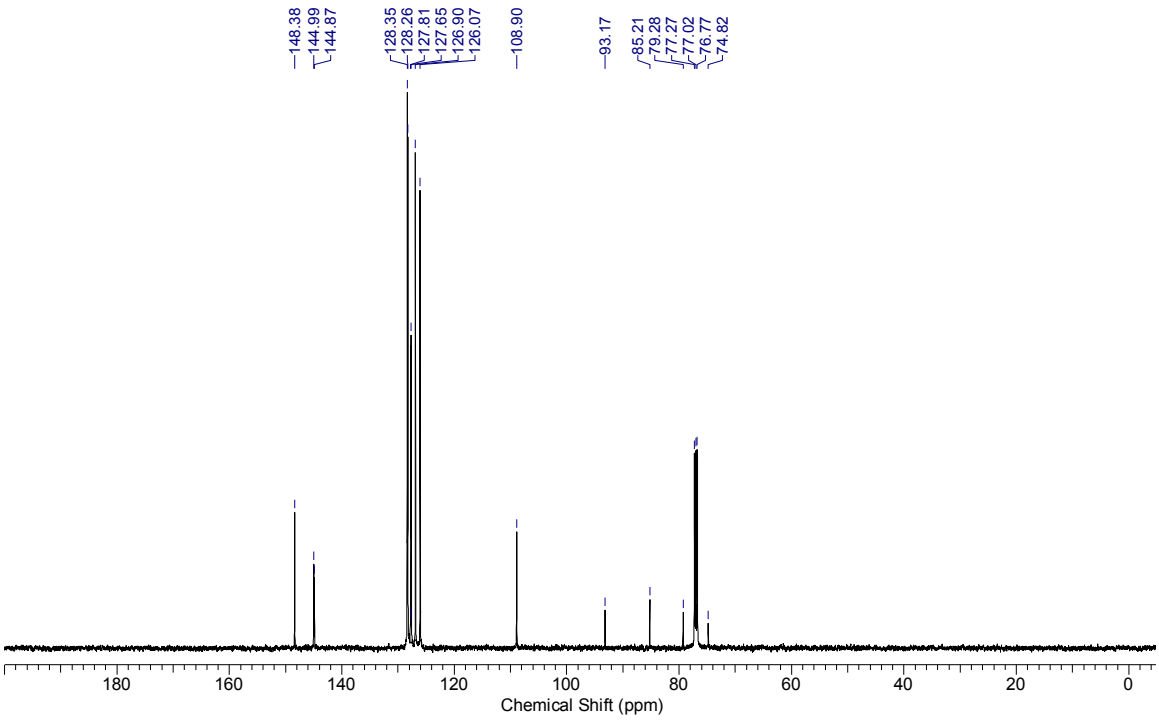
^{13}C NMR spectrum of **1-03c**:



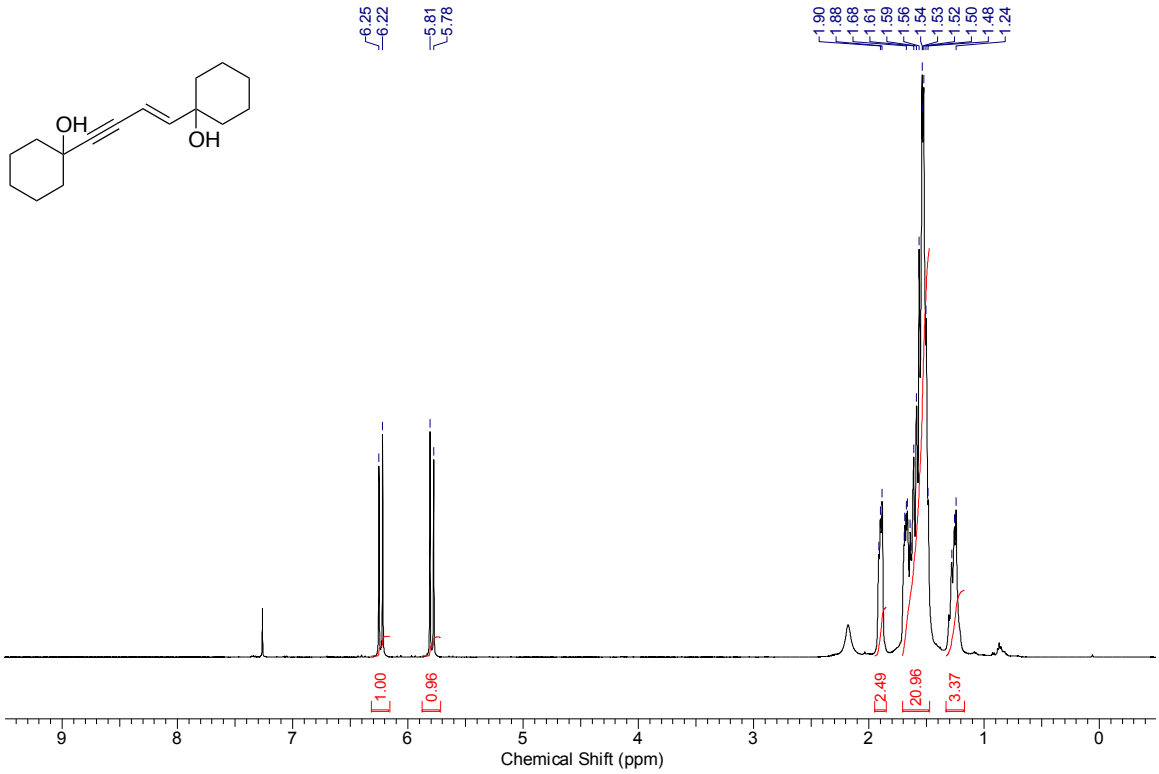
^{1}H NMR spectrum of **1-03ai**:



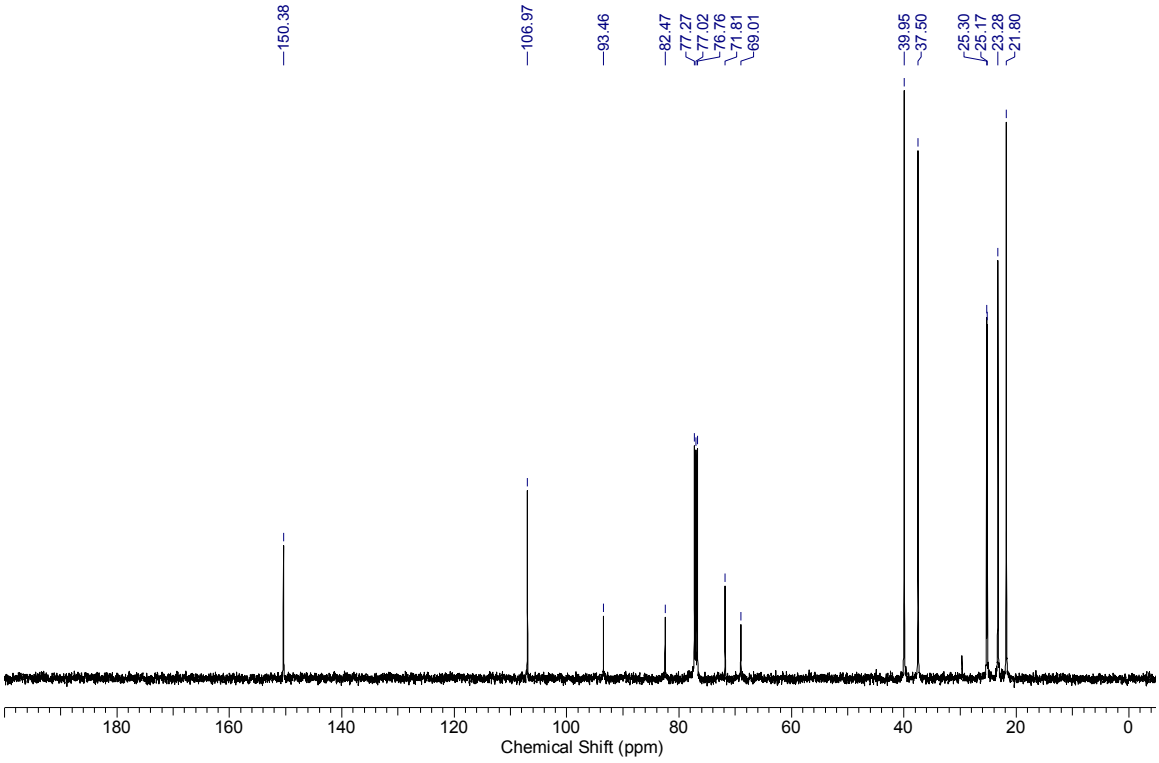
^{13}C NMR spectrum of **1-03ai**:



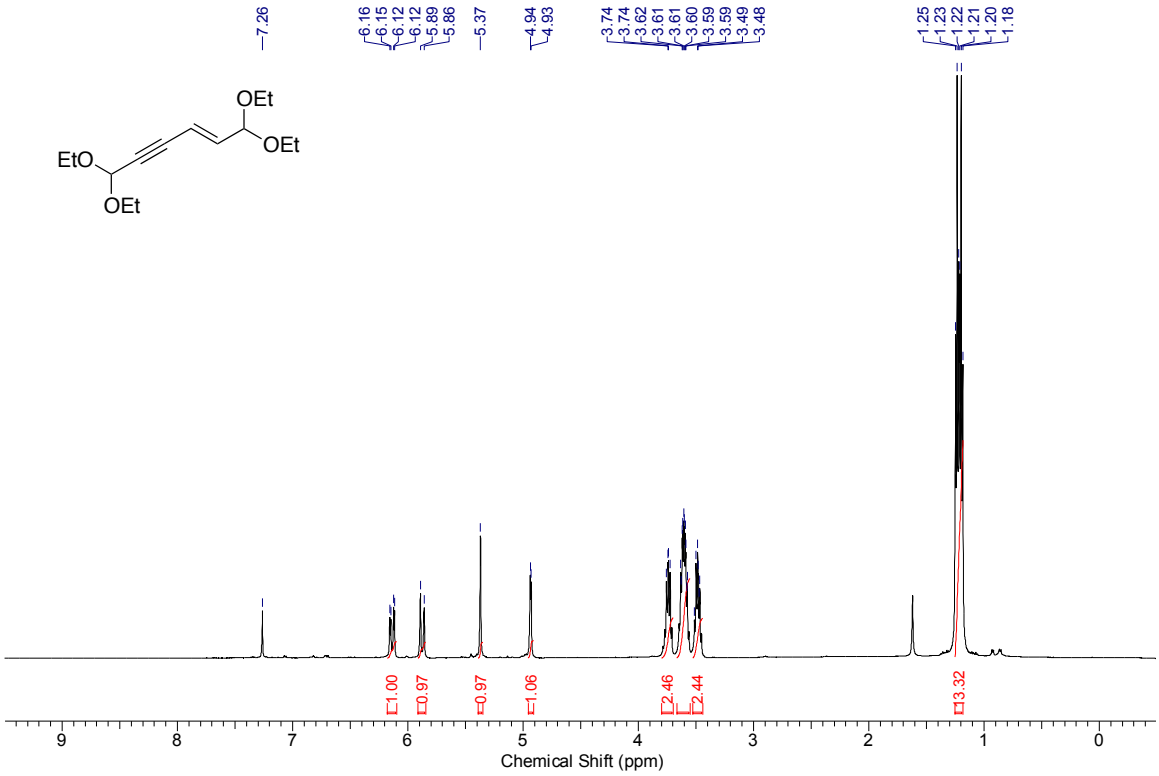
^{1}H NMR spectrum of **1-03aj**:



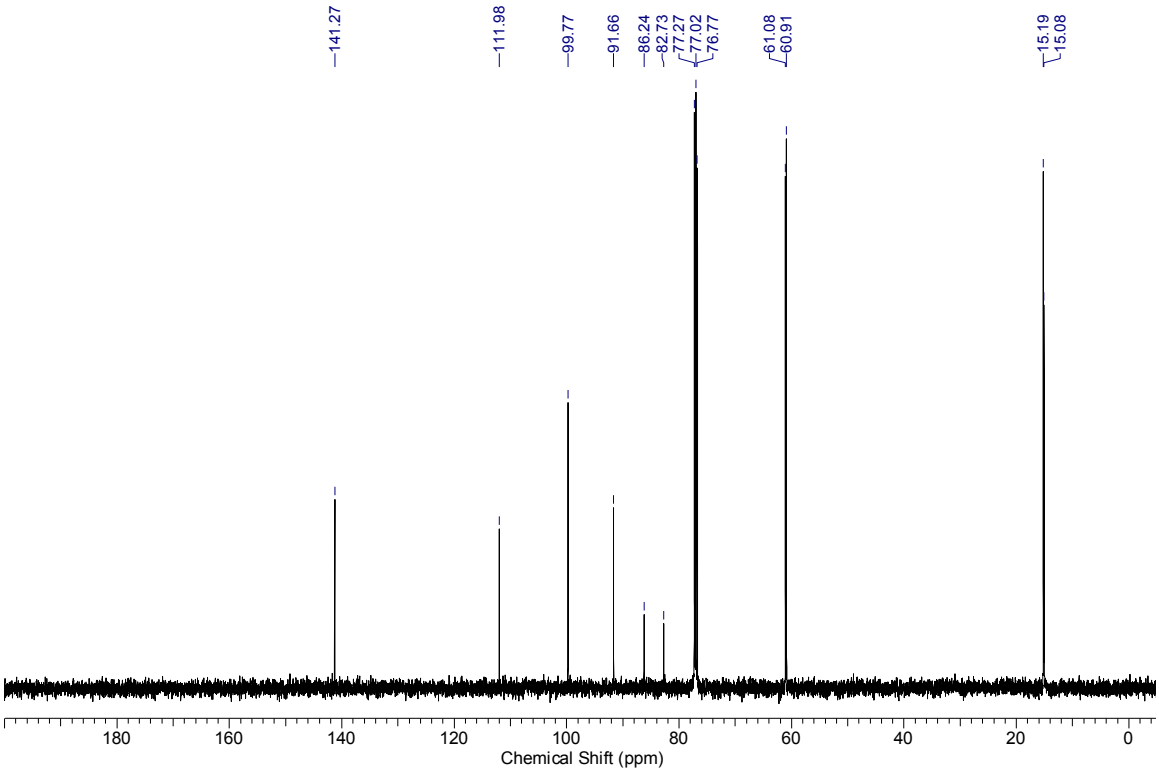
^{13}C NMR spectrum of **1-03aj**:



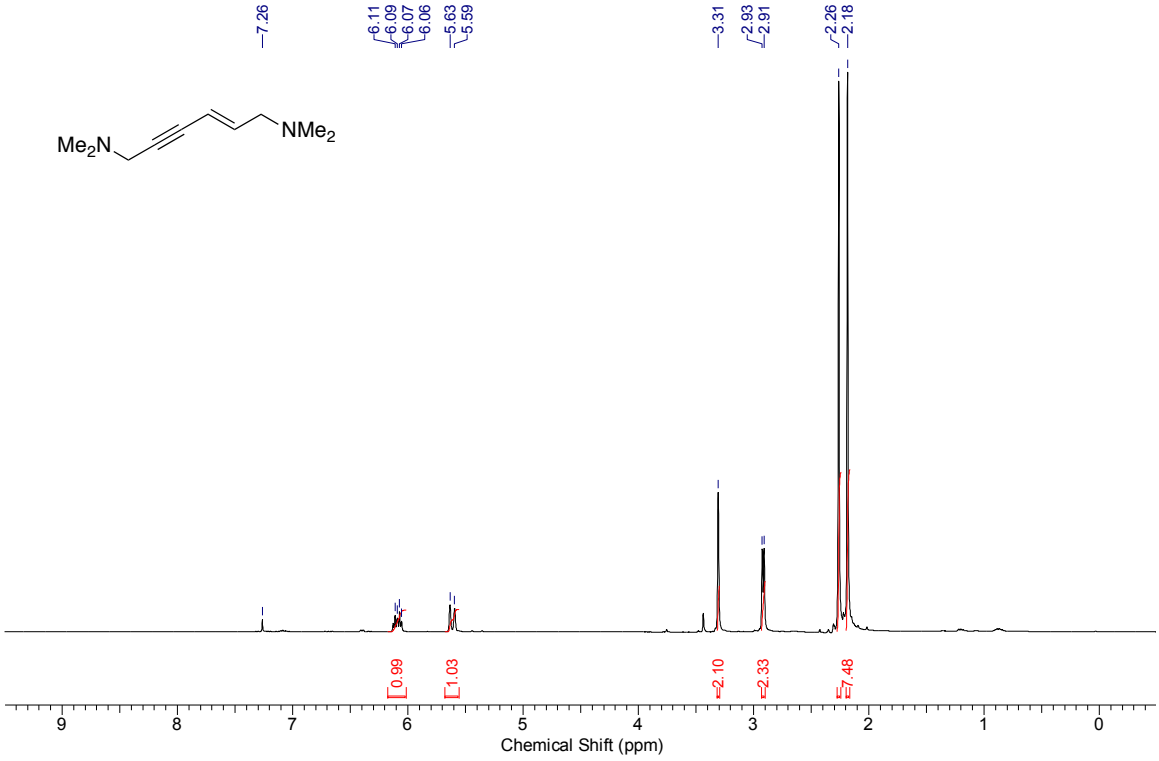
^{1}H NMR spectrum of **1-03ak**:



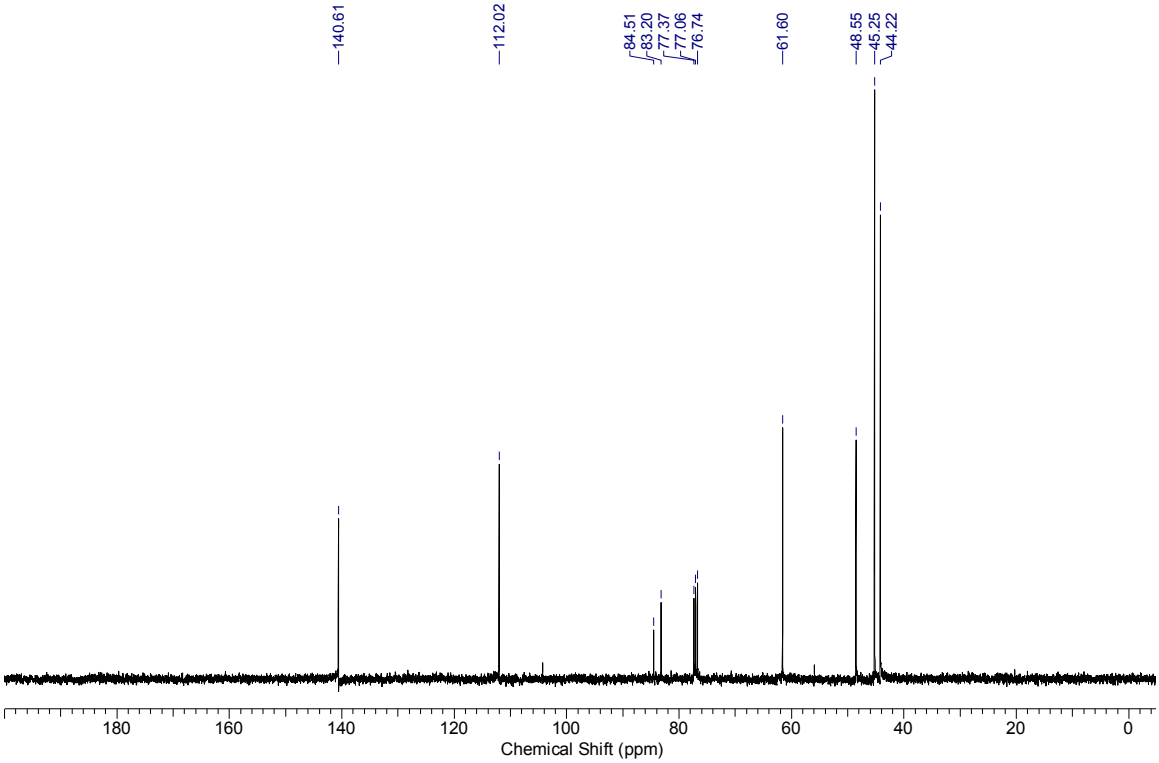
^{13}C NMR spectrum of **1-03ak**:



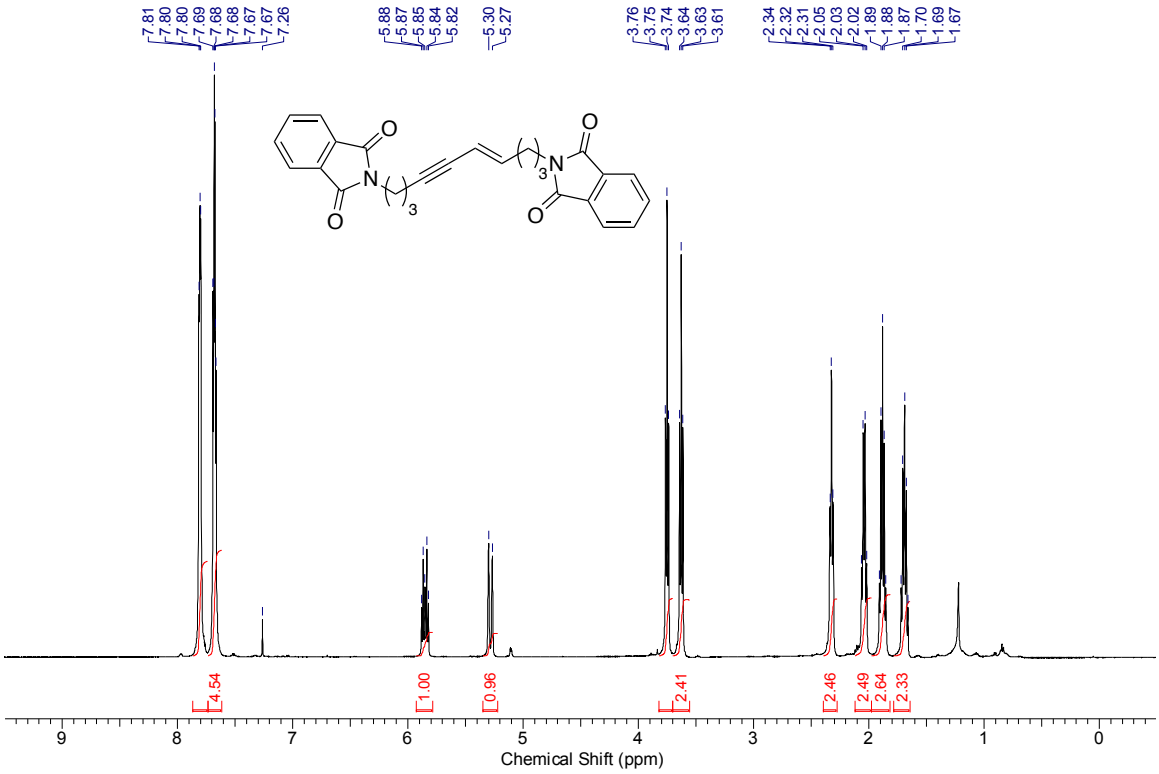
^{1}H NMR spectrum of **1-03al**:



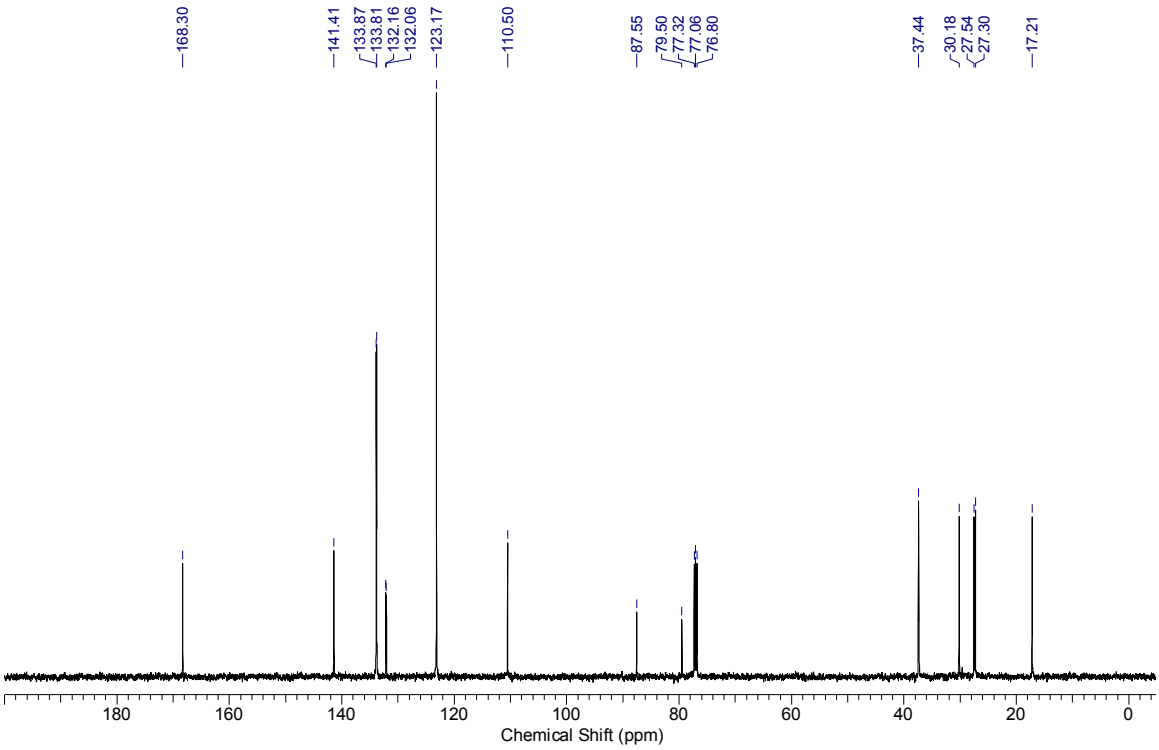
^{13}C NMR spectrum of **1-03al**:



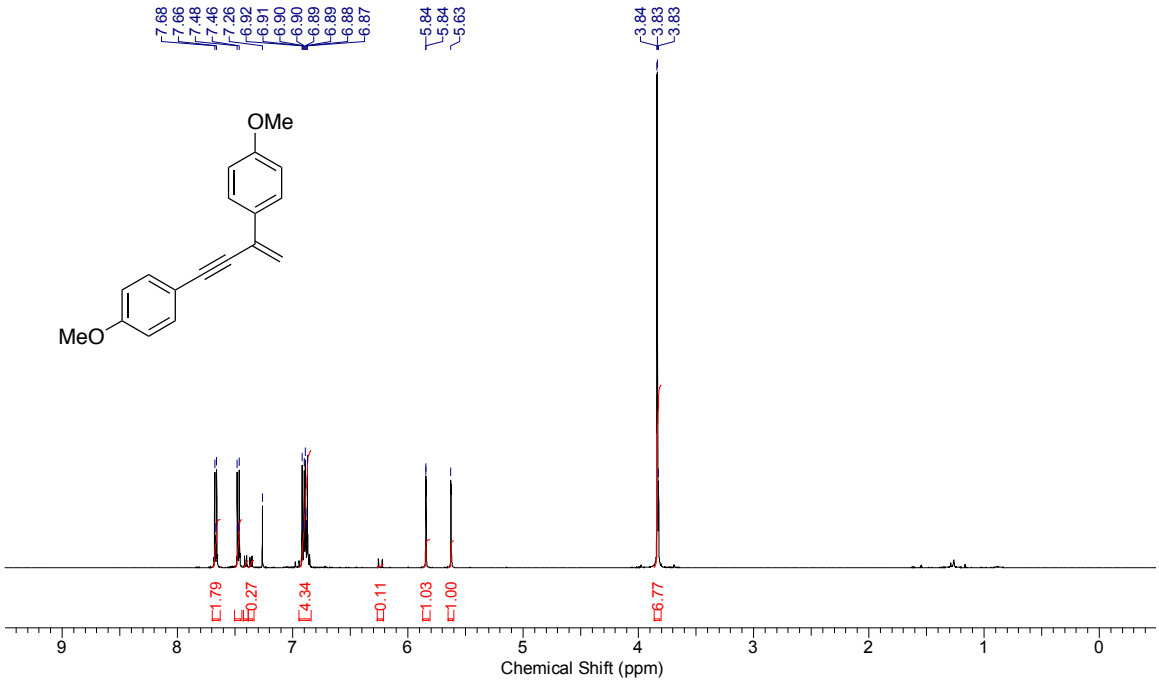
^{1}H NMR spectrum of **1-03am**:



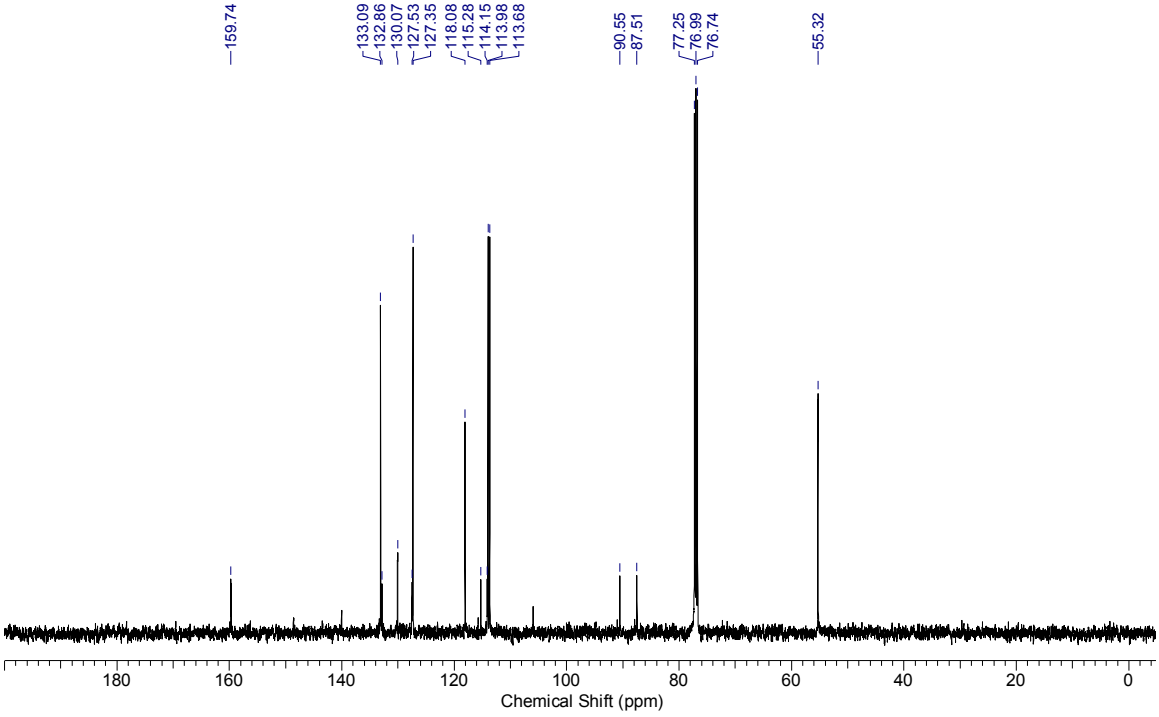
^{13}C NMR spectrum of **1-03am**:



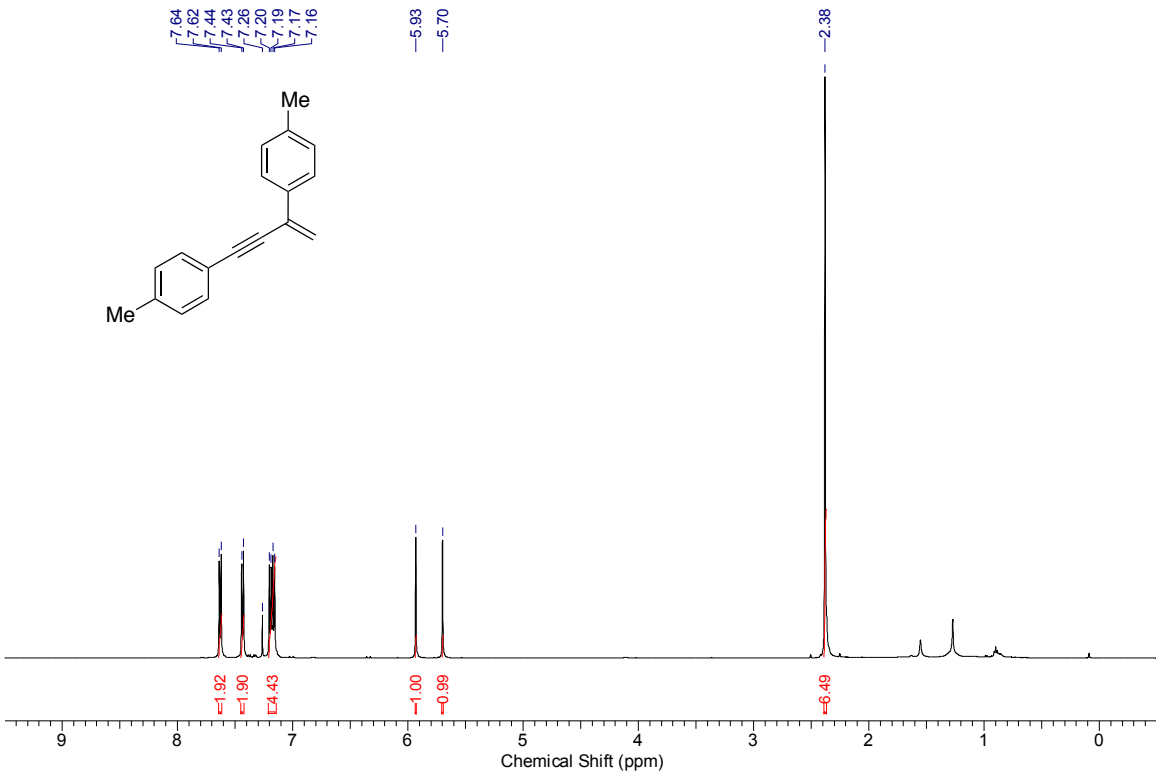
^{1}H NMR spectrum of **1-02j**:



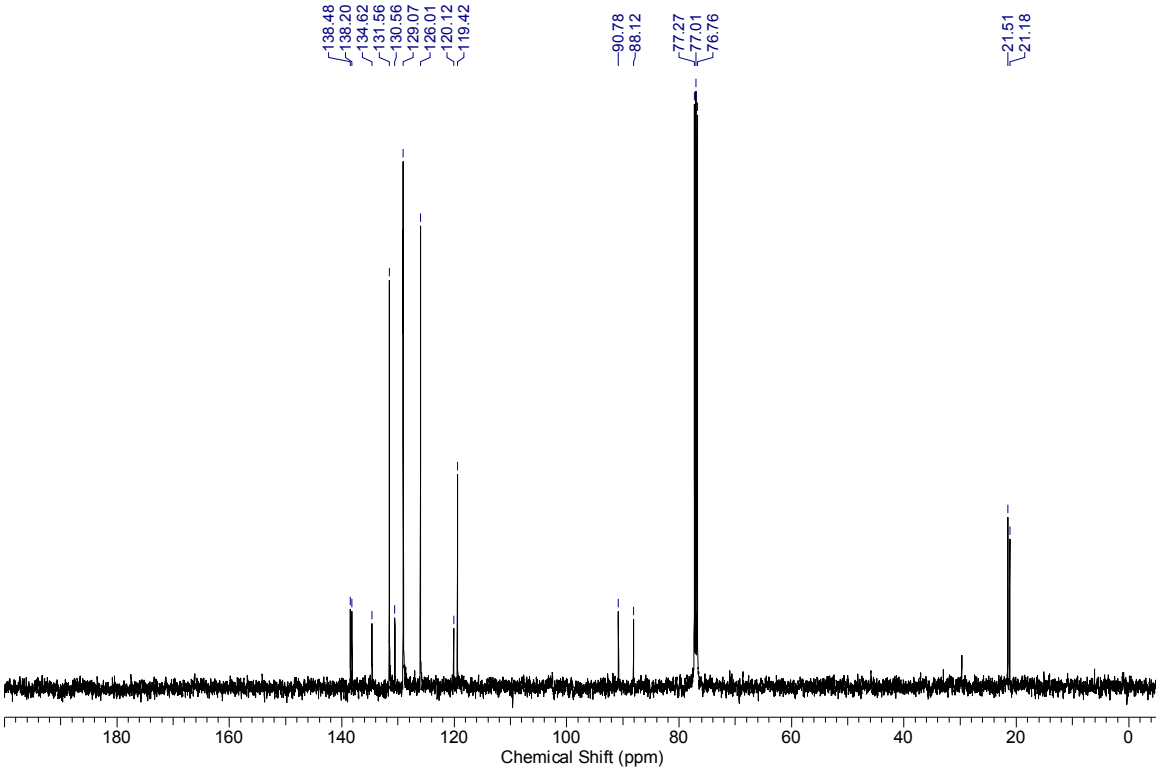
^{13}C NMR spectrum of **1-02j**:



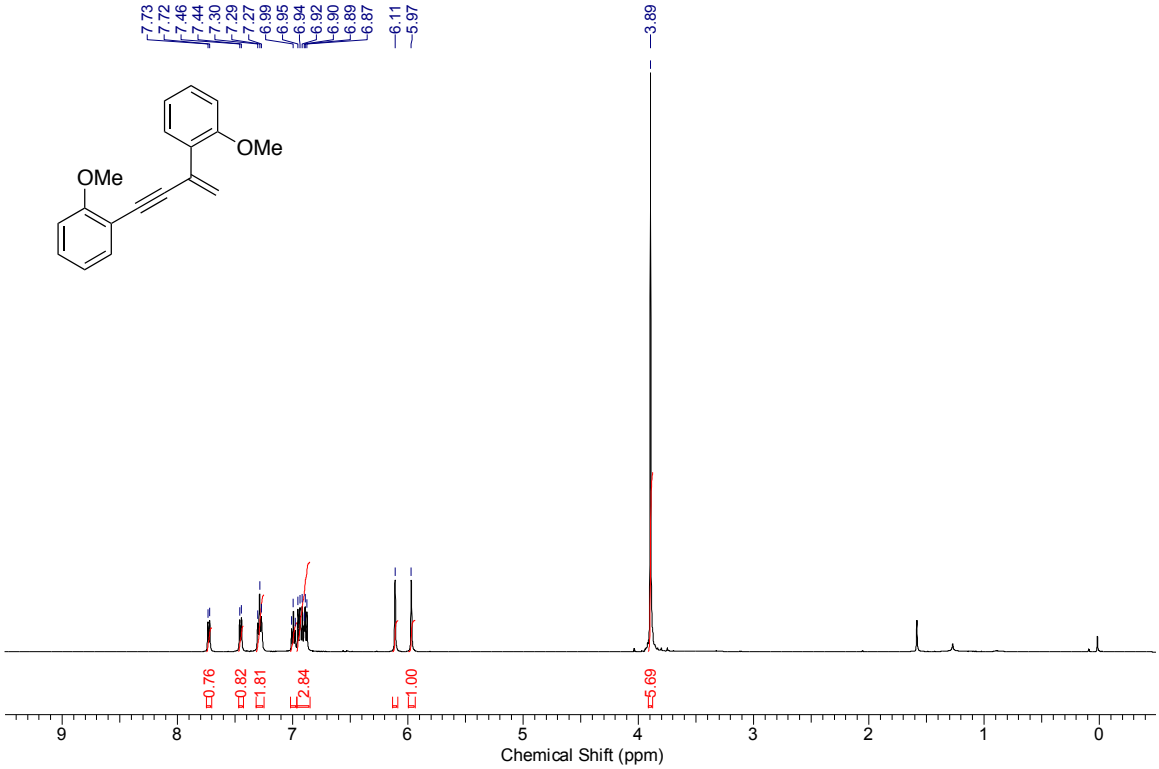
^{1}H NMR spectrum of **1-02i**:



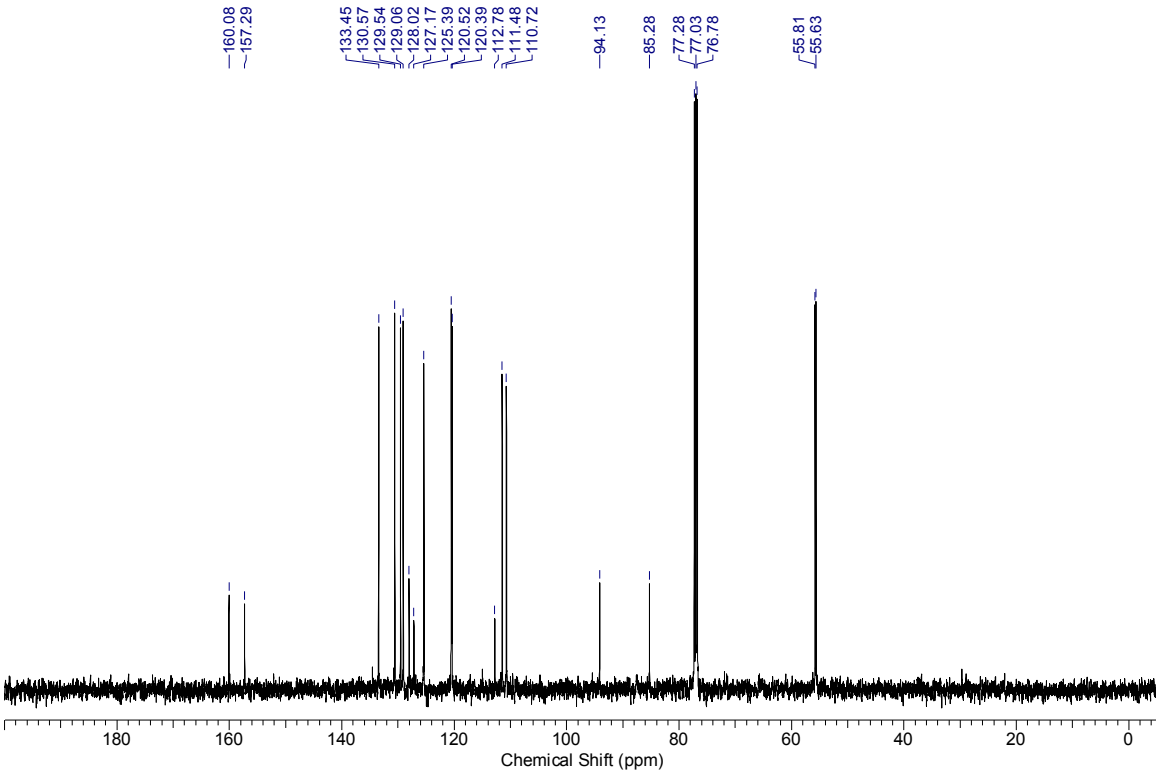
^{13}C NMR spectrum of **1-02i**:



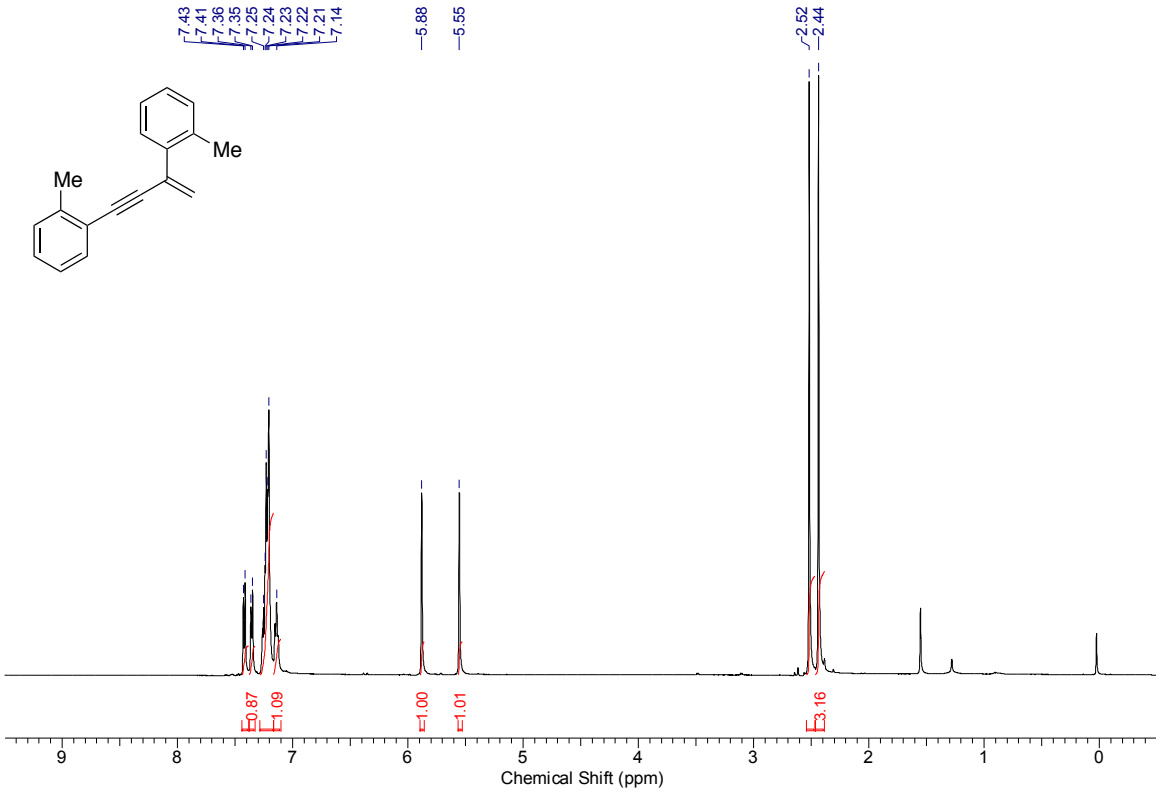
^{1}H NMR spectrum of **1-02z**:



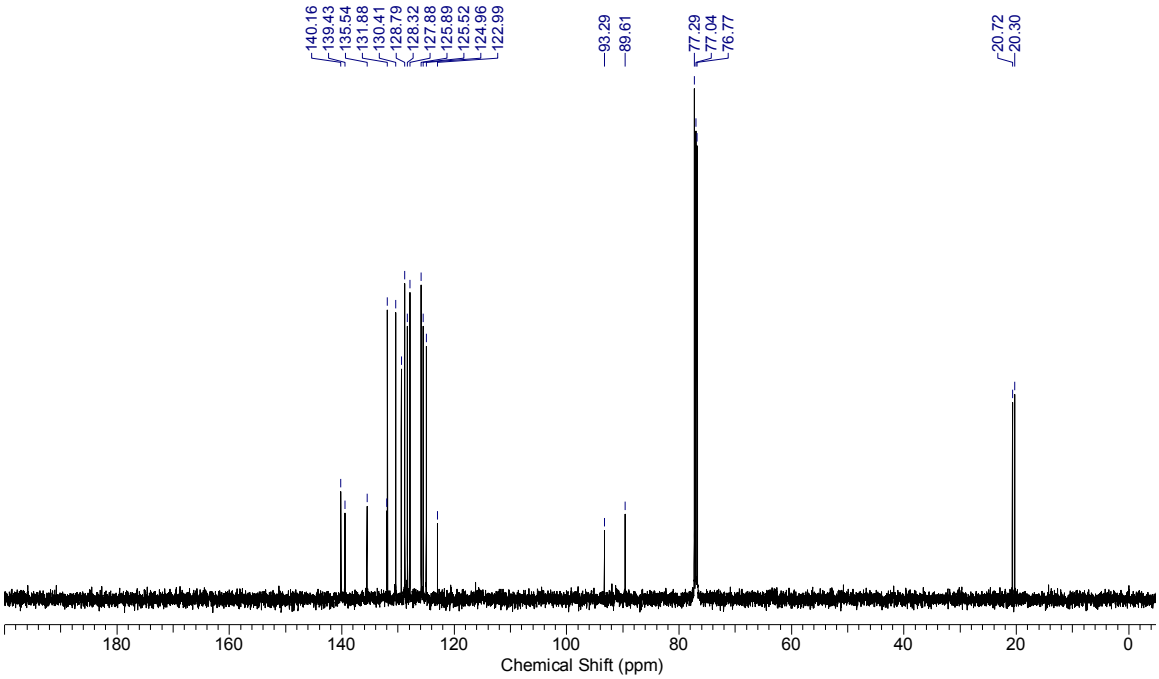
^{13}C NMR spectrum of **1-02z**:



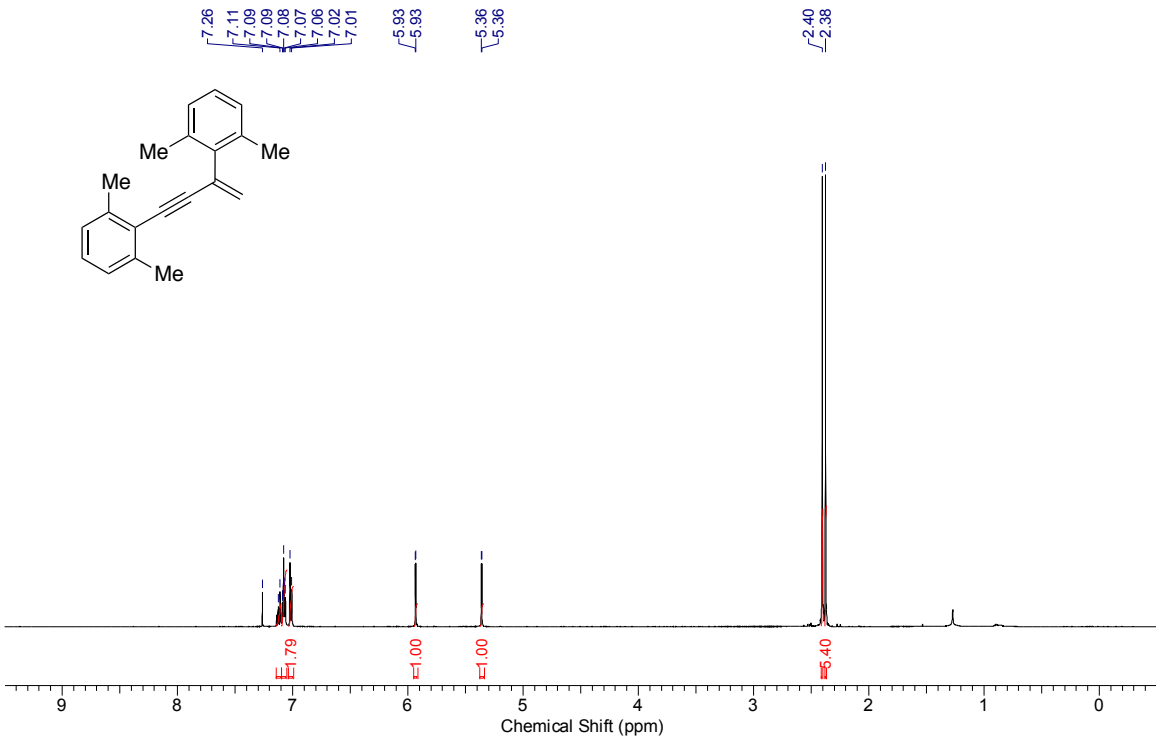
^{1}H NMR spectrum of **1-02q**:



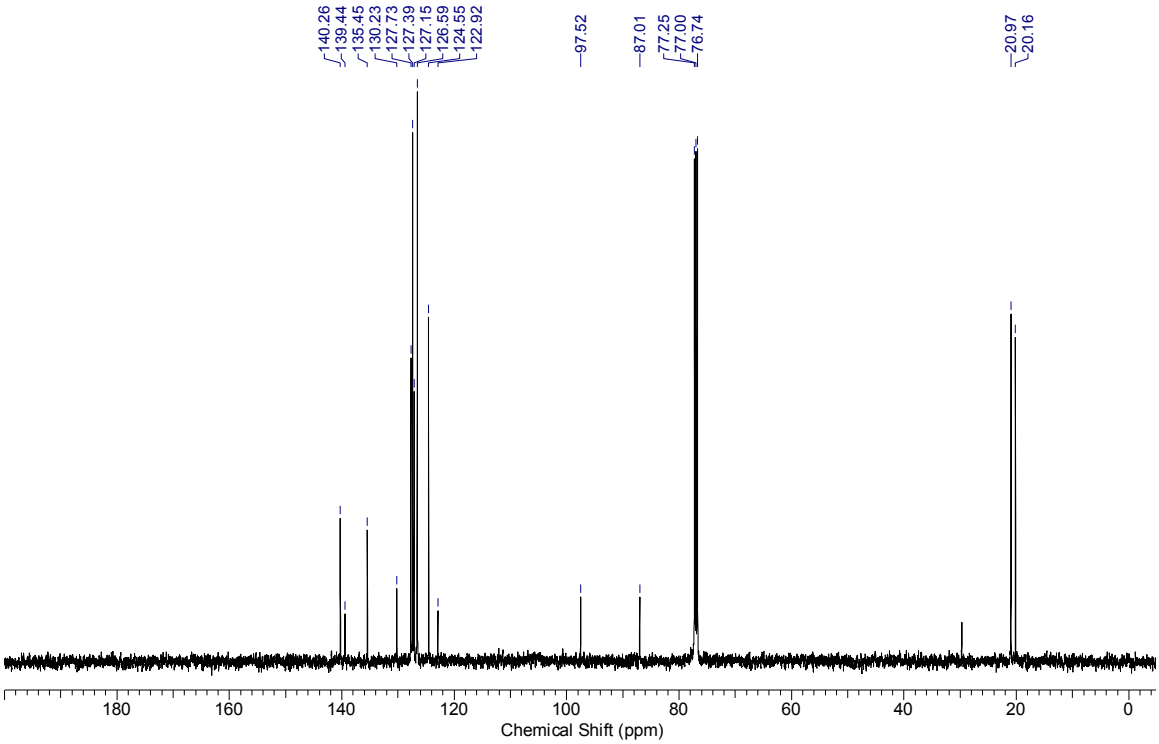
^{13}C NMR spectrum of **1-02q**:



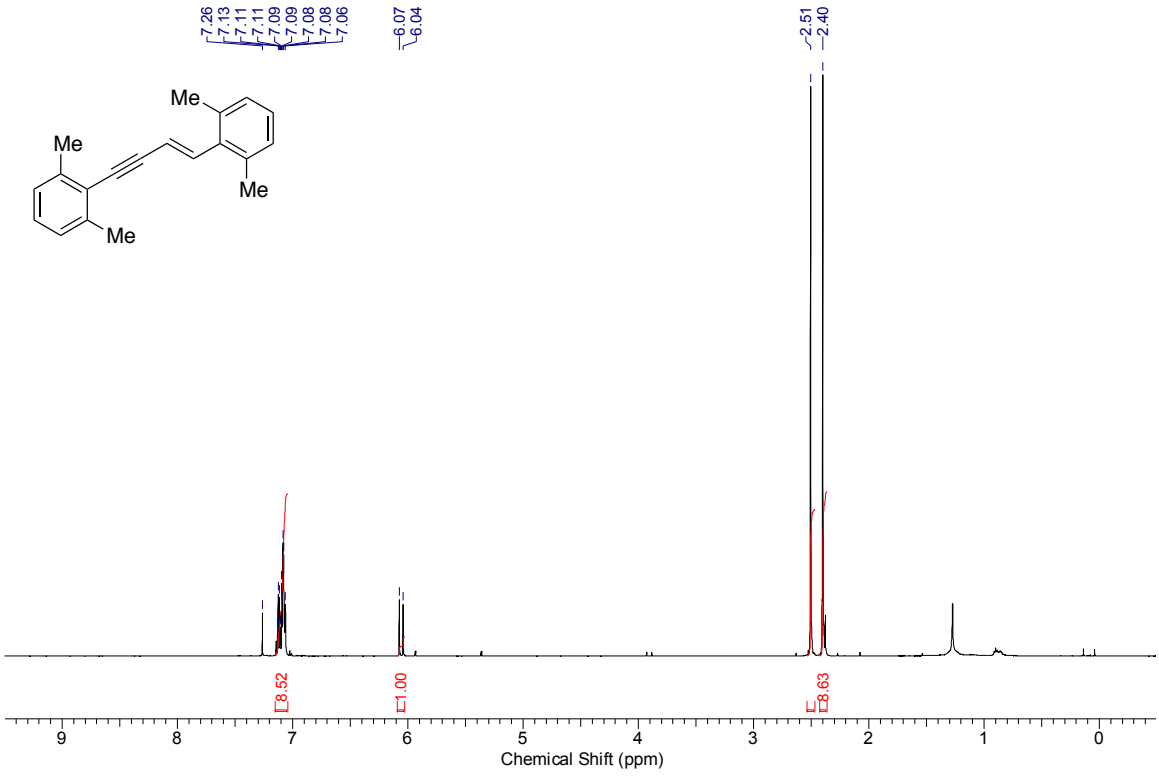
^{1}H NMR spectrum of **1-02r**:



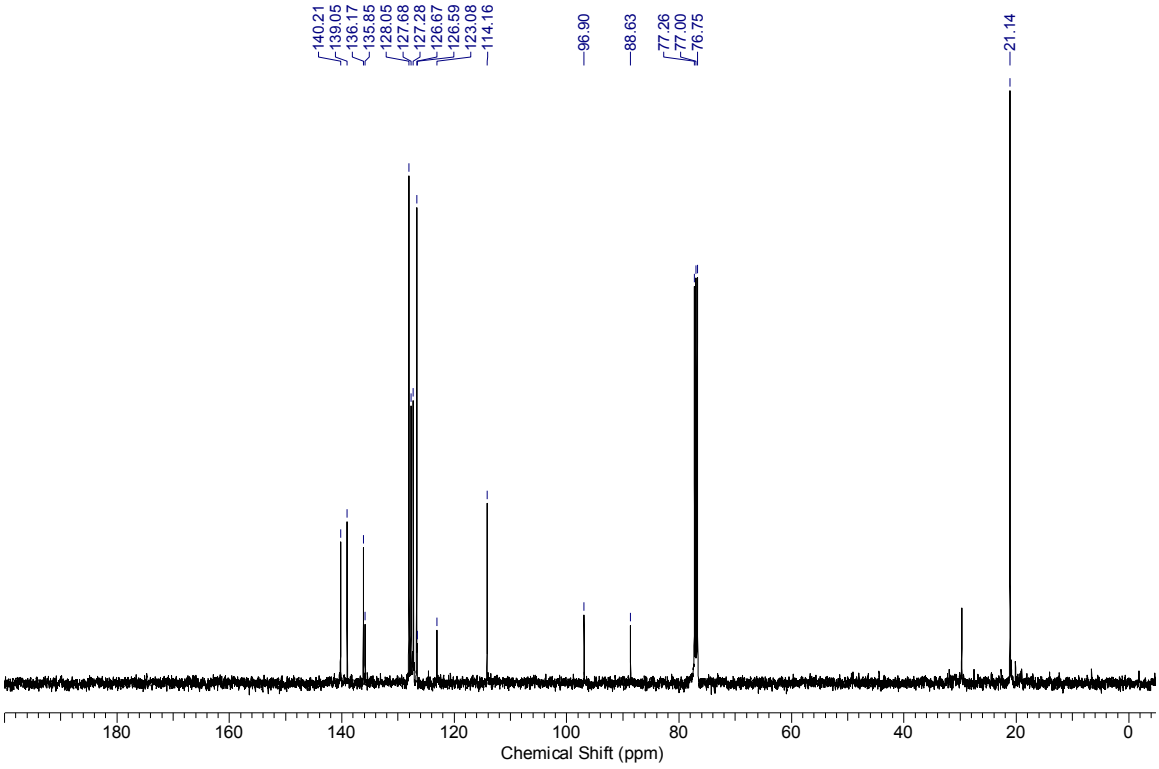
^{13}C NMR spectrum of **1-02r**:



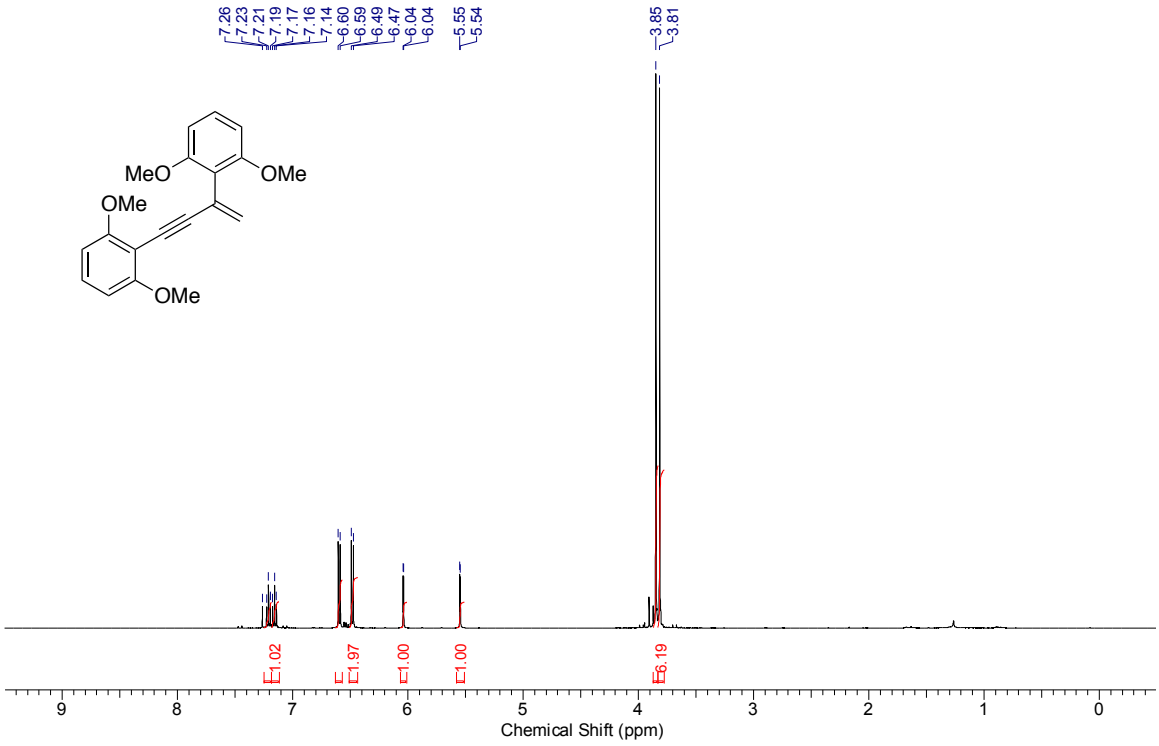
^{1}H NMR spectrum of **1-03r**:



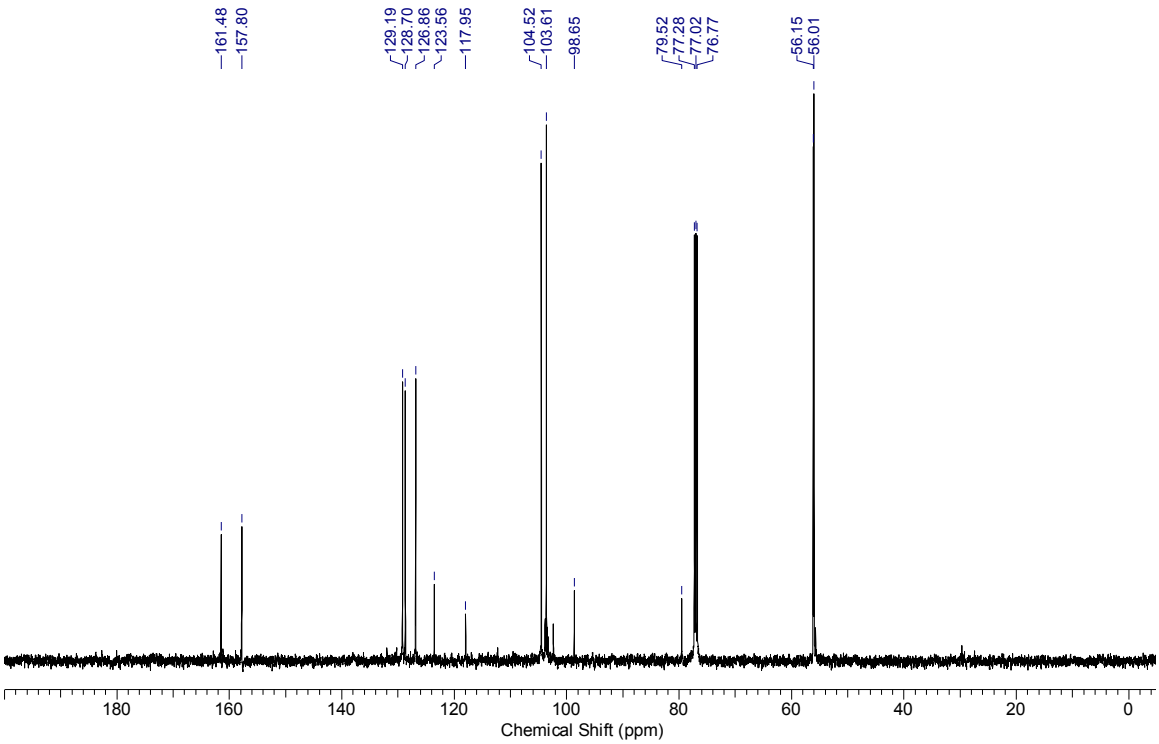
^{13}C NMR spectrum of **1-03r**:



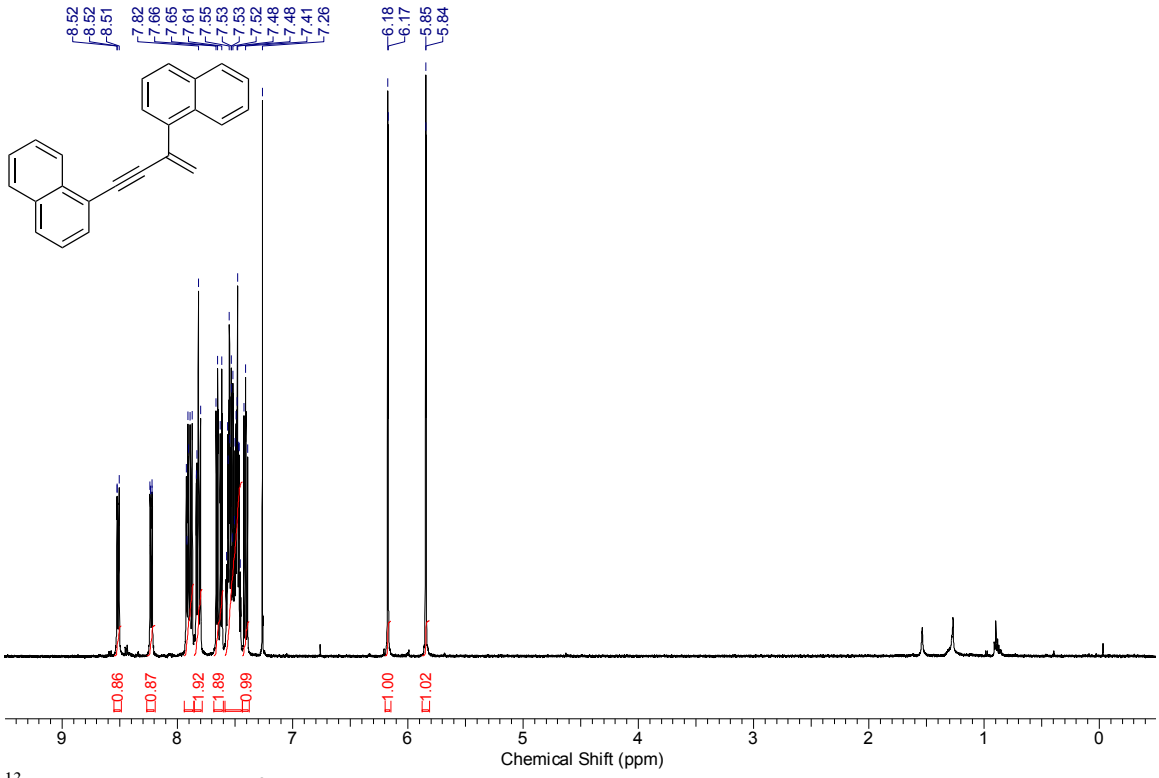
^{1}H NMR spectrum of **1-02t**:



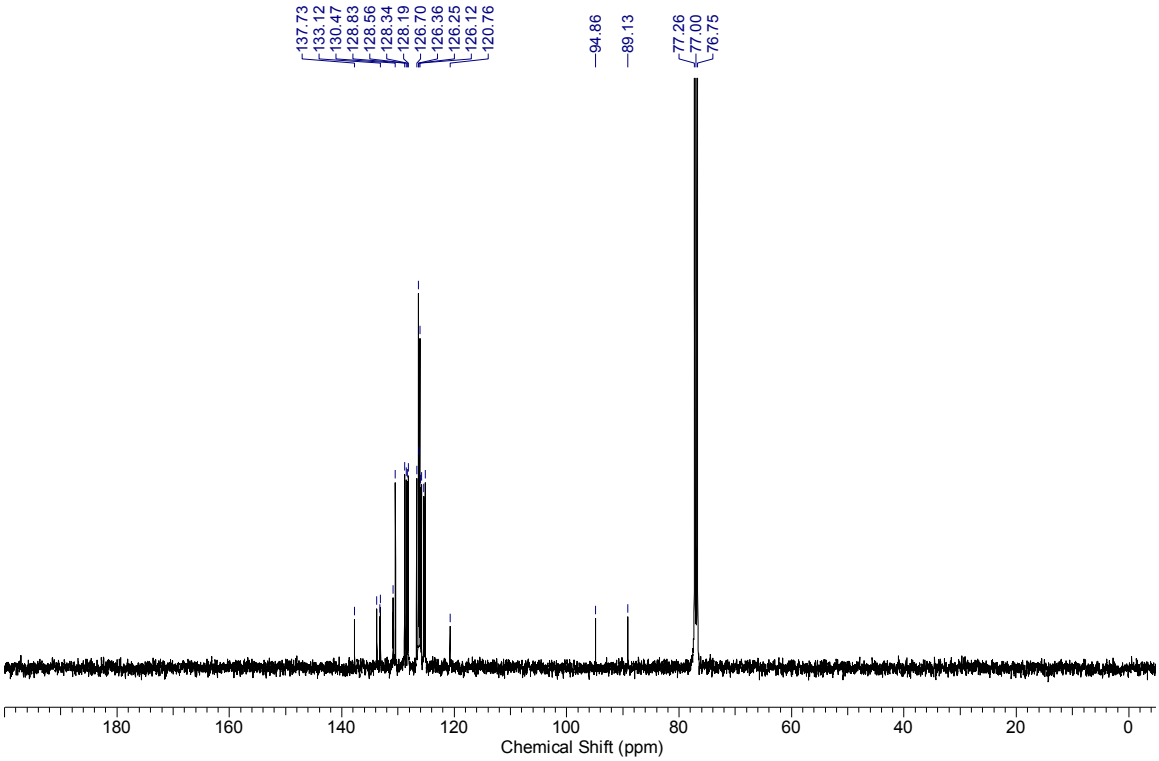
^{13}C NMR spectrum of **1-02t**:



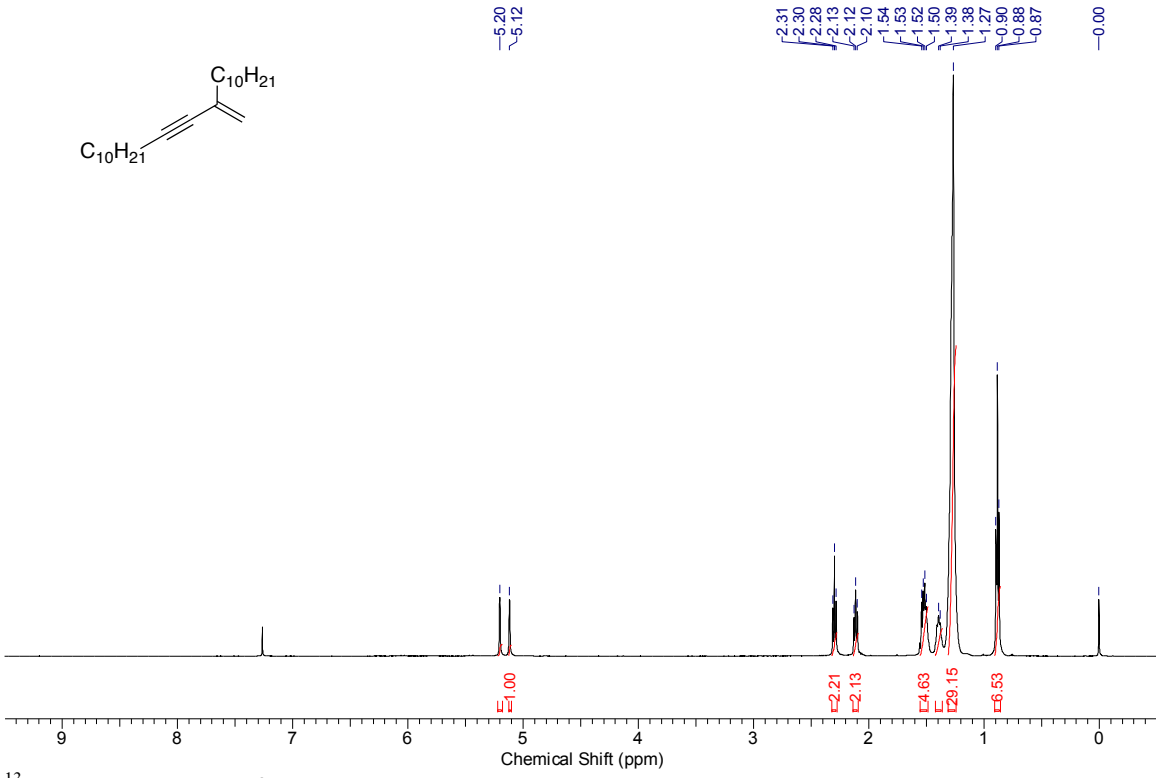
^{1}H NMR spectrum of **1-02n**:



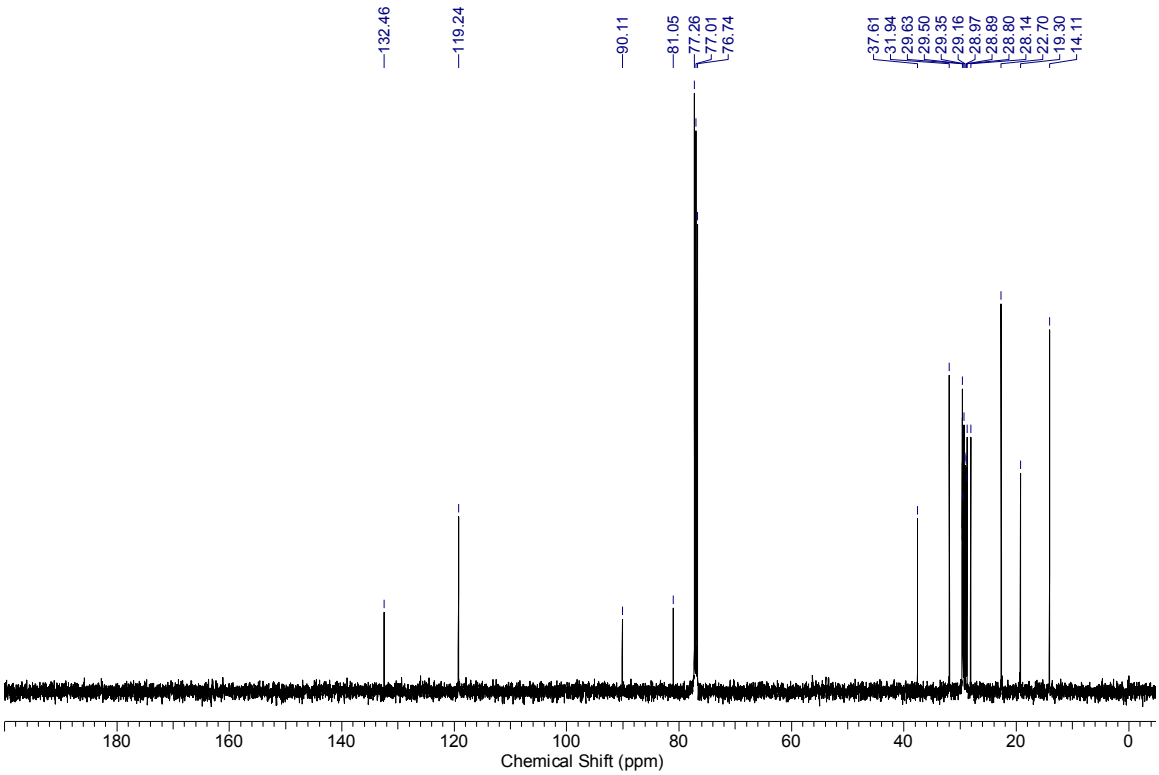
^{13}C NMR spectrum of **1-02n**:



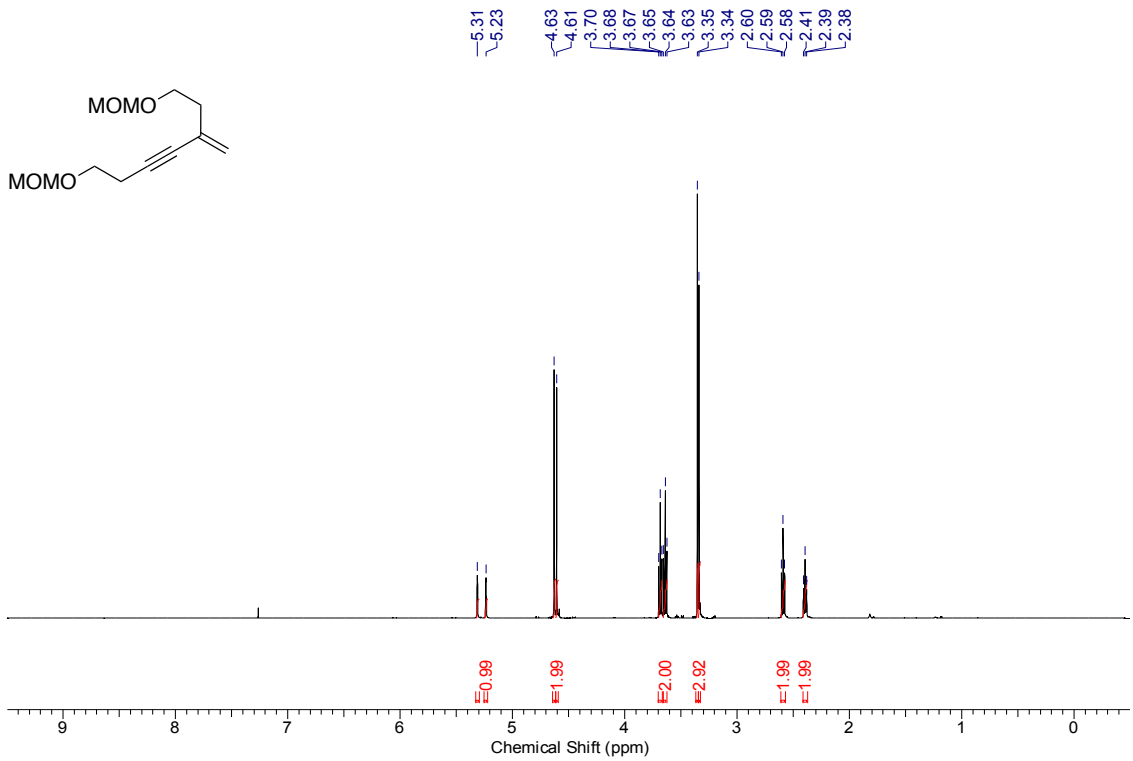
^{1}H NMR spectrum of **1-02ad**:



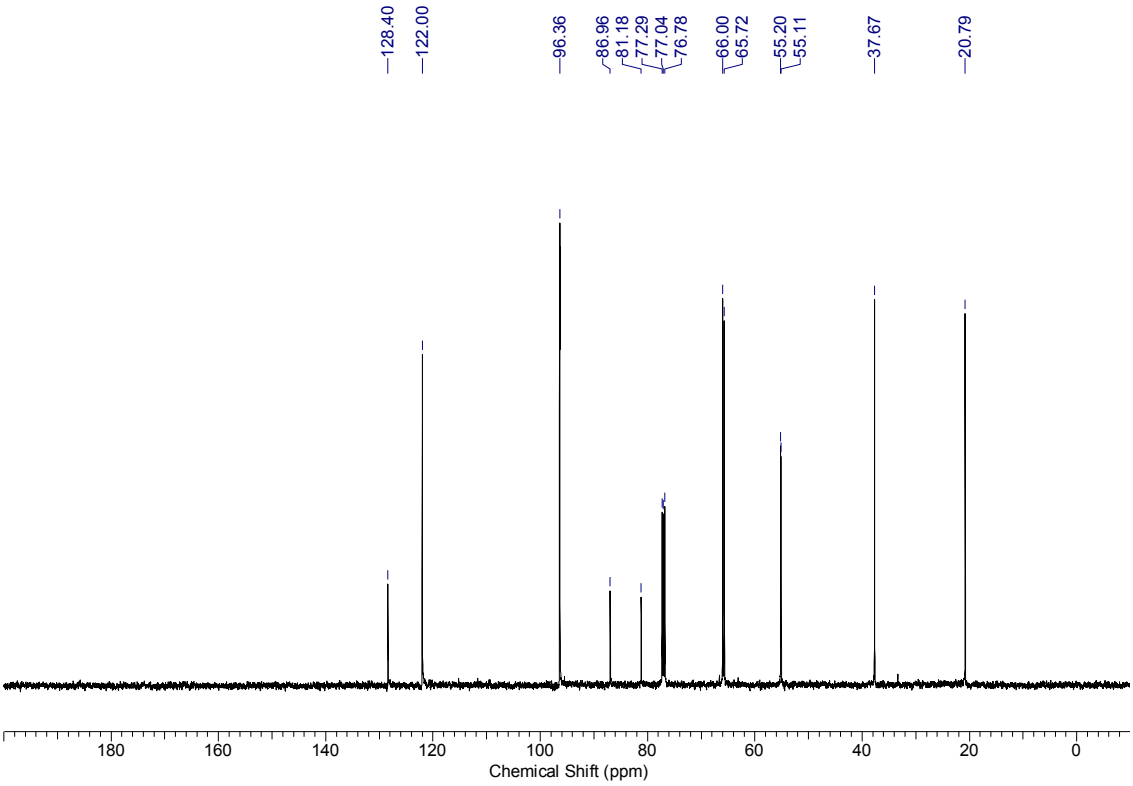
^{13}C NMR spectrum of **1-02ad**:



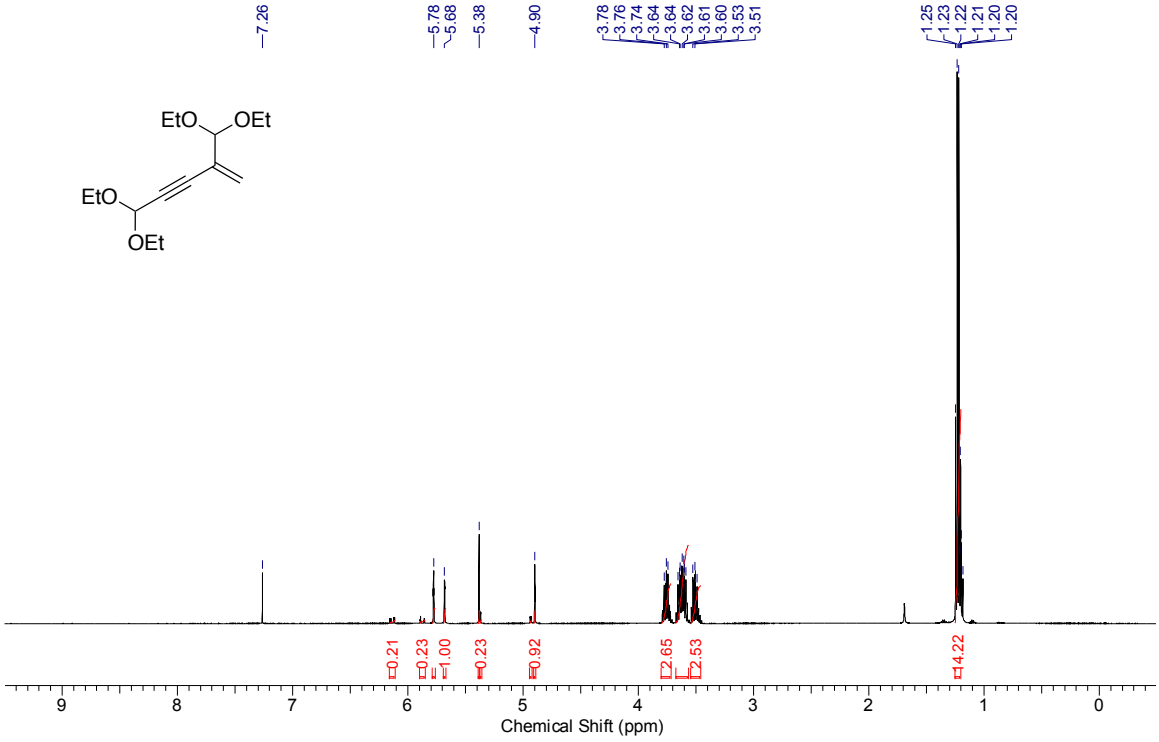
^{1}H NMR spectrum of **1-02ag**:



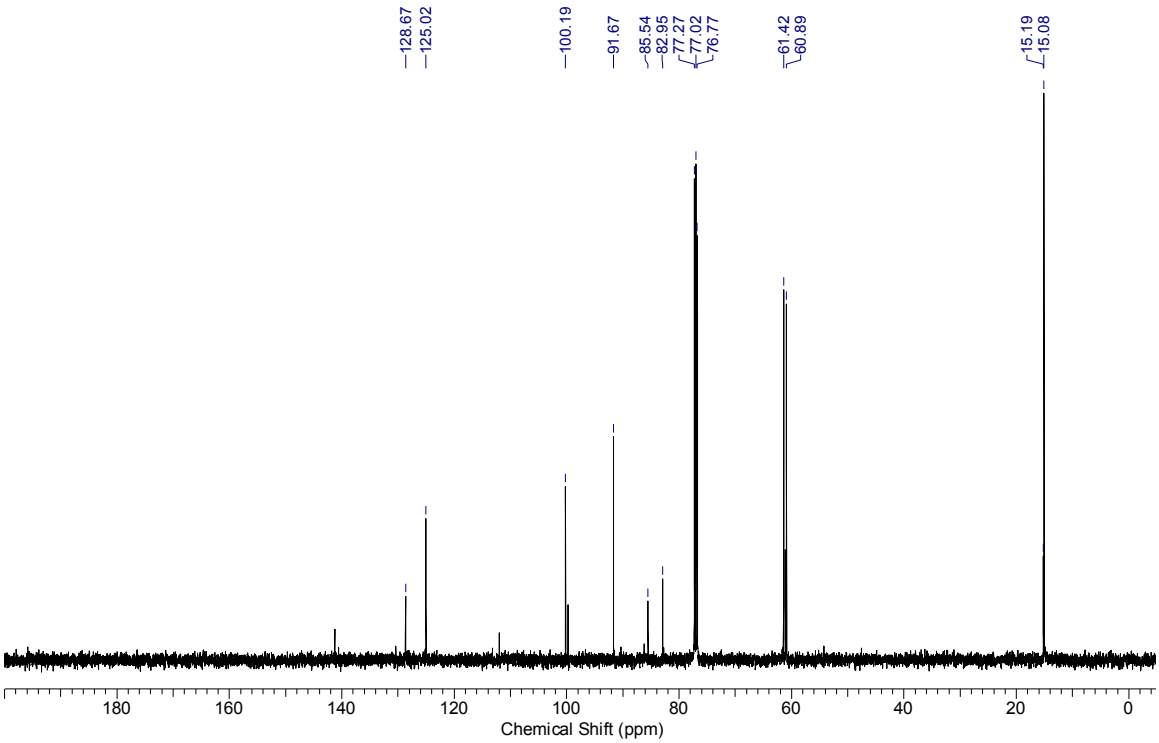
^{13}C NMR spectrum of **1-02ag**:



^{1}H NMR spectrum of **1-02ak**:



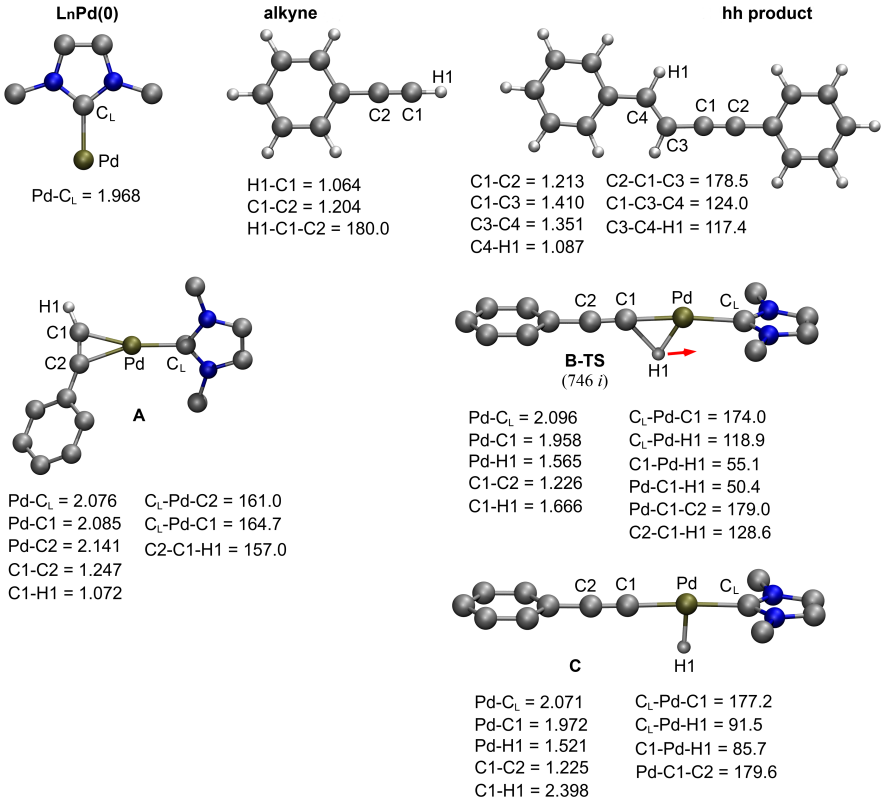
^{13}C NMR spectrum of **1-02ak**:



APPENDIX II

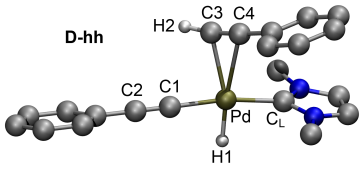
Optimized Molecular Structures for Part One

Optimized Molecular Structures of **L-Pd(0)**, **1-01**, **1-03**, **A**, **B-TS** and **C** at B3LYP/6-311G(d)&SDD Level (normal mode corresponding to imaginary frequency in the transition state is visualized, interatomic distances in Å, valence angles in degrees; hydrogen atoms of the complexes are omitted for clarity with the exception of reacting H1 atom):



Optimized Molecular Structures of **D-hh**, **E-TS-hh**, **F-hh**, **G-TS-hh**, **H-hh** at the B3LYP/6-311G(d)&SDD Level (normal mode corresponding to imaginary frequency in the transition state is visualized, interatomic distances in Å, valence angles in degrees; hydrogen atoms of the complexes are omitted for clarity with the exception of reacting H1 and H2 atoms):

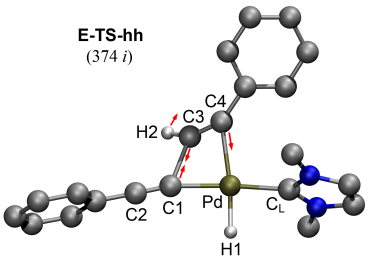
D-hh



$Pd-C_L$ = 2.074
Pd-C1 = 1.998
Pd-C3 = 2.423
Pd-C4 = 2.617
Pd-H1 = 1.543
C1-C2 = 1.223
C3-C4 = 1.215
C3-H2 = 1.065

C_L-Pd-C1 = 170.0
C_L-Pd-H1 = 87.4
C_L-Pd-C4 = 88.6
C1-Pd-H1 = 82.6
Pd-C1-C2 = 179.3
H2-C3-C4 = 168.9

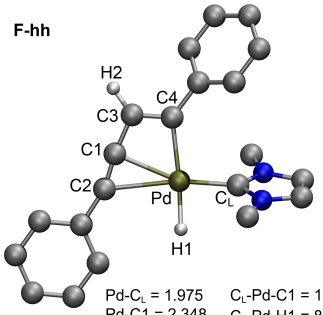
E-TS-hh
(374 *i*)



$Pd-C_L$ = 2.037
Pd-C1 = 2.031
Pd-C3 = 2.294
Pd-C4 = 2.216
Pd-H1 = 1.589
C1-C2 = 1.227
C3-C4 = 1.269
C3-H2 = 1.075
C3-C1 = 1.936

C_L-Pd-C1 = 172.0
C_L-Pd-H1 = 84.7
C_L-Pd-C4 = 102.3
C1-Pd-H1 = 90.6
Pd-C1-C2 = 163.6
H2-C3-C4 = 143.2
C1-C3-C4 = 120.4
Pd-C4-C3 = 77.0

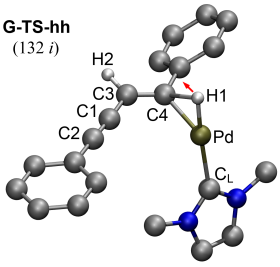
F-hh



$Pd-C_L$ = 1.975
Pd-C1 = 2.348
Pd-C2 = 2.528
Pd-C3 = 2.730
Pd-C4 = 2.152
Pd-H1 = 1.621
C1-C2 = 1.230
C3-C4 = 1.351
C3-H2 = 1.092
C3-C1 = 1.430

C_L-Pd-C1 = 161.1
C_L-Pd-H1 = 84.2
C_L-Pd-C4 = 100.4
C1-Pd-H1 = 114.7
C2-C1-C3 = 172.8
H2-C3-C4 = 128.7
C1-C3-C4 = 110.3
Pd-C4-C3 = 99.8

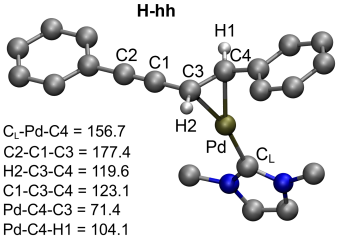
G-TS-hh
(132 *i*)



$Pd-C_L$ = 2.156
Pd-C1 = 3.307
Pd-C3 = 2.947
Pd-C4 = 1.988
Pd-H1 = 1.588
C4-H1 = 1.902
C1-C2 = 1.214
C3-C4 = 1.358
C3-H2 = 1.091
C3-C1 = 1.410

C_L-Pd-C4 = 124.8
C_L-Pd-H1 = 171.9
C2-C1-C3 = 177.2
H2-C3-C4 = 118.2
C1-C3-C4 = 126.0
Pd-C4-C3 = 122.4
Pd-C4-H1 = 48.1
Pd-H1-C4 = 68.8

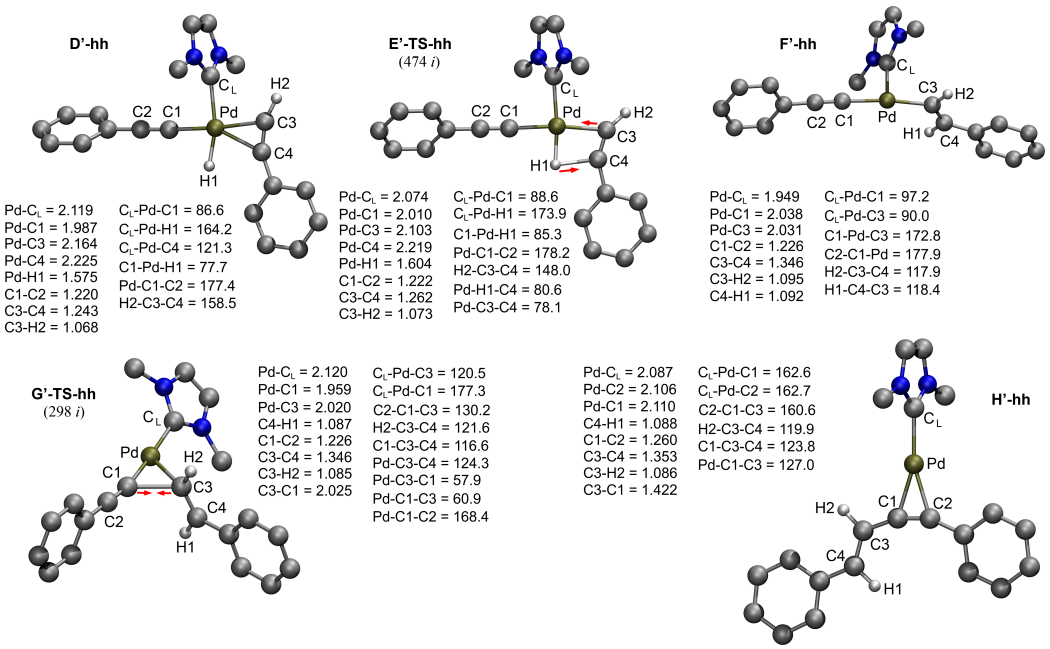
H-hh



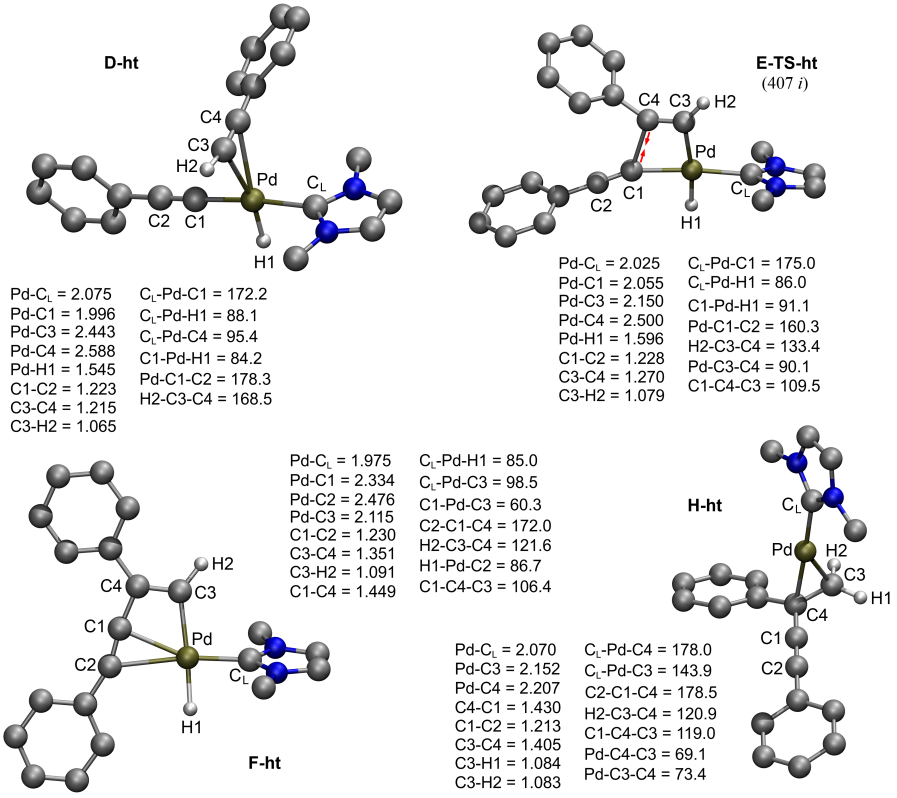
$Pd-C_L$ = 2.079
Pd-C3 = 2.185
Pd-C4 = 2.183
C4-H1 = 1.087
C1-C2 = 1.213
C3-C4 = 1.401
C3-H2 = 1.087
C3-C1 = 1.420

C_L-Pd-C4 = 156.7
C2-C1-C3 = 177.4
H2-C3-C4 = 119.6
C1-C3-C4 = 123.1
Pd-C4-C3 = 71.4
Pd-C4-H1 = 104.1

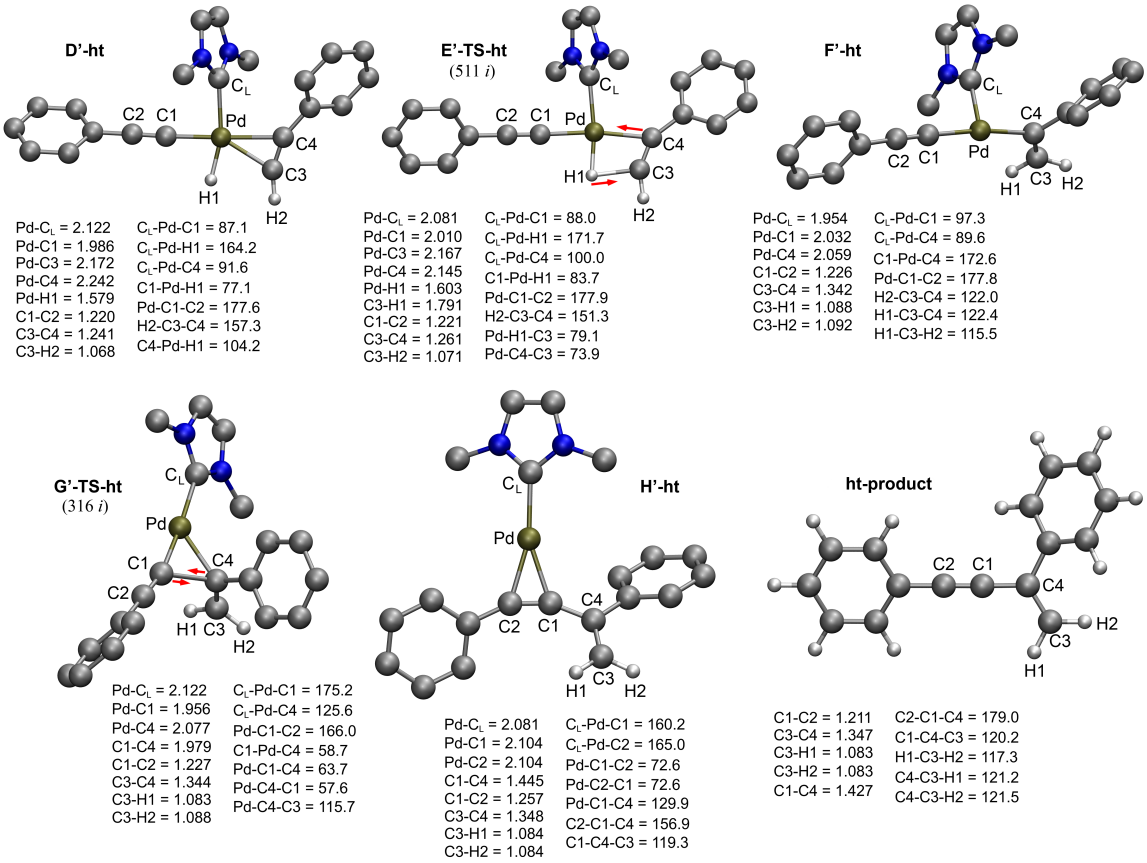
Optimized Molecular Structures of **D'-hh**, **E'-TS-hh**, **F'-hh**, **G'-TS-hh**, **H'-hh** at the B3LYP/6-311G(d)&SDD Level (normal mode corresponding to imaginary frequency in the transition state is visualized, interatomic distances in Å, valence angles in degrees; hydrogen atoms of the complexes are omitted for clarity with the exception of reacting H1 and H2 atoms):



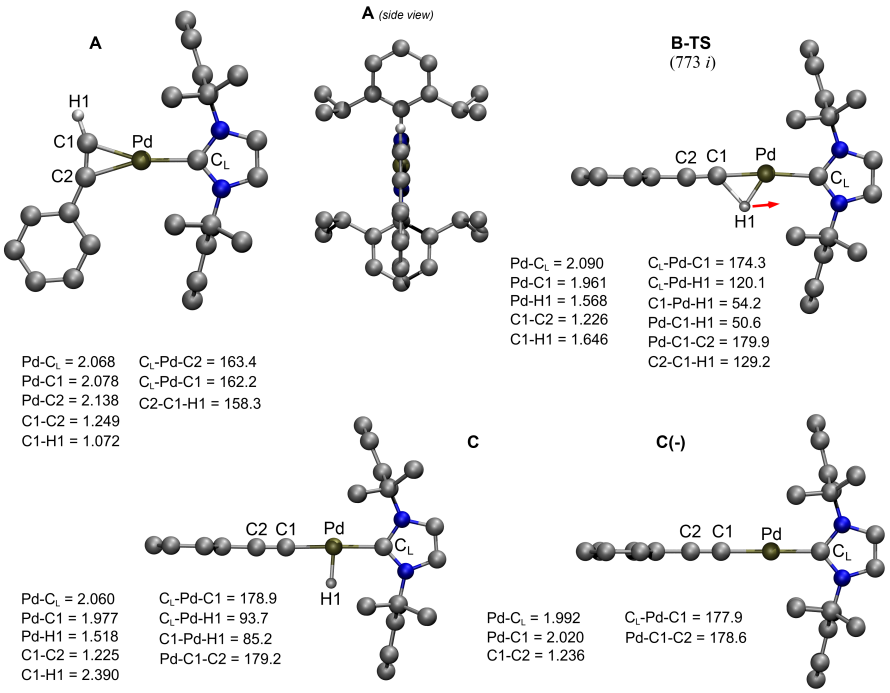
Optimized Molecular Structures of **D-ht**, **E-TS-ht**, **F-ht**, **H-ht** at the B3LYP/6-311G(d)&SDD Level (normal mode corresponding to imaginary frequency in the transition state is visualized, interatomic distances in Å, valence angles in degrees; hydrogen atoms of the complexes are omitted for clarity with the exception of reacting H1 and H2 atoms):



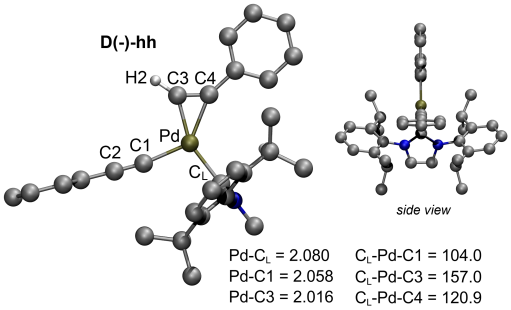
Optimized Molecular Structures of **D'-ht**, **E'-TS-ht**, **F'-ht**, **G'-TS-ht**, **H'-ht**, and **1-02** at the B3LYP/6-311G(d)&SDD level (normal mode corresponding to imaginary frequency in the transition state is visualized, interatomic distances in Angstroms, valence angles in degrees; hydrogen atoms of the complexes are omitted for clarity with the exception of reacting H1 and H2 atoms):



Optimized Molecular Structures of **A**, **B-TS**, **C**, **C(-)** at the B3LYP/6-311G(d)&SDD Level (normal mode corresponding to imaginary frequency in the transition state is visualized, interatomic distances in Å, valence angles in degrees):

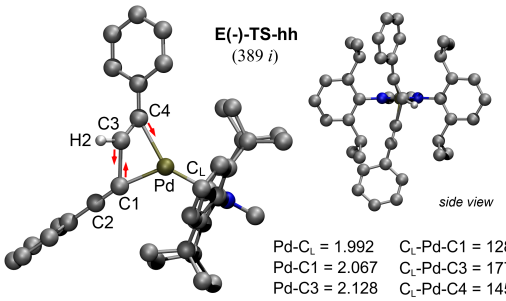


Optimized Molecular Structures of **D(-)-hh**, **E(-)-TS-hh**, **F(-)-hh** at the B3LYP/6-311G(d)&SDD Level (normal mode corresponding to imaginary frequency in the transition state is visualized, interatomic distances in Å, valence angles in degrees):



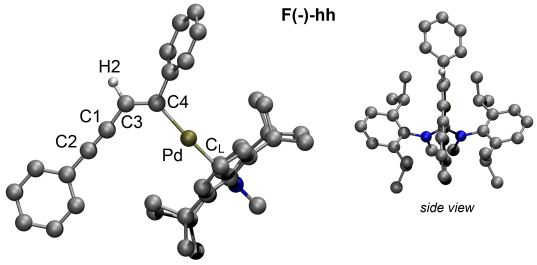
Pd-C_L = 2.080
Pd-C1 = 2.058
Pd-C3 = 2.016
Pd-C4 = 2.138
C1-C2 = 1.234
C3-C4 = 1.291
C3-H2 = 1.082

C_L-Pd-C1 = 104.0
C_L-Pd-C3 = 157.0
C_L-Pd-C4 = 120.9
Pd-C1-C2 = 171.4
H2-C3-C4 = 144.4



Pd-C_L = 1.992
Pd-C1 = 2.067
Pd-C3 = 2.128
Pd-C4 = 2.323
C1-C2 = 1.236
C3-C4 = 1.298
C3-H2 = 1.083

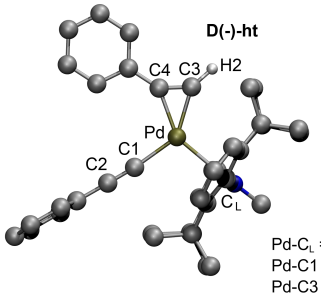
C_L-Pd-C1 = 128.0
C_L-Pd-C3 = 177.1
C_L-Pd-C4 = 145.3
Pd-C1-C2 = 166.9
H2-C3-C4 = 134.8
C1-C3-C4 = 128.2
C1-Pd-C4 = 82.7

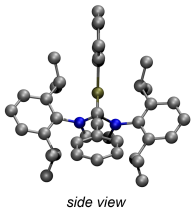


Pd-C_L = 2.006
Pd-C4 = 2.081
C1-C3 = 1.410
C1-C2 = 1.219
C3-C4 = 1.369
C3-H2 = 1.099

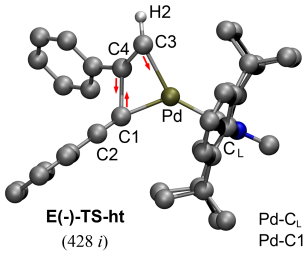
C_L-Pd-C4 = 175.8
H2-C3-C4 = 119.8
C2-C1-C3 = 174.1
C1-C3-C4 = 127.0
Pd-C4-C3 = 131.0

Optimized Molecular Structures of **D(-)-ht**, **E(-)-TS-ht**, **F(-)-ht** at the B3LYP/6-311G(d)&SDD Level (normal mode corresponding to imaginary frequency in the transition state is visualized, interatomic distances in Å, valence angles in degrees):

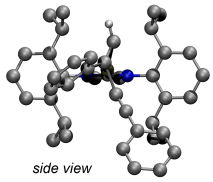




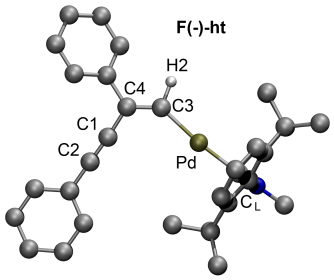
Pd-C_L = 2.072	C_L-Pd-C1 = 104.5
Pd-C1 = 2.066	C_L-Pd-C3 = 113.6
Pd-C3 = 2.074	C_L-Pd-C4 = 149.9
Pd-C4 = 2.068	Pd-C1-C2 = 174.7
C1-C2 = 1.235	H2-C3-C4 = 140.9
C3-C4 = 1.290	
C3-H2 = 1.084	

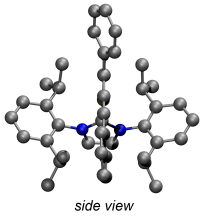


E(-)-TS-ht
(428 *i*)



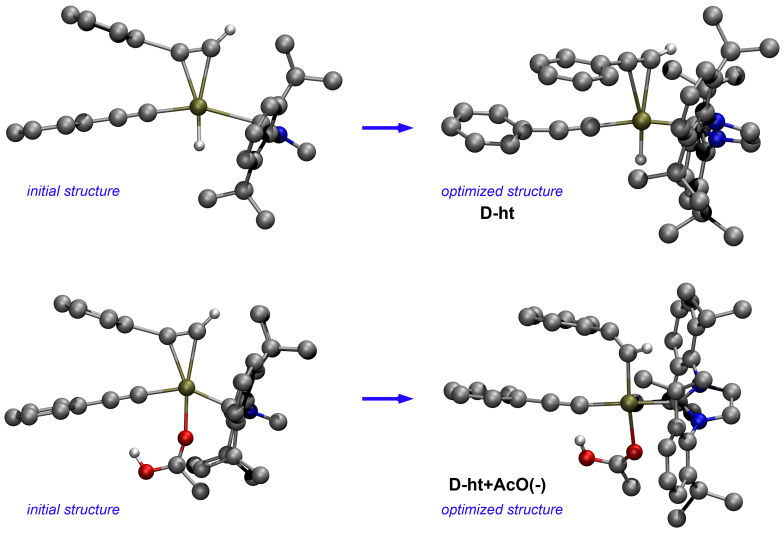
Pd-C_L = 1.987	C_L-Pd-C1 = 129.1
Pd-C1 = 2.070	C_L-Pd-C3 = 144.1
Pd-C3 = 2.262	C_L-Pd-C4 = 175.6
Pd-C4 = 2.262	Pd-C1-C2 = 161.5
C1-C2 = 1.235	H2-C3-C4 = 121.2
C3-C4 = 1.311	C1-C4-C3 = 122.3
C3-H2 = 1.094	C1-Pd-C3 = 82.6



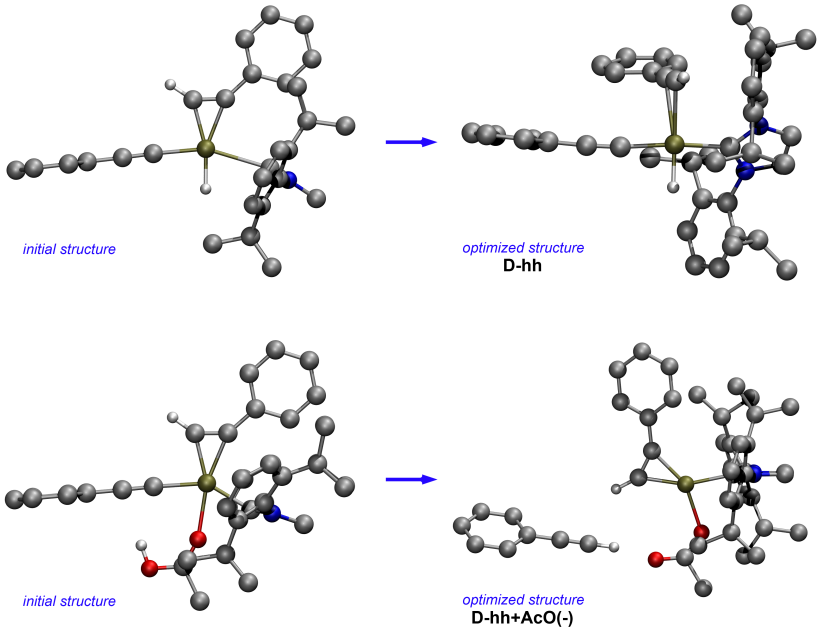


Pd-C_L = 2.009	C_L-Pd-C3 = 174.0
Pd-C3 = 2.050	H2-C3-C4 = 109.5
C1-C4 = 1.422	C2-C1-C4 = 176.3
C1-C2 = 1.218	C1-C4-C3 = 121.2
C3-C4 = 1.379	Pd-C3-C4 = 137.8
C3-H2 = 1.101	

Initial and Optimized Molecular Structures of **D-ht** and **D-ht+AcO(-)**, M06L/DGDZVP&SDD:



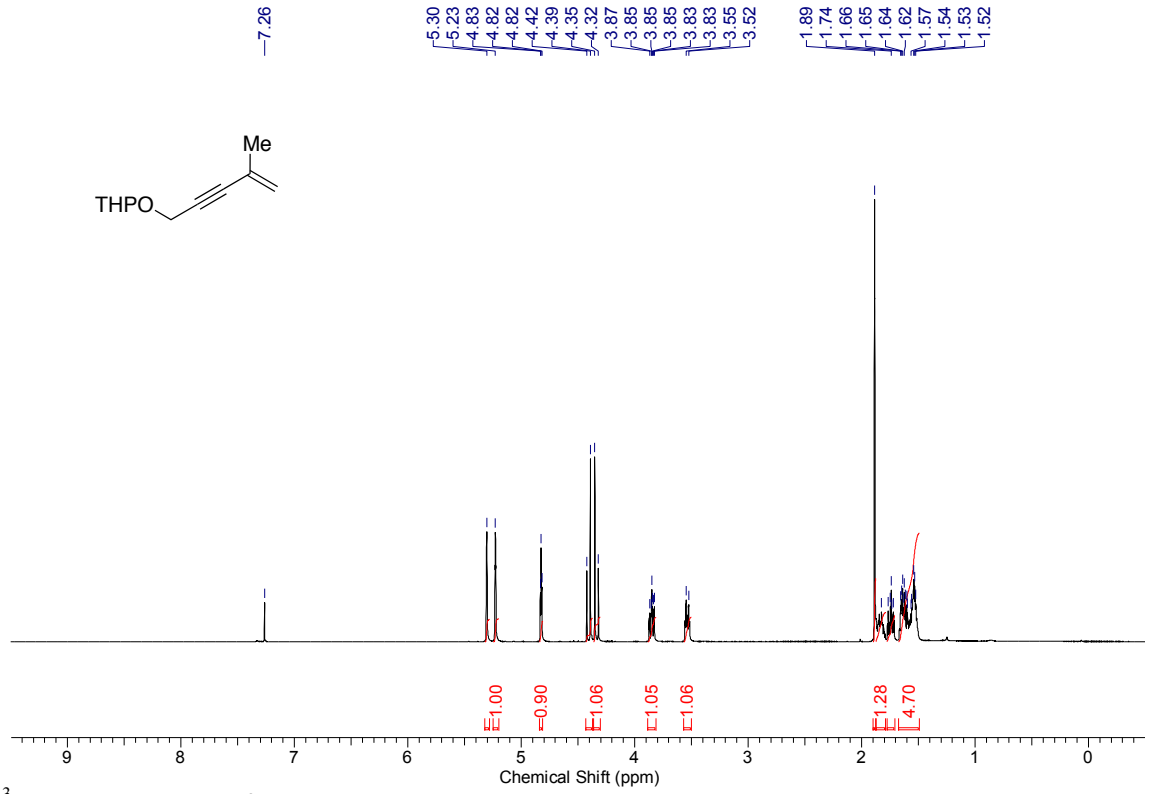
Initial and Optimized Molecular Structures of **D-hh** and **D-hh+AcO(-)**, M06L/DGDZVP&SDD.



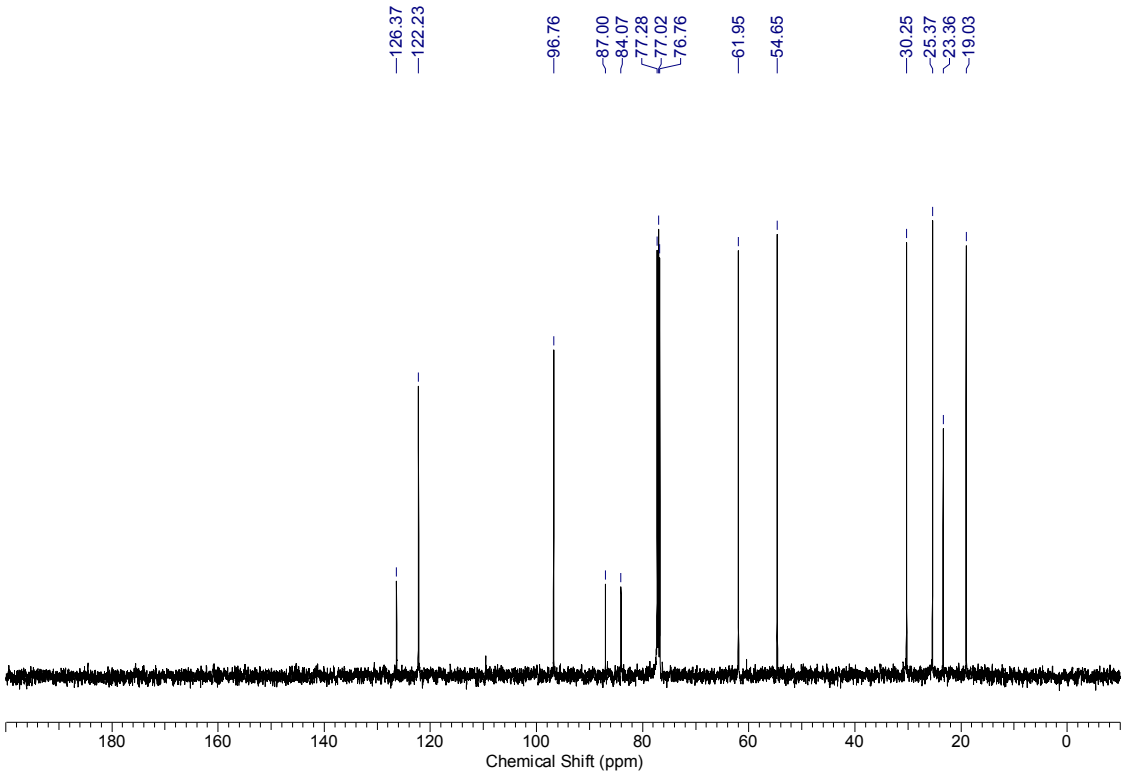
APPENDIX III

Selected NMR Spectra for Part Two

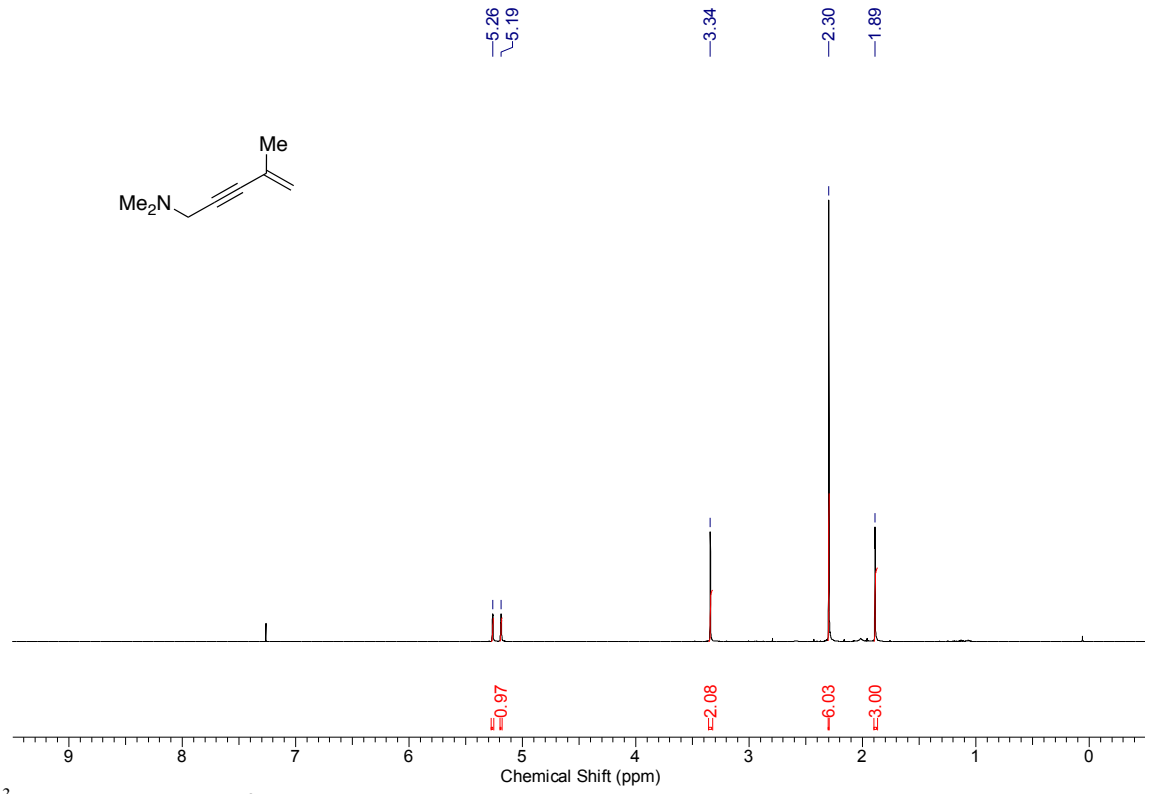
^{1}H NMR spectrum of **2-03j**:



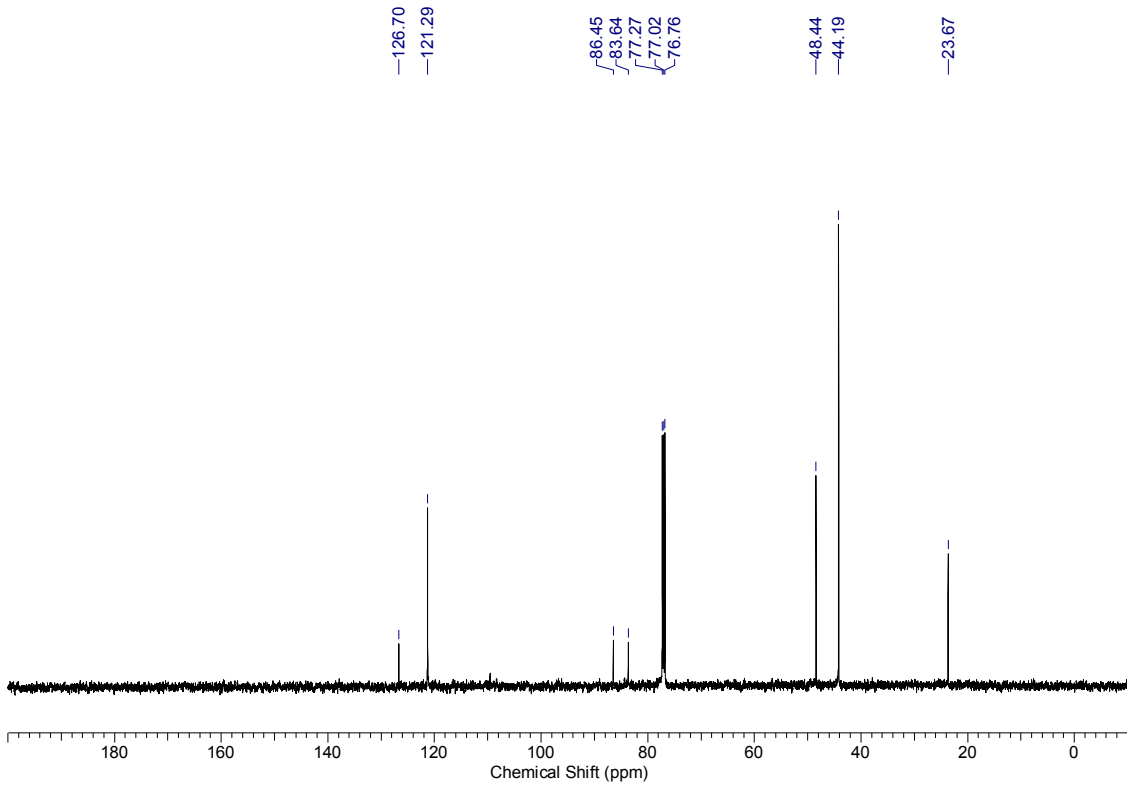
^{13}C NMR spectrum of **2-03j**:



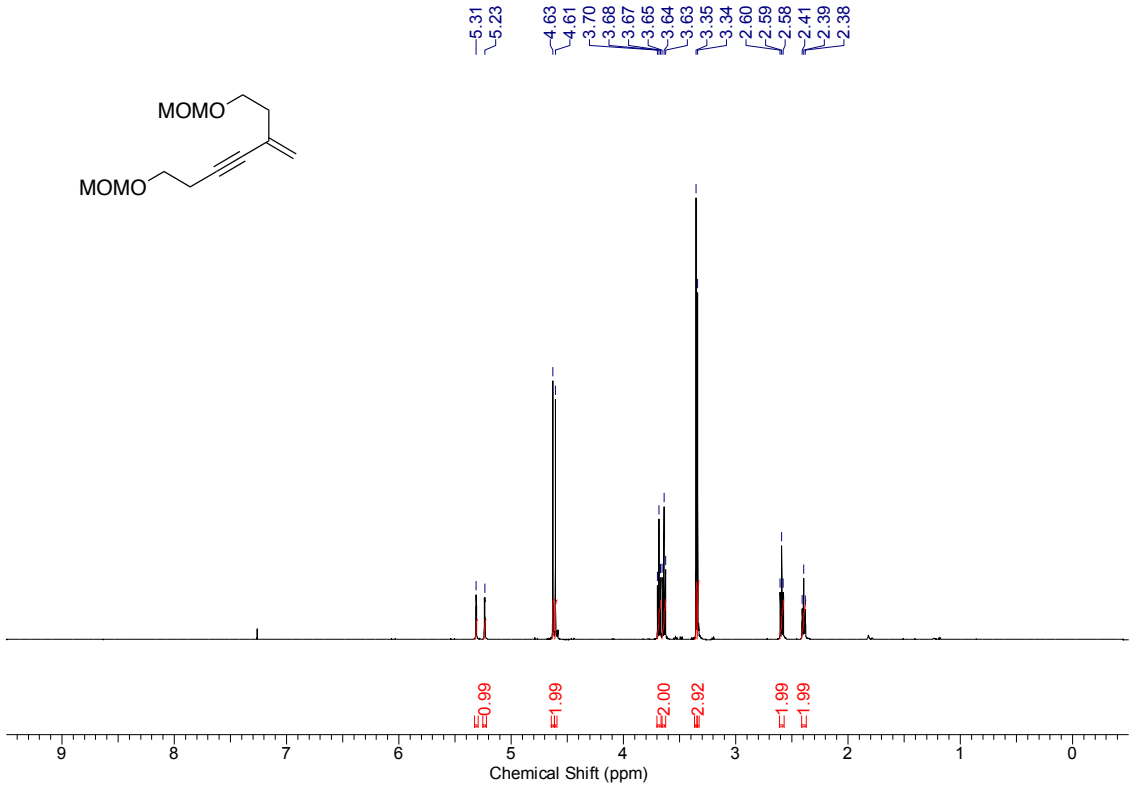
^{1}H NMR spectrum of **2-03l**:



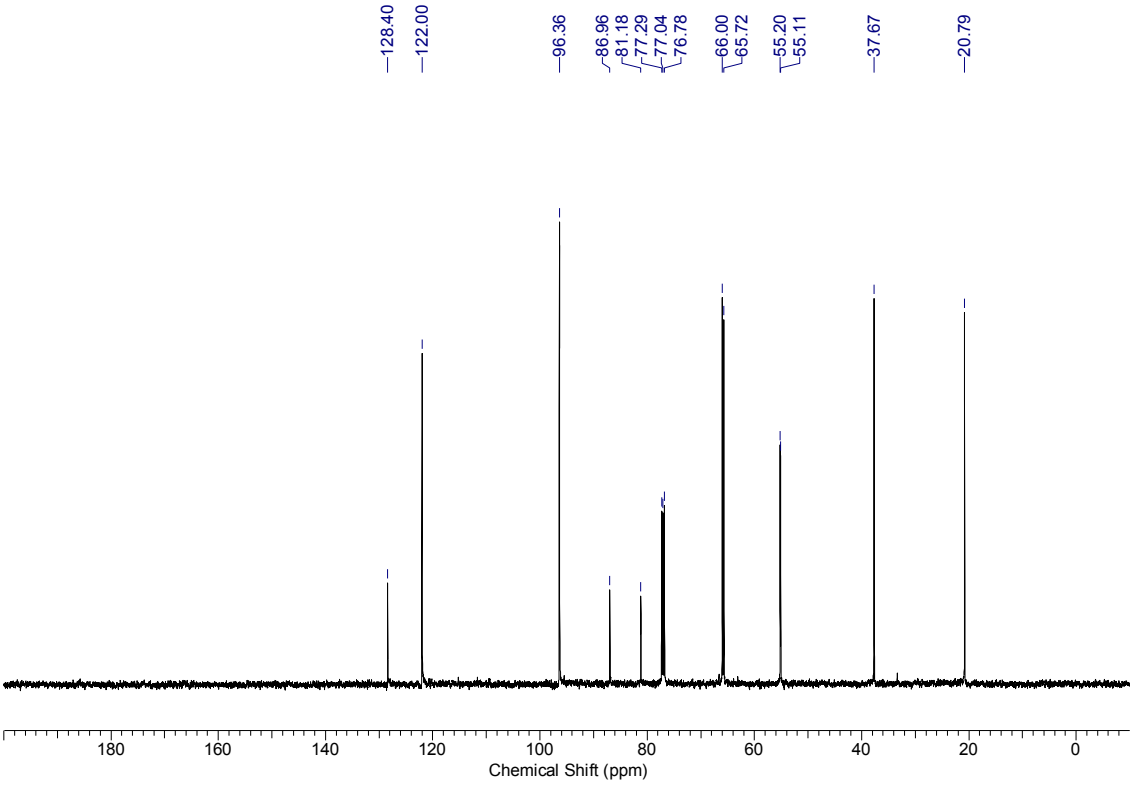
^{13}C NMR spectrum of **2-03l**:



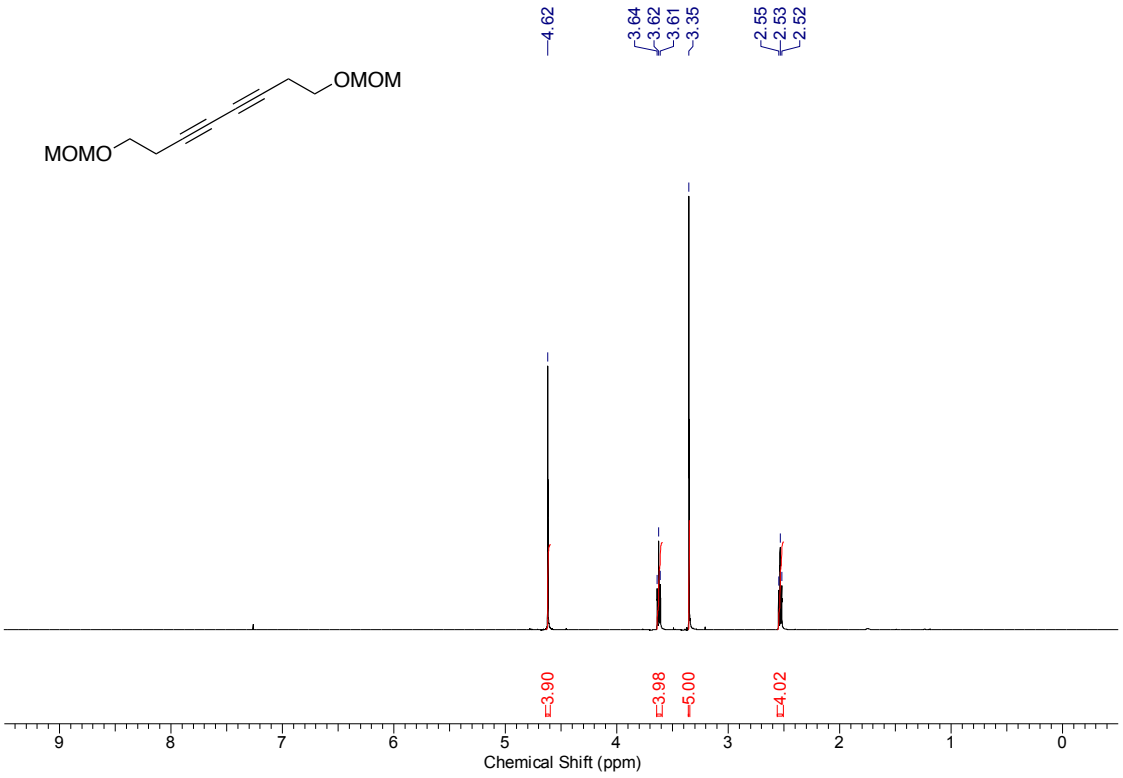
^{1}H NMR spectrum of **2-03k**:



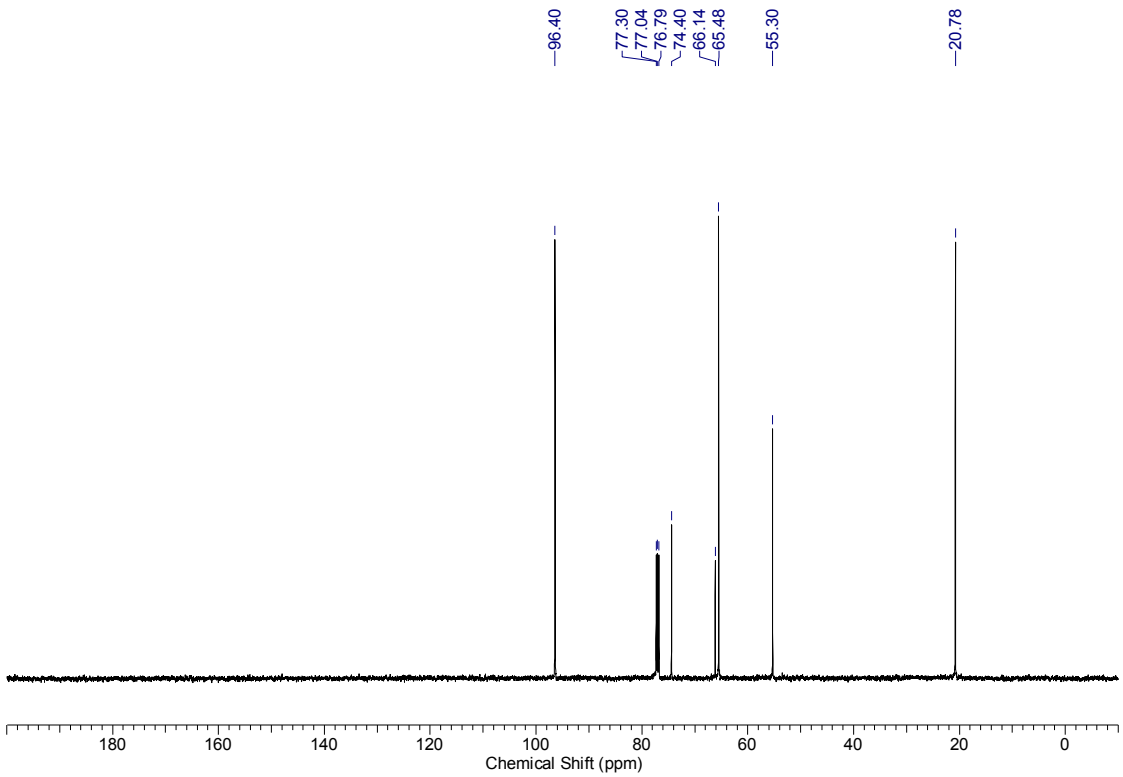
^{13}C NMR spectrum of **2-03k**:



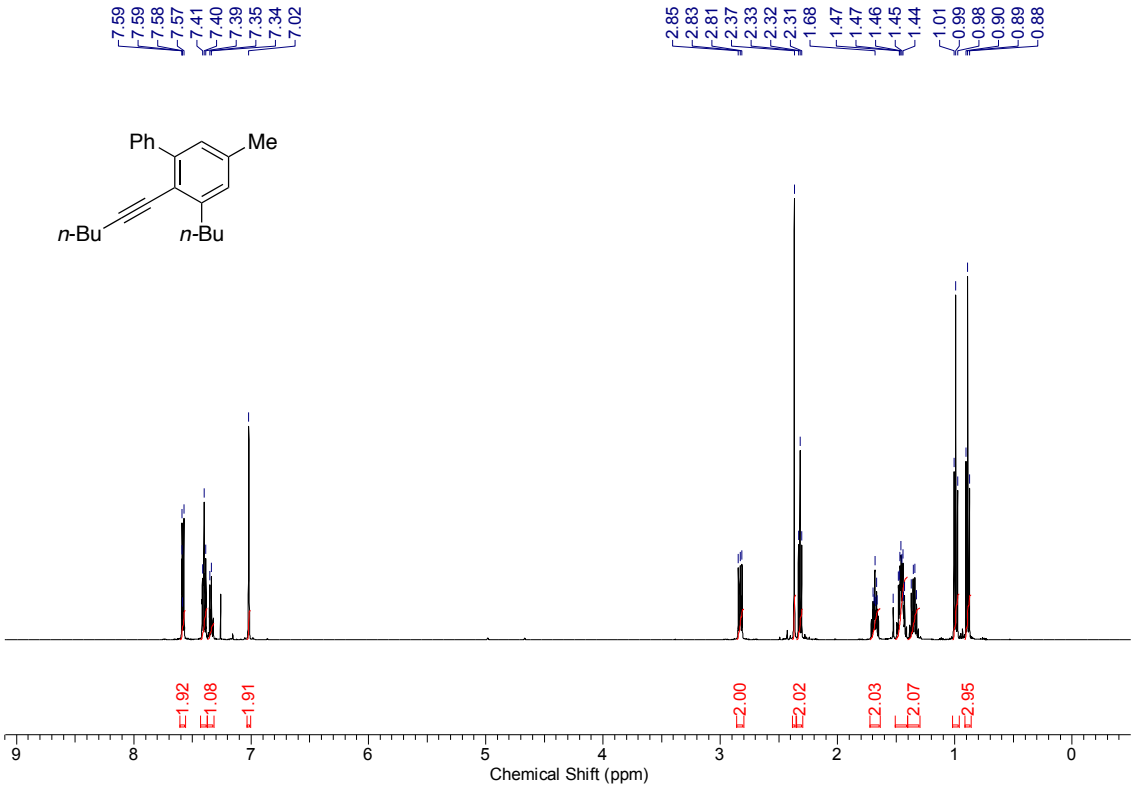
^{1}H NMR spectrum of **2-07e**:



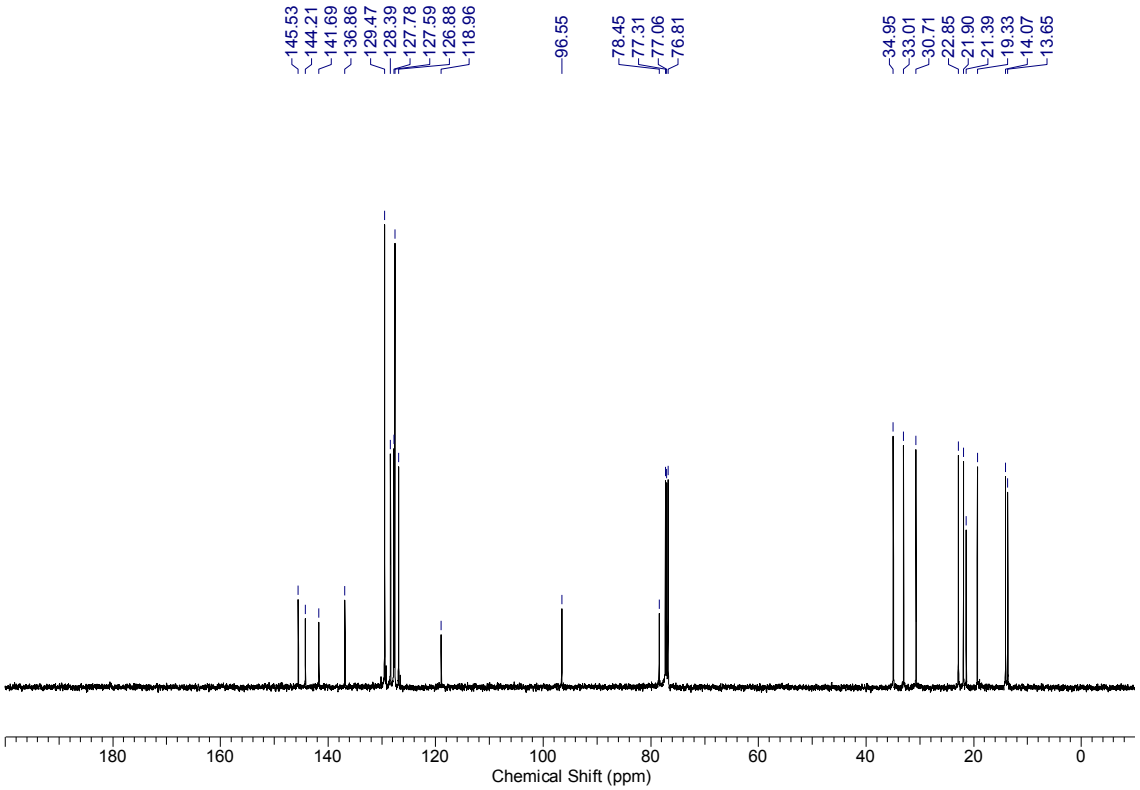
^{13}C NMR spectrum of **2-07e**:



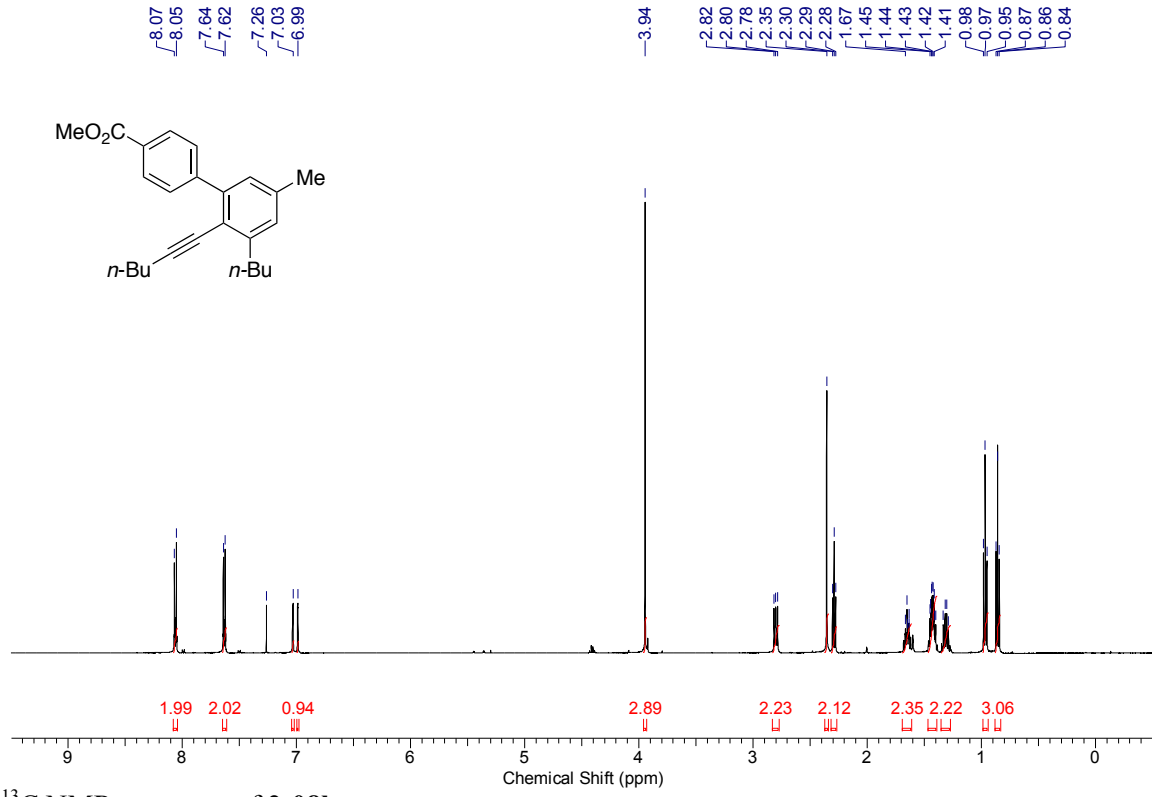
^{1}H NMR spectrum of **2-08aa**:



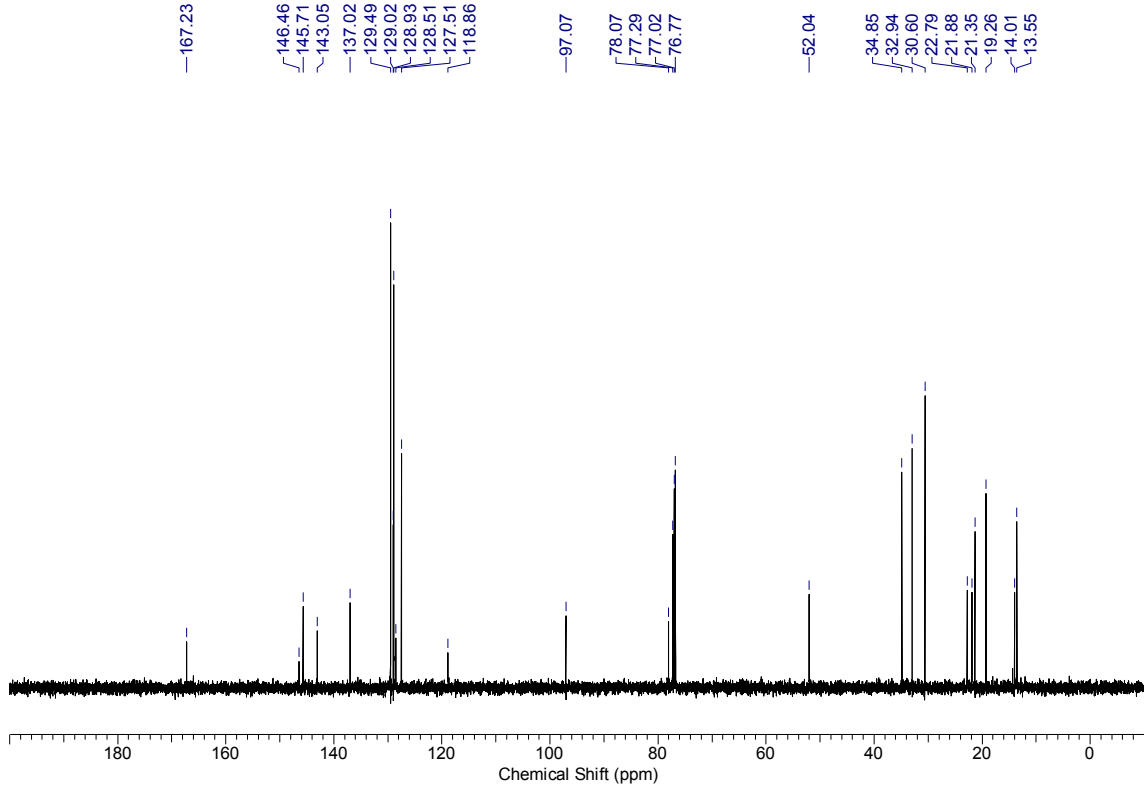
^{13}C NMR spectrum of **2-08aa**:



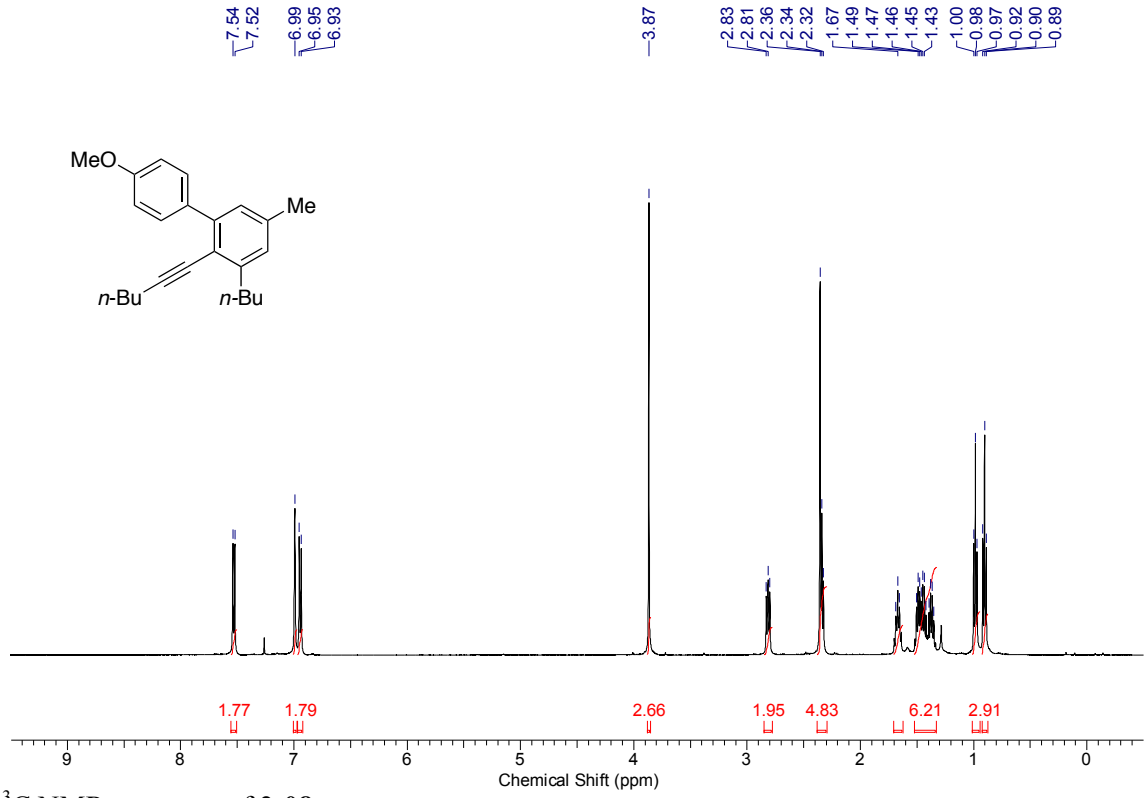
^{1}H NMR spectrum of **2-08ba**:



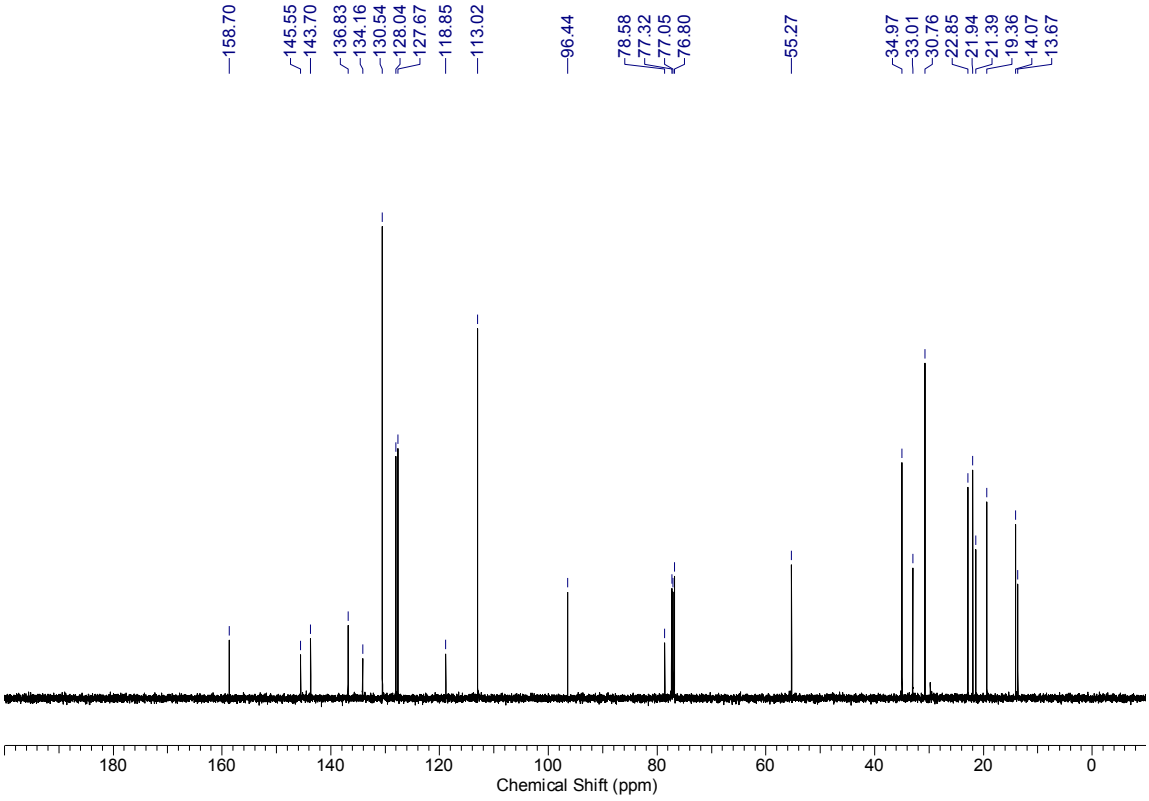
^{13}C NMR spectrum of **2-08ba**:



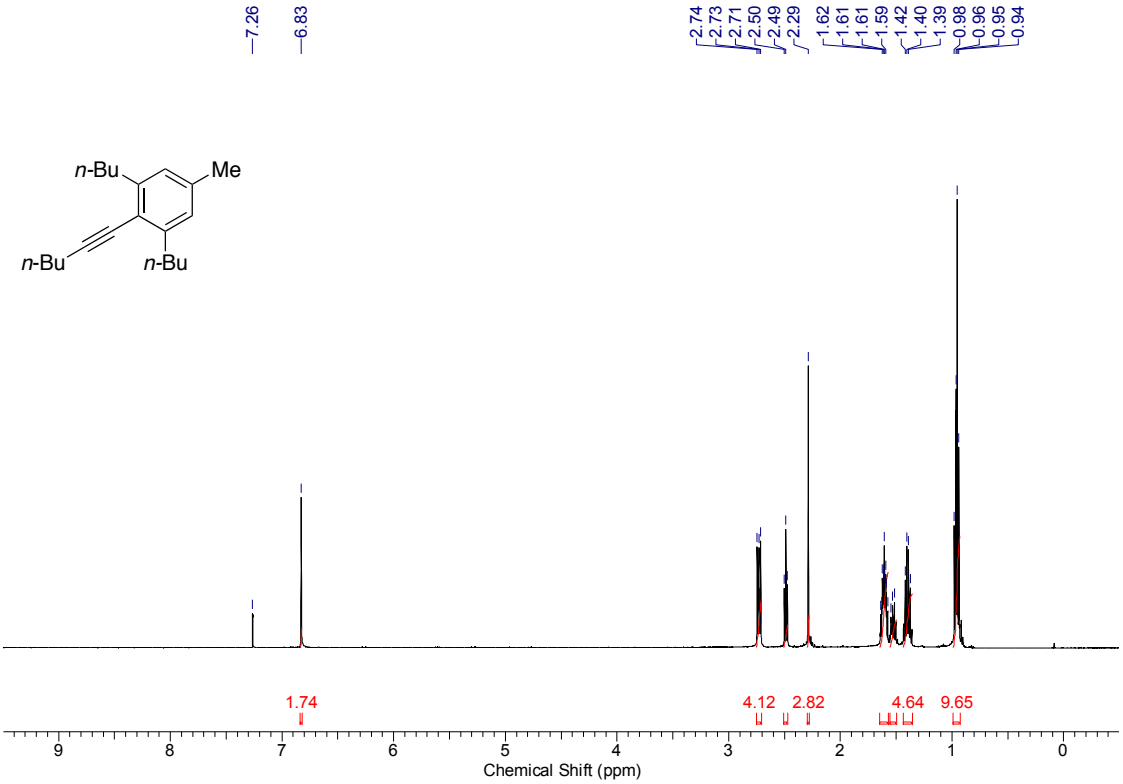
^{1}H NMR spectrum of **2-08ca**:



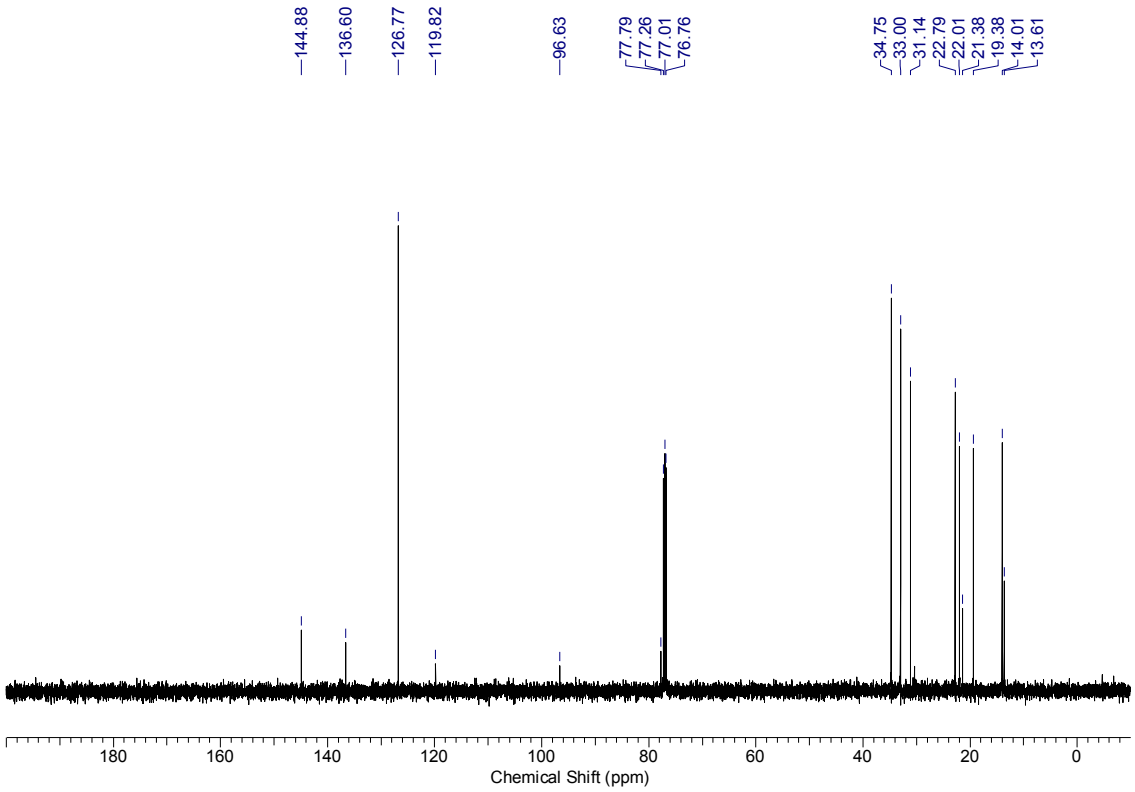
^{13}C NMR spectrum of **2-08ca**:



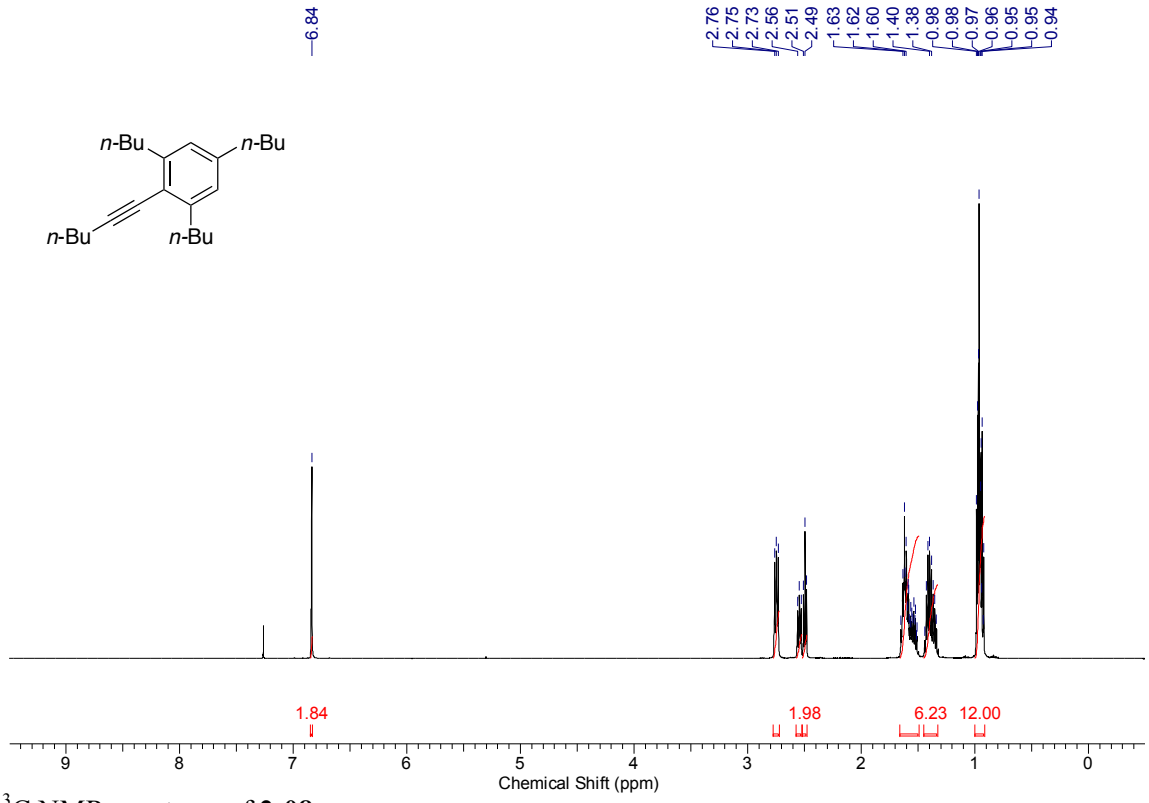
^{1}H NMR spectrum of **2-08da**:



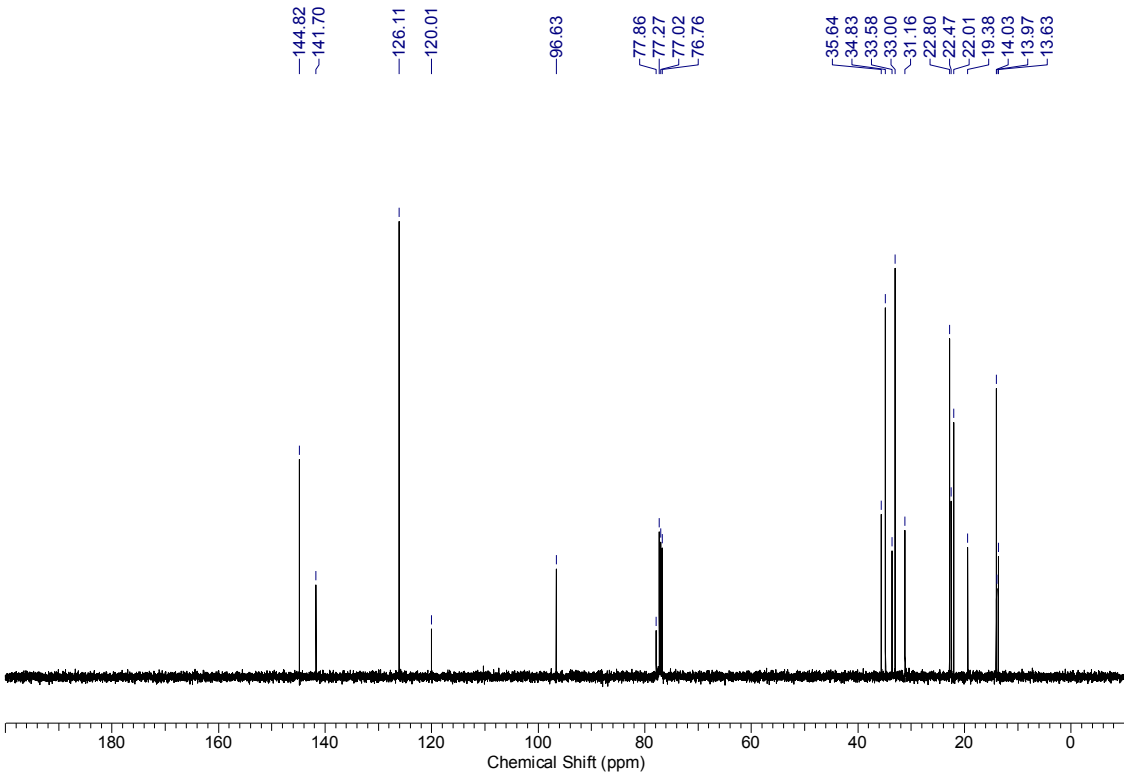
^{13}C NMR spectrum of **2-08da**:



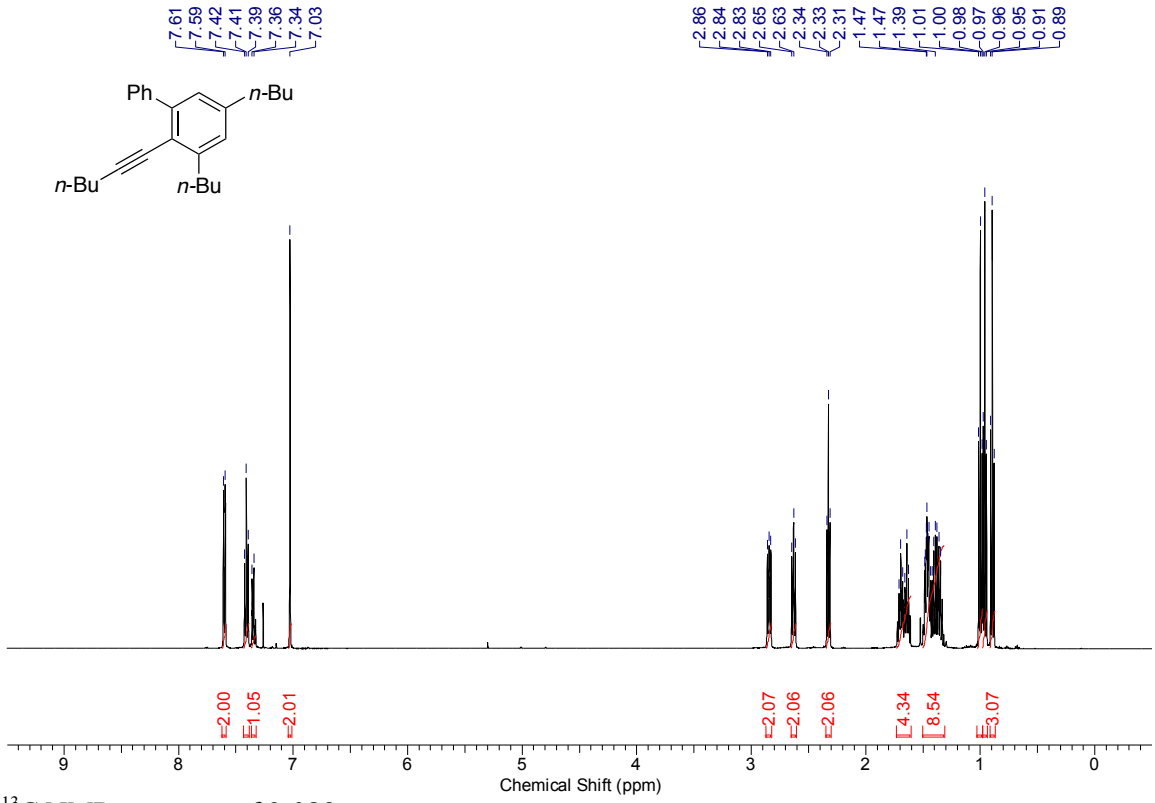
^{1}H NMR spectrum of **2-08ea**:



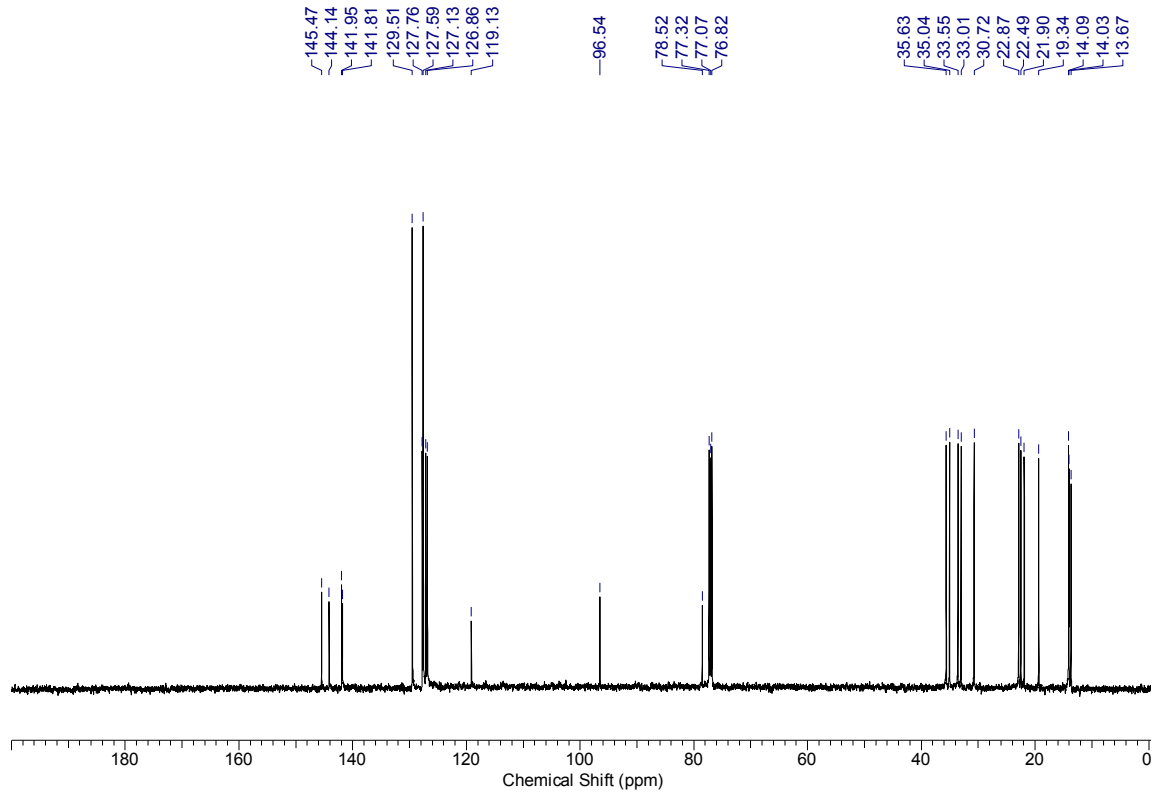
^{13}C NMR spectrum of **2-08ea**:



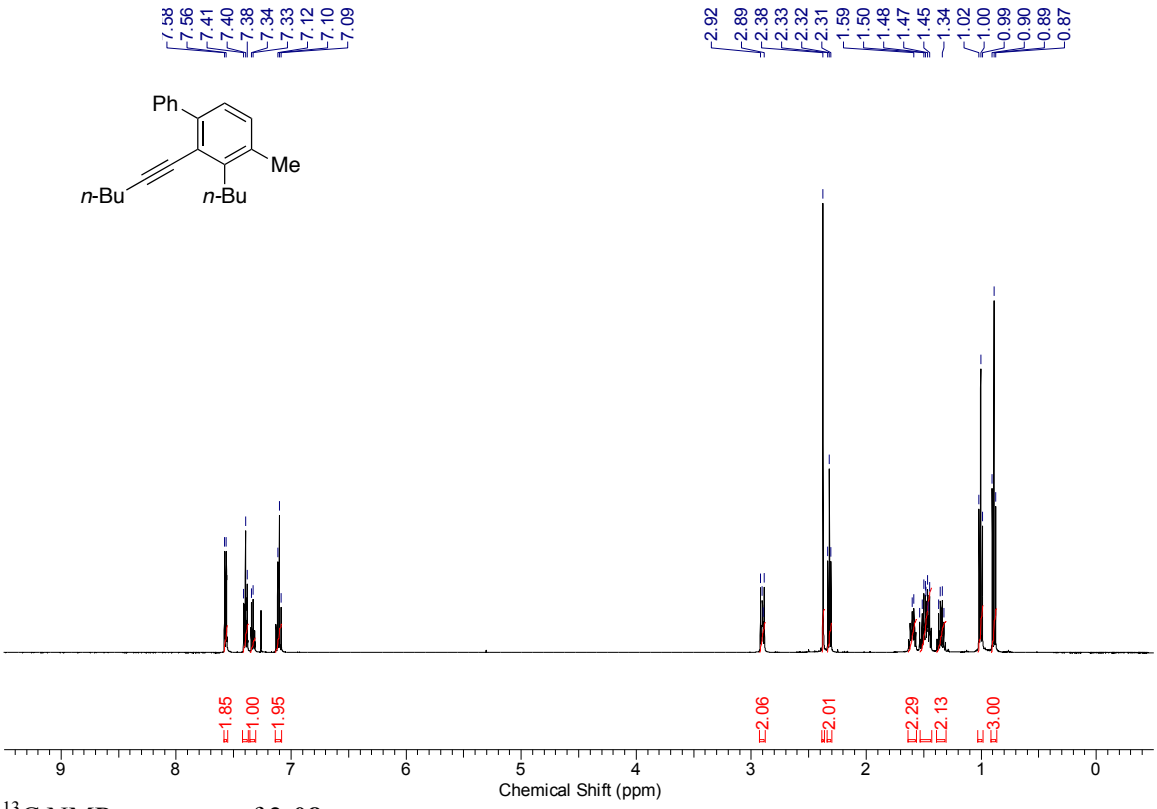
^{1}H NMR spectrum of **2-08fa**:



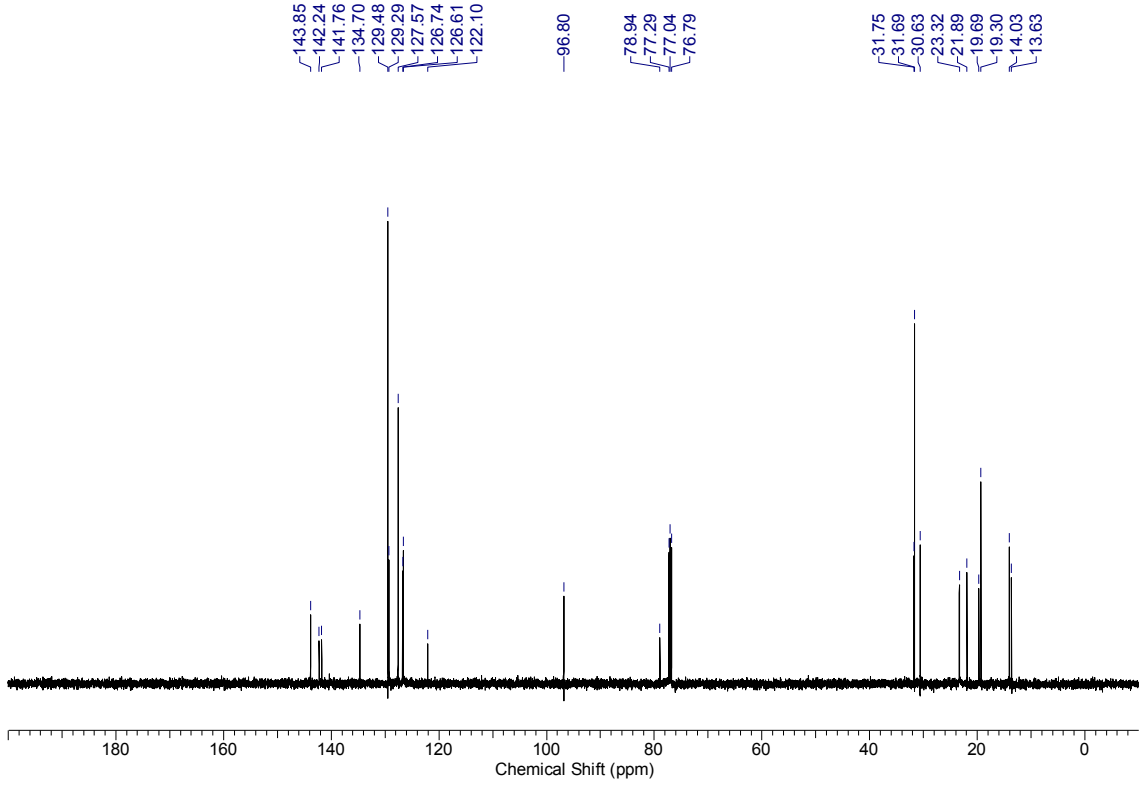
^{13}C NMR spectrum of **2-08fa**:



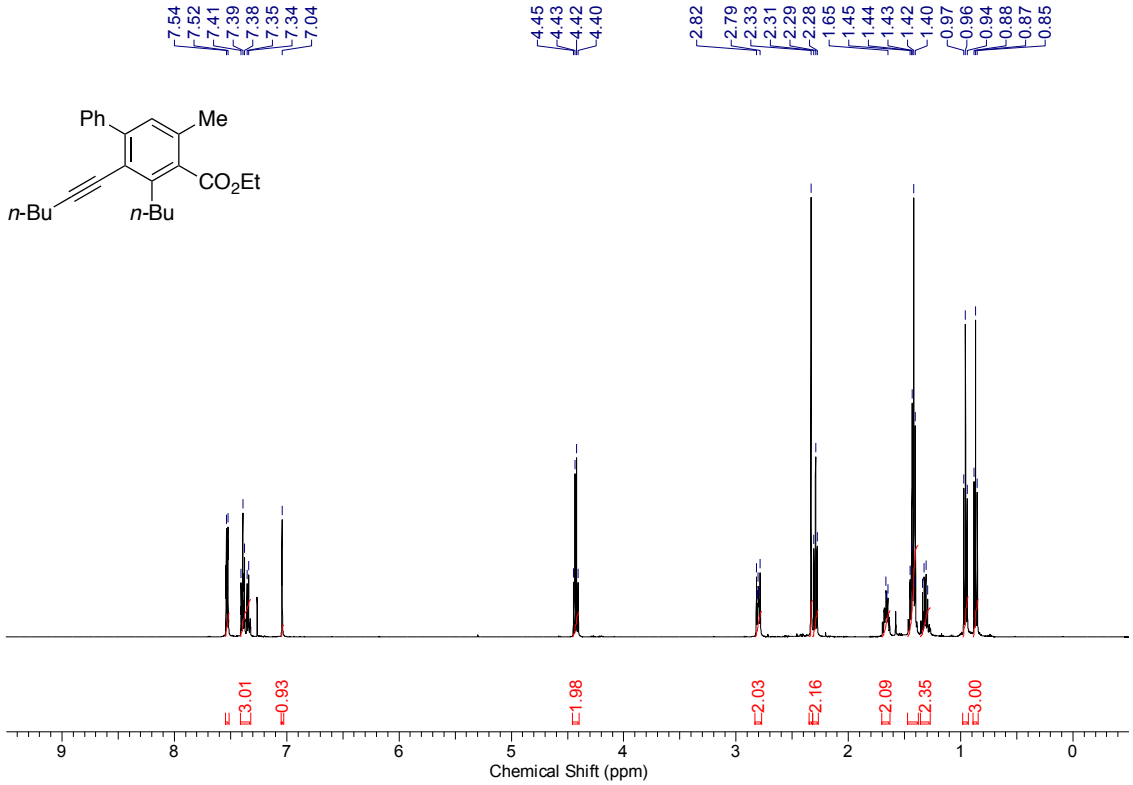
^{1}H NMR spectrum of **2-08ga**:



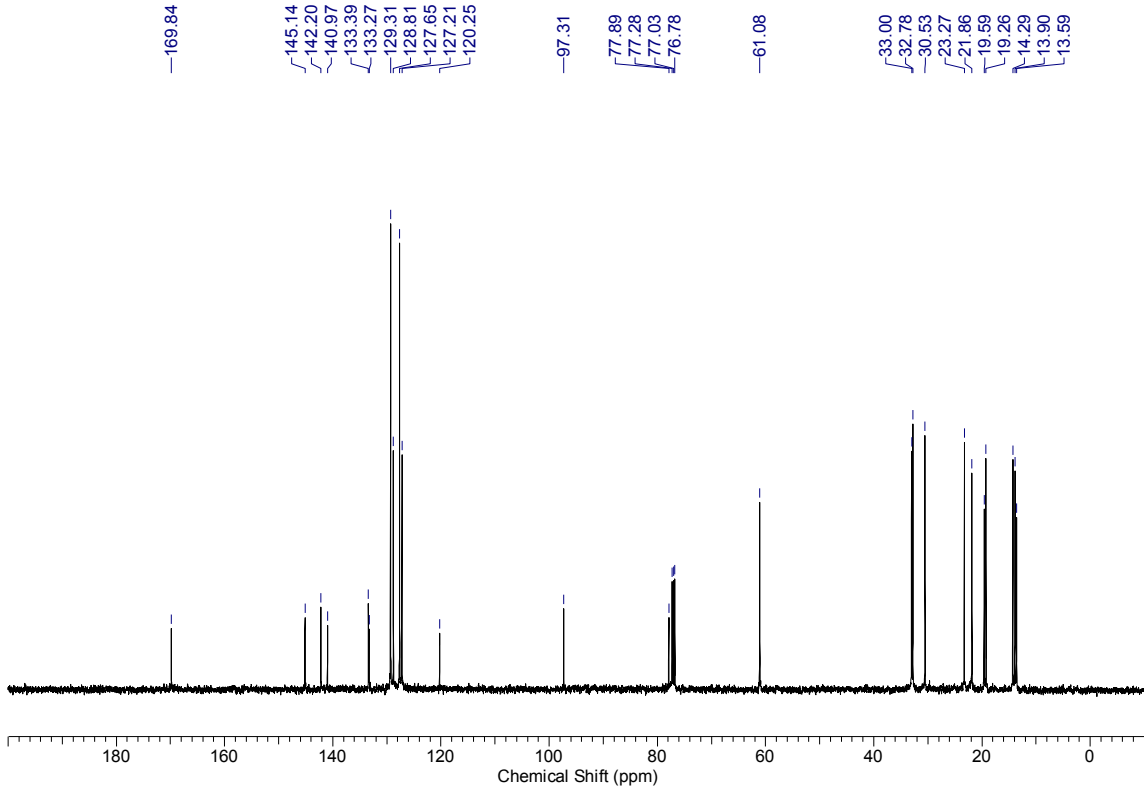
^{13}C NMR spectrum of **2-08ga**:



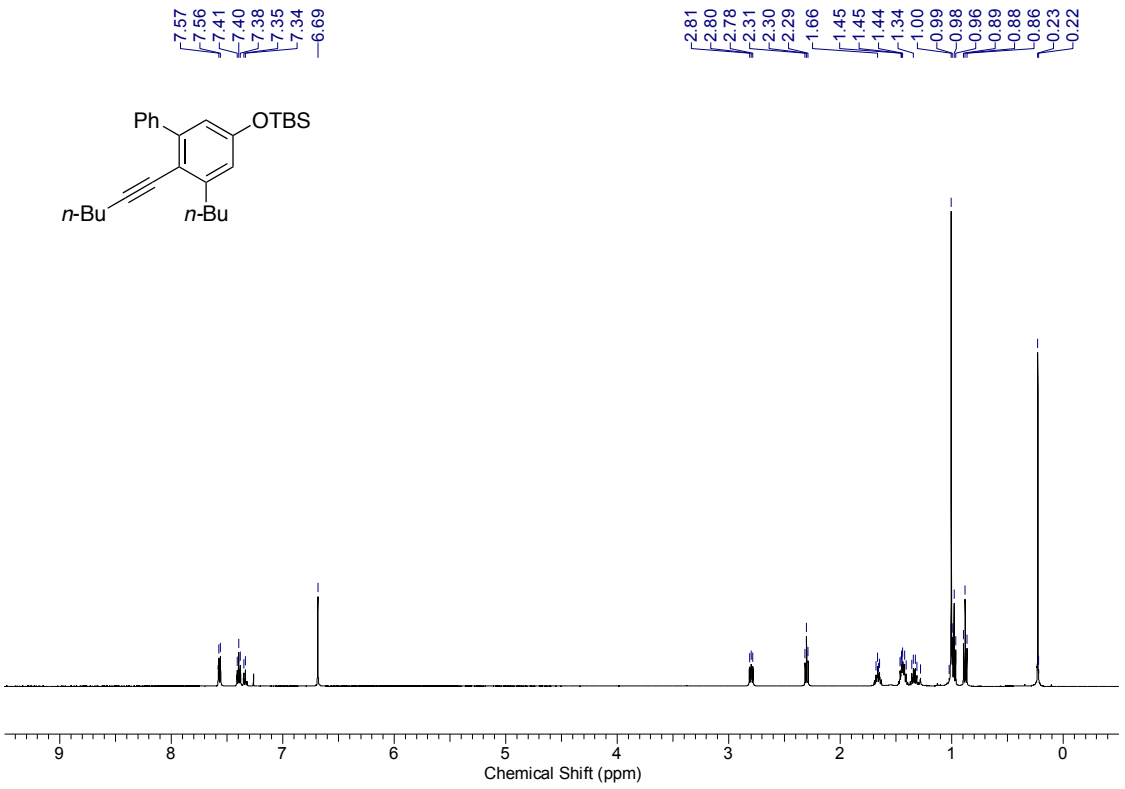
^{1}H NMR spectrum of **2-08ha**:



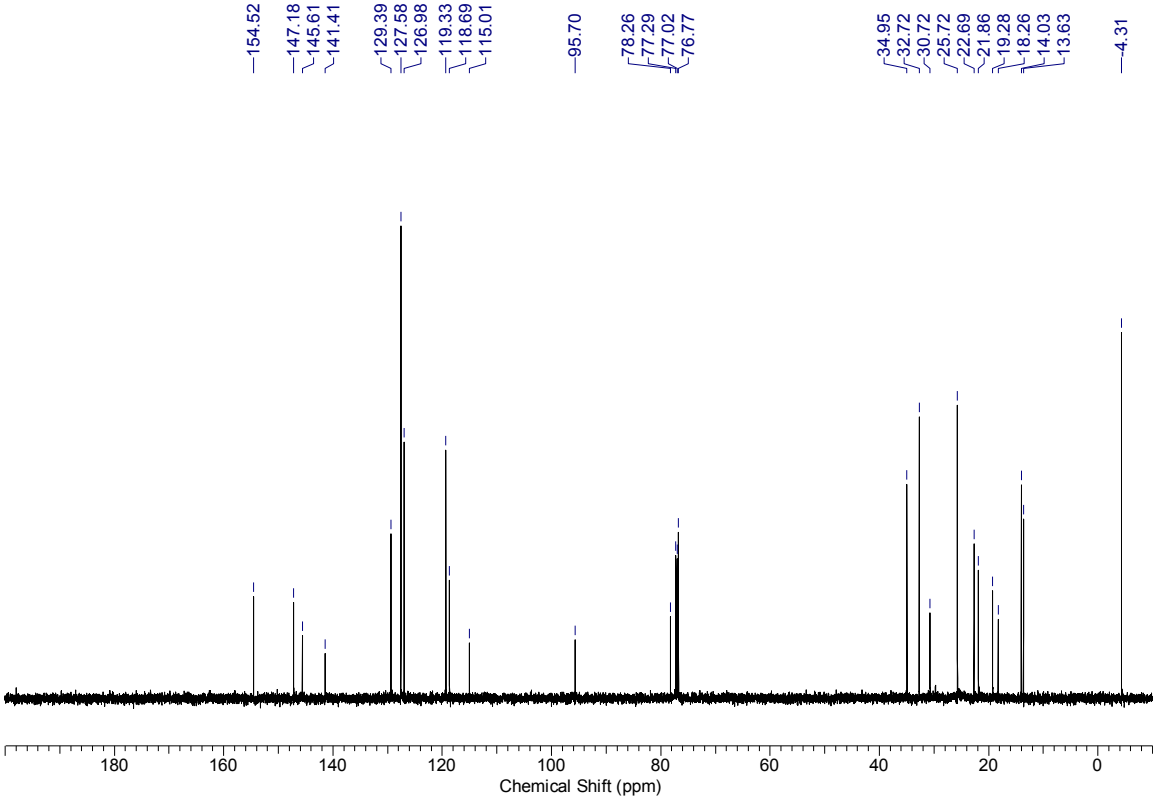
^{13}C NMR spectrum of **2-08ha**:



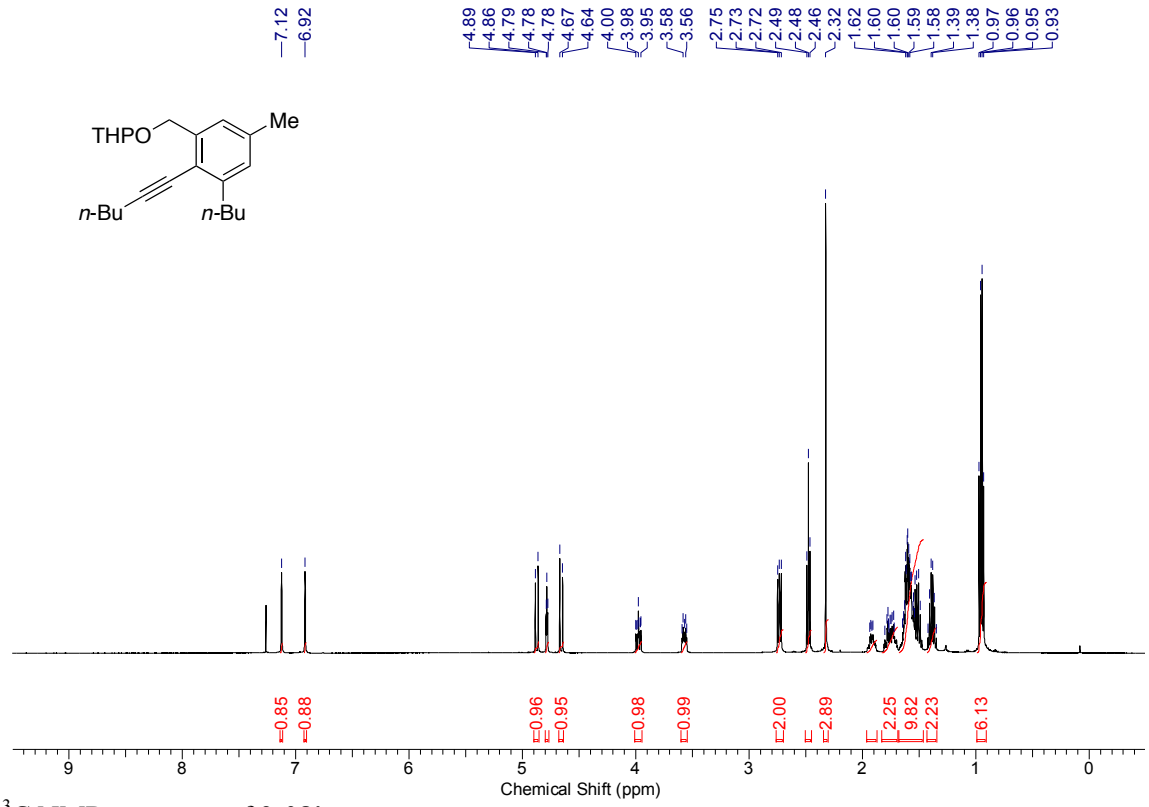
^{1}H NMR spectrum of **2-08ia**:



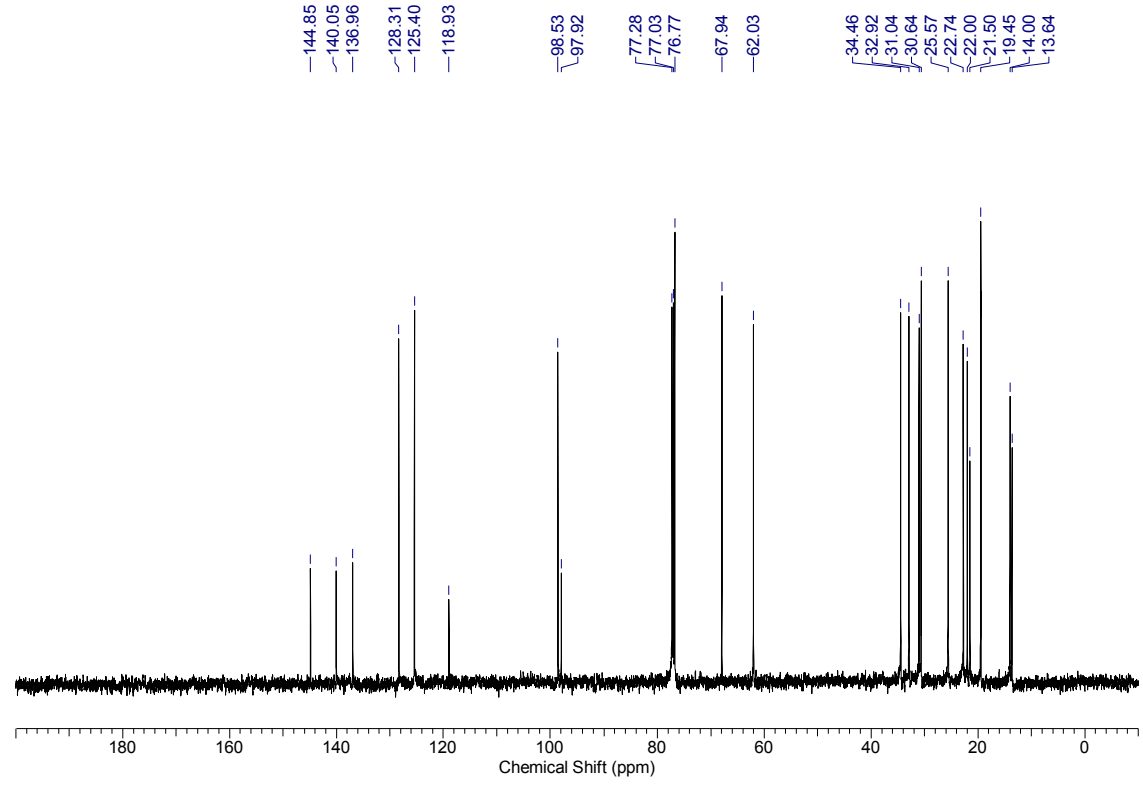
^{13}C NMR spectrum of **2-08ia**:



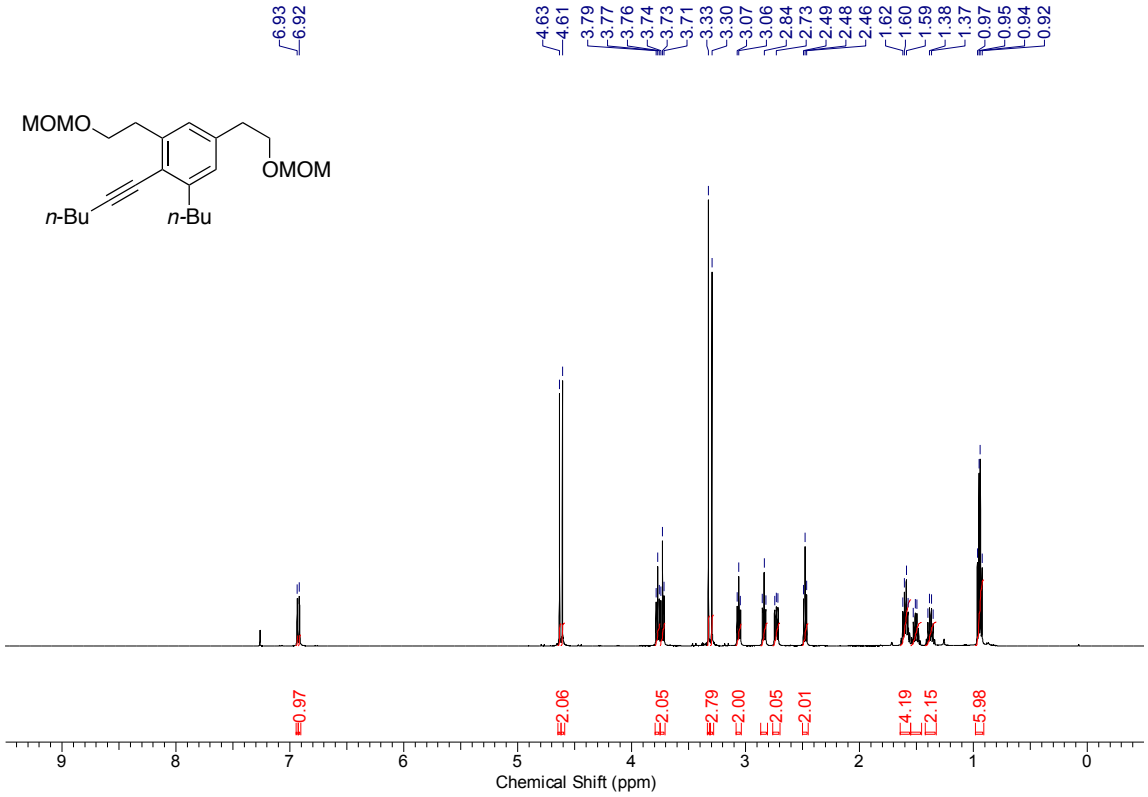
^{1}H NMR spectrum of **2-08ja**:



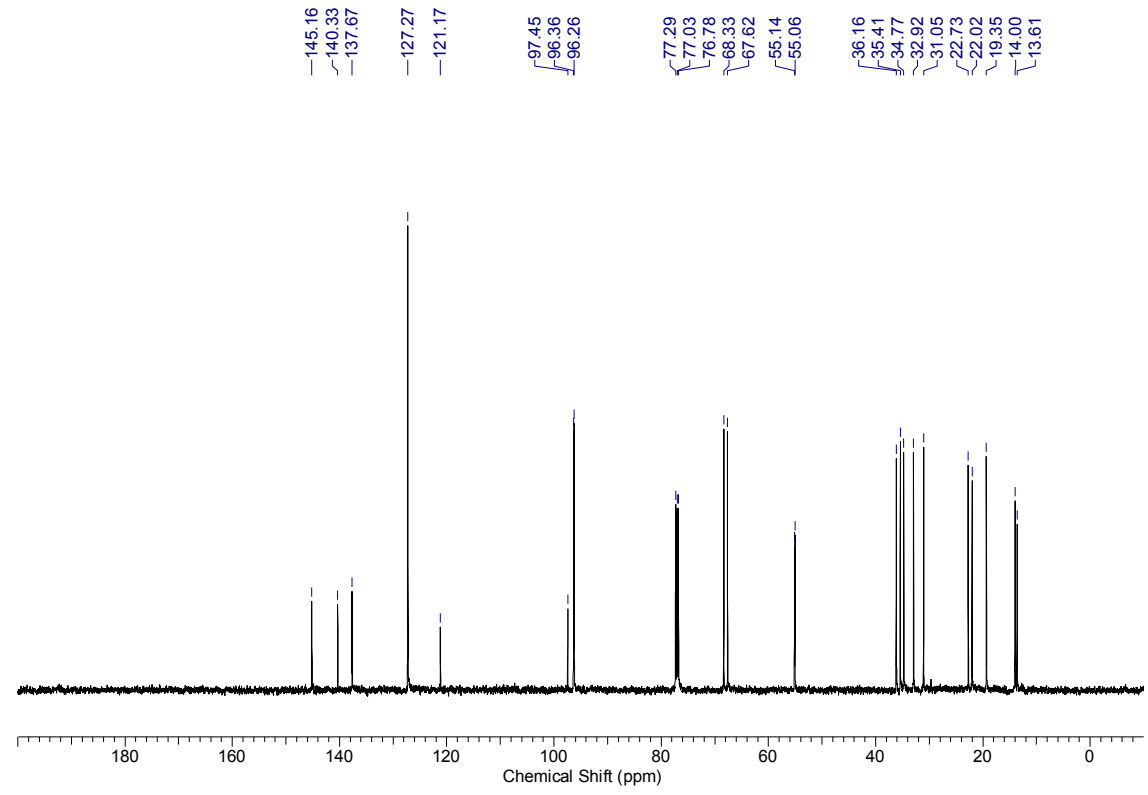
^{13}C NMR spectrum of **2-08ja**:



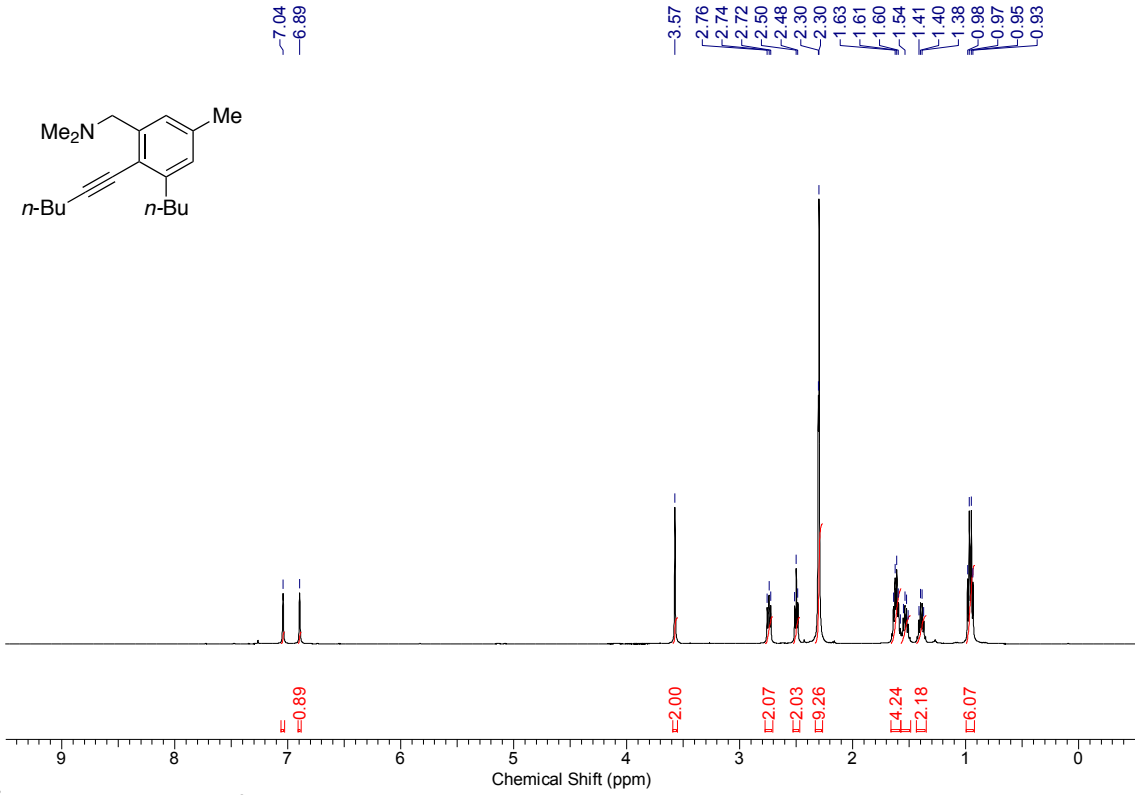
^{1}H NMR spectrum of **2-08ka**:



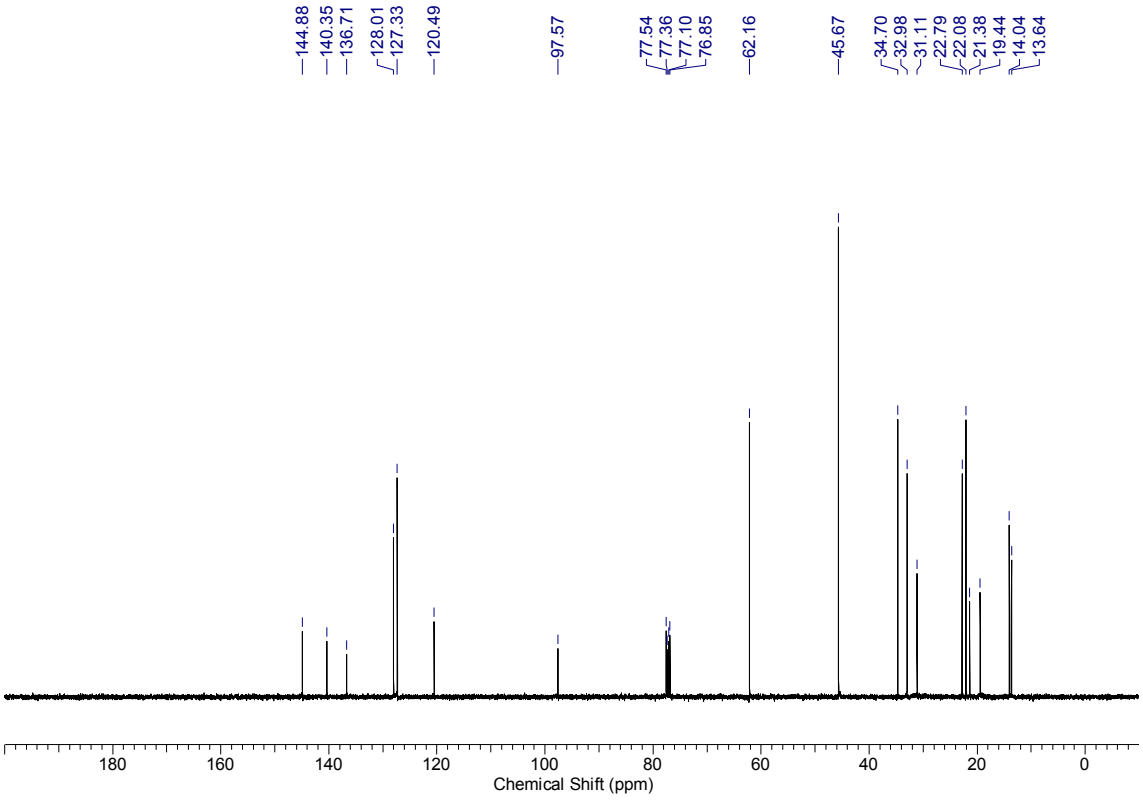
^{13}C NMR spectrum of **2-08ka**:



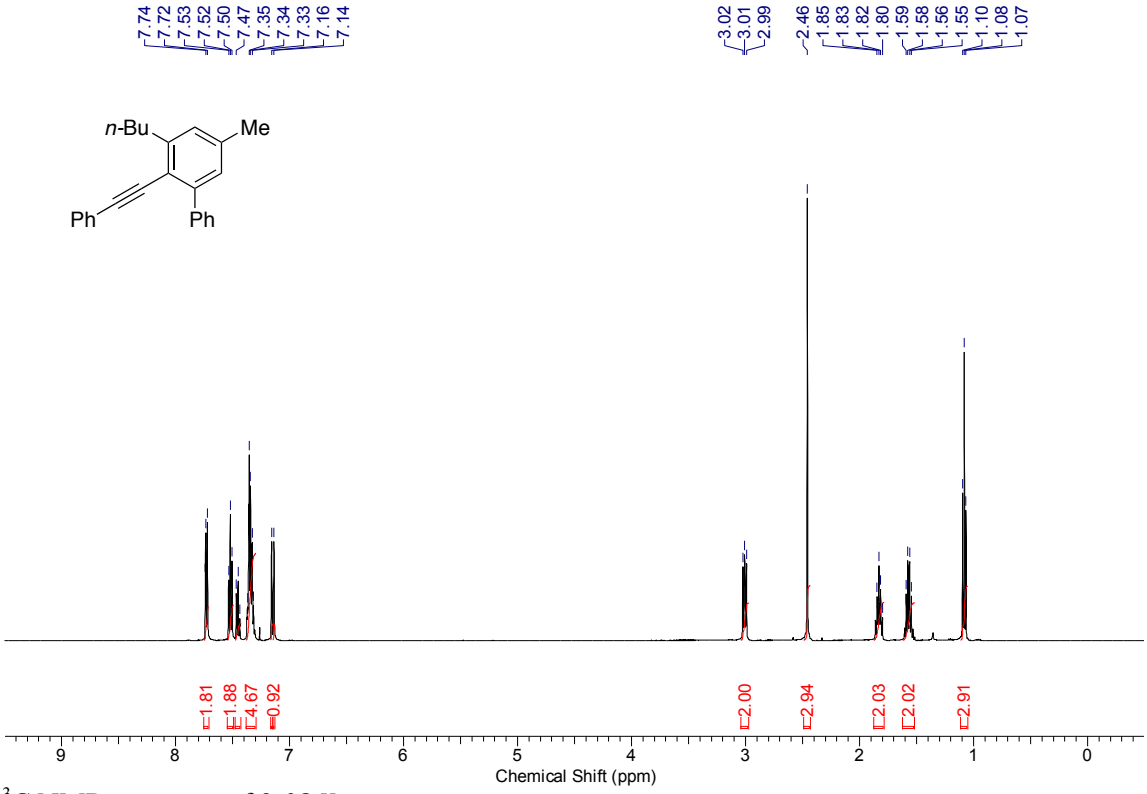
^{1}H NMR spectrum of **2-08la**:



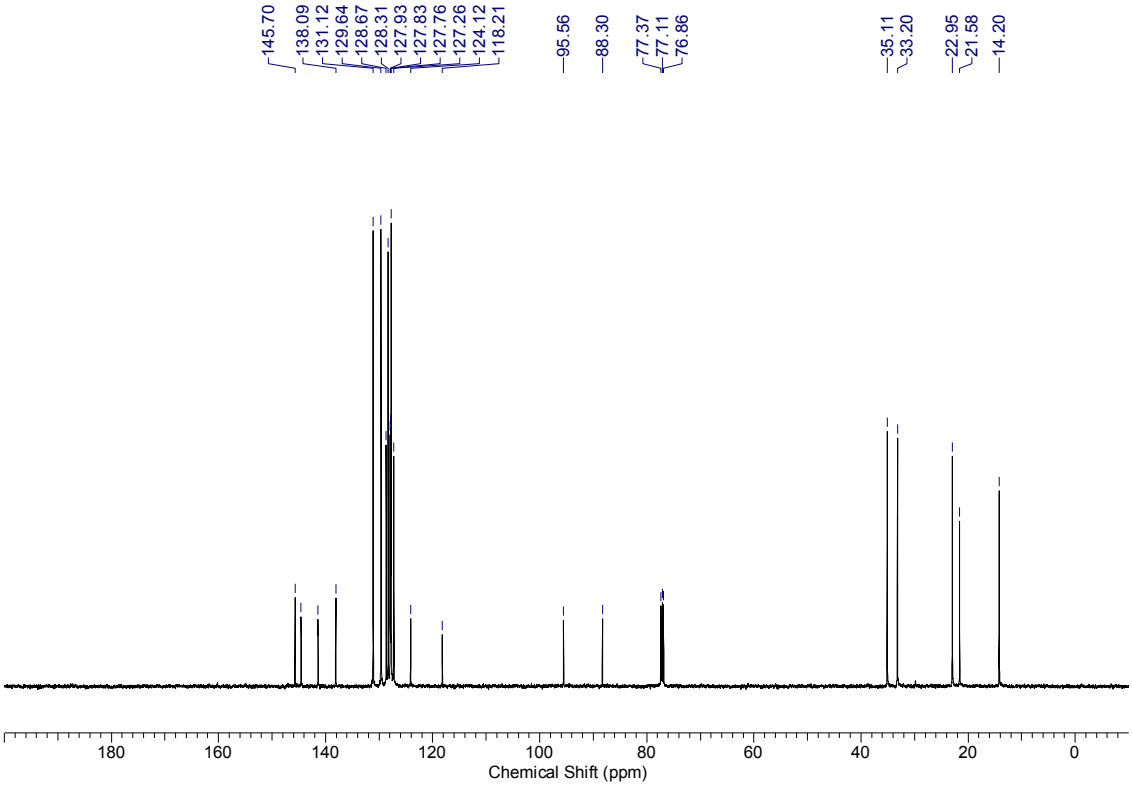
^{13}C NMR spectrum of **2-08la**:



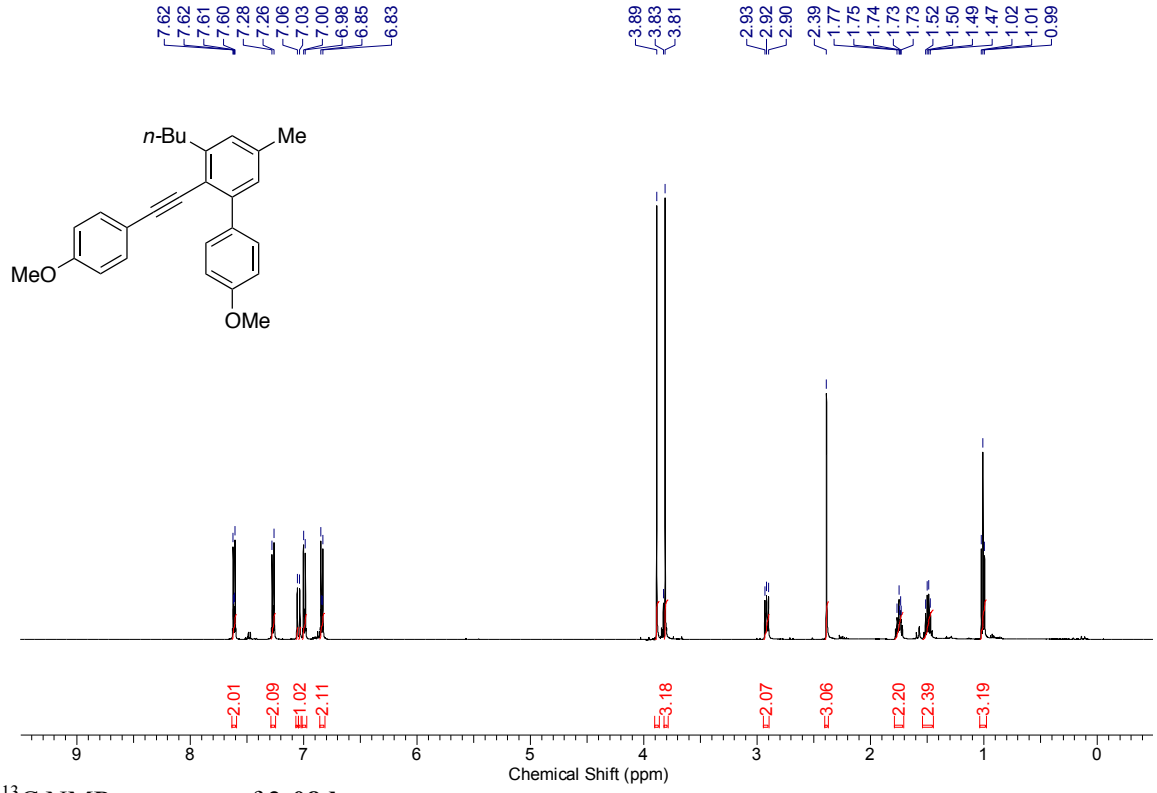
^{1}H NMR spectrum of **2-08db**:



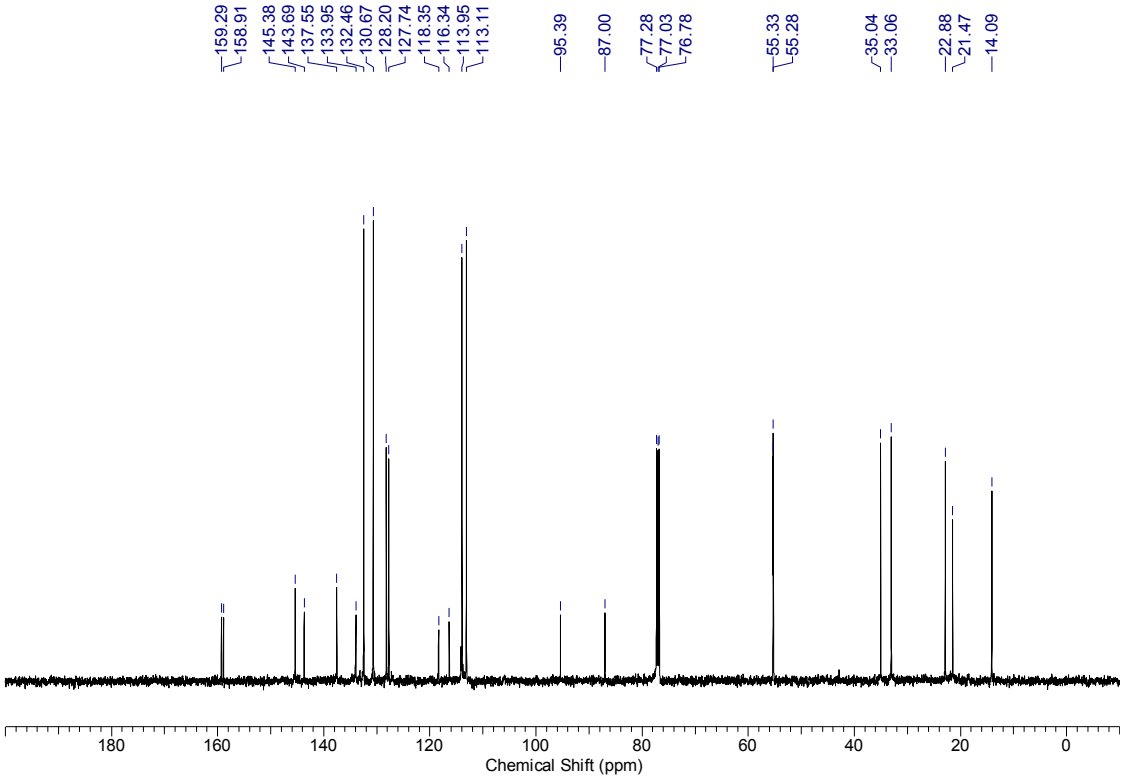
^{13}C NMR spectrum of **2-08db**:



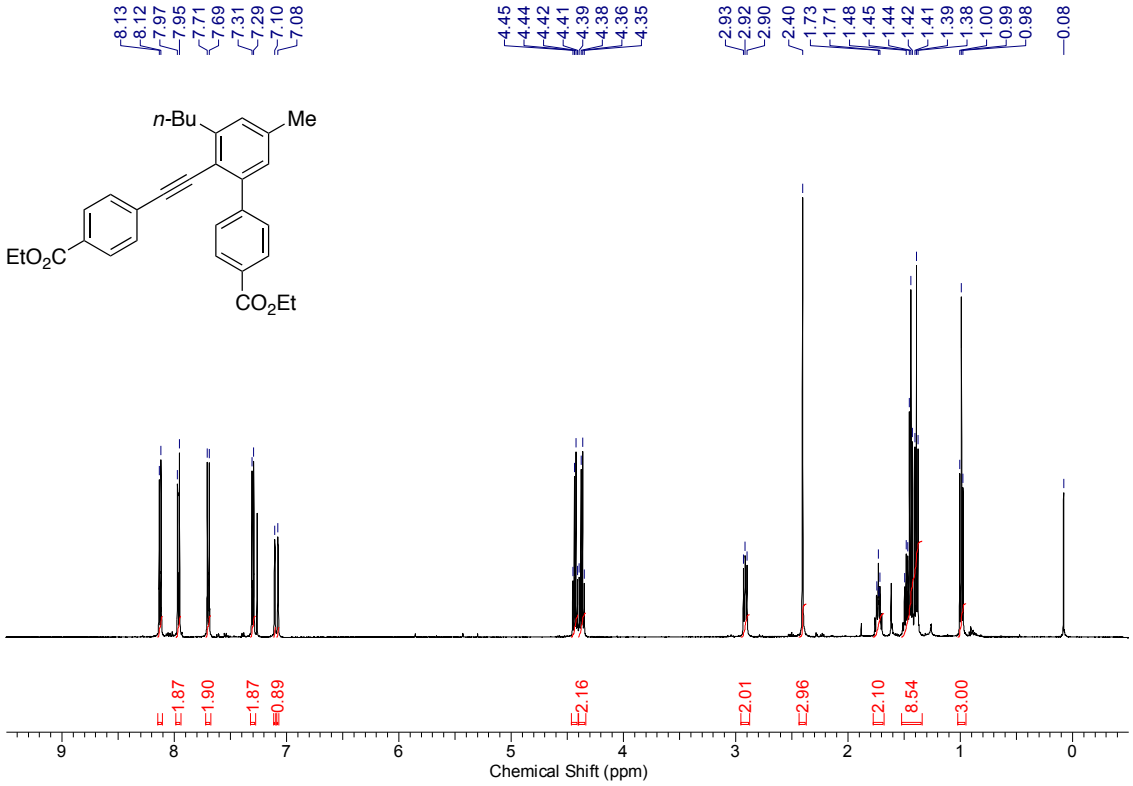
^{1}H NMR spectrum of **2-08dc**:



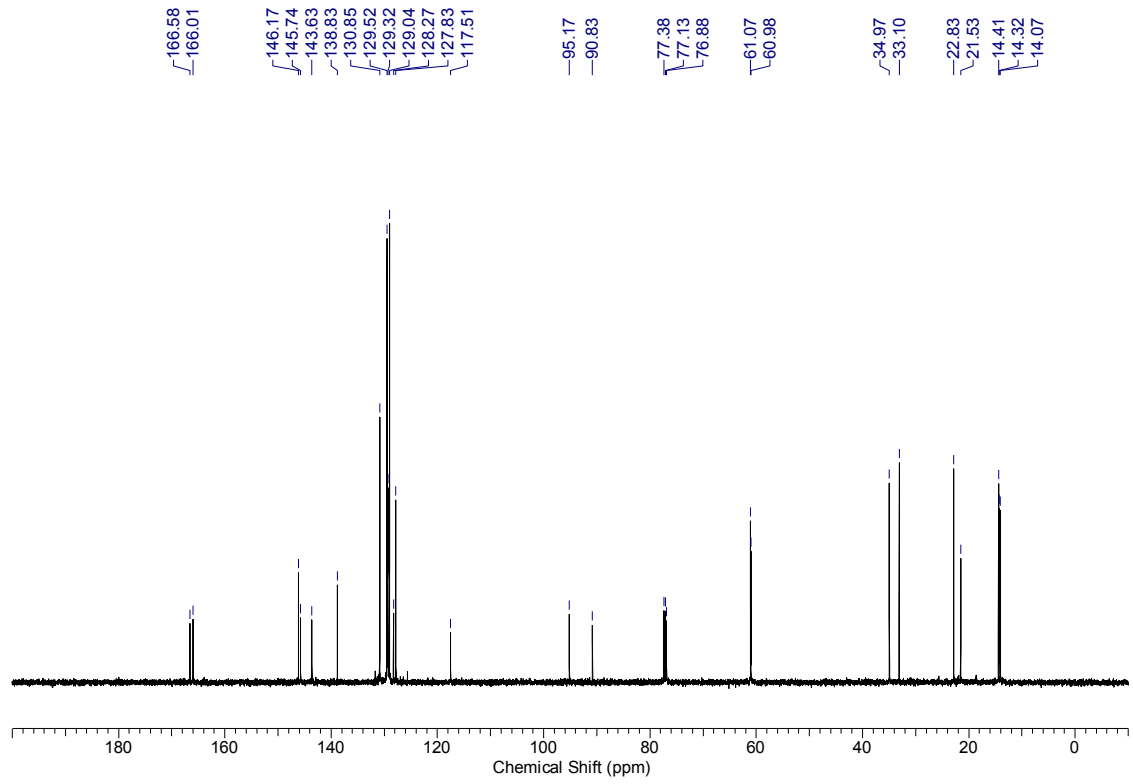
^{13}C NMR spectrum of **2-08dc**:



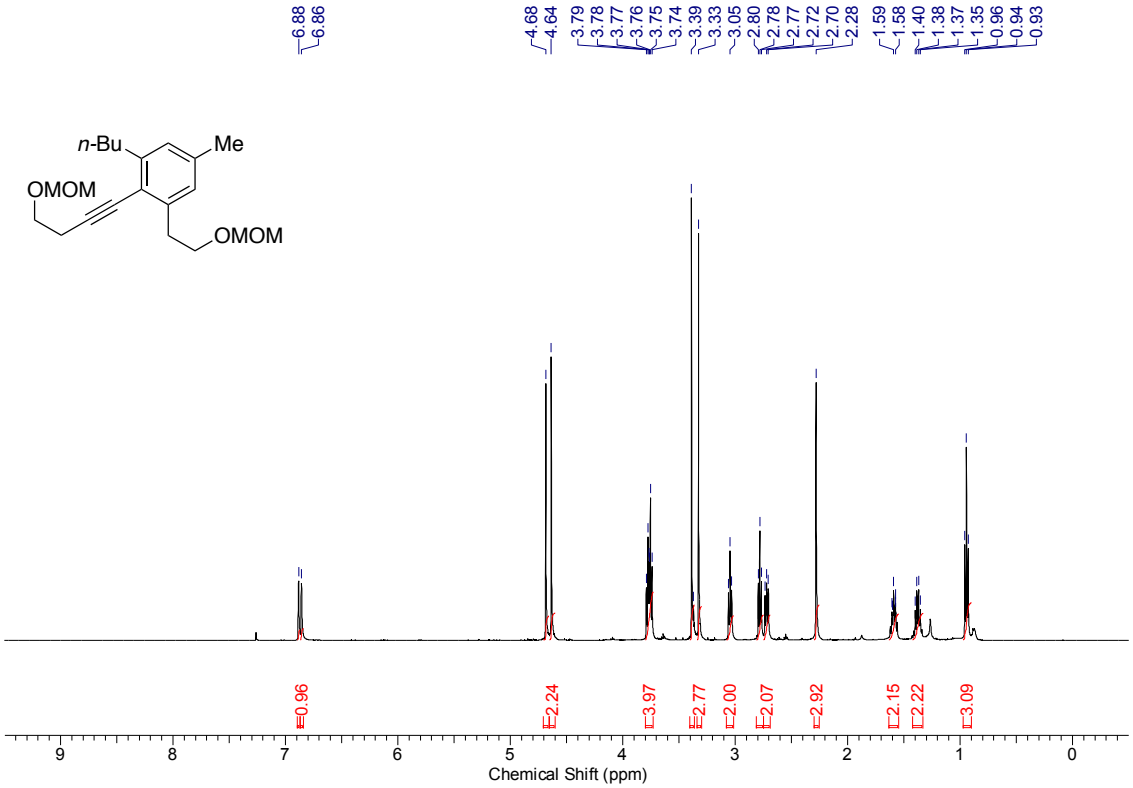
^{1}H NMR spectrum of **2-08dd**:



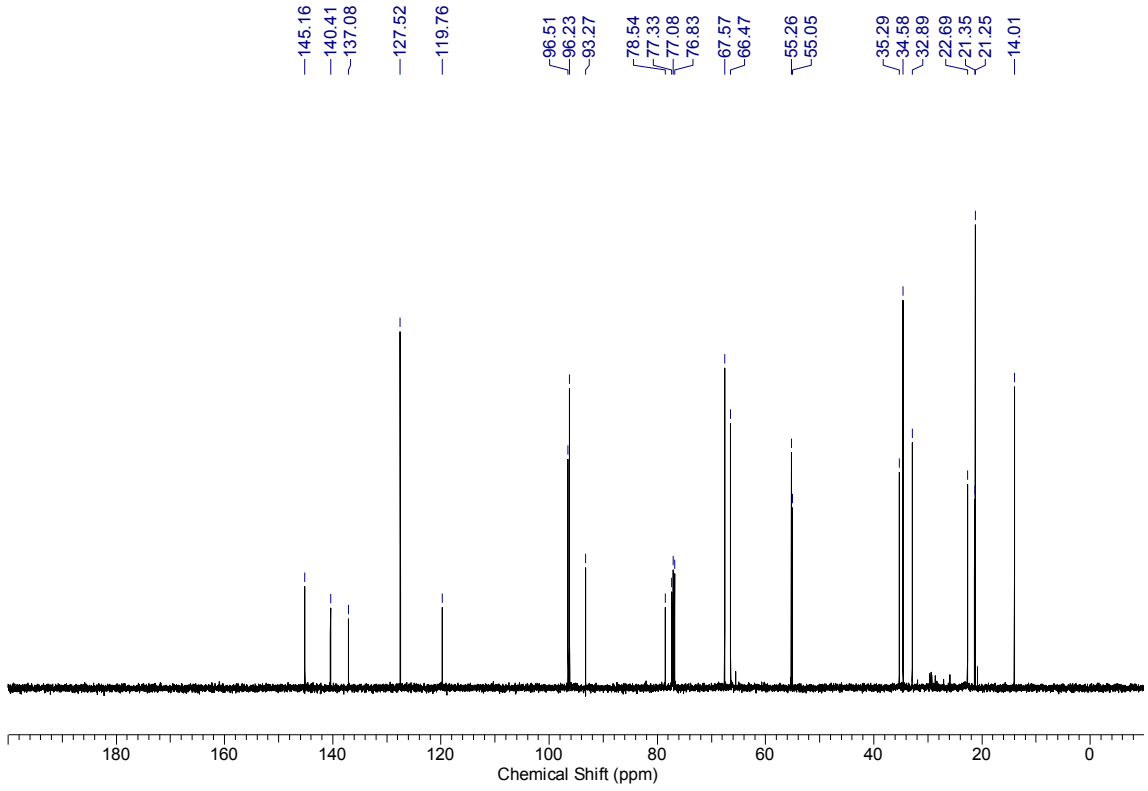
^{13}C NMR spectrum of **2-08dd**:



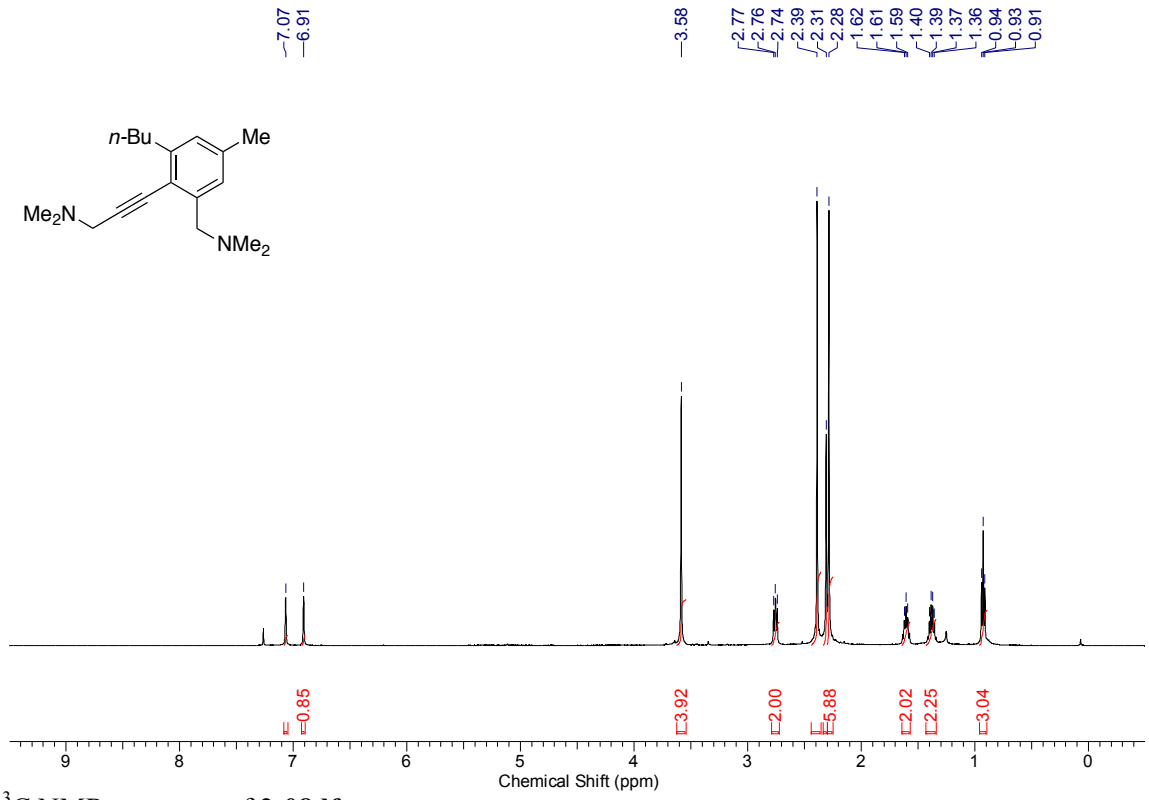
^{1}H NMR spectrum of **2-08de**:



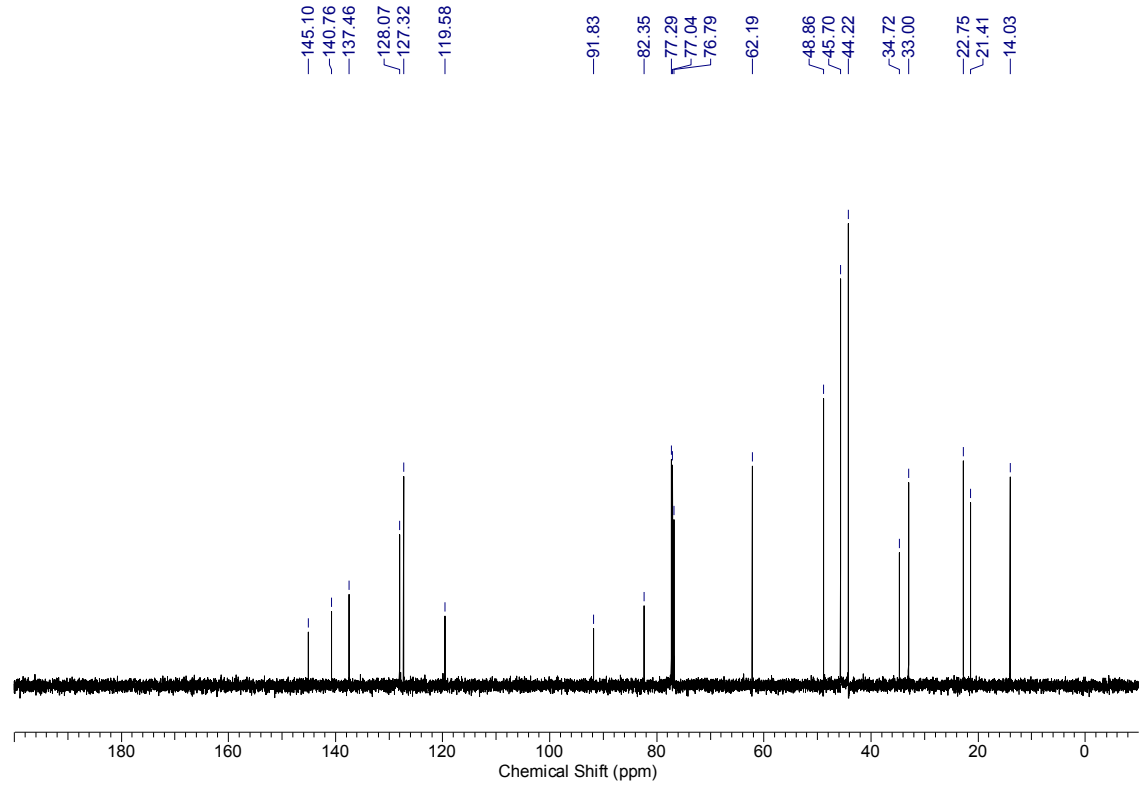
^{13}C NMR spectrum of **2-08de**:



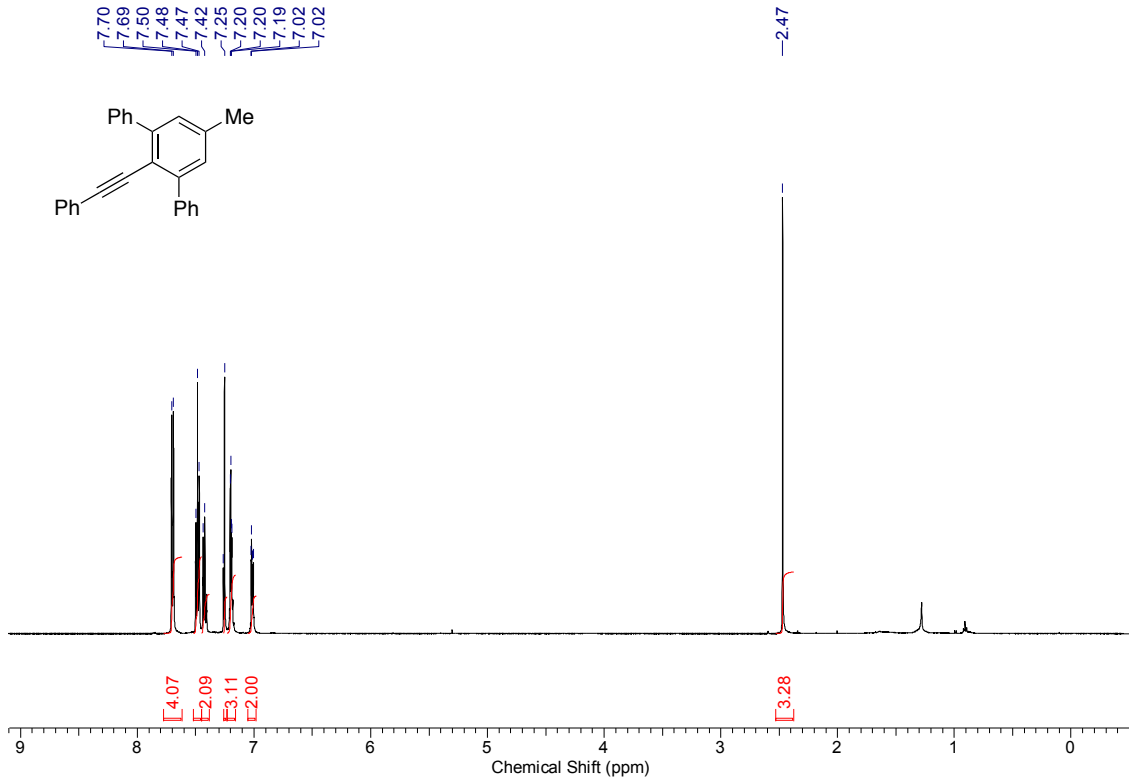
^{1}H NMR spectrum of **2-08df**:



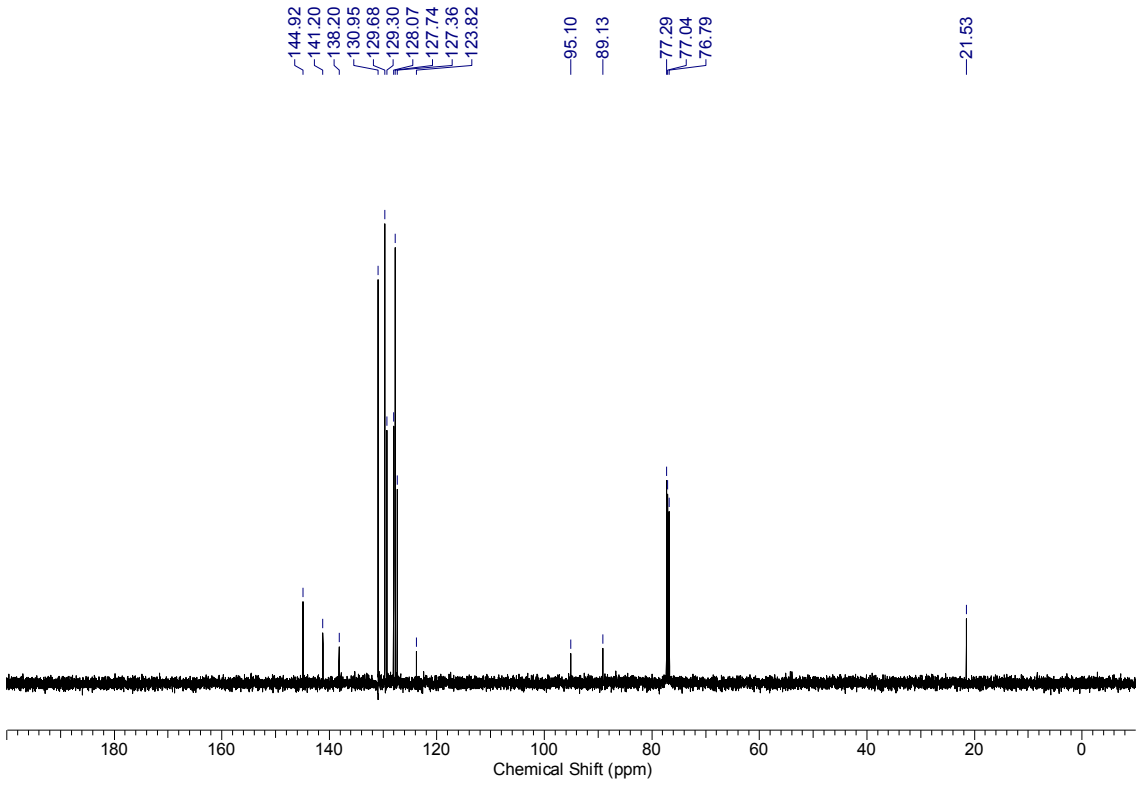
^{13}C NMR spectrum of **2-08df**:



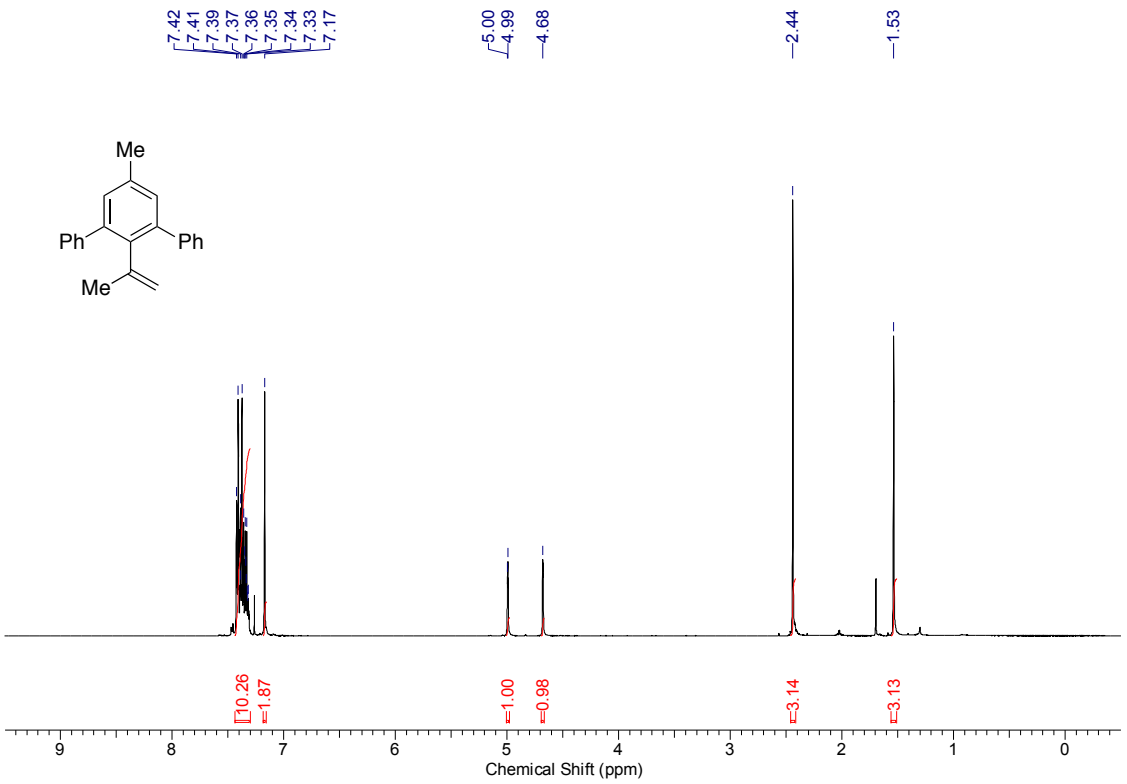
^{1}H NMR spectrum of **2-08ab**:



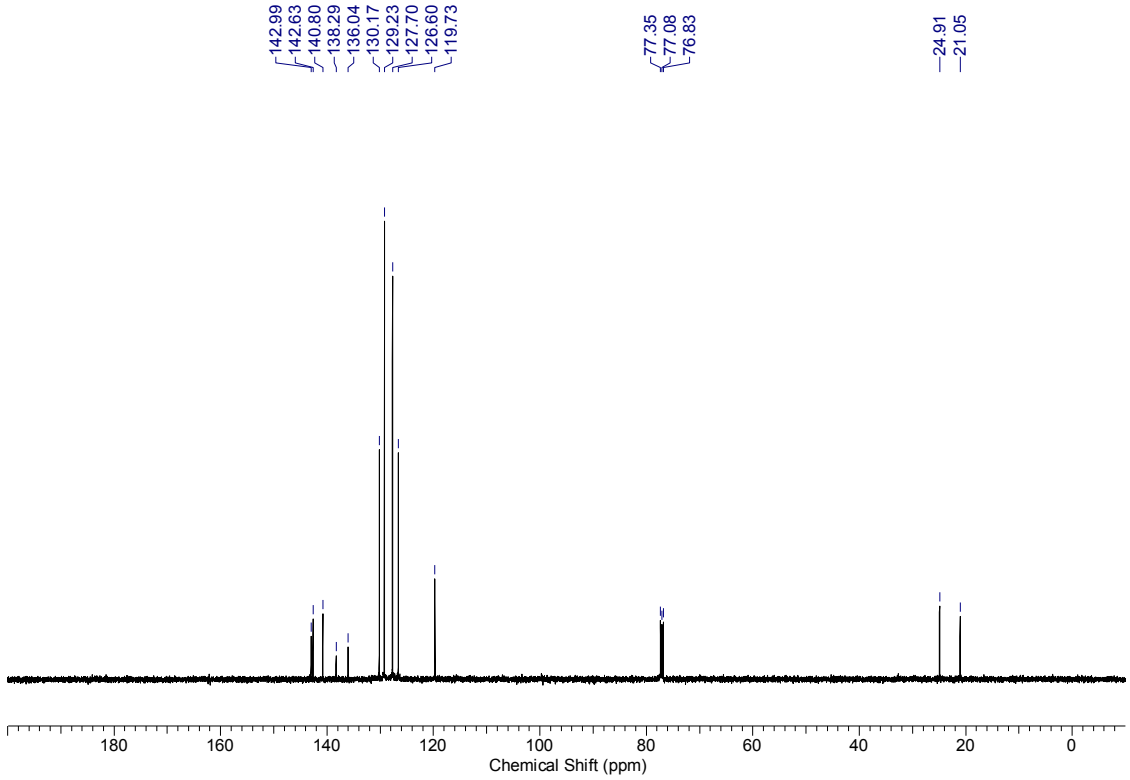
^{13}C NMR spectrum of **2-08ab**:



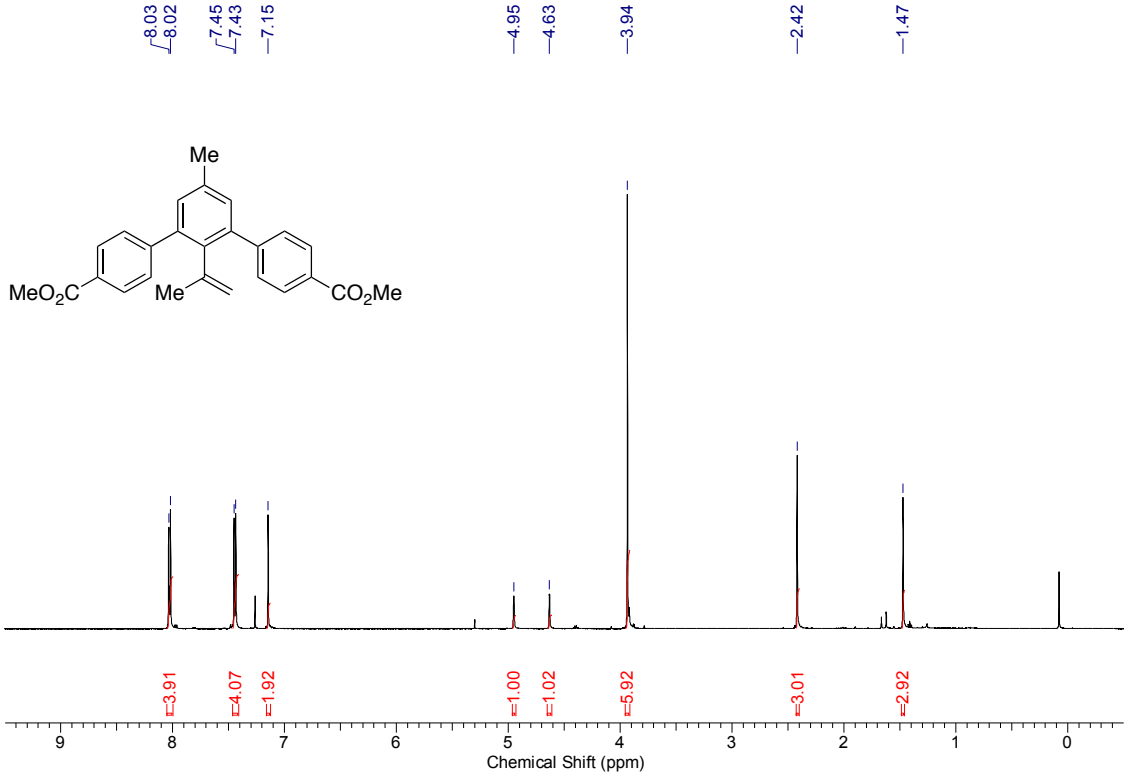
^{1}H NMR spectrum of **2-06aa**:



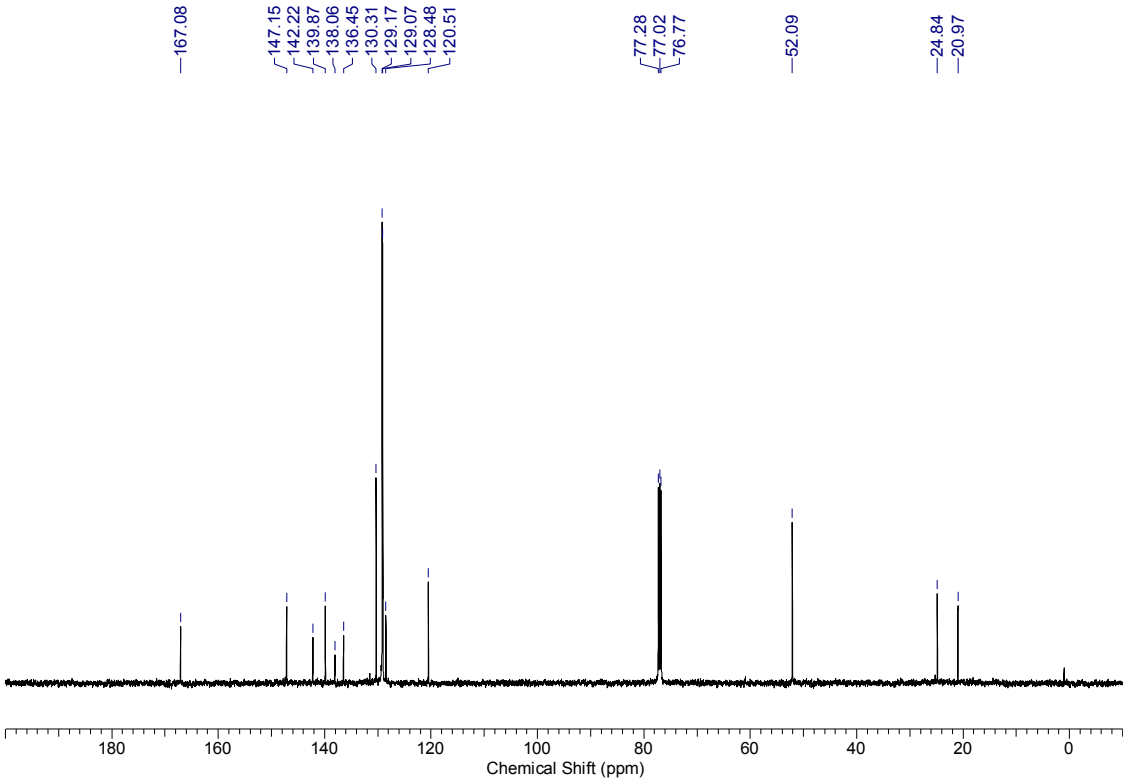
^{13}C NMR spectrum of **2-06aa**:



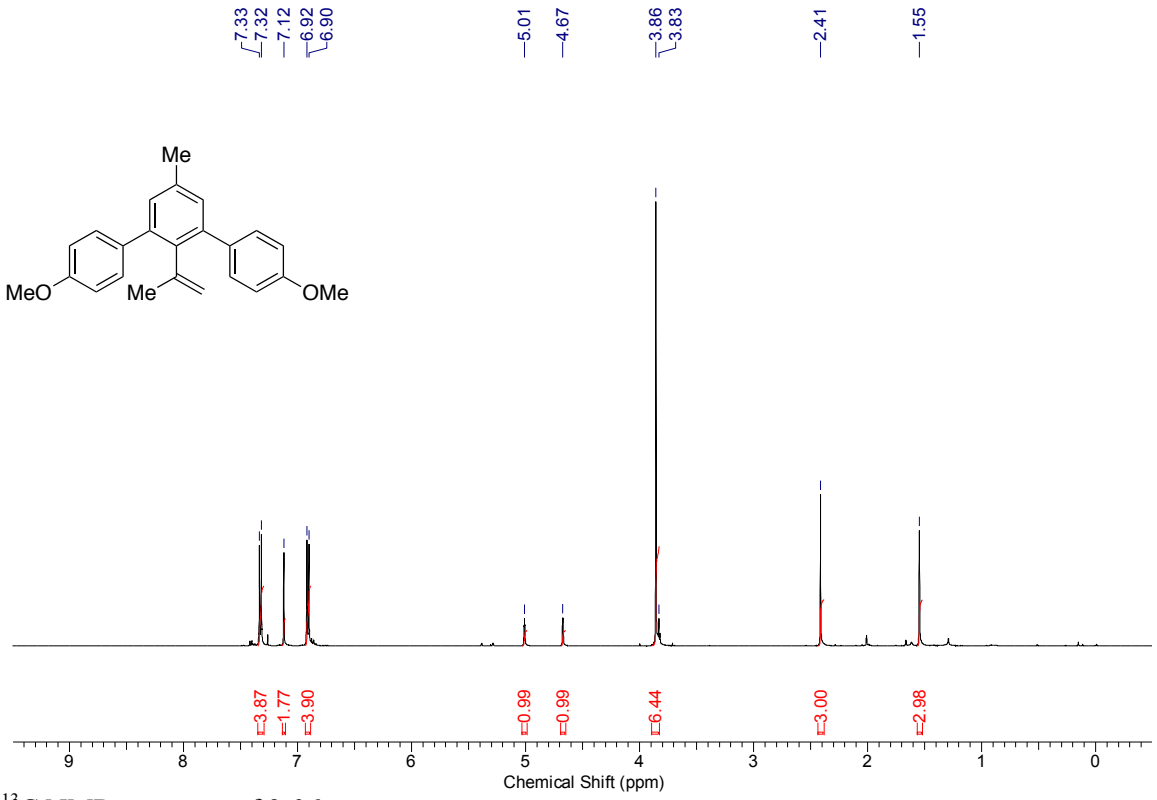
^{1}H NMR spectrum of **2-06bb**:



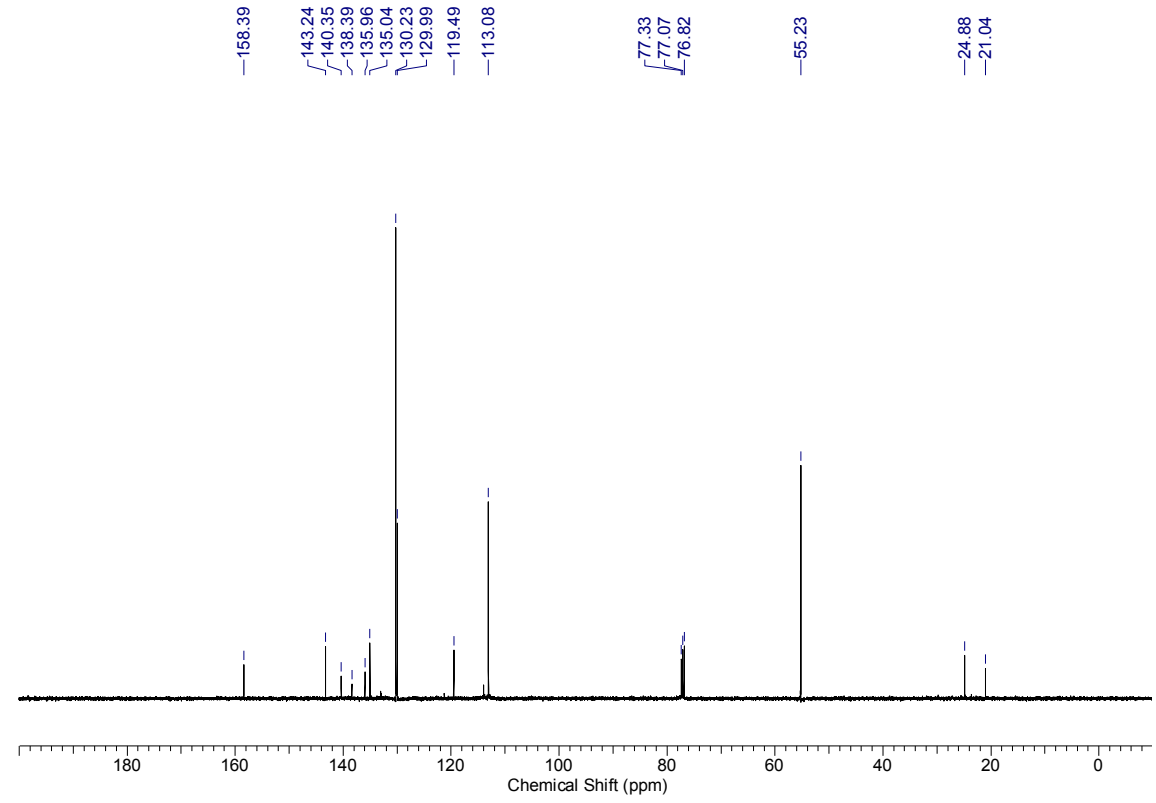
^{13}C NMR spectrum of **2-06bb**:



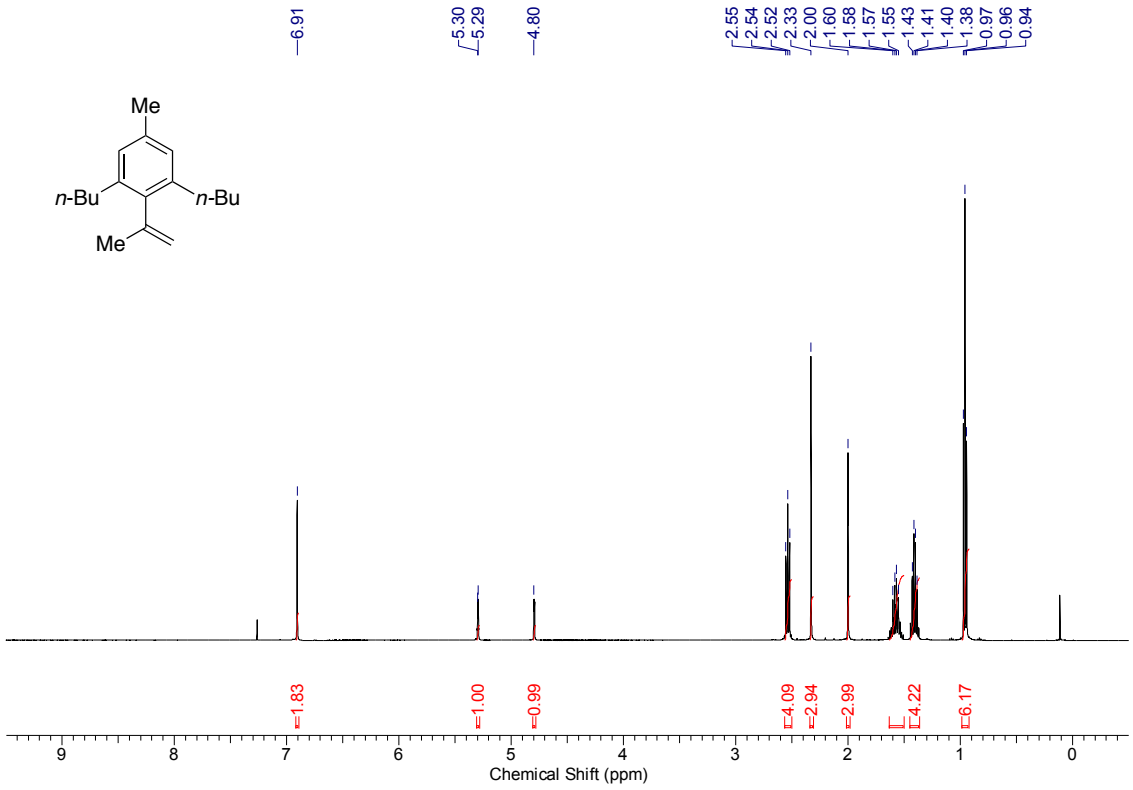
^{1}H NMR spectrum of **2-06cc**:



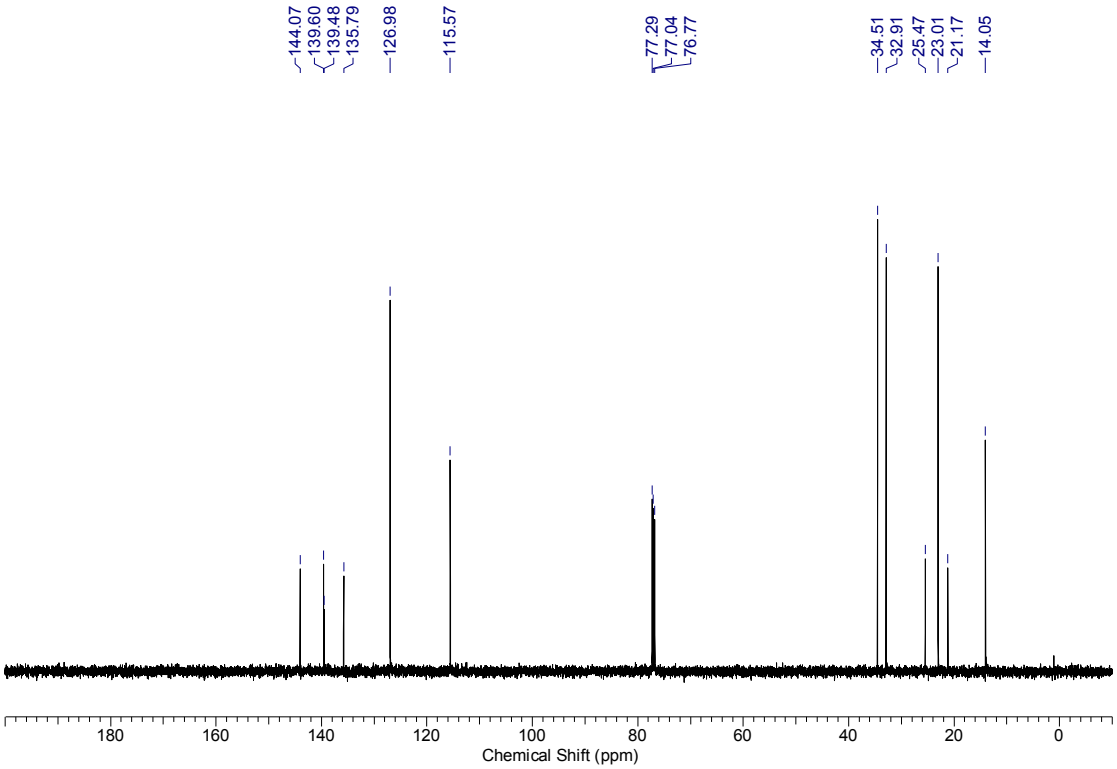
^{13}C NMR spectrum of **2-06cc**:



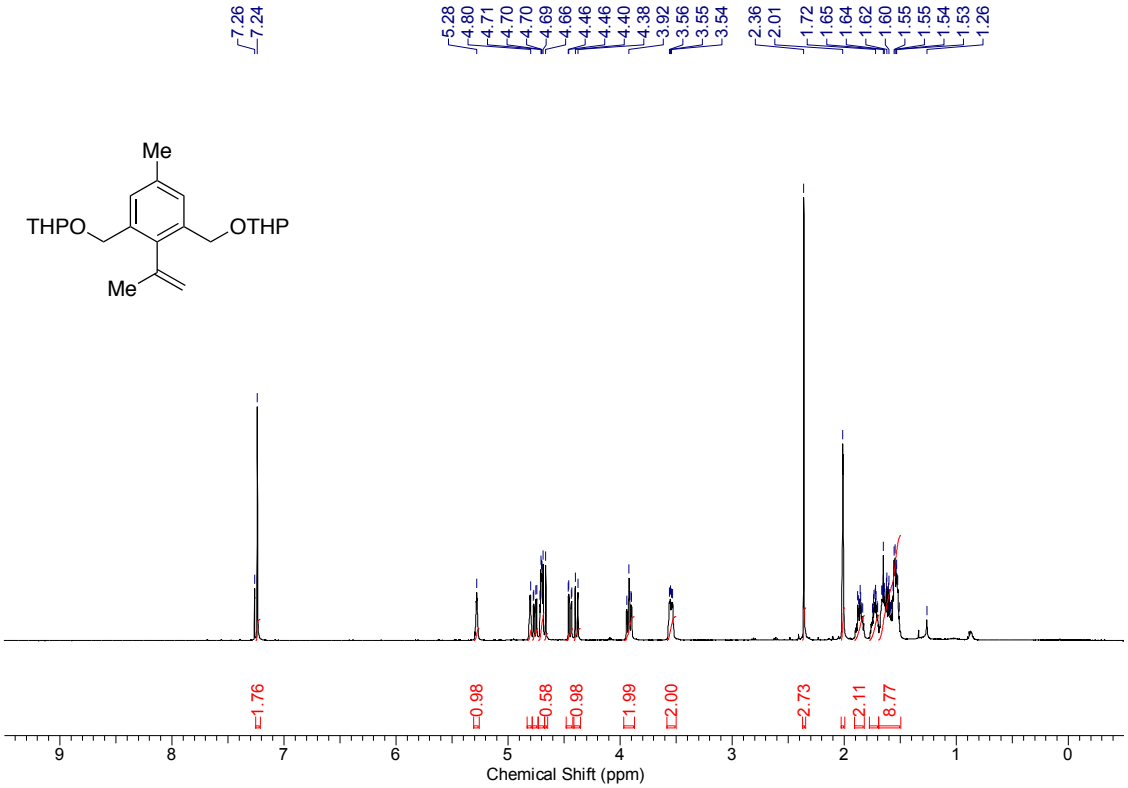
^{1}H NMR spectrum of **2-06dd**:



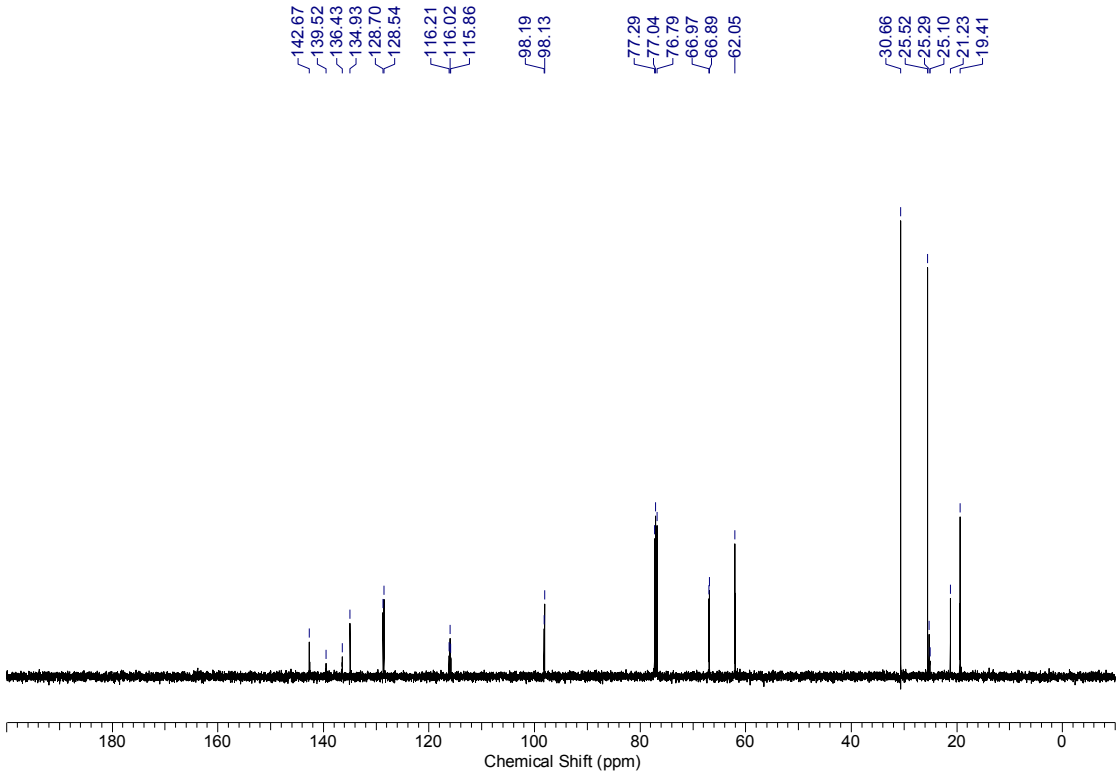
^{13}C NMR spectrum of **2-06dd**:



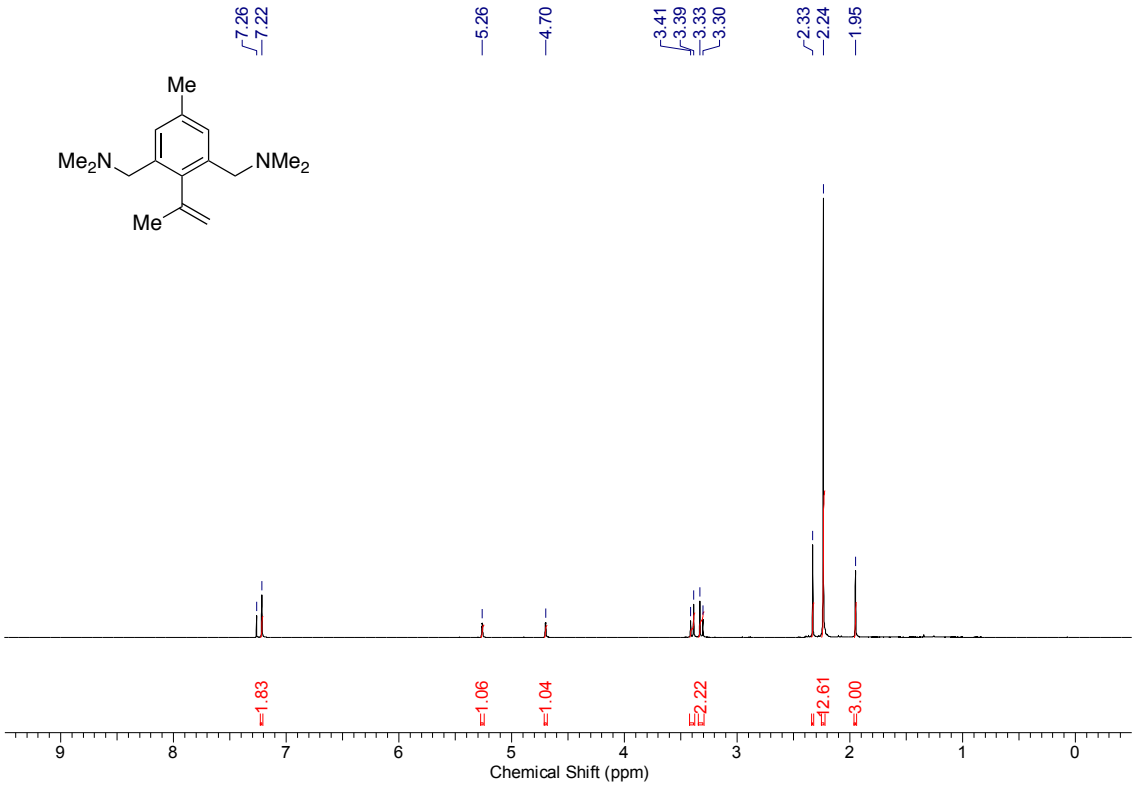
^{1}H NMR spectrum of **2-06jj**:



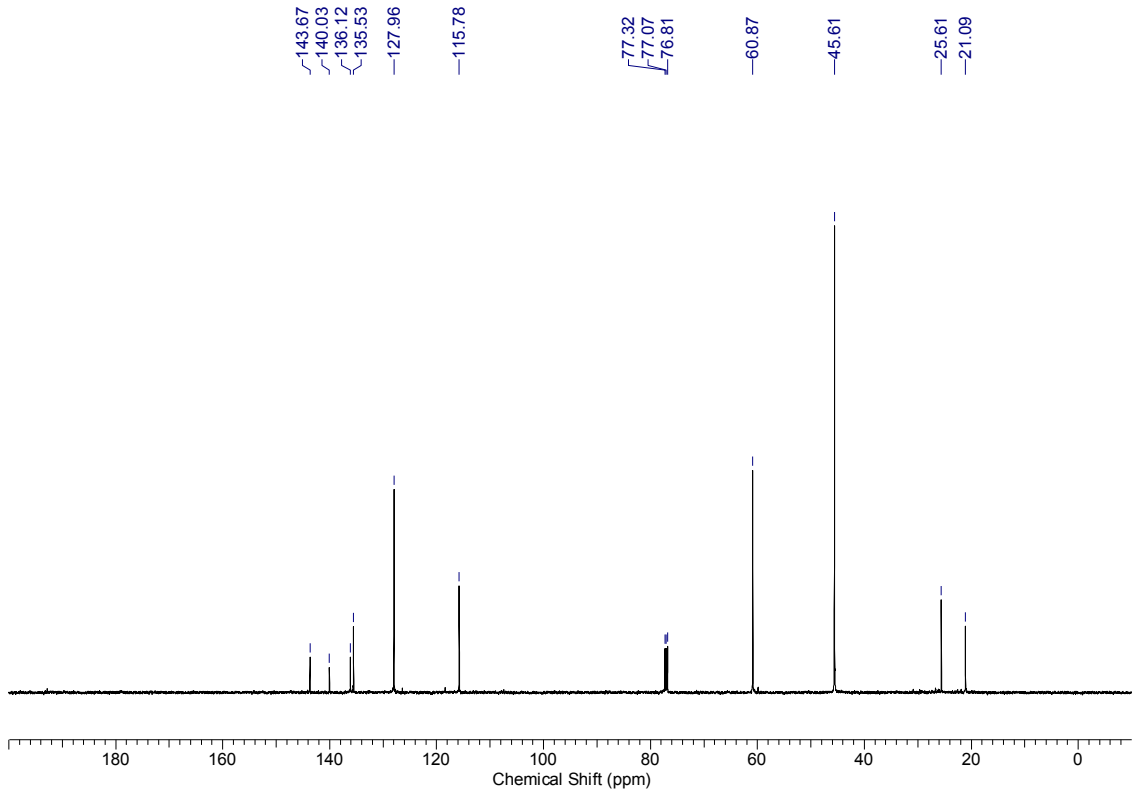
^{13}C NMR spectrum of **2-06jj**:



^{1}H NMR spectrum of **2-06ll**:



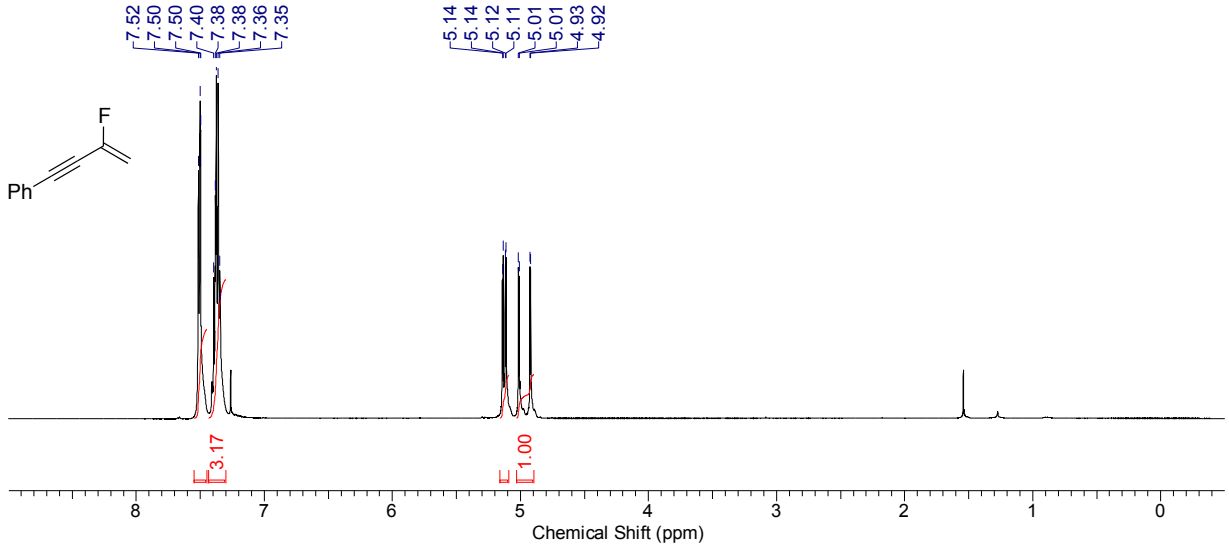
^{13}C NMR spectrum of **2-06ll**:



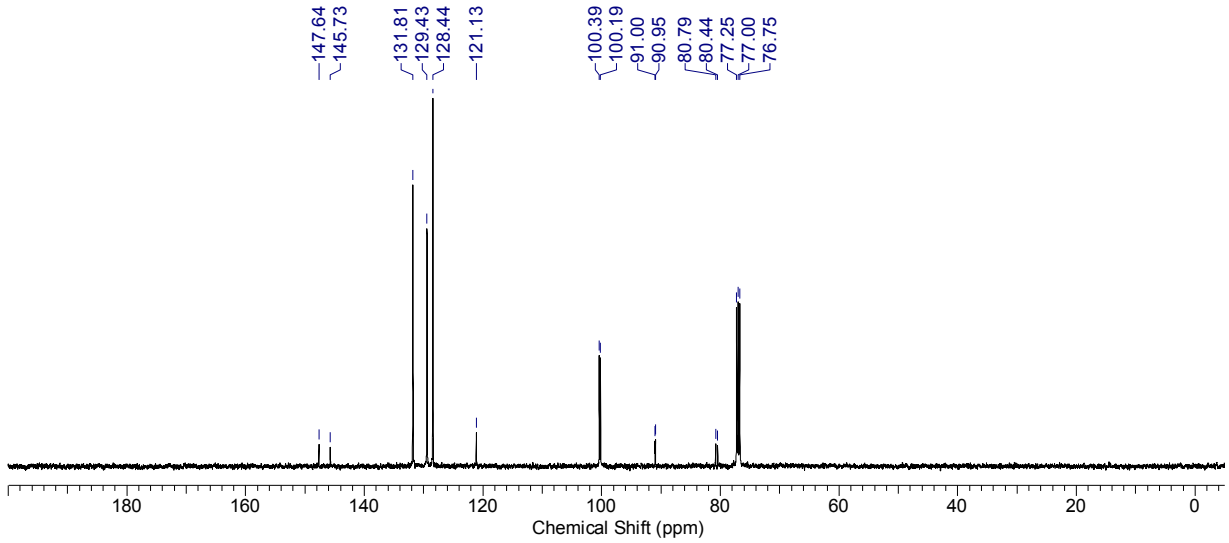
APPENDIX IV

Selected NMR Spectra for Part Three

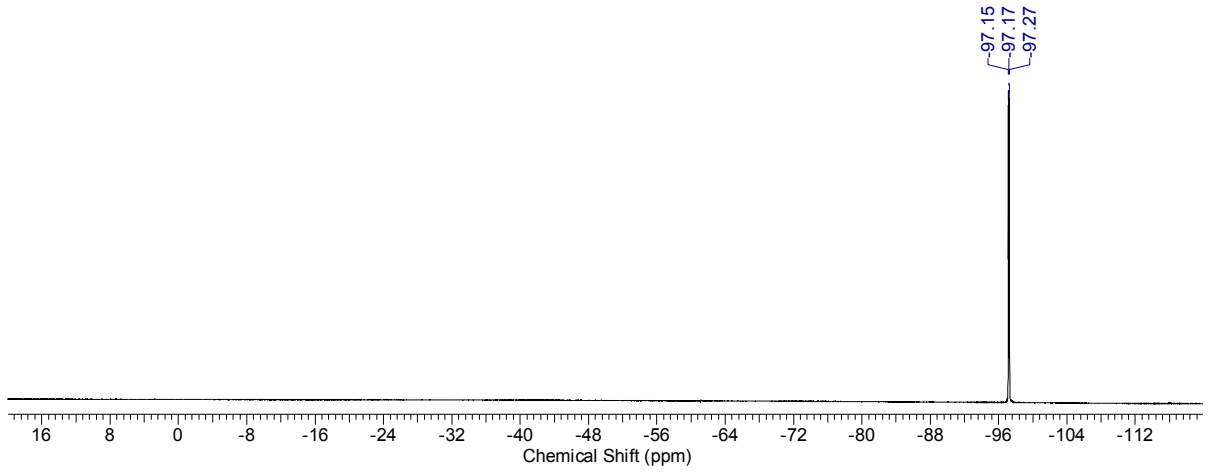
^{1}H spectrum of **3-137a**:



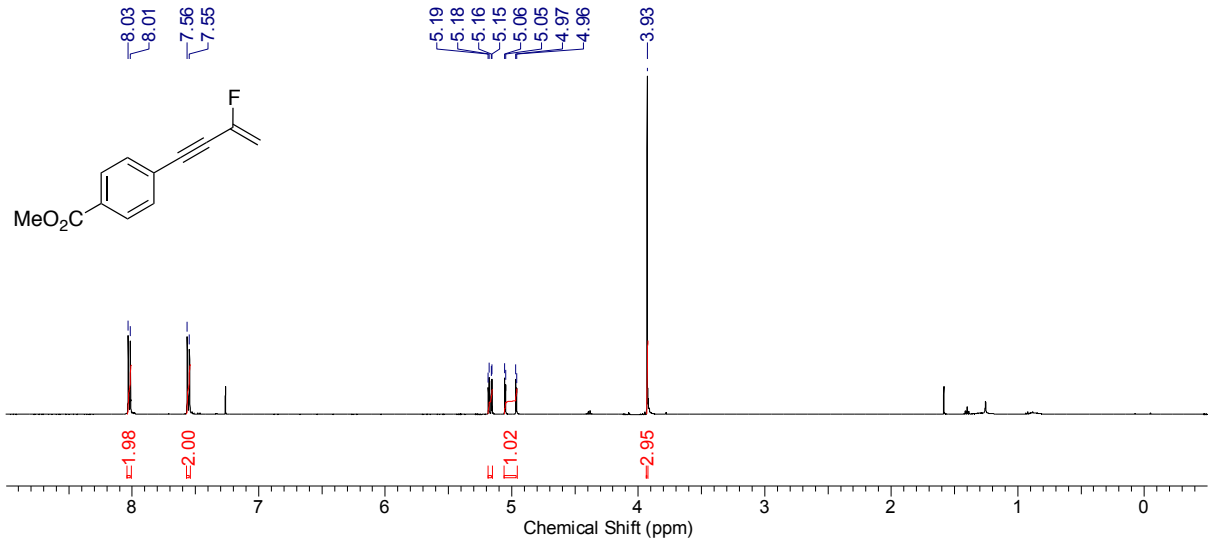
^{13}C spectrum of **3-137a**:



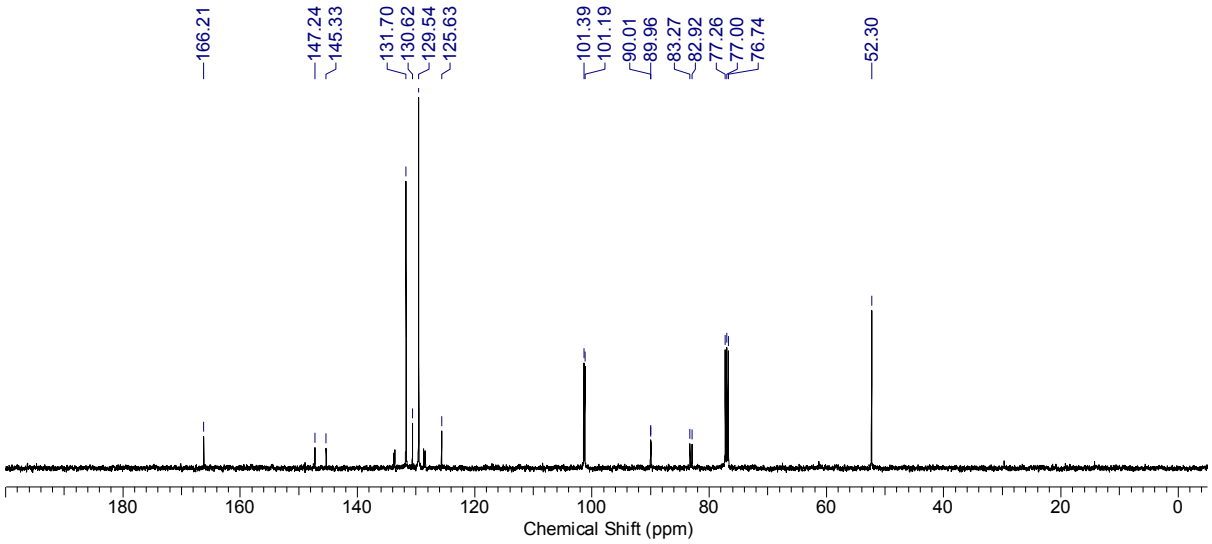
^{19}F spectrum of **3-137a**:



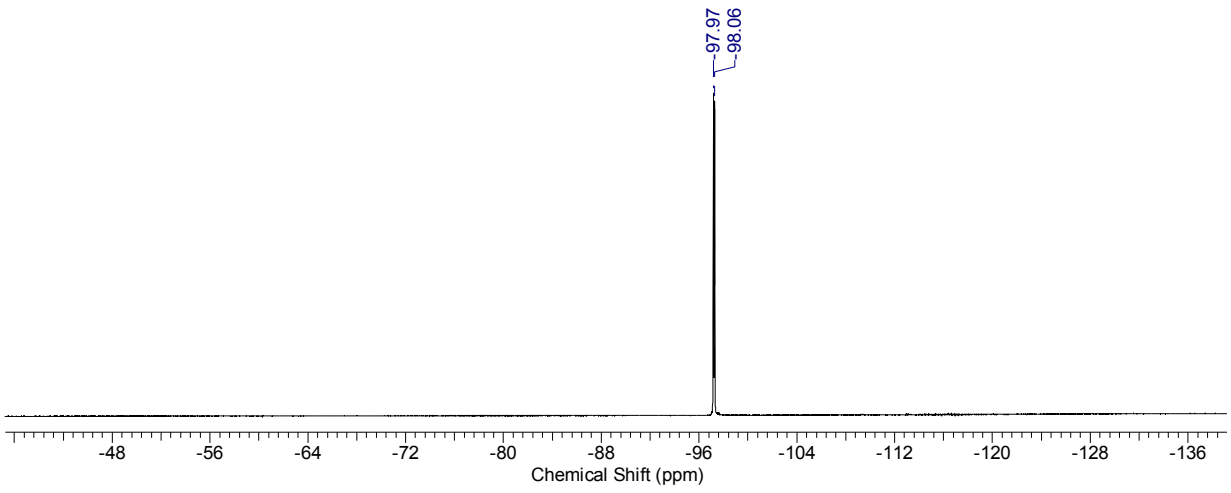
^{1}H spectrum of **3-137b**:



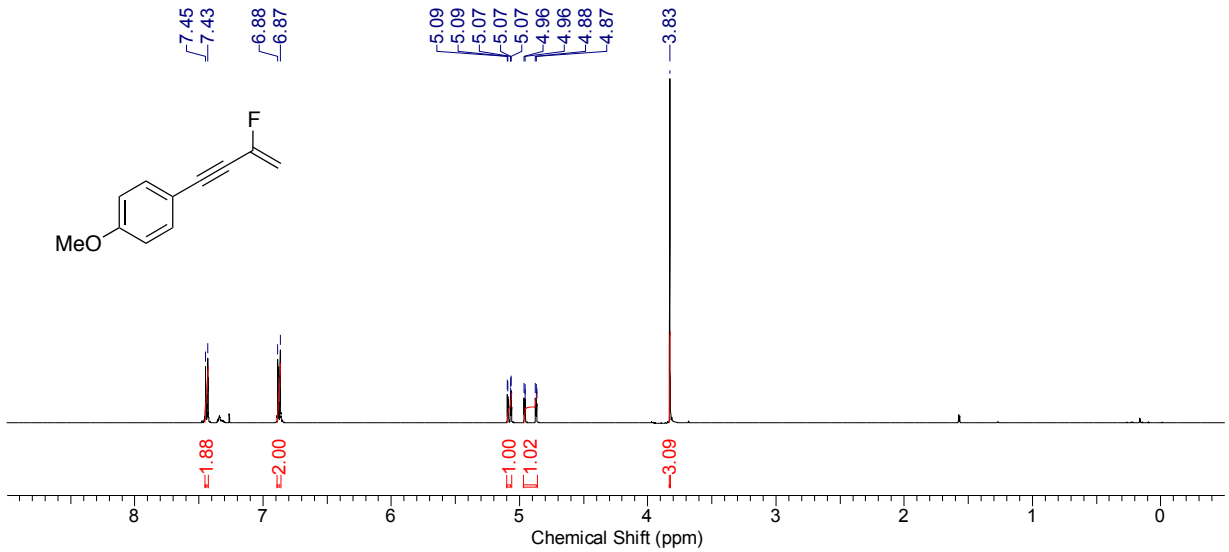
^{13}C spectrum of **3-137b**:



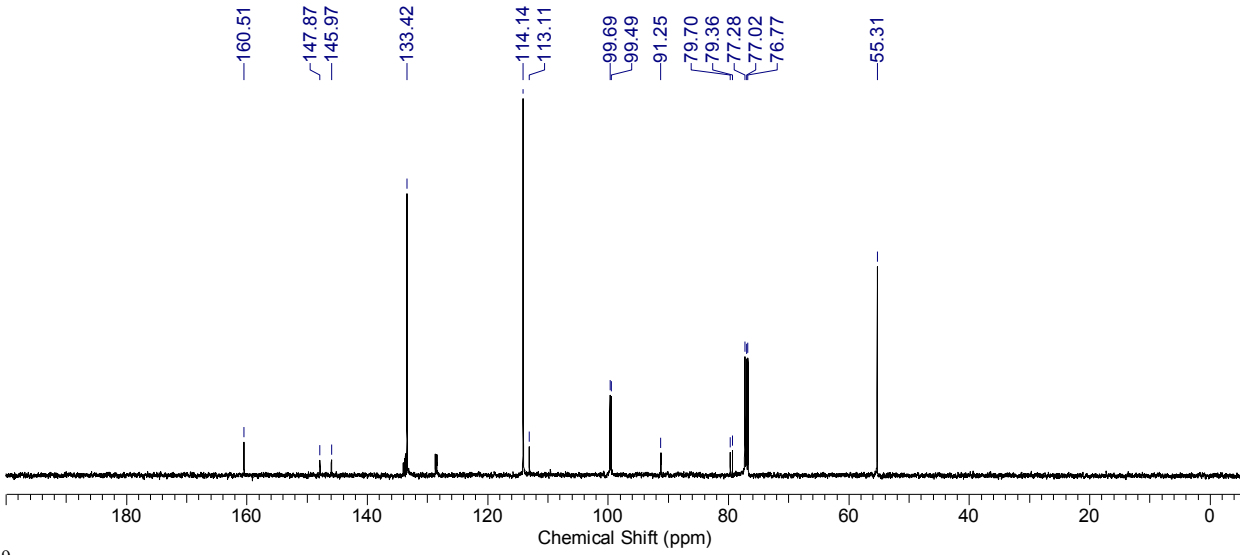
^{19}F spectrum of **3-137b**:



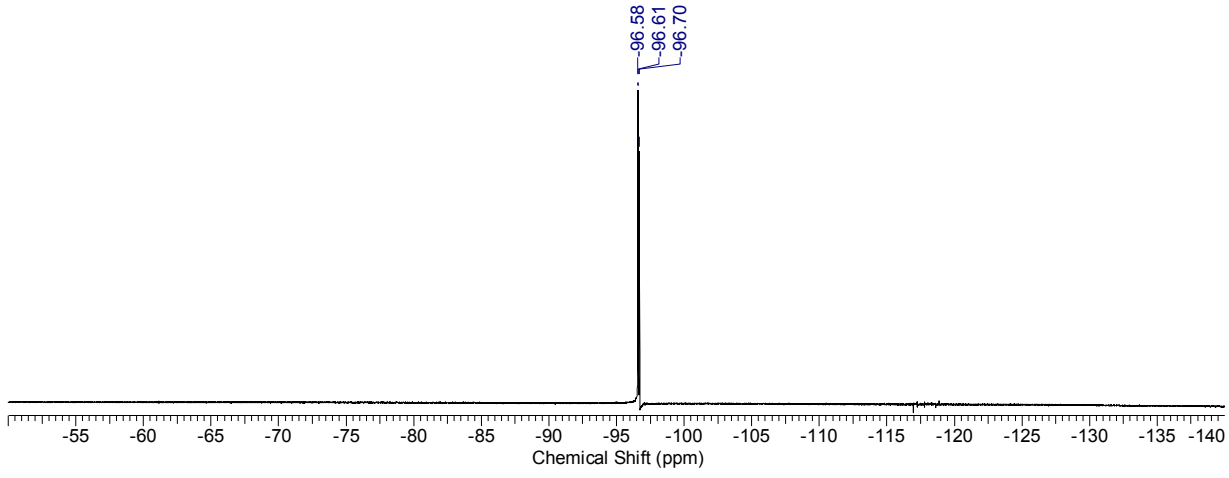
^{1}H spectrum of **3-137c**:



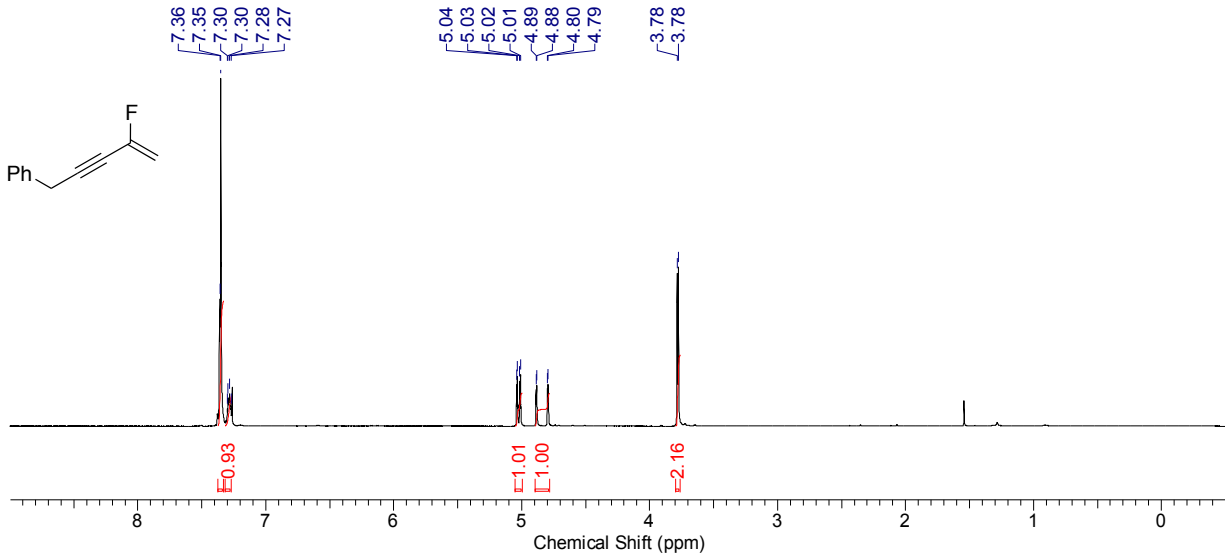
^{13}C spectrum of **3-137c**:



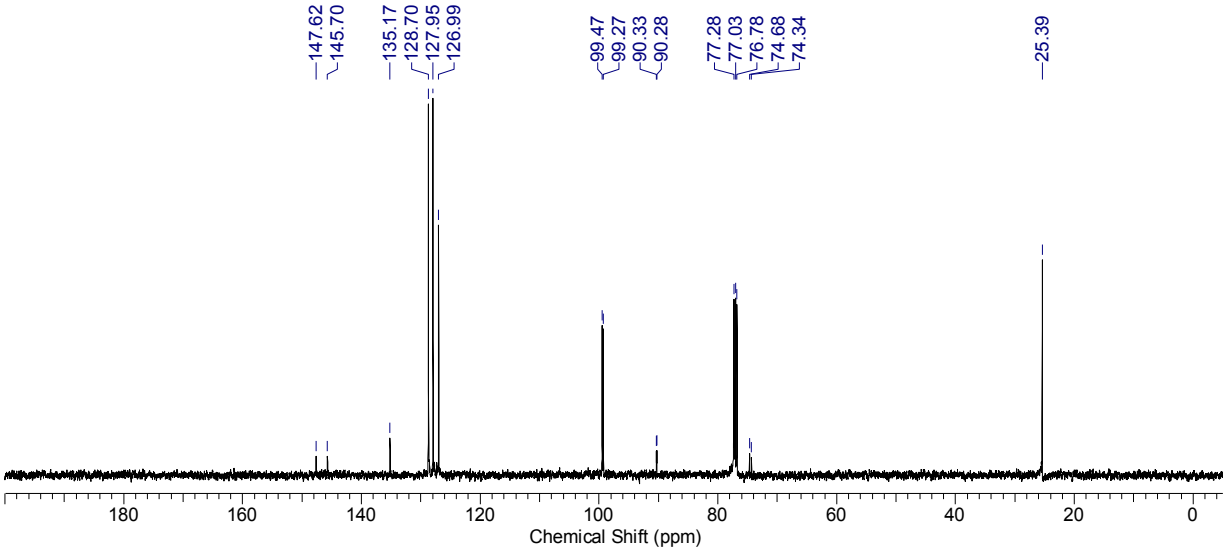
^{19}F spectrum of **3-137c**:



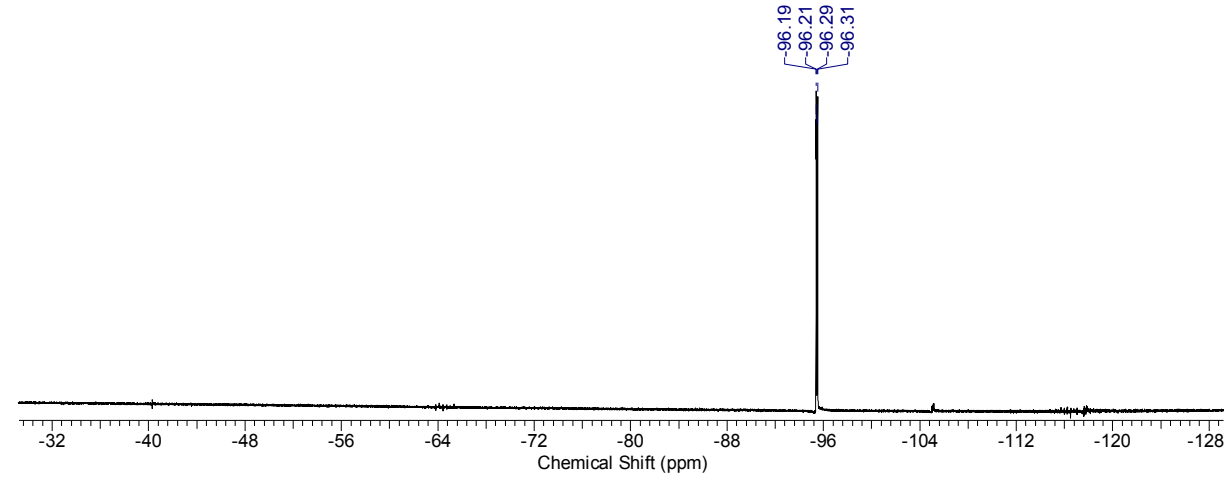
^{1}H spectrum of **3-137d**:



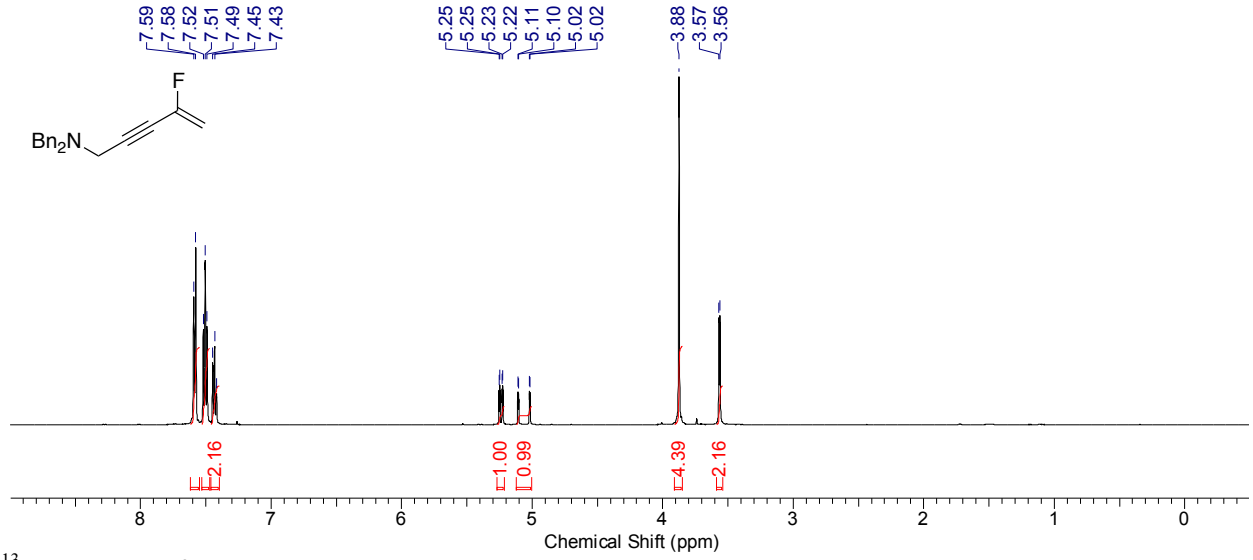
^{13}C spectrum of **3-137d**:



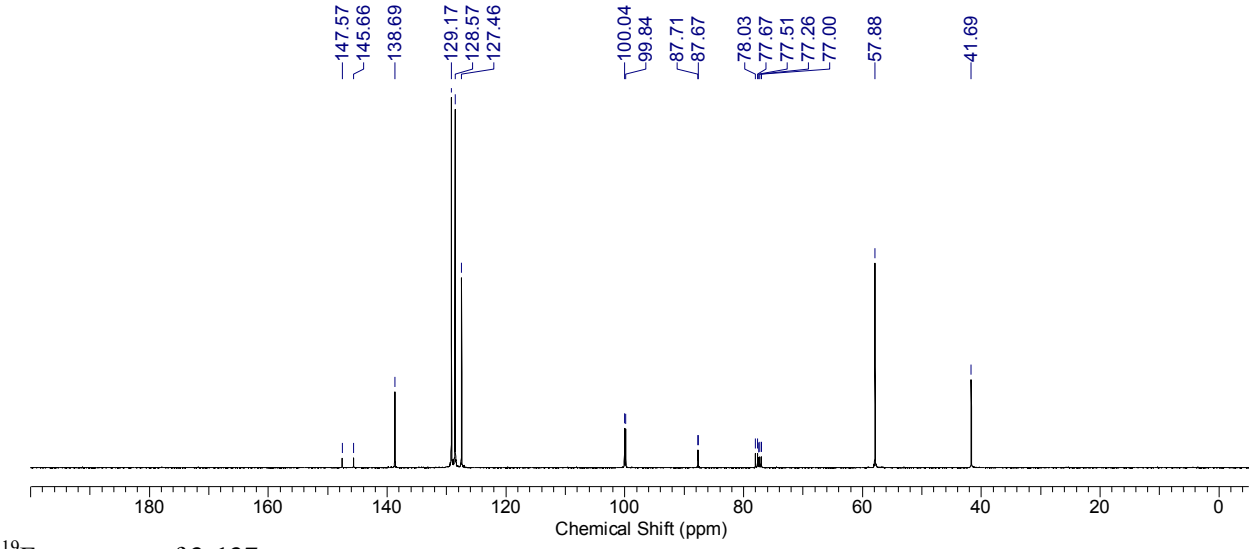
^{19}F spectrum of **3-137d**:



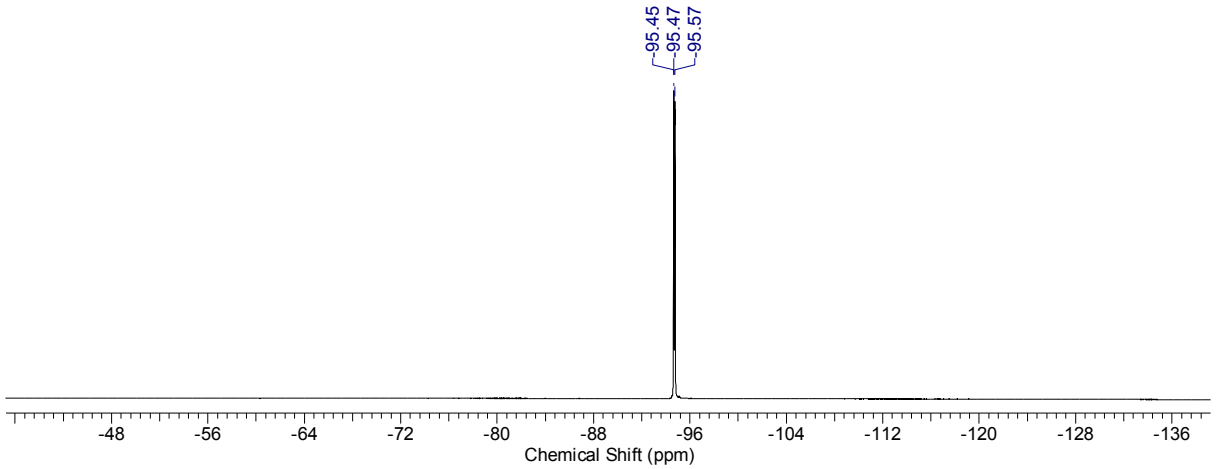
^{1}H spectrum of **3-137e**:



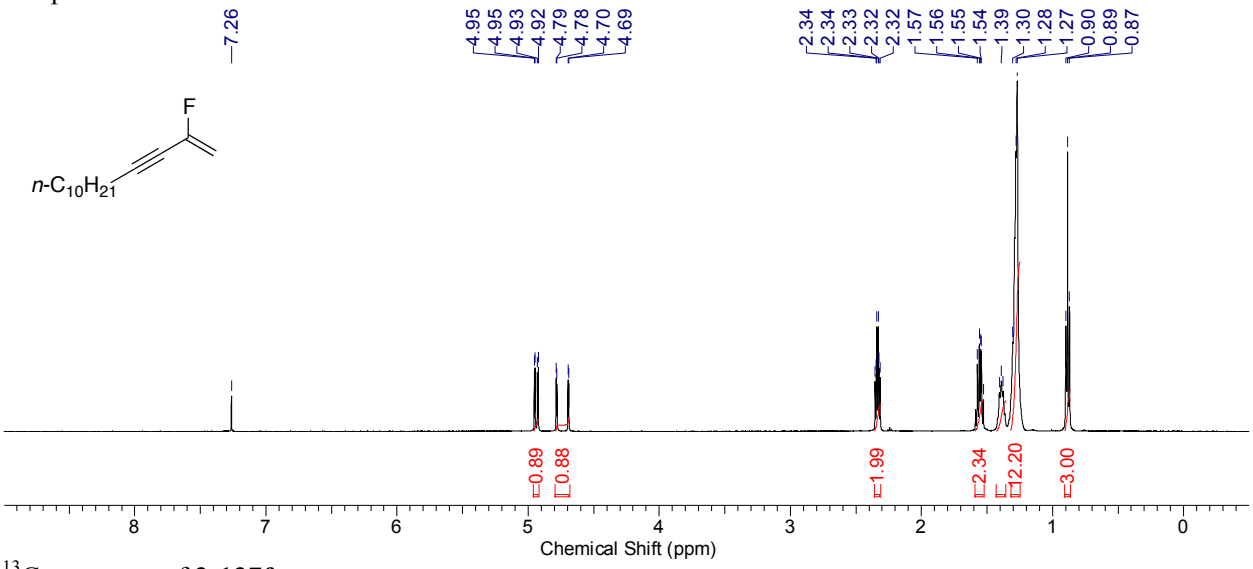
^{13}C spectrum of **3-137e**:



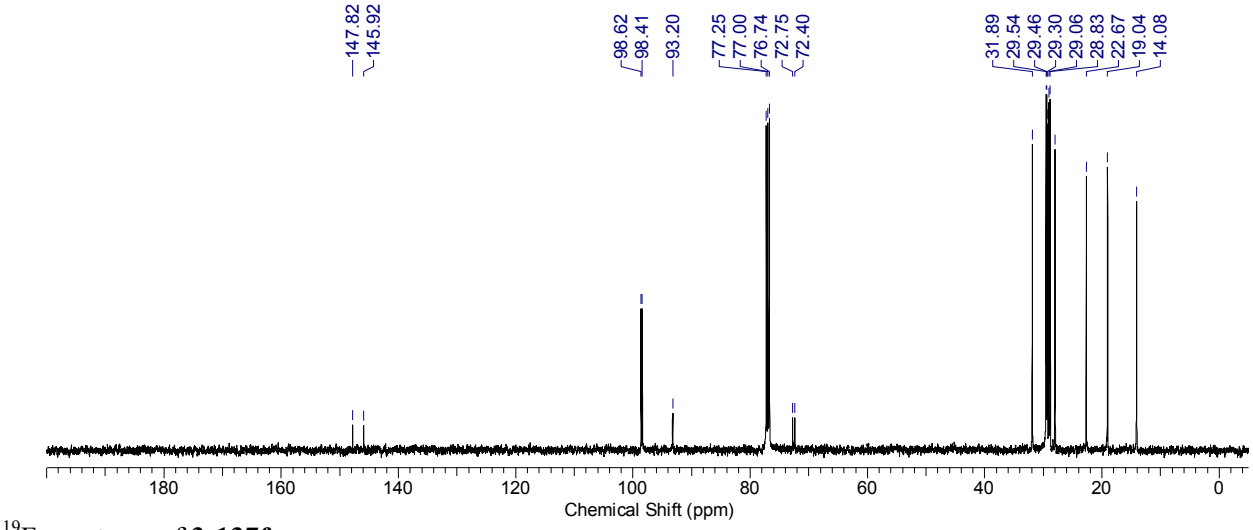
^{19}F spectrum of **3-137e**:



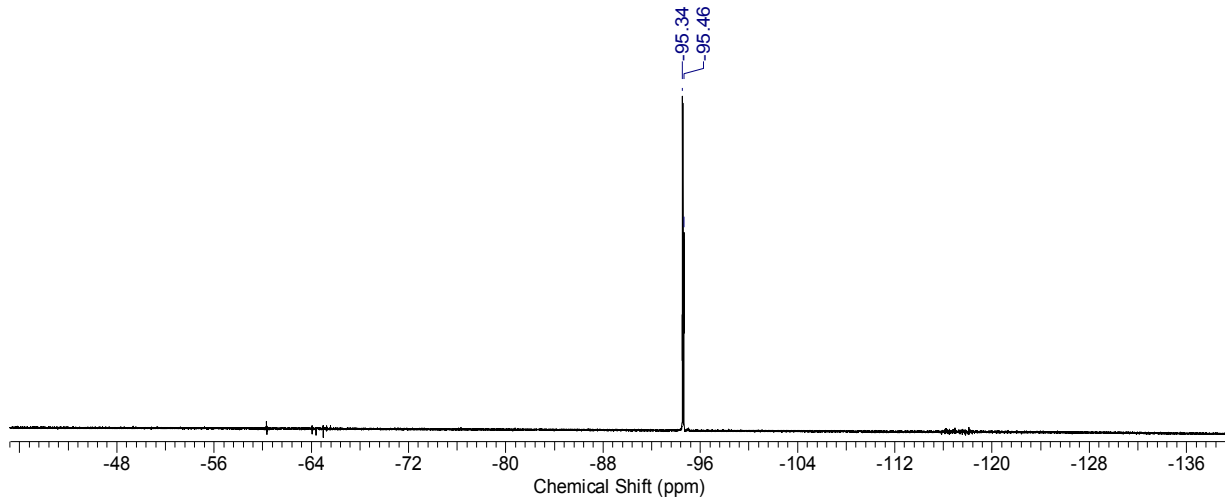
^{1}H spectrum of **3-137f**:



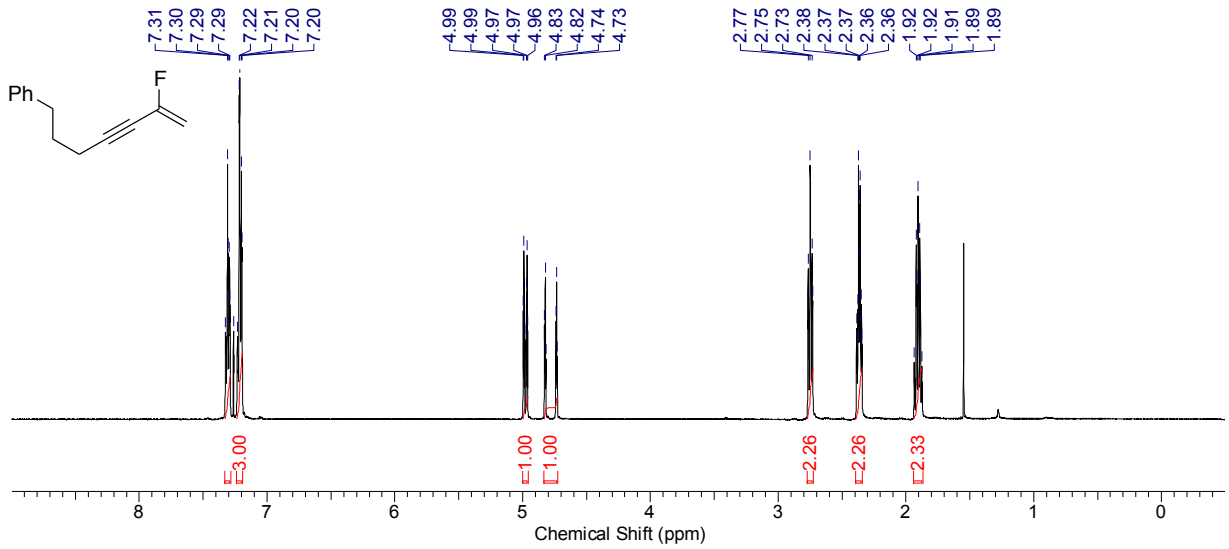
^{13}C spectrum of **3-137f**:



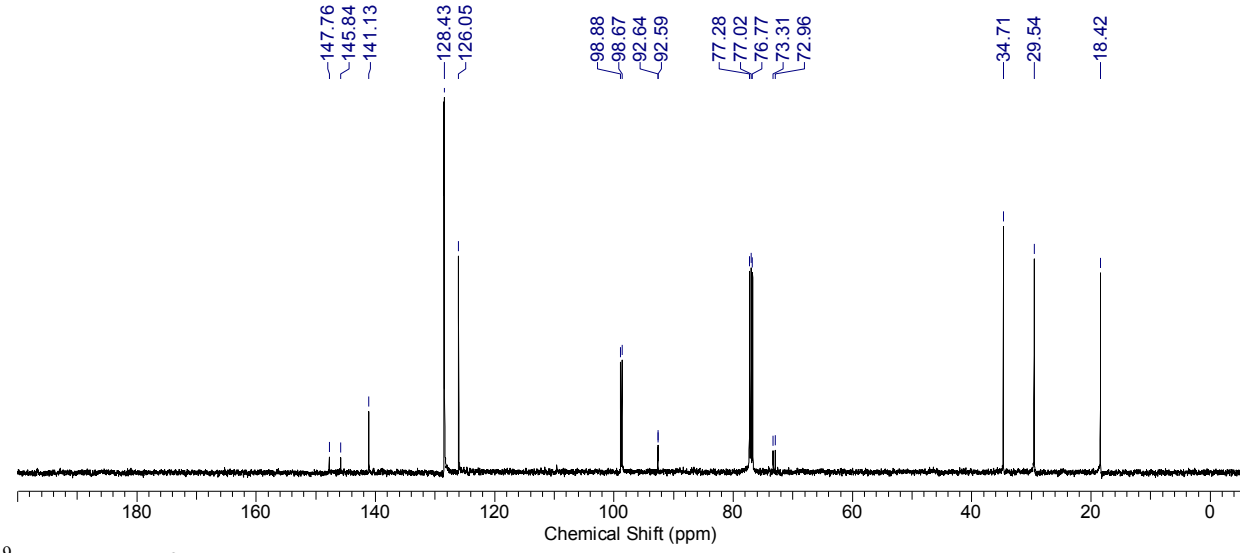
^{19}F spectrum of **3-137f**:



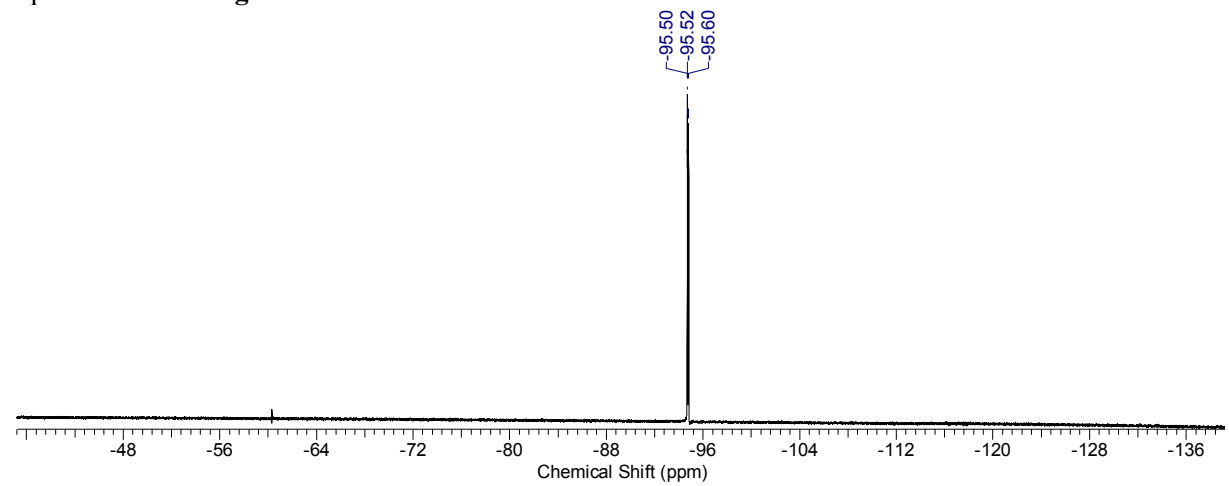
^{1}H spectrum of **3-137g**:



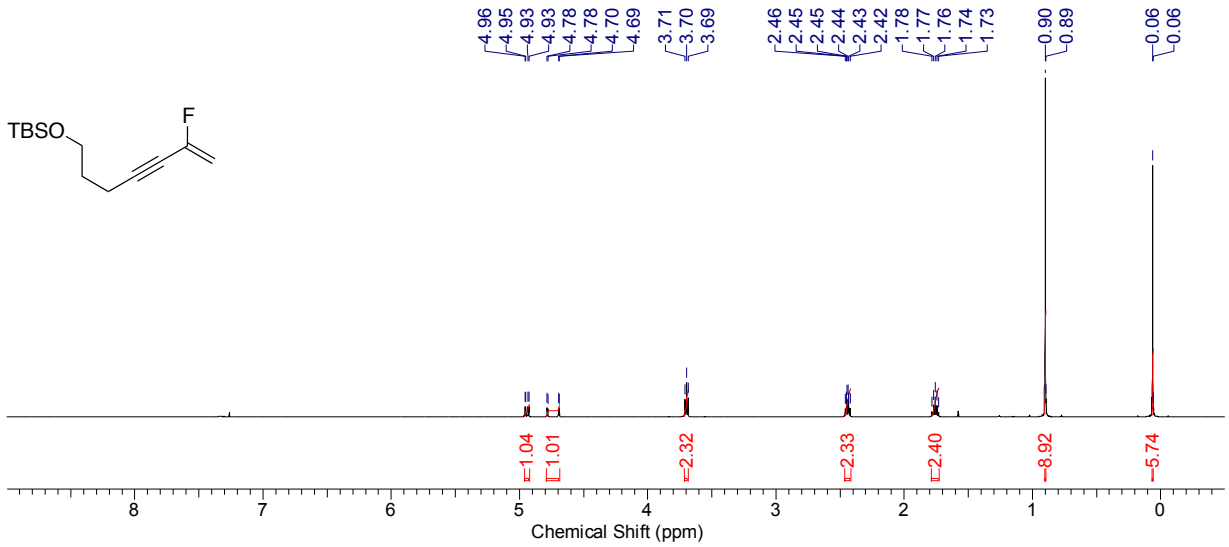
^{13}C spectrum of **3-137g**:



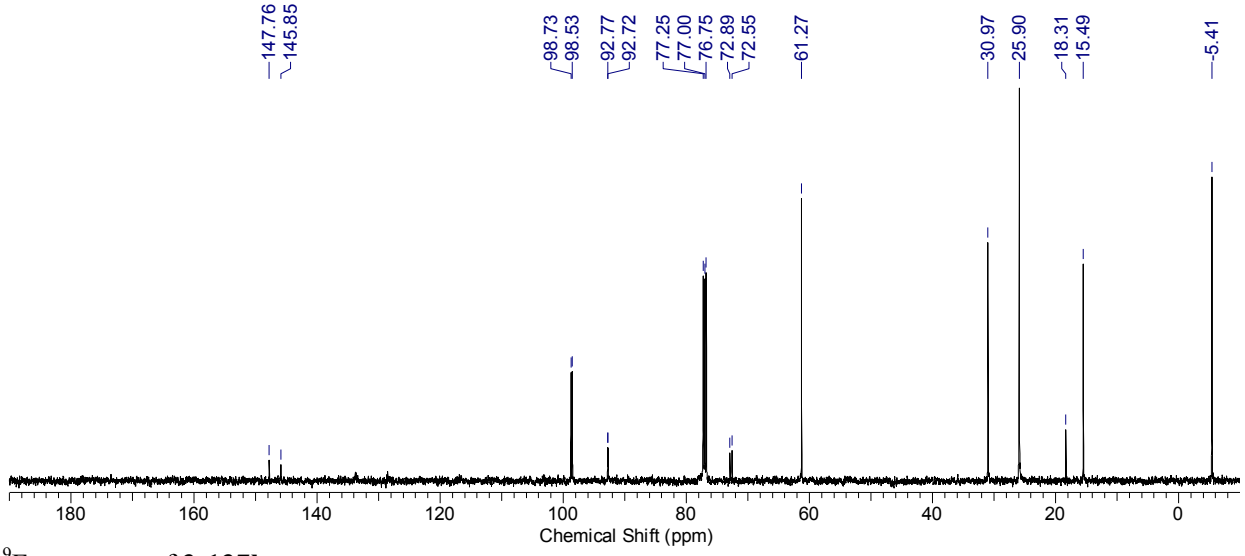
^{19}F spectrum of **3-137g**:



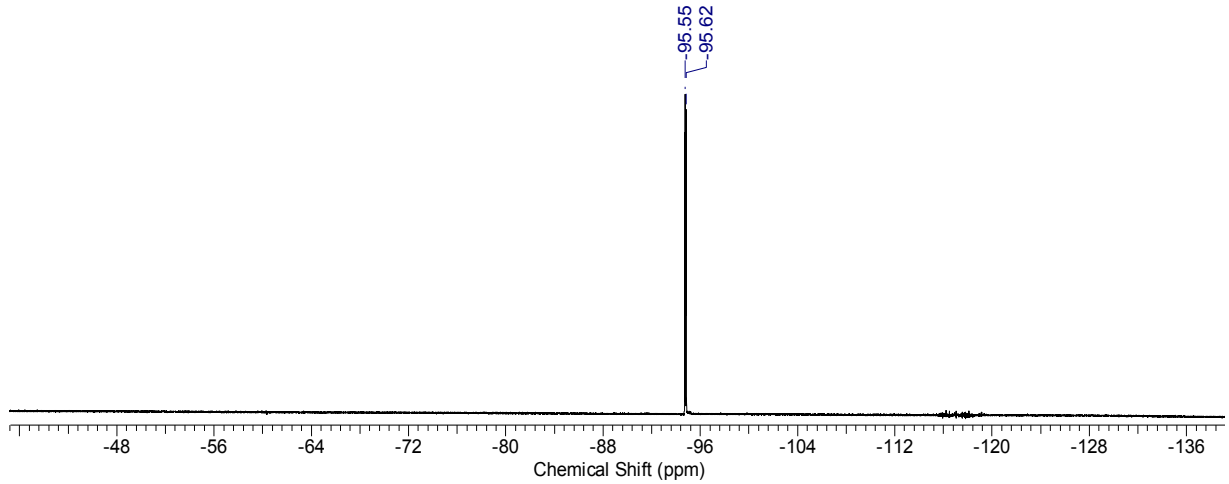
^{1}H spectrum of **3-137h**:



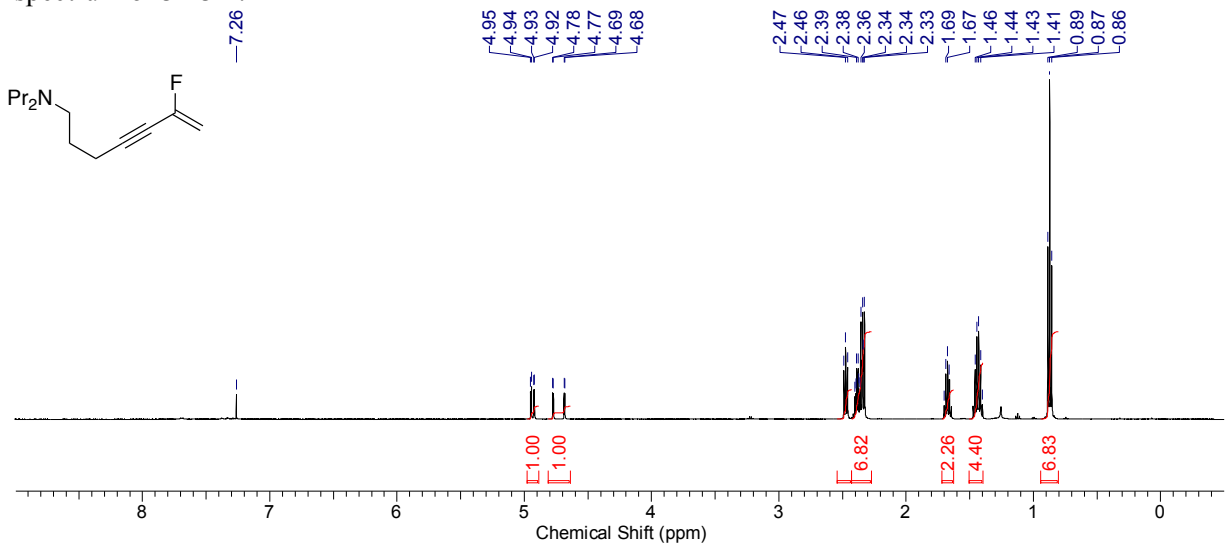
^{13}C spectrum of **3-137h**:



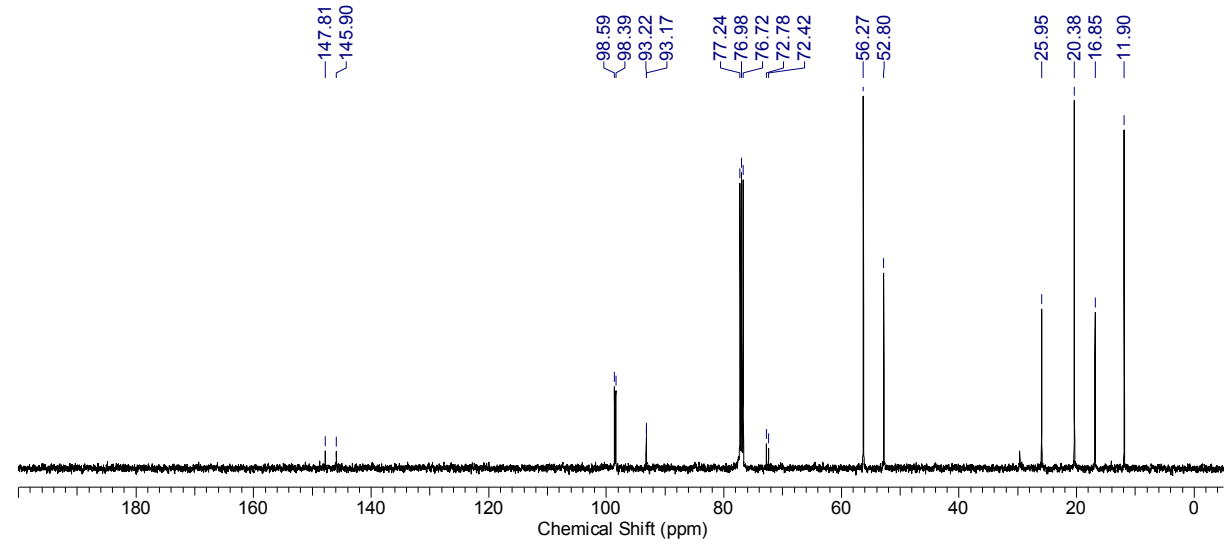
^{19}F spectrum of **3-137h**:



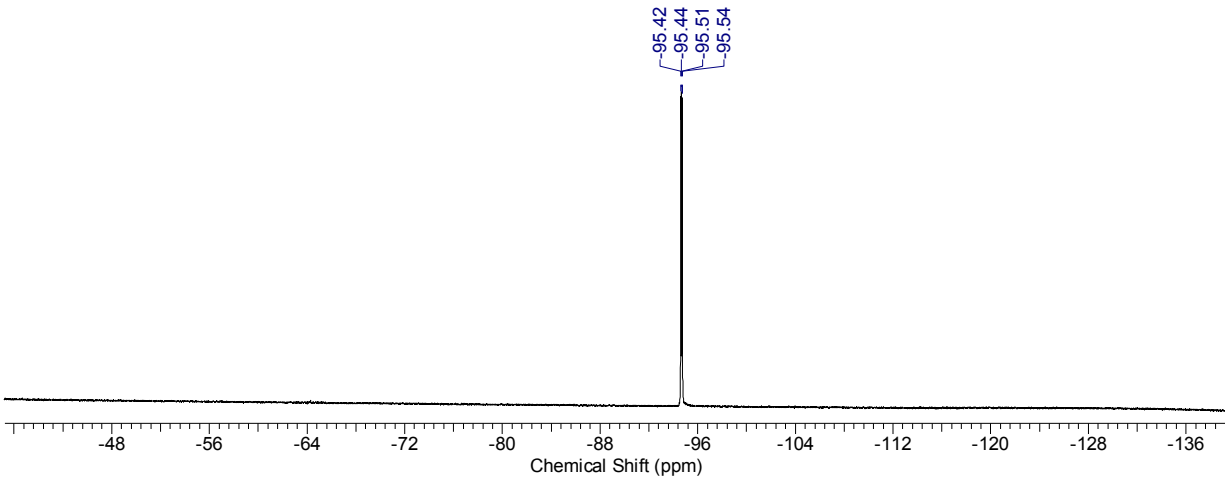
^{1}H spectrum of **3-137i**:



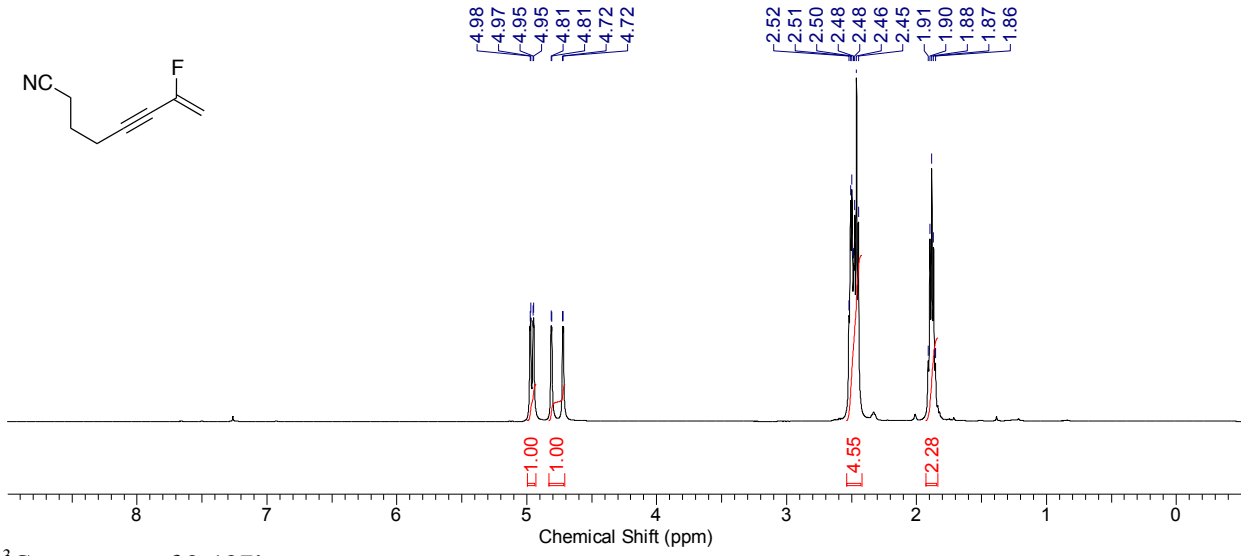
^{13}C spectrum of **3-137i**:



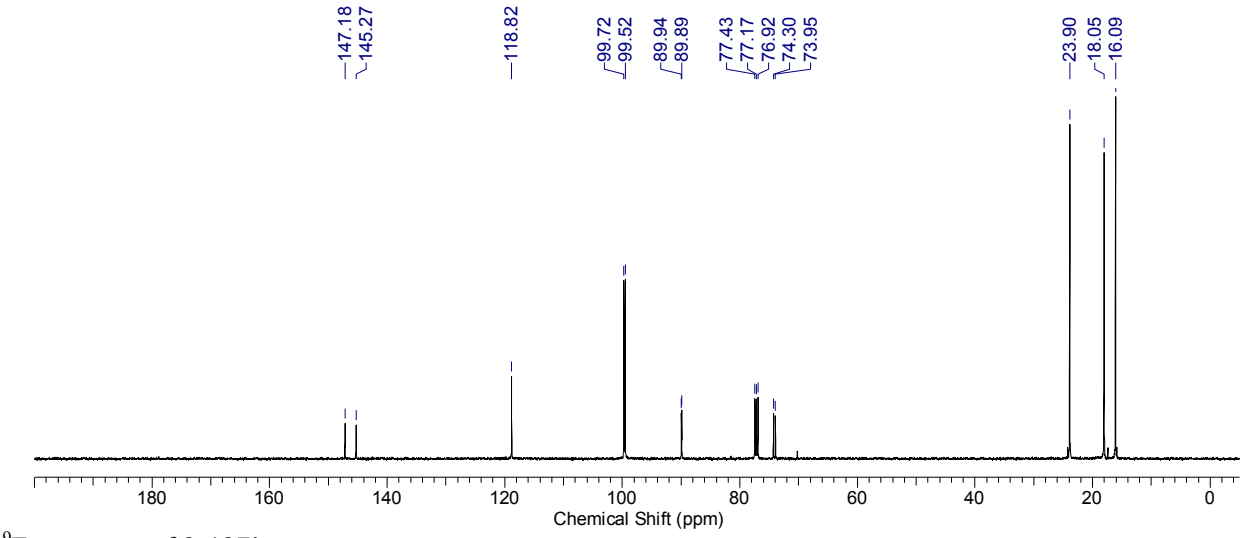
^{19}F spectrum of **3-137i**:



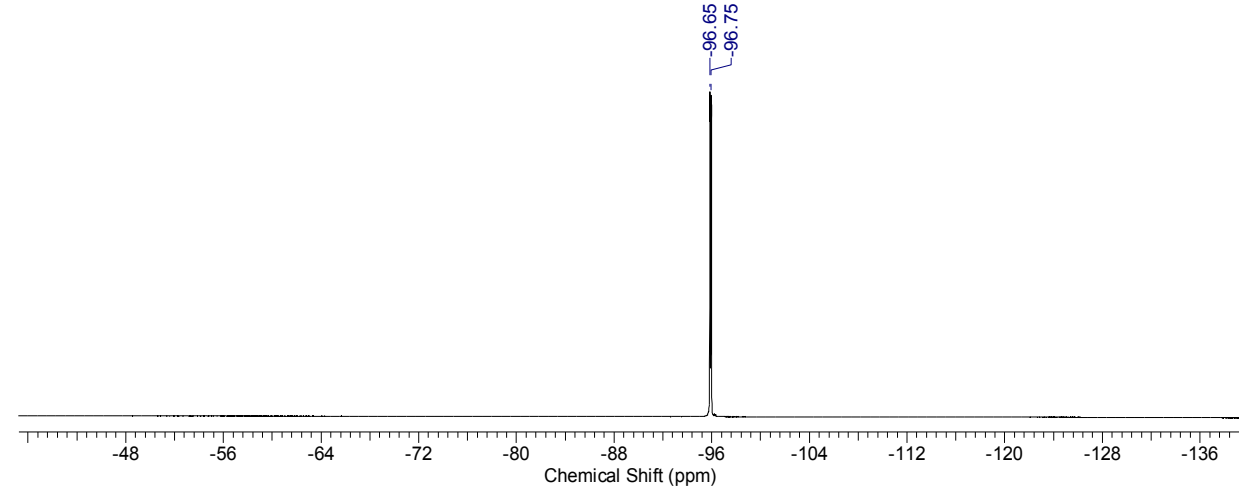
^{1}H spectrum of **3-137j**:



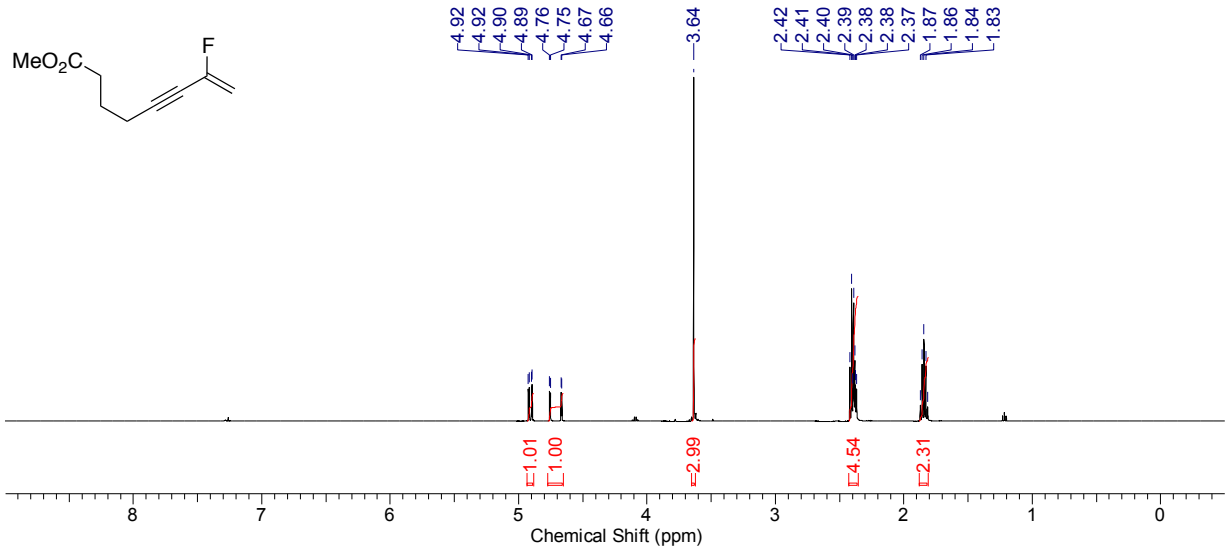
^{13}C spectrum of **3-137j**:



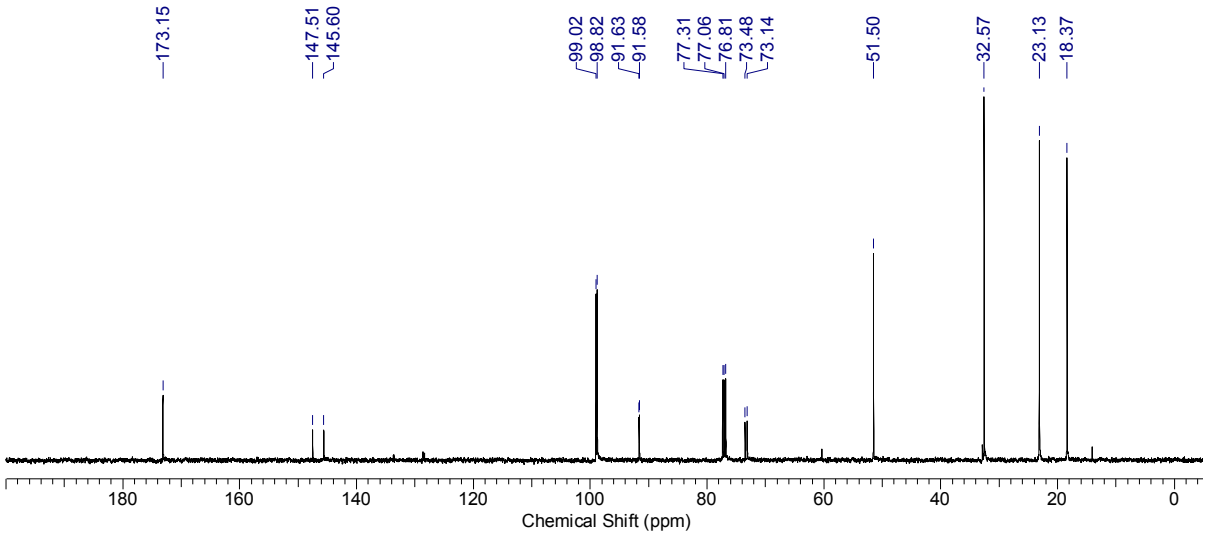
^{19}F spectrum of **3-137j**:



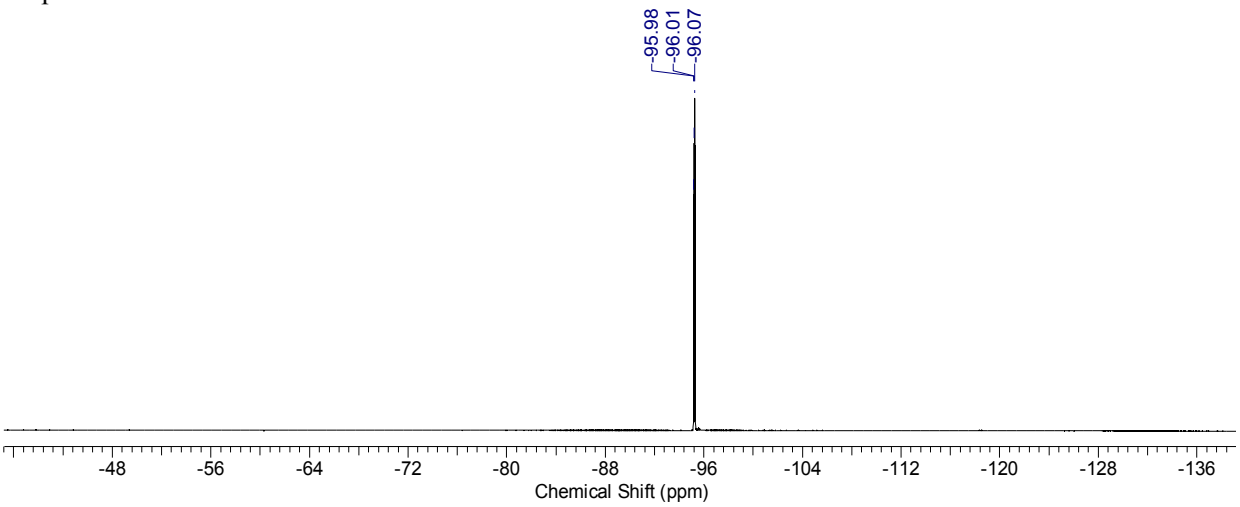
^{1}H spectrum of **3-137k**:



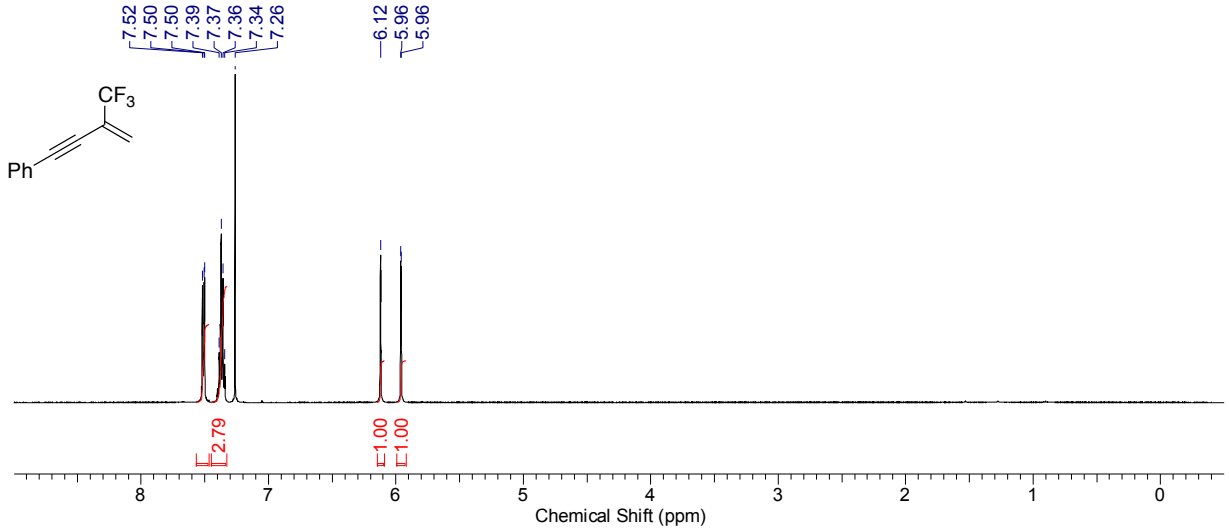
^{13}C spectrum of **3-137k**:



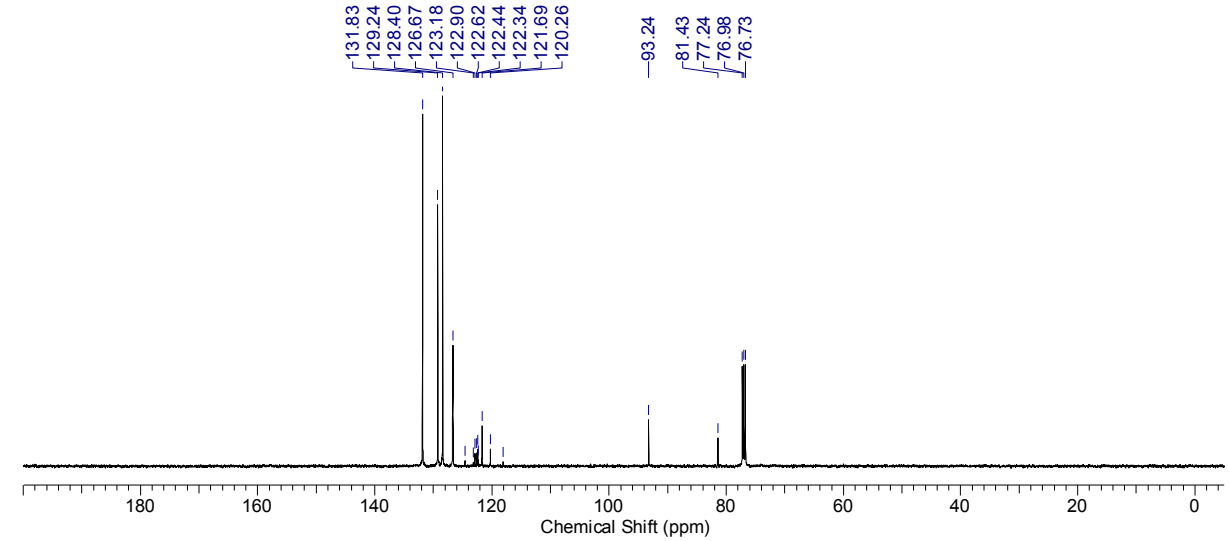
^{19}F spectrum of **3-137k**:



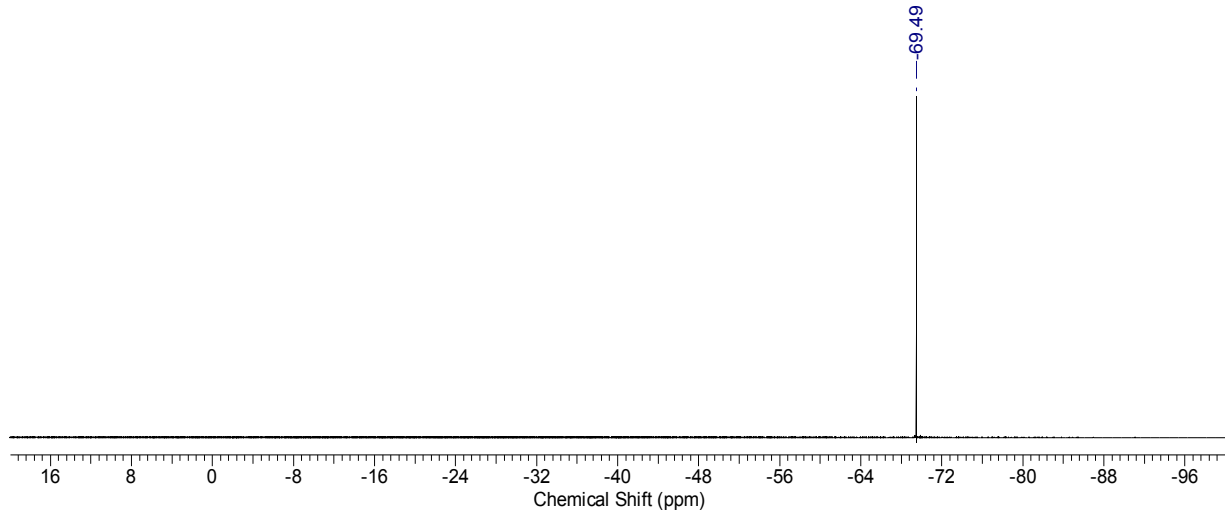
^{1}H spectrum of **3-141a**:



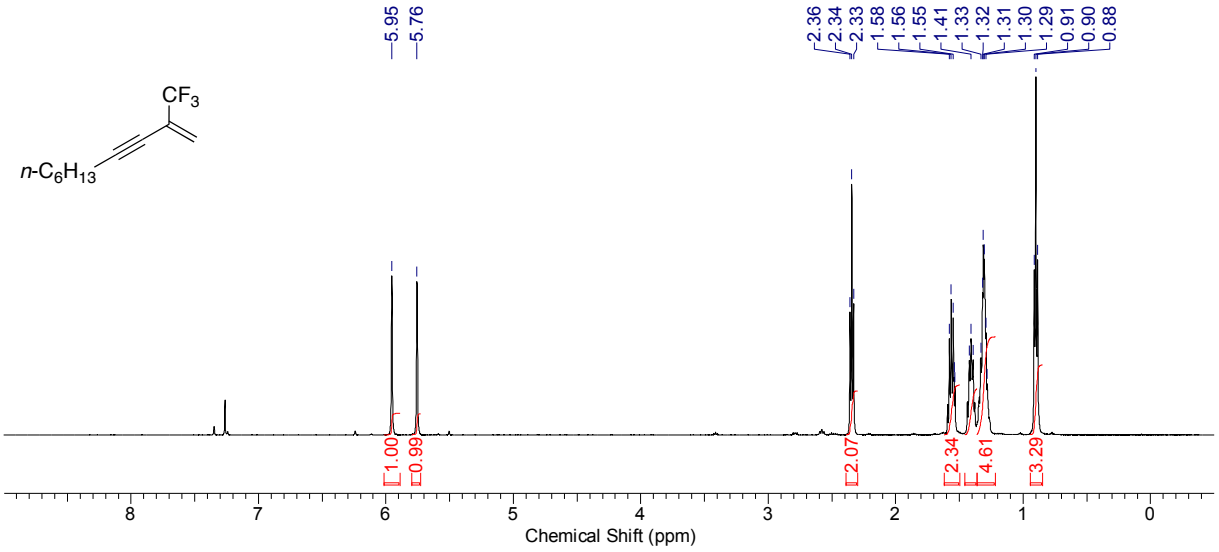
^{13}C spectrum of **3-141a**:



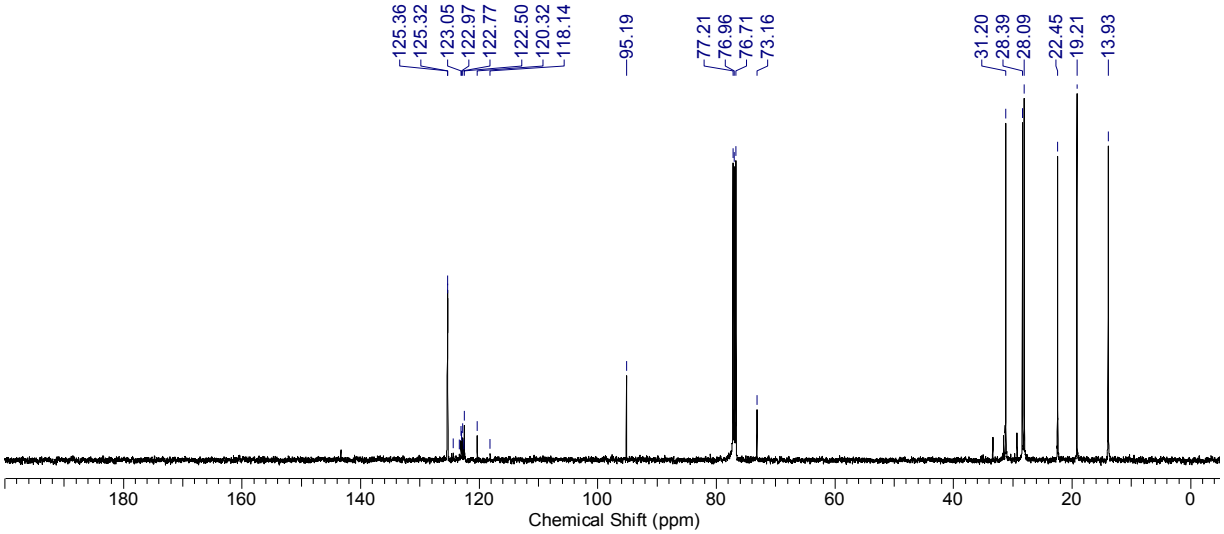
^{19}F spectrum of **3-141a**:



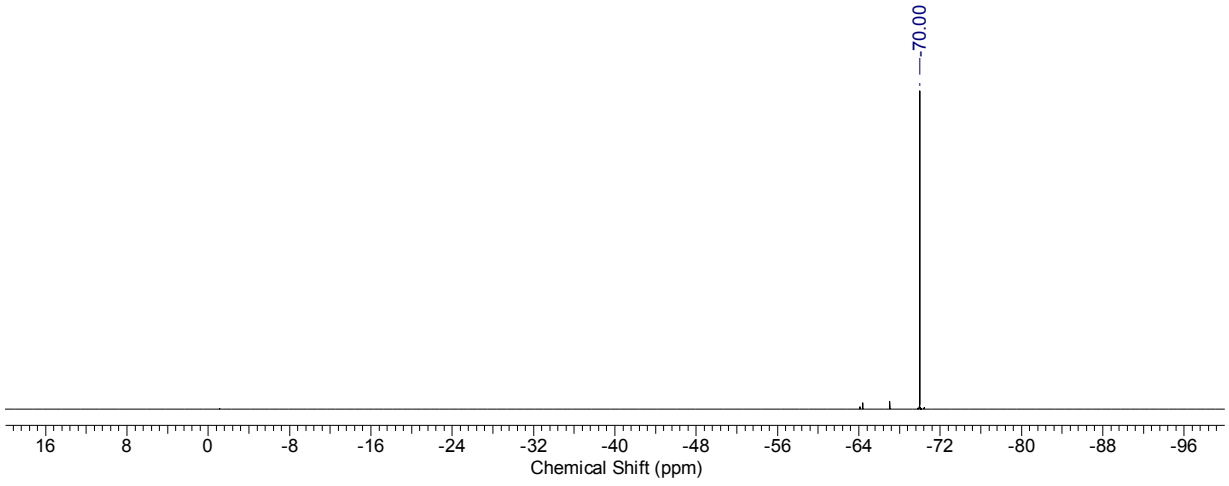
^{1}H spectrum of **3-141d**:



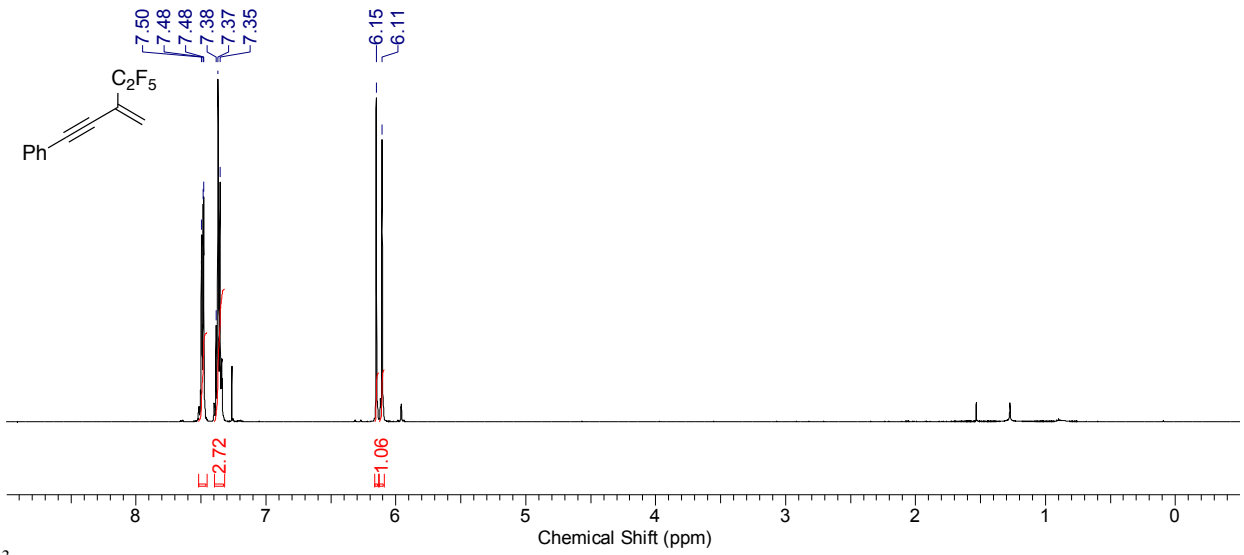
^{13}C spectrum of **3-141d**:



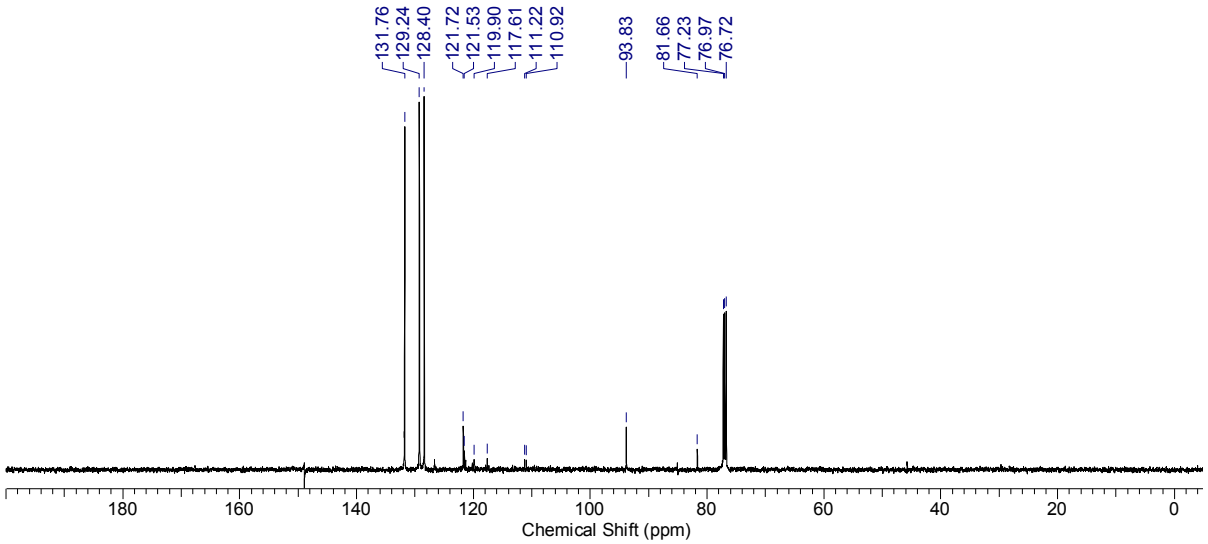
^{19}F spectrum of **3-141d**:



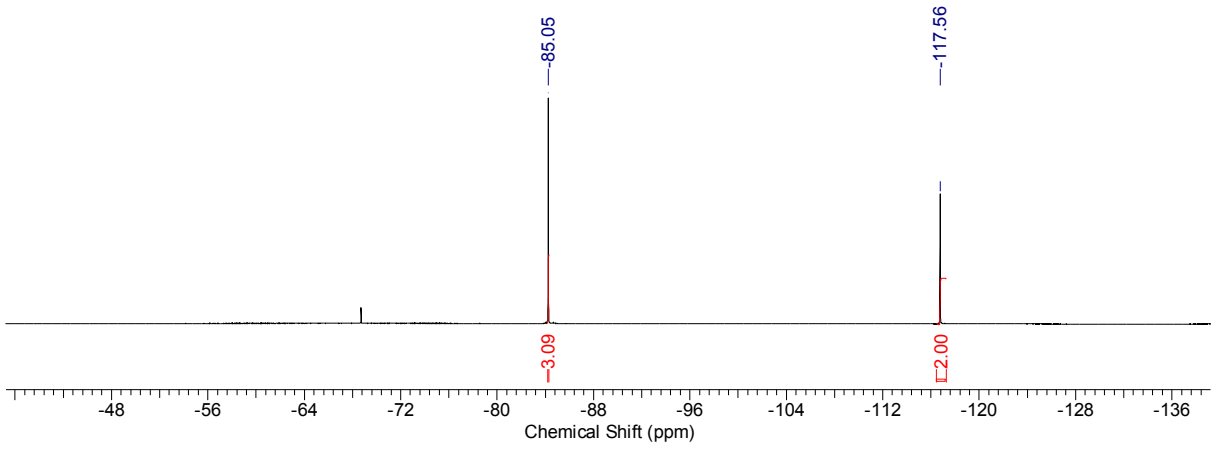
^{1}H spectrum of **3-141b**:



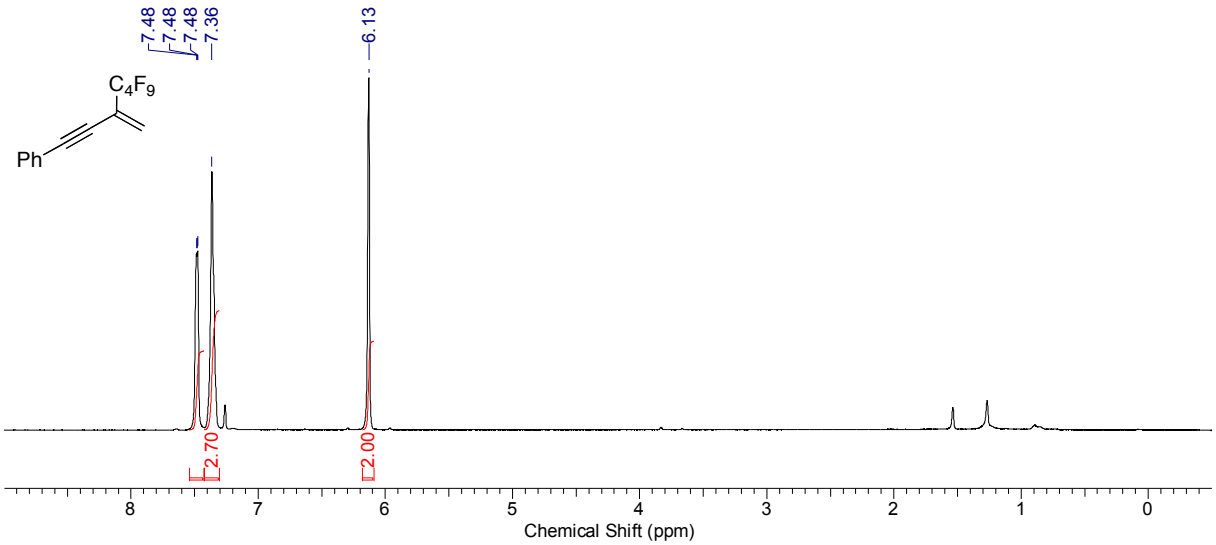
^{13}C spectrum of **3-141b**:



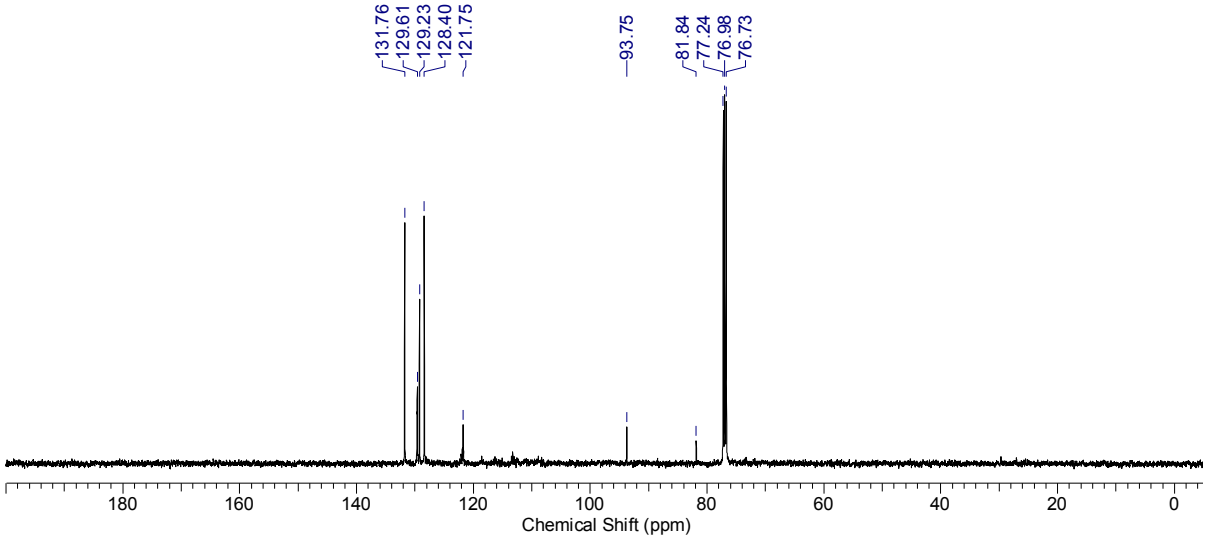
^{19}F spectrum of **3-141b**:



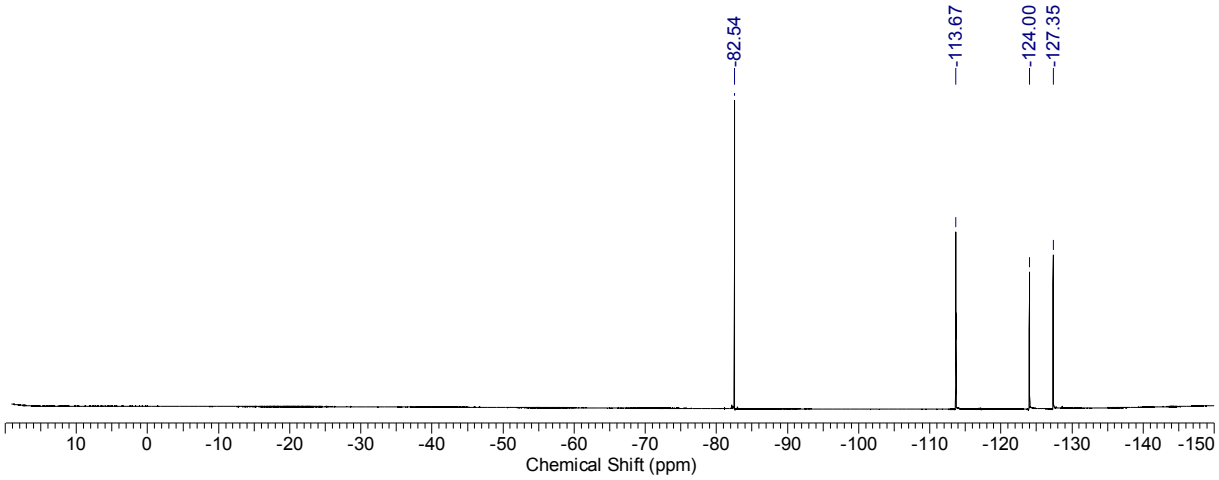
^{1}H spectrum of **3-141c**:



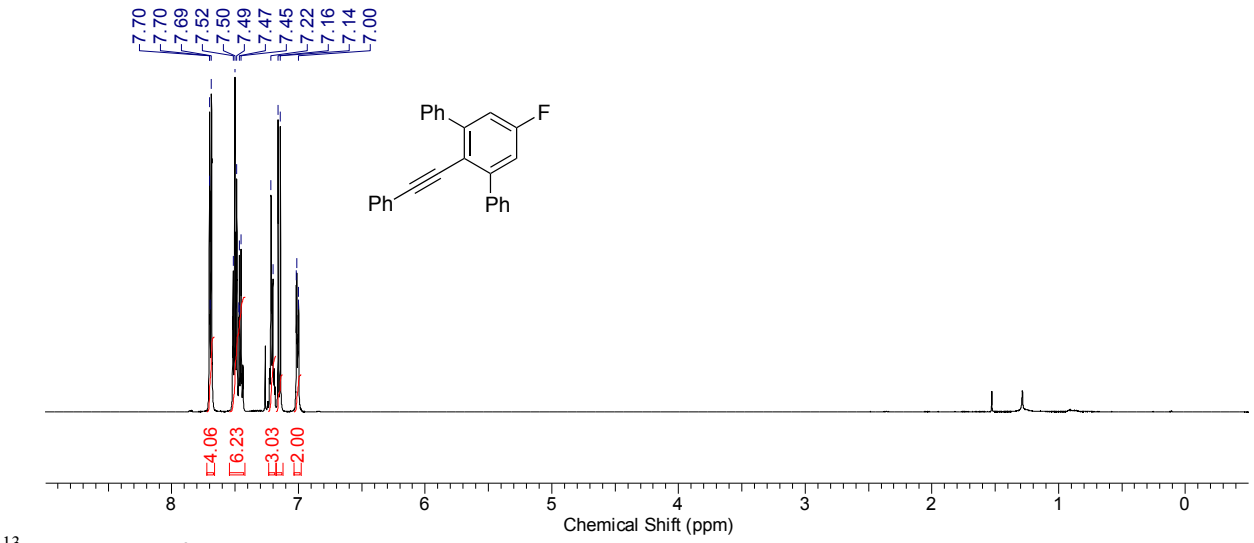
^{13}C spectrum of **3-141c**:



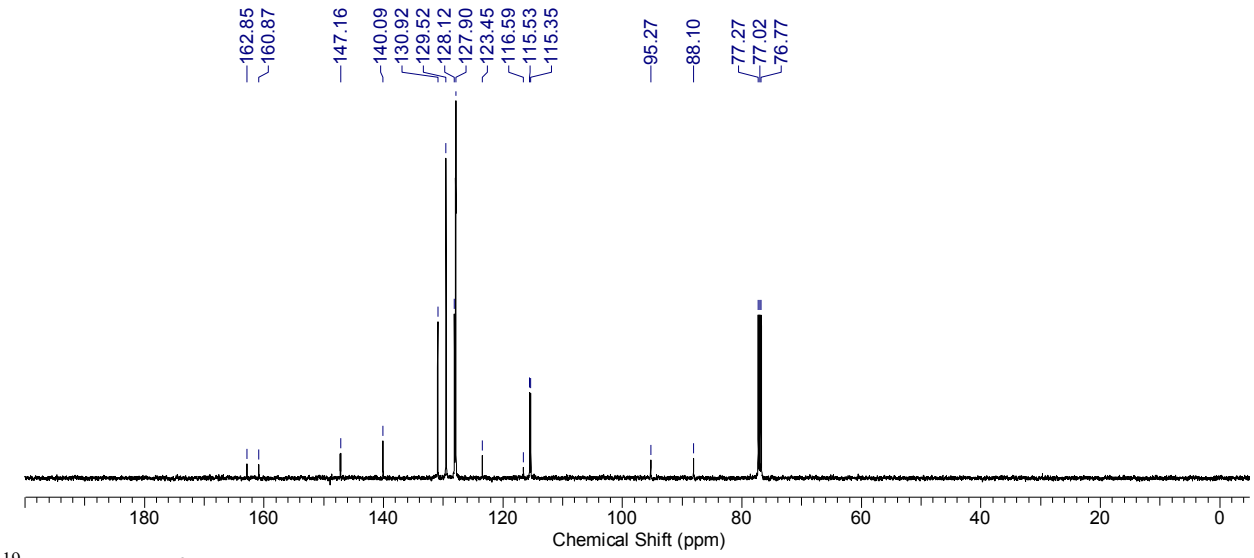
^{19}F spectrum of **3-141c**:



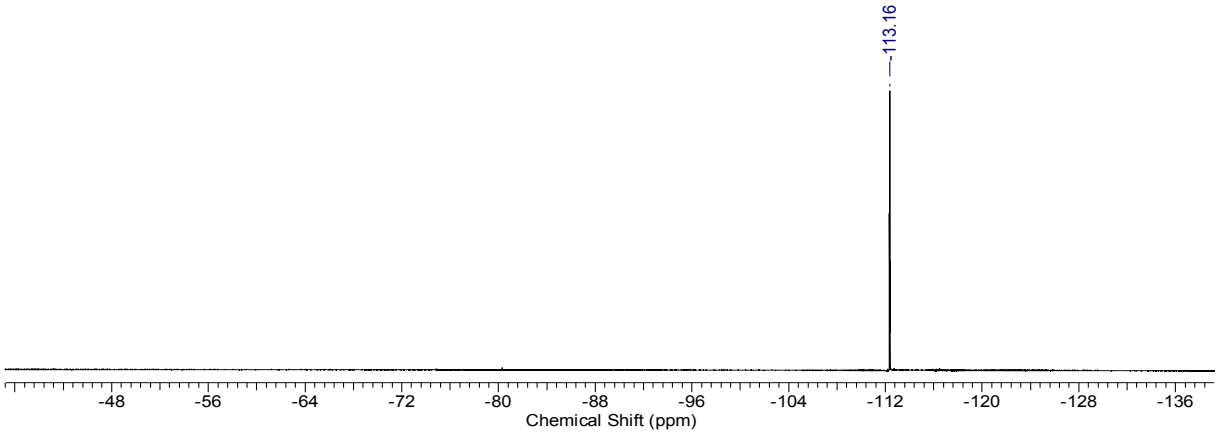
^{1}H spectrum of **3-01aa**:



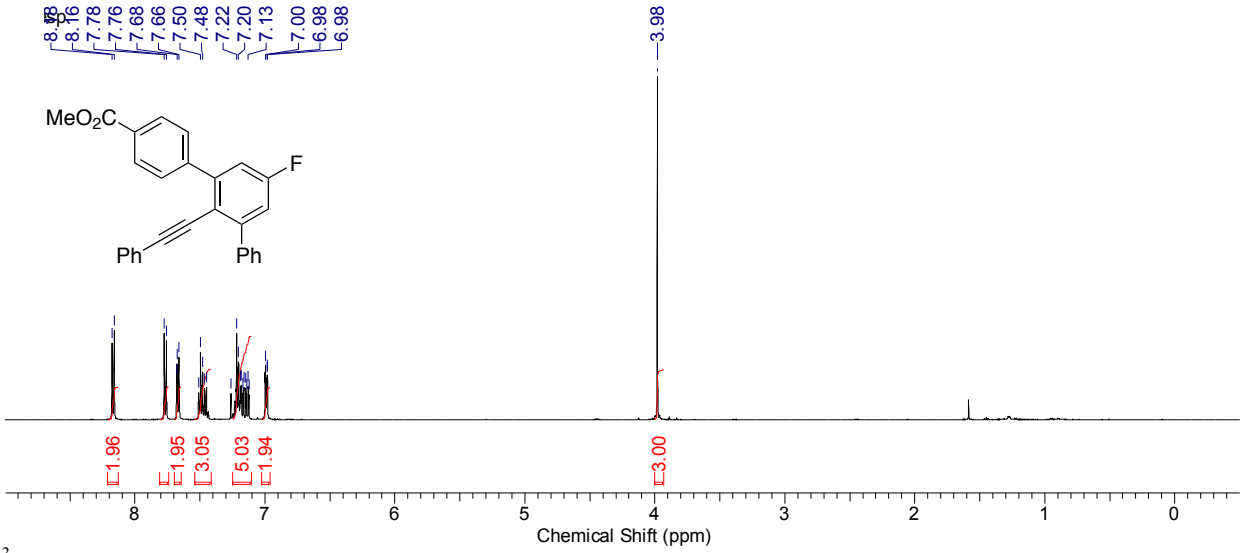
^{13}C spectrum of **3-01aa**:



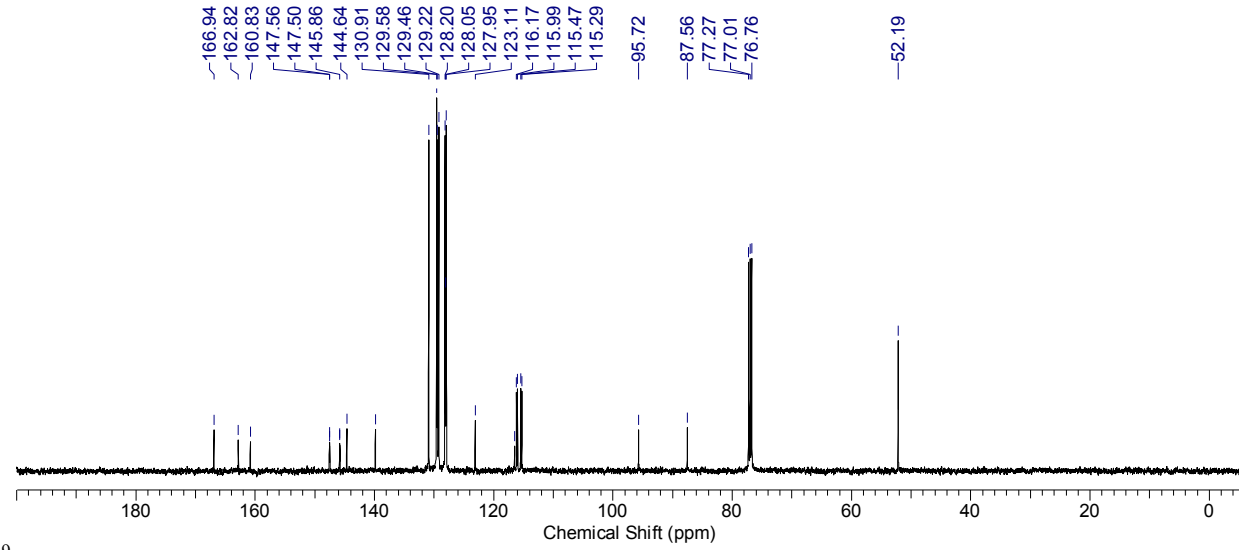
^{19}F spectrum of **3-01aa**:



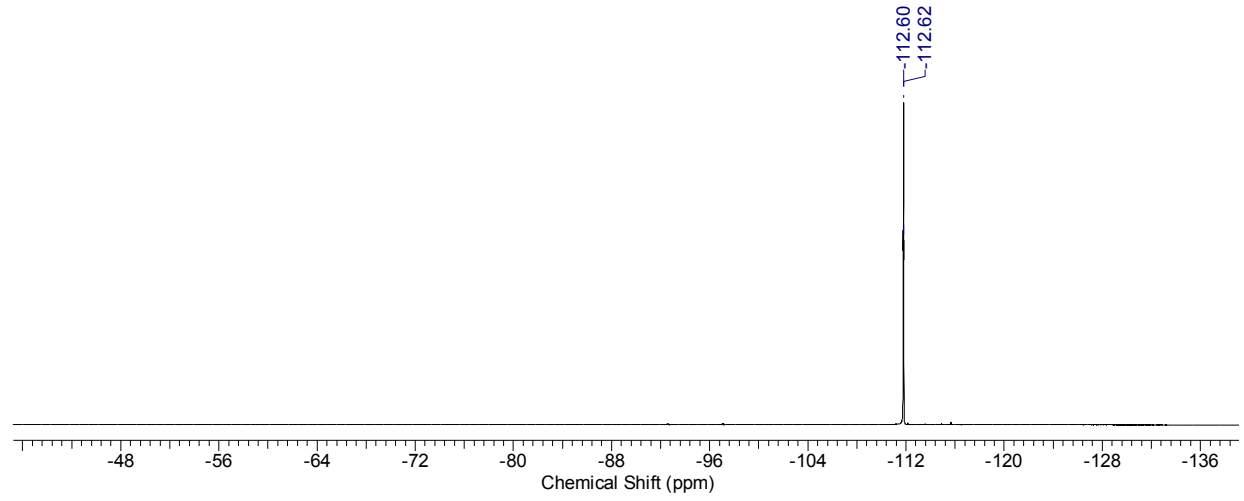
^{1}H spectrum of **3-01ba**:



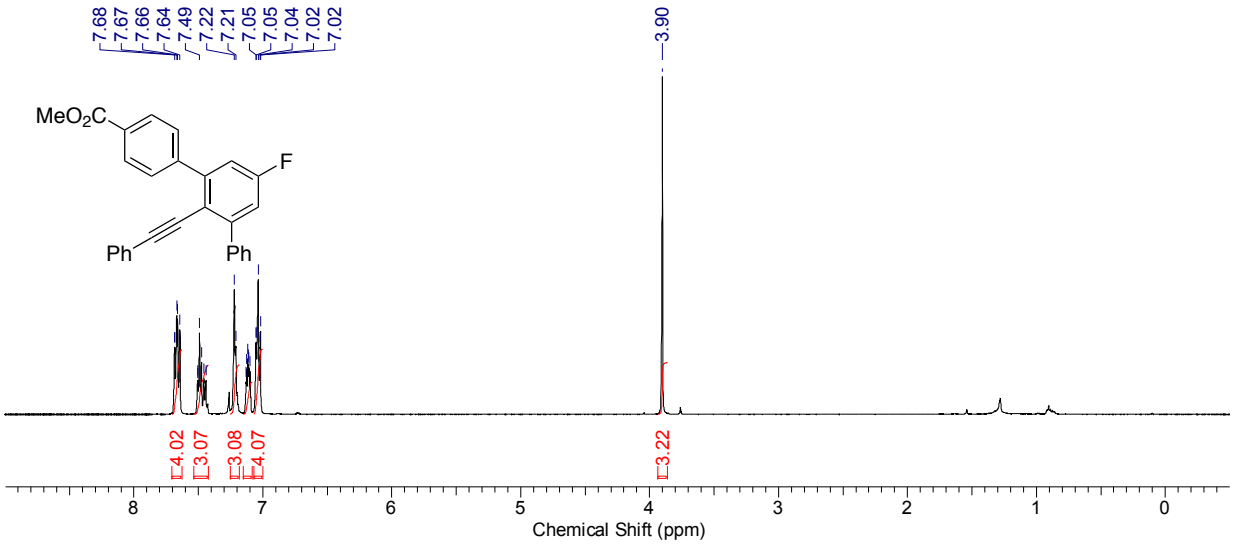
^{13}C spectrum of **3-01ba**:



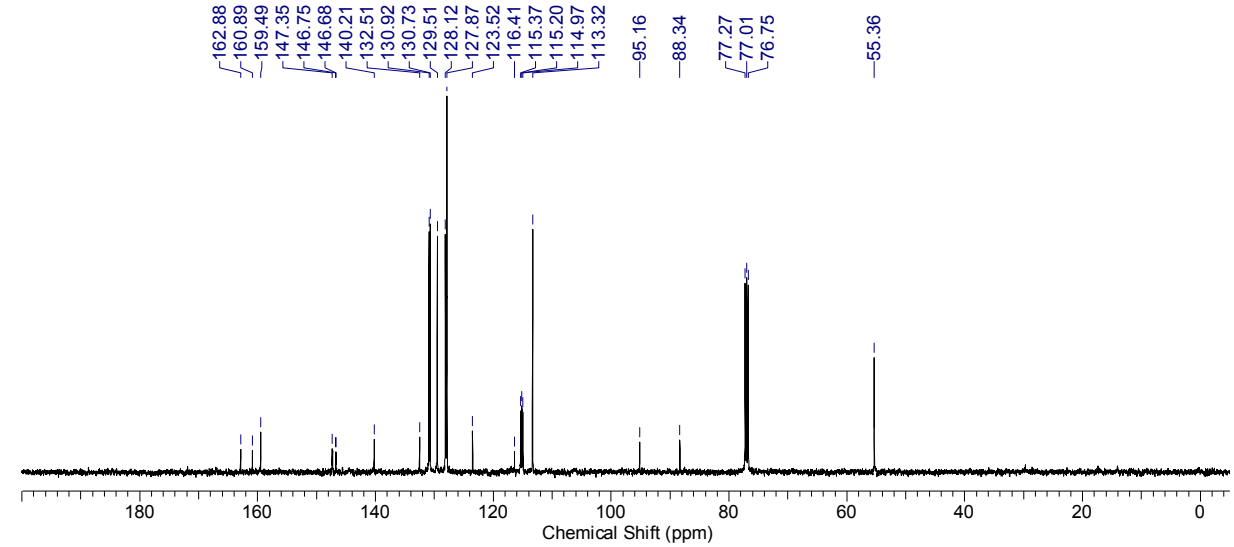
^{19}F spectrum of **3-01ba**:



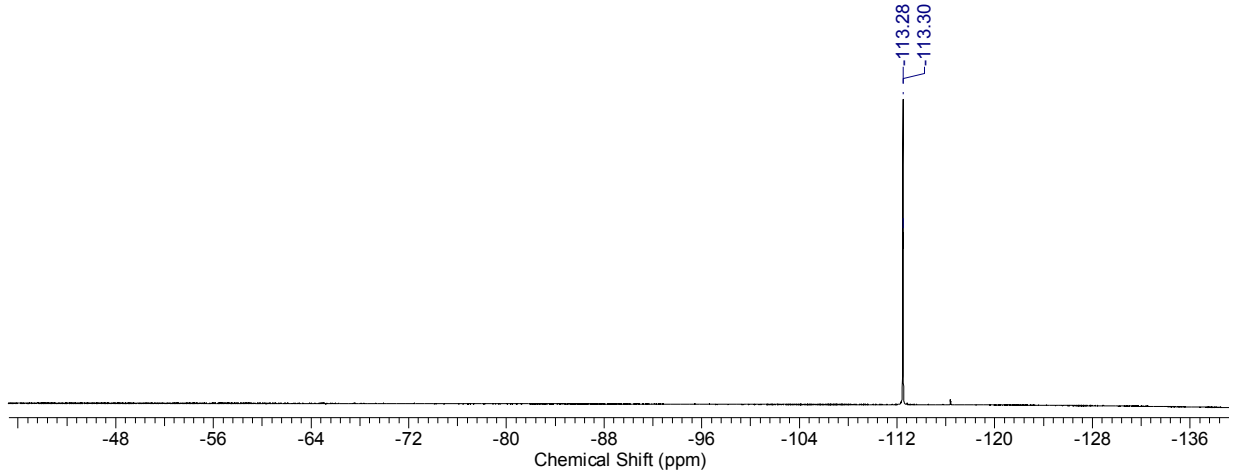
^{1}H spectrum of **3-01ca**:



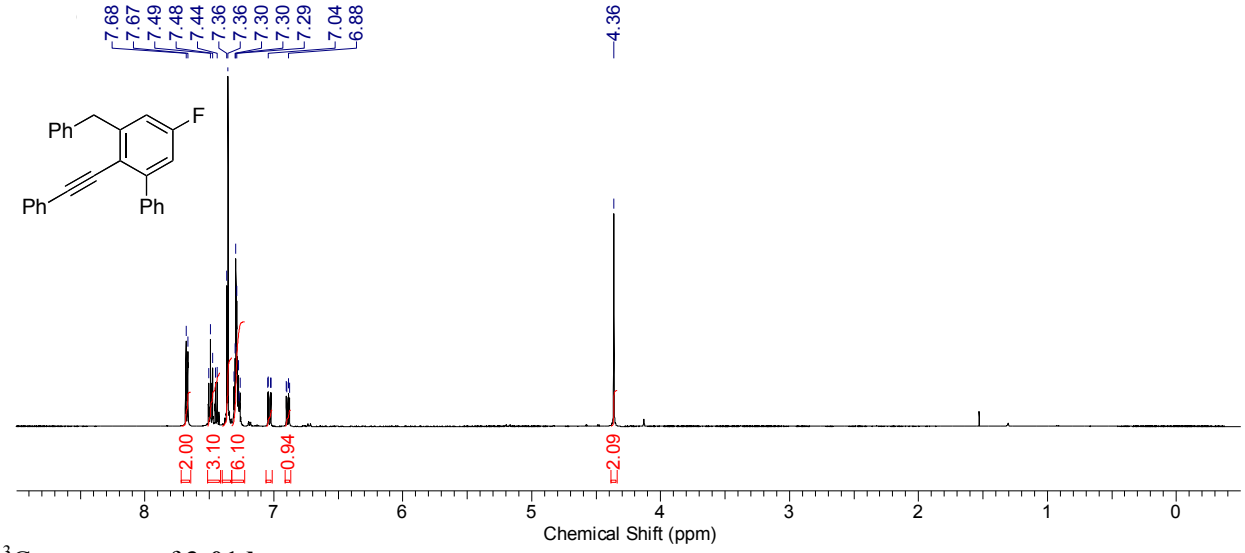
^{13}C spectrum of **3-01ca**:



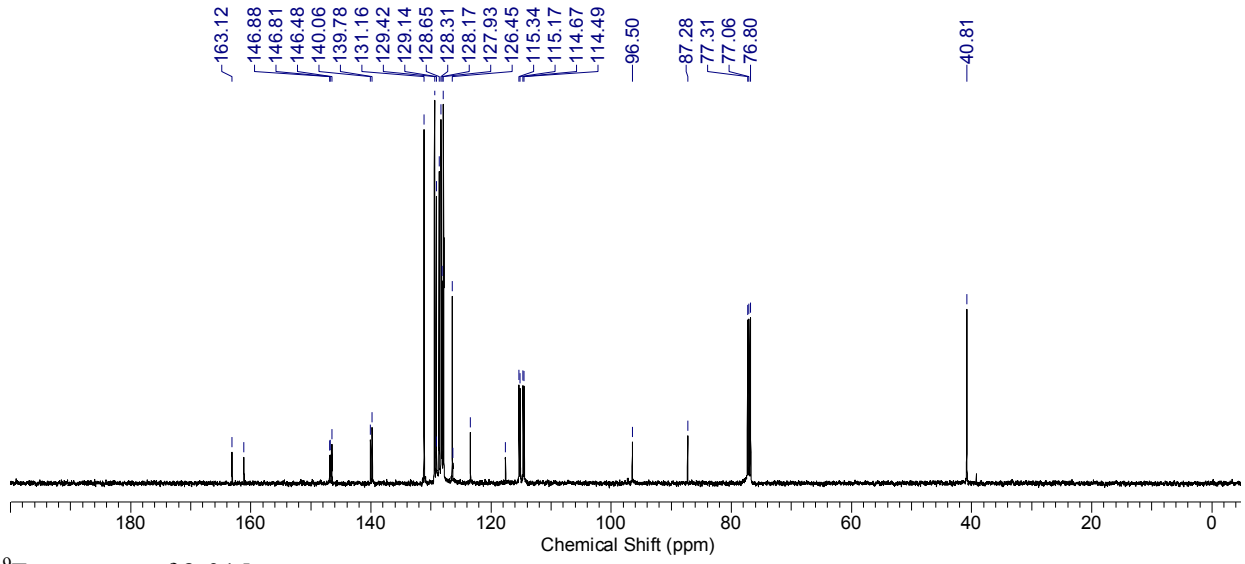
^{19}F spectrum of **3-01ca**:



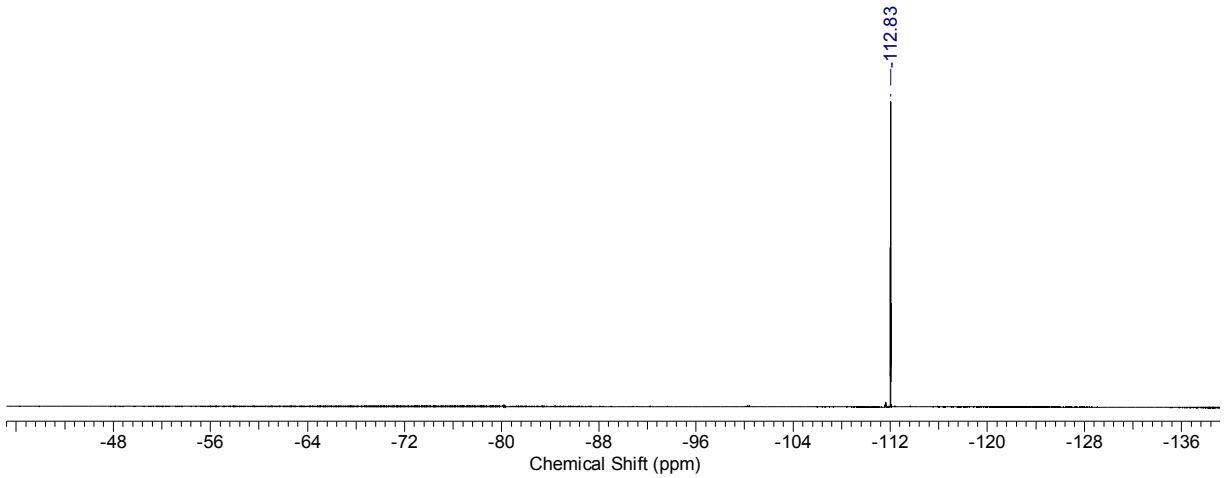
^{1}H spectrum of **3-01da**:



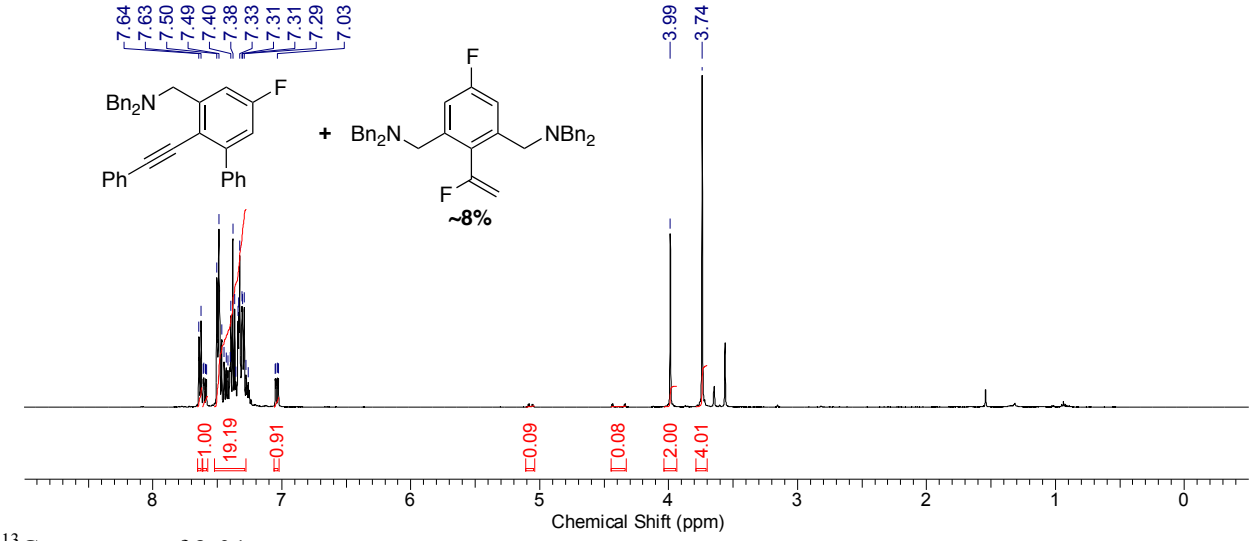
^{13}C spectrum of **3-01da**:



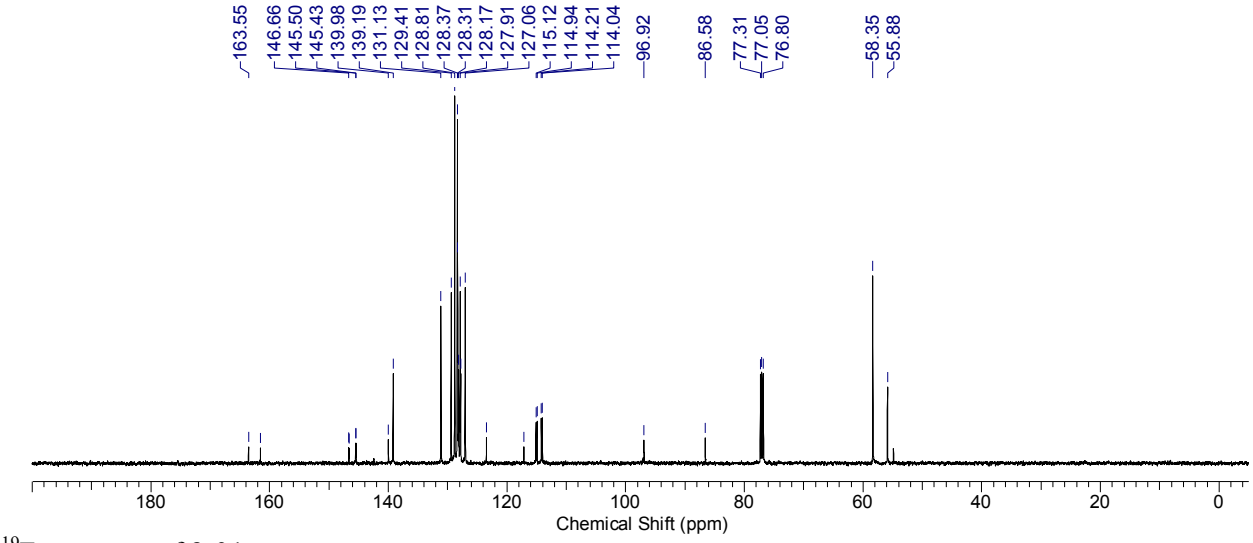
^{19}F spectrum of **3-01da**:



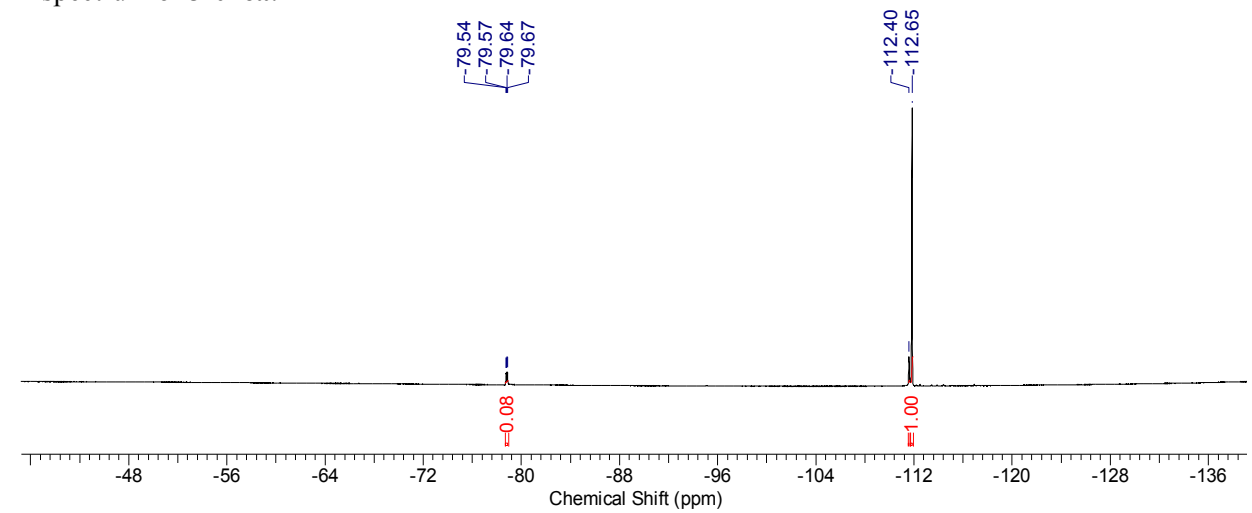
^{1}H spectrum of **3-01ea**:



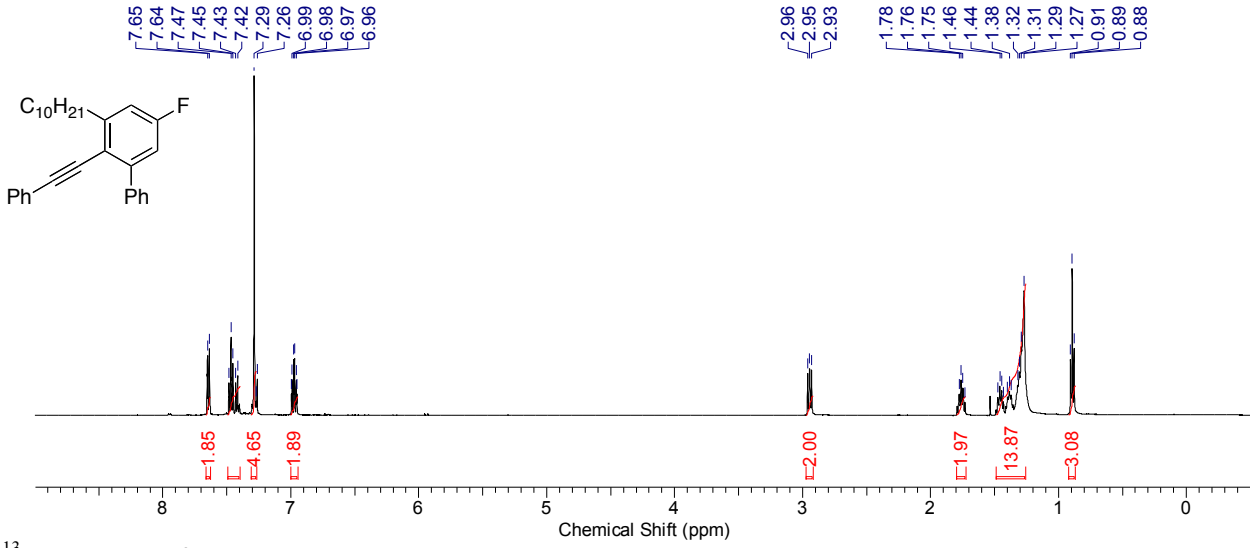
^{13}C spectrum of **3-01ea**:



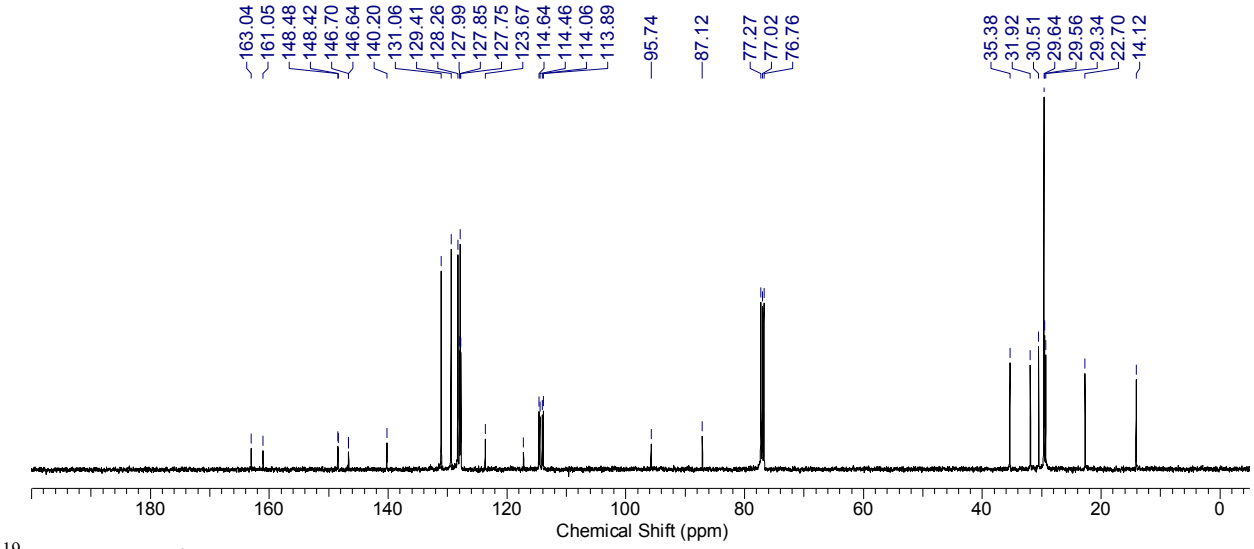
^{19}F spectrum of **3-01ea**:



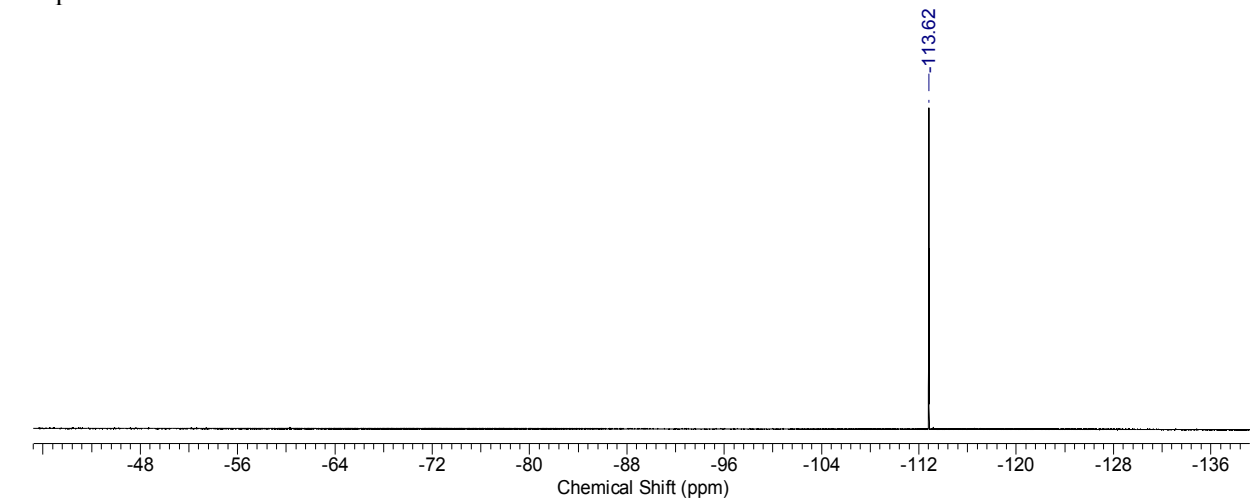
^{1}H spectrum of **3-01fa**:



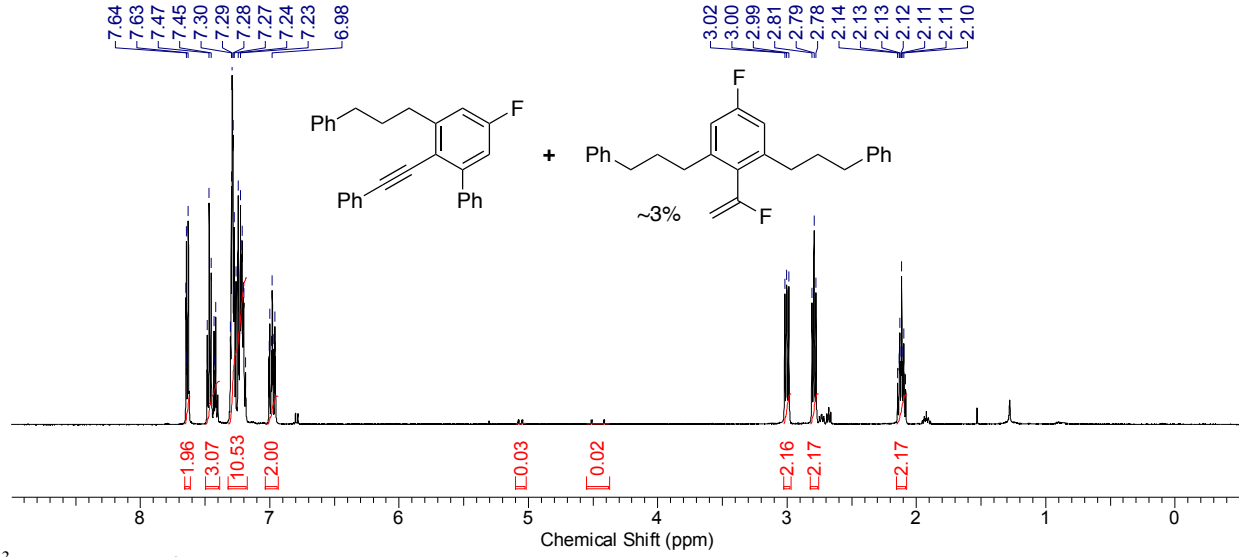
^{13}C spectrum of **3-01fa**:



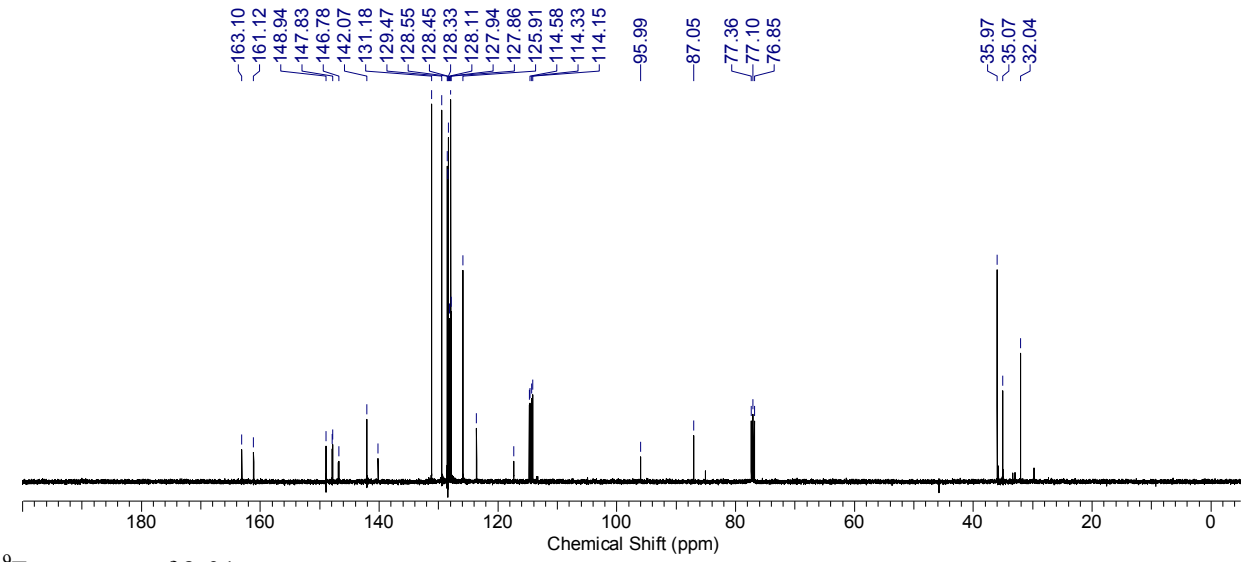
^{19}F spectrum of **3-01fa**:



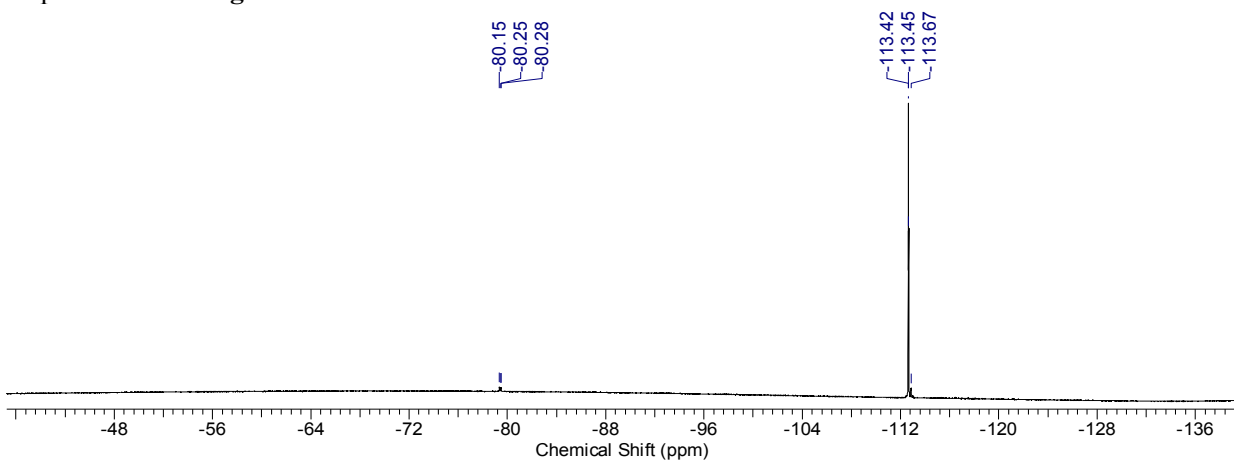
^{1}H spectrum of **3-01ga**:



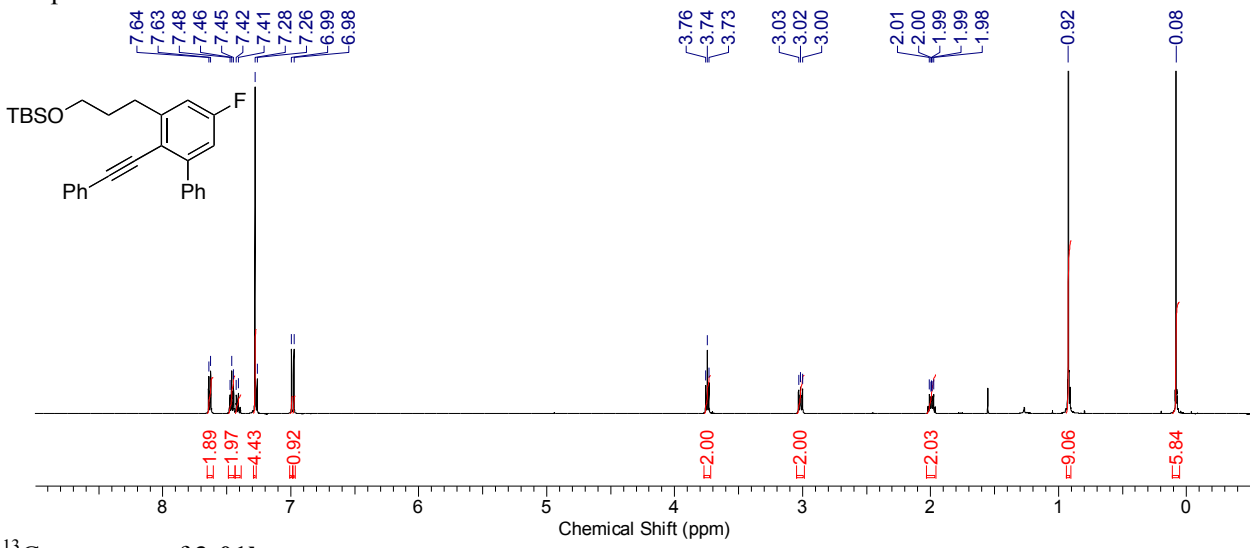
^{13}C spectrum of **3-01ga**:



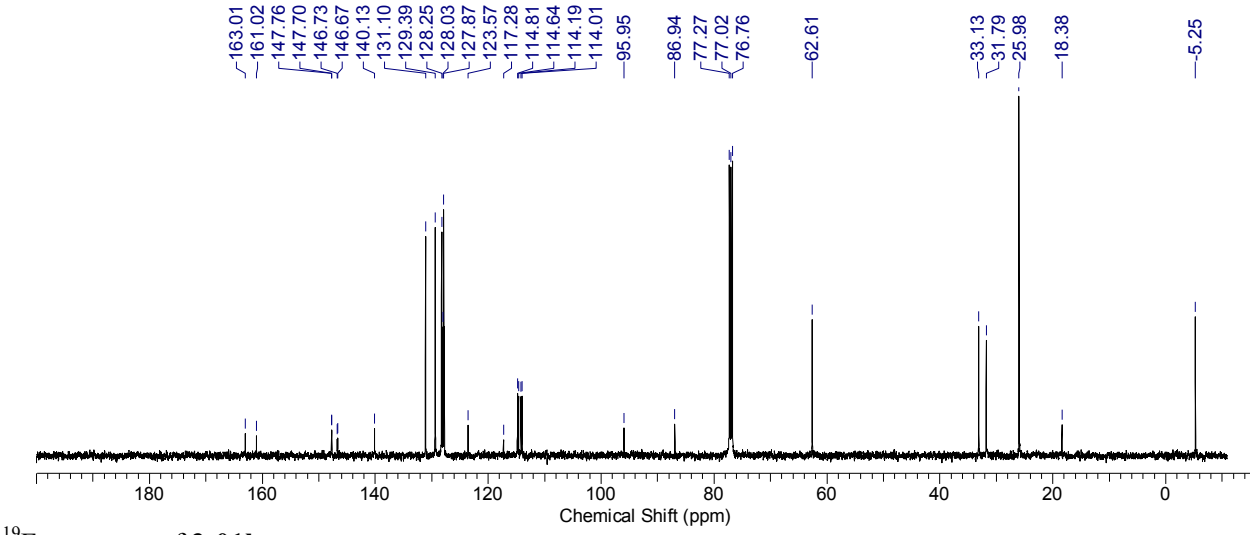
^{19}F spectrum of **3-01ga**:



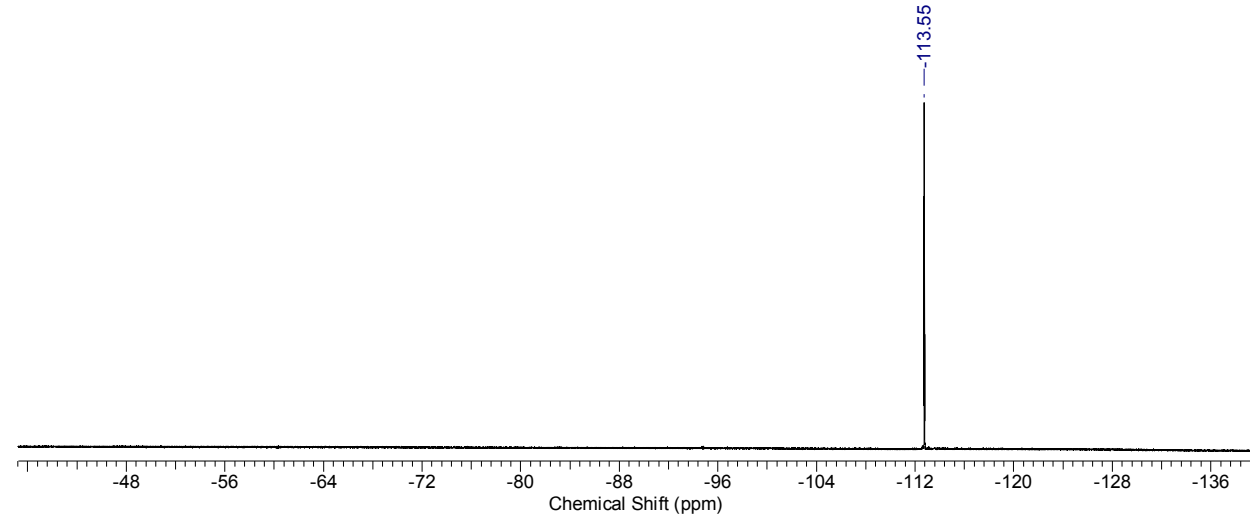
^{1}H spectrum of **3-01ha**:



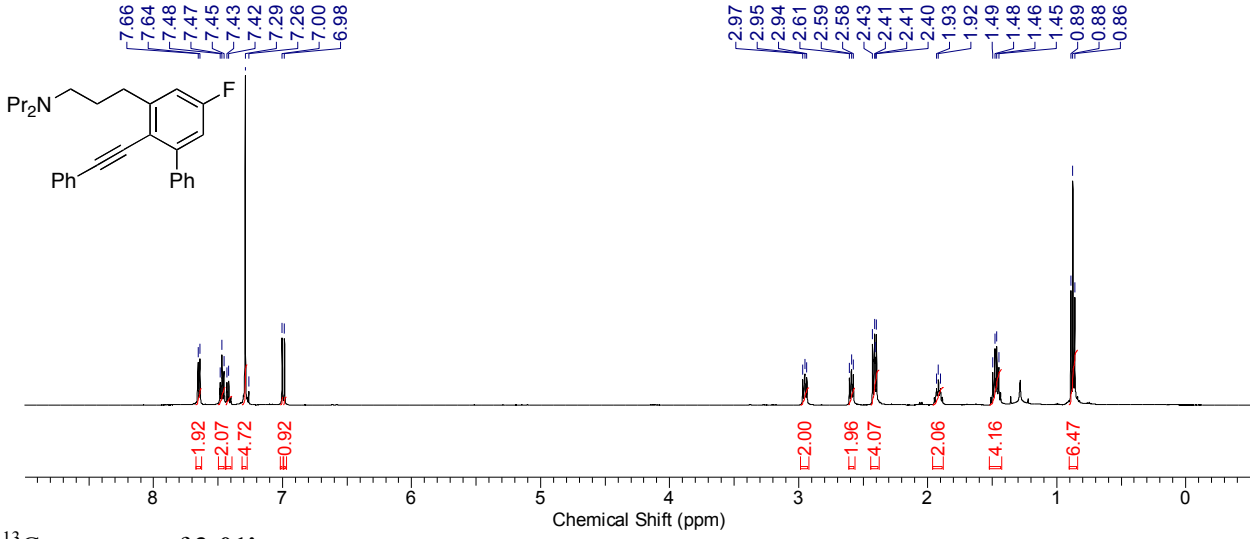
^{13}C spectrum of **3-01ha**:



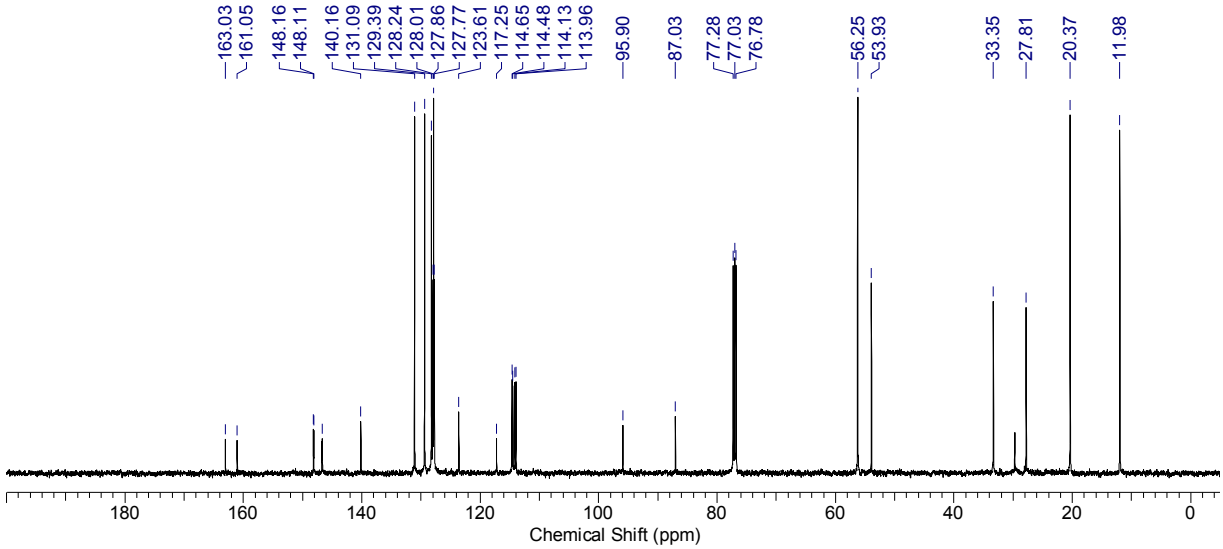
^{19}F spectrum of **3-01ha**:



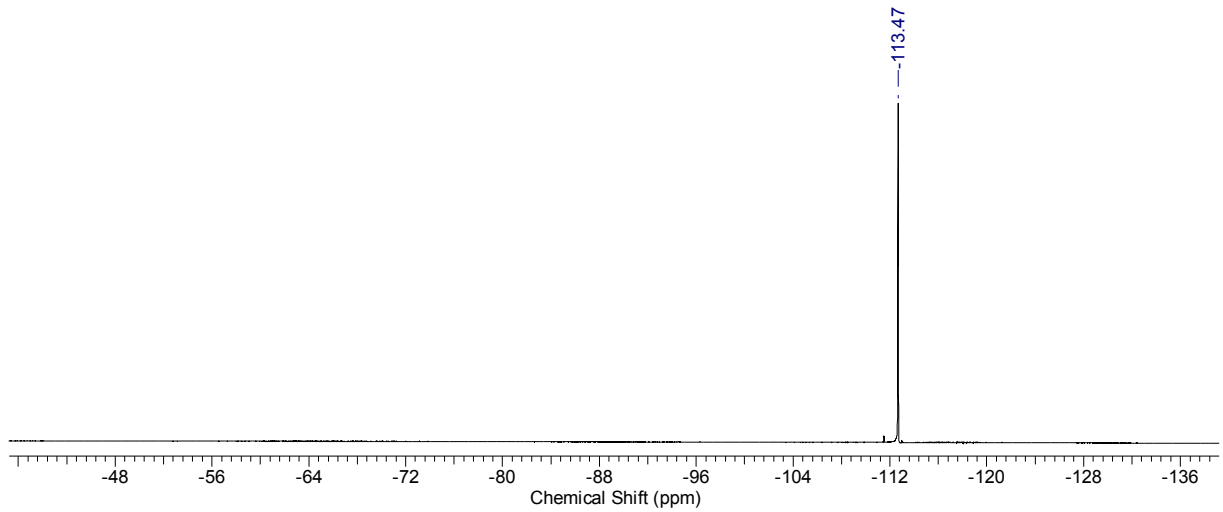
^{1}H spectrum of **3-01ia**:



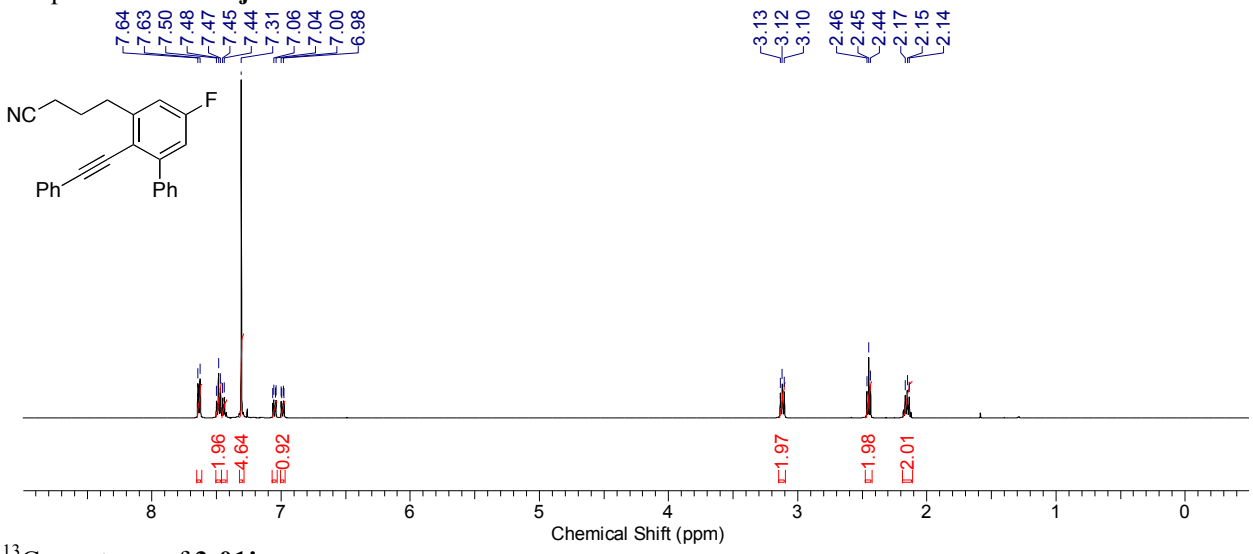
^{13}C spectrum of **3-01ia**:



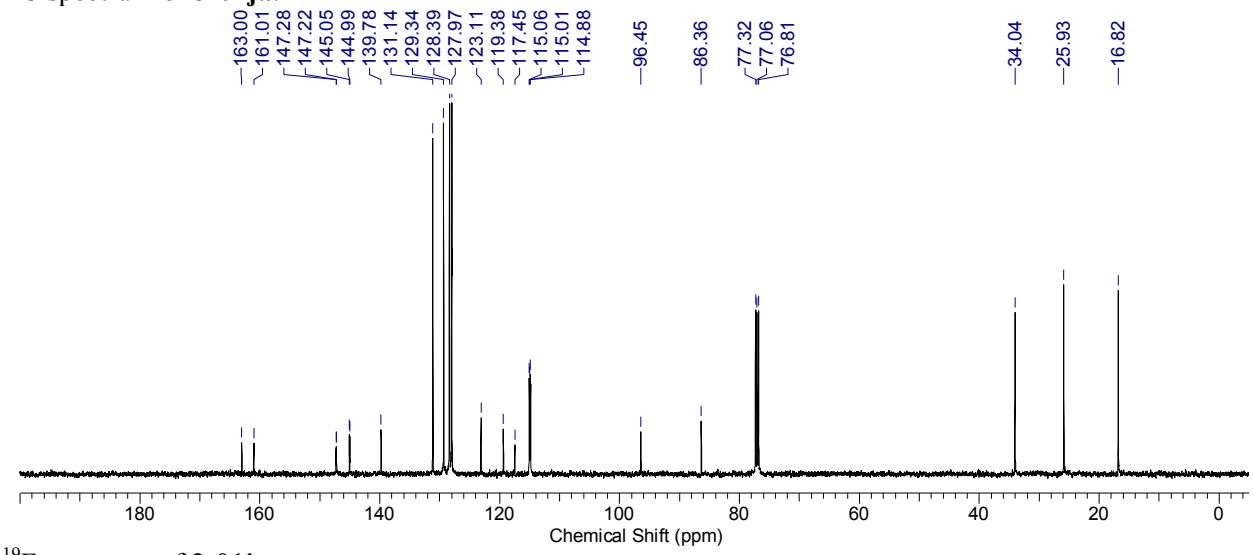
^{19}F spectrum of **3-01ia**:



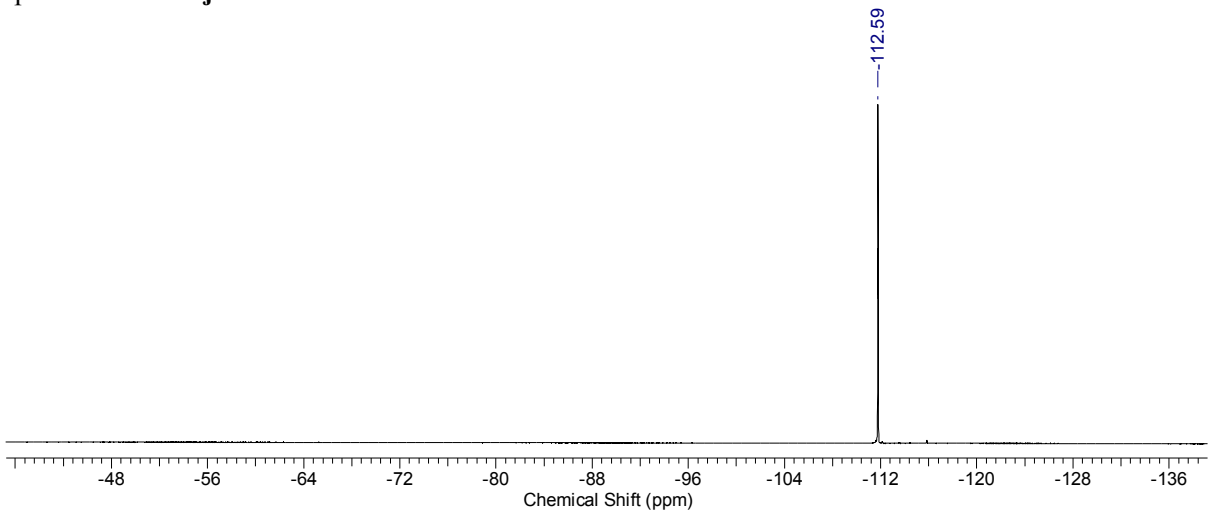
^{1}H spectrum of **3-01ja**:



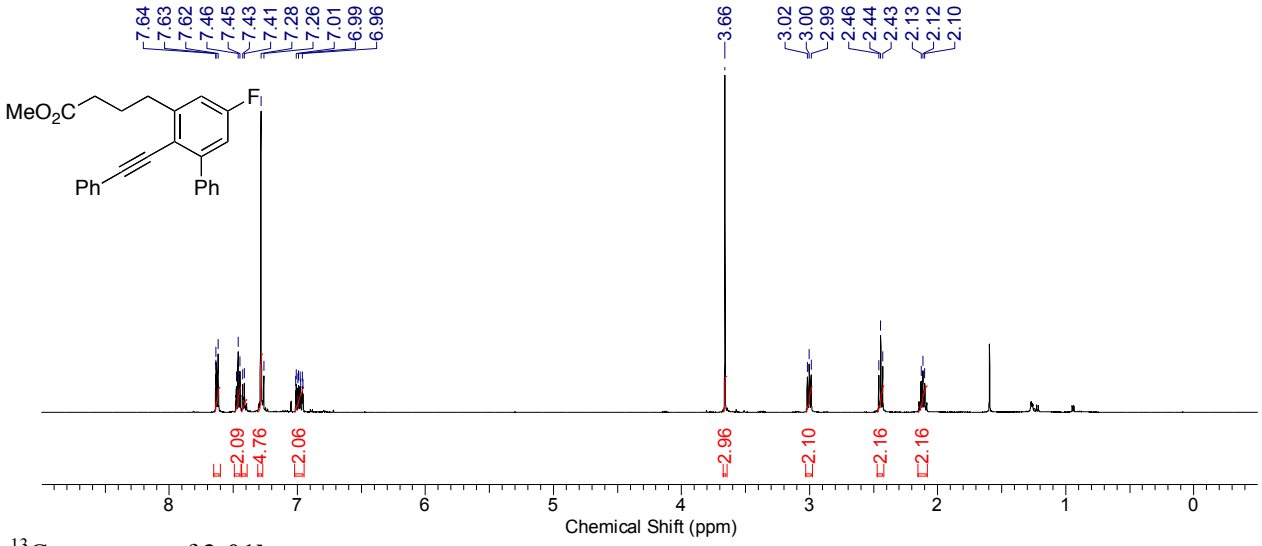
^{13}C spectrum of **3-01ja**:



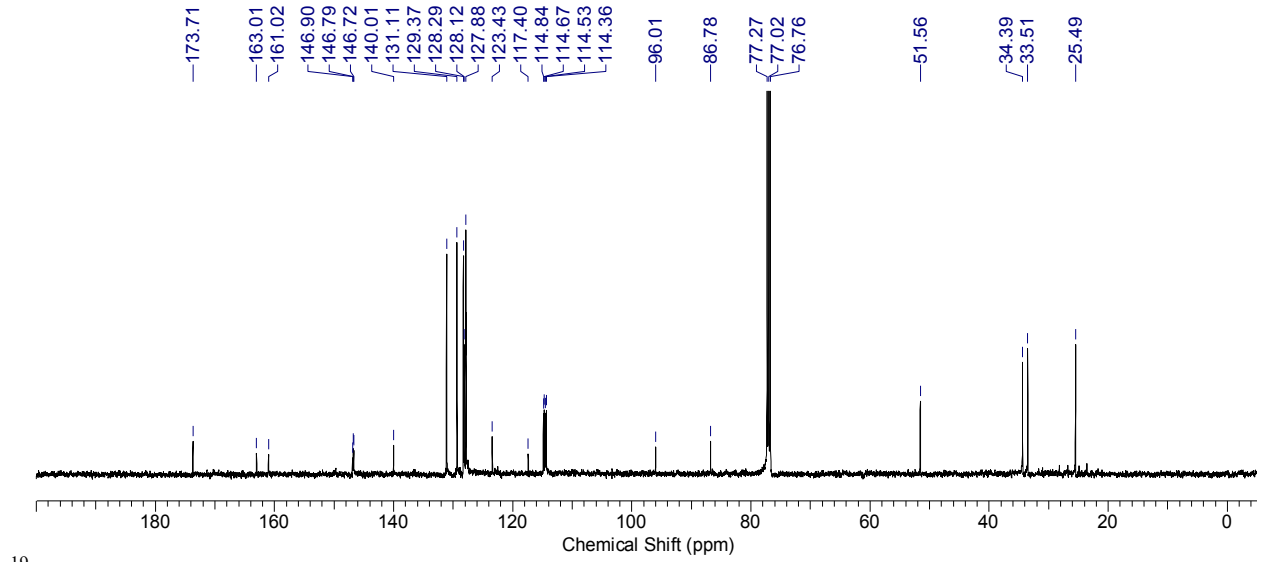
^{19}F spectrum of **3-01ja**:



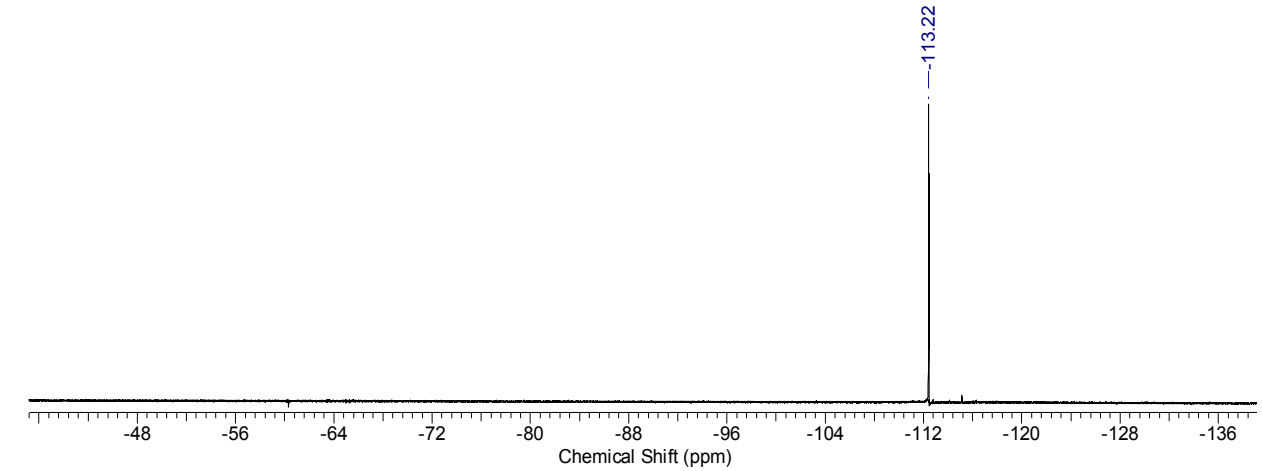
^{1}H spectrum of **3-01ka**:



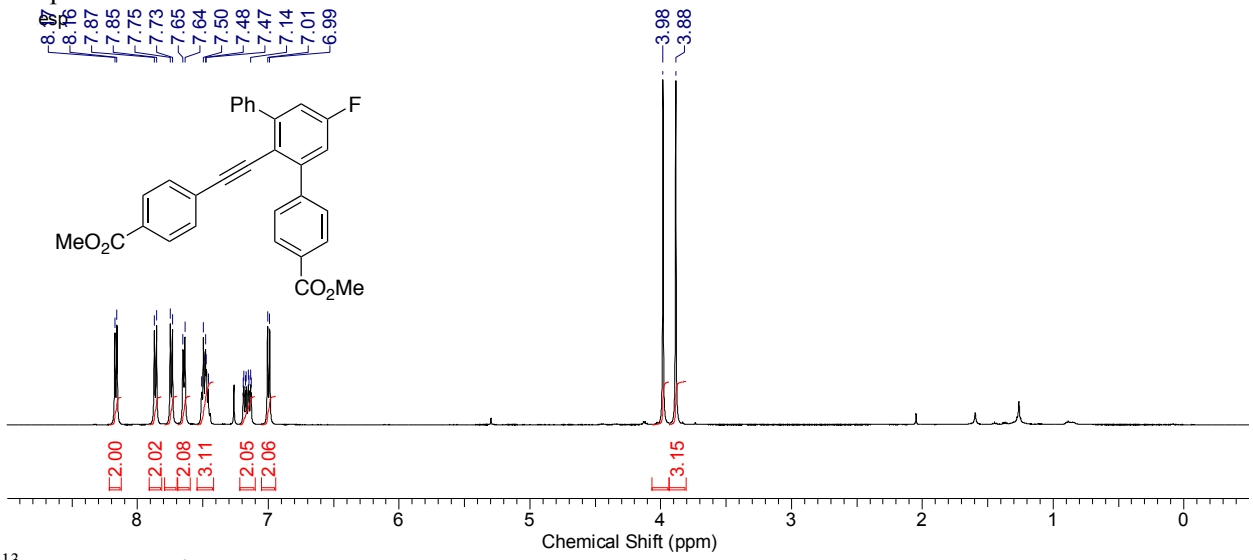
^{13}C spectrum of **3-01ka**:



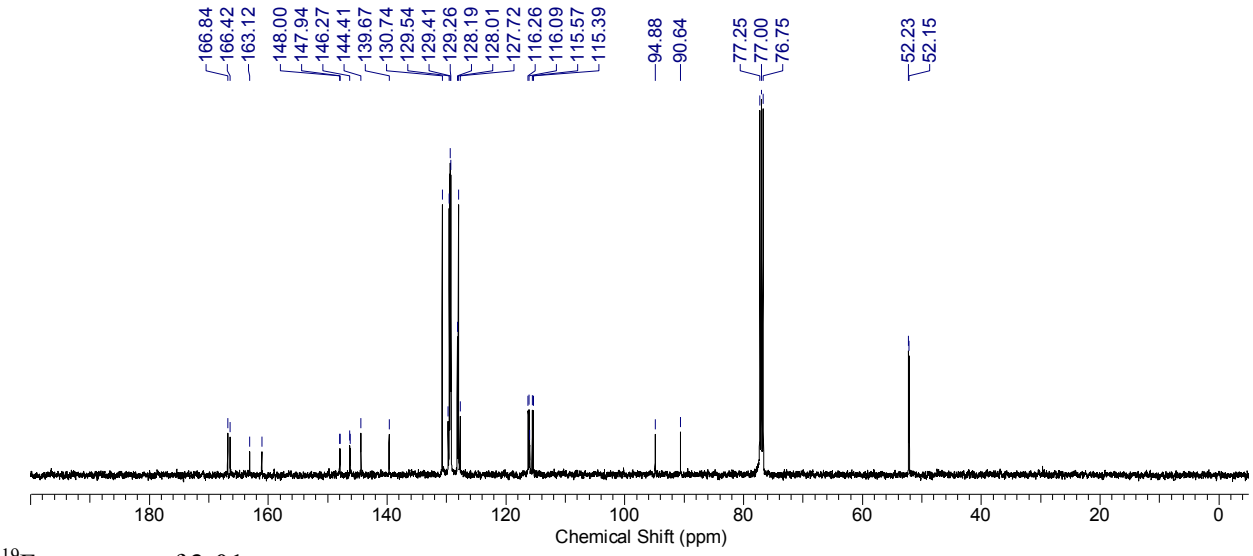
^{19}F spectrum of **3-01ka**:



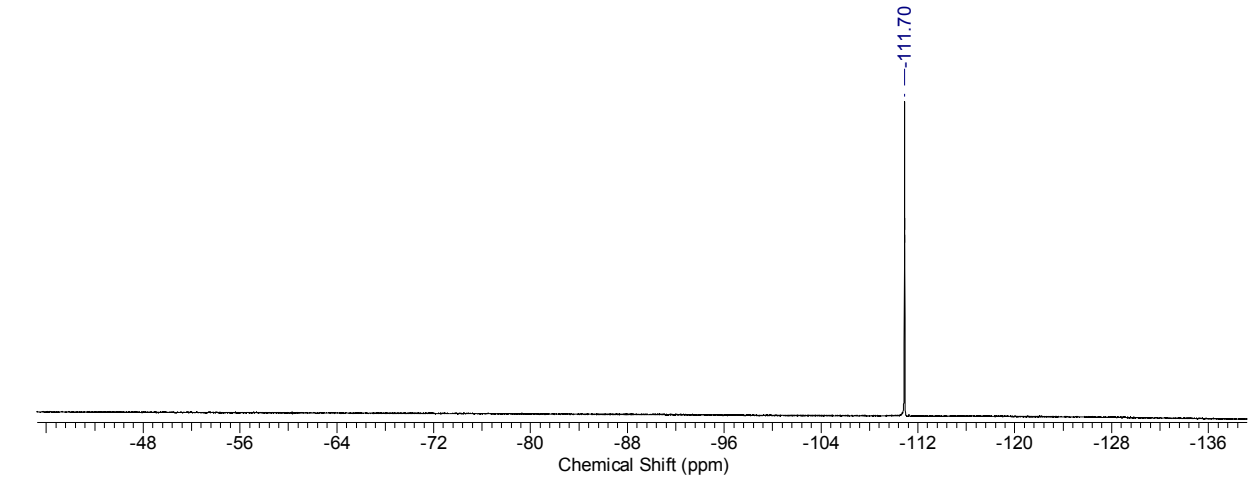
^{1}H spectrum of **3-01ac**:



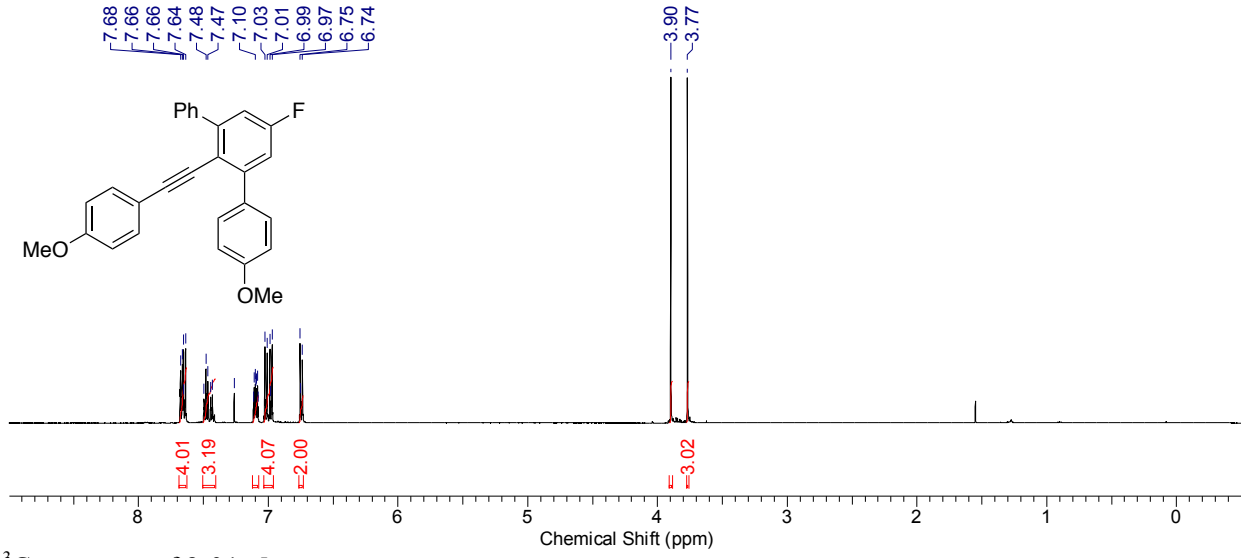
^{13}C spectrum of **3-01ac**:



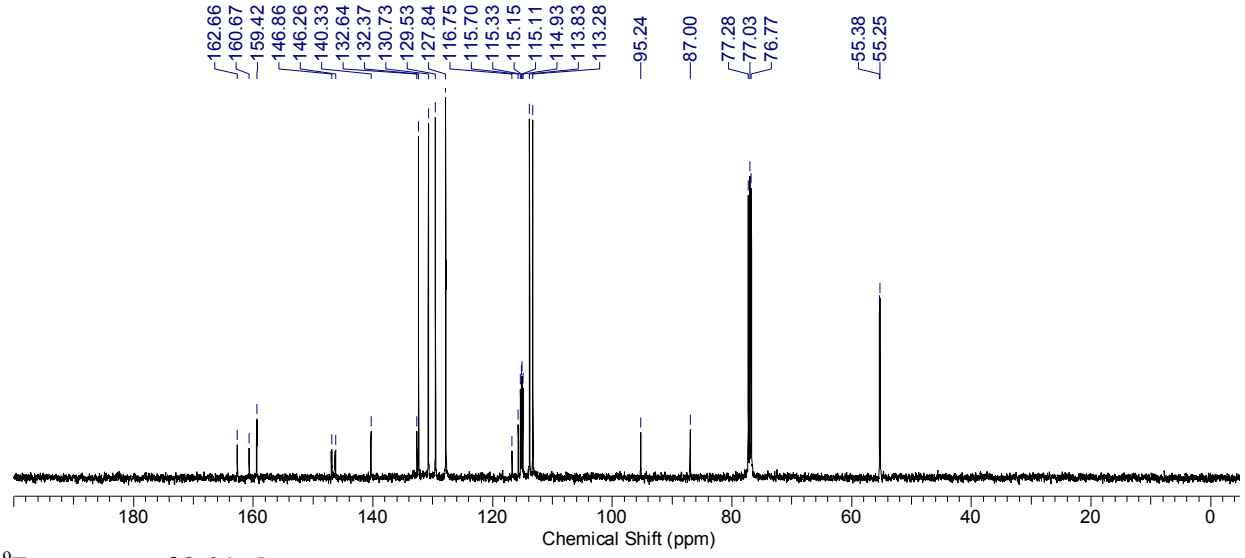
^{19}F spectrum of **3-01ac**:



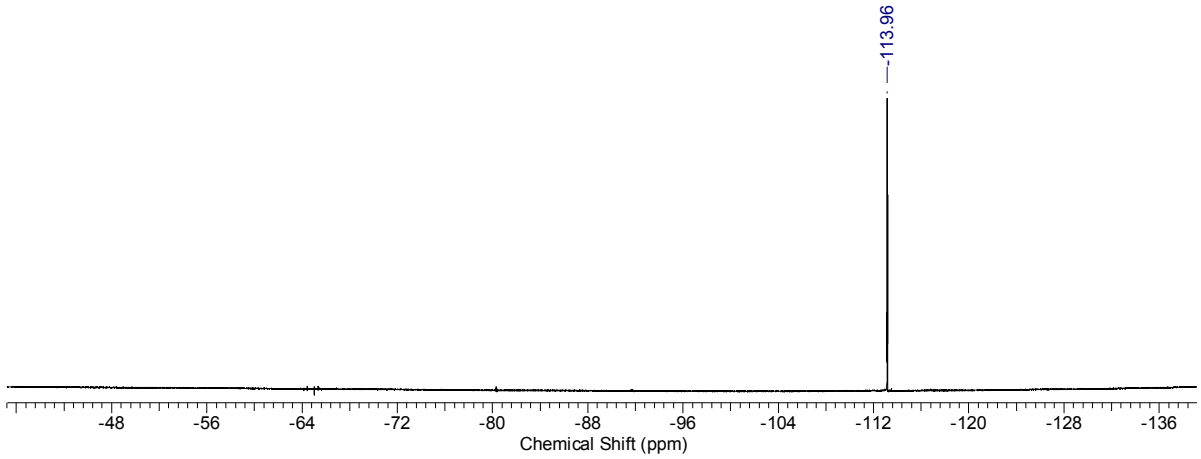
^{1}H spectrum of **3-01ad**:



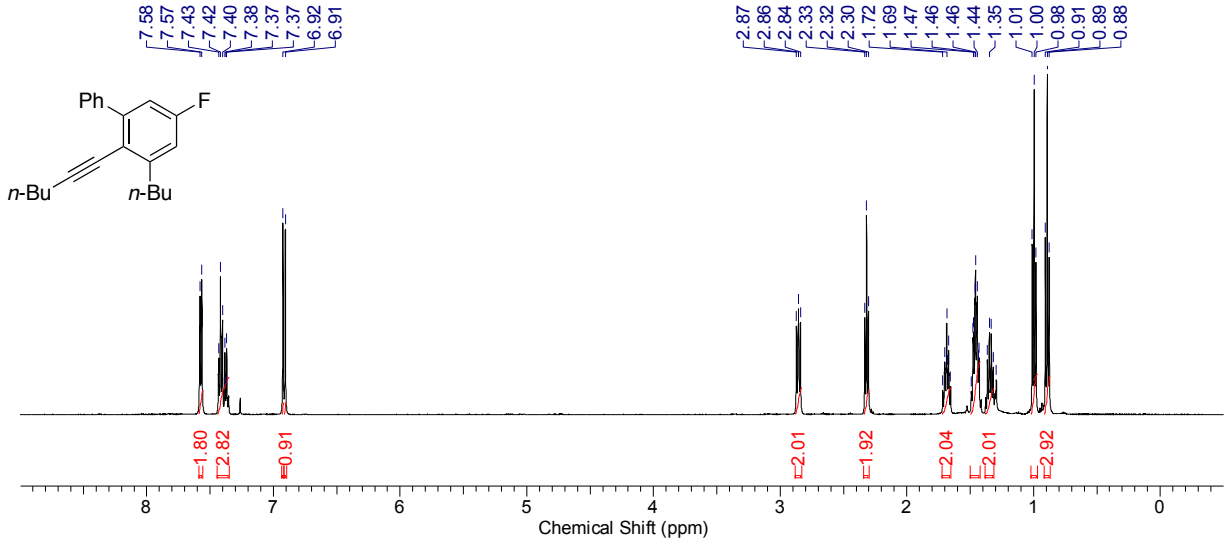
^{13}C spectrum of **3-01ad**:



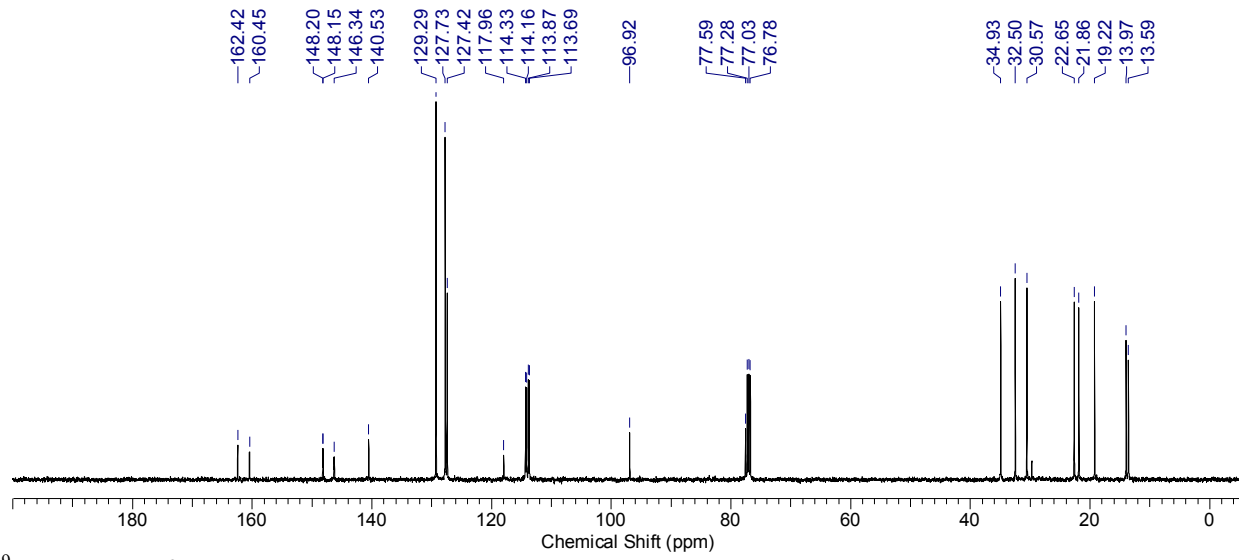
^{19}F spectrum of **3-01ad**:



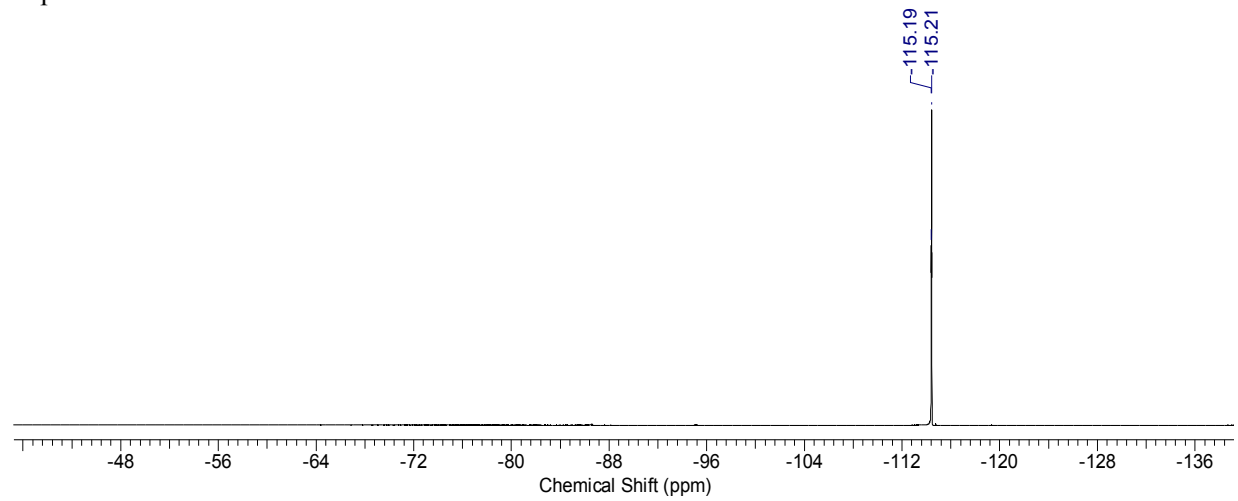
^{1}H spectrum of **3-01ab**:



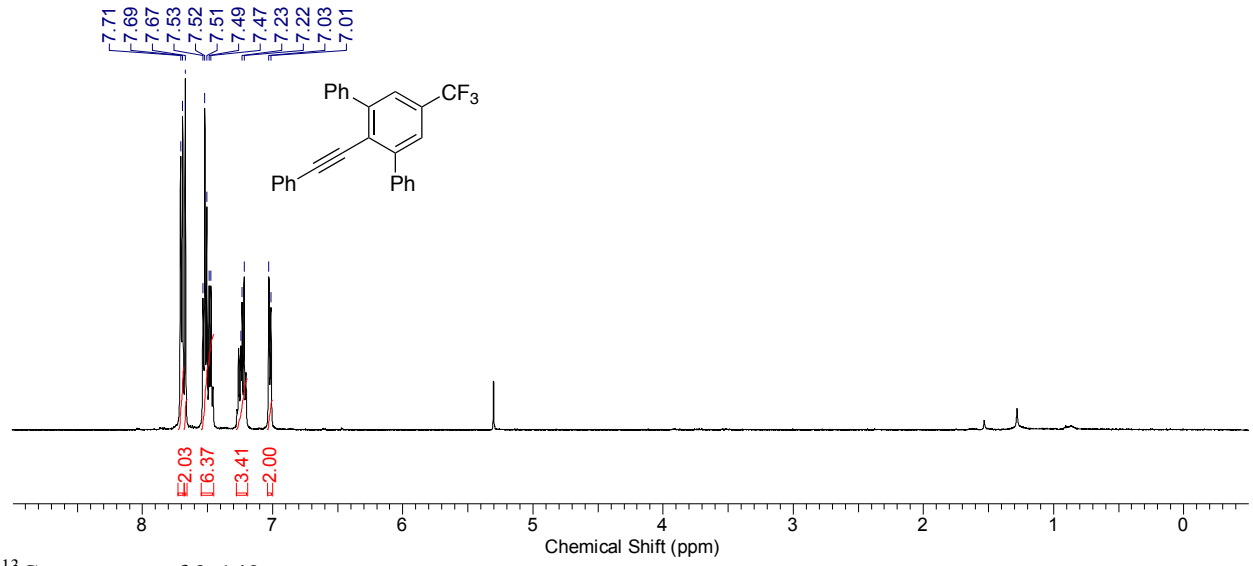
^{13}C spectrum of **3-01ab**:



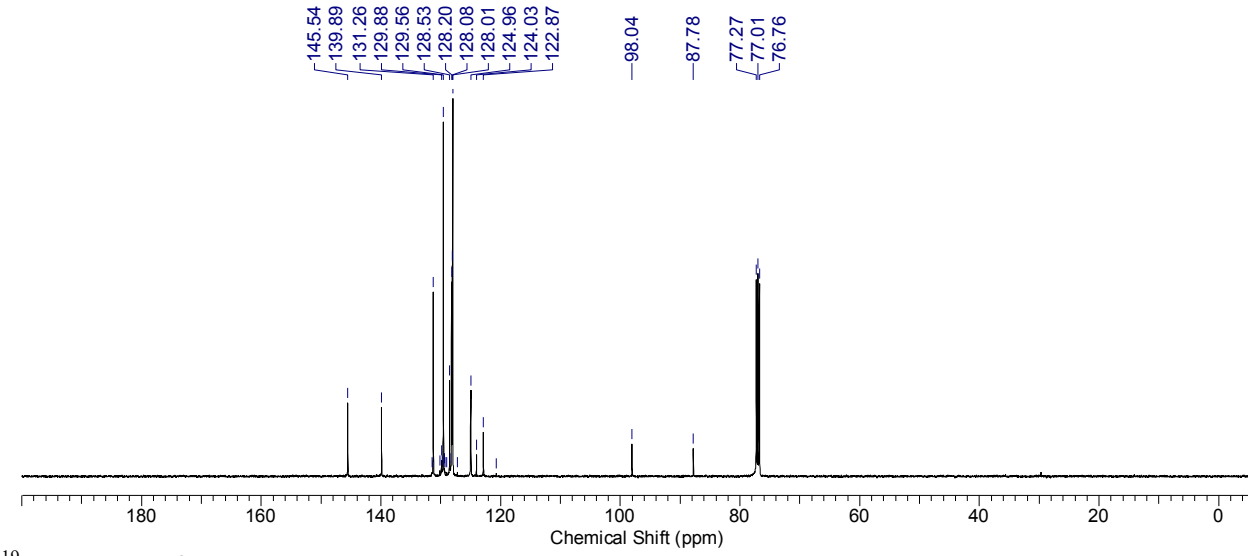
^{19}F spectrum of **3-01ab**:



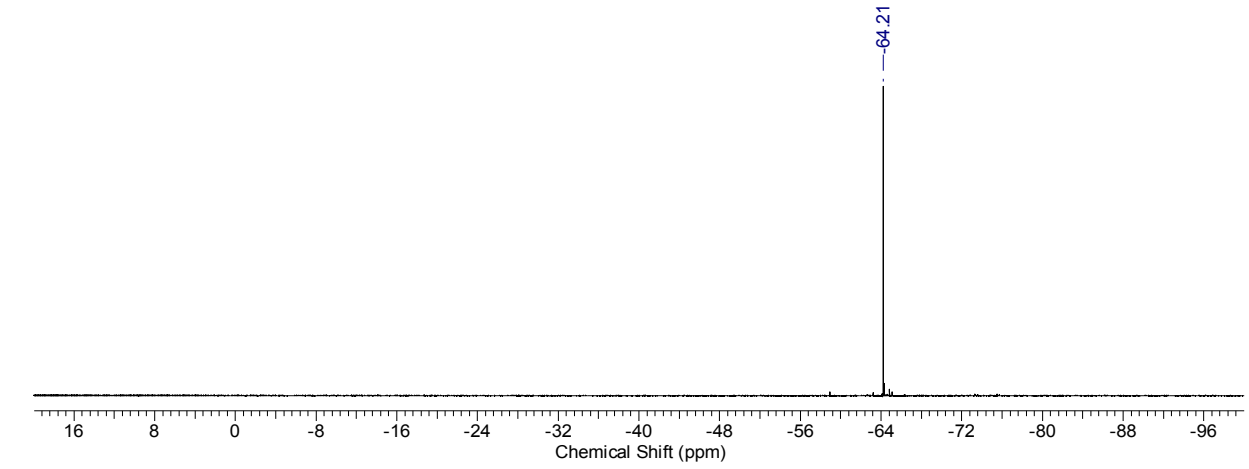
^{1}H spectrum of **3-142aa**:



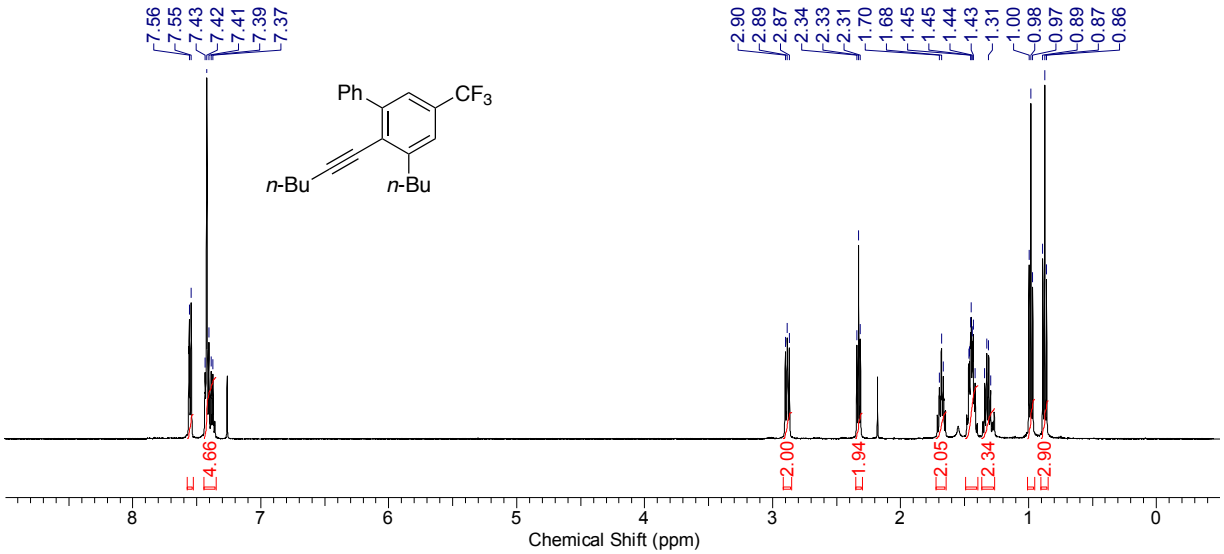
^{13}C spectrum of **3-142aa**:



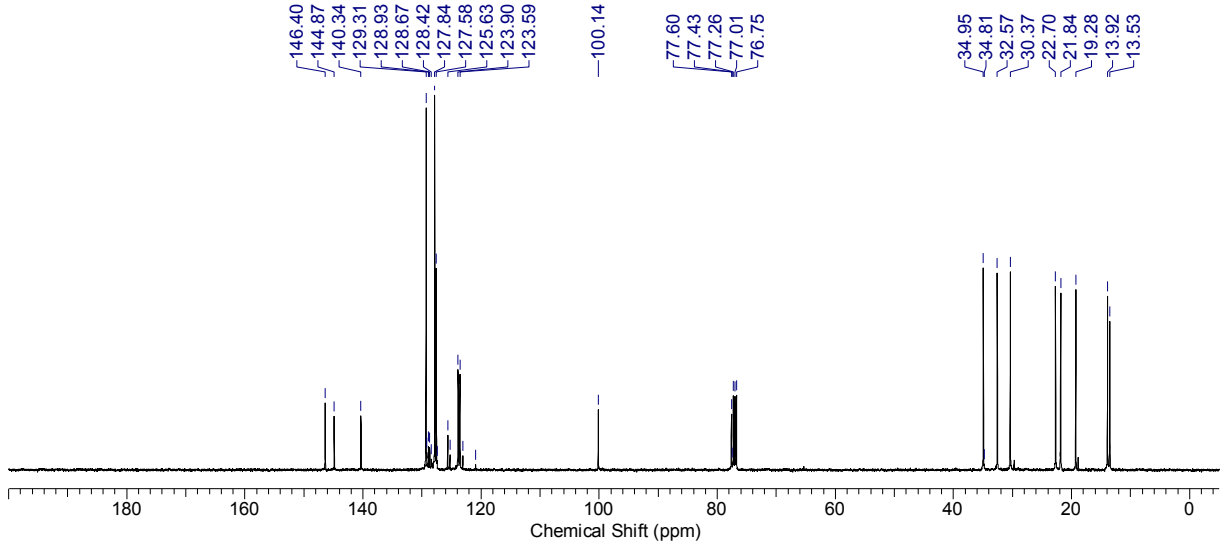
^{19}F spectrum of **3-142aa**:



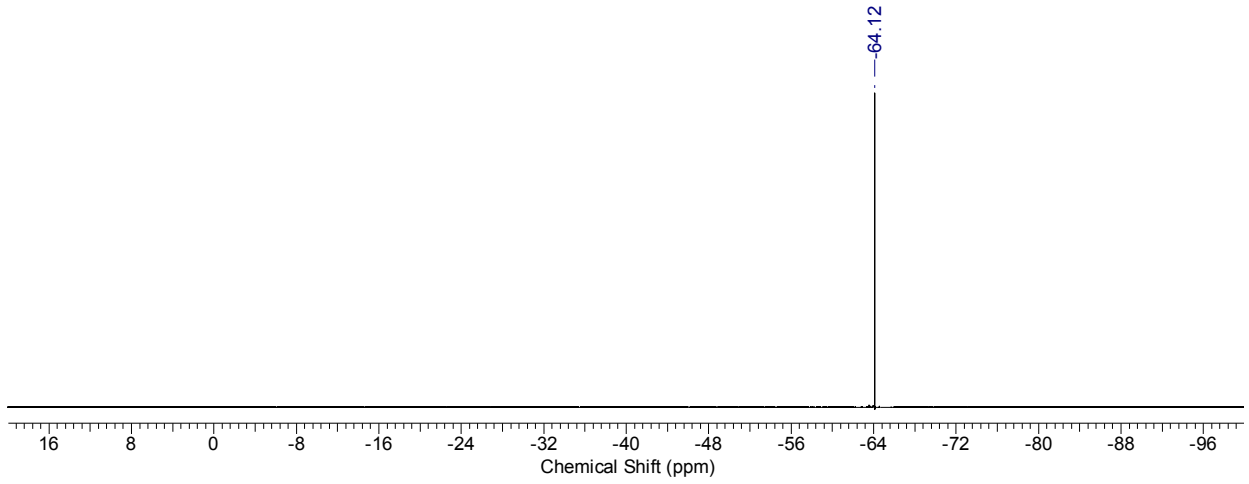
^{1}H spectrum of **3-142ba**:



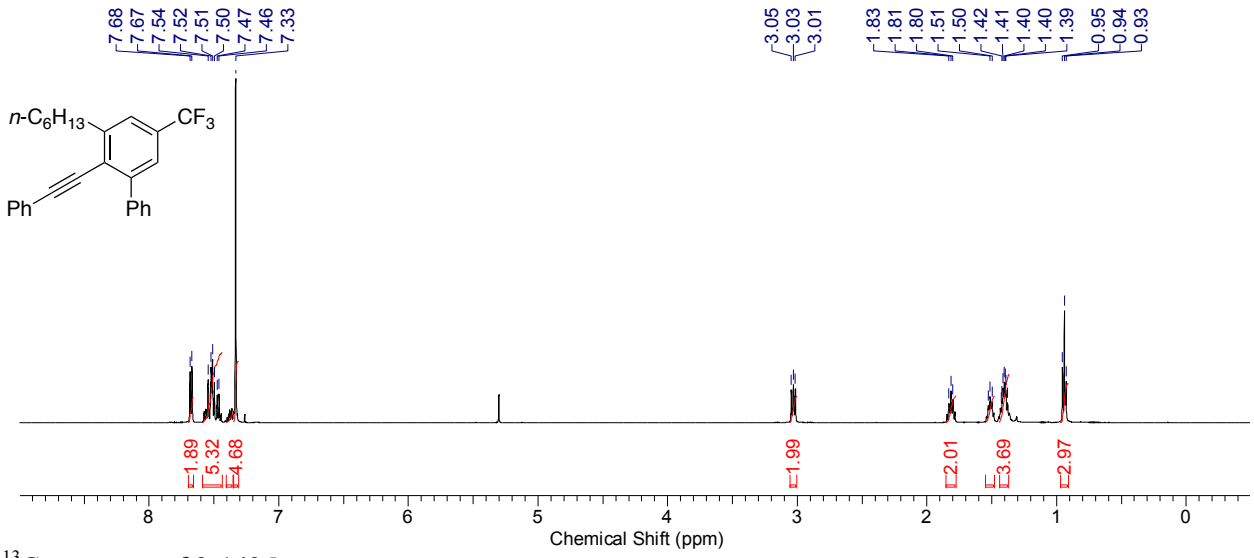
^{13}C spectrum of **3-142ba**:



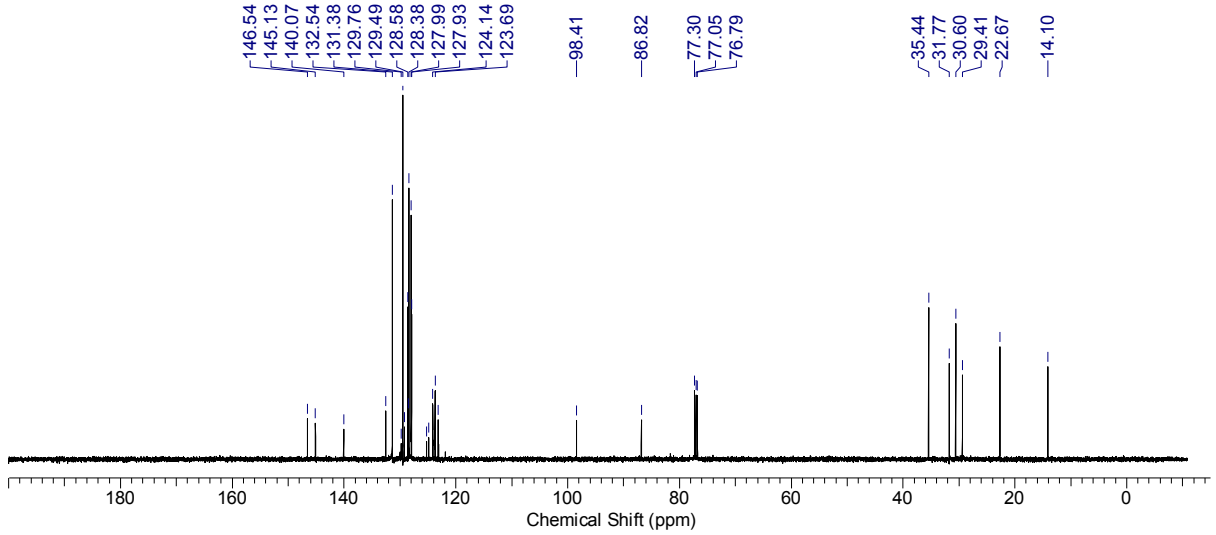
^{19}F spectrum of **3-142ba**:



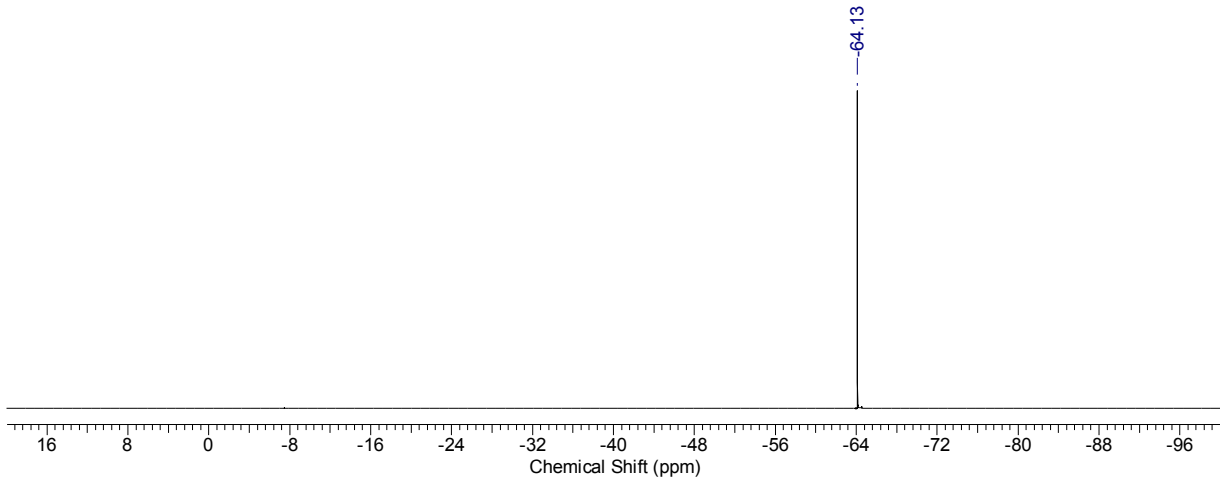
^{1}H spectrum of **3-142da**:



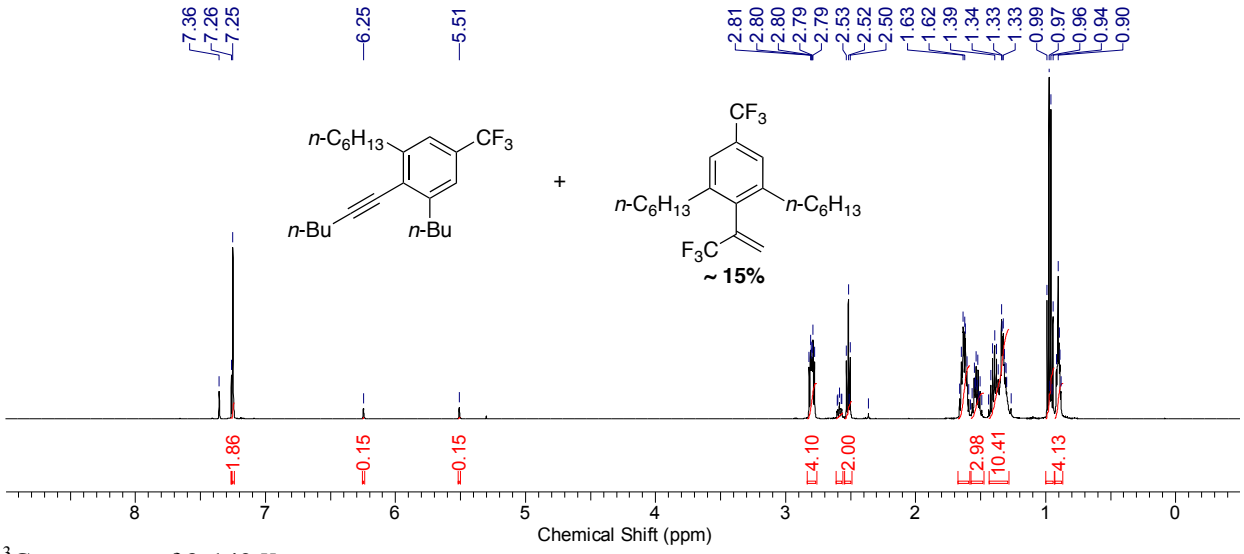
^{13}C spectrum of **3-142da**:



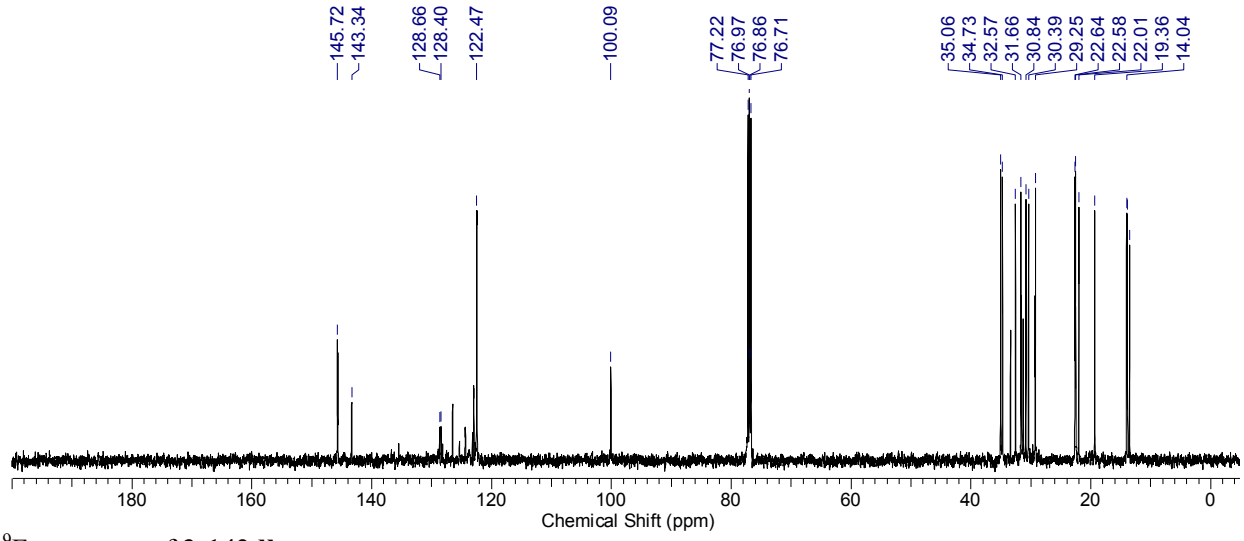
^{19}F spectrum of **3-142da**:



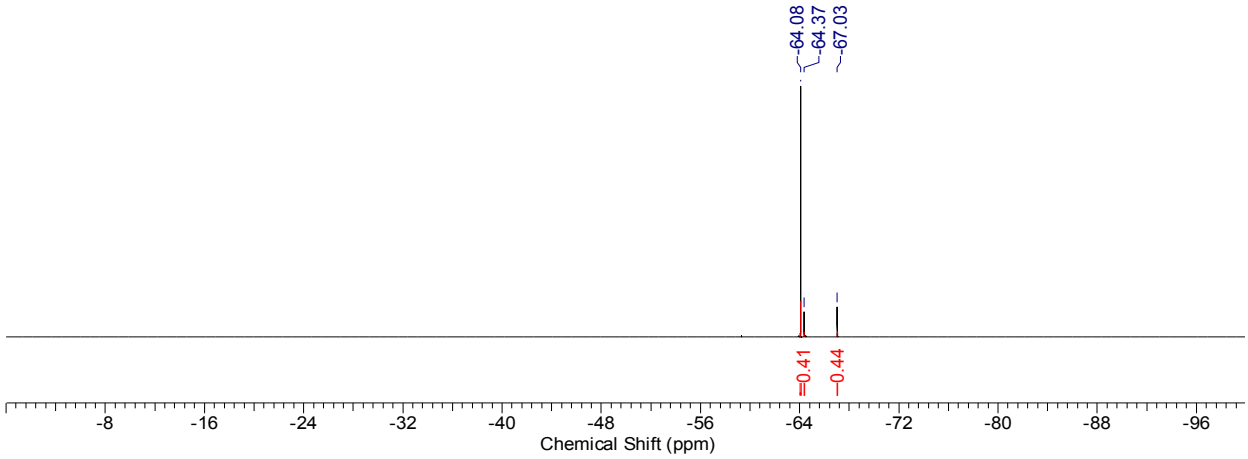
^{1}H spectrum of **3-142db**:



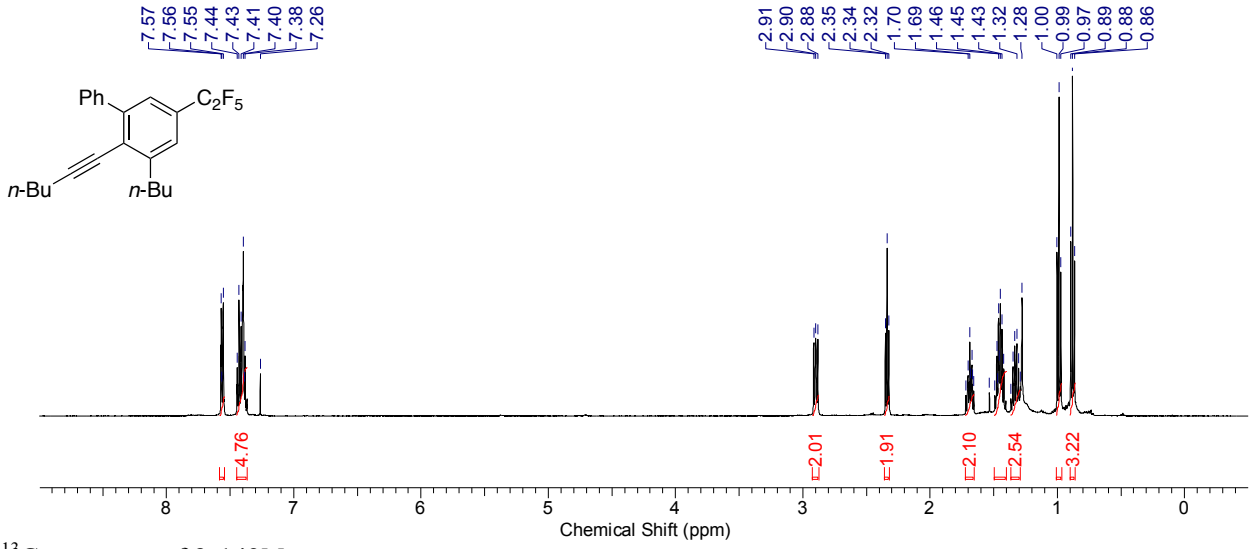
^{13}C spectrum of **3-142db**:



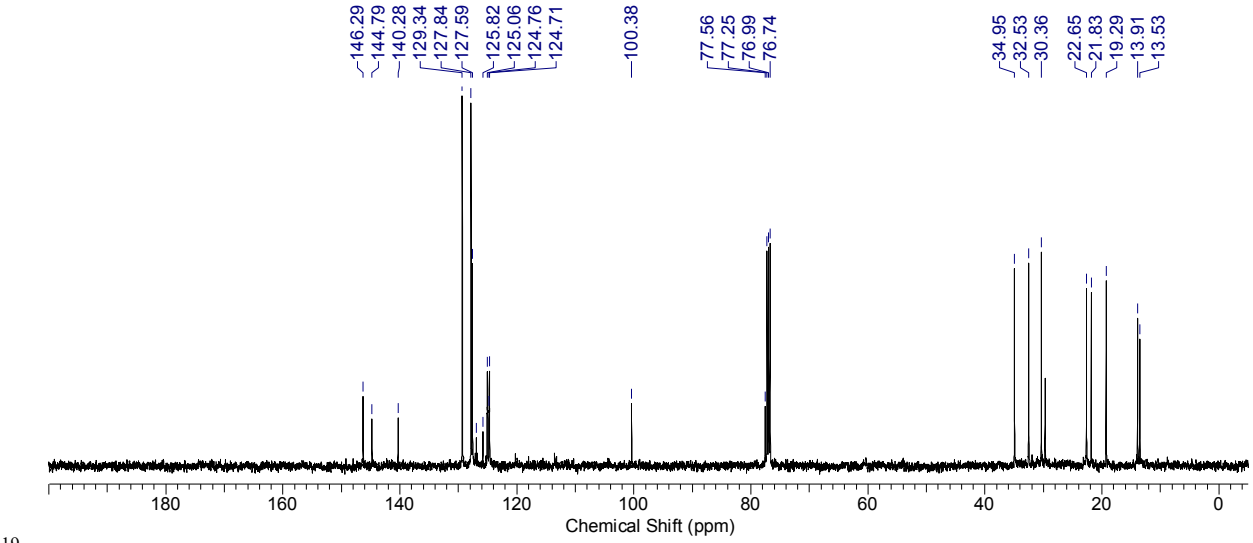
^{19}F spectrum of **3-142db**:



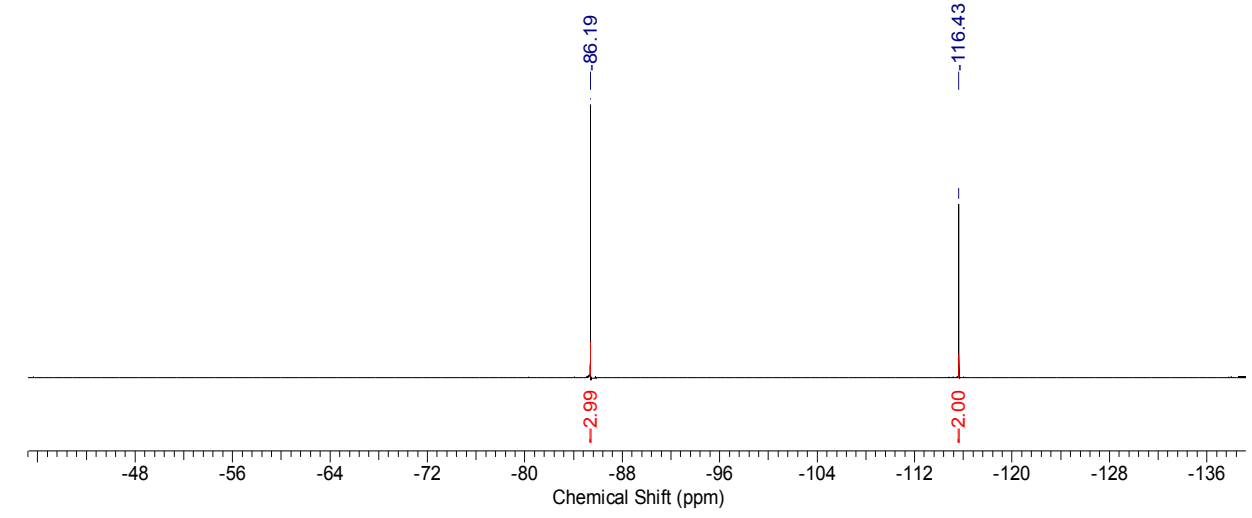
^{1}H spectrum of **3-142bb**:



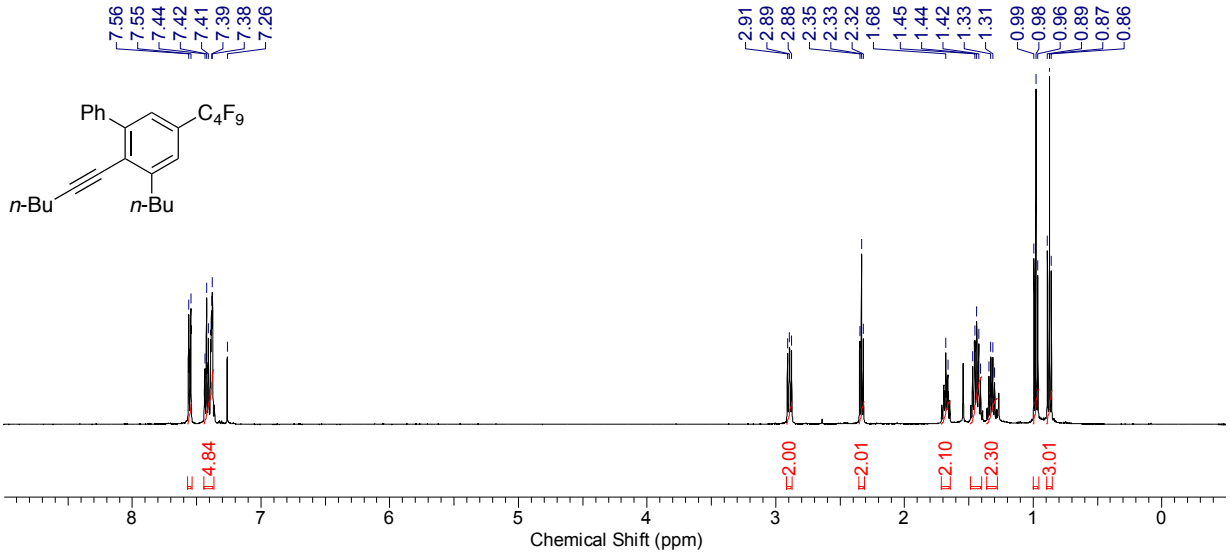
^{13}C spectrum of **3-142bb**:



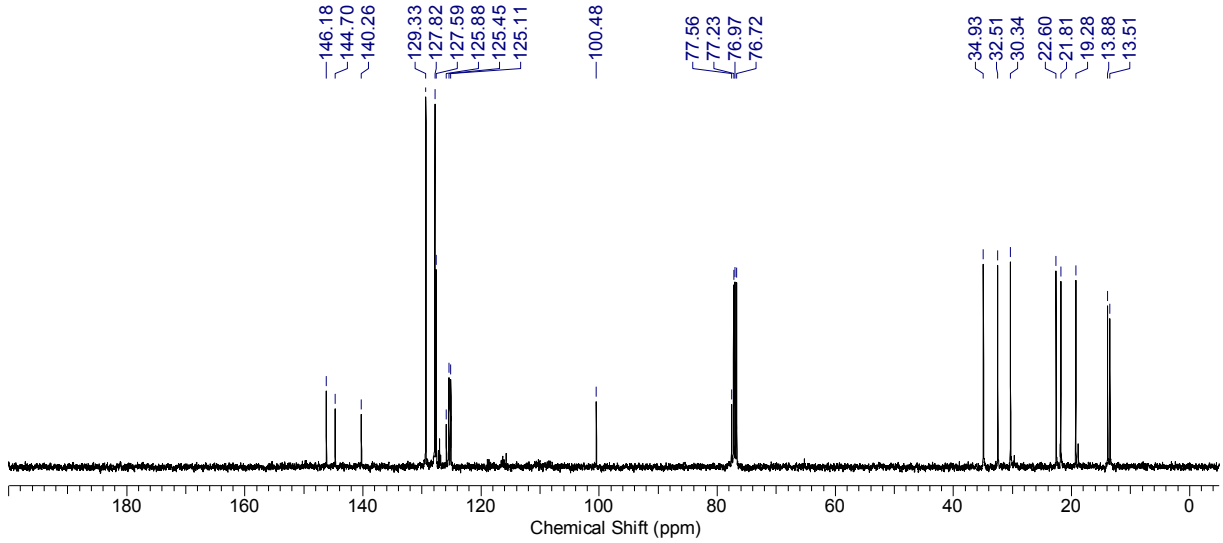
^{19}F spectrum of **3-142bb**:



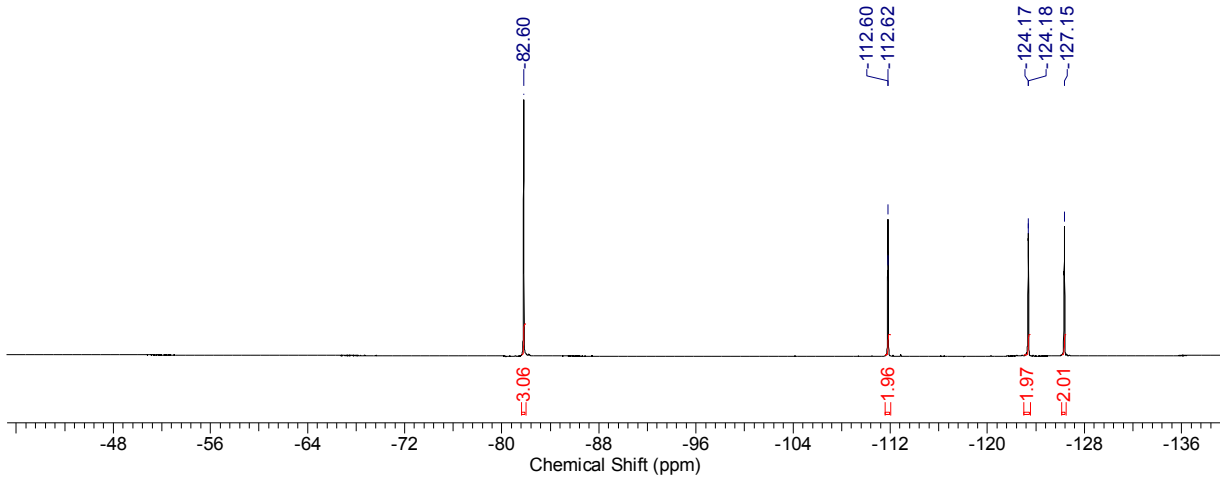
^{1}H spectrum of **3-142cb**:



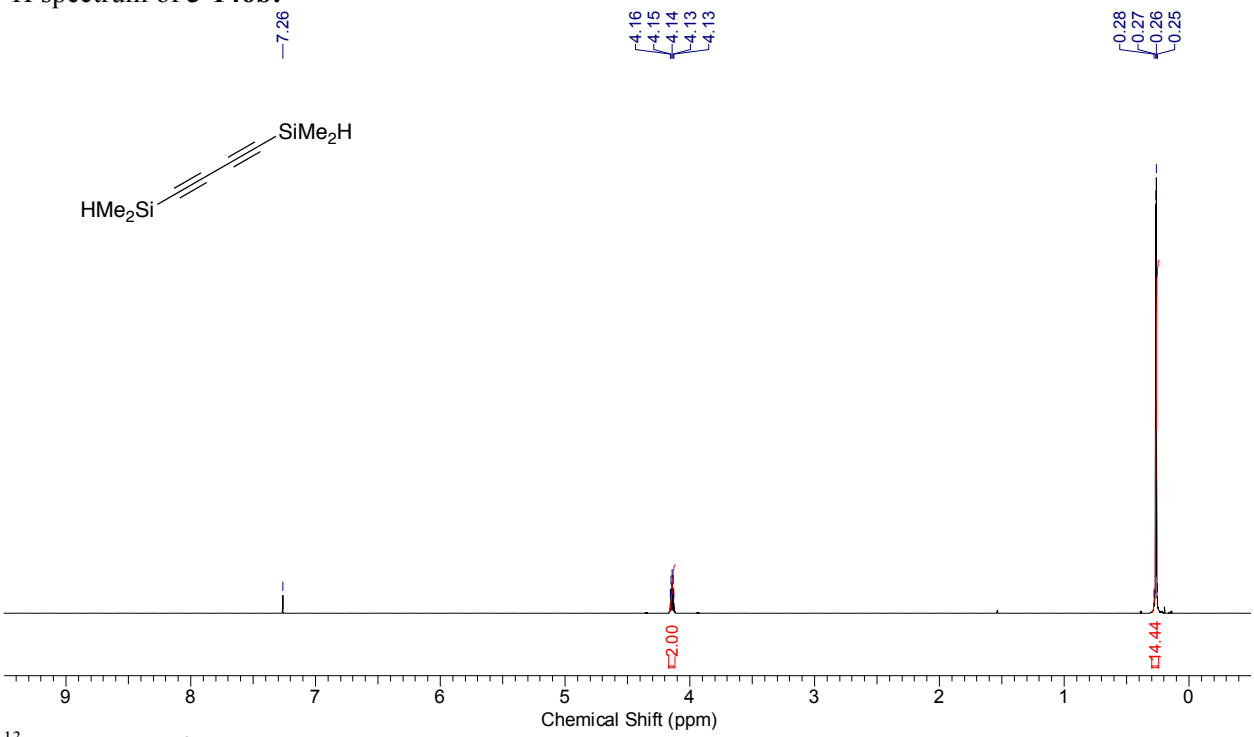
^{13}C spectrum of **3-142cb**:



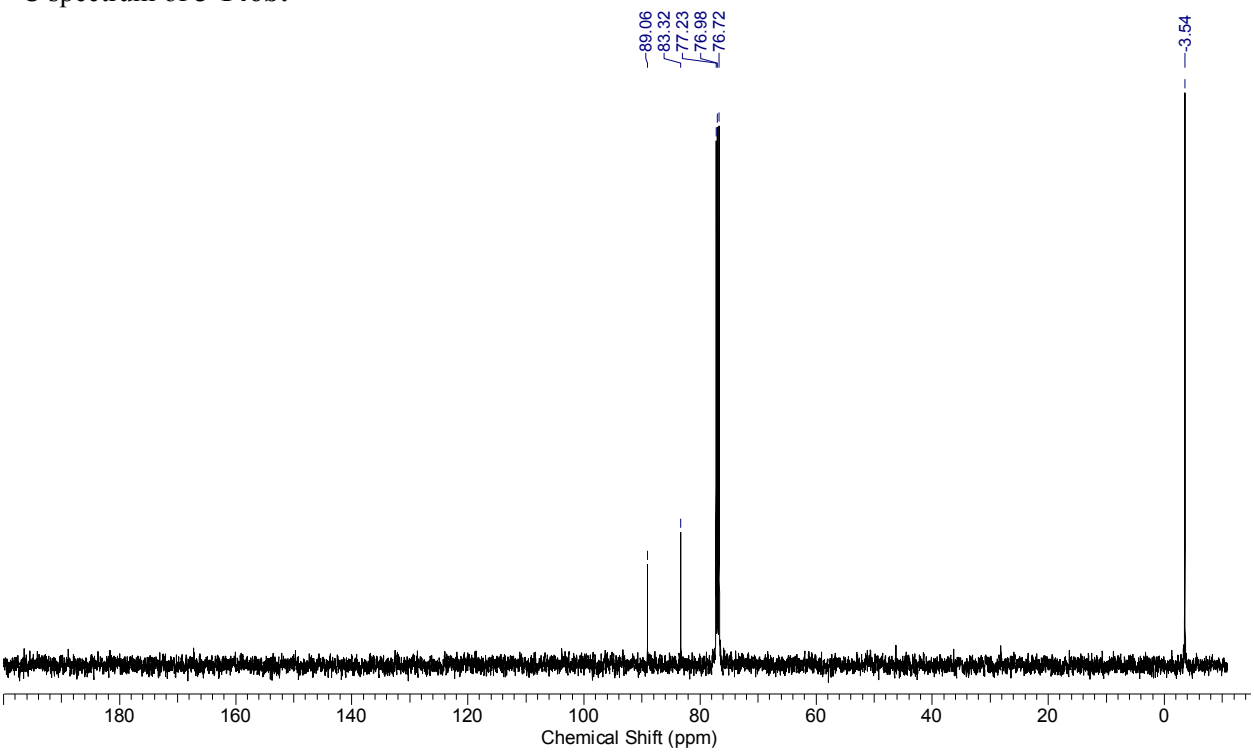
^{19}F spectrum of **3-142cb**:



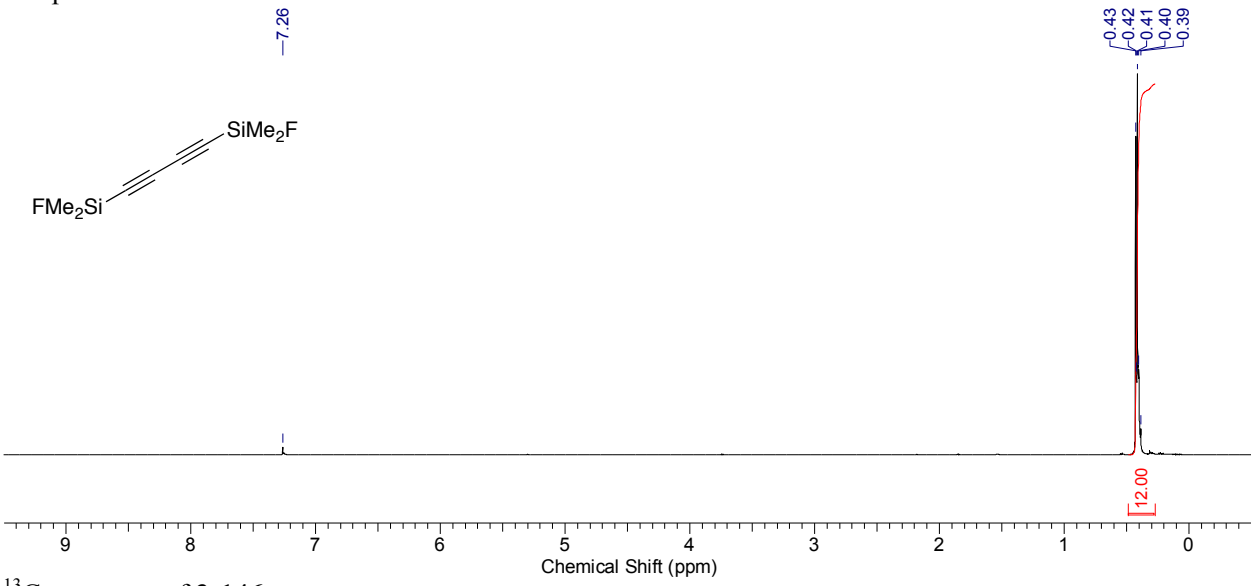
^{1}H spectrum of **3-146b:**



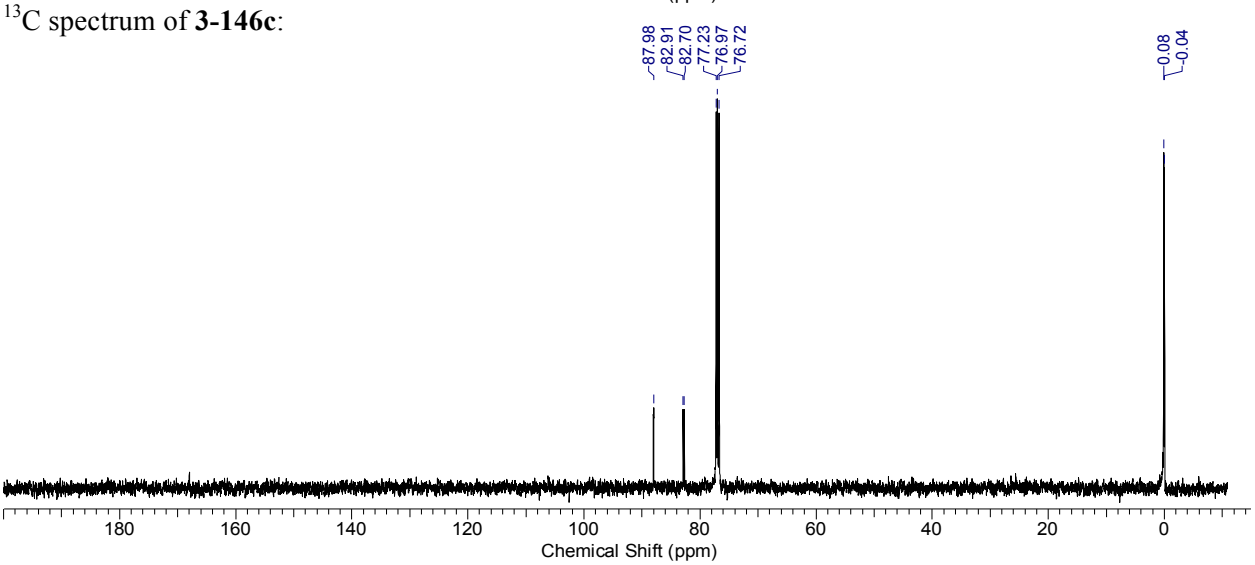
^{13}C spectrum of **3-146b:**



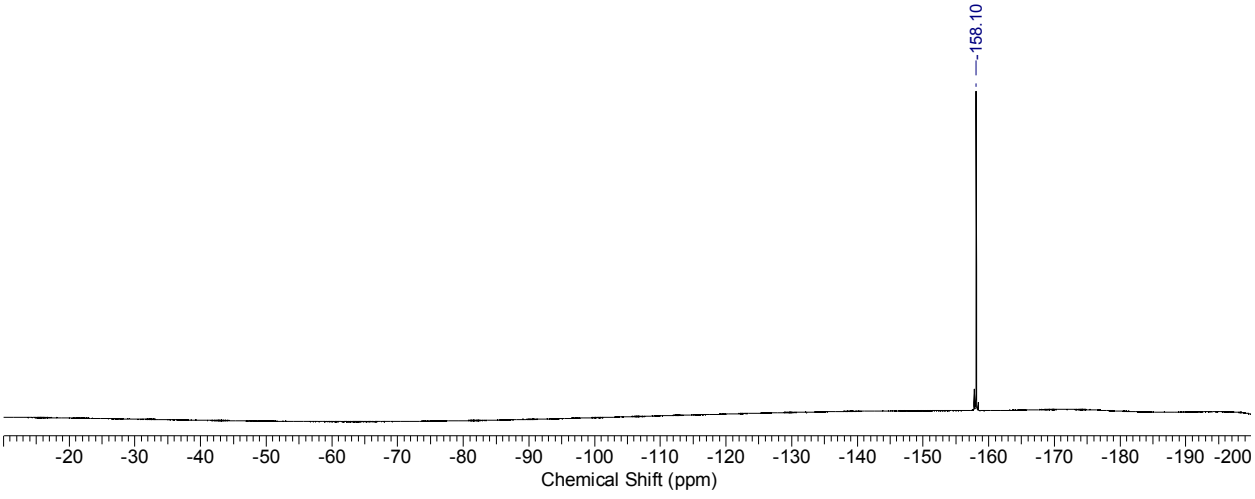
^{1}H spectrum of **3-146c**:



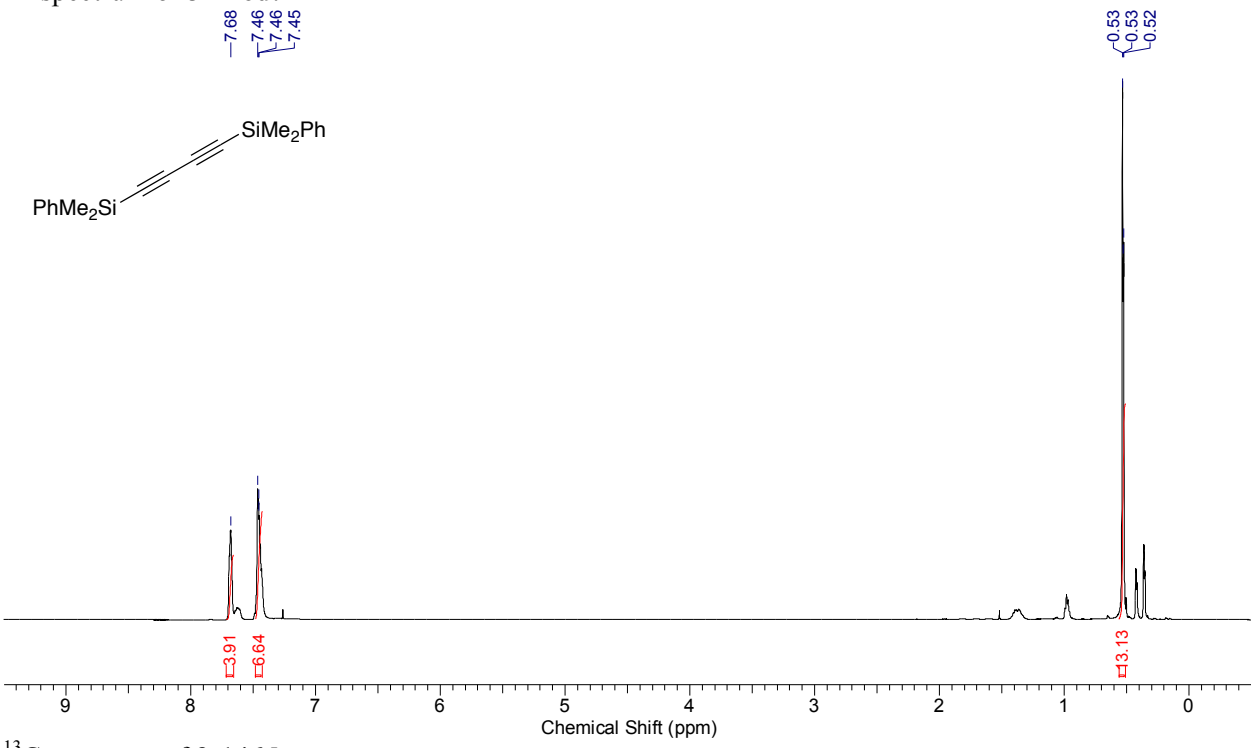
^{13}C spectrum of **3-146c**:



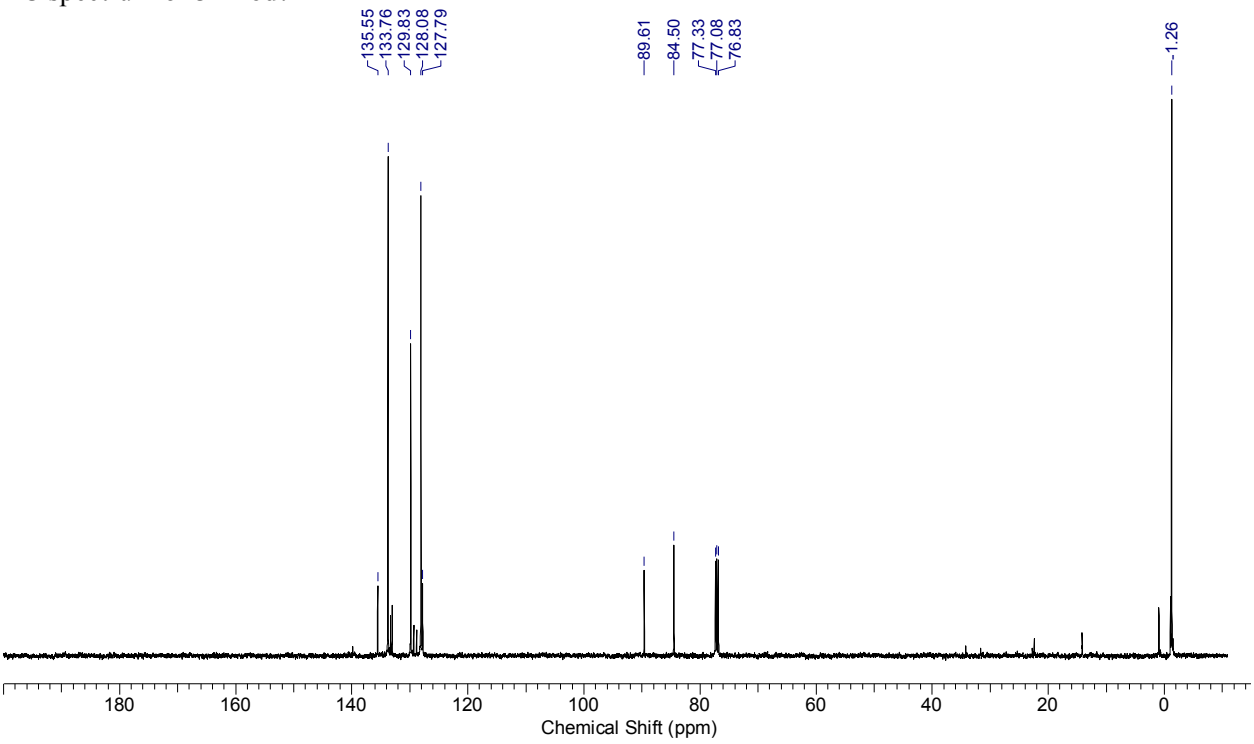
^{19}F spectrum of **3-146c**:



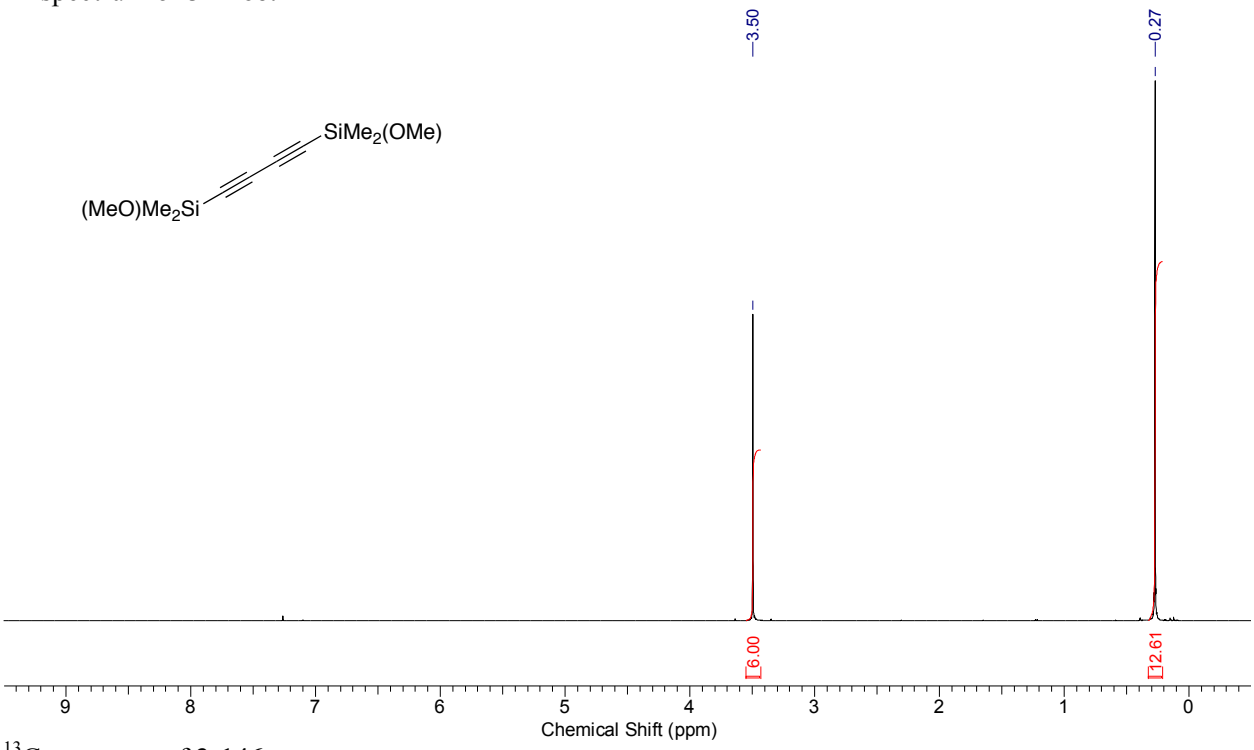
^{1}H spectrum of **3-146d**:



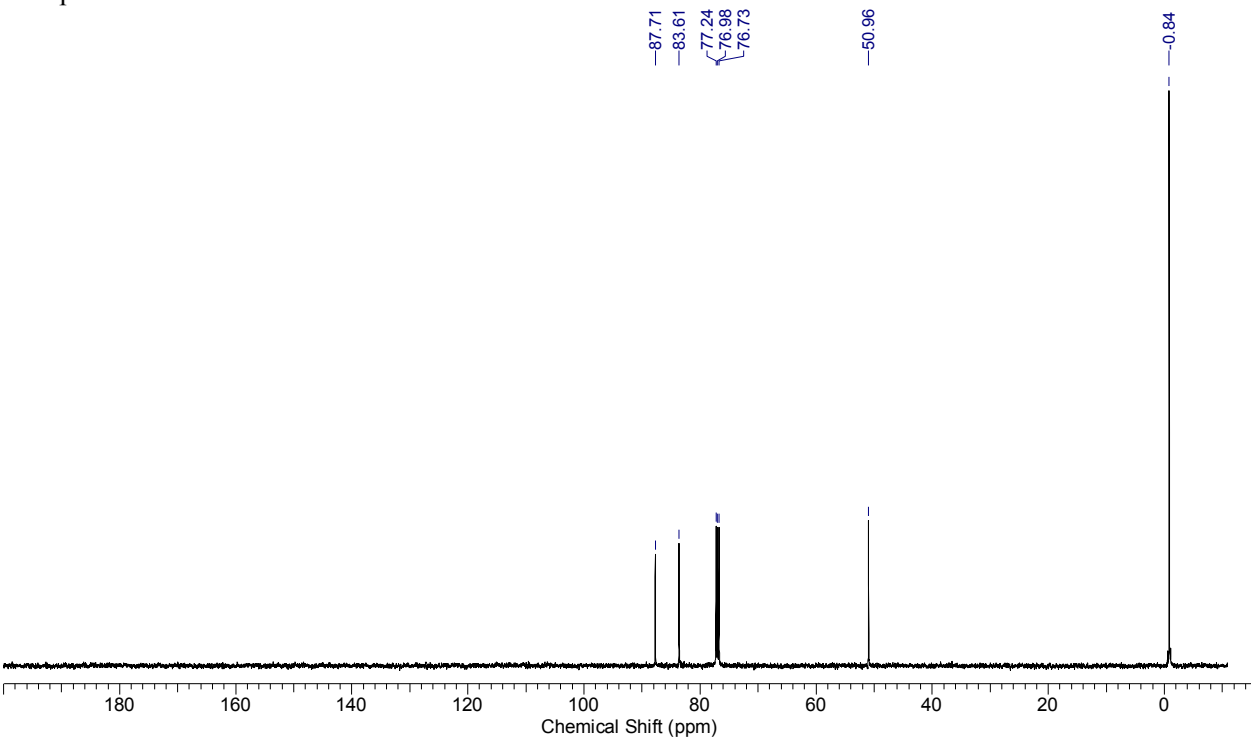
^{13}C spectrum of **3-146d**:



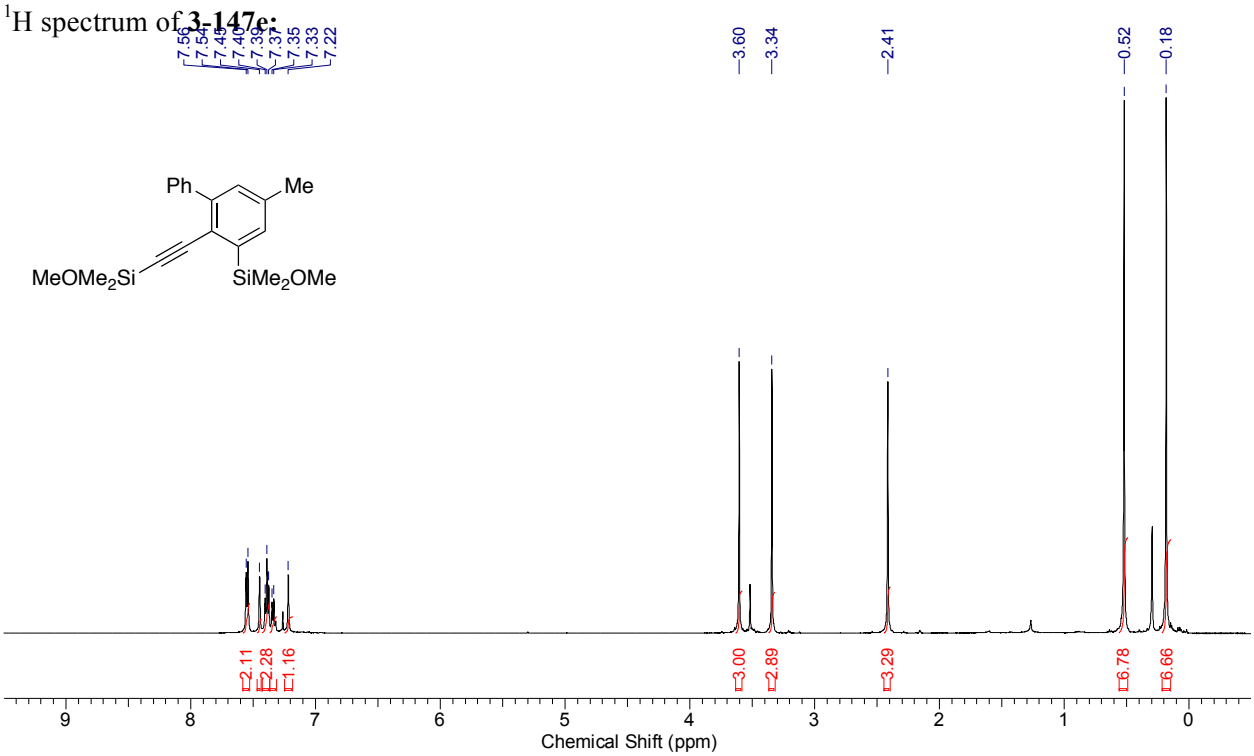
^{1}H spectrum of **3-146e:**



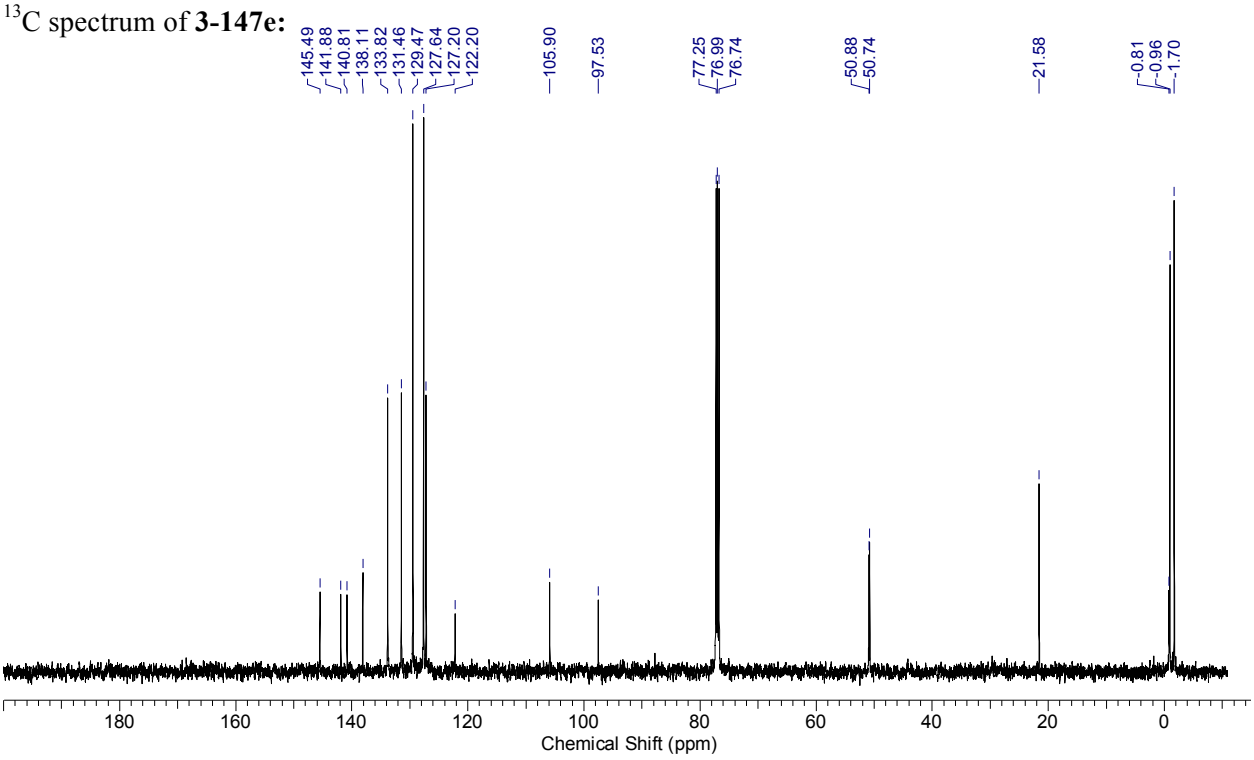
^{13}C spectrum of **3-146e:**



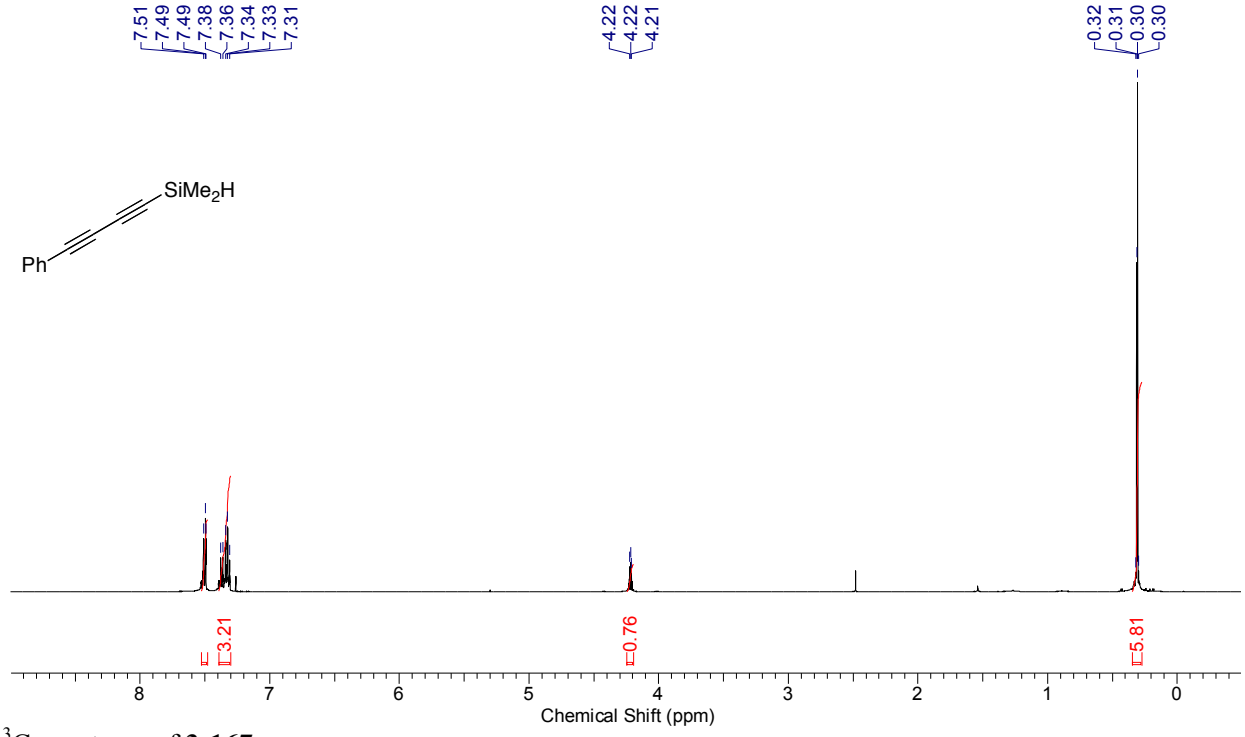
^{1}H spectrum of **3-147e:**



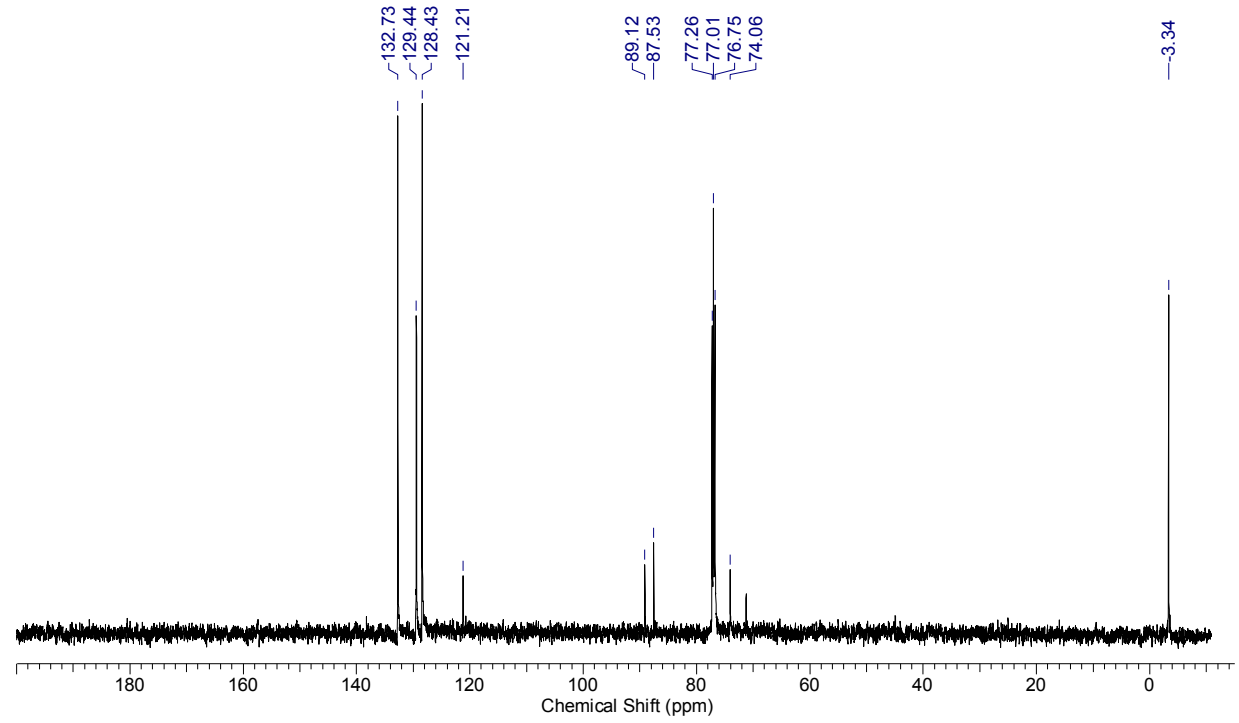
^{13}C spectrum of **3-147e:**



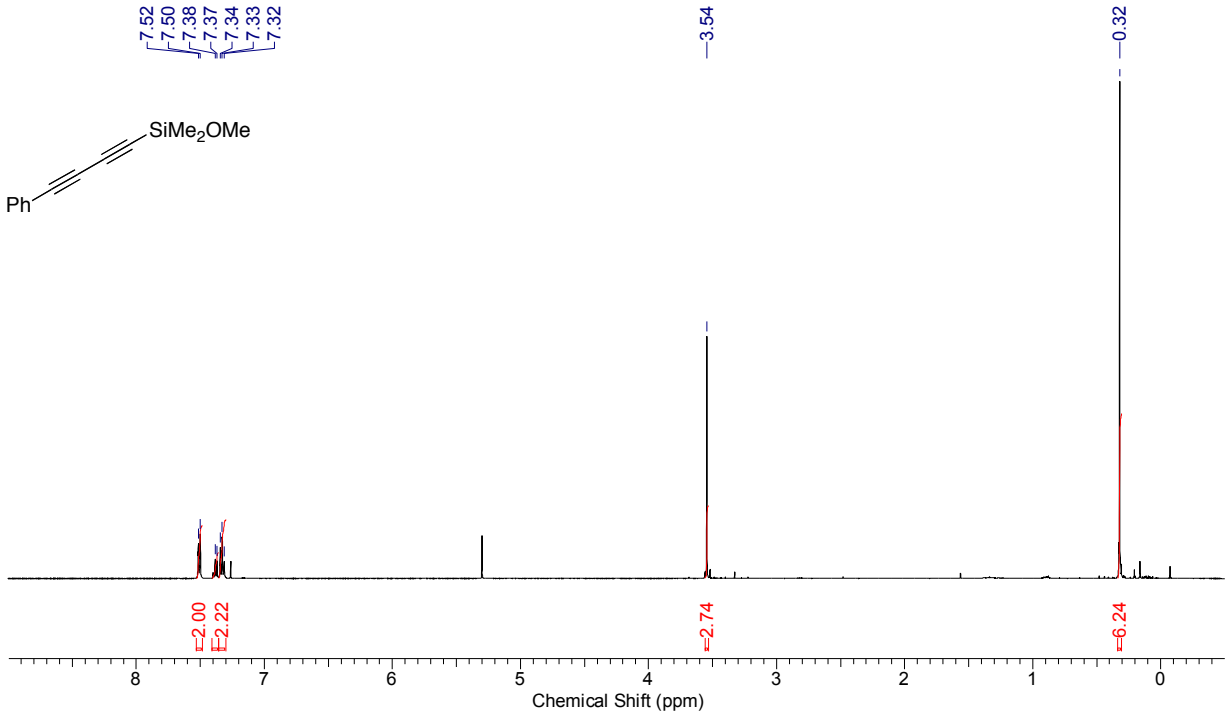
^{1}H spectrum of **3-167**:



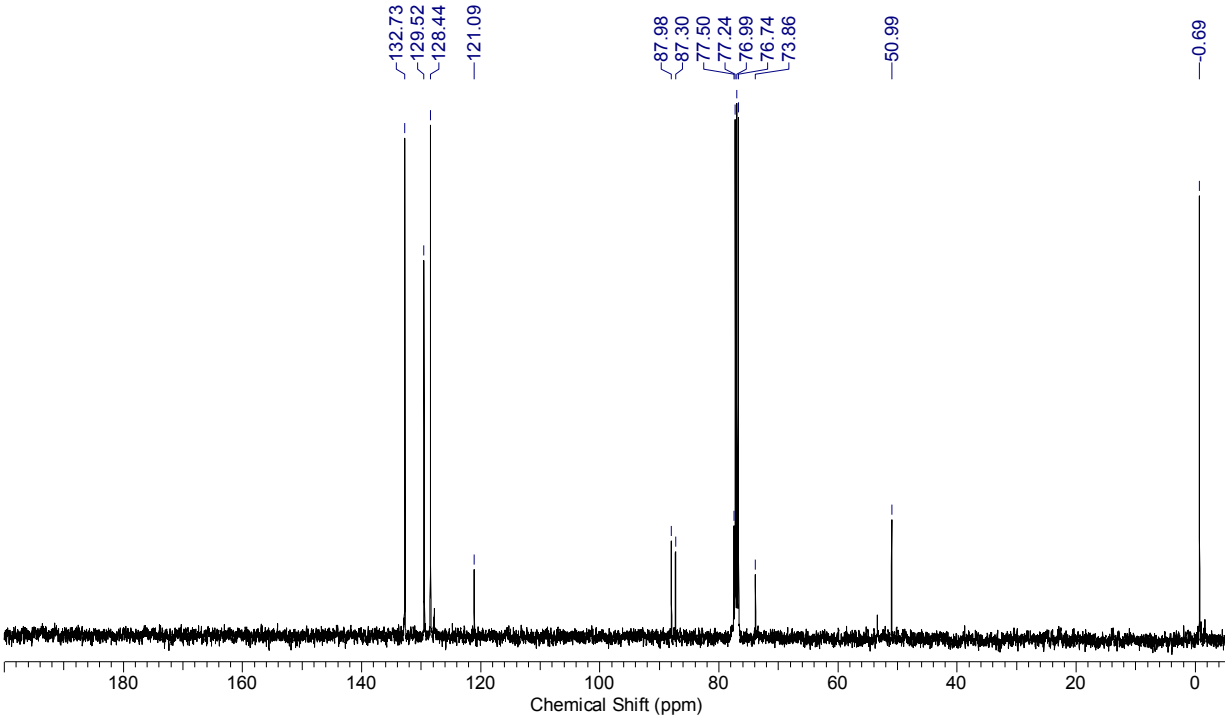
^{13}C spectrum of **3-167**:



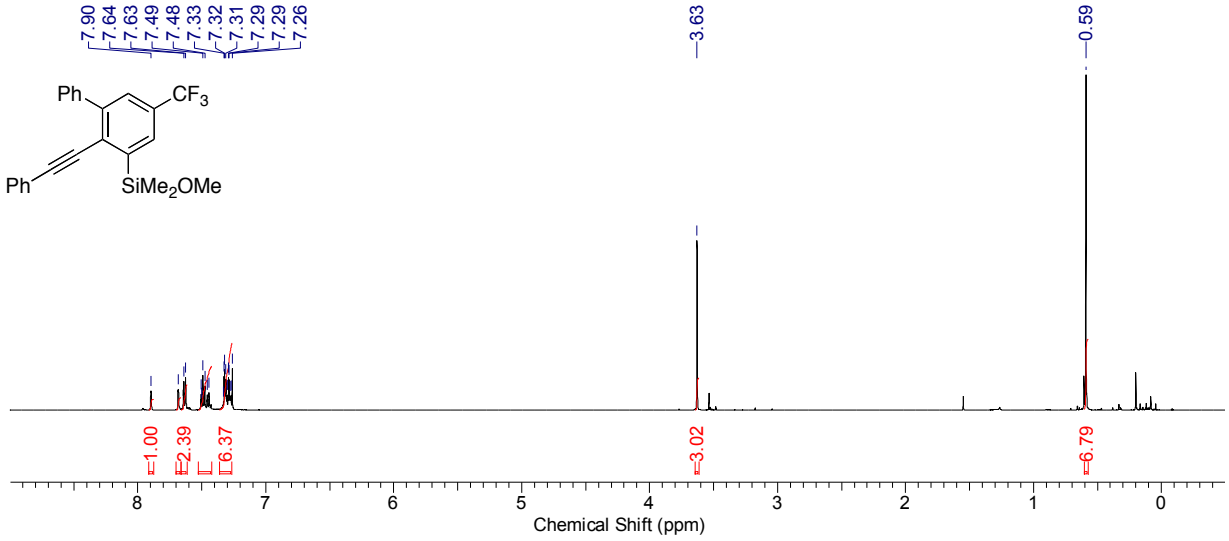
^{1}H spectrum of **3-148**:



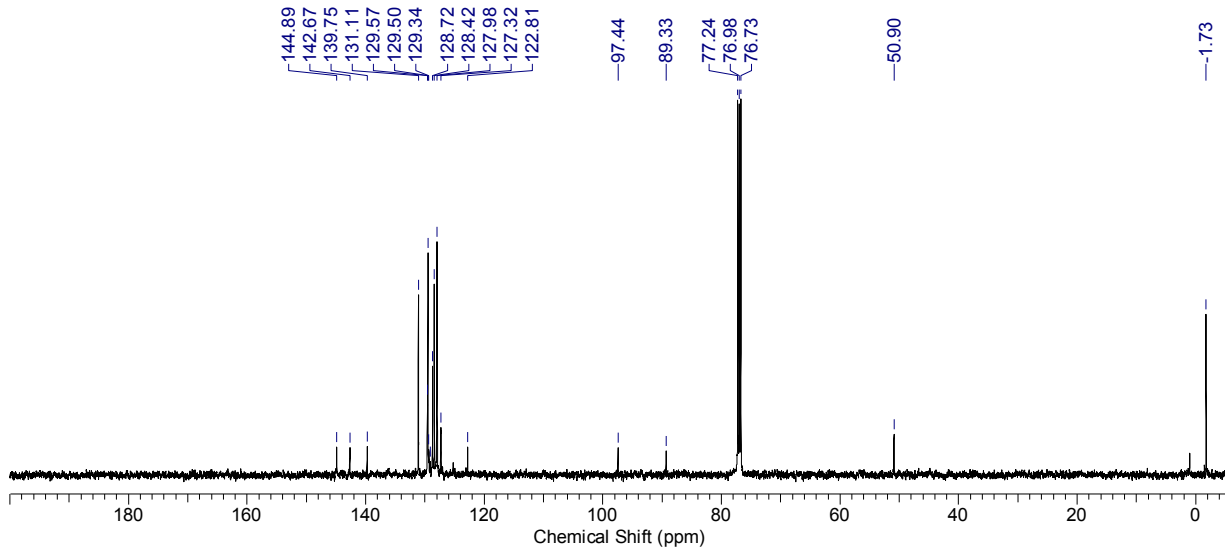
^{13}C spectrum of **3-148**:



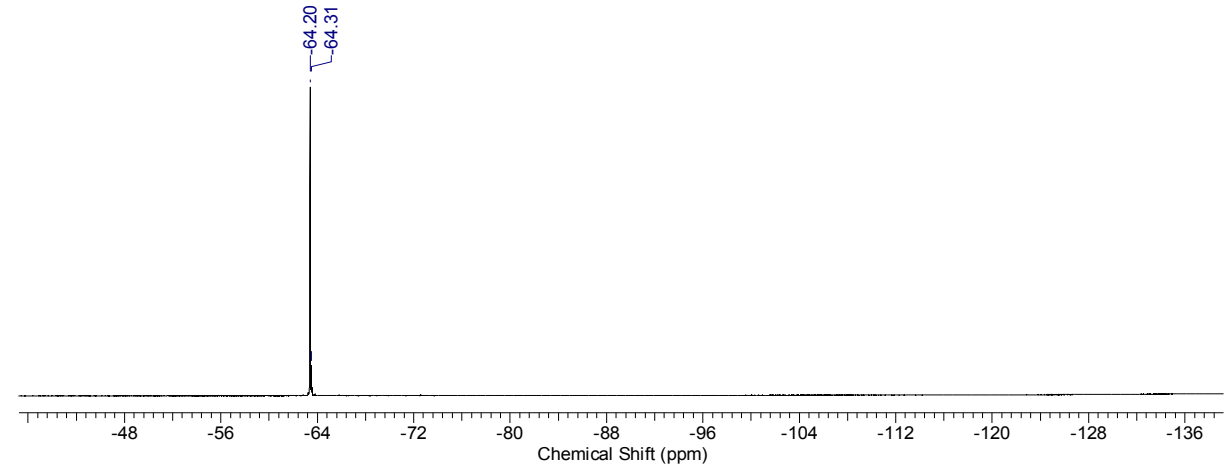
^{1}H spectrum of **3-149**:



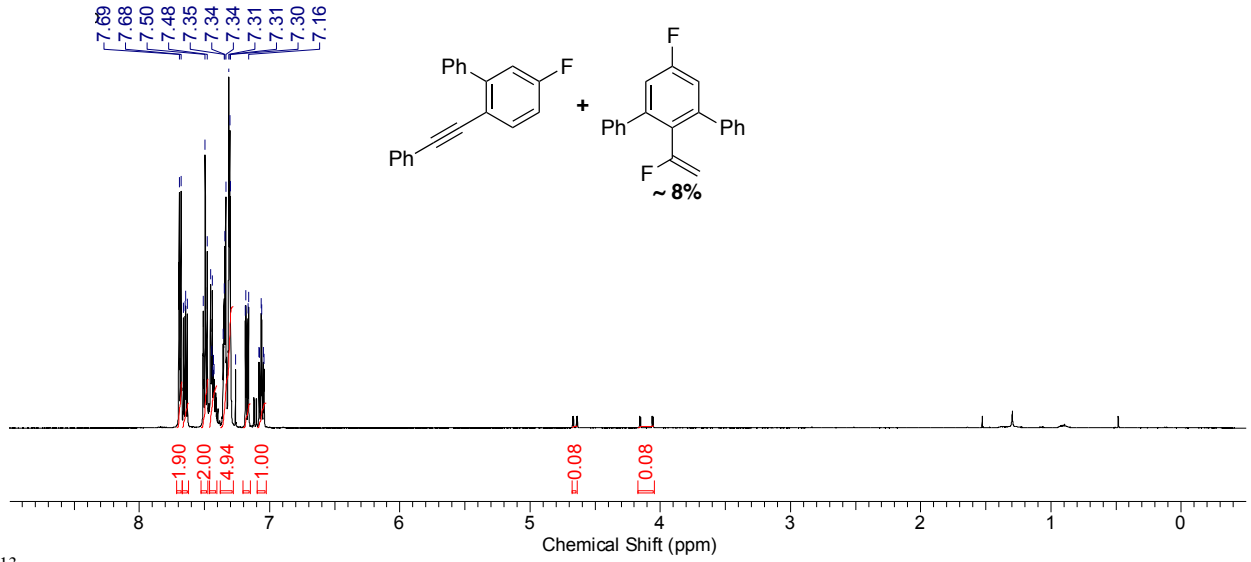
^{13}C spectrum of **3-149**:



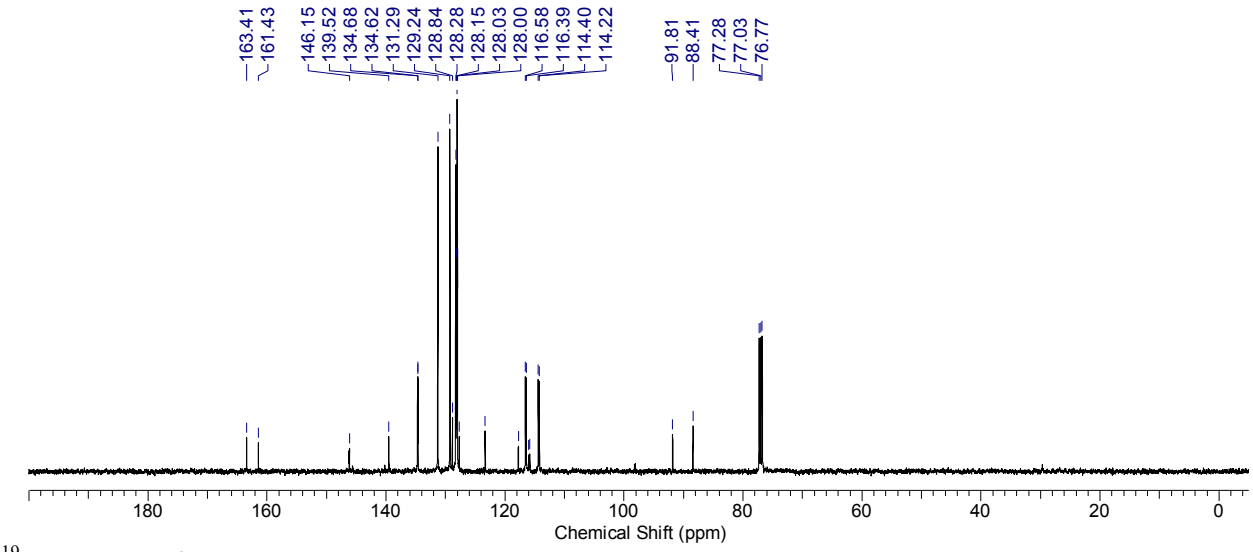
^{19}F spectrum of **3-149**:



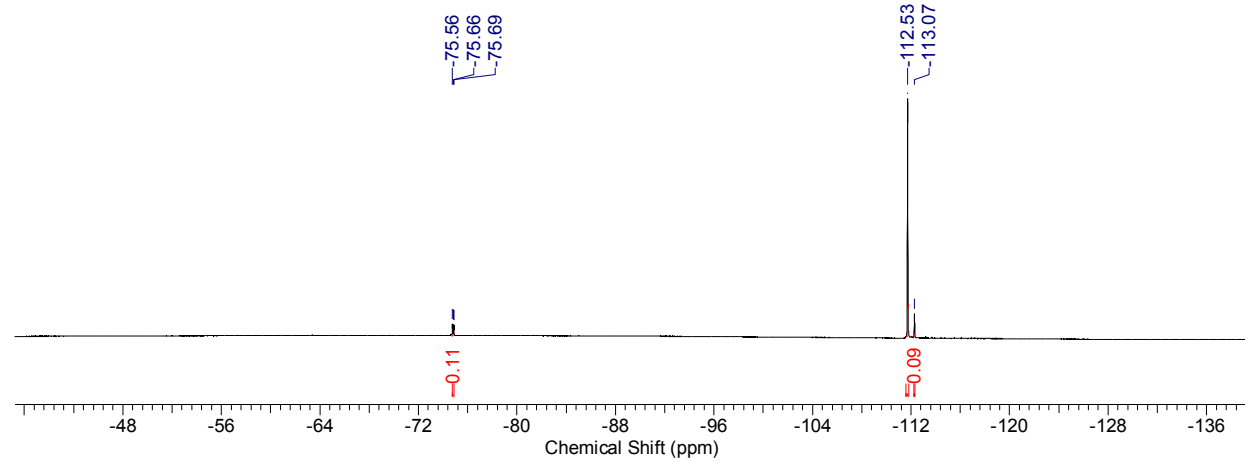
^{1}H spectrum of **3-150**:



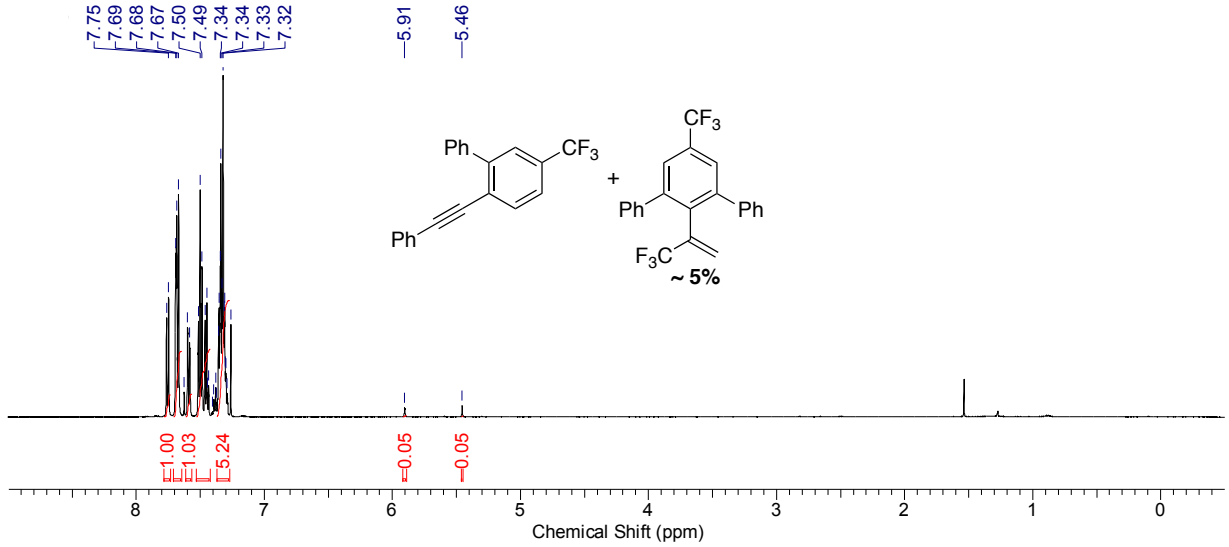
^{13}C spectrum of **3-150**:



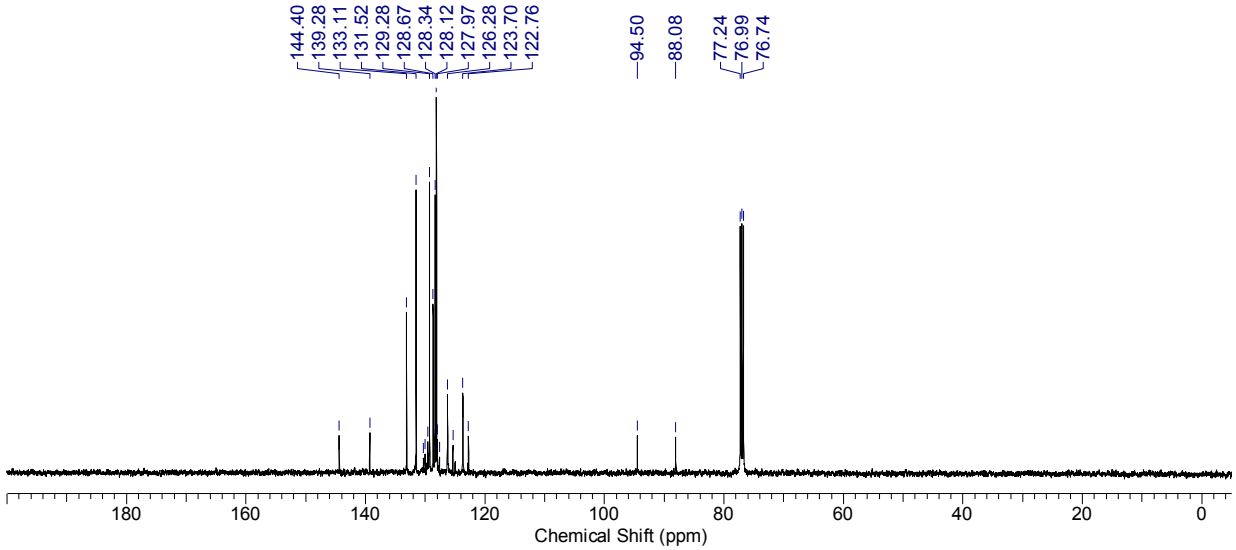
^{19}F spectrum of **3-150**:



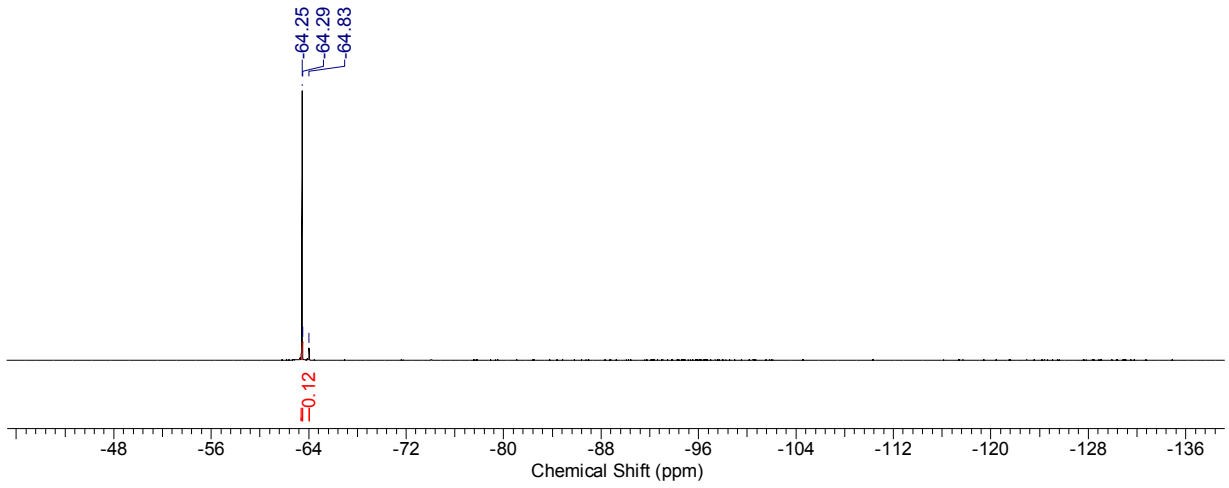
^{1}H spectrum of **3-151**:



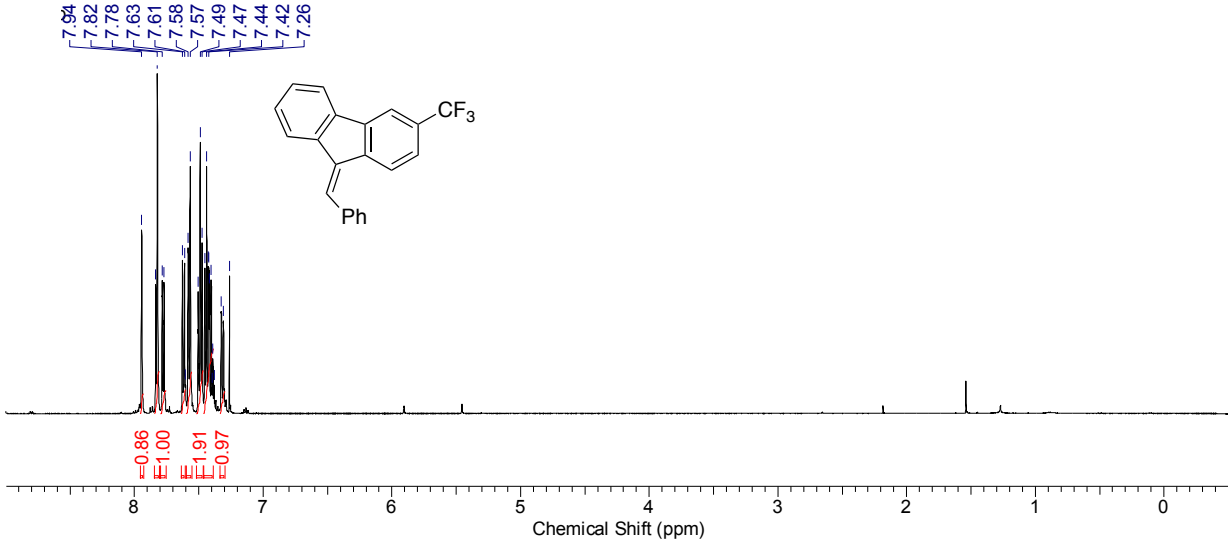
^{13}C spectrum of **3-151**:



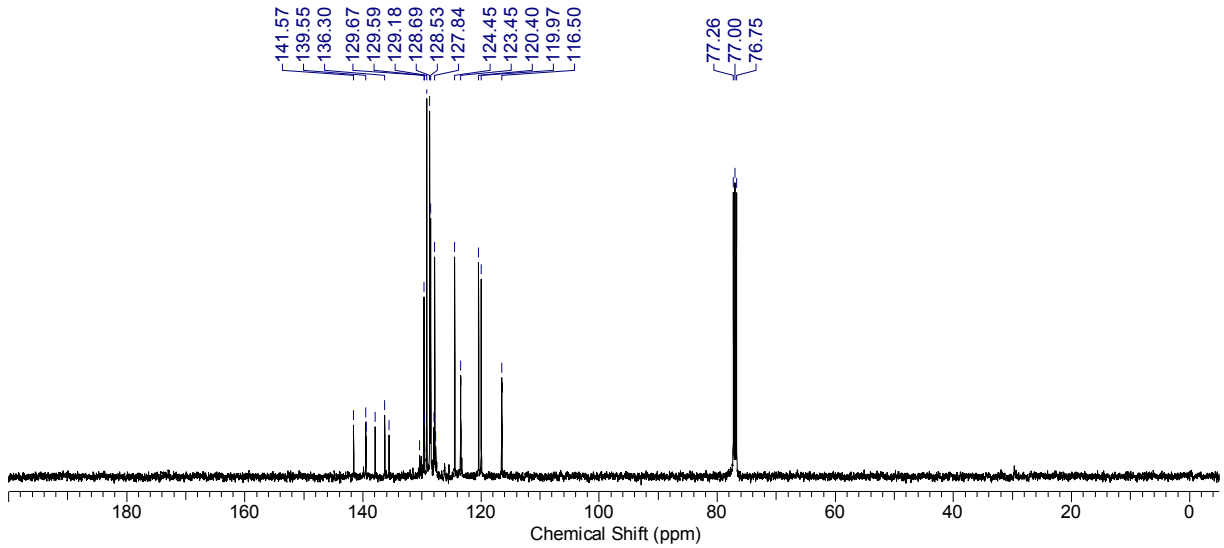
^{19}F spectrum of **3-151**:



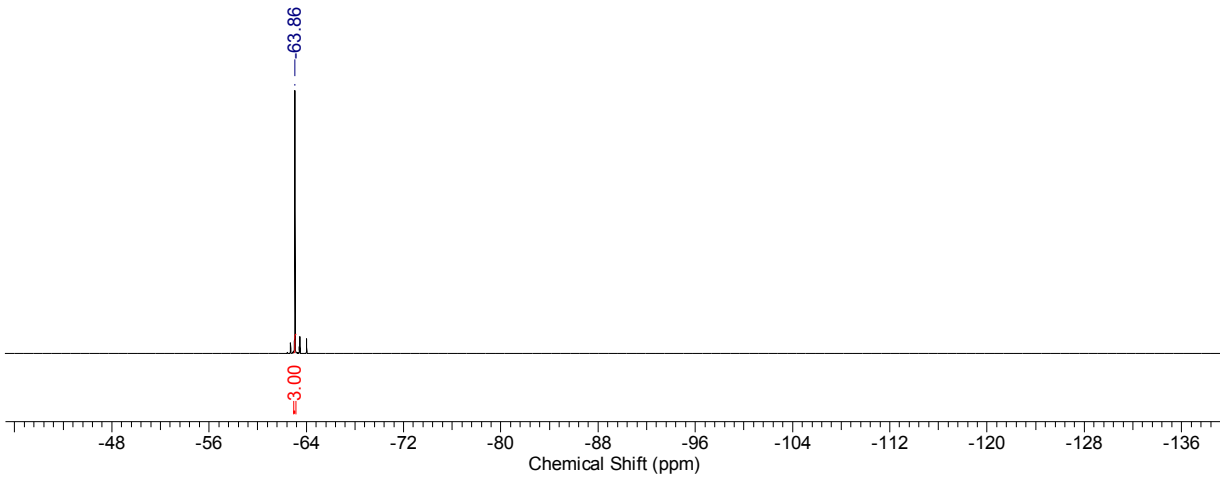
^{1}H spectrum of **3-152**:



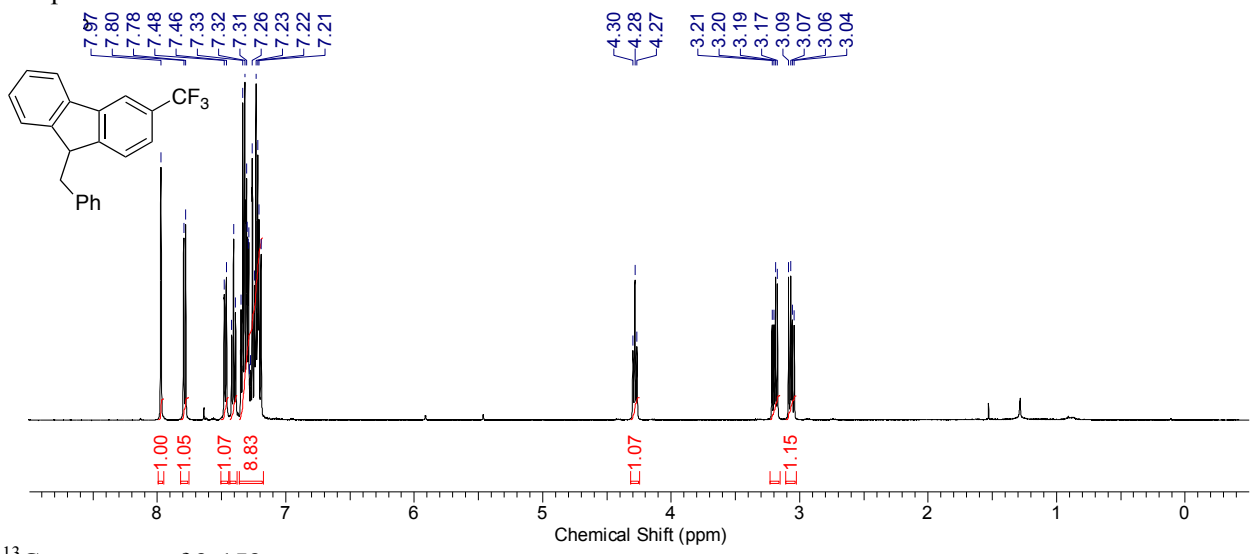
^{13}C spectrum of **3-152**:



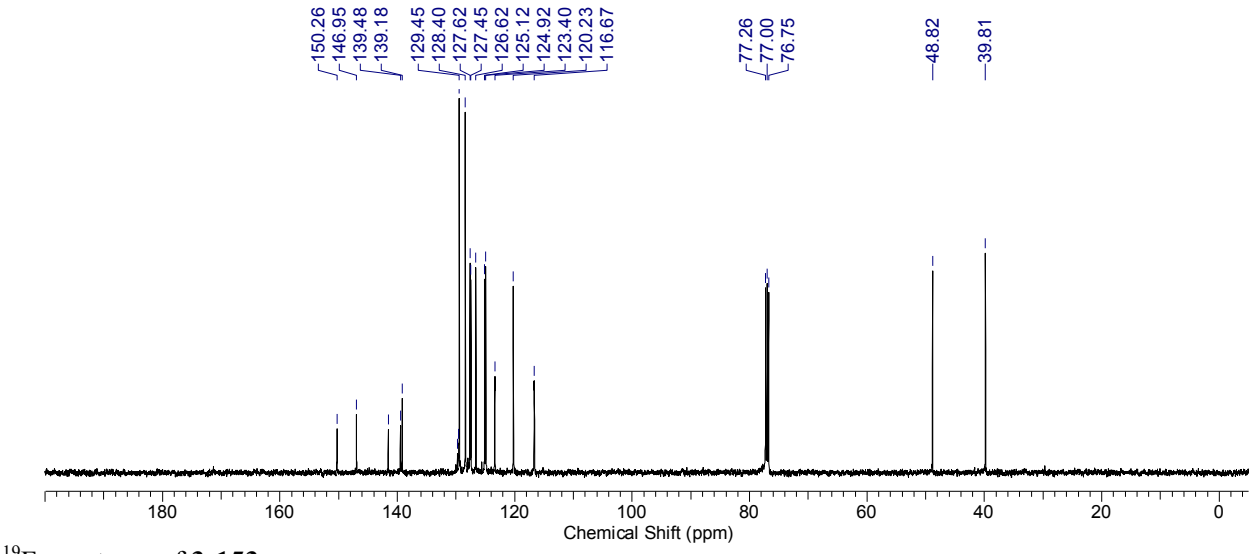
^{19}F spectrum of **3-152**:



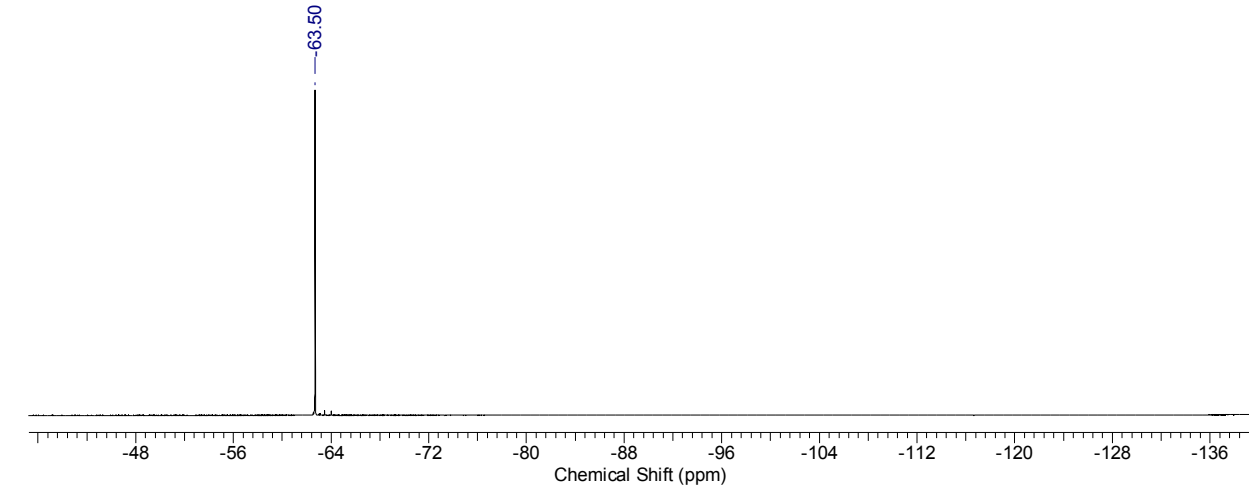
^{1}H spectrum of **3-153**:



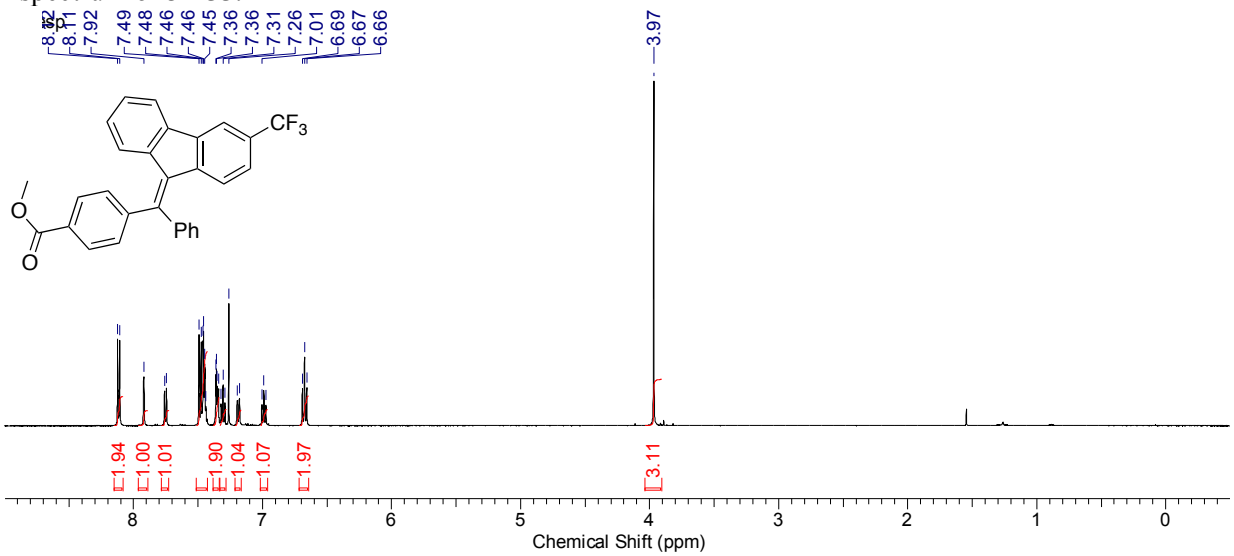
^{13}C spectrum of **3-153**:



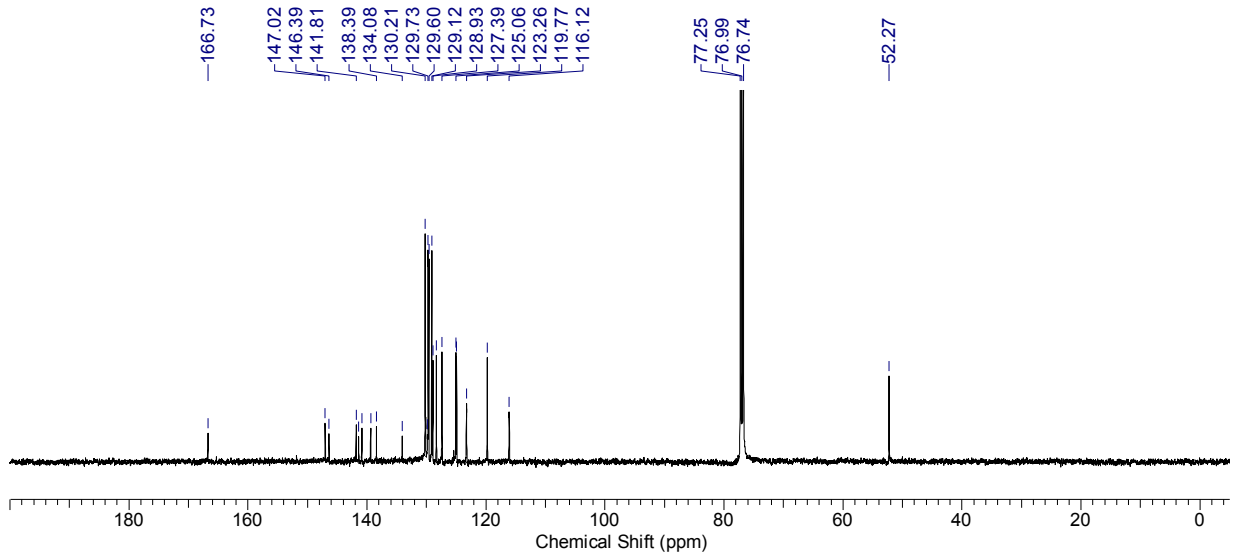
^{19}F spectrum of **3-153**:



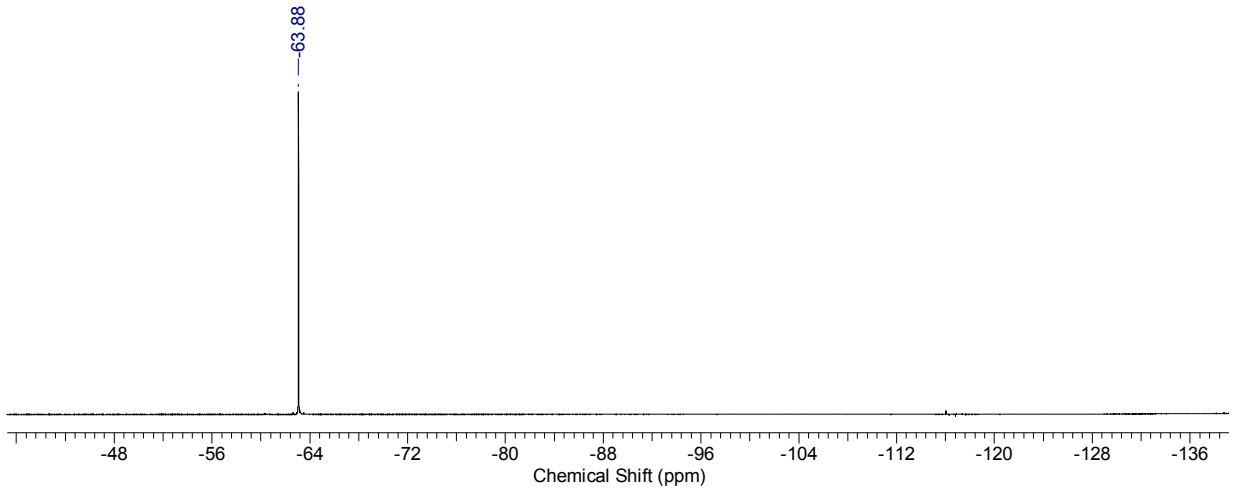
^{1}H spectrum of **3-155**:



^{13}C spectrum of **3-155**:



^{19}F spectrum of **3-155**:



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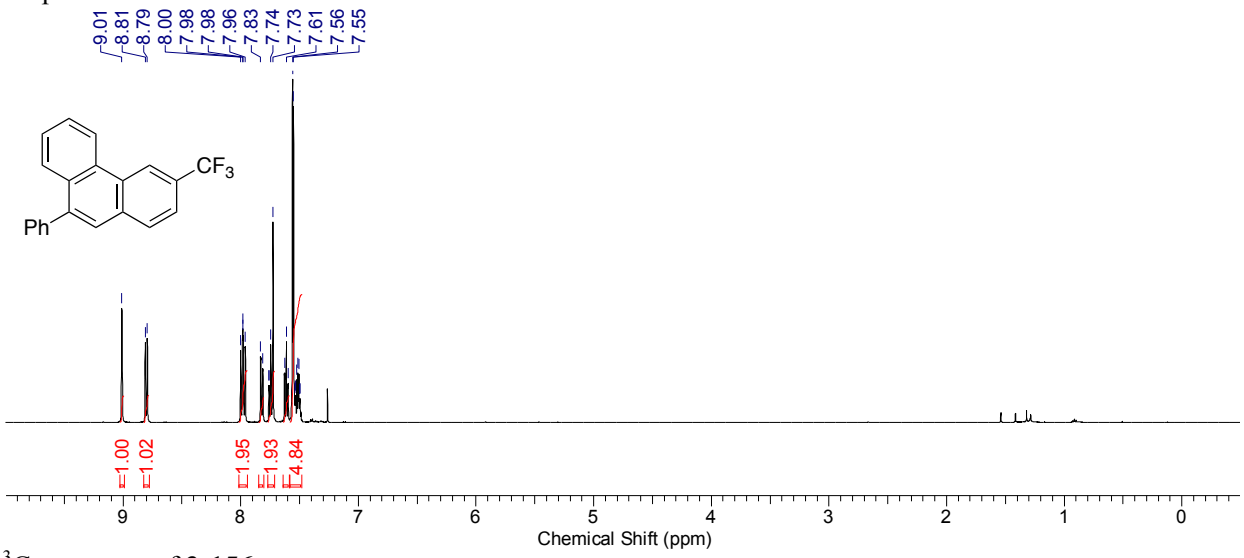

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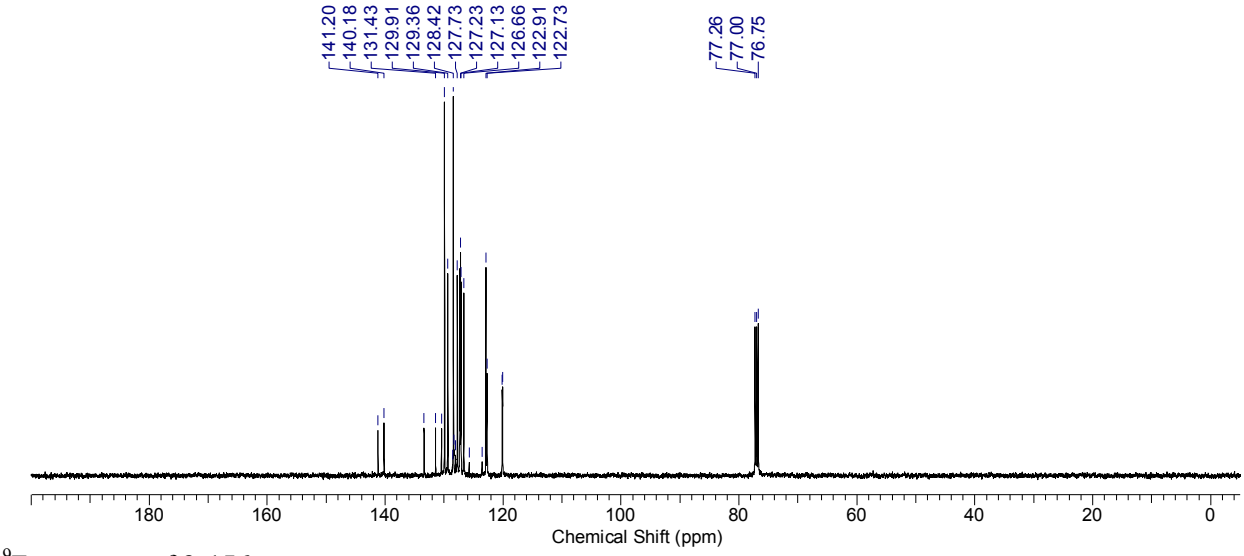

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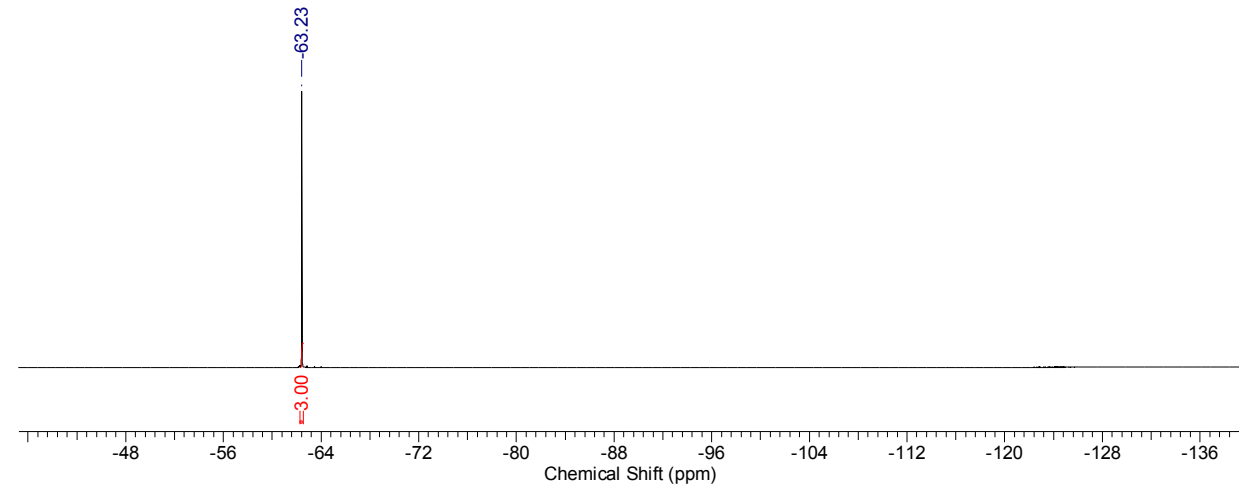

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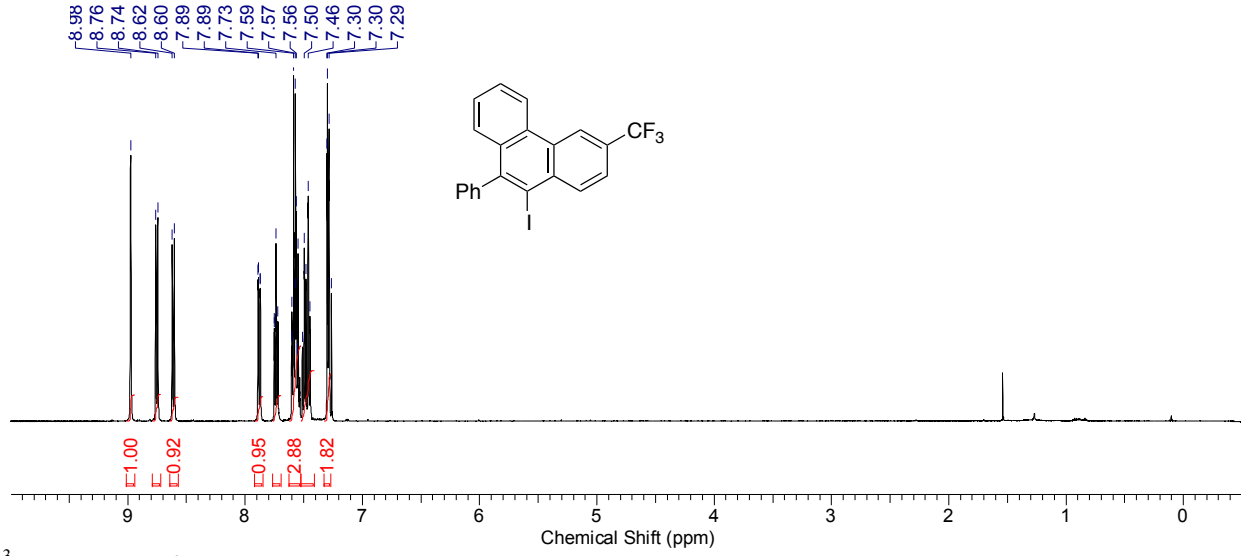

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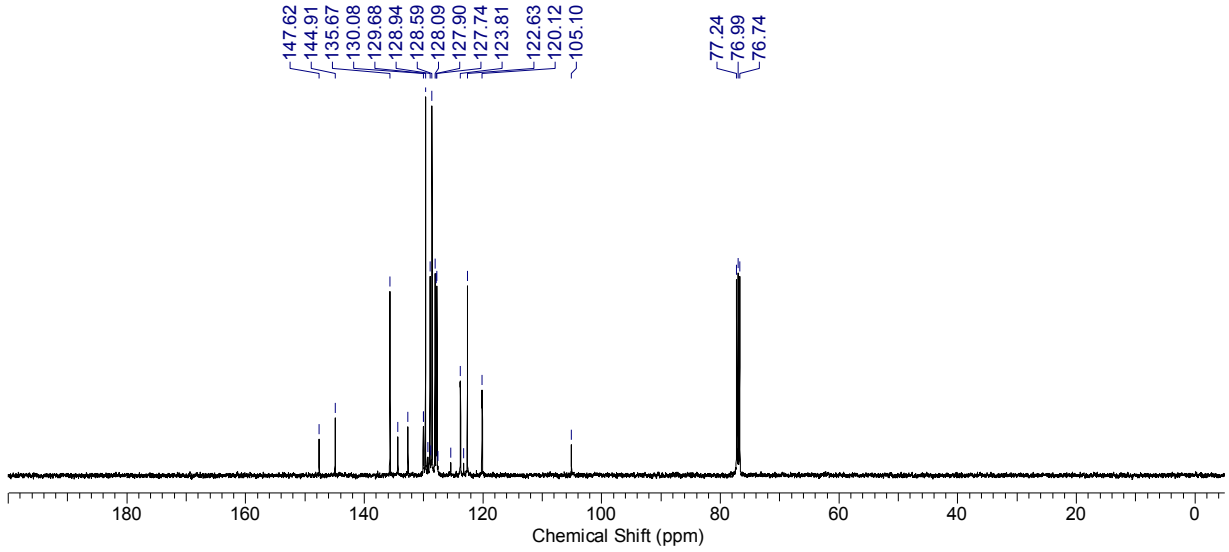

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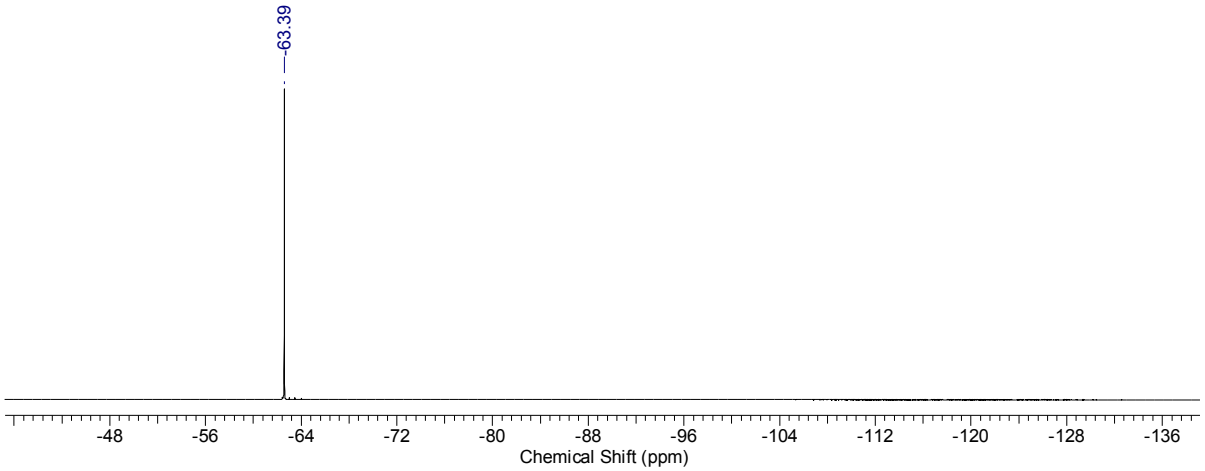

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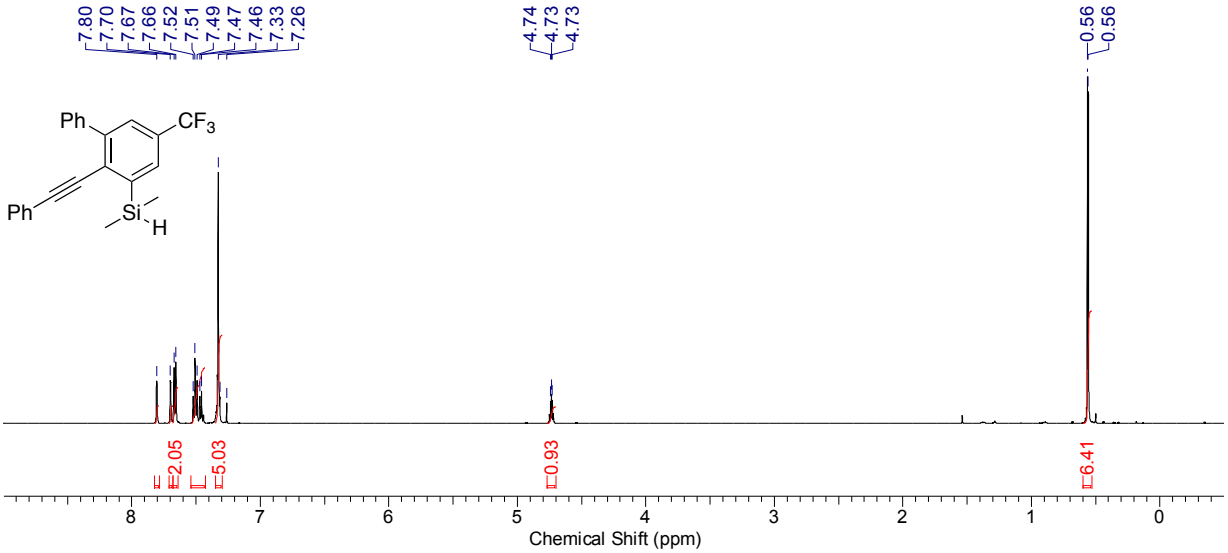

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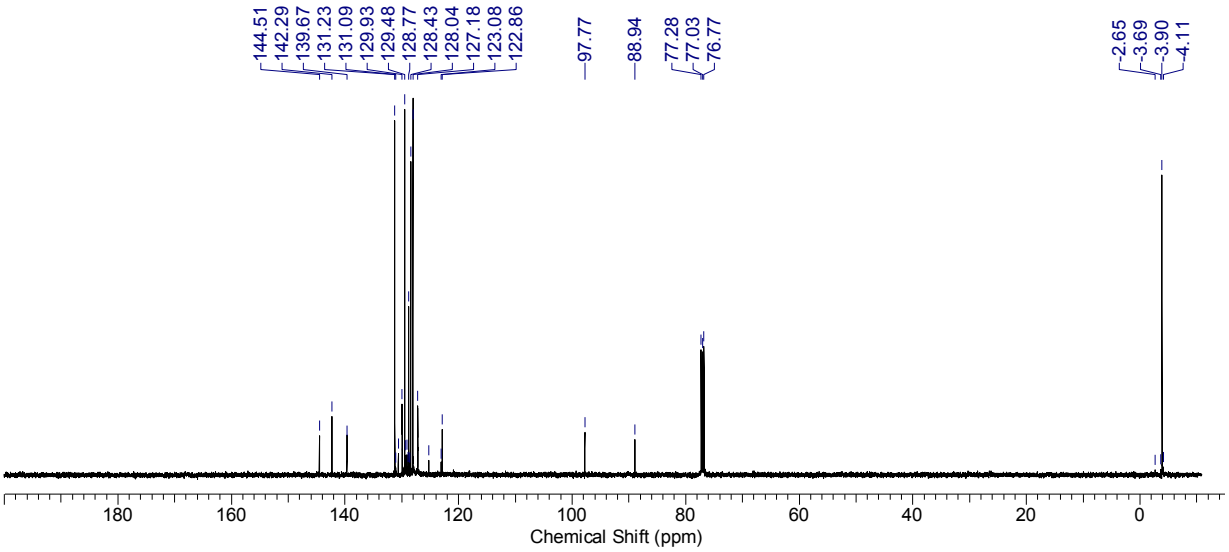

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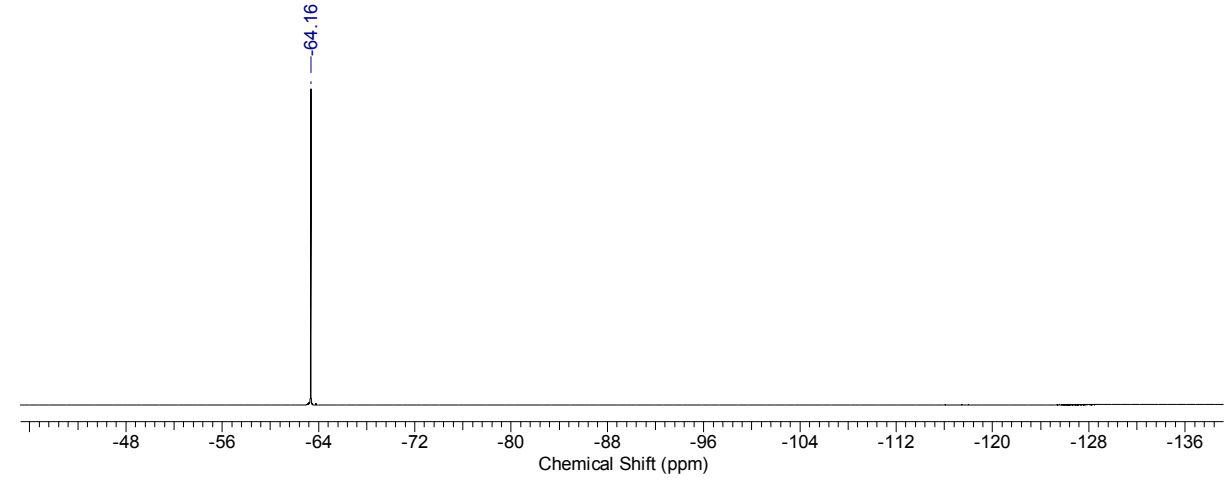

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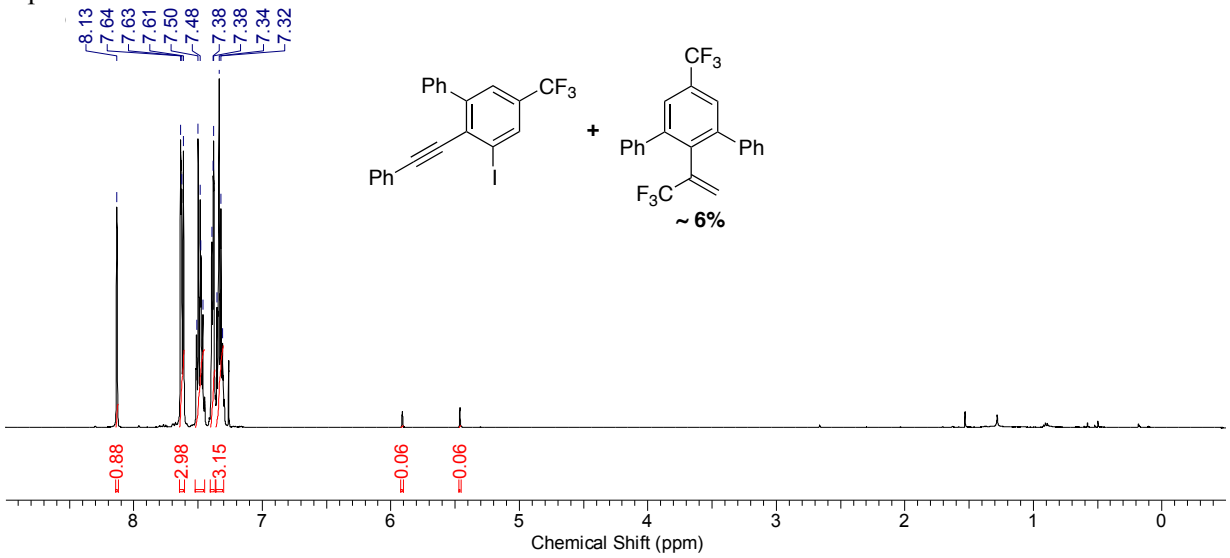

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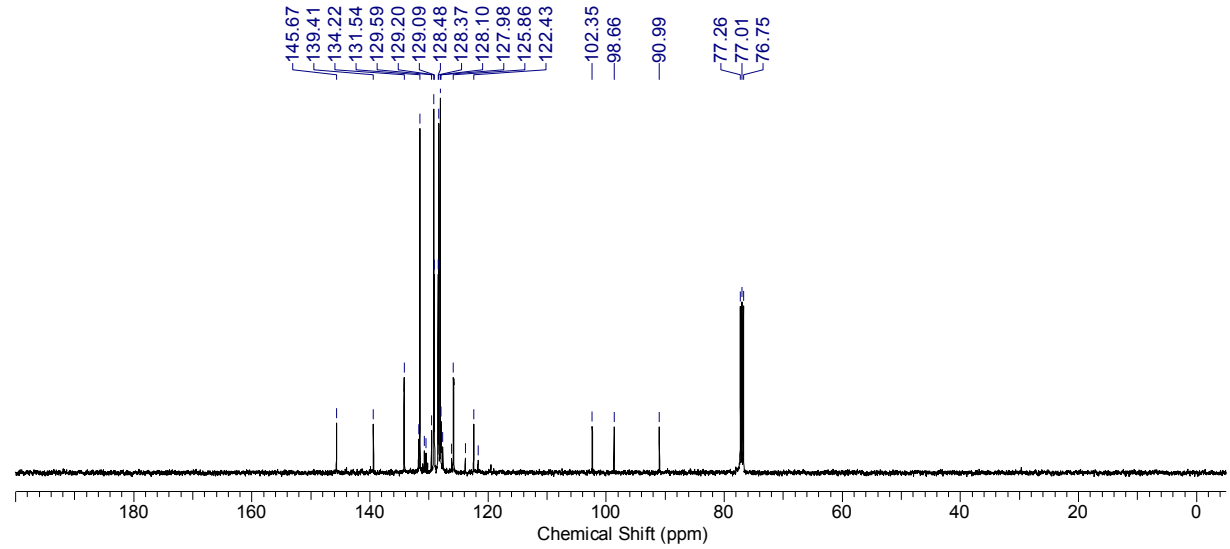

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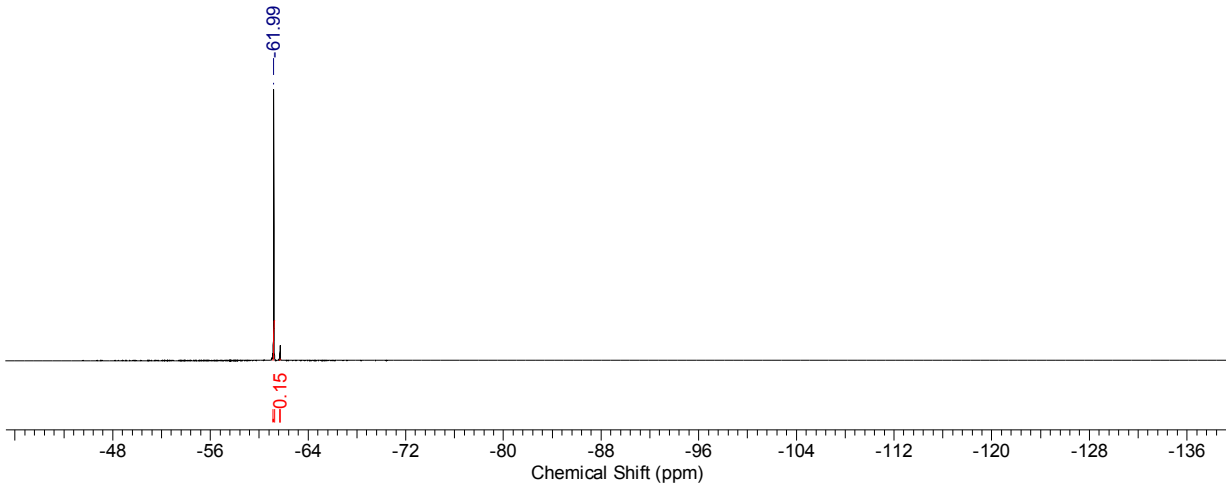

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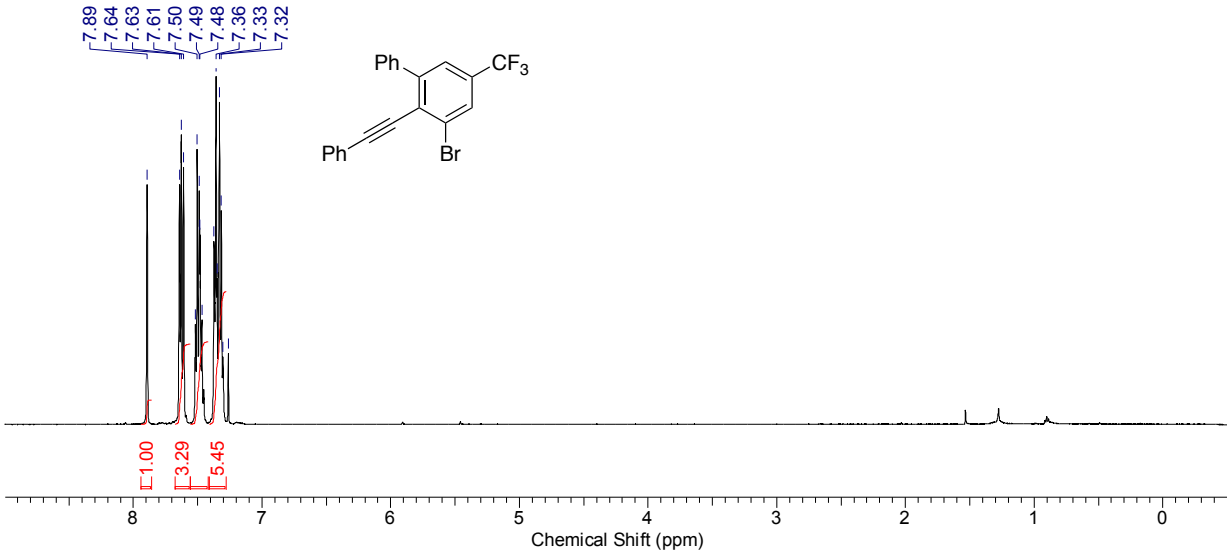

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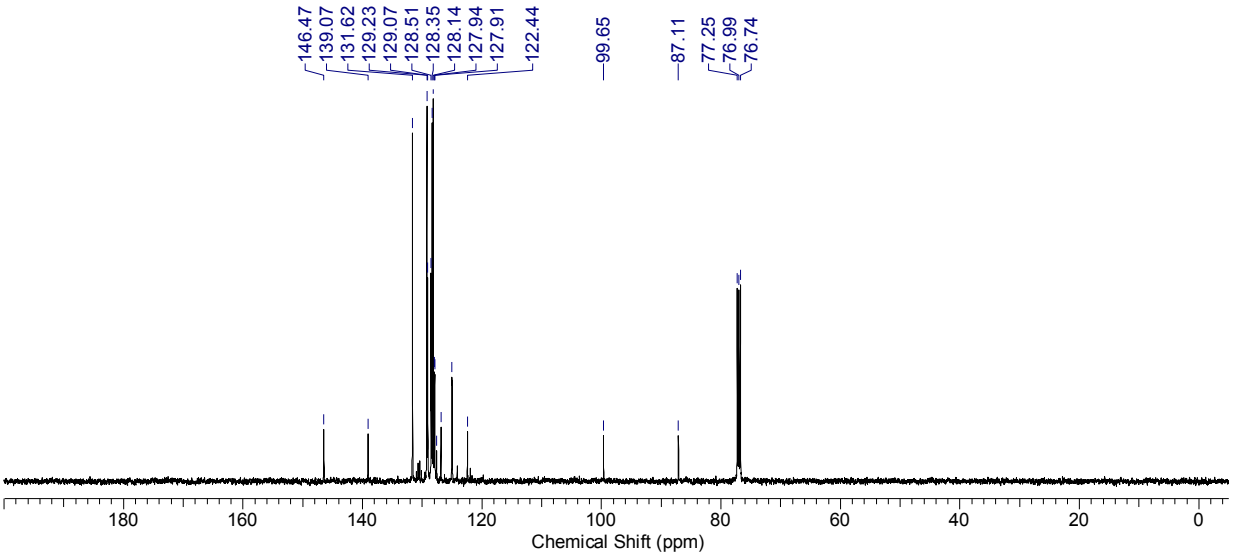

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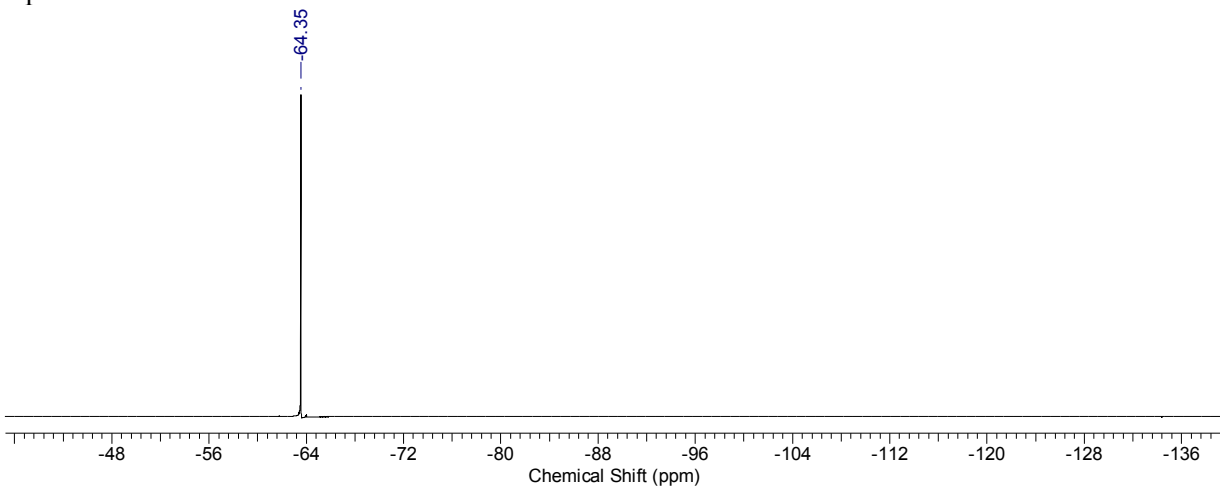

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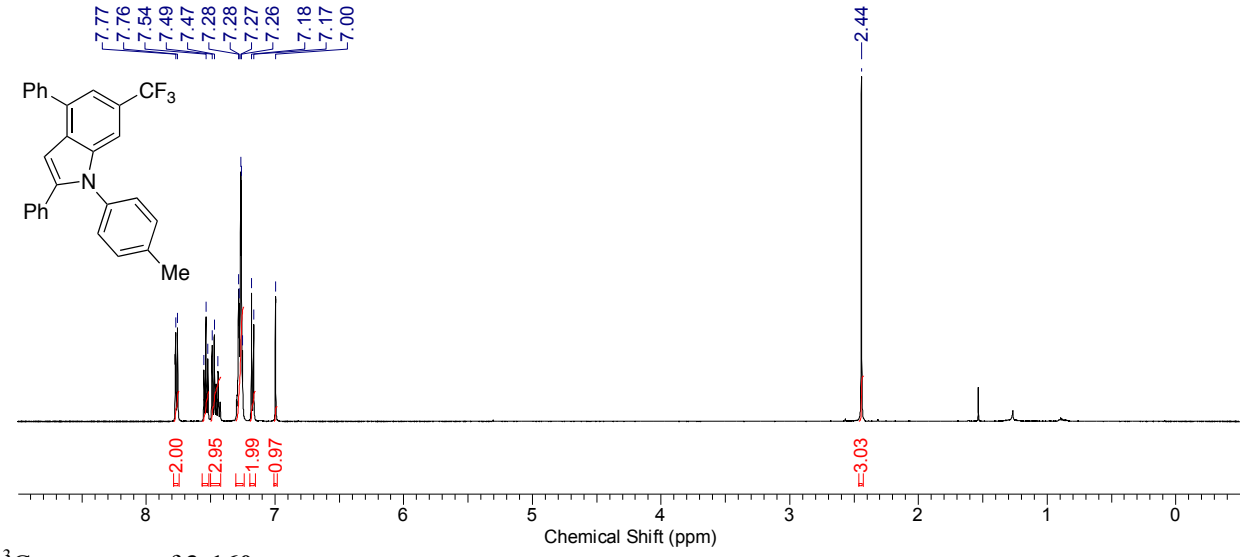

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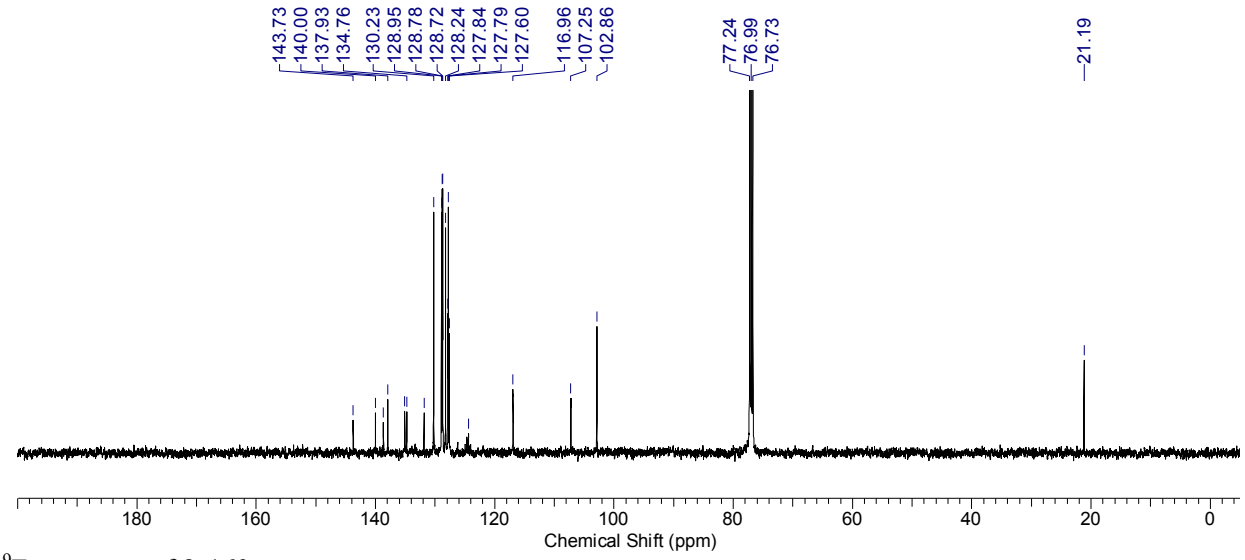

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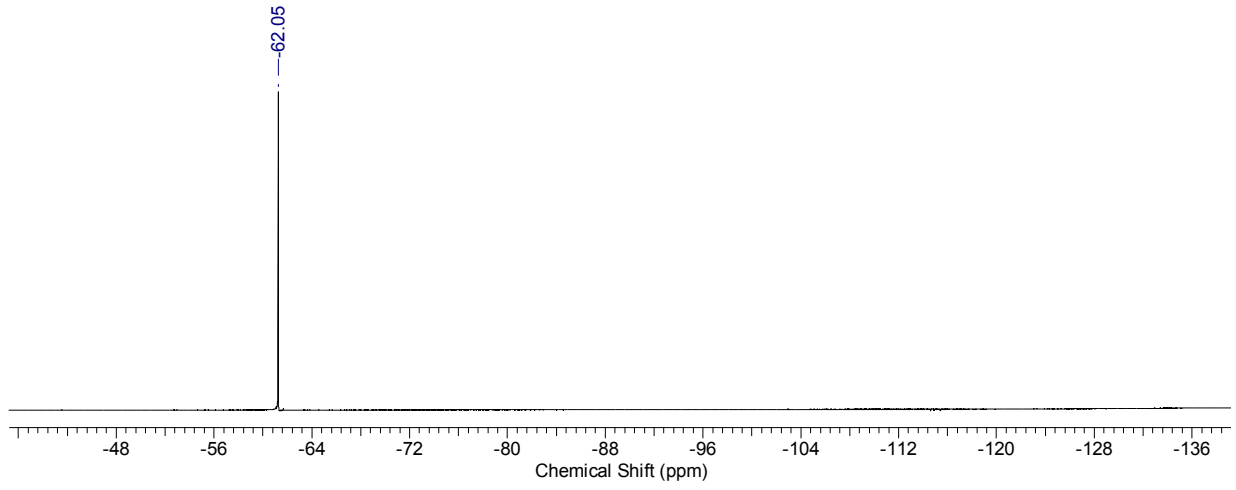

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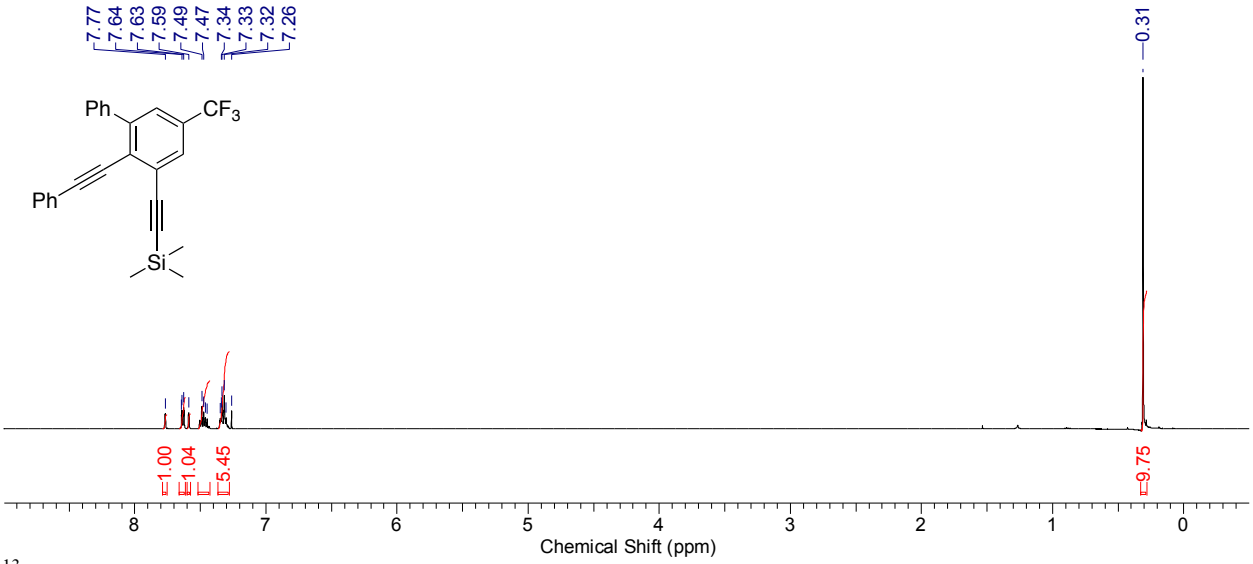

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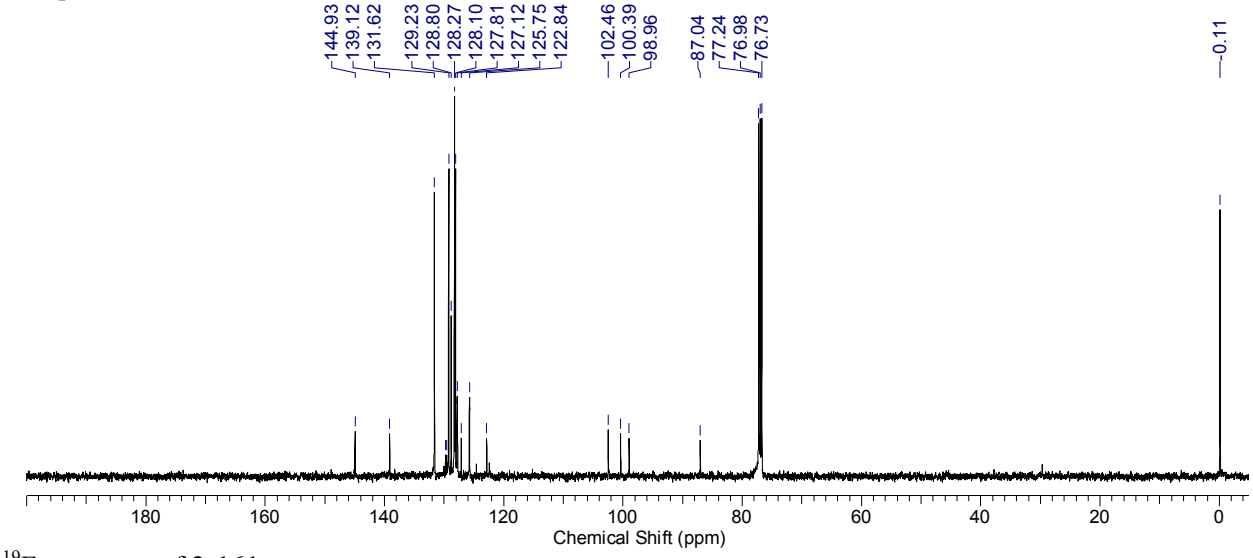

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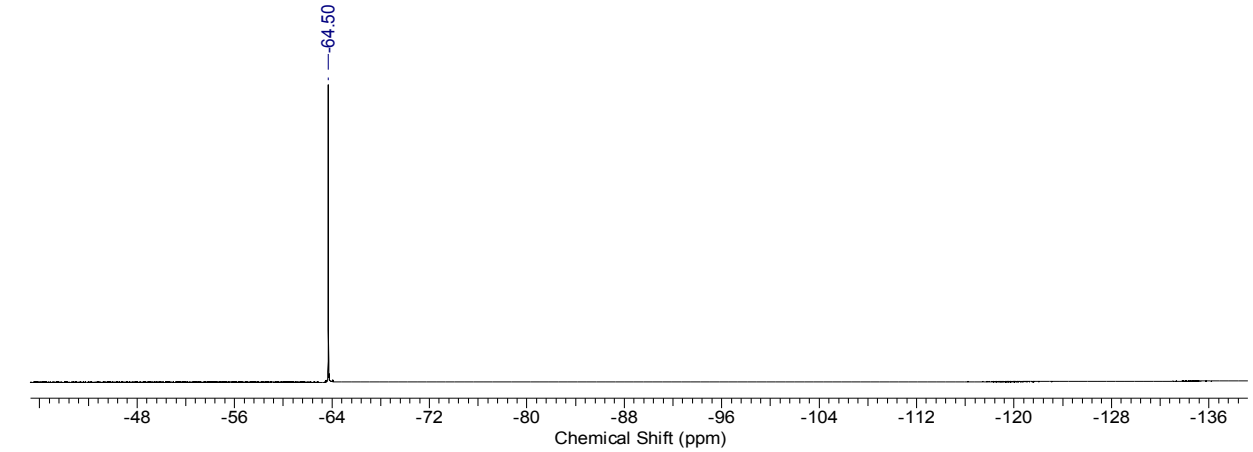

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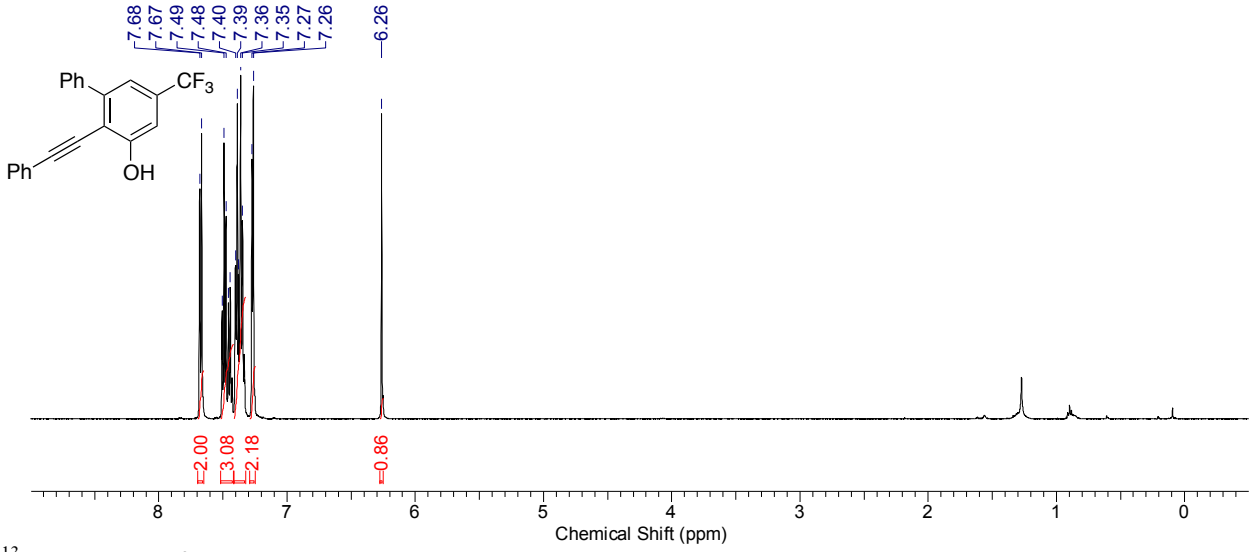

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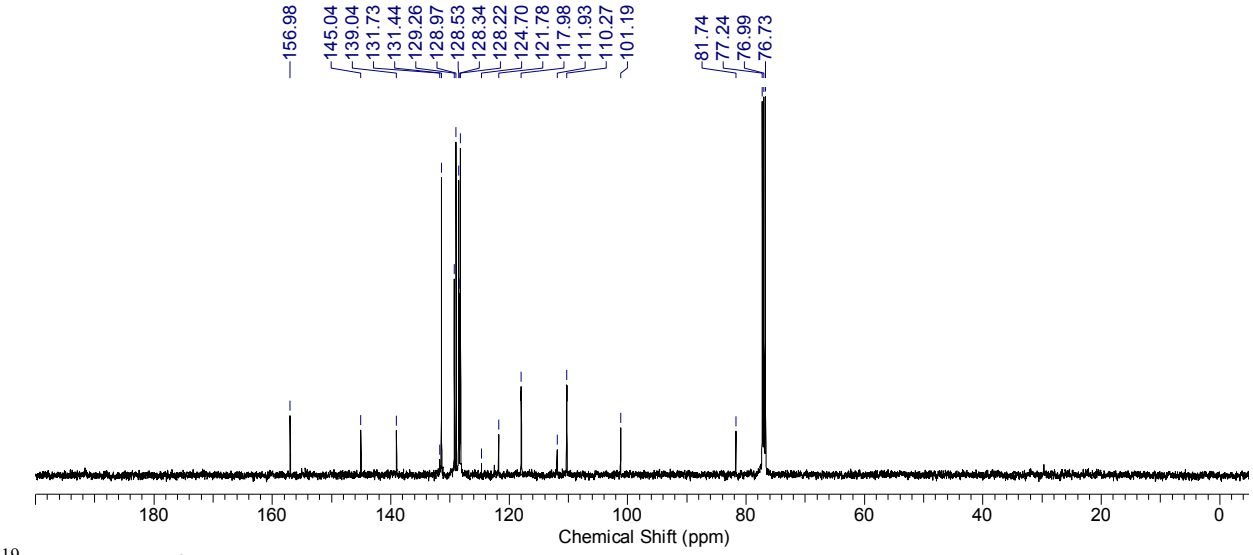

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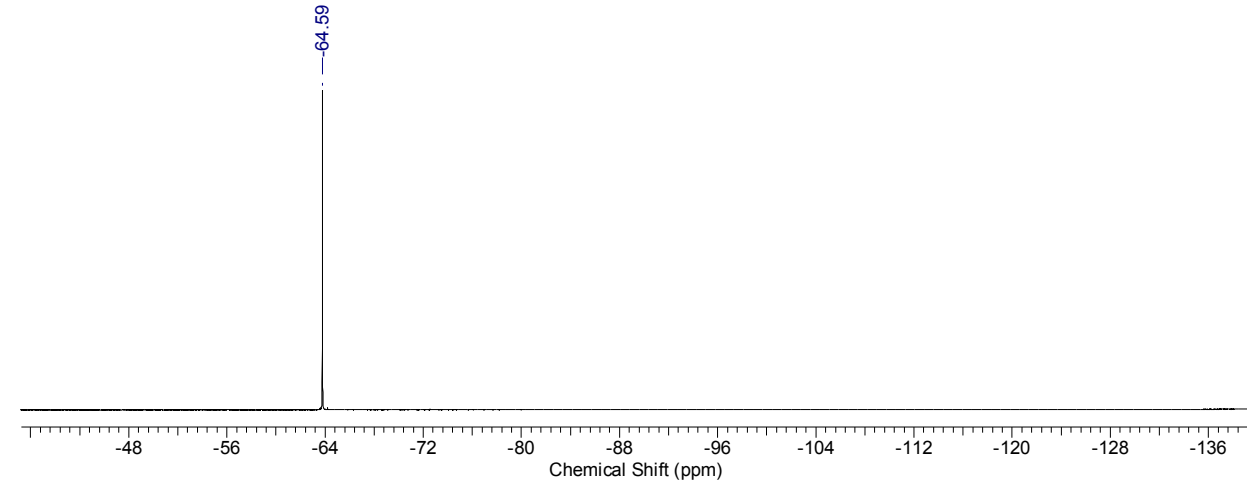

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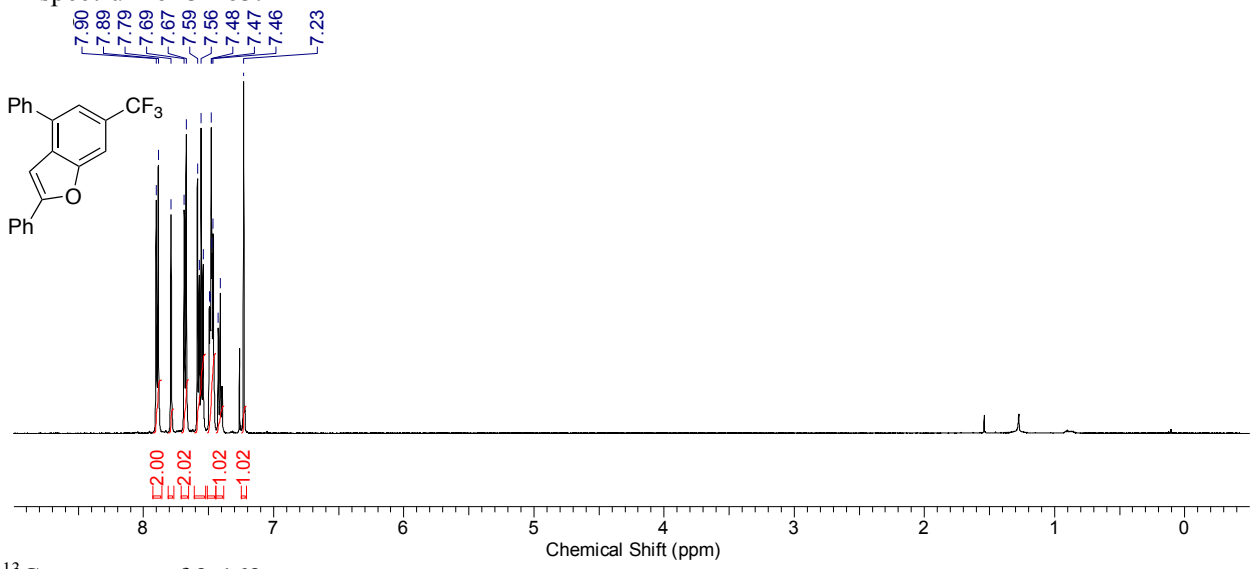

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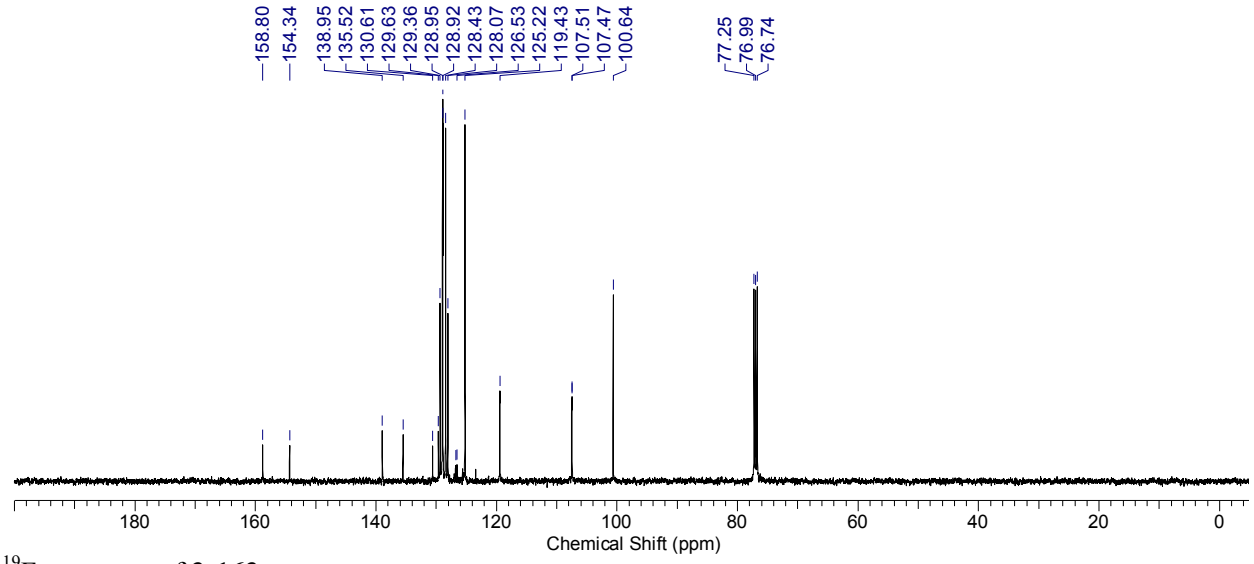

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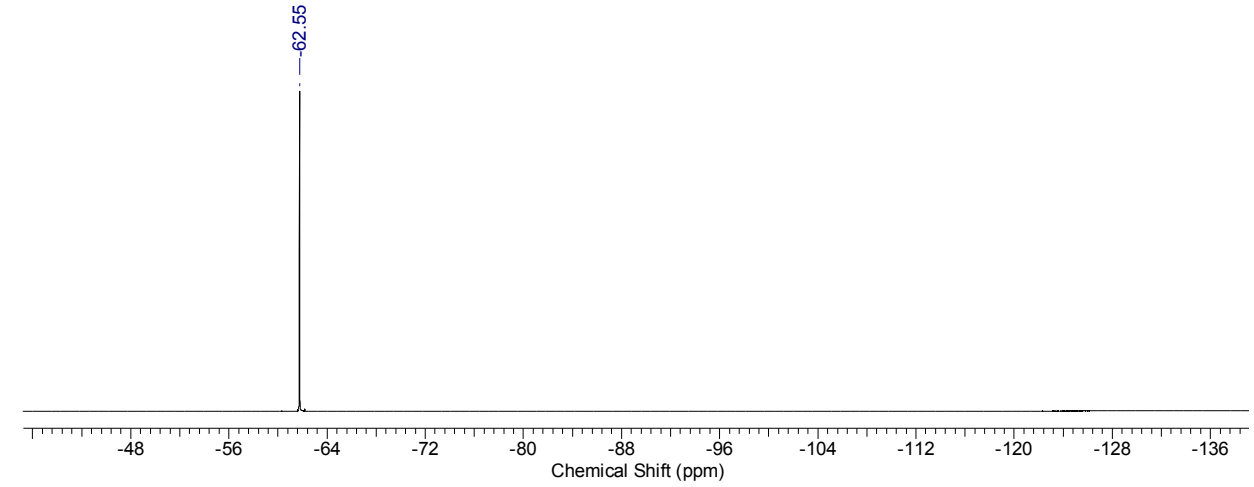

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Author: Claire Jahier, Olga V. Zatolochnaya, Nickolay V. Zvyagintsev, et al

Publication: Organic Letters

Publisher: American Chemical Society

Date: Jun 1, 2012

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